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Strategies Toward Saturated Cyclic Amine Diversification

By

Justin Edward Jurczyk

A dissertation submitted in partial satisfaction of the

requirements for the degree of

Doctor of Philosophy

in

Chemistry

in the

Graduate Division

of the

University of California, Berkeley

Committee in Charge:

Professor Richmond Sarpong, Chair
Professor Thomas Maimone
Professor Greg Aponte

Spring 2022

Abstract

Strategies Toward Saturated Cyclic Amine Diversification

By

Justin Edward Jurczyk

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Professor Richmond Sarpong, Chair

Strategies aimed at the diversification of saturated cyclic amines are appealing due to the prevalence of such aza-cyclic scaffolds within biologically active small molecules. The following dissertation discusses the development of complementary strategies related to this endeavor, specifically those involving peripheral functionalization, topological diversification, and skeletal editing.

Chapter 1 begins with a brief introduction into heterocycle editing. In this chapter, a classification scheme with related nomenclature is provided. From here, each molecular editing subclass is further contextualized by discussing the motivations for these respective areas of investigation. An overview of the state-of-the-art techniques utilized for these transformations is also highlighted.

Chapter 2 then describes our initial efforts toward the peripheral functionalization of cyclic amines using inherently strained ring systems. Under visible light irradiation, we achieve a Norrish–Yang cyclization, generating *N*-fused bicyclo α-hydroxy-β-lactams. The resulting strain embedded in these heterocycles is further exploited to achieve mild cross-couplings, arriving at peripherally functionalized saturated aza-cycles. Notably, this work represents the first palladium catalyzed C–C cleavage/functionalization of α-hydroxy-β-lactams.

Chapter 3 discusses our work toward the topological diversification of amine frameworks. Here, we present a general method for bridged bicyclic amine formation based on Hofmann–Löffler–Freytag reactivity. In our C–H bond amination strategy, we identified the distinct roles of light and heat activation, providing evidence that light promotes N–I bond homolysis and HAT, whereas heat promotes S_N2 ring closure. The expansion of this strategy to fused and spirocyclic bicyclic amines is also reported.

Lastly, Chapter 4 details our most recent work related to the skeletal editing of heterocycles. Through the strategic application of a Norrish type II reaction, we established a versatile method for the ring contraction of piperidines as well as other saturated heterocycles. Initial computational insight also led to development of an asymmetric contraction variant using chiral phosphoric acids.

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Chapter 1. Synthetic Strategies for Heterocycle Editing

1.1 Introduction

Modern approaches to drug discovery are increasingly impacted by the development of novel synthetic methods, with motivations arising from the ability to enact desired chemical transformations in a concise and chemoselective fashion.[1–3] Such innovations provide the ability to circumvent traditional hurdles in drug development, specifically those related to SAR studies, ultimately enabling chemists to synthesize derivatives of promising lead compounds at a late stage. To this end, the field of organic synthesis has become captivated by the idea of "molecular editing," — to rapidly build onto, change, or prune molecules one atom at a time using transformations which are mild and selective enough to be employed at the "late stage" of a synthesis — a call-to-action with metaphorical roots in macroscopic, digital technologies (e.g., can we make synthesis as easy as ChemDraw?).

While a clear definition of molecular editing remains elusive, tied up in this pursuit is the idea of being able to rapidly build and/or subsequently tolerate complexity — privileging those transformations which are mild and selective enough to be employed at a "late stage" or in the context of complex natural product total synthesis. Conceptually, these approaches, once they are broadly developed, would enable the direct interrogation of structure-activity relationships of the kind central to modern medicinal chemistry (Fig. 1.1A).

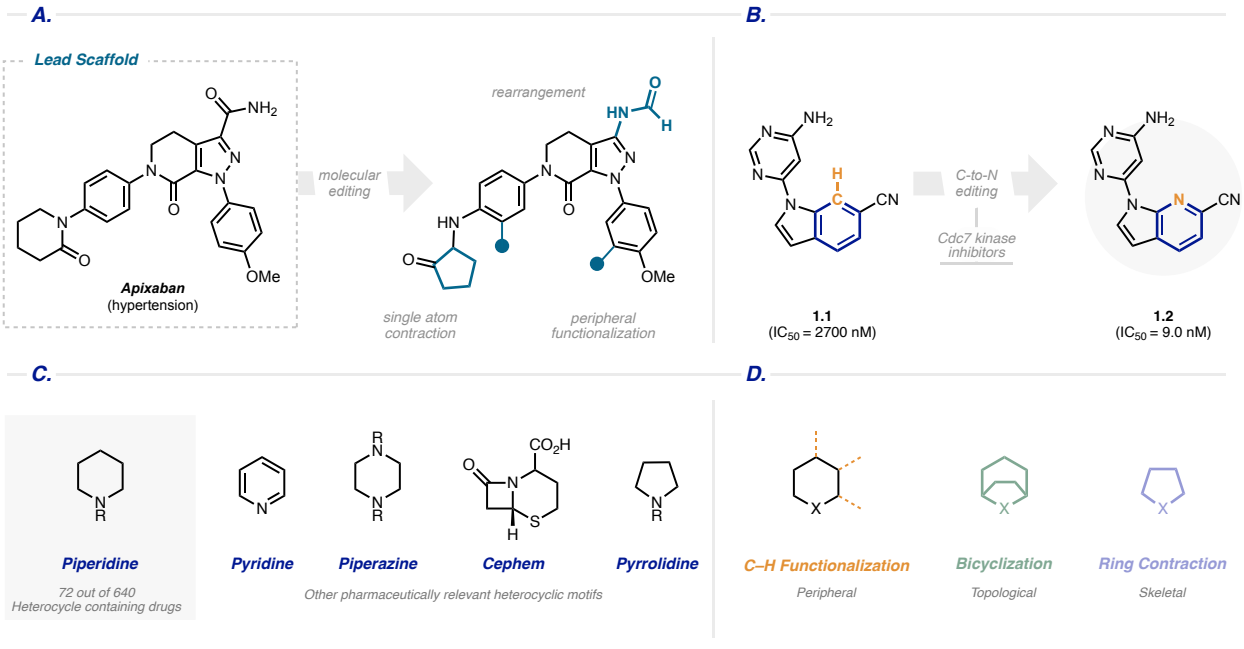

Figure 1.1. The Anatomy of Molecular Editing. (A) Examples of peripheral and skeletal editing conceptually applied toward the diversification of apixaban. (B) Applications of molecular editing in drug discovery. (C) Prevalence of nitrogen heterocycles in bioactive compounds. (D) Classification of selected molecular editing manifolds.

Indeed, one application of this ideology, related to the so-called "necessary nitrogen effect" has prompted lead optimization campaigns to conduct "nitrogen scans," wherein carbon atoms of a lead scaffold are replaced by nitrogen (e.g. **1.1** to **1.2**, Figure 1.1B); in practice, this endeavor requires tedious re-synthesis (often re-engineering the synthetic route altogether) to access the aza-analogues of the lead molecule.[4]

1.2 Heterocycle Editing in Drug Discovery

Molecular editing strategies for saturated heterocyclic compounds are particularly attractive due to the prevalence of such scaffolds within biologically active small molecules.[5,6] Piperidines are especially significant; this structural motif is found in over 10% of the 640 top heterocycle containing drugs on the market (Fig. 1.1C). As a result of the occurrence of these privileged scaffolds in bioactive small molecules, new methods that achieve direct peripheral functionalization (*C–H functionalization*), topological diversification (*bicyclization*), or skeletal editing (*ring contraction / ring expansion*) of saturated heterocyclic frameworks are of increased synthetic interest (Fig. 1.1D) and will be the focus of this thesis. When applied to a compound of interest, these methods provide the ability to tune the physical and biological properties of therapeutic lead scaffolds possessing these structural motifs via selective scaffold diversification.[3]

1.2.1. Peripheral Functionalization

Though the piperidine scaffold itself is a widely represented structural motif found in a variety of biologically active molecules, it is often decorated with one or multiple substituents, which is exemplified by functionalized piperidine ring containing drug molecules **1.3a–1.3c** (Fig. 1.2A).[5] Peripheral substitution patterns are also implicated in the conformational preferences inherent to a given molecule. Related to small molecule drug design, a major consideration is to ensure that the compound of interest will adopt the desired conformation within a given binding pocket. In *N*-acylpiperidine like structures, for example, the nitrogen atom adopts a near planar, sp^2 hybridization.[7,8] The *N*-acyl substituent blocks the equatorial positions adjacent to the nitrogen atom. Because of this, when α-substituents are present, they tend to adopt an axial conformation to avoid pseudo-1,3-allylic strain. This design principle was demonstrated by scientists at Merck Research Labs investigating orexin receptor antagonists.[9] Compared to the non-methylated piperidine where the bulky pyridine-containing aryl ether side chain assumes the lowest energy equatorial conformation (see Fig. 1.2B, **1.4a** *vs* **1.4b**), addition of a *trans* α-methyl substituent results in the molecule adopting the desired bioactive conformation (Fig. 1.2B, **1.5**) marked by the dramatic increase in compound potency. Though this effect is most prominent in *N*-acylpiperidines, similar trends are also observed in several *N*-sulfonyl and *N*-aryl-containing piperidine scaffolds.

Synthetically, C–H bond α-functionalization also represents a transformation of interest as the C–H bonds adjacent to the nitrogen heteroatom are relatively weak, rendering them open to exploitation toward functionalization.[10] Traditional approaches for piperidine acylation involve α-lithiation and addition of an electrophile, or transmetalation to undergo cross-coupling (Fig. 1.2C). More recent strategies have utilized Lewis basic *N*-linked directing groups to achieve direct α-metalation for subsequent cross-coupling, or photoredox catalysis to achieve α-functionalization.

Our lab has developed a complementary approach to achieve α-arylation which represents the first example of using α-hydroxy-β-lactams to achieve α-functionalization via C–C bond cleavage (Fig. 1.2C); this work will be the focus of Chapter 2.

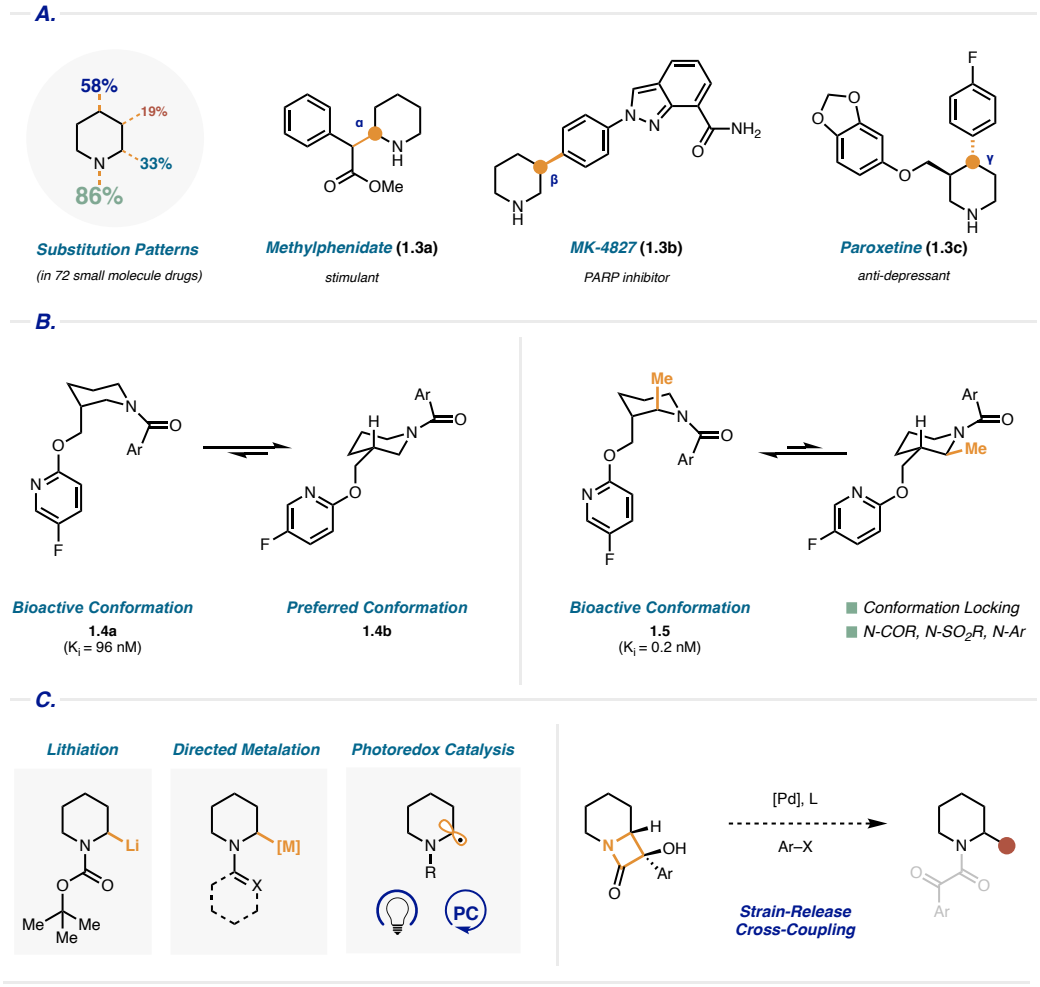

Figure 1.2. Overview of the Peripheral Functionalization of Cyclic Amines. (A) Common peripheral substitution patterns of the 72 top piperidine containing drugs with selected examples of known therapeutic compounds shown. (B) Control of ring conformation through strategic peripheral substitution. (C) Approaches toward piperidine α-functionalization.

1.2.2. Topological Diversification

In addition to simpler monocyclic amine scaffolds, complex bicyclic amines are also well represented among biologically active small molecules and are largely derived from natural product architectures (Fig. 1.3A).[5] The top commonly encountered bicyclic drug cores are all inspired by natural products (morphinan, tropane, and quinuclidine), and can be found in potent therapeutic agents ranging from morphine to cocaine. Similarly, the most frequently occurring fused cores are also natural product or nucleobase derived, and can be found in bioactive drugs like LSD and anticancer or antiretroviral agents respectively.[5]

Importantly, rigid aliphatic bicyclic amines of the bridged, fused, and spirocyclic variety are also known to exhibit enhanced metabolic stability,[11] provide unique substituent vectors,[12,13] and demonstrate differentiated physicochemical properties in comparison with their monocyclic counterparts.[11,14,15] These three classes of bicyclic amines are intrinsically rich in three dimensionality (i.e., high fraction sp^3), which is a parameter known to correlate with clinical success.[16–19] An interesting application of these principles has been demonstrated by Estrada and coworkers toward their development of pyrimidoaminotropanes as selective small molecule kinase inhibitors of the mammalian target of rapamycin (mTOR) (Fig. 1.3B, *right*).[20] Starting from lead compound **1.6**, incorporation of an ethylene bridge on the heteroatom adjacent carbons in **1.7** led to the identification of a clinical candidate with improved mTOR cellular activity (4 nM (**1.6**) vs. 1 nM (**1.7**)), desirable free drug clearance, and increased tumor growth inhibition (60% at 37 mg/kg (**1.6**) vs. 57% at 12.2 mg/kg (**1.7**)). Despite the occurrence of bicyclic motifs within biologically active small molecules, strategies to synthesize diverse bridged bicyclic amines are limited, with a majority of existing methodologies targeting the related classes of spirocyclic or fused aza-cycles (Fig 1.3B, *left*).[13,21,22]

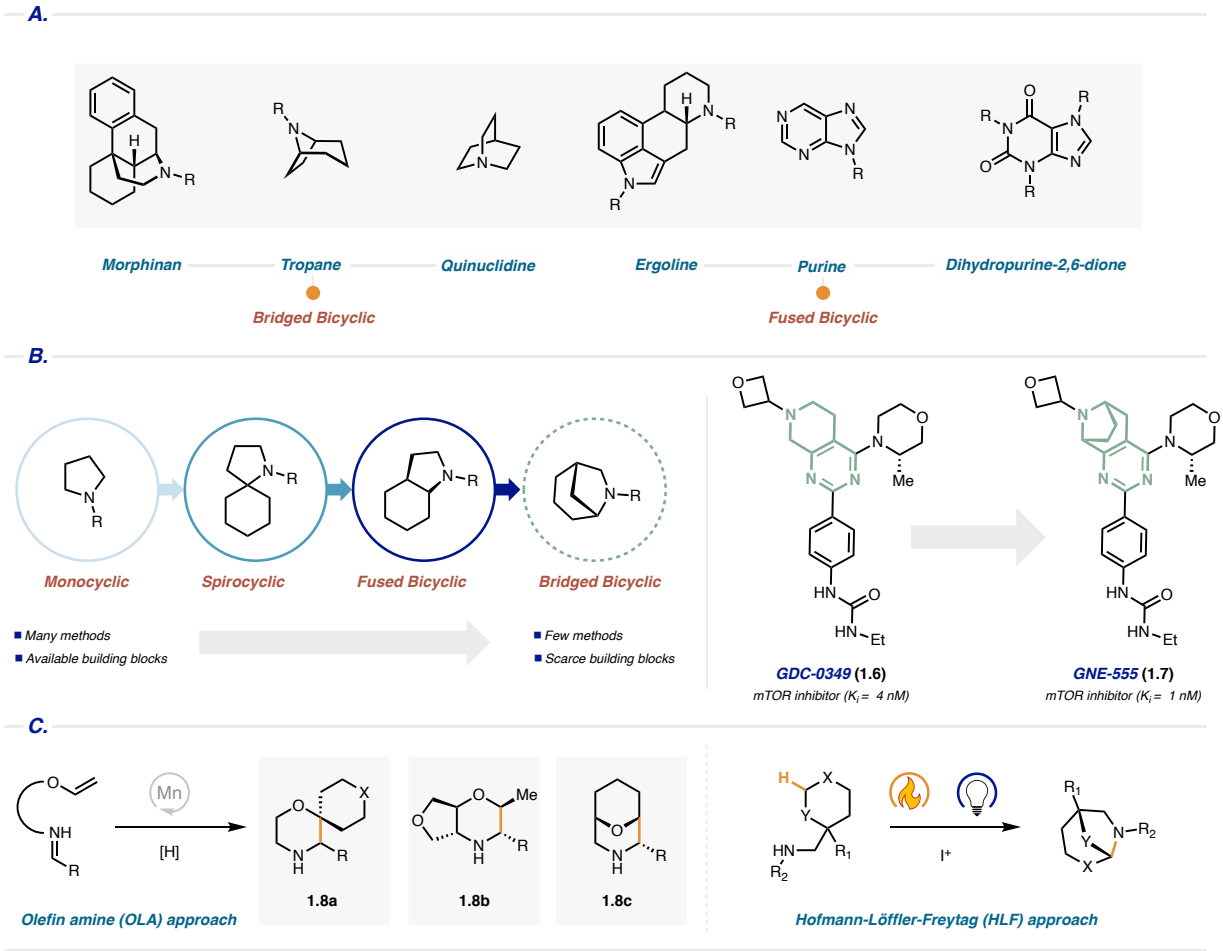

Figure 1.3. Overview of Topologically Diverse Bicyclic Amines. (A) Common bicyclic amine motifs found in known drugs. (B) Classification scheme for bicyclic amines (*left*) and incorporation of bridged bicyclic amines in drug discover to increase favorable properties (*right*). (C) Approaches toward bicyclic amine formation.

In this context, bridged bicyclic aza-cycles remain underrepresented in medicinal chemistry campaigns due to the barrier associated with synthesizing such structures. Inspired by work conducted by Bode et al.,[23] we reported a complementary strategy toward bicyclic amine formation to access bridged, fused, and spirocyclic aza-cycles using a Hofmann-Löffler-Freytag (HLF) reaction (Fig. 1.3C). This work will be highlighted in Chapter 3.

1.2.3. Skeletal Editing

Perhaps the most dramatic of the aforementioned subclasses of heterocycle editing strategies is single atom skeletal editing. Conceptually, the retrosynthetic simplicity of single-atom editing is enabling (Fig. 1.4A, *left*). Rearrangements of molecular skeletons often suffer from being "difficult to see" in a retrosynthetic sense, limiting their adoption. Indeed, the most used reactions in medicinal chemistry (cross-coupling, amide bond formation, S_NAr, reductive amination) have a common retrosynthetic simplicity that, in addition to their broad scope, has propelled their implementation. As such, methods capable of directly modifying late-stage ring systems have the potential to substantially impact lead optimization and analog synthesis in medicinal chemistry and allow access to unique chemical space and potential function.

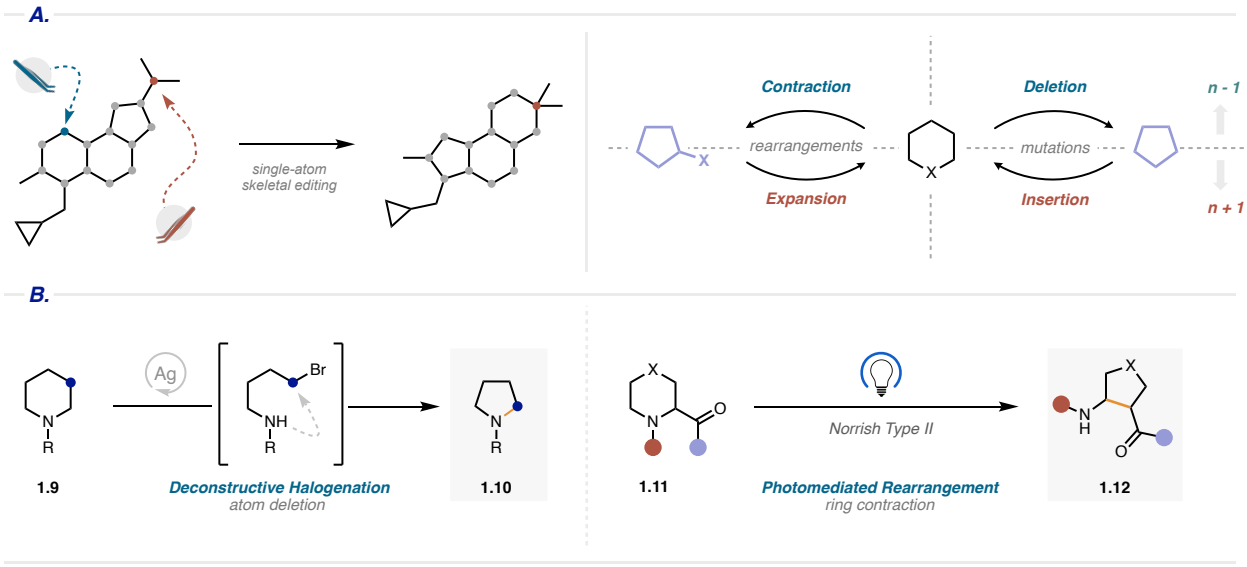

Figure 1.4. Classification of Single Atom Skeletal Editing. (A) Depiction of single atom editing applied to a representative molecule (*left*) and the related classification scheme (*right*). (B) Strategies for aza-cyclic ring contraction featuring rearrangements or mutations.

In single-atom skeletal editing, two major dividing lines can be drawn, resulting in four general reaction classes. The first is straightforward, depending on whether the ring system in question is expanded ($n \rightarrow n+1$) or contracted ($n \rightarrow n-1$). Within this classification, there remains a question of whether the atom being edited begins (or is retained, respectively) as an exocyclic substituent of the ring system. Such transformations can be referred to as rearrangements, subdivided into contraction and expansion. Juxtaposed, deletions and insertions (collectively mutations) denote skeletal edits in which the edited atom is not directly attached to the ring system in question. Figure

1.4A (*right*) provides an overview of this classification scheme for a simple heterocyclic ring system.

Our lab has previously reported a method that formally achieves the deletion of a single carbon from saturated nitrogen heterocycles such as piperidines (**1.9**) (Fig. 1.4B, *left*).[24] Following the proposed silver-catalyzed decarboxylative bromination to an acyclic bromoamide possessing one fewer carbon atom, the ω-bromoamide can undergo base-promoted intramolecular cyclization to furnish ring-contracted amine products (e.g. **1.10**). More recently, we demonstrated a complementary method for aza-cycle skeletal editing (Fig. 1.4B, *left)*. Here, we achieve a photo-mediated ring contraction rearrangement of acyl aza-cyclic scaffolds (**1.11**), wherein formally the nitrogen atom undergoes an endocyclic to exocyclic migration giving rise to amino cyclopentane products (**1.12**). This investigation will be discussed in detail in Chapter 4.

1.3 Conclusion

Innovations in synthetic chemistry continue to push the paradigm in "late-stage" functionalization, ultimately expanding the toolbox of versatile chemical transformations. These endeavors provide opportunities to access novel chemical space and function in a rapid fashion, while simultaneously overcoming synthetic restraints on molecular design. In particular, the concept of molecular editing has emerged as a developing area of interest; the ability to edit a target molecule directly and selectively at a "late-stage" has the potential to obviate the shortcomings traditionally associated with derivatization of medicinally relevant compounds. Chapters 2 through 4 will further describe our efforts aimed at heterocycle editing, specifically strategies for peripheral functionalization, topological diversification, and skeletal editing.

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1.5 Contributors

All the authors contributed to the inception, organization and writing of this manuscript, which was overseen by R.S. and M.D.L. All the figures were finalized by J.J. from initial drafts created by all the co-workers. J.J. led the writing of the section Contractions, S.F.K. wrote the section Deletions, J.W. led the writing of the section Expansions and B.D.D. wrote the Insertions section.

Chapter 2. C–C Cleavage Approach to C–H Functionalization of Saturated Aza-Cycles

Saturated cyclic amines (aza-cycles) are ubiquitous structural motifs found in pharmaceuticals, agrochemicals, and bioactive natural products. Given their importance, methods that directly functionalize aza-cycles are in high demand. Herein, we disclose a fundamentally different approach to functionalizing cyclic amines which relies on C−C cleavage and attendant cross-coupling. The initial functionalization step is the generation of underexplored *N*-fused bicyclo α-hydroxy-β-lactams under mild, visible light conditions using a Norrish−Yang process to effect α-functionalization of saturated cyclic amines. This approach is complementary to previous methods for the C−H functionalization of aza-cycles and provides unique access to various cross-coupling adducts. In the course of these studies, we also uncovered an orthogonal, base-promoted opening of the *N*-fused bicyclo α-hydroxy-β-lactams. Computational studies provided insight into the origin of the complementary C−C cleavage processes.

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2.1 Introduction

Over the last two decades, the emergence of powerful and selective C–H functionalization methods has redefined approaches for synthesizing complex molecules and fine chemicals.[1] Recently, advances in site- and stereo-selective C(sp^3)–H functionalization have revolutionized the practice of late-stage functionalization (LSF) in the pharmaceutical, agrochemical, and materials industries, where there is strong motivation to identify architecturally complex sp^3-rich scaffolds.[2] Among the many bioactive and privileged sp^3-rich scaffolds, piperidines are perhaps the most prevalent.[3,4] As such, synthetic methods for diversifying the piperidine framework are highly coveted. The state-of-the-art techniques that have been developed for this purpose employ directing groups on the piperidine nitrogen and require a highly specific and often harsh set of conditions that can be incompatible with functional groups on complex structures (Fig. 2.1).[5,6]

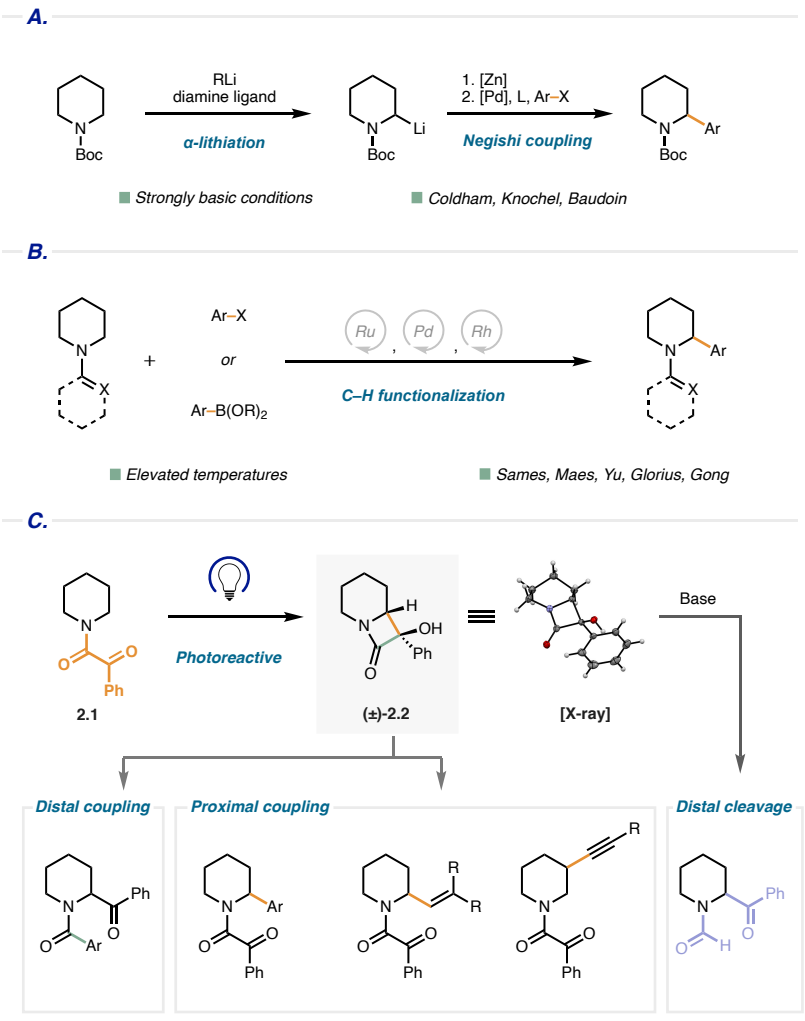


Figure 2.1. Approaches to α-functionalization of piperidines by C–H functionalization. (A) Reported α-functionalization utilizing lithiation/Negishi cross-coupling sequence. (B) Selected examples of C–H functionalization approaches for piperidine α-functionalization. (C) Strain release approach for mild cyclic amine functionalization (*this work*).

For example, Coldham showed that lithiation of *N*-Boc piperidine using Beak/Gawley-inspired conditions[7] followed by transmetalation to an organozinc species set the stage for a Negishi-type cross-coupling (Fig. 2.1A), building on the pyrrolidine arylation precedent of Campos and co-workers.[8] Knochel and co-workers later expanded on this work and demonstrated diastereoselective arylations of substituted piperidines,[9] as well as an example of β-functionalization. In this context, Baudoin and co-workers extended and generalized β-functionalization of *N*-Boc piperidines through ligand control.[10]

Recently, Seidel and co-workers developed an alternative one-pot protecting group-free approach to access α-functionalized cyclic amines,[11] albeit requiring strongly basic conditions. Alternatively, Sames and co-workers have reported one example of α-arylation with piperidines bearing an amidine directing group (see Fig. 2.1B), using Ru catalysis and boronate esters, though in low yield.[12] Similarly, Maes and co-workers reported that pyridyl directing groups could effect the α-ruthenation of piperidines to yield arylated products; however, competing mono- and bis-arylation was observed.[13] In an exciting recent development, Yu and co-workers, Glorius and co-workers, and Gong and co-workers have shown that thioamide derivatives (Fig. 2.1B) now enable enantioselective α-functionalization of a range of saturated aza-heterocycles including piperidines.[14–16] Other strategies have relied on photoredox catalysis,[17–19] intramolecular hydride transfer,[20] and C–H insertions via metal carbenoids.[21]

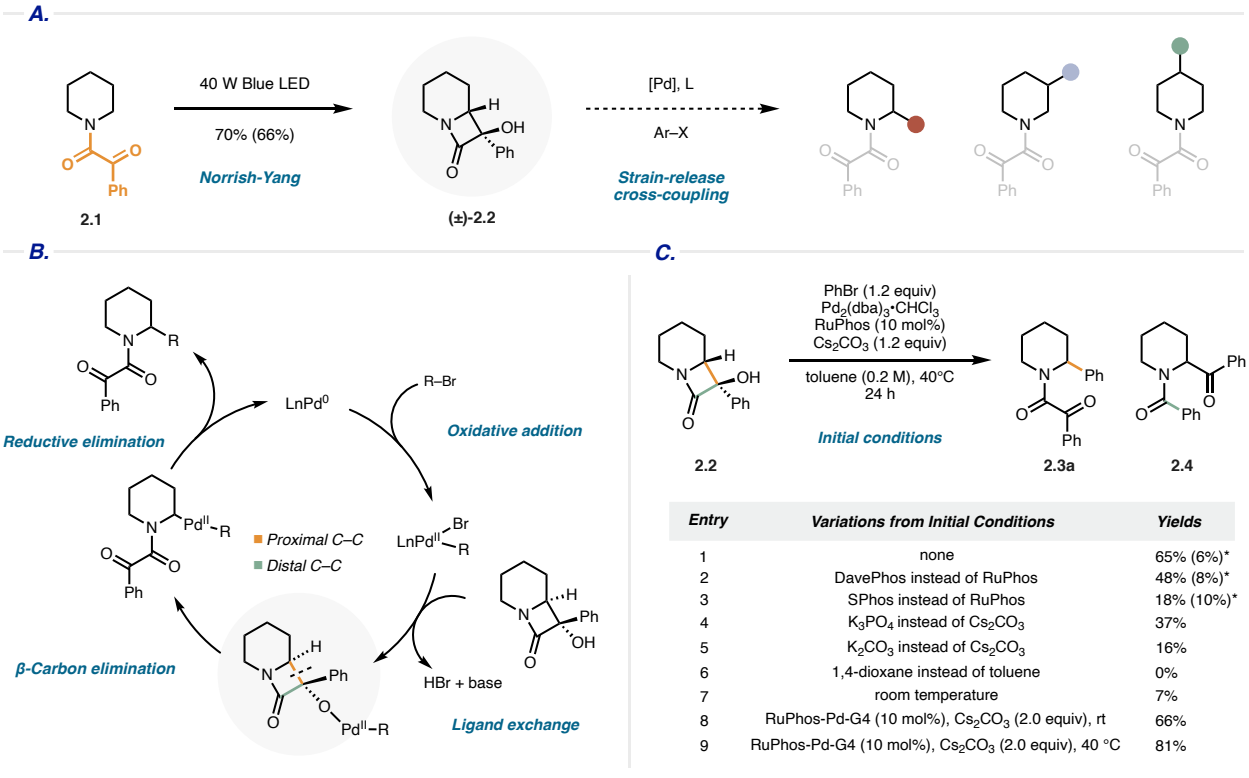
In the context of the cross-coupling step, the use of organozinc nucleophiles, in particular (i.e., Fig. 2.1A), is highly attractive because it reduces the α-arylation of piperidines to a standard cross-coupling reaction (i.e., the Negishi cross-coupling) under well-established and easily optimizable conditions using well-defined palladium complexes. In principle, other main-group metal derivatives (e.g., from Li, Mg, B, Sn, etc.) would serve an analogous purpose. However, given the handling challenges associated with α-zinc-, α-lithio-, α-boryl-, and α-stannyl-derived piperidines,[22] we sought an alternative but easy-to-use and reliable strategy to generate a nucleophile at the α-position of the piperidine framework that would be stable in aerobic and aqueous environments, stored indefinitely, accessible in enantiopure form, and deployed as required.

In this work, we report the utility of *N*-fused bicyclo α-hydroxy-β-lactams (e.g., **2.2**, Fig. 2.1C), which are generated under mild, visible light (λ = 400–450 nm) conditions from phenyl keto amides (e.g., **2.1**),[23,24] as masked nucleophiles for the α-functionalization of piperidines and other saturated aza-cycles. Importantly, using the same α-hydroxy-β-lactam derivative of a saturated cyclic amine, arylation, vinylation, and alkynylation can be easily achieved using mild conditions. This work addresses a key gap in late-stage diversification via C–H functionalization/cross-coupling using a non-obvious C–C bond cleavage of a corresponding strained α-hydroxy-β-lactam. The work described herein represents the first example of using α-hydroxy-β-lactams to achieve α-functionalization via C–C bond cleavage, and importantly, it is the first demonstration of strain-initiated C–C cleavage and arylation at room temperature, attesting to the mildness of this approach to aza-cycle functionalization. Moreover, preliminary results toward β-functionalization of cyclic amines and a transition metal-free α-acylation are reported. The results described herein showcase the potential of the underexplored reactivity of α-hydroxy-β-lactams.

2.2 Results and Discussion

*Synthesis of α-hydroxy-β-lactam piperidine derivative **2.2***

We commenced our studies by optimizing the protocol developed by Aoyama and co-workers[23] for the synthesis of α-hydroxy-β-lactam **2.2** (i.e., (±)-7-hydroxy-7-phenyl-1-azabicyclo[4.2.0]octan-8-one) from keto amide **2.1** (see Fig. 2.2A). Ultimately, we found that irradiating **2.1** in the solid state with blue LEDs provided bicyclic *N*-fused bicyclo[4.2.0] β-lactam **2.2** in 66% isolated yield (70% NMR yield using Ph_3CH as the internal standard). Notably, this Norrish-Yang reaction can be performed on the gram scale (see the Experimental Procedures for details). Importantly, the same approach could easily be applied to related saturated nitrogen heterocycles (e.g., morpholine, azepane, azocane, etc.) and hence represents a programmable strategy for functionalizing these types of structural motifs (*vide infra*). Compared to more traditionally explored cyclobutanol cleavage chemistry, we envisioned that the analogous α-hydroxy-β-lactams could similarly participate in strain induced C–C cleavage/functionalization pathways to decorate the periphery of the aza-cyclic ring systems.



Entry	Variations from Initial Conditions	Yields
1	none	65% (6%)*
2	DavePhos instead of RuPhos	48% (8%)*
3	SPhos instead of RuPhos	18% (10%)*
4	K_3PO_4 instead of Cs_2CO_3	37%
5	K_2CO_3 instead of Cs_2CO_3	16%
6	1,4-dioxane instead of toluene	0%
7	room temperature	7%
8	RuPhos-Pd-G4 (10 mol%), Cs_2CO_3 (2.0 equiv), rt	66%
9	RuPhos-Pd-G4 (10 mol%), Cs_2CO_3 (2.0 equiv), 40 °C	81%

Figure 2.2. Reaction design and development. (A) Norrish-Yang protocol. Yield was determined by ^1H NMR integration using Ph_3CH as the internal standard. Isolated yield is shown in parentheses. (B) Proposed catalytic cycle. (C) Optimization of C–C cleavage, α-arylation reaction. *Yield of **2.4** shown in parentheses when applicable.

Optimization of the C–C cleavage/cross-coupling

With bicyclic hydroxylactam **2.2** in hand, we sought to identify conditions for its cross-coupling with bromobenzene on the basis of the precedent of Uemura.[25] We first set out to optimize the cross-coupling conditions for α-arylation. A four-step mechanism (see Fig. 2.2B) is envisioned for the cross-coupling process, consistent with the proposal by Uemura.[25] This mechanistic scenario includes: (*1*) oxidative addition of Pd(0) to the aryl halide, (*2*) coordination/deprotonation of the tertiary hydroxy group, (*3*) β-C–C cleavage to liberate an α-palladated piperidine, and (*4*) reductive elimination of the Pd(II) species to regenerate the active Pd(0) catalyst and furnish the desired α-arylated product. Although strained ring systems such as tert-cyclobutanols have been employed previously in cross-coupling reactions,[26–28] there are no known examples using α-hydroxy-β-lactams, which introduce additional challenges such as control of their regioselective opening and the presence of other possible coordination sites.

After extensive optimization, we were successful in obtaining productive, regioselective, C–C cleavage/arylation at 40 °C (Fig. 2.2C). Importantly, the RuPhos ligand appeared to be uniquely effective in favoring the desired regioselective lactam ring opening toward (or "proximal") the ring over the alternative, competing "distal" opening away from the ring and toward the carbonyl group of the β-lactam unit (see Fig. 2.2C **2.4**). The use of related Buchwald biaryl phosphine ligands led to diminished yields and selectivities. For example, the use of DavePhos or SPhos as supporting ligands produced the desired α-arylated piperidine in 48 and 18% NMR yields, respectively (entries 2–3). Cs_2CO_3 was identified as the optimal base, while other bases led to lower yields (entries 4–5). The choice of the solvent was critical, as only trace amounts of the desired α-arylated piperidine were obtained when 1,4-dioxane was used in place of toluene (entry 6). When the reaction was carried out at room temperature, only a 7% percent NMR yield of the target compound was observed with the rest of the material accounted for by the recovered starting material (entry 7). Contemporaneous with this effort, we leveraged a parallel data-rich experimentation approach to optimize this cross-coupling, which primarily relied on exploiting the aforementioned ligand effects. We recognized that faster initiation to a Pd(0) complex and a well-defined ligand-to-metal ratio may be beneficial to improving selectivity.[29,30] Indeed, by employing the commercially available KitAlysis technology[31] that features the latest G3/G4 palladium precatalysts of Buchwald's biaryl phosphine ligands, we quickly validated the unique effectiveness of RuPhos as a supporting ligand. The yields realized in this HTE screen were comparable to those obtained in the batch experiments (see the Supporting Information for details). However, by conducting the cross-coupling at room temperature using RuPhos-Pd-G4, we obtained a yield of 66% (Fig. 2.2C entry 8) for the desired adduct, a significant improvement over the previous yield of 7%. Raising the temperature to 40 °C, optimal conditions (entry 9) that were suitable across a wide range of substrates were identified.

Substrate Scope

With the optimized conditions in hand and using **2.2** as a synthetic equivalent of an α-metalated piperidine, the scope of aryl halides in the cross-coupling was explored. Iodobenzene emerged as a superior coupling partner (69% isolated yield), outperforming bromobenzene under the established conditions to yield an α-phenyl piperidine product. While early attempts using phenyl triflate as a cross-coupling partner employing $Pd_2(dba)_3 \cdot CHCl_3$ and RuPhos as ligands led to

complex mixtures, with RuPhos-Pd-G4, **3a** was obtained in 77% yield. Under modified conditions, aryl chlorides could also be used as electrophilic partners, albeit requiring a modification to XPhos as the optimal ligand and elevated temperatures. For instance, using chlorobenzene, α-phenyl piperidine **2.3a** was obtained in 33% yield, along with **2.4** in 32% yield. Despite the diminished yields, aryl chlorides continue to be attractive cross-coupling partners because of their lower

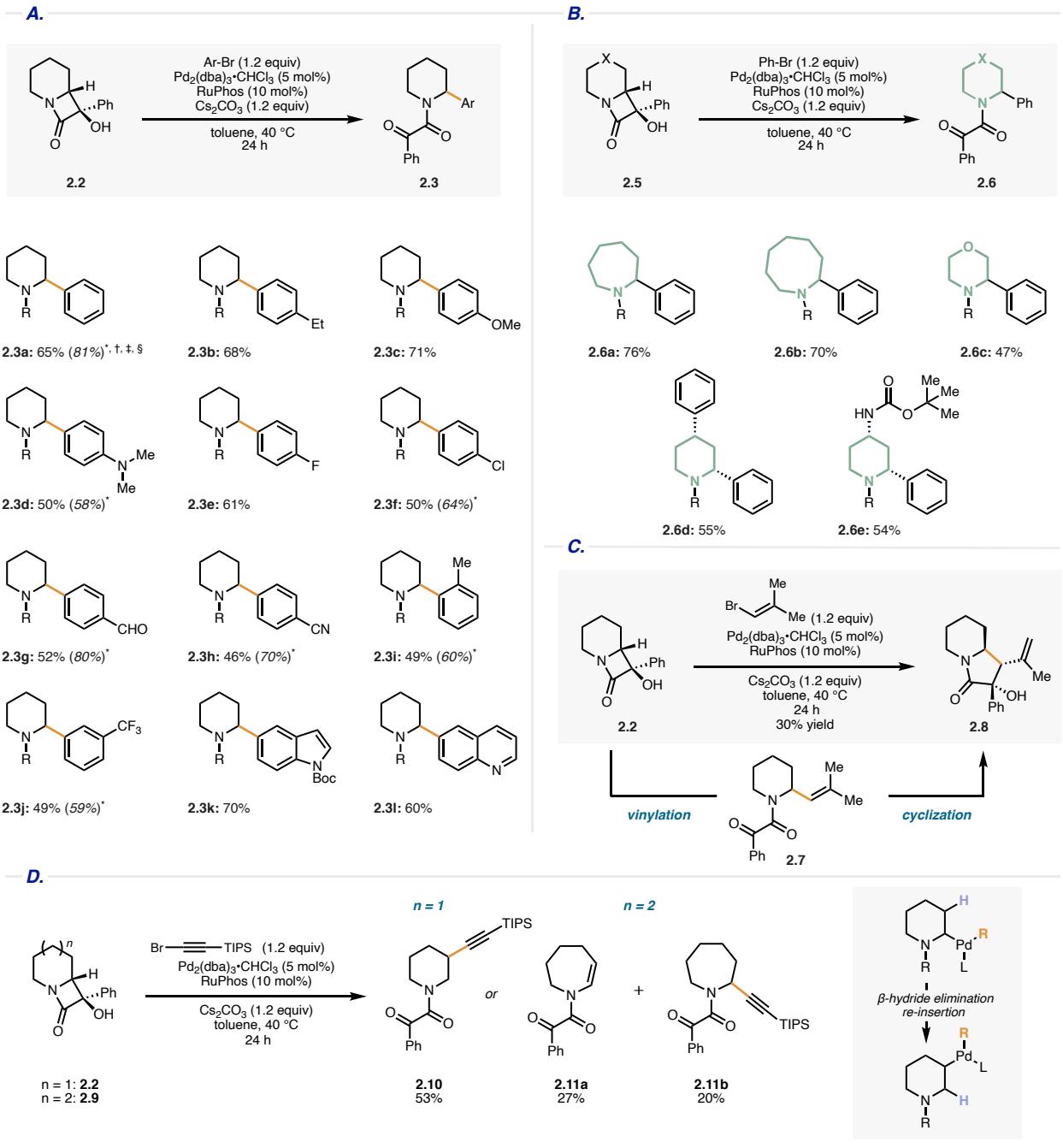


Figure 2.3. Scope of the C–C cleavage/coupling reaction. (A) Scope of aryl halides in the arylation reaction. All yields reported are isolated yields, unless otherwise stated. (B) Scope of aza-cyclic lactams in arylation reaction. (C) Development of α-vinylation. (D) Development of α/β-alkynylation. Reactions were performed with lactam (0.10

mmol), Ar–Br (0.12 mmol), $Pd_2(dba)_3 \cdot CHCl_3$ (5 mol%), RuPhos (10 mol%), Cs_2CO3 (0.12 mmol), and toluene (0.2 M) at 40 °C for 24–48 h. For the vinylation, reactions were performed with 1-bromo-2-methyl-prop-1-ene (0.12 mmol) instead of Ar–Br. For alkynylation, (bromoethynyl)triisopropylsilane (0.12 mmol) was used as the coupling partner. *Reactions were performed with **2.2** (0.10 mmol), Ar–Br (0.12 mmol), RuPhos-Pd-G4 (10 mol %), Cs2CO3 (0.20 mmol), and toluene (0.2 M) at 40 °C for 24–48 h. †Ph–I (0.12 mmol) was used instead of Ph–Br. ‡Ph–Cl (0.12 mmol), Pd2(dba)3·CHCl3 (5 mol %), XPhos (10 mol %), Cs2CO3 (0.12 mmol), and toluene (0.2 M) at 100 °C for 24 h. § Ph–OTf (0.12 mmol) was used instead of Ph–Br. See the Experimental Procedures for detailed conditions of each substrate.

cost and abundance.[32] The α-arylation approach we have developed tolerates varying electronic influences on the aromatic halide. For example, electron-rich aryl halides perform well, providing the desired arylated products in good yield (**2.3a–d**). Ethers and tertiary amine functional groups likewise do not adversely affect the yield of the cross-coupling (see **2.3c** and **2.3d**).

Electron-deficient coupling partners bearing substituents such as fluorine and chlorine efficiently couple as well (see **2.3e** and **2.3f**). Using the optimized conditions, site-selective coupling (aryl bromide vs aryl chloride) can be achieved on multiply-halogenated substrates (see **2.3f**), and the intact C(sp2)–Cl bond in the resulting adduct can be employed as a functional handle for further functionalization.[32] Functional groups such as aldehydes and nitriles were also well accommodated using this method (see **2.3g**, **2.3h**). Importantly, substituents at the ortho position of the aryl halide did not adversely hinder the reaction, and **2.3i** was obtained in 49% yield under our established cross-coupling conditions. An aryl bromide bearing a trifluoromethyl group at the meta position also led to the desired α-arylated product (**2.3j**) in modest yields. Heteroaromatics were also viable cross-coupling electrophiles, leading, for example, to indole **2.3k** and quinoline **2.3l** in 70 and 60% yields, respectively. As indicated above, improved yields were obtained using the precatalyst instead of the mix of $Pd_2(dba)_3 \cdot CHCl_3$ with RuPhos (see Fig. 2.2C, entry 8 for conditions).

In Fig. 2.3A, products **2.3a**, **2.3d**, **2.3f**, **2.3g**, **2.3h**, **2.3i**, and **2.3j** were isolated in higher yields under these conditions (see values in parenthesis). Next, several other saturated heterocycles were examined in our programmed lactamization/arylation protocol (Fig. 2.3B). Pharmaceutically and agrochemically privileged scaffolds, such as morpholine, can be effectively functionalized through the aforementioned photochemical cyclization and importantly undergo C–C cleavage/cross-coupling to arrive at α-functionalized derivatives. For example, **2.6c** was obtained in 47% yield. Saturated heterocycles of varying ring sizes were also competent substrates. For example, azepane **2.6a** and azocane **2.6b** underwent α-arylation in 76 and 70% yields, respectively. Functional groups on the aza-cycle backbone, such as aryl (**2.6d**) and carbamates (**2.6e**), were also tolerated. The *cis* relationship between the phenyl and para substituent in the abovementioned examples is supported by 2D NMR (see the Supporting Information for details). The observed stereochemistry is dependent on the stereochemistry of the starting lactam, which participates in a stereospecific cross-coupling (*vide infra*). 3-substituted piperidines result in mixtures, and we are currently exploring conditions that may achieve selective lactamizations.

Given the complementarity of our approach to existing methods that arrive at α-metalated piperidines, we speculated that bicyclic hydroxylactam **2.2** could also be used to achieve additional α-functionalizations that are not readily realized using the previously established methodologies (Fig. 2.3C and 2.3D).[7–18] Vinylation was readily achieved by employing the optimized conditions for arylation. For example, cross-coupling of α-hydroxy-β-lactam **2.2** with 1-bromo-2-methylprop-1-ene under the cross-coupling conditions led to vinylated intermediate **2.7** which

underwent spontaneous cyclization to provide indolizidinone **2.8** in 30% yield. Next, we turned our attention to alkynylation. Surprisingly, when (bromoethynyl)triisopropylsilane was used as a coupling partner, **2.10** was obtained in 53% yield providing an avenue to β-alkynylation. Alkyne **2.10** presumably arises from β-hydride elimination of an α-palladated intermediate followed by re-insertion to generate the β-functionalized product (see Fig. 2.3D).[9,10] This example constitutes the first β-alkynylation of cyclic amines. Extension of the method to larger ring systems such as azepane (**2.9**) provided the desired α-alkynylated coupling product (**2.11b**) along with enamide **2.11a**, which supports the presumed β-hydride elimination of the initially generated alkyl palladium intermediate (Fig. 2.3D, *right*).[33,34] It is worth noting that the conditions for the alkynylation and vinylation cross-couplings have not been optimized. Furthermore, the C–C cleavage/cross-coupling is substrate-controlled as evidenced by the difference in the reaction outcome in switching from aryl halide to alkynyl halide coupling partners. This example contrasts with the work of Baudoin and co-workers on piperidine derivatives,[10] where selectivity is achieved by means of the ligand control. Further studies are ongoing to understand the factors that lead to β-functionalization and to developing a general ligand-controlled method. Thus, α-hydroxy-β-lactam **2.2** may be applied broadly with various cross-coupling partners.

The functionalization protocol reported here bears several key distinctions from the existing state-of-the-art approaches. First, we have demonstrated that mild conditions can be utilized to achieve the cross-coupling of aryl halides. This includes the coupling of **2.2** to aryl bromide **2.12** in 53% yield (Fig. 2.4A), which contains a sensitive trifluoromethyldiazirine that is unstable to other conditions for α-functionalization such as photoredox conditions. By separating the photomediated functionalization from the cross-coupling, we have now overcome the challenge of cross-coupling photochemically sensitive groups such as the trifluoromethyldiazirine functional group which has been used in photoaffinity-triggered protein labeling.[35] Second, estrogen derivative **2.14** was readily functionalized with α-hydroxy-β-lactam **2.2** using the optimized precatalyst conditions, showcasing the potential for LSF of complex molecules (Fig 2.4B). Additionally, given the recent advances in leveraging Pd(II) oxidative addition complexes in cross-coupling reactions,[36] we demonstrated successful coupling between **2.2** and a stoichiometric coupling partner (*not shown,* see Supporting Information for more details). When enantioenriched lactam (+)-**2.2** was subjected to the optimized cross-coupling conditions (Fig. 2.4C, *top*), α-arylated piperidine **2.3a** was obtained with no appreciable erosion of enantiomeric excess, pointing to high fidelity in the stereospecific cross-coupling. Importantly, because our α-hydroxy-β-lactams are isolable and stable until deployed, this sequence of reactions allows us to broadly diversify aza-cycles with control of stereochemistry, thus achieving a "chiral, enantioenriched, organometallic equivalent" of α-metalated aza-cycles. On the basis of the absolute configuration of both hydroxylactam **2.2** and product **2.3a**, the overall coupling proceeds in a stereoretentive manner. This suggests that our reaction involves an intermediate step in which the C–C scission occurs with attendant stereoretentive palladation (see Fig. 2.2B). Finally, the desired arylated product can be obtained in a one-pot process from ketoamide **2.1** by performing the Norrish–Yang reaction followed by palladium-catalyzed cross-coupling without isolating β-lactam **2.2** (Fig. 2.4C, *bottom*). Future studies will seek to optimize the one-step protocol. It is worth noting that the keto amide group can be easily removed by treatment with NaOH (4 equiv) in THF/MeOH and no chromatographic purification step is required (see the Supporting Information for details).

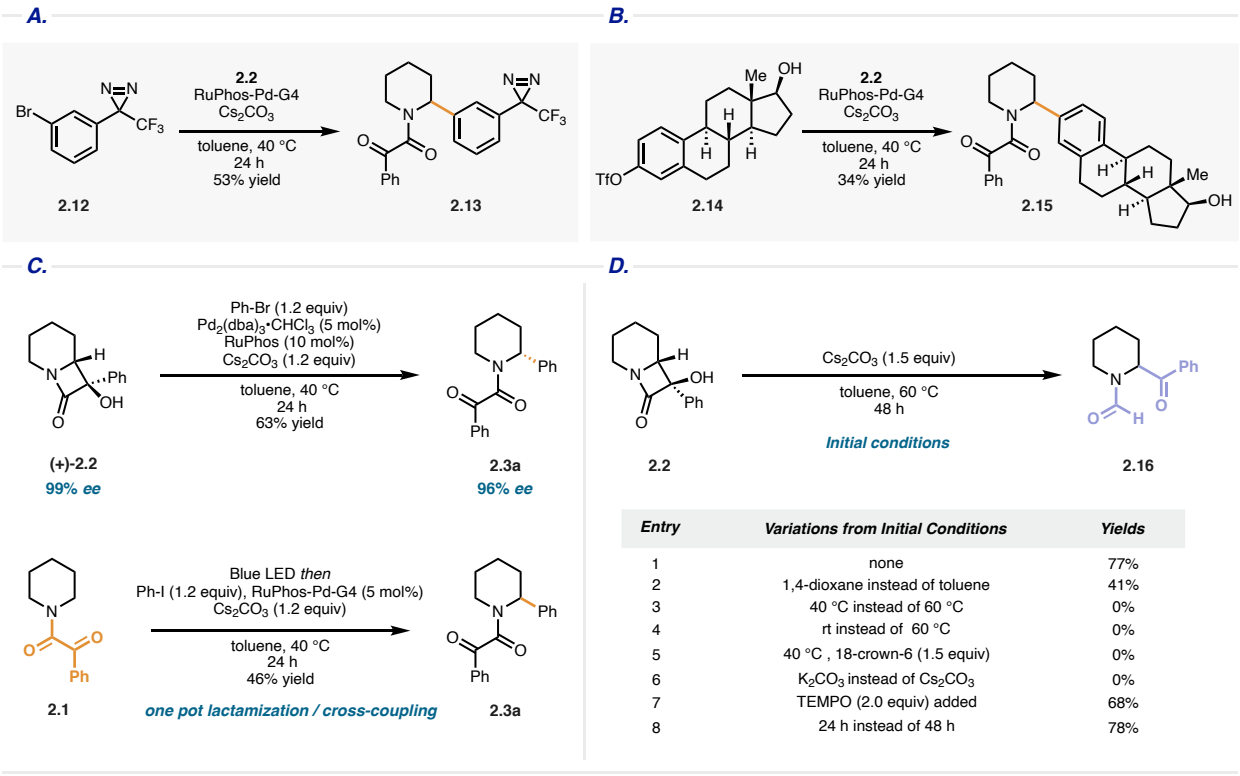


Figure 2.4. Extended scope and additional experimentation. (A) Mild coupling conditions tolerate a trifluoromethyldiazirine functional group. (B) Late-stage functionalization application. (C) Cross-coupling with the enantioenriched material supports a highly stereoretentive process (*top*), and one-pot arylation (*bottom*). (D) Discovery and optimization of a base-promoted rearrangement.

During the optimization process for the cross-coupling reported here, a rearranged product (**2.16**) resulting from cleavage of the distal bond of the β-lactam was isolated (see Fig. 2.4C). Control experiments showed that this process occurs in the presence of Cs_2CO_3 without the need for a transition metal complex (Fig. 2.4C, entry 1). Evaluation of a range of solvents led to the identification of toluene as a superior solvent for obtaining the highest yields (Fig. 2.4C, entry 2). The formation of **2.16** from **2.2** did not proceed at lower temperatures even in the presence of 18-crown-6 (Fig. 2.4C, entries 3–5). Notably, K_2CO_3 did not promote the desired rearrangement, pointing to the importance of the cesium counter cation. Radical scavengers did not shut down the reaction as evidenced by the 68% yield obtained when TEMPO was added to the reaction mixture (Fig. 2.4C, entry 7). Following our initial optimization screen, we discovered that comparable yields of **2.16** can be obtained over a shorter reaction time of 24 h (Fig. 2.4C, entry 8).

Computational Studies and Details

Rationalization of C–C Cleavage/Cross Coupling

In order to shed light on the mechanism of the regioselective ring opening of α-hydroxy-β-lactam **2.2**, we have undertaken an extensive computational study to validate the proposed four-step Pd-catalyzed arylation of **2.2** with RuPhos as a ligand (Fig. 2.5A).The calculations presented here were carried out using the Gaussian 09 suite of programs.[37] The geometries of all reported

reactants, intermediates, transition states (TSs), and products were optimized without symmetry constraints at the B3LYP level of density functional theory (DFT)[38,39] in conjunction with a Lanl2dz basis set and corresponding Hay–Wadt effective core potential (ECP) for Cs and Pd atoms.[40,41] Standard 6-31G(d,p) basis sets were used for all the remaining atoms. Dispersion corrections were included into the calculation at the Grimme's empirical dispersion correction with Becke–Johnson damping for B3LYP.[42] This approach is labeled as [B3LYP-D3BJ]/{Lanl2dz+[6-31G(d,p)]}. Bulk solvent effects are incorporated into calculations at the polarizable continuum model using the integral equation formalism (IEF-PCM) level[43,44] by selecting toluene as the solvent. The nature of each stationary point was characterized by the presence of zero or one imaginary frequency for minima and TS, respectively. The IRC calculations were performed to confirm the nature of each TS. The relative Gibbs free energies (ΔG) and enthalpies (ΔH) are presented as ΔG/ΔH (in kcal/mol) and calculated under standard conditions (1 atm and 298.15 K), although only the ΔG values are discussed.

We have found two lowest energy isomers, (κ2-O,O, **I1**) and (κ2-O,H, **I2**), for the proposed Pd-alcoholate. In the κ2-O,O isomer (**I1**), the β-lactam moiety is coordinated to the Pd(II) center via the carbonyl and hydroxy oxygens, whereas in the κ2-O,H isomer (i.e., **I2**), the β-lactam unit and Pd(II) center interact via the hydroxy oxygen and the hydrogen of the Cα–H bond. As one may expect from these coordination motifs, isomer **I1** is 8.0 kcal/mol more favorable as compared to isomer **I2** (see the Supporting Information for more details), which ultimately leads to the α-arylation product. Alcoholates **I1** and **I2** can interconvert through a small energy barrier; therefore, here, we calculate the regioselectivity controlling energy barriers (see **TS1** and **TS2**) relative to the energetically lowest κ2-O,O isomer (i.e., **I1**). As shown in Fig. 2.5A, in **TS1** and **TS2**, the "proximal" and "distal" β-C–C bonds are elongated to 2.01 and 1.98 Å respectively, and the C–O bond is shortened to 1.31 Å in both cases (among other geometry changes). Calculations show that the free energy barrier associated with **TS1**, leading to the α-arylated product, is 0.9 kcal/mol lower than that associated with **TS2**, which is traversed en route to the carbonyl arylation product (i.e., **2.4**). The calculated free energy difference in the regioselective cross-coupling (i.e., 0.9 kcal/mol) is in good agreement with the experimentally observed distribution of these products (9.8:1 of **2.3a**/**2.4**; ratio determined by ^{1}H NMR integration using Ph_3CH as the internal standard).

Our analysis also reveals that the computed relative lower energy of **TS1** over **TS2** could result from both (*a*) the weaker C^{α}–C^{2} bond as compared to C^{1}–C^{2} (estimated to be 27.7 and 38.0 kcal/mol, respectively; see the Supporting Information for more details) for the Pd-alcoholate intermediates and (*b*) a smaller energy requirement for the requisite geometrical deformations in **TS1** as compared to **TS2**. Distortion–interaction[45] calculations have identified the repulsions between the Pd-bound phenyl and isopropyl groups of the RuPhos ligand as major factors that contribute to the geometry distortion of the catalyst in the calculated TSs (see Supporting Information for details).

Rationalization of Base-Promoted Transition Metal-free Rearrangement

Given that the Cs_2CO_3-promoted rearrangement was observed as a competing background reaction to the cross-coupling, we also sought to elucidate the mechanism of this transformation. First, we calculated the distal (C1–C2) and proximal (Cα–C2) bond dissociation free energies (BDFEs) for **2.2**, which were 45.6 and 39.7 kcal/mol, respectively. For our computational studies, we assume

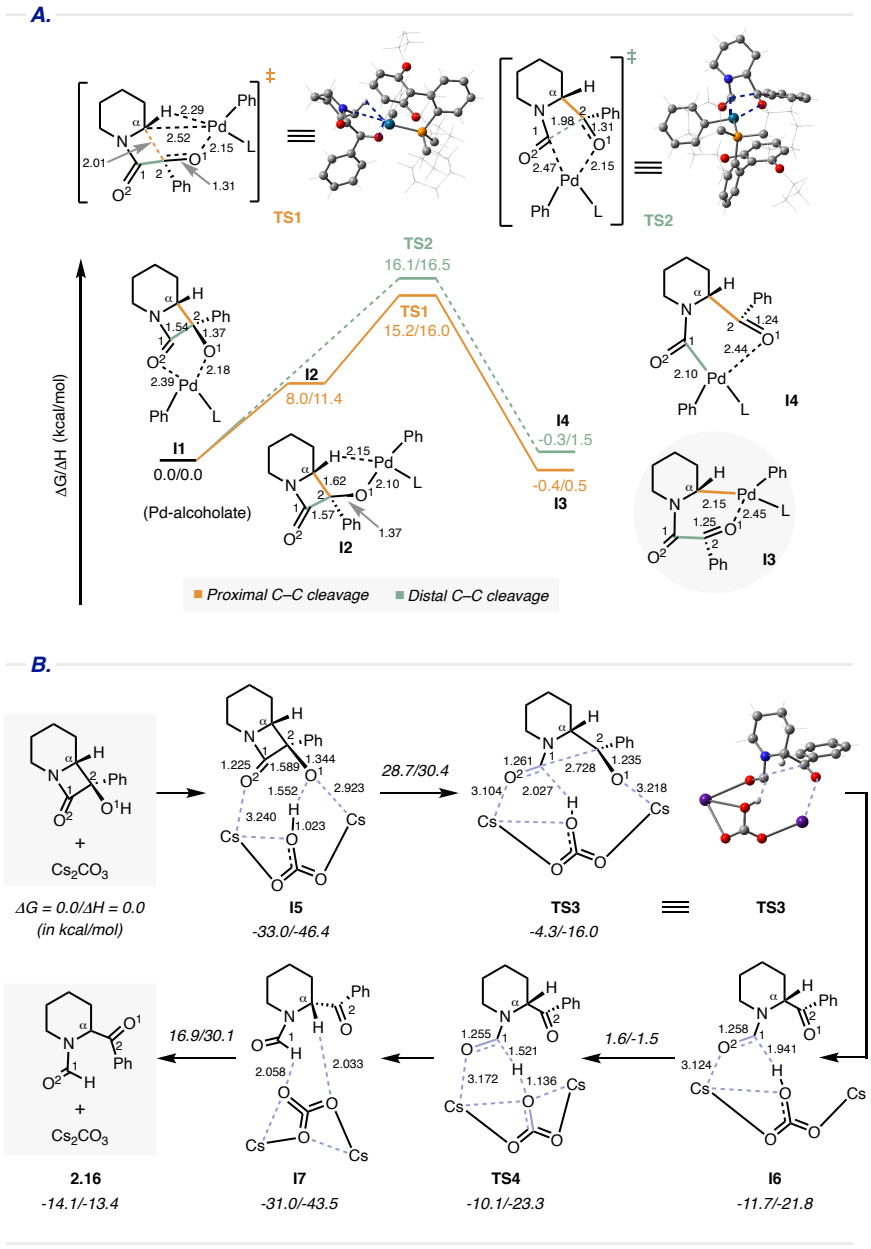


Figure 2.5. Computational Studies. (A) Rationalization of C–C cleavage/cross coupling selectivity. Schematic representation of the free energy surfaces (energies are in kcal/mol), calculated Pd-alcoholate intermediates, regioselectivity-determining TSs, and products of the "proximal" β-C$^{\alpha}$–C^{2} and "distal" β-C^{1}–C^{2} bond cleavage step of α-hydroxy-β-lactam **2.2**. (B) Rationalization of base-promoted transition metal-free rearrangement. Schematic representation of the calculated reactant, intermediates, TSs, and product for the "distal" C^{1}–C^{2} bond cleavage of α-hydroxy-β-lactam **2.2** in the presence of Cs_2CO_3. Bond distances are in Å.

(*a*) that Cs_2CO_3, rather than derivatives such as $CsHCO_3$ or CsOH (or the corresponding dimeric forms) that may formed in situ, mediates this reaction and (*b*) a 1:1 (Cs_2CO_3:**2.2**) binding stoichiometry (see the Supporting Information for full details). In addition, our empirical observation of a dramatic reduction in reaction yield (from 77 to 41% yield) upon changing the

solvent from toluene to dioxane (a more strongly coordinating solvent) indicates the importance of Cs coordination to the substrate. Through our computations, we have identified intermediate **I5** as a prereaction complex (see Fig. 2.5B), where one of the Cs cations coordinates to the oxygen of the α-hydroxy group of β-lactam 2 (labeled O1) and facilitates simultaneous deprotonation of the hydroxy group by CO_3^{2-}.

The calculations reveal that a second Cs cation coordinates (relatively weakly) to the carbonyl oxygen (labeled O2) of the β-lactam. This latter interaction likely contributes to the observed regioselectivity of the reaction. The calculated free energy of this emerging deprotonation (i.e., lactam + Cs_2CO_3 → **I5**) is 33.0 kcal/mol (see Fig. 2.5B). We also observe computationally that the deprotonation of **2.2** by Cs_2CO_3 significantly reduces (by 14–16 kcal/mol) the calculated C–C BDFEs. Specifically, for **I5**, the calculated distal (C1–C2) and proximal (Cα–C2) C–C BDFEs are 31.1 and 23.7 kcal/mol, respectively. The ensuing steps that emerged from intermediate **I5** are a proton transfer from the bicarbonate to C1 (see **TS3**) and accompanying C1–C2 bond weakening. Calculations show that the rotation of the OH bond of the bridging bicarbonate, cleavage of the O1···HO (bicarbonate) hydrogen bond, and formation of the C1···H bond initiate the cleavage of the C1–C2 bond in **TS3**. The calculated free energy barrier for TS3 is 28.7 kcal/mol. The close examination of **TS3** shows that it is a late TS, which is consistent with the high (21.3 kcal/mol) endothermicity computed for this reaction. The IRC calculations lead from **TS3** directly to intermediate **I6**. A subsequent proton transfer from bicarbonate to the C1 center (see **TS4**) is calculated to proceed with only a 1.6 kcal/mol free energy barrier. The overall rearrangement process, which leads to intermediate **I7**, is highly exergonic (by 19.3 kcal/mol). Product release from **I7** requires only 16.9 kcal/mol free energy, which is smaller than the 26.7 kcal/mol free energy required for the reverse reaction. Notably, during the overall transformation, one of the two Cs cations stays coordinated to O2 through **TS4**, pointing to the critical role of Cs_2CO_3. Its strong coordination to the lactam hydroxy and carbonyl groups significantly reduces the C–C BDFEs, provides a strong base (i.e., carbonate) that facilitates proton transfer from the hydroxy group to C1, and leads to facile distal C1–C2 bond cleavage.

To validate the IEF-PCM approach that we employed, we have calculated structures and relative energies of the $Cs_2CO_3[X]_2$ and [lactam]$Cs_2CO_3[X]_2$ (i.e., **I5**$(X)_2$, see Fig. 2.5B) complexes, where X is explicit solvent molecules such as toluene and 1,4-dioxane used in our experiments. We found that solvent molecules only weakly (∼3–4 kcal/mol free energies) coordinate to Cs centers. Therefore, we conclude that the inclusion of explicit solvent molecules into our calculations do not significantly impact the results obtained at the [B3LYP-D3BJ]/{Lanl2dz+[6-31G(d,p)]} with the (IEF-PCM) level of theory.[46] Cartesian coordinates and total energies of all reported structures are given in the Supporting Information.

2.3 Conclusion

In summary, we report a robust and broadly applicable strategy that achieves the functionalization of piperidines and related saturated nitrogen heterocycles through visible light-mediated lactamization followed by C–C cleavage/cross-coupling protocol. Using an HTE approach, we identified RuPhos as a uniquely effective ligand for α-arylation and also applied these conditions to achieve alkynylation and vinylation. Moreover, we have identified opportunities for β-arylation of the saturated azacycles, which can presumably arise through β-hydride elimination/re-insertion

of an α-palladated intermediate. During the course of these studies, a transition metal-free α-acylation was also discovered, demonstrating the unique reactivity of α-hydroxy-β-lactams. Our preliminary studies have identified bases that affect the base-promoted rearrangement (Fig. 2.4D) and uncovered the role of electronics of the aryl ring of the β-lactam on these processes. On the basis of the proposed mechanistic insights, a more extensive range of ligands will be explored to optimize the distal cleavage/cross-coupling and to identify a general method for β-functionalization. An account of subsequent mechanistic investigations will be reported in due course.

2.4 Experimental Procedures

2.4.1. General Consideration

2.4.1.1. Solvents and Reagents

Unless noted below, commercial reagents were purchased from Sigma Aldrich, Acros Organics, Chem-Impex, Combi-blocks, TCI, and/or Alfa Aesar, and used without additional purification. Solvents were purchased from Fisher Scientific, Acros Organics, Alfa Aesar, and Sigma Aldrich. Tetrahydrofuran (THF), and triethylamine (Et_3N) were sparged with argon and dried by passing through alumina columns using argon in a Glass Contour solvent purification system. Dichloromethane (CH_2Cl_2) was freshly distilled over calcium hydride under a N2 atmosphere prior to each use. Toluene (PhMe) was distilled over calcium hydride under a N_2 atmosphere, degassed via freeze-pump-thaw (3 cycles), and stored over 4 Å molecular sieves in a Schlenk flask under N_2. 1,4-Dioxane was purchased in AcroSeal bottling (99.5%, anhydrous, stabilized, over 4 Å molecular sieves) and additionally sparged with N_2 prior to use.

2.4.1.2. Experimental Procedures

Unless otherwise noted in the experimental procedures, reactions were carried out in flame or oven-dried glassware under a positive pressure of N_2 in anhydrous solvents using standard Schlenk techniques. Reaction temperatures above room temperature (22–23 °C) were controlled by an IKA® temperature modulator and monitored using liquid-in-glass thermometers. Reaction progress was monitored using a combination of LC/MS analysis (using a Shimadzu LCMS-2020 (UFLC) equipped with the LC-20AD solvent delivery system, a SPD-20AV prominence UV/Vis detector (SPD-M20A Photo Diode Array), and a Thermo Scientific Hypersil GOLD HPLC column (5 μm particle size, 4.6 × 50 mm)), and thin-layer chromatography (TLC) on SiliCycle Siliaplates (glass backed, extra hard layer, 60 Å, 250 μm thickness, F254 indicator). Flash column chromatography was performed with either glass columns using Silicycle silica gel (40–63 μm particle size) or with a Yamazen Smart Flash EPCLC W-Prep 2XY (dual channel) automated flash chromatography system on prefilled, premium, universal columns using ACS grade solvents. Preparative thin layer chromatography was performed on SiliCycle Siliaplates (glass backed, extra hard layer, 60 Å, 250 μm thickness, F254 indicator).

2.4.1.3. Analytical Instrumentation

^1H NMR and ^{13}C NMR data were recorded on Bruker AVQ-400, AVB-400, RDX-500, AV-600 and AV-700 spectrometers using $CDCl_3$ and DMSO-d_6 as solvents, typically at 20–23 °C. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ 7.26 for ^1H NMR, δ 77.16 for ^{13}C NMR in $CDCl_3$ and δ 2.50 for ^1H NMR, δ 39.52 for ^{13}C NMR in DMSO-d_6). The ^{19}F NMR spectra were acquired on an AVQ-400 spectrometer and internally referenced to $CFCl_3$ (δ 0.00). Data for ^1H and ^{13}C spectroscopy are reported as follows; chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, hept = heptet, m = multiplet, br = broad), coupling constant (Hz), integration. Melting points were determined using a MEL-TEMP™ apparatus and are uncorrected. Optical rotations were measured on a Perkin-

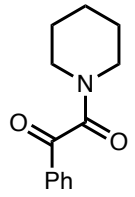
Elmer 241 polarimeter. High-resolution mass spectra (HRMS) were obtained from the Catalysis Facility of the Lawrence Berkeley National Laboratory (supported by the Director, Office of Science, of the US Department of Energy under contract no. DE-AC02-05CH11231) using a PerkinElmer AxION 2 TOF-MS.

Abbreviations Used:

Aq. = aqueous, sat. = saturated, equiv = equivalents, brsm = based on recovered starting materials, Calc'd = calculated, h = hours, min = minutes, s = seconds, rt = room temperature.

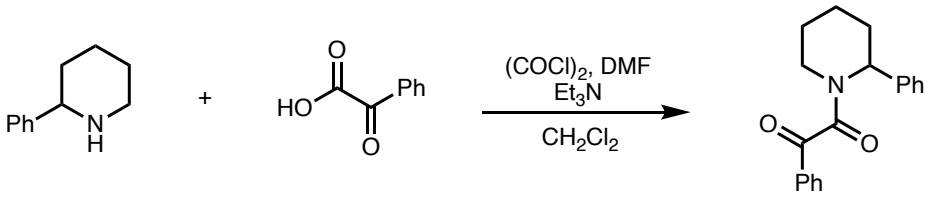
2.4.2. Experimental Procedures for Preparation of Starting Materials

Preparation of α-Ketoamides



2.1

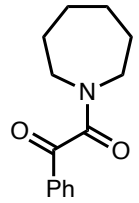
1-Phenyl-2-(piperidin-1-yl)ethane-1,2-dione (2.1) was prepared according to the published procedure. Spectral data were in full agreement with the reported literature values.[47]



2.3a

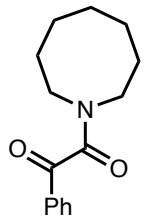
(±)-1-Phenyl-2-(2-phenylpiperidin-1-yl)ethane-1,2-dione (2.3a): A 50 mL round-bottomed flask was charged with a solution of benzoylformic acid (600 mg, 4.00 mmol) in CH_2Cl_2 (20 mL) and cooled to 0 °C. To this solution was added oxalyl chloride (0.34 mL, 4.0 mmol) followed by the addition of one drop of DMF. The resulting solution was warmed to room temperature and stirred until gas evolution had ceased (1.5~2 h). The solution was cooled to 0 °C, and 2-phenylpiperidine (645 mg, 4.00 mmol) and Et_3N (1.7 mL, 12 mmol) were added successively and the resulting mixture was warmed to room temperature. After 21 h, 1 M HCl aq. (5.0 mL) was added and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (5.0 mL × 3). The combined organic layers were washed with brine (5.0 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography

(SiO_2, 25% EtOAc/hexanes) to provide the title compound as an off-white solid (868 mg, 74%, mixture of rotamers 1.0:0.65).
Melting Point: 94–96 °C;
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, *J* = 7.3 Hz, 2.0H), 8.03 (d, *J* = 7.3 Hz, 1.3H), 7.70 (t, *J* = 7.3 Hz, 1.0H), 7.66 (t, *J* = 7.3 Hz, 0.65H), 7.59 (t, *J* = 7.3 Hz, 2.0H), 7.54 (t, *J* = 7.3 Hz, 1.3H), 7.46–7.28 (m, 5.0+3.25H), 6.08 (brs, 1.0H), 4.90 (brs, 0.65H), 4.64 (d, *J* = 14.0 Hz, 0.65H), 3.43 (d, *J* = 14.0 Hz, 1.0H), 3.13 (dt, *J* = 14.0, 7.4 Hz, 1.0H), 2.82 (t, *J* = 11.8 Hz, 0.65H), 2.56 (d, *J* = 14.3 Hz, 1.0H), 2.43 (d, *J* = 14.3 Hz, 0.65H), 2.10–2.03 (m, 1.0H), 1.96–1.90 (m, 0.65H), 1.76–1.58 (m, 4.0+2.6H);
^{13}C NMR (126 MHz, $CDCl_3$): δ 191.9, 191.6, 166.73, 166.68, 138.0, 137.3, 134.9, 134.8, 133.4, 133.3, 129.8, 129.7, 129.2, 129.1, 129.04, 128.98, 127.4, 127.1, 126.82, 126.77, 56.3, 50.6, 43.1, 37.9, 28.5, 27.4, 26.2, 25.7, 19.76, 19.75;
HRMS (ESI): Calc'd for $C_{19}H_{20}NO_2$ $[M+H]^+$: 294.1489, found: 294.1479.



2.S1

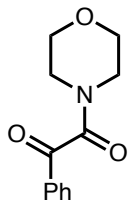
1-(Azepan-1-yl)-2-phenylethane-1,2-dione (2.S1) was prepared from azepane using a procedure analogous to that for the preparation of **2.3a**. Spectral data were in full agreement with the reported values.[48]



2.S2

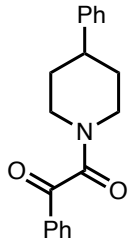
1-(Azocan-1-yl)-2-phenylethane-1,2-dione (2.S2) was prepared from azocane using a procedure analogous to that for the preparation of **2.3a**. The title compound was obtained as a white solid (1.74 g, 71%)
Melting Point: 61–62 °C;
^{1}H NMR (700 MHz, $CDCl_3$): δ 7.96 (d, *J* = 7.3 Hz, 2H), 7.63 (t, *J* = 7.3 Hz, 1H), 7.50 (t, *J* = 7.3 Hz, 2H), 3.63 (t, *J* = 6.1 Hz, 2H), 3.31 (t, *J* = 5.6 Hz, 2H), 1.91–1.86 (m, 2H), 1.68–1.58 (m, 8H);
^{13}C NMR (176 MHz, $CDCl_3$): δ 191.8, 167.4, 134.6, 133.6, 129.8, 129.1, 49.6, 46.2, 26.82, 26.77, 26.2, 25.6, 24.6;

HRMS (ESI): Calc'd for $C_{15}H_{19}NNaO_2$ $[M+Na]^+$: 268.1308, found: 268.1304.



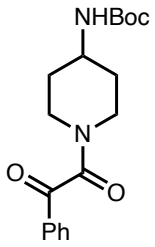
2.S3

1-Morpholino-2-phenylethane-1,2-dione (2.S3) was prepared from morpholine using a procedure analogous to that for the preparation of **2.3a**. The title compound was obtained as a white solid (1.53 g, 70%).
Melting Point: 58–60 °C;
^{1}H NMR (700 MHz, $CDCl_3$): δ 7.96 (d, J = 8.1 Hz, 2H), 7.66 (t, J = 8.1 Hz, 1H), 7.52 (t, J = 8.1 Hz, 2H), 3.82–3.76 (m, 4H), 3.67–3.63 (m, 2H), 3.40–3.36 (m, 2H);
^{13}C NMR (176 MHz, $CDCl_3$): δ 191.3, 165.6, 135.1, 133.2, 129.8, 129.2, 66.9, 66.8, 46.4, 41.8;
HRMS (ESI): Calc'd for $C_{12}H_{13}NNaO_3$ $[M+Na]^+$: 242.0788, found: 242.0788.



2.S4

1-Phenyl-2-(4-phenylpiperidin-1-yl)ethane-1,2-dione (2.S4) was prepared from 4-phenylpiperine using a procedure analogous to that for the preparation of **2.3a**. Spectral data were in full agreement with the reported values.[47]

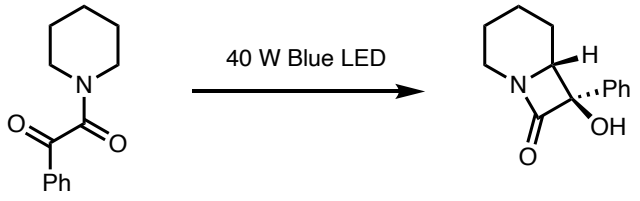


2.S5

***tert*-Butyl (1-(2-Oxo-2-phenylacetyl)piperidin-4-yl)carbamate (2.S5)** was prepared from *tert*-butyl piperidin-4-ylcarbamate using a procedure analogous to that for the preparation of **2.3a**. The title compound was obtained as a yellow solid (1.23 g, 74%).
Melting Point: 142–144 °C;
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.92 (d, *J* = 7.4 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 2H), 4.55 (br, 2H), 3.72 (br, 1H), 3.55 (d, *J* = 13.8 Hz, 1H), 3.12 (t, *J* = 12.5 Hz, 1H), 2.97 (t, *J* = 12.0 Hz, 1H), 2.07 (d, *J* = 12.5 Hz, 1H), 1.94 (d, *J* = 12.5 Hz, 1H), 1.48–1.42 (m, 1H), 1.42 (s, 9H), 1.40–1.33 (m, 1H);
^{13}C NMR (151 MHz, $CDCl_3$): δ 191.7, 165.5, 155.1, 134.9, 133.2, 129.7, 129.2, 45.0, 40.3, 32.8, 32.2, 28.5;
HRMS (ESI): Calc'd for $C_{18}H_{24}N_2NaO_4$ $[M+Na]^+$: 355.1628, found: 355.1627.

2.4.3. Experimental Procedures for Norrish-Yang Reaction of α-Ketoamides

Representative Procedure for Norrish-Yang Reaction of α-Ketoamides

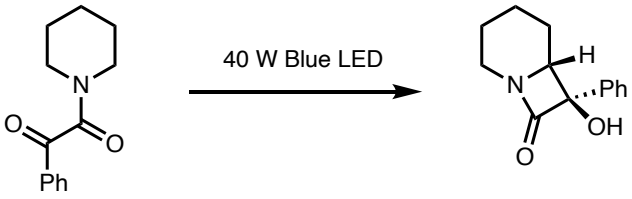


2.1 **2.2**

(±)-7-Hydroxy-7-phenyl-1-azabicyclo[4.2.0]octan-8-one (2.2): A 1-dram vial charged with **2.1** (21.7 mg, 0.100 mmol) was backfilled with nitrogen and irradiated using a 40 W blue LED placed 3 cm away from the vial. After 16 h, the vial was removed from the light and directly purified by preparative thin-layer chromatography (SiO_2, 50% EtOAc/ hexanes) to provide the title compound (14.3 mg, 66%) as a white solid.
Melting Point: 142–145 °C;
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.41–7.39 (m, 2H), 7.35–7.30 (m, 3H), 4.36 (br, 1H), 3.84 (dd, *J* = 13.0, 5.4 Hz, 1H), 3.62 (dd, *J* = 11.3, 4.5 Hz, 1H), 2.80 (dd, *J* = 11.3, 4.3 Hz, 1H), 1.74–1.71 (m,

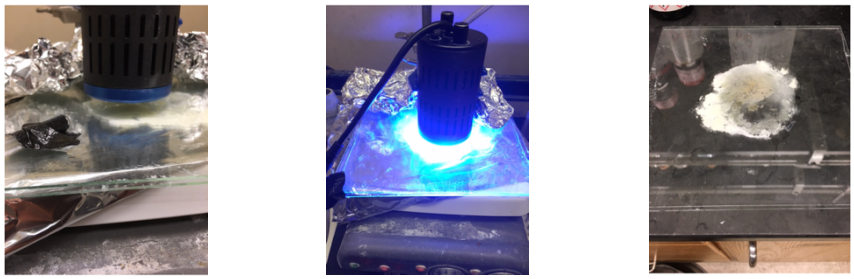
1H), 1.63–1.59 (m, 1H), 1.51–1.48 (m, 1H), 1.36 (qt, J = 13.4, 2.9 Hz, 1H), 1.24 (qdd, J = 13.1, 5.5, 3.3 Hz, 1H), 0.63 (qd, J = 13.1, 3.3 Hz, 1H);
^{13}C NMR (151 MHz, $CDCl_3$): δ 167.2, 137.0, 128.54, 128.52, 127.2, 90.0, 63.2, 38.9, 26.7, 24.5, 21.9;
HRMS (ESI): Calc'd for $C_{13}H_{16}NO_2$ $[M+H]^+$: 218.1176, found: 218.1172.

Gram scale Procedure for Norrish-Yang Reaction of 1-phenyl-2-(piperidin-1-yl)ethane-1,2-dione (2.1)

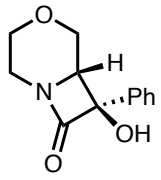


2.1 **2.2**

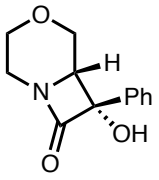
7-Hydroxy-7-phenyl-1-azabicyclo[4.2.0]octan-8-one (2.2): Finely ground **2.1** (1.00 g, 4.60 mmol) was spread onto a glass plate (20 x 20 cm, 250 µm thickness) in a circular manner with the circle having a diameter of approximately 3 inches. Then a second glass plate was pressed on top of the substrate to create a thin layer of substrate in between both glass plates. The two glass plates holding the solid substrate were held together by duct tape. Subsequently the glass plate was placed 1 inch away from a 40W blue LED with a constant airstream to cool down the surface of the glass plates (Pictures 1 and 2). After 7 h the crude reaction mixture (Picture 3) consisting of a pale-yellow oil was scraped with a razorblade and transferred into a flask. Residual reaction mixture was washed into a flask using CH_2Cl_2. Upon concentration under reduced pressure the crude residue was purified by column chromatography (SiO_2, 50% EtOAc/ hexanes) to provide the title compound (448 mg, 45%) as a white solid. The spectroscopic data were in agreement with those reported above.



From left to right: (1) Cooling of the glass surface by constant airflow; (2) Reaction setup; (3) Crude reaction mixture.



2.S6a
Minor

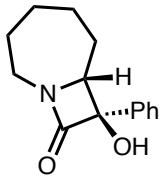


2.S6b
Major

(±)-7-Hydroxy-7-phenyl-4-oxa-1-azabicyclo[4.2.0]octan-8-one (2.S6) was prepared from **2.S3** (0.30 mmol) using a procedure analogous to that for the preparation of **2.2**. Preparative thin-layer chromatography (SiO_2, 50% EtOAc/ hexanes) provided **2.S6a** (7.92 mg, 12%) as a colorless foam and **2.S6b** (22.1 mg, 34%) as a colorless foam.

2.S6a
^{1}H NMR (600 MHz, DMSO-d_6): δ 7.42–7.34 (m, 5H), 6.86 (s, 1H), 3.79 (dd, J = 11.3, 4.7 Hz, 1H), 3.73 (dd, J = 11.3, 4.6 Hz, 1H), 3.69 (dd, J = 10.7, 4.8 Hz, 1H), 3.64 (dd, J = 13.0, 3.5 Hz, 1H), 3.16 (td, J = 11.5, 3.6 Hz, 1H), 3.07 (ddd, J = 13.1, 11.6, 4.7 Hz, 1H), 2.56 (t, J = 11.0 Hz, 1H);
^{13}C NMR (151 MHz, DMSO-d_6): δ 167.3, 137.4, 128.73, 128.70, 127.4, 89.7, 68.8, 65.8, 59.8, 38.8;
HRMS (ESI): Calc'd for $C_{12}H_{13}NNaO_3$ $[M+Na]^+$: 242.0788, found: 242.0786.

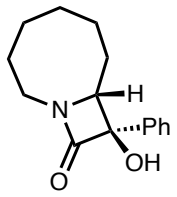
2.S6b
^{1}H NMR (600 MHz, DMSO-d_6): δ 7.48 (d, J = 7.3 Hz, 2H), 7.40 (t, J = 7.5 Hz, 2H), 7.37–7.29 (m, 1H), 6.83 (s, 1H), 4.08 (dd, J = 11.0, 4.6 Hz, 1H), 3.80 (dd, J = 11.3, 4.7 Hz, 1H), 3.72 (t, J = 10.7 Hz, 1H), 3.66 (dd, J = 10.3, 4.6 Hz, 1H), 3.62 (dd, J = 13.4, 3.6 Hz, 1H), 3.40–3.33 (m, 1H), 3.05 (ddd, J = 13.3, 11.7, 4.7 Hz, 1H);
^{13}C NMR (151 MHz, DMSO-d_6): δ 169.1, 140.1, 128.8, 128.4, 125.8, 87.8, 67.4, 65.9, 65.8, 58.0, 38.7;
HRMS (ESI): Calc'd for $C_{12}H_{13}NNaO_3$ $[M+Na]^+$: 242.0788, found: 242.0787.



2.9

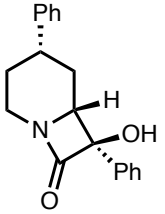
(±)-8-Hydroxy-8-phenyl-1-azabicyclo[5.2.0]nonan-9-one (2.9) was prepared from **2.S1** using a procedure analogous to that for the preparation of **2.2**. The title compound was obtained as a colorless foam (14.6 mg, 63 %).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.40 (d, *J* = 7.0 Hz, 2H), 7.36–7.30 (m, 3H), 3.91 (br, 1H), 3.85 (d, *J* = 11.3 Hz, 1H), 3.51 (d, *J* = 13.2 Hz, 1H), 3.33 (t, *J* = 13.2 Hz, 1H), 1.95–1.86 (m, 2H), 1.73–1.70 (m, 1H), 1.54–1.50 (m, 2H), 1.26–1.13 (m, 2H), 0.73–0.66 (m, 1H);
^{13}C NMR (151 MHz, $CDCl_3$): δ 169.5, 137.2, 128.23, 128.19, 126.9, 86.7, 68.7, 42.8, 32.0, 29.3, 28.2, 26.3;
HRMS (ESI): Calc'd for $C_{14}H_{17}NNaO_2$ $[M+Na]^+$: 254.1151, found: 254.1152.



2.S7

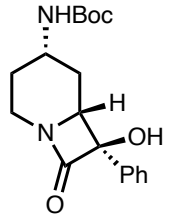
(±)-9-hydroxy-9-phenyl-1-azabicyclo[6.2.0]decan-10-one (2.S7) was prepared from **2.S2** using a procedure analogous to that for the preparation of **2.2**. The title compound was obtained as a colorless oil (13.5 mg, 55%).
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.36–7.31 (m, 2H), 7.33–7.26 (m, 3H), 4.65 (s, 1H), 3.78 (dd, *J* = 10.4, 2.7 Hz, 1H), 3.67 (ddd, *J* = 14.2, 7.6, 2.7 Hz, 1H), 3.09 (ddd, *J* = 14.2, 9.0, 2.7 Hz, 1H), 1.75–1.65 (m, 1H), 1.65–1.38 (m, 6H), 1.36–1.22 (m, 2H), 0.93–0.83 (m, 1H);
^{13}C NMR (151 MHz, $CDCl_3$): δ 170.6, 137.3, 128.4, 128.3, 126.9, 88.1, 68.6, 40.7, 29.9, 26.2, 25.8, 25.6, 24.3.
HRMS (ESI): Calc'd for $C_{15}H_{19}NNaO_2$ $[M+Na]^+$: 268.1308, found: 268.1316.



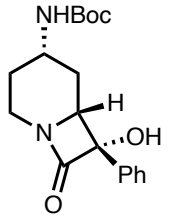
2.S8

(±)-7-hydroxy-4,7-diphenyl-1-azabicyclo[4.2.0]octan-8-one (2.S8) was prepared from **2.S4** using a procedure analogous to that for the preparation of **2.2**. The title compound was obtained as a white solid (10.6 mg, 36%).
Melting Point: 178–181 °C;
^{1}H NMR: (600 MHz, DMSO-d_6): δ 7.42 (d, *J* = 7.5 Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 2H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 2H), 6.83 (s, OH, 1H), 3.89 (dd, *J* = 13.0, 5.5 Hz, 1H), 3.72 (dd, *J* = 11.1, 3.9 Hz, 1H), 2.99 (td, *J* = 12.6, 3.9 Hz, 1H), 2.75 (t, *J* = 12.1, 1H), 1.69 (dt, *J* = 13.0, 3.9 Hz, 1H), 1.56 (dt, *J* = 12.1, 3.9 Hz, 1H), 1.45 (qd, *J* = 12.6, 5.5 Hz, 1H), 0.67 (q, *J* = 12.1 Hz, 1H);

^{13}C NMR: (151 MHz, DMSO-d_6): δ 166.8, 145.6, 137.8, 128.5, 128.2, 128.0, 127.0, 126.6, 126.3, 89.7, 63.0, 39.0, 38.2, 34.6, 31.4;
HRMS (ESI): Calc'd for $C_{19}H_{19}NNaO_2$ $[M+Na]^+$: 316.1308, found: 316.1307.



2.S9a



2.S9b

(±)-*tert*-Butyl (7-hydroxy-8-oxo-7-phenyl-1-azabicyclo[4.2.0]octan-4-yl)carbamate (2.S9) was prepared from **2.S5** using a procedure analogous to that for the preparation of **2.2**. Preparative thin-layer chromatography (SiO_2, 50% EtOAc/ hexanes) provided **2.S9a** (8.3 mg, 25%) as a white amorphous solid and **2.S9b** (8.3 mg, 25%) as a white amorphous solid.

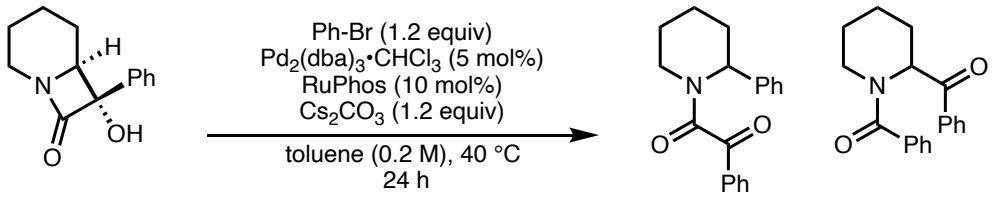
2.S9a
^{1}H NMR: (600 MHz, DMSO-d_6): δ 7.45 (d, J = 7.4 Hz, 2H), 7.37 (t, J = 7.4 Hz, 2H), 7.31 (t, J = 7.4 Hz, 1H), 7.02 (d, J = 7.8 Hz, 1H), 6.69 (s, 1H), 3.74 (dd, J = 13.5, 5.6 Hz, 1H), 3.58 (dd, J = 10.8, 4.5 Hz, 1H), 3.56 – 3.46 (m, 1H), 2.90 (td, J = 13.1, 4.2 Hz, 1H), 1.84 (dt, J = 12.9, 4.0 Hz, 1H), 1.73 (d, J = 12.1 Hz, 1H), 1.60 (q, J = 11.8 Hz, 1H), 1.39 (s, 9H), 1.35–1.20 (m, 1H).
^{13}C NMR: (176 MHz, $CDCl_3$): δ 169.2, 155.1, 139.1, 128.7, 128.4, 125.5, 87.6, 79.8, 61.8, 46.1, 38.0, 31.7, 31.4, 28.5.
HRMS (ESI): Calc'd for $C_{18}H_{25}N_2O_4$ $[M+H]^+$: 333.1809, found: 333.1799.

2.S9b
^{1}H NMR (600 MHz, DMSO-d_6): δ 7.42–7.29 (m, 5H), 6.73–6.62 (m, 1H), 3.80 (dd, J = 13.3, 5.3 Hz, 1H), 3.59 (dd, J = 11.4, 4.5 Hz, 1H), 3.51–3.39 (m, 1H), 2.91 (td, J = 12.9, 4.2 Hz, 1H), 1.71–1.66 (m, 1H), 1.61–1.54 (m, 1H), 1.34 (s, 9H), 1.13 (qd, J = 12.4, 5.8 Hz, 1H), 0.50 (q, J = 11.8 Hz, 1H);
^{13}C NMR (151 MHz, DMSO-d_6): δ 167.0, 155.1, 138.2, 128.6, 128.4, 127.5, 90.1, 78.0, 62.5, 46.3, 37.6, 33.9, 31.4, 28.6;
HRMS (ESI): Calc'd for $C_{18}H_{24}N_2NaO_4$ $[M+Na]^+$: 355.1628, found: 355.1624.

The NMR data are consistent with the overall structure based on HSQC, COSY and HMBC data as well as ^{13}C chemical shifts. Relative stereochemistry was assigned as described below.

2.4.4. Experimental Procedures for C–C cleavage/Cross-Coupling

Representative Procedure for Pd-Catalyzed Ring-Opening/Cross-Coupling Reaction of α-Hydroxylactams



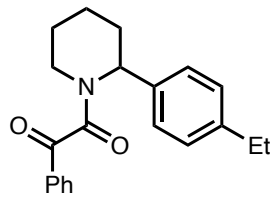
2.2 **2.3a** **2.4**

A 1-dram vial containing a stir bar, **2.2** (21.7 mg, 0.100 mmol), and bromobenzene (18.8 mg,0.120 mmol) was brought into an N_2 atmosphere glovebox. To this vial was sequentially added $Pd_2(dba)_3$•$CHCl_3$ (5.2 mg, 0.0050 mmol), RuPhos (4.7 mg, 0.010 mmol), Cs_2CO_3 (39.0 mg, 0.120 mmol) and toluene (0.5 mL). The vial was sealed with a Teflon cap and the resulting mixture was stirred at 40 °C for 24 h. After cooling to room temperature, the mixture was filtered through Celite® using EtOAc as the eluent. After concentration to dryness, the crude residue was purified by preparative thin-layer chromatography (33% EtOAc/hexanes) to provide **2.3a** (19.1 mg, 65%). The spectroscopic data were in agreement with those reported above for **2.3a** (labeled **2.3a** in main text).

2.4 (Distal cleavage product)

^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.96 (d, *J* = 7.7 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.40 – 7.35 (m, 3H), 7.30 (d, *J* = 6.8 Hz, 2H), 6.23 (d, *J* = 6.3 Hz, 1H), 3.59 (dt, *J* = 13.7, 3.3 Hz, 1H), 3.26 (td, *J* = 13.2, 3.0 Hz, 1H), 2.32 (d, *J* = 13.9 Hz, 1H), 1.89 (tdd, *J* = 13.6, 6.4, 4.2 Hz, 1H), 1.71 – 1.67 (m, 1H), 1.64 – 1.54 (m, 2H), 1.45 – 1.37 (m, 1H).
^{13}C NMR (176 MHz, $CDCl_3$) δ 200.47, 171.38, 136.05, 135.98, 133.18, 129.70, 128.74, 128.58, 128.33, 126.86, 54.94, 46.29, 26.07, 26.03, 20.36.

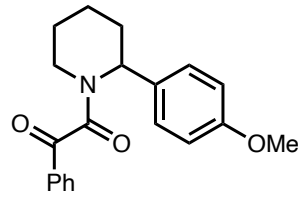
HRMS (ESI): Calc'd for $C_{19}H_{20}NO_2$ $[M+H]^+$: 294.1489, found: 294.1484.



2.3b

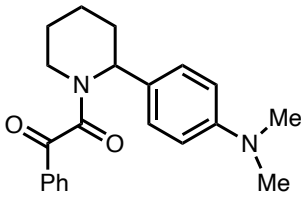
(±)-1-(2-(4-Ethylphenyl)piperidin-1-yl)-2-phenylethane-1,2-dione (2.3b): The title compound was prepared according to the representative procedure using **2.2** and 1-bromo-4-ethylbenzene.

Purification by preparative thin-layer chromatography (33% EtOAc/hexanes) provided the title compound (21.9 mg, 68%, mixture of rotamers 1.0:0.70) as a beige solid.
Melting Point: 77–79 °C;
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.04 (d, *J* = 7.5 Hz, 2.0H), 7.99 (d, *J* = 7.5 Hz, 1.4H), 7.67 (t, *J* = 7.5 Hz, 1.0H), 7.62 (t, *J* = 7.5 Hz, 0.7H), 7.55 (t, *J* = 7.5 Hz, 2.0H), 7.50 (t, *J* = 7.5 Hz, 1.4H), 7.28–7.18 (m, 4.0+2.8H), 6.12 (brs, 1.0H), 4.83 (brs, 0.7H), 4.59 (d, *J* = 12.0 Hz, 0.7H), 3.38 (d, *J* = 14.1 Hz, 1.0H), 3.11 (dt, *J* = 14.1, 8.3 Hz, 1.0H), 2.80 (t, *J* = 12.0 Hz, 0.7H), 2.66 (q, *J* = 7.3 Hz, 2.0H), 2.62 (q, *J* = 7.3 Hz, 1.4H), 2.50 (d, *J* = 13.9 Hz, 1.0H), 2.38 (d, *J* = 13.7 Hz, 0.7H), 2.04–1.99 (m, 1.0H), 1.91–1.86 (m, 0.7H), 1.72–1.65 (m, 4.0+2.8H), 1.25 (t, *J* = 7.3 Hz, 3.0H), 1.22 (t, *J* = 7.3 Hz, 2.1H);
^{13}C NMR (151 MHz, $CDCl_3$): δ 191.9, 191.6, 166.68, 166.67, 143.5, 143.1, 135.2, 134.8, 134.7, 134.5, 133.5, 133.4, 129.8, 129.7, 129.2, 129.1, 128.51, 128.46, 126.84, 126.78, 56.3, 50.5, 43.1, 37.8, 28.6, 28.56, 28.51, 27.5, 26.3, 25.8, 19.799, 19.796, 15.6, 15.5;
HRMS (ESI): Calc'd for $C_{21}H_{23}NNaO_2$ $[M+Na]^+$: 344.1621, found: 344.1632.



2.3c

(±)-1-(2-(4-Methoxyphenyl)piperidin-1-yl)-2-phenylethane-1,2-dione (2.3c): The title compound was prepared according to the representative procedure using **2.2** and 1-bromo-4-methoxybenzene. Purification by preparative thin-layer chromatography (40% EtOAc/hexanes) provided the title compound (23.0 mg, 71%, mixture of rotamers 1.0:0.75) as a pale yellow foam.
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.02 (d, *J* = 7.5 Hz, 2.0H), 7.99 (d, *J* = 7.8 Hz, 1.5H), 7.66 (t, *J* = 7.5 Hz, 1.0H), 7.63 (t, *J* = 7.8 Hz, 0.75H), 7.55 (t, *J* = 7.5 Hz, 2.0H), 7.50 (t, *J* = 7.8 Hz, 1.5H), 7.28 (d, *J* = 8.7 Hz, 2.0H), 7.24 (d, *J* = 8.7 Hz, 1.5H), 6.94 (d, *J* = 8.7 Hz, 2.0H), 6.88 (d, *J* = 8.7 Hz, 1.5H), 5.99 (brs, 1.0H), 4.81 (brs, 0.7H), 4.57 (d, *J* = 12.8 Hz, 0.75H), 3.82 (s, 3H), 3.79 (s, 2.25H), 3.36 (d, *J* = 13.3 Hz, 1.0H), 3.11–3.06 (m, 1H), 2.78 (d, *J* = 11.1 Hz, 0.75H), 2.47 (d, *J* = 14.2 Hz, 1.0H), 2.34 (d, *J* = 13.6 Hz, 0.75H), 2.04–1.98 (m, 1.0H), 1.89–1.84 (m, 0.75H), 1.73–1.52 (m, 4.0+3.0H);
^{13}C NMR (151 MHz, $CDCl_3$): δ 191.9, 191.7, 166.7, 166.6, 158.9, 158.7, 134.8, 134.7, 133.5, 133.4, 130.0, 129.9, 129.8, 129.7, 129.2, 129.1, 128.07, 128.06, 114.4, 114.3, 55.9, 55.43, 55.41, 50.1, 42.9, 37.7, 28.6, 27.5, 26.3, 25.8, 19.8(2*)*;
HRMS (ESI): Calc'd for $C_{20}H_{21}NNaO_3$ $[M+Na]^+$: 346.1414, found: 346.1421.



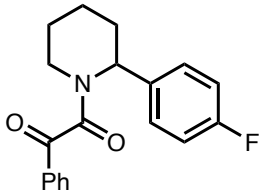
2.3d

(±)-1-(2-(4-(Dimethylamino)phenyl)piperidin-1-yl)-2-phenylethane-1,2-dione (2.3d): The title compound was prepared according to the representative procedure using **2.2** and 4-bromo-N,N-dimethylaniline. Purification by preparative thin-layer chromatography (50% EtOAc/hexanes) provided the title compound (17.7 mg, 56%, mixture of rotamers 1.0:0.8) as a pale–yellow foam.

^{1}H NMR (700 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.2 Hz, 2H), 8.00 (d, *J* = 7.2 Hz, 1.6H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.62 (t, *J* = 7.5 Hz, 0.8H), 7.55 (t, *J* = 7.6 Hz, 2H), 7.50 (t, *J* = 7.7 Hz, 1.6H), 7.23 (d, *J* = 8.5 Hz, 2H), 7.17 (d, *J* = 8.5 Hz, 1.6H), 6.77 (d, *J* = 8.3 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 1.6H), 5.98 (d, *J* = 5.3 Hz, 1H), 4.79 (d, *J* = 4.9 Hz, 0.8H), 4.54 (d, *J* = 13.2 Hz, 0.8H), 3.33 (dt, *J* = 13.8, 3.3 Hz, 1H), 3.15–3.07 (m, 1H), 2.96 (s, 6H), 2.93 (s, 4.8H), 2.85–2.78 (m, 0.8H), 2.47 (d, *J* = 15.8 Hz, 1H), 2.34 (d, *J* = 14.0 Hz, 0.8H), 2.04–1.48 (m, 9H).

^{13}C NMR (176 MHz, $CDCl_3$): δ 192.0, 191.7, 166.6, 149.8, 149.6, 134.8, 134.7, 133.5, 133.4, 129.8, 129.7, 129.2, 129.0, 127.8, 127.7, 125.4, 124.5, 113.0, 112.8, 56.0, 50.1, 42.9, 40.7, 40.6, 37.6, 28.4, 27.3, 26.4, 25.9, 19.8(2);

HRMS (ESI): Calc'd for $C_{21}H_{24}N_2NaO_2$ $[M+Na]^+$: 359.1730, found: 359.1724.



2.3e

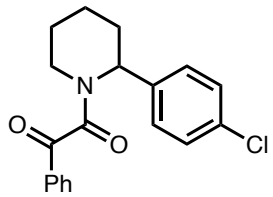
(±)-1-(2-(4-Fluorophenyl)piperidin-1-yl)-2-phenylethane-1,2-dione (2.3e): The title compound was prepared according to the representative procedure using **2.2** and 1-bromo-4-fluorobenzene. Purification by preparative thin-layer chromatography (33% EtOAc/hexanes) provided the title compound (19.0 mg, 61%, mixture of rotamers 1.0:0.65) as an off-white solid.

Melting Point: 81–83 °C;

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.01 (d, *J* = 7.7 Hz, 2.0H), 7.98 (d, *J* = 7.7 Hz, 1.3H), 7.67 (t, *J* = 7.7 Hz, 1.0H), 7.64 (t, *J* = 7.7 Hz, 0.65H), 7.55 (t, *J* = 7.7 Hz, 2.0H), 7.51 (t, *J* = 7.7 Hz, 1.3H), 7.33–7.29 (m, 2.0+1.3H), 7.33–7.29 (m, 2.0+1.3H), 7.11–7.08 (m, 2.0H), 7.06–7.03 (m, 1.3H), 6.00 (brs, 1.0H), 4.82 (brs, 0.65H), 4.60 (d, *J* = 12.1 Hz, 0.65H), 3.39 (d, *J* = 13.7 Hz, 1.0H), 3.09–3.04 (m, 1H), 2.76–2.72 (m, 0.65H), 2.47 (d, *J* = 14.4 Hz, 1H), 2.35 (d, *J* = 13.7 Hz, 0.65H), 2.06–2.00 (m, 1.0H), 1.91–1.85 (m, 0.65H), 1.75–1.51 (m, 4.0+2.6H);

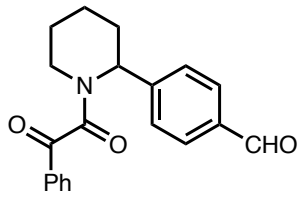
^{13}C NMR (151 MHz, $CDCl_3$): δ 191.8, 191.6, 166.8, 166.6, 162.1 (d, $J_{C\text{-}F}$ = 247.0 Hz), 162.0 (d, $J_{C\text{-}F}$ = 245.4 Hz), 134.93, 134.89, 133.8, 133.4, 133.3, 133.1, 129.73, 129.71, 129.2, 129.15, 128.63

(d, $J_{C\text{-}F}$ = 8.5 Hz), 128.56 (d, $J_{C\text{-}F}$ = 7.7 Hz), 115.9 (d, $J_{C\text{-}F}$ = 7.7 Hz), 115.8 (d, $J_{C\text{-}F}$ = 7.7 Hz), 55.9, 50.1, 43.0, 37.8, 28.7, 27.5, 26.2, 25.7, 19.68, 19.67;
^{19}F NMR (376 MHz, $CDCl_3$): δ −114.6 (s), −115.0 (s);
HRMS (ESI): Calc'd for $C_{19}H_{18}FNNaO_2$ $[M+Na]^+$: 334.1214, found: 334.1212.



2.3f

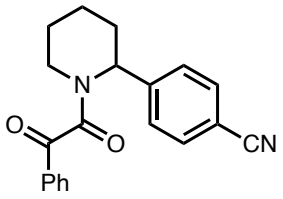
(±)-1-(2-(4-Chlorophenyl)piperidin-1-yl)-2-phenylethane-1,2-dione (2.3f): The title compound was prepared according to the representative procedure using **2.2** and 1-bromo-4-chlorobenzene. Purification by preparative thin-layer chromatography (33% EtOAc/hexanes) provided the title compound (16.4 mg, 50%, mixture of rotamers 1.0:0.6) as a pale yellow foam.
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.01 (d, *J* = 7.6 Hz, 2.0H), 7.98 (d, *J* = 7.7 Hz, 1.2H), 7.69–7.66 (m, 1H), 7.65–7.63 (m, 0.6H), 7.57–7.54 (m, 2H), 7.52–7.50 (m, 1.2H), 7.38 (d, *J* = 6.7 Hz, 2.0H), 7.33 (d, *J* = 6.8 Hz, 1.2H), 7.30–7.26 (m, 2.0+1.2H), 6.00 (brs, 1.0H), 4.82 (brs, 0.6H), 4.60 (d, *J* = 13.4 Hz, 0.6H), 3.40 (d, *J* = 14.5 Hz, 1.0H), 3.08–3.04 (m, 1H), 2.74 (t, *J* = 12.8 Hz, 0.6H), 2.46 (d, *J* = 14.2 Hz, 1H), 2.35 (d, *J* = 14.1 Hz, 0.6H), 2.06–2.01 (m, 1.0H), 1.91–1.86 (m, 0.6H), 1.76–1.53 (m, 4.0+2.4H);
^{13}C NMR (151 MHz, $CDCl_3$): δ 191.8, 191.6, 166.8, 166.6, 136.7, 136.0, 135.0, 134.9, 133.5, 133.4, 133.3, 133.1, 129.8, 129.7, 129.26, 129.21, 129.17, 129.15, 128.35, 128.34, 55.9, 50.2, 43.1, 37.9, 28.6, 27.5, 26.2, 25.7, 19.72, 19.70;
HRMS (ESI): Calc'd for $C_{19}H_{18}ClNNaO_2$ $[M+Na]^+$: 350.0918, found: 350.0919.



2.3g

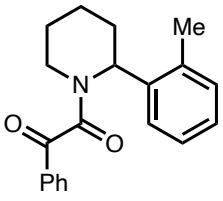
(±)-4-(1-(2-Oxo-2-phenylacetyl)piperidin-2-yl)benzaldehyde (2.3g): The title compound was prepared according to the representative procedure using **2.2** and 4-bromobenzaldehyde with the following modifications: reaction time of 72 h. Purification by preparative thin-layer chromatography (33% EtOAc/hexanes) provided the title compound (16.7 mg, 52%, mixture of rotamers 1.0:0.5) as a pale yellow, sticky oil.
^{1}H NMR (600 MHz, $CDCl_3$): δ 10.03 (s, 1.0H), 10.00 (s, 0.5H), 8.03–7.88 (m, 4.0+2.0H), 7.70–7.42 (m, 5.0+2.5H), 6.08 (brs, 1.0H), 4.91 (brs, 0.5H), 4.66 (d, *J* = 13.4 Hz, 0.5H), 3.46 (d, *J* =

13.4 Hz, 1.0H), 3.08 (brs, 1H), 2.75 (t, *J* = 11.2 Hz, 0.5H), 2.54 (d, *J* = 13.3 Hz, 1H), 2.43 (d, *J* = 11.2 Hz, 0.5H), 2.09 (br, 1.0H), 1.95 (br, 0.5H), 1.78–1.48 (m, 4.0+2.0H);
^{13}C NMR (151 MHz, $CDCl_3$): δ 191.8, 191.72, 191.68, 191.67, 166.9, 166.7, 145.5, 144.7, 135.51, 135.49, 135.1, 135.0, 133.3, 133.2, 130.5, 130.3, 129.8(2), 129.3, 129.2, 127.6, 127.5, 56.5, 50.9, 43.4, 38.2, 28.8, 27.6, 26.0, 25.6, 19.82, 19.80;
HRMS (ESI): Calc'd for $C_{20}H_{19}NNaO_3$ $[M+Na]^+$: 344.1257, found: 344.1253.



2.3h

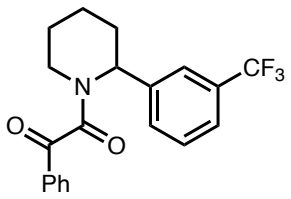
(±)-4-(1-(2-Oxo-2-phenylacetyl)piperidin-2-yl)benzonitrile (2.3h): The title compound was prepared according to the representative procedure using **2.2** and 4-bromobenzonitrile. Purification by preparative thin-layer chromatography (33% EtOAc/hexanes) provided the title compound (14.6 mg, 46%, mixture of rotamers 1.0:0.5) as an off-white solid.
Melting Point: 83–85 °C;
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.01 (d, *J* = 7.0 Hz, 2.0H), 7.97 (d, *J* = 7.0 Hz, 1.0H), 7.72–7.64 (m, 3.0+1.5H), 7.56 (t, *J* = 7.0 Hz, 2.0H), 7.52 (t, *J* = 7.0 Hz, 1.0H), 7.48–7.47 (m, 3.0+1.5H), 6.05 (brs, 1.0H), 4.88 (brs, 0.5H), 4.65 (d, *J* = 12.6 Hz, 0.5H), 3.46 (d, *J* = 14.2 Hz, 1.0H), 3.04 (t, *J* = 10.8 Hz, 1.0H), 2.70 (t, *J* = 13.2 Hz, 0.5H), 2.50 (d, *J* = 14.6 Hz, 1H), 2.38 (d, *J* = 14.3 Hz, 0.5H), 2.11–2.04 (m, 1.0H), 1.96–1.90 (m, 0.5H), 1.79–1.48 (m, 4.0+2.0H);
^{13}C NMR (151 MHz, $CDCl_3$): δ 191.6, 191.5, 167.0, 166.7, 144.0, 143.3, 135.1(2), 133.3, 133.2, 132.9, 132.8, 129.8(2), 129.3, 129.2, 127.8, 127.7, 118.7, 118.6, 111.7, 111.3, 56.3, 50.7, 43.3, 38.1, 28.7, 27.5, 26.0, 25.5, 19.75, 19.71;
HRMS (ESI): Calc'd for $C_{20}H_{18}N_2NaO_2$ $[M+Na]^+$: 341.1260, found: 341.1262.



2.3i

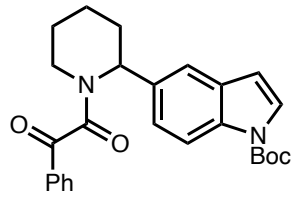
(±)-1-Phenyl-2-(2-(*o*-tolyl)piperidin-1-yl)ethane-1,2-dione (2.3i): The title compound was prepared according to the representative procedure using **2.2** and 1-bromo-2-methylbenzene. Purification by preparative thin-layer chromatography (33% EtOAc/hexanes) provided the title compound (15.1 mg, 49%, mixture of rotamers 1.0:0.5) as a pale yellow, sticky oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.95 (d, *J* = 7.4 Hz, 2.0H), 7.64 (t, *J* = 7.4 Hz, 1.0H), 7.60 (d, *J* = 7.4 Hz, 1.0H), 7.50 (t, *J* = 7.4 Hz, 2.0H), 7.43 (d, *J* = 7.5 Hz, 0.5H), 7.42–7.38 (m, 1.0H), 7.25–7.21 (m, 4.5H), 7.03 (t, *J* = 7.5 Hz, 0.5H), 6.90 (t, *J* = 7.5 Hz, 0.5H), 6.77 (d, *J* = 7.5 Hz, 0.5H), 5.87 (dd, *J* = 6.5, 3.9 Hz, 1.0H), 4.98 (t, *J* = 5.9 Hz, 0.5H), 4.40 (dt, *J* = 13.8, 4.4 Hz, 0.5H), 3.72 (ddd, *J* = 13.8, 10.3, 4.5 Hz, 0.5H), 3.52 (dt, *J* = 13.8, 3.7 Hz, 1.0H), 3.40–3.35 (m, 1H), 2.46 (s, 3H), 2.16–2.04 (m, 2.0H), 2.04 (s, 1.5H), 2.00–1.66 (m, 7.0H);
^{13}C NMR (151 MHz, $CDCl_3$): δ 191.8, 190.9, 168.2, 166.7, 139.9, 138.9, 136.7, 135.0, 134.7, 133.9, 133.5, 132.7, 131.6, 130.7, 129.8, 129.5, 129.1, 128.2, 127.6, 127.3, 127.0, 126.3, 126.1, 125.9, 55.3, 50.6, 43.7, 40.7, 30.0, 28.3, 25.5, 23.9, 20.0, 19.8, 19.5, 19.2;
HRMS (ESI): Calc'd for $C_{20}H_{21}NNaO_2$ $[M+Na]^+$: 330.1465, found: 330.1458.



2.3j

(±)-1-Phenyl-2-(2-(3-(trifluoromethyl)phenyl)piperidin-1-yl)ethane-1,2-dione (2.3j): The title compound was prepared according to the representative procedure using **2.2** and 1-bromo-3-(trifluoromethyl)benzene. Purification by preparative thin-layer chromatography (33% EtOAc/hexanes) provided the title compound (17.7 mg, 49%, mixture of rotamers 1.0:0.5) as a pale yellow oil.
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.03 (d, *J* = 7.7 Hz, 2.0H), 7.99 (d, *J* = 7.7 Hz, 1.0H), 7.68 (t, *J* = 6.9 Hz, 1.0H), 7.64 (t, *J* = 7.5 Hz, 1.0H), 7.61 (s, 1.0H), 7.57–7.49 (m, 8.0H), 6.06 (brs, 1.0H), 4.90 (brs, 0.5H), 4.65 (d, *J* = 12.4 Hz, 0.5H), 3.45 (d, *J* = 14.4 Hz, 1.0H), 3.03 (dt, *J* = 14.8, 8.5 Hz, 1.0H), 2.74 (dt, *J* = 13.1, 3.3 Hz, 0.5H), 2.52 (d, *J* = 14.4 Hz, 1H), 2.41 (d, *J* = 13.4 Hz, 0.5H), 2.12–2.06 (m, 1.0H), 1.96 (tt, *J* = 13.8, 4.4 Hz, 0.5H), 1.79–1.55 (m, 4.0+2.0H);
^{13}C NMR (151 MHz, $CDCl_3$): δ 191.7, 191.5, 167.0, 166.8, 139.5, 138.8, 135.03, 135.00, 133.3, 133.2, 131.48 (q, $J_{C\text{-}F}$ = 32.2 Hz), 131.44 (q, $J_{C\text{-}F}$ = 32.0 Hz), 130.45, 130.44, 130.39, 130.38, 129.8, 129.74, 129.69, 129.6, 129.3, 129.2, 124.5 (q, $J_{C\text{-}F}$ = 3.7 Hz), 124.24 (q, $J_{C\text{-}F}$ = 272.4 Hz), 124.17 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.12 (q, $J_{C\text{-}F}$ = 272.4 Hz), 123.6 (q, $J_{C\text{-}F}$ = 3.8 Hz) (2), 56.1, 50.5, 43.2, 38.0, 28.6, 27.4, 26.0, 25.6, 19.7(2);
^{19}F NMR (376 MHz, $CDCl_3$): δ −61.8 (s);
HRMS (ESI): Calc'd for $C_{20}H_{18}F_3NNaO_2$ $[M+Na]^+$: 384.1182, found: 384.1189.



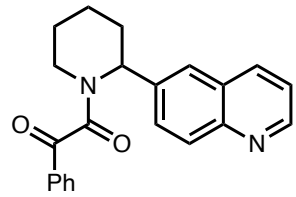
2.3k

(±)-*tert*-Butyl 5-(1-(2-Oxo-2-phenylacetyl)piperidin-2-yl)-1*H*-indole-1-carboxylate (2.3k): The title compound was prepared according to the representative procedure using **2.2** and *tert*-butyl 5-bromo-1*H*-indole-1-carboxylate. Purification by preparative thin-layer chromatography (33% EtOAc/hexanes) provided the title compound (30.3 mg, 70%, mixture of rotamers 1.0:0.7) as a pale yellow foam.

^{1}H NMR (600 MHz, $CDCl_3$): δ 8.16 (brs, 1.0H), 8.10 (brs, 0.7H), 8.06 (d, *J* = 7.9 Hz, 2.0H), 8.01 (d, *J* = 7.9 Hz, 1.4H), 7.68–7.49 (m, 4.0+4.2H), 7.32 (d, *J* = 8.5 Hz, 1.0H), 7.27 (d, *J* = 10.0 Hz, 1.0H), 6.58 (d, *J* = 3.4 Hz, 1.0H), 6.55 (d, *J* = 3.4 Hz, 0.7H), 6.15 (brs, 1.0H), 4.96 (brs, 0.7H), 4.61 (d, *J* = 13.0 Hz, 0.7H), 3.39 (d, *J* = 12.4 Hz, 1.0H), 3.14–3.10 (m, 1.0H), 2.85–2.81 (m, 0.7H), 2.59 (d, *J* = 14.0 Hz, 1H), 2.47 (d, *J* = 13.4 Hz, 0.7H), 2.11–2.05 (m, 1.0H), 1.96–1.91 (m, 0.7H), 1.76–1.63 (m, 4.0+2.8H), 1.68 (s, 9.0H), 1.67 (s, 6.3H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 192.0, 191.7, 166.7(2), 149.83, 149.78, 134.8, 134.7, 133.5, 133.4, 132.34, 132.31, 131.6, 131.2, 129.8, 129.7, 129.2, 129.1, 126.7, 126.6, 123.2, 122.9, 119.4, 119.3, 115.7, 115.6, 107.4(2), 84.0, 83.9, 56.4, 50.7, 43.1, 37.9, 28.9, 28.34, 28.31, 27.7, 26.3, 25.8, 19.9(2);

HRMS (ESI): Calc'd for $C_{26}H_{29}N_2O_4$ $[M+H]^+$: 433.2122, found: 433.2121.

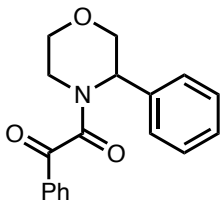


2.3l

(±)-1-Phenyl-2-(2-(quinolin-6-yl)piperidin-1-yl)ethane-1,2-dione (3.3l): The title compound was prepared according to the representative procedure using **3.2** and 6-bromoquinoline. Purification by preparative thin-layer chromatography (50% EtOAc/hexanes) provided the title compound (20.7 mg, 60%, mixture of rotamers 1.0:0.6) as a pale yellow, sticky oil.

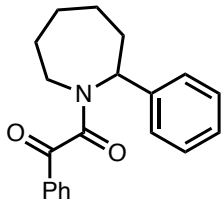
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.92 (dd, *J* = 4.2, 1.5 Hz, 1.0H), 8.91 (dd, *J* = 4.2, 1.6 Hz, 0.6H), 8.19–8.15 (m, 2.0+0.6H), 8.11 (d, *J* = 8.8 Hz, 0.6H), 8.07–8.05 (m, 2.0H), 8.01–8.00 (m, 1.0H), 7.78–7.77 (m, 1.0+0.6H), 7.73 (dd, *J* = 8.9, 1.9 Hz, 1.0H), 7.70–7.68 (m, 1.0+0.6H), 7.64–7.61 (m, 0.6H), 7.59–7.56 (m, 2.0H), 7.52–7.49 (m, 1.0H), 7.45–7.41 (m, 1.0+0.6H), 6.21 (brs, 1.0H), 5.04 (brs, 0.6H), 4.68 (d, *J* = 13.0 Hz, 0.6H), 3.47 (d, *J* = 13.5 Hz, 1.0H), 3.16–3.11 (m, 1.0H), 2.85 (dt, *J* = 13.4, 4.0 Hz, 0.6H), 2.65 (d, *J* = 14.4 Hz, 1H), 2.53 (d, *J* = 13.0 Hz, 0.6H), 2.17–2.10 (m, 1.0H), 2.02–1.96 (m, 0.6H), 1.83–1.58 (m, 4.0+2.4H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 191.8, 191.6, 166.9, 166.8, 150.8, 150.6, 147.51, 147.47, 136.7, 136.4, 136.3, 136.0, 135.0, 134.9, 133.4, 133.3, 130.4, 130.3, 129.79, 129.75, 129.3, 129.2, 128.6, 128.4, 128.3, 128.2, 126.1, 125.7, 121.7, 121.6, 56.4, 50.7, 43.3, 38.1, 28.8, 27.6, 26.2, 25.7, 19.8(2);
HRMS (ESI): Calc'd for $C_{22}H_{21}N_2O_2$ $[M+H]^+$: 345.1598, found: 345.1589.



2.6c

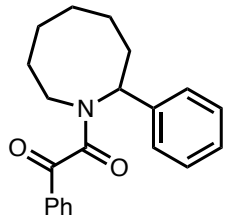
(±)-1-Phenyl-2-(3-phenylmorpholino)ethane-1,2-dione (2.6c): The title compound was prepared according to the representative procedure using **2.S6a** and bromobenzene. Purification by preparative thin-layer chromatography (33% EtOAc/hexanes) provided **2.6c** (14.4 mg, 48%, mixture of rotamers 1.0:0.5) as a yellow oil.
^{1}H NMR (700 MHz, $CDCl_3$): δ 8.00 (d, *J* = 7.0 Hz, 1H), 7.94 (d, *J* = 6.9 Hz, 2H), 7.68–7.63 (m, 4H), 7.54–7.49 (m, 3H), 7.46–7.40 (m, 3H), 7.35 (t, *J* = 6.8 Hz, 1H), 7.34 (t, *J* = 6.8 Hz, 1H), 5.76 (d, *J* = 3.5 Hz, 1H), 4.67 (d, *J* = 2.4 Hz, 0.5H), 4.57 (d, *J* = 12.4 Hz, 1H), 4.42 (d, *J* = 11.6 Hz, 1H), 4.03 (dd, *J* = 11.7, 3.8 Hz, 0.5H), 4.00 (dd, *J* = 12.4, 3.7 Hz, 1H), 3.88 (ddd, *J* = 14.7, 11.7, 3.4 Hz, 1.0+0.5H), 3.76 (td, *J* = 11.9, 2.9 Hz, 0.5H), 3.64 (td, *J* = 11.8, 2.7 Hz, 1H), 3.39 (ddd, *J* = 13.9, 12.0, 3.5 Hz, 1H), 3.24 (d, *J* = 13.7 Hz, 1H), 3.17 (ddd, *J* = 13.8, 12.1, 3.8 Hz, 0.5H);
^{13}C NMR (176 MHz, $CDCl_3$): δ 191.2, 191.1, 166.1, 137.8, 136.7, 135.1, 133.34, 133.29, 130.0, 129.8, 129.3, 129.2, 128.94, 128.88, 128.4, 128.2, 128.0, 127.9, 69.2, 68.8, 67.4, 67.3, 56.3, 51.0, 42.5, 37.8 (Two ^{13}C signals are overlapping with others due to amide rotation);
HRMS (ESI): Calc'd for $C_{18}H_{17}NNaO_3$ $[M+Na]^+$: 318.1101, found: 318.1099.



2.6a

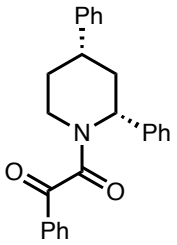
(±)-1-Phenyl-2-(2-phenylazepan-1-yl)ethane-1,2-dione (2.6a): The title compound was prepared according to the representative procedure using **2.9** and bromobenzene. Purification by preparative thin-layer chromatography (33% EtOAc/hexanes) provided the title compound (21.7 mg, 71%, mixture of rotamers 1.0:0.85) as a yellow foam.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.82 (d, *J* = 7.8 Hz, 2.0+1.7H), 7.60 (t, *J* = 7.8 Hz, 1.0H), 7.54 (t, *J* = 7.8 Hz, 0.85H), 7.44 (t, *J* = 7.8 Hz, 2.0H), 7.40–7.35 (m, 4.0+1.7H), 7.31–7.27 (m, 1.0H), 7.23 (t, *J* = 7.4 Hz, 1.7H), 7.18–7.14 (m, 0.85H), 7.09 (d, *J* = 7.4 Hz, 1.7H), 5.57 (dd, *J* = 12.4, 5.9 Hz, 1.0H), 4.73 (dd, *J* = 10.9, 6.5 Hz, 0.85H), 4.53 (d, *J* = 13.6 Hz, 0.85H), 3.62 (d, *J* = 15.3 Hz, 1.0H), 3.36 (ddd, *J* = 15.3, 11.8, 1.5 Hz, 1.0H), 3.05 (ddd, *J* = 13.6, 11.4, 2.2 Hz, 0.85H), 2.44–2.38 (m, 1.0+0.85H), 2.04–1.29 (m, 7.0+5.95H);
^{13}C NMR (176 MHz, $CDCl_3$): δ 191.44, 191.43, 168.21, 168.20, 142.5, 141.9, 134.6, 134.4, 133.5, 133.3, 129.8, 129.1, 128.82, 128.80, 128.7, 127.4, 126.1, 125.7, 61.0, 58.2, 45.1, 42.4, 36.2, 35.0, 30.9, 29.9, 29.4, 28.5, 26.0, 25.5(Two ^{13}C signals are overlapping with others due to amide rotation);
HRMS (ESI): Calc'd for $C_{20}H_{21}NNaO_2$ $[M+Na]^+$: 330.1465, found: 330.1463.



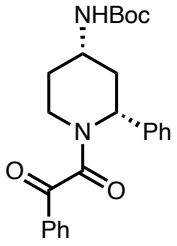
2.6b

(±)-1-Phenyl-2-(2-phenylazocan-1-yl)ethane-1,2-dione (2.6b): The title compound was prepared according to the representative procedure using **2.S7** and bromobenzene. Purification by preparative thin-layer chromatography (20% EtOAc/hexanes) provided the title compound (11.9 mg, 74%, mixture of rotamers 1.0:0.85) as a faint yellow oil.
^{1}H NMR (700 MHz, $CDCl_3$): δ 7.88 (d, *J* = 6.9 Hz, 2.0H), 7.83 (d, *J* = 6.9 Hz, 1.7H), 7.58 (t, *J* = 7.4 Hz, 0.85H), 7.55 (t, *J* = 7.4 Hz, 1.0H), 7.44–7.35 (m, 4.0+3.4H), 7.30 (t, *J* = 7.4 Hz, 0.85H), 7.22 (t, *J* = 7.4 Hz, 2.0H), 7.18 (t, *J* = 7.4 Hz, 1.0H), 7.11 (d, *J* = 7.4 Hz, 1.7H), 5.75 (d, *J* = 12.4 Hz, 0.85H), 4.74 (dd, *J* = 11.3, 3.7 Hz, 1.0H), 4.17 (ddd, *J* = 13.9, 4.9, 3.1 Hz, 1.0H), 3.51 (dt, *J* = 15.5, 4.4 Hz, 0.85H), 3.32 (ddd, *J* = 15.4, 11.0, 4.0 Hz, 0.85H), 3.14 (ddd, *J* = 13.8, 11.9, 3.8 Hz, 1.0H), 2.35–2.26 (m, 1H), 2.24–2.17 (m, 2H), 2.10–2.01 (m, 2H), 1.81–1.53 (m, 5.0+8.5H).
^{13}C NMR (176 MHz, $CDCl_3$): δ 191.5, 191.1, 168.4, 168.1, 141.8, 141.4, 134.5, 134.4, 133.5, 133.4, 130.0, 129.8, 129.0, 128.78, 128.76, 128.7, 127.6, 127.5, 126.9, 126.4, 61.4, 56.9, 42.7, 30.3, 29.8, 29.4, 28.3, 26.62, 26.58, 26.4, 26.1, 26.0, 24.4, 24.3;
HRMS (ESI): Calc'd for $C_{21}H_{23}NNaO_2$ $[M+Na]^+$: 344.1621, found: 344.1614.



2.6d

(±)-1-(2,4-Diphenylpiperidin-1-yl)-2-phenylethane-1,2-dione (2.6d): The title compound was prepared according to the representative procedure using **2.S8** and bromobenzene. Purification by preparative thin-layer chromatography (33% EtOAc/hexanes) provided the title compound (20.3 mg, 55%, mixture of rotamers 1.0:0.3) as a colorless oil.
^{1}H NMR (600 MHz, DMSO-d_6): δ 7.92 (d, J = 7.7 Hz, 2H), 7.78 (t, J = 7.4 Hz, 1H), 7.68 – 7.57 (m, 2H+0.9H), 7.45 – 7.37 (m, 2H + 2.4H + 0.3H), 7.33 – 7.26 (m, 6H), 7.22 – 7.15 (m, 2H), 7.07 (t, J = 7.6 Hz, 0.6H), 7.00 (t, J = 7.3 Hz, 0.3H), 5.37 (dd, J = 11.7, 6.8 Hz, 1H), 4.86 (dd, J = 10.4, 6.1 Hz, 0.3H), 4.23 (dt, J = 12.5, 5.9 Hz, 0.3H), 3.87 (dt, J = 14.2, 7.2 Hz, 0.3H), 3.77 (ddd, J = 14.4, 10.9, 6.7 Hz, 1H), 3.48 (dd, J = 14.5, 7.9 Hz, 1H), 3.06 – 2.95 (m, 1H + 0.3H), 2.27 – 2.21 (m, 1H + 0.3H), 2.20 – 2.12 (m, 1H + 0.6H), 2.04 (dq, J = 11.7, 8.3, 6.0 Hz, 1H), 1.82 – 1.77 (m, 0.3H), 1.64 (ddd, J = 13.1, 9.6, 6.5 Hz, 1H);
^{13}C NMR (151 MHz, DMSO-d_6): δ 191.9, 190.6, 167.3, 166.6, 145.7, 145.5, 141.9, 140.9, 135.3, 134.4, 132.7, 132.4, 129.5, 129.33, 129.25, 128.6, 128.53, 128.47, 128.2, 127.3, 127.09, 127.07, 126.99(2), 126.3, 125.5, 58.4, 55.6, 40.3, 38.3, 38.1, 37.5, 36.7, 35.8, 31.0, 30.3 (Two ^{13}C signals are overlapping with others due to amide rotation);
HRMS (ESI): Calc'd for $C_{25}H_{23}NNaO_2$ $[M+Na]^+$: 392.1621, found: 392.1622.

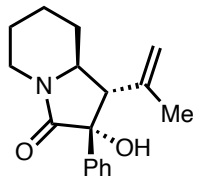


2.6e

(±)-*tert*-Butyl (1-(2-oxo-2-phenylacetyl)-2-phenylpiperidin-4-yl)carbamate (2.6e): The title compound was prepared according to the representative procedure using **2.S9a** and bromobenzene. Purification by preparative thin-layer chromatography (50% EtOAc/hexanes) provided the title compound (20.0 mg, 49%, mixture of rotamers 1:0.5) as a yellow oil.
^{1}H NMR (600 MHz, DMSO-d_6): δ 7.92 (d, J = 7.6 Hz, 2H), 7.80 (t, J = 7.6 Hz, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.68–7.64 (m, 2+0.5H), 7.51 (t, J = 7.6 Hz, 1H), 7.39 (t, J = 7.6 Hz, 2H), 7.31 (d, J = 7.6 Hz, 2H), 7.28 (t, J = 6.7 Hz, 1H), 7.25–7.14 (m, 2H), 7.12 (t, J = 6.7 Hz, 0.5H), 5.45 (t, J = 6.9 Hz, 1H), 4.74 (t, J = 5.9 Hz, 0.5H), 4.22 (d, J = 12.9 Hz, 0.5H), 3.68 (br, 1+0.5H), 3.66–3.57 (m,

1H), 3.53–3.48 (m, 0.5H), 3.35–3.29 (m, 1H), 2.47–2.45 (m, 0.5H), 2.39–2.34 (m, 1H), 2.19–2.12 (m, 1+0.5H), 2.02–1.87 (m, 2+1H), 1.35 (s, 9H), 1.32 (s, 4.5H);
^{13}C NMR (151 MHz, DMSO-d_6): δ 192.3, 191.4, 167.0, 166.7, 155.3, 141.1, 139.9, 135.8, 135.2, 133.1, 132.9, 130.0, 129.7, 129. 7, 129.5, 129.0, 128.7, 127.3, 127.2, 126.7, 125.7, 78.2, 78.1, 56.0, 52.3, 44.7, 43.9, 35.7, 33.7, 33.2, 29.7, 29.3, 28.7 (Three ^{13}C signals are overlapping with others due to amide rotation);
HRMS (ESI): Calc'd for $C_{18}H_{24}N_2NaO_4$ $[M+Na]^+$: 355.1628, found: 355.1624.

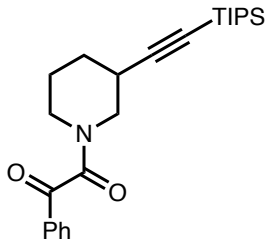
Relative stereochemistry was assigned as shown based on the observed ROE between H6 and H8 (See section: NMR spectra), which is consistent with both methine protons being on the same side.



2.8

(±)-2-Hydroxy-2-phenyl-1-(prop-1-en-2-yl)hexahydroindolizin-3(2*H*)-one (2.8): The title compound was prepared according to the representative procedure using **2.2** and 1-bromo-2-methylprop-1-ene. Purification by preparative thin-layer chromatography (33% EtOAc/hexanes) provided the title compound (9.6 mg, 35%) as a white solid.
Melting Point: 64–66 °C;
^{1}H NMR (600 MHz, DMSO-d_6): δ 7.36–7.29 (m, 4H), 7.25–7.22 (m, 1H), 5.88 (s, 1H), 4.82 (s, 1H), 4.55 (s, 1H), 3.97 (dd, J = 13.1, 4.6 Hz, 1H), 3.61 (td, J = 10.2, 9.0, 3.3 Hz, 1H), 2.72 (td, J = 13.0, 3.5 Hz, 1H), 2.49–2.47 (m, 1H), 1.95–1.87 (m,1H), 1.83 (d, J = 13.4 Hz, 1H), 1.79–1.71 (m, 1H), 1.53 (s, 3H), 1.49–1.41 (m, 1H), 1.38–1.30 (m, 1H), 1.17–1.09 (m, 1H);
^{13}C NMR (151 MHz, DMSO-d_6): δ 172.5, 143.6, 139.9, 127.9, 127.1, 126.7, 114.5, 80.4, 61.7, 56.0, 40.5, 31.4, 24.6, 23.6, 23.5;
HRMS (ESI): Calc'd for $C_{17}H_{21}NNaO_2$ $[M+Na]^+$: 294.1465, found: 294.1472.

Relative stereochemistry was assigned as described below (See Section. NMR spectra).



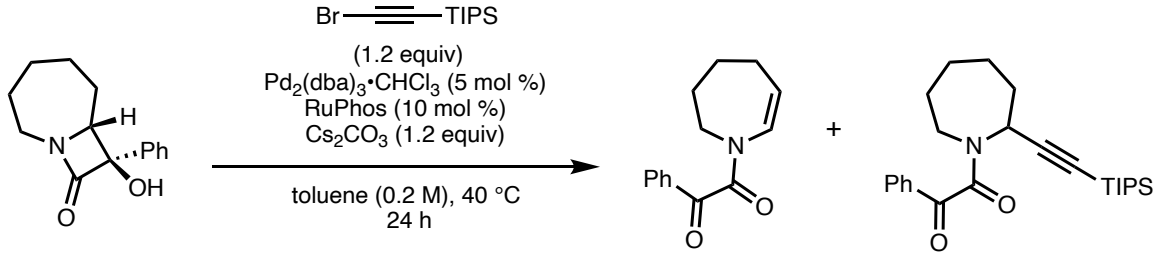
2.10

(±)-1-Phenyl-2-(2-((triisopropylsilyl)ethynyl)piperidin-1-yl)ethane-1,2-dione (2.10): The title compound was prepared according to the representative procedure using **2.2** and (bromoethynyl)triisopropylsilane. Purification by preparative thin-layer chromatography (30% EtOAc/hexanes) provided the title compound (19.1 mg, 53%, mixture of rotamers 1.0:0.7) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.96 (d, *J* = 7.4 Hz, 1.4H), 7.95 (d, *J* = 7.4 Hz, 2.0H), 7.64 (t, *J* = 7.4 Hz, 0.7H), 7.64 (d, *J* = 7.4 Hz, 2.0H), 7.51 (t, *J* = 7.4 Hz, 1.4H), 7.50 (d, *J* = 7.4 Hz, 2.0H), 4.43–4.37 (m, 1.0+0.7H), 3.62 (dd, *J* = 13.5, 4.1 Hz, 0.7H), 3.41 (dt, *J* = 13.6, 4.4 Hz, 1.0H), 3.20–3.09 (m, 2.0+0.7H), 3.00 (ddd, *J* = 13.5, 11.3, 3.1 Hz, 0.7H), 2.68 (tt, *J* = 9.1, 3.9 Hz, 1.0H), 2.56 (dt, *J* = 10.1, 5.0 Hz, 0.7H), 2.16–2.13 (m, 0.7H), 2.11–2.08 (m, 1.0H), 1.86 (dt, *J* = 13.5, 3.8 Hz, 0.7H), 1.76–1.58 (m, 2.0+1.4H), 1.52–1.46 (m, 1.0H), 1.09–1.05 (m, 3.0H), 1.07 (s, 18H), 1.00–0.97 (m, 2.1H), 0.99 (s, 12.6H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 191.6, 191.3, 165.7, 165.6, 134.9, 134.8, 133.4, 133.3, 129.9, 129.8, 129.1, 108.2, 107.9, 83.0, 82.5, 51.0, 46.5, 46.2, 41.7, 31.8, 31.3, 30.3, 29.5, 24.7, 24.1, 18.8, 18.67(2), 11.3, 11.2;

HRMS (ESI): Calc'd for $C_{24}H_{35}NNaO_2Si$ $[M+Na]^+$: 420.2329, found: 420.2323.

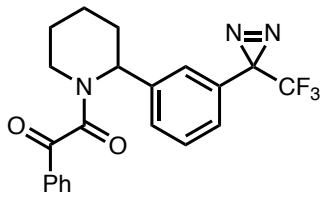


2.9 **2.11a** **2.11b**

1-Phenyl-2-(2,3,4,5-tetrahydro-1*H*-azepin-1-yl)ethane-1,2-dione (2.11a) and **(±)-1-Phenyl-2-(2-((triisopropylsilyl)ethynyl)azepan-1-yl)ethane-1,2-dione (2.11b):** The title compounds were prepared according to the representative procedure using **2.9** and (bromoethynyl)triisopropylsilane. Purification by preparative thin-layer chromatography (20% EtOAc/hexanes) provided **2.11a** (6.2 mg, 27%, mixture of rotamers 1.0:0.65) as a yellow oil, and **2.11b** (8.23 mg, 13%, mixture of rotamers 1.0:0.5) as a yellow oil.

2.11a:
^{1}H NMR (700 MHz, $CDCl_3$): δ 7.97 (d, *J* = 7.0 Hz, 1.3H), 7.92 (d, *J* = 7.0 Hz, 2H), 7.68–7.61 (m, 1.0+0.65H), 7.55–7.49 (m, 2+1.3H), 6.88 (dt, *J* = 9.0, 1.7 Hz, 0.65H), 6.28 (dt, *J* = 8.6, 1.7 Hz, 1H), 5.45 (dt, *J* = 9.0, 5.6 Hz, 0.65H), 5.22 (dt, *J* = 8.6, 5.6 Hz, 1H), 3.92 (dd, *J* = 6.2, 5.1 Hz, 2H), 3.55 (dd, *J* = 6.6, 5.1 Hz, 1.3H), 2.29–2.26 (m, 1.3H), 2.25–2.21 (m, 2H), 1.96 (quint, *J* = 6.2 Hz, 2H), 1.82–1.70 (m, 4.6H);
^{13}C NMR (176 MHz, $CDCl_3$): δ 191.6, 191.1, 166.4, 166.1, 135.0, 134.9, 133.3, 133.2, 129.9, 129.8, 129.19, 129.15, 128.8, 128.1, 122.1, 120.3, 49.4, 45.7, 28.8, 27.8, 26.8, 26.6, 25.1, 25.0;
HRMS (ESI): Calc'd for $C_{14}H_{16}NO_2$ $[M+H]^+$: 230.1176, found: 230.1179.

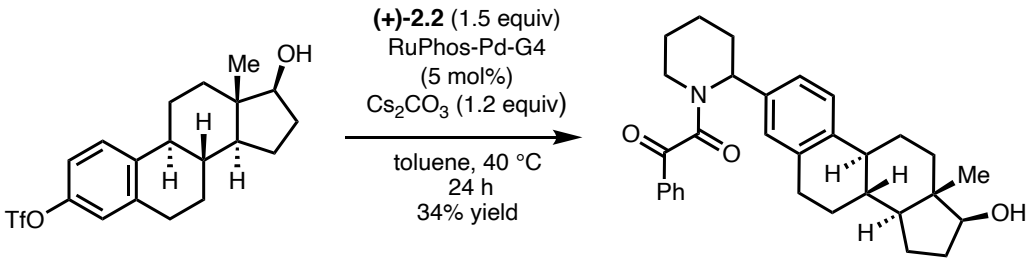
2.11b:
^{1}H NMR (700 MHz, $CDCl_3$): δ 7.97–7.94 (m, 2.0+1.0H), 7.66–7.60 (m,1.0+0.5H), 7.52–7.46 (m, 2.0+1.0H), 5.53 (dd, *J* = 8.0, 5.9 Hz, 1H), 4.47 (dd, *J* = 8.5, 6.5 Hz, 0.5H), 4.33–4.28 (m, 0.5H), 3.51–3.44 (m, 1H), 3.37 (dt, *J* = 15.1, 5.0, 1H), 3.23–3.17 (m, 0.5H), 2.29–1.44 (m, 8.0+4.0H), 1.09 (d, *J* = 2.8 Hz, 21H), 0.99 (d, *J* = 4.8 Hz, 10.5H);
^{13}C NMR (176 MHz, $CDCl_3$): δ 191.8, 191.4, 167.3, 167.2, 134.8, 134.7, 133.42, 133.36, 130.0, 129.7, 129.2, 129.0, 105.8, 105.4, 86.0, 84.9, 49.7, 45.8, 44.3, 41.3, 36.5, 34.7, 29.0, 28.9, 27.7, 27.4, 24.7, 24.2, 18.8, 18.7, 11.3, 11.2;
HRMS (ESI): Calc'd for $C_{25}H_{37}NNaO_2Si$ $[M+Na]^+$: 434.2486, found: 434.2487.



2.13

(±)-1-Phenyl-2-(2-(3-(3-(trifluoromethyl)-3H-diazirin-3-yl)phenyl)piperidin-1-yl)ethane-1,2-dione (2.13): The title compound was prepared according to the representative procedure using **2.2** and 3-(3-bromophenyl)-3-(trifluoromethyl)-3*H*-diazirine **(2.12).** Purification by preparative thin-layer chromatography (50% EtOAc/hexanes) provided the title compound (21.3 mg, 53%, mixture of rotamers 1.0:0.5) as a yellow oil.
^{1}H NMR (500 MHz, DMSO-d_6): δ 7.97 (d, *J* = 7.2 Hz, 2H), 7.92 (d, *J* = 7.4 Hz, 1H), 7.83 (t, *J* = 7.4 Hz, 1H), 7.77 (t, *J* = 7.5 Hz, 0.5H), 7.69 (t, *J* = 7.7 Hz, 2H), 7.63 (m, 2H), 7.56–7.50 (m, 2H), 7.26 (d, *J* = 7.9 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 0.5H), 7.15 (s, 1H), 7.13 (s, 0.5H), 5.81 (d, *J* = 4.8 Hz, 1H), 4.81 (s, 0.5H), 4.43 (d, *J* = 13.9 Hz, 0.5H), 3.32 – 3.26 (m, 1H), 2.96 (t, *J* = 13.6 Hz, 1H), 2.64 (td, *J* = 13.3, 2.8 Hz, 0.5H), 2.49-2.46 (m, 1H), 2.39 (d, *J* = 14.6 Hz, 0.5H), 2.00-1.95(m, 1H), 1.84-1.75 (m, 0.5H), 1.74–1.64 (m, 3.5H), 1.43–1.32 (m, 2.5H);
^{13}C NMR (151 MHz, DMSO-d_6): δ 192.3, 192.1, 166.8, 166.5, 140.3, 139.7, 135.9, 135.7, 133.0, 132.9, 130.7, 130.5, 130.0, 129.9, 129.74, 129.67, 129.3, 129.1, 128.8, 128.6, 125.9, 125.7, 125.0, 124.5, 122.39 ($^1J_{CF}$ = 274.7 Hz), 122.38 ($^1J_{CF}$ = 274.7 Hz), 56.0, 50.6, 43.2, 37.8, 28.66 ($^2J_{CF}$ = 40.1 Hz), 28.65 ($^2J_{CF}$ = 40.1 Hz), 28.6, 27.5, 25.5, 25.1, 19.7, 19.6.;
HRMS (ESI): Calc'd for $C_{21}H_{19}F_3N_3O_2$ $[M+H]^+$: 402.1424, found: 402.1442.

Procedure for Pd-Catalyzed Ring-Opening/Cross-Coupling Reaction of Estradiol-OTf (2.14)



2.14 **2.15**

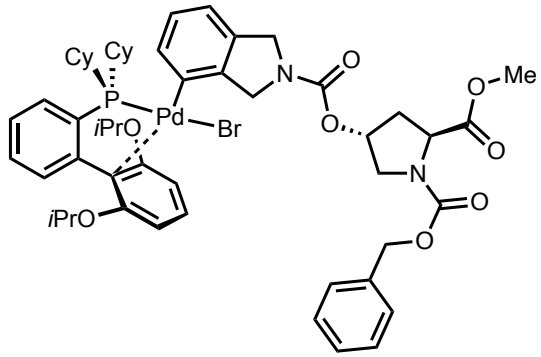
A 1-dram vial containing a stir bar, **(+)-2.2** (16.2 mg, 0.075 mmol) and **2.14**[49] (20.2 mg, 0.050 mmol) was brought into an N_2 atmosphere glovebox. To this vial was sequentially added RuPhos-Pd-G4 (4.3 mg, 0.005 mmol), Cs_2CO_3 (32.5 mg, 0.100 mmol) and toluene (0.25 mL). The vial was sealed with a Teflon cap and the resulting mixture was stirred at 40 °C for 48 h. After cooling to room temperature, the mixture was filtered through Celite® using EtOAc as the eluent. After concentration to dryness, the crude residue was purified by preparative thin-layer chromatography (50% EtOAc/hexanes) to provide **2.15** (8.0 mg, 34%, mixture of rotamers 1:0.75) as a white amorphous solid.

^{1}H NMR (700 MHz, $CDCl_3$): δ 8.07 (d, *J* = 7.7 Hz, 2H), 8.01 (d, *J* = 7.7 Hz, 1.5H), 7.70 (t, *J* = 7.7 Hz, 1 H), 7.65 (t, *J* = 7.7 Hz, 0.75H), 7.58 (t, *J* = 7.7 Hz, 2H), 7.53 (t, *J* = 7.7 Hz, 1.5H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.26 (s, 0.75H), 7.17 (d, *J* = 8.3 Hz, 1H), 7.10 (s, 1.75H), 7.06 (s, 0.75H), 6.01 (s, 1H), 4.83 (s, 0.75H), 4.62 (d, *J* = 13.3 Hz, 0.75H), 3.42 (d, *J* = 13.9 Hz, 1H), 3.15 (dt, *J* = 14.9, 8.0 Hz, 1H), 2.96–2.94 (m, 1.75H), 2.90–2.88 (m, 1.5H), 2.84 (t, *J* = 12.5Hz, 1H), 2.54–2.50 (m, 3H), 2.45–2.21 (m, 5.5H), 2.18–2.12 (m, 2H), 2.09–1.95 (m, 7.75H), 1.87 (t, *J* = 13.7 Hz, 1H), 1.74–1.40 (m, 17.5H), 0.96 (s, 3H), 0.93 (s, 2.25H);

^{13}C NMR (176 MHz, $CDCl_3$): δ 192.0, 191.6, 166.74, 166.71, 139.1, 138.7, 137.20, 137.18, 135.5, 134.9, 134.9, 134.8, 133.5, 133.4, 129.80, 129.77, 129.2, 129.1, 127.53, 127.51, 126.03, 125.99, 124.3, 124.1, 56.2, 50.7, 50.6, 50.4, 48.2, 48.1, 44.5, 44.4, 43.2, 38.3, 38.2, 37.9, 36.02, 36.00, 31.8, 31.7, 29.9, 29.8, 29.7, 28.5, 27.4, 26.7, 26.6, 26.3, 25.9, 25.8, 25.74, 25.66, 21.8, 21.7, 19.9, 14.02, 13.98 (One ^{13}C signal is overlapping with others due to amide rotation);

HRMS (ESI): Calc'd for $C_{31}H_{37}NNaO_3$ $[M+Na]^+$: 494.2666, found: 494.2661.

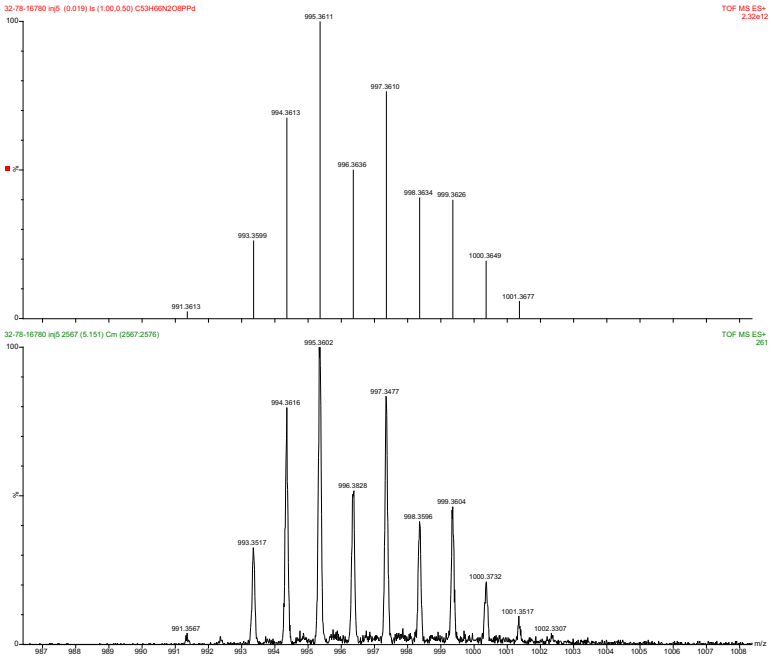
Procedure for synthesis of oxidative addition complex (2.S10)

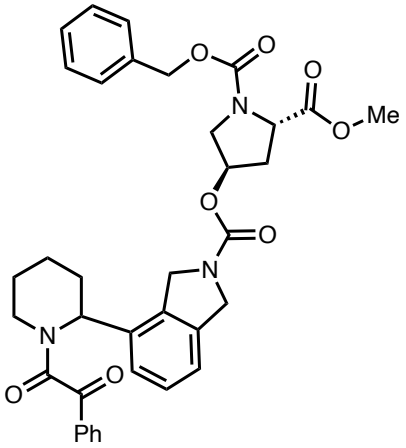


2.S10

According to a modified literature procedure[50], a scintillation vial containing a stir bar, 1-benzyl-2-methyl (2*S*,4*R*)-4-((4-bromoisoindoline-2-carbonyl)oxy)pyrrolidine-1,2-dicarboxylate (343 mg, 0.74 mmol), (1,5-cyclooctadiene)bis(trimethylsilylmethyl)palladium(II) (286 mg, 0.74 mmol), and RuPhos (343 mg, 0.74 mmol) was brought into an N_2 atmosphere glovebox. To this vial was added THF (6.2 mL). The resulting mixture was stirred at rt for 4 h. The mixture was removed from the glovebox and poured into pentanes (50 mL) to precipitate the palladium oxidative addition complex. The solid was isolated by vacuum filtration and washed with additional pentanes to afford an off-white solid (**3.16**, 480 mg, 61%), which was used in the next step without further purification.

HRMS (ESI) *m/z* calc'd for $C_{53}H_{66}N_2O_8PPd$ $[M–Br]^+$: 995.3602, found: 995.3611.

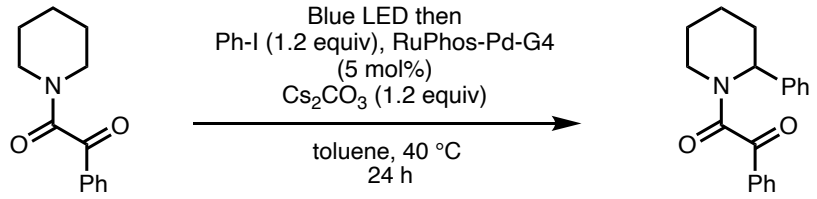




2.S11

1-Benzyl 2-methyl (2*S*,4*R*)-4-((4-(1-(2-oxo-2-phenylacetyl)piperidin-2-yl)isoindoline-2-carbonyl)oxy)pyrrolidine-1,2-dicarboxylate (2.S11): A microwave vial containing a stir bar, **2.2** (8.7 mg, 0.040 mmol), palladium oxidative addition complex **2.S10** (43.1 mg, 0.040 mmol), and Cs_2CO_3 (19.6 mg, 0.06 mmol) was sealed and placed under an N_2 atmosphere. To the vial was added toluene (400 µl). The resulting solution was stirred at rt overnight, filtered through a plug of celite, and washed with CH_2Cl_2. After concentration to dryness, the crude residue was dissolved in 1:1 DMSO/MeCN, filtered, and purified by reversed-phase chromatography (5–95% mecn/H_2O with 0.1% TFA) to provide **2.S11** (6.1 mg, 20%, trifluoroacetic acid salt, mixture of diastereomers, mixture of rotamers) as an off-white solid.
^{1}H NMR (600 MHz, DMSO-d_6) δ 8.00 – 7.87 (m, 2H), 7.84 – 7.75 (m, 1H), 7.73 – 7.56 (m, 2H), 7.46 – 7.21 (m, 9H), 5.64 (m, 1H), 5.31 – 5.03 (m, 3H), 4.84 – 4.56 (m, 3H), 4.52 – 4.26 (m, 1H), 3.67 (d, J = 5.4 Hz, 3H), 3.57 (s, 1H), 3.40 – 3.27 (m, 1H), 3.24 – 3.10 (m, 1H), 2.48 – 2.44 (m, 3H), 2.32 – 2.17 (m, 2H), 2.00 (d, J = 12.2 Hz, 1H), 1.78 – 1.66 (m, 2H), 1.61 (s, 1H) (*Reported resonances are only representative of the apparent spectral peaks*);
^{13}C NMR (151 MHz, DMSO) δ 192.10, 191.98, 172.56, 166.38, 154.58, 154.08, 153.84, 138.43, 137.15, 136.97, 135.72, 135.46, 135.19, 134.99, 133.35, 133.15, 133.08, 129.97, 129.89, 129.84, 129.74, 129.05, 128.86, 128.83, 128.76, 128.72, 128.57, 128.35, 128.29, 128.25, 127.87, 127.81, 127.79, 127.74, 127.61, 122.49, 122.35, 118.56, 73.72, 73.01, 66.89, 66.75, 58.14, 57.72, 52.58, 52.47, 52.27, 51.95, 51.52, 50.72, 43.25, 36.78, 35.74, 27.50, 25.36, 19.42, 1.62 (*Reported resonances are only representative of the apparent spectral peaks*).
HRMS (ESI) *m/z* calc'd for $C_{36}H_{38}N_3O_8$ $[M+H]^+$: 640.2653, found: 640.2637.

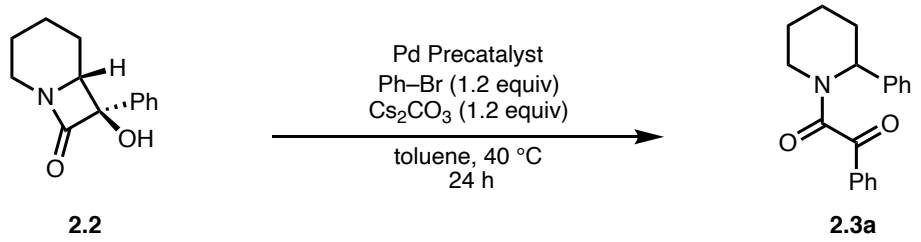
Procedure for one pot arylation



2.1 **2.3a**

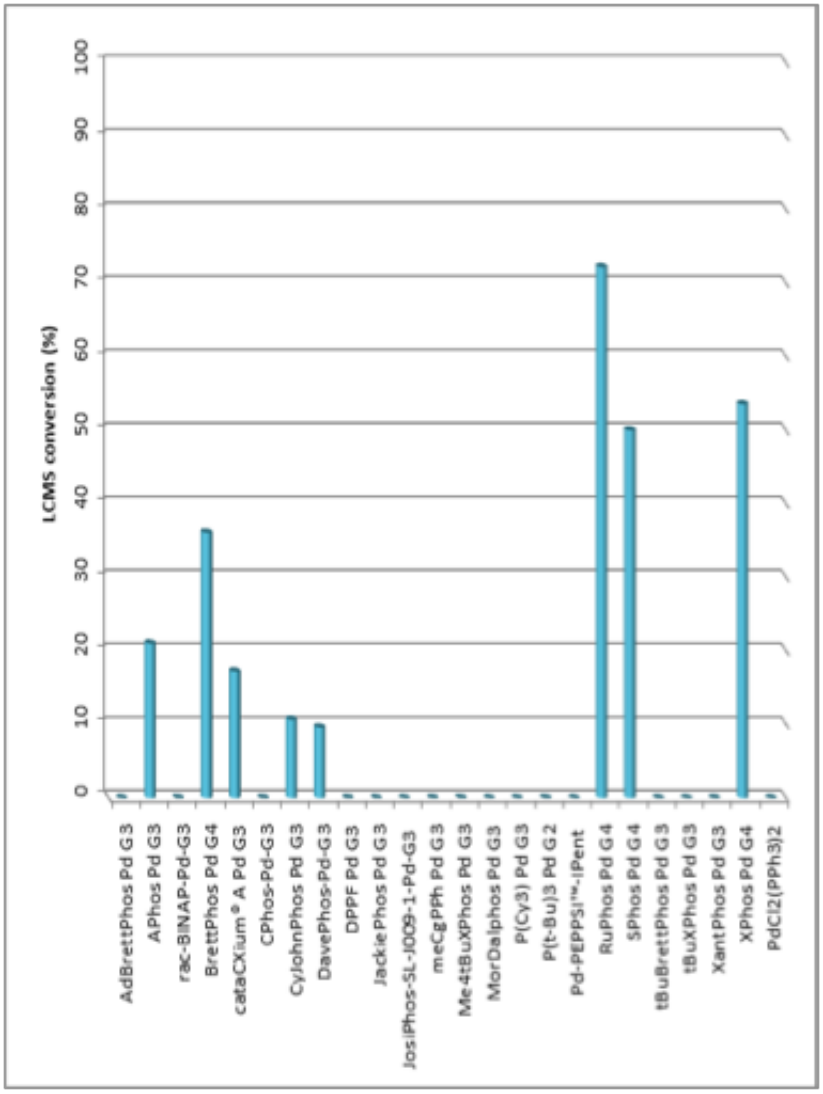
A 1-dram vial charged with **2.1** (21.7 mg, 0.100 mmol) and Et_2O (2.0 mL) was allowed to evaporate. After evaporation, the vial was backfilled with nitrogen and irradiated using a 40 W blue LED placed 3 cm away from the vial. After 16 h, the vial was removed from the light. A stir bar and Iodobenzene (24.4 mg, 0.120 mmol) were added. The vial was brought into an N_2 atmosphere glovebox. To this vial was sequentially added RuPhos-Pd-G4 (4.3 mg, 0.005 mmol), Cs_2CO_3 (39.0 mg, 0.120 mmol) and toluene (0.5 mL). The vial was sealed with a Teflon cap and the resulting mixture was stirred at 40 °C for 24 h. After cooling to room temperature, the mixture was filtered through Celite® using EtOAc as the eluent. After concentration to dryness, the crude residue was purified by preparative thin-layer chromatography (33% EtOAc/hexanes) to provide **2.3a** (13.5 mg, 46%).

2.4.5. Representative Procedure for HTE Screen



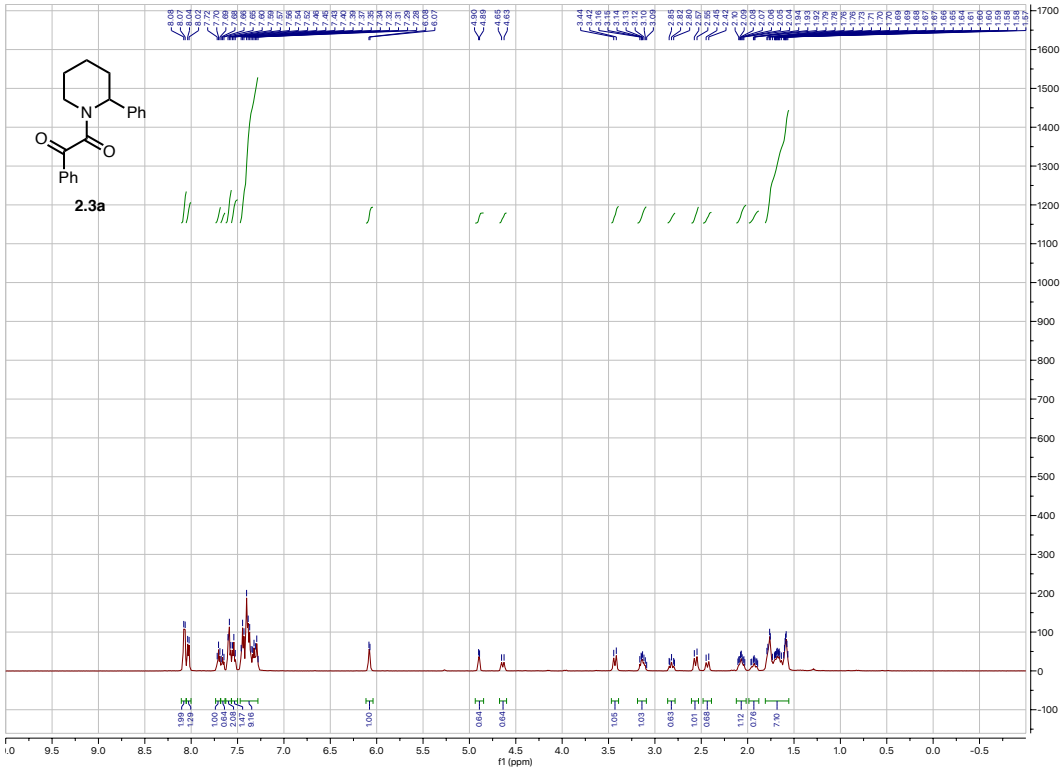
2.2 **2.3a**

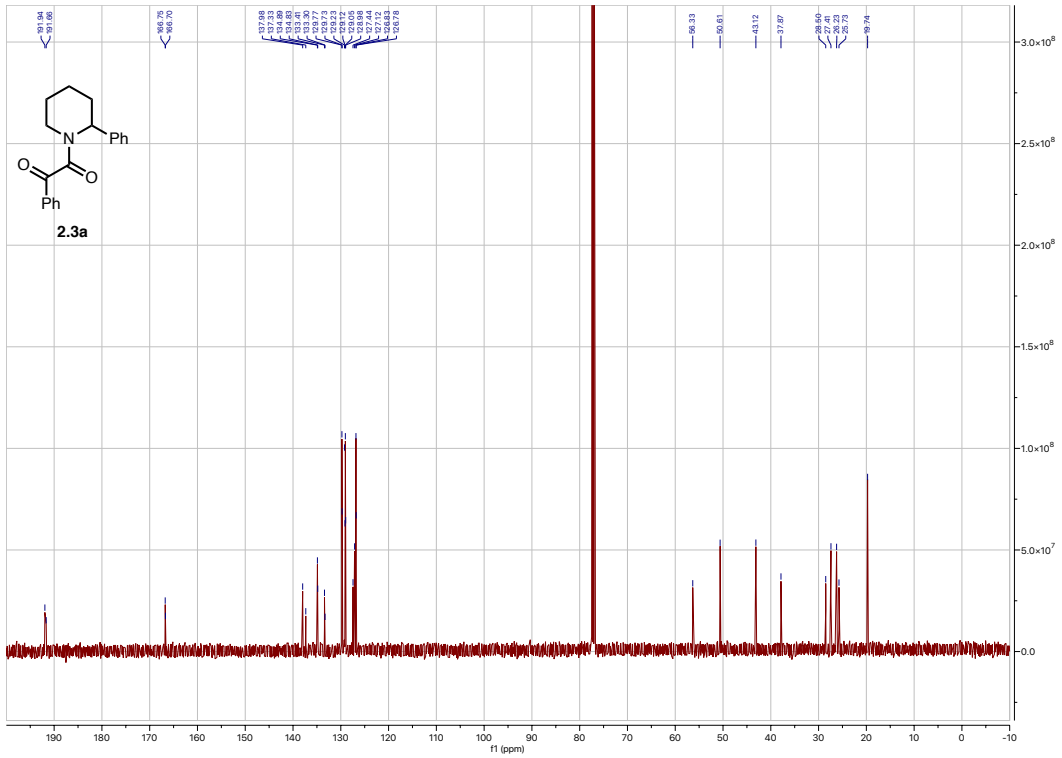
A 1-dram vial containing a stir bar, **2.2** (2.2 mg per reaction, 0.01 mmol per reaction, 25% overage), and Cs_2CO_3 (3.9 mg per reaction, 0.012 mmol per reaction, 25% overage) was sealed with a Teflon cap and placed under an N_2 atmosphere. To the vial was added toluene (100 µL per reaction, 25% overage), and the resulting suspension was vigorously stirred for 5–10 min until a milky suspension was formed. In a benchtop inertion box, to each reaction well of a KitAlysis High-Throughput 24 Pd Precatalyst Reaction Screening Kit (Aldrich) was added 100 µL of the suspension. The reaction block was sealed, and the kit was stirred (tumble stirrer) at 40 ºC for 24 h. After cooling to rt, each reaction vial was analyzed by LCMS.

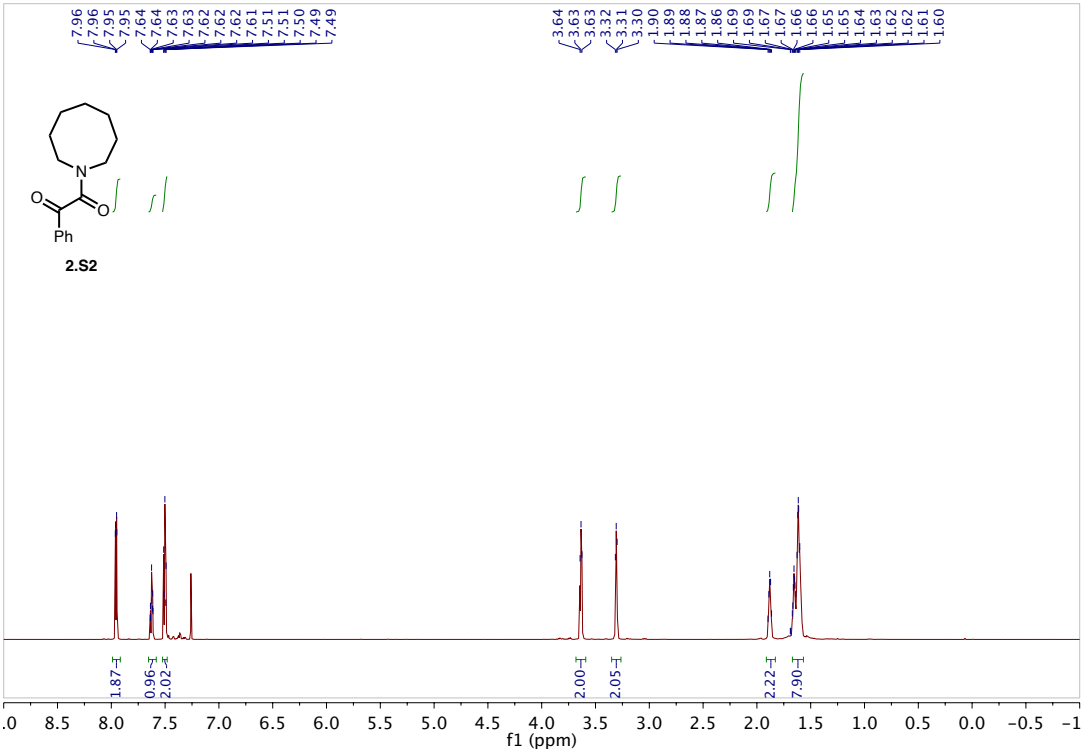


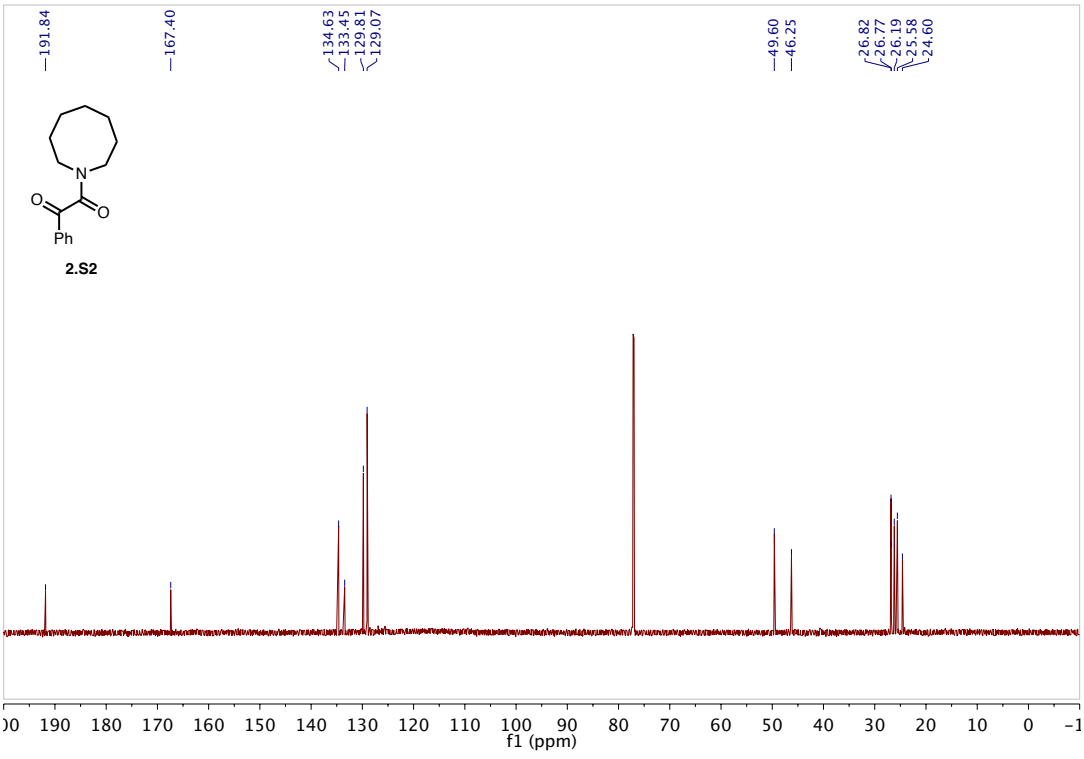
Summary of HTE Screen

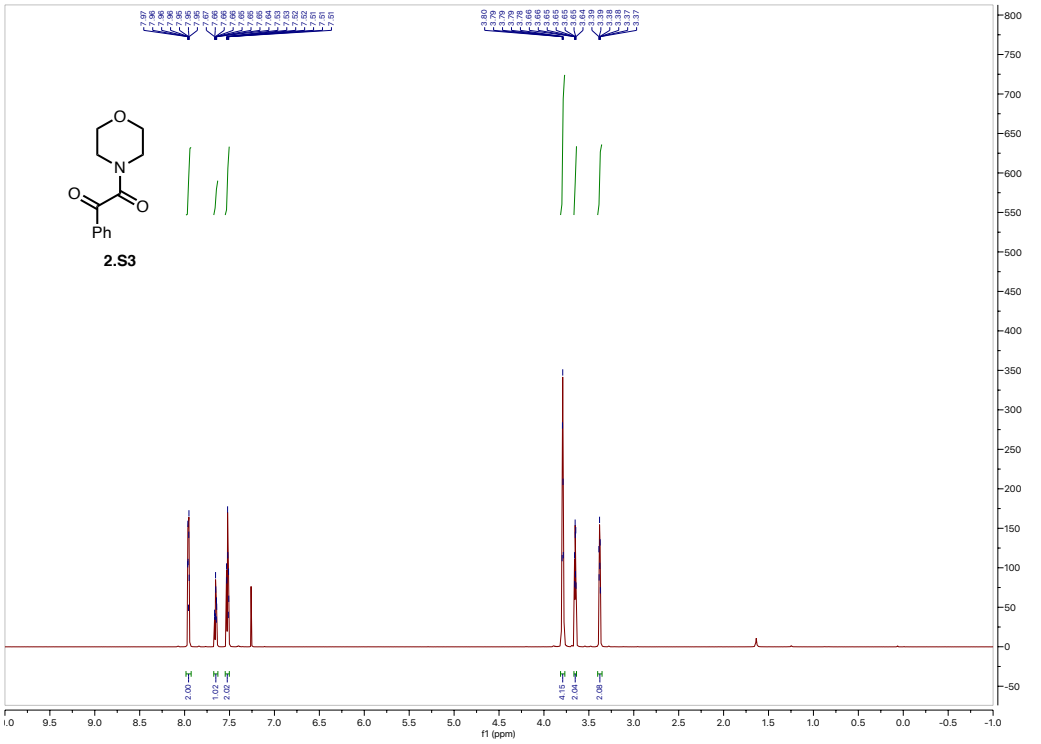
2.4.6. Spectral Data

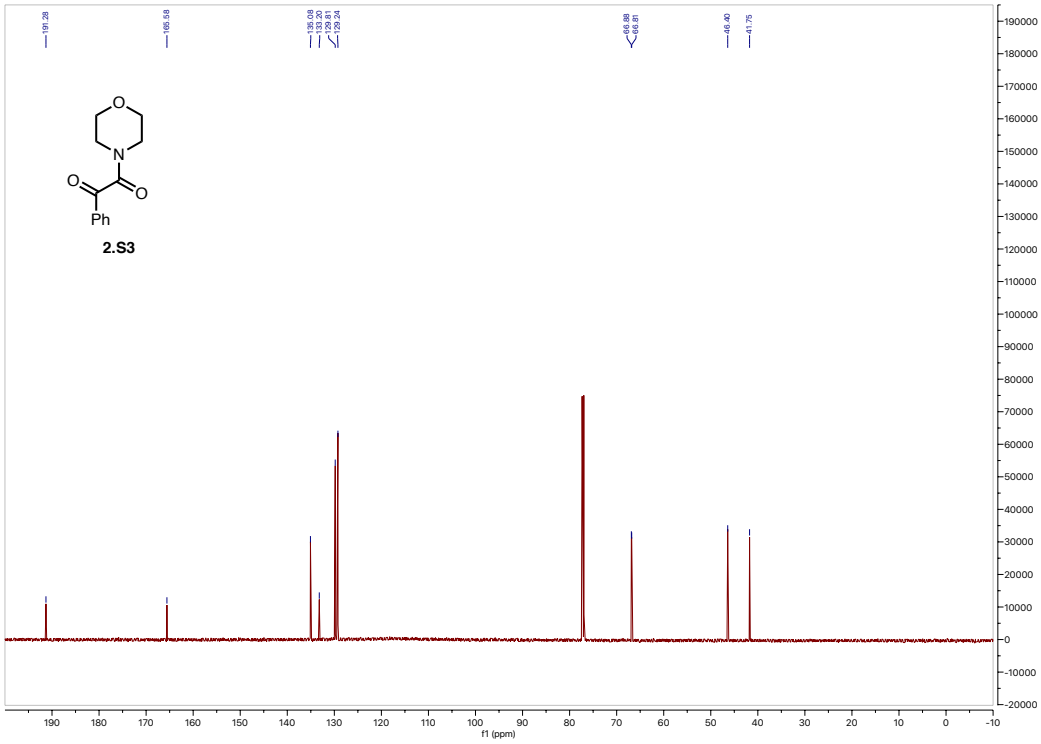


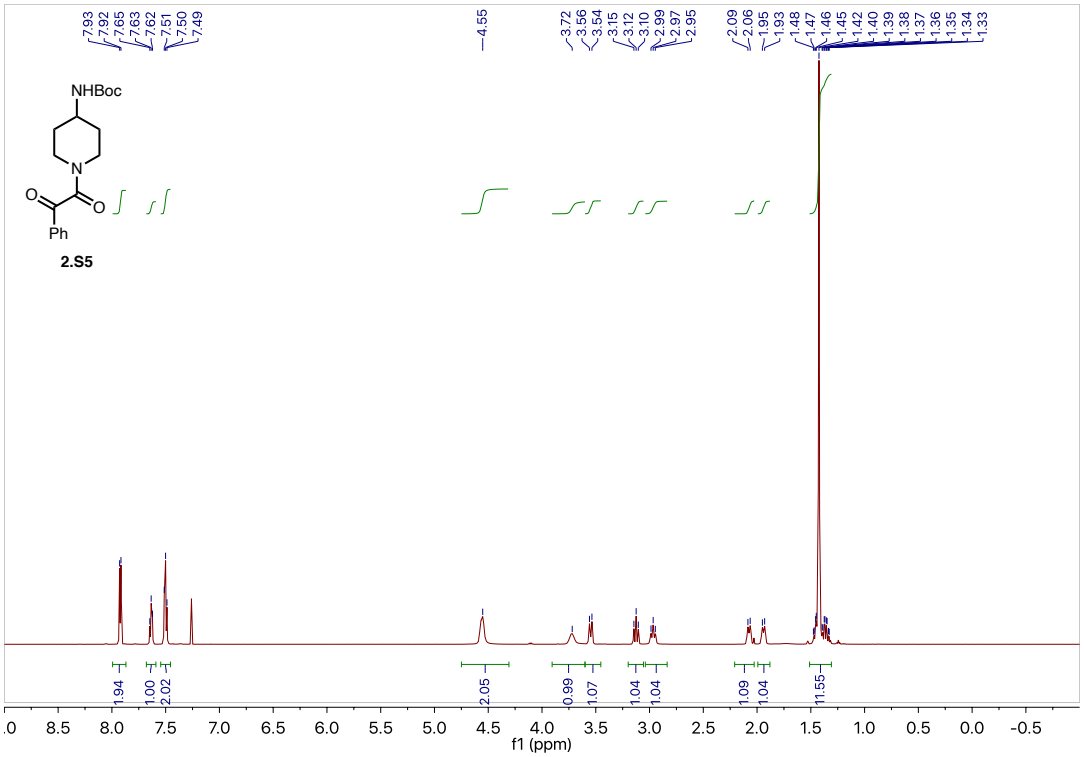


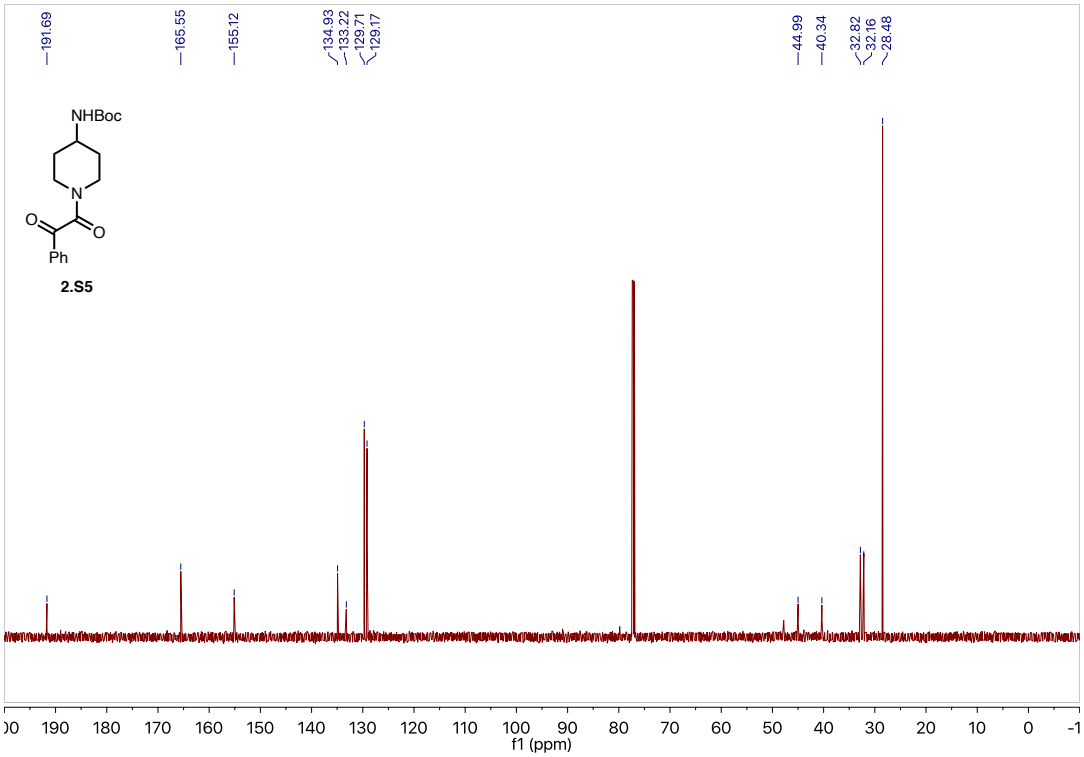

7.96
7.96
7.95
7.95
7.64
7.64
7.63
7.63
7.62
7.62
7.62
7.61
7.51
7.51
7.50
7.49
7.49
3.64
3.63
3.63
3.32
3.31
3.30
1.90
1.89
1.88
1.87
1.86
1.69
1.69
1.67
1.67
1.66
1.66
1.65
1.65
1.64
1.63
1.62
1.62
1.61
1.60
N
O
O
Ph
2.S2
1.87
0.96
2.02
2.00
2.05
2.22
7.90
f1 (ppm)

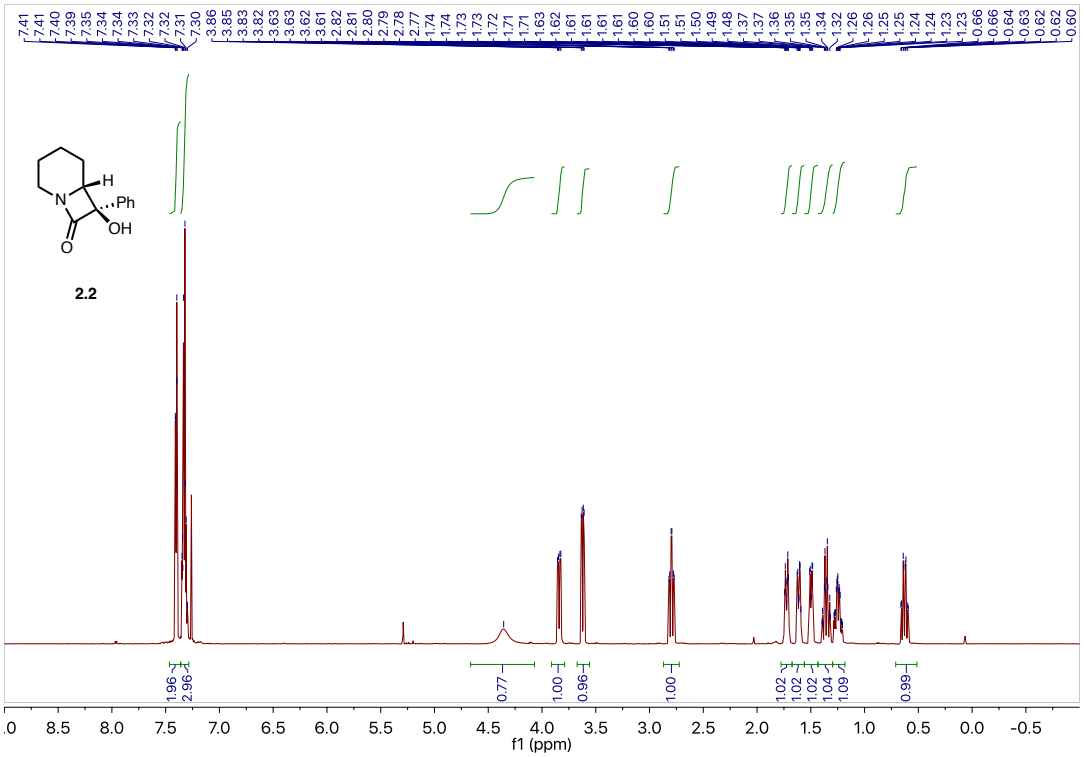

191.84
167.40
134.63
133.45
129.81
129.07
49.60
46.25
26.82
26.77
26.19
25.58
24.60
N
O
O
Ph
2.S2
f1 (ppm)

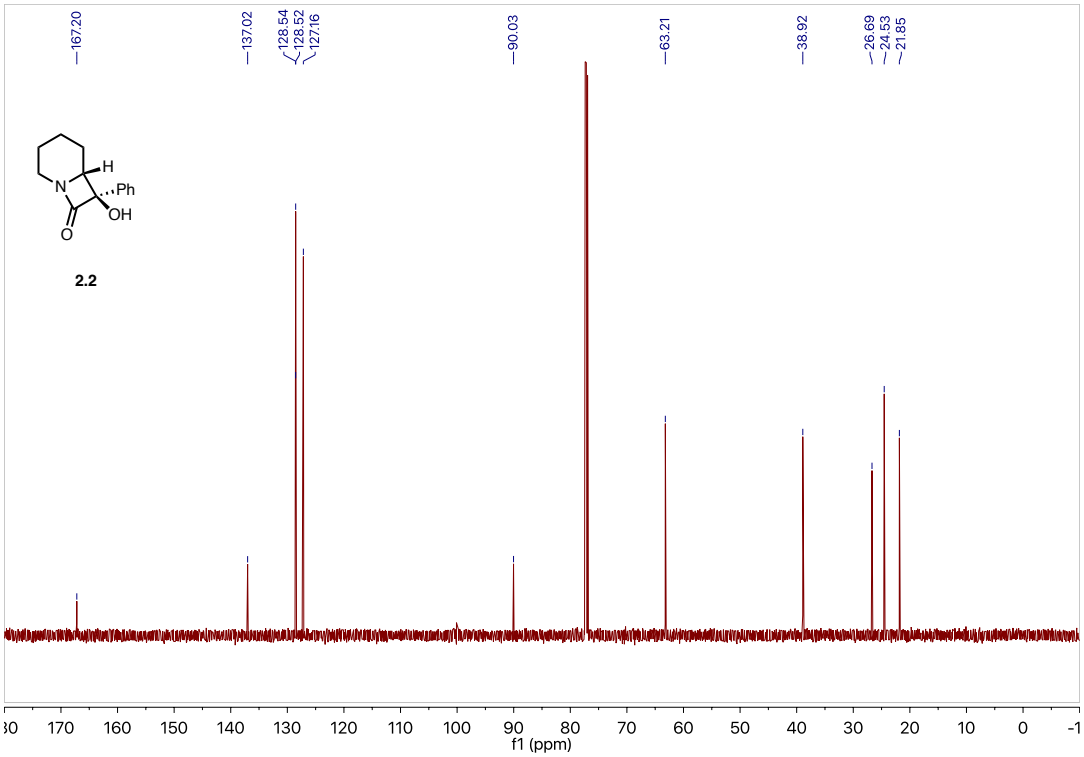

2.S3
f1 (ppm)

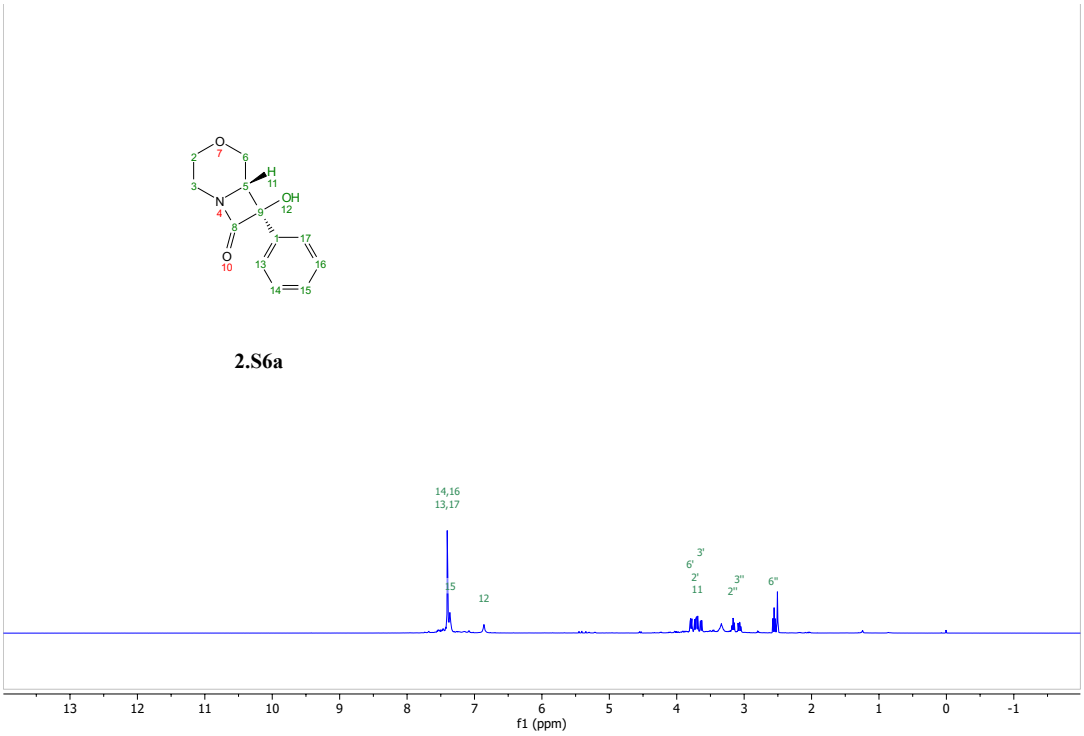

2.S3
f1 (ppm)


7.93
7.92
7.65
7.63
7.62
7.51
7.50
7.49
4.55
3.72
3.56
3.54
3.15
3.12
3.10
2.99
2.97
2.95
2.09
2.06
1.95
1.93
1.48
1.47
1.46
1.45
1.42
1.40
1.39
1.38
1.37
1.36
1.35
1.34
1.33
NHBoc
N
O
O
Ph
2.S5
1.94
1.00
2.02
2.05
0.99
1.07
1.04
1.04
1.09
1.04
11.55
f1 (ppm)

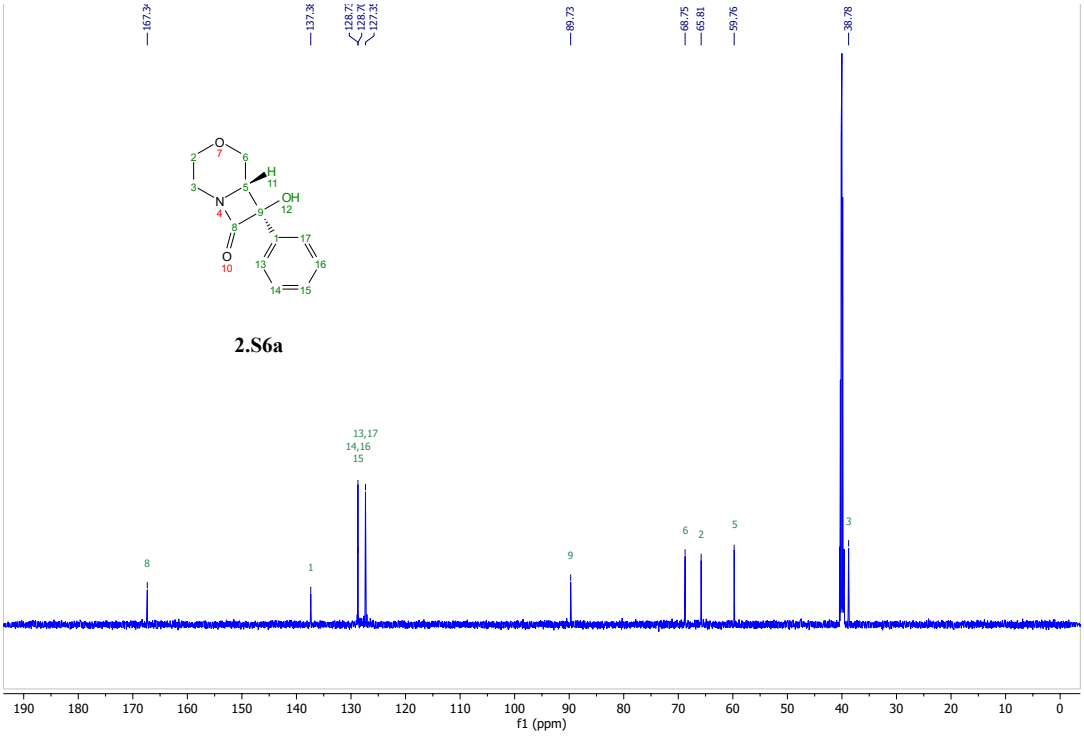

191.69
165.55
155.12
134.93
133.22
129.71
129.17
44.99
40.34
32.82
32.16
28.48
NHBoc
N
O
O
Ph
2.S5
f1 (ppm)


H
N
Ph
OH
O
2.2
f1 (ppm)


167.20
137.02
128.54
128.52
127.16
90.03
63.21
38.92
26.69
24.53
21.85
H
N
Ph
OH
O
2.2
f1 (ppm)

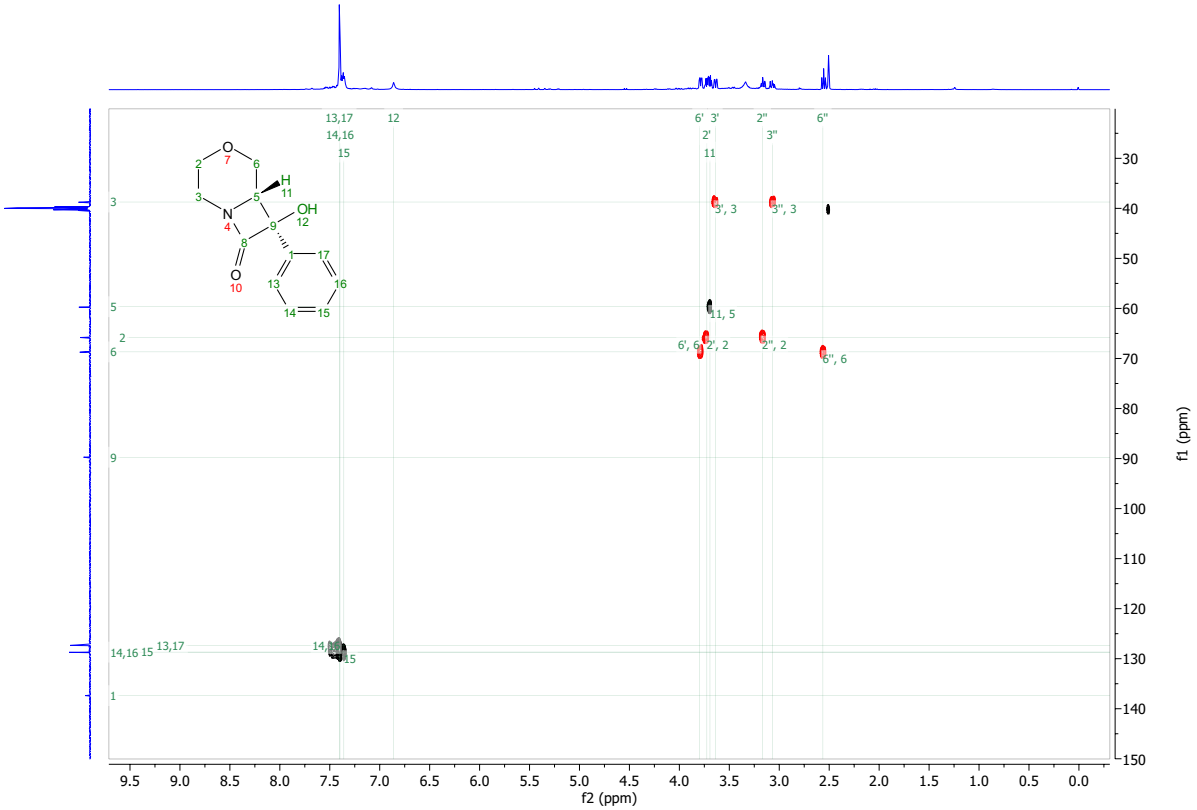

14,16
13,17
15
12
3'
6'
2'
11
3''
2''
6''
f1 (ppm)

2.S6a

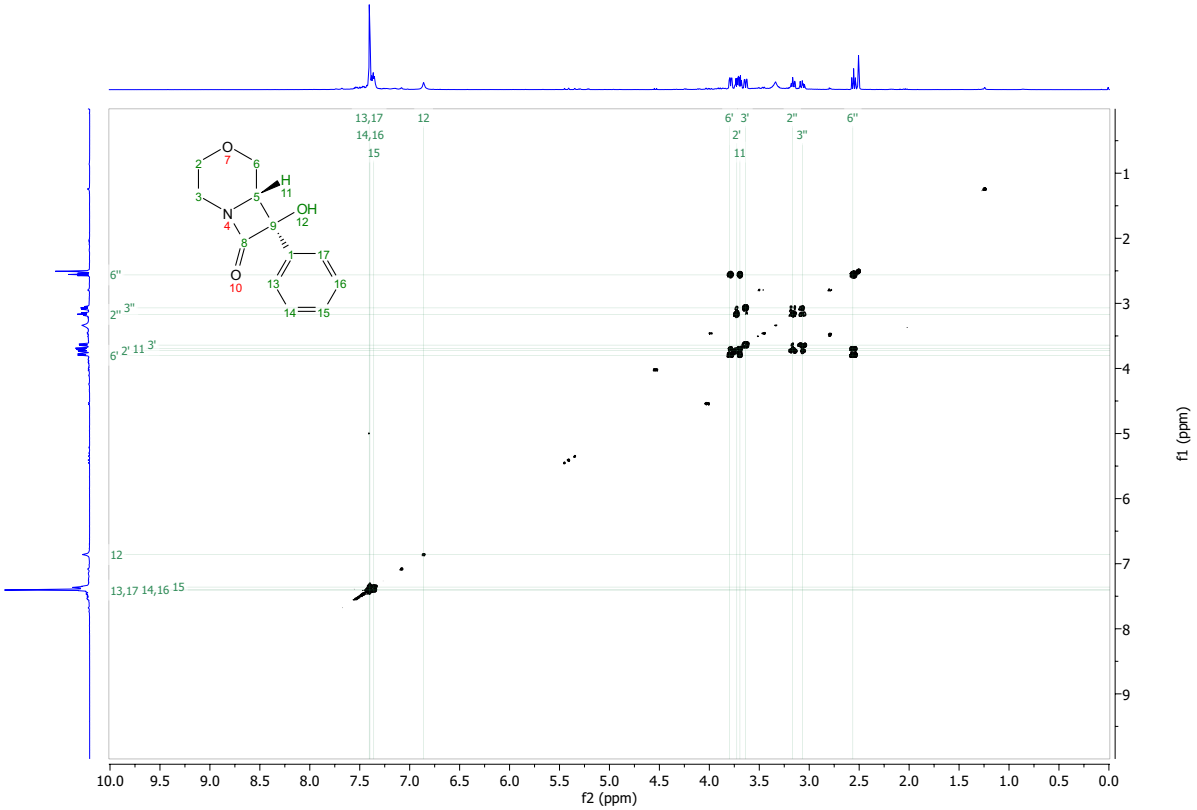

167.34
137.38
128.77
128.74
127.31
89.73
68.75
65.81
59.76
38.78
13,17
14,16
15
8
1
9
6
2
5
3
f1 (ppm)

2.S6a

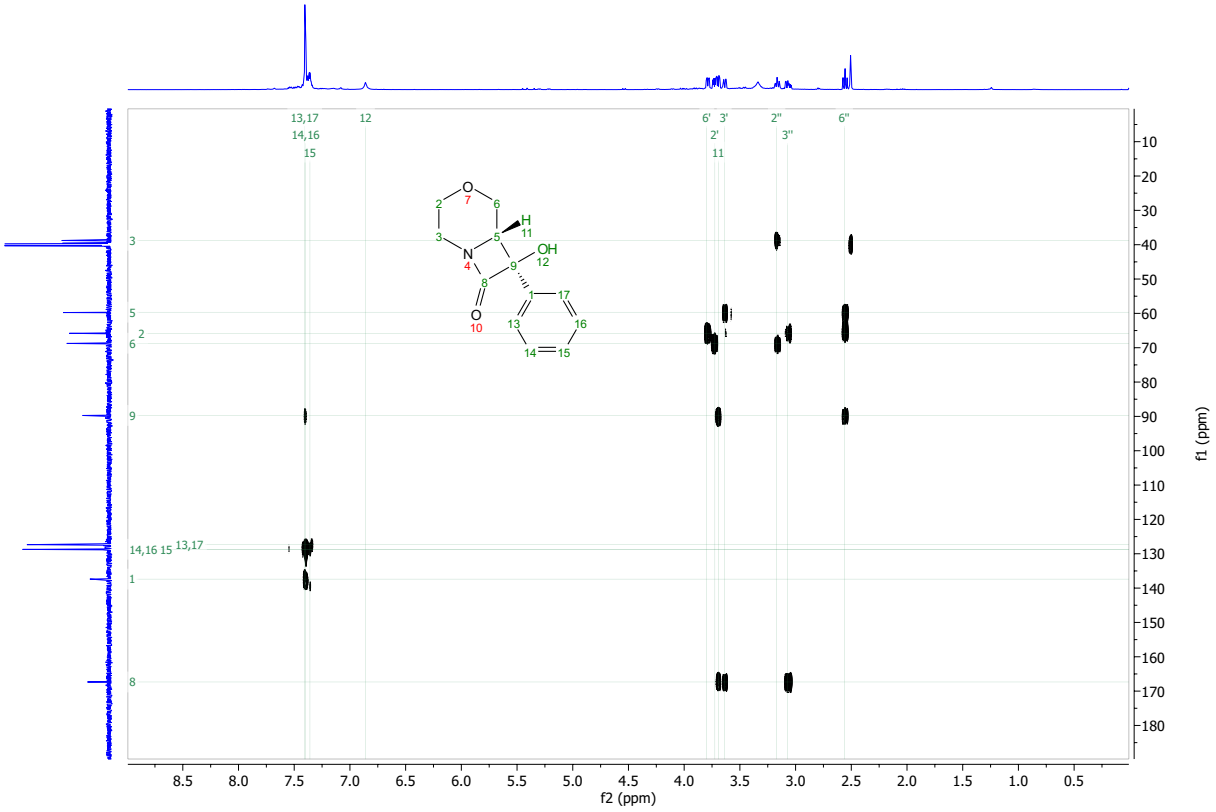
HSQC


f2 (ppm)
f1 (ppm)
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
30 40 50 60 70 80 90 100 110 120 130 140 150
13,17
14,16
15
12
6' 3'
2'
11
2"
3"
6"
3', 3
3", 3
11, 5
6', 6
2', 2
2", 2
6", 6
14,16 15 13,17
O
H
OH
N
O

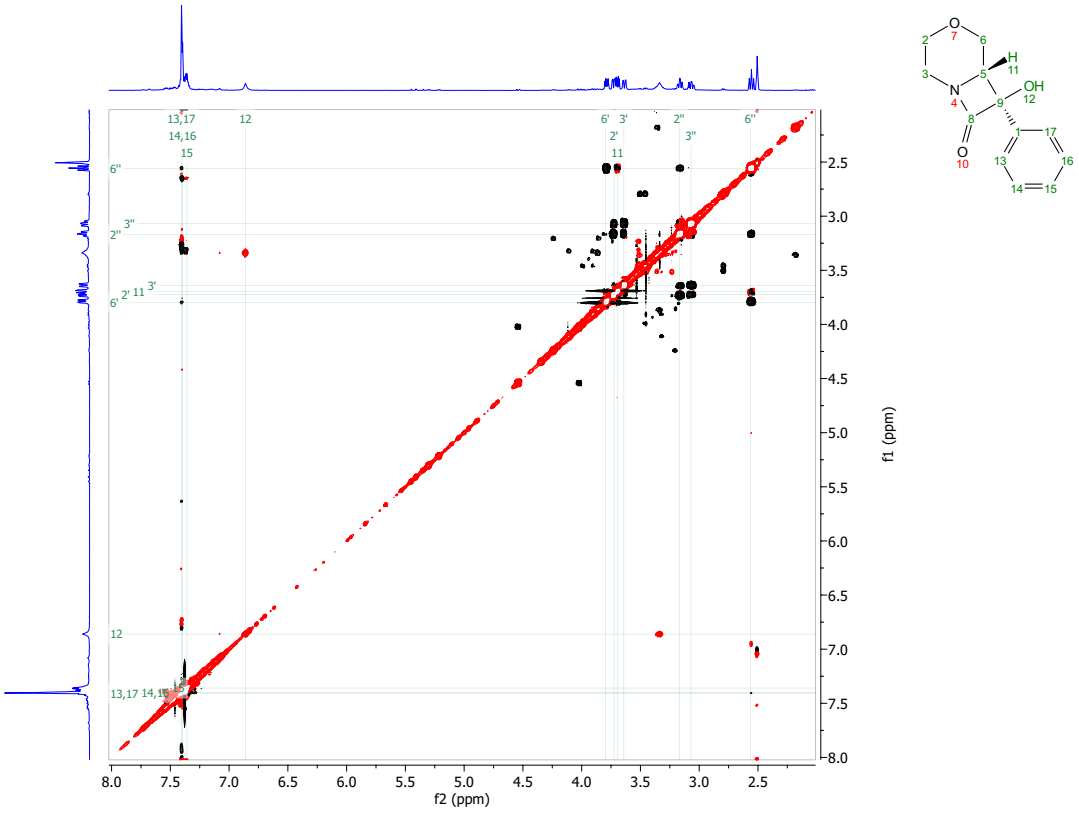
COSY

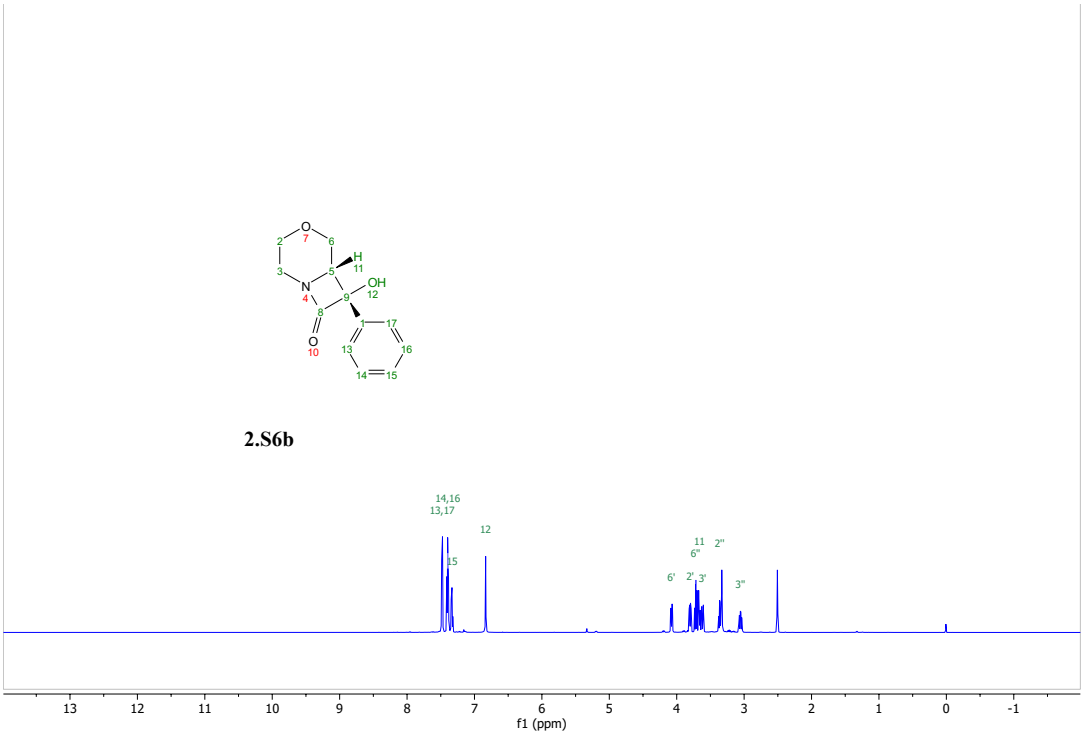

13,17
14,16
15
12
6' 3'
2'
11
2"
3"
6"
6"
2" 3"
6' 2' 11 3'
12
13,17 14,16 15
f2 (ppm)
f1 (ppm)

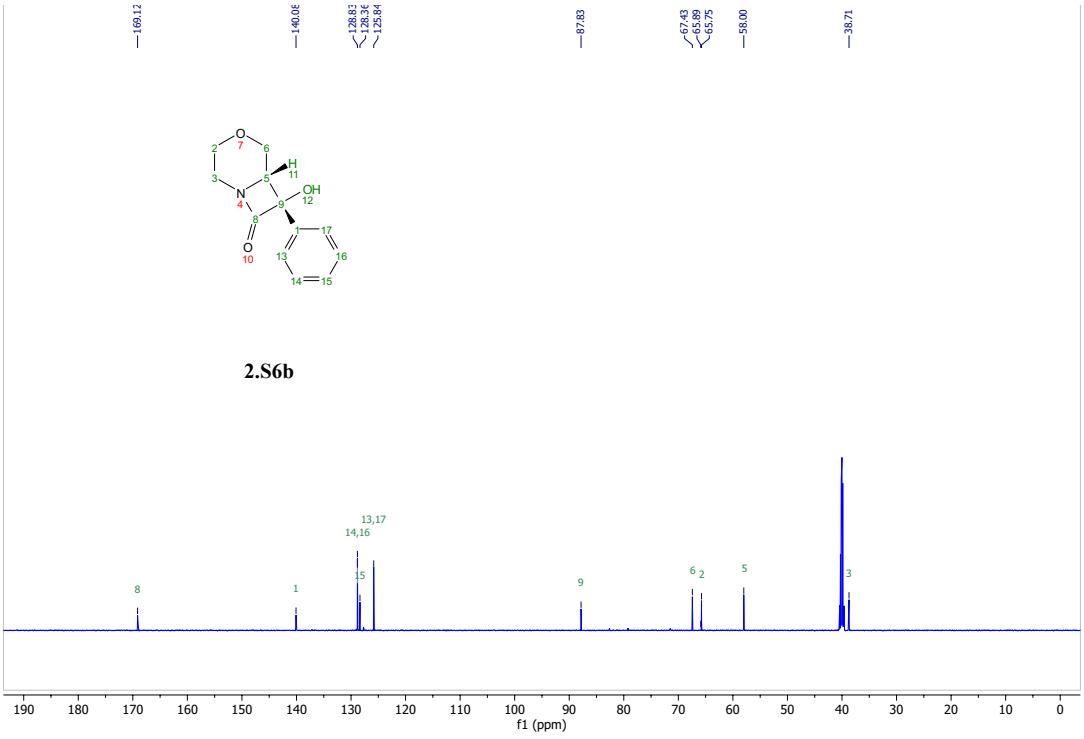
HMBC



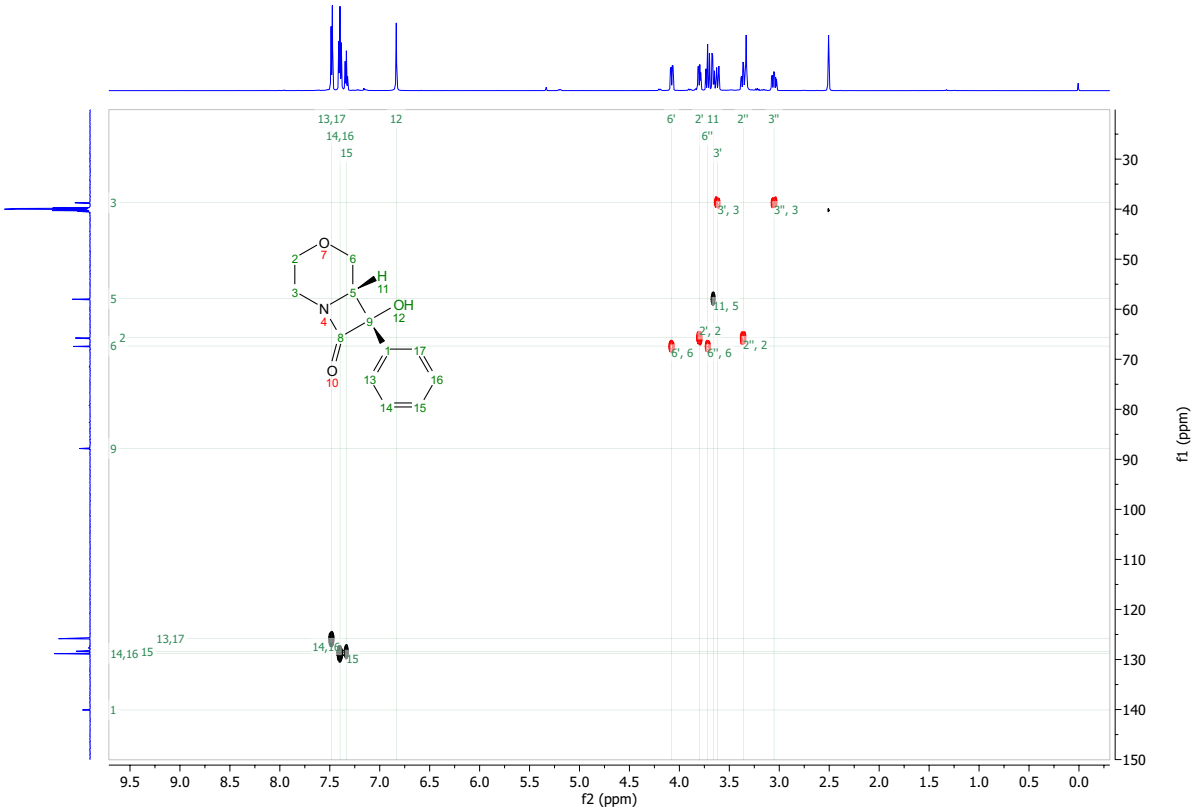
ROESY


13,17
14,16
15
12
6'
3'
2"
6"
2'
11
3"
f2 (ppm)
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5

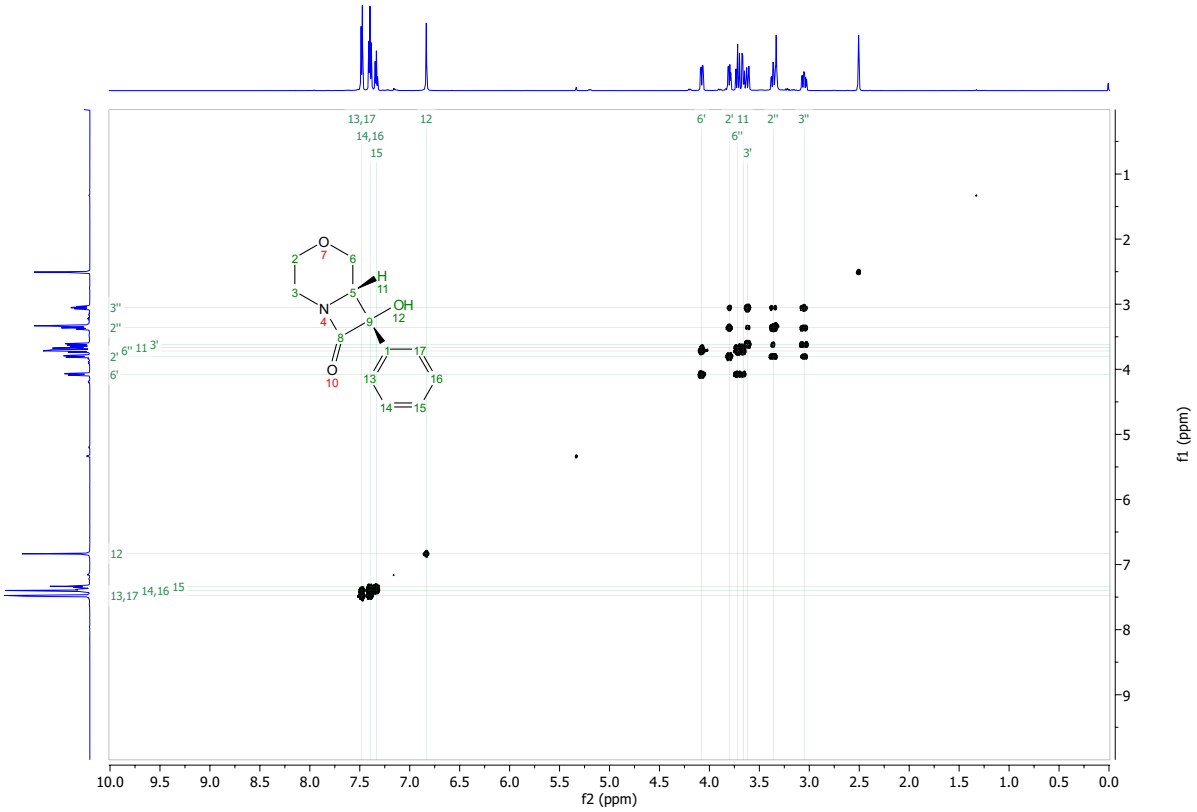

2.S6b
14,16
13,17
12
15
11
6''
2''
6'
2'
3'
3'''
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
f1 (ppm)


169.12
140.08
128.83
128.36
125.84
87.83
67.43
65.89
65.75
58.00
38.71
2.S6b
13,17
14,16
8
1
15
9
6
2
5
3
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

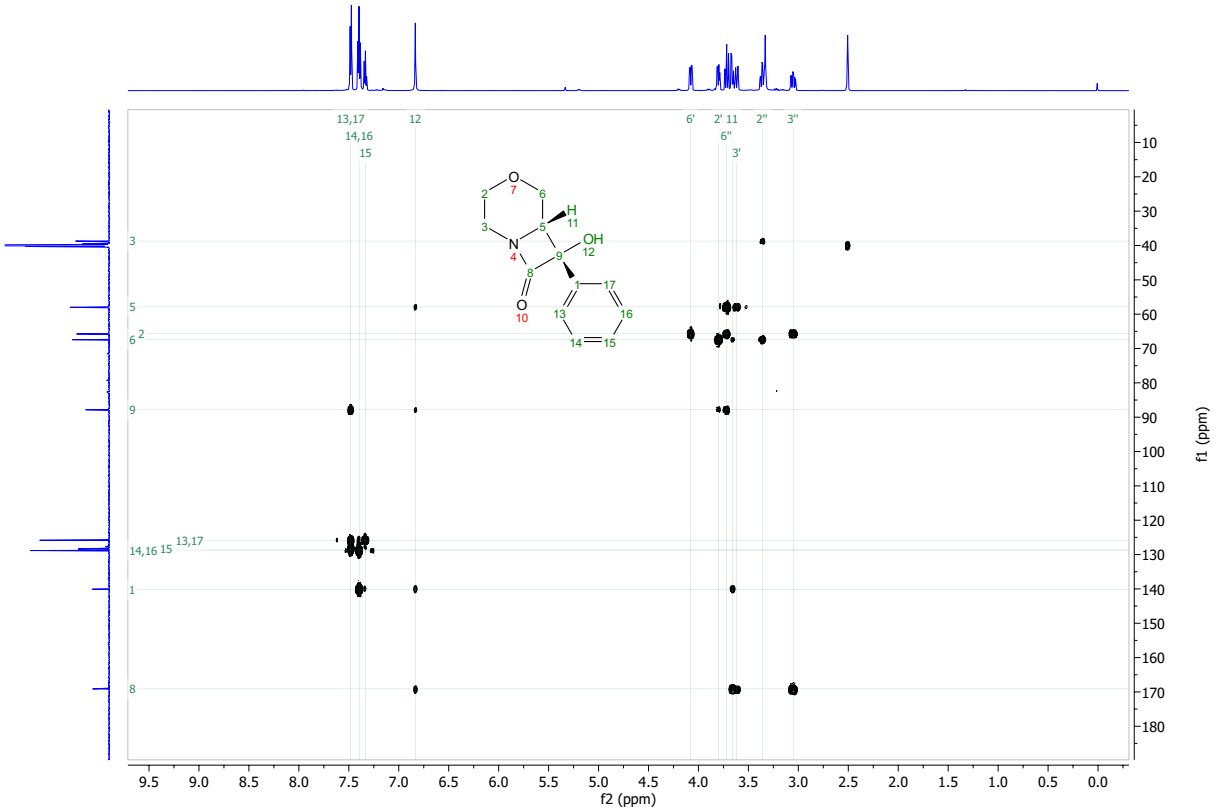
HSQC


f2 (ppm)
f1 (ppm)
13,17
14,16
15
12
6'
2' 11
2"
3"
6"
3'
3', 3
3", 3
11, 5
2', 2
6', 6
6", 6
2", 2
O
H
OH
N
13,17
14,16 15

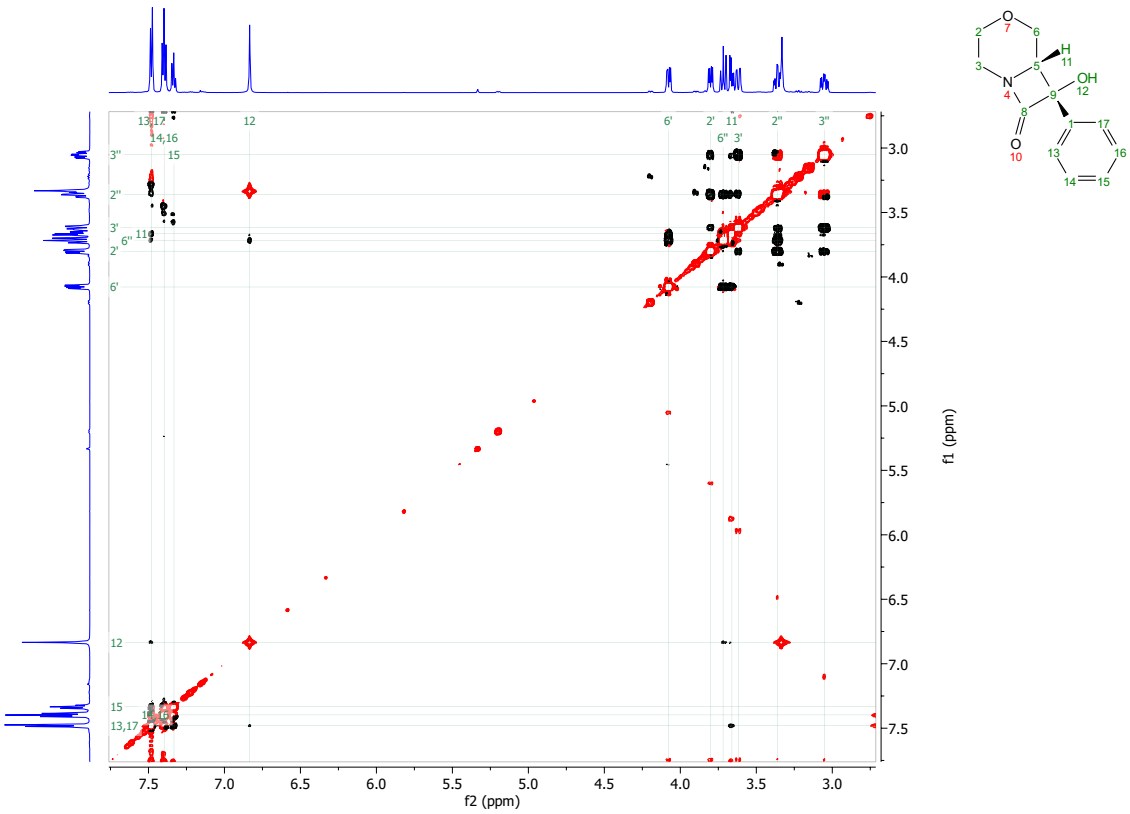
COSY

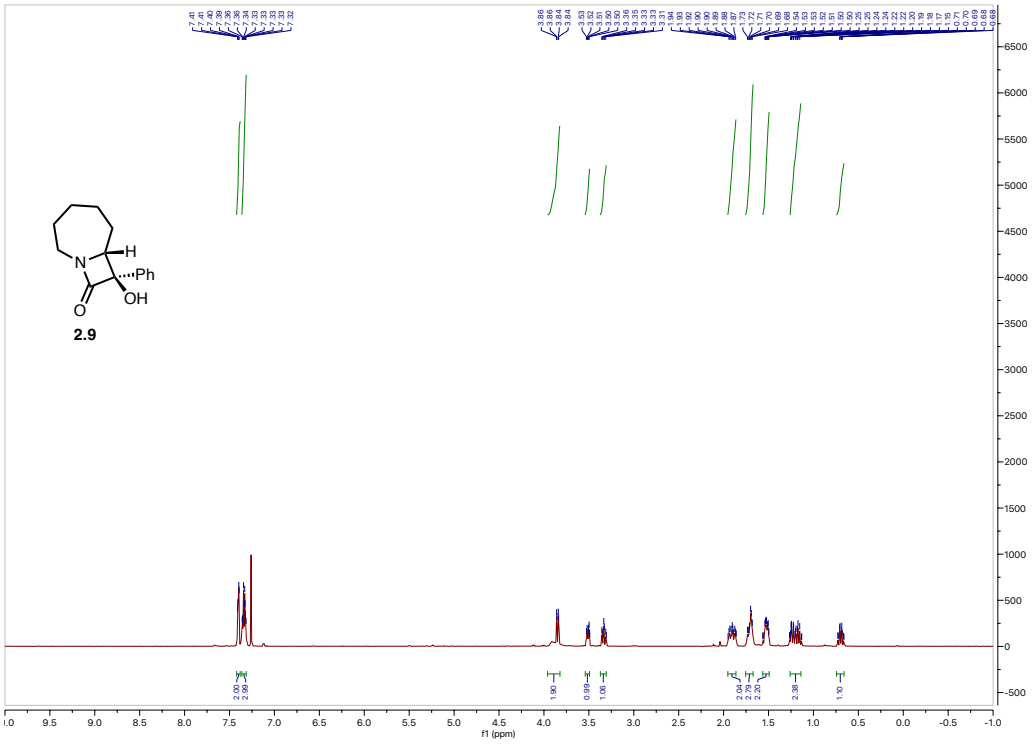

13,17
14,16
15
12
6'
2' 11
6''
3'
2''
3''
3''
2''
2' 6'' 11 3'
6'
12
13,17 14,16 15
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f2 (ppm)
f1 (ppm)

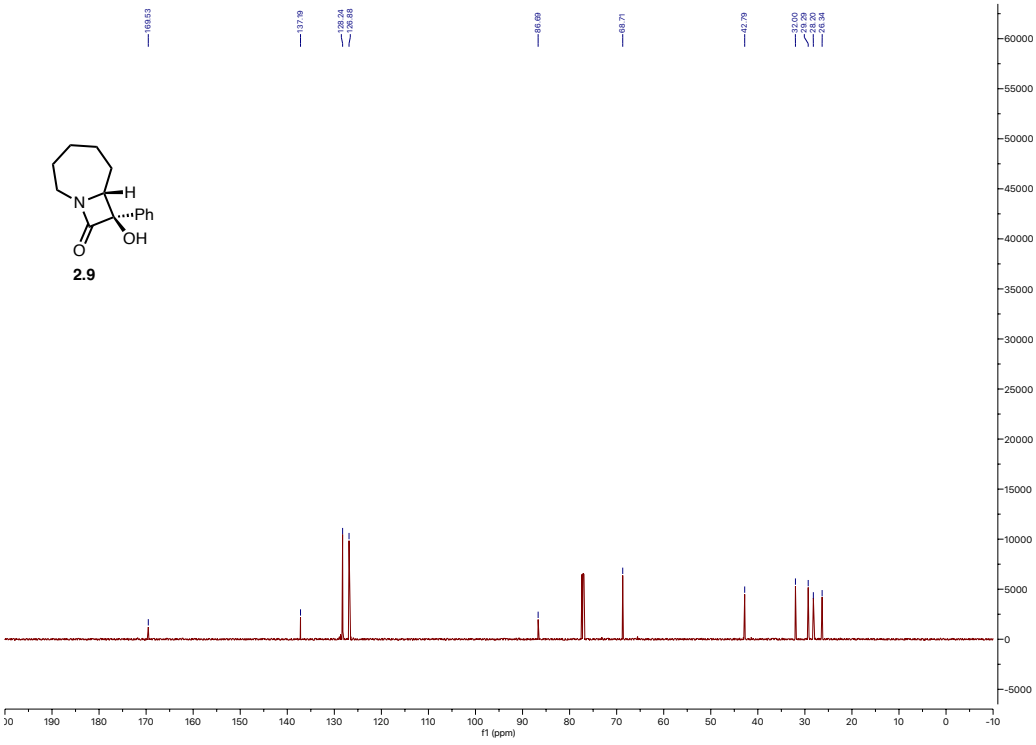
HMBC

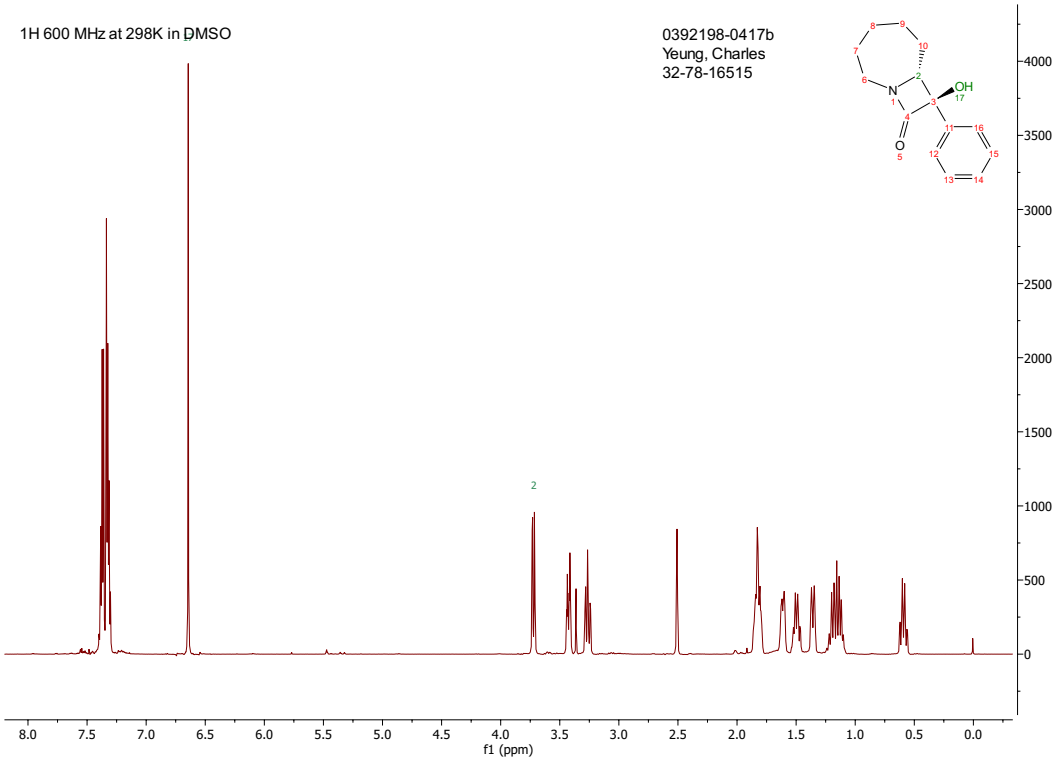


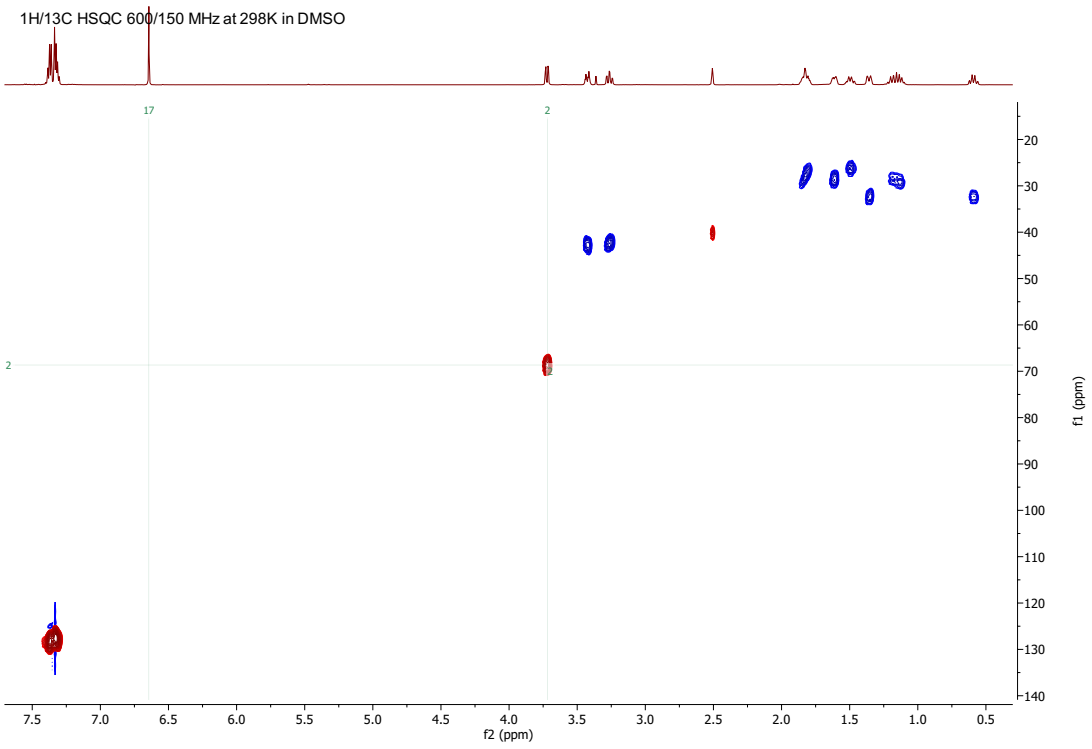
ROESY

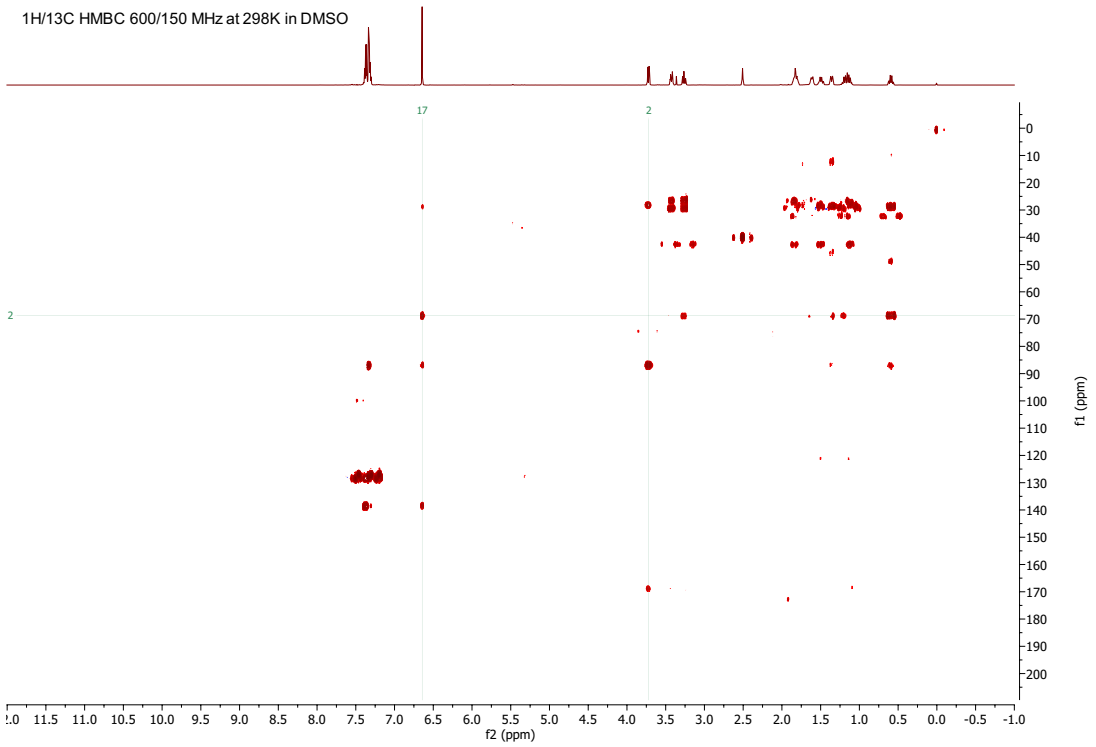


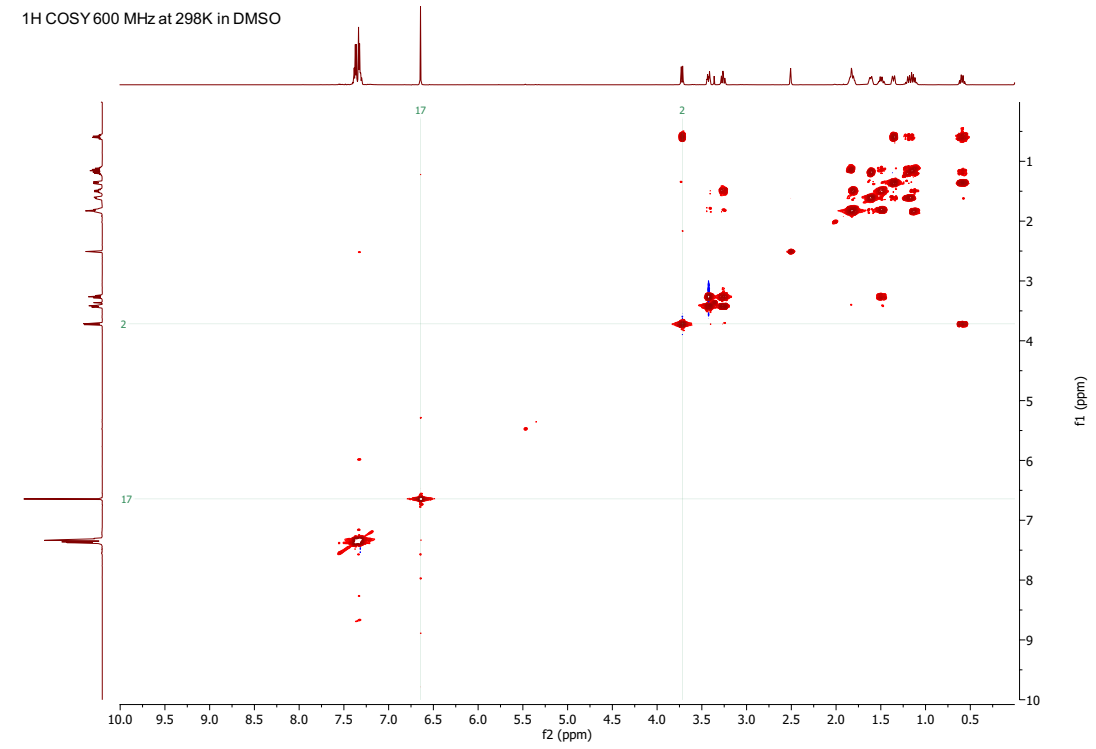

H
Ph
OH
O
N
2.9
f1 (ppm)

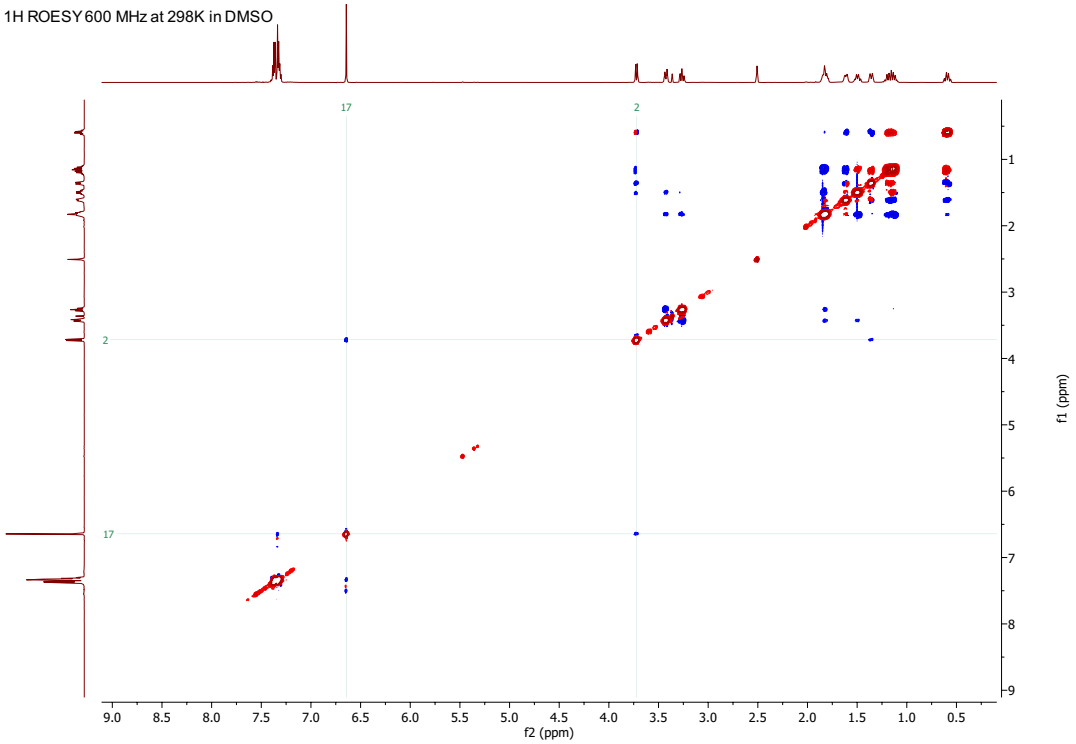

H
Ph
OH
O
N
2.9
f1 (ppm)


1H 600 MHz at 298K in DMSO
0392198-0417b
Yeung, Charles
32-78-16515
OH
17
2
f1 (ppm)

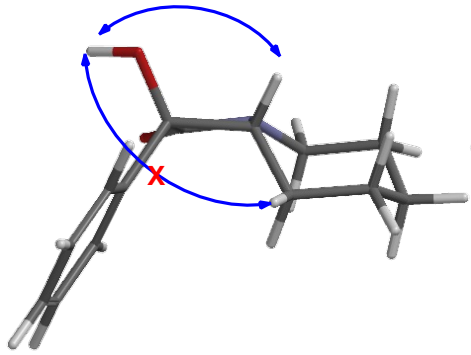

1H/13C HSQC 600/150 MHz at 298K in DMSO
17
2
f2 (ppm)
f1 (ppm)

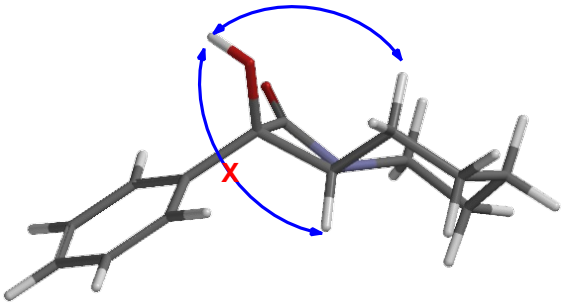

1H/13C HMBC 600/150 MHz at 298K in DMSO
17
2
2
f2 (ppm)
f1 (ppm)


1H COSY 600 MHz at 298K in DMSO
17
2
2
17
f2 (ppm)
f1 (ppm)



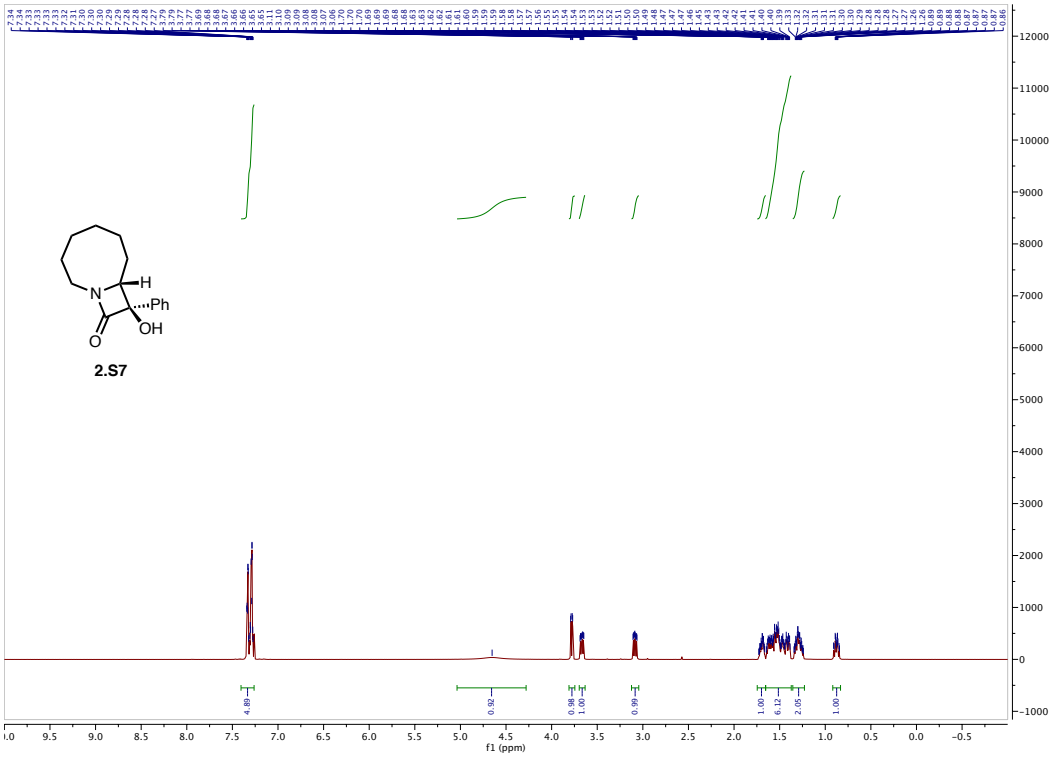
Selected ROE correlations establishing a trans configuration

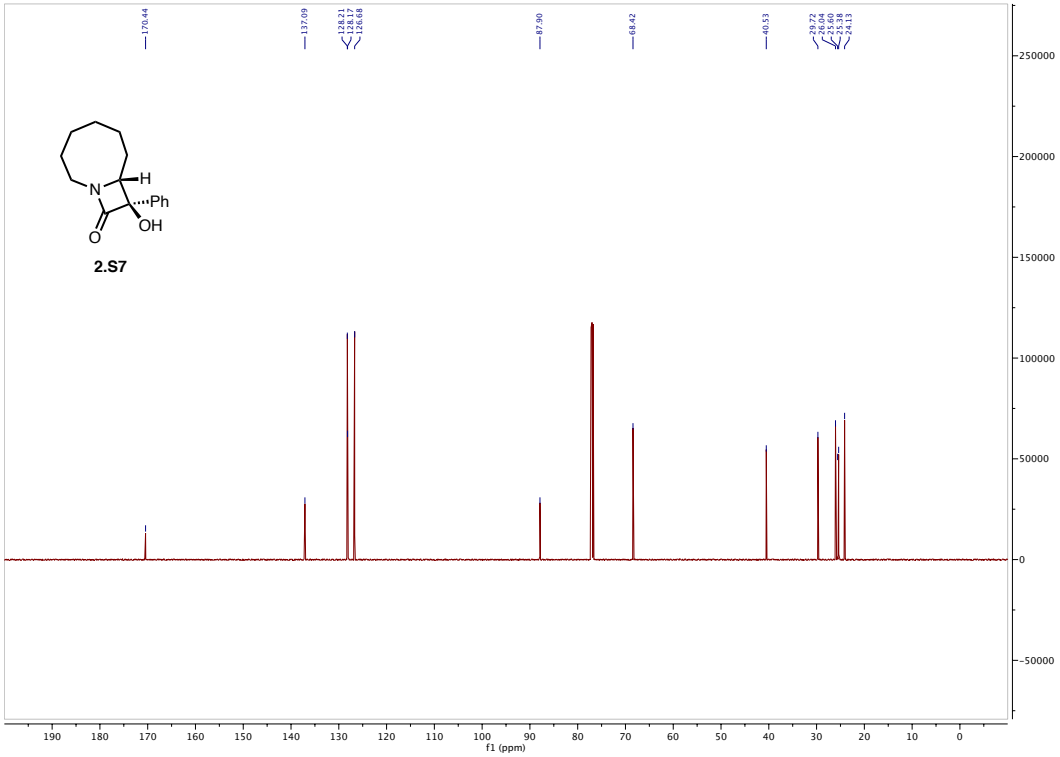




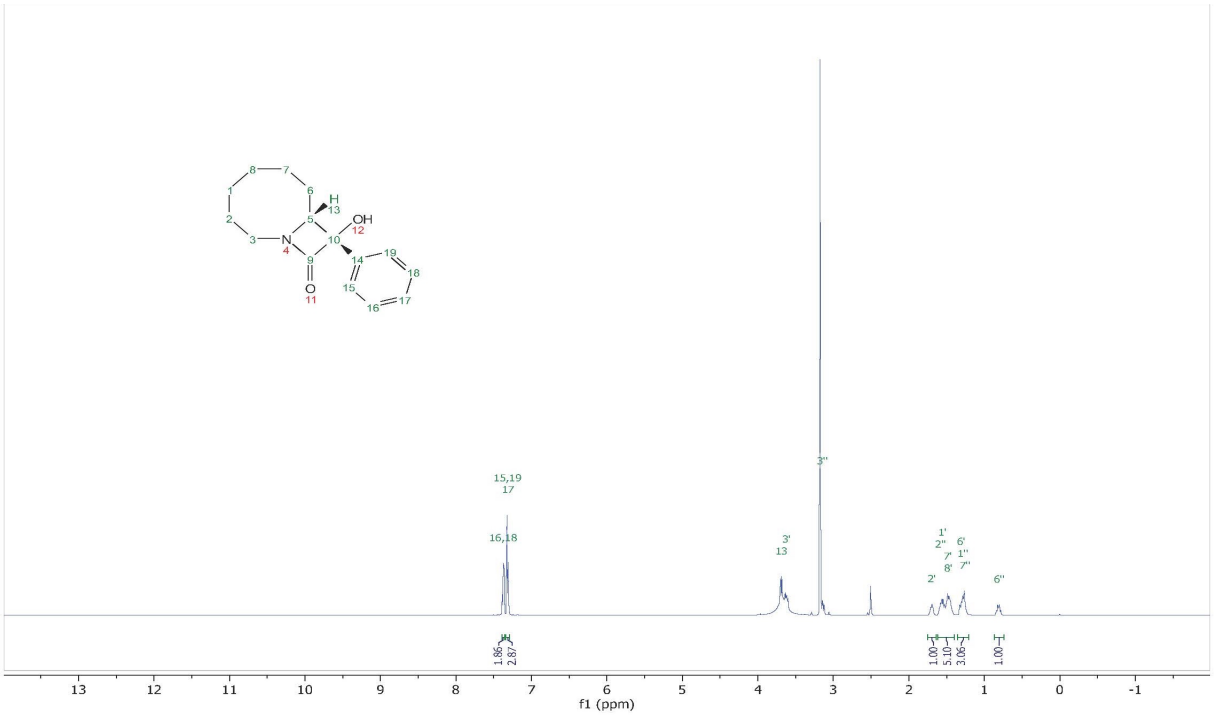
Cis configuration would give opposite ROE signals

This is the set of ROE signals observed

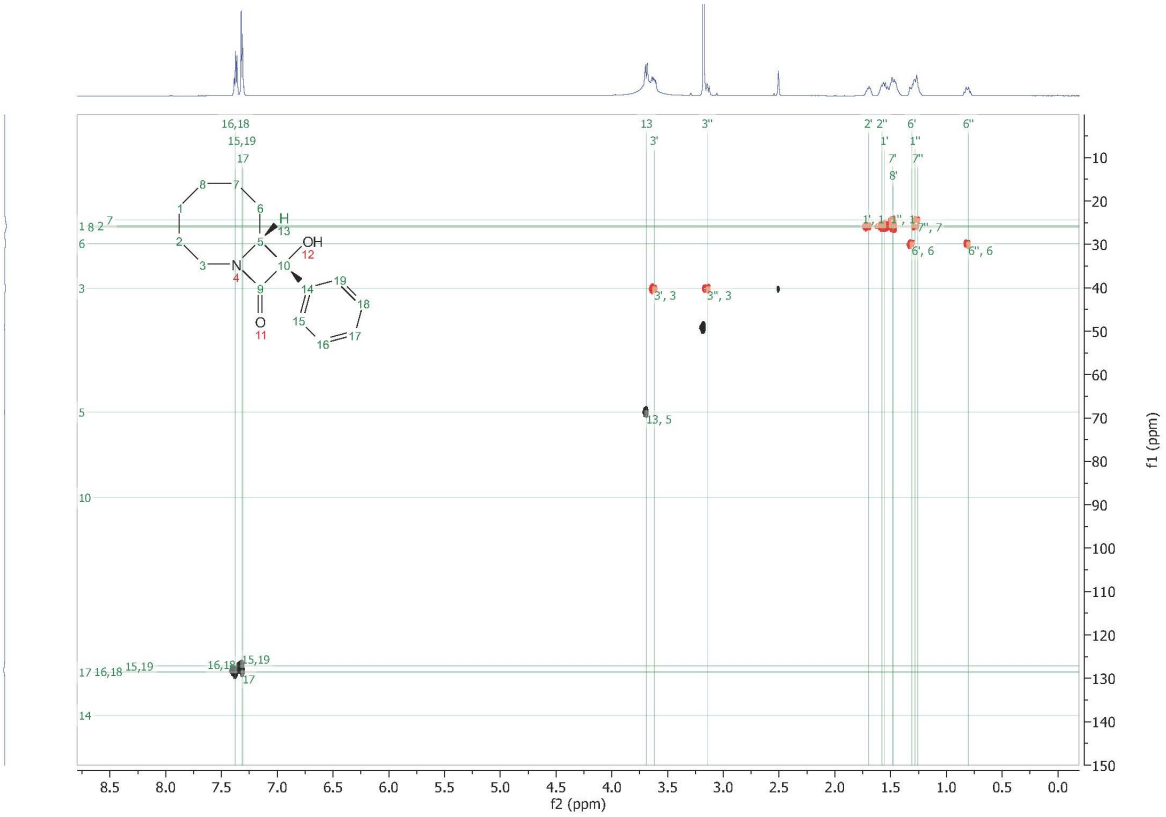

H
Ph
OH
O
N
2.S7
f1 (ppm)


170.44
137.09
128.21
128.17
126.68
87.90
68.42
40.53
29.72
26.04
25.60
25.38
24.13
H
Ph
OH
O
N
2.S7
f1 (ppm)

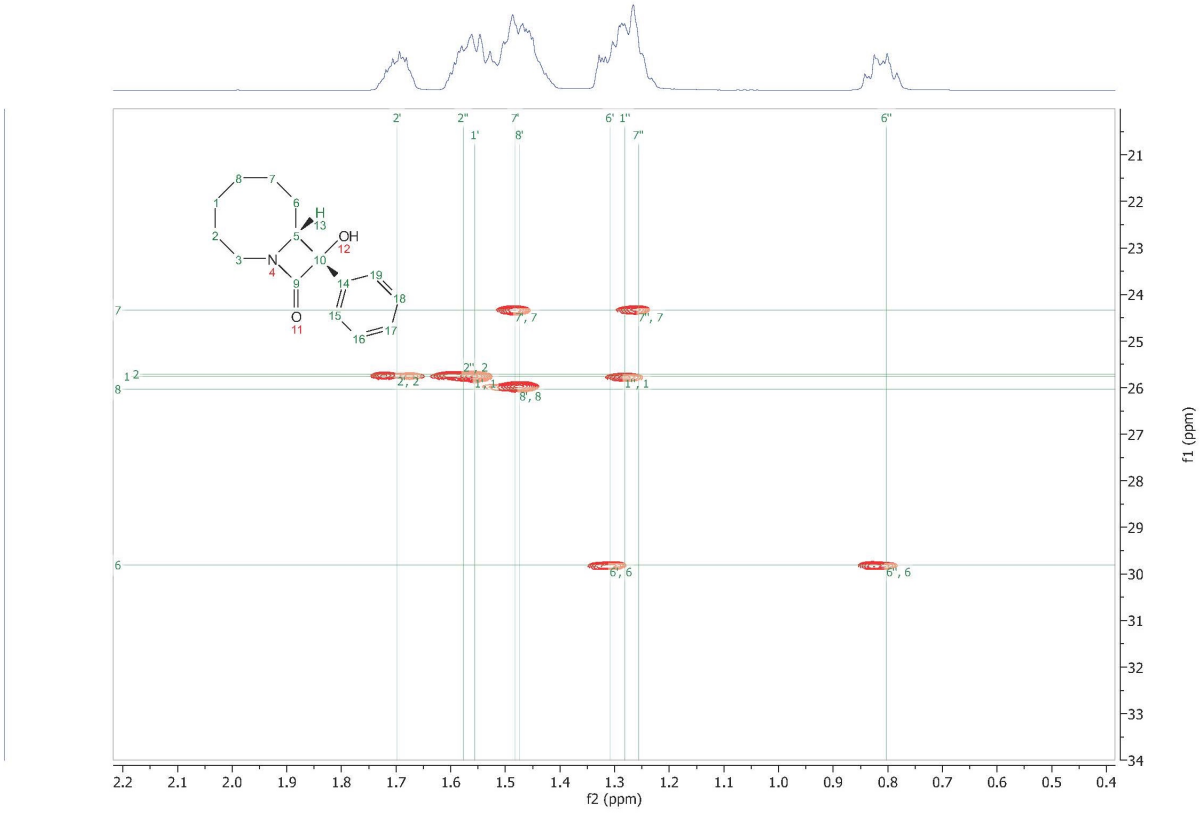
^{1}H NMR



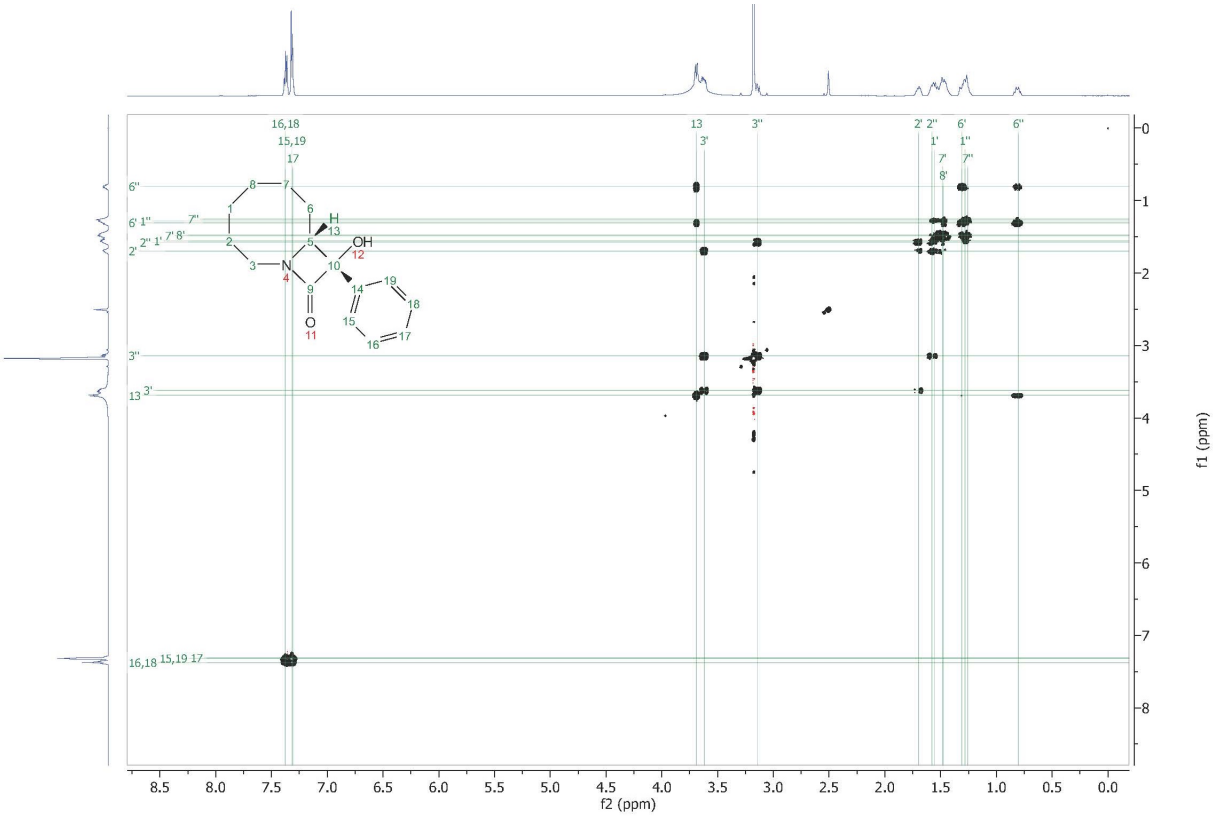
HSQC

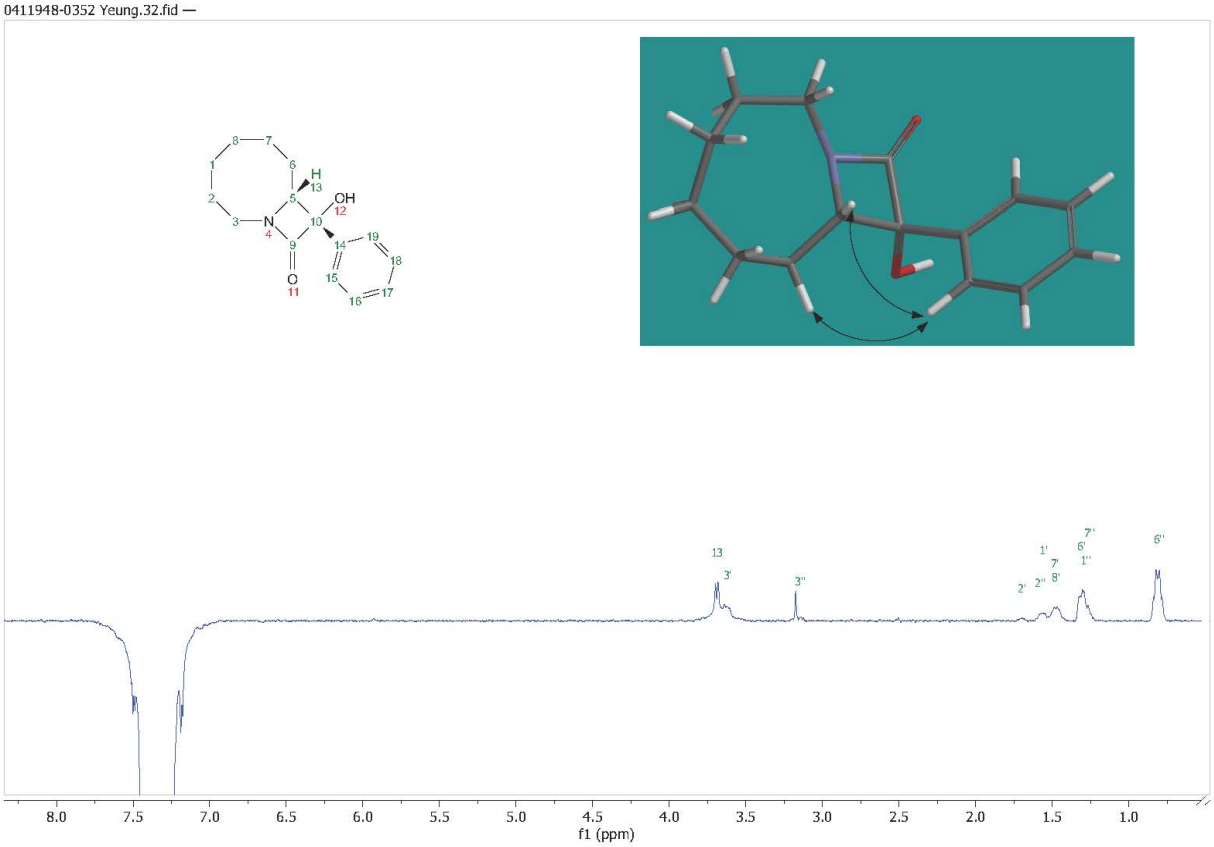


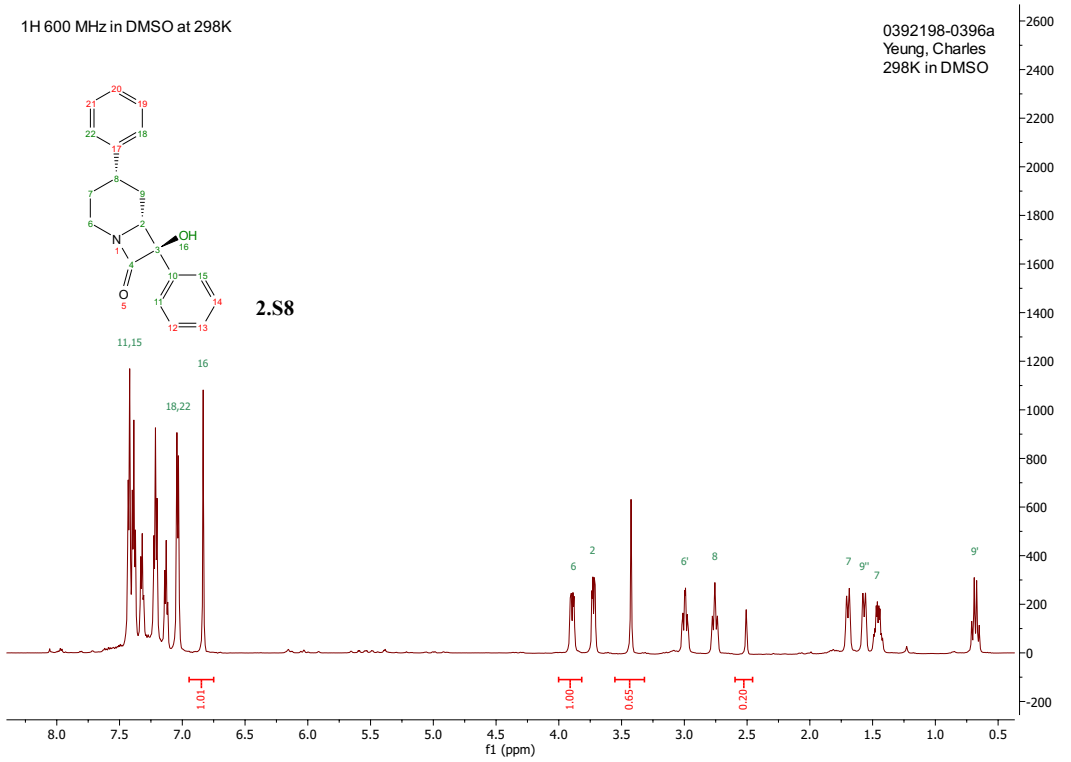
HSQC (*zoom*)

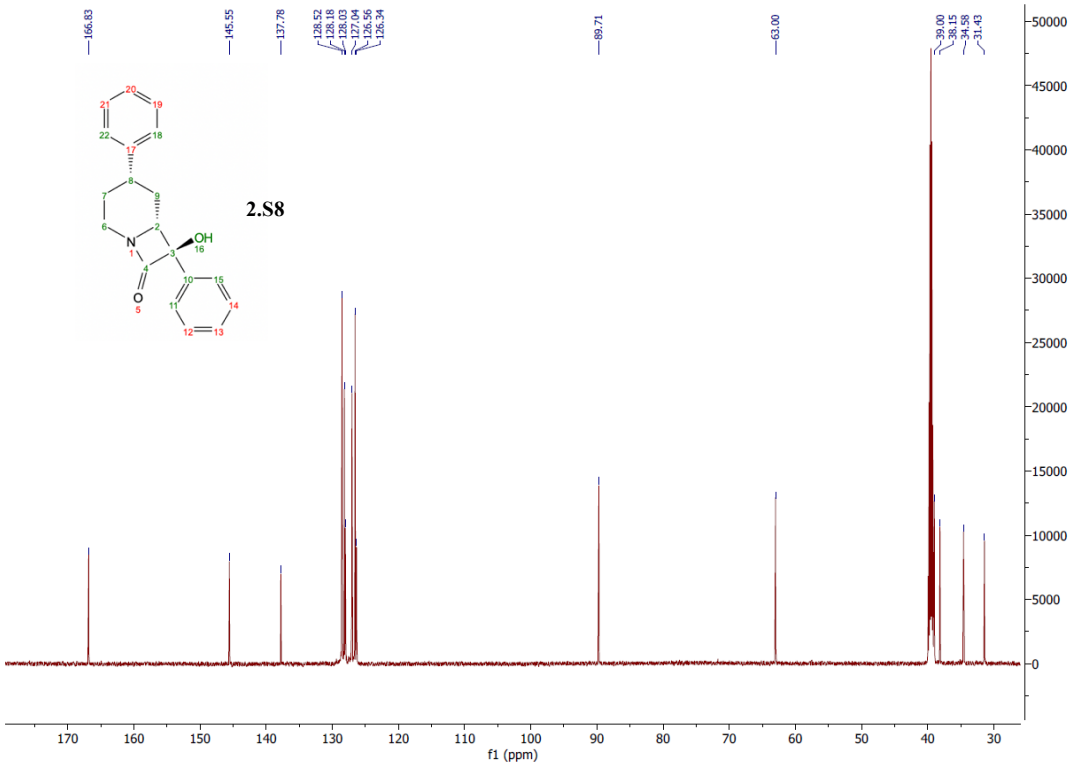


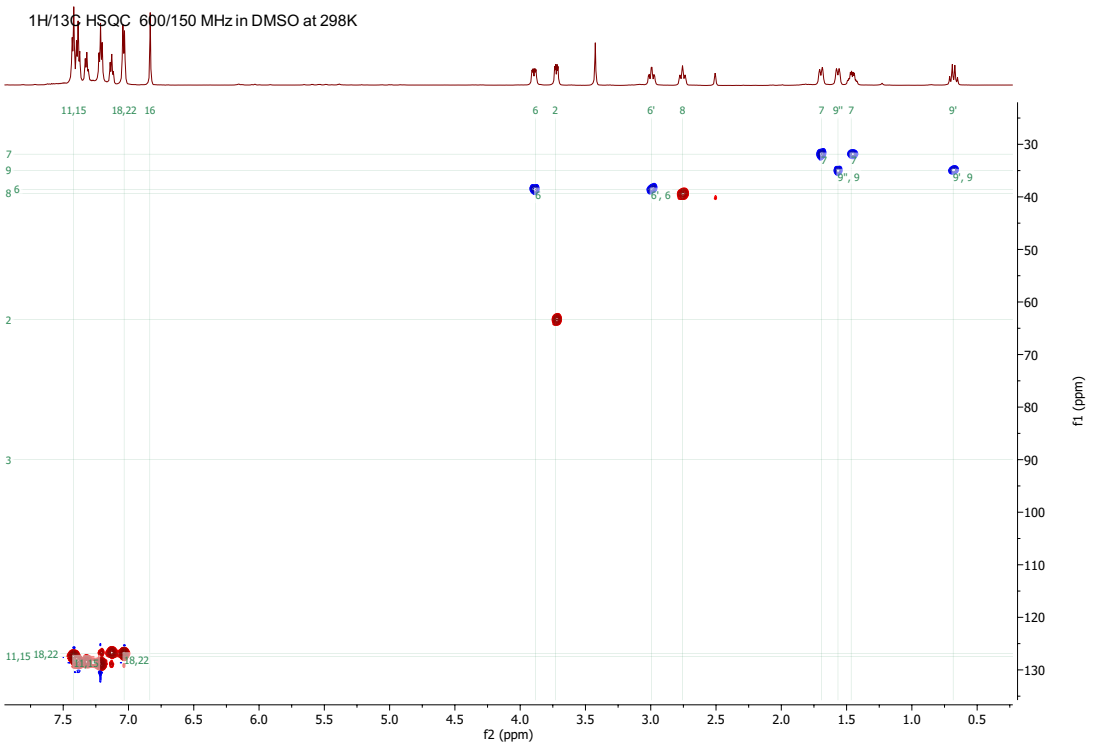
COSY

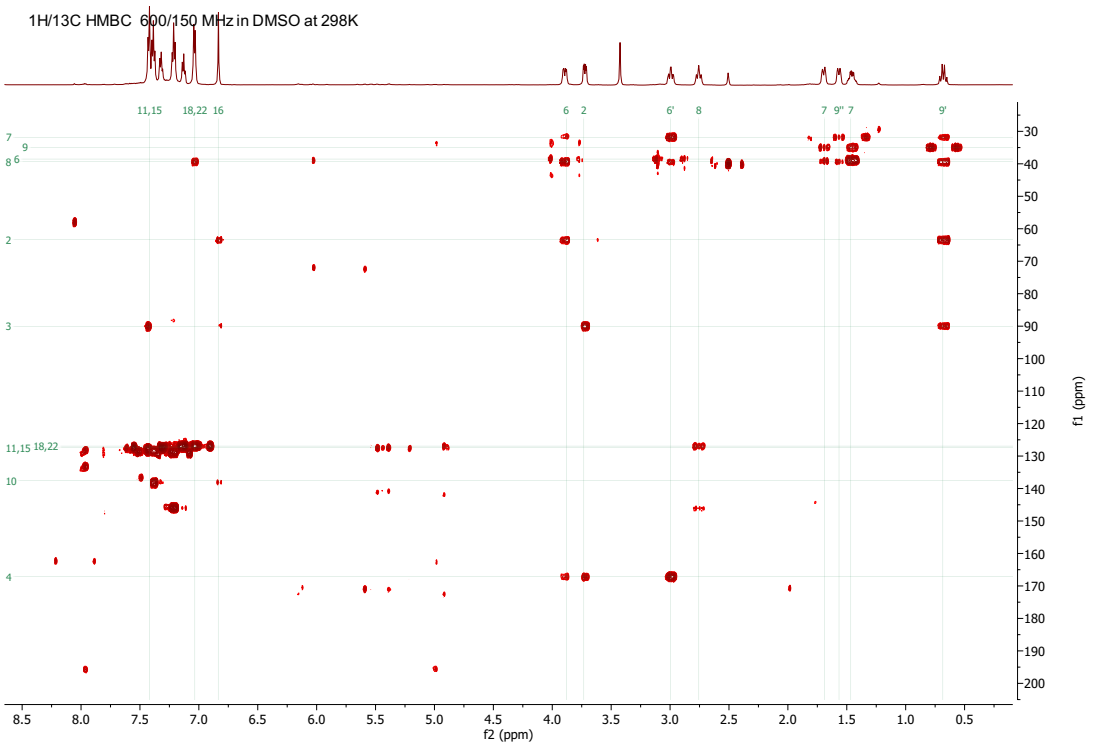

f2 (ppm)
f1 (ppm)
16,18
15,19
17
13
3'
3''
2' 2''
1'
6'
1''
6''
7'
7''
8'
6''
6' 1''
7''
2''
1'
7' 8'
2'
3''
13
3'
16,18
15,19
17
OH
12
N
4
O
11


0411948-0352 Yeung.32.fid
H
OH
O
13
3'
3''
1'
7'
2'
2''
8'
7''
6'
1''
6''
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
f1 (ppm)

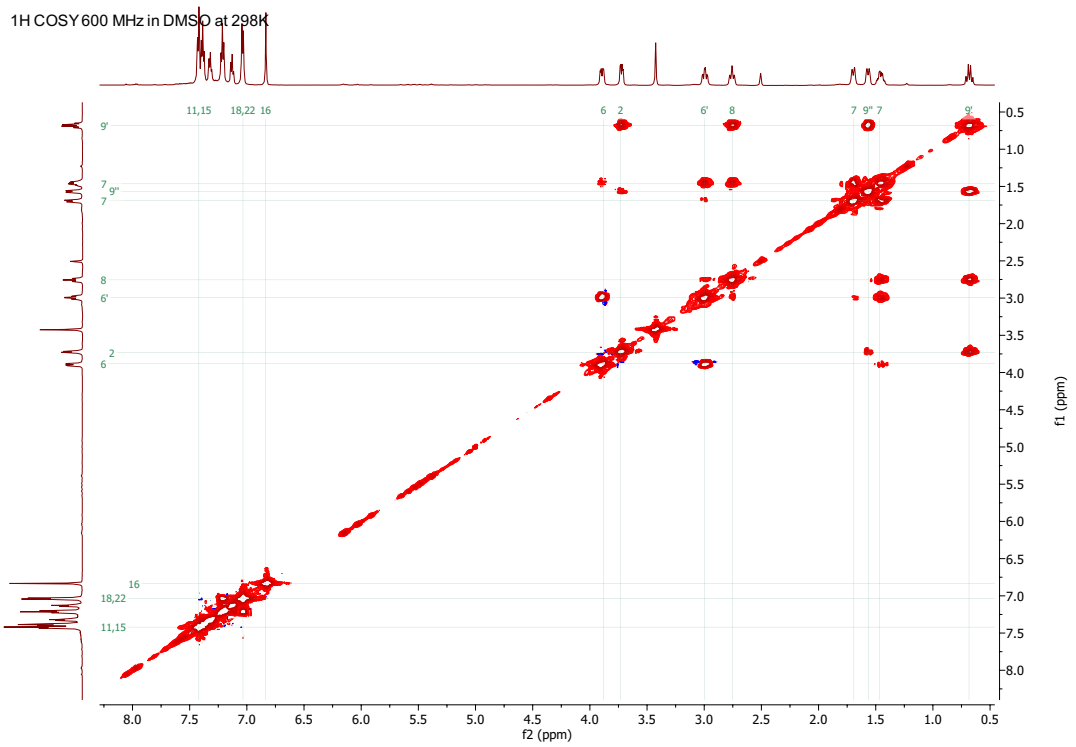

1H 600 MHz in DMSO at 298K
0392198-0396a
Yeung, Charles
298K in DMSO
2.S8
11,15
16
18,22
6
2
6'
8
7
9''
7
9'
1.01
1.00
0.65
0.20
f1 (ppm)


166.83
145.55
137.78
128.52
128.18
128.03
127.64
126.56
126.34
89.71
63.00
39.00
38.15
34.58
31.43
2.S8
f1 (ppm)

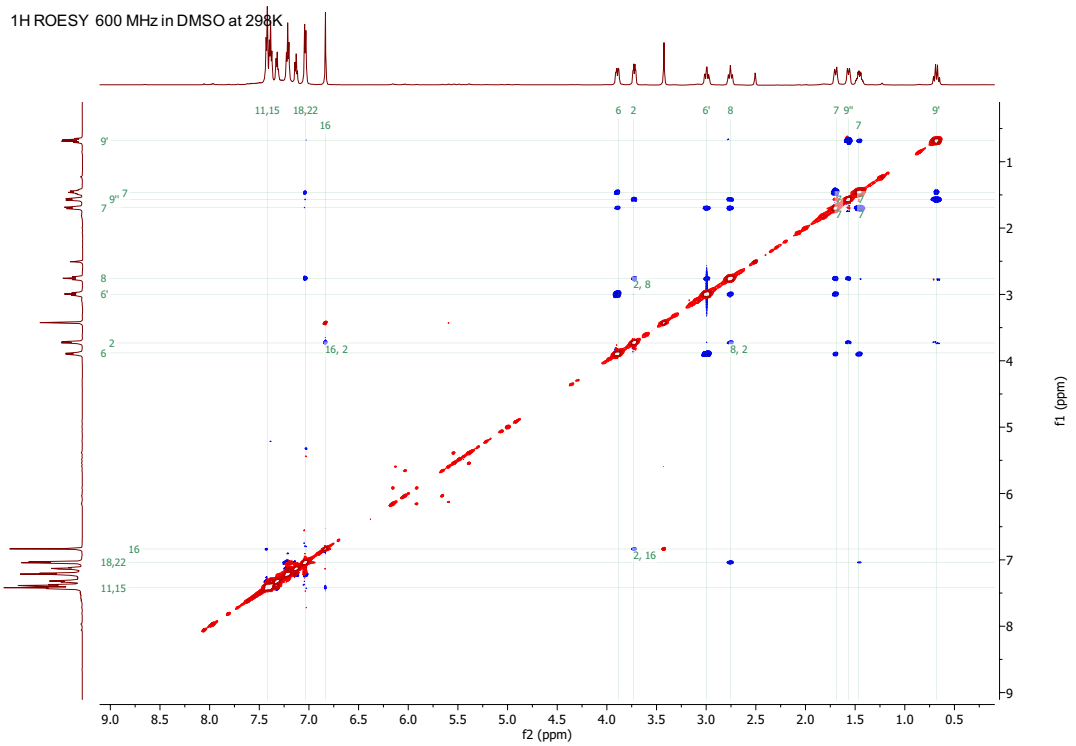

1H/13C HSQC 600/150 MHz in DMSO at 298K
11,15
18,22
16
6
2
6'
8
7
9"
7
9'
f2 (ppm)
f1 (ppm)


1H/13C HMBC 600/150 MHz in DMSO at 298K
11,15
18,22
16
6
2
6'
8
7
9"
7
9'
f2 (ppm)
f1 (ppm)

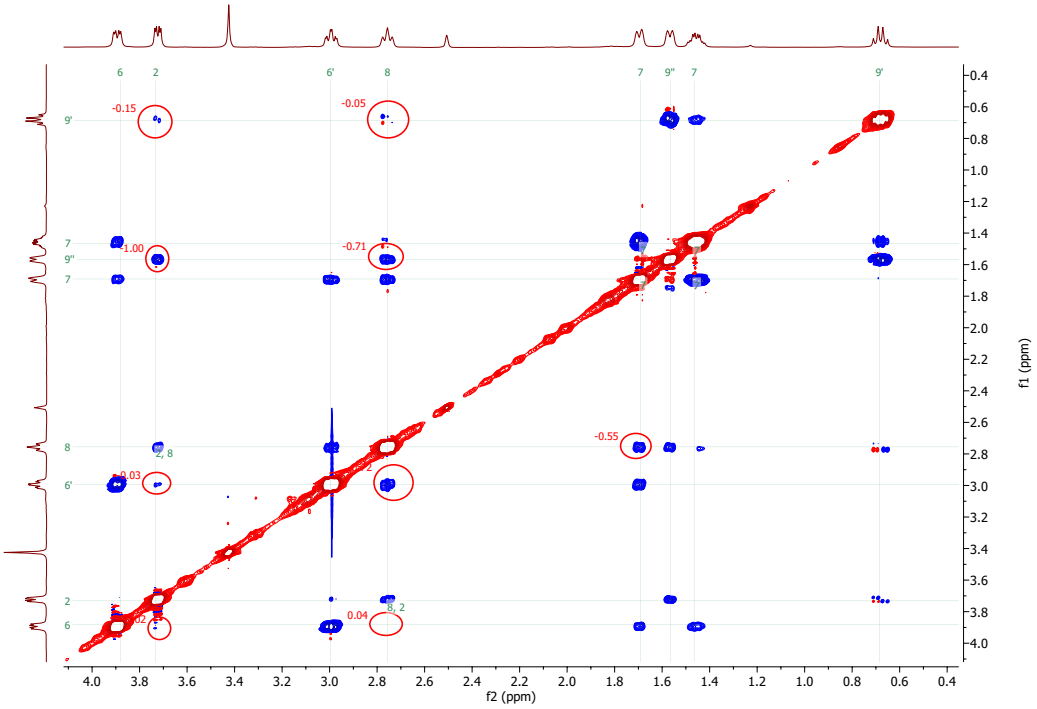
1H COSY 600 MHz in DMSO at 298K



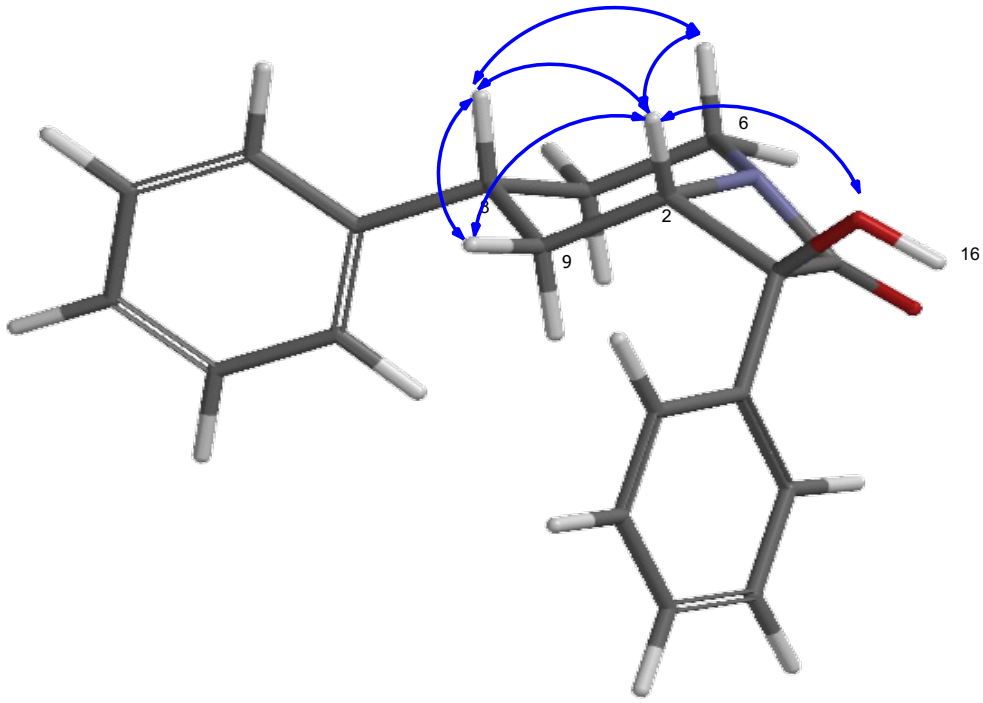
1H ROESY 600 MHz in DMSO at 298K

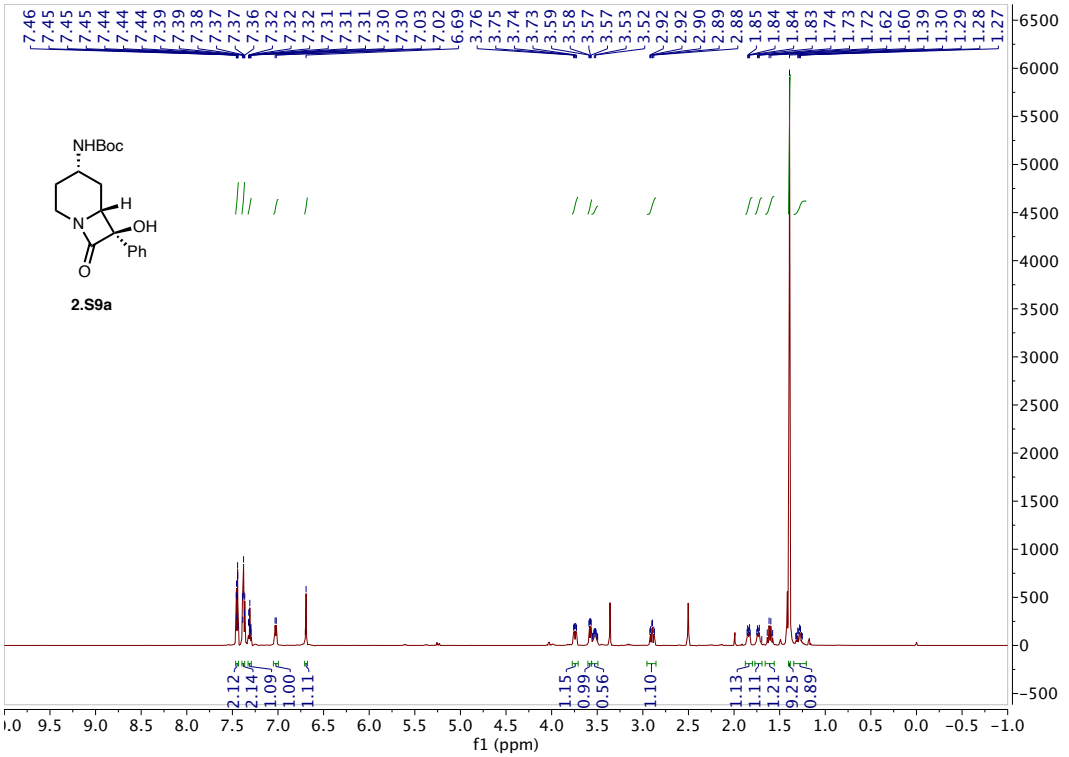


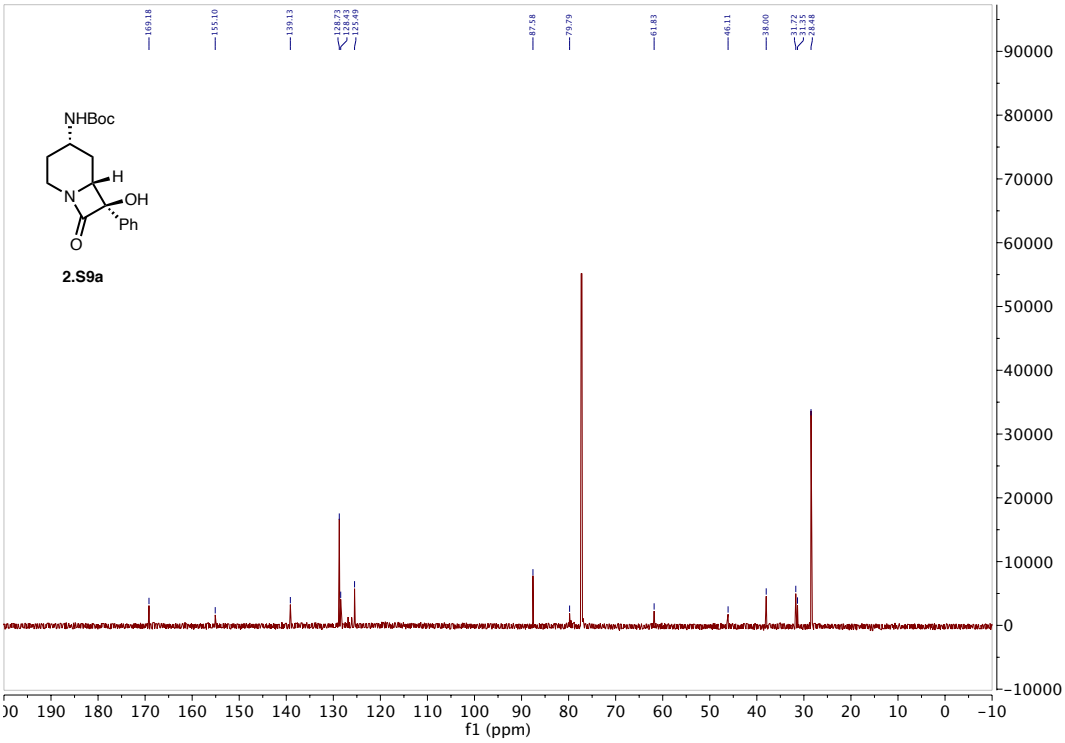
1H ROESY zoomed 600 MHz in DMSO at 298K

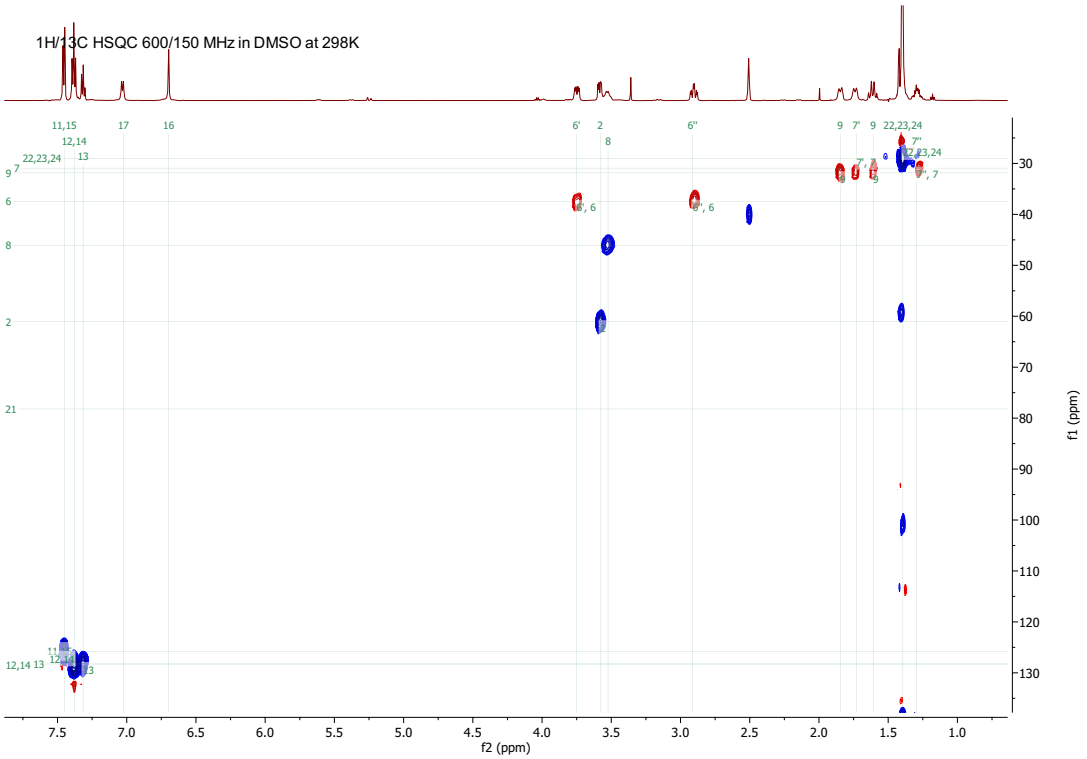


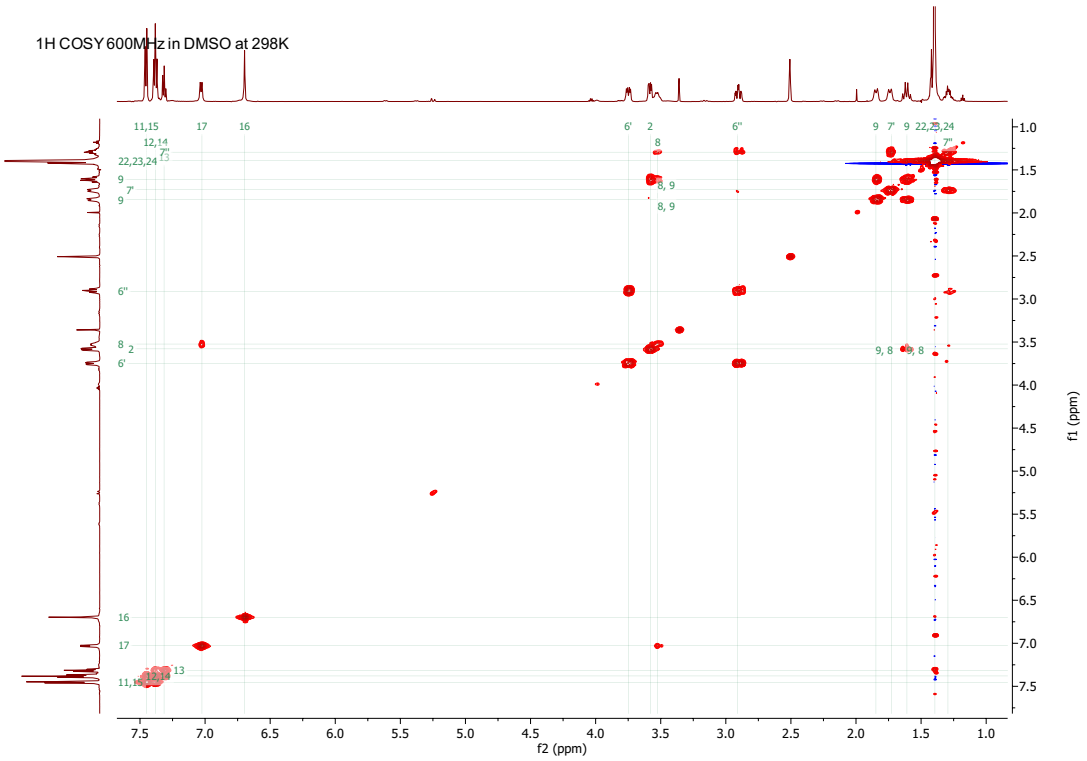
ROE correlations place 8, 2, OH all on the same face

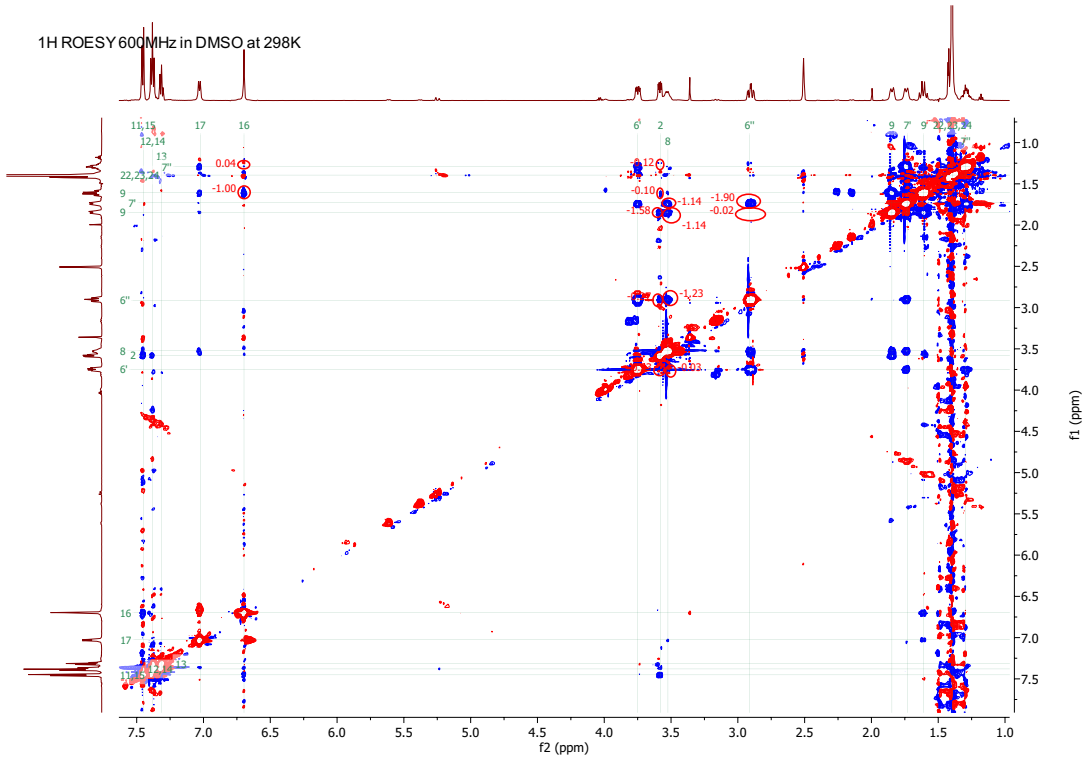


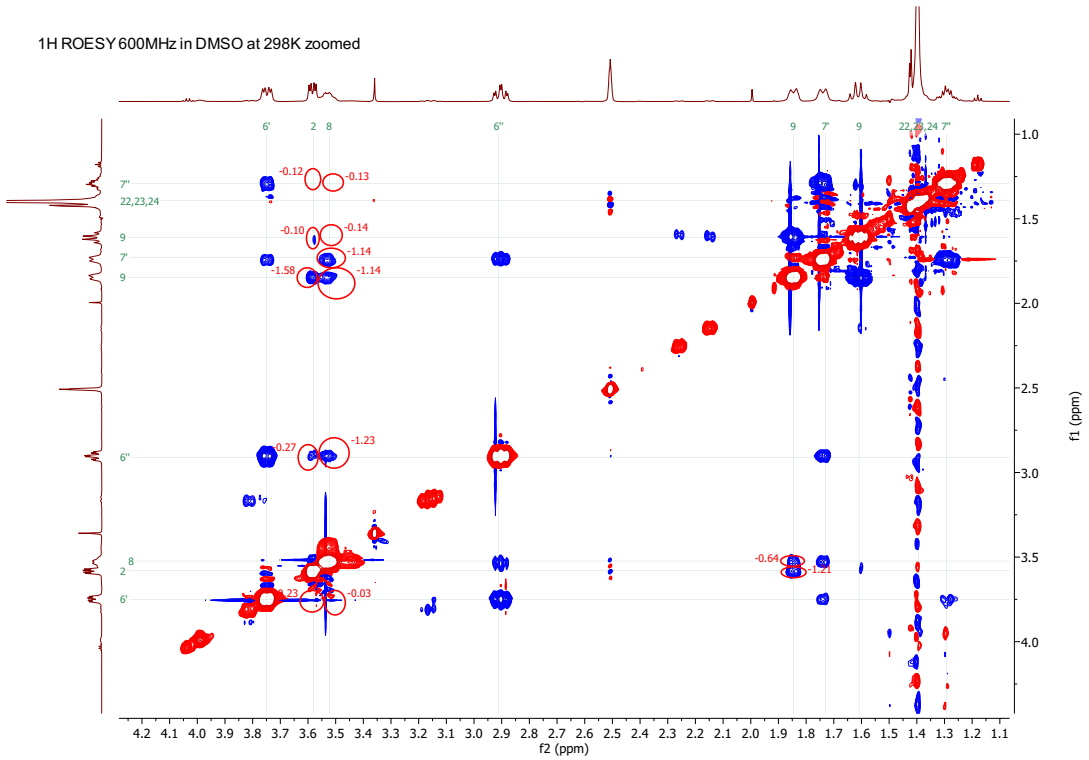

NHBoc
H
N
OH
Ph
O
2.S9a
f1 (ppm)

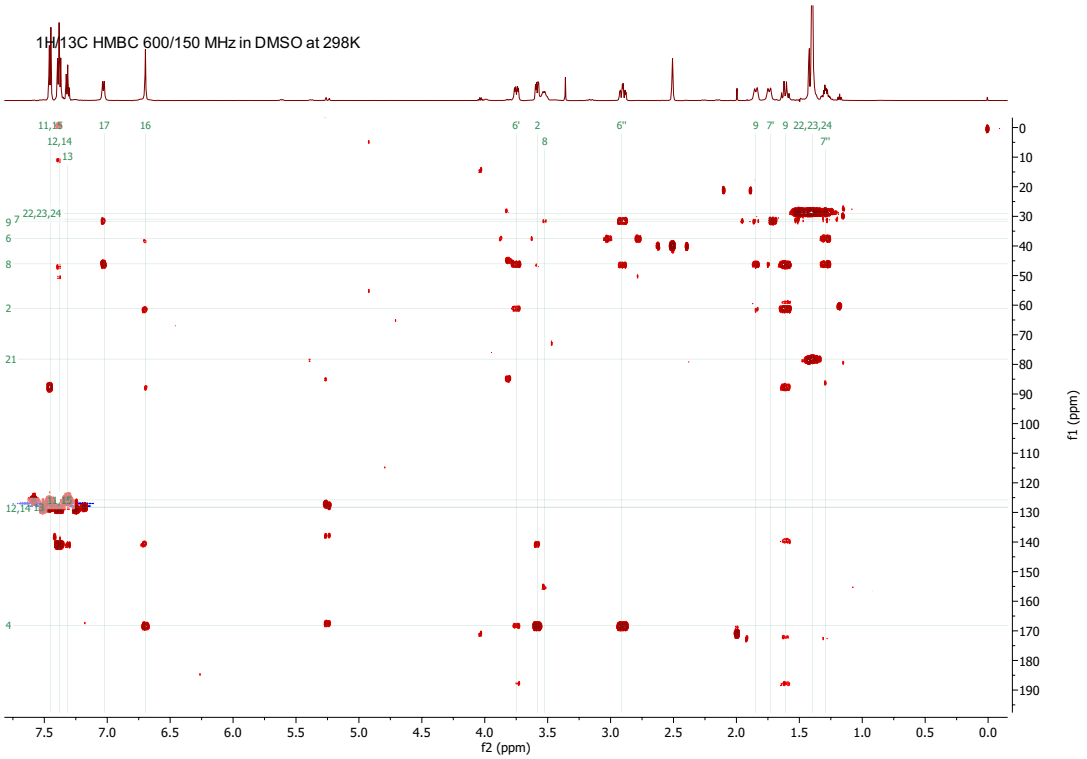

NHBoc
H
N
OH
Ph
O
2.S9a
f1 (ppm)

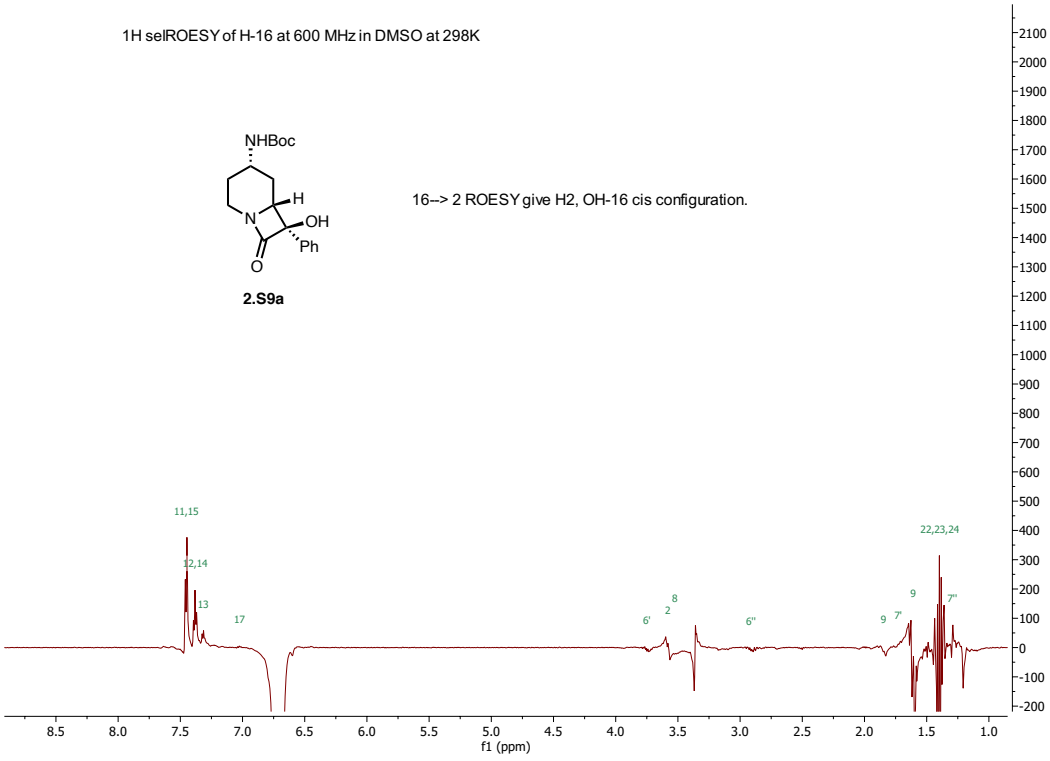

1H/13C HSQC 600/150 MHz in DMSO at 298K
f2 (ppm)
f1 (ppm)


1H COSY 600MHz in DMSO at 298K
f2 (ppm)
f1 (ppm)


1H ROESY 600MHz in DMSO at 298K
f2 (ppm)
f1 (ppm)


1H ROESY 600MHz in DMSO at 298K zoomed
f2 (ppm)
f1 (ppm)


1H/13C HMBC 600/150 MHz in DMSO at 298K
f2 (ppm)
f1 (ppm)

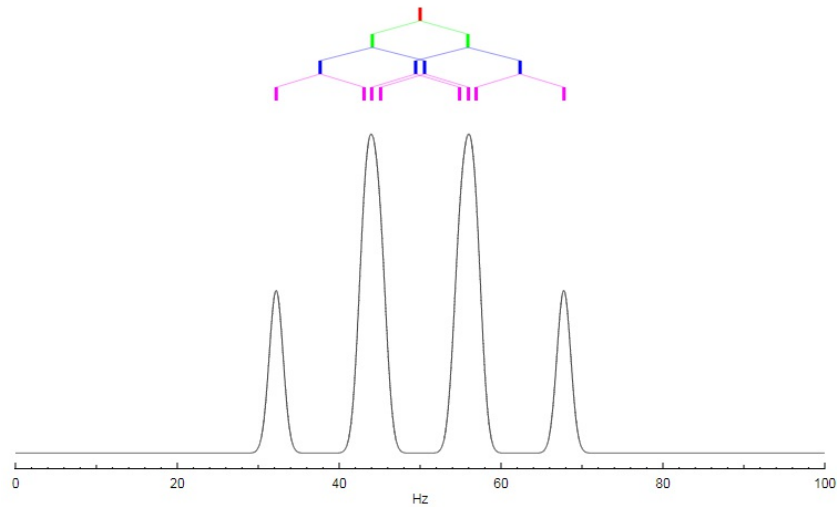

1H selROESY of H-16 at 600 MHz in DMSO at 298K
NHBoc
H
N
OH
Ph
O
2.S9a
16--> 2 ROESY give H2, OH-16 cis configuration.
f1 (ppm)

The proton 9b anti to 2 displays an apparent quartet with a J of 11.8
2 however, is a dd with J 10.85, 4.0
9a is a dt with J 12.90, 4.01

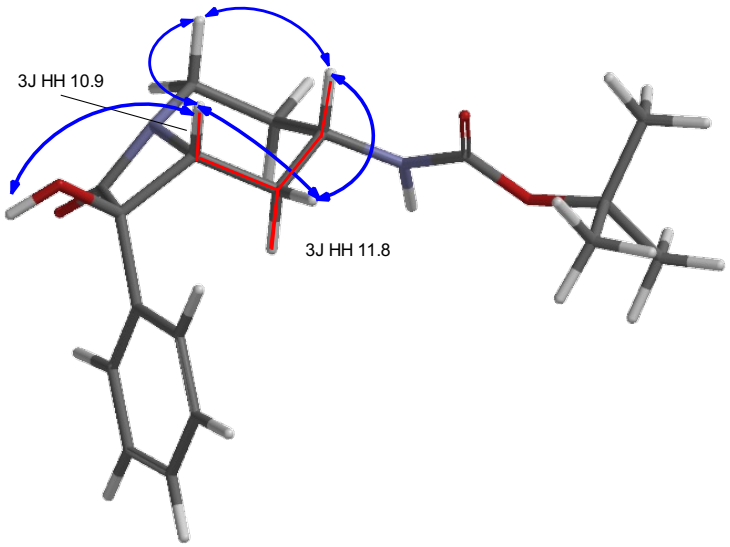
modeling a d,d,d with J 12.9, 11.8, 10.85 reproduces an apparent quartet

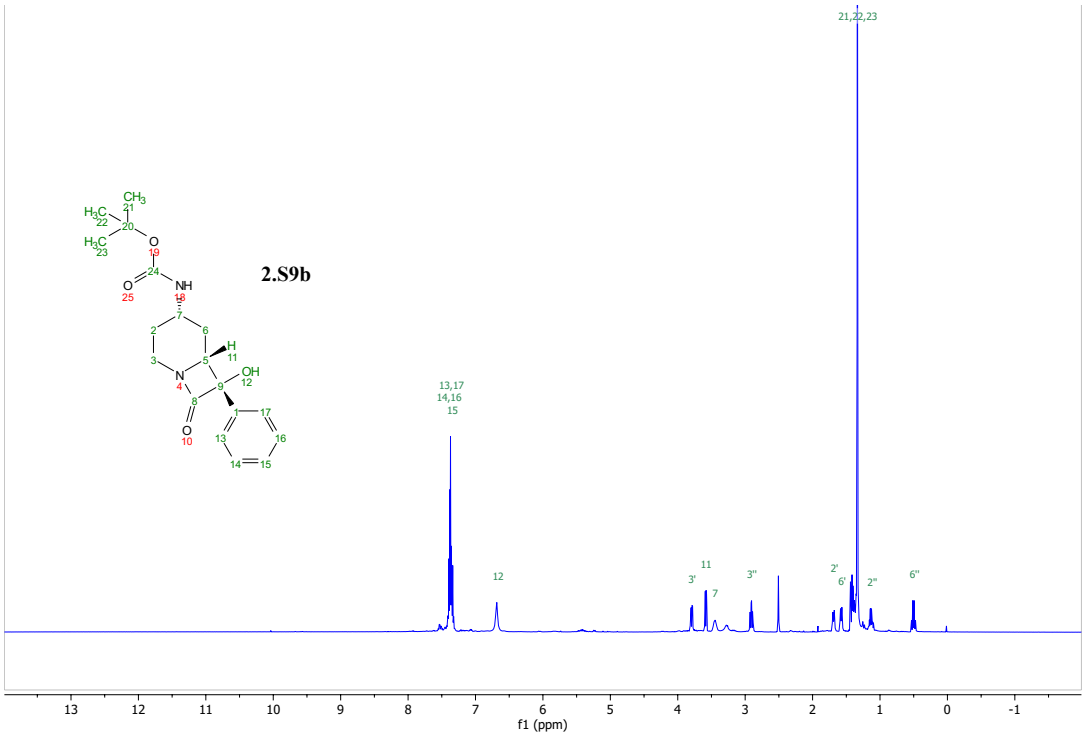
3 J HH of 11.8 would indicate 8 is anti to 9b, which is also anti to 2 (3 J HH 10.85)

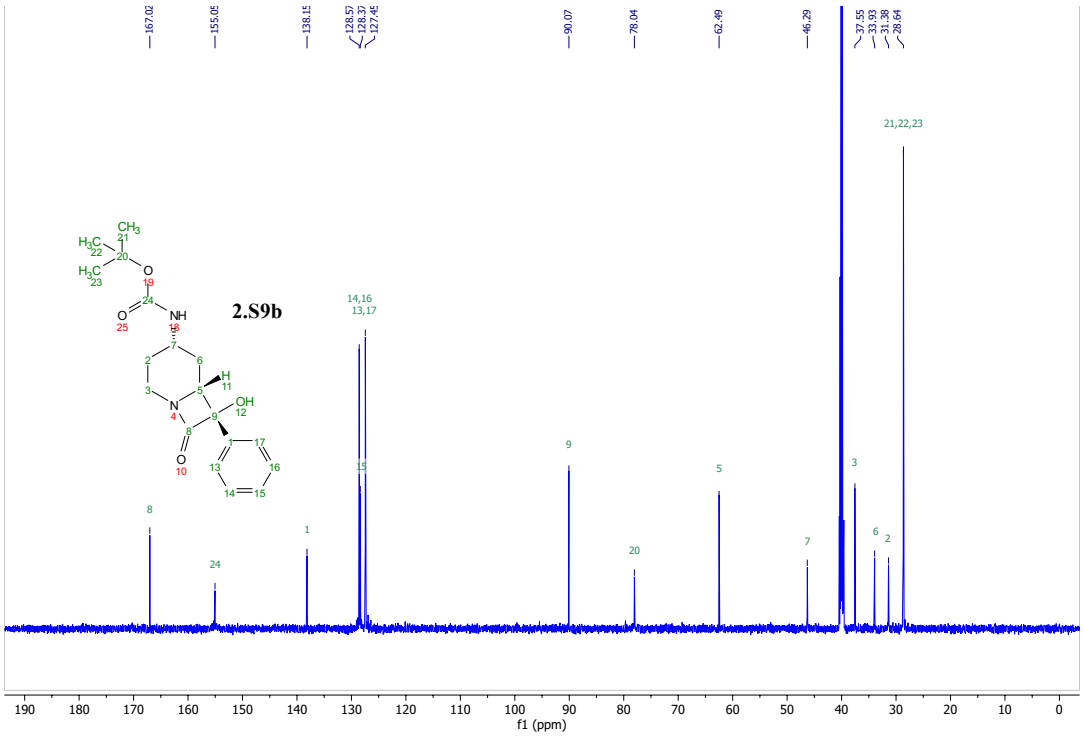
Simulated multiplet - ddd, 12.85, 11.8, 10.85



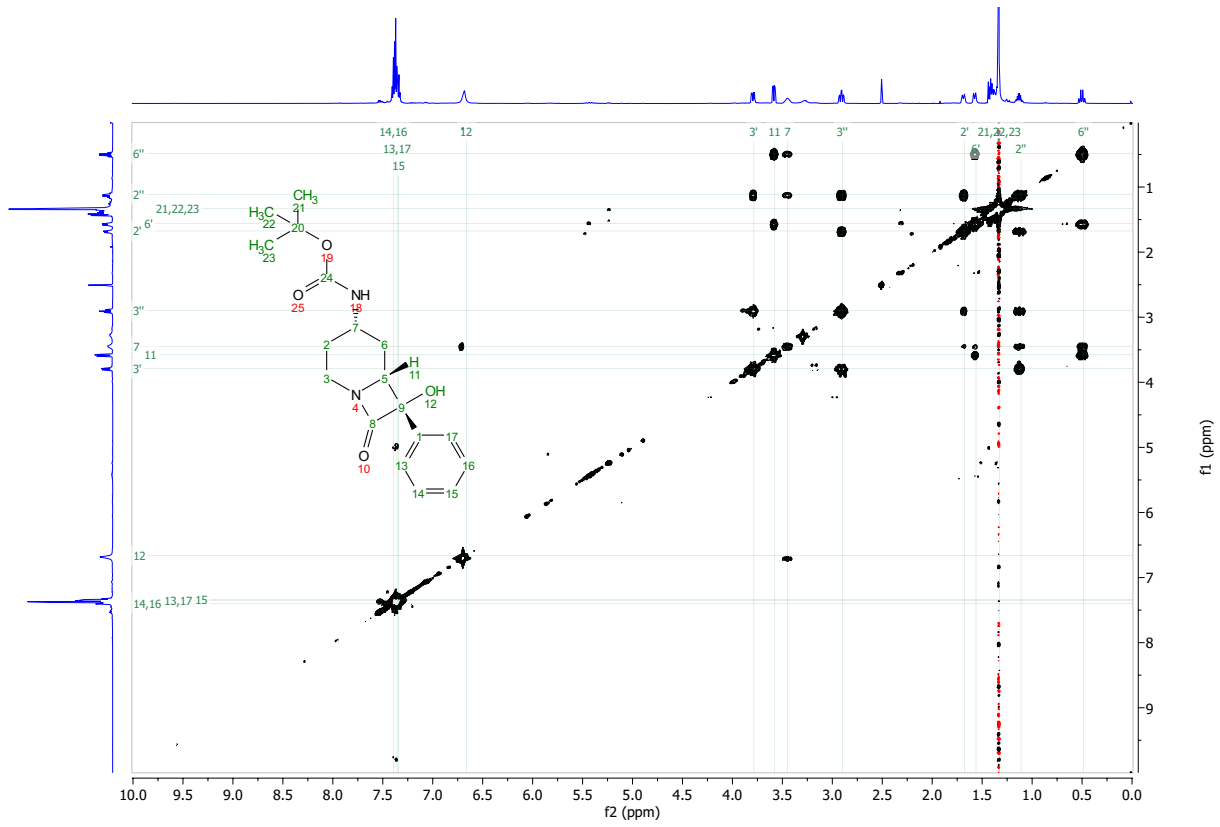
Select 3J HH and ROESY correlations establishing the relative configuration of the compound.



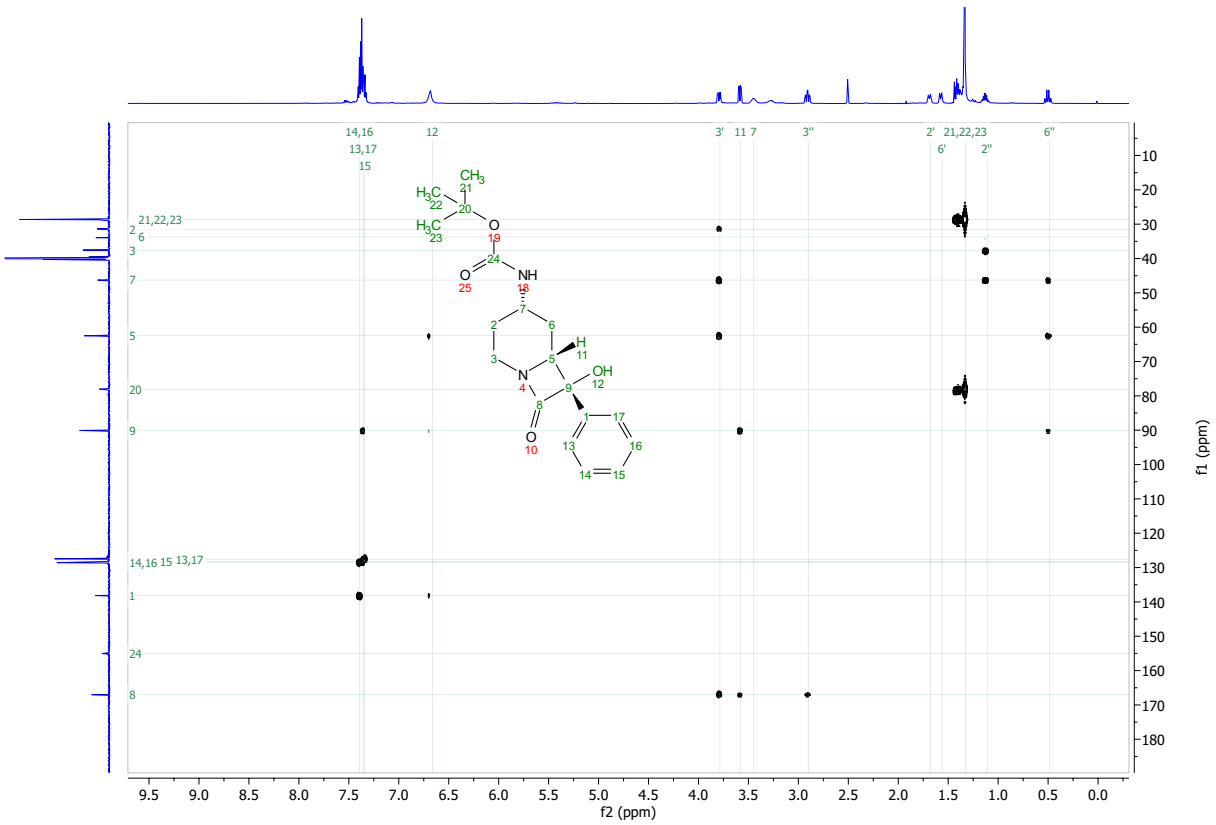

2.S9b
21,22,23
13,17
14,16
15
12
11
3'
7
3''
2'
6'
2''
6''
f1 (ppm)

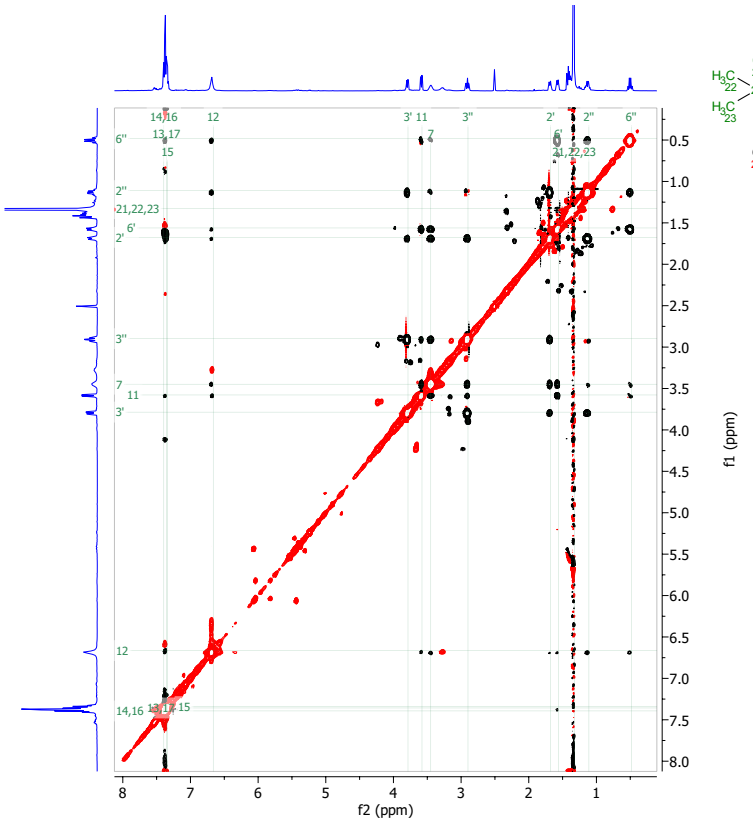

2.S9b
167.02
155.05
138.15
128.57
128.37
127.45
90.07
78.04
62.49
46.29
37.55
33.93
31.38
28.64
21,22,23
14,16
13,17
15
9
5
3
8
24
1
20
7
6
2
f1 (ppm)

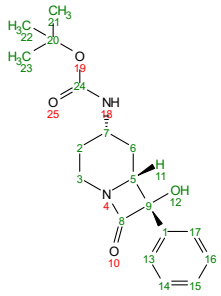
COSY


f2 (ppm)
f1 (ppm)
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
1 2 3 4 5 6 7 8 9

HMBC


14,16
13,17
15
12
3'
11 7
3''
2'
21,22,23
6'
2''
6''
21,22,23
2 6
3
7
5
20
9
14,16 15 13,17
1
24
8
f2 (ppm)
f1 (ppm)



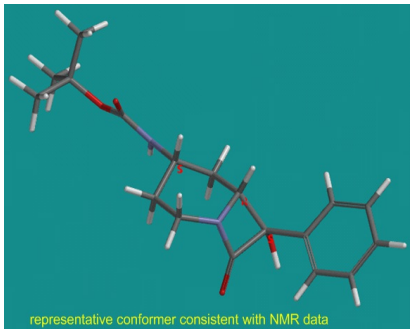


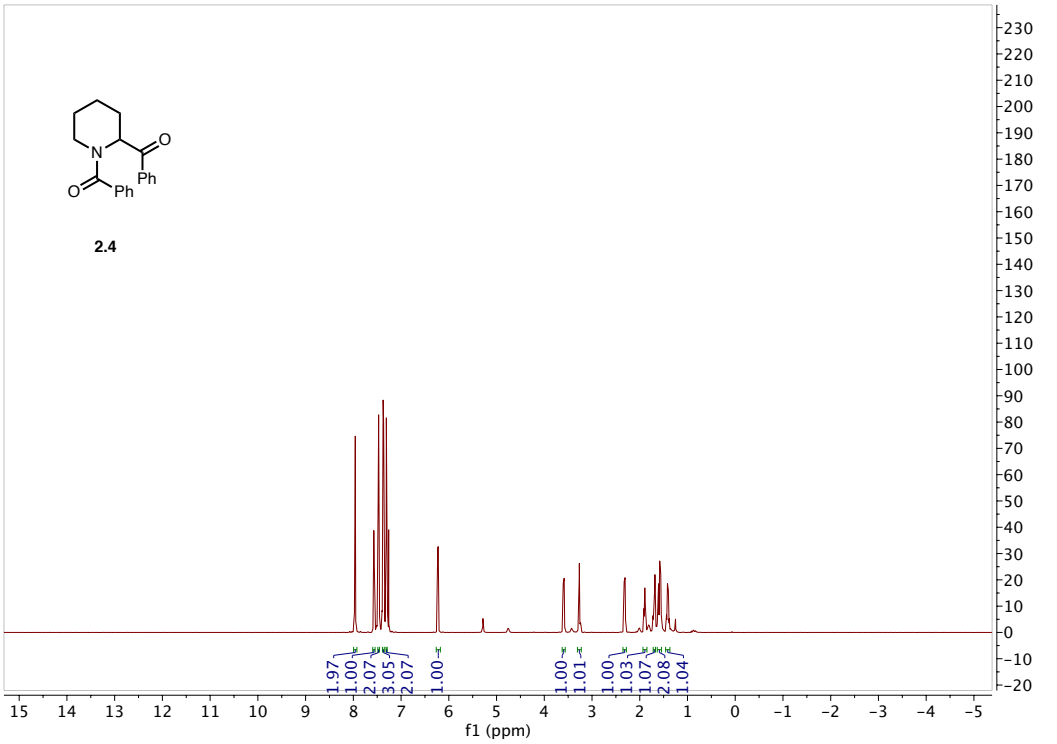
rel. stereochem. determ.
(assumption: H11 is "up")

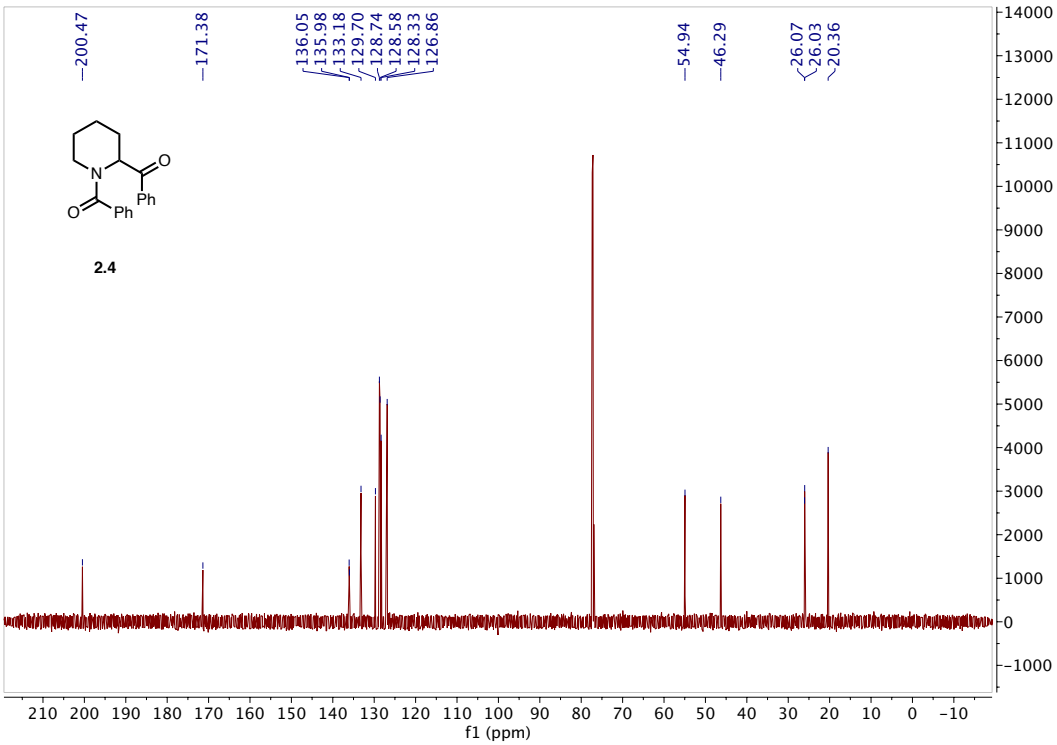
Strong ROE H11-H7 consistent with H7 being on same side as H11 (both are in axial position).

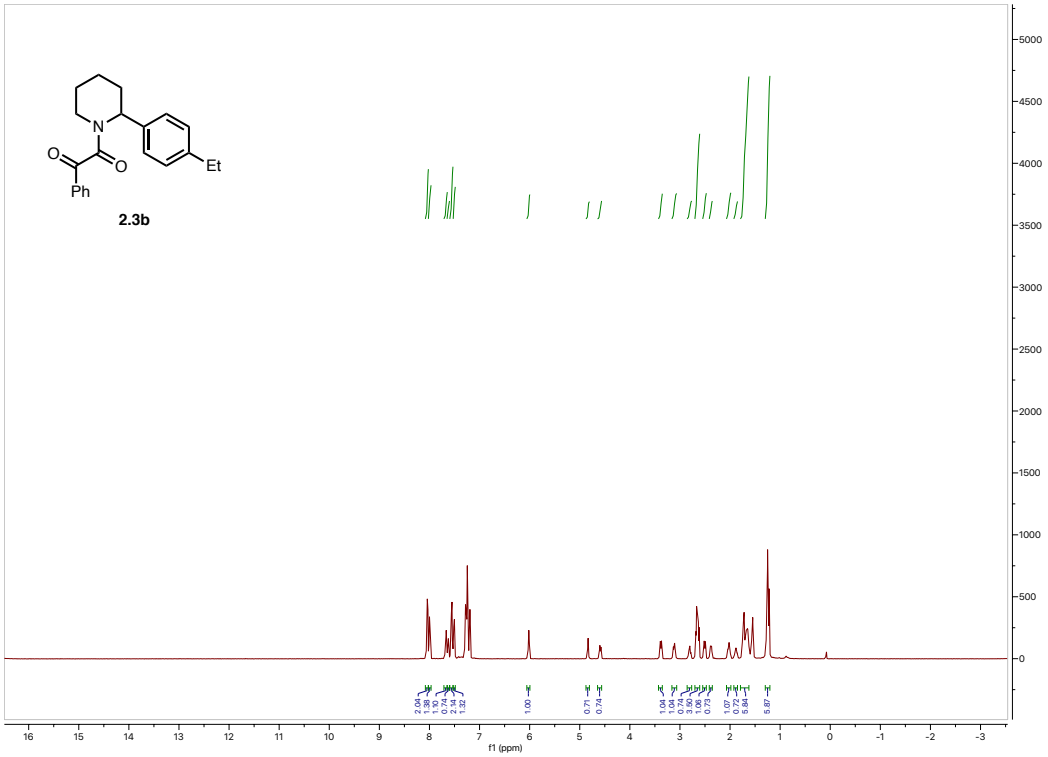
Observed ROE between H11 and aromatic H13/H17 is consistent with phenyl ring being on the same side as H11.

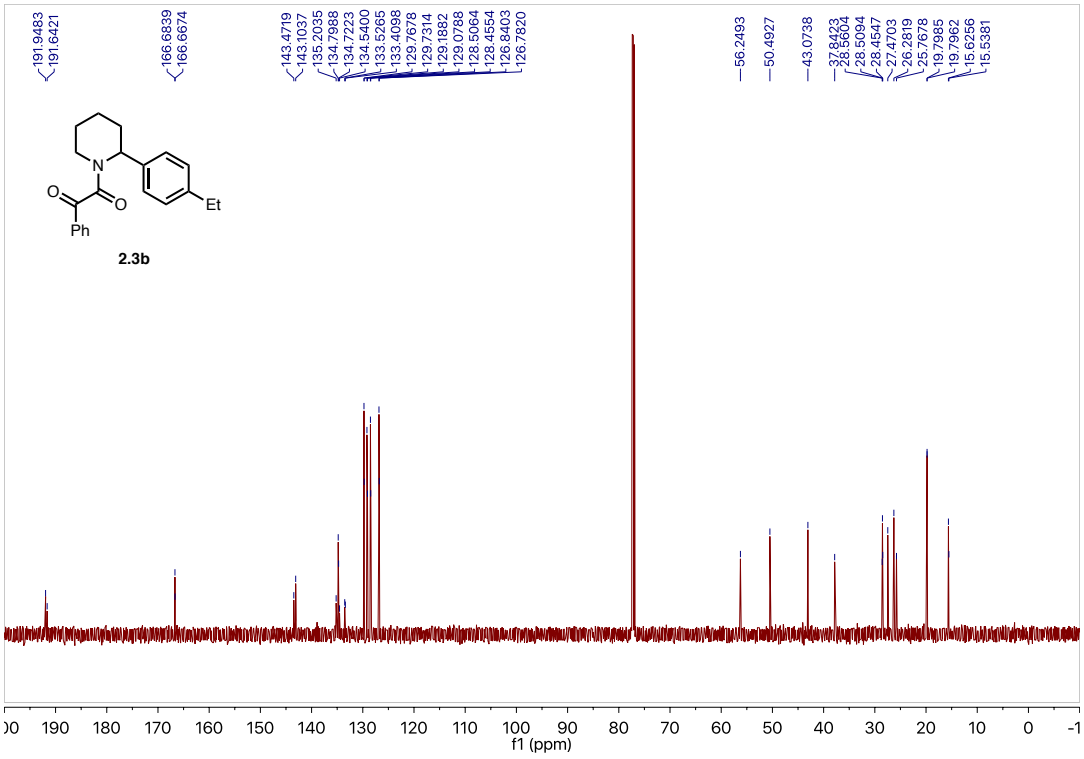
Also, the fact that OH-12 and H11 have strongest ROE to different diasterotopic H6 protons is also consistent with H11 and OH-12 being on opposite sides (therefore with H11 and phenyl on the same side).

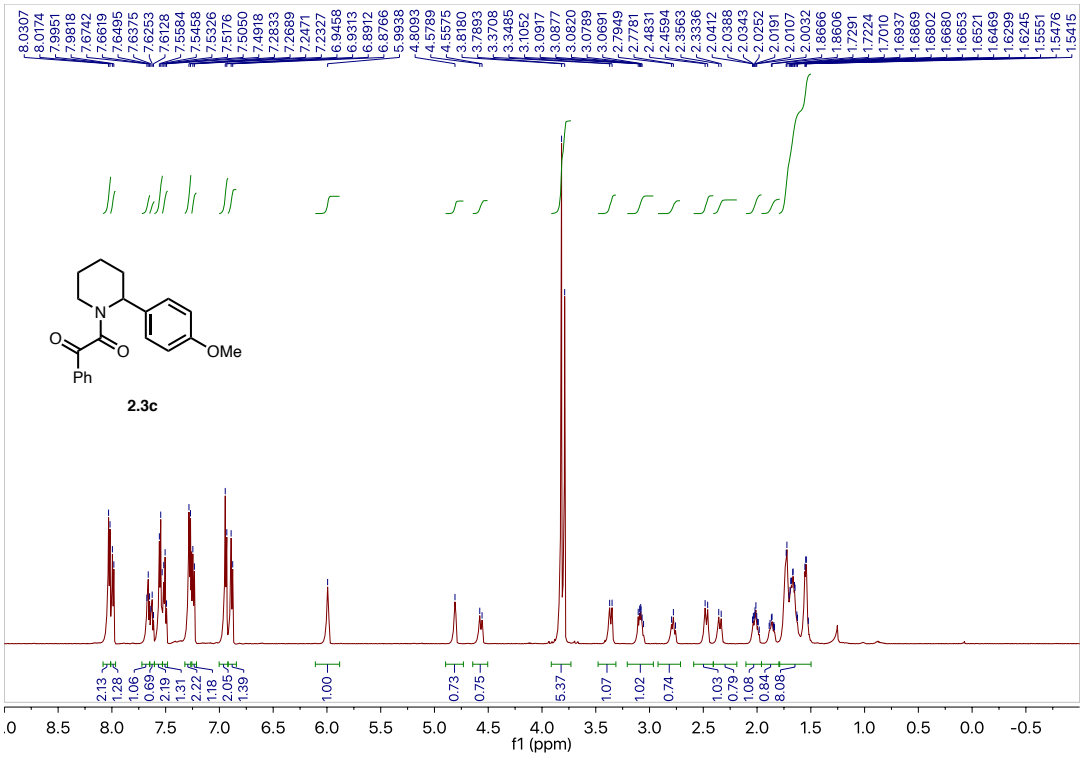


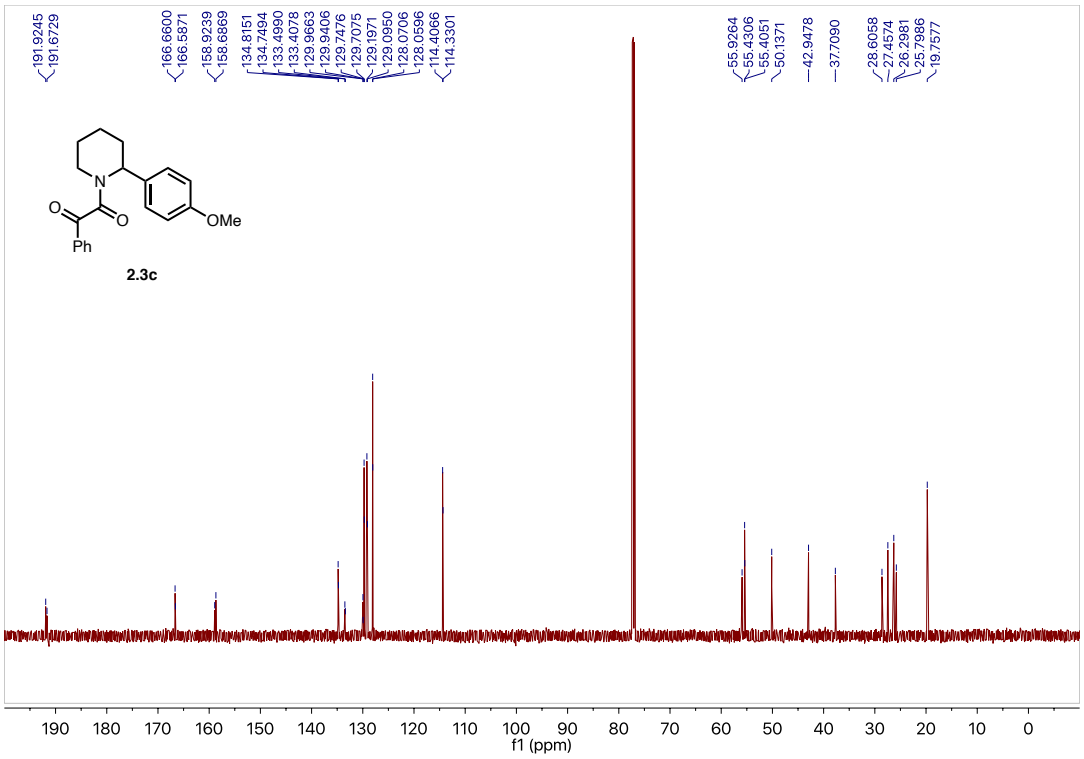

2.4
1.97
1.00
2.07
3.05
2.07
1.00
1.00
1.01
1.00
1.03
1.07
2.08
1.04
f1 (ppm)

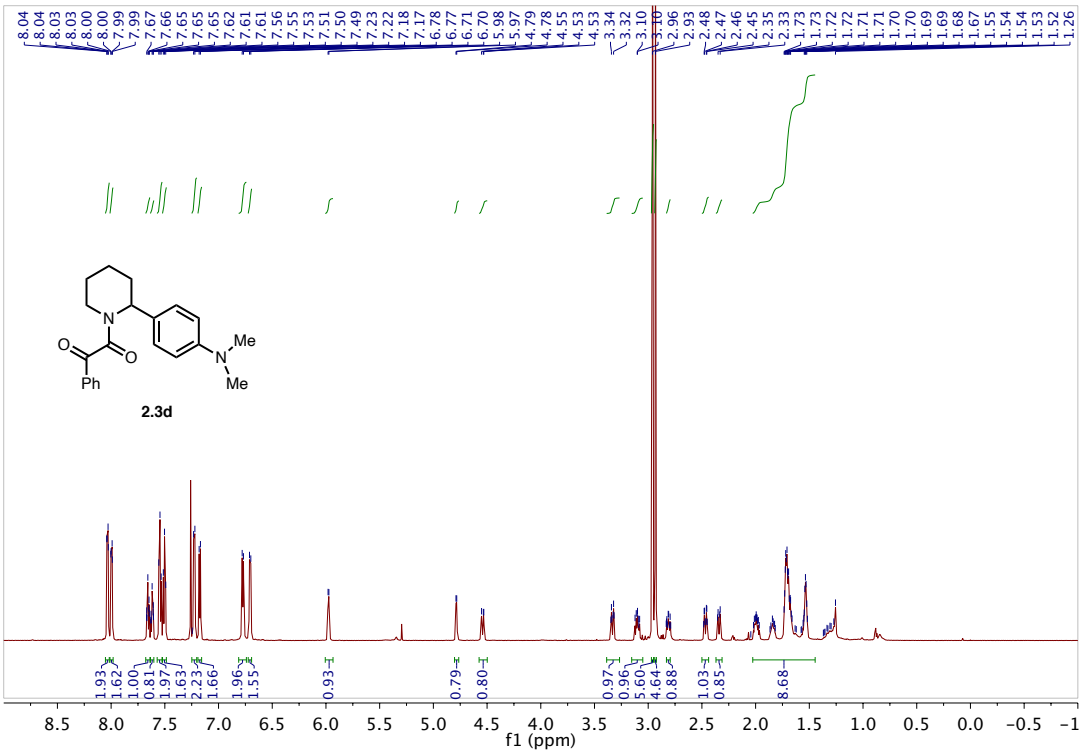

200.47
171.38
136.05
135.98
133.18
129.70
128.74
128.58
128.33
126.86
54.94
46.29
26.07
26.03
20.36
2.4
f1 (ppm)

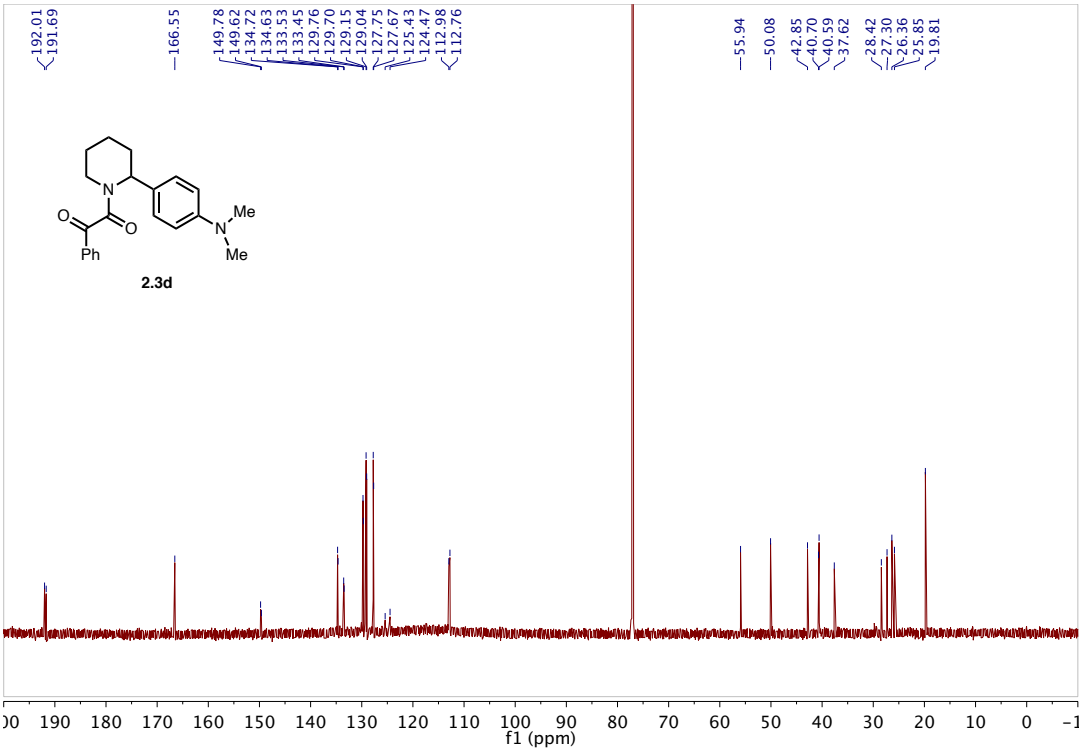

2.3b
f1 (ppm)

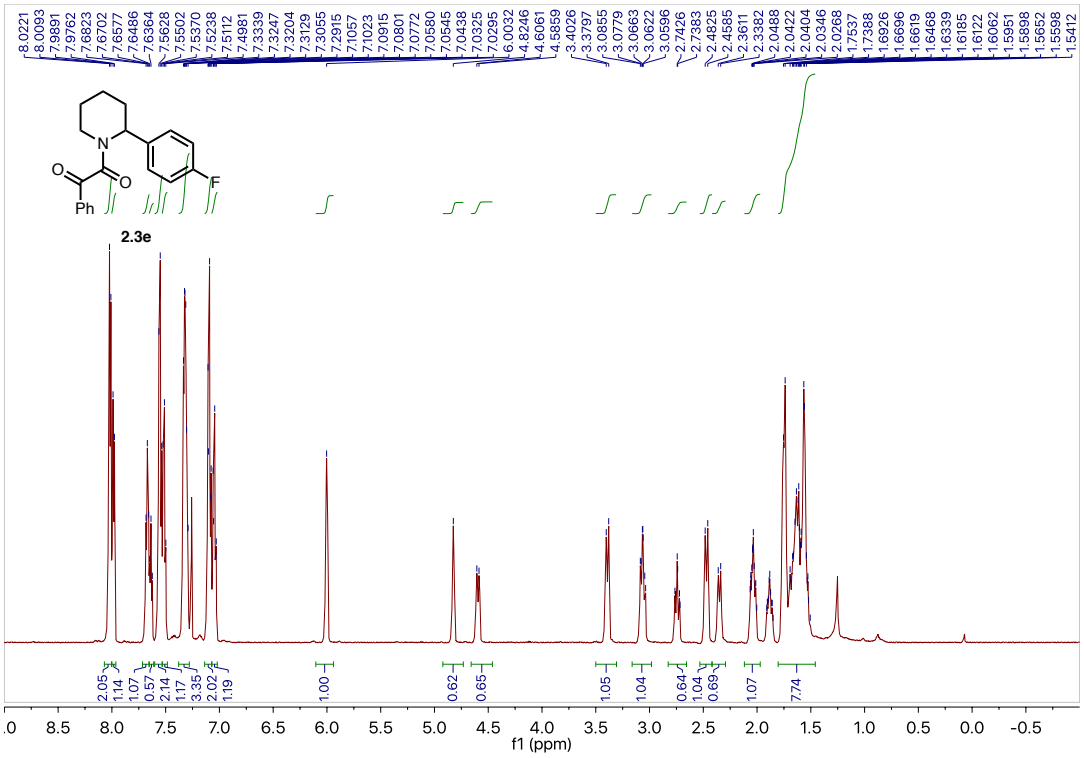

191.9483
191.6421
166.6839
166.6674
143.4719
143.1037
135.2035
134.7988
134.7223
134.5400
133.5265
133.4098
129.7678
129.7314
129.1882
129.0788
128.5064
128.4554
126.8403
126.7820
56.2493
50.4927
43.0738
37.8423
28.5604
28.5094
28.4547
27.4703
26.2819
25.7678
19.7985
19.7962
15.6256
15.5381
2.3b
f1 (ppm)

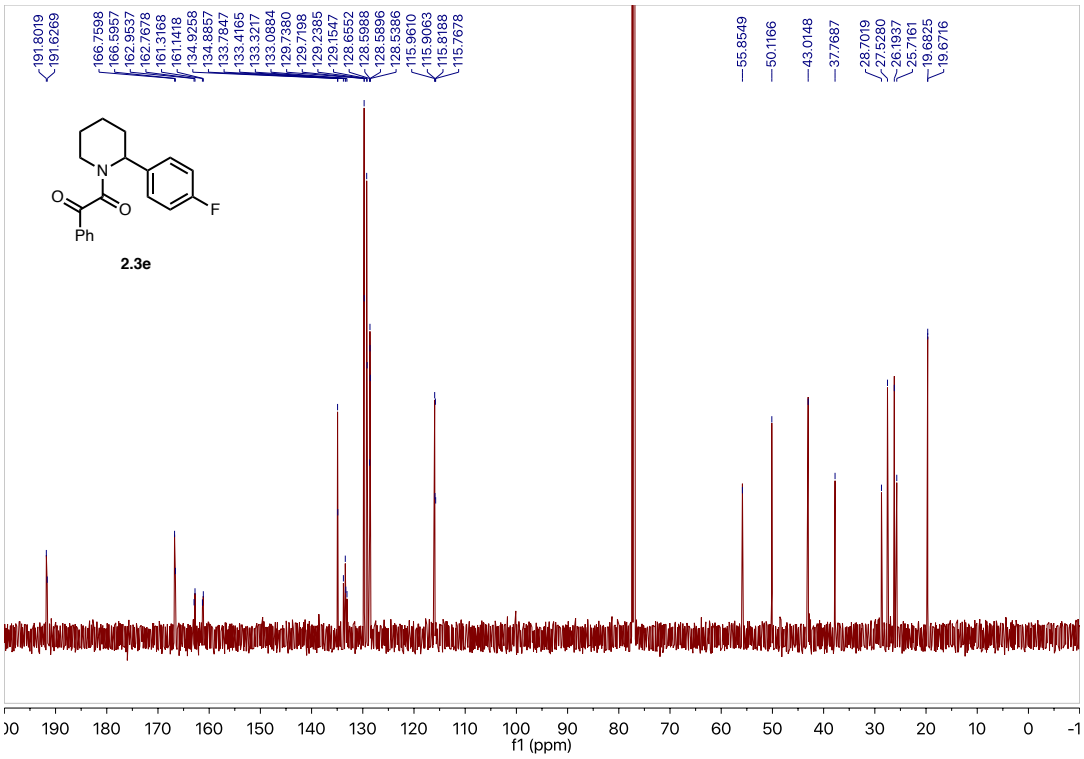

2.3c
f1 (ppm)

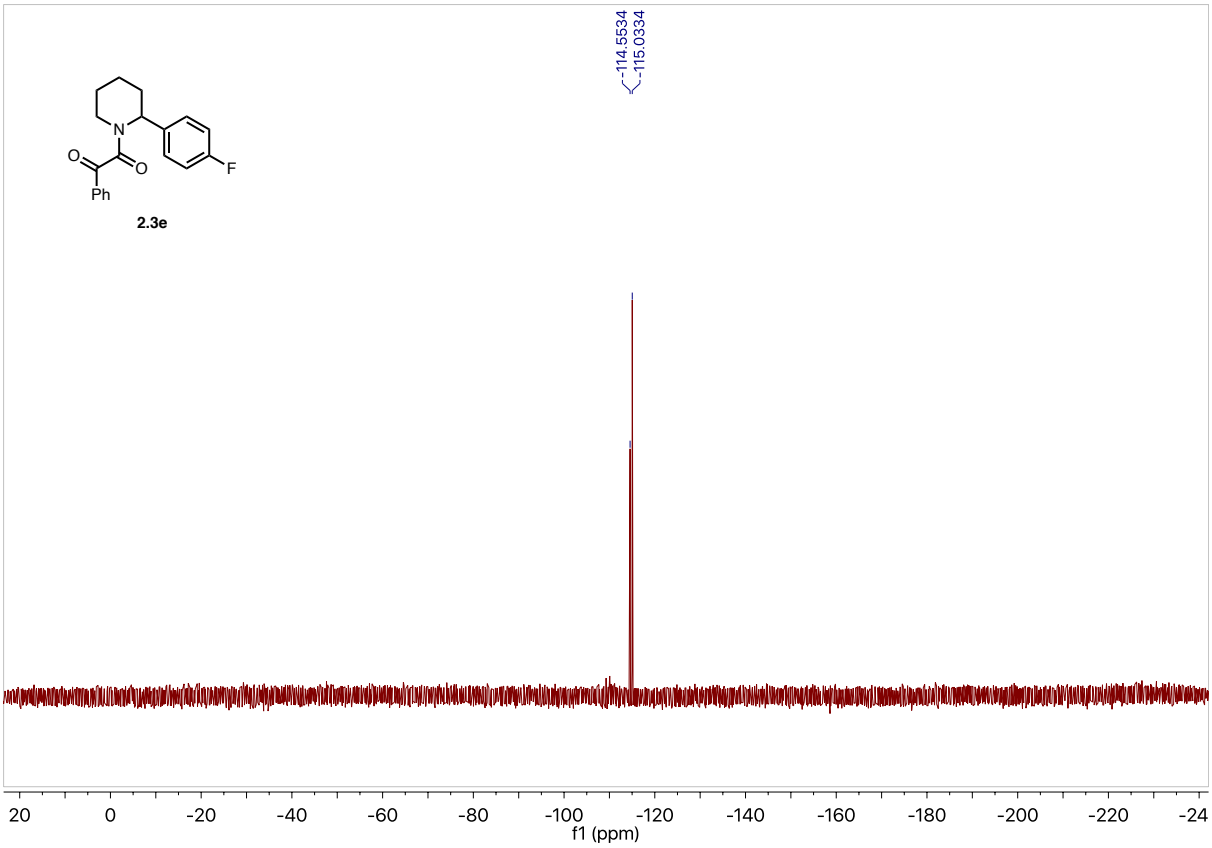

2.3c
f1 (ppm)

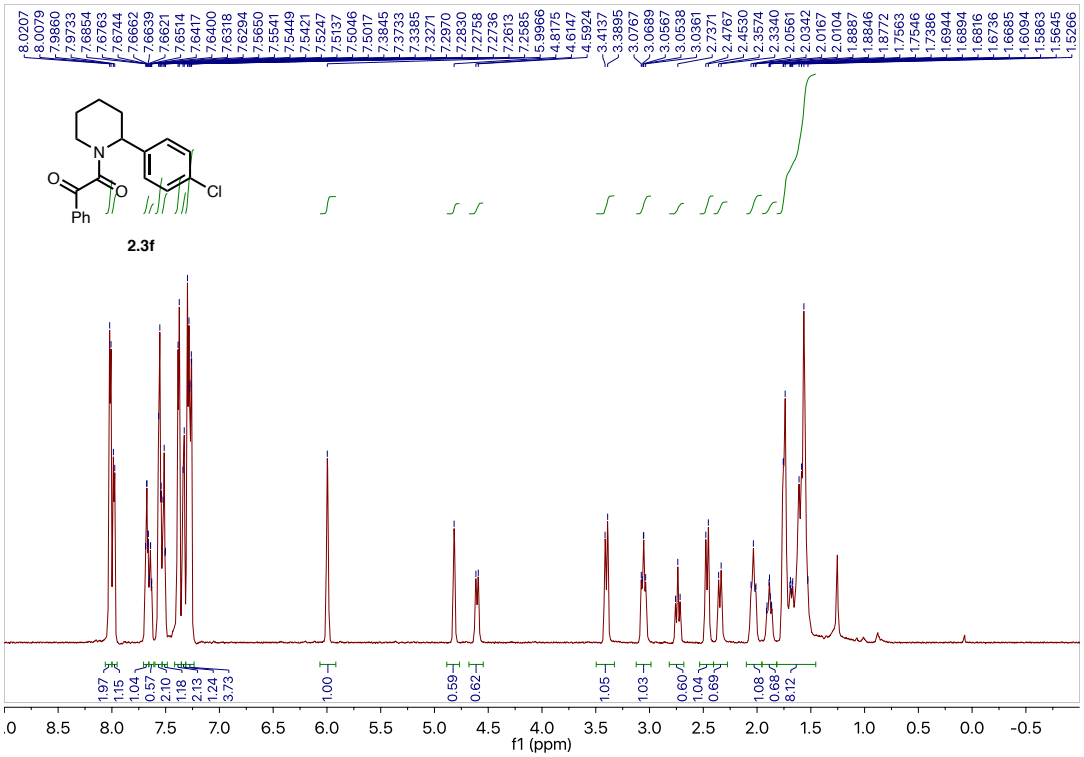

2.3d
f1 (ppm)

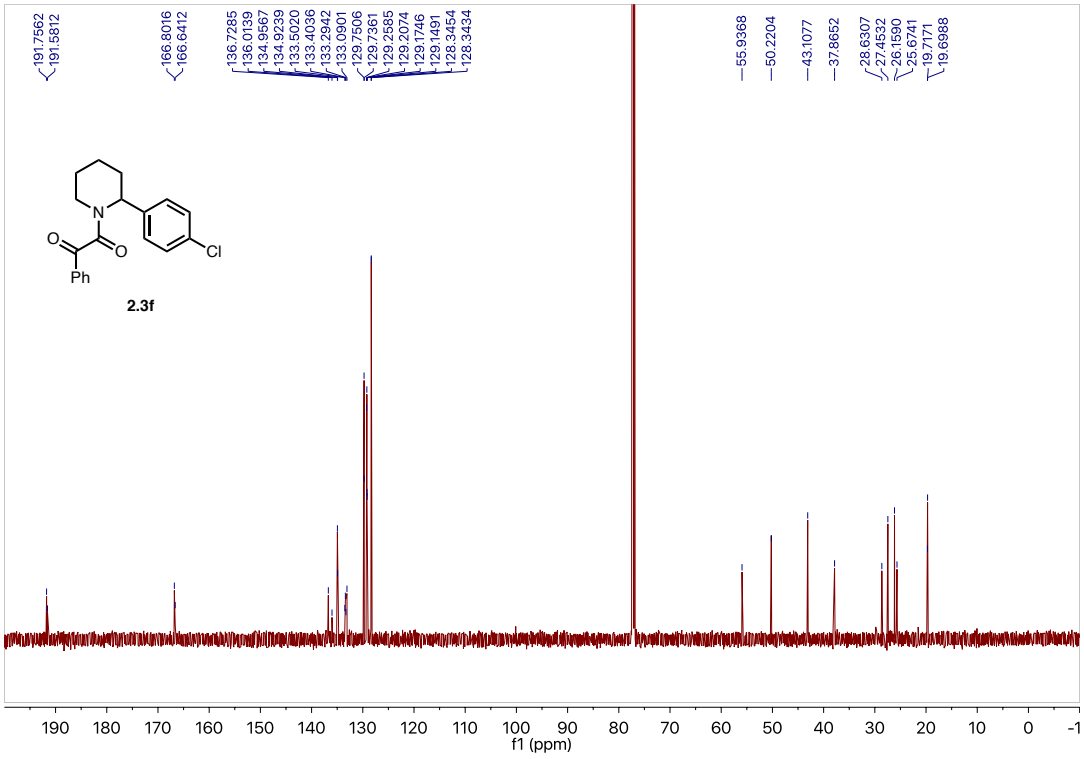

2.3d
f1 (ppm)

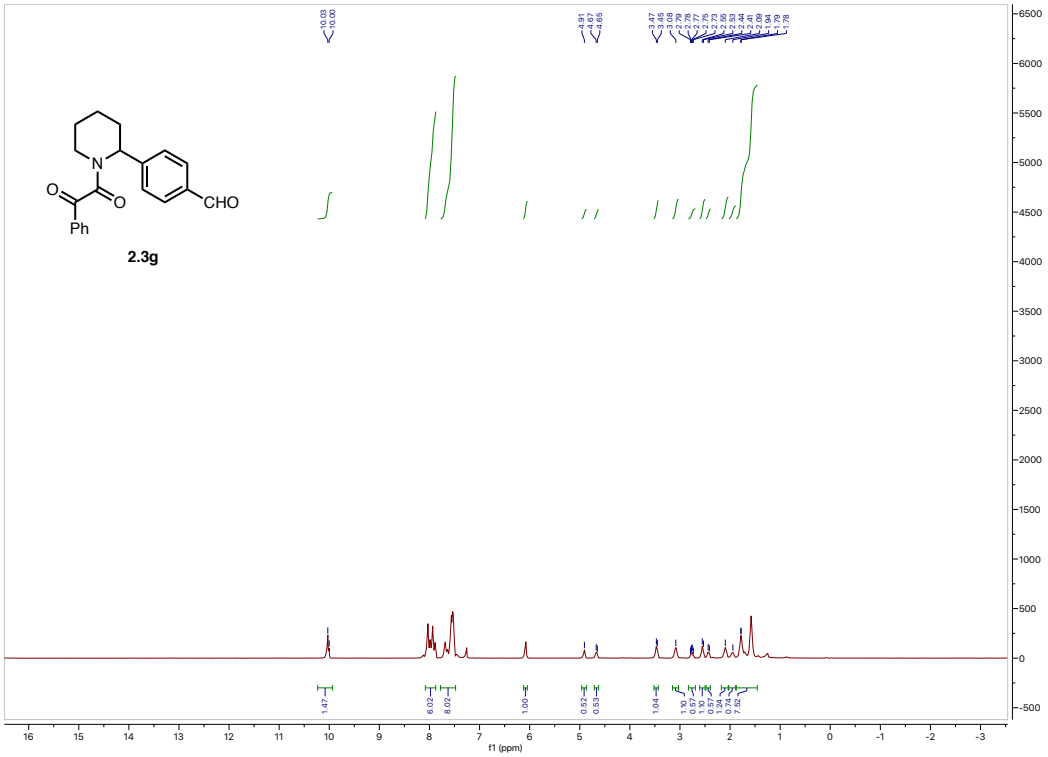

2.3e
f1 (ppm)

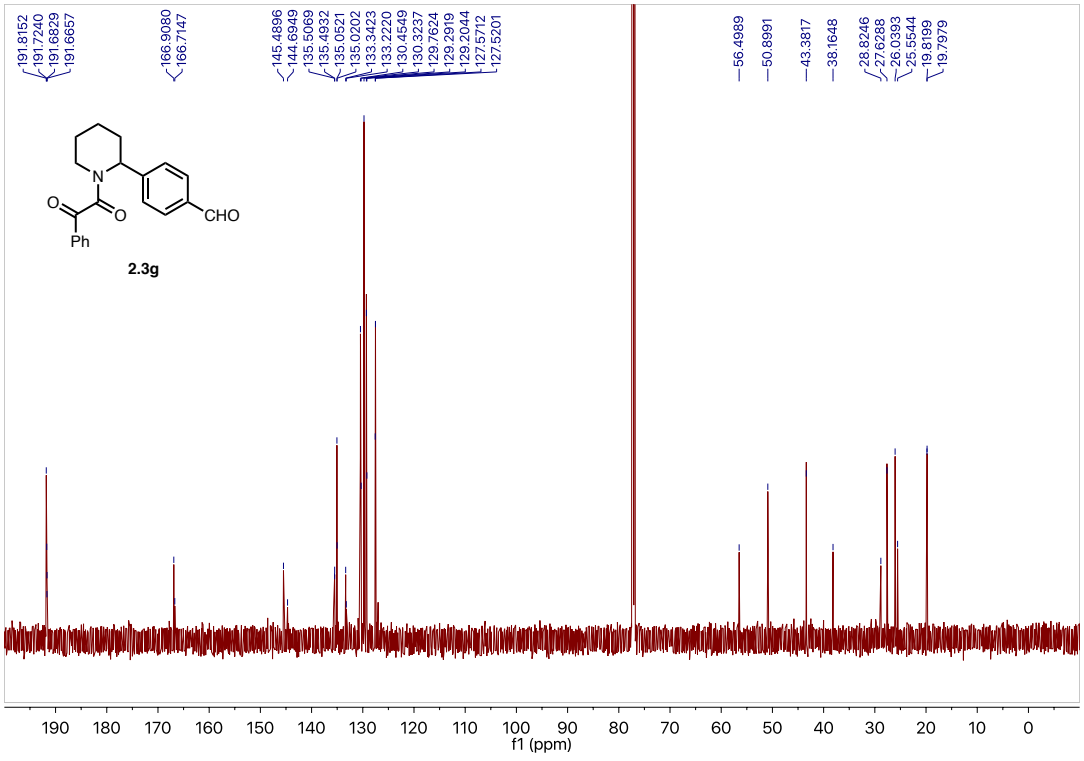

2.3e
f1 (ppm)

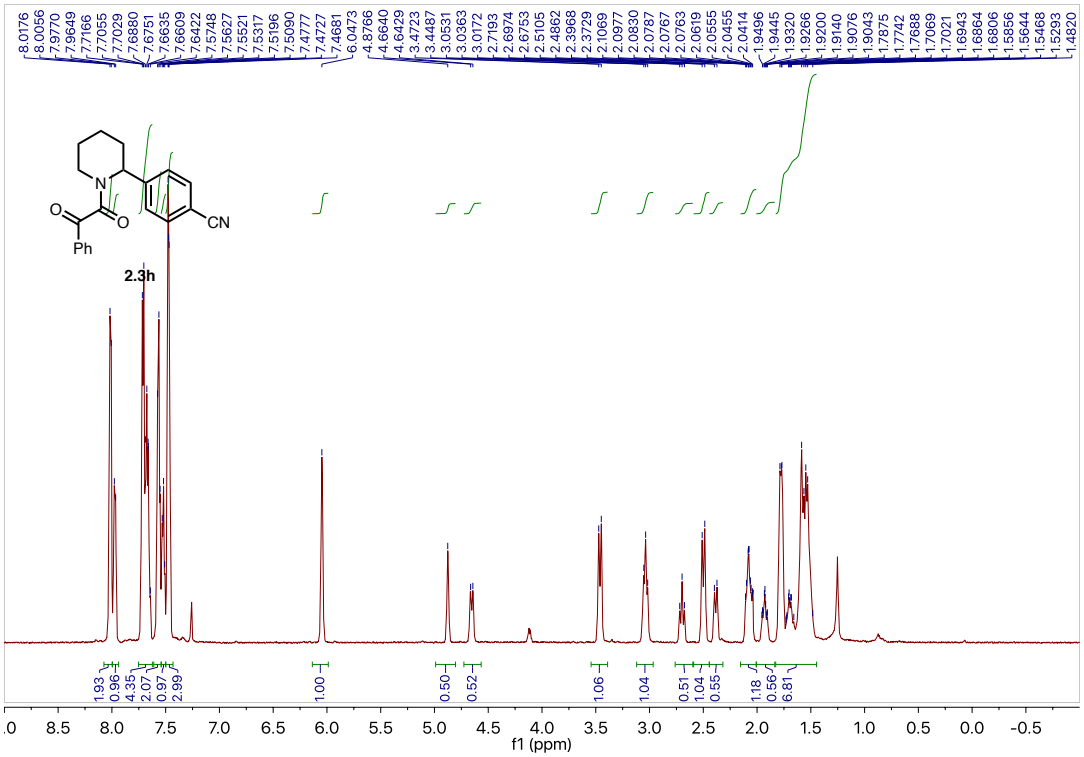

-114.5534
-115.0334
O
O
N
F
Ph
2.3e
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-24
f1 (ppm)

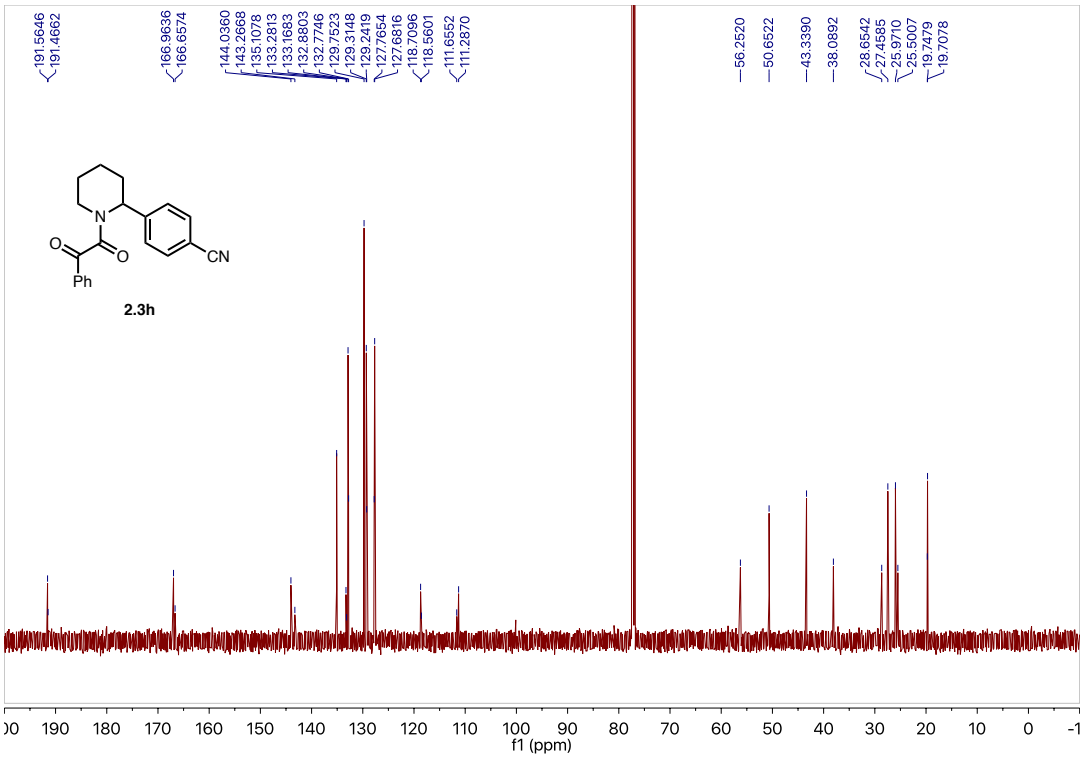

2.3f
f1 (ppm)

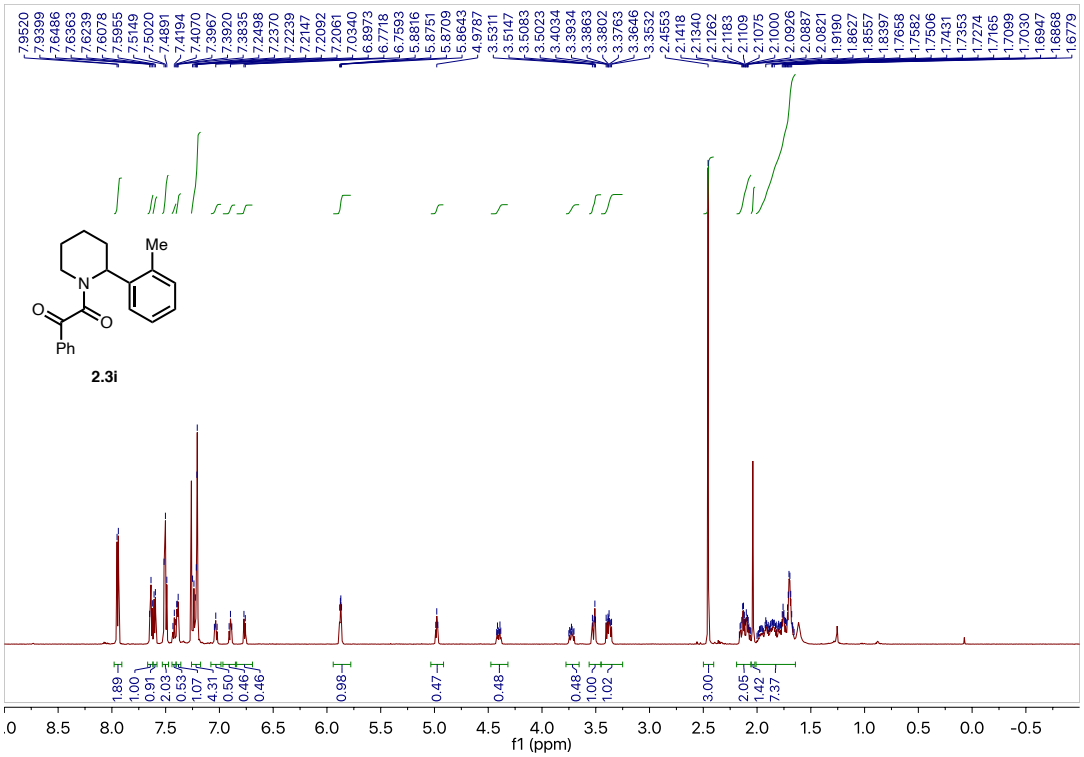

2.3f
f1 (ppm)

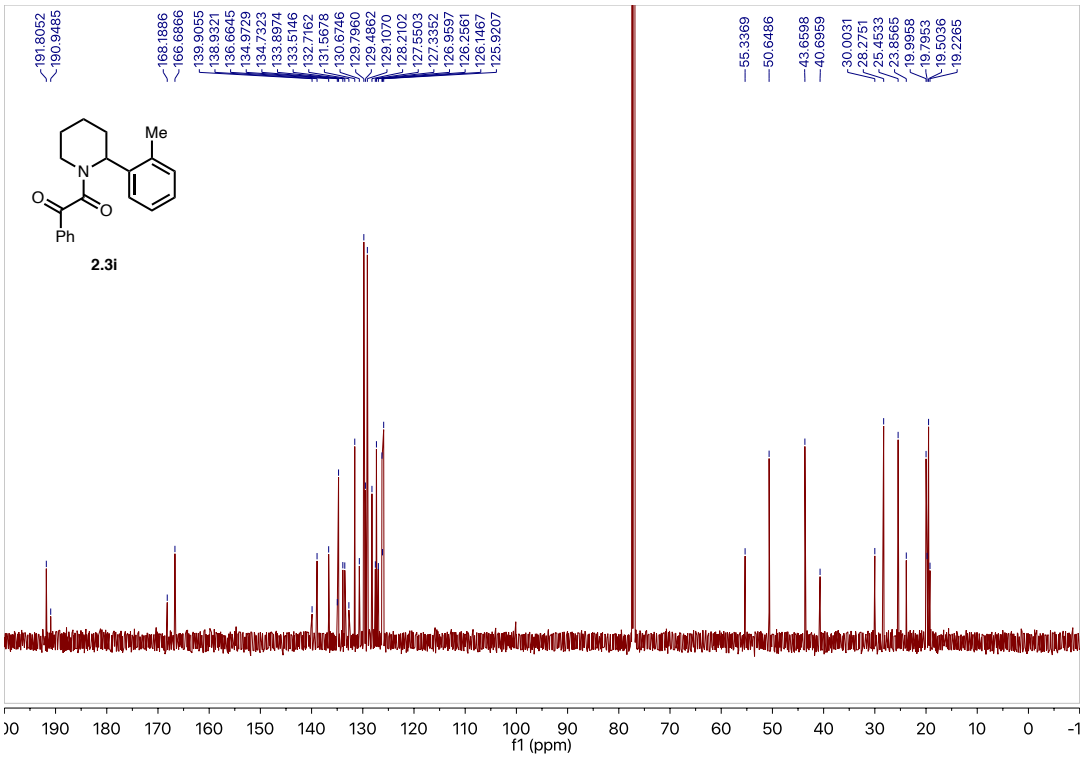

2.3g
f1 (ppm)

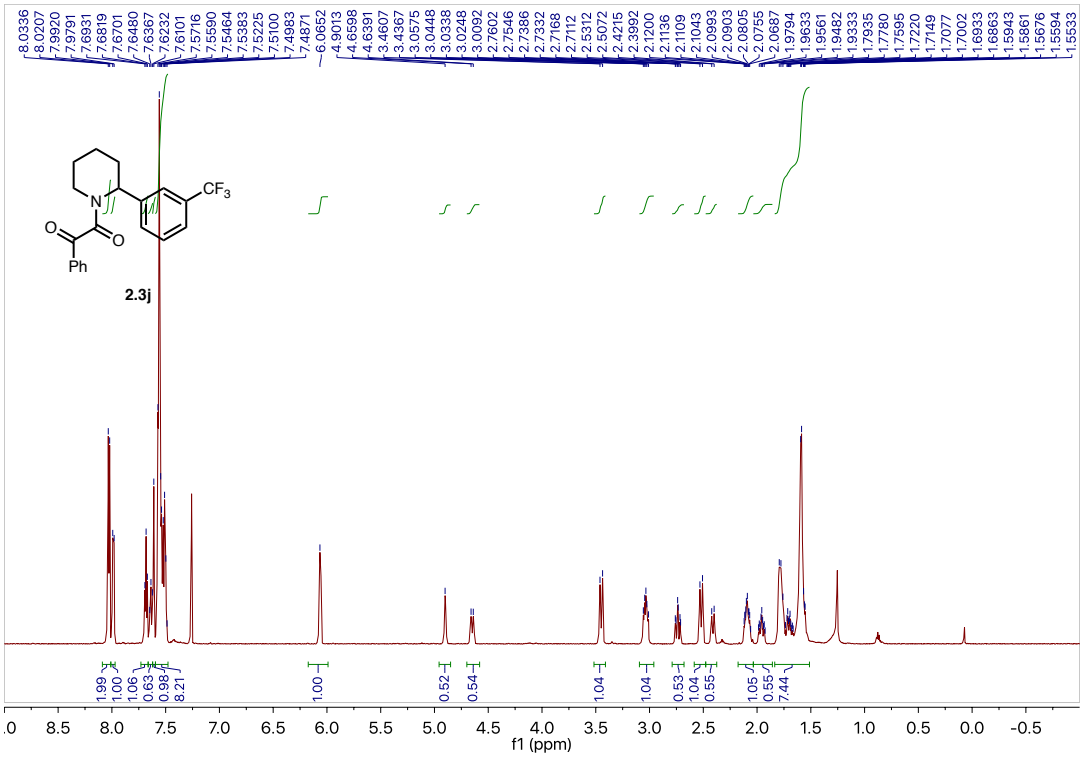

2.3g
f1 (ppm)

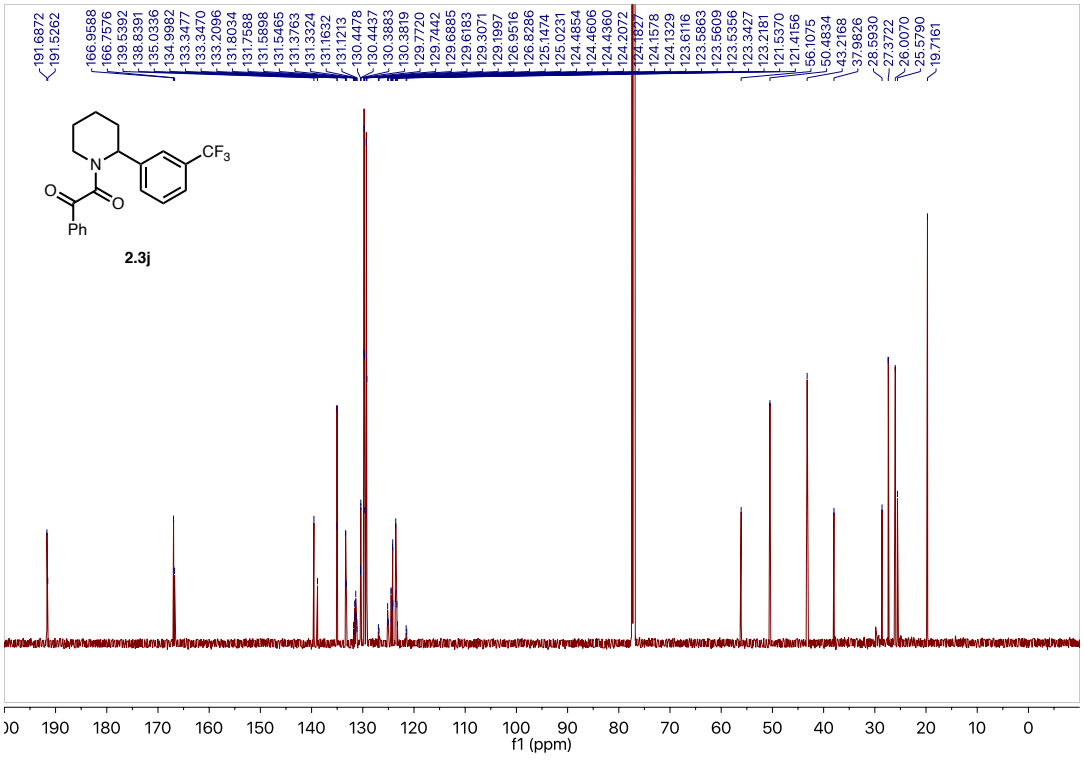

8.0176
8.0056
7.9770
7.9649
7.7166
7.7055
7.7029
7.6880
7.6751
7.6635
7.6609
7.6422
7.5748
7.5627
7.5521
7.5317
7.5196
7.5090
7.4777
7.4727
7.4681
6.0473
4.8766
4.6640
4.6429
3.4723
3.4487
3.0531
3.0363
3.0172
2.7193
2.6974
2.6753
2.5105
2.4862
2.3968
2.3729
2.1069
2.0977
2.0830
2.0787
2.0767
2.0763
2.0619
2.0555
2.0455
2.0414
1.9496
1.9445
1.9320
1.9266
1.9200
1.9140
1.9076
1.9043
1.7875
1.7742
1.7688
1.7069
1.7021
1.6943
1.6864
1.6806
1.5856
1.5644
1.5468
1.5293
1.4820
O
N
O
Ph
CN
2.3h
1.93
0.96
4.35
2.07
0.97
2.99
1.00
0.50
0.52
1.06
1.04
0.51
1.04
0.55
1.18
0.56
6.81
f1 (ppm)

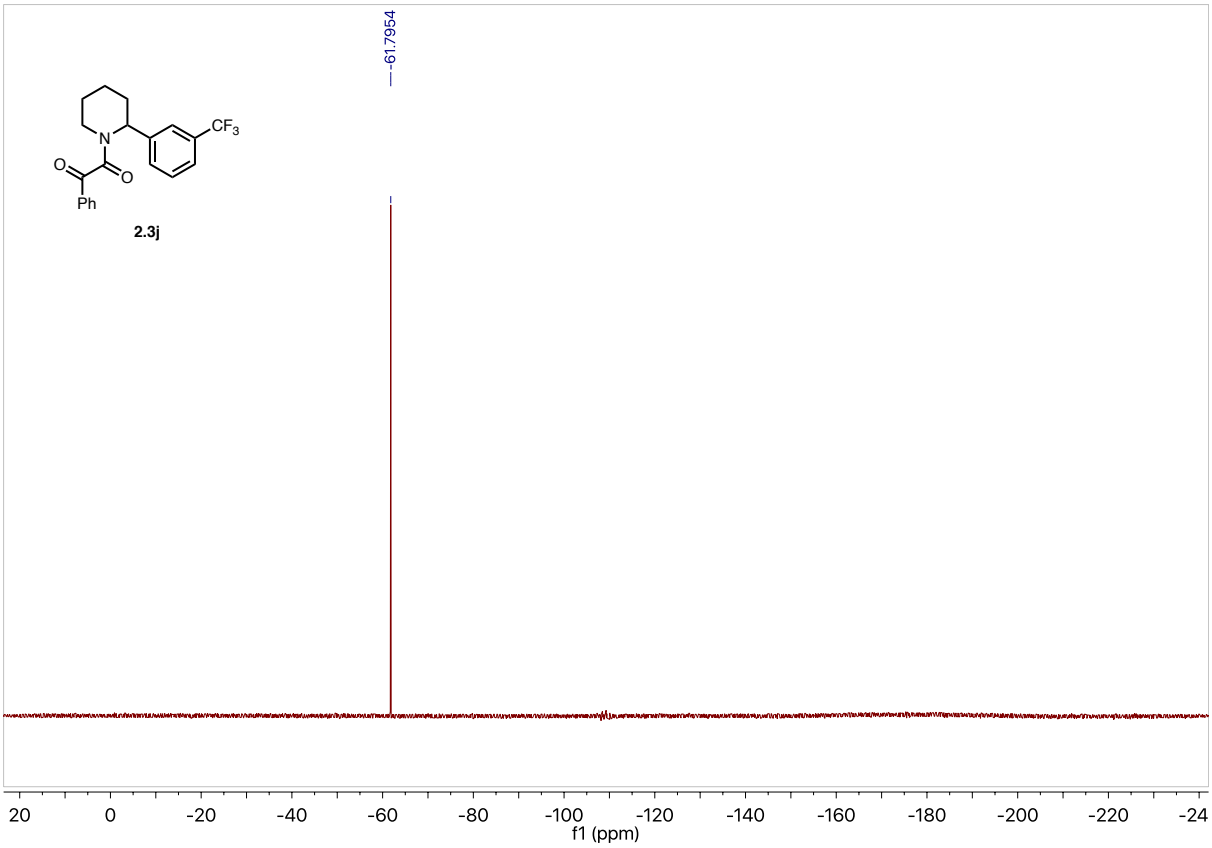

191.5646
191.4662
166.9636
166.6574
144.0360
143.2668
135.1078
133.2813
133.1683
132.8803
132.7746
129.7523
129.3148
129.2419
127.7654
127.6816
118.7096
118.5601
111.6552
111.2870
56.2520
50.6522
43.3390
38.0892
28.6542
27.4585
25.9710
25.5007
19.7479
19.7078
O
N
O
Ph
CN
2.3h
f1 (ppm)

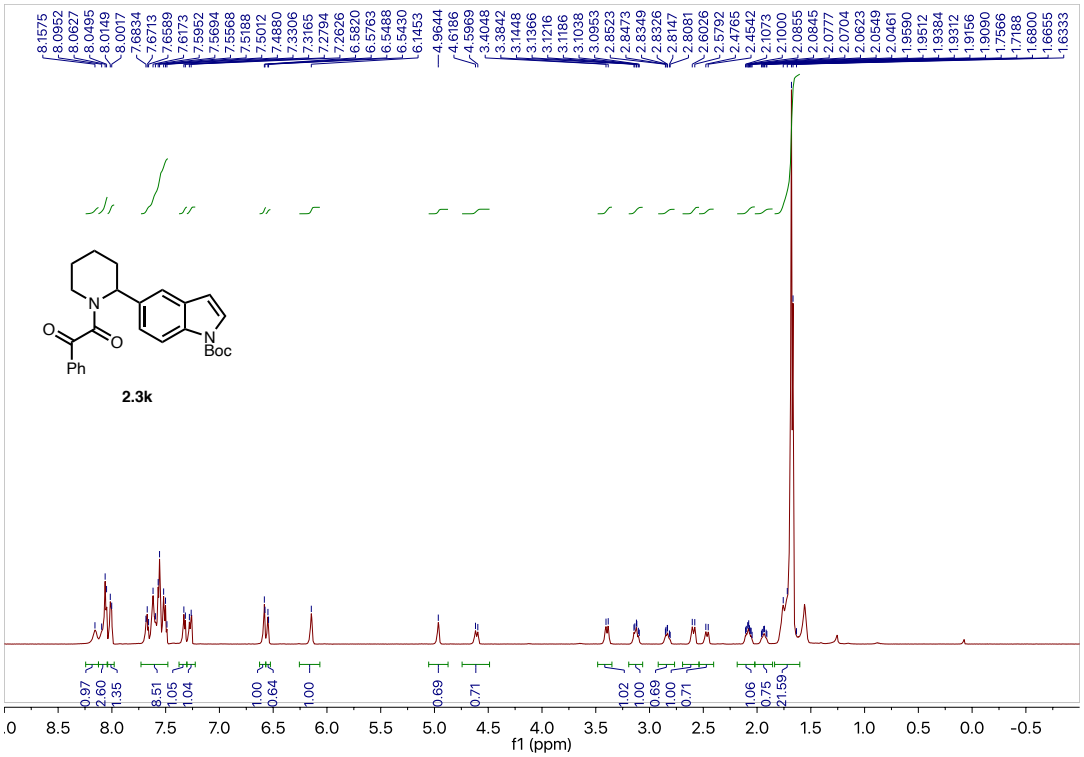

Me
N
O
O
Ph
2.3i
f1 (ppm)

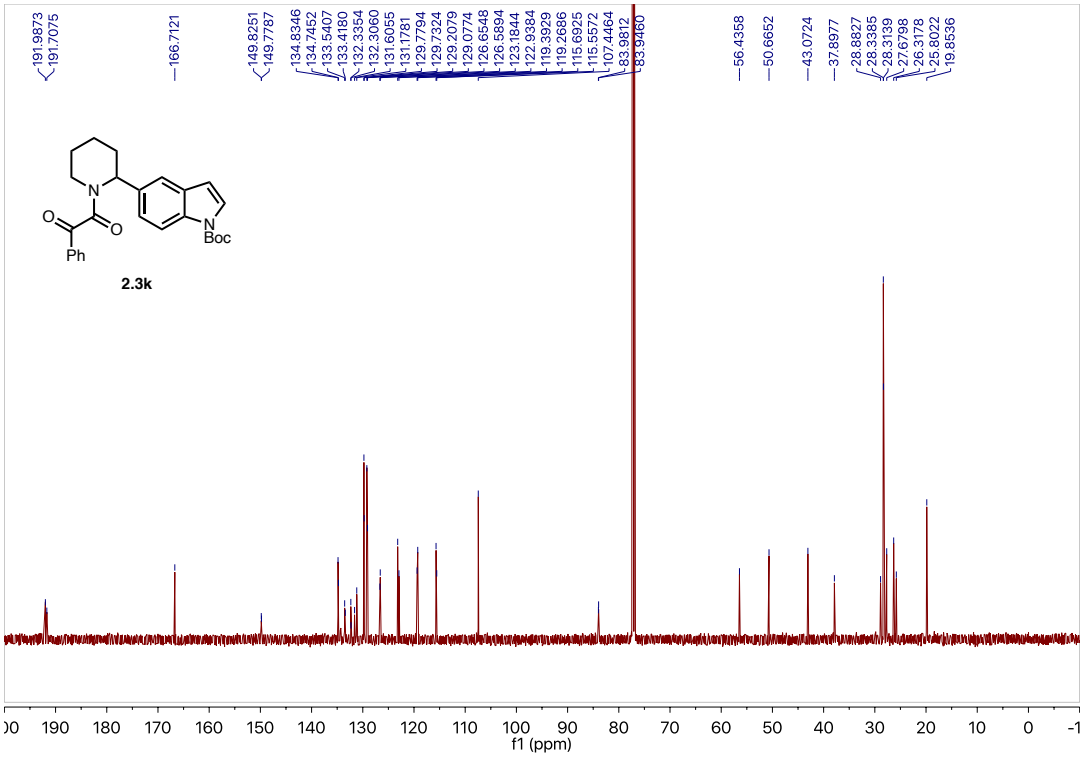

Me
N
O
O
Ph
2.3i
f1 (ppm)

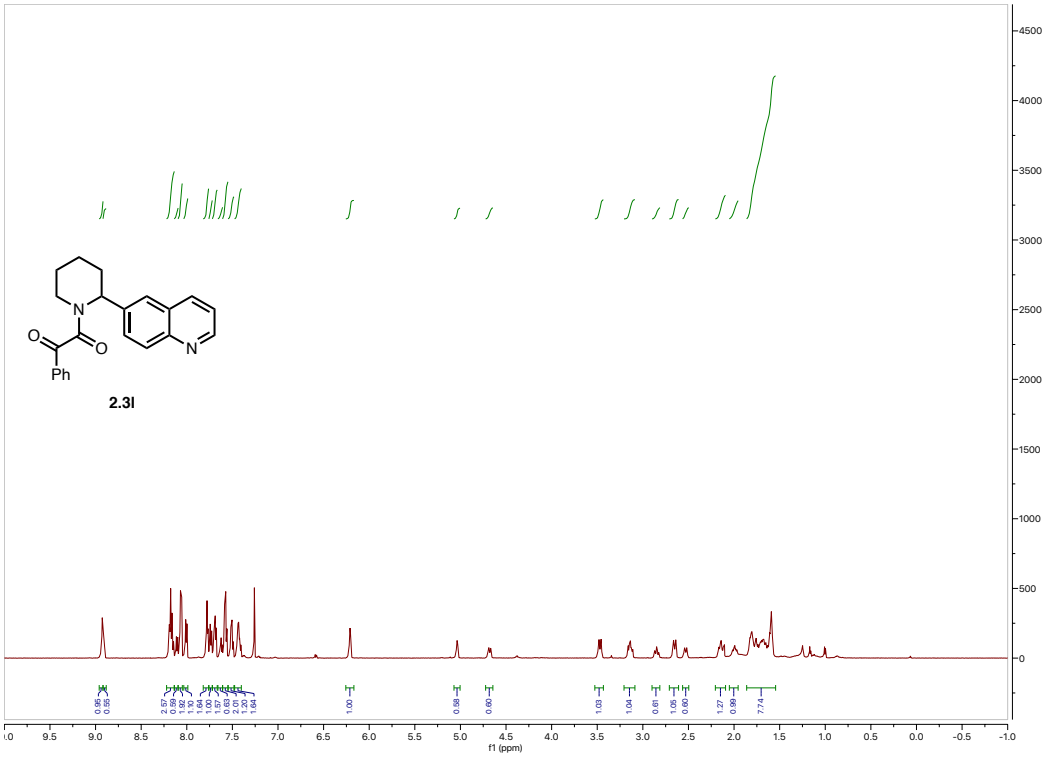

2.3j
f1 (ppm)

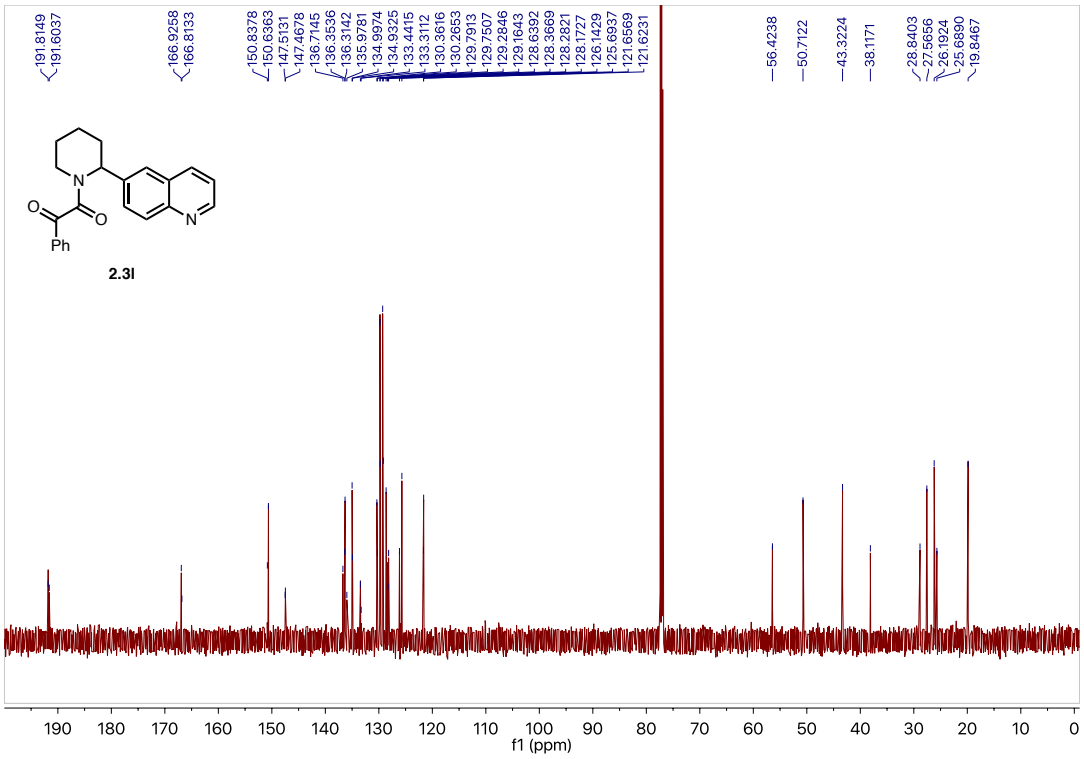

2.3j
f1 (ppm)

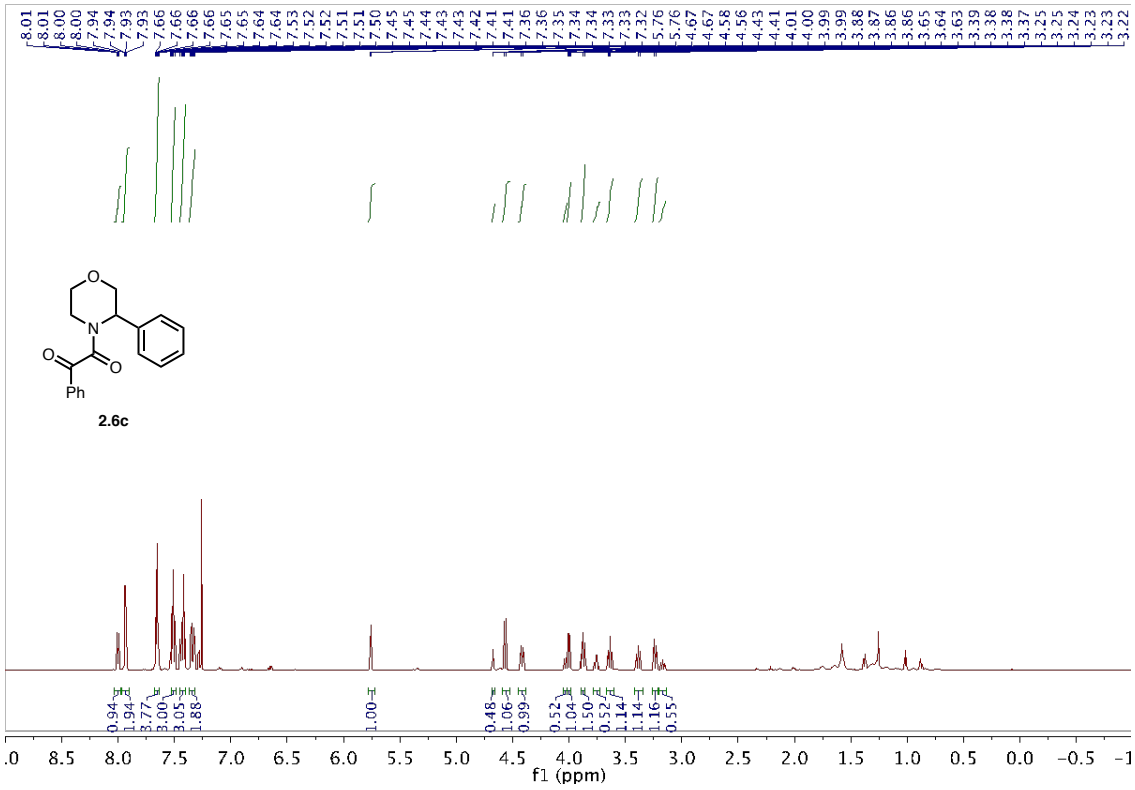

-61.7954
CF3
N
O
O
Ph
2.3j
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
-220
-24
f1 (ppm)

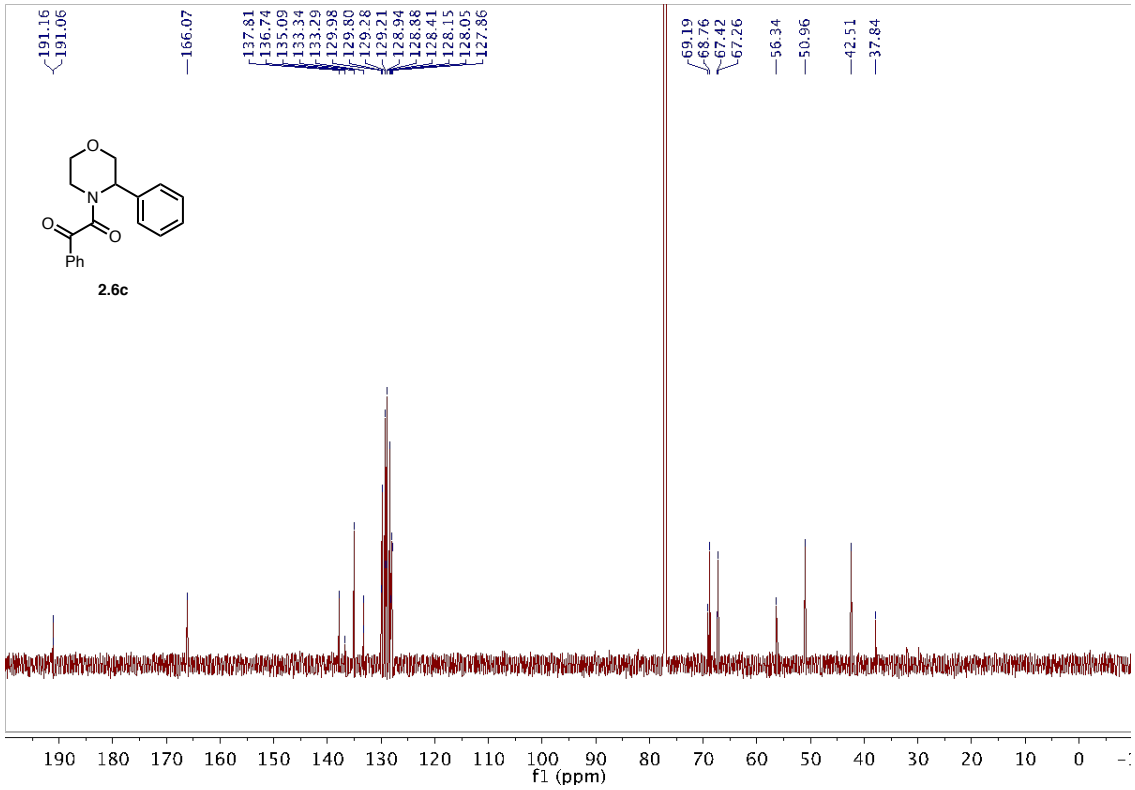

2.3k
f1 (ppm)

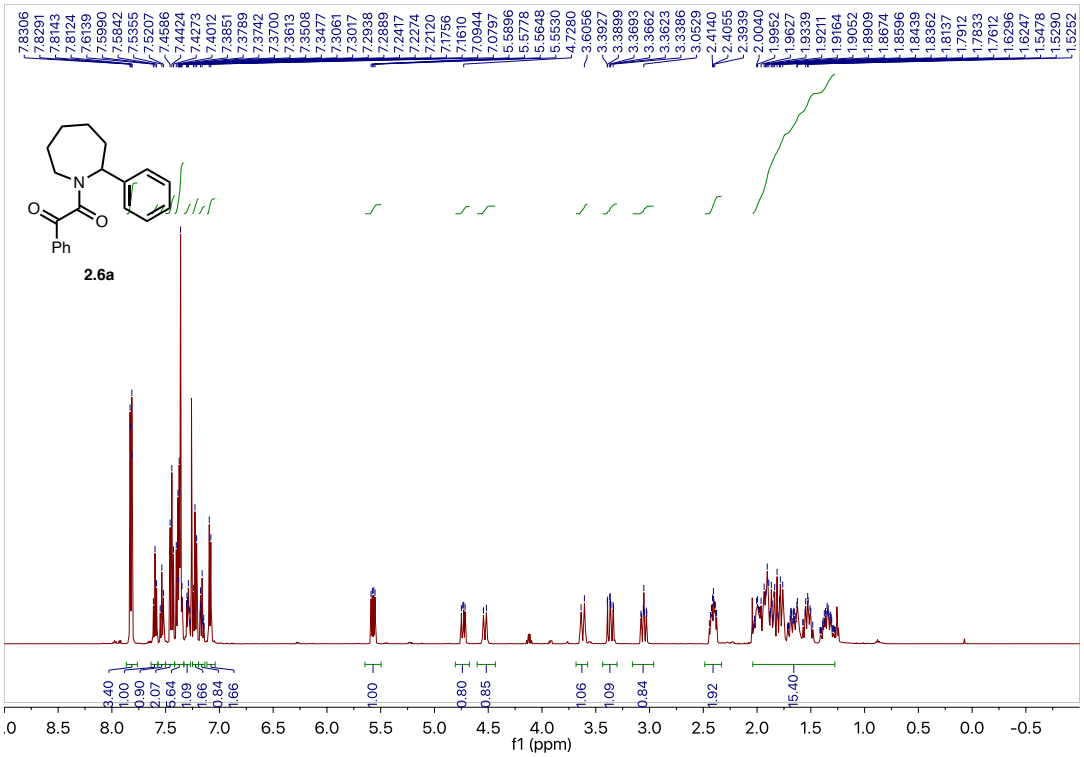

2.3k
f1 (ppm)

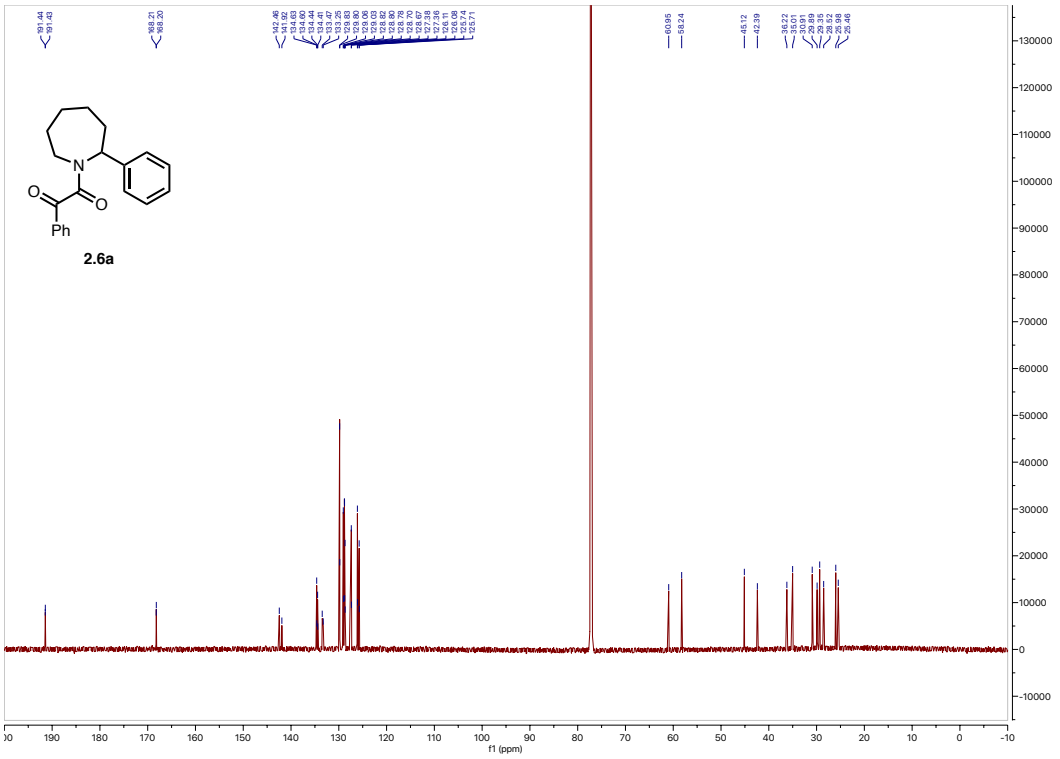

2.3l
f1 (ppm)

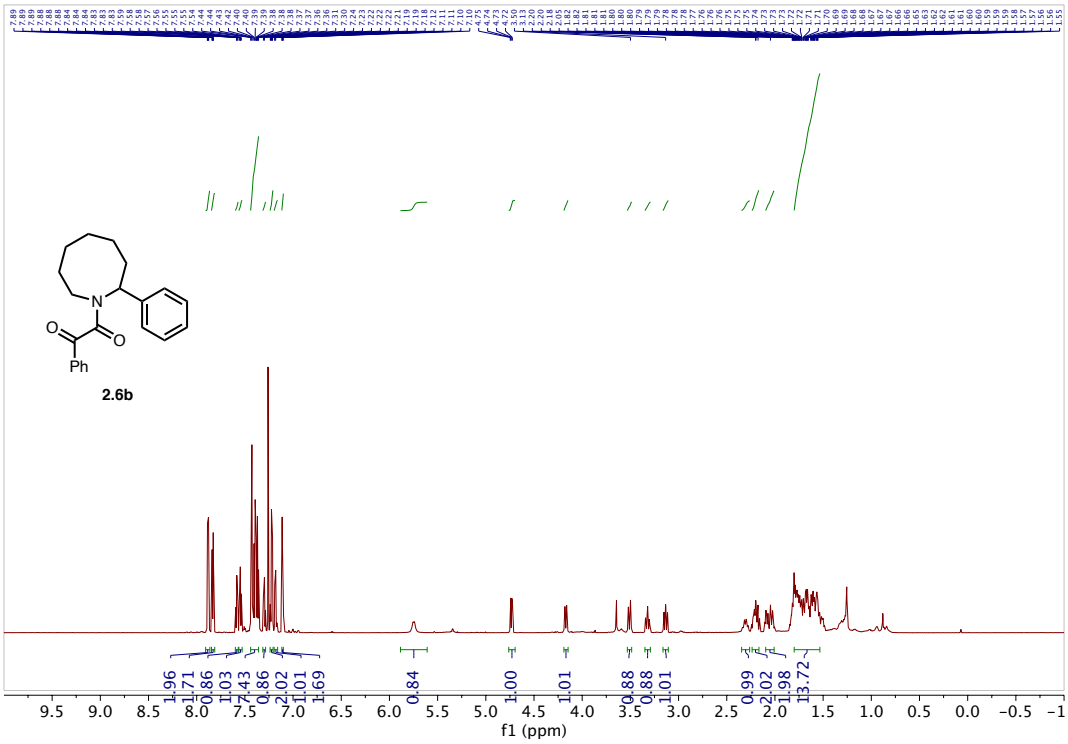

191.8149
191.6037
166.9258
166.8133
150.8378
150.6363
147.5131
147.4678
136.7145
136.3536
136.3142
135.9781
134.9974
134.9325
133.4415
133.3112
130.3616
130.2653
129.7913
129.7507
129.2846
129.1643
128.6392
128.3669
128.2821
128.1727
126.1429
125.6937
121.6569
121.6231
56.4238
50.7122
43.3224
38.1171
28.8403
27.5656
26.1924
25.6890
19.8467
2.3l
f1 (ppm)

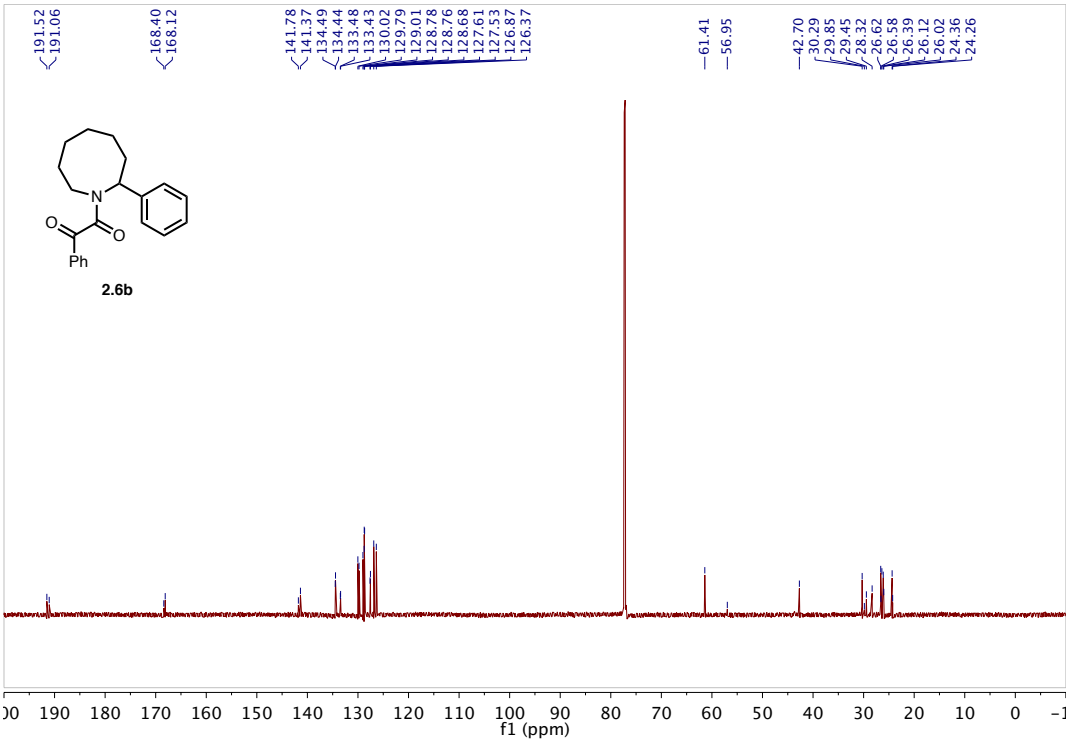

8.01
8.01
8.00
8.00
7.94
7.94
7.93
7.93
7.66
7.66
7.66
7.66
7.65
7.65
7.64
7.64
7.53
7.52
7.52
7.51
7.51
7.50
7.45
7.45
7.44
7.43
7.43
7.42
7.41
7.41
7.36
7.36
7.35
7.34
7.34
7.33
7.33
7.32
5.76
5.76
4.67
4.67
4.58
4.56
4.43
4.41
4.01
4.00
3.99
3.99
3.88
3.87
3.86
3.86
3.65
3.65
3.64
3.63
3.39
3.38
3.38
3.37
3.25
3.25
3.24
3.23
3.23
3.22
O
N
O
O
Ph
2.6c
0.94
1.94
3.77
3.00
3.05
1.88
1.00
0.48
1.06
0.99
0.52
1.04
1.50
0.52
1.14
1.14
1.16
0.55
f1 (ppm)

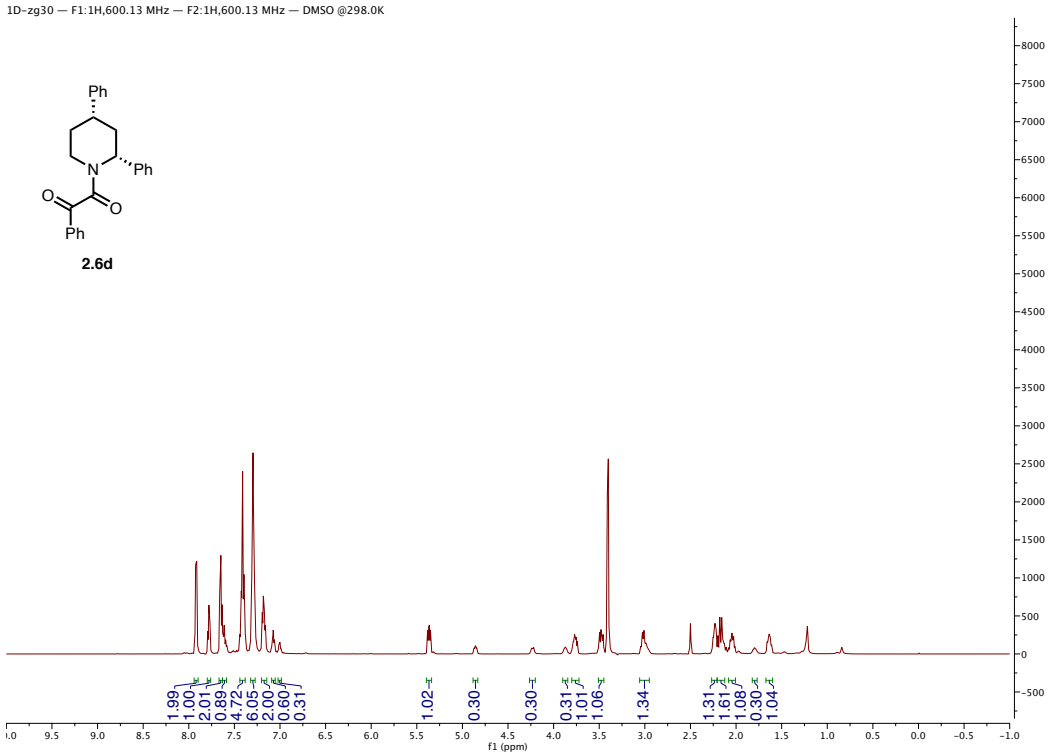

191.16
191.06
166.07
137.81
136.74
135.09
133.34
133.29
129.98
129.80
129.28
129.21
128.94
128.86
128.41
128.15
128.05
127.86
69.19
68.76
67.42
67.26
56.34
50.96
42.51
37.84
O
N
O
O
Ph
2.6c
f1 (ppm)

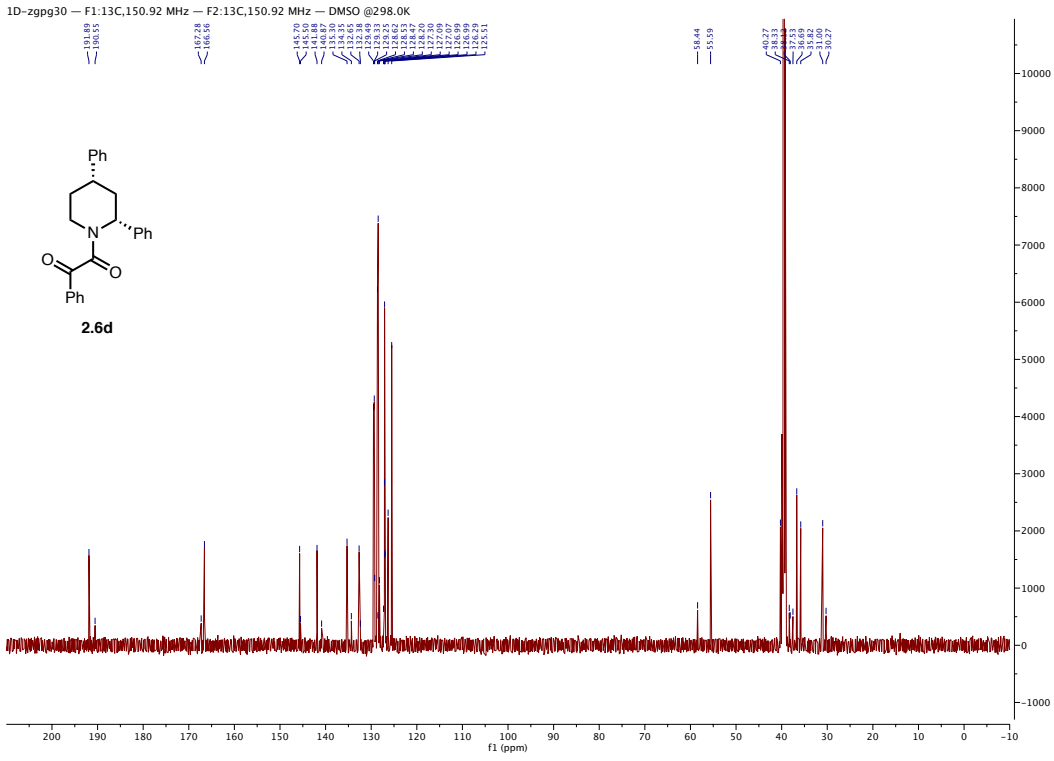

2.6a
f1 (ppm)


2.6a
f1 (ppm)

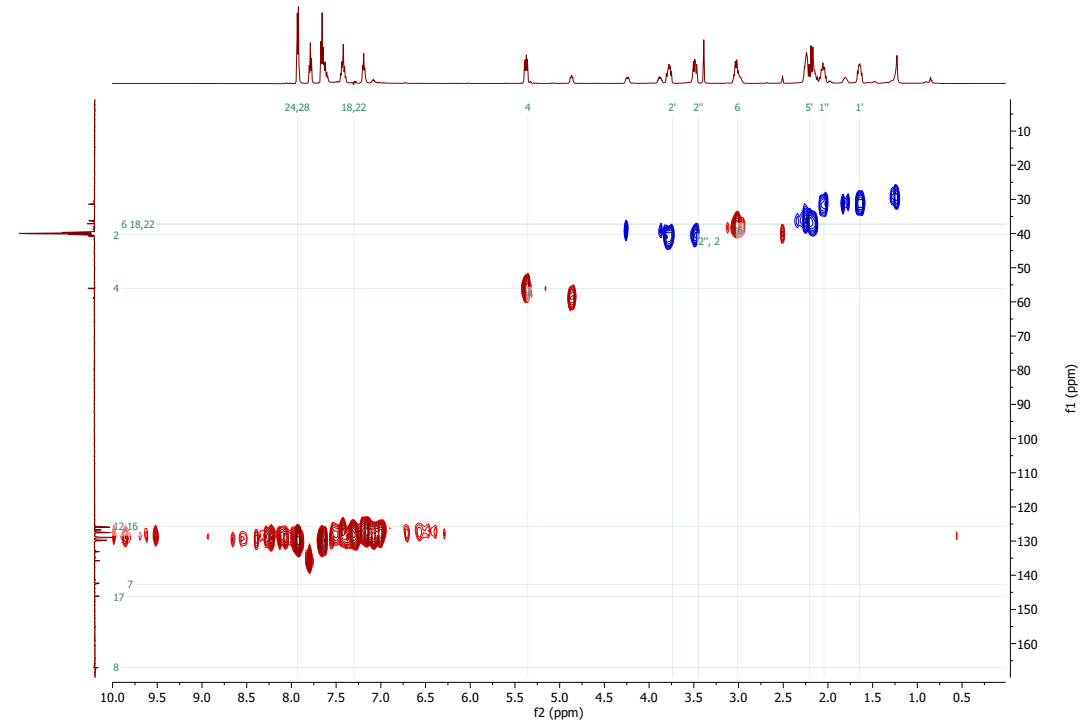

2.6b
1.96
1.71
0.86
1.03
2.43
0.86
2.02
1.01
1.69
0.84
1.00
1.01
0.88
0.88
1.01
0.99
2.02
1.98
13.72
f1 (ppm)


2.6b
191.52
191.06
168.40
168.12
141.78
141.37
134.49
134.44
133.48
133.43
130.02
129.79
129.01
128.78
128.76
128.68
127.61
127.53
126.87
126.37
61.41
56.95
42.70
30.29
29.85
29.45
28.32
26.62
26.58
26.39
26.12
26.02
24.36
24.26
f1 (ppm)

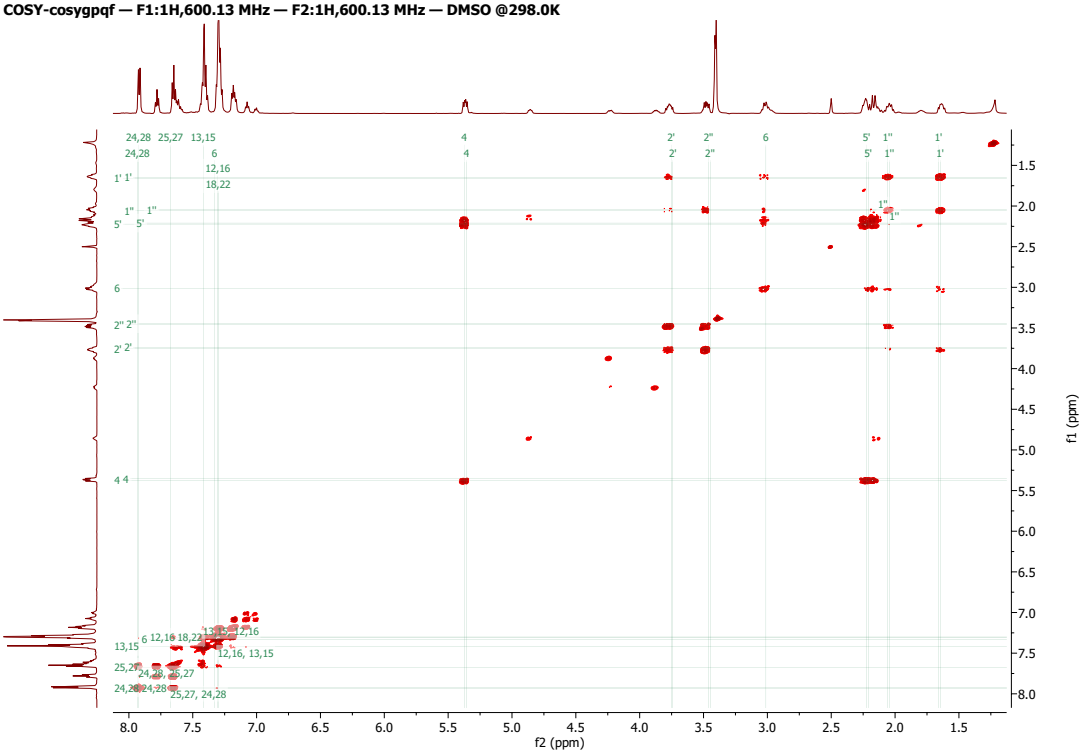

1D-zg30 — F1:1H,600.13 MHz — F2:1H,600.13 MHz — DMSO @298.0K
Ph
N
Ph
O
O
Ph
2.6d
1.99
1.00
2.01
0.89
4.72
6.05
2.00
0.60
0.31
1.02
0.30
0.30
0.31
1.01
1.06
1.34
1.31
1.61
1.08
0.30
1.04
f1 (ppm)


1D-zgpg30 — F1:13C,150.92 MHz — F2:13C,150.92 MHz — DMSO @298.0K
Ph
N
Ph
O
O
Ph
2.6d
f1 (ppm)

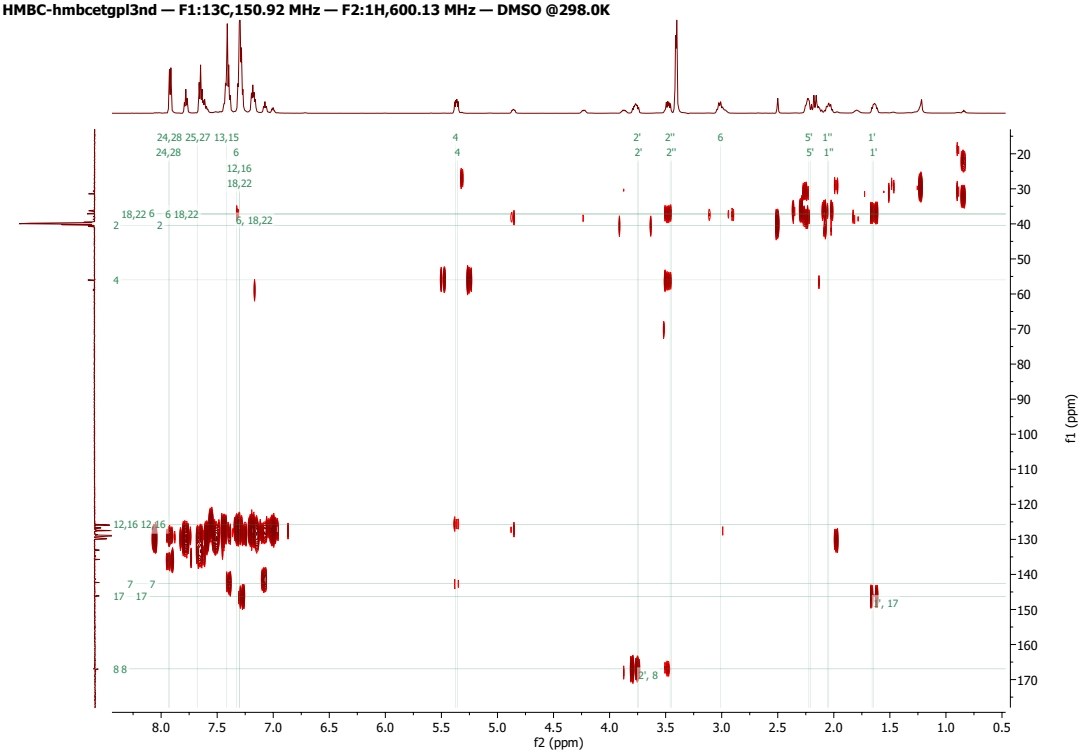
HSQC-EDITED-hsqcedetgpsisp2.3 — F1:13C,150.92 MHz — F2:1H,600.13 MHz — DMSO @298.0K



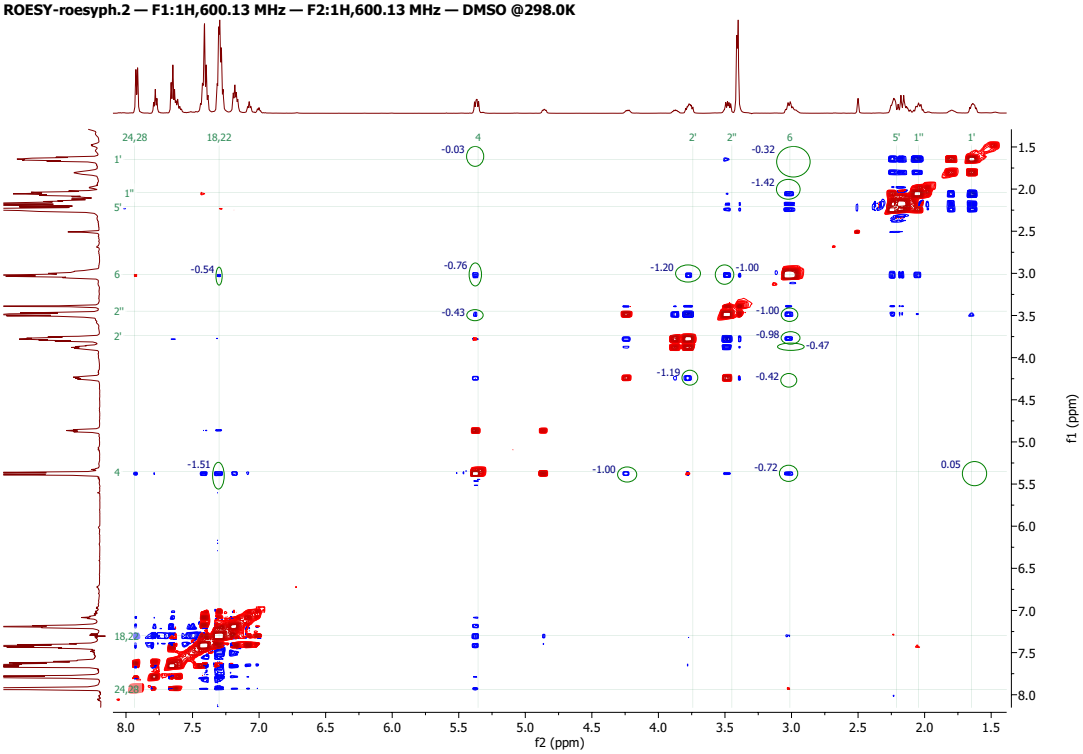
COSY-cosygpqf — F1:1H,600.13 MHz — F2:1H,600.13 MHz — DMSO @298.0K



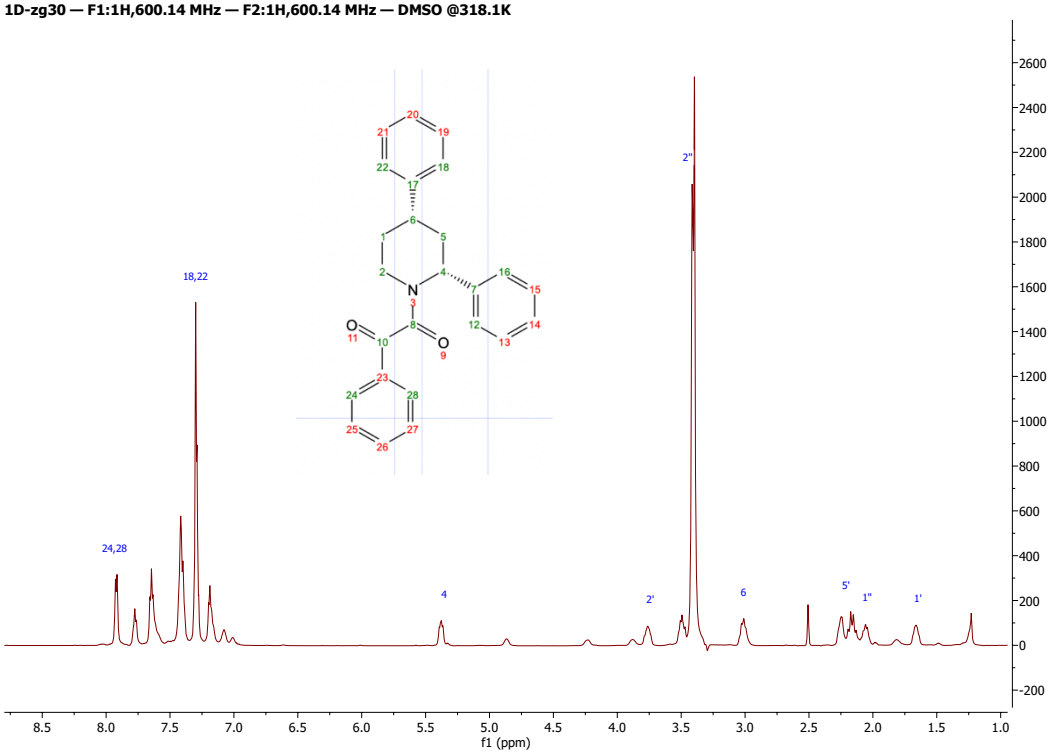
HMBC-hmbcetgpl3nd — F1:13C,150.92 MHz — F2:1H,600.13 MHz — DMSO @298.0K



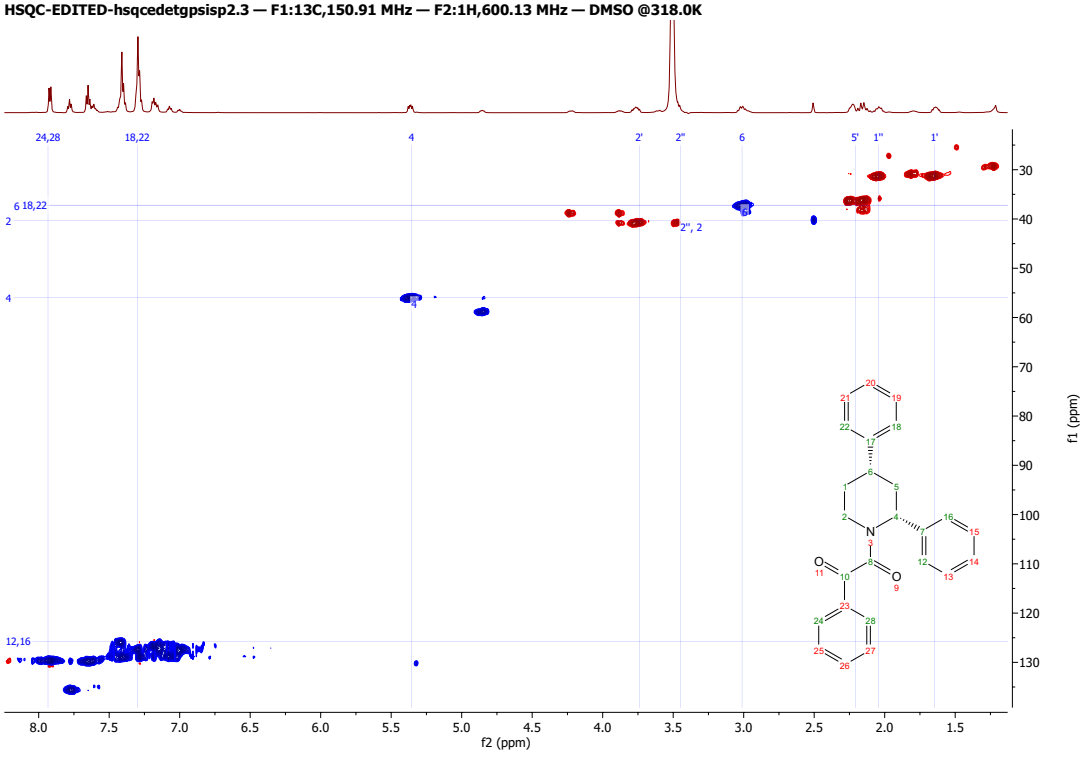
ROESY-roesyph.2 — F1:1H,600.13 MHz — F2:1H,600.13 MHz — DMSO @298.0K

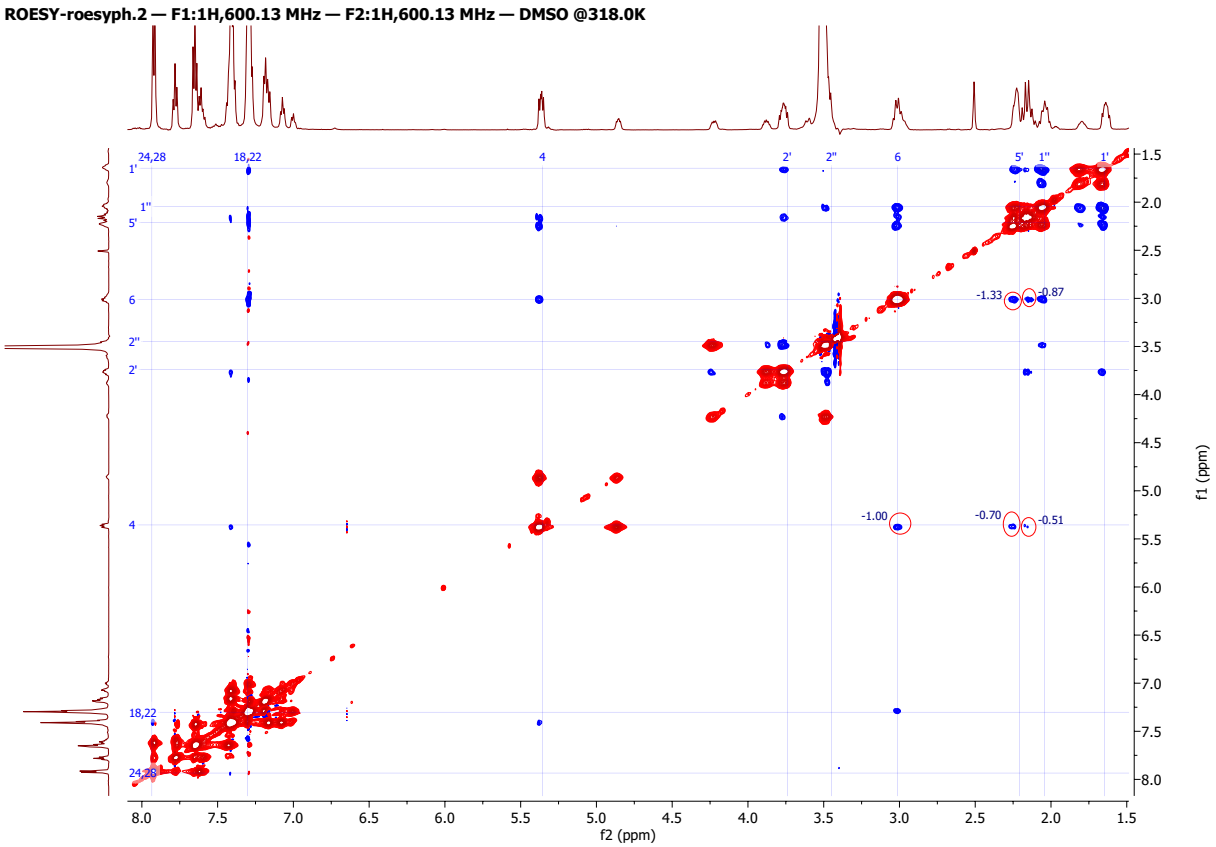


1D-zg30 — F1:1H,600.14 MHz — F2:1H,600.14 MHz — DMSO @318.1K

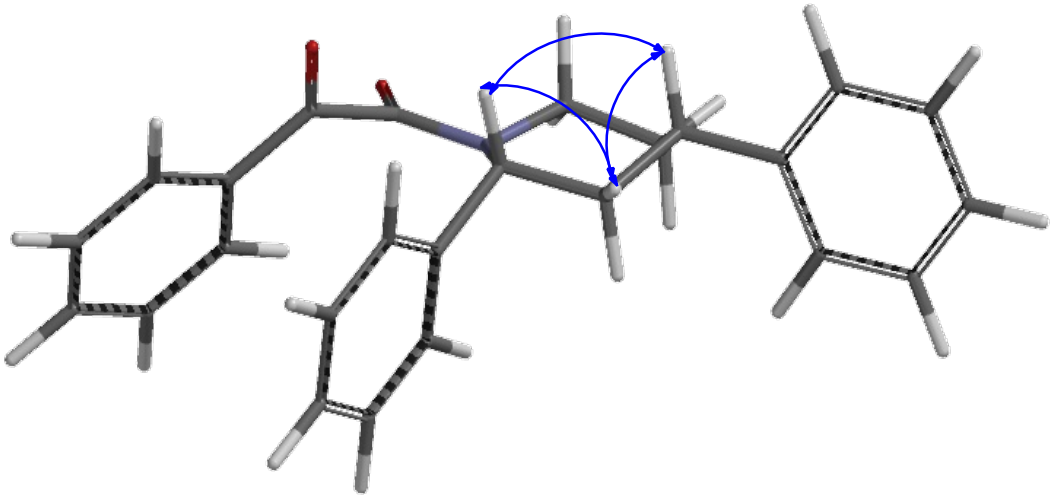


HSQC-EDITED-hsqcedetgpsisp2.3 — F1:13C,150.91 MHz — F2:1H,600.13 MHz — DMSO @318.0K

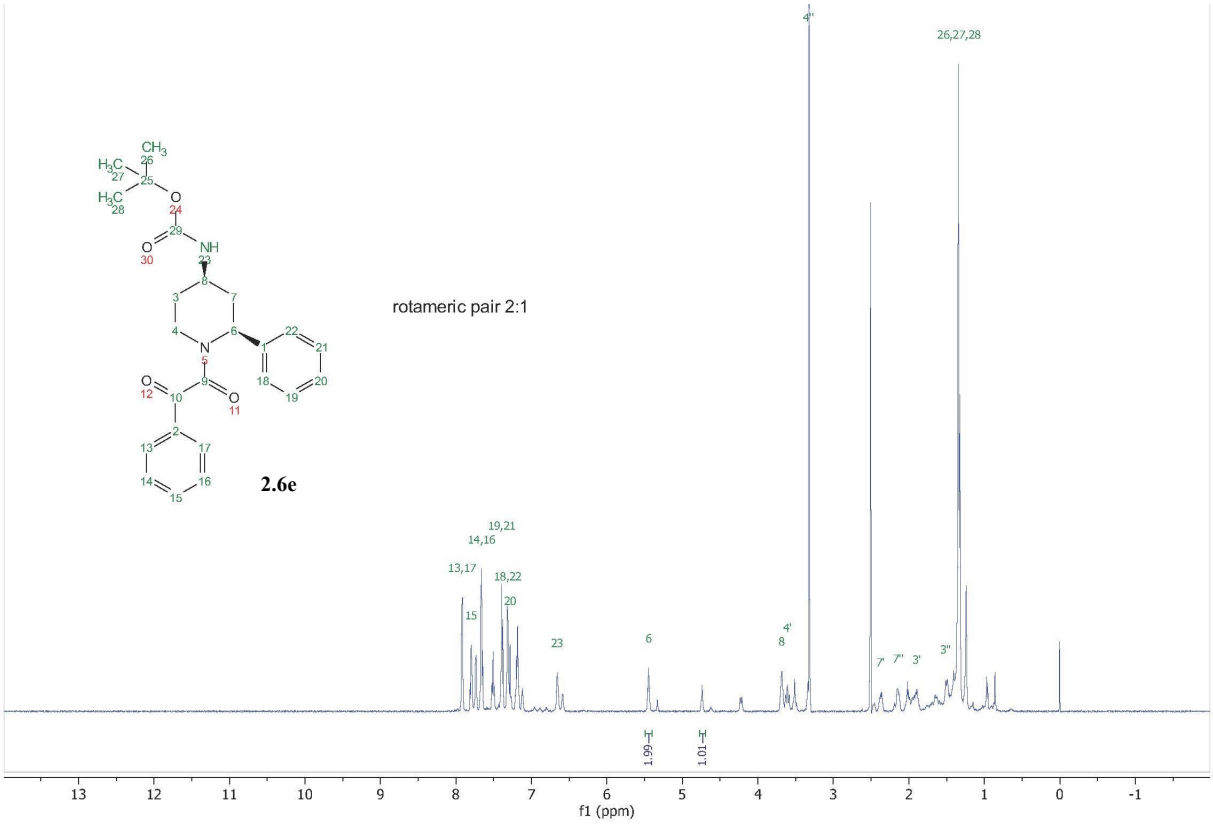




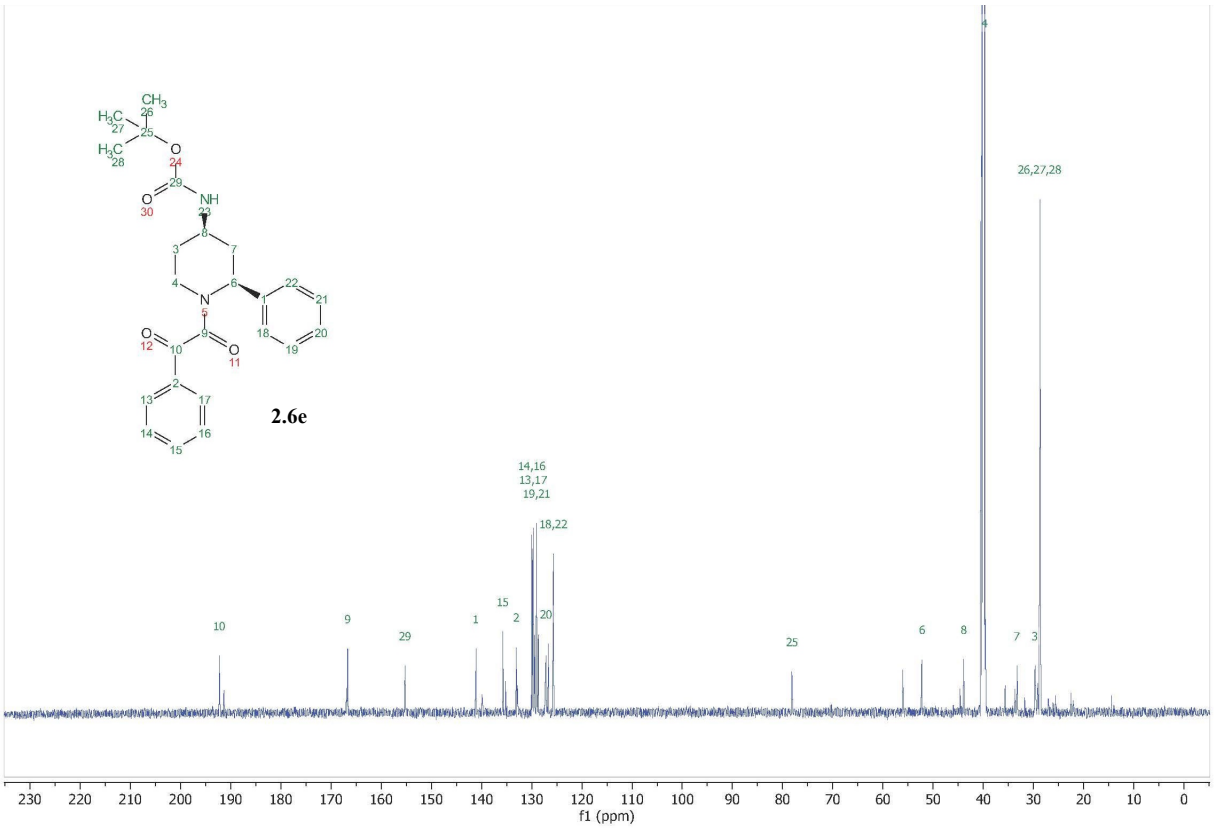
selected correlations indicating a cis relative configuration.



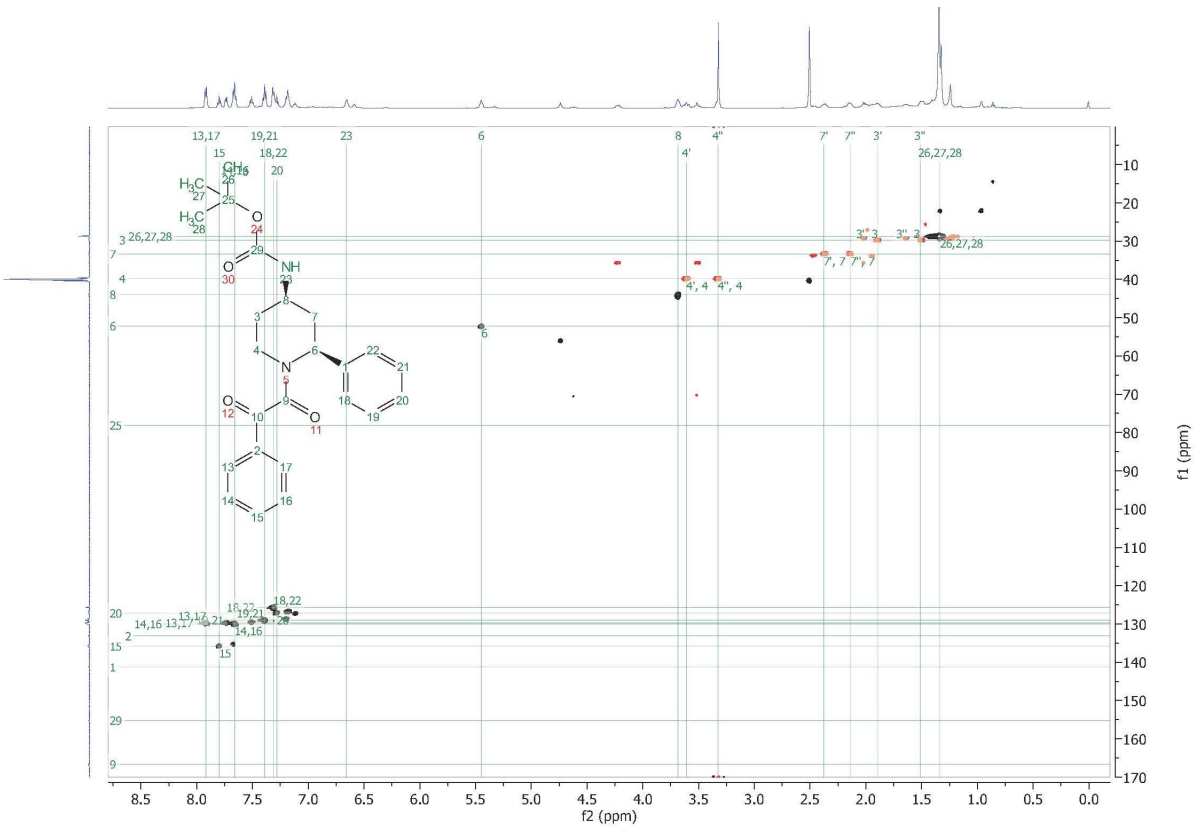
^{1}H


rotameric pair 2:1
2.6e
4''
26,27,28
19,21
14,16
13,17
18,22
20
15
23
6
4'
8
7'
7''
3'
3''
1.99
1.01
f1 (ppm)

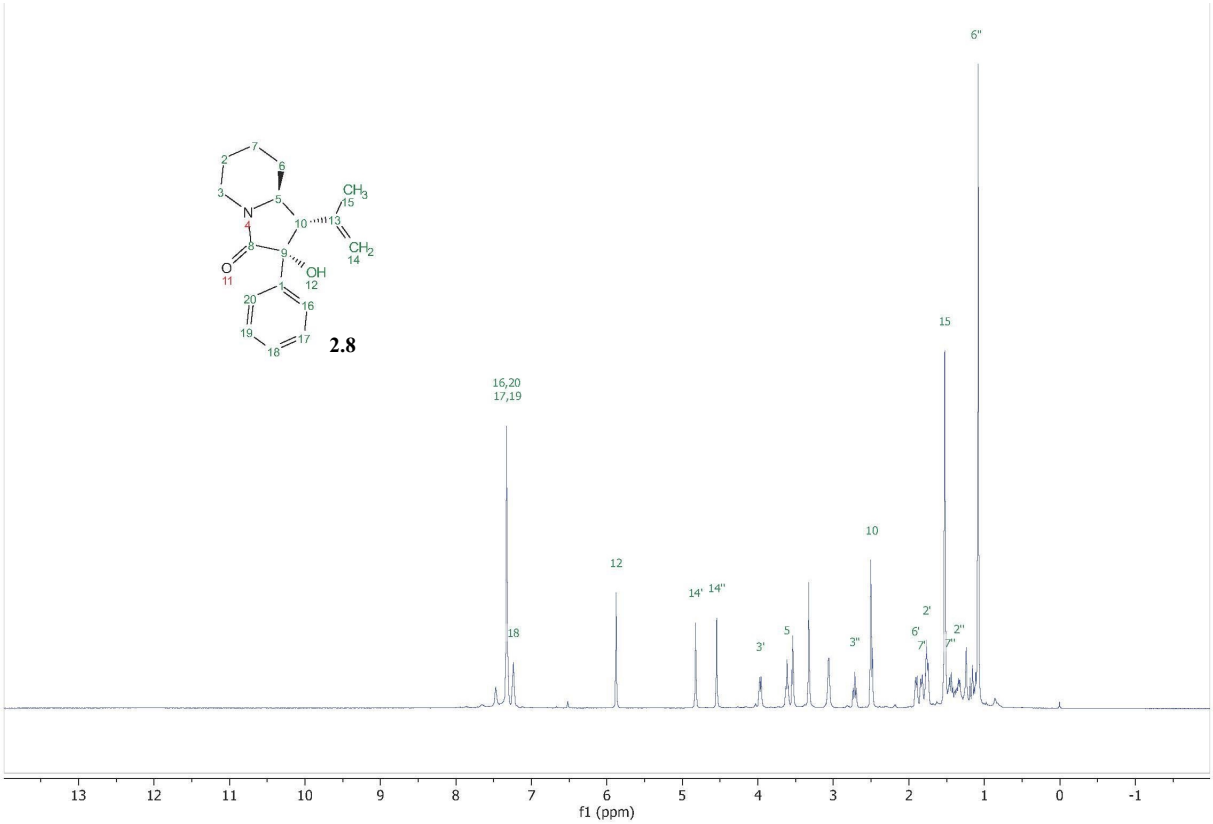
^{13}C


2.6e
14,16
13,17
19,21
18,22
26,27,28
4
10
9
29
1
15
2
20
25
6
8
7
3
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

HSQC

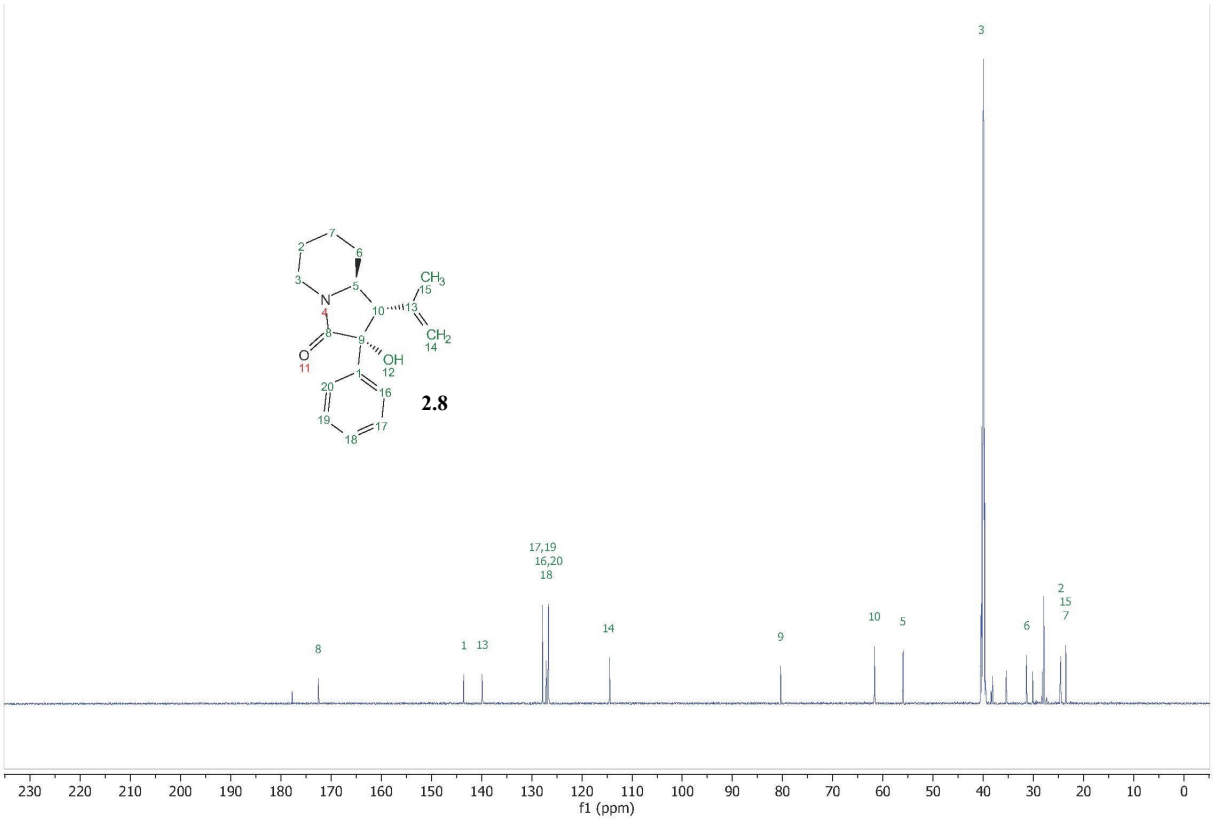

f2 (ppm)
f1 (ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170

^{1}H

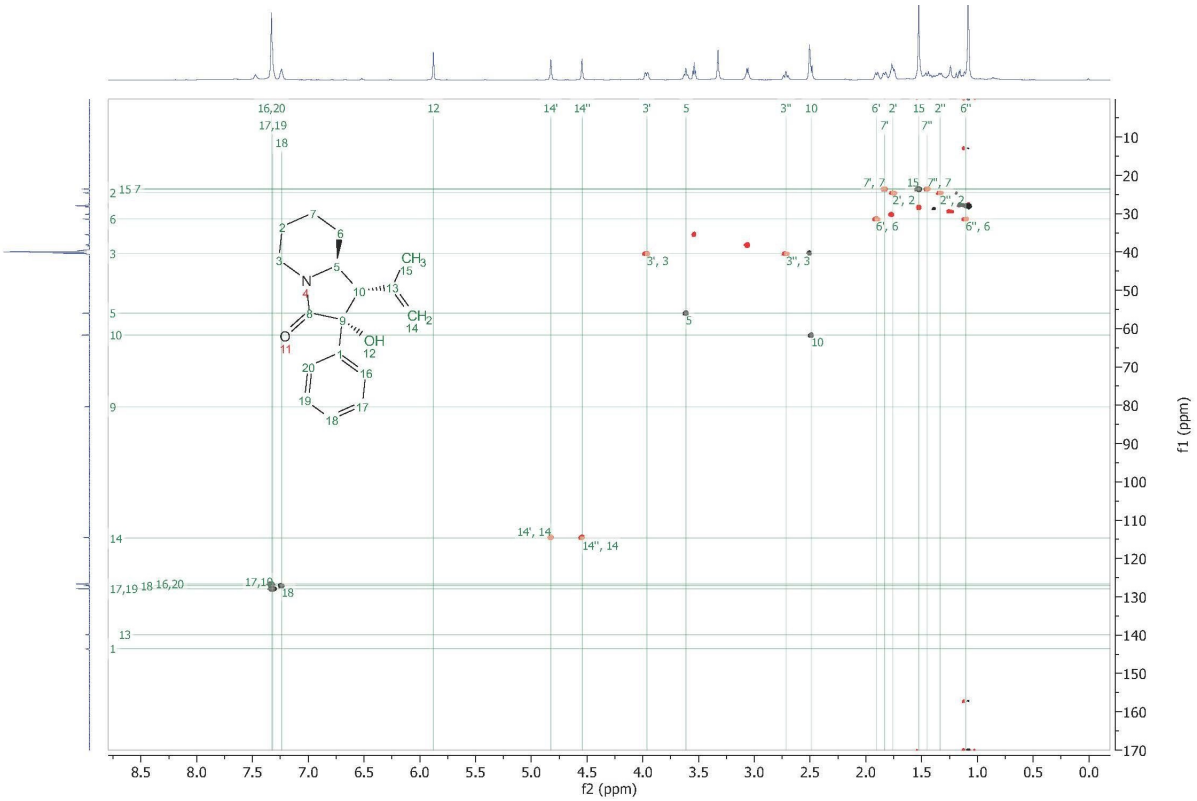

6"
15
16,20
17,19
12
10
14' 14"
18
3'
5
3"
2'
6'
7'
2"
7"
13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
f1 (ppm)

2.8

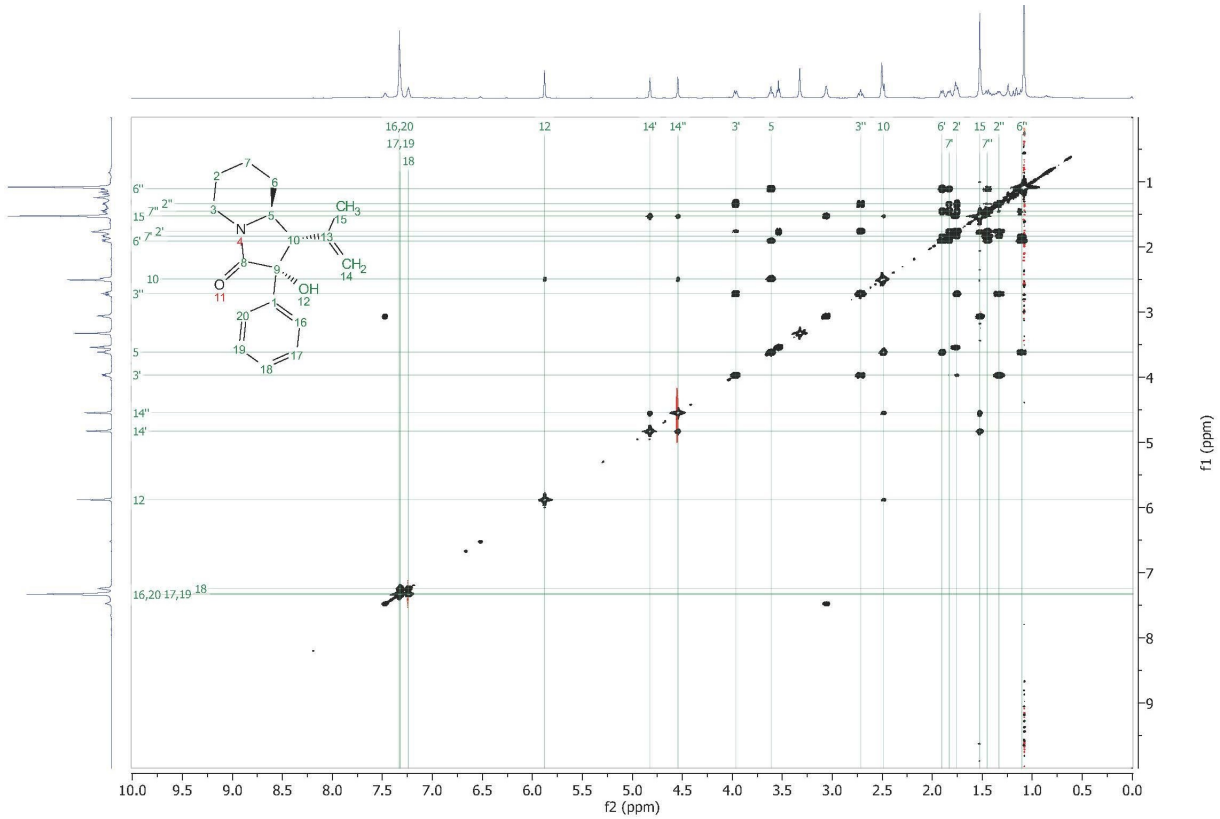
^{13}C



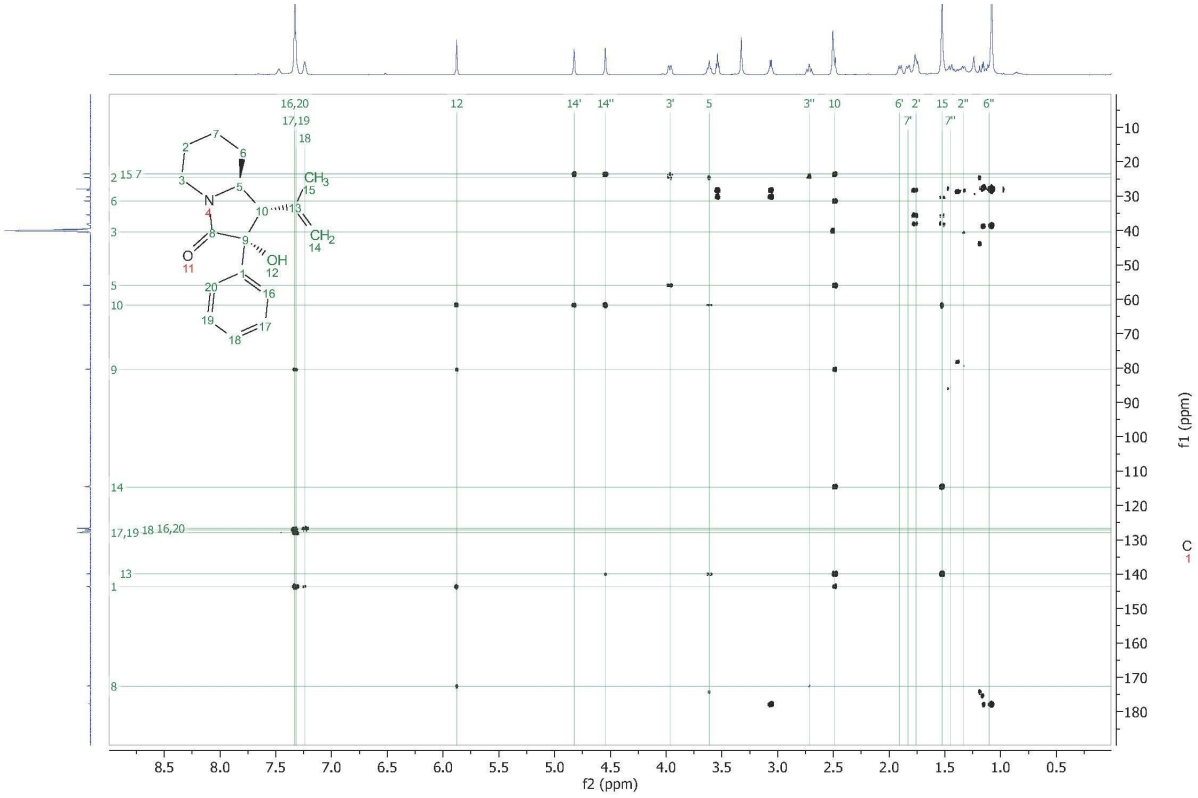
HSQC



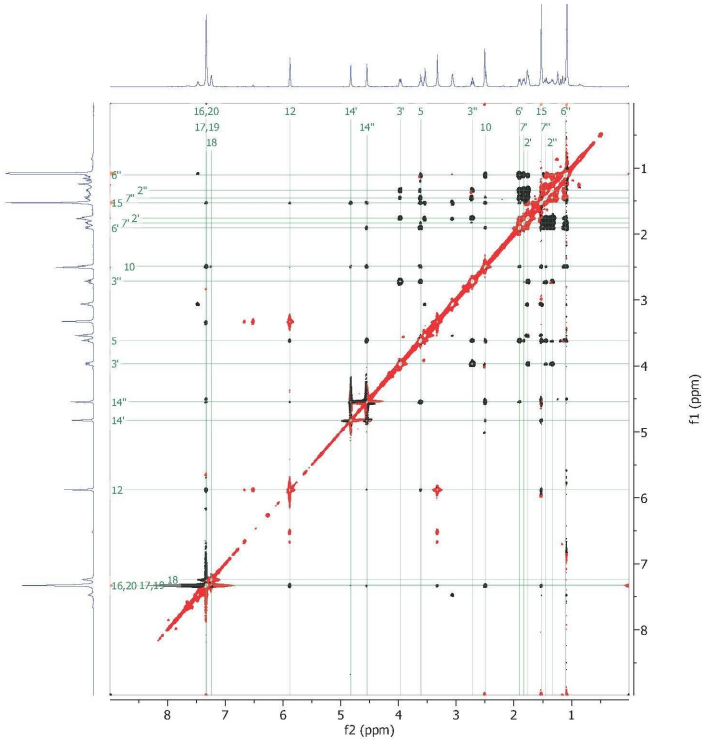
COSY

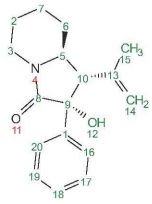


HMBC



ROESY





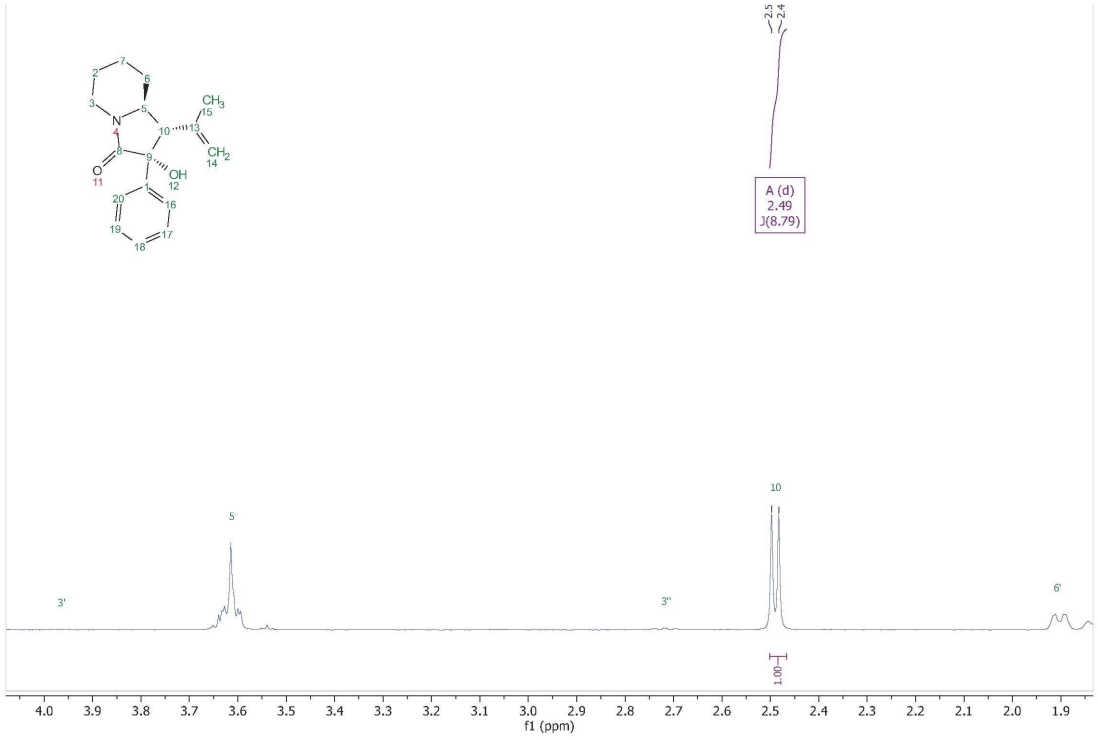
rel. stereochem. determ.
(assumption: H10 is "up")

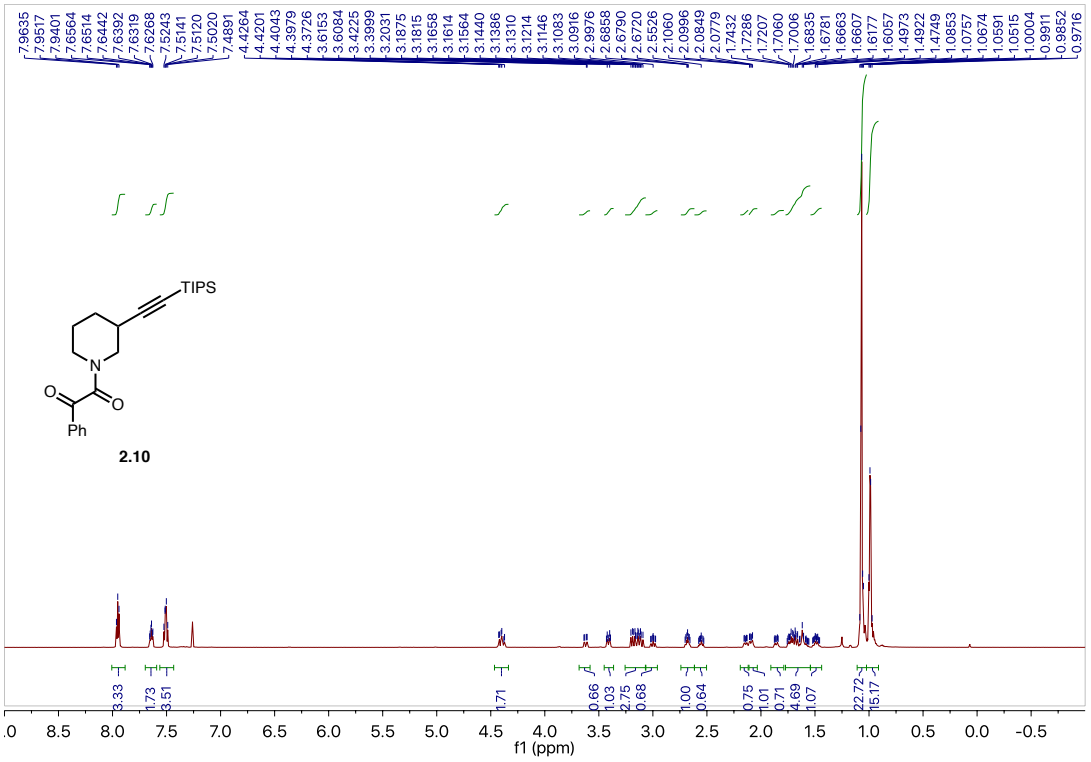
H10 and H5 have strongest ROE to different diastereotopic H6 proton, which is consistent with H10 and H5 being on opposite sides.

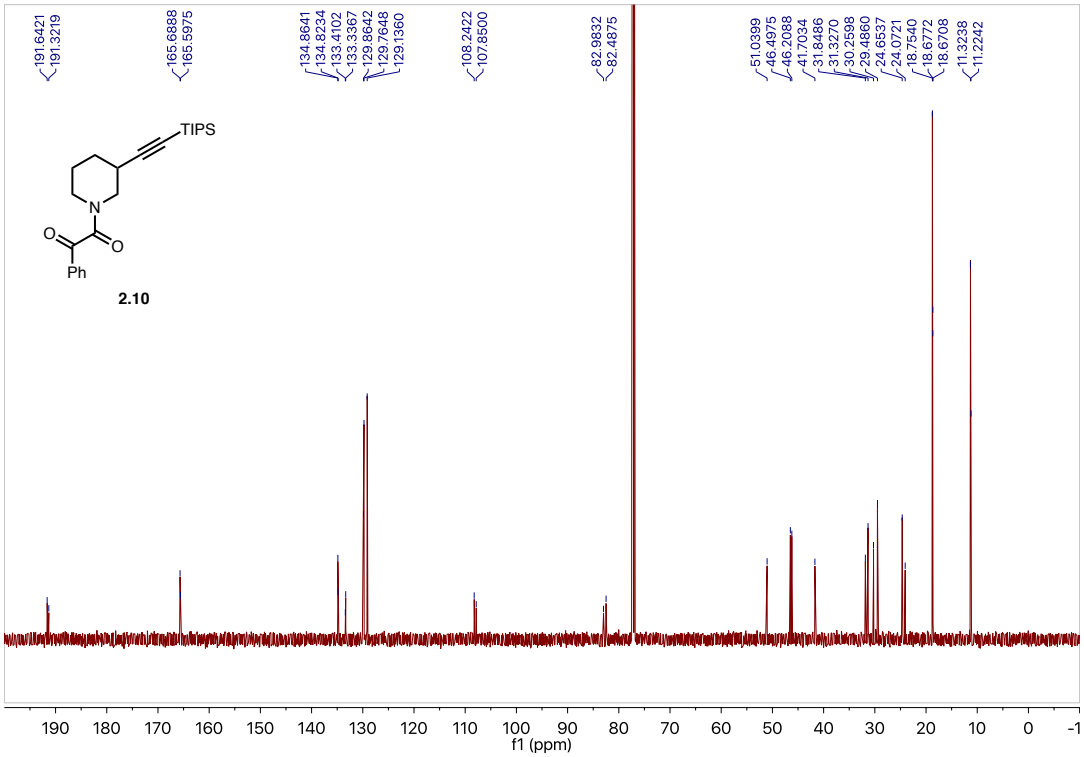
J(H10-H5)=9Hz would also be consisten with this (see next page).

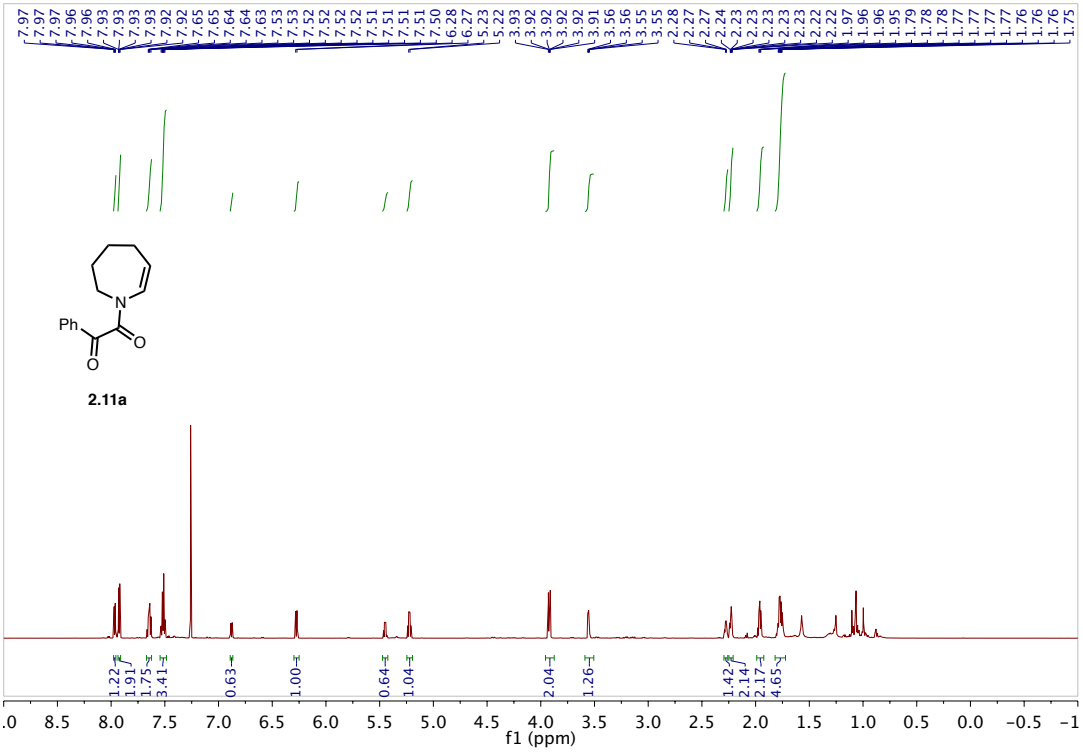
On the other hand, the observed ROE between H10 and aromatics H16/H20 is consistent with both being on the same side.

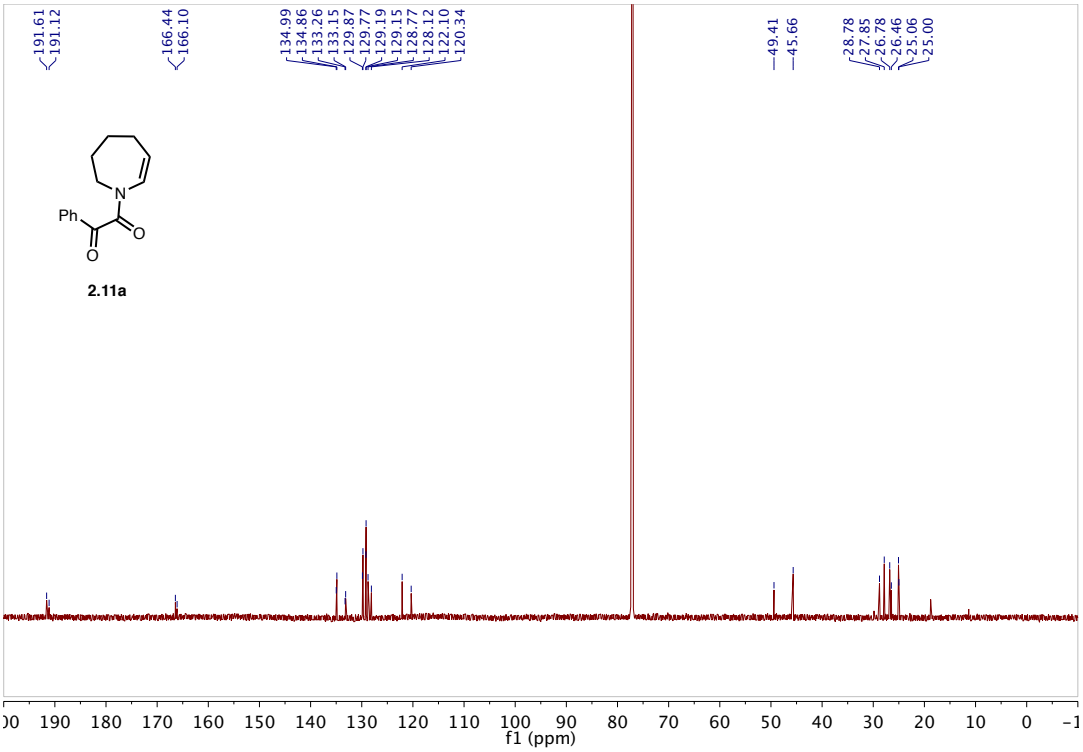
Also consistent withi this is the observed ROE between OH-12 and H5.

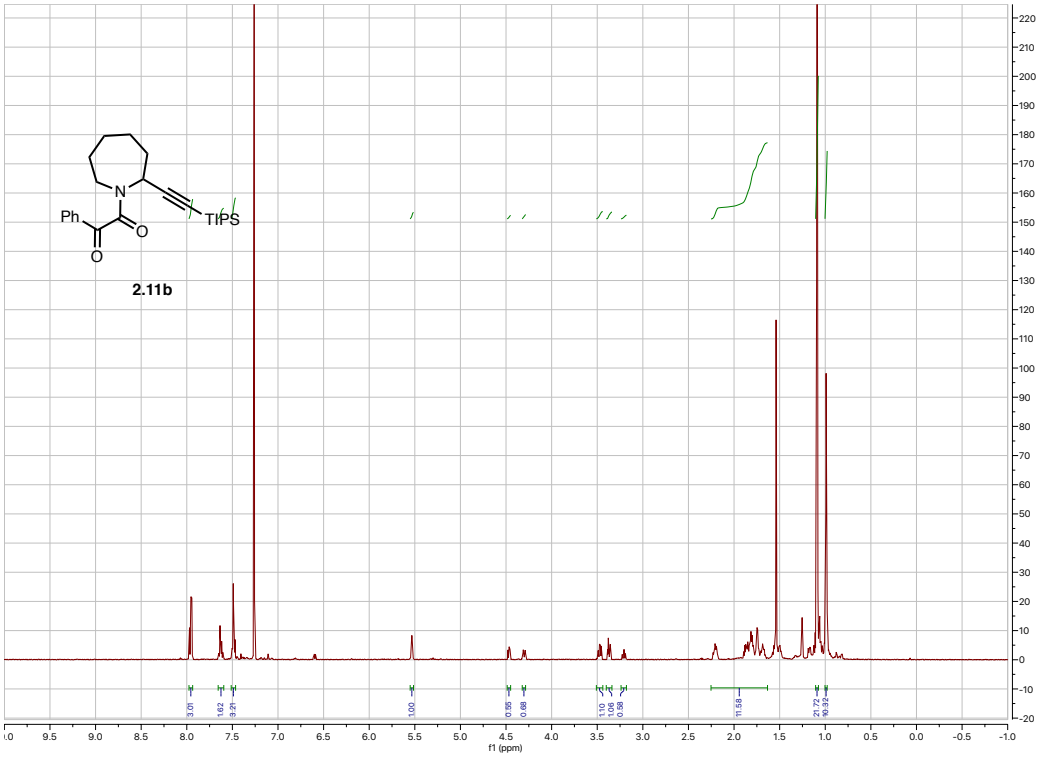


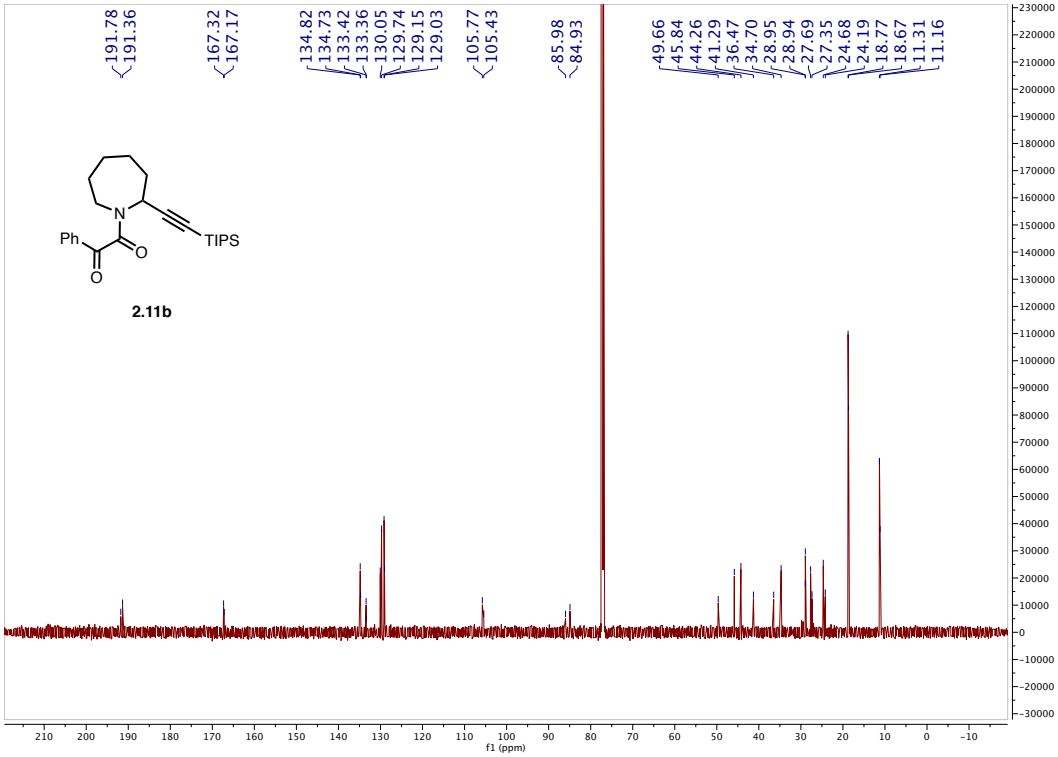

TIPS
N
O
O
Ph
2.10
f1 (ppm)

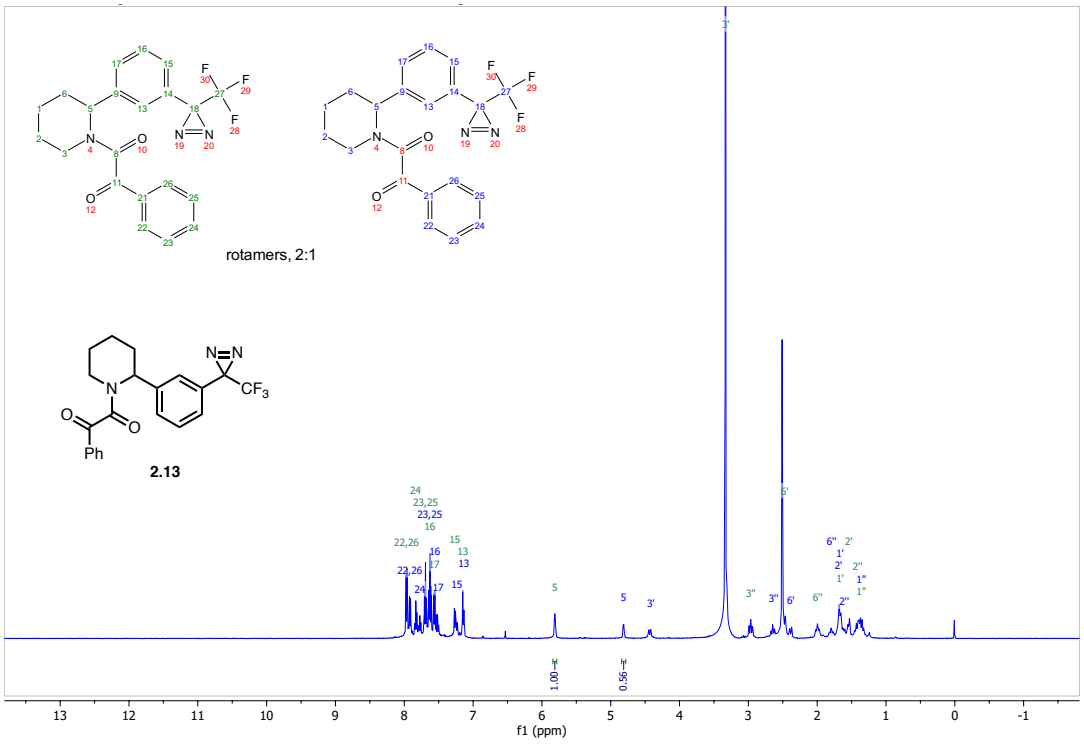

TIPS
N
O
O
Ph
2.10
f1 (ppm)

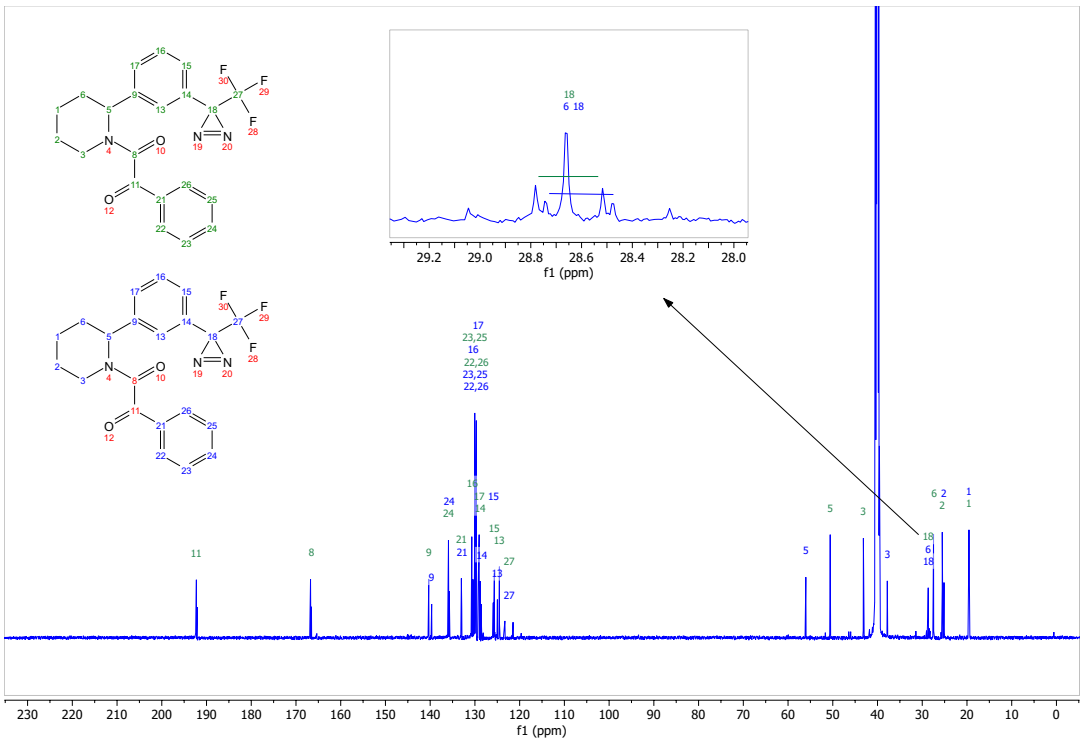

7.97 7.97 7.97 7.96 7.96 7.93 7.93 7.93 7.92 7.92 7.65 7.65 7.64 7.64 7.63 7.53 7.52 7.52 7.52 7.51 7.51 7.51 7.50 6.28 6.27 5.23 5.22 3.93 3.92 3.92 3.92 3.91 3.56 3.56 3.55 3.55 2.28 2.27 2.27 2.24 2.23 2.23 2.23 2.23 2.22 2.22 1.97 1.96 1.96 1.95 1.79 1.78 1.78 1.77 1.77 1.77 1.77 1.76 1.76 1.76 1.75
Ph
O
O
N
2.11a
1.22
1.91
1.75
3.41
0.63
1.00
0.64
1.04
2.04
1.26
1.42
2.14
2.17
4.65
f1 (ppm)

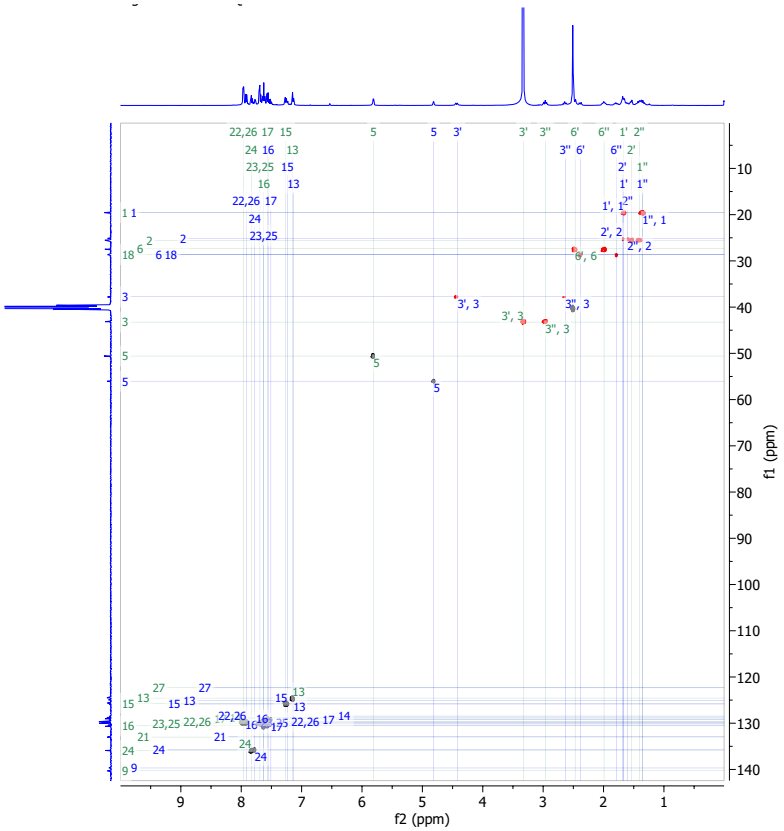

191.61 191.12 166.44 166.10 134.99 134.86 133.26 133.15 129.87 129.77 129.19 129.15 128.77 128.12 122.10 120.34 49.41 45.66 28.78 27.85 26.78 26.46 25.06 25.00
Ph
O
O
N
2.11a
f1 (ppm)

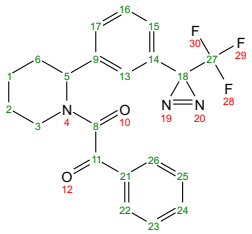

Ph
O
O
N
TIPS
2.11b
f1 (ppm)

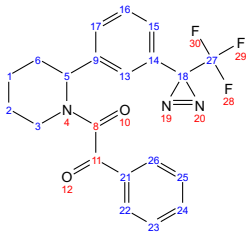

191.78
191.36
167.32
167.17
134.82
134.73
133.42
133.36
130.05
129.74
129.15
129.03
105.77
105.43
85.98
84.93
49.66
45.84
44.26
41.29
36.47
34.70
28.95
28.94
27.69
27.35
24.68
24.19
18.77
18.67
11.31
11.16
Ph
O
O
N
TIPS
2.11b
f1 (ppm)

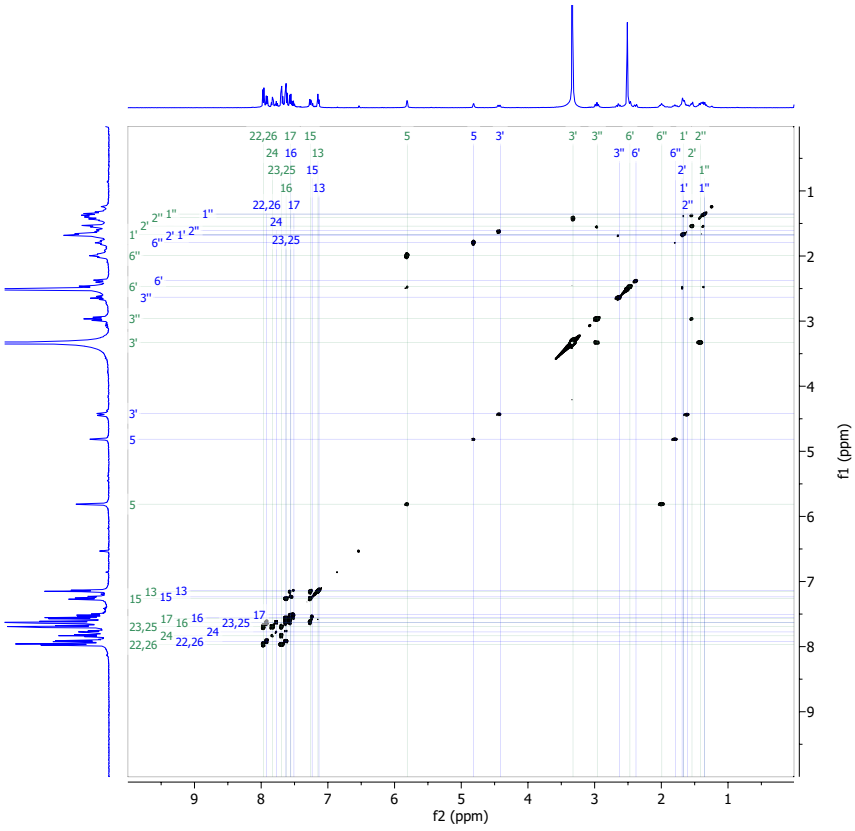

rotamers, 2:1
2.13
f1 (ppm)

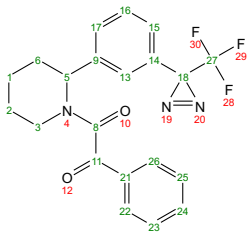

f1 (ppm)
f1 (ppm)

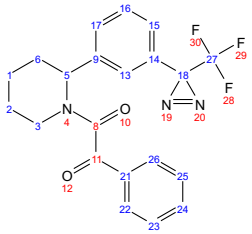

f2 (ppm)
f1 (ppm)

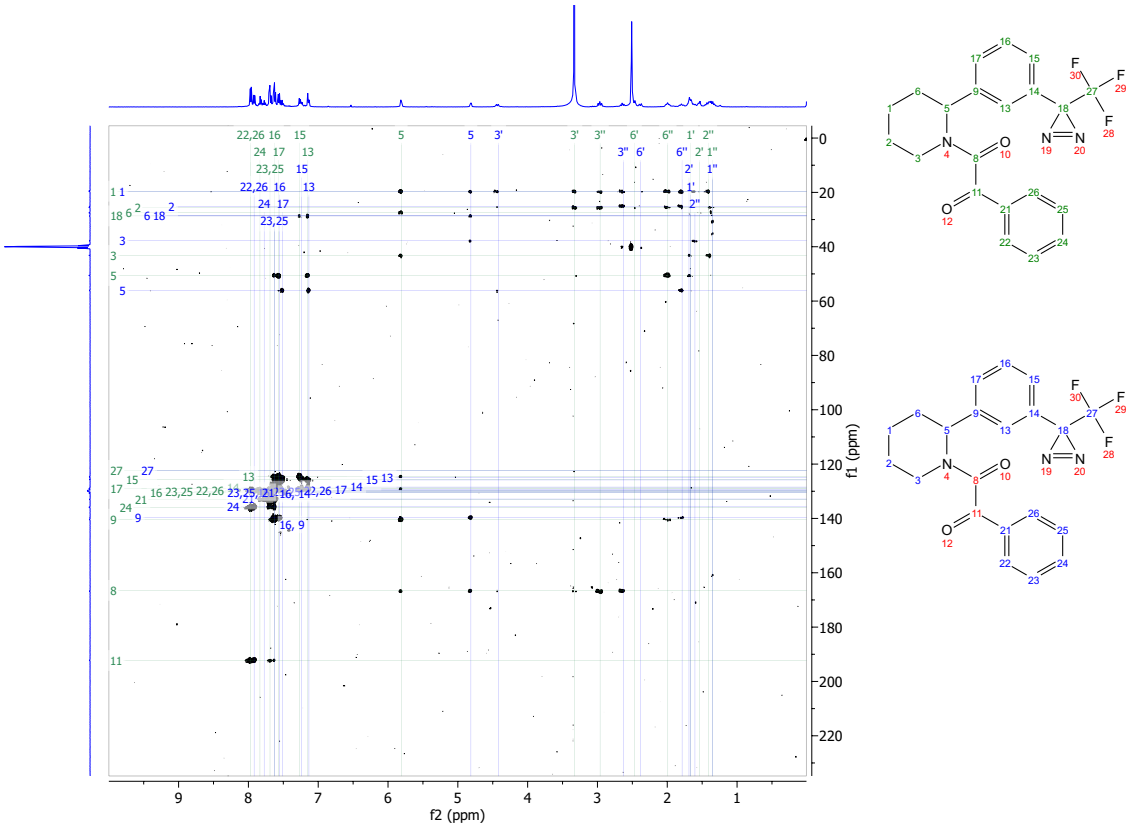


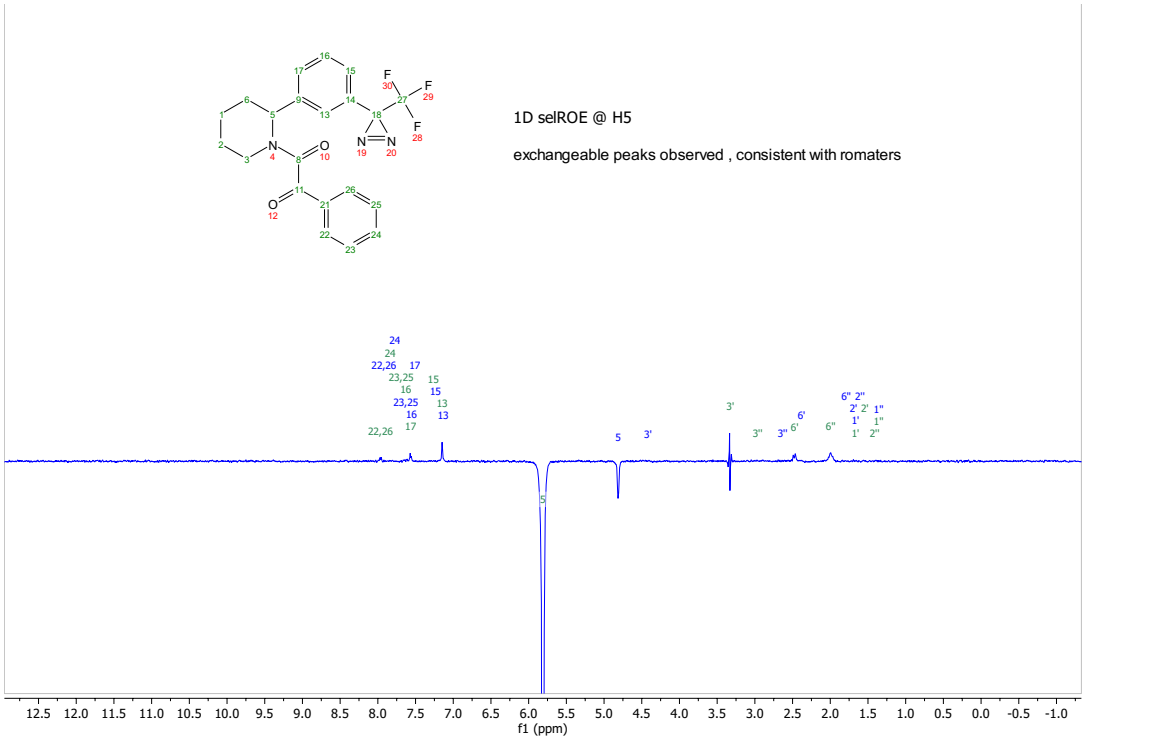


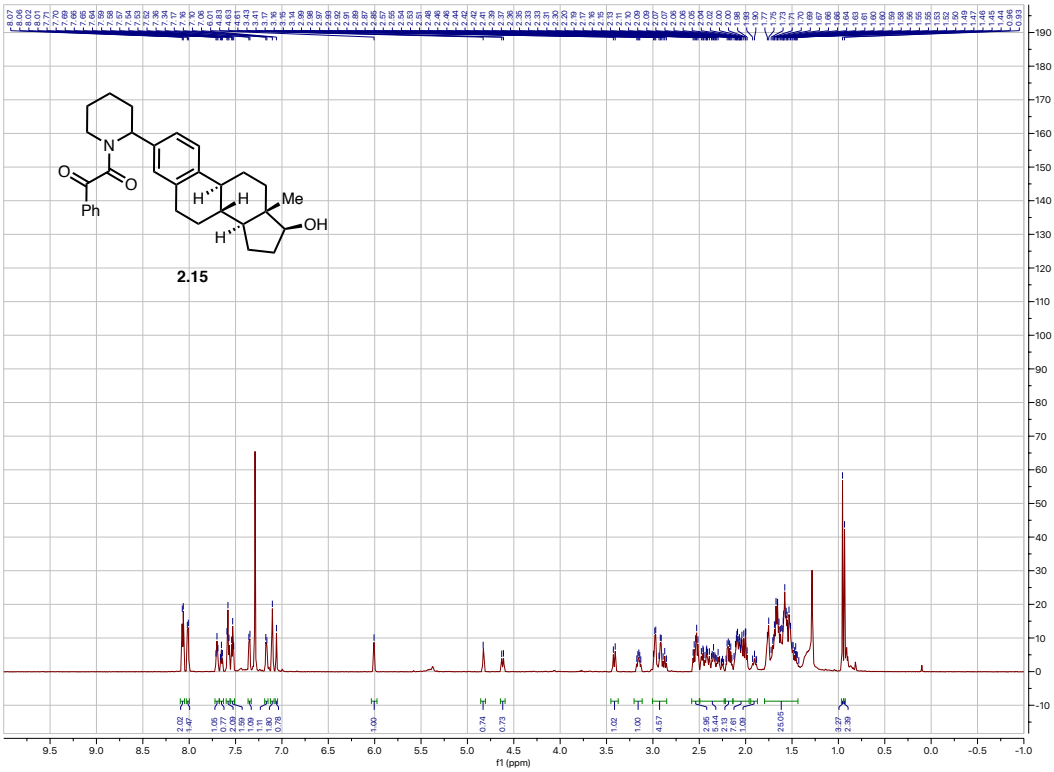

f2 (ppm)
f1 (ppm)

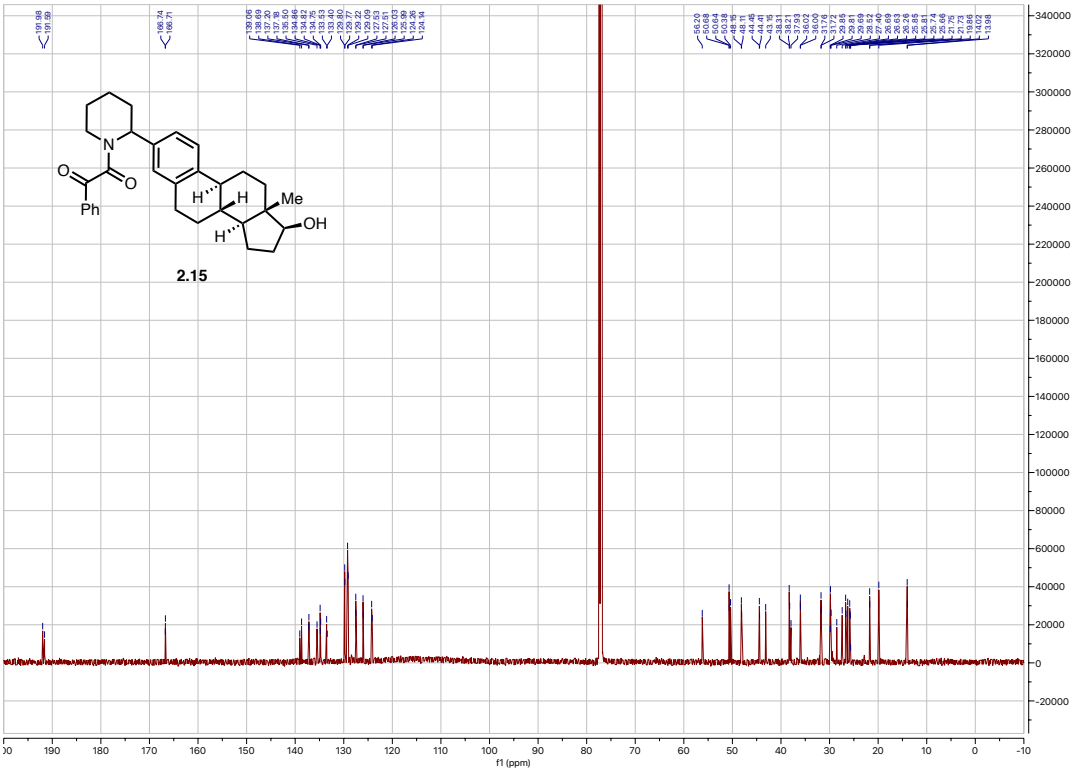


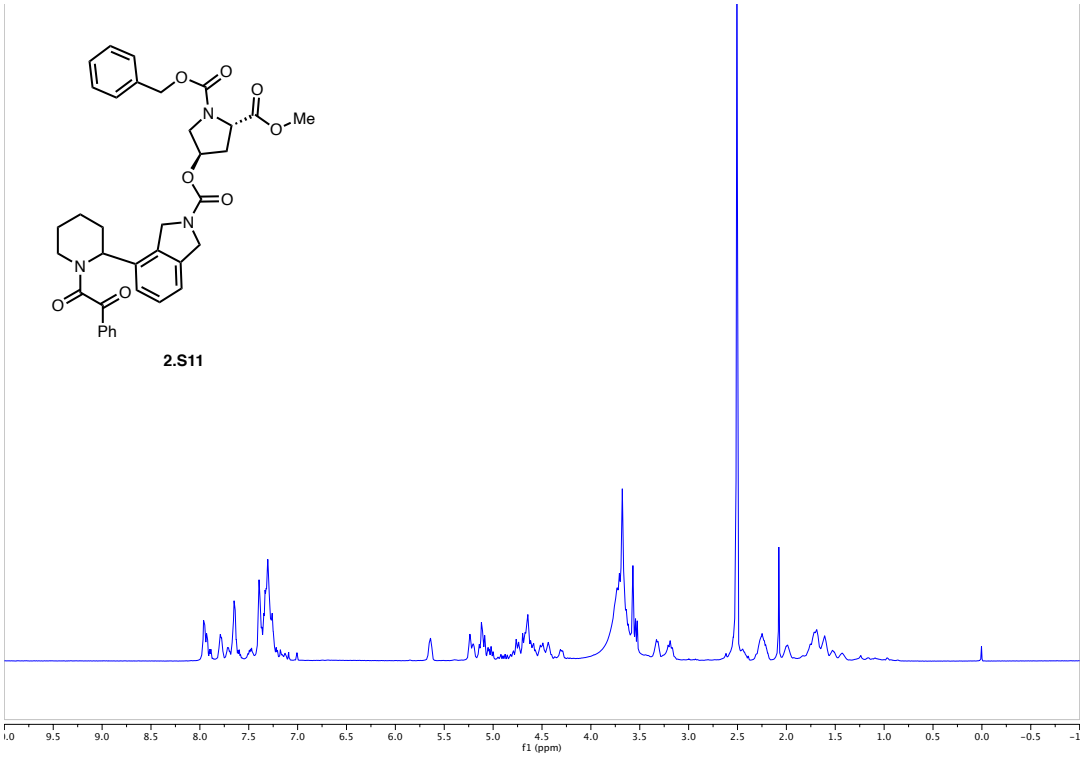



f2 (ppm)
f1 (ppm)

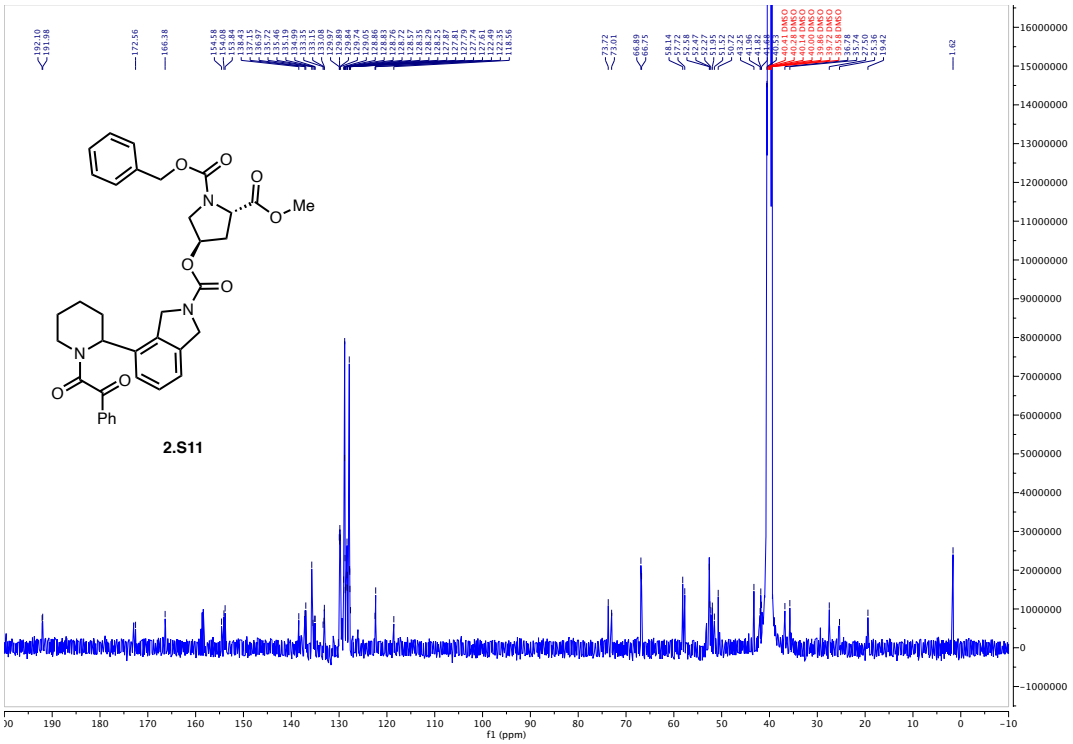

1D selROE @ H5
exchangeable peaks observed , consistent with romaters
f1 (ppm)


N
O
O
Ph
H
H
Me
OH
H
2.15
f1 (ppm)


N
O
O
Ph
H
H
Me
OH
H
2.15
f1 (ppm)



2.S11



2.S11

2.4.7. Determination of absolute configuration of (+)- and (–)-2.2 by VCD & ECD

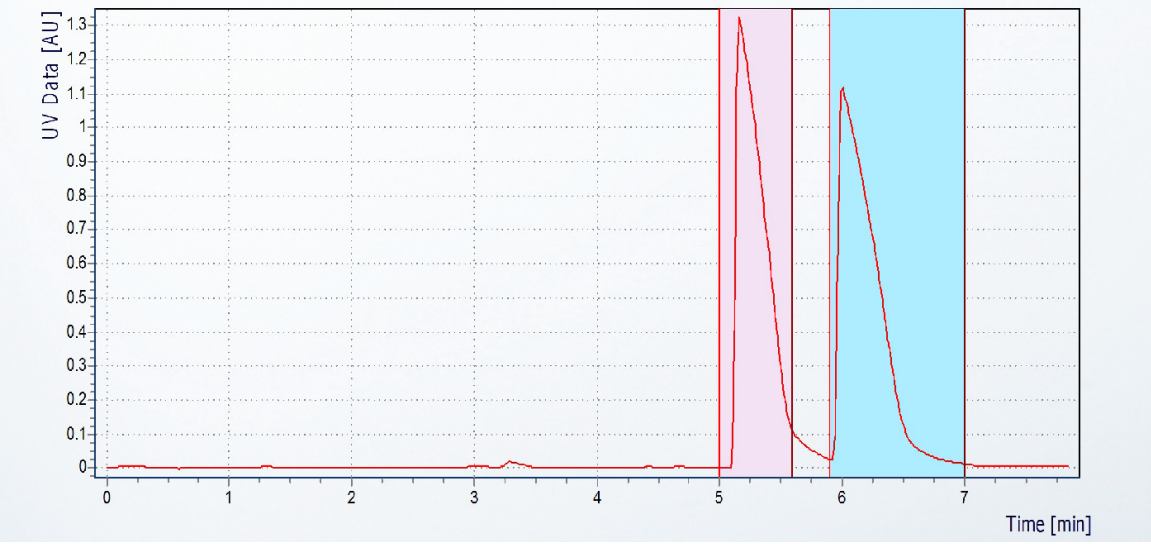
The two enantiomers of **2.2** were resolved by SFC chromatography.

Column & dimensions (mm): Lux-2, 21 x 250
Outlet Pressure (bar): 100
UV wavelength (nm): 220
Flow rate (ml/min): 70
Modifier: MeOH w/ 0.1% NH_4OH
% modifier in CO_2: 15
Sample amount (mg): 2000
Diluent: 1:1 MeOH/CH_3CN
Diluent volume (mL): 20
Injection volume (mL): 0.25
Retention time (min): 5.0, 5.9
Instrument: Sepiatec 1

Result:

peak 1: 879.1 mg
$[\alpha]^{22}D = -178.61$ (*c* 0.51, $CHCl_3$);
peak 2: 866.6 mg
$[\alpha]^{22}D = +181.98$ (*c* 0.51, $CHCl_3$);

Chromatogram:



VCD and ECD Measurements and Calculations

Samples for VCD were dissolved in $CDCl_3$ (50–100 mg/mL for each sample) for VCD studies, and spectra were acquired using a 0.10 mm path length cell with BaF_2 windows. The IR and VCD spectra were recorded using a Chiral*IR*TM VCD spectrometer equipped with the Dual PEM accessory (BioTools, Jupiter, FL), with 4 cm^{-1} resolution. A dry N_2 purge was used to eliminate water from the instrument. Data were collected in blocks, where the instrument recorded ~3000 scans over the course of 1 h and averaged those scans into one block. Each of the runs involved averaging four blocks for each sample, as well as the solvent. The solvent background average was then subtracted from the sample average. Collection times for sample and solvent ranged were approximately 5 h each. Samples for ECD were dissolved in MeCN (0.1–1 mg/mL), and spectra were acquired in a 1.0 mm pathlength Starna Quartz cuvette. The UV and ECD spectra were recorded using a Chirascan qCD Spectrophotometer with the following instrumental parameters: 185–350 nm with a 1 nm step and a 1 nm bandwidth, with data averaging over 0.5 s per point. Only one spectral acquisition was taken without repetitions for each sample, and required approximately 2 mins each. The solvent spectrum was then subtracted from the sample average to give the final compound spectrum.

The general approach for VCD assignment at Merck, including the details computational workflow, has been published elsewhere.[51] A subset of the details of the computational methodology is provided here. Conformers of each test structure were geometry optimized at the B3LYP/6-31G** level and stationary points were confirmed by performing frequency calculations.[52] All calculations were performed using Gaussian 09.[53] Frequency calculations output the IR and VCD spectra.[54] Frequencies were scaled by a value of 0.98, but owing to the secondary scaling and shifting of the calculated VCD and IR spectra (during extraction of VCD by BioTools ViewVCD and during spectra alignment detailed below) in comparison to the experimental spectra, this initial scaling was, to some extent, arbitrary.

Output conformers were ranked according to DFT energy and a clustering was performed to remove duplicates. Initial identification of duplicates was performed solely on an electronic energy basis where compounds were considered identical if the difference in Hartrees was less than 0.01. Rounding the differences led to inconsistencies in identification of duplicates. It became better to cluster the DFT minima by energy and then re-cluster each energy bucket by structure using an all atom RMS of 0.6 Å. This faithfully removed only identical compounds. Two Boltzmann distributions were calculated based on electronic energy (E) and free energy (G).

The in-house method for comparing VCD and IR spectra is based on published methodology.[55] We used the same formulas for calculating similarity for IR and VCD spectra of experimental and observed curves. Based on our experience in matching the curves by hand, we introduced the following modifications to the algorithm: we scale the spectra (0 to 1 for IR, –1 to 1 for VCD) before comparing them; we isolate each peak for movement rather than groups of peaks; we isolate peaks independently for IR and VCD spectra; when looking for the best match, we move the experimental peak only to higher frequencies with a maximum shift of 20 cm^{-1}; if the user sees that the baseline of the spectrum is not corrected the user can ask the program to correct the baseline. For all figures contained in the manuscript, the output intensities from Gaussian for IR

Δε (molar absorptivity) and VCD Δε are D (10–40 esu^2 cm^2) and R (10–44 esu^2 cm^2), respectively. However, owing to scaling all peaks the intensities are labeled only as 'normalized VCD'.

To calculate ECD spectra, B3LYP geometries were used as input for CAM-B3LYP calculations[56] using the 6-31++G** basis set[57] in vacuo. Only conformers which contributed more than 2.0% to the total in vacuo conformer distribution were selected for ECD calculation. Time-dependent Density Functional Theory (TDDFT)[58] methodology was employed using the following keywords: TD=full,singlet, Nstates=100, and integral=ultrafinegrid. Spectral display and Boltzmann weighting were carried out using SpecDis,[59] and were displayed with a band broadening sigma=0.3 eV.

Calculations of the VCD and IR spectra involved modeling the *SS* configuration. Since one enantiomer was determined to be *SS* and the other *RR*, it should be noted that the enantiomer of that modeled is assumed to be equal and opposite (*vida infra*).

Figures 2.S1 and 2.S2 provide overlays of the calculated and measured IR and VCD spectra for both samples, while Figures 2.S3 and 2.S4 provide overlays of the calculated and experimental UV and ECD spectra for both enantiomers. A high degree of confidence is derived from the statistical and visual matching of the spectra. Figure 2.S5 shows the conformers of the *SS* enantiomer that contributed >2% to the Boltzmann weighted spectrum. Assigned absolute configuration of the desired compounds is provided in Scheme 2.S1.

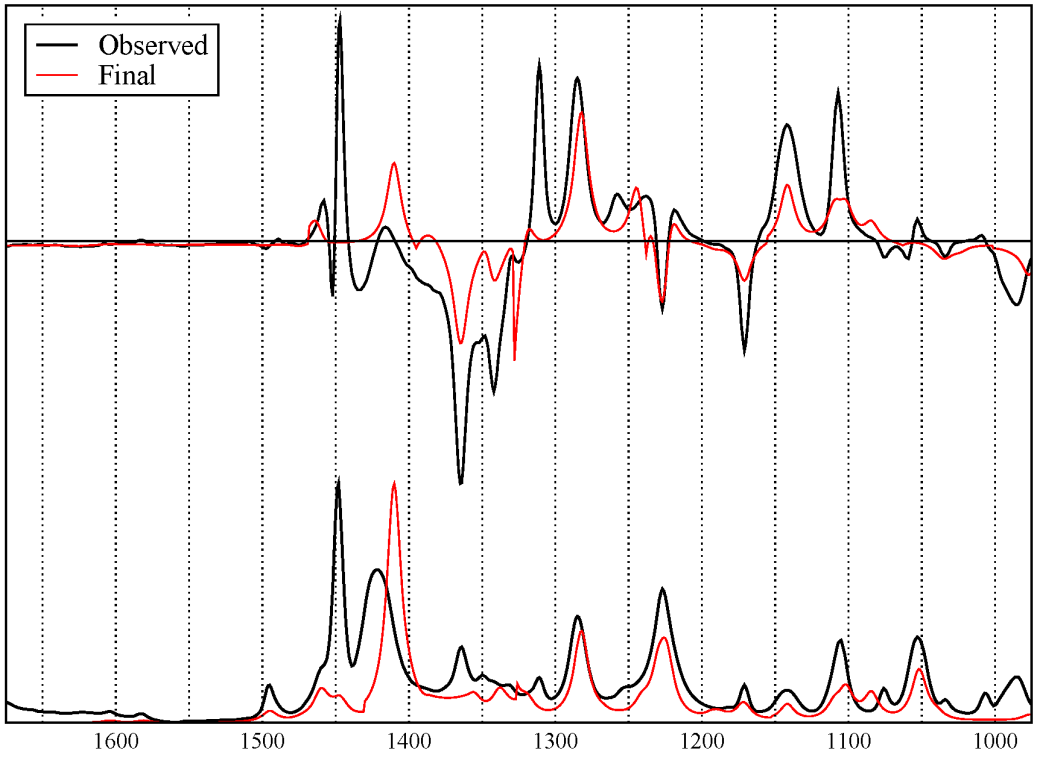


Figure 2.S1. Overlay of measured (black) and calculated (red) VCD and IR spectra between the experimental sample **2.2** peak 1 and the calculated *SS* enantiomer.

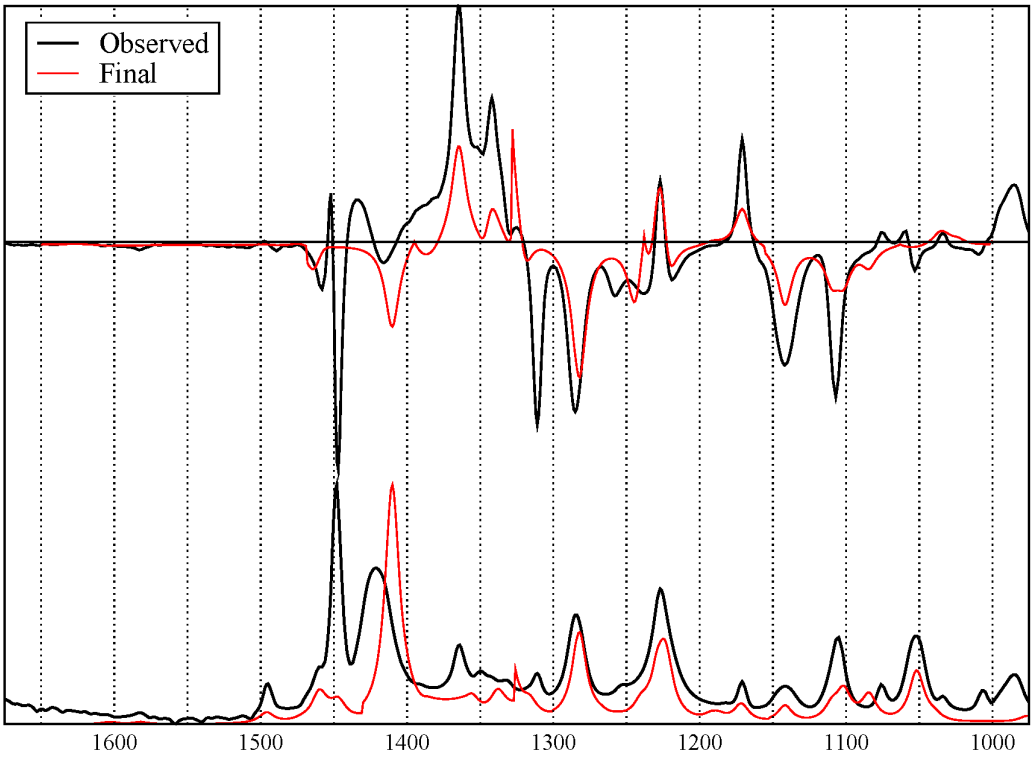


Figure 2.S2. Overlay of measured (black) and calculated (red) VCD and IR spectra between the experimental sample **2.2** peak 2 and the calculated *RR* enantiomer.

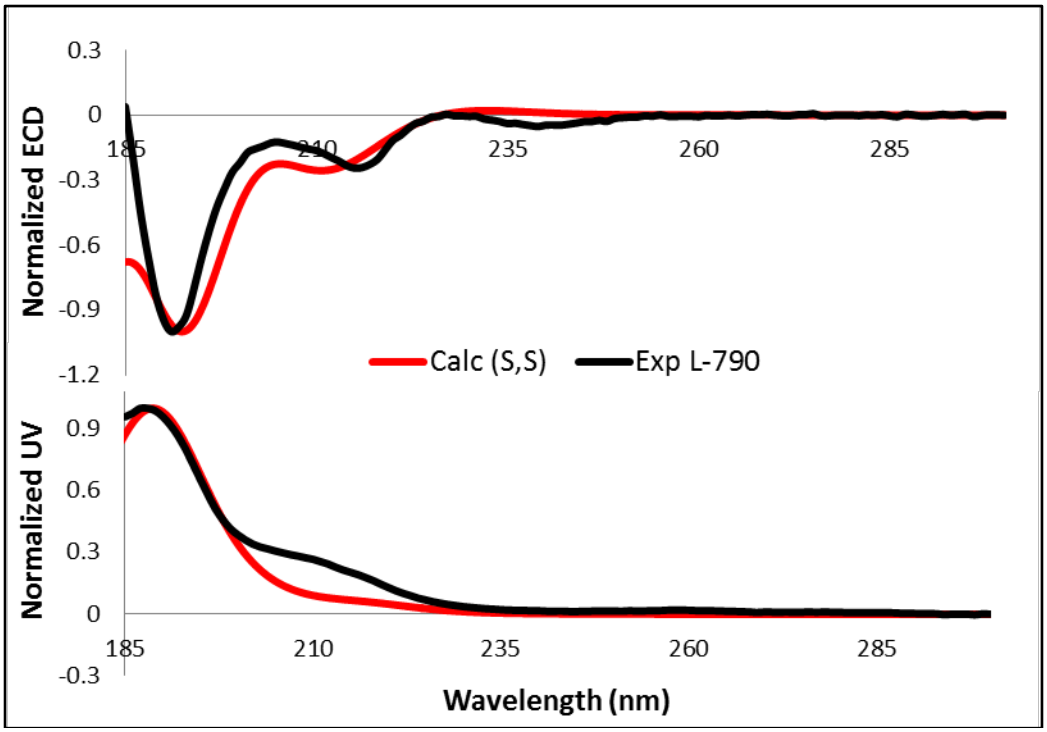


Figure 2.S3. Overlay of measured (black) and calculated (red) ECD and UV spectra between the experimental sample **2.2** peak 1 and the calculated *SS* enantiomer.

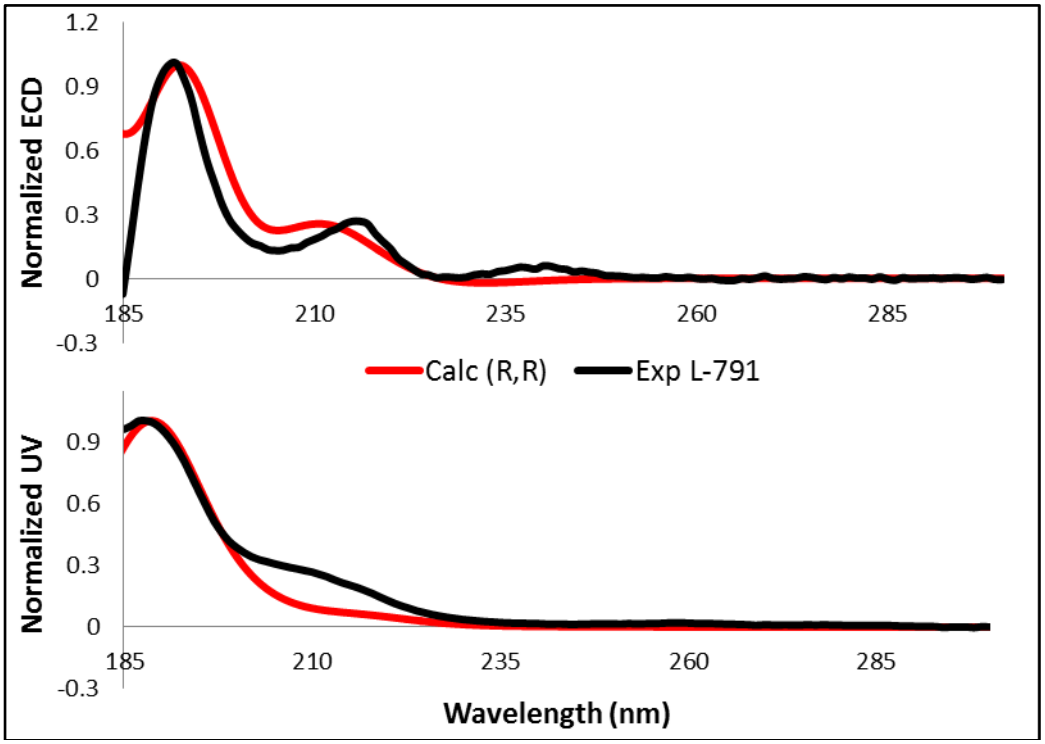
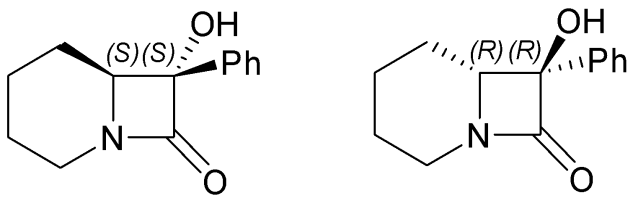
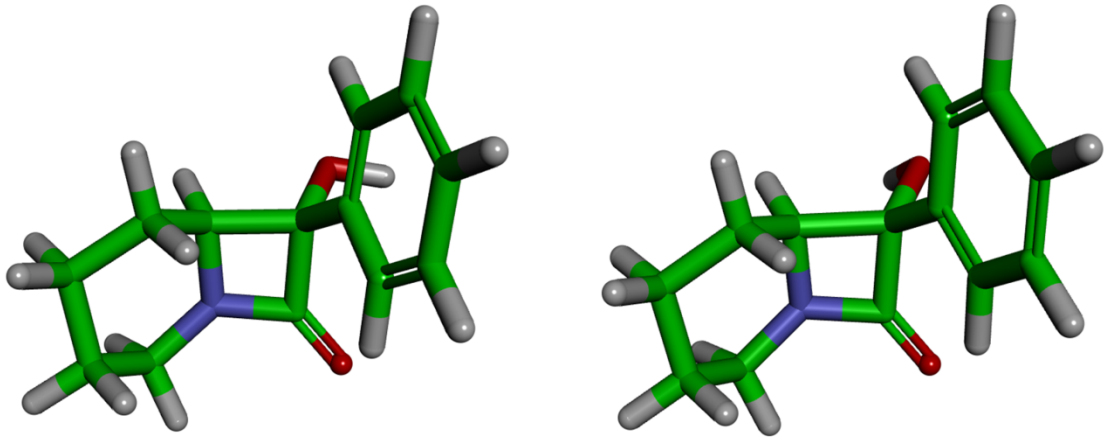


Figure 2.S4. Overlay of measured (black) and calculated (red) *ECD* and UV spectra between the experimental sample **2.2** peak 2 and the calculated *RR* enantiomer.



L-006387790 **L-006387791**

Scheme S1. Assigned absolute configuration for both enantiomers of desired compound.



Conformer 1: 97.2% **Conformer 2:** 2.4%

Figure 2.S5. Conformers of the *SS* minima contributing >5% to the Boltzmann distribution, percentages shown above based on *in vacuo* electronic energies.

Absolute configuration further confirmed by X-Ray analysis.

Coordinates and electronic energies for B3LYP/6-31G** conformational minima contributing >5% to the *in vacuo* Boltzmann distribution.

Conformer 1: -709.660249

6	3.029	1.334	-0.795
6	3.139	-0.182	-0.547
7	1.896	-0.661	0.02
6	1.091	0.034	1.039
6	1.016	1.532	0.751
6	2.427	2.062	0.422
6	0.894	-1.467	-0.442
6	-0.093	-0.924	0.648
8	0.827	-2.26	-1.359
1	1.445	-0.165	2.058

8	-0.324	-1.827	1.719
6	-1.371	-0.291	0.149
6	-2.319	0.143	1.088
6	-3.492	0.768	0.67
6	-3.734	0.963	-0.692
6	-2.802	0.523	-1.631
6	-1.625	-0.104	-1.215
1	4.02	1.737	-1.034
1	2.388	1.505	-1.669
1	3.325	-0.74	-1.469
1	3.963	-0.391	0.149
1	0.358	1.705	-0.109
1	0.581	2.064	1.604
1	2.382	3.139	0.225
1	3.085	1.929	1.292
1	-2.126	-0.025	2.143
1	-4.217	1.102	1.406
1	-4.649	1.449	-1.018
1	-2.991	0.658	-2.692
1	-0.915	-0.471	-1.949
1	-0.913	-2.518	1.383

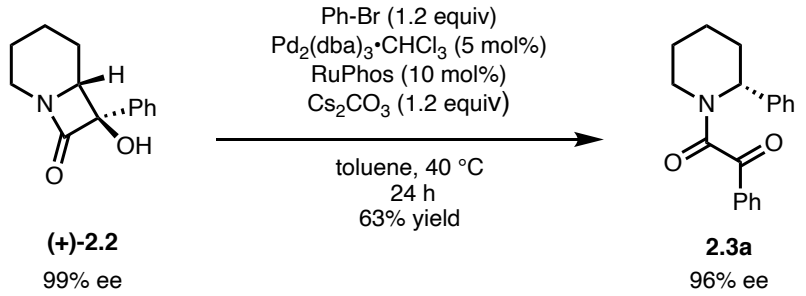
Conformer 2: –709.656754

6	2.985	1.345	-0.841
6	3.135	-0.154	-0.525
7	1.91	-0.65	0.07
6	1.075	0.072	1.045
6	0.97	1.556	0.694
6	2.366	2.11	0.344
6	0.919	-1.467	-0.411
6	-0.092	-0.937	0.667
8	0.892	-2.258	-1.331
1	1.42	-0.065	2.079
8	-0.429	-1.851	1.693
6	-1.371	-0.319	0.162
6	-1.662	-0.232	-1.204
6	-2.836	0.394	-1.632
6	-3.727	0.93	-0.704
6	-3.445	0.835	0.662
6	-2.275	0.214	1.092
1	3.963	1.762	-1.103
1	2.336	1.46	-1.719
1	3.334	-0.747	-1.422
1	3.968	-0.308	0.175
1	0.31	1.674	-0.174
1	0.516	2.111	1.521

1	2.293	3.175	0.102
1	3.028	2.031	1.218
1	-0.985	-0.673	-1.927
1	-3.055	0.452	-2.695
1	-4.639	1.415	-1.039
1	-4.138	1.243	1.391
1	-2.055	0.126	2.151
	0.379	-2.306	1.969

2.4.8. Stereoretentive Cross-Coupling

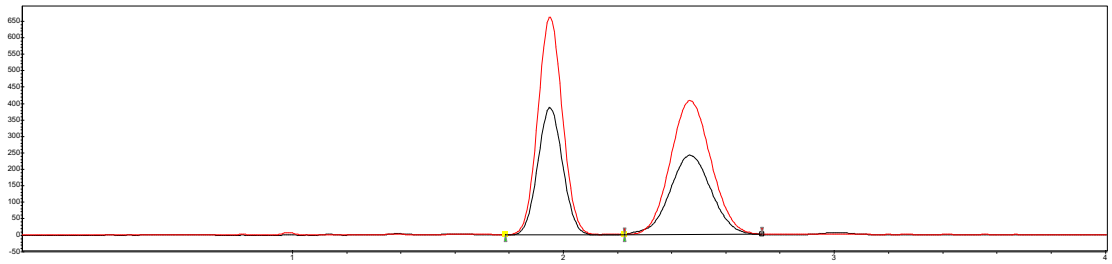
Experimental procedure:



A 1-dram vial containing a stir bar and **(+)-2.2** (21.7 mg, 0.100 mmol) was brought into an N_2 atmosphere glovebox. To this vial was sequentially added $Pd_2(dba)_3$•$CHCl_3$ (5.2 mg, 0.0050 mmol), RuPhos (4.7 mg, 0.010 mmol), Cs_2CO_3 (39.0 mg, 0.120 mmol) and toluene (0.5 mL). The vial was sealed with a Teflon cap and the resulting mixture was stirred at 40 °C for 24 h. After cooling to room temperature, the mixture was filtered through Celite® using EtOAc as the eluent. After concentration to dryness, the crude residue was purified by preparative thin-layer chromatography (33% EtOAc/hexanes) to provide **2.3a** (18.5 mg, 63%). The spectroscopic data were in agreement with those reported above.

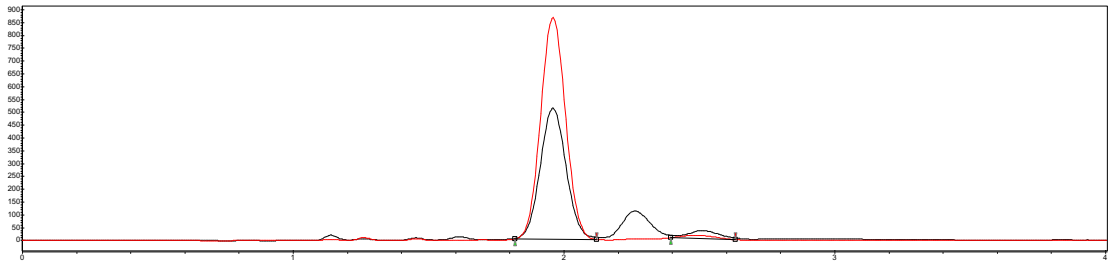
Conditions:
Column & dimensions (mm): CCC, 4.6X250
Outlet Pressure (bar): 100 **UV wavelength** (nm): 220/254 (black/red)
Flow rate (ml/min): 4 **Modifier**: 30% MeOH w/ 0.1% NH_4OH

1-phenyl-2-(2-phenylpiperidin-1-yl)ethane-1,2-dione (racemic)



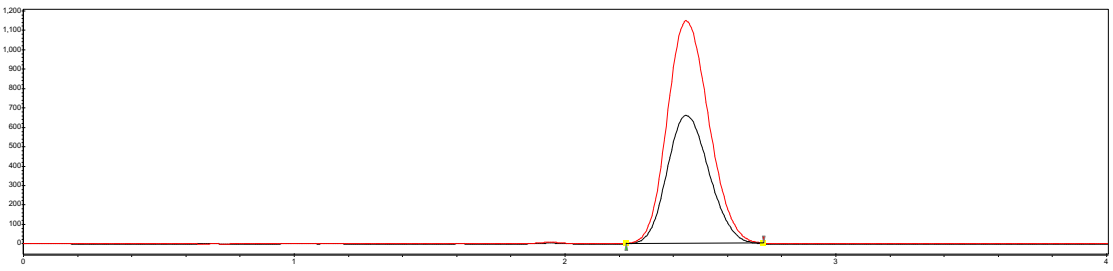
#	Name	Start [Min]	Area [%]
1	PEAK	1.79	49.876
2	PEAK	2.23	50.124

Synthetic sample-1-phenyl-2-(2-phenylpiperidin-1-yl)ethane-1,2-dione (96% ee)



#	Name	Start [Min]	Area [%]
1	PEAK	1.82	98.220
2	PEAK	2.39	1.780

Authentic sample- (*S*)-1-phenyl-2-(2-phenylpiperidin-1-yl)ethane-1,2-dione



#	Name	Start [Min]	Area [%]
1	PEAK	2.23	100.000

2.4.9. X-ray Data

2.4.9.1 X-ray analysis of 2.2

Single-crystal X-ray diffraction experiments were performed a the UC Berkeley CHEXRAY crystallographic facility. Measurements of all compounds were performed on a Bruker APEXII Quazar diffractometer equipped with a micro-focus X-ray source using Mo Kα radiation (λ = 0.71073 Å) and a Bruker APEX-II area detector. Crystals were kept at 100(2) K throughout the collection. Data collection was performed with Bruker APEX2 software (v. 2014.11). Data refinement and reduction were performed with Bruker SAINT (V8.34A). All structures were solved with SHELXT.53.[60] Structures were refined with SHELXL-2014.[61] All non-hydrogen atoms were refined anisotropically, and hydrogen atoms were either included at the geometrically calculated positions and refined using a riding model or located as Q peaks in the Fourier difference map.

Note: The instruments are supported by an NIH Shared Instrument Grant S10-RR027172

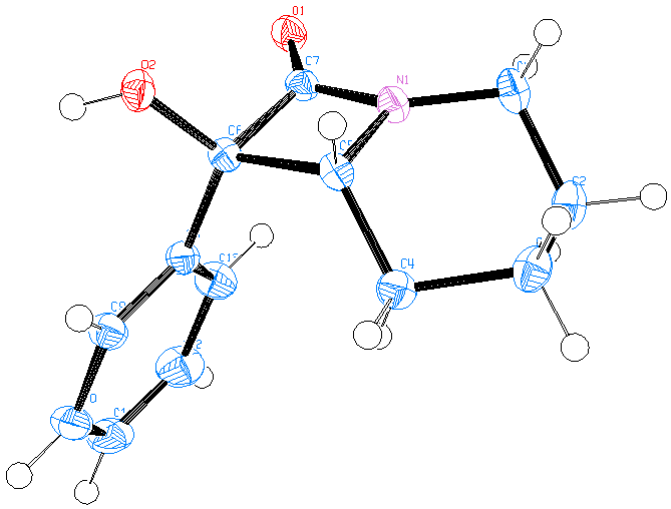


Figure 2.S6. ORTEP representation of rac-**2.2**.

This crystal structure has been deposited at the Cambride Crystallographic Data Center under CCDC 1899655.

Table 2.S1. Crystal data and structure refinement for jr001.

Identification code	jr001
Empirical formula	C13 H15 N O2
Formula weight	217.26
Temperature	100(2) K
Wavelength	0.71073 ≈

Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 8.6719(7) ≈	α= 90∞.
	b = 15.1388(12) ≈	β= 116.469(4)∞.
	c = 9.5746(7) ≈	γ = 90∞.
Volume	1125.21(15) ≈^{3}	
Z	4	
Density (calculated)	1.282 Mg/m^3	
Absorption coefficient	0.087 mm^{-1}	
F(000)	464	
Crystal size	0.300 x 0.100 x 0.050 mm^3	
Theta range for data collection	2.624 to 28.352∞.	
Index ranges	-11<=h<=11, -20<=k<=20, -12<=l<=12	
Reflections collected	43168	
Independent reflections	2809 [R(int) = 0.0366]	
Completeness to theta = 28.000∞	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.746 and 0.713	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2809 / 0 / 149	
Goodness-of-fit on F^2	1.081	
Final R indices [I>2sigma(I)]	R1 = 0.0430, wR2 = 0.1110	
R indices (all data)	R1 = 0.0503, wR2 = 0.1165	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.432 and -0.184 e.≈$^{-3}$	

Table 2.S2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (≈^{2}x 10^3) for jr001. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	7493(2)	4651(1)	731(1)	24(1)
C(2)	7495(2)	5422(1)	-312(1)	26(1)
C(3)	8974(2)	6064(1)	563(1)	24(1)
C(4)	7264(2)	4984(1)	2144(1)	20(1)
C(5)	8734(1)	5606(1)	3073(1)	18(1)
C(6)	8564(1)	6417(1)	4024(1)	16(1)
C(7)	8937(1)	6978(1)	2847(1)	18(1)
C(8)	6798(1)	6557(1)	3940(1)	18(1)
C(9)	6344(2)	6091(1)	4960(1)	22(1)
C(10)	4724(2)	6199(1)	4894(2)	29(1)
C(11)	3545(2)	6768(1)	3817(2)	33(1)
C(12)	3974(2)	7227(1)	2786(2)	33(1)
C(13)	5600(2)	7122(1)	2851(2)	26(1)
N(1)	8976(1)	6260(1)	2048(1)	19(1)
O(1)	9161(1)	7765(1)	2699(1)	22(1)
O(2)	9904(1)	6426(1)	5553(1)	20(1)

Table 2.S3. Bond lengths [≈] and angles [∞] for jr001.

C(1)-C(2)	1.5355(18)
C(1)-C(4)	1.5377(16)
C(1)-H(1A)	0.9900
C(1)-H(1B)	0.9900
C(2)-C(3)	1.5273(18)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-N(1)	1.4520(15)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-C(5)	1.5132(16)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-N(1)	1.4731(14)
C(5)-C(6)	1.5749(15)
C(5)-H(5)	1.0000
C(6)-O(2)	1.4063(13)
C(6)-C(8)	1.5122(15)
C(6)-C(7)	1.5555(15)
C(7)-O(1)	1.2247(14)
C(7)-N(1)	1.3389(15)
C(8)-C(13)	1.3902(17)
C(8)-C(9)	1.3956(16)
C(9)-C(10)	1.3875(18)
C(9)-H(9)	0.9500
C(10)-C(11)	1.383(2)
C(10)-H(10)	0.9500
C(11)-C(12)	1.387(2)
C(11)-H(11)	0.9500
C(12)-C(13)	1.3927(18)
C(12)-H(12)	0.9500
C(13)-H(13)	0.9500
O(2)-H(2)	0.883(19)

C(2)-C(1)-C(4)	111.17(10)
C(2)-C(1)-H(1A)	109.4
C(4)-C(1)-H(1A)	109.4
C(2)-C(1)-H(1B)	109.4
C(4)-C(1)-H(1B)	109.4
H(1A)-C(1)-H(1B)	108.0
C(3)-C(2)-C(1)	111.75(10)
C(3)-C(2)-H(2A)	109.3
C(1)-C(2)-H(2A)	109.3
C(3)-C(2)-H(2B)	109.3
C(1)-C(2)-H(2B)	109.3
H(2A)-C(2)-H(2B)	107.9
N(1)-C(3)-C(2)	107.52(10)
N(1)-C(3)-H(3A)	110.2
C(2)-C(3)-H(3A)	110.2
N(1)-C(3)-H(3B)	110.2
C(2)-C(3)-H(3B)	110.2
H(3A)-C(3)-H(3B)	108.5
C(5)-C(4)-C(1)	108.39(9)
C(5)-C(4)-H(4A)	110.0
C(1)-C(4)-H(4A)	110.0
C(5)-C(4)-H(4B)	110.0
C(1)-C(4)-H(4B)	110.0
H(4A)-C(4)-H(4B)	108.4
N(1)-C(5)-C(4)	111.06(9)
N(1)-C(5)-C(6)	86.48(8)
C(4)-C(5)-C(6)	123.61(9)
N(1)-C(5)-H(5)	111.0
C(4)-C(5)-H(5)	111.0
C(6)-C(5)-H(5)	111.0
O(2)-C(6)-C(8)	113.68(9)
O(2)-C(6)-C(7)	114.00(9)
C(8)-C(6)-C(7)	114.73(9)
O(2)-C(6)-C(5)	111.21(9)
C(8)-C(6)-C(5)	115.58(9)
C(7)-C(6)-C(5)	84.47(8)

O(1)-C(7)-N(1)	132.70(11)
O(1)-C(7)-C(6)	135.16(10)
N(1)-C(7)-C(6)	92.11(9)
C(13)-C(8)-C(9)	119.10(11)
C(13)-C(8)-C(6)	121.73(10)
C(9)-C(8)-C(6)	119.16(10)
C(10)-C(9)-C(8)	120.27(12)
C(10)-C(9)-H(9)	119.9
C(8)-C(9)-H(9)	119.9
C(11)-C(10)-C(9)	120.30(12)
C(11)-C(10)-H(10)	119.9
C(9)-C(10)-H(10)	119.9
C(10)-C(11)-C(12)	119.95(12)
C(10)-C(11)-H(11)	120.0
C(12)-C(11)-H(11)	120.0
C(11)-C(12)-C(13)	119.90(13)
C(11)-C(12)-H(12)	120.1
C(13)-C(12)-H(12)	120.1
C(8)-C(13)-C(12)	120.47(12)
C(8)-C(13)-H(13)	119.8
C(12)-C(13)-H(13)	119.8
C(7)-N(1)-C(3)	137.42(10)
C(7)-N(1)-C(5)	96.78(9)
C(3)-N(1)-C(5)	125.21(10)
C(6)-O(2)-H(2)	108.2(12)

Symmetry transformations used to generate equivalent atoms:

Table 2.S4. Anisotropic displacement parameters ($\approx^2$x 10^3)for jr001. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	25(1)	22(1)	21(1)	-2(1)	8(1)	2(1)
C(2)	32(1)	26(1)	17(1)	-1(1)	9(1)	5(1)
C(3)	31(1)	27(1)	20(1)	0(1)	16(1)	2(1)
C(4)	21(1)	18(1)	23(1)	0(1)	11(1)	1(1)
C(5)	19(1)	18(1)	17(1)	2(1)	10(1)	3(1)
C(6)	16(1)	17(1)	16(1)	2(1)	8(1)	2(1)
C(7)	14(1)	22(1)	17(1)	1(1)	7(1)	1(1)
C(8)	18(1)	17(1)	20(1)	-3(1)	10(1)	0(1)
C(9)	24(1)	22(1)	25(1)	-1(1)	14(1)	-3(1)
C(10)	28(1)	31(1)	36(1)	-9(1)	21(1)	-10(1)
C(11)	19(1)	39(1)	45(1)	-14(1)	18(1)	-5(1)
C(12)	20(1)	35(1)	41(1)	0(1)	10(1)	6(1)
C(13)	21(1)	26(1)	29(1)	4(1)	11(1)	4(1)
N(1)	21(1)	20(1)	18(1)	1(1)	11(1)	0(1)
O(1)	26(1)	20(1)	22(1)	1(1)	13(1)	-2(1)
O(2)	19(1)	25(1)	15(1)	0(1)	7(1)	5(1)

Table 2.S5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (≈^{2}x 10^3) for jr001.

	x	y	z	U(eq)
H(1A)	8593	4324	1099	28
H(1B)	6546	4239	115	28
H(2A)	7598	5186	-1231	31
H(2B)	6386	5743	-692	31
H(3A)	10084	5793	734	29
H(3B)	8810	6612	-49	29
H(4A)	6150	5296	1788	24
H(4B)	7270	4479	2804	24
H(5)	9822	5271	3693	21
H(9)	7149	5699	5704	27
H(10)	4423	5880	5592	35
H(11)	2441	6845	3783	40
H(12)	3160	7613	2037	40
H(13)	5892	7438	2146	31
H(2)	9560(20)	6743(12)	6140(20)	39(5)

2.4.9.2 X-ray analysis of (–)-2.2

A colorless block 0.42 x 0.31 x 0.21 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using omega scans. Crystal-to-detector distance was 30.23 mm and exposure time was 0.50 seconds per frame at low and high angles using a scan width of 0.5°. Data collection was 100% complete to 74.000° in θ. A total of 24011 reflections were collected covering the indices -9<=h<=8, -9<=k<=9, -43<=l<=43. 2251 reflections were found to be symmetry independent, with an R_{int} of 0.0403. Indexing and unit cell refinement indicated a primitive, tetragonal lattice. The space group was found to be P 43 21 2 (No. 96). The data were integrated using the CrysAlis^{Pro} 1.171.40.45a software program and scaled using the SCALE3 ABSPACK scaling algorithm. Solution by intrinsic phasing (SHELXT-2015) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

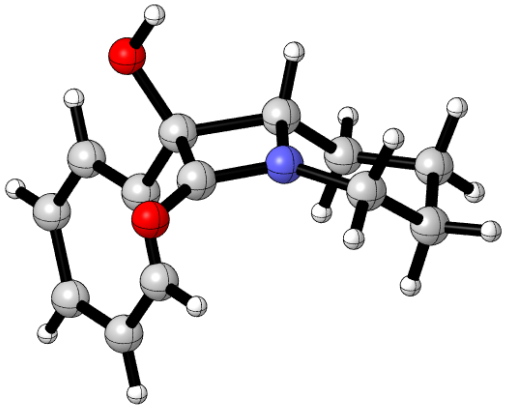


Figure 2.S7. ORTEP representation of **(–)-2.2** (**Sample 2.2** peak 1).

This crystal structure has been deposited at the Cambride Crystallographic Data Center under CCDC 1908809.

Table 2.S6. Crystal data and structure refinement for Jurczyk001_Sarpong.

Identification code	Jurczyk001_Sarpong
Empirical formula	C13 H15 N O2
Formula weight	217.26

Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	Tetragonal	
Space group	P 43 21 2	
Unit cell dimensions	a = 7.97537(5) Å	α= 90°.
	b = 7.97537(5) Å	β= 90°.
	c = 34.7796(3) Å	γ = 90°.
Volume	2212.21(3) $Å^3$	
Z	8	
Density (calculated)	1.305 Mg/m^3	
Absorption coefficient	0.709 mm^{-1}	
F(000)	928	
Crystal size	0.420 x 0.310 x 0.210 mm^3	
Theta range for data collection	5.087 to 74.451°.	
Index ranges	-9<=h<=8, -9<=k<=9, -43<=l<=43	
Reflections collected	24011	
Independent reflections	2251 [R(int) = 0.0403]	
Completeness to theta = 74.000°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.84252	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2251 / 0 / 149	
Goodness-of-fit on F^2	1.058	
Final R indices [I>2sigma(I)]	R1 = 0.0271, wR2 = 0.0699	
R indices (all data)	R1 = 0.0272, wR2 = 0.0700	
Absolute structure parameter	-0.06(5)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.144 and -0.187 $e.Å^{-3}$	

Table 2.S7. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for jurczyk001_sarpong. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	4233(2)	5056(2)	3620(1)	21(1)
C(2)	3008(2)	4036(2)	3863(1)	25(1)
C(3)	2584(2)	4868(2)	4248(1)	23(1)
C(4)	4166(2)	5167(2)	4492(1)	19(1)
C(5)	5359(2)	6259(2)	4263(1)	16(1)
C(6)	7336(2)	6211(2)	4297(1)	16(1)
C(7)	7265(2)	5557(2)	3874(1)	16(1)
C(8)	8113(2)	4982(2)	4576(1)	16(1)
C(9)	8965(2)	5573(2)	4899(1)	19(1)
C(10)	9716(2)	4453(2)	5154(1)	23(1)
C(11)	9608(2)	2742(2)	5091(1)	24(1)
C(12)	8757(2)	2144(2)	4769(1)	22(1)
C(13)	8019(2)	3259(2)	4513(1)	19(1)
N(1)	5586(1)	5612(2)	3869(1)	17(1)
O(1)	8086(1)	7790(1)	4347(1)	20(1)
O(2)	8308(1)	5125(1)	3633(1)	20(1)

Table 2.S8. Bond lengths [Å] and angles [°] for jurczyk001_sarpong.

C(1)-N(1)	1.4540(17)
C(1)-C(2)	1.528(2)
C(2)-C(3)	1.533(2)
C(3)-C(4)	1.538(2)
C(4)-C(5)	1.515(2)
C(5)-N(1)	1.4758(17)
C(5)-C(6)	1.5818(19)
C(6)-O(1)	1.4047(17)
C(6)-C(8)	1.5106(19)
C(6)-C(7)	1.5613(18)
C(7)-O(2)	1.2307(17)
C(7)-N(1)	1.3399(18)
C(8)-C(13)	1.394(2)
C(8)-C(9)	1.3958(19)
C(9)-C(10)	1.393(2)
C(10)-C(11)	1.385(2)
C(11)-C(12)	1.393(2)
C(12)-C(13)	1.391(2)
N(1)-C(1)-C(2)	107.82(11)
C(1)-C(2)-C(3)	113.27(12)
C(2)-C(3)-C(4)	111.55(12)
C(5)-C(4)-C(3)	108.38(11)
N(1)-C(5)-C(4)	111.29(11)
N(1)-C(5)-C(6)	86.50(10)
C(4)-C(5)-C(6)	124.91(12)
O(1)-C(6)-C(8)	109.22(11)
O(1)-C(6)-C(7)	115.44(11)
C(8)-C(6)-C(7)	113.69(11)
O(1)-C(6)-C(5)	114.31(11)
C(8)-C(6)-C(5)	118.22(12)
C(7)-C(6)-C(5)	84.33(10)
O(2)-C(7)-N(1)	132.43(13)
O(2)-C(7)-C(6)	135.34(13)

N(1)-C(7)-C(6)	92.22(11)
C(13)-C(8)-C(9)	119.09(13)
C(13)-C(8)-C(6)	121.13(12)
C(9)-C(8)-C(6)	119.77(13)
C(10)-C(9)-C(8)	120.31(14)
C(11)-C(10)-C(9)	120.35(14)
C(10)-C(11)-C(12)	119.62(14)
C(13)-C(12)-C(11)	120.18(14)
C(12)-C(13)-C(8)	120.45(13)
C(7)-N(1)-C(1)	137.77(12)
C(7)-N(1)-C(5)	96.94(11)
C(1)-N(1)-C(5)	124.73(11)

Symmetry transformations used to generate equivalent atoms:

Table 2.S9. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for jurczyk001_sarpong. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	17(1)	26(1)	20(1)	-6(1)	-3(1)	3(1)
C(2)	17(1)	27(1)	31(1)	-7(1)	-4(1)	-4(1)
C(3)	14(1)	28(1)	26(1)	1(1)	2(1)	-1(1)
C(4)	17(1)	21(1)	20(1)	0(1)	2(1)	-1(1)
C(5)	16(1)	17(1)	14(1)	-1(1)	0(1)	0(1)
C(6)	14(1)	16(1)	17(1)	-1(1)	1(1)	-3(1)
C(7)	17(1)	15(1)	17(1)	2(1)	0(1)	-1(1)
C(8)	12(1)	19(1)	16(1)	1(1)	3(1)	-1(1)
C(9)	17(1)	20(1)	19(1)	-2(1)	1(1)	0(1)
C(10)	19(1)	31(1)	18(1)	-1(1)	0(1)	5(1)
C(11)	23(1)	28(1)	22(1)	8(1)	4(1)	9(1)
C(12)	23(1)	18(1)	26(1)	3(1)	6(1)	2(1)
C(13)	18(1)	20(1)	20(1)	0(1)	2(1)	-1(1)
N(1)	16(1)	20(1)	15(1)	-3(1)	0(1)	0(1)
O(1)	21(1)	15(1)	22(1)	2(1)	-2(1)	-5(1)
O(2)	18(1)	24(1)	19(1)	-2(1)	4(1)	0(1)

Table 2.S10. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for jurczyk001_sarpong.

	x	y	z	U(eq)
H(1A)	4685	4358	3408	25
H(1B)	3655	6036	3505	25
H(2A)	3499	2917	3913	30
H(2B)	1959	3871	3715	30
H(3A)	1798	4144	4393	27
H(3B)	2020	5954	4200	27
H(4A)	3864	5729	4736	23
H(4B)	4708	4083	4554	23
H(5)	4950	7444	4257	19
H(9)	9033	6745	4946	22
H(10)	10305	4866	5371	27
H(11)	10111	1980	5266	29
H(12)	8680	971	4725	27
H(13)	7446	2843	4293	23
H(1)	7510(30)	8580(30)	4198(7)	48(6)

Table 2.S11. Torsion angles [°] for jurczyk001_sarpong.

N(1)-C(1)-C(2)-C(3)	45.70(17)
C(1)-C(2)-C(3)-C(4)	-58.44(17)
C(2)-C(3)-C(4)-C(5)	58.29(16)
C(3)-C(4)-C(5)-N(1)	-49.09(15)
C(3)-C(4)-C(5)-C(6)	-150.16(13)
N(1)-C(5)-C(6)-O(1)	116.08(12)
C(4)-C(5)-C(6)-O(1)	-130.28(14)
N(1)-C(5)-C(6)-C(8)	-113.20(12)
C(4)-C(5)-C(6)-C(8)	0.4(2)
N(1)-C(5)-C(6)-C(7)	0.69(10)
C(4)-C(5)-C(6)-C(7)	114.33(14)
O(1)-C(6)-C(7)-O(2)	65.9(2)
C(8)-C(6)-C(7)-O(2)	-61.4(2)
C(5)-C(6)-C(7)-O(2)	-179.80(17)
O(1)-C(6)-C(7)-N(1)	-115.02(12)
C(8)-C(6)-C(7)-N(1)	117.62(13)
C(5)-C(6)-C(7)-N(1)	-0.76(11)
O(1)-C(6)-C(8)-C(13)	-159.28(13)
C(7)-C(6)-C(8)-C(13)	-28.76(19)
C(5)-C(6)-C(8)-C(13)	67.73(17)
O(1)-C(6)-C(8)-C(9)	19.63(17)
C(7)-C(6)-C(8)-C(9)	150.16(12)
C(5)-C(6)-C(8)-C(9)	-113.36(15)
C(13)-C(8)-C(9)-C(10)	0.3(2)
C(6)-C(8)-C(9)-C(10)	-178.68(13)
C(8)-C(9)-C(10)-C(11)	-0.7(2)
C(9)-C(10)-C(11)-C(12)	0.6(2)
C(10)-C(11)-C(12)-C(13)	-0.1(2)
C(11)-C(12)-C(13)-C(8)	-0.4(2)
C(9)-C(8)-C(13)-C(12)	0.3(2)
C(6)-C(8)-C(13)-C(12)	179.24(12)
O(2)-C(7)-N(1)-C(1)	8.8(3)
C(6)-C(7)-N(1)-C(1)	-170.33(17)
O(2)-C(7)-N(1)-C(5)	179.90(16)

C(6)-C(7)-N(1)-C(5)	0.81(12)
C(2)-C(1)-N(1)-C(7)	127.27(17)
C(2)-C(1)-N(1)-C(5)	-42.01(19)
C(4)-C(5)-N(1)-C(7)	-127.07(12)
C(6)-C(5)-N(1)-C(7)	-0.80(12)
C(4)-C(5)-N(1)-C(1)	45.70(18)
C(6)-C(5)-N(1)-C(1)	171.97(13)

Symmetry transformations used to generate equivalent atoms:

2.4.9.3 X-ray analysis of (+)-2.2

A colorless block 0.27 x 0.16 x 0.10 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using omega scans. Crystal-to-detector distance was 30.23 mm and exposure time was 0.50 seconds per frame at low and high angles using a scan width of 0.5°. Data collection was 100% complete to 74.000° in θ. A total of 24257 reflections were collected covering the indices -9<=h<=9, -8<=k<=9, -43<=l<=43. 2255 reflections were found to be symmetry independent, with an R_{int} of 0.0450. Indexing and unit cell refinement indicated a primitive, tetragonal lattice. The space group was found to be P 41 21 2 (No. 92). The data were integrated using the CrysAlis^{Pro} 1.171.40.45a software program and scaled using the SCALE3 ABSPACK scaling algorithm. Solution by intrinsic phasing (SHELXT-2015) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

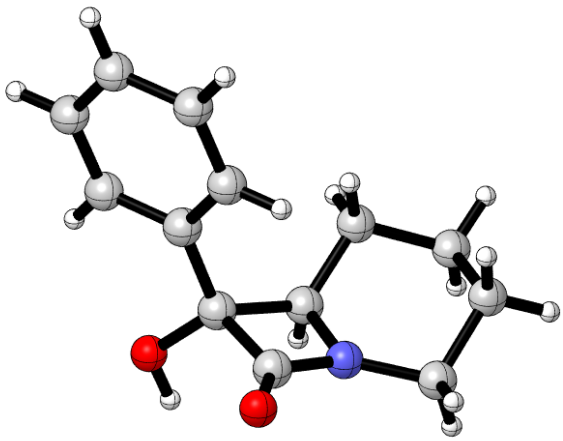


Figure 2.S8. ORTEP representation of **(+)-2.2** (**Sample 2.2** peak 2).

This crystal structure has been deposited at the Cambride Crystallographic Data Center under CCDC 1908887.

Table 2.S12. Crystal data and structure refinement for Jurczyk002_Sarpong.

Identification code	Jurczyk002_Sarpong
Empirical formula	C13 H15 N O2

Formula weight	217.26	
Temperature	100(2) K	
Wavelength	1.54184 Å	
Crystal system	Tetragonal	
Space group	P 41 21 2	
Unit cell dimensions	a = 7.97639(5) Å	α= 90°.
	b = 7.97639(5) Å	β= 90°.
	c = 34.7863(3) Å	γ = 90°.
Volume	2213.20(3) $Å^3$	
Z	8	
Density (calculated)	1.304 Mg/m^3	
Absorption coefficient	0.708 mm^{-1}	
F(000)	928	
Crystal size	0.270 x 0.160 x 0.100 mm^3	
Theta range for data collection	5.086 to 74.419°.	
Index ranges	-9<=h<=9, -8<=k<=9, -43<=l<=43	
Reflections collected	24257	
Independent reflections	2255 [R(int) = 0.0450]	
Completeness to theta = 74.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.64726	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2255 / 0 / 149	

Goodness-of-fit on F^2	1.058
Final R indices [I>2sigma(I)]	R1 = 0.0265, wR2 = 0.0663
R indices (all data)	R1 = 0.0268, wR2 = 0.0665
Absolute structure parameter	0.08(5)
Extinction coefficient	n/a
Largest diff. peak and hole	0.135 and -0.167 e.$Å^{-3}$

Table 2.S13. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for jurczyk002_sarpong. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	4945(2)	4233(2)	3880(1)	22(1)
C(2)	5965(2)	3009(2)	3637(1)	26(1)
C(3)	5131(2)	2587(2)	3252(1)	24(1)
C(4)	4832(2)	4166(2)	3009(1)	21(1)
C(5)	3740(2)	5359(2)	3237(1)	17(1)
C(6)	3789(2)	7335(2)	3203(1)	17(1)
C(7)	4444(2)	7266(2)	3626(1)	18(1)
C(8)	5018(2)	8111(2)	2924(1)	17(1)
C(9)	6743(2)	8020(2)	2987(1)	20(1)
C(10)	7856(2)	8757(2)	2731(1)	24(1)
C(11)	7257(2)	9606(2)	2409(1)	26(1)
C(12)	5546(2)	9715(2)	2347(1)	24(1)
C(13)	4428(2)	8967(2)	2601(1)	20(1)
N(1)	4389(2)	5585(1)	3631(1)	18(1)
O(1)	2210(1)	8086(1)	3154(1)	21(1)
O(2)	4876(1)	8308(1)	3867(1)	22(1)

Table 2.S14. Bond lengths [Å] and angles [°] for jurczyk002_sarpong.

C(1)-N(1)	1.4534(17)
C(1)-C(2)	1.527(2)
C(1)-H(1A)	0.9900
C(1)-H(1B)	0.9900
C(2)-C(3)	1.534(2)
C(2)-H(2A)	0.9900
C(2)-H(2B)	0.9900
C(3)-C(4)	1.536(2)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-C(5)	1.5146(19)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-N(1)	1.4766(16)
C(5)-C(6)	1.5812(18)
C(5)-H(5)	1.0000
C(6)-O(1)	1.4049(17)
C(6)-C(8)	1.5108(19)
C(6)-C(7)	1.5616(18)
C(7)-O(2)	1.2300(17)
C(7)-N(1)	1.3411(17)
C(8)-C(9)	1.395(2)
C(8)-C(13)	1.3970(18)
C(9)-C(10)	1.389(2)
C(9)-H(9)	0.9500
C(10)-C(11)	1.393(2)
C(10)-H(10)	0.9500
C(11)-C(12)	1.385(2)
C(11)-H(11)	0.9500
C(12)-C(13)	1.391(2)
C(12)-H(12)	0.9500
C(13)-H(13)	0.9500
O(1)-H(1)	0.92(2)

N(1)-C(1)-C(2)	107.84(11)
N(1)-C(1)-H(1A)	110.1
C(2)-C(1)-H(1A)	110.1
N(1)-C(1)-H(1B)	110.1
C(2)-C(1)-H(1B)	110.1
H(1A)-C(1)-H(1B)	108.5
C(1)-C(2)-C(3)	113.18(12)
C(1)-C(2)-H(2A)	108.9
C(3)-C(2)-H(2A)	108.9
C(1)-C(2)-H(2B)	108.9
C(3)-C(2)-H(2B)	108.9
H(2A)-C(2)-H(2B)	107.8
C(2)-C(3)-C(4)	111.58(12)
C(2)-C(3)-H(3A)	109.3
C(4)-C(3)-H(3A)	109.3
C(2)-C(3)-H(3B)	109.3
C(4)-C(3)-H(3B)	109.3
H(3A)-C(3)-H(3B)	108.0
C(5)-C(4)-C(3)	108.44(11)
C(5)-C(4)-H(4A)	110.0
C(3)-C(4)-H(4A)	110.0
C(5)-C(4)-H(4B)	110.0
C(3)-C(4)-H(4B)	110.0
H(4A)-C(4)-H(4B)	108.4
N(1)-C(5)-C(4)	111.19(11)
N(1)-C(5)-C(6)	86.49(9)
C(4)-C(5)-C(6)	124.94(12)
N(1)-C(5)-H(5)	110.5
C(4)-C(5)-H(5)	110.5
C(6)-C(5)-H(5)	110.5
O(1)-C(6)-C(8)	109.20(11)
O(1)-C(6)-C(7)	115.45(11)
C(8)-C(6)-C(7)	113.63(11)
O(1)-C(6)-C(5)	114.34(11)
C(8)-C(6)-C(5)	118.20(11)
C(7)-C(6)-C(5)	84.41(10)

O(2)-C(7)-N(1)	132.49(13)
O(2)-C(7)-C(6)	135.35(12)
N(1)-C(7)-C(6)	92.15(11)
C(9)-C(8)-C(13)	118.92(13)
C(9)-C(8)-C(6)	121.20(12)
C(13)-C(8)-C(6)	119.86(13)
C(10)-C(9)-C(8)	120.51(13)
C(10)-C(9)-H(9)	119.7
C(8)-C(9)-H(9)	119.7
C(9)-C(10)-C(11)	120.18(14)
C(9)-C(10)-H(10)	119.9
C(11)-C(10)-H(10)	119.9
C(12)-C(11)-C(10)	119.62(13)
C(12)-C(11)-H(11)	120.2
C(10)-C(11)-H(11)	120.2
C(11)-C(12)-C(13)	120.36(13)
C(11)-C(12)-H(12)	119.8
C(13)-C(12)-H(12)	119.8
C(12)-C(13)-C(8)	120.39(14)
C(12)-C(13)-H(13)	119.8
C(8)-C(13)-H(13)	119.8
C(7)-N(1)-C(1)	137.73(12)
C(7)-N(1)-C(5)	96.94(10)
C(1)-N(1)-C(5)	124.77(11)
C(6)-O(1)-H(1)	110.3(15)

Symmetry transformations used to generate equivalent atoms:

Table 2.S15. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for jurczyk002_sarpong. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	29(1)	19(1)	18(1)	4(1)	-6(1)	-3(1)
C(2)	30(1)	20(1)	29(1)	4(1)	-6(1)	3(1)
C(3)	31(1)	17(1)	24(1)	-2(1)	1(1)	2(1)
C(4)	25(1)	21(1)	18(1)	-1(1)	0(1)	0(1)
C(5)	20(1)	19(1)	13(1)	1(1)	-1(1)	-1(1)
C(6)	19(1)	17(1)	15(1)	-1(1)	-1(1)	3(1)
C(7)	17(1)	20(1)	16(1)	-1(1)	2(1)	2(1)
C(8)	22(1)	15(1)	14(1)	-3(1)	0(1)	1(1)
C(9)	22(1)	20(1)	18(1)	-2(1)	-1(1)	2(1)
C(10)	21(1)	26(1)	25(1)	-7(1)	3(1)	-2(1)
C(11)	31(1)	26(1)	20(1)	-4(1)	7(1)	-8(1)
C(12)	34(1)	22(1)	16(1)	0(1)	-1(1)	-5(1)
C(13)	23(1)	20(1)	17(1)	-1(1)	-2(1)	0(1)
N(1)	22(1)	19(1)	14(1)	0(1)	-3(1)	0(1)
O(1)	18(1)	24(1)	21(1)	2(1)	2(1)	5(1)
O(2)	27(1)	21(1)	17(1)	-4(1)	-2(1)	0(1)

Table 2.S16. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for jurczyk002_sarpong.

	x	y	z	U(eq)
H(1A)	3966	3654	3994	27
H(1B)	5644	4685	4091	27
H(2A)	6131	1960	3784	32
H(2B)	7084	3500	3587	32
H(3A)	4046	2022	3300	29
H(3B)	5855	1800	3107	29
H(4A)	5916	4708	2947	25
H(4B)	4271	3864	2765	25
H(5)	2555	4949	3243	21
H(9)	7159	7450	3207	24
H(10)	9029	8680	2775	29
H(11)	8019	10108	2234	31
H(12)	5134	10304	2129	29
H(13)	3257	9037	2555	24
H(1)	1420(30)	7540(30)	3300(6)	48(6)

Table 2.S17. Torsion angles [°] for jurczyk002_sarpong.

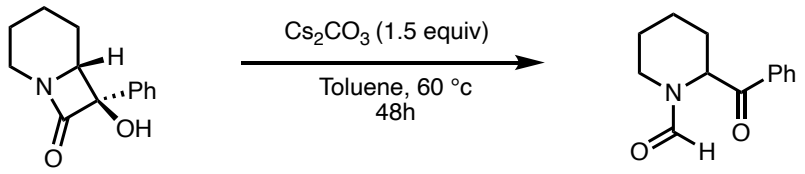
N(1)-C(1)-C(2)-C(3)	-45.67(17)
C(1)-C(2)-C(3)-C(4)	58.45(17)
C(2)-C(3)-C(4)-C(5)	-58.36(16)
C(3)-C(4)-C(5)-N(1)	49.10(15)
C(3)-C(4)-C(5)-C(6)	150.10(13)
N(1)-C(5)-C(6)-O(1)	-116.13(11)
C(4)-C(5)-C(6)-O(1)	130.35(13)
N(1)-C(5)-C(6)-C(8)	113.17(12)
C(4)-C(5)-C(6)-C(8)	-0.34(19)
N(1)-C(5)-C(6)-C(7)	-0.69(10)
C(4)-C(5)-C(6)-C(7)	-114.21(13)
O(1)-C(6)-C(7)-O(2)	-65.8(2)
C(8)-C(6)-C(7)-O(2)	61.5(2)
C(5)-C(6)-C(7)-O(2)	179.84(17)
O(1)-C(6)-C(7)-N(1)	115.09(12)
C(8)-C(6)-C(7)-N(1)	-117.62(12)
C(5)-C(6)-C(7)-N(1)	0.76(11)
O(1)-C(6)-C(8)-C(9)	159.17(12)
C(7)-C(6)-C(8)-C(9)	28.70(18)
C(5)-C(6)-C(8)-C(9)	-67.84(17)
O(1)-C(6)-C(8)-C(13)	-19.61(16)
C(7)-C(6)-C(8)-C(13)	-150.08(12)
C(5)-C(6)-C(8)-C(13)	113.38(15)
C(13)-C(8)-C(9)-C(10)	-0.5(2)
C(6)-C(8)-C(9)-C(10)	-179.29(12)
C(8)-C(9)-C(10)-C(11)	0.5(2)
C(9)-C(10)-C(11)-C(12)	0.1(2)
C(10)-C(11)-C(12)-C(13)	-0.7(2)
C(11)-C(12)-C(13)-C(8)	0.7(2)
C(9)-C(8)-C(13)-C(12)	-0.1(2)
C(6)-C(8)-C(13)-C(12)	178.72(12)
O(2)-C(7)-N(1)-C(1)	-8.8(3)
C(6)-C(7)-N(1)-C(1)	170.35(16)
O(2)-C(7)-N(1)-C(5)	-179.94(16)

C(6)-C(7)-N(1)-C(5)	-0.82(11)
C(2)-C(1)-N(1)-C(7)	-127.24(17)
C(2)-C(1)-N(1)-C(5)	42.07(18)
C(4)-C(5)-N(1)-C(7)	127.08(12)
C(6)-C(5)-N(1)-C(7)	0.81(11)
C(4)-C(5)-N(1)-C(1)	-45.70(18)
C(6)-C(5)-N(1)-C(1)	-171.97(13)

Symmetry transformations used to generate equivalent atoms:

2.4.10. Experimental Procedures for Base Promoted Rearrangement with Spectral Data

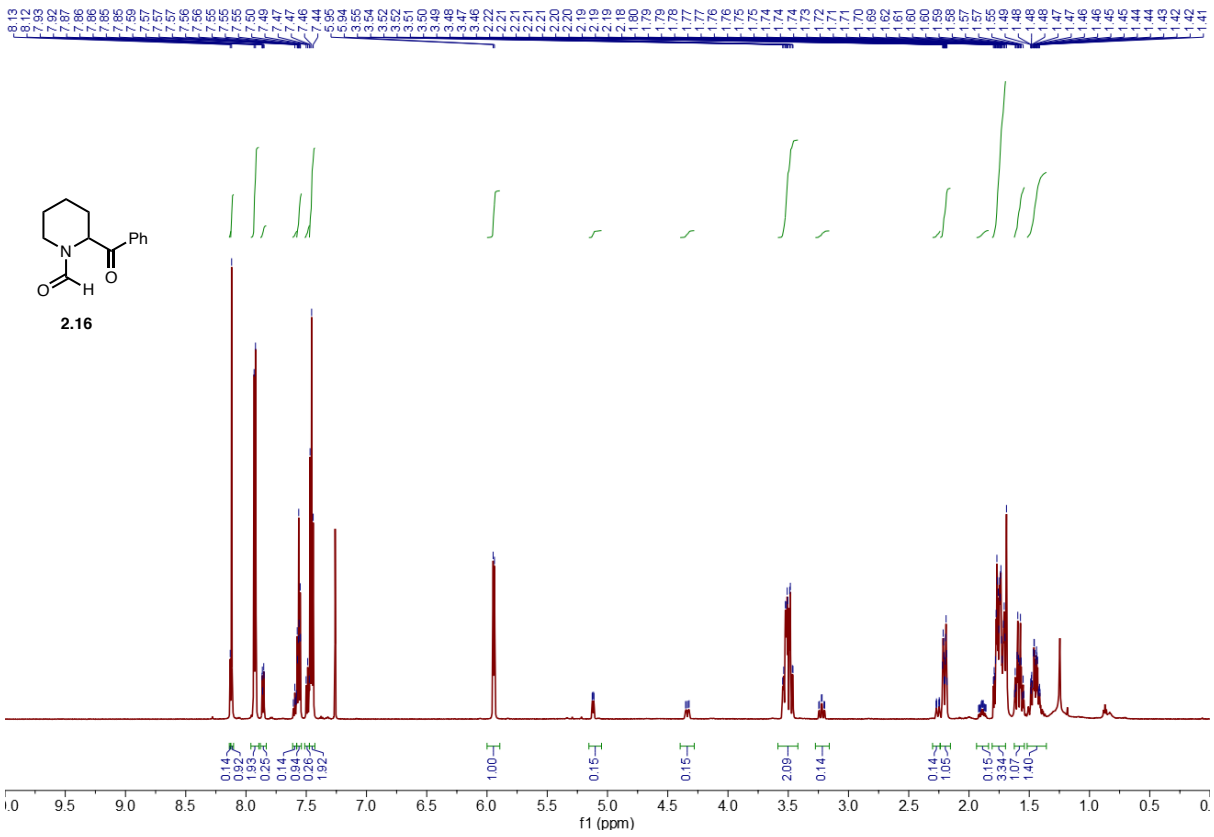
General procedure for base promoted rearrangement.

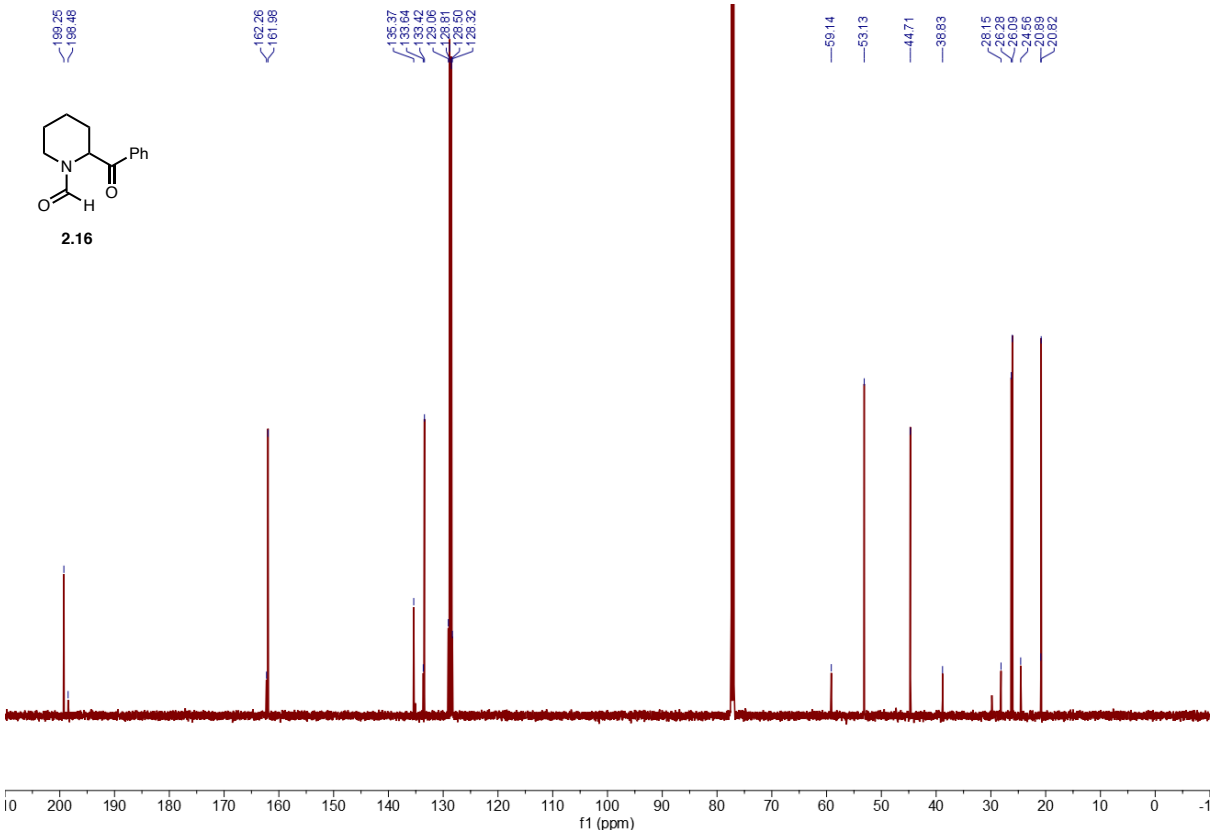


2.2 **2.16**

A 1-dram vial containing a stir bar and **2.2** (21.7 mg, 0.100 mmol) was brought into a nitrogen atmosphere glovebox. To this vial was sequentially added Cs_2CO_3 (48.9 mg, 0.150 mmol) and toluene (0.5 mL). The vial was sealed with a Teflon cap and the resulting mixture was stirred at 60 °C for 48 h. After cooling to room temperature, the mixture was filtered through Celite® using EtOAc as the eluent. After concentration to dryness, the crude residue was purified by preparative thin-layer chromatography (50% EtOAc/hexanes) to provide **2-benzoylpiperidine-1-carbaldehyde** (**2.16**) (16.7 mg, 77% mixture of rotamers 1.0:0.15) as a colorless oil.

^{1}H NMR (700 MHz, Chloroform-*d*) δ 8.01 – 7.96 (m, 2H), 7.18 (t, *J* = 8.6 Hz, 2H), 3.70 (t, *J* = 5.3 Hz, 2H), 3.31 – 3.26 (m, 2H), 1.74 – 1.65 (m, 4H), 1.55 (p, *J* = 5.6 Hz, 2H).
^{1}H NMR (600 MHz, Chloroform-*d*) δ 8.13 (s, 0.15 H), 8.12 (s, 1H), 7.93 (d, *J* = 7.0 Hz, 2H), 7.86 (d, *J* = 7.0 Hz, 0.3H), 7.59 (t, *J* = 7.4 Hz, 0.15H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.9 Hz, 0.30H), 7.46 (t, *J* = 7.8 Hz, 2H), 5.94 (d, *J* = 6.5 Hz, 1H), 5.12 (dd, *J* = 6.8, 1.9 Hz, 0.15H), 4.34 (dd, *J* = 13.0, 4.7 Hz, 0.15H), 3.56 – 3.44 (m, 2H), 3.22 (td, *J* = 13.1, 3.5 Hz, 0.15H), 2.26 (dt, *J* = 13.8, 1.8 Hz, 0.15H), 2.22 – 2.10 (m, 1H), 1.89 (tdd, *J* = 13.6, 6.8, 3.6 Hz, 0.15H), 1.85 – 1.66 (m, 3H+0.30H), 1.58 (qt, *J* = 13.5, 3.3 Hz, 1H), 1.49 – 1.41 (m, 1H+0.30H).
^{13}C NMR (151 MHz, CDCl3) (Major rotamer) δ 199.25, 161.98, 135.37, 133.42, 128.81, 128.50, 53.13, 44.71, 26.28, 26.09, 20.82.
^{13}C NMR (151 MHz, $CDCl_3$) (Minor rotamer) δ 198.48, 162.26, 135.07, 133.64, 129.06, 128.32, 59.14, 38.83, 28.15, 24.56, 20.89.
HRMS (ESI): Calc'd for $C_{13}H_{15}NNaO_2$ $[M+Na]^+$: 240.0995, found: 240.1002.


Ph
O
N
O
H
2.16
f1 (ppm)


Ph
O
N
O
H
2.16
f1 (ppm)

2.4.11. Potential energy surface and 3D geometries for the stereoselective α-hydroxy-β-lactam ring-opening at the distal position in the presence of Cs_2CO_3.

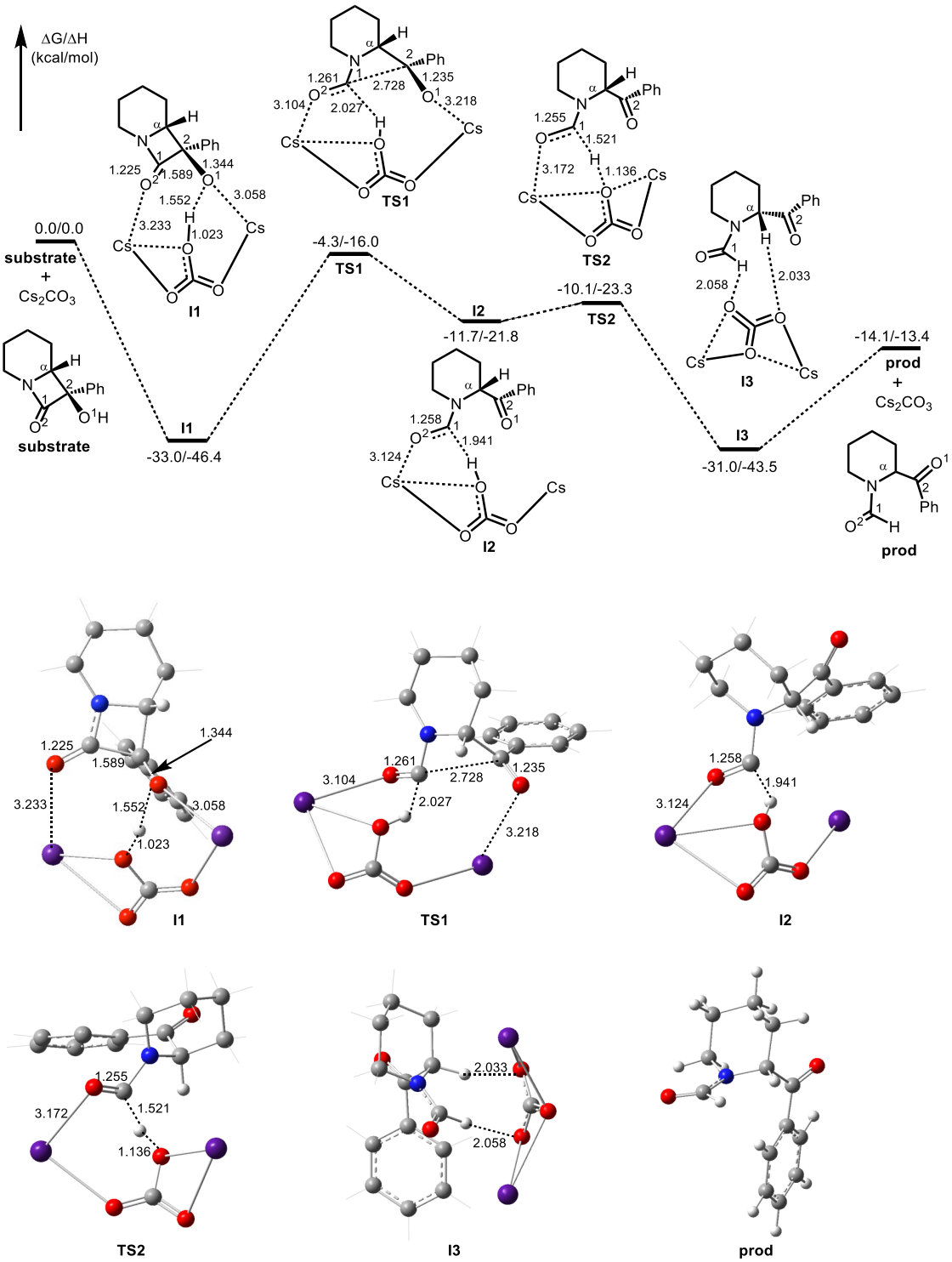


Figure 2.S9. Potential energy surface and 3D geometries for the stereoselective α-hydroxy-β-lactam ring-opening at the distal position in the presence of Cs_2CO_3.

2.4.12. The geometry structures and relative energies of the $Cs_2CO_3(X)_2$ and (Sub)$Cs_2CO_3(X)_2$ systems, where X = toluene and 1,4-dioxane. Distances are given in Å.

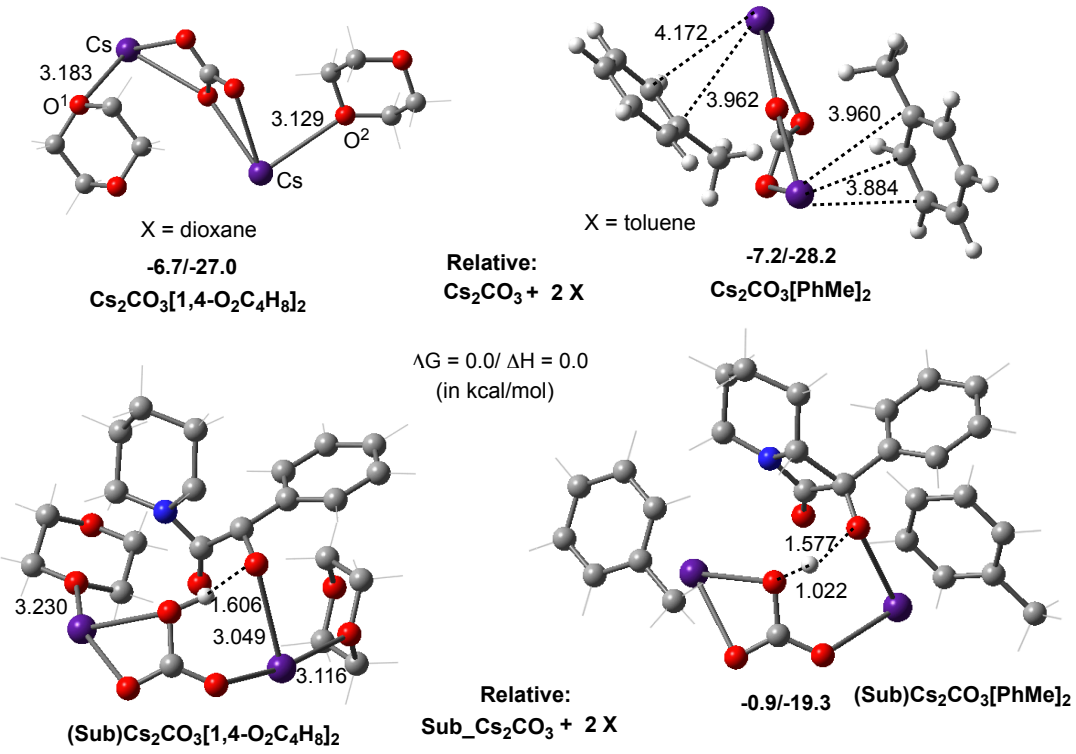


Figure 2.S10. The geometry structures and relative energies of the $Cs_2CO_3(X)_2$ and (Sub)$Cs_2CO_3(X)_2$ systems, where X = toluene and 1,4-dioxane. Distances are given in Å.

2.4.13. Impact of the *para*- and *ortho*-substitution to the calculated distal C-C bond cleavage energy barrier (presented as ΔG/ΔH in kcal/mol).

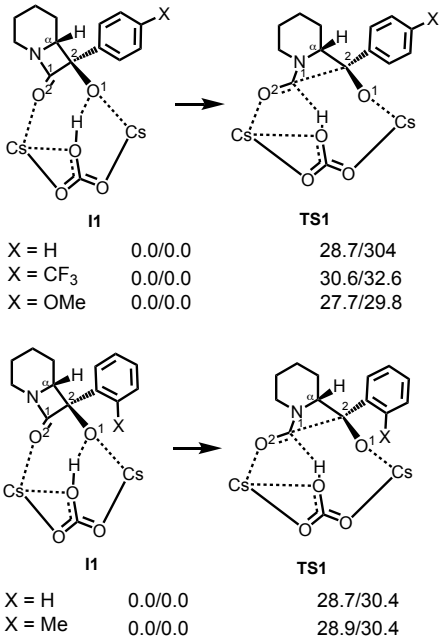


Figure 2.S11. Impact of the *para*- and *ortho*-substitution to the calculated distal C-C bond cleavage energy barrier (presented as ΔG/ΔH in kcal/mol).

2.4.14. Cartesian Coordinates (in Å) of the explicit solvent complexes.

$Cs_2CO_3[PhMe]_2$

Cs	-1.41864200	-5.05289500	-1.35607100
C	0.16657500	-2.29478500	-0.42119300
O	-0.76414200	-2.13204600	-1.33860200
O	0.85523900	-3.39733400	-0.41086100
O	0.38242000	-1.36166100	0.44444200
Cs	-0.07275400	0.79891200	-1.51853000
C	1.95168200	-1.78161600	-3.73913200
C	2.65422300	-1.77913500	-2.51945100
C	2.25460900	-0.79670400	-4.68941100
C	3.63198300	-0.81421800	-2.27091100
H	2.37458600	-2.50130200	-1.75139100
C	3.23084600	0.17399300	-4.43711300
H	1.71711300	-0.78584800	-5.63523200
C	3.92456700	0.16804300	-3.22515200
H	4.15898400	-0.82014500	-1.32031600
H	3.44955200	0.92878500	-5.18800500

H	4.68494400	0.91811700	-3.02572800
C	0.85377500	-2.79077600	-3.96405400
H	0.12729600	-2.69797600	-3.13897200
H	0.35773700	-2.63319800	-4.92777600
H	1.25205800	-3.81294700	-3.95184800
C	-1.01708000	-4.29352400	2.51211500
C	-1.73221700	-5.46892400	2.78332200
C	-1.73058200	-3.16342300	2.06974000
C	-3.12089600	-5.52697500	2.61581400
H	-1.19465600	-6.35099200	3.12455300
C	-3.11582400	-3.21911700	1.90825000
H	-1.17032700	-2.27128100	1.79102300
C	-3.81970000	-4.39970600	2.17771700
H	-3.65366000	-6.44928900	2.83309100
H	-3.64949300	-2.33972400	1.55611000
H	-4.89816900	-4.43850500	2.05030600
C	0.48464300	-4.23298500	2.62219000
H	0.89876000	-5.19468200	2.94304200
H	0.89989700	-3.94807400	1.64229800
H	0.79508300	-3.47111000	3.34644300

Cs_2CO_3[dioxane]$_2$

Cs	-4.13092400	-0.35761900	1.71219200
C	-2.35788500	0.46153200	-1.04466300
O	-3.38170500	-0.35457300	-1.18687400
O	-2.19646700	1.10545500	0.06556400
O	-1.49995900	0.57746800	-2.01312800
Cs	-2.50018500	-1.54319500	-3.79183900
O	-2.30483400	3.62205300	-6.16605000
C	-2.67179400	2.59365500	-7.07451000
C	-1.84412500	3.05719600	-4.93459000
C	-3.73496400	1.68853100	-6.46349500
H	-3.04775700	3.08055100	-7.97986700
H	-1.78915500	1.98718700	-7.34033000
C	-2.88917500	2.15029000	-4.30994400
H	-0.91996500	2.48336900	-5.11269500
H	-1.61164300	3.89270900	-4.26897300
O	-3.26442500	1.11931600	-5.24663000
H	-4.65020700	2.27248000	-6.27622100
H	-3.97674300	0.86027600	-7.13800000
H	-2.48022600	1.64951600	-3.41880100
H	-3.78368300	2.73555400	-4.04644300
O	-1.47692700	-2.08856200	2.01064600
C	-0.62106600	-1.52977200	0.99310300
C	-1.26625700	-3.49198600	2.12502800
C	-0.86704800	-2.23348300	-0.33087200

H	-0.88522500	-0.47128800	0.89241300
H	0.42773500	-1.64590000	1.30696800
C	-1.51439100	-4.18303300	0.78863000
H	-0.23389800	-3.69206100	2.45326000
H	-1.95658900	-3.86253700	2.89028100
O	-0.66578700	-3.65155400	-0.21763400
H	-1.89438700	-2.00764900	-0.65224900
H	-0.17353400	-1.86506500	-1.08920200
H	-1.30382600	-5.25498100	0.86157500
H	-2.57308400	-4.05014600	0.50458300

Cs_2CO_3[dioxane]4

Cs	-4.11646500	-1.20494700	0.02363500
C	-1.02840500	-1.09896200	-1.37170700
O	-2.00215600	-1.27062700	-2.22478200
O	-1.19334200	-1.51758700	-0.13784400
O	0.09122500	-0.58776400	-1.73385400
Cs	0.32860500	-3.05134600	-3.50737900
O	2.56940900	-1.01365900	-4.53341500
C	3.93826500	-1.33389000	-4.76459900
C	2.45737600	0.02206300	-3.53765900
C	4.60411000	-1.78306800	-3.46960900
H	3.96221000	-2.13230200	-5.51361800
H	4.46752900	-0.45541100	-5.16613500
C	3.13771700	-0.41452400	-2.25181500
H	2.91161000	0.94502100	-3.92909800
H	1.39392300	0.16065000	-3.33000400
O	4.51135500	-0.77160900	-2.47687300
H	4.11875100	-2.70756700	-3.11650600
H	5.66792900	-1.98629000	-3.62800500
H	3.13793000	0.39908200	-1.52261300
H	2.58991600	-1.25950800	-1.82272600
O	2.09473600	-3.56519700	-0.91836400
C	1.48898000	-3.11610400	0.31099200
C	3.32748300	-4.23262600	-0.66125000
C	2.45193500	-2.25445500	1.10710800
H	0.59252900	-2.53862200	0.05435700
H	1.20915100	-4.00046600	0.90640700
C	4.27884800	-3.32611500	0.11028500
H	3.14165200	-5.14999200	-0.07940300
H	3.75203400	-4.51139600	-1.63150300
O	3.69217100	-2.92981600	1.34422500
H	2.63542600	-1.31388400	0.56742200
H	2.01128700	-2.02573700	2.08030100
H	5.20523900	-3.85842900	0.35010700
H	4.52376300	-2.44409600	-0.50182300

O	-4.07213300	-4.41856300	-0.34702200
C	-2.90091000	-5.08430700	0.14126800
C	-4.25618400	-4.70004500	-1.73810800
C	-1.67688900	-4.66713800	-0.65978600
H	-2.79230600	-4.79962400	1.19173200
H	-3.04951100	-6.17397700	0.08163600
C	-3.02941600	-4.28143700	-2.53496200
H	-4.44821800	-5.77612800	-1.87295900
H	-5.14203500	-4.14318800	-2.06066900
O	-1.87246200	-4.98245700	-2.05005300
H	-1.50300400	-3.58638300	-0.53303400
H	-0.79407800	-5.22368800	-0.33116900
H	-3.15058000	-4.55920200	-3.58771800
H	-2.85251700	-3.19535100	-2.44680000
O	-2.92681000	-1.14297700	3.00841500
C	-1.96159500	-0.13252500	3.33366800
C	-2.47392300	-2.42840400	3.44299400
C	-0.59889800	-0.47097200	2.74358000
H	-2.34438500	0.80762400	2.92423300
H	-1.89008600	-0.03986500	4.42906800
C	-1.10990300	-2.74630700	2.84326700
H	-2.41451100	-2.44738500	4.54280300
H	-3.22925400	-3.15346000	3.12079600
O	-0.16861300	-1.74790500	3.24286300
H	-0.65522700	-0.51560500	1.64602500
H	0.14787700	0.26132800	3.06562900
H	-0.73954900	-3.70660200	3.21683900
H	-1.18056800	-2.76457800	1.74882100

(lactam_chair)_Cs_2CO_3_2PhMe

C	-3.61990800	-0.52987600	-0.84873500
N	-2.24111600	-0.14874100	-0.63997400
C	-1.77507100	0.97960600	0.17341700
C	-2.64290100	2.21319200	-0.02772800
C	-4.12979900	1.80846800	0.02137900
C	-4.46012900	0.74400800	-1.04114900
H	-3.67751700	-1.18472800	-1.72477100
H	-1.72173400	0.70342700	1.23336800
H	-2.42027300	2.96008200	0.74143200
H	-2.43191800	2.67362000	-0.99863200
H	-5.52326200	0.48183700	-1.00697800
H	-3.99869200	-1.08266700	0.02294100
C	-0.30164600	0.72409200	-0.47187200
O	0.70353900	0.46879500	0.37051700
H	0.32551000	-0.78798300	1.24410900
C	-1.03292300	-0.51271300	-1.14034600

O	-0.70710300	-1.49871900	-1.80652800
C	0.03834000	1.78086700	-1.53621400
C	1.13420400	2.61777800	-1.30056000
C	-0.69036800	1.95508100	-2.72251700
C	1.48656400	3.61458700	-2.21246900
H	1.69243700	2.45663000	-0.38445000
C	-0.34276100	2.95057000	-3.63819700
H	-1.53462500	1.30710500	-2.93923100
C	0.74674200	3.78847800	-3.38508500
H	2.33848300	4.25793300	-2.00818700
H	-0.91810900	3.06707500	-4.55242600
H	1.01891000	4.56211500	-4.09714200
Cs	-1.95297600	-3.67667100	0.29963400
C	0.82930100	-2.60540800	1.93930600
O	-0.10563000	-1.62100700	1.64901900
O	0.32447500	-3.70780300	2.29349200
O	2.04486100	-2.31941000	1.79593300
Cs	2.71007200	-1.36455700	-0.93839500
C	3.98316800	-1.09352600	-4.97622700
C	3.54964700	0.20523100	-4.66793400
C	3.02262900	-2.11404400	-5.05044300
C	2.19798100	0.48108800	-4.44199500
H	4.28071500	1.00748400	-4.59968000
C	1.66955000	-1.84409800	-4.82640600
H	3.33977800	-3.12757600	-5.28414100
C	1.25196200	-0.54558000	-4.51994300
H	1.88244900	1.48696600	-4.18675800
H	0.94260000	-2.64977700	-4.87798300
H	0.20940000	-0.34081900	-4.30554900
C	5.44071500	-1.38052700	-5.24776600
H	5.70395100	-2.40712100	-4.97610400
H	5.67449200	-1.25579100	-6.31210300
H	6.09226000	-0.70039100	-4.69108900
C	-3.09704600	-2.37971500	3.85199100
C	-3.81122100	-3.59032700	3.81412500
C	-3.65738500	-1.26668600	3.20691900
C	-5.03383600	-3.68970200	3.14554700
H	-3.39724700	-4.46321100	4.31328100
C	-4.88623000	-1.35787300	2.54618200
H	-3.12077700	-0.32205000	3.21983600
C	-5.57774700	-2.57125900	2.50512900
H	-5.56703900	-4.63654700	3.13344200
H	-5.30674300	-0.47812600	2.06785000
H	-6.53301900	-2.64178700	1.99334800
C	-1.74841800	-2.30774400	4.51966100
H	-1.43270800	-1.27151500	4.66372800

H	-1.76790800	-2.80445400	5.49576300
H	-0.99370400	-2.80356600	3.89509700
H	-4.37070600	1.41608500	1.01892700
H	-4.76639500	2.68665700	-0.13249800
H	-4.25660000	1.15686400	-2.03688200

(lactam_chair)_Cs_2CO_3_2(dioxane)

C	-3.27449300	-1.08995700	-0.52133500
N	-1.91255400	-0.64933200	-0.31850800
C	-1.52489000	0.67315100	0.18753800
C	-2.34568700	1.78034400	-0.46184500
C	-3.83538200	1.38062000	-0.50071200
C	-4.04634200	0.03701000	-1.22306700
H	-3.27403700	-2.02321000	-1.08912300
H	-1.59756600	0.70975200	1.28079200
H	-2.21447600	2.71790900	0.08859000
H	-2.00118400	1.95714200	-1.48609700
H	-5.11123800	-0.21870700	-1.25875700
H	-3.74983300	-1.28639300	0.45394300
C	0.01025700	0.26815100	-0.19340600
O	0.90294300	0.22947700	0.79901400
H	0.32180900	-0.70466200	1.96863000
C	-0.66567700	-1.10290900	-0.59196100
O	-0.26405600	-2.21909900	-0.94008800
C	0.50138000	1.02166400	-1.43659300
C	1.58218000	1.89761300	-1.28401400
C	-0.07401700	0.88610800	-2.70793100
C	2.07122400	2.62989000	-2.36714100
H	2.02099100	1.97236200	-0.29520100
C	0.40996200	1.61881700	-3.79418800
H	-0.90031000	0.19746600	-2.85775800
C	1.48593500	2.49419400	-3.62845900
H	2.91044200	3.30658500	-2.22857300
H	-0.05023800	1.50160900	-4.77121200
H	1.86473100	3.06133500	-4.47361000
Cs	-1.99189300	-3.73245800	1.69560100
C	0.62029900	-2.20367900	3.27130200
O	-0.21221200	-1.36938900	2.52242300
O	0.01811500	-3.14231300	3.85320200
O	1.85331100	-1.95704200	3.24775300
Cs	2.79513200	-2.13103800	0.42126900
H	-4.22361200	1.29921400	0.52451600
H	-4.42063700	2.16220400	-0.99754200
H	-3.69264100	0.11733500	-2.25864400
O	3.54029200	-1.95750000	-2.59918900
C	2.99859400	-0.90688400	-3.41131700

C	4.00569400	-3.03756500	-3.40488000
C	1.87823600	-1.44966100	-4.28725600
H	3.79926300	-0.48180200	-4.03753400
H	2.62644000	-0.13710400	-2.73120000
C	2.87938500	-3.56904500	-4.28354900
H	4.83916600	-2.69688500	-4.03123600
H	4.37225900	-3.81235400	-2.72167400
O	2.34525400	-2.53055900	-5.09863600
H	1.51664700	-0.67602900	-4.96050800
H	1.04481400	-1.77930300	-3.64954200
H	3.24958100	-4.34632000	-4.95544800
H	2.08662100	-3.99880400	-3.64522300
O	-3.02414800	-4.45174200	-1.27939400
C	-2.01174400	-4.52597500	-2.29676100
C	-4.25632400	-5.00790600	-1.74181300
C	-2.48802600	-3.83492200	-3.56430500
H	-1.78494000	-5.58195700	-2.50598700
H	-1.13755600	-4.01382700	-1.89198400
C	-4.71278700	-4.30386800	-3.01323700
H	-4.12853400	-6.08375900	-1.93845600
H	-4.98615800	-4.87865600	-0.93706300
O	-3.71576600	-4.39702700	-4.02236200
H	-1.75591900	-3.95762200	-4.37024300
H	-2.61519300	-2.75664900	-3.36835300
H	-5.62000300	-4.77939100	-3.41726400
H	-4.93387500	-3.24515200	-2.79049900

2.4.15. Cartesian Coordinates (in Å) of the para- and ortho-substituted intermediates and transition states

I1_o-Me

C	-1.84866200	-0.02742500	0.93717800
N	-0.43591300	-0.11396100	0.64293000
C	0.47803400	1.02476000	0.47324800
C	-0.17879000	2.12979300	-0.34509600
C	-1.60789600	2.38661500	0.17191400
C	-2.46470500	1.10932900	0.10339800
H	-2.30610300	-0.99513300	0.71153100
H	0.84730600	1.40248300	1.43506300
H	0.42318500	3.04430000	-0.30242400
H	-2.53540100	0.78293900	-0.94189900
H	-0.23010900	1.82479700	-1.39653700
H	-3.48364100	1.30823400	0.45351800
H	-1.99520300	0.17364100	2.00820500

C	1.54049400	-0.02404400	-0.13941500
O	2.61697500	-0.24245400	0.64618700
H	3.39970200	-1.43009600	0.15896400
C	0.35656800	-1.05427300	0.06338500
O	0.15351000	-2.24477700	-0.16897600
C	1.84648200	0.22241700	-1.62515800
C	2.96185400	0.98919900	-2.03255300
C	1.00121500	-0.30556500	-2.61593500
C	3.19040400	1.17141200	-3.40411200
C	1.24377300	-0.11729400	-3.97849700
H	0.13789900	-0.89114600	-2.31533600
C	2.35472500	0.62403000	-4.37698600
H	4.05189900	1.75965400	-3.71100300
H	0.56766400	-0.54268000	-4.71558000
Cs	2.27540600	-3.87319900	-2.13173300
C	5.01065900	-2.13970700	-0.85326300
O	3.83179800	-2.32354600	-0.12909600
O	5.22405100	-3.00495100	-1.73657700
O	5.73333500	-1.15248100	-0.53362900
Cs	5.09714100	-0.15614200	2.20749400
H	-1.56741000	2.74251300	1.21131000
H	-2.08389700	3.18086000	-0.41386300
H	2.56614700	0.78320000	-5.43054800
C	3.94508600	1.59946100	-1.06285200
H	3.45653600	1.94861400	-0.15211800
H	4.67704200	0.83389700	-0.78209600
H	4.46993000	2.43532200	-1.53823000

TS1_o-Me

C	-3.61990800	-0.52987600	-0.84873500
N	-2.24111600	-0.14874100	-0.63997400
C	-1.77507100	0.97960600	0.17341700
C	-2.64290100	2.21319200	-0.02772800
C	-4.12979900	1.80846800	0.02137900
C	-4.46012900	0.74400800	-1.04114900
H	-3.67751700	-1.18472800	-1.72477100
H	-1.72173400	0.70342700	1.23336800
H	-2.42027300	2.96008200	0.74143200
H	-2.43191800	2.67362000	-0.99863200
H	-5.52326200	0.48183700	-1.00697800
H	-3.99869200	-1.08266700	0.02294100
C	-0.30164600	0.72409200	-0.47187200
O	0.70353900	0.46879500	0.37051700
H	0.32551000	-0.78798300	1.24410900
C	-1.03292300	-0.51271300	-1.14034600
O	-0.70710300	-1.49871900	-1.80652800

C	0.03834000	1.78086700	-1.53621400
C	1.13420400	2.61777800	-1.30056000
C	-0.69036800	1.95508100	-2.72251700
C	1.48656400	3.61458700	-2.21246900
H	1.69243700	2.45663000	-0.38445000
C	-0.34276100	2.95057000	-3.63819700
H	-1.53462500	1.30710500	-2.93923100
C	0.74674200	3.78847800	-3.38508500
H	2.33848300	4.25793300	-2.00818700
H	-0.91810900	3.06707500	-4.55242600
H	1.01891000	4.56211500	-4.09714200
Cs	-1.95297600	-3.67667100	0.29963400
C	0.82930100	-2.60540800	1.93930600
O	-0.10563000	-1.62100700	1.64901900
O	0.32447500	-3.70780300	2.29349200
O	2.04486100	-2.31941000	1.79593300
Cs	2.71007200	-1.36455700	-0.93839500
H	-4.37070600	1.41608500	1.01892700
H	-4.76639500	2.68665700	-0.13249800
H	-4.25660000	1.15686400	-2.03688200
O	4.39627935	-1.90781312	-3.50665853
C	5.57481468	-0.95658508	-3.55125264
C	4.85561194	-3.35192351	-3.51675422
C	6.46862355	-1.24065540	-4.74119211
H	6.17018814	-1.05666232	-2.60580096
H	5.20293227	0.09956861	-3.60487178
C	5.74877067	-3.63617982	-4.70716183
H	5.41510396	-3.57180789	-2.56967112
H	3.96341535	-4.02982717	-3.54630716
O	6.92684859	-2.68463033	-4.75328273
H	7.36142579	-0.56357026	-4.71044644
H	5.90990511	-1.01894906	-5.68832392
H	6.12103816	-4.69214624	-4.65333126
H	5.15253125	-3.53684756	-5.65220248
O	-4.21977419	-4.77922997	-1.53894961
C	-3.81457293	-6.13132163	-2.08979354
C	-5.51190674	-4.87157815	-0.75256012
C	-4.92259654	-6.74234340	-2.92314956
H	-3.56443290	-6.81983088	-1.24023550
H	-2.89157872	-6.02017380	-2.71618000
C	-6.62014240	-5.48186164	-1.58621005
H	-5.34673719	-5.49715207	0.16380399
H	-5.81823814	-3.84865276	-0.41164046
O	-6.21535960	-6.83336326	-2.13851013
H	-4.61646303	-7.76583167	-3.26261890
H	-5.08655096	-6.11794158	-3.84054805

H	-7.54298397	-5.59345541	-0.95974684
H	-6.87041752	-4.79240444	-2.43502176

I1_p-CF3

C	-1.90190100	-0.17555300	0.80513600
N	-0.48468300	-0.13175500	0.52595200
C	0.35301200	1.07429900	0.51732300
C	-0.35789600	2.24405700	-0.15341400
C	-1.80868800	2.32889400	0.36360100
C	-2.57808000	1.01914000	0.11076200
H	-2.29564800	-1.13287200	0.45167000
H	0.67297000	1.34959200	1.53087000
H	0.17954300	3.17689900	0.04947700
H	-2.61683900	0.82779200	-0.96921600
H	-0.37438600	2.11373800	-1.24017100
H	-3.61172600	1.10728600	0.46252100
H	-2.07239900	-0.12066900	1.89035100
C	1.51543500	0.17021500	-0.13691300
O	2.62702500	0.05495900	0.60609300
H	3.48435200	-1.15861700	0.10112800
C	0.42496700	-0.98323900	-0.01668700
O	0.34542200	-2.17285700	-0.30851900
C	1.77784100	0.43180200	-1.63035400
C	3.09327600	0.67585500	-2.04133800
C	0.78082100	0.31026500	-2.61520700
C	3.41520600	0.77603700	-3.39408200
H	3.87459600	0.69459300	-1.29100700
C	1.09141300	0.41727800	-3.96893400
H	-0.24346700	0.09247900	-2.32915500
C	2.41550100	0.64428800	-4.36196700
H	4.44589900	0.93005900	-3.69545600
H	0.31457900	0.31309800	-4.71937800
Cs	2.49959300	-3.45223900	-2.46562100
C	5.09815400	-1.72684000	-0.96236200
O	3.93000500	-2.00587400	-0.24939800
O	5.40011300	-2.58888500	-1.82134800
O	5.70767700	-0.65920800	-0.67101600
Cs	5.16544200	0.57744500	1.96528400
H	-1.80286300	2.54233400	1.44189100
H	-2.33147300	3.16201900	-0.11886000
C	2.77020300	0.62103200	-5.81579500
F	3.01938300	-0.64665600	-6.24906000
F	1.77153600	1.09666500	-6.59754000
F	3.87766300	1.34384700	-6.09197100

TS1_p-CF_3

C	-0.90271500	-0.62042900	-0.61384800
N	0.46112700	-0.36066900	-0.13448100
C	1.01081900	0.96953100	0.12243100
C	-0.02972000	2.11517800	0.12196800
C	-1.22431500	1.86021000	-0.79654200
C	-1.86787800	0.53748100	-0.38049400
H	-0.87682200	-0.85048000	-1.68942100
H	1.50383000	0.96962100	1.09989200
H	-0.40677500	2.22553400	1.14535700
H	-1.93686200	2.68818700	-0.71423900
H	-2.78985800	0.34725000	-0.94140500
H	-0.90723400	1.80939700	-1.84544900
H	0.47746200	3.05472500	-0.12346400
H	-2.14333800	0.59577600	0.68095400
H	-1.26226900	-1.53299800	-0.12717800
C	2.14824500	1.27235200	-0.85036600
O	3.22442000	1.71364900	-0.43850900
H	2.54118500	-1.70618800	1.39242400
C	1.46733000	-1.33207900	-0.28111800
O	1.08113200	-2.43734300	-0.74740400
C	1.90810400	1.26042700	-2.34131000
C	2.32419500	2.40877100	-3.03662200
C	1.33012400	0.20334600	-3.06219400
C	2.13730000	2.52034500	-4.41048600
H	2.78732400	3.21678800	-2.48103200
C	1.15819100	0.30691100	-4.44127200
H	1.06131800	-0.71716900	-2.56148700
C	1.55045900	1.46588600	-5.11459300
H	2.44126400	3.41984800	-4.93413300
H	0.71737100	-0.51574700	-4.99357700
Cs	0.72224600	-4.66320900	1.39217400
C	3.64149900	-3.17068900	2.10845700
O	2.53747600	-2.29308200	2.18986800
O	3.48312000	-4.24015400	2.73560200
O	4.61088600	-2.78495000	1.40939800
Cs	4.99209400	-0.96301200	-0.84561500
C	1.41249600	1.54557500	-6.60732300
F	0.34761200	0.84468000	-7.05681300
F	1.27097700	2.81909100	-7.03751400
F	2.50315200	1.04089500	-7.23649900

I1_p-OMe

C	-1.81228900	-0.16509200	0.97634400
N	-0.42160300	-0.10685900	0.58960700
C	0.37574200	1.11478300	0.42353100
C	-0.42064500	2.21063400	-0.27482100

C	-1.83146700	2.29863400	0.34209100
C	-2.57545600	0.95383500	0.24665900
H	-2.20014700	-1.15704200	0.72666700
H	0.76536200	1.47483100	1.38505000
H	0.10070400	3.17013000	-0.18449800
H	-2.68519300	0.67871100	-0.81006800
H	-0.51112400	1.99484100	-1.34417700
H	-3.58350400	1.04157700	0.66666400
H	-1.90611100	-0.03058300	2.06413800
C	1.50620000	0.19227100	-0.26282000
O	2.67320000	0.15593800	0.40636300
H	3.55089800	-1.02808600	-0.06052200
C	0.46407600	-0.97112900	0.02769500
O	0.39089800	-2.18130300	-0.17221700
C	1.65291200	0.36782800	-1.78309800
C	2.91540800	0.64771300	-2.30915300
C	0.59899600	0.15353300	-2.69147800
C	3.13879200	0.72141000	-3.68785800
H	3.75253300	0.73169200	-1.62601600
C	0.80089500	0.22819300	-4.06679600
H	-0.39090200	-0.10517300	-2.32586300
C	2.07736000	0.51464100	-4.57570200
H	4.14277600	0.91204400	-4.04778300
H	-0.01264800	0.05847300	-4.76565600
Cs	2.43756600	-3.51305900	-2.30367300
C	5.11157500	-1.61325500	-1.20452800
O	4.03497100	-1.88172500	-0.35762900
O	5.36680100	-2.52452800	-2.02861200
O	5.70220600	-0.50651000	-1.05252000
Cs	5.26789700	0.89792700	1.52151500
H	-1.75410400	2.59458800	1.39804700
H	-2.41442900	3.07829300	-0.16073600
O	2.18361700	0.54955000	-5.94030200
C	3.46859100	0.80002700	-6.49184400
H	3.34264300	0.78242400	-7.57520500
H	3.85378700	1.78123100	-6.18793200
H	4.19090800	0.02855400	-6.19694500

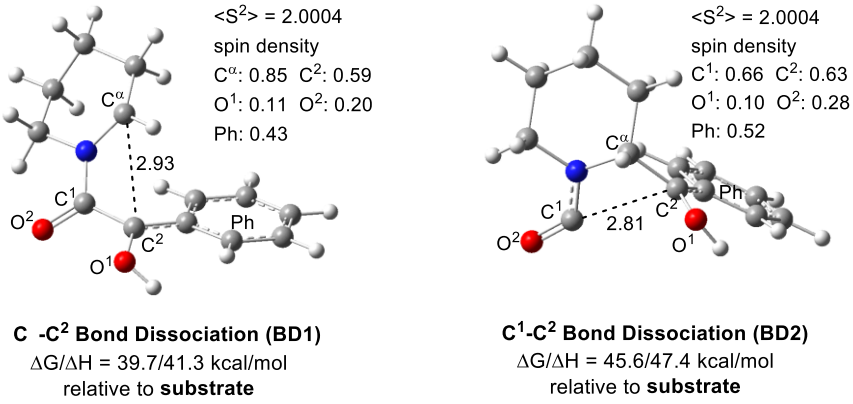
TS1, p-OMe

C	-0.93867300	-0.73029900	-0.54982400
N	0.43446100	-0.41820400	-0.13813300
C	0.95895500	0.92830400	0.08412500
C	-0.09078000	2.06415900	-0.01559100
C	-1.28093700	1.72731300	-0.91270200
C	-1.91127200	0.43484200	-0.39458100
H	-0.94295100	-1.05792300	-1.60103500

H	1.40497700	0.97889000	1.08313800
H	-0.47361900	2.25935900	0.99288400
H	-2.00198000	2.55212800	-0.89504600
H	-2.83721400	0.19661900	-0.93033200
H	-0.96131000	1.59827800	-1.95403900
H	0.40954800	2.98354200	-0.33869500
H	-2.17788900	0.57073600	0.66213600
H	-1.27626900	-1.60097200	0.02346900
C	2.14307100	1.22011300	-0.84025200
O	3.18306500	1.68447800	-0.35981300
H	2.52205400	-1.63164800	1.44988400
C	1.44229300	-1.39748600	-0.21296600
O	1.05057500	-2.53175100	-0.60041700
C	2.01003300	1.15231800	-2.33351700
C	2.70559100	2.12587800	-3.06759500
C	1.26626400	0.19368100	-3.04921400
C	2.64581800	2.18215600	-4.45851200
H	3.29367800	2.85725500	-2.52341900
C	1.21125300	0.22867500	-4.43552900
H	0.78066200	-0.61683900	-2.52602400
C	1.88925700	1.22754400	-5.15198100
H	3.18120000	2.96254200	-4.98501400
H	0.65361900	-0.51872700	-4.99017700
Cs	0.73821500	-4.57607000	1.70969800
C	3.64011000	-3.01520900	2.30410400
O	2.53848200	-2.13364800	2.30703100
O	3.48580300	-4.01922200	3.03376900
O	4.60728400	-2.70329700	1.56542200
Cs	4.94350200	-1.01300100	-0.79926300
O	1.76119100	1.17949600	-6.50500500
C	2.43843700	2.16446700	-7.27709000
H	2.20263200	1.94478700	-8.31856800
H	2.09086200	3.17465600	-7.03071700
H	3.52388900	2.11108600	-7.13090300

2.4.16. Bond dissociation free energy estimation of C^{α}-C^2 and C^1-C^2 for the substrate, substrate with coordination of Cs_2CO_3, and Pd alcoholate.

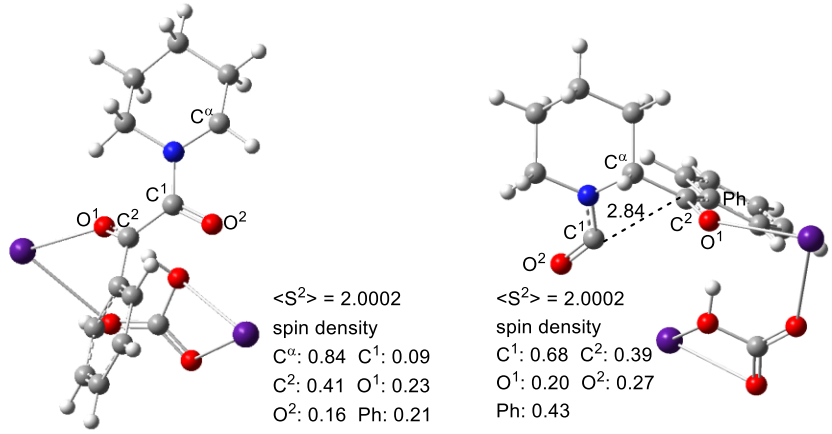
Bond dissociation free energy estimation of C^{α}-C^2 and C^1-C^2 for the substrate (**Figure 2.S12**), substrate with the coordination of Cs_2CO_3 (**Figure 2.S13**), and Pd_alcoholate (**Figure 2.S14)**.



C -C^2 Bond Dissociation (BD1)
ΔG/ΔH = 39.7/41.3 kcal/mol
relative to **substrate**

C^1-C^2 Bond Dissociation (BD2)
ΔG/ΔH = 45.6/47.4 kcal/mol
relative to **substrate**

Figure 2.S12. Bond dissociation free energy estimation of C^{α}-C^2 and C^1-C^2 for the substrate.



C -C^2 Bond Dissociation (BD3)
ΔG/ΔH = 23.7/27.2 kcal/mol
relative to **I1**

C^1-C^2 Bond Dissociation (BD4)
ΔG/ΔH = 31.1/33.1 kcal/mol
relative to **I1**

Figure 2.S13. Bond dissociation free energy estimation of C^{α}-C^2 and C^1-C^2 for the substrate with coordination of Cs_2CO_3.

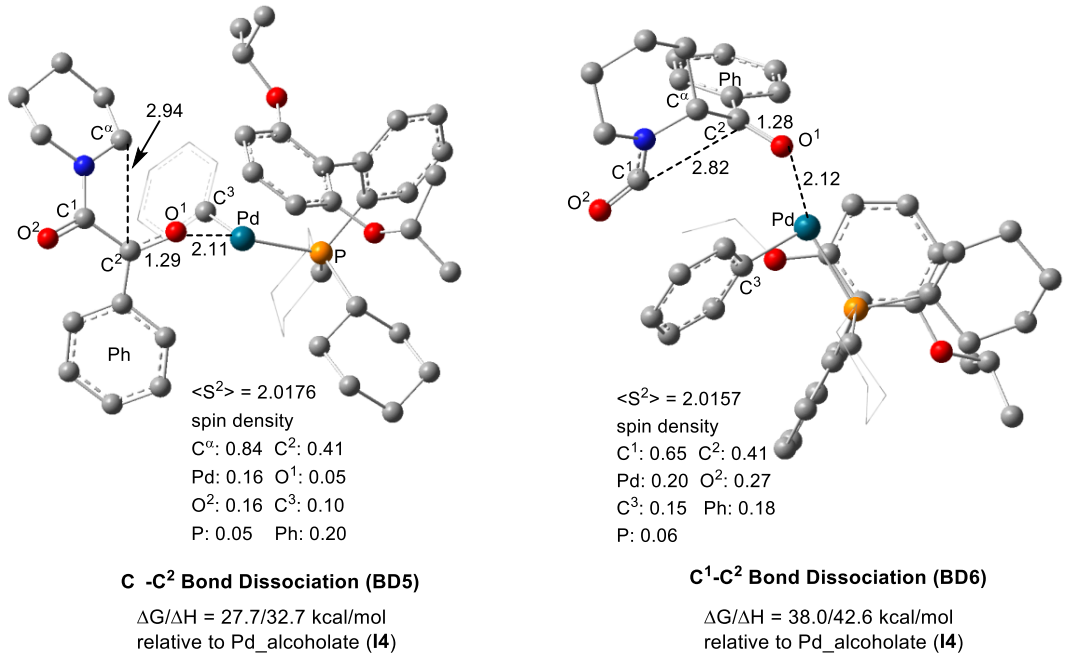


Figure 2.S14. Bond dissociation free energy estimation of C^{α}-C^2 and C^1-C^2 for Pd_alcoholate.

2.4.17. Energy Decomposition Analysis, Geometry Superposition of the Catalyst and Substrate

Energy decomposition analysis (**Figure 2.S14**), geometry superposition of the catalyst and substrate (**Figure 2.S15**).

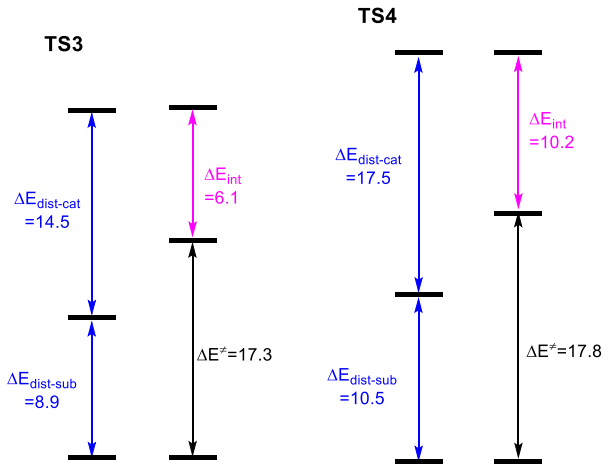
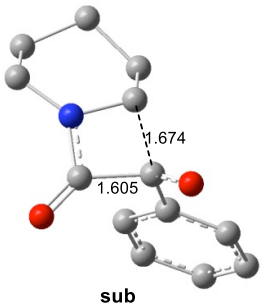
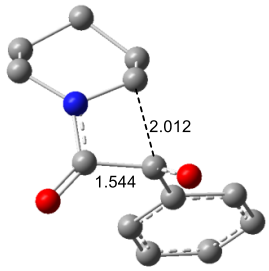


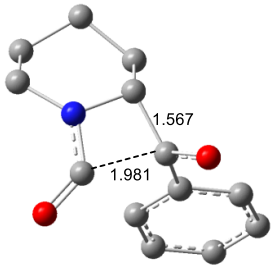
Figure 2.S15. Energy decomposition (distortion-interaction model) analysis on **TS3** and **TS4** (listed as **TS1** and **TS2** in main text).



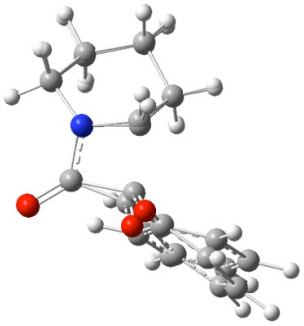
sub
(substrate)



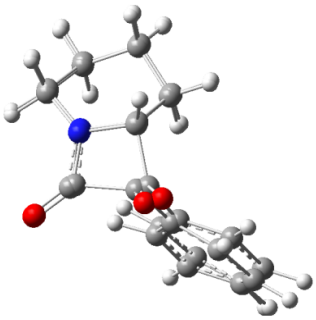
sub-TS3-dist



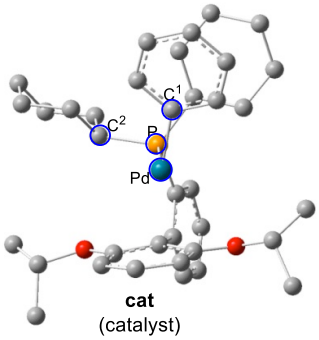
sub-TS4-dist



superposition of **sub-TS3-dist** and **sub**

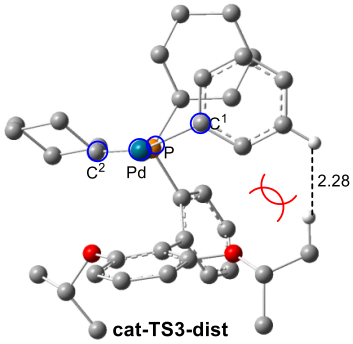


superposition of **sub-TS4-dist** and **sub**



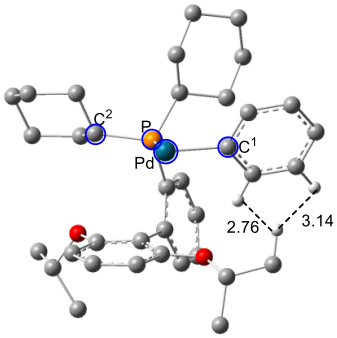
cat
(catalyst)

∠C^1PdPC^2 = -96.49°



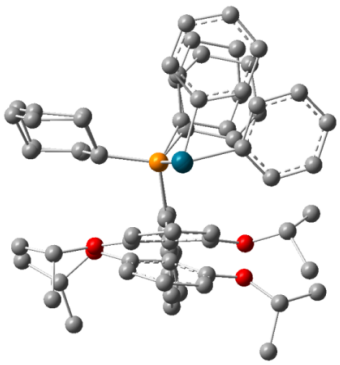
cat-TS3-dist

∠C^1PdPC^2 = -159.76°

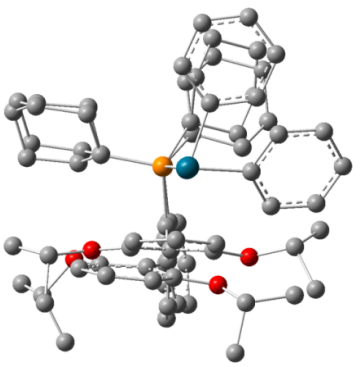


cat-TS4-dist

∠C^1PdPC^2 = -171.51°



superposition of **cat-TS3-dist** and **cat**



superposition of **cat-TS4-dist** and **cat**

Figure 2.S16. Geometry superposition of the catalyst and substrate. ∠C^1PdPC^2 in **cat-TS3-dist** rotates less far away (-159.76º) from **cat** (-96.49º) compared to that in **cat-TS4-dist** (-171.51º). This is because in **cat-TS3-dist** the steric repulsion between Ph group and the isopropyl group on the ligand prevent them from rotating too close, which results in a less distortion geometry compared to **cat-TS4-dist**.

2.4.18. 3D geometries for I4, I5, I6, I7 (*listed as I1, I2, I3, and I4 in main text*).

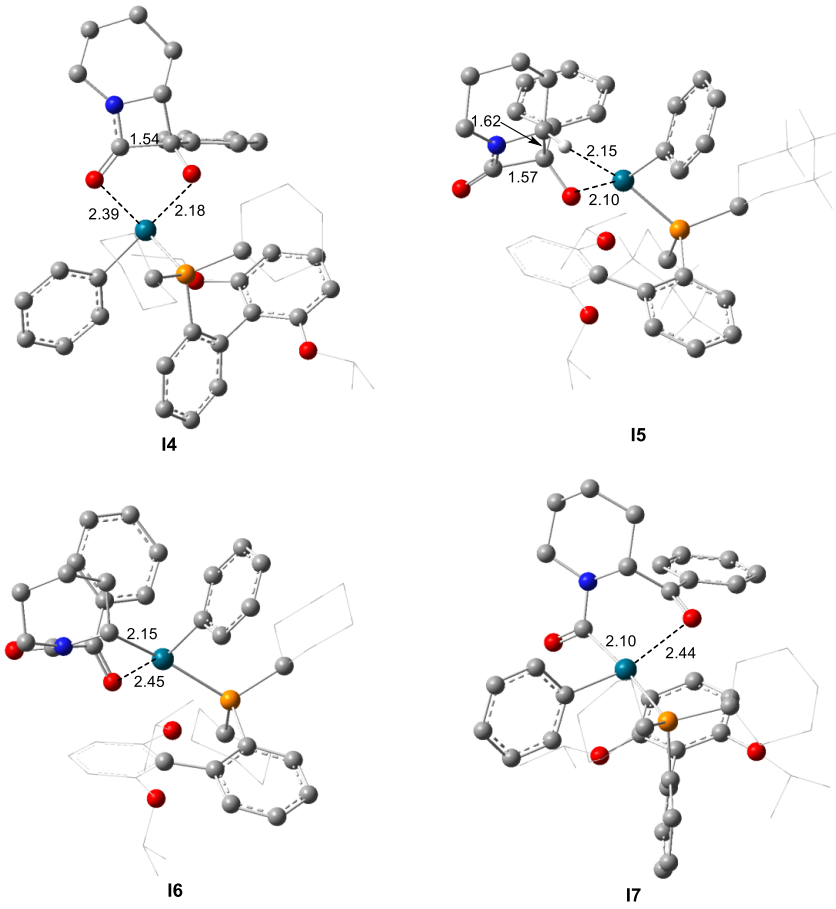


Figure 2.S17. 3D Geometries for the key intermediates **I4**, **I5**, **I6** and **I7**.

2.4.19. Electronic Energy in Solvent, Thermal Correction to Enthalpy and Free Energy, and

Imaginary Frequency.

structures	Electronic energy	Thermal correction to enthalpy	Thermal correction to free energy	Imaginary frequency
Cs_2CO_3	-303.6672862	0.023897	-0.023214	
substrate	-709.685424	0.275079	0.220028	
I1	-1013.427351	0.299709	0.218944	
TS1	-1013.377491	0.298344	0.214690	-46.10
I2	-1013.387262	0.298792	0.212780	
TS2	-1013.384790	0.294015	0.212791	-493.09
I3	-1013.424536	0.301567	0.219286	
prod	-709.706863	0.275158	0.219011	
I4	-2728.726187	1.073453	0.929266	
I5	-2728.706598	1.071972	0.922500	
TS3	-2728.698597	1.071423	0.925957	-246.37
TS4	-2728.697751	1.071297	0.926441	-215.34

I6	-2728.725815	1.073805	0.928234	
I7	-2728.723319	1.073004	0.925989	
BD1	-709.616534	0.272121	0.214411	
BD2	-709.607950	0.273223	0.215241	
BD3	-1013.382323	0.298090	0.211653	
BD4	-1013.373901	0.299033	0.215040	
BD5	-2728.670836	1.070250	0.917980	
BD6	-2728.655999	1.071226	0.919659	

2.4.20. Coordinates.

Cs_2CO_3

Cs	2.866511	-3.090178	-2.239066
C	4.874112	-0.900905	-0.675280
O	3.750034	-1.270843	-0.079018
O	5.180946	-1.412129	-1.823097
O	5.641284	-0.033374	-0.099770
Cs	4.171364	0.374669	2.346826

substrate

C	-2.422007	-0.886830	-0.400137
C	-0.570020	0.864725	0.101372
C	-1.213815	1.839827	-0.876622
C	-2.731898	1.582811	-0.928500
C	-3.040516	0.139115	-1.364906
H	-2.989451	-0.911044	0.539708
H	-2.418714	-1.896326	-0.819237
H	-0.789990	1.688321	-1.875674
H	-0.996186	2.871790	-0.583526
H	-3.203243	2.286635	-1.622014
H	-3.173661	1.770029	0.060046

H	-2.632145	-0.026498	-2.369449
H	-4.122000	-0.023192	-1.420543
H	-0.702222	1.186136	1.140730
N	-1.051486	-0.509490	-0.125420
C	0.161823	-1.048705	-0.430244
C	0.880749	0.313360	-0.144565
O	0.505617	-2.158754	-0.795321
O	1.599807	0.341536	1.076555
H	2.432676	-0.129001	0.929304
C	1.662730	0.913074	-1.287023
C	2.412085	2.075245	-1.057149
C	1.635207	0.361091	-2.573086
C	3.111112	2.682408	-2.098299
H	2.443695	2.491396	-0.055548
C	2.336307	0.970681	-3.615809
H	1.084184	-0.555404	-2.753814
C	3.072631	2.132444	-3.382522
H	3.686165	3.583993	-1.909177
H	2.312005	0.531335	-4.608462
H	3.618315	2.604385	-4.193974

I1

C	-1.883450	-0.186638	0.835386
N	-0.468295	-0.141453	0.548429
C	0.358937	1.069542	0.483442
C	-0.367110	2.204987	-0.228355
C	-1.816005	2.297961	0.292328
C	-2.574131	0.972112	0.095822
H	-2.269513	-1.161388	0.523181
H	0.684711	1.388207	1.482497
H	0.162791	3.150164	-0.066006
H	-2.614070	0.736723	-0.975351
H	-0.386726	2.029732	-1.308618
H	-3.607470	1.064571	0.447668
H	-2.050864	-0.088859	1.918220
C	1.523157	0.147639	-0.146681
O	2.636445	0.070355	0.602703
H	3.521475	-1.130470	0.175461
C	0.443253	-1.004679	0.028616
O	0.367381	-2.206865	-0.212546
C	1.779476	0.370391	-1.647642
C	3.085249	0.646528	-2.069232
C	0.781332	0.214592	-2.625639
C	3.387358	0.775115	-3.427150
H	3.870201	0.682635	-1.322880
C	1.079009	0.349149	-3.983898
H	-0.232687	-0.040390	-2.330459
C	2.386413	0.632803	-4.391455
H	4.412957	0.967630	-3.730356
H	0.292280	0.224346	-4.723518
H	2.621750	0.728772	-5.447718
Cs	2.534838	-3.512355	-2.236437
C	5.151969	-1.728354	-0.854587
O	4.000569	-1.988773	-0.108993
O	5.455589	-2.628301	-1.674432
O	5.750863	-0.639463	-0.627353
Cs	5.156788	0.756648	1.913382
H	-1.807845	2.554356	1.361329
H	-2.348920	3.106345	-0.220496

TS1

C	-0.914273	-0.720592	-0.558707
N	0.454660	-0.396417	-0.140181
C	0.957374	0.954043	0.110677

C	-0.113354	2.072155	0.055457
C	-1.305797	1.740526	-0.840932
C	-1.907061	0.420506	-0.358920
H	-0.910573	-1.008869	-1.620619
H	1.421559	0.988295	1.102196
H	-0.489345	2.229435	1.073080
H	-2.041997	2.550364	-0.790297
H	-2.832450	0.181615	-0.895276
H	-0.993844	1.650235	-1.888414
H	0.367287	3.009921	-0.244102
H	-2.167998	0.517441	0.703482
H	-1.236531	-1.615722	-0.014837
C	2.114316	1.271968	-0.836186
O	3.170868	1.729491	-0.388375
H	2.589792	-1.639690	1.372064
C	1.491597	-1.330382	-0.303203
O	1.134092	-2.456647	-0.742116
C	1.908343	1.271600	-2.330302
C	2.425209	2.382395	-3.020636
C	1.258654	0.264315	-3.063014
C	2.265994	2.506238	-4.399268
H	2.942931	3.148799	-2.453557
C	1.114823	0.384564	-4.446332
H	0.919636	-0.635062	-2.567807
C	1.606203	1.506109	-5.117600
H	2.656426	3.380120	-4.912502
H	0.622018	-0.408316	-5.001370
H	1.484063	1.596162	-6.192926
Cs	0.833406	-4.632843	1.450563
C	3.725054	-3.063758	2.116312
O	2.603227	-2.207633	2.182867
O	3.590947	-4.121902	2.768285
O	4.683879	-2.674266	1.405125
Cs	4.985457	-0.880243	-0.889384

I2

C	-3.306866	1.130772	-0.652766
N	-1.874015	1.203393	-0.375796
C	-1.347045	2.507171	-0.049403
C	-2.124281	3.157345	1.106627
C	-3.633852	3.148641	0.828763
C	-4.121550	1.731447	0.498802
H	-3.546791	1.659689	-1.589126
H	-0.308742	2.309050	0.272664
H	-1.911521	2.571419	2.008951
H	-4.178453	3.552549	1.690090
H	-5.188121	1.738202	0.241991
H	-3.844796	3.813354	-0.018670
H	-1.768028	4.176851	1.271490
H	-4.002508	1.089673	1.382327
H	-3.523298	0.068374	-0.796349
C	-1.208384	3.452298	-1.251618
O	-1.427293	4.652535	-1.129515
H	0.188902	-0.097823	1.373281
C	-1.077912	0.066229	-0.087624
O	-1.634461	-1.043201	-0.289875
C	-0.638678	2.953549	-2.555021
C	0.245941	3.826328	-3.214688
C	-0.932548	1.713249	-3.149050
C	0.852527	3.460324	-4.413781
H	0.450229	4.791474	-2.763765
C	-0.344319	1.361096	-4.367917
H	-1.611424	1.027505	-2.664471
C	0.556775	2.223411	-4.996375

H	1.545484	4.140634	-4.899743
H	-0.594249	0.407779	-4.824852
H	1.017624	1.939784	-5.938066
Cs	-1.631744	-2.827809	2.273988
C	1.428604	-1.462463	2.103258
O	0.396248	-0.520871	2.258656
O	1.379367	-2.416539	2.912386
O	2.250330	-1.252881	1.173262
Cs	2.141884	0.073479	-1.413896

TS2

C	-3.413852	1.014739	-0.688949
N	-2.011129	1.006020	-0.282206
C	-1.448988	2.269107	0.161586
C	-2.316471	2.913451	1.256007
C	-3.791148	2.979949	0.839588
C	-4.299911	1.596281	0.415185
H	-3.548031	1.610438	-1.607459
H	-0.453750	2.035155	0.568730
H	-2.226753	2.307327	2.165928
H	-4.397564	3.382666	1.658777
H	-5.338425	1.653569	0.068291
H	-3.891454	3.677244	-0.001583
H	-1.932000	3.908289	1.486279
H	-4.284239	0.916815	1.278758
H	-3.665451	-0.020906	-0.928235
C	-1.144991	3.278758	-0.965700
O	-1.271144	4.478888	-0.758378
H	0.162465	0.071890	0.276199
C	-1.171522	-0.107874	-0.431210
O	-1.669469	-1.124503	-0.972993
C	-0.527669	2.835290	-2.264649
C	0.495260	3.657554	-2.768658
C	-0.928814	1.717731	-3.014415
C	1.130417	3.354700	-3.969715
H	0.784977	4.532426	-2.197117
C	-0.314901	1.437950	-4.238265
H	-1.720141	1.071424	-2.666118
C	0.723457	2.242192	-4.711957
H	1.932189	3.990151	-4.333066
H	-0.655690	0.588245	-4.823895
H	1.204202	2.012062	-5.658244
Cs	-1.077699	-0.485950	3.229281
C	1.668263	-0.750437	1.508612
O	0.974914	0.343124	1.021881
O	1.876106	-0.761758	2.754274
O	1.987011	-1.653106	0.680677
Cs	1.234982	-1.652882	-2.133076

I3

C	-3.339049	0.656259	-0.432561
N	-1.905010	0.905049	-0.302373
C	-1.464559	2.275811	0.015036
C	-2.254826	2.820036	1.212227
C	-3.768790	2.590099	1.117764
C	-4.084897	1.119974	0.819813
H	-3.718409	1.199970	-1.308882
H	-0.412052	2.197158	0.339949
H	-1.852617	2.325243	2.103322
H	-4.252718	2.901892	2.050468
H	-5.161212	0.971424	0.678249
H	-4.173191	3.215659	0.316181
H	-2.037505	3.886522	1.315674
H	-3.784184	0.489720	1.668880

H	-3.459685	-0.412094	-0.615997
C	-1.611660	3.138106	-1.243821
O	-2.439414	4.041648	-1.302377
H	0.038046	0.282910	-0.451489
C	-0.998908	-0.080818	-0.493138
O	-1.280051	-1.272658	-0.700245
C	-0.762801	2.812377	-2.429954
C	0.509060	2.227104	-2.314881
C	-1.264510	3.148279	-3.698430
C	1.251418	1.977263	-3.472129
H	0.955535	1.959525	-1.352194
C	-0.524234	2.879243	-4.844983
H	-2.240496	3.618029	-3.761596
C	0.739861	2.290510	-4.732585
H	2.242153	1.540812	-3.379074
H	-0.924592	3.130576	-5.822695
H	1.324014	2.085836	-5.625596
Cs	-0.770612	-0.650394	3.203568
C	1.556051	0.521525	1.133398
O	1.995609	0.790647	-0.065935
O	0.804661	1.382612	1.750243
O	1.795737	-0.642021	1.660304
Cs	1.946871	-1.997817	-1.079977

prod

C	-1.340851	0.279976	-1.006712
N	-0.063290	-0.308730	-0.599984
C	0.941234	0.623200	-0.091604
C	0.370039	1.424563	1.089491
C	-0.981523	2.067986	0.740704
C	-1.965356	1.037276	0.169774
H	-1.161086	0.957145	-1.851308
H	1.798647	0.027824	0.248214
H	0.244476	0.728720	1.927092
H	-1.403966	2.540158	1.633871
H	-2.888608	1.526222	-0.159442
H	-0.817367	2.863530	0.006550
H	1.091105	2.187812	1.390865
H	-2.239355	0.309811	0.943966
H	-1.973695	-0.537980	-1.350973
C	1.453079	1.543433	-1.223240
O	1.506074	2.752815	-1.050906
H	1.025144	-1.931484	0.025362
C	0.041688	-1.650779	-0.399814
O	-0.820158	-2.478857	-0.660448
C	1.866141	0.942807	-2.525010
C	1.878751	1.780299	-3.651810
C	2.271626	-0.393683	-2.659634
C	2.268253	1.287080	-4.893008
H	1.575929	2.814490	-3.530367
C	2.678681	-0.881659	-3.899461
H	2.292989	-1.051920	-1.800387
C	2.668994	-0.046060	-5.018490
H	2.263236	1.938374	-5.761337
H	2.999996	-1.914032	-3.992836
H	2.975549	-0.432351	-5.985726

I4

C	-3.859245	-2.406489	0.091052
C	-2.567815	-1.942305	0.438288
C	-2.413916	-0.582760	0.760107
C	-3.486891	0.302893	0.742016
C	-4.753390	-0.153347	0.384629
C	-4.926588	-1.497906	0.070895

C	-4.194237	-3.833407	-0.192193
C	-4.002477	-4.423774	-1.454278
C	-4.335510	-5.771522	-1.659299
C	-4.894821	-6.506108	-0.621460
C	-5.165856	-5.927824	0.617474
C	-4.831124	-4.584941	0.818758
P	-1.053307	-2.985123	0.277887
H	-1.438619	-0.187805	1.007211
H	-3.324751	1.346384	0.993011
H	-5.598579	0.527350	0.353001
H	-5.910530	-1.873039	-0.192024
O	-3.494263	-3.622315	-2.432605
H	-4.162688	-6.243479	-2.613514
H	-5.143999	-7.550031	-0.786925
H	-5.634951	-6.512637	1.396918
Pd	-0.438079	-3.381356	-1.856943
C	-0.495324	-1.390017	-2.101355
C	0.704471	-0.666367	-2.157549
C	-1.697157	-0.718898	-2.359384
C	0.703218	0.697115	-2.471688
H	1.650959	-1.162191	-1.962222
C	-1.698816	0.641096	-2.681654
H	-2.635419	-1.257910	-2.294111
C	-0.499944	1.355469	-2.734887
H	1.643354	1.241867	-2.510471
H	-2.641934	1.144658	-2.878989
H	-0.502664	2.414670	-2.976597
C	-3.638217	-4.039014	-3.817264
H	-3.273868	-5.063795	-3.913455
C	3.319528	-5.525386	-4.571706
C	1.551169	-6.764010	-3.129657
C	1.747332	-8.039658	-3.931815
C	3.189849	-8.072522	-4.479658
C	3.504430	-6.839742	-5.349748
H	4.125616	-5.399719	-3.836013
H	3.320730	-4.652525	-5.229454
H	1.040470	-8.059554	-4.769160
H	1.544782	-8.919085	-3.311917
H	3.345045	-8.982201	-5.069338
H	3.898613	-8.116225	-3.641031
H	2.832687	-6.830845	-6.216859
H	4.529506	-6.892677	-5.730999
H	2.020773	-6.819677	-2.140836
N	2.047919	-5.597184	-3.884947
C	0.938981	-4.853619	-3.745152
C	0.157249	-5.952723	-3.005720
O	0.676280	-3.654581	-3.949551
O	-0.223677	-5.550973	-1.757293
C	-0.958283	-6.597853	-3.811310
C	-1.180038	-6.319117	-5.164687
C	-1.796189	-7.512061	-3.162818
C	-2.226090	-6.936319	-5.856233
H	-0.552954	-5.596999	-5.678572
C	-2.827985	-8.144266	-3.854649
H	-1.640319	-7.696615	-2.105444
C	-3.052335	-7.852233	-5.203759
H	-2.397403	-6.695583	-6.901387
H	-3.468919	-8.853974	-3.338801
H	-3.865526	-8.333043	-5.739201
C	-5.103163	-3.948736	-4.234583
H	-5.214963	-4.278249	-5.271954
H	-5.741378	-4.575698	-3.607448
H	-5.450512	-2.913382	-4.159310
C	-2.745448	-3.136373	-4.650308

H	-3.047498	-2.089897	-4.555882
H	-1.700120	-3.225803	-4.351691
H	-2.827853	-3.430420	-5.701232
O	-5.064519	-3.905505	1.979728
C	-5.833406	-4.504284	3.040276
H	-5.482469	-5.530539	3.201169
C	-5.523493	-3.675489	4.278468
H	-5.807621	-2.631624	4.114336
H	-6.080920	-4.057857	5.138159
H	-4.456095	-3.711748	4.510008
C	-7.317586	-4.497667	2.684788
H	-7.662289	-3.467676	2.550133
H	-7.509793	-5.048499	1.761083
H	-7.901924	-4.957529	3.487530
C	-1.336217	-4.565508	1.212602
C	-0.070288	-5.437374	1.298154
C	-1.976933	-4.410027	2.602580
H	-2.041263	-5.094229	0.562332
C	-0.444301	-6.823390	1.842005
H	0.649850	-4.971884	1.981939
H	0.384297	-5.530181	0.310063
C	-2.356911	-5.793870	3.149652
H	-1.259601	-3.944152	3.285704
H	-2.853425	-3.763900	2.561124
C	-1.141566	-6.729331	3.205845
H	0.453546	-7.448329	1.916486
H	-1.111551	-7.314147	1.120237
H	-2.805954	-5.691256	4.145191
H	-3.122196	-6.233344	2.497755
H	-1.444119	-7.725229	3.550894
H	-0.426514	-6.343524	3.946332
C	0.315516	-2.004744	1.072466
C	0.213631	-1.758546	2.587120
C	1.716704	-2.537473	0.712960
H	0.234503	-1.043097	0.553119
C	1.274968	-0.737940	3.025252
H	0.384652	-2.702003	3.117479
H	-0.785946	-1.413851	2.868200
C	2.781993	-1.518880	1.139418
H	1.900091	-3.490726	1.218084
H	1.775040	-2.734515	-0.361210
C	2.686431	-1.197910	2.637317
H	1.210493	-0.574105	4.107081
H	1.061301	0.227685	2.546107
H	3.780439	-1.899584	0.895318
H	2.642990	-0.597141	0.557682
H	3.423243	-0.434135	2.911320
H	2.938333	-2.099595	3.212886

I5

C	-1.136321	-1.068571	1.249062
C	0.187416	-1.363403	1.658122
C	0.807469	-0.518120	2.597128
C	0.168090	0.610136	3.102864
C	-1.118545	0.922769	2.667228
C	-1.753494	0.086134	1.754928
C	-1.968397	-1.917827	0.344000
C	-2.333951	-1.462492	-0.943819
C	-3.179986	-2.225357	-1.755060
C	-3.704180	-3.423891	-1.269404
C	-3.410811	-3.862013	0.013149
C	-2.562582	-3.097598	0.816213
P	1.141974	-2.814848	1.035576
H	1.810039	-0.738042	2.941880

H	0.676603	1.239847	3.826089
H	-1.628417	1.805151	3.041440
H	-2.762034	0.311395	1.424957
O	-1.829217	-0.247263	-1.307466
H	-3.445427	-1.888172	-2.748295
H	-4.342068	-4.026706	-1.906188
H	-3.799176	-4.804475	0.377594
Pd	0.425701	-3.453964	-1.008249
C	1.509015	-1.981756	-1.828669
C	2.566076	-2.420108	-2.645109
C	1.246195	-0.609121	-1.753327
C	3.331727	-1.509548	-3.380309
H	2.809450	-3.478751	-2.701035
C	2.015094	0.302617	-2.484758
H	0.452142	-0.245582	-1.114179
C	3.060866	-0.141766	-3.296601
H	4.145968	-1.868449	-4.004515
H	1.806953	1.366502	-2.404286
H	3.663814	0.569981	-3.852941
C	-2.435427	0.490480	-2.388913
H	-2.502685	-0.157621	-3.271196
C	-2.821813	-4.902897	-4.551443
C	-0.692197	-4.823880	-3.117737
C	0.181996	-5.064250	-4.339718
C	-0.530625	-4.498538	-5.583629
C	-1.921146	-5.131406	-5.777390
H	-3.149931	-3.854098	-4.513399
H	-3.713256	-5.535572	-4.569623
H	0.340106	-6.141451	-4.463023
H	1.162561	-4.597033	-4.206433
H	0.080600	-4.670270	-6.475883
H	-0.636313	-3.409279	-5.478095
H	-1.804654	-6.210923	-5.933192
H	-2.407788	-4.722555	-6.669347
H	-0.650100	-3.740181	-2.845210
N	-2.069538	-5.213920	-3.358330
C	-2.195946	-6.102658	-2.327917
C	-0.734632	-5.812799	-1.829446
O	-3.136802	-6.792236	-1.974845
O	-0.686605	-5.191311	-0.610698
C	0.241096	-6.971245	-1.949175
C	1.588889	-6.749535	-1.629138
C	-0.152283	-8.247060	-2.363179
C	2.523438	-7.776421	-1.730815
H	1.893389	-5.763276	-1.288945
C	0.783619	-9.281936	-2.460506
H	-1.195980	-8.436905	-2.591583
C	2.122545	-9.050103	-2.148514
H	3.564238	-7.588018	-1.481724
H	0.461723	-10.270211	-2.776390
H	2.849109	-9.853774	-2.224514
C	0.814753	-4.137938	2.322206
C	1.115279	-5.577426	1.866874
C	1.464930	-3.839990	3.685669
H	-0.270720	-4.056200	2.432254
C	0.621809	-6.571522	2.927154
H	2.193917	-5.722119	1.732189
H	0.622656	-5.764618	0.911371
C	0.998040	-4.853101	4.743440
H	2.556818	-3.907028	3.597664
H	1.227158	-2.824847	4.020569
C	1.251563	-6.298156	4.297854
H	0.842029	-7.594605	2.601170
H	-0.471685	-6.496023	3.003187

H	1.506748	-4.648739	5.693151
H	-0.073958	-4.712678	4.923763
H	0.865053	-6.997631	5.048473
H	2.335484	-6.470335	4.234595
C	2.948519	-2.374098	1.231615
C	3.826966	-3.514810	0.678908
C	3.420475	-1.030580	0.646875
H	3.103065	-2.334336	2.317088
C	5.309056	-3.269192	0.997700
H	3.683011	-3.569264	-0.405707
H	3.521202	-4.479231	1.088440
C	4.887589	-0.778773	1.021258
H	3.339900	-1.059001	-0.438314
H	2.791057	-0.205272	0.986438
C	5.783263	-1.903437	0.488618
H	5.914584	-4.072765	0.562950
H	5.452941	-3.321026	2.086018
H	5.206690	0.187885	0.615207
H	4.988995	-0.712915	2.113982
H	6.828204	-1.733456	0.772491
H	5.745322	-1.895472	-0.609298
C	-1.480164	1.634663	-2.692180
H	-0.512585	1.252082	-3.020652
H	-1.894241	2.268563	-3.481404
H	-1.329937	2.246567	-1.797109
C	-3.822759	0.980141	-1.982213
H	-4.280722	1.541094	-2.802330
H	-4.482660	0.148432	-1.725358
H	-3.741016	1.640398	-1.112925
O	-2.276085	-3.484905	2.104293
C	-3.404457	-3.637085	2.999304
H	-4.121022	-4.331597	2.544020
C	-4.077198	-2.288842	3.233709
H	-3.365981	-1.582994	3.672681
H	-4.443376	-1.868650	2.293046
H	-4.928011	-2.403381	3.912195
C	-2.846421	-4.248285	4.272861
H	-3.649263	-4.414620	4.996573
H	-2.362912	-5.205487	4.061996
H	-2.108704	-3.575390	4.721046

TS3

C	-1.164929	-1.062725	1.122337
C	0.148846	-1.365116	1.549653
C	0.758965	-0.514306	2.492098
C	0.115838	0.613725	2.991606
C	-1.169283	0.923531	2.548601
C	-1.791288	0.089083	1.626993
C	-1.987580	-1.891023	0.191853
C	-2.346827	-1.394134	-1.081150
C	-3.216770	-2.110513	-1.907579
C	-3.761158	-3.312573	-1.451706
C	-3.462377	-3.799924	-0.187909
C	-2.592984	-3.076858	0.632596
P	1.105281	-2.835583	0.964146
H	1.759727	-0.729696	2.844280
H	0.619340	1.244790	3.717221
H	-1.685128	1.803050	2.921414
H	-2.795993	0.314115	1.285113
O	-1.798461	-0.188136	-1.417955
H	-3.481222	-1.739495	-2.888972
H	-4.419255	-3.881140	-2.099625
H	-3.865022	-4.746764	0.147558
Pd	0.362671	-3.663763	-1.036693

C	1.505636	-2.354673	-2.039423
C	2.639384	-2.869755	-2.689054
C	1.204156	-0.996586	-2.194784
C	3.456003	-2.046595	-3.470474
H	2.892848	-3.921745	-2.586832
C	2.020344	-0.173062	-2.979262
H	0.347428	-0.570647	-1.687350
C	3.150909	-0.691035	-3.613847
H	4.331001	-2.464623	-3.961572
H	1.784033	0.883744	-3.075680
H	3.789084	-0.046455	-4.211245
C	-2.392732	0.607160	-2.465043
H	-2.500409	-0.008245	-3.366427
C	-2.795103	-4.905520	-4.524747
C	-0.700463	-4.529488	-3.147179
C	0.189673	-4.789610	-4.346349
C	-0.568489	-4.420065	-5.639917
C	-1.907430	-5.169431	-5.750827
H	-3.161636	-3.869475	-4.535895
H	-3.659389	-5.573971	-4.485203
H	0.466532	-5.849842	-4.380992
H	1.110503	-4.207799	-4.268418
H	0.054022	-4.640372	-6.514651
H	-0.756482	-3.337256	-5.649040
H	-1.713919	-6.247391	-5.816365
H	-2.441588	-4.876549	-6.661456
H	-0.825083	-3.445954	-2.979376
N	-2.011275	-5.120430	-3.326574
C	-2.166585	-6.012391	-2.331413
C	-0.793483	-5.859922	-1.642422
O	-3.116261	-6.733474	-2.053122
O	-0.774481	-5.386620	-0.420613
C	0.226924	-6.913523	-2.000136
C	1.560582	-6.756064	-1.596242
C	-0.128286	-8.048286	-2.738041
C	2.519792	-7.707320	-1.929816
H	1.838421	-5.872980	-1.028751
C	0.834056	-9.005974	-3.070420
H	-1.161305	-8.193663	-3.036054
C	2.159271	-8.837644	-2.671486
H	3.550152	-7.568568	-1.614930
H	0.543608	-9.884210	-3.639401
H	2.907427	-9.579640	-2.933796
C	0.821327	-4.094559	2.328169
C	1.251162	-5.528135	1.965134
C	1.393196	-3.682222	3.696360
H	-0.271611	-4.089688	2.386979
C	0.806053	-6.509741	3.057809
H	2.341512	-5.588298	1.872022
H	0.809844	-5.808260	1.009450
C	0.980434	-4.680338	4.790456
H	2.489435	-3.656159	3.645688
H	1.057933	-2.678398	3.973418
C	1.369157	-6.117996	4.428389
H	1.120231	-7.525025	2.789312
H	-0.291632	-6.522530	3.100513
H	1.438308	-4.386926	5.742585
H	-0.105010	-4.626211	4.933325
H	1.019788	-6.810719	5.202976
H	2.465103	-6.200442	4.402183
C	2.899223	-2.323093	1.118022
C	3.836995	-3.443105	0.625579
C	3.273927	-0.991221	0.441427
H	3.066595	-2.208548	2.196572

C	5.307632	-3.083794	0.882731
H	3.677558	-3.589783	-0.446592
H	3.604245	-4.389902	1.115698
C	4.734994	-0.630579	0.739577
H	3.148226	-1.085977	-0.635853
H	2.610672	-0.185808	0.764901
C	5.681072	-1.735767	0.256219
H	5.951410	-3.880740	0.492841
H	5.482478	-3.040292	1.966995
H	4.981011	0.321581	0.255621
H	4.868184	-0.480216	1.820618
H	6.721983	-1.482447	0.488468
H	5.606483	-1.813112	-0.836969
C	-1.395747	1.721125	-2.745901
H	-0.451524	1.310611	-3.108475
H	-1.794542	2.399121	-3.505677
H	-1.203232	2.293625	-1.833443
C	-3.752562	1.136301	-2.017899
H	-4.202822	1.740143	-2.811320
H	-4.438910	0.321449	-1.776165
H	-3.631382	1.763848	-1.129254
O	-2.299762	-3.500854	1.904865
C	-3.423145	-3.716073	2.792721
H	-4.117318	-4.419469	2.317400
C	-4.136612	-2.396267	3.066712
H	-3.446148	-1.682612	3.526146
H	-4.517403	-1.959301	2.139524
H	-4.982274	-2.556073	3.742515
C	-2.846842	-4.346886	4.048241
H	-3.645914	-4.571196	4.760446
H	-2.322880	-5.275445	3.807857
H	-2.140449	-3.659905	4.524275

TS4

C	-3.613162	-1.847890	-0.003794
C	-2.454200	-1.499298	0.731632
C	-2.490218	-0.354546	1.543692
C	-3.595918	0.493250	1.555928
C	-4.689364	0.210161	0.738353
C	-4.696322	-0.959982	-0.018085
C	-3.794785	-3.185409	-0.638719
C	-3.805525	-3.385462	-2.036798
C	-3.992110	-4.672778	-2.558450
C	-4.229035	-5.742609	-1.700070
C	-4.306708	-5.554948	-0.324444
C	-4.104431	-4.274941	0.193003
P	-0.897025	-2.477397	0.604090
H	-1.647974	-0.123308	2.183935
H	-3.594972	1.372766	2.192140
H	-5.544856	0.878203	0.713495
H	-5.566566	-1.220364	-0.611376
O	-3.662485	-2.269484	-2.798001
H	-3.932309	-4.849816	-3.622090
H	-4.352210	-6.735196	-2.117937
H	-4.514127	-6.383226	0.343397
Pd	-0.629947	-3.482470	-1.415361
C	-0.228833	-1.692121	-2.247028
C	1.059127	-1.568294	-2.797125
C	-1.081562	-0.583819	-2.309538
C	1.484895	-0.371401	-3.380933
H	1.744280	-2.412172	-2.767074
C	-0.658970	0.614575	-2.894941
H	-2.082326	-0.648389	-1.903574
C	0.626313	0.730220	-3.425803

H	2.487447	-0.299600	-3.795580
H	-1.339532	1.461809	-2.930229
H	0.956295	1.664695	-3.870643
C	-3.875222	-2.354854	-4.228727
H	-3.308858	-3.209282	-4.606887
C	1.825586	-4.921344	-4.748816
C	1.058354	-6.029984	-2.546511
C	1.613972	-7.364549	-3.049054
C	2.800224	-7.131015	-3.997739
C	2.360494	-6.286394	-5.202128
H	2.660041	-4.287398	-4.417419
H	1.300052	-4.397064	-5.550235
H	0.832773	-7.907966	-3.589605
H	1.904424	-7.979496	-2.190957
H	3.200172	-8.091946	-4.338226
H	3.613329	-6.618772	-3.464724
H	1.571373	-6.819242	-5.746911
H	3.192460	-6.132691	-5.897398
H	1.704223	-5.627060	-1.755297
N	0.893562	-5.078564	-3.644235
C	-0.404600	-4.688186	-3.557495
C	-0.428377	-5.977281	-2.053936
O	-1.096353	-4.152335	-4.409081
O	-0.638579	-5.554763	-0.832389
C	-1.348355	-7.097450	-2.493091
C	-1.764665	-7.317176	-3.811917
C	-1.797655	-7.968716	-1.490732
C	-2.618062	-8.379013	-4.117284
H	-1.459468	-6.637829	-4.598832
C	-2.637847	-9.036968	-1.796551
H	-1.491929	-7.777266	-0.468838
C	-3.057101	-9.243962	-3.113147
H	-2.946109	-8.524361	-5.142438
H	-2.974646	-9.702106	-1.006481
H	-3.722644	-10.067717	-3.353587
C	-1.062736	-3.795416	1.916577
C	0.190339	-4.672831	2.088508
C	-1.559667	-3.274688	3.273657
H	-1.846710	-4.430120	1.492601
C	-0.115226	-5.855167	3.017519
H	0.994144	-4.082699	2.544074
H	0.528500	-5.030607	1.113721
C	-1.830932	-4.452995	4.221195
H	-0.804628	-2.611709	3.718864
H	-2.473918	-2.692763	3.141750
C	-0.610316	-5.365342	4.383161
H	0.780819	-6.476154	3.133199
H	-0.882620	-6.488746	2.552235
H	-2.166999	-4.078767	5.195605
H	-2.655721	-5.040998	3.801296
H	-0.855346	-6.214265	5.032268
H	0.197939	-4.810306	4.880167
C	0.518846	-1.366529	1.129519
C	1.864149	-2.040701	0.770096
C	0.538249	0.059159	0.537804
H	0.446314	-1.293899	2.224438
C	3.047742	-1.248222	1.342855
H	1.938524	-2.077233	-0.321528
H	1.908282	-3.070955	1.120435
C	1.693811	0.871276	1.138688
H	0.676605	-0.011433	-0.541165
H	-0.404752	0.583192	0.691818
C	3.043775	0.204319	0.854207
H	3.985959	-1.743166	1.065970

H	2.995476	-1.265425	2.440666
H	1.676604	1.886671	0.726238
H	1.552422	0.968703	2.224734
H	3.860496	0.768172	1.319827
H	3.222681	0.218099	-0.229542
O	-4.222787	-4.028164	1.546156
C	-5.517918	-4.312580	2.134864
H	-5.683845	-5.397990	2.100823
C	-5.428579	-3.854398	3.581847
H	-6.376144	-4.044868	4.094157
H	-4.634885	-4.379209	4.115573
H	-5.222224	-2.780147	3.620648
C	-6.643308	-3.605503	1.385057
H	-6.502169	-2.522011	1.427470
H	-6.678985	-3.911148	0.336601
H	-7.604635	-3.852662	1.845554
C	-3.288898	-1.084815	-4.822566
H	-2.217642	-1.028404	-4.630944
H	-3.459457	-1.072977	-5.903336
H	-3.766450	-0.200826	-4.387071
C	-5.367188	-2.493618	-4.522887
H	-5.531618	-2.571539	-5.602035
H	-5.793814	-3.380206	-4.048143
H	-5.903454	-1.612710	-4.155004

I6

C	-1.251701	-1.133863	0.771816
C	0.071760	-1.442307	1.165819
C	0.751109	-0.522579	1.987193
C	0.171005	0.674244	2.397260
C	-1.124001	0.985285	1.985771
C	-1.816858	0.084671	1.184677
C	-2.148731	-2.014981	-0.037392
C	-2.575239	-1.606039	-1.322499
C	-3.539253	-2.335939	-2.021889
C	-4.070724	-3.496152	-1.458827
C	-3.691160	-3.908135	-0.189289
C	-2.763267	-3.144431	0.526063
P	0.932719	-3.009858	0.672338
H	1.759839	-0.739507	2.313998
H	0.730400	1.356796	3.029611
H	-1.592475	1.916615	2.289028
H	-2.829160	0.312252	0.867509
O	-1.987255	-0.473009	-1.808129
H	-3.867083	-2.020761	-3.003023
H	-4.789889	-4.079911	-2.024036
H	-4.105150	-4.805402	0.254854
Pd	0.086532	-3.781326	-1.510516
C	1.340482	-2.562115	-2.474882
C	2.519140	-3.098977	-3.013927
C	1.095248	-1.191892	-2.607749
C	3.447691	-2.272148	-3.652421
H	2.714417	-4.165249	-2.942488
C	2.023206	-0.367346	-3.254809
H	0.193705	-0.764239	-2.187698
C	3.204478	-0.900838	-3.773946
H	4.360737	-2.701569	-4.057183
H	1.826033	0.698770	-3.338235
H	3.927180	-0.258349	-4.268404
C	-2.594911	0.243470	-2.904275
H	-2.803461	-0.459908	-3.719262
C	-2.891091	-4.841210	-4.536586
C	-0.858055	-3.918044	-3.434780
C	-0.062799	-4.077298	-4.731883

C	-0.986863	-4.014825	-5.964114
C	-2.152237	-5.007472	-5.868867
H	-3.369523	-3.857507	-4.481274
H	-3.648724	-5.612556	-4.388809
H	0.475634	-5.034308	-4.716690
H	0.689629	-3.292323	-4.806601
H	-0.410370	-4.194042	-6.879708
H	-1.393388	-2.996190	-6.042295
H	-1.774171	-6.036129	-5.927409
H	-2.852370	-4.873352	-6.701797
H	-1.362692	-2.946119	-3.441359
N	-1.927802	-4.934026	-3.438537
C	-1.799635	-6.106865	-2.797704
C	-0.660318	-6.204396	-1.789438
O	-2.519321	-7.103979	-2.934898
O	-0.878971	-5.847650	-0.613473
C	0.588137	-6.880916	-2.220068
C	1.728252	-6.809561	-1.402309
C	0.673697	-7.506166	-3.473577
C	2.938683	-7.331670	-1.843563
H	1.655929	-6.317493	-0.442383
C	1.885665	-8.042718	-3.905160
H	-0.210856	-7.588365	-4.095075
C	3.020719	-7.947761	-3.097442
H	3.819812	-7.257233	-1.213708
H	1.944569	-8.531113	-4.872606
H	3.966603	-8.355175	-3.441074
C	0.639150	-4.062483	2.217061
C	0.900283	-5.566024	2.022284
C	1.343602	-3.556419	3.488107
H	-0.439065	-3.940294	2.349606
C	0.449330	-6.361864	3.255611
H	1.971135	-5.748703	1.868662
H	0.369724	-5.918914	1.139244
C	0.905642	-4.358555	4.724088
H	2.430249	-3.662304	3.377559
H	1.137650	-2.494687	3.650787
C	1.133646	-5.861969	4.532166
H	0.655258	-7.427777	3.102372
H	-0.639514	-6.265814	3.362266
H	1.448679	-3.998149	5.605952
H	-0.158836	-4.175951	4.914067
H	0.772223	-6.416472	5.406213
H	2.213294	-6.056066	4.459774
C	2.762027	-2.594541	0.777967
C	3.589613	-3.820721	0.340895
C	3.224782	-1.348227	0.002347
H	2.973359	-2.418389	1.839246
C	5.093064	-3.572391	0.528465
H	3.377409	-4.032259	-0.711579
H	3.297522	-4.708390	0.906962
C	4.719159	-1.092194	0.238047
H	3.063878	-1.500542	-1.061051
H	2.639602	-0.470309	0.284708
C	5.554860	-2.302432	-0.195136
H	5.656272	-4.443498	0.172851
H	5.308530	-3.475843	1.602100
H	5.027678	-0.198730	-0.317232
H	4.900061	-0.882766	1.302486
H	6.620398	-2.124128	-0.008225
H	5.437724	-2.441640	-1.277919
C	-1.549275	1.243141	-3.376016
H	-0.663362	0.729727	-3.754627
H	-1.961368	1.863284	-4.177039

H	-1.250810	1.895039	-2.549157
C	-3.882829	0.917114	-2.439370
H	-4.350303	1.454833	-3.269548
H	-4.600187	0.187301	-2.056651
H	-3.658174	1.633644	-1.643133
O	-2.444945	-3.474555	1.822345
C	-3.545280	-3.480202	2.767006
H	-4.316858	-4.166712	2.396870
C	-4.133919	-2.080691	2.908891
H	-3.369209	-1.381668	3.259315
H	-4.517741	-1.718877	1.951209
H	-4.960042	-2.091329	3.626344
C	-2.976506	-4.013433	4.070062
H	-3.765160	-4.084639	4.824326
H	-2.540646	-5.005029	3.925483
H	-2.198377	-3.341666	4.444472

I7

C	-3.619481	-1.865014	-0.050508
C	-2.477686	-1.551813	0.725453
C	-2.532001	-0.433298	1.573210
C	-3.634041	0.418891	1.588437
C	-4.711003	0.166832	0.738670
C	-4.701952	-0.974984	-0.058771
C	-3.778258	-3.166079	-0.763901
C	-3.800960	-3.261423	-2.175076
C	-3.956263	-4.509867	-2.794521
C	-4.152390	-5.649225	-2.019957
C	-4.218519	-5.568063	-0.633810
C	-4.050058	-4.326731	-0.017599
P	-0.923996	-2.544328	0.583403
H	-1.702138	-0.226615	2.238028
H	-3.644154	1.278110	2.252076
H	-5.564273	0.837970	0.717391
H	-5.557767	-1.209073	-0.683088
O	-3.706736	-2.087472	-2.849746
H	-3.907915	-4.597774	-3.870069
H	-4.255959	-6.611186	-2.508810
H	-4.388483	-6.451424	-0.029738
Pd	-0.676662	-3.528251	-1.612528
C	-0.078069	-1.771052	-2.394398
C	1.248893	-1.630152	-2.829321
C	-0.915210	-0.650896	-2.435787
C	1.735210	-0.392465	-3.262027
H	1.916600	-2.487153	-2.825154
C	-0.433476	0.583880	-2.885294
H	-1.943691	-0.733682	-2.110939
C	0.894453	0.723065	-3.290903
H	2.770277	-0.303921	-3.582977
H	-1.101152	1.441854	-2.904047
H	1.269477	1.684748	-3.629088
C	-3.908009	-2.071069	-4.285942
H	-3.289254	-2.858755	-4.723850
C	1.303668	-5.194175	-4.976682
C	0.922882	-5.900625	-2.559305
C	1.735607	-7.178889	-2.850874
C	2.760054	-6.962349	-3.965437
C	2.026782	-6.511924	-5.229846
H	2.052541	-4.392563	-4.868459
H	0.653456	-4.921502	-5.808102
H	1.060915	-7.985941	-3.151424
H	2.215996	-7.491103	-1.917948
H	3.316131	-7.889205	-4.140925
H	3.490556	-6.198156	-3.667644

H	1.306831	-7.284868	-5.527931
H	2.722745	-6.376446	-6.064582
H	1.536923	-5.227867	-1.942102
N	0.461741	-5.228935	-3.771594
C	-0.463209	-4.181935	-3.593141
C	-0.314805	-6.249390	-1.714662
O	-0.980560	-3.680547	-4.586922
O	-0.460959	-5.739242	-0.592431
C	-1.285578	-7.282903	-2.171439
C	-1.560487	-7.550900	-3.522168
C	-1.956798	-8.010961	-1.175876
C	-2.493655	-8.527968	-3.863288
H	-1.070823	-6.967009	-4.290213
C	-2.873288	-8.999079	-1.520474
H	-1.746428	-7.784784	-0.137070
C	-3.147985	-9.256424	-2.866691
H	-2.714679	-8.716702	-4.909116
H	-3.379452	-9.563145	-0.743279
H	-3.871559	-10.019308	-3.137586
C	-1.073220	-3.797246	1.975343
C	0.241447	-4.549518	2.249824
C	-1.650086	-3.233490	3.283040
H	-1.793628	-4.516606	1.572179
C	0.020527	-5.681290	3.261023
H	0.975281	-3.855288	2.676176
H	0.651721	-4.942213	1.317630
C	-1.830379	-4.347057	4.325626
H	-0.975762	-2.463961	3.684559
H	-2.611714	-2.754542	3.089377
C	-0.538078	-5.130072	4.577646
H	0.963085	-6.213892	3.434819
H	-0.684111	-6.411515	2.839253
H	-2.216732	-3.923605	5.260527
H	-2.592061	-5.042200	3.955095
H	-0.719130	-5.942225	5.291746
H	0.210740	-4.467934	5.035048
C	0.486821	-1.417968	1.119015
C	1.833135	-2.065304	0.713839
C	0.474391	0.016119	0.550652
H	0.442595	-1.360568	2.216300
C	3.021118	-1.267234	1.268764
H	1.881456	-2.080414	-0.378875
H	1.901908	-3.101454	1.042505
C	1.637468	0.837093	1.124150
H	0.578032	-0.035655	-0.532573
H	-0.469172	0.526733	0.743710
C	2.987418	0.190206	0.796358
H	3.959109	-1.746578	0.963952
H	2.995676	-1.296874	2.367529
H	1.596743	1.856041	0.721470
H	1.526045	0.923673	2.214777
H	3.809596	0.759748	1.245734
H	3.135486	0.216716	-0.291677
O	-4.169438	-4.216524	1.353989
C	-5.487250	-4.525537	1.878725
H	-5.774139	-5.523382	1.521918
C	-5.358134	-4.550329	3.391783
H	-6.333090	-4.749892	3.845866
H	-4.662013	-5.327544	3.713171
H	-4.995897	-3.585171	3.758648
C	-6.517247	-3.508658	1.398746
H	-6.255527	-2.506106	1.747249
H	-6.571252	-3.490391	0.307159
H	-7.507222	-3.770981	1.784637

C	-3.393516	-0.725654	-4.771505
H	-2.322517	-0.634641	-4.592950
H	-3.582882	-0.627229	-5.844606
H	-3.908265	0.090493	-4.253356
C	-5.389095	-2.264070	-4.604908
H	-5.540399	-2.267340	-5.688742
H	-5.776158	-3.203514	-4.204005
H	-5.972041	-1.441203	-4.178343

BD1

C	-2.436801	-0.781432	-0.234953
C	-0.347951	0.412024	-0.761688
C	-1.045990	1.399516	-1.638583
C	-2.552974	1.471373	-1.353216
C	-3.130434	0.054448	-1.308198
H	-2.660912	-0.376181	0.760677
H	-2.768907	-1.818638	-0.246539
H	-0.905923	1.122131	-2.700310
H	-0.574736	2.380978	-1.519965
H	-3.055884	2.073967	-2.116473
H	-2.721354	1.961887	-0.386147
H	-3.002052	-0.429302	-2.285377
H	-4.204391	0.072209	-1.094883
H	0.724646	0.438561	-0.640064
N	-0.973804	-0.786258	-0.424772
C	-0.297182	-1.920411	0.009687
C	1.130254	-2.074913	-0.353319
O	-0.869345	-2.791140	0.676394
O	1.843484	-2.688847	0.626449
H	2.627427	-3.105820	0.240623
C	1.734939	-1.772327	-1.617526
C	3.147103	-1.757204	-1.757180
C	0.954876	-1.499039	-2.772342
C	3.741900	-1.491429	-2.984219
H	3.780970	-1.904915	-0.887512
C	1.561383	-1.233233	-3.991699
H	-0.125413	-1.525419	-2.701627
C	2.956489	-1.227342	-4.111115
H	4.824893	-1.475622	-3.060504
H	0.942337	-1.036946	-4.862013
H	3.424161	-1.016707	-5.067396

BD2

C	-1.923780	-0.932572	-0.701015
C	-0.968698	1.255502	0.083954
C	-2.094053	1.998137	-0.664712
C	-3.351660	1.132723	-0.799818
C	-3.019338	-0.202299	-1.474090
H	-2.290845	-1.212766	0.296682
H	-1.594933	-1.839480	-1.210264
H	-1.740661	2.296748	-1.655802
H	-2.313446	2.916952	-0.111712
H	-4.116748	1.671736	-1.368131
H	-3.772314	0.940485	0.196725
H	-2.677169	-0.026233	-2.501270
H	-3.905850	-0.843416	-1.529791
H	-1.322632	1.066432	1.106702
N	-0.734455	-0.071665	-0.541683
C	0.495309	-0.576198	-0.701350
C	0.283540	2.069033	0.232266
O	0.833662	-1.673937	-1.085261
O	0.629488	2.227621	1.544698
H	1.541697	2.545540	1.604043
C	1.044057	2.664468	-0.809720

C	2.029838	3.653417	-0.526265
C	0.878319	2.284749	-2.173550
C	2.798182	4.213332	-1.536579
H	2.158414	4.022139	0.487738
C	1.651650	2.857158	-3.172235
H	0.161828	1.515813	-2.431362
C	2.620377	3.822588	-2.869209
H	3.534526	4.971752	-1.287211
H	1.507500	2.539968	-4.200911
H	3.222991	4.263711	-3.656318

BD3

C	-2.027581	0.737052	1.192787
N	-0.581411	0.475520	1.096419
C	0.132403	1.163342	0.115848
C	-0.501488	1.399193	-1.219277
C	-1.993653	1.744224	-1.112472
C	-2.683518	0.738909	-0.186993
H	-2.461950	-0.029936	1.826982
H	1.206228	1.082315	0.213030
H	0.045857	2.187645	-1.748521
H	-2.615169	-0.270272	-0.614848
H	-0.404704	0.491246	-1.846371
H	-3.747729	0.975288	-0.072358
H	-2.172868	1.721341	1.663250
C	-0.606004	-1.098395	3.023150
O	-1.623881	-1.772066	2.573315
C	0.120589	-0.165162	2.129027
O	1.363301	-0.029997	2.196730
C	-0.018906	-1.421595	4.319032
C	-0.311858	-2.677508	4.911869
C	0.839699	-0.546775	5.035683
C	0.238638	-3.041991	6.137276
H	-0.911669	-3.385680	4.351892
C	1.378062	-0.917780	6.262508
H	1.085096	0.418250	4.607911
C	1.086469	-2.168322	6.829231
H	0.016576	-4.023074	6.550543
H	2.028708	-0.224674	6.790497
H	1.512484	-2.452611	7.786819
Cs	2.804902	-2.996553	2.594269
C	-0.072450	-4.907072	2.191578
O	0.014298	-3.687636	1.490640
O	1.003781	-5.536468	2.248328
O	-1.200456	-5.190775	2.674534
Cs	-3.787127	-3.806402	2.962271
H	-2.108473	2.753039	-0.694792
H	-2.456424	1.748811	-2.105337
H	-0.746533	-3.123342	1.754452

BD4

C	-1.418237	-0.348907	0.445484
N	-0.101652	0.104073	-0.044284
C	0.365273	1.439225	0.427607
C	-0.730936	2.492009	0.172609
C	-2.095955	2.056331	0.718259
C	-2.494405	0.692487	0.144575
H	-1.630180	-1.307673	-0.030825
H	0.494194	1.351746	1.514356
H	-0.406158	3.423722	0.648224
H	-2.625193	0.769221	-0.942064
H	-0.808302	2.692727	-0.900150
H	-3.447543	0.352662	0.565151
H	-1.349814	-0.512179	1.530466

C	1.742319	1.838011	-0.094107
O	2.642628	2.064121	0.814841
C	0.699750	-0.734318	-0.692618
O	0.516878	-1.881222	-1.063733
C	2.028507	1.947410	-1.492612
C	3.358316	2.291906	-1.907725
C	1.094015	1.665619	-2.544377
C	3.712616	2.349175	-3.246024
H	4.111381	2.448890	-1.145341
C	1.466783	1.728126	-3.881337
H	0.077497	1.380491	-2.304358
C	2.775967	2.069275	-4.260599
H	4.737154	2.602062	-3.511327
H	0.725287	1.505758	-4.645876
H	3.056683	2.119049	-5.308227
Cs	3.733691	-1.553910	-2.244693
C	5.658601	0.421527	-0.142315
O	4.381300	0.037397	0.295258
O	6.250160	-0.448881	-0.816844
O	6.038307	1.578564	0.181160
Cs	4.904040	3.804802	1.719913
H	-2.045923	1.984632	1.813764
H	-2.857260	2.808463	0.483861
H	3.876125	0.838837	0.578816

BD5

C	-4.606268	-3.945805	3.584817
C	-3.754043	-4.664889	4.455371
C	-3.642199	-4.249765	5.792689
C	-4.325428	-3.131077	6.264686
C	-5.134703	-2.400384	5.395078
C	-5.270812	-2.811827	4.071378
C	-4.875613	-4.350350	2.171459
C	-4.343524	-3.612136	1.089405
C	-4.636026	-3.972957	-0.229852
C	-5.478238	-5.054578	-0.478829
C	-6.054302	-5.770115	0.565539
C	-5.760779	-5.403199	1.882866
P	-2.815160	-6.131309	3.855612
H	-3.009089	-4.802499	6.477356
H	-4.219518	-2.830600	7.302464
H	-5.663063	-1.519261	5.746023
H	-5.910520	-2.256620	3.393025
O	-3.547788	-2.559110	1.432494
H	-4.180182	-3.448992	-1.058467
H	-5.679724	-5.342882	-1.505274
H	-6.717462	-6.605754	0.373262
Pd	-2.473410	-6.152795	1.572696
C	-0.667382	-5.281163	1.621163
C	0.475822	-6.002949	1.267725
C	-0.564732	-3.918738	1.920928
C	1.719589	-5.361367	1.219294
H	0.408376	-7.056075	1.020380
C	0.678240	-3.280720	1.856722
H	-1.447950	-3.360290	2.208244
C	1.824580	-3.999939	1.510915
H	2.604829	-5.931565	0.949680
H	0.751864	-2.221419	2.090156
H	2.790199	-3.504518	1.471017
C	-3.241569	-1.546789	0.445722
H	-2.837277	-2.038293	-0.446775
C	-0.968897	-4.339362	-4.029744
C	-1.129991	-4.036652	-1.599073
C	-0.227022	-2.841779	-1.633482

C	-0.156672	-2.185880	-3.017083
C	0.113209	-3.262211	-4.071108
H	-1.934862	-3.902817	-4.319810
H	-0.750564	-5.161760	-4.707932
H	0.792284	-3.152500	-1.338474
H	-0.544212	-2.126444	-0.869521
H	0.620102	-1.413961	-3.037189
H	-1.112364	-1.692575	-3.239837
H	1.090882	-3.725180	-3.884746
H	0.143458	-2.833438	-5.078851
H	-1.435202	-4.453806	-0.655817
N	-1.114588	-4.917666	-2.680492
C	-1.245310	-6.300244	-2.598143
C	-1.560358	-6.930077	-1.278075
O	-1.138294	-7.010234	-3.611308
O	-2.441931	-6.367177	-0.527304
C	-0.954611	-8.208474	-0.925736
C	-1.468835	-8.936014	0.172050
C	0.190189	-8.721550	-1.579118
C	-0.851261	-10.098507	0.618695
H	-2.359390	-8.573099	0.669985
C	0.804238	-9.882969	-1.125817
H	0.589793	-8.196057	-2.437251
C	0.297033	-10.577203	-0.019690
H	-1.269411	-10.635783	1.465816
H	1.690412	-10.251227	-1.634953
H	0.785760	-11.480680	0.332042
C	-3.946029	-7.556337	4.325789
C	-3.796483	-8.766763	3.386558
C	-3.888561	-7.972417	5.803862
H	-4.935326	-7.132334	4.136784
C	-4.845470	-9.839693	3.708044
H	-2.791893	-9.198871	3.469399
H	-3.910080	-8.439464	2.347013
C	-4.951659	-9.039683	6.105853
H	-2.900428	-8.382239	6.047329
H	-4.043080	-7.100227	6.449071
C	-4.797565	-10.255157	5.183368
H	-4.697490	-10.710138	3.058704
H	-5.841519	-9.438721	3.476760
H	-4.882946	-9.344600	7.156551
H	-5.949273	-8.602319	5.967222
H	-5.577525	-10.995343	5.395625
H	-3.834777	-10.743707	5.389461
C	-1.340396	-6.297469	4.983980
C	-0.510806	-7.520676	4.542867
C	-0.450381	-5.044989	5.071209
H	-1.735141	-6.501451	5.987085
C	0.694099	-7.743288	5.467068
H	-0.162038	-7.355322	3.518533
H	-1.131352	-8.421303	4.524674
C	0.733053	-5.282301	6.018879
H	-0.064496	-4.807931	4.079929
H	-1.033095	-4.178598	5.396824
C	1.565548	-6.486308	5.564044
H	1.282569	-8.592834	5.101965
H	0.336520	-8.014703	6.470516
H	1.354558	-4.380363	6.059470
H	0.363110	-5.458327	7.039266
H	2.404410	-6.655312	6.249044
H	1.996188	-6.269330	4.576917
C	-2.162244	-0.677121	1.071647
H	-1.263951	-1.259869	1.280419
H	-1.896421	0.135234	0.389355

H	-2.523475	-0.241296	2.008226
C	-4.493865	-0.746199	0.098645
H	-4.255278	0.015659	-0.649421
H	-5.283128	-1.384436	-0.304296
H	-4.875336	-0.245772	0.994359
O	-6.317714	-6.079785	2.943025
C	-7.762573	-6.085373	3.041727
H	-8.175505	-6.484128	2.106307
C	-8.286094	-4.671997	3.269741
H	-7.868507	-4.257535	4.191893
H	-8.010444	-4.014627	2.440437
H	-9.377390	-4.682543	3.348259
C	-8.089190	-7.030557	4.186440
H	-9.171852	-7.100669	4.323238
H	-7.697715	-8.031283	3.986327
H	-7.643920	-6.662841	5.116346

BD6

C	-4.545603	-7.100705	2.687992
C	-3.358613	-6.443356	3.093904
C	-3.470793	-5.146808	3.627468
C	-4.708368	-4.529679	3.797341
C	-5.874779	-5.200479	3.436072
C	-5.782064	-6.474993	2.882489
C	-4.532956	-8.433723	2.023668
C	-4.246357	-8.533909	0.648966
C	-4.130215	-9.794528	0.042665
C	-4.380060	-10.936339	0.800099
C	-4.768955	-10.858094	2.137431
C	-4.859461	-9.597437	2.740720
P	-1.686156	-7.179635	2.810596
H	-2.585660	-4.592957	3.907681
H	-4.754128	-3.527459	4.212125
H	-6.845202	-4.732302	3.569173
H	-6.678592	-7.003990	2.574775
O	-4.116078	-7.353981	-0.008382
H	-3.872520	-9.879909	-1.003568
H	-4.295875	-11.911594	0.329916
H	-4.995671	-11.759976	2.690818
Pd	-0.934976	-7.361159	0.625682
C	-0.690245	-5.355388	0.487438
C	0.584825	-4.846512	0.211347
C	-1.756046	-4.467504	0.667258
C	0.790281	-3.466180	0.116887
H	1.421132	-5.522911	0.065730
C	-1.548574	-3.088035	0.567049
H	-2.750789	-4.844315	0.877194
C	-0.276542	-2.582818	0.294028
H	1.785505	-3.084181	-0.098181
H	-2.387393	-2.409458	0.700008
H	-0.117821	-1.511130	0.217104
C	-4.226461	-7.318157	-1.455939
H	-3.504520	-8.020156	-1.876945
C	1.425460	-4.189058	-3.674384
C	1.041591	-6.532003	-2.888855
C	1.829015	-7.063832	-4.101163
C	2.867114	-6.042419	-4.581224
C	2.202897	-4.695361	-4.887565

Cs_2CO_3

Cs	2.866511	-3.090178	-2.239066
C	4.874112	-0.900905	-0.675280
O	3.750034	-1.270843	-0.079018
O	5.180946	-1.412129	-1.823097
O	5.641284	-0.033374	-0.099770

Cs	4.171364	0.374669	2.346826

substrate

C	-2.422007	-0.886830	-0.400137
C	-0.570020	0.864725	0.101372
C	-1.213815	1.839827	-0.876622
C	-2.731898	1.582811	-0.928500
C	-3.040516	0.139115	-1.364906
H	-2.989451	-0.911044	0.539708
H	-2.418714	-1.896326	-0.819237
H	-0.789990	1.688321	-1.875674
H	-0.996186	2.871790	-0.583526
H	-3.203243	2.286635	-1.622014
H	-3.173661	1.770029	0.060046
H	-2.632145	-0.026498	-2.369449
H	-4.122000	-0.023192	-1.420543
H	-0.702222	1.186136	1.140730
N	-1.051486	-0.509490	-0.125420
C	0.161823	-1.048705	-0.430244
C	0.880749	0.313360	-0.144565
O	0.505617	-2.158754	-0.795321
O	1.599807	0.341536	1.076555
H	2.432676	-0.129001	0.929304
C	1.662730	0.913074	-1.287023
C	2.412085	2.075245	-1.057149
C	1.635207	0.361091	-2.573086
C	3.111112	2.682408	-2.098299
H	2.443695	2.491396	-0.055548
C	2.336307	0.970681	-3.615809
H	1.084184	-0.555404	-2.753814
C	3.072631	2.132444	-3.382522
H	3.686165	3.583993	-1.909177
H	2.312005	0.531335	-4.608462
H	3.618315	2.604385	-4.193974

I1

C	-1.883450	-0.186638	0.835386
N	-0.468295	-0.141453	0.548429
C	0.358937	1.069542	0.483442
C	-0.367110	2.204987	-0.228355
C	-1.816005	2.297961	0.292328
C	-2.574131	0.972112	0.095822
H	-2.269513	-1.161388	0.523181
H	0.684711	1.388207	1.482497
H	0.162791	3.150164	-0.066006
H	-2.614070	0.736723	-0.975351
H	-0.386726	2.029732	-1.308618
H	-3.607470	1.064571	0.447668
H	-2.050864	-0.088859	1.918220
C	1.523157	0.147639	-0.146681
O	2.636445	0.070355	0.602703
H	3.521475	-1.130470	0.175461
C	0.443253	-1.004679	0.028616
O	0.367381	-2.206865	-0.212546
C	1.779476	0.370391	-1.647642
C	3.085249	0.646528	-2.069232
C	0.781332	0.214592	-2.625639
C	3.387358	0.775115	-3.427150
H	3.870201	0.682635	-1.322880
C	1.079009	0.349149	-3.983898
H	-0.232687	-0.040390	-2.330459
C	2.386413	0.632803	-4.391455
H	4.412957	0.967630	-3.730356
H	0.292280	0.224346	-4.723518

H	2.621750	0.728772	-5.447718
Cs	2.534838	-3.512355	-2.236437
C	5.151969	-1.728354	-0.854587
O	4.000569	-1.988773	-0.108993
O	5.455589	-2.628301	-1.674432
O	5.750863	-0.639463	-0.627353
Cs	5.156788	0.756648	1.913382
H	-1.807845	2.554356	1.361329
H	-2.348920	3.106345	-0.220496

TS1

C	-0.914273	-0.720592	-0.558707
N	0.454660	-0.396417	-0.140181
C	0.957374	0.954043	0.110677
C	-0.113354	2.072155	0.055457
C	-1.305797	1.740526	-0.840932
C	-1.907061	0.420506	-0.358920
H	-0.910573	-1.008869	-1.620619
H	1.421559	0.988295	1.102196
H	-0.489345	2.229435	1.073080
H	-2.041997	2.550364	-0.790297
H	-2.832450	0.181615	-0.895276
H	-0.993844	1.650235	-1.888414
H	0.367287	3.009921	-0.244102
H	-2.167998	0.517441	0.703482
H	-1.236531	-1.615722	-0.014837
C	2.114316	1.271968	-0.836186
O	3.170868	1.729491	-0.388375
H	2.589792	-1.639690	1.372064
C	1.491597	-1.330382	-0.303203
O	1.134092	-2.456647	-0.742116
C	1.908343	1.271600	-2.330302
C	2.425209	2.382395	-3.020636
C	1.258654	0.264315	-3.063014
C	2.265994	2.506238	-4.399268
H	2.942931	3.148799	-2.453557
C	1.114823	0.384564	-4.446332
H	0.919636	-0.635062	-2.567807
C	1.606203	1.506109	-5.117600
H	2.656426	3.380120	-4.912502
H	0.622018	-0.408316	-5.001370
H	1.484063	1.596162	-6.192926
Cs	0.833406	-4.632843	1.450563
C	3.725054	-3.063758	2.116312
O	2.603227	-2.207633	2.182867
O	3.590947	-4.121902	2.768285
O	4.683879	-2.674266	1.405125
Cs	4.985457	-0.880243	-0.889384

I2

C	-3.306866	1.130772	-0.652766
N	-1.874015	1.203393	-0.375796
C	-1.347045	2.507171	-0.049403
C	-2.124281	3.157345	1.106627
C	-3.633852	3.148641	0.828763
C	-4.121550	1.731447	0.498802
H	-3.546791	1.659689	-1.589126
H	-0.308742	2.309050	0.272664
H	-1.911521	2.571419	2.008951
H	-4.178453	3.552549	1.690090
H	-5.188121	1.738202	0.241991
H	-3.844796	3.813354	-0.018670
H	-1.768028	4.176851	1.271490
H	-4.002508	1.089673	1.382327

H	-3.523298	0.068374	-0.796349
C	-1.208384	3.452298	-1.251618
O	-1.427293	4.652535	-1.129515
H	0.188902	-0.097823	1.373281
C	-1.077912	0.066229	-0.087624
O	-1.634461	-1.043201	-0.289875
C	-0.638678	2.953549	-2.555021
C	0.245941	3.826328	-3.214688
C	-0.932548	1.713249	-3.149050
C	0.852527	3.460324	-4.413781
H	0.450229	4.791474	-2.763765
C	-0.344319	1.361096	-4.367917
H	-1.611424	1.027505	-2.664471
C	0.556775	2.223411	-4.996375
H	1.545484	4.140634	-4.899743
H	-0.594249	0.407779	-4.824852
H	1.017624	1.939784	-5.938066
Cs	-1.631744	-2.827809	2.273988
C	1.428604	-1.462463	2.103258
O	0.396248	-0.520871	2.258656
O	1.379367	-2.416539	2.912386
O	2.250330	-1.252881	1.173262
Cs	2.141884	0.073479	-1.413896

TS2

C	-3.413852	1.014739	-0.688949
N	-2.011129	1.006020	-0.282206
C	-1.448988	2.269107	0.161586
C	-2.316471	2.913451	1.256007
C	-3.791148	2.979949	0.839588
C	-4.299911	1.596281	0.415185
H	-3.548031	1.610438	-1.607459
H	-0.453750	2.035155	0.568730
H	-2.226753	2.307327	2.165928
H	-4.397564	3.382666	1.658777
H	-5.338425	1.653569	0.068291
H	-3.891454	3.677244	-0.001583
H	-1.932000	3.908289	1.486279
H	-4.284239	0.916815	1.278758
H	-3.665451	-0.020906	-0.928235
C	-1.144991	3.278758	-0.965700
O	-1.271144	4.478888	-0.758378
H	0.162465	0.071890	0.276199
C	-1.171522	-0.107874	-0.431210
O	-1.669469	-1.124503	-0.972993
C	-0.527669	2.835290	-2.264649
C	0.495260	3.657554	-2.768658
C	-0.928814	1.717731	-3.014415
C	1.130417	3.354700	-3.969715
H	0.784977	4.532426	-2.197117
C	-0.314901	1.437950	-4.238265
H	-1.720141	1.071424	-2.666118
C	0.723457	2.242192	-4.711957
H	1.932189	3.990151	-4.333066
H	-0.655690	0.588245	-4.823895
H	1.204202	2.012062	-5.658244
Cs	-1.077699	-0.485950	3.229281
C	1.668263	-0.750437	1.508612
O	0.974914	0.343124	1.021881
O	1.876106	-0.761758	2.754274
O	1.987011	-1.653106	0.680677
Cs	1.234982	-1.652882	-2.133076

I3

C	-3.339049	0.656259	-0.432561
N	-1.905010	0.905049	-0.302373
C	-1.464559	2.275811	0.015036
C	-2.254826	2.820036	1.212227
C	-3.768790	2.590099	1.117764
C	-4.084897	1.119974	0.819813
H	-3.718409	1.199970	-1.308882
H	-0.412052	2.197158	0.339949
H	-1.852617	2.325243	2.103322
H	-4.252718	2.901892	2.050468
H	-5.161212	0.971424	0.678249
H	-4.173191	3.215659	0.316181
H	-2.037505	3.886522	1.315674
H	-3.784184	0.489720	1.668880
H	-3.459685	-0.412094	-0.615997
C	-1.611660	3.138106	-1.243821
O	-2.439414	4.041648	-1.302377
H	0.038046	0.282910	-0.451489
C	-0.998908	-0.080818	-0.493138
O	-1.280051	-1.272658	-0.700245
C	-0.762801	2.812377	-2.429954
C	0.509060	2.227104	-2.314881
C	-1.264510	3.148279	-3.698430
C	1.251418	1.977263	-3.472129
H	0.955535	1.959525	-1.352194
C	-0.524234	2.879243	-4.844983
H	-2.240496	3.618029	-3.761596
C	0.739861	2.290510	-4.732585
H	2.242153	1.540812	-3.379074
H	-0.924592	3.130576	-5.822695
H	1.324014	2.085836	-5.625596
Cs	-0.770612	-0.650394	3.203568
C	1.556051	0.521525	1.133398
O	1.995609	0.790647	-0.065935
O	0.804661	1.382612	1.750243
O	1.795737	-0.642021	1.660304
Cs	1.946871	-1.997817	-1.079977

prod

C	-1.340851	0.279976	-1.006712
N	-0.063290	-0.308730	-0.599984
C	0.941234	0.623200	-0.091604
C	0.370039	1.424563	1.089491
C	-0.981523	2.067986	0.740704
C	-1.965356	1.037276	0.169774
H	-1.161086	0.957145	-1.851308
H	1.798647	0.027824	0.248214
H	0.244476	0.728720	1.927092
H	-1.403966	2.540158	1.633871
H	-2.888608	1.526222	-0.159442
H	-0.817367	2.863530	0.006550
H	1.091105	2.187812	1.390865
H	-2.239355	0.309811	0.943966
H	-1.973695	-0.537980	-1.350973
C	1.453079	1.543433	-1.223240
O	1.506074	2.752815	-1.050906
H	1.025144	-1.931484	0.025362
C	0.041688	-1.650779	-0.399814
O	-0.820158	-2.478857	-0.660448
C	1.866141	0.942807	-2.525010
C	1.878751	1.780299	-3.651810
C	2.271626	-0.393683	-2.659634
C	2.268253	1.287080	-4.893008
H	1.575929	2.814490	-3.530367

C	2.678681	-0.881659	-3.899461
H	2.292989	-1.051920	-1.800387
C	2.668994	-0.046060	-5.018490
H	2.263236	1.938374	-5.761337
H	2.999996	-1.914032	-3.992836
H	2.975549	-0.432351	-5.985726

I4

C	-3.859245	-2.406489	0.091052
C	-2.567815	-1.942305	0.438288
C	-2.413916	-0.582760	0.760107
C	-3.486891	0.302893	0.742016
C	-4.753390	-0.153347	0.384629
C	-4.926588	-1.497906	0.070895
C	-4.194237	-3.833407	-0.192193
C	-4.002477	-4.423774	-1.454278
C	-4.335510	-5.771522	-1.659299
C	-4.894821	-6.506108	-0.621460
C	-5.165856	-5.927824	0.617474
C	-4.831124	-4.584941	0.818758
P	-1.053307	-2.985123	0.277887
H	-1.438619	-0.187805	1.007211
H	-3.324751	1.346384	0.993011
H	-5.598579	0.527350	0.353001
H	-5.910530	-1.873039	-0.192024
O	-3.494263	-3.622315	-2.432605
H	-4.162688	-6.243479	-2.613514
H	-5.143999	-7.550031	-0.786925
H	-5.634951	-6.512637	1.396918
Pd	-0.438079	-3.381356	-1.856943
C	-0.495324	-1.390017	-2.101355
C	0.704471	-0.666367	-2.157549
C	-1.697157	-0.718898	-2.359384
C	0.703218	0.697115	-2.471688
H	1.650959	-1.162191	-1.962222
C	-1.698816	0.641096	-2.681654
H	-2.635419	-1.257910	-2.294111
C	-0.499944	1.355469	-2.734887
H	1.643354	1.241867	-2.510471
H	-2.641934	1.144658	-2.878989
H	-0.502664	2.414670	-2.976597
C	-3.638217	-4.039014	-3.817264
H	-3.273868	-5.063795	-3.913455
C	3.319528	-5.525386	-4.571706
C	1.551169	-6.764010	-3.129657
C	1.747332	-8.039658	-3.931815
C	3.189849	-8.072522	-4.479658
C	3.504430	-6.839742	-5.349748
H	4.125616	-5.399719	-3.836013
H	3.320730	-4.652525	-5.229454
H	1.040470	-8.059554	-4.769160
H	1.544782	-8.919085	-3.311917
H	3.345045	-8.982201	-5.069338
H	3.898613	-8.116225	-3.641031
H	2.832687	-6.830845	-6.216859
H	4.529506	-6.892677	-5.730999
H	2.020773	-6.819677	-2.140836
N	2.047919	-5.597184	-3.884947
C	0.938981	-4.853619	-3.745152
C	0.157249	-5.952723	-3.005720
O	0.676280	-3.654581	-3.949551
O	-0.223677	-5.550973	-1.757293
C	-0.958283	-6.597853	-3.811310
C	-1.180038	-6.319117	-5.164687

C	-1.796189	-7.512061	-3.162818
C	-2.226090	-6.936319	-5.856233
H	-0.552954	-5.596999	-5.678572
C	-2.827985	-8.144266	-3.854649
H	-1.640319	-7.696615	-2.105444
C	-3.052335	-7.852233	-5.203759
H	-2.397403	-6.695583	-6.901387
H	-3.468919	-8.853974	-3.338801
H	-3.865526	-8.333043	-5.739201
C	-5.103163	-3.948736	-4.234583
H	-5.214963	-4.278249	-5.271954
H	-5.741378	-4.575698	-3.607448
H	-5.450512	-2.913382	-4.159310
C	-2.745448	-3.136373	-4.650308
H	-3.047498	-2.089897	-4.555882
H	-1.700120	-3.225803	-4.351691
H	-2.827853	-3.430420	-5.701232
O	-5.064519	-3.905505	1.979728
C	-5.833406	-4.504284	3.040276
H	-5.482469	-5.530539	3.201169
C	-5.523493	-3.675489	4.278468
H	-5.807621	-2.631624	4.114336
H	-6.080920	-4.057857	5.138159
H	-4.456095	-3.711748	4.510008
C	-7.317586	-4.497667	2.684788
H	-7.662289	-3.467676	2.550133
H	-7.509793	-5.048499	1.761083
H	-7.901924	-4.957529	3.487530
C	-1.336217	-4.565508	1.212602
C	-0.070288	-5.437374	1.298154
C	-1.976933	-4.410027	2.602580
H	-2.041263	-5.094229	0.562332
C	-0.444301	-6.823390	1.842005
H	0.649850	-4.971884	1.981939
H	0.384297	-5.530181	0.310063
C	-2.356911	-5.793870	3.149652
H	-1.259601	-3.944152	3.285704
H	-2.853425	-3.763900	2.561124
C	-1.141566	-6.729331	3.205845
H	0.453546	-7.448329	1.916486
H	-1.111551	-7.314147	1.120237
H	-2.805954	-5.691256	4.145191
H	-3.122196	-6.233344	2.497755
H	-1.444119	-7.725229	3.550894
H	-0.426514	-6.343524	3.946332
C	0.315516	-2.004744	1.072466
C	0.213631	-1.758546	2.587120
C	1.716704	-2.537473	0.712960
H	0.234503	-1.043097	0.553119
C	1.274968	-0.737940	3.025252
H	0.384652	-2.702003	3.117479
H	-0.785946	-1.413851	2.868200
C	2.781993	-1.518880	1.139418
H	1.900091	-3.490726	1.218084
H	1.775040	-2.734515	-0.361210
C	2.686431	-1.197910	2.637317
H	1.210493	-0.574105	4.107081
H	1.061301	0.227685	2.546107
H	3.780439	-1.899584	0.895318
H	2.642990	-0.597141	0.557682
H	3.423243	-0.434135	2.911320
H	2.938333	-2.099595	3.212886

I5

C	-1.136321	-1.068571	1.249062
C	0.187416	-1.363403	1.658122
C	0.807469	-0.518120	2.597128
C	0.168090	0.610136	3.102864
C	-1.118545	0.922769	2.667228
C	-1.753494	0.086134	1.754928
C	-1.968397	-1.917827	0.344000
C	-2.333951	-1.462492	-0.943819
C	-3.179986	-2.225357	-1.755060
C	-3.704180	-3.423891	-1.269404
C	-3.410811	-3.862013	0.013149
C	-2.562582	-3.097598	0.816213
P	1.141974	-2.814848	1.035576
H	1.810039	-0.738042	2.941880
H	0.676603	1.239847	3.826089
H	-1.628417	1.805151	3.041440
H	-2.762034	0.311395	1.424957
O	-1.829217	-0.247263	-1.307466
H	-3.445427	-1.888172	-2.748295
H	-4.342068	-4.026706	-1.906188
H	-3.799176	-4.804475	0.377594
Pd	0.425701	-3.453964	-1.008249
C	1.509015	-1.981756	-1.828669
C	2.566076	-2.420108	-2.645109
C	1.246195	-0.609121	-1.753327
C	3.331727	-1.509548	-3.380309
H	2.809450	-3.478751	-2.701035
C	2.015094	0.302617	-2.484758
H	0.452142	-0.245582	-1.114179
C	3.060866	-0.141766	-3.296601
H	4.145968	-1.868449	-4.004515
H	1.806953	1.366502	-2.404286
H	3.663814	0.569981	-3.852941
C	-2.435427	0.490480	-2.388913
H	-2.502685	-0.157621	-3.271196
C	-2.821813	-4.902897	-4.551443
C	-0.692197	-4.823880	-3.117737
C	0.181996	-5.064250	-4.339718
C	-0.530625	-4.498538	-5.583629
C	-1.921146	-5.131406	-5.777390
H	-3.149931	-3.854098	-4.513399
H	-3.713256	-5.535572	-4.569623
H	0.340106	-6.141451	-4.463023
H	1.162561	-4.597033	-4.206433
H	0.080600	-4.670270	-6.475883
H	-0.636313	-3.409279	-5.478095
H	-1.804654	-6.210923	-5.933192
H	-2.407788	-4.722555	-6.669347
H	-0.650100	-3.740181	-2.845210
N	-2.069538	-5.213920	-3.358330
C	-2.195946	-6.102658	-2.327917
C	-0.734632	-5.812799	-1.829446
O	-3.136802	-6.792236	-1.974845
O	-0.686605	-5.191311	-0.610698
C	0.241096	-6.971245	-1.949175
C	1.588889	-6.749535	-1.629138
C	-0.152283	-8.247060	-2.363179
C	2.523438	-7.776421	-1.730815
H	1.893389	-5.763276	-1.288945
C	0.783619	-9.281936	-2.460506
H	-1.195980	-8.436905	-2.591583
C	2.122545	-9.050103	-2.148514
H	3.564238	-7.588018	-1.481724
H	0.461723	-10.270211	-2.776390

H	2.849109	-9.853774	-2.224514
C	0.814753	-4.137938	2.322206
C	1.115279	-5.577426	1.866874
C	1.464930	-3.839990	3.685669
H	-0.270720	-4.056200	2.432254
C	0.621809	-6.571522	2.927154
H	2.193917	-5.722119	1.732189
H	0.622656	-5.764618	0.911371
C	0.998040	-4.853101	4.743440
H	2.556818	-3.907028	3.597664
H	1.227158	-2.824847	4.020569
C	1.251563	-6.298156	4.297854
H	0.842029	-7.594605	2.601170
H	-0.471685	-6.496023	3.003187
H	1.506748	-4.648739	5.693151
H	-0.073958	-4.712678	4.923763
H	0.865053	-6.997631	5.048473
H	2.335484	-6.470335	4.234595
C	2.948519	-2.374098	1.231615
C	3.826966	-3.514810	0.678908
C	3.420475	-1.030580	0.646875
H	3.103065	-2.334336	2.317088
C	5.309056	-3.269192	0.997700
H	3.683011	-3.569264	-0.405707
H	3.521202	-4.479231	1.088440
C	4.887589	-0.778773	1.021258
H	3.339900	-1.059001	-0.438314
H	2.791057	-0.205272	0.986438
C	5.783263	-1.903437	0.488618
H	5.914584	-4.072765	0.562950
H	5.452941	-3.321026	2.086018
H	5.206690	0.187885	0.615207
H	4.988995	-0.712915	2.113982
H	6.828204	-1.733456	0.772491
H	5.745322	-1.895472	-0.609298
C	-1.480164	1.634663	-2.692180
H	-0.512585	1.252082	-3.020652
H	-1.894241	2.268563	-3.481404
H	-1.329937	2.246567	-1.797109
C	-3.822759	0.980141	-1.982213
H	-4.280722	1.541094	-2.802330
H	-4.482660	0.148432	-1.725358
H	-3.741016	1.640398	-1.112925
O	-2.276085	-3.484905	2.104293
C	-3.404457	-3.637085	2.999304
H	-4.121022	-4.331597	2.544020
C	-4.077198	-2.288842	3.233709
H	-3.365981	-1.582994	3.672681
H	-4.443376	-1.868650	2.293046
H	-4.928011	-2.403381	3.912195
C	-2.846421	-4.248285	4.272861
H	-3.649263	-4.414620	4.996573
H	-2.362912	-5.205487	4.061996
H	-2.108704	-3.575390	4.721046

TS3

C	-1.164929	-1.062725	1.122337
C	0.148846	-1.365116	1.549653
C	0.758965	-0.514306	2.492098
C	0.115838	0.613725	2.991606
C	-1.169283	0.923531	2.548601
C	-1.791288	0.089083	1.626993
C	-1.987580	-1.891023	0.191853
C	-2.346827	-1.394134	-1.081150

C	-3.216770	-2.110513	-1.907579
C	-3.761158	-3.312573	-1.451706
C	-3.462377	-3.799924	-0.187909
C	-2.592984	-3.076858	0.632596
P	1.105281	-2.835583	0.964146
H	1.759727	-0.729696	2.844280
H	0.619340	1.244790	3.717221
H	-1.685128	1.803050	2.921414
H	-2.795993	0.314115	1.285113
O	-1.798461	-0.188136	-1.417955
H	-3.481222	-1.739495	-2.888972
H	-4.419255	-3.881140	-2.099625
H	-3.865022	-4.746764	0.147558
Pd	0.362671	-3.663763	-1.036693
C	1.505636	-2.354673	-2.039423
C	2.639384	-2.869755	-2.689054
C	1.204156	-0.996586	-2.194784
C	3.456003	-2.046595	-3.470474
H	2.892848	-3.921745	-2.586832
C	2.020344	-0.173062	-2.979262
H	0.347428	-0.570647	-1.687350
C	3.150909	-0.691035	-3.613847
H	4.331001	-2.464623	-3.961572
H	1.784033	0.883744	-3.075680
H	3.789084	-0.046455	-4.211245
C	-2.392732	0.607160	-2.465043
H	-2.500409	-0.008245	-3.366427
C	-2.795103	-4.905520	-4.524747
C	-0.700463	-4.529488	-3.147179
C	0.189673	-4.789610	-4.346349
C	-0.568489	-4.420065	-5.639917
C	-1.907430	-5.169431	-5.750827
H	-3.161636	-3.869475	-4.535895
H	-3.659389	-5.573971	-4.485203
H	0.466532	-5.849842	-4.380992
H	1.110503	-4.207799	-4.268418
H	0.054022	-4.640372	-6.514651
H	-0.756482	-3.337256	-5.649040
H	-1.713919	-6.247391	-5.816365
H	-2.441588	-4.876549	-6.661456
H	-0.825083	-3.445954	-2.979376
N	-2.011275	-5.120430	-3.326574
C	-2.166585	-6.012391	-2.331413
C	-0.793483	-5.859922	-1.642422
O	-3.116261	-6.733474	-2.053122
O	-0.774481	-5.386620	-0.420613
C	0.226924	-6.913523	-2.000136
C	1.560582	-6.756064	-1.596242
C	-0.128286	-8.048286	-2.738041
C	2.519792	-7.707320	-1.929816
H	1.838421	-5.872980	-1.028751
C	0.834056	-9.005974	-3.070420
H	-1.161305	-8.193663	-3.036054
C	2.159271	-8.837644	-2.671486
H	3.550152	-7.568568	-1.614930
H	0.543608	-9.884210	-3.639401
H	2.907427	-9.579640	-2.933796
C	0.821327	-4.094559	2.328169
C	1.251162	-5.528135	1.965134
C	1.393196	-3.682222	3.696360
H	-0.271611	-4.089688	2.386979
C	0.806053	-6.509741	3.057809
H	2.341512	-5.588298	1.872022
H	0.809844	-5.808260	1.009450

C	0.980434	-4.680338	4.790456
H	2.489435	-3.656159	3.645688
H	1.057933	-2.678398	3.973418
C	1.369157	-6.117996	4.428389
H	1.120231	-7.525025	2.789312
H	-0.291632	-6.522530	3.100513
H	1.438308	-4.386926	5.742585
H	-0.105010	-4.626211	4.933325
H	1.019788	-6.810719	5.202976
H	2.465103	-6.200442	4.402183
C	2.899223	-2.323093	1.118022
C	3.836995	-3.443105	0.625579
C	3.273927	-0.991221	0.441427
H	3.066595	-2.208548	2.196572
C	5.307632	-3.083794	0.882731
H	3.677558	-3.589783	-0.446592
H	3.604245	-4.389902	1.115698
C	4.734994	-0.630579	0.739577
H	3.148226	-1.085977	-0.635853
H	2.610672	-0.185808	0.764901
C	5.681072	-1.735767	0.256219
H	5.951410	-3.880740	0.492841
H	5.482478	-3.040292	1.966995
H	4.981011	0.321581	0.255621
H	4.868184	-0.480216	1.820618
H	6.721983	-1.482447	0.488468
H	5.606483	-1.813112	-0.836969
C	-1.395747	1.721125	-2.745901
H	-0.451524	1.310611	-3.108475
H	-1.794542	2.399121	-3.505677
H	-1.203232	2.293625	-1.833443
C	-3.752562	1.136301	-2.017899
H	-4.202822	1.740143	-2.811320
H	-4.438910	0.321449	-1.776165
H	-3.631382	1.763848	-1.129254
O	-2.299762	-3.500854	1.904865
C	-3.423145	-3.716073	2.792721
H	-4.117318	-4.419469	2.317400
C	-4.136612	-2.396267	3.066712
H	-3.446148	-1.682612	3.526146
H	-4.517403	-1.959301	2.139524
H	-4.982274	-2.556073	3.742515
C	-2.846842	-4.346886	4.048241
H	-3.645914	-4.571196	4.760446
H	-2.322880	-5.275445	3.807857
H	-2.140449	-3.659905	4.524275

TS4

C	-3.613162	-1.847890	-0.003794
C	-2.454200	-1.499298	0.731632
C	-2.490218	-0.354546	1.543692
C	-3.595918	0.493250	1.555928
C	-4.689364	0.210161	0.738353
C	-4.696322	-0.959982	-0.018085
C	-3.794785	-3.185409	-0.638719
C	-3.805525	-3.385462	-2.036798
C	-3.992110	-4.672778	-2.558450
C	-4.229035	-5.742609	-1.700070
C	-4.306708	-5.554948	-0.324444
C	-4.104431	-4.274941	0.193003
P	-0.897025	-2.477397	0.604090
H	-1.647974	-0.123308	2.183935
H	-3.594972	1.372766	2.192140
H	-5.544856	0.878203	0.713495

H	-5.566566	-1.220364	-0.611376
O	-3.662485	-2.269484	-2.798001
H	-3.932309	-4.849816	-3.622090
H	-4.352210	-6.735196	-2.117937
H	-4.514127	-6.383226	0.343397
Pd	-0.629947	-3.482470	-1.415361
C	-0.228833	-1.692121	-2.247028
C	1.059127	-1.568294	-2.797125
C	-1.081562	-0.583819	-2.309538
C	1.484895	-0.371401	-3.380933
H	1.744280	-2.412172	-2.767074
C	-0.658970	0.614575	-2.894941
H	-2.082326	-0.648389	-1.903574
C	0.626313	0.730220	-3.425803
H	2.487447	-0.299600	-3.795580
H	-1.339532	1.461809	-2.930229
H	0.956295	1.664695	-3.870643
C	-3.875222	-2.354854	-4.228727
H	-3.308858	-3.209282	-4.606887
C	1.825586	-4.921344	-4.748816
C	1.058354	-6.029984	-2.546511
C	1.613972	-7.364549	-3.049054
C	2.800224	-7.131015	-3.997739
C	2.360494	-6.286394	-5.202128
H	2.660041	-4.287398	-4.417419
H	1.300052	-4.397064	-5.550235
H	0.832773	-7.907966	-3.589605
H	1.904424	-7.979496	-2.190957
H	3.200172	-8.091946	-4.338226
H	3.613329	-6.618772	-3.464724
H	1.571373	-6.819242	-5.746911
H	3.192460	-6.132691	-5.897398
H	1.704223	-5.627060	-1.755297
N	0.893562	-5.078564	-3.644235
C	-0.404600	-4.688186	-3.557495
C	-0.428377	-5.977281	-2.053936
O	-1.096353	-4.152335	-4.409081
O	-0.638579	-5.554763	-0.832389
C	-1.348355	-7.097450	-2.493091
C	-1.764665	-7.317176	-3.811917
C	-1.797655	-7.968716	-1.490732
C	-2.618062	-8.379013	-4.117284
H	-1.459468	-6.637829	-4.598832
C	-2.637847	-9.036968	-1.796551
H	-1.491929	-7.777266	-0.468838
C	-3.057101	-9.243962	-3.113147
H	-2.946109	-8.524361	-5.142438
H	-2.974646	-9.702106	-1.006481
H	-3.722644	-10.067717	-3.353587
C	-1.062736	-3.795416	1.916577
C	0.190339	-4.672831	2.088508
C	-1.559667	-3.274688	3.273657
H	-1.846710	-4.430120	1.492601
C	-0.115226	-5.855167	3.017519
H	0.994144	-4.082699	2.544074
H	0.528500	-5.030607	1.113721
C	-1.830932	-4.452995	4.221195
H	-0.804628	-2.611709	3.718864
H	-2.473918	-2.692763	3.141750
C	-0.610316	-5.365342	4.383161
H	0.780819	-6.476154	3.133199
H	-0.882620	-6.488746	2.552235
H	-2.166999	-4.078767	5.195605
H	-2.655721	-5.040998	3.801296

H	-0.855346	-6.214265	5.032268
H	0.197939	-4.810306	4.880167
C	0.518846	-1.366529	1.129519
C	1.864149	-2.040701	0.770096
C	0.538249	0.059159	0.537804
H	0.446314	-1.293899	2.224438
C	3.047742	-1.248222	1.342855
H	1.938524	-2.077233	-0.321528
H	1.908282	-3.070955	1.120435
C	1.693811	0.871276	1.138688
H	0.676605	-0.011433	-0.541165
H	-0.404752	0.583192	0.691818
C	3.043775	0.204319	0.854207
H	3.985959	-1.743166	1.065970
H	2.995476	-1.265425	2.440666
H	1.676604	1.886671	0.726238
H	1.552422	0.968703	2.224734
H	3.860496	0.768172	1.319827
H	3.222681	0.218099	-0.229542
O	-4.222787	-4.028164	1.546156
C	-5.517918	-4.312580	2.134864
H	-5.683845	-5.397990	2.100823
C	-5.428579	-3.854398	3.581847
H	-6.376144	-4.044868	4.094157
H	-4.634885	-4.379209	4.115573
H	-5.222224	-2.780147	3.620648
C	-6.643308	-3.605503	1.385057
H	-6.502169	-2.522011	1.427470
H	-6.678985	-3.911148	0.336601
H	-7.604635	-3.852662	1.845554
C	-3.288898	-1.084815	-4.822566
H	-2.217642	-1.028404	-4.630944
H	-3.459457	-1.072977	-5.903336
H	-3.766450	-0.200826	-4.387071
C	-5.367188	-2.493618	-4.522887
H	-5.531618	-2.571539	-5.602035
H	-5.793814	-3.380206	-4.048143
H	-5.903454	-1.612710	-4.155004

I6

C	-1.251701	-1.133863	0.771816
C	0.071760	-1.442307	1.165819
C	0.751109	-0.522579	1.987193
C	0.171005	0.674244	2.397260
C	-1.124001	0.985285	1.985771
C	-1.816858	0.084671	1.184677
C	-2.148731	-2.014981	-0.037392
C	-2.575239	-1.606039	-1.322499
C	-3.539253	-2.335939	-2.021889
C	-4.070724	-3.496152	-1.458827
C	-3.691160	-3.908135	-0.189289
C	-2.763267	-3.144431	0.526063
P	0.932719	-3.009858	0.672338
H	1.759839	-0.739507	2.313998
H	0.730400	1.356796	3.029611
H	-1.592475	1.916615	2.289028
H	-2.829160	0.312252	0.867509
O	-1.987255	-0.473009	-1.808129
H	-3.867083	-2.020761	-3.003023
H	-4.789889	-4.079911	-2.024036
H	-4.105150	-4.805402	0.254854
Pd	0.086532	-3.781326	-1.510516
C	1.340482	-2.562115	-2.474882
C	2.519140	-3.098977	-3.013927

C	1.095248	-1.191892	-2.607749
C	3.447691	-2.272148	-3.652421
H	2.714417	-4.165249	-2.942488
C	2.023206	-0.367346	-3.254809
H	0.193705	-0.764239	-2.187698
C	3.204478	-0.900838	-3.773946
H	4.360737	-2.701569	-4.057183
H	1.826033	0.698770	-3.338235
H	3.927180	-0.258349	-4.268404
C	-2.594911	0.243470	-2.904275
H	-2.803461	-0.459908	-3.719262
C	-2.891091	-4.841210	-4.536586
C	-0.858055	-3.918044	-3.434780
C	-0.062799	-4.077298	-4.731883
C	-0.986863	-4.014825	-5.964114
C	-2.152237	-5.007472	-5.868867
H	-3.369523	-3.857507	-4.481274
H	-3.648724	-5.612556	-4.388809
H	0.475634	-5.034308	-4.716690
H	0.689629	-3.292323	-4.806601
H	-0.410370	-4.194042	-6.879708
H	-1.393388	-2.996190	-6.042295
H	-1.774171	-6.036129	-5.927409
H	-2.852370	-4.873352	-6.701797
H	-1.362692	-2.946119	-3.441359
N	-1.927802	-4.934026	-3.438537
C	-1.799635	-6.106865	-2.797704
C	-0.660318	-6.204396	-1.789438
O	-2.519321	-7.103979	-2.934898
O	-0.878971	-5.847650	-0.613473
C	0.588137	-6.880916	-2.220068
C	1.728252	-6.809561	-1.402309
C	0.673697	-7.506166	-3.473577
C	2.938683	-7.331670	-1.843563
H	1.655929	-6.317493	-0.442383
C	1.885665	-8.042718	-3.905160
H	-0.210856	-7.588365	-4.095075
C	3.020719	-7.947761	-3.097442
H	3.819812	-7.257233	-1.213708
H	1.944569	-8.531113	-4.872606
H	3.966603	-8.355175	-3.441074
C	0.639150	-4.062483	2.217061
C	0.900283	-5.566024	2.022284
C	1.343602	-3.556419	3.488107
H	-0.439065	-3.940294	2.349606
C	0.449330	-6.361864	3.255611
H	1.971135	-5.748703	1.868662
H	0.369724	-5.918914	1.139244
C	0.905642	-4.358555	4.724088
H	2.430249	-3.662304	3.377559
H	1.137650	-2.494687	3.650787
C	1.133646	-5.861969	4.532166
H	0.655258	-7.427777	3.102372
H	-0.639514	-6.265814	3.362266
H	1.448679	-3.998149	5.605952
H	-0.158836	-4.175951	4.914067
H	0.772223	-6.416472	5.406213
H	2.213294	-6.056066	4.459774
C	2.762027	-2.594541	0.777967
C	3.589613	-3.820721	0.340895
C	3.224782	-1.348227	0.002347
H	2.973359	-2.418389	1.839246
C	5.093064	-3.572391	0.528465
H	3.377409	-4.032259	-0.711579

H	3.297522	-4.708390	0.906962
C	4.719159	-1.092194	0.238047
H	3.063878	-1.500542	-1.061051
H	2.639602	-0.470309	0.284708
C	5.554860	-2.302432	-0.195136
H	5.656272	-4.443498	0.172851
H	5.308530	-3.475843	1.602100
H	5.027678	-0.198730	-0.317232
H	4.900061	-0.882766	1.302486
H	6.620398	-2.124128	-0.008225
H	5.437724	-2.441640	-1.277919
C	-1.549275	1.243141	-3.376016
H	-0.663362	0.729727	-3.754627
H	-1.961368	1.863284	-4.177039
H	-1.250810	1.895039	-2.549157
C	-3.882829	0.917114	-2.439370
H	-4.350303	1.454833	-3.269548
H	-4.600187	0.187301	-2.056651
H	-3.658174	1.633644	-1.643133
O	-2.444945	-3.474555	1.822345
C	-3.545280	-3.480202	2.767006
H	-4.316858	-4.166712	2.396870
C	-4.133919	-2.080691	2.908891
H	-3.369209	-1.381668	3.259315
H	-4.517741	-1.718877	1.951209
H	-4.960042	-2.091329	3.626344
C	-2.976506	-4.013433	4.070062
H	-3.765160	-4.084639	4.824326
H	-2.540646	-5.005029	3.925483
H	-2.198377	-3.341666	4.444472

I7

C	-3.619481	-1.865014	-0.050508
C	-2.477686	-1.551813	0.725453
C	-2.532001	-0.433298	1.573210
C	-3.634041	0.418891	1.588437
C	-4.711003	0.166832	0.738670
C	-4.701952	-0.974984	-0.058771
C	-3.778258	-3.166079	-0.763901
C	-3.800960	-3.261423	-2.175076
C	-3.956263	-4.509867	-2.794521
C	-4.152390	-5.649225	-2.019957
C	-4.218519	-5.568063	-0.633810
C	-4.050058	-4.326731	-0.017599
P	-0.923996	-2.544328	0.583403
H	-1.702138	-0.226615	2.238028
H	-3.644154	1.278110	2.252076
H	-5.564273	0.837970	0.717391
H	-5.557767	-1.209073	-0.683088
O	-3.706736	-2.087472	-2.849746
H	-3.907915	-4.597774	-3.870069
H	-4.255959	-6.611186	-2.508810
H	-4.388483	-6.451424	-0.029738
Pd	-0.676662	-3.528251	-1.612528
C	-0.078069	-1.771052	-2.394398
C	1.248893	-1.630152	-2.829321
C	-0.915210	-0.650896	-2.435787
C	1.735210	-0.392465	-3.262027
H	1.916600	-2.487153	-2.825154
C	-0.433476	0.583880	-2.885294
H	-1.943691	-0.733682	-2.110939
C	0.894453	0.723065	-3.290903
H	2.770277	-0.303921	-3.582977
H	-1.101152	1.441854	-2.904047

H	1.269477	1.684748	-3.629088
C	-3.908009	-2.071069	-4.285942
H	-3.289254	-2.858755	-4.723850
C	1.303668	-5.194175	-4.976682
C	0.922882	-5.900625	-2.559305
C	1.735607	-7.178889	-2.850874
C	2.760054	-6.962349	-3.965437
C	2.026782	-6.511924	-5.229846
H	2.052541	-4.392563	-4.868459
H	0.653456	-4.921502	-5.808102
H	1.060915	-7.985941	-3.151424
H	2.215996	-7.491103	-1.917948
H	3.316131	-7.889205	-4.140925
H	3.490556	-6.198156	-3.667644
H	1.306831	-7.284868	-5.527931
H	2.722745	-6.376446	-6.064582
H	1.536923	-5.227867	-1.942102
N	0.461741	-5.228935	-3.771594
C	-0.463209	-4.181935	-3.593141
C	-0.314805	-6.249390	-1.714662
O	-0.980560	-3.680547	-4.586922
O	-0.460959	-5.739242	-0.592431
C	-1.285578	-7.282903	-2.171439
C	-1.560487	-7.550900	-3.522168
C	-1.956798	-8.010961	-1.175876
C	-2.493655	-8.527968	-3.863288
H	-1.070823	-6.967009	-4.290213
C	-2.873288	-8.999079	-1.520474
H	-1.746428	-7.784784	-0.137070
C	-3.147985	-9.256424	-2.866691
H	-2.714679	-8.716702	-4.909116
H	-3.379452	-9.563145	-0.743279
H	-3.871559	-10.019308	-3.137586
C	-1.073220	-3.797246	1.975343
C	0.241447	-4.549518	2.249824
C	-1.650086	-3.233490	3.283040
H	-1.793628	-4.516606	1.572179
C	0.020527	-5.681290	3.261023
H	0.975281	-3.855288	2.676176
H	0.651721	-4.942213	1.317630
C	-1.830379	-4.347057	4.325626
H	-0.975762	-2.463961	3.684559
H	-2.611714	-2.754542	3.089377
C	-0.538078	-5.130072	4.577646
H	0.963085	-6.213892	3.434819
H	-0.684111	-6.411515	2.839253
H	-2.216732	-3.923605	5.260527
H	-2.592061	-5.042200	3.955095
H	-0.719130	-5.942225	5.291746
H	0.210740	-4.467934	5.035048
C	0.486821	-1.417968	1.119015
C	1.833135	-2.065304	0.713839
C	0.474391	0.016119	0.550652
H	0.442595	-1.360568	2.216300
C	3.021118	-1.267234	1.268764
H	1.881456	-2.080414	-0.378875
H	1.901908	-3.101454	1.042505
C	1.637468	0.837093	1.124150
H	0.578032	-0.035655	-0.532573
H	-0.469172	0.526733	0.743710
C	2.987418	0.190206	0.796358
H	3.959109	-1.746578	0.963952
H	2.995676	-1.296874	2.367529
H	1.596743	1.856041	0.721470

H	1.526045	0.923673	2.214777
H	3.809596	0.759748	1.245734
H	3.135486	0.216716	-0.291677
O	-4.169438	-4.216524	1.353989
C	-5.487250	-4.525537	1.878725
H	-5.774139	-5.523382	1.521918
C	-5.358134	-4.550329	3.391783
H	-6.333090	-4.749892	3.845866
H	-4.662013	-5.327544	3.713171
H	-4.995897	-3.585171	3.758648
C	-6.517247	-3.508658	1.398746
H	-6.255527	-2.506106	1.747249
H	-6.571252	-3.490391	0.307159
H	-7.507222	-3.770981	1.784637
C	-3.393516	-0.725654	-4.771505
H	-2.322517	-0.634641	-4.592950
H	-3.582882	-0.627229	-5.844606
H	-3.908265	0.090493	-4.253356
C	-5.389095	-2.264070	-4.604908
H	-5.540399	-2.267340	-5.688742
H	-5.776158	-3.203514	-4.204005
H	-5.972041	-1.441203	-4.178343

BD1

C	-2.436801	-0.781432	-0.234953
C	-0.347951	0.412024	-0.761688
C	-1.045990	1.399516	-1.638583
C	-2.552974	1.471373	-1.353216
C	-3.130434	0.054448	-1.308198
H	-2.660912	-0.376181	0.760677
H	-2.768907	-1.818638	-0.246539
H	-0.905923	1.122131	-2.700310
H	-0.574736	2.380978	-1.519965
H	-3.055884	2.073967	-2.116473
H	-2.721354	1.961887	-0.386147
H	-3.002052	-0.429302	-2.285377
H	-4.204391	0.072209	-1.094883
H	0.724646	0.438561	-0.640064
N	-0.973804	-0.786258	-0.424772
C	-0.297182	-1.920411	0.009687
C	1.130254	-2.074913	-0.353319
O	-0.869345	-2.791140	0.676394
O	1.843484	-2.688847	0.626449
H	2.627427	-3.105820	0.240623
C	1.734939	-1.772327	-1.617526
C	3.147103	-1.757204	-1.757180
C	0.954876	-1.499039	-2.772342
C	3.741900	-1.491429	-2.984219
H	3.780970	-1.904915	-0.887512
C	1.561383	-1.233233	-3.991699
H	-0.125413	-1.525419	-2.701627
C	2.956489	-1.227342	-4.111115
H	4.824893	-1.475622	-3.060504
H	0.942337	-1.036946	-4.862013
H	3.424161	-1.016707	-5.067396

BD2

C	-1.923780	-0.932572	-0.701015
C	-0.968698	1.255502	0.083954
C	-2.094053	1.998137	-0.664712
C	-3.351660	1.132723	-0.799818
C	-3.019338	-0.202299	-1.474090
H	-2.290845	-1.212766	0.296682
H	-1.594933	-1.839480	-1.210264

H	-1.740661	2.296748	-1.655802
H	-2.313446	2.916952	-0.111712
H	-4.116748	1.671736	-1.368131
H	-3.772314	0.940485	0.196725
H	-2.677169	-0.026233	-2.501270
H	-3.905850	-0.843416	-1.529791
H	-1.322632	1.066432	1.106702
N	-0.734455	-0.071665	-0.541683
C	0.495309	-0.576198	-0.701350
C	0.283540	2.069033	0.232266
O	0.833662	-1.673937	-1.085261
O	0.629488	2.227621	1.544698
H	1.541697	2.545540	1.604043
C	1.044057	2.664468	-0.809720
C	2.029838	3.653417	-0.526265
C	0.878319	2.284749	-2.173550
C	2.798182	4.213332	-1.536579
H	2.158414	4.022139	0.487738
C	1.651650	2.857158	-3.172235
H	0.161828	1.515813	-2.431362
C	2.620377	3.822588	-2.869209
H	3.534526	4.971752	-1.287211
H	1.507500	2.539968	-4.200911
H	3.222991	4.263711	-3.656318

BD3

C	-2.027581	0.737052	1.192787
N	-0.581411	0.475520	1.096419
C	0.132403	1.163342	0.115848
C	-0.501488	1.399193	-1.219277
C	-1.993653	1.744224	-1.112472
C	-2.683518	0.738909	-0.186993
H	-2.461950	-0.029936	1.826982
H	1.206228	1.082315	0.213030
H	0.045857	2.187645	-1.748521
H	-2.615169	-0.270272	-0.614848
H	-0.404704	0.491246	-1.846371
H	-3.747729	0.975288	-0.072358
H	-2.172868	1.721341	1.663250
C	-0.606004	-1.098395	3.023150
O	-1.623881	-1.772066	2.573315
C	0.120589	-0.165162	2.129027
O	1.363301	-0.029997	2.196730
C	-0.018906	-1.421595	4.319032
C	-0.311858	-2.677508	4.911869
C	0.839699	-0.546775	5.035683
C	0.238638	-3.041991	6.137276
H	-0.911669	-3.385680	4.351892
C	1.378062	-0.917780	6.262508
H	1.085096	0.418250	4.607911
C	1.086469	-2.168322	6.829231
H	0.016576	-4.023074	6.550543
H	2.028708	-0.224674	6.790497
H	1.512484	-2.452611	7.786819
Cs	2.804902	-2.996553	2.594269
C	-0.072450	-4.907072	2.191578
O	0.014298	-3.687636	1.490640
O	1.003781	-5.536468	2.248328
O	-1.200456	-5.190775	2.674534
Cs	-3.787127	-3.806402	2.962271
H	-2.108473	2.753039	-0.694792
H	-2.456424	1.748811	-2.105337
H	-0.746533	-3.123342	1.754452

BD4

C	-1.418237	-0.348907	0.445484
N	-0.101652	0.104073	-0.044284
C	0.365273	1.439225	0.427607
C	-0.730936	2.492009	0.172609
C	-2.095955	2.056331	0.718259
C	-2.494405	0.692487	0.144575
H	-1.630180	-1.307673	-0.030825
H	0.494194	1.351746	1.514356
H	-0.406158	3.423722	0.648224
H	-2.625193	0.769221	-0.942064
H	-0.808302	2.692727	-0.900150
H	-3.447543	0.352662	0.565151
H	-1.349814	-0.512179	1.530466
C	1.742319	1.838011	-0.094107
O	2.642628	2.064121	0.814841
C	0.699750	-0.734318	-0.692618
O	0.516878	-1.881222	-1.063733
C	2.028507	1.947410	-1.492612
C	3.358316	2.291906	-1.907725
C	1.094015	1.665619	-2.544377
C	3.712616	2.349175	-3.246024
H	4.111381	2.448890	-1.145341
C	1.466783	1.728126	-3.881337
H	0.077497	1.380491	-2.304358
C	2.775967	2.069275	-4.260599
H	4.737154	2.602062	-3.511327
H	0.725287	1.505758	-4.645876
H	3.056683	2.119049	-5.308227
Cs	3.733691	-1.553910	-2.244693
C	5.658601	0.421527	-0.142315
O	4.381300	0.037397	0.295258
O	6.250160	-0.448881	-0.816844
O	6.038307	1.578564	0.181160
Cs	4.904040	3.804802	1.719913
H	-2.045923	1.984632	1.813764
H	-2.857260	2.808463	0.483861
H	3.876125	0.838837	0.578816

BD5

C	-4.606268	-3.945805	3.584817
C	-3.754043	-4.664889	4.455371
C	-3.642199	-4.249765	5.792689
C	-4.325428	-3.131077	6.264686
C	-5.134703	-2.400384	5.395078
C	-5.270812	-2.811827	4.071378
C	-4.875613	-4.350350	2.171459
C	-4.343524	-3.612136	1.089405
C	-4.636026	-3.972957	-0.229852
C	-5.478238	-5.054578	-0.478829
C	-6.054302	-5.770115	0.565539
C	-5.760779	-5.403199	1.882866
P	-2.815160	-6.131309	3.855612
H	-3.009089	-4.802499	6.477356
H	-4.219518	-2.830600	7.302464
H	-5.663063	-1.519261	5.746023
H	-5.910520	-2.256620	3.393025
O	-3.547788	-2.559110	1.432494
H	-4.180182	-3.448992	-1.058467
H	-5.679724	-5.342882	-1.505274
H	-6.717462	-6.605754	0.373262
Pd	-2.473410	-6.152795	1.572696
C	-0.667382	-5.281163	1.621163
C	0.475822	-6.002949	1.267725

C	-0.564732	-3.918738	1.920928
C	1.719589	-5.361367	1.219294
H	0.408376	-7.056075	1.020380
C	0.678240	-3.280720	1.856722
H	-1.447950	-3.360290	2.208244
C	1.824580	-3.999939	1.510915
H	2.604829	-5.931565	0.949680
H	0.751864	-2.221419	2.090156
H	2.790199	-3.504518	1.471017
C	-3.241569	-1.546789	0.445722
H	-2.837277	-2.038293	-0.446775
C	-0.968897	-4.339362	-4.029744
C	-1.129991	-4.036652	-1.599073
C	-0.227022	-2.841779	-1.633482
C	-0.156672	-2.185880	-3.017083
C	0.113209	-3.262211	-4.071108
H	-1.934862	-3.902817	-4.319810
H	-0.750564	-5.161760	-4.707932
H	0.792284	-3.152500	-1.338474
H	-0.544212	-2.126444	-0.869521
H	0.620102	-1.413961	-3.037189
H	-1.112364	-1.692575	-3.239837
H	1.090882	-3.725180	-3.884746
H	0.143458	-2.833438	-5.078851
H	-1.435202	-4.453806	-0.655817
N	-1.114588	-4.917666	-2.680492
C	-1.245310	-6.300244	-2.598143
C	-1.560358	-6.930077	-1.278075
O	-1.138294	-7.010234	-3.611308
O	-2.441931	-6.367177	-0.527304
C	-0.954611	-8.208474	-0.925736
C	-1.468835	-8.936014	0.172050
C	0.190189	-8.721550	-1.579118
C	-0.851261	-10.098507	0.618695
H	-2.359390	-8.573099	0.669985
C	0.804238	-9.882969	-1.125817
H	0.589793	-8.196057	-2.437251
C	0.297033	-10.577203	-0.019690
H	-1.269411	-10.635783	1.465816
H	1.690412	-10.251227	-1.634953
H	0.785760	-11.480680	0.332042
C	-3.946029	-7.556337	4.325789
C	-3.796483	-8.766763	3.386558
C	-3.888561	-7.972417	5.803862
H	-4.935326	-7.132334	4.136784
C	-4.845470	-9.839693	3.708044
H	-2.791893	-9.198871	3.469399
H	-3.910080	-8.439464	2.347013
C	-4.951659	-9.039683	6.105853
H	-2.900428	-8.382239	6.047329
H	-4.043080	-7.100227	6.449071
C	-4.797565	-10.255157	5.183368
H	-4.697490	-10.710138	3.058704
H	-5.841519	-9.438721	3.476760
H	-4.882946	-9.344600	7.156551
H	-5.949273	-8.602319	5.967222
H	-5.577525	-10.995343	5.395625
H	-3.834777	-10.743707	5.389461
C	-1.340396	-6.297469	4.983980
C	-0.510806	-7.520676	4.542867
C	-0.450381	-5.044989	5.071209
H	-1.735141	-6.501451	5.987085
C	0.694099	-7.743288	5.467068
H	-0.162038	-7.355322	3.518533

H	-1.131352	-8.421303	4.524674
C	0.733053	-5.282301	6.018879
H	-0.064496	-4.807931	4.079929
H	-1.033095	-4.178598	5.396824
C	1.565548	-6.486308	5.564044
H	1.282569	-8.592834	5.101965
H	0.336520	-8.014703	6.470516
H	1.354558	-4.380363	6.059470
H	0.363110	-5.458327	7.039266
H	2.404410	-6.655312	6.249044
H	1.996188	-6.269330	4.576917
C	-2.162244	-0.677121	1.071647
H	-1.263951	-1.259869	1.280419
H	-1.896421	0.135234	0.389355
H	-2.523475	-0.241296	2.008226
C	-4.493865	-0.746199	0.098645
H	-4.255278	0.015659	-0.649421
H	-5.283128	-1.384436	-0.304296
H	-4.875336	-0.245772	0.994359
O	-6.317714	-6.079785	2.943025
C	-7.762573	-6.085373	3.041727
H	-8.175505	-6.484128	2.106307
C	-8.286094	-4.671997	3.269741
H	-7.868507	-4.257535	4.191893
H	-8.010444	-4.014627	2.440437
H	-9.377390	-4.682543	3.348259
C	-8.089190	-7.030557	4.186440
H	-9.171852	-7.100669	4.323238
H	-7.697715	-8.031283	3.986327
H	-7.643920	-6.662841	5.116346

BD6

C	-4.545603	-7.100705	2.687992
C	-3.358613	-6.443356	3.093904
C	-3.470793	-5.146808	3.627468
C	-4.708368	-4.529679	3.797341
C	-5.874779	-5.200479	3.436072
C	-5.782064	-6.474993	2.882489
C	-4.532956	-8.433723	2.023668
C	-4.246357	-8.533909	0.648966
C	-4.130215	-9.794528	0.042665
C	-4.380060	-10.936339	0.800099
C	-4.768955	-10.858094	2.137431
C	-4.859461	-9.597437	2.740720
P	-1.686156	-7.179635	2.810596
H	-2.585660	-4.592957	3.907681
H	-4.754128	-3.527459	4.212125
H	-6.845202	-4.732302	3.569173
H	-6.678592	-7.003990	2.574775
O	-4.116078	-7.353981	-0.008382
H	-3.872520	-9.879909	-1.003568
H	-4.295875	-11.911594	0.329916
H	-4.995671	-11.759976	2.690818
Pd	-0.934976	-7.361159	0.625682
C	-0.690245	-5.355388	0.487438
C	0.584825	-4.846512	0.211347
C	-1.756046	-4.467504	0.667258
C	0.790281	-3.466180	0.116887
H	1.421132	-5.522911	0.065730
C	-1.548574	-3.088035	0.567049
H	-2.750789	-4.844315	0.877194
C	-0.276542	-2.582818	0.294028
H	1.785505	-3.084181	-0.098181
H	-2.387393	-2.409458	0.700008

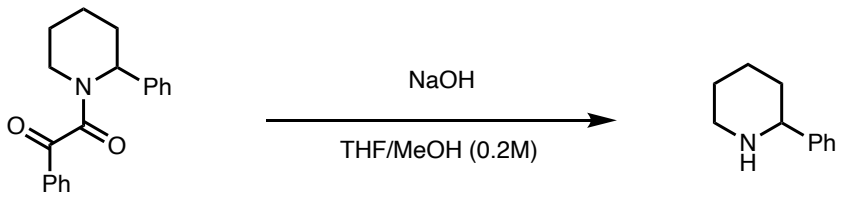
H	-0.117821	-1.511130	0.217104
C	-4.226461	-7.318157	-1.455939
H	-3.504520	-8.020156	-1.876945
C	1.425460	-4.189058	-3.674384
C	1.041591	-6.532003	-2.888855
C	1.829015	-7.063832	-4.101163
C	2.867114	-6.042419	-4.581224
C	2.202897	-4.695361	-4.887565
H	2.113185	-3.961577	-2.846917
H	0.853842	-3.287356	-3.898221
H	1.136320	-7.301509	-4.914221
H	2.315633	-7.999897	-3.807607
H	3.389290	-6.422567	-5.465715
H	3.626439	-5.901993	-3.799633
H	1.511407	-4.806176	-5.731936
H	2.951134	-3.947760	-5.173473
H	1.754380	-6.376954	-2.068309
N	0.466196	-5.210365	-3.214175
C	-0.755728	-4.853002	-2.803011
C	0.028613	-7.521592	-2.331945
O	-1.320999	-3.787588	-2.894493
O	0.184562	-7.851569	-1.102410
C	-0.992713	-8.160295	-3.144054
C	-1.453730	-7.635075	-4.374744
C	-1.573461	-9.367307	-2.683103
C	-2.456571	-8.279136	-5.092671
H	-1.048407	-6.702045	-4.746238
C	-2.554501	-10.018266	-3.420198
H	-1.227630	-9.777722	-1.741100
C	-3.015109	-9.474078	-4.626004
H	-2.808976	-7.843794	-6.023358
H	-2.969779	-10.953592	-3.054441
H	-3.793024	-9.975195	-5.193329
C	-5.641893	-7.679721	-1.895403
H	-5.699892	-7.658288	-2.987766
H	-5.933490	-8.677868	-1.560346
H	-6.357885	-6.955200	-1.494112
C	-3.835385	-5.910006	-1.858601
H	-4.521535	-5.179048	-1.418053
H	-2.822089	-5.682600	-1.533037
H	-3.870781	-5.814358	-2.946849
O	-5.218592	-9.394593	4.042701
C	-5.959023	-10.403487	4.758516
H	-5.416713	-11.355672	4.701664
C	-5.982101	-9.930562	6.204507
H	-6.482729	-8.960101	6.274289
H	-6.523608	-10.648208	6.827116
H	-4.967007	-9.826068	6.593918
C	-7.359222	-10.555793	4.171122
H	-7.895923	-9.604617	4.242824
H	-7.323004	-10.854638	3.120989
H	-7.920079	-11.314560	4.724908
C	-1.688353	-8.871888	3.595878
C	-0.316081	-9.557367	3.460688
C	-2.218407	-8.988746	5.034186
H	-2.374770	-9.422865	2.945650
C	-0.424671	-11.037224	3.851223
H	0.410304	-9.068072	4.119220
H	0.063763	-9.456969	2.436906
C	-2.320897	-10.469642	5.430062
H	-1.536342	-8.481432	5.723782
H	-3.194320	-8.507265	5.118369
C	-0.977587	-11.193828	5.273497
H	0.555803	-11.519703	3.766008

H	-1.092955	-11.545407	3.142370
H	-2.681429	-10.557753	6.461728
H	-3.067561	-10.954803	4.789171
H	-1.085860	-12.255169	5.525498
H	-0.255240	-10.772429	5.986621
C	-0.516337	-6.052117	3.725685
C	-0.674324	-5.917811	5.250844
C	0.965525	-6.317966	3.392785
H	-0.749339	-5.084839	3.261935
C	0.161572	-4.730572	5.754282
H	-0.312561	-6.835364	5.728585
H	-1.721127	-5.802954	5.543974
C	1.819866	-5.136669	3.870480
H	1.301439	-7.231580	3.895485
H	1.091363	-6.474351	2.319652
C	1.640980	-4.886782	5.374459
H	0.056861	-4.632288	6.841057
H	-0.233544	-3.804283	5.314100
H	2.875704	-5.322512	3.641223
H	1.526895	-4.241660	3.305454
H	2.207713	-4.001394	5.685059
H	2.060063	-5.738483	5.928486

H	0.853842	-3.287356	-3.898221
H	1.136320	-7.301509	-4.914221
H	2.315633	-7.999897	-3.807607
H	3.389290	-6.422567	-5.465715
H	3.626439	-5.901993	-3.799633
H	1.511407	-4.806176	-5.731936
H	2.951134	-3.947760	-5.173473
H	1.754380	-6.376954	-2.068309
N	0.466196	-5.210365	-3.214175
C	-0.755728	-4.853002	-2.803011
C	0.028613	-7.521592	-2.331945
O	-1.320999	-3.787588	-2.894493
O	0.184562	-7.851569	-1.102410
C	-0.992713	-8.160295	-3.144054
C	-1.453730	-7.635075	-4.374744
C	-1.573461	-9.367307	-2.683103
C	-2.456571	-8.279136	-5.092671
H	-1.048407	-6.702045	-4.746238
C	-2.554501	-10.018266	-3.420198
H	-1.227630	-9.777722	-1.741100
C	-3.015109	-9.474078	-4.626004
H	-2.808976	-7.843794	-6.023358
H	-2.969779	-10.953592	-3.054441
H	-3.793024	-9.975195	-5.193329
C	-5.641893	-7.679721	-1.895403
H	-5.699892	-7.658288	-2.987766
H	-5.933490	-8.677868	-1.560346
H	-6.357885	-6.955200	-1.494112
C	-3.835385	-5.910006	-1.858601
H	-4.521535	-5.179048	-1.418053
H	-2.822089	-5.682600	-1.533037
H	-3.870781	-5.814358	-2.946849
O	-5.218592	-9.394593	4.042701
C	-5.959023	-10.403487	4.758516
H	-5.416713	-11.355672	4.701664
C	-5.982101	-9.930562	6.204507
H	-6.482729	-8.960101	6.274289
H	-6.523608	-10.648208	6.827116
H	-4.967007	-9.826068	6.593918
C	-7.359222	-10.555793	4.171122
H	-7.895923	-9.604617	4.242824

H	-7.323004	-10.854638	3.120989
H	-7.920079	-11.314560	4.724908
C	-1.688353	-8.871888	3.595878
C	-0.316081	-9.557367	3.460688
C	-2.218407	-8.988746	5.034186
H	-2.374770	-9.422865	2.945650
C	-0.424671	-11.037224	3.851223
H	0.410304	-9.068072	4.119220
H	0.063763	-9.456969	2.436906
C	-2.320897	-10.469642	5.430062
H	-1.536342	-8.481432	5.723782
H	-3.194320	-8.507265	5.118369
C	-0.977587	-11.193828	5.273497
H	0.555803	-11.519703	3.766008
H	-1.092955	-11.545407	3.142370
H	-2.681429	-10.557753	6.461728
H	-3.067561	-10.954803	4.789171
H	-1.085860	-12.255169	5.525498
H	-0.255240	-10.772429	5.986621
C	-0.516337	-6.052117	3.725685
C	-0.674324	-5.917811	5.250844
C	0.965525	-6.317966	3.392785
H	-0.749339	-5.084839	3.261935
C	0.161572	-4.730572	5.754282
H	-0.312561	-6.835364	5.728585
H	-1.721127	-5.802954	5.543974
C	1.819866	-5.136669	3.870480
H	1.301439	-7.231580	3.895485
H	1.091363	-6.474351	2.319652
C	1.640980	-4.886782	5.374459
H	0.056861	-4.632288	6.841057
H	-0.233544	-3.804283	5.314100
H	2.875704	-5.322512	3.641223
H	1.526895	-4.241660	3.305454
H	2.207713	-4.001394	5.685059
H	2.060063	-5.738483	5.928486

2.4.21. Procedure for Directing Group Removal.



2.3a

2-phenylpiperidine : This procedure was adapted from a known procedure.[63] To a one-dram vial equipped with stir bar was added (±)-1-Phenyl-2-(2-phenylpiperidin-1-yl)ethane-1,2-dione (**2.3a**) (29.3mg, 0.1 mmol) and sodium hydroxide (16.0 mg, 0.4 mmol). A solution of 4:1 THF/MeOH (0.5 mL,0.2M) was added, and the resulting mixture was stirred at 80°C for 2 hours. The reaction mixture was cooled to room temperature and diluted with H2O (0.5 mL). The aqueous phase was extracted with EtOAc (~1.0 mL x 3). The combined organic layers were dried over MgSO4 and evaporated under reduced pressure to give 2-phenylpiperidine as a clear liquid (12 mg, 74%).

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2.6 Experimental Contributors

The work presented in this chapter was published in 2020: Roque, J. B.; Kuroda, Y.; Jurczyk, J.; Xu, L.-P.; Ham, J. S.; Göttemann, L. T.; Roberts, C. A.; Adpressa, D.; Saurí, J.; Joyce, L. A.; Musaev, D. G.; Yeung, C. S.; Sarpong, R. C–C Cleavage Approach to C–H Functionalization of Saturated Aza-Cycles. *ACS Catal.* **2020**, *10*, 2929–2941. The work has been reprinted with permission from the American Chemical Society. J.B.R discovered the cross-coupling reaction, and optimized the synthesis of **2.2** from ketoamide **2.1**. J.J. optimized the gram scale irradiation of **2.1** and the one-pot irradiation-cross-coupling protocol. Optimization studies were led by J.B.R with assistance from Y.K. and J.J. The scope of the reaction was investigated by J.B.R. with aid from J.J., Y.K., L.T.G., and C.A.R.. D.A., J.S., and L.A.J. helped with NMR studies. L.-P.X., and D.G.M performed the computational studies. D.G.M., C.S.Y., and R.S. directed the research.

Chapter 3. Synthesis of Bridged Bicyclic Amines by Intramolecular Amination of Remote C–H Bonds: Synergistic Activation by Light and Heat

The construction of complex aza-cycles is of interest to drug discovery due to the prevalence of nitrogen-containing heterocycles in pharmaceutical agents. Herein, we report an intramolecular C–H amination approach to afford value-added and complexity-enriched bridged bicyclic amines. Guided by density functional theory and nuclear magnetic resonance investigations, we determined the unique roles of light and heat activation in the bicyclization mechanism. We applied both light and heat activation in a synergistic fashion, achieving gram-scale bridged aza-cycle synthesis.

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3.1 Introduction

In drug discovery, the rapid synthesis of bioactive compounds is enabled by access to diverse arrays of building blocks.[1] General approaches toward complex aza-cycles would positively impact drug design, given the prevalence of nitrogen-containing heterocycles in pharmaceutical agents.[2] Bridged bicyclic amines can be difficult to synthesize but are of significant interest in drug discovery because they have a high sp^3 content, a parameter known to correlate with clinical success.[2c,3] Moreover, the incorporation of rigid bridged bicyclic amines into bioactive structures can reduce *in vivo* metabolism,[2b] provide access to unique substituent vectors,[2b,4] and favorably alter physicochemical properties.[2b] Currently, strategies to synthesize diverse bridged amines are limited. State-of-the-art methodologies typically target the related classes of spirocyclic or fused aza-cycles,[4a,5] or target specific ring types in the context of natural product total synthesis.[4,6] As a consequence, bridged aza-cycles remain underrepresented in medicinal chemistry optimization campaigns, not due to a lack of interest but because of the barrier to synthesizing these structures.

In this work, we report a general approach to saturated, medium-sized, bridged bicyclic nitrogen heterocycles (Fig. 3.1). Our work is motivated by Bode's bicyclic morpholine synthesis using olefin-amine and aldehyde starting materials.[7] We approached bridged amines in a conceptually distinct manner, relying instead on the construction of a new C–N bond using C–H functionalization onto an existing monocyclic amine.

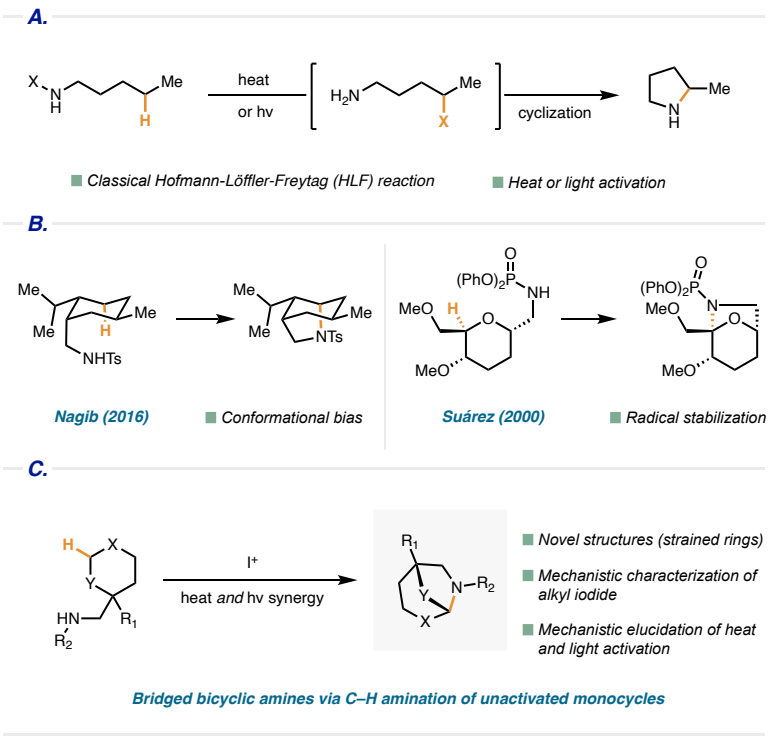


Figure 3.1. Approaches to bicyclic amine formation. (a) HLF Reaction toward Pyrrolidines, (b) Previous Work: Bridged Bicyclic Aza-Cycles Rely on Conformational Restriction or Radical Stabilizing Functional Groups, and (c) This Work: A Comprehensive Approach toward Bridged Bicyclic Pyrrolidines

To accomplish this goal, we drew inspiration from the Hofmann–Löffler–Freytag (HLF) reaction (Fig. 3.1A),[8] a common approach toward pyrrolidine synthesis.[8c] To our surprise, this robust transformation has rarely been used in crafting bridged systems, likely due to the increased ring strain of bicycles. As a consequence, conformational bias and/or radical stabilization is typically required for productive bridged aza-cycle formation (Fig. 3.1B).[8c] Herein we describe a broadly applicable method toward the syntheses of diverse complex bridged aza-cycles that does not rely on functionalization of activated C–H bonds or conformationally biased scaffolds (Fig. 3.1C). Our mechanistic studies highlight the importance of the activation method, revealing that heat and light accelerate different elementary steps in the C–H amination and are therefore synergistic. Ultimately, this work has led to the construction of numerous bridged aza-cycles containing diverse functionality on up to gram-scale.

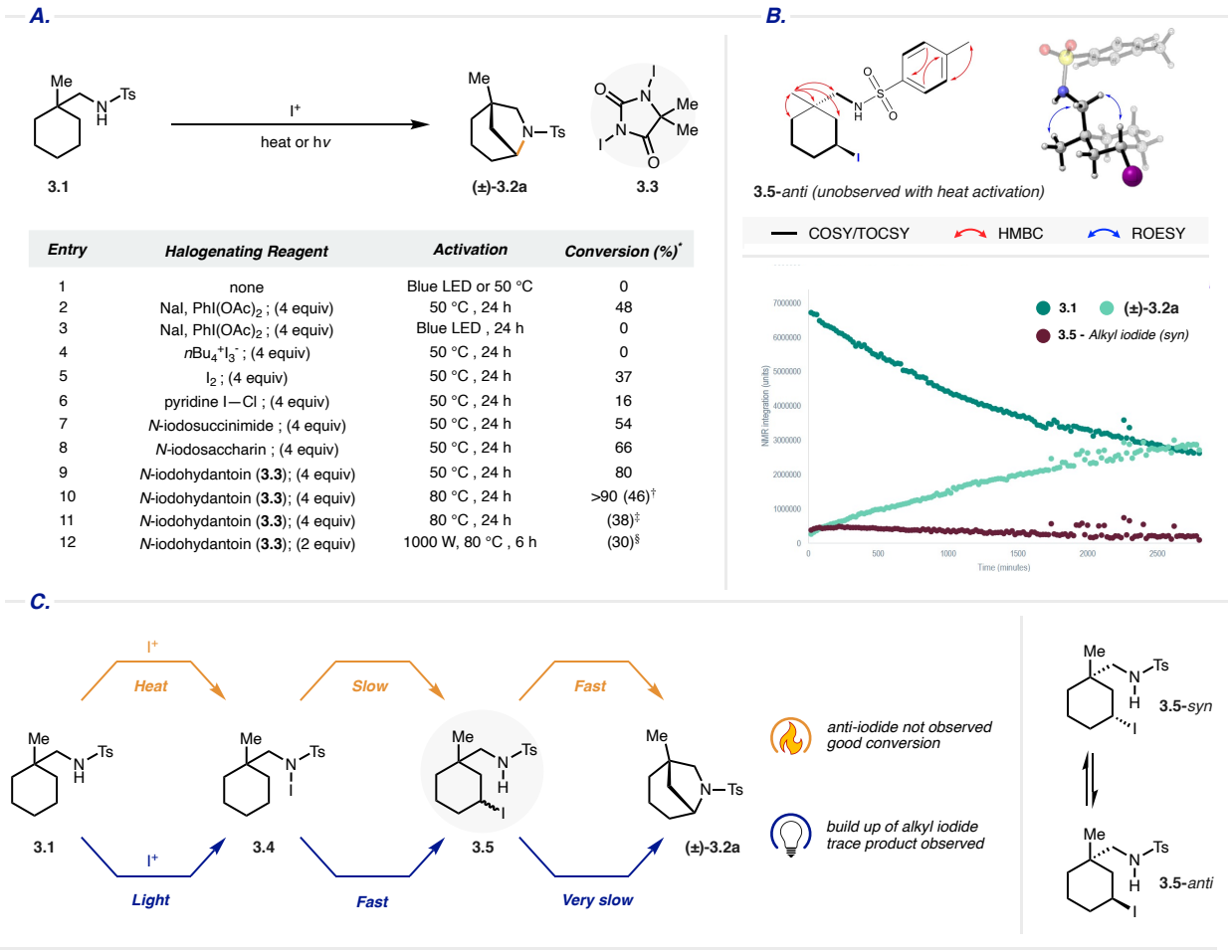
3.2 Results and Discussion

Synthesis of Bridged Bicyclic Amines

We initiated our investigations with monocyclic sulfonamide **3.1**, which would produce bridged bicyclic amine (±)-**3.2a** upon intramolecular C–H bond amination (Fig. 3.2A).[9] The modified Suárez conditions developed by Nagib[10] failed to provide the desired product using light activation (Fig. 3.2A, entry 3); instead, when we applied heat, we observed (±)-**3.2a** (entry 2). This observation is striking given that known HLF reactions proceed through *either* heat or light activation. Employing triiodide as the halogenating agent failed to yield the bicyclization product (entry 4), whereas I_2 produced (±)-**3.2a** in modest yield (entry 5), further distinguishing the mechanism from Nagib's report.[10] Using *N*-iodosuccinimide (entry 7), *N*-iodosaccharin (entry 8), or *N*-iodohydantoin (**3.3**, entry 9) as the halogenating agent afforded enhanced levels of product formation, as did raising the reaction temperature to 80 °C (entry 10). Other solvents were less effective, as were other halogenating reagents (Cl^+ or Br^+).

The observation that heat and light activation each led to disparate results prompted us to investigate the reaction mechanism. Whereas blue light-emitting diodes (LEDs) failed to promote the desired reaction (Fig. 3.2A, entry 3), Hg-lamp irradiation, which provides higher intensity and shorter wavelengths of light, produced alkyl iodide **3.5**, with only trace amounts of desired product (±)-**3.2a** (Fig. 3.2C). This experiment suggests that light-mediated N–I bond homolysis and hydrogen atom transfer (HAT) occur, but light alone is ineffective in promoting cyclization. In contrast, early quenching of the heat-mediated reaction (< 50% conversion) revealed the presence of both the alkyl iodide intermediate **3.5** and the product (±)-**3.2a**, indicating that elevated temperature promotes HAT and rapid cyclization. Next, carrying out the reaction at 70 °C, we observed only **3.5**-*syn* by *in situ* NMR (see Fig. 3.2B). In contrast, the Hg-lamp-promoted reaction produced an equimolar mixture of **3.5**-*syn* and **3.5**-*anti*.[11] Because we observe the buildup of alkyl iodide **3.5**-*syn* under thermal conditions, we speculate that rapid S_N2 cyclization of **3.5**-*anti* proceeds immediately upon its formation, precluding detection. We hypothesize that the halogenation of a carbon-centered radical occurs indiscriminately in both the light- and heat-mediated reactions to form both diastereomers of alkyl iodide **3.5**, but cyclization to (±)-**3.2a** effectively occurs only upon thermal activation. Furthermore, epimerization of the alkyl iodide intermediate takes place, likely via isodesmic exchange, which is consistent with our kinetic data[12] (see the Experimental Procedures). Comparing Hg-lamp irradiation with thermal activation in a head-to-head fashion, we observed that **3.5** was more quickly formed under Hg-lamp

irradiation. Accordingly, the synergistic application of heat and photoirradiation using a 1000 W LED flood lamp provided significant rate acceleration and a reduced loading of **3.3** in a gram-scale experiment (Fig. 3.2A, entry 12, light and heat, compared with entry 11, heat only), affording 600 mg of (±)-**3.2a** (2.1 mmol) in 6 h. For practical reasons, we used only heat activation for milligram-scale experiments.[13]



Entry	Halogenating Reagent	Activation	Conversion (%)*
1	none	Blue LED or 50 °C	0
2	NaI, $PhI(OAc)_2$; (4 equiv)	50 °C , 24 h	48
3	NaI, $PhI(OAc)_2$; (4 equiv)	Blue LED , 24 h	0
4	$nBu_4^+I_3^-$; (4 equiv)	50 °C , 24 h	0
5	I_2 ; (4 equiv)	50 °C , 24 h	37
6	pyridine I—Cl ; (4 equiv)	50 °C , 24 h	16
7	*N*-iodosuccinimide ; (4 equiv)	50 °C , 24 h	54
8	*N*-iodosaccharin ; (4 equiv)	50 °C , 24 h	66
9	*N*-iodohydantoin (**3.3**); (4 equiv)	50 °C , 24 h	80
10	*N*-iodohydantoin (**3.3**); (4 equiv)	80 °C , 24 h	>90 (46)†
11	*N*-iodohydantoin (**3.3**); (4 equiv)	80 °C , 24 h	(38)‡
12	*N*-iodohydantoin (**3.3**); (2 equiv)	1000 W, 80 °C , 6 h	(30)§

Figure 3.2. Reaction development and optimization. (A) Reaction optimization of the bridged bicyclization via intramolecular C–H bond amination. *Conditions: **3.1** (0.05 mmol), halogenating reagent (0.2 mmol), MeCN (1 mL). Conversion determined by LCMS. †Isolated yield on 0.2 mml scale. ‡Isolated yield on a 1 g (3.6 mmol) scale. §Isolated yield on a 2 g (7.2 mmol) scale. (B) In situ NMR analysis of the thermally promoted bicyclization, and key NMR data for the characterization of **3.5**-*anti.* (C) Mechanistic hypothesis for heat and light activation in the formation of bridged bicycles.

Given the effectiveness of the tosyl activating group, a range of substituted phenylsulfonyl groups on nitrogen were evaluated (Fig. 3.3A, *left*). Phenylsulfonyl-protected amines featuring electron-withdrawing substituents, such as esters (**3.2b**), ketones (**3.2c**), and nitriles (**3.2d**), provided the desired bridged aza-cycle product, albeit in reduced yields compared to the tosyl substrate (**3.2a**). In contrast, sulfonamides bearing electron-donating substituents—including methoxy (**3.2g**), amide (**3.2h** and **3.2i**), and carbamate (**3.2j**)—were also competent substrates for bicyclization,

affording improved yields. We speculate that the increased yield of products such as **3.2g** stems from the increased nucleophilicity of the more electron-rich sulfonamide substrate, increasing the rate of nucleophilic displacement of the intermediate alkyl halide in the S_N2 elementary step.

Next, we examined monocyclic amine starting materials that contained diverse backbone functionality, including substrates bearing different functional groups, heteroatoms, linker lengths, and ring sizes (Fig 3.3A). An ester-bearing substrate underwent cyclization to afford **3.2k**, a bicyclic γ-aminobutyric acid (GABA). When benzannulated and heterocyclic sulfonamides were subjected to the reaction conditions, we obtained bicyclic tetrahydronaphthalene **3.2l**, tetrahydroisoquinoline **3.2m**, and tetrahydropyrans **3.2n–q**. Of note, bicyclic *N*,*O*-aminals would be challenging to access using alternative strategies.[14] Additionally, a tertiary aliphatic fluoride remained intact in the amination (see **3.2p**), and a tetrahydropyran-containing bicyclic α-amino acid could be accessed (**3.2q**), albeit as a mixture of diastereomers (3:1 d.r.), presumably resulting from epimerization at the ester-bearing stereocenter. Given the observation that a *N*- or an *O*- atom could enhance isolated yields,[15] we found the HAT barrier for **3.1** (**TS-1**) was 4.6 kcal•mol^{-1} higher in energy than that for **3.7** (**TS-1**) (see Fig. 3.3B; density functional theory (DFT); see the Experimental Procedures for more details), which can potentially explain this effect. Moreover, it is also feasible that neighboring heteroatoms may promote an S_N1 pathway through an oxonium or iminium intermediate.

The conditions identified for amination onto six-membered rings were readily extended to five-, seven-, and eight-membered rings (Fig. 3.3A, *right*). Cyclopentane-derived substrates were readily converted to the corresponding bicyclic amine products **3.6a** and **3.6b** in synthetically useful yields, and cycloheptane- and cyclooctane-derived substrates underwent bicyclization to afford **3.6c** and **3.6d**, respectively. It is worth noting that precursor cyclobutanes were unproductive in the bicyclization (not shown). Transannular C–H bond amination efforts (without the methylene linker) also effectively provided bicyclic amines **3.6e**–**i**. Whereas amines directly attached to a cycloheptane underwent rapid bicyclization, substrates bearing smaller rings, including cyclohexanes, did not react efficiently (not shown). Bicyclization also proceeded smoothly for substrates bearing ester (**3.6f**) or nitrile (**3.6g**) functionalities in place of the quaternary methyl, forming bicyclic α-amino acid and α-amino nitrile derivatives, respectively. To our delight, amide- and oxepane-derived sulfonamides were likewise competent substrates for the transannular bicyclization, forming **3.6h** and **3.6i** respectively.

We then explored systems with preinstalled chiral information (see Fig. 3.3C). When we employed chiral monocyclic sulfonamide (*S*)-**3.8** as a substrate, we observed only one diastereomer of the anticipated product ((1R,5S,7S)-**3.9**, Fig, 3.3C, *left*). This observation highlights the utility of our strategy toward enantioenriched bridged bicyclic amines given that the stereochemistry of the starting material is fully translated to the product. Using DFT, we found that the 1,5-HAT transition structure *en route* to (1R,5S,7S)-**3.9** (**TS-3**) is 3.1 kcal mol^{-1} lower in energy than the transition state leading to the alternative diastereomer (**TS-4**) due to steric hinderance between the methyl group and the cyclohexane ring (see the Experimental Procedures for more details). Finally, the removal of the tosyl activating group on **3.2a** was successful upon treatment with hydrobromic acid and phenol, affording the corresponding N–H azacycle as a hydrobromide salt on a 500 mg scale (*not shown*; see the Experimental Procedures for details).

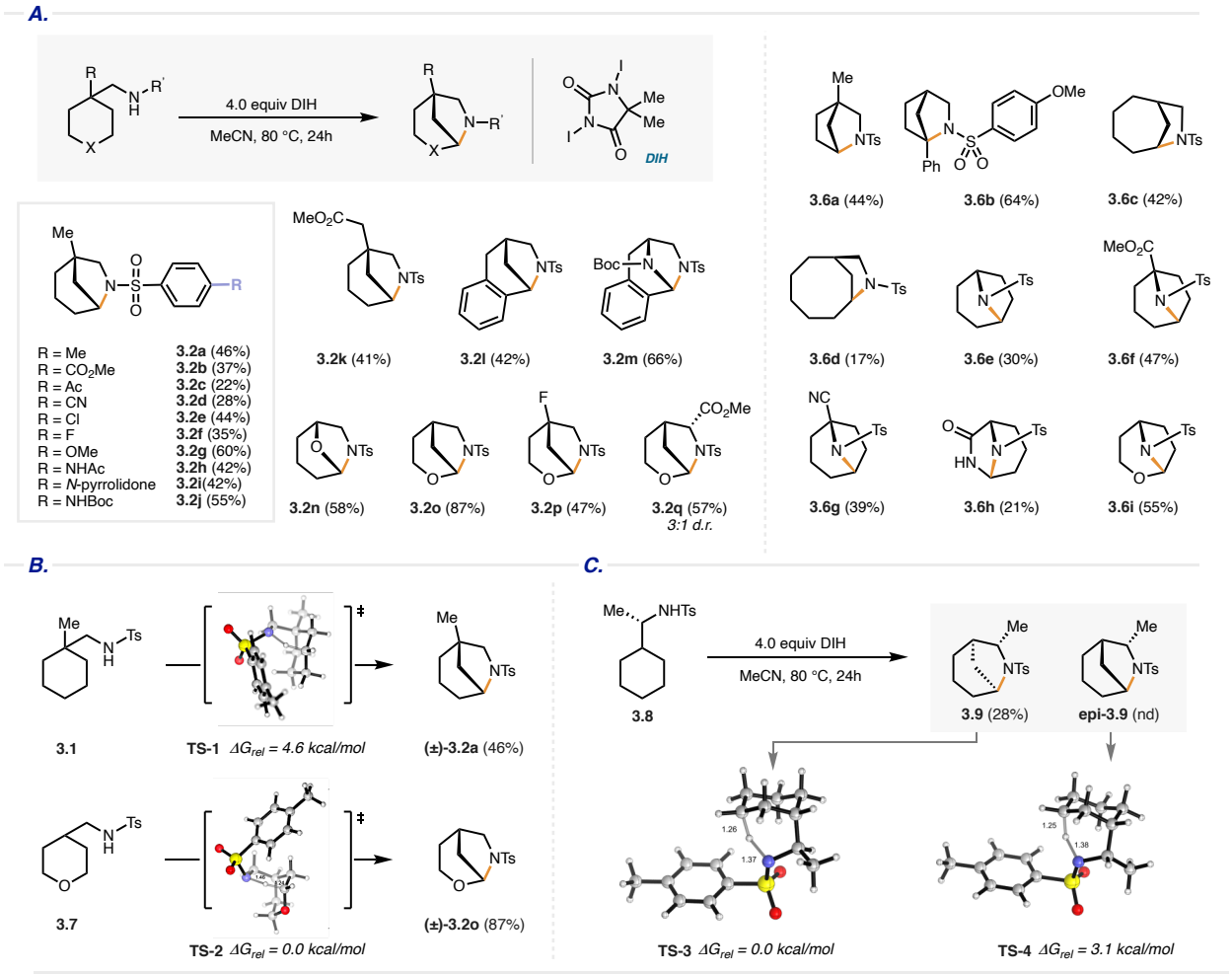


Figure 3.3. Scope of amines in bridged bicyclization. (A) Substrate scope of bridged six-, seven-, eight-, and nine-membered bicyclic amines from insertions into five-, six- seven-, and eight-membered rings. General reaction conditions: starting material (0.2 mmol), *N*-iodohydantoin (0.8 mmol), MeCN (4 mL), 24 h, 80 ºC. Isolated yields reported. Reported d.r. was determined by ^{1}H NMR analysis of the crude product. (B) 1,5-HAT transition states for carbocycle **3.1** and heterocycle **3.7**. (C) Observed chirality transfer in the C–N bicyclization of **3.8**.

Unified Approach to the Synthesis of Fused and Spirocyclic Amines

Having demonstrated a robust protocol toward bridged aza-cycles, we sought to expand the scope of our C–H amination to the construction of fused and spirocyclic bicyclic amines. Given the value of a unified approach to complex amine synthesis and the known preference for pyrrolidine formation in HLF reactions, we envisaged that by manipulating the alkyl chain length between the sulfonamide and the carbocycle, we could bias the reaction toward formation of the desired fused and spirocyclic architectures. We demonstrate that a two-carbon linker between the nitrogen atom and the monocycle affords a fused bicycle (Fig. 3.4A), and a three-carbon linker affords a spirocycle (Fig. 3.4B).

Applying our aforementioned optimized reaction conditions, a variety of differentially substituted 5,5-fused amine bicycles were readily formed in synthetically useful yields (Fig. 3.4A, **3.11a–d**). Moreover, 5,7-fused **3.11e** could be synthesized under this manifold. These examples are noteworthy, because hydrogenation approaches, which are commonly employed for highly saturated fused ring systems, would be ineffective for synthesizing these substrates. Next, racemic amino acid derivative (±)-**3.10f** was converted to a mixture of diastereomeric products (**3.11f**).

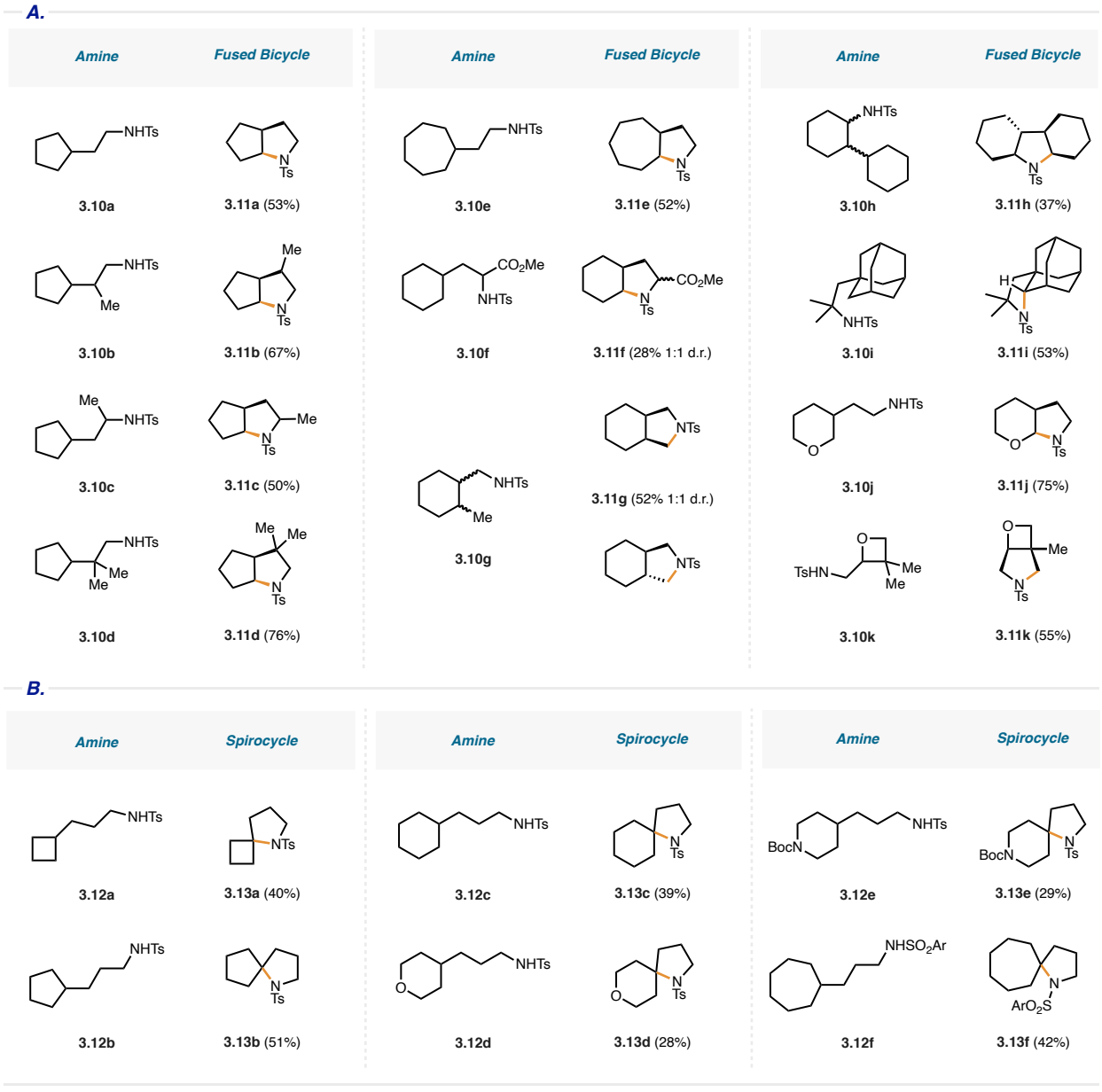


Figure 3.4. Unified approach for bicyclic amine formation. (A) Substrate scope of fused bicyclic amine synthesis.(B) Substrate scope of spirocyclic amine synthesis. Reaction conditions: starting material (0.2 mmol), *N*-iodohydantoin (0.8 mmol), MeCN (4 mL), 24 h, 80 °C. Isolated yields reported.

Additionally, sulfonamide **3.10h** (subjected as a 1:1 mixture of cis/trans isomers) afforded tricyclic motif **3.11h** as a single stereoisomer and adamantane derivative **3.10i** inserted into the axial position exclusively to afford tetracyclic motif **3.11i**. In a related system, **3.10g** (which is an 1:1 mixture of cis/trans isomers) gave a roughly 1:1 ratio of cis and trans products **3.11g** through a rare primary C–H activation.[10,16,17]

Heterocyclic substrates also undergo cyclization, including tetrahydropyran **3.10j**, resulting in a high yield of fused-ring product **3.11j**. In this case where two possible 1,5-HAT steps could result in different products, C–H activation occurs adjacent to the heteroatom, in line with our previous observation regarding *N,O*-aminal formation. Next, subjecting oxetane **3.10k**, which features two exocyclic methyl groups, led to the generation of a fused 4,5-bicycle **3.11k**. In this case, primary C–H bond activation occurs rather than insertion α-to the oxygen. We reason that this is likely due to high strain energy required in the 1,5-HAT due to a contorted four-membered ring. Finally, a variety of monocyclic propyl-linked sulfonamides were explored as precursors to spirocyclic amine products. Under the same reaction conditions employed for the synthesis of bridged and fused bicyclic amines, we observed that insertions into 4-, 5-, 6-, and 7-membered carbocyclic and heterocyclic rings resulted in the generation of spirocyclic products **3.13a–f** (Fig. 3.4B).

Unique Reactivity of N-Tosyl Leelamine

Leelamine is a naturally occurring diterpene alkaloid with a rigid carbocyclic skeleton suitable for further evaluating our intramolecular C–H amination chemistry. In contrast to our model system (**3.2a**), which exists as a mixture of axial and equatorial conformers, *N*-tosyl leelamine (**3.14a**) exhibits a much higher degree of rigidity due to the presence of the nearby 6,6-ring junction. Given the propensity for 1,5-HAT in this reaction, we expected C–H activation to occur at either of the anticipated methylene C–H bonds (Fig. 3.5A). To our surprise, when we subjected *N*-tosyl leelamine (**3.14a**) to our optimized conditions, we observed two new products — fused azetidine **3.15a** and rearranged bridged bicyclic amine **3.15b**. With the observation that **3.14a** affords azetidine **3.15a**, it would appear that an initial 1,4-HAT process might be at play.[18–20] However, this 1,4-HAT step is predicted to be less favourable than the usual 1,5-HAT process by about 3 kcal/mol. Therefore, we propose that radical generation resulting from 1,5-HAT results in the production of an alkyl iodide (**3.14d**). Because of the rigidity of the scaffold and the vicinity of the apical methyl group, we reason that iodination occurs from the alpha face. However, since S_N2 requires an anti-periplanar geometry, no productive cyclization occurs. Instead, we speculate that secondary alkyl iodide **3.14d** undergoes ionization to afford carbocation **3.14e**, followed by a 1,2-hydride shift, generating a tertiary carbocation (**3.14f**). At this point, direct trapping of **3.14f** by the sulfonamide nitrogen would afford azetidine **3.15a**. Alternatively, **3.14f** can undergo a 1,2-methyl shift to form an alternative tertiary carbocation (not shown) which would result in the production of rearranged bridged pyrrolidine **3.15b**. Ultimately, this is a rare example of azetidine formation and skeletal rearrangement in this steroid-like framework.[21]

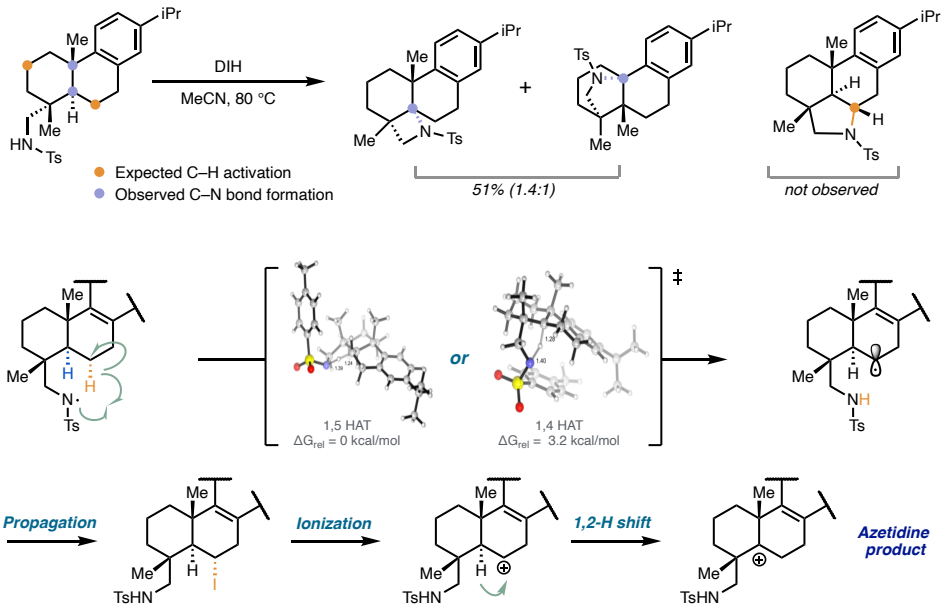


Figure 3.5. Bicyclic amine synthesis on *N*-tosyl leelamine. (A) Expected (*orange*) vs observed (*blue*) positions for C–H activation. (B) Mechanistic rationalization for observed selectivity.

3.3 Conclusion

In conclusion, we have developed a robust and functional-group-tolerant method for C–H bond amination based on HLF reactivity, providing a general approach to bridged bicyclic amines. These scaffolds are of interest to the medicinal chemistry and academic communities alike. Bridged bicyclic amines with rich functional group diversity have been prepared, and our reaction can be successfully carried out on a gram-scale. Informed by the elucidation of alkyl iodide intermediates, we deconvoluted the roles of light and heat activation, providing evidence that light promotes N–I bond homolysis and HAT, whereas heat promotes S_N2 ring closure. The expansion of this technology to fused and spirocyclic bicyclic amines has been explored as part of a unified strategy toward bicyclic amine formation. Gaining deeper understanding of the physicochemical properties and metabolic stabilities of bridged bicyclic amines, as well as further optimization of multigram-scale building block syntheses are the subjects of ongoing investigation and will be reported in due course.

3.4 Experimental Procedures

3.4.1. General Consideration

3.4.1.1. Solvents and Reagents

All reagents and solvents were purchased from commercial sources (Sigma-Aldrich, Alfa Aesar, Strem, Acros, Enamine, etc.) and used without further purification unless otherwise specified. Deuterated solvents were purchased from Cambridge Isotope Laboratories and used without further purification unless otherwise specified. $CDCl_3$ was treated with and stored over K_2CO_3.

3.4.1.2. Experimental Procedures

All reactions were performed in scintillation or microwave vials under a nitrogen atmosphere unless otherwise specified. Reactions were monitored by liquid chromatography/mass spectrometry (LCMS) or by thin layer chromatography (TLC) on Silica Gel 60 F_{254} plates (EMD) and visualized with UV light (254 nm). Flash chromatography was performed using pre-packed RediSep R_f silica gel columns on a Teledyne Isco CombiFlash R_f automated chromatography system. Organic solutions were concentrated under reduced pressure on a Heidolph rotary evaporator. Reversed-phase high-performance liquid chromatography was carried out using an Agilent 1100 HPLC-MSD system consisting of a 6130B single quadrupole mass-selective detector (MSD), G1315B diode array detector, G2258A autosampler, two G1361A preparative pumps, one G1379A quaternary pump with degasser, one G1312A binary pump, and three G1364B fraction collectors from Agilent Technologies. System control and data analysis was performed using Agilent's ChemStation software, revision B.03.01-SR.1. A Waters XBridge C18 OBD Prep Column, 100 Å, 5 μm, 19 mm × 150 mm column was used as the stationary phase (Waters Corporation). Gradient elution was carried out using water and acetonitrile as the mobile phase. An aqueous 10% trifluoroacetic acid or 10% ammonium hydroxide solution was teed into the mobile phase as a modifier using a static mixer prior to the column, pumped at 1% of the total mobile phase flow rate. ESI mass-triggered fraction collected was employed using positive ion polarity scanning to monitor for the target mass. Aqueous fractions were concentrated using a SP Industries, Inc. Genevac HT-12 Series 3i instrument. SFC purifications were performed with either a Waters ACQUITY UPC^2 system or a Sepiatec Prep SFC 100.

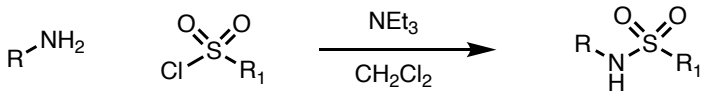
3.4.1.3. Analytical Instrumentation

Proton nuclear magnetic resonance (^{1}H NMR) spectra and proton-decoupled carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian 500 (500 MHz) NMR spectrometer at ambient temperature. All chemical shifts (δ) are reported in parts per million (ppm). Proton resonances are referenced to residual protium in the NMR solvent. Carbon resonances are referenced to the carbon resonances of the NMR solvent. Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (*J*) in Hertz (Hz), integration. Proton nuclear magnetic resonance (^{1}H NMR) spectra and proton-decoupled carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian 500 (500 MHz) NMR spectrometer at ambient temperature. All chemical shifts (δ) are reported in parts per million (ppm). Proton resonances are referenced to residual protium in the NMR solvent. Carbon resonances are referenced to the carbon resonances

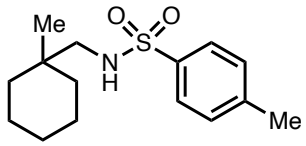
of the NMR solvent. Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (*J*) in Hertz (Hz), integration. LCMS samples were run on an Agilent 1100 or 1200 system. High-resolution mass spectrometry (HRMS) data were recorded on a Waters Xevo G2 QTof instrument in either ESI^+ or ESI^- (electrospray) ionization mode. Optical rotations were taken using a Perkin-Elmer 241 Polarimeter.

Abbreviations Used:
aq = aqueous, b.r.s.m. = based on recovered starting materials, calc'd = calculated, h = hours, min = minutes, s = seconds, rt = room temperature.

3.4.2. Experimental Procedures for Preparation of Starting Materials
Sulfonylation of Primary Amines

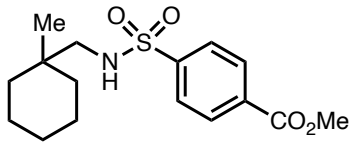


General Procedure A: To a 40 mL scintillation vial was added amine or ammonium salt (2–4 mmol), CH_2Cl_2 (20 mL, 0.1–0.2 M), triethylamine (1.2 equiv, with an additional 1 equiv per ammonium salt). To the resulting solution was added sulfonyl chloride (1 equiv), and the reaction mixture was stirred at rt until complete as determined by LCMS analysis. The reaction mixture was diluted with EtOAc, and then washed with sat'd NH_4Cl (aq). The layers were separated, and the organic layer was washed twice more with sat'd NH_4Cl (aq). Finally, the separated organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel to afford analytically pure product.



3.1

4-Methyl-*N*-((1-methylcyclohexyl)methyl)benzenesulfonamide (3.1): The material was synthesized according to general procedure A. 3.3 g, 82% yield. 0–25% EtOAc/hexanes. White solid.
^{1}H NMR (600 MHz, $CDCl_3$); δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 4.27 (s, 1H), 2.72 (d, *J* = 6.9 Hz, 2H), 2.43 (s, 3H), 1.49 – 1.35 (m, 5H), 1.24 (dt, *J* = 20.3, 6.2 Hz, 5H), 0.85 (s, 3H);
^{13}C NMR (151 MHz, $CDCl_3$): δ 143.46, 137.30, 129.86, 127.27, 53.58, 35.35, 33.87, 26.29, 21.77, 21.71 (two C's are overlapping);
HRMS (ESI) *m/z* calc'd for $C_{15}H_{23}NO_2S^+$ [M+H]: 282.1527, found: 282.1536.



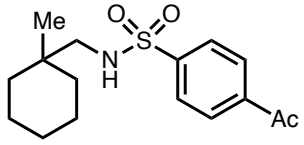
3.S1b

Methyl 4-(*N*-((1-methylcyclohexyl)methyl)sulfamoyl)benzoate (3.S1b): The material was synthesized according to general procedure A. 261 mg, 24% yield. 0–100% EtOAc/hexanes. White solid.

^{1}H NMR (600 MHz, CD_3CN): δ 8.14 (d, *J* = 8.5 Hz, 2H), 7.92 (d, *J* = 8.5 Hz, 2H), 5.63 (t, *J* = 6.7 Hz, 1H), 3.91 (s, 3H), 2.66 (d, *J* = 6.9 Hz, 2H), 1.40 (dd, *J* = 10.3, 5.4 Hz, 5H), 1.23 (dtt, *J* = 24.0, 13.4, 5.4 Hz, 5H), 0.84 (s, 3H);

^{13}C NMR (151 MHz, CD_3CN): δ 167.0, 146.0, 135.0, 131.4, 128.4, 54.3, 53.6, 36.2, 34.9, 27.3, 24.0, 22.8;

HRMS (ESI) *m/z* calc'd for $C_{16}H_{23}NO_4S^+$ [M+H]: 326.1426, found: 326.1420.



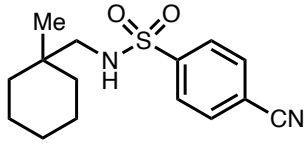
3.S1c

4-Acetyl-N-((1-methylcyclohexyl)methyl)benzenesulfonamide (3.S1c): The material was synthesized according to general procedure A. 570 mg, 51% yield. 20–50% EtOAc/hexanes. White solid.

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.5 Hz, 2H), 7.96 (d, *J* = 8.5 Hz, 2H), 4.73 (t, *J* = 6.7 Hz, 1H), 2.75 (d, *J* = 6.7 Hz, 2H), 2.65 (s, 3H), 1.50 – 1.35 (m, 5H), 1.29 – 1.17 (m, 5H), 0.85 (s, 3H);

^{13}C NMR (151 MHz, $CDCl_3$): δ 197.0, 144.2, 140.0, 129.1, 127.4, 53.6, 35.2, 33.9, 27.0, 26.1, 23.1, 21.7;

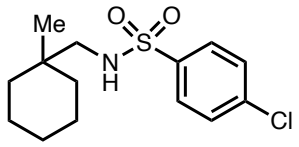
HRMS (ESI) *m/z* calc'd for $C_{16}H_{22}NO_3S$ [M–H]: 308.1326, found 308.1328.



3.S1d

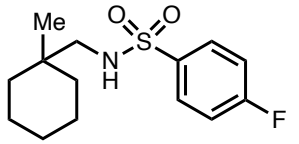
4-Cyano-*N*-((1-methylcyclohexyl)methyl)benzenesulfonamide (3.S1d): The material was synthesized according to general procedure A. 0.75 g, 92% yield. 0–20% EtOAc/hexanes. White solid.

^{1}H NMR (700 MHz, $CDCl_3$): δ 7.97 (d, *J* = 8.3 Hz, 2H), 7.82 (d, *J* = 8.3 Hz, 2H), 4.64 (t, *J* = 6.8 Hz, 1H), 2.78 (d, *J* = 6.7 Hz, 2H), 1.50 – 1.44 (m, 1H), 1.41 (p, *J* = 6.4 Hz, 4H), 1.29 – 1.18 (m, 5H), 0.86 (s, 3H);
^{13}C NMR (176 MHz, $CDCl_3$): δ 144.7, 133.1, 127.8, 117.5, 116.4, 35.2, 33.9, 26.2, 21.7 (two C's are overlapping);
HRMS (ESI) *m/z* calc'd for $C_{15}H_{19}N_2O_2S$ [M–H]: 291.1173, found: 291.1174.



3.S1e

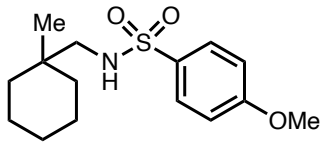
4-Chloro-*N*-((1-methylcyclohexyl)methyl)benzenesulfonamide (**3.S1e**): The material was synthesized according to general procedure A. 0.88 g, 93% yield. 0–20% EtOAc/hexanes. White solid.
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.6 Hz, 2H), 7.49 (d, *J* = 8.6 Hz, 2H), 4.51 (br. s, 1H), 2.74 (d, *J* = 6.8 Hz, 2H), 1.48 – 1.43 (m, 1H), 1.41 (p, *J* = 6.0 Hz, 4H), 1.29 – 1.19 (m, 5H), 0.86 (s, 3H);
^{13}C NMR (151 MHz, $CDCl_3$) δ 139.1, 138.8, 129.5, 128.6, 53.6, 35.3, 33.9, 26.2, 23.1, 21.7;
HRMS (ESI) *m/z* calc'd for $C_{14}H_{19}ClNO_2S$ [M–H]: 300.0831, found: 300.0832.



3.S1f

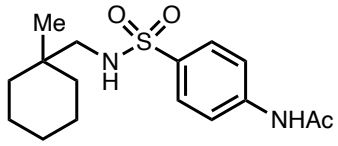
4-Fluoro-*N*-((1-methylcyclohexyl)methyl)benzenesulfonamide (**3.S1f**): The material was synthesized according to general procedure A. 605 mg, 56% yield. 0–25% EtOAc/hexanes. White solid.

^{1}H NMR (700 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 8.7, 5.1 Hz, 2H), 7.19 (t, *J* = 8.5 Hz, 2H), 4.57 (t, *J* = 6.8 Hz, 1H), 2.73 (d, *J* = 6.8 Hz, 2H), 1.44 (td, *J* = 10.3, 9.9, 4.9 Hz, 1H), 1.39 (p, *J* = 6.0 Hz, 4H), 1.28 – 1.23 (m, 1H), 1.21 (t, *J* = 6.0 Hz, 4H), 0.85 (s, 3H);
^{13}C NMR (176 MHz, $CDCl_3$): δ 165.1 (d, *J* = 254.5 Hz), 136.3 (d, *J* = 3.3 Hz), 129.9 (d, *J* = 9.4 Hz), 116.4 (d, *J* = 22.5 Hz), 35.3, 33.9, 26.2, 21.7 (two C's are overlapping);
HRMS (ESI) *m/z* calc'd for $C_{14}H_{20}FNO_2S^+$ [M+H]: 286.1277, found: 286.1263.



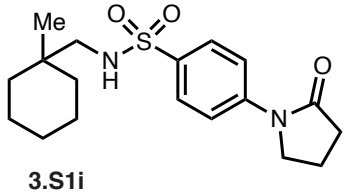
3.S1g

4-Methoxy-*N*-((1-methylcyclohexyl)methyl)benzenesulfonamide (**3.S1g**): The material was synthesized according to general procedure A. 666 mg, 62% yield. 0–20% EtOAc/hexanes. White solid.
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.9 Hz, 2H), 4.51 (t, *J* = 6.9 Hz, 1H), 3.87 (s, 3H), 2.70 (d, *J* = 6.9 Hz, 2H), 1.45 – 1.36 (m, 5H), 1.27 – 1.19 (m, 5H), 0.85 (s, 3H);
^{13}C NMR (176 MHz, $CDCl_3$): δ 162.88, 131.86, 129.32, 114.33, 55.73, 35.31, 33.80, 26.24, 21.73, 21.52 (two C's are overlapping);
HRMS (ESI) *m/z* calc'd for $C_{15}H_{24}NO_3S$ $[M+H]^+$: 298.1471, found: 298.1475.



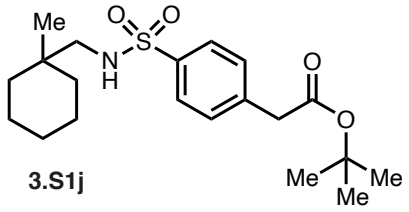
3.S1h

***N*-(4-(*N*-((1-Methylcyclohexyl)methyl)sulfamoyl)phenyl)acetamide (3.S1h):** The material was synthesized according to general procedure A. 0.71 g, 69% yield. 0–100% EtOAc/hexanes. White solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, *J* = 8.7 Hz, 2H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.34 (s, 1H), 4.30 (s, 1H), 2.72 (d, *J* = 6.9 Hz, 2H), 2.23 (s, 3H), 1.50 – 1.35 (m, 5H), 1.23 (dt, *J* = 23.0, 5.8 Hz, 5H), 0.85 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 168.7, 141.8, 135.1, 128.6, 119.5, 53.5, 35.4, 33.9, 26.3, 25.0, 22.7, 21.8.
HRMS (ESI) m/z calc'd for $C_{16}H_{25}N_2O_3S^+$ [M+H]: 325.1586, found: 325.1580.



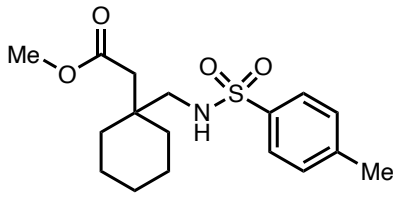
3.S1i

***N*-((1-Methylcyclohexyl)methyl)-4-(2-oxopyrrolidin-1-yl)benzenesulfonamide (3.S1i):** The material was synthesized according to general procedure A. 663 mg, 91% yield. 0–80% EtOAc/Hexanes. White solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.9 Hz, 2H), 7.80 (d, *J* = 9.0 Hz, 2H), 4.31 (s, 1H), 3.91 (t, *J* = 7.0 Hz, 2H), 2.71 (d, *J* = 6.9 Hz, 2H), 2.66 (t, *J* = 8.1 Hz, 2H), 2.21 (p, *J* = 7.6 Hz, 2H), 1.49 – 1.43 (m, 1H), 1.40 (dq, *J* = 9.0, 4.8 Hz, 4H), 1.31 – 1.19 (m, 4H), 0.85 (s, 3H);
^{13}C NMR (151 MHz, $CDCl_3$) δ 175.0, 143.2, 135.1, 128.2, 119.4, 53.6, 48.7, 35.4, 33.9, 33.0, 26.3, 23.2, 21.8, 18.0;
HRMS (ESI) *m/z* calc'd for $C_{18}H_{26}N_2O_3S^+$ [M+H]: 351.1742, found: 351.1754.



3.S1j

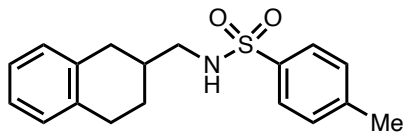
***tert*-Butyl (4-(*N*-((1-methylcyclohexyl)methyl)sulfamoyl)phenyl)carbamate (3.S1j):** The material was synthesized according to general procedure A. 566 mg, 60% yield. 0–30% EtOAc/hexanes. White solid.
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.8 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 6.74 (s, 1H), 4.39 (t, *J* = 6.9 Hz, 1H), 2.69 (d, *J* = 6.9 Hz, 2H), 1.53 (s, 9H), 1.48 – 1.34 (m, 5H), 1.28 – 1.17 (m, 5H), 0.84 (s, 3H);
^{13}C NMR (151 MHz, $CDCl_3$) δ 152.4, 142.6, 133.6, 128.5, 118.1, 81.6, 53.4, 35.3, 33.8, 28.4, 26.2, 21.7 (2 C's are overlapping);
HRMS (ESI) *m/z* calc'd for $C_{19}H_{29}N_2O_4S$ [M–H]: 381.1854, found 381.1865.



3.S1k

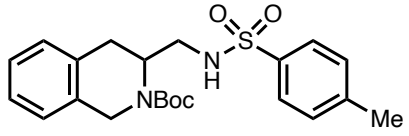
Methyl 2-(1-(((4-methylphenyl)sulfonamido)methyl)cyclohexyl)acetate (3.S1k): The material was synthesized according to general procedure A. 735 mg, 83% yield. 0–35% EtOAc/hexanes. White solid.
^{1}H NMR (499 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 5.14 (t, *J* = 7.2 Hz, 1H), 3.61 (s, 3H), 2.85 (d, *J* = 7.3 Hz, 2H), 2.43 (s, 3H), 2.31 (s, 2H), 1.48 – 1.32 (m, 10H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.23, 143.35, 137.50, 129.89, 127.16, 53.61, 51.79, 37.15, 34.23, 25.95, 21.70, 21.45 (two C's are overlapping);
HRMS (ESI) *m/z* calc'd for $C_{17}H_{25}NO_4S^+$ [M+H]: 340.1582, found: 340.1588.



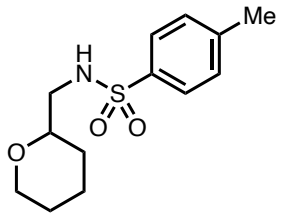
3.S1l

(±)-4-Methyl-*N*-((1,2,3,4-tetrahydronaphthalen-2-yl)methyl)benzenesulfonamide (3.S1l): The material was synthesized according to general procedure A. 725 mg, 90% yield. 0–25% EtOAc/Hexanes. White solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.15 – 6.97 (m, 4H), 4.44 (s, 1H), 2.96 (t, *J* = 6.6 Hz, 2H), 2.78 (dddt, *J* = 33.1, 16.7, 11.2, 5.1 Hz, 3H), 2.43 (s, 4H), 1.98 – 1.84 (m, 2H), 1.38 (dtd, *J* = 13.3, 11.2, 5.8 Hz, 1H);
^{13}C NMR (151 MHz, $CDCl_3$) δ 143.65, 137.19, 136.40, 135.33, 129.94, 129.33, 129.03, 127.27, 126.02, 125.91, 48.68, 34.79, 33.57, 28.59, 26.93, 21.72;
HRMS (ESI) *m/z* calc'd for $C_{18}H_{22}NO_2S^+$ [M+H]: 316.1371, found: 316.1366.



3.S1m

(±)-*tert*-Butyl-3-(((4-methylphenyl)sulfonamido)methyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxylate (1e): The material was synthesized according to general procedure A. Material was isolated as a mixture of rotamers. 257 mg, 24% yield. 0–45% EtOAc/hexanes. White solid.
^{1}H NMR (500 MHz, 85 °C, DMSO-d_6) δ 7.63 (d, *J* = 7.9 Hz, 2H), 7.47 – 7.30 (m, 3H), 7.21 – 7.06 (m, 4H), 4.62 (d, *J* = 16.8 Hz, 1H), 4.37 (s, 1H), 4.17 (d, *J* = 16.8 Hz, 1H), 3.05 (s, 1H), 2.91 (dd, *J* = 15.9, 5.4 Hz, 1H), 2.86 – 2.73 (m, 2H), 2.65 (dd, *J* = 12.7, 7.8 Hz, 1H), 2.38 (s, 3H), 1.44 (s, 9H);
^{13}C NMR (126 MHz, DMSO) δ 154.84, 142.92, 138.57, 133.67, 132.99, 129.93, 129.37, 127.04, 126.90, 126.57, 126.31, 79.77, 49.95, 44.18, 43.19, 30.30, 28.62, 21.28;
HRMS (ESI) *m/z* calc'd for $C_{22}H_{28}N_2O_4S^+$ [M+H]: 417.1848, found: 417.1837.



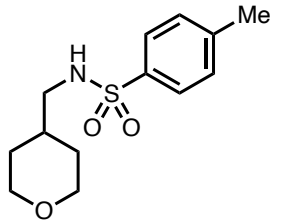
3.S1n

(±)-4-Methyl-*N*-((tetrahydro-2*H*-pyran-2-yl)methyl)benzenesulfonamide (3.S1n): The material was synthesized according to general procedure A. 940 mg, 70% yield. 0–40% EtOAc/hexanes. White solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.83 (d, *J* = 5.1 Hz, 1H), 3.94 – 3.87 (m, 1H), 3.34 (qd, *J* = 11.1, 9.6, 3.3 Hz, 2H), 3.07 (ddd, *J* = 11.9, 8.4, 3.2 Hz, 1H), 2.77 (ddd, *J* = 12.1, 8.3, 3.6 Hz, 1H), 2.42 (s, 3H), 1.85 – 1.76 (m, 1H), 1.57 (s, 3H), 1.46 (dddt, *J* = 16.2, 12.3, 8.1, 4.2 Hz, 4H), 1.30 – 1.21 (m, 1H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 143.50, 137.07, 129.87, 127.26, 75.89, 68.47, 48.14, 28.99, 25.93, 22.95, 21.70;

HRMS (ESI) *m/z* calc'd for $C_{13}H_{19}NO_3S^+$ [M+H]: 270.1164, found: 270.1179.



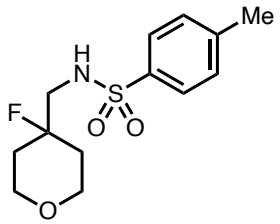
3.S1o

4-Methyl-*N*-((tetrahydro-2*H*-pyran-4-yl)methyl)benzenesulfonamide (3.S1o): The material was synthesized according to general procedure A. 1.19 g, 92% yield. 0–55% EtOAc/hexanes. White solid. (*Listed as compound* **3.7** *in main text*.)

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 4.39 (s, 1H), 3.94 (dd, *J* = 10.9, 3.7 Hz, 2H), 3.32 (td, *J* = 11.9, 2.0 Hz, 2H), 2.82 (t, *J* = 6.7 Hz, 2H), 2.43 (s, 3H), 1.69 (ddh, *J* = 15.2, 7.0, 3.6 Hz, 1H), 1.61 – 1.56 (m, 2H), 1.22 (qd, *J* = 12.1, 4.6 Hz, 2H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 143.53, 136.97, 129.77, 127.07, 67.43, 48.86, 35.41, 30.39, 21.54;

HRMS (ESI) *m/z* calc'd for $C_{13}H_{20}NO_3S^+$ [M+H]: 270.1164, found: 270.1158.



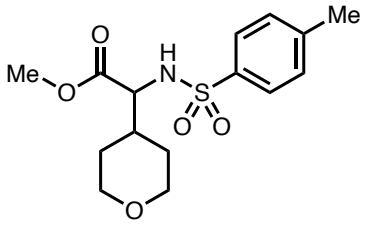
3.S1p

***N*-((4-Fluorotetrahydro-2*H*-pyran-4-yl)methyl)-4-methylbenzenesulfonamide (3.S1p):** The material was synthesized according to general procedure A. 0.68 g, 90% yield. 0–40% EtOAc/hexanes. Colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 4.62 (s, 1H), 3.79 (ddd, *J* = 11.6, 4.8, 2.7 Hz, 2H), 3.67 (td, *J* = 11.5, 2.2 Hz, 2H), 3.09 (dd, *J* = 20.6, 6.7 Hz, 2H), 2.44 (s, 3H), 1.88 – 1.77 (m, 2H), 1.76 – 1.60 (m, 2H);

^{13}C NMR (151 MHz, $CDCl_3$) δ 143.93, 137.01, 130.04, 127.17, 92.89 (d, *J* = 173.5 Hz), 63.48 (d, *J* = 1.9 Hz), 50.95 (d, *J* = 21.9 Hz), 33.37 (d, *J* = 21.1 Hz), 21.73;

HRMS (ESI) *m/z* calc'd for $C_{13}H_{18}FNNaO_3S^+$ [M+Na]: 310.0889, found: 310.0884.



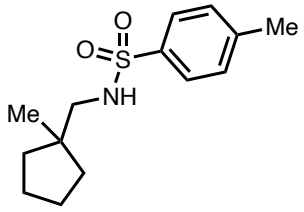
3.S1q

(±)-Methyl 2-((4-methylphenyl)sulfonamido)-2-(tetrahydro-2*H*-pyran-4-yl)acetate (3.S1q): The material was synthesized according to general procedure A. 0.71 g, 84% yield. 0–60% EtOAc/hexanes. White solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.05 (d, *J* = 10.1 Hz, 1H), 3.96 (t, *J* = 11.7 Hz, 2H), 3.75 (dd, *J* = 10.0, 6.2 Hz, 1H), 3.46 (s, 3H), 3.36 – 3.24 (m, 2H), 2.42 (s, 3H), 1.88 (tdd, *J* = 12.0, 6.7, 3.7 Hz, 1H), 1.54 – 1.48 (m, 1H), 1.39 (ddd, *J* = 25.2, 11.8, 4.2 Hz, 2H);

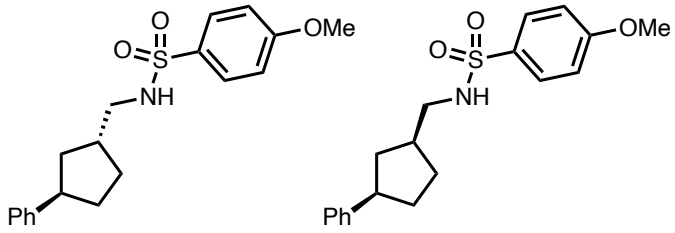
^{13}C NMR (151 MHz, $CDCl_3$) δ 171.44, 143.99, 136.67, 129.83, 127.52, 67.66, 67.49, 60.26, 52.50, 38.84, 29.14, 28.48, 21.73;

HRMS (ESI) *m/z* calc'd for $C_{15}H_{22}NO_5S^+$ [M+H]: 328.1219, found: 328.1213.



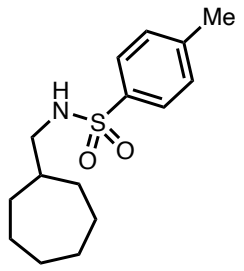
3.S2a

4-Methyl-*N*-((1-methylcyclopentyl)methyl)benzenesulfonamide (3.S2a): The material was synthesized according to general procedure A. 1.5 g, 89% yield. 0–20% EtOAc/hexanes. White solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 4.37 (s, 1H), 2.77 (d, *J* = 6.7 Hz, 2H), 2.43 (s, 3H), 1.71 – 1.50 (m, 5H), 1.37 (dt, *J* = 13.5, 7.2 Hz, 2H), 1.29 (dq, *J* = 13.0, 7.8, 6.1 Hz, 2H), 0.94 (s, 3H);
^{13}C NMR (151 MHz, $CDCl_3$) δ 143.50, 137.25, 129.90, 127.30, 53.06, 42.72, 37.35, 25.12, 24.84, 21.74;
HRMS (ESI) *m/z* calc'd for $C_{14}H_{21}NO_2S^+$ [M+H]: 268.1371, found: 268.1378.



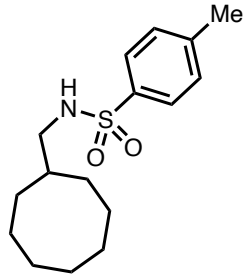
3.S2b-*major* **3.S2b-*minor***

(±)-4-Methyl-*N*-((3-phenylcyclopentyl)methyl)benzenesulfonamide, inseparable ~3:1 mixture of *anti*- to *syn*-isomers, peaks solely attributable to the minor diastereomer are marked with an asterisk (3.S2b): The material was synthesized according to general procedure A. 0.64 g, 83% yield. 0–20% EtOAc/hexanes. White solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 – 7.74 (m, 2H), 7.28 (d, *J* = 7.8 Hz, 2H), 7.16 (dd, *J* = 7.1, 3.3 Hz, 3H), 6.99 (d, *J* = 8.9 Hz, 2H), 4.33 (s, 1H), 3.87 (s, 3H), 3.03 (dt, *J* = 16.9, 8.8 Hz, 1H), 2.98 – 2.88 (m, 2H), 2.26 (dp, *J* = 15.5, 7.7 Hz, 1H), 2.21 – 2.14 (m, 0.33H),* 2.08 (ddt, *J* = 14.3, 9.2, 4.7 Hz, 1H), 1.97 (dtd, *J* = 12.7, 7.6, 2.5 Hz, 1H), 1.86 (dd, *J* = 12.8, 8.5 Hz, 0.33H),* 1.76 (ddt, *J* = 21.5, 13.3, 8.4 Hz, 2H), 1.63 (dtd, *J* = 12.5, 10.3, 7.7 Hz, 1H), 1.44 (s, 0.33H),* 1.28 (ddt, *J* = 12.8, 10.5, 7.6 Hz, 1H), 1.22 – 1.17 (m, 0.33H).*
^{13}C NMR (151 MHz, $CDCl_3$) δ 162.89, 145.47, 131.60, 129.23, 128.34, 126.95, 125.96, 114.27, 55.62, 48.40, 44.29, 38.74, 37.73, 34.50, 30.62.
HRMS (ESI) *m/z* calc'd for $C_{19}H_{24}NO_3S^+$ [M+H]: 346.1477, found: 346.1471.



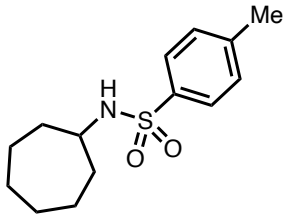
3.S2c

***N*-(Cycloheptylmethyl)-4-methylbenzenesulfonamide (3.S2c):** The material was synthesized according to general procedure A. 0.75 g, 88% yield. 0–5% EtOAc/CH_2Cl_2. Light yellow solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.28 (t, *J* = 6.7 Hz, 1H), 2.76 (t, *J* = 6.6 Hz, 2H), 2.43 (s, 3H), 1.62 (ddddd, *J* = 34.4, 13.5, 9.8, 6.9, 3.2 Hz, 6H), 1.52 (dd, *J* = 6.8, 3.6 Hz, 1H), 1.48 – 1.41 (m, 2H), 1.40 – 1.32 (m, 2H), 1.12 (dtd, *J* = 12.5, 9.7, 2.9 Hz, 2H);
^{13}C NMR (151 MHz, $CDCl_3$) δ 143.49, 137.29, 129.86, 127.27, 49.83, 39.50, 31.98, 28.47, 26.38, 21.71;
HRMS (ESI) *m/z* calc'd for $C_{15}H_{23}NO_2S^+$ [M+H]: 282.1527, found: 282.1530.



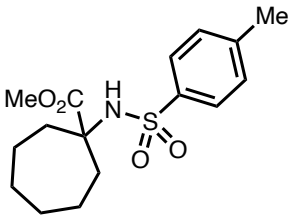
3.S2d

***N*-(Cyclooctylmethyl)-4-methylbenzenesulfonamide (3.S2d):** The material was synthesized according to general procedure A. 769 mg, 97% yield. 0–25% EtOAc/hexanes. White solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 4.34 (s, 1H), 2.75 (t, *J* = 6.5 Hz, 2H), 2.43 (s, 3H), 1.70 – 1.33 (m, 14H), 1.23 – 1.16 (m, 2H);
^{13}C NMR (151 MHz, $CDCl_3$) δ 143.48, 137.34, 129.86, 127.26, 50.20, 37.63, 30.28, 26.95, 26.42, 25.41, 21.70;
HRMS (ESI) *m/z* calc'd for $C_{16}H_{25}NO_2S^+$ [M+H]: 296.1684, found: 296.1682.



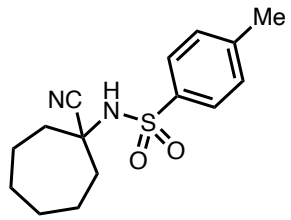
3.S2e

***N*-Cycloheptyl-4-methylbenzenesulfonamide (3.S2e):** The material was synthesized according to general procedure A. 0.93 g, 98% yield. 0–20% EtOAc/hexanes. Colorless oil.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 4.30 (d, *J* = 6.8 Hz, 1H), 3.34 (ddq, *J* = 13.0, 8.7, 4.5 Hz, 1H), 2.43 (s, 3H), 1.81 – 1.70 (m, 2H), 1.55 – 1.30 (m, 10H);
^{13}C NMR (151 MHz, $CDCl_3$) δ 143.31, 138.41, 129.82, 127.17, 54.97, 36.10, 28.11, 23.70, 21.71;
HRMS (ESI) *m/z* calc'd for $C_{14}H_{21}NO_2S^+$ [M+H]: 268.1371, found: 268.1373.



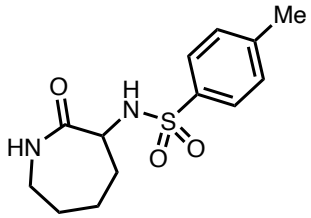
3.S2f

Methyl 1-((4-methylphenyl)sulfonamido)cycloheptane-1-carboxylate (3.S2f): The material was synthesized according to general procedure A. 0.32 g, 44% yield. 0–30% EtOAc/hexanes. White solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 4.81 (s, 1H), 3.59 (s, 3H), 2.42 (s, 3H), 2.18 – 2.01 (m, 2H), 1.84 (dd, *J* = 14.9, 9.0 Hz, 2H), 1.53 – 1.43 (m, 6H), 1.42 – 1.33 (m, 2H);
^{13}C NMR (151 MHz, $CDCl_3$) δ 174.95, 143.49, 139.02, 129.62, 127.49, 65.51, 52.63, 36.55, 29.78, 22.17, 21.72;
HRMS (ESI) *m/z* calc'd for $C_{16}H_{23}NO_4S^+$ [M+H]: 326.1426, found: 326.1427.



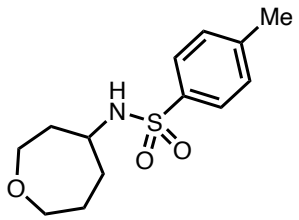
3.S2g

***N*-(1-Cyanocycloheptyl)-4-methylbenzenesulfonamide (3.S2g):** The material was synthesized according to general procedure A. 2.6 g, 24% yield. 80–90% EtOAc/petroleum ether. White solid. **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 4.68 (s, 1H), 2.44 (s, 3H), 2.22 (dd, *J* = 14.5, 8.1 Hz, 2H), 2.02 – 1.94 (m, 2H), 1.62 (ddt, *J* = 37.9, 20.9, 9.2 Hz, 8H);
^{13}C NMR (151 MHz, $CDCl_3$) δ 144.44, 137.61, 129.97, 127.75, 120.00, 57.36, 39.97, 27.86, 21.82, 21.70;
HRMS (ESI) *m/z* calc'd for $C_{15}H_{21}N_2O_2S^+$ [M+H]: 293.1324, found: 293.1318.



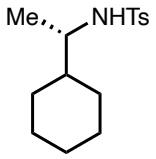
3.S2h

(±)-4-Methyl-*N*-(2-oxoazepan-3-yl)benzenesulfonamide (3.S2h): The material was synthesized according to general procedure A. 0.37 g, 51% yield. 100% EtOAc. White solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 6.14 (d, *J* = 5.0 Hz, 1H), 5.82 (s, 1H), 3.86 – 3.78 (m, 1H), 3.17 (dt, *J* = 13.0, 6.4 Hz, 1H), 3.07 (ddd, *J* = 15.6, 11.7, 5.1 Hz, 1H), 2.41 (s, 3H), 2.17 (d, *J* = 14.7 Hz, 1H), 2.01 (d, *J* = 14.7 Hz, 1H), 1.85 – 1.75 (m, 1H), 1.72 – 1.60 (m, 2H), 1.40 – 1.30 (m, 1H);
^{13}C NMR (151 MHz, $CDCl_3$) δ 174.32, 143.60, 137.13, 129.90, 127.21, 55.55, 42.48, 33.62, 28.88, 28.17, 21.73;
HRMS (ESI) *m/z* calc'd for $C_{13}H_{18}N_2O_3S^+$ [M+H]: 283.1116, found: 283.1122.



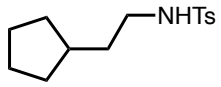
3.S2i

(±)-4-Methyl-*N*-(oxepan-4-yl)benzenesulfonamide (3.S2i): The material was synthesized according to general procedure A. 0.54 g, 46% yield. 0–50% EtOAc/hexanes. White solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.7 Hz, 2H), 7.29 (d, *J* = 7.9 Hz, 2H), 4.79 (d, *J* = 8.8 Hz, 1H), 3.75 (dt, *J* = 11.1, 5.0 Hz, 1H), 3.67 (ddd, *J* = 18.4, 12.4, 7.5 Hz, 2H), 3.58 – 3.45 (m, 2H), 2.43 (s, 3H), 1.85 – 1.77 (m, 1H), 1.70 (tt, *J* = 13.2, 6.9 Hz, 3H), 1.66 – 1.58 (m, 2H);
^{13}C NMR (151 MHz, $CDCl_3$) δ 143.45, 138.54, 129.88, 127.11, 69.41, 65.69, 52.61, 36.12, 33.92, 26.06, 21.71;
HRMS (ESI) *m/z* calc'd for $C_{13}H_{19}NO_3S^+$ [M+H]: 270.1164, found: 270.1170.



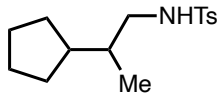
3.8

(*S*)-*N*-(1-Cyclohexylethyl)-4-methylbenzenesulfonamide (3.8): The material was synthesized according to general procedure A. 706 mg, 95% yield. 0–20% EtOAc/hexanes. White solid.
^{1}H NMR (499 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 4.14 (d, *J* = 8.7 Hz, 1H), 3.15 (dq, *J* = 13.4, 6.7 Hz, 1H), 2.42 (s, 3H), 1.76 – 1.59 (m, 4H), 1.52 (d, *J* = 9.5 Hz, 1H), 1.24 (ddt, *J* = 11.8, 5.3, 2.8 Hz, 1H), 1.20 – 1.03 (m, 3H), 0.97 (td, *J* = 12.3, 3.2 Hz, 1H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.88 – 0.76 (m, 1H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 143.30, 138.49, 129.77, 127.23, 54.59, 43.67, 28.83, 28.72, 26.48, 26.30, 26.24, 21.71, 18.67.
HRMS (ESI) *m/z* calc'd for $C_{15}H_{14}NO_2S^+$ [M+H]: 282.1528, found: 282.1522.
$[\alpha]^{25}_D$ –0.18 (c 0.66, $CHCl_3$).



3.10a

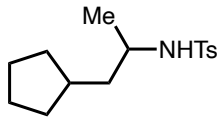
***N*-(2-Cyclopentylethyl)-4-methylbenzenesulfonamide (3.10a):** The material was synthesized according to general procedure A. 0.82 g, 93% yield. 0–15% EtOAc/Hexanes. White solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.23 (s, 1H), 3.01 – 2.85 (m, 2H), 2.43 (s, 3H), 1.81 – 1.63 (m, 3H), 1.61 – 1.52 (m, 3H), 1.50 – 1.41 (m, 3H), 1.11 – 0.92 (m, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 143.5, 137.2, 129.9, 127.3, 42.8, 37.5, 36.1, 32.6, 25.2, 21.7.
HRMS (ESI) *m/z* calc'd for $C_{14}H_{22}NO_2S^+$ [M+H]: 268.1371, found: 268.1366.



3.10b

(±)-*N*-(2-Cyclopentylpropyl)-4-methylbenzenesulfonamide ((±)-3.10b): The material was synthesized according to general procedure A. 0.28 g, 76% yield. 0–20% EtOAc/hexanes. Colorless oil.

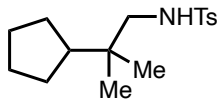
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 4.11 (d, *J* = 8.1 Hz, 1H), 3.29 (dq, *J* = 14.2, 7.2, 6.5 Hz, 1H), 2.42 (s, 3H), 1.74 – 1.63 (m, 2H), 1.53 – 1.46 (m, 2H), 1.46 – 1.35 (m, 3H), 1.29 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.04 (d, *J* = 6.5 Hz, 3H), 1.00 – 0.84 (m, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 143.4, 138.4, 129.8, 127.3, 49.7, 44.4, 36.8, 32.8, 32.7, 25.1, 25.1, 22.6, 21.7.
HRMS (ESI) *m/z* calc'd for $C_{15}H_{24}NO_2S^+$ [M+H]: 282.1528, found: 282.1522.



3.10c

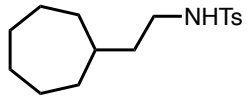
(±)-*N*-(1-Cyclopentylpropan-2-yl)-4-methylbenzenesulfonamide ((±)-3.10c): The material was synthesized according to general procedure A. 0.66 g, 89% yield. 0–20% EtOAc/hexanes. Colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 4.24 (s, 1H), 2.98 (ddd, *J* = 12.3, 6.4, 4.4 Hz, 1H), 2.78 – 2.67 (m, 1H), 2.43 (s, 3H), 1.73 – 1.60 (m, 2H), 1.54 – 1.37 (m, 4H), 1.06 (dt, *J* = 19.1, 9.6 Hz, 2H), 0.88 (d, *J* = 6.7 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 143.5, 137.2, 129.9, 127.3, 48.6, 43.7, 38.7, 30.8, 30.3, 25.5, 25.3, 21.7, 16.3.
HRMS (ESI) *m/z* calc'd for $C_{15}H_{24}NO_2S^+$ [M+H]: 282.1527, found: 282.1530.



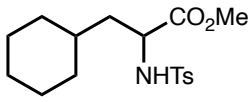
3.10d

***N*-(2-Cyclopentyl-2-methylpropyl)-4-methylbenzenesulfonamide (3.10d):** The material was synthesized according to general procedure A. 702 mg, 90% yield. 0–20% EtOAc/hexanes. White solid.
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 4.84 (t, *J* = 6.8 Hz, 1H), 2.68 (d, *J* = 6.8 Hz, 2H), 2.42 (s, 3H), 1.70 (tt, *J* = 10.3, 7.4 Hz, 1H), 1.54 – 1.42 (m, 6H), 1.19 – 1.09 (m, 2H), 0.79 (s, 6H).
^{13}C NMR (176 MHz, $CDCl_3$) δ 143.3, 137.2, 129.8, 127.2, 53.3, 46.9, 35.7, 26.8, 25.6, 22.5, 21.6.
HRMS (ESI) *m/z* calc'd for $C_{16}H_{24}NO_2S$ [M-H]: 294.1533, found 294.1534.



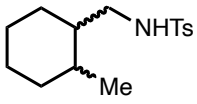
3.10e

***N*-(2-Cycloheptylethyl)-4-methylbenzenesulfonamide (3.10e):** The material was synthesized according to general procedure A. 0.98 g, 97% yield. 0–20% EtOAc/hexanes. White solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 4.21 (s, 1H), 3.06 – 2.89 (m, 2H), 2.46 (s, 3H), 1.63 – 1.58 (m, 4H), 1.57 – 1.53 (m, 3H), 1.49 – 1.42 (m, 3H), 1.42 – 1.35 (m, 3H), 1.16 – 1.08 (m, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 143.4, 137.0, 129.7, 127.1, 41.5, 37.7, 36.4, 34.3, 28.4, 26.2, 21.5.
HRMS (ESI) *m/z* calc'd for $C_{16}H_{25}NO_2S^+$ [M+H]: 296.1684, found: 296.1696.



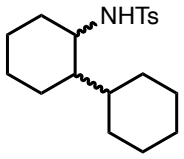
3.10f

(±)-Methyl 3-cyclohexyl-2-((4-methylphenyl)sulfonamido)propanoate ((±)-3.10f): The material was synthesized according to general procedure A. 0.72 g, 96% yield. 0–30% EtOAc/hexanes. White solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 4.96 (d, *J* = 10.0 Hz, 1H), 3.98 (td, *J* = 9.4, 5.2 Hz, 1H), 3.48 (s, 3H), 2.44 (s, 3H), 1.73 – 1.61 (m, 5H), 1.48 (tdd, *J* = 18.3, 9.0, 5.2 Hz, 3H), 1.28 – 1.08 (m, 3H), 0.97 – 0.78 (m, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 172.9, 143.7, 136.7, 129.6, 127.4, 53.6, 52.3, 40.9, 33.5, 33.4, 32.1, 26.3, 26.1, 25.9, 21.5.
HRMS (ESI) *m/z* calc'd for $C_{17}H_{26}NO_4S^+$ [M+H]: 340.1583, found: 340.1577.



3.10g

(±)-4-Methyl-*N*-((2-methylcyclohexyl)methyl)benzenesulfonamide, 1:1 mixture of *trans*- and *cis*-isomers ((±)-3.10g): The material was synthesized according to general procedure A. 604 mg, 82% yield. 0–20% EtOAc/hexanes. White amorphous solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.3, 2.2 Hz, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 4.24 – 4.16 (m, 1H), 3.05 (ddd, *J* = 12.4, 6.5, 3.4 Hz, 1H), 2.86 – 2.73 (m, 2H), 2.43 (s, 3H), 1.84 (s, 1H), 1.72 – 1.62 (m, 2H), 1.40 (d, *J* = 4.2 Hz, 1H), 1.24 – 1.10 (m, 3H), 1.05 (dd, *J* = 11.4, 7.3 Hz, 1H), 0.99 – 0.91 (m, 1H), 0.79 (dd, *J* = 33.0, 6.8 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 143.5, 137.2, 137.1, 129.9, 129.9, 127.3, 127.3, 46.7, 44.0, 40.2, 35.6, 34.6, 32.5, 30.3, 26.3, 26.2, 25.4, 21.7, 20.1.
HRMS (ESI) *m/z* calc'd for $C_{15}H_{24}NO_2S^+$ [M+H]: 282.1527, found: 282.1534.



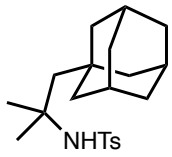
3.10h

(±)-*N*-((1*S*)-[1,1'-Bi(cyclohexan)]-2-yl)-4-methylbenzenesulfonamide ((±)-3.10h): The material was synthesized according to general procedure A. 0.32 g, 36% yield. 0–25% EtOAc/hexanes. White solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 4.06 (d, *J* = 8.9 Hz, 1H), 3.03 (dd, *J* = 9.2, 4.2 Hz, 1H), 2.42 (s, 3H), 1.92 (d, *J* = 10.6 Hz, 1H), 1.73 – 1.55 (m, 6H), 1.49 (s, 1H), 1.27 (q, *J* = 8.3, 7.2 Hz, 1H), 1.23 – 1.03 (m, 6H), 0.99 (t, *J* = 9.1 Hz, 2H), 0.86 – 0.71 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 143.3, 138.7, 129.8, 127.2, 54.3, 49.0, 37.0, 35.8, 31.9, 27.2, 26.9, 26.6, 26.0, 25.7, 25.4, 21.7 (2 C's overlapping).

HRMS (ESI) *m/z* calc'd for $C_{19}H_{29}NO_2S^+$ [M+H]: 336.1997, found: 336.1995.



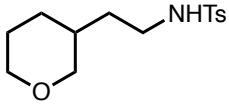
3.10i

(±)-*N*-(1-((3*r*,5*r*,7*r*)-Adamantan-1-yl)-2-methylpropan-2-yl)-4-methylbenzenesulfonamide ((±)-3.10i): The material was synthesized according to general procedure A. 0.56 g, 78% yield. 0–20% EtOAc/hexanes. White solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.28 (s, 2H), 4.43 (s, 1H), 2.42 (s, 3H), 1.92 (s, 3H), 1.67 (d, *J* = 12.1 Hz, 3H), 1.59 (s, 9H), 1.36 (s, 2H), 1.25 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 142.9, 141.0, 129.6, 127.3, 58.7, 57.6, 44.1, 37.0, 34.2, 30.0, 28.9, 21.7.

HRMS (ESI) *m/z* calc'd for $C_{21}H_{31}NO_2S^+$ [M+H]: 362.2153, found: 362.2138.



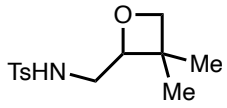
3.10j

(±)-4-Methyl-N-(2-(tetrahydro-2*H*-pyran-3-yl)ethyl)benzenesulfonamide ((±)-3.10j): The material was synthesized according to general procedure A. 0.59 g, 71% yield. 0–20% EtOAc/hexanes. White solid**.**

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 4.29 (s, 1H), 3.89 – 3.80 (m, 1H), 3.75 (dd, *J* = 11.1, 2.3 Hz, 1H), 3.40 – 3.31 (m, 1H), 3.04 (dd, *J* = 11.0, 9.8 Hz, 1H), 2.97 (tq, *J* = 12.7, 6.6 Hz, 2H), 2.46 (s, 3H), 1.84 – 1.75 (m, 1H), 1.66 – 1.52 (m, 4H), 1.39 (dq, *J* = 14.3, 6.8 Hz, 1H), 1.32 (dt, *J* = 13.9, 7.0 Hz, 1H), 1.18 – 1.08 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 143.7, 137.0, 129.9, 127.3, 72.9, 68.6, 40.9, 33.5, 32.4, 29.6, 25.6, 21.7.

HRMS (ESI) *m/z* calc'd for $C_{14}H_{21}NO_3S^+$ [M+H]: 284.1320, found: 284.1320.



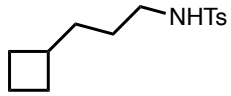
3.10k

(±)-*N*-((3,3-Dimethyloxetan-2-yl)methyl)-4-methylbenzenesulfonamide ((±)-3.10k): The material was synthesized according to general procedure A. 0.52 g, 74% yield. 0–40% EtOAc/hexanes. Colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 4.62 (s, 1H), 4.37 (dd, *J* = 6.8, 5.2 Hz, 1H), 4.27 (d, *J* = 5.6 Hz, 1H), 4.17 (d, *J* = 5.6 Hz, 1H), 3.18 (ddd, *J* = 7.3, 5.1, 2.6 Hz, 2H), 2.44 (s, 3H), 1.27 (s, 3H), 1.14 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 143.8, 136.9, 130.0, 127.3, 88.3, 82.0, 44.8, 37.6, 27.3, 21.7, 20.8.

HRMS (ESI) *m/z* calc'd for $C_{13}H_{19}NO_3S^+$ [M+H]: 270.1164, found: 270.1170.



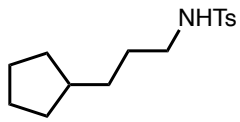
3.12a

***N*-(3-Cyclobutylpropyl)-4-methylbenzenesulfonamide (3.12a):** The material was synthesized according to general procedure A. 0.51 g, 88% yield. 0–20% EtOAc/hexanes. White solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.23 (s, 1H), 2.91 (q, *J* = 6.6 Hz, 2H), 2.43 (s, 3H), 2.16 (dt, *J* = 15.1, 7.7 Hz, 1H), 2.00 – 1.92 (m, 2H), 1.89 – 1.69 (m, 2H), 1.53 – 1.46 (m, 2H), 1.34 (qq, *J* = 8.5, 4.4, 3.8 Hz, 4H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 143.5, 137.2, 129.9, 127.3, 43.5, 35.6, 33.9, 28.4, 27.5, 21.7, 18.5.

HRMS (ESI) *m/z* calc'd for $C_{14}H_{22}NO_2S^+$ [M+H]: 268.1371, found: 268.1366.

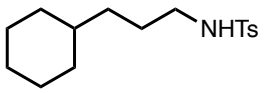


3.12b

***N*-(3-Cyclopentylpropyl)-4-methylbenzenesulfonamide (3.12b):** The material was synthesized according to general procedure A. 0.56 g, 94% yield. 0–20% EtOAc/hexanes. White solid.

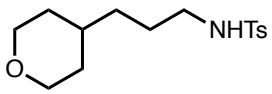
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 4.23 (s, 1H), 2.93 (q, *J* = 6.9 Hz, 2H), 2.43 (s, 3H), 1.66 (tt, *J* = 14.9, 6.6 Hz, 3H), 1.57 (dd, *J* = 9.6, 6.3 Hz, 2H), 1.50 – 1.42 (m, 4H), 1.28 – 1.21 (m, 2H), 1.03 – 0.94 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 143.5, 137.2, 129.9, 127.3, 43.7, 39.8, 33.1, 32.7, 29.0, 25.3, 21.7.
HRMS (ESI) *m/z* calc'd for $C_{15}H_{24}NO_2S^+$ [M+H]: 282.1527, found: 282.1523.



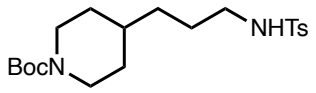
3.12c

***N*-(3-Cyclohexylpropyl)-4-methylbenzenesulfonamide (3.12c):** The material was synthesized according to general procedure A. 0.48 g, 77% yield. 0–20% EtOAc/hexanes. White solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 4.25 (d, *J* = 19.7 Hz, 1H), 2.91 (q, *J* = 6.8 Hz, 2H), 2.43 (s, 3H), 1.72 – 1.59 (m, 5H), 1.45 (dq, *J* = 14.5, 7.1, 6.6 Hz, 2H), 1.26 – 1.06 (m, 6H), 0.80 (q, *J* = 9.9, 9.3 Hz, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 143.5, 137.2, 129.9, 127.3, 43.7, 37.3, 34.4, 33.4, 27.1, 26.7, 26.4, 21.7.
HRMS (ESI) *m/z* calc'd for $C_{16}H_{26}NO_2S^+$ [M+H]: 296.1684, found: 296.1698.



3.12d

4-Methyl-*N*-(3-(tetrahydro-2*H*-pyran-4-yl)propyl)benzenesulfonamide (3.12d): The material was synthesized according to general procedure A. 709 mg, 91% yield. 0–40% EtOAc/hexanes. Colorless oil.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 4.26 (s, 1H), 3.92 (dd, *J* = 11.3, 4.2 Hz, 2H), 3.32 (td, *J* = 11.9, 1.9 Hz, 2H), 2.94 (q, *J* = 6.9 Hz, 2H), 2.43 (s, 3H), 1.52 – 1.45 (m, 3H), 1.39 (ddp, *J* = 14.4, 6.9, 3.3 Hz, 1H), 1.23 – 1.17 (m, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 143.6, 137.2, 129.9, 127.3, 68.2, 43.6, 34.7, 33.9, 33.1, 26.7, 21.7.
HRMS (ESI) *m/z* calc'd for $C_{15}H_{24}NO_3S^+$ [M+H]: 298.1477, found: 298.1471.



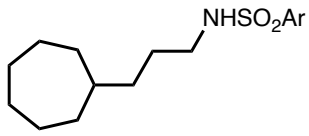
3.12e

***tert*-Butyl 4-(3-((4-methylphenyl)sulfonamido)propyl)piperidine-1-carboxylate (3.12e):** The material was synthesized according to general procedure A. 833 mg, 80% yield. 0–30% EtOAc/hexanes. Colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.25 (s, 1H), 4.04 (d, *J* = 10.2 Hz, 2H), 2.93 (q, *J* = 6.9 Hz, 2H), 2.62 (t, *J* = 12.3 Hz, 2H), 2.43 (s, 3H), 1.56 (s, 1H), 1.48 (dd, *J* = 15.3, 7.7 Hz, 2H), 1.45 (s, 8H), 1.32 – 1.24 (m, 2H), 1.24 – 1.14 (m, 2H), 1.01 (qd, *J* = 12.7, 4.4 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 155.0, 143.6, 137.2, 129.9, 127.3, 79.5, 44.1, 43.6, 35.7, 33.5, 32.2, 28.7, 27.0, 21.7.

HRMS (ESI) *m/z* calc'd for $C_{20}H_{32}N_2O_4S^+$ [M+H]: 397.2161, found: 397.2152.



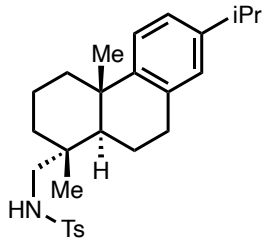
3.12f

***N*-(3-Cycloheptylpropyl)-4-methoxybenzenesulfonamide (3.12f):** The material was synthesized according to general procedure A. 646 mg, 82% yield. 0–40% EtOAc/hexanes. White solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.9 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 4.25 (s, 1H), 3.87 (s, 3H), 2.90 (q, *J* = 6.7 Hz, 2H), 1.64 – 1.48 (m, 7H), 1.44 (dq, *J* = 12.2, 7.3 Hz, 4H), 1.40 – 1.29 (m, 3H), 1.23 – 1.03 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.0, 131.8, 129.4, 114.4, 55.8, 43.7, 38.9, 35.1, 34.6, 28.6, 27.6, 26.6.

HRMS (ESI) *m/z* calc'd for $C_{17}H_{27}NO_3S^+$ [M+H]: 326.1790, found: 326.1802.



3.14a

***N*-(((1*R*,4a*S*,10a*R*)-7-isopropyl-1,4a-dimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-1-yl)methyl)-4-methylbenzenesulfonamide (20):** The material was synthesized according to general procedure A. 780 mg, 60% yield. After initial purification (0-30% EtOAc/hexanes), the mixture was further separated by SFC chromatography using a Biphenyl 21mm x 250mm column, and Sepiatec 1 instrument. The eluant was 15% MeOH w/ 0.1% NH_4OH in CO_2. White solid.

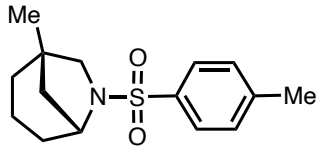
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.1 Hz, 2H), 7.14 (d, J = 8.2 Hz, 1H), 7.01 – 6.95 (m, 1H), 6.87 (s, 1H), 4.26 (t, J = 6.5 Hz, 1H), 3.49 (d, J = 5.5 Hz, 1H), 2.83 (dtt, J = 23.3, 12.3, 5.6 Hz, 4H), 2.69 (dd, J = 12.6, 7.3 Hz, 1H), 2.43 (s, 3H), 2.26 (d, J = 12.7 Hz, 1H), 1.78 – 1.59 (m, 4H), 1.52 – 1.43 (m, 1H), 1.39 – 1.31 (m, 2H), 1.22 (d, J = 6.9 Hz, 6H), 1.18 (s, 3H), 0.89 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 147.1, 145.9, 143.5, 137.3, 134.7, 129.9, 127.2, 127.0, 124.3, 124.0, 54.0, 45.2, 38.4, 37.6, 37.1, 36.0, 33.6, 30.0, 25.3, 24.2, 24.2, 21.7, 18.9, 18.7.

HRMS (ESI) m/z calc'd for $C_{27}H_{37}NO_2S^+$ [M+H]: 440.2623, found: 440.2621.

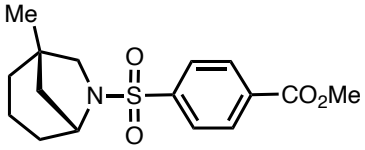
3.4.3. Intramolecular C-H bond amination

General Procedure B: To a 20 mL scintillation vial was added sulfonamide (0.2 mmol), 1,3-diiodo-5,5- dimethylhydantoin (304 mg, 0.8 mmol, 4 equiv), and MeCN (4 mL, 0.05 M). The resulting suspension was stirred at rt for 5 min, and then heated to 80 °C for 24 h using an aluminum heating block. The mixture was diluted with CH_2Cl_2, and then quenched with sat'd $Na_2S_2O_3$ (aq). The organic layer was separated using a phase separator. The aqueous layer was extracted twice with CH_2Cl_2. Finally, the combined organic layers were concentrated in vacuo. The crude residue was purified by flash column chromatography on silica gel to afford analytically pure product.



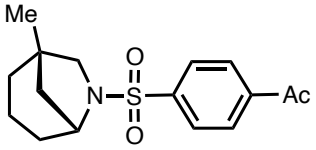
3.2a

(±)-(1*S*,5*R*)-1-Methyl-6-tosyl-6-azabicyclo[3.2.1]octane (3.2a): The material was synthesized according to general procedure A 34.0 mg, 61% yield. 0–5% EtOAc/CH_2Cl_2. Orange solid.
^{1}H NMR (600 MHz, DMSO-d_6) δ 7.68 (d, J = 8.2 Hz, 2H), 7.41 (d, J = 8.0 Hz, 2H), 4.01 (t, J = 5.1 Hz, 1H), 3.12 (*d*, J = 9.5 Hz, 1H), 2.78 – 2.73 (m, 1H), 2.38 (s, 3H), 1.64 – 1.58 (m, 1H), 1.52 – 1.39 (m, 3H), 1.33 – 1.23 (2H), 1.21 (d, J = 11.0 Hz, 1H), 0.93 – 0.88 (m, 1H), 0.86 (s, 3H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 143.46, 135.59, 130.13, 127.19, 59.24, 57.73, 43.49, 40.30, 36.92, 30.96, 24.58, 21.29, 19.20.
HRMS (ESI) *m/z* calc'd for $C_{15}H_{22}NO_2S^+$ [M+H]: 280.1371, found: 280.1362.



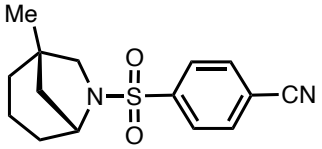
3.2b

(±)-Methyl 4-(((1*S*,5*R*)-1-methyl-6-azabicyclo[3.2.1]octan-6-yl)sulfonyl)benzoate (3.2b): The material was synthesized according to general procedure B. 23.7 mg, 37%. 0-30% EtOAc/hexanes. White solid.
^{1}H NMR (600 MHz, CD_3CN) δ 8.14 (d, *J* = 8.4 Hz, 2H), 7.92 (d, *J* = 8.4 Hz, 2H), 4.11 (t, *J* = 5.2 Hz, 1H), 3.91 (s, 3H), 3.23 (d, *J* = 9.5 Hz, 1H), 2.86 (dd, *J* = 9.5, 1.6 Hz, 1H), 1.76 – 1.69 (m, 1H), 1.59 – 1.52 (m, 2H), 1.50 – 1.44 (m, 1H), 1.39 – 1.30 (m, 2H), 1.26 (d, *J* = 11.2 Hz, 1H), 1.10 – 1.04 (m, 1H), 0.91 (s, 3H).
^{13}C NMR (151 MHz, CD_3CN) δ 166.6, 143.7, 134.8, 131.0, 128.1, 60.7, 58.5, 53.2, 44.4, 41.1, 37.8, 31.8, 24.5, 20.0.
HRMS (ESI) *m/z* calc'd for $C_{16}H_{22}NO_4S^+$ [M+H]: 324.1270, found: 324.1274.



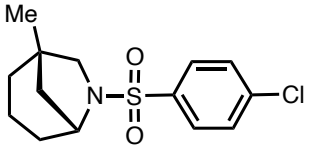
3.2c

1-(4-((1-methyl-6-azabicyclo[3.2.1]octan-6-yl)sulfonyl)phenyl)ethan-1-one (3.2c): The material was synthesized according to general procedure B. 13.5 mg, 22%. 0-30% EtOAc/hexanes. Ran at 80°C for 48h. White solid.
^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, *J* = 8.5 Hz, 2H), 7.93 (d, *J* = 8.5 Hz, 2H), 4.16 (t, *J* = 5.3 Hz, 1H), 3.24 (dd, *J* = 9.3, 1.1 Hz, 1H), 2.88 (dd, *J* = 9.3, 1.8 Hz, 1H), 2.65 (s, 3H), 1.89 – 1.78 (m, 1H), 1.66 – 1.53 (m, 2H), 1.51 – 1.41 (m, 1H), 1.39 – 1.16 (m, 4H), 0.95 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$): δ 197.1, 143.3, 139.8, 129.0, 127.4, 59.8, 57.9, 44.4, 40.6, 37.6, 31.3, 27.0, 24.7, 19.3.
HRMS (ESI): Calc'd for $C_{16}H_{22}NO_3S$ $[M+H]^+$: 308.1315, found 308.1315.



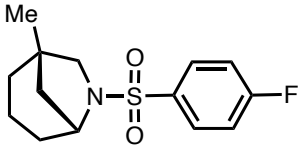
3.2d

(±)-4-((1-methyl-6-azabicyclo[3.2.1]octan-6-yl)sulfonyl)benzonitrile (3.2d): The material was synthesized according to general procedure B. 16.6 mg, 28% (36% b.r.s.m). 0-20% EtOAc/hexanes. White solid.
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.81 (d, *J* = 8.4 Hz, 2H), 4.15 (t, *J* = 5.2 Hz, 1H), 3.24 (dd, *J* = 9.3, 1.1 Hz, 1H), 2.86 (dd, *J* = 9.2, 1.9 Hz, 1H), 1.84 (dtd, *J* = 13.3, 4.9, 4.4, 1.6 Hz, 1H), 1.63 – 1.52 (m, 2H), 1.52 – 1.48 (m, 1H), 1.38 – 1.28 (m, 3H), 1.28 – 1.23 (m, 1H), 0.97 (s, 3H).
^{13}C NMR (176 MHz, $CDCl_3$) δ 143.7, 133.0, 127.6, 117.6, 116.2, 60.0, 57.9, 44.5, 40.6, 37.5, 31.2, 24.7, 19.3.
HRMS (ESI) *m/z* calc'd for $C_{15}H_{19}N_2O_2S$ $[M+H]^+$: 291.1162, found 291.1176.



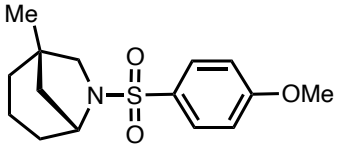
3.2e

(±)-(1*S*,5*R*)-6-((4-Chlorophenyl)sulfonyl)-1-methyl-6-azabicyclo[3.2.1]octane (3.2e): The material was synthesized according to general procedure B. 26.3 mg, 44%. 0-20% EtOAc/hexanes. White solid.
^{1}H NMR (600 MHz, CD_3CN) δ 7.80 (d, *J* = 8.6 Hz, 2H), 7.57 (d, *J* = 8.6 Hz, 2H), 4.08 (t, *J* = 5.2 Hz, 1H), 3.20 (d, *J* = 9.4 Hz, 1H), 2.83 (dd, *J* = 9.5, 1.6 Hz, 1H), 1.74 – 1.68 (m, 1H), 1.61 – 1.54 (m, 2H), 1.50 – 1.44 (m, 1H), 1.39 – 1.31 (m, 2H), 1.26 (d, *J* = 11.2 Hz, 1H), 1.13 – 1.05 (m, 1H), 0.92 (s, 3H).
^{13}C NMR (151 MHz, CD_3CN) δ 139.2, 138.6, 130.3, 129.7, 60.6, 58.5, 44.4, 41.1, 37.8, 31.9, 24.6, 20.0.
HRMS (ESI) *m/z* calc'd for $C_{14}H_{19}ClNO_2S^+$ [M+H]: 300.0825, found: 300.0814.



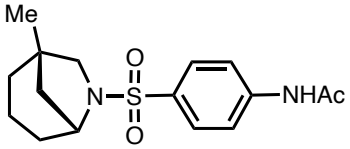
3.2f

(±)-6-((4-fluorophenyl)sulfonyl)-1-methyl-6-azabicyclo[3.2.1]octane (3.2f): The material was synthesized according to general procedure B. 20.1 mg, 35%. 0-25% EtOAc/hexanes. White solid.
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.85 (ddd, *J* = 9.9, 5.1, 2.5 Hz, 2H), 7.21 – 7.15 (m, 2H), 4.13 (t, *J* = 5.3 Hz, 1H), 3.21 (dd, *J* = 9.3, 1.1 Hz, 1H), 2.85 (dd, *J* = 9.4, 1.8 Hz, 1H), 1.86 – 1.80 (m, 1H), 1.66 – 1.55 (m, 2H), 1.50 – 1.45 (m, 1H), 1.32 (qdd, *J* = 12.0, 11.0, 6.0, 3.2 Hz, 2H), 1.27 – 1.18 (m, 2H), 0.95 (s, 3H).
^{13}C NMR (176 MHz, $CDCl_3$) δ 165.0 (d, *J* = 253.9 Hz), 135.5 (d, *J* = 3.2 Hz), 129.7 (d, *J* = 9.1 Hz), 116.3 (d, *J* = 22.4 Hz), 59.7, 57.9, 44.4, 40.6, 37.6, 31.3, 24.7, 19.4.
HRMS (ESI) *m/z* calc'd for $C_{14}H_{19}FNO_2S$ $[M+H]^+$: 284.1115, found 284.1116.



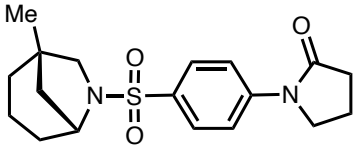
3.2g

(±)-6-((4-Methoxyphenyl)sulfonyl)-1-methyl-6-azabicyclo[3.2.1]octane (3.2g): The material was synthesized according to general procedure B. 35.4 mg, 60% yield. 0–20% EtOAc/hexanes. White solid.
^{1}H NMR (700 MHz, $CDCl_3$ δ 7.77 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 8.8 Hz, 2H), 4.11 (t, *J* = 5.2 Hz, 1H), 3.86 (s, 3H), 3.19 (d, *J* = 9.4 Hz, 1H), 2.86 (dd, *J* = 9.4, 1.8 Hz, 1H), 1.83 (dt, *J* = 12.4, 5.9 Hz, 1H), 1.70 – 1.63 (m, 1H), 1.57 (dt, *J* = 13.4, 5.8 Hz, 1H), 1.50 – 1.45 (m, 1H), 1.30 (qd, *J* = 13.4, 4.9 Hz, 2H), 1.23 – 1.14 (m, 2H), 0.94 (s, 3H).
^{13}C NMR (176 MHz, $CDCl_3$) δ 162.73, 131.08, 129.23, 114.20, 59.45, 57.90, 55.67, 44.26, 40.62, 37.68, 31.38, 24.78, 19.41.
HRMS (ESI) *m/z* calc'd for $C_{15}H_{21}NNaO_3S$ $[M+Na]^+$: 318.1134, found 318.1135.



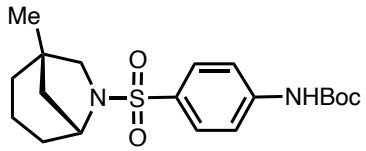
3.2h

(±)-*N*-(4-((1-methyl-6-azabicyclo[3.2.1]octan-6-yl)sulfonyl)phenyl)acetamide (3.2h): The material was synthesized according to general procedure B. 28.9 mg, 42%. 0-75% EtOAc/hexanes. Yellow oil.
^{1}H NMR (499 MHz, $CDCl_3$) δ 7.86 – 7.72 (m, 4H), 4.11 (q, *J* = 4.4, 3.6 Hz, 1H), 3.89 (t, *J* = 7.0 Hz, 2H), 3.19 (d, *J* = 9.3 Hz, 1H), 2.89 – 2.79 (m, 1H), 2.64 (t, *J* = 8.1 Hz, 2H), 2.19 (p, *J* = 7.7 Hz, 2H), 1.86 – 1.78 (m, 1H), 1.61 (dtt, *J* = 32.9, 13.6, 6.3 Hz, 2H), 1.52 – 1.40 (m, 1H), 1.37 – 1.12 (m, 4H), 0.93 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0, 143.0, 134.1, 128.1, 119.1, 59.6, 57.9, 48.6, 44.3, 40.6, 37.7, 33.0, 31.4, 24.7, 19.4, 18.0.
HRMS (ESI) *m/z* calc'd for $C_{16}H_{23}N_2O_3S^+$ [M+H]: 323.1429, found: 323.1434.



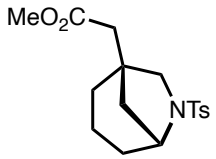
3.2i

(±)-1-(4-(((1*S*,5*R*)-1-methyl-6-azabicyclo[3.2.1]octan-6-yl)sulfonyl)phenyl)pyrrolidin-2-one (3.2i): The material was synthesized according to general procedure B. 28.9 mg, 41.5%. 0-50% EtOAc/hexanes. White solid.
^{1}H NMR (499 MHz, $CDCl_3$) δ 7.86 – 7.72 (m, 4H), 4.11 (q, *J* = 4.4, 3.6 Hz, 1H), 3.89 (t, *J* = 7.0 Hz, 2H), 3.19 (d, *J* = 9.3 Hz, 1H), 2.89 – 2.79 (m, 1H), 2.64 (t, *J* = 8.1 Hz, 2H), 2.19 (p, *J* = 7.7 Hz, 2H), 1.86 – 1.78 (m, 1H), 1.61 (dtt, *J* = 32.9, 13.6, 6.3 Hz, 2H), 1.52 – 1.40 (m, 1H), 1.37 – 1.12 (m, 4H), 0.93 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0, 143.0, 134.1, 128.1, 119.1, 59.6, 57.9, 48.6, 44.3, 40.6, 37.7, 33.0, 31.4, 24.7, 19.4, 18.0.
HRMS (ESI) *m/z* calc'd for $C_{18}H_{25}N_2O_3S^+$ [M+H]: 349.1586, found: 349.1590.



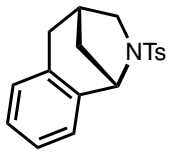
3.2j

(±)-*tert*-Butyl(4-(((1*S*,5*R*)-1-methyl-6-azabicyclo[3.2.1]octan-6-yl)sulfonyl)phenyl) carbamate (3.2j): The material was synthesized according to general procedure B. 42.1 mg, 55%. 0-30% EtOAc/hexanes. Yellow oil.
^{1}H NMR (600 MHz, CD_3CN) δ 7.89 (s, 1H), 7.72 (d, *J* = 8.8 Hz, 2H), 7.58 (d, *J* = 8.8 Hz, 2H), 4.05 (t, *J* = 5.2 Hz, 1H), 3.16 (d, *J* = 9.5 Hz, 1H), 2.83 (dd, *J* = 9.6, 1.6 Hz, 1H), 1.73 – 1.67 (m, 1H), 1.63 – 1.55 (m, 2H), 1.50 (s, 9H), 1.48 – 1.43 (m, 1H), 1.40 – 1.29 (m, 2H), 1.22 (d, *J* = 11.1 Hz, 1H), 1.06 – 1.00 (m, 1H), 0.90 (s, 3H).
^{13}C NMR (151 MHz, CD_3CN) δ 153.6, 144.3, 132.8, 129.1, 118.6, 81.3, 60.3, 58.6, 44.3, 41.1, 37.9, 31.9, 28.4, 24.7, 20.1.
HRMS (ESI) *m/z* calc'd for $C_{19}H_{29}N_2O_4S^+$ [M+H]: 381.1848, found: 381.1841.



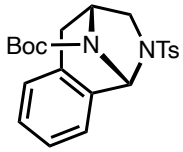
3.2k

(±)-Methyl 2-((1*S*,5*R*)-6-tosyl-6-azabicyclo[3.2.1]octan-1-yl)acetate (3.2k): The material was synthesized according to general procedure B. 27.9 mg, 41%. 0-35%. Colorless oil.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.15 (t, *J* = 5.2 Hz, 1H), 3.60 (s, 3H), 3.40 (d, *J* = 9.9 Hz, 1H), 3.08 (dd, *J* = 9.9, 1.6 Hz, 1H), 2.42 (s, 3H), 2.33 – 2.19 (m, 2H), 1.91 – 1.83 (m, 1H), 1.71 – 1.58 (m, 3H), 1.43 – 1.27 (m, 3H), 1.27 – 1.21 (m, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 171.51, 143.27, 136.23, 129.82, 127.30, 58.77, 56.37, 51.71, 43.36, 42.88, 42.43, 35.10, 31.43, 21.71, 19.13.
HRMS (ESI) *m/z* calc'd for $C_{17}H_{24}NO_4S^+$ [M+H]: 338.1426, found: 338.1425.



3.2l

(±)-(1*S*,4*S*)-2-Tosyl-2,3,4,5-tetrahydro-1H-1,4-methanobenzo[c]azepine (3.2l): The material was synthesized according to general procedure B. 26.4 mg, 42% yield. 0–15% EtOAc/hexanes. Colorless oil.
^{1}H NMR (600 MHz, CD_3CN) δ 7.62 – 7.58 (m, 2H), 7.30 (d, *J* = 8.2 Hz, 2H), 7.19 – 7.15 (m, 1H), 7.14 – 7.08 (m, 2H), 7.05 (d, *J* = 7.5 Hz, 1H), 4.76 (d, *J* = 5.1 Hz, 1H), 3.44 – 3.37 (m, 1H), 3.15 (d, *J* = 10.0 Hz, 1H), 3.07 (dd, *J* = 17.5, 5.0 Hz, 1H), 2.73 (d, *J* = 17.9 Hz, 1H), 2.70 (d, *J* = 5.3 Hz, 1H), 2.39 (s, 3H), 1.69 (d, *J* = 11.4 Hz, 1H), 1.53 – 1.47 (m, 1H).
^{13}C NMR (151 MHz, CD_3CN) δ 144.38, 140.38, 136.60, 135.05, 130.46, 130.37, 128.78, 128.14, 127.60, 126.55, 61.10, 54.98, 36.59, 34.76, 34.44, 21.41.
HRMS (ESI) *m/z* calc'd for $C_{18}H_{20}NO_2S^+$ [M+H]: 314.1215, found: 314.1215.

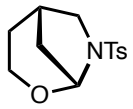


3.2m

(±)-*tert*-Butyl-(1*R*,4*R*)-2-tosyl-2,3,4,5-tetrahydro-1H-1,4-epiminobenzo[c]azepine-10-carboxylate (3.2m): The material was synthesized according to general procedure B. 55 mg, 66% yield. 0–60% EtOAc/hexanes. White solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.7 Hz, 2H), 7.29 – 7.26 (m, 1H), 7.26 – 7.24 (m, 2H), 7.22 (td, *J* = 7.4, 1.6 Hz, 1H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.07 (d, *J* = 7.4 Hz, 1H), 6.27 (s, 1H), 4.65 (s, 1H), 3.58 (t, *J* = 8.7 Hz, 1H), 3.36 (dd, *J* = 17.6, 4.9 Hz, 1H), 3.21 (d, *J* = 10.0 Hz, 1H), 2.64 (d, *J* = 17.0 Hz, 1H), 2.40 (s, 3H), 1.33 (s, 9H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 152.22, 143.75, 137.09, 135.56, 131.48, 129.79, 129.63, 128.71, 128.08, 126.71, 126.03, 81.23, 72.13, 53.00, 52.08, 34.60, 28.33, 21.58.
HRMS (ESI) *m/z* calc'd for $C_{22}H_{27}N2O_4S^+$ [M+H]: 415.1691, found: 415.1697.

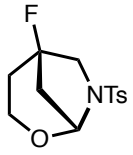
3.2n

(±)-(1*R*,5*S*)-6-Tosyl-8-oxa-6-azabicyclo[3.2.1]octane (3.2n): The material was synthesized according to general procedure B. 31.2 mg, 58% yield. 0–30% EtOAc/hexanes. Colorless oil.
^{1}H NMR (600 MHz, CD_3CN) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 2H), 5.48 (s, 1H), 4.39 – 4.30 (m, 1H), 3.33 (d, *J* = 9.6 Hz, 1H), 3.22 (dd, *J* = 9.4, 6.3 Hz, 1H), 2.42 (s, 3H), 1.91 – 1.82 (m, 1H), 1.76 – 1.69 (m, 2H), 1.66 – 1.59 (m, 2H), 1.45 (dd, *J* = 14.1, 4.9 Hz, 1H).
^{13}C NMR (151 MHz, CD_3CN) δ 145.16, 135.07, 130.73, 128.74, 89.82, 76.32, 50.90, 32.37, 29.32, 21.45, 16.18.
HRMS (ESI) *m/z* calc'd for $C_{13}H_{18}NO_3S^+$ [M+H]: 268.1007, found: 268.1008.



3.2o

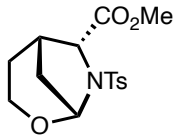
(±)-(1*R*,5*S*)-7-Tosyl-2-oxa-7-azabicyclo[3.2.1]octane (3.2o): The material was synthesized according to general procedure B. 46.4 mg, 87% yield. 0–30% EtOAc/hexanes. Colorless oil.
^{1}H NMR (600 MHz, CD_3CN) δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 5.44 (d, *J* = 3.1 Hz, 1H), 3.52 (dd, *J* = 11.8, 6.9 Hz, 1H), 3.32 – 3.24 (m, 3H), 2.54 (s, 1H), 2.41 (s, 3H), 1.83 – 1.76 (m, 1H), 1.73 (d, *J* = 11.4 Hz, 1H), 1.42 – 1.36 (m, 2H).
^{13}C NMR (151 MHz, CD_3CN) δ 144.70, 137.47, 130.57, 127.88, 87.25, 59.95, 51.77, 39.28, 33.34, 31.02, 21.40.
HRMS (ESI) *m/z* calc'd for $C_{13}H_{18}NO_3S^+$ [M+H]: 268.1007, found: 268.0994.



3.2p

(±)-(1*R*,5*R*)-5-Fluoro-7-tosyl-2-oxa-7-azabicyclo[3.2.1]octane (3.2p): The material was synthesized according to general procedure B. 26.9 mg, 47% yield. 0–40% EtOAc/hexanes. Colorless oil. Prolonged exposure to ambient light leads to decomposition.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 5.66 (t, *J* = 3.8 Hz, 1H), 3.75 (ddd, *J* = 11.3, 7.0, 3.7 Hz, 1H), 3.51 – 3.35 (m, 2H), 3.14 (td, *J* = 12.2, 4.6 Hz,

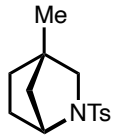
1H), 2.44 (s, 3H), 2.13 (dtd, *J* = 14.9, 8.1, 7.6, 4.2 Hz, 2H), 1.92 (d, *J* = 10.3 Hz, 1H), 1.82 (ddt, *J* = 12.0, 8.0, 3.9 Hz, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 143.95, 136.00, 129.81, 127.22, 94.65 (d, *J* = 202.6 Hz), 86.97 (d, *J* = 7.7 Hz), 59.73 (d, *J* = 10.5 Hz), 52.21 (d, *J* = 30.8 Hz), 43.57 (d, *J* = 16.3 Hz), 35.99 (d, *J* = 19.7 Hz), 21.59.
HRMS (ESI) m/z calc'd for $C_{13}H_{17}FNO_3S^+$ [M+H]: 286.0913, found: 286.0905.



3.2q

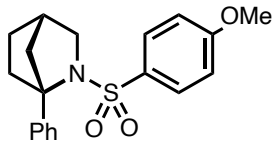
(±)-Methyl (1*R*,5*S*,6*R*)-7-tosyl-2-oxa-7-azabicyclo[3.2.1]octane-6-carboxylate (3.2q, major diastereomer): The material was synthesized according to general procedure B. 37.2 mg, 57% yield. 0–25% EtOAc/hexanes. Colorless oil.
^{1}H NMR (600 MHz, CD_3CN) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.1 Hz, 2H), 5.42 (d, *J* = 3.6 Hz, 1H), 4.32 (d, *J* = 4.7 Hz, 1H), 4.07 (td, *J* = 12.0, 4.7 Hz, 1H), 3.73 (s, 3H), 3.59 (dd, *J* = 11.5, 7.4 Hz, 1H), 2.81 – 2.76 (m, 1H), 2.42 (s, 3H), 1.91 – 1.84 (m, 1H), 1.74 (d, *J* = 11.4 Hz, 1H), 1.37 (dq, *J* = 13.9, 3.8 Hz, 1H), 1.26 (dq, *J* = 11.2, 4.2 Hz, 1H).
^{13}C NMR (151 MHz, CD_3CN) δ 170.79, 145.17, 137.29, 130.64, 128.17, 88.33, 65.37, 59.96, 52.83, 39.14, 37.39, 27.98, 21.48.
HRMS (ESI) *m/z* calc'd for $C_{15}H_{20}NO_5S^+$ [M+H]: 326.1062, found: 326.1065.

(±)-Methyl (1*R*,5*S*,6*S*)-7-tosyl-2-oxa-7-azabicyclo[3.2.1]octane-6-carboxylate (3.2q, minor diastereomer): The material was synthesized according to general procedure B. 13.6 mg, 21% yield. 0–25% EtOAc/hexanes. Colorless oil.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 5.60 (d, *J* = 3.1 Hz, 1H), 4.17 (s, 1H), 3.71 (s, 3H), 3.53 – 3.46 (m, 1H), 2.99 (td, *J* = 12.4, 4.5 Hz, 1H), 2.69 – 2.61 (m, 1H), 2.43 (s, 4H), 2.21 – 2.13 (m, 1H), 1.93 – 1.84 (m, 1H), 1.76 (d, *J* = 11.4 Hz, 1H), 1.60 (s, 1H), 1.55 – 1.49 (m, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 171.62, 144.01, 136.94, 129.70, 127.90, 87.07, 63.09, 58.93, 52.69, 38.84, 37.34, 31.13, 21.77.
HRMS (ESI) *m/z* calc'd for $C_{15}H_{20}NO_5S^+$ [M+H]: 326.1062, found: 326.1059.



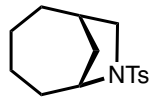
3.6a

(±)-(1*R*,4*S*)-4-Methyl-2-tosyl-2-azabicyclo[2.2.1]heptane (3.6a): The material was synthesized according to general procedure B. 23.1 mg, 44% yield. 0–15% EtOAc/hexanes. Colorless oil.
^{1}H NMR (600 MHz, DMSO-d_6) δ 7.68 (d, J = 8.2 Hz, 2H), 7.42 (d, J = 8.0 Hz, 2H), 4.04 (s, 1H), 2.93 (d, J = 8.7 Hz, 1H), 2.77 (dd, J = 8.8, 2.8 Hz, 1H), 2.40 (s, 3H), 1.68 – 1.55 (m, 2H), 1.41 – 1.30 (m, 2H), 1.12 (d, J = 9.7 Hz, 1H), 1.04 (s, 3H), 0.68 – 0.59 (m, 1H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 143.16, 135.21, 129.83, 127.23, 60.96, 59.05, 44.71, 42.39, 33.60, 31.69, 21.02, 17.71.
HRMS (ESI) *m/z* calc'd for $C_{14}H_{20}NO_2S^+$ [M+H]: 266.1515, found: 266.1519.



3.6b

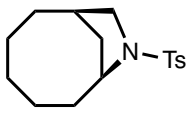
(±)-(1*R*,4*S*)-2-((4-Methoxyphenyl)sulfonyl)-1-phenyl-2-azabicyclo[2.2.1]heptane (3.6b): The material was synthesized according to general procedure B. 44.1 mg, 64% yield. 0–20% EtOAc/hexanes. Yellow oil.
^{1}H NMR (600 MHz, CD_3CN) δ 7.44 – 7.40 (m, 2H), 7.37 (dd, J = 6.5, 3.2 Hz, 2H), 7.28 – 7.21 (m, 3H), 6.92 – 6.88 (m, 2H), 3.83 (s, 3H), 3.53 – 3.46 (m, 2H), 2.54 (s, 1H), 2.38 (tq, J = 9.0, 3.3 Hz, 1H), 2.20 (d, J = 10.0 Hz, 2H), 2.10 (td, J = 12.4, 5.3 Hz, 2H), 1.91 – 1.84 (m, 1H), 1.68 – 1.63 (m, 1H), 1.56 – 1.49 (m, 1H).
^{13}C NMR (151 MHz, CD_3CN) δ 163.47, 139.60, 134.46, 129.97, 129.21, 128.50, 128.27, 114.74, 74.84, 57.99, 56.35, 48.40, 37.59, 33.28, 28.87.
HRMS (ESI) *m/z* calc'd for $C_{19}H_{22}NO_3S^+$ [M+H]: 344.1320, found: 344.1312.



3.6c

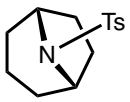
(±)-(1*S*,6*R*)-7-Tosyl-7-azabicyclo[4.2.1]nonane (3.6c): The material was synthesized according to general procedure B. 23.2 mg, 42% yield. 0–20% EtOAc/hexanes. Colorless oil.
^{1}H NMR (600 MHz, CD_3CN) δ 7.69 (d, J = 8.3 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 3.98 (ddd, J = 8.7, 4.4, 2.1 Hz, 1H), 3.13 (dd, J = 9.5, 6.9 Hz, 1H), 3.08 (d, J = 9.6 Hz, 1H), 2.41 (s, 3H), 2.38

(tt, *J* = 7.1, 3.9 Hz, 1H), 1.92 – 1.86 (m, 1H), 1.71 – 1.62 (m, 3H), 1.61 (d, *J* = 12.6 Hz, 1H), 1.59 – 1.53 (m, 2H), 1.50 – 1.38 (m, 3H).
^{13}C NMR (151 MHz, CD_3CN) δ 144.47, 135.48, 130.52, 128.30, 60.49, 55.07, 37.01, 35.39, 35.17, 33.83, 25.34, 24.27, 21.39.
HRMS (ESI) *m/z* calc'd for $C_{15}H_{22}NO_2S^+$ [M+H]: 280.1371, found: 280.1363.



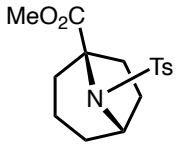
3.6d

(±)-(1*S*,7*R*)-8-Tosyl-8-azabicyclo[5.2.1]decane (3.6d): The material was synthesized according to general procedure B. 9.8 mg, 17% yield. 0–15% EtOAc/hexanes. Yellow oil.
^{1}H NMR (600 MHz, CD_3CN) δ 7.71 – 7.66 (m, 2H), 7.40 (d, *J* = 7.9 Hz, 2H), 3.66 (ddt, *J* = 11.5, 6.1, 2.0 Hz, 1H), 3.36 (d, *J* = 9.7 Hz, 1H), 3.04 (dd, *J* = 9.6, 7.3 Hz, 1H), 2.42 (s, 3H), 2.17 – 2.13 (m, 1H), 2.02 – 1.96 (m, 1H), 1.88 – 1.82 (m, 1H), 1.81 – 1.70 (m, 4H), 1.69 – 1.65 (m, 1H), 1.60 – 1.53 (m, 2H), 1.52 – 1.45 (m, 2H), 1.27 – 1.20 (m, 1H).
^{13}C NMR (151 MHz, CD_3CN) δ 144.61, 134.07, 130.47, 128.67, 58.48, 54.58, 37.90, 36.73, 35.50, 35.10, 27.85, 26.64, 26.02, 21.39.
HRMS (ESI) *m/z* calc'd for $C_{16}H_{24}NO_2S^+$ [M+H]: 294.1527, found: 294.1531.



3.6e

(±)-(1*R*,5*S*)-8-Tosyl-8-azabicyclo[3.2.1]octane (3.6e): The material was synthesized according to general procedure B. 15.8 mg, 30% yield. 0–15% EtOAc/hexanes.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 4.19 (s, 2H), 2.41 (s, 3H), 1.81 (ddd, *J* = 20.7, 8.6, 2.7 Hz, 2H), 1.62 – 1.54 (m, 2H), 1.53 – 1.50 (m, 4H), 1.50 – 1.45 (m, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 143.34, 137.75, 129.71, 127.53, 57.34, 32.55, 28.23, 21.70, 16.76.
HRMS (ESI) *m/z* calc'd for $C_{14}H_{20}NO_2S^+$ [M+H]: 266.1215, found: 266.1209.



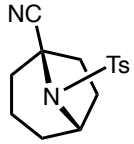
3.6f

(±)-Methyl (1*R*,5*S*)-8-tosyl-8-azabicyclo[3.2.1]octane-1-carboxylate (3.6f): The material was synthesized according to general procedure B. 30.6 mg, 47% yield. 0–30% EtOAc/hexanes. White solid.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.0 Hz, 2H), 4.18 – 4.08 (m, 1H), 3.70 (s, 3H), 2.41 (s, 3H), 2.30 (qd, *J* = 13.9, 13.4, 6.6 Hz, 2H), 2.22 (td, *J* = 12.4, 11.1, 5.3 Hz, 1H), 1.96 (dtt, *J* = 14.2, 9.4, 5.4 Hz, 2H), 1.91 – 1.85 (m, 1H), 1.77 (td, *J* = 12.2, 11.3, 5.4 Hz, 2H), 1.65 (ddd, *J* = 13.1, 9.4, 3.0 Hz, 1H), 1.48 – 1.38 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 172.11, 143.02, 139.46, 129.40, 127.19, 69.30, 59.42, 52.54, 34.40, 33.43, 29.84, 28.21, 21.67, 17.32.

HRMS (ESI) *m/z* calc'd for $C_{16}H_{22}NO_4S^+$ [M+H]: 324.1269, found: 324.1276.



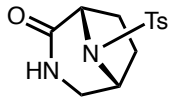
3.6g

(±)-(1*R*,5*S*)-8-Tosyl-8-azabicyclo[3.2.1]octane-1-carbonitrile (3.6g): The material was synthesized according to general procedure B. 22.6 mg, 39% yield. 0–30% EtOAc/hexanes. Colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 4.52 (dd, *J* = 7.0, 3.0 Hz, 1H), 2.43 (s, 3H), 2.38 (td, *J* = 12.5, 6.7 Hz, 1H), 2.18 (qt, *J* = 13.0, 7.3 Hz, 2H), 2.08 – 1.90 (m, 2H), 1.87 – 1.82 (m, 1H), 1.76 (dt, *J* = 10.5, 4.5 Hz, 2H), 1.67 (ddd, *J* = 13.3, 9.1, 5.0 Hz, 1H), 1.56 – 1.51 (m, 1H).

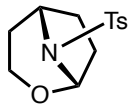
^{13}C NMR (151 MHz, $CDCl_3$) δ 144.14, 137.78, 129.84, 127.90, 118.68, 58.90, 57.61, 36.88, 35.87, 30.68, 27.61, 21.78, 16.95.

HRMS (ESI) *m/z* calc'd for $C_{15}H_{19}N_2O_2S^+$ [M+H]: 293.1324, found: 293.1318.



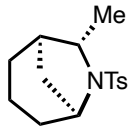
3.6h

(±)-(1*S*,5*R*)-8-Tosyl-6,8-diazabicyclo[3.2.1]octan-7-one (3.6h): The material was synthesized according to general procedure B. 11.9 mg, 21% yield. Purified via reverse phase chromatography (eluent: 2–55% ACN in water with 0.1% NH_4OH modifier).
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 5.32 (s, 1H), 5.25 (s, 1H), 4.04 (t, *J* = 3.1 Hz, 1H), 2.42 (s, 3H), 2.13 – 1.88 (m, 4H), 1.83 – 1.65 (m, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 174.12, 144.85, 134.32, 130.25, 127.98, 69.59, 59.24, 29.39, 26.11, 21.86, 16.57.
HRMS (ESI) *m/z* calc'd for $C_{13}H_{17}N_2O_3S^+$ [M+H]: 281.0960, found: 281.0951.



3.6i

(±)-(1*S*,5*S*)-8-Tosyl-2-oxa-8-azabicyclo[3.2.1]octane (3.6i): The material was synthesized according to general procedure B. 29.3 mg, 55% yield. 0–35% EtOAc/hexanes. Yellow solid.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 5.61 (d, *J* = 4.1 Hz, 1H), 4.32 – 4.23 (m, 1H), 3.87 (td, *J* = 12.3, 4.2 Hz, 1H), 3.62 (dd, *J* = 12.1, 6.5 Hz, 1H), 2.42 (s, 4H), 2.16 – 2.00 (m, 4H), 1.93 (tdd, *J* = 12.7, 6.5, 3.0 Hz, 1H), 1.76 – 1.69 (m, 1H), 1.08 (dt, *J* = 13.2, 3.2 Hz, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 143.49, 138.53, 129.68, 127.88, 86.34, 58.88, 55.57, 29.93, 29.79, 28.06, 21.72.
HRMS (ESI) *m/z* calc'd for $C_{13}H_{18}NO_3S^+$ [M+H]: 268.1007, found: 268.1010.

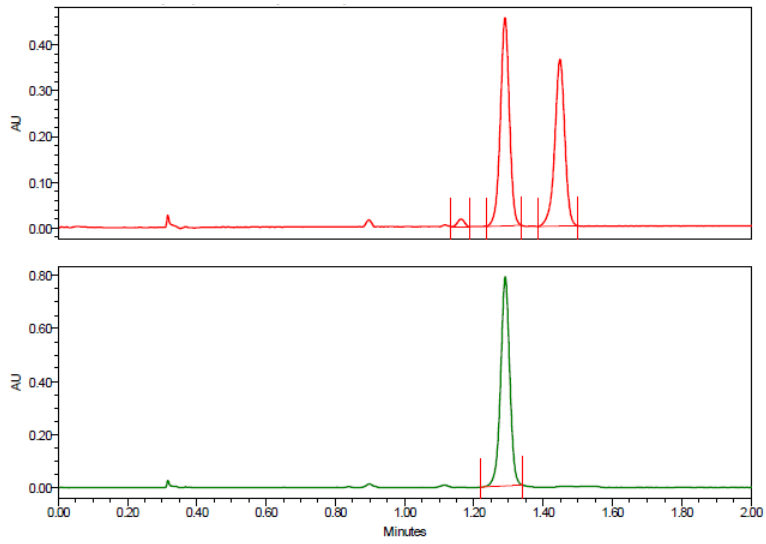


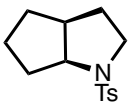
3.9

(1*R*,5*S*,7*S*)-7-Methyl-6-tosyl-6-azabicyclo[3.2.1]octane (2s): The material was synthesized according to general procedure B. 15.6 mg, 28% yield. 0–15% EtOAc/hexanes. Colorless oil.
^{1}H NMR (499 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 4.06 (t, *J* = 5.0 Hz, 1H), 3.52 – 3.41 (m, 1H), 2.42 (s, 3H), 2.01 (d, *J* = 3.0 Hz, 1H), 1.93 – 1.67 (m, 3H), 1.65 – 1.54 (m, 2H), 1.48 (d, *J* = 6.6 Hz, 3H), 1.41 – 1.33 (m, 1H), 1.23 (d, *J* = 11.1 Hz, 1H), 1.01 (dtd, *J* = 11.0, 6.1, 5.4, 3.5 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.22, 135.13, 129.69, 127.74, 60.20, 59.81, 39.58, 37.08, 31.84, 25.88, 21.69, 18.68, 16.00.
HRMS (ESI) *m/z* calc'd for $C_{15}H_{22}NO_2S^+$ [M+H]: 280.1371, found: 280.1386.
$[\alpha]^{25}_D$ –0.09 (c 0.18, $CHCl_3$).

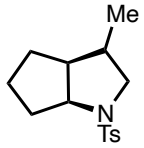
A chiral SFC trace of **3.9** (bottom trace) in comparison to a racemic standard (top trace) using a (*R*,*R*)-Whelk-01 4.6 mm x 100 mm column on a Sepiatec instrument (eluent: 20% MeOH w/ 0.1% NH_4OH in CO_2).





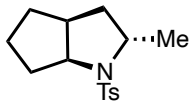
3.11a

(±)-(3*aR*,6*aR*)-1-Tosyloctahydrocyclopenta[b]pyrrole (3.11a): The material was synthesized according to general procedure B. 28 mg, 53% yield. 0–15% EtOAc/hexanes. Yellow oil.
^{1}H NMR (600 MHz, CD_3CN) δ 7.69 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 8.0 Hz, 2H), 3.77 – 3.70 (m, 1H), 3.41 – 3.33 (m, 1H), 2.99 (dt, *J* = 10.1, 7.3 Hz, 1H), 2.48 – 2.43 (m, 1H), 2.42 (s, 3H), 1.93 – 1.88 (m, 1H), 1.76 – 1.69 (m, 1H), 1.68 – 1.37 (m, 6H).
^{13}C NMR (151 MHz, CD_3CN) δ 144.7, 135.0, 130.5, 128.6, 66.0, 50.6, 44.1, 35.4, 32.4, 31.5, 25.1, 21.4.
HRMS (ESI) *m/z* calc'd for $C_{14}H_{20}NO_2S^+$ [M+H]: 266.1215, found: 266.1209.

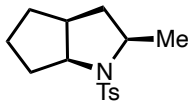


3.11b

(±)-(3a*S*,6a*S*)-3-Methyl-1-tosyloctahydrocyclopenta[*b*]pyrrole (3.11b): The material was synthesized according to general procedure B. Isolated as an inseparable ~1:1 mixture of isomers. 37.6 mg, 67% yield. 0–15% EtOAc/hexanes. Colorless oil.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 7.6, 3.2 Hz, 3H), 7.31 (d, *J* = 8.1 Hz, 2H), 7.28 (d, *J* = 8.1 Hz, 2H), 4.06 (q, *J* = 6.4 Hz, 1H), 3.75 – 3.67 (m, 1H), 3.53 (dd, *J* = 8.8, 6.6 Hz, 1H), 3.49 (dd, *J* = 11.1, 7.5 Hz, 1H), 2.88 (t, *J* = 11.2 Hz, 1H), 2.46 (d, *J* = 9.1 Hz, 1H), 2.43 (s, 3H), 2.41 (s, 3H), 2.39 (d, *J* = 7.7 Hz, 1H), 2.14 – 2.06 (m, 1H), 1.99 – 1.81 (m, 4H), 1.77 (dq, *J* = 13.7, 7.0 Hz, 1H), 1.72 – 1.61 (m, 3H), 1.60 – 1.37 (m, 6H), 0.87 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 143.4, 143.1, 136.4, 133.5, 129.7, 129.6, 128.1, 127.3, 66.7, 65.1, 57.0, 54.2, 51.7, 48.7, 38.3, 35.4, 35.2, 34.7, 30.7, 26.1, 25.3, 24.3, 21.7, 16.9, 13.0.
HRMS (ESI) *m/z* calc'd for $C_{15}H_{22}NO_2S^+$ [M+H]: 280.1371, found: 280.1373.

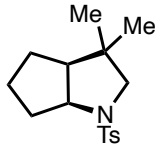


3.11c-1



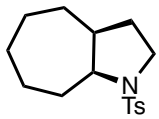
3.11c-2

(±)-(2*S*,3a*S*,6a*S*)-2-Methyl-1-tosyloctahydrocyclopenta[*b*]pyrrole (3.11c-1) and (±)-(2*R*,3a*S*,6a*S*)-2-methyl-1-tosyloctahydrocyclopenta[*b*]pyrrole (3.11c-2): The material was synthesized according to general procedure B. Isolated as an inseparable 2:1 mixture of **(±)-3.11c-1**: **(±)-3.11c-2**. 27.8 mg, 50% yield. 0–15% EtOAc/hexanes. Colorless oil. Peaks that can solely be attributed to the minor diastereomer are denoted with an asterisk.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.70* (d, *J* = 8.3 Hz, 1H), 7.30* (d, *J* = 8.0 Hz, 1H), 7.28 – 7.24 (m, 2H), 4.10 (pd, *J* = 6.4, 2.6 Hz, 1H), 4.02 (td, *J* = 7.6, 4.8 Hz, 1H), 3.89* (td, *J* = 7.9, 3.5 Hz, 0H), 3.42 – 3.30* (m, 0H), 2.80 (qd, *J* = 9.7, 8.4, 3.0 Hz, 1H), 2.42 (s, 1H), 2.41 (s, 3H), 2.28* (pd, *J* = 8.7, 2.8 Hz, 1H), 2.04 – 1.93 (m, 1H), 1.86 – 1.69 (m, 3H), 1.68 – 1.44 (m, 7H), 1.39 (d, *J* = 6.2 Hz, 2H), 1.31 – 1.25 (m, 1H), 1.14 (d, *J* = 6.4 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 143.3,* 142.9, 139.2, 134.5,* 129.7,* 129.5, 128.0,* 127.4, 67.6,* 64.2, 58.8,* 42.0, 41.2,* 40.5,* 39.4, 35.5,* 33.0, 31.9,* 31.3, 24.9, 24.0,* 22.6,* 21.7,* 21.6, 20.0.
HRMS (ESI) *m/z* calc'd for $C_{15}H_{22}NO_2S^+$ [M+H]: 280.1371, found: 280.1370.



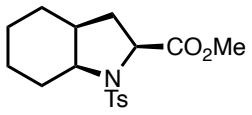
3.11d

(±)-3,3-Dimethyl-1-tosyloctahydrocyclopenta[*b*]pyrrole (3.11d): The material was synthesized according to general procedure B. 44.5 mg, 76% yield. 0–20% EtOAc/hexanes. White solid.
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 4.02 (dt, *J* = 7.3, 4.9 Hz, 1H), 3.13 (d, *J* = 10.4 Hz, 1H), 3.07 (d, *J* = 10.4 Hz, 1H), 2.40 (s, 3H), 2.00 (q, *J* = 8.1 Hz, 1H), 1.96 (td, *J* = 7.5, 5.0 Hz, 2H), 1.73 – 1.66 (m, 1H), 1.58 – 1.50 (m, 1H), 1.47 – 1.34 (m, 2H), 0.94 (s, 3H), 0.53 (s, 3H).
^{13}C NMR (176 MHz, $CDCl_3$): δ 143.1, 136.2, 129.6, 127.4, 65.5, 59.7, 55.9, 39.7, 35.0, 28.2, 27.5, 26.1, 22.1, 21.6.
HRMS (ESI) *m/z* calc'd for $C_{16}H_{24}NO_2S^+$ [M+H]: 294.1527, found: 294.1529.

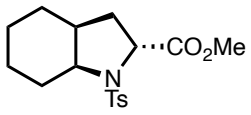


3.11e

(±)-(3a*S*,8a*S*)-1-Tosyldecahydrocyclohepta[*b*]pyrrole (3.11e): The material was synthesized according to general procedure B. 30.6 mg, 52% yield. 0–20% EtOAc/hexanes. Colorless oil.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 3.55 (ddd, *J* = 11.2, 8.8, 2.3 Hz, 1H), 3.47 (ddd, *J* = 9.3, 7.4, 1.9 Hz, 1H), 2.94 (ddd, *J* = 10.6, 9.5, 6.3 Hz, 1H), 2.43 (s, 3H), 2.08 (dd, *J* = 13.9, 7.1 Hz, 1H), 1.92 (ddt, *J* = 11.3, 8.9, 5.7 Hz, 1H), 1.88 – 1.82 (m, 1H), 1.79 (dt, *J* = 13.9, 6.9 Hz, 2H), 1.72 (dddd, *J* = 16.3, 12.0, 8.1, 4.9 Hz, 2H), 1.67 – 1.52 (m, 4H), 1.36 – 1.25 (m, 1H), 1.25 – 1.14 (m, 2H), 1.14 – 1.04 (m, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 143.3, 134.5, 129.7, 127.8, 65.2, 48.6, 43.5, 33.0, 32.0, 31.5, 31.1, 27.7, 26.9, 21.7.
HRMS (ESI) *m/z* calc'd for $C_{16}H_{24}NO_3S^+$ [M+H]: 294.1527, found: 294.1536.



3.11f-1



3.11f-2

(±)-Methyl (2*S*,3a*S*,7a*S*)-1-tosyloctahydro-1*H*-indole-2-carboxylate (3.11f-1) and (±)-methyl (2*R*,3a*S*,7a*S*)-1-tosyloctahydro-1*H*-indole-2-carboxylate (13f-2): The material was synthesized according to general procedure B. Isolated as an inseparable 1:1 mixture of **(±)-13f-1**:**(±)-13f-2**. 17.2 mg, 25% yield. 0–20% EtOAc/hexanes. Yellow oil. The mixture was further separated by SFC chromatography for structural characterization.

(±)-Methyl (2*S*,3a*S*,7a*S*)-1-tosyloctahydro-1H-indole-2-carboxylate ((±)-13f-1):

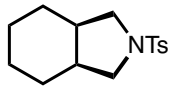
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.25 – 4.16 (m, 1H), 3.78 (s, 3H), 3.66 (dt, *J* = 12.4, 6.3 Hz, 1H), 2.43 (s, 3H), 2.11 – 2.00 (m, 2H), 1.88 – 1.80 (m, 2H), 1.61 (q, *J* = 13.2, 10.9 Hz, 3H), 1.50 (ddt, *J* = 18.8, 10.2, 5.0 Hz, 2H), 1.41 (dd, *J* = 9.6, 3.8 Hz, 1H), 1.16 – 1.07 (m, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 173.3, 143.7, 136.0, 129.8, 127.8, 60.7, 60.6, 52.7, 37.6, 33.0, 29.8, 25.9, 23.9, 21.7, 20.6.
HRMS (ESI) *m/z* calc'd for $C_{17}H_{24}NO_4S^+$ [M+H]: 338.1426, found: 338.1424.

(±)-Methyl (2*R*,3a*S*,7a*S*)-1-tosyloctahydro-1H-indole-2-carboxylate ((±)-13f-2):

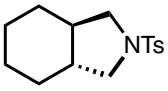
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 4.38 (dd, *J* = 9.6, 1.2 Hz, 1H), 3.82 – 3.76 (m, 1H), 3.67 (s, 3H), 2.61 (dd, *J* = 11.5, 5.0 Hz, 1H), 2.42 (s, 3H), 2.30 (td, *J* = 13.0, 9.7 Hz, 1H), 2.09 (dd, *J* = 10.5, 4.8 Hz, 1H), 1.82 – 1.75 (m, 1H), 1.62 (dt, *J* = 12.3, 4.5 Hz, 2H), 1.42 (d, *J* = 13.5 Hz, 1H), 1.22 – 1.16 (m, 2H), 1.12 – 1.05 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.4, 143.4, 138.1, 129.6, 127.8, 59.9, 59.3, 52.5, 36.0, 32.6, 28.9, 25.9, 23.6, 21.7, 20.4.

HRMS (ESI) *m/z* calc'd for $C_{17}H_{24}NO_4S^+$ [M+H]: 338.1426, found: 338.1440.

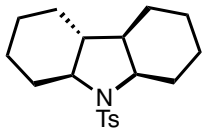


3.11g-1



3.11g-2

(±)-(3a*R*,7a*S*)-2-Tosyloctahydro-1*H*-isoindole (3.11g-1) and (±)-(3a*R*,7a*R*)-2-tosyloctahydro-1*H*-isoindole (3.11g-2): The material was synthesized according to general procedure B. Isolated as an inseparable 1.44:1 mixture of diastereomers **(±)-3.11g-1:(±)-3.11g-2**. 28.9 mg, 52% yield. 0–15% EtOAc/hexanes. Peaks that can be solely attributed to the minor diastereomer are marked with an asterisk.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 – 7.68 (m, 4H), 7.30 (d, *J* = 8.1 Hz, 4H), 3.49 (dd, *J* = 9.3, 6.6 Hz, 2H), 3.25* (dd, *J* = 9.6, 6.8 Hz, 2H), 3.14* (dd, *J* = 9.6, 5.5 Hz, 1H), 2.79 – 2.73 (m, 2H), 2.41 (d, *J* = 8.1 Hz, 6H), 2.05* (dt, *J* = 10.3, 6.1 Hz, 2H), 1.79 (d, *J* = 13.0 Hz, 2H), 1.73 – 1.69 (m, 2H), 1.44 (dq, *J* = 13.4, 4.7, 4.1 Hz, 2H), 1.40 – 1.32 (m, 2H), 1.24 (dddd, *J* = 36.5, 14.1, 8.9, 5.1 Hz, 6H), 1.18 – 1.13 (m, 2H), 1.02 – 0.92 (m, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 143.3,* 143.2, 135.0, 134.7,* 129.8, 129.7,* 127.5,* 127.4, 53.2, 51.7,* 44.6, 37.5,* 28.4, 25.6,* 25.5, 22.7, 21.7.
HRMS (ESI) *m/z* calc'd for $C_{15}H_{22}NO_2S^+$ [M+H]: 280.1371, found: 280.1372.



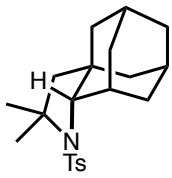
3.11h

(±)-(4a*S*,4b*S*,8a*R*,9a*S*)-9-Tosyldodecahydro-1*H*-carbazole (3.11h): The material was synthesized according to general procedure B. 24.8 mg, 37% yield. 0–25% EtOAc/hexanes. Colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 4.40 (d, *J* = 7.3 Hz, 1H), 3.63 (dd, *J* = 7.8, 3.1 Hz, 1H), 2.42 (s, 3H), 1.79 – 1.68 (m, 4H), 1.68 – 1.62 (m, 1H), 1.49 – 1.38 (m, 3H), 1.33 (dddd, *J* = 17.0, 13.4, 8.4, 3.6 Hz, 2H), 1.25 (s, 1H), 1.23 – 1.16 (m, 1H), 1.16 – 0.95 (m, 5H), 0.91 – 0.81 (m, 2H), 0.72 (qd, *J* = 12.5, 3.5 Hz, 1H), 0.59 (qd, *J* = 12.5, 3.4 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 143.3, 138.5, 129.8, 127.2, 50.3, 46.6, 38.2, 31.7, 30.7, 30.6, 26.6, 26.6, 26.3, 26.0, 24.1, 21.7, 20.0.

HRMS (ESI) *m/z* calc'd for $C_{19}H_{28}NO_2S^+$ [M+H]: 334.1840, found: 334.1846.



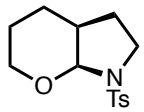
3.11i

(±)-(3a*S*,5*R*,7*S*,9*R*,9a*S*)-2,2-Dimethyl-1-tosyldecahydro-3a,7:5,9dimethanocycloocta[*b*]pyrrole (3.11i): The material was synthesized according to general procedure B. 38.4 mg, 53% yield. 0–15% EtOAc/hexanes. Colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.3 Hz, 2H), 7.26 – 7.24 (m, 2H), 3.07 (s, 1H), 2.56 – 2.49 (m, 1H), 2.41 (s, 3H), 2.09 (d, *J* = 14.0 Hz, 1H), 1.91 (s, 1H), 1.78 (ddd, *J* = 28.4, 12.6, 2.6 Hz, 3H), 1.71 (s, 3H), 1.67 – 1.56 (m, 5H), 1.55 (s, 6H), 1.38 (s, 4H), 1.35 (d, *J* = 12.4 Hz, 2H), 1.31 – 1.22 (m, 3H).

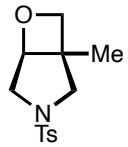
^{13}C NMR (151 MHz, $CDCl_3$) δ 142.6, 139.2, 129.4, 127.9, 69.0, 65.9, 54.7, 42.9, 38.5, 38.3, 37.2, 36.9, 31.9, 30.9, 30.1, 30.1, 28.8, 27.9, 21.7.

HRMS (ESI) *m/z* calc'd for $C_{21}H_{30}NO_2S^+$ [M+H]: 360.1997, found: 360.1992.



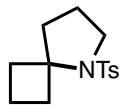
3.11j

(±)-(4a*R*,7a*R*)-7-Tosyloctahydropyrano[2,3-*b*]pyrrole (3.11j): The material was synthesized according to general procedure B. 42.4 mg, 75% yield. 0–40% EtOAc/hexanes. Colorless oil.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 5.12 (d, *J* = 3.3 Hz, 1H), 3.87 – 3.79 (m, 1H), 3.42 (td, *J* = 11.9, 2.1 Hz, 1H), 3.34 (dd, *J* = 8.9, 6.8 Hz, 2H), 2.41 (s, 3H), 2.18 – 1.99 (m, 2H), 1.90 – 1.72 (m, 3H), 1.69 – 1.61 (m, 1H), 1.32 (ddt, *J* = 11.4, 4.8, 2.5 Hz, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 143.3, 136.9, 129.6, 127.9, 87.5, 65.5, 46.4, 38.1, 25.9, 23.9, 21.7, 20.3.
HRMS (ESI) *m/z* calc'd for $C_{14}H_{20}NO_3S^+$ [M+H]: 282.1164, found: 282.1177.



3.11k

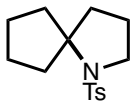
(±)-(1*R*,5*S*)-1-Methyl-3-tosyl-6-oxa-3-azabicyclo[3.2.0]heptane (3.11k): The material was synthesized according to general procedure B. 29.3 mg, 55% yield. 0–35% EtOAc/hexanes. Colorless oil.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 4.73 (d, *J* = 3.3 Hz, 1H), 4.52 (d, *J* = 5.8 Hz, 1H), 4.38 (d, *J* = 5.8 Hz, 1H), 3.79 (d, *J* = 11.6 Hz, 1H), 3.62 (d, *J* = 10.1 Hz, 1H), 2.70 (dd, *J* = 11.6, 3.4 Hz, 1H), 2.46 (s, 4H), 2.42 (d, *J* = 10.1 Hz, 1H), 1.33 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 144.0, 132.6, 129.8, 128.2, 89.5, 80.1, 57.4, 55.6, 45.7, 21.7, 19.7.
HRMS (ESI) *m/z* calc'd for $C_{13}H_{18}NO_3S^+$ [M+H]: 268.1007, found: 268.1007.



3.13a

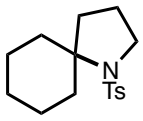
5-Tosyl-5-azaspiro[3.4]octane (3.13a): The material was synthesized according to general procedure B. 27.8 mg, 40% yield. 0–20% EtOAc/hexanes. Colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 3.36 (t, *J* = 6.7 Hz, 2H), 2.98 (qd, *J* = 9.8, 2.7 Hz, 2H), 2.41 (s, 3H), 1.98 (t, *J* = 6.7 Hz, 2H), 1.82 (tt, *J* = 8.6, 2.4 Hz, 2H), 1.79 – 1.72 (m, 3H), 1.56 – 1.54 (m, 1H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 142.8, 138.8, 129.7, 127.0, 66.3, 49.9, 40.5, 35.6, 22.3, 21.7, 14.5.
HRMS (ESI) *m/z* calc'd for $C_{14}H_{20}NO_2S^+$ [M+H]: 266.1214, found: 266.1221.



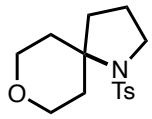
3.13b

1-Tosyl-1-azaspiro[4.4]nonane (3.13b): The material was synthesized according to general procedure B. 28.7 mg, 51% yield. 0–15% EtOAc/hexanes. Colorless oil.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.28 – 7.26 (m, 2H), 3.39 (t, *J* = 6.6 Hz, 2H), 2.41 (s, 3H), 2.41 – 2.37 (m, 2H), 1.80 (dt, *J* = 13.0, 6.4 Hz, 4H), 1.74 (t, *J* = 6.4 Hz, 2H), 1.52 – 1.44 (m, 4H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 142.7, 139.0, 129.6, 127.2, 74.4, 49.6, 41.9, 37.4, 23.4, 23.0, 21.6.
HRMS (ESI) *m/z* calc'd for $C_{15}H_{22}NO_2S^+$ [M+H]: 280.1371, found: 280.1371.



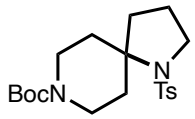
3.13c

1-Tosyl-1-azaspiro[4.5]decane (3.13c): The material was synthesized according to general procedure B. 23.1 mg, 39% yield. 0–15% EtOAc/hexanes. Colorless oil.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.26 – 7.24 (m, 2H), 3.38 (t, *J* = 6.6 Hz, 2H), 2.41 (s, 3H), 2.33 (dt, *J* = 12.2, 6.0 Hz, 2H), 1.84 (t, *J* = 6.9 Hz, 2H), 1.76 (p, *J* = 6.7 Hz, 2H), 1.70 (d, *J* = 5.3 Hz, 2H), 1.50 (d, *J* = 11.4 Hz, 3H), 1.24 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 142.6, 139.4, 129.5, 127.3, 69.9, 49.3, 36.7, 25.2, 24.8, 22.9, 21.6.
HRMS (ESI) *m/z* calc'd for $C_{16}H_{24}NO_2S^+$ [M+H]: 294.1527, found: 294.1531.



3.13d

1-Tosyl-8-oxa-1-azaspiro[4.5]decane (3.13d): The material was synthesized according to general procedure B. 16.5 mg, 28% yield. 0–40% EtOAc/hexanes. Colorless oil.
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.2 Hz, 2H), 3.94 (dd, *J* = 11.7, 5.0 Hz, 2H), 3.43 (t, *J* = 6.6 Hz, 2H), 3.41 – 3.33 (m, 2H), 2.75 (td, *J* = 12.9, 5.0 Hz, 2H), 2.41 (s, 3H), 1.97 (t, *J* = 7.0 Hz, 2H), 1.82 (p, *J* = 6.8 Hz, 2H), 1.36 (d, *J* = 13.4 Hz, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 142.9, 139.2, 129.6, 127.3, 66.5, 66.5, 49.4, 37.3, 36.3, 22.7, 21.7.
HRMS (ESI) *m/z* calc'd for $C_{15}H_{22}NO_3S^+$ [M+H]: 296.1320, found: 296.1307.



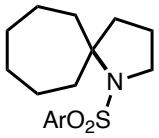
3.13e

***tert*-Butyl 1-tosyl-1,8-diazaspiro[4.5]decane-8-carboxylate (3.13e):** The material was synthesized according to general procedure B. 22.9 mg, 29% yield. 0–40% EtOAc/hexanes. Colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 4.07 (s, 2H), 3.51 – 3.32 (m, 2H), 2.56 (s, 4H), 2.41 (s, 3H), 1.89 (s, 2H), 1.86 – 1.79 (m, 2H), 1.47 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 154.9, 143.0, 139.0, 129.7, 127.3, 79.9, 67.5, 49.4, 35.7, 28.6, 22.7, 21.7 (3 C's overlapping).

HRMS (ESI) *m/z* calc'd for $C_{20}H_{31}N_2O_4S^+$ [M+H]: 395.2004, found: 395.2012.



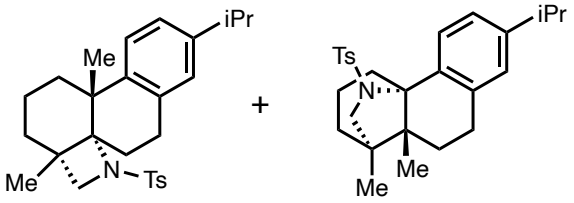
3.13f

1-((4-Methoxyphenyl)sulfonyl)-1-azaspiro[4.6]undecane (3.13f): The material was synthesized according to general procedure B. 27.4 mg, 42% yield. 0–25% EtOAc/hexanes. Colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 3.85 (s, 3H), 3.32 (t, *J* = 6.6 Hz, 2H), 2.40 (ddd, *J* = 13.7, 11.4, 2.1 Hz, 2H), 1.84 (t, *J* = 6.7 Hz, 2H), 1.80 – 1.70 (m, 4H), 1.70 – 1.49 (m, 7H), 1.30 (td, *J* = 10.6, 9.7, 4.0 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 162.4, 134.2, 129.3, 114.0, 73.1, 55.7, 49.2, 39.9, 39.0, 28.1, 23.5, 22.6.

HRMS (ESI) *m/z* calc'd for $C_{17}H_{26}NO_3S^+$ [M+H]: 324.1633, found: 324.1640.



3.15a **3.15b**

(3a*S*,11b*R*)-9-isopropyl-3a,11b-dimethyl-5-tosyl-1,3,3a,4,5,6,7,11b-octahydro-2*H*-phenanthro[10a,1-b]azete (3.15a) and (1*R*,10a*R*)-7-isopropyl-1,10a-dimethyl-11-tosyl-1,3,4,10a-tetrahydro-2*H*-4a,1-(epiminomethano)phenanthrene (3.15b): were isolated as a 1.4:1 mixture of **3.15a** to **3.15b**. 44.8 mg, 51%. 0-20% EtOAc/hexanes. Yellow oil. The mixture was further separated by SFC chromatography for structural characterization using a Lux-2 21mm x 250mm column, and Sepiatec 2 instrument. The eluant was 25% MeOH w/ 0.1% NH_4OH in CO_2.

(3a*S*,11b*R*)-9-isopropyl-3a,11b-dimethyl-5-tosyl-1,3,3a,4,5,6,7,11b-octahydro-2*H*-phenanthro[10a,1-b]azete (3.15a):

^{1}H NMR (499 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 1H), 7.11 – 7.06 (m, 1H), 6.86 (d, *J* = 8.2 Hz, 2H), 6.81 (d, *J* = 8.3 Hz, 2H), 6.64 – 6.55 (m, 1H), 3.75 (d, *J* = 9.3 Hz, 1H), 3.34 (dd, *J* = 9.2, 1.4 Hz, 1H), 2.84 (dq, *J* = 14.0, 7.0 Hz, 2H), 2.57 (ddd, *J* = 18.4, 12.0, 7.1 Hz, 1H), 2.27 (s, 3H), 2.19

– 2.00 (m, 2H), 1.78 (dq, *J* = 12.8, 6.5 Hz, 2H), 1.61 (dq, *J* = 12.3, 5.6 Hz, 3H), 1.41 – 1.29 (m, 3H), 1.26 (d, *J* = 3.4 Hz, 3H), 1.24 (d, *J* = 3.5 Hz, 3H), 0.92 (s, 3H), 0.79 (s, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 148.4, 141.4, 139.2, 136.7, 131.7, 129.3, 128.6, 126.3, 126.1, 123.6, 69.8, 58.7, 45.8, 41.1, 33.8, 33.5, 30.8, 26.1, 25.8, 24.3, 24.1, 21.5, 19.1, 18.6, 13.2.
HRMS (ESI) *m/z* calc'd for $C_{27}H_{36}NO_2S^+$ [M+H]: 438.2467, found: 438.2472.

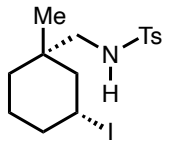
(1*R*,10a*R*)-7-isopropyl-1,10a-dimethyl-11-tosyl-1,3,4,10a-tetrahydro-2*H*-4a,1-(epiminomethano)phenanthrene (3.15b):

^{1}H NMR (499 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 1H), 7.09 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.89 – 6.75 (m, 4H), 6.37 (d, *J* = 1.8 Hz, 1H), 5.88 (d, *J* = 9.8 Hz, 1H), 5.81 (d, *J* = 9.8 Hz, 1H), 3.92 (d, *J* = 8.5 Hz, 1H), 3.17 (dd, *J* = 8.5, 1.6 Hz, 1H), 2.96 (dd, *J* = 13.1, 6.5 Hz, 1H), 2.80 (p, *J* = 6.9 Hz, 1H), 2.28 (s, 3H), 2.15 (ddq, *J* = 23.8, 17.4, 8.6, 8.1 Hz, 1H), 1.88 – 1.73 (m, 3H), 1.51 – 1.46 (m, 1H), 1.32 – 1.28 (m, 1H), 1.22 (d, *J* = 6.9 Hz, 6H), 1.09 (s, 3H), 0.77 (s, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 148.8, 141.1, 139.3, 132.9, 132.4, 129.2, 128.4, 127.9, 126.7, 125.9, 125.1, 124.1, 69.2, 61.6, 50.4, 41.7, 33.7, 33.6, 27.9, 24.2, 24.0, 21.5, 19.1, 19.0, 13.2.
HRMS (ESI) *m/z* calc'd for $C_{27}H_{34}NO_3S^+$ [M+H]: 436.2310, found: 436.2313.

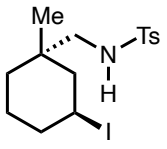
3.4.4. Tosyl Group Removal

General Procedure C: The tosylated bi-cyclic amine (1 equiv.) was charged into a round bottom flask. Phenol (3 equiv) and HBr (31 equiv., 48 wt% aqueous solution) were added. The reaction was stirred at 130 °C for 5 h and the reaction was monitored by LCMS analysis. The reaction was cooled to 25 °C, and diluted with CH_2Cl_2 (200 mL). The phases were separated, and the aqueous phase was washed with CH_2Cl_2 (3 x 100 mL). The aqueous phase was concentrated *in vacuo* and then lyophilized to provide the deprotected material as the HBr salt.

3.4.5. Characterization of Alkyl Iodide Intermediates and Kinetic Data



3.5-*syn*



3.5-*anti*

(±)-*N*-(((1*R*,3*S*)-3-Iodo-1-methylcyclohexyl)methyl)-4-methylbenzenesulfonamide ((±)-3.5-*syn*) and (±)-*N*-(((1*R*,3*R*)-3-iodo-1-methylcyclohexyl)methyl)-4-methylbenzenesulfonamide ((±)-3.5-*anti*): The molecular formula of **3.5** was determined to be $C_{15}H_{21}NO_2I$ by analysis of HRESIMS data (*m/z* calc'd for $C_{15}H_{21}NO_2INa$ [M+Na]$^+$: 430.0314, found: 430.0308). Analysis of COSY, TOCSY, HSQC, HMBC, and ROESY allowed for the full assignment of carbon and proton signals of **(±)-3.5** within the mixture of *cis* and *trans*. Briefly, COSY and TOCSY revealed the

presence of a coupling system containing four methylenes and a methine (H-2a/b to H-3, H-3 to H-4a/b, H4a/4b to H-5a/b, and H-5a/b to H-6a/b) and another comprised of the sulfonamide and remaining methylene (NH to H-7a/b) in addition to the aromatic tosylate spin system. HSQC revealed the lone methine to possess chemical shifts indicative of an iodo substituent effect (^{1}H – 4.41 ppm, ^{13}C –28.5 ppm).[1] HMBC correlations from CH_3-16 to C-1, C-7, C-6 established the rest of the planar structure about the cyclohexyl ring. For **(±)-3.5**-*syn*, a ROESY correlation from H-3 to CH_3-16 sets the relative configuration, while in **(±)-3.5**-*anti* a ROESY correlation between H-3 and H-7a/b set the relative configuration.

((±)-3.5-*syn*):

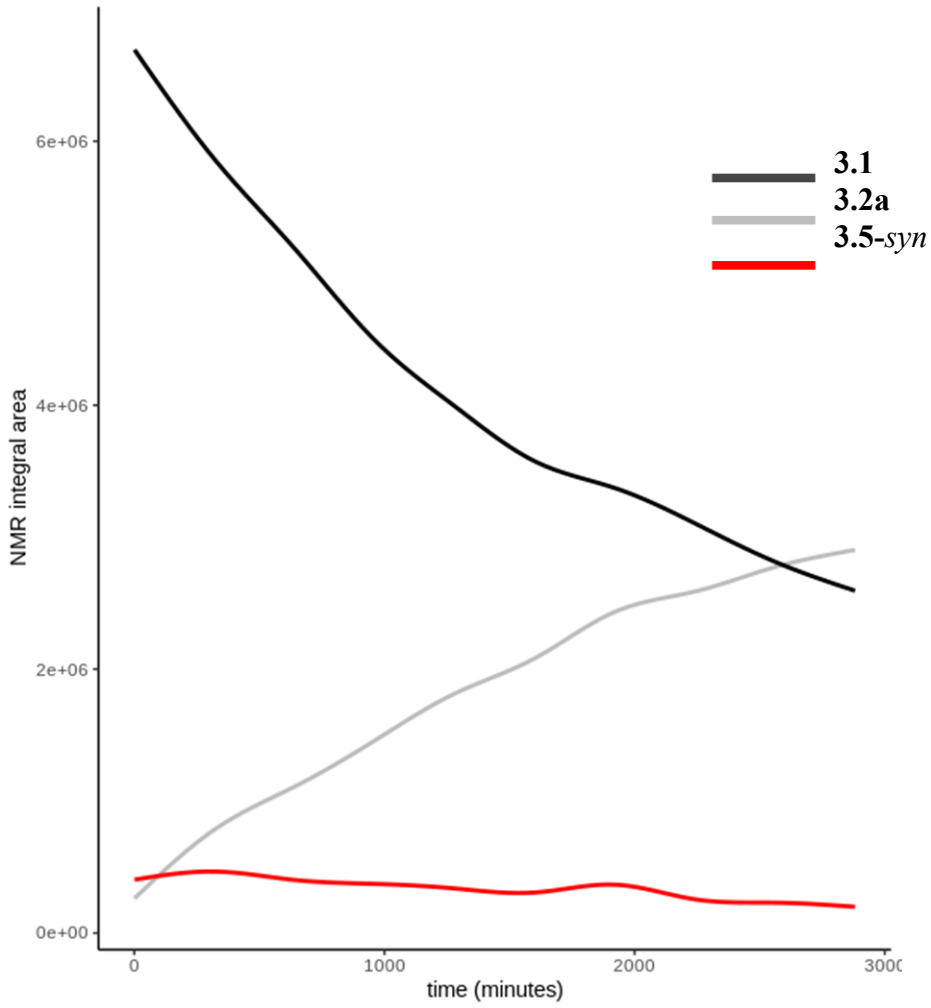
^{1}H NMR (600 MHz, CD_3CN) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 7.9 Hz, 2H), 5.57 (t, *J* = 7.4 Hz, 1H), 4.41 (tt, *J* = 12.6, 4.1 Hz, 1H), 2.56 (d, *J* = 7.2 Hz, 2H), 2.41 (s, 3H), 2.04 (dt, *J* = 12.9, 4.1, 2.1 Hz, 1H), 1.79 (dd, *J* = 25.3, 4.1 Hz, 1H), 1.79 (p, 1H), 1.53 (qt, *J* = 13.3, 3.7 Hz, 1H), 1.49 – 1.41 (m, 1H), 1.37 – 1.33 (m, 1H), 1.24 – 1.17 (m, 1H), 0.88 (s, 3H).
^{13}C NMR (151 MHz, CD_3CN) δ 144.4, 138.9, 130.7, 127.8, 56.0, 49.8, 41.5, 39.3, 33.9, 28.4, 24.7, 21.6, 20.4.

((±)-3.5-*anti*):

^{1}H NMR (600 MHz, CD_3CN) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 7.4 Hz, 2H), 5.53 (t, *J* = 6.9 Hz, 1H), 4.33 (tt, *J* = 12.5, 4.1 Hz, 1H), 2.84 (dd, *J* = 13.2, 7.4 Hz, 1H), 2.69 – 2.64 (m, 1H), 2.42 (s, 3H), 2.38 – 2.28 (m, 1H), 1.77 – 1.72 (m, 1H), 1.59 – 1.56 (m, 1H), 1.38 – 1.35 (m, 1H), 0.83 (s, 3H).
^{13}C NMR (151 MHz, CD_3CN) δ 144.4, 138.8, 130.7, 127.8, 49.5, 48.4, 41.0, 39.0, 34.6, 24.7, 21.6.

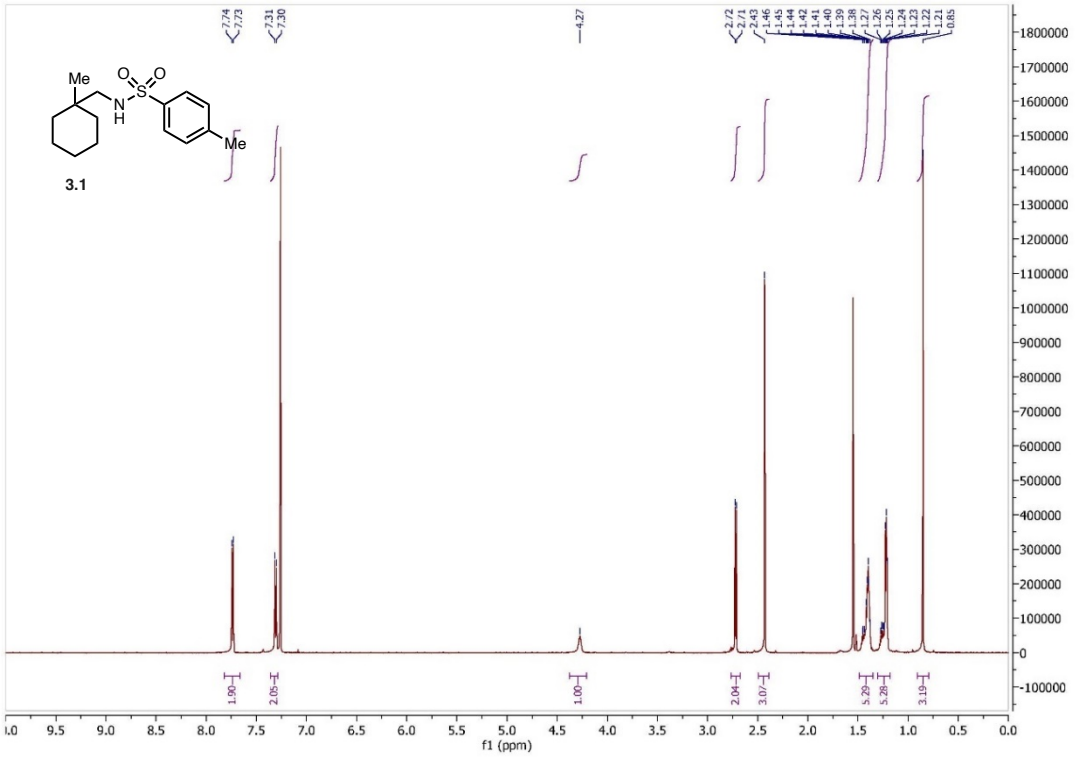
[1] Wiberg, K. B.; Pratt, W. E.; Bailey, W. F. Nature of substituent effects in nuclear magnetic resonance spectroscopy. 1. Factor analysis of carbon-13 chemical shifts in aliphatic halides. *J. Org. Chem.* **1980**, *45*, 4936–4947

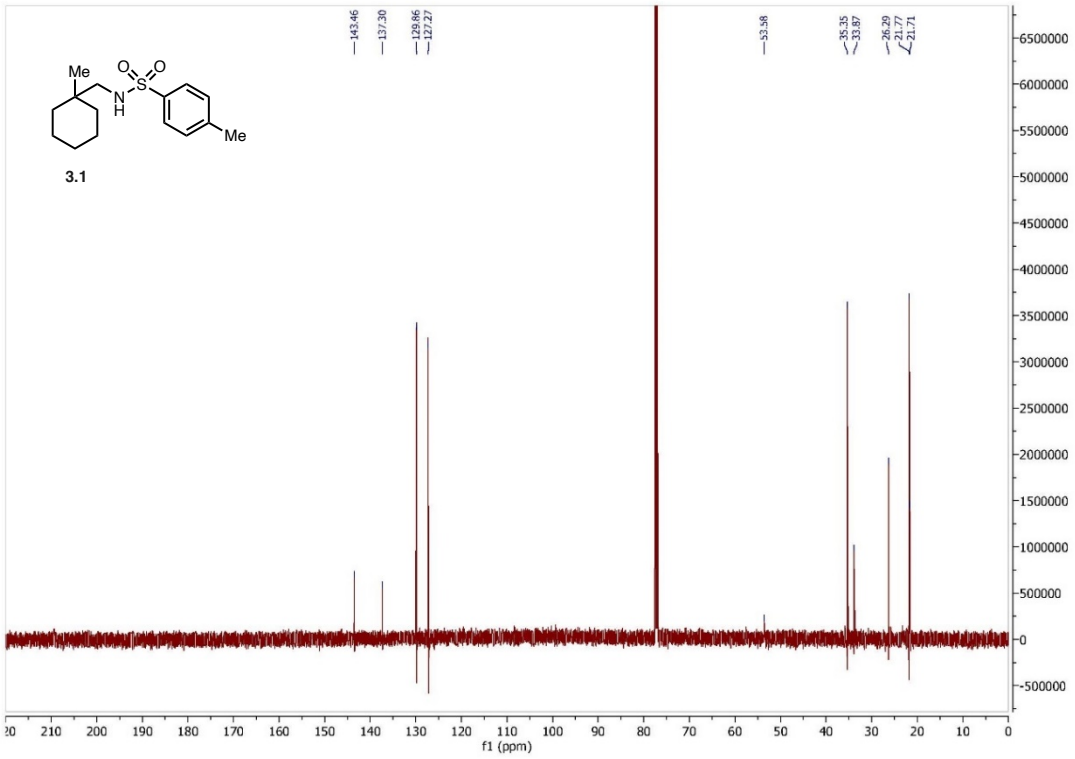
*^{1}H NMR time course of the reaction of substrate **3.1** with N-iodohydantoin (**3.3**) at 70 °C*

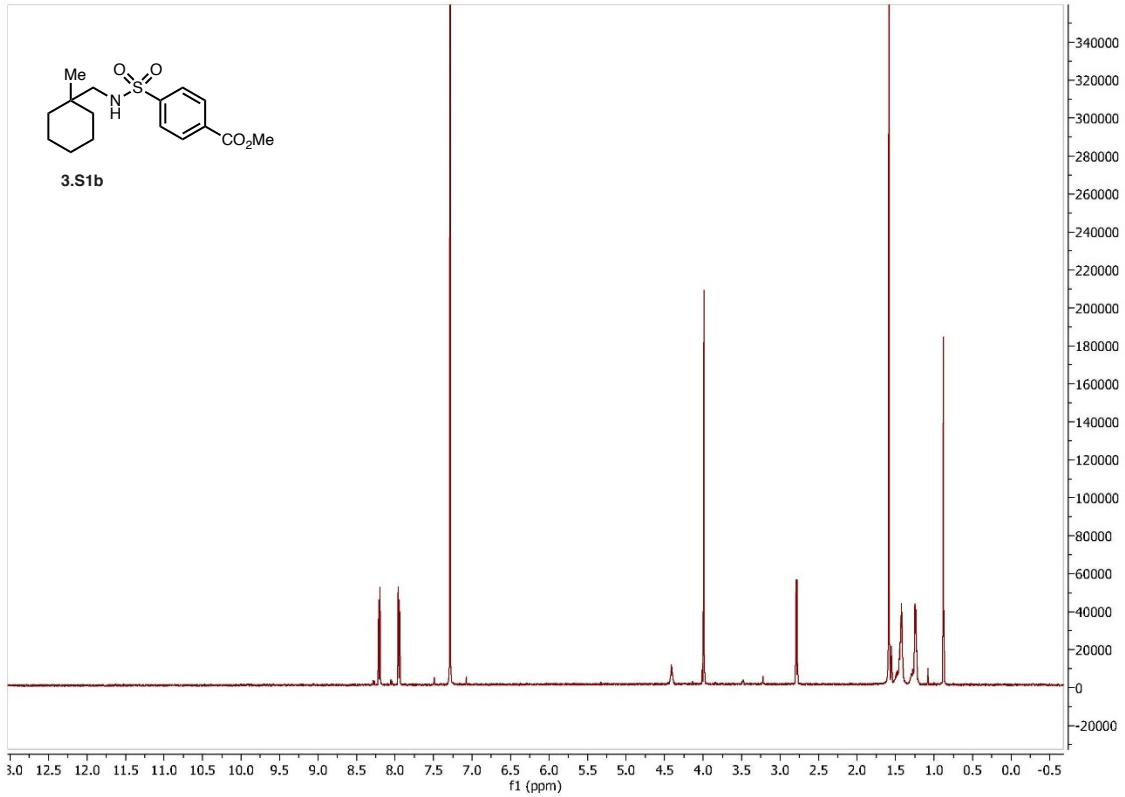


The reaction was performed at 70 °C in CD_3CN with sample rotation at 120 Hz. Proton spectra were recorded with the following parameters for approximately two days. Carbon decoupled proton spectra with a 30° flip angle were acquired for 8 scans across a sweep width of 7462.7 Hz for 2 s of acquisition with a 1.6 s relaxation delay providing for a 29 s total acquisition time per experiment, allowing for one acquisition to be acquired every 30 s. The amine proton of the starting material was integrated from 5.390 to 5.184 ppm, the product on the methine proton alpha to the amine from 4.210 to 4.074 ppm, and the iodo-intermediate was integrated on the iodo-methine proton from 4.563 to 4.417 ppm. Experiments were performed on a 500 MHz spectrometer equipped with a Bruker Avance NEO console and a Bruker Iprobe SmartProbe. The smoothed line plot was generated in R utilizing the ggplot2 package.

3.4.6. Spectral Data



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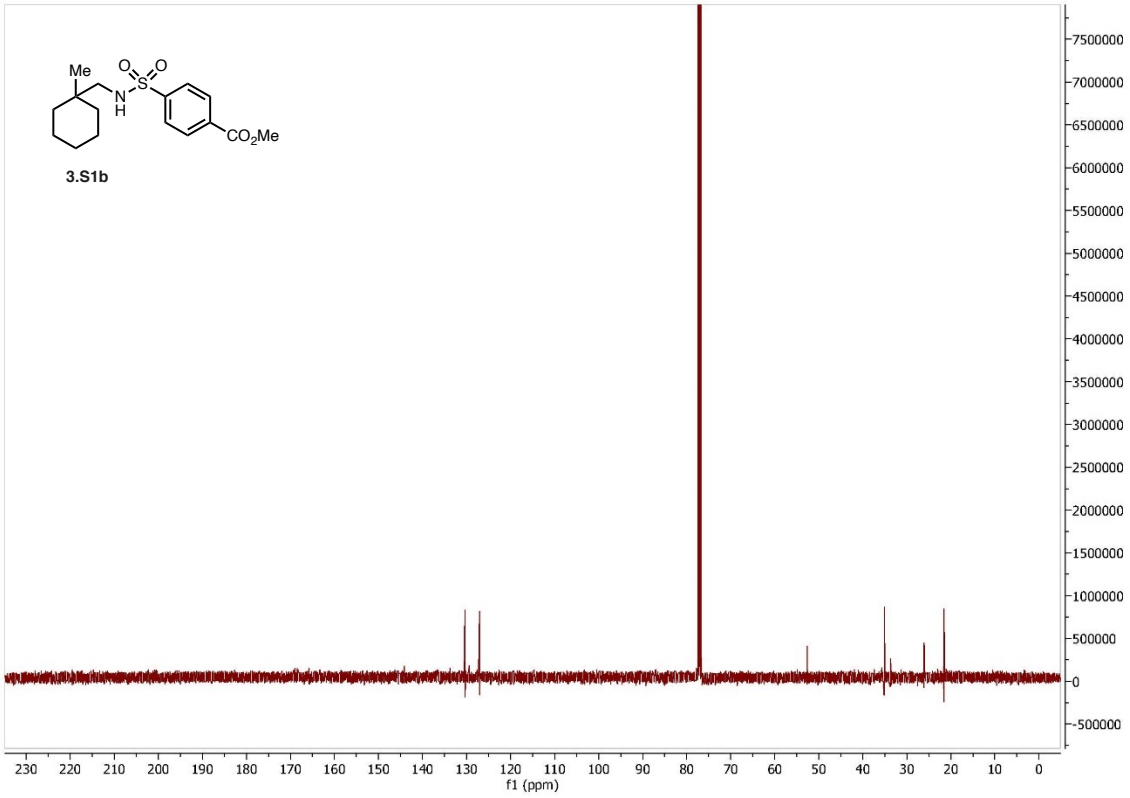
S
N
H
CO2Me
3.S1b
340000
320000
300000
280000
260000
240000
220000
200000
180000
160000
140000
120000
100000
80000
60000
40000
20000
0
-20000
3.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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S
N
H
CO2Me
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7000000
6500000
6000000
5500000
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
-500000
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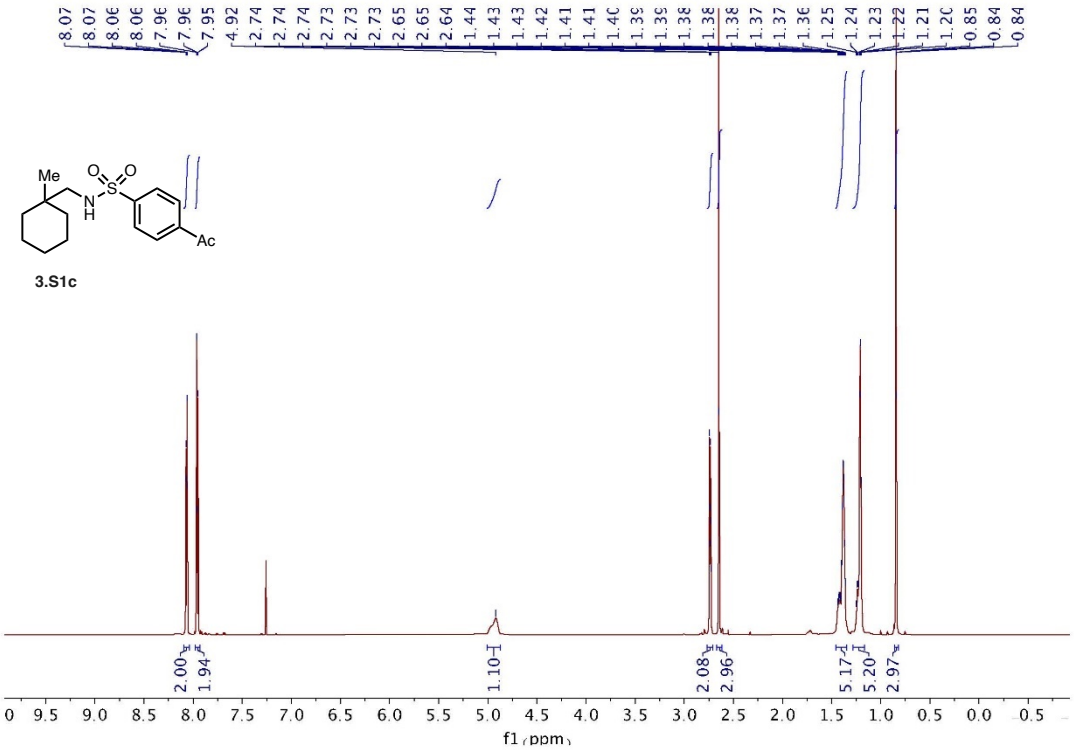
f1 (ppm)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H
O
S
O
Ac
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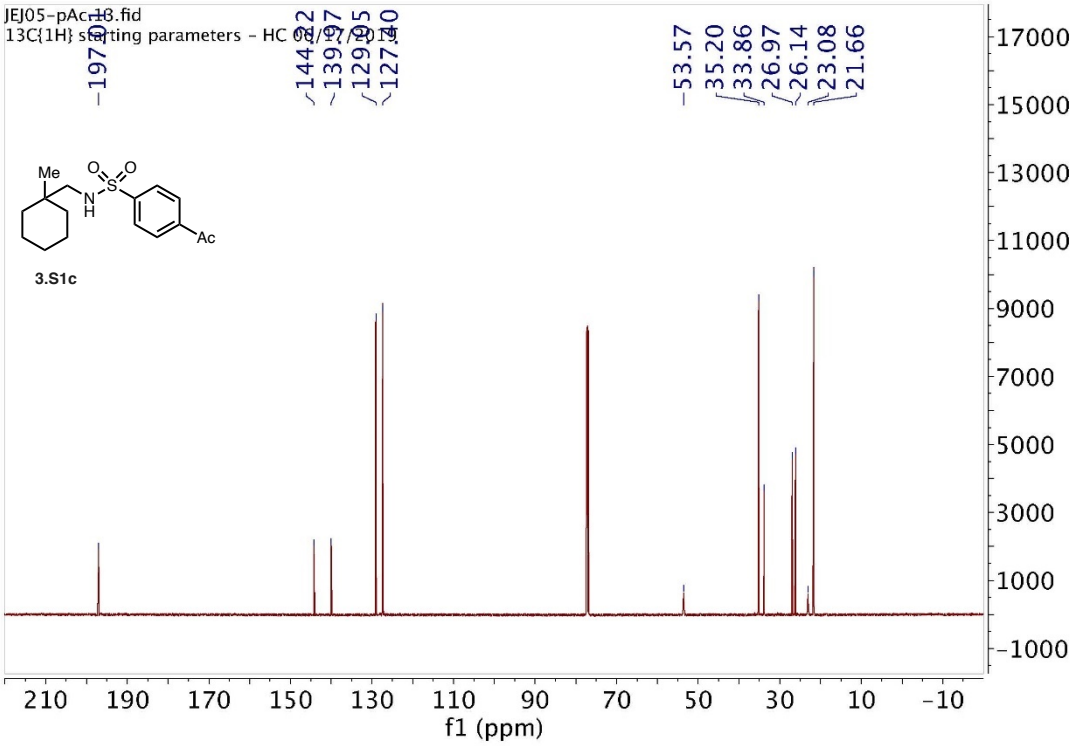
f1 (ppm)


JEJ05-pAc-13.fid
13C{1H} starting parameters - HC 08/17/2019
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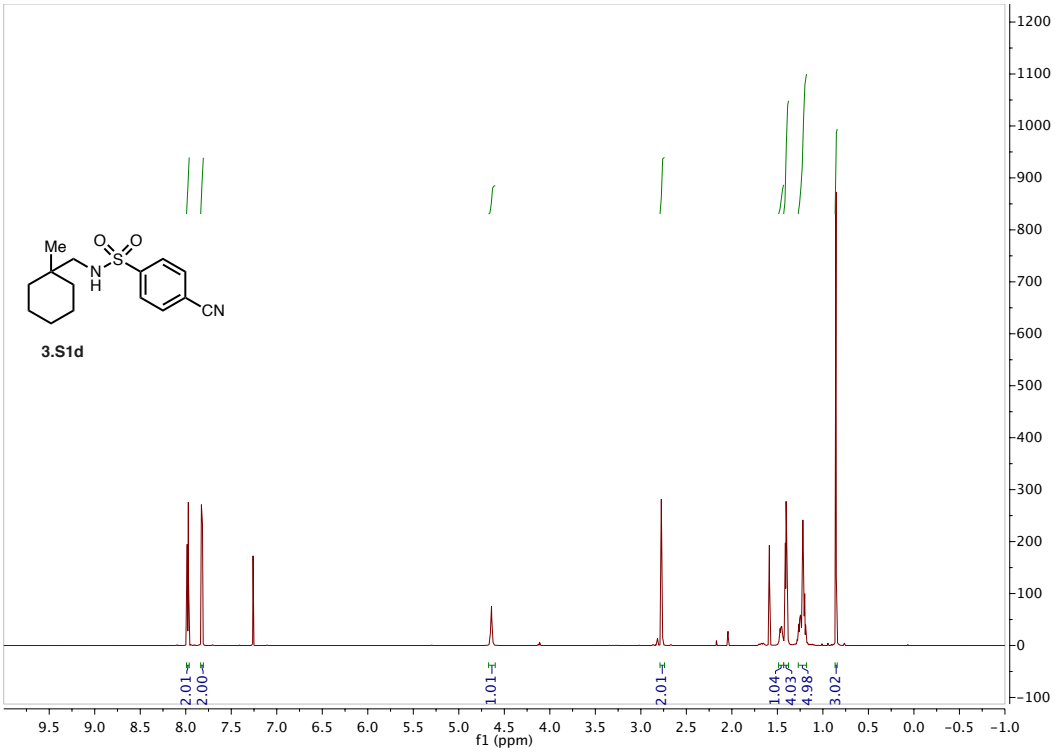
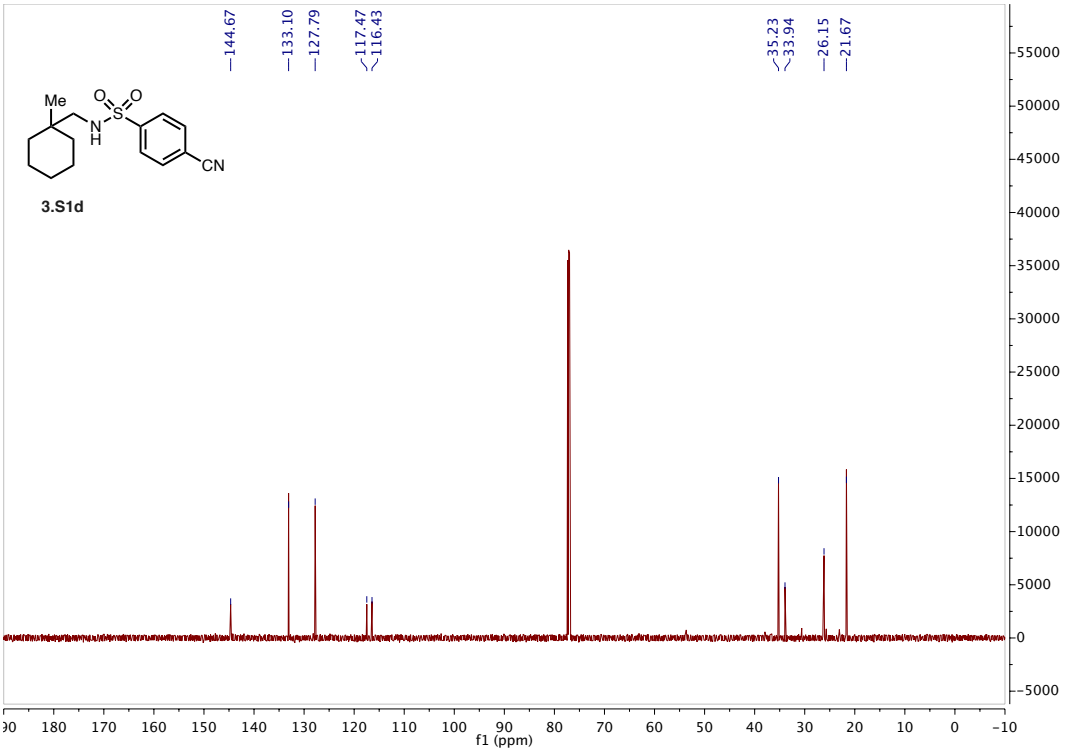
N
H
O
S
O
Ac
3.S1c
f1 (ppm)


Me
O
S
O
N
H
CN
3.S1d
2.01
2.00
1.01
2.01
1.04
4.03
4.98
3.02
f1 (ppm)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127.79
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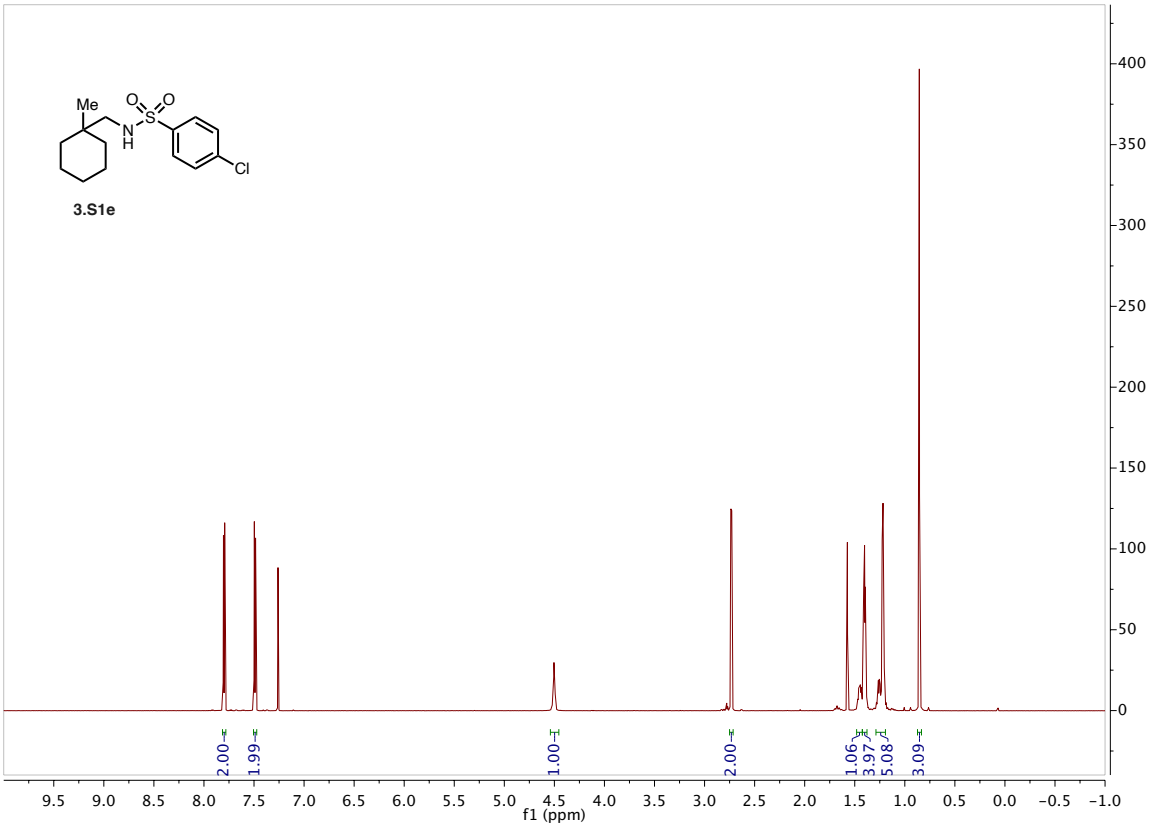
26.15
21.67
Me
O
S
O
N
H
CN
3.S1d
f1 (ppm)


Me
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O
S
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Cl
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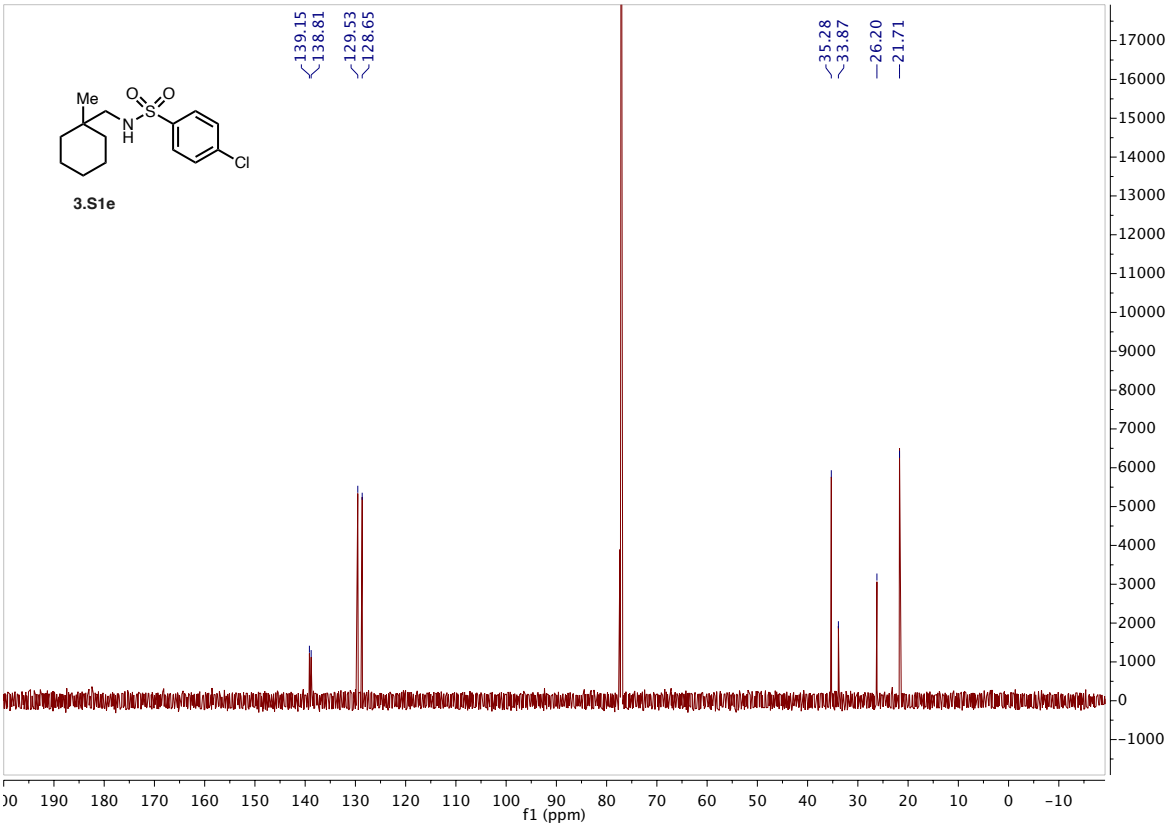
3.09
f1 (ppm)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O
S
N
H
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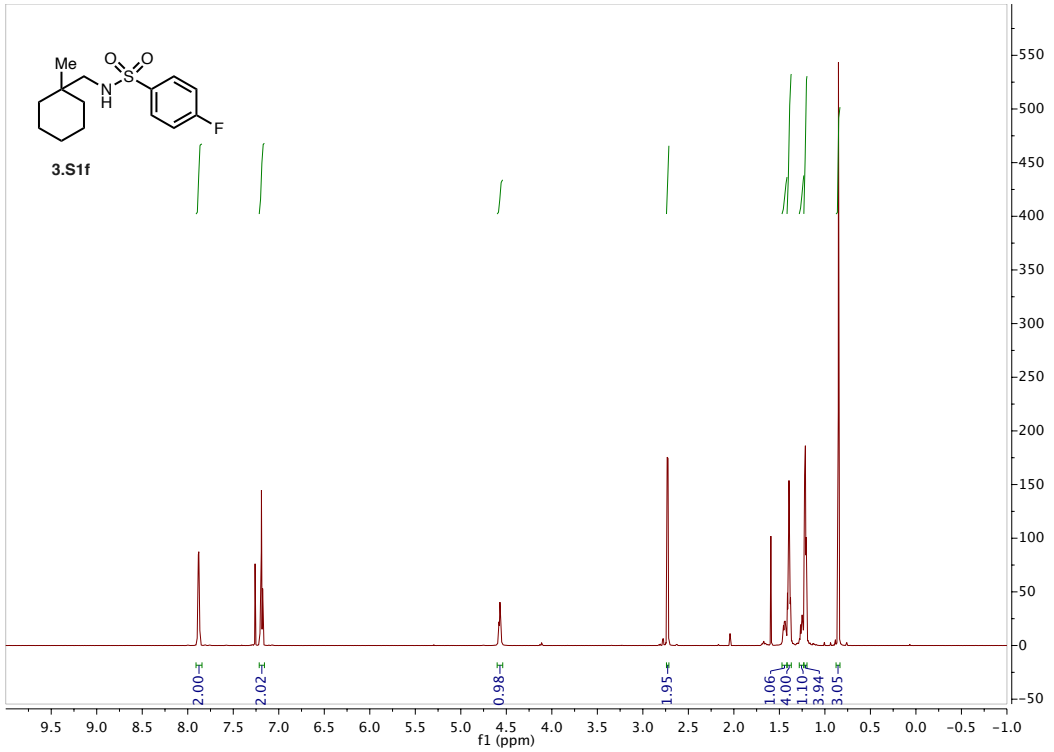
3.S1e
f1 (ppm)


Me
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S
O
N
H
F
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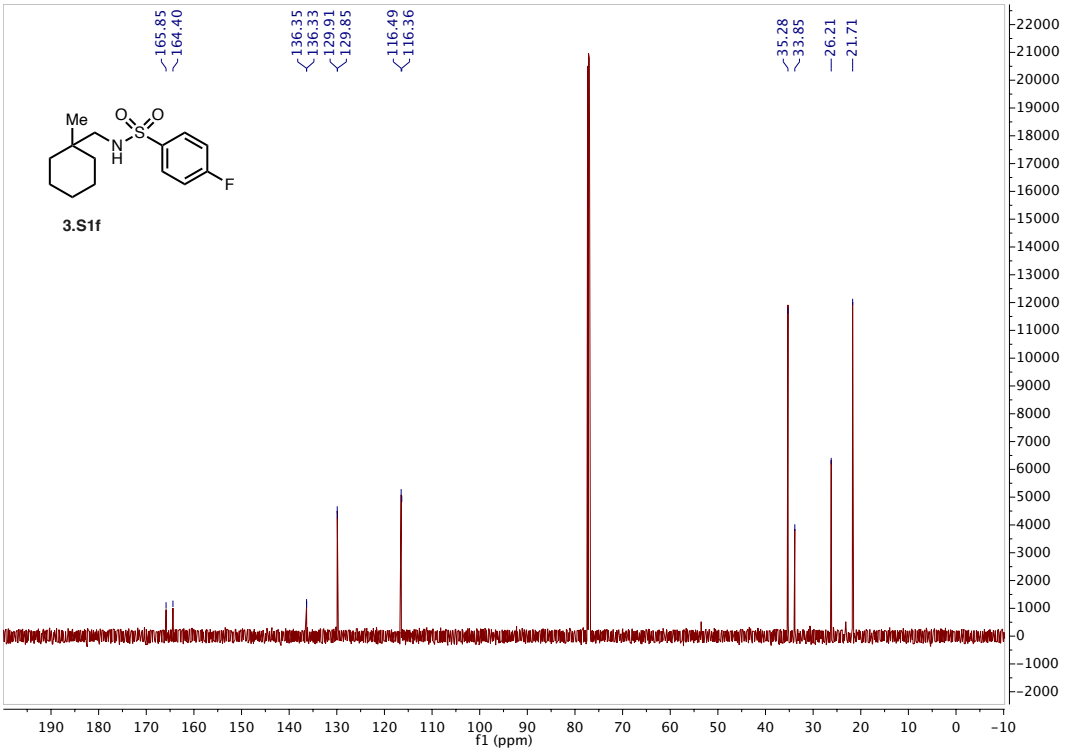
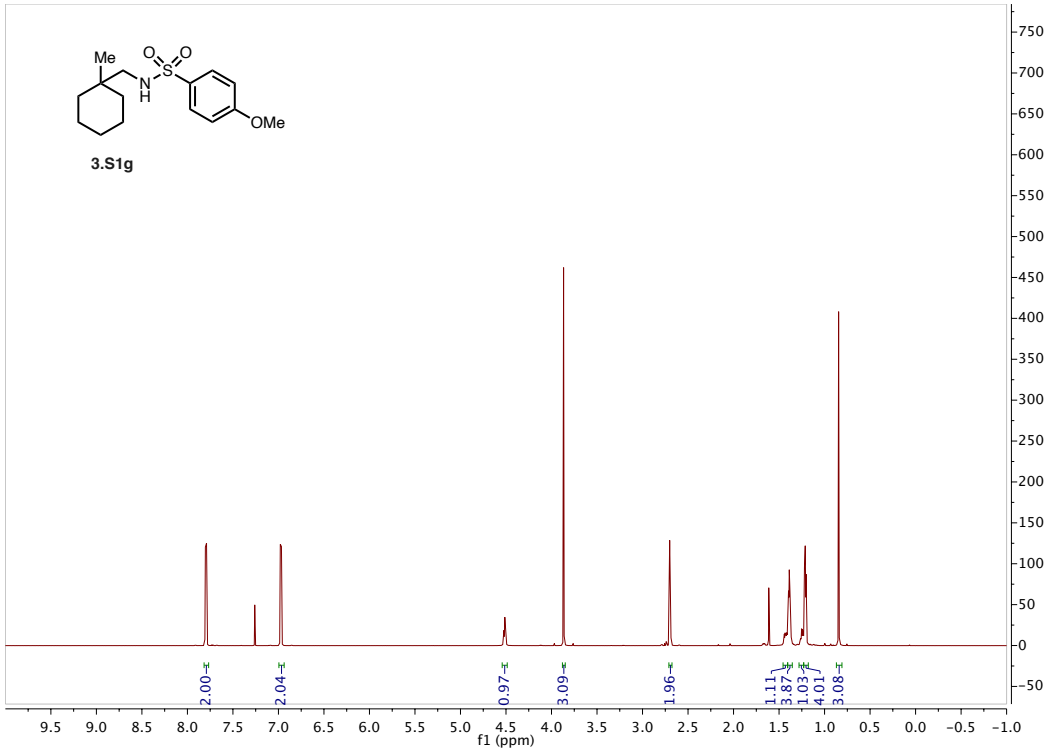
1.10
3.94
3.05
f1 (ppm)


165.85
164.40
136.35
136.33
129.91
129.85
116.49
116.36
35.28
33.85
26.21
21.71
Me
O
S
O
N
H
F
3.S1f
f1 (ppm)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S
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H
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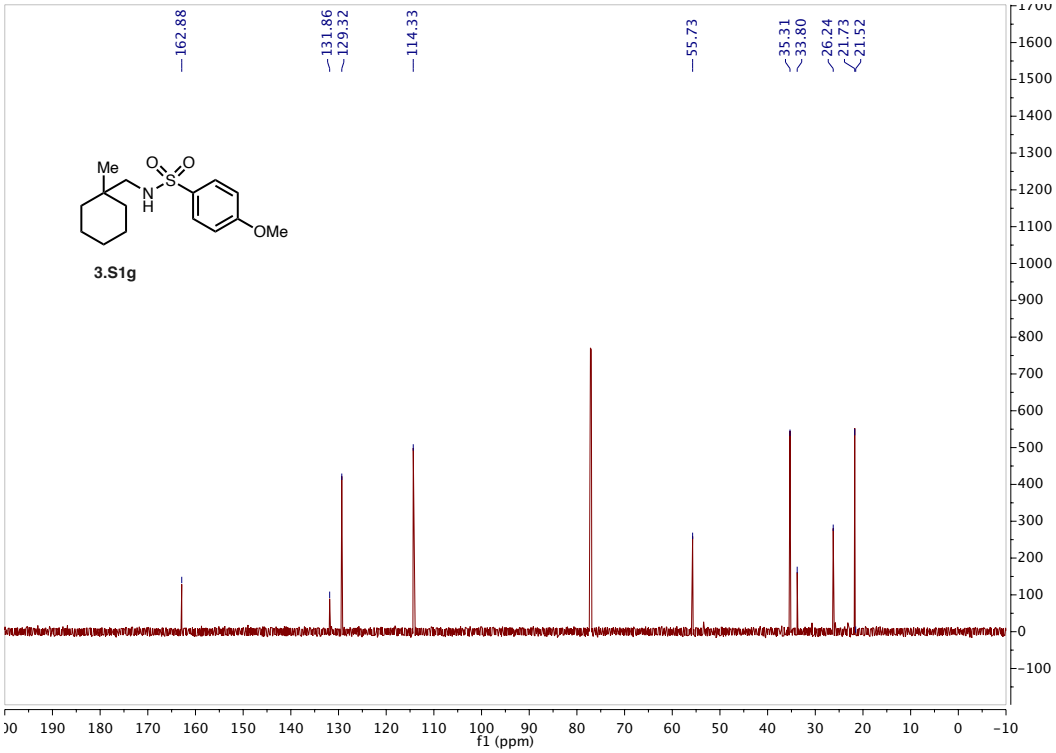
1.03
4.01
3.08
f1 (ppm)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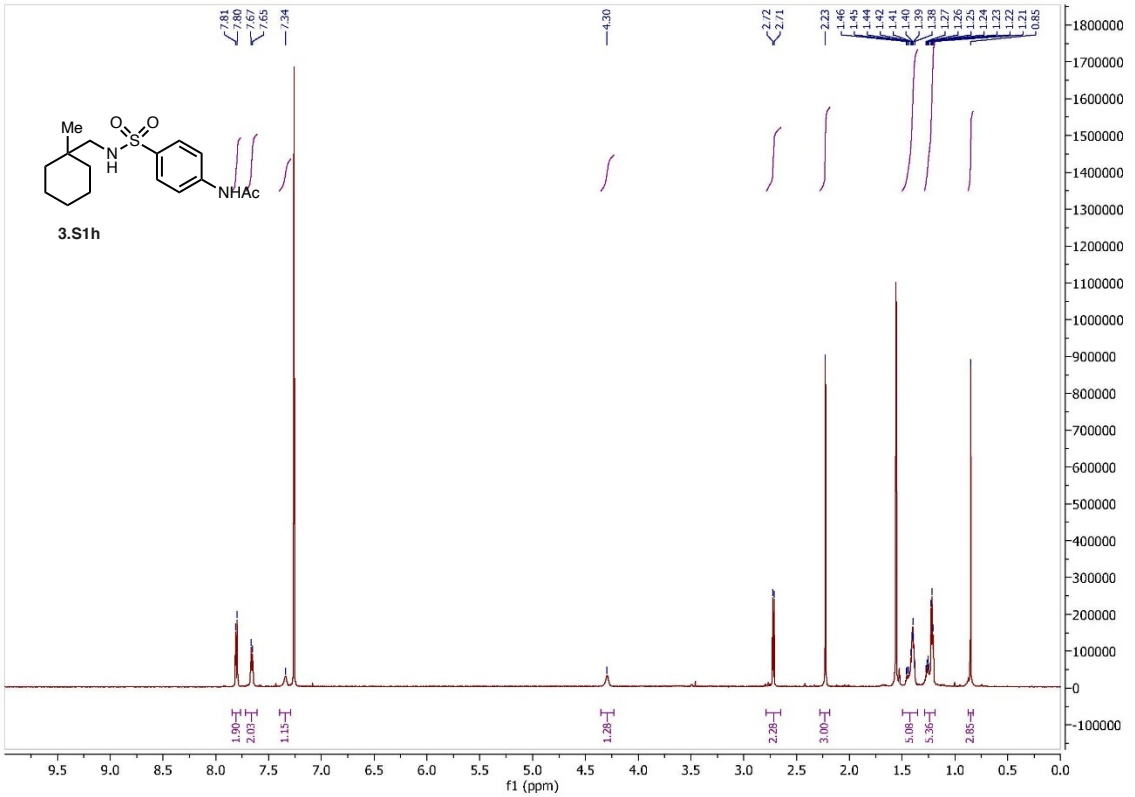
131.86
129.32
114.33
55.73
35.31
33.80
26.24
21.73
21.52
Me
O
O
S
N
H
OMe
3.S1g
f1 (ppm)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S
N
H
NHAc
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7.65
7.34
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2.72
2.71
2.23
1.46
1.45
1.44
1.42
1.41
1.40
1.39
1.38
1.27
1.26
1.25
1.24
1.23
1.22
1.21
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1.28
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3.00
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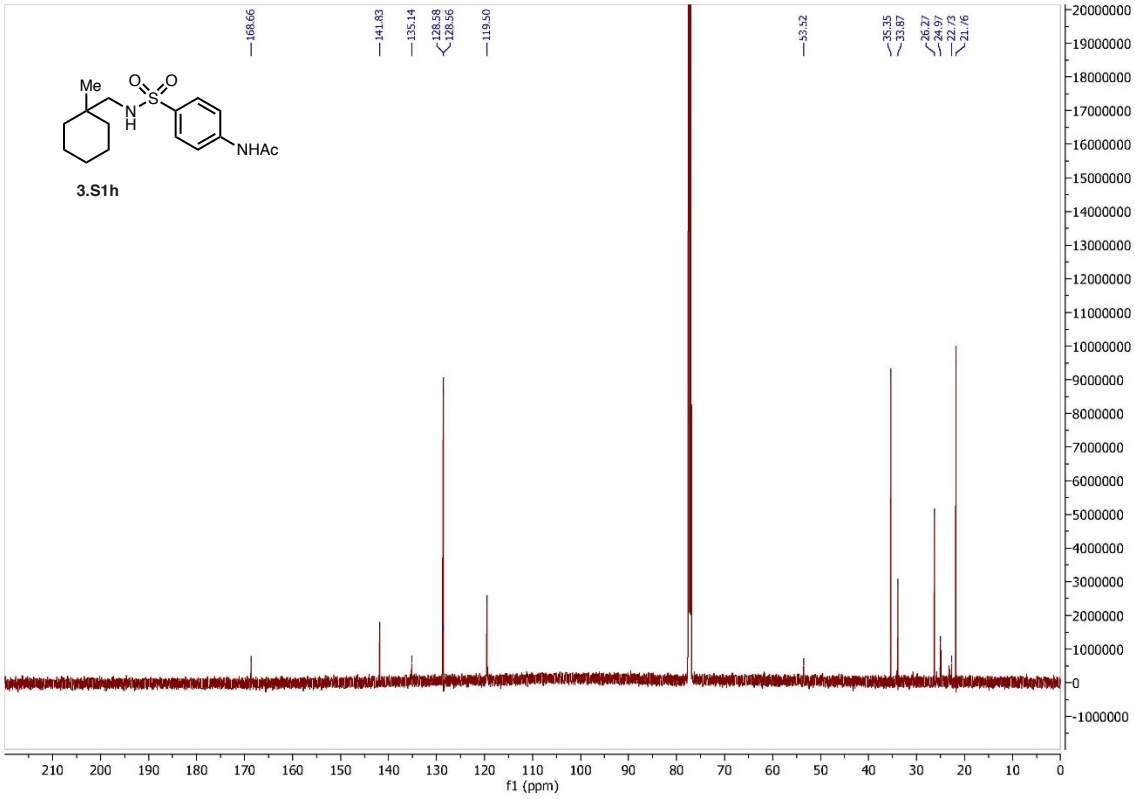
2.85
f1 (ppm)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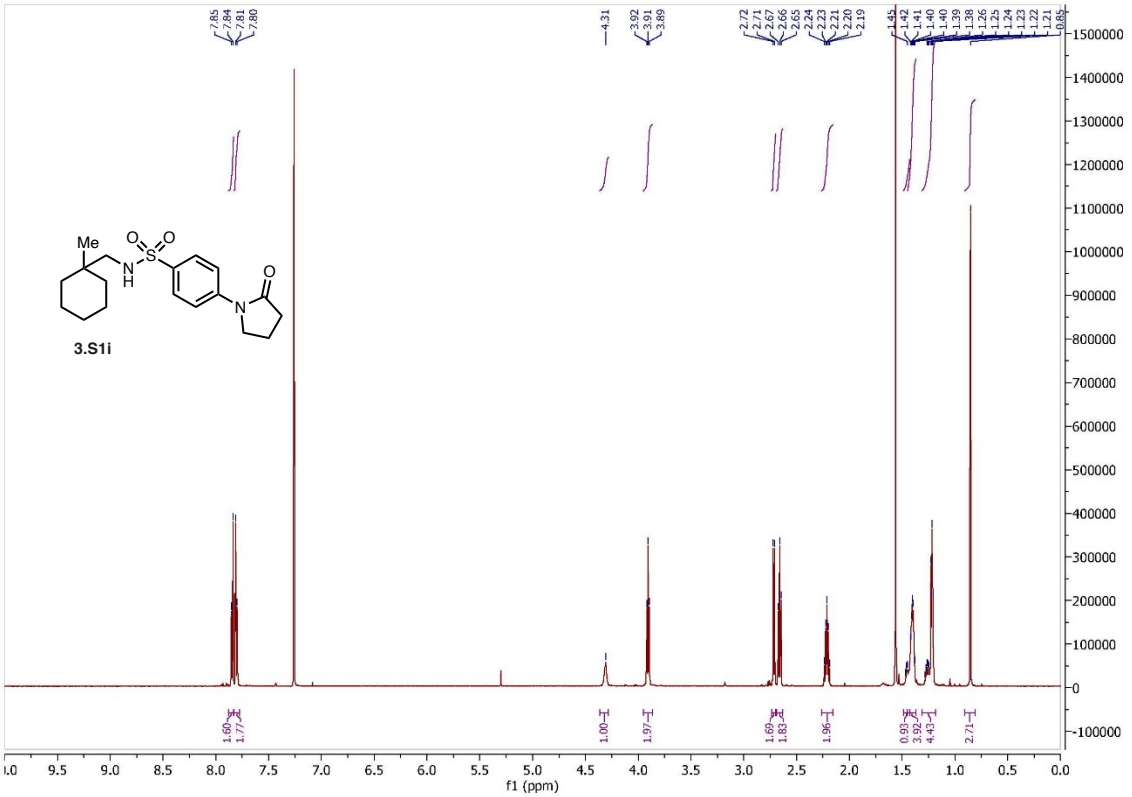
21.76
f1 (ppm)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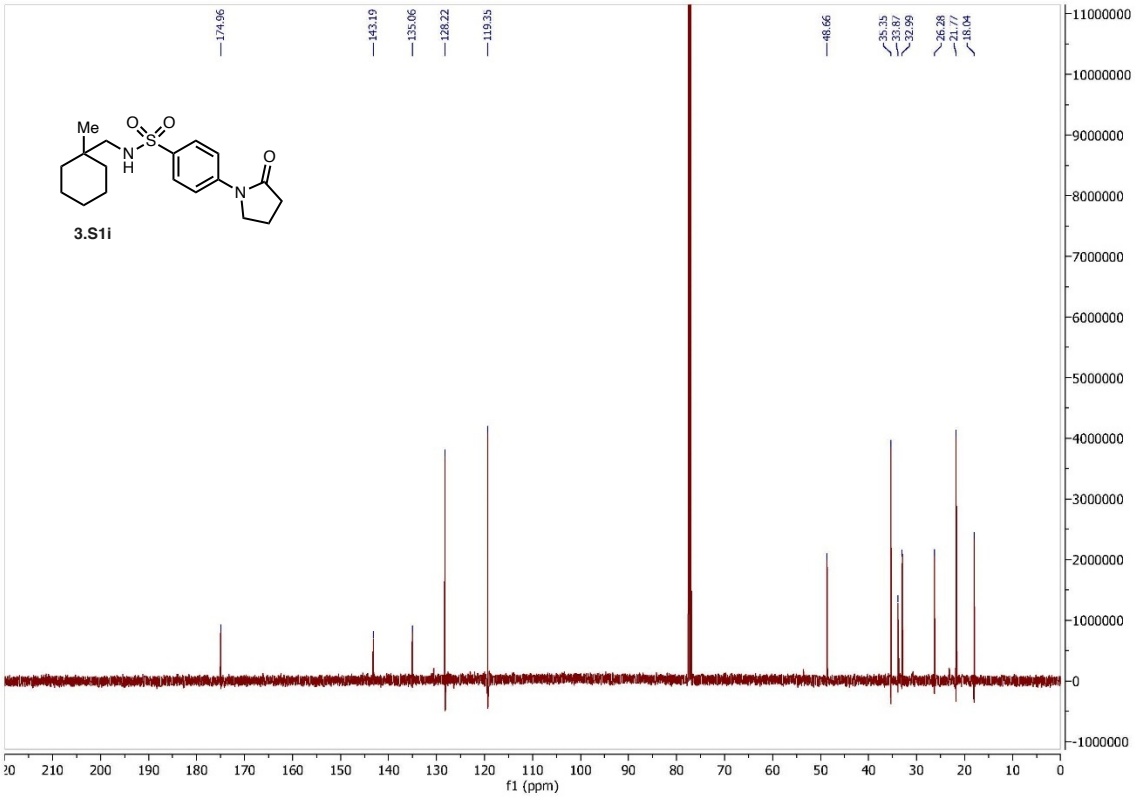
S
O
N
H
O
N
3.S1i
f1 (ppm)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S
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N
H
O
N
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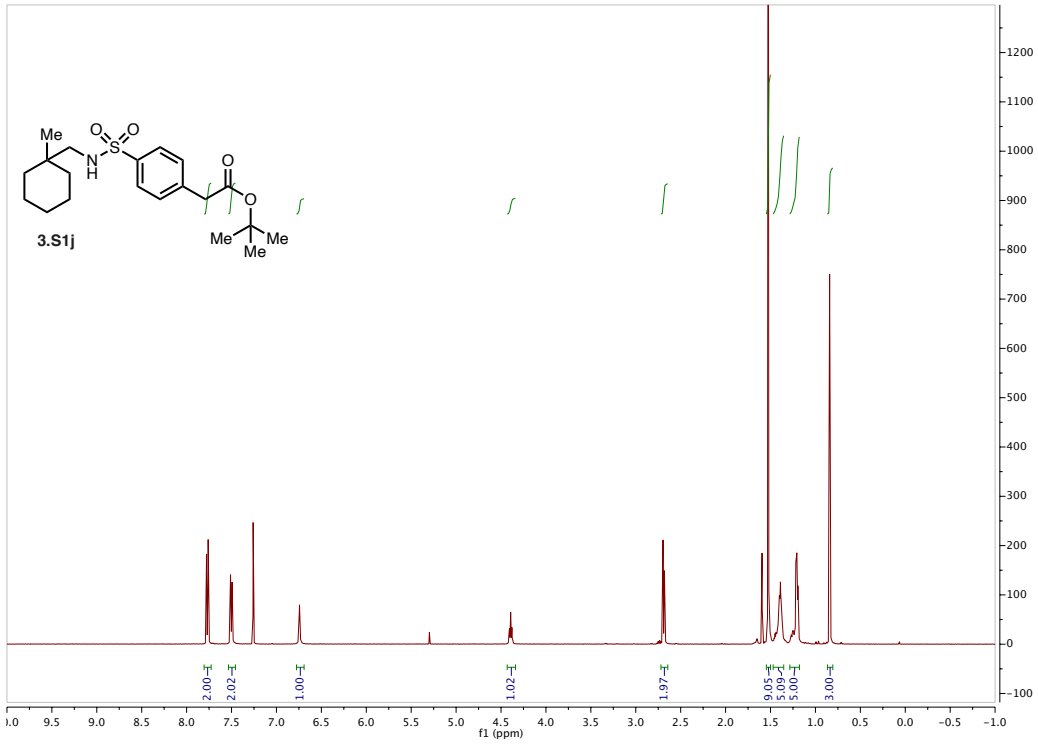
f1 (ppm)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1.02
1.97
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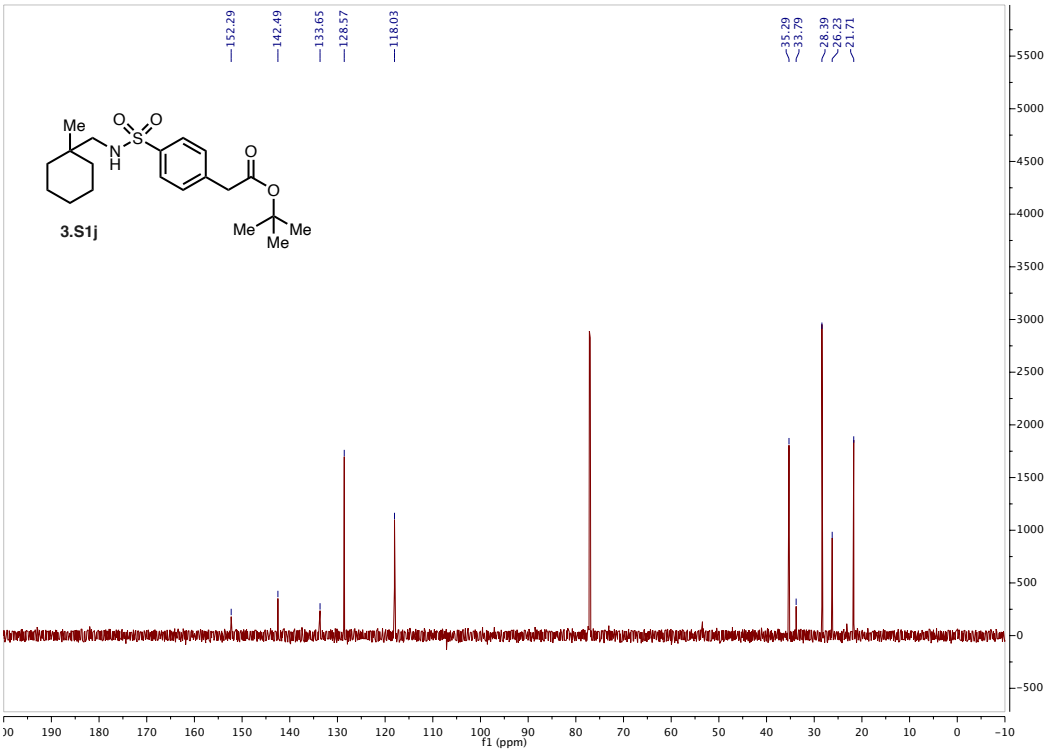
5.00
3.00
f1 (ppm)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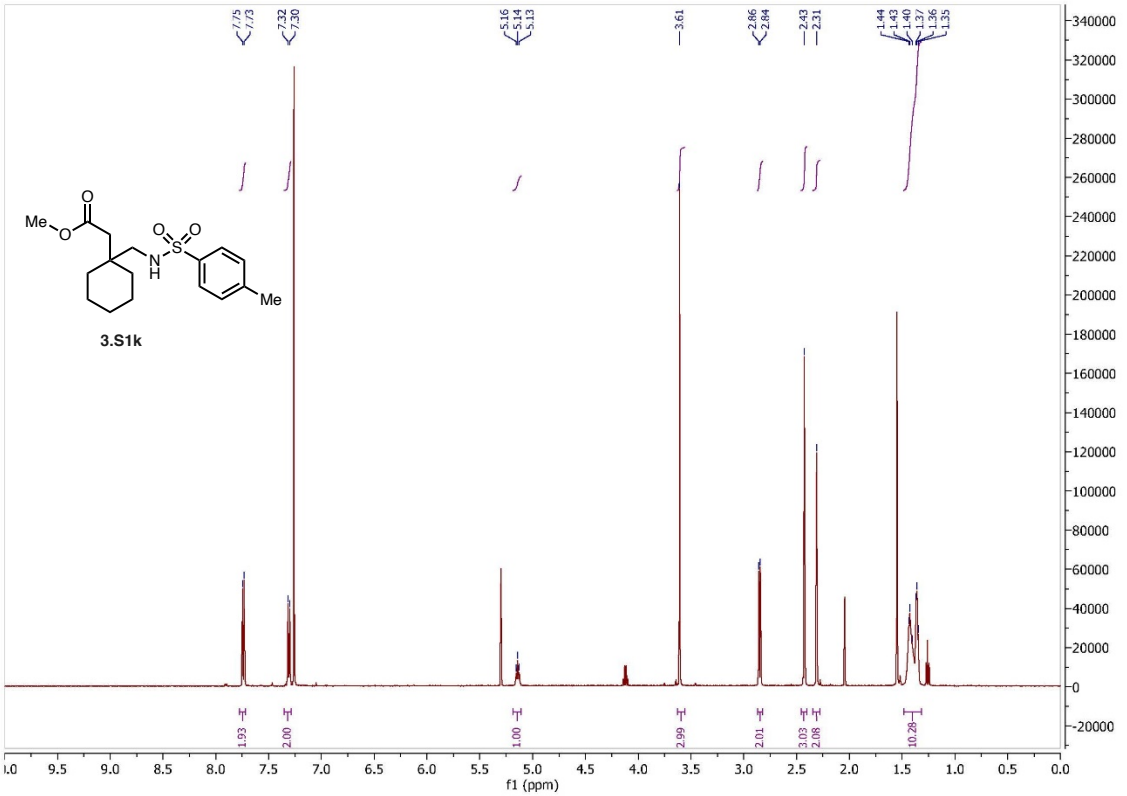
3.S1j
f1 (ppm)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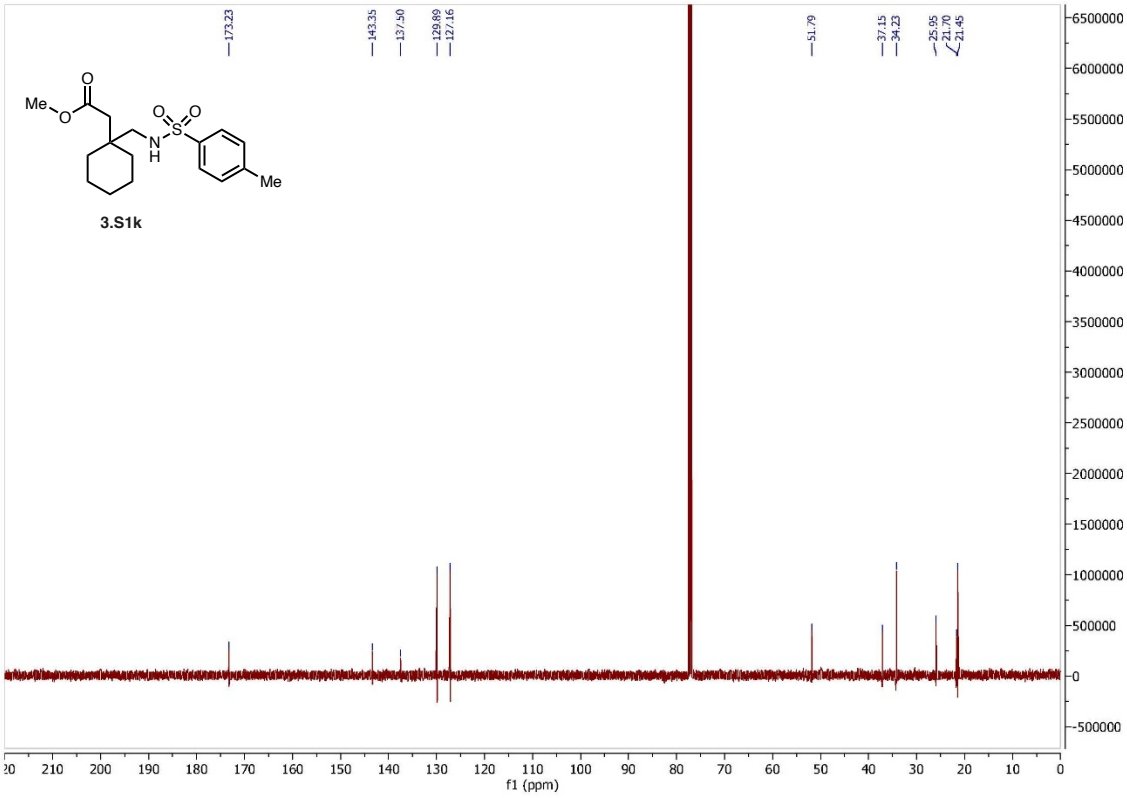
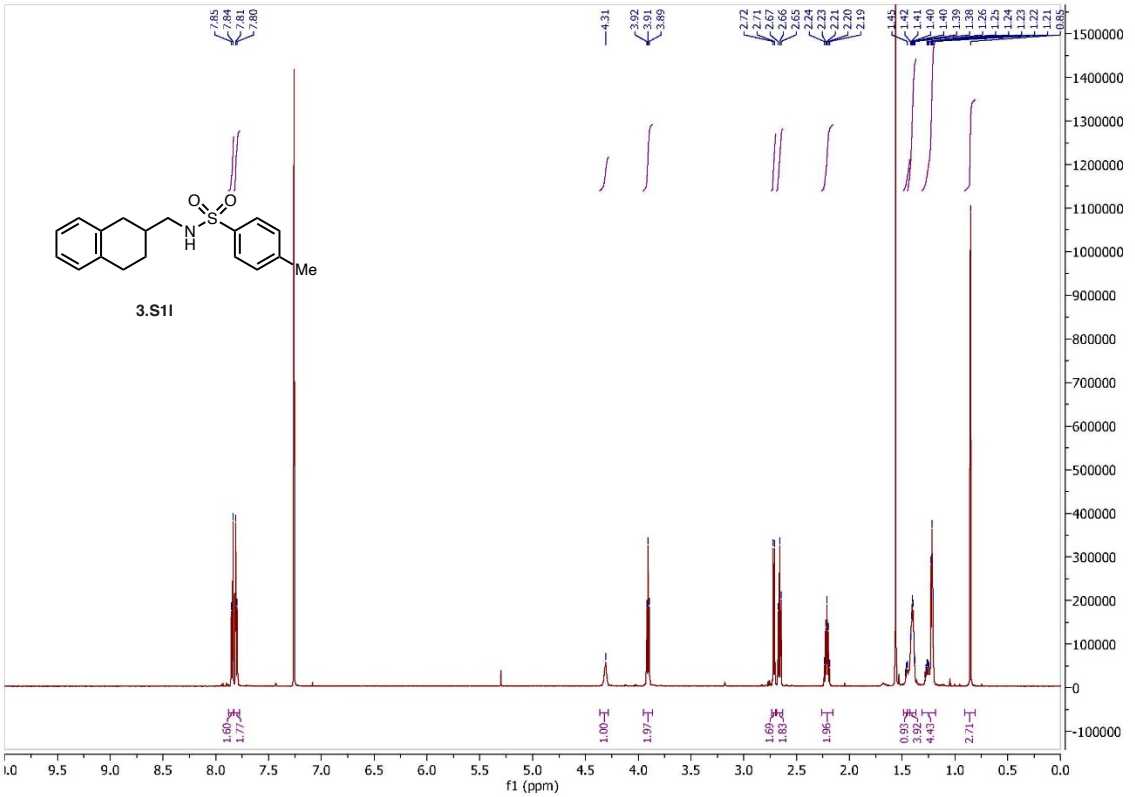
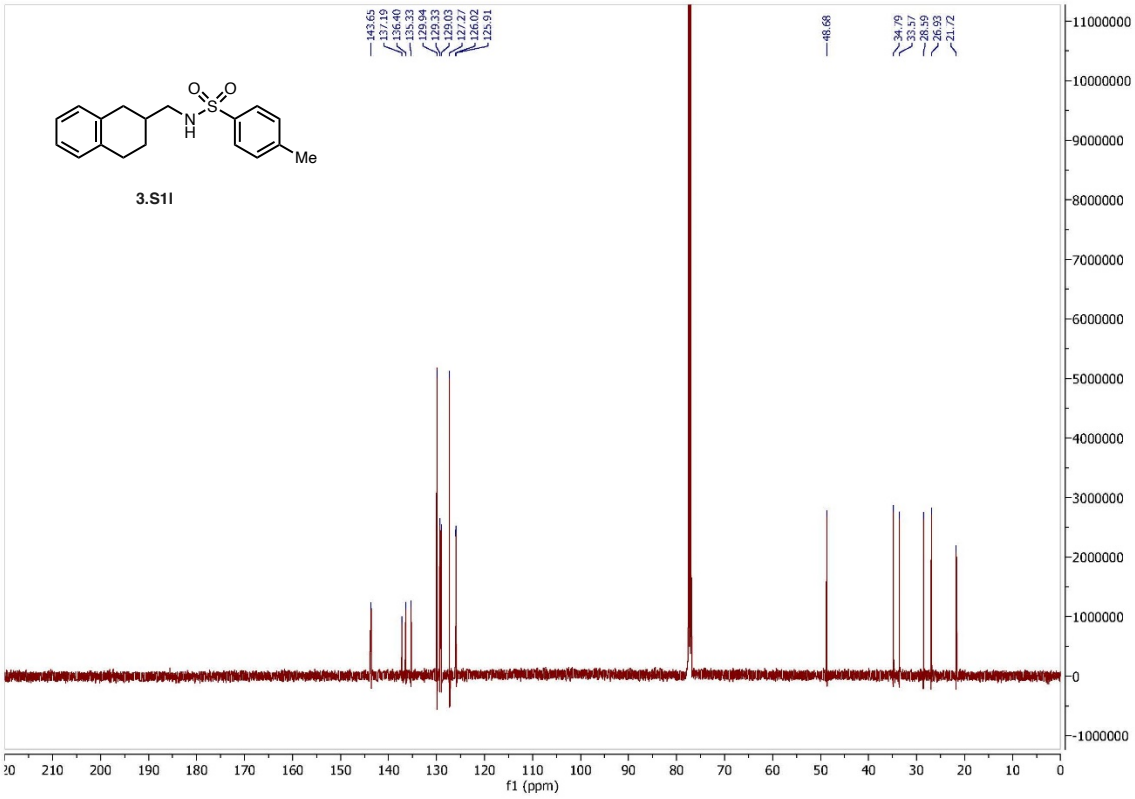
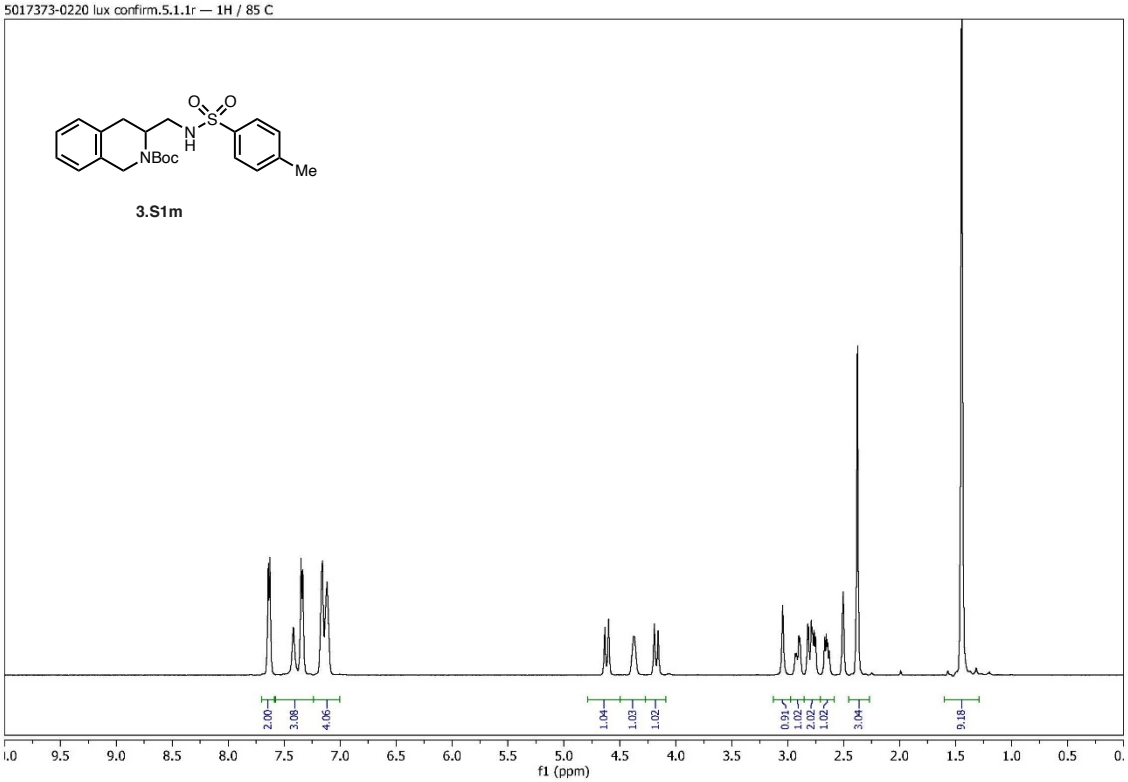

3.S1k
f1 (ppm)


7.85
7.84
7.81
7.80
4.31
3.92
3.91
3.89
2.72
2.71
2.67
2.66
2.65
2.24
2.23
2.21
2.20
2.19
1.45
1.42
1.41
1.40
1.40
1.39
1.38
1.26
1.25
1.24
1.24
1.23
1.22
1.21
0.85
O
O
S
N
H
Me
3.S1l
1.60
1.77
1.00
1.97
1.69
1.83
1.96
0.93
3.92
4.43
2.71
f1 (ppm)


143.65
137.19
136.40
135.33
129.94
129.33
129.03
127.27
126.02
125.91
48.68
34.79
33.57
28.99
26.93
21.72
O
O
S
N
H
Me
3.S1l
f1 (ppm)

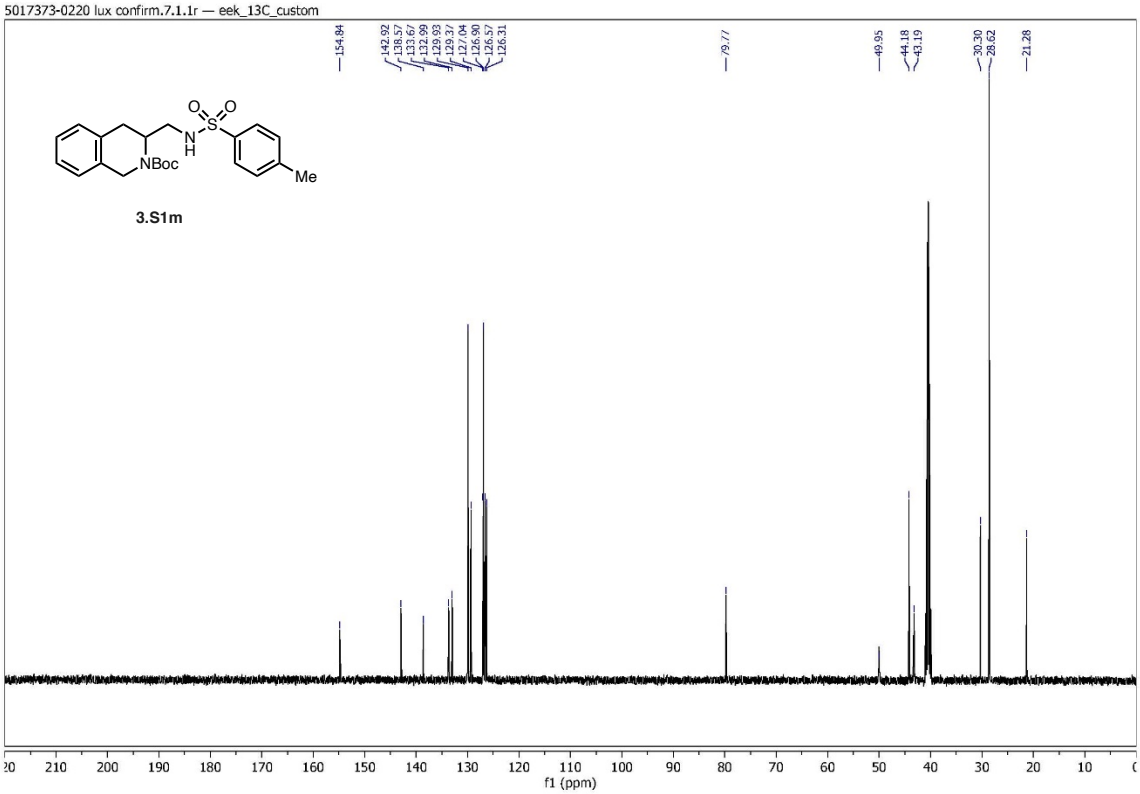
5017373-0220 lux confirm.5.1.1r — 1H / 85 C

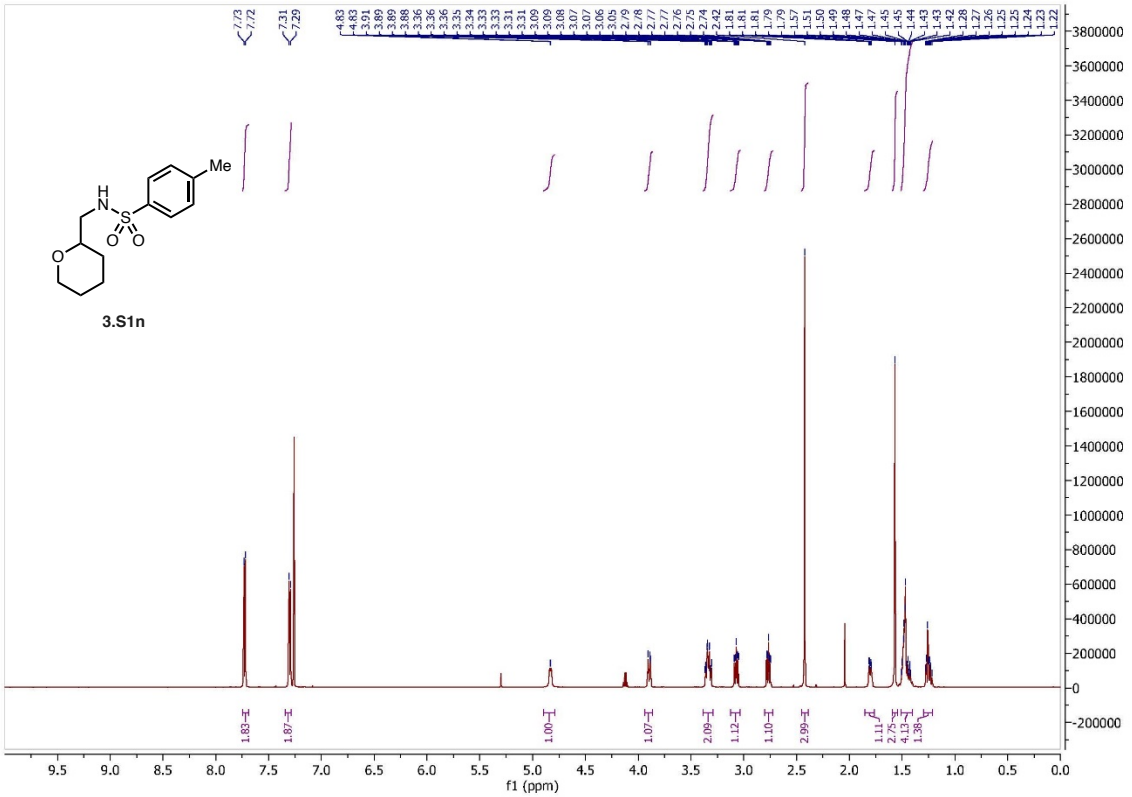
3.S1m

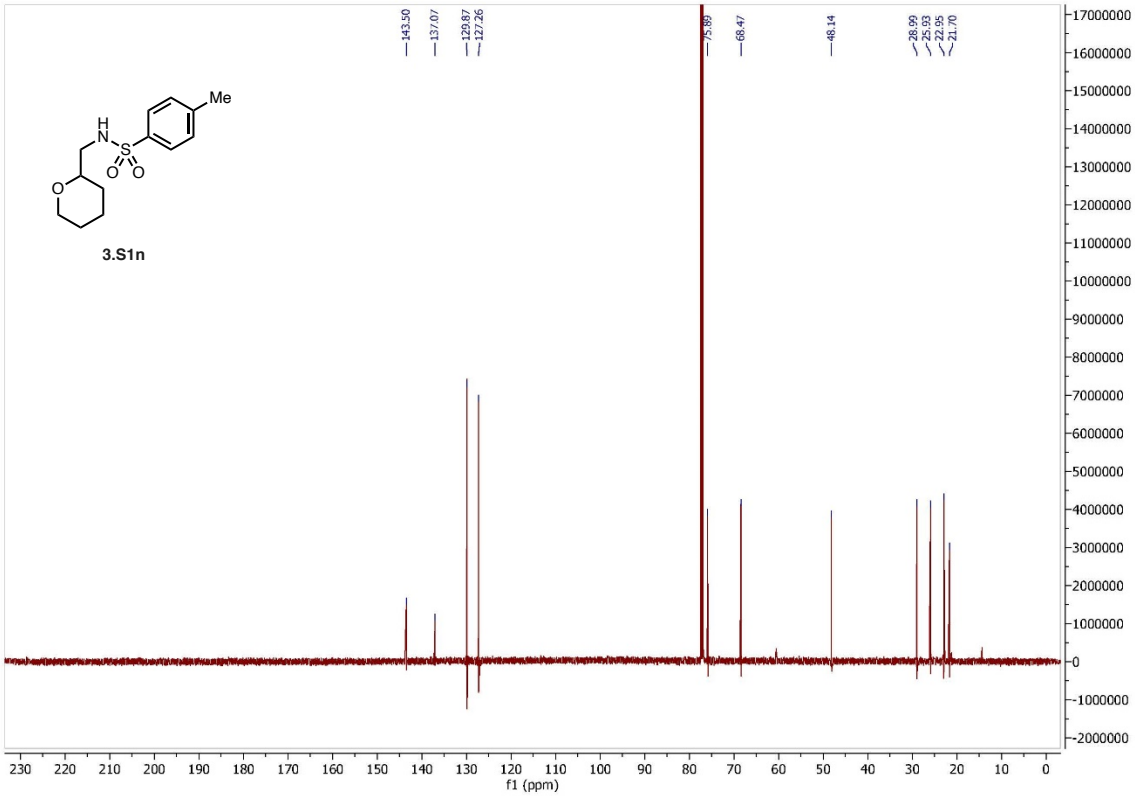


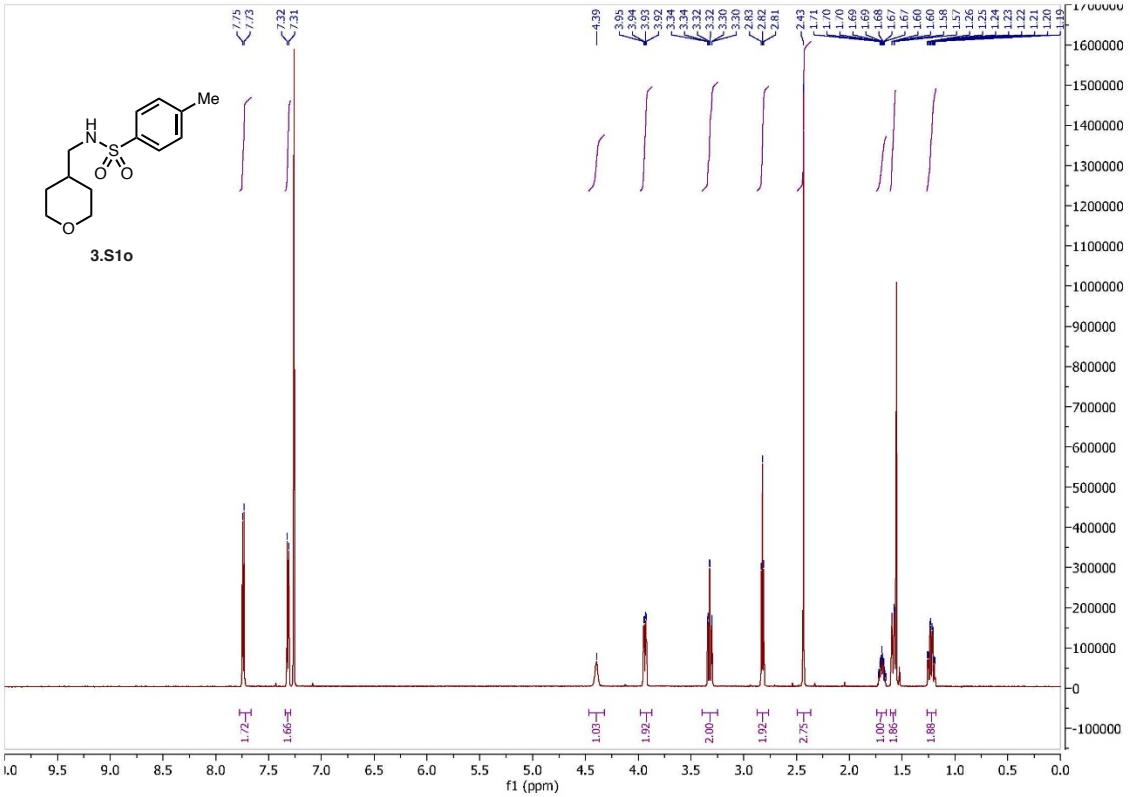
5017373-0220 lux confirm.7.1.1r — eek_13C_custom

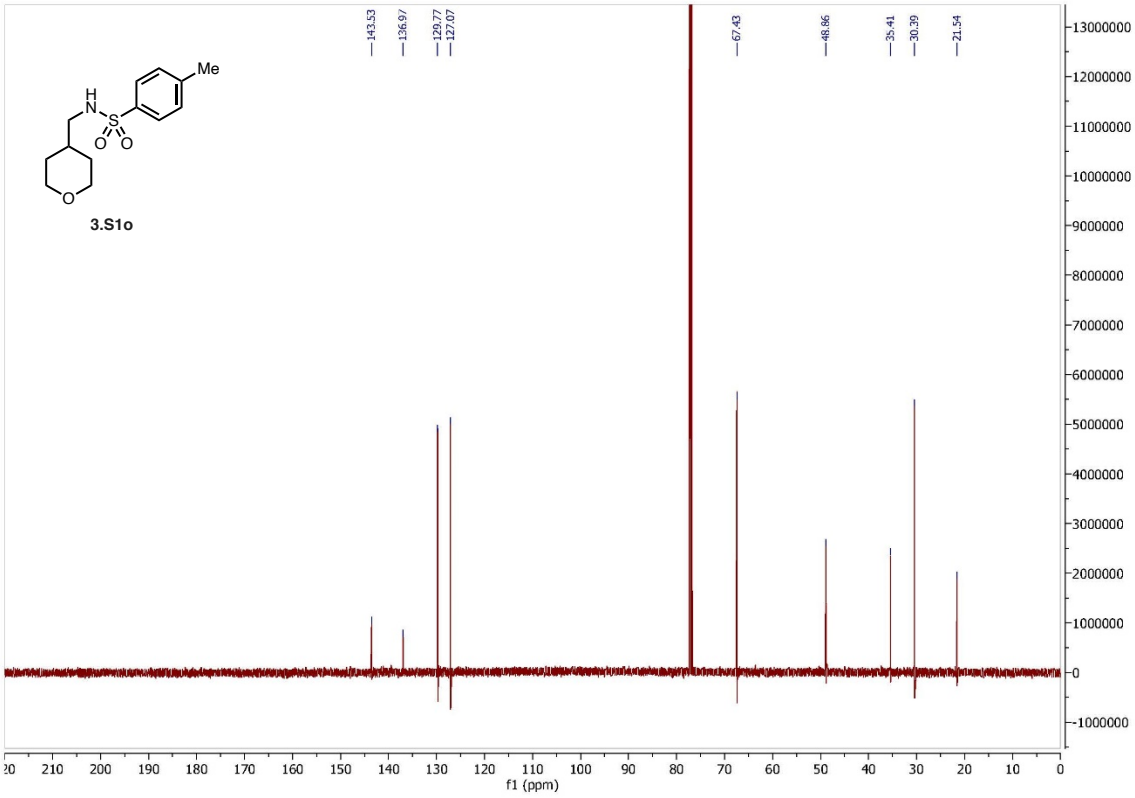
3.S1m

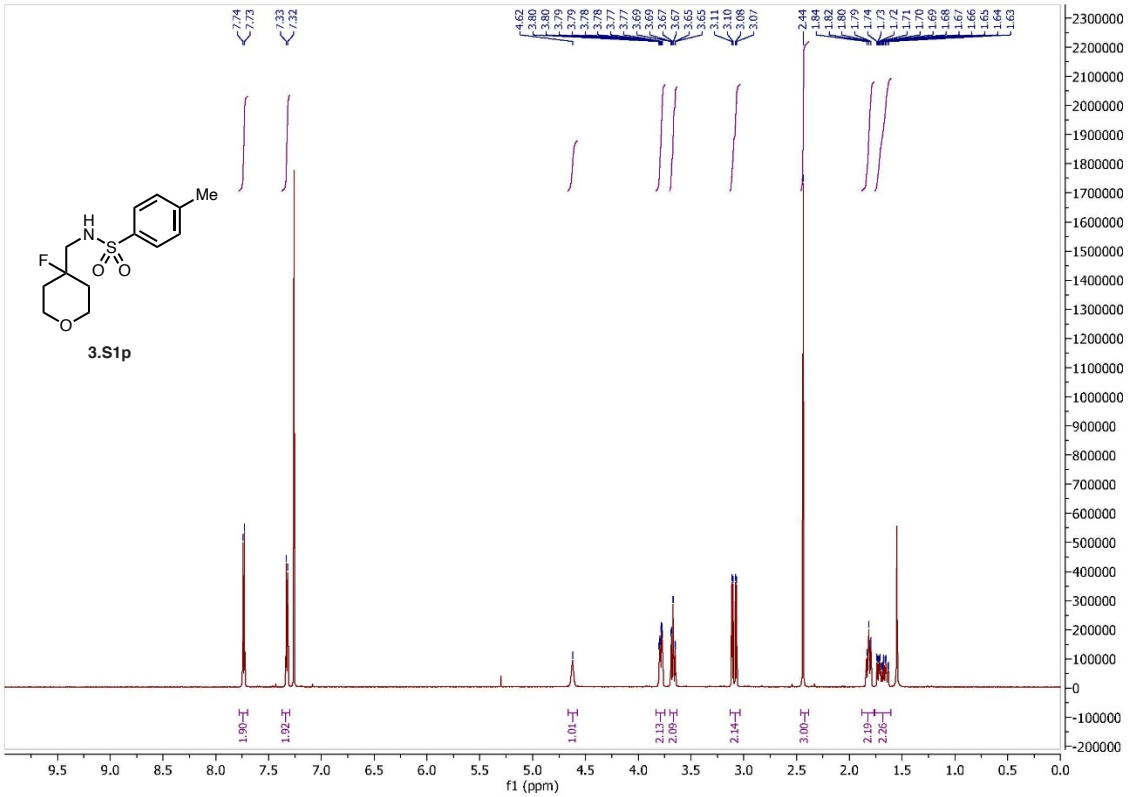


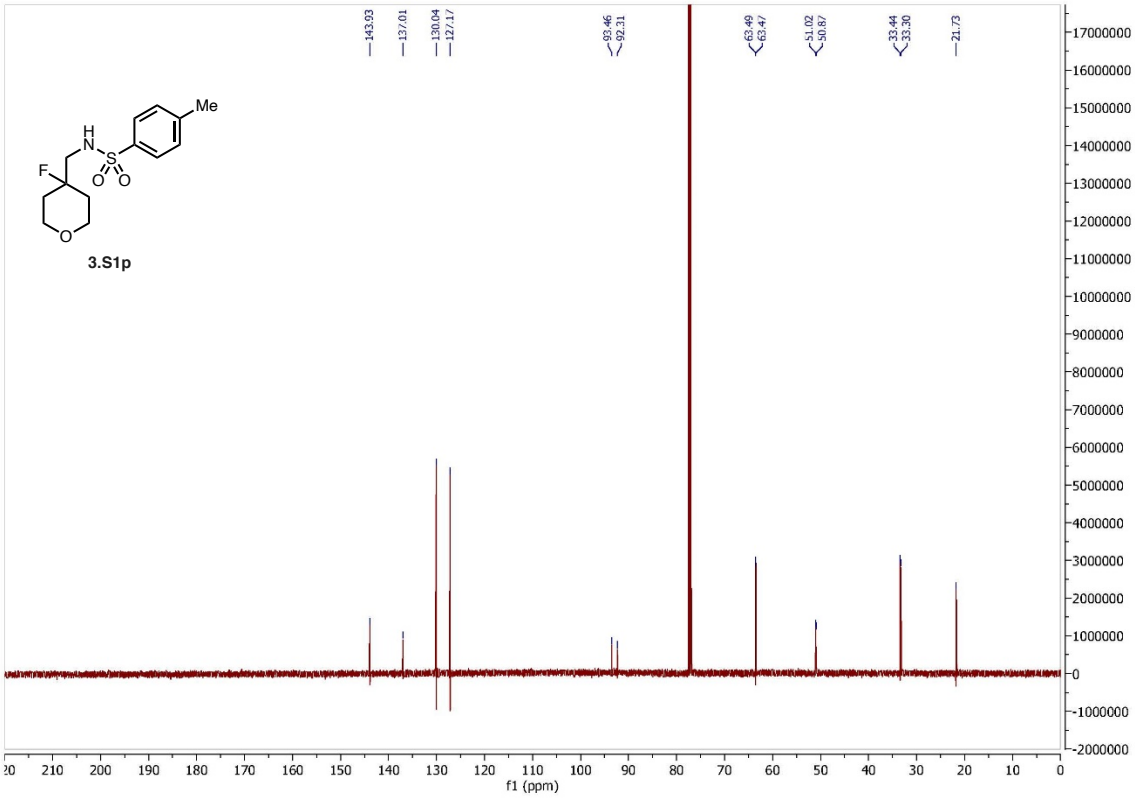

Me
H
N
S
O
O
O
3.S1n
7.73
7.72
7.31
7.29
1.83
1.87
1.00
1.07
2.09
1.12
1.10
2.99
1.11
2.75
4.13
1.38
f1 (ppm)

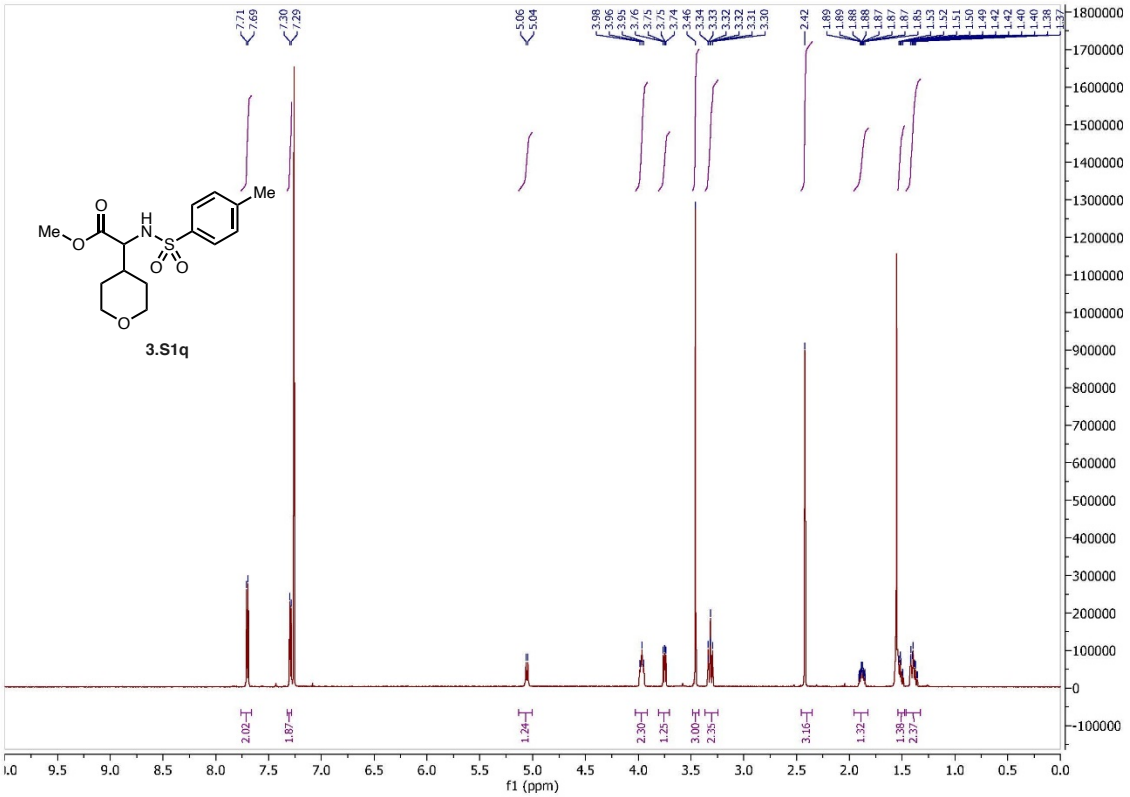

Me
H
N
S
O
O
O
3.S1n
143.50
137.07
129.87
127.26
75.89
68.47
48.14
28.99
25.93
22.95
21.70
f1 (ppm)

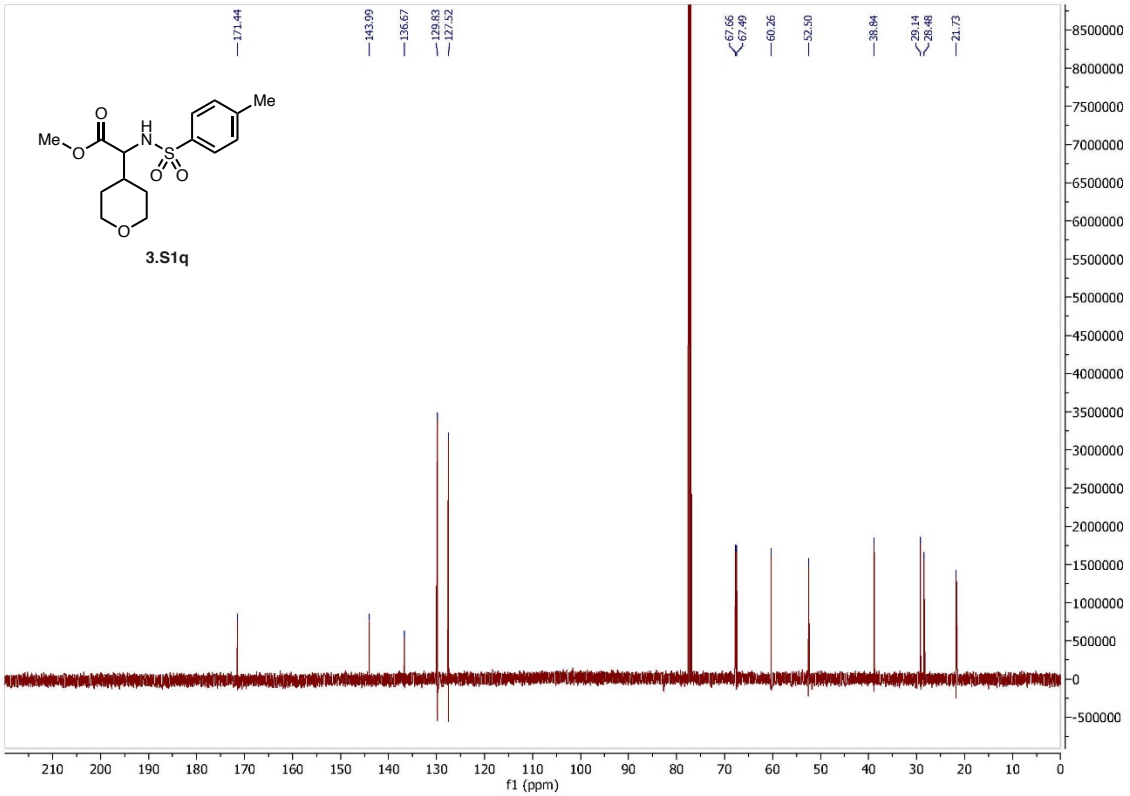

Me
H
N
S
O
O
O
3.S1o
7.75
7.73
7.32
7.31
4.39
3.95
3.94
3.93
3.92
3.34
3.34
3.32
3.32
3.30
3.30
2.83
2.82
2.81
2.43
1.71
1.70
1.70
1.69
1.69
1.68
1.67
1.67
1.60
1.60
1.58
1.57
1.26
1.25
1.24
1.23
1.22
1.21
1.20
1.19
1.72
1.66
1.03
1.92
2.00
1.92
2.75
1.00
1.86
1.88
f1 (ppm)

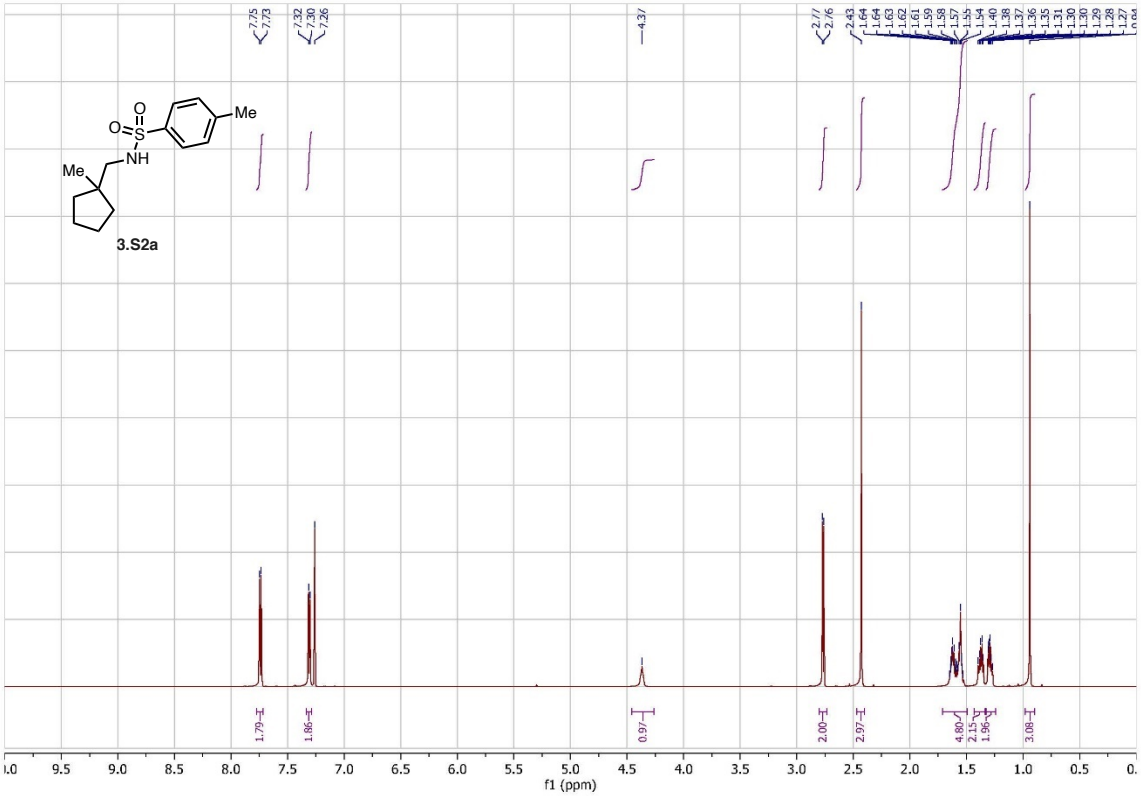

Me
H
N
S
O
O
O
3.S1o
143.53
136.97
129.77
127.07
67.43
48.86
35.41
30.39
21.54
f1 (ppm)

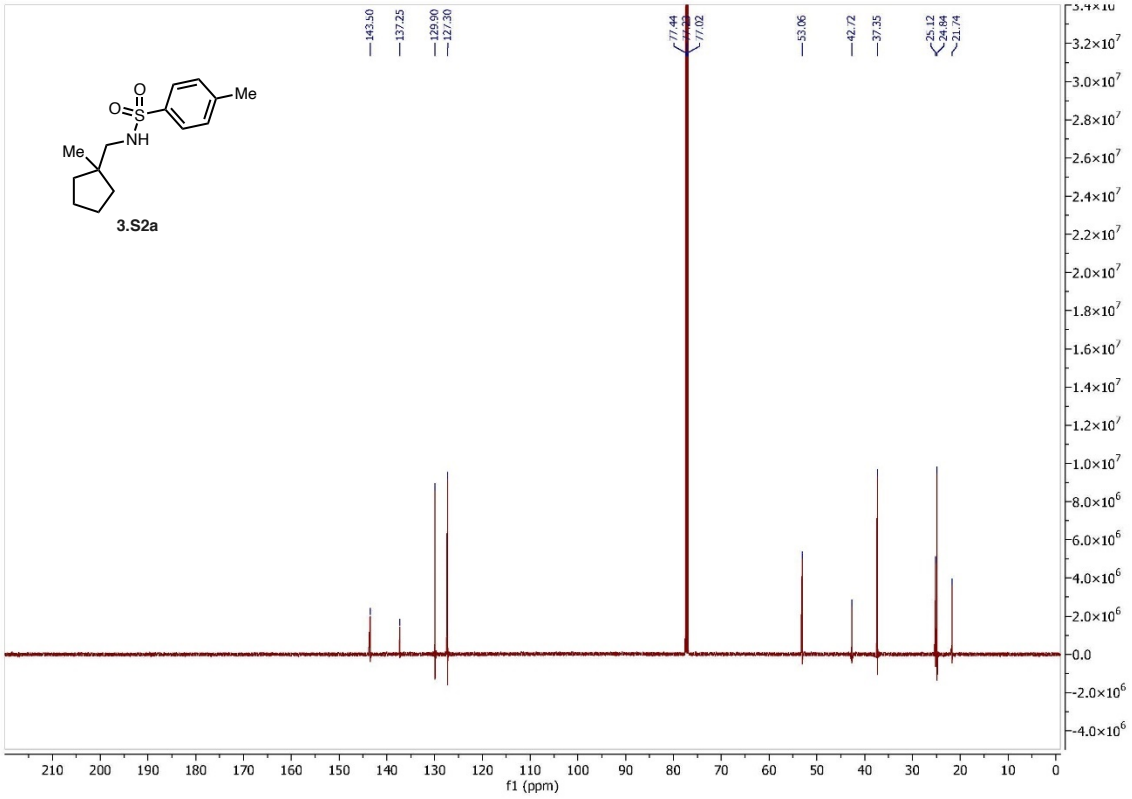

Me
H
N
S
O
O
F
O
3.S1p
f1 (ppm)

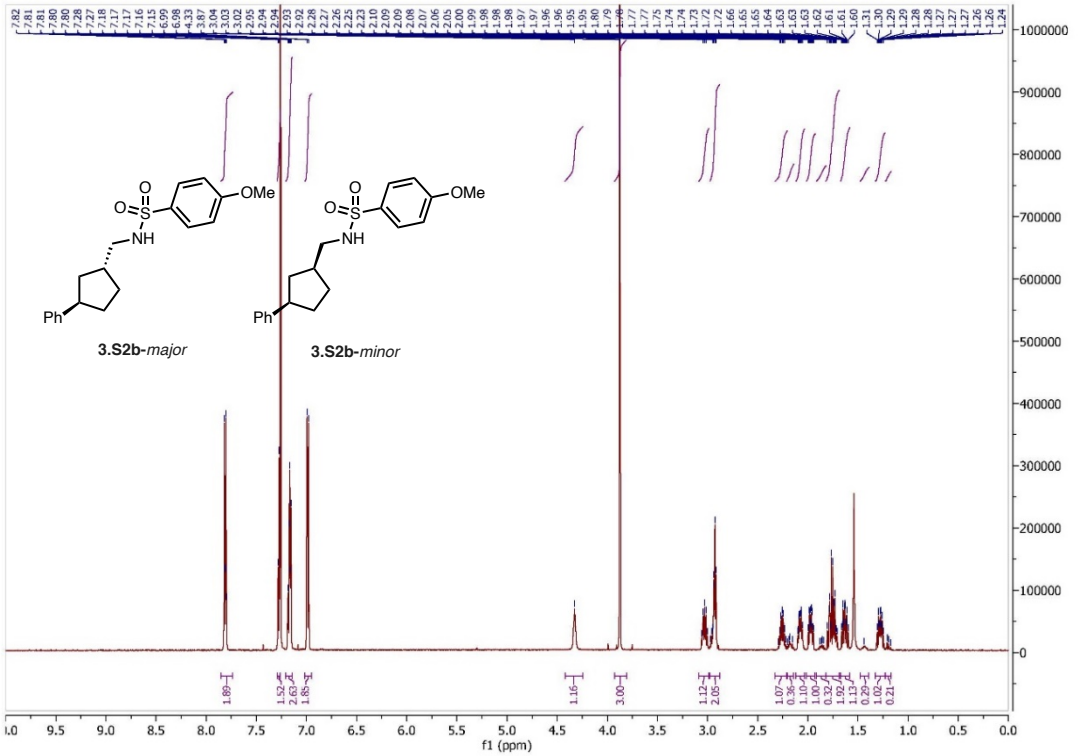

Me
H
N
S
O
O
F
O
3.S1p
f1 (ppm)

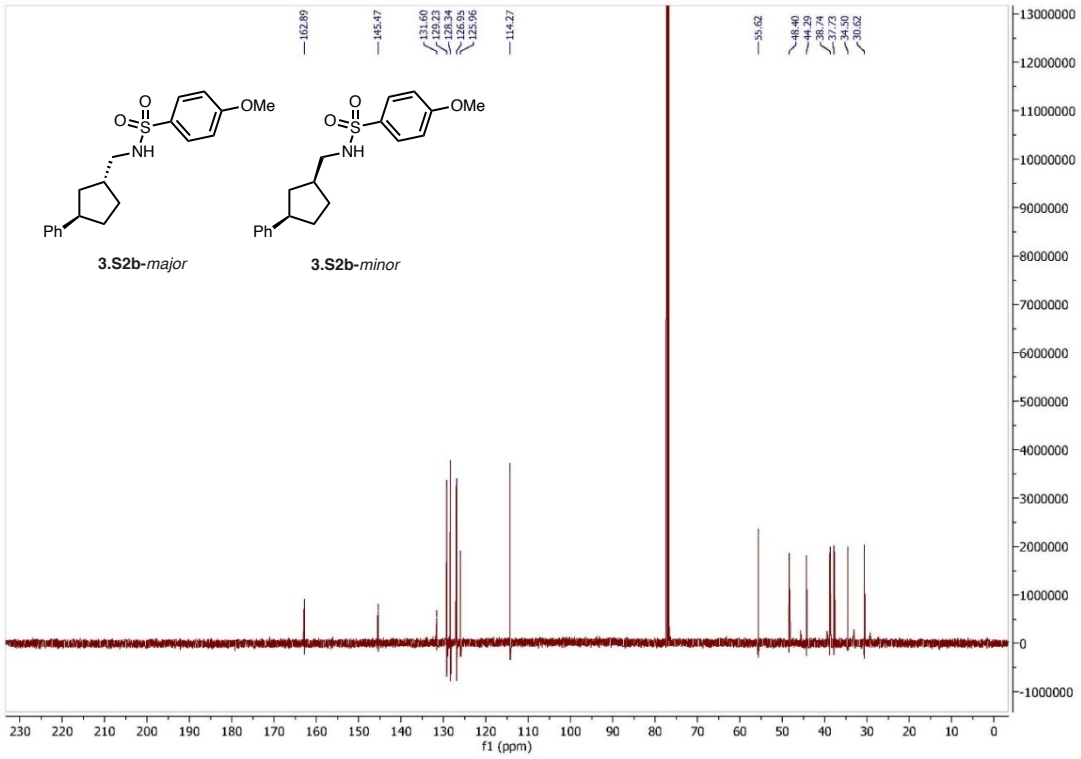

3.S1q
f1 (ppm)

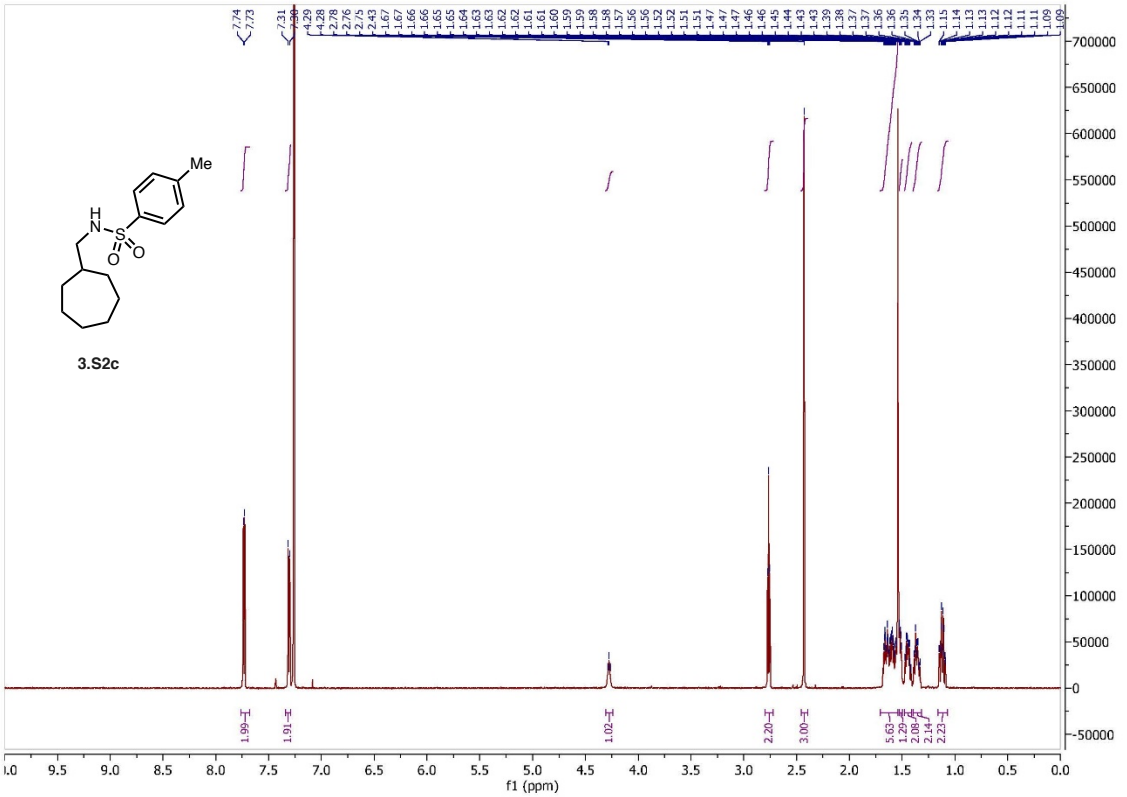

3.S1q
f1 (ppm)

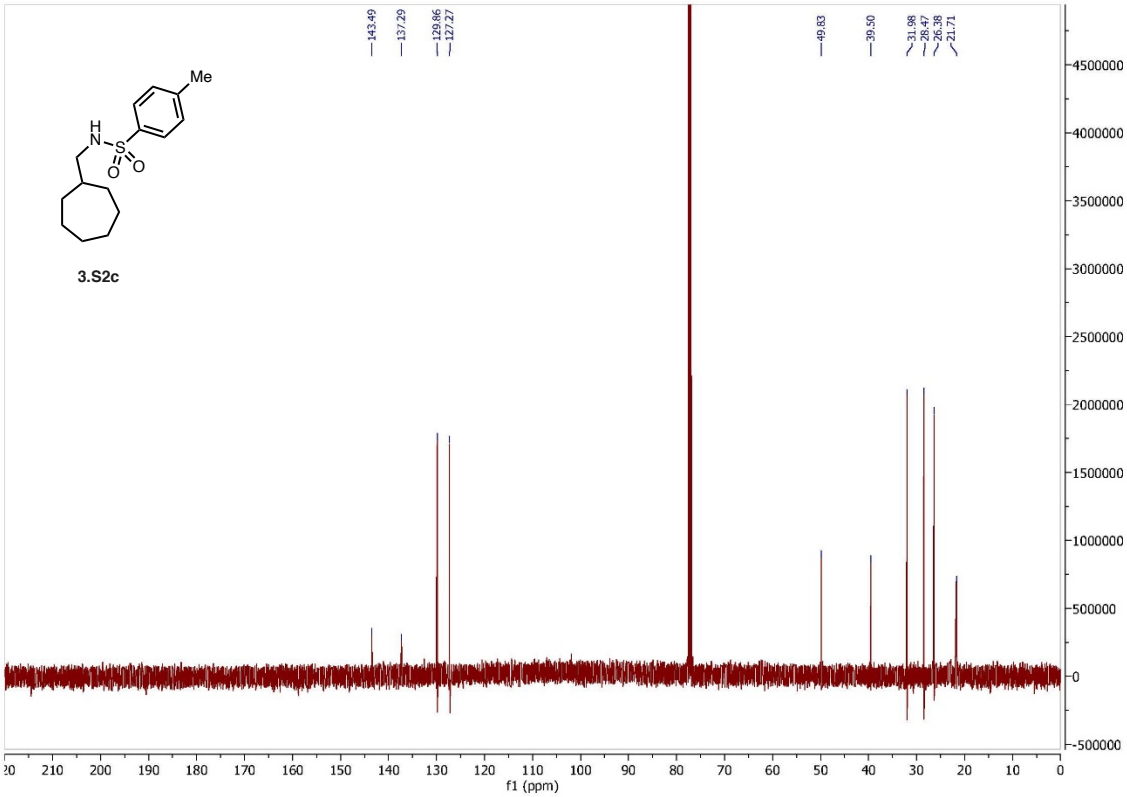

Me
O
O
S
NH
Me
3.S2a
f1 (ppm)

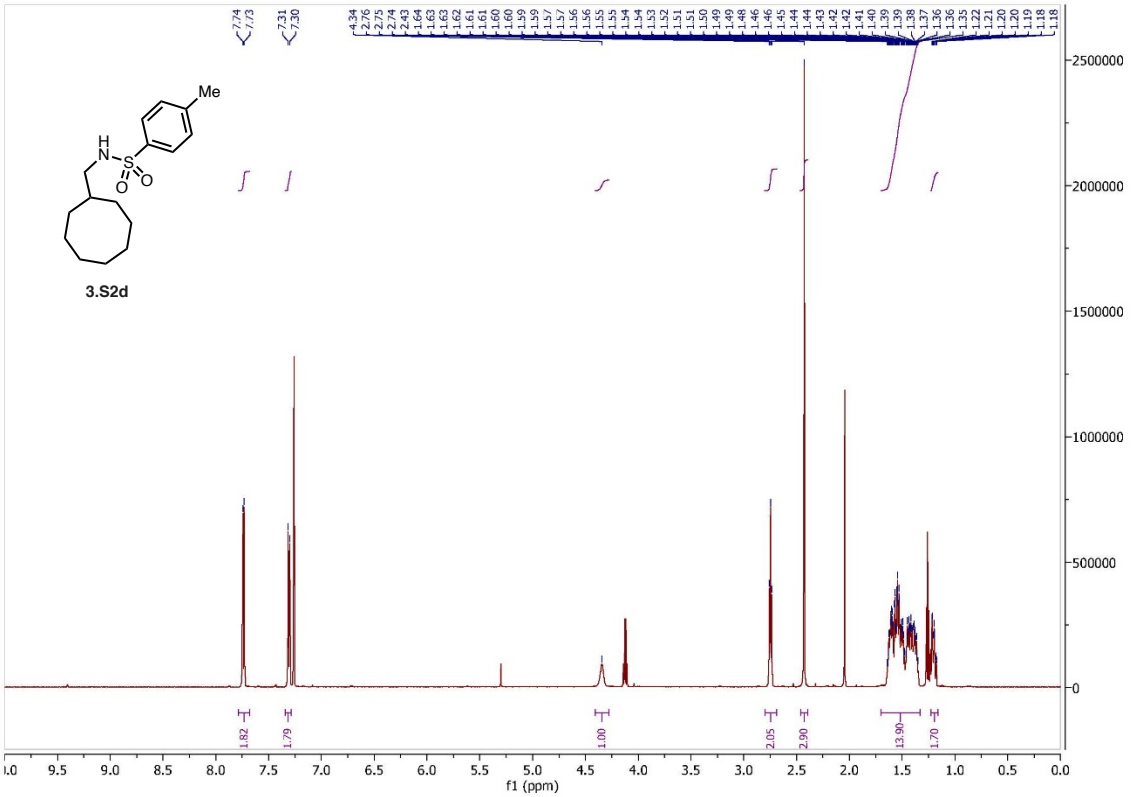

Me
O
O
S
NH
Me
3.S2a
f1 (ppm)

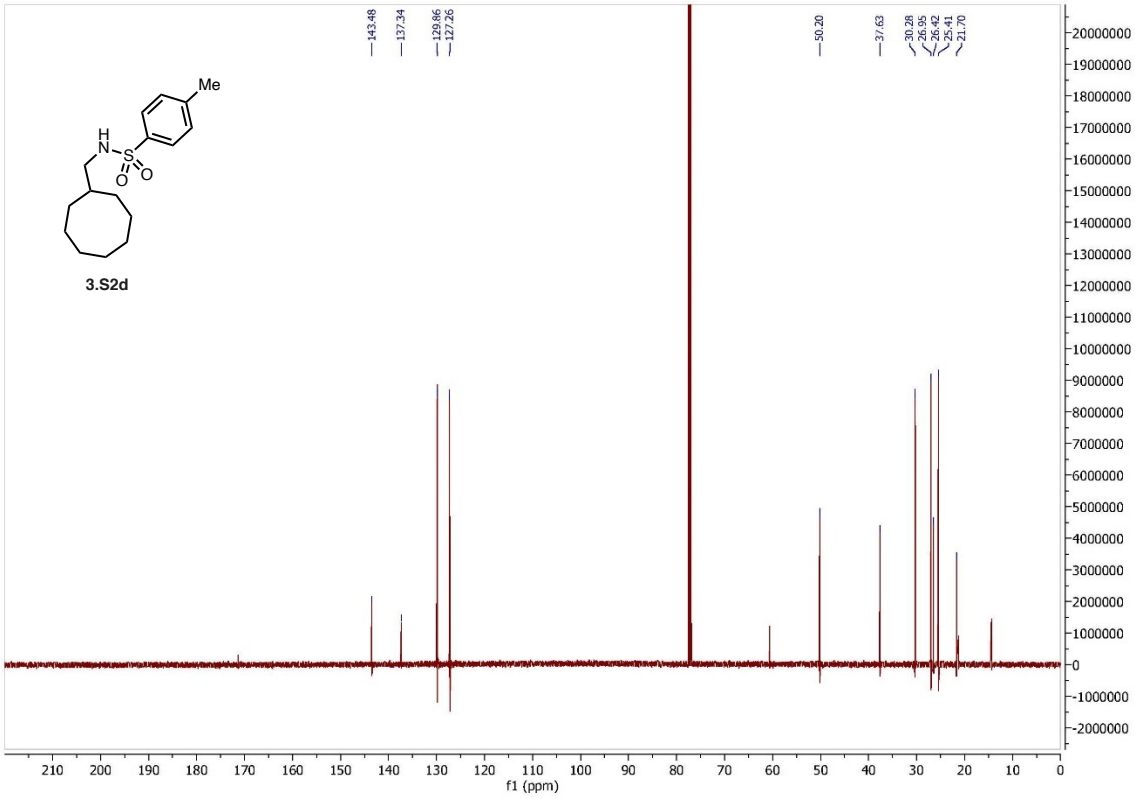

OMe
NH
Ph
3.S2b-major
3.S2b-minor
f1 (ppm)


OMe
NH
Ph
3.S2b-major
3.S2b-minor
f1 (ppm)


Me
H
N
S
O
O
3.S2c
f1 (ppm)


Me
H
N
S
O
O
3.S2c
143.49
137.29
129.86
127.27
49.83
39.50
31.98
28.47
26.38
21.71
f1 (ppm)


Me
H
N
S
O
O
3.S2d
7.74
7.73
7.31
7.30
4.34
2.76
2.75
2.74
2.43
1.64
1.63
1.62
1.61
1.60
1.59
1.57
1.56
1.55
1.54
1.53
1.52
1.51
1.50
1.49
1.48
1.46
1.45
1.44
1.43
1.42
1.41
1.40
1.39
1.38
1.37
1.36
1.35
1.22
1.21
1.20
1.19
1.18
1.82
1.79
1.00
2.05
2.90
13.90
1.70
f1 (ppm)


Me
H
N
S
O
O
3.S2d
143.48
137.34
129.86
127.26
50.20
37.63
30.28
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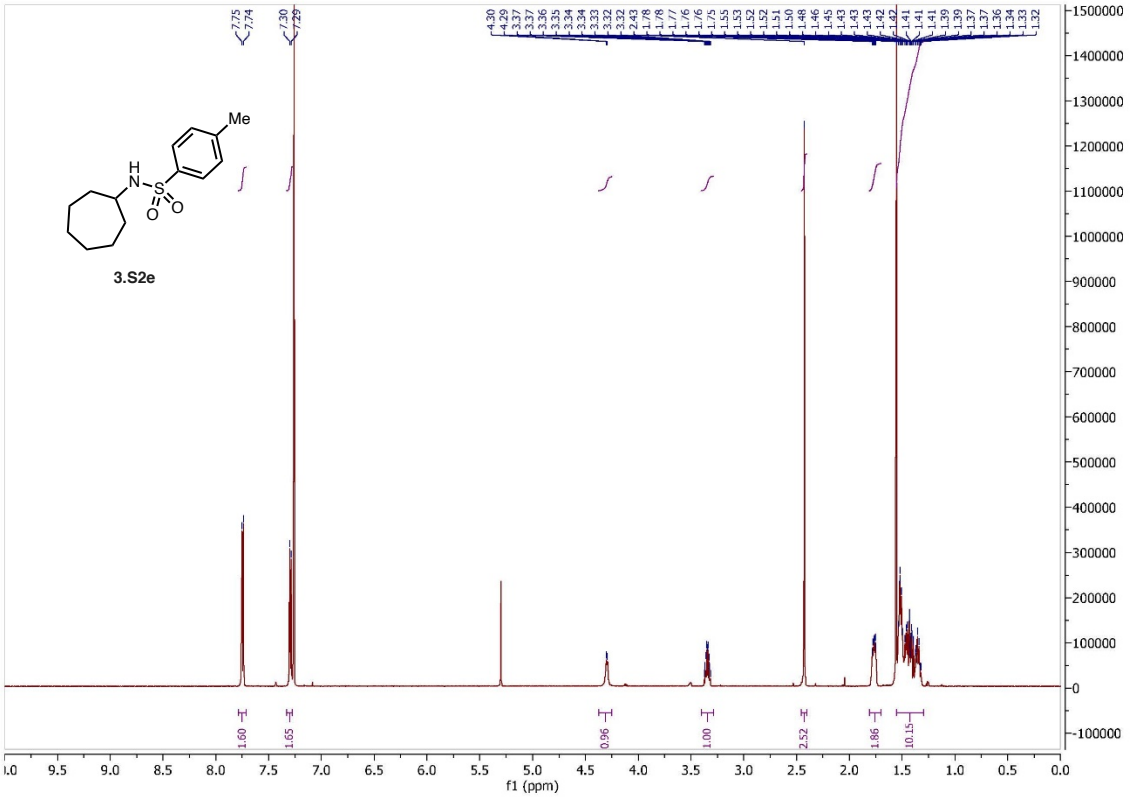
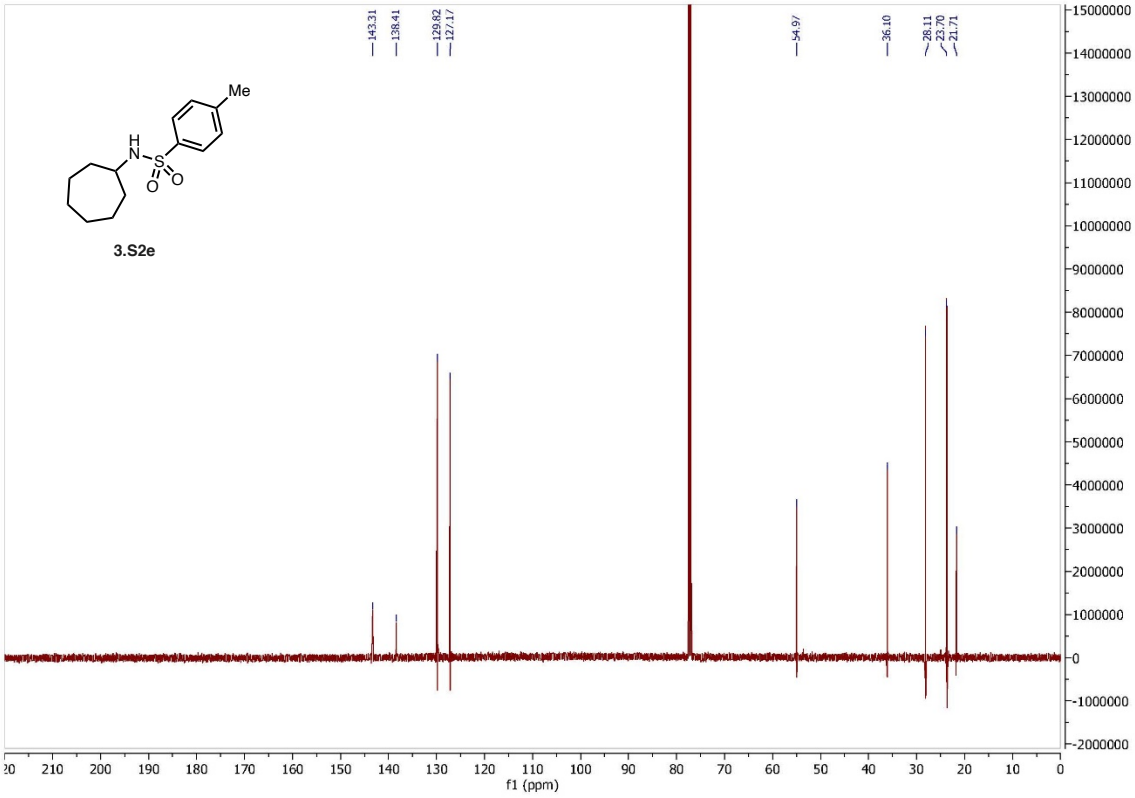
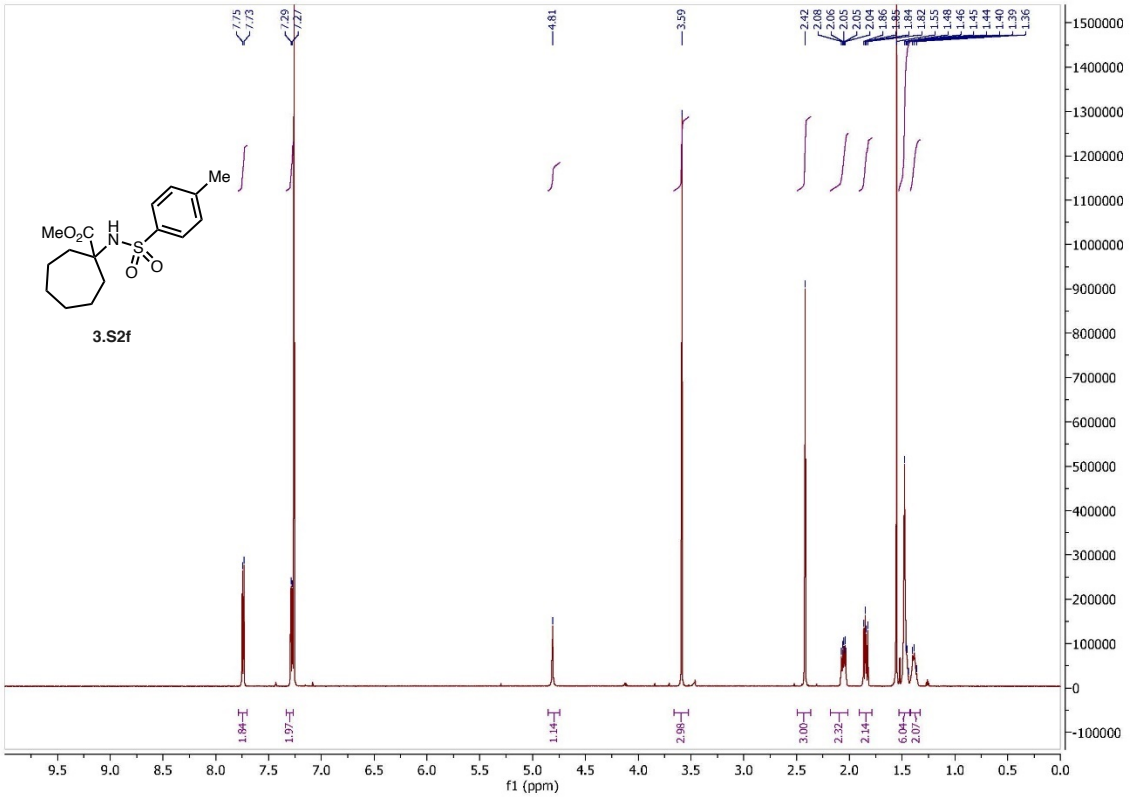
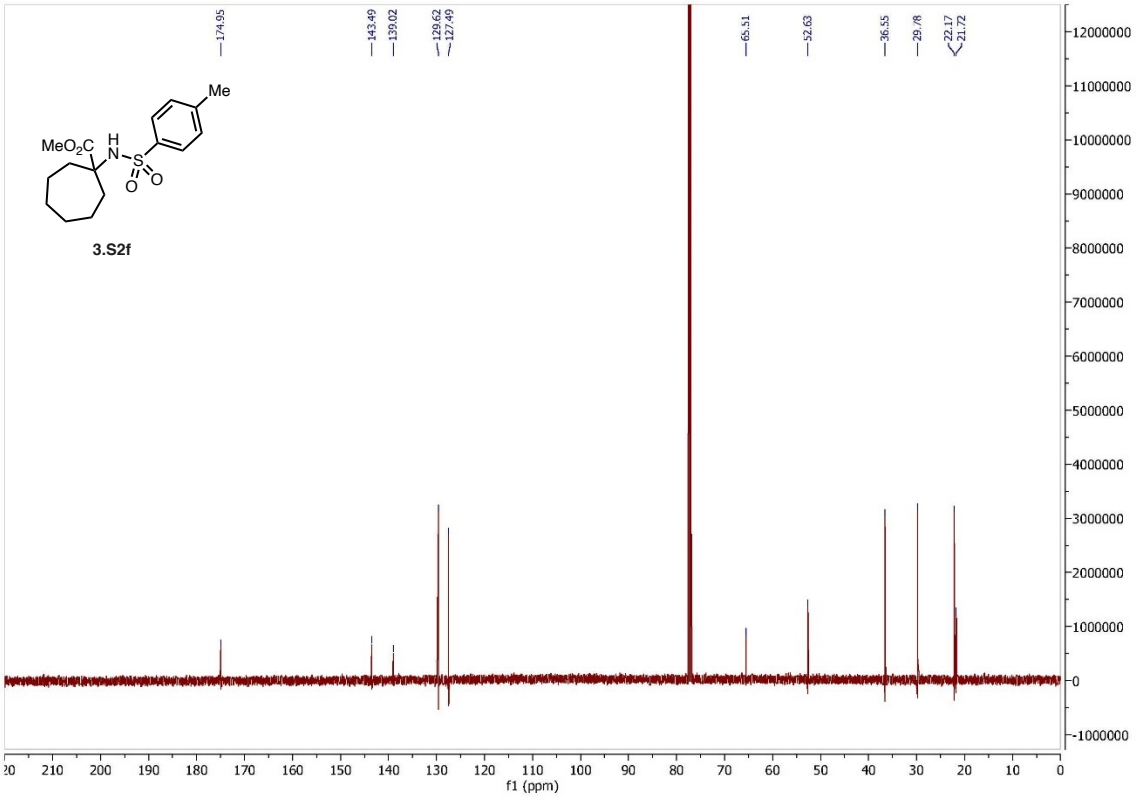
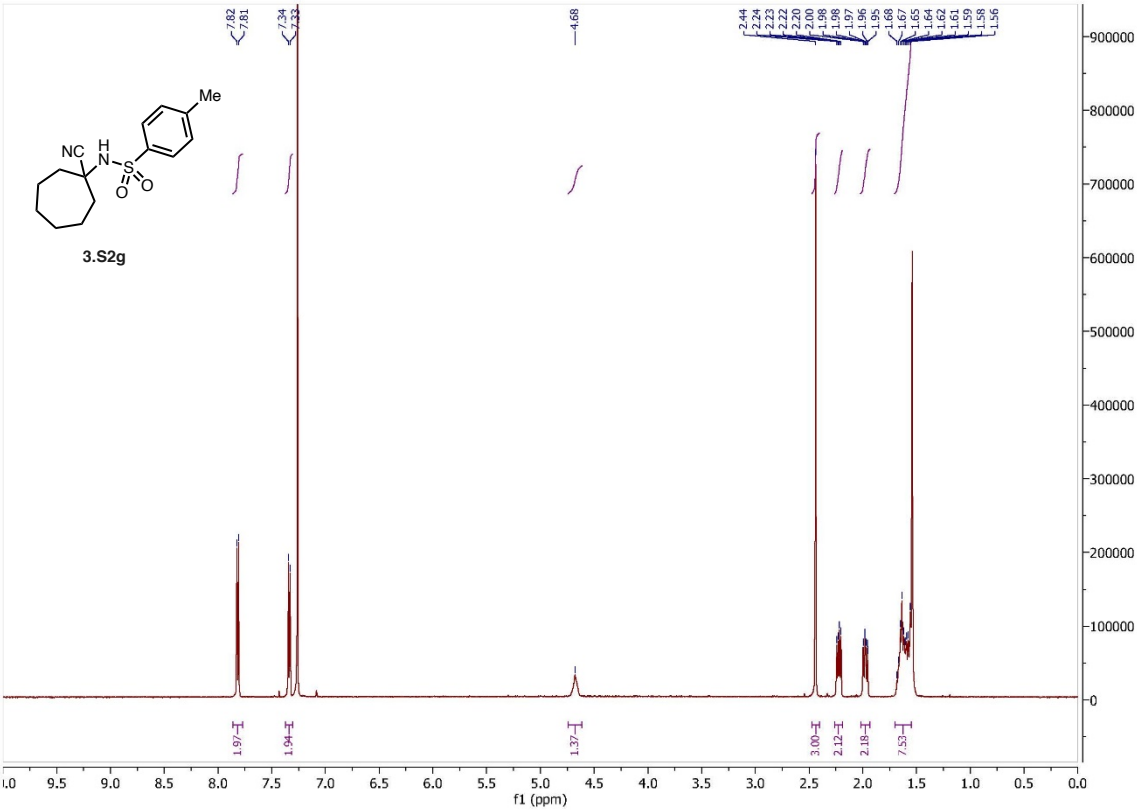
25.41
21.70
f1 (ppm)

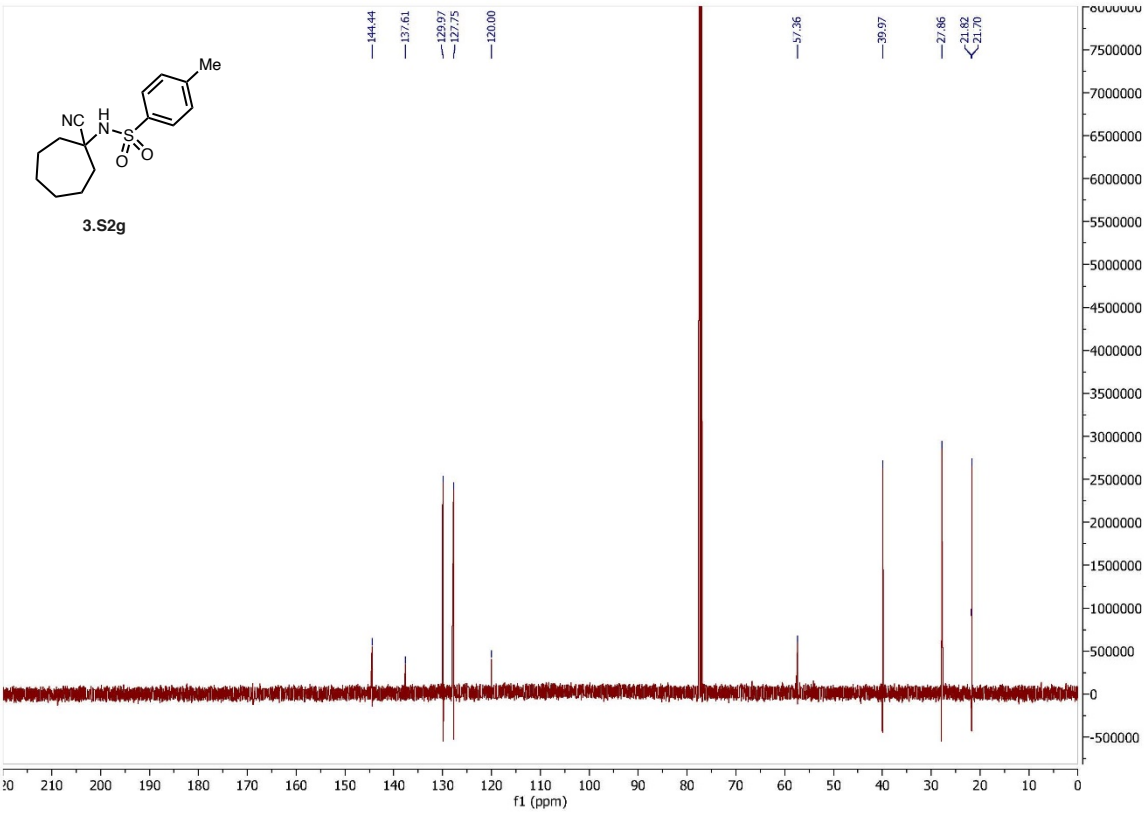

Me
H
N
S
O
O
3.S2e
7.75
7.74
7.30
7.29
1.60
1.65
0.96
1.00
2.52
1.86
10.15
f1 (ppm)

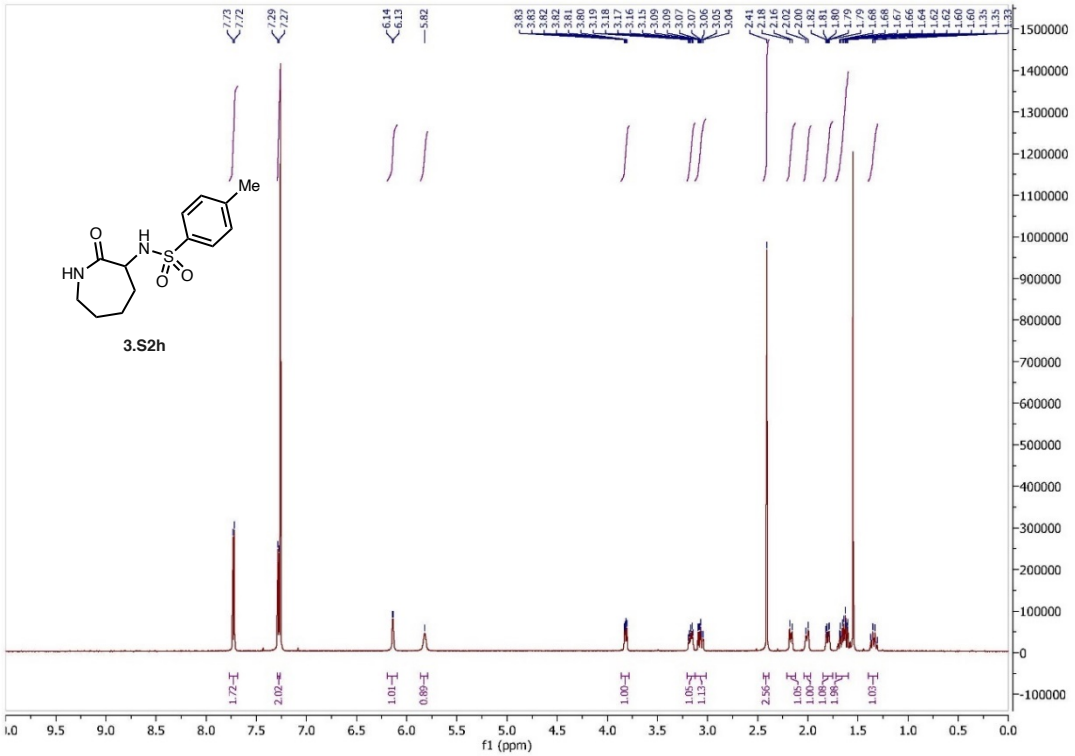

Me
H
N
S
O
O
3.S2e
143.31
138.41
129.62
127.17
54.97
36.10
28.11
23.70
21.71
f1 (ppm)

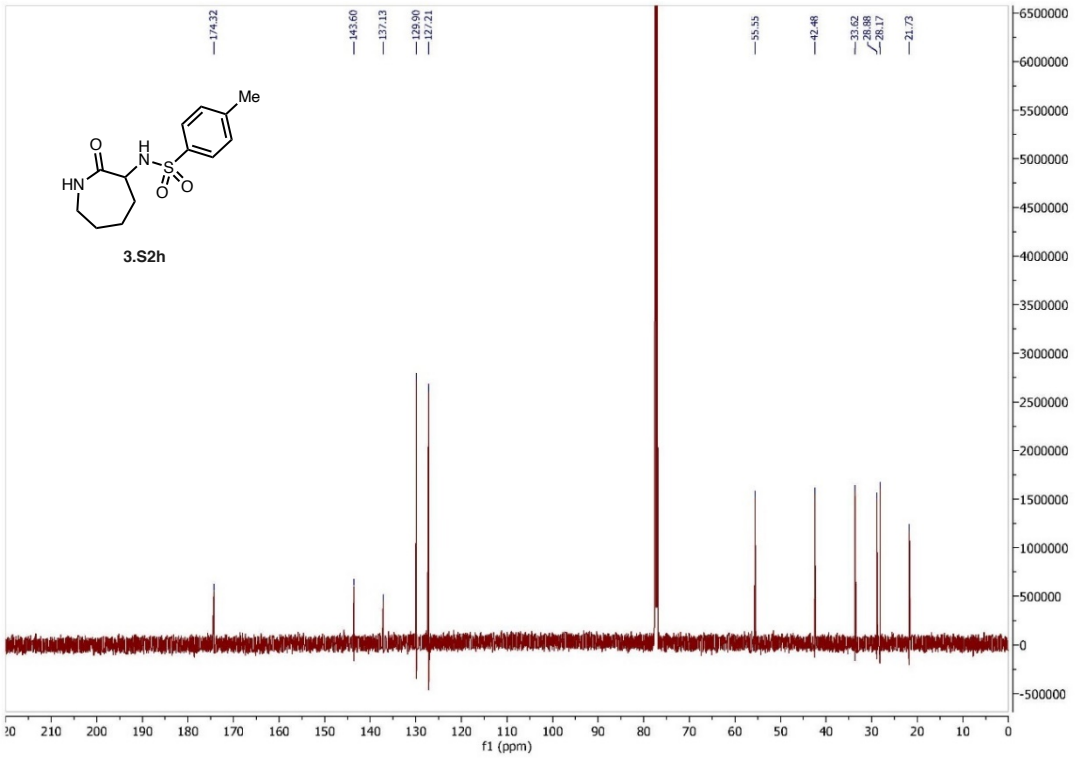

MeO2C
Me
3.S2f
f1 (ppm)

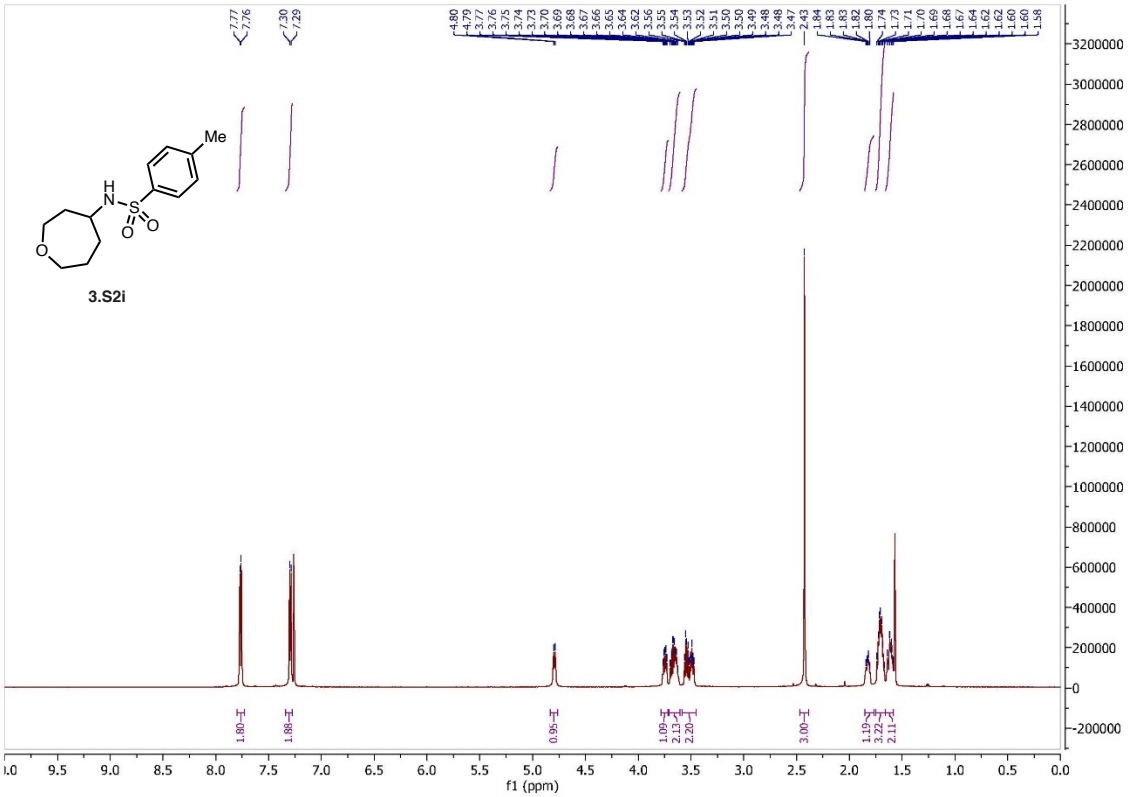

MeO2C
Me
3.S2f
f1 (ppm)


Me
NC
H
N
S
O
O
3.S2g
7.82
7.81
7.34
7.33
4.68
2.44
2.24
2.23
2.22
2.20
2.00
1.98
1.97
1.96
1.95
1.68
1.67
1.65
1.64
1.62
1.61
1.59
1.58
1.56
1.97
1.94
1.37
3.00
2.12
2.18
7.53
f1 (ppm)


Me
NC
H
N
S
O
O
3.S2g
144.44
137.61
129.97
127.75
120.00
57.36
39.97
27.86
21.82
21.70
f1 (ppm)


Me
O
H
N
S
O
O
HN
3.S2h
f1 (ppm)


Me
O
H
N
S
O
O
HN
3.S2h
f1 (ppm)


Me
H
N
S
O
O
O
3.S2i
7.77
7.76
7.30
7.29
4.80
4.79
3.77
3.76
3.75
3.74
3.73
3.70
3.69
3.68
3.67
3.66
3.65
3.64
3.62
3.56
3.55
3.54
3.53
3.52
3.51
3.50
3.49
3.48
3.47
2.43
1.84
1.83
1.83
1.82
1.80
1.74
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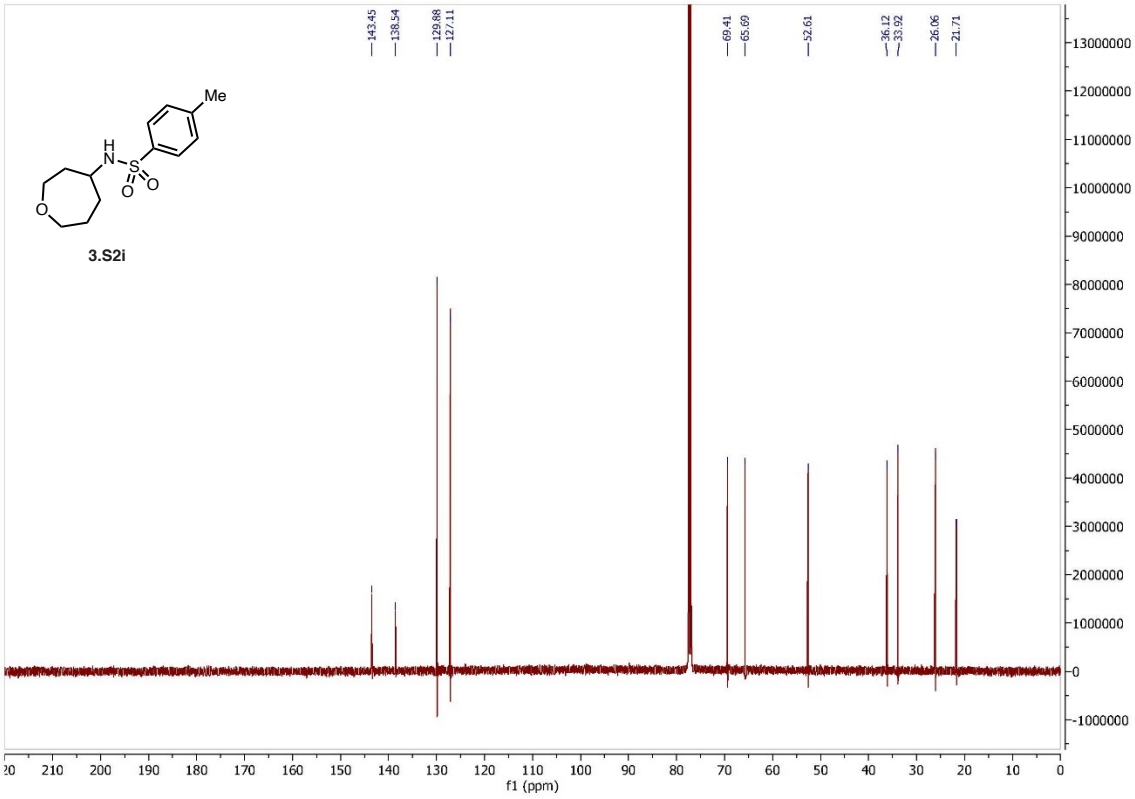
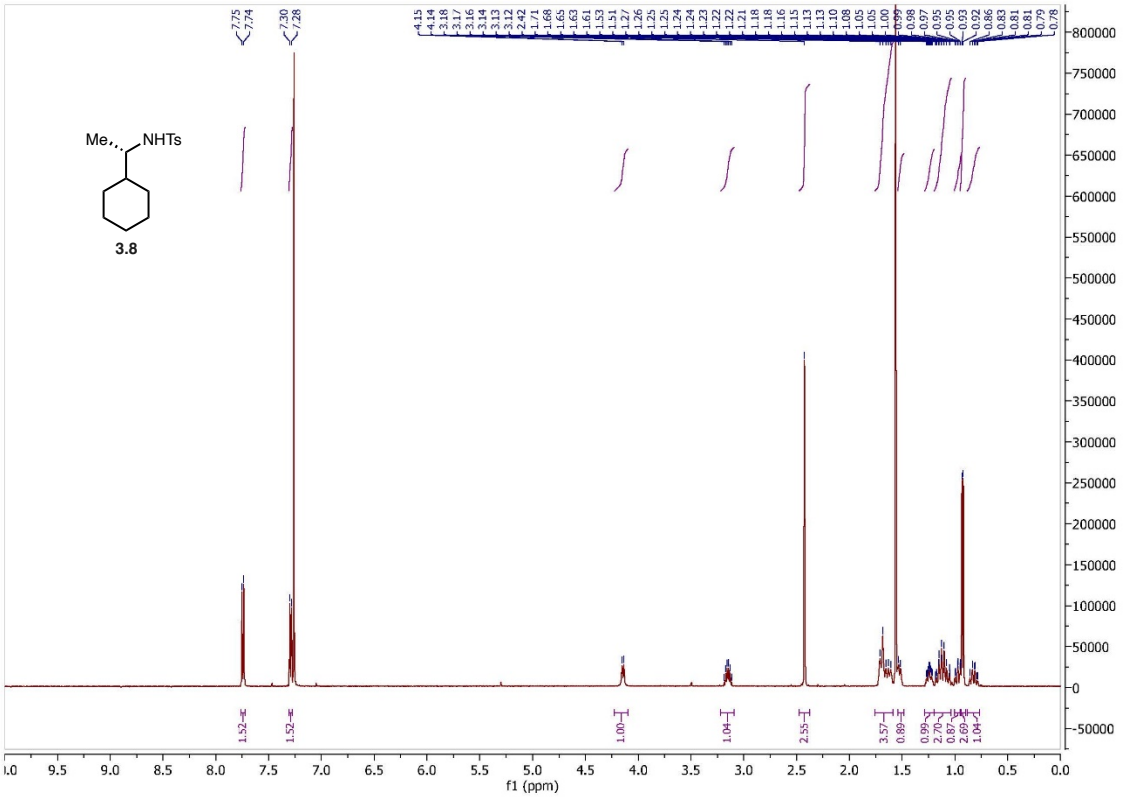
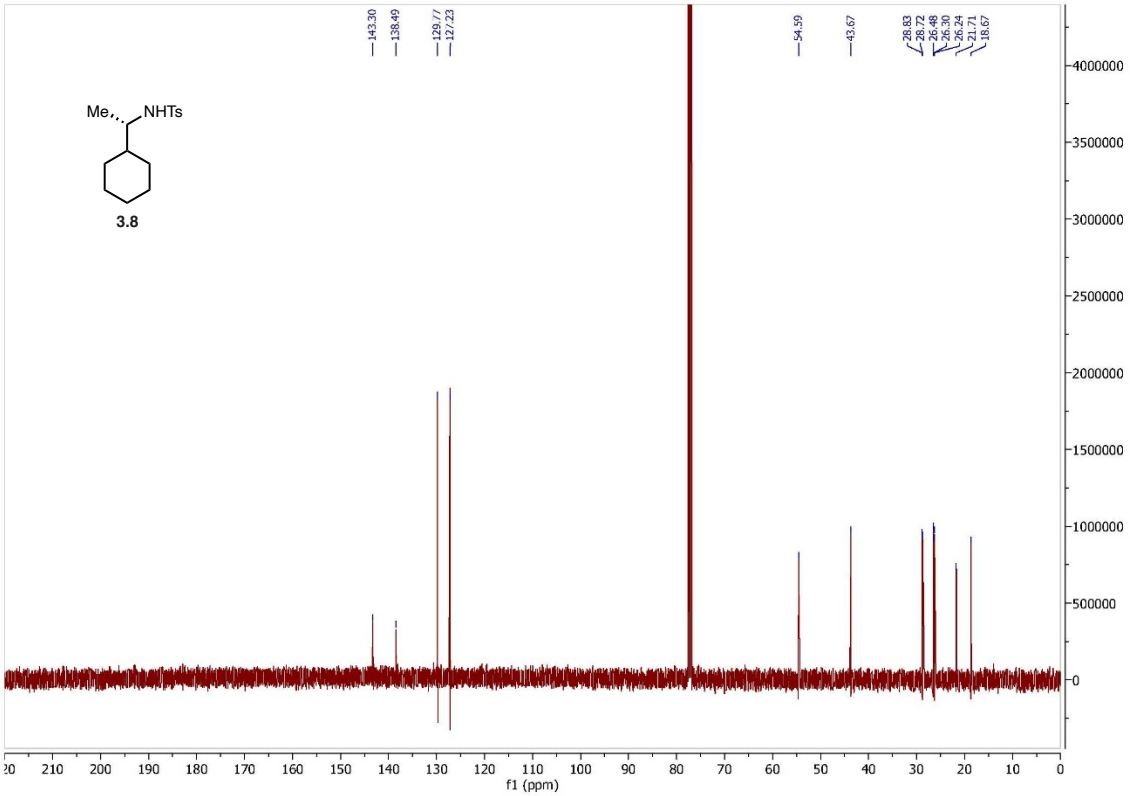
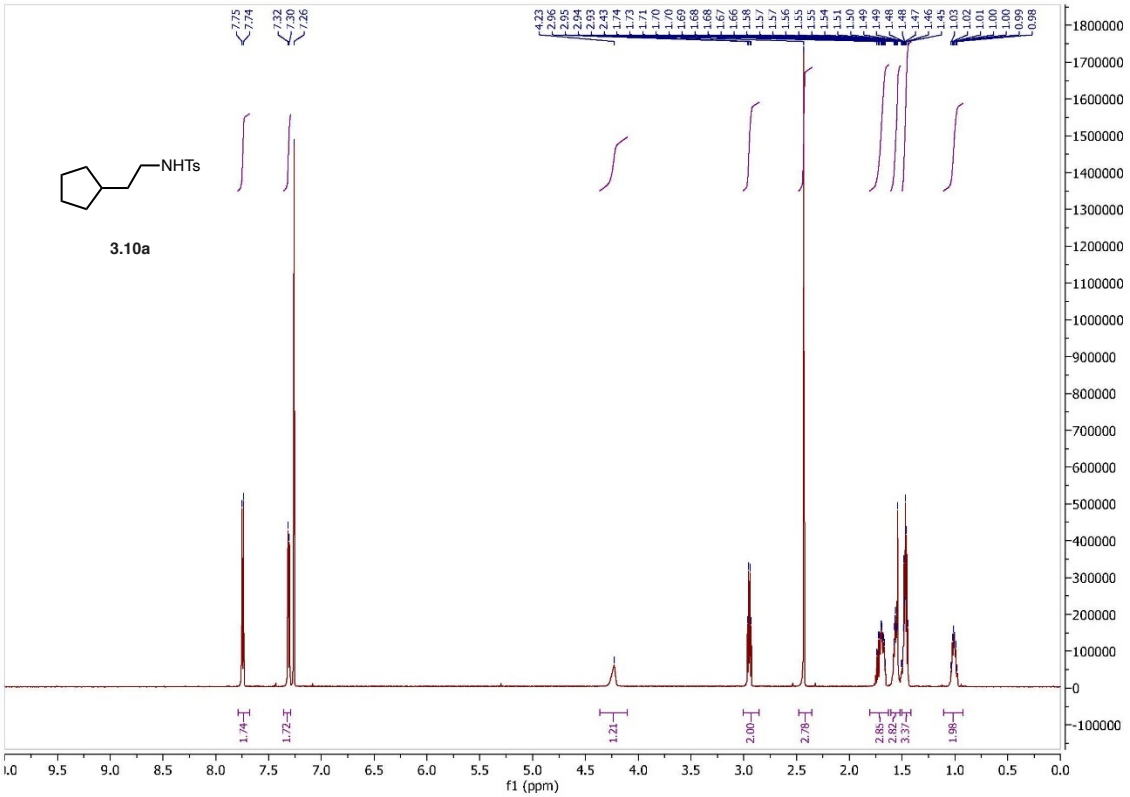
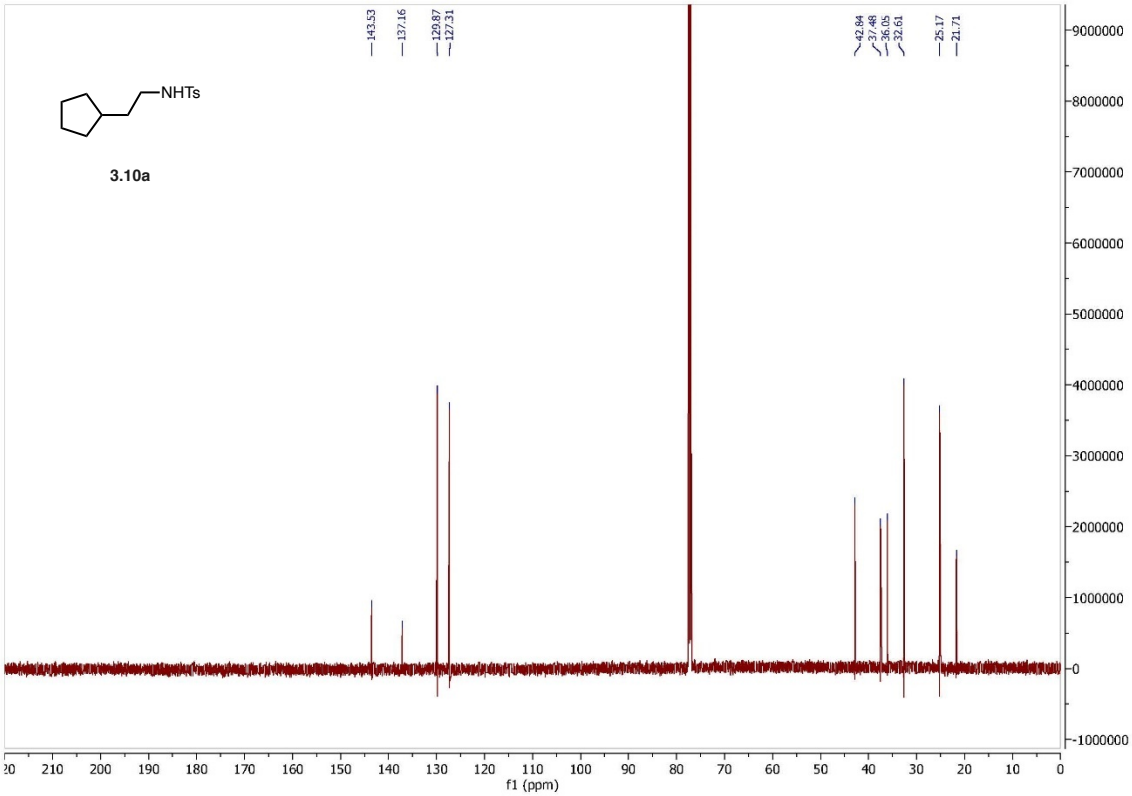
1.71
1.70
1.69
1.68
1.67
1.64
1.62
1.62
1.60
1.60
1.58
1.80
1.88
0.95
1.09
2.13
2.20
3.00
1.19
3.22
2.11
f1 (ppm)

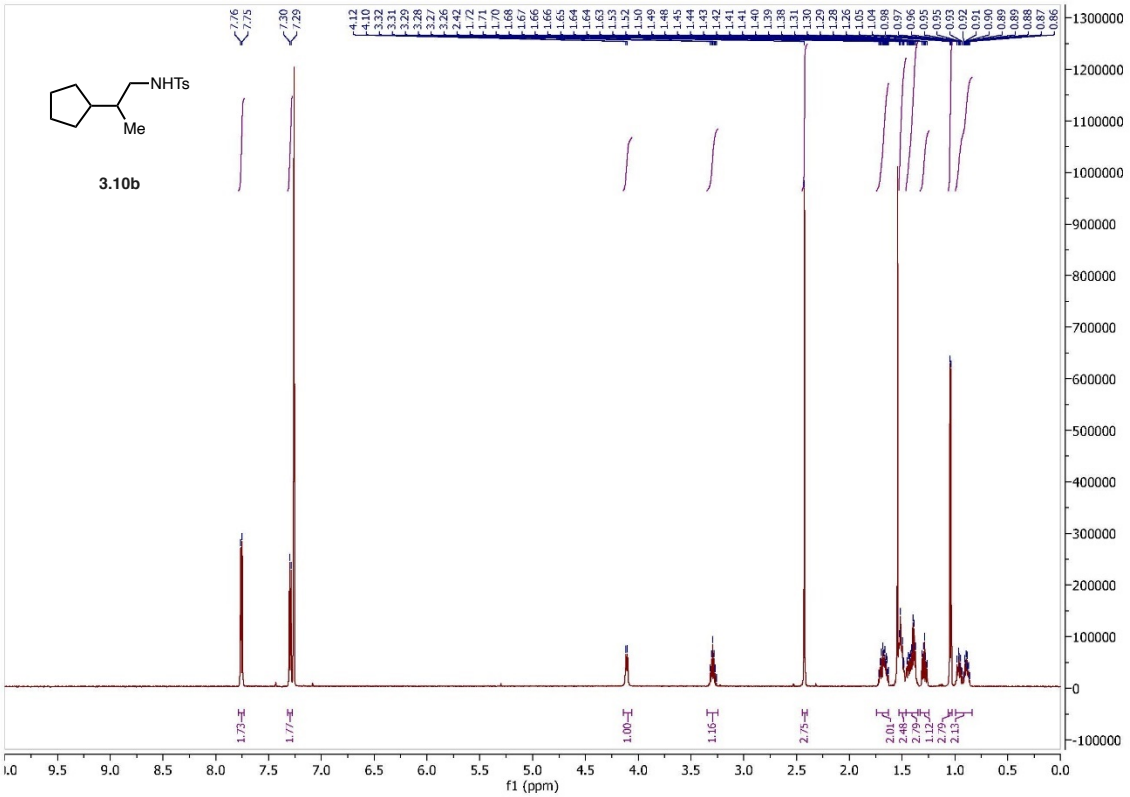

Me
H
N
S
O
O
O
3.S2i
143.45
138.54
129.88
127.11
69.41
65.69
52.61
36.12
33.92
26.06
21.71
f1 (ppm)

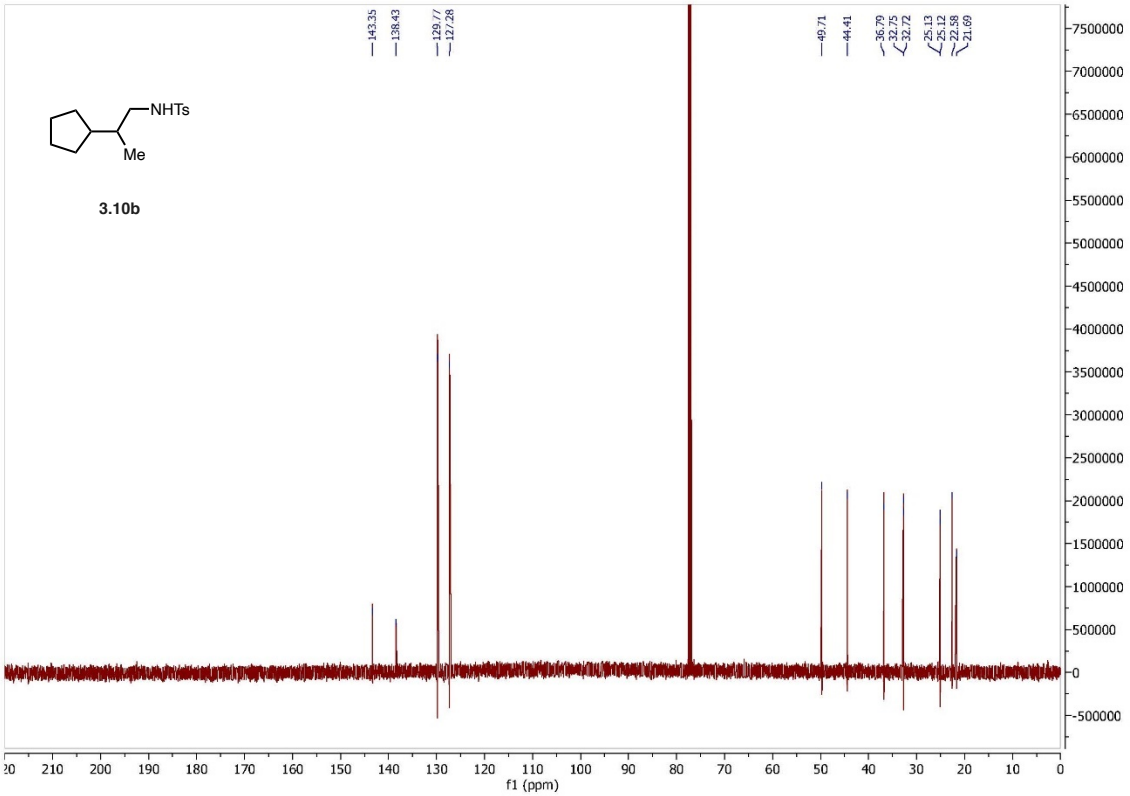

Me
NHTs
3.8
f1 (ppm)

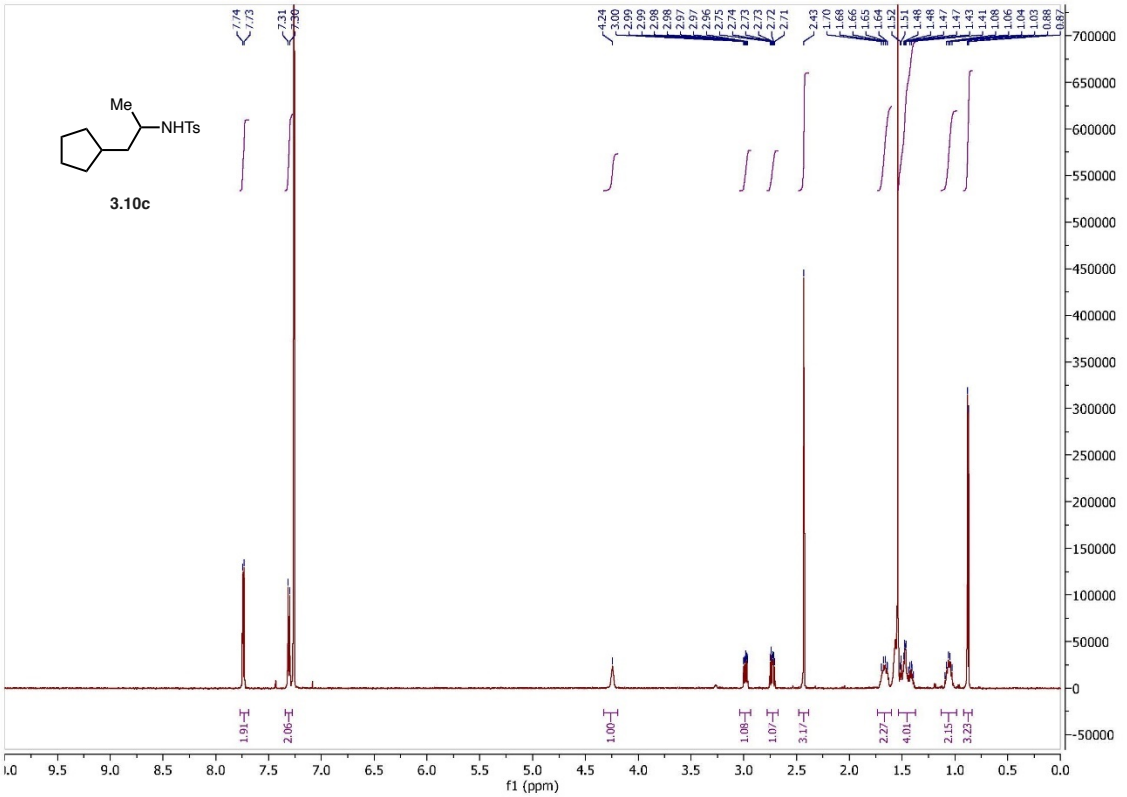

Me
NHTs
3.8
f1 (ppm)

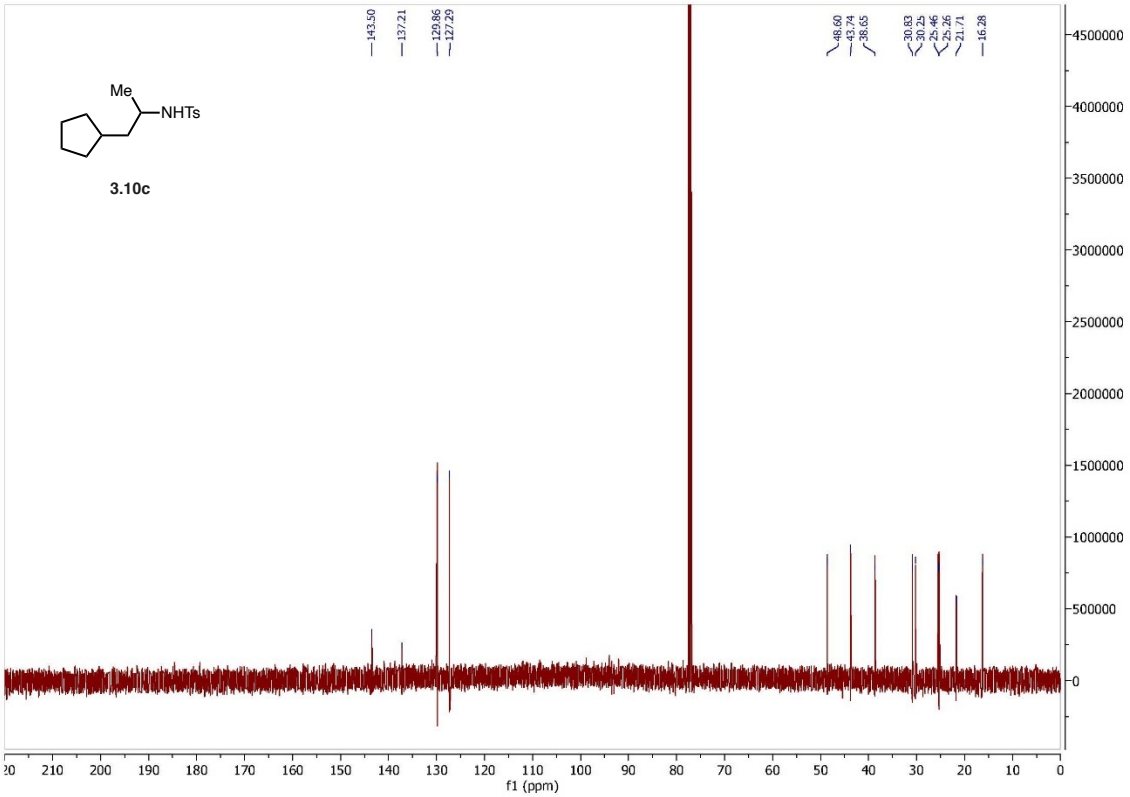

NHTs
3.10a
f1 (ppm)

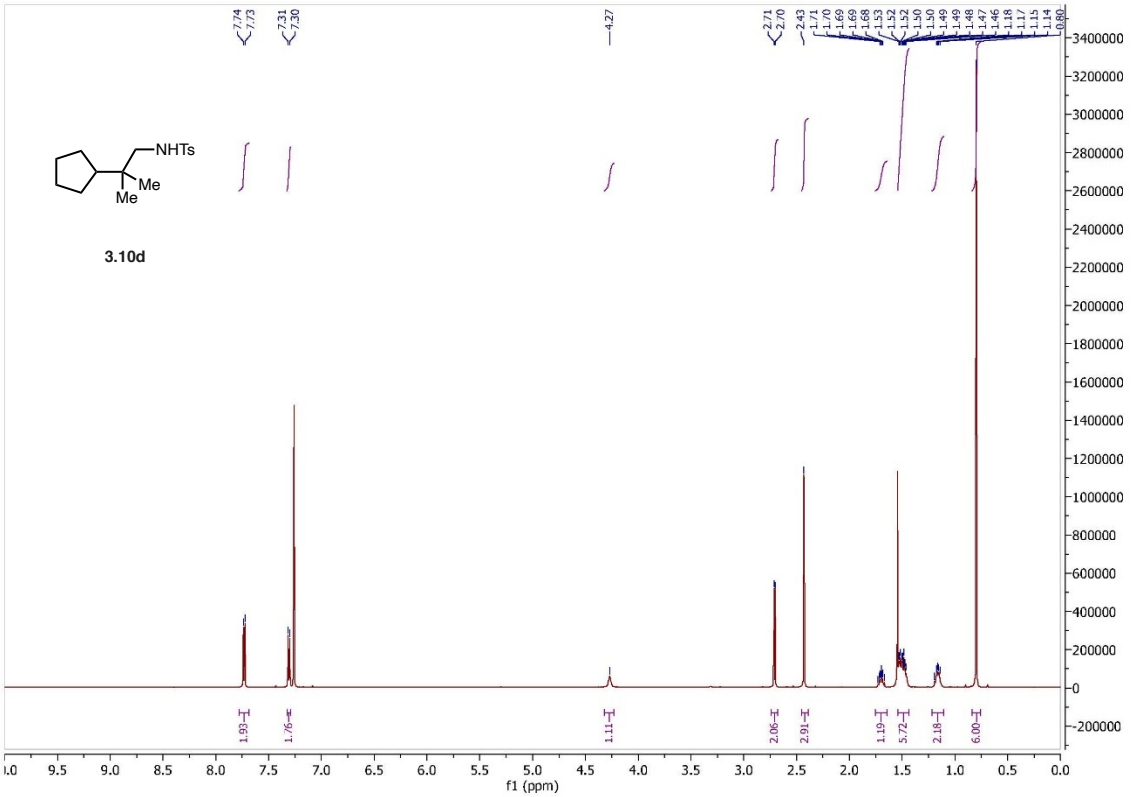

NHTs
3.10a
f1 (ppm)

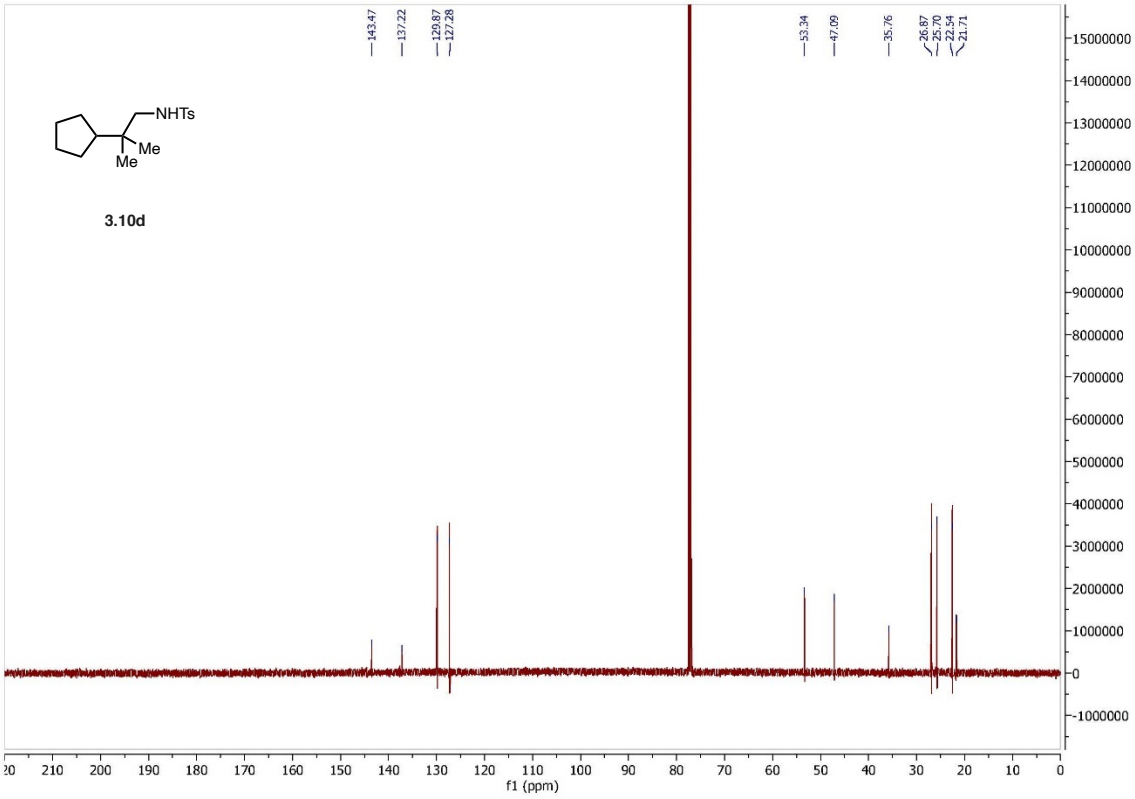

NHTs
Me
3.10b
f1 (ppm)

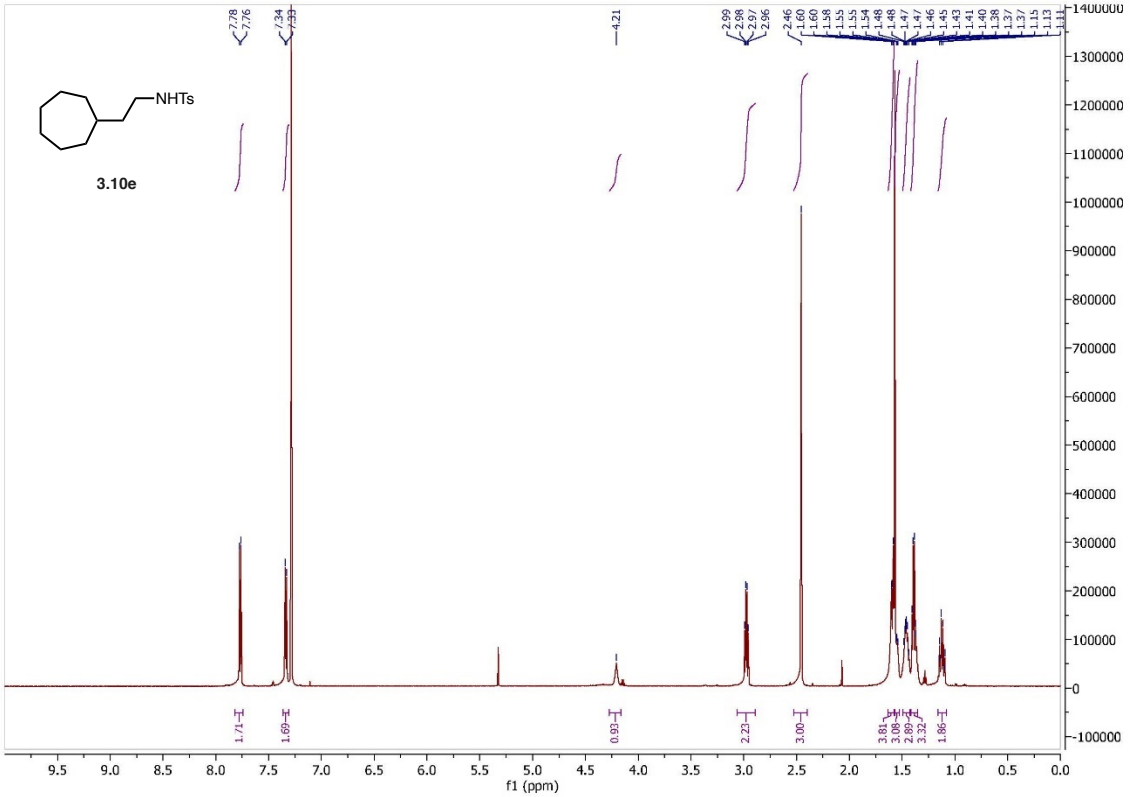

NHTs
Me
3.10b
f1 (ppm)

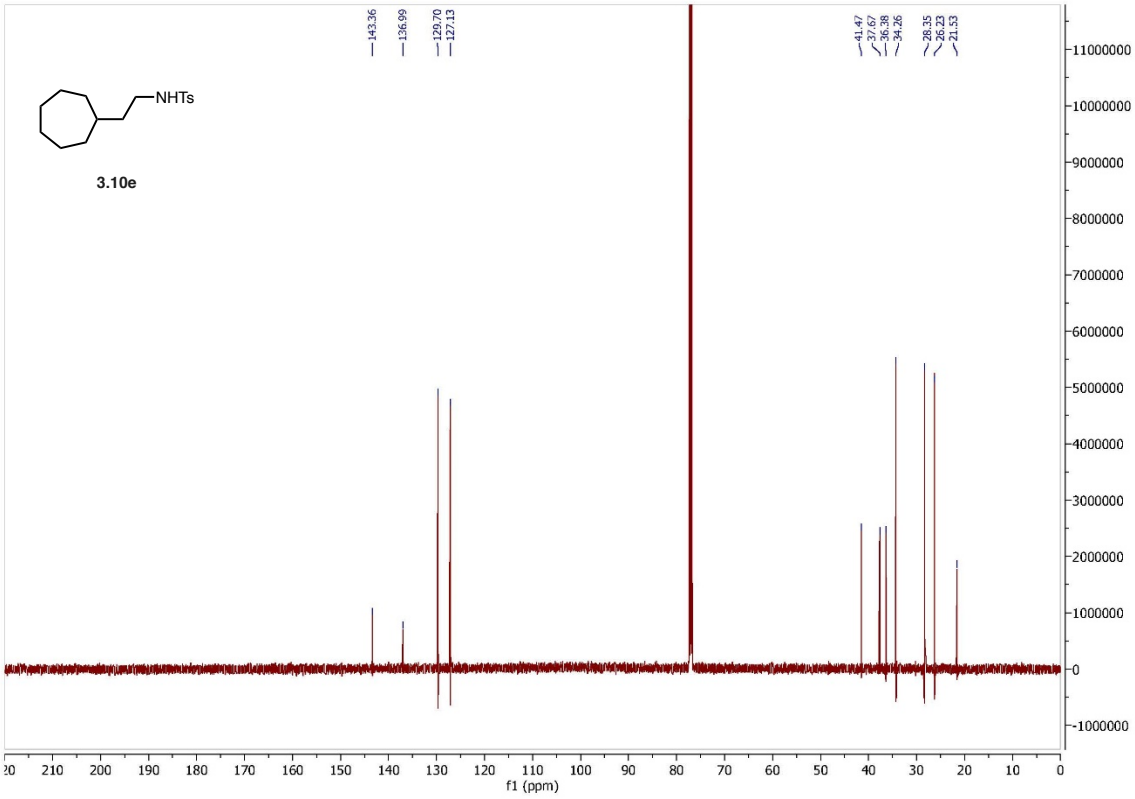

Me
NHTs
3.10c
f1 (ppm)

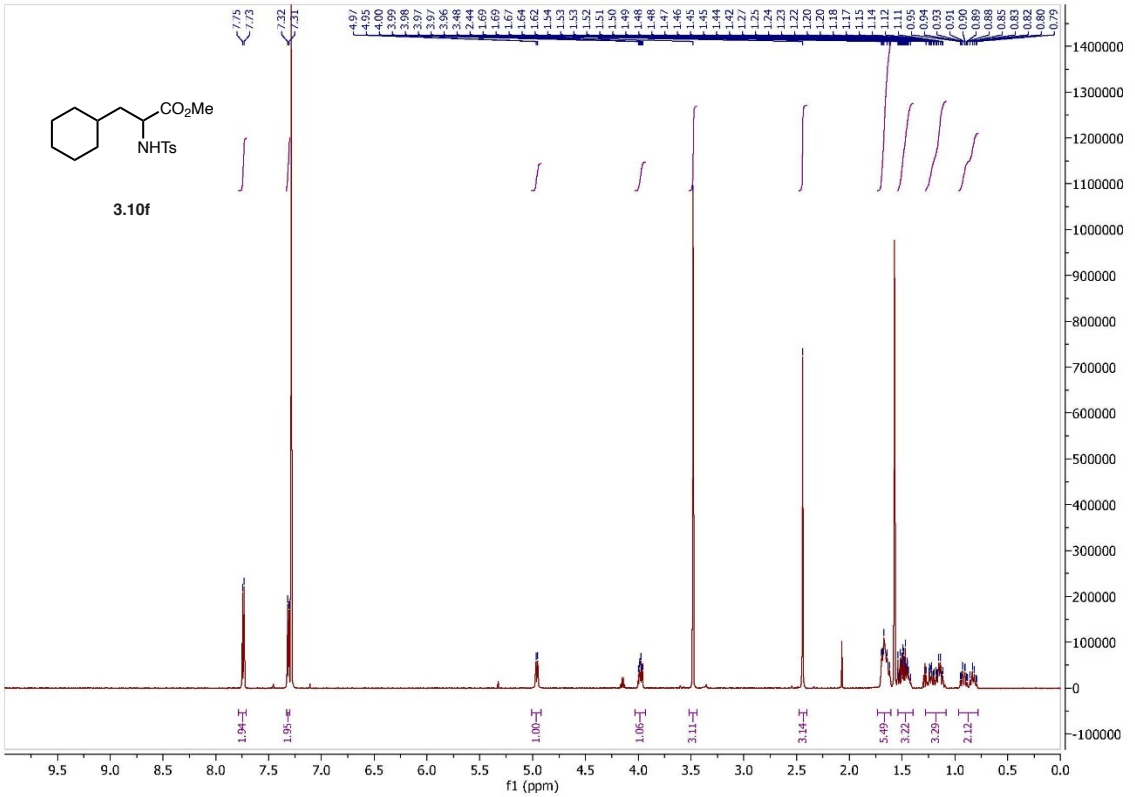

Me
NHTs
3.10c
f1 (ppm)

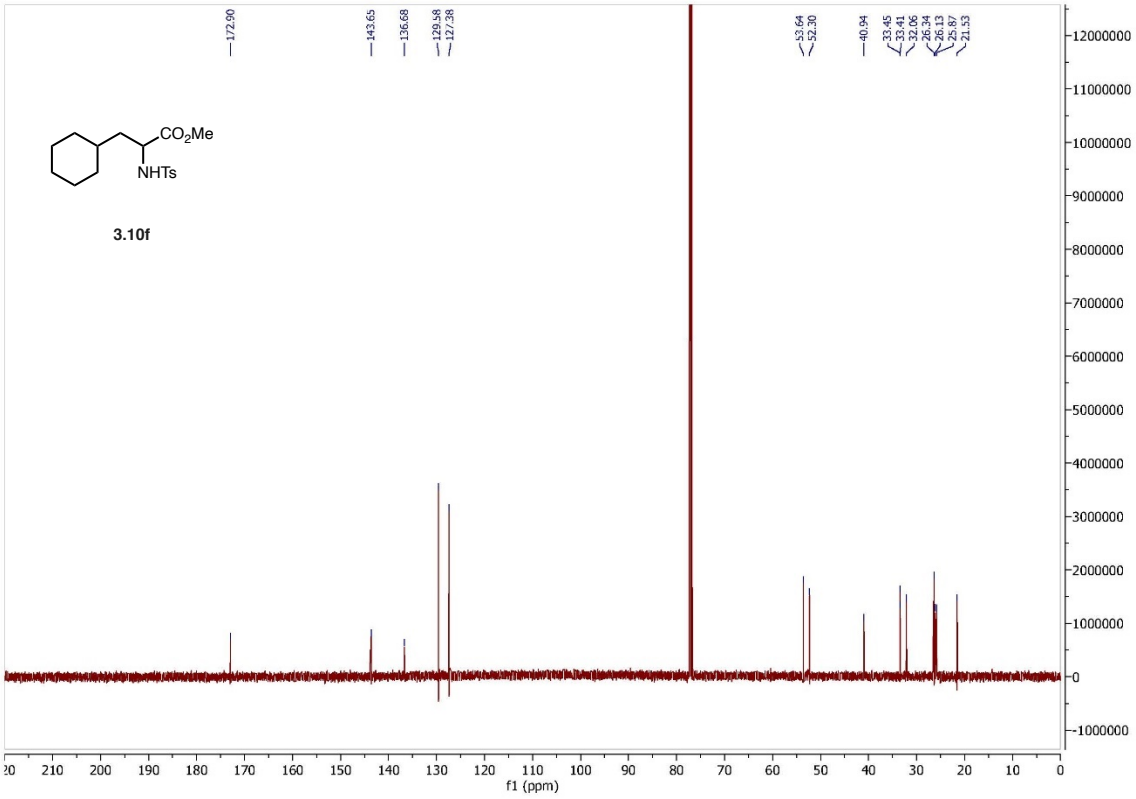

NHTs
Me
Me
3.10d
f1 (ppm)

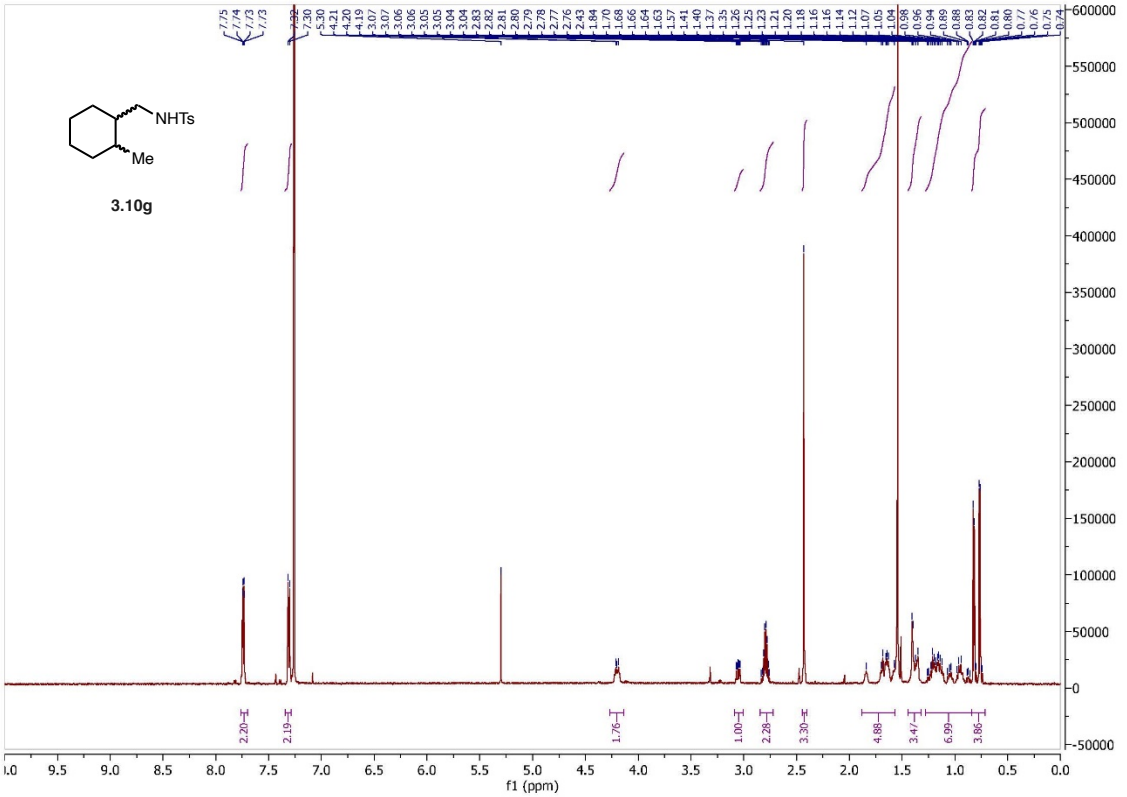

NHTs
Me
Me
3.10d
f1 (ppm)

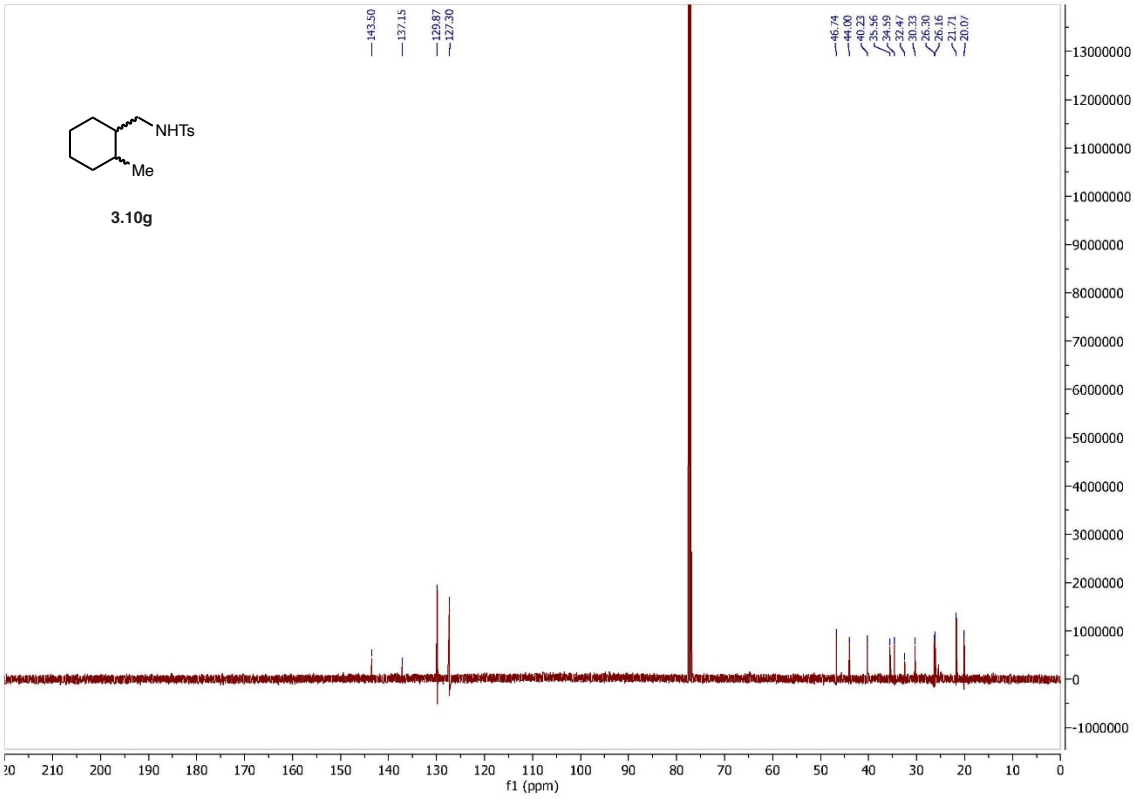

NHTs
3.10e
f1 (ppm)


NHTs
3.10e
f1 (ppm)


CO2Me
NHTs
3.10f
f1 (ppm)


CO2Me
NHTs
3.10f
f1 (ppm)


NHTs
Me
3.10g
f1 (ppm)


NHTs
Me
3.10g
143.50
137.15
129.87
127.30
46.74
44.00
40.23
35.56
34.59
32.47
30.33
26.30
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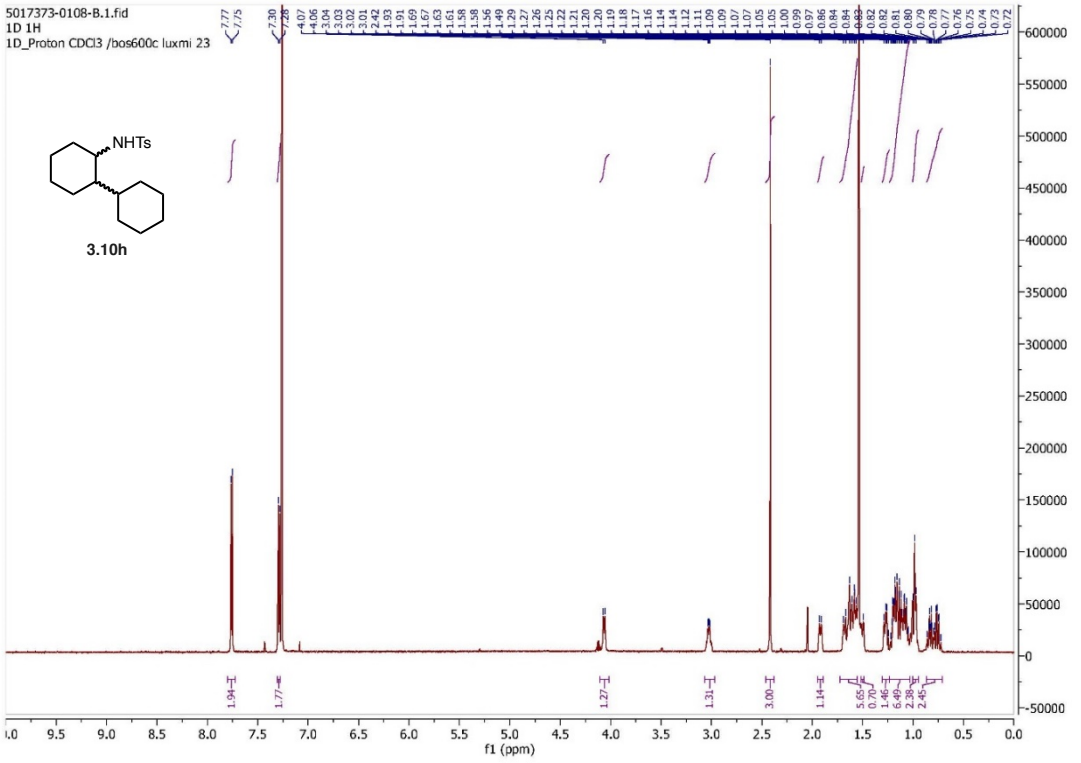
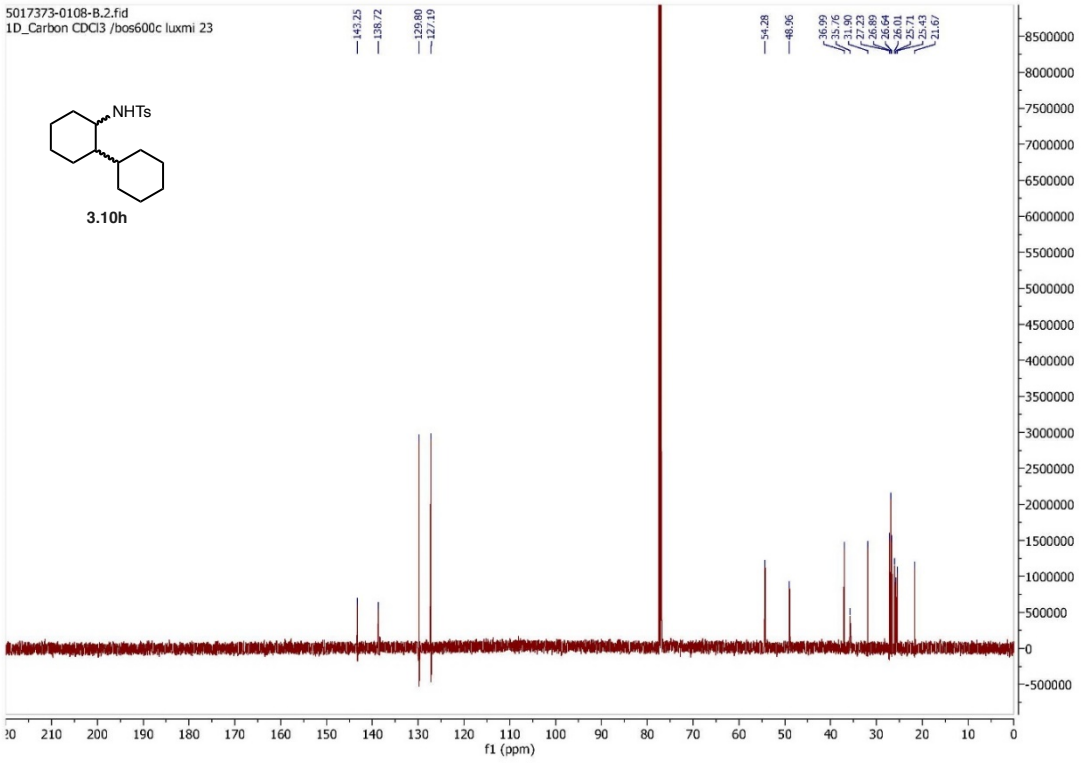
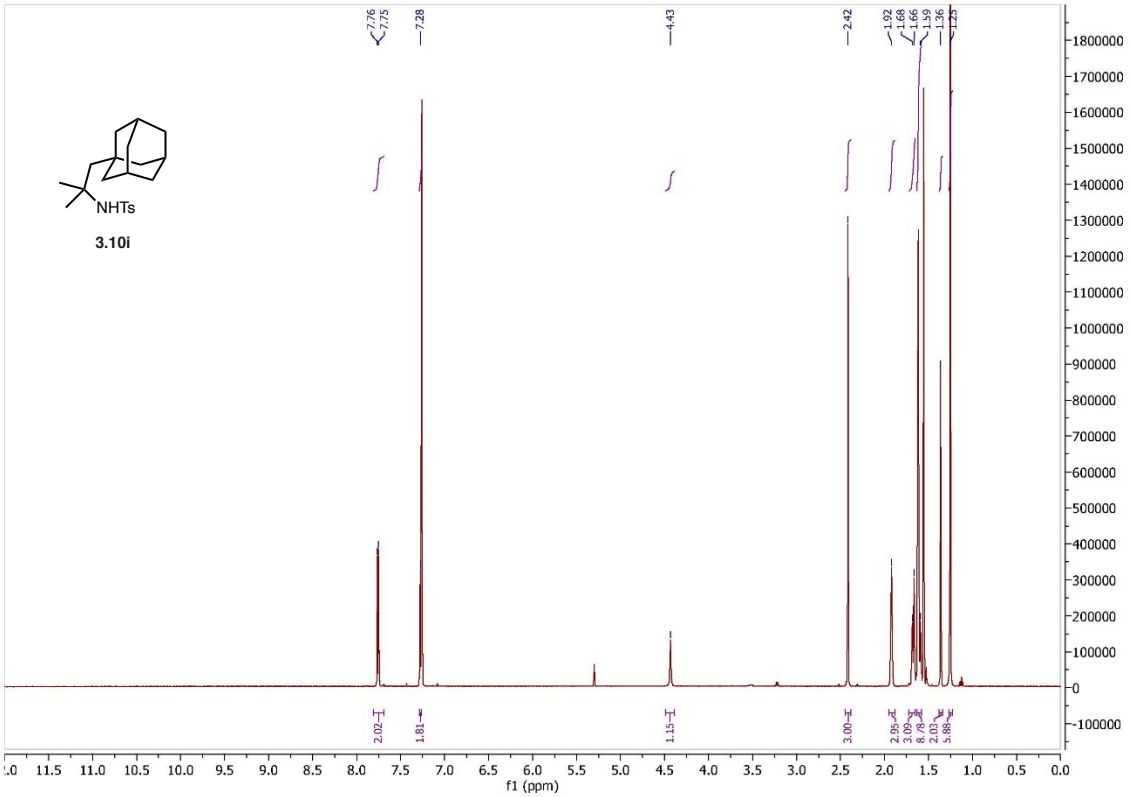
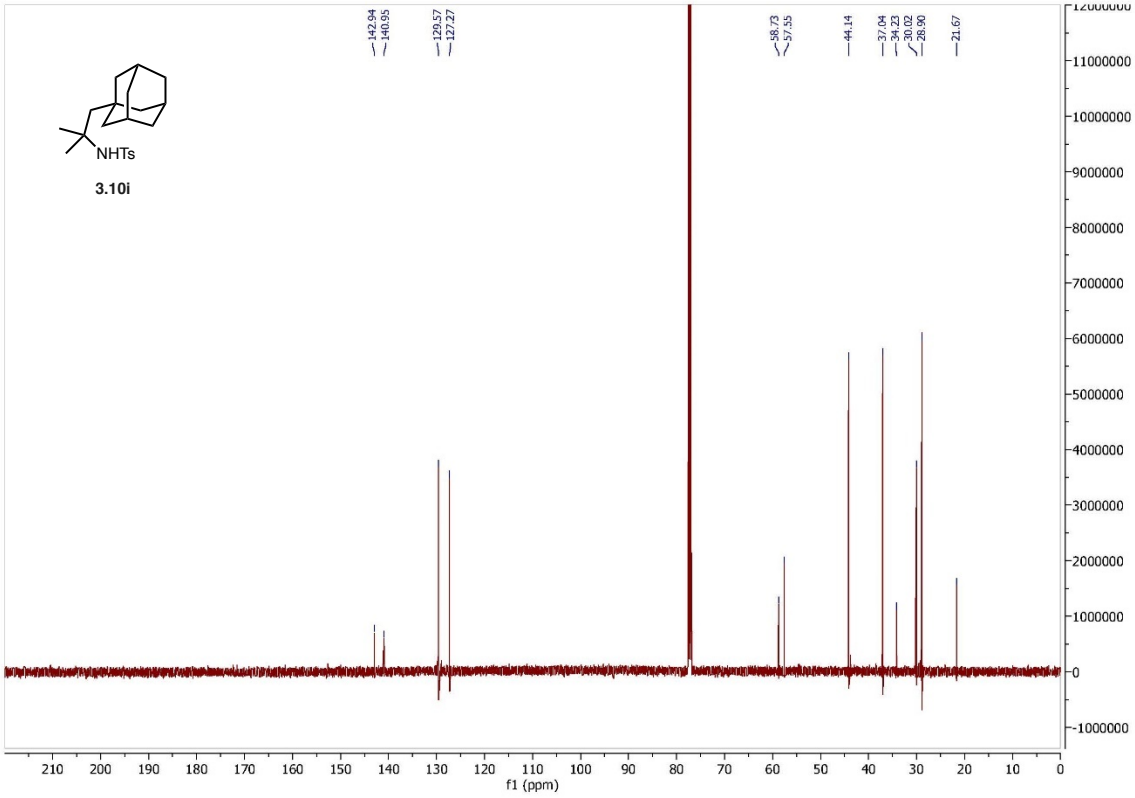
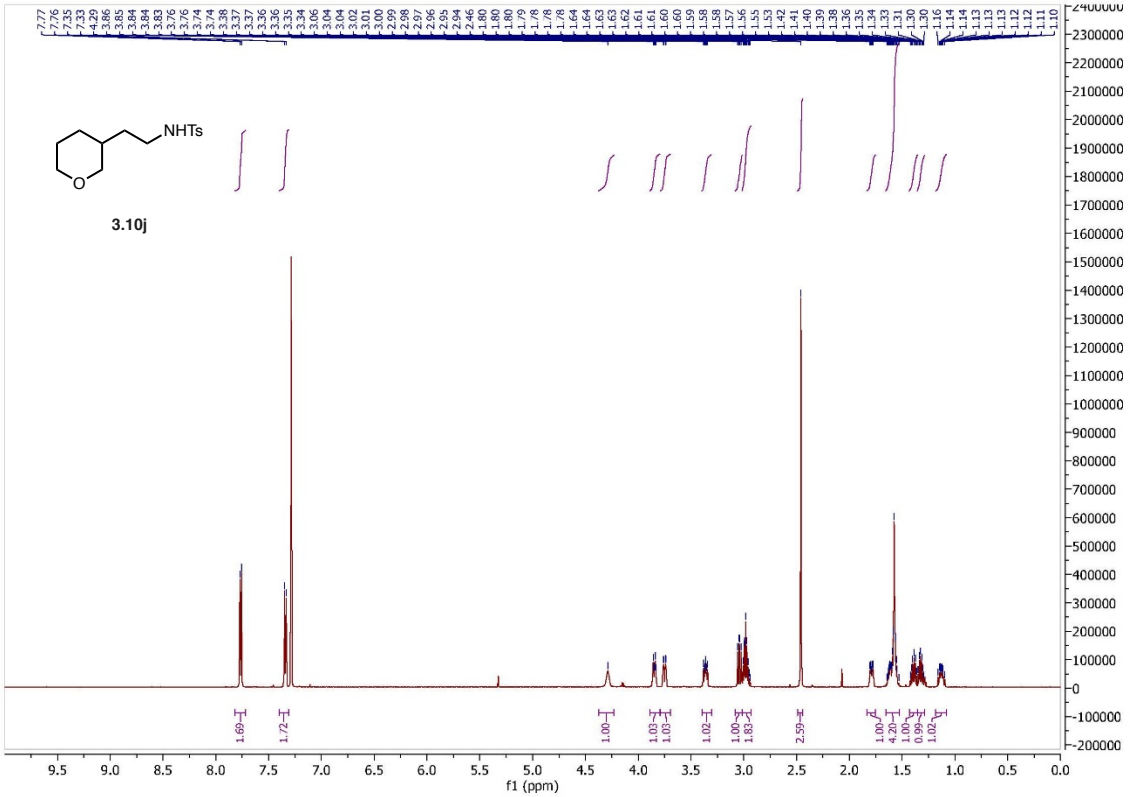
21.71
20.07
f1 (ppm)

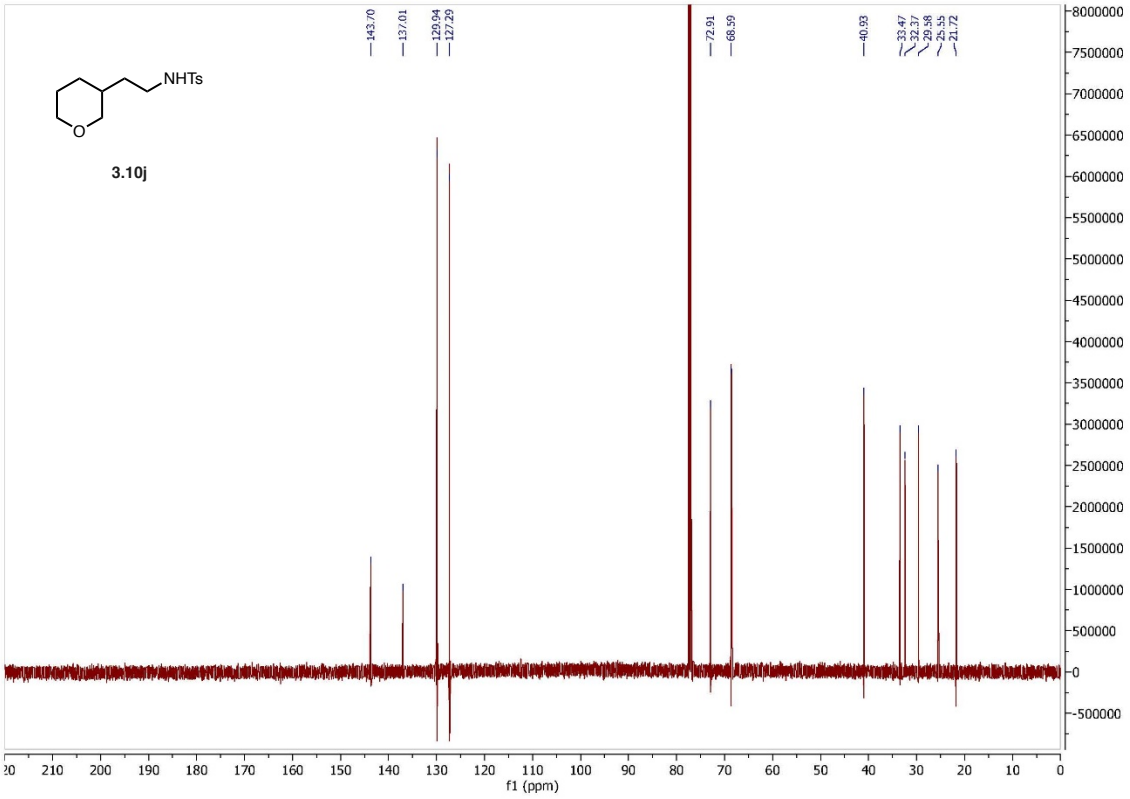

5017373-0108-B.1.fid
1D 1H
1D_Proton CDCl3 /bos600c luxmi 23
NHTs
3.10h
f1 (ppm)

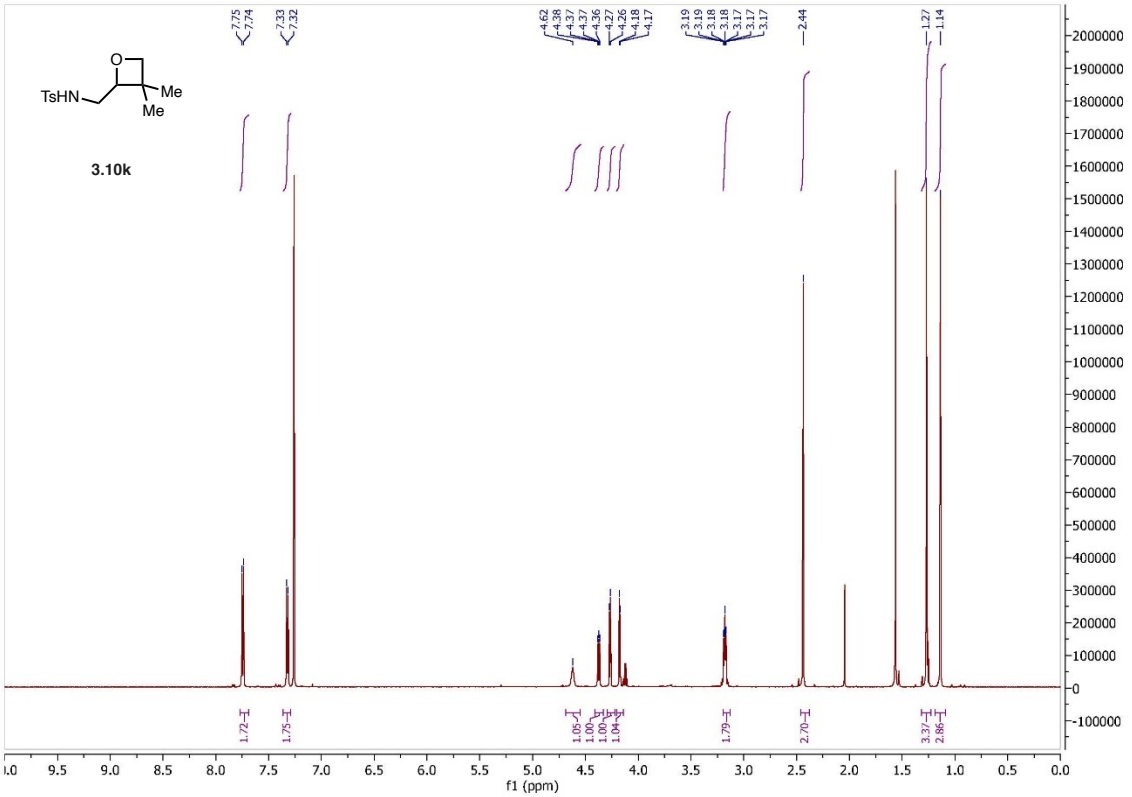

5017373-0108-B.2.fid
1D_Carbon CDCl3 /bos600c luxmi 23
NHTs
3.10h
f1 (ppm)

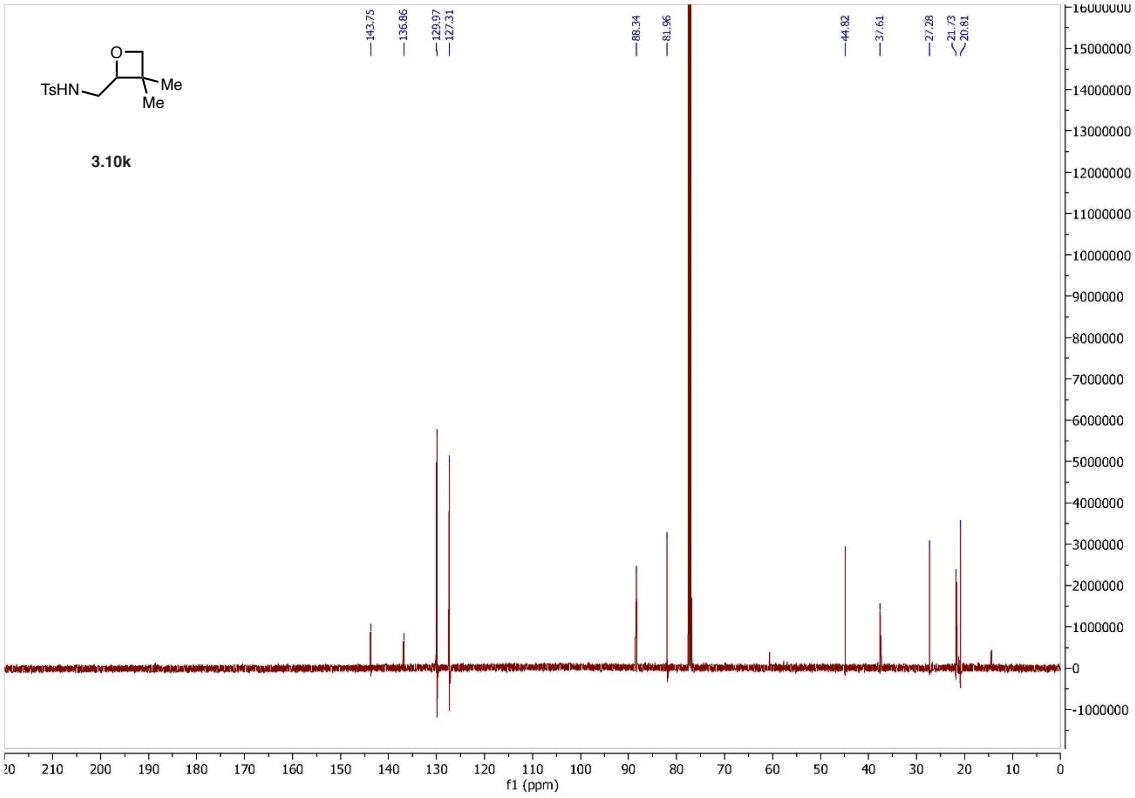

NHTs
3.10i
7.76
7.75
7.28
4.43
2.42
1.92
1.68
1.66
1.59
1.36
1.25
2.02
1.81
1.15
3.00
2.06
3.09
8.78
2.03
5.88
f1 (ppm)

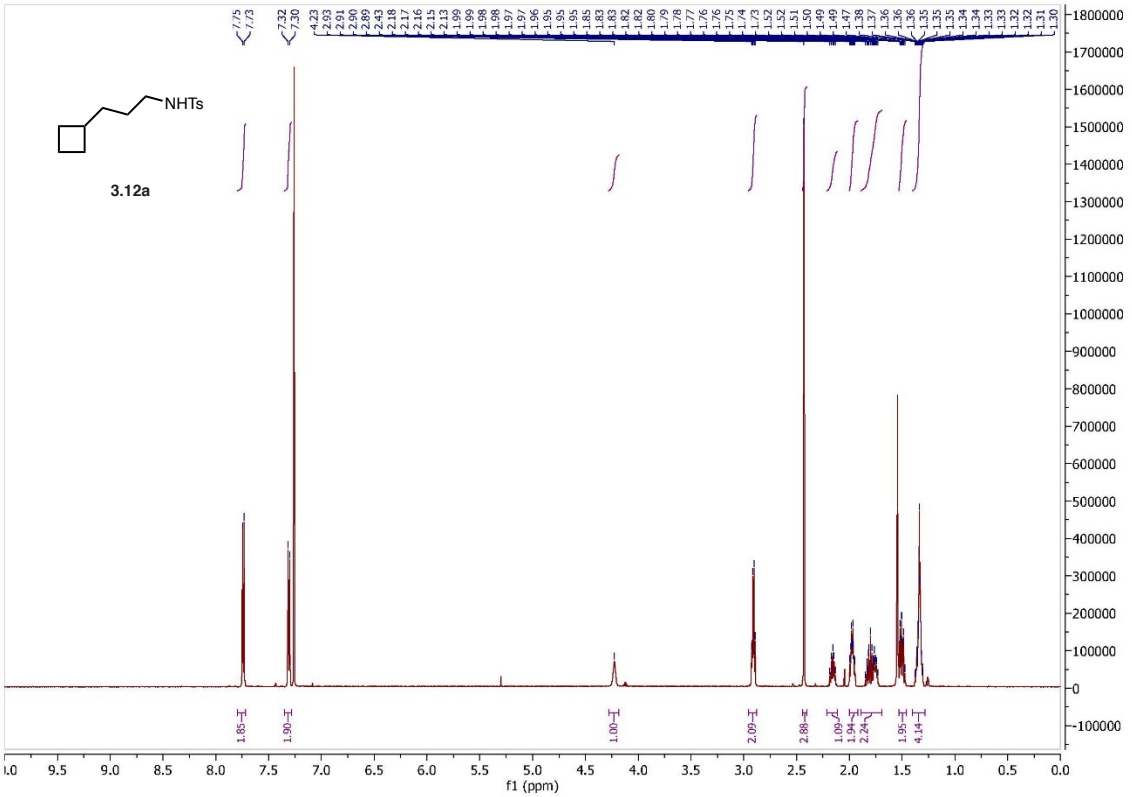

NHTs
3.10i
142.94
140.95
129.57
127.27
58.73
57.55
44.14
37.04
34.23
30.02
28.90
21.67
f1 (ppm)

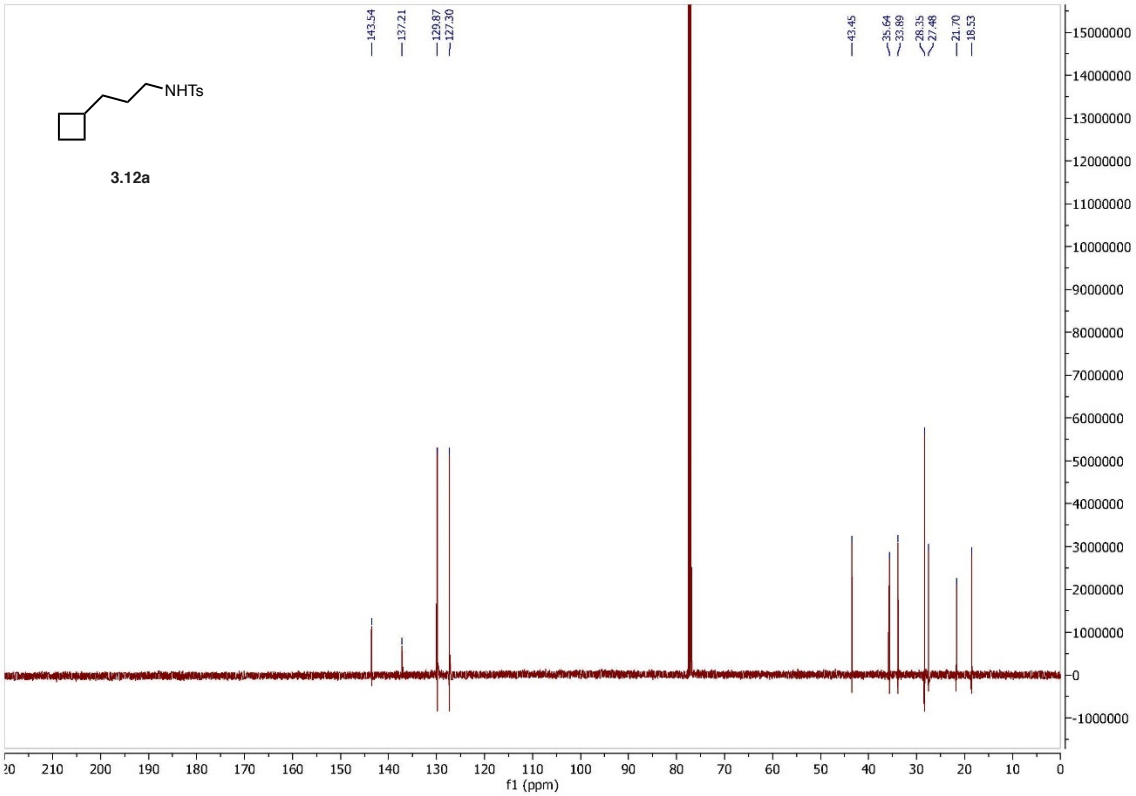

NHTs
O
3.10j
f1 (ppm)

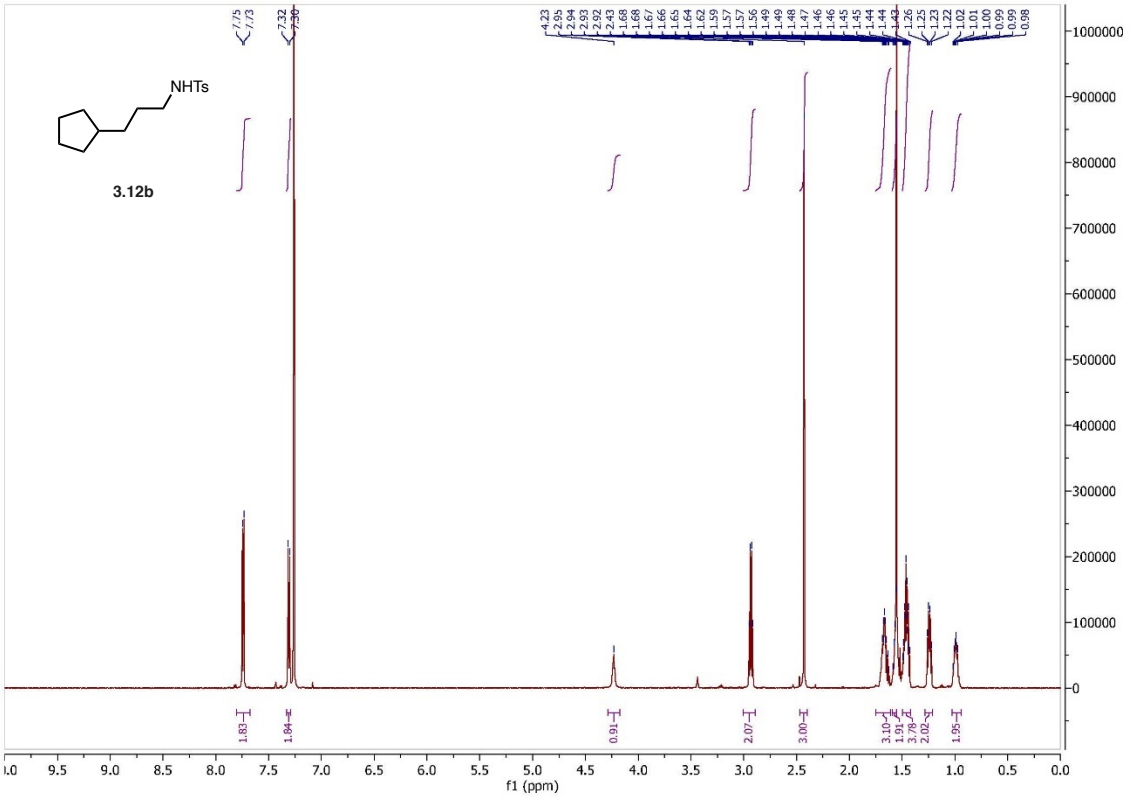

NHTs
O
3.10j
143.70
137.01
129.94
127.29
72.91
68.59
40.93
33.47
32.37
29.58
25.55
21.72
f1 (ppm)

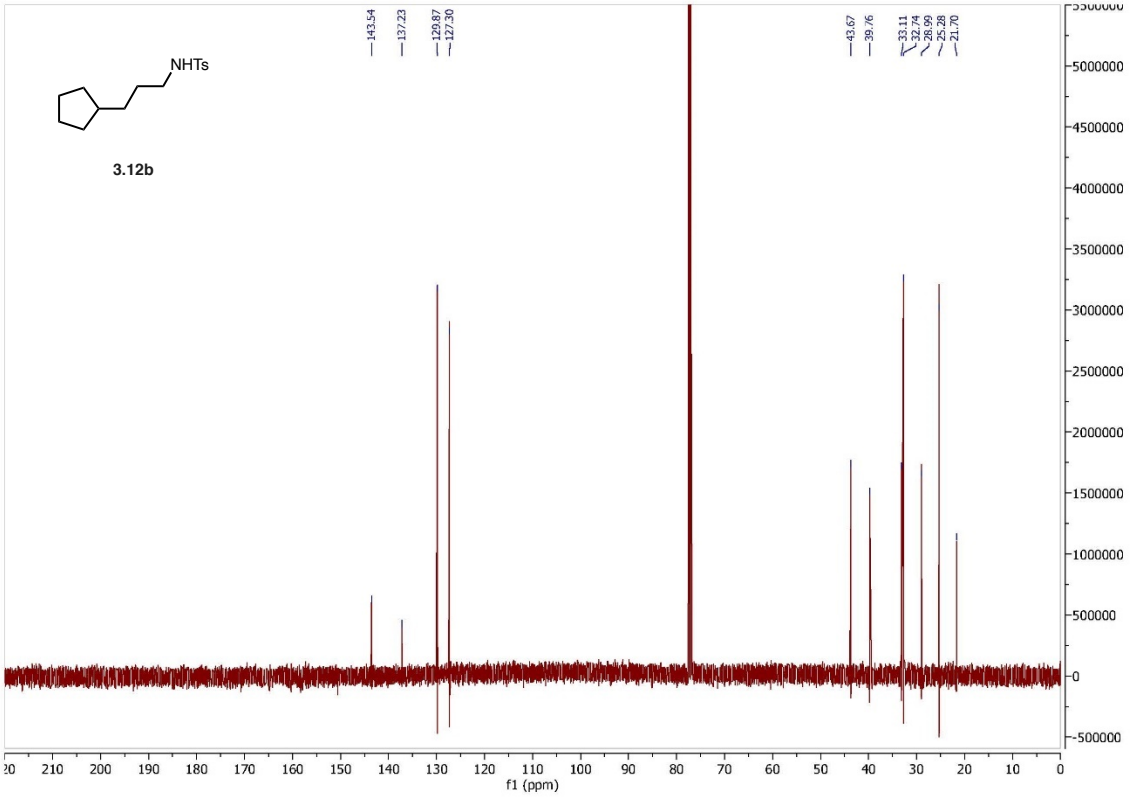

TsHN
Me
Me
3.10k
f1 (ppm)

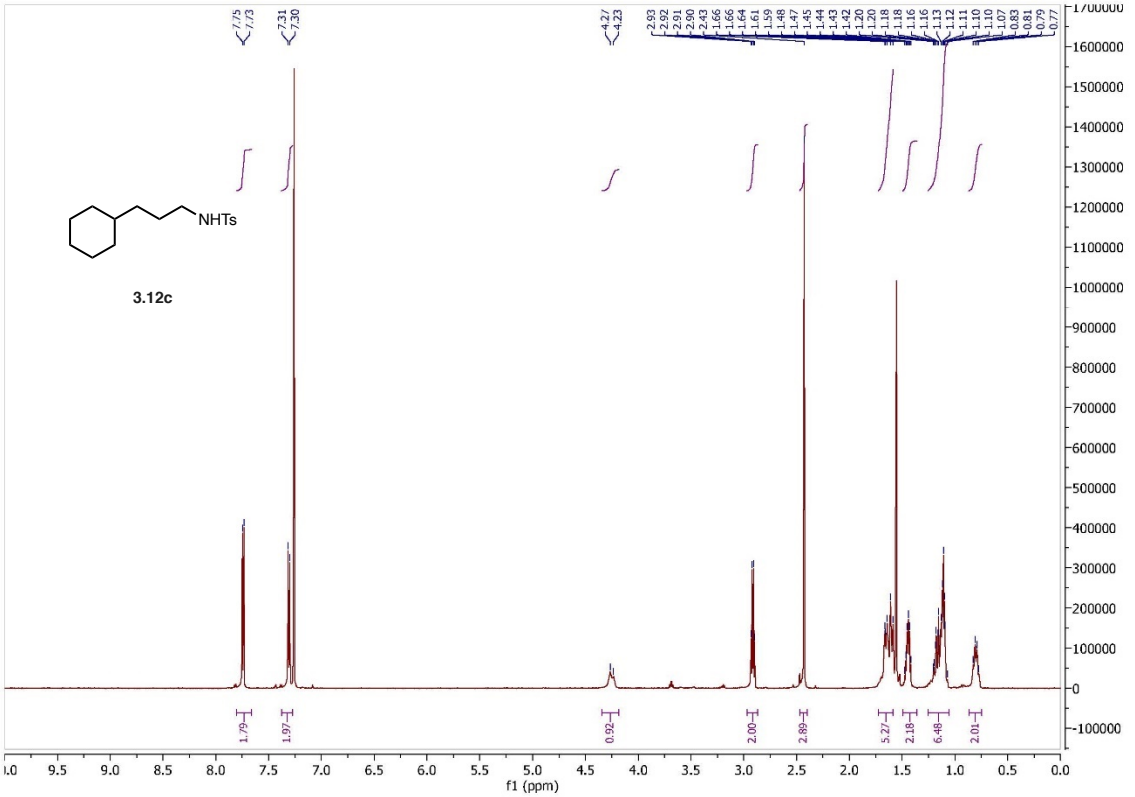

TsHN
Me
Me
3.10k
f1 (ppm)

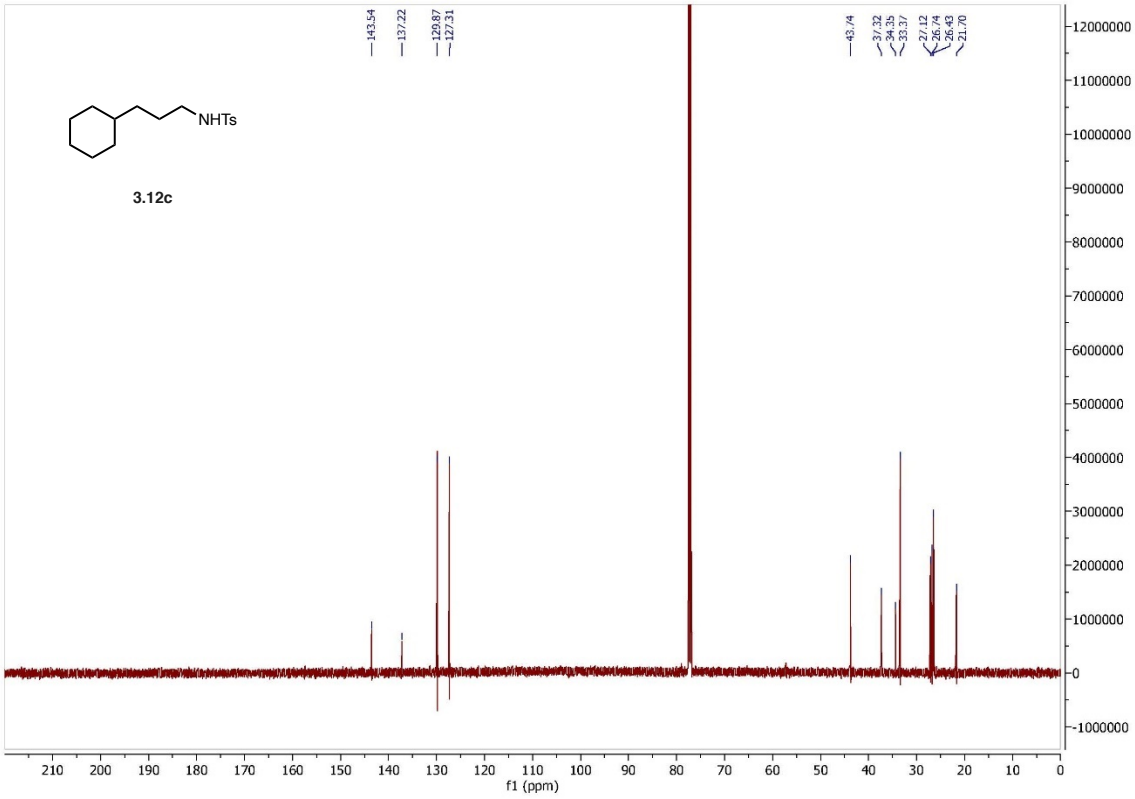

NHTs
3.12a
f1 (ppm)

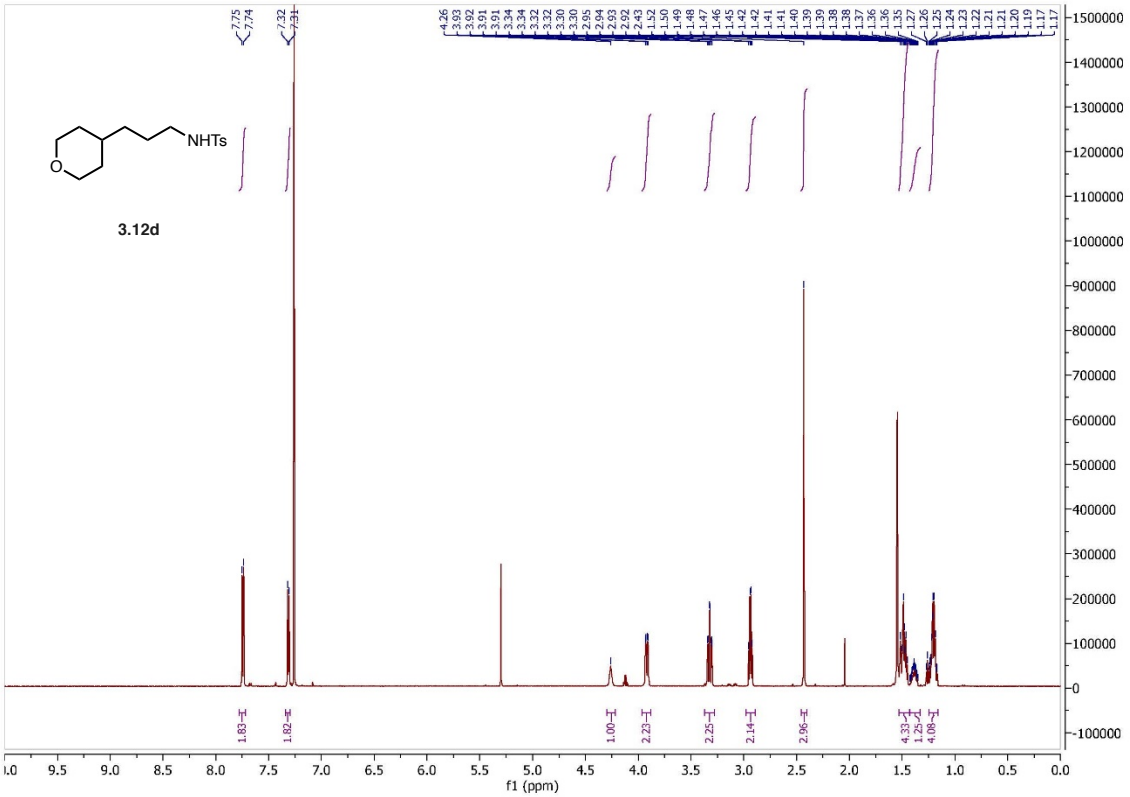

NHTs
3.12a
143.54
137.21
129.87
127.30
43.45
35.64
33.89
28.35
27.48
21.70
18.53
f1 (ppm)

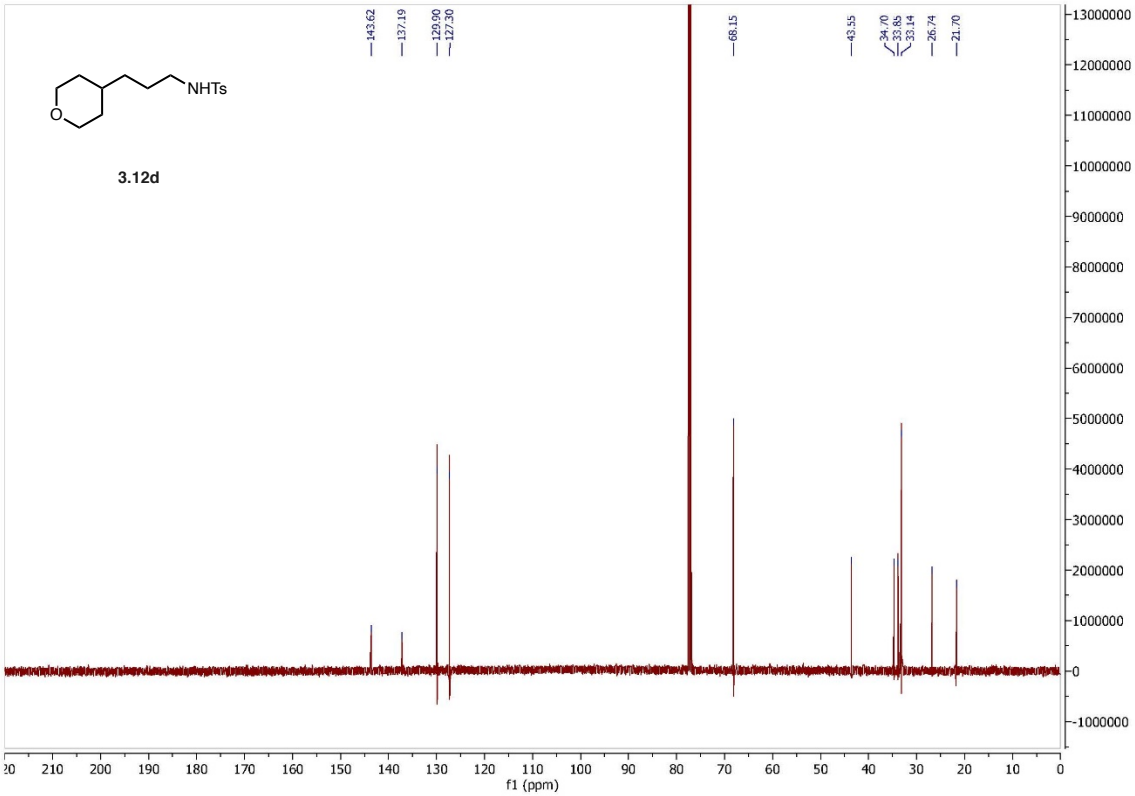

NHTs
3.12b
f1 (ppm)

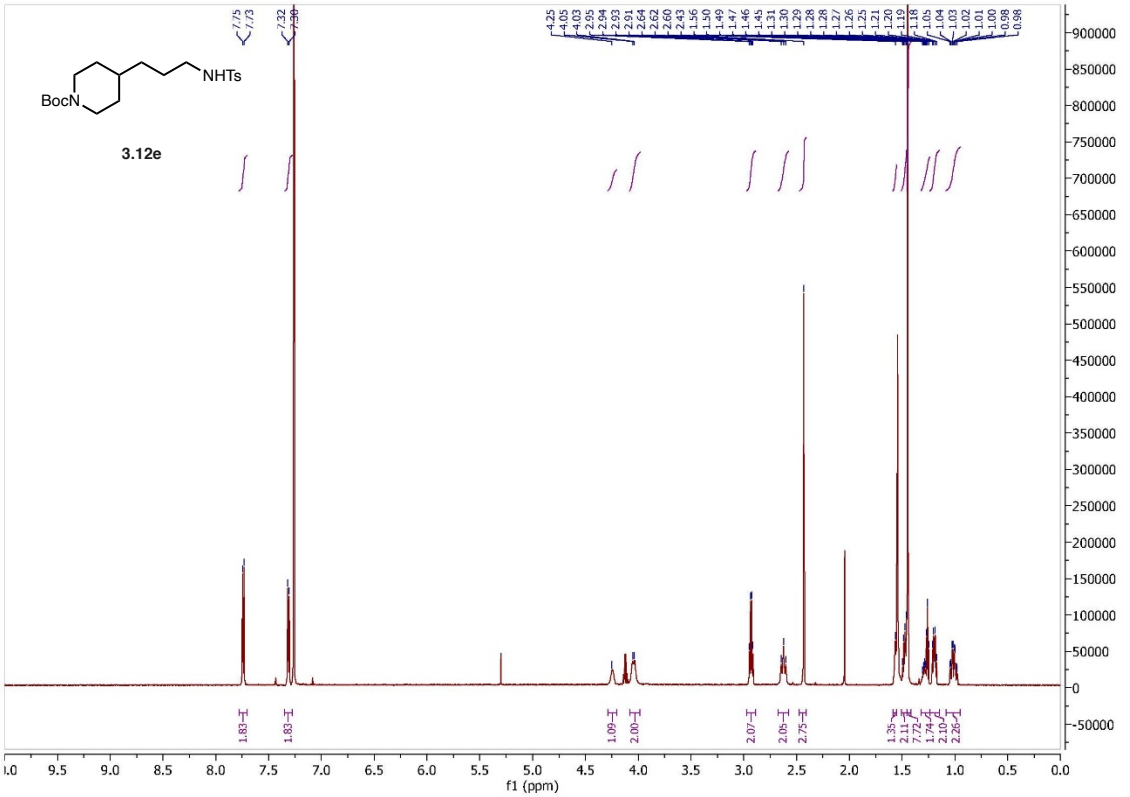

NHTs
3.12b
f1 (ppm)

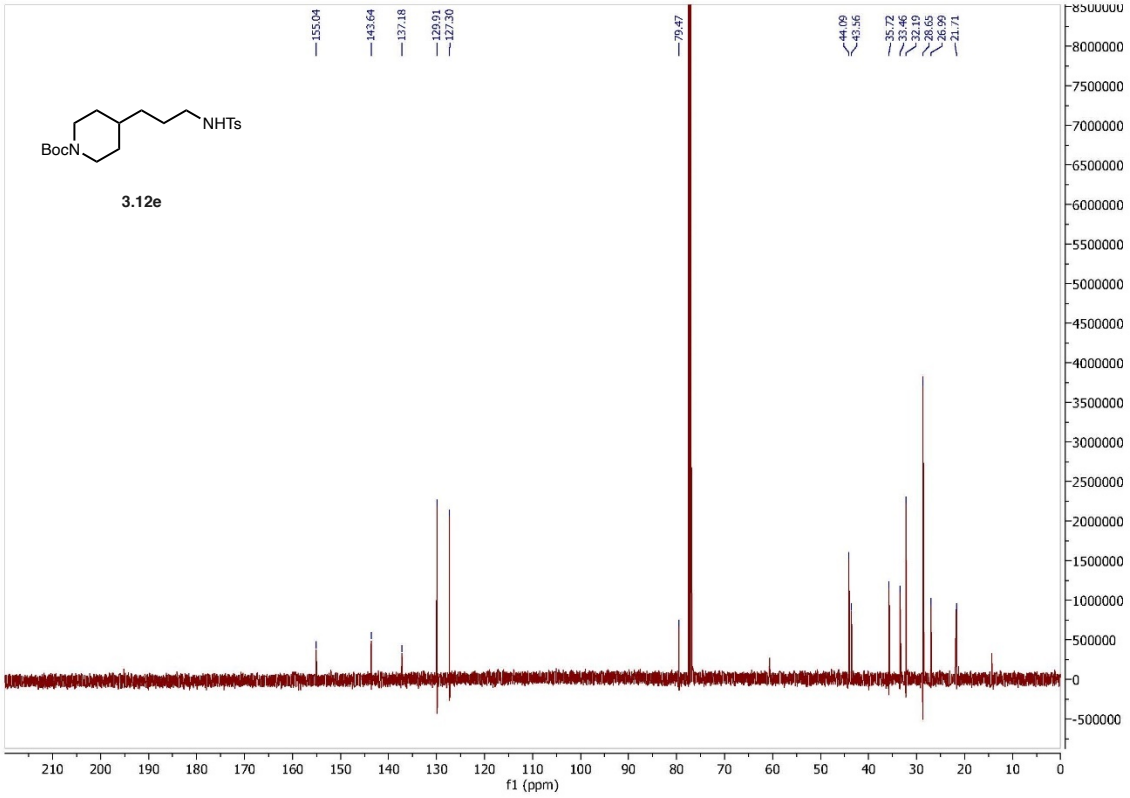

NHTs
3.12c
f1 (ppm)

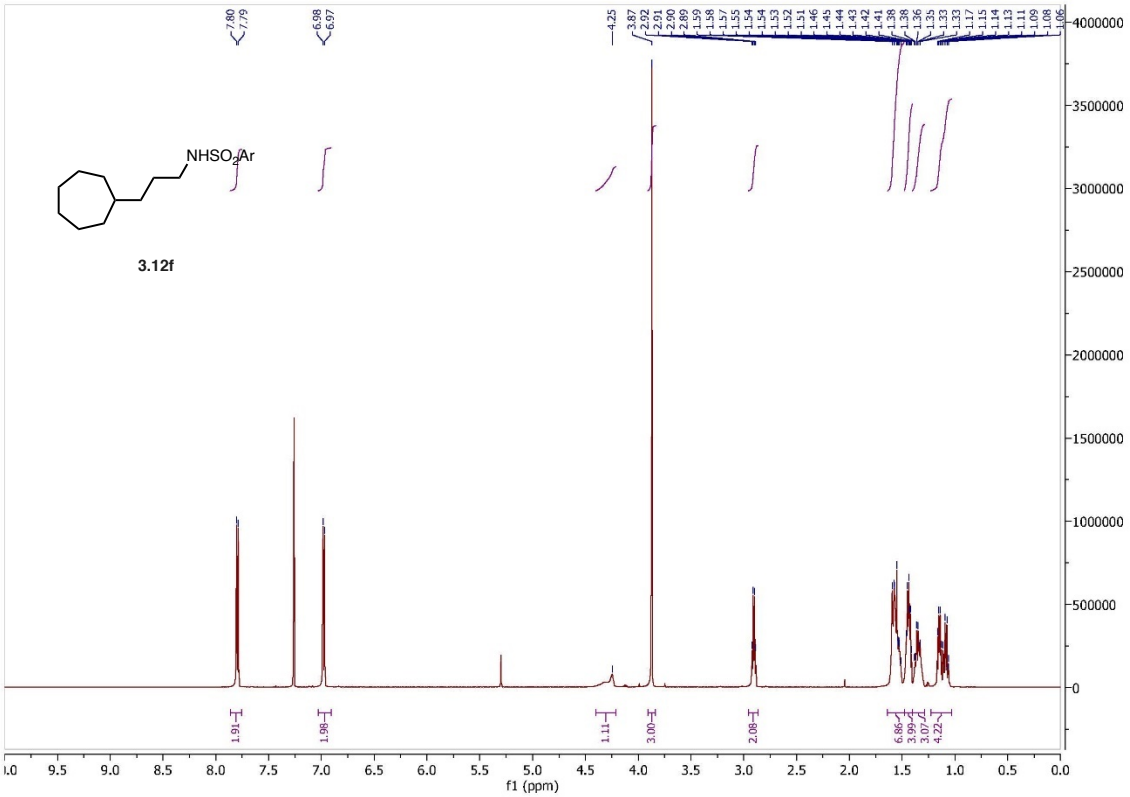

NHTs
3.12c
f1 (ppm)

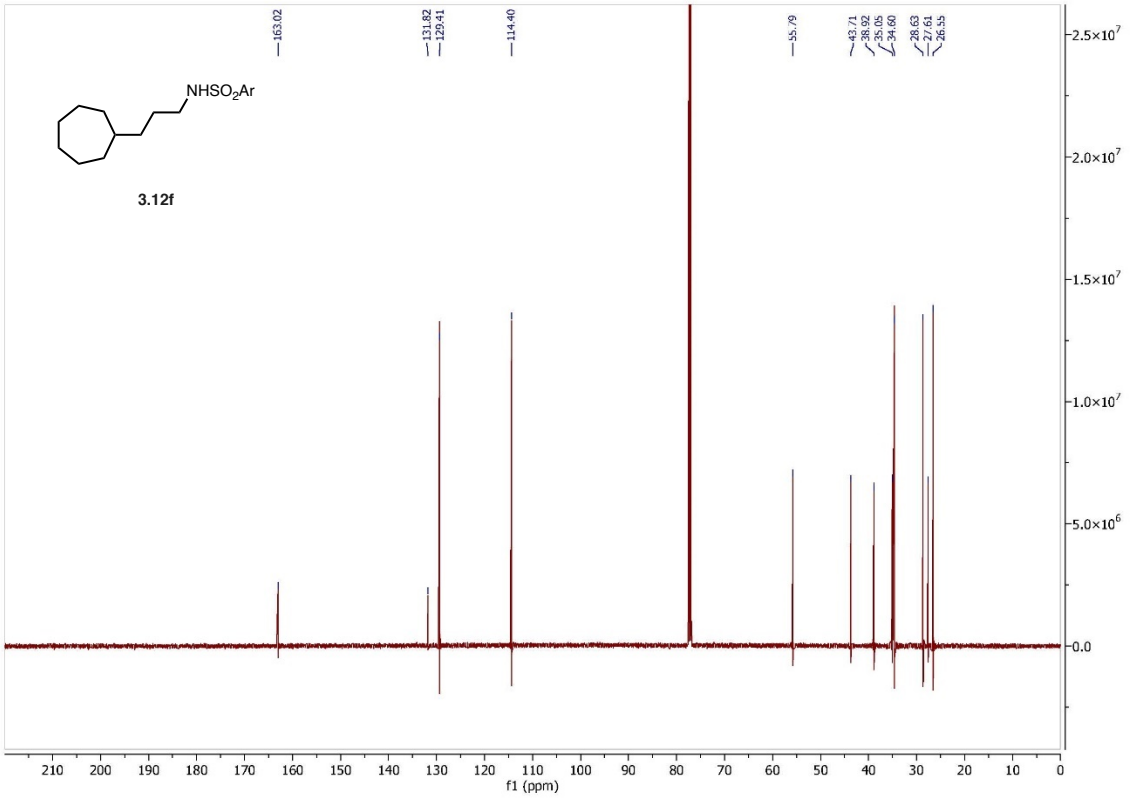

NHTs
O
3.12d
f1 (ppm)

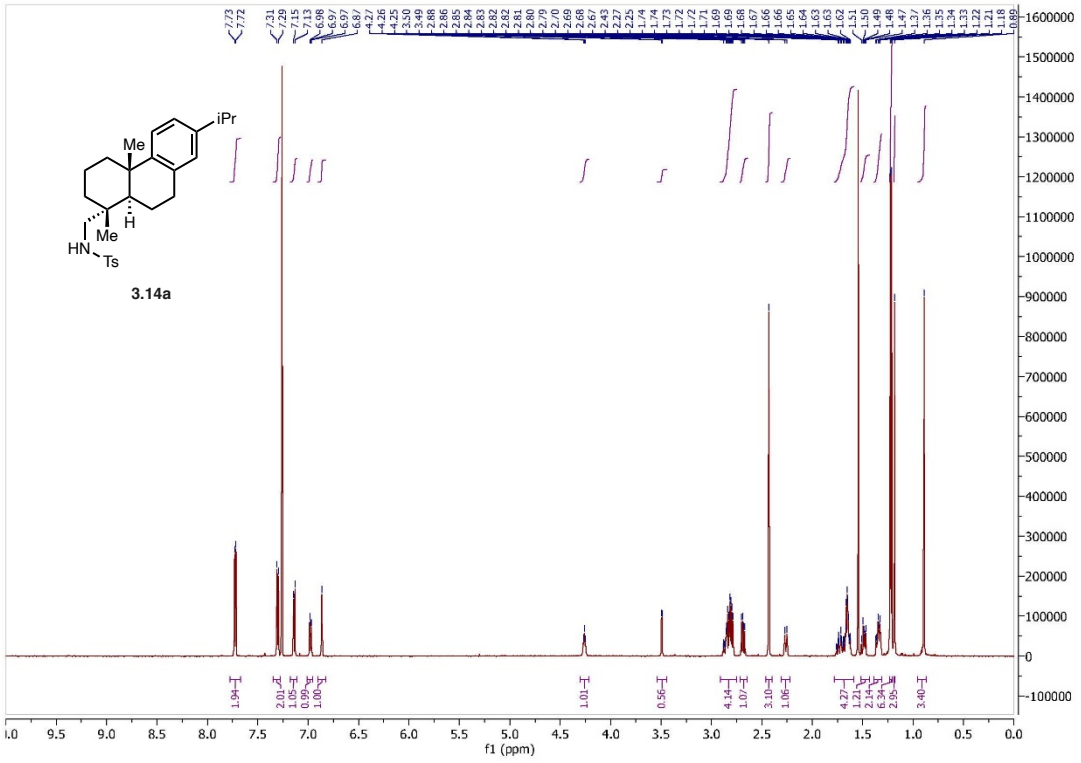

NHTs
O
3.12d
f1 (ppm)

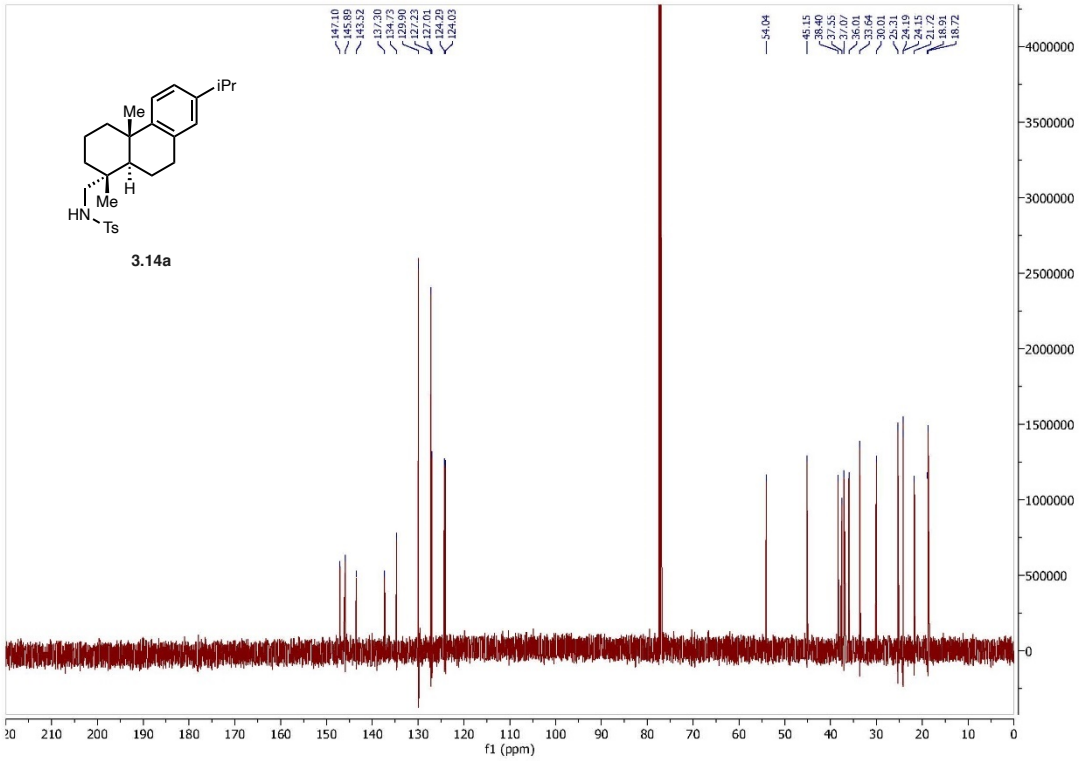

BocN
NHTs
3.12e
f1 (ppm)

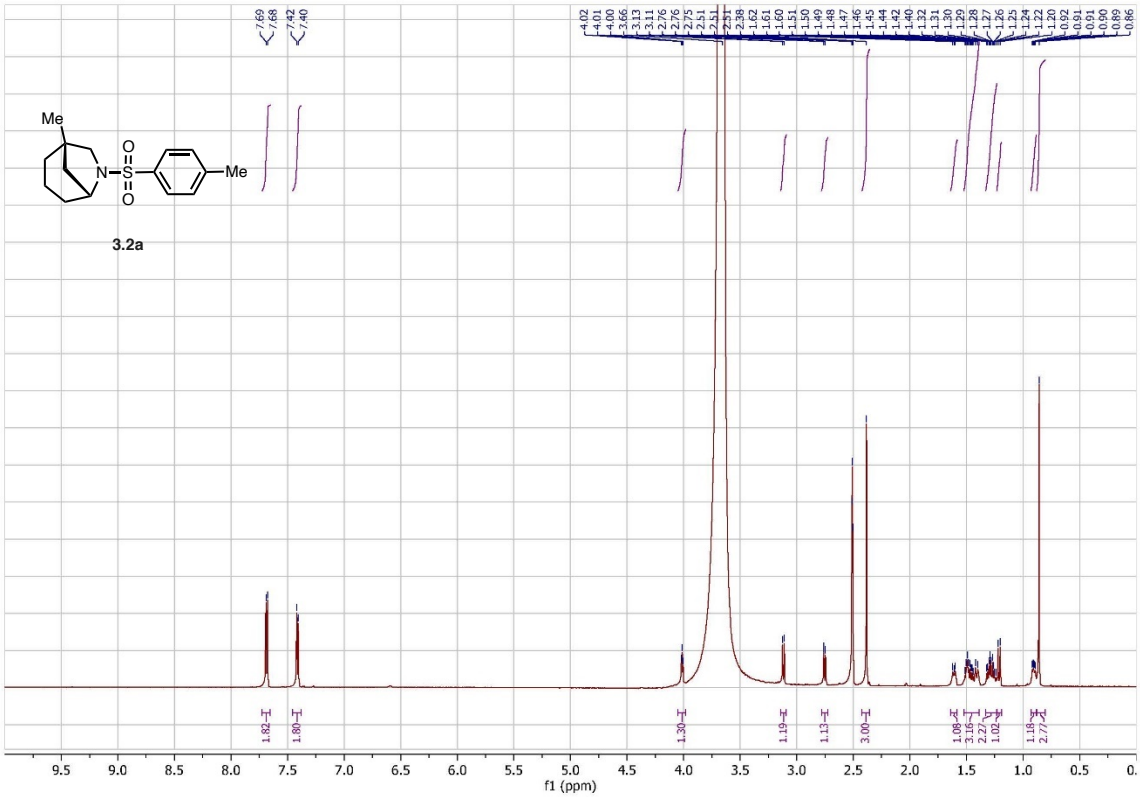

BocN
NHTs
3.12e
f1 (ppm)

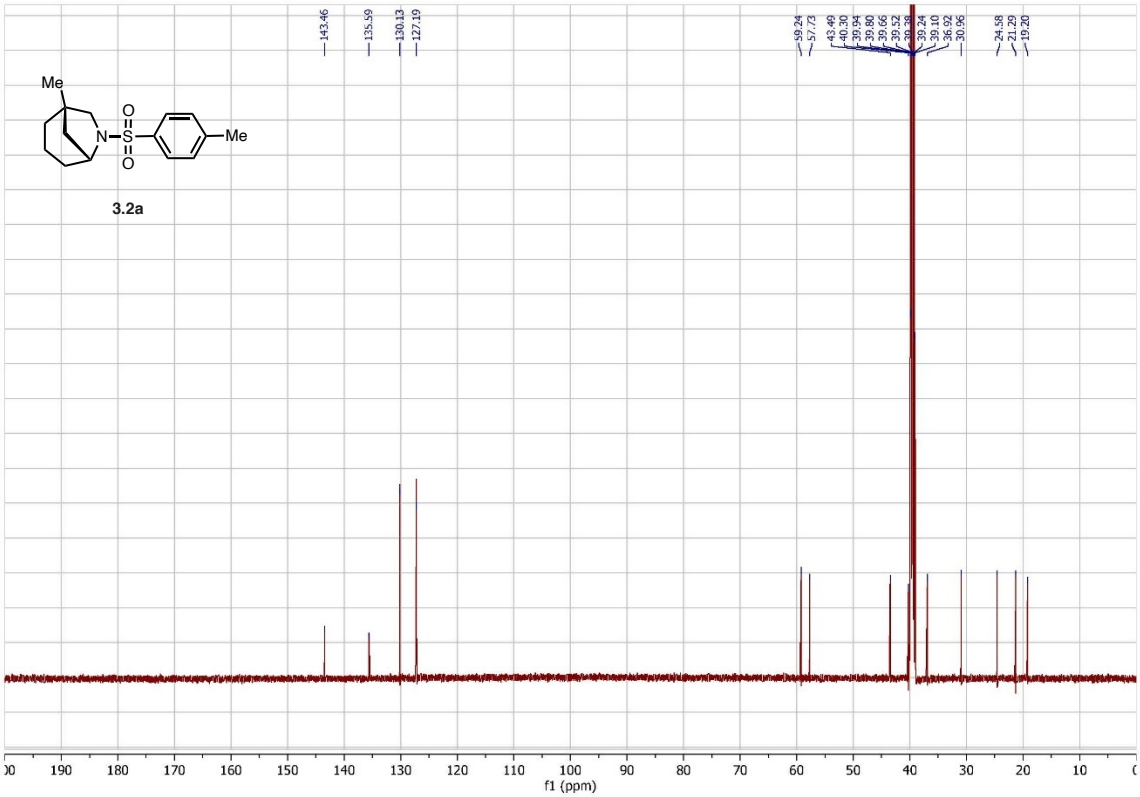

NHSO2Ar
3.12f
f1 (ppm)

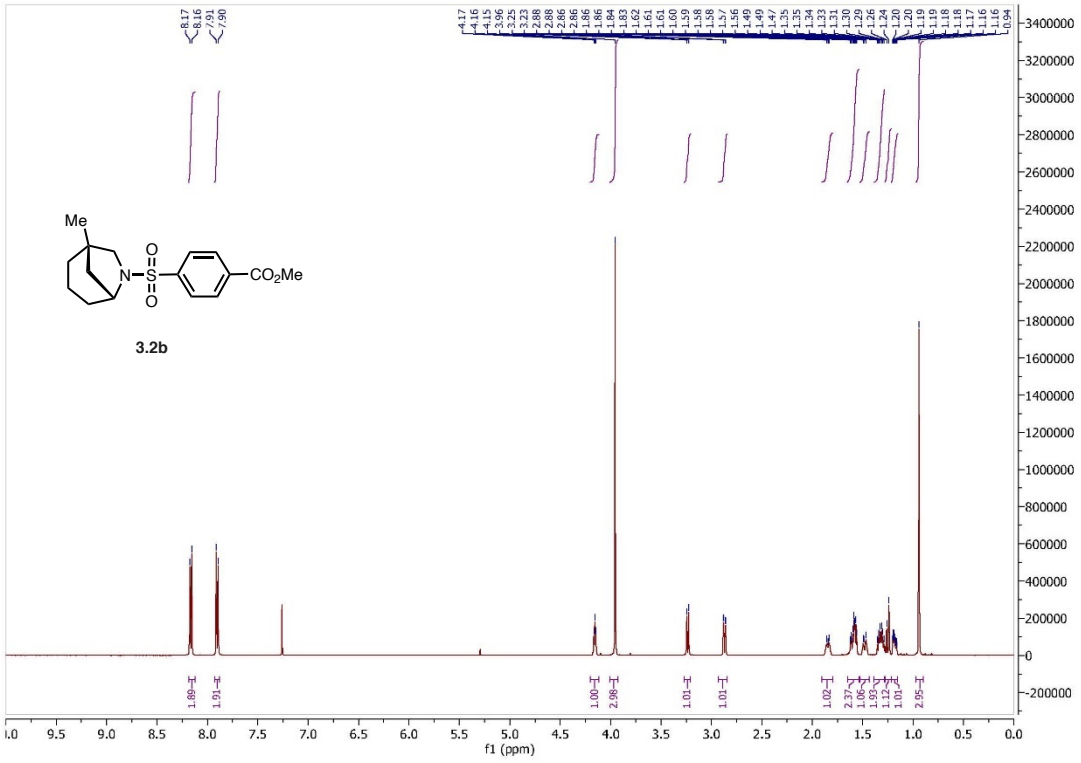

NHSO2Ar
3.12f
f1 (ppm)

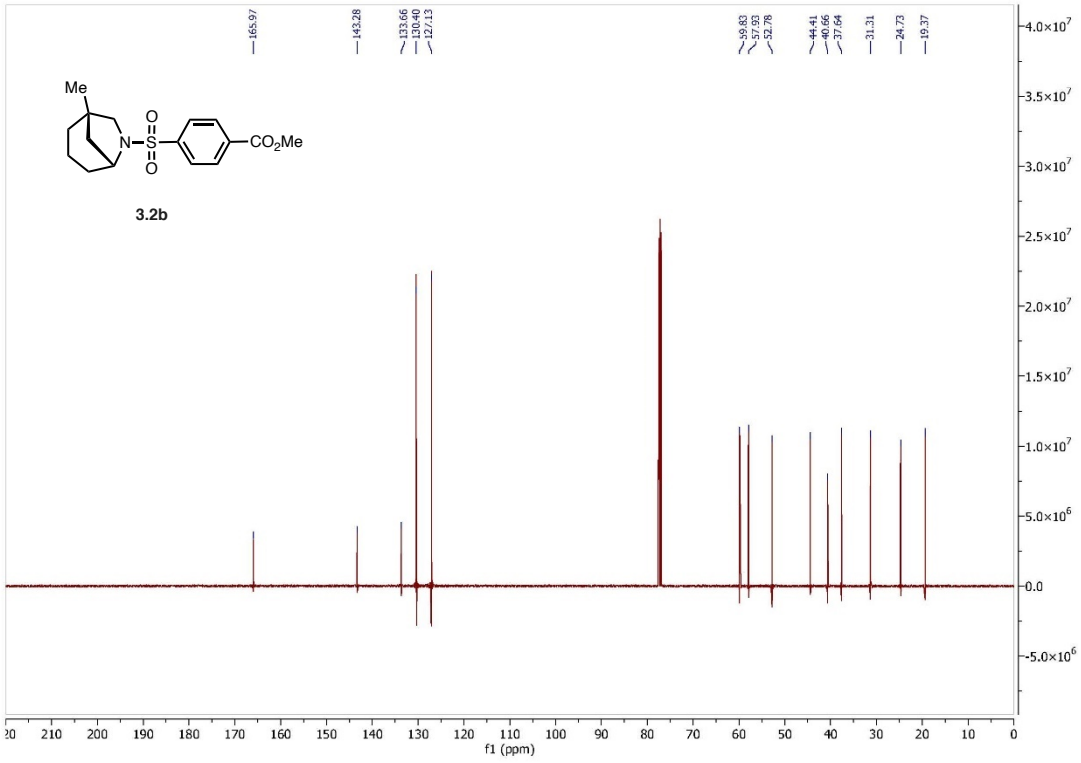

iPr
Me
H
Me
HN
Ts
3.14a
f1 (ppm)

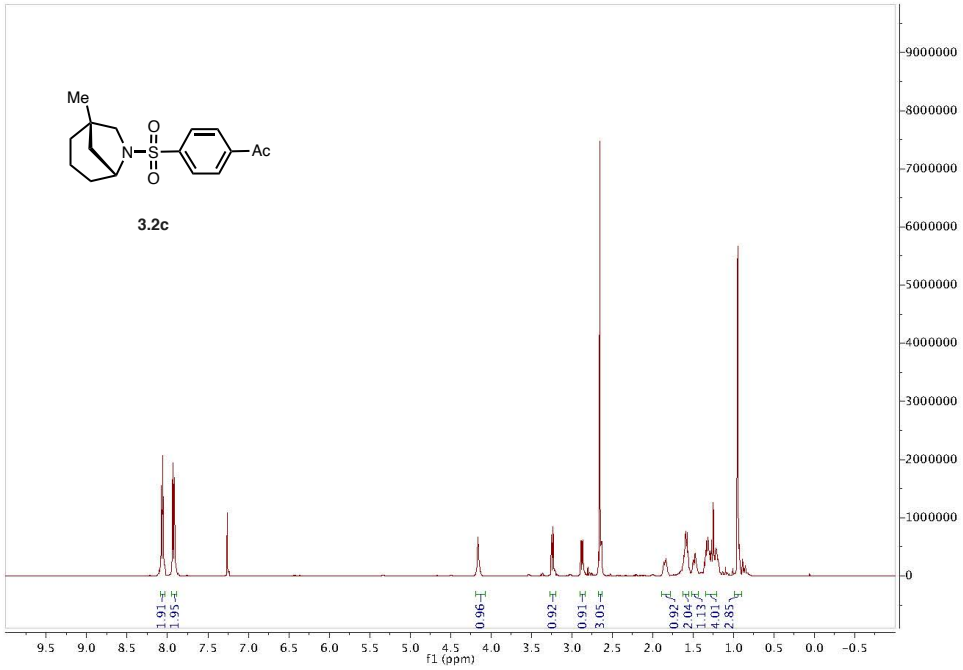

iPr
Me
H
Me
HN
Ts
3.14a
f1 (ppm)

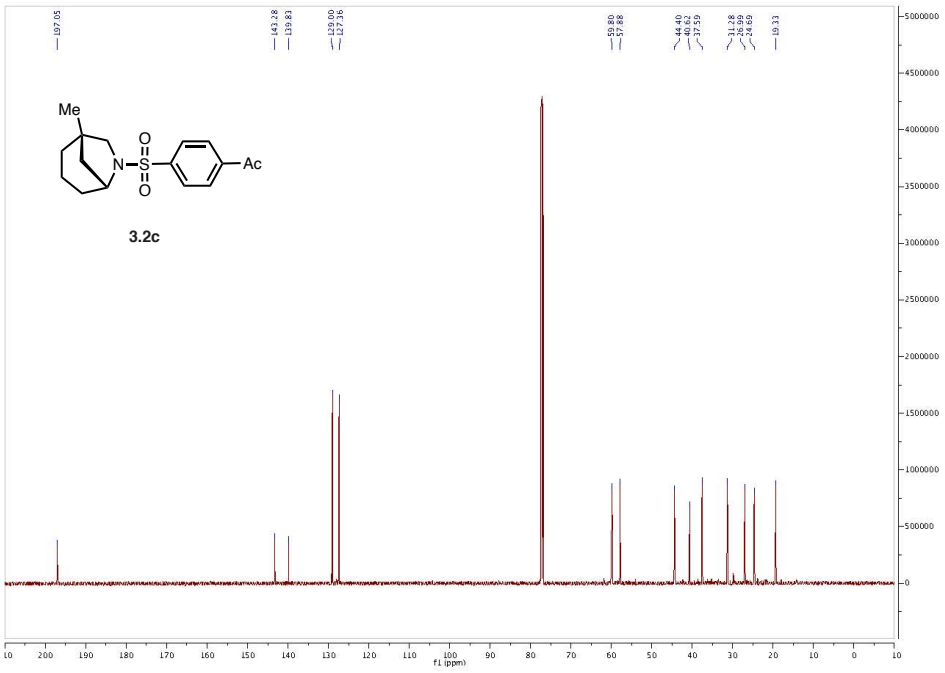

Me
O
N
S
O
Me
3.2a
f1 (ppm)

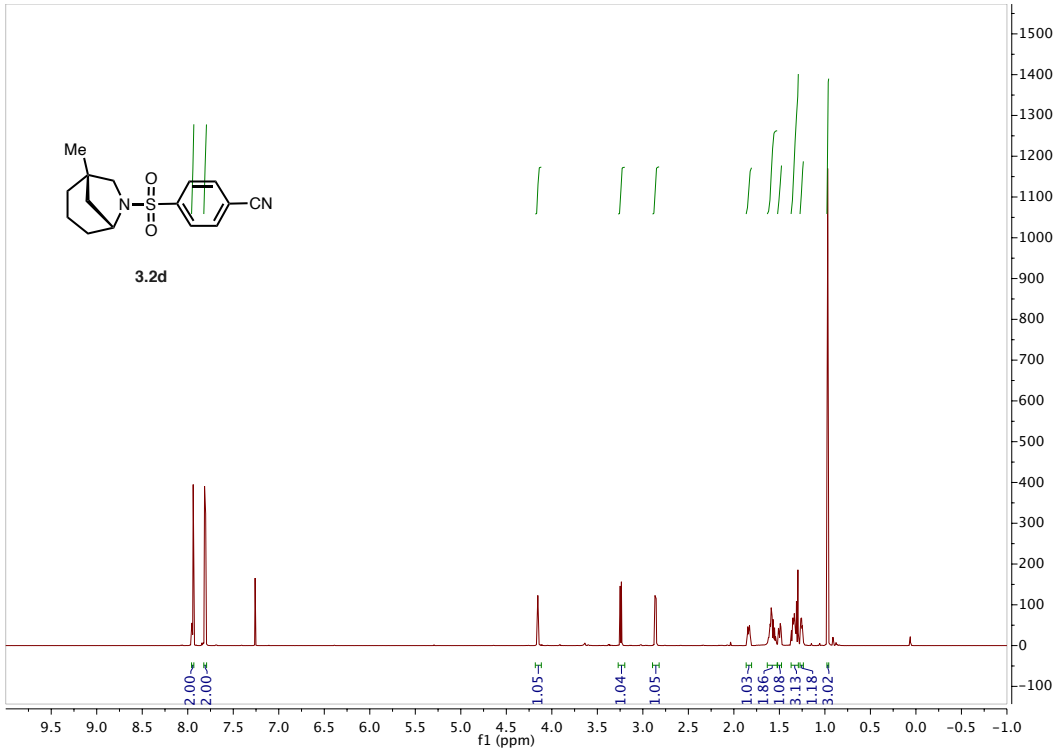

Me
O
N
S
O
Me
3.2a
f1 (ppm)

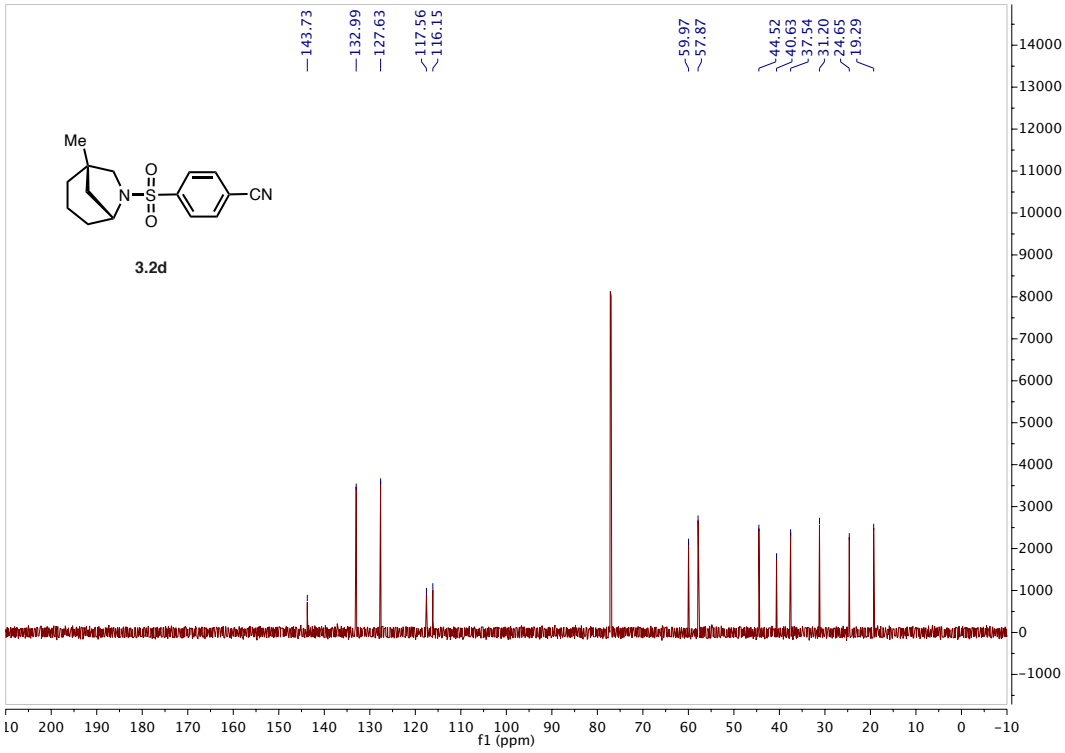

Me
O
N
S
O
CO2Me
3.2b
f1 (ppm)

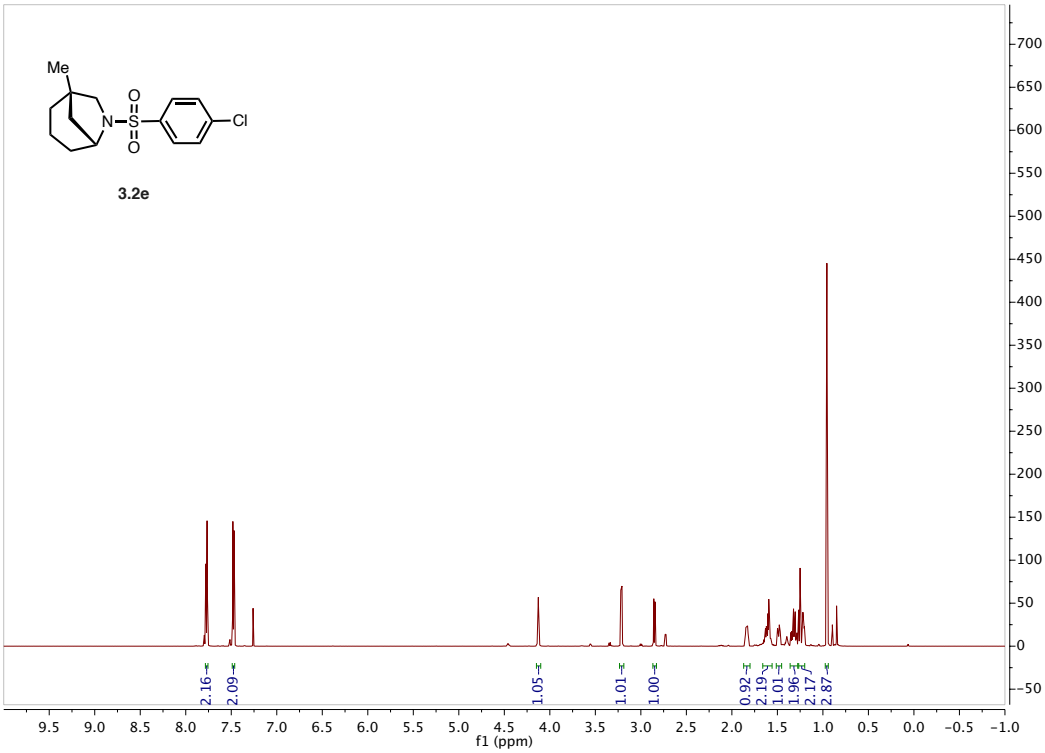

Me
O
N
S
O
CO2Me
3.2b
f1 (ppm)

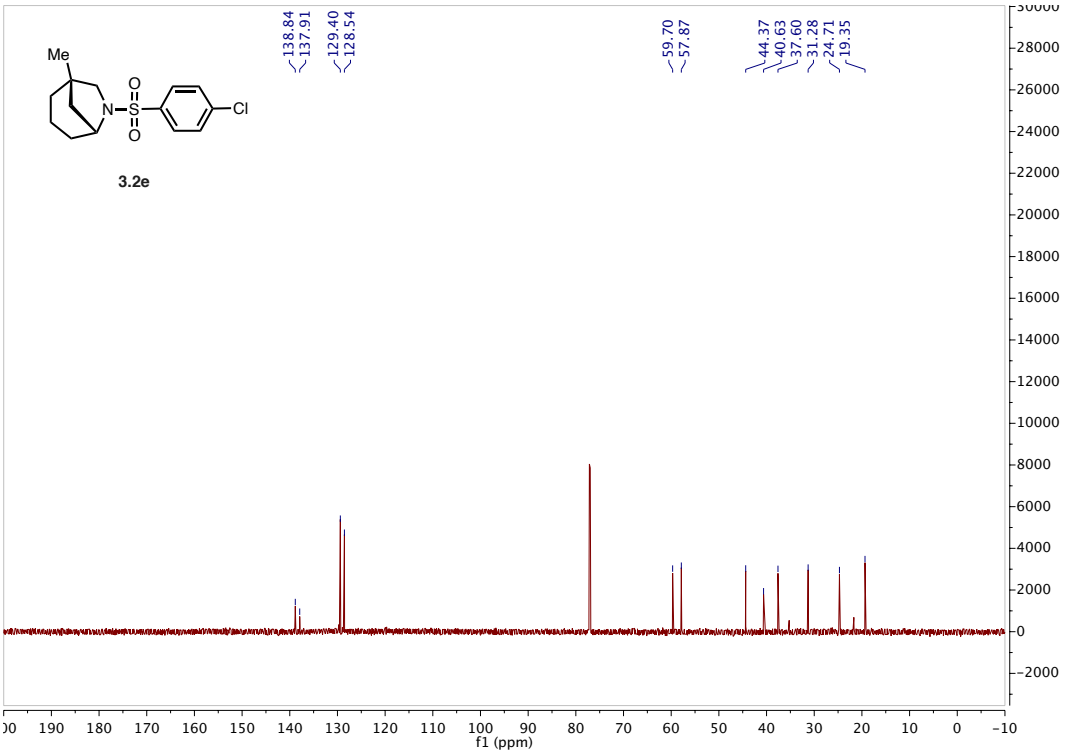

Me
O
N
S
O
Ac
3.2c
1.91
1.95
0.96
0.92
0.91
3.05
0.92
2.04
1.13
4.01
2.85
f1 (ppm)

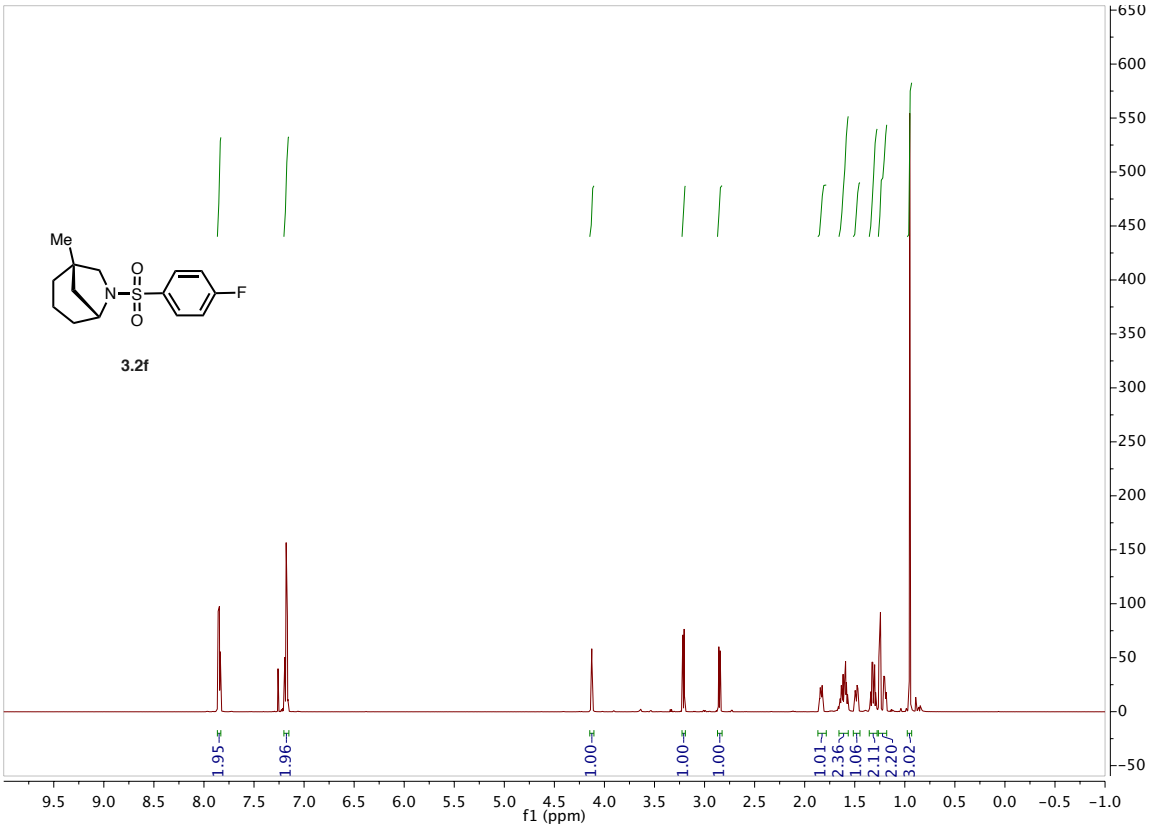

197.05
143.28
139.83
129.00
127.36
59.80
57.88
44.40
43.62
37.59
31.28
25.50
24.69
10.33
Me
O
N
S
O
Ac
3.2c
f1 (ppm)

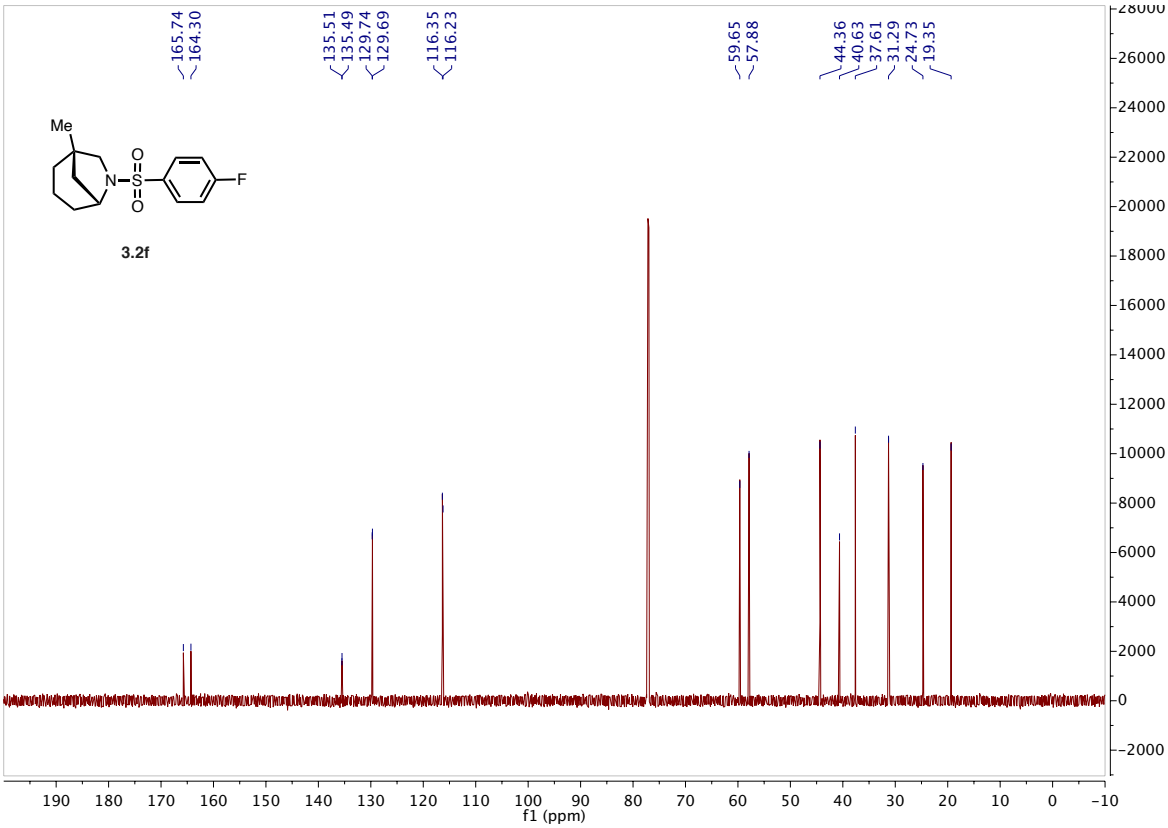

Me
O
N
S
O
CN
3.2d
2.00
2.00
1.05
1.04
1.05
1.03
1.86
1.08
3.13
1.18
3.02
f1 (ppm)

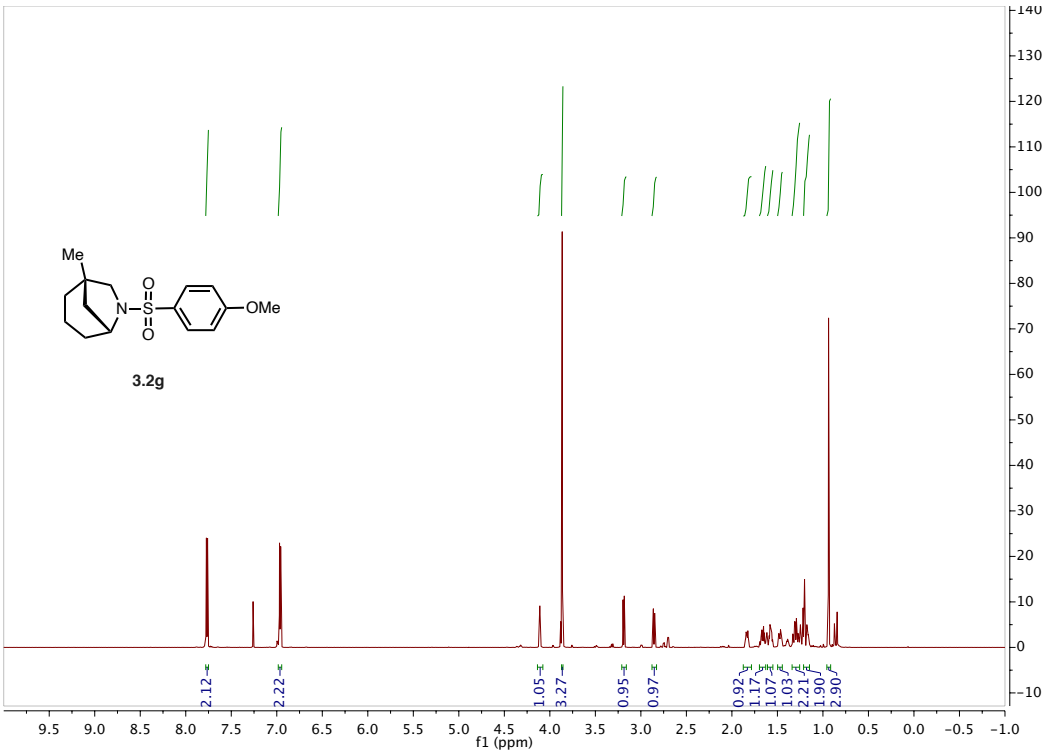

143.73
132.99
127.63
117.56
116.15
59.97
57.87
44.52
40.63
37.54
31.20
24.65
19.29
Me
O
N
S
O
CN
3.2d
f1 (ppm)

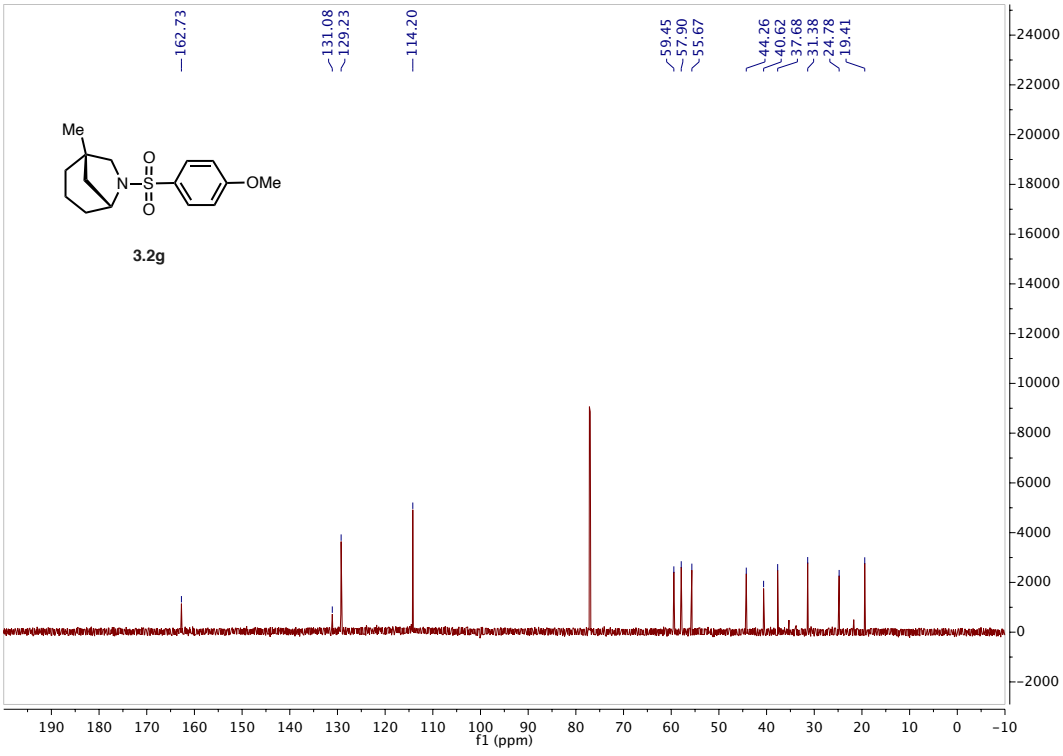

Me
O
N
S
O
Cl
3.2e
2.16
2.09
1.05
1.01
1.00
0.92
2.19
1.01
1.96
2.17
2.87
f1 (ppm)

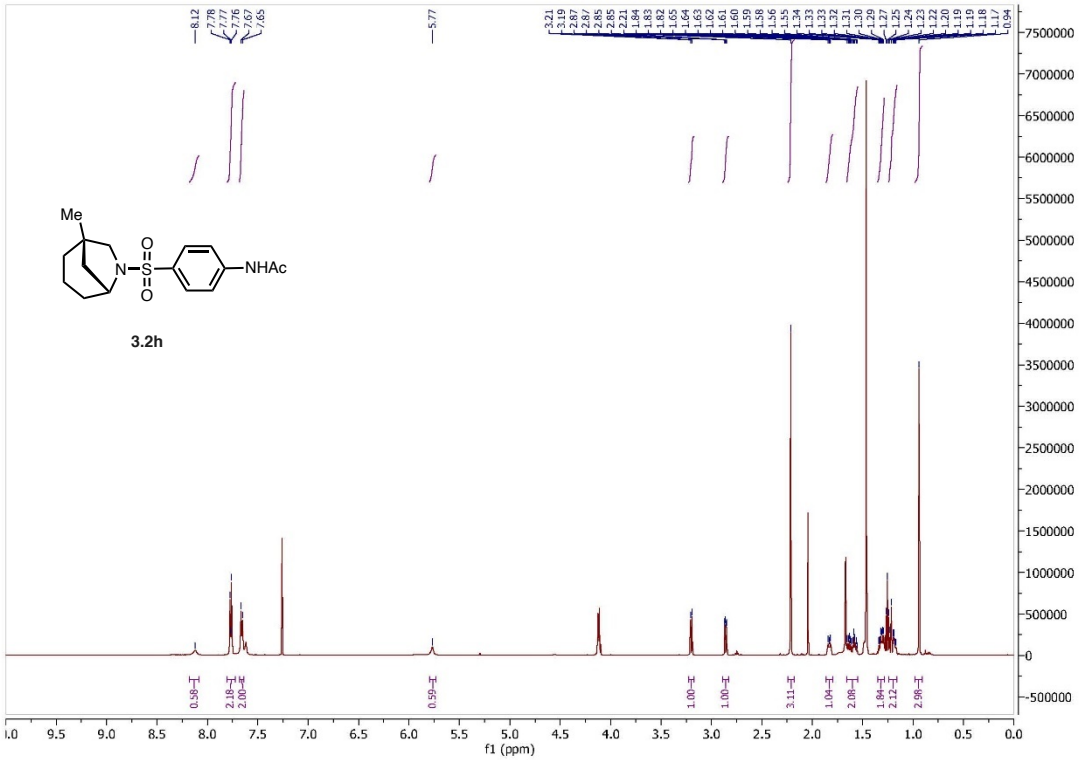

Me
O
N
S
O
Cl
3.2e
138.84
137.91
129.40
128.54
59.70
57.87
44.37
40.63
37.60
31.28
24.71
19.35
f1 (ppm)

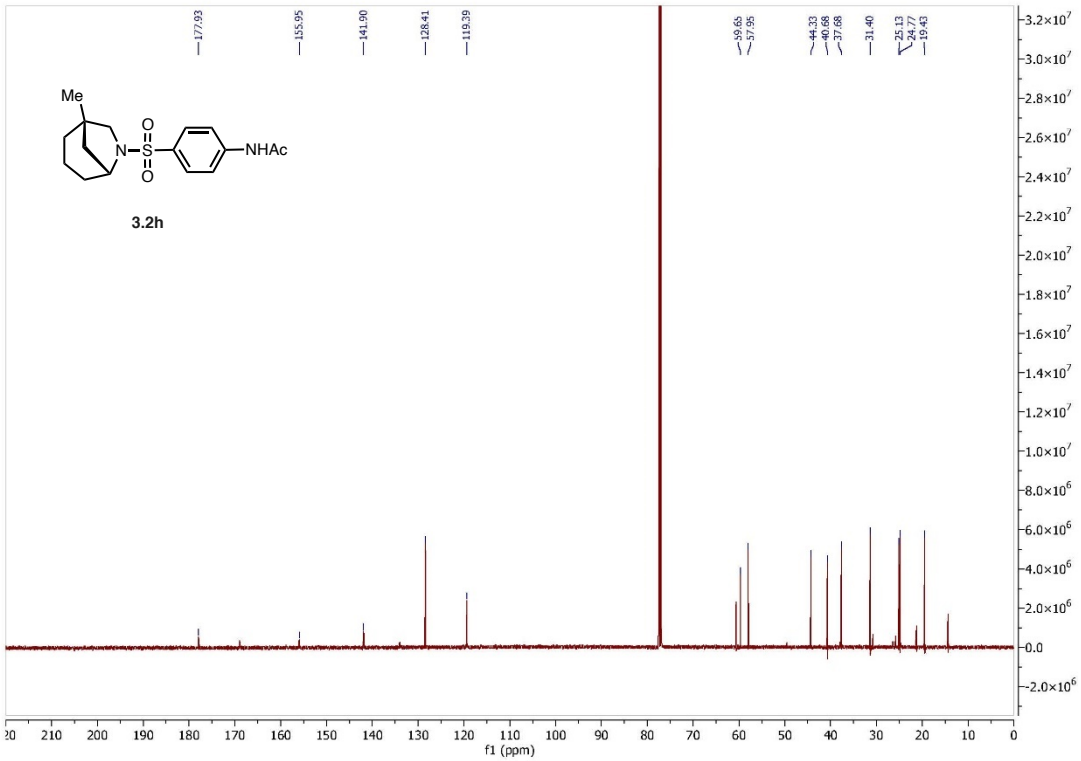

Me
O
O
N
S
F
3.2f
1.95
1.96
1.00
1.00
1.00
1.01
2.36
1.06
2.11
2.20
3.02
f1 (ppm)

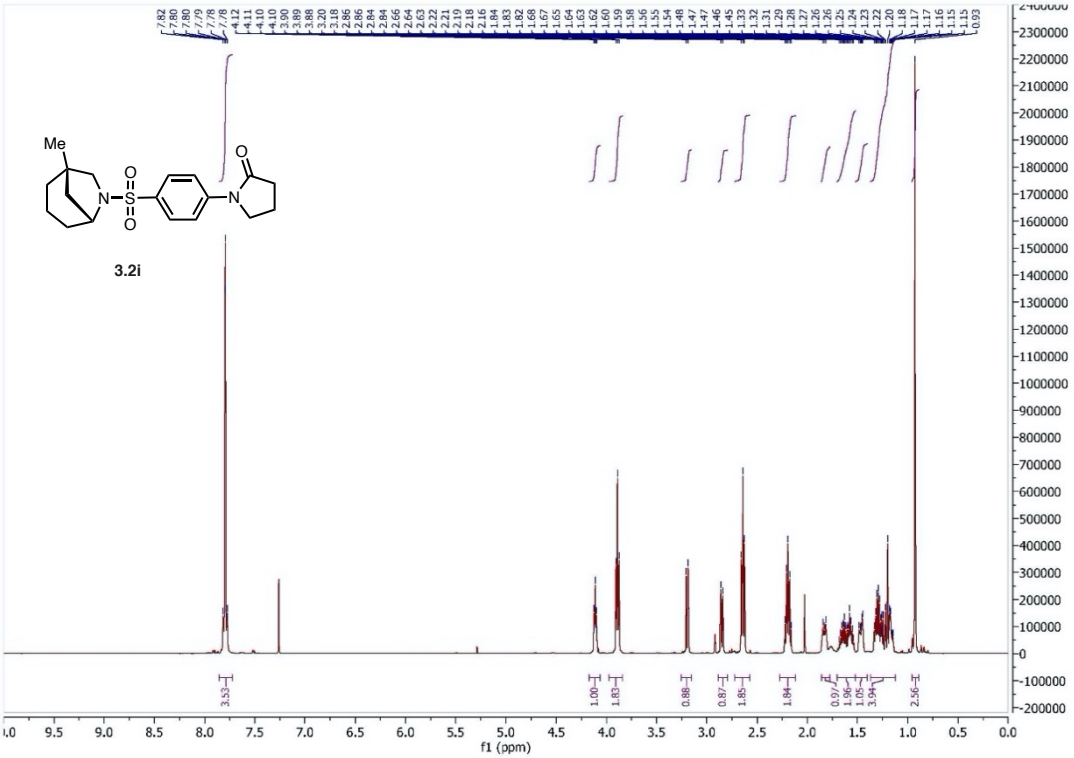

165.74
164.30
135.51
135.49
129.74
129.69
116.35
116.23
59.65
57.88
44.36
40.63
37.61
31.29
24.73
19.35
Me
O
O
N
S
F
3.2f
f1 (ppm)

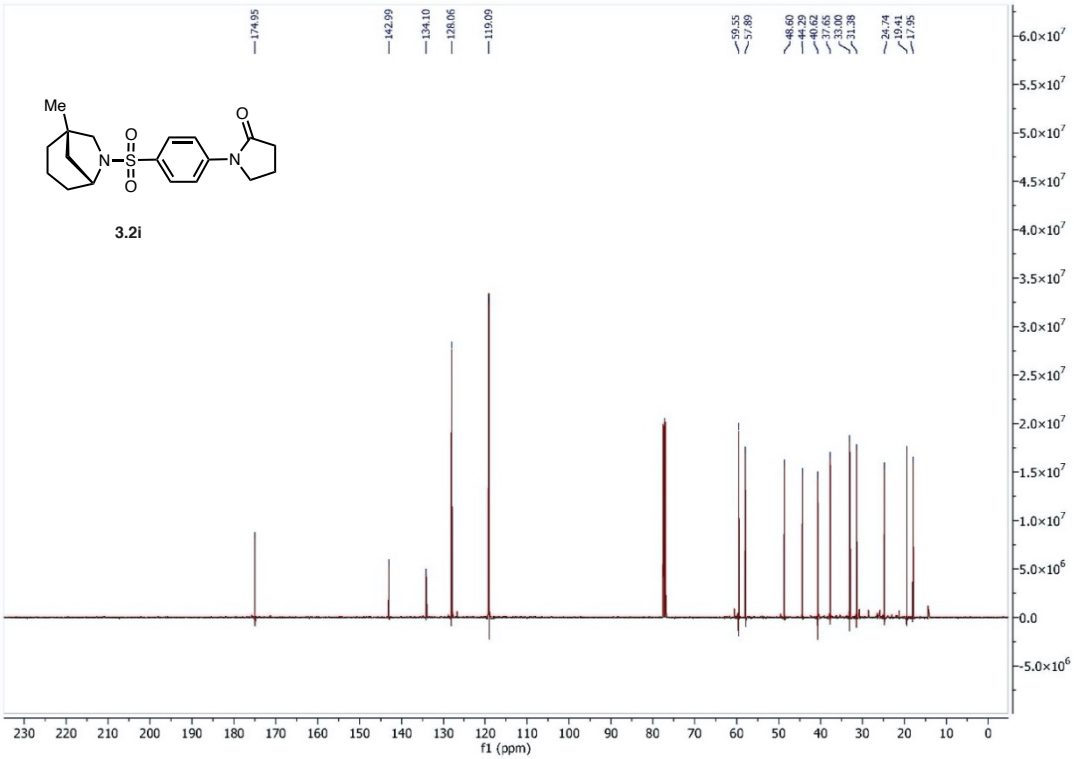

Me
N
S
O
O
OMe
3.2g
2.12
2.22
1.05
3.27
0.95
0.97
0.92
1.17
1.07
1.03
2.21
1.90
2.90
f1 (ppm)

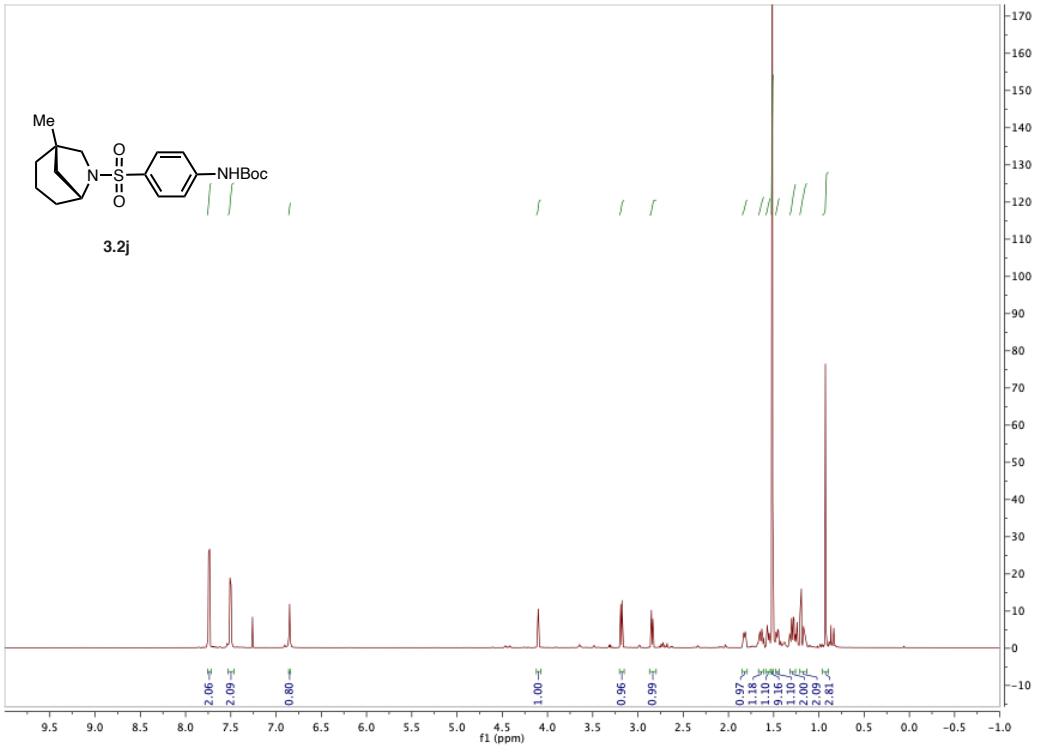

162.73
131.08
129.23
114.20
59.45
57.90
55.67
44.26
40.62
37.68
31.38
24.78
19.41
Me
N
S
O
O
OMe
3.2g
f1 (ppm)

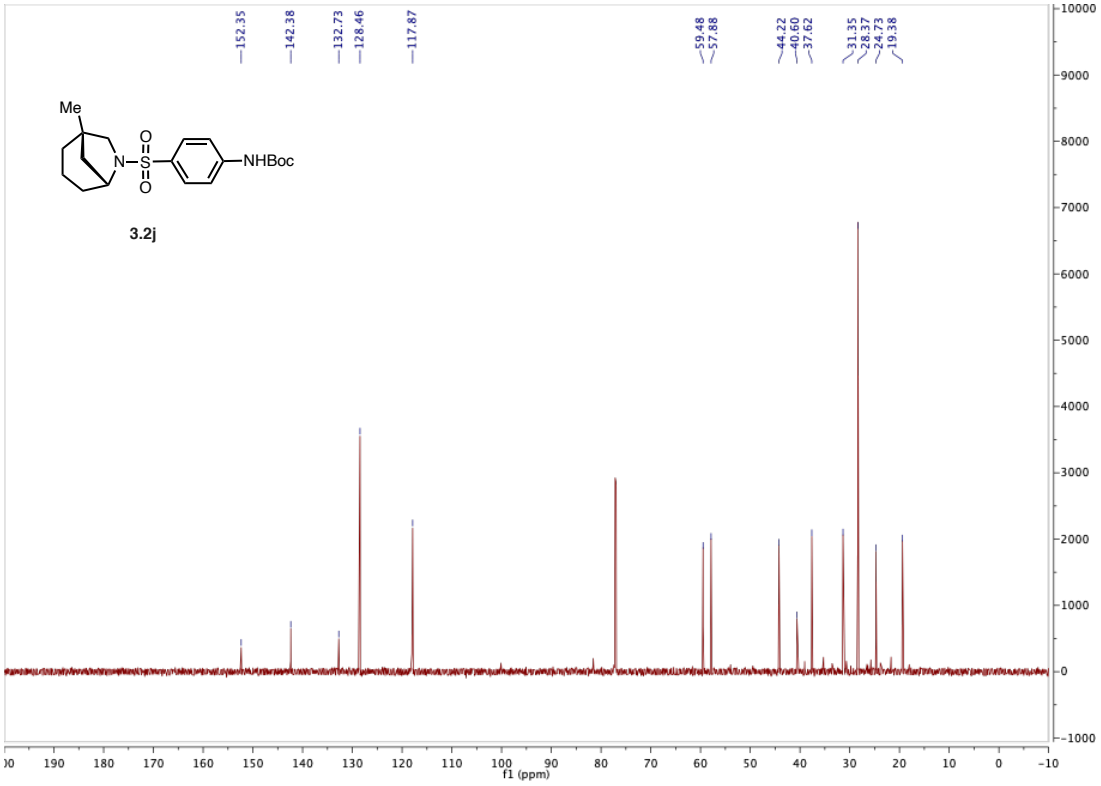

Me
O
O
N
S
NHAc
3.2h
f1 (ppm)

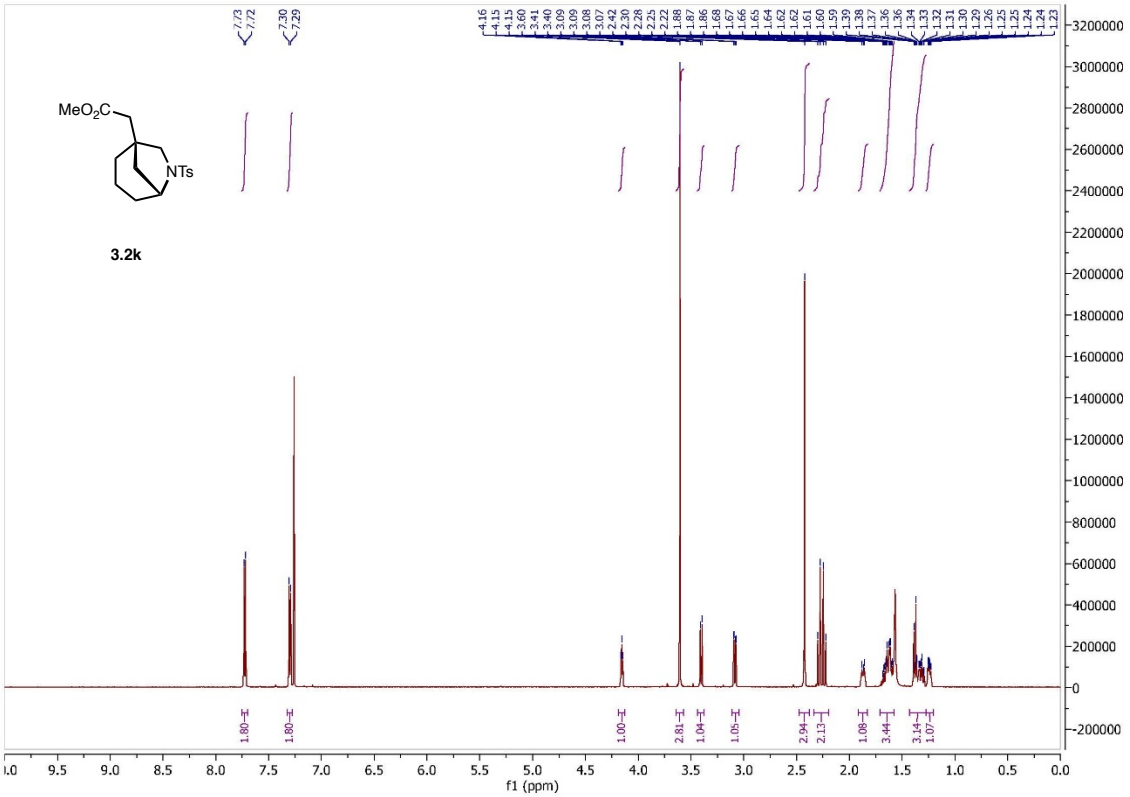

Me
O
O
N
S
NHAc
3.2h
f1 (ppm)

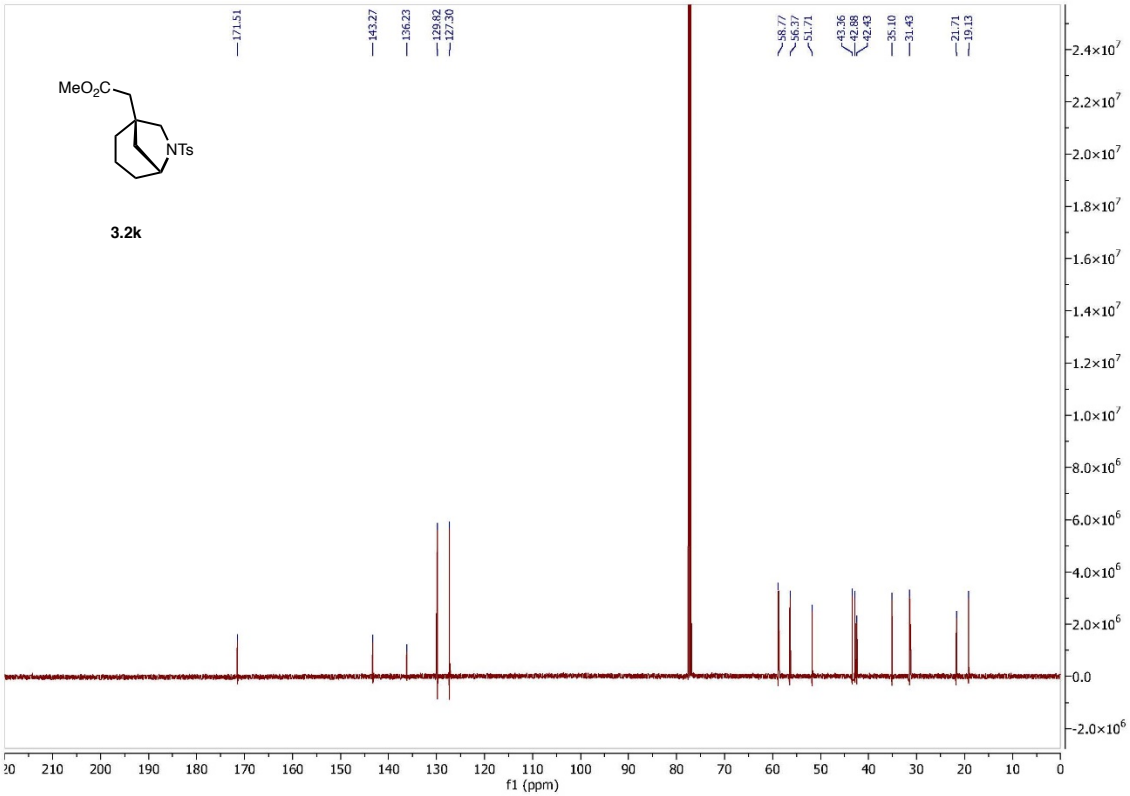

Me
O
O
N
S
O
N
O
3.2i
f1 (ppm)

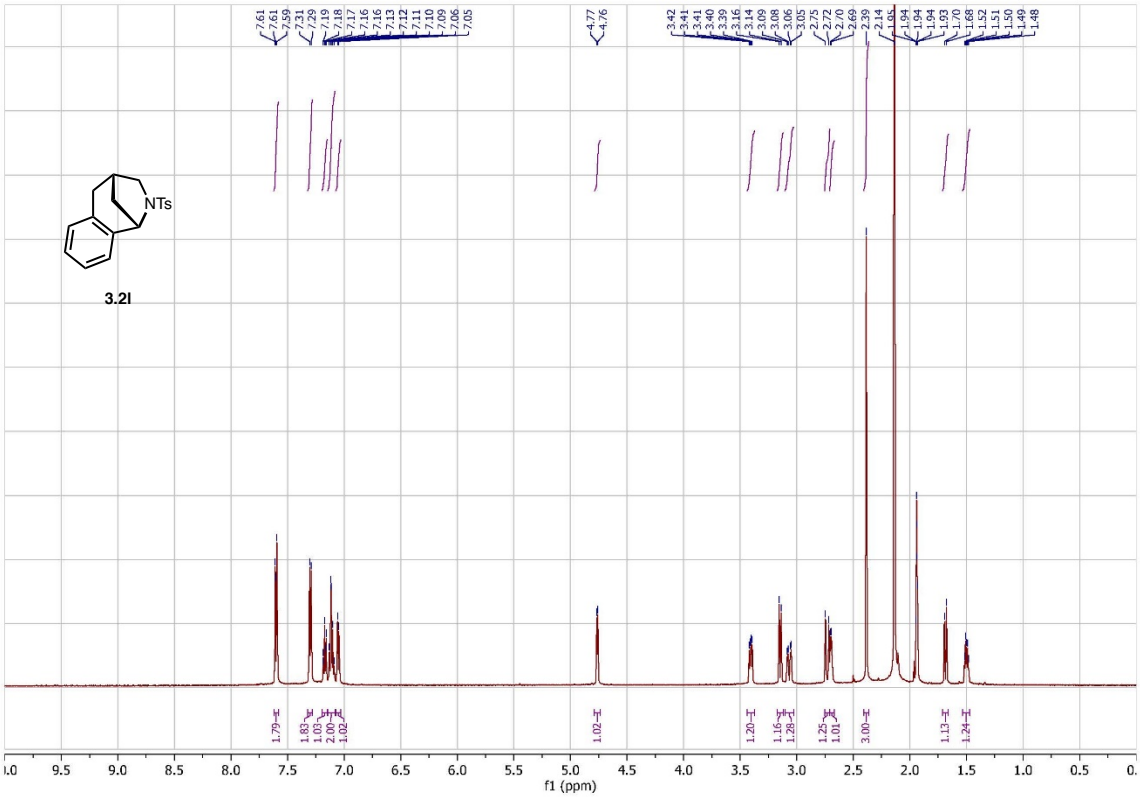

Me
O
O
N
S
O
N
O
3.2i
f1 (ppm)

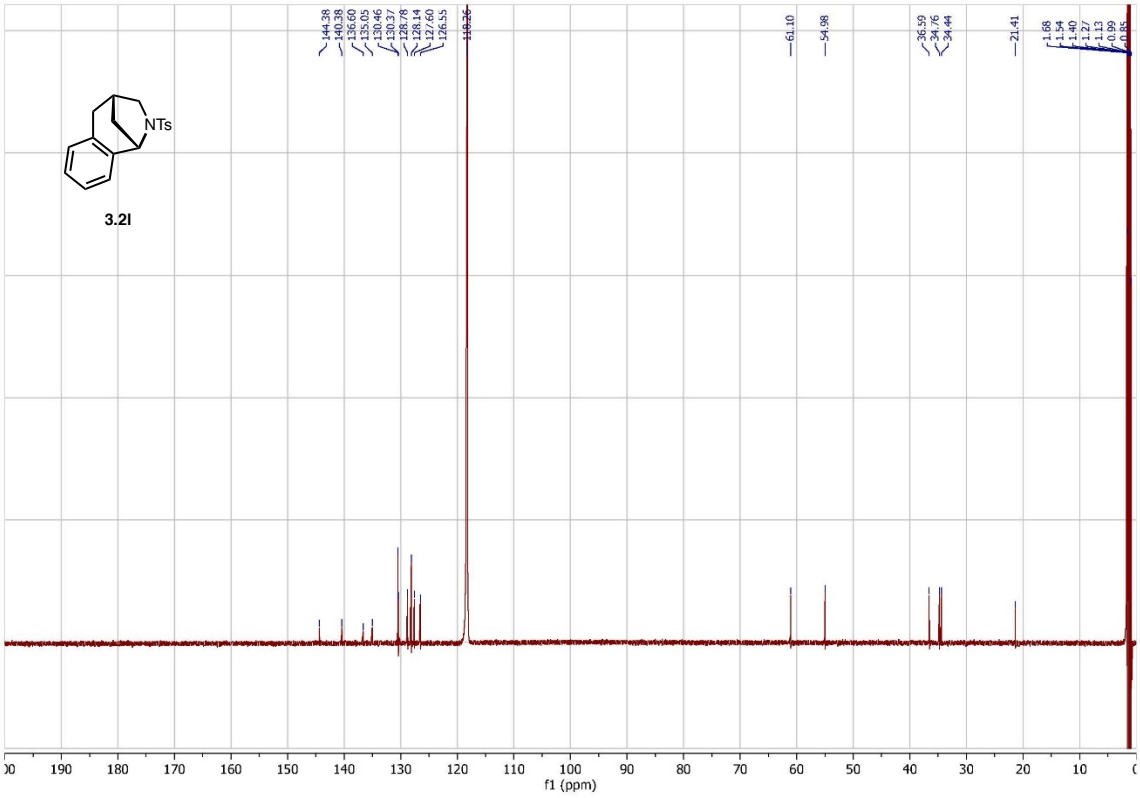

Me
O
S
O
N
NHBoc
3.2j
f1 (ppm)


152.35
142.38
132.73
128.46
117.87
59.48
57.88
44.22
40.60
37.62
31.35
28.37
24.73
19.38
Me
O
S
O
N
NHBoc
3.2j
f1 (ppm)

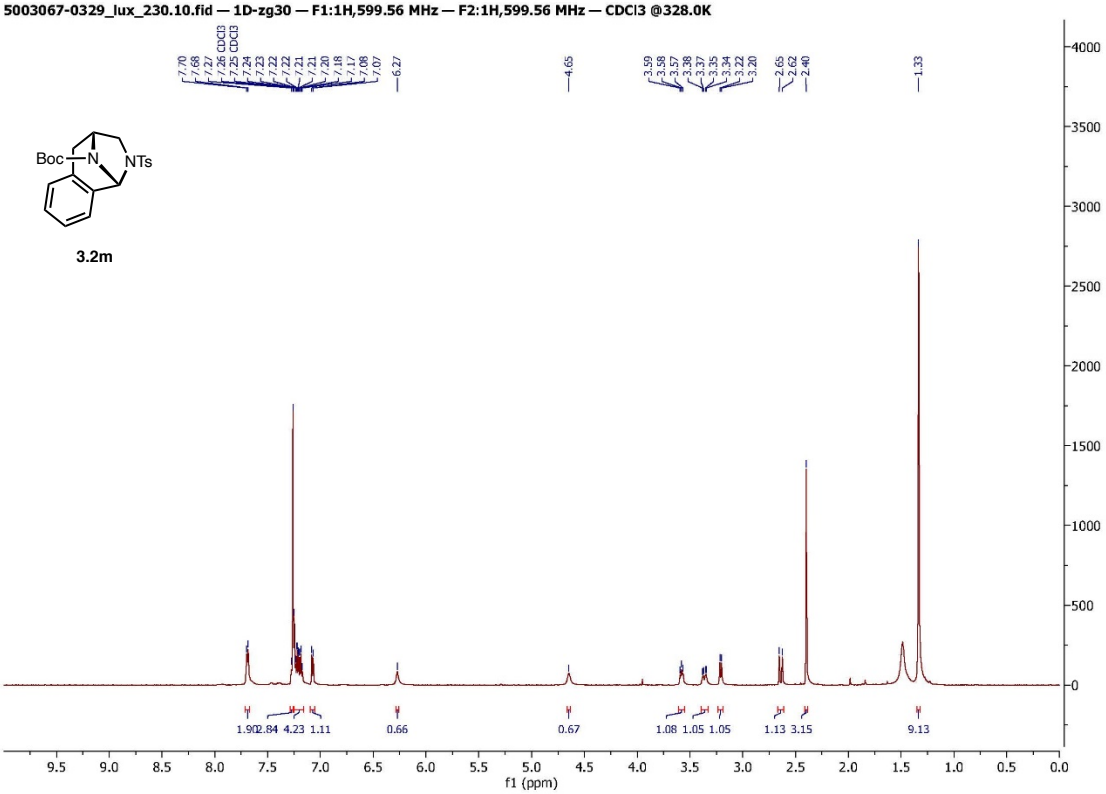

MeO2C
NTs
3.2k
f1 (ppm)


MeO2C
NTs
3.2k
f1 (ppm)


NTs
3.2l
f1 (ppm)

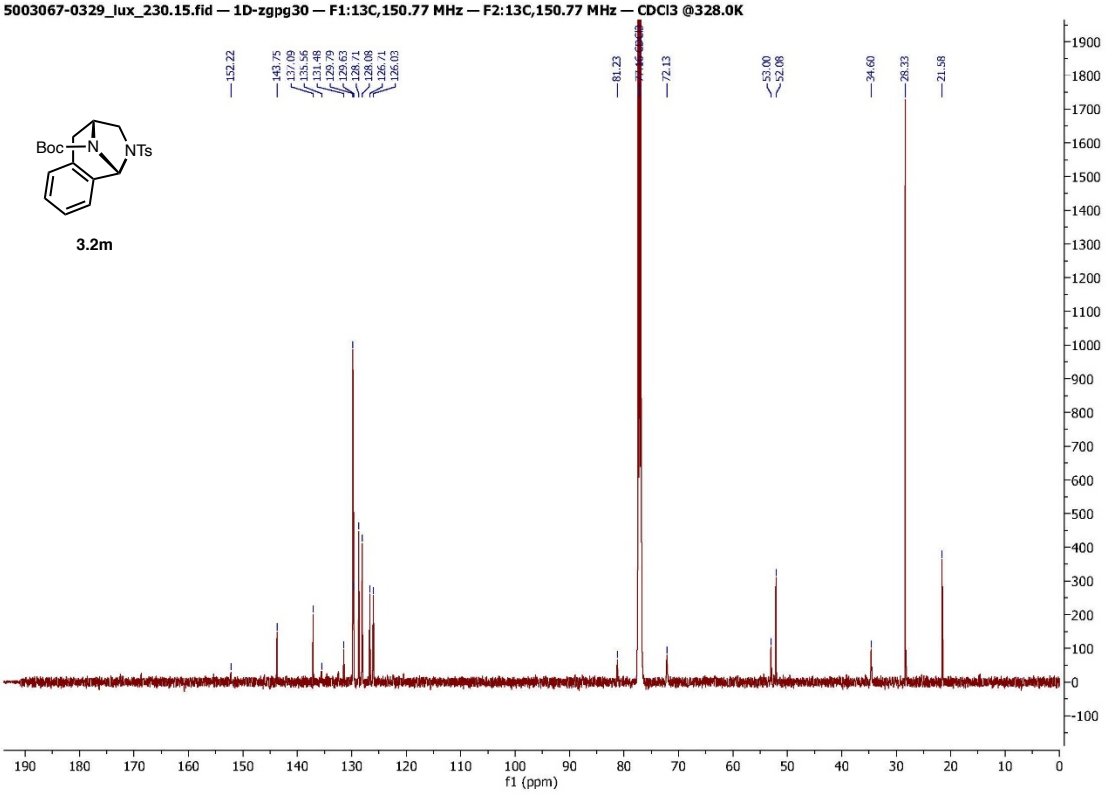

NTs
3.2l
f1 (ppm)

5003067-0329_lux_230.10.fid — 1D-zg30 — F1:1H,599.56 MHz — F2:1H,599.56 MHz — CDCl3 @328.0K

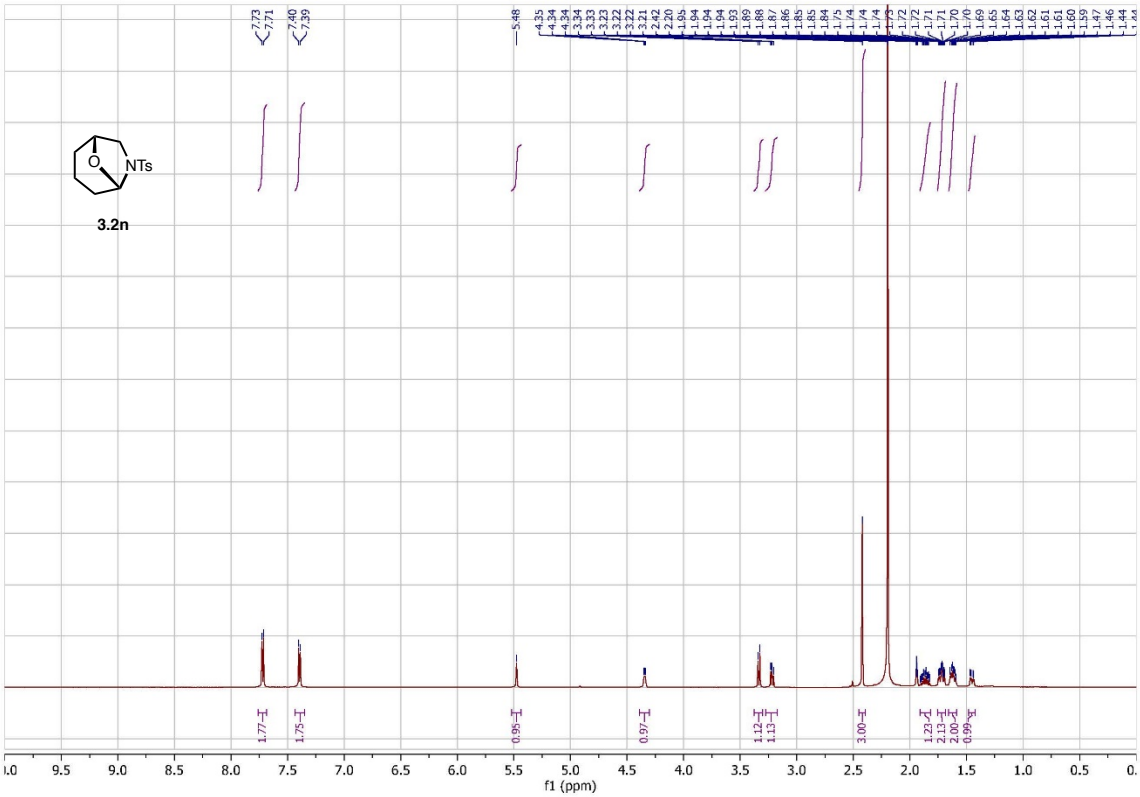


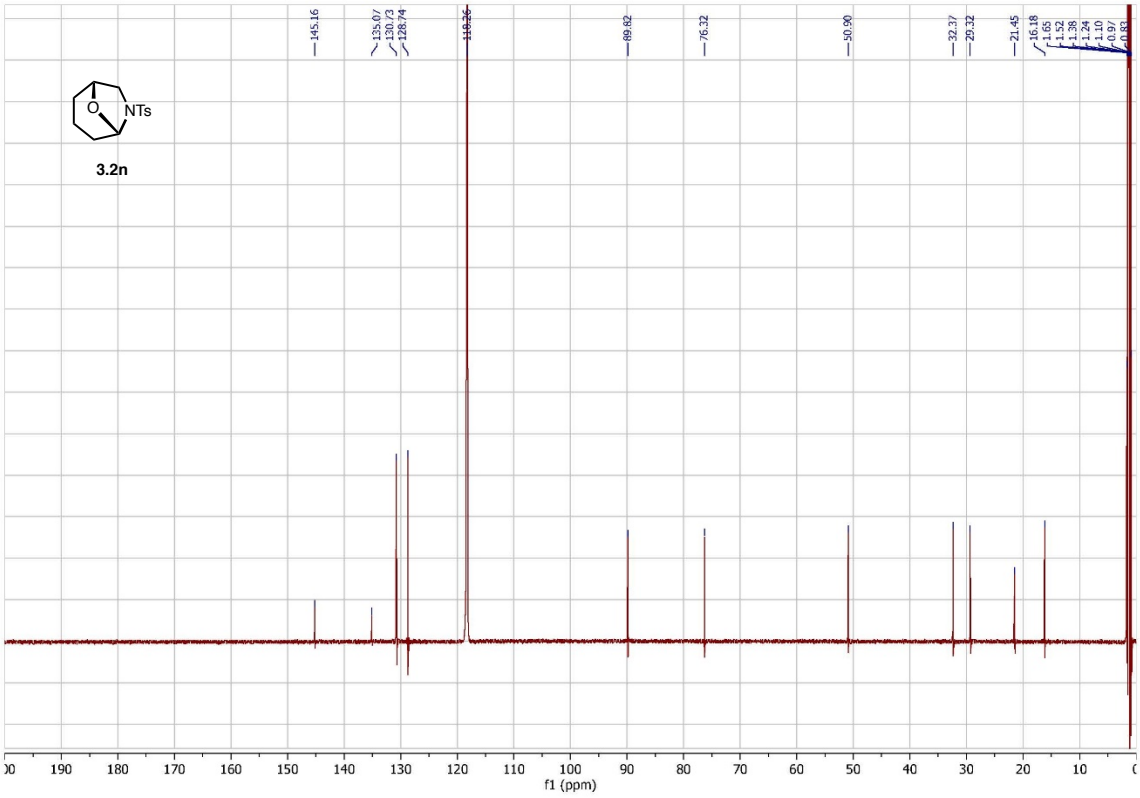
3.2m

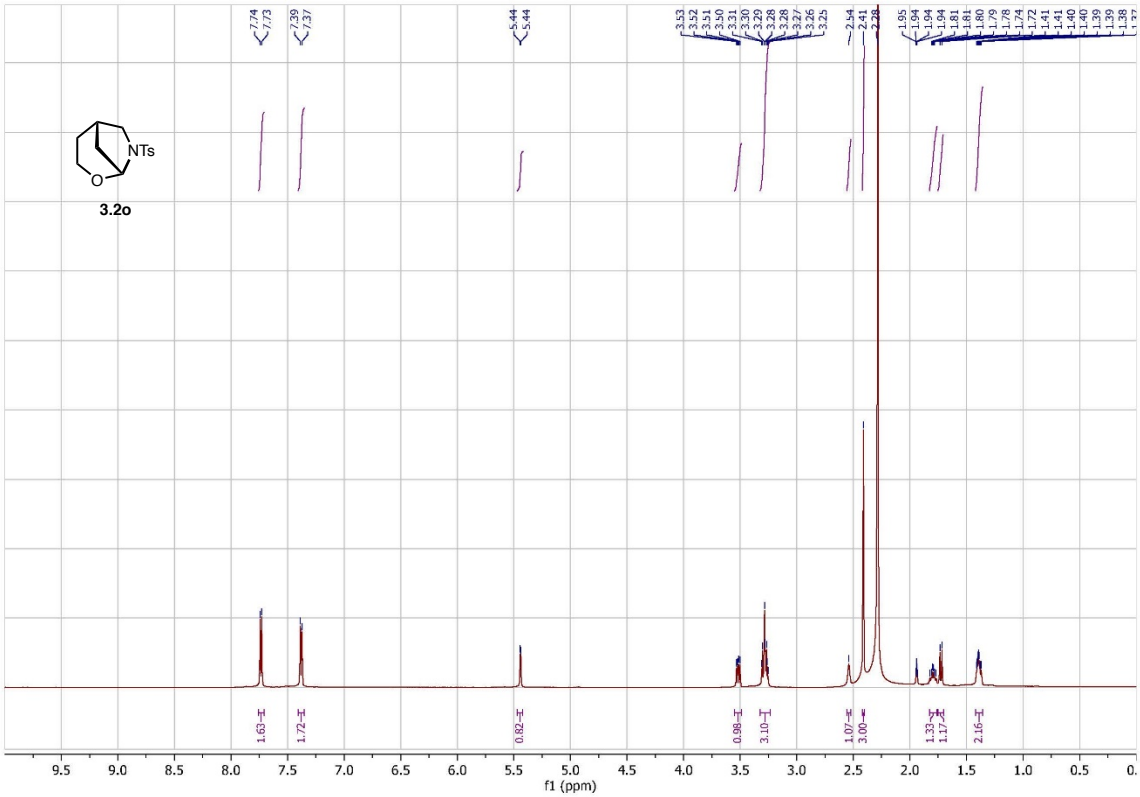
5003067-0329_lux_230.15.fid — 1D-zgpg30 — F1:13C,150.77 MHz — F2:13C,150.77 MHz — CDCl3 @328.0K

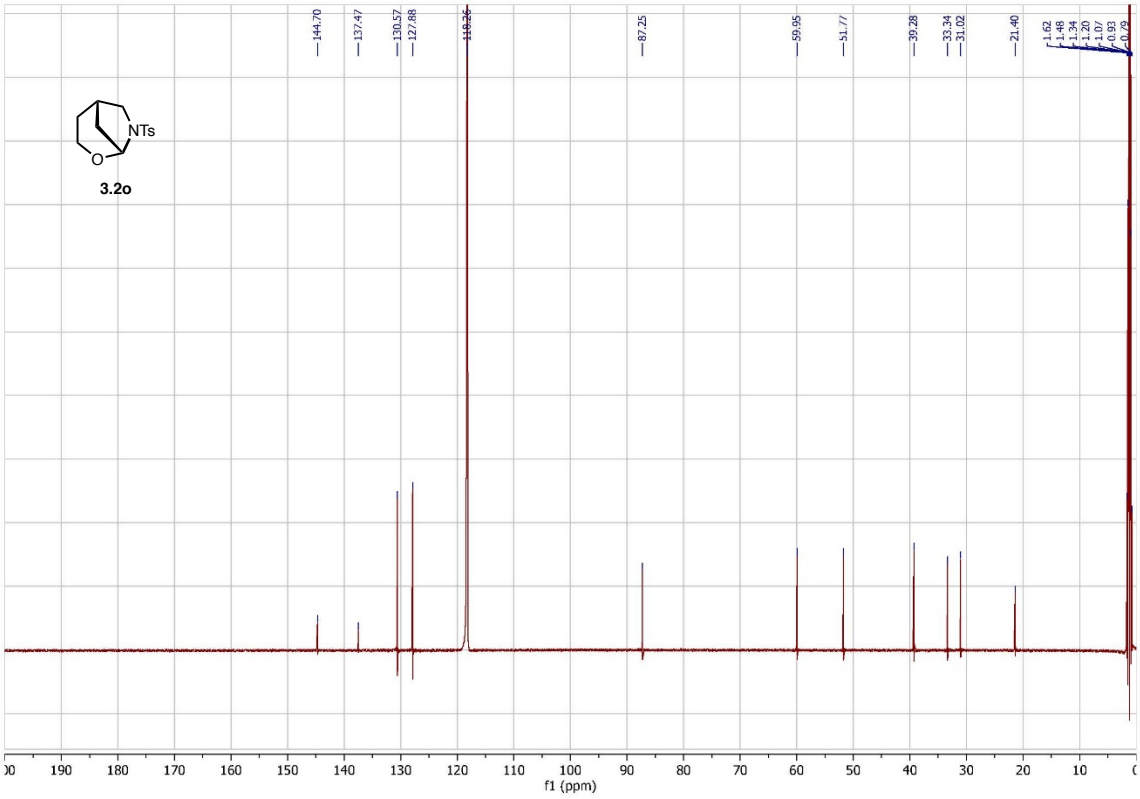


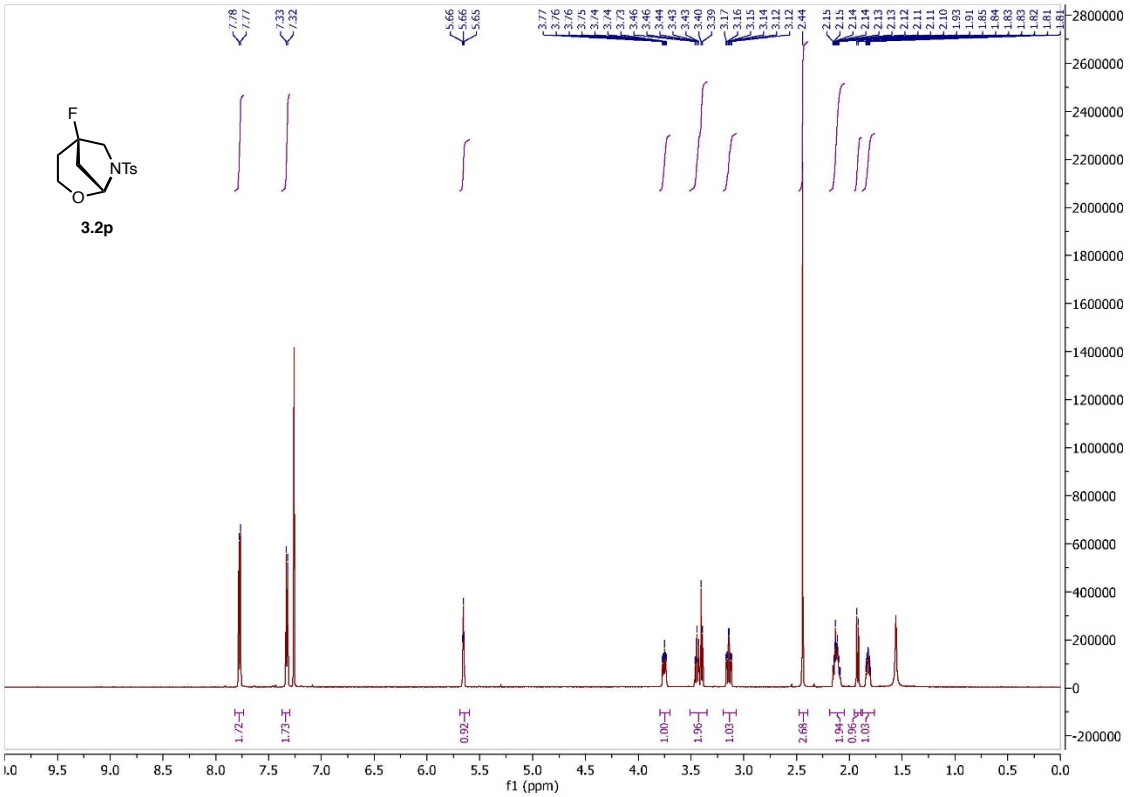
3.2m

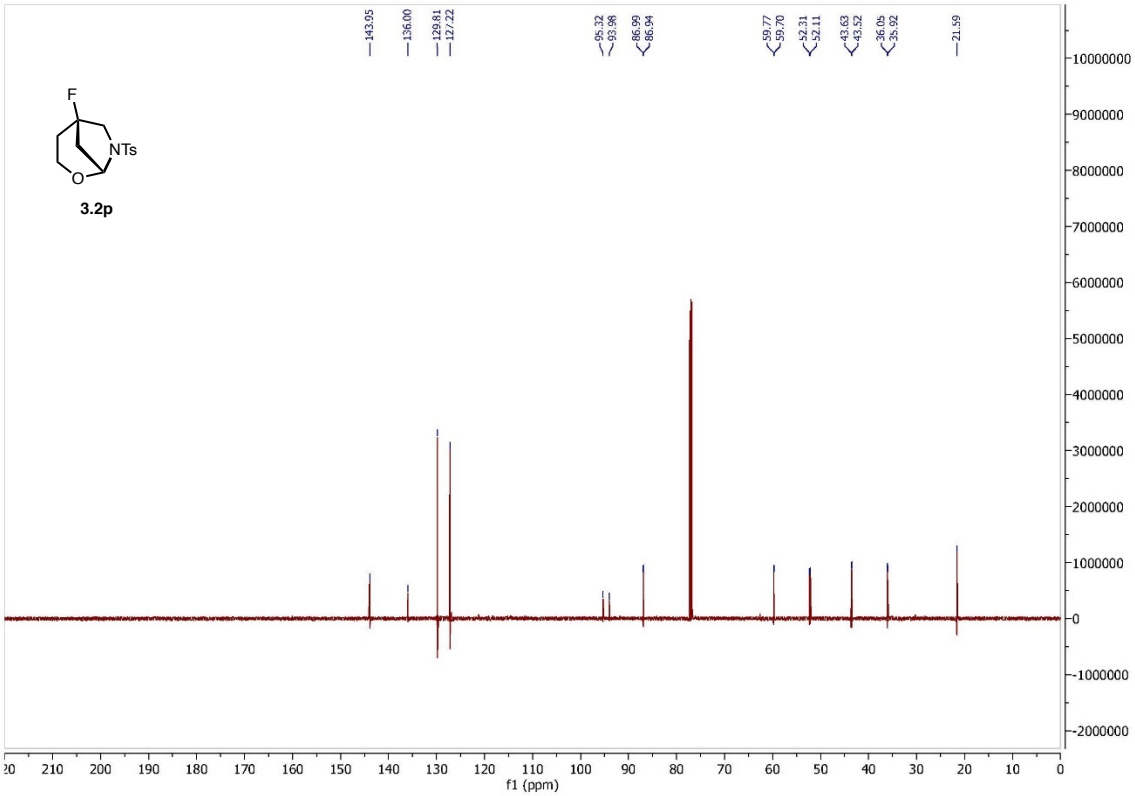

NTs
3.2n
f1 (ppm)

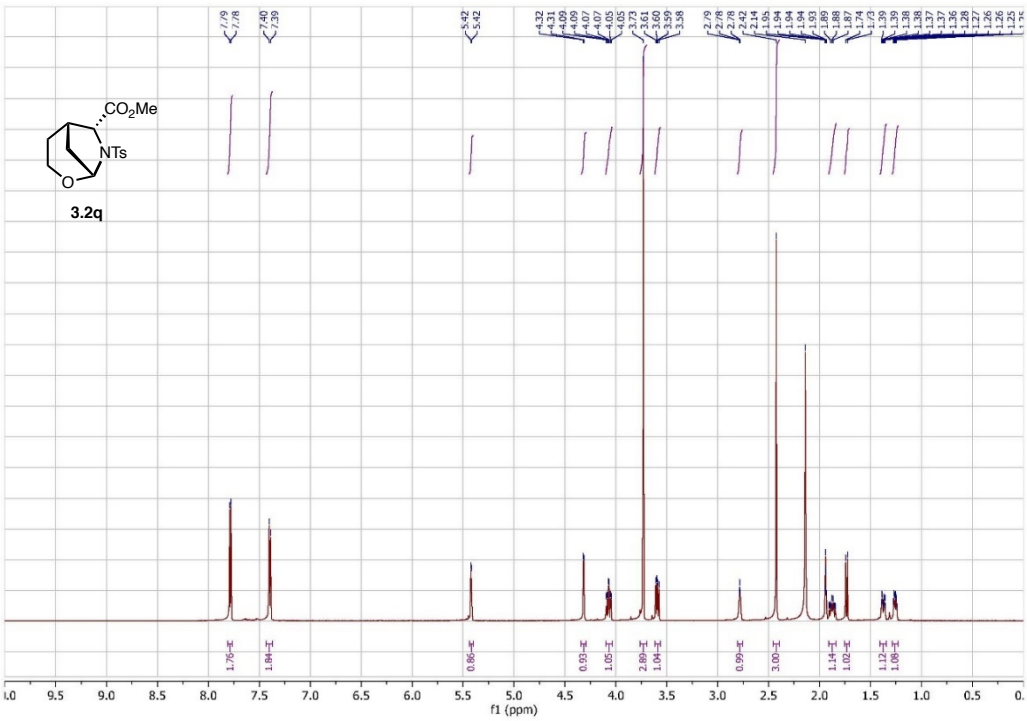

NTs
3.2n
f1 (ppm)

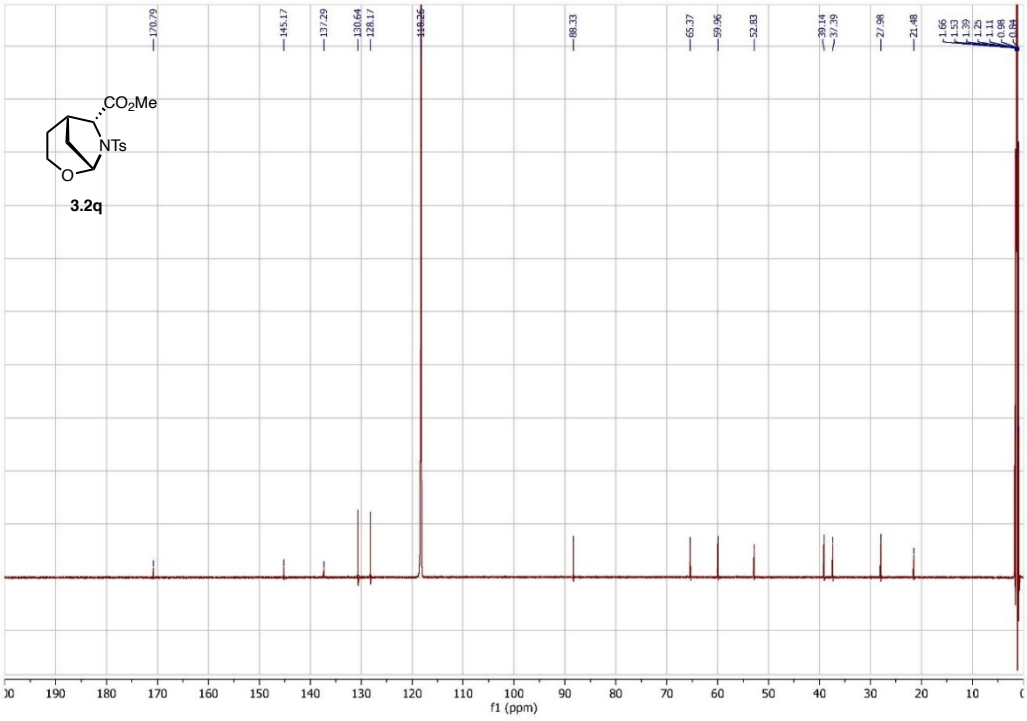

NTs
O
3.2o
f1 (ppm)

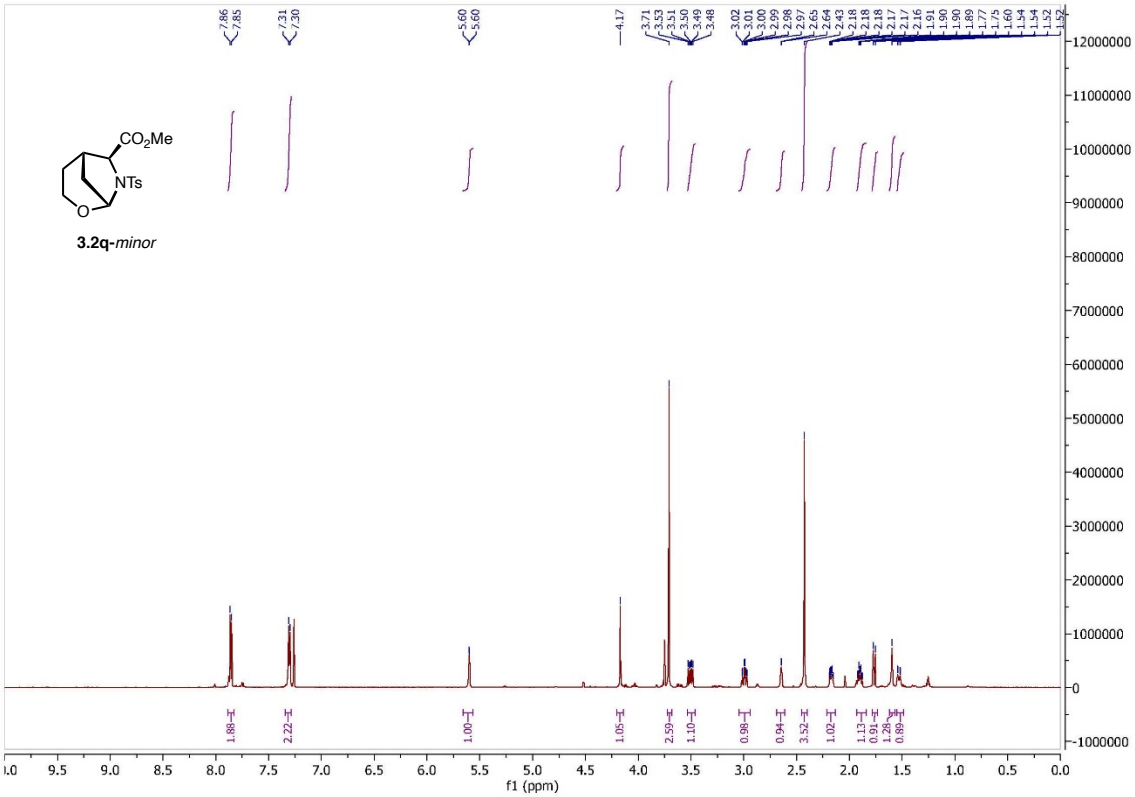

NTs
O
3.2o
f1 (ppm)

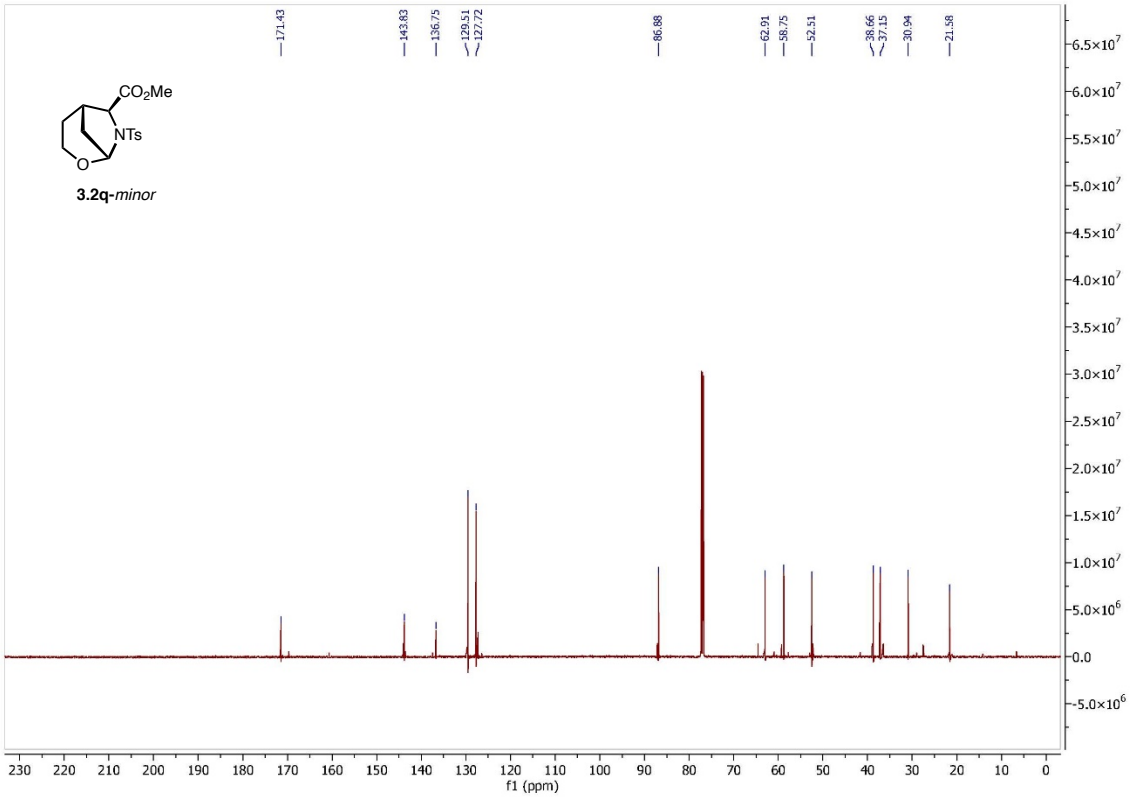

F
NTs
O
3.2p
f1 (ppm)

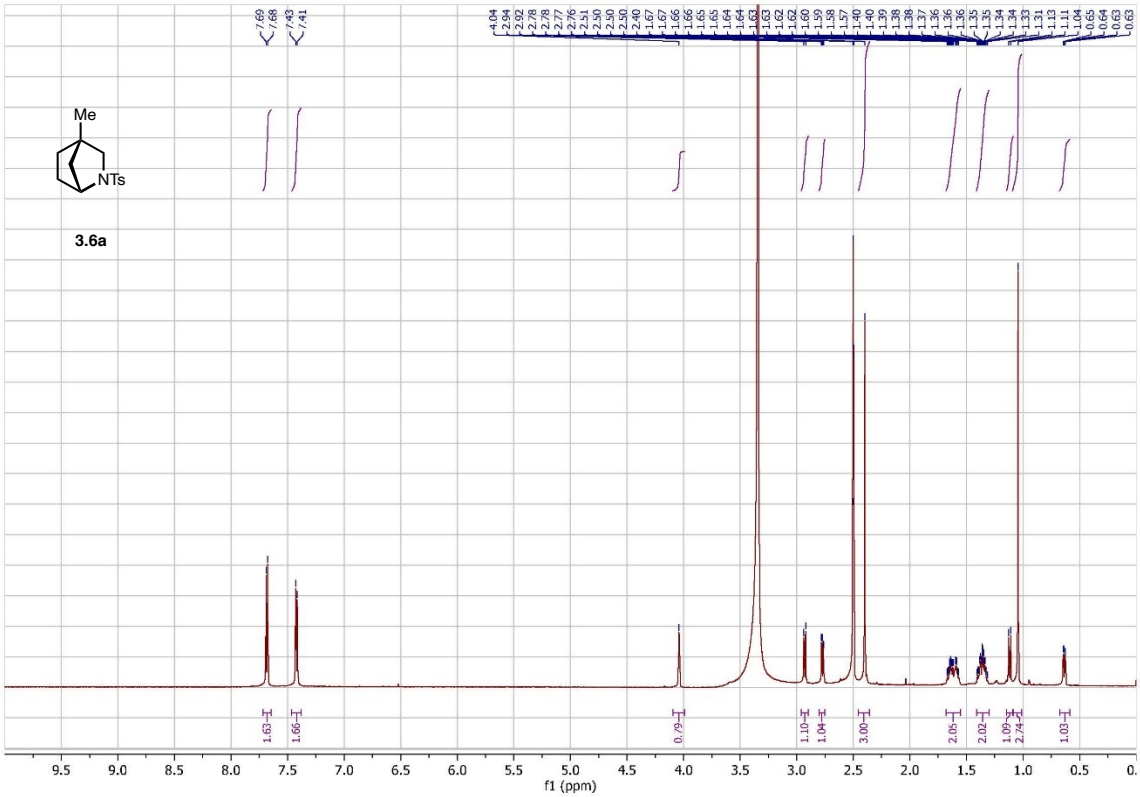

F
NTs
O
3.2p
f1 (ppm)

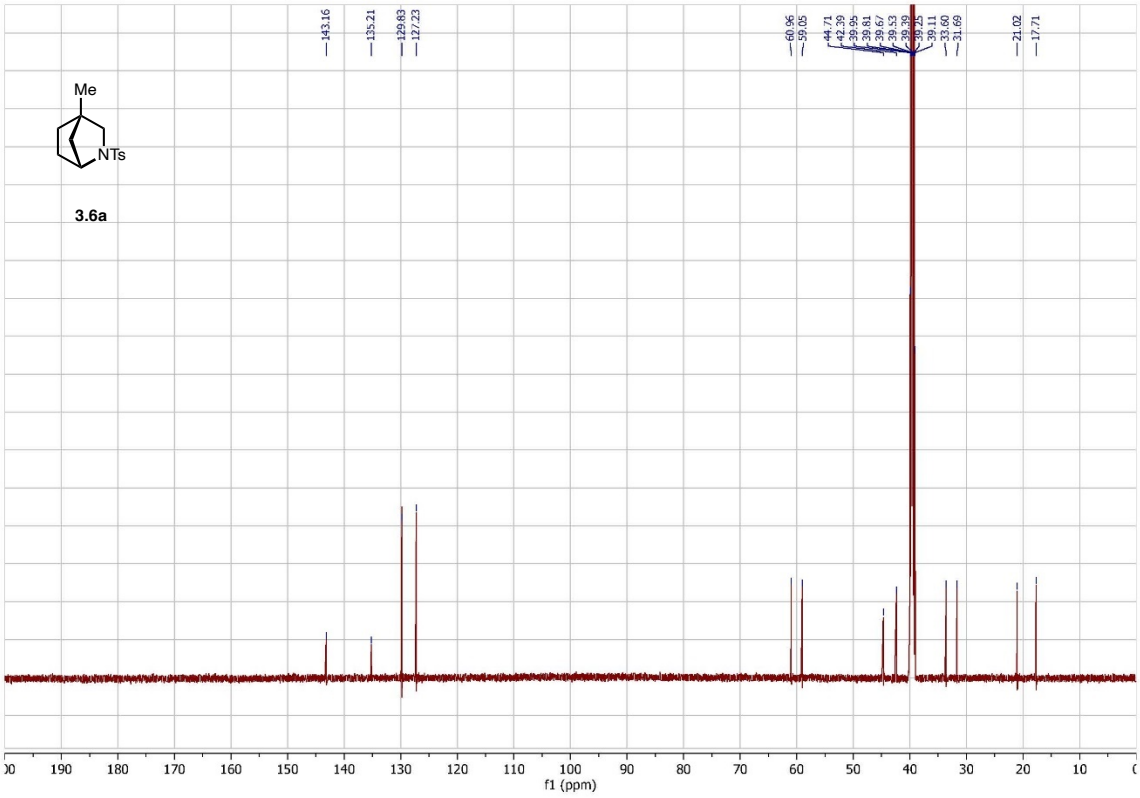

CO2Me
NTs
O
3.2q
f1 (ppm)

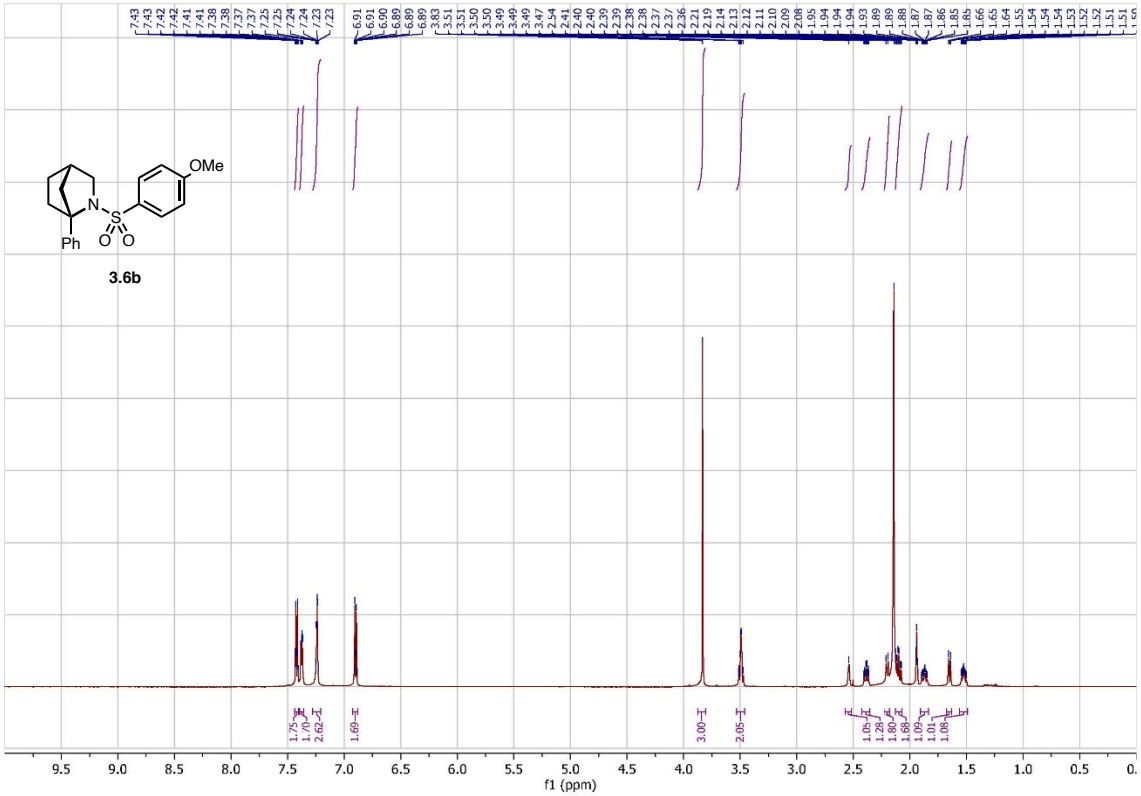

CO2Me
NTs
O
3.2q
f1 (ppm)

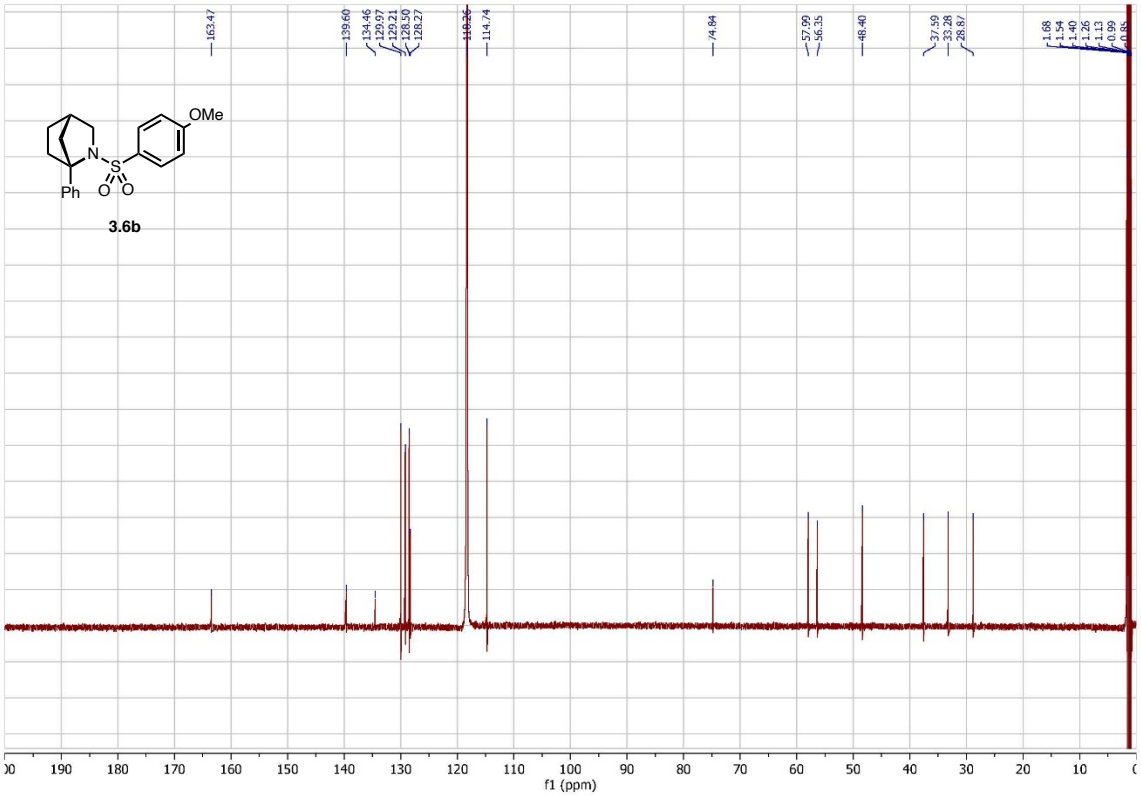

CO2Me
NTs
O
3.2q-minor
f1 (ppm)

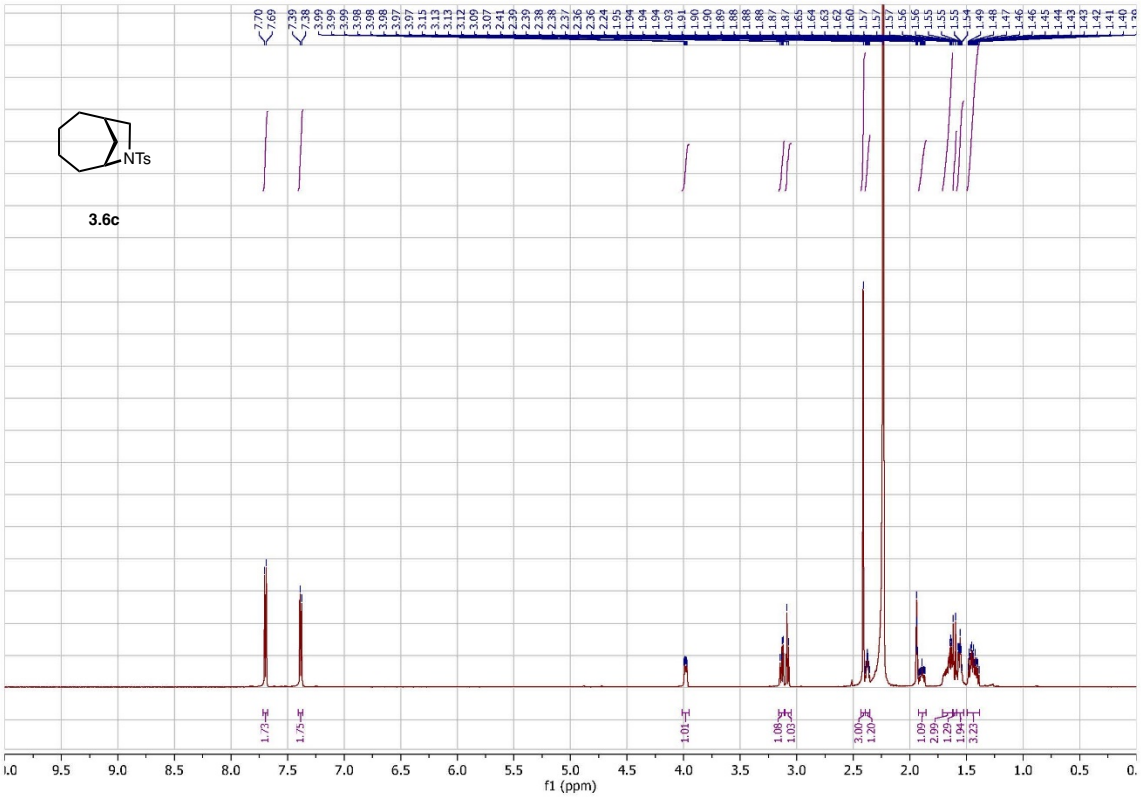

CO2Me
NTs
O
3.2q-minor
f1 (ppm)

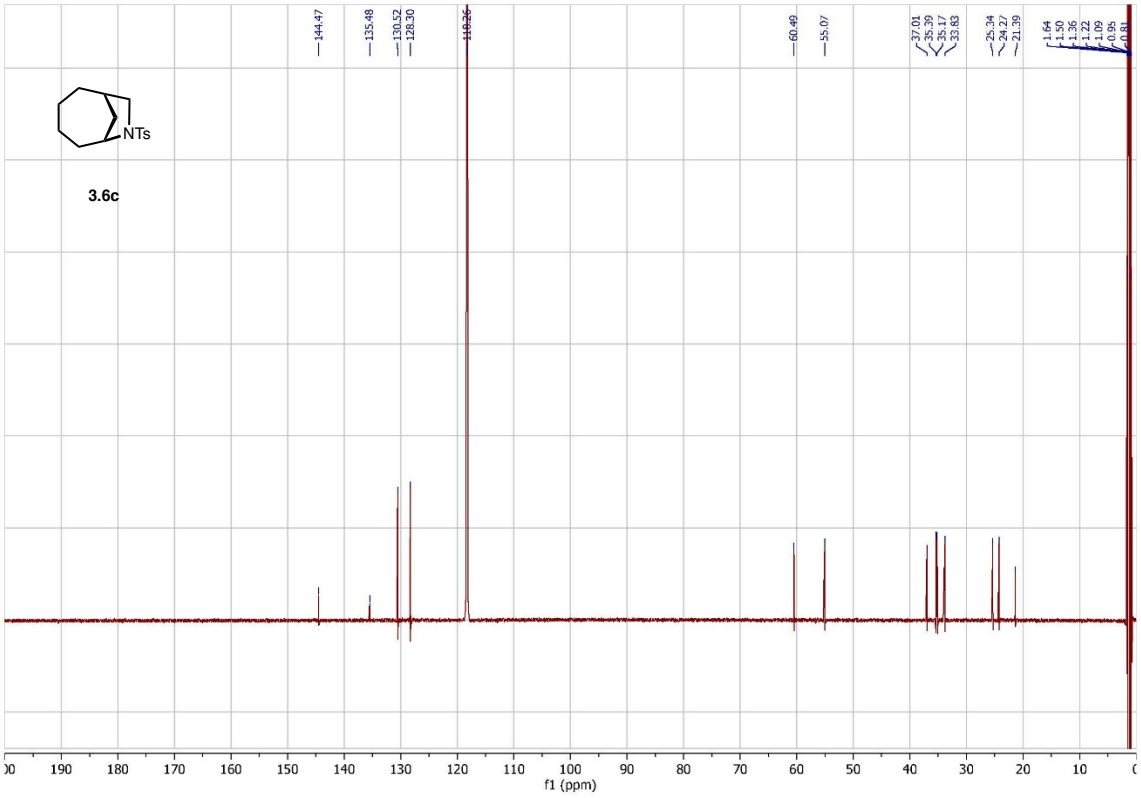

Me
NTs
3.6a
f1 (ppm)

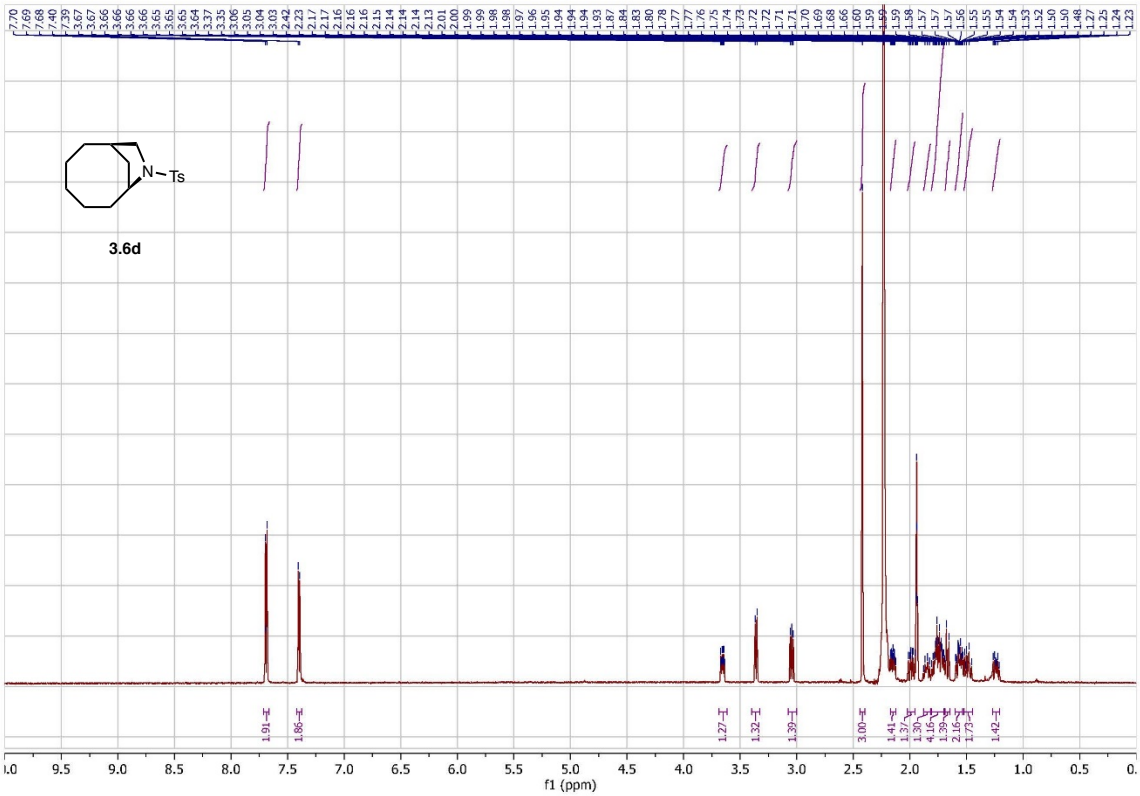

Me
NTs
3.6a
f1 (ppm)

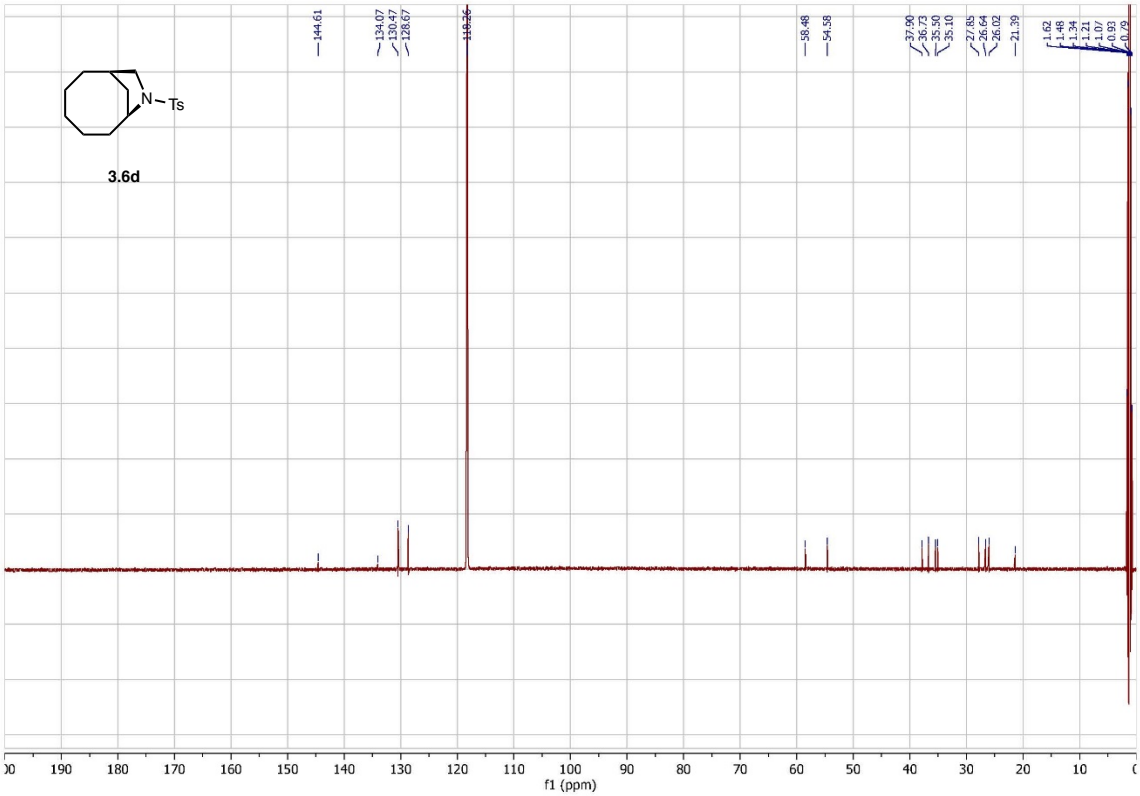

OMe
N
S
O O
Ph
3.6b
f1 (ppm)

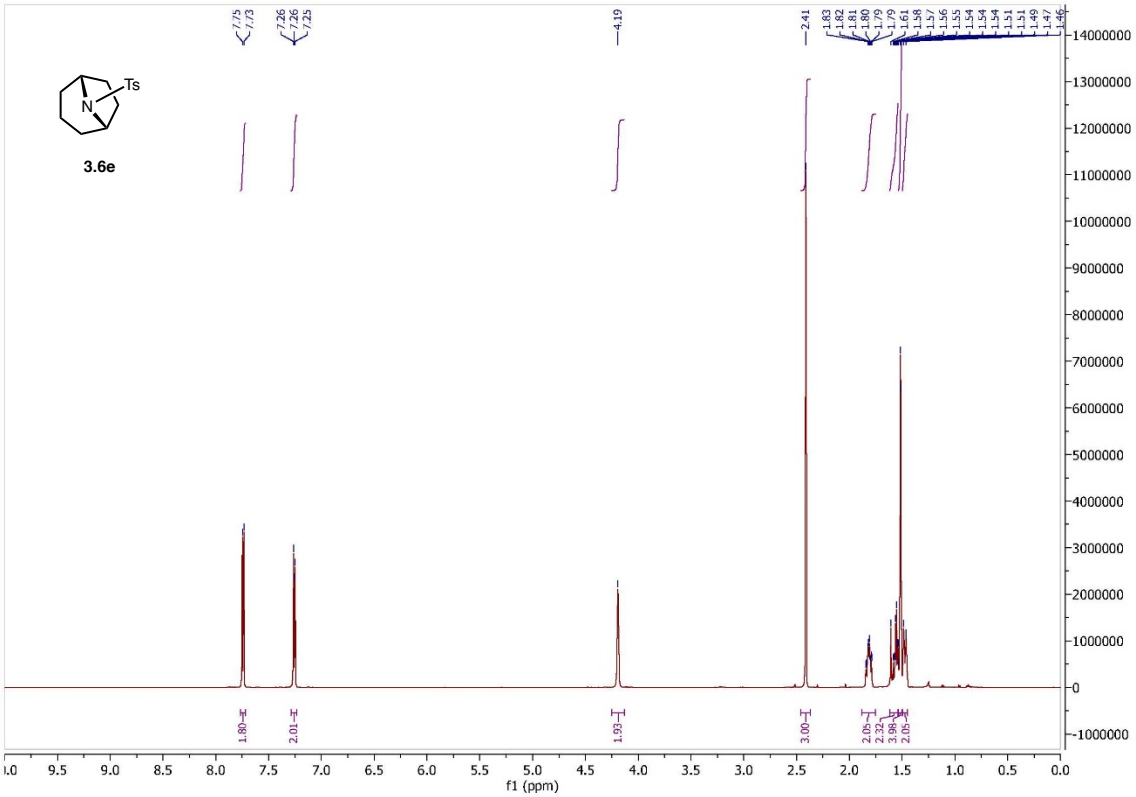

OMe
N
S
O O
Ph
3.6b
f1 (ppm)

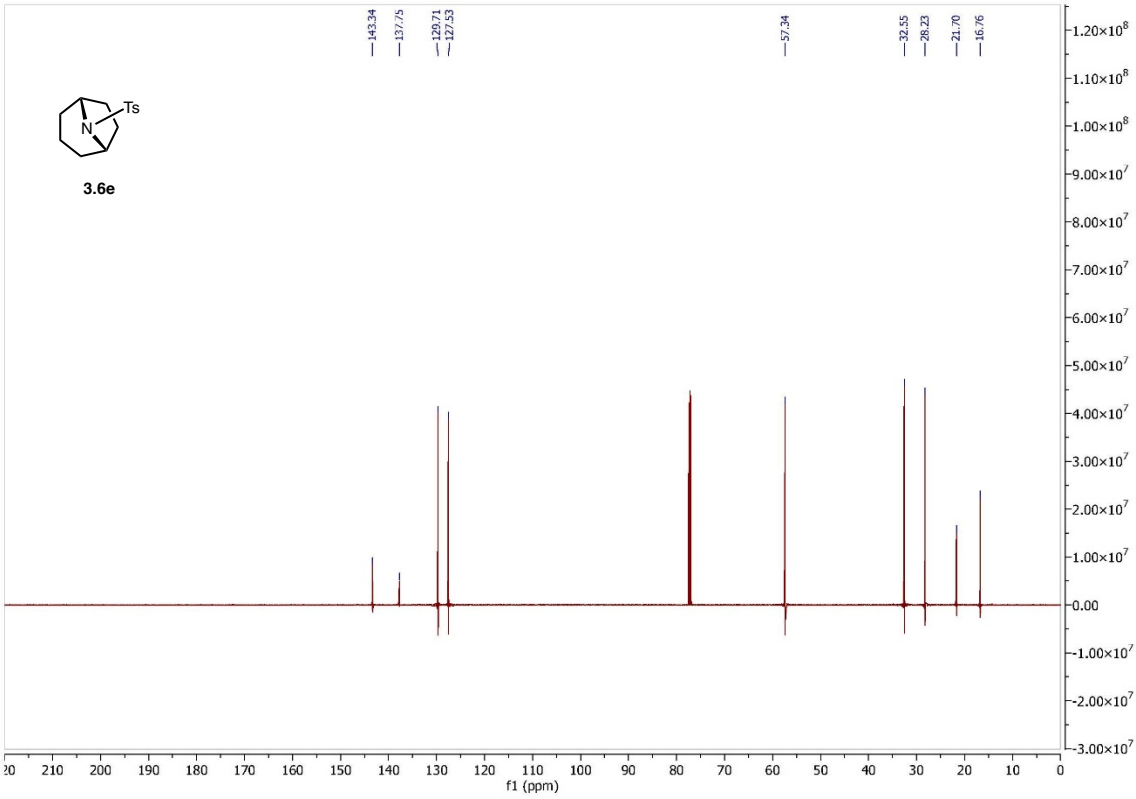

NTs
3.6c
f1 (ppm)

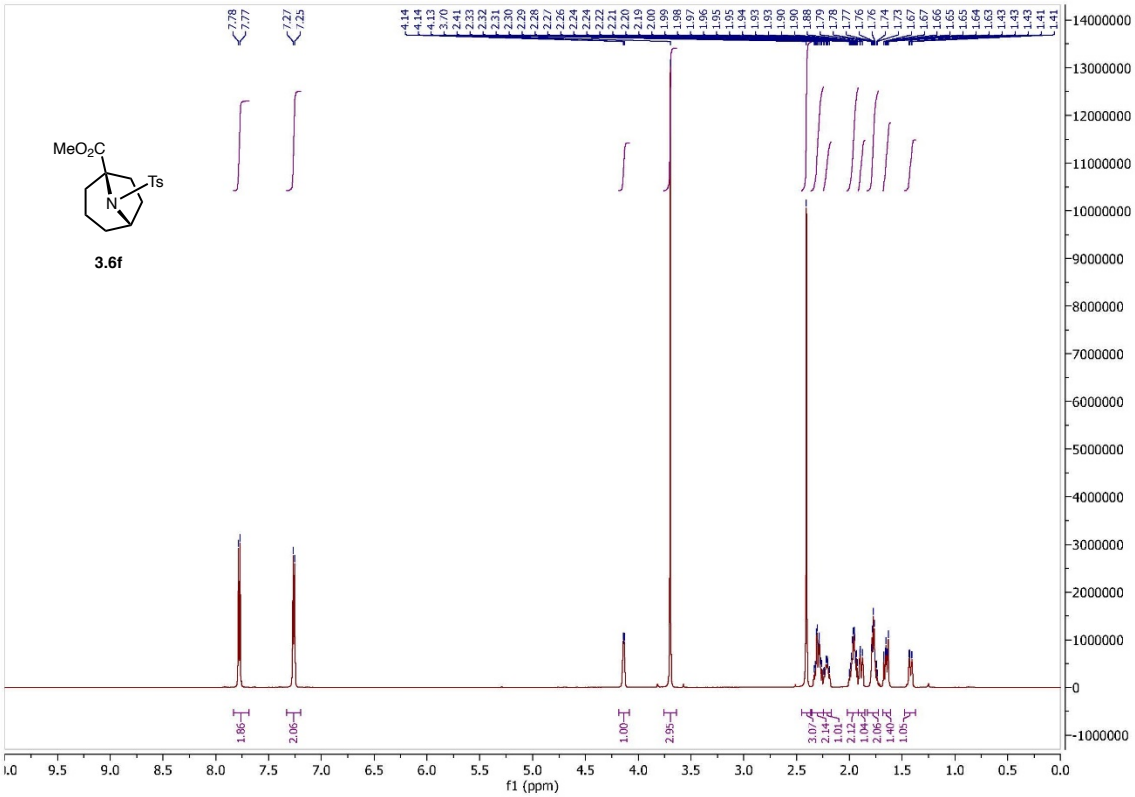

NTs
3.6c
f1 (ppm)

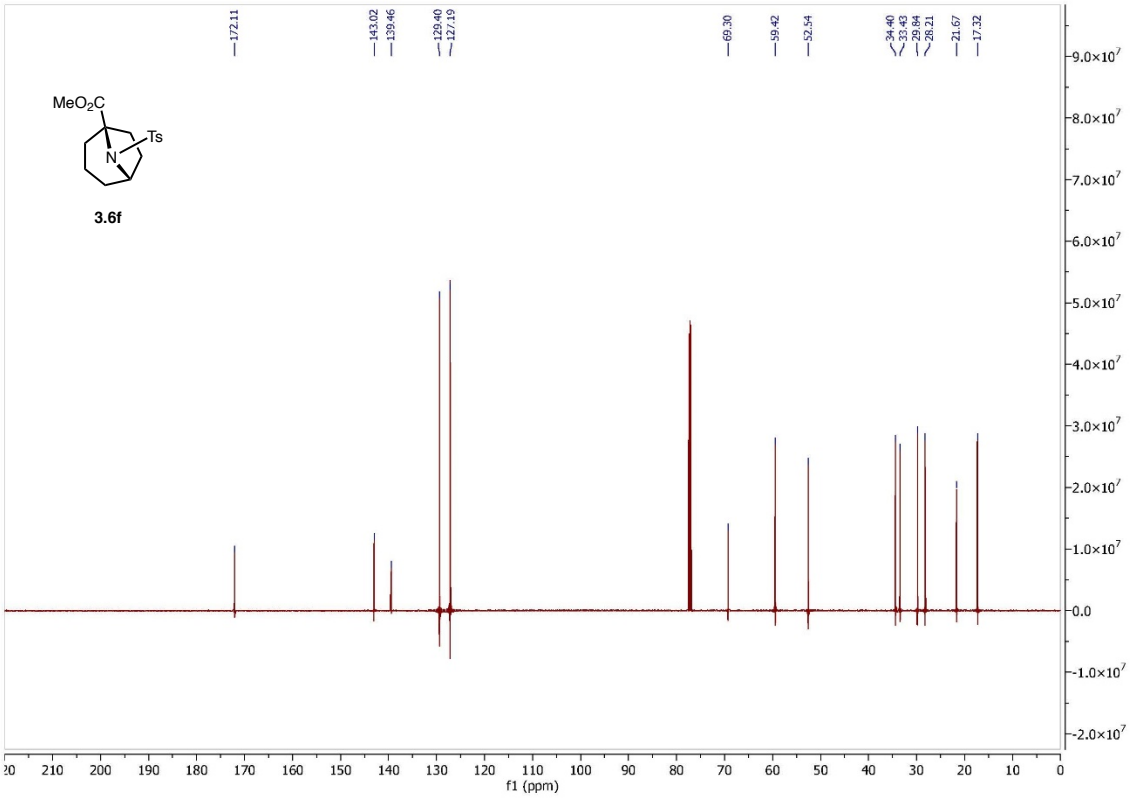

N
Ts
3.6d
f1 (ppm)

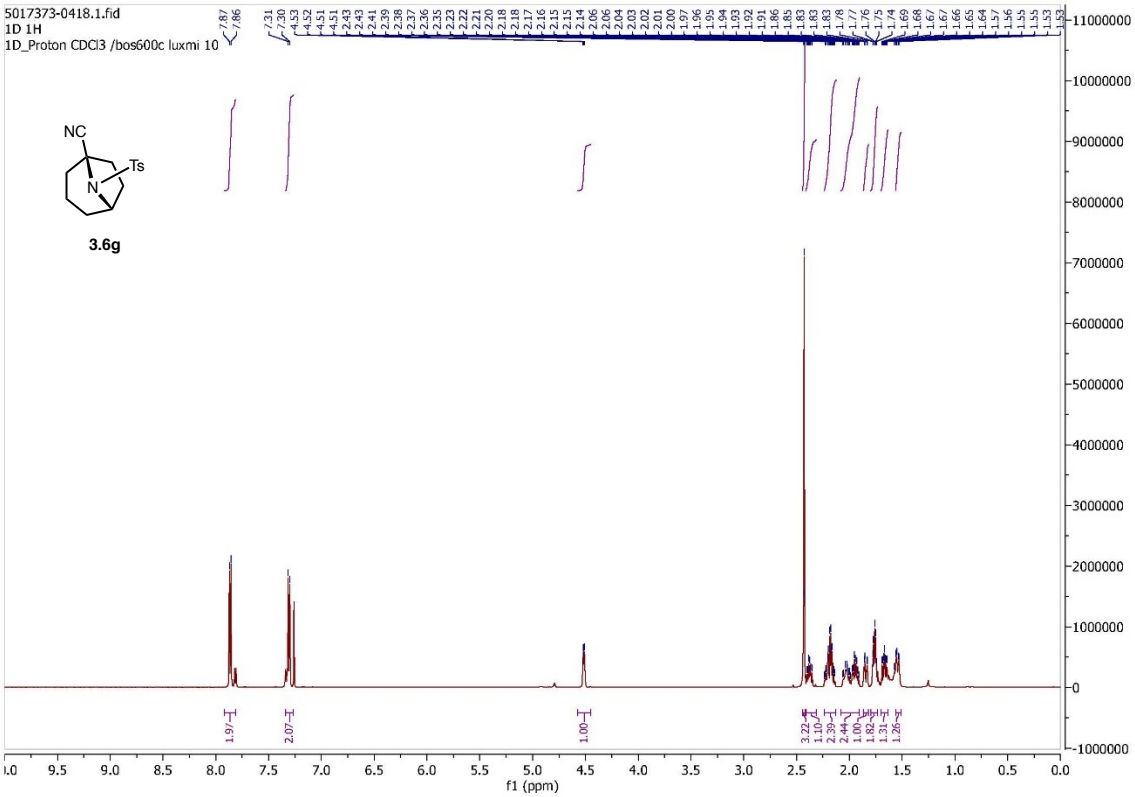

N
Ts
3.6d
f1 (ppm)

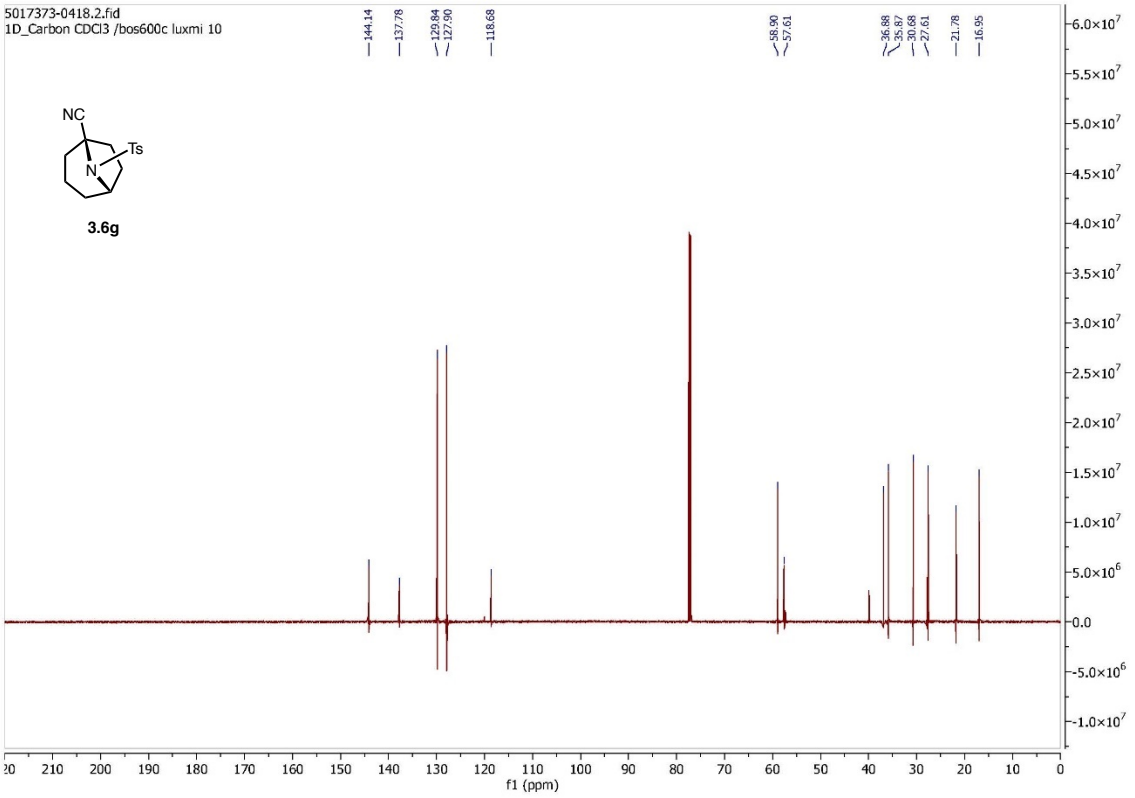

Ts
N
3.6e
7.75
7.73
7.26
7.26
7.25
4.19
2.41
1.83
1.82
1.81
1.80
1.79
1.61
1.58
1.57
1.56
1.55
1.54
1.54
1.54
1.51
1.51
1.49
1.47
1.46
1.80
2.01
1.93
3.00
2.06
2.32
3.98
2.05
f1 (ppm)

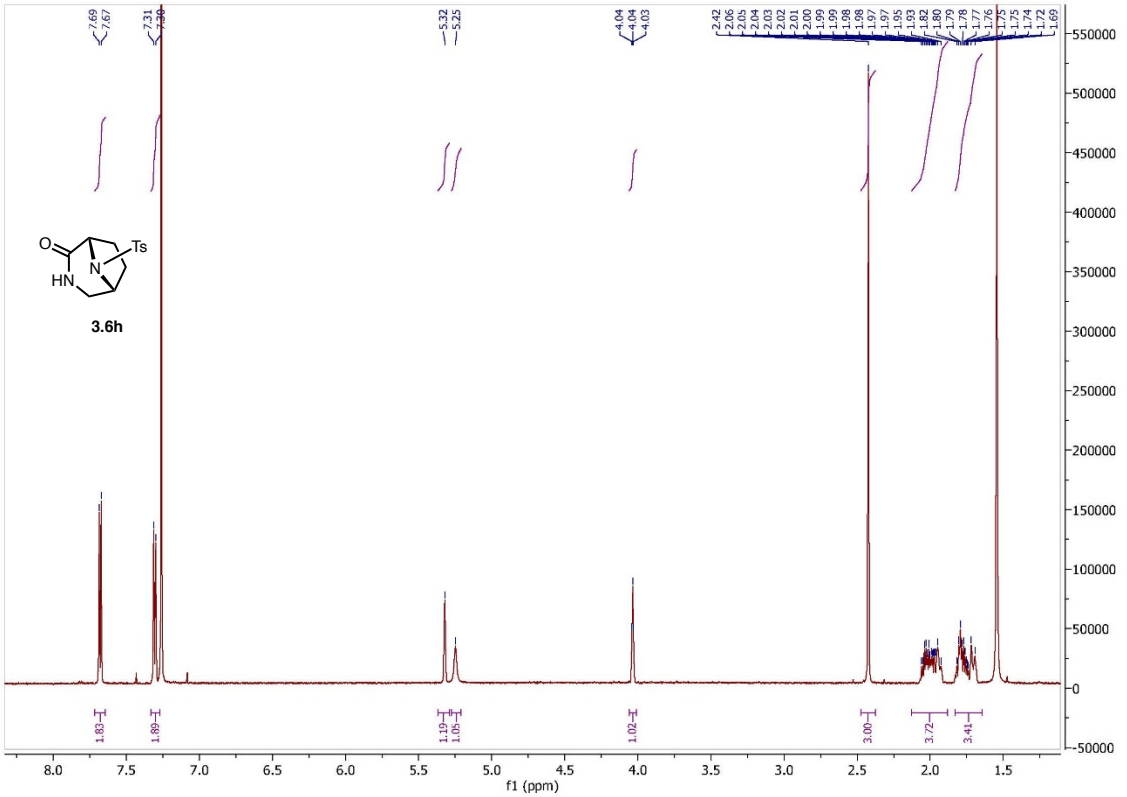

Ts
N
3.6e
143.34
137.75
129.71
127.53
57.34
32.55
28.23
21.70
16.76
f1 (ppm)

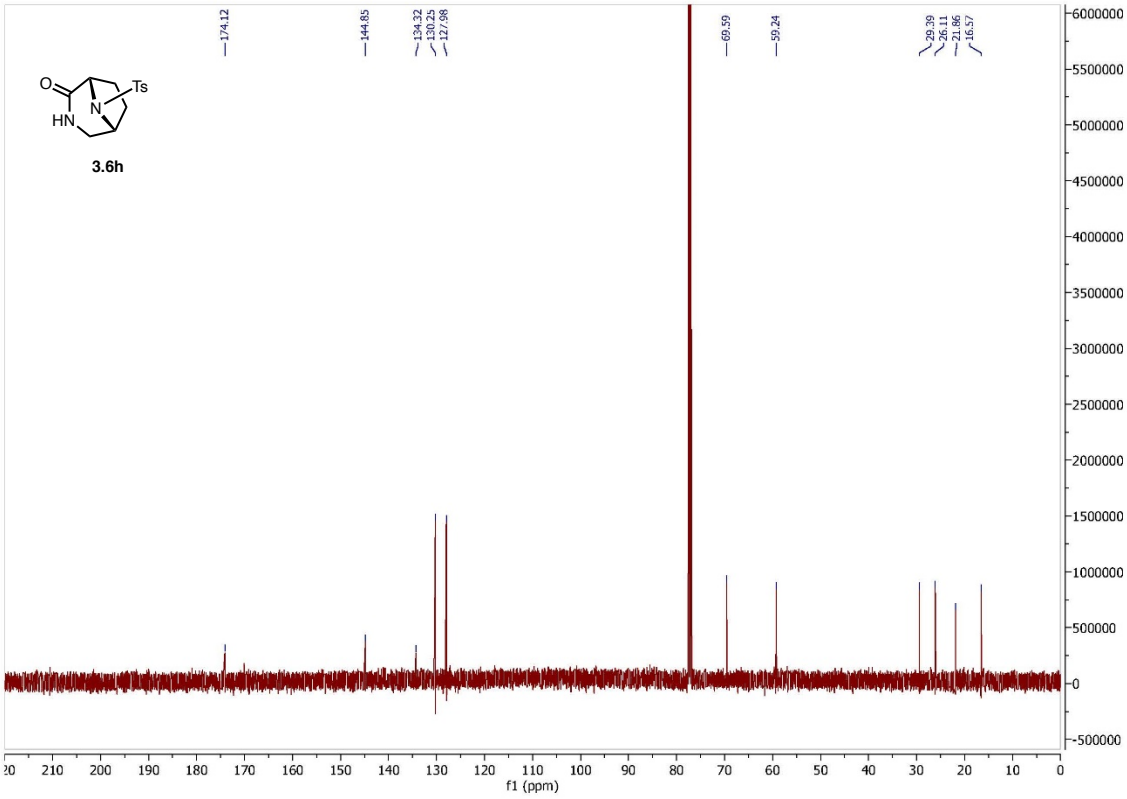

MeO2C
Ts
N
3.6f
f1 (ppm)

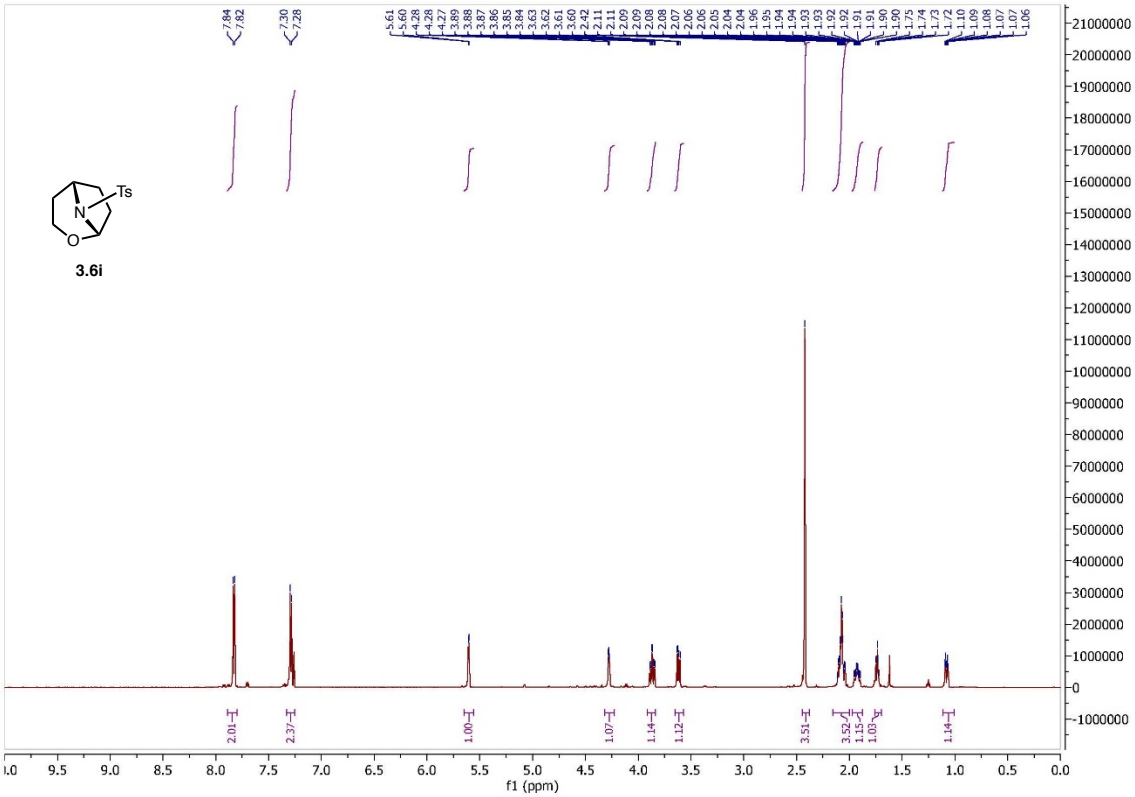

MeO2C
Ts
N
3.6f
f1 (ppm)

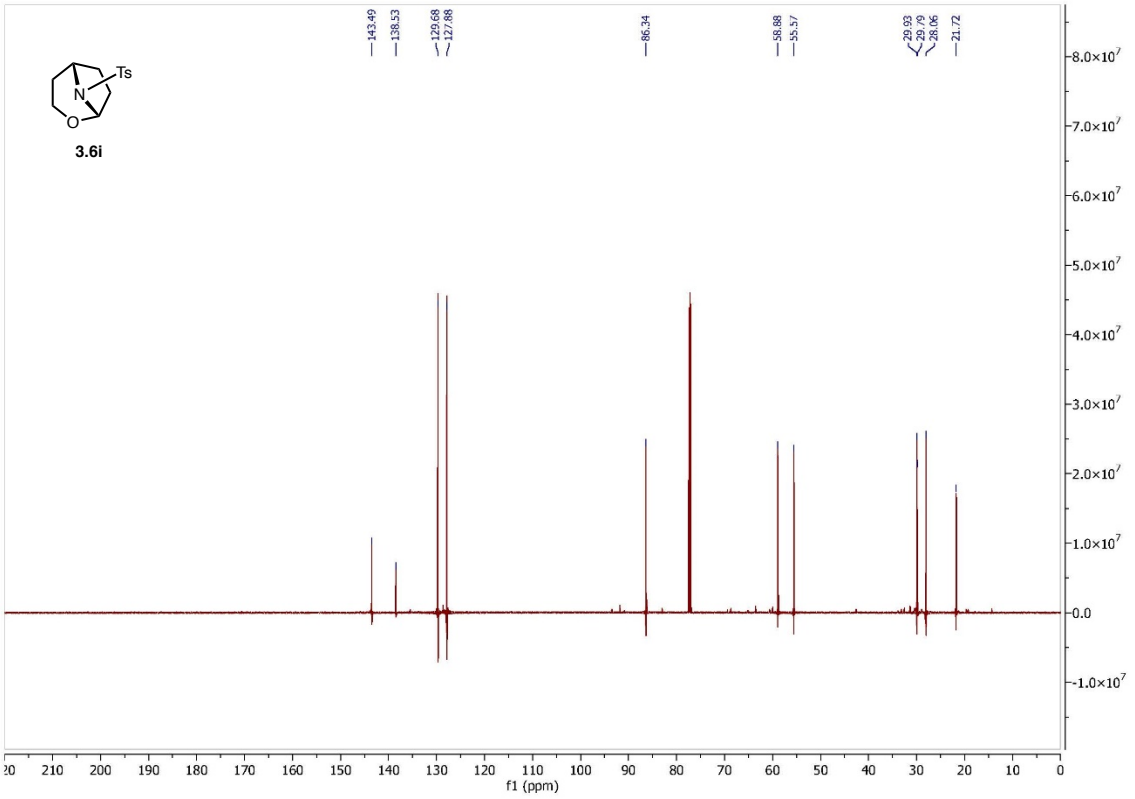

5017373-0418.1.fid
1D 1H
1D_Proton CDCl3 /bos600c luxmi 10
NC
Ts
N
3.6g
f1 (ppm)

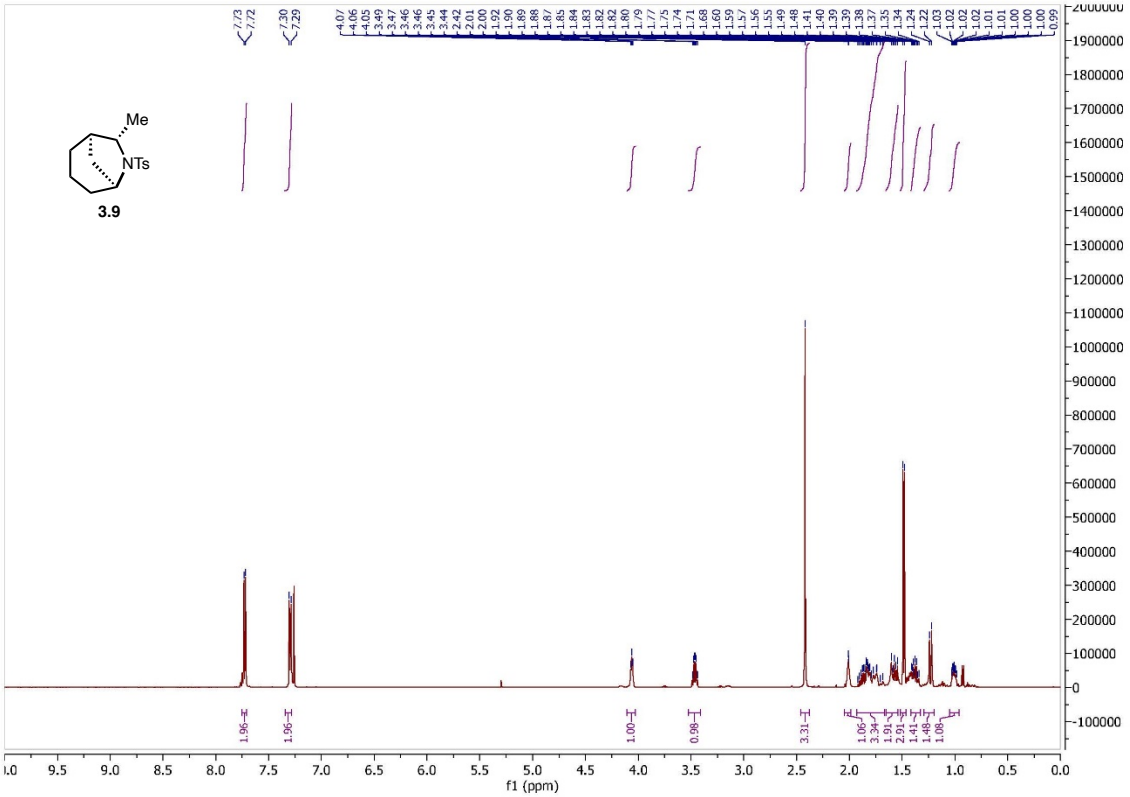

5017373-0418.2.fid
1D_Carbon CDCl3 /bos600c luxmi 10
144.14
137.78
129.84
127.90
118.68
58.90
57.61
36.88
35.87
30.68
27.61
21.78
16.95
NC
Ts
N
3.6g
f1 (ppm)

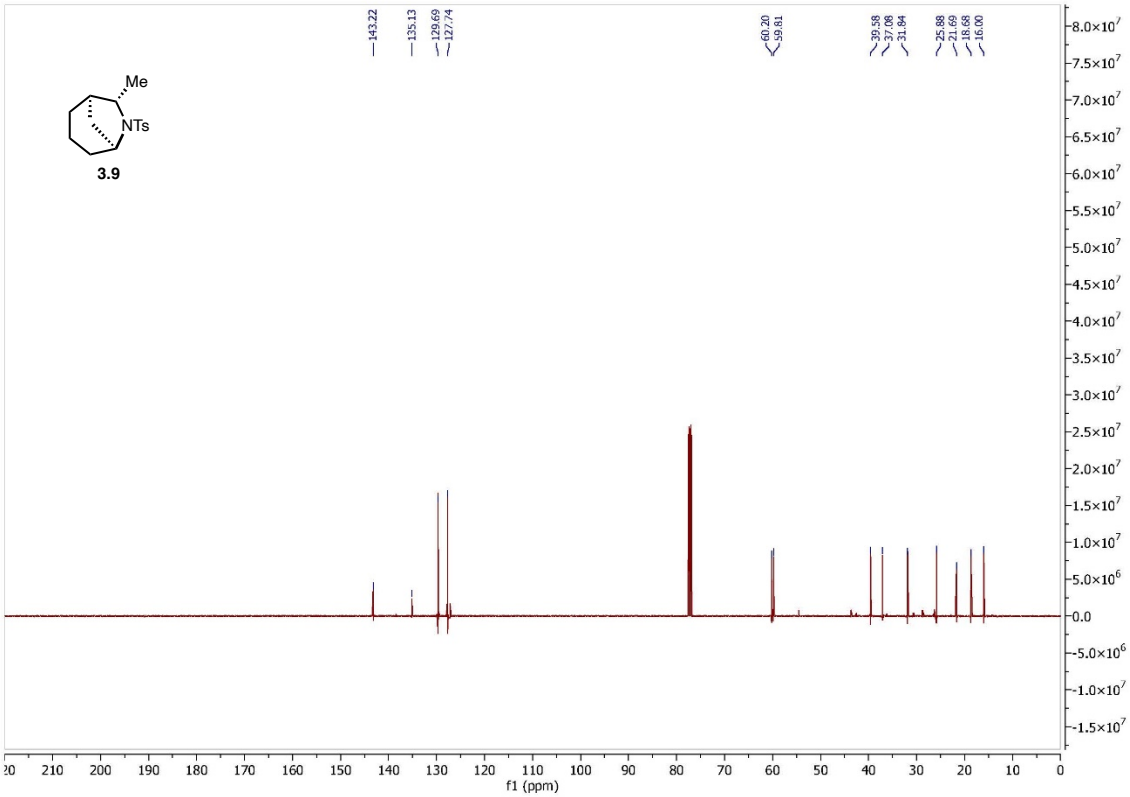

7.69
7.67
7.31
7.30
5.32
5.25
4.04
4.04
4.03
2.42
2.06
2.05
2.04
2.03
2.02
2.01
2.00
1.99
1.99
1.98
1.98
1.97
1.97
1.95
1.93
1.82
1.80
1.79
1.78
1.77
1.76
1.75
1.75
1.74
1.72
1.69
O
HN
N
Ts
3.6h
1.83
1.89
1.19
1.05
1.02
3.00
3.72
3.41
f1 (ppm)

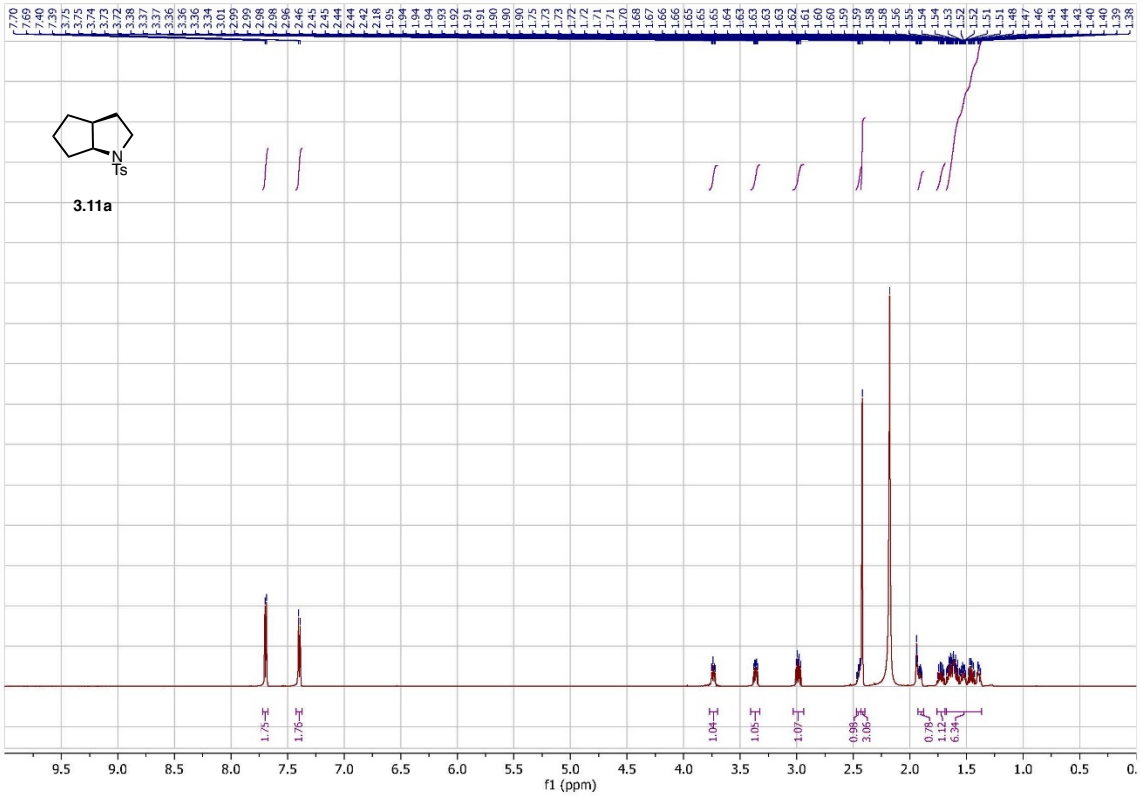

174.12
144.85
134.32
130.25
127.98
69.59
59.24
29.39
26.11
21.86
16.57
O
HN
N
Ts
3.6h
f1 (ppm)

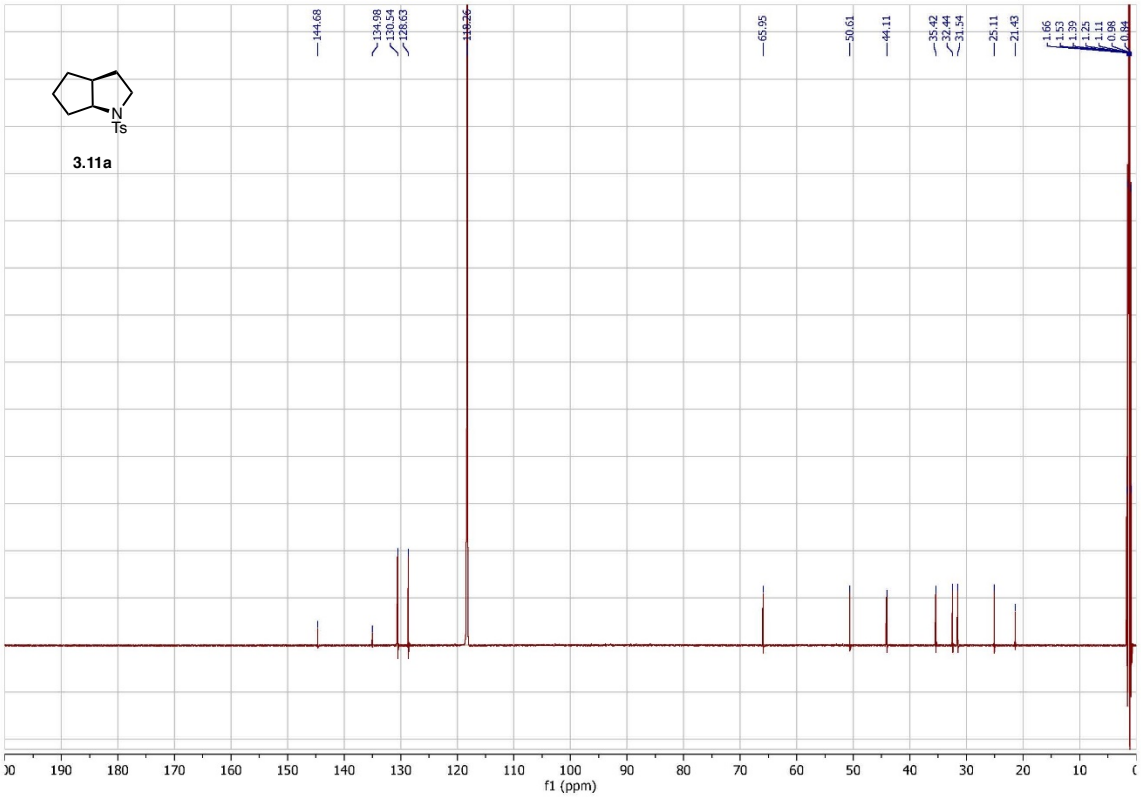

Ts
N
O
3.6i
f1 (ppm)


Ts
N
O
3.6i
f1 (ppm)


Me
NTs
3.9
f1 (ppm)


Me
NTs
3.9
f1 (ppm)


N
Ts
3.11a
f1 (ppm)


N
Ts
3.11a
144.68
134.98
130.54
128.63
118.26
65.95
50.61
44.11
35.42
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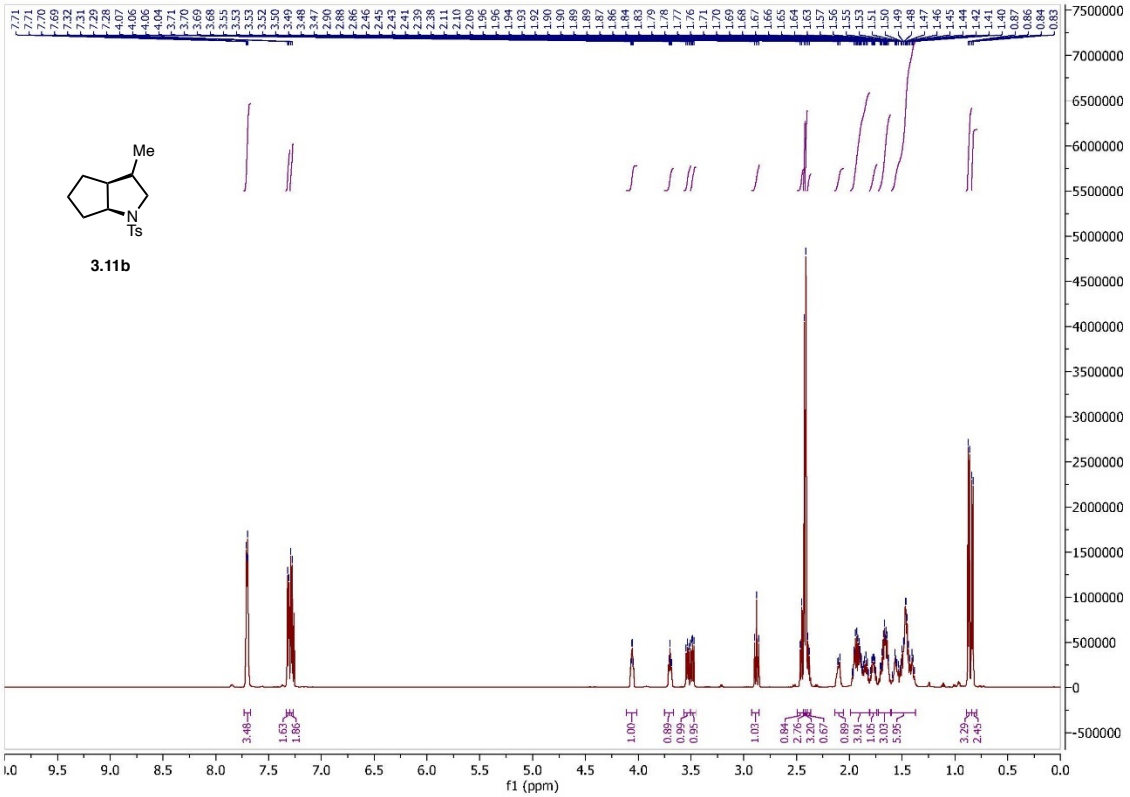
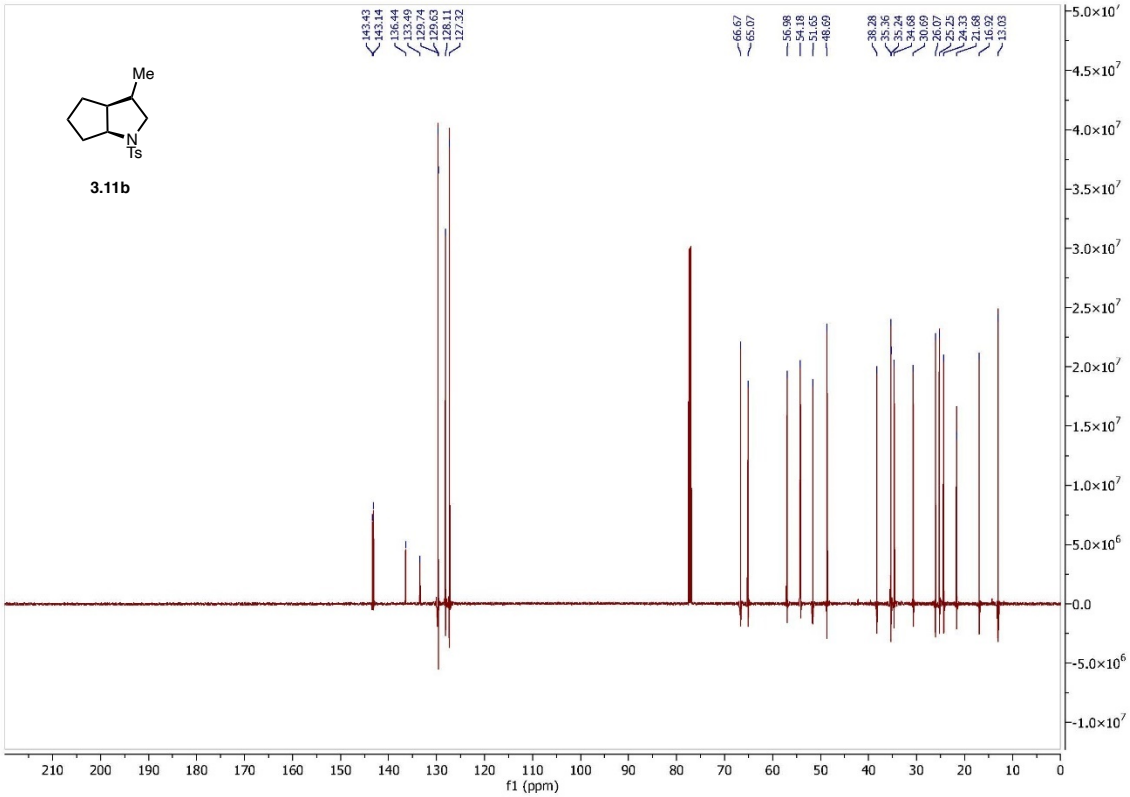
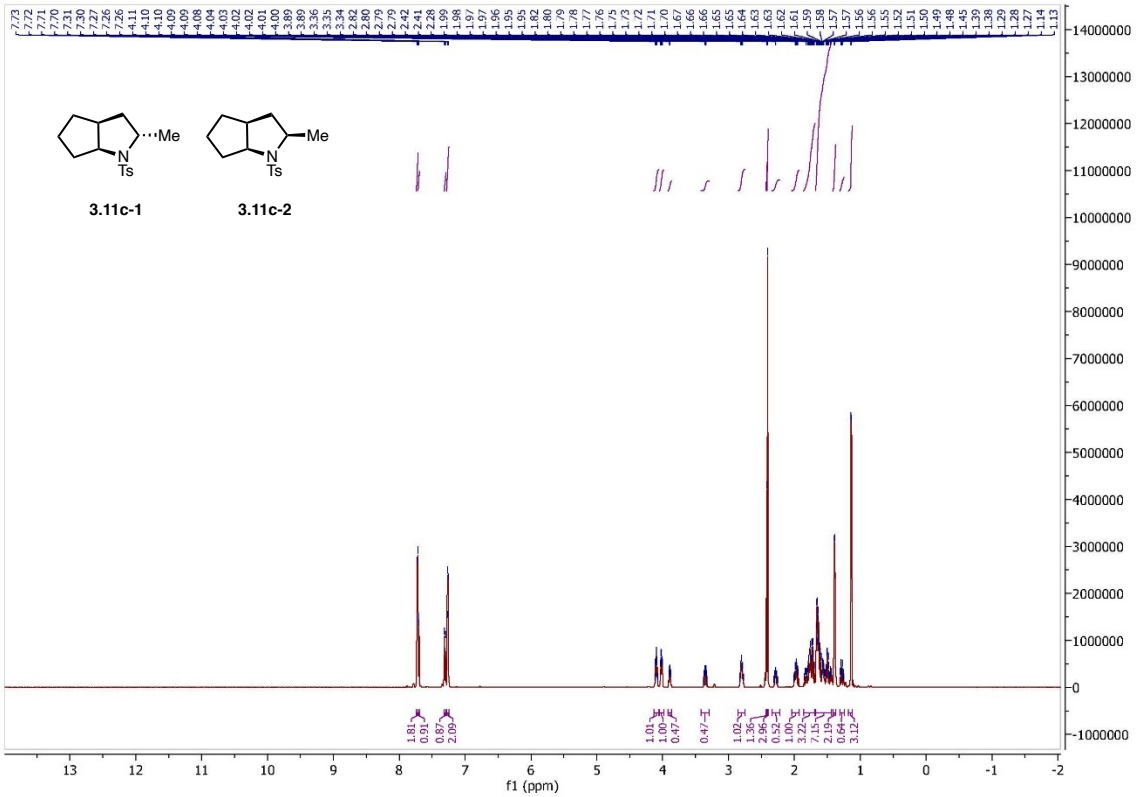
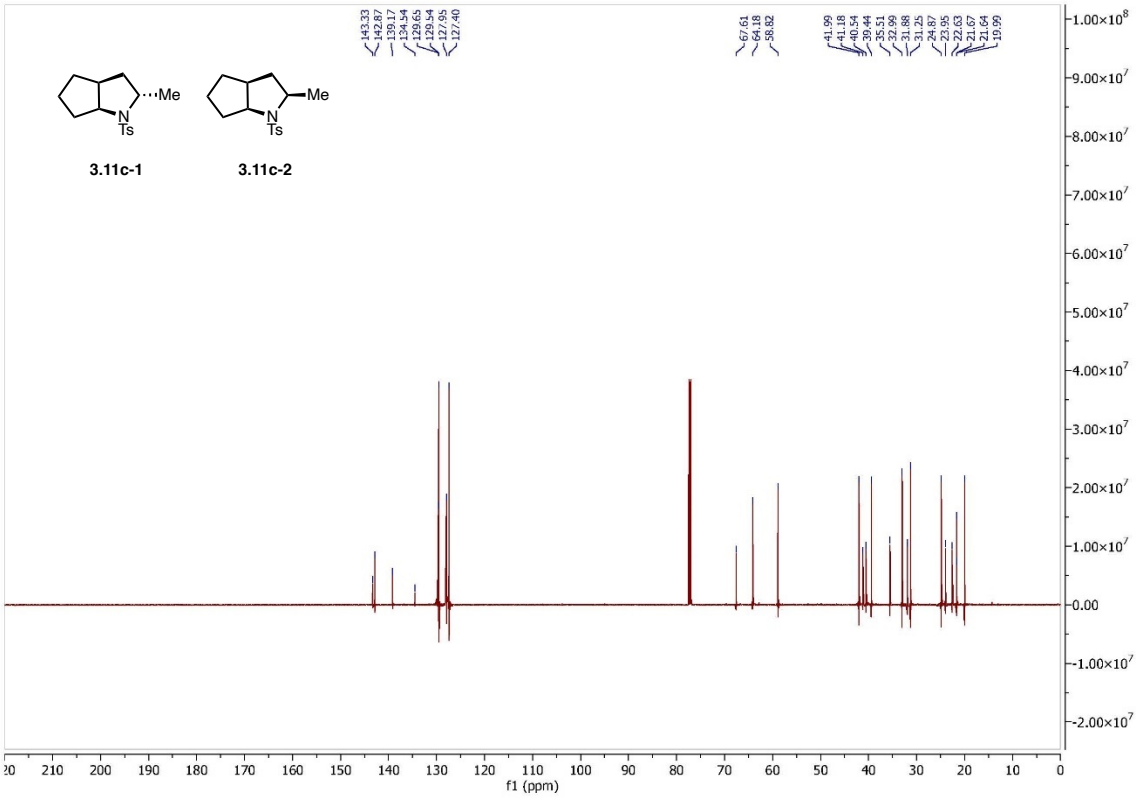
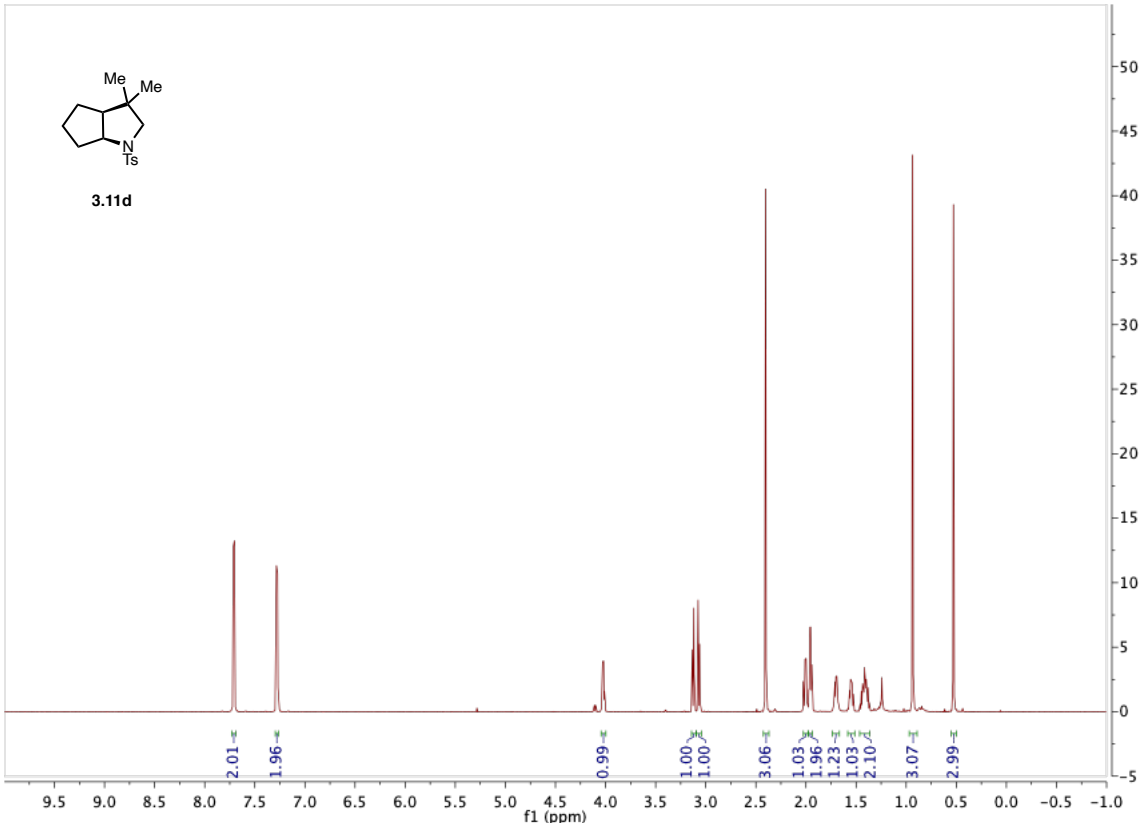
21.43
f1 (ppm)

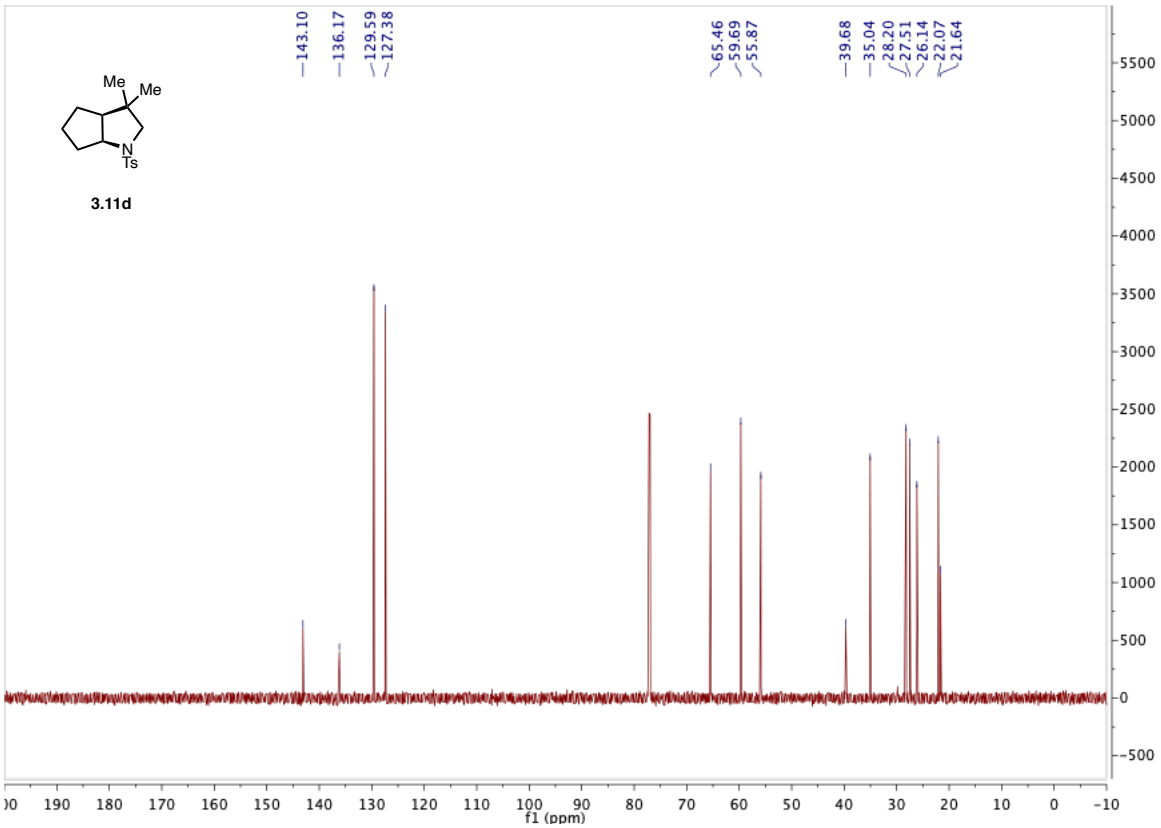

Me
N
Ts
3.11b
f1 (ppm)

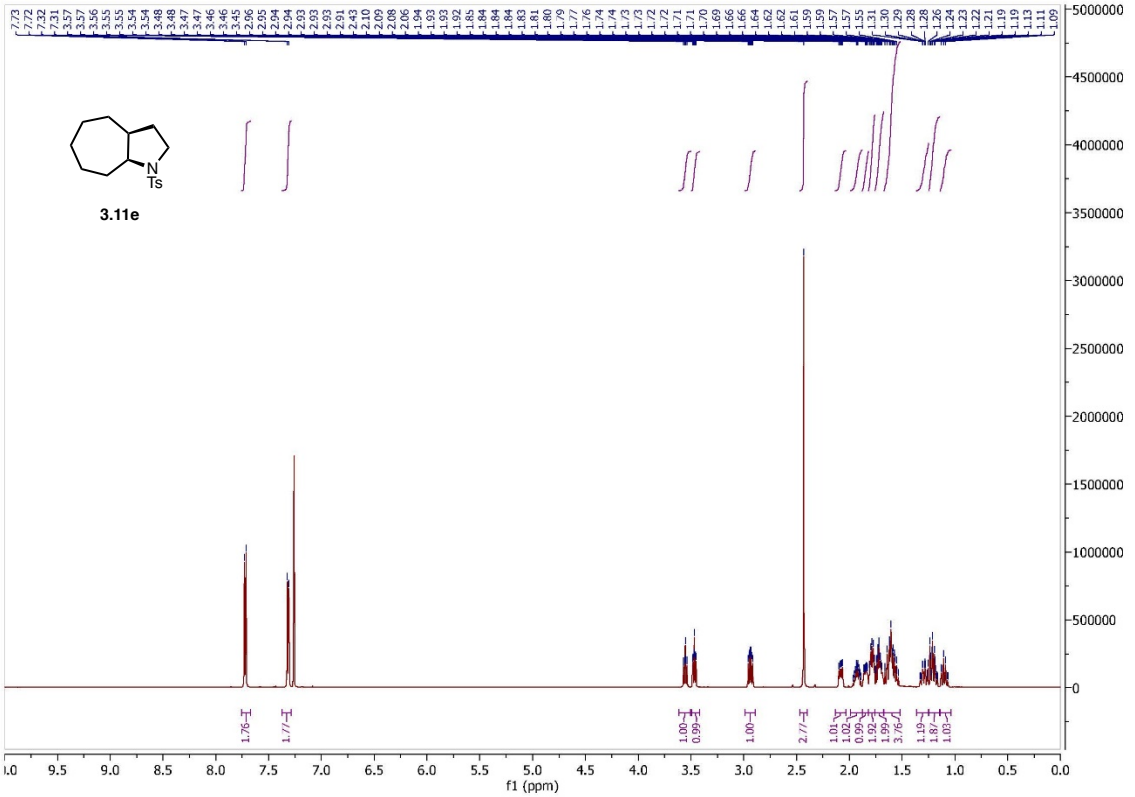

Me
N
Ts
3.11b
f1 (ppm)

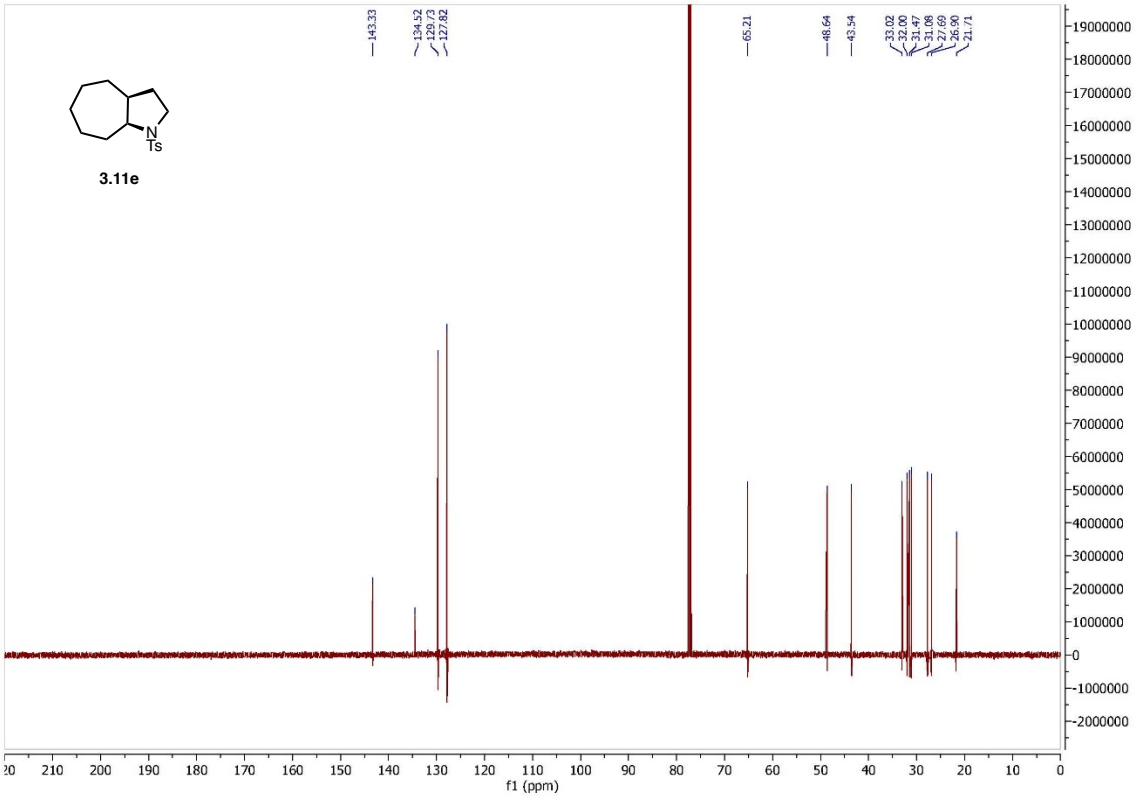

Me
N
Ts
Me
N
Ts
3.11c-1
3.11c-2
f1 (ppm)

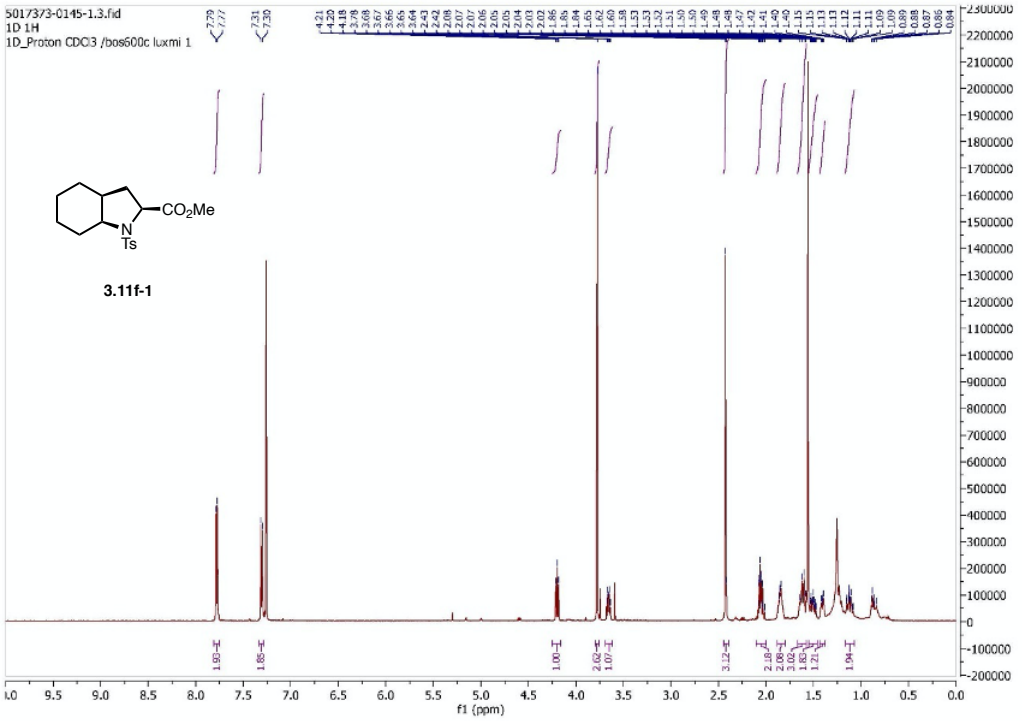

Me
N
Ts
Me
N
Ts
3.11c-1
3.11c-2
f1 (ppm)


Me
Me
N
Ts
3.11d
2.01
1.96
0.99
1.00
1.00
3.06
1.03
1.96
1.23
1.03
2.10
3.07
2.99
f1 (ppm)

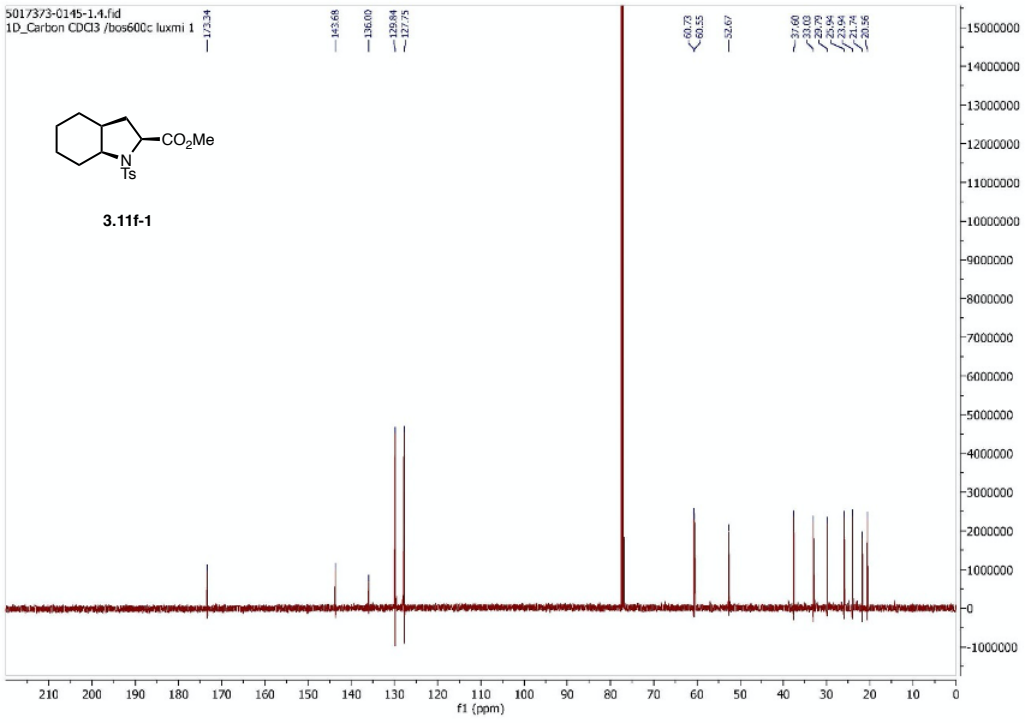

143.10
136.17
129.59
127.38
65.46
59.69
55.87
39.68
35.04
28.20
27.51
26.14
22.07
21.64
Me
Me
N
Ts
3.11d
f1 (ppm)


N
Ts
3.11e
f1 (ppm)

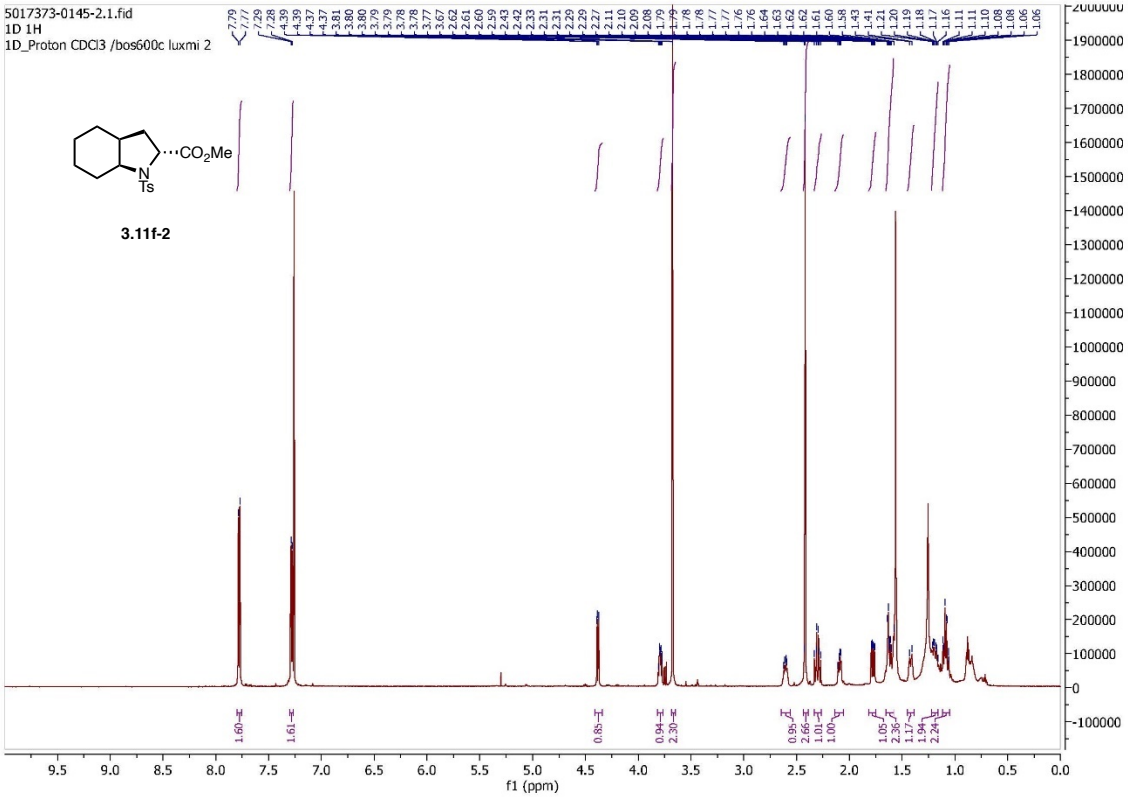

N
Ts
3.11e
143.33
134.52
129.73
127.82
65.21
48.64
43.54
33.02
32.00
31.47
31.08
27.69
26.90
21.71
f1 (ppm)

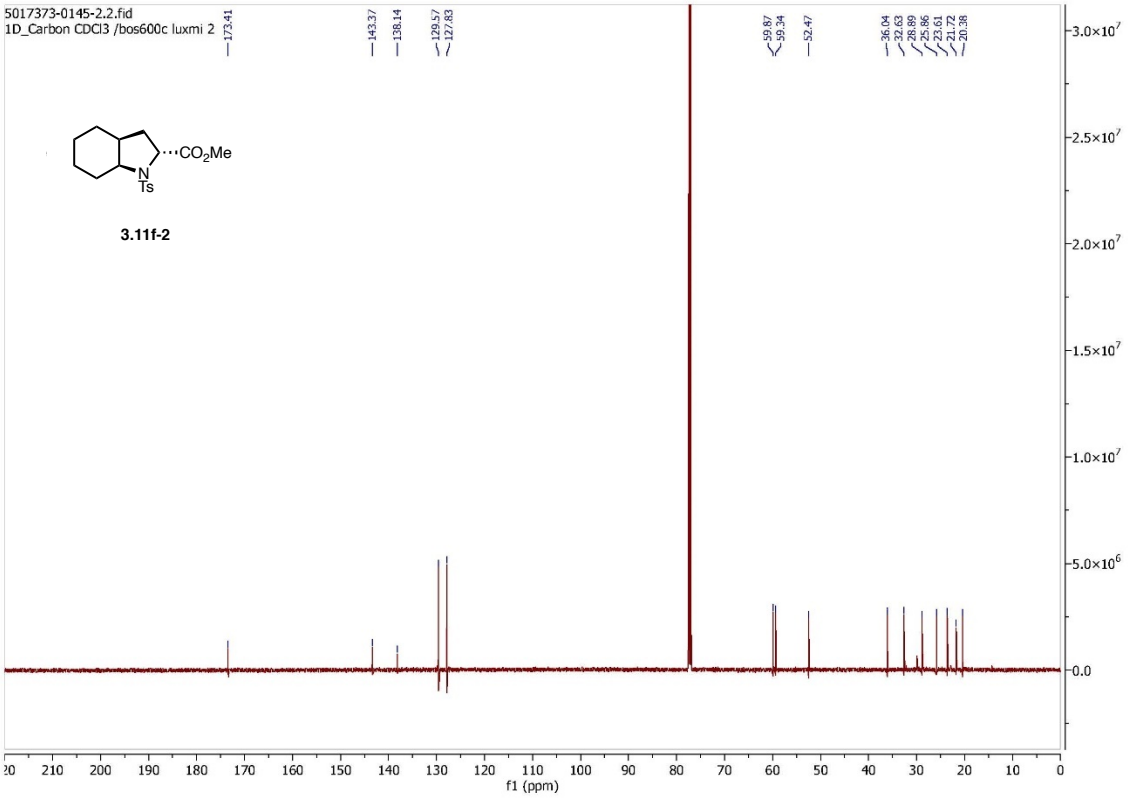

5017373-0145-1.3.fid
1D 1H
1D_Proton CDCl3 /bos600c luxmi 1
CO2Me
N
Ts
f1 (ppm)

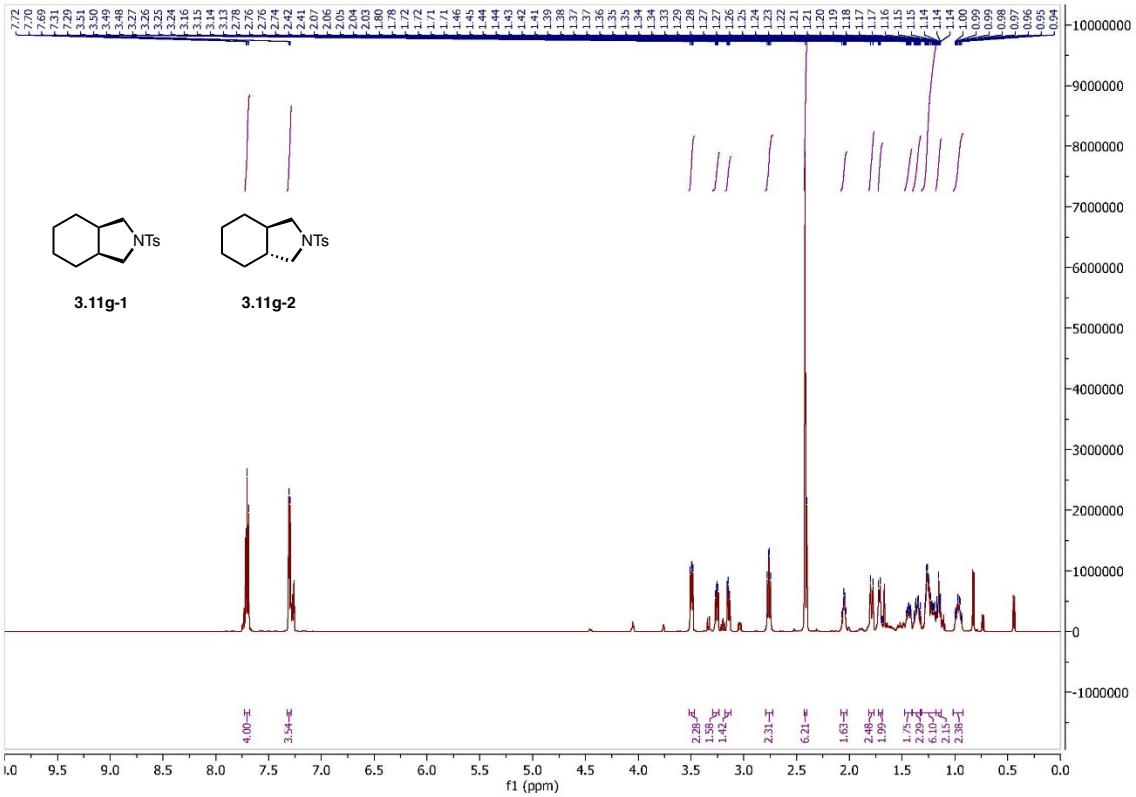
3.11f-1

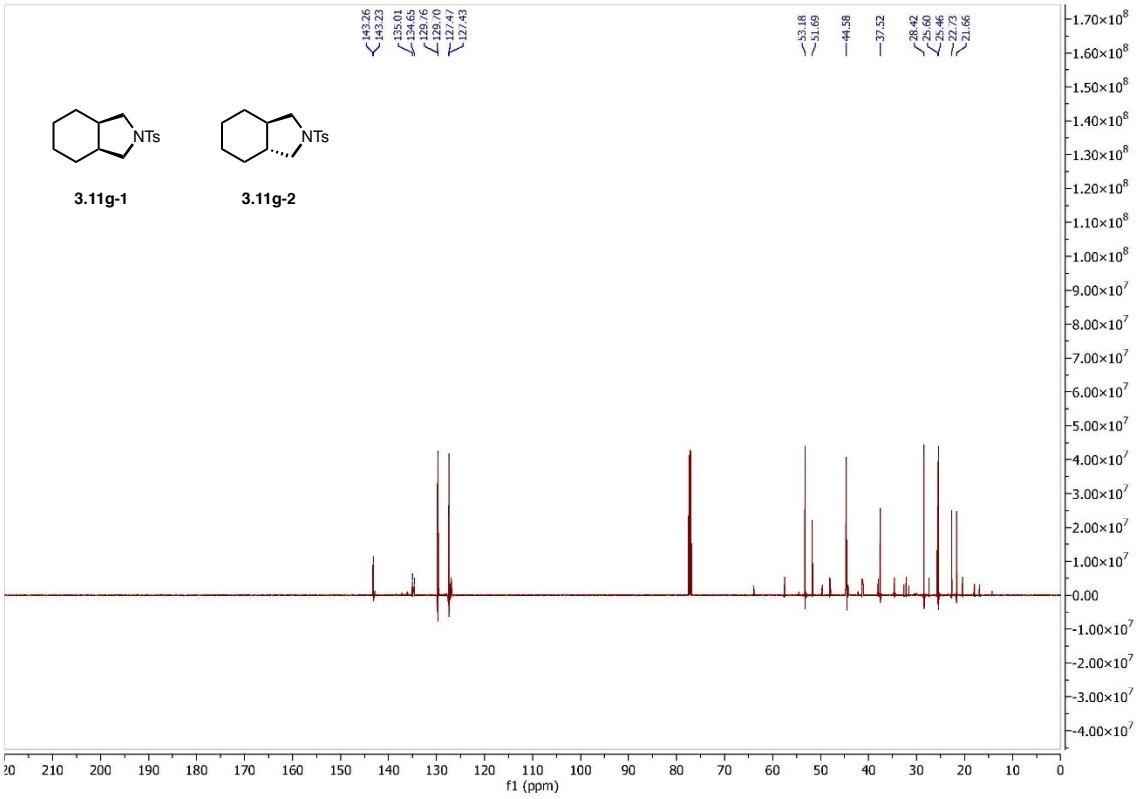

5017373-0145-1.4.fid
1D_Carbon CDCl3 /bos600c luxmi 1
CO2Me
N
Ts
f1 (ppm)

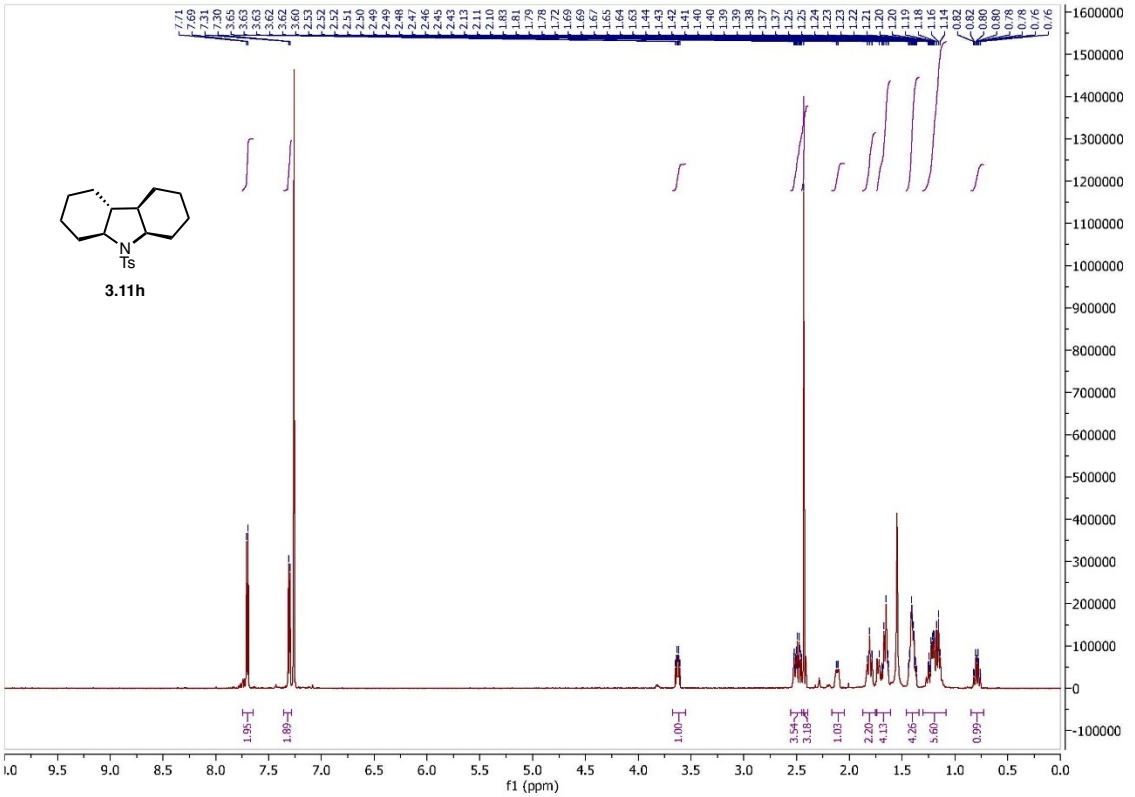
3.11f-1

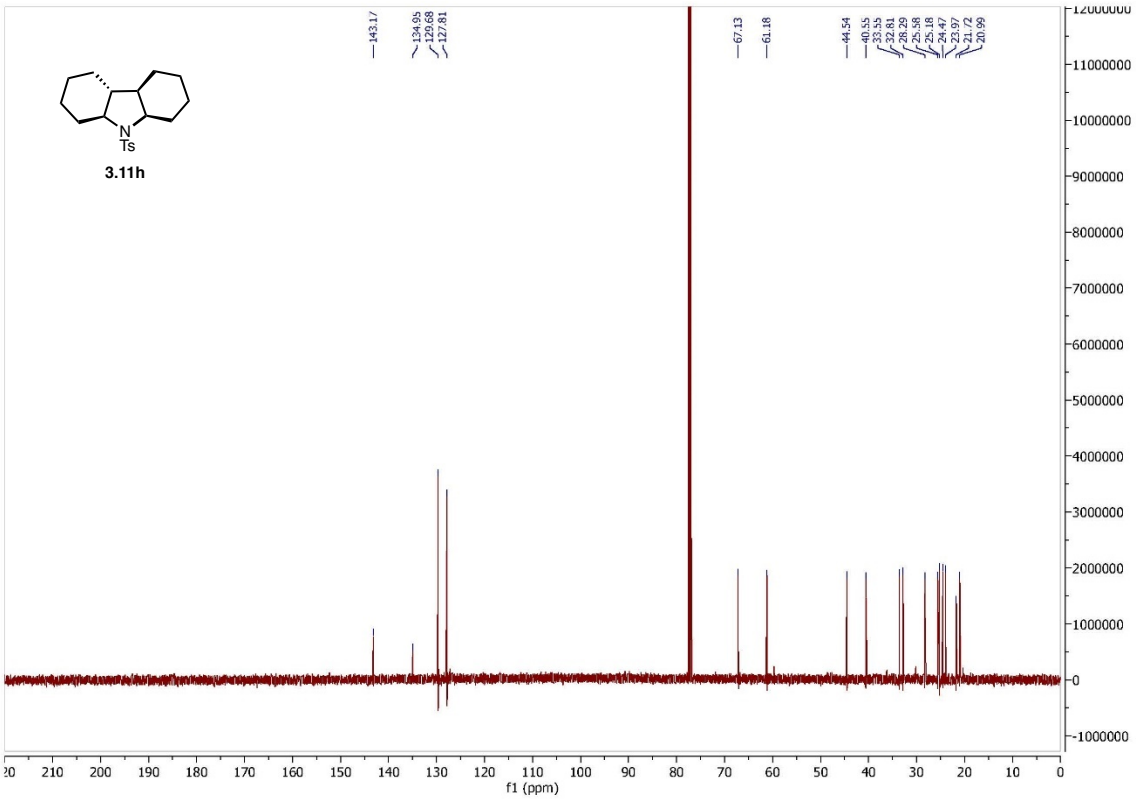

5017373-0145-2.1.fid
1D 1H
1D_Proton CDCl3 /bos600c luxmi 2
CO2Me
N
Ts
3.11f-2
f1 (ppm)

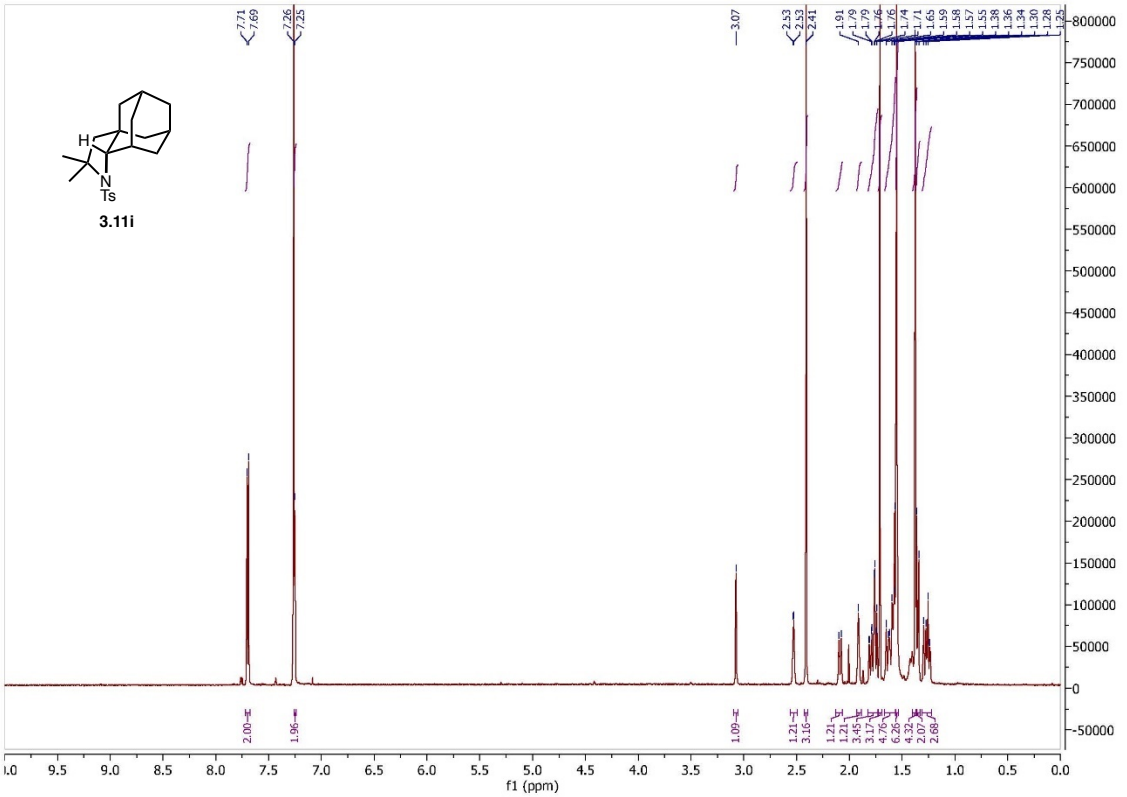

5017373-0145-2.2.fid
1D_Carbon CDCl3 /bos600c luxmi 2
CO2Me
N
Ts
3.11f-2
f1 (ppm)

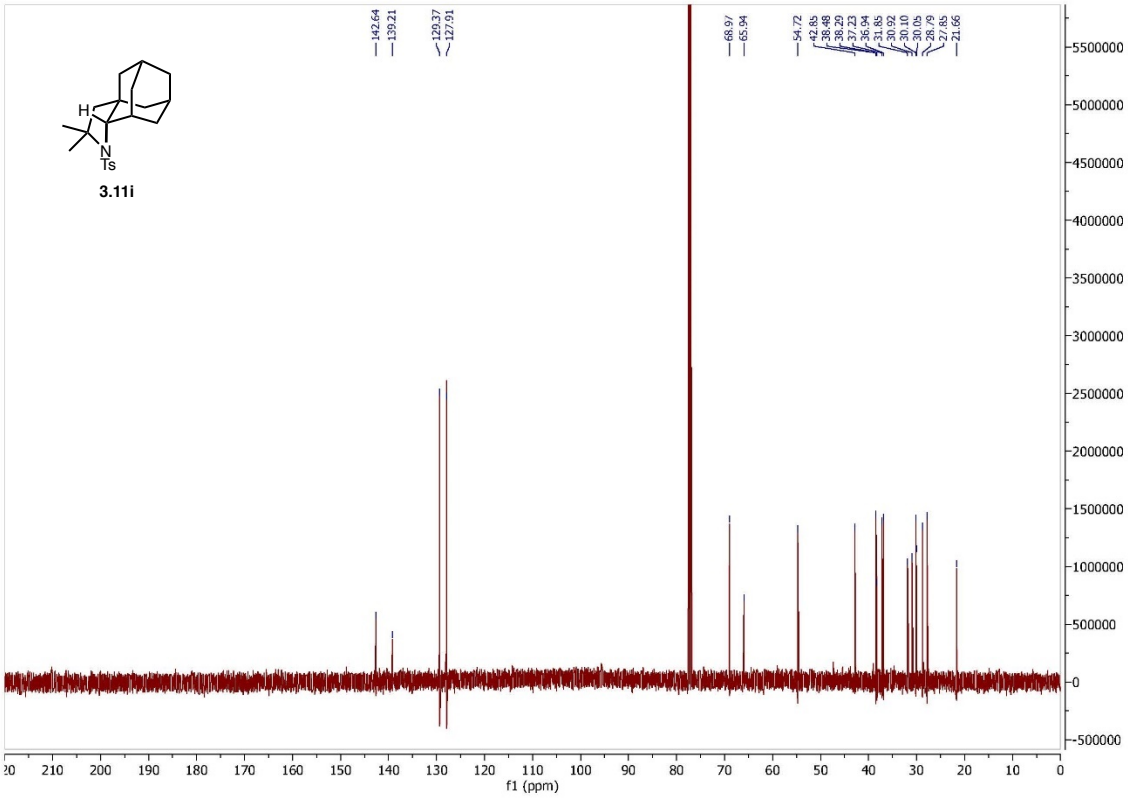

NTs
NTs
3.11g-1
3.11g-2
f1 (ppm)

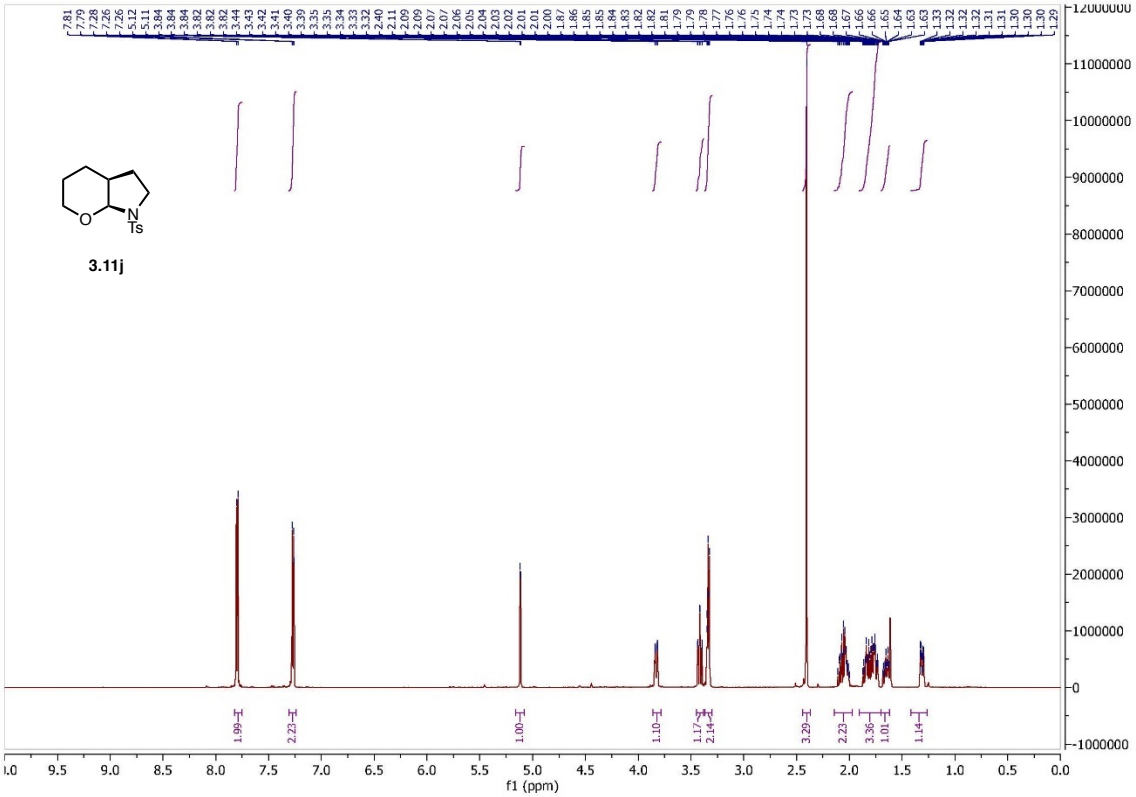

NTs
NTs
3.11g-1
3.11g-2
f1 (ppm)

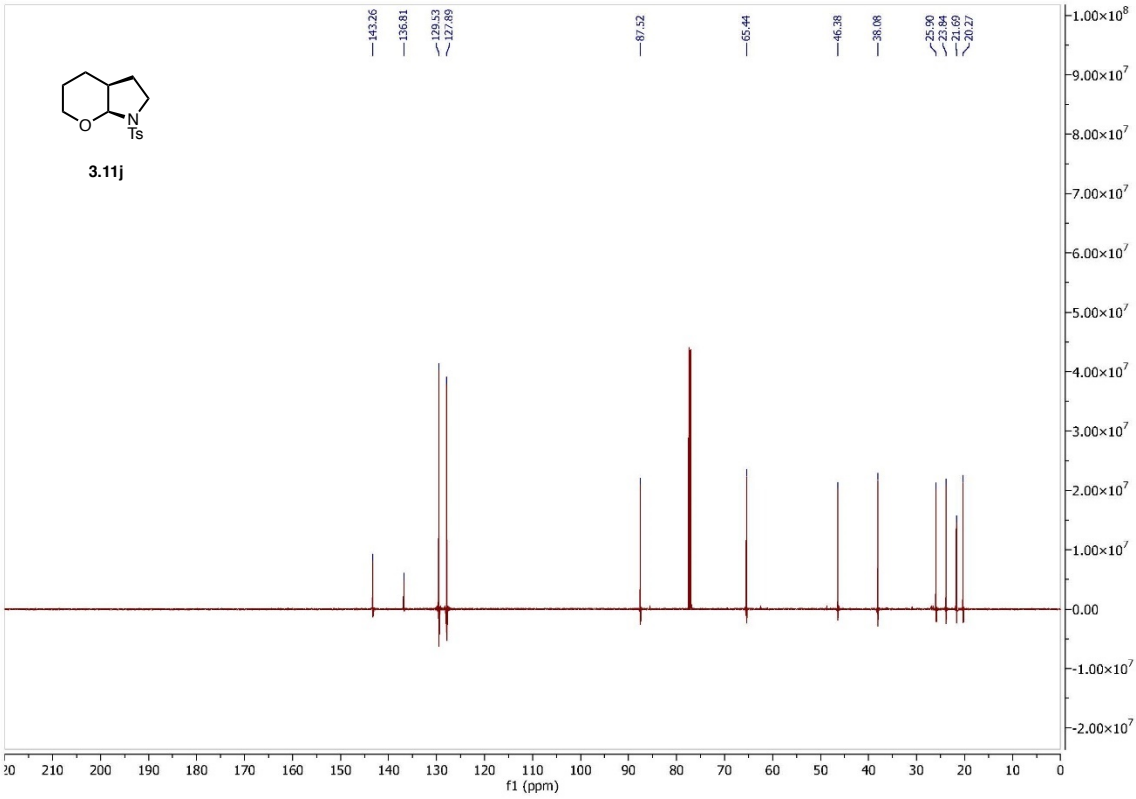

N
Ts
3.11h
f1 (ppm)

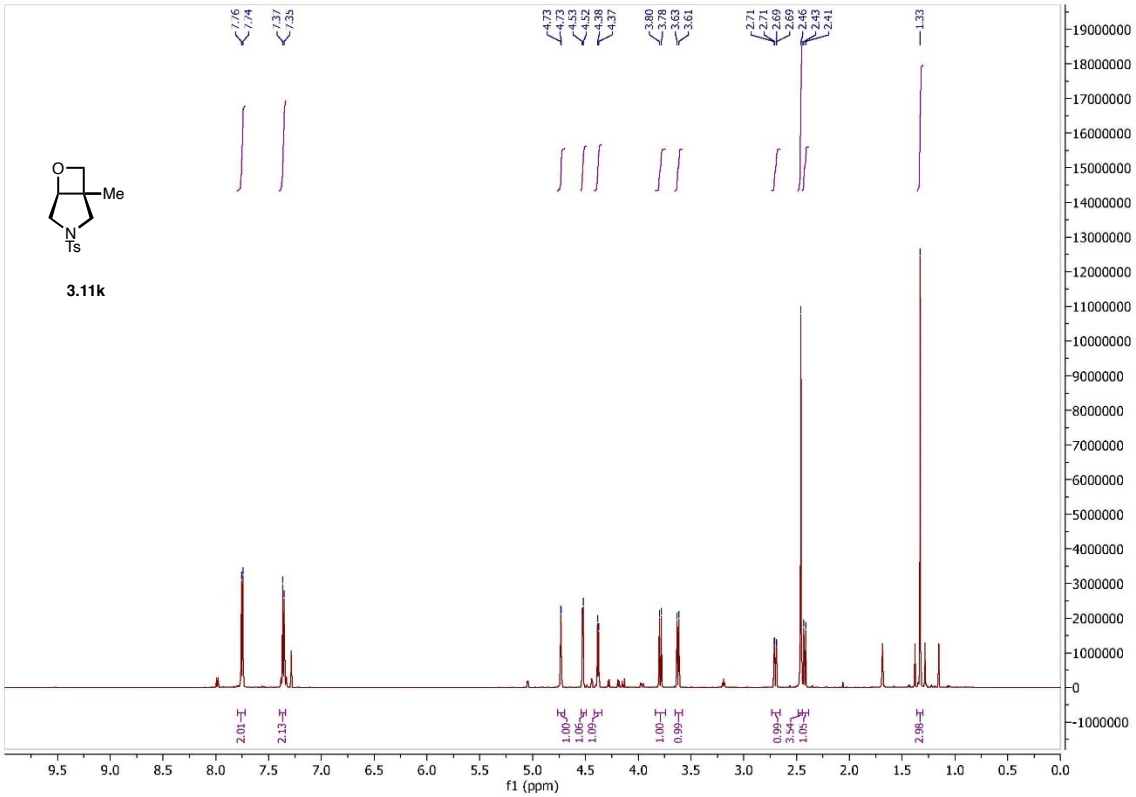

N
Ts
3.11h
f1 (ppm)

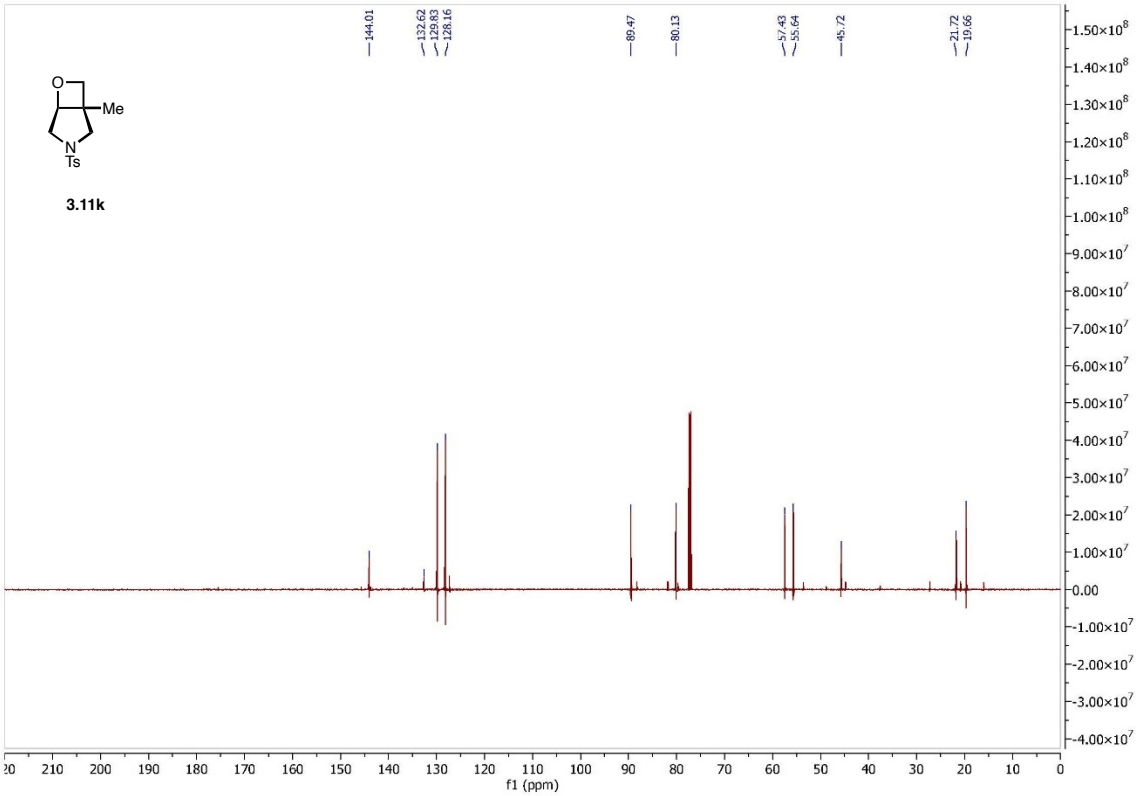

H
N
Ts
3.11i
f1 (ppm)

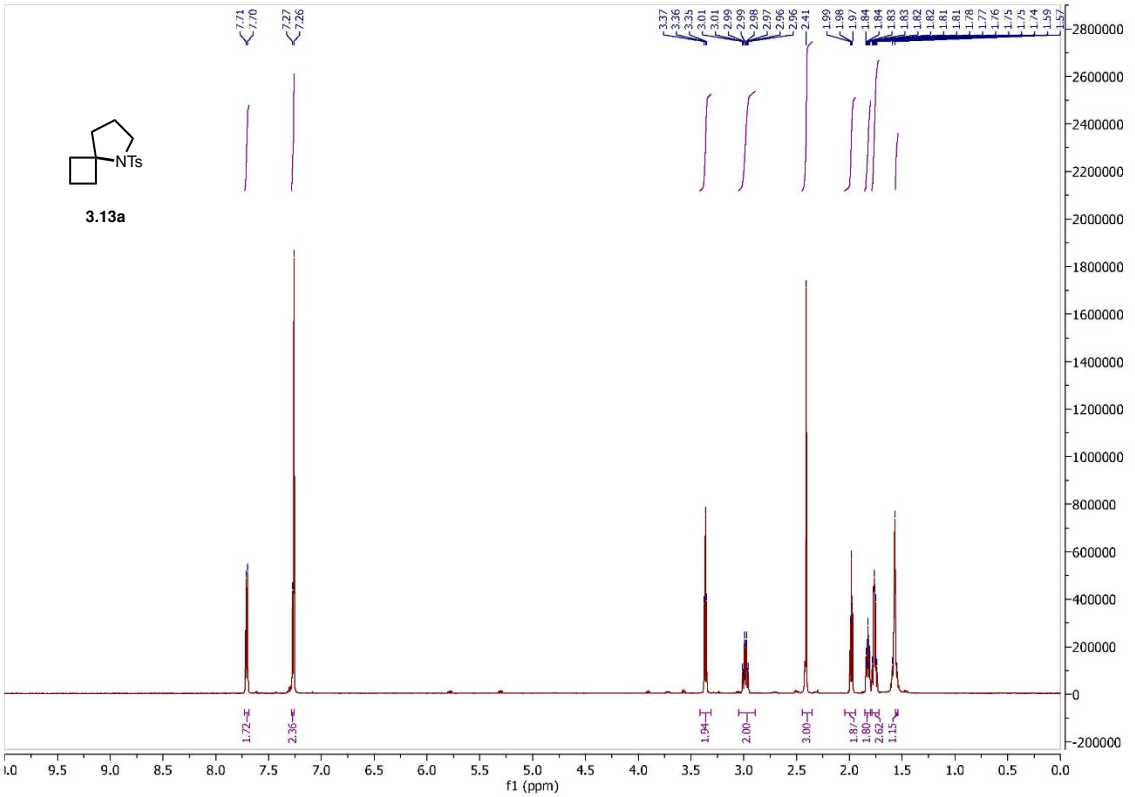

H
N
Ts
3.11i
f1 (ppm)

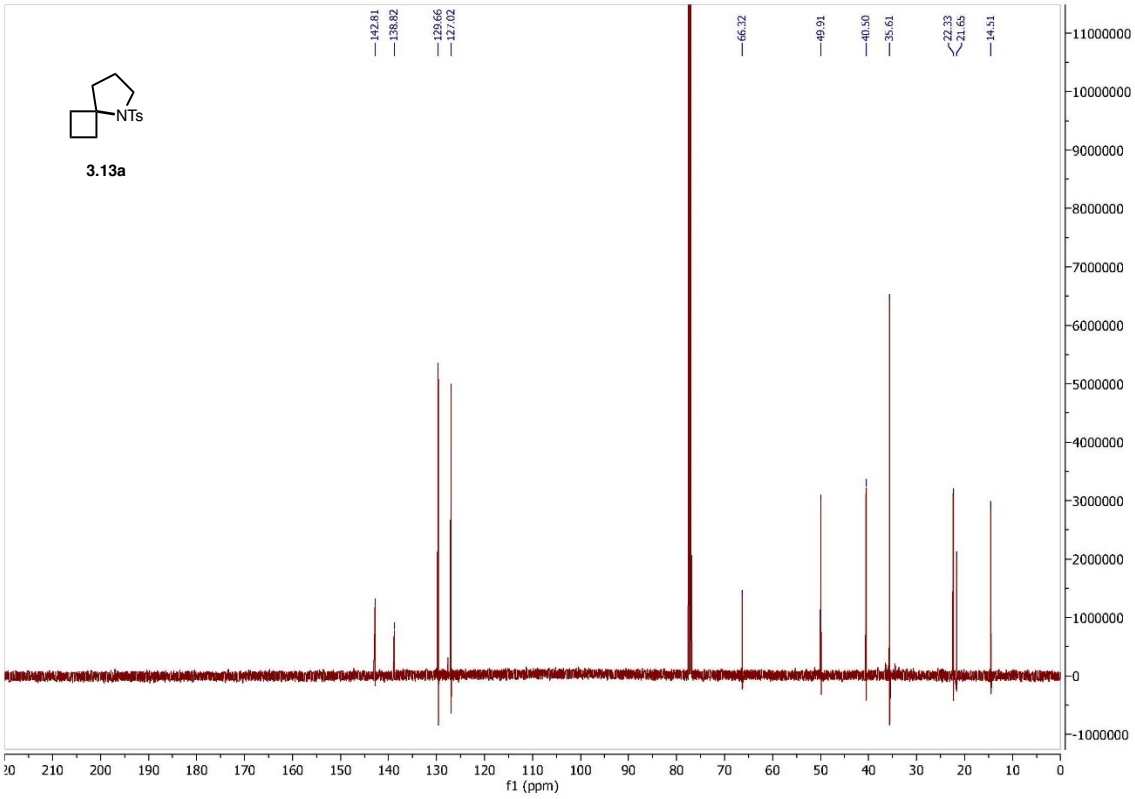

3.11j
f1 (ppm)

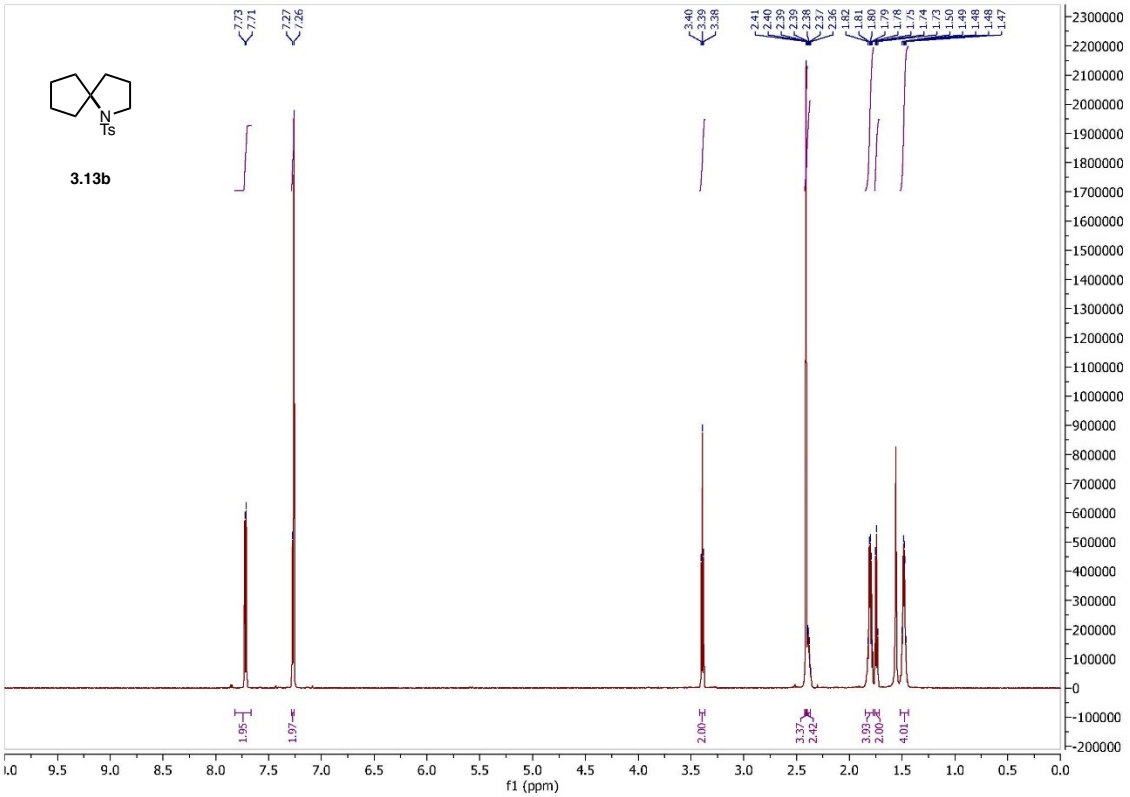

3.11j
f1 (ppm)

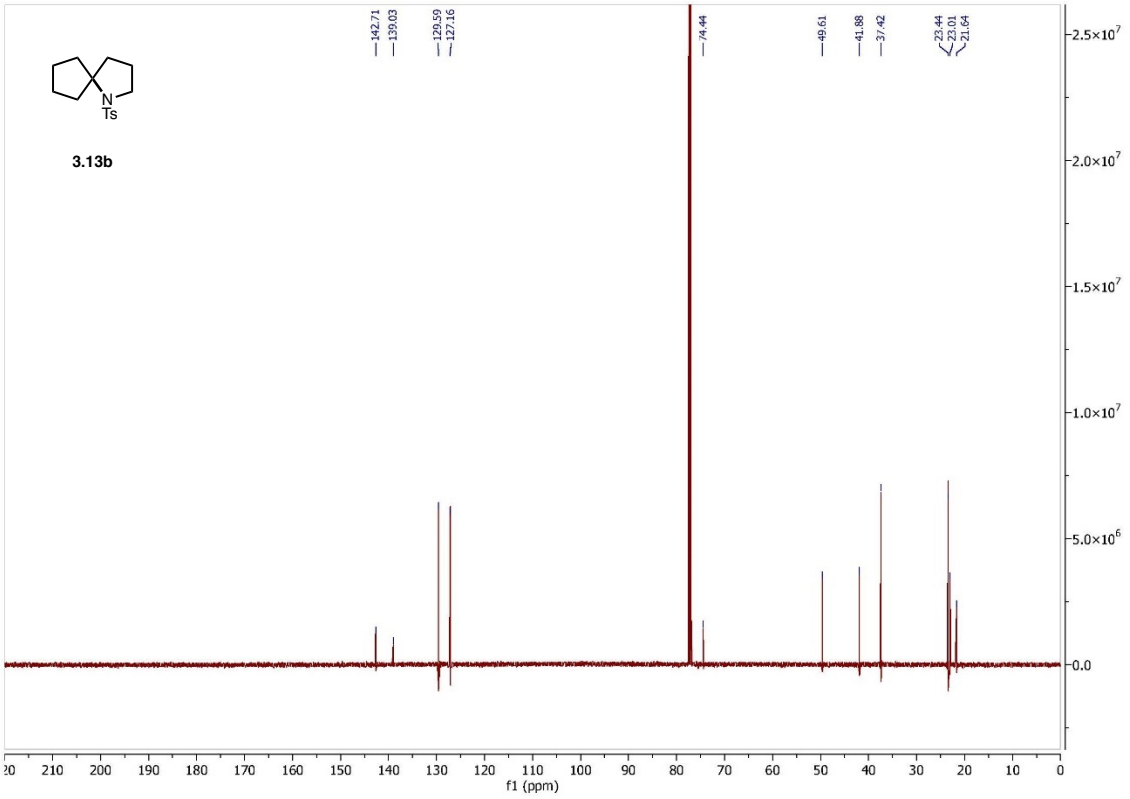

7.76
7.74
7.37
7.35
4.73
4.73
4.53
4.52
4.38
4.37
3.80
3.78
3.63
3.61
2.71
2.71
2.69
2.69
2.46
2.43
2.41
1.33
O
Me
N
Ts
3.11k
2.01
2.13
1.00
1.06
1.08
1.00
0.99
0.99
3.54
1.06
2.98
f1 (ppm)

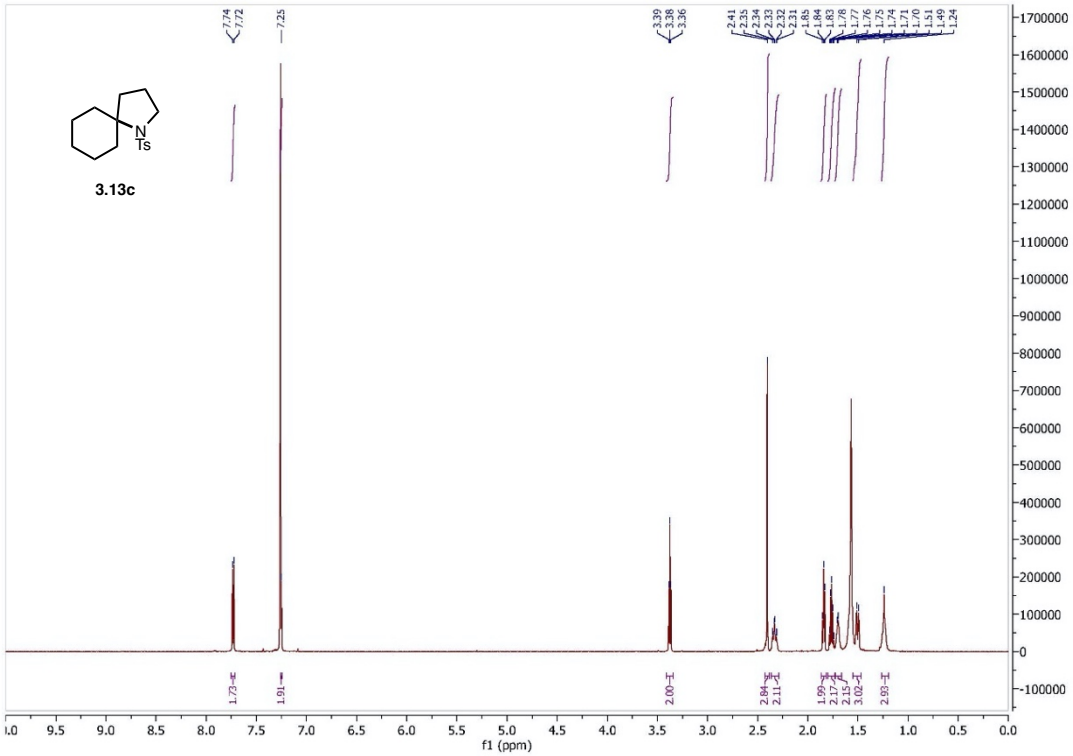

144.01
132.62
129.83
128.16
89.47
80.13
57.43
55.64
45.72
21.72
19.66
O
Me
N
Ts
3.11k
f1 (ppm)

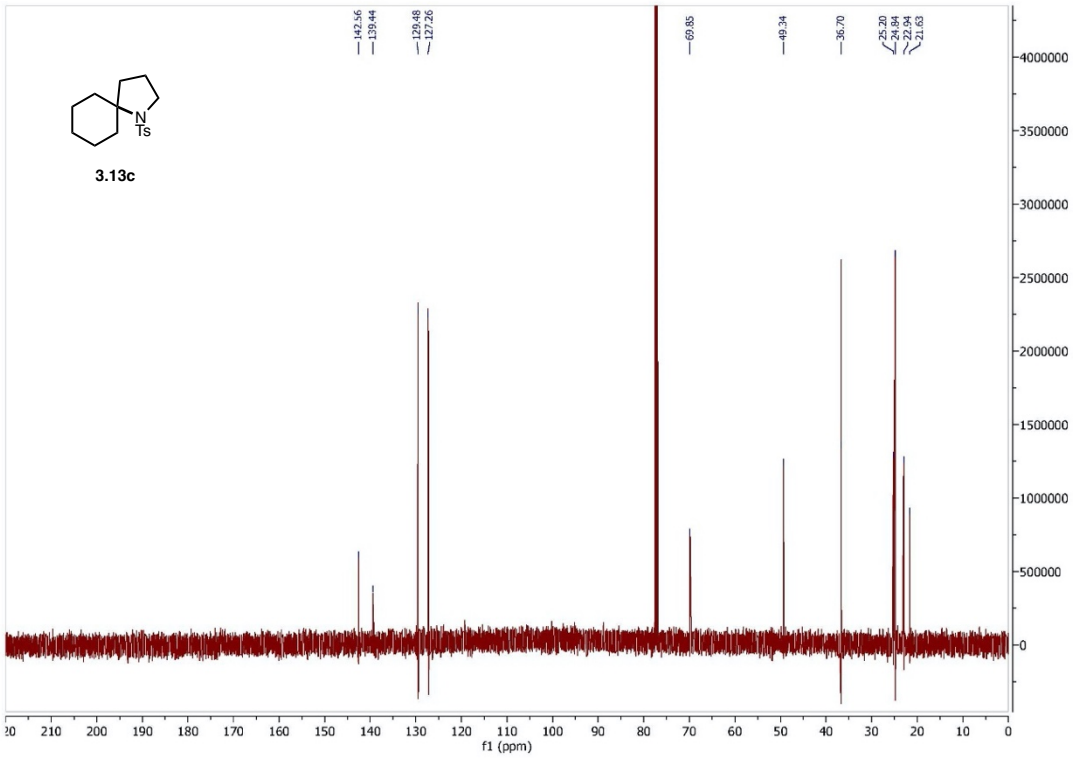

NTs
3.13a
f1 (ppm)

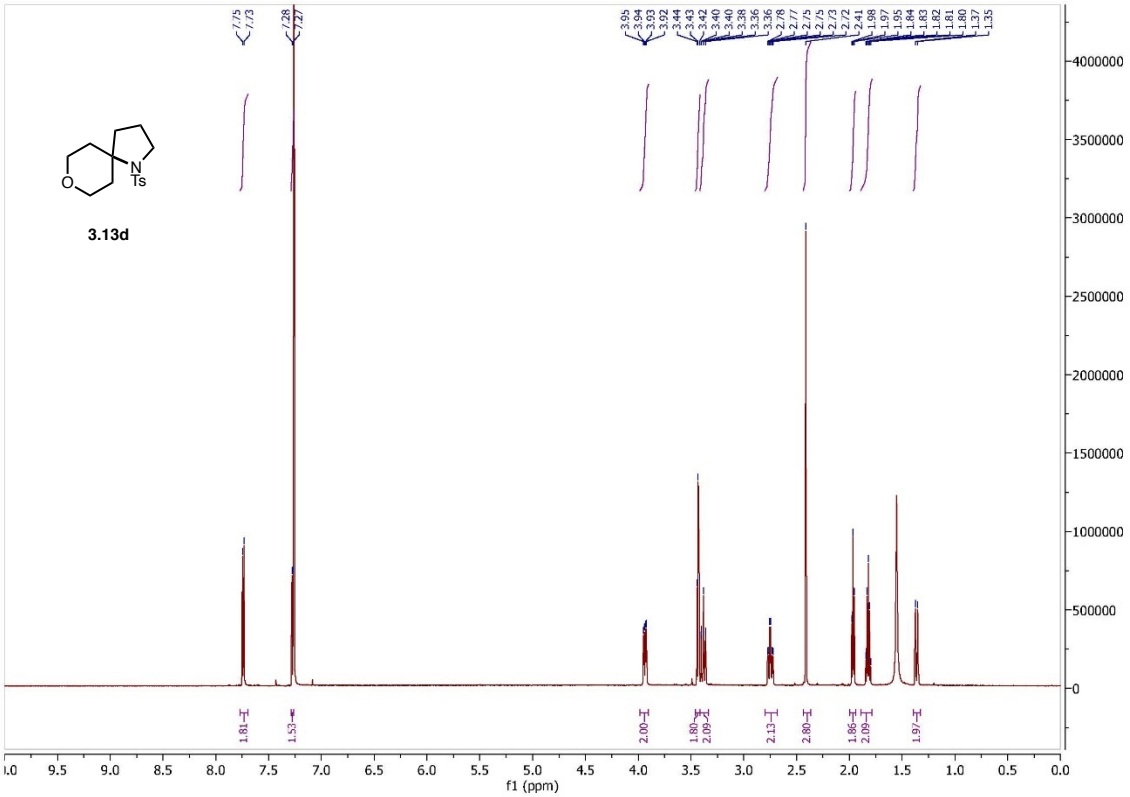

NTs
3.13a
142.81
138.82
129.66
127.02
66.32
49.91
40.50
35.61
22.33
21.65
14.51
f1 (ppm)

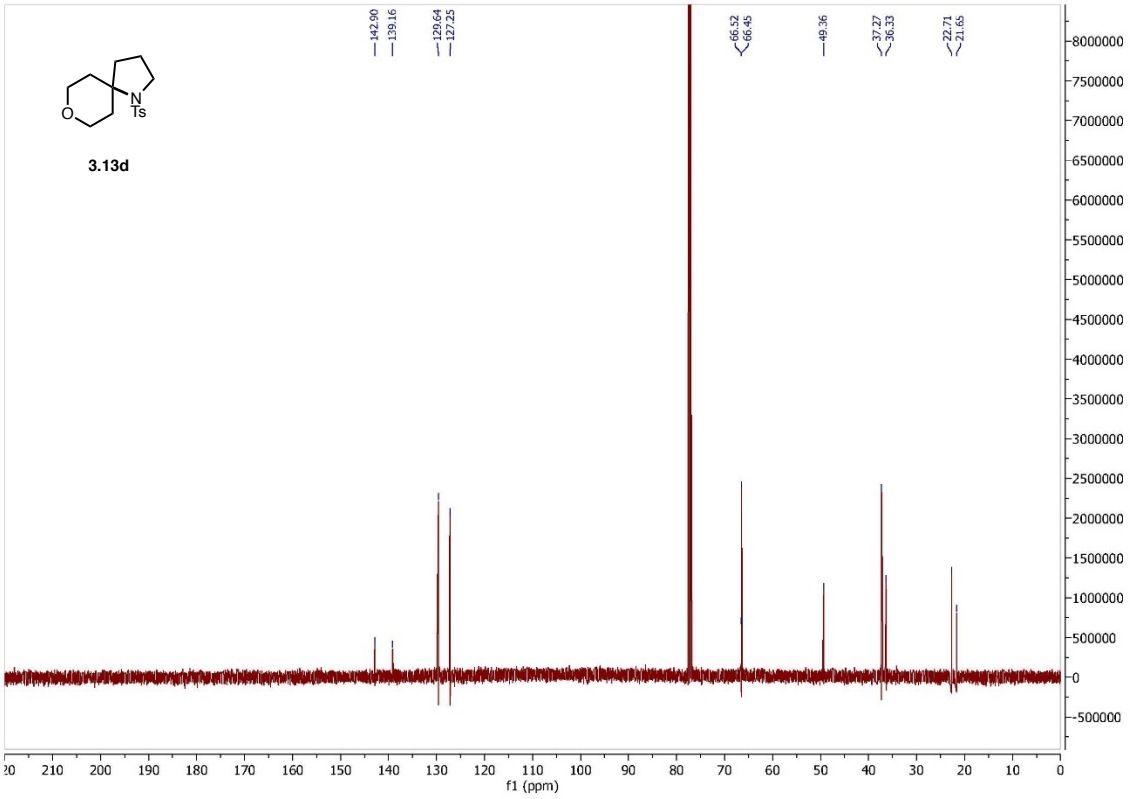

7.73
7.71
7.27
7.26
3.40
3.39
3.38
2.41
2.40
2.39
2.39
2.38
2.37
2.36
1.82
1.81
1.80
1.79
1.78
1.75
1.74
1.73
1.50
1.49
1.48
1.48
1.47
N
Ts
3.13b
1.95
1.97
2.00
3.37
2.42
3.93
2.00
4.01
f1 (ppm)

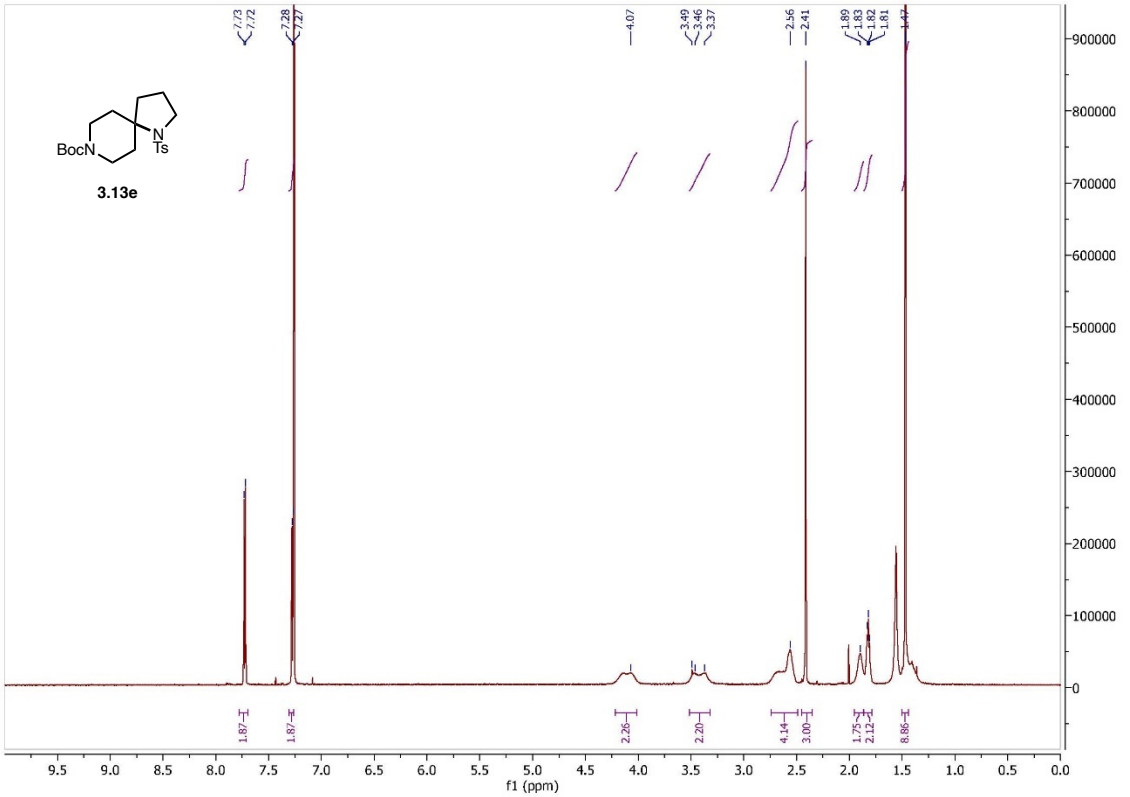

142.71
139.03
129.59
127.16
74.44
49.61
41.88
37.42
23.44
23.01
21.64
N
Ts
3.13b
f1 (ppm)

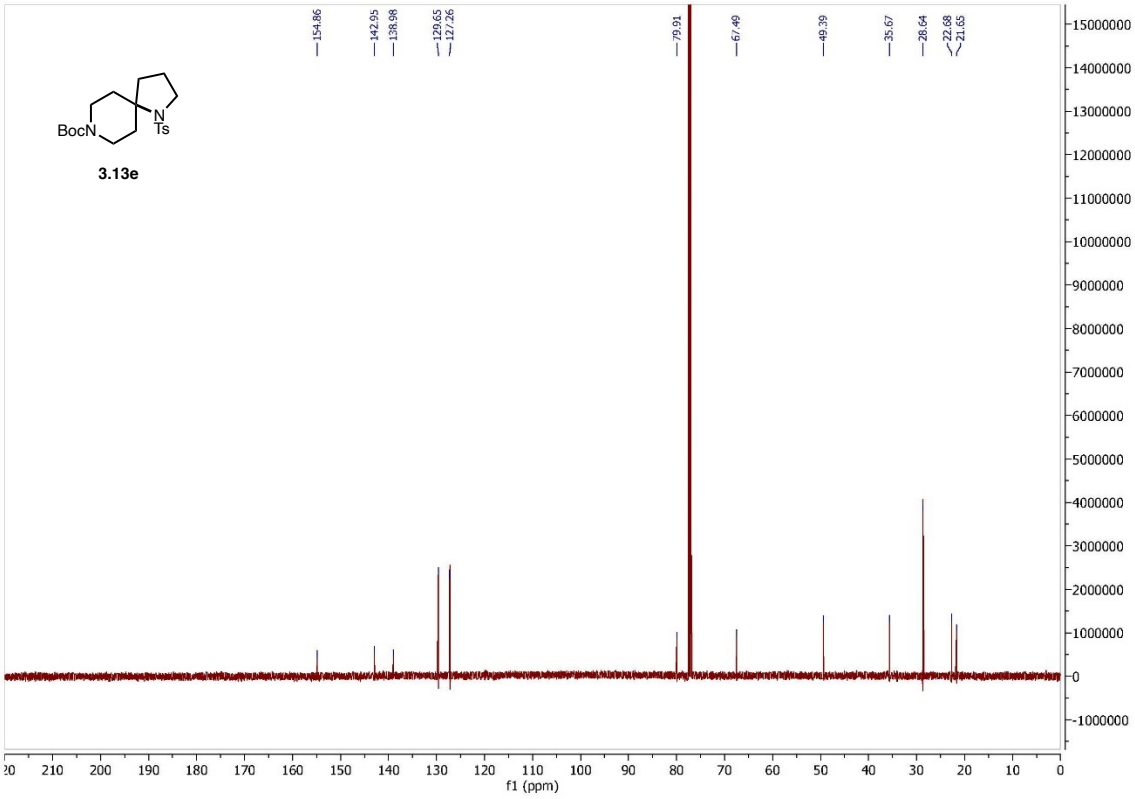

N
Ts
3.13c
7.74
7.72
7.25
3.39
3.38
3.36
2.41
2.34
2.33
2.32
2.31
1.85
1.84
1.83
1.78
1.77
1.76
1.75
1.74
1.71
1.70
1.51
1.49
1.24
1.73
1.91
2.00
2.84
2.11
1.99
2.17
2.15
3.02
2.93
f1 (ppm)

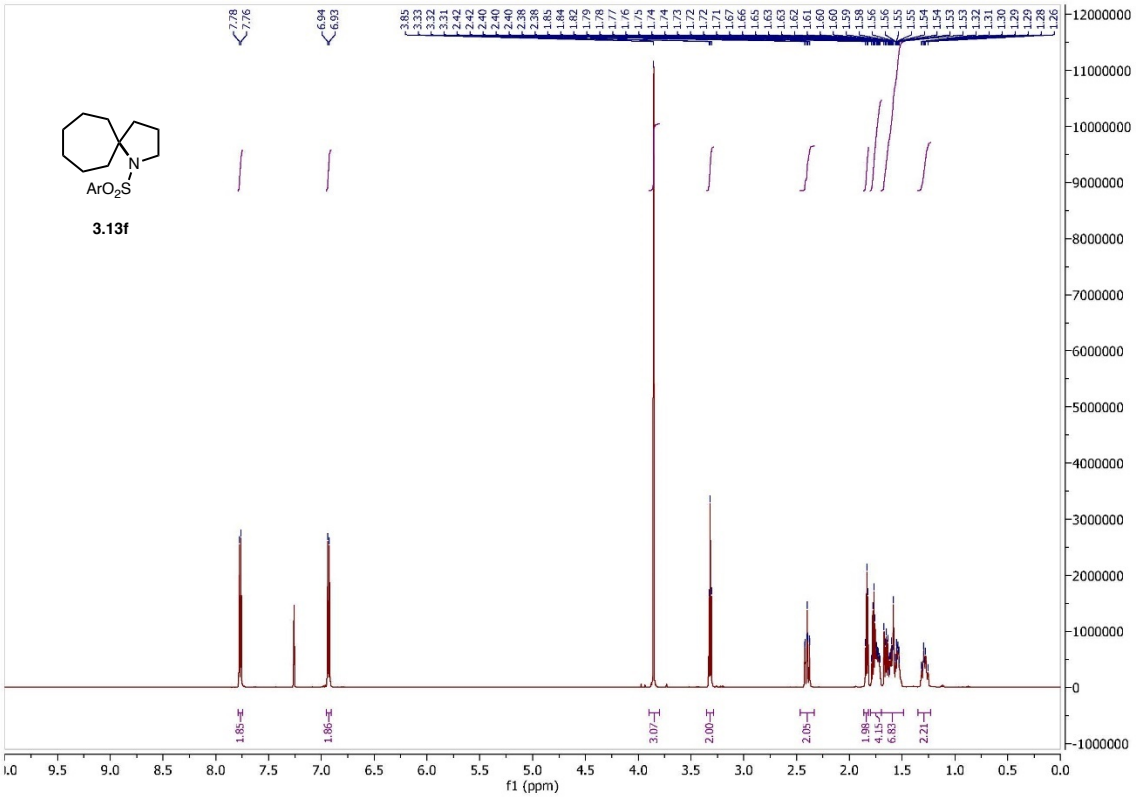

N
Ts
3.13c
142.56
139.44
129.48
127.26
69.85
49.34
36.70
25.20
24.84
22.94
21.63
f1 (ppm)

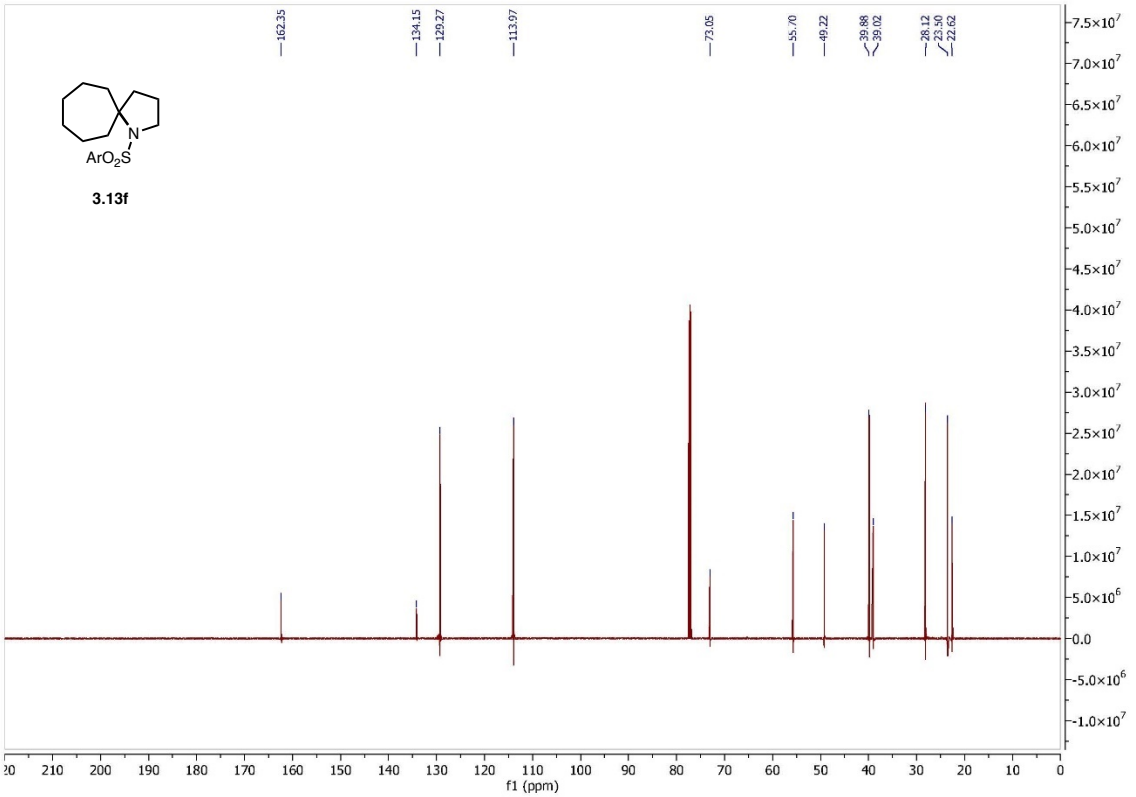

3.13d
f1 (ppm)

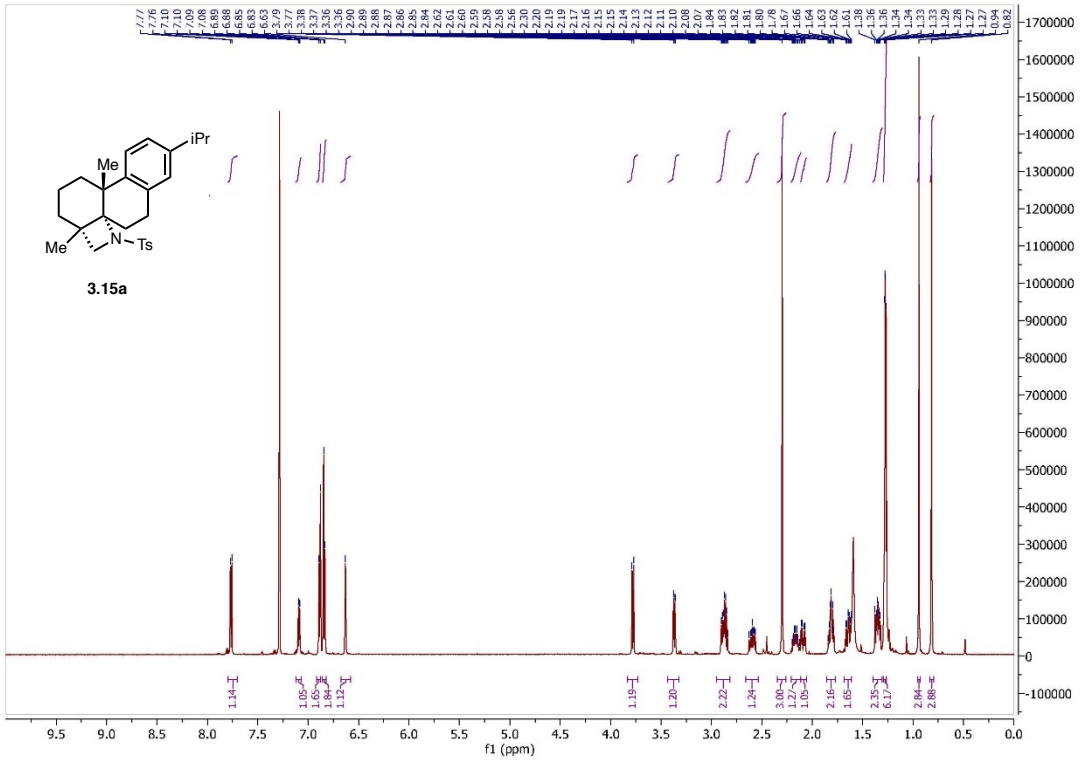

3.13d
f1 (ppm)

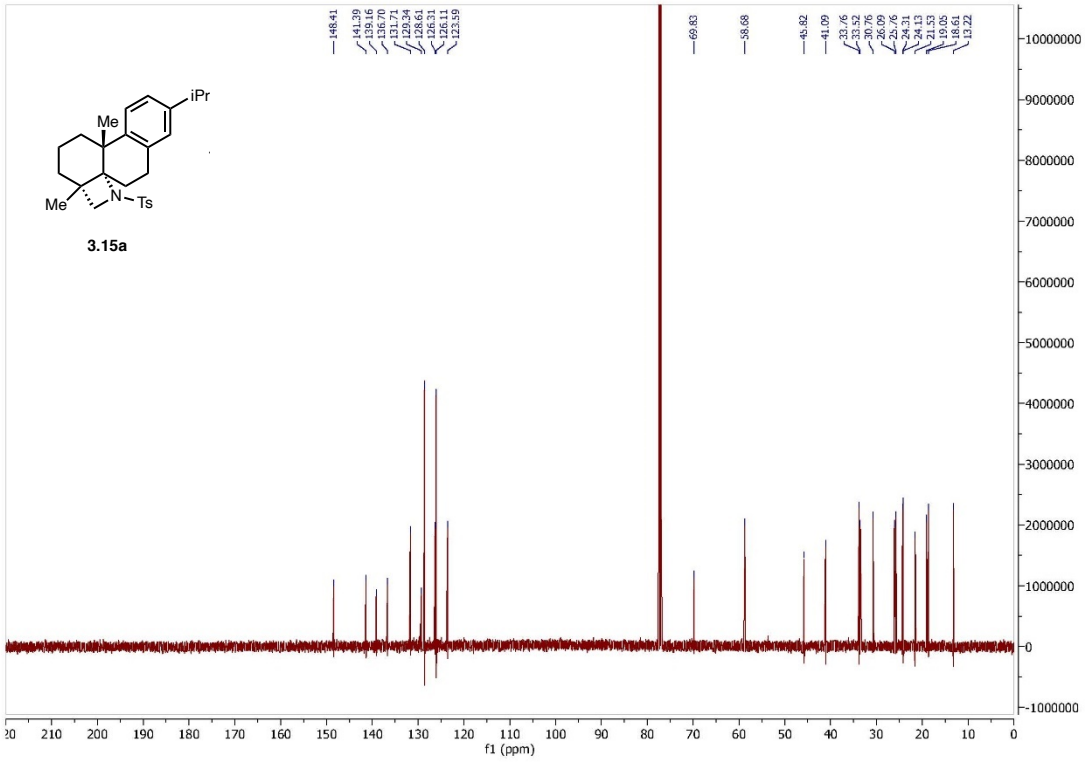

BocN
N
Ts
3.13e
7.73
7.72
7.28
7.27
4.07
3.49
3.46
3.37
2.56
2.41
1.89
1.83
1.82
1.81
1.47
1.87
1.87
2.26
2.20
4.14
3.00
1.75
2.12
8.86
f1 (ppm)


BocN
N
Ts
3.13e
154.86
142.95
136.98
129.65
127.26
79.91
67.49
49.39
35.67
28.64
22.68
21.65
f1 (ppm)

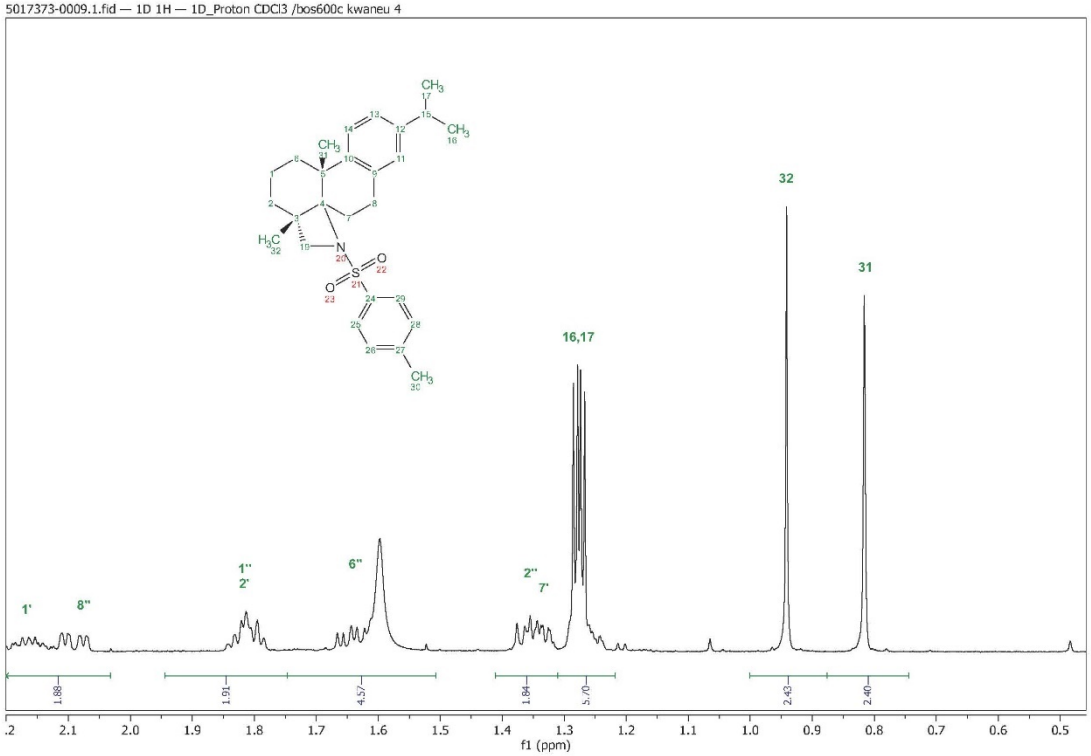

ArO2S
3.13f
f1 (ppm)


ArO2S
3.13f
f1 (ppm)

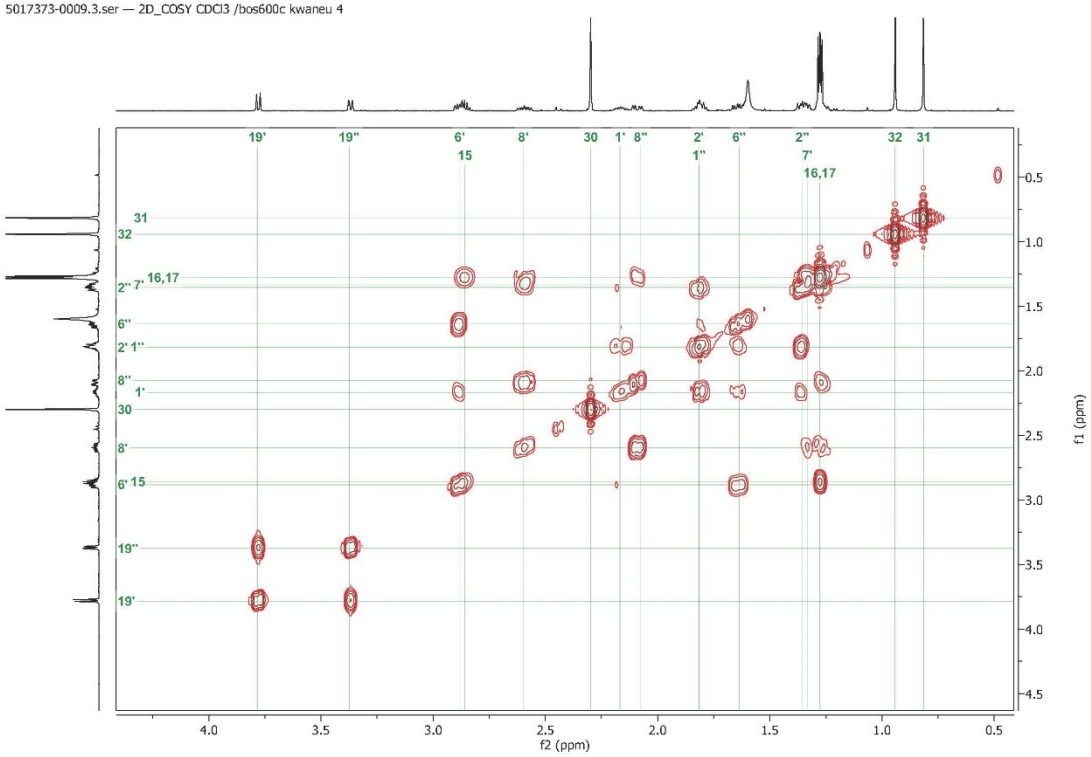

iPr
Me
Me
N
Ts
3.15a
f1 (ppm)


iPr
Me
Me
N
Ts
3.15a
f1 (ppm)

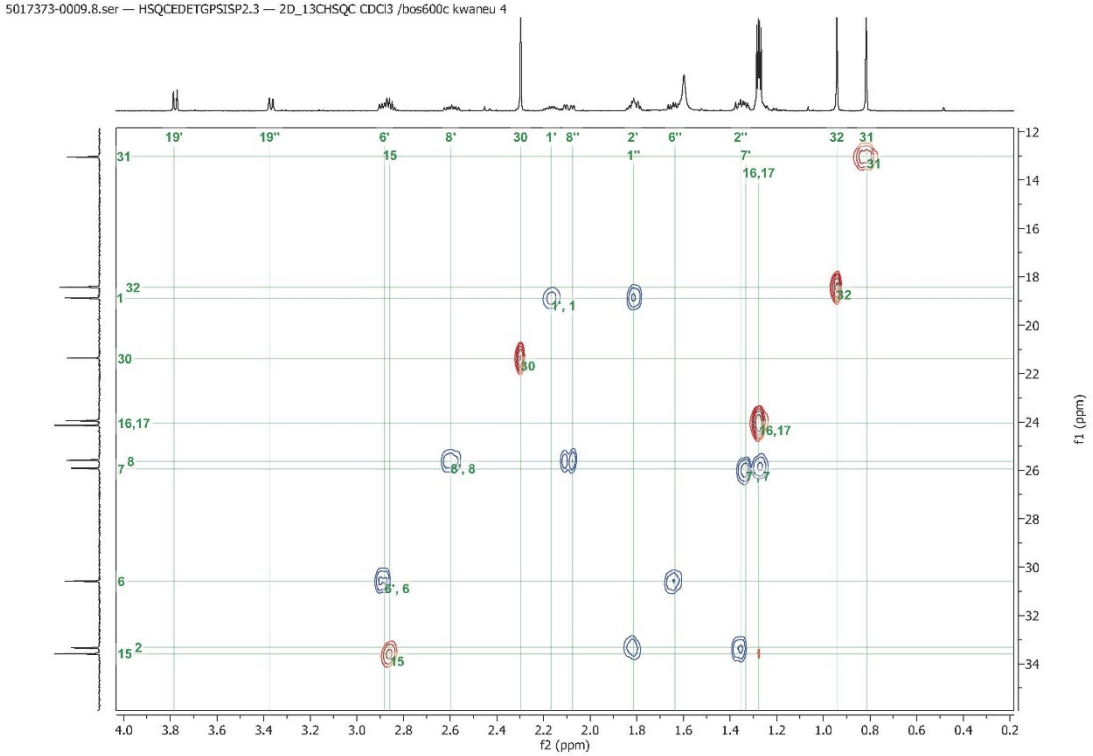
5017373-0009.1.fid — 1D 1H — 1D_Proton CDCl3 /bos600c kwaneu 4



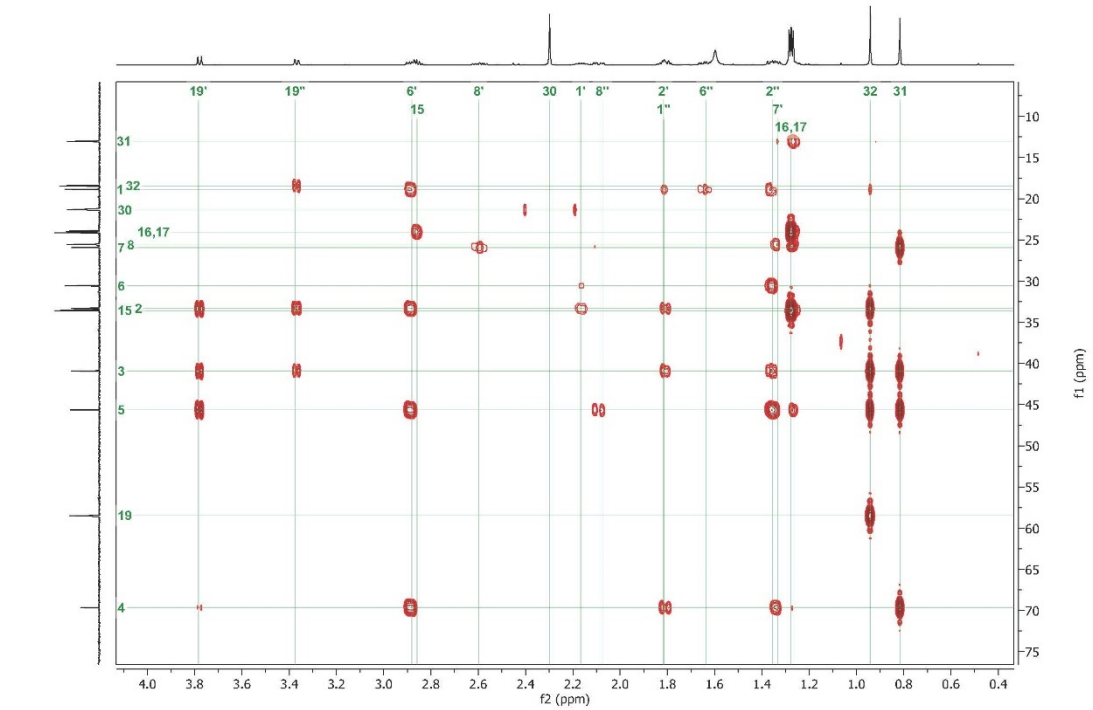
5017373-0009.3.ser — 2D_COSY CDCl3 /bos600c kwaneu 4



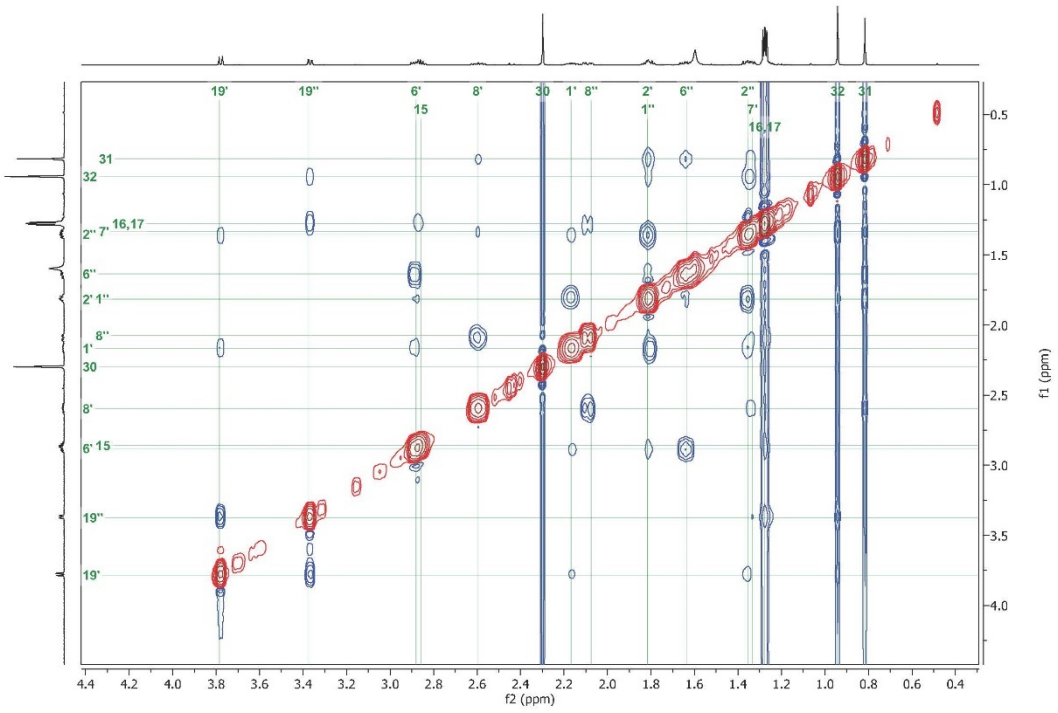
5017373-0009.8.ser — HSQCEDETGPSISP2.3 — 2D_13CHSQC CDCl3 /bos600c kwaneu 4

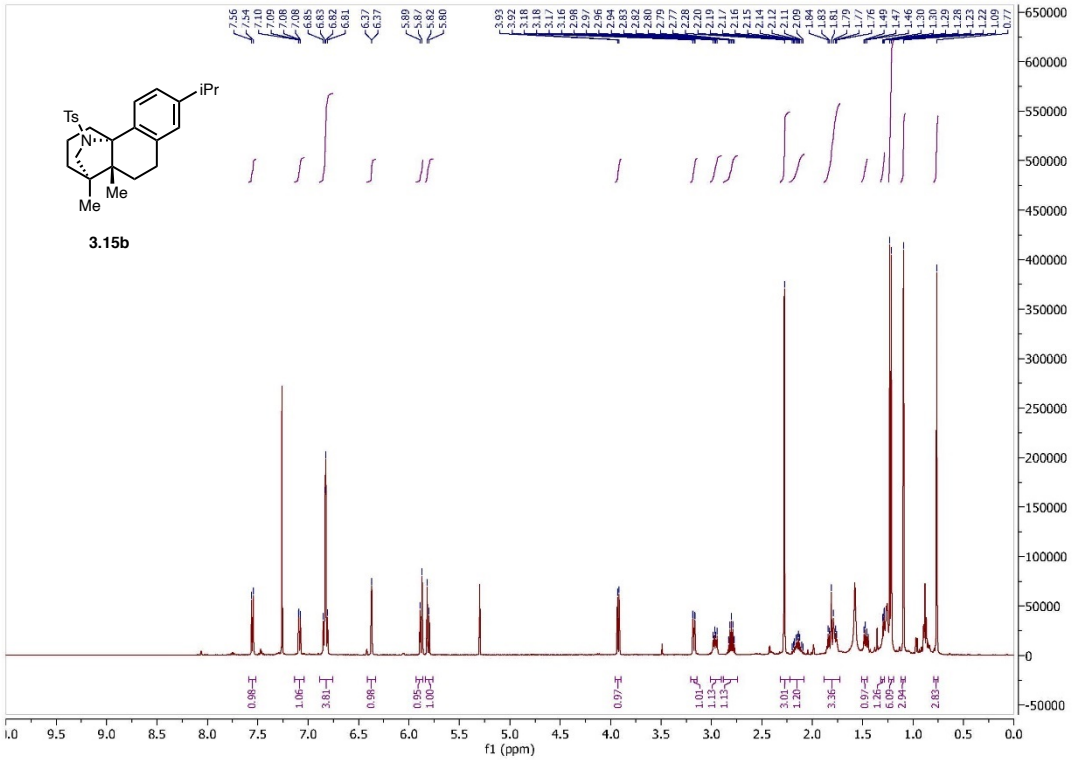


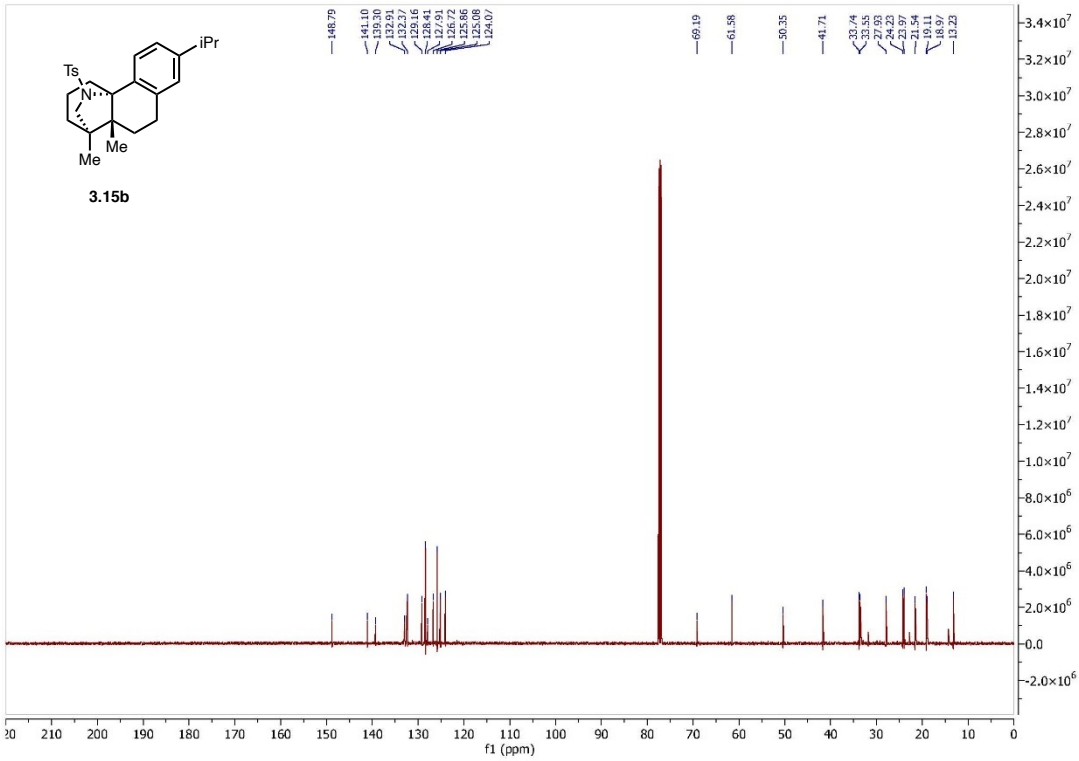
5017373-0009.5.ser — HMBCGP — — 2D_13CHMBC CDCl3 /bos600c kwaneu 4



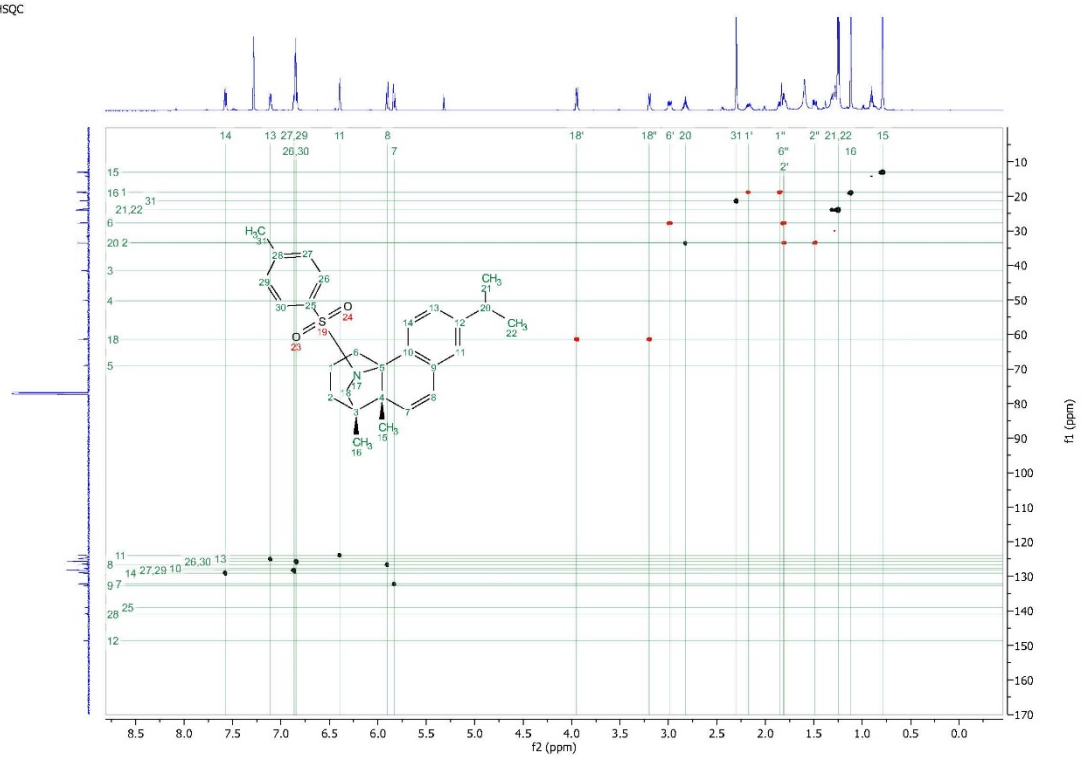
5017373-0009.6.ser — NOESYPHPR — — 2D_NOESY CDCl3 /bos600c kwaneu 4



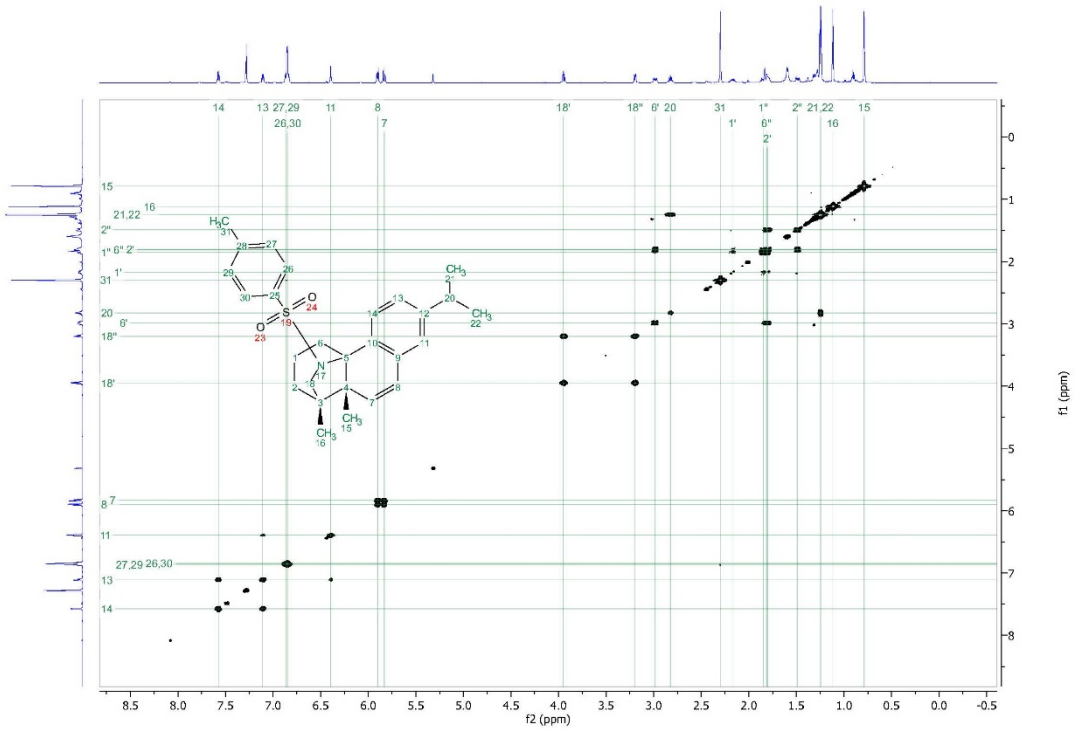

iPr
Ts
N
Me
Me
3.15b
f1 (ppm)


iPr
Ts
N
Me
Me
3.15b
f1 (ppm)

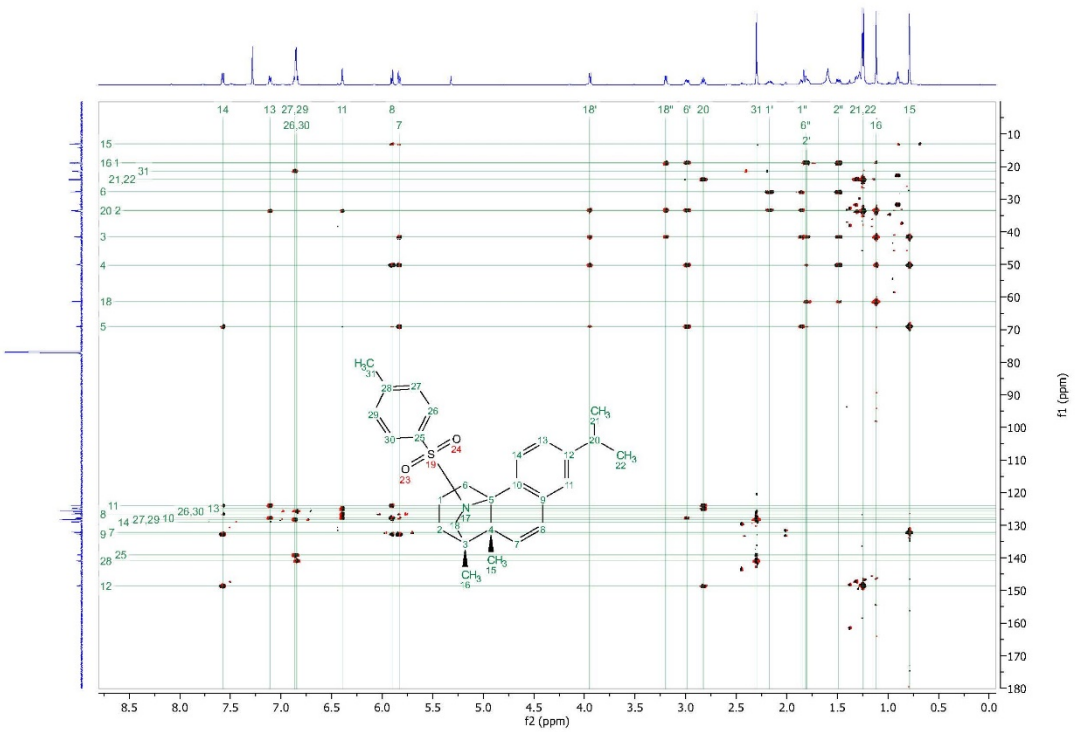
HSQC



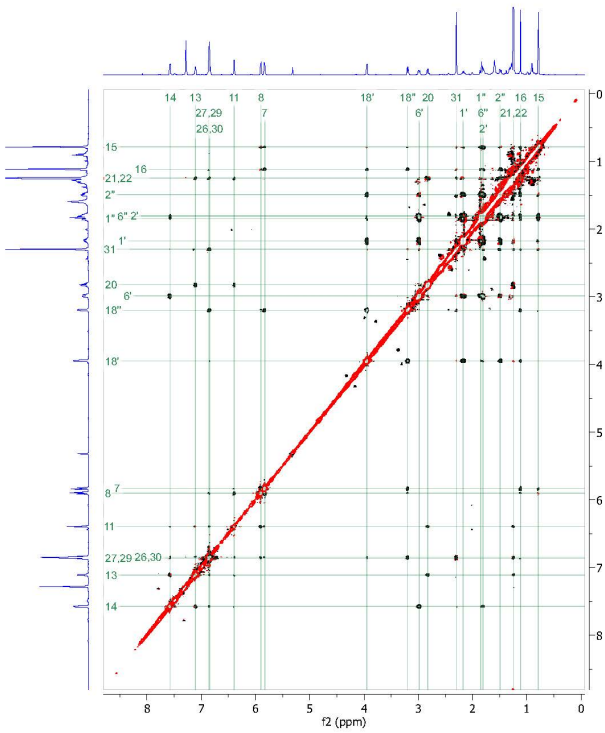
COSY

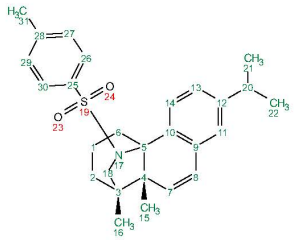


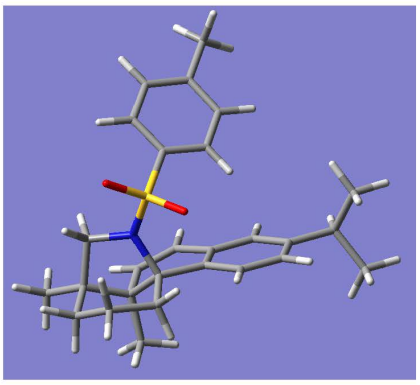
HMBC



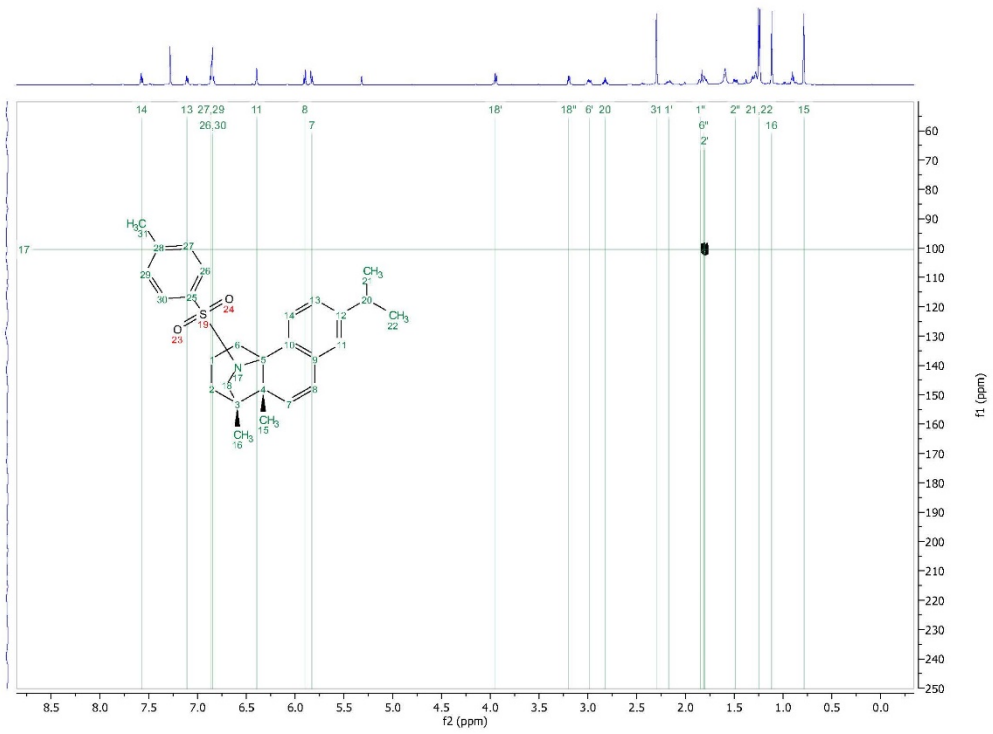
ROSEY







15N-HMBC


14
13 27,29
26,30
11
8
7
18'
18"
6'
20
31
1'
1"
6"
2'
2"
21,22
16
15
17
f2 (ppm)
f1 (ppm)

3.4.7. Computational Details and Cartesian Coordinates

Computational results

For substrate **3.7**, on the basis of DFT calculations, the 1,5-HAT, which features an α-heteroatom, has a lower energy barrier (by 4.6 kcal mol^{-1}) as compared to a 1,5-HAT, on the carbocycle **3.1** (Fig. 3.S1).

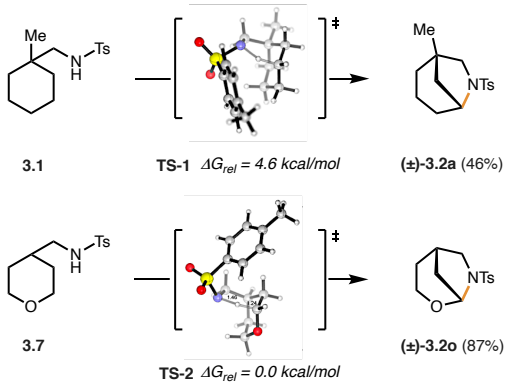


Figure 3.S1. 1,5-HAT transition states for carbacycle **3.1** and heterocycle **3.7**, modeled at the M06-2X/6-311++G**–SMD(CH_3CN)//M06-2X/6-31G**–SMD(CH_3CN) level of theory.

For substrate **3.8**, on the basis of DFT calculations, the 1,5-HAT, which features the methyl group pointing out, has a lower energy barrier (by 3.1 kcal mol^{-1}) as compared to a 1,5-HAT, with the methyl group sterically occluding with the cyclohexane ring (Fig. 3.S2).

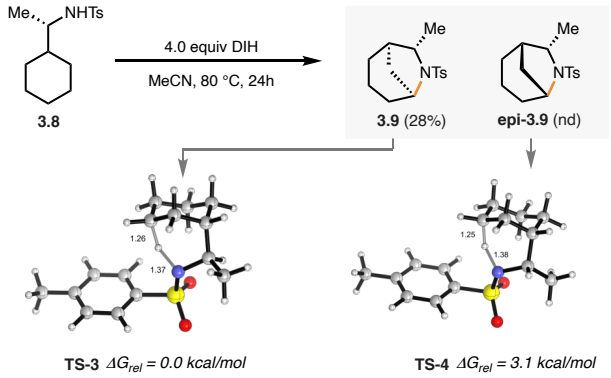


Figure 3.S2. Chirality transfer in C–N bi-cyclization. The transition states were modeled at the M06-2X/6-311++G**–SMD(CH_3CN)//M06-2X/6-31G**–SMD(CH_3CN) level.

Computational methods, Cartesian coordinates, and energies

All of the quantum chemical calculations were performed using the *Gaussian 16* program.[2] Geometry optimizations and frequency calculations were performed at the M06-2X[3]/6-31G** level of theory with the SMD model[4] for implicit solvation by acetonitrile.[5] Single-point (SP) energies were then computed on the optimized geometries at the M06-2X/6-311++G** level with the same SMD model. An "ultrafine" integration grid and a two-electron integral accuracy of 10^{-14} (`int=(Acc2E=14,ultrafine)`) were used. The stationary points were characterized as minima or transition structures by the presence of only positive eigenvalues or a single negative eigenvalue of the Hessian, respectively. The free energies were calculated for 298.15 K and 1 atm using the quasi-harmonic approximation proposed by Cramer and Truhlar,[4] in which all of the real vibrational frequencies lower than 100 cm^{-1} were set to 100 cm^{-1} before the thermal corrections were computed with the usual harmonic oscillator model. The illustrations of the optimized geometries in the main text were prepared using *CYLView.*[6]

[2] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; et al. Gaussian 16. Gaussian, Inc.: Wallingford, CT.

[3] Zhao, Y.; Truhlar, D. G. The M06 Suite of Density Functionals for Main Group Thermochemistry, Thermochemical Kinetics, Noncovalent Interactions, Excited States, and Transition Elements: Two New Functionals and Systematic Testing of Four M06-Class Functionals and 12 Other Function. *Theor. Chem. Acc.* **2008**, *120*, 215–241.

[4] Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Universal Solvation Model Based on Solute Electron Density and on a Continuum Model of the Solvent Defined by the Bulk Dielectric Constant and Atomic Surface Tensions. *J. Phys. Chem. B* **2009**, *113*, 6378–6396.

[5] Ribeiro, R. F.; Marenich, A. V.; Cramer, C. J.; Truhlar, D. G. Use of Solution-Phase Vibrational Frequencies in Continuum Models for the Free Energy of Solvation. *J. Phys. Chem. B* **2011**, *115*, 14556–14562.

[6] Legault, C. Y. *CYLview*, 1.0b. *Université de Sherbrooke*. 2009.

Structure: N-centered radical derived from 3.1

Charge = 0, Multiplicity = 2

SCF Energy: -1187.789624 hartree

SCF Energy + ZPVE: -1187.438394 hartree

Enthalpy: -1187.418645 hartree

Free Energy: -1187.485909 hartree

Free Energy with quasiharmonic correction: -1187.483149 hartree

SCF Energy (SP): -1188.01233877 hartree

6 -3.486060 -0.646756 1.285594
6 -2.523720 0.143173 0.397181
6 -1.662424 -0.845294 -0.413503
7 -0.903930 -1.703982 0.464341
16 0.525018 -2.313302 -0.223104
6 1.549713 -0.881448 -0.095047
6 1.912855 -0.194434 -1.249599
6 2.671306 0.965583 -1.122545
6 3.045823 1.446846 0.136115
6 3.829868 2.722179 0.274095
6 2.660547 0.732376 1.280079
6 1.915415 -0.433463 1.176613
8 0.993419 -3.349134 0.688466
8 0.319067 -2.640311 -1.633031
6 -3.331678 1.015329 -0.582844
6 -2.480555 2.004216 -1.386019
6 -1.631578 2.877631 -0.460141
6 -0.765393 2.015540 0.460575
6 -1.625966 1.041890 1.269640
1 -2.944043 -1.282848 1.991812
1 -4.118479 0.038072 1.859549
1 -4.138567 -1.286589 0.680527
1 -1.025422 -0.338336 -1.150192
1 -2.327380 -1.512012 -0.992648
1 1.610577 -0.566167 -2.223287
1 2.972983 1.508376 -2.013398
1 4.654432 2.598919 0.981383
1 3.186655 3.520971 0.658625
1 4.235087 3.044984 -0.686831
1 2.953853 1.096573 2.260536
1 1.624694 -0.989331 2.063137
1 -4.060622 1.584724 0.009951
1 -3.908592 0.367193 -1.254943
1 -3.135971 2.628390 -2.002867
1 -1.822127 1.466762 -2.080697
1 -2.296271 3.501069 0.153898
1 -1.005455 3.558162 -1.047038

1 -0.186347 2.647323 1.143707
1 -0.035624 1.459923 -0.144053
1 -2.279467 1.619381 1.937885
1 -0.995499 0.410509 1.909573

Structure: 3.1-TS
Charge = 0, Multiplicity = 2
SCF Energy: -1187.762105 hartree
SCF Energy + ZPVE: -1187.415738 hartree
Enthalpy: -1187.396608 hartree
Free Energy: -1187.463622 hartree
Free Energy with quasiharmonic correction: -1187.459450 hartree
SCF Energy (SP): -1187.98545166 hartree
16 0.118318 1.733017 0.335065
8 0.327048 3.066663 -0.235154
8 -0.300566 1.668127 1.739515
6 3.862620 -0.792130 -0.217938
6 3.101003 -0.898731 0.949824
6 1.963372 -0.118372 1.137404
6 1.595115 0.776540 0.138215
6 2.333769 0.907983 -1.036527
6 3.463768 0.118768 -1.205496
6 5.104883 -1.619280 -0.406478
6 -3.126305 -1.059720 0.957644
6 -1.756926 -1.429022 1.533066
6 -0.937239 -2.260236 0.541272
6 -4.493715 -0.155194 -0.928423
1 -2.520759 1.433345 0.614132
1 -2.797146 1.638907 -1.134032
1 3.401689 -1.600980 1.721925
1 1.370418 -0.198835 2.043237
1 2.027838 1.615092 -1.801286
1 4.048962 0.207450 -2.116421
1 5.102003 -2.492986 0.248739
1 5.198536 -1.955842 -1.442084
1 5.995777 -1.026774 -0.172162
1 -3.659351 -0.395672 1.649270
1 -3.732088 -1.971240 0.860980
1 -1.887483 -1.980508 2.469756
1 -1.204198 -0.514843 1.780256
1 -1.383360 -3.262385 0.441982
1 0.085992 -2.402164 0.903512
1 -0.204565 -2.009425 -1.535650
1 -2.876607 -2.264926 -1.495950
1 -2.233330 -0.874307 -2.386140

1 -4.491033 0.239268 -1.949866
1 -5.065654 -1.088435 -0.921404
1 -5.012281 0.564947 -0.285677
6 -0.935114 -1.614395 -0.825617
6 -2.308738 -1.328348 -1.391401
6 -3.068912 -0.396836 -0.432289
6 -2.346582 0.990216 -0.374705
7 -0.911846 0.916841 -0.691900
1 -0.591374 -0.411605 -0.677044

Structure: N-radical derived from 3.7
Charge = 0, Multiplicity = 2
SCF Energy: -1184.376852 hartree
SCF Energy + ZPVE: -1184.077425 hartree
Enthalpy: -1184.059093 hartree
Free Energy: -1184.125452 hartree
Free Energy with quasiharmonic correction: -1184.121010 hartree
SCF Energy (SP): -1184.60924012 hartree
6 2.402758 3.937603 -0.265072
1 1.888924 4.451234 0.551721
1 3.470583 4.162361 -0.172112
1 2.052233 4.345850 -1.214958
16 1.453110 -2.021052 0.068737
8 2.257797 -2.619023 1.126331
8 1.469919 -2.613329 -1.267689
6 2.175397 2.453398 -0.192716
6 1.886047 1.715097 -1.345480
6 1.688304 0.339715 -1.283962
6 1.794958 -0.294362 -0.048034
6 2.084285 0.413530 1.120813
6 2.272381 1.785456 1.036658
6 -3.383623 -0.642498 -0.760093
6 -4.393457 0.381147 -0.253397
8 -3.787935 1.642792 -0.029132
1 -2.606660 -1.210170 1.165147
1 -1.591249 -2.695456 -0.538747
1 -0.748072 -1.324174 -1.273276
1 1.812505 2.224778 -2.301456
1 1.463663 -0.235728 -2.176264
1 2.160523 -0.103624 2.072301
1 2.498681 2.352381 1.935111
1 -2.996246 -0.307455 -1.730965
1 -3.878681 -1.608066 -0.911177
1 -4.853841 0.018373 0.680523
1 -5.189310 0.542157 -0.985412

```
1 -3.210576 1.218780 1.911279
1 -0.898948 0.559472 1.327021
1 -1.169024 1.012912 -0.364598
6 -2.774065 1.561062 0.958232
6 -1.656488 0.614847 0.536404
6 -2.224962 -0.774438 0.231411
6 -1.147282 -1.707879 -0.324139
7 -0.131772 -1.946133 0.674881
1 -2.395616 2.576556 1.102066
```

Structure: 3.7-TS

Charge = 0, Multiplicity = 2

SCF Energy: -1184.357340 hartree

SCF Energy + ZPVE: -1184.061230 hartree

Enthalpy: -1184.043969 hartree

Free Energy: -1184.106603 hartree

Free Energy with quasiharmonic correction: -1184.103859 hartree

SCF Energy (SP): -1184.59006498 hartree

6 4.509096 -2.075563 -0.127567
1 5.411558 -1.679504 0.350164
1 4.753977 -2.312007 -1.165135
1 4.244024 -3.000458 0.391296
16 -0.030253 1.930507 0.234324
8 0.114723 2.916431 -0.838244
8 -0.133540 2.380862 1.619141
6 3.391198 -1.072277 -0.046265
6 2.687214 -0.894670 1.153065
6 1.667093 0.041893 1.251442
6 1.345531 0.811654 0.132594
6 2.033907 0.663776 -1.068286
6 3.053489 -0.281651 -1.148279
6 -3.431054 -1.230723 -0.976726
6 -3.718335 -0.873289 0.476882
8 -2.783989 -1.463222 1.390309
1 -1.799241 -1.426905 -2.362042
1 -0.538855 0.474442 -1.936760
1 -2.227201 1.019053 -1.986945
1 2.947662 -1.497227 2.018796
1 1.127836 0.182422 2.183365
1 1.782564 1.286067 -1.921205
1 3.596613 -0.405171 -2.080760
1 -3.686324 -2.283346 -1.141959
1 -4.081479 -0.627481 -1.618631
1 -4.700922 -1.236209 0.784375
1 -3.689977 0.214132 0.619614
1 -0.818422 -1.594057 1.858540
1 -0.028543 -1.642241 -0.521074
1 -1.306730 -2.873182 -0.395371
6 -1.464701 -1.285009 1.034428
6 -1.098497 -1.797536 -0.342498
6 -1.956511 -1.033513 -1.353512
6 -1.497895 0.441970 -1.405562
7 -1.411822 1.059965 -0.074044
1 -1.320491 -0.069138 0.844916

Structure: 3.8-TS3

Charge = 0, Multiplicity = 2

SCF Energy: -1187.762728 hartree

SCF Energy + ZPVE: -1187.415973 hartree

Enthalpy: -1187.396811 hartree

Free Energy: -1187.464393 hartree

Free Energy with quasiharmonic correction: -1187.459816 hartree

SCF Energy (SP): -1187.98537965 hartree

16 0.046905 1.464088 0.646748
8 -0.033848 2.895525 0.339955
8 0.456032 1.096901 2.007107
6 -3.913752 -0.566479 -0.295671
6 -3.098465 -1.042147 0.736826
6 -1.895578 -0.414802 1.045789
6 -1.512455 0.698739 0.304210
6 -2.300875 1.196304 -0.730685
6 -3.499505 0.557227 -1.022266
6 -5.227228 -1.230910 -0.606079
6 3.346419 -1.415928 0.634397
6 2.042917 -1.869646 1.298222
6 1.110415 -2.559234 0.296253
1 4.088253 -0.340627 -1.069719
6 3.015569 1.914532 -1.201628
1 2.662486 1.048429 0.747601
1 -3.410602 -1.912840 1.306212
1 -1.263353 -0.778216 1.850313
1 -1.980830 2.068010 -1.292739
1 -4.126004 0.932904 -1.826311
1 -5.244605 -2.260528 -0.242354
1 -5.422098 -1.233299 -1.681387
1 -6.049641 -0.691442 -0.124083
1 3.955221 -0.852771 1.350883
1 3.930704 -2.298522 0.342725
1 2.264920 -2.543930 2.131594
1 1.527921 -0.999139 1.722992
1 1.532257 -3.536040 0.011225
1 0.131946 -2.755574 0.746416
1 0.156598 -2.039789 -1.634982
1 2.814350 -2.264801 -1.926689
1 2.082134 -0.772744 -2.536759
6 0.961746 -1.734207 -0.962509
6 2.267683 -1.358700 -1.630443
6 3.113696 -0.566025 -0.623807
6 2.452093 0.813349 -0.304764
7 0.989839 0.762806 -0.532598

1 0.648881 -0.563231 -0.622930
1 2.870923 1.653609 -2.254879
1 4.085970 2.038835 -1.013458
1 2.511659 2.864794 -1.007016

Structure: 3.8-TS4
Charge = 0, Multiplicity = 2
SCF Energy: -1187.758280 hartree
SCF Energy + ZPVE: -1187.411230 hartree
Enthalpy: -1187.392238 hartree
Free Energy: -1187.459153 hartree
Free Energy with quasiharmonic correction: -1187.454913 hartree
SCF Energy (SP): -1187.98083212 hartree
16 0.020845 1.474269 -0.369399
8 -0.072129 2.857294 0.112168
8 0.456613 1.279982 -1.757285
6 -3.999652 -0.607826 0.126968
6 -3.172960 -0.907122 -0.959807
6 -1.948222 -0.266210 -1.126310
6 -1.554191 0.679478 -0.185879
6 -2.354868 0.998713 0.909097
6 -3.574408 0.351290 1.056452
6 -5.335377 -1.281077 0.288426
6 3.543295 -1.119528 -0.408590
6 2.398592 -1.483503 -1.357864
6 1.389225 -2.423783 -0.689069
1 3.953907 -0.437281 1.580738
6 3.016406 1.781985 -0.013939
1 2.443359 1.180214 1.956170
1 -3.492662 -1.649097 -1.685714
1 -1.307614 -0.491190 -1.973098
1 -2.026078 1.741483 1.629255
1 -4.209531 0.589791 1.904974
1 -5.384653 -2.205482 -0.290902
1 -5.534073 -1.512171 1.338082
1 -6.138526 -0.622840 -0.059916
1 4.214662 -0.398360 -0.885031
1 4.143622 -2.017544 -0.211203
1 2.802195 -1.949454 -2.262780
1 1.877140 -0.572521 -1.673682
1 1.841752 -3.419662 -0.560356
1 0.504710 -2.556737 -1.320330
1 0.131332 -2.404063 1.134129
1 2.731350 -2.570288 1.771697
1 1.802558 -1.300796 2.586962

```
6 0.995568 -1.913704 0.679545
6 2.159880 -1.645553 1.610749
6 3.067725 -0.595143 0.956141
6 2.344389 0.792007 0.935074
7 0.880186 0.624461 0.762344
1 0.641127 -0.720087 0.552195
1 2.930379 1.472030 -1.057278
1 2.574919 2.776323 0.089319
1 4.077028 1.849844 0.245715
```

3.5 References

1. (a) Campos, K. R.; Coleman, P. J.; Alvarez, J. C.; Dreher, S. D.; Garbaccio, R. M.; Terrett, N. K.; Tillyer, R. D.; Truppo, M. D.; Parmee, E. R. The importance of synthetic chemistry in the pharmaceutical industry. Science **2019**, *363*, No. eaat0805. (b) Walters, W. P.; Green, J.; Weiss, J. R.; Murcko, M. A. What Do Medicinal Chemists Actually Make? A 50-Year Retrospective. *J. Med. Chem.* **2011**, *54*, 6405−6416.
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3.6 Experimental Contributors

The work presented in this chapter was published in 2020: Lux, M. C.; Jurczyk, J.; Y.-h Lam.; Song, Z. J.; Ma, C.; Roque, J. B.; Ham, J. S.; Sciammetta, N.; Adpressa, D.; Sarpong, R.; Yeung, C. S. Synthesis of Bridged Bicyclic Amines by Intramolecular Amination of Remote C–H Bonds: Synergistic Activation by Light and Heat. *Org. Lett.* **2020**, *22*, 6578–6583. The work has been reprinted with permission from the American Chemical Society. C.S.Y discovered the bicyclization reaction. M.C.L and J.J. optimized the bicyclization protocol. The scope of the reaction was investigated by M.C.L and J.J.. D.A. led the NMR studies. Y.-h.L, performed the computational studies. C.S.Y., and R.S. directed the research.

Chapter 4. Photomediated Ring Contraction of Saturated Heterocycles

Saturated heterocycles are found in numerous therapeutics and bioactive natural products and are abundant in many medicinal and agrochemical compound libraries. To access new chemical space and function, many methods for functionalization on the periphery of these structures have been developed. Comparatively fewer methods are known for restructuring their core framework. Herein, we describe a visible light–mediated ring contraction of α-acylated saturated heterocycles. This unconventional transformation is orthogonal to traditional ring contractions, challenging the paradigm for diversification of heterocycles including piperidine, morpholine, thiane, tetrahydropyran, and tetrahydroisoquinoline derivatives. The success of this Norrish type II variant rests on reactivity differences between photoreactive ketone groups in specific chemical environments. This strategy was applied to late-stage remodeling of pharmaceutical derivatives, peptides, and sugars.

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4.1 Introduction

Saturated heterocycles, especially piperidines, are among the most frequently encountered scaffolds in biologically active small molecules.[1,2] The prevalence of the piperidine scaffold in pharmaceutical and agrochemical compound libraries has resulted in increased interest in the development of methods for its site-selective derivatization (Fig. 4.1A) to access new chemical space. Recent advancements in C(sp^3)–H functionalization have provided many powerful methods for peripheral functionalization of the piperidine framework,[3–12] shifting the paradigm in late-stage functionalization. By comparison, methods that modify the piperidine skeleton are less abundant, prompting a quest for methods for this purpose. Such methods would be especially valuable for drug discovery, in which maximizing structural diversity, specifically at a late stage, is highly valued.[13] To this end, we sought to develop a ring contraction of piperidines and related saturated heterocycles to carbocyclic frameworks to achieve core, rather than peripheral, modification.

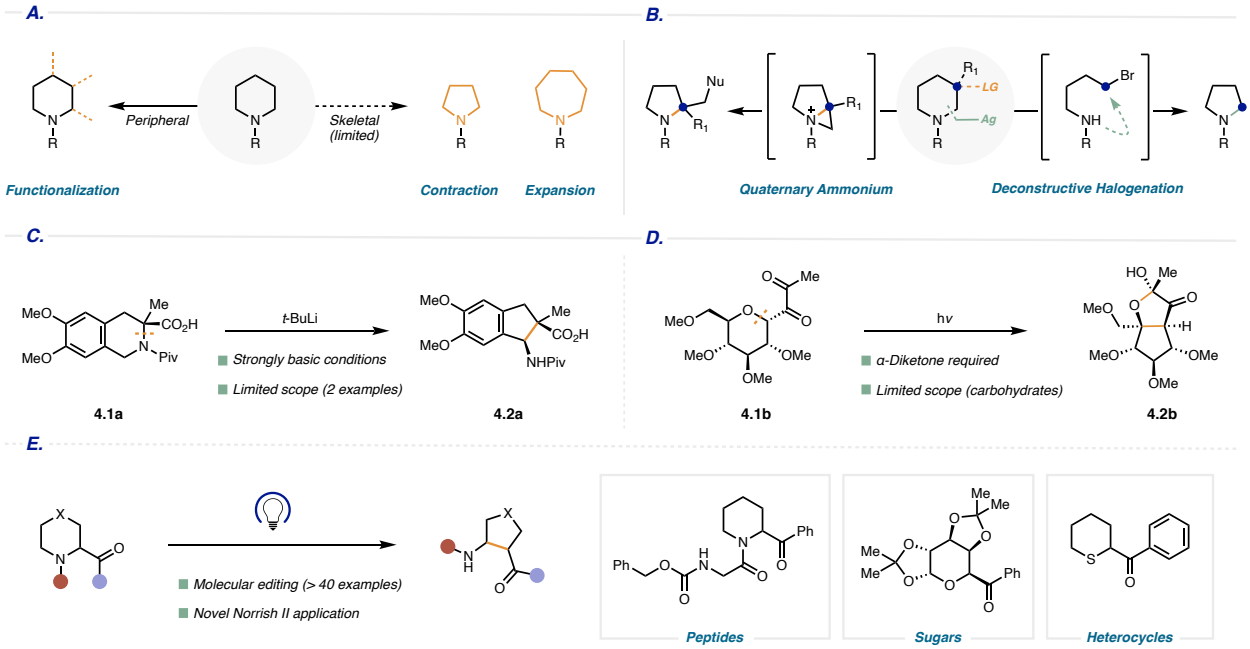


Figure 4.1. Approaches to piperidine diversification. (A) Peripheral functionalization and skeletal remodeling. (B) Selected examples of ring contractions on piperidine frameworks. (C) Seminal report of Seebach and co-workers' unusual THIQ ring contraction.[20] (D) Contraction of carbohydrates reported by Suárez and co-workers.[21] (E) Norrish type II approach to piperidine skeletal framework modification (*this work*).

Relatively few methods for piperidine ring contraction exist compared with those available for the ring contraction of carbocycles bearing functional handles. For example, in cyclohexanone derivatives alone, anionic, carbene, and cationic intermediates have all been exploited to achieve ring contraction. By contrast, for saturated nitrogen–containing heterocycles (azacycles), commonly used ring contraction strategies predominantly leverage bicyclic, quaternary-ammonium intermediates, which undergo a formal ring contraction upon attack from an exogenous nucleophile (Fig. 4.1B).[14,15] More recently, we reported an approach for piperidine ring contraction through oxidative C(sp^3)–N bond cleavage, wherein silver-mediated deconstructive bromination

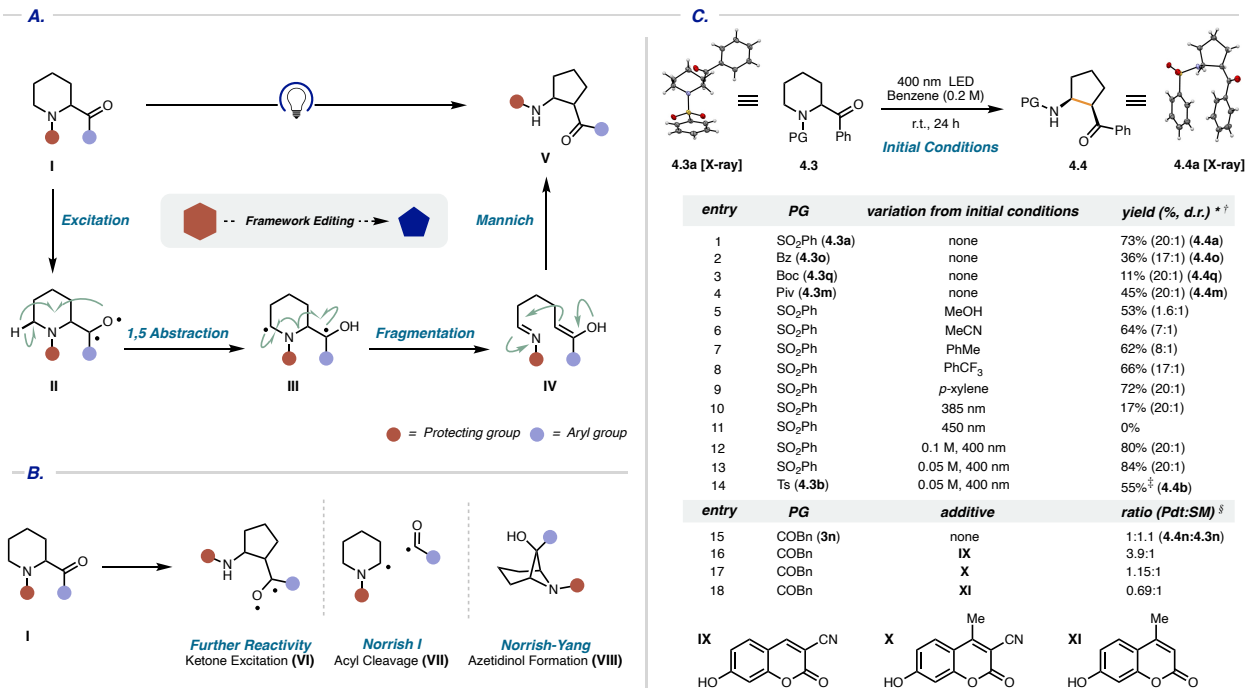
of *N*-benzoyl piperidines followed by intramolecular C–N bond reformation in the resulting acyclic bromoamine furnishes the corresponding *N*-benzoyl pyrrolidine scaffolds in two steps (Fig. 4.1B).[16] Although useful, these tactics are limited to piperidine-to-pyrrolidine scaffold conversions, require specific substitution patterns,[14,15] and use strongly oxidizing conditions that pose a challenge for late-stage diversification.[16,17] The ring contractions of unsaturated azacyclic systems such as pyridiniums and dihydropyridines have also been explored, for example, by using light.[18,19] However, these transformations are limited to substrates with well-recognized photoreactivity profiles.

We sought to develop a complementary and mechanistically distinct approach to piperidine ring contraction that could also be applied to a wide range of saturated heterocycles to provide access to underexplored, skeletally diverse substrates. We drew inspiration from an unusual transformation reported by Seebach and co-workers (Fig. 4.1C), in which an α-carboxyl tetrahydroisoquinoline (THIQ) derivative (**4.1a**) underwent contraction to the corresponding indane scaffold (**4.2a**) under strongly basic conditions. This transformation features a curious endo-to-exocyclic nitrogen atom transposition, giving rise to a β–amino acid structural motif.[20] Despite its novelty, only two examples were reported, and the requisite strongly basic conditions limit its potential application to skeletal modification of drug-like molecules bearing base-reactive functional groups. A more functional-group-compatible, albeit similarly specific, variant of this type of transformation was reported by Suárez and co-workers for α-diketonyl sugars (e.g., **4.1b**), which undergo light-mediated ring contraction with a subsequent hemiketalization to give fused [5,5] ring systems (i.e., **4.2b**) (Fig. 4.1D).[21,22] Notably, the α-diketone moiety required for the reaction is derivatized in the resulting product. Our design of a complementary ring contraction sought broad functional group compatibility and a widened scope beyond α-diketonyl-derived sugars. Herein, we report the visible light–mediated ring contraction of α-acylated cyclic piperidines to furnish *cis*-1,2–disubstituted cyclopentane scaffolds (Fig. 4.1E) and the extension of this method to other saturated heterocycles including tetrahydropyrans and thianes. The success of these Norrish type II transformations hinged on predicted (*and observed*) photophysical differences between the ketone groups in the starting substrates and products (*vide infra*). An asymmetric variant of this transformation is also described.

4.2 Results and Discussion

Development of photomediated ring contraction

We commenced our studies by focusing on piperidine ring contractions (Fig. 4.2A). We envisioned that upon irradiation, α-acylated precursors such as **I**, in which the aroyl group is disposed pseudoaxially to avoid pseudo $A^{1,3}$-like strain,[23] would undergo excitation and intersystem crossing to afford **II** in the triplet state. A subsequent Norrish type II 1,5-hydrogen atom transfer (HAT) would yield the corresponding 1,4-diradical (**III**), which would undergo homolytic C–N bond fragmentation, leading to imine-enol **IV**. The desired cyclopentane product would then result from an intramolecular enol attack on the tethered imine (Mannich reaction) to afford cyclopentane **V**. Under photoirradiation, however, we also recognized the potential for undesired reactivity (Fig. 4.2B), especially further reactivity of the reaction product (**V**) to form additional excited species such as **VI**.



entry	PG	variation from initial conditions	yield (%, d.r.) *,†
1	SO_2Ph (**4.3a**)	none	73% (20:1) (**4.4a**)
2	Bz (**4.3o**)	none	36% (17:1) (**4.4o**)
3	Boc (**4.3q**)	none	11% (20:1) (**4.4q**)
4	Piv (**4.3m**)	none	45% (20:1) (**4.4m**)
5	SO_2Ph	MeOH	53% (1.6:1)
6	SO_2Ph	MeCN	64% (7:1)
7	SO_2Ph	PhMe	62% (8:1)
8	SO_2Ph	$PhCF_3$	66% (17:1)
9	SO_2Ph	*p*-xylene	72% (20:1)
10	SO_2Ph	385 nm	17% (20:1)
11	SO_2Ph	450 nm	0%
12	SO_2Ph	0.1 M, 400 nm	80% (20:1)
13	SO_2Ph	0.05 M, 400 nm	84% (20:1)
14	Ts (**4.3b**)	0.05 M, 400 nm	55%‡ (**4.4b**)
entry	**PG**	**additive**	**ratio (Pdt:SM)** §
15	COBn (**3n**)	none	1:1.1 (**4.4n:4.3n**)
16	COBn	**IX**	3.9:1
17	COBn	**X**	1.15:1
18	COBn	**XI**	0.69:1

Figure 4.2. Reaction development. (A) Proposed mechanism for piperidine ring contraction. (B) Potential undesired side reactivity through Norrish type I and Norrish–Yang cyclization processes. (C) Reaction optimization for light-mediated ring contraction. Reactions were performed on a 0.05 mmol scale. Relative stereochemistry is depicted. *Yields were determined by ^{1}H NMR integration using Ph_3CH as an internal standard. †Diastereomeric ratio (d.r.) was determined by ^{1}H NMR integration of resonances corresponding to diastereomers in the crude mixture. ‡Reaction was performed on a 1-g scale in flow, with an isolated yield of major diastereomer reported. §High throughput experimentation (HTE) conducted to identify 3-cyanoumbelliferone. Conversion was determined by liquid chromatography–mass spectrometry analysis.

In principle, the success of the reaction would depend on subtle differences in reactivity between the starting material (**I**) and the reaction product (**V**; an anticipated "photostationary" state), because both bear a photoreactive phenyl ketone that could participate in Norrish-type processes (see **VI**). In their studies (Fig. 4.1D), Suárez and co-workers had achieved success primarily because a photostationary state was reached upon hemiketalization of the α-diketone in the product.[21,22] We envisioned that even though chemical transformation of the photoreactive moiety would not be realized upon product formation in our case, differences in the n→π* photoabsorption profiles of **I** and **V** could arise by virtue of an intramolecular H-bond that is established in **V**. As is well known for spatially forbidden n→π* transitions, increased polarity in the local environment can lead to a hypsochromic (blue) shift for λ_{max},[24] which we anticipated would lead to differences in the photoreactivity of **I** and **V**. Additionally, we recognized that other photochemical processes could outcompete our desired ring contraction reaction. For example, although more prominent for dialkyl ketones, Norrish type I C–C bond homolysis from the triplet excited state (i.e., **II**) could lead to the formation of undesired alkyl-acyl radical pairs (see **VII**).[24] Another possible complication could arise after 1,5-hydrogen atom abstraction, in which radical recombination of diradical **III** could occur to give the corresponding [3.1.1]-bicycle (**VIII**), i.e., a Norrish–Yang cyclization. We imagined that a Norrish type II C–N fragmentation of **III** (to

ultimately afford **V**) would outcompete a Norrish–Yang cyclization on the basis of an anticipated unfavorable conformational bias against ring closure to azetidinol **VIII** and a slower rate for intersystem crossing to the requisite singlet diradical for cyclobutanol C–C bond formation.[25]

Despite the potential challenges associated with side reactions and overreactions of our phenyl ketone substrate, on the basis of the anticipated differences in absorptivity for **I** and **V,** we reasoned that tuning the wavelength of light could selectively promote the desired reactivity while minimizing the photoreactivity of the resulting products. Gratifyingly, photoirradiation of **4.3a** using a 400-nm blue LED lamp provided 1,2-disubstituted cyclopentane **4.4a** in 73% yield at room temperature (Fig. 4.2C, entry 1). Empirically, the photomediated ring contraction proceeded best with a 400-nm-wavelength light source; longer wavelength irradiation (centered at 450 nm; lower energy) did not result in any conversion, whereas shorter wavelength light sources (e.g., centered at 385 nm; higher energy), which more closely aligned with the calculated and measured absorptivity curves of both product and starting material, led to competing nonspecific oligomerization. Sulfonyl groups on the piperidine nitrogen were especially effective in providing the desired product in good to high yields, presumably enhancing the intramolecular H-bond in **4.4a** that accounts for its stability under the reaction conditions. Other electron-withdrawing groups on the piperidine nitrogen, such as benzoyl, Boc, or pivaloyl (Fig. 4.2C, entries 2 to 4), resulted in lower yields of the ring contraction product. The choice of solvent was also critical. Benzene, which can enhance H-bonding in **4.4a**, gave the highest yields and diastereoselectivity.[26] Other solvents, such as methanol (Fig. 4.2C, entry 5), acetonitrile (Fig. 4.2C, entry 6), toluene (Fig. 4.2C, entry 7), and trifluorotoluene (Fig. 4.2C, entry 8), led to diminished yields and lower diastereoselectivity. Given the toxicity concerns of using benzene, we have also identified *p*-xylene as a serviceable solvent alternative (Fig. 4.2C, entry 9; see the Experimental Procedures for full solvent screen, and select substrates using *p*-xylene as the solvent). Lowering the concentration of the substrate also led to improvements in yield; a concentration of 0.05 M, which presumably slows the rate of competing unproductive intermolecular side reactions, was determined to be optimal. From these observations, we identified an optimized set of conditions for sulfonyl derivatives of the piperidine substrates, which afforded **4.4a** in 84% isolated yield and high diastereoselectivity (Fig. 4.2C, entry 13). The reaction could be performed at gram scale under continuous (flow) conditions (Fig. 4.2C, entry 14; see the Experimental Procedures for additional details). For substrates bearing other protecting groups, such as amide and carbamate substrates, we observed reduced conversion to the desired product. This observation was intriguing because, ostensibly, the photoreactive phenyl ketone group in the starting substrates was conserved. We posited that changing the group on nitrogen (e.g., sulfonyl to acyl or carbamoyl) could lead to discrete differences in the triplet state energy of the phenyl ketone. We hypothesized that a photosensitizer or photocatalyst could improve the efficacy of the reaction, and thus we initiated a screen of 46 known photosensitizers and photocatalysts using amide substrate **4.3n**. 3-Cyanoumbelliferone (**IX**; Fig. 4.2C, entry 16) emerged as an effective additive that improved the efficiency of the reaction: Piperidine **4.3m**, **4.3o**, **4.3s**, and **4.3t** were converted to their corresponding cyclopentylamines with improved yields (average of 11% increase, *vide infra*). The observed effect appeared to be subtle and substrate dependent. Efforts to further understand the role of cyanoumbelliferone **IX** are ongoing.

Scope of the Photomediated Ring Contraction

With optimized conditions in hand, the scope of the visible-light mediated ring contraction was explored (Fig. 4.3A). The generality of the group on the nitrogen atom was investigated first. Arylsulfonyl-derivatized piperidines featuring electron-withdrawing substituents, such as ketones (e.g., **4.3h**), esters (e.g., **4.3i**), and halogens (**4.3e** to **4.3g**), led to good to modest yields of the respective ring-contracted products. Likewise, arylsulfonyl-derivatized piperidines bearing electron-donating groups such as ethers (e.g., **4.3c** and **4.3d**) were also competent in the ring contraction transformation. The presence of a *p*-nitro substituent (**4.3j**) resulted in the complete recovery of starting material, likely resulting from photoquenching.[27–29] Although arylsulfonyl substituents on the piperidine nitrogen led to the highest ring contraction product yields, substrates bearing acyl (e.g., **4.3m** to **4.3p**), carbamoyl (**4.3q**), and urea-type groups (e.g., **4.3r** and **4.3s**) on the nitrogen also led to successful ring contraction in the presence of cyanoumbelliferone (**IX**) (Fig. 4.3A). Phosphoramidite-containing substrates (**4.3t** and **4.3u**) were also competent, providing the cyclopentane products in yields comparable to those observed for substrates bearing a sulfonyl group. In these cases, the phosphoramidyl group is easily removed under acidic conditions.[30] The efficacy of the additive was also found to vary depending on the substrate, with the conversion of **4.3q** to **4.4q** being minimally affected upon adding **IX**. Here, the persisting low yield likely involves reduced productive hydrogen atom transfer because of a preference for an unproductive conformation of the starting material (see the Experimental Procedures for more details).

Next, we investigated the scope of the ring contraction with respect to the nature of the α-aroyl group (Fig. 4.3B). Here, the reaction was shown to be sensitive to sterics, with *p*-methyl substitution (**4.5a**) giving rise to higher yields and diastereoselectivity compared with the isomeric *o*-methyl–substituted **4.5b**. Aryl ketones featuring electron-donating substituents, such as ethers (**4.5c**) and thioethers (**4.5d**), led to good yields and diastereoselectivity for the desired product. Halogen-containing α-aryl-ketone **4.5e** was also competent in the ring contraction chemistry, affording an additional functional handle for modification after ring contraction. By comparison, electron-withdrawing groups such as *p*-CN and *p*-CF_3 (e.g., **4.5f**and **4.5g**) led to the formation of the desired product in modest yield and lower diastereoselectivity. This is likely the result of the increased acidity of the α-keto-proton in the product, which could undergo epimerization. On the basis of our calculations, epimerization through a retro–Mannich-Mannich pathway is unlikely (*vide infra*). Additionally, in the case of substrate **4.5g**, we observed an ensuing ring opening of the product through Norrish type II cleavage, evidencing the potential overreactivity of the cyclopentane products in some cases (see the Experimental Procedures for more details). Other aromatic ketones were also examined. For example, extended aromatic systems such as naphthalenyl ketones (**4.5h**) performed comparably, as did heteroaromatics such as thiophenyl ketones (see **4.5k**). Although the conditions identified were optimized for α-aroyl groups, several substrates bearing non–aryl-substituted ketones also participated successfully in the ring contraction transformation. Specifically, the desired products were observed for an alkynyl C(sp)–bearing substrate (**4.5l**) and a vinyl C(sp^2)–bearing substrate (**4.5m**). In the case of **4.5l**, the substantial decrease in yield can be attributed to a competing Norrish–Yang cyclization process leading to an azetidinol side product (see the Experimental Procedures for more details). Using more forcing, higher-energy (mercury lamp) irradiation, alkyl C(sp^3)–substituted ketone **4.5n** was converted to **4.6n** in 25% yield, highlighting, even in this case, the differential reactivity of the ketone groups in the starting material and product.

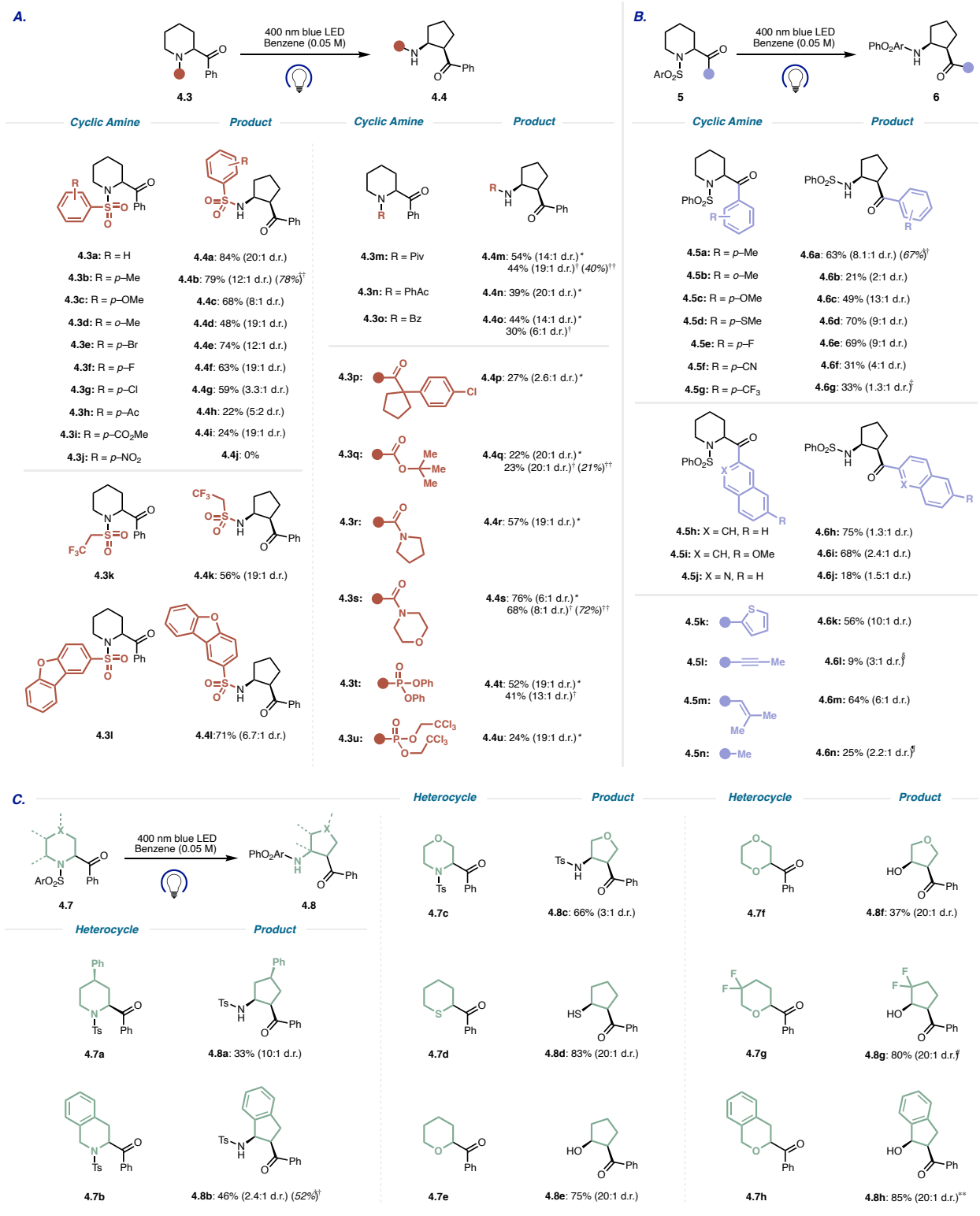


Figure 4.3. Scope of substrates in piperidine ring contraction. Reaction conditions: Starting material (0.2 mmol), benzene (0.05 M), 400 nm LED, 18 to 24 hours. Isolated yields reported and relative stereochemistry are shown. Diastereomeric ratio was determined by ^{1}H NMR integration of resonances corresponding to diastereomers in the crude. (A) Scope of protecting groups in ring contraction. *Additive IX (30 mol%) was added to the reaction mixture.

[†]0.2 mmol scale trials conducted in the absence of additive IX. (B) Scope of aryl ketone in ring contraction. [‡]Ring-opened product after a subsequent Norrish type II process is also observed. [§](With *N*-Ts) Norrish–Yang azetidinol product observed in 12% (19% *brsm*). [¶](With *N*-Ts) Reaction irradiated with a medium-pressure mercury lamp for 24 hours. (C) Scope of heterocyclic core in ring contraction. [#]Reaction conducted on a 0.14 mmol scale. [**]Reaction conducted on a 0.11 mmol scale. [††]Selected examples conducted on a 0.05 mmol scale using *p*-xylene (0.05 M) as a solvent. Yield was determined by ^{1}H NMR integration using Ph_3CH as an internal standard (see the Experimental Procedures for more details).

Substituted piperidines and several other saturated heterocycles were then examined for their propensity to undergo this type of ring contraction (Fig. 4.3C). Single substituents at the γ-position were tolerated (see **4.7a**), imparting stereocontrol. Benzannulated substrates such as tetrahydroisoquinoline **4.7b** successfully underwent the ring contraction transformation, providing the corresponding amino indane scaffolds (i.e., **4.8b**) in good yields and under mild conditions. Additionally, upon irradiation of substrates containing a morpholine scaffold, the tetrahydrofuran heterocycle (**4.8c**) was formed. The ring contraction methodology was also extended beyond azacyclic frameworks to α-acylated thiane and tetrahydropyran derivatives. These were also competent substrates, leading to the formation of cyclopentane thiol and alcohol products (see **4.8d** to **4.8h**), respectively. In the case of **4.7d**, formation of the resulting thiol (**4.8d**) could be viewed as the unveiling of a covalent modifier upon photoirradiation.

Finally, we turned our attention toward the application of the ring contraction methodology to biologically active small molecules to demonstrate the potential for late-stage derivatization of drug candidates. Upon irradiation, MDMC (**4.9a**, stimulant), rimiterol (**4.9b**, bronchodilator),

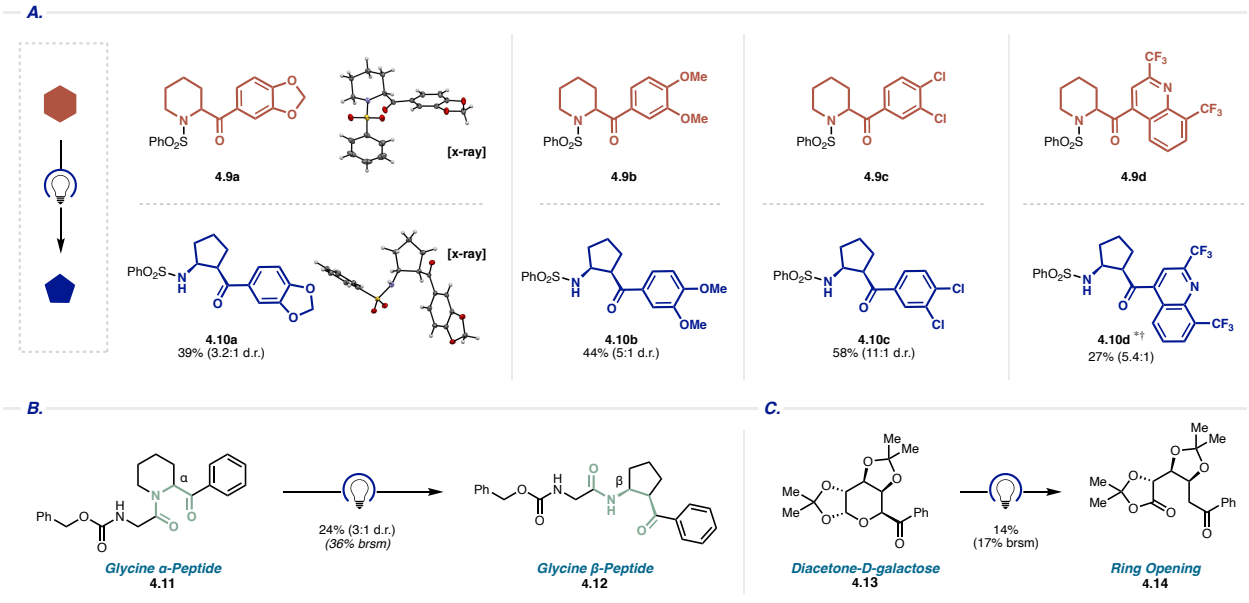


Figure 4.4. Applications toward biologically relevant compounds. (A) Selected examples of bioactive drug molecule contraction. (B) Ring contraction–mediated peptide editing (see the Experimental Procedures for more details). (C) Sugar editing enabled by targeted "digestion." Reaction conditions: Starting material (0.2 mmol), benzene (0.05 M), 400 nm LED, 24 hours. Isolated yields reported and relative stereochemistry are shown. Diastereomeric

ratio was determined by ^{1}H NMR integration of resonances corresponding to diastereomers in the crude. *Reaction conducted on a 0.1 mmol scale, where yield was determined by ^{1}H NMR integration using Ph_3CH as an internal standard and d.r. was determined by ^{1}H NMR integration of resonances corresponding to diastereomers in the crude. †Ring-opened product also observed in 4.5% yield (see the Experimental Procedures for more details).

cathinone (**4.9c**, DAT reuptake inhibitor),[31] and mefloquine (**4.9d**, antimalarial) derivatives underwent contraction to their corresponding cyclopentane isomers (Fig. 4.4A). In the case of **4.9d**, a ring-opened aldehyde side product was also observed, potentially arising from hydrolysis of the imine intermediate before Mannich-type ring closure. We speculate that these events were likely due to the electron-deficient bis-trifluoromethylquinoline group in **4.9d**.

The ring contraction transformation was also leveraged in peptide diversification (Fig. 4.4B). Here, glycine-containing peptide **4.11** was converted to the corresponding amino cyclopentane (**4.12**), unveiling an H-bond donor. In this example, irradiation converts the α-peptide grouping to the corresponding β-amino ketone, accomplishing a nonintuitive peptide modification. Prospective applications include unveiling peptide-turn mimics upon irradiation. Because of the participation of cyclic ether derivatives in these light-mediated ring contractions, we also explored this rearrangement in sugar editing (Fig. 4.4C). When subjected to 400-nm irradiation conditions, D-galactose–derived bis-acetonide **4.13** gave isomeric ring–opened product **4.14**. Here, the enol resulting from the Norrish type II ring opening presumably tautomerizes to the aryl ketone and does not engage the lactone carbonyl group, offering a powerful targeted "digestion" of sugar derivatives.

Computational Insight

To gain insight into the proposed mechanism and origin of stereoselectivity for these photomediated ring contractions, we performed a computational study for the reaction of N-tosyl piperidine derivative **4.3b** (Fig. 4.5A). All of the quantum chemical calculations in the transition state modeling presented were performed using the Gaussian 16 program.[32] Geometry optimizations and frequency calculations were performed at the M06-2X/6-31+G** level of theory with the SMD model for implicit solvation by benzene (see the Experimental Procedures for more details).[33–35] We initially postulated that the positional selectivity for 1,5-HAT could be attributed to the greater hydricity and lower bond dissociation energy of the α-amino hydrogen atom (Fig. 4.5A, ^{3}**4.3b** → ^{3}**A**). Using density functional theory (DFT) calculations, we found that the more hydridic and polarity matched α-piperidinyl hydrogen atom had a HAT transition state 9.0 kcal/mol lower in energy than the potentially competing C–H abstraction at the γ-position.[36,37] The calculations also revealed a conformational preference in the transition state for the N–S bond wherein maximal separation is maintained between the carbonyl and sulfonyl oxygens (see the Experimental Procedures for more details).

We also reasoned that the diastereoselective formation of the cis-disposed amino cyclopentane products (e.g., **4.4b**) would potentially result from a series of noncovalent interactions such as π-stacking and H-bonding in the transition state for the Mannich-type ring closure. Computed transition state structures support the Mannich-type cyclization/C–C bond formation proceeding

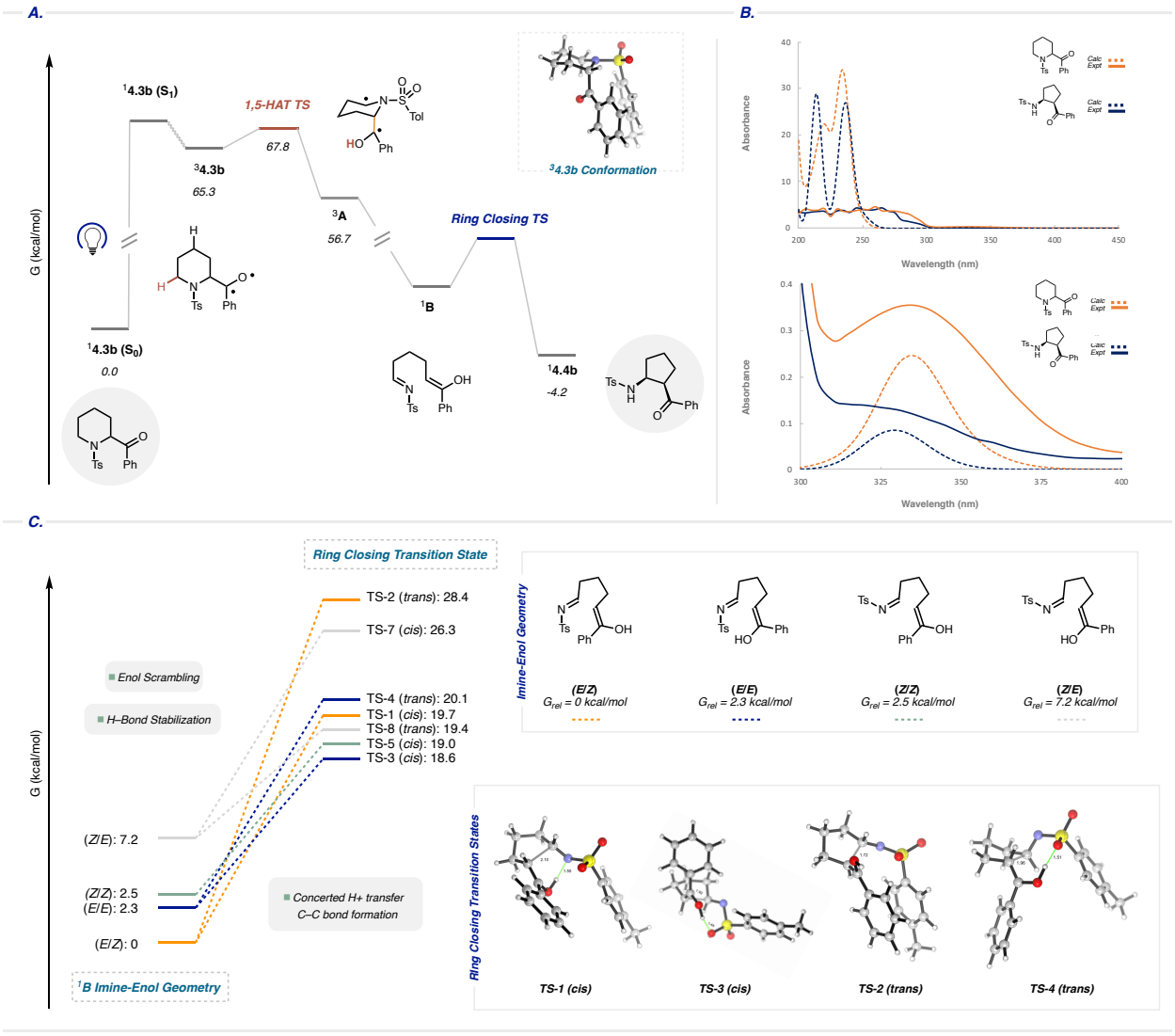


Figure 4.5. Computational studies on ring contraction mechanism. (A) Reaction profile for the piperidine ring contraction. (B) Experimentally and computationally (normalized) determined absorption profiles for the starting material (**4.3b**) and product (**4.4b**). (C) Imine-enol geometries and transition states calculated for the diastereoselective ring closure.

in concert with proton transfer from the enol moiety to the *N*-tosyl group, consistent with the proposal by Suárez and co-workers for the aldol-type cyclization in hexopyranose carbohydrates.[22] Three scenarios could be envisaged that qualitatively support the experimentally observed diastereoselectivity (Fig. 4.5C, *top right*). In the first scenario, only the (*E*/*Z*) imine–enol is productive. This geometry arises when fragmentation of diradical intermediate **^{3}A** occurs faster than acyl bond rotation (Fig. 4.5A, see **^{3}A** orange bond). Alternatively, if interconversion of the (*Z*) and (*E*) forms for both the enol (C=C) and the imine (C=N) bonds is facile, then all four possible imine–enol double-bond geometries can be accessed in the Mannich cyclization. However, the requisite triplet 1,4-diradical conformer that would afford the (*Z*)-imine (Ts-axial) is high in energy, and the contributions from a (*Z*)-imine geometry to the stereochemical outcome

are expected to be negligible (see the Experimental Procedures for a complete discussion). We propose, therefore, that the most likely scenario is one in which the diradical is long-lived enough to allow acyl bond rotation and subsequent sampling of both enol diastereomers.[38,39] In this scenario, only the (*E*/*Z*) and (*E*/*E*) imine–enols are accessible and the energy differences between **TS-1**–**4** would determine the stereochemical outcome. The Boltzmann average of these four transition states predicted a ratio of 14:1 in favor of the *cis* cyclopentane isomer, in good agreement with the experimentally determined 12:1 ratio. The *cis* diastereoselectivity mainly originates from the energy difference between **TS-3** and **TS-4**, which could be rationalized by a shorter and presumably stronger H-bond, as well as a more staggered arrangement of substituents about the forming C–C bond in **TS-3** (Fig. 4.5C, ^{1}**B** → ^{1}**4b**). The overall transformation of *N*-tosyl piperidine **4.3b** to either cyclopentane product was calculated to be exergonic (–4.2 kcal mol^{-1} for the **4.4b** compared with –3.3 kcal mol^{-1} for the *trans*-isomer of **4.4b**).

Insight into the selective reactivity of the starting material compared with the product under the reaction conditions was also supported by the DFT-calculated and empirically measured absorption profiles of **4.3b** and **4.4b**. Even though the calculated λ_{max} values for the starting material and product (Fig. 4.5B, *top*) did not differ markedly, we observed secondary absorption peaks associated with the expected n→π* occurring from 300 to 375 nm (Fig. 4.5B, *bottom*). Here, a hypsochromic shift was observed for amino cyclopentane product **4.4b** relative to starting piperidine **4.3b**, likely accounting for the selective excitation of the starting material. Also observed empirically was an overall decrease in absorptivity for the product (e.g., ε_{340} = 48.0 L cm^{-1} mol^{-1} for **4.3b** versus ε_{320} = 19.2 L cm^{-1} mol^{-1} for **4.4b**). Although predictions and rationalizations of photochemical processes tend to focus on λ_{max} values, in our system, irradiation at λ_{max} would have led to indiscriminate reaction of both the starting materials and products. By focusing on the secondary, n→π* absorption region of 300 to 375 nm, we were able to modulate the reactivity of the ketone group that is conserved in both the starting material and product by exploiting subtle differences in the absorbance wavelengths and extinction coefficients (see the Experimental Procedures for more details).[40] The emission spectrum of the 400-nm light source slightly overlaps with the wavelength of light absorbed by the starting material but negligibly with the product. However, the empirically established optimal use of a commercially acquired 400-nm blue LED light source remains to be fully reconciled with the measured absorption values.

Toward a General Asymmetric Variant

Our insights into the observed diastereoselectivity for these transformations, which arises from highly organized transition states of an achiral imine-enol intermediate (as revealed from our calculations), combined with the successes of other powerful enantioselective photomediated processes,[41,42] inspired us to pursue enantioselective variants. We observed the formation of racemic product **4.4b** when enantioenriched **4.3b** was subjected to the ring contraction conditions, confirming that in this formal radical polar crossover the imine–enol intermediate is achiral. Therefore, we could circumvent the inherent challenges associated with stereocontrol of radical intermediates by effecting enantioselective closure of the achiral imine-enol intermediate under a two-electron reaction manifold.[43] Given the ample literature precedent and predictive models for chiral phosphoric acid–catalyzed reactions of imines, we postulated that rate enhancement of the Mannich step would occur after imine protonation and attendant deprotonation of the enol, leading to an organized transition state favoring attack on one enantioface (see Fig. 4.6 and the

Experimental Procedures for more details). The combination of H-bonding and ion pairing that would be realized in this case was anticipated to yield enantioenriched Mannich products (Fig. 4.6).[44–48]

Consistent with this hypothesis, ring contraction of **4.3b** with 10 mol% of (*R*)-TRIP (CPA1) as an additive provided (–)-**4.4b** in 92:8 enantiomeric ratio (e.r.) 84% enantiomeric excess (*ee*) with yields and diastereoselectivity consistent with those obtained under the standard reaction conditions for the formation of the racemate; using the SPINOL-derived phosphoric acid (*R*)-XYL-SPA (CPA2) gave (+)-**4.4b** in 95:5 e.r. (90% *ee*). Enantioselectivity, albeit modest, was also observed for amide, urea, THIQ, morpholine, and tetrahydropyran derivatives, giving rise to the enantioenriched products **4.4m**, **4.4s**, **4.8b**, **4.8c**, **4.8e**, and **4.8g**, respectively.

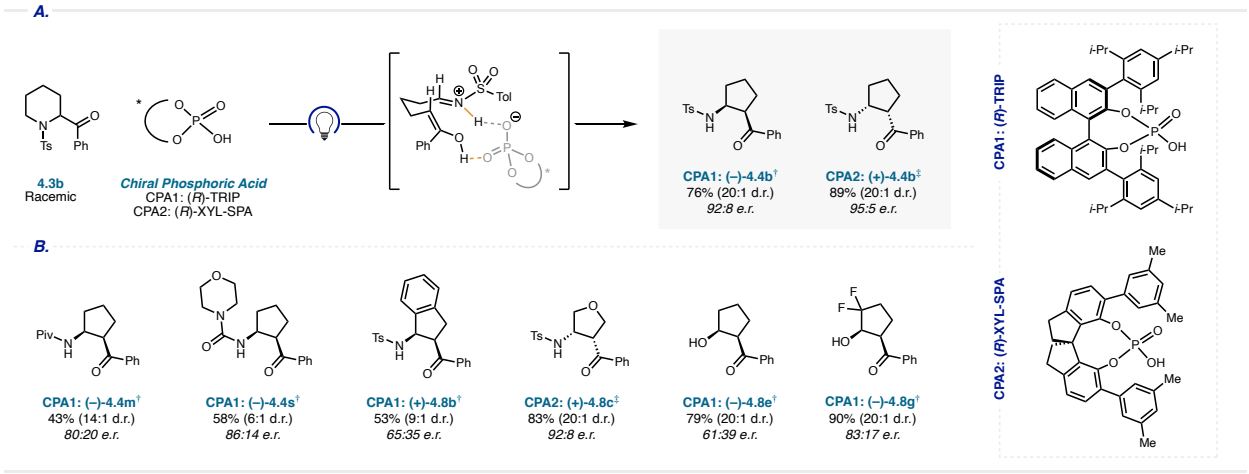


Figure 4.6. Development of an asymmetric ring contraction variant. *Reaction conducted on a 0.05 mmol scale in which yields were determined by ^{1}H NMR integration using Ph_3CH as an internal standard and d.r. was determined by ^{1}H NMR integration of resonances corresponding to diastereomers in the crude. For the major diastereomer, e.r. was determined by SFC analysis. †10 mol% (*R*)-TRIP (CPA1) used as chiral phosphoric acid. ‡10 mol% (*R*)-XYL-SPA (CPA2) used as chiral phosphoric acid.

4.3 Conclusion

Using a Norrish type II reaction, we have established a versatile method for the scaffold remodeling of piperidines as well as other saturated heterocycles. The overall transformation is robust, and the conditions tolerate a wide range of functional groups. Key to the success of these transformations is the "photoprotection" of a pendant ketone group in the product through intramolecular H-bonding, an observation supported by our experimental and computational findings. This reaction has been rendered enantioselective using chiral phosphoric acids. Ongoing work will continue to investigate the asymmetric ring contraction across a range of substrates, and will also aim to develop a protocol for installation and removal of the aryl ketone to render the photoreactive handle traceless. A full account of these efforts will be reported in due course.

4.4 Experimental Procedures

4.4.1. General Consideration

4.4.1.1. Solvents and Reagents

Unless otherwise described, commercial reagents were purchased from Sigma Aldrich, Acros Organics, Chem-Impex, Combi-blocks, TCI, Strem, Enamine and/or Alfa Aesar, and used without additional purification. Solvents were obtained from Fisher Scientific, Acros Organics, Alfa Aesar, and Sigma Aldrich. Tetrahydrofuran (THF), diethyl ether (Et_2O) and triethylamine (Et_3N) were sparged with argon and dried by passing through alumina columns using argon in a Glass Contour solvent purification system. Dichloromethane (CH_2Cl_2) was freshly distilled over calcium hydride under a N_2 atmosphere prior to each use. Benzene (PhH), methanol (MeOH), and acetonitrile (MeCN) were sparged with argon and dried by passing through alumina columns using argon in a Glass Contour solvent purification system and were further degassed by sparging with nitrogen prior to usage. Deuterated solvents were purchased from Cambridge Isotope Laboratories and were used without further purification unless otherwise specified.

4.4.1.2. Experimental Procedures

Unless otherwise noted in the experimental procedures, reactions were carried out in flame- or oven-dried glassware under a positive pressure of N_2 in anhydrous solvents using standard Schlenk techniques. All reactions were performed in scintillation or microwave vials under a nitrogen atmosphere unless otherwise specified. Reaction temperatures above room temperature (22–23 °C) were controlled by an IKA® temperature modulator and monitored using liquid-in-glass thermometers. Reaction progress was monitored using a combination of LC/MS analysis (using a Shimadzu LCMS-2020 (UFLC) equipped with the LC-20AD solvent delivery system, a SPD-20AV prominence UV/Vis detector (SPD-M20A Photo Diode Array), and a Thermo Scientific Hypersil GOLD HPLC column (5 μm particle size, 4.6 × 50 mm), and thin-layer chromatography (TLC) on SiliCycle Siliaplates (glass backed, extra hard layer, 60 Å, 250 μm thickness, F254 indicator). Flash column chromatography was performed with either glass columns using Silicycle silica gel (40–63 μm particle size) or with a Yamazen Smart Flash EPCLC W-Prep 2XY (dual channel) automated flash chromatography system on prefilled, premium, universal columns using ACS grade solvents. Preparative thin layer chromatography was performed on SiliCycle Siliaplates (glass backed, extra hard layer, 60 Å, 250 μm thickness, F254 indicator) or Merck KGaA TLC Aluminium oxide 60 F_{254} basic plates. Reversed-phase high-performance liquid chromatography was carried out using an Agilent 1100 HPLC-MSD system consisting of a 6130B single quadrupole mass-selective detector (MSD), G1315B diode array detector, G2258A autosampler, two G1361A preparative pumps, one G1379A quaternary pump with degasser, one G1312A binary pump, and three G1364B fraction collectors from Agilent Technologies. System control and data analysis was performed using Agilent's ChemStation software, revision B.03.01-SR.1. A Waters XBridge C18 OBD Prep Column, 100 Å, 5 μm, 19 mm × 150 mm column was used as the stationary phase (Waters Corporation). Gradient elution was carried out using water and acetonitrile as the mobile phase. An aqueous 10% trifluoroacetic acid or 10% ammonium hydroxide solution was added into the mobile phase as a modifier using a static mixer prior to the column, pumped at 1% of the total mobile phase flow rate. Photoreactions were performed using

either a Penn OC M2 photoreactor equipped with a 400 nm light source or a Hepatochem photoreactor with 390 nm Kessil lamp (Fig. S1), or with an Ace Glass Incorporated medium pressure, quartz, mercury-vapor lamp.

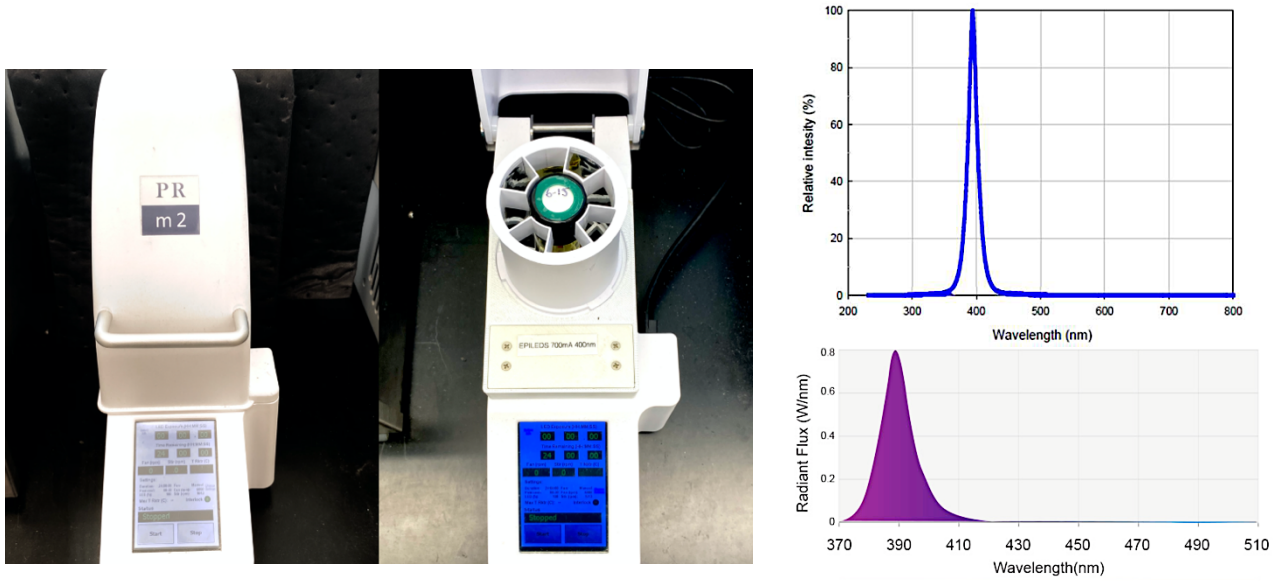


Figure 4.S1: Penn OC M2 photoreactor (*left*) with 400 nm light source emission spectrum (*top right)* and 390 nm Kessil lamp emission spectrum (*bottom right*).

4.4.1.3. Analytical Instrumentation

Proton (^{1}H NMR) and proton-decoupled carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Bruker AVQ-400, AVB-400, AV-500, AV-600 and AV-700 spectrometers, and on a Varian 500 spectrometer using $CDCl_3$, CD_3CN, and DMSO-d_6 as solvents, typically at 20–23 °C. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ 7.26 for ^{1}H NMR, δ 77.16 for ^{13}C NMR in $CDCl_3$ and δ 2.50 for ^{1}H NMR, δ 39.52 for ^{13}C NMR in DMSO-d_6). Data for ^{1}H and ^{13}C spectroscopy are reported as follows; chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, hept = heptet, m = multiplet, br = broad), coupling constant (Hz), integration. High-resolution mass spectra (HRMS) were obtained from the Catalysis Facility of the Lawrence Berkeley National Laboratory (supported by the Director, Office of Science, of the US Department of Energy under contract no. DE-AC02-05CH11231) using a PerkinElmer AxION 2 TOF-MS, or on a Waters Xevo G2 QTof instrument in either ESI+ or ESI– (electrospray) ionization mode. Absorption spectra were recorded using a Varian Cary 60 spectrophotometer. Samples for absorption measurements were contained in a 0.35 x 1 cm quartz cuvette (1.4 mL volume, Starma). SFC purification and analysis was performed with either a Waters ACQUITY UPC2 system or a Sepiatec Prep SFC 100.

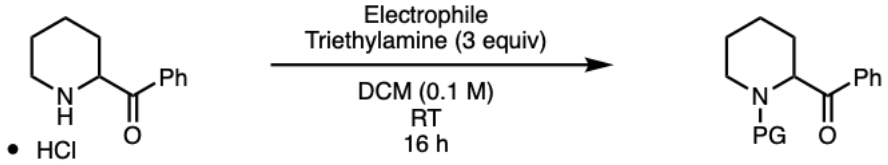
Abbreviations Used:

Aq. = aqueous, sat. = saturated, equiv = equivalents, brsm = based on recovered starting materials, Calc'd = calculated, h = hours, min = minutes, s = seconds, rt = room temperature.

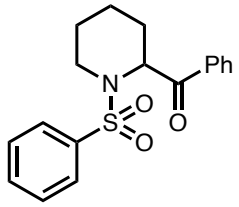
4.4.2. Experimental Procedures for Preparation of Starting Materials

4.4.2.1. Preparation of *N*-Protected α-Acyl Piperidines

General Procedure A



A vial equipped with a stir bar was charged with phenyl(2-piperidinyl)methanone hydrochloride (1.1 equiv) and anhydrous DCM (0.1 M). To this suspension was added triethylamine (3 equiv), followed by the electrophile (1 equiv). The vial was sealed with a Teflon cap, and the reaction mixture was stirred overnight at room temperature. After stirring for 16 h, H_2O was added. The aqueous phase was extracted three times with DCM, and the combined organic phase was dried over $MgSO_4$. Solvent was removed under reduced pressure, and the resulting residue was purified by column chromatography (hexanes / ethyl acetate mobile phase) to afford the desired product.



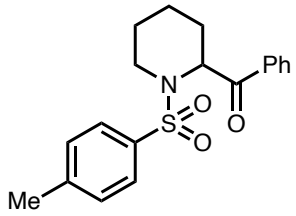
4.3a

Phenyl(1-(phenylsulfonyl)piperidin-2-yl)methanone (4.3a) was synthesized according to General Procedure A on a 0.64 mmol scale using benzenesulfonyl chloride. Purification using column chromatography (EtOAc/hexanes = 1:2) provided **4.3a** (199 mg, 94%) as a clear oil that solidifies upon standing.

^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.83 (d, *J* = 6.9 Hz, 2H), 7.71 (d, *J* = 8.1 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.44 (t, *J* = 7.8 Hz, 2H), 7.40 (t, *J* = 7.9 Hz, 2H), 5.65 (d, *J* = 6.9 Hz, 1H), 3.80 (dd, *J* = 12.3, 3.1 Hz, 1H), 3.55 (td, *J* = 12.5, 3.3 Hz, 1H), 2.01 (d, *J* = 13.3 Hz, 1H), 1.90 (tdd, *J* = 13.8, 6.9, 3.6 Hz, 1H), 1.69 – 1.63 (m, 1H), 1.57 – 1.52 (m, 1H), 1.52 – 1.46 (m, 1H), 1.28 (qt, *J* = 13.0, 3.3 Hz, 1H);

^{13}C NMR: (176 MHz, $CDCl_3$) δ 198.8, 139.7, 135.4, 133.4, 132.5, 128.8, 128.8, 128.2, 127.2, 56.7, 43.1, 27.5, 24.7, 19.1;

HRMS (ESI): *m/z* Calc'd for $C_{18}H_{19}NNaO_3S$ $[M+Na]^+$: 352.0978, found: 352.0978.



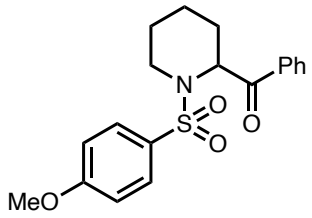
4.3b

Phenyl(1-tosylpiperidin-2-yl)methanone (4.3b) was synthesized according to General Procedure A on a 0.64 mmol scale using tosyl chloride. Purification using column chromatography (EtOAc/hexanes = 1:2) provided **4.3b** (208 mg, 95%) as a pale-yellow oil that solidifies upon standing.

^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.0 Hz, 2H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.9 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 5.62 (d, *J* = 4.4 Hz, 1H), 3.75 (d, *J* = 12.4 Hz, 1H), 3.51 (td, *J* = 12.5, 3.3 Hz, 1H), 2.35 (s, 3H), 1.99 (d, *J* = 13.9 Hz, 1H), 1.87 (tdd, *J* = 13.7, 6.8, 3.6 Hz, 1H), 1.65 – 1.60 (m, 1H), 1.55 – 1.50 (m, 1H), 1.49 – 1.44 (m, 1H), 1.28 (qt, *J* = 13.1, 3.5 Hz, 1H);

^{13}C NMR: (176 MHz, $CDCl_3$) δ 198.9, 143.1, 136.8, 135.4, 133.3, 129.4, 128.8, 128.2, 127.3, 56.6, 43.0, 27.4, 24.6, 21.5, 19.0;

HRMS (ESI): *m/z* Calc'd for $C_{19}H_{21}NNaO_3S$ $[M+Na]^+$: 366.1134, found: 366.1135.



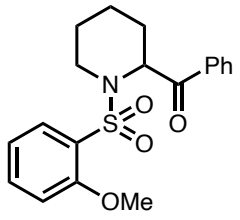
4.3c

(1-((4-Methoxyphenyl)sulfonyl)piperidin-2-yl)(phenyl)methanone (4.3c) was synthesized according to General Procedure A on a 0.64 mmol scale using 4-methoxybenzenesulfonyl chloride. Purification using column chromatography (EtOAc/hexanes = 1:3) provided **4.3c** (205 mg, 89%) as a pale-yellow oil.

^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.0 Hz, 2H), 7.64 (d, *J* = 7.3 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 2H), 6.87 (d, *J* = 7.2 Hz, 2H), 5.62 (d, *J* = 6.7 Hz, 1H), 3.83 (s, 3H), 3.76 (dd, *J* = 12.9, 4.2 Hz, 1H), 3.52 (td, *J* = 13.7, 12.9, 3.3 Hz, 1H), 2.04 – 1.98 (m, 1H), 1.91 (tdd, *J* = 13.8, 6.8, 3.6 Hz, 1H), 1.69 – 1.65 (m, 1H), 1.58 – 1.47 (m, 2H), 1.37 – 1.28 (m, 1H);

^{13}C NMR: (176 MHz, $CDCl_3$) δ 199.2, 162.8, 135.6, 133.4, 131.5, 129.5, 128.9, 128.3, 114.1, 56.7, 55.6, 43.1, 27.6, 24.7, 19.2;

HRMS (ESI): *m/z* Calc'd for $C_{19}H_{21}NNaO_4S$ $[M+Na]^+$: 382.1083, found: 382.1084.



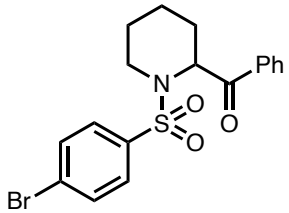
4.3d

(1-((2-Methoxyphenyl)sulfonyl)piperidin-2-yl)(phenyl)methanone (4.3d) was synthesized according to General Procedure A on a 1.1 mmol scale using 2-methoxybenzenesulfonyl chloride. Purification using column chromatography (EtOAc/hexanes = 0–40%) provided **4.3d** (363 mg, 91%) as a yellow oil.

^{1}H NMR: (499 MHz, $CDCl_3$) δ 7.89 – 7.83 (m, 3H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.48 – 7.41 (m, 3H), 6.93 (t, *J* = 7.6 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 5.77 (d, *J* = 5.9 Hz, 1H), 3.90 (dd, *J* = 12.8, 4.5 Hz, 1H), 3.68 (td, *J* = 12.8, 3.0 Hz, 1H), 3.60 (s, 3H), 2.04 (d, *J* = 8.1 Hz, 1H), 1.97 (tdd, *J* = 13.8, 6.8, 3.7 Hz, 1H), 1.68 (d, *J* = 12.9 Hz, 1H), 1.65 – 1.57 (m, 1H), 1.50 (dt, *J* = 13.0, 4.2 Hz, 1H), 1.38 – 1.25 (m, 1H);

^{13}C NMR: (126 MHz, $CDCl_3$) δ 198.7, 156.8, 135.6, 134.3, 133.3, 131.0, 128.9, 128.4 128.3, 120.2, 112.2, 56.8, 55.9, 43.3, 28.1, 25.5, 19.6;

HRMS (ESI): *m/z* Calc'd for $C_{19}H_{22}NO_4S$ $[M+H]^+$: 360.1269, found: 360.1275.



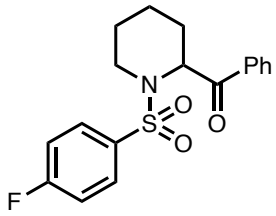
4.3e

(1-((4-Bromophenyl)sulfonyl)piperidin-2-yl)(phenyl)methanone (4.3e) was synthesized according to General Procedure A on a 0.64 mmol scale using 4-bromobenzenesulfonyl chloride. Purification using column chromatography (EtOAc/hexanes = 1:3) provided **4.3e** (187 mg, 72%) as a yellow oil.

^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.2 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.56 – 7.53 (m, 4H), 7.47 (t, *J* = 7.6 Hz, 2H), 5.65 (d, *J* = 4.9 Hz, 1H), 3.84 – 3.76 (m, 1H), 3.54 (td, *J* = 12.6, 3.3 Hz, 1H), 2.09 – 2.04 (m, 1H), 1.95 (tdd, *J* = 13.8, 6.9, 3.5 Hz, 1H), 1.75 – 1.67 (m, 1H), 1.62 – 1.50 (m, 2H), 1.32 – 1.25 (m, 1H);

^{13}C NMR: (176 MHz, $CDCl_3$) δ 198.8, 138.8, 135.3, 133.6, 132.2, 129.0, 128.9, 128.3, 127.5, 56.9, 43.2, 27.8, 24.9, 19.1;

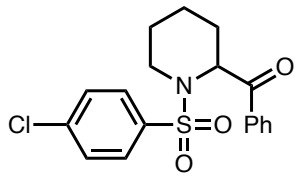
HRMS (ESI): *m/z* Calc'd for $C_{18}H_{18}BrNNaO_3S$ $[M+Na]^+$: 430.0083, found: 430.0082.



4.3f

(1-((4-Fluorophenyl)sulfonyl)piperidin-2-yl)(phenyl)methanone (4.3f) was synthesized according to General Procedure A on a 1.1 mmol scale using 4-fluorobenzenesulfonyl chloride. Purification using column chromatography (EtOAc/hexanes = 0–30%) provided **4.3f** (351 mg, 91%) as a white solid.

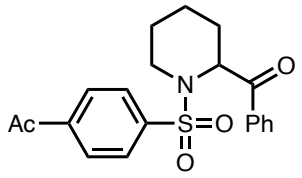
^{1}H NMR: NMR (600 MHz, $CDCl_3$) δ 7.88 – 7.79 (m, 2H), 7.76 – 7.67 (m, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.16 – 7.03 (m, 2H), 5.66 (d, *J* = 5.2 Hz, 1H), 3.85 – 3.75 (m, 1H), 3.54 (td, *J* = 12.4, 3.1 Hz, 1H), 2.05 (d, *J* = 13.9 Hz, 1H), 1.95 (tdd, *J* = 13.8, 6.8, 3.5 Hz, 1H), 1.72 (d, *J* = 13.2 Hz, 1H), 1.58 (ddd, *J* = 16.5, 9.4, 4.0 Hz, 2H), 1.38 – 1.23 (m, 1H);
^{13}C NMR: (151 MHz, $CDCl_3$) δ 199.0, 165.1 (d, *J* = 254.2 Hz), 135.9 (d, *J* = 2.9 Hz), 135.5, 133.7, 130.1 (d, *J* = 9.2 Hz), 129.1, 128.3, 116.2 (d, *J* = 22.5 Hz), 56.9, 43.3, 27.9, 24.9, 19.2;
HRMS (ESI): *m/z* Calc'd for $C_{18}H_{19}FNO_3S$ $[M+H]^+$: 348.1069, found: 348.1081.



4.3g

(1-((4-Chlorophenyl)sulfonyl)piperidin-2-yl)(phenyl)methanone (4.3g) was synthesized according to General Procedure A on a 0.64 mmol scale using 4-chlorobenzenesulfonyl chloride. Purification using column chromatography (EtOAc/hexanes = 1:3) provided **4.3g** (161 mg, 69%) as an orange solid.

^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.1 Hz, 2H), 7.63 (d, *J* = 6.7 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 7.38 (d, *J* = 8.6 Hz, 2H), 5.65 (d, *J* = 6.8 Hz, 1H), 3.81 (dd, *J* = 12.2, 4.7 Hz, 1H), 3.54 (tt, *J* = 12.5, 2.4 Hz, 1H), 2.08 – 2.02 (m, 1H), 1.99 – 1.91 (m, 1H), 1.71 (d, *J* = 13.4 Hz, 1H), 1.61 – 1.53 (m, 2H), 1.32 – 1.26 (m, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 198.8, 139.0, 138.3, 135.3, 133.6, 129.2, 129.0, 128.8, 128.3, 56.9, 43.2, 27.8, 24.9, 19.1;
HRMS (ESI): *m/z* Calc'd for $C_{18}H_{18}ClNNaO_3S$ $[M+Na]^+$: 386.0588, found: 386.0588.



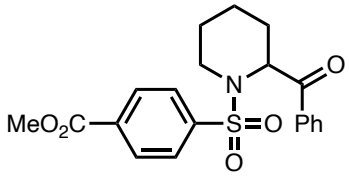
4.3h

1-(4-((2-Benzoylpiperidin-1-yl)sulfonyl)phenyl)ethan-1-one (4.3h) was synthesized according to General Procedure A on a 1.1 mmol scale using 4-acetylbenzenesulfonyl chloride. Purification using column chromatography (EtOAc/hexanes = 0–40%) provided **4.3h** (270 mg, 66%) as a yellow oil.

^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.5 Hz, 2H), 7.86 – 7.76 (m, 3H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 5.69 (d, *J* = 5.4 Hz, 1H), 3.92 – 3.84 (m, 1H), 3.56 (td, *J* = 12.5, 3.1 Hz, 1H), 2.62 (s, 3H), 2.13 – 2.01 (m, 1H), 1.96 (tdd, *J* = 13.8, 6.9, 3.5 Hz, 1H), 1.73 (d, *J* = 13.1 Hz, 1H), 1.63 – 1.55 (m, 2H), 1.33 – 1.24 (m, 1H);

^{13}C NMR: δ 198.8, 197.0, 143.8, 139.8, 135.4, 133.7, 129.1, 128.9, 128.3, 127.7, 57.1, 43.4, 28.0, 27.0, 25.0, 19.2;

HRMS (ESI): *m/z* Calc'd for $C_{20}H_{22}NO_4S$ $[M+H]^+$: 372.1269, found: 372.1260.



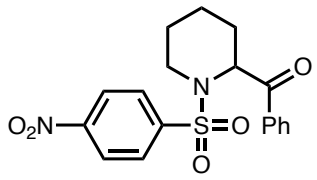
4.3i

Methyl 4-((2-benzoylpiperidin-1-yl)sulfonyl)benzoate (4.3i) was synthesized according to General Procedure A on a 1.1 mmol scale using methyl 4-(chlorosulfonyl)benzoate. Purification using column chromatography (EtOAc/hexanes 0–40%) provided **4.3i** (320 mg, 77%) as a white solid.

^{1}H NMR: (600 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.5 Hz, 2H), 7.84 – 7.80 (m, 2H), 7.76 (d, *J* = 8.5 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 5.68 (d, *J* = 5.5 Hz, 1H), 3.94 (s, 3H), 3.86 (d, *J* = 12.0 Hz, 1H), 3.56 (td, *J* = 12.6, 3.2 Hz, 1H), 2.10 – 2.03 (m, 1H), 1.95 (tdd, *J* = 13.8, 6.9, 3.6 Hz, 1H), 1.72 (d, *J* = 12.6 Hz, 1H), 1.61 – 1.55 (m, 1H), 1.35 – 1.20 (m, 1H);

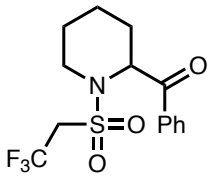
^{13}C NMR: (151 MHz, $CDCl_3$) δ 198.7, 165.9, 143.8, 135.4, 133.7, 130.2, 129.1, 128.3, 127.4, 57.0, 52.7, 43.4, 27.9, 24.9, 19.2 (2 C's overlapping);

HRMS (ESI): *m/z* Calc'd for $C_{20}H_{22}NO_5S$ $[M+H]^+$: 388.1218, found: 388.1215.



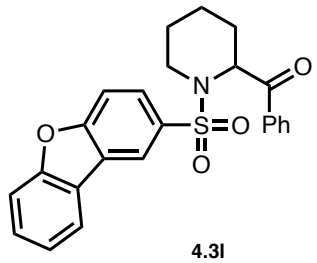
4.3j

(1-((4-Nitrophenyl)sulfonyl)piperidin-2-yl)(phenyl)methanone (4.3j) was synthesized according to General Procedure A on a 0.64 mmol scale using 4-nitrobenzene sulfonyl chloride. Purification using column chromatography (EtOAc/hexanes 1:2) provided **4.3j** (212 mg, 88%) as an orange solid.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 8.25 (d, *J* = 8.8 Hz, 2H), 7.85 (d, *J* = 9.0 Hz, 2H), 7.78 (d, *J* = 7.7 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 5.70 (d, *J* = 9.3 Hz, 1H), 3.90 (d, *J* = 9.6 Hz, 1H), 3.54 (td, *J* = 12.3, 3.2 Hz, 1H), 2.11 (d, *J* = 15.3 Hz, 1H), 2.00 (tdd, *J* = 14.0, 6.9, 3.3 Hz, 1H), 1.78 – 1.72 (m, 1H), 1.64 – 1.56 (m, 2H), 1.24 – 1.18 (m, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 198.5, 149.9, 145.4, 135.0, 133.9, 129.1, 128.5, 128.2, 124.1, 57.4, 43.4, 28.1, 24.9, 19.0;
HRMS (ESI): *m/z* Calc'd for $C_{18}H_{18}N_2NaO_5S$ $[M+Na]^+$: 397.0829, found: 397.0836.



4.3k

Phenyl(1-((2,2,2-trifluoroethyl)sulfonyl)piperidin-2-yl)methanone (4.3k) was synthesized according to General Procedure A on a 0.93 mmol scale using 2,2,2-trifluoroethane-1-sulfonyl chloride. Purification using column chromatography (EtOAc/hexanes 0–30%) provided **4.3k** (212 mg, 68%) as a colorless solid.
^{1}H NMR: (499 MHz, $CDCl_3$) δ 7.87 (d, *J* = 7.3 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.8 Hz, 2H), 5.62 (d, *J* = 5.7 Hz, 1H), 3.87 (dq, *J* = 15.0, 9.2 Hz, 2H), 3.76 – 3.56 (m, 2H), 2.22 (d, *J* = 14.2 Hz, 1H), 2.03 (dddt, *J* = 14.0, 10.6, 7.1, 3.5 Hz, 1H), 1.78 (q, *J* = 13.1 Hz, 1H), 1.69 – 1.57 (m, 2H), 1.32 – 1.19 (m, 1H);
^{13}C NMR: (151 MHz, DMSO) δ 199.9, 134.9, 133.8, 129.0, 128.3, 122.0 (q, *J* = 277.6 Hz), 58.8, 54.1 (q, *J* = 32.4 Hz), 43.4, 28.3, 24.9, 19.3;
HRMS (ESI): *m/z* Calc'd for $C_{14}H_{17}F_3NO_3S$ $[M+H]_+$: 336.0881, found 336.0872.



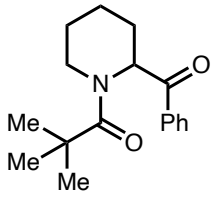
4.3l

(1-(Dibenzo[*b*,*d*]furan-2-ylsulfonyl)piperidin-2-yl)(phenyl)methanone (4.3l) was synthesized according to General Procedure A on a 0.32 mmol scale using dibenzo[*b*,*d*]furan-2-sulfonyl chloride. Purification using column chromatography (EtOAc/hexanes 1:3%) provided **4.3l** (134 mg, 99%) as a white foam.

^{1}H NMR: (700 MHz, $CDCl_3$) δ 8.30 (d, *J* = 2.0 Hz, 1H), 7.84 – 7.77 (m, 4H), 7.60 – 7.54 (m, 3H), 7.51 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H), 7.43 (dd, *J* = 8.3, 7.4 Hz, 2H), 7.36 (td, *J* = 7.5, 1.0 Hz, 1H), 5.73 (dd, *J* = 6.8, 2.2 Hz, 1H), 3.87 (dt, *J* = 12.6, 3.5 Hz, 1H), 3.59 (td, *J* = 12.5, 3.4 Hz, 1H), 2.07 – 2.03 (m, 1H), 1.97 (tdd, *J* = 13.8, 6.8, 3.6 Hz, 1H), 1.74 – 1.70 (m, 1H), 1.60 – 1.56 (m, 2H), 1.37 – 1.29 (m, 1H);

^{13}C NMR: (176 MHz, $CDCl_3$) δ 199.0, 158.1, 157.1, 135.5, 134.3, 133.5, 129.0, 128.4, 128.3, 126.5, 124.8, 123.6, 123.4, 121.3, 120.9, 112.2, 112.1, 56.6, 43.3, 27.6, 24.8, 19.1;

HRMS (ESI): *m/z* Calc'd for $C_{24}H_{21}NNaO_4S$ $[M+Na]^+$: 442.1083, found 442.1084.



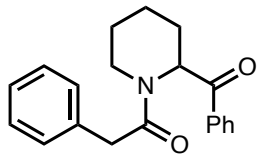
4.3m

1-(2-Benzoylpiperidin-1-yl)-2,2-dimethylpropan-1-one (4.3m) was synthesized according to General Procedure A on a 0.64 mmol scale using pivaloyl chloride. Purification using column chromatography (EtOAc/hexanes = 1:2) provided **4.3m** (163 mg, 93%) as a clear oil.

^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.1 Hz, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 2H), 5.99 (d, *J* = 4.2 Hz, 1H), 3.99 (d, *J* = 12.6 Hz, 1H), 3.25 (td, *J* = 13.5, 12.9, 2.9 Hz, 1H), 2.16 (d, *J* = 12.7 Hz, 1H), 1.78 – 1.69 (m, 1H), 1.67 – 1.55 (m, 3H), 1.50 – 1.42 (m, 1H), 1.21 (s, 9H);

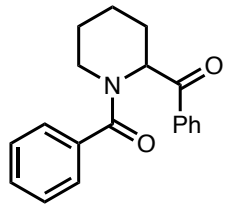
^{13}C NMR: (176 MHz, $CDCl_3$) δ 201.4, 177.4, 136.2, 132.8, 128.5, 128.1, 56.2, 45.0, 38.8, 28.2, 25.8, 25.7, 20.2;

HRMS (ESI): *m/z* Calc'd for $C_{17}H_{23}NNaO_2$ $[M+Na]^+$: 296.1621, found 296.1622.



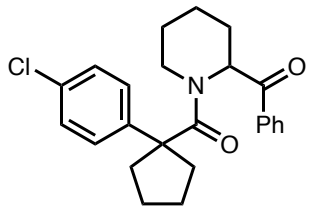
4.3n

1-(2-Benzoylpiperidin-1-yl)-2-phenylethan-1-one (4.3n) was synthesized according to General Procedure A on a 0.6 mmol scale using 2-phenylacetyl chloride. Purification using column chromatography (EtOAc/hexanes = 0–25%) provided **4.3n** (126 mg, 68%) as a yellow oil.
^{1}H NMR: (600 MHz, $CDCl_3$ δ 7.94 – 7.89 (m, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 2H), 7.23 (d, *J* = 7.3 Hz, 1H), 7.19 (d, *J* = 7.3 Hz, 2H), 6.15 (d, *J* = 5.5 Hz, 1H), 3.78 (s, 2H), 3.75 (d, *J* = 12.8 Hz, 1H), 3.31 (td, *J* = 13.2, 2.7 Hz, 1H), 2.17 (d, *J* = 13.9 Hz, 1H), 1.76 (tdd, *J* = 13.6, 6.6, 3.9 Hz, 1H), 1.61 (d, *J* = 11.9 Hz, 2H), 1.54 – 1.48 (m, 1H), 1.30 – 1.25 (m, 1H);
^{13}C NMR: (151 MHz, $CDCl_3$) δ 200.7, 170.9, 136.0, 135.1, 133.2, 128.9, 128.8, 128.8, 128.4, 126.9, 54.9, 44.7, 41.2, 26.2, 25.6, 20.1;
HRMS (ESI): *m/z* Calc'd for $C_{20}H_{22}NO_2$ $[M+H]^+$: 308.1650, found 308.1653.



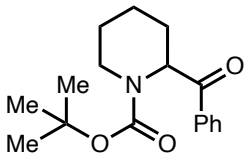
4.3o

Piperidine-1,2-diylbis(phenylmethanone*)* (3o) was synthesized according to the General Procedure A on a 0.64 mmol scale using benzyl chloride. Purification using a pipette column (EtOAc/hexanes = 1:2) provided **3o** (148 mg, 79%) as a white solid. Spectral data was in full agreement with that previously reported.[9]
HRMS (ESI): *m/z* Calc'd for $C_{19}H_{19}NNaO_2$ $[M+Na]^+$: 316.1308, found 316.1309.



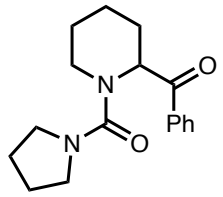
4.3p

(2-Benzoylpiperidin-1-yl)(1-(4-chlorophenyl)cyclopentyl)methanone (4.3p) was synthesized according to General Procedure A on a 1.2 mmol scale using 1-(4-chlorophenyl)cyclopentane-1-carbonyl chloride. Purification using column chromatography (EtOAc/hexanes = 0–40%) provided **4.3p** (491 mg, quant.) as a yellow oil.
^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.2 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 2H), 6.13 (d, *J* = 4.2 Hz, 1H), 3.36 (d, *J* = 13.8 Hz, 1H), 2.87 (td, *J* = 13.2, 3.0 Hz, 1H), 2.53 – 2.44 (m, 1H), 2.29 – 2.20 (m, 1H), 2.14 (d, *J* = 10.4 Hz, 1H), 1.97 – 1.83 (m, 2H), 1.77 – 1.64 (m, 4H), 1.50 – 1.37 (m, 2H), 1.31 – 1.22 (m, 1H), 0.98 – 0.87 (m, 1H);
^{13}C NMR: (126 MHz, $CDCl_3$) δ 201.3, 175.5, 144.4, 136.5, 133.0, 132.0, 128.9, 128.7, 128.5, 128.2, 126.7, 58.3, 55.6, 44.5, 39.7, 37.9, 26.1, 25.6, 25.6, 24.5, 20.0; (2 C's overlapping)
HRMS (ESI): *m/z* Calc'd for $C_{24}H_{27}ClNO_2$ $[M+H]^+$: 396.1730, found 396.1742.



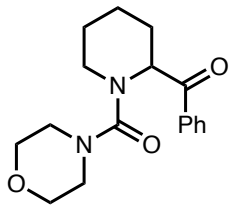
4.3q

***tert*-Butyl 2-benzoylpiperidine-1-carboxylate (4.3q)** was synthesized according to General Procedure A on a 0.32 mmol scale using Boc_2O. Purification using a pipette column (EtOAc/hexanes = 1:2) provided **4.3q** (89 mg, 96%) as a white solid. Spectral data was in full agreement with that previously reported.[49]
HRMS (ESI): *m/z* Calc'd for $C_{17}H_{23}NNaO_3$ $[M+Na]^+$: 312.1570, found 312.1572.



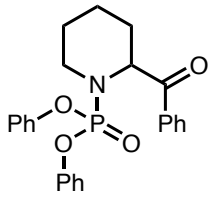
4.3r

(2-Benzoylpiperidin-1-yl)(pyrrolidin-1-yl)methanone (4.3r) was synthesized according to General Procedure A on a 0.82 mmol scale using pyrrolidine-1-carbonyl chloride. Purification using column chromatography (EtOAc/hexanes = 0–50%) provided **4.3r** (154 mg, 67%) as a yellow oil.
^{1}H NMR: (499 MHz, $CDCl_3$ δ 7.90 (d, *J* = 7.3 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.6 Hz, 2H), 5.28 (t, *J* = 5.3 Hz, 1H), 3.52 – 3.42 (m, 1H), 3.42 – 3.32 (m, 2H), 3.32 – 3.20 (m, 2H), 1.99 – 1.69 (m, 6H), 1.59 (dtd, *J* = 26.9, 9.5, 4.8 Hz, 3H);
^{13}C NMR: (151 MHz, DMSO) δ 200.0, 162.2, 136.0, 132.4, 128.3, 127.8, 58.3, 47.5, 45.3, 26.6, 24.9, 21.3 (2 C's overlap);
HRMS (ESI): *m/z* Calc'd for $C_{17}H_{23}N_2O_2$ $[M+H]^+$: 287.1759, found 287.1766.



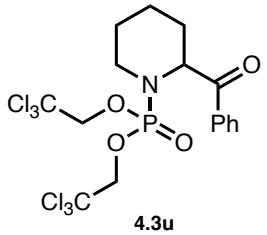
4.3s

(2-Benzoylpiperidin-1-yl)(morpholino)methanone (4.3s) was synthesized according to General Procedure A on a 0.6 mmol scale using morpholine-4-carbonyl chloride. Purification using column chromatography (EtOAc/hexanes = 0–100%) provided **4.3s** (175 mg, 96%) as a yellow oil.
^{1}H NMR: (499 MHz, $CDCl_3$) δ 7.92 – 7.86 (m, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.45 (q, *J* = 7.5, 6.4 Hz, 2H), 5.27 (t, *J* = 5.3 Hz, 1H), 3.63 (qp, *J* = 6.0, 3.0 Hz, 4H), 3.46 – 3.38 (m, 1H), 3.34 – 3.26 (m, 3H), 3.19 (ddd, *J* = 13.2, 5.8, 3.5 Hz, 2H), 2.01 – 1.86 (m, 2H), 1.63 (ddt, *J* = 14.0, 10.3, 5.3 Hz, 3H), 1.55 – 1.51 (m, 1H);
^{13}C NMR: (126 MHz, $CDCl_3$) δ 200.8, 164.5, 136.3, 133.0, 128.7, 128.4, 66.9, 58.3, 47.4, 47.2, 27.0, 25.6, 21.7;
HRMS (ESI): *m/z* Calc'd for $C_{17}H_{23}N_2O_3$ $[M+H]^+$: 303.1708, found 303.1716.



4.3t

Diphenyl (2-benzoylpiperidin-1-yl)phosphonate (4.3t) was synthesized according to General Procedure A on a 0.6 mmol scale using diphenyl phosphorochloridate. Purification using column chromatography (EtOAc/hexanes = 0–50%) provided **4.3t** (130 mg, 51%) as a yellow oil.
^{1}H NMR: (600 MHz, DMSO) δ 7.94 (d, *J* = 7.4 Hz, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 7.38 (dt, *J* = 21.4, 7.9 Hz, 4H), 7.29 – 7.15 (m, 6H), 5.39 (t, *J* = 7.4 Hz, 1H), 3.52 (s, 1H), 3.45 (ddd, *J* = 10.4, 7.7, 2.7 Hz, 1H), 1.93 (d, *J* = 13.8 Hz, 1H), 1.68 (dtt, *J* = 13.6, 6.6, 3.6 Hz, 1H), 1.53 (dd, *J* = 37.5, 12.4 Hz, 2H), 1.26 – 1.15 (m, 2H);
^{13}C NMR: (151 MHz, DMSO) δ 199.9, 150.5 (d, *J* = 6.6 Hz), 150.3 (d, *J* = 6.9 Hz), 135.1, 133.2, 129.8, 129.7, 128.7, 128.0, 124.9 (d, *J* = 9.1 Hz), 120.2 (d, *J* = 4.5 Hz), 119.8 (d, *J* = 5.2 Hz), 55.6 (d, *J* = 3.0 Hz), 41.4, 26.8 (d, *J* = 4.2 Hz), 24.3 (d, *J* = 3.4 Hz), 19.1;
HRMS (ESI): *m/z* Calc'd for $C_{24}H_{25}NO_4P$ $[M+H]^+$: 422.1521, found 422.1523.

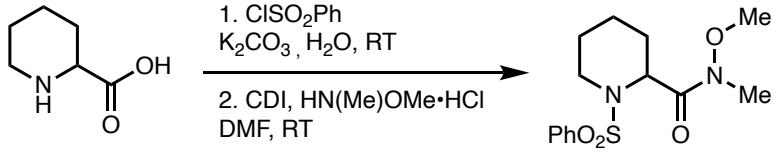


4.3u

Bis(2,2,2-trichloroethyl) phosphorochloridate (4.3u) was synthesized according to General Procedure A on a 0.6 mmol scale using bis(2,2,2-trichloroethyl) phosphorochloridate. Purification using column chromatography (EtOAc/hexanes = 0–50%) provided **4.3u** (249 mg, 78%) as a yellow oil.
^{1}H NMR: (499 MHz, $CDCl_3$) δ 7.88 (d, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 2H), 5.36 – 5.30 (m, 1H), 4.63 – 4.52 (m, 2H), 4.51 – 4.44 (m, 2H), 3.53 (s, 1H), 3.47 – 3.33 (m, 1H), 2.16 (d, *J* = 13.5 Hz, 1H), 1.96 (tdd, *J* = 13.9, 6.8, 3.6 Hz, 1H), 1.71 – 1.57 (m, 3H), 1.44 – 1.34 (m, 1H);
^{13}C NMR: (126 MHz, $CDCl_3$)) δ 200.9, 135.9, 133.3, 128.9, 128.4, 95.3, 76.4 (dd, *J* = 36.7, 4.0 Hz), 56.9 (d, *J* = 3.9 Hz), 42.1 (d, *J* = 1.8 Hz), 27.6 (d, *J* = 3.8 Hz), 25.1 (d, *J* = 3.4 Hz), 20.1;
HRMS (ESI): *m/z* Calc'd for $C_{16}H_{19}Cl_6NO_4P$ $[M+H]^+$: 531.9155, found 531.9131.

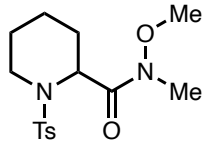
4.4.2.2. Preparation of Aryl Ketone Modified Starting Materials

Representative Procedure B



4.S1

***N*-Methoxy-*N*-methyl-1-((phenylperoxy)thio)piperidine-2-carboxamide (4.S1):** To a 500 mL round-bottomed flask was added piperidine-2-carboxylic acid (7.75 g, 60 mmol, 1.1 equiv) and sat. aq. K_2CO_3 (300 mL, 0.2M). Phenylsulfonyl chloride (9.54 g, 54 mmol, 1.0 equiv) was added in one portion, and the biphasic mixture was stirred overnight at room temperature. 1M HCl was added until a pH = 1 was obtained (as judged by pH paper). A white precipitate formed. The aqueous phase was extracted three times with EtOAc, and the combined organic phase was dried over $MgSO_4$. Solvent was removed under reduced pressure to give phenylsulfonyl protected piperidine-2-carboxylic acid (10.9 g, 75% yield) as a clear oil, which was used without further purification. To a 500 mL round-bottomed flask equipped with stir bar was added phenylsulfonyl protected piperidine-2-carboxylic acid (10.9 g, 40.4 mmol, 1.0 equiv) and CDI (7.20 g, 44.4 mmol, 1.1 equiv), followed by DMF (80 mL, 0.5M). The solution was stirred at room temperature for 20 minutes, then NH(Me)OMe•HCl (4.33 g, 44.4 mmol, 1.1 equiv) was added in one portion. The reaction mixture was stirred overnight at room temperature, then volatiles were removed under reduced pressure. The crude mixture was purified by filtering over a silica plug, eluting with 1:1 Hexanes:EtOAc, to give **4.S1** (12.1 g, 96%) as a white solid.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.0 Hz, 2H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 5.06 (d, *J* = 6.5 Hz, 1H), 3.77 (s, 3H), 3.75 – 3.69 (m, 2H), 3.01 (s, 3H), 1.92 – 1.85 (m, 1H), 1.82 – 1.74 (m, 1H), 1.73 – 1.68 (m, 1H), 1.60 – 1.56 (m, 1H), 1.54 – 1.43 (m, 2H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 171.9, 139.7, 132.5, 128.8, 127.3, 61.6, 51.0, 43.0, 31.9, 27.6, 24.9, 18.8;
HRMS (ESI): *m/z* Calc'd for $C_{14}H_{20}N_2NaO_4S$ $[M+Na]^+$: 335.1036, found: 335.1034.

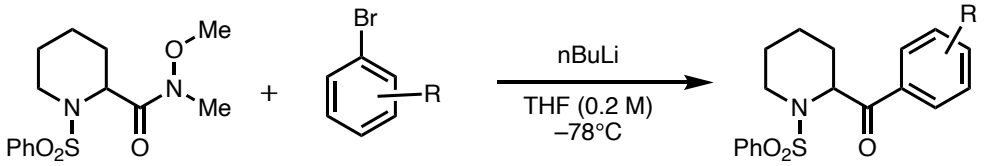


4.S2

***N*-Methoxy-*N*-methyl-1-tosylpiperidine-2-carboxamide (4.S2)** was synthesized according to Representative Procedure B starting from piperidine-2-carboxylic acid (2.0 g, 15.5 mmol, 1.1 equiv) and tosyl chloride (2.68 g, 14.1 mmol, 1.0 equiv). Purification by filtering over a silica plug, eluting with 1:1 Hexanes:EtOAc provided **4.S2** (3.44 g, 67% over two steps) as white solid.

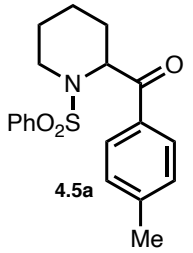
^{1}H NMR (700 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 5.04 (d, *J* = 6.5 Hz, 1H), 3.77 (s, 3H), 3.73 – 3.65 (m, 2H), 3.02 (s, 3H), 2.39 (s, 3H), 1.90 – 1.83 (m, 1H), 1.76 (tdd, *J* = 13.6, 6.6, 3.9 Hz, 1H), 1.71 – 1.66 (m, 1H), 1.59 – 1.54 (m, 1H), 1.52 – 1.44 (m, 2H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 172.0, 143.1, 136.7, 129.4, 127.3, 61.6, 50.9, 42.9, 31.9, 27.5, 24.9, 21.6, 18.8;
HRMS (ESI): *m/z* Calc'd for $C_{15}H_{22}N_2NaO_4S$ [M+Na]+: 349.1192, found 349.1195.

General Procedure C1



4.S1

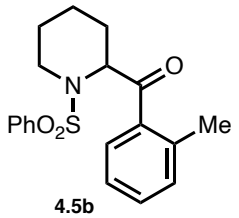
To an oven-dried microwave vial charged with arylbromide (1 mmol, 2 equiv) under a N_2 atmosphere was added THF (1.5 mL). The solution was cooled to –78°C and 1.6M *n*-BuLi (1 mmol, 0.625 mL, 2 equiv) was added dropwise. The resulting mixture was stirred at –78 °C for 30 mins, then **4.S1** (0.5 mmol, 1 equiv) in THF (1.0 mL) was added dropwise. The reaction mixture was stirred for 30 mins or until full consumption of **4.S1** (as judged by TLC) and was then quenched with 3 mL of sat. aq. NH_4Cl. 1 mL of water was added, and the aqueous phase was extracted 3x with 2 mL of Et_2O. The combined organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (hexanes / ethyl acetate mobile phase) afforded the desired aryl ketone.
Alternate Procedure C2: *If the lithiate or Grignard reagent was commercially available, 1 mmol (2 equiv) was added directly to* **4.S1** *in THF (*2.5 mL, 0.2M*) at* –78 °C *(for the lithiate) or* 0 °C *(for the Grignard reagent).*



4.5a

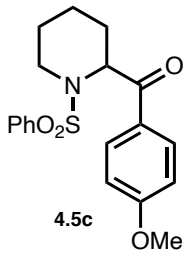
(1-((Phenylperoxy)thio)piperidin-2-yl)(*p*-tolyl)methanone (4.5a) was synthesized according to General Procedure C1 on a 0.5 mmol scale using **4.S1** and 1-bromo-4-methylbenzene. Purification using column chromatography (EtOAc/hexanes = 1:4) provided **4.5a** (132 mg, 77%) as a pale yellow solid.

^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.0 Hz, 2H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.51 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 2H), 7.25 (d, *J* = 7.6 Hz, 2H), 5.64 (dd, *J* = 7.0, 2.1 Hz, 1H), 3.82 (dd, *J* = 15.1, 3.4 Hz, 1H), 3.57 (td, *J* = 12.5, 3.2 Hz, 1H), 2.41 (s, 3H), 2.04 – 2.00 (m, 1H), 1.92 (tdd, *J* = 13.8, 6.9, 3.5 Hz, 1H), 1.70 – 1.64 (m, 1H), 1.58 – 1.50 (m, 2H), 1.34 – 1.27 (m, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 198.4, 144.4, 139.8, 132.9, 132.5, 129.6, 128.9, 128.4, 127.3, 56.6, 43.2, 27.8, 24.8, 21.8, 19.1;
HRMS (ESI): *m/z* Calc'd for $C_{19}H_{21}NNaO_3S$ $[M+Na]^+$: 366.1134, found: 366.1135.



4.5b

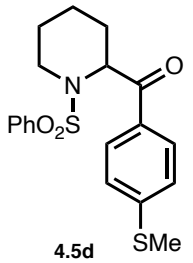
(1-((Phenylperoxy)thio)piperidin-2-yl)(*o*-tolyl)methanone (4.5b) was synthesized according to General Procedure C1 on a 0.5 mmol scale using **4.S1** and 1-bromo-2-methylbenzene. Purification using column chromatography (EtOAc/hexanes = 1:4) provided **4.5a** (50 mg, 29%) as a pale yellow solid.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.1 Hz, 2H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 5.52 (dd, *J* = 7.0, 2.0 Hz, 1H), 3.81 (dd, *J* = 12.6, 3.8 Hz, 1H), 3.46 (td, *J* = 12.8, 3.2 Hz, 1H), 2.34 (s, 3H), 1.95 – 1.89 (m, 1H), 1.79 (tdd, *J* = 13.9, 6.9, 3.7 Hz, 1H), 1.70 – 1.64 (m, 1H), 1.64 – 1.57 (m, 1H), 1.54 – 1.46 (m, 1H), 1.33 – 1.26 (m, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) (176 MHz, $CDCl_3$) δ 203.1, 140.1, 137.7, 136.8, 132.5, 131.9, 131.4, 129.0, 127.7, 127.3, 126.0, 59.2, 43.0, 26.7, 24.8, 20.4, 19.7;
HRMS (ESI): *m/z* Calc'd for $C_{19}H_{21}NNaO_3S$ $[M+Na]^+$: 366.1134, found: 366.1137.



4.5c

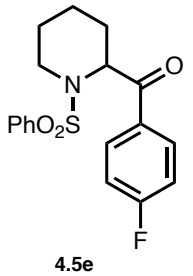
(4-Methoxyphenyl)(1-((phenylperoxy)thio)piperidin-2-yl)methanone (4.5c) was synthesized according to General Procedure C1 on a 0.5 mmol scale using **4.S1** and 1-bromo-4-methoxylbenzene. Purification using column chromatography (EtOAc/hexanes = 1:4) provided **4.5c** (126 mg, 70%) as a pale yellow solid.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.8 Hz, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.61 (dd, *J* = 6.8, 2.1 Hz, 1H), 3.87 (s,

3H), 3.81 (dd, *J* = 12.5, 4.5 Hz, 1H), 3.59 (td, *J* = 12.6, 3.2 Hz, 1H), 2.03 – 1.99 (m, 1H), 1.92 (tdd, *J* = 13.7, 6.8, 3.6 Hz, 1H), 1.70 – 1.65 (m, 1H), 1.58 – 1.48 (m, 2H), 1.37 – 1.30 (m, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 197.2, 163.8, 139.8, 132.5, 130.7, 128.9, 128.2, 127.3, 114.1, 56.2, 55.6, 43.2, 27.9, 24.8, 19.1;
HRMS (ESI): *m/z* Calc'd for $C_{19}H_{21}NNaO_4S$ $[M+Na]^+$: 382.1083, found: 382.1085.



4.5d

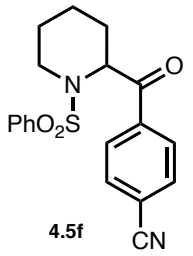
(4-(Methylthio)phenyl)(1-((phenylperoxy)thio)piperidin-2-yl)methanone (4.5d) was synthesized according to General Procedure C1 on a 0.5 mmol scale using **4.S1** and (4-bromophenyl)(methyl)sulfane. Purification using column chromatography (EtOAc/hexanes = 1:4) provided **4.5d** (109 mg, 58%) as a yellow solid.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 7.3 Hz, 2H), 7.51 (t, *J* = 8.1 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 5.59 (d, *J* = 6.8 Hz, 1H), 3.80 (dd, *J* = 12.4, 4.8 Hz, 1H), 3.56 (td, *J* = 12.6, 3.3 Hz, 1H), 2.52 (s, 3H), 2.02 – 1.97 (m, 1H), 1.95 – 1.87 (m, 1H), 1.70 – 1.64 (m, 1H), 1.58 – 1.46 (m, 2H), 1.36 – 1.27 (m, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 197.7, 146.6, 139.8, 132.6, 131.5, 128.9, 128.7, 127.3, 125.2, 56.4, 43.2, 27.7, 24.7, 19.1, 14.8;
HRMS (ESI): *m/z* Calc'd for $C_{19}H_{21}NNaO_3S_2$ $[M+Na]^+$: 398.0855, found: 398.0856.



4.5e

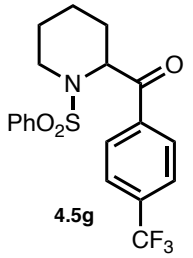
(4-Fluorophenyl)(1-((phenylperoxy)thio)piperidin-2-yl)methanone (4.5e) was synthesized according to General Procedure C1 on a 0.5 mmol scale using **4.S1** and 1-bromo-4-fluorobenzene. Purification using column chromatography (EtOAc/hexanes = 1:4) provided **4.5e** (150 mg, 86%) as a pale yellow solid.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.92 – 7.87 (m, 2H), 7.71 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.43 (dd, *J* = 8.3, 7.4 Hz, 2H), 7.14 (t, *J* = 8.6 Hz, 2H), 5.58 (dd, *J* = 6.8, 2.2 Hz, 1H), 3.79 (dd, *J* = 12.6, 8.0 Hz, 1H), 3.53 (td, *J* = 12.6, 3.2 Hz, 1H), 2.03 – 1.97 (m, 1H), 1.91 (tdd, *J* = 13.7, 6.8, 3.7 Hz, 1H), 1.67 (dt, *J* = 13.4, 3.7 Hz, 1H), 1.57 (dtd, *J* = 13.6, 3.6, 1.1 Hz, 1H), 1.51 (dtt, *J* = 16.7, 8.0, 4.3 Hz, 1H), 1.33 (qt, *J* = 13.1, 3.6 Hz, 1H);

^{13}C NMR: (176 MHz, $CDCl_3$) δ 197.3, 165.9 (d, *J* = 255.8), 139.7, 132.7, 131.8, 131.1 (d, *J* = 9.3 Hz), 129.0, 127.4, 116.1 (d, *J* = 21.9 Hz), 56.7, 43.3, 27.5, 24.6, 19.2;
HRMS (ESI): *m/z* Calc'd for $C_{18}H_{18}FNNaO_3S$ $[M+Na]^+$: 370.0884, found: 370.0885.



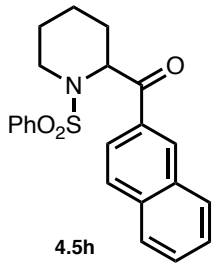
4.5f

4-(1-((Phenylperoxy)thio)piperidine-2-carbonyl)benzonitrile (4.5f) was synthesized according to General Procedure C1 on a 0.5 mmol scale using **4.S1** and 4-bromobenzonitrile. Purification using column chromatography (EtOAc/hexanes = 1:4) provided **4.5f** (113 mg, 64%) as a pale yellow solid.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* = 8.5 Hz, 2H), 7.72 (d, *J* = 7.1 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.45 (dd, *J* = 8.3, 7.4 Hz, 2H), 5.50 (dd, *J* = 6.6, 2.5 Hz, 1H), 3.71 (dt, *J* = 12.7, 4.0 Hz, 1H), 3.42 (td, *J* = 12.6, 3.2 Hz, 1H), 1.99 – 1.94 (m, 1H), 1.85 (dddd, *J* = 14.0, 12.9, 6.6, 3.8 Hz, 1H), 1.66 – 1.60 (m, 1H), 1.57 – 1.52 (m, 1H), 1.44 (tdt, *J* = 15.9, 8.3, 4.1 Hz, 1H), 1.36 – 1.27 (m, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 197.9, 139.5, 138.6, 132.9, 132.7, 129.1, 128.8, 127.3, 117.9, 116.6, 57.6, 43.5, 26.8, 24.3, 19.2;
HRMS (ESI): *m/z* Calc'd for $C_{19}H_{18}N_2NaO_3S$ $[M+Na]^+$: 377.0930, found 377.0930.



4.5g

(1-((Phenylperoxy)thio)piperidin-2-yl)(4-(trifluoromethyl)phenyl)methanone (4.5g) was synthesized according to General Procedure C1 on a 0.5 mmol scale using **4.S1** and 1-bromo-4-trifluoromethylbenzene. Purification using column chromatography (EtOAc/hexanes = 1:4) provided **4.5g** (158 mg, 80%) as a clear oil that solidifies upon standing.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.3 Hz, 2H), 7.73 (dd, *J* = 10.8, 7.6 Hz, 4H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 5.59 (d, *J* = 6.7 Hz, 1H), 3.77 (d, *J* = 12.6 Hz, 1H), 3.46 (td, *J* = 12.6, 3.2 Hz, 1H), 2.00 (dd, *J* = 14.1, 3.0 Hz, 1H), 1.91 (tdd, *J* = 13.6, 6.8, 3.8 Hz, 1H), 1.70 – 1.64 (m, 1H), 1.59 – 1.55 (m, 1H), 1.54 – 1.46 (m, 1H), 1.33 – 1.26 (m, 1H);
^{13}C NMR: (151 MHz, CDCl3) δ 198.2, 139.7, 138.4, 134.8 (q, *J* = 32.9 Hz), 132.8, 129.1, 128.7, 127.4, 126.0 (q, *J* = 3.7 Hz), 123.62 (d, *J* = 272.6 Hz), 57.4, 43.4, 27.1, 24.5, 19.3;
HRMS (ESI): *m/z* Calc'd for $C_{19}H_{18}F_3NNaO_3S$ $[M+Na]^+$: 420.0852, found 420.0855.



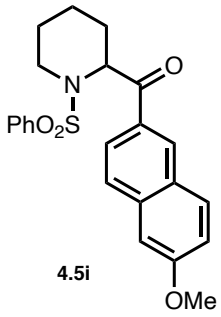
4.5h

Naphthalen-2-yl(1-((phenylperoxy)thio)piperidin-2-yl)methanone (4.5h) was synthesized according to General Procedure C1 on a 0.5 mmol scale using **4.S1** and 2-bromonaphthalene. Purification using column chromatography (EtOAc/hexanes = 1:4) provided **4.5h** (174 mg, 94%) as a clear oil that solidifies upon standing.

^{1}H NMR: (700 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.98 (d, *J* = 8.1 Hz, 1H), 7.89 (t, *J* = 8.3 Hz, 2H), 7.84 (d, *J* = 10.5 Hz, 1H), 7.73 (d, *J* = 7.9 Hz, 2H), 7.62 (t, *J* = 7.2 Hz, 1H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 2H), 5.83 (dd, *J* = 6.9, 2.1 Hz, 1H), 3.86 (dt, *J* = 11.6, 4.2 Hz, 1H), 3.62 (td, *J* = 12.4, 3.2 Hz, 1H), 2.12 – 2.08 (m, 1H), 2.00 (tdd, *J* = 13.9, 6.9, 3.5 Hz, 1H), 1.75 – 1.68 (m, 1H), 1.62 – 1.55 (m, 2H), 1.39 – 1.31 (m, 1H);

^{13}C NMR: (176 MHz, $CDCl_3$) δ 198.9, 139.8, 135.7, 132.7, 132.6, 129.9, 129.8, 128.9, 128.8(8), 128.8(6), 127.9, 127.3, 127.2, 124.0, 56.7, 43.3, 27.9, 24.8, 19.2 (2 C's overlapping);

HRMS (ESI): *m/z* Calc'd for $C_{22}H_{21}NNaO_3S$ $[M+Na]^+$: 402.1134, found 402.1136.



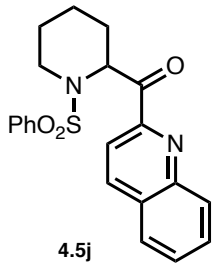
4.5i

(6-Methoxynaphthalen-2-yl)(1-((phenylperoxy)thio)piperidin-2-yl)methanone (4.5i) was synthesized according to General Procedure C1 on a 0.5 mmol scale using **4.S1** and 2-bromo-6-methoxynaphthalene. Purification using column chromatography (EtOAc/hexanes = 1:4) provided **4.5i** (142 mg, 69%) as an off-white amorphous solid.

^{1}H NMR: (700 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.86 (d, *J* = 8.9 Hz, 1H), 7.82 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.76 (d, *J* = 8.6 Hz, 1H), 7.72 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.39 (dd, *J* = 8.3, 7.4 Hz, 2H), 7.22 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.15 (d, *J* = 2.5 Hz, 1H), 5.81 (dd, *J* = 6.9, 2.1 Hz, 1H), 3.96 (s, 3H), 3.90 – 3.78 (m, 1H), 3.63 (td, *J* = 12.4, 3.2 Hz, 1H), 2.12 – 2.07 (m, 1H), 2.00 (tdd, *J* = 13.8, 6.9, 3.6 Hz, 1H), 1.75 – 1.67 (m, 1H), 1.61 – 1.52 (m, 2H), 1.40 – 1.32 (m, 1H);

^{13}C NMR: (176 MHz, $CDCl_3$) δ 198.3, 160.0, 139.7, 137.4, 132.4, 131.2, 130.5, 129.7, 128.8, 127.8, 127.4, 127.2, 124.6, 120.0, 105.7, 56.3, 55.5, 43.2, 27.9, 24.8, 19.0;

HRMS (ESI): *m/z* Calc'd for $C_{23}H_{23}NNaO_4S$ $[M+Na]^+$: 432.1240, found 432.1236



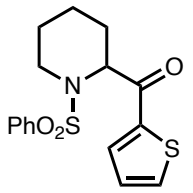
4.5j

(1-((Phenylperoxy)thio)piperidin-2-yl)(quinolin-2-yl)methanone (4.5j) was synthesized according to General Procedure C1 on a 0.5 mmol scale using **4.S1** and 2-bromoquinoline. Purification using column chromatography (EtOAc/hexanes = 20–100%) provided **4.5j** (110 mg, 58%) as a yellow amorphous solid.

^{1}H NMR: (700 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.5 Hz, 1H), 8.21 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 1H), 7.86 (dd, *J* = 8.1, 1.4 Hz, 1H), 7.82 – 7.78 (m, 1H), 7.76 – 7.73 (m, 2H), 7.69 – 7.64 (m, 1H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.37 (t, *J* = 7.9 Hz, 2H), 6.43 (dd, *J* = 7.1, 2.3 Hz, 1H), 3.92 (dt, *J* = 8.2, 5.0 Hz, 1H), 3.75 (td, *J* = 12.4, 3.2 Hz, 1H), 2.32 – 2.27 (m, 1H), 2.07 – 2.01 (m, 1H), 1.77 – 1.70 (m, 1H), 1.62 – 1.55 (m, 2H), 1.33 – 1.23 (m, 1H);

^{13}C NMR: (176 MHz, $CDCl_3$) δ 199.8, 151.4, 147.1, 140.2, 137.2, 132.3, 130.8, 130.3, 129.7, 129.0, 128.8, 127.7, 127.2, 118.4, 56.0, 43.2, 28.0, 25.3, 19.6;

HRMS (ESI): *m/z* Calc'd for $C_{21}H_{20}N_2NaO_3S$ $[M+Na]^+$: 403.1087, found 403.1087.



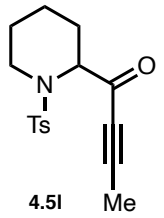
4.5k

(1-((Phenylperoxy)thio)piperidin-2-yl)(thiophen-2-yl)methanone (4.5k) was synthesized in a procedure analogous to Alternate Procedure C2 on a 0.5 mmol scale using **4.S1** and thiophen-2-yllithium. Purification using column chromatography (EtOAc/hexanes = 20%) provided **4.5k** (142 mg, 85%) as a yellow amorphous solid.

^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.82 (dd, *J* = 3.9, 1.1 Hz, 1H), 7.70 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.66 (dd, *J* = 4.9, 1.1 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.42 (dd, *J* = 8.4, 7.4 Hz, 2H), 7.15 (dd, *J* = 4.9, 3.8 Hz, 1H), 5.43 (dd, *J* = 6.6, 2.2 Hz, 1H), 3.82 (dt, *J* = 12.8, 3.8 Hz, 1H), 3.55 (td, *J* = 12.4, 3.2 Hz, 1H), 2.13 – 2.06 (m, 1H), 1.91 (dddd, *J* = 17.4, 13.7, 6.6, 3.8 Hz, 1H), 1.70 – 1.65 (m, 1H), 1.61 – 1.56 (m, 1H), 1.53 – 1.43 (m, 2H);

^{13}C NMR: (176 MHz, $CDCl_3$) δ 191.4, 142.1, 139.6, 134.6, 132.7, 132.7, 129.0, 128.5, 127.3, 57.2, 43.6, 28.0, 24.6, 19.1;

HRMS (ESI): *m/z* Calc'd for $C_{16}H_{17}NNaO_3S_2$ $[M+Na]^+$: 358.0542, found 358.0544.



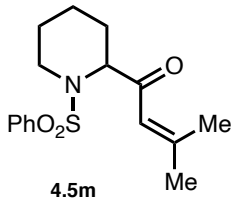
4.5l

1-(1-Tosylpiperidin-2-yl)but-2-yn-1-one (4.5l) was synthesized according to Alternate Procedure C2 on a 0.25 mmol scale using **4.S2** and prop-1-yn-1-ylmagnesium bromide (0.5 mmol) at 0°C. Purification using column chromatography (EtOAc/hexanes = 1:4) provided **4.5l** (54.1 mg, 71%) as a clear oil.

^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.27 (d, *J* = 8.0 Hz, 2H), 4.72 (dd, *J* = 4.7, 1.5 Hz, 1H), 3.73 (ddd, *J* = 13.3, 3.4, 1.9 Hz, 1H), 3.14 (td, *J* = 13.0, 3.0 Hz, 1H), 2.40 (s, 3H), 2.39 – 2.35 (m, 1H), 2.01 (s, 3H), 1.70 – 1.64 (m, 1H), 1.64 – 1.58 (m, 1H), 1.57 – 1.50 (m, 1H), 1.37 (qdd, *J* = 13.0, 4.8, 3.7 Hz, 1H), 1.26 – 1.17 (m, 1H);

^{13}C NMR: (176 MHz, $CDCl_3$) δ 186.2, 143.2, 137.6, 129.6, 127.4, 93.6, 78.8, 62.8, 43.1, 26.3, 24.5, 21.6, 20.1, 4.4;

HRMS (ESI): *m/z* Calc'd for $C_{16}H_{19}NNaO_3S$ $[M+Na]^+$: 328.0978, found 328.0979.



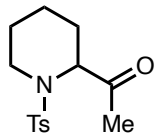
4.5m

3-Methyl-1-(1-((phenylperoxy)thio)piperidin-2-yl)but-2-en-1-one (4.5m) was synthesized according to a modified version of Alternate Procedure C2 on a 1.0 mmol scale using **4.S1** and (2-methylprop-1-en-1-yl)magnesium bromide (2.0 mmol) at –20 °C. Purification using column chromatography (EtOAc/hexanes = 1:5) provided **4.5m** (79.6 mg, 26%) as a clear oil.

^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.81 (d, *J* = 9.6 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 6.28 (s, 1H), 4.55 (d, *J* = 5.2 Hz, 1H), 3.79 (dt, *J* = 14.4, 3.6 Hz, 1H), 3.20 (td, *J* = 12.8, 2.9 Hz, 1H), 2.09 (d, *J* = 15.6 Hz, 1H), 2.07 (s, 3H), 1.89 (s, 3H), 1.53 – 1.44 (m, 3H), 1.32 – 1.25 (m, 2H);

^{13}C NMR: (176 MHz, $CDCl_3$) δ 198.3, 158.6, 140.6, 132.5, 129.1, 127.2, 120.6, 61.4, 43.8, 28.2, 25.4, 24.3, 21.0, 19.9;

HRMS (ESI): *m/z* Calc'd for $C_{16}H_{21}NNaO_3S$ $[M+Na]^+$: 330.1134, found 330.1137.

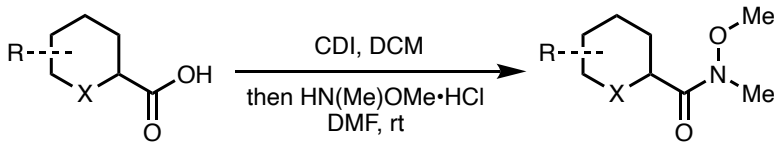


4.5n

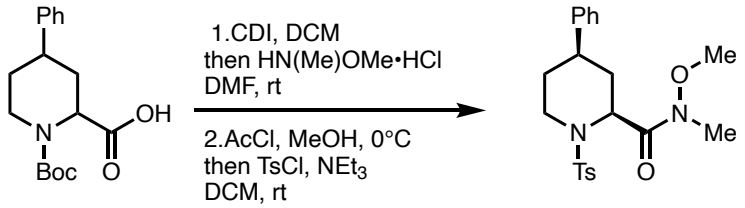
1-(1-Tosylpiperidin-2-yl)ethan-1-one (4.5n): was synthesized using a procedure analogous to General Procedure A on a 1.84 mmol scale using 1-(piperidin-2-yl)ethan-1-one hydrochloride and tosyl chloride. Purification using column chromatography (EtOAc/hexanes = 0–30%) provided **4.5n** (497 mg, 96%) as a white solid.
^{1}H NMR: (499 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.46 (d, *J* = 5.4 Hz, 1H), 3.70 (d, *J* = 13.5 Hz, 1H), 3.15 – 3.06 (m, 1H), 2.43 (s, 3H), 2.23 (s, 3H), 2.09 (dd, *J* = 13.1, 2.9 Hz, 1H), 1.53 – 1.40 (m, 3H), 1.27 (dt, *J* = 14.3, 8.1 Hz, 3H);
^{13}C NMR: (126 MHz, $CDCl_3$) δ 207.3, 143.6, 137.3, 129.9, 127.4, 62.4, 44.0, 27.1, 25.1, 24.2, 21.8, 20.3;
HRMS (ESI): *m/z* Calc'd for $C_{14}H_{20}NO_3S$ $[M+H]^+$: 282.1164, found 282.1170.

4.4.2.3 Preparation of Aryl Ketone Modified Starting Materials

General Procedure D

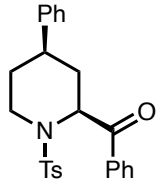


To a vial equipped with a stir bar was added the heterocyclic carboxylic acid (1.0 equiv) and anhydrous DCM (0.3 M). To this solution was added CDI (1.2 equiv), and the mixture was stirred at room temperature until bubbling ceased and solids had dissolved. HN(Me)OMe•HCl (1.2 equiv) was added in one portion, followed by 3–5 drops of DMF, and the reaction mixture was stirred overnight at room temperature. After stirring overnight, the reaction mixture was quenched with water, and the aqueous phase was extracted three times with DCM. The combined organic phase was dried over $MgSO_4$, and concentrated to give the crude Weinreb amide, which was used without further purification.



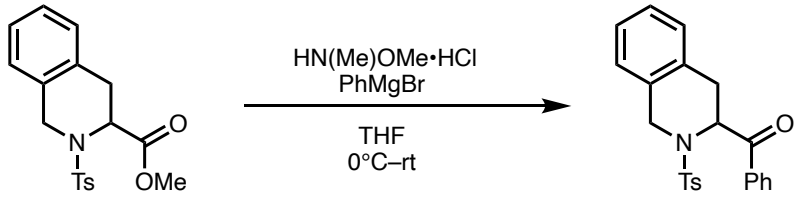
4.S3

***cis*-*N*-methoxy-*N*-methyl-4-phenyl-1-tosylpiperidine-2-carboxamide (4.S3):** 1-(tert-butoxycarbonyl)-4-phenylpiperidine-2-carboxylic acid (2 mmol) was converted to the corresponding Weinreb amide using a procedure analogous to General Procedure D and was carried forward without additional purification. The crude Weinreb amide was dissolved in 4 mL of methanol and the 0.5 M solution was cooled to 0°C. Then acetyl chloride (1.6 mL) was added to the solution dropwise and the solution was warmed to room temperature. The solution was stirred until the reaction was judged complete by LCMS analysis. The solvent was removed by rotary evaporation and then the crude material was dissolved in 10 mL dichloromethane (0.2 M). Tosyl chloride (2 mmol, 381 mg, 1 equiv) was added to the solution in a single portion and then triethyl amine (2.4 equiv, 4.8 mmol, 0.67 mL) was added to the solution dropwise. The solution was allowed to stir overnight and then the reaction mixture was quenched with sat. aq. ammonium chloride solution. The mixture was filtered through a phase separator, washing with dichloromethane, and the combined organic extracts were concentrated. The crude residue (mixture of *cis* and *trans* isomers) was purified by column chromatography on a silica gel Redisep Rf Gold column (4 g), eluting with EtOAc/hexanes 0–40% to give *cis*-*N*-methoxy-*N*-methyl-4-phenyl-1-tosylpiperidine-2-carboxamide (**4.S3**) (319.6 mg, 0.794 mmol, 39.7 % yield) as an impure colorless oil which was carried forward without additional purification.
HRMS (ESI): *m/z* Calc'd for $C_{21}H_{27}N_2O_4S$ $[M+Na]^+$: 403.1691; Found 403.1700.



4.7a

***cis*-Phenyl-(4-phenyl-1-tosylpiperidin-2-yl)methanone (4.7a):** was synthesized according to a procedure analogous to Alternate Procedure C2 using *cis*-**4.S3** and PhMgBr (2 equiv). Purification using column chromatography (EtOAc/hexanes = 0–30%) provided **4.7a** (50 mg, 15%) as a colorless oil.
^{1}H NMR: (499 MHz, $CDCl_3$) δ 8.17 (d, *J* = 7.4 Hz, 2H), 7.75 (d, *J* = 8.2 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.24 (d, *J* = 7.6 Hz, 2H), 7.17 (t, *J* = 7.3 Hz, 1H), 7.09 (d, *J* = 7.3 Hz, 2H), 4.40 (dd, *J* = 11.0, 4.4 Hz, 1H), 3.89 (dt, *J* = 12.1, 4.2 Hz, 1H), 2.85 (td, *J* = 11.5, 3.9 Hz, 1H), 2.60 (tt, *J* = 11.6, 3.8 Hz, 1H), 2.46 (s, 3H), 2.16 – 1.87 (m, 4H);
^{13}C NMR: (151 MHz, $CDCl_3$) δ 197.2, 144.3, 143.8, 135.5, 133.2, 133.1, 129.8, 129.4, 128.8, 128.7, 128.7, 127.0, 126.8, 63.9, 46.8, 40.2, 36.8, 31.1, 21.8.
HRMS (ESI): *m/z* Calc'd for $C_{25}H_{25}NNaO_3S$ [M+Na]+: 442.1447, found 442.1458.



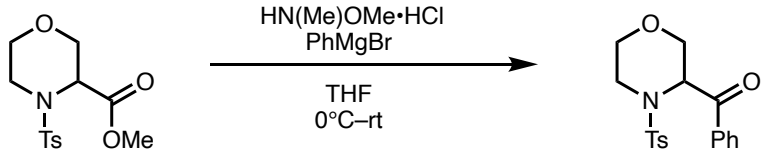
4.7b

Phenyl(2-tosyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methanone (4.7b) was synthesized according to a modified literature procedure (*44*). To a flame-dried microwave vial equipped with a stir bar was added methyl 2-tosyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (1 equiv) and HN(Me)OMe•HCl (1.2 equiv). The vial was evacuated and refilled with nitrogen three times, then anhydrous THF (36 mL) was added to achieve a 0.05 M solution. The resulting solution was cooled to 0 °C, and PhMgBr (4.5 equiv) was added dropwise. The reaction mixture was stirred overnight, warming to room temperature, then an additional portion of PhMgBr (4.5 equiv) was added. The reaction mixture was stirred until full conversion to ketone **4.7b** (as judged by LCMS analysis). The reaction mixture was quenched with a solution of sat. aq. NH_4Cl, then basified with 10% NaOH dropwise. The mixture was extracted three times with EtOAc, and the combined organic phase was dried over Na_2SO_4. The organic phase was filtered, concentrated under reduced pressure, and purified by column chromatography (EtOAc/hexanes = 0–40%) providing **4.7b** (392 mg, 56%) as a yellow oil.

^{1}H NMR: (499 MHz, $CDCl_3$) δ 7.94 – 7.89 (m, 2H), 7.64 (d, *J* = 8.3 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.14 (dd, *J* = 21.3, 7.7 Hz, 3H), 7.07 (t, *J* = 7.2 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.90 (d, *J* = 7.5 Hz, 1H), 5.84 (dd, *J* = 7.0, 2.6 Hz, 1H), 4.76 (d, *J* = 15.9 Hz, 1H), 4.55 (d, *J* = 16.0 Hz, 1H), 3.17 (dd, *J* = 16.4, 7.0 Hz, 1H), 3.08 (dd, *J* = 16.3, 2.4 Hz, 1H), 2.35 (s, 3H);

^{13}C NMR: (126 MHz, $CDCl_3$) δ 197.5, 143.8, 136.2, 135.1, 133.7, 131.9, 130.6, 129.7, 129.0, 128.7, 128.7, 127.6, 127.0, 126.8, 126.1, 56.0, 45.4, 30.6, 21.7;

HRMS (ESI): *m/z* Calc'd for $C_{23}H_{22}NO_3S$ $[M+H]^+$: 392.1320, found 392.1329.

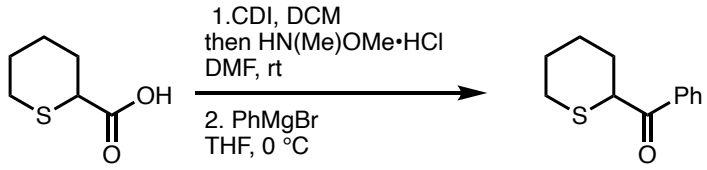


4.7c

Phenyl(4-tosylmorpholin-3-yl)methanone (4.7c) was synthesized according to a modified literature procedure (*50*). To a flame-dried microwave vial equipped with a stir bar was added methyl 4-tosylmorpholine-3-carboxylate (1 equiv) and HN(Me)OMe•HCl (1.2 equiv). The vial was evacuated and refilled with nitrogen three times, then anhydrous THF (0.05 M) was added. The resulting solution was cooled to 0 °C, and PhMgBr (4.5 equiv) was added dropwise. The reaction mixture was stirred overnight, warming to room temperature, then an additional portion of PhMgBr (4.5 equiv) was added. The reaction mixture was stirred until full conversion to ketone **7b** (as determined by LCMS analysis). The reaction mixture was quenched with a solution of sat. aq. NH_4Cl, then basified by dropwise addition of 10% NaOH. The mixture was extracted three

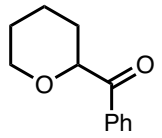
times with EtOAc, and the combined organic phase was dried over Na_2SO_4. The organic phase was filtered, concentrated under reduced pressure, and purified by column chromatography (EtOAc/hexanes = 0–60%) providing **4.7c** (26 mg, 41%) as a yellow oil.
^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.82 – 7.78 (m, 2H), 7.63 – 7.57 (m, 3H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 5.40 (d, *J* = 3.9 Hz, 1H), 4.20 (d, *J* = 11.9 Hz, 1H), 3.92 – 3.86 (m, 2H), 3.79 (td, *J* = 11.9, 11.2, 3.6 Hz, 1H), 3.60 (td, *J* = 12.4, 11.9, 3.2 Hz, 2H), 2.40 (s, 3H);
^{13}C NMR: (151 MHz, $CDCl_3$) δ 196.3, 143.8, 136.3, 135.3, 133.7, 129.8, 129.1, 128.3, 127.6, 68.5, 67.0, 57.6, 42.5, 21.8;
HRMS (ESI): *m/z* Calc'd for $C_{18}H_{19}NO_4SNa$ $[M+H]^+$: 368.0933, found 368.0931.

Representative Procedure E



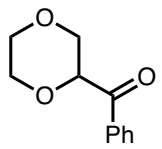
4.7d

Phenyl(tetrahydro-2*H*-thiopyran-2-yl)methanone (4.7d): Tetrahydro-2*H*-thiopyran-2-carboxylic acid was converted to the corresponding Weinreb amide using a procedure analogous to General Procedure D on a 0.5 mmol scale and was carried forward without additional purification. To an oven dried microwave vial equipped with a stir bar was added the crude Weinreb amide (1.0 equiv). The vial was evacuated and backfilled three times with nitrogen, and then 5 mL of anhydrous THF was added to make a 0.1 M solution. The resulting solution was cooled to 0 °C, and PhMgBr (1.0 equiv) was added dropwise. The reaction mixture was stirred at 0 °C until consumption of the Weinreb amide (as judged by TLC). The reaction mixture was quenched with sat. aq. NH_4Cl, and water. The aqueous phase was extracted three times with Et_2O, and the combined organic phase was dried over $MgSO_4$. Volatiles were removed under reduced pressure, and the resulting crude residue was purified by column chromatography (EtOAc/hexanes = 1:3) to provide **4.7d** (36 mg, 36% over 2 steps) as a white solid.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.1 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 4.39 (dd, *J* = 7.7, 3.2 Hz, 1H), 2.76 (ddd, *J* = 13.5, 6.9, 3.4 Hz, 1H), 2.71 (ddd, *J* = 13.5, 9.0, 3.1 Hz, 1H), 2.14 – 2.04 (m, 3H), 1.90 (dtt, *J* = 13.6, 6.8, 3.4 Hz, 1H), 1.80 (tdd, *J* = 12.5, 6.5, 3.3 Hz, 1H), 1.60 – 1.53 (m, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 197.7, 135.6, 133.2, 128.8, 128.7, 45.0, 29.1, 28.6, 26.8, 24.3.
HRMS (EI): *m/z* Calc'd for $C_{12}H_{14}OS$ [M]+: 206.0760, found 206.0766.



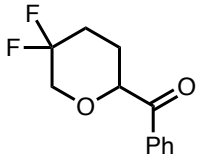
4.7e

Phenyl(tetrahydro-2*H*-pyran-2-yl)methanone (4.7e) was synthesized in a two-step procedure analogous to Representative Procedure E using tetrahydro-2*H*-pyran-2-carboxylic acid. Purification using column chromatography (EtOAc/hexanes = 1:3) provided **4.7e** (56 mg, 59% over 2 steps) as a clear oil. Spectral data was in full agreement with that previously reported.[51]



4.7f

(1,4-Dioxan-2-yl)(phenyl)methanone (4.7f) was synthesized in a two-step procedure analogous to Representative Procedure E using 1,4-dioxane-2-carboxylic acid. Purification using column chromatography (EtOAc/hexanes = 1:3) provided **4.7f** (47 mg, 49% over 2 steps) as a clear oil. Spectral data was in full agreement with that previously reported.[51]



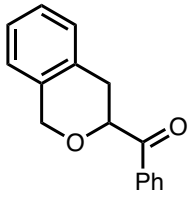
4.7g

(5,5-Difluorotetrahydro-2*H*-pyran-2-yl)(phenyl)methanone (4.7g) was synthesized in a two-step procedure analogous to Representative Procedure E using 5,5-difluorotetrahydro-2H-pyran-2-carboxylic acid. Purification using preparative TLC (EtOAc/hexanes = 1:3) provided **4.7g** (24 mg, 53% over 2 steps) as a white solid.

^{1}H NMR: (700 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.2 Hz, 2H), 7.59 (t, *J* = 7.5 Hz, 1H), 7.47 (t, *J* = 7.9 Hz, 2H), 4.73 (dd, *J* = 8.6, 4.2 Hz, 1H), 4.02 (dtd, *J* = 12.2, 7.8, 2.4 Hz, 1H), 3.83 – 3.56 (m, 1H), 2.33 (ddtd, *J* = 17.5, 10.1, 5.0, 2.4 Hz, 1H), 2.18 – 2.12 (m, 2H), 2.11 – 2.03 (m, 1H);

^{13}C NMR: (176 MHz, $CDCl_3$): δ 196.77, 134.78, 133.79, 129.23, 128.75, 117.8 (t, *J* = 244.2 Hz), 78.37, 69.4 (t, *J* = 33.2 Hz), 30.8 (t, *J* = 23.7), 25.1 (t, *J* = 4.6 Hz);

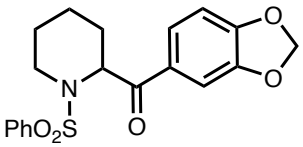
HRMS (ESI): *m/z* Calc'd for $C_{12}H_{12}F_2NaO_2$ $[M+Na]^+$: 249.0698, found 249.0699.



4.7h

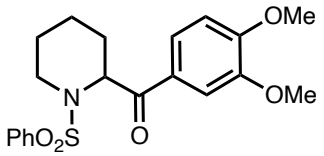
Isochroman-3-yl(phenyl)methanone (4.7h) was synthesized in a two-step procedure analogous to Representative Procedure E using isochromane-3-carboxylic acid. Purification using column chromatography (EtOAc/hexanes = 1:3 provided **4.7h** (34 mg, 28% over 2 steps) as a white solid.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 8.05 (d, *J* = 9.7 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.50 (dd, *J* = 8.3, 7.4 Hz, 2H), 7.23 – 7.20 (m, 2H), 7.18 – 7.15 (m, 1H), 7.05 (dd, *J* = 5.3, 3.7 Hz, 1H), 5.09 (dd, *J* = 10.7, 3.7 Hz, 1H), 5.06 – 4.93 (m, 2H), 3.22 (dd, *J* = 16.5, 10.8 Hz, 1H), 3.02 (dd, *J* = 16.4, 3.7 Hz, 1H).
^{13}C NMR: (176 MHz, CDCl3) δ 197.5, 135.0, 134.0, 133.7, 132.2, 129.1, 129.1, 128.8, 126.9, 126.6, 124.4, 76.7, 68.4, 30.7.
HRMS (ESI): *m/z* Calc'd for $C_{16}H_{14}NaO_2$ $[M+Na]^+$: 261.0886, found 261.0888.

4.4.2.4 Preparation of Biologically Relevant Starting Materials



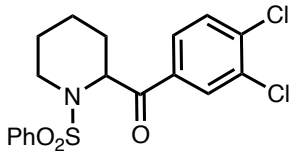
4.9a

Benzo[*d*][1,3]dioxol-5-yl(1-((phenylperoxy)thio)piperidin-2-yl)methanone (4.9a) was synthesized according to General Procedure C1 using **4.S1** and 5-bromobenzo[*d*][1,3]dioxole (1.0 mmol). Purification using column chromatography (EtOAc/hexanes = 1:3) provided **4.9a** (108 mg, 58%) as a pale yellow solid.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 8.4, 1.3 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.49 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.41 (dd, *J* = 8.3, 7.4 Hz, 2H), 7.27 (d, *J* = 1.7 Hz, 1H), 6.85 (d, *J* = 8.2 Hz, 1H), 6.08 – 6.02 (m, 2H), 5.56 (dd, *J* = 6.8, 2.1 Hz, 1H), 3.80 (ddd, *J* = 11.1, 5.3, 2.1 Hz, 1H), 3.57 (td, *J* = 12.6, 3.3 Hz, 1H), 2.03 – 1.97 (m, 1H), 1.91 (tdd, *J* = 13.8, 6.8, 3.6 Hz, 1H), 1.71 – 1.66 (m, 1H), 1.58 – 1.48 (m, 2H), 1.37 – 1.27 (m, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 196.8, 152.1, 148.4, 139.7, 132.6, 130.0, 128.9, 127.3, 124.6, 108.2, 108.2, 102.1, 56.2, 43.2, 28.0, 24.8, 19.0;
HRMS (ESI): *m/z* Calc'd for $C_{19}H_{19}NNaO_5S$ $[M+Na]^+$: 396.0875, found 396.0877.



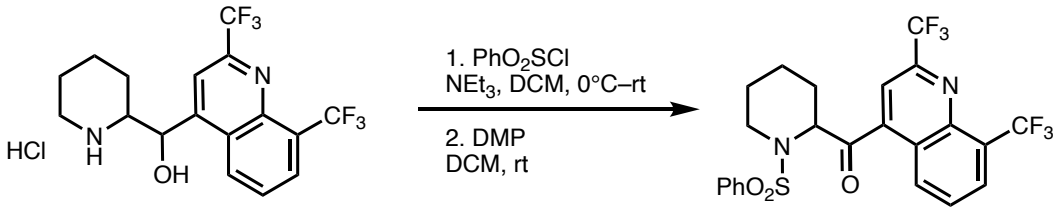
4.9b

(3,4-Dimethoxyphenyl)(1-((phenylperoxy)thio)piperidin-2-yl)methanone (4.9b) was synthesized according to General Procedure C1 using **4.S1** and 4-bromo-1,2-dimethoxybenzene (1.0 mmol). Purification using column chromatography (EtOAc/hexanes = 1:3) provided **4.9b** (121 mg, 62%) as a pale yellow solid.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.1 Hz, 2H), 7.56 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.35 (d, *J* = 2.0 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 1H), 3.95 (s, 3H), 3.89 (s, 3H), 3.80 (ddd, *J* = 12.6, 5.2, 2.4 Hz, 1H), 3.56 (td, *J* = 12.5, 3.2 Hz, 1H), 2.05 – 2.00 (m, 1H), 1.91 (tdd, *J* = 13.7, 6.8, 3.8 Hz, 1H), 1.69 – 1.65 (m, 1H), 1.58 – 1.53 (m, 1H), 1.52 – 1.48 (m, 1H), 1.36 (qt, *J* = 13.0, 3.5 Hz, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 197.3, 153.6, 149.3, 139.8, 132.5, 128.9, 128.4, 127.3, 122.9, 110.6, 110.2, 56.2, 56.1, 56.0, 43.3, 27.9, 24.7, 19.1;
HRMS (ESI): *m/z* Calc'd for $C_{20}H_{23}NNaO_5S$ $[M+Na]^+$: 412.1189, found 412.1193.



4.9c

(3,4-Dichlorophenyl)(1-((phenylperoxy)thio)piperidin-2-yl)methanone (4.9c) was synthesized according to General Procedure C1 using **4.S1** and 4-bromo-1,2-dichlorobenzene (1.0 mmol). Purification using column chromatography (EtOAc/hexanes = 1:3) provided **4.9c** (128 mg, 64%) as a yellow foam.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.93 (d, *J* = 2.1 Hz, 1H), 7.74 – 7.70 (m, 3H), 7.56 – 7.53 (m, 2H), 7.45 (t, *J* = 7.9 Hz, 2H), 5.49 (dd, *J* = 6.7, 2.4 Hz, 1H), 3.75 (dt, *J* = 12.6, 3.9 Hz, 1H), 3.47 (td, *J* = 12.6, 3.2 Hz, 1H), 2.00 – 1.95 (m, 1H), 1.89 (tdd, *J* = 13.7, 6.7, 3.7 Hz, 1H), 1.68 – 1.63 (m, 1H), 1.57 (dp, *J* = 11.2, 3.8 Hz, 1H), 1.53 – 1.46 (m, 1H), 1.35 – 1.28 (m, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 196.8, 139.6, 138.1, 134.9, 133.7, 132.8, 131.0, 130.4, 129.1, 127.4, 127.3, 57.0, 43.4, 27.2, 24.5, 19.2;
HRMS (ESI): *m/z* Calc'd for $C_{18}H_{17}Cl_2NNaO_3S$ $[M+Na]^+$: 420.0198, found 420.0207.



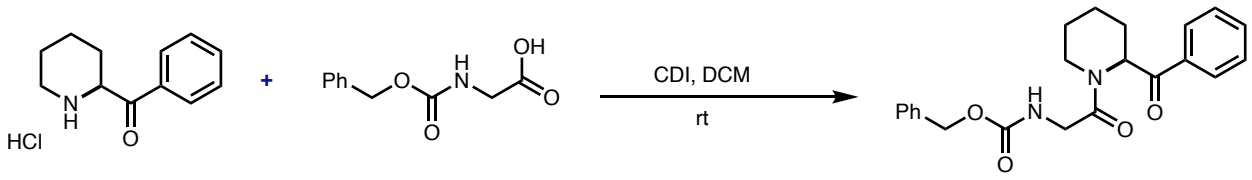
4.9d

(2,8-Bis(trifluoromethyl)quinolin-4-yl)(1-((phenylperoxy)thio)piperidin-2-yl)methanone (4.9d): To a 2-dram vial equipped with a stir bar was added (2,8-bis(trifluoromethyl)quinolin-4-yl)(piperidin-2-yl)methanol hydrochloride (0.66 mmol, 1.1 equiv). The vial was evacuated and backfilled with N_2 three times. DCM (6 mL, 0.1M) was added, followed by NEt_3 (1.2 mmol, 2.0 equiv). The suspension was stirred until all solids dissolved, then PhO_2SCl (0.64 mmol, 1.0 equiv) was added in one portion. The reaction mixture was stirred overnight at room temperature, then was quenched with 1 mL of water. The aqueous phase was extracted three times with DCM. The combined organic phase was dried over $MgSO_4$, and then was concentrated under reduced pressure to give the crude sulfonamide. The crude residue was purified by pipette column (EtOAc/hexanes = 1:2) to give (2,8-bis(trifluoromethyl)quinolin-4-yl)(1-((phenylperoxy)thio)piperidin-2-yl)methanol (288 mg, 87%) as a mixture of diastereomers. A 20 mL vial was then charged with (2,8-bis(trifluoromethyl)quinolin-4-yl)(1-((phenylperoxy)thio)piperidin-2-yl)methanol (0.54 mmol, 1 equiv) and DMP (0.65 mmol, 1.2 equiv). To the solids was added DCM, and the slurry was stirred overnight at room temperature. The reaction mixture was quenched with $Na_2S_2O_3$ and $NaHCO_3$ and the aqueous phase was extracted three times with EtOAc. The combined organic phase was dried over Na_2SO_4 and the volatiles were removed under reduced pressure. The crude residue was purified by column chromatography (EtOAc/hexanes = 1:3) to give **4.9d** (243 mg, 87%) as a pale yellow solid.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.6 Hz, 1H), 8.23 (d, *J* = 6.8 Hz, 1H), 8.03 (s, 1H), 7.81 – 7.74 (m, 3H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 5.53 (dd, *J* = 6.7, 2.2 Hz, 1H), 3.81 (d, *J* = 12.4 Hz, 1H), 3.34 (td, *J* = 12.9, 2.5 Hz, 1H), 2.03 – 1.93 (m, 1H), 1.80 (tdd, *J* = 13.9, 6.4, 2.9 Hz, 1H), 1.72 – 1.64 (m, 2H), 1.49 – 1.38 (m, 2H);

^{13}C NMR: (151 MHz, CDCl3) δ 201.2, 148.2 (q , *J* = 35.8), 145.0, 144.5, 139.9, 133.0, 129.8 (dd, *J* = 9.7, 4.1), 129.2, 129.0, 127.2, 125.4, 124.3, 122.5, 121.8, 120.0, 115.5, 60.4, 43.6, 25.8, 24.3, 19.9;

HRMS (ESI): *m/z* Calc'd for $C_{23}H_{18}F_6N_2NaO_3S$ $[M+Na]^+$: 539.0835, found 539.0829.



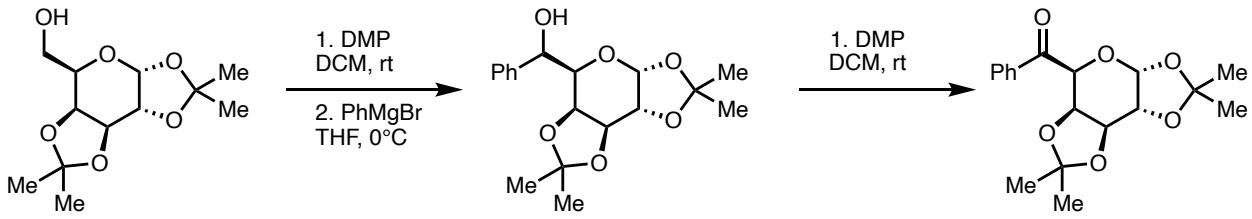
4.11

Benzyl-2-(2-benzoylpiperidin-1-yl)-2-oxoethyl)carbamate (4.11) was synthesized according to a procedure analogous to General Procedure D using phenyl(piperidin-2-yl)methanone hydrochloride and ((benzyloxy)carbonyl)glycine. Purification using column chromatography (EtOAc/hexanes = 0–50%) provided **4.11** (117 mg, 51%) as a colorless oil.

^{1}H NMR: (499 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.5 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.7 Hz, 2H), 7.35 (d, *J* = 4.1 Hz, 3H), 7.32 (d, *J* = 9.2 Hz, 2H), 6.06 (d, *J* = 6.1 Hz, 1H), 5.77 (s, 1H), 5.12 (s, 2H), 4.19 (dd, *J* = 16.9, 4.7 Hz, 1H), 4.01 (dd, *J* = 16.8, 3.6 Hz, 1H), 3.60 (d, *J* = 12.3 Hz, 1H), 3.54 – 3.42 (m, 1H), 2.19 (d, *J* = 13.9 Hz, 1H), 1.79 (d, *J* = 30.1 Hz, 2H), 1.66 (s, 1H), 1.50 (d, *J* = 10.7 Hz, 2H);

^{13}C NMR: (151 MHz, $CDCl_3$): δ 199.9, 169.7, 168.4, 136.8, 135.7, 133.4, 128.9, 128.7, 128.5, 128.3, 128.2, 67.1, 55.3, 43.2, 43.0, 26.4, 25.3, 20.0;

HRMS (ESI): *m/z* Calc'd for $C_{22}H_{24}N_2NaO_4$ $[M+Na]^+$: 403.1628, found 403.1633.



4.13

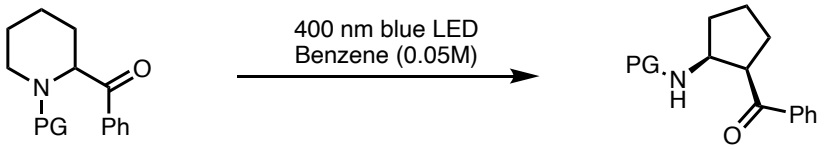
Phenyl((3a*R*,5*S*,5a*R*,8a*S*,8b*R*)-2,2,7,7-tetramethyltetrahydro-5*H*-bis([1,3]dioxolo)[4,5-*b*:4',5'-*d*]pyran-5-yl)methanone (4.13) was prepared in a three-step, known, oxidation,[52] Grignard reagent addition–oxidation[53] sequence on a 0.5 mmol scale. Purification using column chromatography (EtOAc/hexanes 1:3) provided **4.13** (98 mg, 59% over three steps) as a white solid. Spectral data was in full agreement with that previously reported.[53]

HRMS (ESI): *m/z* Calc'd for $C_{18}H_{22}NaO_6$ $[M+Na]^+$: 357.1309, found 357.1307.

4.4.3. Experimental Procedures for Racemic Ring Contraction

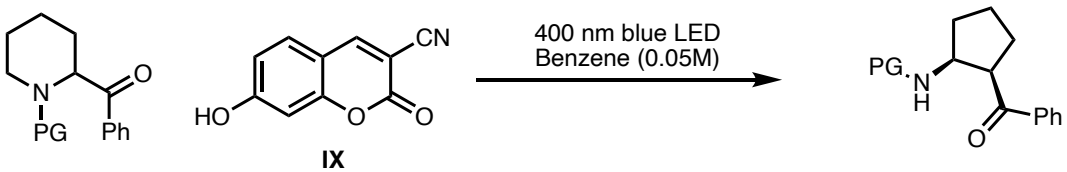
4.4.3.1. Protecting Group Modified Substrates

General Procedure F



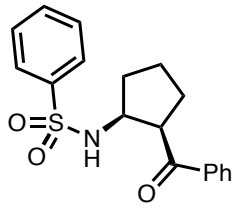
To an oven-dried, 20 mL scintillation vial equipped with stir bar was added N-protected 2-acyl piperidine (0.2 mmol). The system was evacuated and backfilled three times with N_2. N_2 sparged benzene (4 mL, 0.05M) was added, and the solution was irradiated with a 400 nm LED for 18–24 h. Volatiles were then evaporated, and the diastereomeric ratio was determined by ^{1}H NMR integration of resonances corresponding to diastereomers in the crude mixture. Purification by column chromatography (hexanes / ethyl acetate mobile phase) afforded the desired cyclopentane product. *The determination of relative stereochemistry was done by 2-D NMR analysis and/or single crystal x-ray analysis, or by analogy to a similar compound with known relative stereochemistry. The relative configuration of selected molecules across several classes of protecting groups was assigned by ^{3}JHX and chemical shift analysis in corroboration with DFT computed chemical shifts and coupling constants, as well as by NOE analysis. The cis N-H bond presents downfield of the trans N-H bond in sulfonamide substrates. A consistent trend was noted wherein the amide proton for the cis configured isomer presents downfield of the trans isomer and exhibits a coupling constant on the order of 7-8 Hz. Additionally, carbon chemical shifts for the methines consistently presented as more highly resolved in the cis isomer (generally Δ5-6 ppm) whereas the trans isomer chemical shifts were less resolved, typically presenting with a difference of approximately 3 ppm.*

General Procedure G – Photosensitizer Enabled Contraction



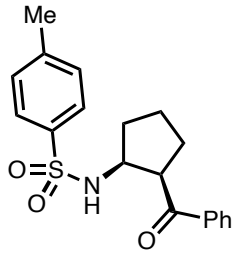
To an oven-dried, 20 mL scintillation vial equipped with a stir bar was added N-protected 2-acyl piperidine (0.2 mmol) and 3-cyanoumbelliferone (**IX**, 11.2 mg 30 mol%). The system was evacuated and backfilled three times with N_2. N_2 sparged benzene (4 mL, 0.05M) was added, and the solution was irradiated with a 400 nm LED for 18–24 h. Volatiles were then evaporated, and diastereomeric ratio was determined by ^{1}H NMR integration of resonances corresponding to diastereomers in the crude mixture. Purification by column chromatography (hexanes / ethyl acetate mobile phase unless stated otherwise) afforded the desired cyclopentane product. *The*

determination of relative stereochemistry was done by 2-D NMR analysis and or single crystal x-ray analysis, or by analogy to a similar compound with known relative stereochemistry.



4.4a

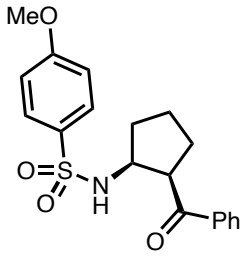
***cis-N*-(2-Benzoylcyclopentyl)benzenesulfonamide (4.4a)** was synthesized according to General Procedure F from **4.3a** (0.2 mmol). The reaction was run for 18 h. Purification using column chromatography (EtOAc/hexanes = 1:2) provided **4.4a** (55.3 mg, 84%, 20:1 d.r.) as a clear oil that solidifies upon standing.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.73 (d, *J* = 7.7 Hz, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.29 (t, *J* = 7.7 Hz, 2H), 5.79 (d, *J* = 9.6 Hz, 1H), 3.96 (ddd, *J* = 16.3, 9.3, 7.0 Hz, 1H), 3.72 (dt, *J* = 9.1, 6.0 Hz, 1H), 2.08 – 2.01 (m, 1H), 1.97 – 1.91 (m, 1H), 1.89 (dd, *J* = 12.9, 8.5 Hz, 1H), 1.86 – 1.81 (m, 1H), 1.76 (dtt, *J* = 14.2, 9.4, 5.3 Hz, 1H), 1.64 – 1.57 (m, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 202.2, 140.7, 135.9, 133.6, 132.4, 129.0, 128.6, 128.4, 127.0, 56.9, 47.0, 33.0, 29.5, 21.9;
HRMS (ESI): *m/z* Calc'd for $C_{18}H_{19}NNaO_3S$ $[M+Na]^+$: 352.0978, found 352.0978.
Relative Stereochemistry: *determined by 2-D and x-ray analysis*



4.4b

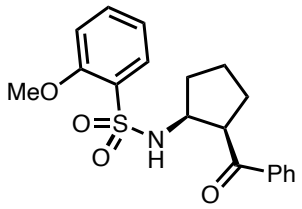
***cis-N*-(2-Benzoylcyclopentyl)-4-methylbenzenesulfonamide (4.4b)** was synthesized according to General Procedure F from **4.3b** (0.2 mmol). The reaction was run for 24 h. Purification using column chromatography (EtOAc/hexanes = 1:3) provided **4.4b** (54.3 mg, 79%, 12:1 d.r.) as a white solid.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.1 Hz, 2H), 7.58 (d, *J* = 8.3 Hz, 2H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.37 (t, 2H), 6.99 (d, *J* = 7.8 Hz, 2H), 5.70 (d, *J* = 9.8 Hz, 1H), 3.91 (tt, *J* = 9.4, 7.1 Hz, 1H), 3.63 (ddd, *J* = 9.3, 6.8, 5.0 Hz, 1H), 2.17 (s, 3H), 2.04 – 1.91 (m, 2H), 1.90 – 1.82 (m, 1H), 1.81 – 1.69 (m, 2H), 1.63 – 1.52 (m, 1H);

^{13}C NMR: (176 MHz, $CDCl_3$) δ 202.1, 143.1, 137.7, 135.9, 133.4, 129.6, 128.5, 128.4, 127.0, 56.9, 46.6, 33.1, 29.6, 21.8, 21.4;
HRMS (ESI): *m/z* Calc'd for $C_{19}H_{21}NNaO_3S$ $[M+Na]^+$: 366.1134, found: 366.1132.
Relative Stereochemistry: *determined by comparison to* **4.4a**, *and x-ray analysis*



4.4c

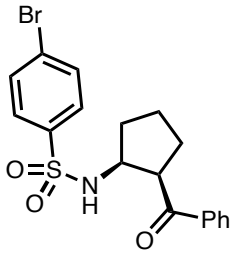
***cis-N*-(2-Benzoylcyclopentyl)-4-methoxybenzenesulfonamide (4.4c)** was synthesized according to General Procedure F from **4.3c** (0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 1:3) provided **4.4c** (49.0 mg, 68%, 8:1 d.r.) as a white solid.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.0 Hz, 2H), 7.63 (d, *J* = 8.8 Hz, 2H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 2H), 6.67 (d, *J* = 9.0 Hz, 2H), 5.65 (d, *J* = 9.7 Hz, 1H), 3.91 (tt, *J* = 9.2, 7.1 Hz, 1H), 3.68 – 3.63 (m, 4H), 2.03 – 1.97 (m, 1H), 1.97 – 1.92 (m, 1H), 1.90 – 1.83 (m, 1H), 1.82 – 1.76 (m, 1H), 1.75 – 1.69 (m, 1H), 1.61 – 1.54 (m, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 202.1, 162.6, 136.0, 133.4, 132.2, 129.1, 128.5, 128.4, 114.1, 56.9, 55.4, 46.7, 33.2, 29.6, 21.8;
HRMS (ESI): *m/z* Calc'd for $C_{19}H_{21}NNaO_4S$ $[M+Na]^+$: 382.1083, found: 382.1082.
Relative Stereochemistry: *determined by comparison to* **4.4a**



4.4d

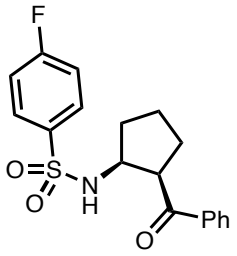
***cis-N*-(2-Benzoylcyclopentyl)-2-methoxybenzenesulfonamide (4.4d)** was synthesized according to General Procedure F from **4.3d** (0.2 mmol). The reaction was run for 48 h. Purification using column chromatography (EtOAc/hexanes = 0–40%) provided **4.4d** (34.5 mg, 48%, 19:1 d.r.) (*60% brsm*) as a colorless oil.
^{1}H NMR: (499 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.70 (d, *J* = 7.3 Hz, 2H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.32 – 7.27 (m, 1H), 6.95 (t, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 8.3 Hz, 1H), 6.06 (d, *J* = 9.7 Hz, 1H), 4.01 – 3.92 (m, 1H), 3.80 (s, 3H), 3.65 (ddd, *J* = 10.4, 6.7, 4.1 Hz, 1H), 2.00 – 1.64 (m, 5H), 1.58 (dd, *J* = 8.6, 3.5 Hz, 1H);

^{13}C NMR: (126 MHz, $CDCl_3$) δ 201.6, 156.2, 136.0, 134.3, 133.5, 129.7, 128.7, 128.6, 128.5, 120.5, 111.9, 57.3, 56.0, 46.9, 31.8, 29.2, 21.6;
HRMS (ESI): *m/z* Calc'd for $C_{19}H_{22}NO_4S$ $[M+H]^+$: 360.1269, found: 360.1285.
Relative Stereochemistry: *determined by comparison to* **4.4a**



4.4e

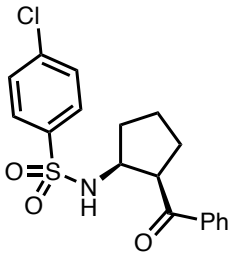
***cis-N*-(2-Benzoylcyclopentyl)-4-bromobenzenesulfonamide (4.4e)** was synthesized according to General Procedure F from **4.3e** (0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 1:4) provided **4.4e** (60.8 mg, 74%, 12:1 d.r.) as a white solid.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.0 Hz, 2H), 7.59 – 7.54 (m, 3H), 7.42 – 7.39 (m, 2H), 7.35 – 7.32 (m, 2H), 5.74 (d, *J* = 9.5 Hz, 1H), 3.93 (ddd, *J* = 16.5, 8.4, 7.0 Hz, 1H), 3.69 (ddd, *J* = 9.2, 6.7, 5.6 Hz, 1H), 2.03 – 1.94 (m, 2H), 1.93 – 1.87 (m, 1H), 1.87 – 1.81 (m, 1H), 1.79 – 1.72 (m, 1H), 1.64 – 1.56 (m, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 202.0, 139.7, 135.7, 133.8, 132.3, 128.8, 128.6, 128.3, 127.4, 57.0, 46.9, 33.4, 29.5, 21.9;
HRMS (ESI): *m/z* Calc'd for $C_{18}H_{17}BrNO_3S$ $[M-H]^-$: 406.0118, found: 406.0125.
Relative Stereochemistry: *determined by comparison to* **4.4a**



4.4f

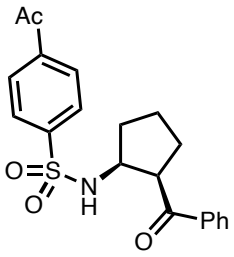
***cis-N*-(2-Benzoylcyclopentyl)-4-fluorobenzenesulfonamide (4.4f)** was synthesized according to General Procedure F from **4.3f** (0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 0–30%) provided **4.4f** (44.0 mg, 63%, 19:1 d.r.) as a white solid.
^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.77 – 7.68 (m, 4H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 2H), 6.94 – 6.86 (m, 2H), 5.69 (d, *J* = 9.4 Hz, 1H), 3.98 – 3.88 (m, 1H), 3.72 (dt, *J* = 9.1, 6.1 Hz, 1H), 2.03 (ddt, *J* = 14.6, 8.9, 4.5 Hz, 1H), 1.96 (dtd, *J* = 12.7, 7.8, 5.0 Hz, 1H), 1.87 (dddd, *J* = 22.0, 19.4, 13.3, 7.1 Hz, 2H), 1.77 (dtd, *J* = 17.2, 8.7, 4.3 Hz, 1H), 1.66 – 1.58 (m, 1H);

^{13}C NMR: (151 MHz, $CDCl_3$) δ 202.1, 164.9 (d, *J* = 254.6 Hz), 136.9 (d, *J* = 3.1 Hz), 135.9, 133.8, 129.8 (d, *J* = 9.3 Hz), 128.8, 128.4, 116.3 (d, *J* = 22.5 Hz), 57.1, 47.1, 33.4, 29.6, 22.0;
HRMS (ESI): *m/z* Calc'd for $C_{18}H_{18}FNNaO_3S$ $[M+Na]^+$: 370.0889, found: 370.0888.
Relative Stereochemistry: *determined by comparison to* **4.4a**



4.4g

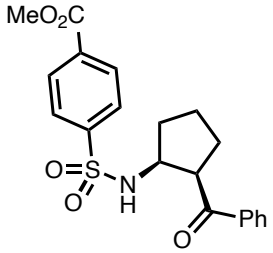
***cis-N*-(2-Benzoylcyclopentyl)-4-chlorobenzenesulfonamide (4.4g)** was synthesized according to General Procedure F from **4.3g** (0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 1:2) provided **4.4g** (43 mg, 59%, 3.3:1 d.r.) as a white solid.
^{1}H NMR: 700 MHz, $CDCl_3$) δ 7.69 (d, *J* = 7.5 Hz, 2H), 7.63 (d, *J* = 8.7 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.40 (t, *J* = 6.9 Hz, 2H), 7.17 (d, *J* = 8.7 Hz, 2H), 5.73 (d, *J* = 9.5 Hz, 1H), 3.93 (p, *J* = 8.5, 7.9 Hz, 1H), 3.70 (qd, *J* = 7.4, 7.0, 1.7 Hz, 1H), 2.04 – 1.99 (m, 1H), 1.98 – 1.94 (m, 1H), 1.92 – 1.87 (m, 1H), 1.87 – 1.81 (m, 1H), 1.80 – 1.72 (m, 1H), 1.64 – 1.57 (m, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 202.0, 139.2, 138.9, 135.8, 133.8, 129.3, 128.8, 128.5, 128.3, 57.0, 46.9, 33.4, 29.5, 21.9;
HRMS (ESI): *m/z* Calc'd for $C_{18}H_{18}ClNNaO_3S$ $[M+Na]^+$: 386.0588, found 386.0588.
Relative Stereochemistry: *determined by comparison to* **4.4a**



4.4h

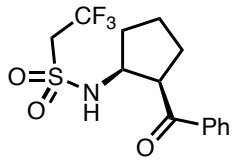
***cis-N*-(2-Benzoylcyclopentyl)-4-acetylbenzenesulfonamide (4.4h)** was synthesized according to General Procedure F from **4.3h** (0.2 mmol). The reaction was run for 48 h. Purification using column chromatography (EtOAc/hexanes = 0–40%) provided **4.4h** (16.4 mg, 22%, 5:2 d.r.) as a yellow solid.
^{1}H NMR: (499 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.5 Hz, 2H), 7.77 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 7.4 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 2H), 5.81 (d, *J* = 9.5 Hz, 1H), 3.98 (p, *J* =

8.5, 7.9 Hz, 1H), 3.67 (dt, *J* = 9.3, 5.8 Hz, 1H), 2.47 (s, 3H), 2.01 (dqd, *J* = 19.9, 8.1, 3.9 Hz, 2H), 1.94 – 1.87 (m, 1H), 1.78 (ddtd, *J* = 27.2, 14.0, 8.9, 5.7 Hz, 2H), 1.61 (dd, *J* = 13.3, 7.5 Hz, 1H);
^{13}C NMR: (126 MHz, $CDCl_3$) δ 201.9, 196.5, 144.8, 139.6, 135.7, 133.8, 129.0, 128.7, 128.5, 127.4, 57.1, 46.7, 33.4, 29.8, 26.9, 22.0;
HRMS (ESI): *m/z* Calc'd for $C_{20}H_{20}NO_4S$ $[M-H]^-$: 370.1113, found 370.1114.
Relative Stereochemistry: *determined by comparison to* **4.4a**



4.4i

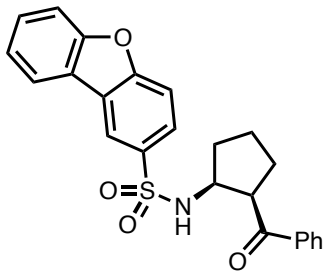
***cis*-Methyl-4-(*N*-(2-benzoylcyclopentyl)sulfamoyl)benzoate (4.4i)** was synthesized according to General Procedure F from **4.3i** (0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 0–35%) provided **4.4i** (18.6 mg, 24%, 19:1 d.r.) (*39% brsm*) as a white solid.
^{1}H NMR: (499 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.2 Hz, 2H), 7.79 (d, *J* = 8.2 Hz, 2H), 7.66 (d, *J* = 7.7 Hz, 2H), 7.50 (t, *J* = 7.2 Hz, 1H), 7.35 (t, *J* = 7.6 Hz, 2H), 5.77 (d, *J* = 9.5 Hz, 1H), 4.03 – 3.94 (m, 1H), 3.91 (s, 3H), 3.73 – 3.64 (m, 1H), 2.10 – 1.92 (m, 2H), 1.92 – 1.70 (m, 3H), 1.62 (dd, *J* = 14.3, 6.7 Hz, 1H);
^{13}C NMR: (126 MHz, $CDCl_3$) δ 202.0, 165.5, 144.7, 135.7, 133.6, 133.5 130.4, 128.7, 128.5, 127.1, 57.1, 52.6, 46.9, 33.4, 29.7, 22.0;
HRMS (ESI): *m/z* Calc'd for $C_{20}H_{22}NO_5S$ $[M+H]^+$: 388.1218, found 388.1223.
Relative Stereochemistry: *determined by comparison to* **4.4a**



4.4k

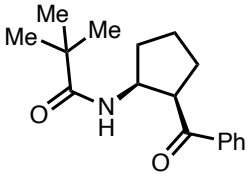
***cis*-*N*-(2-Benzoylcyclopentyl)-2,2,2-trifluoroethane-1-sulfonamide (4.4k)** was synthesized according to General Procedure F from **4.3k** (0.2 mmol). The reaction was run for 48 h. Purification using column chromatography (EtOAc/hexanes = 0–30%) provided **4.4k** (37.3 mg, 56%, 19:1 d.r.) as a white solid.
^{1}H NMR: (499 MHz, $CDCl_3$) δ 7.97 – 7.90 (m, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.49 (t, *J* = 7.7 Hz, 2H), 5.85 (d, *J* = 9.4 Hz, 1H), 4.16 – 4.07 (m, 1H), 4.07 – 3.99 (m, 1H), 3.69 (qd, *J* = 8.9, 1.5 Hz,

2H), 2.15 (dtq, *J* = 15.6, 8.0, 4.4, 3.7 Hz, 2H), 2.08 – 1.89 (m, 2H), 1.88 – 1.76 (m, 1H), 1.76 – 1.64 (m, 1H);
^{13}C NMR: (151 MHz, $CDCl_3$) δ 202.3, 136.0, 133.9, 129.0, 128.8, 121.7 (q, *J* = 277.6 Hz), 57.4, 55.6 (q, *J* = 31.2 Hz), 48.1, 33.0, 29.5, 22.1;
HRMS (ESI): *m/z* Calc'd for for $C_{14}H_{15}F_3NO_3S$ $[M-H]^-$: 334.0725, found 334.0708.
Relative Stereochemistry: *determined by comparison to* **4.4a**



4.4l

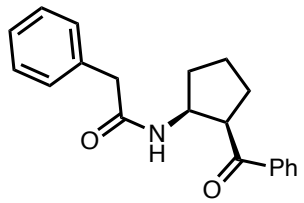
***cis-N*-(2-Benzoylcyclopentyl)-dibenzo[*b,d*]furan-2-sulfonamide (4.4l)** was synthesized according to General Procedure F from **4.3l** (83.9 mg, 0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 1:4) provided **4.4g** (59.6 mg, 71%, 6.7:1 d.r.) as a clear oil that solidifies upon standing.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 8.28 (d, *J* = 2.0 Hz, 1H), 7.83 (t, *J* = 8.5 Hz, 2H), 7.54 – 7.50 (m, 2H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.34 (d, *J* = 8.5 Hz, 1H), 7.17 (t, *J* = 7.4 Hz, 1H), 6.99 (t, *J* = 7.7 Hz, 2H), 5.76 (d, *J* = 9.6 Hz, 1H), 4.01 (tt, *J* = 9.1, 7.1 Hz, 1H), 3.61 (ddd, *J* = 9.3, 6.8, 5.3 Hz, 1H), 2.06 – 2.00 (m, 1H), 2.00 – 1.95 (m, 1H), 1.95 – 1.89 (m, 1H), 1.80 – 1.70 (m, 2H), 1.61 – 1.55 (m, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 201.8, 157.8, 156.9, 135.4, 135.1, 133.2, 128.5, 128.2, 127.9, 126.2, 125.0, 123.6, 123.1, 121.3, 120.5, 112.2, 112.0, 57.1, 46.4, 33.6, 29.7, 21.9;
HRMS (ESI): *m/z* Calc'd for $C_{24}H_{21}NNaO_4S$ $[M+Na]^+$: 422.1083, found 442.1084.
Relative Stereochemistry: *determined by comparison to* **4.4a**



4.4m

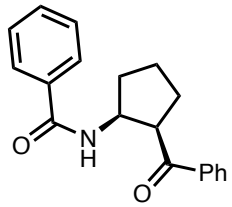
***cis-N*-(2-Benzoylcyclopentyl)pivalamide (4.4m)** was synthesized according to General Procedure G from **4.3m** (54.7 mg, 0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 1:2) provided **4.4m** (29.5 mg, 54%, 14:1 d.r.) as white solid.

^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.93 (d, *J* = 7.1 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.44 (t, 2H), 6.18 (d, *J* = 8.8 Hz, 1H), 4.65 (ddd, *J* = 16.0, 8.5, 7.2 Hz, 1H), 4.09 (td, *J* = 8.1, 6.3 Hz, 1H), 2.07 – 2.01 (m, 3H), 1.88 – 1.80 (m, 1H), 1.75 (dq, *J* = 12.4, 8.4 Hz, 1H), 1.70 – 1.62 (m, 1H), 0.97 (s, 9H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 203.2, 178.0, 137.0, 133.4, 128.8, 128.5, 52.6, 47.5, 38.6, 33.1, 29.2, 27.4, 22.9;
HRMS: *m/z* Calc'd for $C_{17}H_{23}NNaO_2$ $[M+Na]^+$: 296.1621, found 296.1622.
Relative Stereochemistry: *determined by 2-D and x-ray analysis*



4.4n

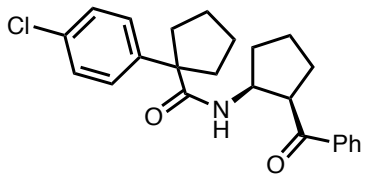
***cis-N*-(2-Benzoylcyclopentyl)-2-phenylacetamide (4.4n)** was synthesized according to General Procedure G from **4.3n** (0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 0–30%) provided **4.4n** (23.9 mg, 39%, 20:1 d.r.) (*59% brsm*) as a colorless oil.
^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.90 – 7.87 (m, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.8 Hz, 2H), 7.25 (td, *J* = 5.5, 2.6 Hz, 3H), 7.02 (dd, *J* = 7.2, 2.0 Hz, 2H), 5.93 (d, *J* = 8.5 Hz, 1H), 4.65 (p, *J* = 8.5, 8.0 Hz, 1H), 4.09 – 3.98 (m, 1H), 3.45 – 3.27 (m, 2H), 2.03 – 1.93 (m, 3H), 1.78 (ddt, *J* = 17.8, 8.4, 4.6 Hz, 1H), 1.69 – 1.62 (m, 2H);
^{13}C NMR: (126 MHz, $CDCl_3$) δ 202.7, 170.8, 137.0, 134.7, 133.5, 129.4, 129.0, 128.8, 128.6, 127.4, 53.0, 47.6, 44.0, 32.8, 29.1, 22.7;
HRMS (ESI): *m/z* Calc'd for $C_{20}H_{22}NO_2$ $[M+H]^+$: 308.1650, found 308.1655.
Relative Stereochemistry: *determined by comparison to* **4.4m**



4.4o

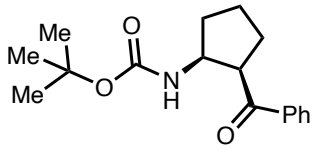
***cis-N*-(2-Benzoylcyclopentyl)benzamide (4.4o)** was synthesized according to General Procedure G from **4.3o** (0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 1:2) provided **4.4o** (26 mg, 44%, 14:1 d.r.) as a white solid.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.0 Hz, 2H), 7.63 (d, *J* = 7.0 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.47 – 7.41 (m, 3H), 7.36 (t, *J* = 7.7 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 1H), 4.86 (ddd, *J* =

15.8, 8.5, 7.2 Hz, 1H), 4.15 (ddd, *J* = 8.8, 7.3, 6.0 Hz, 1H), 2.19 – 2.12 (m, 2H), 2.11 – 2.05 (m, 1H), 1.98 – 1.92 (m, 1H), 1.91 – 1.86 (m, 1H), 1.78 – 1.72 (m, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 203.4, 167.0, 136.8, 134.6, 133.6, 131.4, 128.8, 128.6, 126.9, 53.1, 47.8, 33.0, 29.5, 22.7 (2 C's overlapping);
HRMS: *m/z* Calc'd for $C_{19}H_{19}NNaO_2$ $[M+Na]^+$: 316.1308, found 316.1310.
Relative Stereochemistry: *determined by comparison to* **4.4m**, and 2-D analysis



4.4p

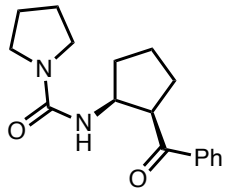
***cis-N*-(2-Benzoylcyclopentyl)-1-(4-chlorophenyl)cyclopentane-1-carboxamide (4.4p)** was synthesized according to General Procedure G from **4.3p** (0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 0–30%) provided **4.4p** (21.2 mg, 27%, 2.6:1 d.r.) (*49% brsm*) as a white solid.
^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.85 – 7.79 (m, 2H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 7.14 (d, *J* = 8.5 Hz, 2H), 7.10 – 7.04 (m, 2H), 5.78 (d, *J* = 8.5 Hz, 1H), 4.57 (p, *J* = 7.7 Hz, 1H), 3.99 (q, *J* = 7.7 Hz, 1H), 2.33 (dq, *J* = 13.6, 7.9, 6.6 Hz, 1H), 2.19 (dt, *J* = 12.8, 6.8 Hz, 1H), 1.96 (ddp, *J* = 18.2, 13.0, 6.1 Hz, 3H), 1.87 (dt, *J* = 12.9, 7.5 Hz, 1H), 1.78 – 1.70 (m, 3H), 1.69 – 1.50 (m, 8H), 0.86 (dt, *J* = 23.4, 6.7 Hz, 2H);
^{13}C NMR: (151 MHz, $CDCl_3$) δ 202.7, 175.3, 142.6, 136.9, 133.5, 128.8, 128.8, 128.5, 128.1, 59.0, 53.1, 47.6, 36.6, 36.5, 33.2, 29.9, 29.3, 23.8, 23.7, 23.0;
HRMS (ESI): *m/z* Calc'd for $C_{24}H_{27}ClNO_2$ $[M+H]^+$: 396.1730, found 397.1736.
Relative Stereochemistry: *determined by comparison to* **4.4m**



4.4q

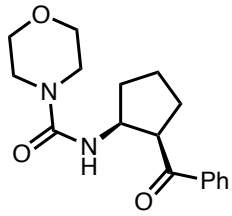
***cis-tert*-Butyl (2-benzoylcyclopentyl)carbamate (4.4q)** was synthesized according to General Procedure G from **4.3q** (57.8 mg, 0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 1:3) provided **4.4q** (12.5 mg, 22%, 20:1 d.r.) (*58% brsm*) as clear oil that solidifies upon standing.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.96 (d, *J* = 9.7 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.8 Hz, 2H), 4.97 (d, *J* = 9.3 Hz, 1H), 4.39 (p, *J* = 8.1 Hz, 1H), 4.06 (q, *J* = 7.5 Hz, 1H), 2.08 – 2.02 (m, 2H), 2.01 – 1.95 (m, 1H), 1.84 (dtt, *J* = 12.9, 8.7, 4.6 Hz, 1H), 1.76 (dq, *J* = 12.5, 8.4 Hz, 1H), 1.69 – 1.60 (m, 1H), 1.28 (s, 9H);

^{13}C NMR: (176 MHz, $CDCl_3$) δ 202.9, 155.4, 137.3, 133.2, 128.7, 128.6, 79.2, 54.6, 48.0, 33.0, 28.8, 28.4, 22.6;
HRMS: *m/z* Calc'd for $C_{17}H_{23}NNaO_3$ $[M+Na]^+$: 312.1570, found 312.1572.
Relative Stereochemistry: *determined by comparison to* **4.4m**, and 2-D analysis



4.4r

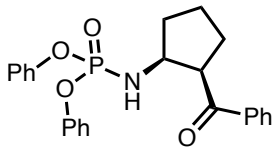
***cis-N*-(2-Benzoylcyclopentyl)pyrrolidine-1-carboxamide (4.4r)** was synthesized according to General Procedure G from **4.3r** (0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 0–50%) provided **4.4r** (32.8 mg, 57%, 19:1 d.r.) as a colorless oil.
^{1}H NMR: (499 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.4 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 4.87 (d, *J* = 8.5 Hz, 1H), 4.60 (p, *J* = 8.0 Hz, 1H), 4.09 (q, *J* = 7.2 Hz, 1H), 3.18 (t, *J* = 6.6 Hz, 2H), 3.11 (s, 2H), 2.09 – 1.97 (m, 3H), 1.91 – 1.78 (m, 3H), 1.77 (d, *J* = 6.3 Hz, 3H), 1.66 (ddd, *J* = 13.0, 8.4, 4.5 Hz, 1H);
^{13}C NMR: (151 MHz, DMSO) δ 202.1, 155.6, 137.5, 132.6, 128.2, 128.0, 54.4, 47.9, 44.9, 31.6, 26.8, 24.7, 21.8.
HRMS (ESI): *m/z* Calc'd for $C_{17}H_{23}N_2O_2$ $[M+H]^+$: 287.1759, found 287.1770.
Relative Stereochemistry: *determined by comparison to* **4.4s**



4.4s

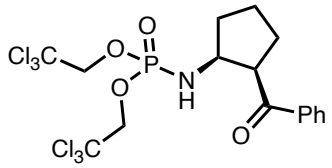
***cis-N*-(2-Benzoylcyclopentyl)morpholine-4-carboxamide (4s)** was synthesized according to General Procedure G from **3s** (0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 0–50%) provided **4s** (46 mg, 76%, 6:1 d.r.) as a colorless oil.
^{1}H NMR: (499 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.3 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.51 – 7.40 (m, 2H), 5.28 (d, *J* = 8.8 Hz, 1H), 4.58 (p, *J* = 7.8 Hz, 1H), 4.12 – 4.03 (m, 1H), 3.62 – 3.46 (m, 4H), 3.26 – 3.19 (m, 2H), 3.15 (ddd, *J* = 12.7, 6.0, 3.7 Hz, 2H), 2.12 – 1.97 (m, 3H), 1.88 – 1.76 (m, 2H), 1.72 – 1.65 (m, 1H);
^{13}C NMR: (126 MHz, $CDCl_3$) δ 204.0, 157.4, 137.1, 133.6, 128.9, 128.6, 66.6, 54.5, 47.7, 44.0, 33.3, 29.4, 22.7;
HRMS (ESI): *m/z* Calc'd for $C_{17}H_{23}N_2O_3$ $[M+H]^+$: 303.1708, found 303.1719.

Relative Stereochemistry: *determined by* 2-D analysis



4.4t

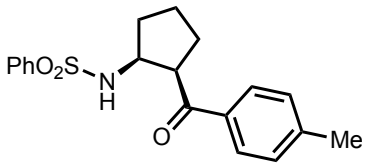
***cis*-Diphenyl-(2-benzoylcyclopentyl)phosphoramidate (4.4t)** was synthesized according to General Procedure G from **4.3t** (0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 0–50%) provided **4.4t** (43.9 mg, 52%, 19:1 d.r.) as a colorless oil.
^{1}H NMR: (499 MHz, $CDCl_3$) δ 7.86 – 7.80 (m, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.24 (t, *J* = 7.9 Hz, 2H), 7.16 (t, *J* = 7.7 Hz, 4H), 7.09 (d, *J* = 8.5 Hz, 3H), 7.02 (t, *J* = 7.3 Hz, 1H), 4.06 (dq, *J* = 16.1, 8.8 Hz, 1H), 4.01 – 3.92 (m, 1H), 3.82 (dt, *J* = 9.0, 6.0 Hz, 1H), 2.01 (ddp, *J* = 24.0, 12.2, 4.4, 3.8 Hz, 2H), 1.94 – 1.84 (m, 2H), 1.76 (ddq, *J* = 13.4, 8.1, 4.4, 3.4 Hz, 1H), 1.65 – 1.58 (m, 1H);
^{13}C NMR: (126 MHz, $CDCl_3$) δ 202.4, 150.8 (d, *J* = 6.8 Hz), 150.7 (d, *J* = 6.8 Hz), 136.5, 133.2, 129.6, 129.5, 128.6, 128.5, 124.8, 124.8, 120.2 (d, *J* = 4.7 Hz), 120.1 (d, *J* = 4.9 Hz), 56.0, 48.2 (d, *J* = 4.9 Hz), 34.1 (d, *J* = 4.6 Hz), 29.1, 22.1;
HRMS (ESI): *m/z* Calc'd for $C_{24}H_{25}NO_4P$ $[M+H]^+$: 422.1521, found 422.1524.
Relative Stereochemistry: *determined by* 2-D analysis



4.4u

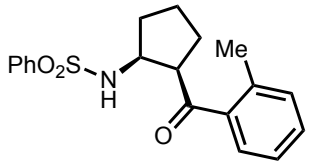
***cis*-Bis(2,2,2-trichloroethyl)-(2-benzoylcyclopentyl)phosphoramidate (4.4u)** was synthesized according to General Procedure G from **4.3u** (0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 0–50%) provided **4.4u** (26.0 mg, 24%, 19:1 d.r.) as a yellow oil.
^{1}H NMR: (499 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.4 Hz, 2H), 7.58 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.7 Hz, 2H), 4.49 – 4.40 (m, 2H), 4.36 (dd, *J* = 11.1, 5.8 Hz, 1H), 4.23 (dd, *J* = 11.1, 5.7 Hz, 1H), 4.03 (hept, *J* = 7.6 Hz, 2H), 3.85 (t, *J* = 11.2 Hz, 1H), 2.05 (dddt, *J* = 47.2, 35.3, 12.8, 6.6 Hz, 4H), 1.84 (tdd, *J* = 14.0, 8.6, 5.7 Hz, 1H), 1.68 (dq, *J* = 13.5, 7.8 Hz, 1H);
^{13}C NMR: (126 MHz, $CDCl_3$) δ 202.0, 136.7, 133.7, 129.0, 128.7, 95.2 (dd, *J* = 11.9, 8.1 Hz), 76.4 (dd, *J* = 9.1, 4.3 Hz), 56.1, 48.5 (d, *J* = 5.9 Hz), 34.7, 28.9, 22.4;
HRMS (ESI): *m/z* Calc'd for $C_{16}H_{19}Cl_6NO_4P$ $[M+H]^+$: 529.9183, found 529.9190.
Relative Stereochemistry: *determined by comparison to* **4.4t**

4.4.3.2. Aryl Ketone Modified Substrates



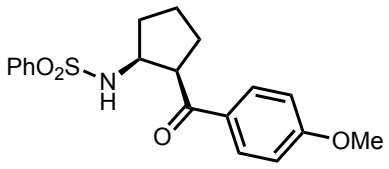
4.6a

***cis-N*-(2-(4-Methylbenzoyl)cyclopentyl)benzenesulfonamide (4.6a)** was synthesized according to General Procedure F from **4.5a** (0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 1:5) provided **4.6a** (43.1 mg, 63%, 8.1:1 d.r.) as a white solid.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.3 Hz, 2H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 1H), 7.29 (t, *J* = 8.2 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 5.82 (d, *J* = 9.4 Hz, 1H), 3.93 (tt, *J* = 9.0, 7.1 Hz, 1H), 3.67 (ddd, *J* = 9.3, 6.7, 5.3 Hz, 1H), 2.42 (s, 3H), 2.05 – 1.97 (m, 1H), 1.94 – 1.85 (m, 2H), 1.85 – 1.78 (m, 1H), 1.77 – 1.70 (m, 1H), 1.62 – 1.53 (m, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 201.9, 144.5, 140.8, 133.5, 132.3, 129.3, 129.0, 128.6, 127.0, 57.0, 46.9, 33.0, 29.6, 21.9, 21.8;
HRMS (ESI): *m/z* Calc'd for $C_{19}H_{21}NNaO_3S$ $[M+Na]^+$: 366.1134, found: 366.1134.
Relative Stereochemistry: *determined by comparison to* **4.4a**



4.6b

***cis-N*-(2-(2-Methylbenzoyl)cyclopentyl)benzenesulfonamide (4.6b)** was synthesized according to General Procedure F from **4.5b** (0.21 mmol). Purification using column chromatography (EtOAc/hexanes = 1:3) provided **4.6b** (15.1 mg, 21%, 2:1 d.r.) as a clear oil that solidifies upon standing.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.6 Hz, 2H), 7.43 (t, *J* = 7.4 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.34 (t, *J* = 6.8 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 7.6 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 5.73 (d, *J* = 9.2 Hz, 1H), 3.91 (p, *J* = 7.5 Hz, 1H), 3.64 (dt, *J* = 8.9, 5.8 Hz, 1H), 2.42 (s, 3H), 1.97 – 1.90 (m, 1H), 1.88 – 1.84 (m, 2H), 1.82 – 1.72 (m, 2H), 1.61 – 1.53 (m, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 206.6, 141.0, 138.9, 137.1, 132.5, 132.2, 131.8, 129.2, 128.7, 127.0, 125.7, 57.1, 50.0, 32.9, 29.3, 21.9, 21.5;
HRMS: *m/z* Calc'd for $C_{19}H_{21}NNaO_3S$ $[M+Na]^+$: 366.1134, found: 366.1136.
Relative Stereochemistry: *determined by comparison to* **4.4a**



4.6c

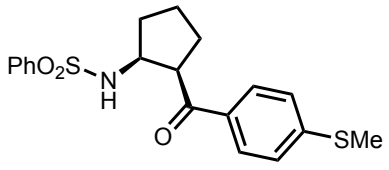
***cis-N*-(2-(4-Methoxybenzoyl)cyclopentyl)benzenesulfonamide (4.6c)** was synthesized according to General Procedure F from **4.5c** (0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 1:4) provided **4.6c** (35.0 mg, 49%, 13:1 d.r.) (*88% brsm*) as a white solid.

^{1}H NMR: ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.0 Hz, 2H), 7.69 (d, *J* = 8.9 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 2H), 6.85 (d, *J* = 8.9 Hz, 2H), 5.82 (d, *J* = 9.3 Hz, 1H), 3.90 (ddd, *J* = 17.5, 9.5, 7.7 Hz, 1H), 3.87 (s, 3H), 3.62 (ddd, *J* = 9.2, 6.8, 5.3 Hz, 1H), 2.02 – 1.95 (m, 1H), 1.91 – 1.83 (m, 2H), 1.83 – 1.76 (m, 1H), 1.76 – 1.69 (m, 1H), 1.60 – 1.51 (m, 1H);

^{13}C NMR: (176 MHz, $CDCl_3$) δ 200.8, 163.9, 140.8, 132.3, 130.8, 129.1, 129.0, 127.0, 113.8, 57.0, 55.7, 46.6, 33.0, 29.7, 21.9;

HRMS (ESI): *m/z* Calc'd for $C_{19}H_{21}NNaO_4S$ $[M+Na]^+$: 382.1083, found: 382.1082.

Relative Stereochemistry: *determined by comparison to* **4.4a**



4.6d

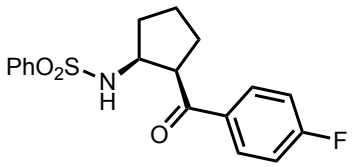
***cis-N*-(2-(4-(Methylthio)benzoyl)cyclopentyl)benzenesulfonamide (4.6d)** was synthesized according to General Procedure F from **4.5d** (0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 1:4) provided **4.6d** (52.5 mg, 70%, 9:1 d.r.) as a white solid.

^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.2 Hz, 2H), 7.61 (d, *J* = 8.6 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 2H), 7.17 (d, *J* = 8.6 Hz, 2H), 5.75 (d, *J* = 9.5 Hz, 1H), 3.91 (tt, *J* = 9.1, 7.0 Hz, 1H), 3.63 (ddd, *J* = 9.3, 6.8, 5.3 Hz, 1H), 2.51 (s, 3H), 2.02 – 1.95 (m, 1H), 1.92 – 1.82 (m, 2H), 1.82 – 1.75 (m, 1H), 1.75 – 1.69 (m, 1H), 1.60 – 1.53 (m, 1H).

^{13}C NMR: (176 MHz, $CDCl_3$) δ 201.1, 146.7, 140.7, 132.4, 132.2, 129.0, 128.8, 127.0, 124.9, 57.0, 46.8, 33.0, 29.5, 21.9, 14.8;

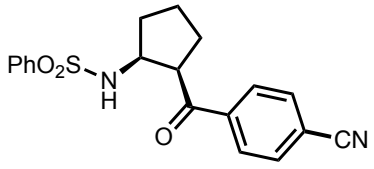
HRMS (ESI): *m/z* Calc'd for $C_{19}H_{21}NNaO_3S_2$ $[M+Na]^+$: 398.0855, found: 398.0854.

Relative Stereochemistry: *determined by comparison to* **4.4a**



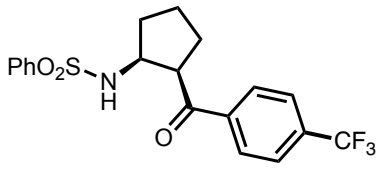
4.6e

***cis-N*-(2-(4-Fluorobenzoyl)cyclopentyl)benzenesulfonamide (4.6e)** was synthesized according to General Procedure F from **4.5e** (0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 1:4) provided **4.6e** (48.3 mg, 69%, 9:1 d.r.) as a white solid.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.76 – 7.73 (m, 4H), 7.34 (t, *J* = 7.4 Hz, 1H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.05 (t, *J* = 8.6 Hz, 2H), 5.67 (d, *J* = 9.7 Hz, 1H), 3.93 (tt, *J* = 9.3, 7.1 Hz, 1H), 3.66 (ddd, *J* = 9.2, 6.8, 5.2 Hz, 1H), 2.03 – 1.97 (m, 1H), 1.93 – 1.87 (m, 1H), 1.87 – 1.76 (m, 2H), 1.77 – 1.68 (m, 1H), 1.61 – 1.54 (m, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 200.4, 165.9 (d, *J* = 255.8 Hz), 140.6, 132.34, 132.30, 131.0 (d, *J* = 9.3 Hz), 129.0, 126.9, 115.7 (d, *J* = 21.8 Hz), 56.8, 46.9, 32.8, 29.3, 21.8;
HRMS (ESI): *m/z* Calc'd for $C_{18}H_{18}FNNaO_3S$ $[M+Na]^+$: 370.0884, found: 370.0883.
Relative Stereochemistry: *determined by comparison to* **4.4a**

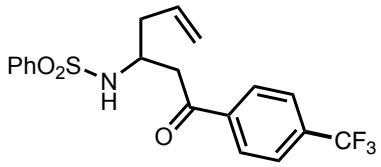


4.6f

***cis-N*-(2-(4-Cyanobenzoyl)cyclopentyl)benzenesulfonamide (4.6f)** was synthesized according to General Procedure F from **4.5f** (0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 1:2) provided **4.6f** (21.7 mg, 31%, 4:1 d.r.) as a clear oil that solidifies upon standing.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.2 Hz, 2H), 7.74 (d, *J* = 8.1 Hz, 2H), 7.69 (d, *J* = 8.1 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.31 (t, *J* = 7.6 Hz, 2H), 5.48 (d, *J* = 9.9 Hz, 1H), 3.98 (ddd, *J* = 16.4, 9.3, 7.3 Hz, 1H), 3.74 (ddd, *J* = 9.2, 6.8, 5.1 Hz, 1H), 2.05 – 1.98 (m, 1H), 1.93 – 1.87 (m, 1H), 1.84 – 1.76 (m, 2H), 1.75 – 1.70 (m, 1H), 1.62 – 1.56 (m, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 200.7, 140.6, 139.1, 132.5, 132.5, 129.1, 128.8, 127.0, 117.9, 116.6, 56.9, 47.7, 32.8, 29.1, 21.9;
HRMS (ESI): *m/z* Calc'd for $C_{19}H_{18}N_2NaO_3S$ $[M+Na]^+$: 377.0930, found: 377.0931.
Relative Stereochemistry: *determined by comparison to* **4.4a**



4.6g



4.6g-(II)

***cis-N*-(2-(4-Trifluoromethylbenzoyl)cyclopentyl)benzenesulfonamide (4.6g) and *N*-(1-oxo-1-(4-(trifluoromethyl)phenyl)hex-5-en-3-yl)benzenesulfonamide (4.6g-(II))** were prepared according to General Procedure F from **4.5g** (0.2 mmol). Purification via column chromatography (EtOAc/hexanes = 1:2) provided **4.6g** (26.2 mg, 33%, 1.3:1 d.r.) as a white solid and **4.6g-(II)** (0.7 mg, 1%) as a clear oil.

^{1}H NMR (4.6g): (499 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.2 Hz, 2H), 7.74 (d, *J* = 7.4 Hz, 2H), 7.66 (d, *J* = 8.2 Hz, 2H), 7.30 (dt, *J* = 14.8, 7.1 Hz, 3H), 5.49 (d, *J* = 9.8 Hz, 1H), 3.98 (p, *J* = 7.8 Hz, 1H), 3.78 – 3.66 (m, 1H), 2.02 (ddd, *J* = 14.1, 9.3, 5.3 Hz, 1H), 1.94 (ddd, *J* = 12.1, 8.6, 4.6 Hz, 1H), 1.89 – 1.65 (m, 3H), 1.63 (d, *J* = 8.6 Hz, 1H); **Relative Stereochemistry**: *determined by comparison to* **4.4a**;

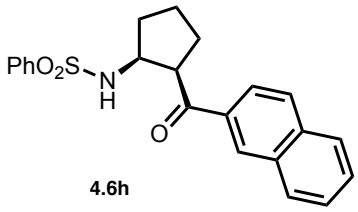
^{13}C NMR (4.6g): (126 MHz, $CDCl_3$) δ 201.1, 140.8, 138.8, 135.0, 134.7, 132.6, 129.2, 128.8, 127.1, 125.78 (q, *J* = 3.8 Hz), 57.0, 47.6, 33.1, 29.3, 22.0;

HRMS (ESI) (4.6g): *m/z* Calc'd for $C_{19}H_{18}F_3NNaO_3S$ $[M+Na]^+$: 420.0852, found: 420.0853.

^{1}H NMR (4.6g-(II)): (499 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.1 Hz, 2H), 7.85 (d, *J* = 7.4 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.5 Hz, 2H), 5.55 – 5.41 (m, 1H), 5.09 (d, *J* = 7.8 Hz, 1H), 5.05 – 4.91 (m, 2H), 3.85 – 3.74 (m, 1H), 3.35 (dd, *J* = 17.5, 4.1 Hz, 1H), 3.12 (dd, *J* = 17.5, 6.6 Hz, 1H), 2.33 (dtd, *J* = 28.5, 14.3, 7.2 Hz, 2H);

^{13}C NMR (4.6g-(II)): (151 MHz, $CDCl_3$) δ 197.6, 140.8, 139.4, 133.4, 132.9, 129.3, 128.6, 127.5, 127.3, 125.99 (q, *J* = 4.0 Hz), 119.5, 50.3, 42.7, 39.1.

HRMS (ESI) (4.6g-(II)): *m/z* Calc'd for $C_{19}H_{19}F_3NO_3S$ $[M+H]^+$: 398.1032, found: 398.1045.

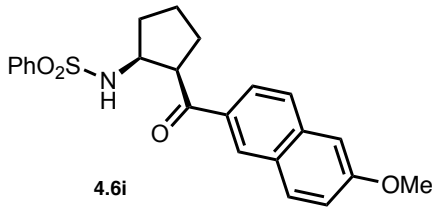


4.6h

***cis-N*-(2-(2-Naphthoyl)cyclopentyl)benzenesulfonamide (4.6h)** was synthesized according to General Procedure F from **4.5h** (0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 1:3) provided **4.6h** (57 mg, 75%, 1.3:1 d.r.) as a white solid.

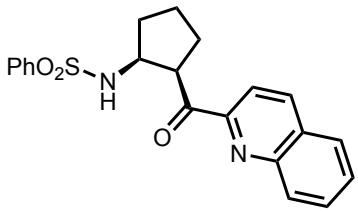
^{1}H NMR: (700 MHz, CDCl3) δ 8.14 (s, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.87 (d, *J* = 8.0 Hz, 1H), 7.82 (q, *J* = 8.6 Hz, 2H), 7.72 (d, *J* = 7.7 Hz, 2H), 7.62 (t, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.15 (t, *J* = 7.7 Hz, 2H), 7.08 (t, *J* = 7.4 Hz, 1H), 5.74 (d, *J* = 9.6 Hz, 1H), 4.00 (p, *J* = 7.9 Hz, 1H), 3.86 (dt, *J* = 9.3, 6.3 Hz, 1H), 2.11 – 2.04 (m, 1H), 2.01 – 1.95 (m, 1H), 1.95 – 1.85 (m, 2H), 1.82 – 1.75 (m, 1H), 1.67 – 1.57 (m, 1H);

^{13}C NMR: (176 MHz, $CDCl_3$) δ 202.1, 140.6, 135.8, 133.3, 132.4, 132.3, 130.4, 129.7, 129.0, 128.9, 128.6, 127.9, 127.0, 127.0, 123.9, 57.1, 47.1, 33.3, 29.7, 22.0;
HRMS (ESI): *m/z* Calc'd for $C_{22}H_{21}NNaO_3S$ $[M+Na]^+$: 402.1134, found: 402.1136.
Relative Stereochemistry: *determined by comparison to* **4.4a** *and by x-ray analysis (not included)*

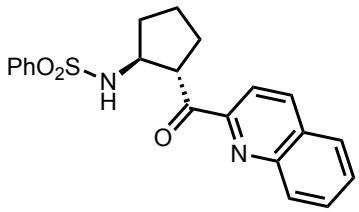


4.6i

***cis-N*-(2-(6-Methoxy-2-naphthoyl)cyclopentyl)benzenesulfonamide (4.6i)** was synthesized according to General Procedure F from **4.5i** (0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 1:4) provided **4.6i** (55.4 mg, 68%, 2.4:1 d.r.) as a cloudy oil.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 8.06 (s, 1H), 7.78 – 7.75 (m, 2H), 7.73 – 7.66 (m, 3H), 7.20 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.17 – 7.13 (m, 3H), 7.10 (t, *J* = 7.4 Hz, 1H), 5.80 (d, *J* = 9.4 Hz, 1H), 4.00 – 3.96 (m, 1H), 3.96 (s, 3H), 3.81 (ddd, *J* = 9.2, 6.8, 5.5 Hz, 1H), 2.10 – 2.02 (m, 1H), 1.99 – 1.90 (m, 2H), 1.90 – 1.84 (m, 1H), 1.82 – 1.73 (m, 1H), 1.64 – 1.57 (m, 1H).
^{13}C NMR: (176 MHz, $CDCl_3$) δ 201.8, 160.1, 140.6, 137.6, 132.2, 131.4, 131.3, 130.2, 128.9, 127.7, 127.2, 127.0, 124.7, 120.0, 105.8, 57.1, 55.6, 46.8, 33.3, 29.8, 22.0;
HRMS (ESI): *m/z* Calc'd for $C_{23}H_{23}NNaO_4S$ $[M+Na]^+$: 432.1240, found: 432.1238.
Relative Stereochemistry: *determined by comparison to* **4.4a**



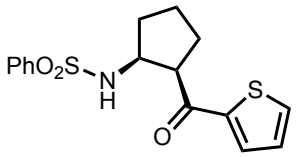
4.6j



***epi*-4.6j**

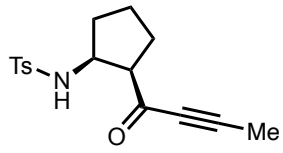
***cis-N*-2-(Quinoline-2-carbonyl)cyclopentyl)benzenesulfonamide (4.6j)** was synthesized according to General Procedure F from **4.5j** (0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 1:2) provided **4.6j** and ***epi*-4.6j** (13.5 mg, 18%, 1.5:1 d.r.) (*33% brsm*) as a yellow oil.
^{1}H NMR (*Isolated as a 1:0.7 mixture of diastereomers*) **Peaks solely attributed to the minor diastereomer are marked with an asterisk**: (700 MHz, $CDCl_3$) δ 8.34 (d, *J* = 1.1 Hz, 1H), 8.27 (d, *J* = 8.4 Hz, 1H), 8.19* (d, *J* = 8.4 Hz, 0.7H), 8.05* (d, *J* = 8.5 Hz, 0.7H), 7.96 (t, *J* = 8.4 Hz, 1.7H), 7.93 – 7.89 (m, 2H), 7.86* (dd, *J* = 8.3, 1.5 Hz, 0.7H), 7.78* (ddd, *J* = 8.4, 6.8, 1.4 Hz, 0.7H), 7.74 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.67* (ddd, *J* = 8.1, 6.8, 1.2 Hz, 0.7H), 7.62 – 7.60* (m, 1.4H), 7.61 – 7.59 (m, 1H), 7.37 (d, *J* = 7.0 Hz, 2H), 7.28 – 7.23 (m, 1H), 7.05 – 7.02 (m, 2H),

7.02 – 7.00* (m, 1.4H), 6.95* (t, *J* = 7.4 Hz, 0.7H), 5.58* (d, *J* = 8.6 Hz, 0.7H), 4.57* (dt, *J* = 9.0, 7.2 Hz, 0.7H), 4.23 – 4.12 (m, 1.7H), 3.36 (qd, *J* = 7.7, 2.5 Hz, 1H), 2.30 – 2.22 (m, 1H), 2.18 – 2.12 (m, 1H), 2.09 – 2.00* (m, 1.4H), 1.99 – 1.95* (m, 0.7H), 1.96 – 1.89 (m, 2.7H), 1.88 – 1.81 (m, 1.7H), 1.78 – 1.71 (m, 1H), 1.70 – 1.65* (m, 0.7H);
^{13}C NMR: (176 MHz, $CDCl_3$) (176 MHz, $CDCl_3$) δ 202.9, 200.4, 152.4, 152.0, 146.9, 146.4, 140.2, 139.1, 137.7, 136.9, 132.2, 131.8, 131.1, 130.6, 130.1, 130.0, 129.6, 129.3, 128.8, 128.6, 128.5, 127.7, 127.6, 126.8, 126.7, 118.9, 118.2, 58.5, 57.4, 51.8, 46.9, 35.3, 34.3, 28.1, 27.1, 24.0, 22.1 (2 C's overlaps);
HRMS (ESI): *m/z* Calc'd for $C_{21}H_{20}N_2NaO_3S$ $[M+Na]^+$: 403.1087, found: 403.1088.
Relative Stereochemistry: *determined by comparison to* **4.4a**

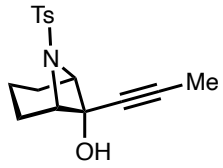


4.6k

***cis-N*-2-(Thiophene-2-carbonyl)cyclopentyl)benzenesulfonamide (4.6k)** was synthesized according to General Procedure F from **4.5k** (0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 1:2) provided **4.6k** (37.8 mg, 56%, 10:1 d.r.) as a white solid.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.0 Hz, 2H), 7.61 (dd, *J* = 4.9, 1.3 Hz, 1H), 7.41 (dd, *J* = 3.7, 1.1 Hz, 1H), 7.36 – 7.32 (m, 1H), 7.29 (dd, *J* = 8.2, 6.8 Hz, 2H), 7.04 (dd, *J* = 4.9, 3.8 Hz, 1H), 5.67 (d, *J* = 9.4 Hz, 1H), 3.91 (tt, *J* = 9.0, 7.1 Hz, 1H), 3.53 (ddd, *J* = 9.1, 6.9, 5.4 Hz, 1H), 2.05 – 1.97 (m, 1H), 1.93 – 1.81 (m, 3H), 1.79 – 1.72 (m, 1H), 1.60 – 1.54 (m, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 195.0, 143.6, 140.7, 134.6, 132.7, 132.4, 129.0, 128.2, 127.0, 57.1, 48.4, 33.2, 30.0, 22.0;
HRMS (ESI): *m/z* Calc'd for $C_{16}H_{17}NNaO_3S_2$ $[M+Na]^+$: 358.0542, found: 358.0543.
Relative Stereochemistry: *determined by comparison to* **4.4a**



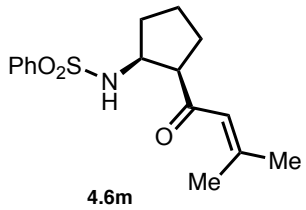
4.6l



4.S4

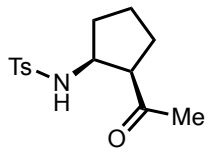
***cis-N*-2-(But-2-ynoyl)cyclopentyl)-4-methylbenzenesulfonamide (4.6l) and 7-(prop-1-yn-1-yl)-6-tosyl-6-azabicyclo[3.1.1]heptan-7-ol (4.S4)** were synthesized according to General Procedure F from **4.5l** (0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 3:1) provided **4.6l** (5.6 mg, 9%, 3:1 d.r.) (*12% brsm*) and **4.S4** (8.8 mg, 12%) (*19% brsm*) as clear oils.

^{1}H NMR (4.6l): (499 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 5.38 (d, *J* = 9.4 Hz, 1H), 3.77 (p, *J* = 7.6 Hz, 1H), 2.96 (dt, *J* = 8.5, 5.8 Hz, 1H), 2.42 (s, 3H), 1.97 (s, 3H), 1.96 – 1.83 (m, 2H), 1.80 – 1.74 (m, 1H), 1.71 – 1.61 (m, 2H), 1.56 – 1.51 (m, 1H); (**4.6l-*anti):*** (499 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 4.55 (d, *J* = 4.4 Hz, 1H), 3.95 – 3.85 (m, 1H), 2.86 (dt, *J* = 9.4, 6.8 Hz, 1H), 2.43 (s, 2H), 2.08 – 1.92 (m, 5H), 1.90 – 1.82 (m, 1H), 1.73 – 1.65 (m, 1H), 1.63 – 1.56 (m, 1H), 1.51 – 1.42 (m, 1H); **Relative Stereochemistry**: *determined by comparison to* **4.4a**.
^{13}C NMR (reported as a diastereomeric mixture of 4.6l and 4.6l-anti): (151 MHz, $CDCl_3$) δ 189.4, 188.2, 143.7, 143.4, 138.0, 137.2, 129.8, 127.5, 127.3, 92.2, 91.7, 80.2, 79.4, 60.2, 56.5, 56.4, 55.0, 33.9, 31.9, 27.9, 27.5, 23.1, 21.7, 21.7, 21.2, 4.32, 4.30 (2 C's overlapping);
HRMS (ESI) (4.6l): *m/z* Calc'd for $C_{16}H_{19}NNaO_3S$ $[M+Na]^+$: 328.0978, found: 328.0978;
^{1}H NMR (4.S4): (499 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.12 (d, *J* = 3.5 Hz, 2H), 2.77 (s, 1H), 2.43 (s, 3H), 2.34 – 2.20 (m, 2H), 2.14 – 2.05 (m, 2H), 1.90 (s, 3H), 1.88 – 1.73 (m, 2H);
^{13}C NMR (4.S4): (126 MHz, $CDCl_3$) δ 144.0, 137.2, 129.8, 127.6, 87.1, 75.9, 74.6, 74.5, 26.9, 21.8, 14.2, 3.9;
HRMS (ESI) (4.S4): *m/z* Calc'd for $C_{16}H_{19}NNaO_3S$ $[M+Na]^+$: 328.0978, found: 328.0978.



4.6m

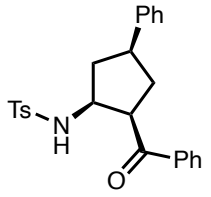
***cis*-4-Methyl-*N*-2-(3-methylbut-2-enoyl)cyclopentyl)benzenesulfonamide (4.6m)** was synthesized according to General Procedure F from **4.5m** (0.2 mmol). Purification using preparative thin layer chromatography (EtOAc/hexanes = 1:3) provided **4.6m** (39.2 mg, 64%, 6:1 d.r.) as a white solid.
^{1}H NMR: (600 MHz, $CDCl_3$) δ 7.82 (d, *J* = 7.1 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 2H), 5.78 (d, *J* = 8.9 Hz, 1H), 5.76 (p, *J* = 1.3 Hz, 1H), 3.75 (dq, *J* = 8.8, 7.4 Hz, 1H), 2.84 (dt, *J* = 8.9, 6.0 Hz, 1H), 2.08 (d, *J* = 1.2 Hz, 3H), 1.87 – 1.82 (m, 1H), 1.82 (d, *J* = 1.3 Hz, 3H), 1.76 – 1.71 (m, 3H), 1.68 – 1.64 (m, 1H), 1.53 – 1.47 (m, 1H);
^{13}C NMR: (151 MHz, $CDCl_3$) δ 202.5, 158.1, 141.1, 132.4, 129.1, 127.2, 123.6, 56.7, 53.0, 32.7, 28.2, 28.0, 21.7, 21.1;
HRMS (ESI): *m/z* Calc'd for $C_{16}H_{21}NNaO_3S$ $[M+Na]^+$: 330.1134, found: 330.1135.
Relative Stereochemistry: *determined by comparison to* **4.4a**



4.6n

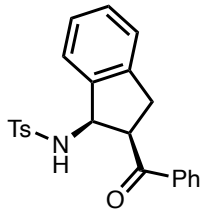
***cis-N*-2-Acetylcyclopentyl-4-methylbenzenesulfonamide (4.6n)** was synthesized using a procedure analogous to General Procedure F from **4.5n** (0.2 mmol) using medium pressure mercury lamp irradiation. Purification using preparative thin layer chromatography (EtOAc/hexanes = 1:2) provided **4.6n** (14.1 mg, 25%, 2.2:1 d.r.) (*35% brsm*) as a white solid.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.1 Hz, 2H), 5.40 (d, *J* = 9.3 Hz, 1H), 3.80 – 3.68 (m, 1H), 2.95 (dt, *J* = 8.8, 6.2 Hz, 1H), 2.42 (s, 3H), 1.95 (s, 3H), 1.89 – 1.84 (m, 1H), 1.78 – 1.70 (m, 2H), 1.68 – 1.60 (m, 2H), 1.55 – 1.47 (m, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 211.1, 143.5, 138.0, 129.8, 127.3, 56.4, 52.9, 32.4, 30.3, 27.6, 21.7, 21.6;
HRMS (ESI): *m/z* Calc'd for $C_{14}H_{19}NNaO_3S$ $[M+Na]^+$: 304.0978, found: 304.0984.
Relative Stereochemistry: *determined by comparison to* **4.4a**

4.4.3.3. Heterocyclic Core Modified Substrates



4.8a

***cis-N*-(2-Benzoyl-4-phenylcyclopentyl)-4-methylbenzenesulfonamide (4.8a)** was synthesized according to General Procedure F from **4.7a** (0.12 mmol). Purification using column chromatography (EtOAc/hexanes = 0–30%) provided **4.8a** (16.4 mg, 33%, 10:1 d.r.) (51% *brsm*) as a clear oil.
^{1}H NMR: (499 MHz, Chloroform-*d*) δ 7.69 (d, *J* = 7.5 Hz, 2H), 7.62 (d, *J* = 8.1 Hz, 2H), 7.55 (t, *J* = 7.3 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.24 (d, *J* = 7.5 Hz, 2H), 7.19 – 7.12 (m, 3H), 7.01 (d, *J* = 8.1 Hz, 2H), 5.88 (d, *J* = 10.5 Hz, 1H), 4.13 (tt, *J* = 10.9, 5.6 Hz, 1H), 3.84 (q, *J* = 7.7 Hz, 1H), 3.10 (dt, *J* = 18.6, 10.4 Hz, 1H), 2.53 (dt, *J* = 13.6, 9.1 Hz, 1H), 2.29 (dt, *J* = 12.3, 6.3 Hz, 1H), 2.17 (s, 3H), 2.11 (q, *J* = 12.0 Hz, 1H), 1.76 (ddd, *J* = 13.7, 10.3, 7.0 Hz, 1H);
^{13}C NMR: (151 MHz, $CDCl_3$) δ 202.4, 143.3, 137.9, 136.1, 133.6, 129.8, 128.7, 128.7, 128.6, 127.1, 127.1, 126.7, 56.4, 45.5, 42.4, 41.5, 38.9, 21.5;
HRMS (ESI): *m/z* Calc'd for $C_{25}H_{25}NNaO_3S$ [M+Na]+: 442.1447, found 442.1448.
Relative Stereochemistry: *determined by comparison to* **4.4a**



4.8b

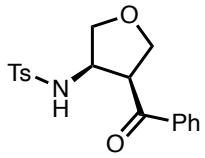
***cis-N*-(2-Benzoyl-2,3-dihydro-1H-inden-1-yl)-4-methylbenzenesulfonamide (4.8b)** was synthesized according to General Procedure F from **4.7b** (0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 0–40%) provided **4.8b** (35.9 mg, 46%, 2.4:1 d.r.) as a white solid.

^{1}H NMR: (499 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.3 Hz, 2H), 7.63 (d, *J* = 8.2 Hz, 1H), 7.56 (t, *J* = 7.4 Hz, 1H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.25 – 7.16 (m, 2H), 7.09 (d, *J* = 7.2 Hz, 1H), 7.00 (d, *J* = 8.0 Hz, 2H), 5.99 (d, *J* = 10.6 Hz, 1H), 5.25 (dd, *J* = 10.4, 7.1 Hz, 1H), 4.20 – 4.11 (m, 1H), 3.25 (dd, *J* = 16.4, 9.1 Hz, 1H), 3.06 (dd, *J* = 16.3, 2.8 Hz, 1H), 2.18 (s, 3H);

^{13}C NMR: (126 MHz, $CDCl_3$) δ 199.7, 143.4, 142.0, 138.4, 138.1, 135.4, 133.6, 129.8, 128.7, 128.6, 128.5, 127.7, 127.2, 124.9, 123.9, 60.0, 48.1, 35.4, 21.5;

HRMS (ESI): *m/z* Calc'd for $C_{23}H_{20}NO_3S$ $[M-H]^-$: 390.1164, found 390.1171.

Relative Stereochemistry: *determined by comparison to* **4.4a**



4.8c

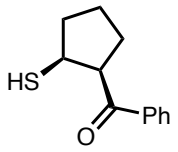
***cis-N*-(4-Benzoyltetrahydrofuran-3-yl)-4-methylbenzenesulfonamide (4.8c)** was synthesized according to General Procedure F from **4.7c** (0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 0–40%) provided **4.8c** (45.3 mg, 66%, 3:1 d.r.) as an orange solid.

^{1}H NMR: (600 MHz, Chloroform-*d*) δ 7.72 – 7.65 (m, 2H), 7.60 – 7.53 (m, 3H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 5.64 (d, *J* = 10.3 Hz, 1H), 4.30 (dq, *J* = 10.3, 6.8 Hz, 1H), 4.09 (t, *J* = 7.6 Hz, 1H), 4.04 – 3.93 (m, 3H), 3.72 (dd, *J* = 8.9, 6.6 Hz, 1H), 2.21 (s, 3H);

^{13}C NMR: (151 MHz, $CDCl_3$) δ 199.0, 143.6, 137.1, 136.1, 134.0, 129.9, 128.8, 128.5, 127.1, 73.3, 70.9, 55.9, 47.0, 21.6;

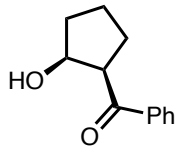
HRMS (ESI): *m/z* Calc'd for $C_{18}H_{20}NO_4S$ $[M+H]^+$: 346.1113, found 346.1113.

Relative Stereochemistry: *determined by comparison to* **4.4a**



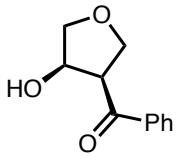
4.8d

***cis*-2-Mercaptocyclopentyl)(phenyl)methanone (4.8d)** was synthesized according to General Procedure F from **4.7d** (0.22 mmol). Purification using a pipette column (EtOAc/hexanes = 1:4) provided **4.8d** (38.8 mg. 83%, 20:1 d.r.) as a clear oil.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.5 Hz, 2H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 2H), 3.99 (q, *J* = 7.7 Hz, 1H), 3.64 – 3.58 (m, 1H), 2.35 – 2.22 (m, 2H), 2.00 – 1.93 (m, 1H), 1.92 – 1.86 (m, 2H), 1.74 – 1.67 (m, 1H), 1.49 (d, *J* = 8.1 Hz, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 200.2, 137.7, 133.0, 128.8, 128.4, 52.3, 42.0, 37.6, 26.3, 22.9;
HRMS (ESI): *m/z* Calc'd for $C_{12}H_{13}OS$ $[M-H]^-$: 205.0693, found 205.0698.
Relative Stereochemistry: *determined by comparison to* **4.8g**



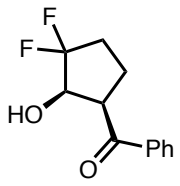
4.8e

***cis*-2-Hydroxycyclopentyl)(phenyl)methanone (4.8e)** was synthesized according to General Procedure F from **4.7e** (0.29 mmol). Purification using preparative thin layer chromatography (EtOAc/hexanes = 1:2) provided **4.8e** (42 mg, 75%, 20:1 d.r.) as a clear oil. Spectral data was in full agreement with that previously reported.[54]



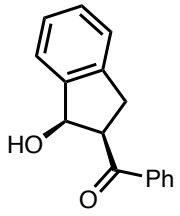
4.8f

***cis*-2-Hydroxycyclopentyl)(phenyl)methanone (4.8f)** was synthesized according to General Procedure F from **4.7f** (0.24 mmol). Purification using preparative thin layer chromatography (EtOAc/hexanes = 1:1) provided **4.8f** (17.2 mg, 37%, 20:1 d.r.) as a clear oil. Spectral data was in full agreement with that previously reported.[55]



4.8g

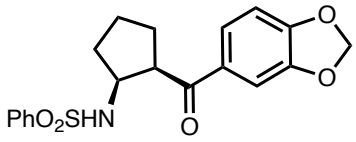
***cis*-3,3-Difluoro-2-hydroxycyclopentyl)(phenyl)methanone (4.8g)** was synthesized according to General Procedure F from **4.7g** (0.11 mmol). Purification using preparative thin layer chromatography (EtOAc/hexanes = 1:3) provided **4.8g** (19.3 mg, 80%, 20:1 d.r.) as a white solid.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.95 (d, *J* = 6.8 Hz, 2H), 7.62 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.8 Hz, 2H), 4.38 (dd, *J* = 7.2, 4.5 Hz, 1H), 3.95 (dp, *J* = 8.5, 4.4 Hz, 1H), 3.84 (br s, 1H), 2.49 – 2.35 (m, 2H), 2.24 – 2.17 (m, 1H), 2.14 – 2.07 (m, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 200.9, 136.4, 134.1, 129.0, 128.5, 75.11 (dd, *J* = 35.3, 21.8 Hz), 46.52 (d, *J* = 3.2 Hz), 31.15 (t, *J* = 24.0 Hz), 23.1(3), 23.1(0);
HRMS (ESI): *m/z* Calc'd for $C_{12}H_{12}F_2NaO_2$ $[M+Na]^+$: 249.0698, found 249.0698.
Relative Stereochemistry: *determined by 2-D analysis*



4.8h

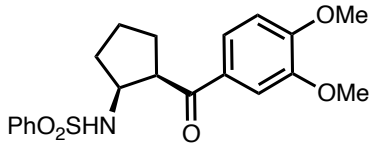
***cis*-1-Hydroxy-2,3-dihydro-1*H*-inden-2-yl)(phenyl)methanone (4.8h)** was synthesized according to General Procedure F from **4.7h** (0.14 mmol). Purification using preparative thin layer chromatography (EtOAc/hexanes = 1:2) provided **4.8h** (29.0 mg, 85%, 20:1 d.r.) as a white solid. Spectral data was in full agreement with that previously reported.[56]

4.4.3.4. Biologically Relevant Substrates



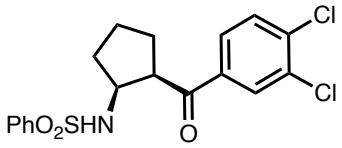
4.10a

***cis-N*-(2-(Benzo[*d*][1,3]dioxole-5-carbonyl)cyclopentyl)benzenesulfonamide (4.10a)** was synthesized according to General Procedure F from **4.9a** (0.2 mmol). Purification using preparative thin layer chromatography (EtOAc/hexanes = 1:3) provided **4.10a** (29.2 mg, 39%, 3.2:1 d.r.) (*75% brsm*) as a white foam.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 8.4, 1.4 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 7.33 – 7.28 (m, 3H), 7.20 (d, *J* = 1.8 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.05 (dd, *J* = 8.9, 1.5 Hz, 2H), 5.72 (d, *J* = 9.4 Hz, 1H), 3.90 (tt, *J* = 8.5, 7.1 Hz, 1H), 3.60 (ddd, *J* = 9.2, 6.8, 5.3 Hz, 1H), 2.02 – 1.95 (m, 1H), 1.90 – 1.77 (m, 3H), 1.76 – 1.69 (m, 1H), 1.60 – 1.54 (m, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 200.2, 152.2, 148.3, 140.8, 132.3, 130.9, 129.0, 127.1, 124.9, 108.2, 107.9, 102.1, 57.0, 46.9, 33.1, 29.7, 21.9;
HRMS (ESI): *m/z* Calc'd for $C_{19}H_{19}NNaO_5S$ $[M+Na]^+$: 396.0876, found 396.0877.
Relative Stereochemistry: *determined by comparison to* **4.4a**, *and x-ray analysis*



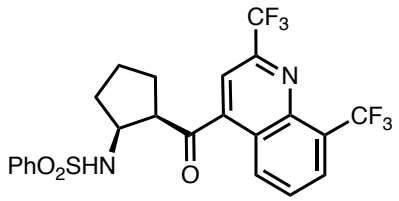
4.10b

***cis-N*-(2-(3,4-Dimethoxybenzoyl)cyclopentyl)benzenesulfonamide (4.10b)** was synthesized according to General Procedure F from **4.9b** (0.2 mmol). Purification using preparative thin layer chromatography (EtOAc/hexanes = 1:2) provided **4.10b** (34.1 mg, 44%, 5:1 d.r.) as a clear oil that solidifies upon standing.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.1 Hz, 2H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.33 (d, *J* = 2.0 Hz, 1H), 7.31 – 7.27 (m, 3H), 6.79 (d, *J* = 8.4 Hz, 1H), 5.75 (d, *J* = 9.4 Hz, 1H), 3.94 (s, 3H), 3.92 – 3.88 (m, 4H), 3.68 (ddd, *J* = 9.1, 6.8, 5.4 Hz, 1H), 1.99 (dtd, *J* = 13.4, 9.1, 5.8 Hz, 1H), 1.91 – 1.80 (m, 3H), 1.77 – 1.71 (m, 1H), 1.61 – 1.54 (m, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 200.8, 153.8, 149.1, 140.8, 132.3, 129.3, 129.0, 127.0, 123.3, 110.4, 109.9, 57.1, 56.2, 56.1, 46.7, 33.1, 29.7, 22.0;
HRMS (ESI): *m/z* Calc'd for $C_{20}H_{23}NNaO_5S$ $[M+Na]^+$: 412.1189, found 412.1192.
Relative Stereochemistry: *determined by comparison to* **4.4a**

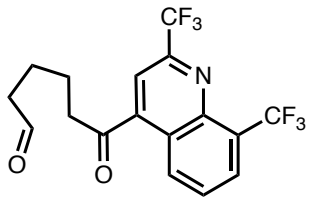


4.10c

***cis-N*-(2-(3,4-Dichlorobenzoyl)cyclopentyl)benzenesulfonamide (4.10c)** was synthesized according to General Procedure F from **4.9c** (0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 1:3) provided **4.10c** (46.1 mg, 58%, 11:1 d.r.) as white solid.
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.74 – 7.73 (m, 1H), 7.72 (d, *J* = 1.9 Hz, 2H), 7.54 (dd, *J* = 8.4, 2.1 Hz, 1H), 7.46 (d, *J* = 8.3 Hz, 1H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.30 (dd, *J* = 8.4, 7.0 Hz, 2H), 5.45 (d, *J* = 9.8 Hz, 1H), 3.96 (dq, *J* = 9.6, 7.2 Hz, 1H), 3.64 (ddd, *J* = 9.2, 6.9, 5.3 Hz, 1H), 2.01 (ddt, *J* = 12.7, 8.9, 4.6 Hz, 1H), 1.98 – 1.92 (m, 1H), 1.87 – 1.78 (m, 2H), 1.77 – 1.71 (m, 1H), 1.63 – 1.59 (m, 1H);
^{13}C NMR: (176 MHz, $CDCl_3$) δ 199.7, 140.6, 138.2, 135.6, 133.4, 132.5, 130.8, 130.4, 129.1, 127.4, 127.0, 57.0, 47.3, 33.2, 29.2, 21.9;
HRMS (ESI): *m/z* Calc'd for $C_{18}H_{17}Cl_2NNaO_3S$ $[M+Na]^+$: 420.0198, found 420.0204.
Relative Stereochemistry: *determined by comparison to* **4.4a**



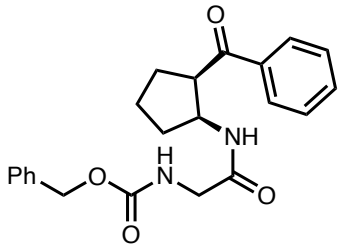
4.10d



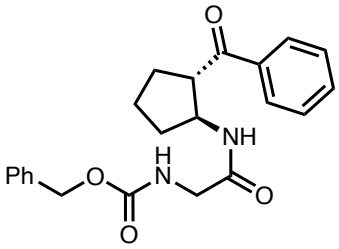
4.S5

***cis-N*-(2-(2,8-bis(trifluoromethyl)quinoline-4-carbonyl)cyclopentyl)benzenesulfonamide (4.10d) and 6-(2,8-bis(trifluoromethyl)quinolin-4-yl)-6-oxohexanal (4.S5)** were synthesized according to General Procedure F from **4.9d** (0.2 mmol) in 27% yield (5.4:1 d.r.) and 4.5% yield respectively, as determined by ^{1}H NMR integration using Ph_3CH as an internal standard.
^{1}H NMR (4.10d): (500 MHz, $CDCl_3$) δ 8.52 (d, *J* = 8.6 Hz, 1H), 8.24 (d, *J* = 7.1 Hz, 1H), 7.82 (t, *J* = 8.3 Hz, 1H), 7.77 (d, *J* = 7.5 Hz, 2H), 7.67 (s, 1H), 7.47 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 2H), 5.48 (d, *J* = 9.8 Hz, 1H), 4.05 (dq, *J* = 9.6, 7.3 Hz, 1H), 3.84 (ddd, *J* = 9.1, 6.9, 5.4 Hz, 1H), 2.08 – 2.03 (m, 1H), 2.03 – 1.98 (m, 1H), 1.96 – 1.91 (m, 1H), 1.91-1.81 (m,1H), 1.87 – 1.83 (m, 1H), 1.74-1.64 (m, 1H); **(4.S5):** (500 MHz, $CDCl_3$) δ 9.80 (s, 1H), 8.53 (d, *J* = 8.6 Hz, 1H), 7.95 (s, 1H), 3.12 (t, *J* = 7.0 Hz, 2H), 2.56 (td, *J* = 7.0, 1.4 Hz, 2H), 1.90 – 1.85 (m, 2H), 1.81 – 1.77 (m, 2H);
^{13}C NMR (4.10d): (126 MHz, $CDCl_3$) δ 203.93, 147.95 (q, *J* = 36.0 Hz), 145.01, 140.27, 129.68, 129.67, 129.66, 129.27-128.17 (m), 129.15, 129.14, 129.01, 128.87, 126.87, 125.88-119.72 (m), 124.75 – 119.66 (m), 115.61 (qf, *J* = 2.1 Hz), 57.11, 51.65, 32.83, 28.49, 21.84; **(4.S5):** (126 MHz, $CDCl_3$) δ 201.95, 148.65-147.65(m), 148.22 (q, *J* = 36.1 Hz), 145.94, 144.65, 129.27, 127.29,

125.05, 126.71-120-18 (m), 124.62 – 122.03 (m), 119.92, 115.63 (q, *J* = 2.0 Hz), 43.72, 42.28, 23.29, 21.47;
HRMS (ESI) (4.10d): *m/z* Calc'd for $C_{23}H_{18}F_6N_2NaO_3S$ $[M+Na]^+$: 539.0835, found: 539.0837.
Relative Stereochemistry: *determined by 2-D analysis*

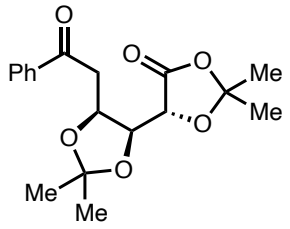


4.12



***epi*-4.12**

***cis*-Benzyl (2-((-2-benzoylcyclopentyl)amino)-2-oxoethyl)carbamate (4.12)** was synthesized according to General Procedure G from **4.11** (0.2 mmol). Purification using reversed phase chromatography (MeCN/H_2O = 15–70% with 0.1% TFA) provided the TFA salt of **4.12** (17.9 mg, 24%, 3:1 d.r.) (*36% brsm*) as a colorless oil comprised of a mixture of *cis* and *trans* diastereomers.
^{1}H NMR of Major diastereomer (*cis*): (499 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.7 Hz, 2H), 7.58 – 7.53 (m, 1H), 7.44 (d, *J* = 7.8 Hz, 2H), 7.34 (s, 5H), 7.00 (d, *J* = 7.4 Hz, 1H), 5.33 (s, 1H), 5.11 (s, 2H), 4.64 (p, *J* = 7.4 Hz, 1H), 4.04 (d, *J* = 6.9 Hz, 1H), 3.73 (q, *J* = 10.7, 8.3 Hz, 2H), 2.09 (ddt, *J* = 18.0, 8.8, 4.8 Hz, 3H), 1.88 – 1.77 (m, 3H); **Minor diastereomer (*trans*):** (499 MHz, CCl_3) δ 7.94 (d, *J* = 7.7 Hz, 2H), 7.60 – 7.57 (m, 1H), 7.47 – 7.46 (m, 2H), 7.34 – 7.33 (m, 5H), 6.48 (s, 1H), 5.55 (s, 1H), 5.07 (s, 2H), 4.56 (p, *J* = 6.8 Hz, 1H), 3.79 (d, *J* = 5.8 Hz, 2H), 3.70 (d, *J* = 5.9 Hz, 1H), 2.04 – 1.94 (m, 3H), 1.70 (dd, *J* = 18.9, 8.6 Hz, 3H);
^{13}C NMR (Peaks solely attributed to the minor diastereomer are marked with an asterisk): (151 MHz, $CDCl_3$) δ 202.8, 201.0,* 169.9,* 169.7, 157.1,* 156.7, 136.7,* 136.5, 134.1,* 133.8,* 133.7, 133.3, 128.9,* 128.9, 128.8,* 128.8, 128.7,* 128.7, 128.6, 128.4,* 128.3, 128.3*, 67.6,* 67.5, 54.5,* 52.9, 52.6,* 47.7, 44.9,* 44.5, 38.2,* 32.6, 29.9, 29.4,* 24.0,* 22.7;
HRMS (ESI): *m/z* Calc'd for $C_{22}H_{24}N_2NaO_4$ $[M+Na]^+$: 403.1628, found: 403.1630.



4.14

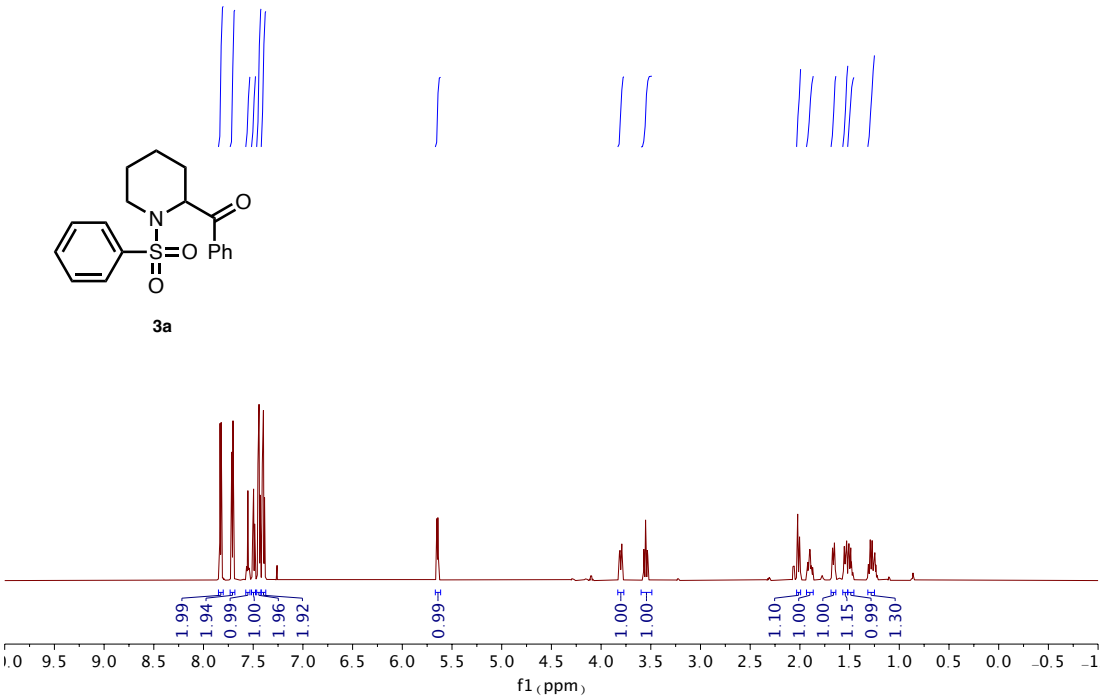
2,2,2',2'-Tetramethyl-5'-(2-oxo-2-phenylethyl)-[4,4'-bi(1,3-dioxolan)]-5-one (4.14) was synthesized according to Representative Procedure F from **4.13** (0.2 mmol). Purification using column chromatography (EtOAc/hexanes = 1:3) provided a co-elution of **4.13** and **4.14** (22 mg total, 1.35:1 ratio by ^{1}H NMR, corresponding to 19% yield of recovered **4.13** and 14% yield of **4.14**) (*17% brsm*) as a white solid.

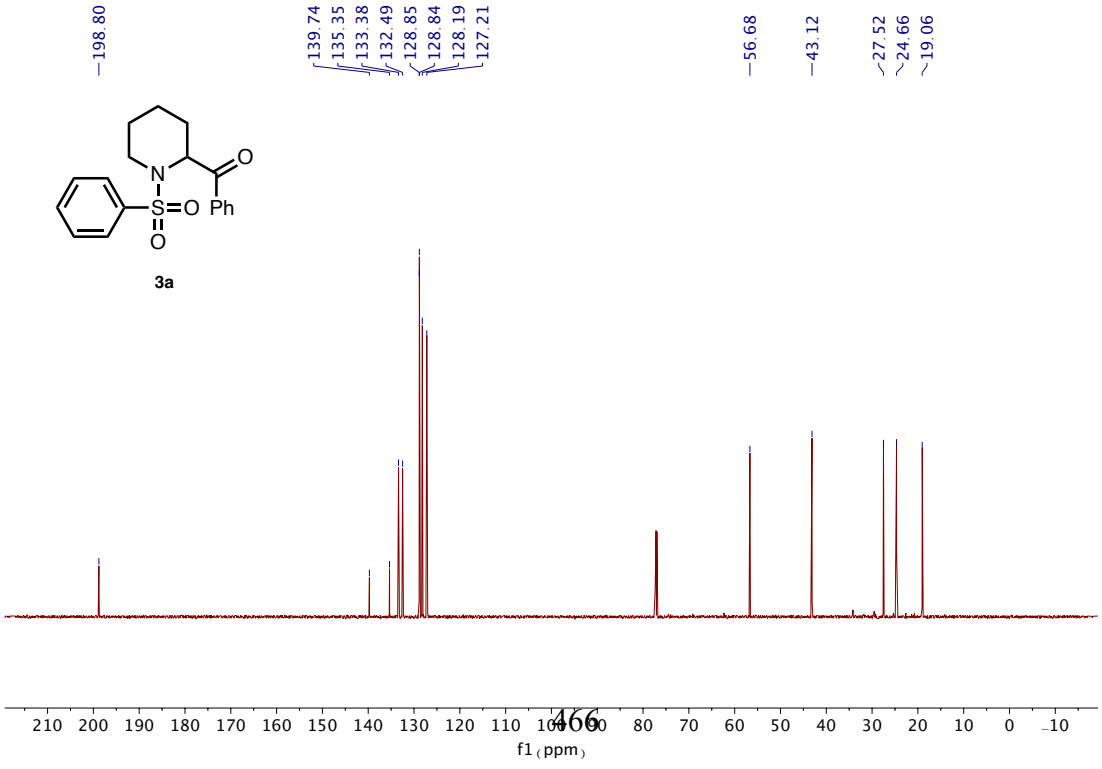
^{1}H NMR: (700 MHz, $CDCl_3$) δ 7.97 (d, *J* = 8.2 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.49 (dd, *J* = 8.3, 7.4 Hz, 2H), 4.93 (ddd, *J* = 8.7, 6.9, 5.0 Hz, 1H), 4.74 (dd, *J* = 6.9, 1.6 Hz, 1H), 4.34 (d, *J* = 1.6 Hz, 1H), 3.59 (dd, *J* = 17.8, 5.0 Hz, 1H), 3.54 (dd, *J* = 17.8, 8.7 Hz, 1H), 1.65 (s, 3H), 1.52 (s, 3H), 1.42 (s, 3H), 1.39 (s, 3H).

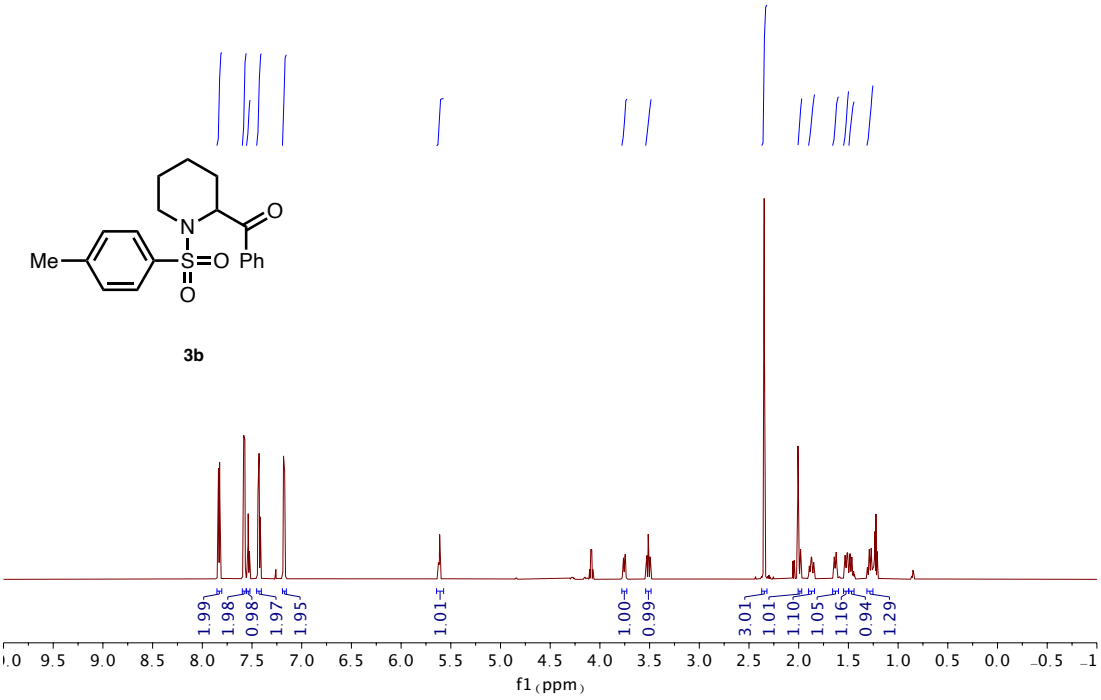
^{13}C NMR: (176 MHz, $CDCl_3$) δ 198.1, 170.9, 136.5, 133.8, 128.9, 128.2, 111.4, 108.8, 76.0, 73.9, 73.0, 40.6, 26.9, 26.8, 26.6, 24.9;

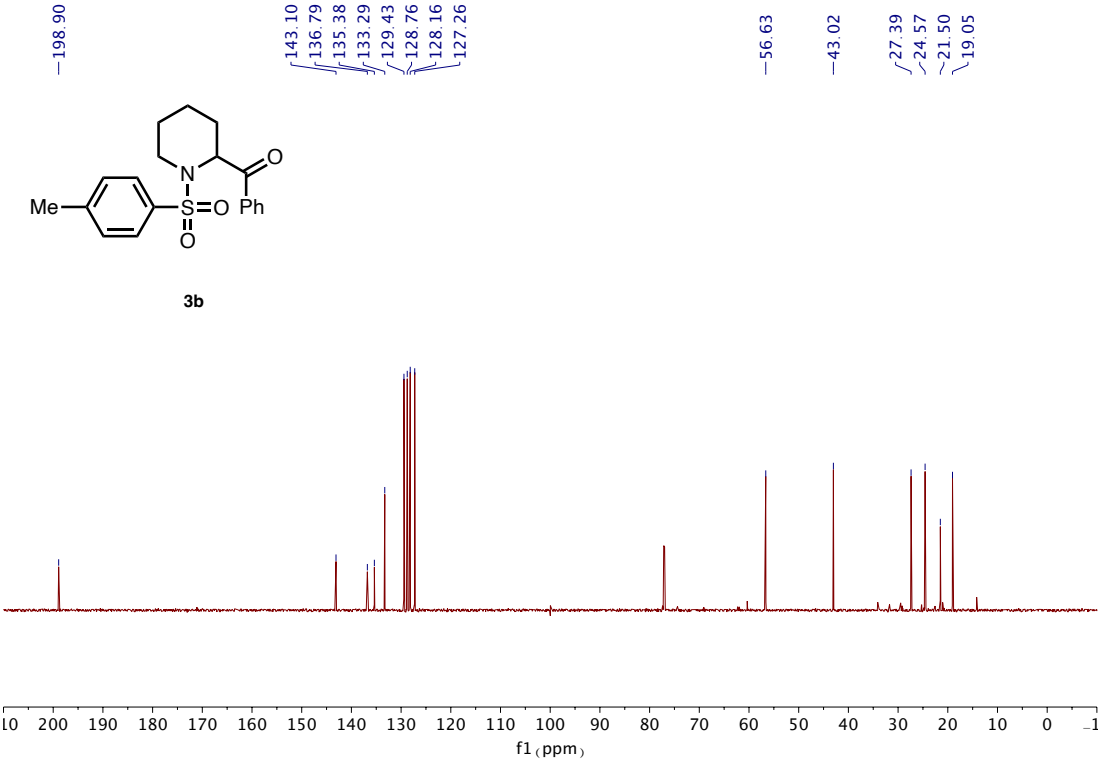
HRMS (ESI): *m/z* Calc'd for $C_{18}H_{22}NaO_6$ $[M+Na]^+$: 357.1309, found 357.1309.

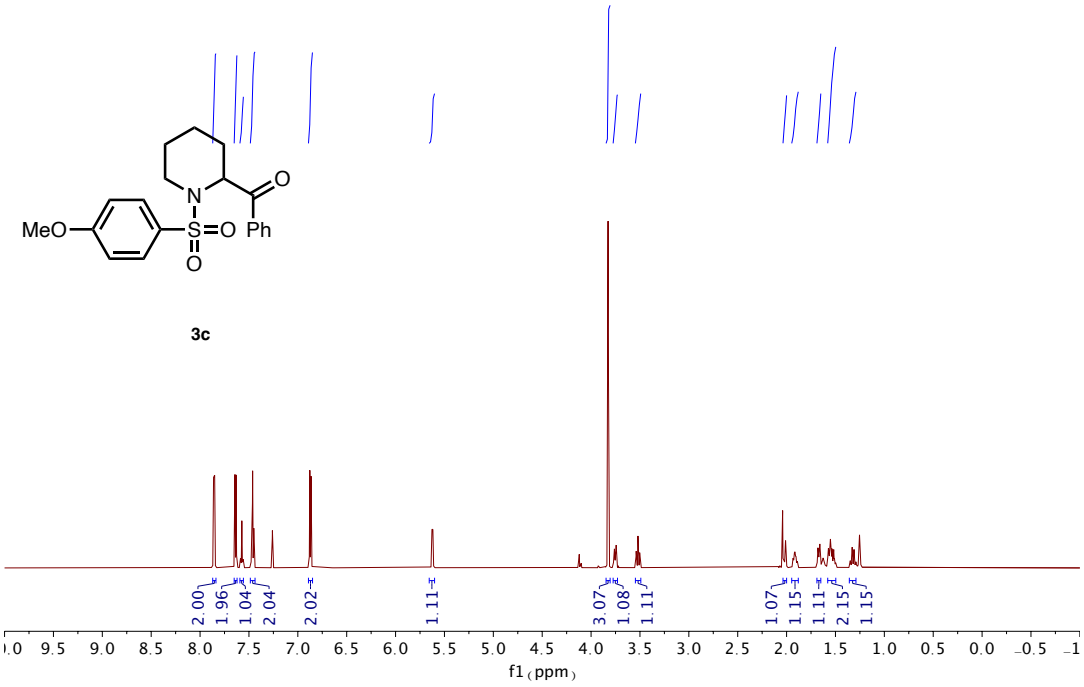
4.4.4. Spectral Data



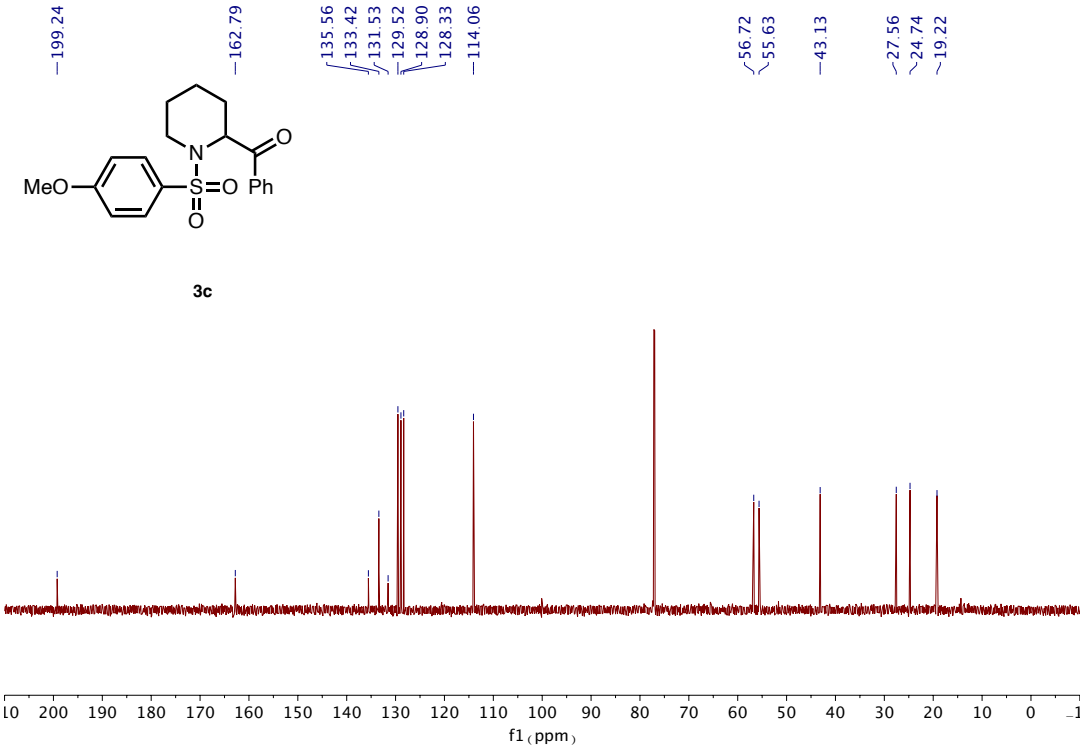



Me
S
O
O
N
O
Ph
3b
1.99
1.98
0.98
1.97
1.95
1.01
1.00
0.99
3.01
1.01
1.10
1.05
1.16
0.94
1.29
f1 (ppm)


198.90
143.10
136.79
135.38
133.29
129.43
128.76
128.16
127.26
56.63
43.02
27.39
24.57
21.50
19.05
Me
S
O
O
N
O
Ph
3b
f1 (ppm)


MeO
S
O
N
O
Ph
O
2.00
1.96
1.04
2.04
2.02
1.11
3.07
1.08
1.11
1.07
1.15
1.11
2.15
1.15
f1 (ppm)

3c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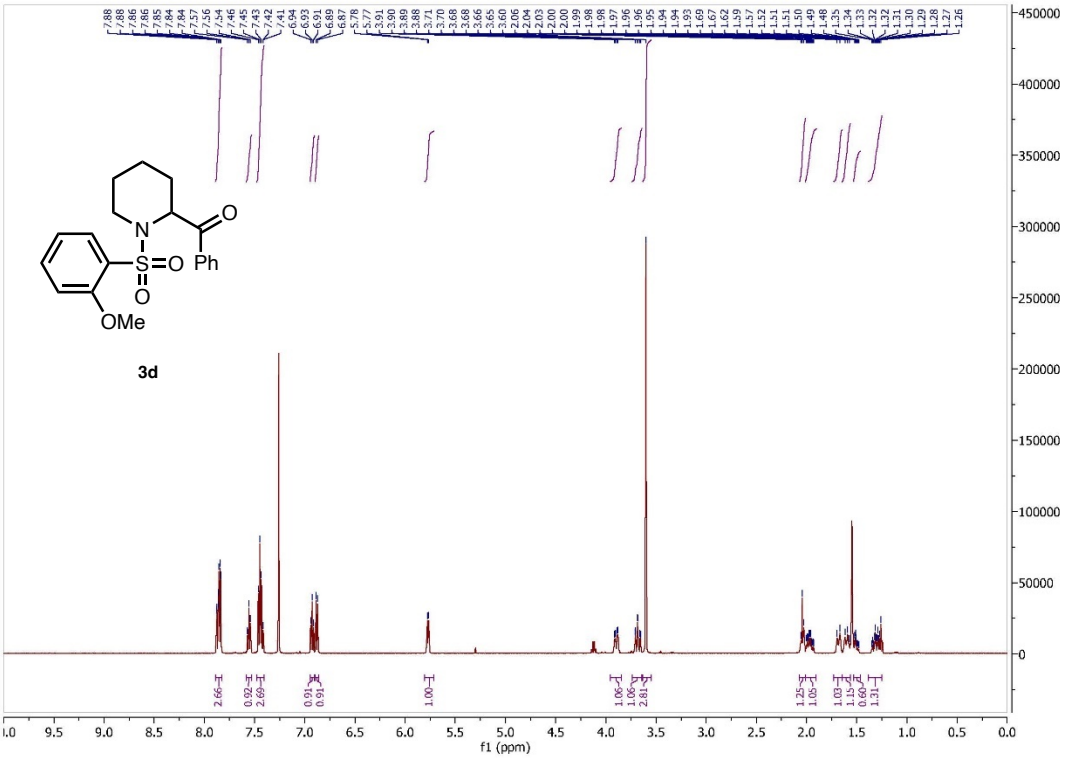
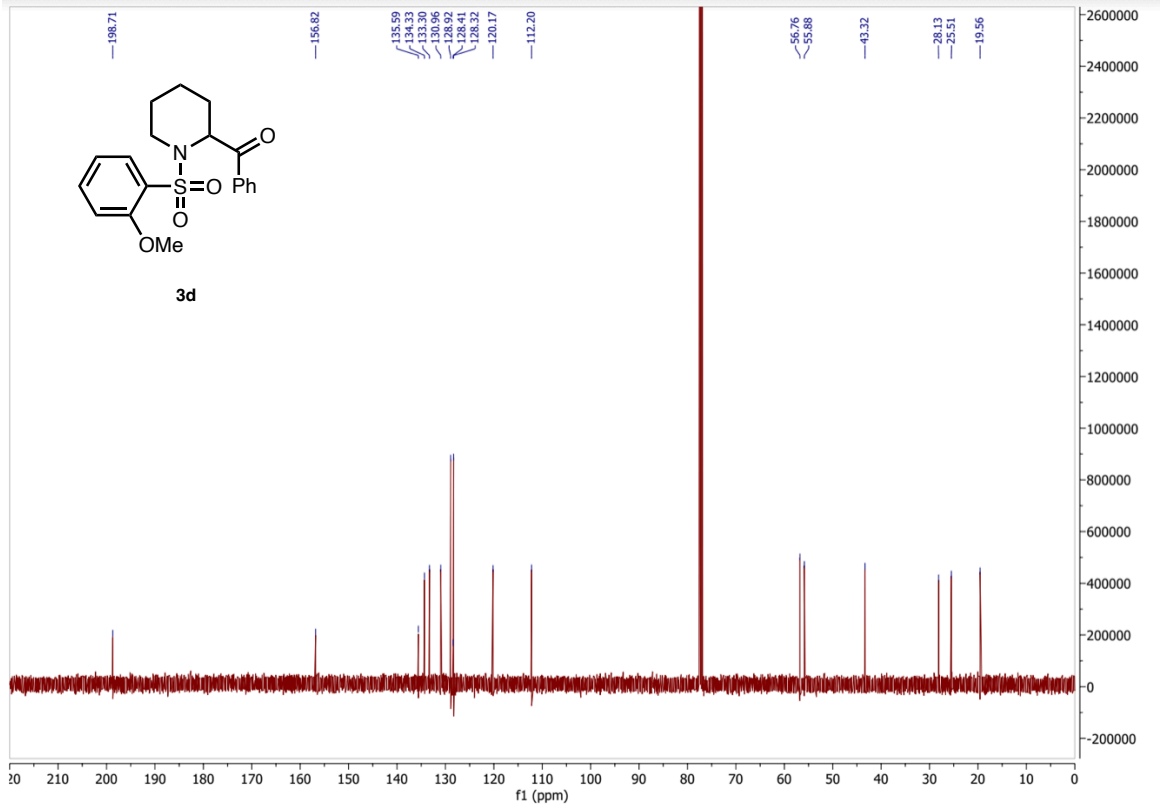
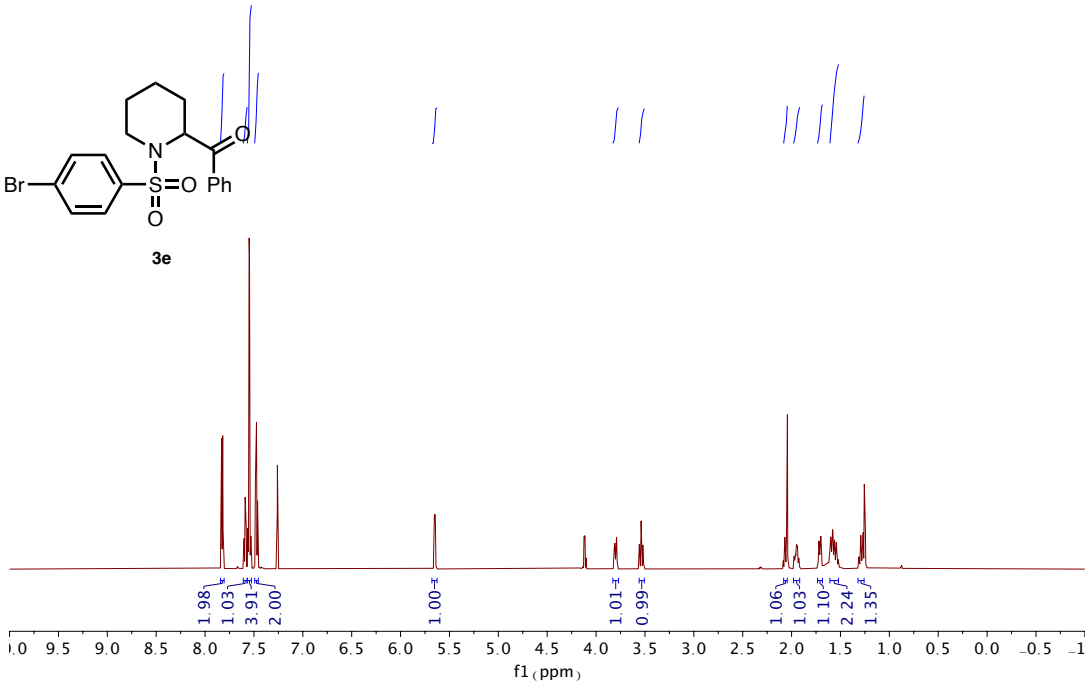
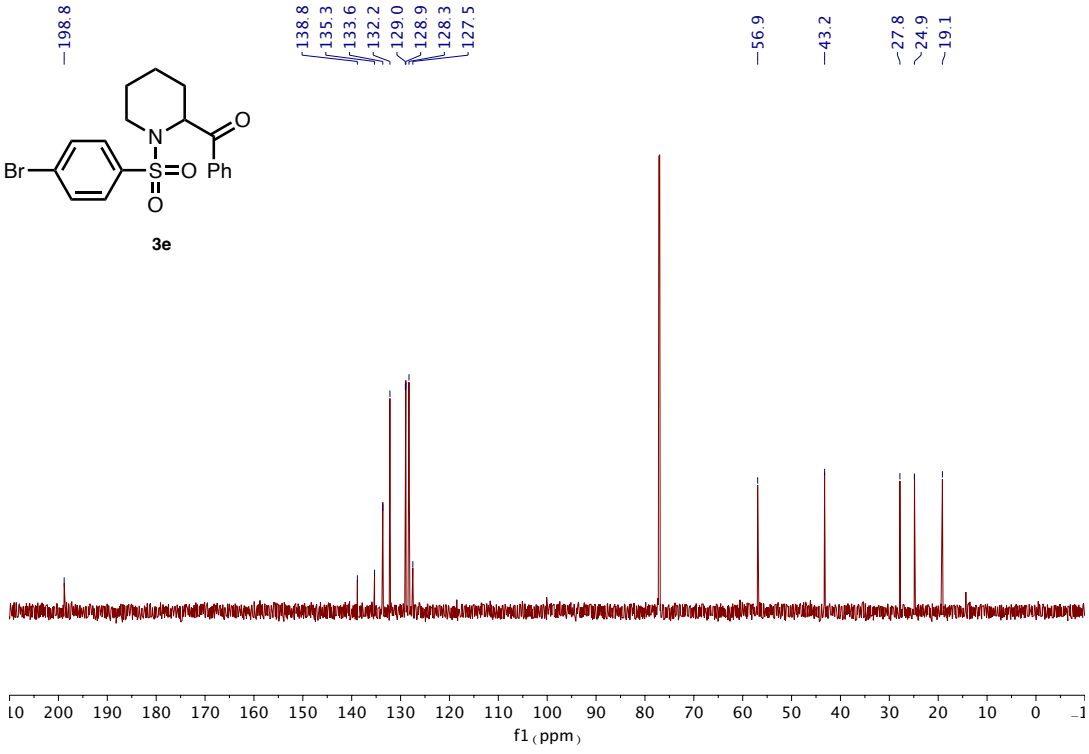
162.79
135.56
133.42
131.53
129.52
128.90
128.33
114.06
56.72
55.63
43.13
27.56
24.74
19.22
MeO
S
O
N
O
Ph
O
f1 (ppm)

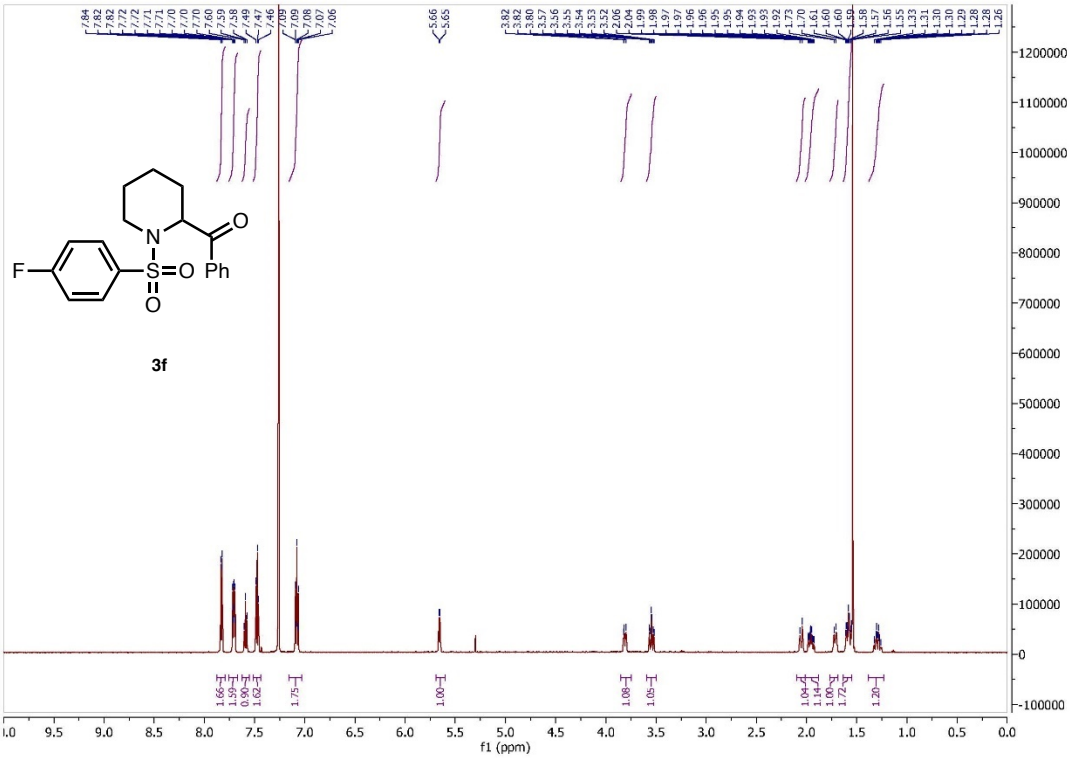
3c

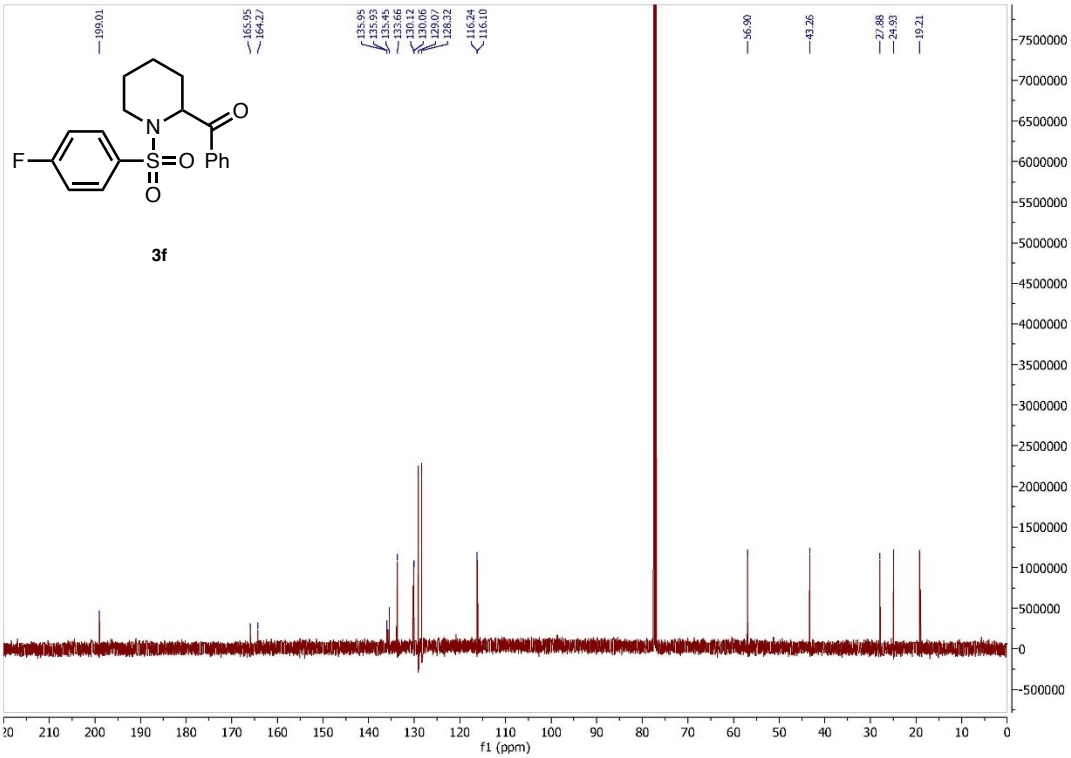

3d
f1 (ppm)

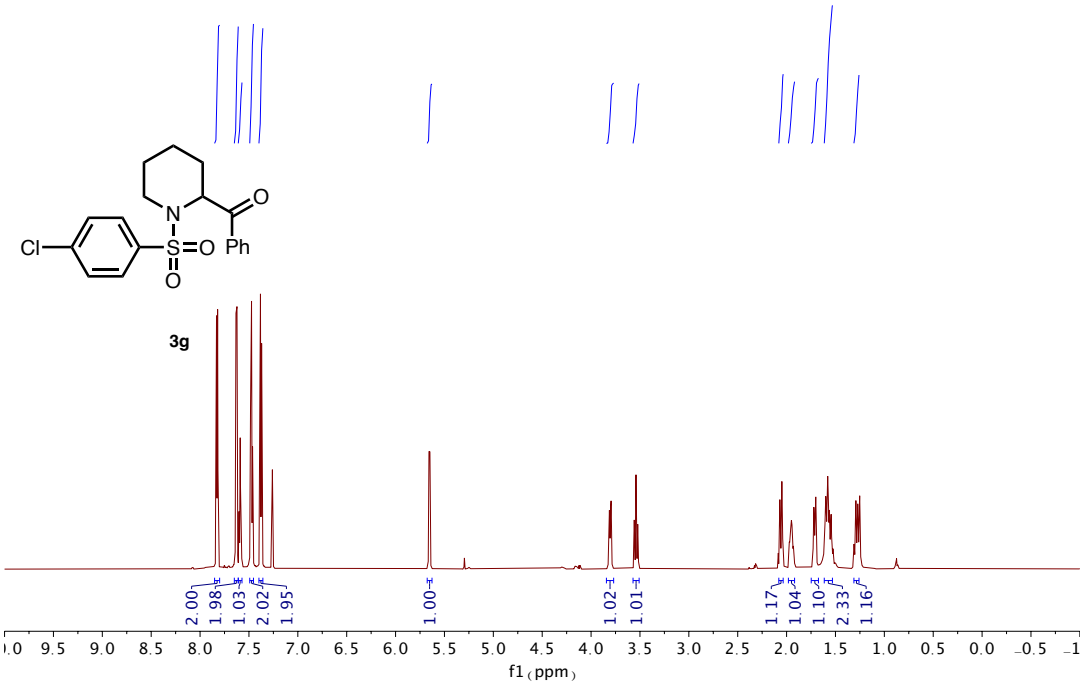

3d
f1 (ppm)


Br
N
S
O
O
O
Ph
3e
1.98
1.03
3.91
2.00
1.00
1.01
0.99
1.06
1.03
1.10
2.24
1.35
f1 (ppm)


198.8
138.8
135.3
133.6
132.2
129.0
128.9
128.3
127.5
56.9
43.2
27.8
24.9
19.1
Br
N
S
O
O
O
Ph
3e
f1 (ppm)


F
N
S
O
O
O
Ph
3f
f1 (ppm)


F
N
S
O
O
O
Ph
3f
f1 (ppm)


Cl
N
S
O
O
O
Ph
3g
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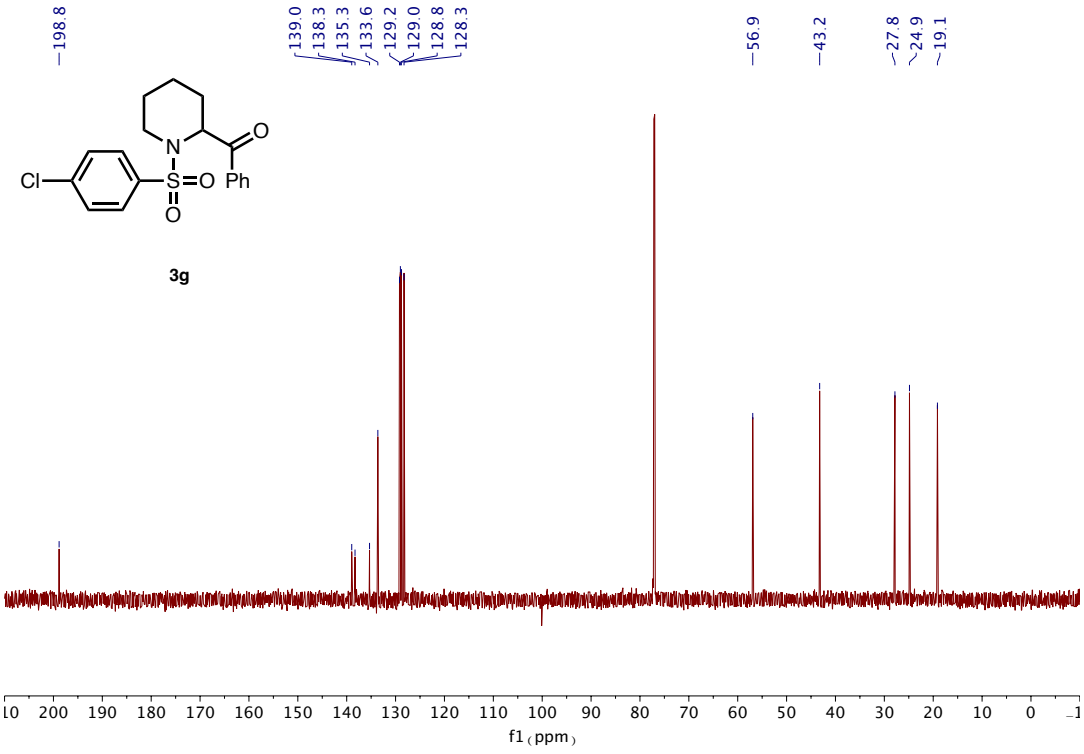
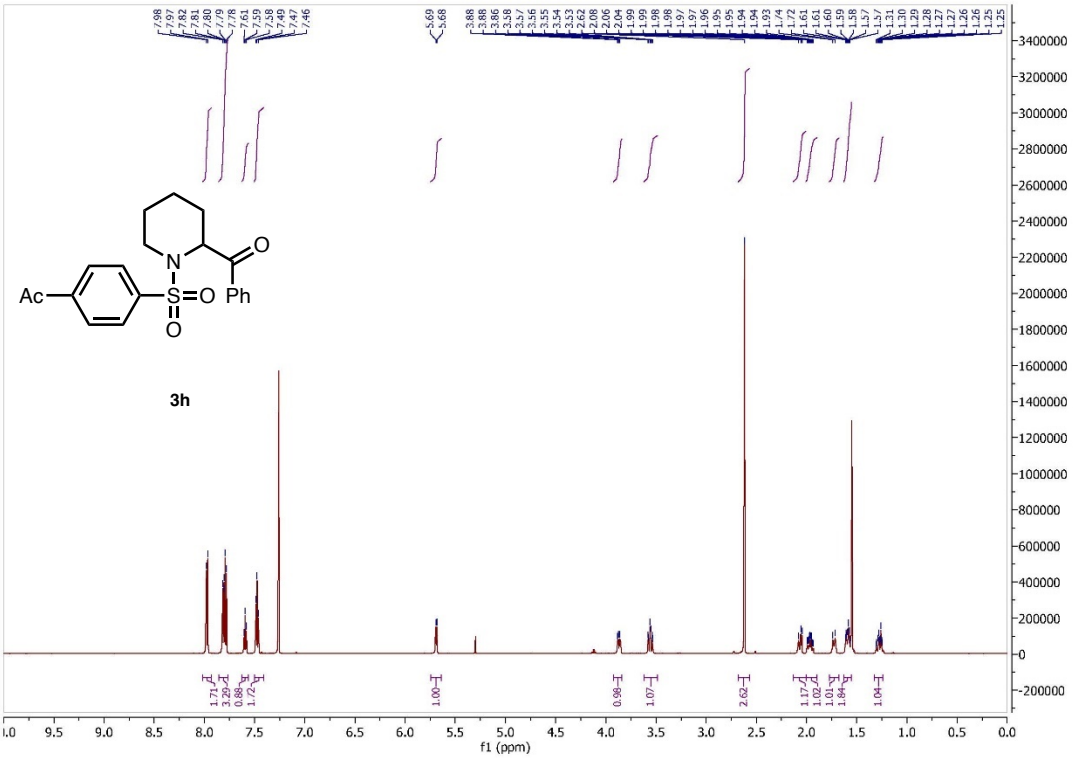
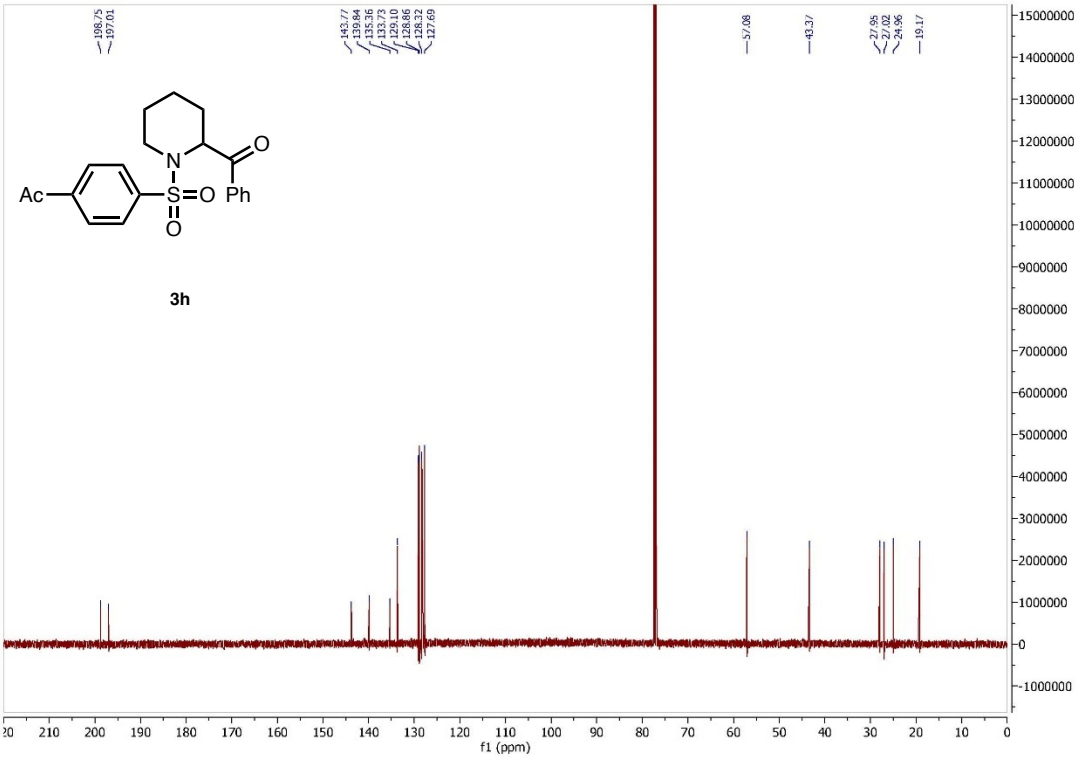
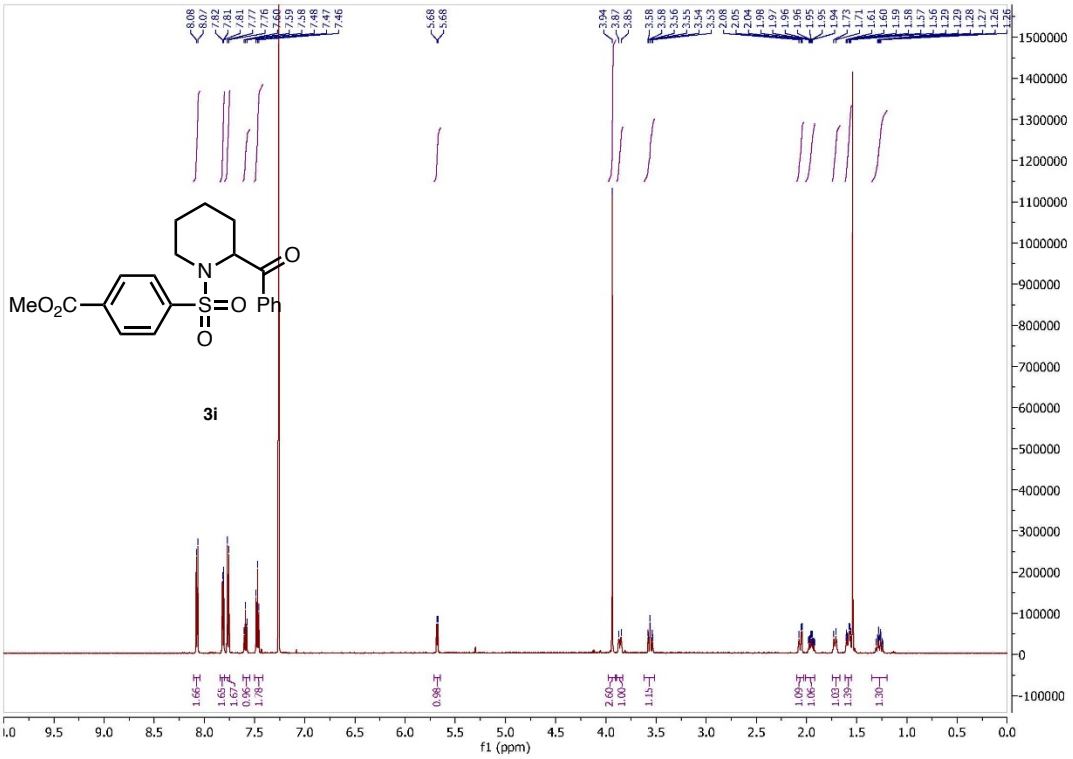
1.98
1.03
2.02
1.95
1.00
1.02
1.01
1.17
1.04
1.10
2.33
1.16
f1 (ppm)


198.8
139.0
138.3
135.3
133.6
129.2
129.0
128.8
128.3
56.9
43.2
27.8
24.9
19.1
Cl
N
S
O
O
O
Ph
3g
f1 (ppm)


Ac
N
S
O
O
O
Ph
3h
f1 (ppm)


Ac
N
S
O
O
O
Ph
3h
f1 (ppm)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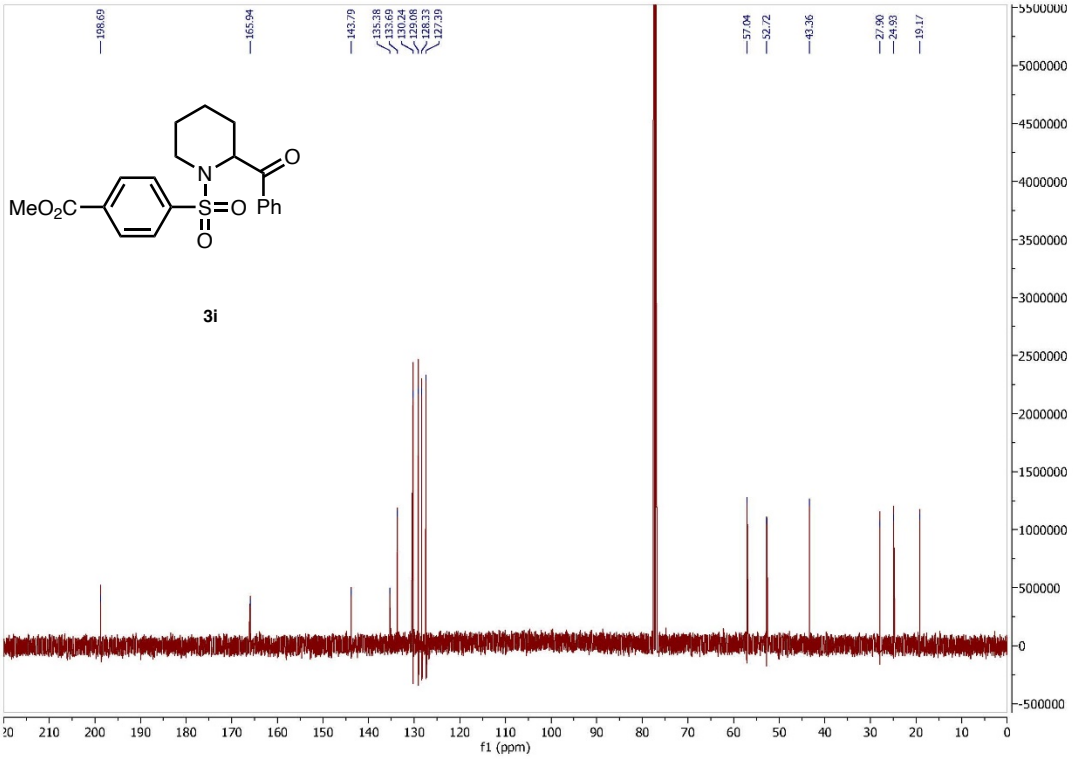
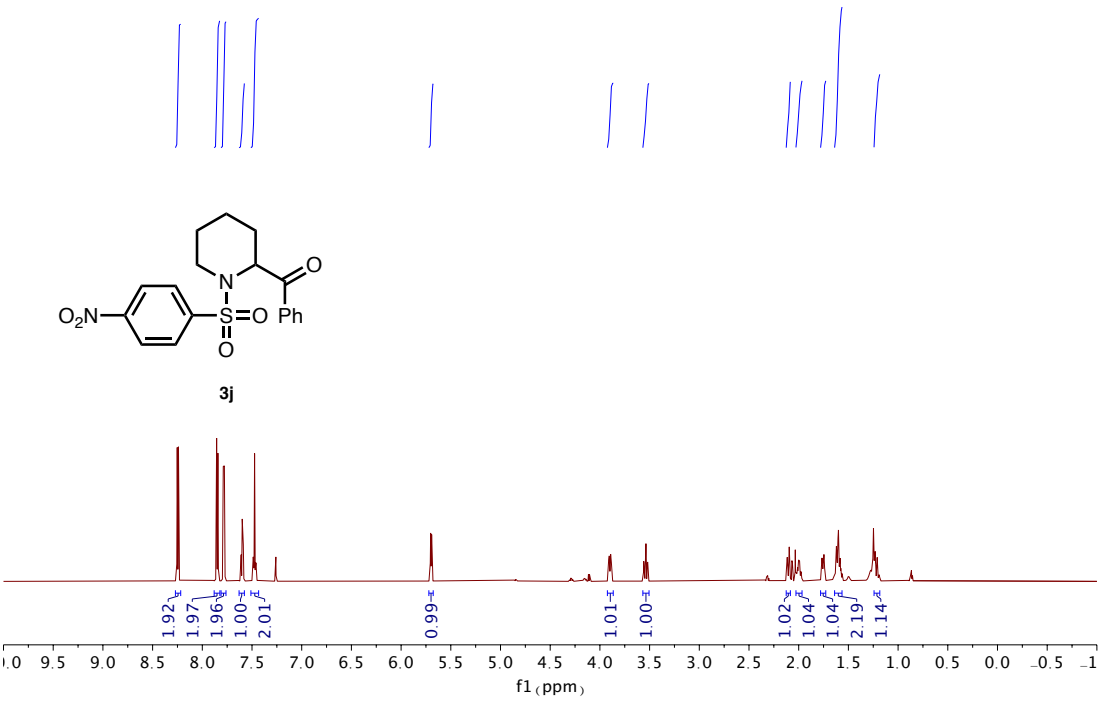
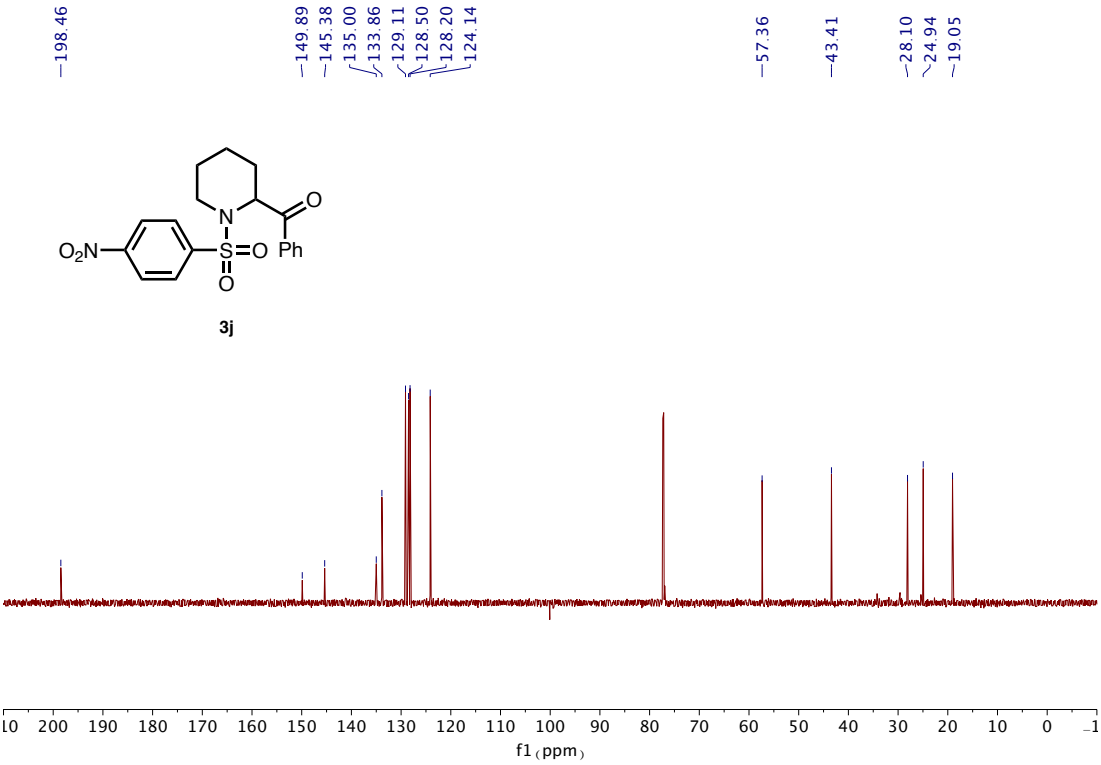
N
S
O
O
O
Ph
3i
f1 (ppm)


MeO2C
N
S
O
O
O
Ph
3i
f1 (ppm)


O2N
N
S
O
O
O
Ph
1.92
1.97
1.96
1.00
2.01
0.99
1.01
1.00
1.02
1.04
1.04
2.19
1.14
f1 (ppm)

3j


198.46
149.89
145.38
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129.11
128.50
128.20
124.14
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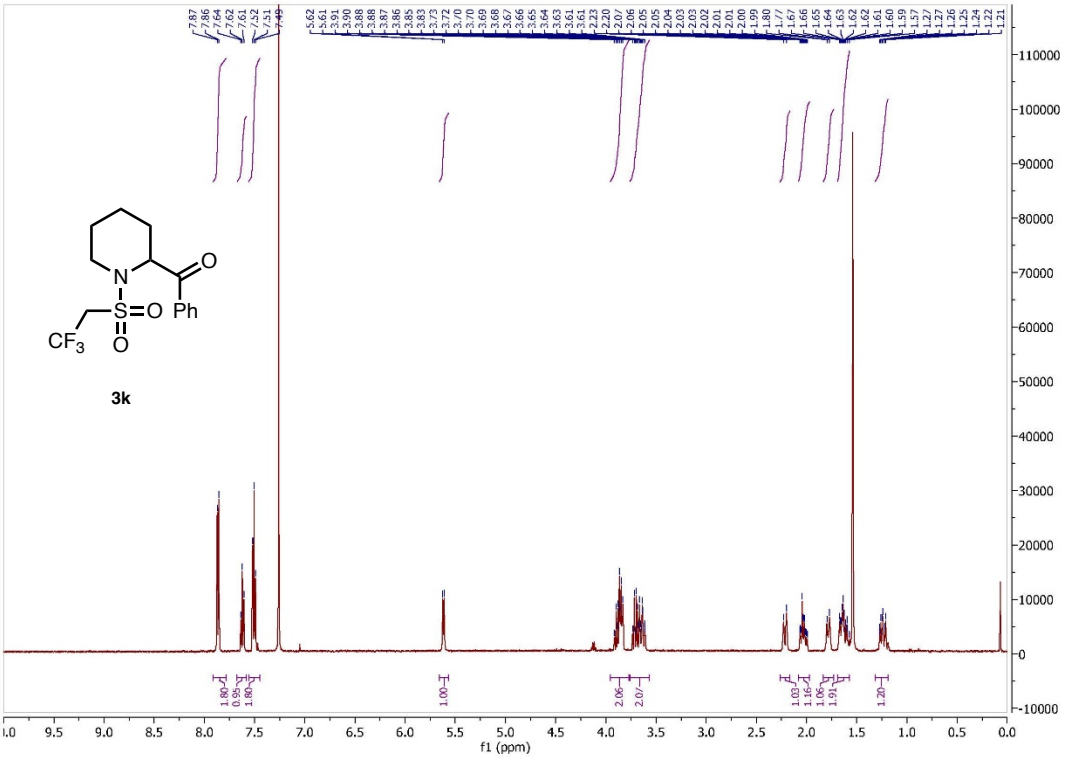
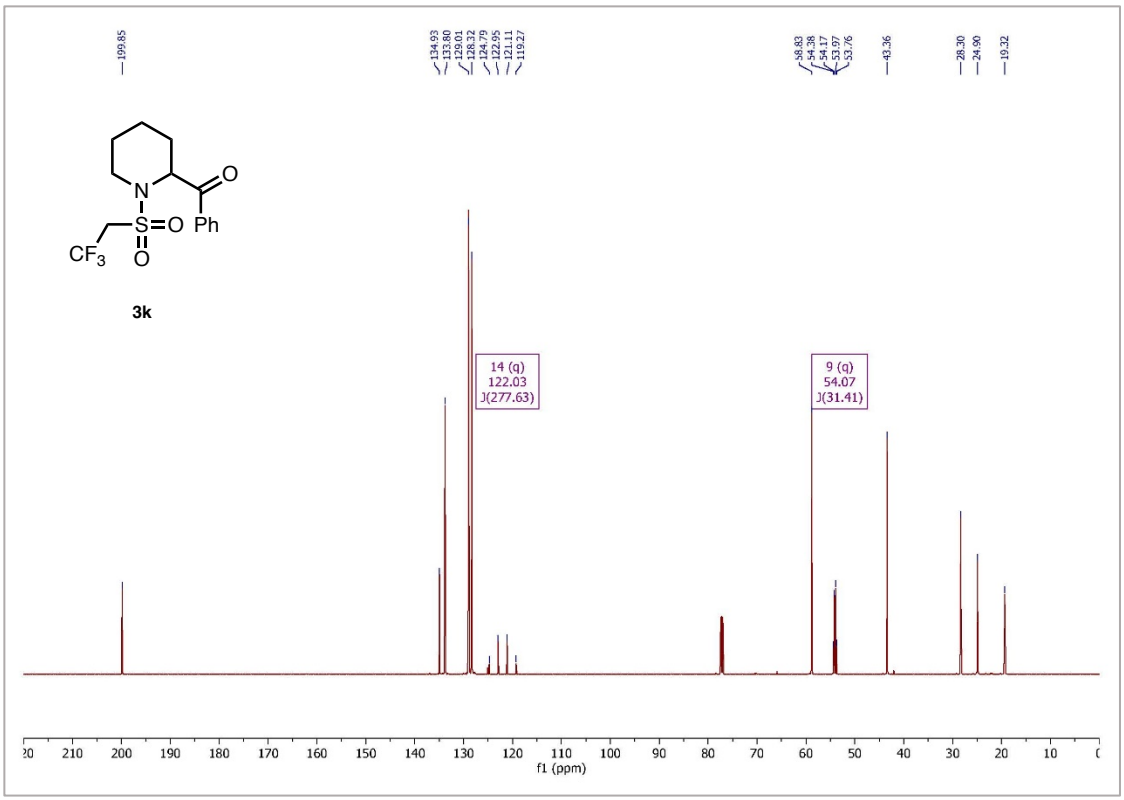
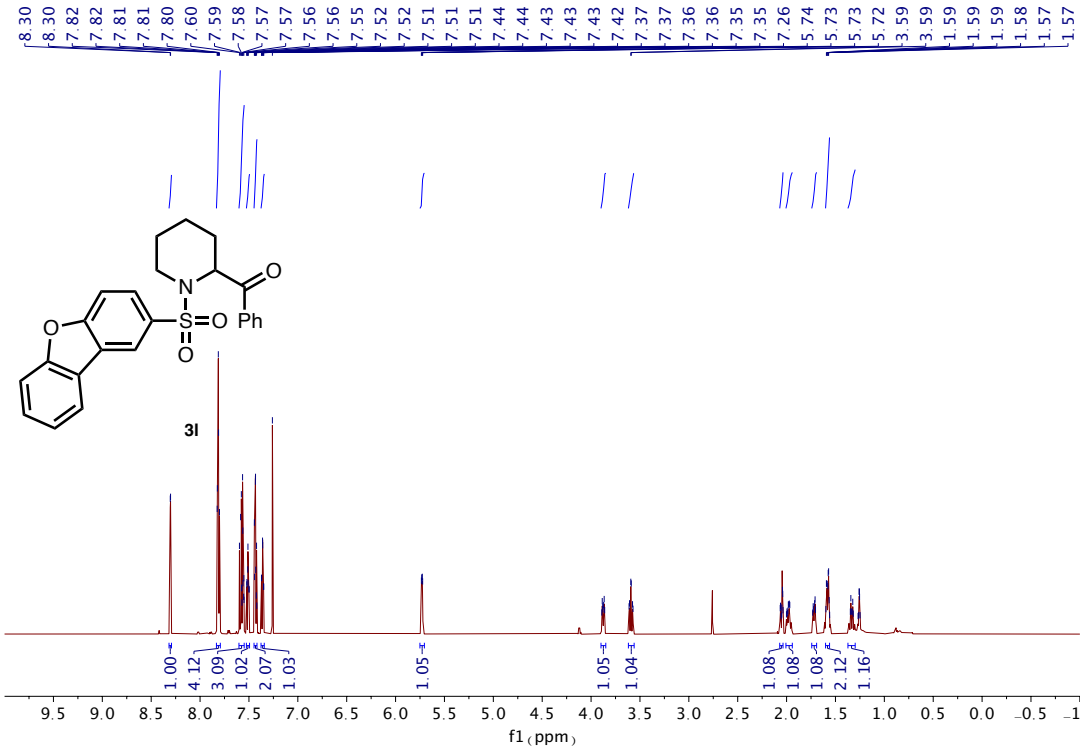
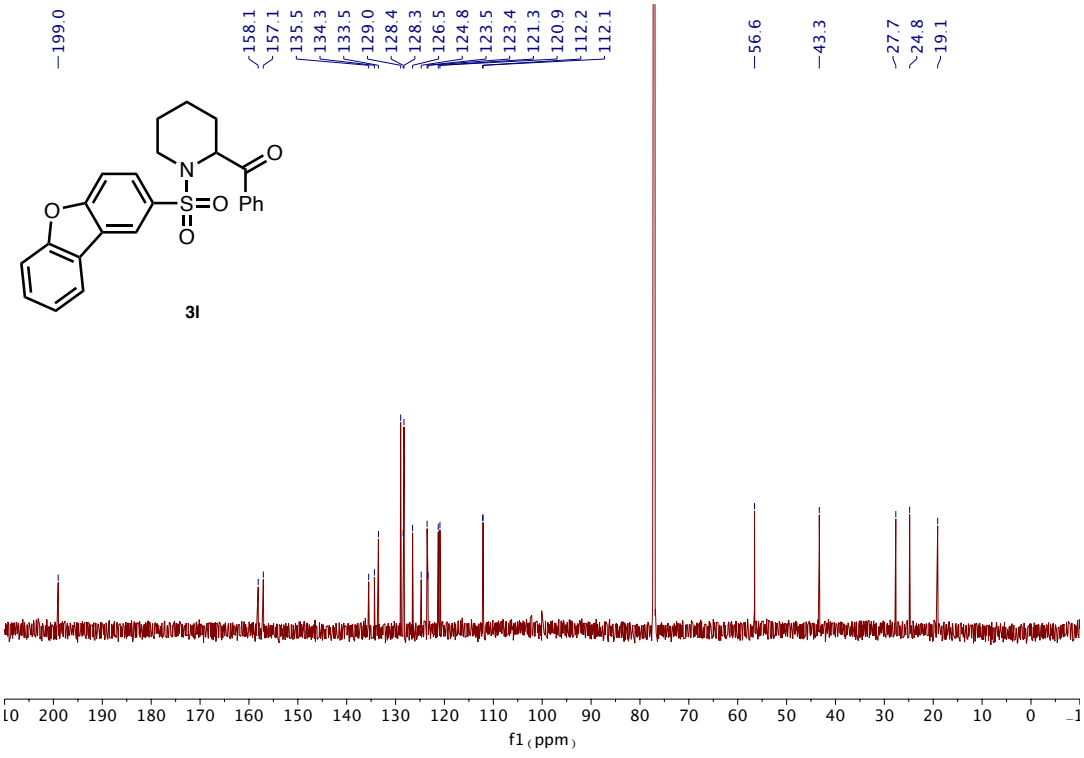
28.10
24.94
19.05
O2N
N
S
O
O
O
Ph
f1 (ppm)

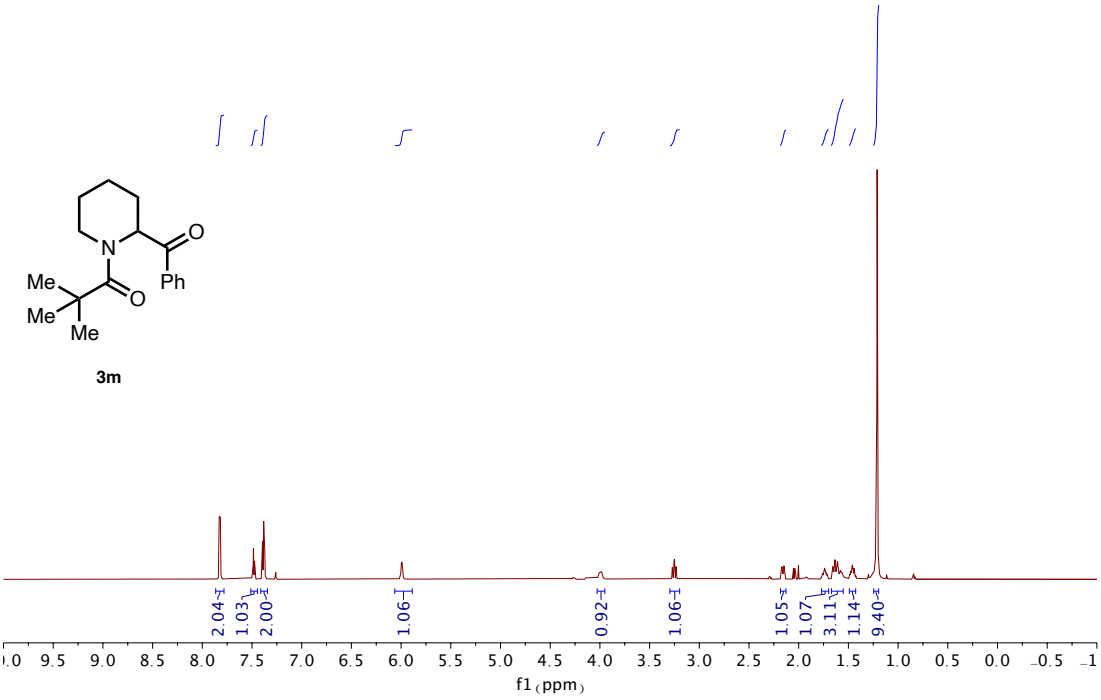
3j

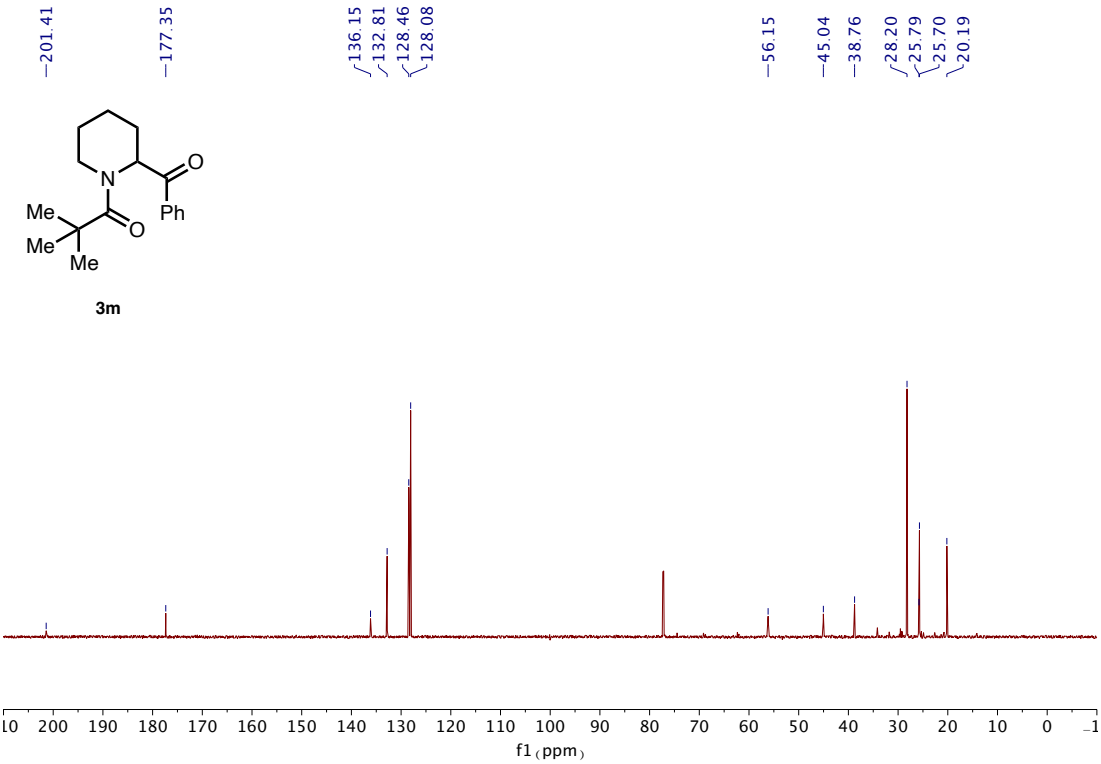

3k
f1 (ppm)


3k
14 (q)
122.03
J(277.63)
9 (q)
54.07
J(31.41)
f1 (ppm)


8.30 8.30 7.82 7.82 7.81 7.81 7.80 7.60 7.59 7.58 7.57 7.57 7.56 7.56 7.55 7.52 7.52 7.51 7.51 7.51 7.44 7.44 7.43 7.43 7.43 7.42 7.37 7.37 7.36 7.36 7.35 7.35 7.26 5.74 5.73 5.73 5.72 3.59 3.59 1.59 1.59 1.59 1.58 1.57 1.57
N
S=O Ph
O
O
O
3l
1.00 4.12 3.09 1.02 2.07 1.03 1.05 1.05 1.04 1.08 1.08 1.08 2.12 1.16
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


199.0
158.1 157.1 135.5 134.3 133.5 129.0 128.4 128.3 126.5 124.8 123.5 123.4 121.3 120.9 112.2 112.1
56.6
43.3
27.7 24.8 19.1
N
S=O Ph
O
O
O
3l
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


Me
Me
Me
N
O
O
Ph
3m
2.04
1.03
2.00
1.06
0.92
1.06
1.05
1.07
3.11
1.14
9.40
f1 (ppm)


201.41
177.35
136.15
132.81
128.46
128.08
56.15
45.04
38.76
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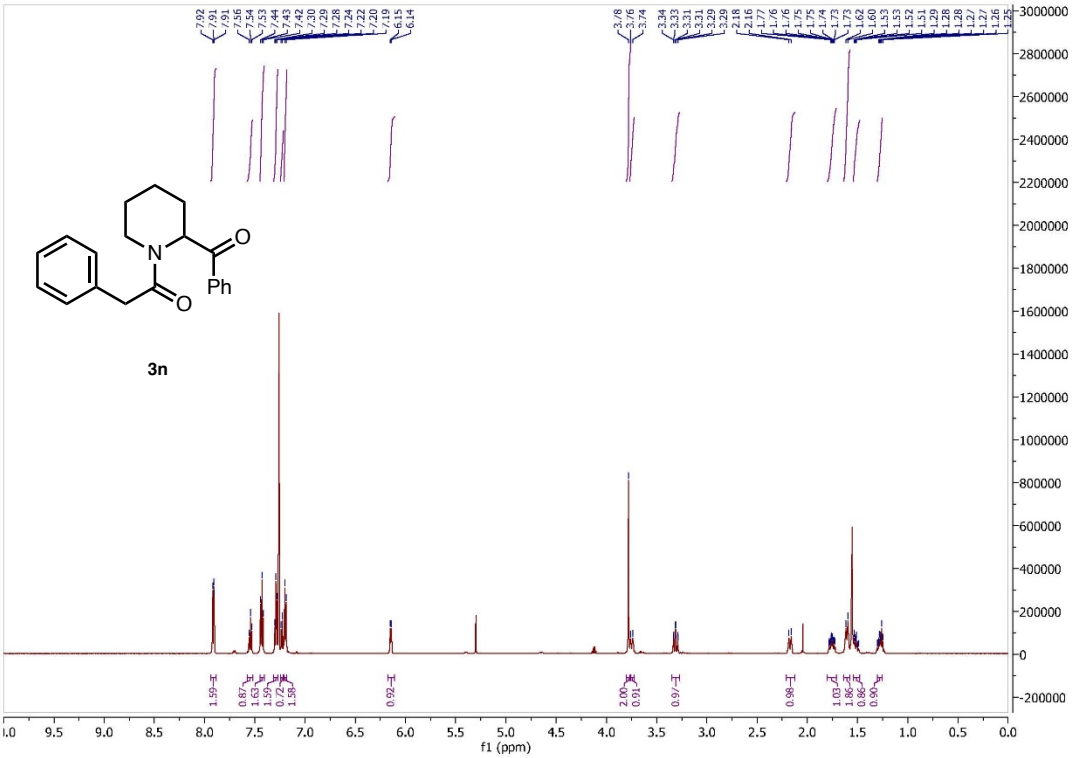
25.79
25.70
20.19
Me
Me
Me
N
O
O
Ph
3m
f1 (ppm)


7.92
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7.91
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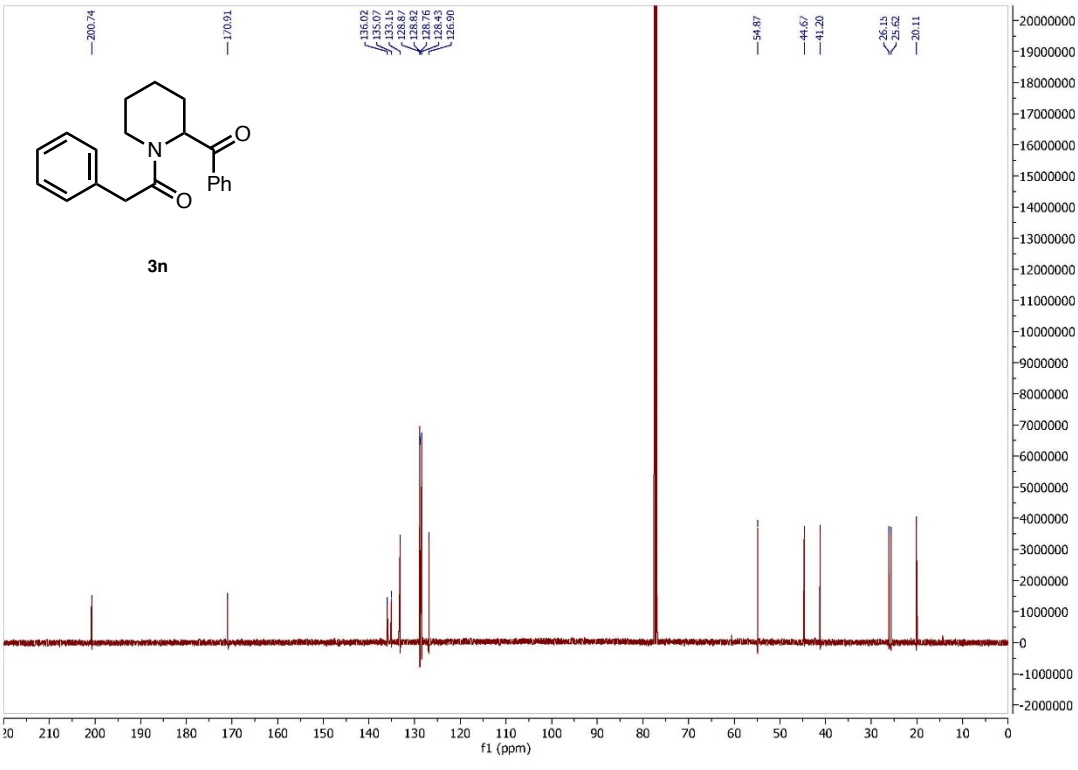
7.54
7.53
7.44
7.43
7.42
7.30
7.29
7.28
7.24
7.22
7.20
7.19
6.15
6.14
3.78
3.76
3.74
3.34
3.33
3.31
3.31
3.29
3.29
2.18
2.16
1.77
1.76
1.76
1.75
1.75
1.74
1.73
1.73
1.62
1.60
1.53
1.53
1.52
1.51
1.29
1.28
1.28
1.27
1.27
1.26
1.25
N
O
O
Ph
1.59
0.87
1.59
0.72
1.58
0.92
2.00
0.91
0.97
0.98
1.03
1.86
1.86
0.86
0.90
f1 (ppm)

3n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170.91
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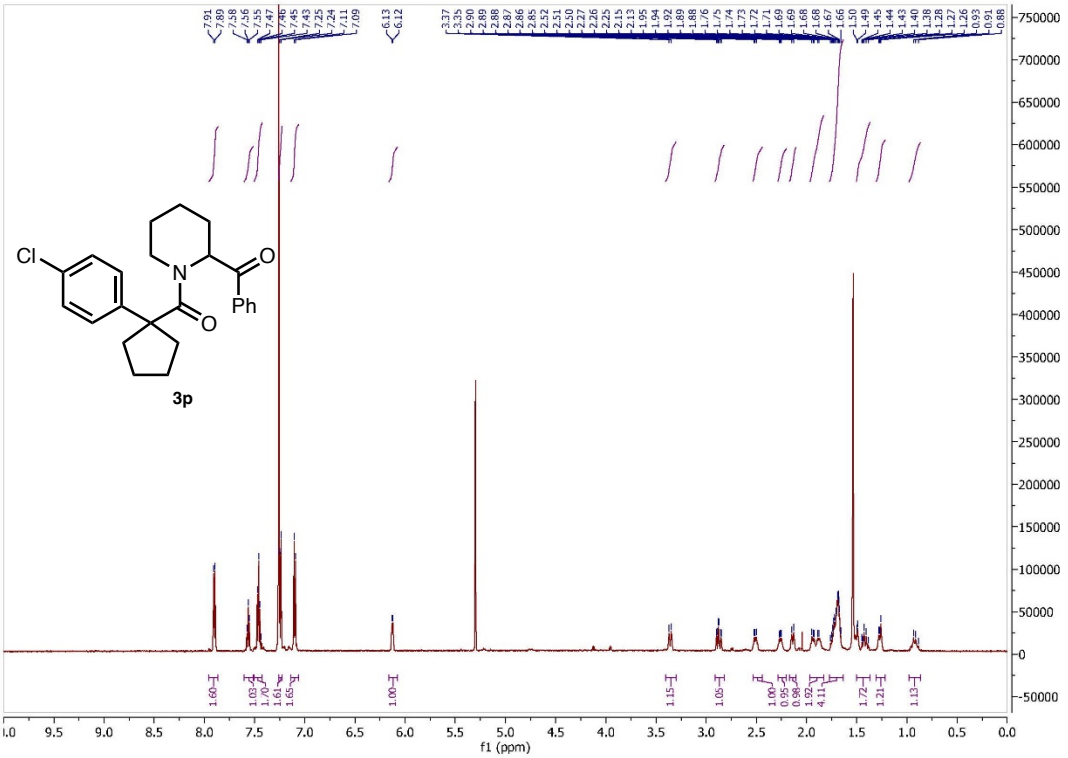
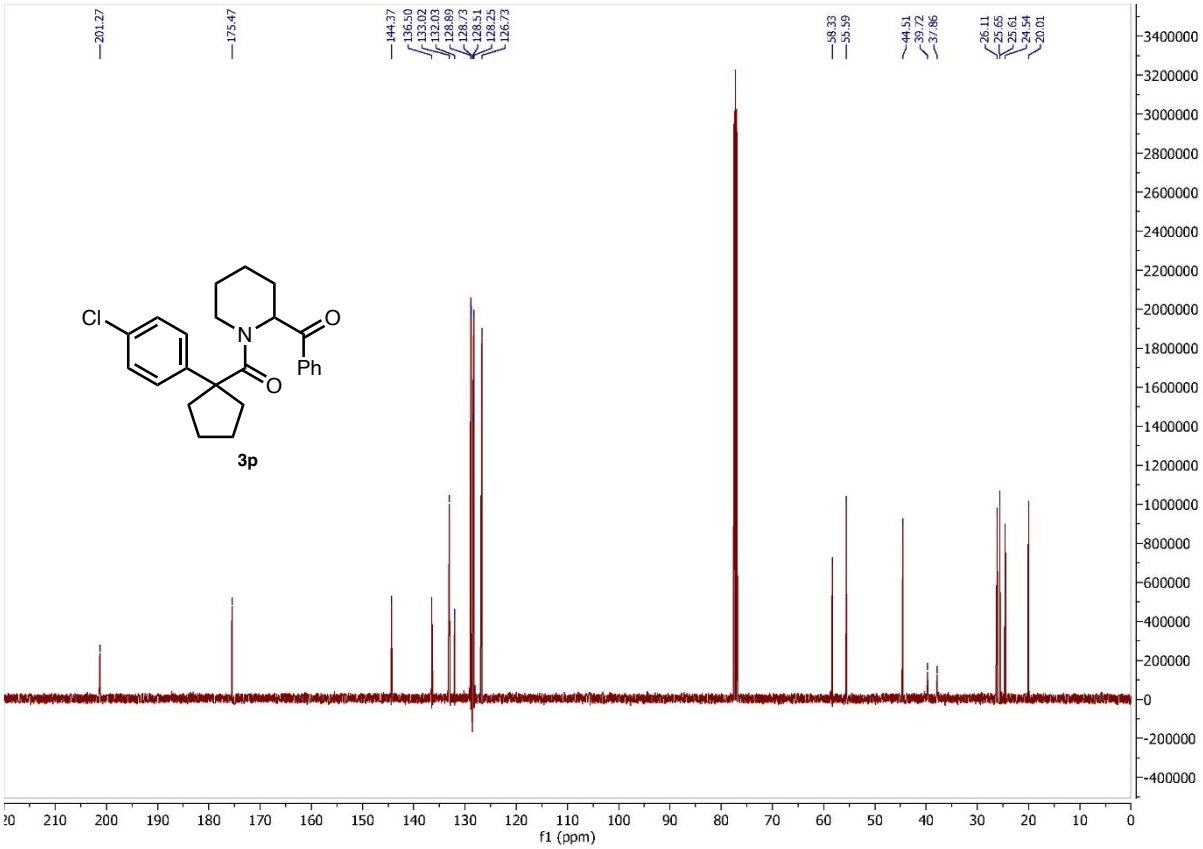
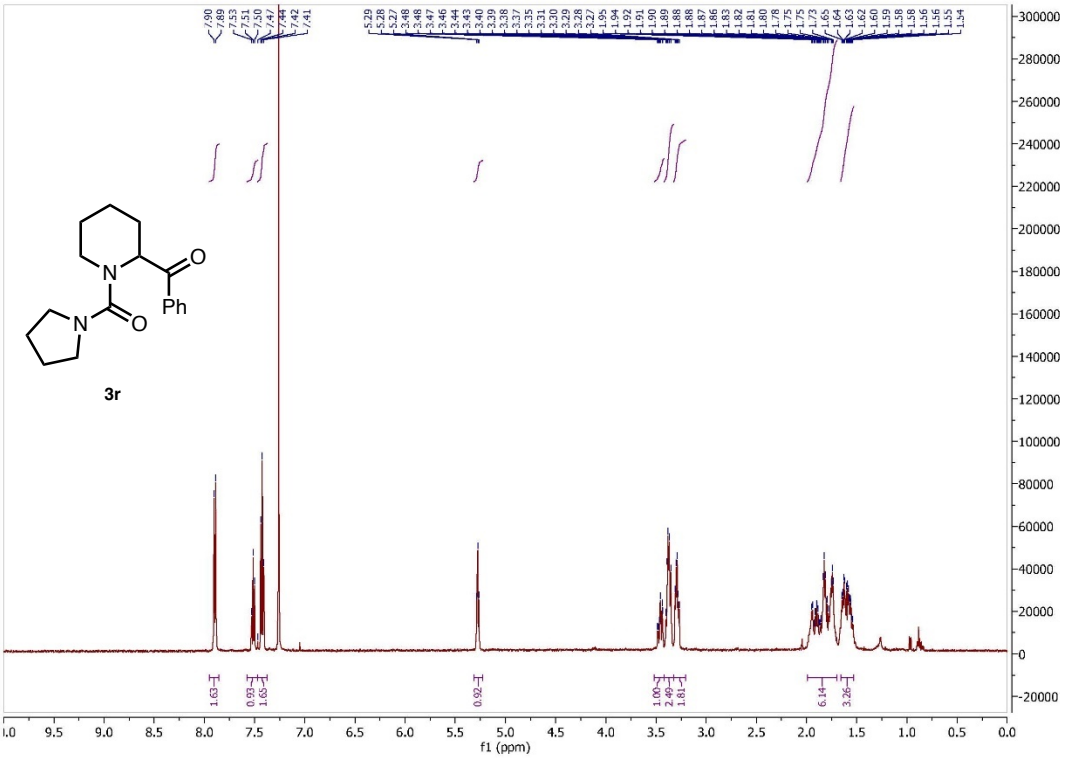
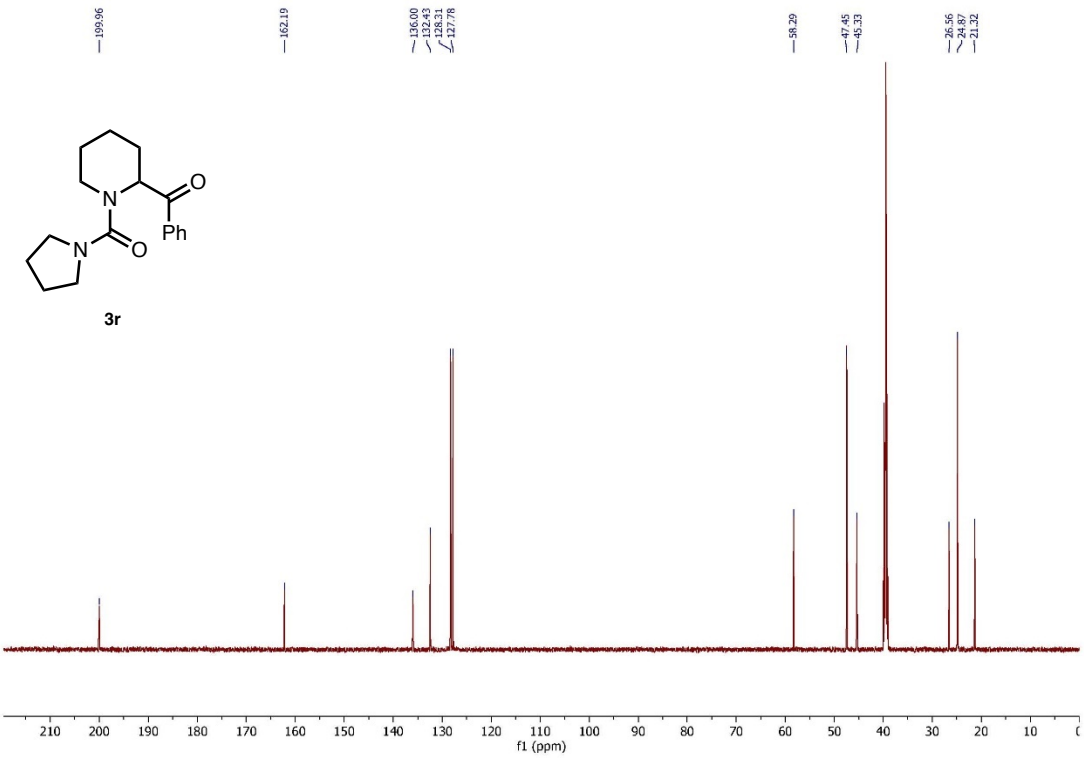
135.07
133.15
128.87
128.82
128.76
128.43
126.90
54.87
44.67
41.20
26.15
25.62
20.11
N
O
O
Ph
f1 (ppm)

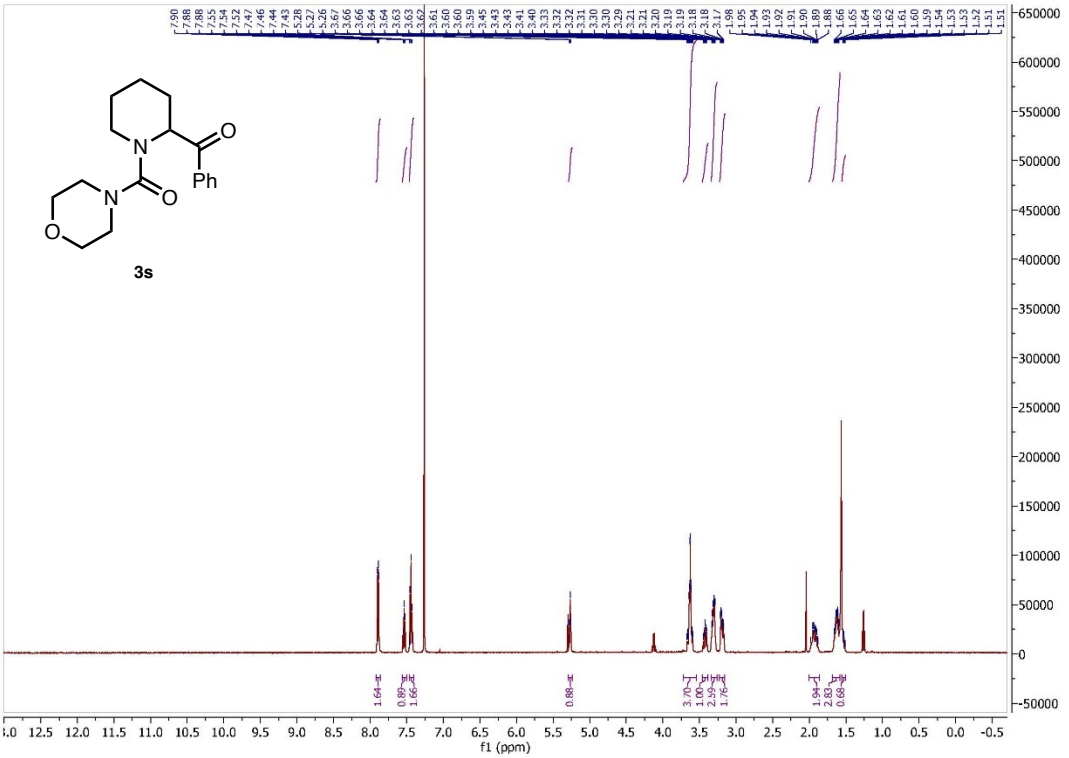
3n

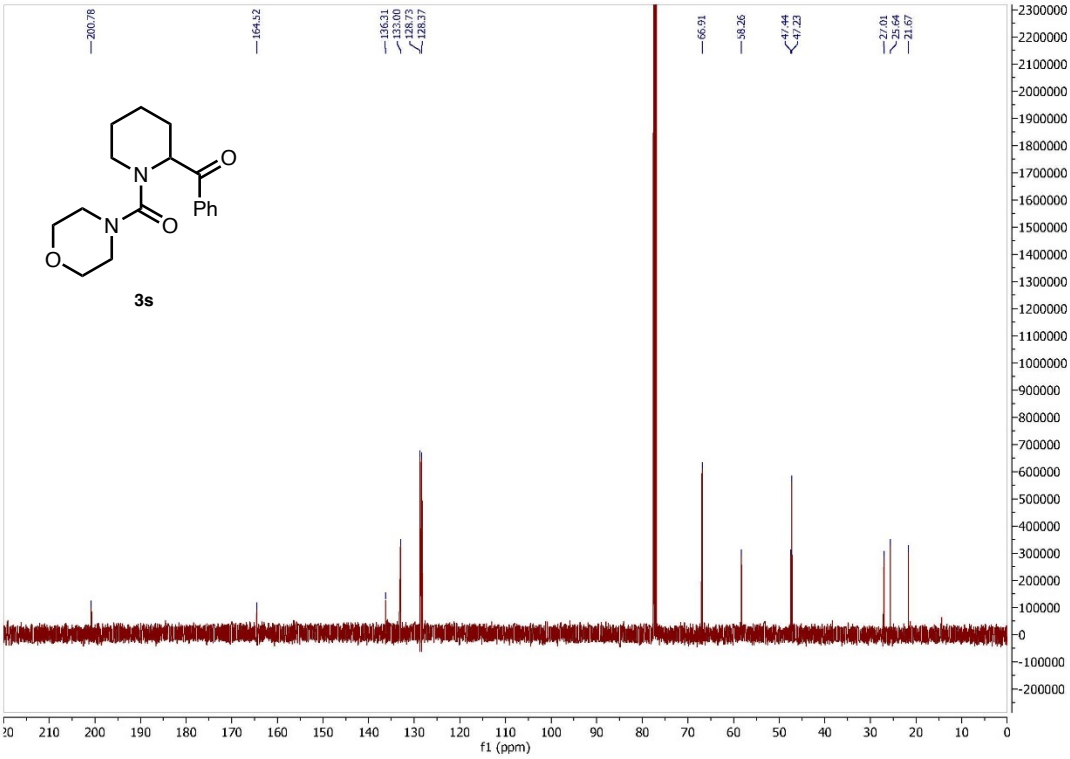

Cl
N
O
O
Ph
3p
f1 (ppm)

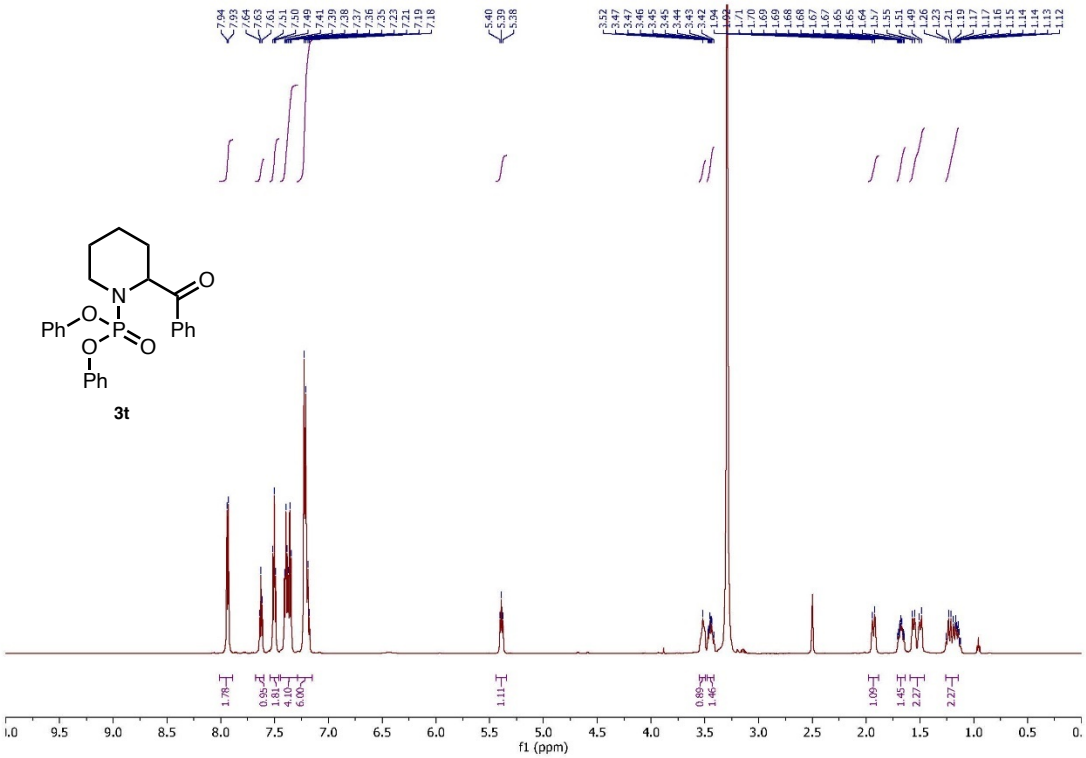

Cl
N
O
O
Ph
3p
f1 (ppm)

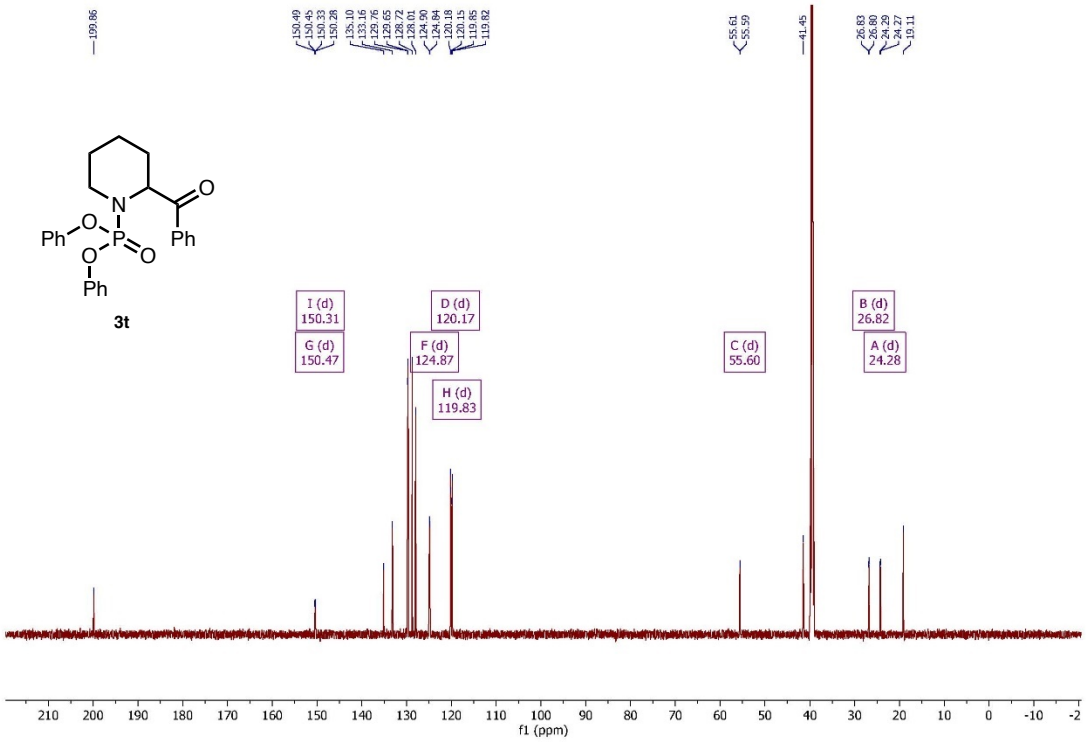

3r
f1 (ppm)

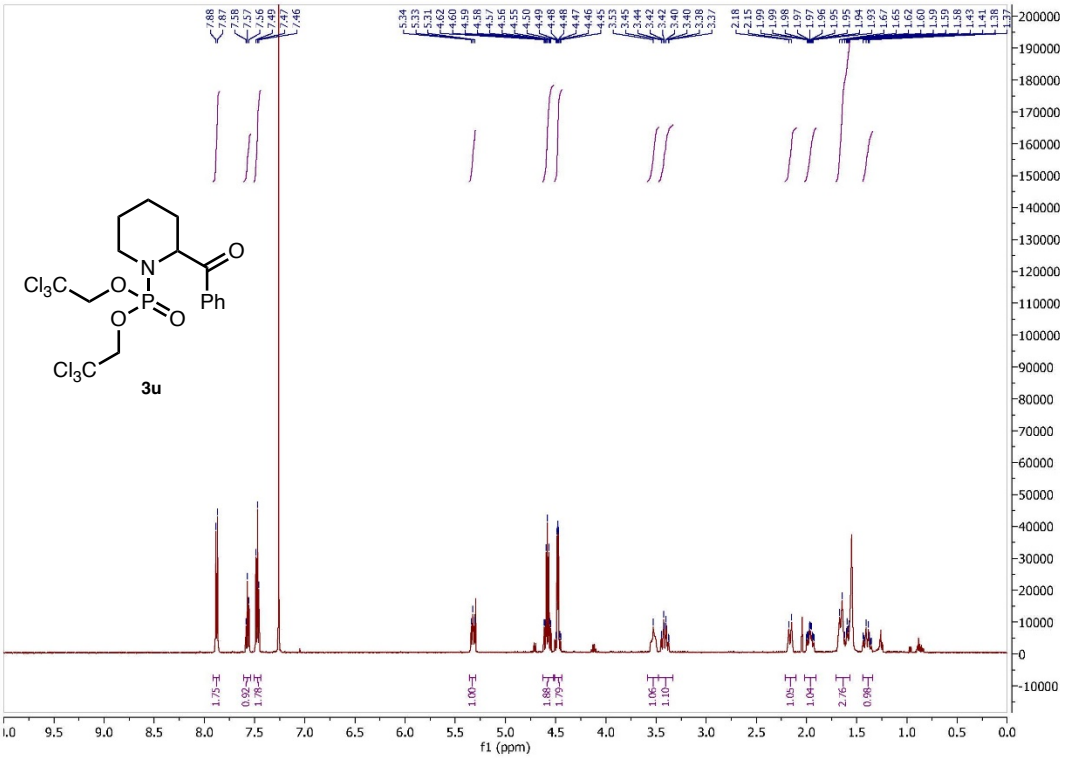

3r
f1 (ppm)

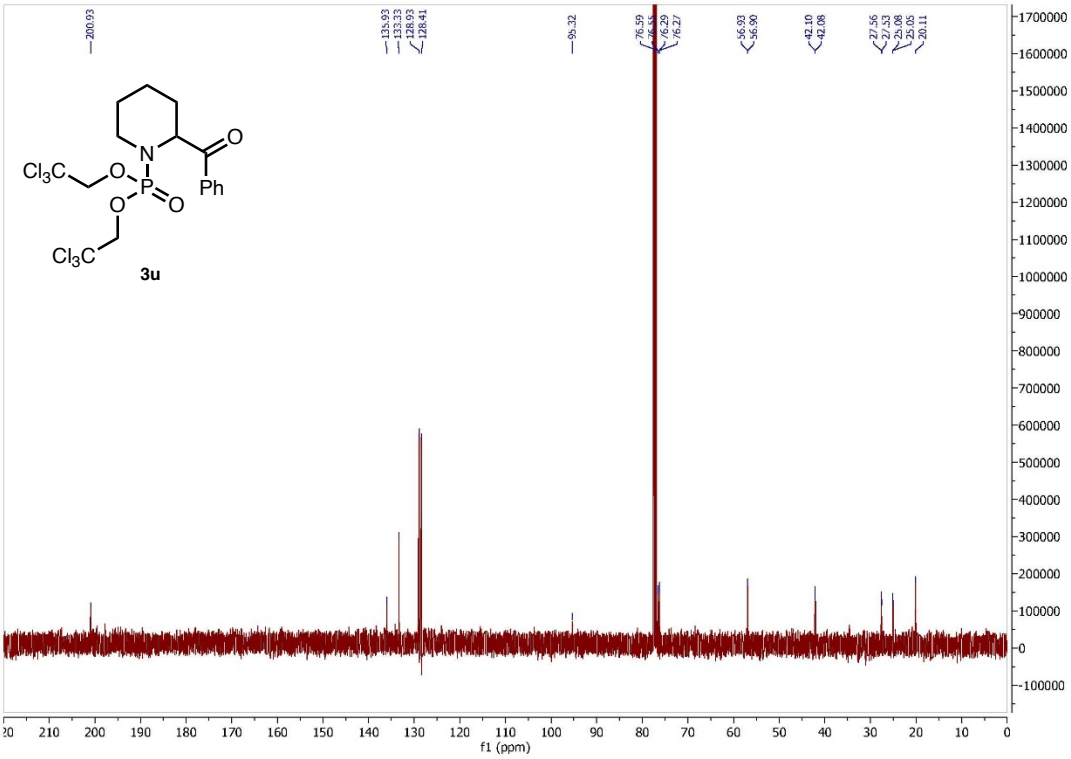

3s
f1 (ppm)

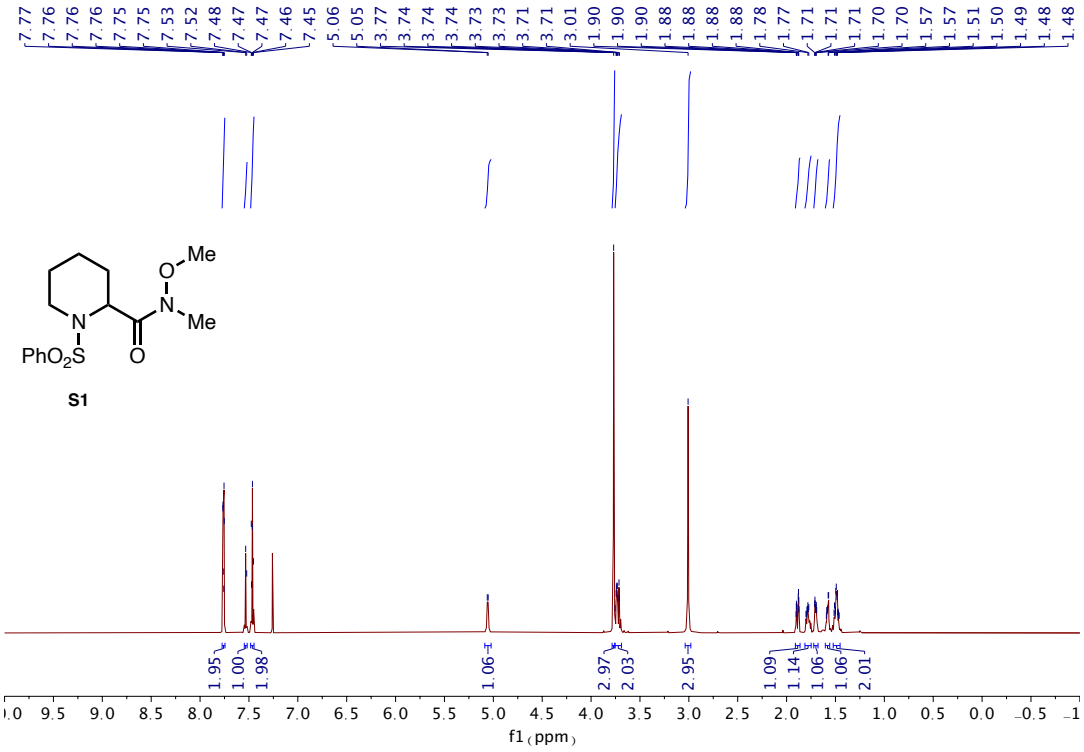

3s
f1 (ppm)

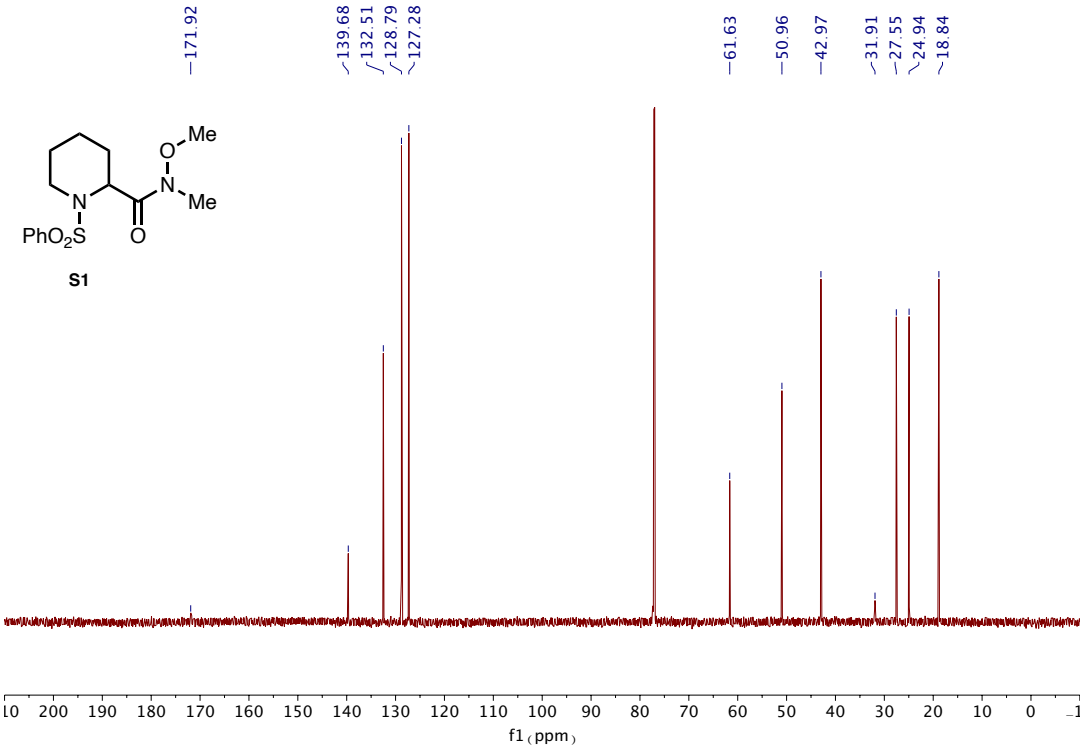

3t
f1 (ppm)

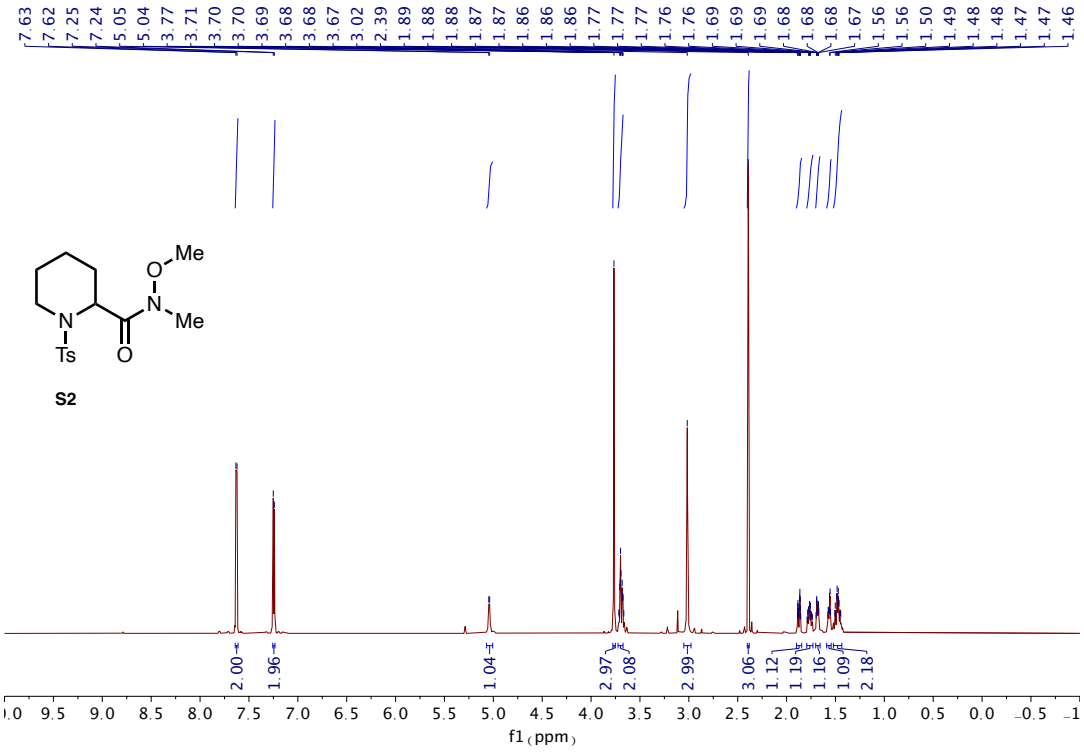

3t
I (d) 150.31
G (d) 150.47
D (d) 120.17
F (d) 124.87
H (d) 119.83
C (d) 55.60
B (d) 26.82
A (d) 24.28
f1 (ppm)

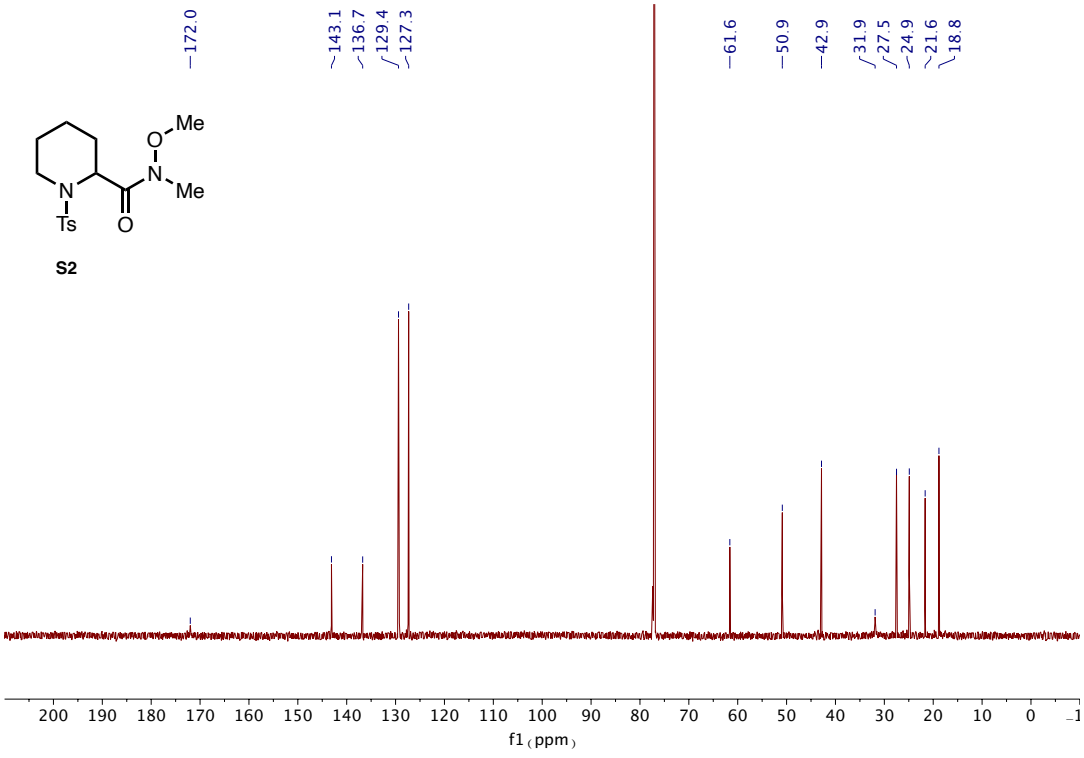

3u
f1 (ppm)

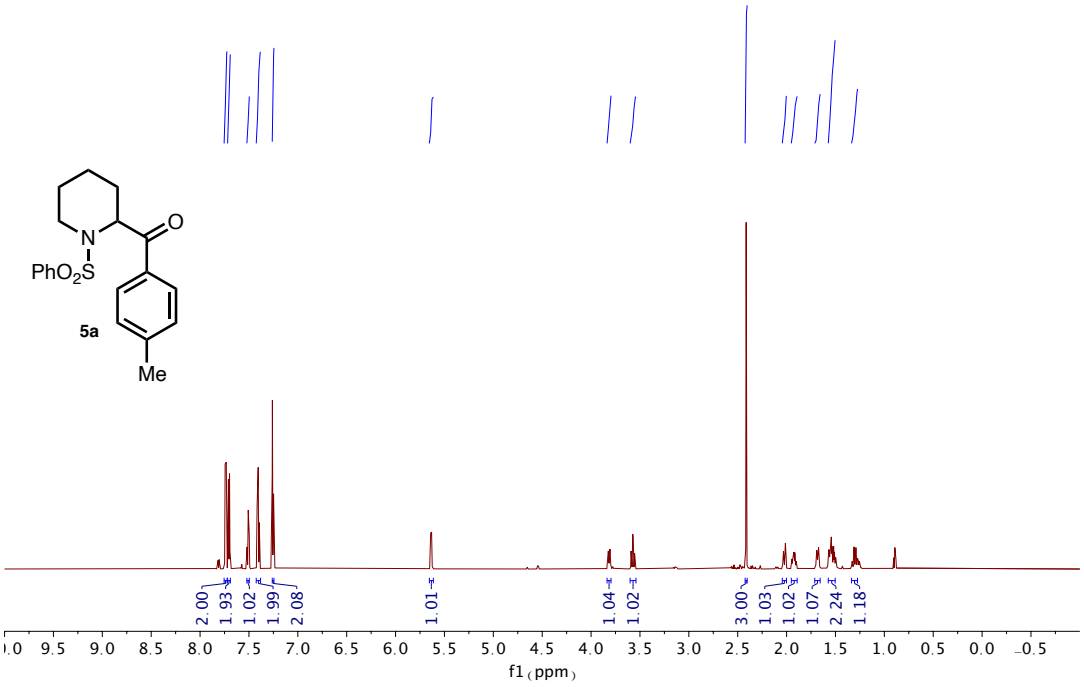

3u
f1 (ppm)

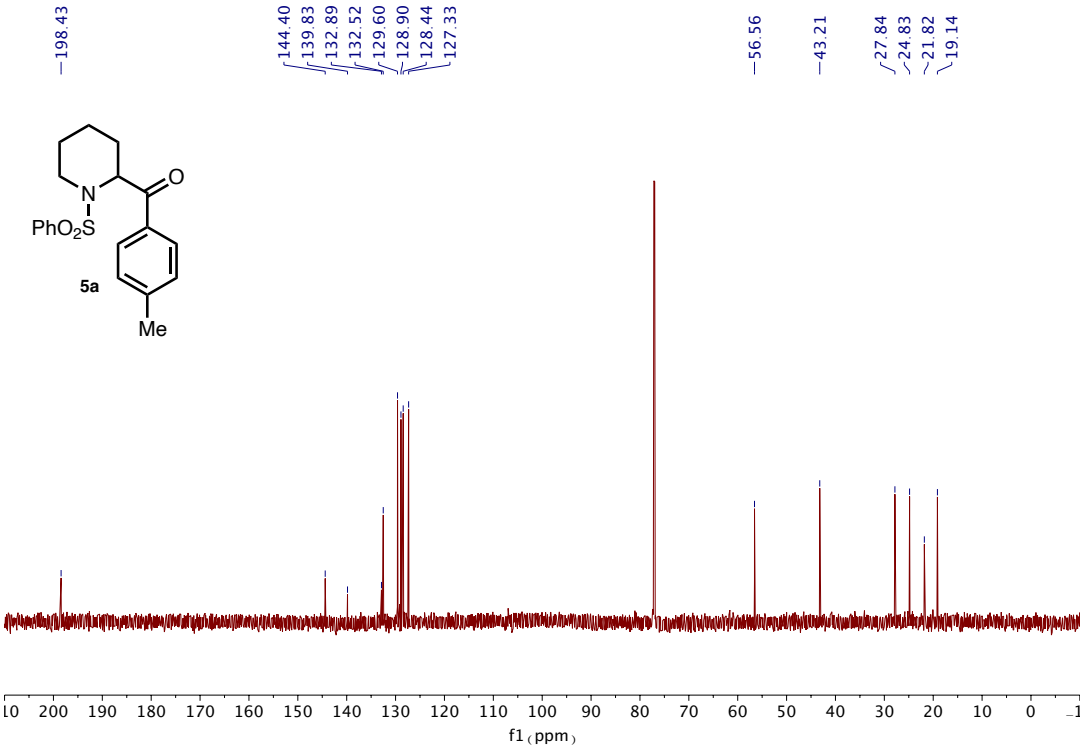

7.77 7.76 7.76 7.76 7.75 7.75 7.53 7.52 7.48 7.47 7.47 7.46 7.45
5.06 5.05 3.77 3.74 3.74 3.74 3.73 3.73 3.71 3.71 3.01 1.90 1.90 1.90 1.88 1.88 1.88 1.88 1.78 1.77 1.71 1.71 1.71 1.70 1.70 1.57 1.57 1.51 1.50 1.49 1.48 1.48
Me
O
N
Me
N
PhO2S
O
S1
1.95 1.00 1.98 1.06 2.97 2.03 2.95 1.09 1.14 1.06 1.06 2.01
f1 (ppm)

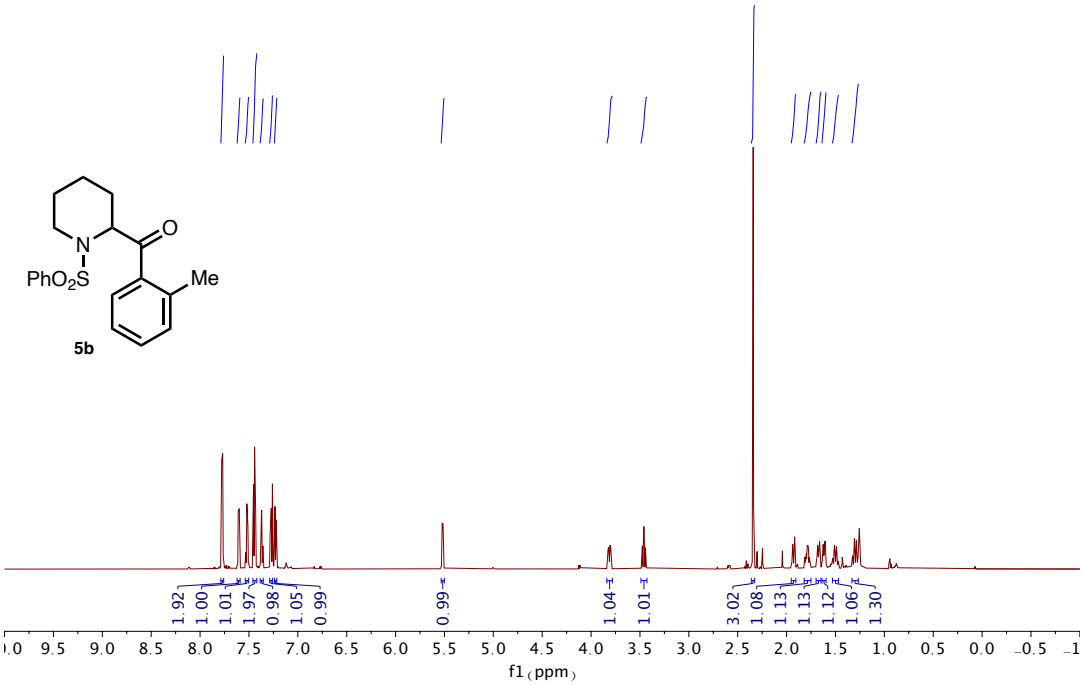

171.92
139.68 132.51 128.79 127.28
61.63 50.96 42.97 31.91 27.55 24.94 18.84
Me
O
N
Me
N
PhO2S
O
S1
f1 (ppm)

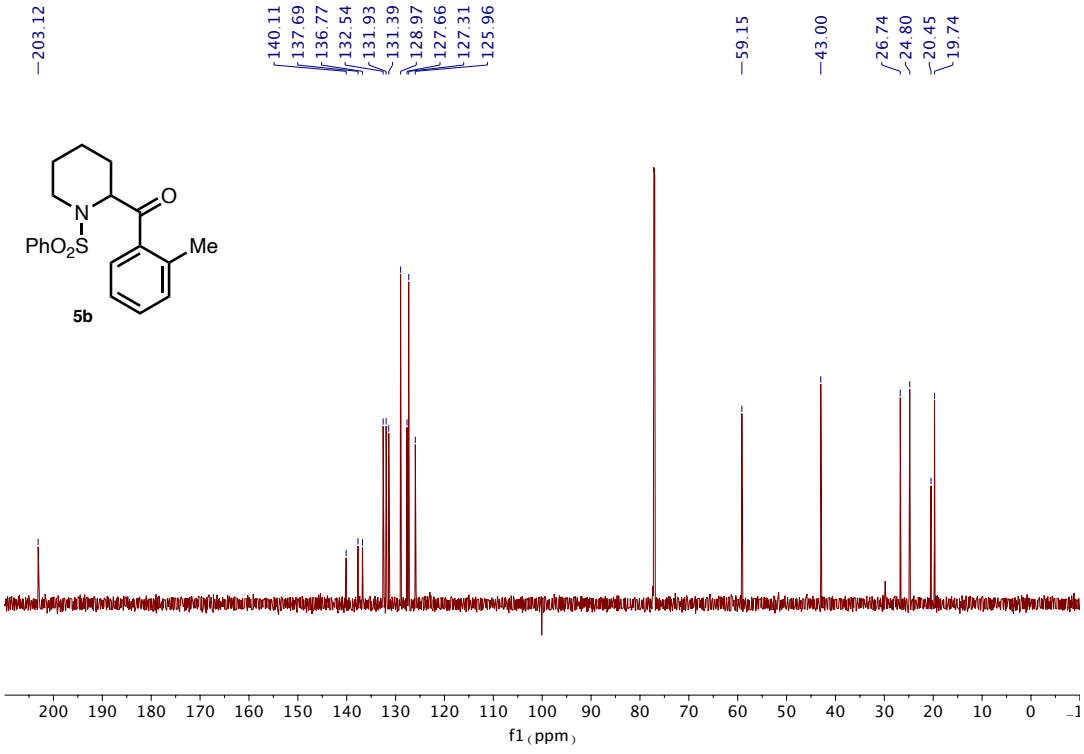

7.63 7.62 7.25 7.24 5.05 5.04 3.77 3.71 3.70 3.70 3.69 3.68 3.68 3.67 3.02 2.39 1.89 1.88 1.88 1.87 1.87 1.86 1.86 1.86 1.77 1.77 1.77 1.76 1.76 1.69 1.69 1.69 1.68 1.68 1.68 1.67 1.56 1.56 1.50 1.49 1.48 1.48 1.47 1.47 1.46
Me
O
N
Me
N
Ts
O
S2
2.00 1.96 1.04 2.97 2.08 2.99 3.06 1.12 1.19 1.16 1.09 2.18
f1 (ppm)

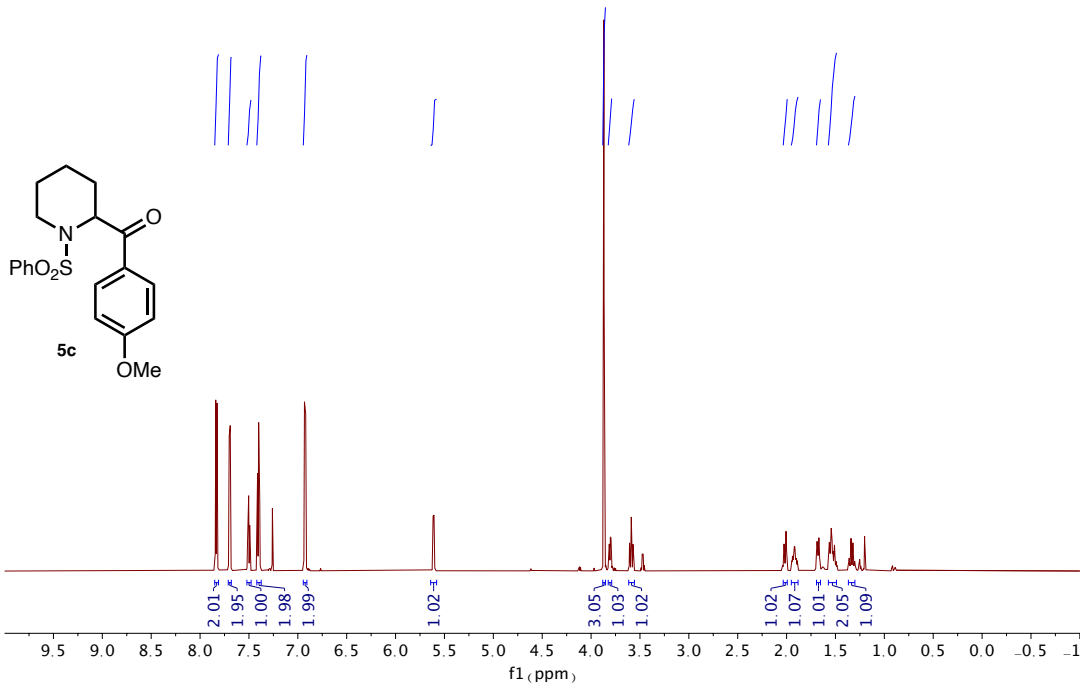

172.0
143.1
136.7
129.4
127.3
61.6
50.9
42.9
31.9
27.5
24.9
21.6
18.8
Me
O
N
Me
N
Ts
O
S2
f1 (ppm)

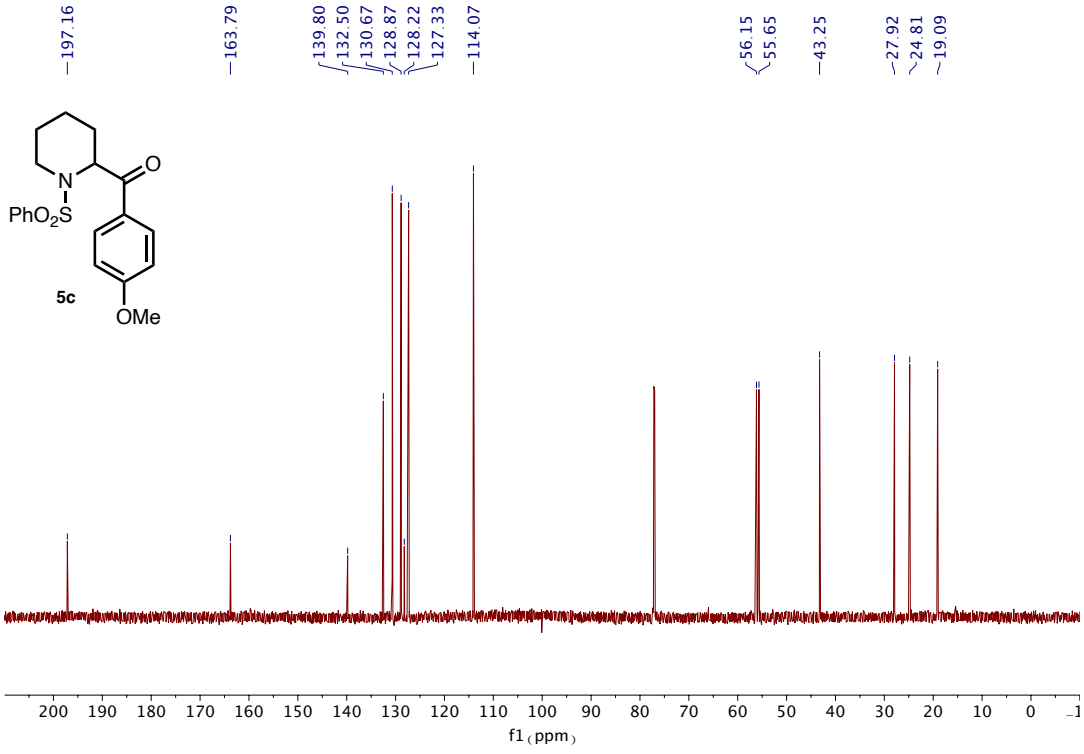

N
O
PhO2S
5a
Me
2.00
1.93
1.02
1.99
2.08
1.01
1.04
1.02
3.00
1.03
1.02
1.07
2.24
1.18
f1 (ppm)

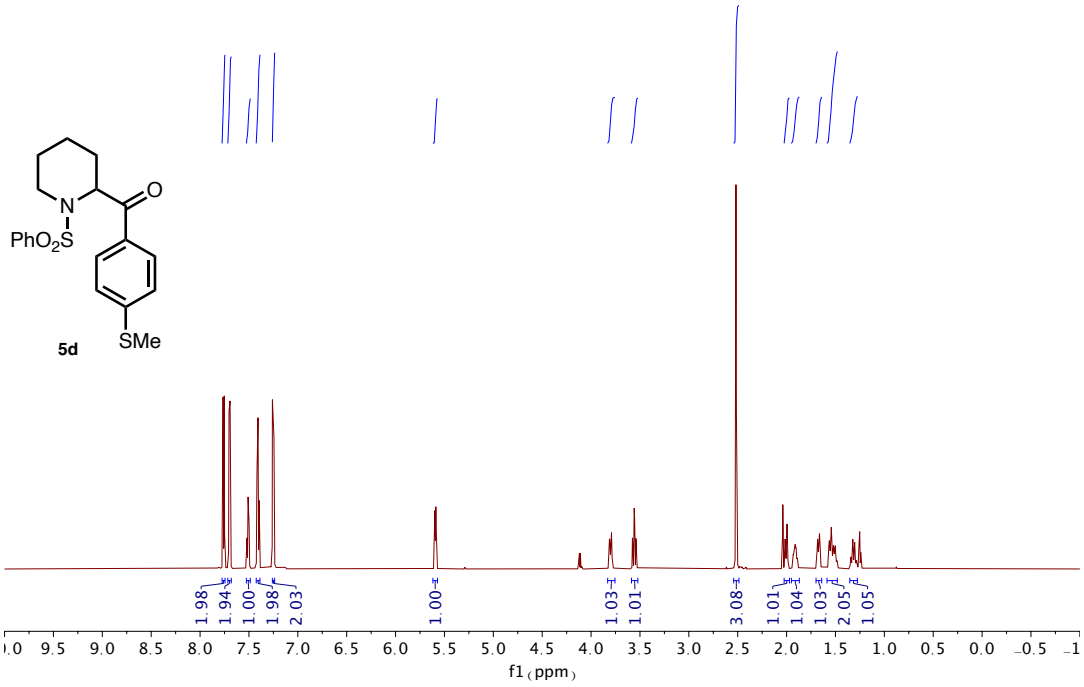

198.43
144.40
139.83
132.89
132.52
129.60
128.90
128.44
127.33
56.56
43.21
27.84
24.83
21.82
19.14
N
O
PhO2S
5a
Me
f1 (ppm)

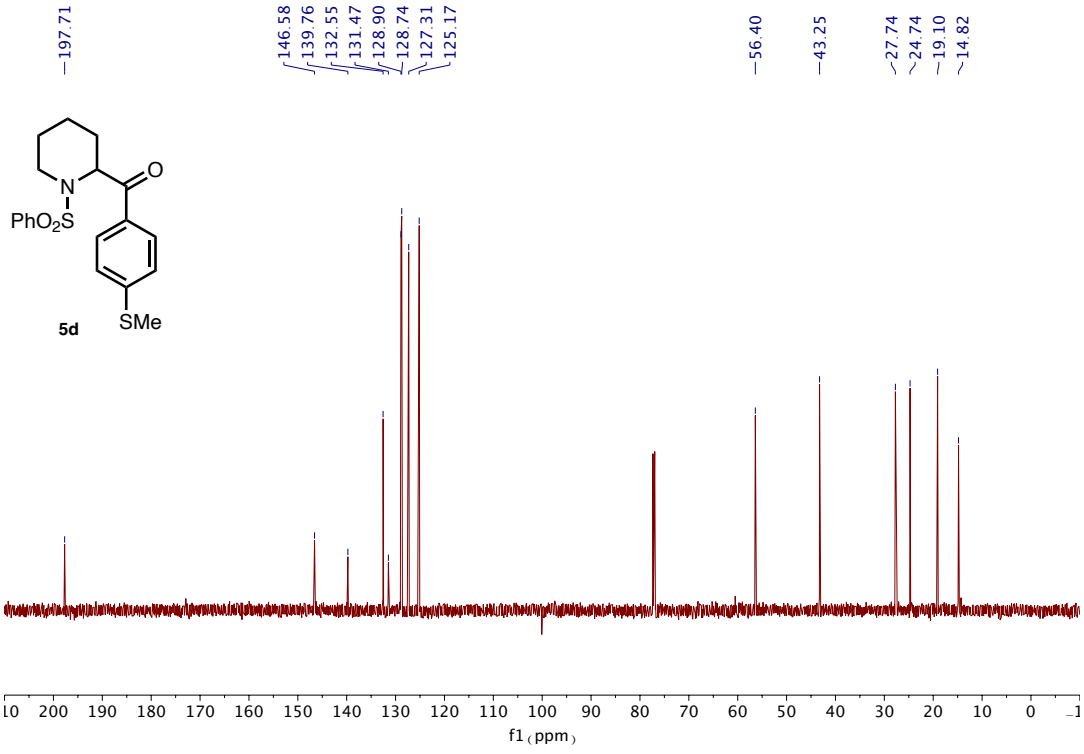

O
N
PhO2S
Me
5b
1.92
1.00
1.01
1.97
0.98
1.05
0.99
0.99
1.04
1.01
3.02
1.08
1.13
1.13
1.12
1.06
1.30
f1 (ppm)

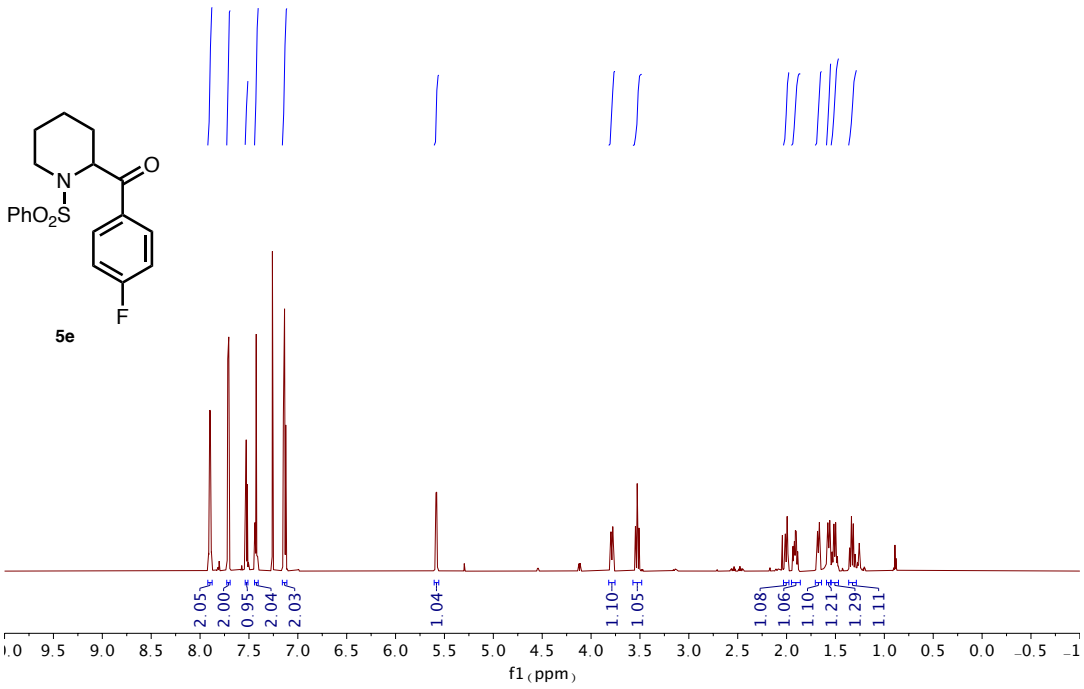

203.12
140.11
137.69
136.77
132.54
131.93
131.39
128.97
127.66
127.31
125.96
59.15
43.00
26.74
24.80
20.45
19.74
O
N
PhO2S
Me
5b
f1 (ppm)

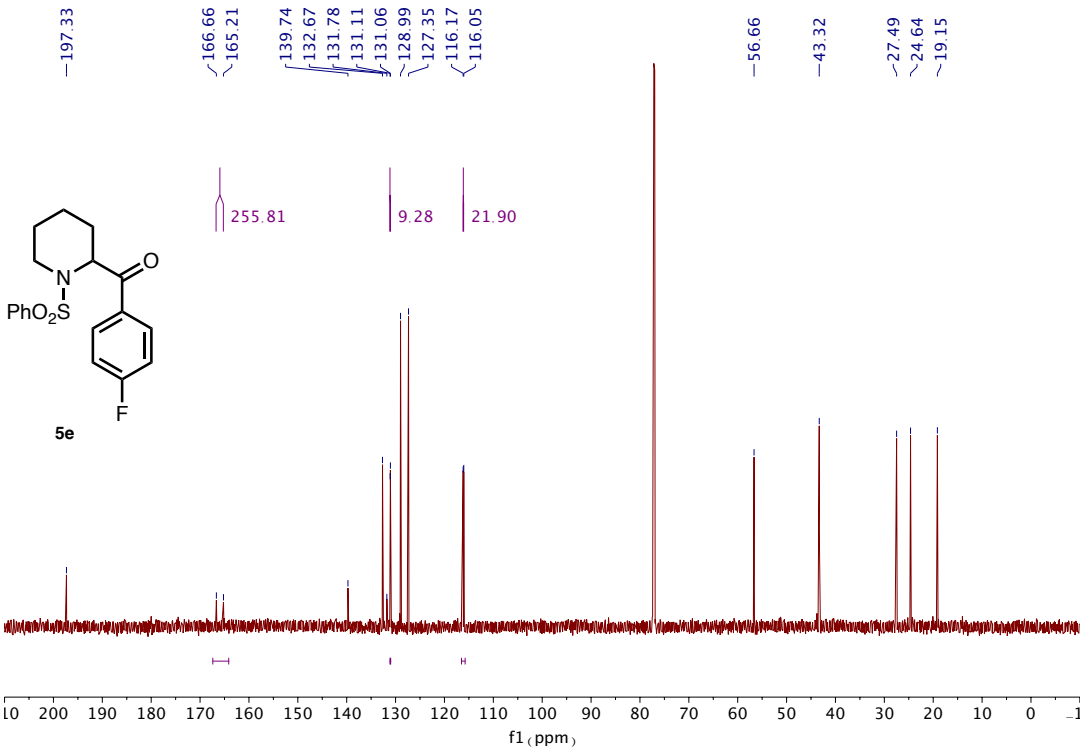

PhO2S
N
O
OMe
5c
2.01
1.95
1.00
1.98
1.99
1.02
3.05
1.03
1.02
1.02
1.07
1.01
2.05
1.09
f1 (ppm)

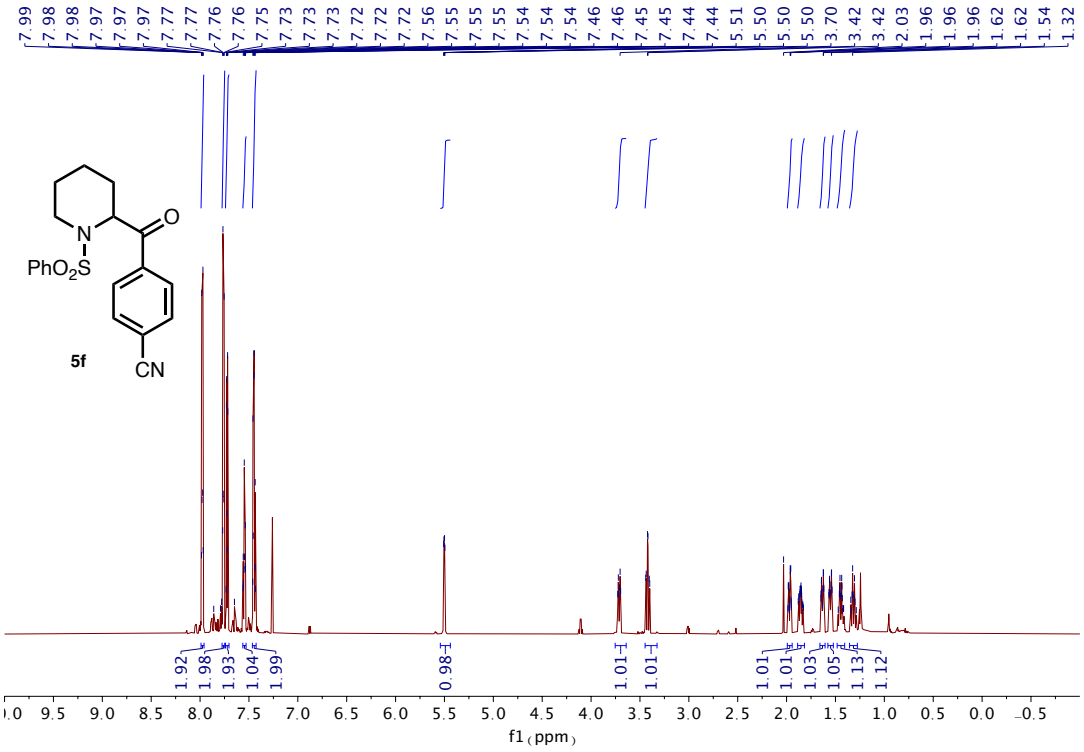

197.16
163.79
139.80
132.50
130.67
128.87
128.22
127.33
114.07
56.15
55.65
43.25
27.92
24.81
19.09
PhO2S
N
O
OMe
5c
f1 (ppm)

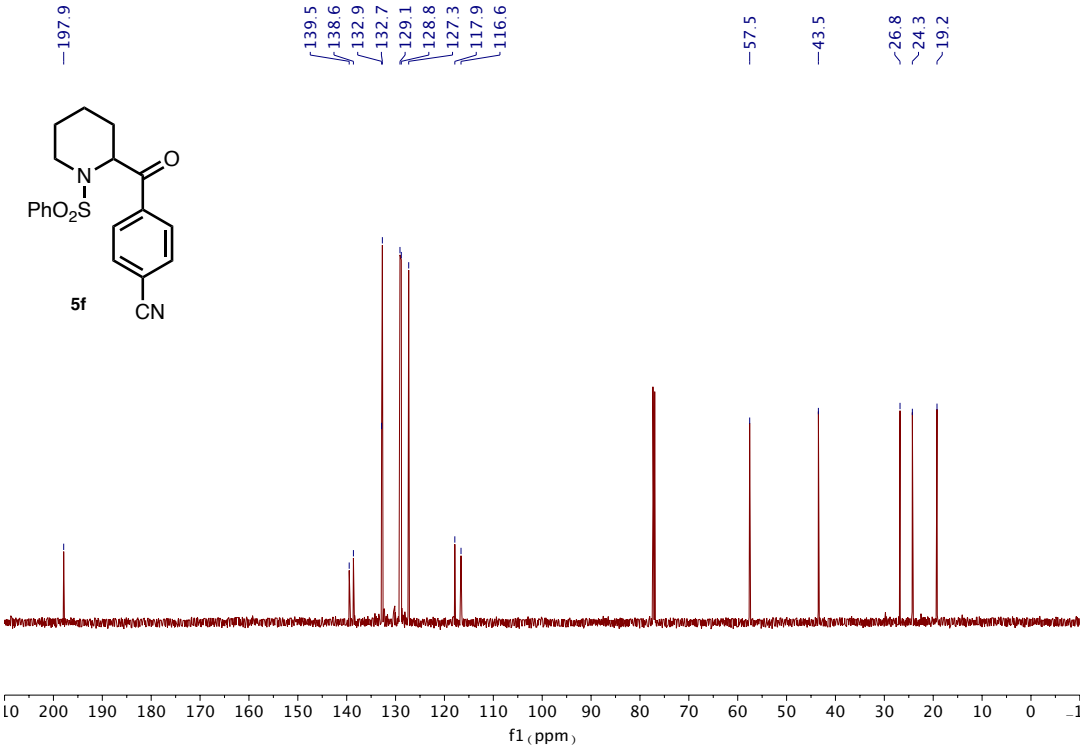

O
N
PhO2S
SMe
5d
1.98
1.94
1.00
1.98
2.03
1.00
1.03
1.01
3.08
1.01
1.04
1.03
2.05
1.05
f1 (ppm)

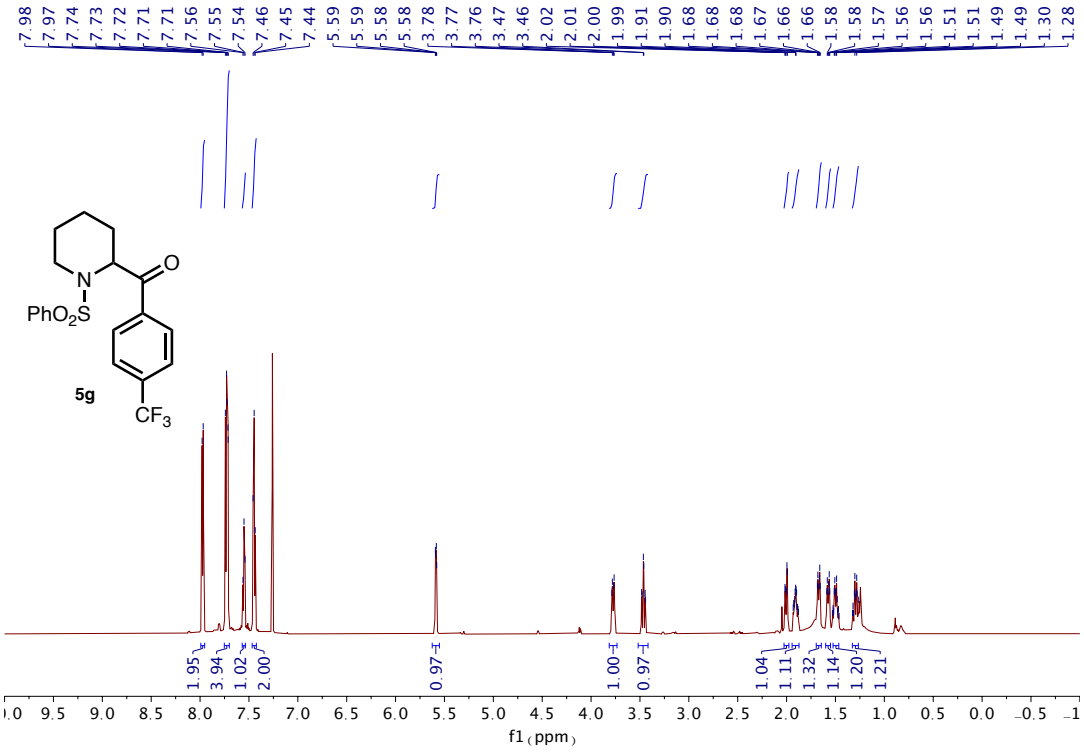

197.71
146.58
139.76
132.55
131.47
128.90
128.74
127.31
125.17
56.40
43.25
27.74
24.74
19.10
14.82
O
N
PhO2S
SMe
5d
f1 (ppm)

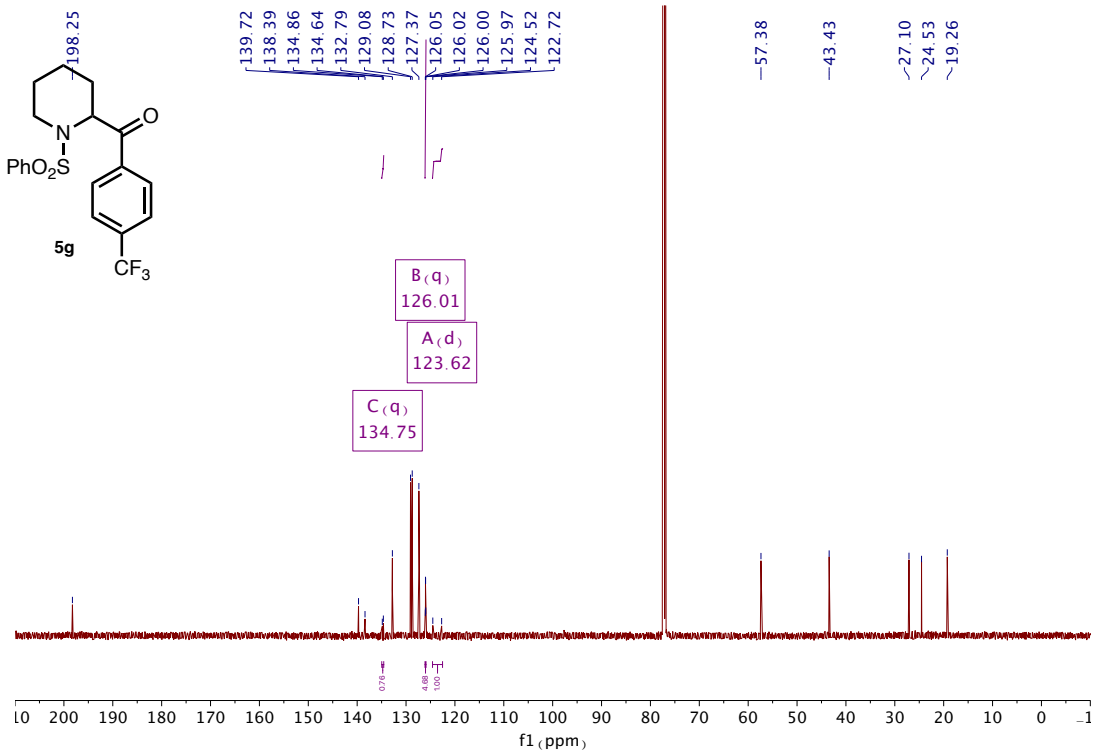

O
N
PhO2S
F
5e
2.05
2.00
0.95
2.04
2.03
1.04
1.10
1.05
1.08
1.06
1.10
1.21
1.29
1.11
f1 (ppm)

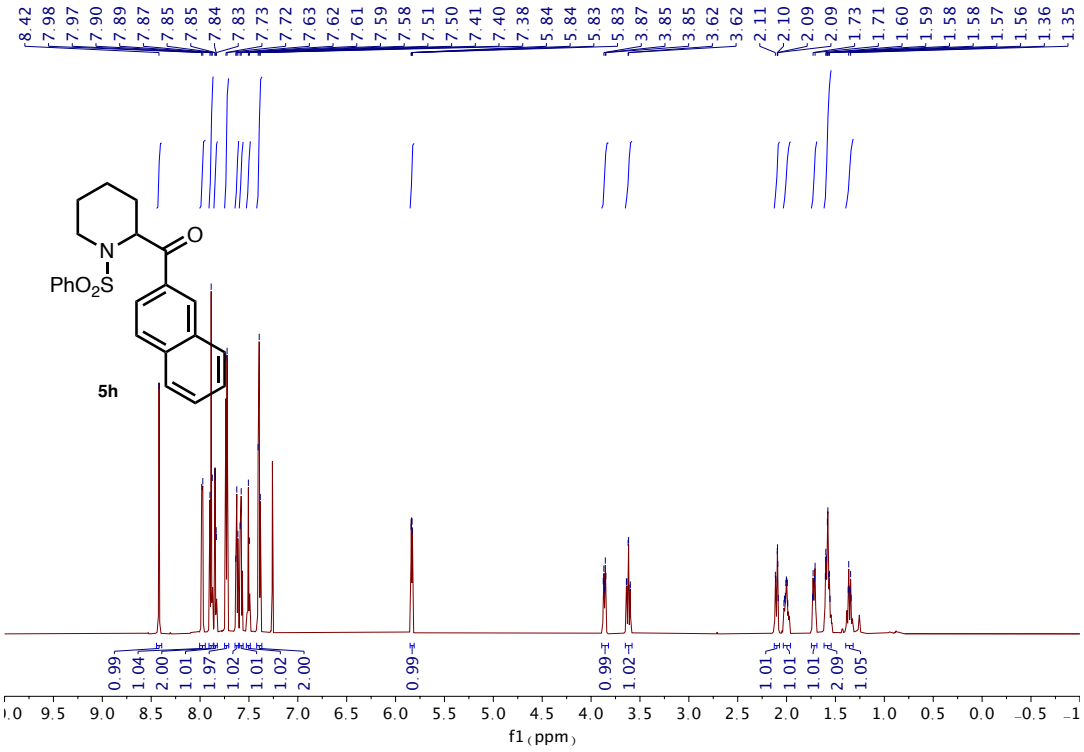

197.33
166.66
165.21
139.74
132.67
131.78
131.11
131.06
128.99
127.35
116.17
116.05
56.66
43.32
27.49
24.64
19.15
255.81
9.28
21.90
O
N
PhO2S
F
5e
f1 (ppm)

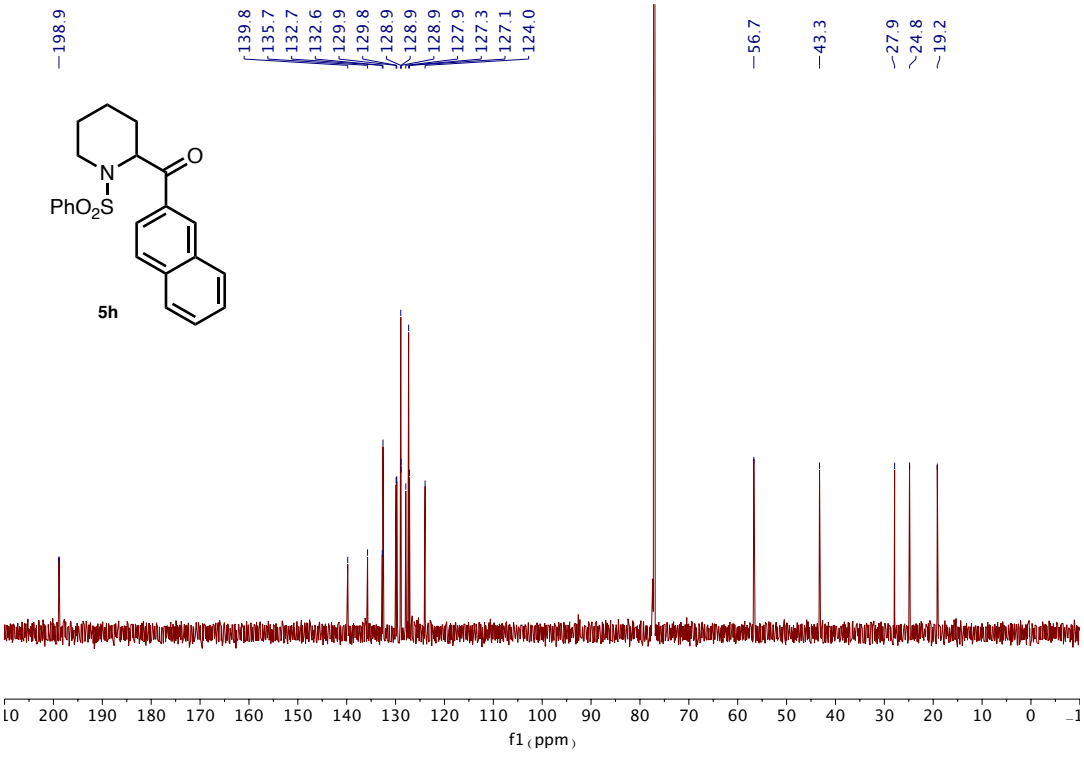

7.99 7.98 7.98 7.97 7.97 7.97 7.77 7.77 7.76 7.76 7.75 7.73 7.73 7.73 7.72 7.72 7.72 7.56 7.55 7.55 7.55 7.54 7.54 7.54 7.46 7.46 7.45 7.45 7.44 7.44 5.51 5.50 5.50 5.50 3.70 3.42 3.42 2.03 1.96 1.96 1.96 1.62 1.62 1.54 1.32
N
O
PhO2S
5f
CN
1.92 1.98 1.93 1.04 1.99 0.98 1.01 1.01 1.01 1.01 1.03 1.05 1.13 1.12
f1 (ppm)

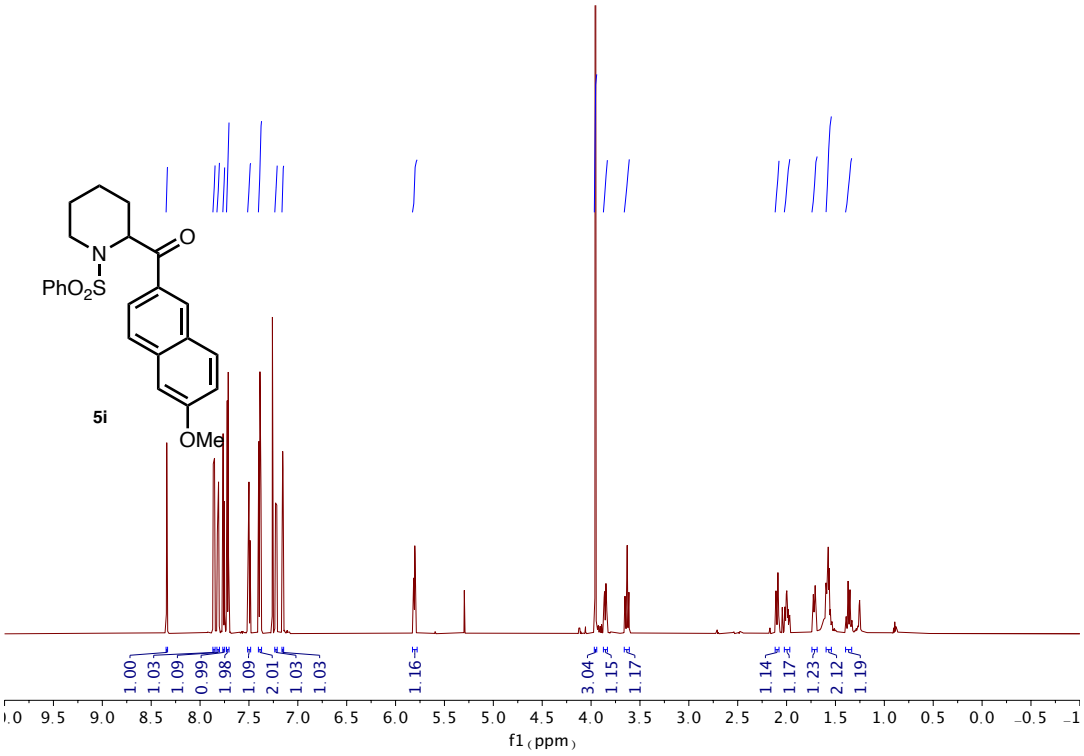

197.9
139.5 138.6 132.9 132.7 129.1 128.8 127.3 117.9 116.6
57.5 43.5 26.8 24.3 19.2
N
O
PhO2S
5f
CN
f1 (ppm)

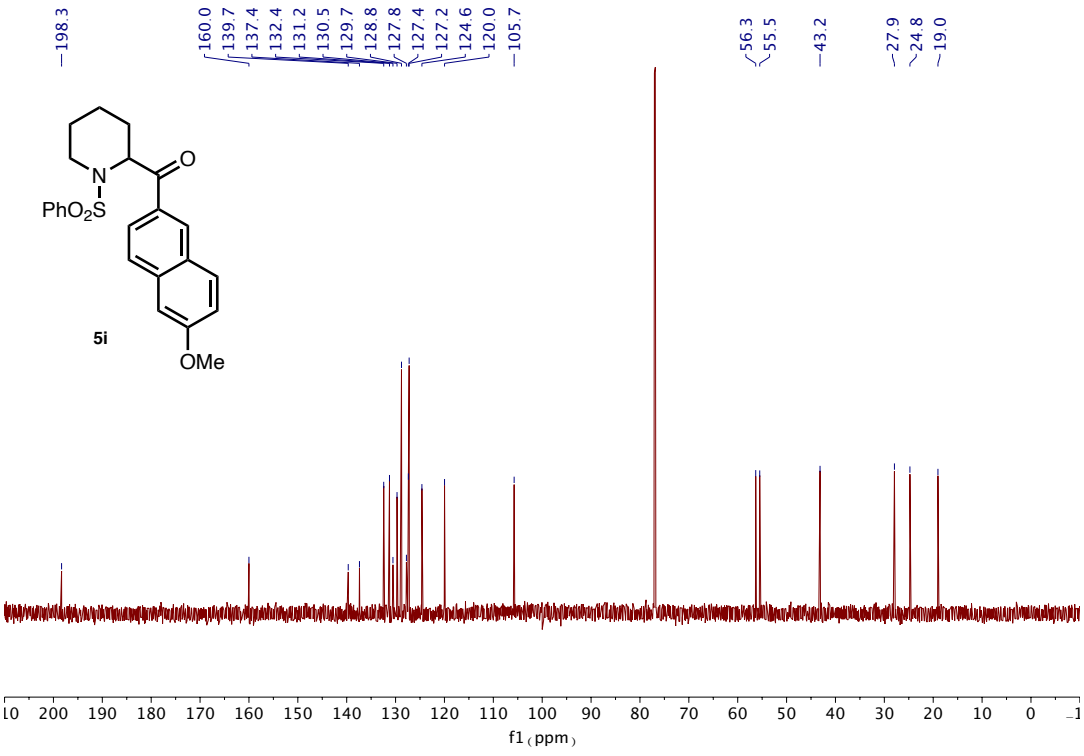

7.98 7.97 7.74 7.73 7.72 7.71 7.71 7.56 7.55 7.54 7.46 7.45 7.44
5.59 5.59 5.58 5.58 3.78 3.77 3.76 3.47 3.46 2.02 2.01 2.00 1.99 1.91 1.90 1.68 1.68 1.68 1.67 1.66 1.66 1.58 1.58 1.57 1.56 1.56 1.51 1.51 1.49 1.49 1.30 1.28
PhO2S
5g
CF3
1.95 3.94 1.02 2.00 0.97 1.00 0.97 1.04 1.11 1.32 1.14 1.20 1.21
f1 (ppm)

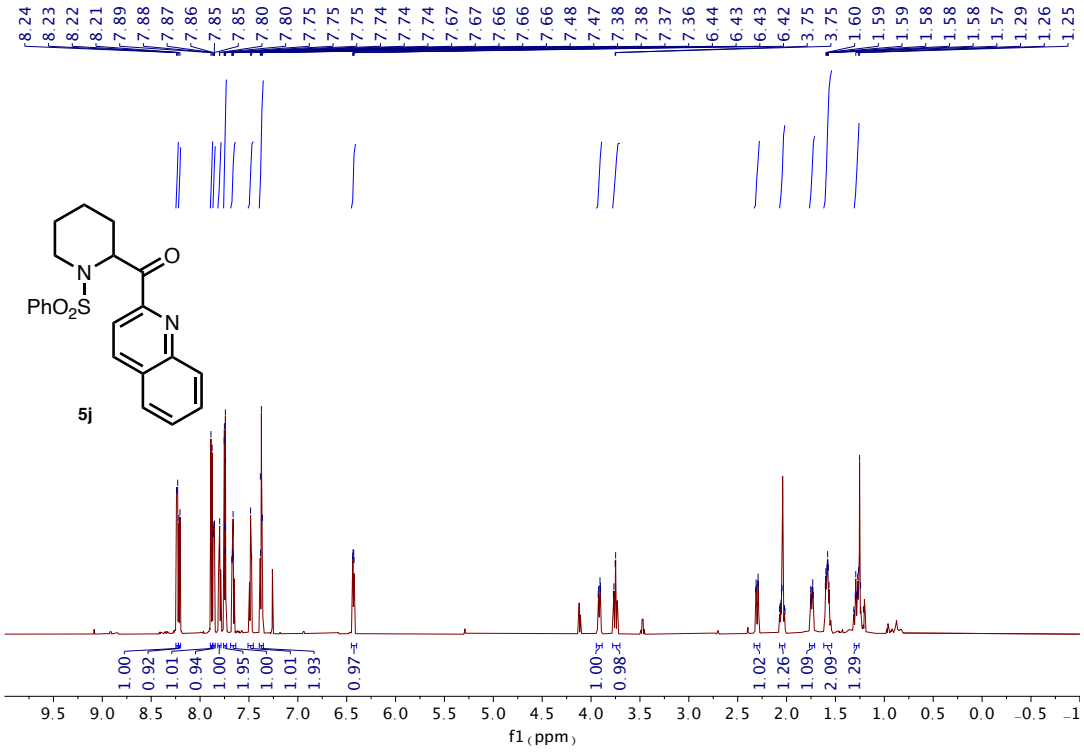

198.25
139.72 138.39 134.86 134.64 132.79 129.08 128.73 127.37 126.05 126.02 126.00 125.97 124.52 122.72
57.38 43.43 27.10 24.53 19.26
PhO2S
5g
CF3
B (q) 126.01
A (d) 123.62
C (q) 134.75
f1 (ppm)

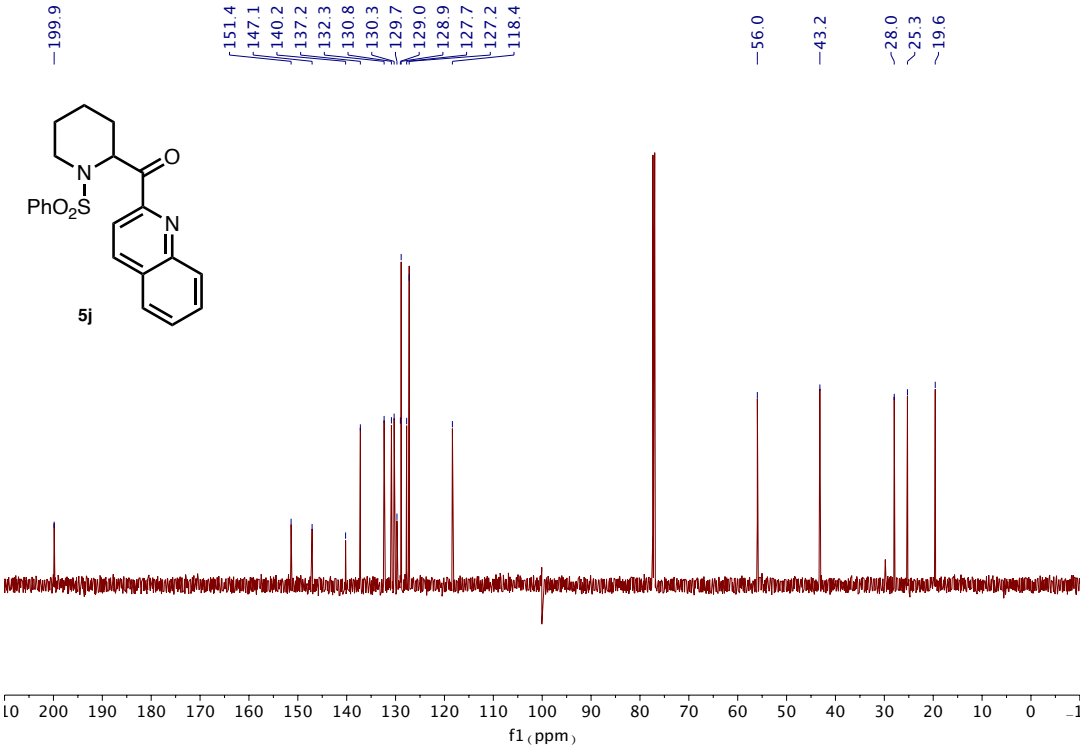

8.42 7.98 7.97 7.90 7.89 7.87 7.85 7.85 7.84 7.83 7.73 7.72 7.63 7.62 7.61 7.59 7.58 7.51 7.50 7.41 7.40 7.38 5.84 5.84 5.83 5.83 3.87 3.85 3.85 3.62 2.11 2.10 2.09 2.09 1.73 1.71 1.60 1.59 1.58 1.58 1.57 1.56 1.36 1.35
N
O
PhO2S
5h
0.99 1.04 2.00 1.01 1.97 1.02 1.01 1.02 2.00 0.99 0.99 1.02 1.01 1.01 1.01 2.09 1.05
f1 (ppm)

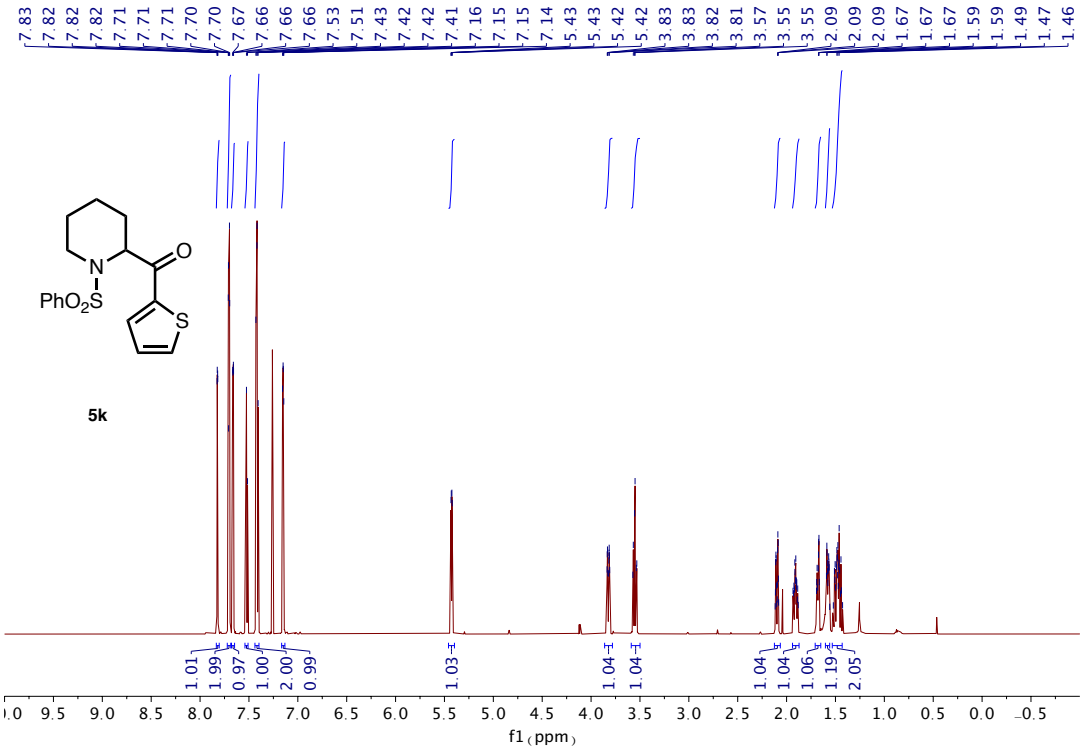

198.9
139.8 135.7 132.7 132.6 129.9 129.8 128.9 128.9 128.9 127.9 127.3 127.1 124.0
56.7
43.3
27.9 24.8 19.2
N
O
PhO2S
5h
f1 (ppm)

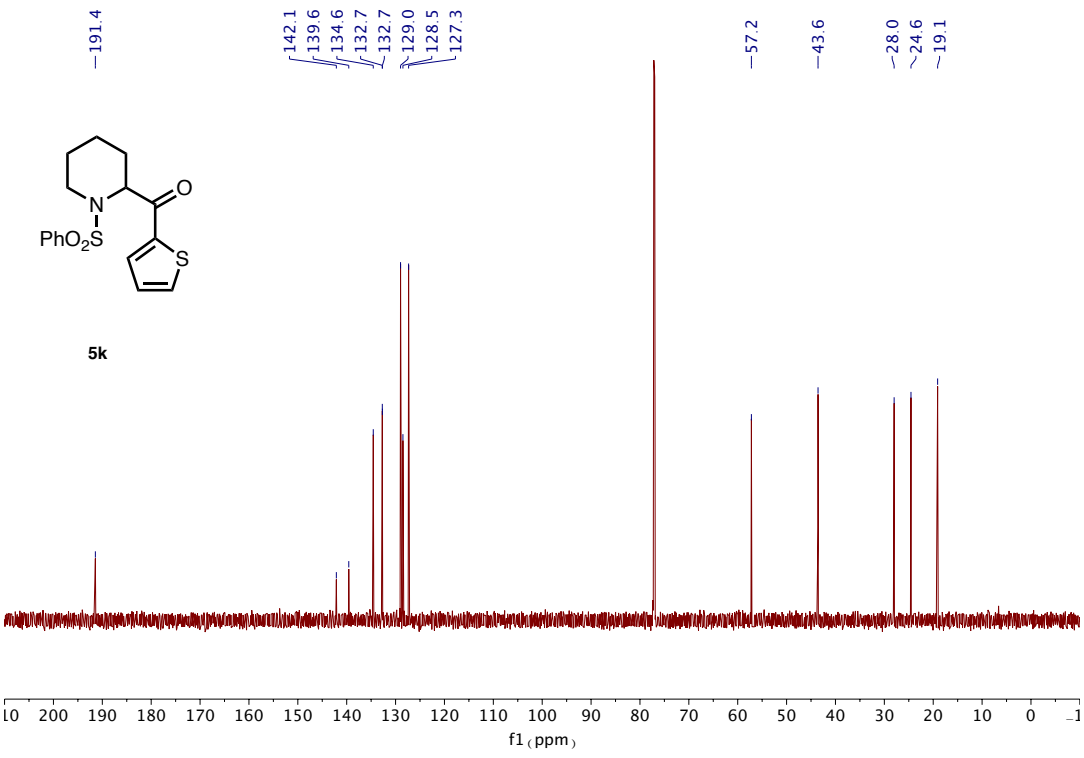

O
N
PhO2S
OMe
5i
1.00
1.03
1.09
0.99
1.98
1.09
2.01
1.03
1.03
1.16
3.04
1.15
1.17
1.14
1.17
1.23
2.12
1.19
f1 (ppm)

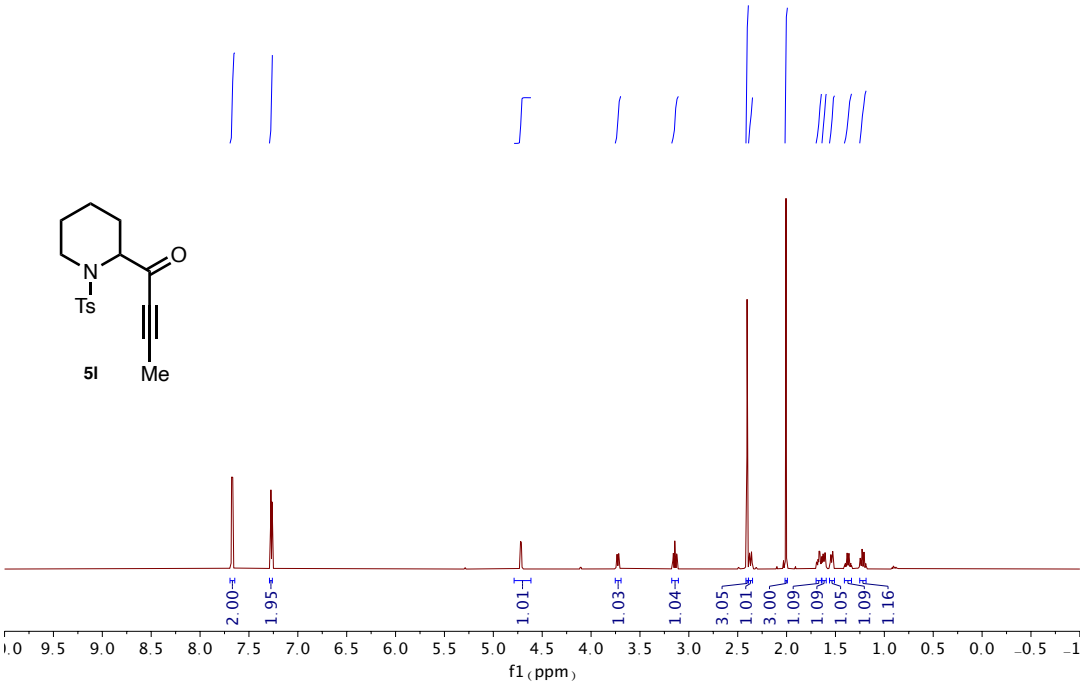

198.3
160.0
139.7
137.4
132.4
131.2
130.5
129.7
128.8
127.8
127.4
127.2
124.6
120.0
105.7
56.3
55.5
43.2
27.9
24.8
19.0
O
N
PhO2S
OMe
5i
f1 (ppm)

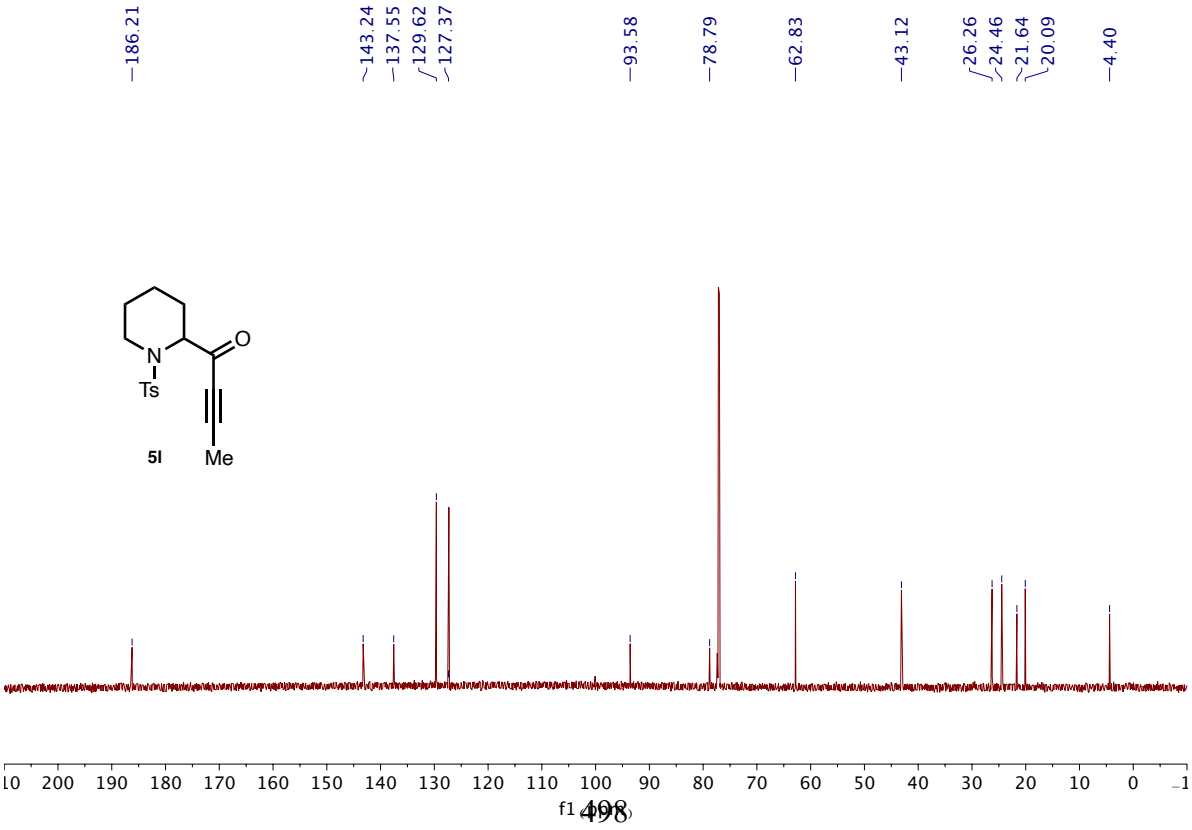

8.24 8.23 8.22 8.21 7.89 7.88 7.87 7.86 7.85 7.85 7.80 7.80 7.75 7.75 7.75 7.74 7.74 7.74 7.67 7.67 7.66 7.66 7.66 7.48 7.47 7.38 7.38 7.37 7.36 6.44 6.43 6.43 6.42 3.75 3.75 1.60 1.59 1.59 1.58 1.58 1.58 1.57 1.29 1.26 1.25
PhO2S
N
O
N
5j
1.00 0.92 1.01 0.94 1.00 1.95 1.00 1.01 1.93 0.97 1.00 0.98 1.02 1.26 1.09 2.09 1.29
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

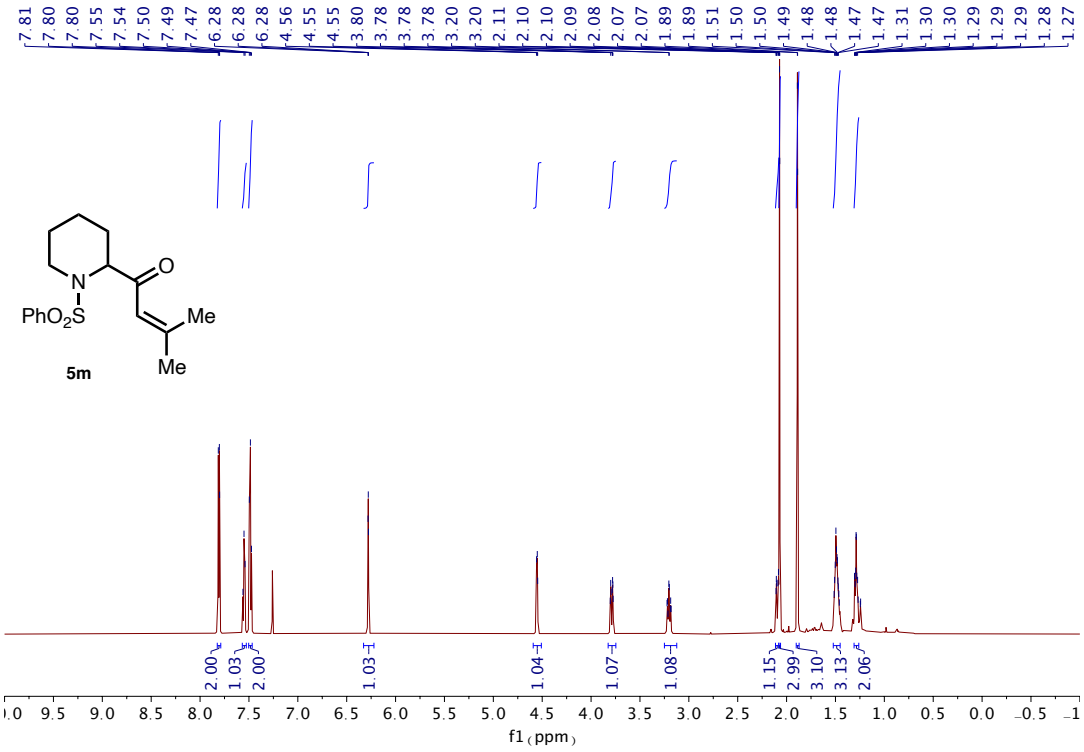

199.9
151.4 147.1 140.2 137.2 132.3 130.8 130.3 129.7 129.0 128.9 127.7 127.2 118.4
56.0 43.2 28.0 25.3 19.6
PhO2S
N
O
N
5j
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

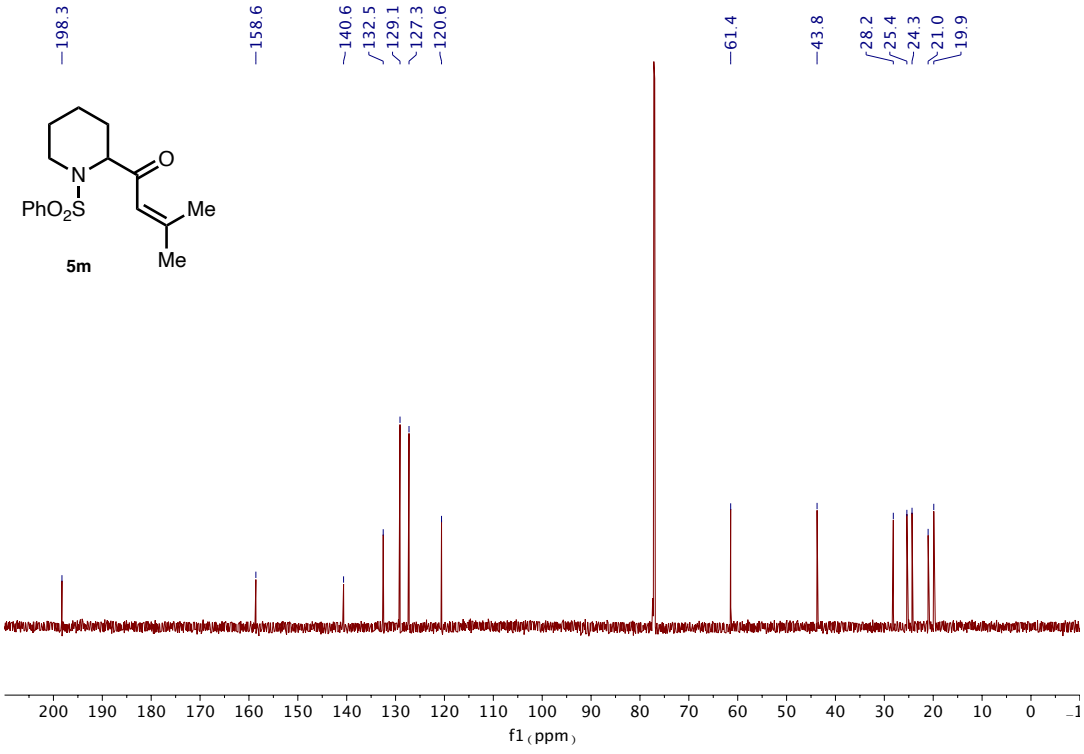

7.83 7.82 7.82 7.82 7.71 7.71 7.71 7.70 7.70 7.67 7.66 7.66 7.66 7.53 7.51 7.43 7.42 7.42 7.41 7.16 7.15 7.15 7.14 5.43 5.43 5.42 5.42 5.42 3.83 3.83 3.82 3.81 3.57 3.55 3.55 2.09 2.09 1.67 1.67 1.67 1.59 1.59 1.49 1.47 1.46
N
O
PhO2S
S
5k
1.01 1.99 0.97 1.00 2.00 0.99 1.03 1.04 1.04 1.04 1.04 1.06 1.19 2.05
f1 (ppm)

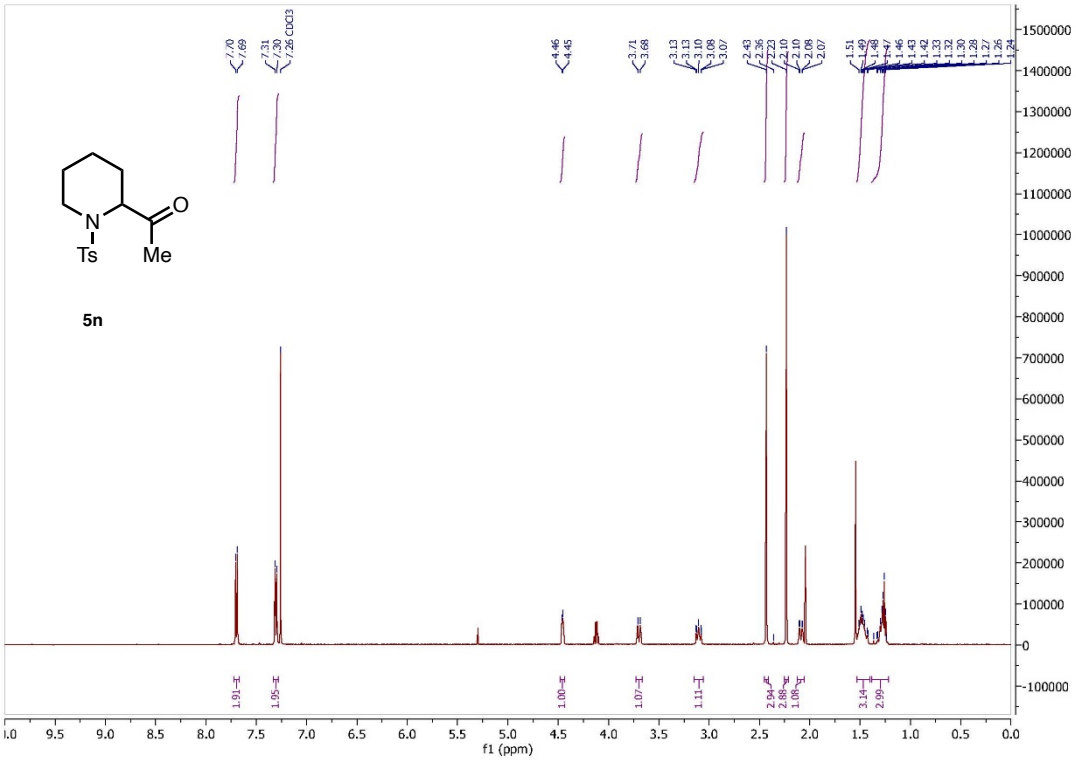

191.4
142.1 139.6 134.6 132.7 132.7 129.0 128.5 127.3
57.2
43.6
28.0 24.6 19.1
N
O
PhO2S
S
5k
f1 (ppm)

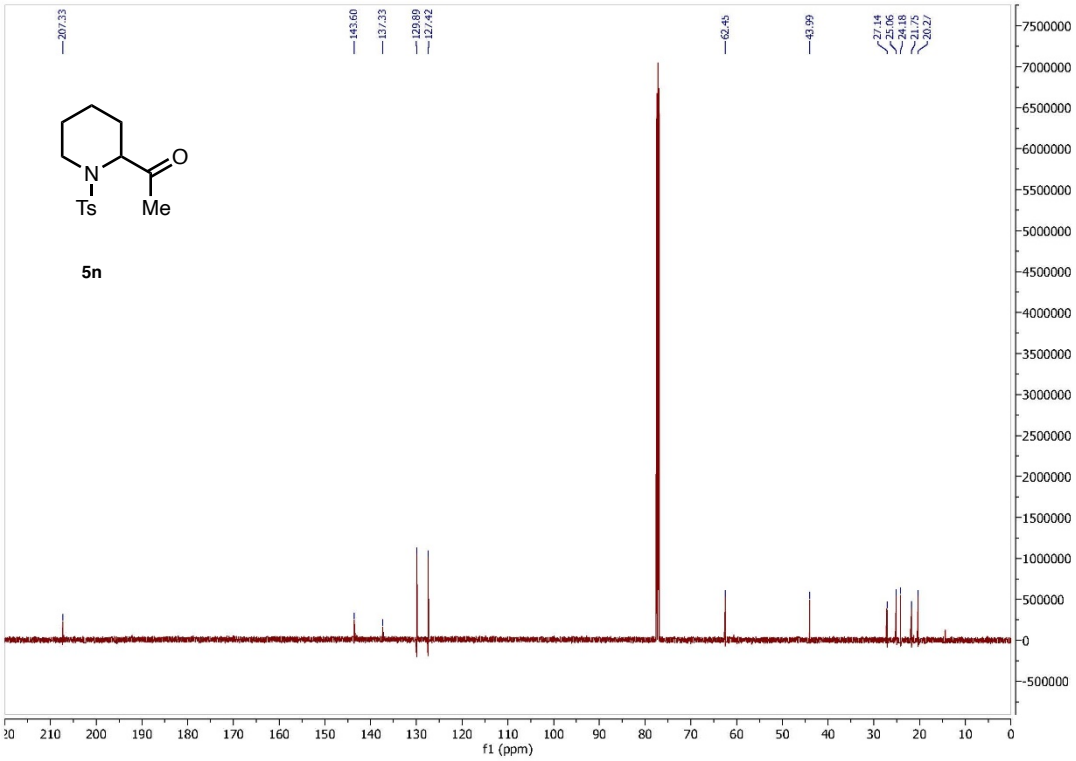

N
Ts
O
5l
Me
2.00
1.95
1.01
1.03
1.04
3.05
1.01
3.00
1.09
1.09
1.05
1.09
1.16
f1 (ppm)

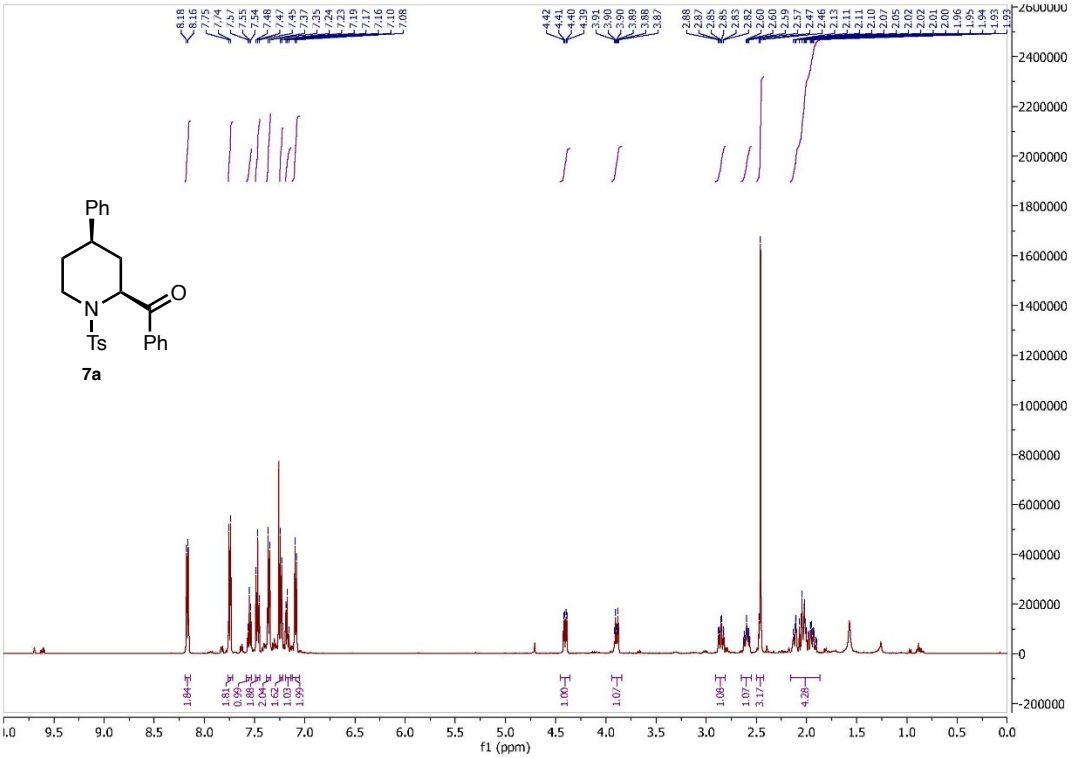

186.21
143.24
137.55
129.62
127.37
93.58
78.79
62.83
43.12
26.26
24.46
21.64
20.09
4.40
N
Ts
O
5l
Me
f1 (ppm)

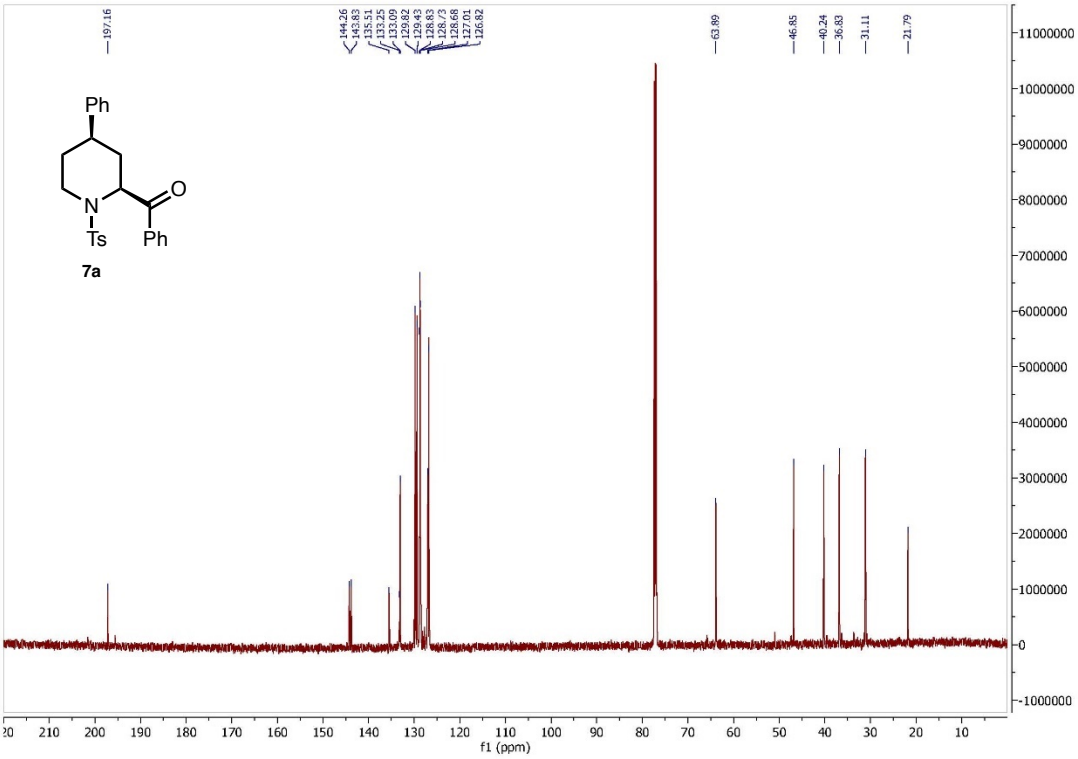

7.81 7.80 7.80 7.55 7.54 7.50 7.49 7.47 6.28 6.28 6.28 4.56 4.55 4.55 3.80 3.78 3.78 3.78 3.20 3.20 2.11 2.10 2.10 2.09 2.08 2.07 2.07 1.89 1.89 1.51 1.50 1.50 1.49 1.48 1.48 1.47 1.47 1.31 1.30 1.30 1.29 1.29 1.29 1.28 1.27
O
N
PhO2S
Me
Me
5m
2.00 1.03 2.00 1.03 1.04 1.07 1.08 1.15 2.99 3.10 3.13 2.06
f1 (ppm)

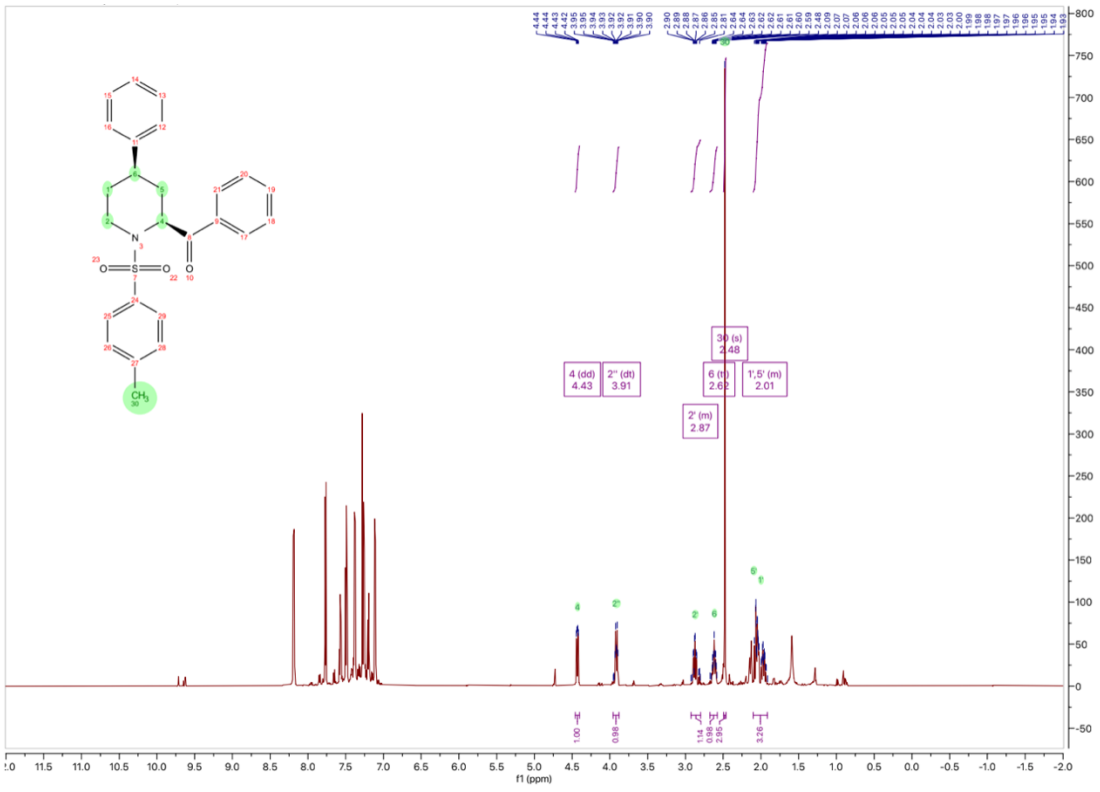

198.3 158.6 140.6 132.5 129.1 127.3 120.6 61.4 43.8 28.2 25.4 24.3 21.0 19.9
O
N
PhO2S
Me
Me
5m
f1 (ppm)

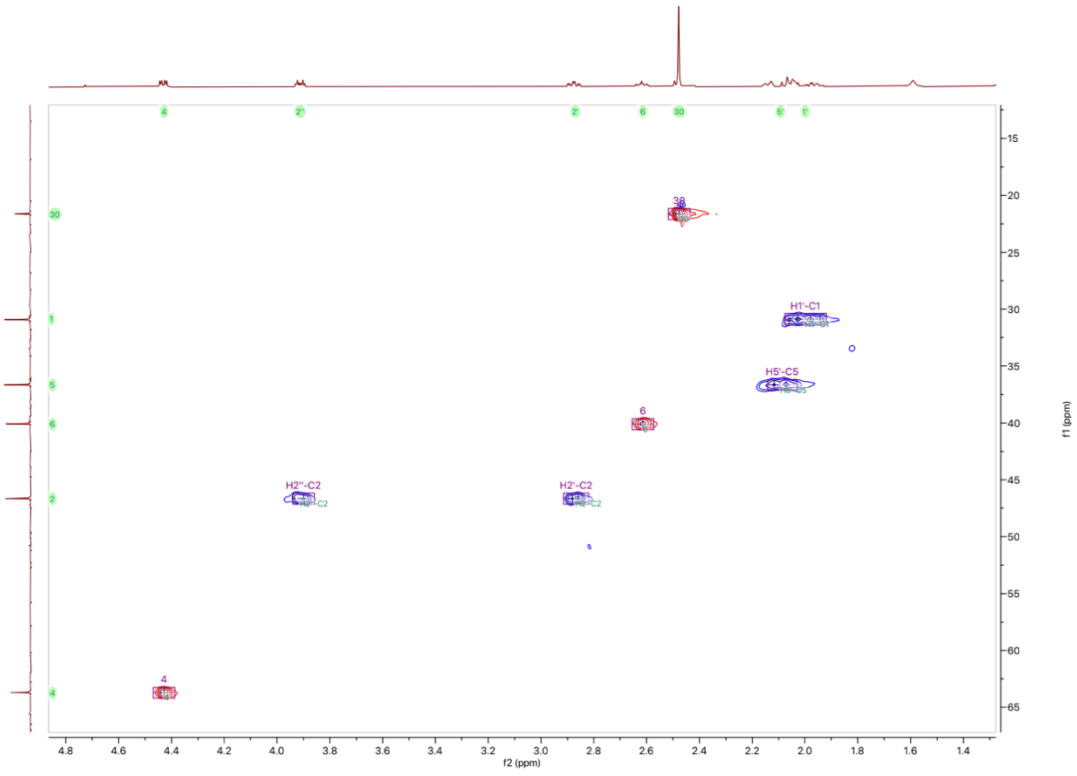

7.70
7.69
7.31
7.30
7.26 CDCl3
4.46
4.45
3.71
3.68
3.13
3.13
3.10
3.08
3.07
2.43
2.36
2.23
2.10
2.10
2.08
2.07
1.51
1.49
1.48
1.47
1.46
1.45
1.42
1.33
1.32
1.30
1.28
1.27
1.25
1.24
N
Ts
O
Me
5n
1.91
1.95
1.00
1.07
1.11
2.94
2.88
1.08
3.14
2.99
f1 (ppm)

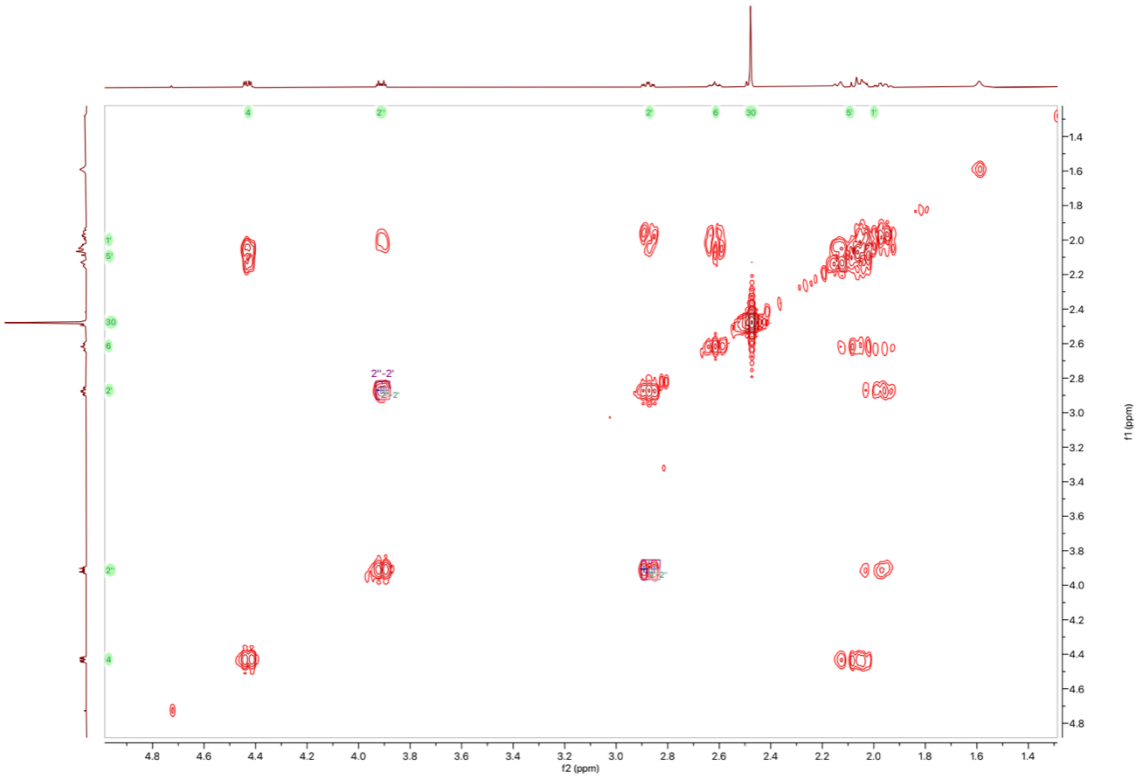

207.33
143.60
137.33
129.89
127.42
62.45
43.99
27.14
25.06
24.18
21.75
20.27
N
Ts
O
Me
5n
f1 (ppm)

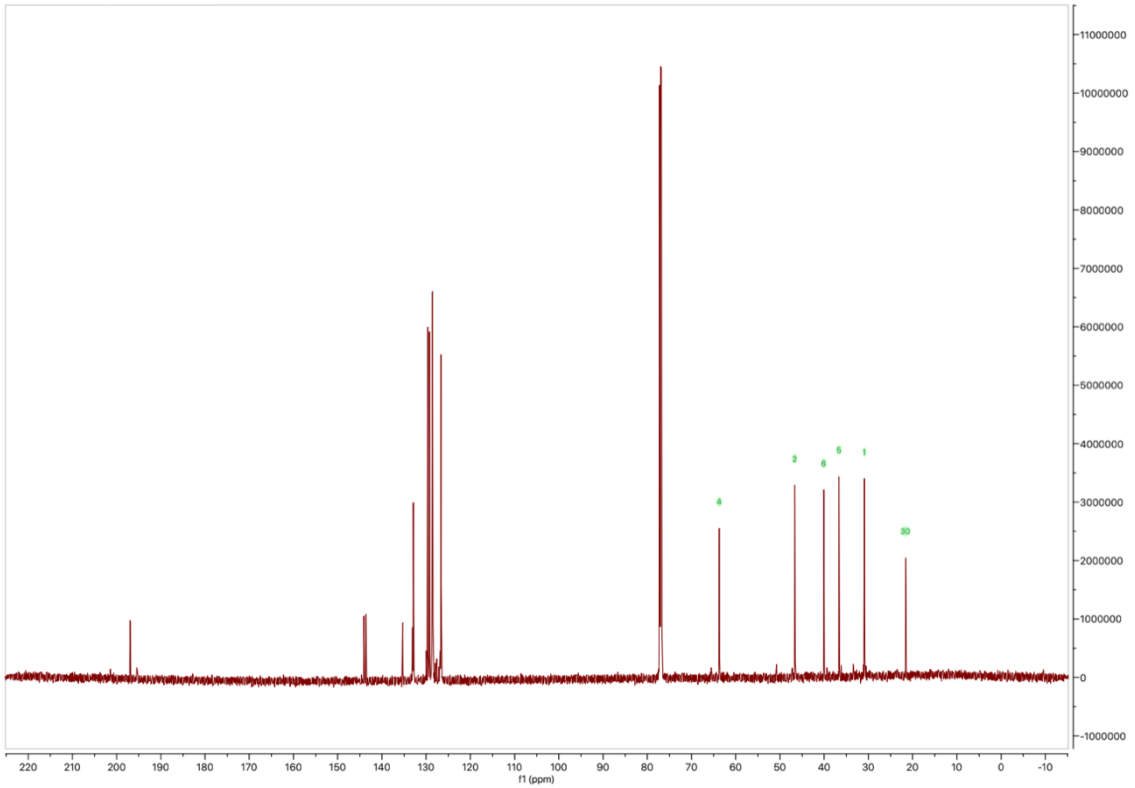

Ph
N
Ts
O
Ph
7a
f1 (ppm)

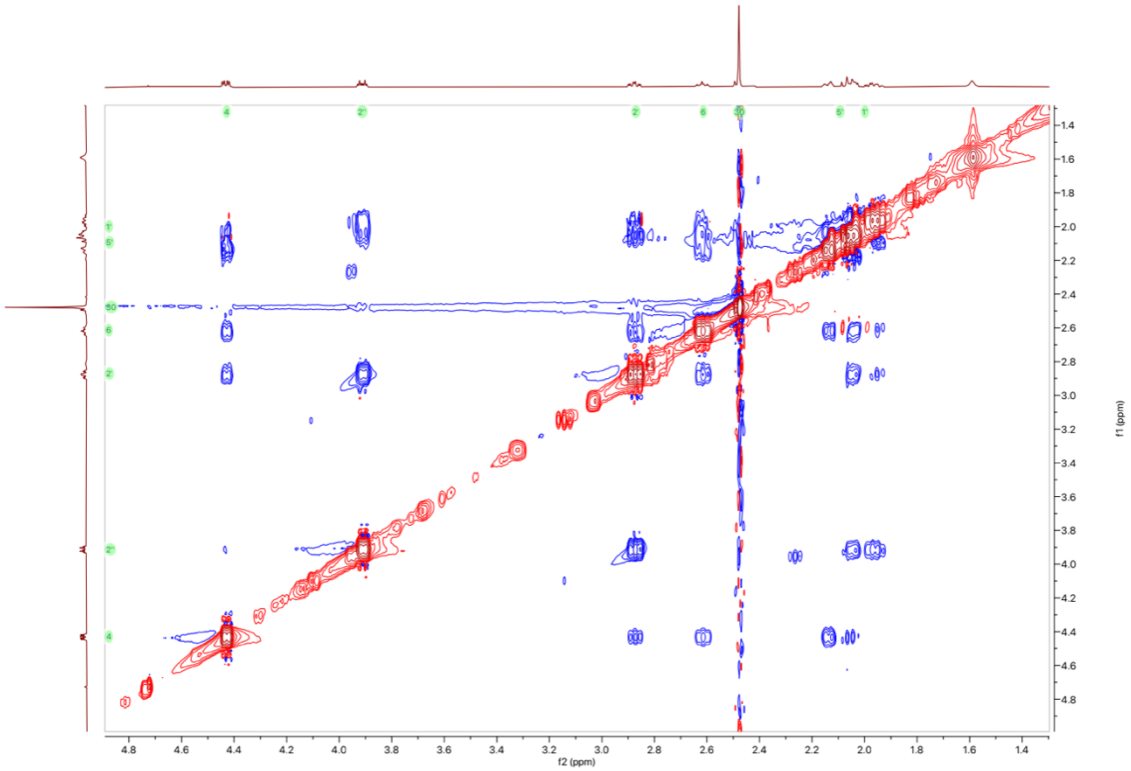

Ph
N
Ts
O
Ph
7a
f1 (ppm)

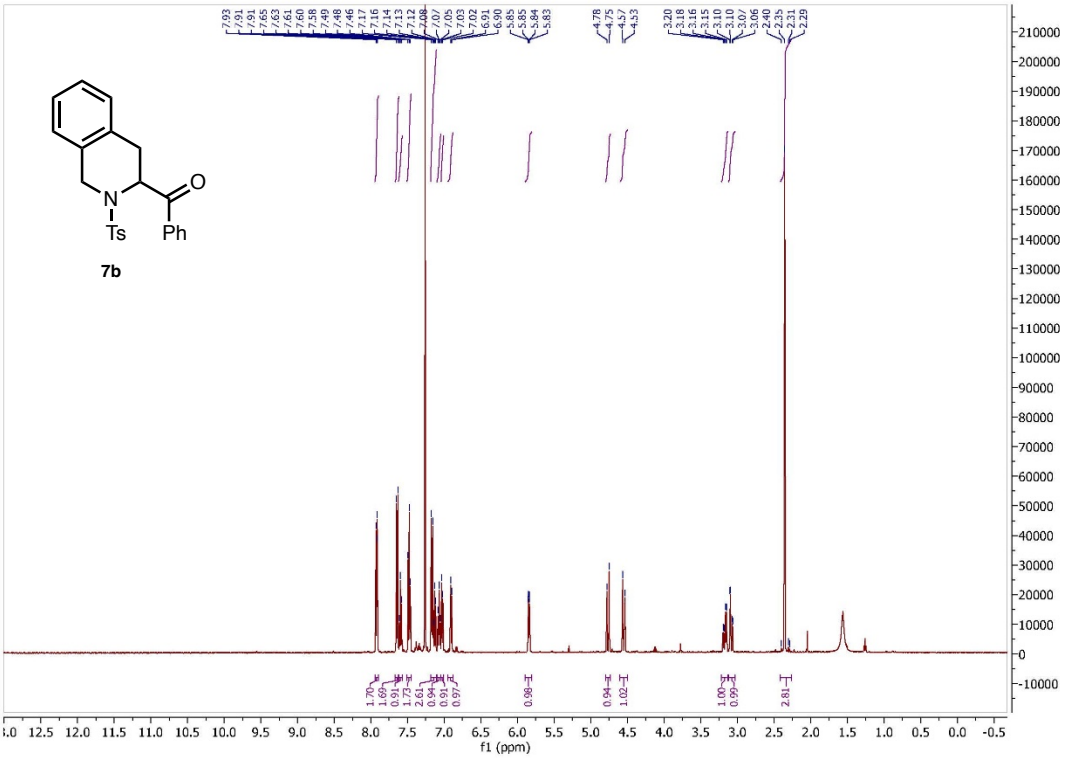

4 (dd)
4.43
2'' (dt)
3.91
30 (s)
2.48
6 (t)
2.62
1',5' (m)
2.01
2' (m)
2.87
f1 (ppm)

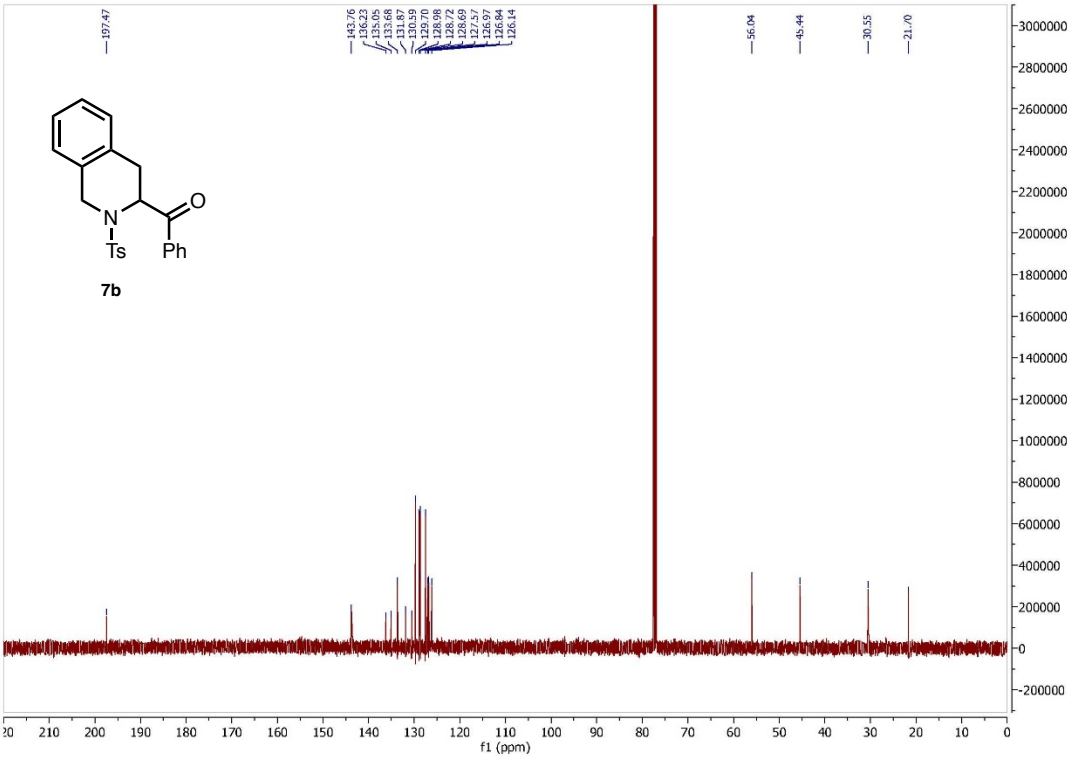

H1'-C1
H5'-C5
H2''-C2
H2'-C2
f2 (ppm)
f1 (ppm)

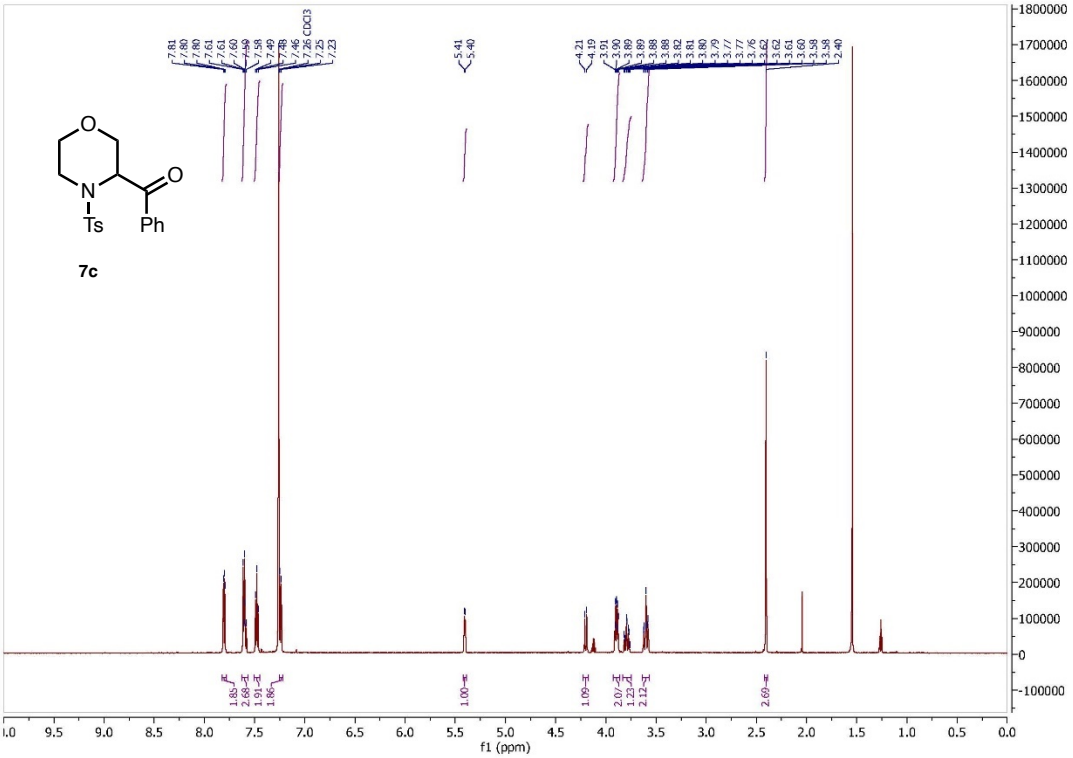

f2 (ppm)
f1 (ppm)

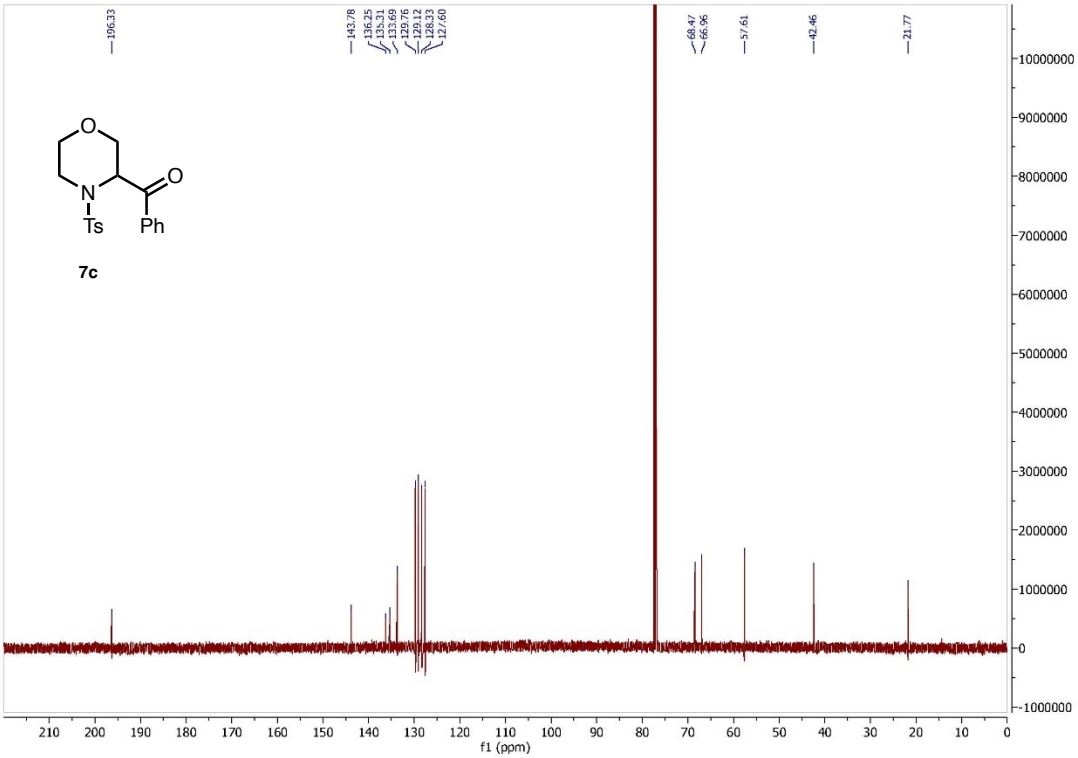

f1 (ppm)

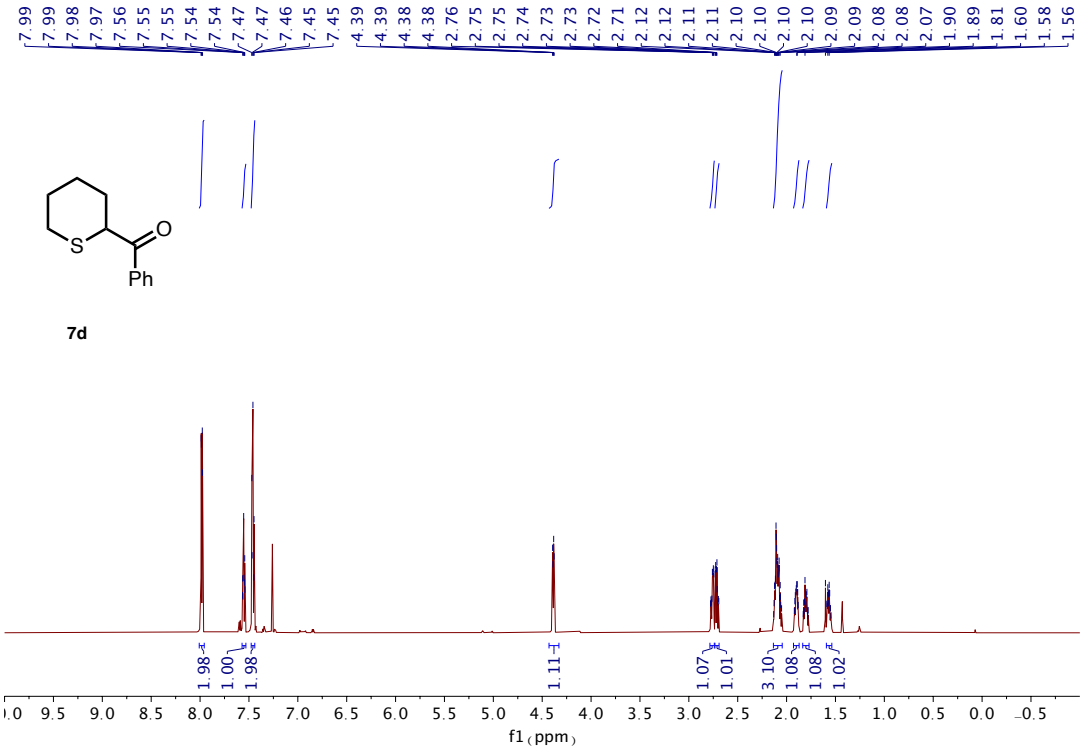

f2 (ppm)
f1 (ppm)


7b
f1 (ppm)

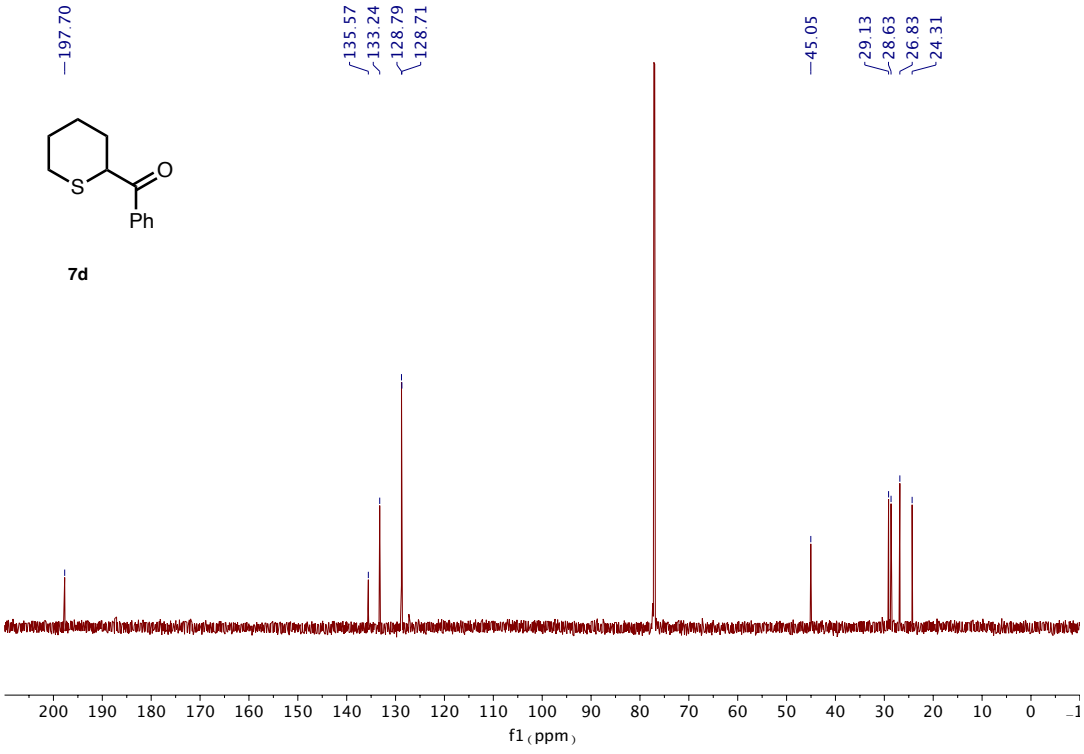

7b
f1 (ppm)


7.81
7.80
7.80
7.61
7.61
7.60
7.59
7.58
7.49
7.48
7.26 CDCl3
7.25
7.23
5.41
5.40
4.21
4.19
4.01
3.90
3.89
3.89
3.88
3.88
3.82
3.81
3.80
3.79
3.77
3.77
3.76
3.62
3.62
3.61
3.60
3.59
3.58
2.40
1.85
2.68
1.91
1.86
1.00
1.09
2.07
1.23
2.12
2.69
f1 (ppm)

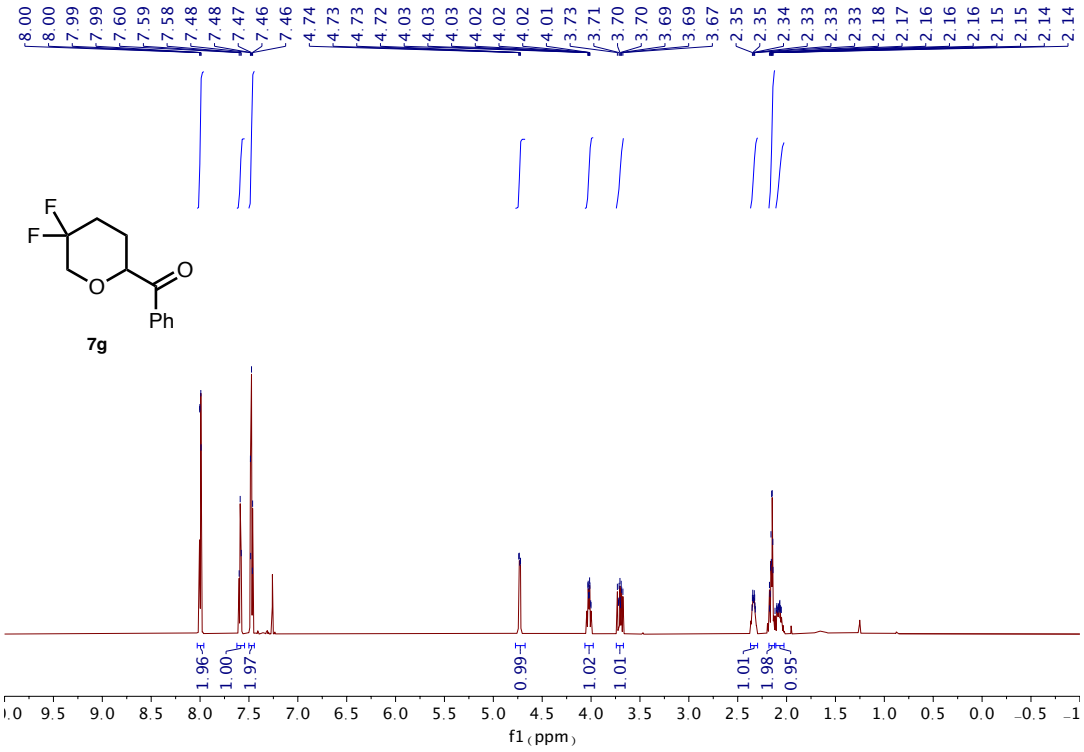

196.33
143.78
136.25
135.21
133.69
129.76
129.12
128.33
127.60
68.47
66.96
57.61
42.46
21.77
f1 (ppm)

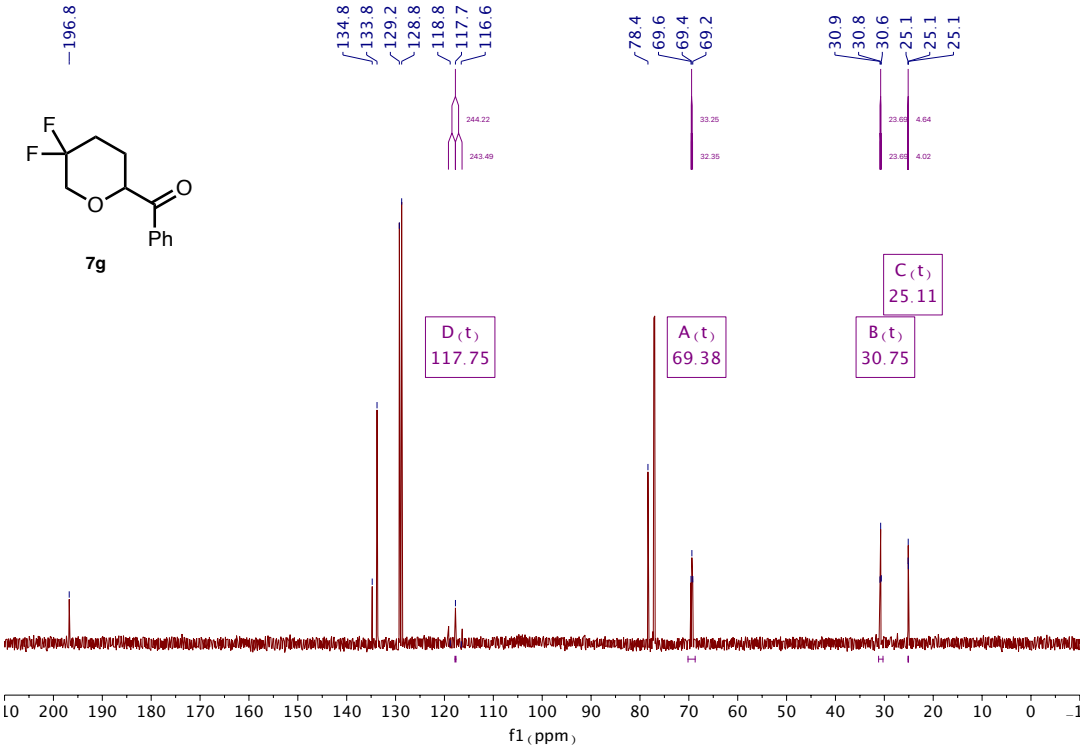

7.99 7.99 7.98 7.97 7.56 7.55 7.55 7.54 7.54 7.47 7.47 7.46 7.45 7.45
4.39 4.39 4.38 4.38 2.76 2.75 2.75 2.74 2.73 2.73 2.72 2.71 2.12 2.12 2.11 2.11 2.10 2.10 2.10 2.10 2.09 2.09 2.08 2.08 2.07 1.90 1.89 1.81 1.60 1.58 1.56
S
O
Ph
1.98 1.00 1.98 1.11 1.07 1.01 3.10 1.08 1.08 1.02
f1 (ppm)

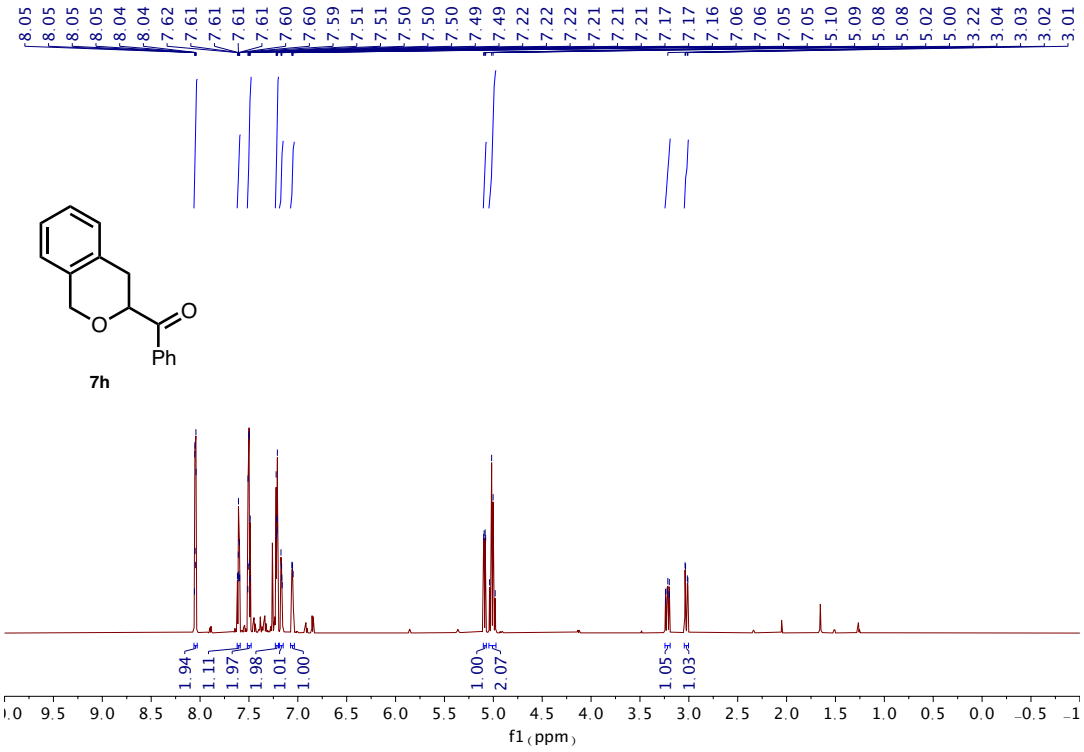
7d

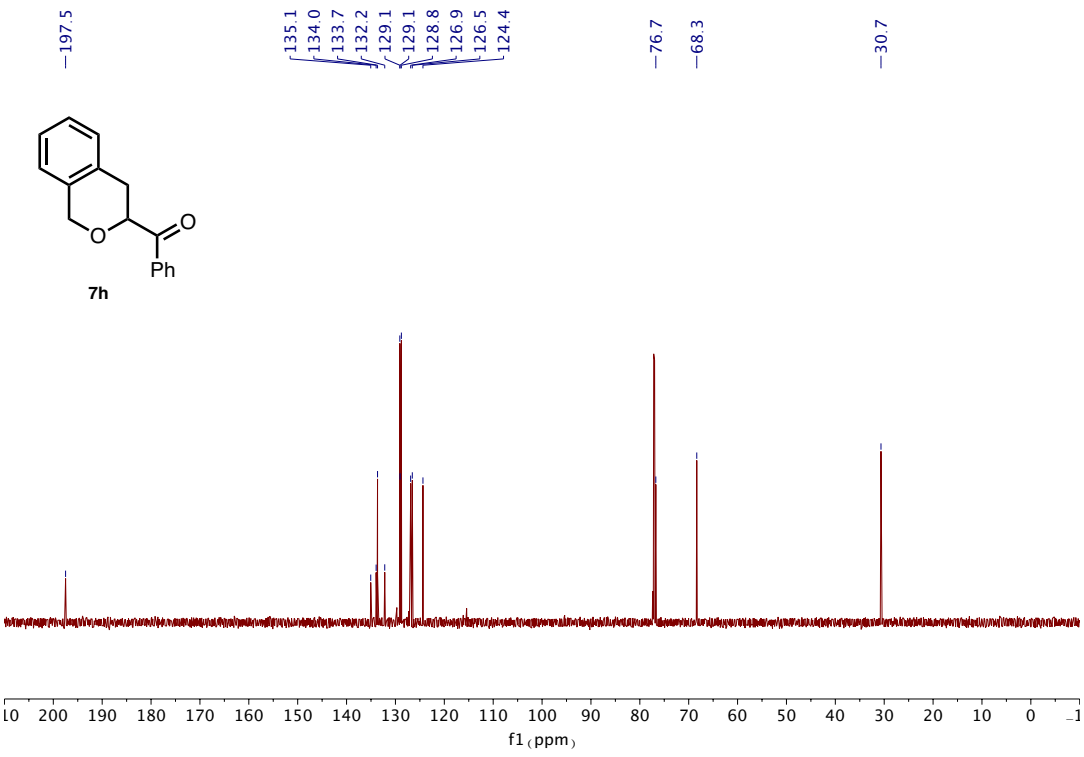

197.70
135.57 133.24 128.79 128.71
45.05
29.13 28.63 26.83 24.31
S
O
Ph
f1 (ppm)

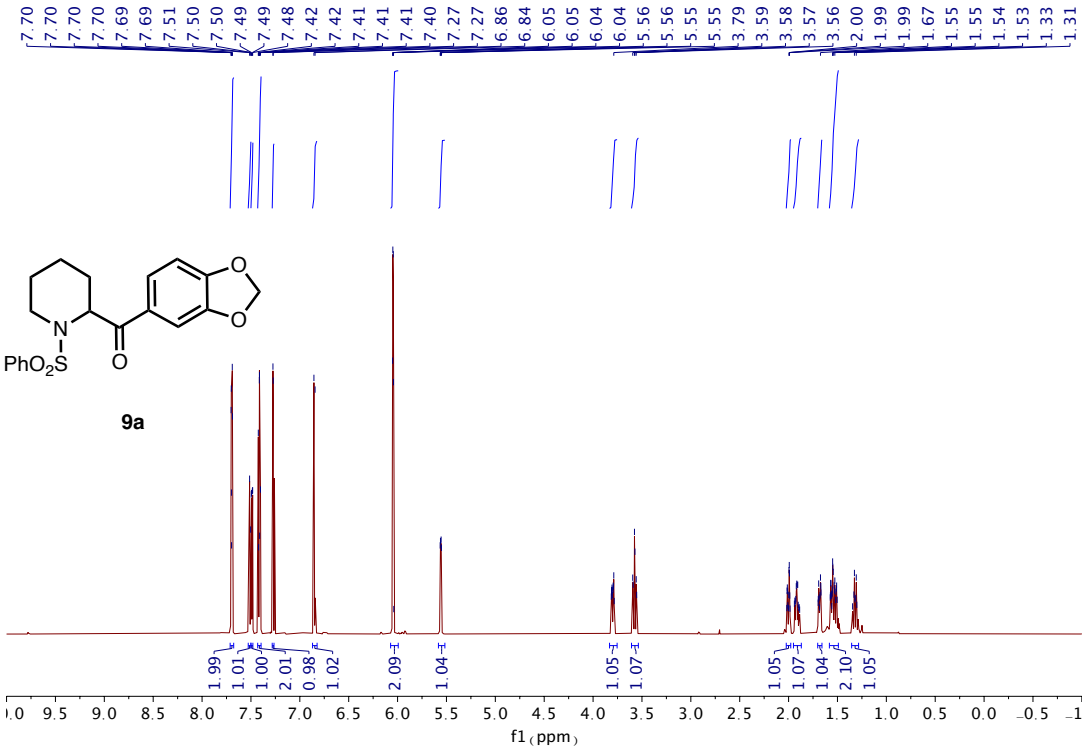
7d

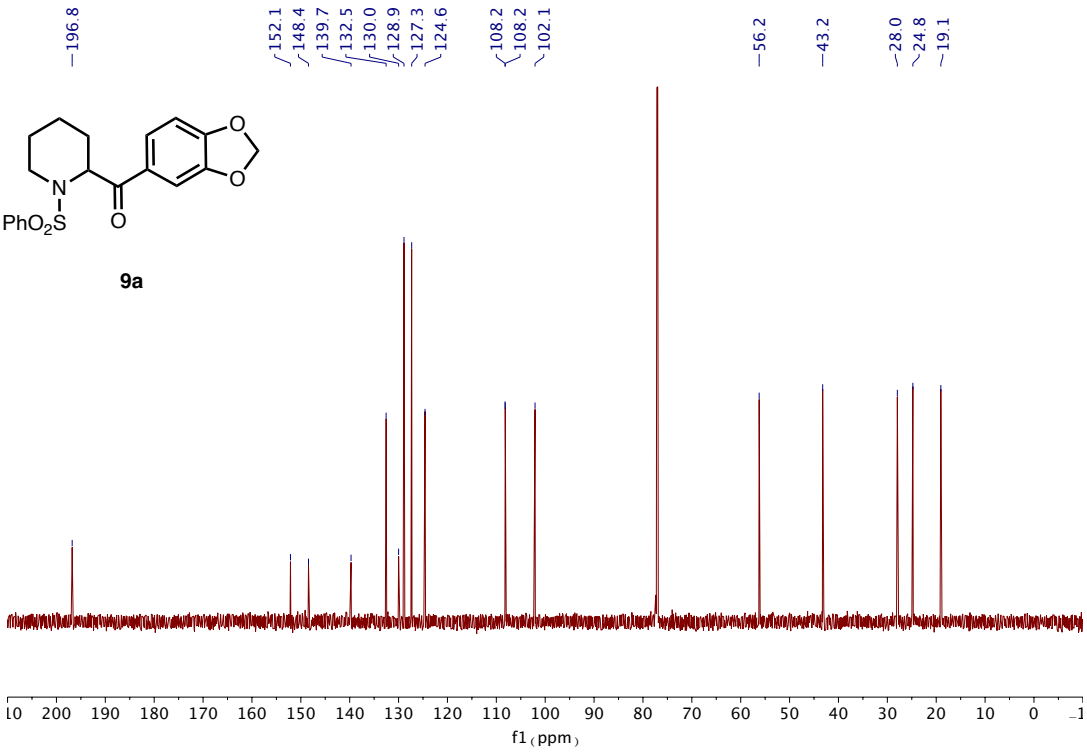

F
F
O
O
Ph
7g
f1 (ppm)

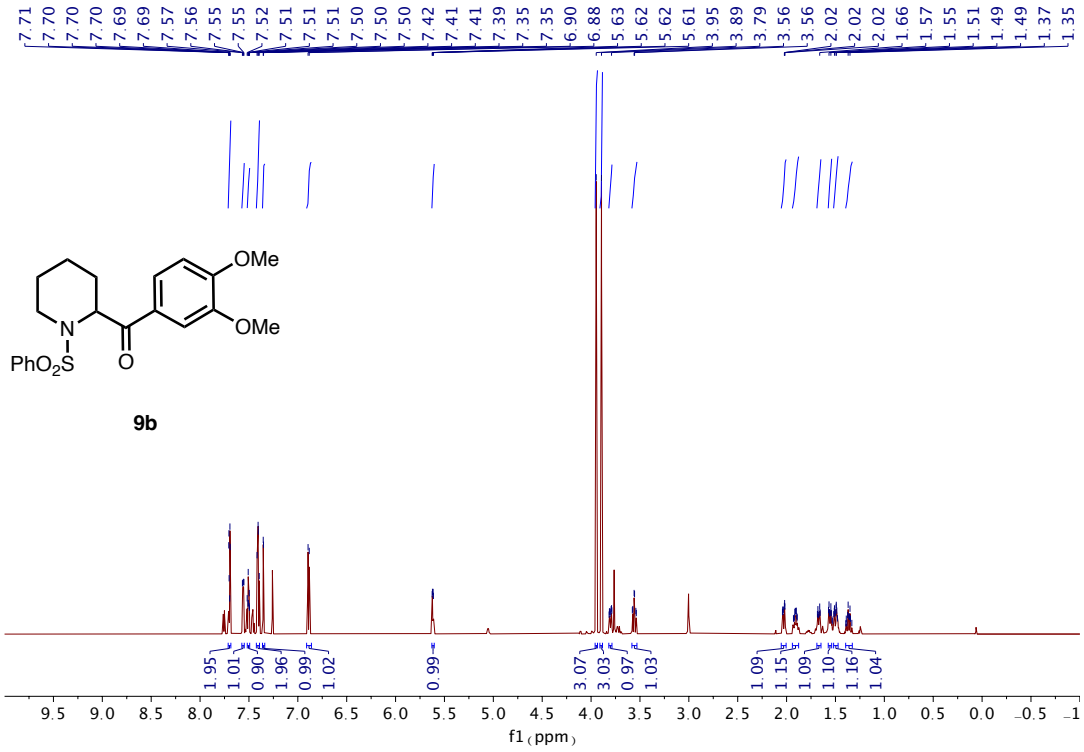

F
F
O
O
Ph
7g
D (t)
117.75
A (t)
69.38
B (t)
30.75
C (t)
25.11
f1 (ppm)


8.05 8.05 8.05 8.05 8.04 8.04 7.62 7.61 7.61 7.61 7.61 7.60 7.60 7.59 7.51 7.51 7.50 7.50 7.50 7.49 7.49 7.22 7.22 7.22 7.21 7.21 7.21 7.17 7.17 7.16 7.06 7.05 7.05 5.10 5.09 5.08 5.08 5.02 5.00 3.22 3.04 3.03 3.02 3.01
O
O
Ph
7h
1.94 1.11 1.97 1.98 1.01 1.00 1.00 2.07 1.05 1.03
f1 (ppm)

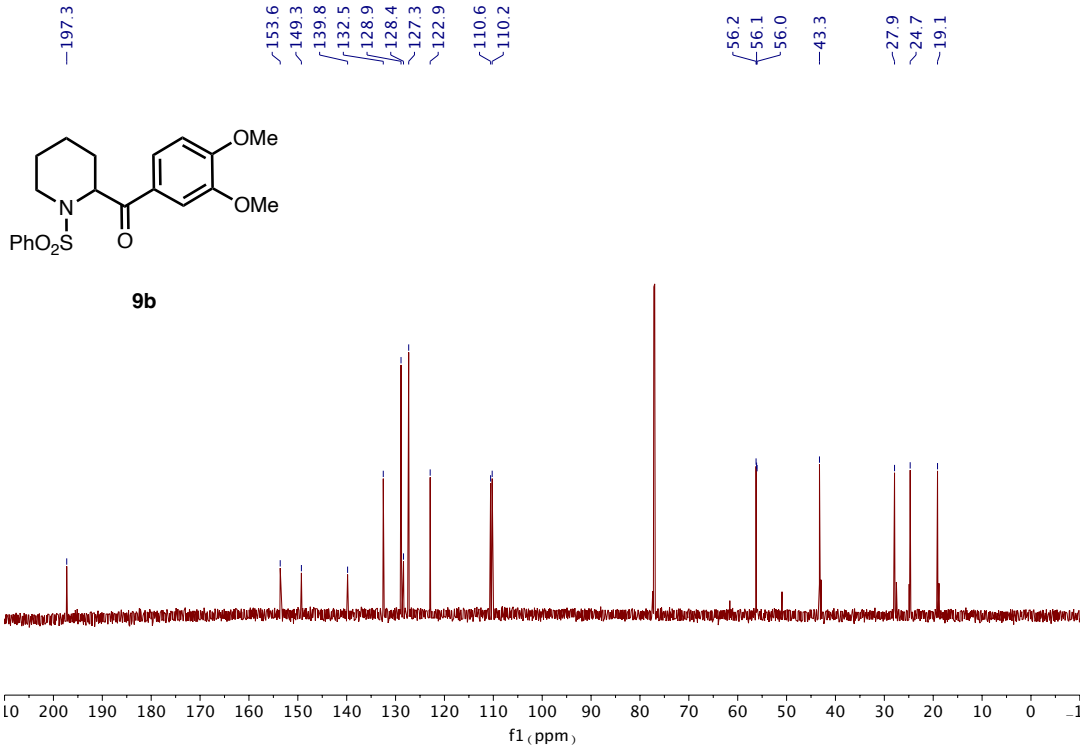

197.5
135.1 134.0 133.7 132.2 129.1 129.1 128.8 126.9 126.5 124.4
76.7
68.3
30.7
O
O
Ph
7h
f1 (ppm)


7.70 7.70 7.70 7.70 7.69 7.69 7.51 7.50 7.50 7.49 7.49 7.48 7.42 7.42 7.41 7.41 7.41 7.40 7.27 7.27 6.86 6.84 6.05 6.05 6.04 6.04 5.56 5.56 5.55 5.55 3.79 3.59 3.58 3.57 3.56 2.00 1.99 1.99 1.67 1.55 1.55 1.54 1.53 1.33 1.31
PhO2S
O
O
O
N
9a
1.99 1.01 1.00 2.01 0.98 1.02 2.09 1.04 1.05 1.07 1.05 1.07 1.04 2.10 1.05
f1 (ppm)

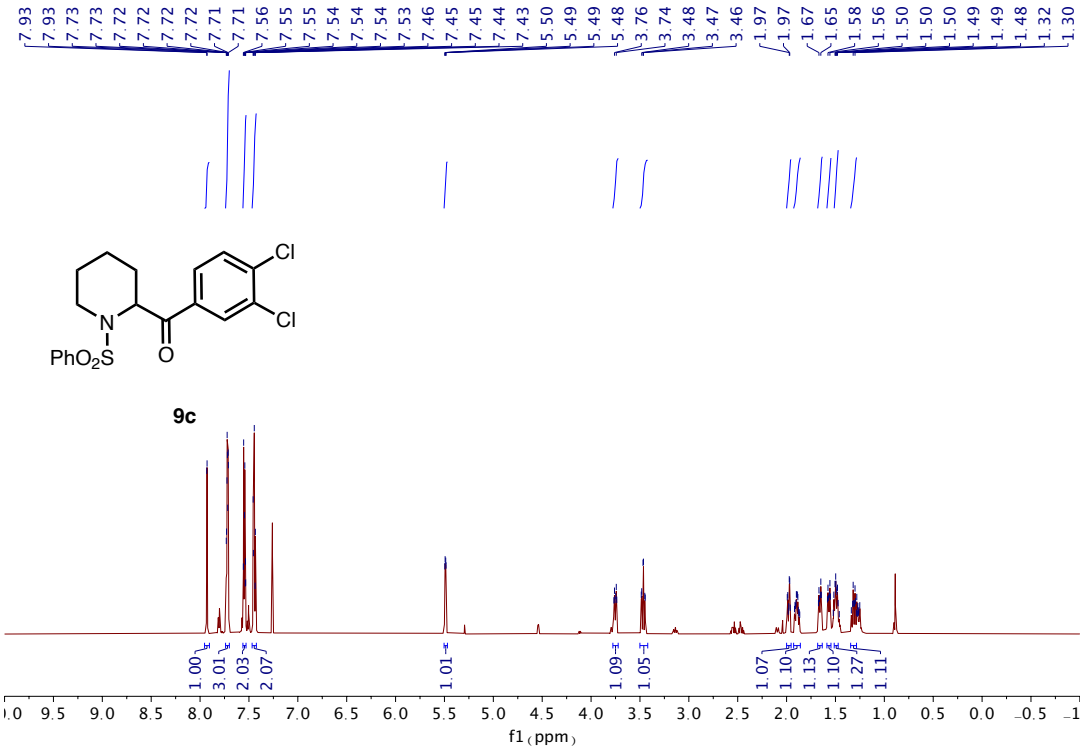

196.8
152.1 148.4 139.7 132.5 130.0 128.9 127.3 124.6 108.2 108.2 102.1
56.2 43.2 28.0 24.8 19.1
PhO2S
O
O
O
N
9a
f1 (ppm)

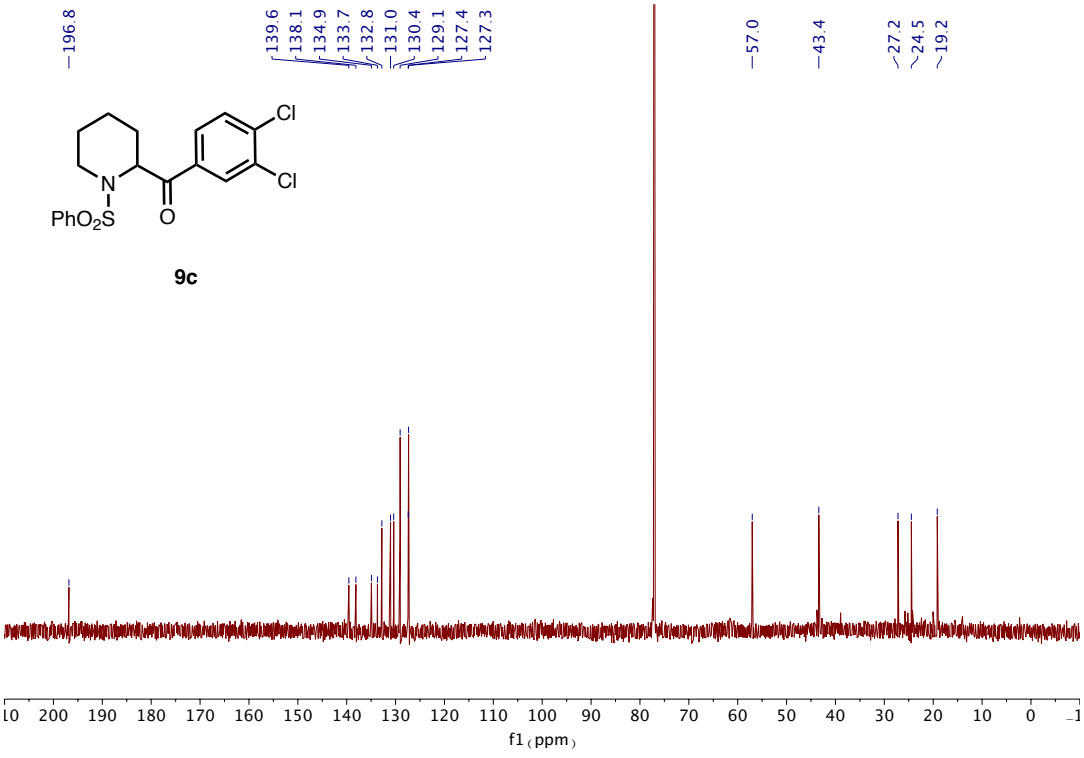

7.71 7.70 7.70 7.70 7.69 7.69 7.57 7.56 7.55 7.55 7.52 7.51 7.51 7.51 7.50 7.50 7.50 7.42 7.41 7.41 7.39 7.35 7.35 6.90 6.88 5.63 5.62 5.62 5.61 3.95 3.89 3.79 3.56 3.56 2.02 2.02 1.66 1.57 1.55 1.51 1.49 1.49 1.37 1.35
OMe
OMe
N
PhO2S
O
1.95 1.01 0.90 1.96 0.99 1.02 0.99 3.07 3.03 0.97 1.03 1.09 1.15 1.09 1.10 1.16 1.04
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

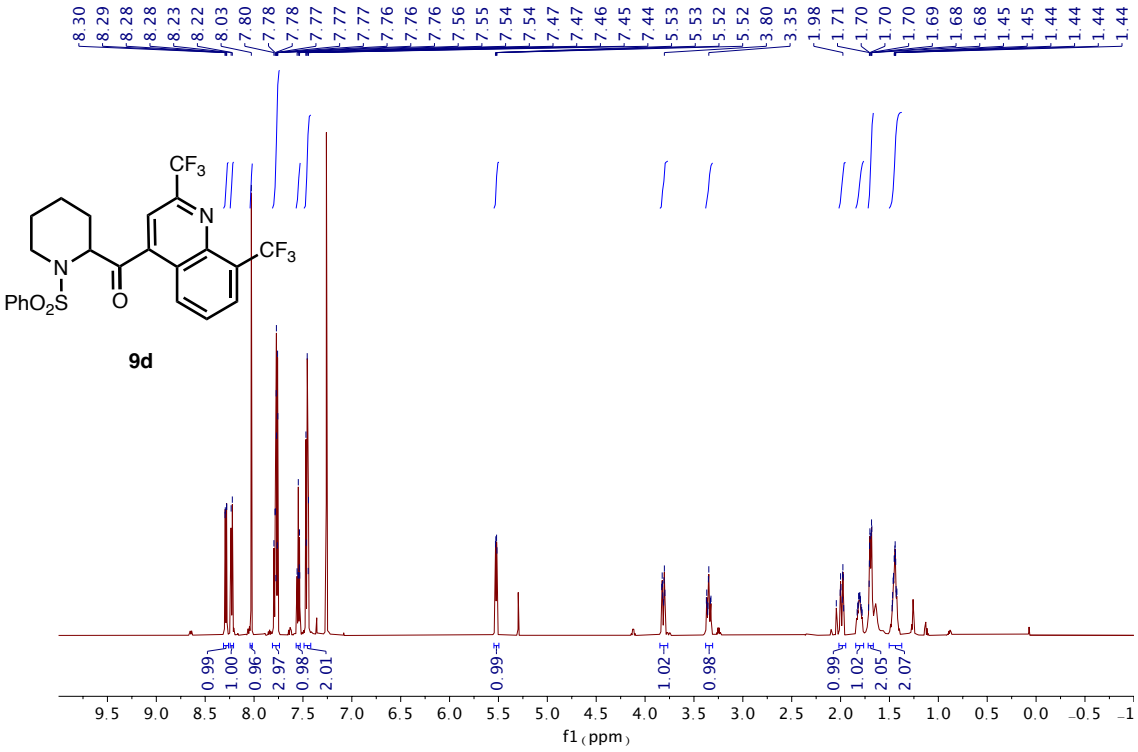
9b

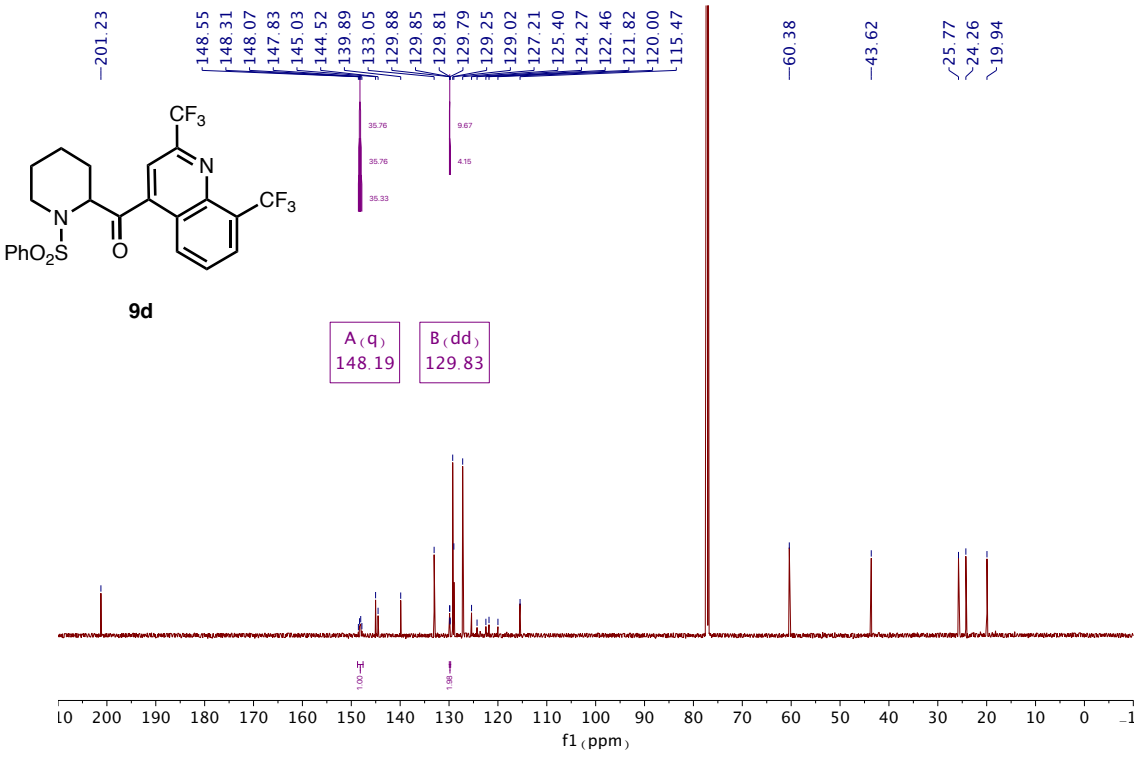

197.3
153.6 149.3 139.8 132.5 128.9 128.4 127.3 122.9 110.6 110.2
56.2 56.1 56.0 43.3 27.9 24.7 19.1
OMe
OMe
N
PhO2S
O
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

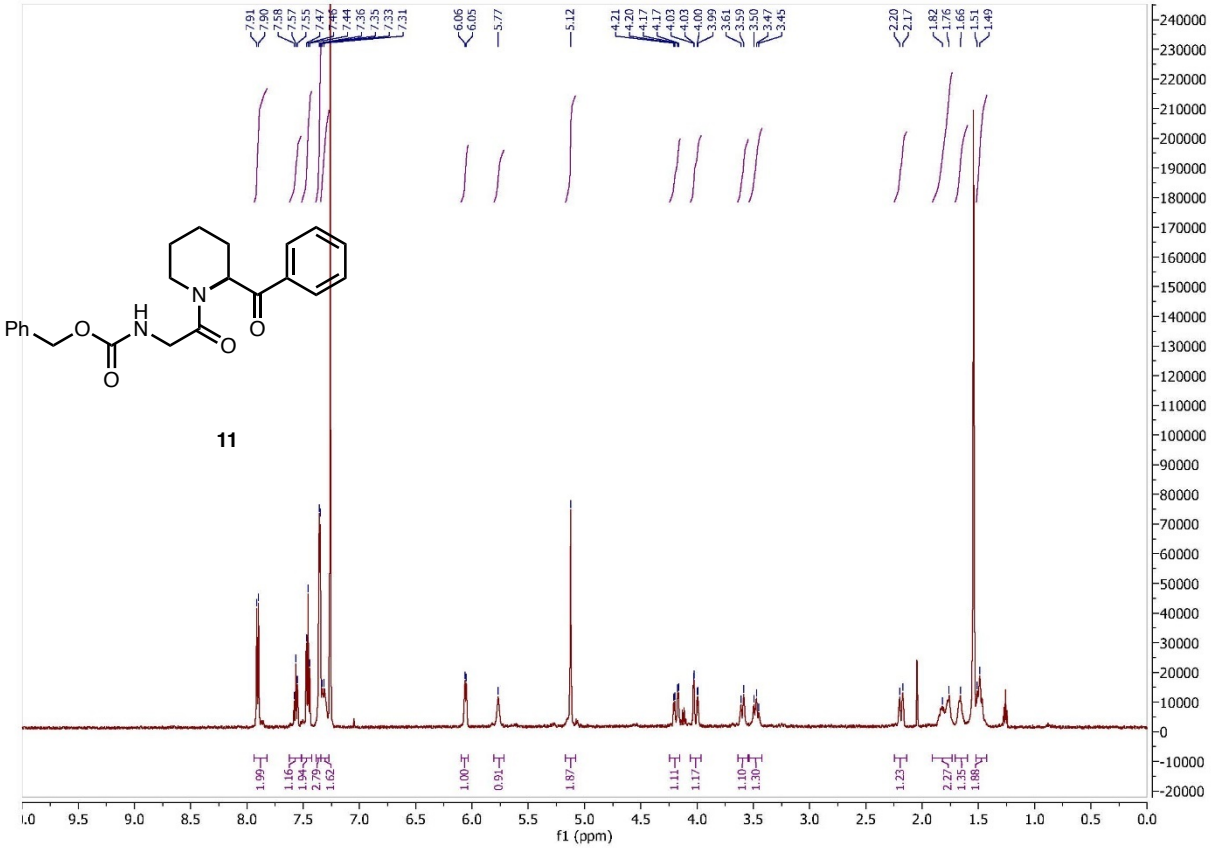
9b


7.93 7.93 7.73 7.73 7.72 7.72 7.72 7.72 7.71 7.71 7.56 7.55 7.55 7.54 7.54 7.54 7.53 7.46 7.45 7.45 7.44 7.43 5.50 5.49 5.49 5.48 3.76 3.74 3.48 3.47 3.46 1.97 1.97 1.67 1.65 1.58 1.56 1.50 1.50 1.50 1.49 1.49 1.48 1.32 1.30
Cl
Cl
N
PhO2S
O
9c
1.00 3.01 2.03 2.07 1.01 1.09 1.05 1.07 1.10 1.13 1.10 1.27 1.11
f1 (ppm)

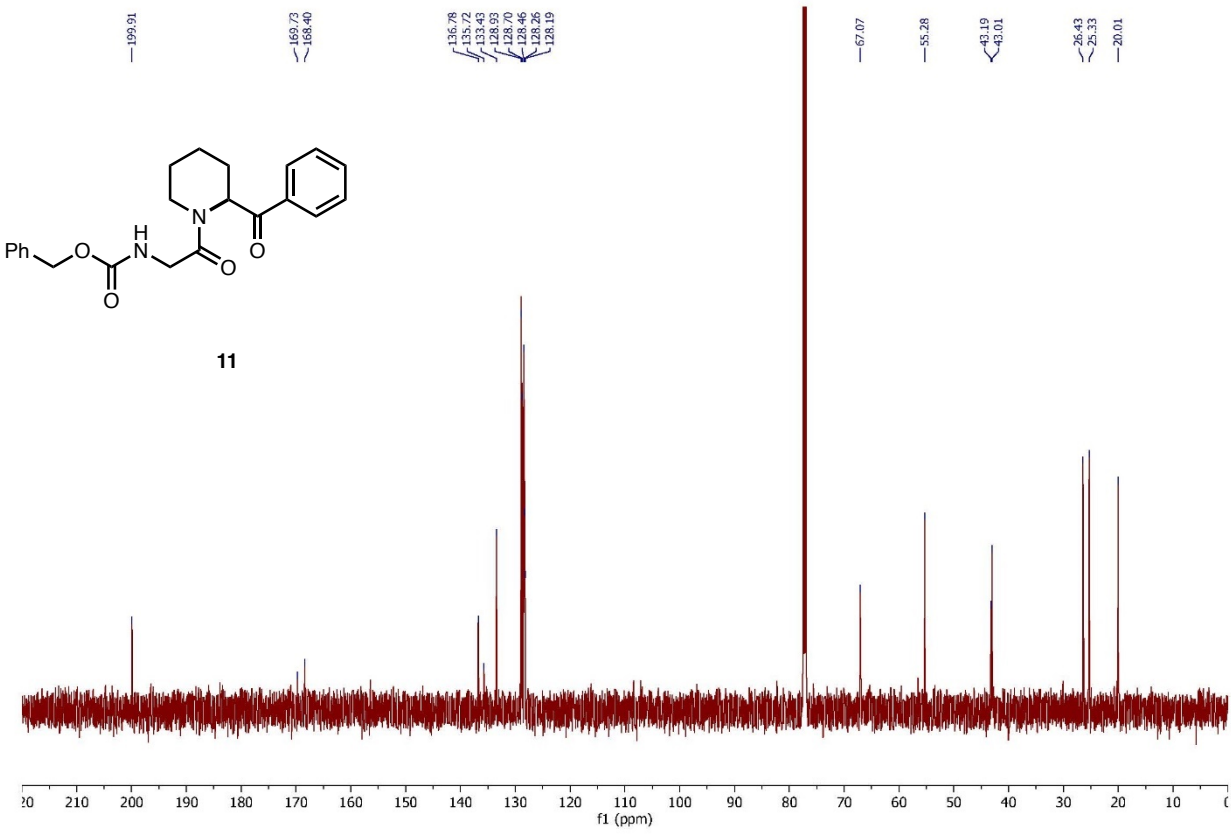

196.8
139.6 138.1 134.9 133.7 132.8 131.0 130.4 129.1 127.4 127.3
57.0
43.4
27.2 24.5 19.2
Cl
Cl
N
PhO2S
O
9c
f1 (ppm)


8.30 8.29 8.28 8.28 8.23 8.22 8.03 7.80 7.78 7.78 7.77 7.77 7.77 7.76 7.76 7.76 7.56 7.55 7.54 7.54 7.47 7.47 7.46 7.45 7.44 5.53 5.53 5.52 5.52 3.80 3.35 1.98 1.71 1.70 1.70 1.70 1.69 1.68 1.68 1.45 1.45 1.44 1.44 1.44 1.44
CF3
N
CF3
N
PhO2S
O
9d
0.99 1.00 0.96 2.97 0.98 2.01 0.99 1.02 0.98 0.99 1.02 2.05 2.07
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

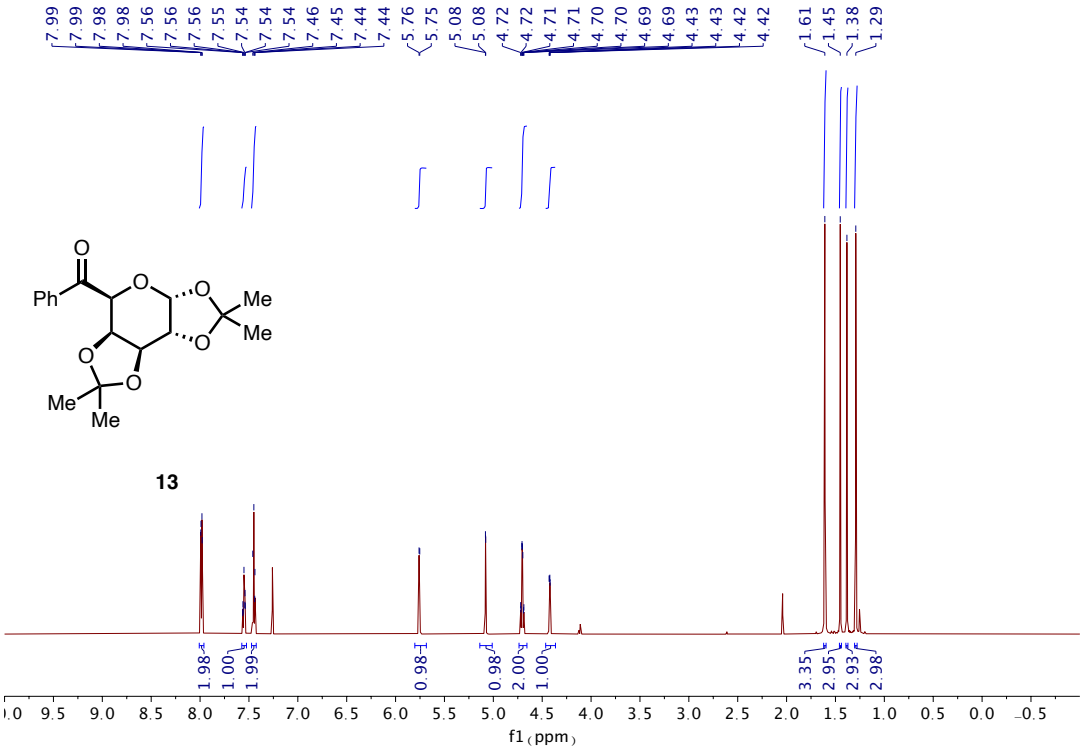

201.23
148.55 148.31 148.07 147.83 145.03 144.52 139.89 133.05 129.88 129.85 129.81 129.79 129.25 129.02 127.21 125.40 124.27 122.46 121.82 120.00 115.47
60.38
43.62
25.77 24.26 19.94
35.76 35.76 35.33 9.67 4.15
CF3
N
CF3
N
PhO2S
O
9d
A (q) 148.19
B (dd) 129.83
1.00 1.88
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

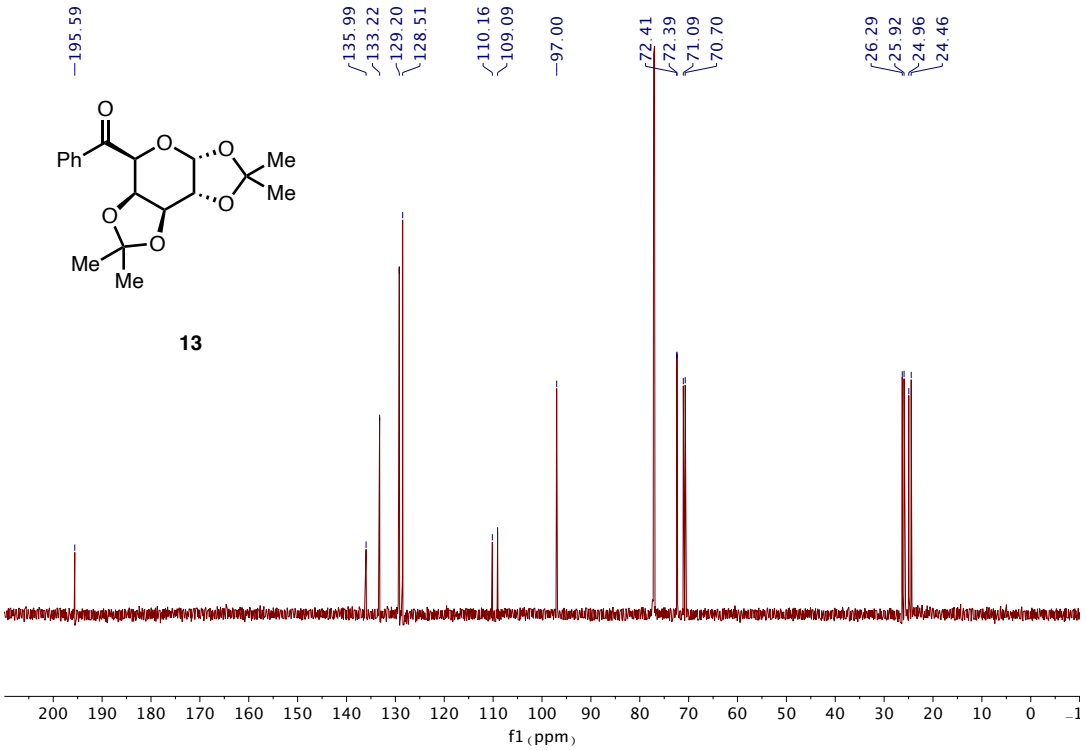

7.91
7.90
7.58
7.57
7.55
7.47
7.46
7.44
7.36
7.35
7.33
7.31
6.06
6.05
5.77
5.12
4.21
4.20
4.17
4.17
4.03
4.03
4.00
3.99
3.61
3.59
3.50
3.47
3.45
2.20
2.17
1.82
1.76
1.66
1.51
1.49
1.99
1.16
1.94
2.79
1.62
1.00
0.91
1.87
1.11
1.17
1.10
1.30
1.23
2.27
1.35
1.88
f1 (ppm)

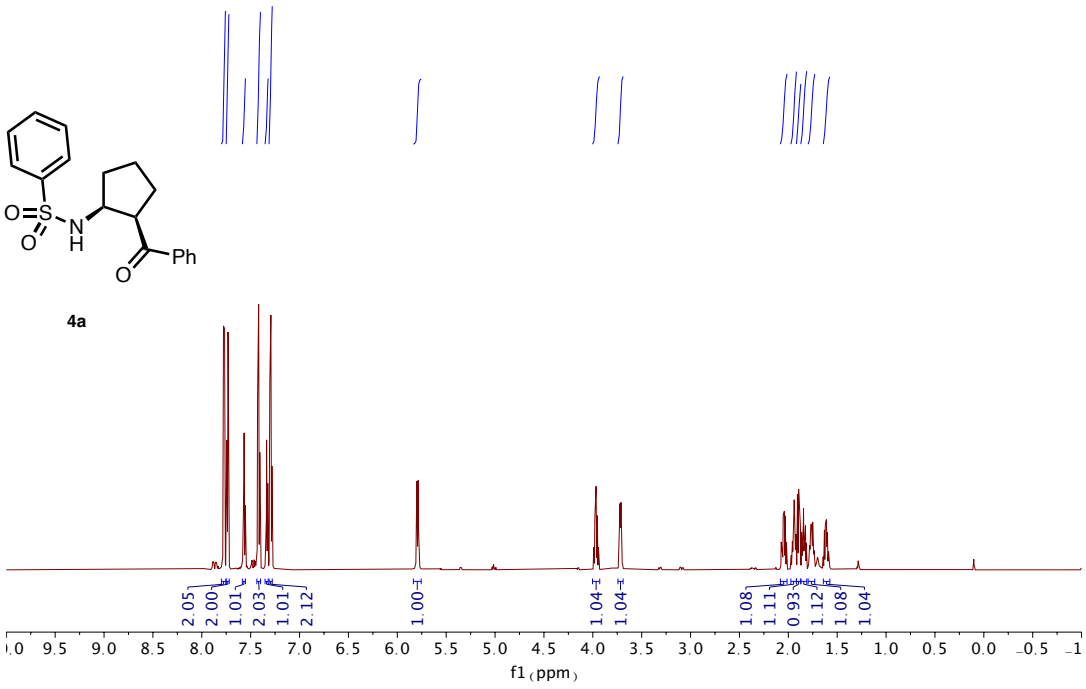
11

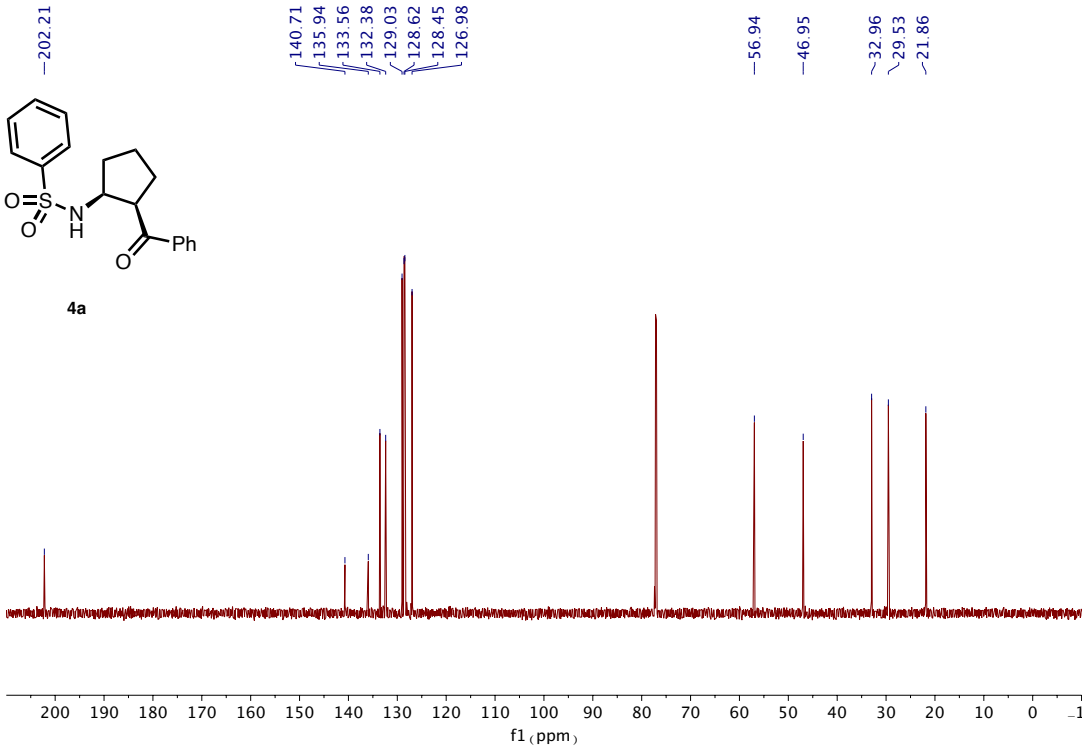

199.91
169.73
168.40
136.78
135.72
133.43
128.93
128.70
128.46
128.26
128.19
67.07
55.28
43.19
43.01
26.43
25.33
20.01
f1 (ppm)

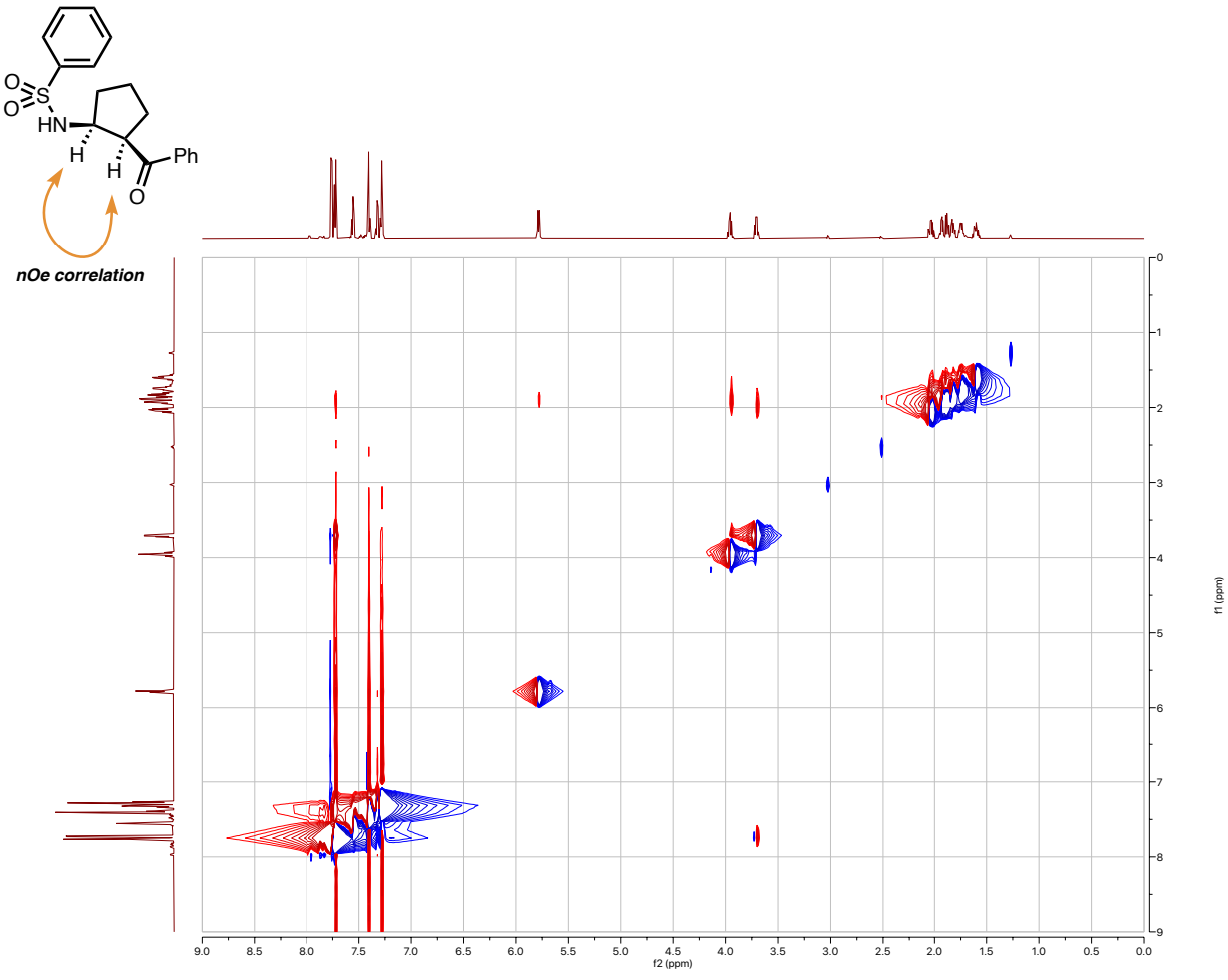
11

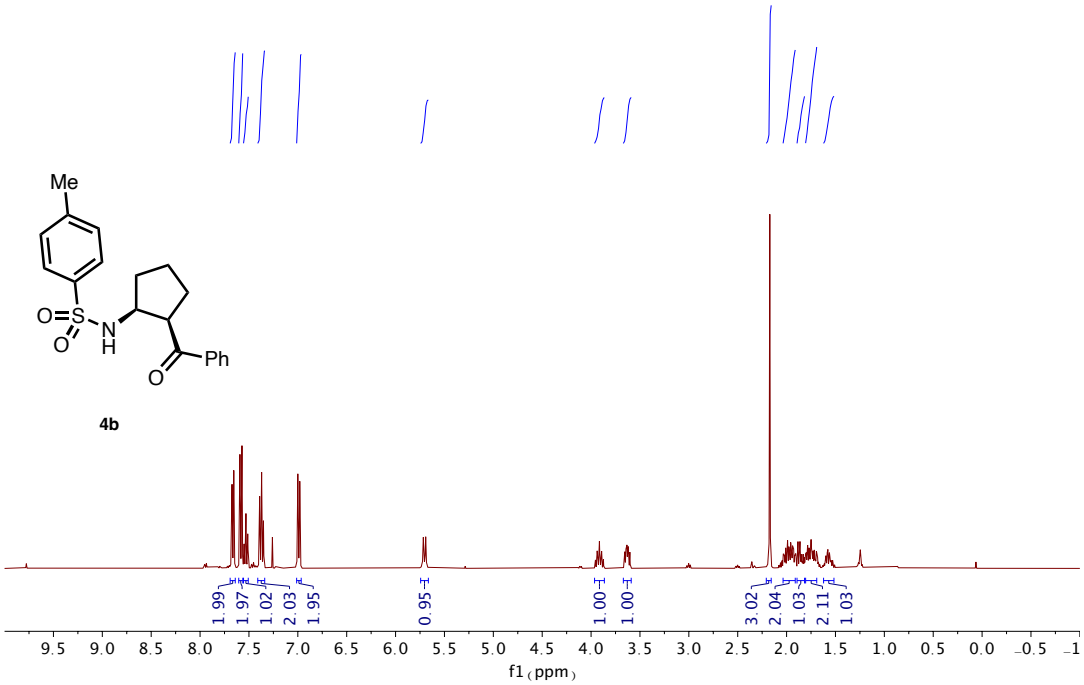

7.99
7.99
7.98
7.98
7.56
7.56
7.56
7.55
7.54
7.54
7.54
7.46
7.45
7.44
7.44
5.76
5.75
5.08
5.08
4.72
4.72
4.71
4.71
4.70
4.70
4.69
4.69
4.43
4.43
4.42
4.42
1.61
1.45
1.38
1.29
Ph
O
O
O
O
O
O
Me
Me
Me
Me
13
1.98
1.00
1.99
0.98
0.98
2.00
1.00
3.35
2.95
2.93
2.98
f1 (ppm)

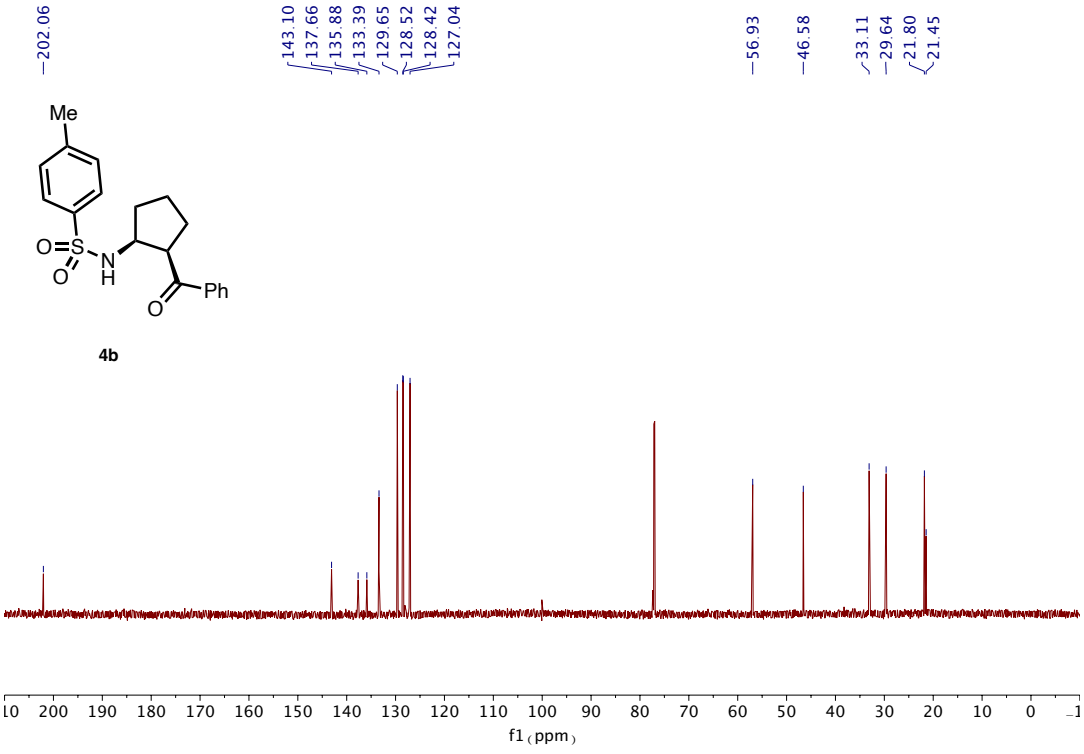

195.59
135.99
133.22
129.20
128.51
110.16
109.09
97.00
72.41
72.39
71.09
70.70
26.29
25.92
24.96
24.46
Ph
O
O
O
O
O
O
Me
Me
Me
Me
13
f1 (ppm)

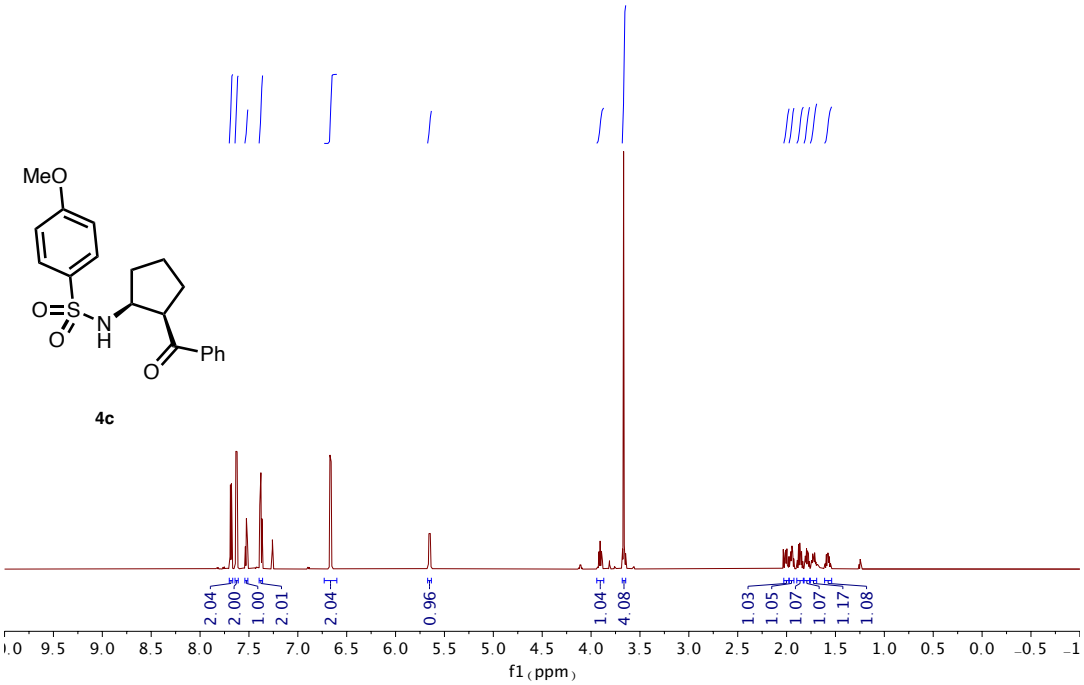

4a
2.05
2.00
1.01
2.03
1.01
2.12
1.00
1.04
1.04
1.08
1.11
0.93
1.12
1.08
1.04
f1 (ppm)

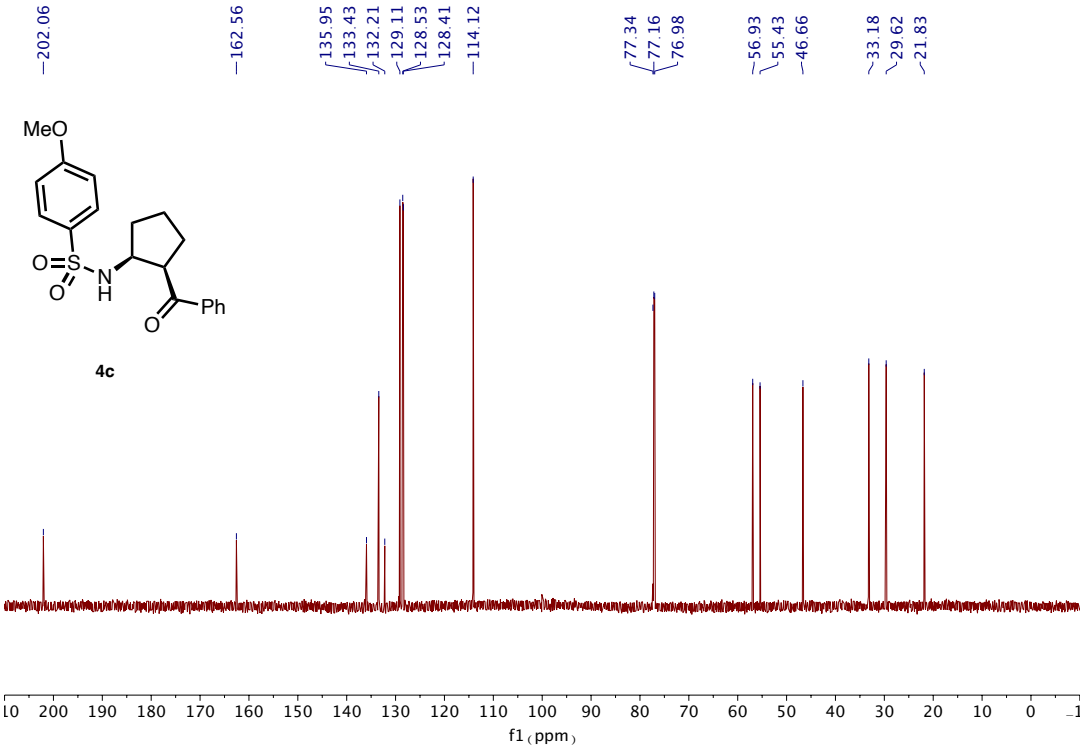

202.21
140.71
135.94
133.56
132.38
129.03
128.62
128.45
126.98
56.94
46.95
32.96
29.53
21.86
4a
f1 (ppm)

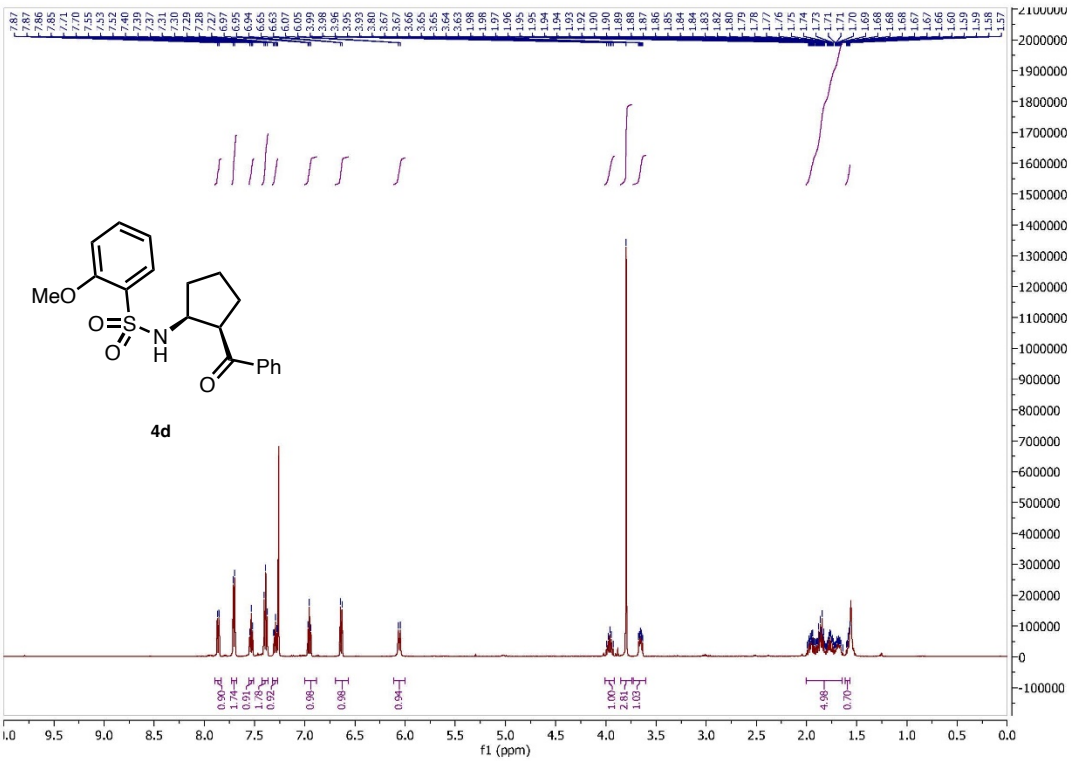

O
O
S
HN
H
H
Ph
O
nOe correlation
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)
f1 (ppm)

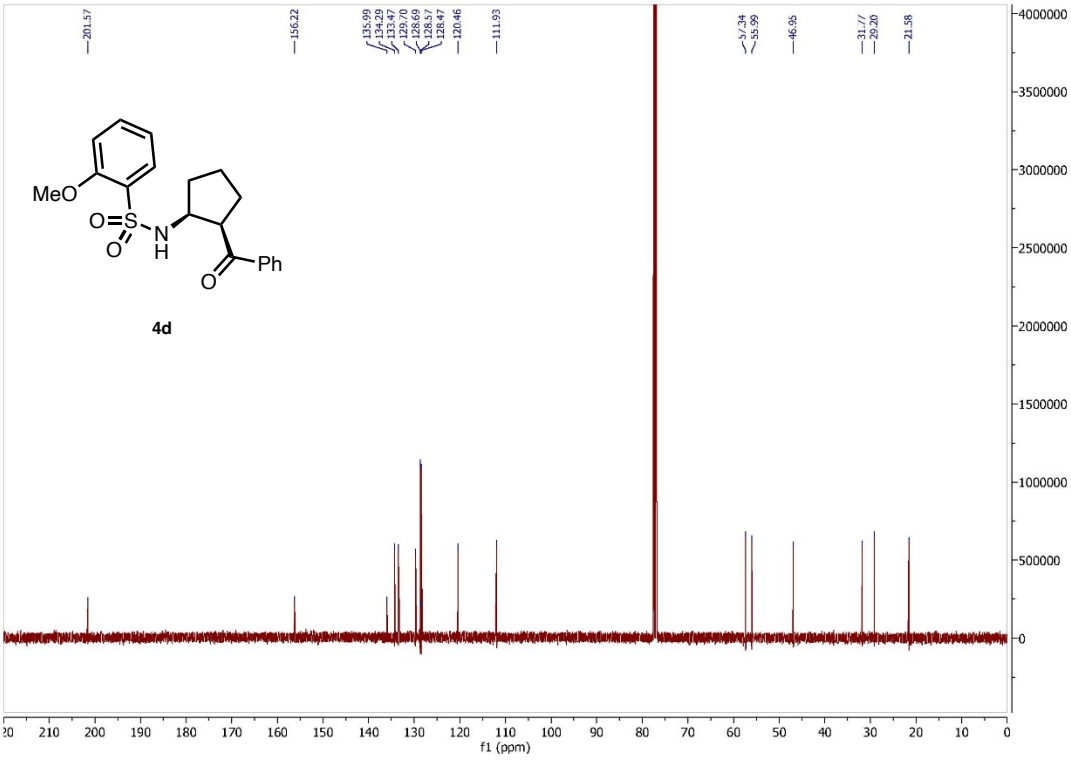

Me
O=S
O
N
H
Ph
O
4b
1.99
1.97
1.02
2.03
1.95
0.95
1.00
1.00
3.02
2.04
1.03
2.11
1.03
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5 −1
f1 (ppm)

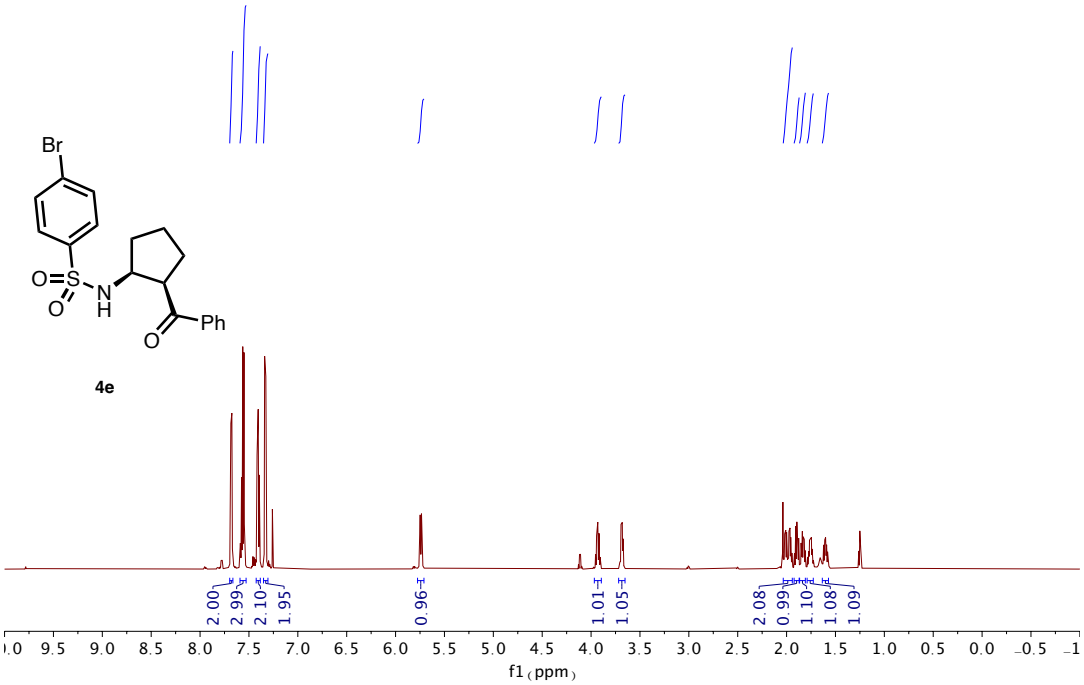

202.06
143.10
137.66
135.88
133.39
129.65
128.52
128.42
127.04
56.93
46.58
33.11
29.64
21.80
21.45
Me
O=S
O
N
H
Ph
O
4b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −1
f1 (ppm)

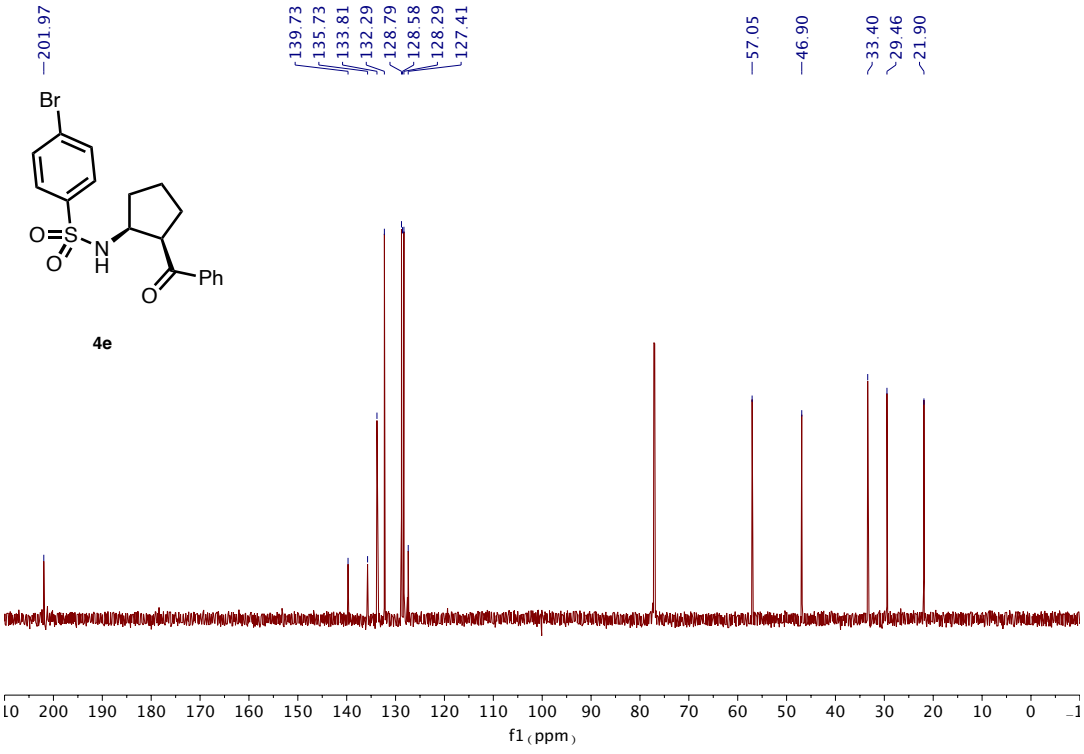

MeO
O=S
O
N
H
Ph
O
4c
2.04
2.00
1.00
2.01
2.04
0.96
1.04
4.08
1.03
1.05
1.07
1.07
1.17
1.08
f1 (ppm)

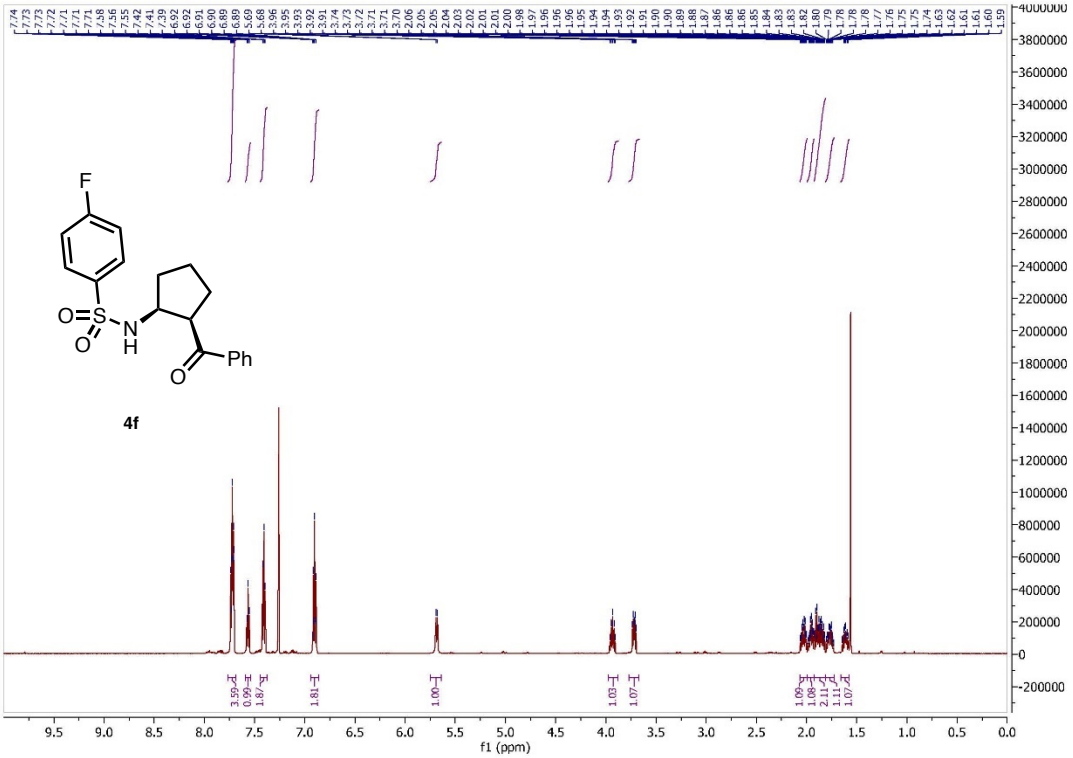

202.06
162.56
135.95
133.43
132.21
129.11
128.53
128.41
114.12
77.34
77.16
76.98
56.93
55.43
46.66
33.18
29.62
21.83
MeO
O=S
O
N
H
Ph
O
4c
f1 (ppm)

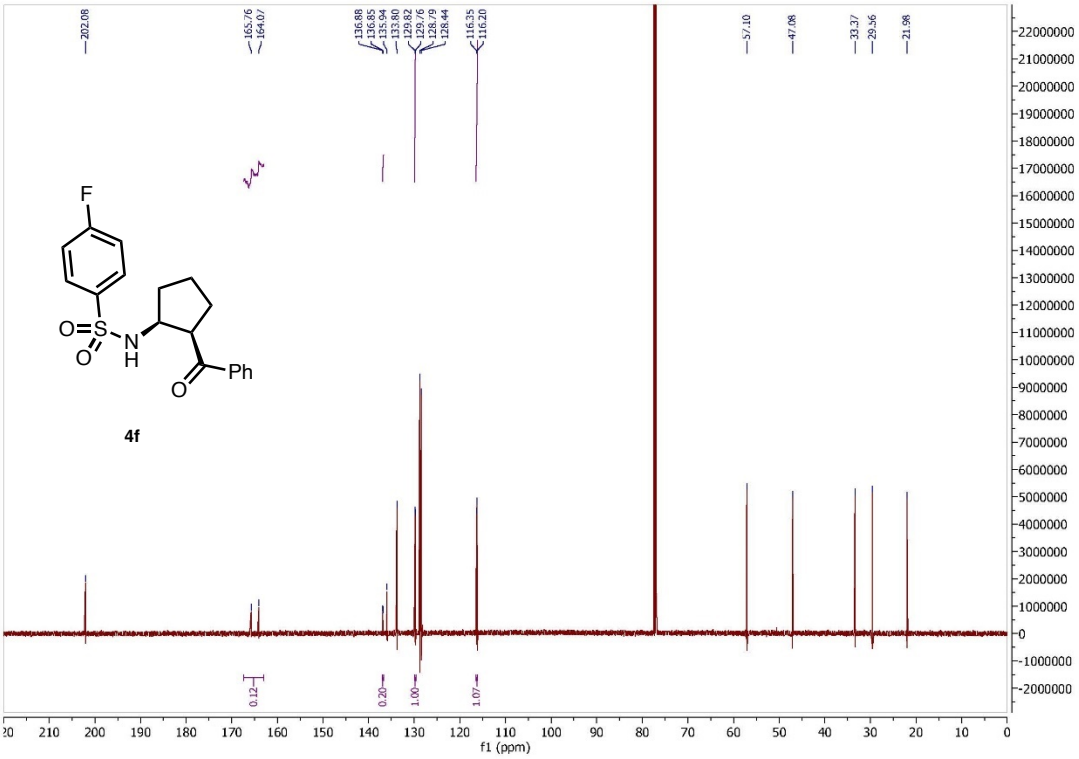

MeO
O
S
O
N
H
O
Ph
4d
f1 (ppm)

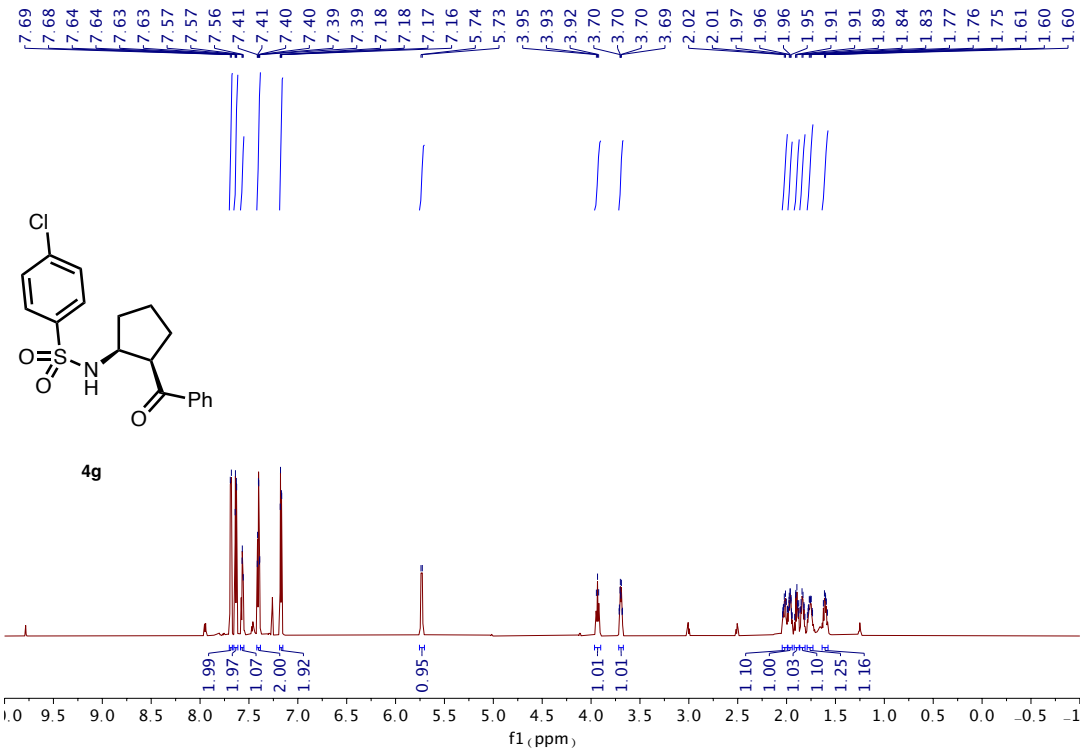

MeO
O
S
O
N
H
O
Ph
4d
f1 (ppm)

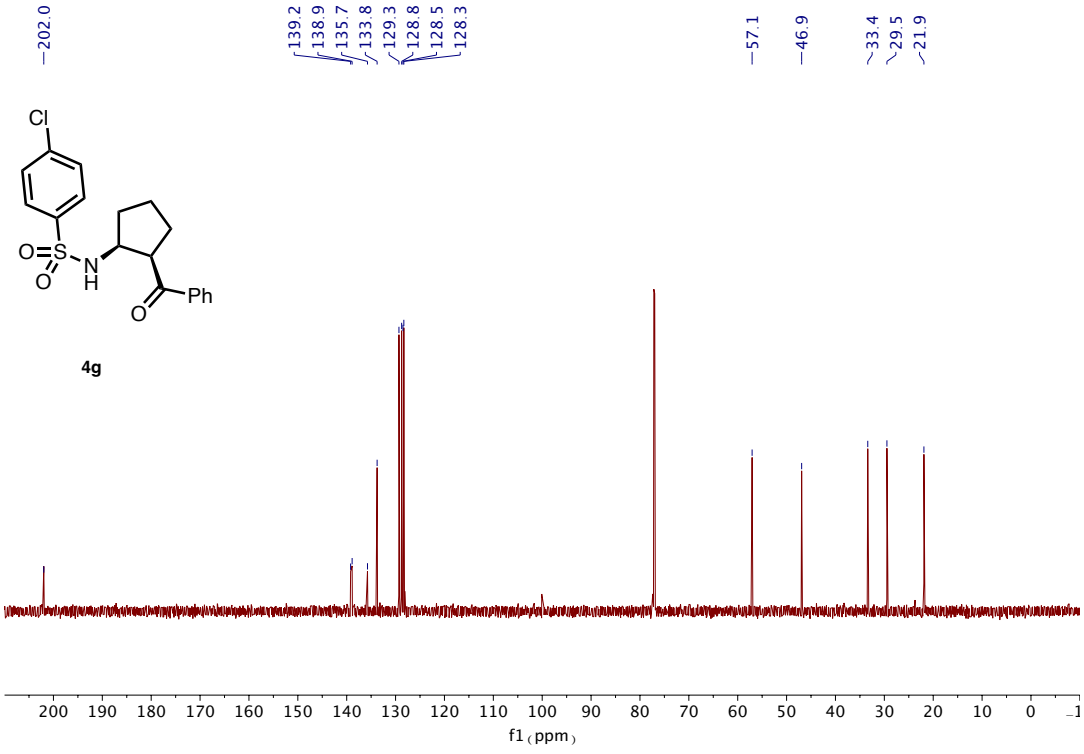

Br
O=S
O
N
H
O
Ph
4e
2.00
2.99
2.10
1.95
0.96
1.01
1.05
2.08
0.99
1.10
1.08
1.09
f1 (ppm)

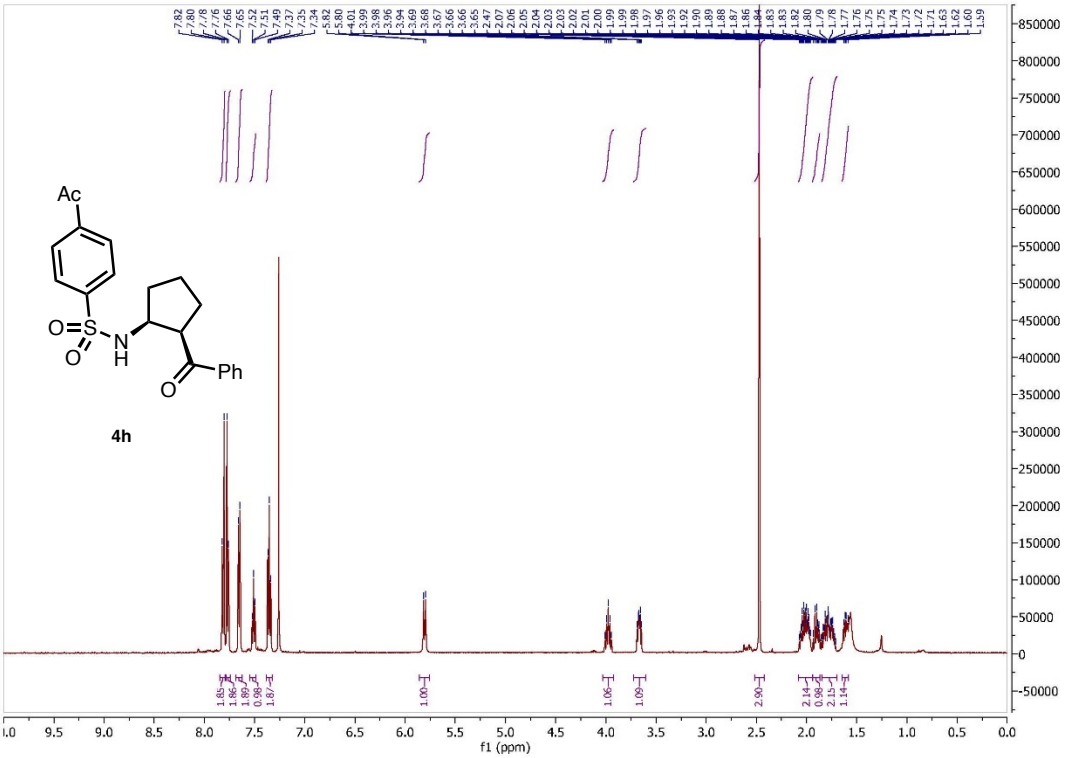

201.97
139.73
135.73
133.81
132.29
128.79
128.58
128.29
127.41
57.05
46.90
33.40
29.46
21.90
Br
O=S
O
N
H
O
Ph
4e
f1 (ppm)

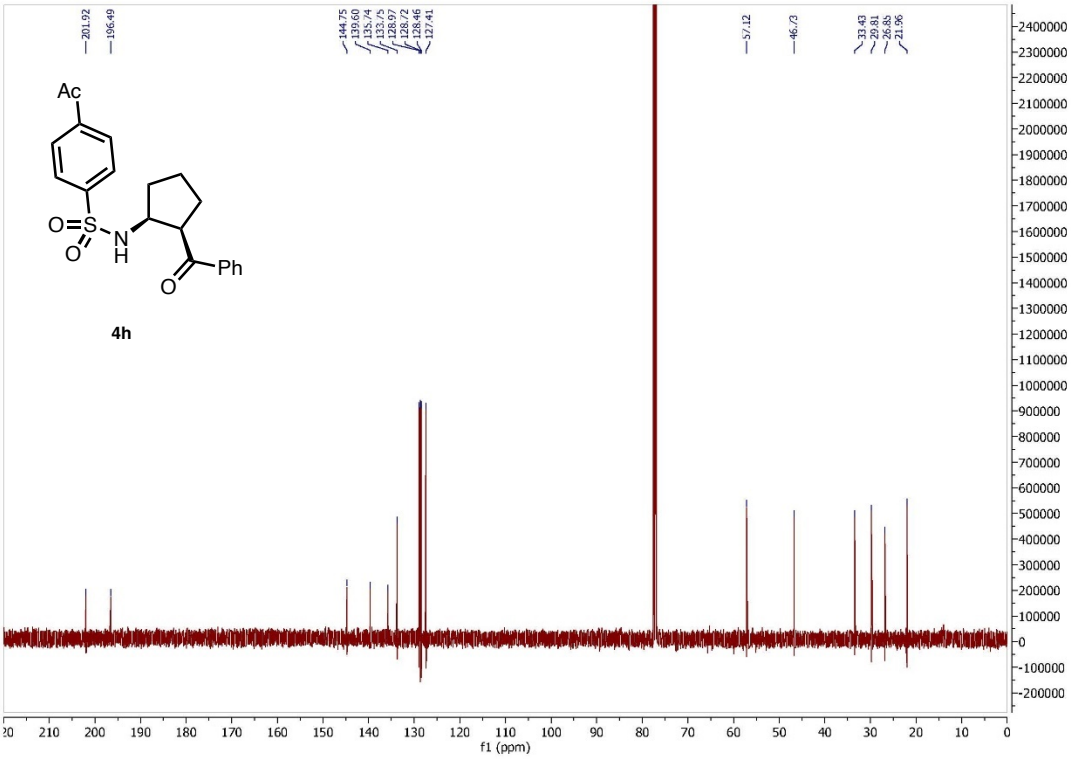

F
O
S
N
H
O
O
Ph
4f
f1 (ppm)

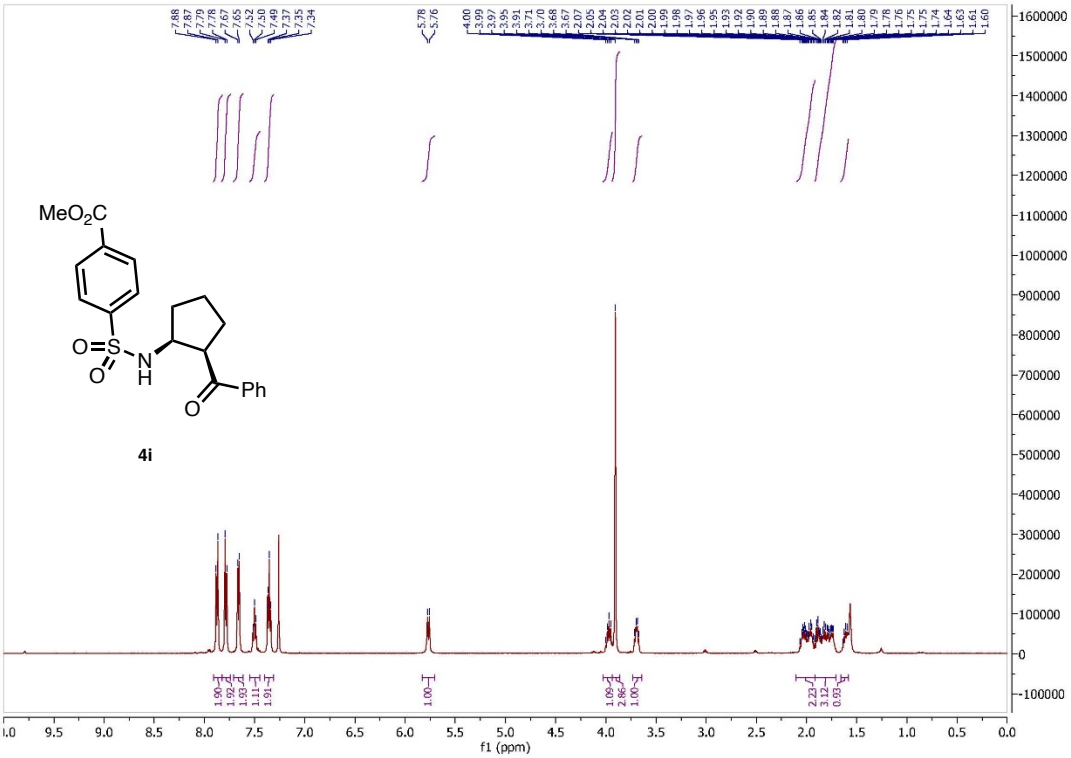

F
O
S
N
H
O
O
Ph
4f
f1 (ppm)

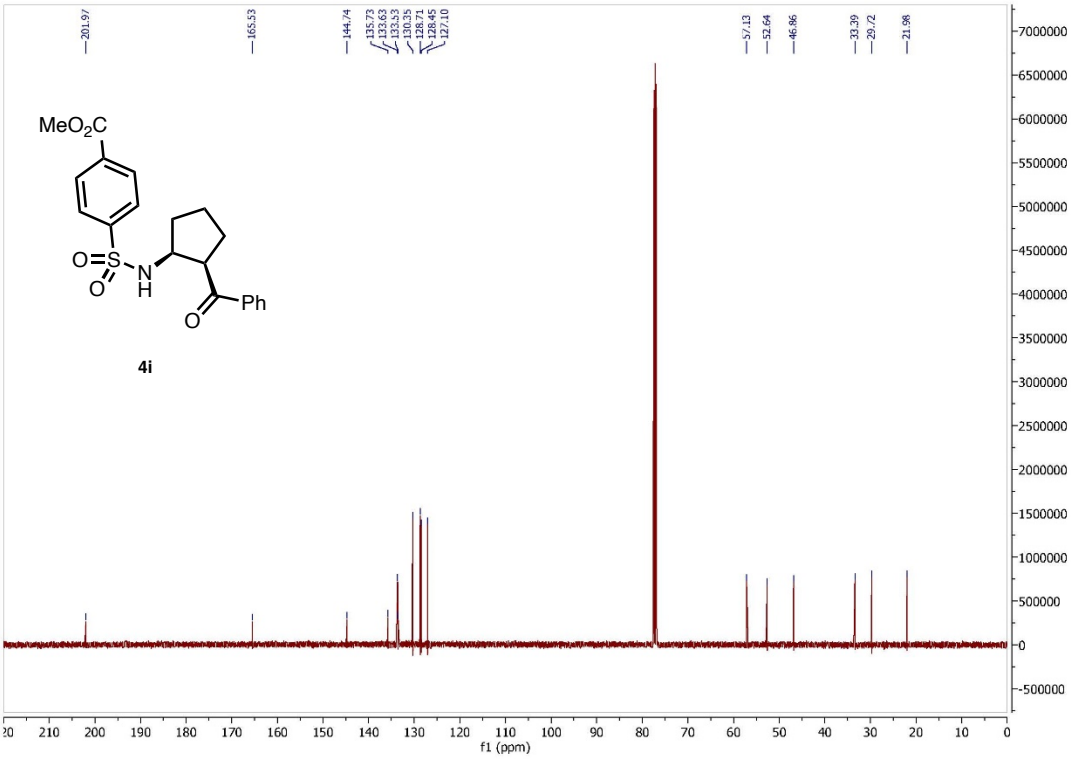

7.69
7.68
7.64
7.64
7.63
7.63
7.57
7.57
7.56
7.41
7.41
7.40
7.40
7.39
7.39
7.18
7.18
7.17
7.16
5.74
5.73
3.95
3.93
3.92
3.70
3.70
3.70
3.69
2.02
2.01
1.97
1.96
1.96
1.95
1.91
1.91
1.89
1.84
1.83
1.77
1.76
1.75
1.61
1.60
1.60
Cl
O
S
O
N
H
O
Ph
4g
1.99
1.97
1.07
2.00
1.92
0.95
1.01
1.01
1.10
1.00
1.03
1.10
1.25
1.16
f1 (ppm)

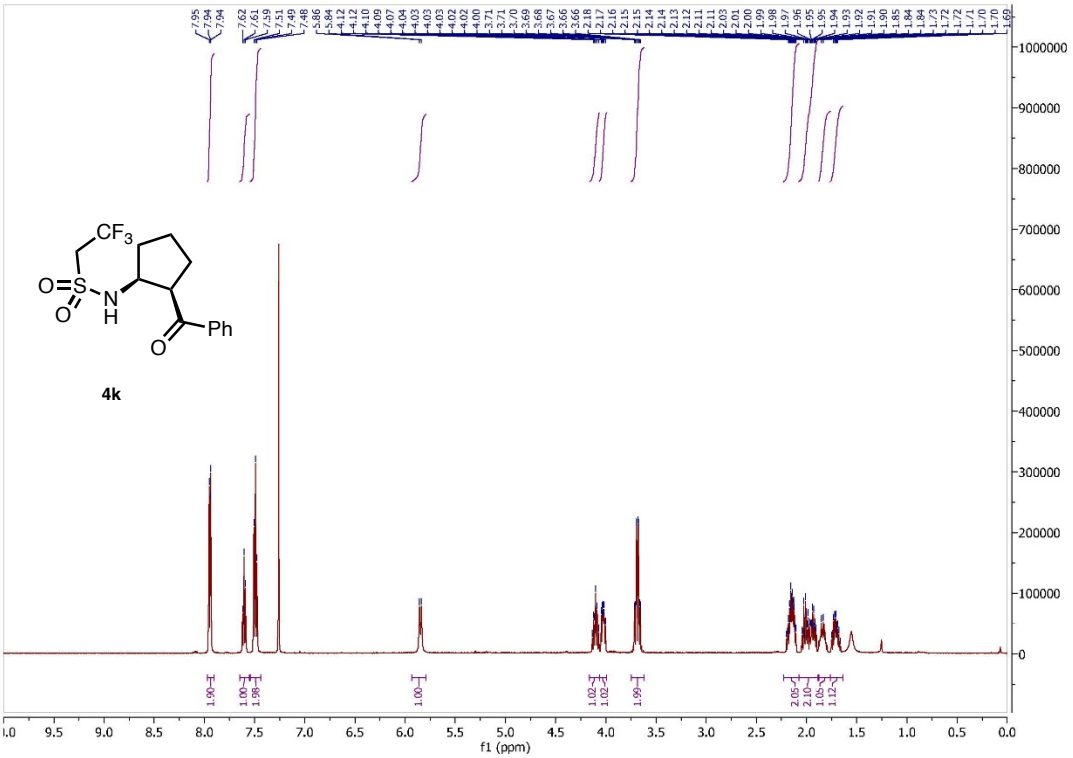

202.0
139.2
138.9
135.7
133.8
129.3
128.8
128.5
128.3
57.1
46.9
33.4
29.5
21.9
Cl
O
S
O
N
H
O
Ph
4g
f1 (ppm)

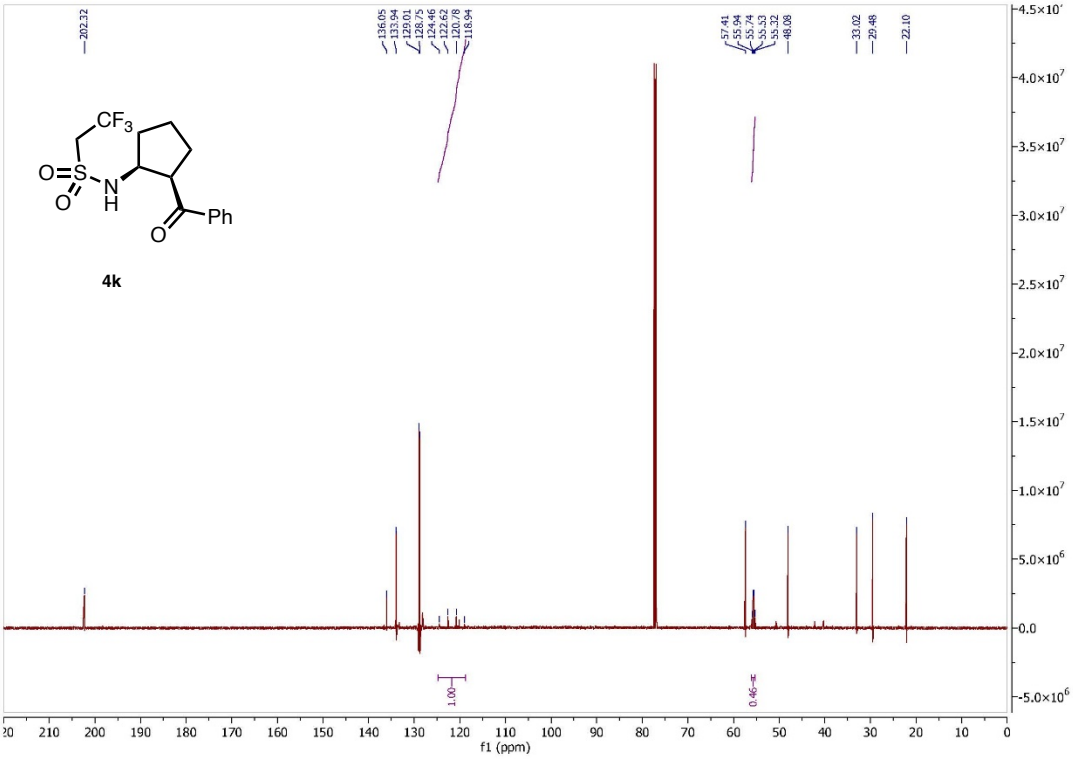

Ac
O=S
O
N
H
Ph
O
4h
f1 (ppm)

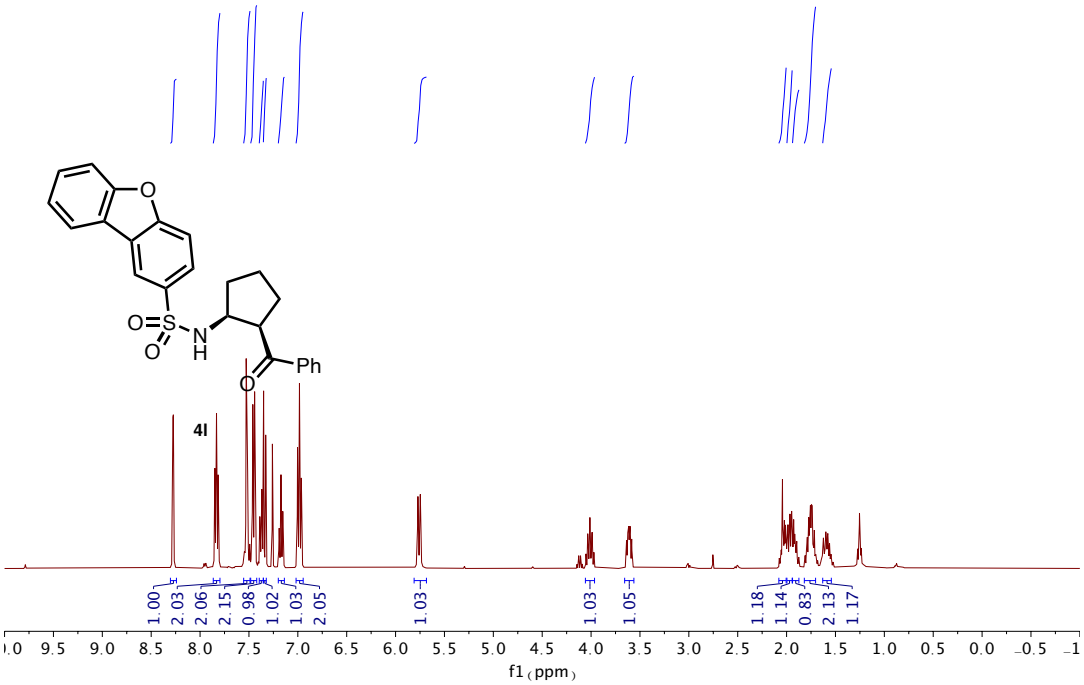

Ac
O=S
O
N
H
Ph
O
4h
f1 (ppm)

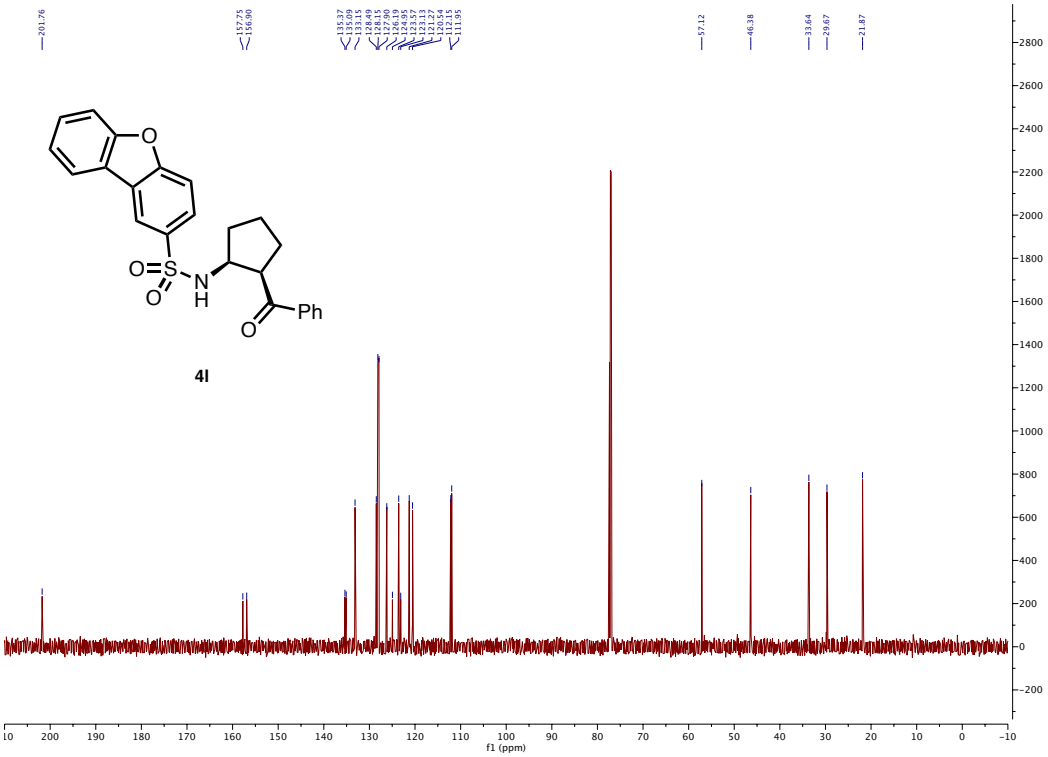

MeO2C
O
S
O
N
H
O
Ph
4i
f1 (ppm)

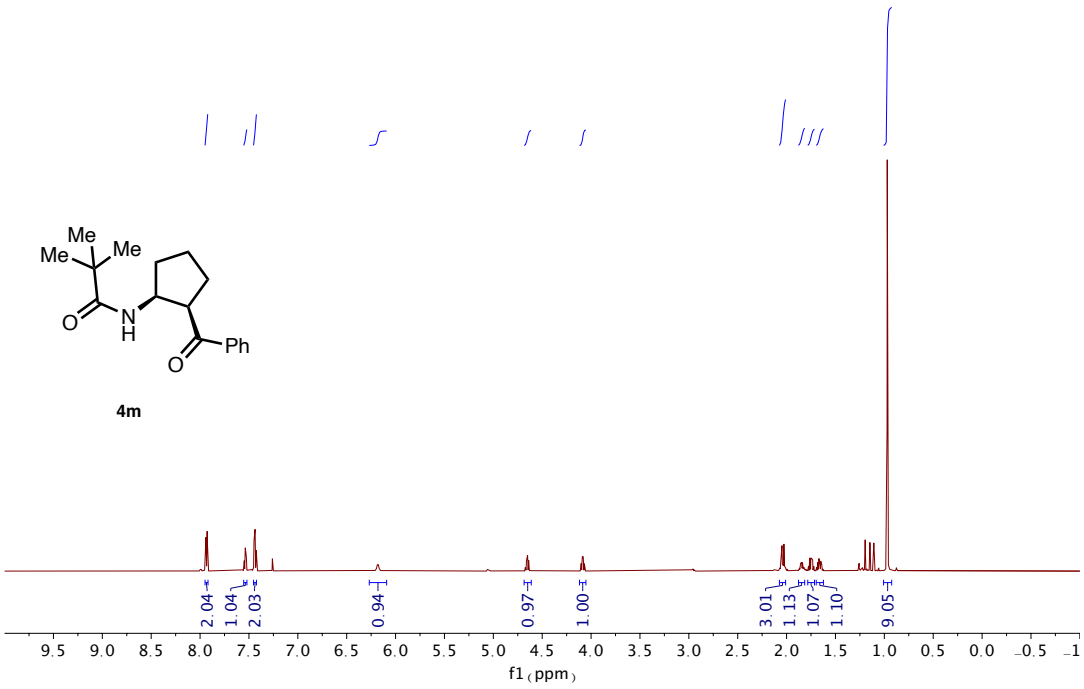

MeO2C
O
S
O
N
H
O
Ph
4i
f1 (ppm)

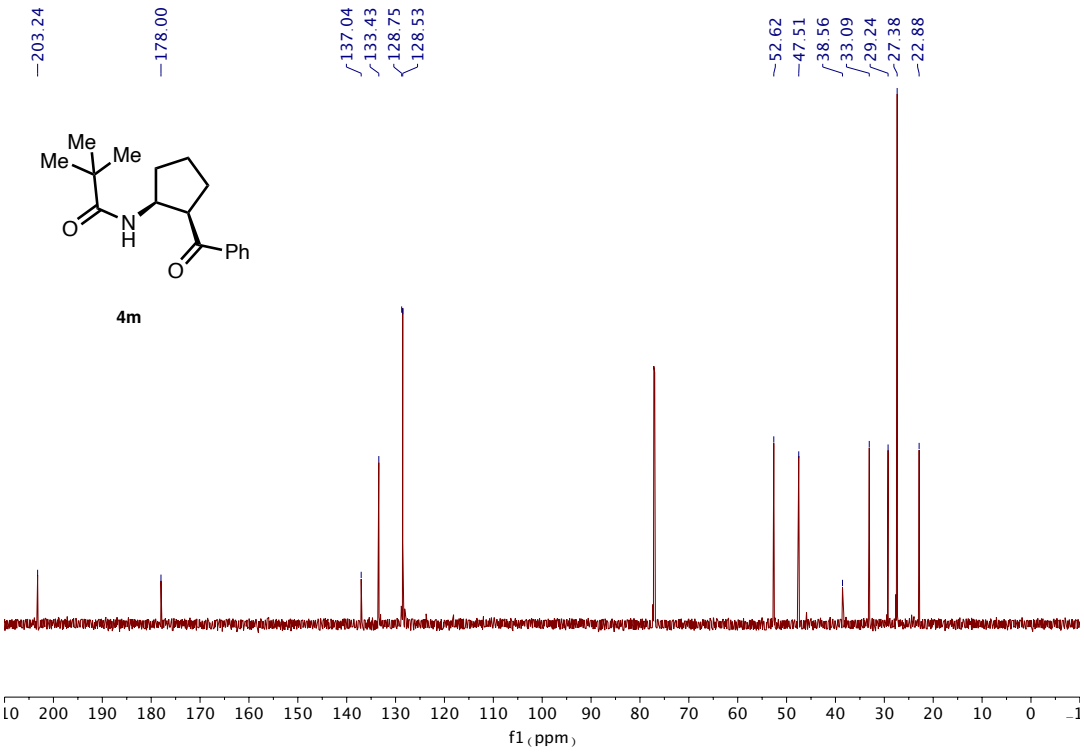

4k
f1 (ppm)

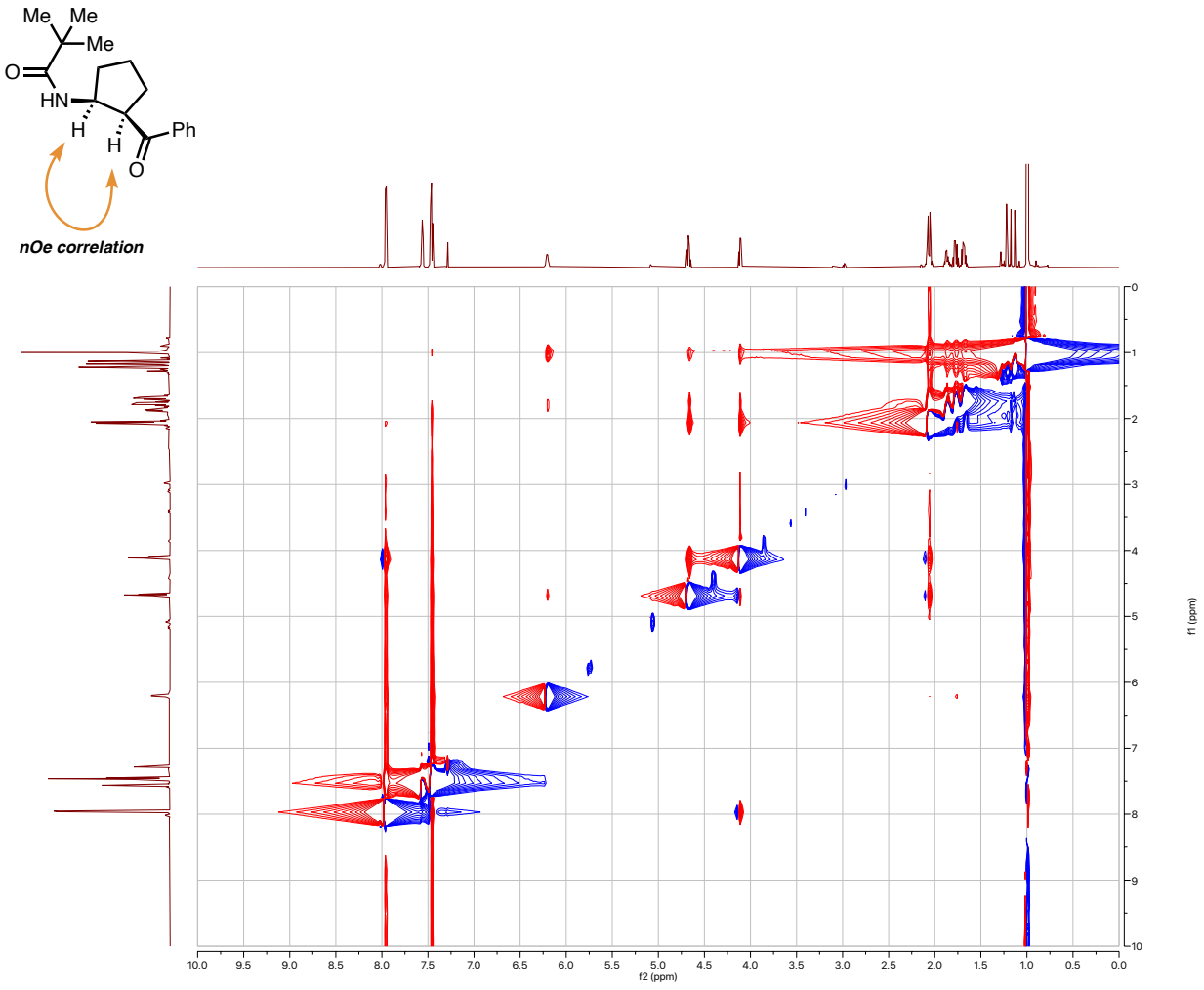

4k
f1 (ppm)

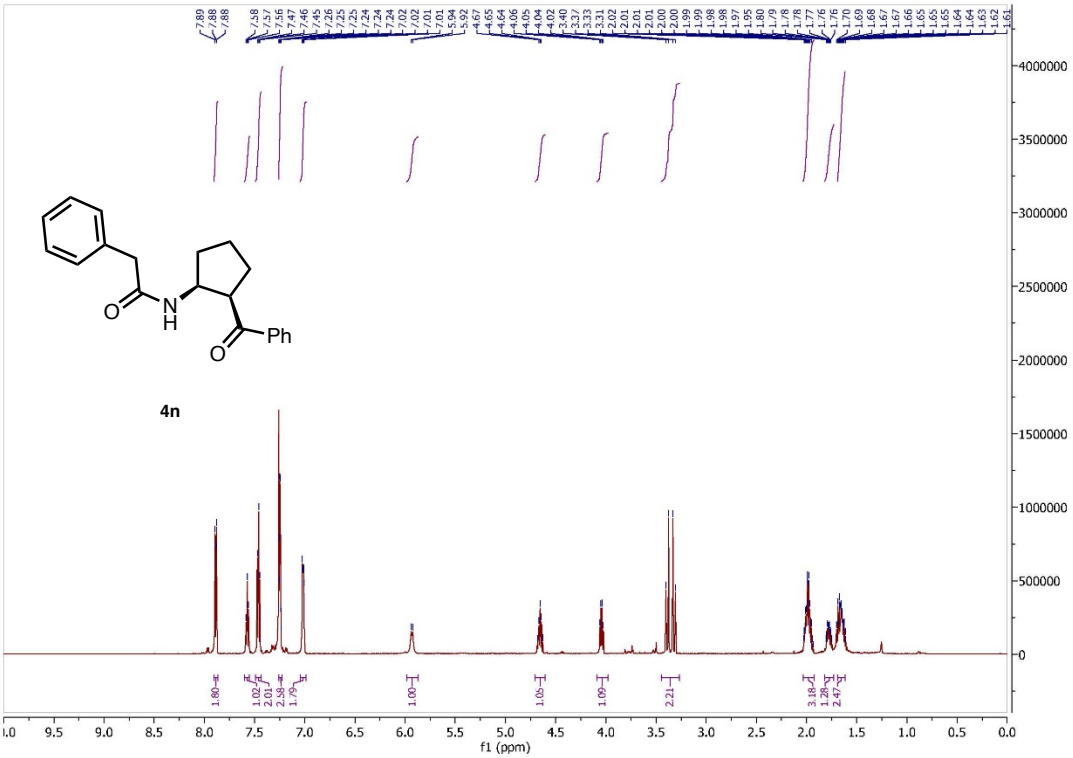

4l
1.00
2.03
2.06
2.15
0.98
1.02
1.03
2.05
1.03
1.03
1.05
1.18
1.14
0.83
2.13
1.17
f1 (ppm)

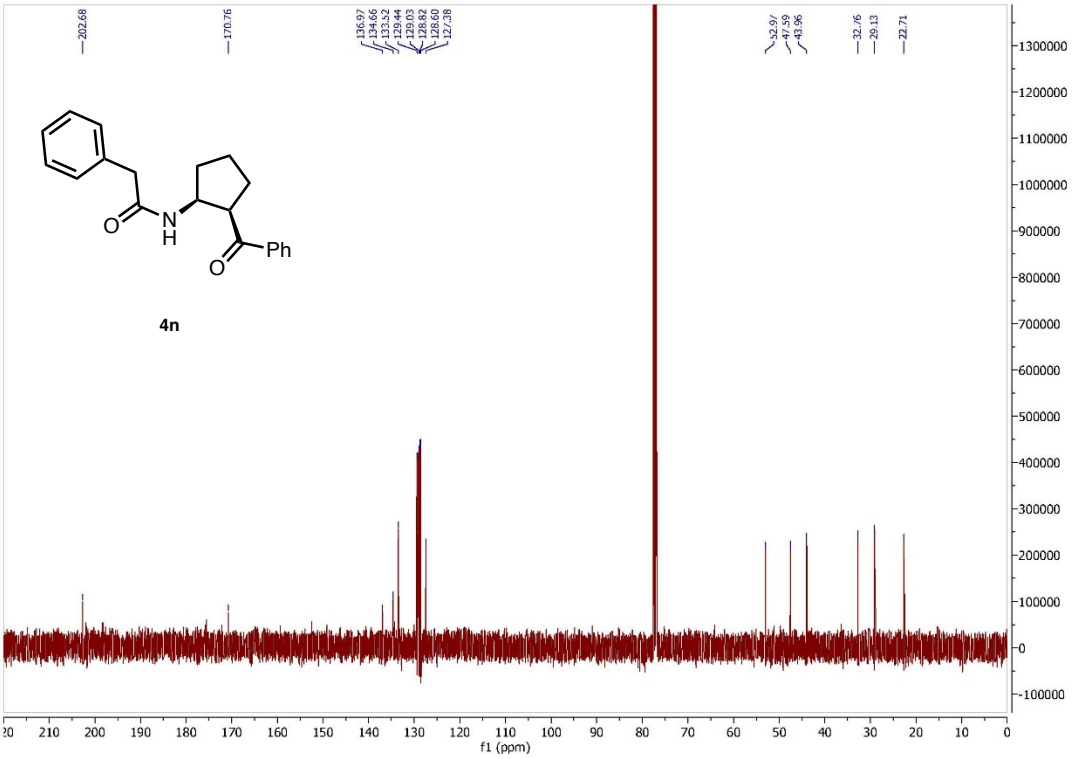

201.76
157.75
156.90
135.37
135.09
133.15
128.49
128.45
127.90
124.95
123.57
123.13
121.27
120.54
111.51
111.95
57.12
46.38
33.64
29.67
21.87
4l
f1 (ppm)

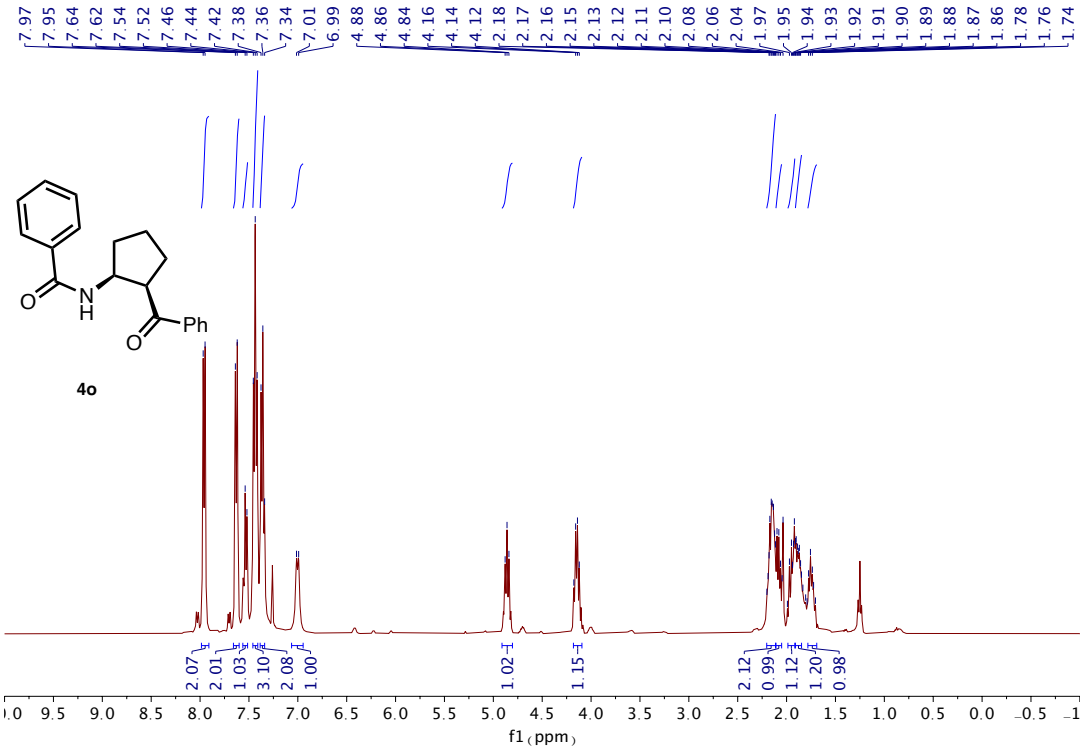

Me
Me
Me
O
N
H
Ph
O
4m
2.04
1.04
2.03
0.94
0.97
1.00
3.01
1.13
1.07
1.10
9.05
f1 (ppm)

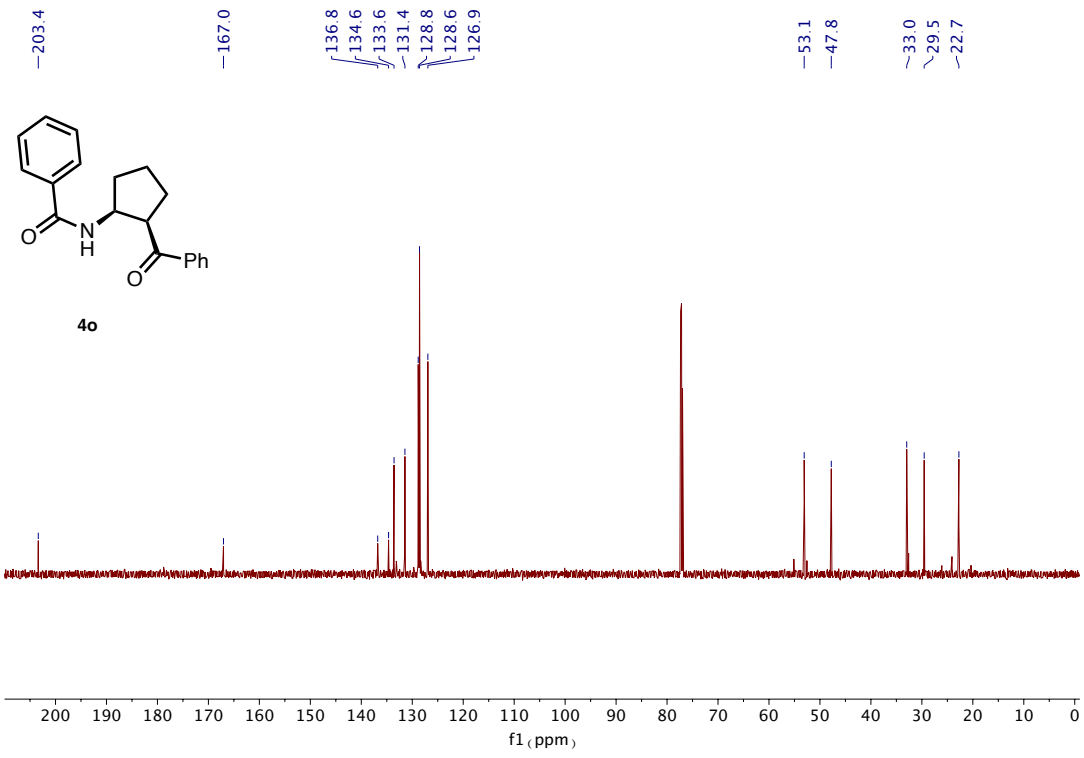

203.24
178.00
137.04
133.43
128.75
128.53
52.62
47.51
38.56
33.09
29.24
27.38
22.88
Me
Me
Me
O
N
H
Ph
O
4m
f1 (ppm)

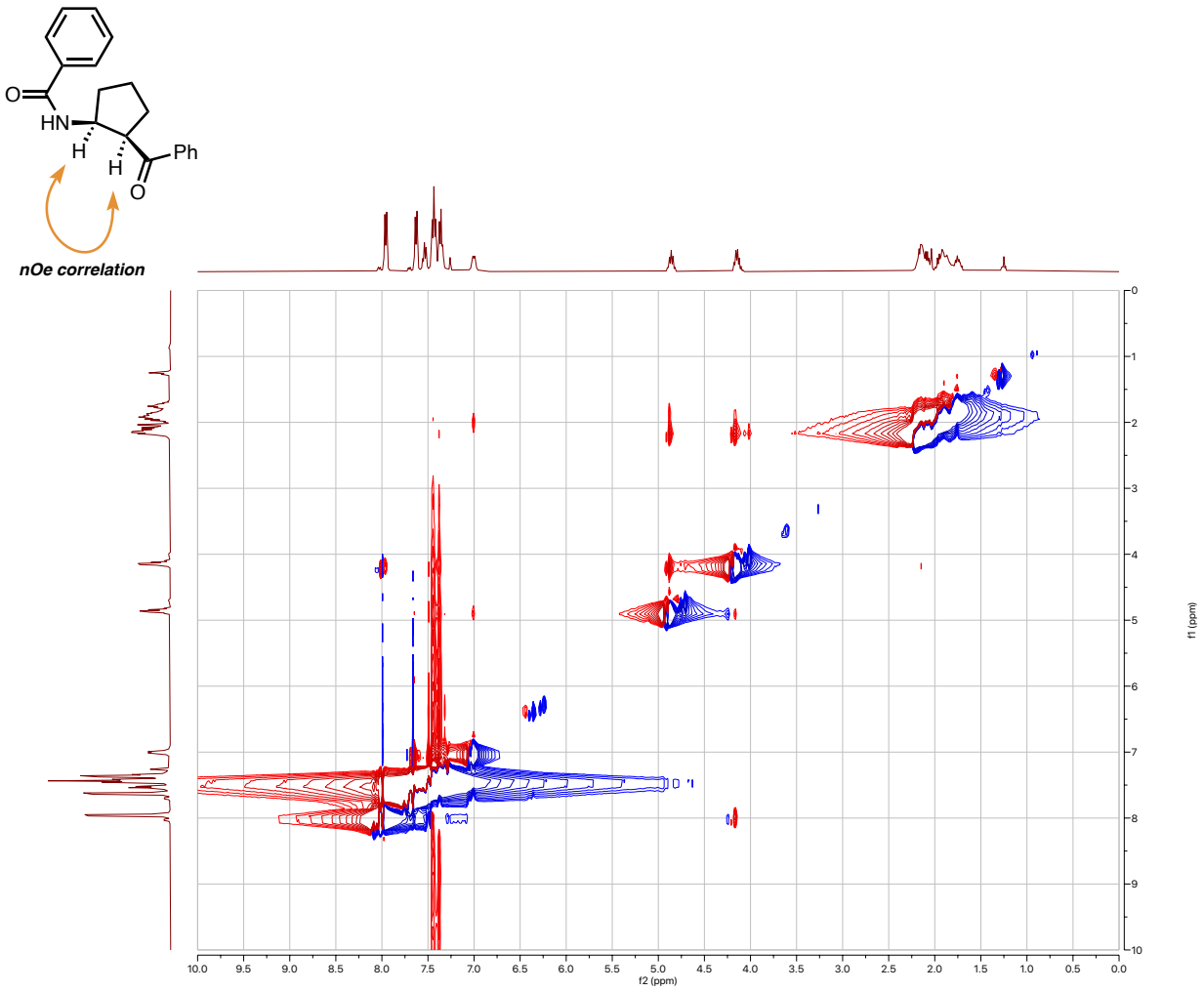

Me
Me
Me
O
HN
H
H
Ph
O
nOe correlation
f2 (ppm)
f1 (ppm)

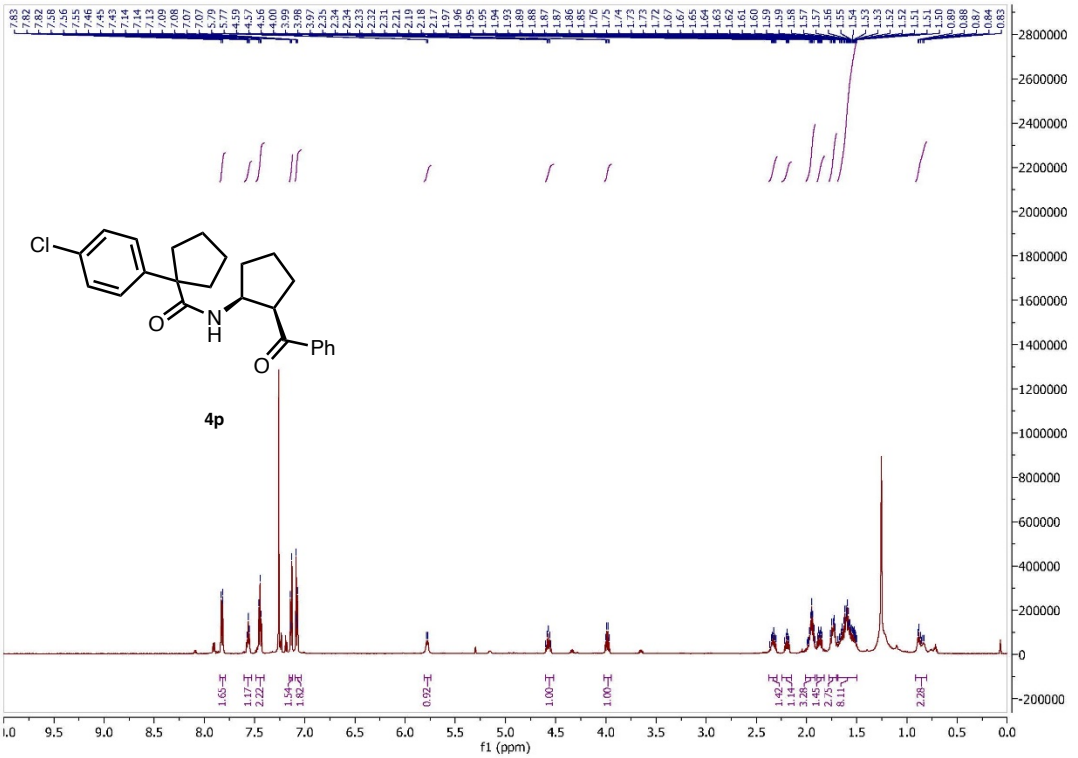

4n
f1 (ppm)

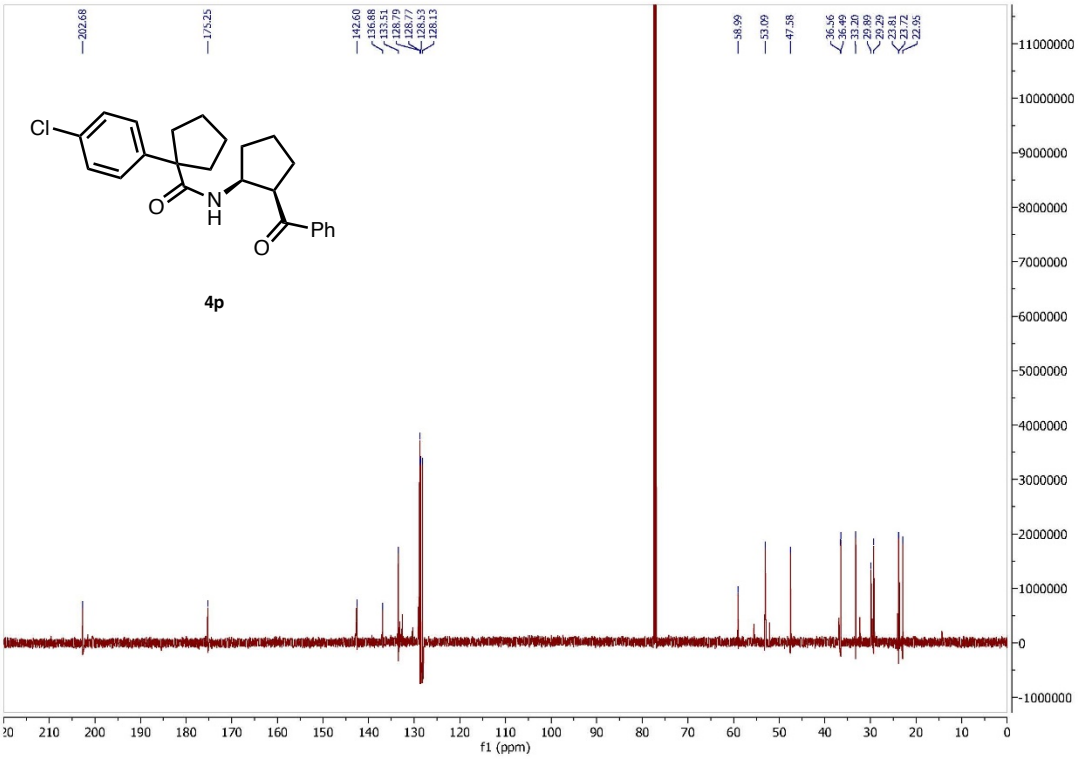

4n
f1 (ppm)

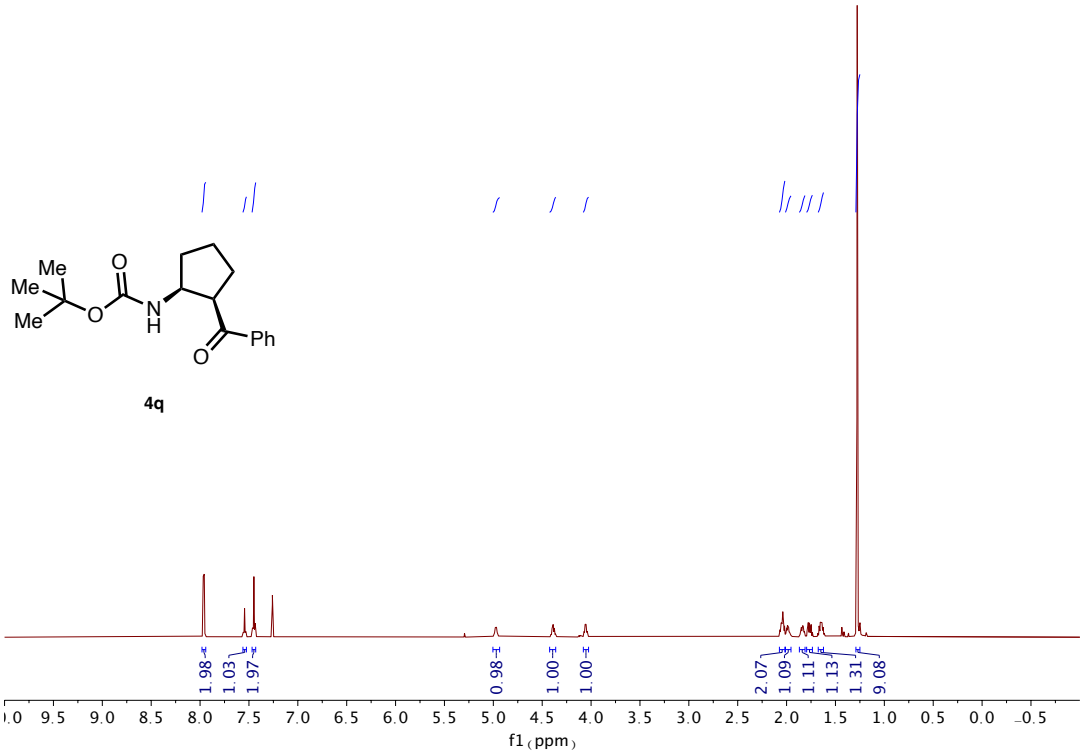

7.97
7.95
7.64
7.62
7.54
7.52
7.46
7.44
7.42
7.38
7.36
7.34
7.01
6.99
4.88
4.86
4.84
4.16
4.14
4.12
2.18
2.17
2.16
2.15
2.13
2.12
2.11
2.10
2.08
2.06
2.04
1.97
1.95
1.94
1.93
1.92
1.91
1.90
1.89
1.88
1.87
1.86
1.78
1.76
1.74
O
N
H
O
Ph
4o
2.07
2.01
1.03
3.10
2.08
1.00
1.02
1.15
2.12
0.99
1.12
1.20
0.98
f1 (ppm)

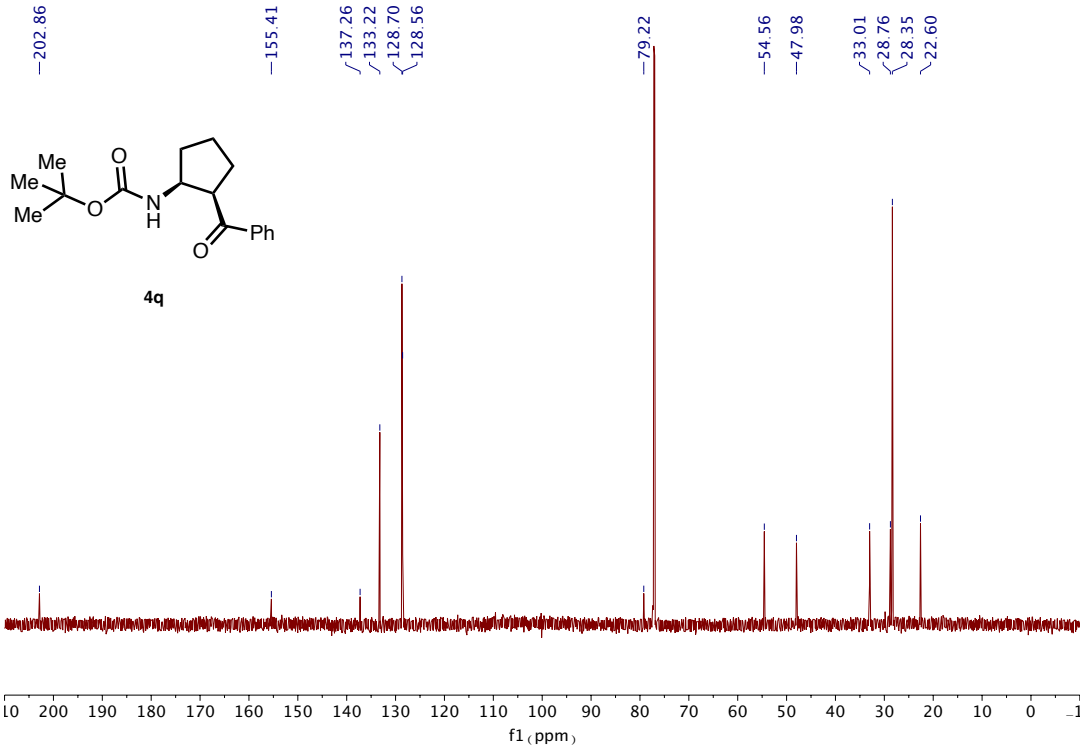

203.4
167.0
136.8
134.6
133.6
131.4
128.8
128.6
126.9
53.1
47.8
33.0
29.5
22.7
O
N
H
O
Ph
4o
f1 (ppm)

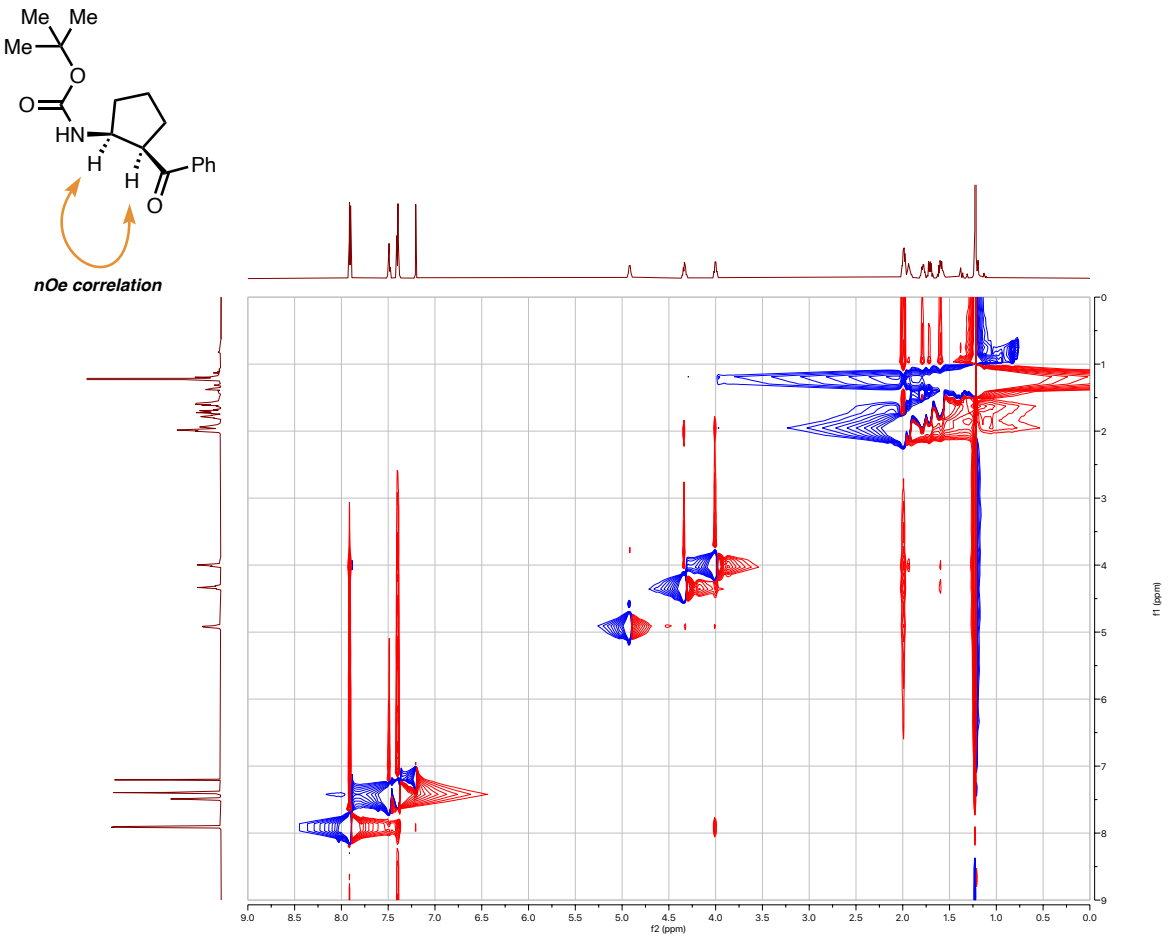

O
HN
H
H
Ph
O
nOe correlation
f2 (ppm)
f1 (ppm)

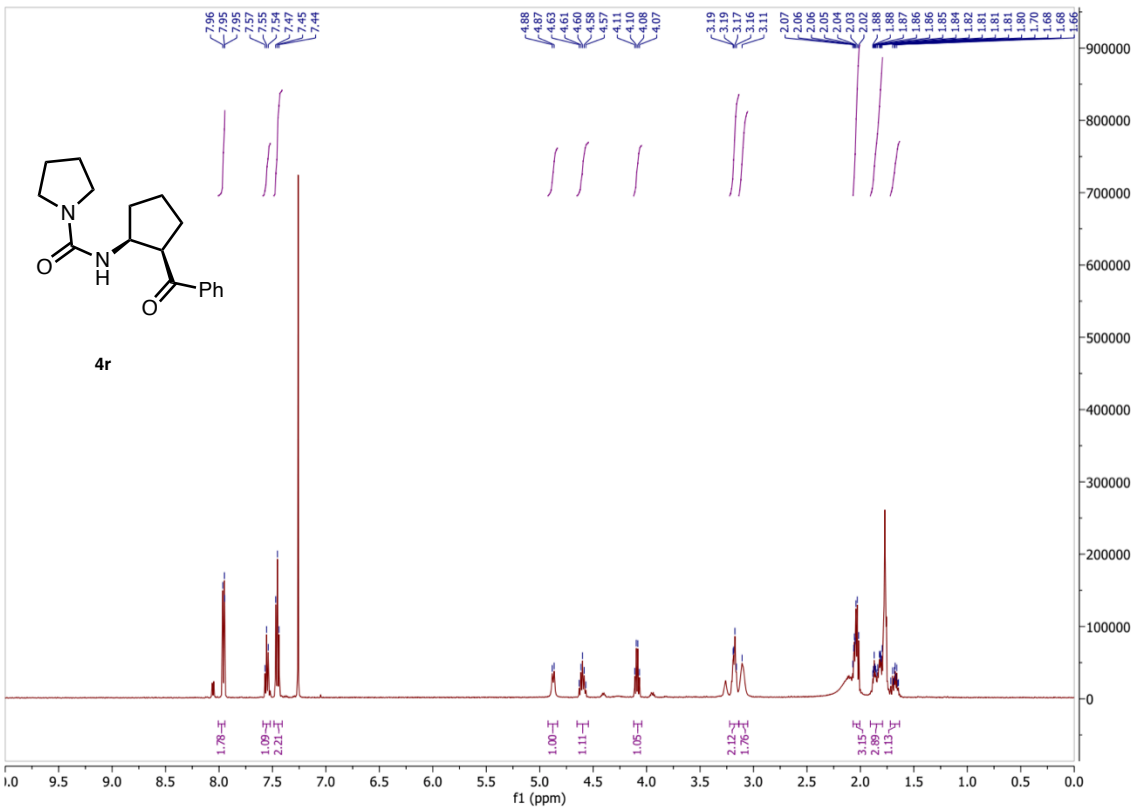

Cl
O
N
H
O
Ph
4p
f1 (ppm)

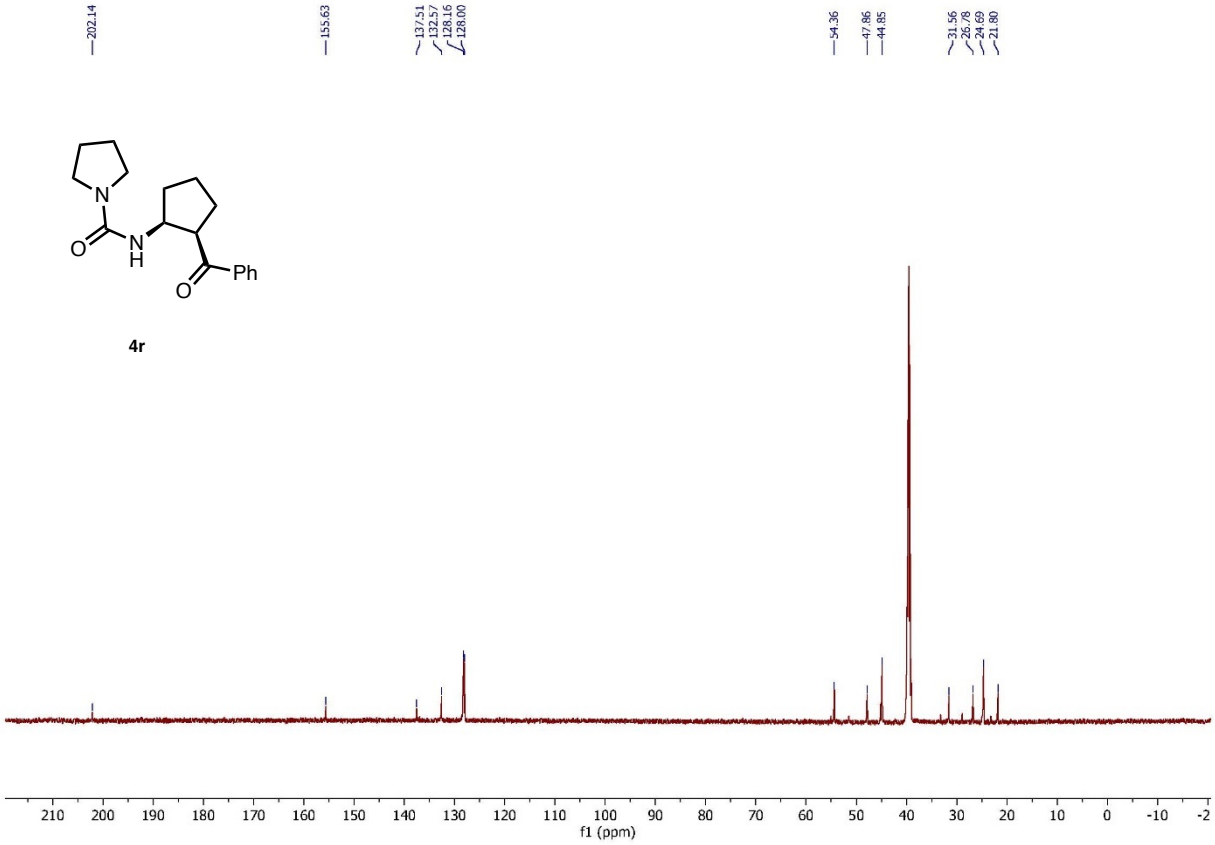

Cl
O
N
H
O
Ph
4p
f1 (ppm)

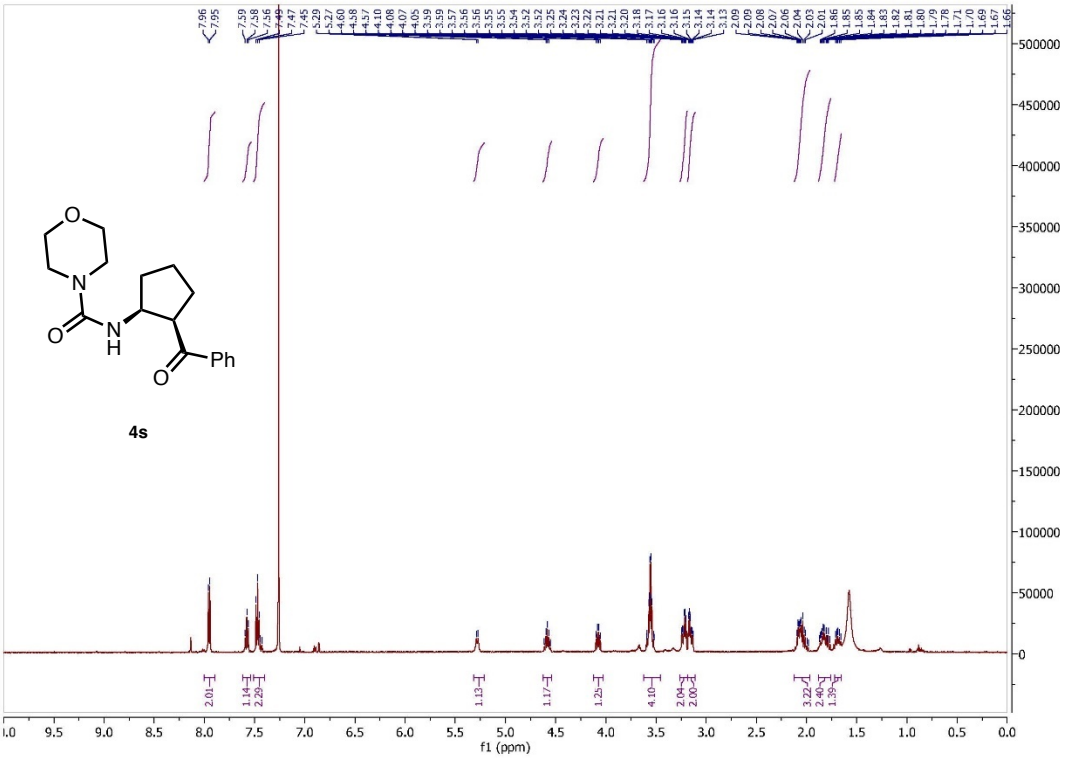

Me
Me
Me
O
O
N
H
Ph
O
4q
1.98
1.03
1.97
0.98
1.00
1.00
2.07
1.09
1.11
1.13
1.31
9.08
f1 (ppm)

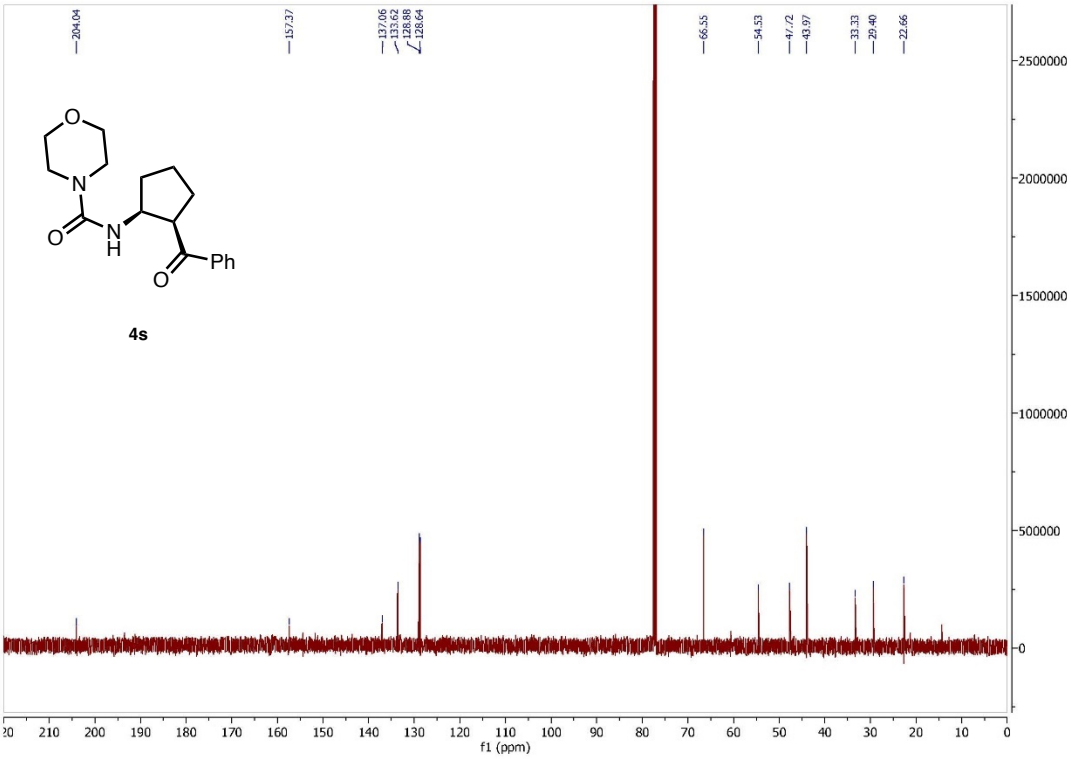

202.86
155.41
137.26
133.22
128.70
128.56
79.22
54.56
47.98
33.01
28.76
28.35
22.60
Me
Me
Me
O
O
N
H
Ph
O
4q
f1 (ppm)

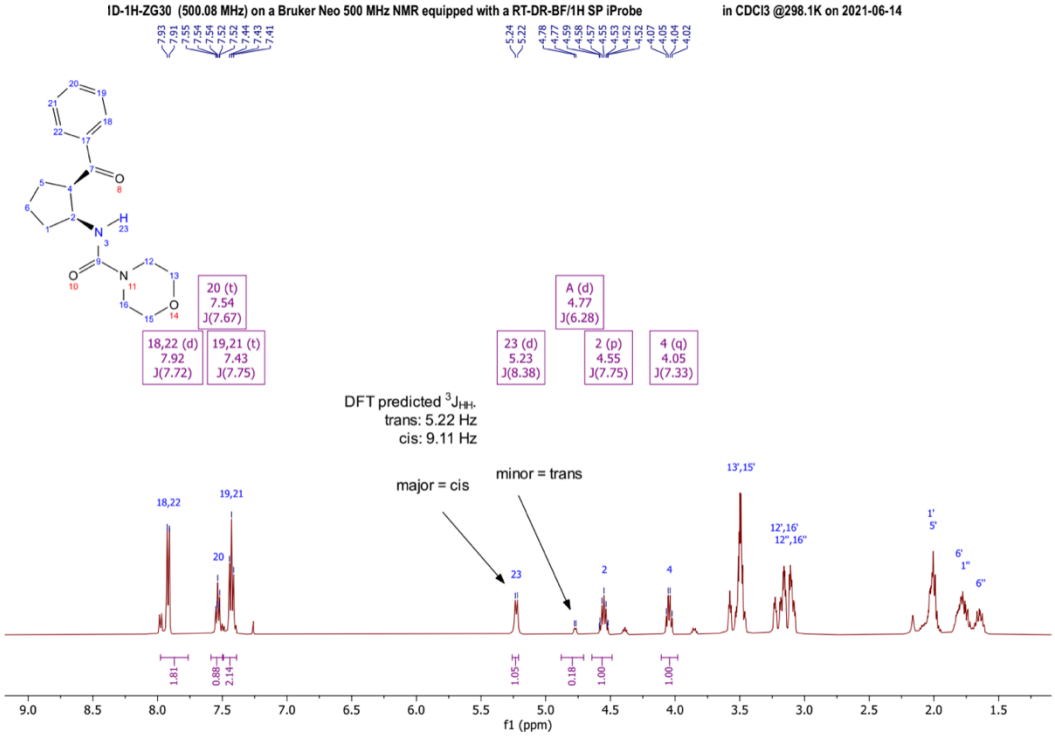

Me
Me
Me
O
O
HN
H
H
Ph
O
nOe correlation
f2 (ppm)
f1 (ppm)

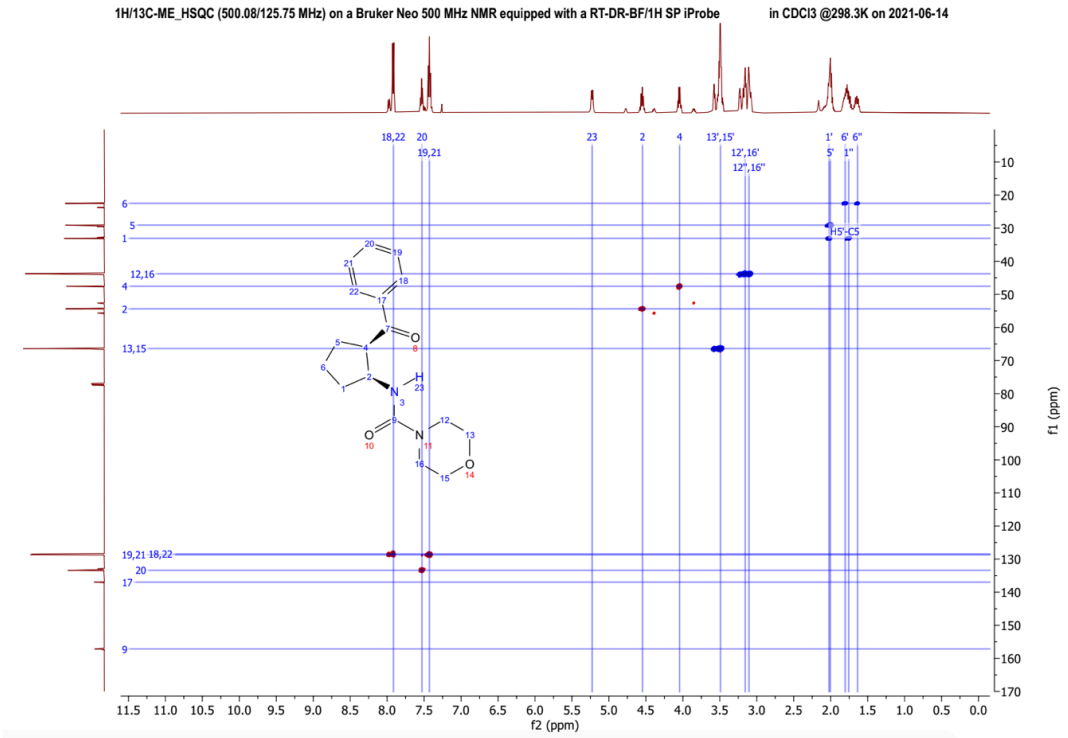

4r
f1 (ppm)

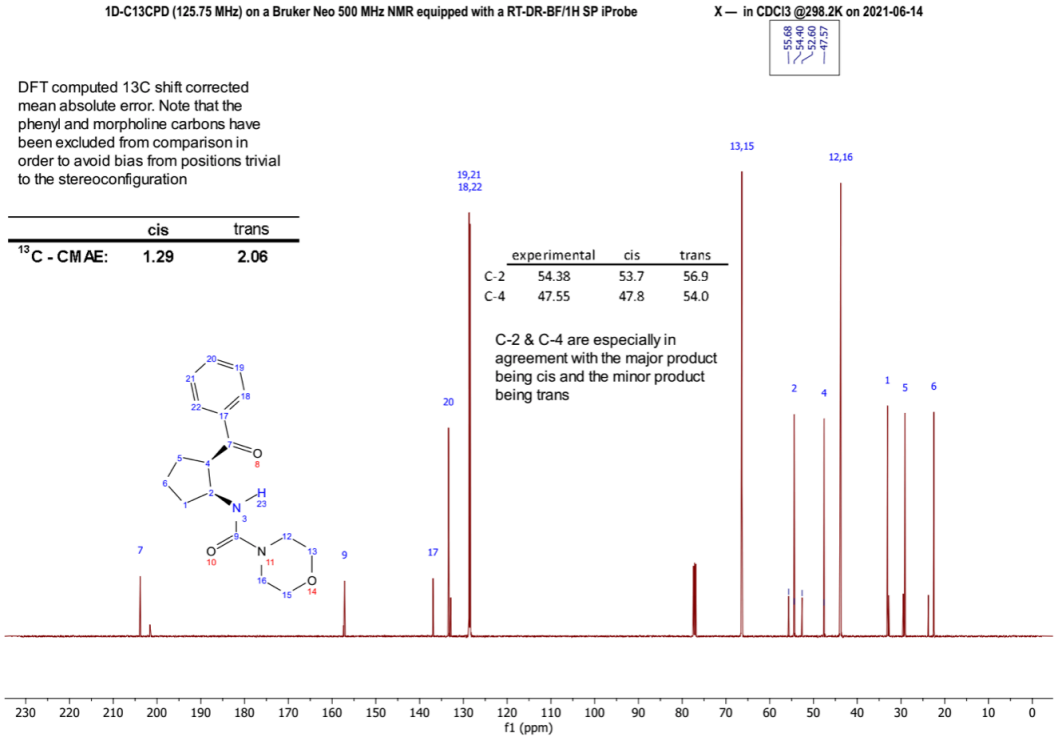

4r
f1 (ppm)

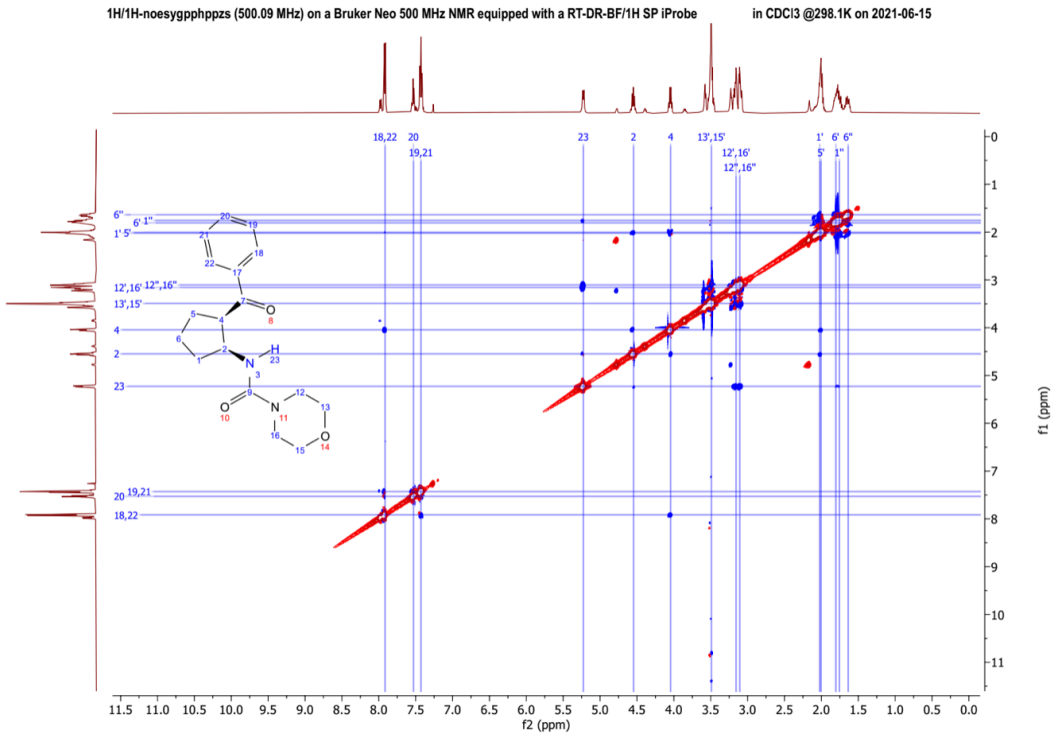

4s
f1 (ppm)

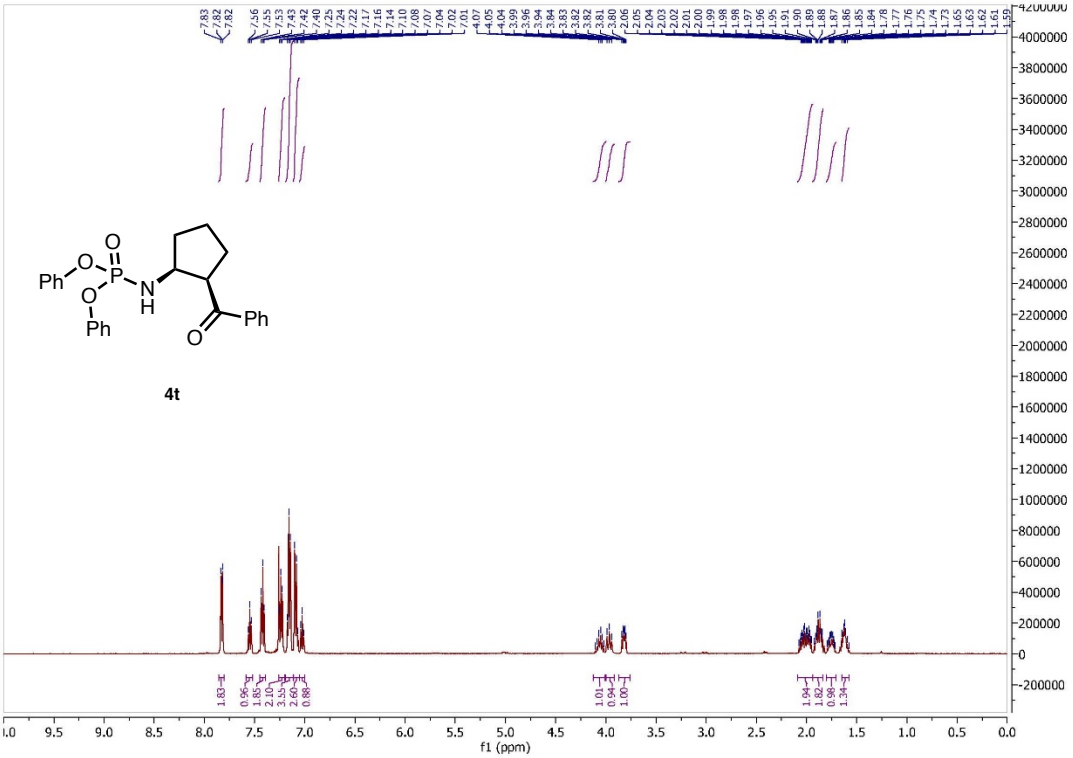

4s
f1 (ppm)

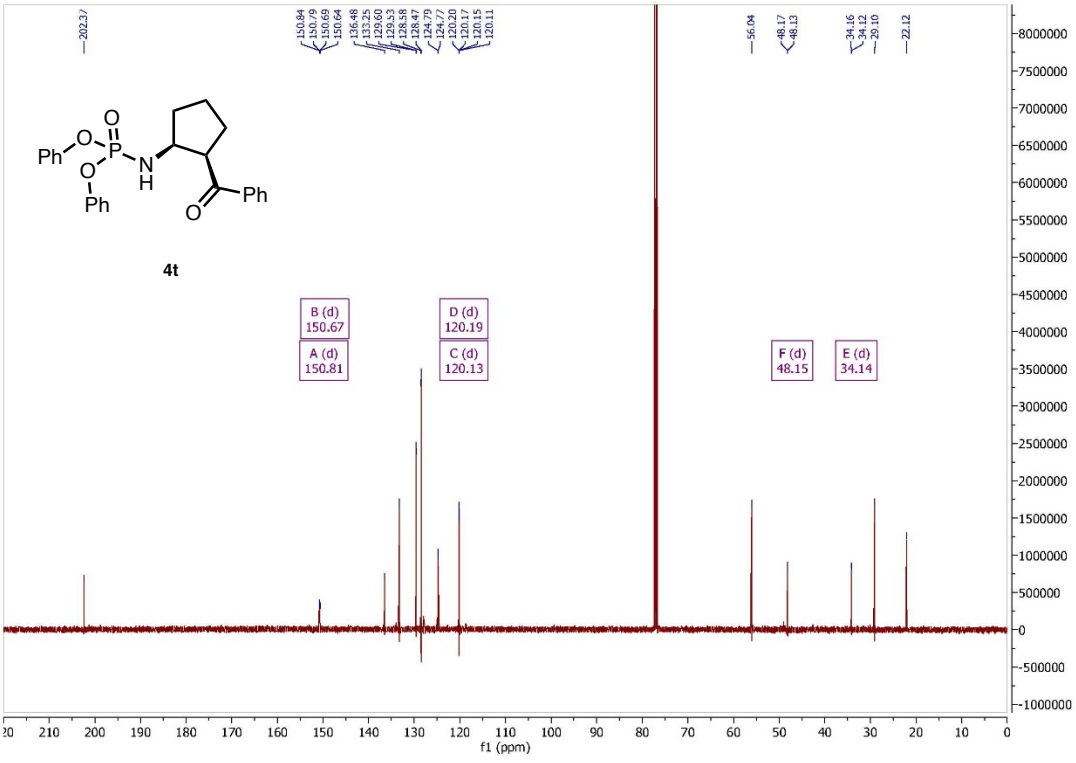

1D-1H-ZG30 (500.08 MHz) on a Bruker Neo 500 MHz NMR equipped with a RT-DR-BF/1H SP iProbe
in CDCl3 @298.1K on 2021-06-14
20 (t)
7.54
J(7.67)
18,22 (d)
7.92
J(7.72)
19,21 (t)
7.43
J(7.75)
A (d)
4.77
J(6.28)
23 (d)
5.23
J(8.38)
2 (p)
4.55
J(7.75)
4 (q)
4.05
J(7.33)
DFT predicted 3JHH,
trans: 5.22 Hz
cis: 9.11 Hz
major = cis
minor = trans
f1 (ppm)

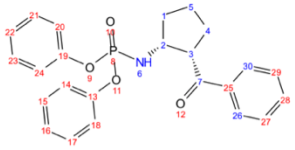

1H/13C-ME_HSQC (500.08/125.75 MHz) on a Bruker Neo 500 MHz NMR equipped with a RT-DR-BF/1H SP iProbe
in CDCl3 @298.3K on 2021-06-14
f2 (ppm)
f1 (ppm)


1D-C13CPD (125.75 MHz) on a Bruker Neo 500 MHz NMR equipped with a RT-DR-BF/1H SP iProbe
X — in CDCl3 @298.2K on 2021-06-14
55.68
54.40
54.00
47.57
DFT computed 13C shift corrected mean absolute error. Note that the phenyl and morpholine carbons have been excluded from comparison in order to avoid bias from positions trivial to the stereoconfiguration
cis trans
13C - CMAE: 1.29 2.06
experimental cis trans
C-2 54.38 53.7 56.9
C-4 47.55 47.8 54.0
C-2 & C-4 are especially in agreement with the major product being cis and the minor product being trans
13,15
12,16
19,21
18,22
20
2
4
1
5
6
7
9
17
f1 (ppm)

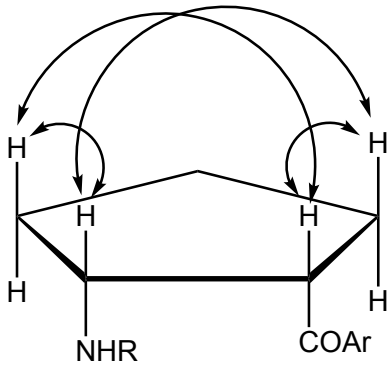

1H/1H-noesygpphppzs (500.09 MHz) on a Bruker Neo 500 MHz NMR equipped with a RT-DR-BF/1H SP iProbe
in CDCl3 @298.1K on 2021-06-15
18,22
20
19,21
23
2
4
13',15'
12',16'
12",16"
1'
6'
6"
5'
1"
f2 (ppm)
f1 (ppm)

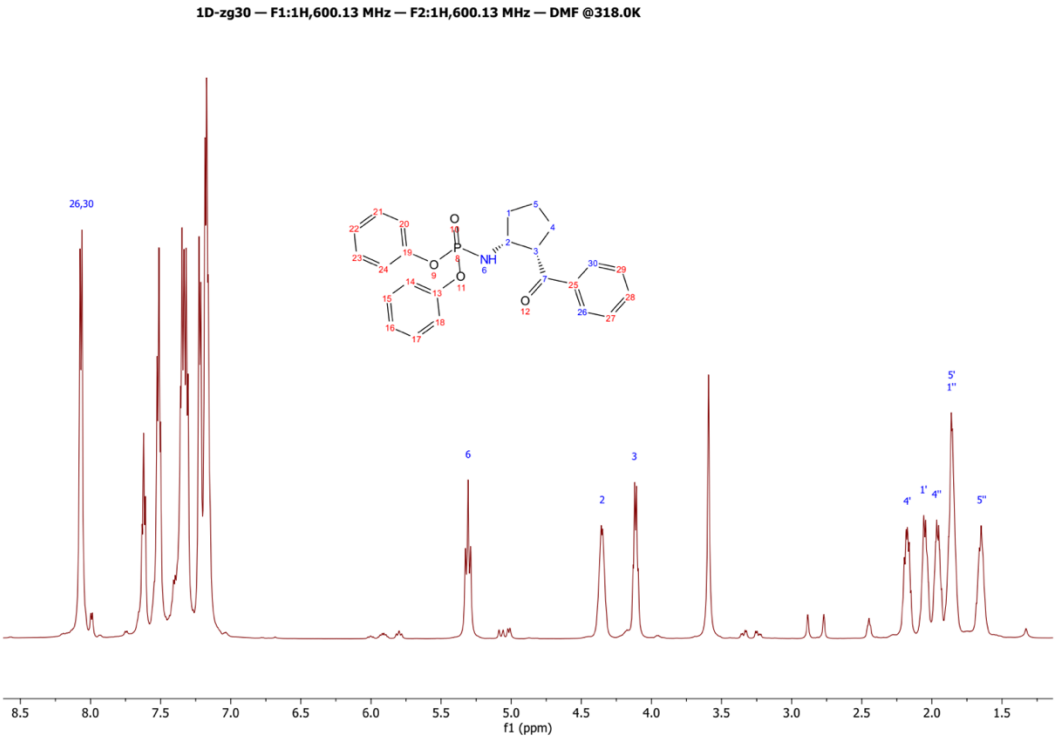

4t
f1 (ppm)

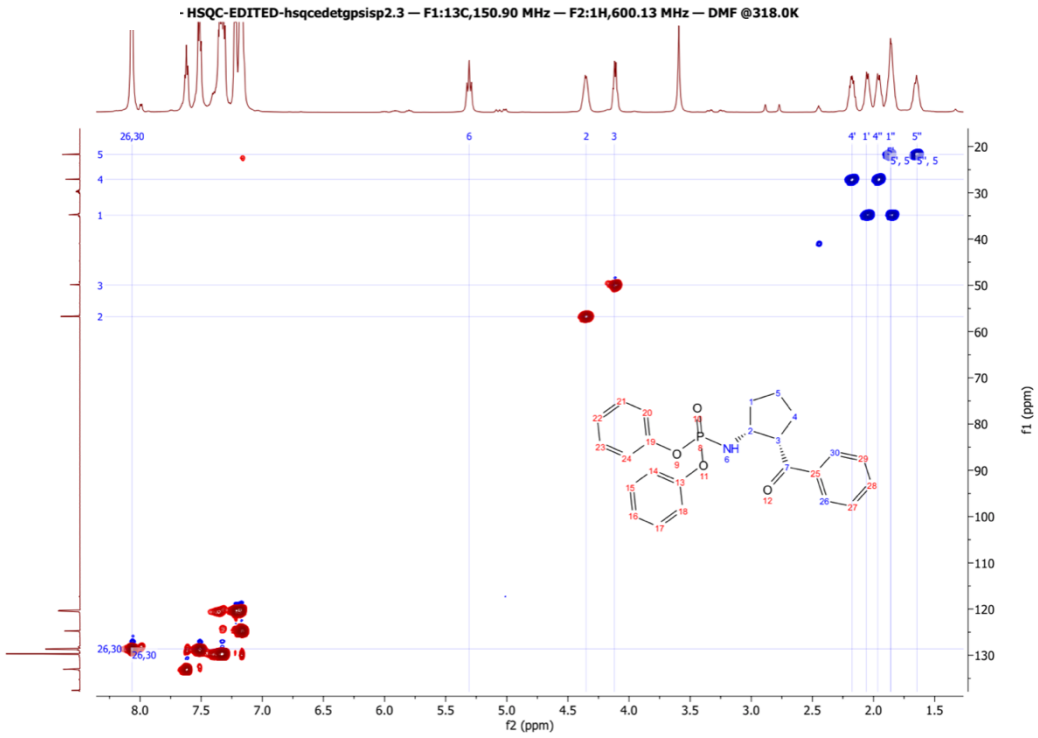

4t
B (d)
150.67
A (d)
150.81
D (d)
120.19
C (d)
120.13
F (d)
48.15
E (d)
34.14
f1 (ppm)

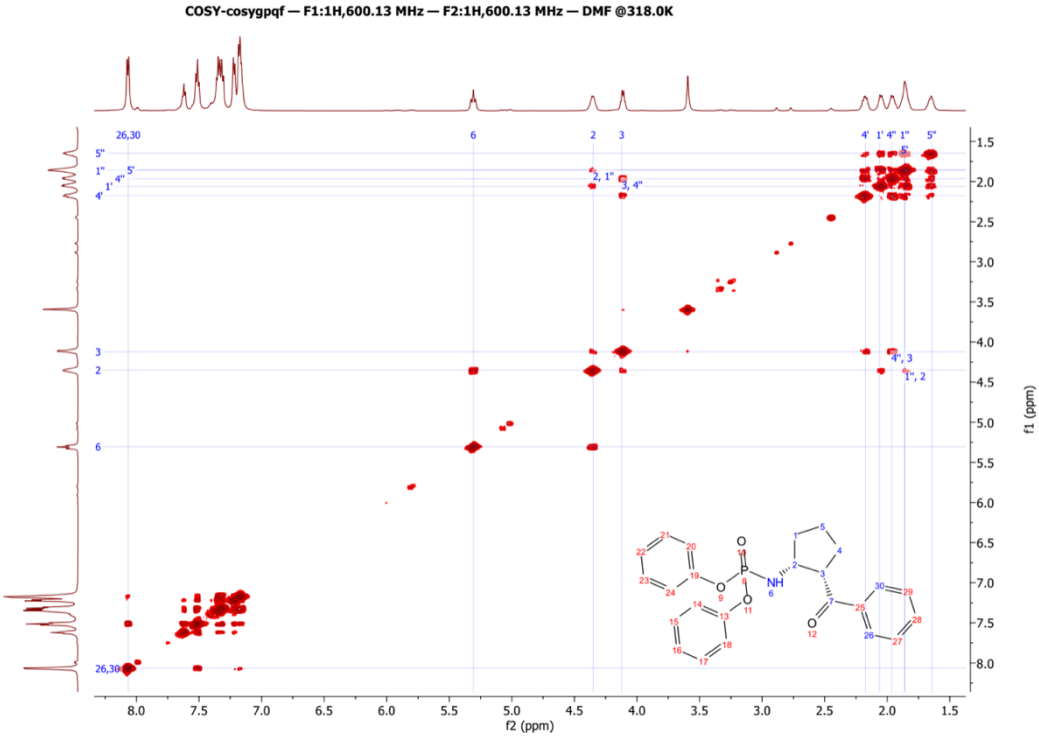


Analysis of NOESY correlations confidently assigns the relative configuration of **4t** as *cis*

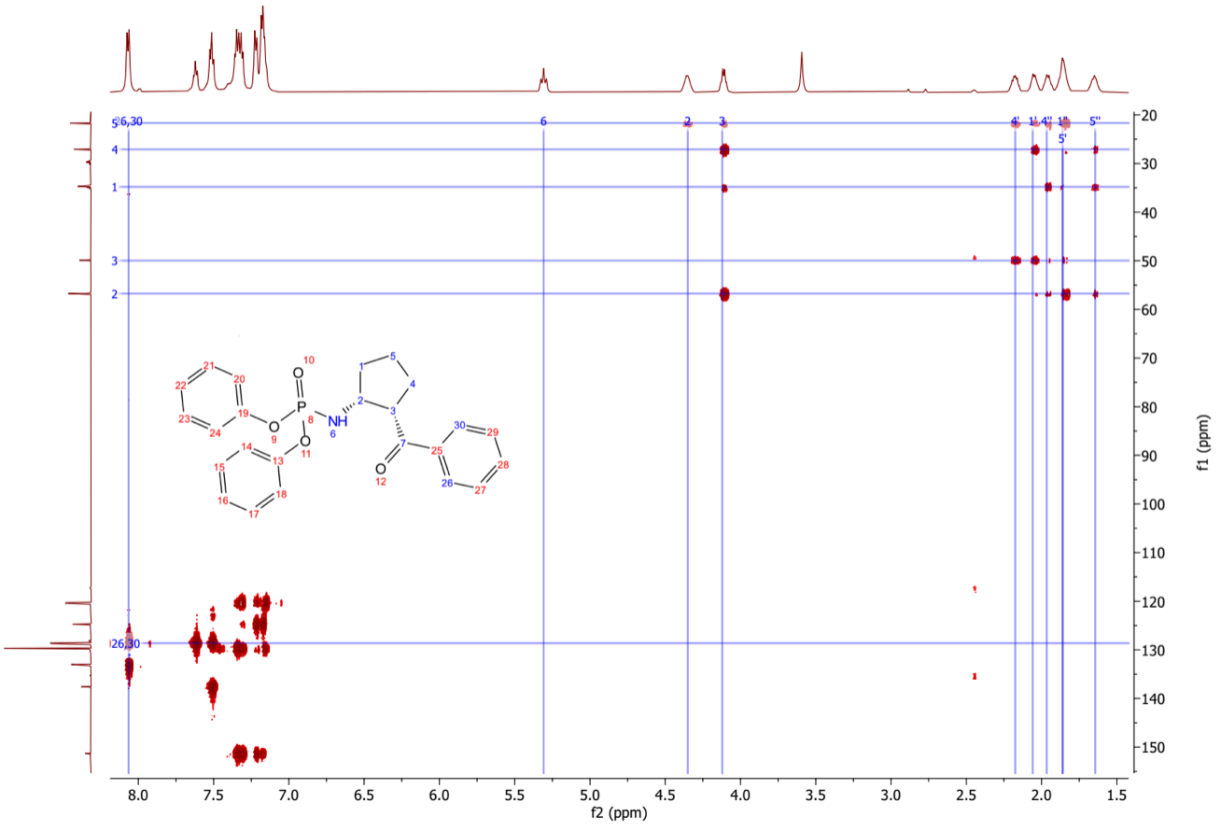




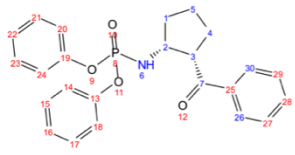

HSQC-EDITED-hsqcedetgpsisp2.3 — F1:13C,150.90 MHz — F2:1H,600.13 MHz — DMF @318.0K
f2 (ppm)
f1 (ppm)


COSY-cosygpqf — F1:1H,600.13 MHz — F2:1H,600.13 MHz — DMF @318.0K
f2 (ppm)
f1 (ppm)

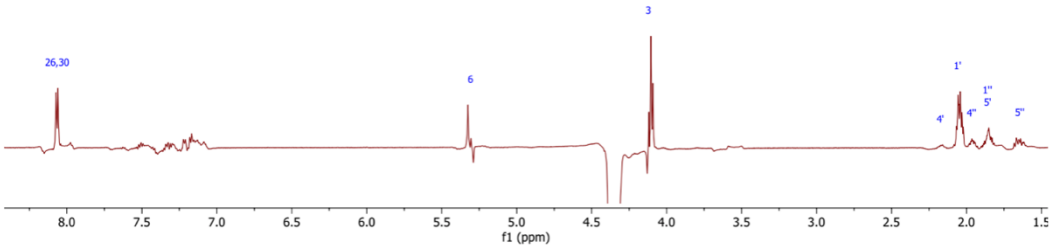
HMBC-hmbcetgpl3nd — F1:13C,150.90 MHz — F2:1H,600.13 MHz — DMF @318.0K



1D-selnogpzs.2 — F1:1H,600.13 MHz — F2:1H,600.13 MHz — DMF @318.0K

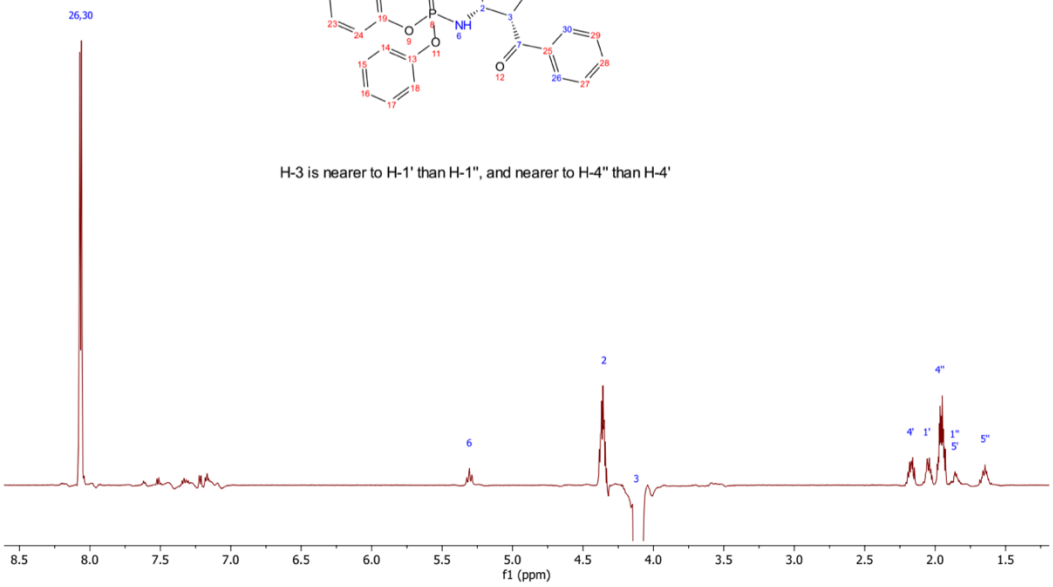


H-2 is nearer to H-1' than H-1" and nearer to H4" than H-4'

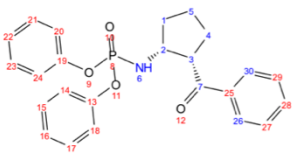


1D-selnogpzs.2 — F1:1H,600.13 MHz — F2:1H,600.13 MHz — DMF @318.0K

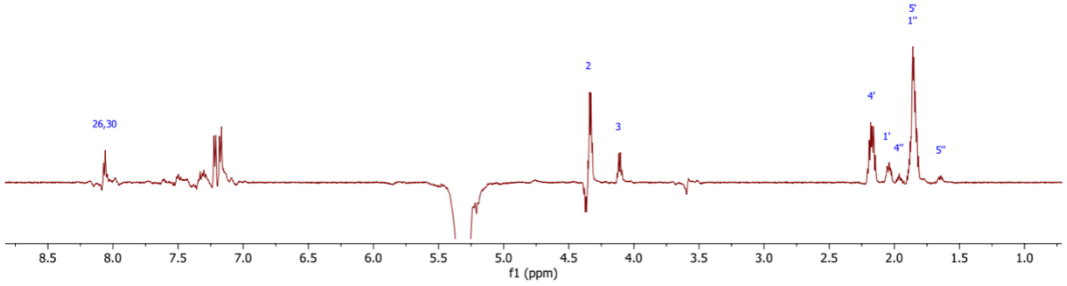
H-3 is nearer to H-1' than H-1", and nearer to H-4" than H-4'

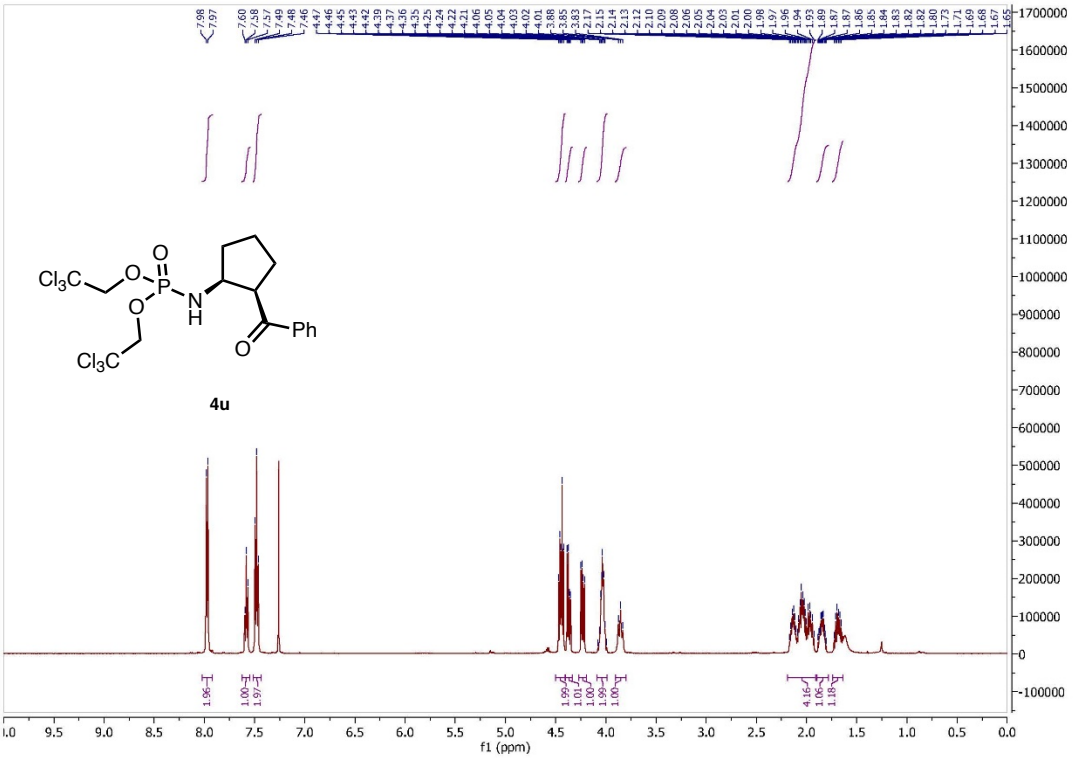


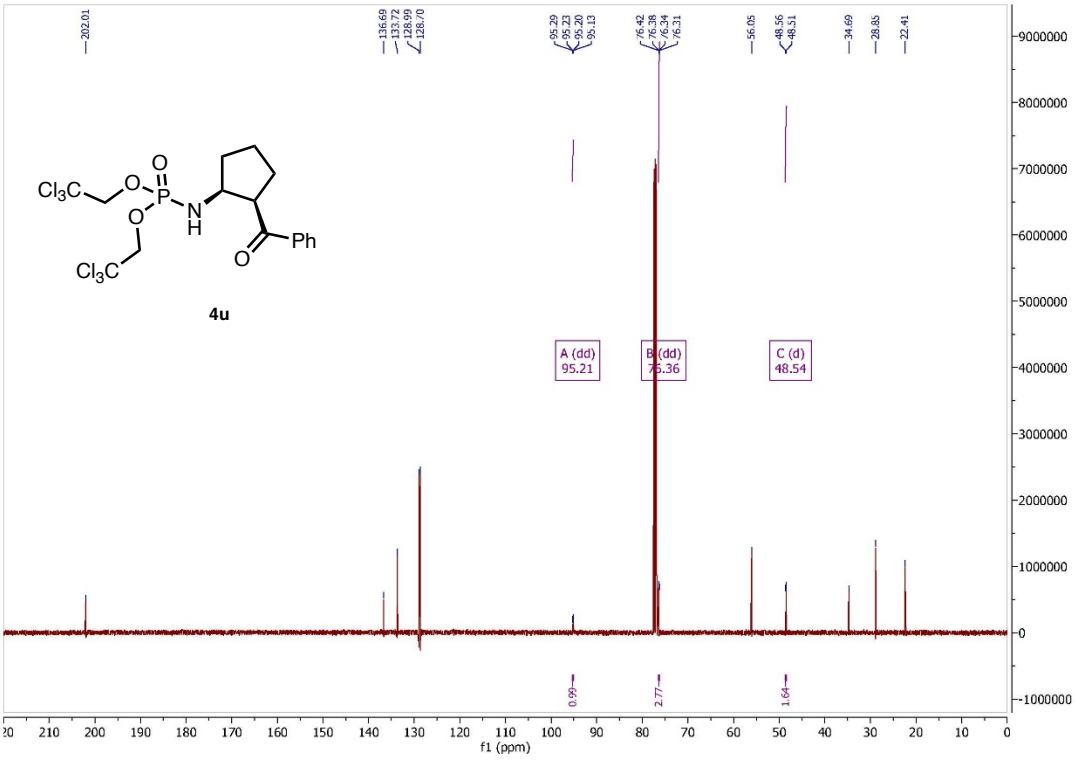
· 1D-selnogpzs.2 — F1:1H,600.13 MHz — F2:1H,600.13 MHz — DMF @318.0K

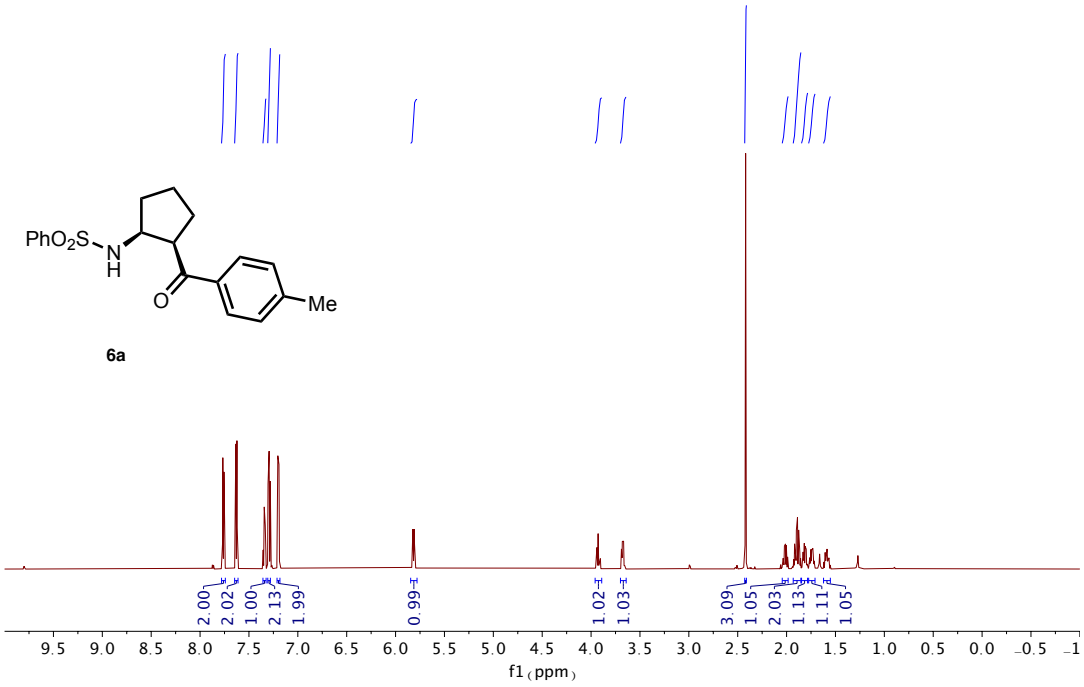


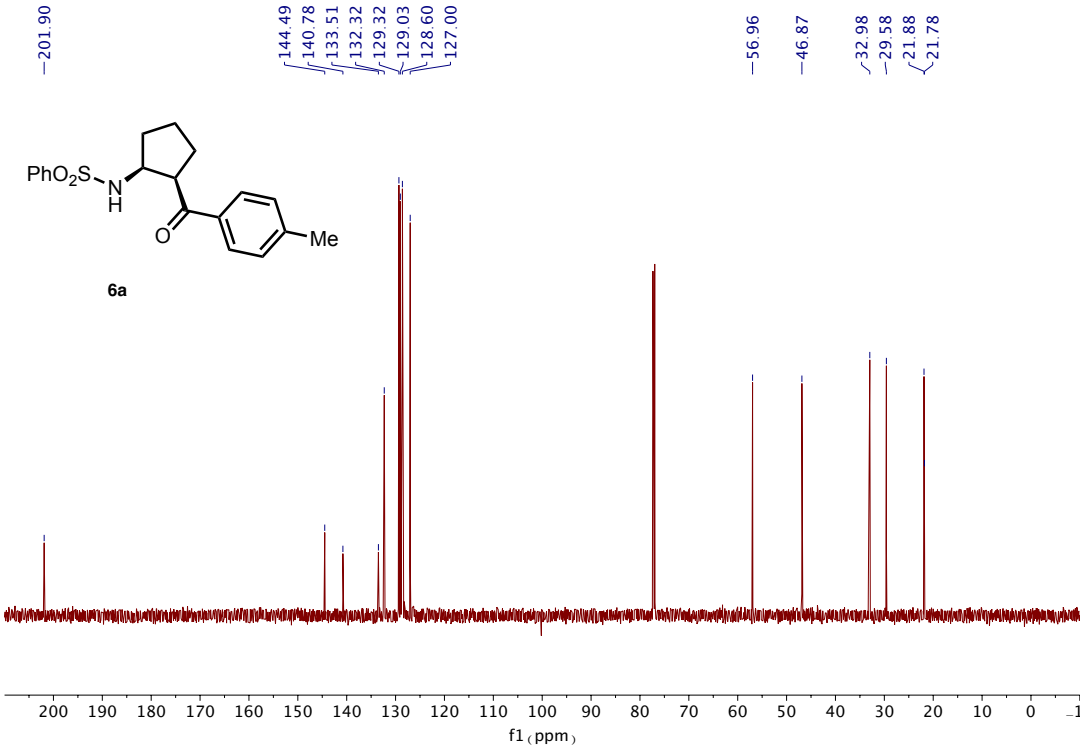
NH-6 is nearer H-4' than H-4", nearer to H-1", than H-1'

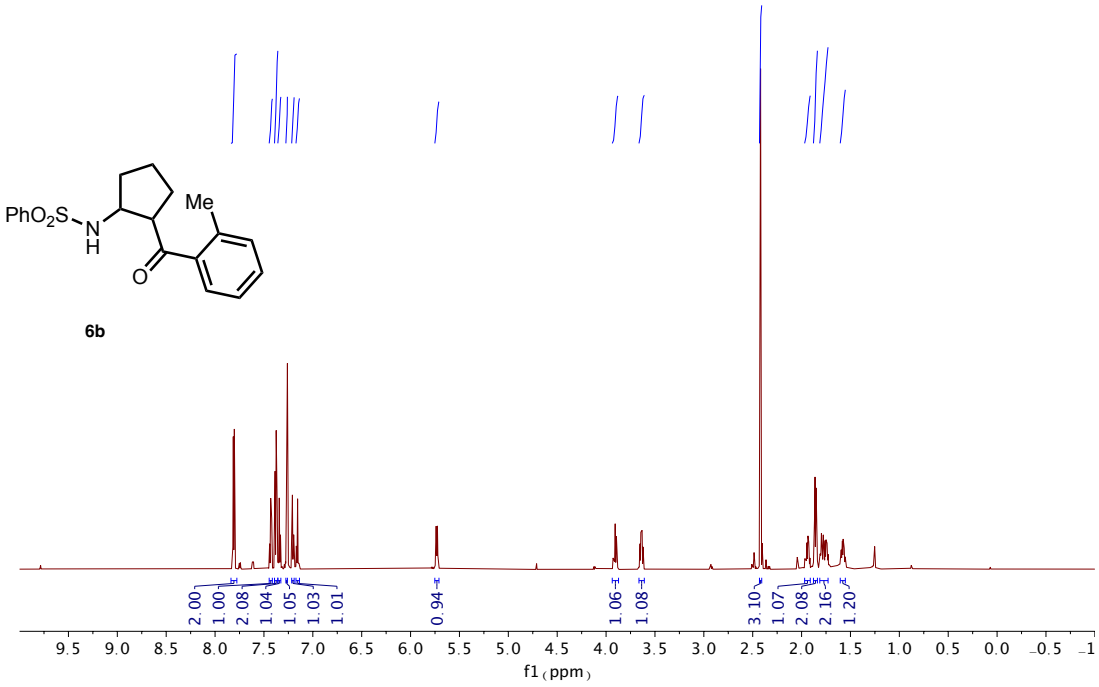


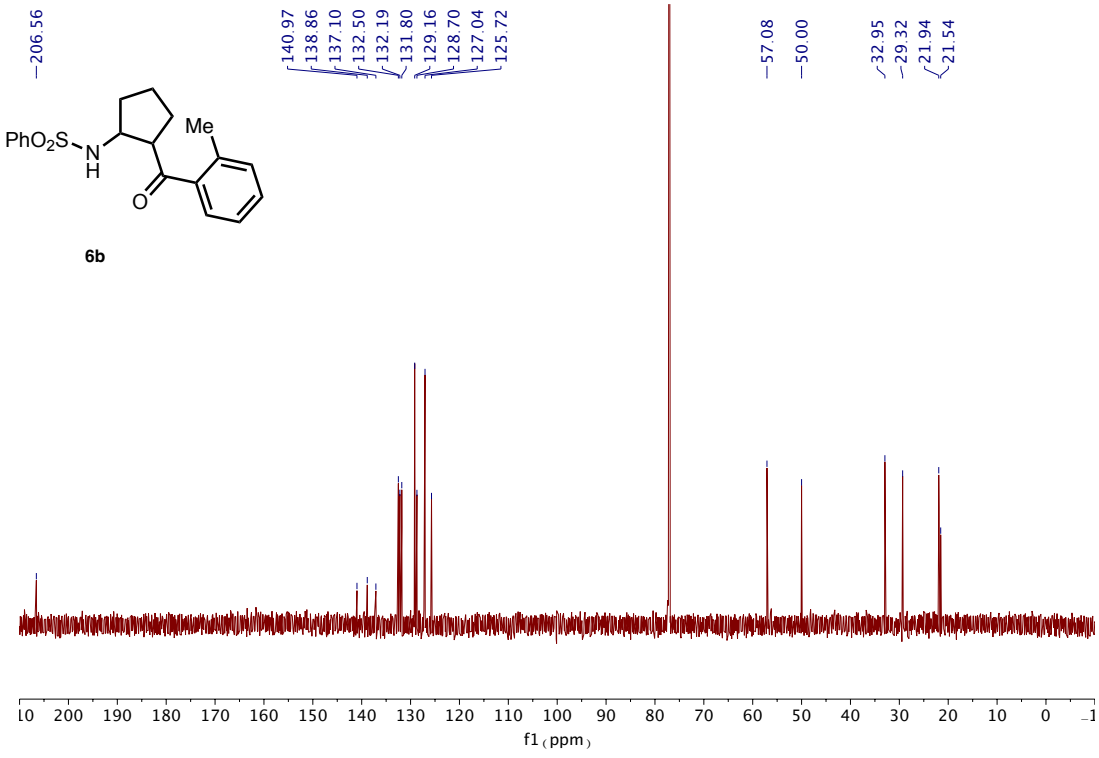

4u
f1 (ppm)

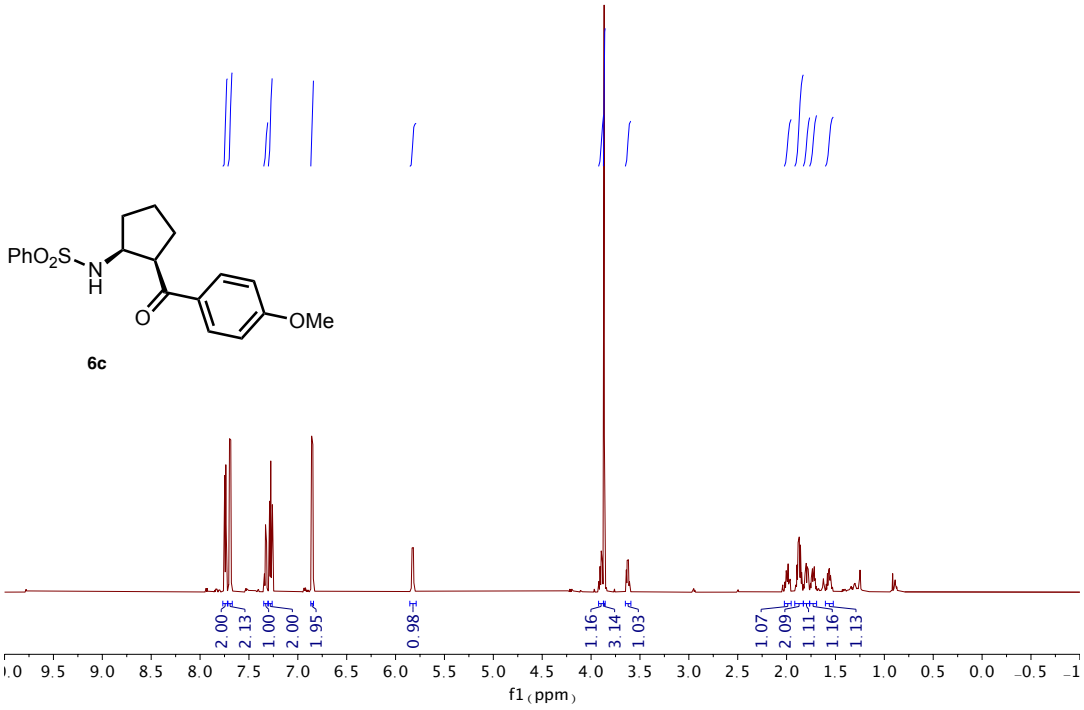

4u
A (dd)
95.21
B (dd)
76.36
C (d)
48.54
f1 (ppm)

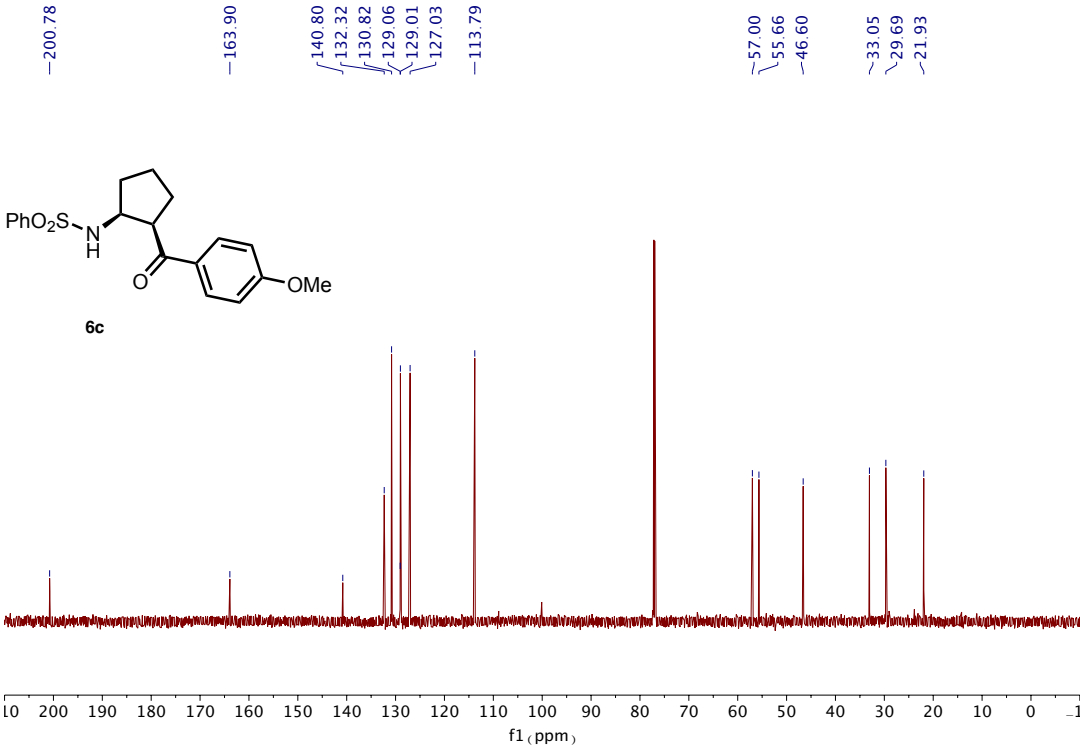

PhO2S
N
H
O
Me
6a
2.00
2.02
1.00
2.13
1.99
0.99
1.02
1.03
3.09
1.05
2.03
1.13
1.11
1.05
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

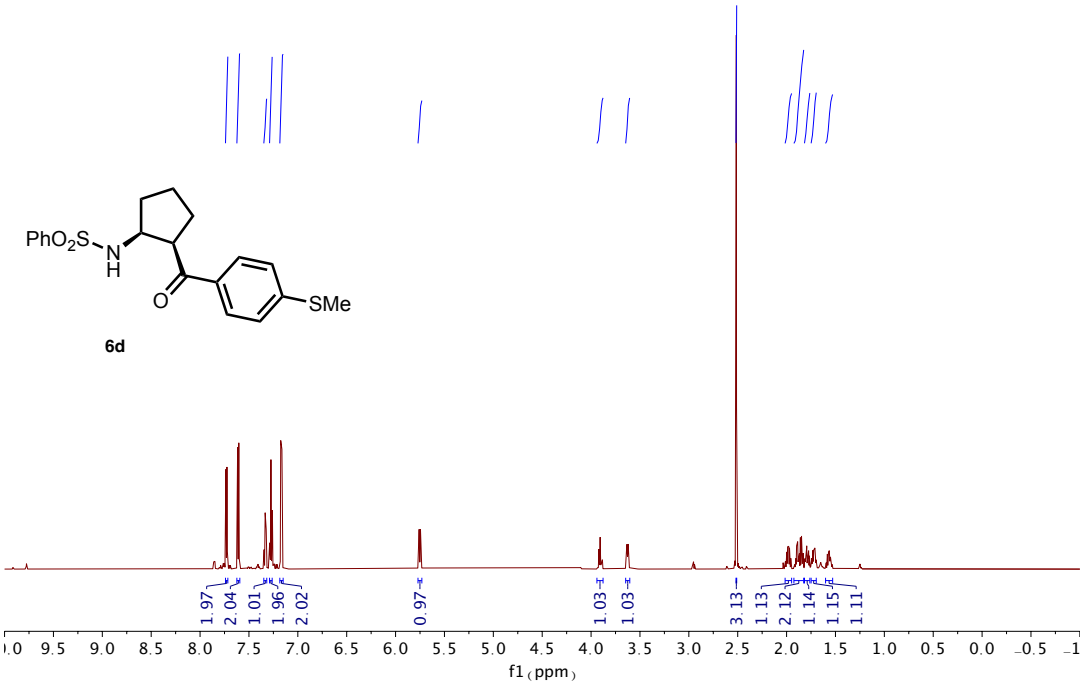

201.90
144.49
140.78
133.51
132.32
129.32
129.03
128.60
127.00
56.96
46.87
32.98
29.58
21.88
21.78
PhO2S
N
H
O
Me
6a
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

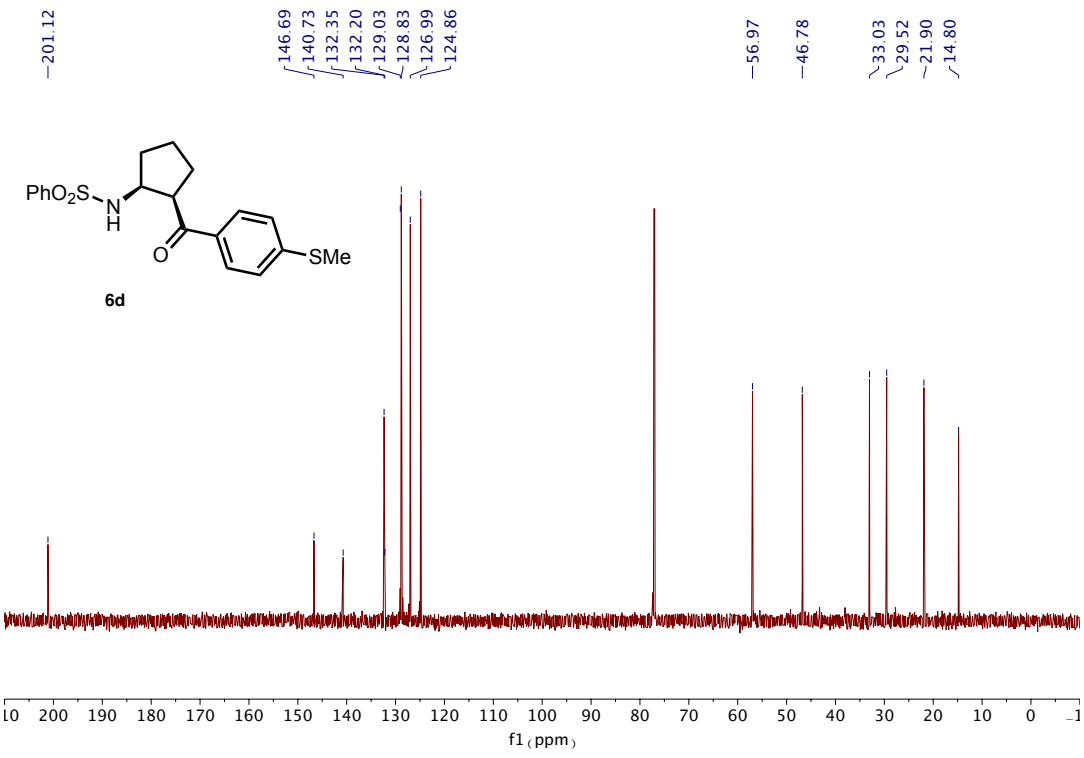

PhO2S
N
H
Me
O
6b
2.00
1.00
2.08
1.04
1.05
1.03
1.01
0.94
1.06
1.08
3.10
1.07
2.08
2.16
1.20
f1 (ppm)

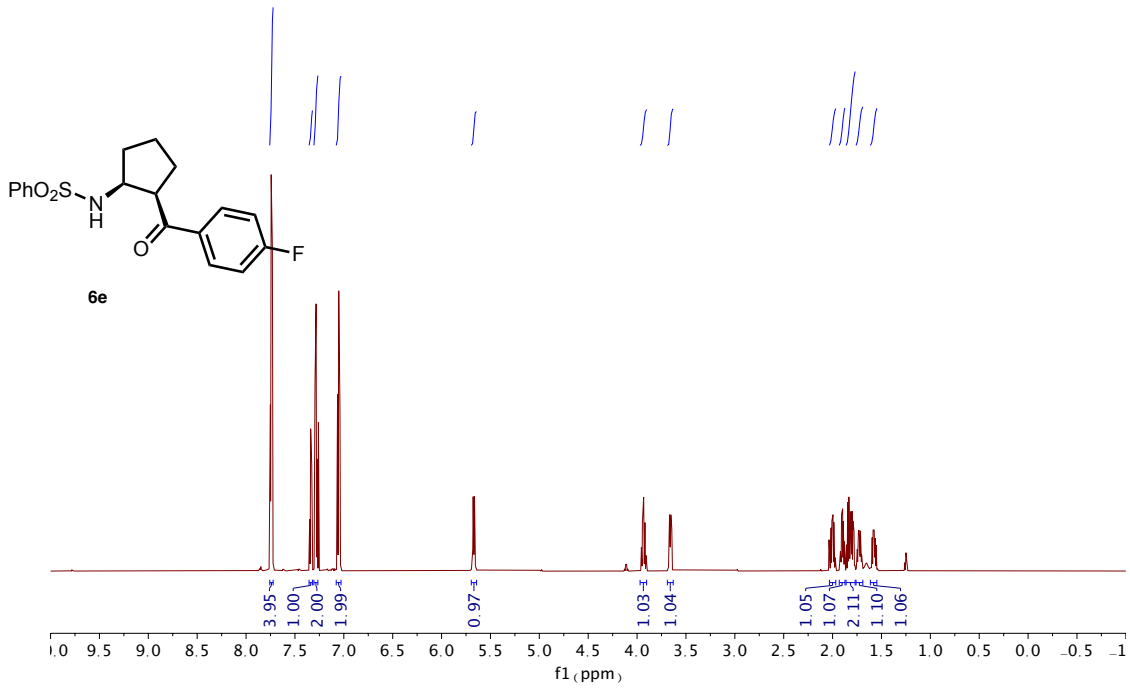

206.56
140.97
138.86
137.10
132.50
132.19
131.80
129.16
128.70
127.04
125.72
57.08
50.00
32.95
29.32
21.94
21.54
PhO2S
N
H
Me
O
6b
f1 (ppm)

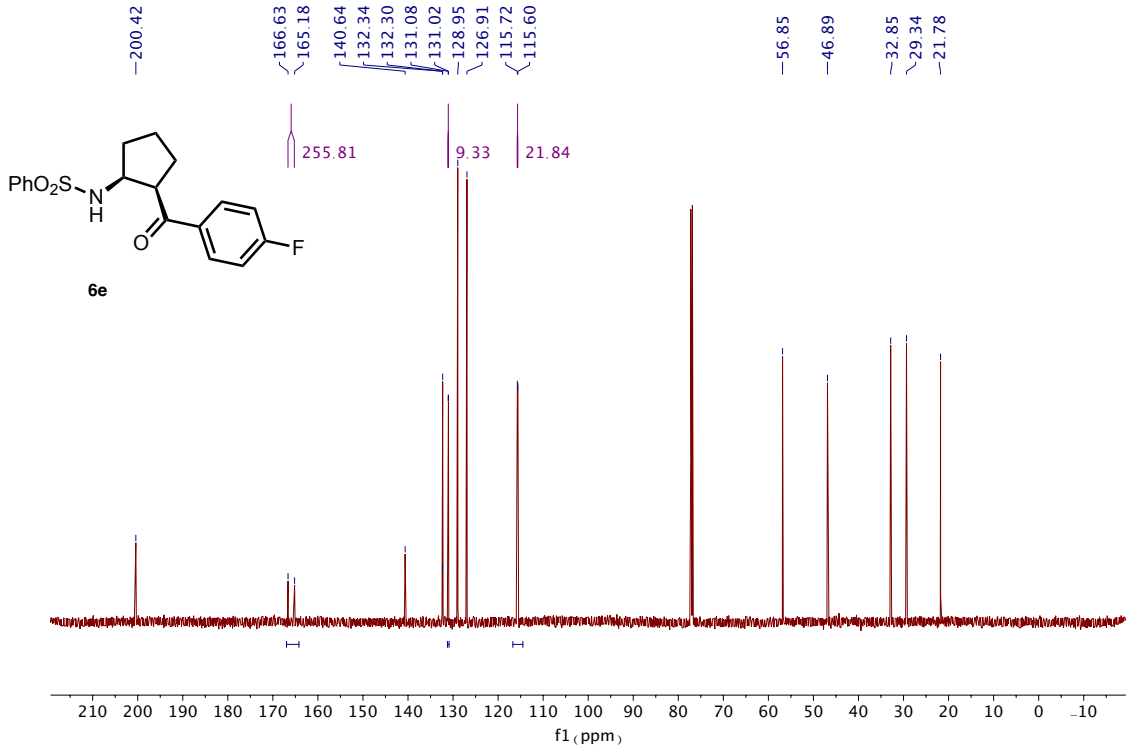

PhO2S
N
H
O
OMe
6c
2.00
2.13
1.00
2.00
1.95
0.98
1.16
3.14
1.03
1.07
2.09
1.11
1.16
1.13
f1 (ppm)

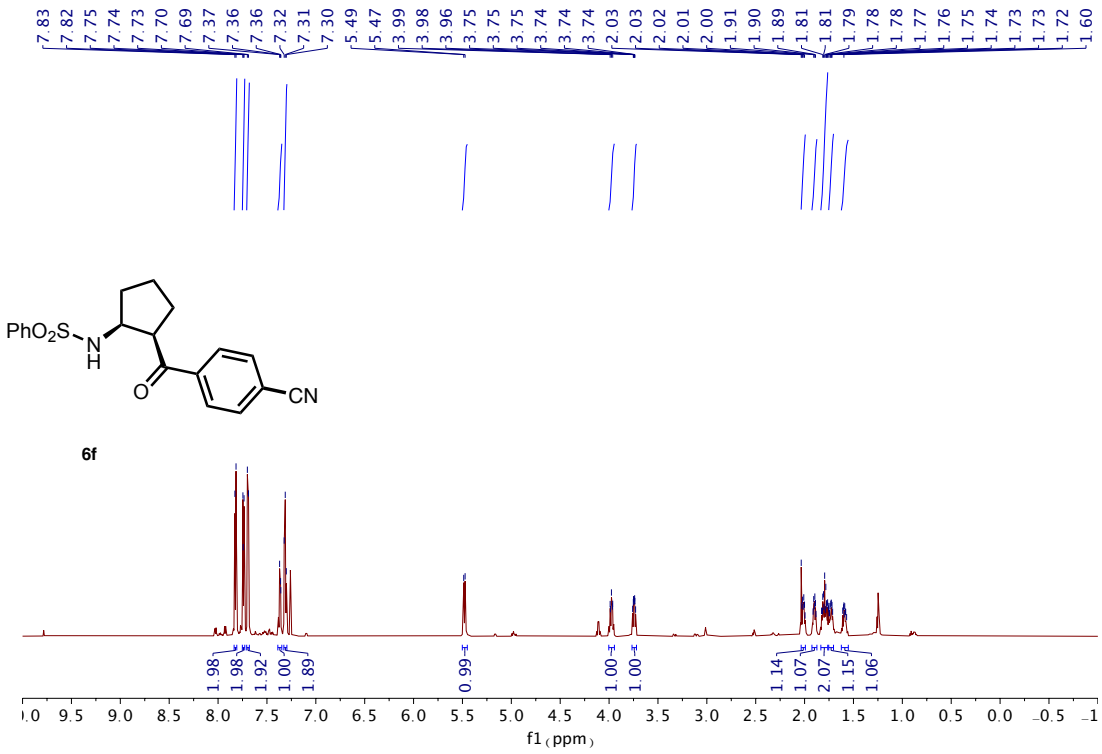

200.78
163.90
140.80
132.32
130.82
129.06
129.01
127.03
113.79
57.00
55.66
46.60
33.05
29.69
21.93
PhO2S
N
H
O
OMe
6c
f1 (ppm)

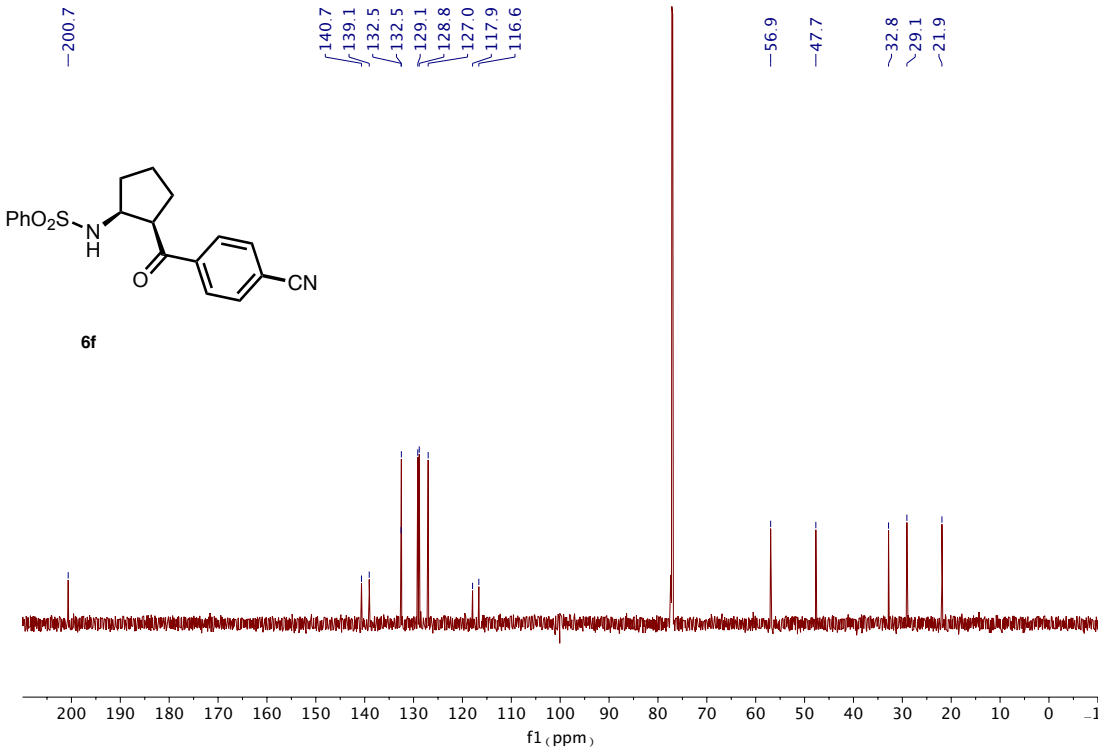

PhO2S
N
H
O
SMe
6d
1.97
2.04
1.01
1.96
2.02
0.97
1.03
1.03
3.13
1.13
2.12
1.14
1.15
1.11
f1 (ppm)

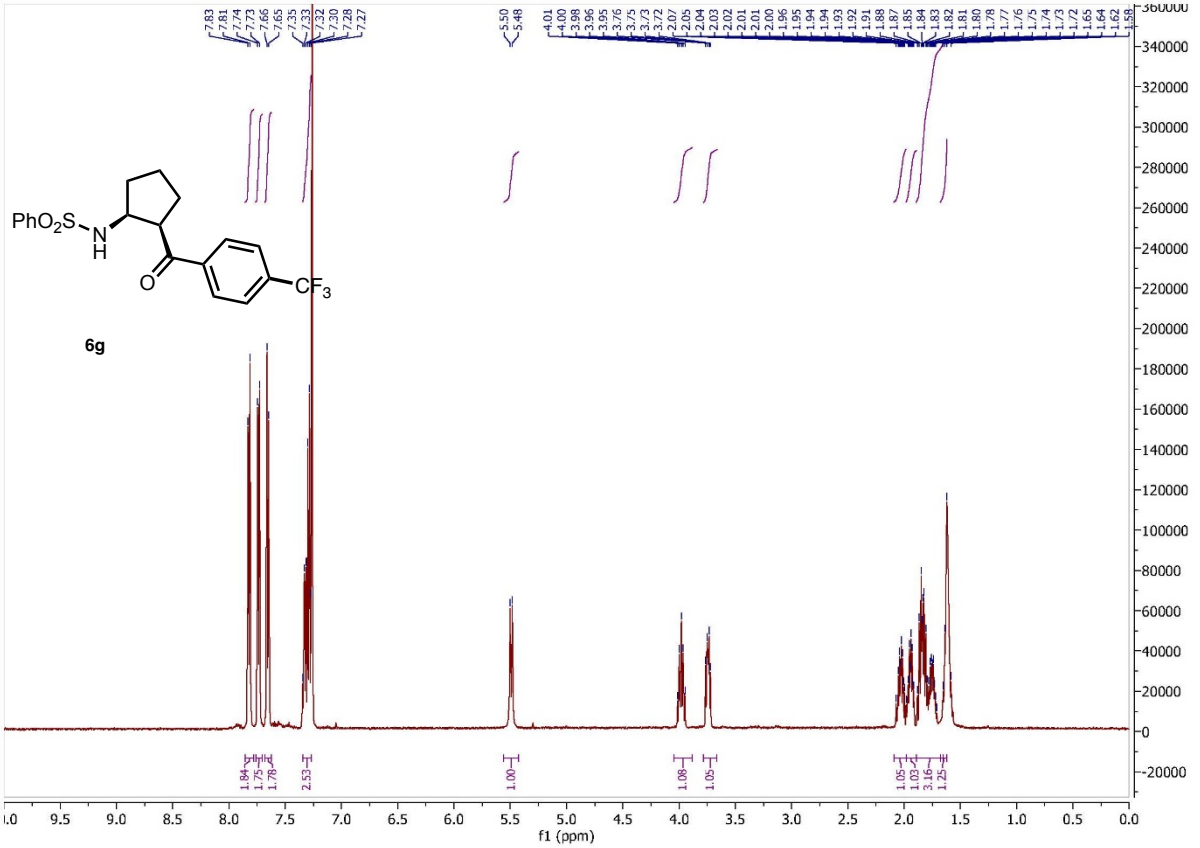

201.12
146.69
140.73
132.35
132.20
129.03
128.83
126.99
124.86
56.97
46.78
33.03
29.52
21.90
14.80
PhO2S
N
H
O
SMe
6d
f1 (ppm)

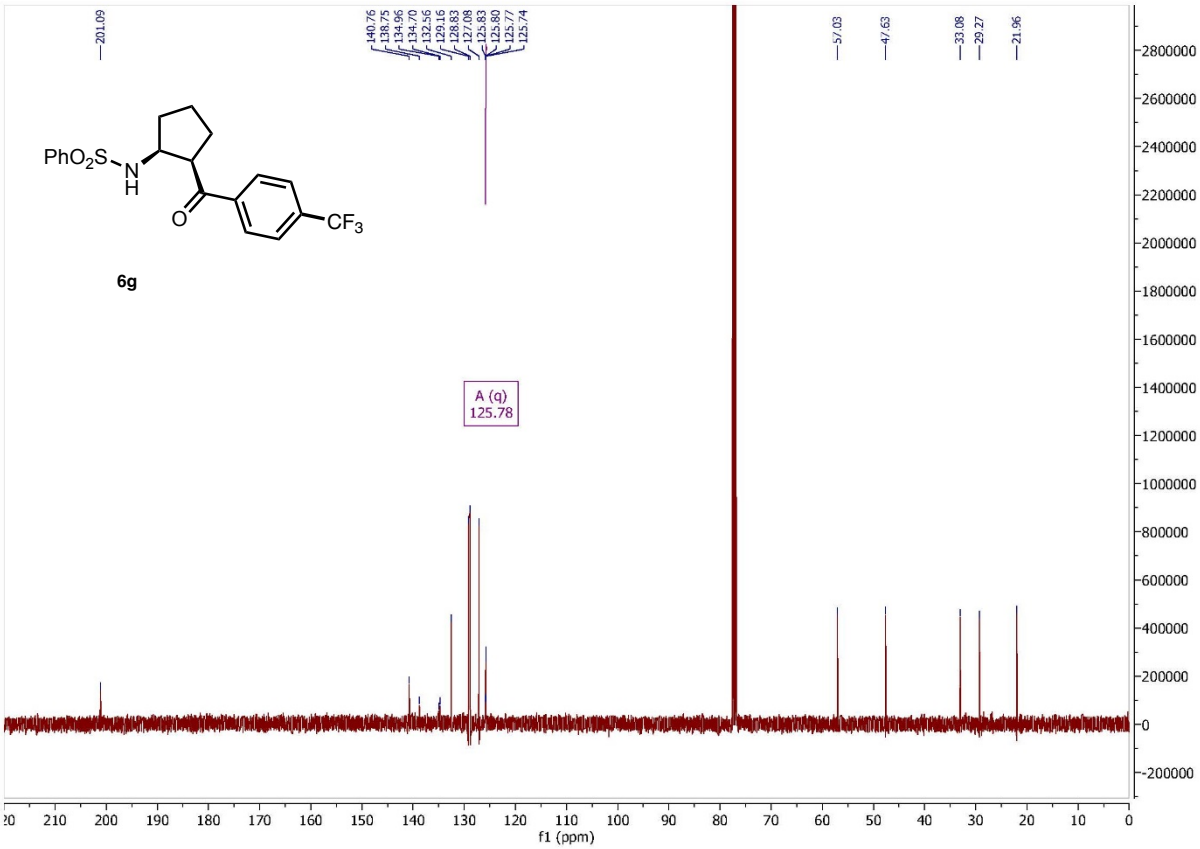

PhO2S
N
H
O
F
6e
3.95
1.00
2.00
1.99
0.97
1.03
1.04
1.05
1.07
2.11
1.10
1.06
f1 (ppm)

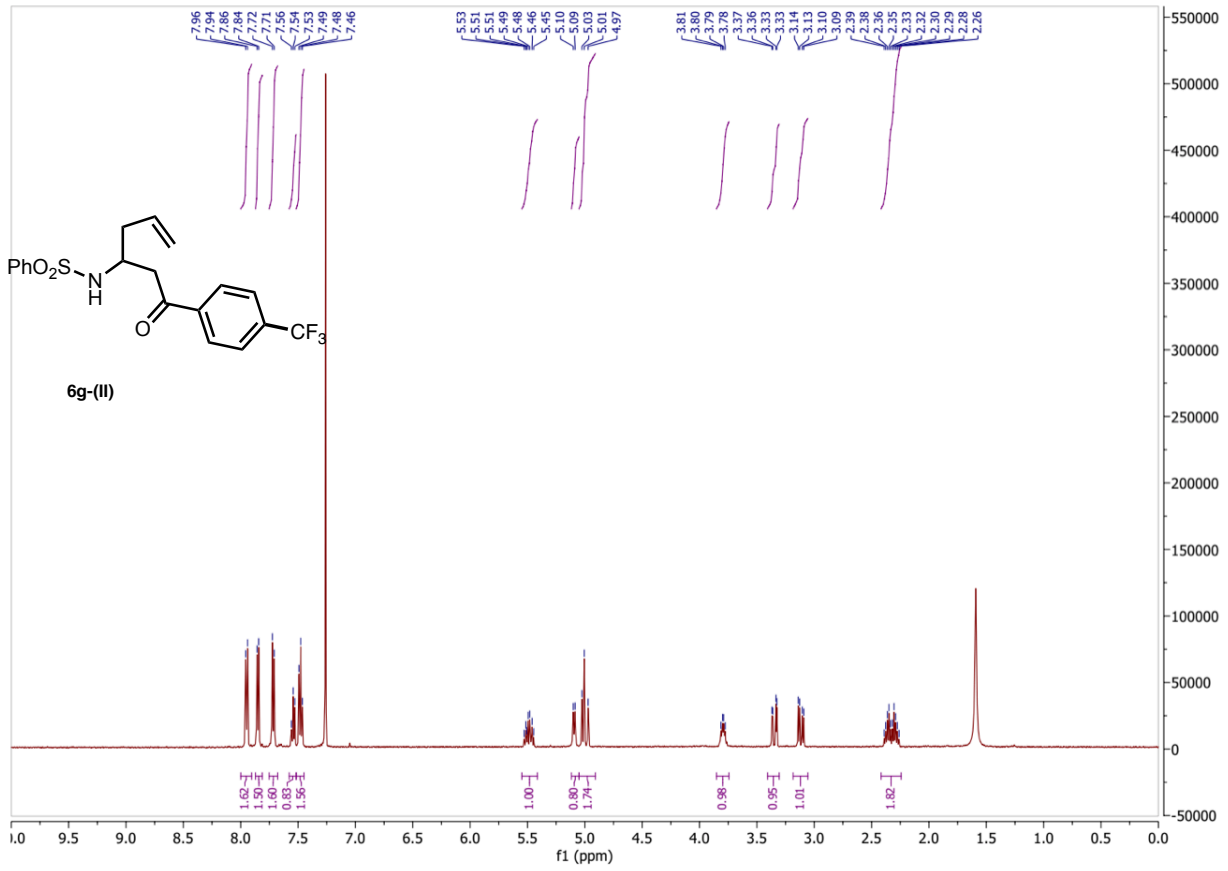

200.42
166.63
165.18
140.64
132.34
132.30
131.08
131.02
128.95
126.91
115.72
115.60
56.85
46.89
32.85
29.34
21.78
255.81
9.33
21.84
PhO2S
N
H
O
F
6e
f1 (ppm)

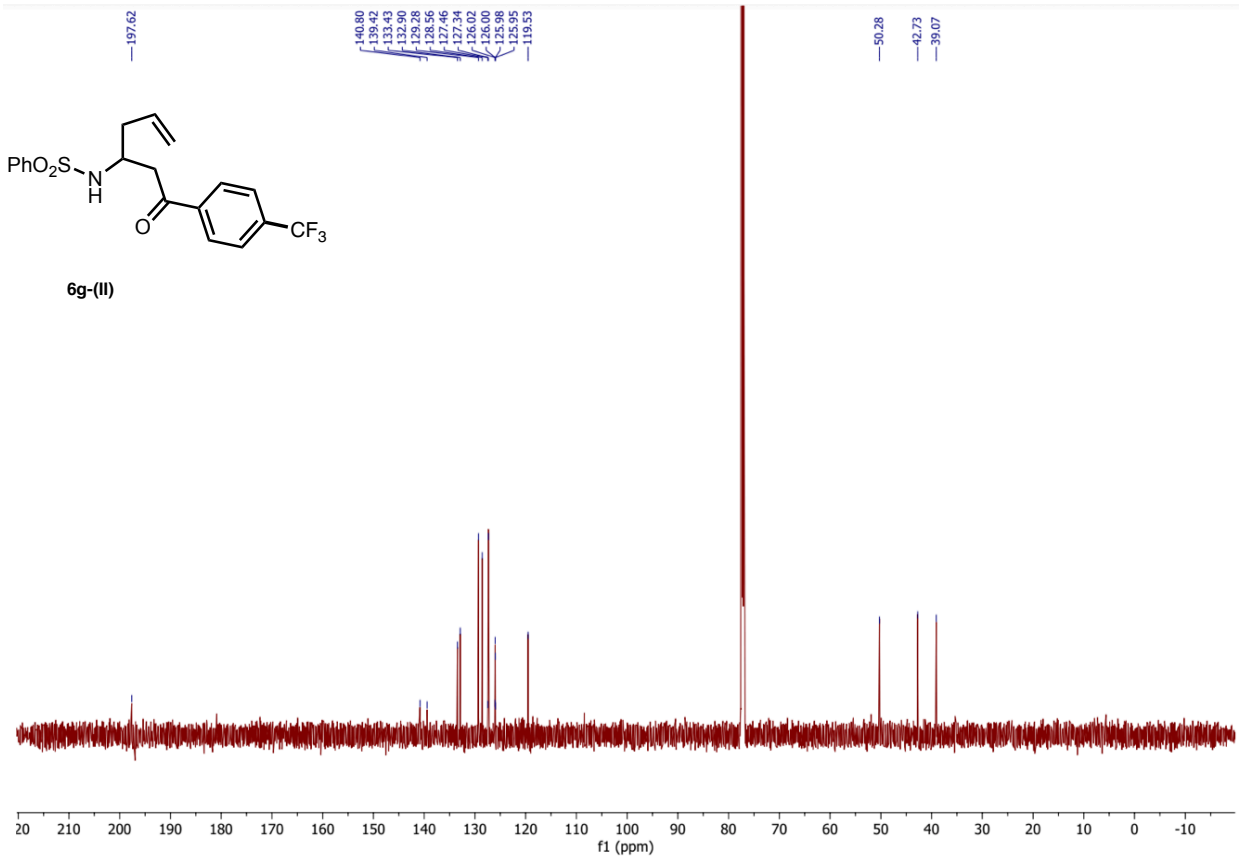

7.83
7.82
7.75
7.74
7.73
7.70
7.69
7.37
7.36
7.36
7.32
7.31
7.30
5.49
5.47
3.99
3.98
3.96
3.75
3.75
3.75
3.74
3.74
3.74
2.03
2.03
2.02
2.01
2.00
1.91
1.90
1.89
1.81
1.81
1.79
1.78
1.78
1.77
1.76
1.75
1.74
1.73
1.73
1.72
1.60
PhO2S
N
H
O
CN
6f
1.98
1.98
1.92
1.00
1.89
0.99
1.00
1.00
1.14
1.07
2.07
1.15
1.06
f1 (ppm)

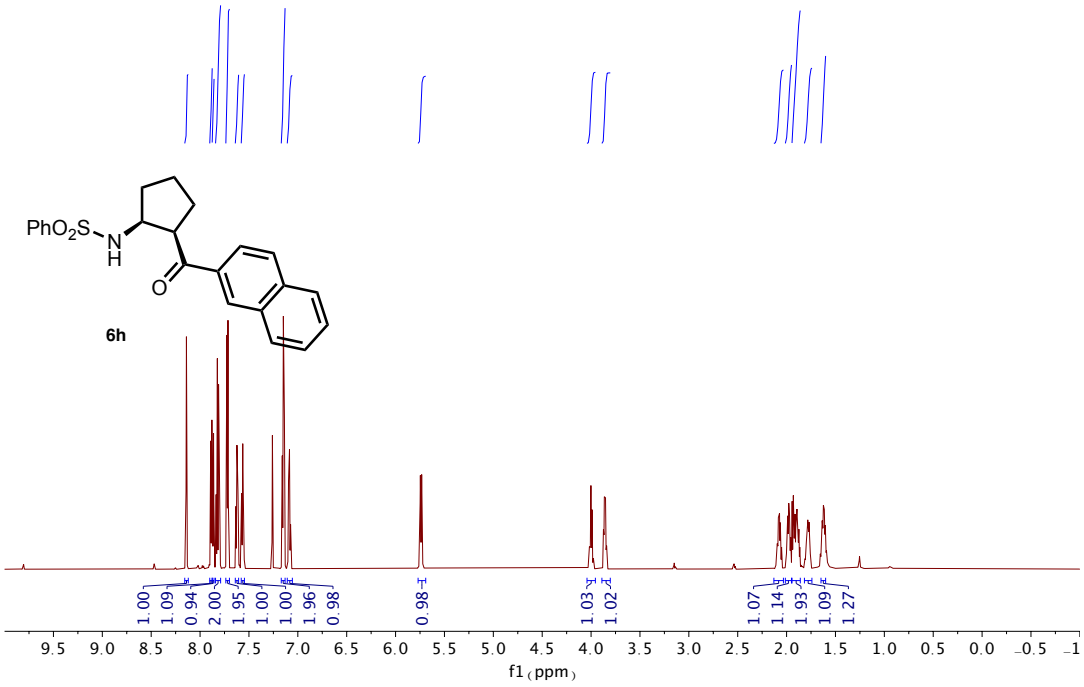

200.7
140.7
139.1
132.5
132.5
129.1
128.8
127.0
117.9
116.6
56.9
47.7
32.8
29.1
21.9
PhO2S
N
H
O
CN
6f
f1 (ppm)

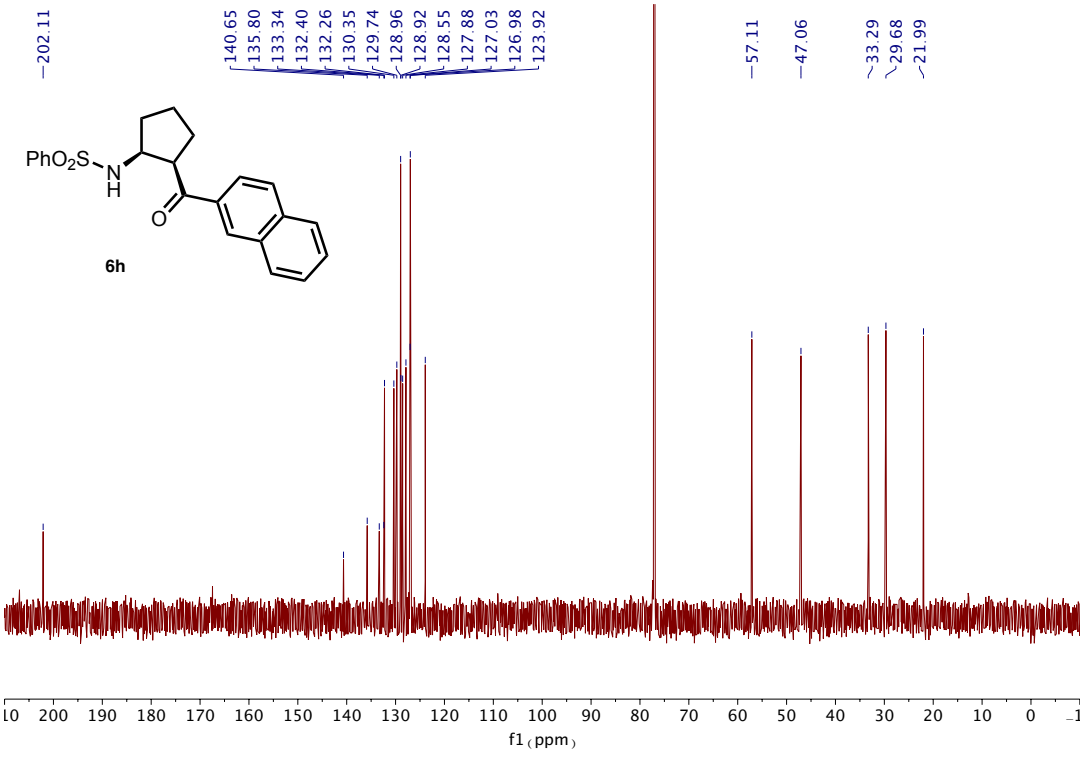

PhO2S
N
H
O
CF3
6g
f1 (ppm)

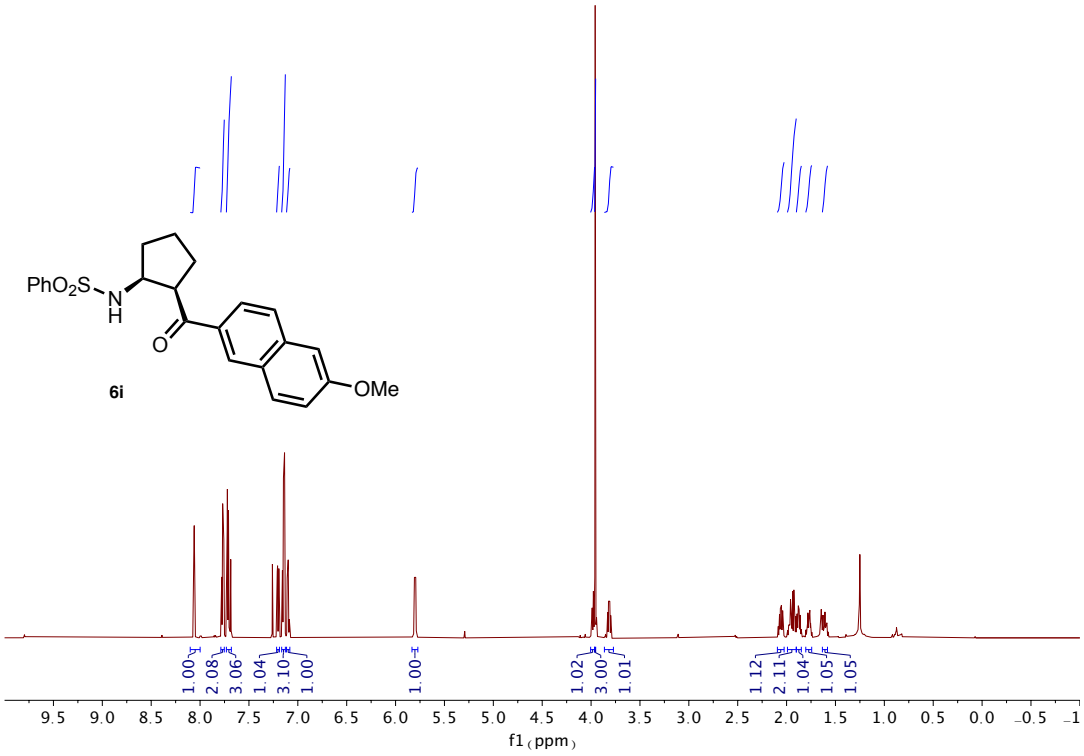

PhO2S
N
H
O
CF3
6g
A (q)
125.78
f1 (ppm)

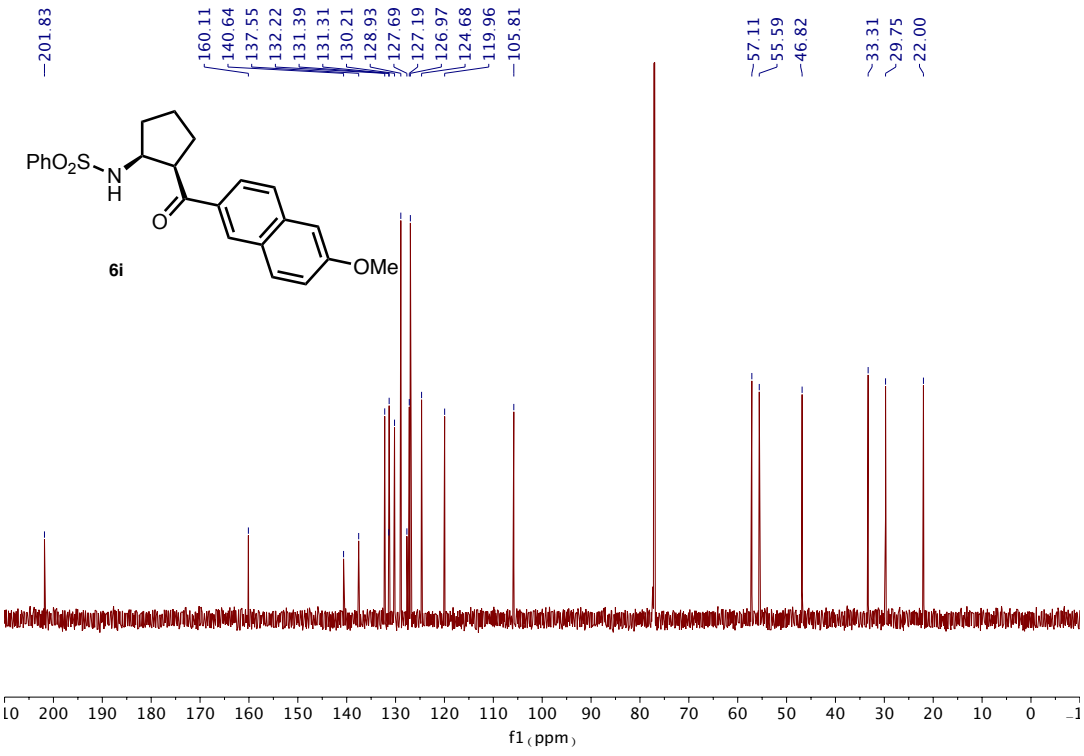

7.96
7.94
7.86
7.84
7.72
7.71
7.56
7.54
7.53
7.49
7.48
7.46
5.53
5.51
5.51
5.49
5.48
5.46
5.45
5.10
5.09
5.03
5.01
4.97
3.81
3.80
3.79
3.78
3.37
3.36
3.33
3.33
3.14
3.13
3.10
3.09
2.39
2.38
2.36
2.35
2.33
2.32
2.30
2.29
2.28
2.26
PhO2S
N
H
O
CF3
6g-(II)
1.62
1.59
1.60
0.83
1.36
1.00
0.80
1.74
0.98
0.95
1.01
1.82
f1 (ppm)

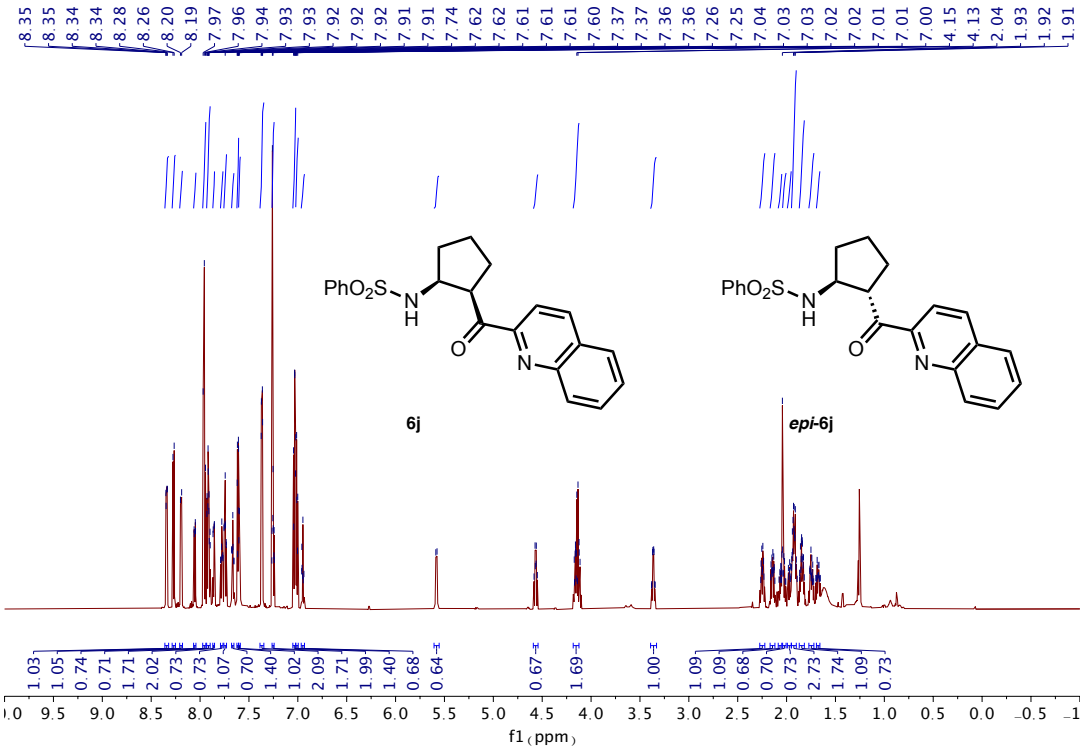

197.62
140.80
139.42
133.43
132.90
129.28
128.56
127.46
127.34
126.02
126.00
125.98
125.95
119.53
50.28
42.73
39.07
PhO2S
N
H
O
CF3
6g-(II)
f1 (ppm)

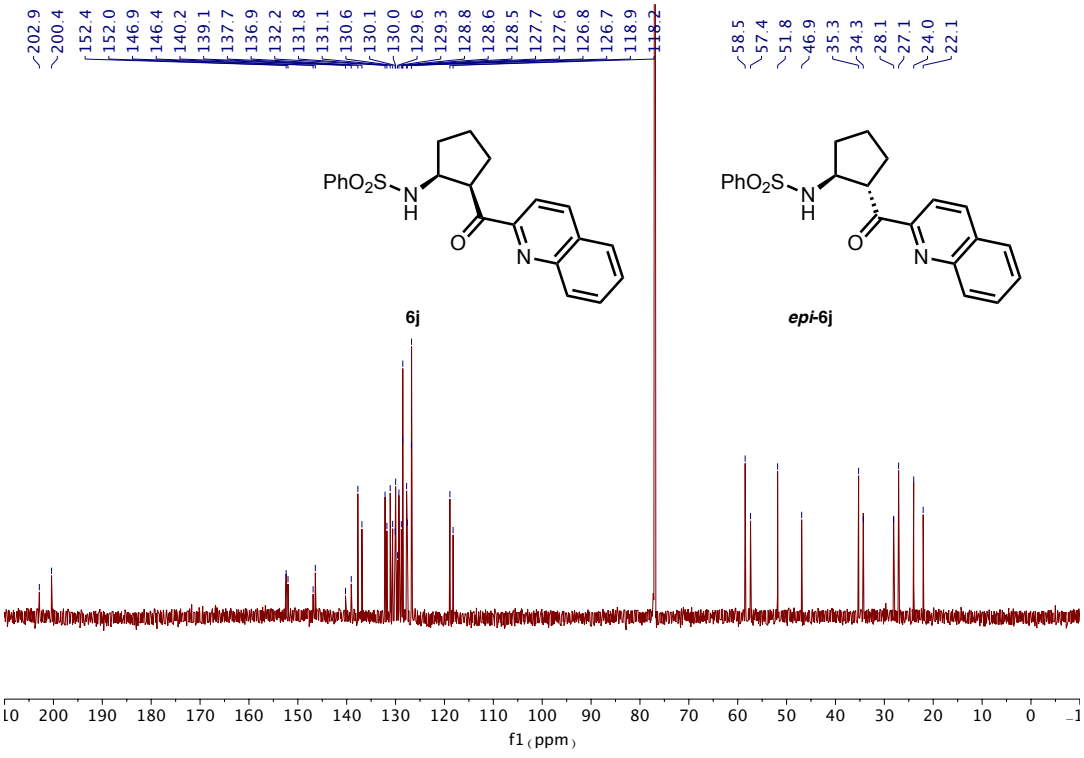

PhO2S
N
H
O
6h
1.00
1.09
0.94
2.00
1.95
1.00
1.00
1.96
0.98
0.98
1.03
1.02
1.07
1.14
1.93
1.09
1.27
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

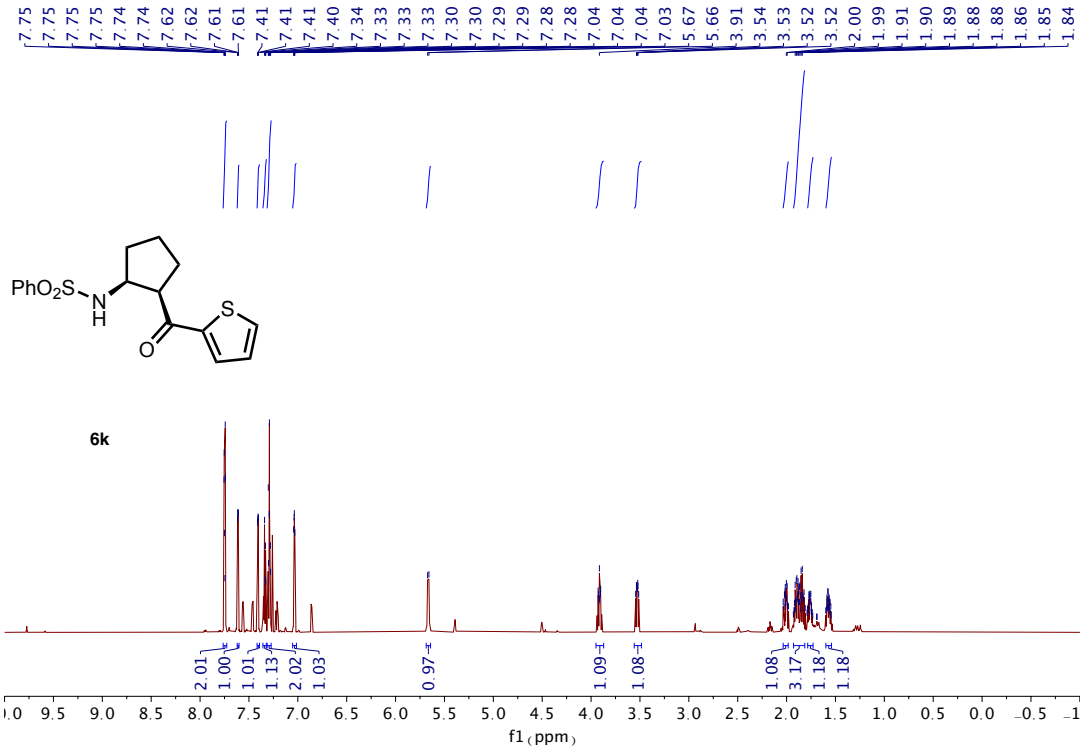

202.11
140.65
135.80
133.34
132.40
132.26
130.35
129.74
128.96
128.92
128.55
127.88
127.03
126.98
123.92
57.11
47.06
33.29
29.68
21.99
PhO2S
N
H
O
6h
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)

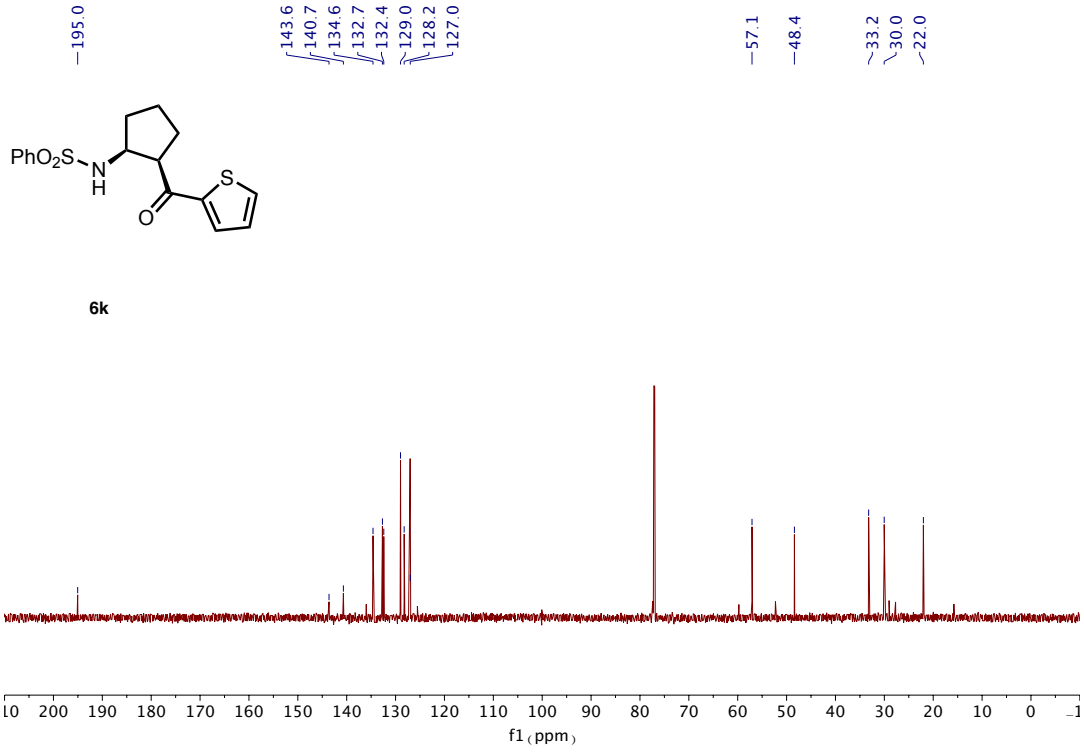

PhO2S
N
H
O
OMe
6i
1.00
2.08
3.06
1.04
3.10
1.00
1.00
1.02
3.00
1.01
1.12
2.11
1.04
1.05
1.05
f1 (ppm)

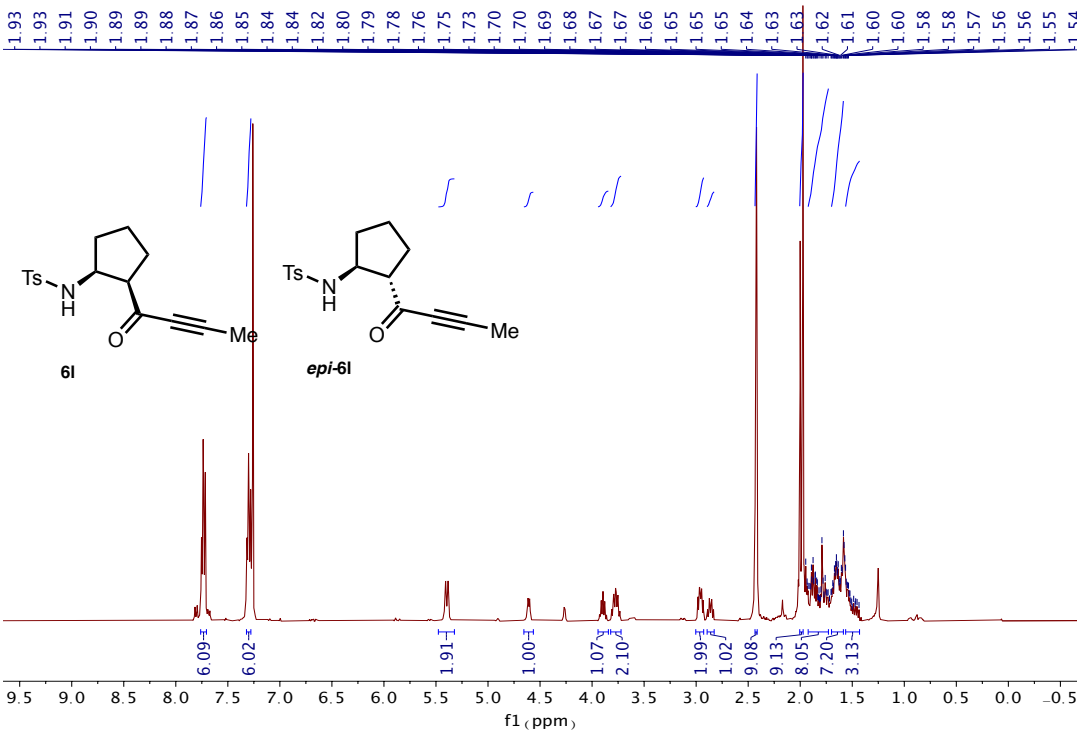

201.83
160.11
140.64
137.55
132.22
131.39
131.31
130.21
128.93
127.69
127.19
126.97
124.68
119.96
105.81
57.11
55.59
46.82
33.31
29.75
22.00
PhO2S
N
H
O
OMe
6i
f1 (ppm)

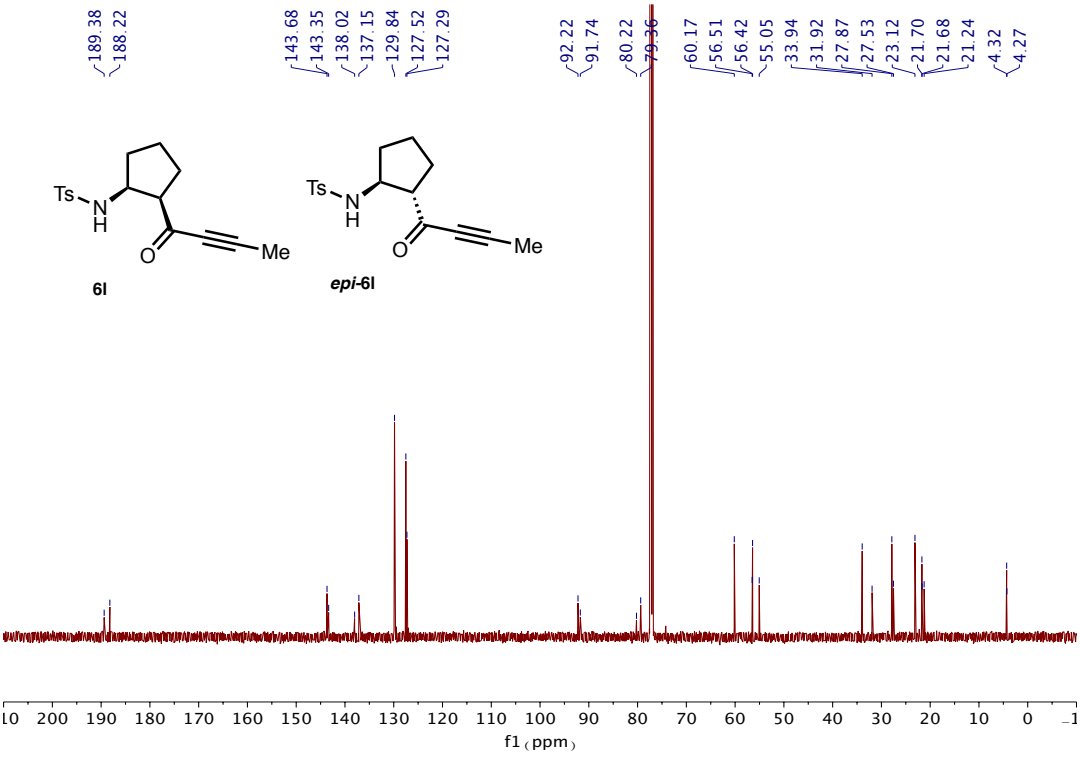

8.35 8.35 8.34 8.34 8.28 8.26 8.20 8.19 7.97 7.96 7.94 7.93 7.93 7.92 7.92 7.92 7.91 7.91 7.74 7.62 7.62 7.61 7.61 7.61 7.60 7.37 7.37 7.36 7.36 7.26 7.25 7.04 7.03 7.03 7.02 7.02 7.01 7.01 7.00 4.15 4.13 2.04 1.93 1.92 1.91
PhO2S N H O N
6j
PhO2S N H O N
epi-6j
1.03 1.05 0.74 0.71 1.71 2.02 0.73 0.73 1.07 0.70 1.40 1.02 2.09 1.71 1.99 1.40 0.68 0.64 0.67 1.69 1.00 1.09 1.09 0.68 0.70 0.73 2.73 1.74 1.09 0.73
f1 (ppm)

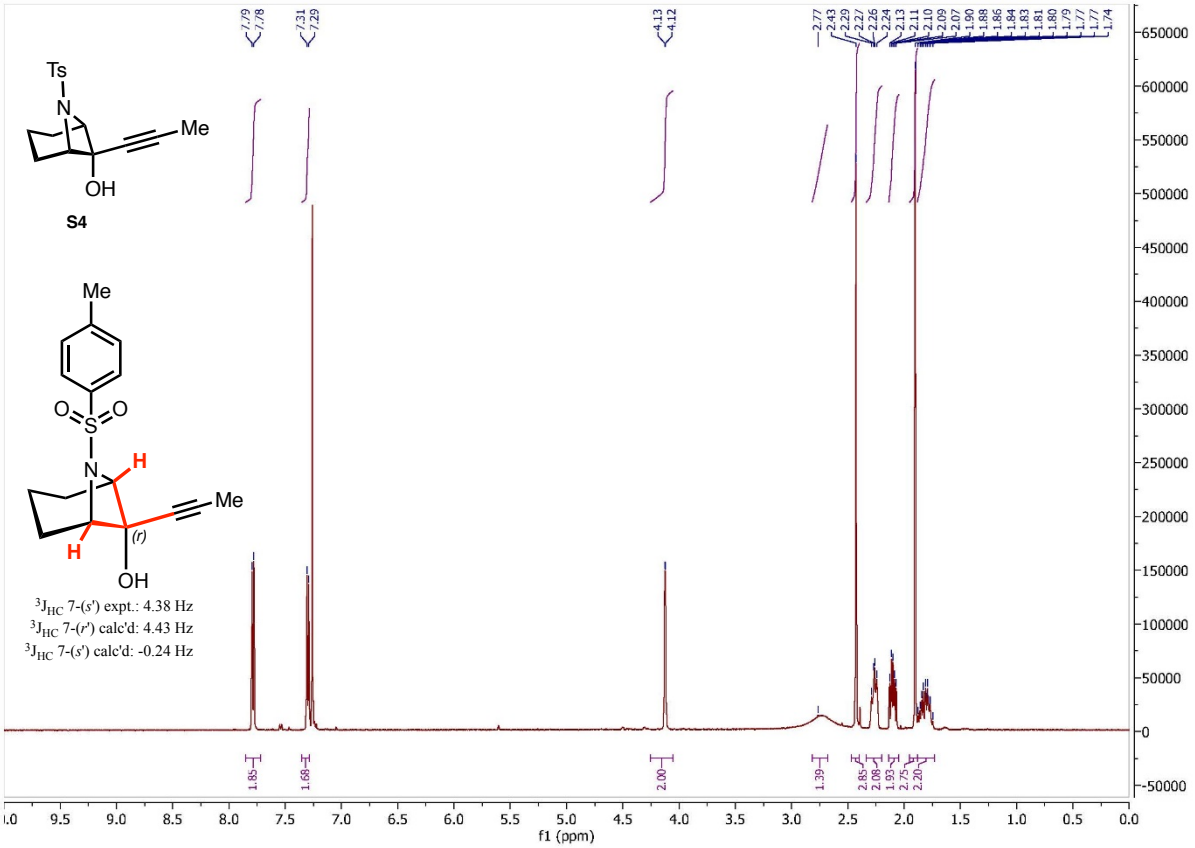

202.9 200.4 152.4 152.0 146.9 146.4 140.2 139.1 137.7 136.9 132.2 131.8 131.1 130.6 130.1 130.0 129.6 129.3 128.8 128.6 128.5 127.7 127.6 126.8 126.7 118.9 118.2
58.5 57.4 51.8 46.9 35.3 34.3 28.1 27.1 24.0 22.1
PhO2S N H O N
6j
PhO2S N H O N
epi-6j
f1 (ppm)

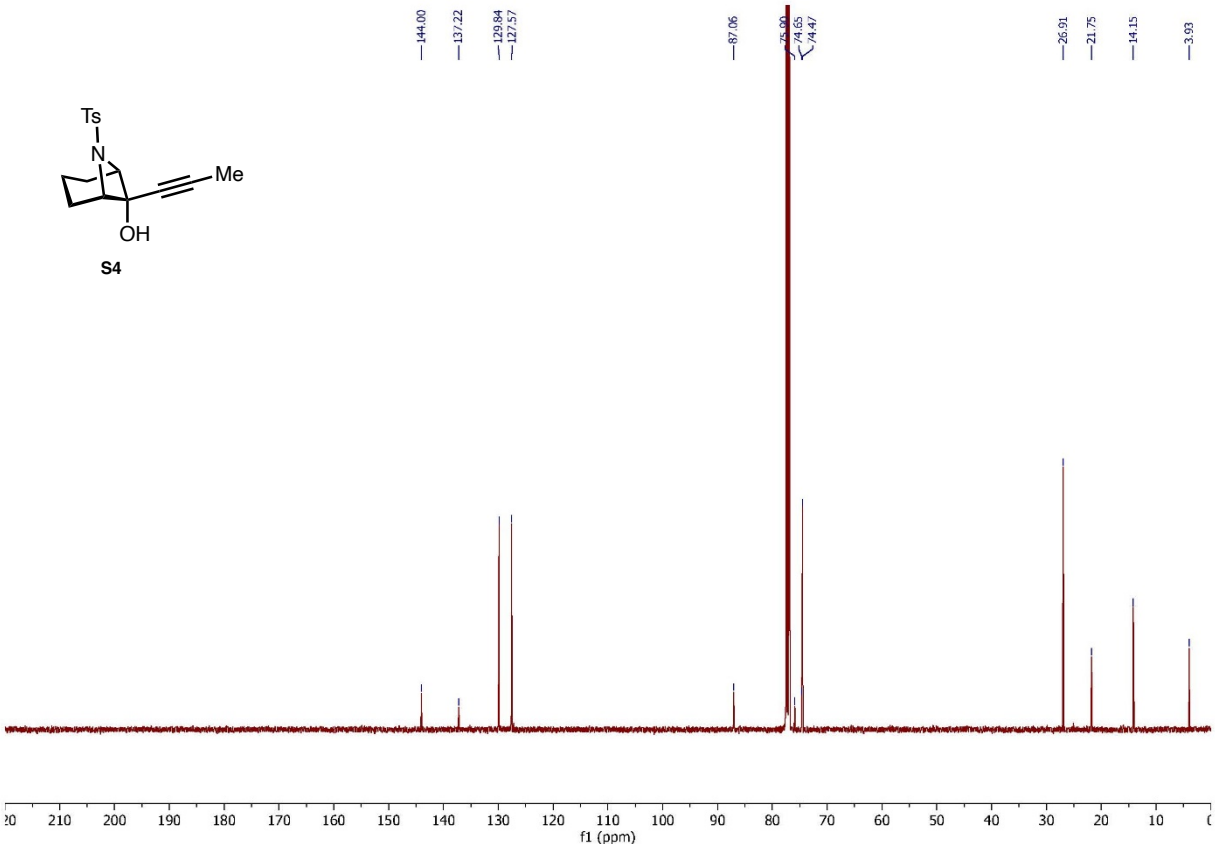

7.75 7.75 7.75 7.75 7.74 7.74 7.62 7.62 7.61 7.61 7.41 7.41 7.41 7.40 7.34 7.33 7.33 7.33 7.30 7.30 7.29 7.29 7.28 7.28 7.04 7.04 7.04 7.03 5.67 5.66 3.91 3.54 3.53 3.52 3.52 2.00 1.99 1.91 1.90 1.89 1.88 1.88 1.86 1.85 1.84
PhO2S
N
H
S
O
6k
2.01 1.00 1.01 1.13 2.02 1.03 0.97 1.09 1.08 1.08 3.17 1.18 1.18
f1 (ppm)

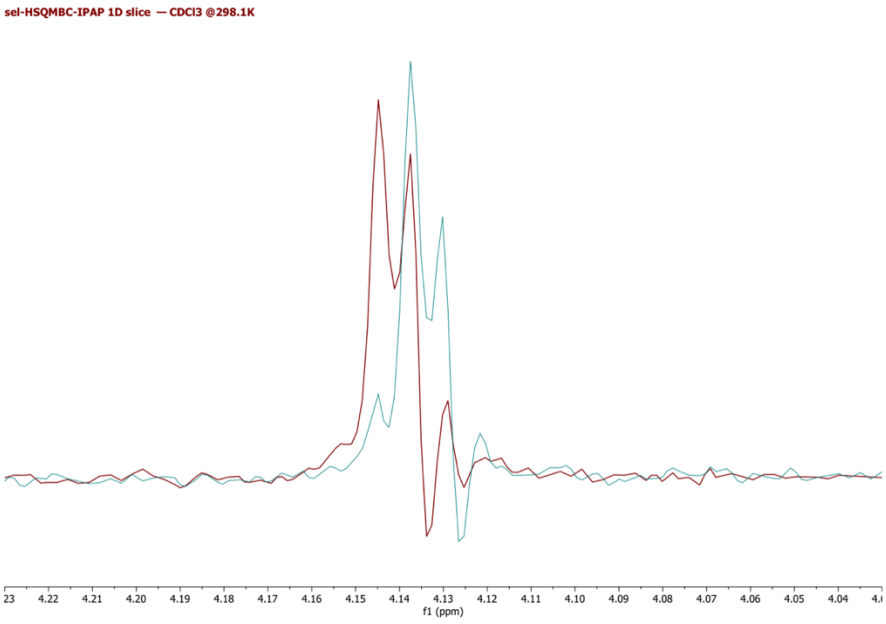

195.0
143.6 140.7 134.6 132.7 132.4 129.0 128.2 127.0
57.1 48.4 33.2 30.0 22.0
PhO2S
N
H
S
O
6k
f1 (ppm)

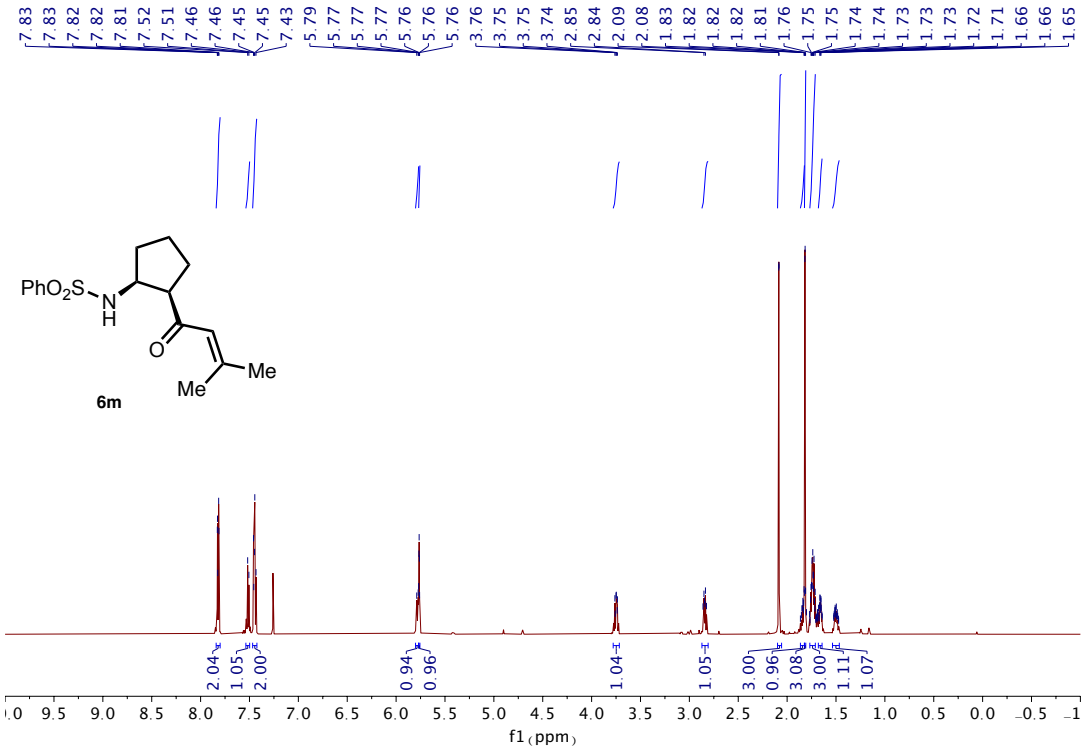

Ts
N
H
O
Me
6l
epi-6l
f1 (ppm)

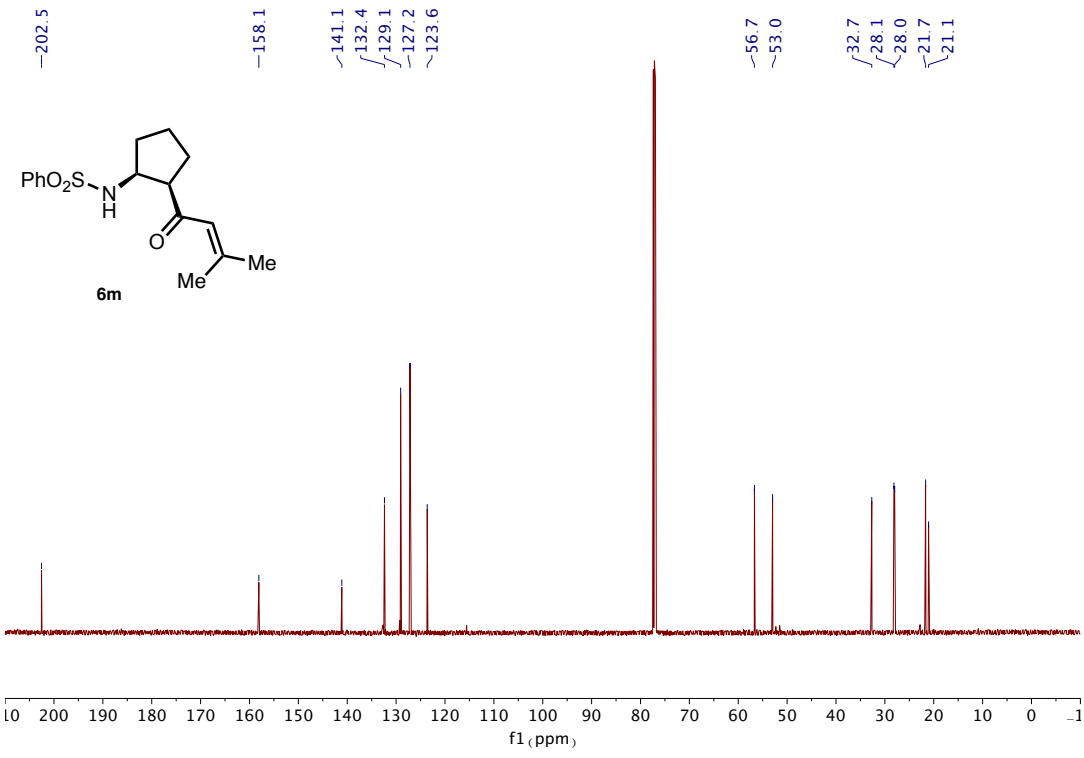

Ts
N
H
O
Me
6l
epi-6l
f1 (ppm)

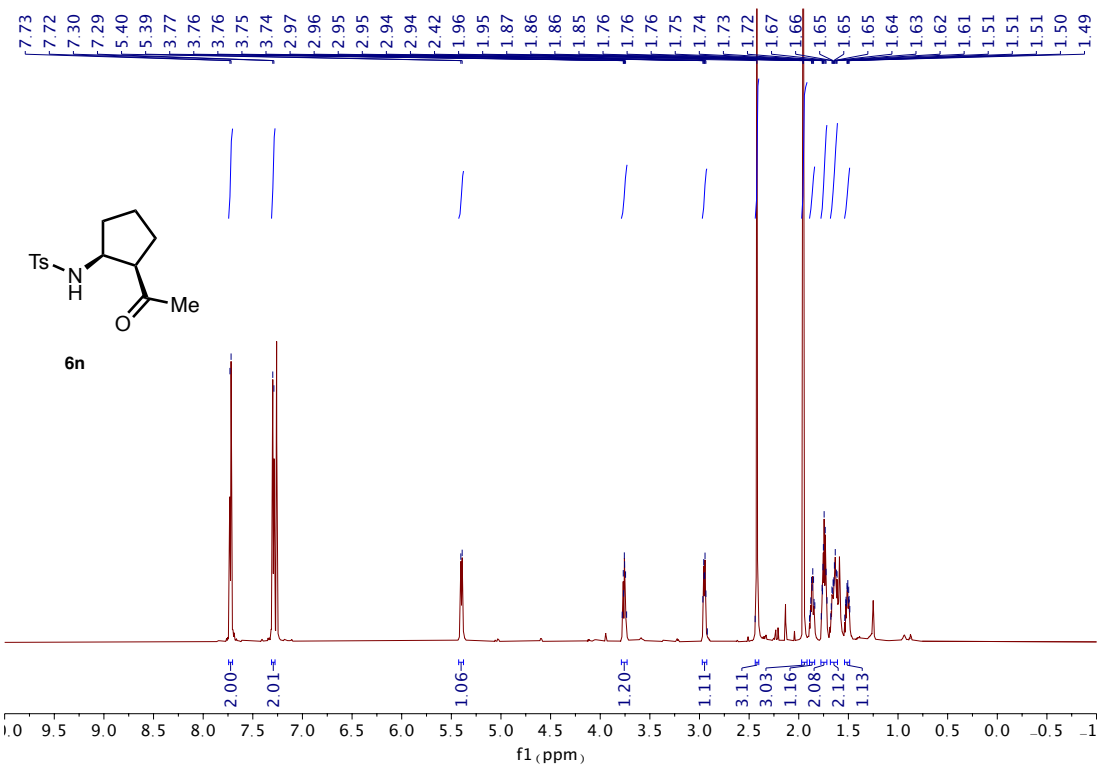

Ts
N
Me
OH
S4
Me
O
S
O
N
H
Me
(r)
H
OH
$^3J_{HC}$ 7-(s') expt.: 4.38 Hz
$^3J_{HC}$ 7-(r') calc'd: 4.43 Hz
$^3J_{HC}$ 7-(s') calc'd: -0.24 Hz
f1 (ppm)

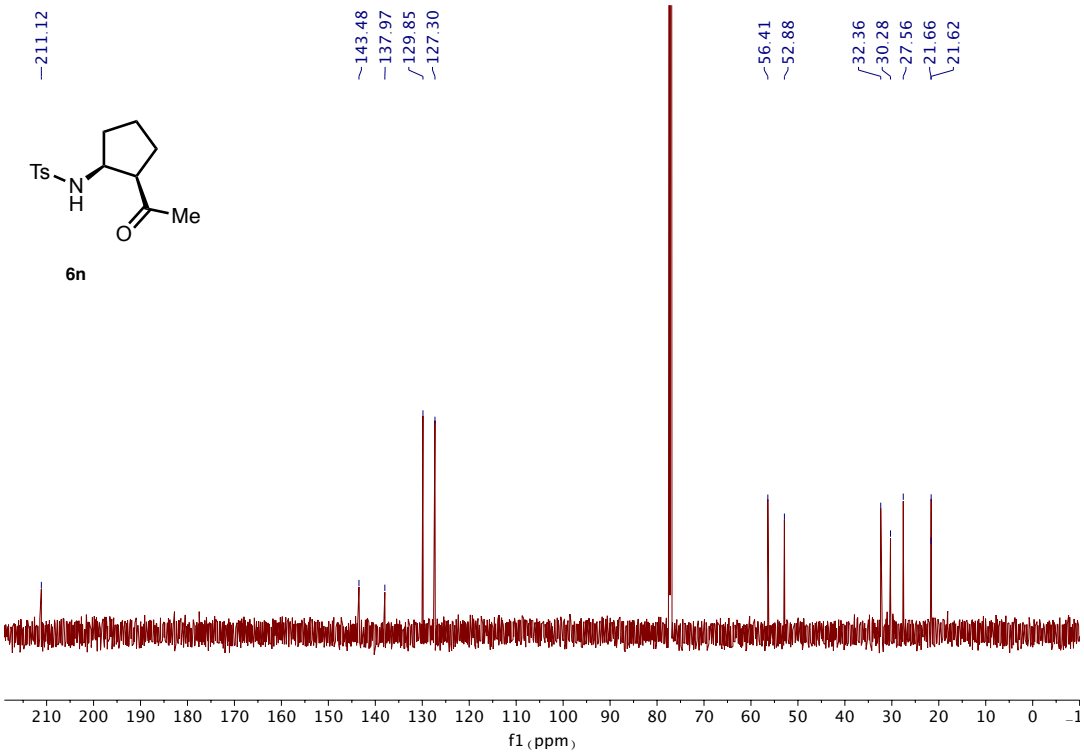

Ts
N
Me
OH
S4
144.00
137.22
129.84
127.57
87.06
75.00
74.65
74.47
26.91
21.75
14.15
3.93
f1 (ppm)

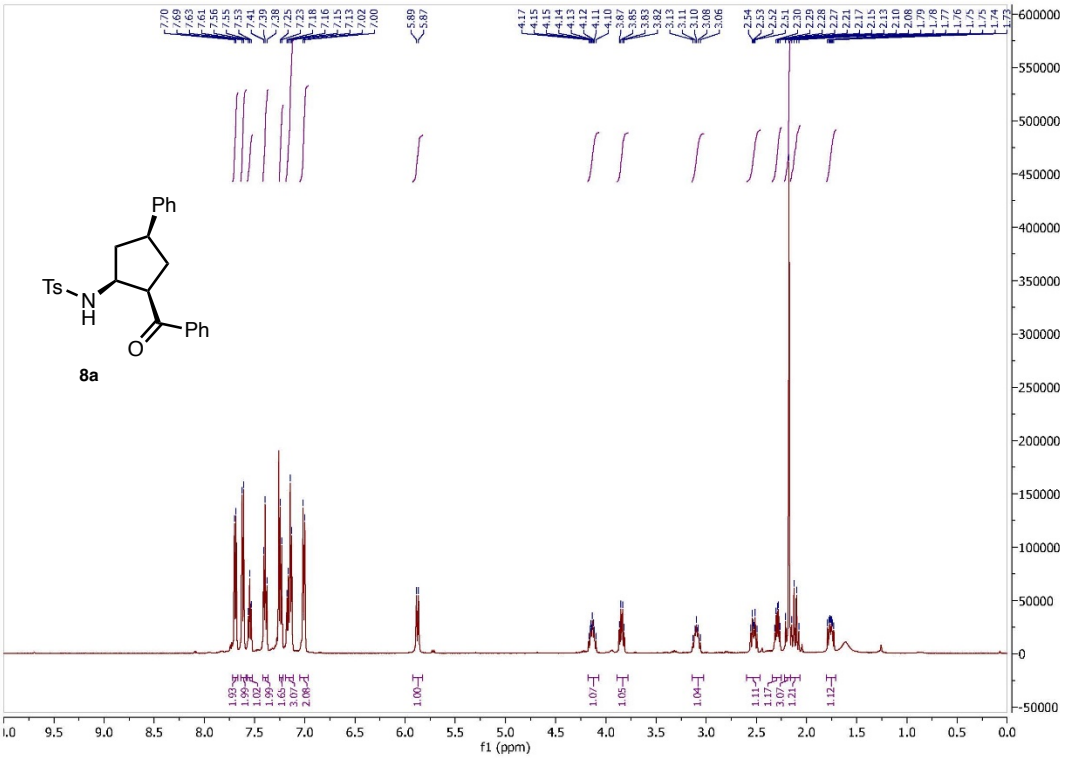

sel-HSQMBC-IPAP 1D slice — CDCl3 @298.1K
23 4.22 4.21 4.20 4.19 4.18 4.17 4.16 4.15 4.14 4.13 4.12 4.11 4.10 4.09 4.08 4.07 4.06 4.05 4.04
f1 (ppm)

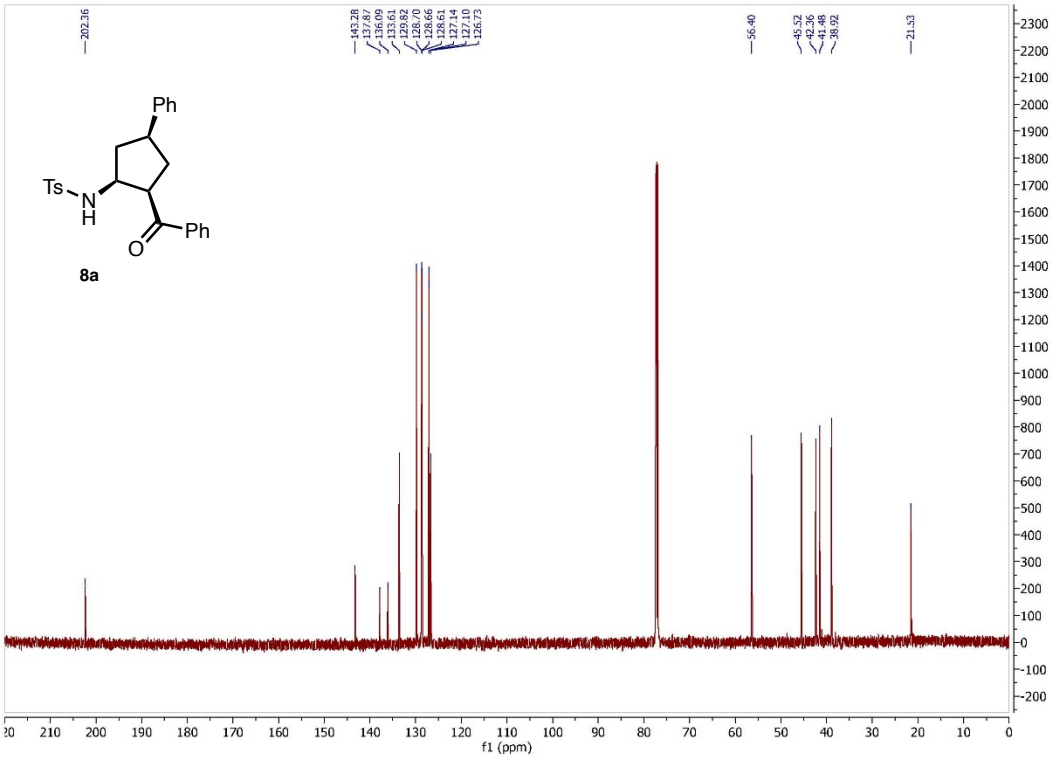

7.83 7.83 7.82 7.82 7.81 7.52 7.51 7.46 7.46 7.45 7.45 7.43
5.79 5.77 5.77 5.77 5.76 5.76 5.76
3.76 3.75 3.75 3.74 2.85 2.84 2.09 2.08 1.83 1.82 1.82 1.82 1.81 1.76 1.75 1.75 1.74 1.74 1.73 1.73 1.73 1.72 1.71 1.66 1.66 1.65
PhO2S
N
H
O
Me
Me
6m
2.04 1.05 2.00 0.94 0.96 1.04 1.05 3.00 0.96 3.08 3.00 1.11 1.07
f1 (ppm)


202.5
158.1
141.1
132.4
129.1
127.2
123.6
56.7
53.0
32.7
28.1
28.0
21.7
21.1
PhO2S
N
H
O
Me
Me
6m
f1 (ppm)

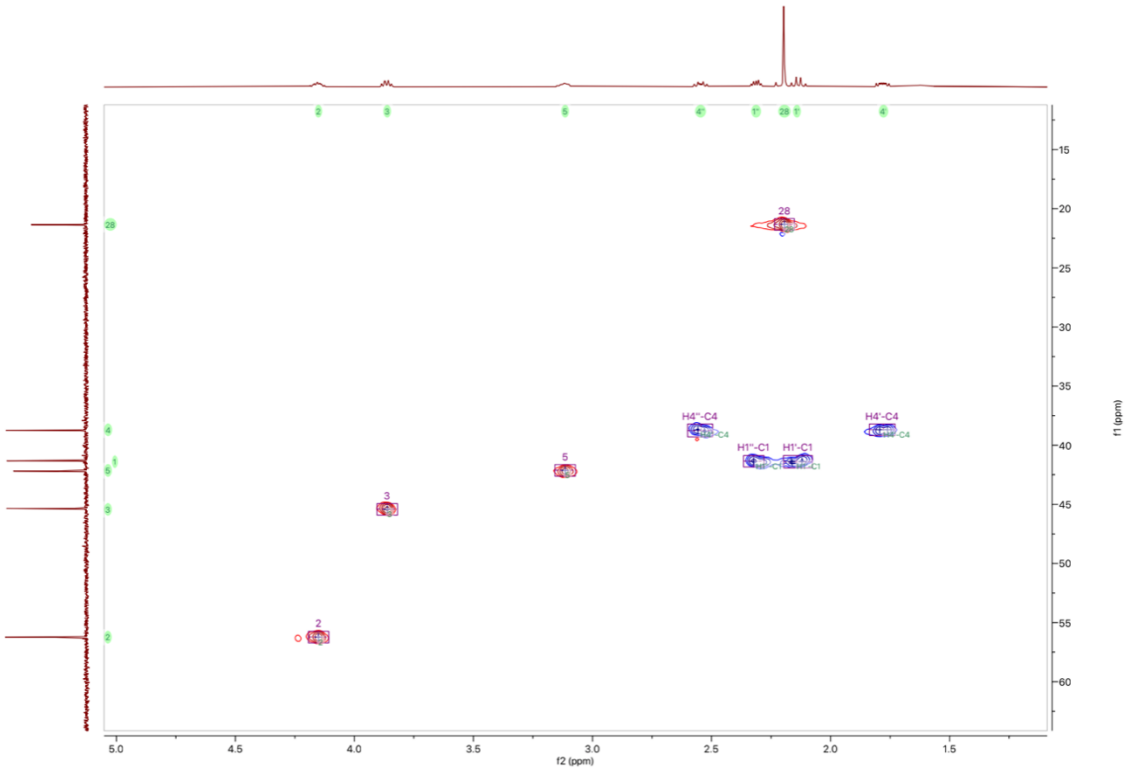

7.73 7.72 7.30 7.29 5.40 5.39 3.77 3.76 3.76 3.75 3.74 2.97 2.96 2.95 2.95 2.94 2.94 2.42 1.96 1.95 1.87 1.86 1.86 1.85 1.76 1.76 1.76 1.75 1.74 1.73 1.72 1.67 1.66 1.65 1.65 1.65 1.64 1.63 1.62 1.61 1.51 1.51 1.51 1.50 1.49
Ts
N
H
O
Me
6n
2.00 2.01 1.06 1.20 1.11 3.11 3.03 1.16 2.08 2.12 1.13
f1 (ppm)

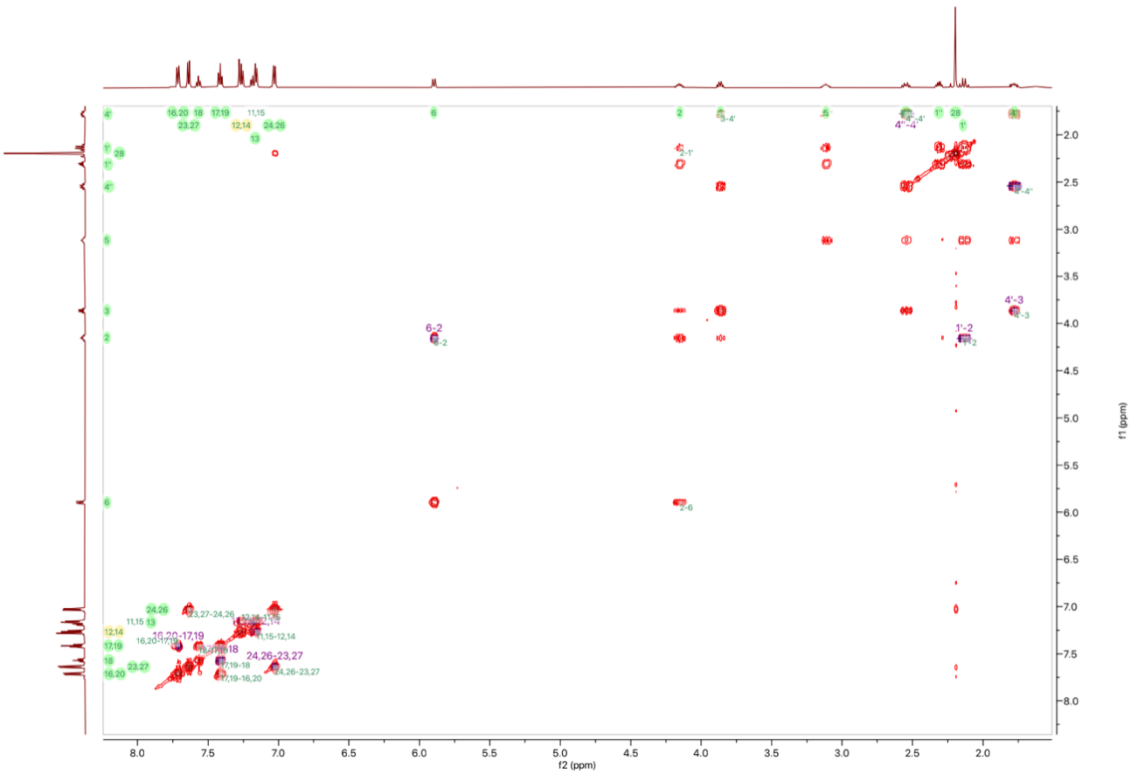

211.12
143.48 137.97 129.85 127.30
56.41 52.88
32.36 30.28 27.56 21.66 21.62
Ts
N
H
O
Me
6n
f1 (ppm)

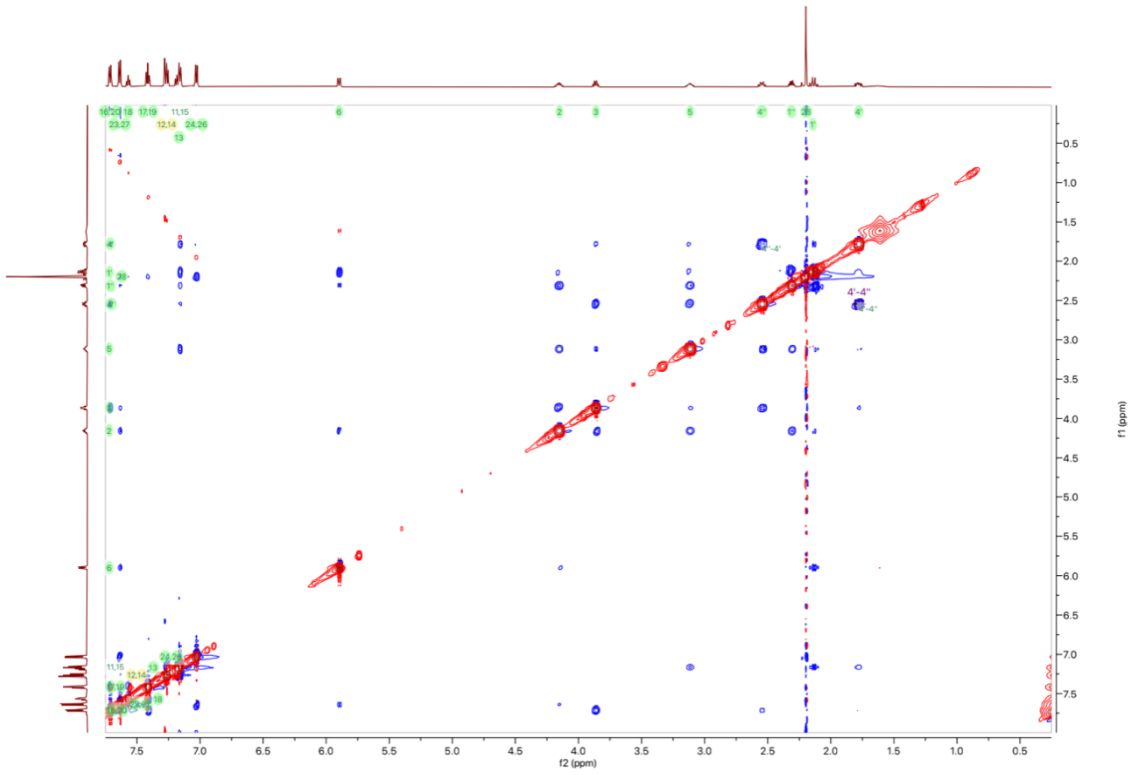

Ph
Ts
N
H
O
Ph
8a
f1 (ppm)

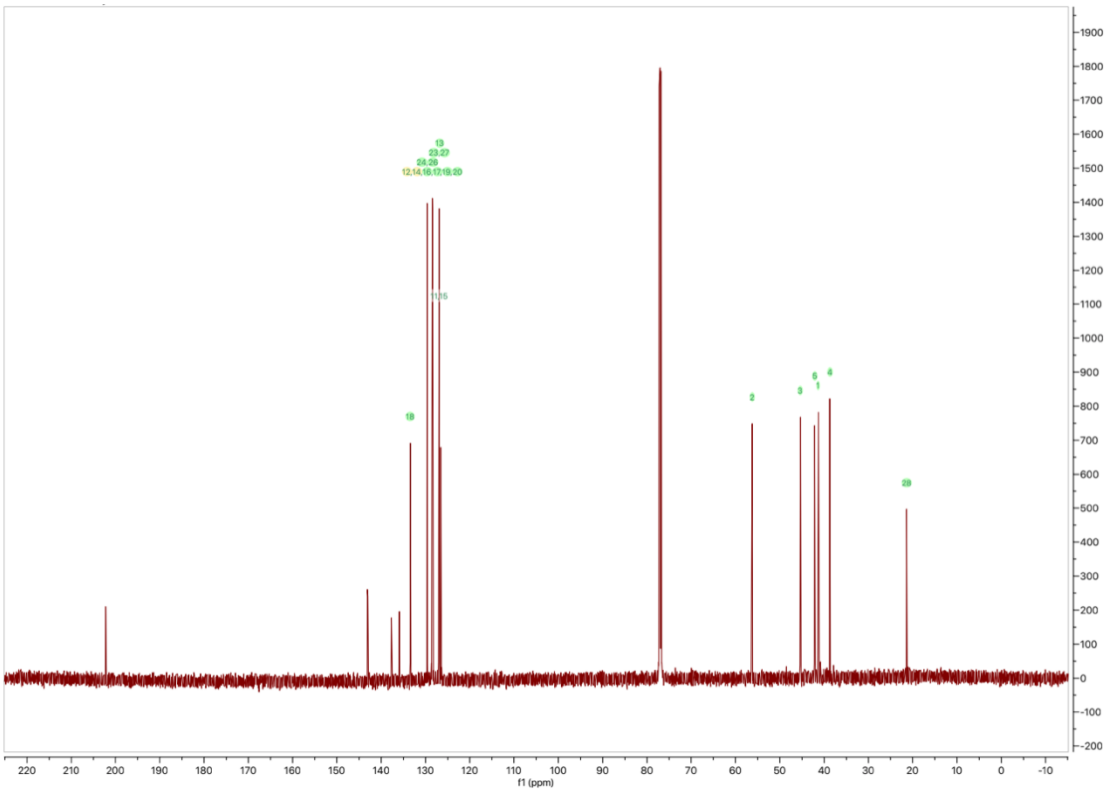

Ph
Ts
N
H
O
Ph
8a
f1 (ppm)

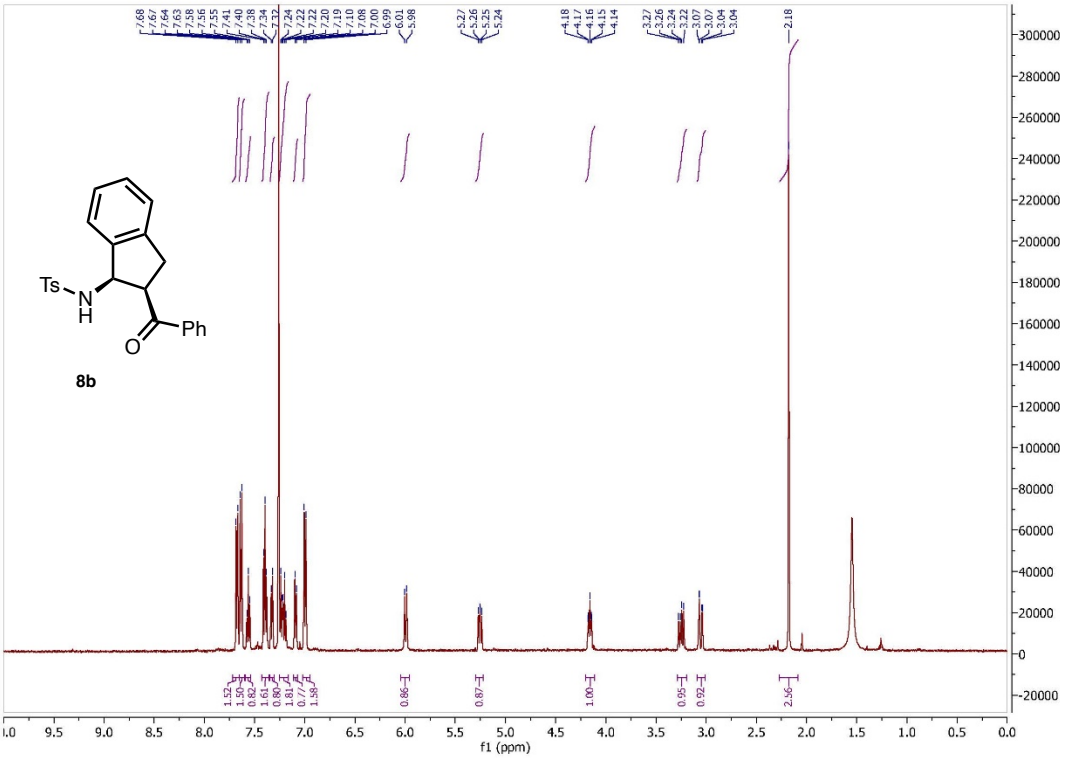
12,14 (m)
7.27
17,19 (t)
7.41
24,26 (d)
7.03
23,27 (d)
7.64
6 (d)
5.90
2 (m)
4.15
3 (dt)
3.87
5 (p)
3.12
4'' (dt)
2.55
4' (ddd)
1.78
1' (q)
2.13
28 (s)
2.20
1'' (dt)
2.31
18 (t)
7.57
16,22 (d)
7.71
11,13,15 (m)
7.17
f1 (ppm)

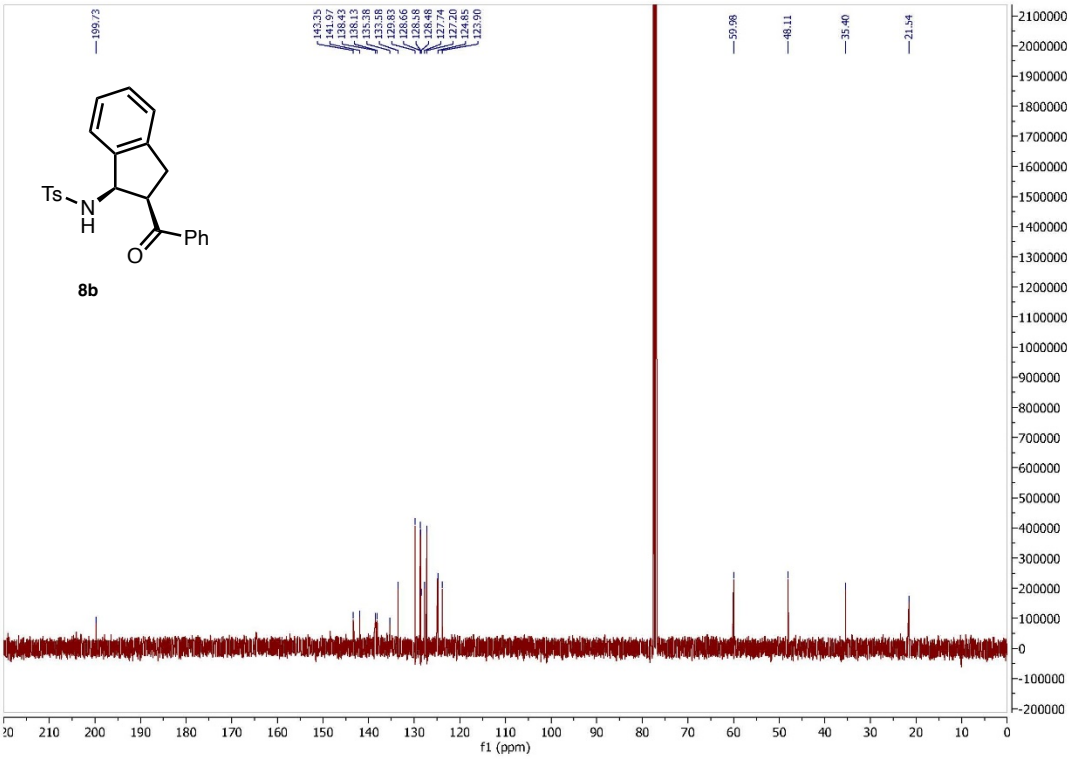

H4''-C4
H1''-C1
H1'-C1
H4'-C4
f2 (ppm)
f1 (ppm)

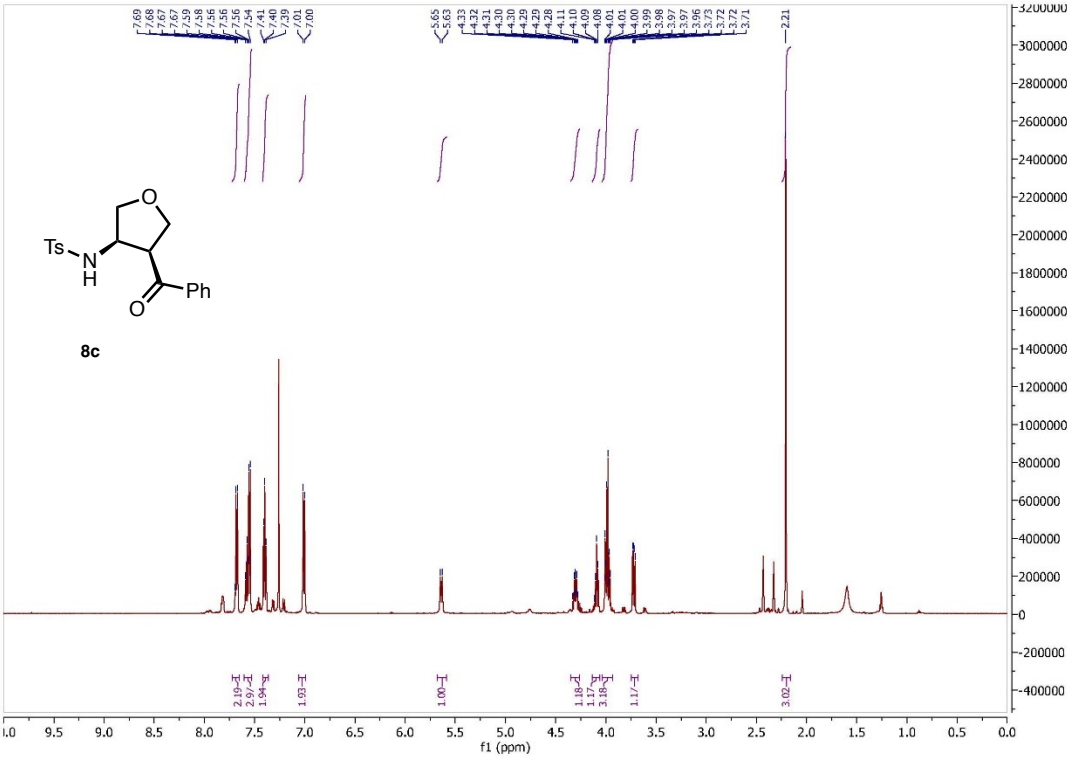

f2 (ppm)
f1 (ppm)
6-2
1'-2
4'-3
4'-4
24,26-23,27
16,20-17,19

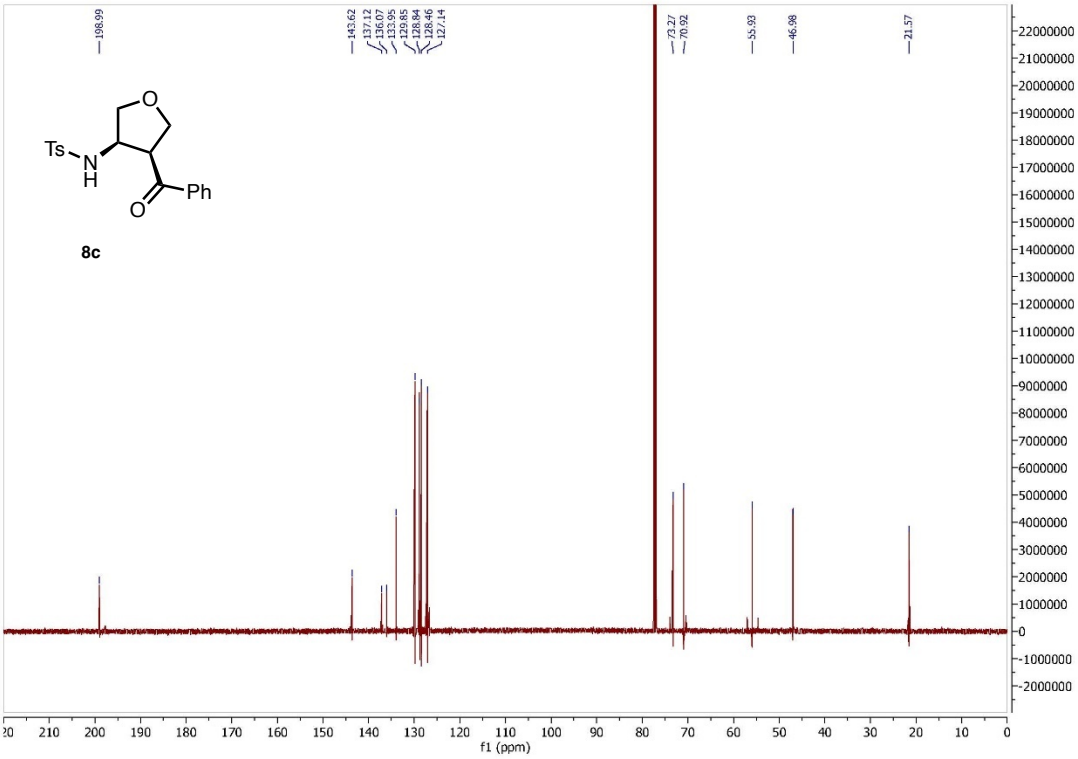

f2 (ppm)
f1 (ppm)
4'-4"

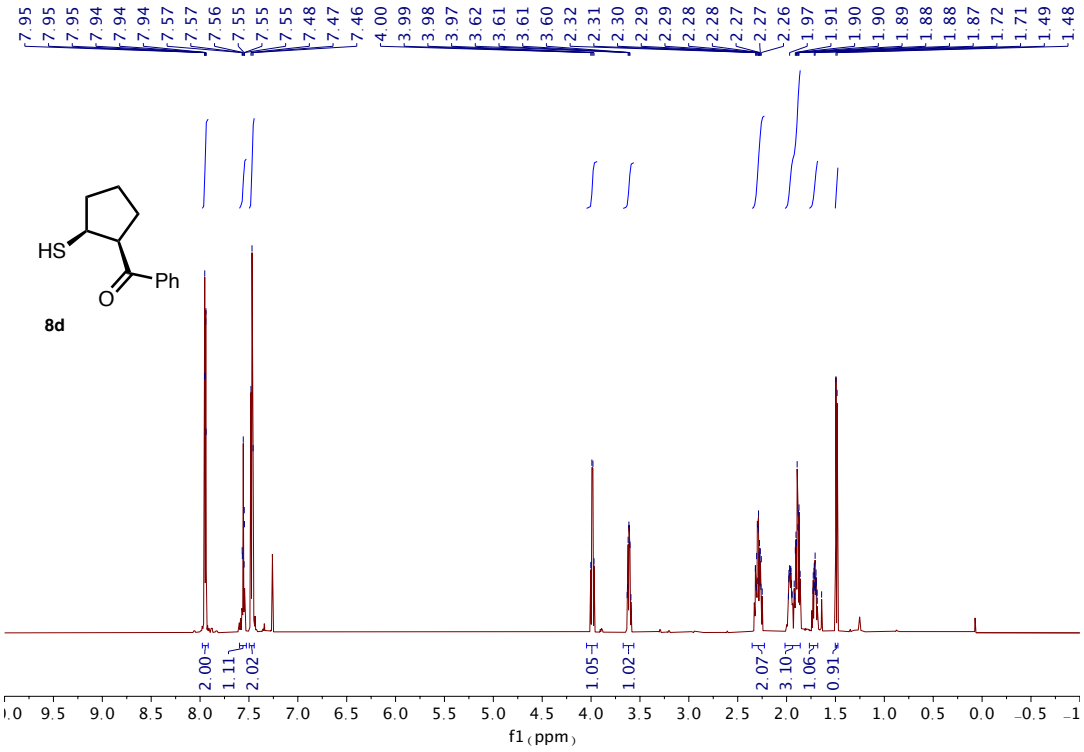

13
23.27
28.09
12,14,16,17,19,20
11,15
18
2
3
5
1
4
29
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
600
500
400
300
200
100
0
-100
-200
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

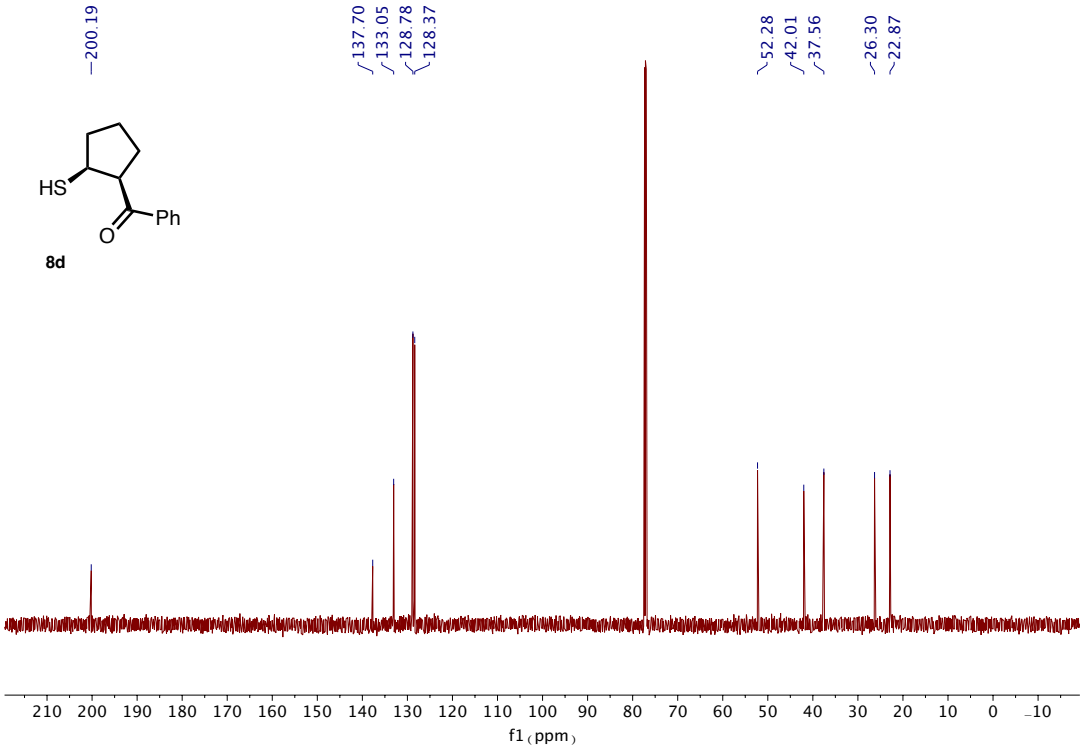

Ts
N
H
O
Ph
8b
f1 (ppm)

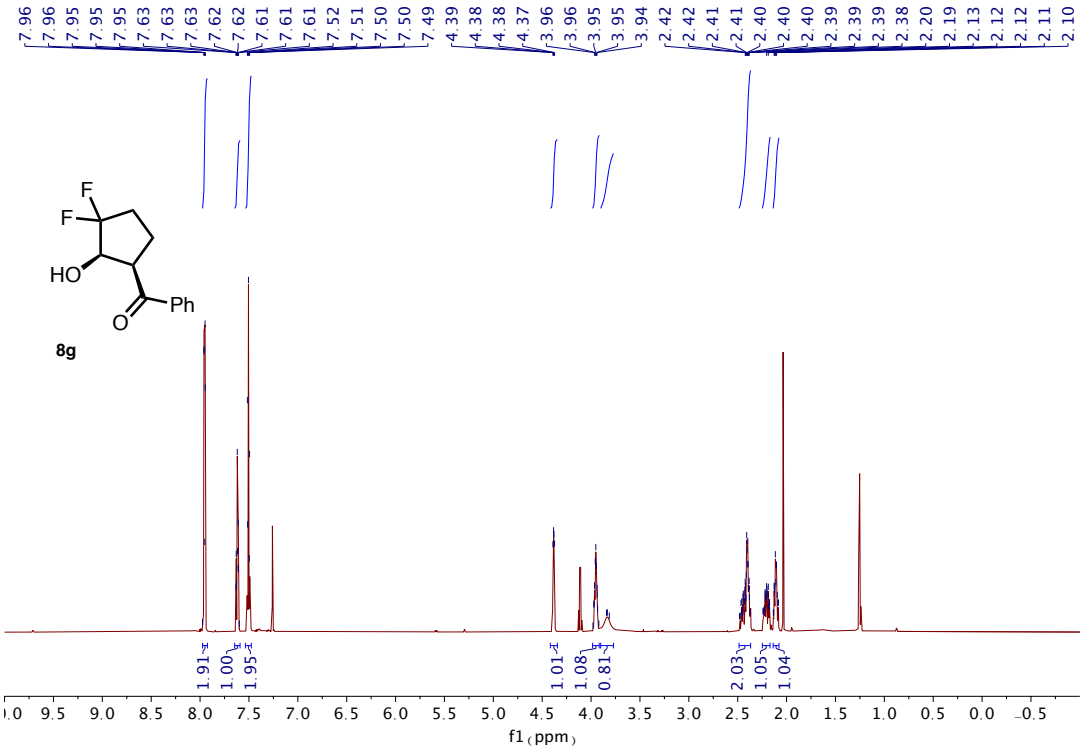

Ts
N
H
O
Ph
8b
f1 (ppm)

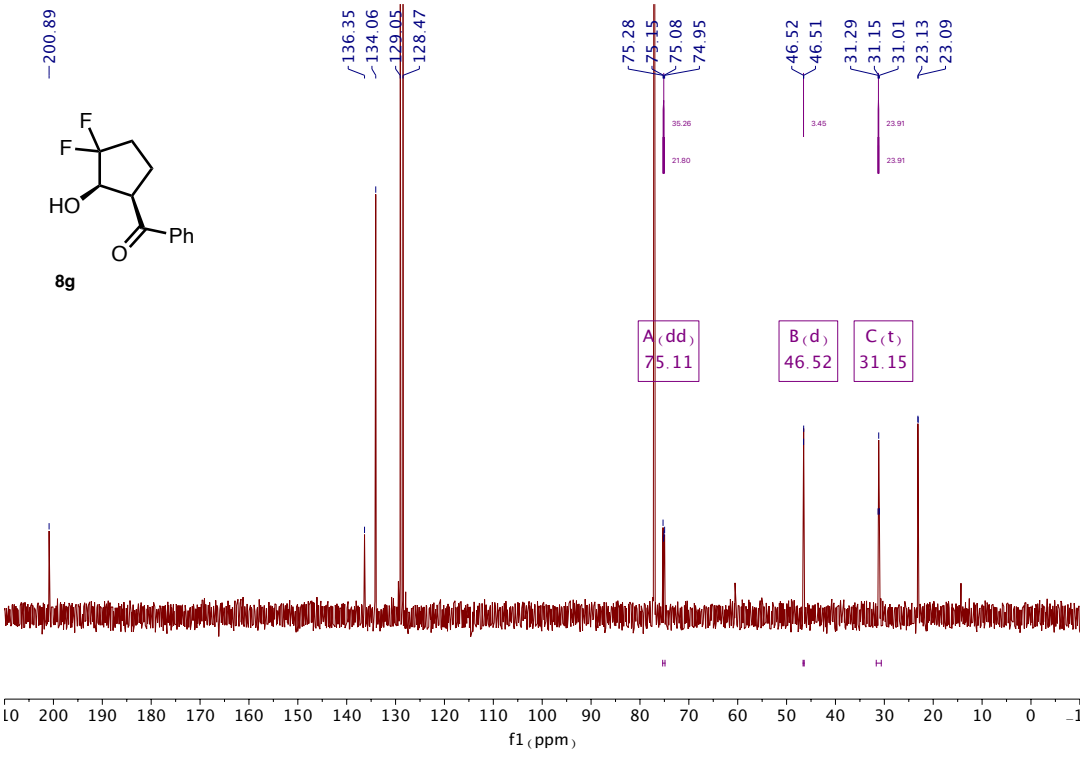

Ts
N
H
O
O
Ph
8c
f1 (ppm)

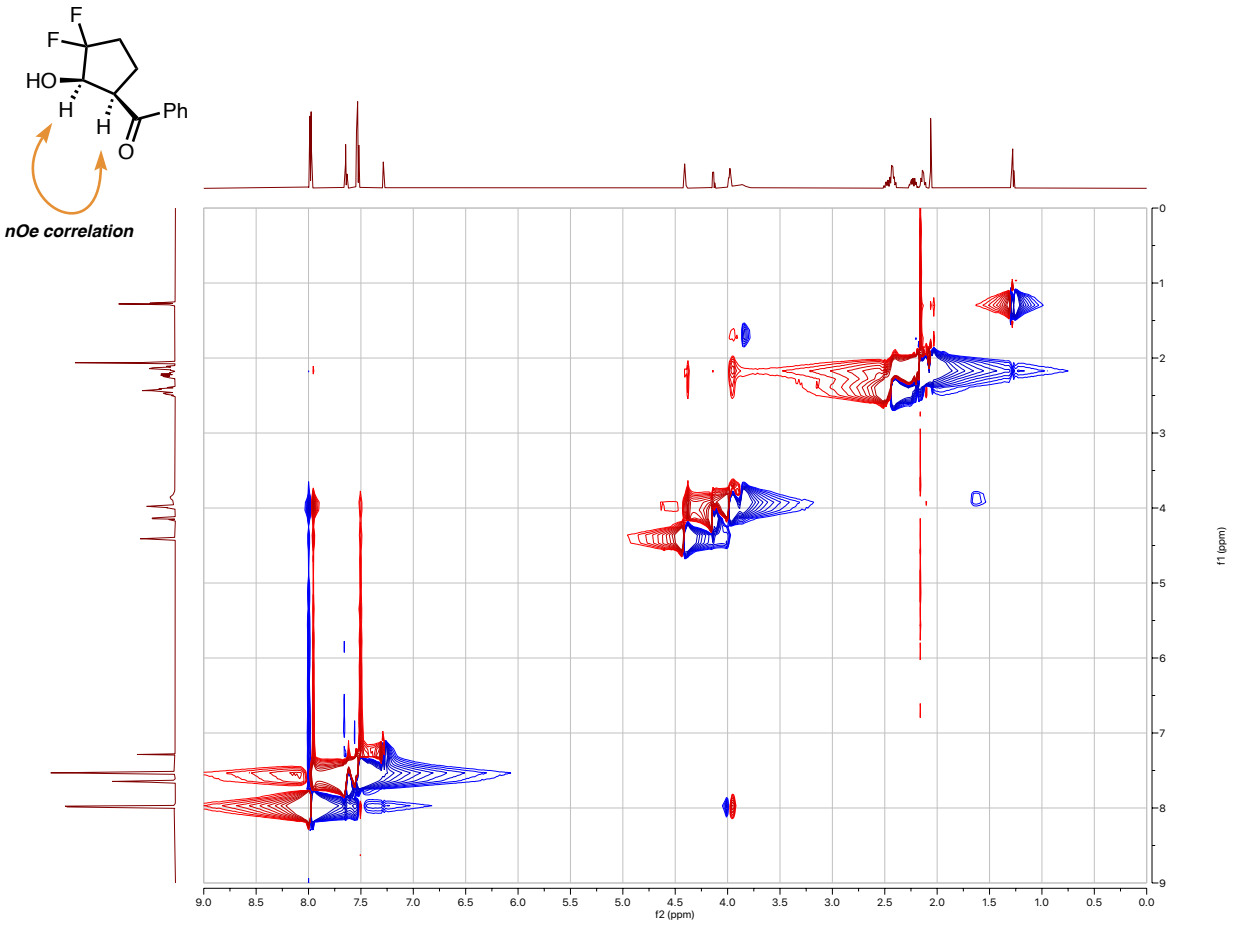

Ts
N
H
O
O
Ph
8c
f1 (ppm)

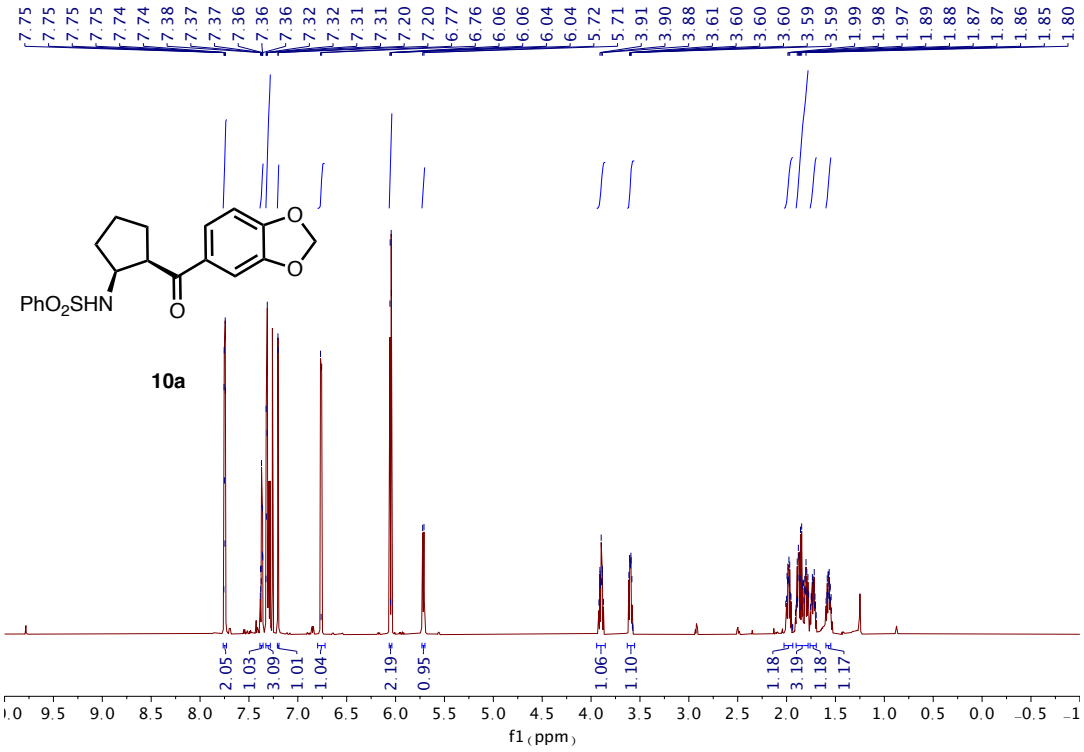

7.95 7.95 7.95 7.94 7.94 7.94 7.57 7.57 7.56 7.55 7.55 7.55 7.48 7.47 7.46
4.00 3.99 3.98 3.97 3.62 3.61 3.61 3.60 2.32 2.31 2.30 2.29 2.29 2.28 2.28 2.27 2.27 2.26
1.97 1.91 1.90 1.90 1.89 1.88 1.88 1.87 1.72 1.71 1.49 1.48
HS
Ph
O
8d
2.00 1.11 2.02 1.05 1.02 2.07 3.10 1.06 0.91
f1 (ppm)

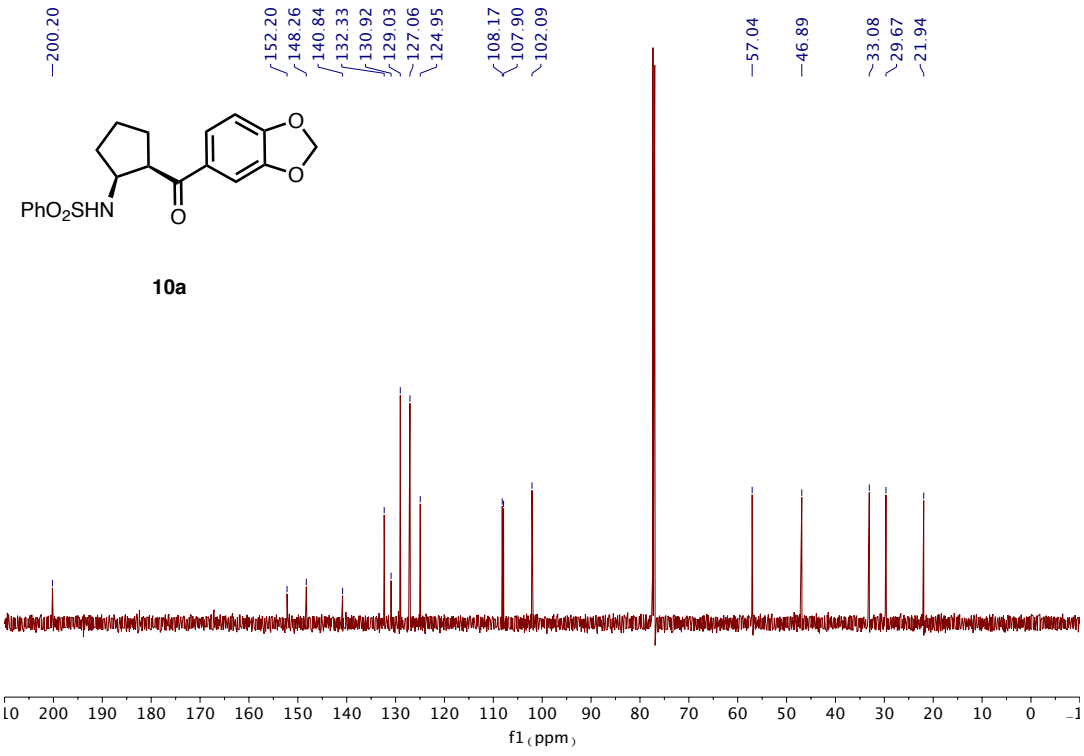

200.19
137.70 133.05 128.78 128.37
52.28 42.01 37.56 26.30 22.87
HS
Ph
O
8d
f1 (ppm)

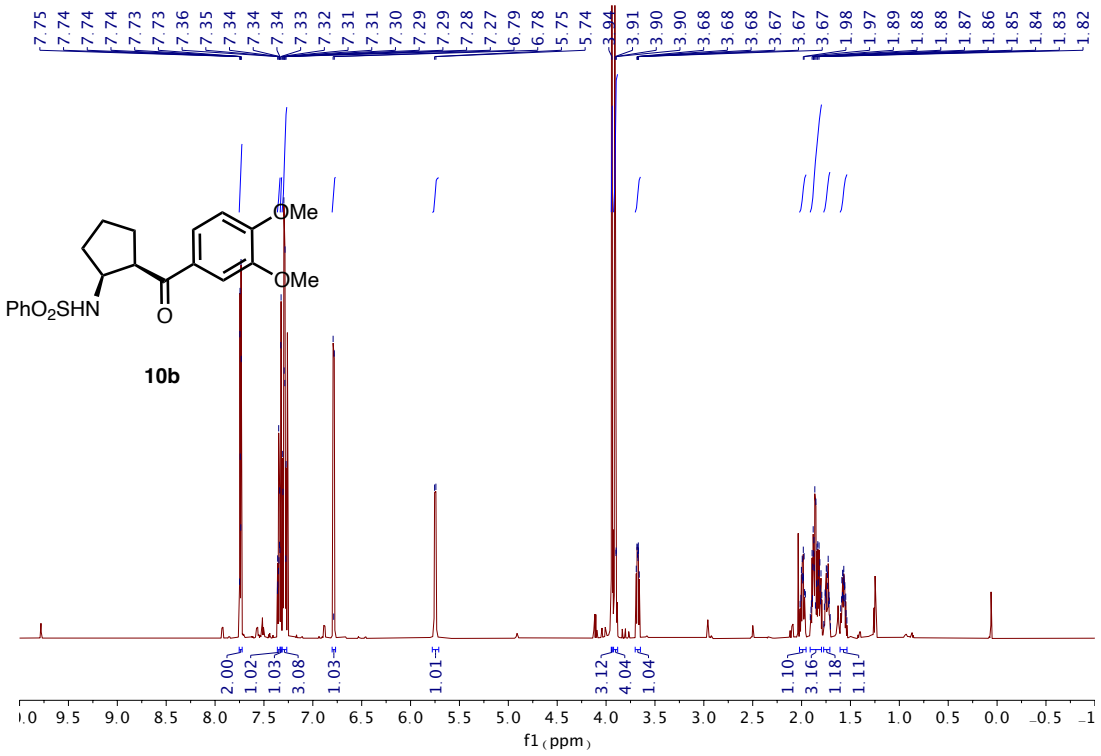

F
F
HO
O
Ph
8g
f1 (ppm)

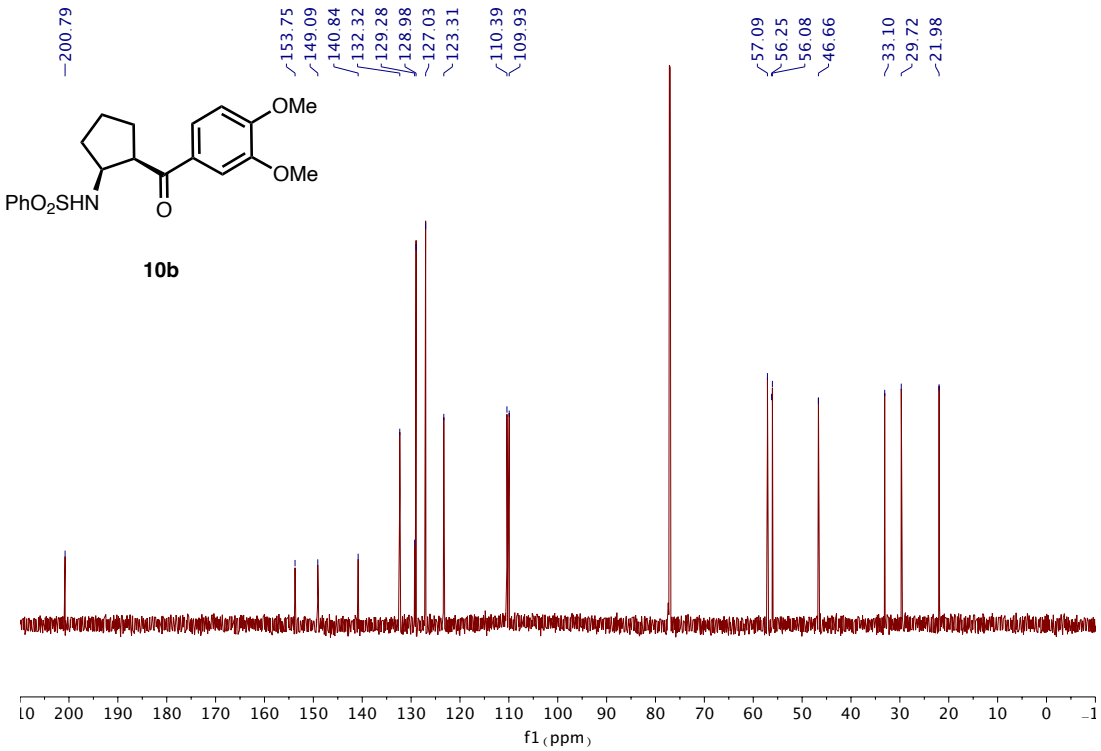

F
F
HO
O
Ph
8g
A (dd)
75.11
B (d)
46.52
C (t)
31.15
f1 (ppm)

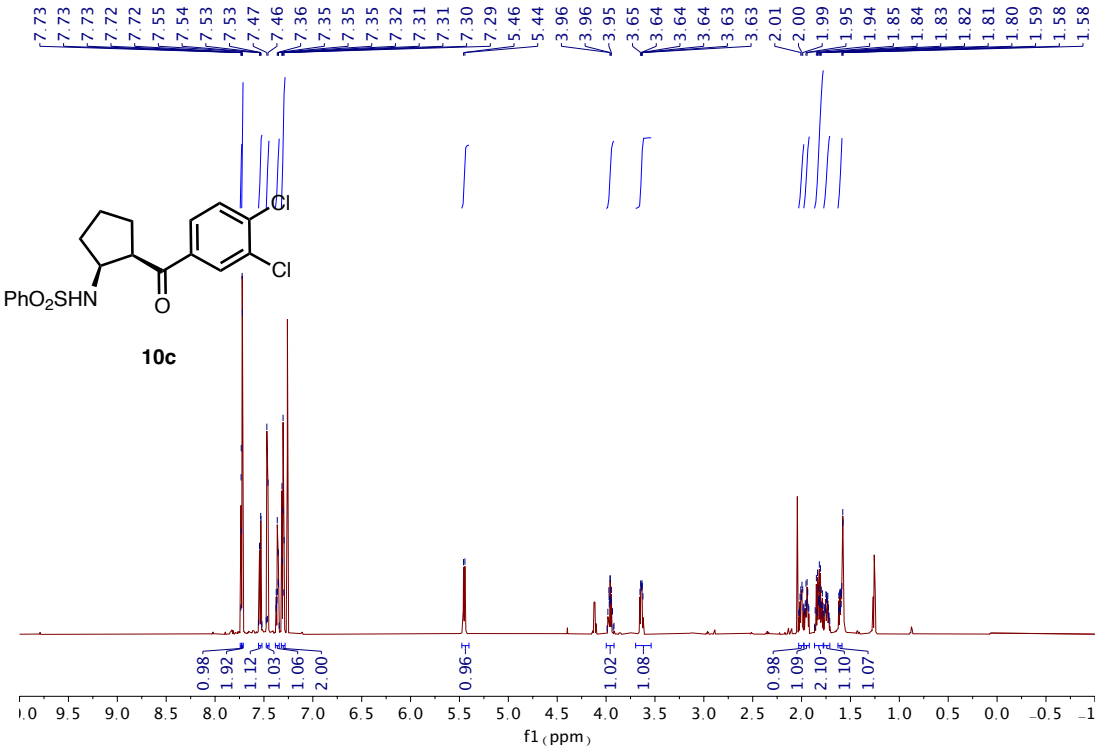

F
F
HO
H
H
Ph
O
nOe correlation
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)
0
1
2
3
4
5
6
7
8
9
f1 (ppm)

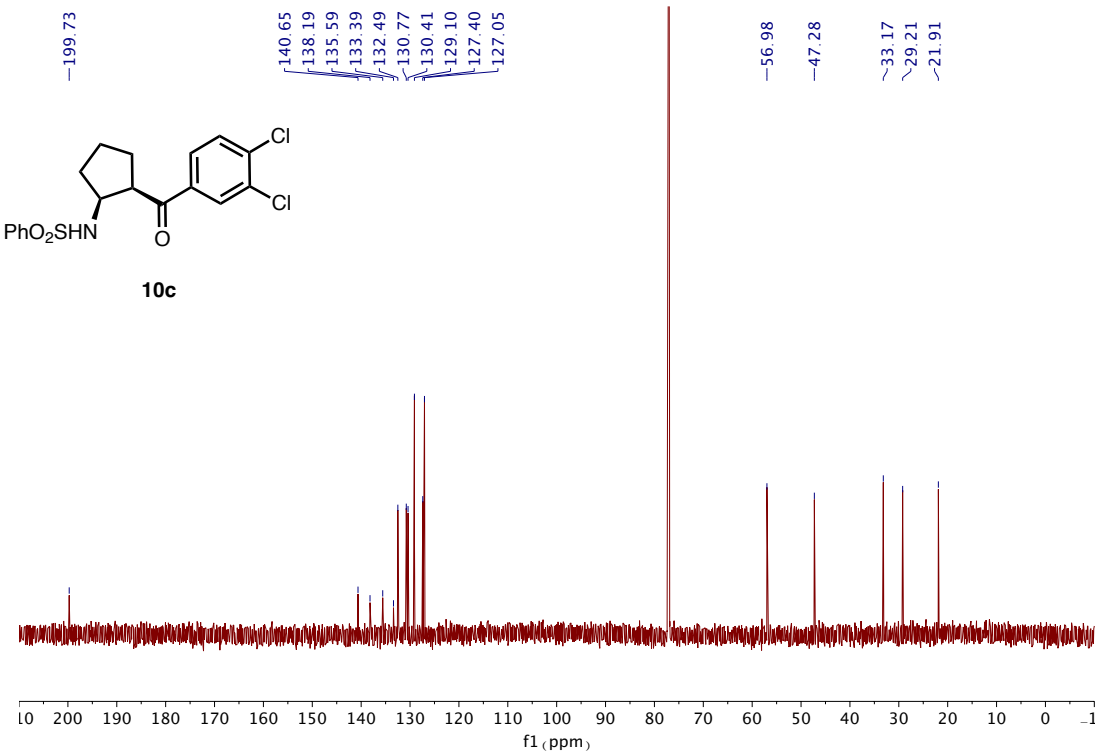

7.75 7.75 7.75 7.75 7.74 7.74 7.38 7.37 7.37 7.36 7.36 7.36 7.32 7.32 7.31 7.31 7.20 7.20 6.77 6.76 6.06 6.06 6.04 6.04 5.72 5.71 3.91 3.90 3.88 3.61 3.60 3.60 3.60 3.59 3.59 1.99 1.98 1.97 1.89 1.88 1.87 1.87 1.86 1.85 1.80
PhO2SHN
10a
2.05 1.03 3.09 1.01 1.04 2.19 0.95 1.06 1.10 1.18 3.19 1.18 1.17
f1 (ppm)

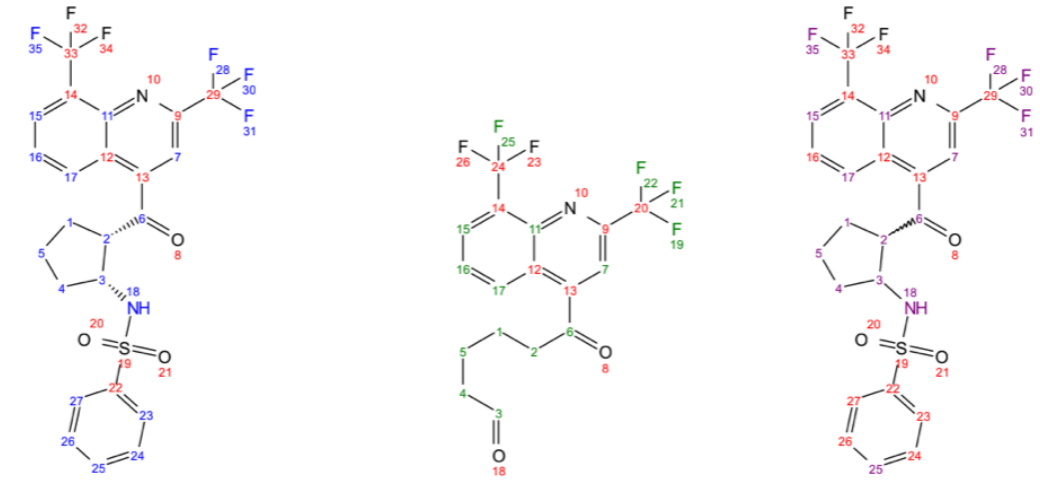

200.20
152.20 148.26 140.84 132.33 130.92 129.03 127.06 124.95 108.17 107.90 102.09 57.04 46.89 33.08 29.67 21.94
PhO2SHN
10a
f1 (ppm)


OMe
OMe
PhO2SHN
O
10b
f1 (ppm)


OMe
OMe
PhO2SHN
O
10b
f1 (ppm)

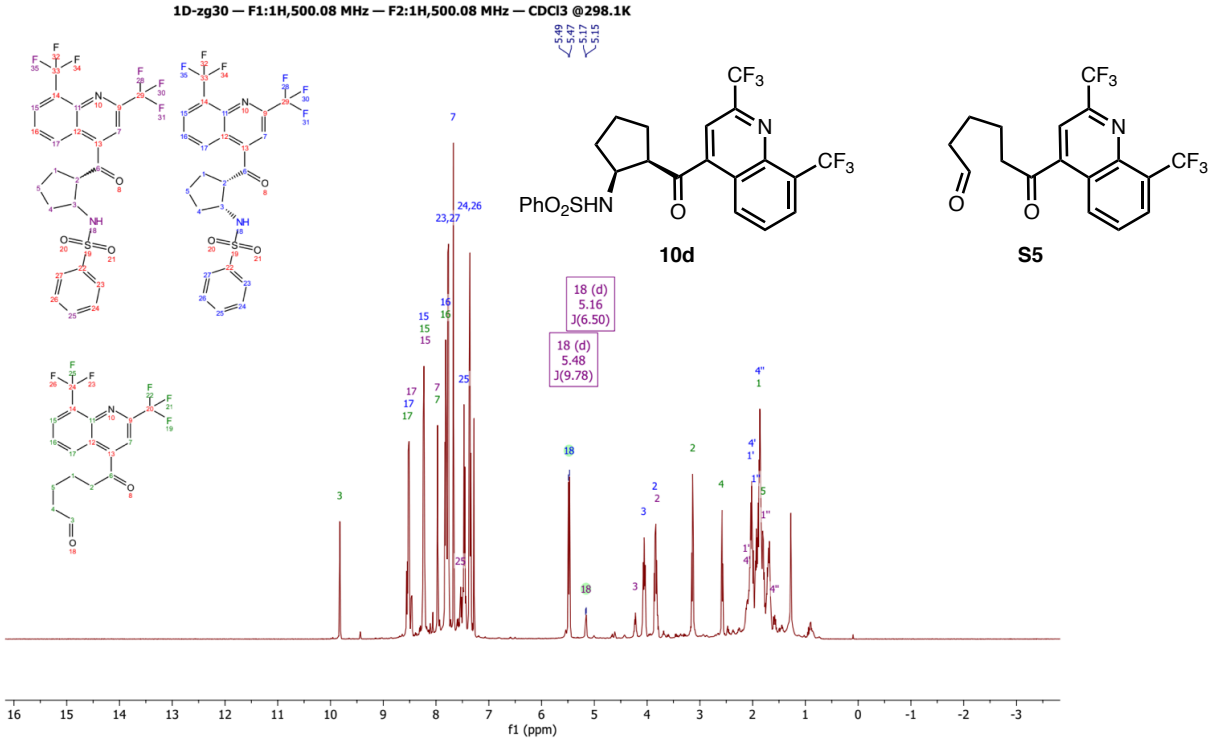

7.73 7.73 7.73 7.72 7.72 7.55 7.54 7.53 7.53 7.47 7.46 7.36 7.35 7.35 7.35 7.32 7.31 7.31 7.30 7.29 5.46 5.44 3.96 3.96 3.95 3.65 3.64 3.64 3.64 3.63 3.63 2.01 2.00 1.99 1.95 1.94 1.85 1.84 1.83 1.82 1.81 1.80 1.59 1.58 1.58
Cl
Cl
PhO2SHN
O
10c
0.98 1.92 1.12 1.03 1.06 2.00 0.96 1.02 1.08 0.98 1.09 2.10 1.10 1.07
f1 (ppm)

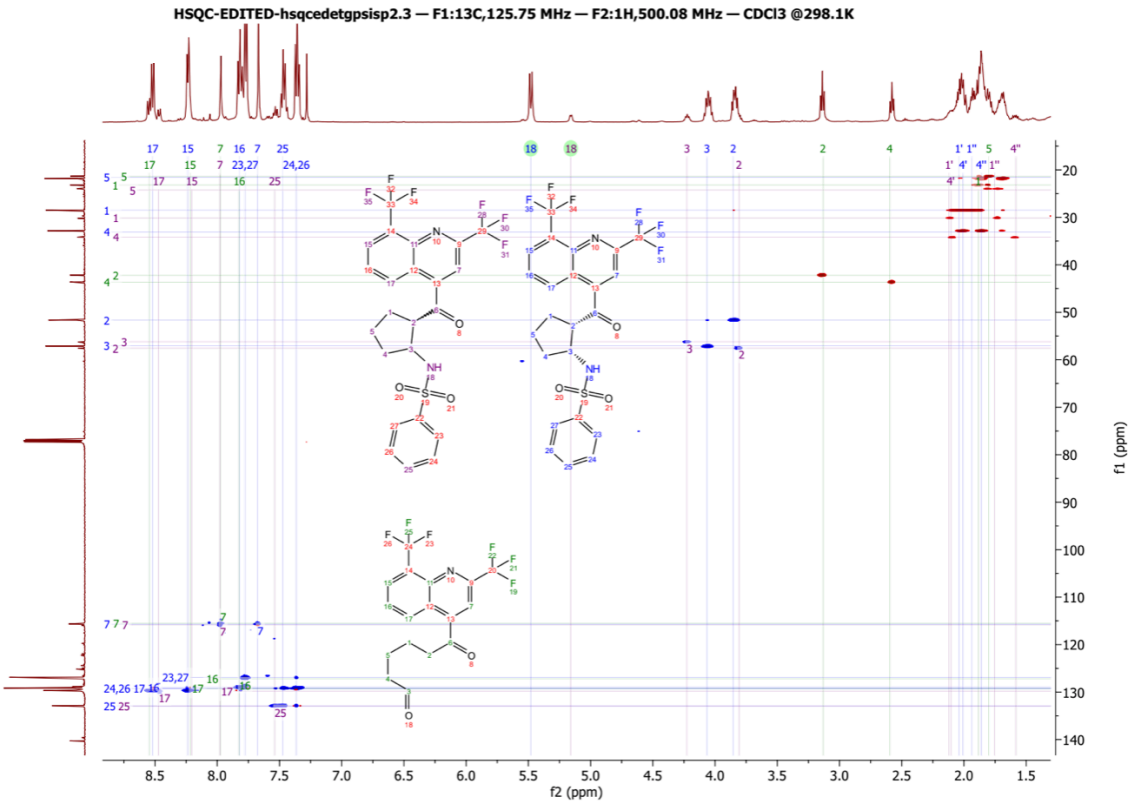

199.73
140.65 138.19 135.59 133.39 132.49 130.77 130.41 129.10 127.40 127.05
56.98 47.28 33.17 29.21 21.91
Cl
Cl
PhO2SHN
O
10c
f1 (ppm)

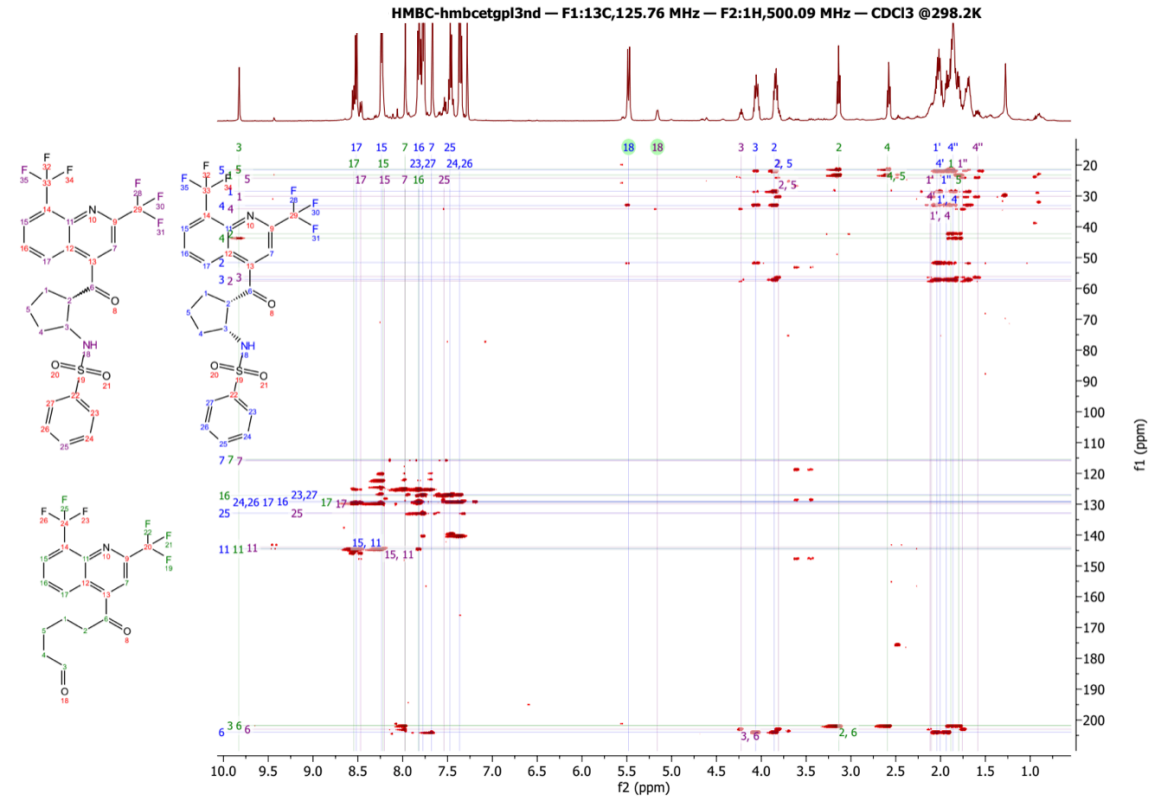


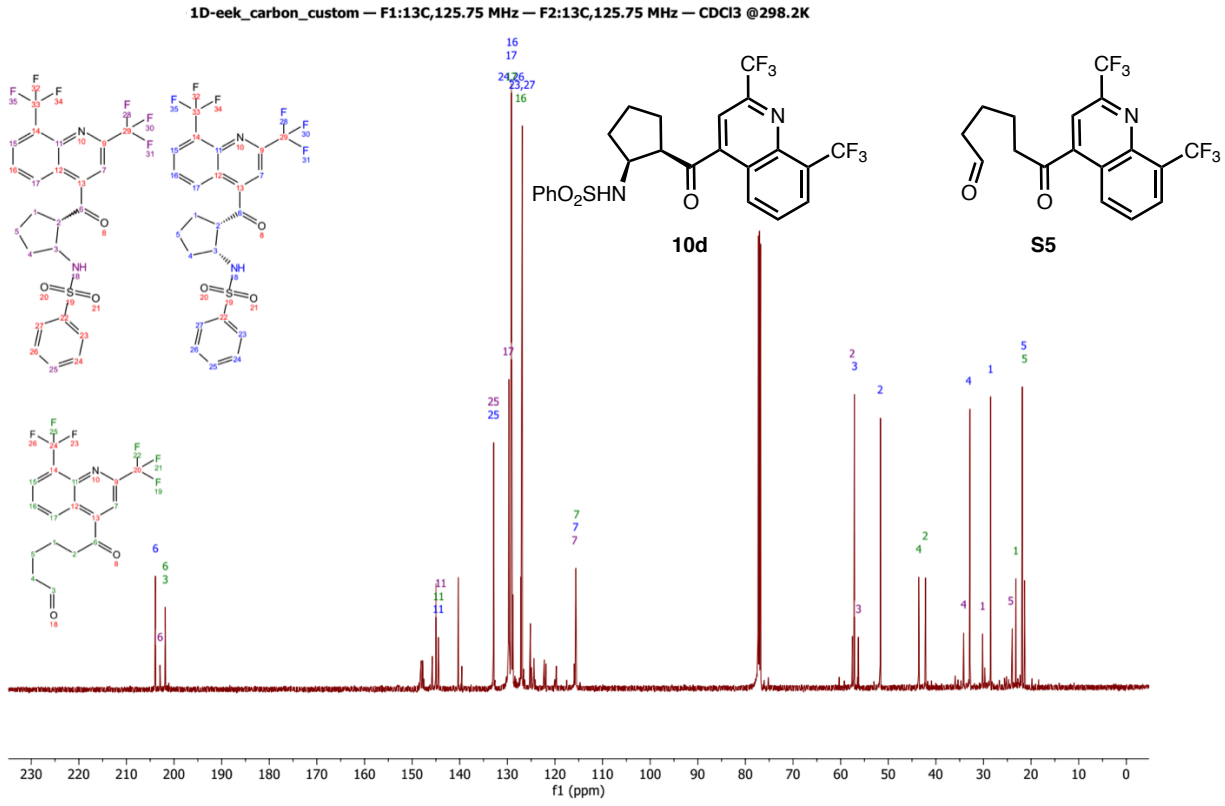
major product | second most abundant product | third most abundant product

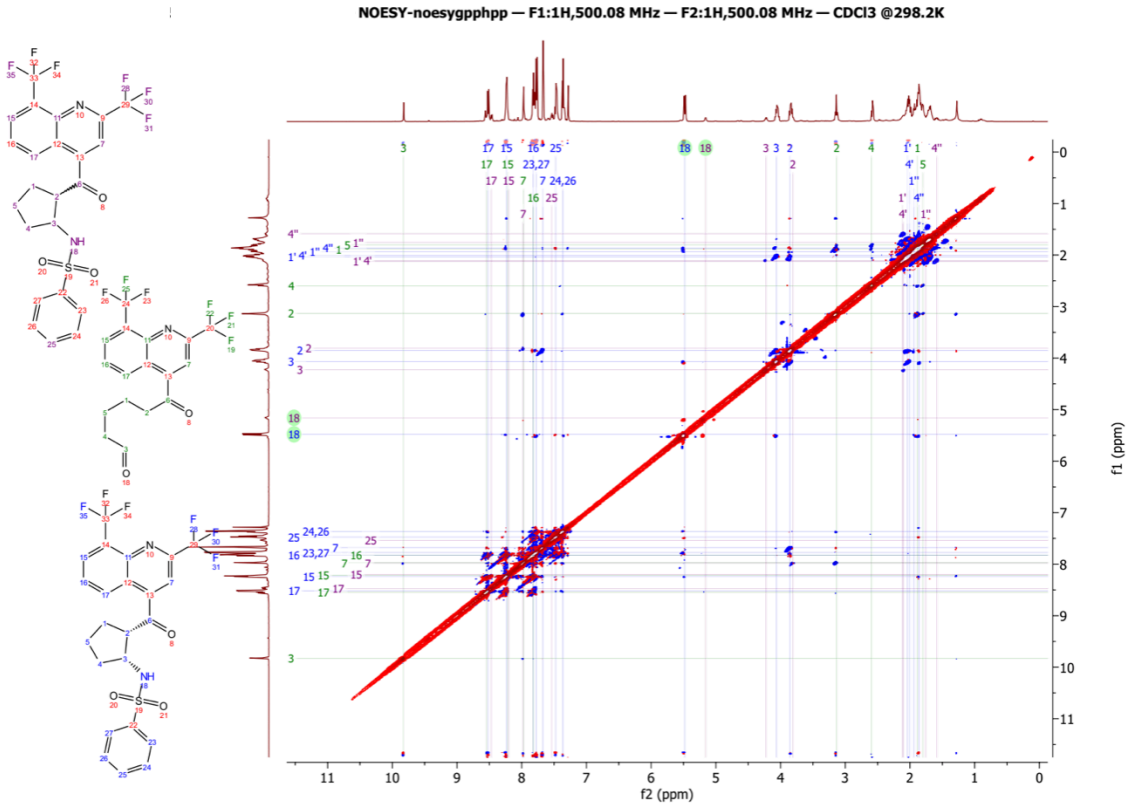
Based on NOE correlations and the trend of chemical shifts and coupling constants among other products, the major component of this complex product mixture is **10d**, the *cis* product, as indicated. The second most abundant species is the aldehyde hydrolysis product **S5** and the most abundant of the remaining products in the mixture is the *trans* isomer of **10d**.



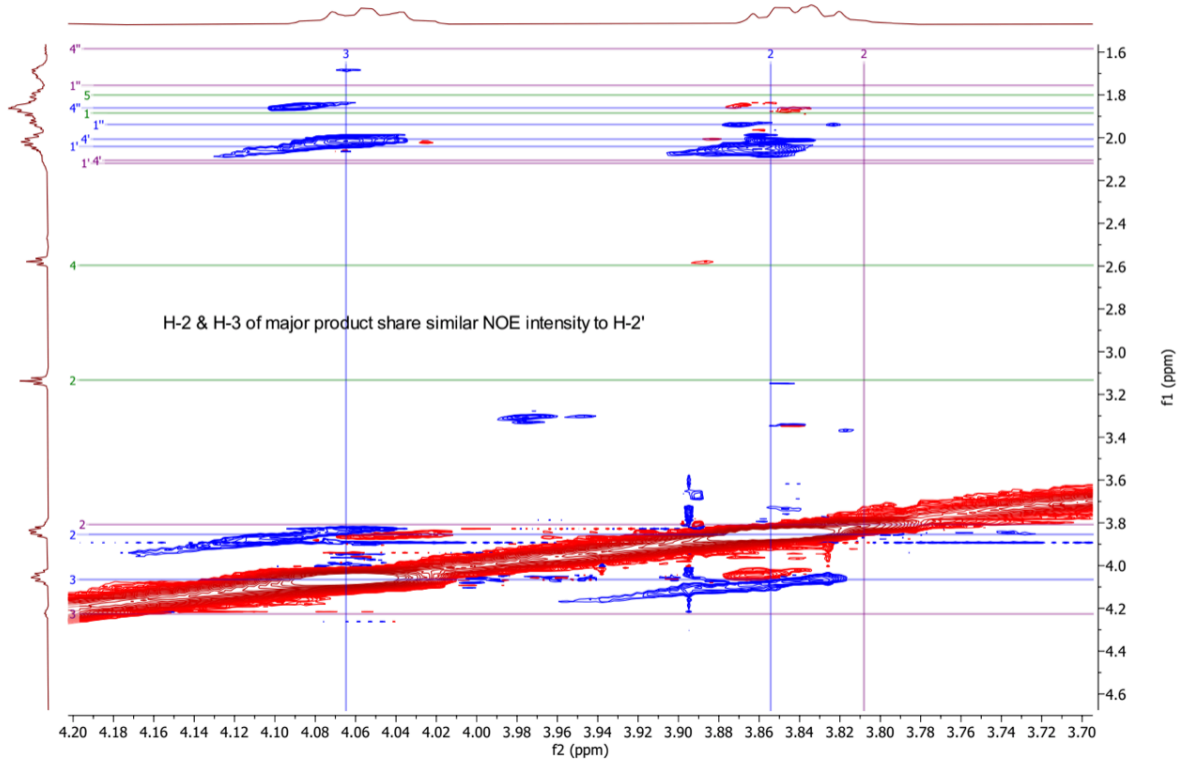

HSQC-EDITED-hsqcedetgpsisp2.3 — F1:13C,125.75 MHz — F2:1H,500.08 MHz — CDCl3 @298.1K
f2 (ppm)
f1 (ppm)


HMBC-hmbcetgpl3nd — F1:13C,125.76 MHz — F2:1H,500.09 MHz — CDCl3 @298.2K
f2 (ppm)
f1 (ppm)

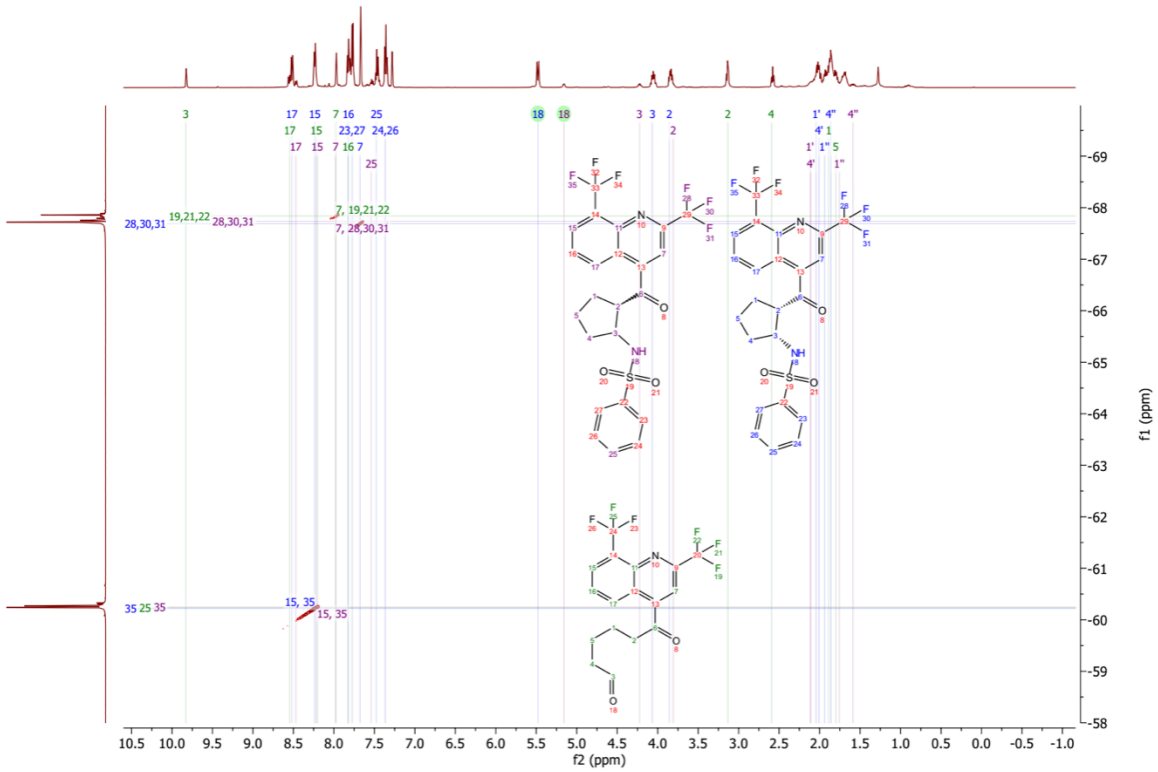

1D-eek_carbon_custom — F1:13C,125.75 MHz — F2:13C,125.75 MHz — CDCl3 @298.2K
CF3
N
CF3
PhO2SHN
O
10d
S5
f1 (ppm)

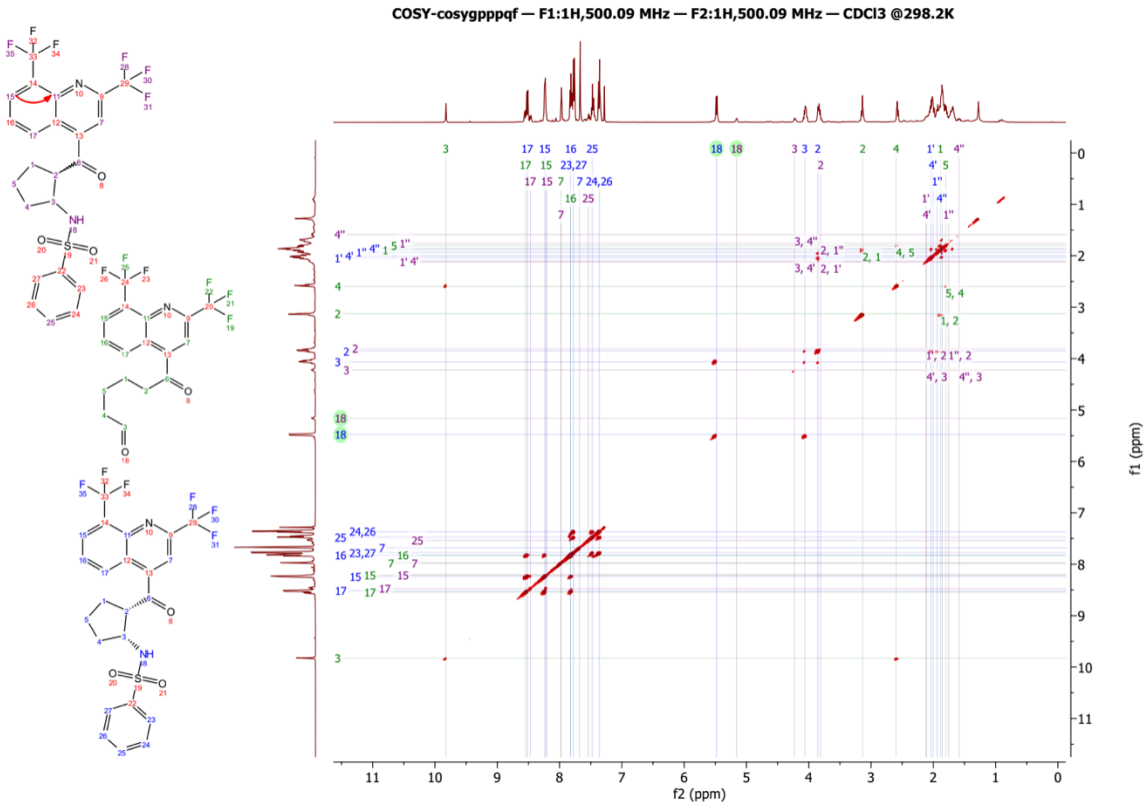

NOESY-noesygpphpp — F1:1H,500.08 MHz — F2:1H,500.08 MHz — CDCl3 @298.2K
f2 (ppm)
f1 (ppm)

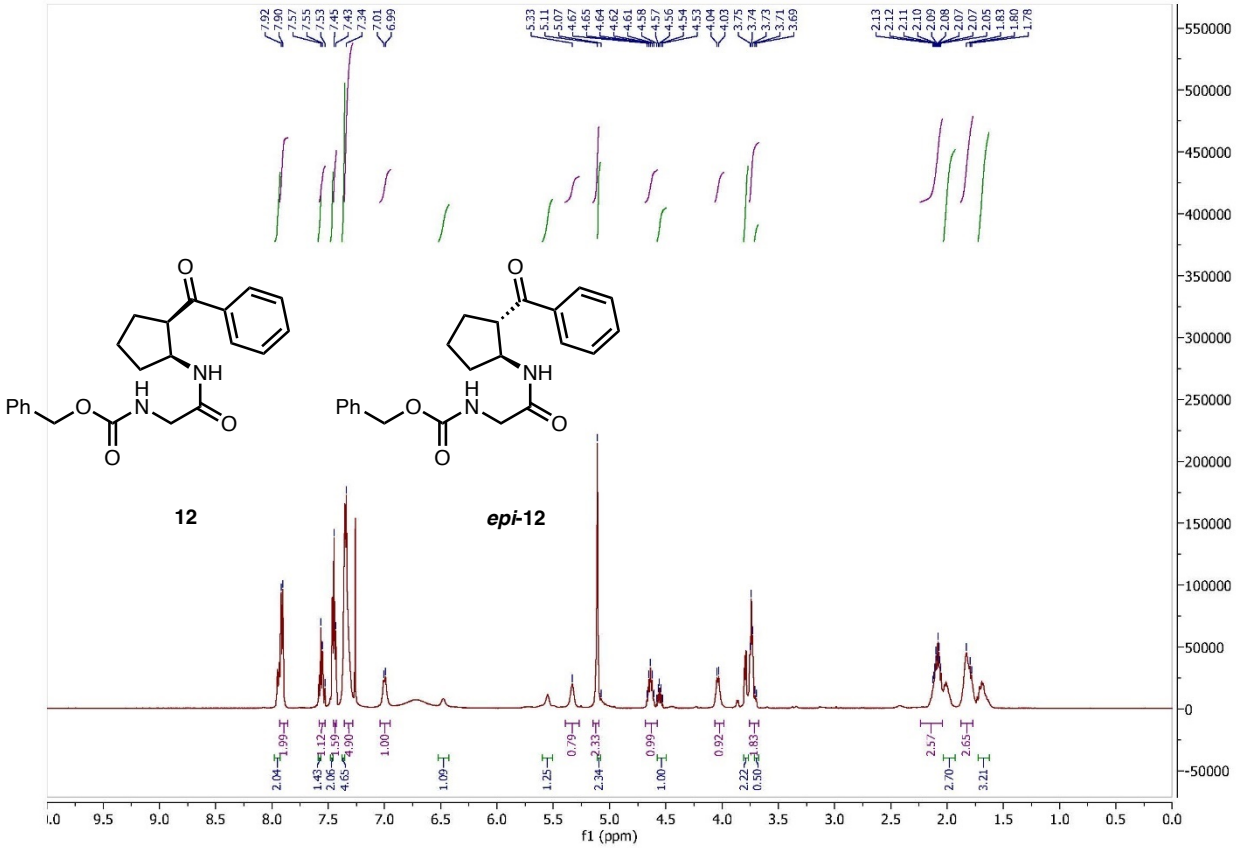
NOESY-noesygpphpp — F1:1H,500.08 MHz — F2:1H,500.08 MHz — CDCl3 @298.2K

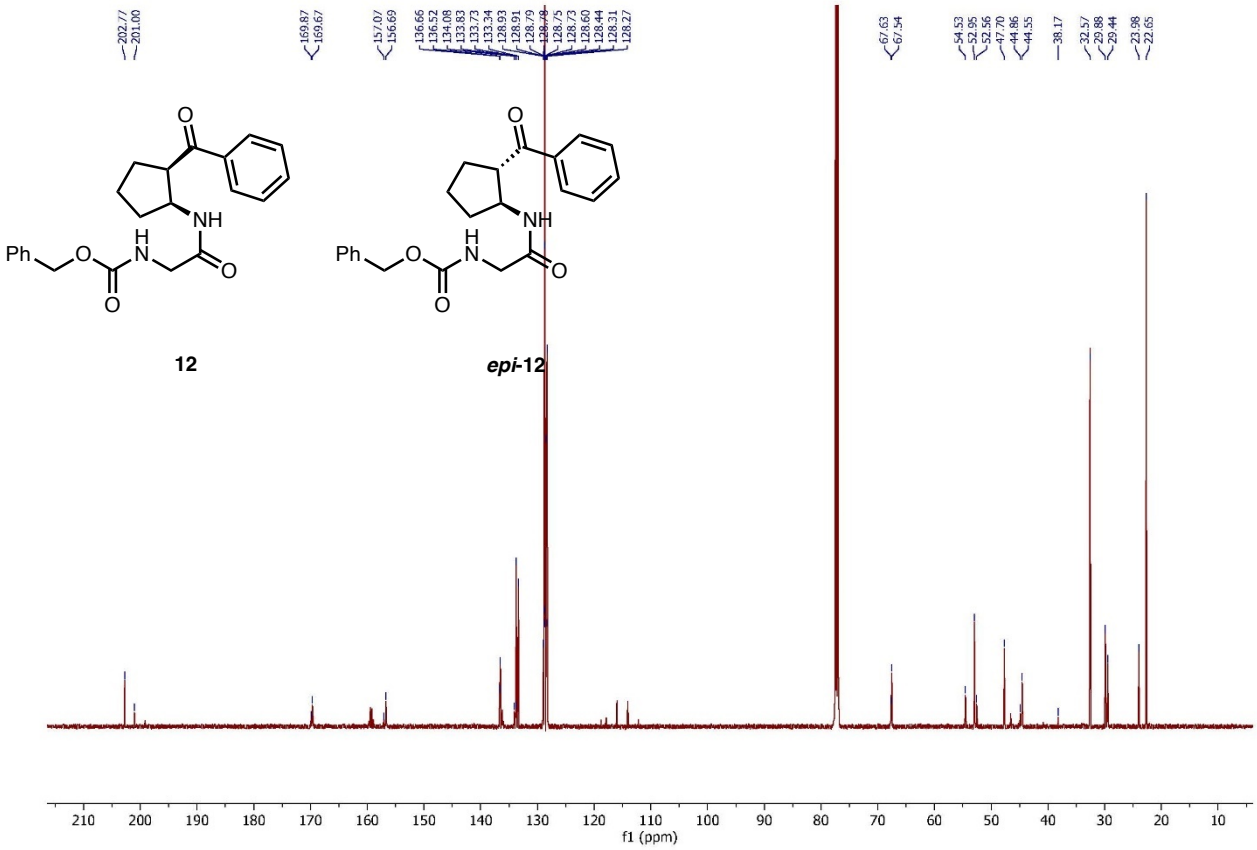


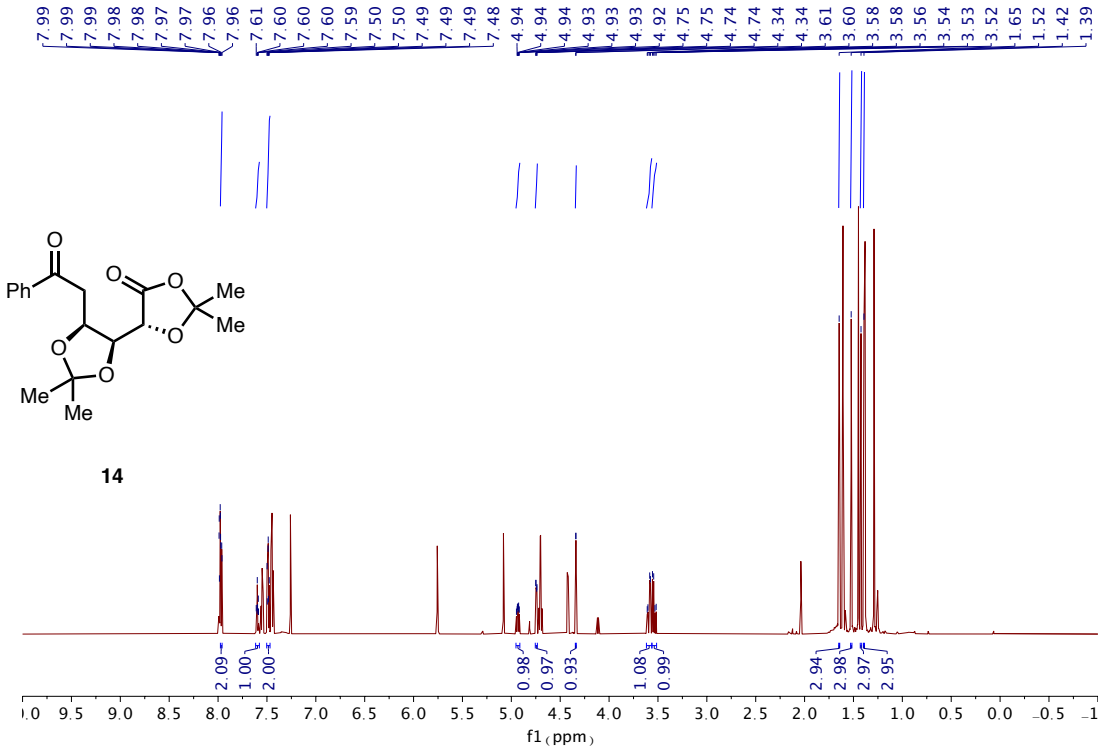
5041862-0031.17.1.2rr — 2D-NOESY-js_1H19F_hoesy_cpd_off — F1:19F,470.55 MHz — F2:1H,500.08 MHz — CDCl3 @298.1K

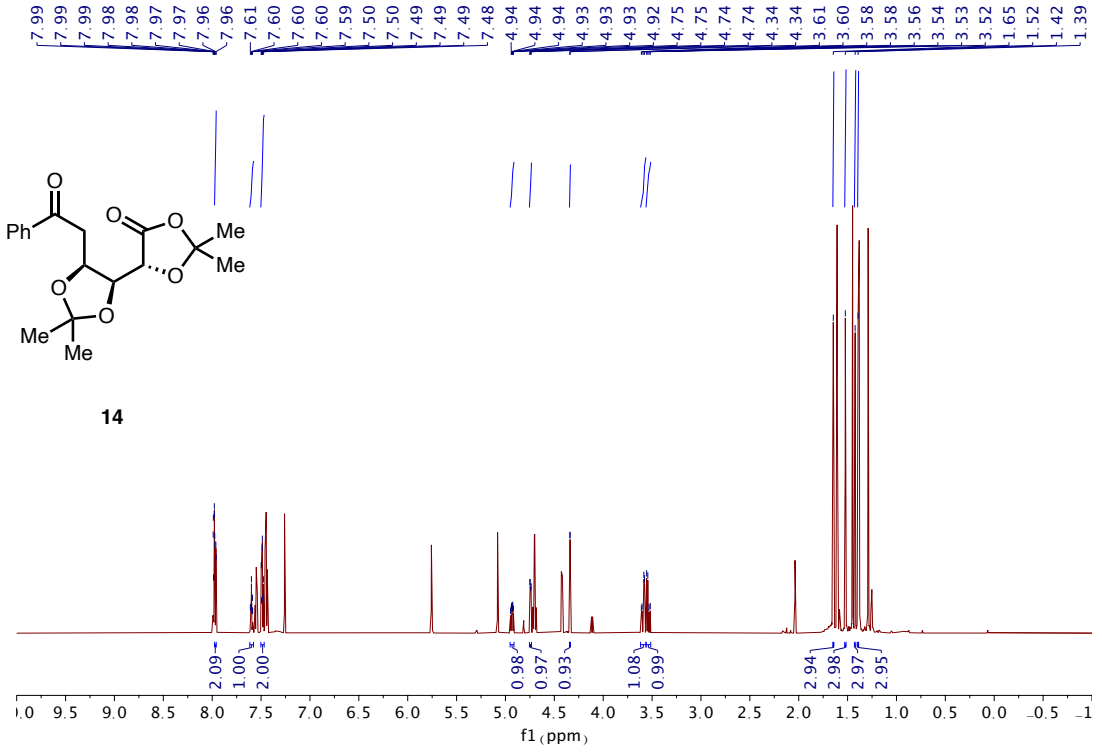


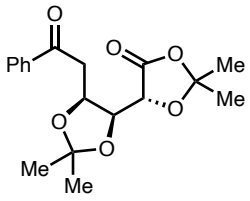

COSY-cosygpppqf — F1:1H,500.09 MHz — F2:1H,500.09 MHz — CDCl3 @298.2K
f2 (ppm)
f1 (ppm)


12
epi-12
f1 (ppm)


12
epi-12
f1 (ppm)

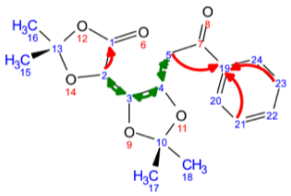

7.99 7.99 7.99 7.98 7.98 7.97 7.97 7.96 7.96 7.61 7.60 7.60 7.60 7.59 7.50 7.50 7.49 7.49 7.48
4.94 4.94 4.94 4.93 4.93 4.92 4.75 4.75 4.74 4.74 4.34 4.34 3.61 3.60 3.58 3.58 3.56 3.54 3.53 3.52 1.65 1.52 1.42 1.39
Ph
O
O
O
O
O
Me
Me
O
O
Me
Me
14
2.09 1.00 2.00 0.98 0.97 0.93 1.08 0.99 2.94 2.98 2.97 2.95
f1 (ppm)


7.99 7.99 7.99 7.98 7.98 7.97 7.97 7.96 7.96 7.61 7.60 7.60 7.60 7.59 7.50 7.50 7.49 7.49 7.48
4.94 4.94 4.94 4.93 4.93 4.92 4.75 4.75 4.74 4.74 4.34 4.34 3.61 3.60 3.58 3.58 3.56 3.54 3.53 3.52 1.65 1.52 1.42 1.39
Ph
O
O
O
O
O
Me
Me
O
O
Me
Me
14
2.09 1.00 2.00 0.98 0.97 0.93 1.08 0.99 2.94 2.98 2.97 2.95
f1 (ppm)

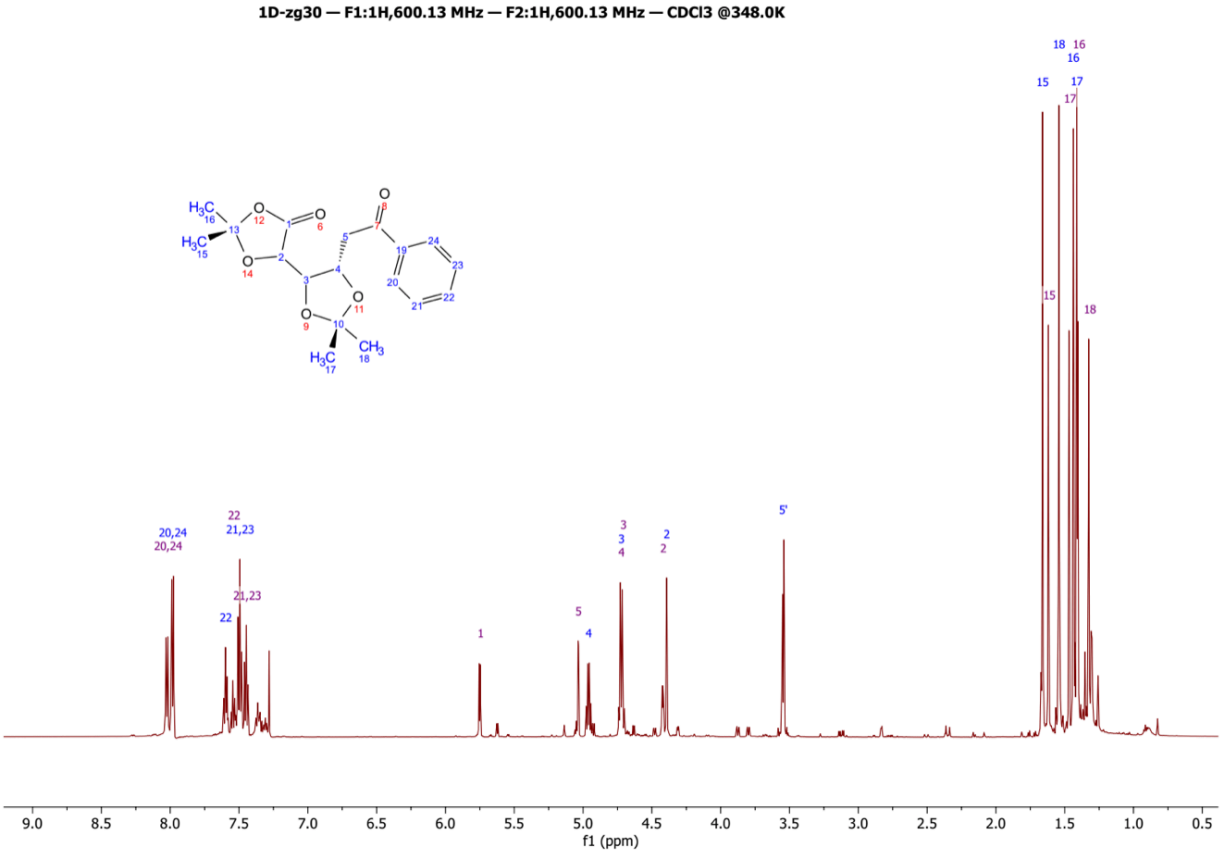


14

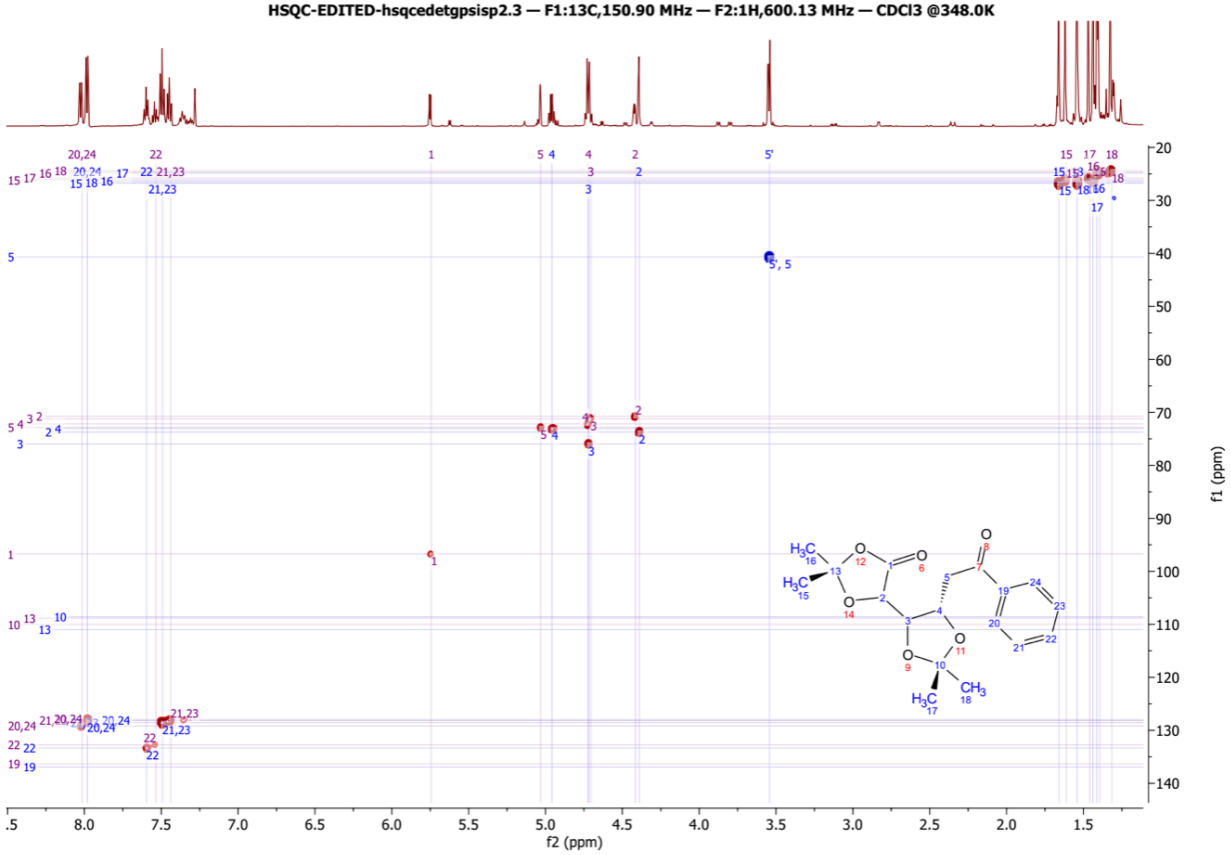
Assignment of the relative configuration of the molecule was not attempted by NMR. The current depiction assumes stereoretention, however, no experiments were performed to ensure retention.



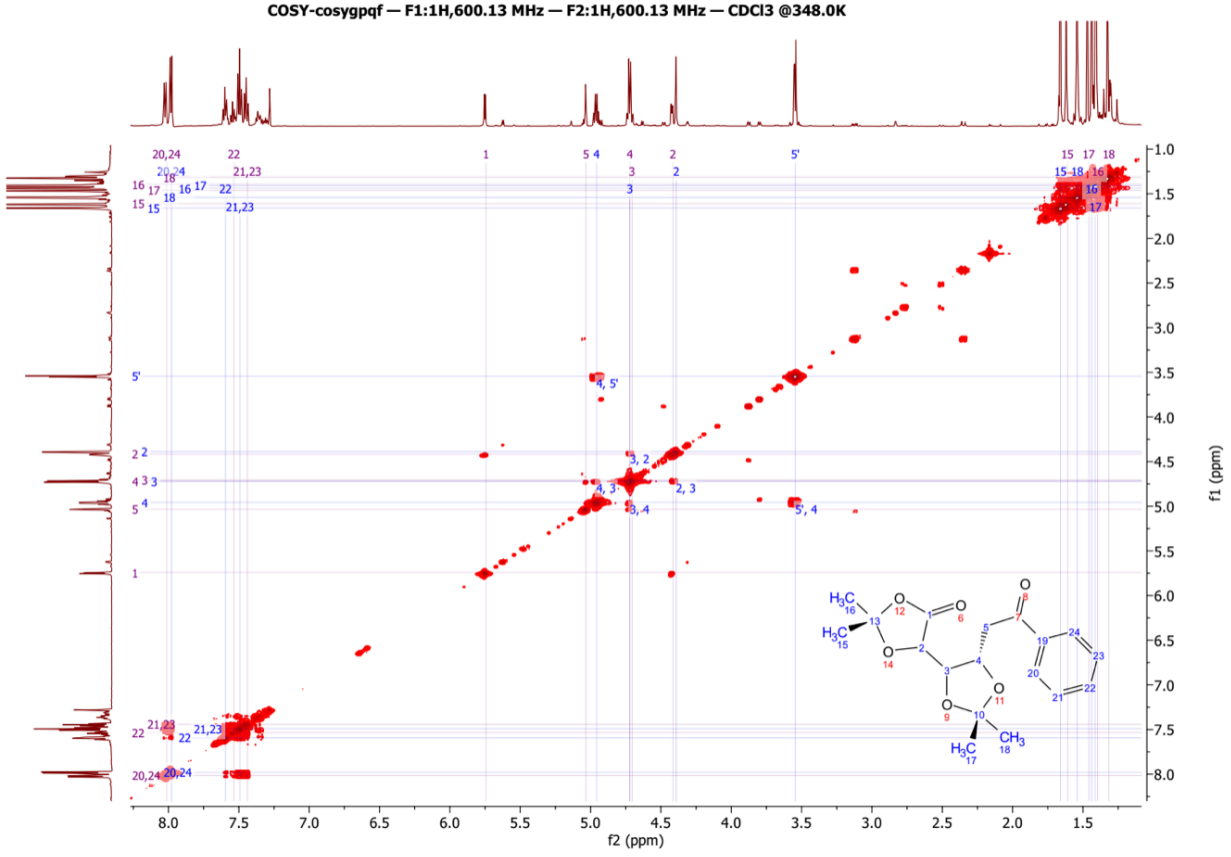
COSY (green) and HMBC (red) supporting assignment of the unknown compound

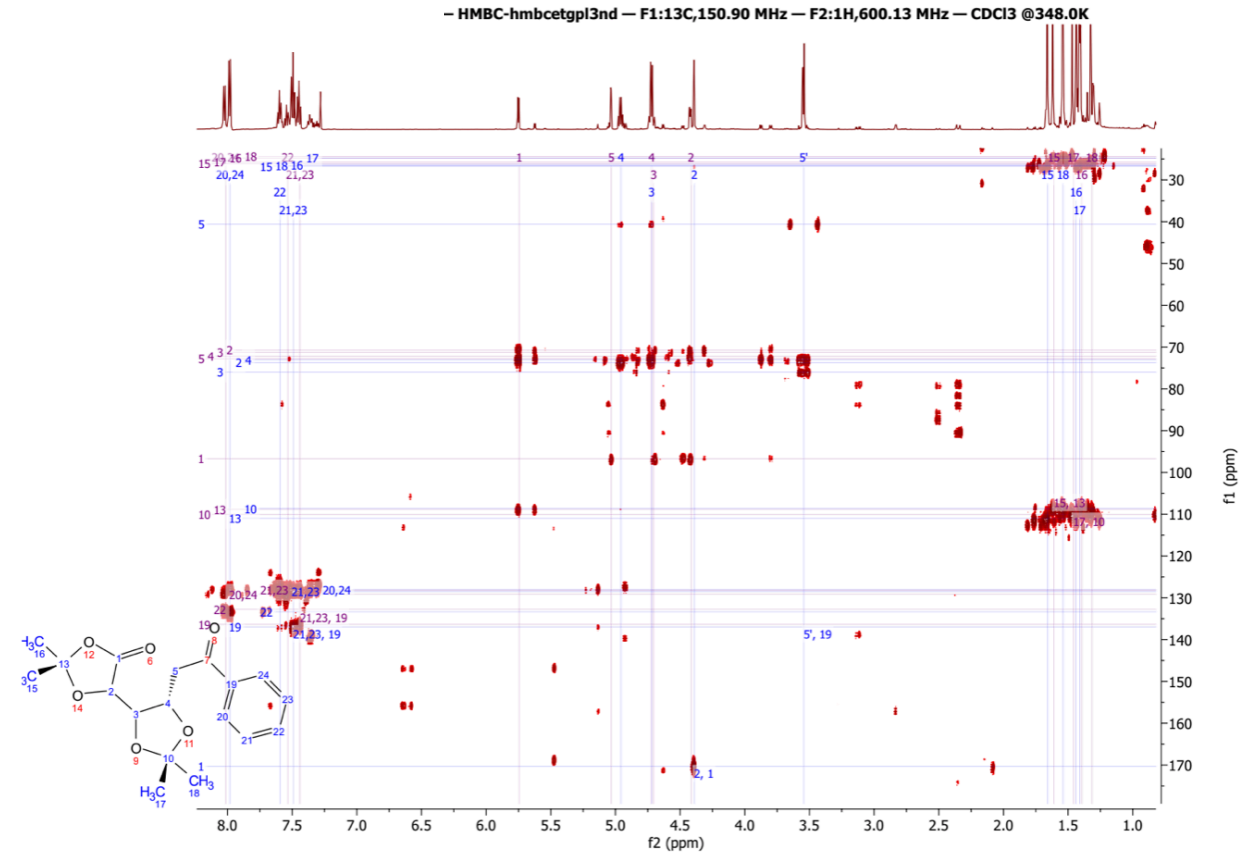


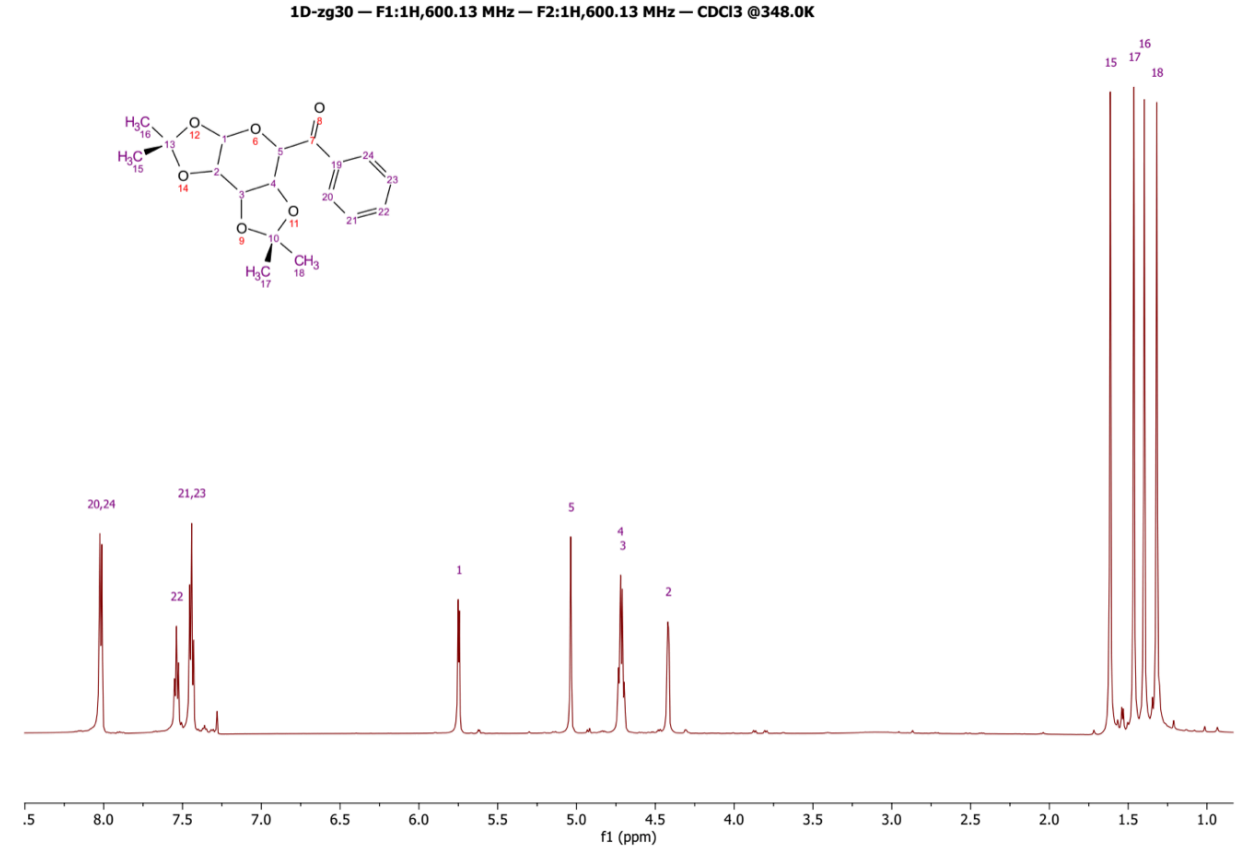
HSQC-EDITED-hsqcedetgpsisp2.3 — F1:13C,150.90 MHz — F2:1H,600.13 MHz — CDCl3 @348.0K

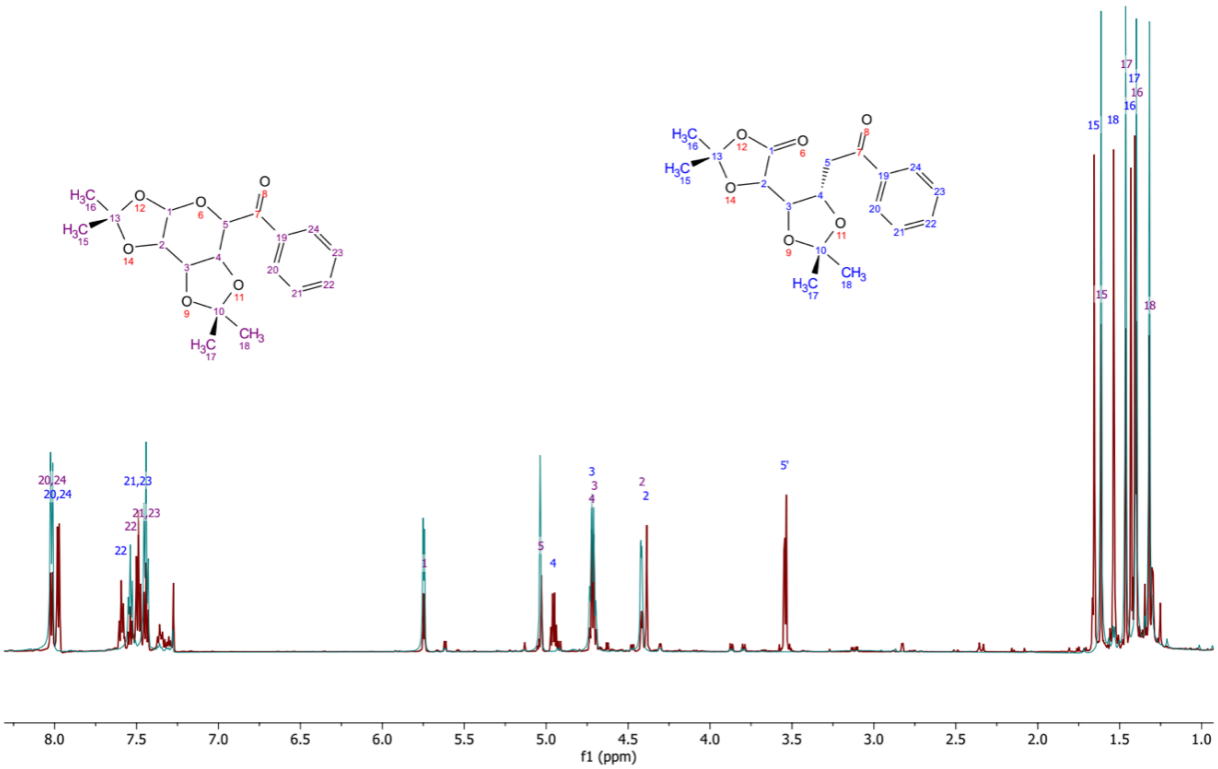


COSY-cosygpqf — F1:1H,600.13 MHz — F2:1H,600.13 MHz — CDCl3 @348.0K




– HMBC-hmbcetgpl3nd — F1:13C,150.90 MHz — F2:1H,600.13 MHz — CDCl3 @348.0K
f2 (ppm)
f1 (ppm)


1D-zg30 — F1:1H,600.13 MHz — F2:1H,600.13 MHz — CDCl3 @348.0K
f1 (ppm)


1D-zg30 — F1:1H,600.13 MHz — F2:1H,600.13 MHz — CDCl3 @348.0K
f1 (ppm)

4.4.5 Experimental Procedures for Gram-Scale Ring Contraction

Flow instrumentation and experimental information

All flow reactions were performed in a Vapourtec UV-150 photoreactor attached to Vapuortec R-Series flow system equipped with an autosampler. The entire continuous flow system was under inert atmosphere during the course of the reaction. The experimental details are included below.

The starting material phenyl(1-tosylpiperidin-2-yl)methanone (**4.3b**) (1.00 g, 2.91 mmol) was added to a 200 mL round-bottomed flask and then was dissolved in benzene (0.05M, 58 mL). The reaction mixture was degassed with nitrogen for 30 mins. Then using the Vapourtec R-series flow system, the reaction was run under continuous recirculating flow (i.e., the input and output tubes of the reaction were in the same vessel) using a 5 mL reaction loop. The reaction loop was heated to 50 ºC and the reaction mixture was irradiated with 400 nm light. The reaction mixture was allowed to recirculate for 32 h and was monitored by LCMS to determine conversion. After 32 h, the reaction setup was dismantled, the tubing was flushed with benzene (7 mL) and the crude reaction mixture was concentrated. The residue was purified by column chromatography on a silica gel Redisep Rf Gold column (12 g), eluting with EtOAc/hexanes to give the starting material phenyl(1-tosylpiperidin-2-yl)methanone (202 mg, 0.587 mmol, 20.16 % yield) as a colorless oil and the product *N*-(2-benzoylcyclopentyl)-4-methylbenzenesulfonamide (**4.4b**) (552 mg, 1.609 mmol, 55 % yield) as a colorless solid.

4.4.6. Experimental Procedures for Asymmetric Ring Contraction

Ring Contraction of Enantioenriched Material

SFC purification of *rac*-**4.3b**

Purification Conditions:

Column & Dimensions: AS-H, 21X250mm, 5um
UV Wavelength: 215nm
Flow Rate: 70ml/min
Modifier: 25% MeOH w/ 0.1% NH_4OH
Outlet Pressure: 100bar
Sample Amount: 240mg
Diluent: 1:1 MeOH/CH3CN
Diluent Volume: 10ml
Injection Volume: 0.25ml
Instrument: Sepiatec 1

Collected Fractions (Time in Mins)		
FRACTION_NAME	FRACTION_TIME	FRACTION_NOTE
PK1	1.7500	
PK2	2.1000	

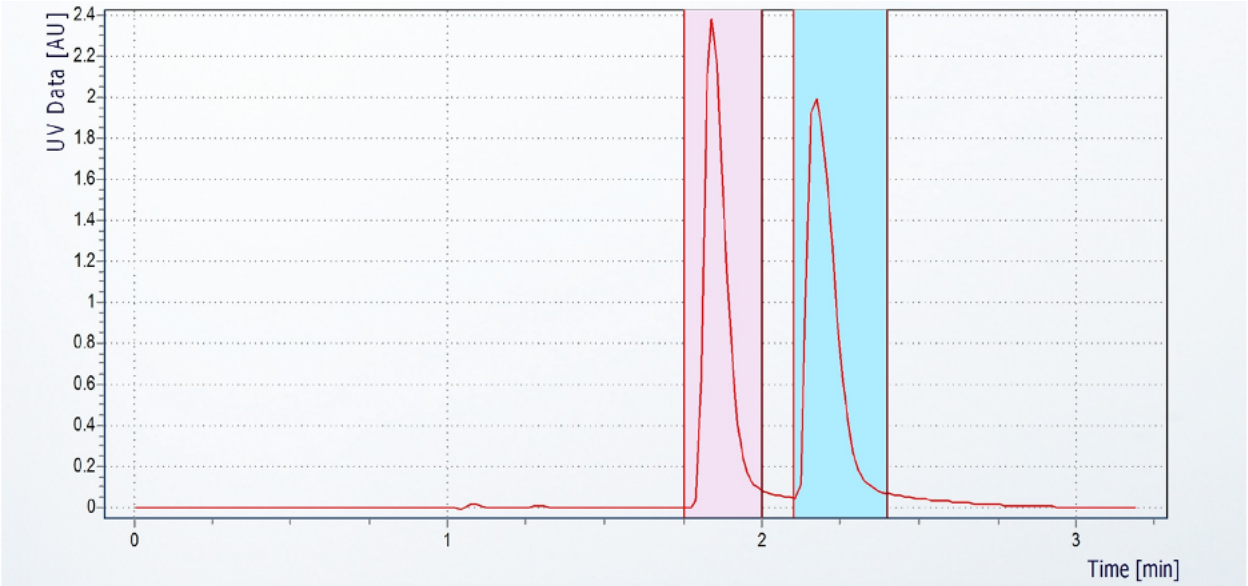
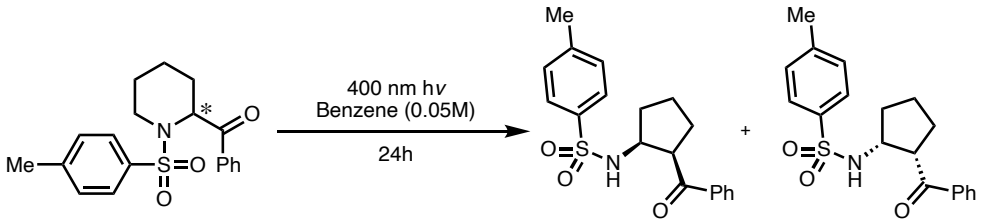


Figure 4.S2: HPLC chromatogram for the SFC purification of *rac*-**4.3b**

Peak 2: $[\alpha]_D^{23°C}$ = +54.94 degrees (*c* 0.42, $CHCl_3$)

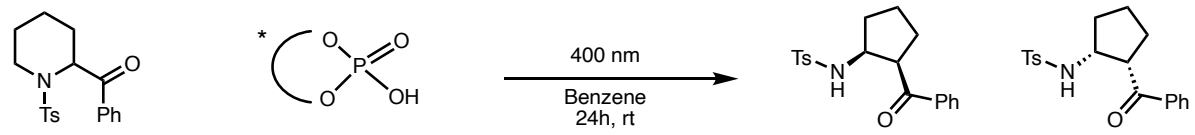
Ring Contraction of Enantioenriched 3b (Peak 2)



4.3b **± 4.4b**

***Rac-cis-N*-(2-benzoylcyclopentyl)-4-methylbenzenesulfonamide (±4.4b):** When the enantiomer associated with peak 2 of **4.3b** was subjected to the reaction conditions, it formed both enantiomers of the product (as determined by chiral SFC analysis). The recovered starting material was determined to be a single enantiomer indicating that the starting material does not racemize under the reaction conditions.

Asymmetric Ring Contraction of 4.3b



3b
Racemic

Chiral Phosphoric Acid
CPA1: (*R*)-TRIP
CPA2: (*R*)-XYL-SPA

CPA1: (–)-4b
76% (20:1 d.r.)
92:8 e.r.

CPA2: (+)-4b
89% (20:1 d.r.)
95:5 e.r.

(–)/(+)-*cis*-*N*-(2-benzoylcyclopentyl)-4-methylbenzenesulfonamide (4.4b) were synthesized according to a modified version of General Procedure D. To a 1-dram vial was added **4.3b** (0.05 mmol) and chiral phosphoric acid (10 mol%). The vial was evacuated and backfilled with nitrogen three times, and degassed benzene was added. The reaction mixture was irradiated with a 400 nm light source for 24 h, then volatiles were removed under reduced pressure. Yields for the major diastereomer were determined by ^{1}H NMR integration using Ph_3CH as an internal standard. Enantiomeric ratios were determined by SFC analysis.

(CPA1): 76%, 20:1 d.r., 92:8 e.r.
Peak 2: $[\alpha]_D^{27°C}$ = -54.2 degrees (*c* 0.54, $CHCl_3$) *Absolute stereochemistry determined by x-ray analysis*

(CPA2): 89%, 20:1 d.r., 95:5 e.r.
Peak 1: $[\alpha]_D^{29°C}$ = 68.2 degrees (*c* 0.66, $CHCl_3$) *Absolute stereochemistry assigned by comparison to (–)-4.4b*

Purification Conditions:

Column & Dimensions: IA-3, 4.6X100mm, 3um
UV Wavelength: PDA Max Plot
Flow Rate: 3.5 ml/min
Modifier: 25% MeOH w/ 0.1% NH_4OH
Outlet Pressure: 2000 psi

	Retention Time (mins)	% Area	Target Mass 1 (Da)	Base Peak (m/z)
(Racemic)	1.391	50.01	343.00	344.26
(Racemic)	1.626	49.99	343.00	344.26
(CPA1)	1.390	8.28	343.00	344.28
(CPA1)	1.589	91.72	343.00	344.25
(CPA2)	1.360	95.27	343.10	344.27
(CPA2)	1.626	4.73	343.10	344.29

.

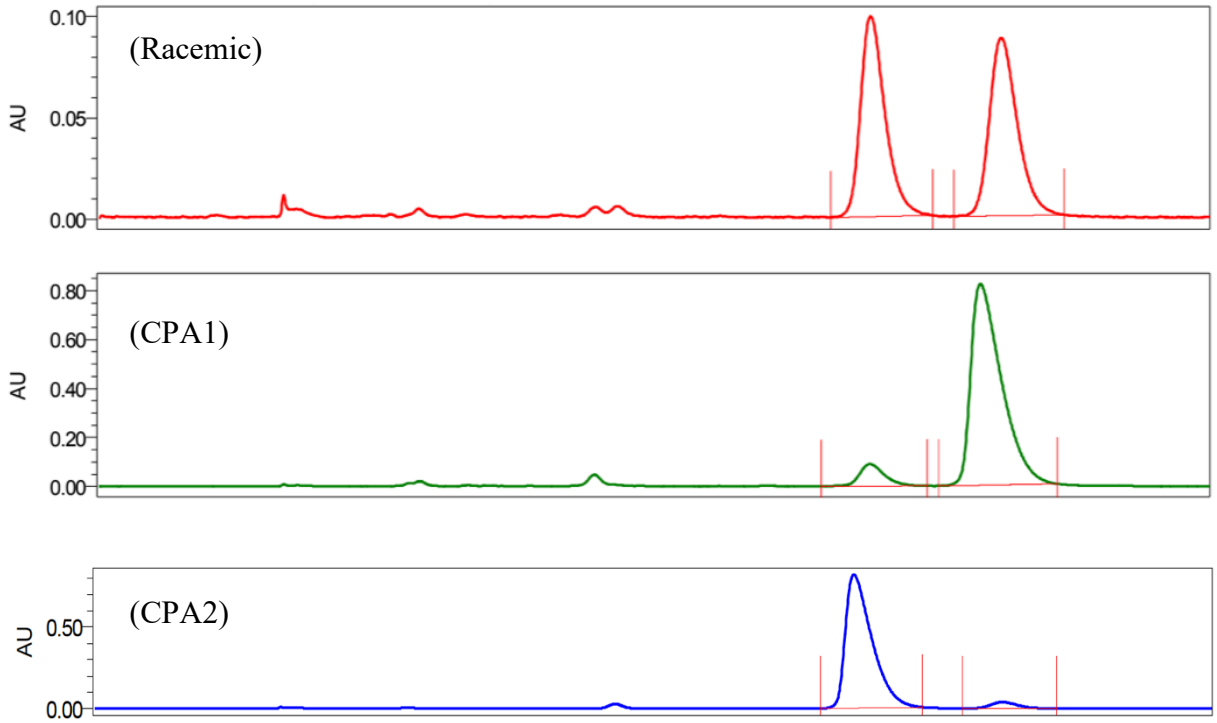
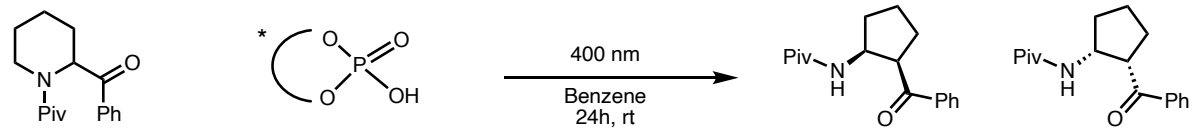


Figure 4.S3: HPLC chromatogram for the SFC purification of **4.4b.**

Asymmetric Ring Contraction of 4.3m



4.3m
Racemic

Chiral Phosphoric Acid
CPA1: (*R*)-TRIP
CPA2: (*R*)-XYL-SPA

CPA1: (–)-4.4m
43% (14:1 d.r.)
80:20 e.r.

CPA2: (+)-4.4m
40% (12:1 d.r.)
72:28 e.r.

(–)/(+)-*cis*-*N*-(2-benzoylcyclopentyl)pivalamide (4.4m) were synthesized according to a modified version of General Procedure D. To a 1-dram vial was added **4.3m** (0.05 mmol) and chiral phosphoric acid (10 mol%). The vial was evacuated and backfilled with nitrogen three times, and degassed benzene was added. The reaction mixture was irradiated with a 400 nm light source for 24 h, then volatiles were removed under reduced pressure. Yields for the major diastereomer were determined by ^{1}H NMR integration using Ph_3CH as an internal standard. Enantiomeric ratios were determined by SFC analysis.

(CPA1): 43%, 14:1 d.r., 80:20 e.r.
Peak 2: $[\alpha]_D^{27°C}$ = -43.7 degrees (*c* 0.27, $CHCl_3$) *Absolute stereochemistry assigned by analogy to (–)-4.4b*

(CPA2): 40%, 12:1 d.r., 72:28 e.r.
Peak 1: $[\alpha]_D^{30°C}$ = 24.2 degrees (*c* 0.35, $CHCl_3$) *Absolute stereochemistry assigned by analogy to (+)-4.4b*

Purification Conditions:

Column & Dimensions: IG, 4.6X100mm
UV Wavelength: PDA Max Plot
Flow Rate: 3.5 ml/min
Modifier: 25% MeOH w/ 0.1% NH_4OH
Outlet Pressure: 2000 psi

	Retention Time (mins)	% Area	Target Mass 1 (Da)	Base Peak (m/z)
(Racemic)	1.043	47.68	273.00	274.35
(Racemic)	1.113	52.32	273.00	274.34
(CPA1)	1.043	20.53	273.00	274.35
(CPA1)	1.110	79.47	273.00	274.36
(CPA2)	1.055	71.70	273.00	274.37
(CPA2)	1.127	28.30	273.00	274.38

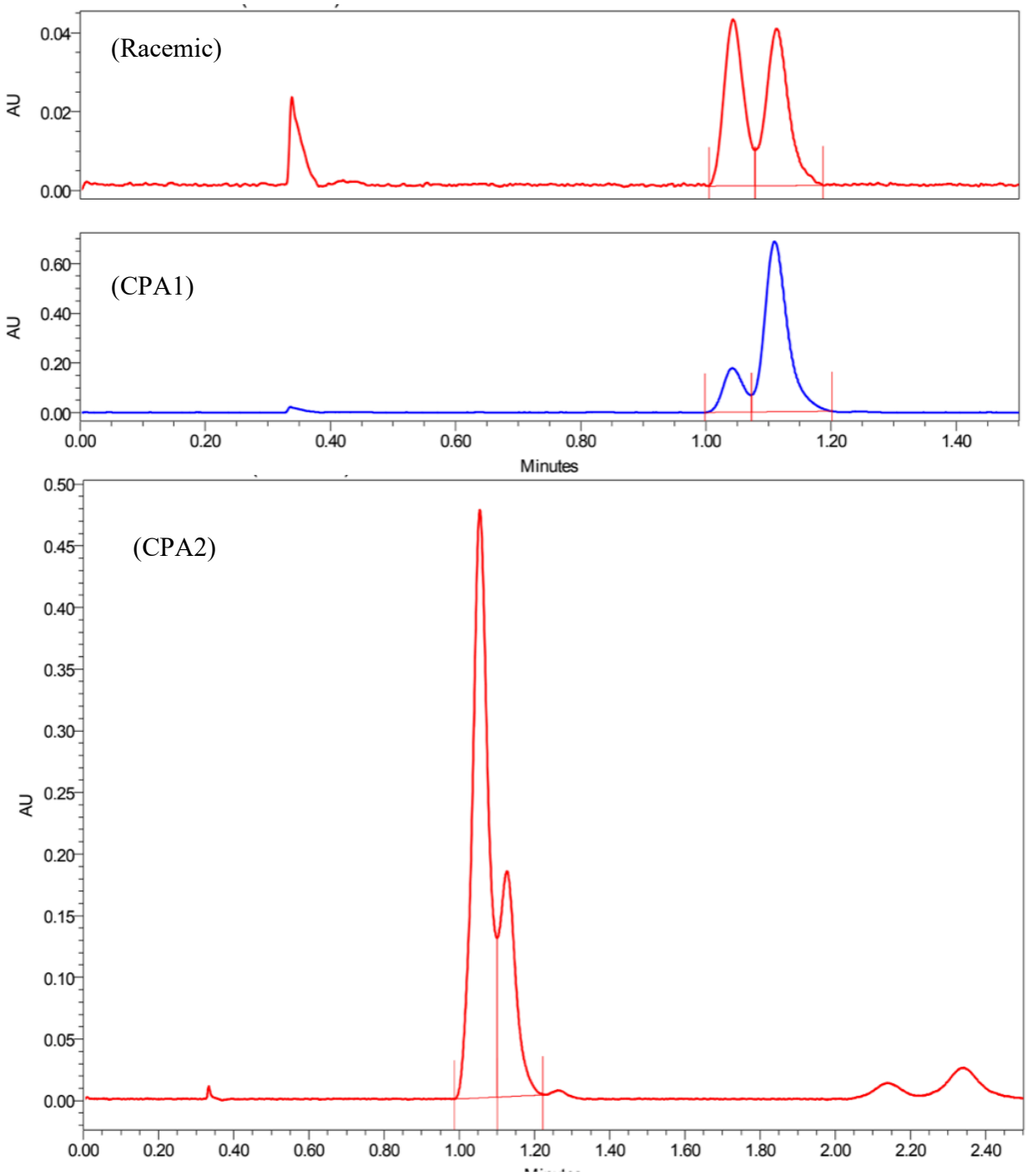
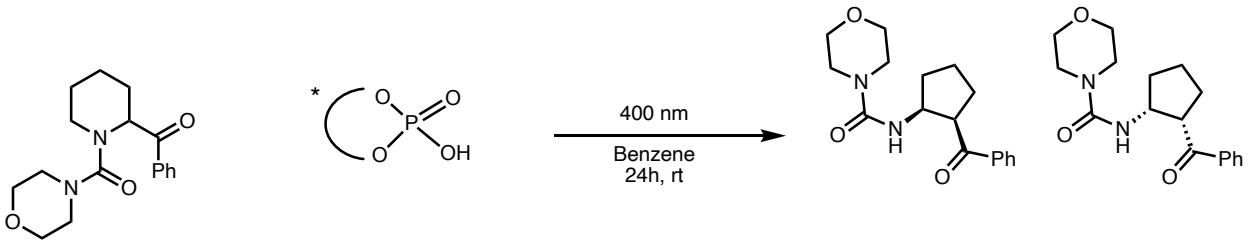


Figure 4.S4: HPLC chromatogram for the SFC purification of **4.4m.**

Asymmetric Ring Contraction of 4.3s



4.3s
Racemic

Chiral Phosphoric Acid
CPA1: (*R*)-TRIP
CPA2: (*R*)-XYL-SPA

CPA1: (–)-4.4s
58% (6:1 d.r.)
86:14 e.r.

CPA2: (+)-4.4s
49% (5:1 d.r.)
81:19 e.r.

(–)/(+)-*cis*-*N*-(2-benzoylcyclopentyl)morpholine-4-carboxamide (4s) were synthesized according to a modified version of General Procedure D. To a 1-dram vial was added **3s** (0.05 mmol) and chiral phosphoric acid (10 mol%). The vial was evacuated and backfilled with nitrogen three times, and degassed benzene was added. The reaction mixture was irradiated with a 400 nm light source for 24 h, then volatiles were removed under reduced pressure. Yields for the major diastereomer were determined by ^{1}H NMR integration using Ph_3CH as an internal standard. Enantiomeric ratios were determined by SFC analysis.

(CPA1): 58%, 6:1 d.r. 86:14 e.r.
Peak 2: $[\alpha]_D^{28°C}$ = -25.2 degrees (*c* 0.08, $CHCl_3$) *Absolute stereochemistry assigned by analogy to (–)-4.4b*

(CPA2): 49%, 5:1 d.r. 81:19 e.r.
Peak 1: $[\alpha]_D^{32°C}$ = 19.8 degrees (*c* 0.64, $CHCl_3$) *Absolute stereochemistry assigned by analogy to (+)-4.4b*

Purification Conditions:

Column & Dimensions: IG, 4.6X100mm
UV Wavelength: PDA Max Plot
Flow Rate: 3.5 ml/min
Modifier: 25% MeOH w/ 0.1% NH_4OH
Outlet Pressure: 2000 psi

	Retention Time (mins)	% Area	Target Mass 1 (Da)	Base Peak (m/z)
(Racemic)	1.007	45.76	302.00	303.29
	1.127	3.25	302.00	303.28
	1.277	4.79	302.00	303.30
(Racemic)	1.519	46.20	302.00	303.30

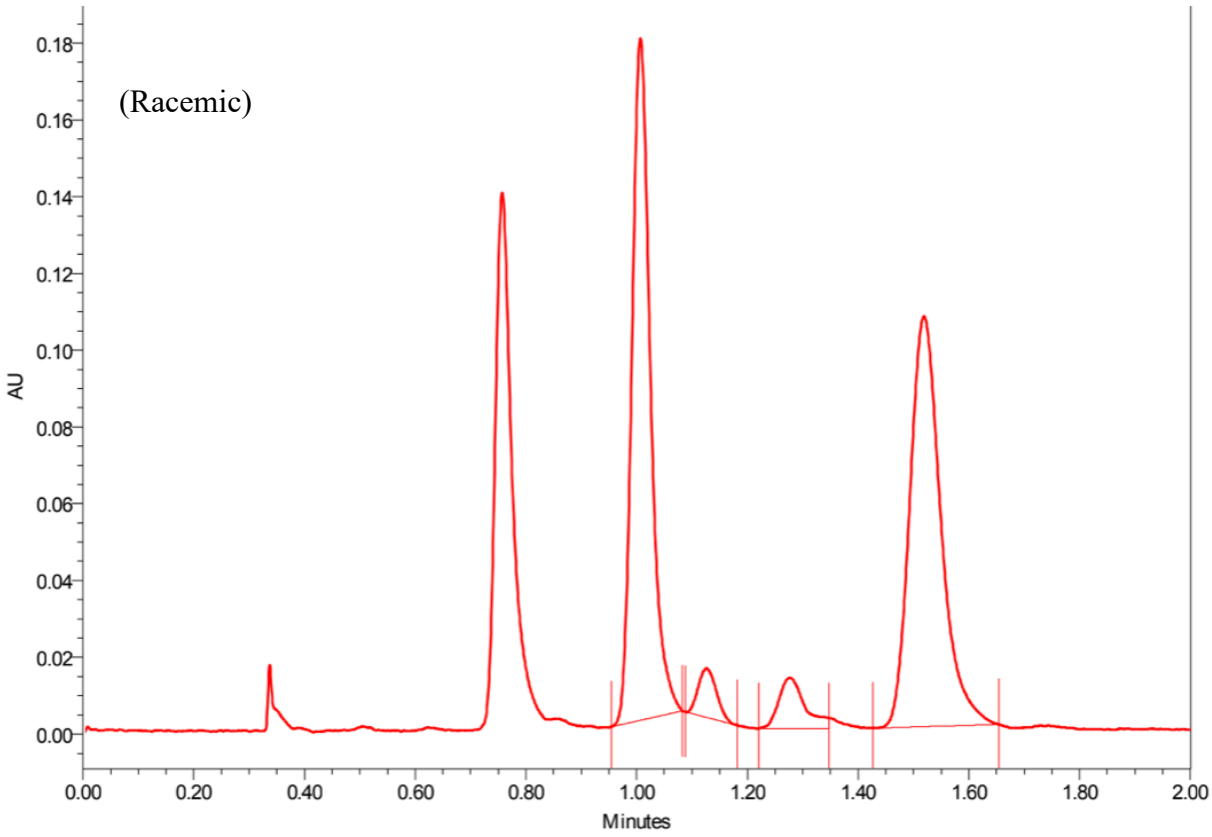


Figure 4.S5: HPLC chromatogram for the SFC purification of racemic **4.4s.**

	Retention Time (mins)	% Area	Target Mass 1 (Da)	Base Peak (m/z)
(CPA1)	1.006	13.53	302.00	303.30
	1.127	1.66	302.00	303.30
	1.277	0.71	302.00	303.26
(CPA1)	1.500	84.11	302.00	303.31

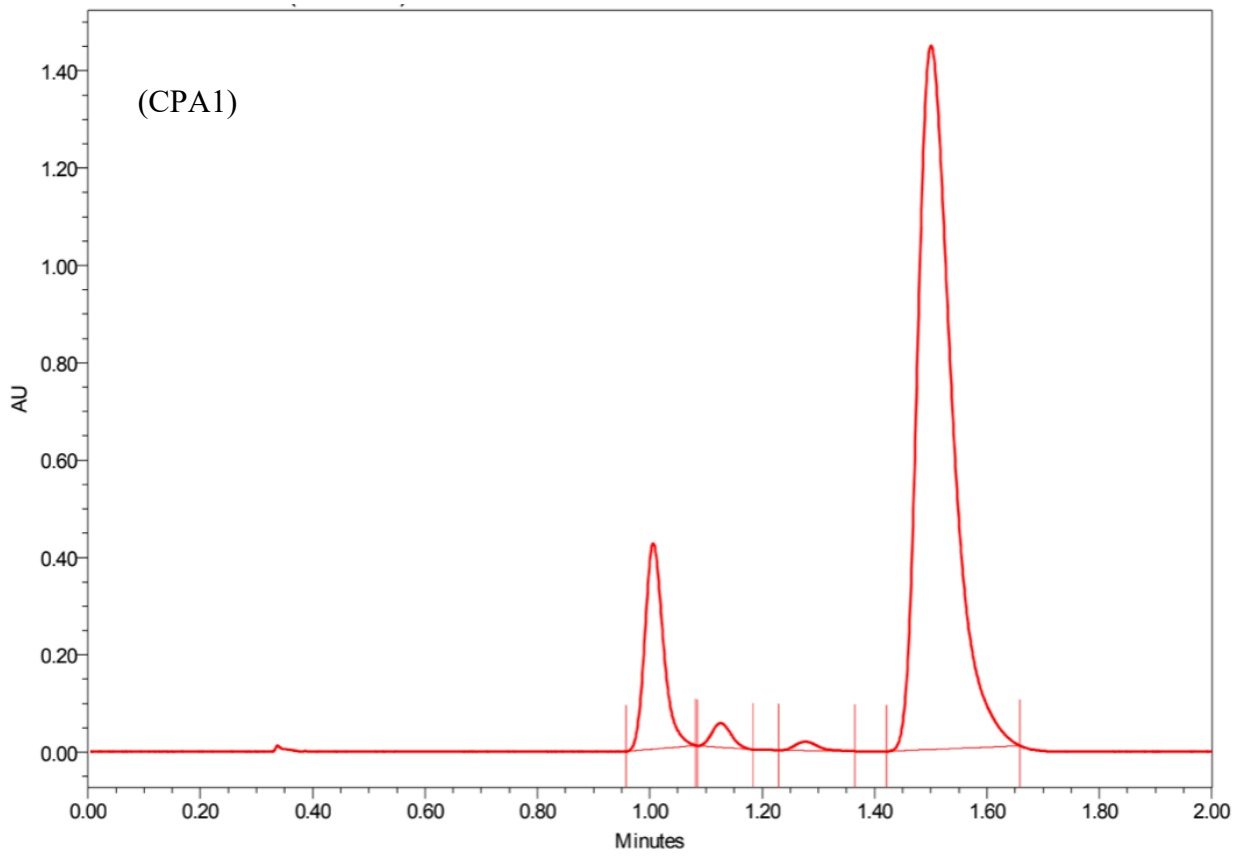


Figure 4.S6: HPLC chromatogram for the SFC purification of enantioenriched **4.4s.**

	Retention Time (mins)	% Area	Target Mass 1 (Da)	Base Peak (m/z)
(CPA2)	1.005	80.84	302.00	303.30
(CPA2)	1.524	19.16	302.00	303.29

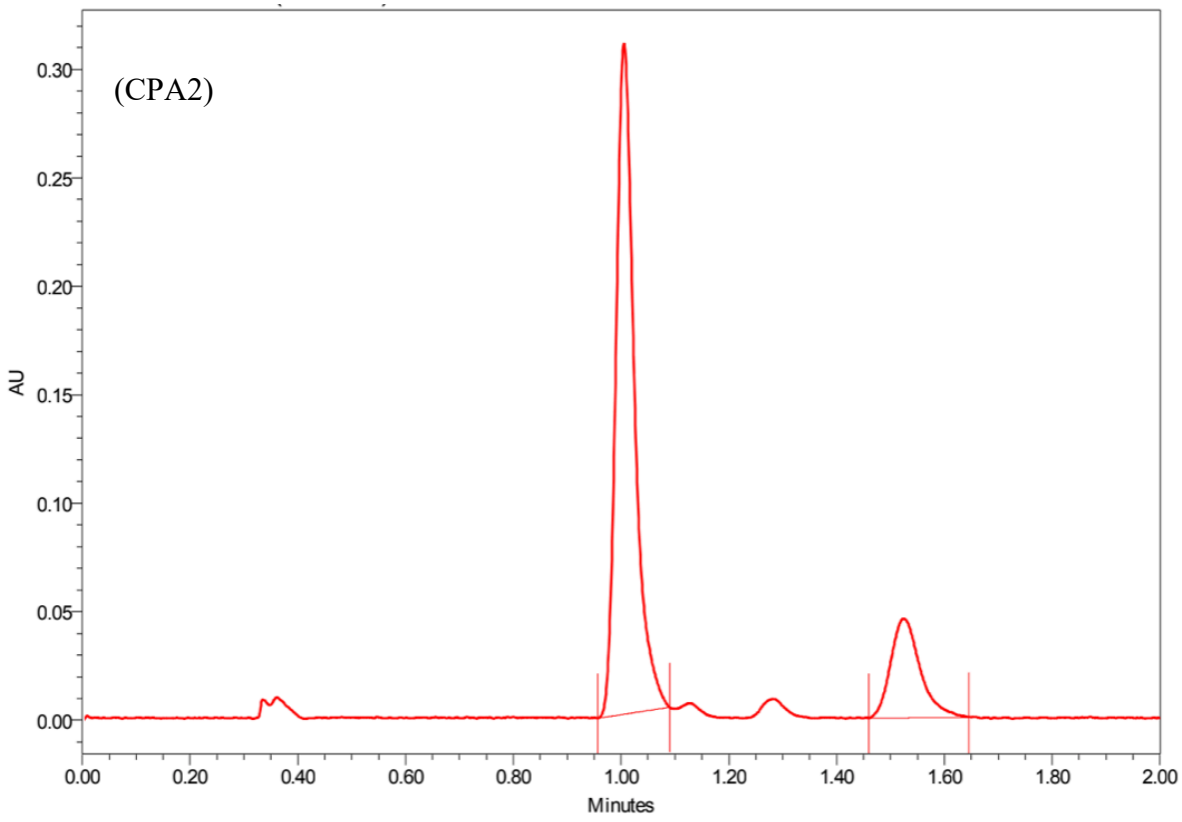
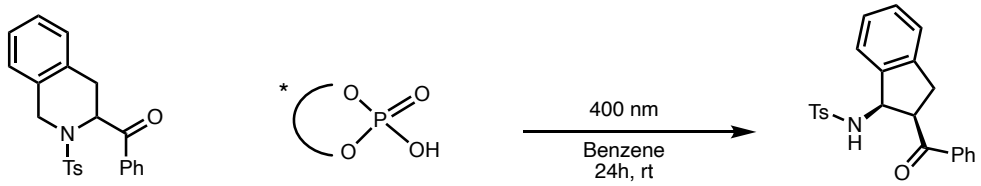


Figure 4.S7: HPLC chromatogram for the SFC purification of enantioenriched **4.4s.**

Asymmetric Ring Contraction of 4.7b



4.7b
Racemic

Chiral Phosphoric Acid
CPA1: (*R*)-TRIP

CPA1: (+)-4.8b
53% (9:1 d.r.)
65:35 e.r.

(+)-*cis*-*N*-(2-benzoyl-2,3-dihydro-1*H*-inden-1-yl)-4-methylbenzenesulfonamide (4.8b) was synthesized according to a modified version of General Procedure D. To a 1-dram vial was added **4.7b** (0.05 mmol) and chiral phosphoric acid (10 mol%). The vial was evacuated and backfilled with nitrogen three times, and degassed benzene was added. The reaction mixture was irradiated with a 400 nm light source for 24 h, then volatiles were removed under reduced pressure. Yields for the major diastereomer were determined by ^{1}H NMR integration using Ph_3CH as an internal standard. Enantiomeric ratios were determined by SFC analysis.

(CPA1): 53%, 9:1 d.r.
Major Diastereomer 65:35 e.r.
Peak 1: $[\alpha]_D^{31°C}$ = 98.9 degrees (*c* 0.32, $CHCl_3$) *Absolute stereochemistry assigned by analogy to (–)-4.4b*

Minor Diastereomer 76:24 e.r.

Column & Dimensions: IA-3, 4.6X100mm
UV Wavelength: PDA Max Plot
Flow Rate: 3.5 ml/min
Modifier: 35% MeOH w/ 0.1% NH_4OH
Outlet Pressure: 2000 psi

	Retention Time (mins)	% Area	Target Mass 1 (Da)	Base Peak (m/z)
(CPA1) major	1.117	64.92		221.28
(CPA1) major	1.412	35.08		221.29
(CPA1) minor	1.019	76.17		409.37
(CPA1) minor	1.262	23.83		409.36
(Racemic)	1.025	13.63		409.38
(Racemic)	1.114	36.87		414.31
(Racemic)	1.264	13.30		409.36
(Racemic)	1.398	36.20		414.34

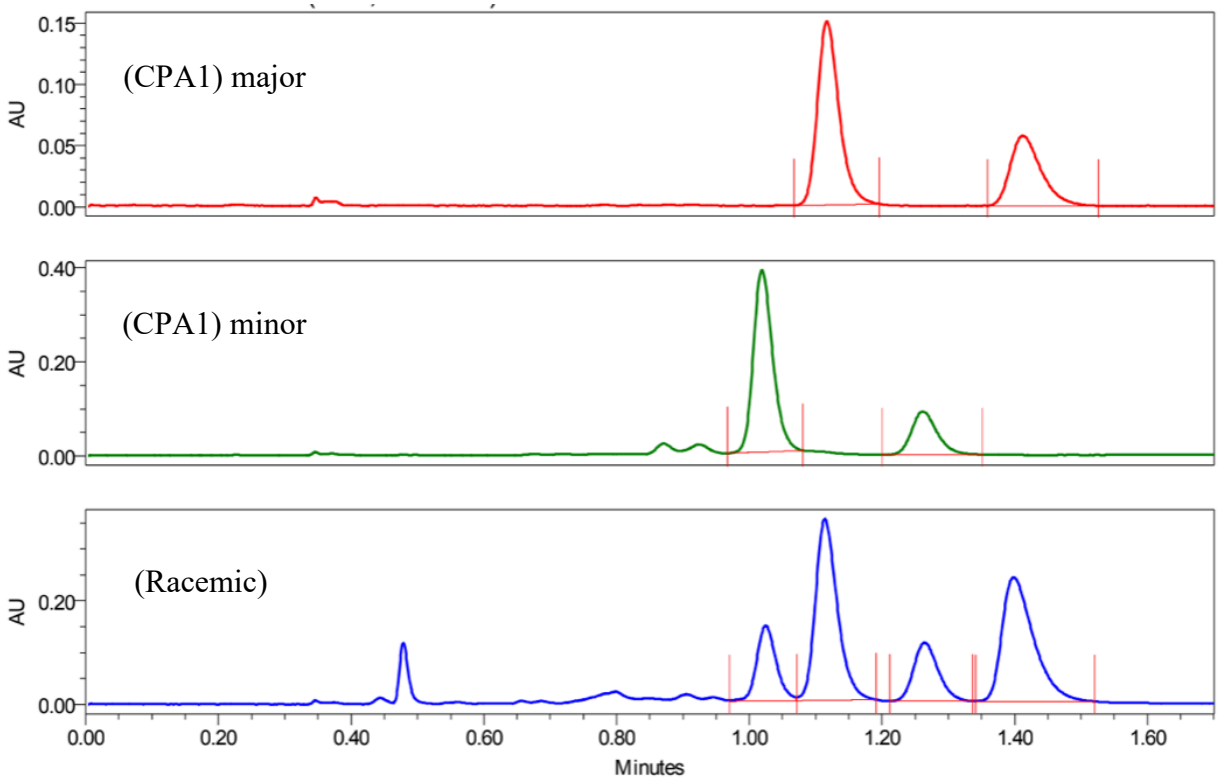
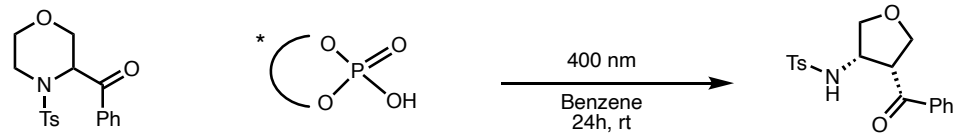


Figure 4.S8: HPLC chromatogram for the SFC purification of enantioenriched **4.8b.**

Asymmetric Ring Contraction of 4.7c



4.7c
Racemic

Chiral Phosphoric Acid
CPA2: (*R*)-XYL-SPA

CPA2: (+)-4.8c
83% (20:1 d.r.)
92:8 e.r.

(+)-*cis*-*N*-(4-benzoyltetrahydrofuran-3-yl)-4-methylbenzenesulfonamide (4.8c) was synthesized according to a modified version of General Procedure D. To a 1-dram vial was added **4.7c** (0.05 mmol) and chiral phosphoric acid (10 mol%). The vial was evacuated and backfilled with nitrogen three times, and degassed benzene was added. The reaction mixture was irradiated with a 400 nm light source for 24 h, then volatiles were removed under reduced pressure. Yields for the major diastereomer were determined by ^{1}H NMR integration using Ph_3CH as an internal standard. Enantiomeric ratios were determined by SFC analysis.

(CPA2): 83%, 20:1 d.r. 92:8 e.r.
Peak 1: $[\alpha]_D^{31°C}$ = 45.6 degrees (*c* 0.58, $CHCl_3$) *Absolute stereochemistry assigned by analogy to (+)-4.4b*

Column & Dimensions: IA-3, 4.6X100mm
UV Wavelength: PDA Max Plot
Flow Rate: 3.5 ml/min
Modifier: 30% MeOH w/ 0.1% NH_4OH
Outlet Pressure: 2000 psi

	Retention Time (mins)	% Area	Target Mass 1 (Da)	Base Peak (m/z)
(CPA2)	1.518	91.81	345.00	346.24
(CPA2)	1.789	8.19	345.00	346.24
	0.912	15.13	345.00	346.26
(Racemic)	1.527	36.56	345.00	346.24
(Racemic)	1.780	36.03	345.00	346.24
	1.987	12.29	345.00	346.27

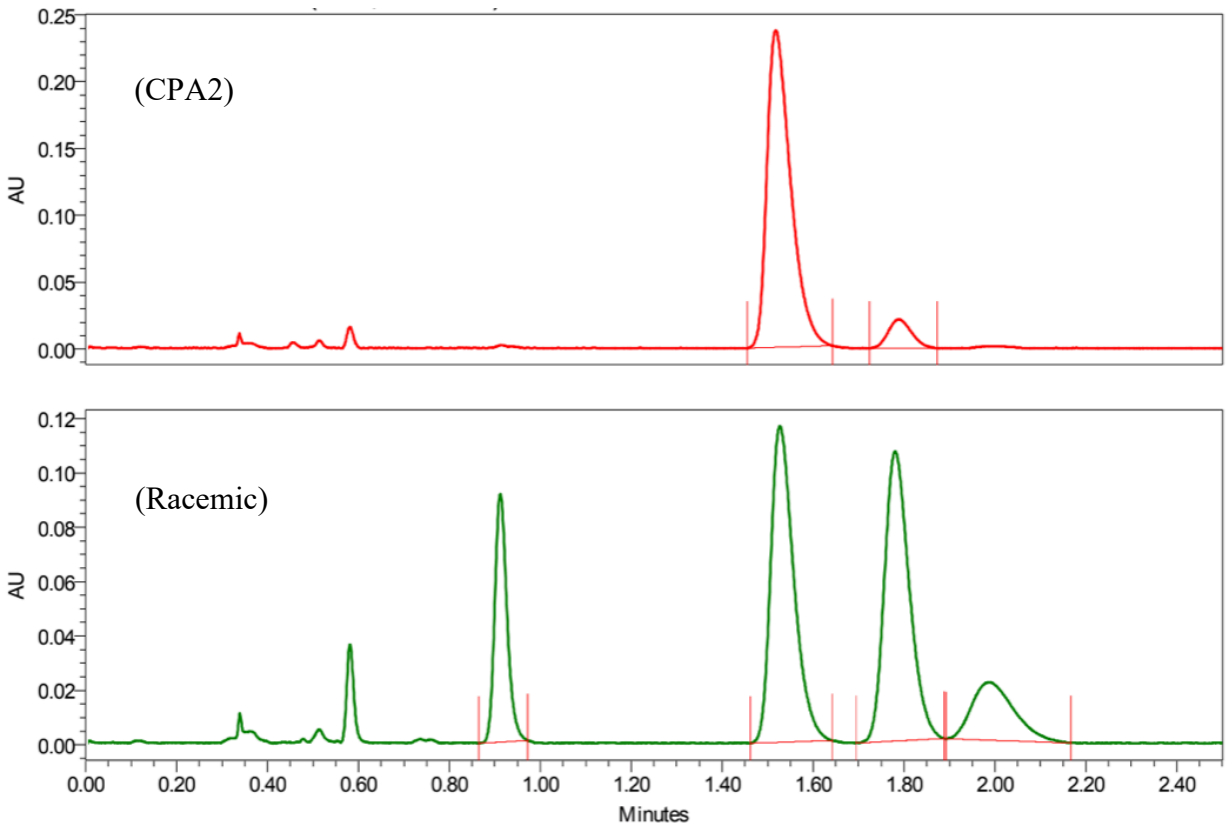
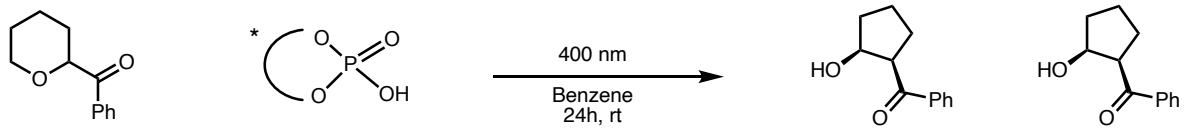


Figure 4,S9: HPLC chromatogram for the SFC purification of enantioenriched **4.8c.**

Asymmetric Ring Contraction of 4.7e



4.7e
Racemic

Chiral Phosphoric Acid
CPA1: (*R*)-TRIP
CPA2: (*R*)-XYL-SPA

CPA1: (–)-4.8e
79% (20:1 d.r.)
61:39 e.r.

CPA2: (–)-4.8e
70% (20:1 d.r.)
62:38 e.r.

(–)-*cis*-2-hydroxycyclopentyl)(phenyl)methanone (4.8e) was synthesized according to a modified version of General Procedure D. To a 1-dram vial was added **4.7e** (0.05 mmol) and chiral phosphoric acid (10 mol%). The vial was evacuated and backfilled with nitrogen three times, and degassed benzene was added. The reaction mixture was irradiated with a 400 nm light source for 24 h, then volatiles were removed under reduced pressure. Yields for the major diastereomer were determined by ^{1}H NMR integration using Ph_3CH as an internal standard. Enantiomeric ratios were determined by SFC analysis.

(CPA1): 79%, 20:1 d.r., 61:39 e.r.
Peak 1: $[\alpha]_D^{28°C}$ = -4.1 degrees (*c* 0.34, $CHCl_3$) *Absolute stereochemistry assigned by analogy to (–)-4.4b*

(CPA2): 70%, 20:1 d.r. 62:38 e.r.
Peak 1: $[\alpha]_D^{32°C}$ = -0.002 degrees (*c* 0.46, $CHCl_3$)

Purification Conditions:

Column & Dimensions: IA-3, 4.6X100mm, 3um
UV Wavelength: PDA Max Plot
Flow Rate: 3.5 ml/min
Modifier: 25% MeOH w/ 0.1% NH_4OH
Outlet Pressure: 2000 psi

	Retention Time (mins)	% Area	Target Mass 1 (Da)	Base Peak (m/z)
(Racemic)	0.702	50.30	190.00	191.26
(Racemic)	0.858	49.70	190.00	191.26
(CPA1)	0.699	61.39	190.00	191.26
(CPA1)	0.855	38.61	190.00	191.29
(CPA2)	0.706	61.91	190.00	191.26
(CPA2)	0.861	38.09	190.00	191.25

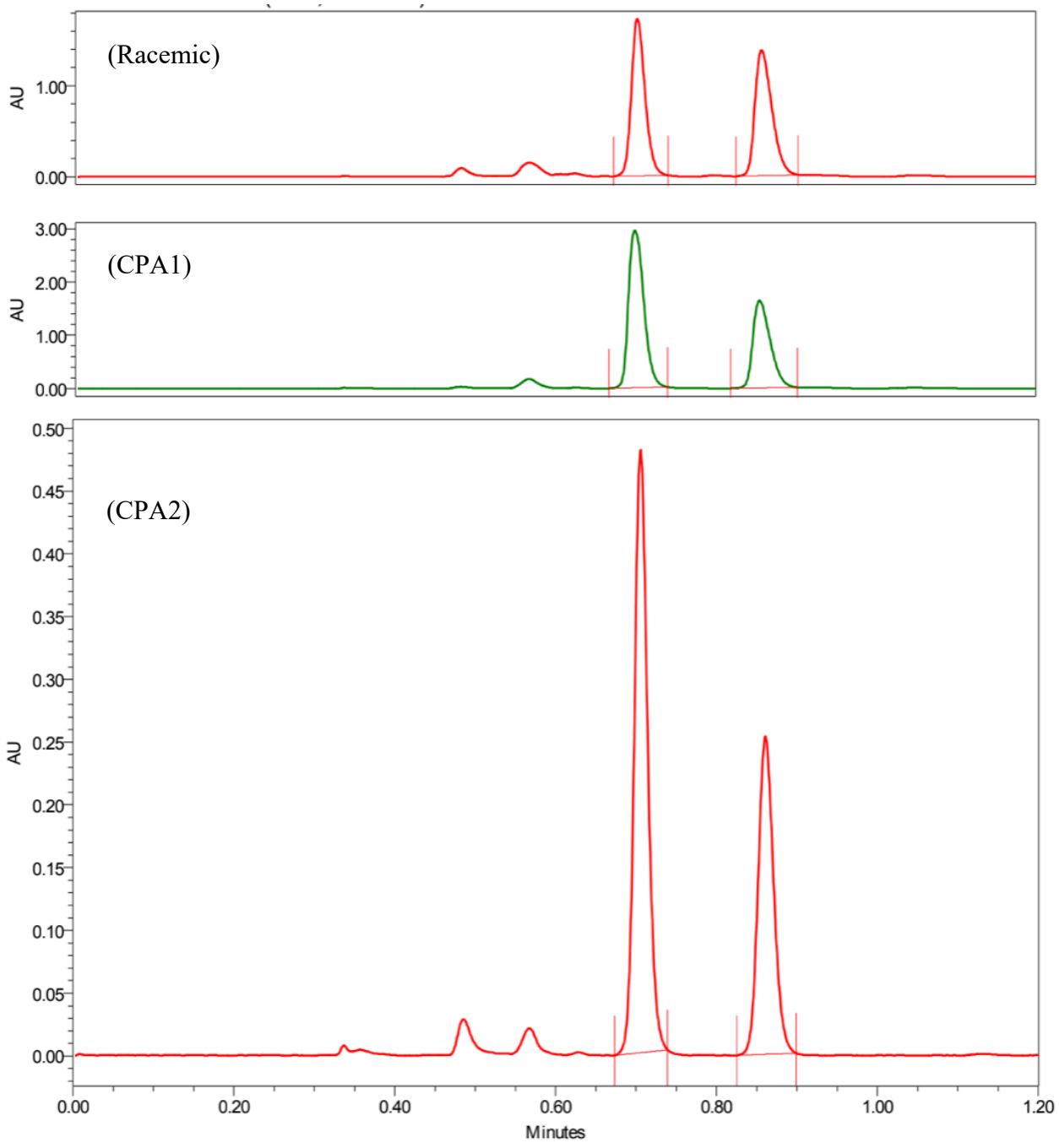
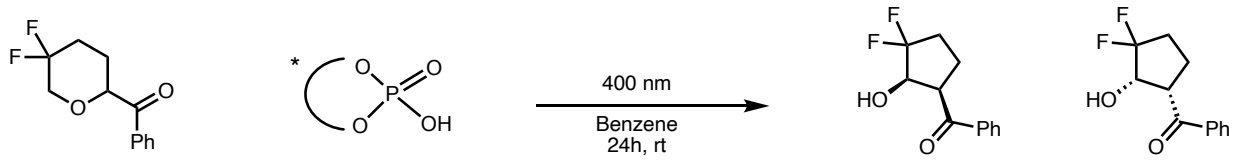


Figure 4.S10: HPLC chromatogram for the SFC purification of **4.8e.**

Asymmetric Ring Contraction of 4.7g



4.7g
Racemic

Chiral Phosphoric Acid
CPA1: (*R*)-TRIP
CPA2: (*R*)-XYL-SPA

CPA1: (–)-4.8g
90% (20:1 d.r.)
83:17 e.r.

CPA2: (+)-4.8g
91% (20:1 d.r.)
80:20 e.r.

(–)/(+)-*cis*-3,3-difluoro-2-hydroxycyclopentyl)(phenyl)methanone (4.8g) were synthesized according to a modified version of Representative Procedure D. To a 1-dram vial was added **4.7g** (0.05 mmol) and chiral phosphoric acid (10 mol%). The vial was evacuated and backfilled with nitrogen three times, and degassed benzene was added. The reaction mixture was irradiated with a 400 nm light source for 24 h, then volatiles were removed under reduced pressure. Yields for the major diastereomer were determined by ^{1}H NMR integration using Ph_3CH as an internal standard. Enantiomeric ratios were determined by SFC analysis.

(CPA1): 90%, 20:1 d.r., 83:17 e.r.
Peak 2: $[\alpha]_D^{28°C}$ = -11.9 degrees (*c* 0.46, $CHCl_3$) *Absolute stereochemistry assigned by analogy to (–)-4.4b*

(CPA2): 91%, 20:1 d.r., 80:20 e.r.
Peak 1: $[\alpha]_D^{33°C}$ = 7.3 degrees (*c* 0.62, $CHCl_3$) *Absolute stereochemistry assigned by analogy to (+)-4.4b*

Purification Conditions:

Column & Dimensions: IA-3, 4.6X100mm, 3um
UV Wavelength: PDA Max Plot
Flow Rate: 3.5 ml/min
Modifier: 25% MeOH w/ 0.1% NH_4OH
Outlet Pressure: 2000 psi

	Retention Time (mins)	% Area	Target Mass 1 (Da)	Base Peak (m/z)
(Racemic)	0.608	48.69	226.00	227.28
(Racemic)	0.776	51.31	226.00	227.28
(CPA1)	0.607	16.73	226.00	227.30
(CPA1)	0.765	83.27	226.00	227.28
(CPA2)	0.610	79.66	226.00	227.30
(CPA2)	0.774	20.34	226.00	227.30

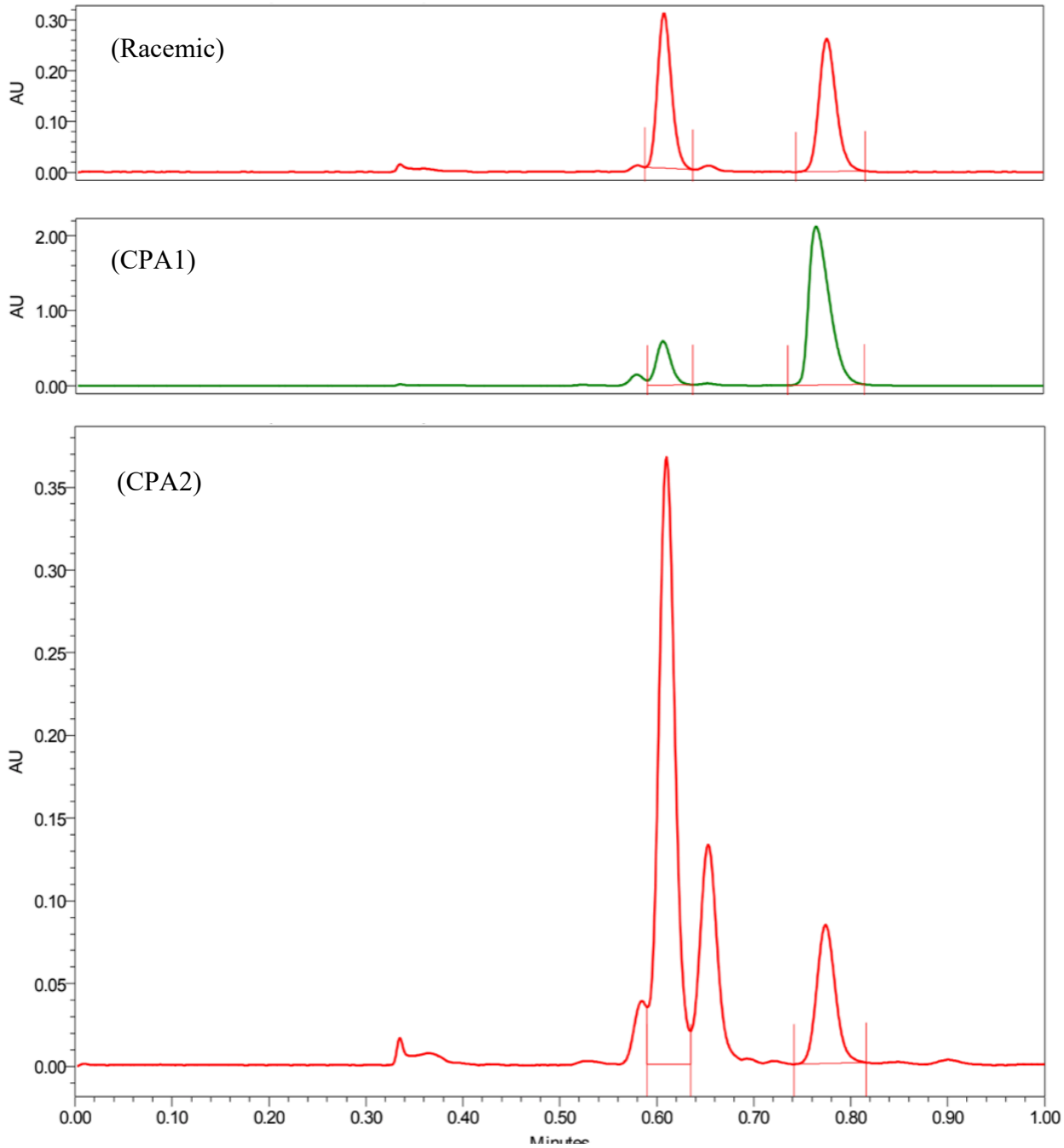


Figure 4.S11: HPLC chromatogram for the SFC purification of **4.8g.**

4.4.7. Photosensitizer HTE Screen

HTE experiments:

In a glovebox, a 0.05 mM stock solution of 1-(2-benzoylpiperidin-1-yl)-2-phenylethan-1-one (0.15 mmol, 3 mL, 0.6 mL overage) (**4.3n**) was prepared using degassed benzene in a glovebox. 100 uL of the stock solution was added by pipette into a plate of vials pre-loaded with 10 mol% of photocatalyst/photosensitizer (see table below for photocatalyst/photosensitizer information). The plate was sealed and then was irradiated with a Lumidox UV 365nm Ultraviolet 96-Well LED Array while in a tumble stirrer. The reaction plate was diluted and then was analyzed by LCMS to determine if there was conversion to the desired product.

The photosensitizers and photocatalysts tested are listed below in a quarter well-plate format. Catalysts/sensitizers that were observed to work are highlighted in green, those that did not work are highlighted in red. It was observed that only 3-cyanoumbelliferone (**IX**) promoted the reaction.

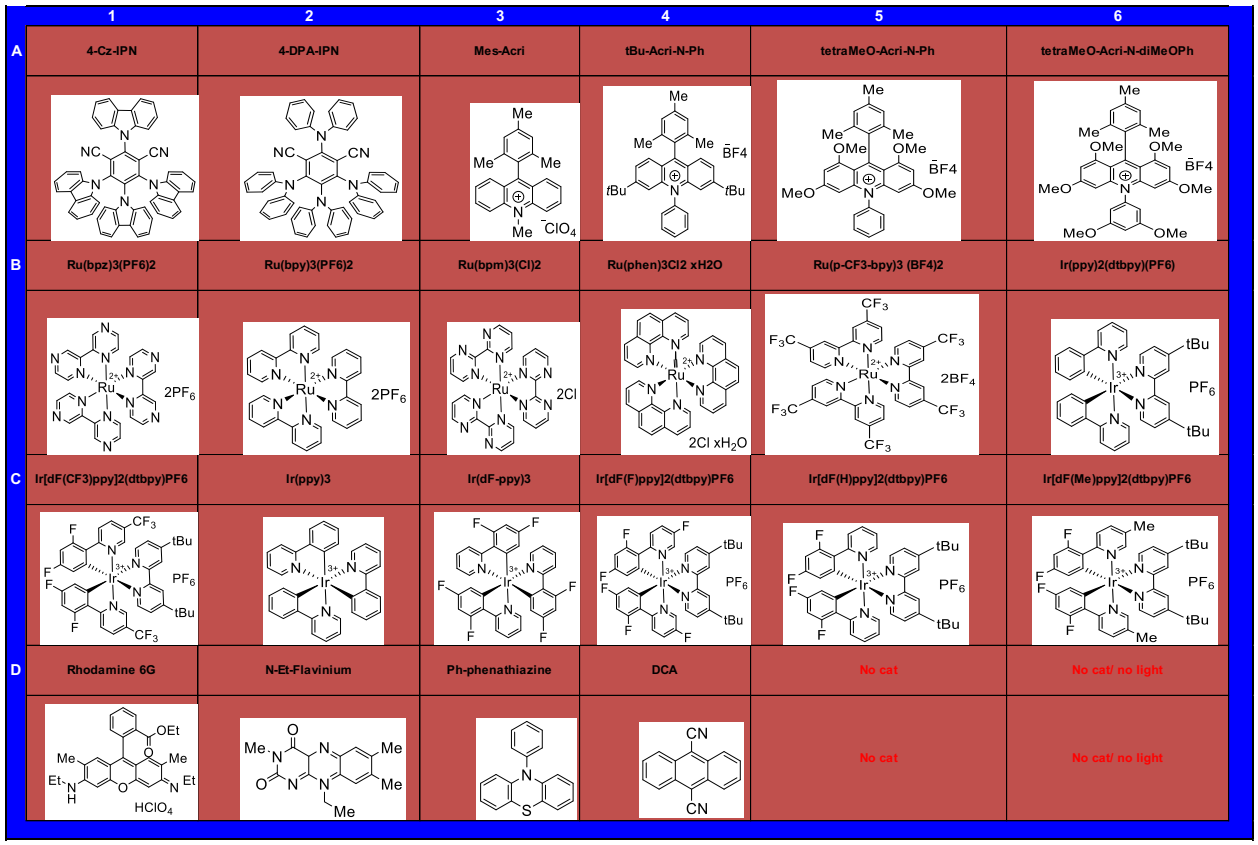


Figure 4.S12: HTE screen of various photocatalysts tested in the ring contraction of **4.3n.**

	1	2	3	4	5	6
A	(4-Methoxyphenyl)(4-(trifluoroMethyl)phenyl)Methanone	9-fluorenone	xanthone	thioxanthone	9-10-anthraquinone	5,12-Naphthacenequinone
B	Aceanthrenequinone	9,10-dicyanoanthracene	pyrene	Methylene blue	2-benzoyl-2-naphthol	9-Acetylphenanthrene
C	2-Acetylanthracene	1-Acetylpyrene	N,N-Dimethyl-6-propionyl-2-naphthylamine	Coumarin 153	3-Cyanoumbelliferone	Coumarin 102
D	2,4-Bis[4-(N,N-diphenylamino)-2,6-dihydroxyphenyl]squaraine	Copper(II) phthalocyanine	Zinc 1,2,3,4,8,9,10,11,15,16,17,18,22,23,24,25-hexadecafluoro-29H,31H-phthalocyanine	Cobalt(II) 1,2,3,4,8,9,10,11,15,16,17,18,22,23,24,25-hexadecafluoro-29H,31H-phthalocyanine	9-ethyl-3,6-dimethoxy-9H-carbazole	N,N'-Dioctyl-3,4,9,10-perylenedicarboximide

Figure 4.S13: HTE screen of various photosensitizers tested in the ring contraction of **4.3n** with 3-cyanoumbelliferone (**IX,** *green box*) identified as an effective additive.

4.4.8. UV-Vis Data

Instrument: Cary 60
Instrument Version: 2.0
Start: 800 nm
Stop: 200 nm
X Mode: Nanometers
Y Mode: Absorbance

UV-Vis Scan Rate (nm/min): 24000.000
UV-Vis Data Interval (nm): 5.00
UV-Vis Ave. Time (sec): 0.0125
Beam Mode: Dual Beam

Concentration **4.3b**: 2.5 mg/mL Absorptivity **4.3b**: ε_{340} = 48.0 L•cm^{-1}•mol^{-1}
Concentration **4.4b**: 2.5 mg/mL Absorptivity **4.4b**: ε_{320} = 19.2 L•cm^{-1}•mol^{-1}

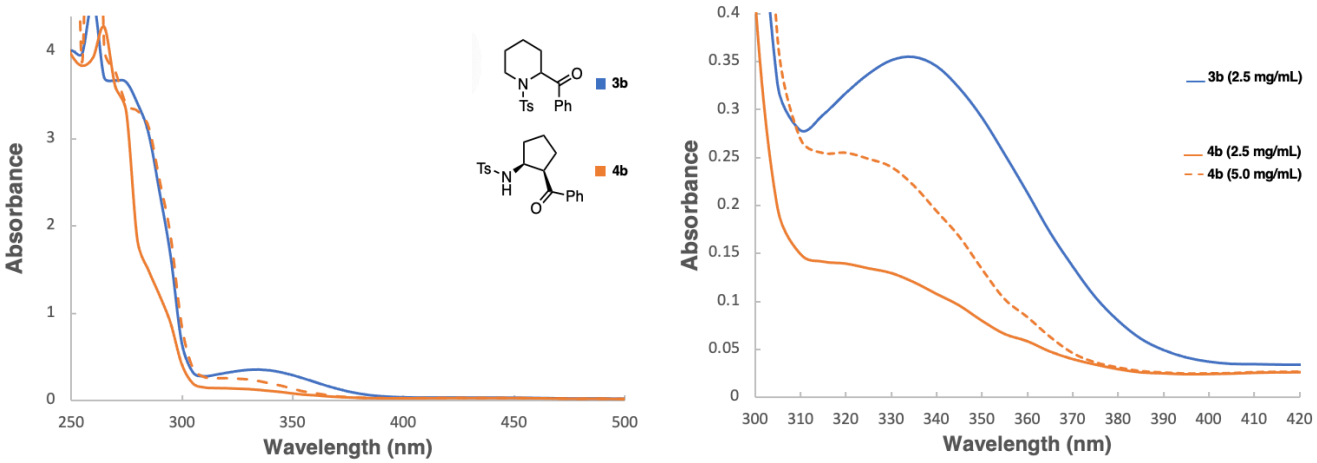


Figure 4.S14: UV-Vis spectra for starting material **4.3b** and product **4.4b**.

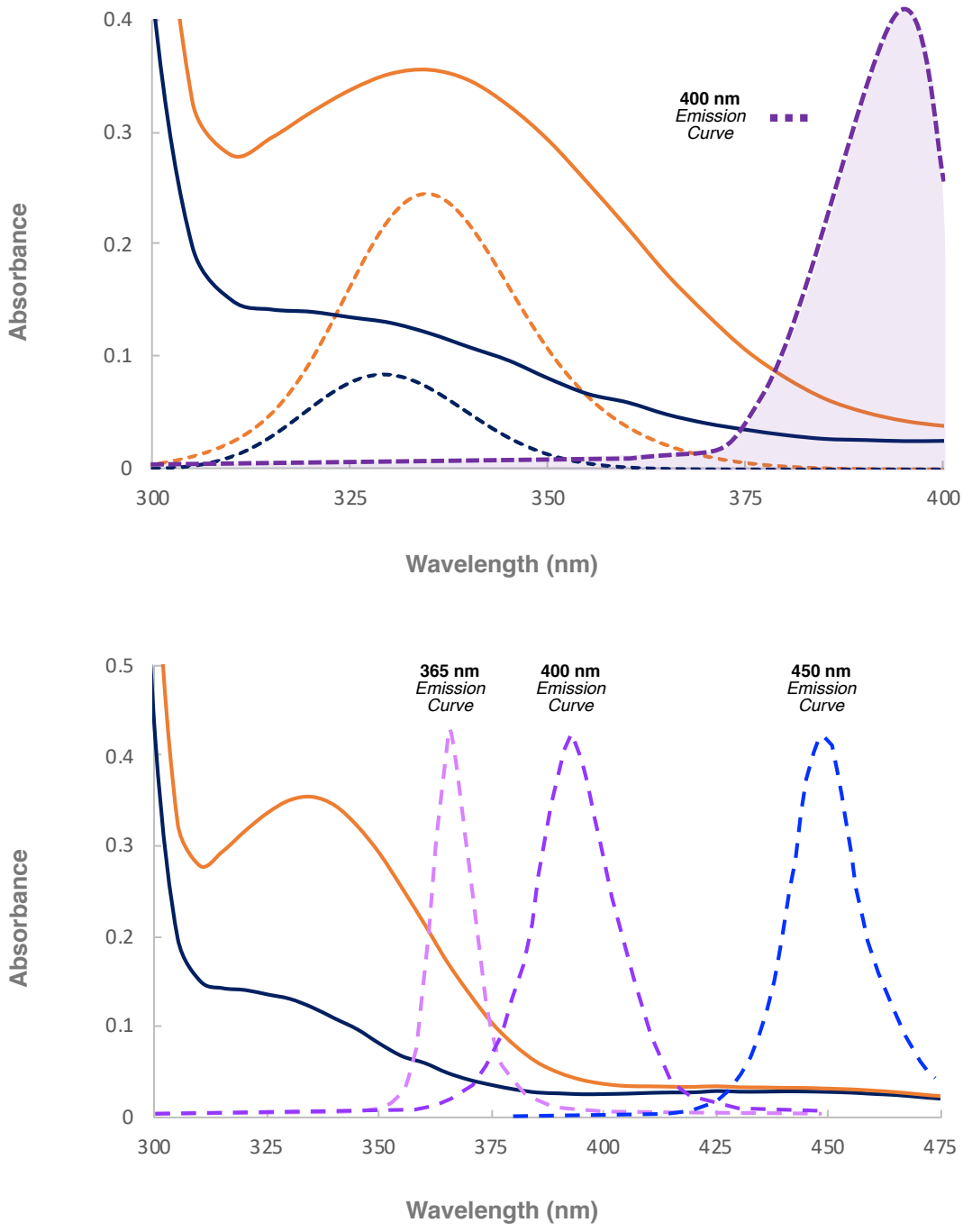
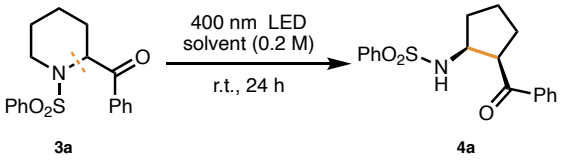


Figure 4S15: UV-Vis spectra for starting material **4.3b** (orange) and product **4.4b** (blue) with: (A) Adjusted overlay of 400 nm emission curve. (B) Adjusted overlay of 365 nm (magenta dotted), 400 nm (purple dotted) and 450 nm (blue dotted) emission curves.[57]

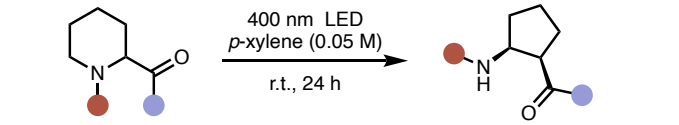
4.4.9. Ring Contraction Solvent Screen

Table 4.S1. Solvent screening for light-mediated ring contraction. *Reactions were carried out on a 0.05 mmol scale. Yields were determined by ^{1}H NMR integration using Ph_3CH as an internal standard. †Diastereomeric ratio was determined by ^{1}H NMR integration of resonances corresponding to diastereomers in the crude mixture.

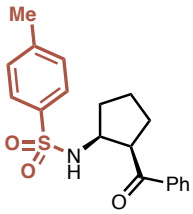


entry	solvent	yield (%, d.r.)*,†
1	PhMe	62% (8:1)
2	$PhCF_3$	66% (17:1)
3	THF	45% (2:1)
4	CH_2Cl_2	63% (8:1)
5	ethyl acetate	66% (9:1)
6	*p*-xylene	72% (>20:1)
7	2-MeTHF	48% (1.7:1)
8	isopropyl acetate	64% (4:1)
9	PhH	73% (>20:1)

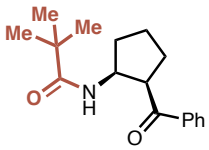
*Reactions conducted on a 0.05 mmol scale. ^{1}H NMR yields obtained using Ph_3CH as an internal standard; †Diastereomeric ratio determined by integration of signals corresponding to each diastereomer in the crude.



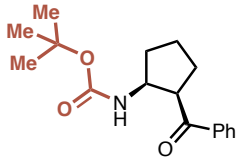
Selected Substrate Scope*,†



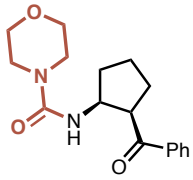
4b: 78% (14:1 d.r.)



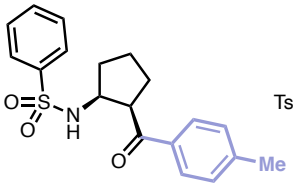
4m: 40% (19:1 d.r.)



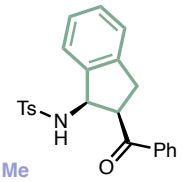
4q: 21% (20:1 d.r.)



4s: 72% (6:1 d.r.)



6a: 67% (10:1 d.r.)



8b: 52% (2.2:1 d.r.)

Given the known toxicity of benzene ($D = 2.3$, REL (recommended exposure limit) = 0.1 ppm), a screen of additional solvents with reduced toxicity was conducted. Toluene and trifluorotoluene resulted in reduced yields and diastereoselectivity for the desired product. Given the importance of safety, and considerations for applicability, we found that trials with *p*-xylene (D = 2.3, REL = 100 ppm) as a solvent resulted in similar yield and diastereoselectivity (Table S1. *left)*. Notably, *p*-xylene has dramatically reduced carcinogenicity. Similar yields and diastereoselectivity were also observed for additional substrates using *p*-xylene as a solvent (Table 4.S1. *right)*.

4.4.10. X-Ray Crystallographic Data

4.4.10.1 X-Ray Analysis of 4.3a

A colorless block 0.26 x 0.17 x 0.14 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using omega scans. Crystal-to-detector distance was 30.23 mm and exposure time was 0.50 seconds per frame at low and high angles, using a scan width of 0.5°. Data collection was 100% complete to 74.000° in θ. A total of 16658 reflections were collected covering the indices -13<=h<=13, -13<=k<=11, -17<=l<=17. 3291 reflections were found to be symmetry independent, with an R_{int} of 0.0541. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21/n (No. 14). The data were integrated using the CrysAlis^{Pro} 1.171.40.68a software program and scaled using the SCALE3 ABSPACK scaling algorithm. Solution by intrinsic phasing (SHELXT-2015) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Note: The instruments are supported by an NIH Shared Instrument Grant S10-RR027172

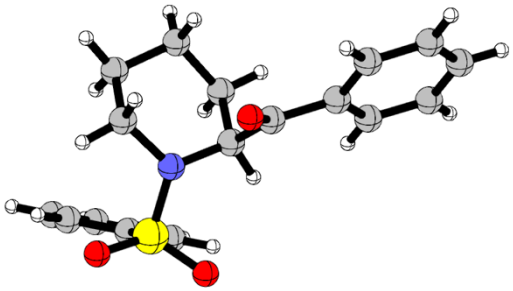


Figure 4.S16: CYLview representation of **4.3a**

This crystal structure has been deposited at the Cambridge Crystallographic Data Center under CCDC 2061160.

Table 4.S2. Crystal data and structure refinement for **4.3a**

Identification code	Jurczyk006_Sarpong
Empirical formula	C18 H19 N O3 S
Formula weight	329.40
Temperature	100(2) K
Wavelength	1.54184 Å
Crystal system	Monoclinic
Space group	P 21/n

Unit cell dimensions	a = 10.9164(3) Å	α= 90°.
	b = 10.6423(3) Å	β= 96.969(3)°.
	c = 14.0240(4) Å	γ = 90°.
Volume	1617.21(8) $Å^3$	
Z	4	
Density (calculated)	1.353 Mg/m^3	
Absorption coefficient	1.901 mm^{-1}	
F(000)	696	
Crystal size	0.260 x 0.170 x 0.140 mm^3	
Theta range for data collection	4.858 to 74.500°.	
Index ranges	-13<=h<=13, -13<=k<=11, -17<=l<=17	
Reflections collected	16658	
Independent reflections	3291 [R(int) = 0.0541]	
Completeness to theta = 74.000°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.86319	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3291 / 0 / 208	
Goodness-of-fit on F^2	1.119	
Final R indices [I>2sigma(I)]	R1 = 0.0450, wR2 = 0.1284	
R indices (all data)	R1 = 0.0467, wR2 = 0.1310	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.510 and -0.546 $e.Å^{-3}$	

4.4.10.2 X-Ray Analysis of 4.4a

A colorless block 0.16 x 0.13 x 0.12 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using omega scans. Crystal-to-detector distance was 30.23 mm and exposure time was 0.50 seconds per frame at low and high angles, using a scan width of 0.5°. Data collection was 99% complete to 74.000° in θ. A total of 33988 reflections were collected covering the indices -22<=h<=21, -9<=k<=9, -29<=l<=28. 3255 reflections were found to be symmetry independent, with an R_{int} of 0.0771. Indexing and unit cell refinement indicated a body-centered, monoclinic lattice. The space group was found to be I 2/a (No. 15). The data were integrated using the CrysAlis^{Pro} 1.171.40.68a software program and scaled using the SCALE3 ABSPACK scaling algorithm. Solution by intrinsic phasing (SHELXT-2015) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Note: The instruments are supported by an NIH Shared Instrument Grant S10-RR027172

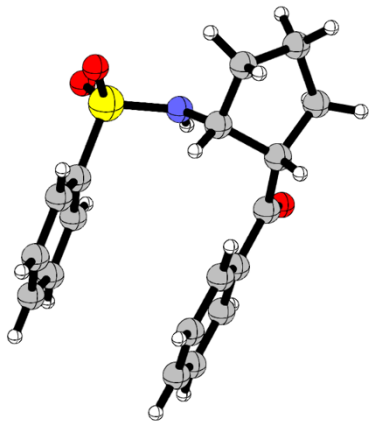


Figure 4.S17: CYLview representation of **4.4a**

This crystal structure has been deposited at the Cambridge Crystallographic Data Center under CCDC 2061161.

Table S3. Crystal data and structure refinement for **4.4a.**

Identification code	Jurczyk004_Sarpong
Empirical formula	C18 H19 N O3 S
Formula weight	329.40
Temperature	100(2) K
Wavelength	1.54184 Å
Crystal system	Monoclinic

Space group	I 2/a	
Unit cell dimensions	a = 18.1476(2) Å	α= 90°.
	b = 7.56120(10) Å	β= 93.6140(10)°.
	c = 23.2488(2) Å	γ = 90°.
Volume	3183.80(6) $Å^3$	
Z	8	
Density (calculated)	1.374 Mg/m^3	
Absorption coefficient	1.931 mm^{-1}	
F(000)	1392	
Crystal size	0.160 x 0.130 x 0.120 mm^3	
Theta range for data collection	3.810 to 74.492°.	
Index ranges	-22<=h<=21, -9<=k<=9, -29<=l<=28	
Reflections collected	33988	
Independent reflections	3255 [R(int) = 0.0771]	
Completeness to theta = 74.000°	99.4 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.80623	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3255 / 0 / 212	
Goodness-of-fit on F^2	1.068	
Final R indices [I>2sigma(I)]	R1 = 0.0375, wR2 = 0.1022	
R indices (all data)	R1 = 0.0381, wR2 = 0.1029	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.388 and -0.521 $e.Å^{-3}$	

4.4.10.3 X-Ray Analysis of 4.4m

A colorless block 0.24 x 0.20 x 0.12 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using omega scans. Crystal-to-detector distance was 30.23 mm and exposure time was 0.50 seconds per frame at low and high angles using a scan width of 0.5°. Data collection was 100% complete to 74.000° in θ. A total of 16035 reflections were collected covering the indices -12<=h<=12, -11<=k<=10, -18<=l<=19. 3007 reflections were founded to be symmetry independent, with an Rint of 0.0377. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21/n (No. 14). The data were integrated using the CrysAlisPro 1.171.40.84a software program and scaled using the SCALE3 ABSPACK scaling algorithm. Solution by intrinsic phasing (SHELXT-2015) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Note: The instruments are supported by an NIH Shared Instrument Grant S10-RR027172

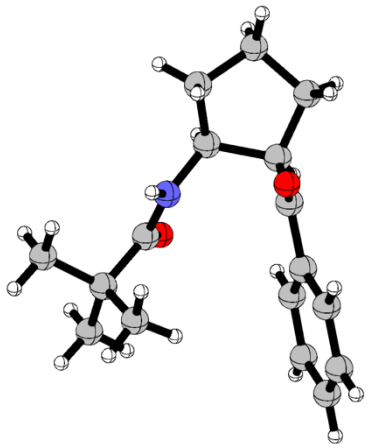


Figure 4.S18: CYLview representation of **4.4m**

This crystal structure has been deposited at the Cambridge Crystallographic Data Center under CCDC 2061162.

Table 4.S4. Crystal data and structure refinement for **4.4m**.

Identification code	Jurczyk007_Sarpong
Empirical formula	C17 H23 N O2
Formula weight	273.36
Temperature	100(2) K
Wavelength	1.54184 Å
Crystal system	Monoclinic
Space group	P 21/n

Unit cell dimensions	a = 9.98870(10) Å	α= 90°.
	b = 9.5475(2) Å	β= 90.7050(10)°.
	c = 15.4702(2) Å	γ = 90°.
Volume	1475.24(4) $Å^3$	
Z	4	
Density (calculated)	1.231 Mg/m^3	
Absorption coefficient	0.630 mm^{-1}	
F(000)	592	
Crystal size	0.240 x 0.200 x 0.120 mm^3	
Theta range for data collection	5.242 to 74.463°.	
Index ranges	-12<=h<=12, -11<=k<=10, -18<=l<=19	
Reflections collected	16035	
Independent reflections	3007 [R(int) = 0.0377]	
Completeness to theta = 74.000°	99.7 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.78692	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3007 / 0 / 188	
Goodness-of-fit on F^2	1.060	
Final R indices [I>2sigma(I)]	R1 = 0.0409, wR2 = 0.1121	
R indices (all data)	R1 = 0.0425, wR2 = 0.1133	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.252 and -0.230 $e.Å^{-3}$	

4.4.10.4 X-Ray Analysis of 4.9a

A colorless block 0.38 x 0.21 x 0.18 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using omega scans. Crystal-to-detector distance was 30.23 mm and exposure time was 0.50 seconds per frame at low and high angles using a scan width of 0.5°. Data collection was 99% complete to 74.000° in θ. A total of 23178 reflections were collected covering the indices -13<=h<=13, -13<=k<=13, -18<=l<=18. 3434 reflections were founded to be symmetry independent, with an R_{int} of 0.0529. Indexing and unit cell refinement indicated a primitive, monoclinic lattice. The space group was found to be P 21/c (No. 14). The data were integrated using the CrysAlis^{Pro} 1.171.40.84a software program and scaled using the SCALE3 ABSPACK scaling algorithm. Solution by intrinsic phasing (SHELXT-2015) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Note: The instruments are supported by an NIH Shared Instrument Grant S10-RR027172

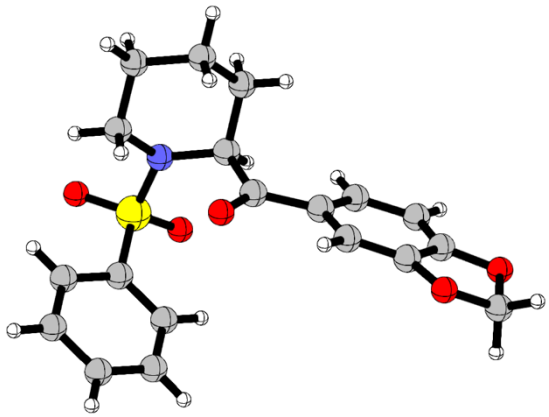


Figure 4.S19: CYLview representation of **4.9a**

This crystal structure has been deposited at the Cambridge Crystallographic Data Center under CCDC 2061169.

Table 4.S5. Crystal data and structure refinement for **4.9a.**

Identification code	Jurczyk008_Sarpong
Empirical formula	C19 H19 N O5 S
Formula weight	373.41
Temperature	100(2) K
Wavelength	1.54184 Å
Crystal system	Monoclinic
Space group	P 21/c

Unit cell dimensions	a = 11.02670(10) Å	α= 90°.
	b = 11.01150(10) Å	β= 108.6240(10)°.
	c = 14.6875(2) Å	γ = 90°.
Volume	1689.98(3) $Å^3$	
Z	4	
Density (calculated)	1.468 Mg/m^3	
Absorption coefficient	1.984 mm^{-1}	
F(000)	784	
Crystal size	0.380 x 0.210 x 0.180 mm^3	
Theta range for data collection	4.231 to 74.499°.	
Index ranges	-13<=h<=13, -13<=k<=13, -18<=l<=18	
Reflections collected	23178	
Independent reflections	3434 [R(int) = 0.0529]	
Completeness to theta = 74.000°	99.3 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.83095	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3434 / 0 / 235	
Goodness-of-fit on F^2	1.086	
Final R indices [I>2sigma(I)]	R1 = 0.0359, wR2 = 0.0967	
R indices (all data)	R1 = 0.0368, wR2 = 0.0974	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.265 and -0.558 $e.Å^{-3}$	

4.4.10.5 X-Ray Analysis of 4.10a

A colorless block 0.12 x 0.11 x 0.07 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using omega scans. Crystal-to-detector distance was 30.23 mm and exposure time was 0.50 seconds per frame at low and high angles using a scan width of 0.5°. Data collection was 100% complete to 74.000° in θ. A total of 15169 reflections were collected covering the indices -6<=h<=6, -18<=k<=17, -26<=l<=26. 3396 reflections were founded to be symmetry independent, with an R_{int} of 0.0600. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be P 21 21 21 (No. 19). The data were integrated using the CrysAlis^{Pro} 1.171.40.84a software program and scaled using the SCALE3 ABSPACK scaling algorithm. Solution by intrinsic phasing (SHELXT-2015) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Note: The instruments are supported by an NIH Shared Instrument Grant S10-RR027172

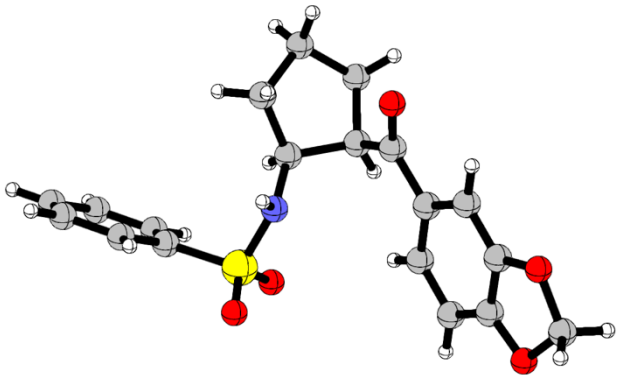


Figure 4.S20: CYLview representation of **4.10a**

This crystal structure has been deposited at the Cambridge Crystallographic Data Center under CCDC 2061170.

Table 4.S6. Crystal data and structure refinement for **4.10a.**

Identification code	Jurczyk009_Sarpong
Empirical formula	C19 H19 N O5 S
Formula weight	373.41
Temperature	100(2) K
Wavelength	1.54184 Å
Crystal system	Orthorhombic

Space group	P 21 21 21	
Unit cell dimensions	a = 5.38670(10) Å	α= 90°.
	b = 14.4393(2) Å	β= 90°.
	c = 21.3498(3) Å	γ = 90°.
Volume	1660.59(4) $Å^3$	
Z	4	
Density (calculated)	1.494 Mg/m^3	
Absorption coefficient	2.019 mm^{-1}	
F(000)	784	
Crystal size	0.700 x 0.120 x 0.110 mm^3	
Theta range for data collection	3.696 to 74.502°.	
Index ranges	-6<=h<=6, -18<=k<=17, -26<=l<=26	
Reflections collected	15169	
Independent reflections	3396 [R(int) = 0.0600]	
Completeness to theta = 74.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.77442	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3396 / 0 / 239	
Goodness-of-fit on F^2	1.066	
Final R indices [I>2sigma(I)]	R1 = 0.0354, wR2 = 0.0947	
R indices (all data)	R1 = 0.0362, wR2 = 0.0953	
Absolute structure parameter	-0.027(12)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.283 and -0.382 $e.Å^{-3}$	

4.4.10.6 X-Ray Analysis of (–)-4.4b

A colorless plate 0.30 x 0.08 x 0.05 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using omega scans. Crystal-to-detector distance was 30.23 mm and exposure time was 0.50 seconds per frame at low and high angles, using a scan width of 0.5°. Data collection was 100% complete to 74.000° in θ. A total of 18291 reflections were collected covering the indices -6<=h<=7, -15<=k<=19, -23<=l<=23. 3399 reflections were founded to be symmetry independent, with an R_{int} of 0.0276. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be P 21 21 21 (No. 19). The data were integrated using the CrysAlis^{Pro} 1.171.41.99a software program and scaled using the SCALE3 ABSPACK scaling algorithm. Solution by intrinsic phasing (SHELXT-2015) produced a heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014.

Note: The instruments are supported by an NIH Shared Instrument Grant S10-RR027172

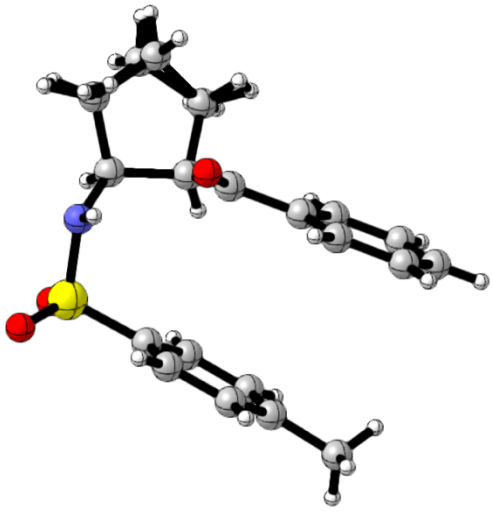


Figure 4.S21: CYLview representation of **(–)4.4b**

This crystal structure has been deposited at the Cambridge Crystallographic Data Center under CCDC 2071240.

Table 4.S7. Crystal data and structure refinement for **(–)4.4b**.

Identification code	Jurczyk10_Sarpong
Empirical formula	C19 H21 N O3 S
Formula weight	343.43
Temperature	100(2) K
Wavelength	1.54184 Å
Crystal system	Orthorhombic

Space group	P 21 21 21	
Unit cell dimensions	a = 5.60800(10) Å	α= 90°.
	b = 15.7105(2) Å	β= 90°.
	c = 18.9971(2) Å	γ = 90°.
Volume	1673.73(4) $Å^3$	
Z	4	
Density (calculated)	1.363 Mg/m^3	
Absorption coefficient	1.859 mm^{-1}	
F(000)	728	
Crystal size	0.300 x 0.080 x 0.050 mm^3	
Theta range for data collection	3.651 to 74.500°.	
Index ranges	-6<=h<=7, -15<=k<=19, -23<=l<=23	
Reflections collected	18291	
Independent reflections	3399 [R(int) = 0.0276]	
Completeness to theta = 74.000°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.58990	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3399 / 0 / 238	
Goodness-of-fit on F^2	1.046	
Final R indices [I>2sigma(I)]	R1 = 0.0259, wR2 = 0.0699	
R indices (all data)	R1 = 0.0264, wR2 = 0.0702	
Absolute structure parameter	-0.002(5)	
Extinction coefficient	n/a	
Largest diff. peak and hole	0.281 and -0.277 $e.Å^{-3}$	

4.4.11. Additional Computational Results, Methods, Cartesian Coordinates, and Energies

4.11.1 Conformational Analysis

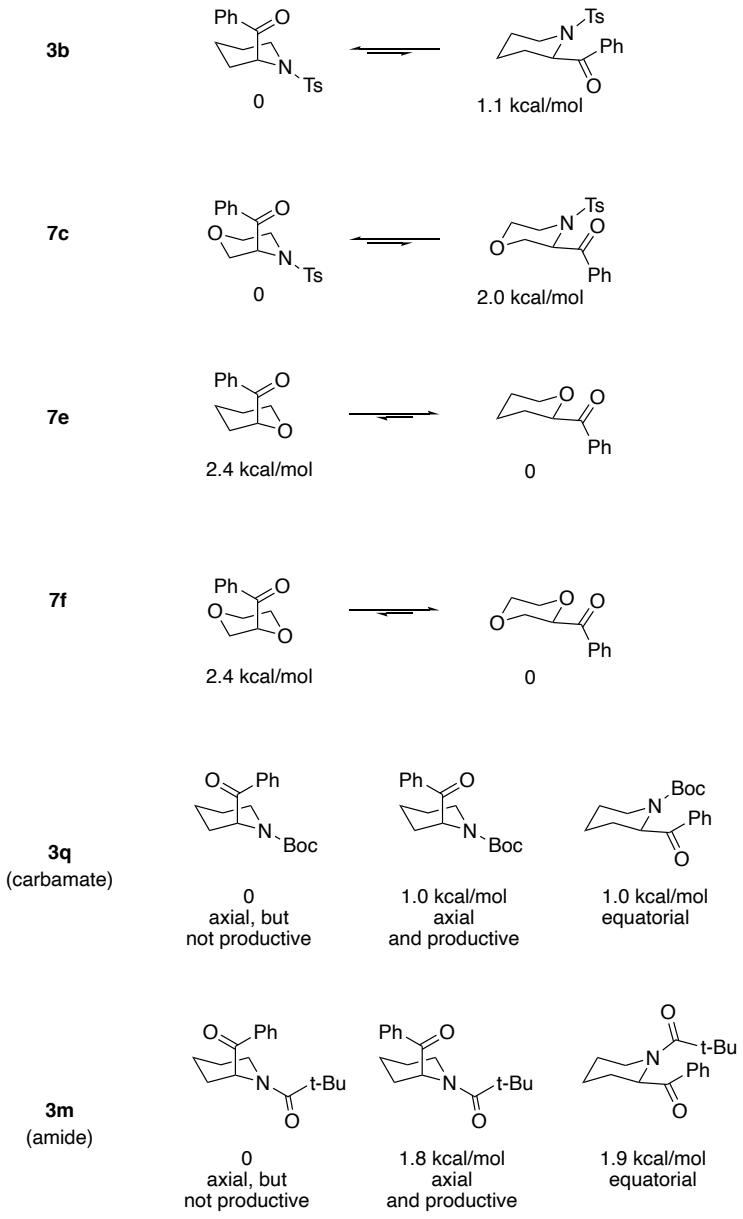


Figure 4.S22. Conformational analysis for selected acylated heterocyclic compounds, with productive and unproductive conformations shown for **4.3q** and **4.3m.**

In **4.3b**, **4.7c**, **4.3q**, and **4.3m**, the aroyl group prefers to be axial to minimize the steric clash with the *N*-substituent (Ts, Boc, Piv). Absent of the *N*-substituent, the aroyl group prefers an equatorial disposition. For **4.3q** and **4.3m**, the planar amide/carbamate is less bulky and is sterically compatible with a number of different orientations of the aroyl group at the axial position. In the global minimum conformer of these compounds, the carbonyl group points at an axial hydrogen on C4. Interestingly, the axial conformer with a reactive orientation (i.e., pointing to an axial hydrogen on C2) is approximately isoenergetic with the lowest energy equatorial conformer.

For **4.3b** and **4.7c**, the tetrahedral Ts group imposes more steric constrain on which orientation can be adopted by an axial aroyl group. Indeed, in the global minimum conformations of these compounds, the aroyl carbonyl group was found to be oriented towards the hydridic hydrogen. Here, the global minimum conformer is also a reactive conformer.

4.4.11.2 HAT transition states

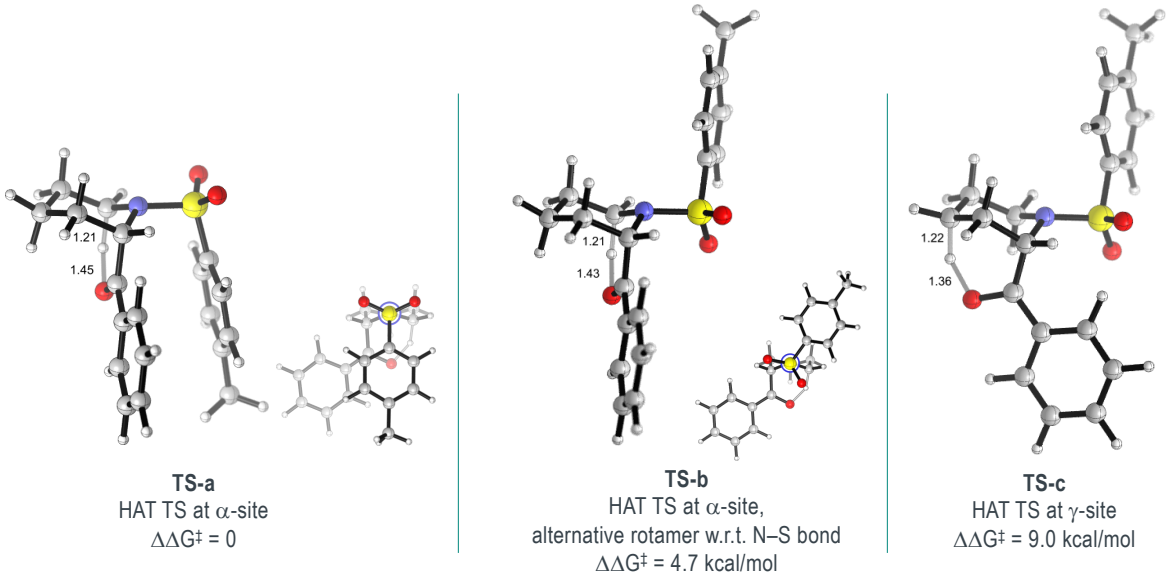


Figure 4.S23. Hydrogen atom transfer transition states. **TS-a** is the lowest-energy HAT transition state denoted as "1,5-HAT TS" in the main text.

4.4.11.3 Diastereoselectivity of the intramolecular Mannich step

4.4.11.3.1 Geometrical isomers of enol and imine moieties

We propose that the most likely scenario for stereocontrol in the Mannich step is one in which the diradical is long-lived enough to allow acyl bond rotation and subsequent sampling of both enol diastereomers. As shown in Fig. S24, in the triplet 1,4-diradical formed after the 1,5-HAT, the O-C-C-C dihedral angle of 88° is practically midway between the dihedral angle of 0° that would be found in a *Z* enol and 180° in an *E* enol, suggesting the formation of either configuration of the enol should be facile.

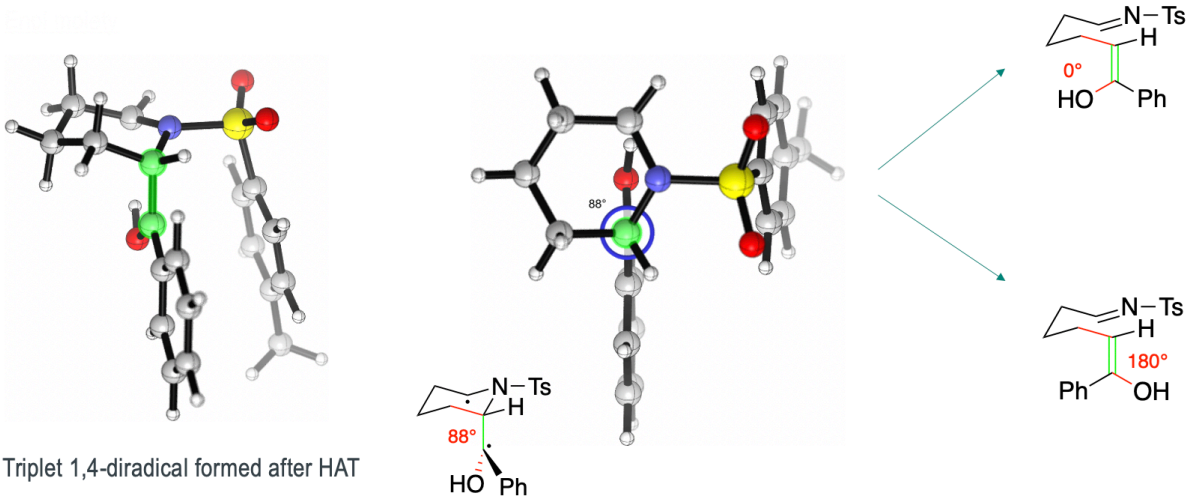


Figure 4.S24. Geometry of the triplet 1,4-diradical formed after 1,5-HAT.

We also considered whether the *Z*-imine may be formed in the reaction. We explored the possible formation of the *Z*-imine by performing a relaxed scan on ^{3}**A**, changing the C-C-N-S dihedral from −163° (the dihedral angle found in the triplet 1,4-diradical directly after HAT) to −58° (≈ −60°, the dihedral angle for an axial orientation of the NTs group) (Fig. S25). The energy as a function of the scanned dihedral increases monotonically; no minimum was found in the region near −60°. Additionally, all optimizations of a Ts-axial structure yielded a conformation resembling the triplet 1,4-diradical formed after HAT. Thus, the participation of a *Z*-imine was considered to be less likely.

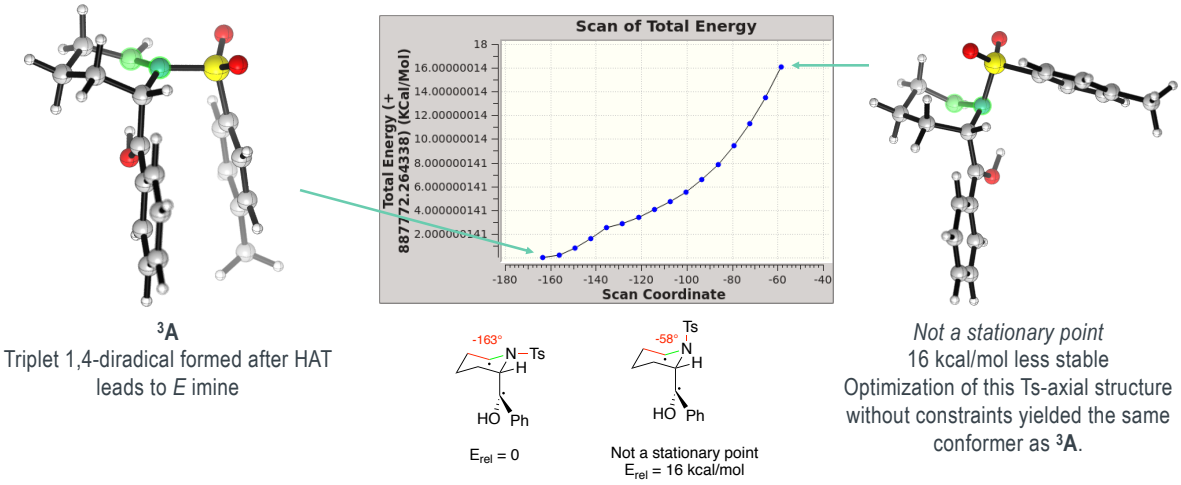


Figure 4.S25. A relaxed scan on ^{3}**A** changing the CCNS dihedral from −163° to −58° in 7° increments revealed no other preferred orientation of the N–S bond.

We therefore propose that the most likely scenario for diastereocontrol involves the *E*/*Z* or *E*/*E* diastereomer of ^{1}**B**.

4.4.11.3.2. Diastereoselectivity-determining Mannich transition states

Fig. 4.S26 illustrates the energies of the four possible geometrical isomers of imine–enol ^{1}**B** and the intramolecular Mannich TSs arising therefrom.

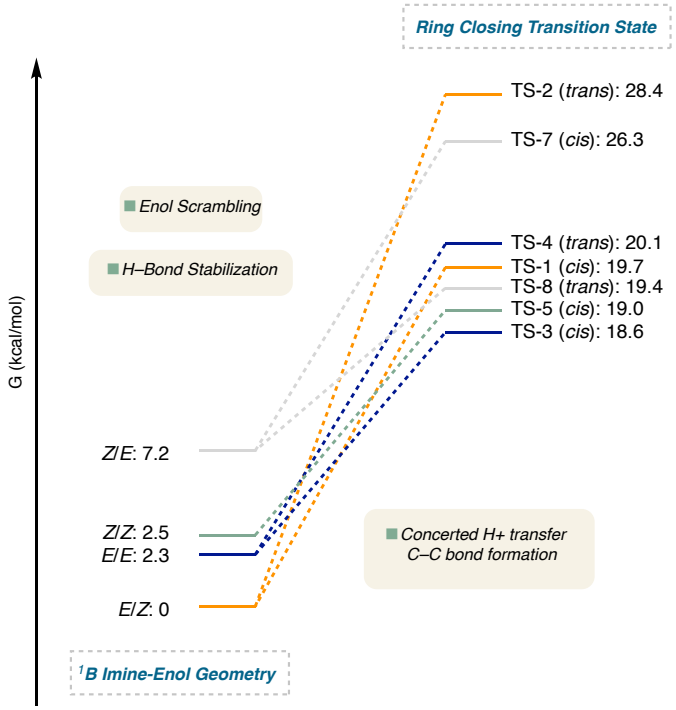


Figure 4.S26. Energies of the four possible geometrical isomers of imine–enol ^{1}**B** and the intramolecular Mannich transition structures arising therefrom (**TS-1**–**TS-8**). **TS-6**, which leads to the trans diastereomer of the cyclopentane product, could not be located after repeated attempts starting from various conformations of (*Z*/*Z*)-^{1}**B**.

The lowest-energy cis- and trans- transition states that could be located for each of the four possible geometrical isomers of ^{1}**B** are illustrated in Fig. 4.S27. With the exception of **TS-2**, all of the C–C bond-forming transition states feature concomitant proton transfer from enol OH to either N or a sulfonyl O.

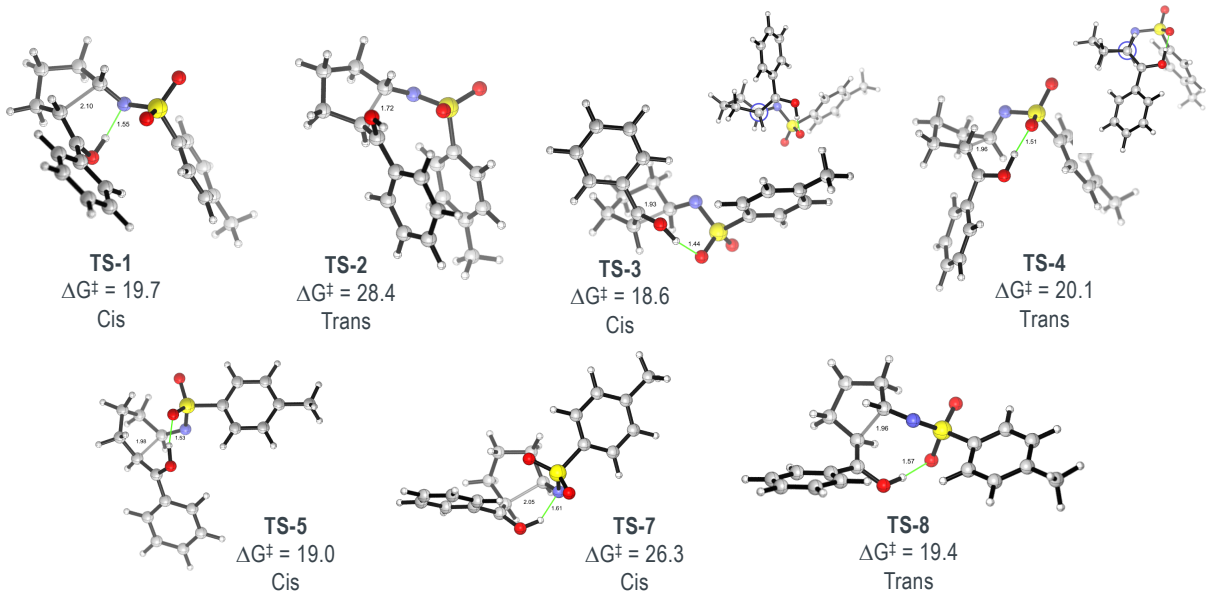


Figure S27. Intramolecular Mannich transition states. The $\Delta G^{\ddagger}$ values are reported in kcal/mol relative to (*E*/*Z*)-[1]**B**.

In the scenario where only the *E*/*Z* or the *E*/*E* isomers of [1]**B** are viable in the Mannich step, only **TS-1**–**TS-4** will determine the stereochemical outcome. The Boltzmann average of these four transition states predicts a ratio of 14:1 in favor of the cis cyclopentane isomer, in good agreement with the experimentally determined ratio of 12:1. The main determinants for the computationally predicted ratio result from the energy difference between **TS-3** and **TS-4**, which likely originates from a shorter (and presumably stronger) hydrogen bond in **TS-3**. A more staggered arrangement of substituents about the forming C–C bond in **TS-3**, as illustrated by the Newman projections for **TS-3** and **TS-4**, may also contribute the lower energy of **TS-3**.

4.4.11.4 Origin of asymmetric induction by (*R*)-TRIP

The origin of enantiocontrol in the reactions of imines catalyzed by BINOL-phosphoric acids is well understood, owing to the extensive theoretical work by Goodman and coworkers.[47,58] Most of the existing stereochemical models for this class of reactions are based on the projection shown for (*R*)-TRIP in Fig. 4.S28A. Across the C_2-axis of the BINOL-phosphoric acid; the two BINOL oxygens and the phosphorus atom are in the plane. As shown in Fig. S28B, the phosphoric acid's OH group and the imine to which it is hydrogen-bonded are at the front, while the phosphoryl oxygen atom and the nucleophilic enol are at the back. Thus, the nucleophile attacks the imine trigonal carbon from behind.

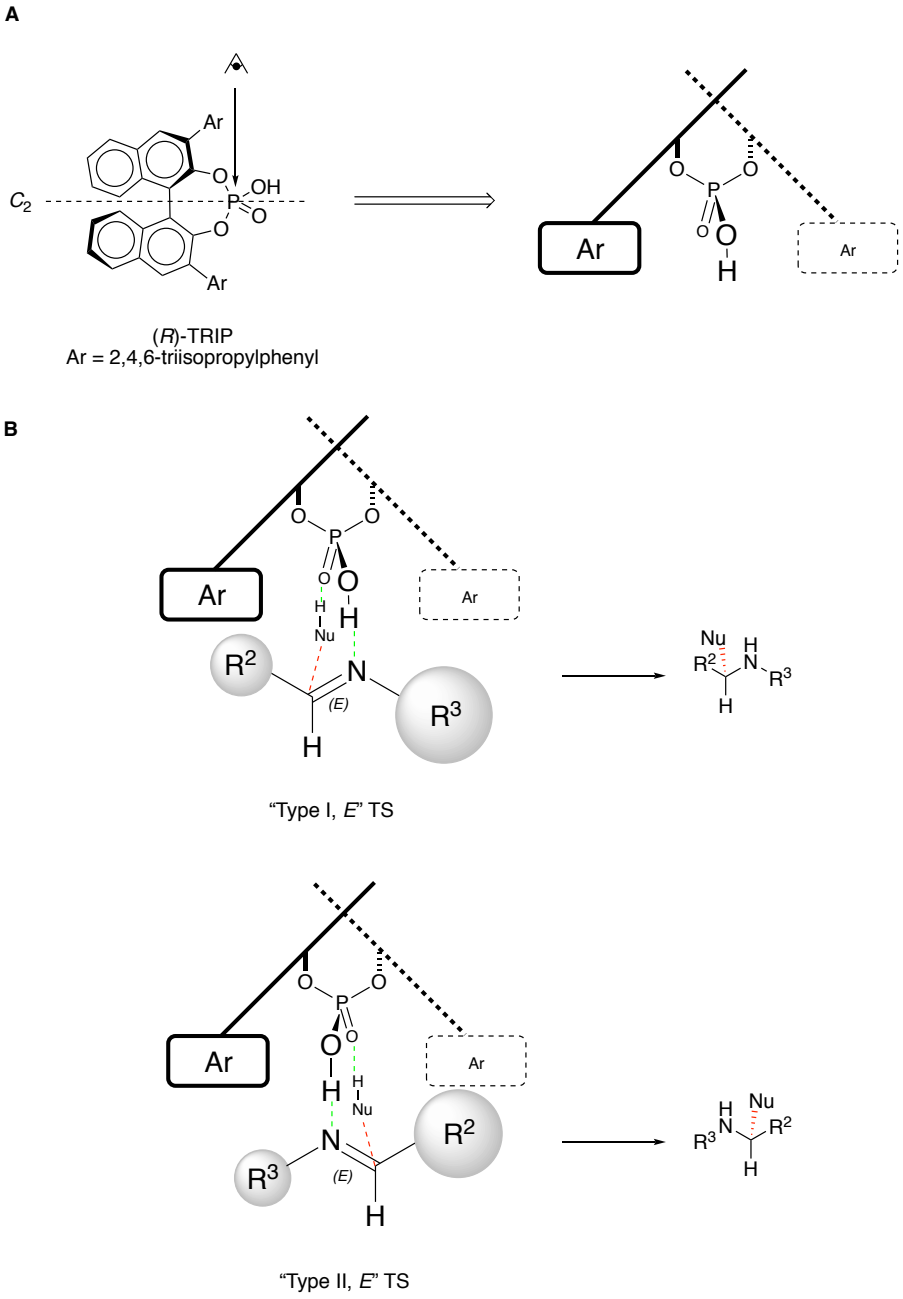


Figure 4.S28. (A) Goodman's Projection of (*R*)-TRIP. Atoms closer to the viewer are represented by larger font sizes. (B) A "Type I, *E*" and a "Type II, *E*" transition state and their respective stereochemical consequences.

According to Goodman and coworkers, two types of transition states that differ in the orientation of the imine can be discerned: Type I and Type II (Fig. 4.S28B). In a Type I TS, the *N*-substituent of the imine is directed towards the empty side of the oxygen to which the imine is hydrogen-bonded. In a Type II TS, the

imine *N*-substituent is directed towards the bulky catalyst group. Type II TSs typically have a higher energy because of the additional steric interactions.

Goodman and coworkers found that whether Type I or Type II is favored depends on a multitude of factors. Factors that favor Type I include a large *N*-imine group (R^3 in Fig. 4.S28B) and a small group *trans* to the *N*-imine group (R^2 in Fig. 4.S28B). For our intramolecular Mannich imine–enol reactant, we may regard the tosyl group as a large R^3 group and the unsubstituted hydrocarbon tether as the considerably smaller R^2 group. A potential factor that may favor a Type II orientation is the fact that the nucleophilic enol may be regarded as a so-called displaced nucleophile, meaning the H-bond that holds the nucleophile to the catalyst is not in line with the nucleophilic site (as opposed to, e.g., HCN), but displaced to one side. Goodman found that this can promote a Type II process, but only if it is reinforced by a large co-planar substituent and a small *N*-imine group,[47] which is absent in our substrate. Therefore, we deem a Type I TS more likely.

The second factor that is critical to determining which face of the imine is attacked is the *E*/*Z* configuration of the imine. Simón and Goodman[58] calculated the energies of the TSs for nucleophilic addition to imines derived from both aldimines and ketimines in both *E* and *Z* configurations. They found that the aldimine TSs always prefer *E*.

Bearing these two considerations in mind, we expect the "Type I, *E*" TS to be the most plausible transition state geometry to explain our Mannich reactions. Fig. 4.S29 shows the application of Goodman's model to deduce the absolute configuration of the major enantiomer arising from ^{1}**B** upon cis ring closure catalyzed by (*R*)-TRIP. The *Re* face of the *N*-tosylimine is exposed for nucleophilic attack.

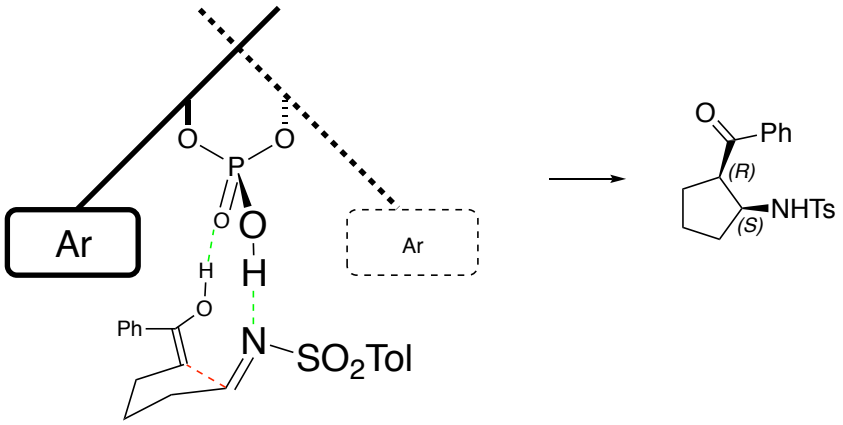


Figure 4.S29. Application of Goodman's model to deduce the absolute stereochemistry of ring closure of ^{1}**B**

An alternative projection to understand the stereochemistry of the Mannich ring closure is the Quadrant Projection. When (*R*)-TRIP is viewed down the C_2-axis, as illustrated in Fig. 4.S30A, two symmetrically equivalent quadrants, I and IV, can be seen to be hindered, while quadrants II and III are available for substrate recognition. Fig. 4.30B shows the quadrant projection of the "Type I, *E*" cis transition state model in Fig. 4.S29. This projection makes it easier to visualize the spatial complementarity of the ring-closing

TS and the chiral binding site of (*R*)-TRIP. Specifically, the aryl ring of the N-tosyl group and the phenyl ring of the enol moiety are well accommodated in quadrants II and III, respectively.

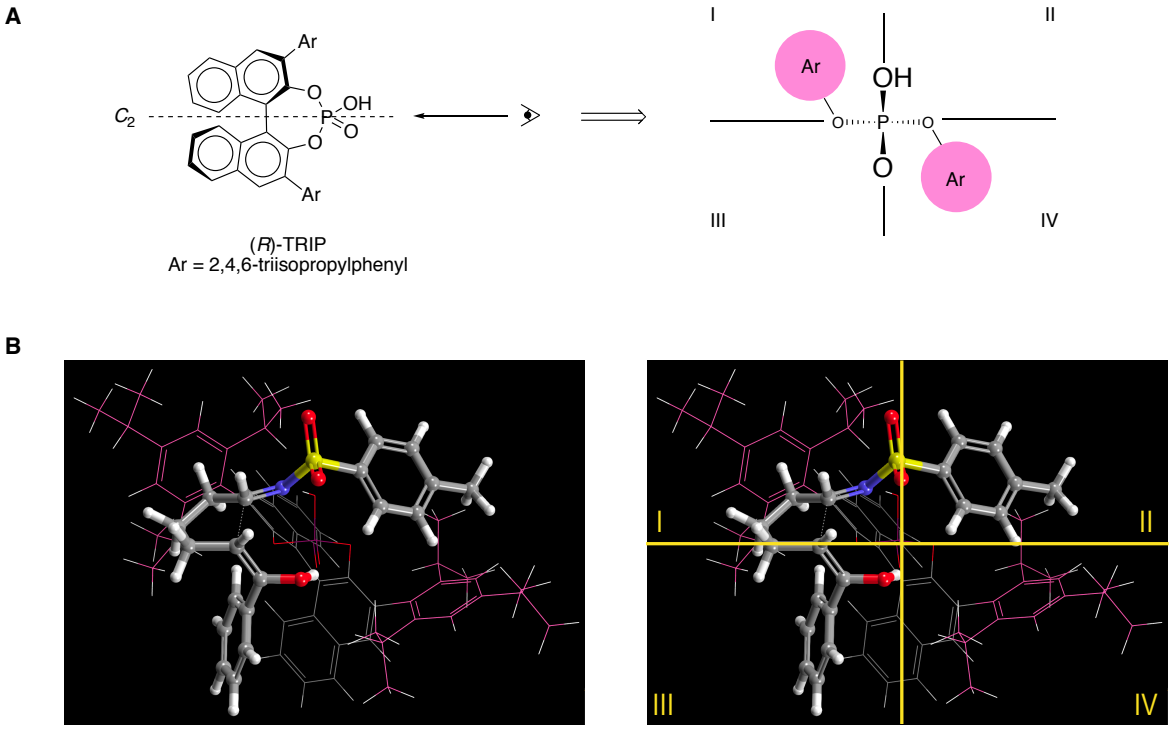


Figure 4.S30 (A) Quadrant projection of (*R*)-TRIP. (B) A qualitative illustration of the chiral recognition of the lowest-energy cis transition structure, **TS-3**, by (*R*)-TRIP. For clarity, two identical diagrams are included and the diagram on the right is annotated with the quadrants. The atoms belonging to the cyclization TS are represented by balls and sticks. The atoms of (*R*)-TRIP are represented by a wireframe, with the 2,4,6-triisopropylphenyl rings colored in pink.

4.4.11.5 Computational method, Cartesian coordinates, and energies

For the mechanistic modeling calculations, conformational searches were first performed using the OPLS3e force field[60] and the mixed torsional/low-mode sampling method in Macromodel.[61] Conformers within 10 kcal/mol of the global minimum were saved, keeping only unique conformers based on an RMSD cutoff of 0.25 Å. The conformers were then submitted to geometry optimizations and frequency calculations in Gaussian 16[32] at the M06-2X/6-31+G(d,p) level of theory[33] with the SMD model[34] for implicit solvation by benzene using an "ultrafine" integration grid and a two-electron integral accuracy of 10^{-14} (int=(ultrafine,Acc2E=14)). The stationary points were characterized as minima or transition structures by the presence of only positive eigenvalues or a single negative eigenvalue of the Hessian, respectively. The free energies were calculated for 298.15 K and 1 atm using the quasi-harmonic approximation proposed by Cramer and Truhlar,[35] in which all of the real vibrational frequencies lower than 100 cm^{-1} were set to 100 cm^{-1} before the thermal corrections were computed with the usual harmonic oscillator model.

To identify the lowest-energy conformers of the imine–enol [1]**B** and its reactive conformations for the intramolecular Mannich step, force field conformational searches were performed on each of the four geometrical isomers of imine–enol [1]**B** as described above. The conformers in which the distance between the bond-forming carbons is shorter than 4.0 Å were used in transition structure searches. Some of the DFT-optimized transition structures obtained in this manner were manually modified to generate additional input geometries for the optimization of stereoisomeric transition structures of interest.

The optimized geometries were graphically rendered by *CYLview*.[59]

For DFT chemical shift prediction, conformers of the *cis* and *trans* isomers of the selected molecules were generated by MacroModel[61] using mixed torsional/low-mode sampling for a maximum of 100,000 steps in the OPLS3e force field[60] to find all conformations below 10 kcal/mol. Conformational ensembles were submitted to geometry optimizations and frequency calculations using Gaussian 16[32] at the M06-2X/6-31+G** level of theory[33] with an IEF-PCM implicit solvent model[62,63] in chloroform. Carbon chemical shifts were computed at the ωB97XD/def2-SVP level of theory[64,65] with implicit solvation in chloroform and coupling constants were computed at the B3LYP/6-31G* level of theory.[66–69] Isotropic shielding values were scaled to arrive at chemical shifts according to the equation

$$\delta = \frac{196.0386 - \sigma}{-1.0065}$$

where σ is the GIAO derived shielding value and δ is the resulting ^{13}C chemical shift. Gibbs free energies were utilized for Boltzmann averaging the derived NMR parameters across the respective conformational ensembles.

```
Structure: 4.3b Axial-benzoyl conformer
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SCF Energy:          -1414.846509 hartree
SCF Energy + ZPVE:  -1414.474994 hartree
Enthalpy:            -1414.452478 hartree
Free Energy:         -1414.528999 hartree
Free Energy with quasiharmonic correction:  -1414.521698 hartree
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C -2.168612 -0.773614 -0.137740
C -3.035041 0.007778 -0.913300
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C -4.870932 -0.555338 0.546930
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Structure: 4.3b Equatorial-benzoyl conformer
Charge = 0, Multiplicity = 1
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SCF Energy + ZPVE: -1414.473074 hartree
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Free Energy with quasiharmonic correction: -1414.519911 hartree
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H -5.478362 -2.757167 -0.602841
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H -4.777170 0.683733 1.875909
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SCF Energy + ZPVE: -1450.382943 hartree
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Free Energy: -1450.436909 hartree
Free Energy with quasiharmonic correction: -1450.429584 hartree
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H -3.397750 -2.000589 -2.228490
H -5.844561 -3.007398 -1.285110
H -6.766030 -1.681508 -0.557690
H -6.059570 -1.497868 -2.172630
H -5.568390 -0.647798 1.221320
H -3.449650 0.217001 2.213240

Structure: 4.7e Equatorial-benzoyl conformer
Charge = 0, Multiplicity = 1
SCF Energy: -615.932672 hartree
SCF Energy + ZPVE: -615.693674 hartree
Enthalpy: -615.680970 hartree
Free Energy: -615.732481 hartree
Free Energy with quasiharmonic correction: -615.730882 hartree
O 0.092579 2.289751 -0.111390
C 0.141650 1.088121 0.065970
C 1.449150 0.358401 0.046920
C 2.591860 1.064732 -0.347270
C 3.835520 0.443132 -0.348650
C 3.948601 -0.888728 0.054150
C 2.815541 -1.596488 0.452710
C 1.567251 -0.978319 0.444940
C -1.139500 0.298660 0.349480
C -2.390940 1.164530 0.305490
C -3.629530 0.289470 0.514920
C -3.620169 -0.880670 -0.471000
C -2.293669 -1.622660 -0.384370
O -1.194469 -0.747250 -0.607510
H -1.040030 -0.142719 1.360720
H 2.485670 2.101752 -0.649690
H 4.717130 0.994483 -0.660360
H 4.919821 -1.374457 0.056050
H 2.902551 -2.632328 0.765310
H 0.687111 -1.540369 0.737850
H -2.320970 1.946440 1.067430
H -2.433270 1.662430 -0.669790
H -3.630830 -0.101770 1.541960
H -4.540060 0.885599 0.399950
H -4.441019 -1.576771 -0.266630
H -3.747530 -0.506810 -1.494200
H -2.184209 -2.093480 0.607960
H -2.213829 -2.403100 -1.145060

Structure: 4.7e Axial-benzoyl conformer
Charge = 0, Multiplicity = 1
SCF Energy: -615.929410 hartree
SCF Energy + ZPVE: -615.690016 hartree
Enthalpy: -615.677409 hartree
Free Energy: -615.728568 hartree
Free Energy with quasiharmonic correction: -615.727057 hartree
O -0.418530 1.854560 -0.199880
C -0.090380 0.698810 -0.384000
C 1.337930 0.276441 -0.174990
C 2.183760 1.158141 0.508350
C 3.518820 0.831941 0.720410
C 4.025410 -0.377048 0.241390
C 3.192250 -1.257699 -0.446690
C 1.852200 -0.935959 -0.651300
C -1.108550 -0.358810 -0.826720
C -1.341180 -1.418280 0.267860
C -2.207670 -0.855490 1.394930
C -3.504170 -0.303710 0.802760
C -3.179290 0.735810 -0.259750
O -2.314580 0.215820 -1.272470
H -0.690430 -0.847670 -1.714490
H 1.775119 2.097721 0.866490
H 4.165970 1.519222 1.256310
H 5.068600 -0.631388 0.402760
H 3.584941 -2.195789 -0.826080
H 1.221040 -1.634559 -1.191580
H -1.858619 -2.264690 -0.199210
H -0.384660 -1.786060 0.650110
H -2.413250 -1.636990 2.133160
H -1.669430 -0.052500 1.917730
H -4.080070 -1.122421 0.352580
H -4.129020 0.157399 1.575290
H -4.078490 1.050209 -0.795710
H -2.721600 1.619590 0.197910

Structure: 4.7f Equatorial-benzoyl conformer
Charge = 0, Multiplicity = 1
SCF Energy: -651.816677 hartree
SCF Energy + ZPVE: -651.601469 hartree
Enthalpy: -651.589037 hartree
Free Energy: -651.640053 hartree
Free Energy with quasiharmonic correction: -651.638534 hartree
O -0.042599 2.258879 0.059169
C -0.122390 1.054919 -0.096831
C -1.438440 0.349480 -0.054271
C -2.563010 1.077650 0.352789
C -3.815510 0.475481 0.376519
C -3.954691 -0.857169 -0.016381
C -2.839641 -1.585550 -0.428151
C -1.581761 -0.987420 -0.443191
C 1.143620 0.247738 -0.379361
C 2.397310 1.107857 -0.295831

O 3.544410 0.302847 -0.515081
C 3.614119 -0.745903 0.436859
C 2.367939 -1.607172 0.359989
O 1.205899 -0.811132 0.564289
H 1.071239 -0.172942 -1.399141
H -2.435769 2.114680 0.646979
H -4.683960 1.041911 0.697679
H -4.933341 -1.327418 -0.000701
H -2.948242 -2.621340 -0.733791
H -0.714921 -1.563601 -0.748231
H 2.392301 1.881947 -1.065101
H 2.449510 1.587367 0.692159
H 4.506949 -1.332214 0.204619
H 3.713579 -0.325233 1.449329
H 2.366058 -2.371212 1.141289
H 2.309658 -2.096162 -0.624981

Structure: 4.7f Axial-benzoyl conformer
Charge = 0, Multiplicity = 1
SCF Energy: -651.813544 hartree
SCF Energy + ZPVE: -651.597932 hartree
Enthalpy: -651.585634 hartree
Free Energy: -651.636266 hartree
Free Energy with quasiharmonic correction: -651.634773 hartree
O -0.425780 1.885171 -0.272300
C -0.105730 0.722981 -0.416030
C 1.313870 0.288361 -0.190530
C 2.159180 1.162041 0.503400
C 3.487310 0.821012 0.733580
C 3.986941 -0.394168 0.262750
C 3.154281 -1.266358 -0.436390
C 1.820851 -0.929829 -0.659520
C -1.134949 -0.334819 -0.834550
C -1.358599 -1.393119 0.256330
O -2.077299 -0.847349 1.341340
C -3.343909 -0.374130 0.902540
C -3.156020 0.714030 -0.134190
O -2.361290 0.240720 -1.222820
H -0.747739 -0.834859 -1.730380
H 1.755060 2.104991 0.857610
H 4.134310 1.500902 1.278890
H 5.024631 -0.660198 0.439730
H 3.541951 -2.208958 -0.809600
H 1.191001 -1.621119 -1.211060
H -1.923039 -2.228689 -0.186120
H -0.415129 -1.772979 0.653740
H -3.921179 -1.213210 0.483340
H -3.864400 0.013730 1.781640
H -4.115740 1.004150 -0.569510
H -2.684130 1.591890 0.317620

Structure: 4.3q Axial-benzoyl unproductive conformer
Charge = 0, Multiplicity = 1
SCF Energy: -941.795091 hartree

SCF Energy + ZPVE: -941.415215 hartree
Enthalpy: -941.394234 hartree
Free Energy: -941.464573 hartree
Free Energy with quasiharmonic correction: -941.460466 hartree
N 0.206240 0.853470 0.012330
C -0.810250 1.348360 -0.911750
C -0.736870 2.875810 -1.013510
C -0.754450 3.547420 0.364040
C 0.306700 2.944500 1.288420
C 0.148380 1.426330 1.358000
C -2.200320 0.850570 -0.481110
O -3.135790 1.623090 -0.397110
C -2.385690 -0.606860 -0.183250
C -3.485700 -0.982680 0.596130
C -3.714980 -2.324080 0.884420
C -2.853780 -3.300610 0.381590
C -1.764090 -2.932310 -0.406840
C -1.522470 -1.588600 -0.684500
C 1.280540 0.179190 -0.488670
O 1.366070 -0.186420 -1.653970
C 3.363700 -0.900710 0.170220
C 2.902540 -2.300010 -0.227060
C 4.084250 -0.937880 1.512980
C 4.247190 -0.255450 -0.892540
O 2.208160 -0.053270 0.454050
H -0.600870 0.900700 -1.888740
H 0.199070 3.118940 -1.531320
H -1.564560 3.238270 -1.628590
H -0.592470 4.624050 0.249700
H -1.744850 3.417540 0.815640
H 1.312630 3.174350 0.913160
H 0.225300 3.366170 2.295970
H -0.829680 1.170510 1.790630
H 0.916050 0.961130 1.972300
H -4.151560 -0.210420 0.969110
H -4.564940 -2.609660 1.496360
H -3.034230 -4.348520 0.602040
H -1.098650 -3.691320 -0.806610
H -0.671980 -1.315570 -1.303170
H 2.196570 -2.688580 0.514460
H 2.426230 -2.300310 -1.208490
H 3.768590 -2.968650 -0.257350
H 4.369400 0.071980 1.822760
H 3.439230 -1.370590 2.283540
H 4.989650 -1.546070 1.434060
H 3.755370 -0.242760 -1.865640
H 4.495840 0.770880 -0.603790
H 5.180450 -0.821510 -0.975450

Structure: 4.3q Axial-benzoyl productive conformer
Charge = 0, Multiplicity = 1
SCF Energy: -941.793228 hartree
SCF Energy + ZPVE: -941.413296 hartree
Enthalpy: -941.392144 hartree

Free Energy: -941.463345 hartree
Free Energy with quasiharmonic correction: -941.458839 hartree
N 1.226070 1.384220 -0.202351
C -0.120230 1.015839 -0.627341
C -0.861591 2.217598 -1.241371
C -0.768052 3.463109 -0.364731
C 0.702168 3.800560 -0.135591
C 1.420449 2.639730 0.537269
C -0.910440 0.398238 0.536069
O -0.506460 0.494039 1.678849
C -2.194699 -0.321392 0.241509
C -3.038129 -0.620003 1.318559
C -4.233059 -1.299324 1.109269
C -4.592848 -1.695834 -0.179781
C -3.755768 -1.408464 -1.256831
C -2.562349 -0.719873 -1.049601
C 2.125980 0.385881 0.084479
O 3.180570 0.565241 0.667069
C 2.472372 -2.019859 -0.164881
C 2.606312 -2.287659 1.330819
C 3.825542 -1.928138 -0.862601
C 1.601693 -3.085600 -0.821191
O 1.702711 -0.801290 -0.390711
H -0.020770 0.248849 -1.397291
H -0.404101 2.427809 -2.215411
H -1.903971 1.939818 -1.422551
H -1.289982 4.295158 -0.847621
H -1.263202 3.286178 0.600049
H 1.180178 4.021500 -1.098641
H 0.809497 4.687330 0.496949
H 1.051469 2.512400 1.563809
H 2.494219 2.819451 0.585219
H -2.738309 -0.311243 2.314999
H -4.883728 -1.522294 1.949069
H -5.524348 -2.229015 -0.344101
H -4.030588 -1.720584 -2.259421
H -1.922019 -0.508742 -1.900481
H 1.621322 -2.263480 1.807729
H 3.035583 -3.283599 1.479579
H 3.251162 -1.551609 1.812099
H 3.690542 -1.662188 -1.916051
H 4.467921 -1.185948 -0.387381
H 4.320523 -2.903468 -0.817711
H 1.473513 -2.873990 -1.887311
H 2.069463 -4.068509 -0.715521
H 0.614463 -3.116140 -0.349601

Structure: 4.3q Equatorial-benzoyl conformer
Charge = 0, Multiplicity = 1
SCF Energy: -941.793017 hartree
SCF Energy + ZPVE: -941.413623 hartree
Enthalpy: -941.392681 hartree
Free Energy: -941.461830 hartree
Free Energy with quasiharmonic correction: -941.458856 hartree

N -1.391400 -0.455539 -0.737250
C -1.221250 -1.277650 0.463880
C -2.405250 -1.081099 1.409270
C -3.708750 -1.406899 0.668640
C -3.829280 -0.639239 -0.652530
C -2.577450 -0.828509 -1.512060
C 0.142970 -1.153990 1.152370
O 0.196540 -1.052310 2.361320
C 1.399840 -1.290240 0.340530
C 2.619550 -1.082611 0.995950
C 3.819400 -1.177231 0.299340
C 3.812070 -1.492671 -1.060820
C 2.603110 -1.722031 -1.715040
C 1.399200 -1.620970 -1.019480
C -0.981509 0.852030 -0.817750
O -1.238089 1.584130 -1.757920
C 0.558391 2.413920 0.259840
C 1.224951 2.365700 1.628970
C -0.322868 3.653540 0.140940
C 1.596281 2.323160 -0.853470
O -0.258239 1.200780 0.258270
H -1.243830 -2.319570 0.100430
H -2.287820 -1.719619 2.288720
H -2.400680 -0.041119 1.758440
H -3.735250 -2.485769 0.459200
H -4.568080 -1.190248 1.311170
H -4.714350 -0.966828 -1.208420
H -3.948299 0.433521 -0.451610
H -2.604450 -0.215459 -2.412260
H -2.467490 -1.879499 -1.808560
H 2.607340 -0.845831 2.055340
H 4.759930 -1.007482 0.814280
H 4.747580 -1.564562 -1.607430
H 2.594240 -1.975691 -2.770410
H 0.464900 -1.788780 -1.543900
H 1.874952 3.236339 1.755190
H 0.472251 2.370260 2.422890
H 1.829571 1.460249 1.729990
H 0.284312 4.541580 0.343870
H -0.760678 3.742660 -0.853140
H -1.127478 3.614980 0.882380
H 2.278281 3.176389 -0.782850
H 1.123591 2.337900 -1.837810
H 2.183131 1.403289 -0.749620

Structure: 4.3m Axial-benzoyl unproductive conformer
Charge = 0, Multiplicity = 1
SCF Energy: -866.574992 hartree
SCF Energy + ZPVE: -866.199467 hartree
Enthalpy: -866.179492 hartree
Free Energy: -866.246626 hartree
Free Energy with quasiharmonic correction: -866.243624 hartree
N -0.785120 0.438130 0.083451
C -0.015349 1.326030 0.962101

C -0.685969 2.700550 1.053691
C -0.951649 3.308220 -0.327019
C -1.678889 2.312540 -1.232879
C -0.931399 0.979420 -1.268569
C 1.442621 1.408760 0.485991
O 1.996651 2.484450 0.361341
C 2.178590 0.135400 0.196351
C 3.297070 0.197519 -0.642549
C 4.025320 -0.953531 -0.925089
C 3.649800 -2.171351 -0.355709
C 2.545170 -2.235150 0.493121
C 1.802360 -1.087690 0.763501
C -1.471800 -0.603290 0.654131
O -1.360110 -0.817890 1.861331
C -2.330070 -1.558000 -0.208709
C -3.535130 -0.838779 -0.844519
C -2.895040 -2.635610 0.728281
C -1.452400 -2.271600 -1.253129
H -0.000169 0.859040 1.951341
H -1.634379 2.559510 1.586341
H -0.061359 3.367620 1.653621
H 0.002211 3.588400 -0.787809
H -1.539479 4.225590 -0.220939
H -2.695879 2.133500 -0.859219
H -1.764319 2.706840 -2.251379
H 0.077001 1.127850 -1.682629
H -1.428170 0.263640 -1.912749
H 3.582491 1.156119 -1.065179
H 4.886820 -0.902741 -1.583659
H 4.220920 -3.069561 -0.570829
H 2.259130 -3.179620 0.945811
H 0.945480 -1.147610 1.429381
H -4.094110 -0.281999 -0.084419
H -4.210880 -1.590179 -1.266929
H -3.278520 -0.147709 -1.648609
H -2.097000 -3.177540 1.240621
H -3.543670 -2.199259 1.492041
H -3.480470 -3.348119 0.138011
H -2.068320 -2.982280 -1.815019
H -0.974950 -1.603650 -1.972519
H -0.658290 -2.837870 -0.754739

Structure: 4.3m Axial-benzoyl productive conformer
Charge = 0, Multiplicity = 1
SCF Energy: -866.571762 hartree
SCF Energy + ZPVE: -866.196324 hartree
Enthalpy: -866.176124 hartree
Free Energy: -866.244707 hartree
Free Energy with quasiharmonic correction: -866.240751 hartree
N 1.255050 0.485669 -0.262890
C -0.158100 0.526560 -0.636170
C -0.598189 1.936320 -1.068150
C -0.194169 3.003370 -0.056420
C 1.312771 2.927789 0.161290

C 1.717071 1.540909 0.649260
C -1.035240 -0.028510 0.495440
O -0.584250 -0.200800 1.611500
C -2.476380 -0.333970 0.205090
C -3.341510 -0.500989 1.292940
C -4.684410 -0.796029 1.085190
C -5.173590 -0.938059 -0.214240
C -4.316790 -0.782209 -1.302690
C -2.973380 -0.476419 -1.095940
C 1.837380 -0.759791 -0.385850
O 1.184030 -1.685050 -0.861340
C 3.316880 -0.997381 -0.000210
C 3.526400 -0.906181 1.524580
C 4.253130 -0.053251 -0.774860
C 3.666860 -2.433701 -0.416790
H -0.274580 -0.149570 -1.484380
H -0.118739 2.151640 -2.030530
H -1.679229 1.939740 -1.234750
H -0.489429 3.993500 -0.417420
H -0.714299 2.837750 0.897200
H 1.832321 3.149799 -0.780290
H 1.642541 3.662459 0.903040
H 1.294871 1.361739 1.646530
H 2.797511 1.494669 0.728970
H -2.941790 -0.396469 2.296640
H -5.350030 -0.918589 1.933900
H -6.221050 -1.172719 -0.377990
H -4.692790 -0.901429 -2.313890
H -2.319330 -0.366120 -1.955240
H 4.502100 -1.338441 1.771800
H 3.512830 0.110429 1.919090
H 2.761230 -1.483991 2.053980
H 4.138620 -0.207011 -1.853100
H 4.087461 1.007029 -0.573630
H 5.291990 -0.281752 -0.512420
H 4.722490 -2.620901 -0.193890
H 3.060380 -3.163131 0.125470
H 3.500910 -2.592261 -1.484920

Structure: 4.3m Equatorial-benzoyl conformer
Charge = 0, Multiplicity = 1
SCF Energy: -866.571418 hartree
SCF Energy + ZPVE: -866.196496 hartree
Enthalpy: -866.176518 hartree
Free Energy: -866.243322 hartree
Free Energy with quasiharmonic correction: -866.240572 hartree
N 0.985730 -0.215439 0.459550
C 0.562860 -1.597799 0.195770
C 1.676350 -2.376860 -0.499350
C 2.932230 -2.355560 0.379080
C 3.314240 -0.929120 0.787480
C 2.117860 -0.186900 1.390500
C -0.793560 -1.706539 -0.503500
O -0.971220 -2.544799 -1.363490

C -1.932690 -0.865078 -0.005450
C -3.018690 -0.659828 -0.862600
C -4.109459 0.094092 -0.443830
C -4.130729 0.636293 0.842970
C -3.056879 0.424922 1.705690
C -1.955080 -0.316978 1.280870
C 0.780441 0.700731 -0.550320
O 0.226041 0.339451 -1.583900
C 1.127901 2.190951 -0.339320
C 2.641771 2.444680 -0.468660
C 0.570321 2.697391 1.001030
C 0.433112 2.977091 -1.460320
H 0.399770 -2.045449 1.191130
H 1.347829 -3.402099 -0.687380
H 1.865760 -1.909670 -1.472990
H 2.742939 -2.948380 1.285070
H 3.767239 -2.834200 -0.142140
H 4.138460 -0.941590 1.509320
H 3.657800 -0.372160 -0.094440
H 2.377991 0.836520 1.643970
H 1.793800 -0.678210 2.317730
H -2.984790 -1.090828 -1.858270
H -4.944109 0.260043 -1.117960
H -4.984479 1.221153 1.172090
H -3.073989 0.839092 2.709260
H -1.118700 -0.467799 1.956730
H 2.817602 3.525620 -0.492560
H 3.233451 2.037350 0.353710
H 3.024511 2.025860 -1.405630
H -0.513939 2.547501 1.040710
H 1.005651 2.209291 1.875490
H 0.765522 3.771731 1.088890
H -0.648149 2.815651 -1.444920
H 0.630222 4.045211 -1.321600
H 0.800941 2.677291 -2.444200

Structure: Singlet 4.3b
Charge = 0, Multiplicity = 1
SCF Energy: -1414.846323 hartree
SCF Energy + ZPVE: -1414.474825 hartree
Enthalpy: -1414.452526 hartree
Free Energy: -1414.527066 hartree
Free Energy with quasiharmonic correction: -1414.521388 hartree

O	2.58947	2.52429	-0.71296
C	2.26253	1.35820	-0.60486
C	3.28178	0.30897	-0.28875
C	4.46914	0.72239	0.32744
C	5.46612	-0.20236	0.61857
C	5.28984	-1.54448	0.27824
C	4.11567	-1.95825	-0.34953
C	3.10726	-1.03808	-0.62628
C	0.78643	0.95440	-0.81640
N	0.38031	0.05582	0.27138
S	-0.49166	-1.31663	-0.05127
C	-2.22277	-0.89798	-0.07947
C	-2.79026	-0.42016	-1.25883
C	-4.12503	-0.02899	-1.25292
C	-4.89900	-0.11728	-0.08876
C	-6.35137	0.27816	-0.10386
C	-4.30529	-0.61644	1.07618
C	-2.97069	-1.01216	1.08952
O	-0.29323	-2.21030	1.08256
O	-0.11427	-1.72373	-1.40314
C	0.20013	0.70343	1.58128
C	-0.75322	1.89609	1.50506
C	-0.29516	2.88386	0.43016
C	-0.12775	2.18012	-0.92020
H	4.59484	1.77246	0.57280
H	6.38035	0.12112	1.10641
H	6.06850	-2.26750	0.50206
H	3.97876	-3.00054	-0.61939
H	2.19737	-1.37380	-1.11319
H	0.75921	0.37670	-1.74751
H	-2.19670	-0.36705	-2.16658
H	-4.57724	0.34362	-2.16812
H	-6.68487	0.60082	0.88551
H	-6.97476	-0.57113	-0.40460
H	-6.53343	1.08980	-0.81287
H	-4.89649	-0.70133	1.98396
H	-2.51352	-1.41134	1.98954
H	1.19506	1.03380	1.91115
H	-0.13401	-0.05467	2.29270
H	-0.79019	2.38200	2.48595
H	-1.76649	1.54223	1.27668
H	-1.01971	3.69839	0.33252
H	0.65856	3.33567	0.72553
H	-1.10682	1.83978	-1.27773
H	0.27989	2.86750	-1.66548

Structure: Triplet 4.3b
Charge = 0, Multiplicity = 3
SCF Energy: -1414.737052 hartree
SCF Energy + ZPVE: -1414.369437 hartree
Enthalpy: -1414.346704 hartree
Free Energy: -1414.422844 hartree
Free Energy with quasiharmonic correction: -1414.417299 hartree

O	-0.22252	-0.68290	-1.83689
C	-0.10929	-1.28106	-0.70512
C	1.11604	-1.86381	-0.26043
C	1.27513	-2.51756	0.99059
C	2.51109	-3.02071	1.36757
C	3.62914	-2.90106	0.53464
C	3.48618	-2.25870	-0.69991
C	2.26200	-1.74717	-1.09804
C	-1.45800	-1.38255	0.10841
N	-2.08170	-0.10090	0.32417
S	-1.38961	0.91846	1.47692
C	-0.00581	1.71030	0.69528
C	-0.23405	2.81350	-0.12870
C	0.84449	3.39018	-0.78740
C	2.14244	2.88406	-0.62992
C	3.29556	3.52661	-1.35352
C	2.33985	1.78770	0.21511
C	1.27233	1.19395	0.88385
O	-0.88994	0.04015	2.52644
O	-2.39594	1.93438	1.75094
C	-2.71552	0.53500	-0.83355
C	-3.74937	-0.40758	-1.44336
C	-3.11258	-1.75040	-1.79502
C	-2.44097	-2.35096	-0.56357
H	0.44384	-2.62568	1.67853
H	2.60433	-3.51335	2.33103
H	4.58992	-3.29979	0.84230
H	4.34270	-2.15595	-1.36042
H	2.16501	-1.24417	-2.05528
H	-1.15789	-1.76822	1.08128
H	-1.23533	3.21902	-0.23697
H	0.68051	4.25092	-1.43049
H	3.11671	3.54188	-2.43316
H	4.22898	2.99056	-1.16870
H	3.42768	4.56357	-1.02803
H	3.34027	1.38746	0.35379
H	1.42865	0.34355	1.54018
H	-3.18129	1.46215	-0.49501
H	-1.93845	0.77301	-1.58200
H	-4.56257	-0.55223	-0.72250
H	-4.17240	0.06939	-2.33263
H	-2.36904	-1.60890	-2.58913
H	-3.86639	-2.44470	-2.17877
H	-3.20103	-2.59718	0.18863
H	-1.90334	-3.27179	-0.80789

Structure: 1,5-HAT TS
Charge = 0, Multiplicity = 3
SCF Energy: -1414.730652 hartree
SCF Energy + ZPVE: -1414.366146 hartree
Enthalpy: -1414.344330 hartree
Free Energy: -1414.417631 hartree
Free Energy with quasiharmonic correction: -1414.413250 hartree

O	-0.09525	-0.52730	-1.64890
C	0.07273	-1.13181	-0.49881
C	1.37132	-1.57846	-0.11411
C	1.61883	-2.27510	1.09998
C	2.90821	-2.64744	1.45202
C	3.99636	-2.35405	0.62302
C	3.76671	-1.67665	-0.58047
C	2.48737	-1.29391	-0.94998
C	-1.16945	-1.38657	0.39233
N	-2.13147	-0.31101	0.20517
S	-1.92668	1.10895	1.12880
C	-0.42971	1.84327	0.54128
C	-0.47845	2.70292	-0.55217
C	0.71894	3.18741	-1.07187
C	1.94823	2.81176	-0.52000
C	3.24620	3.30283	-1.10125
C	1.96053	1.95344	0.58847
C	0.77824	1.46451	1.12693
O	-1.72214	0.64256	2.49072
O	-3.05243	1.95659	0.76843
C	-2.55535	-0.18680	-1.14724
C	-3.24167	-1.45303	-1.65093
C	-2.37867	-2.69321	-1.40695
C	-1.85207	-2.72007	0.02826
H	0.80203	-2.53293	1.76690
H	3.06738	-3.17872	2.38619
H	5.00048	-2.65147	0.90660
H	4.60066	-1.44467	-1.23751
H	2.32054	-0.76154	-1.88085
H	-0.86820	-1.39067	1.44107
H	-1.43316	2.99370	-0.97933
H	0.69773	3.86209	-1.92283
H	3.07720	3.99703	-1.92727
H	3.83754	2.46053	-1.47595
H	3.84647	3.81160	-0.34071
H	2.90941	1.65372	1.02570
H	0.78834	0.79638	1.98267
H	-3.11419	0.73443	-1.31583
H	-1.48656	-0.13753	-1.71108
H	-4.19865	-1.54000	-1.12030
H	-3.46262	-1.33313	-2.71512
H	-1.53240	-2.68969	-2.10328
H	-2.95798	-3.59856	-1.61020
H	-2.67162	-2.87757	0.73935
H	-1.12659	-3.52816	0.16165

Structure: Triplet A

Charge = 0, Multiplicity = 3
SCF Energy: -1414.755098 hartree
SCF Energy + ZPVE: -1414.386888 hartree
Enthalpy: -1414.364165 hartree
Free Energy: -1414.439369 hartree
Free Energy with quasiharmonic correction: -1414.434896 hartree

O	0.18463	-0.31429	-1.58214
C	0.38429	-1.07227	-0.47991
C	1.73314	-1.34415	-0.12777
C	2.07674	-2.18769	0.96256
C	3.40474	-2.40946	1.29585
C	4.43733	-1.81235	0.56572
C	4.11558	-0.98247	-0.51377
C	2.79432	-0.74762	-0.86136
C	-0.81268	-1.64917	0.24697
N	-1.97946	-0.74151	0.20187
S	-1.98487	0.57014	1.27267
C	-0.79883	1.71806	0.62779
C	-1.18795	2.59748	-0.37914
C	-0.22546	3.42500	-0.95222
C	1.10837	3.37628	-0.53376
C	2.15495	4.25248	-1.16795
C	1.46386	2.48730	0.48975
C	0.51943	1.65488	1.07701
O	-1.48049	0.04706	2.53347
O	-3.31149	1.15841	1.16578
C	-2.72101	-0.64331	-0.98925
C	-3.01024	-1.92706	-1.71118
C	-1.81375	-2.88143	-1.72656
C	-1.24280	-3.01718	-0.31692
H	1.30224	-2.67473	1.54697
H	3.63946	-3.05865	2.13437
H	5.47366	-1.99282	0.83174
H	4.90846	-0.51359	-1.08981
H	2.55411	-0.09810	-1.69603
H	-0.56011	-1.76731	1.30192
H	-2.22529	2.64387	-0.69629
H	-0.51646	4.12019	-1.73451
H	1.70956	4.96436	-1.86638
H	2.88120	3.64434	-1.71766
H	2.70652	4.81458	-0.40838
H	2.49584	2.44334	0.82792
H	0.79544	0.96588	1.86906
H	-3.47756	0.13325	-0.97420
H	-0.76030	-0.10003	-1.68965
H	-3.85382	-2.42660	-1.20445
H	-3.34728	-1.69581	-2.72589
H	-1.03891	-2.50897	-2.40730
H	-2.12534	-3.86076	-2.10093
H	-1.99827	-3.43973	0.35679
H	-0.37042	-3.67785	-0.30491

Structure: Singlet (E/Z)-B
Charge = 0, Multiplicity = 1

```
SCF Energy:         -1414.816516 hartree
SCF Energy + ZPVE:  -1414.448181 hartree
Enthalpy:           -1414.424574 hartree
Free Energy:        -1414.503358 hartree
Free Energy with quasiharmonic correction:  -1414.496240 hartree
O         -1.18021       -0.43961        0.50330
C         -2.16100       -0.58637       -0.42947
C         -3.43650        0.03456        0.00432
C         -3.68730        0.22536        1.36907
C         -4.89007        0.78438        1.79629
C         -5.85637        1.16785        0.86823
C         -5.60755        0.99535       -0.49402
C         -4.40598        0.44012       -0.92303
C         -1.98407       -1.23558       -1.59367
C         -0.66529       -1.84736       -1.98164
C         -0.37591       -3.16774       -1.23679
C          1.10057       -3.54854       -1.25233
C          1.97114       -2.68170       -0.39985
N          1.48865       -1.71703        0.28403
S          2.59665       -0.82672        1.23807
C          2.48805        0.76075        0.46211
C          1.39398        1.57631        0.74979
C          1.30013        2.80781        0.11406
C          2.28289        3.23270       -0.79094
C          2.16406        4.57784       -1.45575
C          3.36916        2.39123       -1.05241
C          3.48022        1.14940       -0.43204
O          1.99892       -0.76864        2.56314
O          3.95053       -1.34940        1.06195
H         -0.37881       -0.95723        0.29804
H         -2.93494       -0.07360        2.09089
H         -5.07145        0.91949        2.85841
H         -6.79239        1.60566        1.20141
H         -6.34653        1.30728       -1.22601
H         -4.21163        0.34050       -1.98650
H         -2.83803       -1.35936       -2.24988
H         -0.64468       -2.03602       -3.05986
H          0.14297       -1.13012       -1.78368
H         -0.71035       -3.09184       -0.19556
H         -0.96426       -3.97189       -1.68921
H          1.25432       -4.57927       -0.90563
H          1.51482       -3.52095       -2.27073
H          3.04449       -2.90213       -0.37191
H          0.63294        1.24949        1.45126
H          0.45124        3.45273        0.32491
H          1.20648        4.67040       -1.97720
H          2.21141        5.38063       -0.71288
H          2.96628        4.73668       -2.17975
H          4.14076        2.71251       -1.74618
H          4.32558        0.49681       -0.62579

Structure: Singlet (E/E)-B
Charge =  0, Multiplicity = 1
SCF Energy:         -1414.812491 hartree
```

SCF Energy + ZPVE: -1414.444433 hartree
Enthalpy: -1414.420986 hartree
Free Energy: -1414.496886 hartree
Free Energy with quasiharmonic correction: -1414.492585 hartree

O	-0.58535	0.10507	1.96338
C	-1.67490	0.48781	1.23457
C	-1.41914	1.75103	0.50131
C	-0.18124	1.93871	-0.12697
C	0.07890	3.11176	-0.83036
C	-0.88626	4.11652	-0.90003
C	-2.11250	3.94533	-0.25771
C	-2.37709	2.76987	0.44153
C	-2.80065	-0.24587	1.18404
C	-3.93399	-0.09287	0.20878
C	-4.05425	-1.33462	-0.69047
C	-2.79270	-1.59794	-1.52149
C	-1.62498	-2.04228	-0.69973
N	-0.42248	-1.74782	-1.02363
S	0.76852	-2.42043	-0.01976
C	1.95914	-1.10993	-0.01024
C	2.37454	-0.56510	1.19951
C	3.30089	0.47400	1.18112
C	3.80908	0.96759	-0.02489
C	4.81963	2.08317	-0.03039
C	3.37582	0.38979	-1.22647
C	2.45693	-0.65244	-1.22971
O	0.25401	-2.60001	1.34796
O	1.31672	-3.58009	-0.71473
H	-0.58496	-0.85849	2.08885
H	0.57093	1.15807	-0.06189
H	1.03886	3.24196	-1.32156
H	-0.68006	5.03381	-1.44332
H	-2.85956	4.73253	-0.29128
H	-3.32154	2.64654	0.96412
H	-2.84365	-1.12263	1.83361
H	-4.88506	0.05338	0.73582
H	-3.77941	0.78444	-0.42610
H	-4.27280	-2.21793	-0.07548
H	-4.90260	-1.20919	-1.37076
H	-2.99369	-2.41472	-2.22908
H	-2.50127	-0.72227	-2.11122
H	-1.84045	-2.67217	0.17248
H	1.96673	-0.93274	2.13459
H	3.62295	0.91640	2.11953
H	4.78708	2.64350	-0.96810
H	4.64529	2.77803	0.79503
H	5.83256	1.68104	0.08215
H	3.76080	0.76512	-2.17056
H	2.11452	-1.08997	-2.16248

Structure: Singlet (Z/Z)-B
Charge = 0, Multiplicity = 1
SCF Energy: -1414.812607 hartree
SCF Energy + ZPVE: -1414.444456 hartree

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Enthalpy:           -1414.421130 hartree
Free Energy:        -1414.497019 hartree
Free Energy with quasiharmonic correction:  -1414.492313 hartree
O         -2.67578        0.65777        1.66779
C         -2.56899        1.09083        0.37389
C         -1.42169        1.98554        0.08135
C         -0.85015        2.74683        1.11052
C          0.22850        3.59070        0.85386
C          0.75870        3.68066       -0.43321
C          0.20832        2.91301       -1.46018
C         -0.86652        2.06617       -1.20351
C         -3.49952        0.71972       -0.52232
C         -4.54608       -0.31480       -0.22177
C         -4.16271       -1.70087       -0.77875
C         -2.74224       -2.13246       -0.39317
C         -1.70237       -1.44934       -1.23374
N         -0.46141       -1.21365       -1.01896
S          0.21486       -1.64804        0.46685
C          1.88196       -1.11023        0.21822
C          2.15211        0.25685        0.27327
C          3.45736        0.68207        0.06963
C          4.48782       -0.23676       -0.18163
C          5.89744        0.25012       -0.38882
C          4.18004       -1.59878       -0.22749
C          2.87452       -2.04773       -0.03121
O         -0.35746       -0.81486        1.53417
O          0.18494       -3.10021        0.62043
H         -1.82382        0.26303        1.92431
H         -1.26596        2.68512        2.11139
H          0.65248        4.18081        1.66081
H          1.60008        4.33739       -0.63356
H          0.62937        2.95776       -2.45995
H         -1.26093        1.44455       -2.00133
H         -3.46468        1.15859       -1.51649
H         -4.67039       -0.39270        0.86136
H         -5.51203       -0.01924       -0.64514
H         -4.87709       -2.44285       -0.40922
H         -4.24767       -1.70250       -1.87361
H         -2.55076       -1.97691        0.67414
H         -2.61782       -3.20790       -0.58474
H         -2.03661       -1.14877       -2.23309
H          1.35435        0.96880        0.47296
H          3.68485        1.74444        0.10930
H          6.57510       -0.57682       -0.61239
H          5.94452        0.96481       -1.21642
H          6.26636        0.76054        0.50665
H          4.96976       -2.32008       -0.41712
H          2.63025       -3.10470       -0.06348

Structure: Singlet (E/Z)-B
Charge =  0, Multiplicity = 1
SCF Energy:         -1414.804933 hartree
SCF Energy + ZPVE:  -1414.436762 hartree
Enthalpy:           -1414.413226 hartree
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Free Energy:        -1414.490649 hartree
Free Energy with quasiharmonic correction:  -1414.484823 hartree
O         -0.97120        0.45579        2.00577
C         -2.06182        0.15738        1.23782
C         -2.50812        1.31980        0.43215
C         -1.55520        2.11364       -0.21910
C         -1.95504        3.20029       -0.99234
C         -3.30915        3.51568       -1.11135
C         -4.26218        2.74001       -0.45215
C         -3.86363        1.64851        0.31700
C         -2.60436       -1.07217        1.21026
C         -3.57758       -1.58087        0.18293
C         -3.03392       -2.83378       -0.54453
C         -1.51204       -2.81741       -0.78170
C         -1.00371       -1.49004       -1.26176
N          0.11153       -0.90371       -1.02960
S          1.22177       -1.66438        0.00301
C          2.52129       -0.46163        0.00560
C          3.69235       -0.73050       -0.68941
C          4.70941        0.22341       -0.67751
C          4.55858        1.42857        0.01234
C          5.65728        2.45744        0.03352
C          3.35973        1.66809        0.70126
C          2.33637        0.73055        0.70613
O          0.65953       -1.73390        1.36129
O          1.70761       -2.89768       -0.60945
H         -0.45792       -0.36019        2.13622
H         -0.50313        1.86129       -0.12597
H         -1.20905        3.80247       -1.50211
H         -3.61939        4.36754       -1.70896
H         -5.31597        2.99062       -0.52768
H         -4.60223        1.05616        0.85009
H         -2.18207       -1.81142        1.89207
H         -4.54624       -1.83504        0.63035
H         -3.77418       -0.79526       -0.55286
H         -3.25762       -3.73130        0.04083
H         -3.56161       -2.94447       -1.49802
H         -0.97673       -3.11968        0.12034
H         -1.25532       -3.54957       -1.55983
H         -1.66356       -0.93051       -1.93432
H          3.80573       -1.66930       -1.22173
H          5.63365        0.02426       -1.21239
H          5.29086        3.42573       -0.32114
H          6.03171        2.60175        1.05213
H          6.49635        2.15664       -0.59767
H          3.23148        2.60198        1.24227
H          1.40912        0.91891        1.24159

Structure: Mannich TS-1
Charge =  0, Multiplicity = 1
SCF Energy:         -1414.784690 hartree
SCF Energy + ZPVE:  -1414.418076 hartree
Enthalpy:           -1414.395833 hartree
Free Energy:        -1414.470544 hartree
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Free Energy with quasiharmonic correction: -1414.464847 hartree

O	0.69713	-0.08470	-1.49282
C	1.81436	0.15167	-0.84511
C	2.02918	1.54125	-0.40215
C	0.96052	2.44744	-0.44131
C	1.14599	3.76669	-0.04777
C	2.40111	4.19765	0.38647
C	3.47237	3.30583	0.41458
C	3.29052	1.98495	0.01528
C	2.66312	-0.91947	-0.55213
C	3.03500	-1.97055	-1.58005
C	3.14437	-3.30670	-0.85366
C	1.78729	-3.47873	-0.19054
C	1.31948	-2.18626	0.45268
N	0.04007	-1.84996	0.17406
S	-0.66971	-0.91347	1.35981
C	-2.12775	-0.34841	0.51809
C	-2.98894	-1.27753	-0.06592
C	-4.14258	-0.82025	-0.68836
C	-4.45221	0.54772	-0.72632
C	-5.70883	1.01811	-1.40982
C	-3.57561	1.45109	-0.12144
C	-2.40808	1.01161	0.50261
O	-1.06042	-1.78348	2.47088
O	0.16549	0.25267	1.67428
H	0.26357	-0.93524	-1.06008
H	-0.01069	2.09604	-0.77234
H	0.31204	4.46135	-0.07381
H	2.54476	5.22831	0.69638
H	4.45241	3.64113	0.73889
H	4.13672	1.30537	0.01328
H	3.46189	-0.69483	0.15297
H	2.26767	-2.02627	-2.36045
H	3.97810	-1.68562	-2.05991
H	3.37250	-4.13582	-1.52917
H	3.94328	-3.25700	-0.10378
H	1.03742	-3.76018	-0.93684
H	1.78584	-4.24853	0.58955
H	1.72594	-1.95076	1.43968
H	-2.75283	-2.33683	-0.03458
H	-4.81973	-1.53324	-1.15174
H	-5.83614	2.09828	-1.30863
H	-5.68319	0.77704	-2.47749
H	-6.59039	0.52861	-0.98426
H	-3.80578	2.51282	-0.13731
H	-1.72191	1.70814	0.97473

Structure: Mannich TS-2
Charge = 0, Multiplicity = 1
SCF Energy: -1414.773114 hartree
SCF Energy + ZPVE: -1414.404374 hartree
Enthalpy: -1414.382254 hartree
Free Energy: -1414.455243 hartree
Free Energy with quasiharmonic correction: -1414.450904 hartree

O	-2.34187	2.00803	-0.88652
C	-1.48351	1.47724	-0.05222
C	-0.07138	1.85066	-0.15093
C	0.47286	2.27037	-1.37670
C	1.78615	2.71136	-1.44087
C	2.57335	2.72952	-0.28654
C	2.04883	2.29167	0.92729
C	0.73139	1.84935	0.99857
C	-2.05334	0.61181	0.93379
C	-3.33743	1.13392	1.63431
C	-4.48466	0.17202	1.28744
C	-3.78887	-1.15469	1.02668
C	-2.60811	-0.80696	0.12857
N	-1.66527	-1.82621	0.02734
S	-0.59241	-1.64571	-1.13577
C	0.98140	-1.40544	-0.29589
C	1.14815	-1.75000	1.04008
C	2.39473	-1.56844	1.64372
C	3.47596	-1.05417	0.92578
C	4.82231	-0.85018	1.57094
C	3.28322	-0.71996	-0.42228
C	2.04824	-0.89148	-1.03471
O	-0.42240	-2.86030	-1.94137
O	-0.81515	-0.38265	-1.89485
H	-1.91018	2.56975	-1.55060
H	-0.10160	2.18106	-2.29557
H	2.20586	3.01786	-2.39323
H	3.60281	3.07064	-0.34016
H	2.66297	2.29243	1.82197
H	0.32384	1.52991	1.95159
H	-1.29855	0.24643	1.62740
H	-3.14542	1.12113	2.71105
H	-3.56109	2.16616	1.35331
H	-5.22723	0.12194	2.08791
H	-4.99729	0.50583	0.37821
H	-3.41339	-1.60194	1.95493
H	-4.41980	-1.89436	0.52526
H	-2.96708	-0.39846	-0.82647
H	0.30707	-2.15354	1.59520
H	2.52685	-1.83858	2.68858
H	5.59430	-1.43430	1.05964
H	5.12526	0.20179	1.52290
H	4.81031	-1.15188	2.62113
H	4.11487	-0.31505	-0.99516
H	1.90258	-0.62207	-2.07715

Structure: Mannich TS-3
Charge = 0, Multiplicity = 1
SCF Energy: -1414.787106 hartree
SCF Energy + ZPVE: -1414.420086 hartree
Enthalpy: -1414.397956 hartree
Free Energy: -1414.472953 hartree
Free Energy with quasiharmonic correction: -1414.466649 hartree

```
O          0.84775        0.25570       -1.63389
C          1.92480       -0.09491       -1.01479
C          2.66726        1.06297       -0.45902
C          1.95330        1.95565        0.34875
C          2.59894        3.06304        0.89241
C          3.94238        3.29933        0.60215
C          4.64674        2.42268       -0.22396
C          4.01569        1.29674       -0.74560
C          2.20407       -1.45124       -0.73817
C          3.48236       -1.87621       -0.02560
C          3.11474       -2.46050        1.35631
C          1.85793       -1.72374        1.80187
C          0.89768       -1.81083        0.63939
N         -0.21612       -1.01838        0.65276
S         -1.38579       -1.56121       -0.31077
C         -2.65852       -0.34596       -0.08938
C         -3.87521       -0.74023        0.44884
C         -4.87935        0.21460        0.61307
C         -4.67461        1.54540        0.24494
C         -5.75601        2.57911        0.41723
C         -3.43396        1.91056       -0.29989
C         -2.42351        0.97488       -0.47149
O         -0.92521       -1.47203       -1.75170
O         -1.93121       -2.87997        0.02622
H          0.16081       -0.52113       -1.79968
H          0.90563        1.75775        0.55974
H          2.05128        3.74536        1.53469
H          4.44127        4.17013        1.01631
H          5.68819        2.61539       -0.46097
H          4.55941        0.61470       -1.39306
H          1.80357       -2.13037       -1.48953
H          4.04045       -2.59594       -0.63047
H          4.13277       -1.01483        0.13069
H          2.89400       -3.53110        1.27421
H          3.93957       -2.35074        2.06451
H          1.38847       -2.18716        2.67632
H          2.05850       -0.67210        2.03950
H          0.75756       -2.85146        0.31889
H         -4.02948       -1.77642        0.73154
H         -5.83538       -0.08405        1.03381
H         -6.04538        3.00341       -0.54960
H         -6.64711        2.14883        0.87991
H         -5.40923        3.40464        1.04685
H         -3.26359        2.94311       -0.59408
H         -1.46478        1.26229       -0.89386

Structure: Mannich TS-4
Charge =  0, Multiplicity = 1
SCF Energy:         -1414.785491 hartree
SCF Energy + ZPVE:  -1414.417515 hartree
Enthalpy:           -1414.395493 hartree
Free Energy:        -1414.468999 hartree
Free Energy with quasiharmonic correction:  -1414.464275 hartree
O         -1.02271        0.05330       -1.87464
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C         -1.77990       -0.34894       -0.88802
C         -2.71946        0.69095       -0.42142
C         -3.30504        1.53260       -1.37837
C         -4.19127        2.52814       -0.98335
C         -4.47520        2.71558        0.36983
C         -3.87140        1.90253        1.32747
C         -3.00259        0.88755        0.93588
C         -1.60943       -1.63195       -0.33976
C         -2.61539       -2.35071        0.53677
C         -1.80482       -3.03784        1.64204
C         -0.79916       -1.98801        2.10932
C         -0.08934       -1.42084        0.88668
N          0.92834       -2.20012        0.43162
S          1.84960       -1.62696       -0.74928
C          2.44752       -0.01393       -0.25508
C          3.20858        0.06687        0.91360
C          3.69322        1.30186        1.32178
C          3.43109        2.46339        0.57893
C          3.97606        3.79130        1.03406
C          2.66818        2.35425       -0.58467
C          2.17267        1.12009       -1.00919
O          2.99611       -2.50853       -0.92887
O          1.03834       -1.38549       -1.99133
H         -0.23958       -0.59106       -2.02677
H         -3.06840        1.39139       -2.42786
H         -4.65465        3.16387       -1.73095
H         -5.15982        3.49969        0.67775
H         -4.07300        2.05945        2.38223
H         -2.52158        0.27384        1.68919
H         -1.07778       -2.29484       -1.01898
H         -3.34224       -1.65864        0.96975
H         -3.17467       -3.07825       -0.06016
H         -2.43750       -3.39800        2.45805
H         -1.26124       -3.89564        1.23082
H         -1.31668       -1.18201        2.64017
H         -0.04072       -2.40491        2.77776
H          0.05900       -0.33197        0.89049
H          3.41670       -0.83025        1.49027
H          4.28923        1.37118        2.22831
H          3.65811        4.01491        2.05720
H          5.07089        3.78396        1.02553
H          3.63723        4.60269        0.38581
H          2.45686        3.24324       -1.17245
H          1.58800        1.04186       -1.91928

Structure: Mannich TS-5
Charge =  0, Multiplicity = 1
SCF Energy:         -1414.787488 hartree
SCF Energy + ZPVE:  -1414.419645 hartree
Enthalpy:           -1414.397605 hartree
Free Energy:        -1414.471835 hartree
Free Energy with quasiharmonic correction:  -1414.466040 hartree
O          1.15710        0.19274        1.49694
C          2.16603       -0.09278        0.72639
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C          2.92935        1.08355        0.26759
C          4.27692        0.98215       -0.10497
C          4.96367        2.10706       -0.54979
C          4.31013        3.33681       -0.63539
C          2.96907        3.44334       -0.26668
C          2.28140        2.32426        0.19027
C          2.39347       -1.37919        0.22670
C          2.04444       -2.65318        0.97998
C          1.18526       -3.57628        0.08088
C          1.11280       -2.93012       -1.30575
C          1.01995       -1.40861       -1.19509
N         -0.12186       -0.73314       -0.90346
S         -1.26133       -1.38470        0.02462
C         -2.50974       -0.12116       -0.02158
C         -2.22948        1.13909        0.50602
C         -3.21992        2.11046        0.48561
C         -4.48737        1.84073       -0.05360
C         -5.54794        2.91000       -0.05876
C         -4.73760        0.56914       -0.57148
C         -3.75336       -0.42051       -0.55835
O         -1.86419       -2.63376       -0.45674
O         -0.77273       -1.45425        1.44887
H          0.45391       -0.55027        1.57551
H          4.79802        0.03401       -0.01783
H          6.01067        2.02628       -0.82378
H          4.84766        4.21243       -0.98625
H          2.45879        4.39851       -0.33741
H          1.23670        2.39357        0.47284
H          3.28140       -1.45135       -0.39673
H          2.98238       -3.14352        1.25851
H          1.51622       -2.42781        1.90935
H          1.61814       -4.57738        0.00621
H          0.18432       -3.69105        0.50092
H          2.02251       -3.15722       -1.87124
H          0.25348       -3.29199       -1.87903
H          1.59032       -0.86581       -1.95023
H         -1.24952        1.34876        0.92485
H         -3.01367        3.09596        0.89568
H         -5.20135        3.80114       -0.59154
H         -6.46327        2.55934       -0.54093
H         -5.79703        3.21489        0.96286
H         -5.71457        0.34411       -0.99015
H         -3.94465       -1.41185       -0.95592

Structure: Mannich TS-7
Charge =  0, Multiplicity = 1
SCF Energy:         -1414.775432 hartree
SCF Energy + ZPVE:  -1414.407841 hartree
Enthalpy:           -1414.385747 hartree
Free Energy:        -1414.459983 hartree
Free Energy with quasiharmonic correction:  -1414.454307 hartree
O          1.88494        0.14243        2.08644
C          2.38111        0.69007        1.00356
C          3.24769       -0.19691        0.20170
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C          4.40033        0.30088       -0.42059
C          5.23889       -0.55591       -1.12648
C          4.93030       -1.91348       -1.21757
C          3.79466       -2.41700       -0.58265
C          2.96038       -1.56720        0.13602
C          1.98487        1.99802        0.69164
C          2.13398        2.62890       -0.67524
C          1.10139        1.94100       -1.57483
C         -0.24548        2.00186       -0.84496
C         -0.05688        1.82488        0.66348
N         -0.47496        0.79525        1.44090
S         -0.83178       -0.66303        0.73818
C         -2.51510       -0.48560        0.17401
C         -2.82465       -0.73991       -1.15587
C         -4.15233       -0.63551       -1.57254
C         -5.16216       -0.28016       -0.67596
C         -6.59694       -0.16976       -1.11960
C         -4.81815       -0.03112        0.66161
C         -3.50336       -0.13467        1.09476
O          0.00695       -0.91773       -0.44259
O         -0.82618       -1.64485        1.82026
H          0.90438        0.45138        2.19281
H          4.66343        1.34831       -0.31548
H          6.13749       -0.16747       -1.59524
H          5.58203       -2.58067       -1.77366
H          3.55898       -3.47457       -0.64521
H          2.07221       -1.94690        0.62842
H          1.91140        2.64239        1.56302
H          1.90320        3.69724       -0.59318
H          3.13730        2.55304       -1.09805
H          1.03965        2.40621       -2.56332
H          1.37889        0.88876       -1.70639
H         -0.69361        2.99158       -0.98668
H         -0.93890        1.26209       -1.24647
H         -0.14728        2.76094        1.21230
H         -2.03700       -1.01827       -1.84941
H         -4.40345       -0.83573       -2.61051
H         -6.69713       -0.35910       -2.19077
H         -7.22428       -0.89134       -0.58639
H         -6.99494        0.82811       -0.91003
H         -5.59594        0.24309        1.36984
H         -3.24009        0.05347        2.13149

Structure: Mannich TS-8
Charge =  0, Multiplicity = 1
SCF Energy:         -1414.786313 hartree
SCF Energy + ZPVE:  -1414.418252 hartree
Enthalpy:           -1414.395961 hartree
Free Energy:        -1414.470999 hartree
Free Energy with quasiharmonic correction:  -1414.465294 hartree
O         -0.95218        0.61260        1.44529
C         -2.00430        0.09407        0.87034
C         -2.95584        1.09387        0.35042
C         -4.33953        0.90135        0.44338
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C         -5.20942        1.87188       -0.04516
C         -4.70316        3.02601       -0.64294
C         -3.32468        3.22050       -0.73810
C         -2.45053        2.26453       -0.23145
C         -2.06714       -1.28242        0.63839
C         -3.20151       -2.04209       -0.00425
C         -2.55505       -3.21059       -0.79693
C         -1.06469       -2.88870       -0.99317
C         -0.87321       -1.37783       -0.90789
N          0.31828       -0.74700       -0.77006
S          1.41174       -1.34589        0.24958
C          2.74985       -0.19561        0.04230
C          4.00925       -0.68305       -0.27598
C          5.06891        0.21670       -0.40070
C          4.87746        1.58569       -0.20866
C          6.01707        2.56111       -0.34206
C          3.59197        2.04656        0.11531
C          2.52679        1.16669        0.24312
O          0.89484       -1.17178        1.65419
O          1.92669       -2.69148       -0.02986
H         -0.23436       -0.08625        1.63213
H         -4.73117        0.01118        0.92541
H         -6.28159        1.72872        0.04278
H         -5.38437        3.77720       -1.03085
H         -2.93191        4.11890       -1.20330
H         -1.37595        2.40462       -0.29461
H         -1.44672       -1.86557        1.31868
H         -3.91740       -2.41259        0.73583
H         -3.74968       -1.38791       -0.68829
H         -2.66368       -4.15404       -0.25643
H         -3.06232       -3.33424       -1.75732
H         -0.44511       -3.38234       -0.24113
H         -0.69462       -3.21311       -1.97215
H         -1.50802       -0.84057       -1.62006
H          4.15313       -1.74829       -0.42407
H          6.05825       -0.15583       -0.65128
H          5.81191        3.29433       -1.12867
H          6.16722        3.11418        0.59063
H          6.95057        2.05012       -0.58876
H          3.42971        3.11060        0.26819
H          1.53199        1.52738        0.48753

Structure: Cis-4.4b
Charge =  0, Multiplicity = 1
SCF Energy:         -1414.852245 hartree
SCF Energy + ZPVE:  -1414.480796 hartree
Enthalpy:           -1414.458448 hartree
Free Energy:        -1414.532144 hartree
Free Energy with quasiharmonic correction:  -1414.528029 hartree
C         -1.12434        1.35417       -0.69379
C         -2.53565        0.82865       -0.34200
C         -3.30666        2.04057        0.23246
C         -2.50039        3.29098       -0.18096
C         -1.44116        2.78818       -1.17647
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C         -0.19783        1.41122        0.50406
N         -2.62946       -0.31272        0.56526
S         -2.16980       -1.82189        0.07091
O         -2.53457       -2.71583        1.16249
O         -2.70534       -1.99958       -1.27427
C         -0.38753       -1.86008       -0.05802
C          0.37202       -1.88860        1.11043
C          1.75900       -1.92365        1.01343
C          2.39643       -1.93813       -0.23323
C          1.60783       -1.91092       -1.38905
C          0.21792       -1.87350       -1.31187
C          3.89690       -2.01446       -0.32734
O         -0.64855        1.43547        1.64067
C          1.28249        1.47853        0.27946
C          2.12043        1.46879        1.40191
C          3.50132        1.50570        1.24976
C          4.06018        1.55848       -0.02943
C          3.23397        1.57540       -1.15129
C          1.84899        1.53325       -0.99867
H         -0.66652        0.75699       -1.48567
H         -2.99981        0.51013       -1.27957
H         -4.32835        2.05249       -0.15466
H         -3.36903        1.95850        1.32049
H         -3.12795        4.06983       -0.62082
H         -2.00856        3.72348        0.69520
H         -0.55732        3.43124       -1.22558
H         -1.86230        2.72239       -2.18600
H         -2.30342       -0.11261        1.51018
H         -0.11518       -1.89165        2.08142
H          2.35773       -1.93960        1.92033
H          2.08873       -1.92181       -2.36390
H         -0.39621       -1.86680       -2.20724
H          4.26316       -1.51931       -1.23055
H          4.37118       -1.54688        0.53943
H          4.22375       -3.05994       -0.36417
H          1.66789        1.42266        2.38757
H          4.14407        1.49326        2.12478
H          5.13922        1.58545       -0.15010
H          3.66569        1.61895       -2.14648
H          1.22036        1.54444       -1.88360

Structure: TS-b in Fig. S23
Charge =  0, Multiplicity = 3
SCF Energy:         -1414.722424 hartree
SCF Energy + ZPVE:  -1414.358345 hartree
Enthalpy:           -1414.336289 hartree
Free Energy:        -1414.411117 hartree
Free Energy with quasiharmonic correction:  -1414.405822 hartree
O         -1.94154        0.85020       -1.60350
C         -2.16446        0.36217       -0.40446
C         -3.45021       -0.17013       -0.08448
C         -3.78750       -0.63462        1.21533
C         -5.04908       -1.14720        1.47857
C         -6.02310       -1.21628        0.47725
```

C	-5.70771	-0.75655	-0.80639
C	-4.45312	-0.24221	-1.09027
C	-1.07805	0.54631	0.67819
N	0.24151	0.50043	0.05980
S	0.89025	-1.04064	-0.28166
C	2.62346	-0.72743	-0.07018
C	3.11404	-0.48930	1.21435
C	4.47186	-0.25496	1.37541
C	5.34290	-0.25800	0.27421
C	6.81389	-0.01328	0.47770
C	4.81932	-0.50185	-0.99772
C	3.45740	-0.73895	-1.18148
O	0.65820	-1.38594	-1.67650
O	0.40828	-1.89893	0.79051
C	0.40201	1.50126	-0.94237
C	0.27708	2.90699	-0.36832
C	-1.02219	3.06849	0.42523
C	-1.22098	1.90307	1.39551
H	-3.06306	-0.59554	2.02233
H	-5.27739	-1.49824	2.48101
H	-7.00706	-1.61938	0.69306
H	-6.45268	-0.80359	-1.59589
H	-4.21700	0.10613	-2.09023
H	-1.14376	-0.27414	1.39258
H	2.44197	-0.49471	2.06747
H	4.86986	-0.07208	2.37002
H	6.98239	0.92970	1.00674
H	7.34640	0.02750	-0.47488
H	7.25687	-0.81182	1.08156
H	5.48264	-0.51152	-1.85785
H	3.04704	-0.93875	-2.16626
H	1.28643	1.33539	-1.56133
H	-0.58918	1.30548	-1.61054
H	1.14703	3.07873	0.27990
H	0.32720	3.62960	-1.18754
H	-1.86809	3.10789	-0.27022
H	-1.01239	4.01532	0.97310
H	-0.47266	1.93612	2.19700
H	-2.21196	1.94740	1.85738

Structure: TS-c in Fig. S23
Charge = 0, Multiplicity = 3
SCF Energy: -1414.714952 hartree
SCF Energy + ZPVE: -1414.351545 hartree
Enthalpy: -1414.329502 hartree
Free Energy: -1414.404381 hartree
Free Energy with quasiharmonic correction: -1414.398898 hartree

O	-2.68880	2.05432	0.69515
C	-2.37290	0.99523	-0.05727
C	-3.27759	-0.11333	-0.02696
C	-3.03493	-1.31092	-0.74741
C	-3.94962	-2.35295	-0.70979
C	-5.12676	-2.25329	0.03803
C	-5.37432	-1.08252	0.76065

```
C         -4.47284       -0.02929        0.73545
C         -1.09829        1.06824       -0.88827
C         -0.75131        3.36895       -0.12348
C          0.40735        2.96117        0.76433
H         -2.12096       -1.43676       -1.31757
H         -3.73560       -3.26067       -1.26649
H         -5.83448       -3.07561        0.06202
H         -6.28220       -0.99090        1.35023
H         -4.67871        0.87498        1.29852
H         -1.16909        0.38449       -1.73397
H         -0.86384        4.44520       -0.27287
H         -1.76235        3.02009        0.46297
H          1.34762        3.16496        0.23247
H          0.41616        3.54391        1.68978
C         -0.89764        2.51331       -1.36186
H         -1.75454        2.83071       -1.96252
H          0.00488        2.55722       -1.98430
C          0.34498        1.46988        1.10433
H          1.28703        1.14702        1.55553
H         -0.46175        1.26759        1.82131
N          0.12916        0.71044       -0.13375
S          0.60282       -0.88887       -0.09760
O          0.16404       -1.56075        1.12166
O          0.23521       -1.44385       -1.39911
C          2.37350       -0.72741       -0.01162
C          3.05602       -1.28122        1.06352
C          3.04631       -0.07656       -1.04658
C          4.44726       -1.18075        1.09971
H          2.50538       -1.78309        1.85268
C          4.42975        0.01513       -0.99225
H          2.48997        0.34750       -1.87752
C          5.14978       -0.53576        0.07984
H          4.99118       -1.61293        1.93477
H          4.96628        0.51751       -1.79303
C          6.65102       -0.42973        0.11281
H          7.06246       -0.89441        1.01147
H          7.09298       -0.92241       -0.75908
H          6.96832        0.61766        0.09290

Structure: Trans-4.4b
Charge =  0, Multiplicity = 1
SCF Energy:         -1414.850047 hartree
SCF Energy + ZPVE:  -1414.479419 hartree
Enthalpy:           -1414.456773 hartree
Free Energy:        -1414.532120 hartree
Free Energy with quasiharmonic correction:  -1414.526681 hartree
O          3.11906       -2.50552       -0.86592
S          2.50772       -1.57804        0.07978
N          2.83616       -0.07470       -0.53118
C          2.26414        1.12215        0.08343
C          3.16477        2.34231       -0.17604
C          2.19532        3.52162       -0.16421
C          0.99816        2.98111       -0.95385
C          0.85541        1.51473       -0.44976
```

C	-0.20730	1.48798	0.63612
C	-1.64863	1.35852	0.23370
C	-2.60950	1.29302	1.25054
C	-3.95624	1.14882	0.93891
C	-4.35873	1.07363	-0.39667
C	-3.41019	1.14481	-1.41464
C	-2.05841	1.28532	-1.10152
O	0.09093	1.62680	1.80958
C	0.74141	-1.82358	0.02479
C	-0.00169	-1.72579	1.19658
C	-1.37979	-1.92978	1.13927
C	-2.01781	-2.22113	-0.06900
C	-3.50105	-2.47239	-0.11983
C	-1.24328	-2.30340	-1.23559
C	0.13285	-2.11438	-1.19721
O	2.88959	-1.55933	1.48452
H	2.20343	0.93229	1.15886
H	0.56181	0.84181	-1.25961
H	2.84727	-0.08787	-1.54904
H	3.97320	2.41133	0.55508
H	3.61924	2.24607	-1.17114
H	1.89289	3.75136	0.86398
H	2.61579	4.42944	-0.60467
H	0.08502	3.56840	-0.81653
H	1.22890	2.97536	-2.02525
H	-2.27737	1.35059	2.28243
H	-4.69415	1.09516	1.73362
H	-5.41067	0.95974	-0.64169
H	-3.72019	1.09149	-2.45372
H	-1.33497	1.34158	-1.90877
H	0.49526	-1.50108	2.13489
H	-1.96693	-1.85556	2.05068
H	-4.00761	-2.02618	0.73940
H	-3.70544	-3.54910	-0.10954
H	-3.94053	-2.05998	-1.03214
H	-1.72721	-2.53076	-2.18208
H	0.73238	-2.20961	-2.09839

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4.6. Experimental Contributors

The work presented in this chapter was published in 2021: Jurczyk, J.; Lux, M. C.; Adpressa, D.; Kim, S. F.; Lam, Y.-h.; Yeung, C. S.; Sarpong, R. Photomediated Ring Contraction of Saturated Heterocycles. *Science* **2021**, *373*, 1004–1012. The work has been reprinted with permission from AAAS. J.J., M.C.L., C.S.Y., and R.S. conceived and designed the experiments reported in this work. J.J., M.C.L., and S.F.K. performed all laboratory experiments. D.A. assisted in structural elucidation. Y.-h.L. designed and completed the DFT calculations. J.J., M.C.L., S.F.K., Y.-h.L., C.S.Y., and R.S. wrote the manuscript. C.S.Y. and R.S. directed the research.

Appendix A

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Chapter 1. Synthetic Strategies in Heterocycle Editing

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Chapter 2. C–C Cleavage Approach to C–H Functionalization of Saturated Aza-Cycles

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C–C Cleavage Approach to C–H Functionalization of Saturated Aza-Cycles

Author: Jose B. Roque, Yusuke Kuroda, Justin Jurczyk, et al

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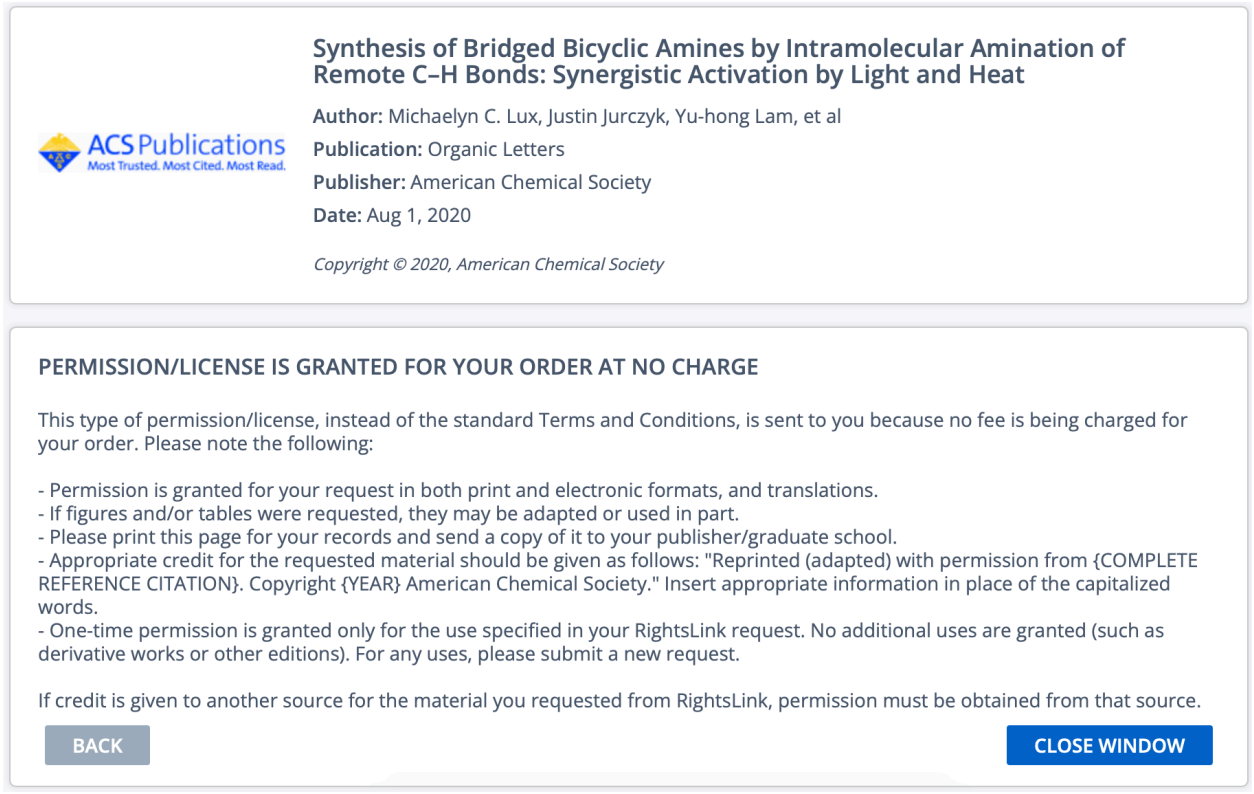

Synthesis of Bridged Bicyclic Amines by Intramolecular Amination of Remote C–H Bonds: Synergistic Activation by Light and Heat

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