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Expanding the Palette of Organic Synthesis in Water:

I. Carbonyl Iron Powder as a Reagent for Nitro Group Reduction

II. *B*-alkyl Suzuki-Miyaura Couplings in Water

III. Coolade: Development of a Low-Foaming Surfactant for Organic Synthesis in Water

IV. "ppm" Tsuji-Trost Allylations in Water

A dissertation submitted in partial satisfaction of the requirements for the degree Doctor of Philosophy in Chemistry

By

Nicholas R. Lee

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Professor Donald H. Aue

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December 2021

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October 2021

ACKNOWLEDEGEMENTS

I would like to express my sincerest thanks to the UCSB chemistry community, it has been quite a unique experience coming to graduate school here. In particular, special thanks to Bruce Lipshutz for being an excellent PI. Bruce has captained the ship admirably over the last 6 years. He's always been available, enthusiastic about the chemistry, has great connections with people in industry and academia, and of course he makes sure the funding keeps coming in so that the research continues, all while managing 20+ graduate students and post-docs. Special thanks to the lab mates who made this an interesting experience…you know who you are. I feel very fortunate to have joined Lipshutz group at a time when we had a lot of really exceptional graduate students and post-docs who were willing to help out the new students like myself. Without their help and advice, I would have been lost. And I would like to wish the best of luck to the new and upcoming graduate students, may your journey be insightful and filled with an appropriate amount of failure & struggle to make you really think and make the successes taste that much sweeter.

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One-Pot Synthesis of Indoles and Pyrazoles via Pd-Catalyzed Couplings/Cyclizations Enabled by Aqueous Micellar Catalysis

Evan B. Landstrom, Nnamdi Akporji, Nicholas R. Lee, Christopher M. Gabriel, Felipe C. Braga, and Bruce H. Lipshutz.

Organic Letters **2020**, 22, 6543–6546.

Sustainable Palladium-Catalyzed Tsuji–Trost Reactions Enabled by Aqueous Micellar Catalysis.

Nicholas R. Lee, Farbod A. Moghadam, Felipe C. Braga, Daniel J. Lippincott, Bingchun Zhu, Fabrice Gallou, & Bruce H. Lipshutz.

Organic Letters **2020**, *22*, 4949–4954.

Synthetic Chemistry in Water: Applications to Peptide Synthesis and Nitro-Group Reductions

Margery Cortes-Clerget, Nicholas R. Lee & Bruce H. Lipshutz.

Nature Protocols **2019**, *14*, 1108-1129.

Coolade. A Low-Foaming Surfactant for Organic Synthesis in Water

Nicholas R. Lee, Margery Cortes-Clerget, Alex B. Wood, Daniel J. Lippincott, Haobo Pang, Farbod A. Moghadam, Fabrice Gallou, & Bruce H. Lipshutz.

ChemSusChem **2019**, *12*, 3159 –3165.

***B*-Alkyl sp^3–sp^2 Suzuki–Miyaura Couplings under Mild Aqueous Micellar Conditions**

Nicholas R. Lee, Roscoe T. H. Linstadt, Danielle J. Gloisten, Fabrice Gallou, & Bruce H. Lipshutz.

Organic Letters **2018**, *20*, 2902-2905.

Carbonyl Iron Powder: A Reagent for Nitro Group Reductions under Aqueous Micellar Catalysis Conditions

Nicholas R. Lee, Agata A. Bikovtseva, Margery Cortes-Clerget, Fabrice Gallou, & Bruce H. Lipshutz.

Organic Letters **2017**, *19*, 6518-6521.

S_NAr Reactions in Aqueous Nanomicelles: From Milligrams to Grams with No Dipolar Aprotic Solvents Needed

Nicholas R. Lee, Fabrice Gallou, & Bruce H. Lipshutz.

Organic Process Research & Development **2017**, *21*, 218-221.

Effects of Co-solvents on Reactions Run under Micellar Catalysis Conditions

Christopher M. Gabriel, Nicholas R. Lee, Florence Bigorne, Piyatida Klumphu, Michael Parmentier, Fabrice Gallou, & Bruce H. Lipshutz.

Organic Letters **2017**, *19*, 194-197.

ABSTRACT

Expanding the Palette of Organic Synthesis in Water:

I. Carbonyl Iron Powder as a Reagent for Nitro Group Reduction.

II. *B*-alkyl Suzuki-Miyaura Couplings in Water.

III. Development of a Low-Foaming Surfactant for Organic Synthesis in Water

IV. "ppm" Tsuji-Trost Allylations in Water

By: Nicholas R. Lee

I. In searching for a broadly applicable method for nitro group reduction in water, carbonyl iron powder (CIP) was identified as a commercially available source of Fe(0) which was uniquely suited to this task. The method was found to work well on substrates which were difficult to reduce by other means, and in a mild and environmentally friendly fashion, while ensuring good-to-perfect chemoselectivity.

II. While much research has been conducted on Suzuki-Miyaura couplings in aqueous medium, very little exists in the synthetic literature related to *B*-alkyl Suzuki-Miyaura couplings conducted in water. A partially oxidized derivative of the venerable 9-BBN reagent was found to be especially suitable for *B*-alkyl Suzuki couplings in water. A general methodology for use of these "OBBD" reagents in water was developed, as well as studies on the bench stability and air tolerance of the coupling reactions themselves.

III. The development of new "designer" surfactants specifically tailored to organic synthesis in water has been a reoccurring theme in Lipshutz Group for the last decade. In this chapter of surfactant development, we developed a new surfactant with

low-foaming properties. This property of low-foaming is particularly important in reactions which produce gas, or otherwise introduce gas into the reaction medium, as this will cause a large reaction volume increase when conducted with “typical” surfactants. Several types of reactions which suffer from this gas-evolution problem are presented, as well as a number of other reaction types. The development of this surfactant, as well as reaction comparison trials are presented, as compared to what is considered benchmark-surfactant: TPGS-750-M.

IV. The use of palladium catalysis has been ubiquitous in modern organic synthesis. However, with increasing palladium prices and a growing awareness of the endangered status of palladium as a precious metal, there is an ever-increasing move toward sustainable catalysis practices. In the simplest interpretation, this means using as low amounts of palladium as possible in coupling reactions. The study of palladium catalyzed allylic substitution reactions or “Tsuji-Trost” reactions under very low catalysts loadings is presented. A number of reaction types which have not been previously reported in water were explored, and the results of these explorations are presented. In addition to more “typical” reaction types like allylic aminations, some of these previously-not-known-to-water were found to be suitable at very favorable palladium loadings of 1000 ppm (0.1 mol%).

Table of Contents

I. Carbonyl Iron Powder as a Reagent for Nitro Group Reduction.

1.1 Introduction

Reduction of nitro compounds to the corresponding amine or aniline is a fundamental and widely used method in synthetic chemistry in both academic and industrial settings. The development and improvement of methods for nitro group reduction has a rich history in organic synthesis, and especially in recent years, the number of new approaches has grown continually.[1] This development is driven by the fact that most existing methods involve some undesirable aspects, such as high pressure, fire hazards, pyrophoric materials, toxic or dangerous reagents, precious or toxic metals, long reaction times, expensive ligands, non-commercially available materials, lack of broad functional group tolerance, and variable yields (Scheme 1). Arguably, the most common approaches oftentimes focus on catalytic hydrogenation utilizing a variety of metal catalysts, in conjunction with reducing agents such as hydrogen gas, formic acid,[2] hydrazines,[3] and silanes[4]. Various metals have also played an important role, such as tin, zinc, platinum, cobalt, and nickel.[5] Stoichiometric iron-based reagents, in particular, have been fundamental to these

[1] For recent reviews on reductions of nitroarenes, see: (a) Orlandi, M.; Brenna, D.; Harms, R.; Jost, S.; Benaglia, M. *Org. Process Res. Dev.* **2018**, *22*, 430–445. (b) Kadam, H. K.; Tilve, S. G. *RSC Adv*. **2015**, *5*, 83391; (c) Blaser, H-U.; Steiner, H.; Studer, M. *ChemCatChem* **2009**, *1*, 210;

[2] For selected examples of reductions with formic acid, see: (a) Wienhöfer, G.; Sorribes, I.; Boddien, A.; Westerhaus, F.; Junge, K.; Junge, H.; Llusar, R.; Beller, M. *J. Am. Chem. Soc*. **2011**, *133*, 12875; (b) Berthold, H.; Schotten, T.; Hönig, H. *Synthesis* **2002**, 1607; (c) Wei, Y.; Wu, J.; Xue, D.; Wang, C.; Liu, Z.; Zhang, Z.; Chen, G.; Xiao, J. *Synlett* **2014**, *25*, 1295.

[3] For selected examples of reductions with hydrazines, see: (a) Jagadeesh, R. V.; Wienhöfer, G.; Westerhaus, F. A.; Surkus, A-E; Pohl, M-M; Junge, H.; Junge, K.; Beller, M. *Chem. Commun*. **2011**, *47*, 10972; (b) Moghaddam, M. M., Pieber, B.; Glasnov, T.; Kappe, O. *ChemSusChem* **2014**, *7*, 3122; (c) Mokhov, V.M., Popov, Y.V.; Nebykov, D.N. *Russ. J. Gen. Chem*. **2014**, *84*, 1515. (d) Zhao, Z.; Yang, H.; Li, Y.; Guo, X. *Green Chem.* **2014**, *16*, 1274; Shi, Q.; Lu, R.; Lu, L.; Fu, X.; Zhao, D. *Adv. Synth. Catal*. **2007**, *349*, 1877; (e) Li, F.; Frett, B.; Li, H.-y. *Synlett* **2014**, *25*, 1403.

[4] For selected examples of reductions with silanes, see: (a) Jagadeesh, R. V.; Wienhöfer, G.; Westerhaus, F. A.; Surkus, A-E; Pohl, M-M; Junge, H.; Junge, K.; Beller, M. *Chem. Commun*. **2010**, *46*, 1769; (b) Pehlivan, L.; Métay, E.; Laval, S.; Dayoub, W.; Demonchaux, P.; Mignani, G.; Lemaire, M. *Tet. Lett*. **2010**, *51*, 1939; (c) Rahaim, R. J.; Maleczka (Jr.), R. E. *Org. Lett*. **2005**, *7*, 5087.

[5] For selected examples of reductions with metals other than iron, see: (a) Matthews, J. M.; Greco, M. N.; Hecker, L. R.; Hoekstra, W. J.; Andrade-Gordon, P.; de Garavilla, L.; Demarest, K. T.; Ericson, E.; Gunnet, J. W.; Hageman, W.; Look, R.; Moore, J. B.; Maryanoff, B. E. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 753; (b) William P. Gallagher, W. P.; Marlatt, M.; Livingston, R.; Kiau, S.; Muslehiddinoglu, J. *Org. Process Res. Dev.* **2012**, *16*, 1665; (c) Lara, P. Philippot, K. *Catal. Sci. Technol*. **2014**, *4*, 2445; (d) Jagadeesh, R. V.; Banerjee, D.; Arockiam, P. B.; Junge, H.; Junge, K.; Pohl, M-M.; Radnik, J.; Brückner, A.; Beller, M. *Green Chem*. **2015**, *17*, 898.

reductions, with Fe/HCl, Fe/AcOH, and Fe/NH_4Cl as textbook cases.[6] Nonetheless, these reagents are considered relatively harsh and may be functional group-intolerant; from a modern perspective, they are certainly not environmentally friendly. In an effort to develop a method which is commercially available, inexpensive, and safe, we found that carbonyl iron powder (CIP) can be used under micellar catalysis conditions in water to effect the facile and efficient reduction of functionalized aryl nitro compounds. This method is operationally simple, requiring no specialized equipment, occurring under mild conditions, and showing very good tolerance of functional groups typically problematic for many existing nitro reduction methods.

Scheme 1: Reagents employed in nitro reduction and associated hazards

Non-metal reducing agents	**Metal reducing agents**	**Metals used as catalysts**
H_2 silanes hydrazines HCOOH glucose $Na_2S_2O_8$ WGSR* DHA** vasicine, $NaBH_4$ LAH	Fe $SnCl_2$ Zn In Sm	Pd Pt Co Fe Ru Au Rh Re Ni

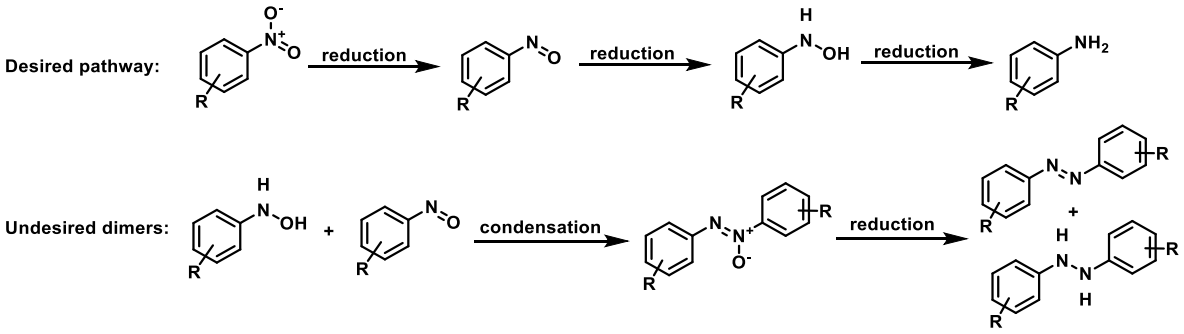
[6] (a) For methods utilizing iron based nanoparticles, and iron metal in acidic medium, see: (a) Ramadas, K. Srinivasan, N. *Synth. Commun*. **1992**, *22*, 3189; (b) Liu, Y.; Lu, Y.; Prashad, M.; Repic, O.; Blacklock, T. J. *Adv. Synth. Catal*. **2005**, *347*, 217; (c) Dey, R.; Mukherjee, N.; Ahammed, S.; Ranu, B. C. *Chem. Commun*. **2012**, *48*, 7982; (d) Wang, L.; Li, P.; Wu, Z.; Yan, J.; Wang, M.; Ding Y. *Synthesis* **2003**, 2001; (e) Desai, D. G.; Swami, S. S.; Dabhade, S. K.; Ghagare, M. G. *Synth. Commun*. **2001**, *31*, 1249. (f) *Seixas, J. D.; Luengo-Arratta S. A.; Diaz, R.; Saldivia, M.; Rojas-Barros, D. I.; Manzano, P.; Gonzalez, S.; Berlanga, M.; Smith, T. K.; Navarro, M.; Pollastri, M. P. J. Med. Chem.* **2014**, *57*, 4834; (g) Wang, S.; Li, Z.; Hua, W. *Synth. Commun*. **2002**, *32*, 3339.

Flammability/explosion	Pressurized equipment	Toxic waste
H_2 silanes hydrazines formic acid $NaBH_4$ LAH organic solvents	H_2 WGSR	$SnCl_2$ Sm Ni Pd Rh

*WGSR = water-gas shift reaction, **DHA = dihydroanthracene

The electronic properties imparted by a nitro group is highly useful for manipulating reactivity of aromatic and aliphatic groups alike for other coupling reactions like S_NAr, S_EAr, and metal coupling reactions like Suzuki-Miyaura, Buchwald-Hartwig, Sonogashira, and may others. The nitro group functions as a masked amine, which is typically unreactive under most non-reducing reaction conditions. Furthermore, nitration of aromatic rings is typically the method of this functional group incorporation. Therefore, anilines commonly result from the reduction of a nitro group in the synthesis of pharmaceuticals and various commercial chemicals. The reaction involves a redox cycle between the nitro compound and some type of reducing agent. This goes through several intermediates, and in many cases can lead to incomplete reaction, or dimerized byproducts. The formation of byproducts, or rather, the mitigation of these byproducts was one of the main purposes of this work. By viewing the routes which the nitro reduction can proceed, this shows that there are several possible intermediates and byproducts which can result from this reaction (Scheme 2).

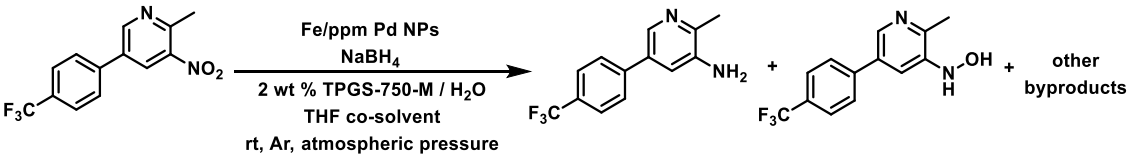
Scheme 2: Pathways of nitro reduction and common byproducts



1.2 Project background

During our previous co-solvent study, one substrate was screened which produced varying amounts of byproducts depending on the conditions used (Table 1 below). While this substrate showed large improvements by the addition of co-solvent (from 16% to 64% with addition of THF co-solvent), yield could not be improved further. Initially, it was unclear which product was the correct product, and a simple method of producing reference material was needed in order to compare with reaction products.

Table 1: Screening nitro reduction conditions for a difficult compound



Trial	THF co-solvent (% by vol.)	MBH_4 source (equiv)	Time (h)	Isolated yield of the aniline (%) Isolated yield of the hydroxylamine (%)[a]
NL164.1	None	$NaBH_4$ (2.5)	24	16
NL169.1	None	KBH_4 (2.5)	4.5	19
NL173.1	None	$NaBH_4$ (6)	5	31
NL174.1	None	KBH_4 (6)	5	29, 26 [a]
NL190.1	None	KBH_4 (3)	10	25
NL166	15	$NaBH_4$ (2.5)	24	63
NL169.2	20	KBH_4 (2.5)	4.5	58
NL173.2	20	$NaBH_4$ (6)	5	58
NL164.2	35	$NaBH_4$ (2.5)	24	63
NL162	35	KBH_4 (2.5)	48	73
NL174.2	35	KBH_4 (6)	5	29
NL186	35	KBH_4 (1)	48	36, 59[a]
NL190.2	25	KBH_4 (3)	10	59, 38[a]

Of the readily available literature methods, Pd/C with H_2 was initially considered, but the presence of a potentially reducible pyridine group, coupled with a hesitancy to use possibly flammable Pd/C conditions led us to consider iron powder. Indeed, refluxing this otherwise "unruly" substrate in EtOH/H_2O produced the desired product in essentially quantitative yield with no purification other than filtration and extraction (Figure 1).

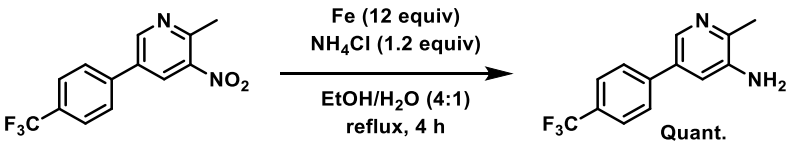
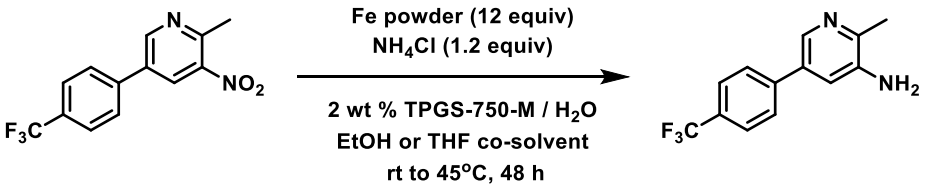


Figure 1: Fe/NH_4Cl reduction

Due to the simplicity and ease of this method an attempt was made to adapt this to use in surfactant medium. Indeed, the same reagent ratios worked well in surfactant, but only in the presence of co-solvent, presumably due to the extremely poor solubility of this nitro compound. This was considered as an inclusion in the co-solvent study, as it showed the desired improvement in conversion and yield upon addition of co-solvent (Table 2), but was ultimately "put on the shelf."

Table 2: Initial trials to adapt to an aqueous surfactant medium

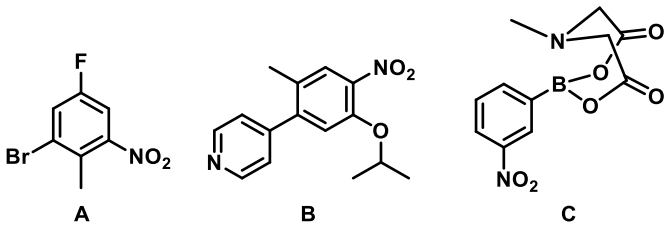


Trial	Co-solvent	result
NL179.1	None	Trace conversion
NL179.2	20 vol. % THF	Complete
NL179.3	20 vol. % EtOH	Complete (>95% isolated)

The method was then attempted again after our collaborators provided samples of several API intermediates as substrates for testing of new nitro reduction methods. While the

development of a substrate scope of ones choosing is a test of a method, testing using real-world compounds is always a good test.

Scheme 3: Screening API intermediates



Method	Substrate A	Substrate B	Substrate C
Fe/ppm Pd/Ni NPs + $NaBH_4$	✓	✗	✗
Fe/NH_4Cl	✓	✓	✗

Both methods were amenable to compound **A**, whereas compound **B** gave clean conversion with Fe/NH_4Cl, where decomposition products including reduction of the pyridine ring resulted in the NP reduction. Neither method was capable of cleanly reducing compound **C**, giving mixtures of de-borylated material and incomplete reduction. Because of the success on substrate **B**, this method was submitted to our collaborators for evaluation, and we later received positive feedback about the method. Due to this interest, it was then decided to further develop a methodology from these conditions.

1.3 Selection of iron source

Iron powder is produced commercially in several different primary methods. Reduced grade iron is produced from the reduction of iron oxides (usually in the form of iron ore) in the presence of hydrogen containing gasses. This is the cheapest method, and it produces the low purity material. Electrolytic grade iron is produced from electrolysis of iron salts in solution, and it produces a much higher purity iron powder. However, both methods tend to produce non-uniform and "jagged" iron particles and tend to be fairly large in size, i.e. ~50 μm. In the pursuit of a small particle size iron, we initially found "nano-iron" powder in listings from chemical suppliers. This material was quite expensive, and also was dishearteningly listed as "pyrophoric". In searching for a small particle size, but cheaper material, we discovered carbonyl iron powder (CIP). CIP is a very small particle size, commercial iron powder which is produced in huge quantities by companies such as BASF.[7] In this process, an iron source is treated with carbon monoxide to produce liquid $Fe(CO)_5$, which is purified by distillation. The purified $Fe(CO)_5$ is thermally decomposed to Fe(0) and deposited. This process affords the reagent as uniform, layered, spherical particles described as "onion-like" in appearance. In addition, this material is typically of very small particle size (1.5-10 μm average particle size, depending on grade). CIP finds many uses including in the manufacture of automotive and electrical parts as well as radar-absorptive materials, industrial diamonds, and in magnetorheological fluids; applications where very small and uniform particle size and high purity are necessary. Bulk quotes for this material were surprisingly affordable,

[7] https://www.dispersions-pigments.basf.com/portal/basf/em/ dt.jsp? setCursor=1_827860

1 metric ton quantities were quoted at 5000-8000$ (or 5-8$/kg), [8] putting it in the "commodity chemicals" range, and making it potentially attractive as a reagent for synthesis on industrial scale. The use of this material in organic synthesis, and specifically for nitro group-containing intermediates en route to APIs, however, had not been reported, notwithstanding reports on other types of iron powders that have been applied for similar purposes.[6]

Table 3: Particle size of common iron powders

Common iron powder types	Particle size
Reduced grade 325 mesh	44 μm maximum
Electrolytic grade	25-35 μm average
Carbonyl iron powder	1.5-6 μm average

Carbonyl iron powder (Figure 2a) consists of spherical particles of extremely high purity iron. While average particle size listed stated 1.5-3.5 μm for this sample, cryo-TEM imaging of mixtures of this material in TPGS-750-M surfactant solution shows the presence of many nano-scale particles (Figure 2b).

[8] Quotations for a metric ton from three different suppliers ranged from $5000 to $8000 as of April 2, 2017: Taian Health Chemical Co., Ltd ($5000); Chengdu Nuclear 857 New Chemicals Co., Ltd. ($5900); Sichuan Kehui Industrial CO., Ltd ($8000).

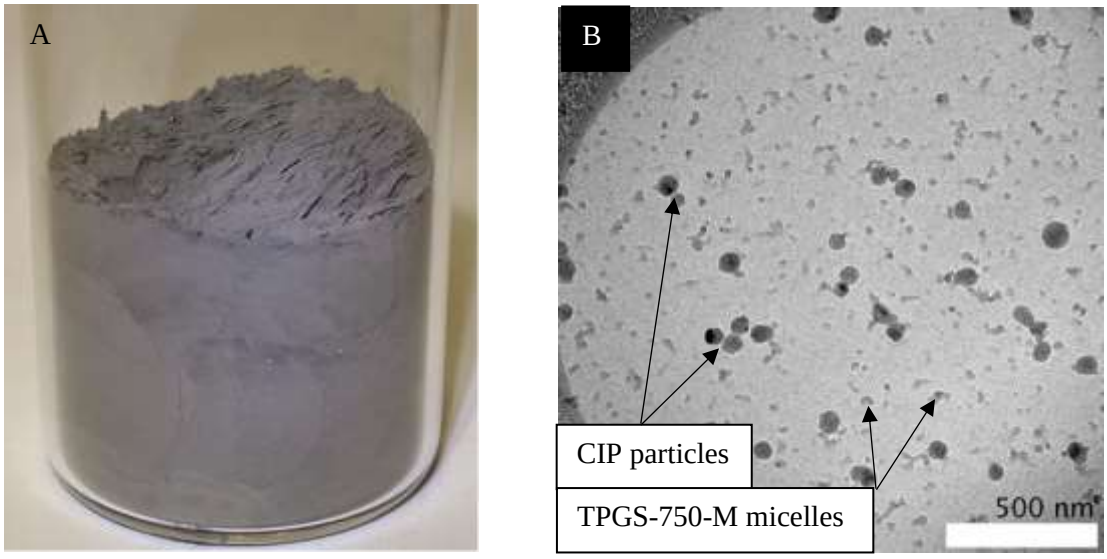
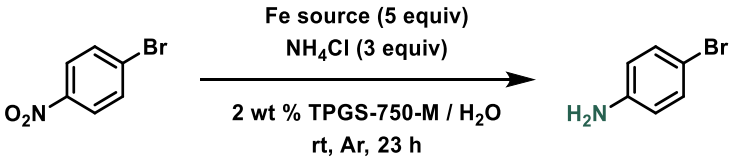


Figure 2: Images of (A) CIP and (B) TEM of CIP in TPGS-750-M solution

Table 4: Initial comparison of common reduced grade iron powder against CIP



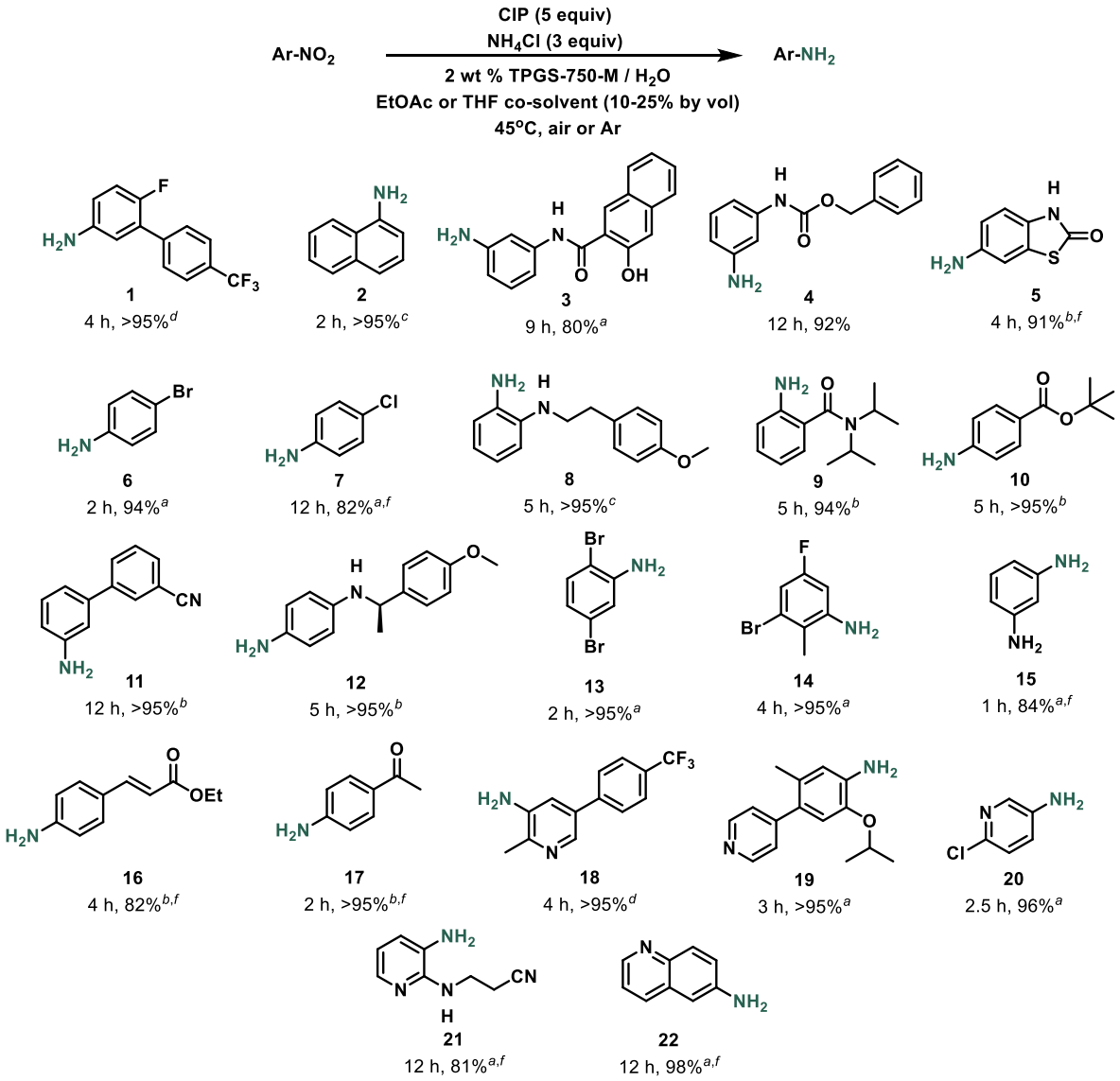
Trial	Iron Source	Result at 1.5 h	Result at 23 h
NL-2-149.1	Reduced grade 325 mesh	<50 % conversion	~50% conversion
NL-2-149.2	CIP	Nearly complete	Complete

Initial comparison trials of a standard “lab grade” reduced grade 325 mesh iron powder against CIP showed that conversion appeared much faster using the smaller particle size CIP (Table 4). In addition, it was noted that while typical lab-grade iron powder showed significant abrasion of PTFE coated stir bars used in the reactions, the smaller and spherical CIP showed no noticeable abrasion. While this issue might be of small

importance to a lab-scale reaction, this issue could become much more costly and problematic on a large scale when using expensive and possibly sensitive equipment.

1.4 Substrate scope

Scheme 4: Substrate scope of the method



Co-solvent amounts by percentage of total reaction volume: [a]10% THF, [b]20% THF, [c]25% THF, [d]20% EtOAc, [e]25% EtOAc, [f]Conc. HCl (1 equiv) added

During substrate scope development the typical temperature was increased from ambient to 45°C. While some substrates (e.g., precursors to products **2**, **6** and **19**) were fully reduced

at room temperature, reaction times were shortened significantly by some heating. Insofar as earlier processes developed using micellar catalysis conditions, the CIP method is similar to that based on zinc;[9] however, iron is a notable improvement from a sustainability perspective in terms of earth abundance.[10] In comparison with other nitro reduction methods conducted under micellar conditions, CIP has some other advantages. CIP reductions have no complications with stirring larger scale reactions, which were problematic during attempts at scaling Zn/NH_4Cl reductions. No aggregation of solids using CIP was noted at any point, including during the scale-up experiment (vide infra). Use of Fe nanoparticles (NPs), in conjunction with $NaBH_4$ (or KBH_4), causes an immediate release of hydrogen, which can cause troublesome foaming.[11,12] Introduction of a co-solvent can decrease the extent of foaming, but may necessitate use of a larger vessel to assure that any foaming can be accommodated. With CIP, on the other hand, with no gas evolution involved, obviates these practical considerations. However, one noteworthy drawback of the CIP approach is the requirement for disposal of large amounts of solid waste (in the form of iron and iron oxides).

1.5 Co-solvent selection

While some substrates were capable of full conversion in the absence of co-solvent (i.e. *p*-bromo nitrobenzene, see Table 4 above), many larger and more crystalline substrates showed only trace conversion, due to poor solubility. Addition of small amounts of co-

[9] Kelly, S. M.; Lipshutz, B. H. *Org. Lett.* **2014**, *16*, 98.
[10] Diederen, A. M. *Metal minerals scarcity: a call for managed austerity and elements of hope* (no 03/10/2009, The Hague Center for Strategic Studies, The Hague, Netherlands, **2009**).
[11] Pang, H.; Gallou, F.; Sohn, H.; Camacho-Bunquin, J.; Delferro, M.; Lipshutz, B. H. *Green. Chem.* **2018**, *20*, 130–135.
[12] Gabriel, C. M.; Parmentier, M.; Riegert, C.; Lanz, M.; Handa, S.; Lipshutz, B. H.; Gallou, F. *Org. Process Res. Dev.* **2017**, *21*, 247–252.

solvent[13] greatly decreased reaction times. While some sparingly soluble nitro compounds will eventually reach completion in surfactant solution alone, co-solvent functions to solubilize a greater proportion of the bulk starting material and intermediates. The addition of either EtOAc or THF co-solvents was determined empirically (Table 5), typically screening 10-25% co-solvent by volume, depending on the solubility of each substrate to ensure stirrability and operability of the bulk reaction mixture. THF was found to give better conversion than EtOAc in some cases, but EtOAc was often comparable. EtOAc is typically the solvent used for extraction, it is cheaper than THF, and does not pose peroxide formation issues. Because of these attributes, ethyl acetate is the more desirable co-solvent.

[13] (a) Gallou, F.; Guo, P.; Parmentier, M.; Zhou, J. A general and Practical Alternative to Polar Aprotic Solvents Exemplified on an Amide Bond Formation. *Org. Process Res. Dev.* **2016**, 20, 1388-1391. (b) Gabriel, C. M.; Lee, N. R. ; Bigorne, F.; Klumphu, P.; Parmentier, M.; Gallou, F.; Lipshutz, B. H. *Org. Lett.*, **2017**, *19*, 194.

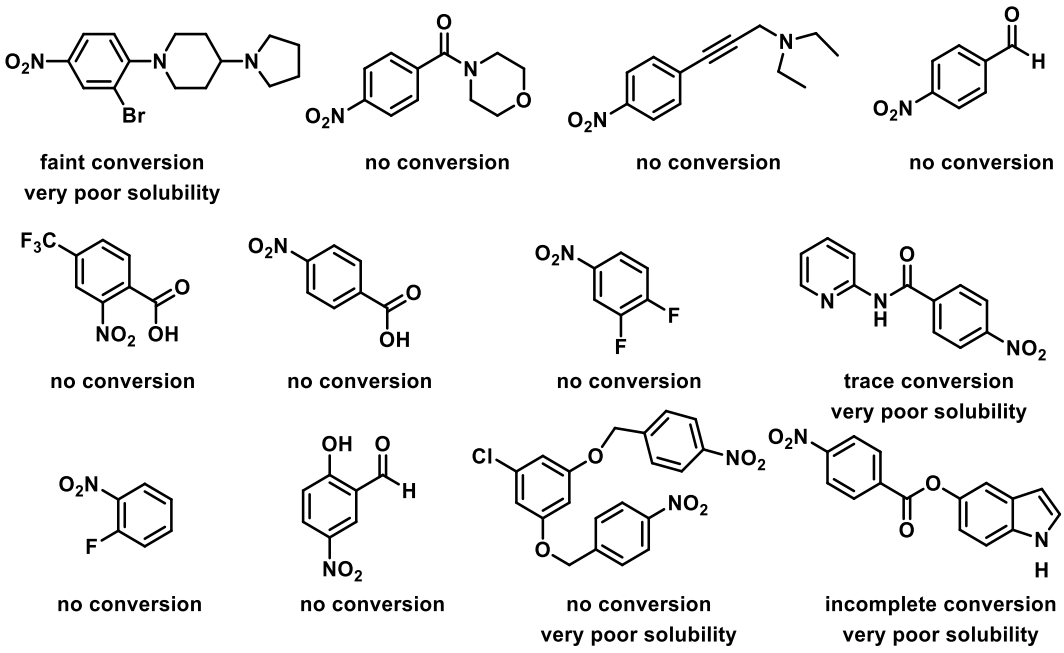
Table 5: Typical co-solvent screening protocol for 0.5 mmol scale trials

Trial	2 wt % TPGS-750-M / H_2O (mL)	Co-solvent	Co-solvent volume (mL)
1	1.0	None	0.0
2	0.9	THF	0.1
3	0.8	THF	0.2
4	0.75	THF	0.25
5	0.9	EtOAc	0.1
6	0.8	EtOAc	0.2
7	0.75	EtOAc	0.25

1.6 Comments on difficult substrates and functional group compatibility

While many of the substrates worked flawlessly, a number of substrates were either sluggish or showed no conversion at all (Scheme 5). Some of these substrates were very insoluble even in the presence of co-solvent, which may explain this, but many of these difficult substrates exhibited very good solubility. In general, substrates bearing withdrawing groups proved to be very reactive towards FeNPs,[11] whereas those with electron-donating residues appear to be the most receptive to reduction with CIP, though exceptions exist to this generalization. Overall, these reagents/approaches appear to be complimentary.

Scheme 5: Difficult substrates



In developing a substrate scope, some interesting notes about functional group compatibility were made, notably that almost all water-stable functional groups except the nitro group itself were stable to the reaction conditions. As a comparison to arguably the most common reduction method for nitro compounds; Pd/C in conjunction with hydrogen gas, Table 6 shows a brief comparison of functional group tolerance. While Pd/C with H_2 is a very common nitro reduction method, hydrogenations of this type have a number of functional group incompatibilities. During this study, it was noted that CIP/NH_4Cl in surfactant medium was very tolerant of other potentially reducible functional groups. Notable examples were aryl bromides, CBz protected amine, and alkynes. Because of this high functional group tolerance, this method should find use in

settings such as medicinal chemistry, where new and likely sensitive compounds are routinely synthesized and a gentle but robust and simple method is desirable.

Table 6: Comparison of functional group compatibility between Pd/C + H_2 and CIP/NH_4Cl

Functional group	**Pd/C + H_2**	**CIP/NH_4Cl**
Ar-Cl or Br	dehalogenation	Compatible
nitrile	Reduction	Compatible
N-CBz	Deprotection	Compatible
aldehyde	Reduction	Compatible
Alkene	Hydrogenation	Compatible
Alkyne	Hydrogenation	Compatible
heteroaromatic	dearomatization	Combatible

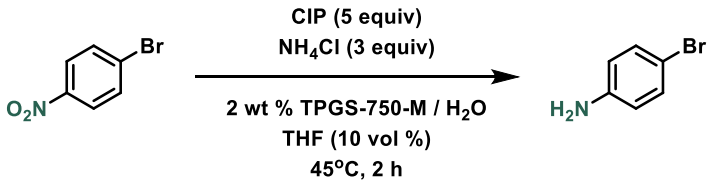
Green = fully compatible, orange = possible problems, Red = most likely incompatible

1.7 E Factor and recycling studies

In typical synthetic organic chemistry, the aqueous phase which is generated during workup is considered waste and is typically disposed of as such. The ability to recycle surfactant media used for reactions in water is an important aspect for decreasing waste generation.[14] Flexibility to customize recycling of several components of these reactions is a remarkable attribute of this method.

[14] Lipshutz, B. H.; Isley, N. A.; Fennewald, J. C.; Slack, E. D. *Angew. Chem. Int. Ed*. **2013**, *52*, 10952.

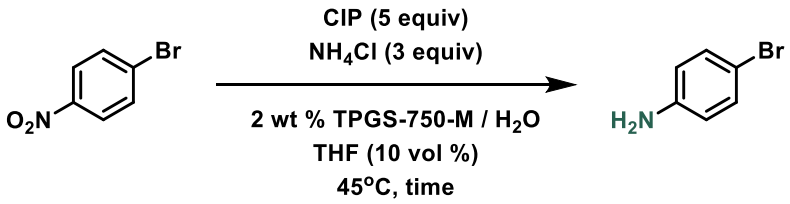
Table 7: Recycle of TPGS-750-M reaction medium



	Reaction	1st recycle	2nd recycle
Isolated yield (%)	95	93	96
E Factor (organic solvent)	5.5	5.5	5.5
E Factor (including water)	16.5	5.5	5.5

In the simplest form of recycling, the TPGS-750-M reaction medium can be reused with full conversion to the desired product (Table 7). After each reaction, the reaction medium is mixed with a minimum of ethyl acetate, filtered and the organic layer removed. The surfactant medium is then used in a subsequent reaction.

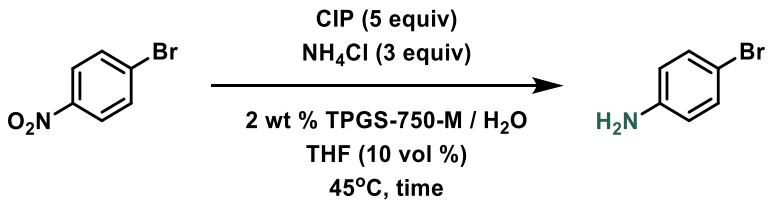
Table 8. Recycling of the aqueous reaction media & CIP



	Reaction	1st recycle	2nd recycle
Isolated yield (%)	94	92	NR
Reaction time (h)	2	5	N/A
Additional NH_4Cl added	none	3 equiv	3 equiv

In addition to the reaction medium alone, the question arose whether the CIP material retained enough residual activity to perform a second reaction. While previous optimization trials on substrate **19** showed that between 3-4 equivalents was necessary for full conversion in a reasonable reaction time, *p*-bromonitrobenzene was found to require slightly less CIP. In this case (Table 8), *p*-bromonitrobenzene was capable of two full reductions using 5 equivalents of CIP. Attempting to conduct a 2nd recycle of CIP resulted in little to no conversion.

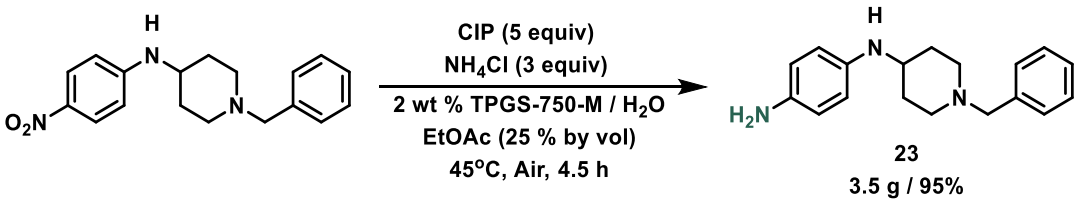
Table 9. Recycle Using Repeated Addition of CIP & NH_4Cl



	Reaction	1st recycle	2nd recycle	3rd recycle
Isolated yield (%)	94	93	93	96
Reaction time (h)	2	2	2	2.5
CIP added (eq)	none	2.5	2.5	2.5
NH_4Cl added (eq)	none	3	3	3

The third form of recycle involves in-flask recycling, where upon the end of reaction, a minimum of EtOAc is added and the product is extracted. Additional substrate, CIP, and NH_4Cl is added and the reaction is run again (Table 9). Continuing this cycle proceeded smoothly until the 3rd recycle, whereupon the reaction mixture had become too concentrated and viscous to mix properly and it was deemed to be at the practical limit of use.

1.8 Scale-up & tandem 3-step, 1-pot reaction



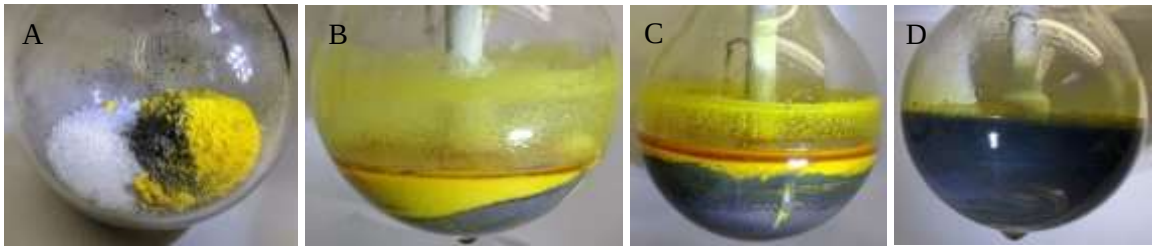


Figure 3: (a) Solid reagents in flask, (b) slurrying solids in EtOAc, (c) after addition of TPGS-750-M solution, (d) reaction after stirring 20 minutes

To demonstrate the potential for practical application of this method on a larger scale, a multi-gram scale-up was conducted (Figure 3). While smaller scale (i.e. 1 gram) scale reactions were attempted with magnetic stirring, this was found to dramatically slow the rate of the reaction due to the magnetic CIP powder adhering to the stir bar. This effect results in less surface area exposed, and while reactions will still proceed to completion, the reaction time is greatly lengthened (i.e. from 3-4 hours to 3-4 days). To avoid this problem, this reaction was conducted using an overhead stirrer, eliminating the magnetic-clumping issue. Due to the very small particle size and somewhat viscous surfactant solution, the CIP was found to remain suspended in the medium during stirring. This example proceeded without any difficulties arising from aggregation of solids (whether nitro compound or CIP material), therefore it appears this method is easily scalable. Reports from collaborators of this reaction performed up to 80 g scale have corroborated

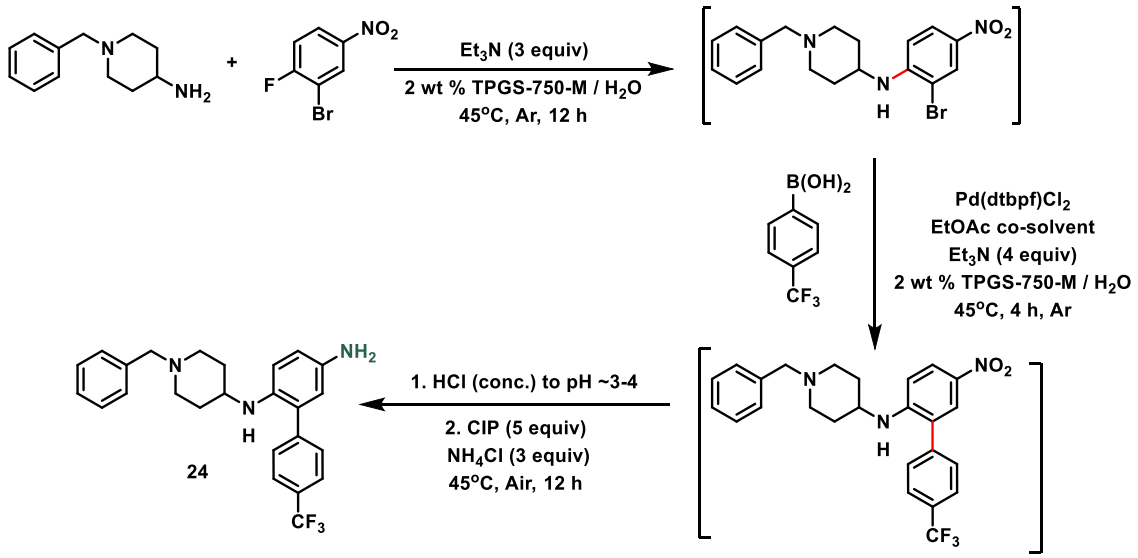
this finding. No noticeable exotherm was noted in this trial, in contrast to common literature methods such as Fe/HCl or Fe/AcOH, which produce strong exotherms as well as sometimes making difficult to filter very fine sediment or mud-like material. While the thermodynamic/calorimetric behavior of small lab-scale reactions is of little importance to academic chemists, but is an area of concern and caution for industrial settings seeking to scale-up new methods.

A wide variety of synthetic methods can now be effectively conducted in surfactant media,[15] and various conditions needed for these different methods are frequently compatible. The ability to conduct different classes of reactions in the same medium lends itself to "tandem" or "telescoped" processes, eliminating the need to isolate and purify material between steps, a savings in both time, and waste generation. To show the ability for multiple reaction types to be run sequentially in the same reaction vessel using this method, a 3-step-1-pot sequence was conducted to synthesize a highly functionalized product (Scheme 6). Complimentary steps including S_NAr,[16] Suzuki, and nitro reduction were chosen because they are complimentary methods in terms of the electronics in each step. The strong withdrawing nature of the nitro group as well as the effect of the aryl bromide are necessary for the S_NAr. The analogous S_NAr with *p*-fluoronitrobenzene with the same nucleophile proceeds very slowly, requiring several days for completion. In this case, the S_NAr must be conducted first, as attempting the Suzuki then S_NAr resulted in incomplete conversion in the S_NAr step. Also noteworthy,

[15] (a) Ghorai, S.; Lipshutz, B. H. *Green Chem*., **2014**, *16*, 3660; (b) La Sorella, G.; Strukul, G.; Scarso, A. *Green Chem.*, **2015**, *17*, 644.
[16] Isley, N. A.; Linstadt, R. T. H.; Kelly, S. M.; Gallou, F.; Lipshutz, B. H. *Org. Lett*., **2015**, *17*, 4734.

while K_3PO_4 is typically the base of choice for these S_NAr reactions, in this case the use of Et_3N produced much finer particles and improved the solubility of the subsequent Suzuki coupling. Nitro reduction of the intermediate furnishes the final product, however the nitro reduction medium must be acidic or little to no conversion is seen. As a testament to the robust nature of this reaction, the nitro reduction proceeded cleanly and to full conversion, despite the wide variety of reagents and material already present in the flask.

Scheme 6: 3-step-1-pot tandem sequence



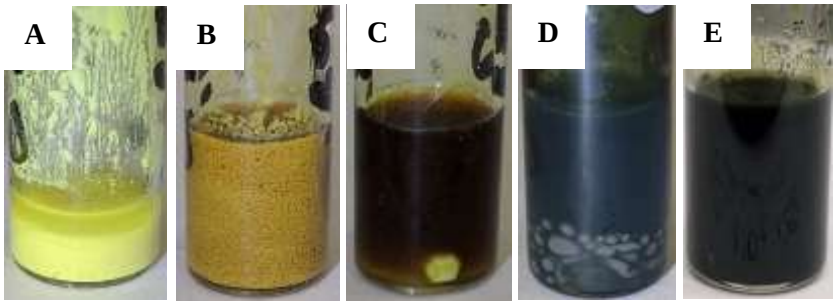


Figure 4: 3-Step-1-Pot Tandem Sequence: (a) SnAr, (b) Suzuki in Progress, (c) Completed Suzuki, (d) Nitro Reduction In Progress, (e) Completed Nitro Reduction

1.9 Conclusions

Carbonyl iron powder (CIP), a readily available and inexpensive material, has been identified as a valuable reagent for nitro group reduction. These reactions are conducted under environmentally responsible conditions, and possess several advantages over many existing methods. This new technology relies on the one element, iron, among the transition metals, that is both of great synthetic value and yet, is not endangered. The procedure requires no specialized equipment or reagents, and avoids troublesome pyrophoric conditions common to many existing methods. The method is effective on a wide substrate scope with a very broad functional group tolerance. Both the reagent and the reaction medium are recyclable, and is also scalable and compatible with other classes of reactions conducted in surfactant medium. And while numerous nitro reduction processes exist, including some using iron, there are few of recent vintage which are considerate of sustainability in terms of selection of reagents, energy investment and avoidance of organic solvents as the bulk reaction medium.

1.10 Experimental

1.10.1 General information

A solution of 2 wt % TPGS-750-M / H_2O was prepared by dissolving TPGS-750-M in degassed HPLC grade water and was stored under argon, and connected to a Schlenk manifold. TPGS-750-M was synthesized as previously described[17] and is available from

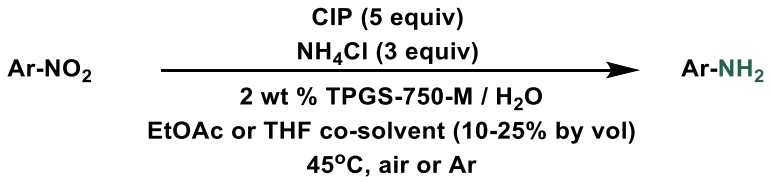
[17] B. H. Lipshutz, S. Ghorai, A. R. Abela, R. Moser, T. Nishikata, C. Duplais, A. Krasovskiy, *J. Org. Chem.* **2011**, *76,* 4379.

Sigma-Aldrich (catalog #733857). All commercially available reagents were used without further purification unless otherwise noted. Thin layer chromatography (TLC) was conducted using Silica Gel 60 F254 plates (Merck, 0.25 mm thick). Flash chromatography was conducted in glass columns using Silica Gel 60 (EMD, 40-63 μm). ^{1}H and ^{13}C NMR were recorded at 25 °C on a Varian Unity Inova 400 MHz, a Varian Unity Inova 500 MHz or on a Varian Unity Inova 600 MHz spectrometers in the following solvents: $CDCl_3$ with residual $CHCl_3$ (^{1}H = 7.26 ppm, ^{13}C = 77.20 ppm), in $(CD_3)_2SO$ with residual $(CH_3)_2SO$ (^{1}H =2.50 ppm, ^{13}C = 39.52 ppm) or in CD_3OD with residual MeOH (^{1}H = 4.78 ppm, ^{13}C = 49.00 ppm) as internal standards. Chemical shifts are reported in parts per million (ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublets, ddd= doublet of doublet of doublets, t = triplet, td = triplet of doublets, q = quartet, sept = septet, m = multiplet), coupling constant (if applicable) and integration. Carbonyl iron powder (CIP) used for reductions was 99.9% purity, R10 grade, with average particle size of 2.5-3.5 μm. This material was stored in air with no special precautions. Ammonium chloride was Fisher brand, ACS grade. Organic solvents such as THF and EtOAc were used as-is without any special precautions such as drying or degassing.

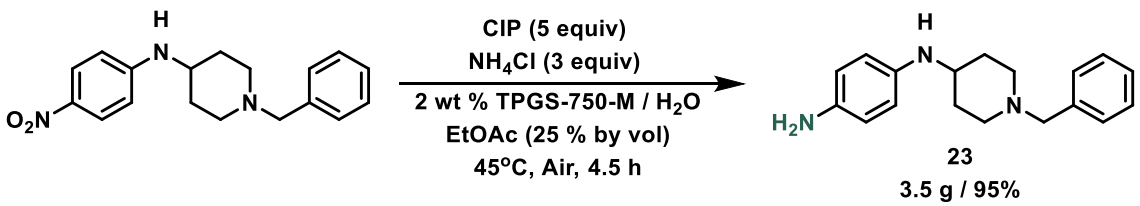
1.10.2 General Procedures

Several different procedures for nitro group reduction are presented. **Procedure A** is to be conducted on small scale reactions (i.e. up to 1.0 mmol), in a 1 dr (4 mL) glass vial, with magnetic stirring. In larger scale reactions (i.e. >1.0 mmol), the magnetic carbonyl iron powder adheres to the stir bar and the reaction proceeds very slowly. Use of overhead

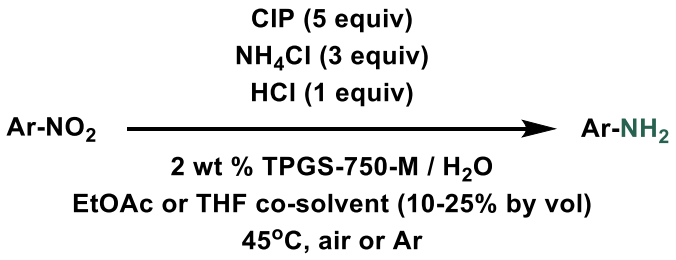
mechanical (**Procedure B**) stirring eliminates this problem and resulted in a 13 mmol/~4 g scale reaction that behaved exactly like the initial 0.5 mmol reaction in terms of reaction time and yield. We recommend testing a small scale (i.e. 0.5 mmol) scale reaction until a satisfactory result is obtained before attempting a larger scale reaction. Amounts of reagents and solvents can be scaled directly without modification of stoichiometry or concentrations. **Procedure C** is for "difficult substrates", which are those which did not give satisfactory conversion using **Procedure A**.



General Procedure A (scale < 1.0 mmol): To a 4 mL vial with a stir bar was added the nitro compound (1.0 equiv), carbonyl iron powder (5.0 equiv.), and NH_4Cl (3.0 equiv). The vial was briefly purged with Argon, and co-solvent was added (if needed). The vial was capped with either a septum or a cap and then stirred in a block reactor at ~300 rpm at 45 ^oC for ~2 min. Next, 2 wt % TPGS-750-M / H_2O solution was added (typical reaction concentration of 0.5 M with respect to nitro compound), and the vial was placed back in the 45 ^oC block reactor and stirred at ~300 rpm until completion.



General Procedure B (scale-up applied to compound 23): To a 100 mL round-bottom flask with 24/40 neck was added NH_4Cl (2.09 g, 39 mmol, 3 equiv), carbonyl iron powder (3.63 g, 65 mmol, 5 equiv), and finely ground nitro compound (4.05 g, 13.0 mmol, 1 equiv). The flask was fitted with a mechanical stirrer with PTFE coated blade, and EtOAc (6.5 mL) was added and stirred at 45 °C for ~2 min. Next, a solution of TPGS-750-M/H_2O 2 wt % (19.5 mL) was added via a syringe and the reaction was stirred at 45 °C until completion (4.5 h). The reaction was filtered via a Buchner funnel with a layer of Celite and extracted with EtOAc. The organic phase was washed with brine (note: TPGS-750-M appears in the NMR spectrum as a PEG peak at ~3.63 ppm. A wash with water, brine, or dilute EDTA solution eliminates this peak. If removal of TPGS-750-M isn't necessary, this wash can be omitted). The organic layer was then dried with anhydrous Na_2SO_4 and filtered through a short plug of silica gel (fritted funnel with ~2" silica gel – small portion of 10/90 MeOH/DCM). The product was concentrated under vacuum to yield a dark red solid (3.48 g/~95%).



General Procedure C (difficult compounds): Into a 4 mL vial with a stir bar was added the nitro compound (1.0 equiv), carbonyl iron powder (5.0 equiv.), and NH_4Cl (3.0 equiv). The vial was vial was briefly purged with argon, then TPGS-750-M/H_2O was added (2 wt % solution to [0.5 M]). Co-solvent and concentrated HCl (1.0 equiv) were added

sequentially via syringe. The vial was capped with either a septum or a cap and then stirred in a block reactor at ~300 rpm until completion. 100 μL of a saturated $NaHCO_3$ solution was added to the reaction and stirred briefly, then followed by the workup.

Workup: The reaction workup typically involves **(1)**, dilution of the reaction mixture with ethyl acetate and filtration through Celite, although the reaction can be extracted directly in the vessel (**2**). Direct extraction without prior filtration frequently causes emulsions, therefore **(1)** is the preferred workup.

(1) ~0.5 mL of EtOAc was added to the vial and stirred briefly, then the contents of the vial were filtered through ~1 cm of Celite in a pipette and rinsed with EtOAc (Note: filtration without prior addition of EtOAc has been found to be more difficult/slow). Next, the combined organic extracts were washed vigorously with ~1 mL of water to remove residual TPGS-750-M (Note: the water wash for removal of TPGS-750-M is optional, if surfactant will be used in the next step of the synthesis, this may be uncessary). The organic phase was dried with anhydrous Na_2SO_4 and then filtered through ~5 cm of silica gel in a pipette and the silica rinsed with a solvent of appropriate polarity to elute the product. The solvent was removed by rotary evaporator and the product concentrated under vacuum until constant mass.

(2) After reaction completion, ~0.5 mL of EtOAc was added to the vial, stirred briefly and allowed to settle. Either centrifuging or placing a magnet against the bottom of the vial helps pull solids to the bottom (for difficult emulsions, the vial can be gently heated). The

organic layer was removed via pipette, and extraction was repeated as necessary. Drying and purification was conducted in the same manner as **(1)**.

Recycle Studies

Either TPGS-750-M alone, or TPGS-750-M and carbonyl iron powder can be recycled.

Recycling of aqueous TPGS-750-M solution:

After following procedure A, the content of the vial was filtered through a pad of Celite (~5 mm of Celite in a pipette) and rinsed with EtOAc. The organic layer was separated and the Celite was rinsed again with EtOAc, which was used to further extract the aqueous phase. Organic extracts were combined and concentrated under vacuum. The aqueous phase was returned to the vial, and any additional TPGS-750-M/H_2O needed to reach the desired volume was added. Next, nitro compound (0.5 mmol), carbonyl Fe powder (2.5 mmol) and NH_4Cl (1.5 mmol) were added, the vial purged with argon, and returned to the block reactor at 45 °C until completion. This procedure was repeated twice.

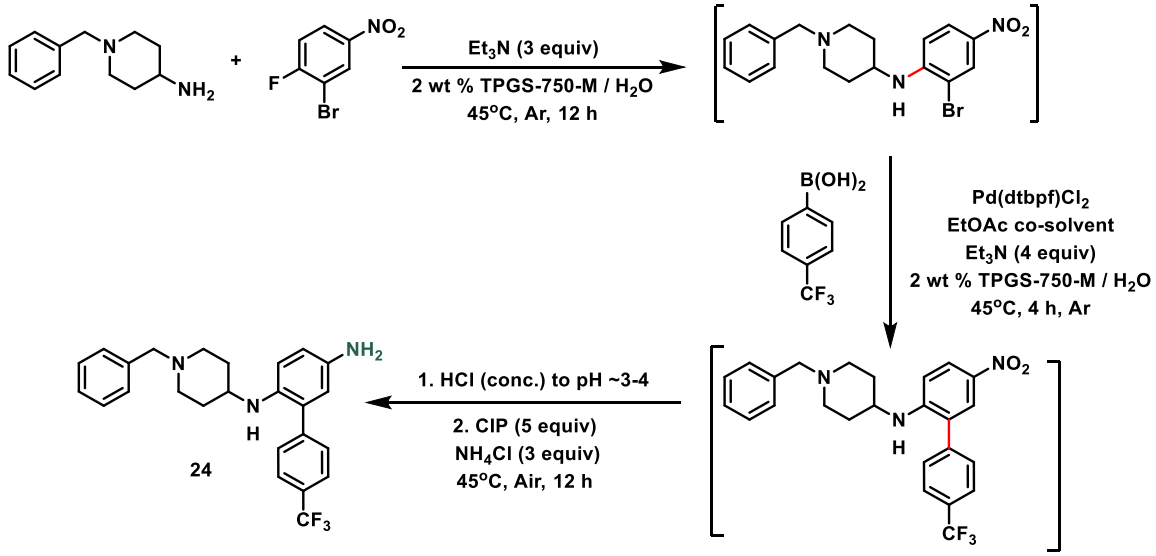
Recycling of both TPGS-750-M and CIP:

After following procedure A, EtOAc was added to the vial, stirred and extracted. The use of either centrifuge or placing a magnet against the vial aided in separating the phases. The organic phase was removed, and the extraction was repeated as needed. Next, NH_4Cl (1.5 mmol) and nitro compound (0.5 mmol) were added to the vial. The vial was purged with argon and placed in the block reactor and stirred at 45 °C until completion. Note: only one

recycle of CIP has been found to be possible, further recycling resulted in incomplete reaction.

Co-solvent Selection: Several co-solvents have been screened for this nitro group reduction reaction. THF has been found to be the most general co-solvent, when added in 10-25% by volume. In one substrate (see scale-up example below), EtOAc at 20-25% was found to be just as effective at THF, and is advantageous because of its later use in extraction as well as avoiding other problems like peroxide buildup during waste storage, etc.. However, EtOAc has proven to be less than optimal for some other substrates. Ethanol and methanol were not found to be particularly useful, as THF and EtOAc produced faster reactions in the screened substrates. Screening between 0-25% co-solvent for both ethyl acetate and THF for a particular substrate is a recommended.

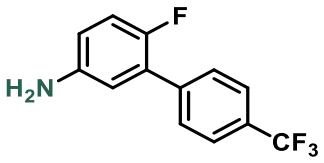
Procedure for the 3-step tandem sequence



To a 4 mL vial with stir bar was added 2-bromo-1-fluoro-4-nitrobenzene (110 mg, 0.5 mmol, 1.0 equiv). The vial was capped with a septum and briefly purged with argon. Via a syringe, 4-amino-1-benzylpiperidine (95.2 mg, 0.5 mmol, 1.0 equiv), Et_3N (152 mg, 1.5 mmol, 3 equiv), and 2 wt % TPGS-750-M / H_2O (0.5 mL) were injected sequentially through the septum. The vial was stirred vigorously at 45 ^oC overnight (12 h), solids must break down to very fine particles before proceeding. To a separate vial with a stir bar was added Pd(dtbpf)Cl_2 (6.5 mg, 0.01 mmol), 4-trifluoromethylphenyl boronic acid (95 mg, 0.5 mmol). The vial was capped with a septum and purged with argon. Next, TPGS-750-M/H_2O (2 wt %; 0.25 mL) and EtOAc (100 uL) was added to the catalyst + boronic acid vial, and stirred to dissolve/suspend. This suspension was transferred to the reaction vial via syringe (while vigorously stirring the reaction vial at 45 ^oC), rinsing with an additional 2 x 100 uL EtOAc, 250 uL TPGS-750-M, and 3 x 100 uL Et_3N. The vial was stirred vigorously at 45 ^oC for 4 h, at which point the solids had dissolved and the reaction was very homogenous in appearance. The septum was then removed and the reaction neutralized with 12 M HCl to a pH of ~4-5 and then NH_4Cl (80 mg, 1.5 mmol) and carbonyl iron powder (140 mg, 2.5 mmol) were added. The vial was capped again and stirred at 45 ^oC overnight (12 h). Upon completion, the reaction was worked up according to General Procedure A, workup (). After purification by silica gel column chromatography (40:60 EtOAc/hexanes), the product **24** was obtained with a global yield of 89% (189.8 mg).

1.10.3 Characterization of Compounds

6-Fluoro-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-amine (**1**)



2-Fluoro-5-nitro-4'-(trifluoromethyl)-1,1'-biphenyl (0.25 mmol) was reduced following general procedure (A) with 20% EtOAc as co-solvent, and work-up (2) to yield, in 4 h, the corresponding amine (**1**) as a reddish brown oil (64.0 mg, quantitative).

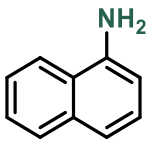
R_f: 0.8 (DCM/MeOH 90:10)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 7.7 Hz, 2H), 7.64 (d, J = 7.2 Hz, 2H), 6.99 (t, J = 9.3 Hz, 2H), 6.78 – 6.70 (m, 1H), 6.70 – 6.62 (m, 1H), 3.70 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 154.4, 152.5, 142.8 (d, J = 2.5 Hz), 139.8, 129.7 (d, J = 32.6 Hz), 129.4 (d, J = 3.1 Hz), 128.1 (d, J = 14.5 Hz), 125.4 (q, J = 3.8 Hz), 123.3, 117.1, 116.9, 116.6 (d, J = 2.6 Hz), 116.3 (d, J = 7.7 Hz).

HRMS: (EI, [$C_{13}H_9F_4N$ + H]) calcd, 256.0749; found m/z 256.0682

Naphthalen-1-amine (**2**)



1-Nitronaphthalene (0.5 mmol) was reduced following general procedure (A) using 25% THF as co-solvent and work-up (1) to yield, in 2 h, the corresponding amine (**2**) as a purple solid (70.3 mg, 98%).

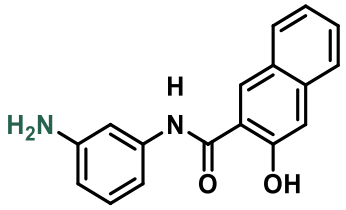
R_f: 0.8 (hexanes/EtOAc 60:40)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 – 7.76 (m, 2H), 7.58 – 7.43 (m, 2H), 7.34 (dt, *J* = 15.1, 7.7 Hz, 2H), 6.80 (d, *J* = 6.7 Hz, 1H), 4.12 (bs, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.1, 134.4, 128.6, 126.4, 125.9, 124.9, 123.7, 120.8, 119.0, 109.7.

mp 42-43 °C (lit. 47-49 °C).[18]

N-(3-Aminophenyl)-3-hydroxy-2-naphthamide (**3**)



3-Hydroxy-*N*-(3-nitrophenyl)-2-naphthamide (0.5 mmol) was reduced following procedure (A) with 10% THF as co-solvent and work-up (1) to yield, in 9 h, the corresponding amine (**3**) as a white solid (112.0 mg, 80%).

R_f: 0.3 (hexanes/EtOAc 60:40)

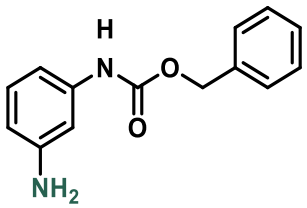
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.52 (s, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.32 (s, 1H), 7.08 (t, *J* = 2.1 Hz, 1H), 7.01 (t, *J* = 7.9 Hz, 1H), 6.85 (dd, *J* = 7.7, 1.9 Hz, 1H), 6.36 (dd, *J* = 7.9, 2.0 Hz, 1H), 5.17 (bs, 2H), 3.38 (bs, 2H).

^{13}C NMR (101 MHz, $(CD_3)_2CO$) δ 165.3, 153.9, 139.0, 135.8, 130.5, 129.1, 128.8, 128.1, 126.9, 125.8, 123.8, 121.6, 110.6, 110.2, 108.3, 106.1, 39.5.

[18] Lombardi, C.; Day, J.; Chandrasoma, N.; Mitchell, D.; Rodriguez, M. J.; Farmer, J. L.; Organ, M. G. *Organometallics*. **2017**, *36*, 251.

mp 180-183 ºC (lit. 186-190 °C)[19]

Benzyl (3-aminophenyl)carbamate (**4**)



Benzyl (3-nitrophenyl)carbamate (0.1 mmol) was reduced following procedure (A) and work-up (1) to yield, in 12 h, the corresponding amine (**4**) as a pale yellow solid (22.3 mg, 92%).

R_f: 0.72 by TLC w/ 10% MeOH/90% DCM – Ninhydrin: brown spot

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.32 (m, 5H), 7.06 (t, *J* = 8.0 Hz, 1H), 6.97 (bs, 1H), 6.68 – 6.57 (m, 2H), 6.40 (ddd, *J* = 8.0, 2.2, 0.9 Hz, 1H), 5.19 (s, 2H).

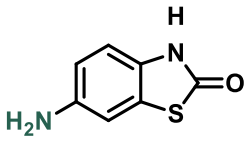
^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4, 138.9, 136.2, 129.9, 128.8, 128.5, 128.4, 110.4, 110.1, 108.8, 105.3, 67.1.

mp 70-72 °C (MTBE) (lit. syrup)[3]

[3]Kelly, M. G.; Kincaid, J.; Duncton, M.; Sahasrabudhe, K.; Janagani, S.; Upasani, R. B.; Wu, G.; Fang, Y., Wei, Z. Amide derivatives as ion-channel ligands and pharmaceutical compositions and methods of using the same. US2006/194801 A1, 2006.

[19] Kogyo, K. Z.; *Chem. Abstr*. **1958**, *61*, 1179.

6-Amino-2-benzothiazolinone (**5**)



6-Nitro-2-benzothiazolinone (0.14 mmol) was reduced following procedure (C) with 20% THF as co-solvent, 1.0 equiv of HCl and work-up (1) to yield, in 4 h, the corresponding amine (**5**) as a off-white to pale yellow powder (20.7 mg, 91%).

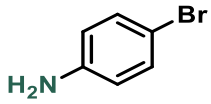
R_f: 0.63 (EtOAc)

^{1}H NMR (600 MHz, CH_3OD) δ 6.82 (d, *J* = 8.5 Hz, 1H), 6.76 (d, *J* = 2.3 Hz, 1H), 6.61 (dd, *J* = 8.6, 2.3 Hz, 1H), 4.51 (s, 0.1H).

^{13}C NMR (101 MHz, CH_3OD) δ 173.4, 145.1, 129.4, 126.1, 115.7, 113.2, 109.8.

mp 203-205 °C (hexanes) (lit. 222-223 °C - H_2O)[20]

4-Bromoaniline (**6**)



1-Bromo-4-nitrobenzene (0.5 mmol) was reduced following procedure (A) with 10% of THF and work-up (1) to yield, in 2 h, the corresponding amine (**6**) as a tan solid (80.2 mg, 92%).

R_f: 0.6 (Et_2O)

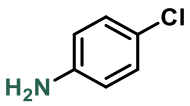
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.6 Hz, 2H), 6.56 (d, J = 8.6 Hz, 2H), 3.57 (s, 2H).

[20] Jacobson; Kwaysser. *Justus Liebigs Ann. Chem*. **1893**, *277*, 244.

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.5, 132.2, 116.9, 110.4.

mp 60-61 °C (lit. 60-61°C)[21]

4-Chloroaniline (**7**)



1-Chloro-4-nitrobenzene (0.50 mmol) was reduced following procedure (C) with 10% THF as co-solvent and work-up (1) to yield, in 12 h, the corresponding amine (**7**) as a tan solid (52.3 mg, 82%).

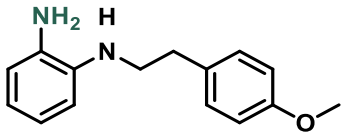
R_f: 0.3 (Hexanes/EtOAc 60:40)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, J = 8.7 Hz, 2H), 6.60 (d, J = 8.7 Hz, 2H), 3.64 (bs, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.1, 129.2, 123.3, 116.4.

mp 65-66 °C (lit. 63-65 °C)[22]

N-(4-Methoxyphenethyl)benzene-1,2-diamine (**8**)



[21] Keenan, C. S.; Murphree, S. S. *Synth.Comm.* **2017**, *47*, 1085.

[22] Noshita, M.; Shimizu, Y.; Morimoto, H.; Ohshima, T. *Org. Lett.* **2016**, *18*, 6062.

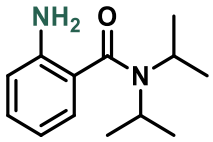
N-(4-Methoxyphenethyl)-2-nitroaniline (0.25 mmol) was reduced following procedure (A) with 25% THF as co-solvent and work-up (1) to yield, in 5 h, the corresponding amine (**8**) as a red oil (61.4 mg, quantitative).[23]

R_f: 0.5 (hexanes/EtOAc 60/40)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.5 Hz, 2H), 6.87 – 6.81 (m, 1H), 6.72 (m, 3H), 3.82 (s, 1H), 3.37 (t, J = 7.1 Hz, 2H), 3.29 (bs, 2H), 2.93 (t, J = 7.0 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 137.7, 134.4, 131.6, 130.0, 129.8, 120.8, 118.8, 116.6, 114.1, 114.0, 112.0, 55.4, 45.7, 35.0.

2-Amino-*N*,*N*-diisopropylbenzamide (**9**)



2-Amino-*N*,*N*-diisopropylbenzamide (0.50 mmol) was reduced following procedure (A) with 20% of THF as co-solvent and work-up (1) to yield, in 5 h, the corresponding amine (**9**) as a yellow solid (83.0 mg, 94%).

R_f: 0.5 (hexanes/Et_2O 25:75)

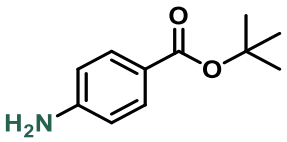
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (td, *J* = 7.9, 1.4 Hz, 1H), 7.02 – 6.95 (dd, *J* = 7.5, 1.1 Hz, 1H), 6.70 (t, *J* = 7.8 Hz, 2H), 3.95 (bs, 2H), 3.73 (bs, 2H), 1.34 (s, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.4, 144.4, 129.6, 126.1, 123.9, 117.8, 116.6, 21.0.

[23] Zellner, H.; Zellner, G. *Helvetica Chimica Acta*, **1966**, *49*, 913.

mp 87-90 °C (lit. 105-106 °C)[24] (lit. oil)[25]

t-Butyl 4-aminobenzoate (**10**)



t-Butyl 4-nitrobenzoate (0.44 mmol) was reduced following procedure (A) with 20% of THF as co-solvent and work-up (1) to yield, in 5 h, the corresponding amine (**10**) as a tan solid (85.4 mg, 98%).

R_f: 0.3 (hexanes/EtOAc 60:40)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 2H), 6.60 (d, *J* = 8.5 Hz, 2H), 4.07 (s, 2H), 1.56 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 150.6, 131.5, 121.6, 113.8, 80.1, 28.4.

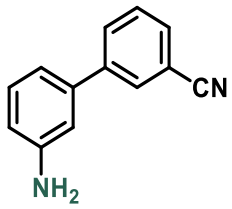
mp 102-104 °C (lit. 106-108 °C)[26]

[24] Murphy, J. A.; Roome, S. J. Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry **1995**, *11*, 1349.

[25] Feng, J; Handa, S; Gallou, F; Lipshutz, B. H. *Angew. Chem. Int. Ed.* **2016**, *55*, 8979.

[26] Venkatachalam; H.; Yu; U. *Synth. Commun.* **2004**, *34*, 1489.

3'-Amino-[1,1'-biphenyl]-3-carbonitrile (**11**)



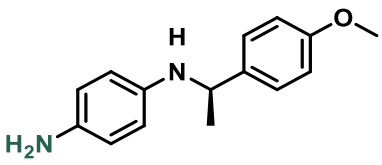
3'-Nitro-[1,1'-biphenyl]-3-carbonitrile (0.25 mmol) was reduced following procedure (A) with 20% of THF as co-solvent and work-up (1) to yield, in 12 h, the corresponding amine (**11**) as a green oil (48.0 mg, 98%).[27]

R_f: 0.5 hexanes/EtOAc (60:40)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 1H), 6.85 (s, 1H), 6.74 (d, *J* = 7.9 Hz, 1H), 3.82 (bs, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.2, 142.7, 140.2, 131.6, 130.8, 130.8, 130.2, 129.6, 119.1, 117.5, 115.2, 113.6, 112.9.

(*R*)-*N*^{1}-(1-(4-Methoxyphenyl)ethyl)benzene-1,4-diamine (**12**)



(*R*)-*N*-(1-(4-Methoxyphenyl)ethyl)-4-nitroaniline (0.50 mmol) was reduced following procedure (A) with 20% of THF as co-solvent and work-up (1) to yield, in 5 h, the corresponding amine (**12**) as a purple solid (122.0 mg, quantitative).

[27] Tang, J.; Liu, F.; Nagy, E.; Miller, L.; Kirby, K. A.; Wilson, D. J.; Wu, B.; Sarafianos, S. G.; Parniak, M. A.; Wang, Z. *J. Med. Chem.* **2016**, *59*, 2648.

R_f: 0.2 (60/40 hexanes/EtOAc)

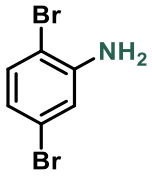
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.53 (d, *J* = 8.6 Hz, 2H), 6.43 (d, *J* = 8.6 Hz, 2H), 4.38 (q, *J* = 6.7 Hz, 1H), 3.79 (s, 3H), 3.38 (bs, 3H), 1.48 (d, J = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.4, 140.6, 137.8, 137.6, 127.0, 116.8, 115.1, 114.0, 55.3, 53.8, 25.2.

mp 71-74 °C

HRMS: (EI,[$C_{15}H_{18}N_2O$ + Na]) calcd. 265.1317; found m/z 265.1269

2,5-Bibromoaniline (**13**)



1,4-Dibromo-2-nitrobenzene (0.25 mmol) was reduced following procedure (A) with 10% of THF as co-solvent and work-up (1) to yield, in 2 h, the corresponding amine (**13**) as a brown solid (63.0 mg, quantitative).

R_f: 0.5 (hexanes/Et_2O 50:50)

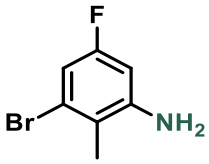
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.4 Hz, 1H), 6.89 (d, *J* = 2.2 Hz, 1H), 6.73 (dd, *J* = 8.5, 2.2 Hz, 1H), 4.13 (bs, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.4, 133.7, 122.3, 121.9, 118.2, 107.9.

mp 40-43 °C (lit. 51-53 °C)[28]

[28] Berrier, C.; Jacquesy, J. C.; Renoux, A. *Bul. Soc. Chim. Fr.* **1990**, 93.

3-Bromo-5-fluoro-2-methylaniline (**14**)



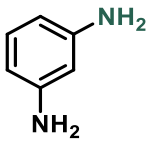
3-Bromo-5-fluoro-2-methylaniline (0.5 mmol) was reduced following procedure (A) with 10% of THF as co-solvent and work-up (1) to yield, in 4 h, the corresponding amine (**14**) as a brown semi-solid (101 mg, quantitative).[29]

R_f: 0.4 (hexanes/EtOAc 80:20)

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.34 (dd, *J* = 10.1, 2.5 Hz, 1H), 3.78 (bs, 2H), 2.20 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.3 (d, *J* = 244.6 Hz), 146.6 (d, *J* = 11.3 Hz), 125.3 (d, *J* = 12.3 Hz), 117.6 (d, *J* = 3.1 Hz), 109.6 (d, *J* = 24.5 Hz), 101.1 (d, *J* = 24.2 Hz), 16.3.

Benzene-1,3-diamine (**15**)



3-Nitroaniline (0.50 mmol) was reduced following procedure (C) with 10% of THF as co-solvent and work-up (1) to yield, in 1 h, the corresponding amine (**15**) as a brown oil (45.2 mg, 84%).

R_f: 0.2 (hexanes/EtOAc 60:40).[30]

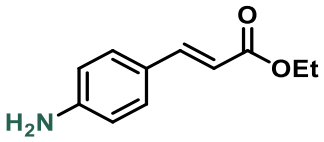
[29] Goldberg, K.; Hamilton, N.; Jones, S.; Jordan, A.; Lyons, A.; Newton, R.; Ogilvie, D.; Waszkowycz, B. Quinazoline Compounds. Patent: WO2015/79251 A1, 2015.

[30] Rai, R. K.; Mahata, A.; Mukhopadhyay, S.; Gupta, S.; Li, P.; Nguyen, K. T.; Zhao, Y.; Pathak, B.; Singh, S. K. *Inorg. Chem.* **2014**, *53*, 2904.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (t, *J* = 7.8 Hz, 1H), 6.13 (d, *J* = 1.8 Hz, 1H), 6.12 – 6.08 (d, *J* = 1.8 Hz, 1H), 6.02 (s, 1H), 3.56 (bs, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 130.3, 106.1, 102.1.

Ethyl-4-aminocinnamate (**16**)



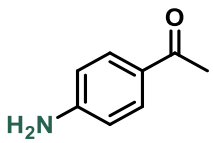
Ethyl-3-(4-nitrophenyl)acrylate (0.14 mmol) was reduced following procedure (C) with 20% of THF as co-solvent, 1.0 equiv of HCl and work-up (1) to yield, in 4 h, the corresponding amine (**16**) as a yellow oil (22.1 mg, 82%).[31]

R_f: 0.77 by TLC 1:1 hexanes/EtOAc – Ninhydrin: dark red spot

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.60 (d, *J* = 15.9 Hz, 1H), 7.40 – 7.32 (m, 2H), 6.66 (d, *J* = 8.5 Hz, 2H), 6.24 (d, *J* = 15.9 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 4.00 (bs, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 167.8, 148.7, 144.9, 132.7, 130.0, 125.0, 115.0, 114.3, 113.9, 60.3, 14.5.

4-Aminoacetophenone (**17**)



[31] Jagadeesh, R. V.; Banerjee, D.; Arockiam, P. B.; Junge, H.; Junge, K.; Pohl, M.; Radnik, J.; Brückner, A.; Beller, M. *Green Chem.* **2015**, *17*, 898.

4-Nitroacetophenone (0.28 mmol) was reduced following procedure (C) with 20% of THF as co-solvent, 1.0 equiv of HCl and work-up (1) to yield, in 2 h, the corresponding amine (**17**) as a white powder (37.2 mg, quantitative).[32]

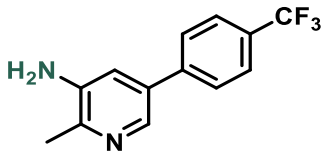
R_f: 0.45 by TLC 1:1 hexanes/EtOAc – Ninhydrin: pink spot

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.6 Hz, 2H), 6.65 (d, *J* = 8.6 Hz, 2H), 4.37 – 3.67 (bs, 2H), 2.50 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 196.6, 151.3, 130.9, 127.9, 113.8, 26.2.

mp 103 °C (MeOH) (lit. 103-107 °C).

2-Methyl-5-(4-(trifluoromethyl)phenyl)pyridin-3-amine (**18**)



2-Methyl-3-nitro-5-(4-(trifluoromethyl)phenyl)pyridine (0.25 mmol) was reduced following procedure (A) with 20% of EtOAc as co-solvent and work-up (1) to yield, in 4 h, the corresponding amine (**18**) as a tan powder(64.0 mg, quantitative).

R_f: 0.50 (100 % EtOAc)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.74 – 7.58 (m, 4H), 7.11 (s, 1H), 3.74 (s, 2H), 2.47 (s, 3H).

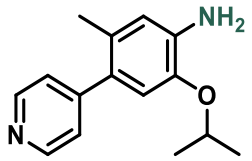
^{13}C NMR (101 MHz, $CDCl_3$) δ 143.9, 142.0, 140.6, 137.8, 134.2, 130.1, 127.4, 126.0, 119.6, 20.3.

mp 160 °C

[32] Zhou, Y.; Zhou, H.; Liu, S.; Pi, D.; Shen, G. *Tetrahedron* **2017**, *73*, 3898.

HRMS: (EI, [$C_{13}H_{11}F_3N_2$ + H]) calcd. 253.0953; found *m/z* 253.0955

3-((3-Aminopyridin-2-yl)amino)propa2-isopropoxy-5-methyl-4-(pyridin-4-yl)aniline (**19**)



4-(5-Isopropoxy-2-methyl-4-nitrophenyl)pyridine (0.25 mmol) was reduced following procedure (A) with 10% of THF as co-solvent and work-up (1) to yield, in 1.5 h, the corresponding amine (**19**) as a yellow solid (61.0 mg, quantitative).

R_f: 0.5 (DCM/MeOH 90:10)

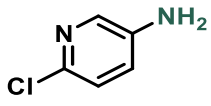
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 1.5 Hz, 1H), 8.58 (d, *J* = 1.5 Hz, 1H), 7.24 (d, *J* = 1.5 Hz, 1H), 7.23 (d, *J* = 1.5 Hz, 1H), 6.68 (s, 1H), 6.63 (s, 1H), 4.50 (sept, *J* = 6.0 Hz, 1H), 3.86 (s, 1H), 2.18 (s, 3H), 1.35 (d, *J* = 6.1 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.3, 149.6, 143.7, 137.8, 128.8, 128.0, 124.6, 117.4, 115.3, 71.3, 22.5, 19.7.

mp 90-92 °C

[17]Yu, L.; Guo, M.; Yang, Q.; Liu, H. Patent: CN105646333 A, **2016**.

6-Chloropyridin-3-amine (**20**)



2-Chloro-5-nitropyridine (0.50 mmol) was reduced following procedure (A) with 10% of THF as co-solvent and work-up (1) to yield, in 2.5 h, the corresponding amine (**20**) as a off-white solid or clear crystals (62.0 mg, 96%).

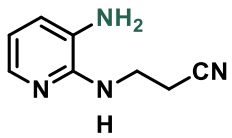
Rf: 0.2 (hexanes/EtOAc 60:40)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 2.7 Hz, 1H), 7.06 (d, *J* = 8.5 Hz, 1H), 6.94 (dd, *J* = 8.5, 3.0 Hz, 1H), 3.72 (bs, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 141.9, 140.2, 136.4, 125.0, 124.2.

mp 58-62 °C (lit. 78-81 °C)[33]

3-((3-Aminopyridin-2-yl)amino)propanenitrile (**21**)



3-((3-Nitropyridin-2-yl)amino)propanenitrile (0.25 mmol) was reduced following procedure (C) with 10% of THF as co-solvent and work-up (1) to yield, in 12 h, the corresponding amine (**21**) as a brown oil (32.5 mg, 81%).[34]

Rf: 0.4 (100% EtOAc)

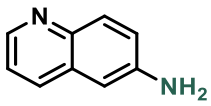
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 5.0, 1.4 Hz, 1H), 6.87 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.57 (dd, *J* = 7.4, 5.1 Hz, 1H), 4.66 (bs, 1H), 3.73 (q, *J* = 6.1 Hz, 2H), 3.24 (bs, 2H), 2.79 (t, *J* = 6.2 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.0, 139.0, 128.8, 122.6, 119.4, 114.5, 37.9, 18.7.

[33] Westland, R. D.; Cooley, R.; Holmes, J. L.; Hong, J. S.; Lin, M. H.; Zwiesler, M. L. *J. Med. Chem.* **1973**, *16*, 319.

[34] Ortho-McNeil Pharmaceutical, Inc. DIPYRIDOIMIDAZOLDERIVATIVES USEFUL IN TREATING CENTRAL NERVOUS SYSTEM DISORDERS, Patent: EP1023291 B1, 2004.

Quinolin-6-amine (**22**)



6-Nitroquinoline (0.25 mmol) was reduced following procedure (C) with 10% of THF as co-solvent and work-up (1) to yield, overnight, the corresponding amine (**22**) as a tan solid (35.5 mg, 98%).

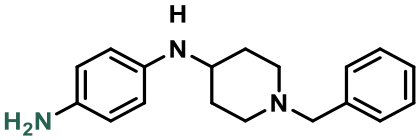
R_f: 0.4 (hexanes/EtOAc 20:80)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (dd, *J* = 4.1, 1.4 Hz, 1H), 7.92 – 7.83 (2xd, *J* = 9.2, 8.2 Hz, 2H), 7.24 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.13 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.86 (d, *J* = 2.4 Hz, 1H), 3.96 (bs, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 146.9, 144.8, 143.5, 133.9, 130.6, 129.9, 121.7, 121.5, 107.5.

mp 90-92 °C (lit. 98-100°C)[2035]

N^1-(1-Benzylpiperidin-4-yl)benzene-1,4-diamine (**23**)



1-Benzyl-N-(4-nitrophenyl)piperidin-4-amine (13.01 mmol) was reduced following procedure (B) with 25% of EtOAc as co-solvent to yield, in 4.5 h, the corresponding amine (**23**) as a red solid (3.48 g, 95 %).

R_f: 0.4 (DCM:MeOH 90:10)

[35] Carta, A.; Palomba, M.; Corona, P. *Heterocycles* **2006**, *68*, 1715.

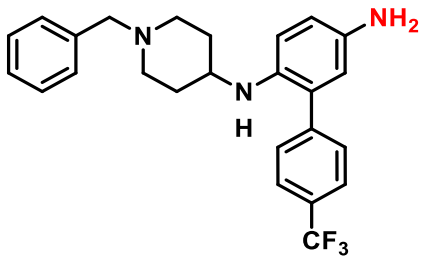
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (d, *J* = 4.4 Hz, 4H), 7.29 – 7.23 (m, 1H), 6.59 (d, *J* = 8.7 Hz, 2H), 6.51 (d, *J* = 8.6 Hz, 2H), 3.53 (s, 2H), 3.28 – 3.11 (m, 3H), 2.85 (d, *J* = 11.7 Hz, 2H), 2.12 (t, *J* = 10.4 Hz, 2H), 2.01 (d, *J* = 10.3 Hz, 2H), 1.43 (q, *J* = 10.3 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 140.1, 138.3, 137.8, 129.2, 128.2, 127.0, 116.9, 115.6, 70.6, 63.1, 52.5, 51.3, 32.7.

mp 30-40 °C

HRMS: (EI, [$C_{18}H_{23}N_3$ + H]) calcd. 282.1970; found 282.1960

N^{2}-(1-Benzylpiperidin-4-yl)-4'-(trifluoromethyl)-[1,1'-biphenyl]-2,5-diamine (**24**)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.9 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 2H), 7.36 – 7.26 (m, 5H), 6.74 – 6.61 (m, 2H), 6.51 (d, *J* = 2.4 Hz, 1H), 3.50 (s, 2H), 3.32 (bs, 2H), 3.22 (m, 1H), 2.75 (d, *J* = 11.4 Hz, 2H), 2.11 (t, *J* = 11.2 Hz, 2H), 1.97 (d, *J* = 12.1 Hz, 2H), 1.34 (q, *J* = 12.4, 10.8 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.6, 137.7, 136.9, 129.8, 129.3, 128.4, 128.4, 127.2, 125.9 (q, *J* = 3.7 Hz), 118.2, 117.0, 114.6, 63.2, 52.3, 51.1, 32.6.

HRMS: (EI, [$C_{25}H_{26}F_3N_3$ + H]) calcd. 426.2157; found *m/z* 426.2163

1.10.4 NMR Spectra

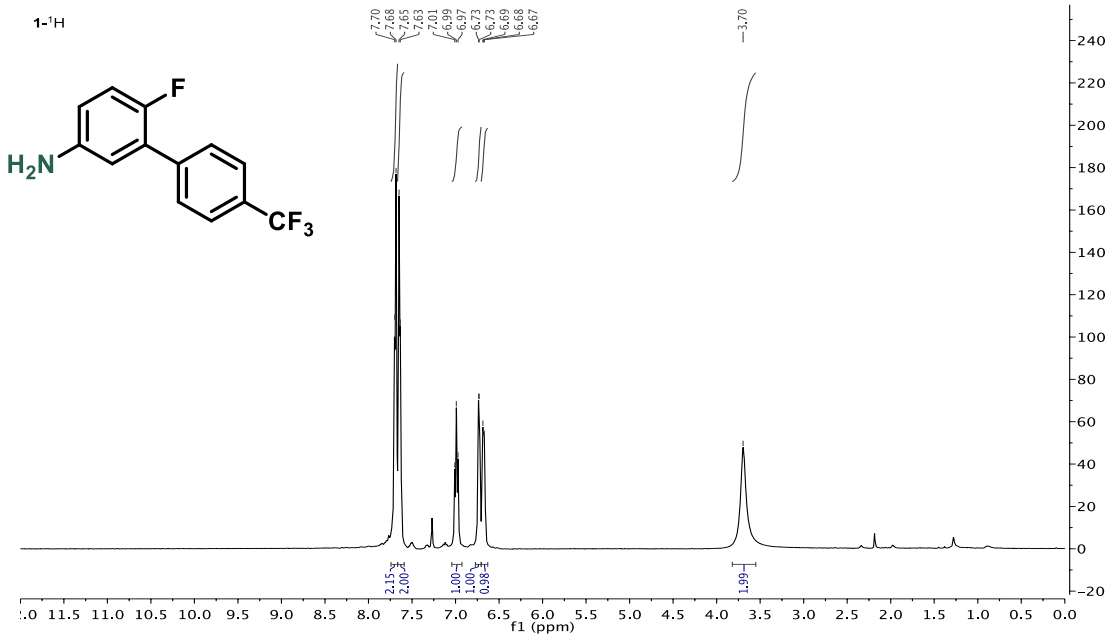


Figure : ^{1}H NMR spectra of 6-fluoro-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-amine (**1**)

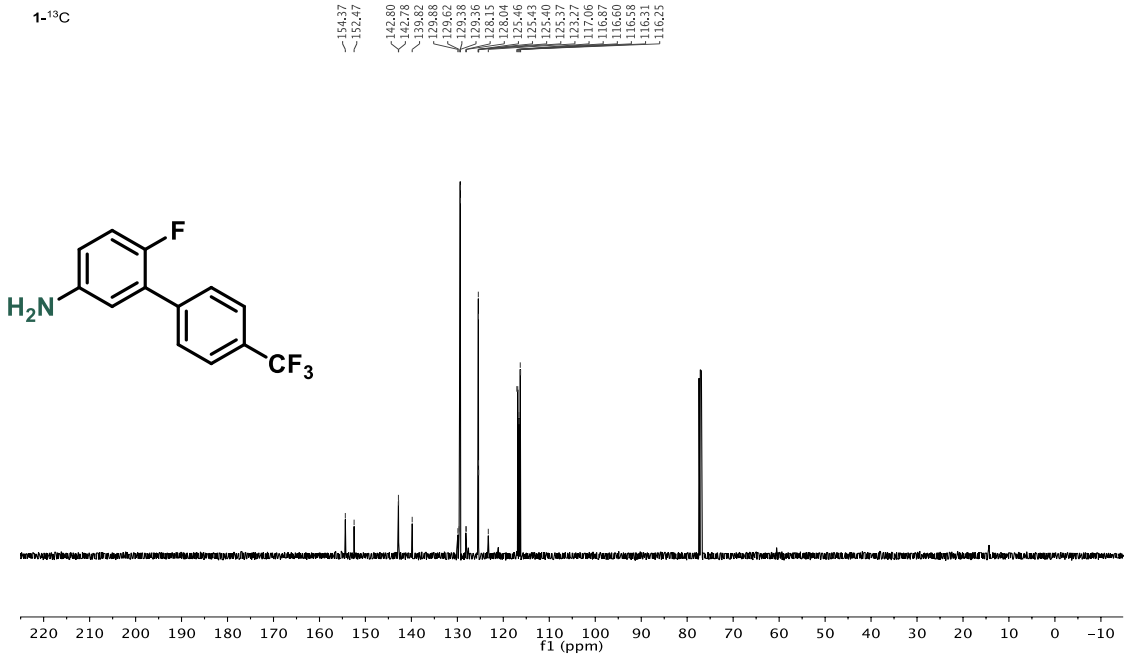


Figure 1: ^{13}C NMR spectra of 6-fluoro-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-amine (**1**)

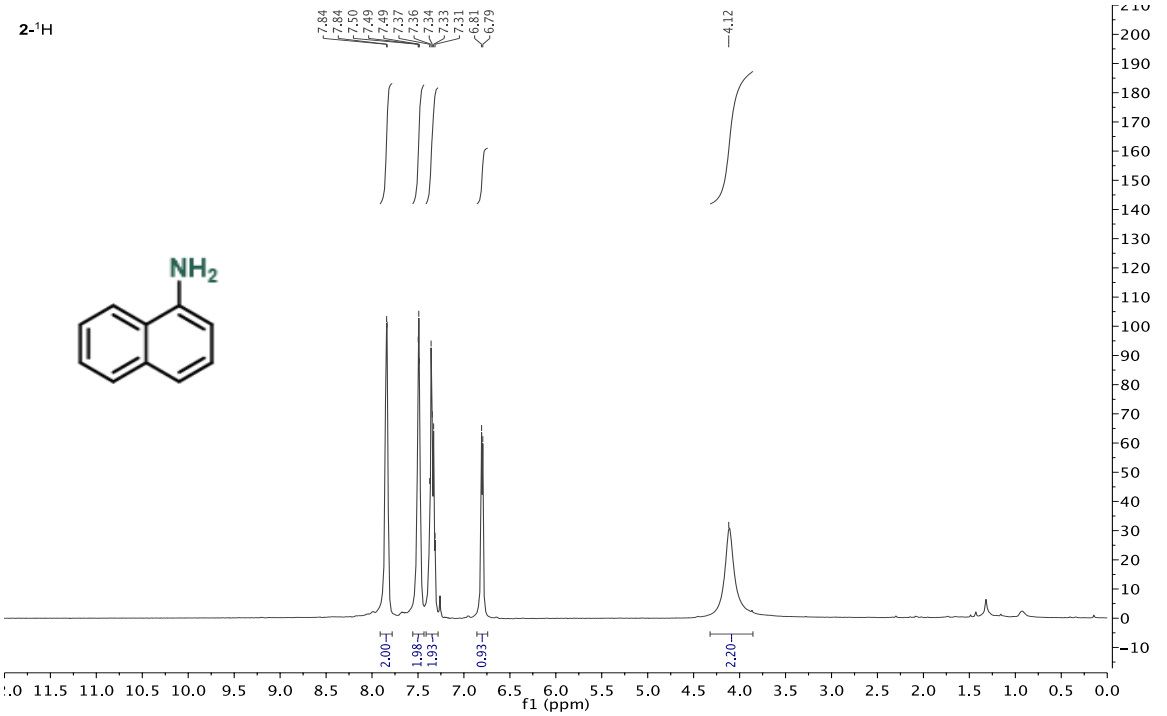


Figure 2: ^{1}H NMR spectra of naphthalen-1-amine (**2**)

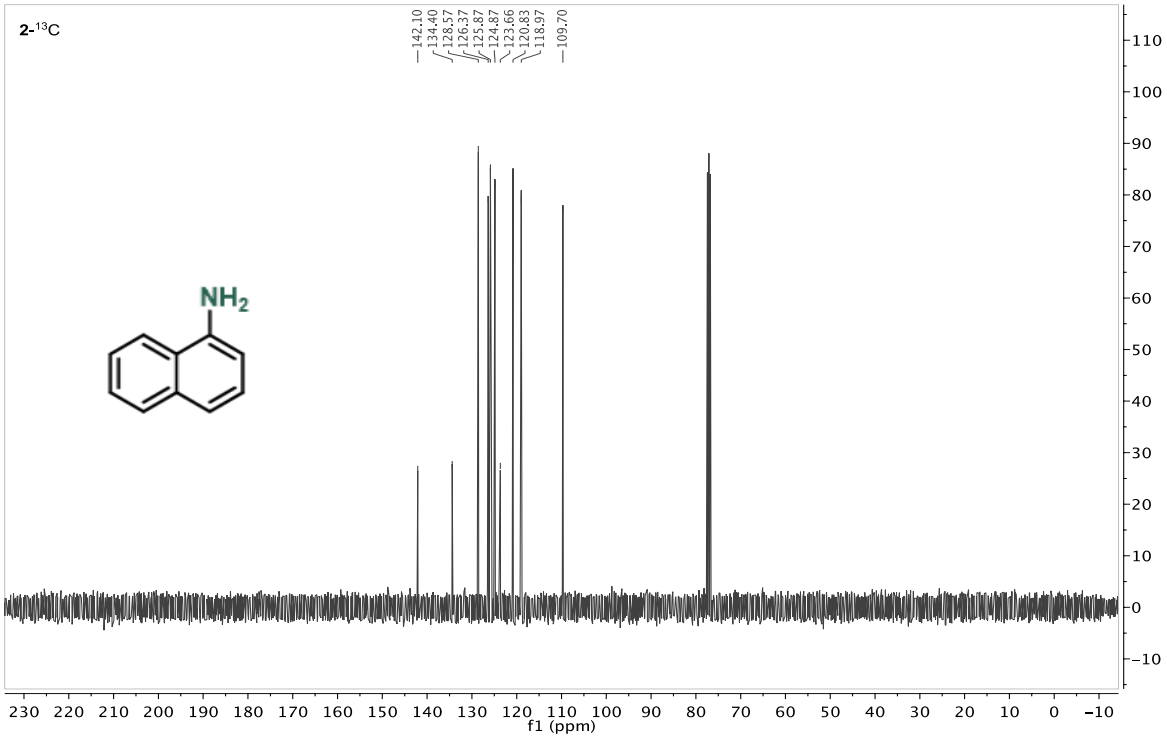


Figure 3: ^{13}C NMR spectra of naphthalen-1-amine (**2**)

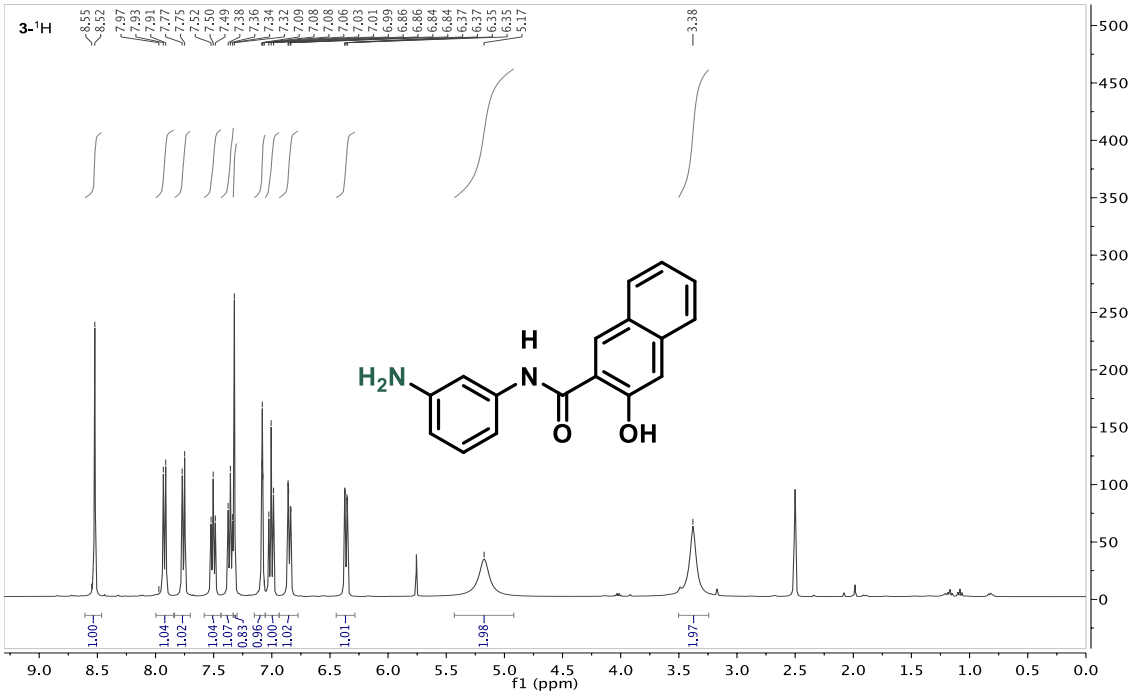


Figure 4: ^{1}H NMR spectra of N-(3-aminophenyl)-3-hydroxy-2-naphthamide (**3**)

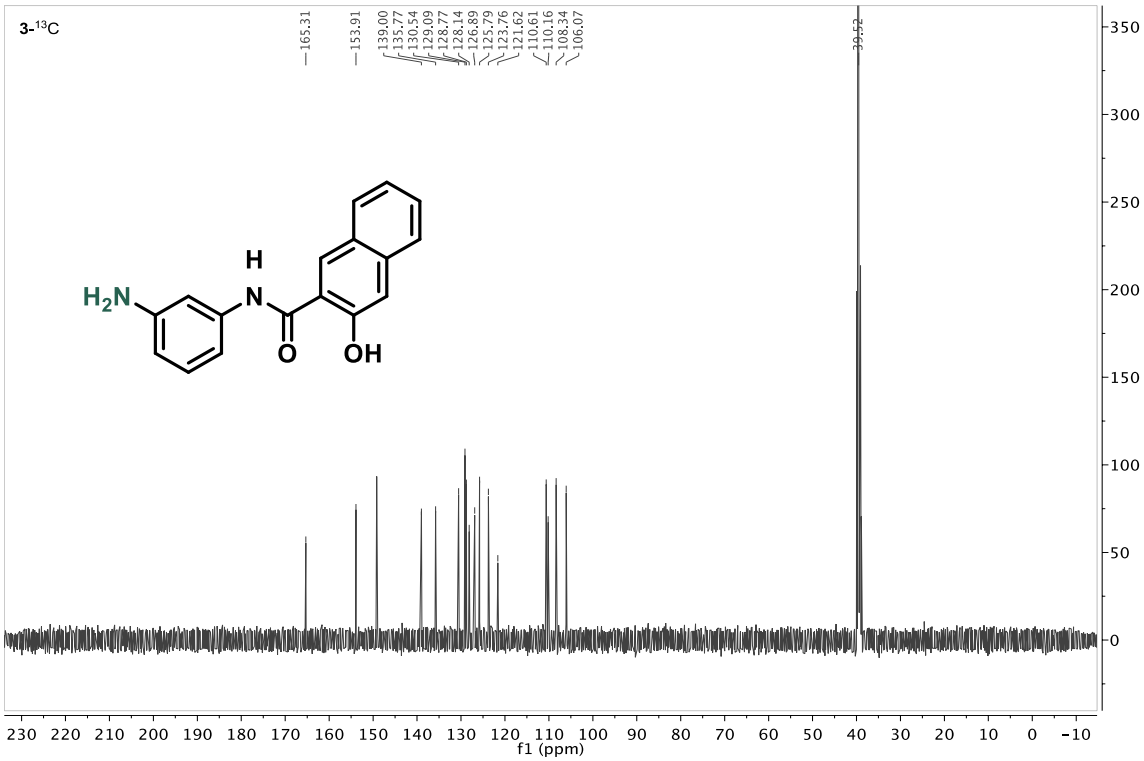


Figure 5: ^{13}C NMR spectra of N-(3-aminophenyl)-3-hydroxy-2-naphthamide (**3**)

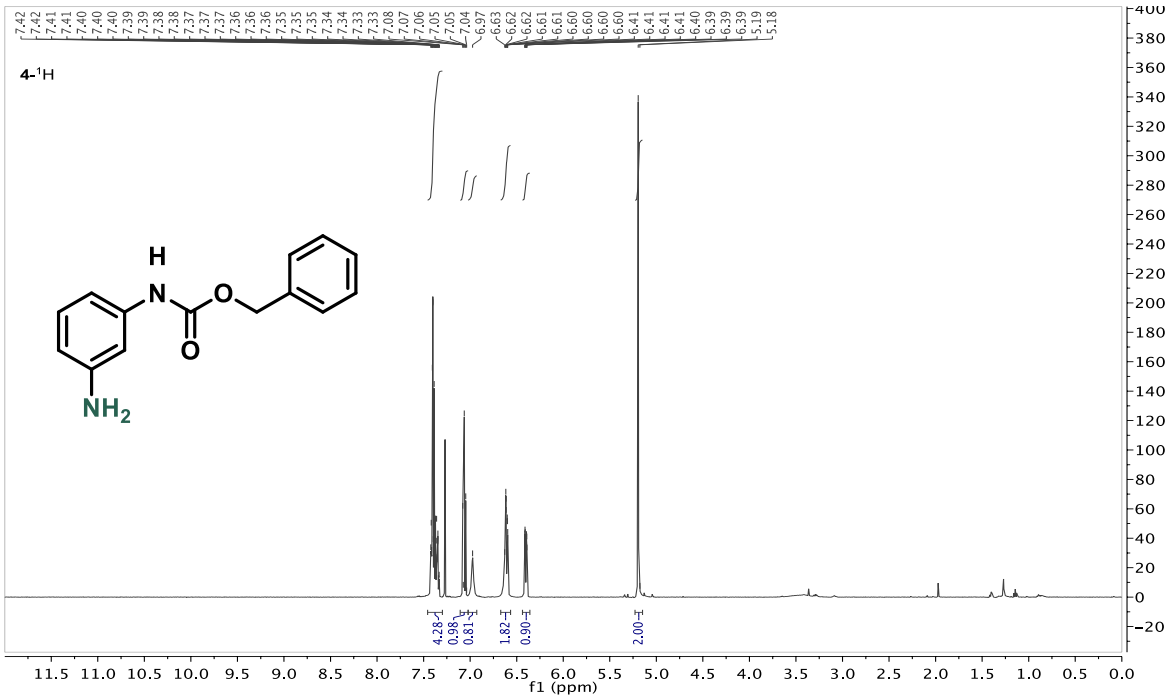


Figure 6: ^{1}H NMR spectra of benzyl (3-aminophenyl)carbamate (**4**)

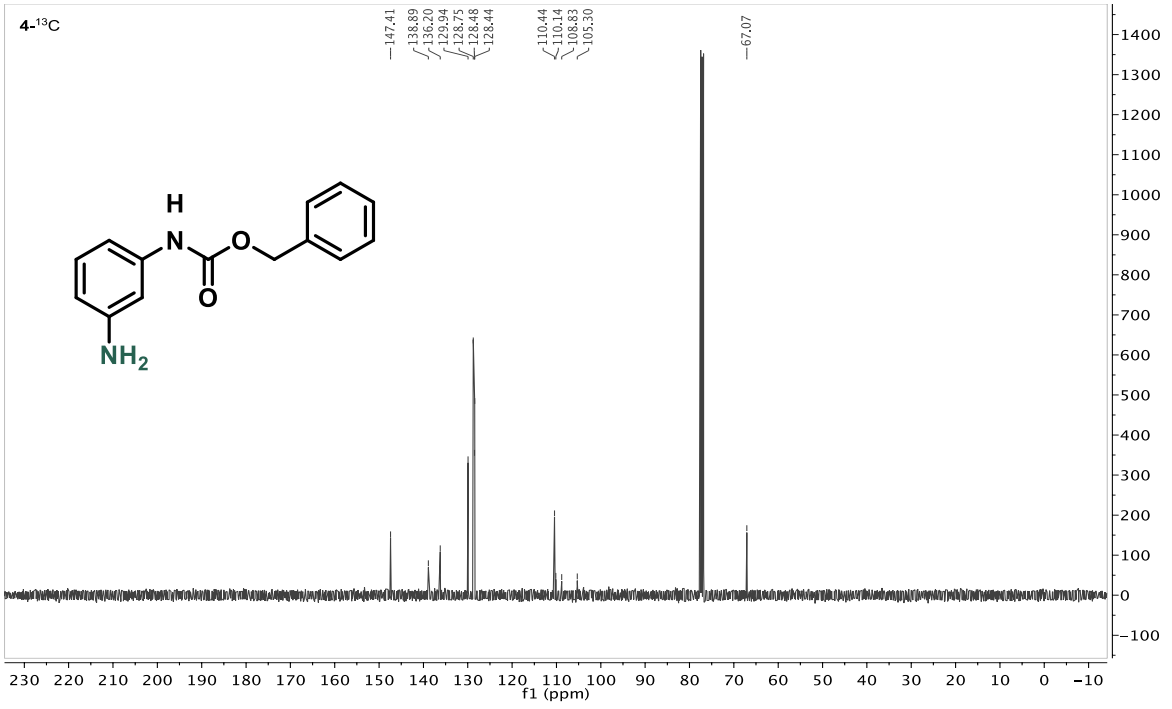


Figure 7: ^{13}C NMR spectra of benzyl (3-aminophenyl)carbamate (**4**)

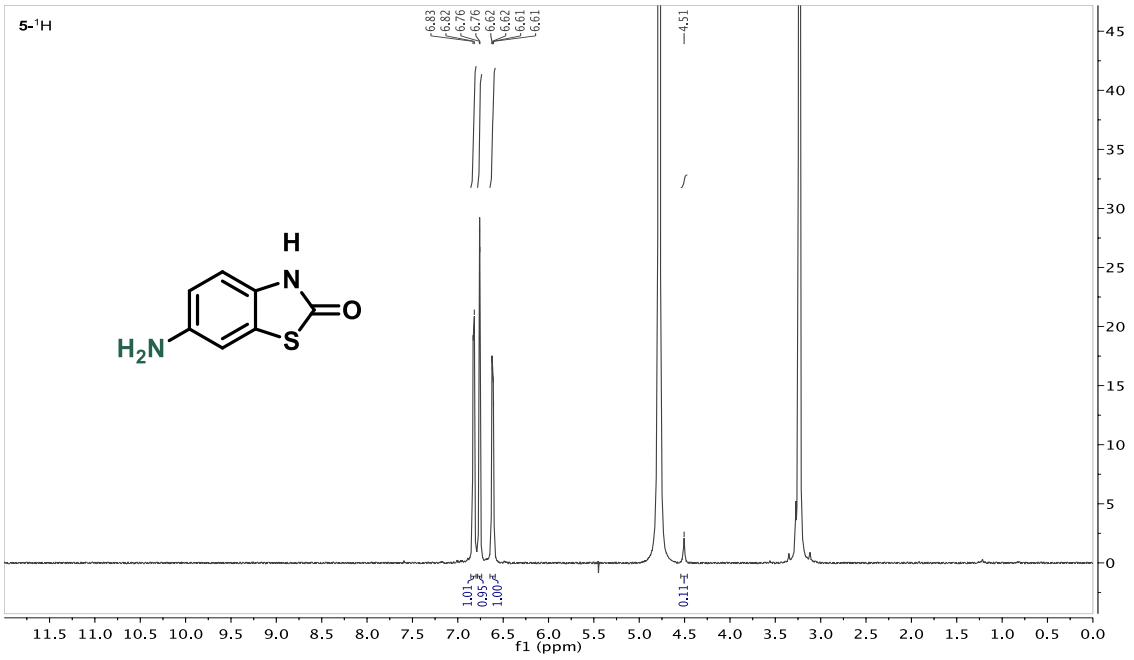


Figure 8: ^{1}H NMR spectra of 6-aminobenzothiazolinone (**5**)

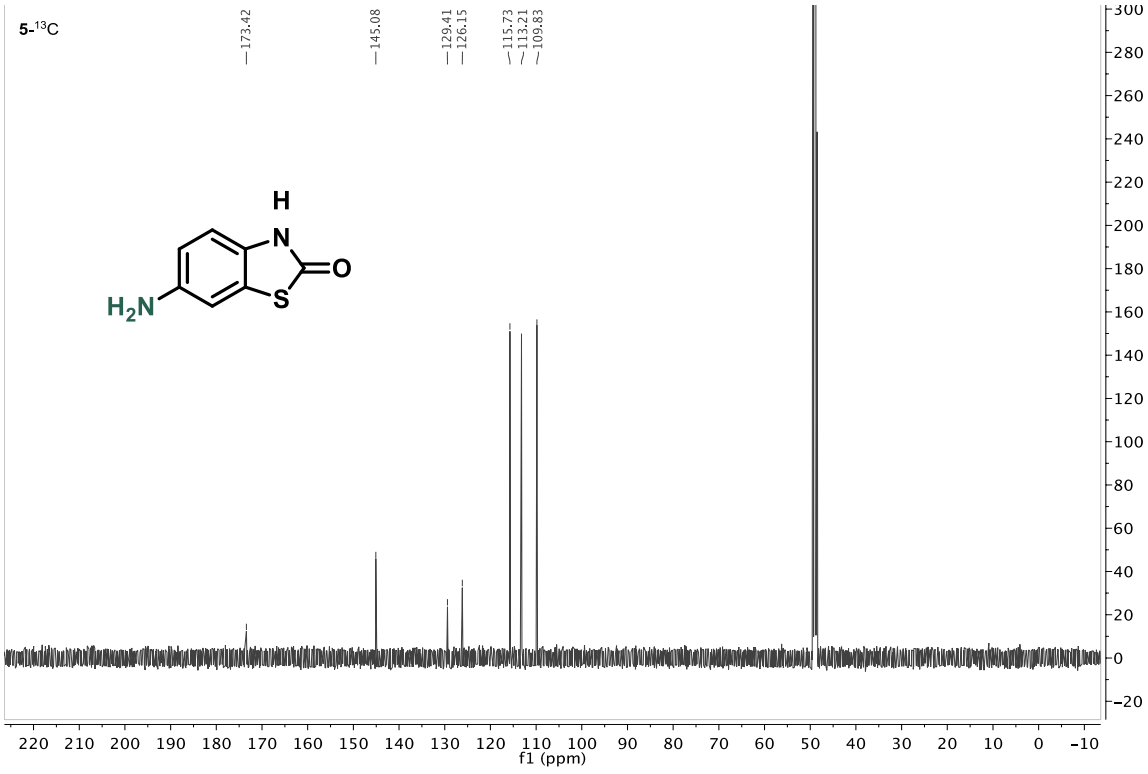


Figure 9: ^{13}C NMR spectra of 6-aminobenzothiazolinone (**5**)

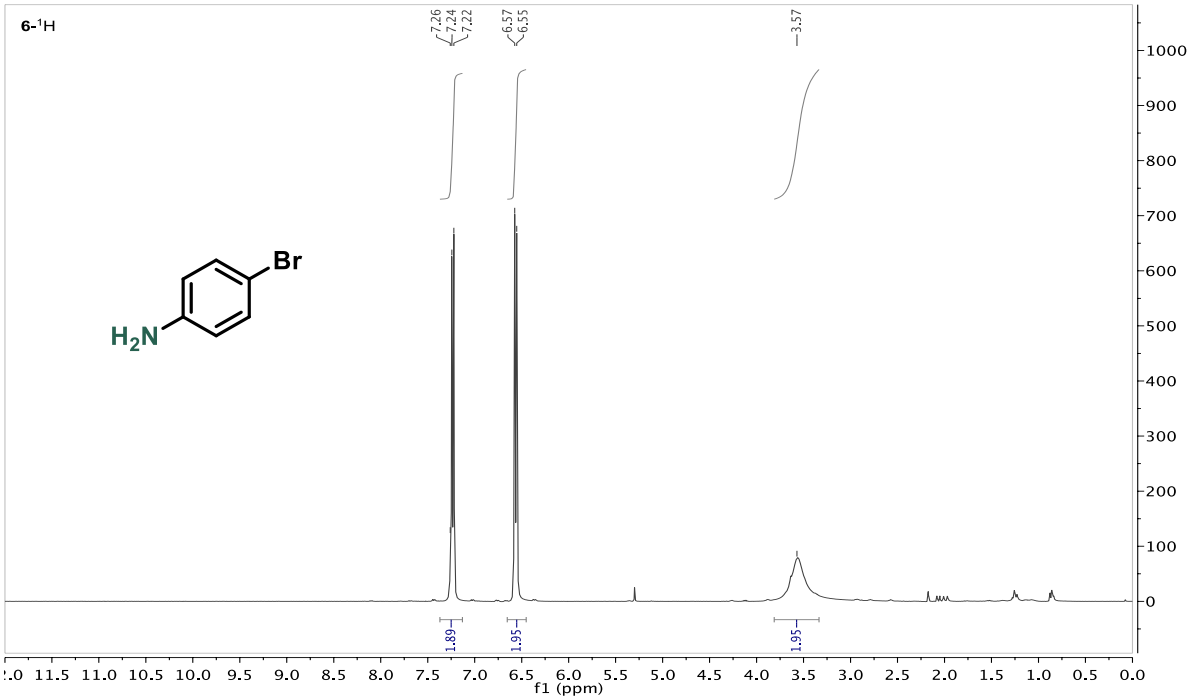


Figure 10: ^{1}H NMR spectra of 4-bromoaniline (**6**)

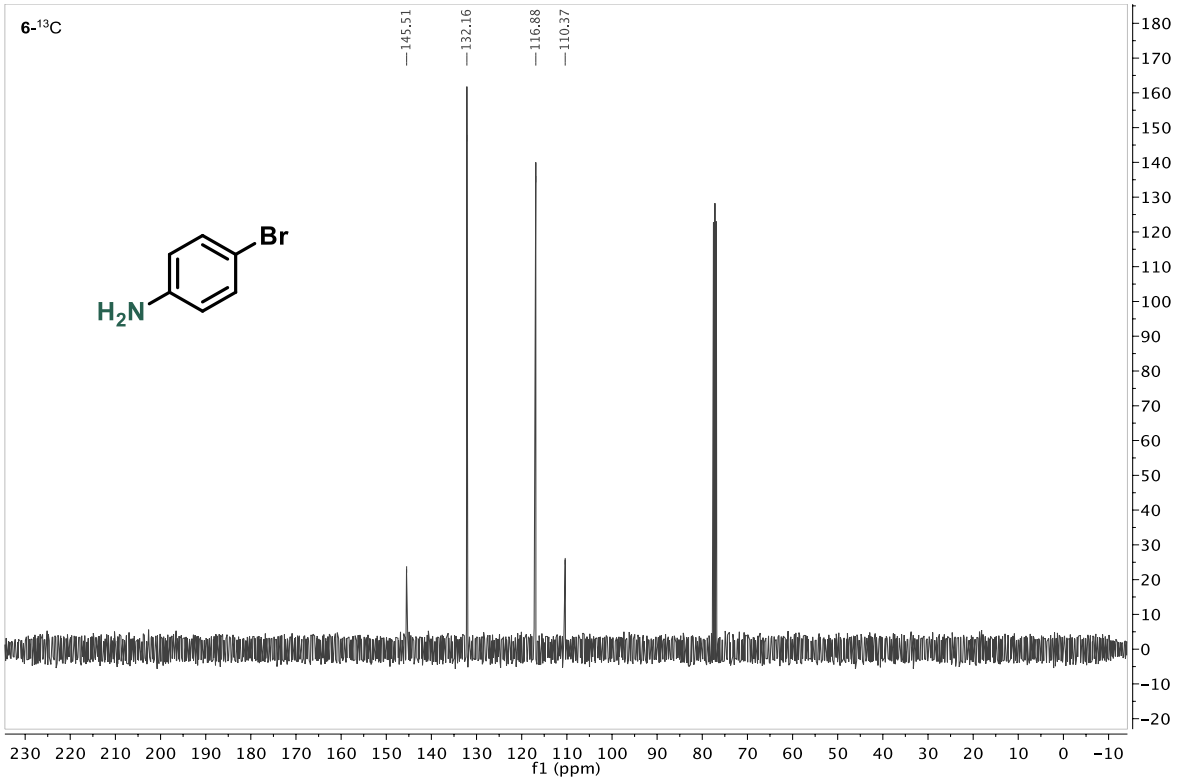


Figure 11: ^{13}C NMR spectra of 4-bromoaniline **(6)**

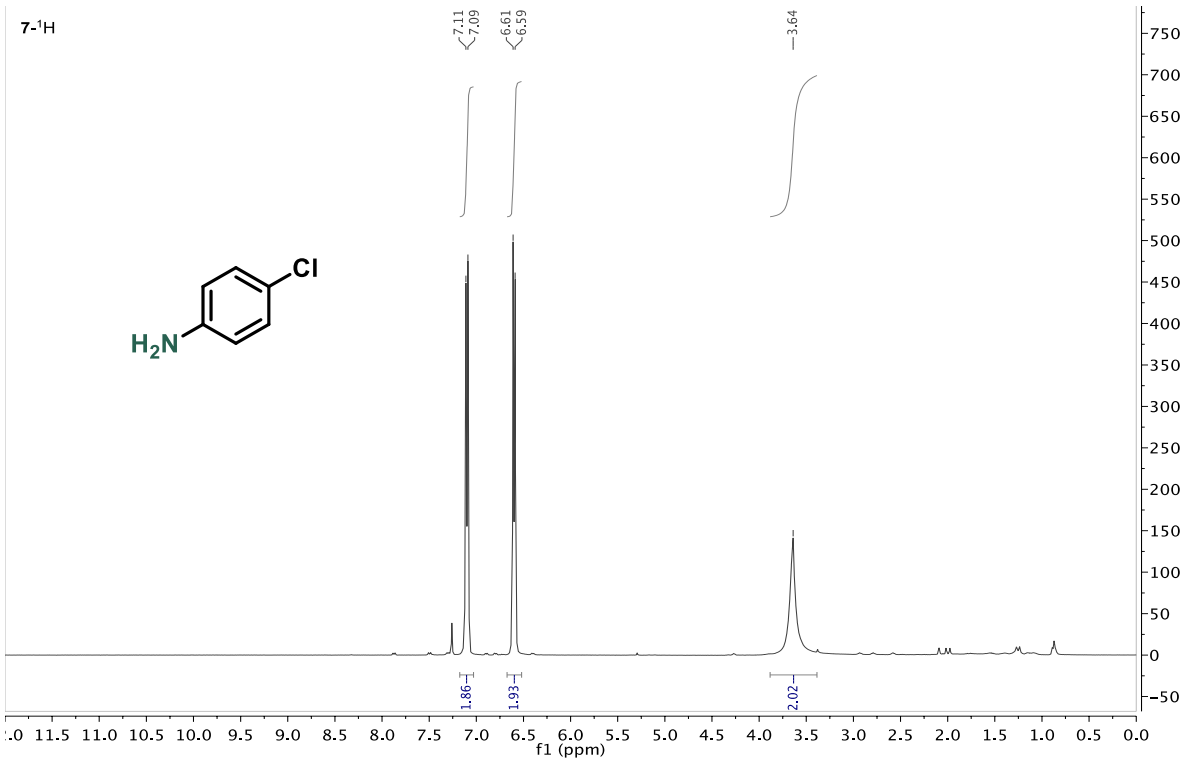


Figure 12: ^{1}H NMR spectra of 4-chloroaniline (**7**)

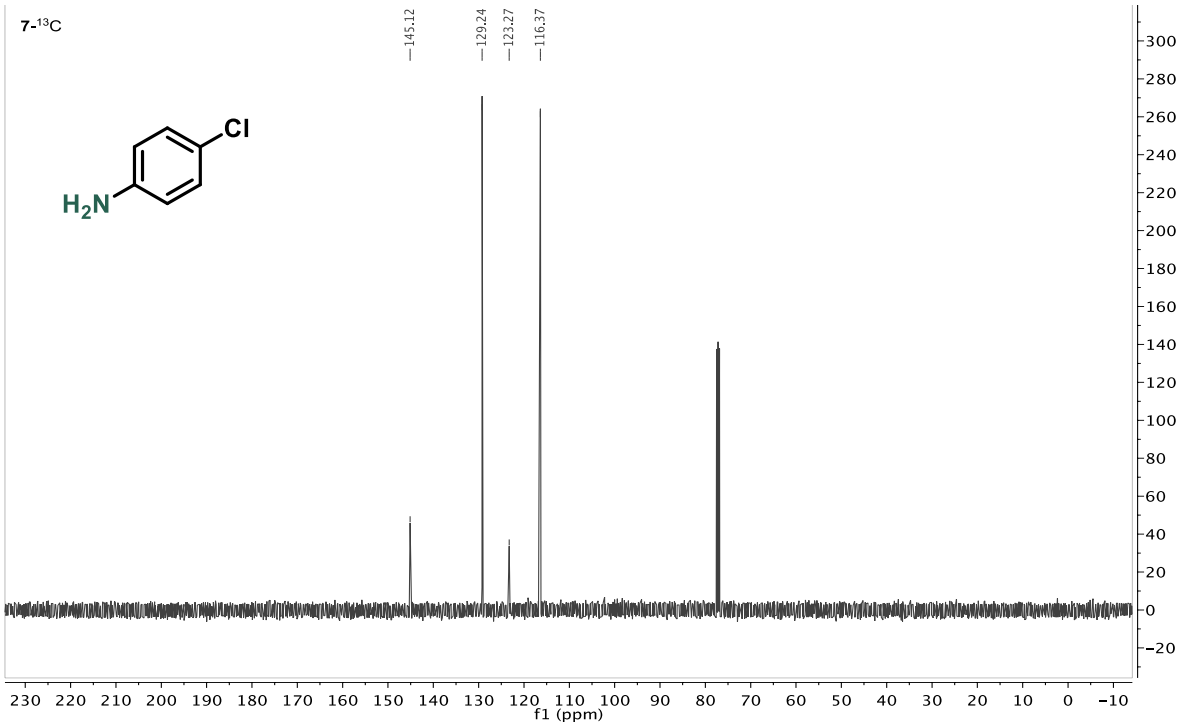


Figure 13: ^{13}C NMR spectra of 4-chloroaniline (**7**)

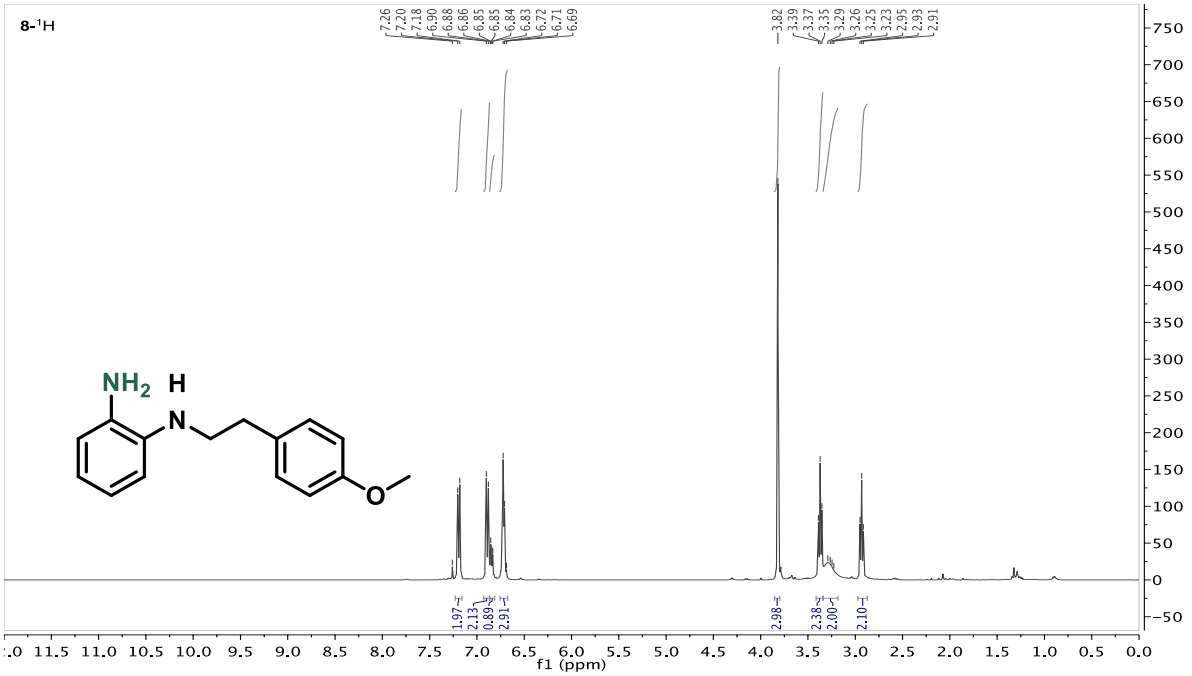


Figure 14: ^{1}H NMR spectra of N-(4-methoxyphenethyl)benzene-1,2-diamine (**8**)

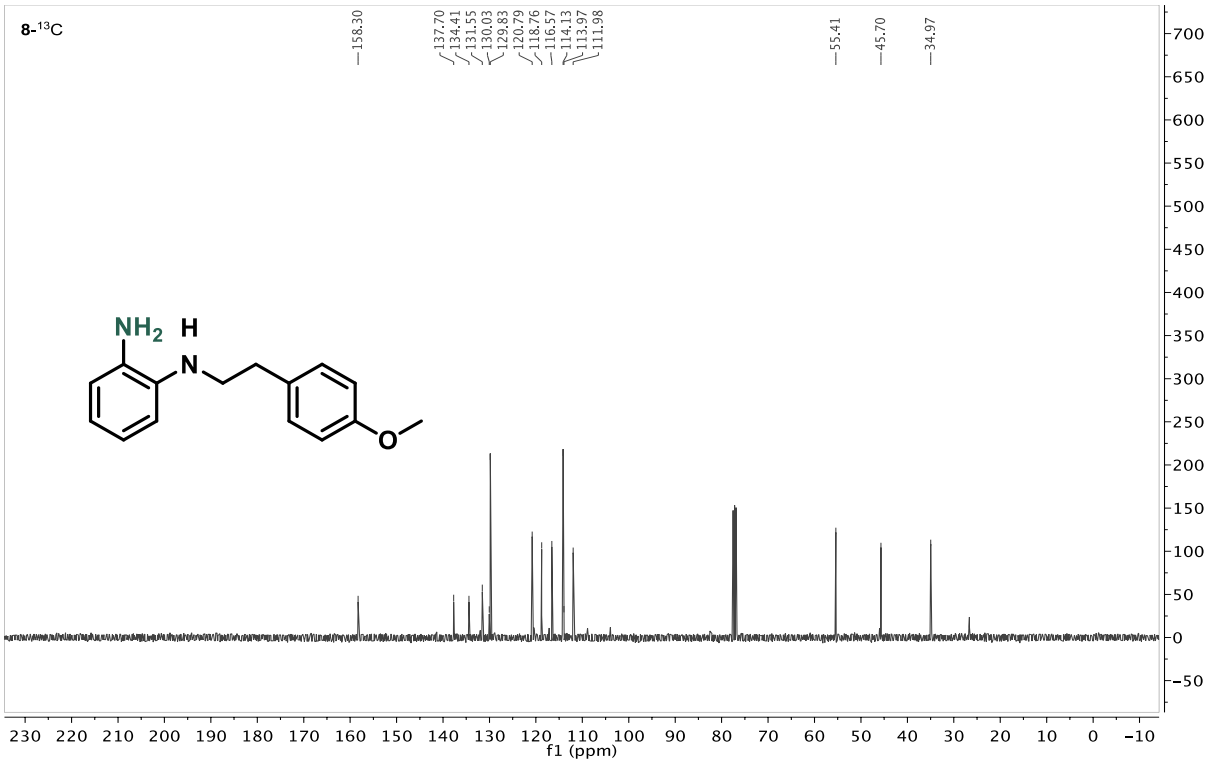


Figure 15: ^{13}C NMR spectra of N-(4-methoxyphenethyl)benzene-1,2-diamine (**8**)

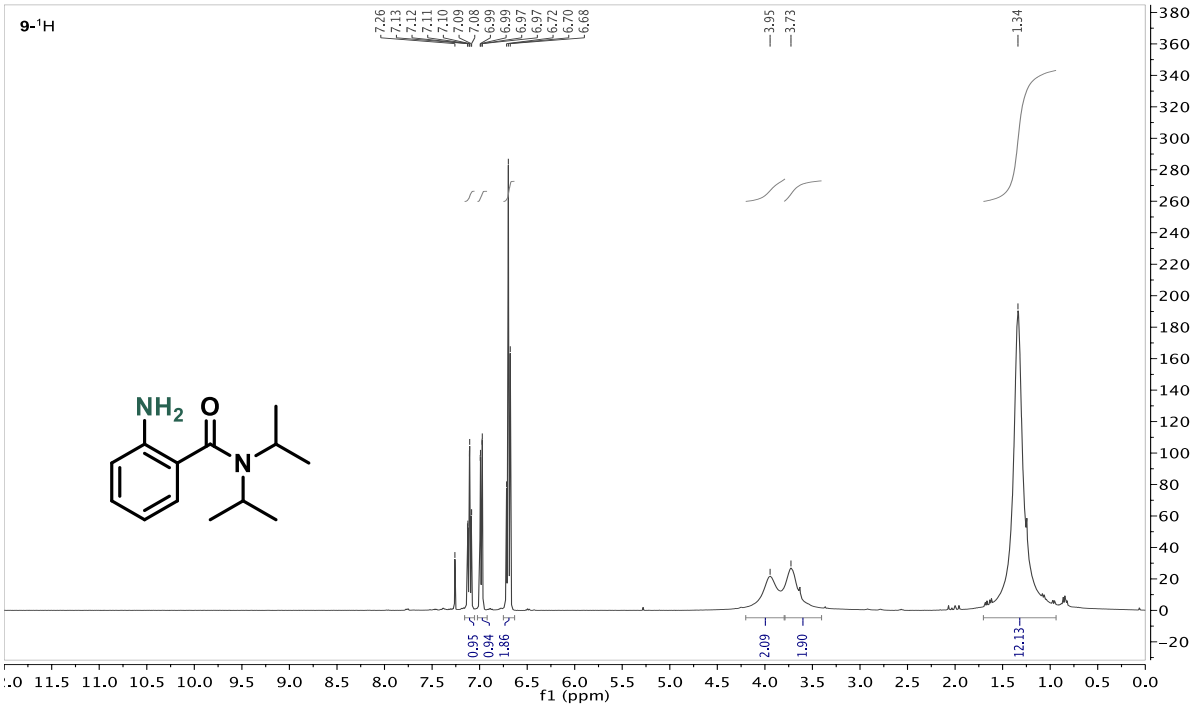


Figure 16: ^{1}H NMR spectra of 2-amino-N,N-diisopropylbenzamide (**9**)

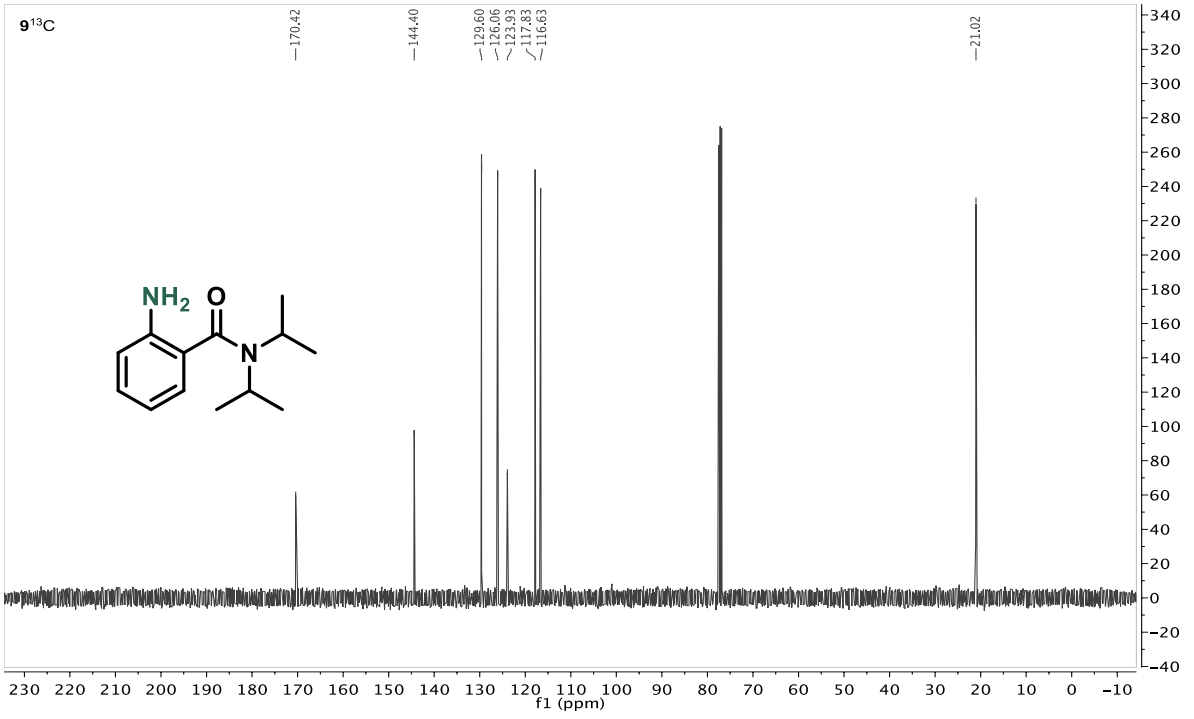


Figure 17:^{13}C NMR spectra of 2-amino-N,N-diisopropylbenzamide (**9**)

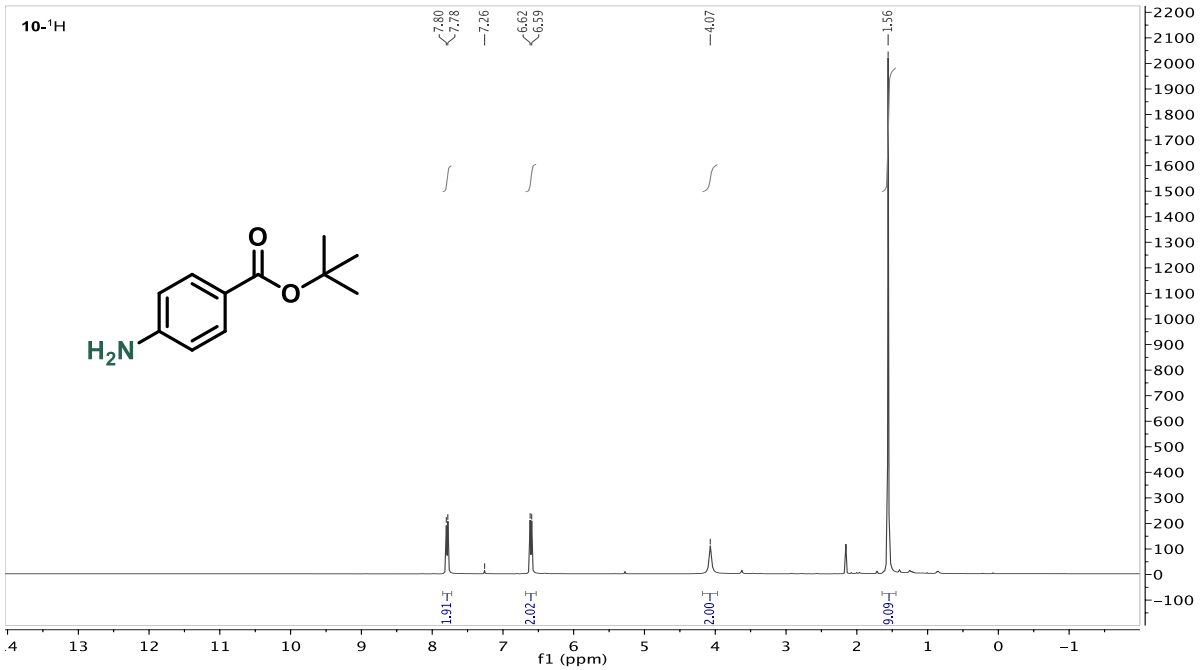


Figure 18: ^{1}H NMR spectra of tert-butyl 4-aminobenzoate (**10**)

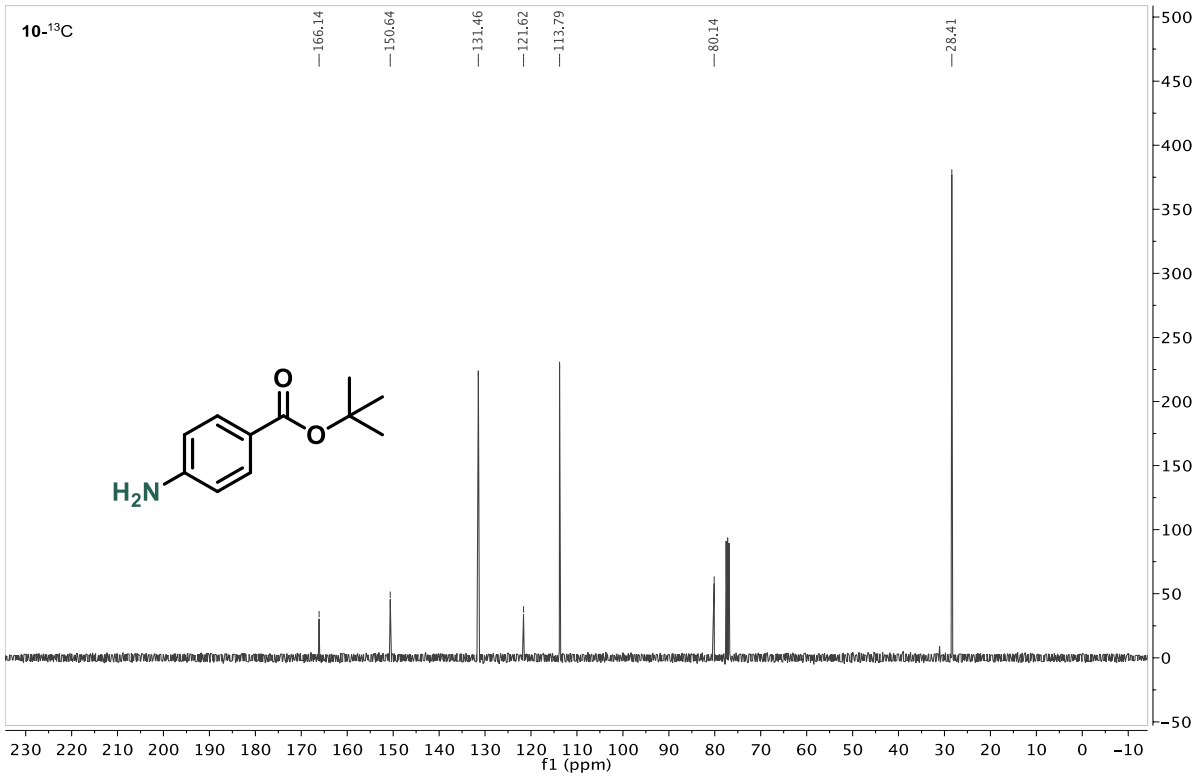


Figure 19: ^{13}C NMR spectra of tert-butyl 4-aminobenzoate (**10**)

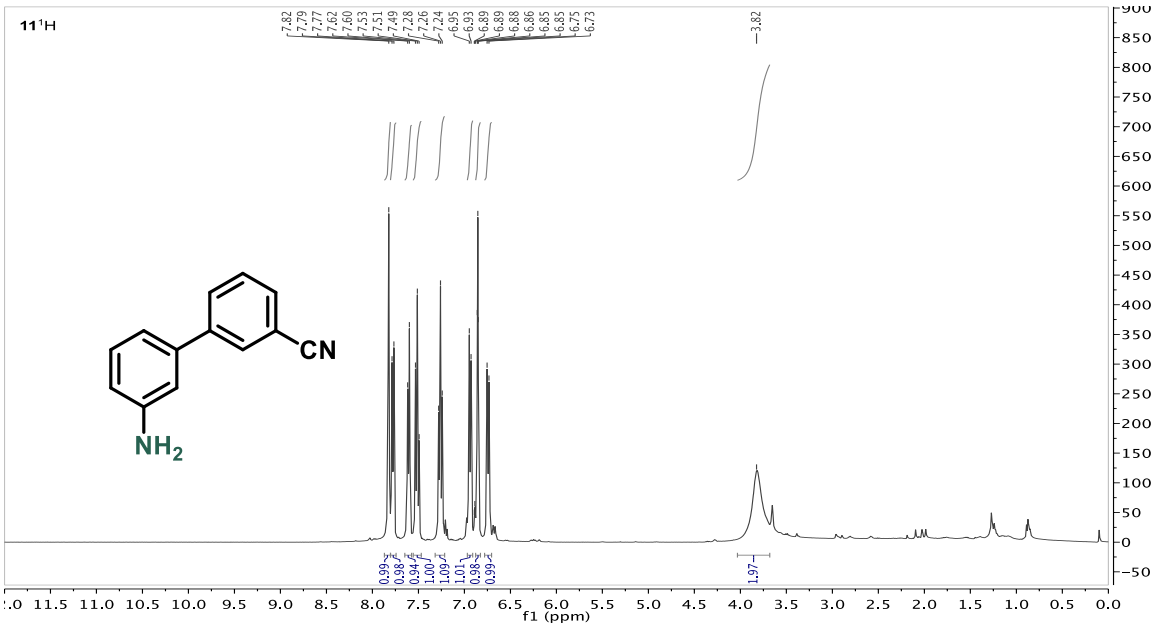


Figure 20: ^{1}H NMR spectra of 3'-amino-[1,1'-biphenyl]-3-carbonitrile (**11**)

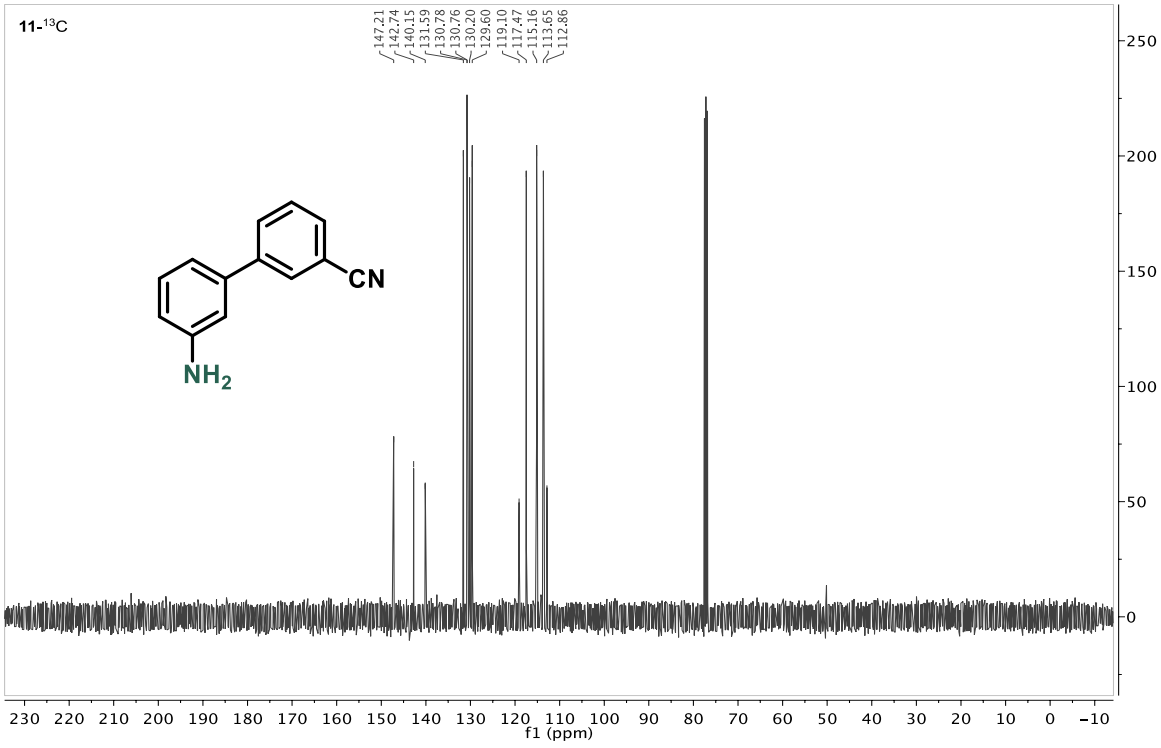


Figure 21: ^{13}C NMR spectra of 3'-amino-[1,1'-biphenyl]-3-carbonitrile (**11**)

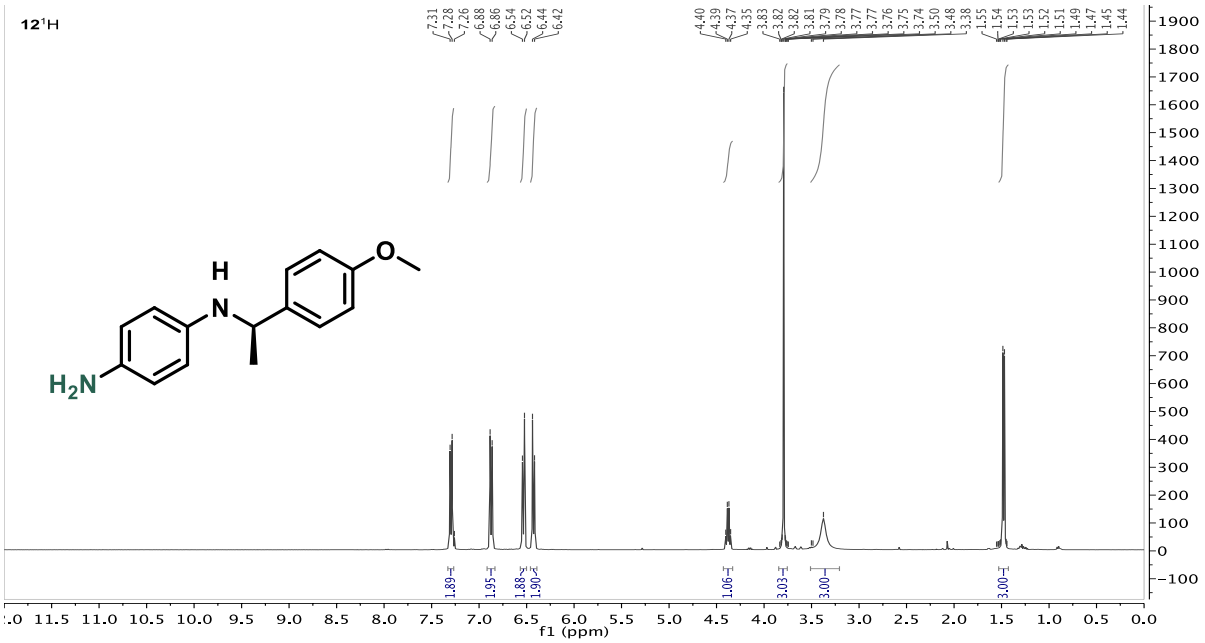


Figure 22: [1]H NMR spectra of (R)-N-(1-(4-methoxyphenyl)ethyl)benzene-1,4-diamine (**12**)

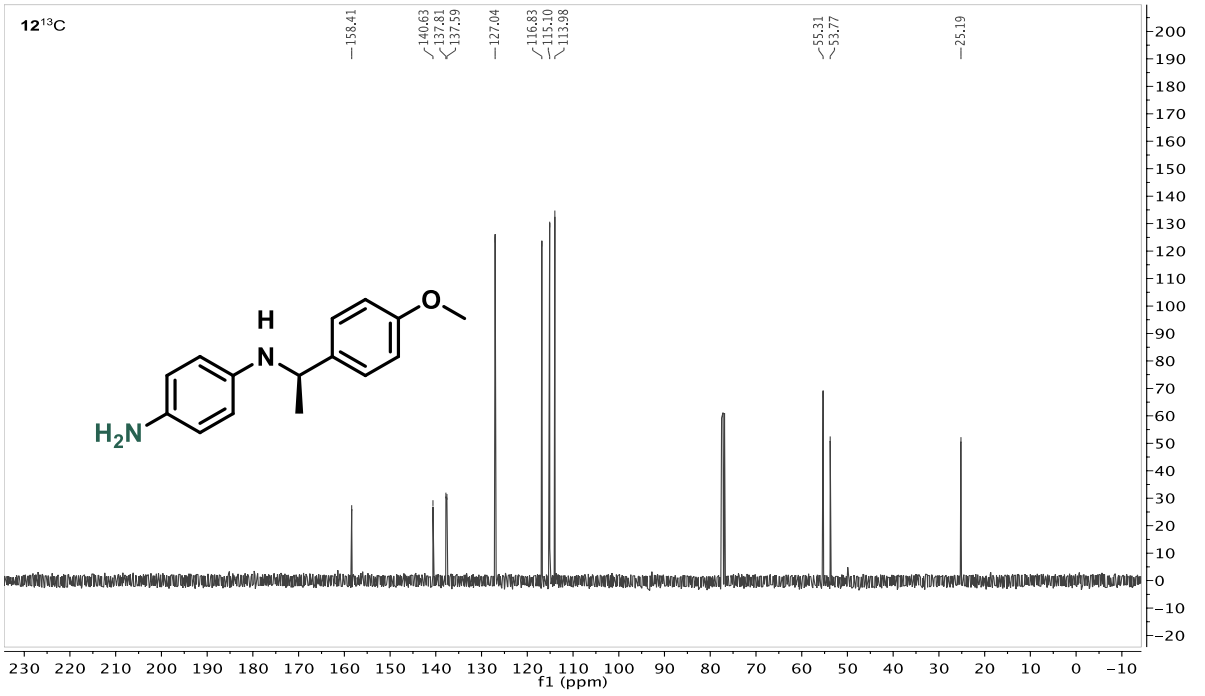


Figure 23: [13]C NMR spectra of (R)-N-(1-(4-methoxyphenyl)ethyl)benzene-1,4-diamine (**12**)

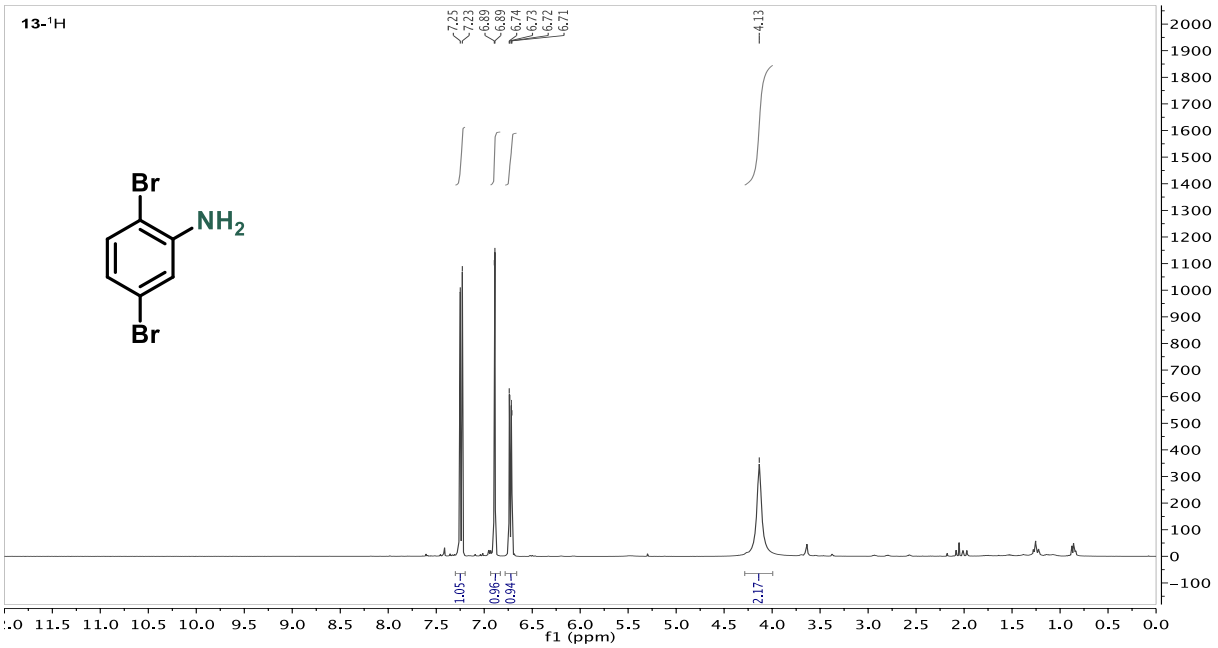


Figure 24: ^{1}H NMR spectra of 2,5-dibromoaniline (**13**)

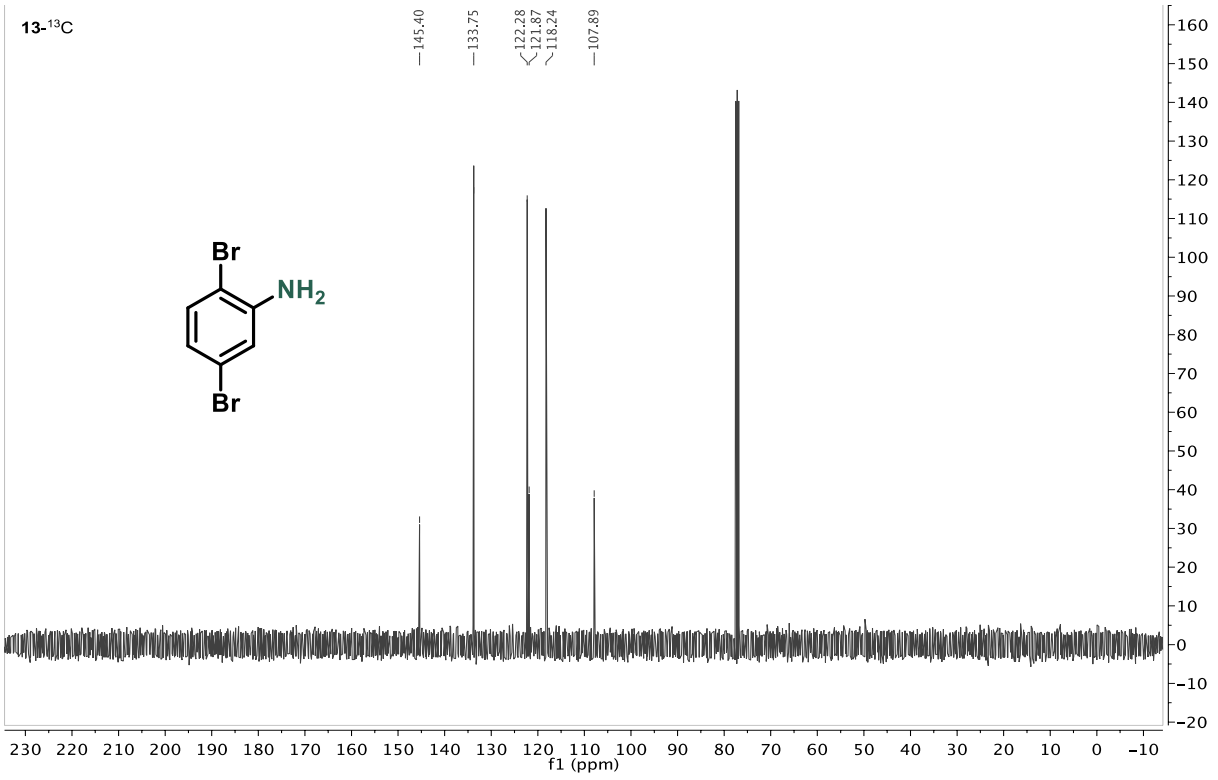


Figure 25: ^{13}C NMR spectra of 2,5-dibromoaniline (**13**)

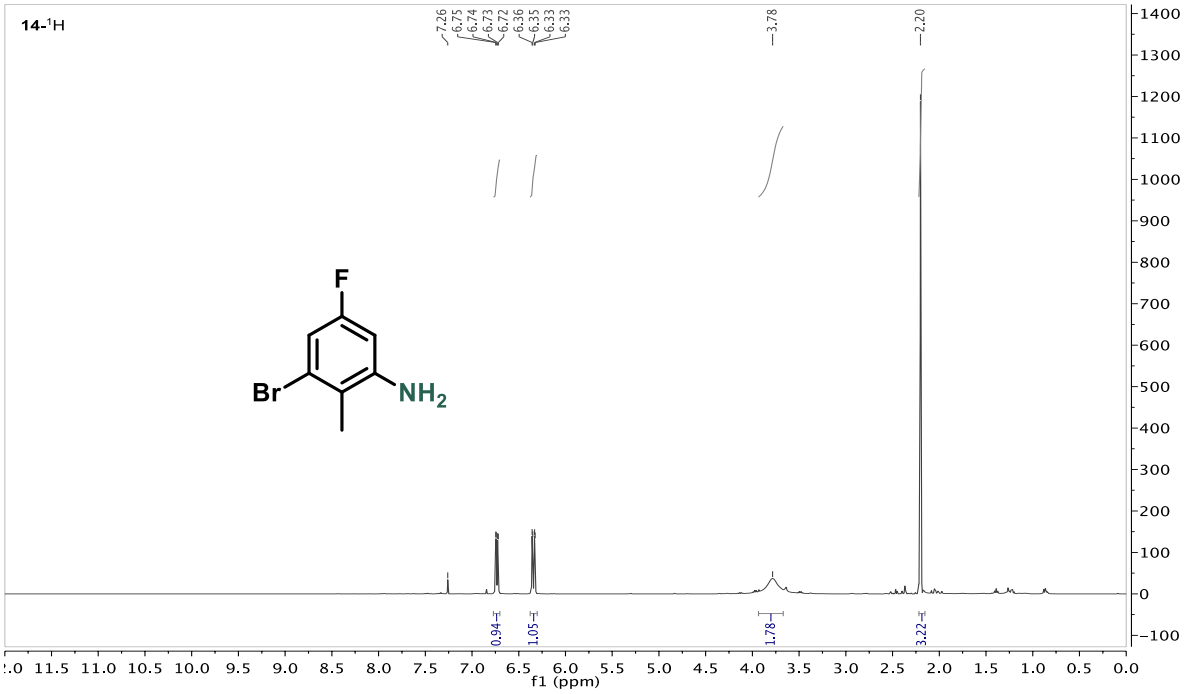


Figure 26: ^{1}H NMR spectra of 3-bromo-5-fluoro-2-methylaniline (**14**)

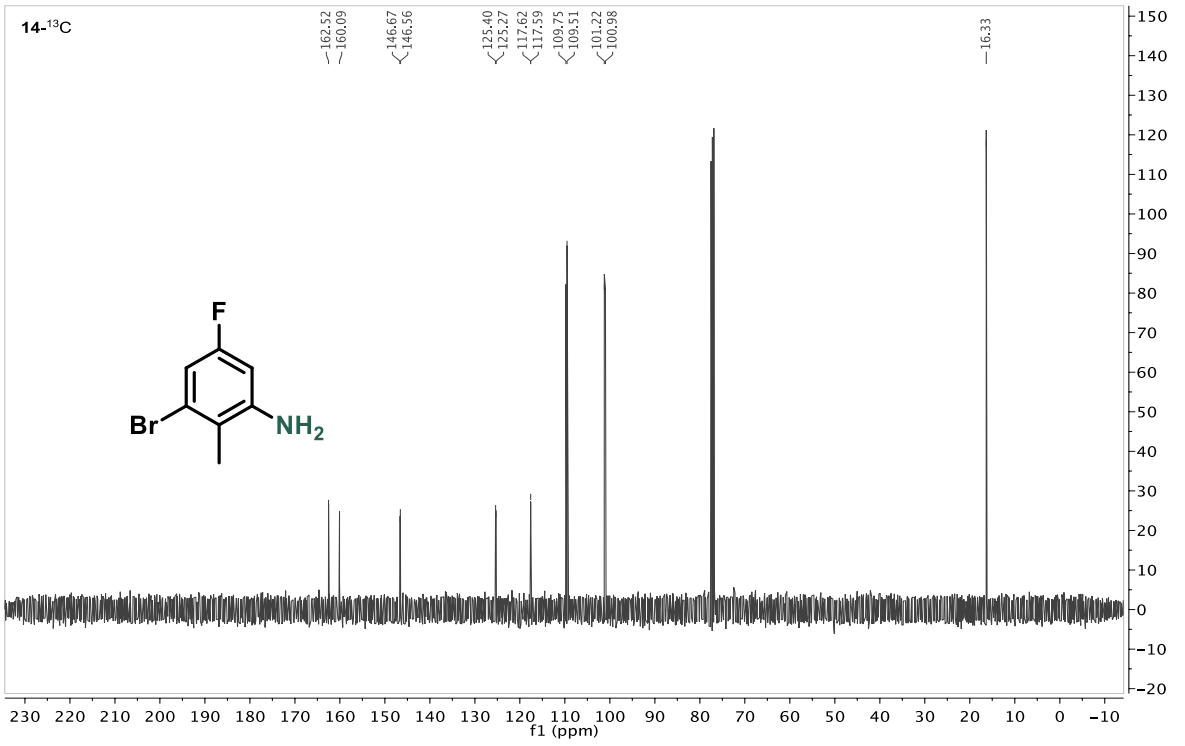


Figure 27: ^{13}C NMR spectra of 3-bromo-5-fluoro-2-methylaniline (**14**)

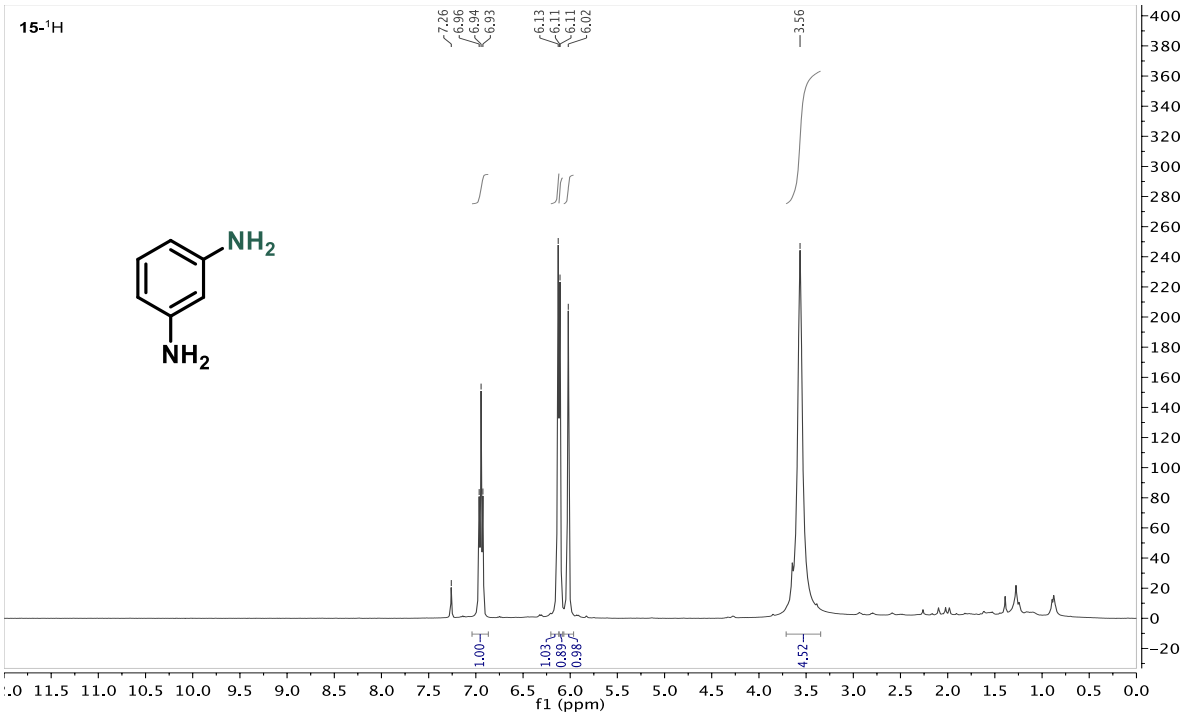


Figure 28: ^{1}H NMR spectra of benzene-1,3-diamine (**15**)

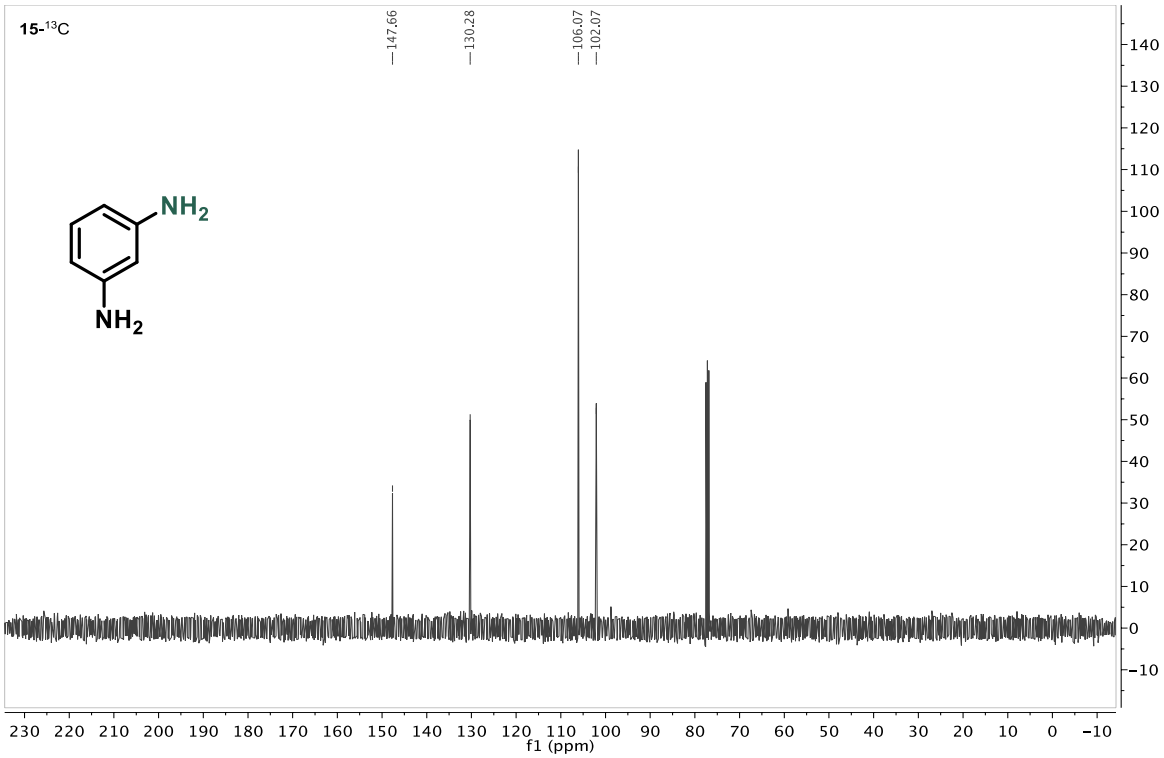


Figure 29: ^{13}C NMR spectra of benzene-1,3-diamine (**15**)

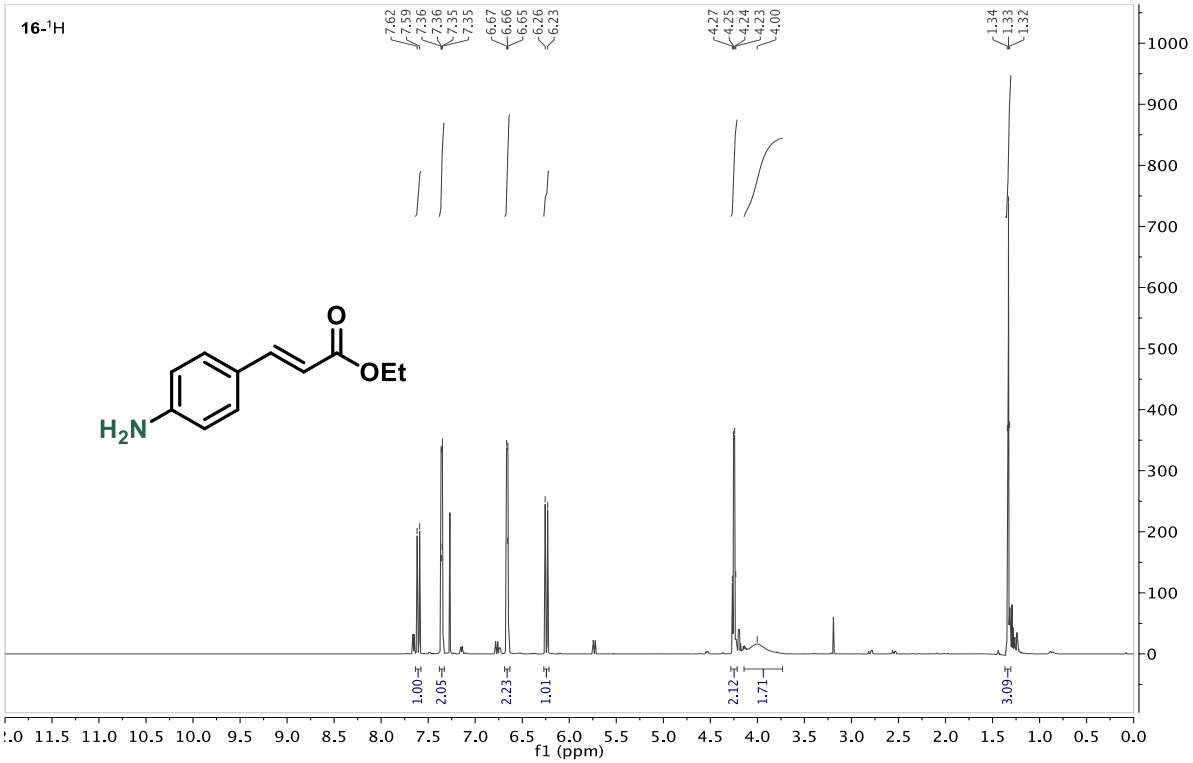


Figure 30: ^{1}H NMR spectra of ethyl-4-aminocinnamate (**16**)

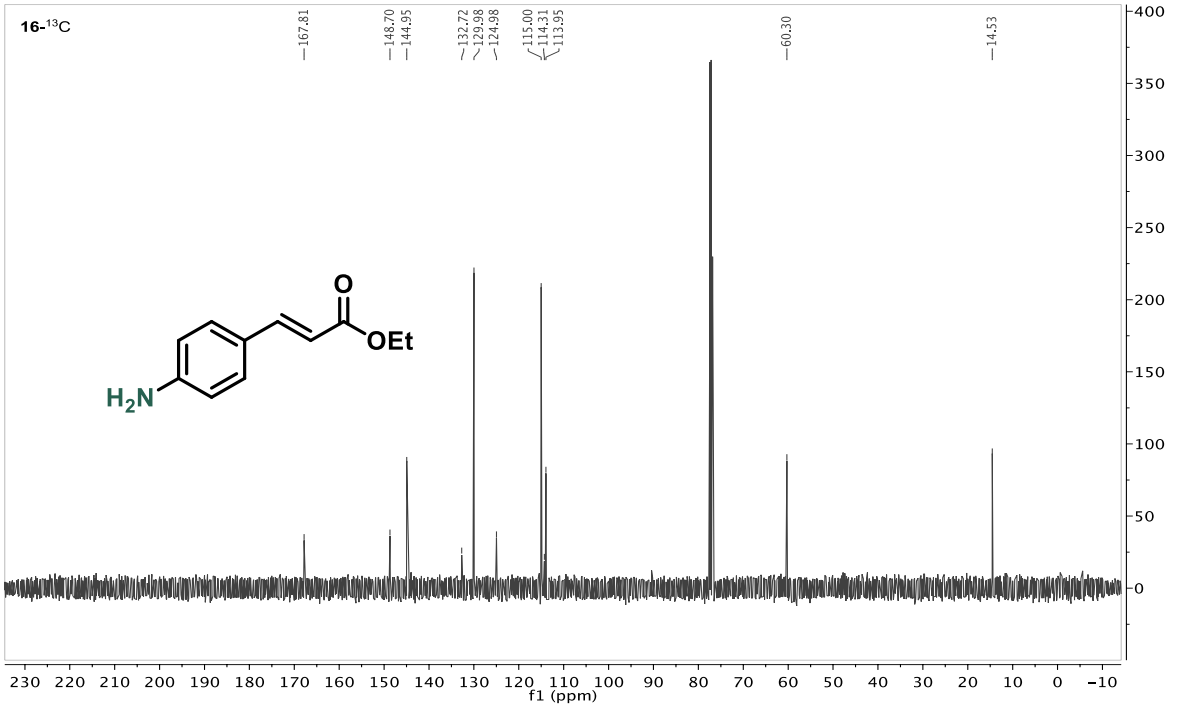


Figure 31: ^{13}C NMR spectra of ethyl-4-aminocinnamate (**16**)

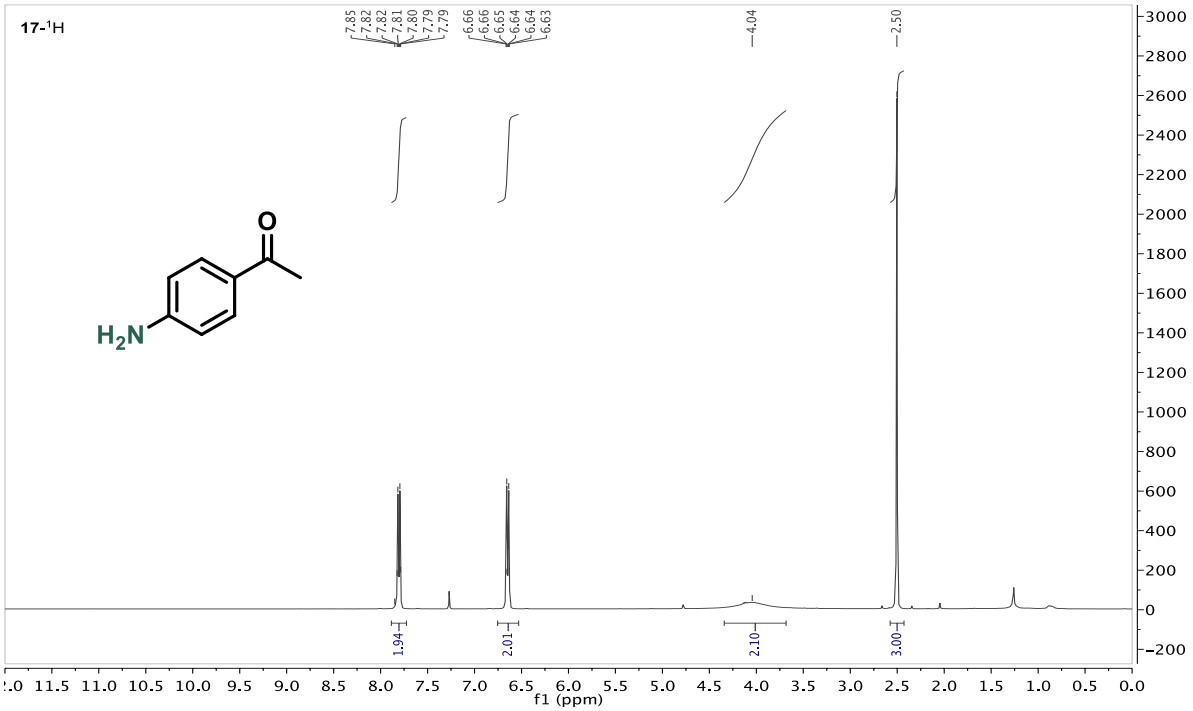


Figure 32: ^{1}H NMR spectra of 4-aminoacetophenone (**17**)

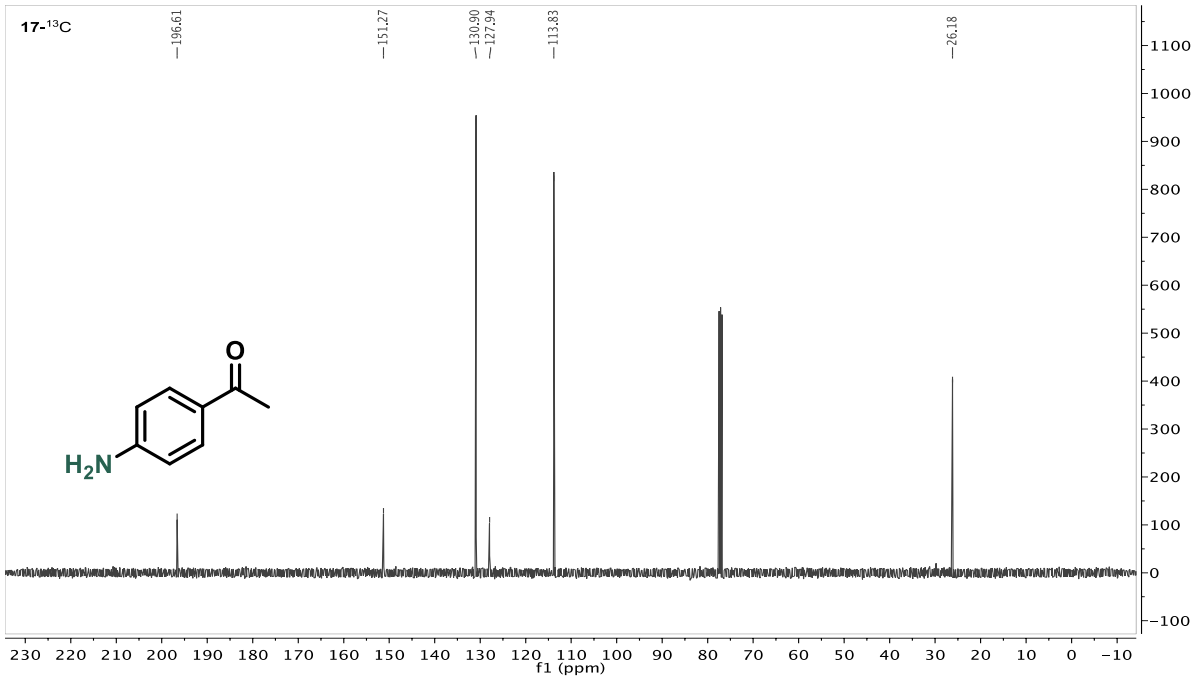


Figure 33: ^{13}C NMR spectra of 4-aminoacetophenone (**17**)

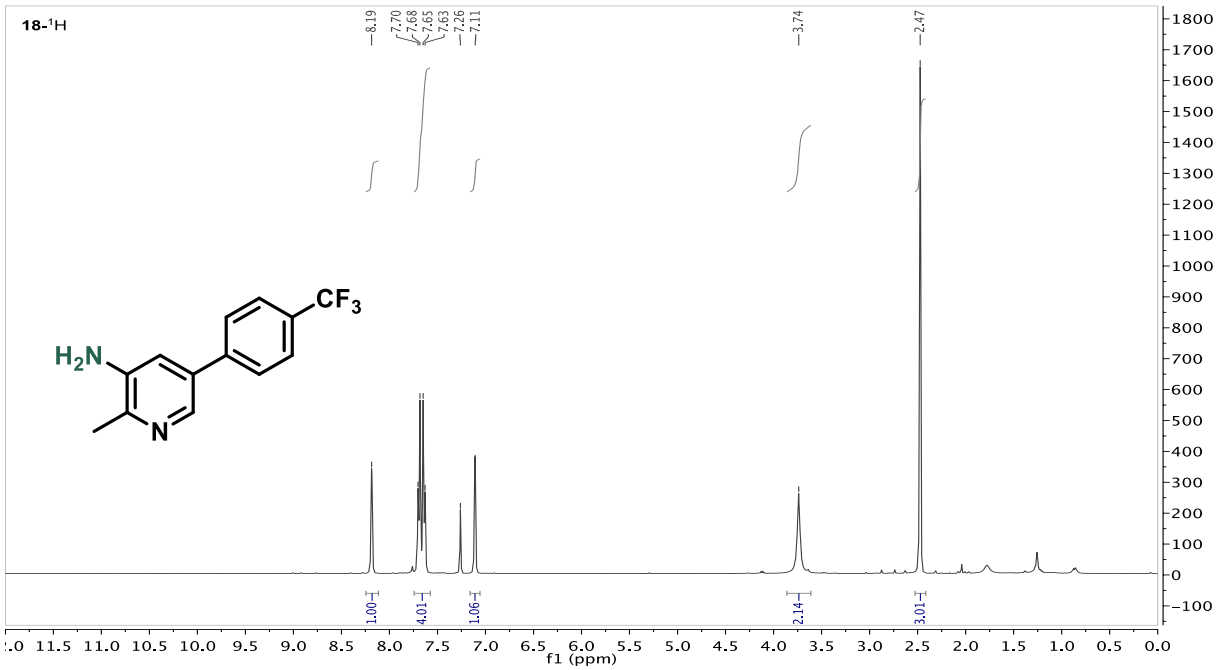


Figure 34: ^{1}H NMR spectra of 2-methyl-5-(4-(trifluoromethyl)phenyl)pyridin-3-amine (**18**)

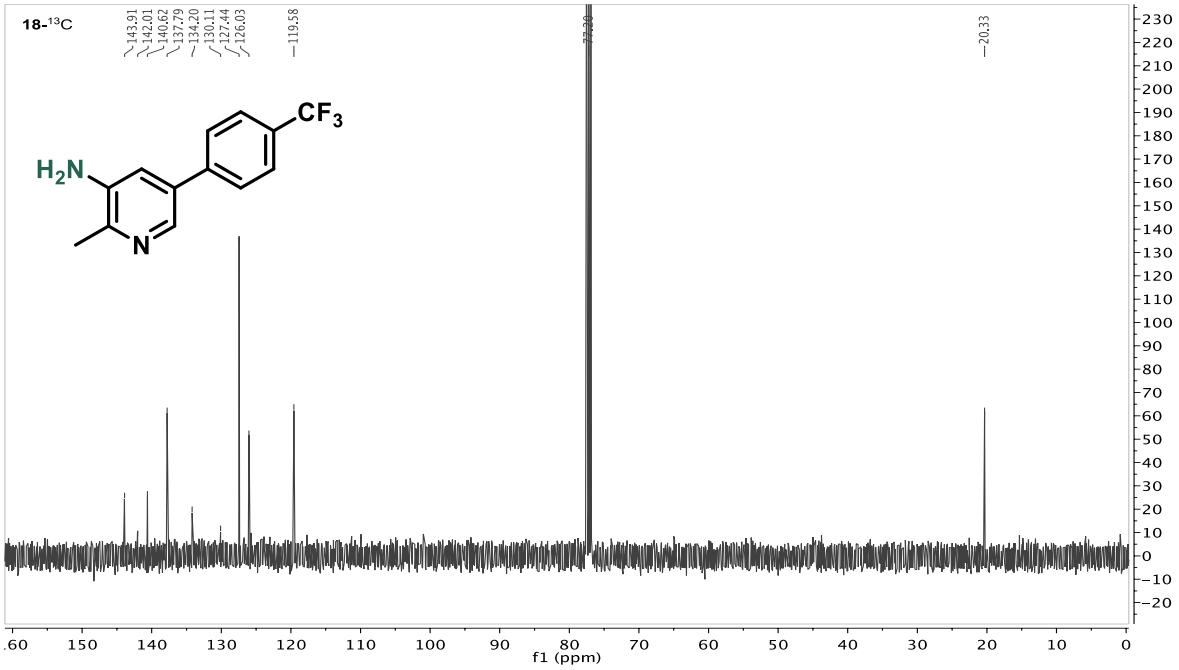


Figure 35: ^{13}C NMR spectra of 2-methyl-5-(4-(trifluoromethyl)phenyl)pyridin-3-amine (**18**)

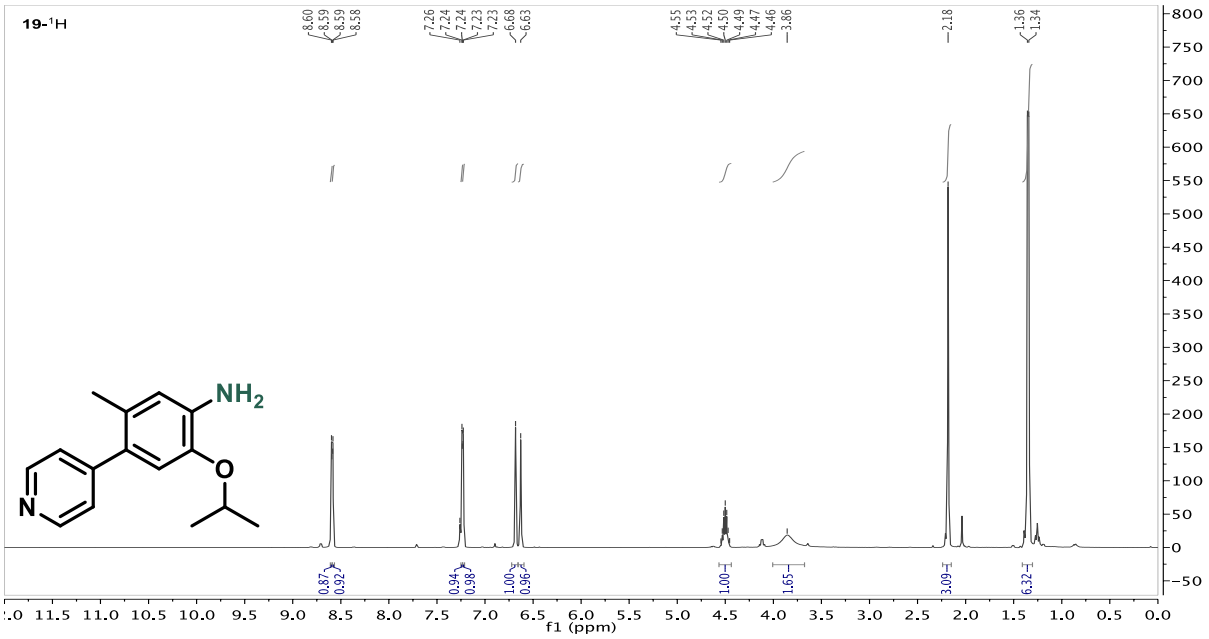


Figure 36: ^{1}H NMR spectra of 2-isopropoxy-5-methyl-4-(pyridin-4-yl)aniline (**19**)

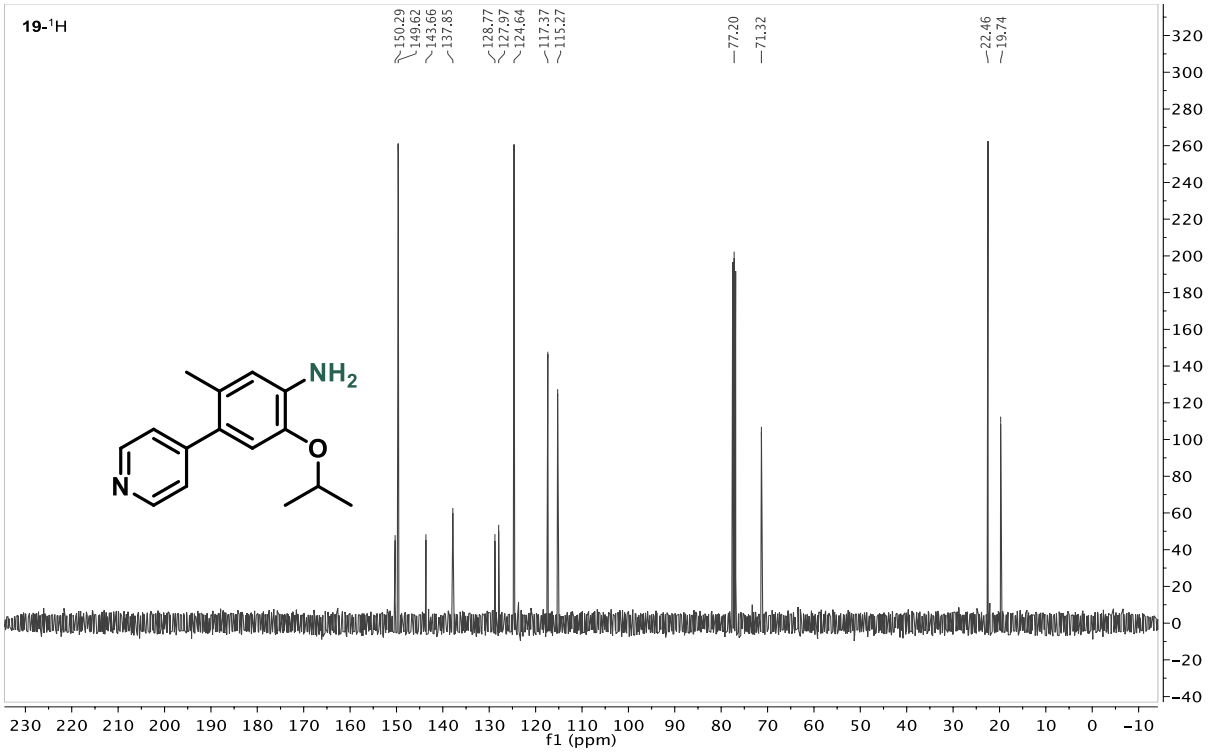


Figure 37: ^{13}C NMR spectra of 2-isopropoxy-5-methyl-4-(pyridin-4-yl)aniline (**19**)

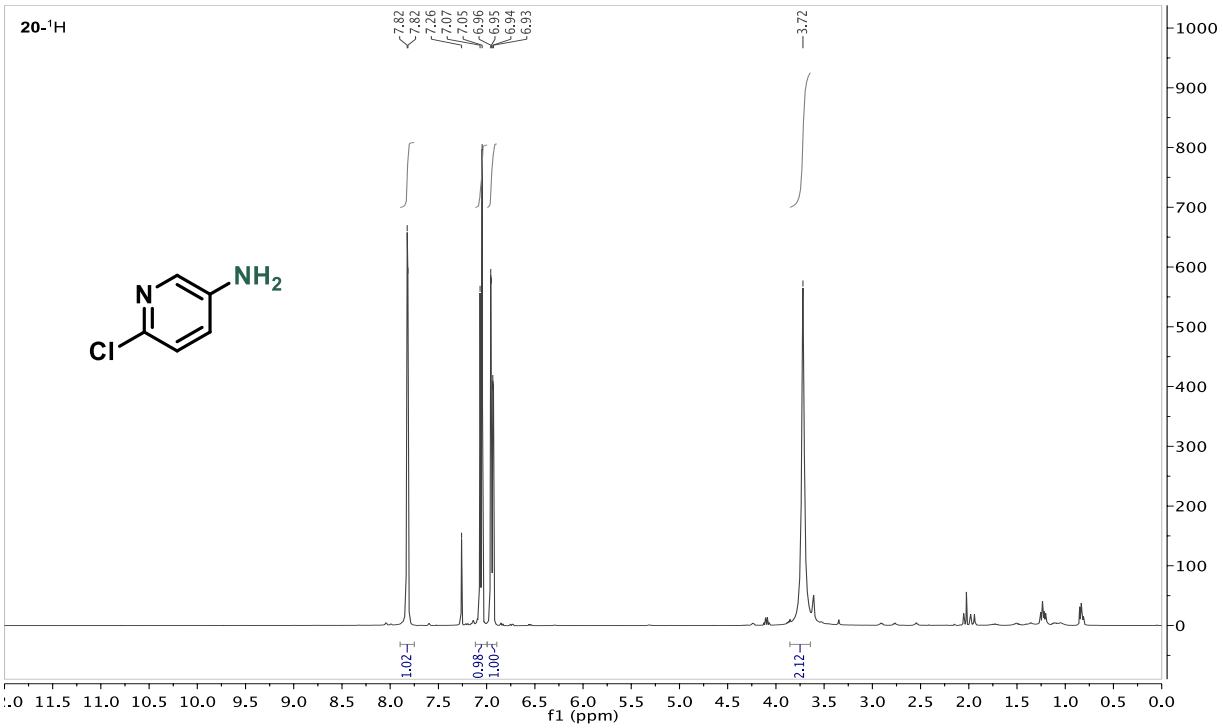


Figure 38: ^{1}H NMR spectra of 6-chloropyridin-3-amine (**20**)

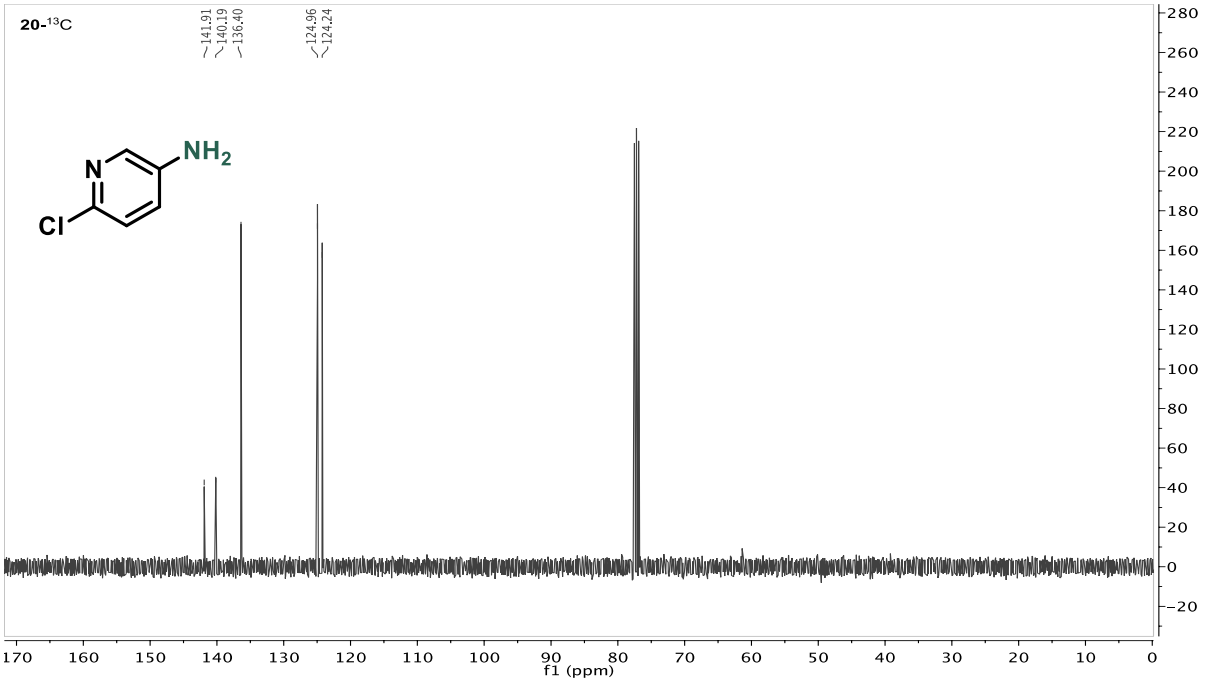


Figure 39: ^{13}C NMR spectra of 6-chloropyridin-3-amine (**20**)

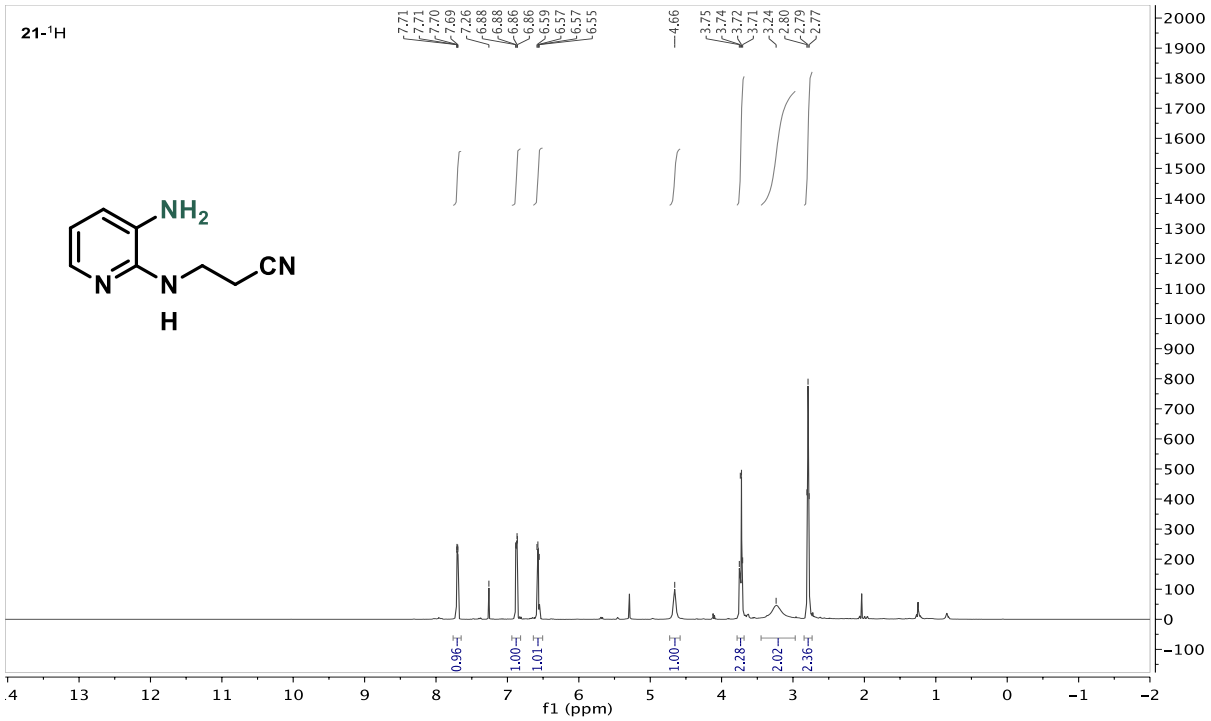


Figure 40: ^{1}H NMR spectra of 3-((3-aminopyridin-2-yl)amino)propanenitrile (**21**)

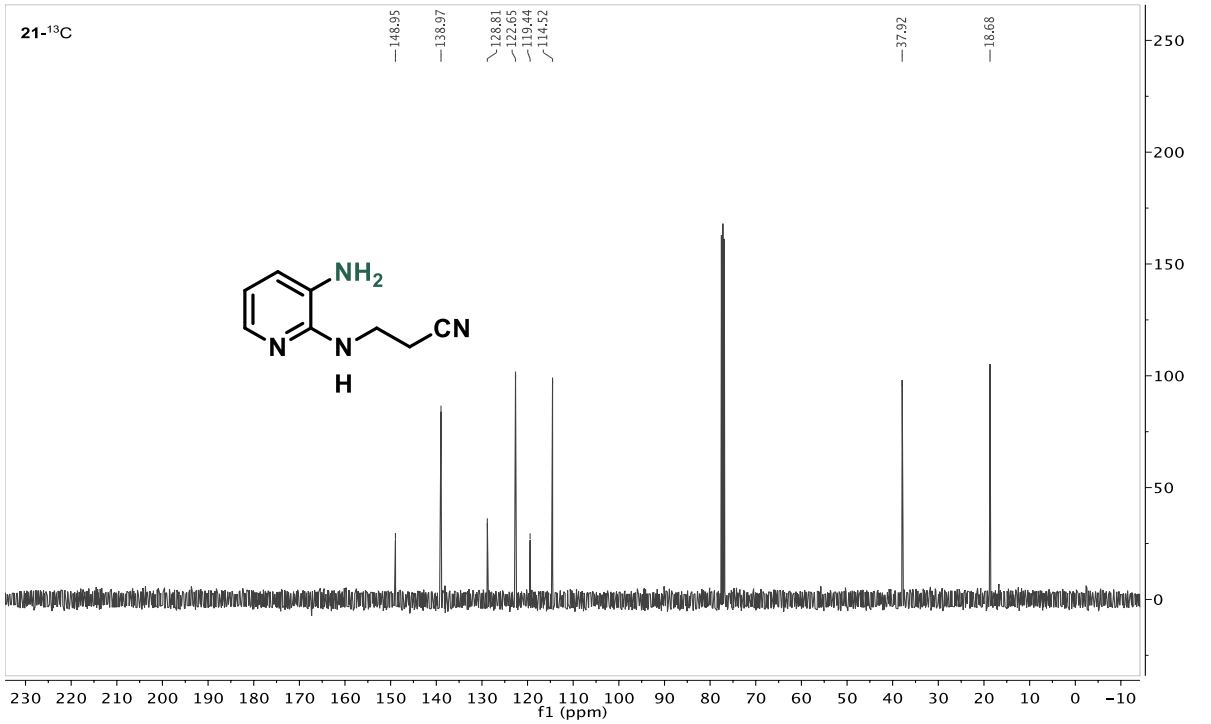


Figure 41: ^{13}C NMR spectra of 3-((3-aminopyridin-2-yl)amino)propanenitrile (**21**)

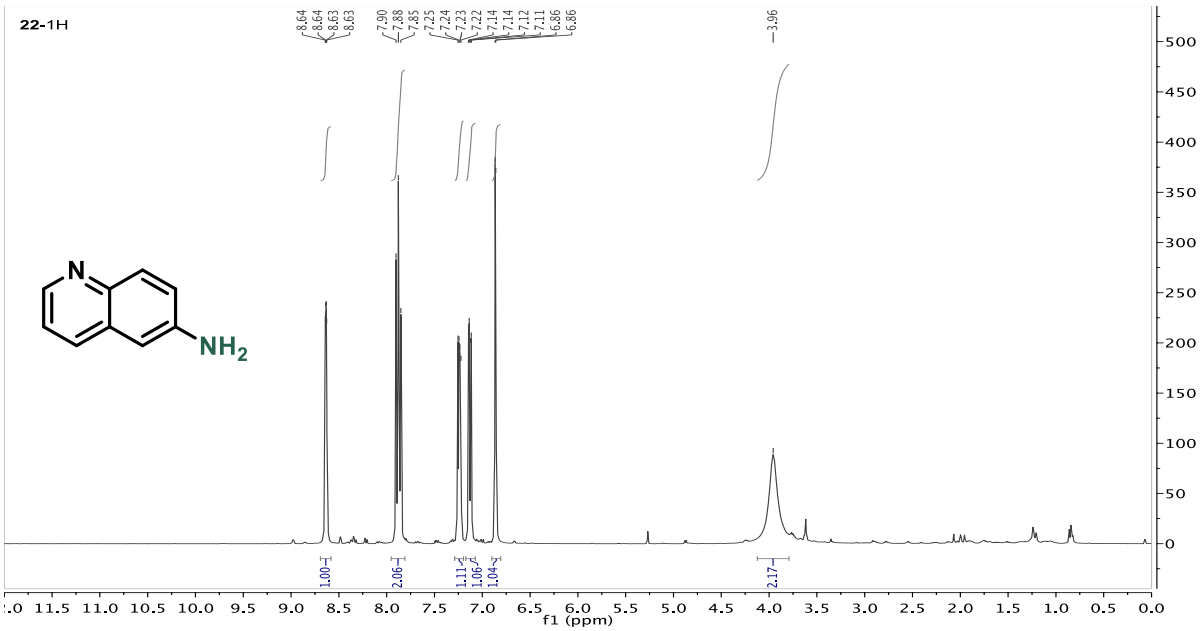


Figure 42: ^{1}H NMR spectra of quinolin-6-amine (**22**)

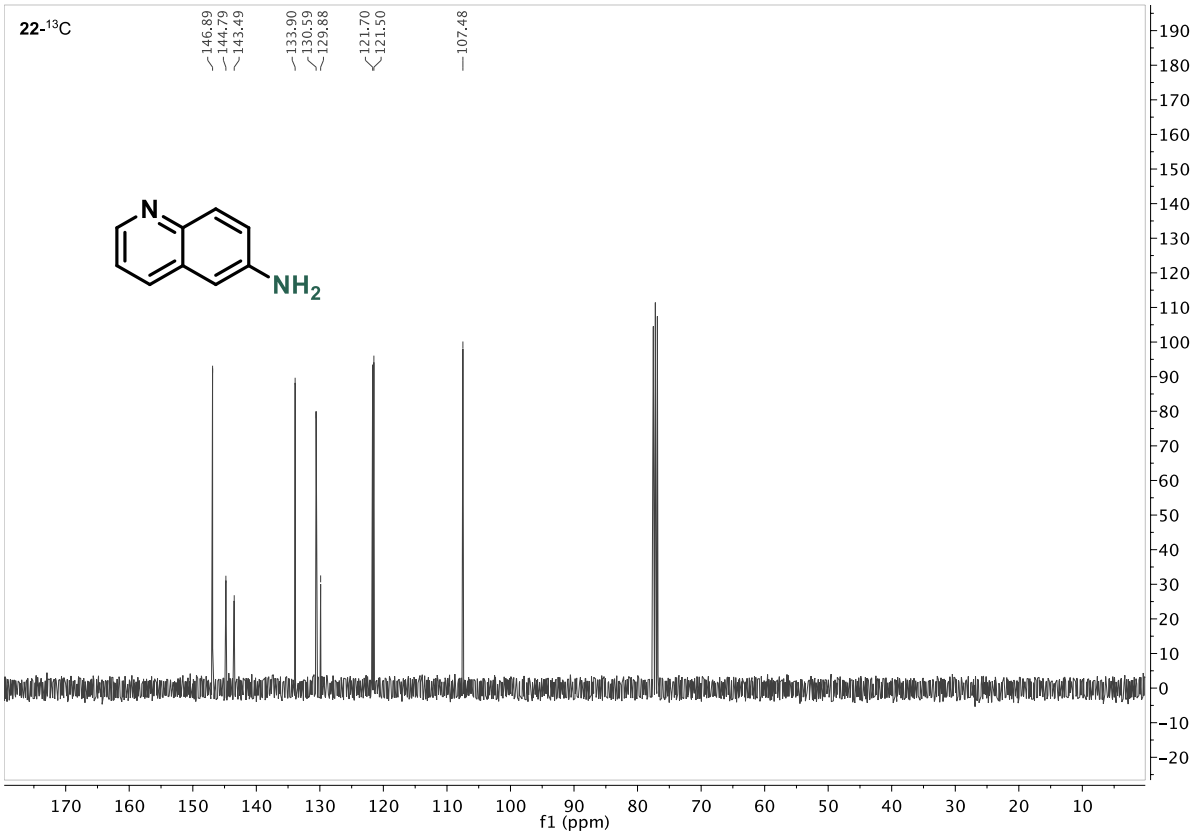


Figure 43: ^{13}C NMR spectra of quinolin-6-amine (**22**)

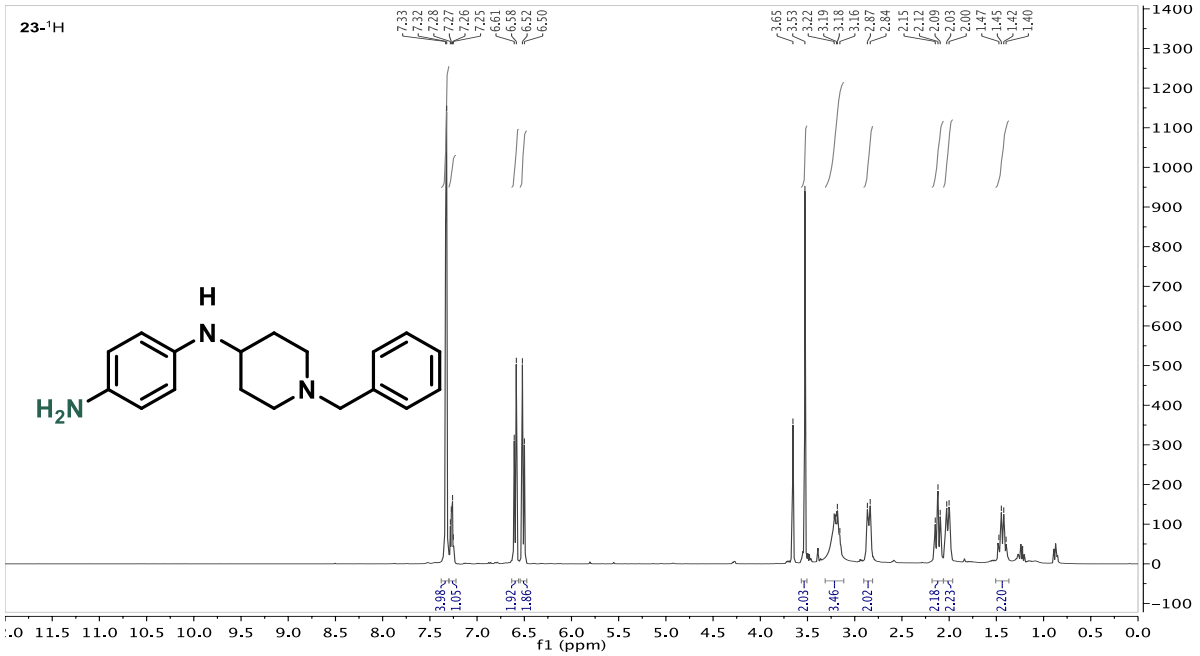


Figure 44: ^{1}H NMR spectra of N-(1-benzylpiperidin-4-yl)benzene-1,4-diamine (**23**)

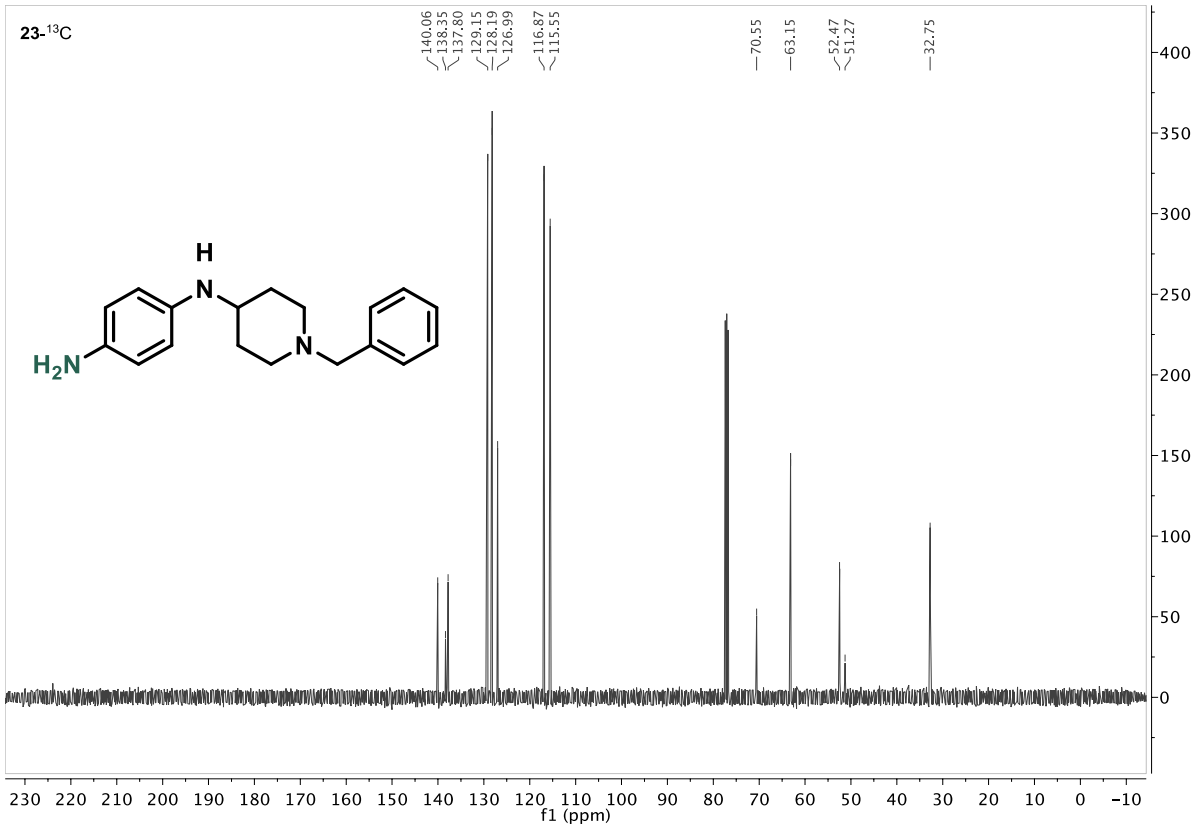


Figure 45: ^{13}C NMR spectra of N-(1-benzylpiperidin-4-yl)benzene-1,4-diamine (**23**)

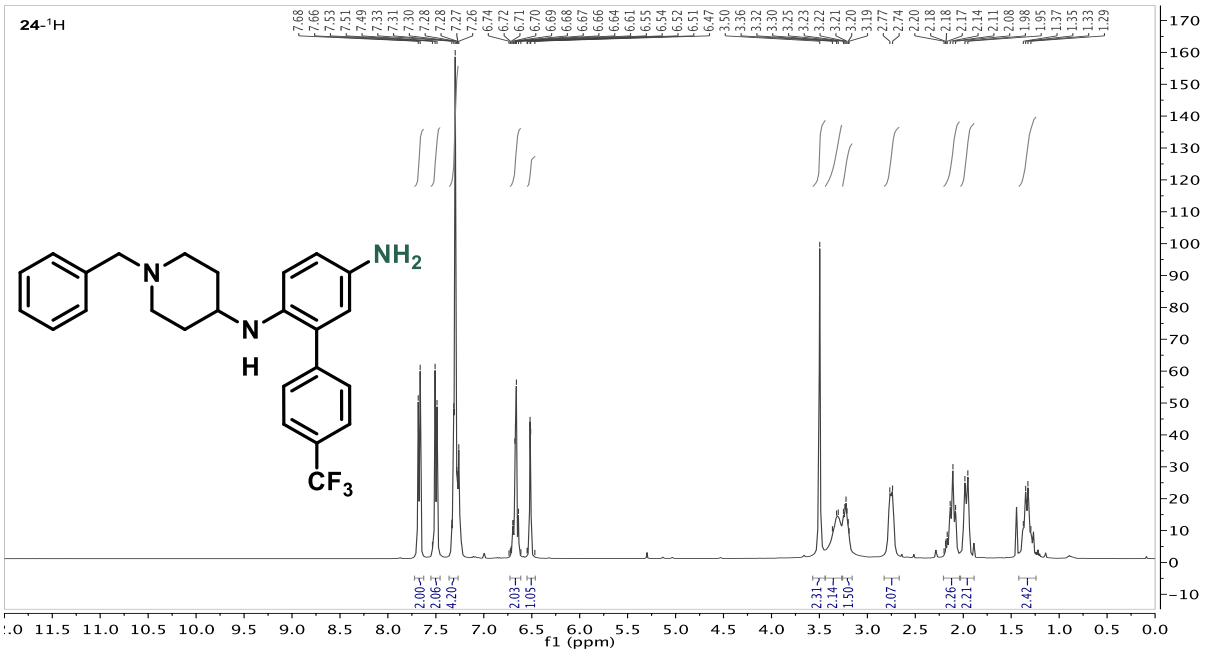


Figure 46: ^{1}H NMR spectra of N^{2}-(1-benzylpiperidin-4-yl)-4'-(trifluoromethyl)-[1,1'-biphenyl]-2,5-diamine (**24**)

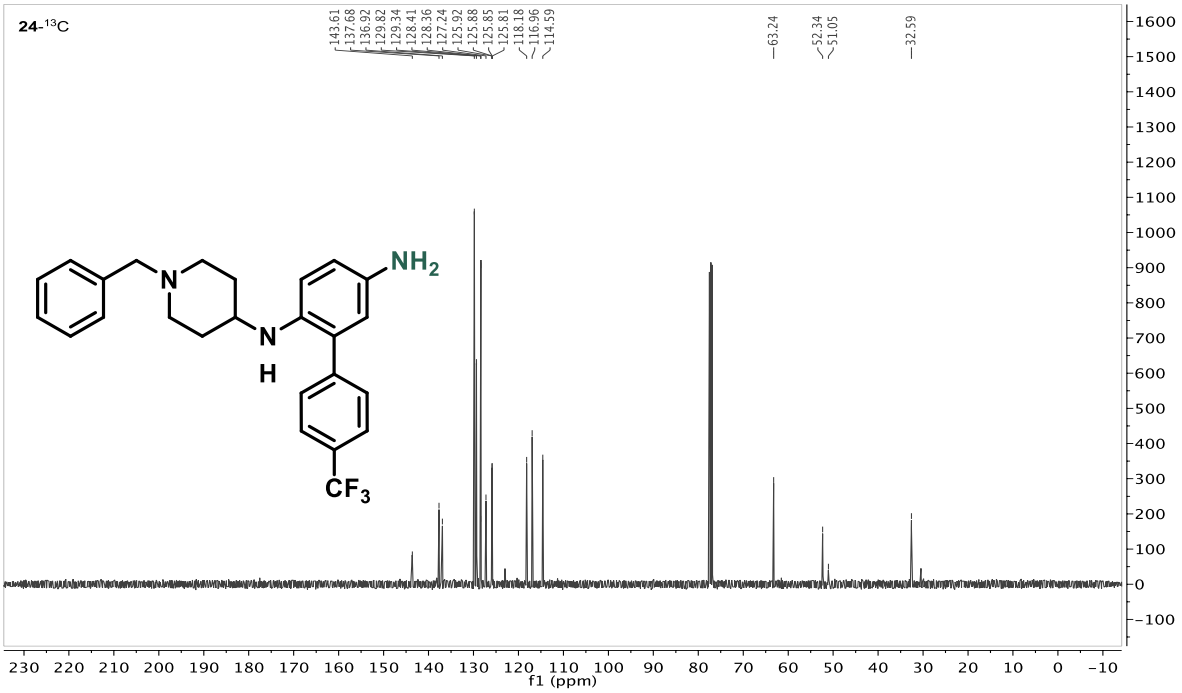
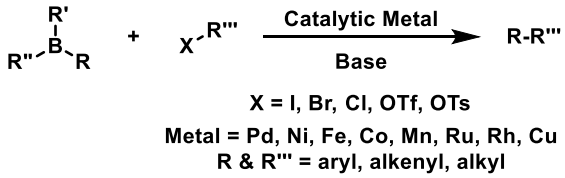


Figure 47: ^{13}C NMR spectra of N^{2}-(1-benzylpiperidin-4-yl)-4'-(trifluoromethyl)-[1,1'-biphenyl]-2,5-diamine (**24**)

II. *B*-Alkyl Suzuki Couplings in Water

2.1 Introduction

Scheme 1: General scheme of the Suzuki-Miyaura coupling



The metal catalyzed coupling of organoboron reagents to various electrophiles is known as the Suzuki-Miyaura coupling (Scheme 1). Since the first reports by Suzuki and Miyaura,[36] innumerable variations and applications have been developed.[37] The ability to selectively cross couple substrates catalytically and under mild conditions is difficult to achieve by other means. The number of methods for conducting Suzuki-Miyaura couplings in purely aqueous or predominantly aqueous reaction medium has grown greatly in recent years.[38] While all of the literature examples of Suzuki coupling in largely or purely aqueous media had so far been focused on sp^2-sp^2 bond formation, the sp^3-sp^2 coupling is an important variation which has been reported frequently in literature examples using organic solvent as the reaction medium.[39] It is also noteworthy to mention that some very rare examples of sp^3-sp^3 Suzuki coupling exist (the rarity due to the difficulty of this type coupling), but this is beyond the scope of the current discussion.[40] While the *B*-alkyl sp^3-sp^2 Suzuki coupling significantly broadens the scope

[36] (a) N. Miyaura, T. Yanagi and A. Suzuki, Synth. Commun., 1981, 11, 513–519. (b) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437–3440.
[37] Reviews on SM couplings: (a) Miyaura, N.; Suzuki, A. *Chem. Rev.*1995, 95, 2457. (b) Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem., Int. Ed.* 2012, 51, 5062. (c) Maluenda, I.; Navarro, O. *Molecules* 2015, 20, 7528. (d) Lennox, A. J. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev.* 2014, 43, 412.
[38] (a) Polshettiwar, V.; Decottignies, A.; Len, C.; Fihri, A. *ChemSusChem* **2010**, *3*, 502–522. (b) Hooshmand, S. E.; Heidari, B.; Sedghi, R.; Varma, R. S. *Green Chem.* **2019**, *21*, 381–405.
[39] Reviews on B-alkyl SM couplings: (a) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* 2001, 40, 4544. (b) Seidel, G.; Furstner, *A. Chem. Commun.* 2012, 48, 2055.
[40] (a) Lu, Z.; Fu, G. C. *Angew. Chem., Int. Ed.* **2010**, *49*, 6676–6678. (b) Saito, B.; Fu, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 9602–9603. (c) Hatakeyama, T.; Hashimoto, T.; Kathriarachchi, K. K. A. D. S.; Zenmyo, T.; Seike, H.;

of coupling possibilities, it has specific requirements in terms of boron reagents. It is therefore helpful to first briefly review the boron reagents employed for Suzuki coupling. A wide variety of boron reagents have been applied to Suzuki couplings, each with various applications and limitations in terms of their synthesis and reactivity. While it is out of the scope here to give an overview of every type of boron reagent developed and employed, several of the most common are shown below (Figure 1).

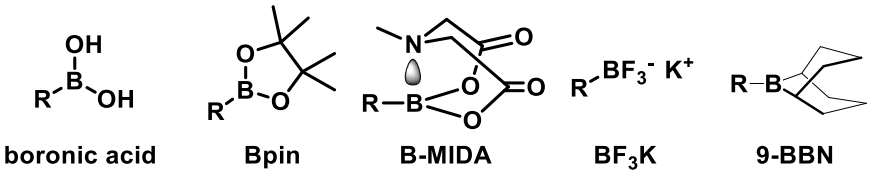


Figure 1: A selection of common boron reagents applied to Suzuki coupling

The boronic acid and pinacol boronate (Bpin) are arguably the most commonly encountered reagents in regards to Suzuki coupling. The *N*-methyliminodiacetic acid boronate (B-MIDA) is employed for its greater stability when coupling unstable substrates, and because of this stability it has found uses in iterative or orthogonal cross coupling processes.[41] All three of these reagents are typically only applied to sp^2-sp^2 couplings, and are usually not effective for sp^2-sp^3 couplings. The BF_3K reagent is somewhat of an intermediate reagent,[42] where some sp^2-sp^3 couplings are known,[43] but they are frequently limited in scope and reaction conditions. However, in the realm of

Nakamura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 8834–8837. (d) Netherton, M. R.; Dai, C.; Neuschütz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099–10100.

[41] (a) Wang, C.; Glorius, F. *Angew. Chem., Int. Ed.* **2009**, *48*, 5240–5244. (b) Tobisu, M.; Chatani, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 3565–3568.

[42] (a) Dreher, S. D.; Lim, S.-E.; Sandrock, D. L.; Molander, G. A. *J. Org. Chem.* 2009, 74, 3626. (b) Yamashita, Y.; Tellis, J. C.; Molander, G. A. *Proc. Natl. Acad. Sci. U. S. A.* 2015, 112, 12026. (c) Karakaya, I.; Primer, D. N.; Molander, G. A. *Org. Lett.* 2015, 17, 3294. (d) Molander, G. A.; Yun, C.-S.; Ribagorda, M.; Biolatto, B. *J. Org. Chem.* 2003, 68, 5534. (e) Molander, G. A.; Shin, I. *Org. Lett.* 2013, 15, 2534.

[43] Molander, G. A.; Canturk, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 9240–9261.

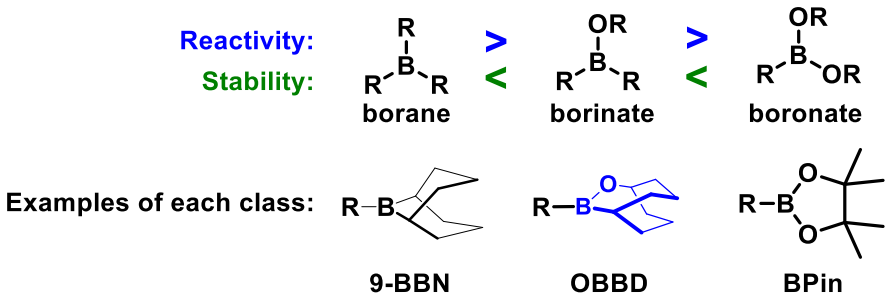
sp^2-sp^3 couplings, the 9-Borabicyclo[3.3.1]nonane (9-BBN) reagent is probably the most common. Though there are reports of symmetrical trialkyl boranes (i.e. R_3B where $R_1 = R_2 = R_3$, such as Et_3B) used in coupling reactions, these are rare[44].

While sp^2-sp^2 Suzuki couplings in water been extensively studied, no sp^2-sp^3 type couplings had been reported at the start of this project. This left a significant deficiency in the literature on Suzuki couplings in water. While boronic acid, B-pin, and MIDA boronate have been extensively studied for Suzuki couplings in water, no protocol for *B*-alkyl Suzuki couplings using a 9-BBN or equivalent reagent had been developed.

2.2 Selection of Boron Reagents for *B*-alkyl Suzuki Coupling

In selecting an appropriate *B*-alkyl boron reagent for alkyl Suzuki coupling, it is helpful to review the general trends in reactivity versus stability of alkyl boron compounds (scheme 2).

Scheme 2: Trends in reactivity versus stability in B-alkyl reagents for Suzuki coupling



Reagent	9-BBN	OBBD	Bpin
Air-stability	<1 h	24-48 h	stable
Competence in *B*-alkyl Suzuki	Highly reactive	Moderately reactive	Unreactive

[44] (a) Li, H.; Zhong, Y.-L.; Chen, C.; Ferraro, A. E.; Wang, D. *Org. Lett.* **2015**, *17*, 3616–3619. (b) Sun, H.-X.; Sun, Z.-H.; Wang, B. *Tetrahedron Lett.* **2009**, *50*, 1596–1599.

As a simple comparison of the reactivity versus stability, Scheme 2 shows the overall reactivity trend. 9-BBN derivatives are very unstable, giving a large degree of decomposition/oxidation within 1 hour of exposure to air (or potentially igniting). 9-oxa-10-borabicyclo[3.3.2]decane (OBBD) reagents begin to decompose in ~24-48 h when exposed to air, and Bpin reagents are overall stable, but usually unreactive in *B*-alkyl Suzuki coupling. Studies on the reactivity of OBBD vs. 9-BBN derivatives showed that this stability comes at a cost. The OBBD is significantly less reactive than the analogous 9-BBN as shown in competition experiments.[45] 9-BBN derivatives are common for alkyl Suzuki couplings, so at first glance it would seem than trialkyl borane reagents such as a 9-BBN would be the choice for this task. However, trialkylboranes have some serious limitations. While they are not necessarily water sensitive, trialkylboranes are very air sensitive and some lower molecular weight trialkylboranes (such as B-methyl-9-BBN, and especially Et_3B) are spontaneously flammable in air.[46] Some trialkylboranes are commercially available (such as triethylborane), however no functionalized 9-BBN derivatives are available. These reagents are almost always prepared in-situ and used immediately. This makes these reagents inconvenient for a long-term project because of this need to prepare and utilize a very sensitive and pyrophoric reagent each time a trial is conducted. However, the 9-BBN framework can be selectively oxidized to the borinate or OBBD which makes the compound far more stable to air. This OBBD can be isolated and

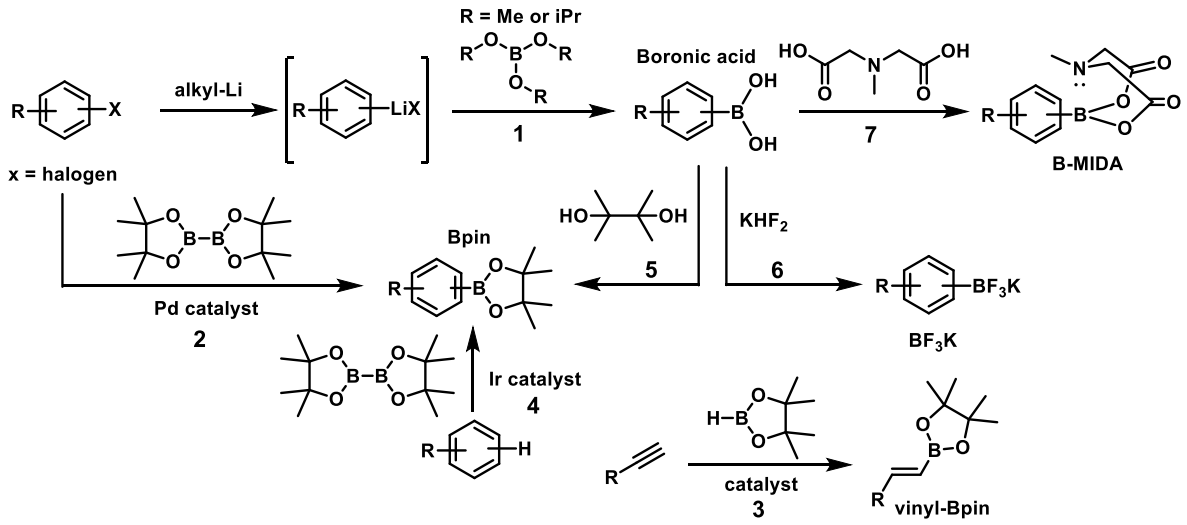
[45] Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461–470.
[46] (a) Atkins, W. J.; Burkhardt, E. R.; Matos, K. Safe Handling of Boranes at Scale. *Org. Process Res. Dev.* **2006**, *10*, 1292–1295.
(b) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Sato, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314.

stored for long periods of time, making it a more convenient and safer reagent for use than a trialkyl borane.

2.3 Preparation of Boron Reagents for Suzuki Coupling

As a general review of methods for generation of boron reagents for Suzuki coupling, the most common routes to the first three types of boron reagents discussed is given below (Scheme 3).

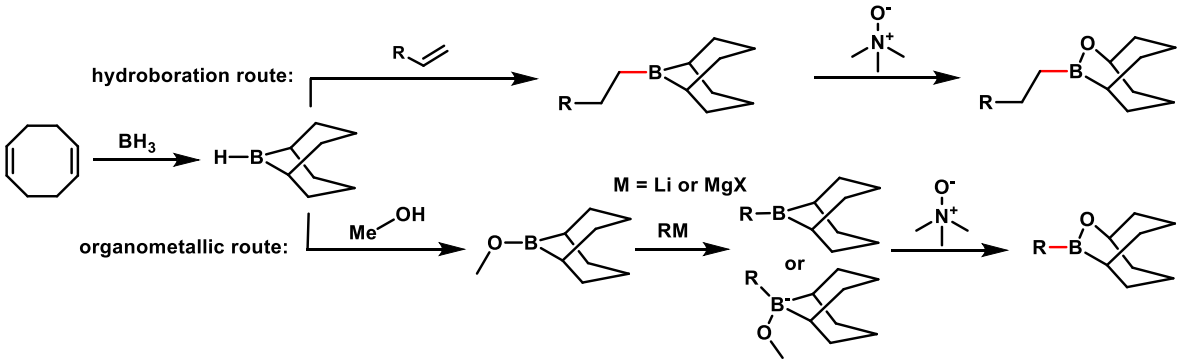
Scheme 3: Common routes to Sp^2 boron reagents



Aryl/sp^2 boron reagents for Suzuki coupling are synthesized by borylation in 4 main methods, though lesser utilized methods exist. Lithiation of an sp^2 halide followed by quenching with a trialkoxy borate (such as triisopropyl borate) is probably the most common method (route **1**). Palladium catalyzed Miyaura borylation using B_2Pin_2 (and also tetrahydroxy diboron to give the analogous boronic acid) gives the Bpin reagent directly (route **2**). Hydroboration of alkynes to generate the vinyl-Bpin gives vinyl-Bpin derivatives (Route **4**), and C-H activation using iridium catalysis also produces B-pin derivatives but this is far less common 9 (Route **4**). Boronic acids can be further

functionalized to the BPin (Route 5), BF_3K (Route 6), and BMIDA (Route 7), as well as a number of other niche derivatives.

Scheme 4: Preparation of *B*-alkyl 9-BBN and OBBD reagents

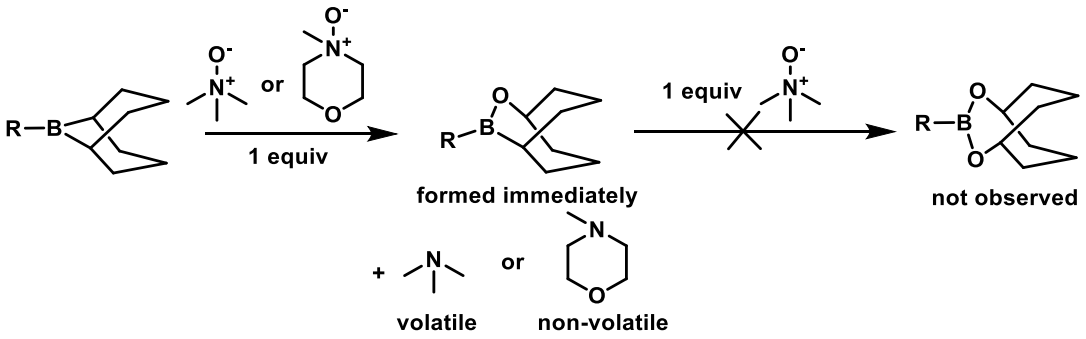


To synthesize *B*-alkyl 9-BBN derivatives, 9-BBN (or H-9-BBN) is first prepared by hydroboration of cyclooctadiene (Scheme 4).[47] From there, two main routes exist to generate *B*-alkyl 9-BBN or subsequent OBBD derivatives. This 9-BBN reagent can be used in a second hydroboration with an alkene or alkyne. Typically, an alkene is used because in the case of an alkyne, over addition is hard to avoid and this results in a mixture of mono and di-borylated products. The hydroboration route is the most straightforward preparation of alkyl 9-BBN reagents and is probably the most utilized route. In addition, the bulkiness of the 9-BBN reagent is further important, because it exaggerates the anti-Markovnikov tendency in hydroboration. In practice, this means that the hydroboration is very regioselective for the linear product, often >99:1 ratio. Hydroboration with less bulky boranes is far less selective. This method however has obvious limitations, an alkene is required, and the product will always have a $CH_{(x)}CH_2$

[47] Soderquist, J. A.; Brown, H. C. *J. Org. Chem.* **1981**, *46*, 4599–4600.

moiety present which limits its applications. To supplement this limitation, a second method is available to synthesized alkyl-9-BBN reagents. The methanolysis of 9-BBN results in MeO-9-BBN, which is a versatile electrophilic reagent for preparation of alkylated 9-BBN reagents. Reaction of the MeO-9-BBN with alkyl organometallics furnishes the *B*-alkyl-9-BBN. Br-9-BBN is another derivative utilized, but was not explored in the present study. Regardless of route, the *B*-alkyl-9-BBN can then be oxidized to the OBBD using a suitable oxidizing agent.

Scheme 5: Selective oxidation of *B*-alkyl-9-BBN derivatives to *B*-alkyl-OBBD derivatives



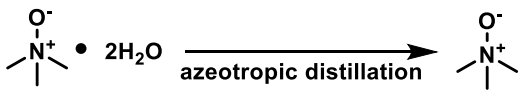
The oxidation of 9-BBN derivative to OBBD, which might appear difficult or problematic at first glance, is remarkably straightforward (Scheme 5)[48]. The use of H_2O_2 or other common oxidizing agents was found to be problematic. The oxidation of 9-BBN to OBBD was found to require a gentle non-aqueous oxidizing agent to prevent over oxidation and/or hydrolysis. TMANO (trimethylamine *N*-oxide) or NMO (*N*-methyl morpholine *N*-oxide) are both very effective at producing this selective oxidation, reacting rapidly and quantitatively with the 9-BBN reagent to form the OBBD.

[48] Soderquist, J. A.; Najafi, M. R. *J. Org. Chem.* **1986**, *51*, 1330–1336.

Interestingly, the overoxidation product was not seen, even when an extra equivalent of TMANO was added and the reaction mixture refluxed for prolonged periods. In practice, this means that this oxidation is very forgiving and exact stoichiometry and care are not needed with the exception of preventing air from entering the reaction. At the start of this project, NMO was used as the oxidizing agent, as per the procedure outlined for use with allenoate electrophiles. While NMO was effective as an oxidizing agent, the N-methylmorpholine product was somewhat annoyingly difficult to remove completely. Due to the difficulty in removing this byproduct, TMANO was screened and found to work extremely well. The trimethylamine produced is volatile, and easily removed by rotary evaporation, but unfortunately has a very offensive and lingering smell even in small amounts, triggering alarm in nearby labmates.

TMANO is typically available as the dihydrate, which is relatively cheap ($1/g). Unfortunately, the solubility of this reagent is extremely low in most organic solvents. While the 9-BBN intermediate is not water sensitive, the use of TMANO dihydrate is not effective due to this solubility problem, as it is not soluble in the THF solvent usually used for synthesis of 9-BBN derivatives. Anhydrous TMANO however, is very expensive (~$30-50/g). However, its preparation is fairly straightforward (Scheme 6).[49]

Scheme 6: Synthesis of anhydrous TMANO



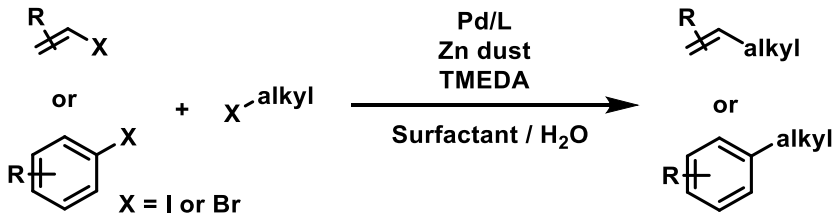
[49] Soderquist, J. A.; Anderson, C. L. *Tetrahedron Lett.* **1986**, *27*, 3961–3962.

TMANO dihydrate can be dehydrated via azeotropic distillation. Either toluene or DMF are the preferred solvents for this process. If toluene is used, the product is typically purified by sublimation after the azeotropic distillation step. If DMF is used, the product can be directly crystallized in the distillation flask, and conveniently isolated without need for sublimation. Though not a "green" solvent, DMF was used in this study as the distillation solvent purely out of convenience. If this process were pursued for an industry application, likely a "greener" solvent should be found. In the original procedure, the DMF is removed by vacuum at an extremely high vacuum. In my hands however, it was impossible to remove all of the DMF, so the TMANO was stored and used still "wet" with DMF. This anhydrous TMANO is extremely hygroscopic, and was a somewhat soggy material, which was very inconvenient to weigh out before it absorbed water. Initially this product was stored in the glovebox, but to the extremely potent aroma coming off the material, it was banned from the glovebox for fear of harming sensitive catalysts or the purification system/circulation system. In the second iteration, a stock solution of TMANO in DCM (which is the solvent it is dissolved in before addition to the 9-BBN reagent) was prepared. This stock solution worked well upon preparation, however after ~1 month, the synthesis of an OBBD compound failed. It was noticed that a white precipitate had formed in the flask. This solid was isolated, but the nature could not be ascertained by NMR. Overall, it appears that TMANO will react with DCM if given enough time, and that while the idea of making a stock solution seemed sound at the outset, it created far more trouble than it was worth, and ruined quite a lot of carefully prepared anhydrous TMANO.

2.4 Precedence for sp^3-sp^2 Couplings in Water

The formation of sp^3-sp^2 carbon-carbon bonds is a valuable disconnection because of the possibility to connect nearly any alkyl group desired to an sp^2 electrophile. The precedence for this type of coupling in aqueous medium is very limited. At the time of this project, the only well studied method for the alkylation of aryl/vinyl halides was the "Negishi-like" coupling using alkyl halides with suitable sp^2 bromides and iodides shown in Scheme 7 below.[50]

Scheme 7: Precedence for Sp^3-Sp^2 couplings in water

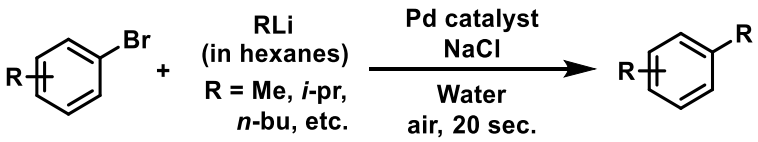


This method is interesting from a perspective that alkyl zinc reagents would be expected to be too water intolerant for coupling to occur, and that they can be prepared in-situ. However, some limitations exist with this method, including the use of multiple equivalents of zinc, TMEDA, and large excesses of the alkyl halide due to dehalogenation and/or quenching due to the presence of water. While these reactions were well studied, there was no real alternative to couple sp^3-sp^2 groups. Because of these limitations, this project was conducted to fill this need, and further broaden the types of coupling reagents useful in surfactant medium.

[50] (a) Krasovskiy, A.; Duplais, C.; Lipshutz, B. H. *J. Am. Chem. Soc.* **2009**, *131*, 15592–15593. (b) Duplais, C.; Krasovskiy, A.; Lipshutz, B. H. *Organometallics* **2011**, *30*, 6090–6097. (c) Krasovskaya, V.; Krasovskiy, A.; Bhattacharjya, A.; Lipshutz, B. H. *Chem. Commun.* **2011**, *47*, 5717–5719. (d) Bhonde, V. R.; O'Neill, B. T.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2016**, *55*, 1849–1853.

An interesting and seemingly highly unfavorable sp^3-sp^2 Murahashi coupling in water (Scheme 8) was published[51] after our report on sp^3-sp^2 Suzuki couplings in water discussed here (2019 vs 2018).[52] Though this is not a Suzuki coupling, it is noteworthy to mention here because it accomplishes the same type of bond formation.

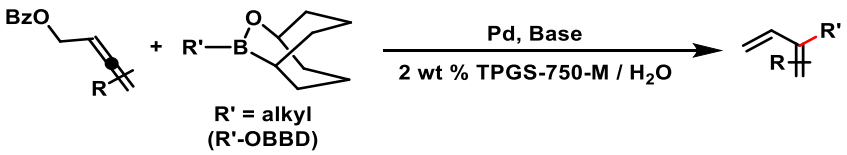
Scheme 8: Precedence for Murahashi coupling in water



This work is not only notable for the successful use of water sensitive alkyl lithium reagents in water, but also the method was scalable to 1 g of material, conducted under air, and that the catalyst and reaction medium could be recycled/reused multiple times.

Alkyl boron reagents have been applied to other types of reactions in surfactant medium. Reaction of an alkyl-OBBD (*B*-alkyl-9-oxa-10-borabicyclo[3.3.2]-decane) with an allenoate furnishes the alkyl butadiene[53], or dendralene[54] (Scheme 9).

Scheme 9: Precedence for use of OBBD reagents in water



During these studies, a number of boron reagents were screened for these reactions. Various alkyl boronic acids, Bpin, BF_3K, and B-MIDA reagents were screened, but

[51] Dilauro, G.; Francesca Quivelli, A.; Vitale, P.; Capriati, V.; Perna, F. M. *Angew. Chem. Int. Ed.* **2019**, *58*, 1799–1802.
[52] Lee, N. R.; Linstadt, R. T. H.; Gloisten, D. J.; Gallou, F.; Lipshutz, B. H. *Org. Lett.* **2018**, *20*, 2902–2905.
[53] Lippincott, D. J.; Linstadt, R. T. H.; Maser, M. R.; Gallou, F.; Lipshutz, B. H. *Org. Lett.* **2018**, *20*, 4719–4722.
[54] Lippincott, D. J.; Linstadt, R. T. H.; Maser, M. R.; Lipshutz, B. H. *Angew. Chem.* **2017**, *129*, 865–868.

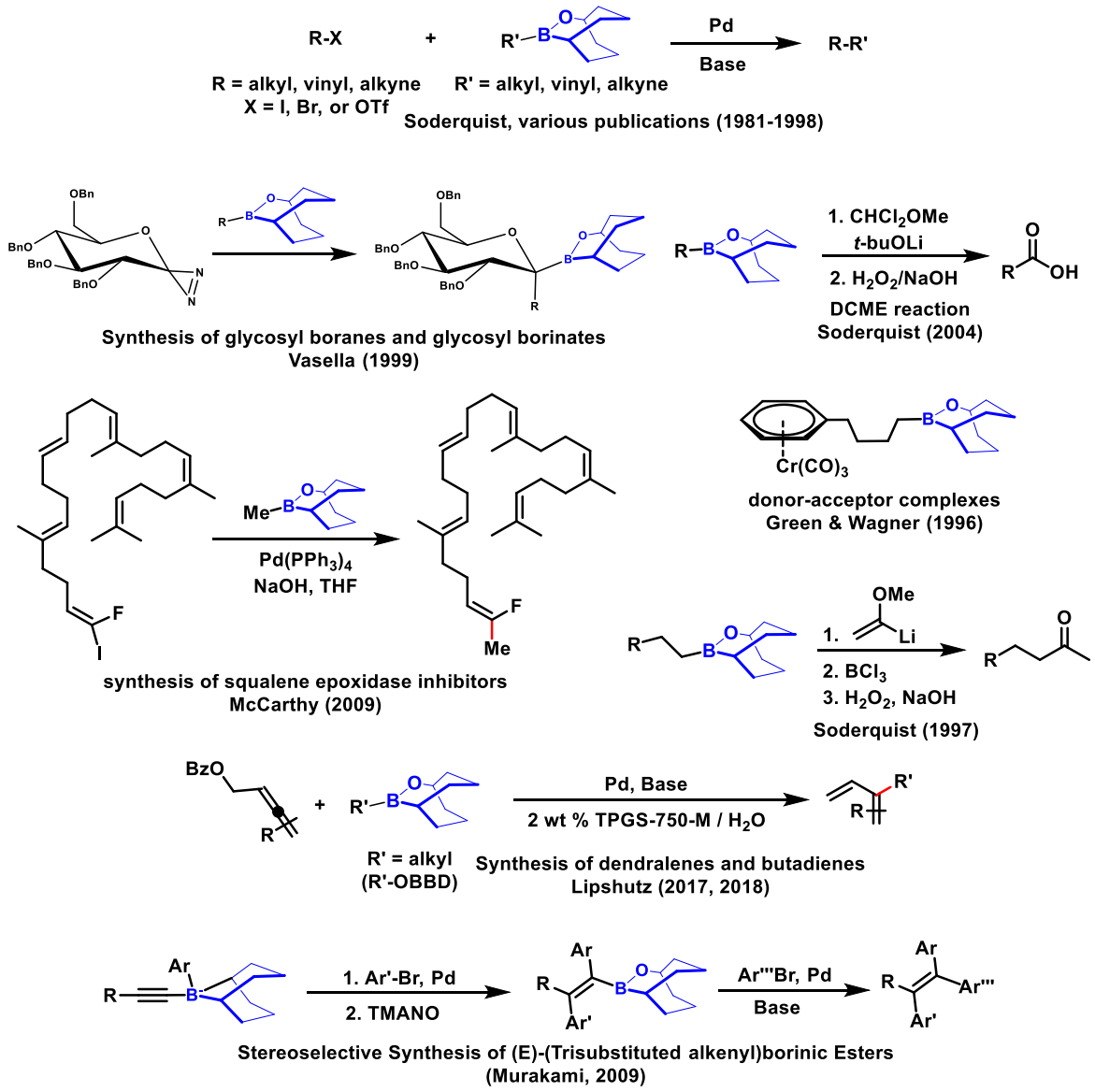
typically gave no reaction, or unsatisfactory performance. The OBBD reagents however were very reactive, conveniently isolable, and had good storage lifetime which made them uniquely suited to this application.[55]

2.5 Literature Precedence for OBBD Reagents

OBBD reagents are somewhat uncommon, the literature precedence for their use for Suzuki couplings primarily involves John Soderquist's work.[56] In addition to their use in Suzuki couplings, they have also been applied to a number of other reaction types and applications (Scheme 10). Synthesis of glycosyl borinates from diazirines,[57] use in DCME homologation reaction for the synthesis of carboxylic acids,[58] and the synthesis of a borinate bound chromium complex[59] to act as an arene π-donor group and a boron σ-acceptor are notable variations.

[55] PhD thesis of Daniel J. Lippincott
[56] (a) Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461–470. (b) Soderquist, J. A.; León, G.; Colberg, J. C.; Martínez, I. *Tetrahedron Letters* **1995**, *36*, 3119–3122. (c) Soderquist, J. A.; Rane, A. M.; Matos, K.; Ramos, J. *Tetrahedron Lett.* **1995**, *36*, 6847–6850. (d) Rivera, I.; Colberg, J. C.; Soderquist, J. A. *Tetrahedron Lett.* **1992**, *33*, 6919–6922. (e) Soderquist, J. A.; Santiago, B.; Rivera, I. *Tetrahedron Lett.* **1990**, *31*, 4981–4984. (f) Soderquist, J. A.; Martinez, J.; Oyola, Y.; Kock, I. *Tetrahedron Lett.* **2004**, *45*, 5541–5543. (g) Soderquist, J. A.; Ramos, J.; Matos, K. *Tetrahedron Lett.* **1997**, *38*, 6639–6642.
[57] Vasella, A.; Wenger, W.; Rajamannar, T. *Chem. Commun.* **1999**, *0*, 2215–2216.
[58] Soderquist, J. A.; Martinez, J.; Oyola, Y.; Kock, I. *Tetrahedron Lett.* **2004**, *45*, 5541–5543.
[59] Green, M. L. H.; Wagner, M. *J. Chem. Soc., Dalton Trans.* **1996**, *0*, 2467–2473.

Scheme 10: Literature precedence for the use of OBBD reagents



Their use as *B*-sp^3-alkyl partners in Suzuki-Miyaura (SM) couplings, however, has not been much explored outside of Soderquist's original reports, with the exception of methylations in the synthesis of squalene epoxidase inhibitors, and the synthesis of trisubstituted alkenyl borinates and their subsequent Suzuki coupling.[60] The only literature

[60] Ishida, N.; Shimamoto, Y.; Murakami, M. *Org. Lett.* **2009**, *11*, 5434–5437.

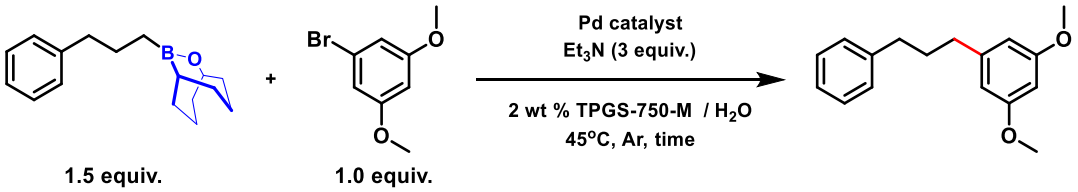
on their use in water or predominantly aqueous reaction mixtures is their reaction with allenoates to form functionalized dendralenes[61] and butadienes.[62]

2.6 Initial Studies & Discovery Conditions

The idea for the project arose from the prior application of OBBD reagents to deliver alkyl groups to allenoates for the synthesis of functionalized butadienes and dendralenes. Roscoe Lindstadt suggested that I should do an alkyl Suzuki coupling using the OBBD reagents because of their success in coupling with the π-allyl/allenyl system of allenoates. He mentioned that he had coupled iodobenzene with an OBBD using $Pd(OAc)_2$/Handaphos at 1 mol % Pd, Et_3N as base, and of course TPGS-750-M solution as solvent/reaction medium. Some of the desired Suzuki product was formed after 48 h reaction time, though no further optimization or substrate scope development was tested. Given those starting conditions, I set about making a simple "model" OBBD substrate for use in reaction conditions screening. Initial trials were meant to determine the feasibility of this coupling using aryl bromides in surfactant as iodides are typically less common, more expensive, and less stable. Roscoe's initial trial had been conducted with Handaphos / $Pd(OAc)_2$, so this was included in the initial screening as well as several other common catalyst combinations known to work with either Suzuki couplings in water, or with OBBD couplings to allenoates (Table 1).

[61] Lippincott, D. J.; Linstadt, R. T. H.; Maser, M. R.; Lipshutz, B. H. *Angew. Chem.* **2017**, *129*, 865–868.
[62] Lippincott, D. J.; Linstadt, R. T. H.; Maser, M. R.; Gallou, F.; Lipshutz, B. H. *Org. Lett.* **2018**, *20*, 4719–4722.

Table 1: Initial Discovery Conditions



Entry	Catalyst	mol % Pd	Time (h)	Isolated Yield (%)
NL255.1	$Pd(OAc)_2$/Handaphos	1.0	48	80
NL263.5	$Pd(OAc)_2$/Handaphos	1.0	18	44
NL263.6	$Pd(OAc)_2$/Handaphos [a]	1.0	18	36
NL255.2	$Pd(OAc)_2$/Handaphos	0.5	48	28
NL255.3	$Pd(OAc)_2$/Handaphos	0.1	48	NR[b]
NL263.1	$Pd(dtbpf)Cl_2$	2.0	18	63
NL263.2	$Pd(DPEPhos)Cl_2$	2.0	18	58
NL263.3	$[Pd(allyl)Cl]_2$ / Sphos	2.0	18	44
NL263.4	$Pd(PPh_3)_2Cl_2$	5.0	18	77

[a] with 10 vol % THF co-solvent

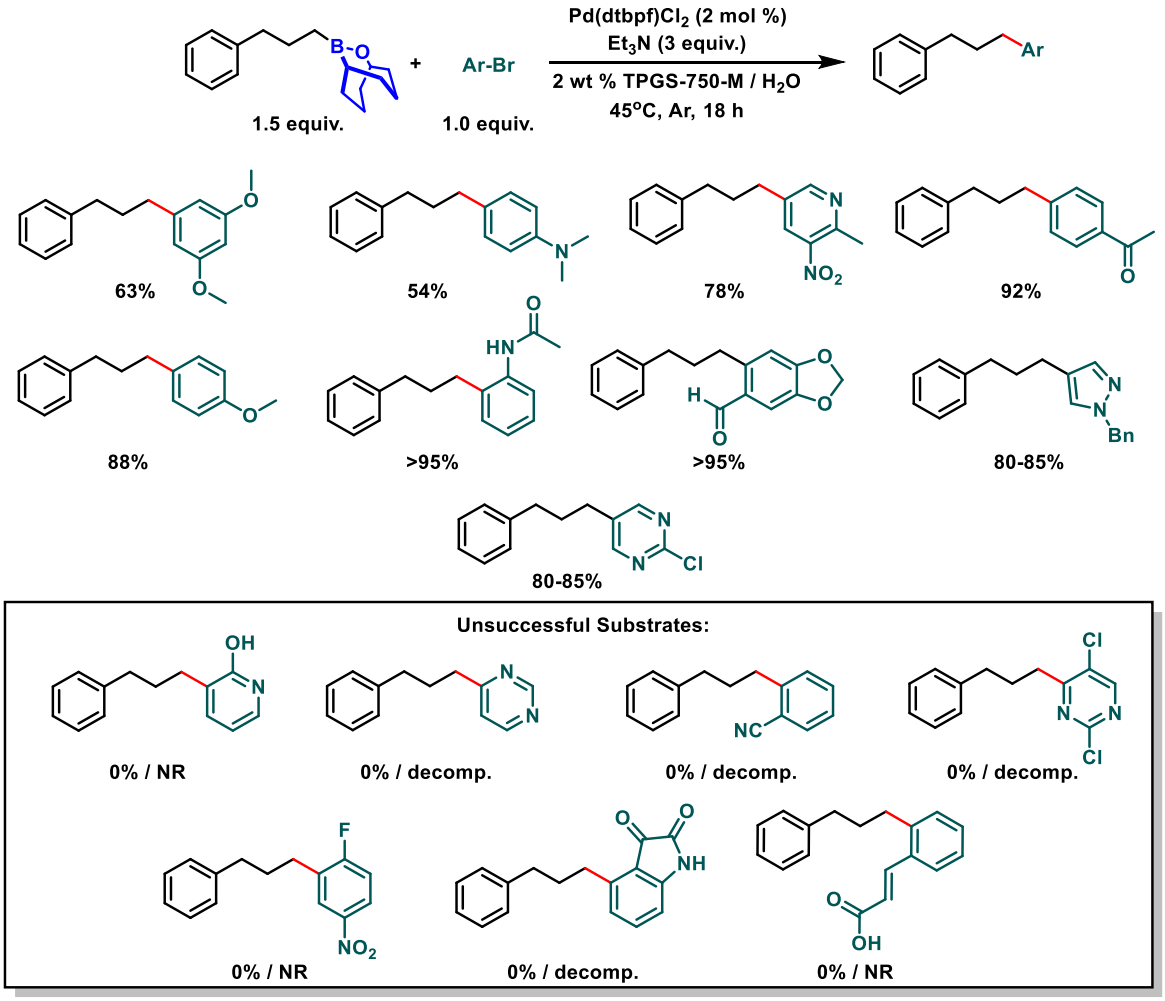
[b] NR = no reaction

Based on initial screening trials, it appeared that most ligands and Pd sources were amenable to the coupling. An optimized procedure had not yet been established, and while these were not completely comparable trials, it served to give an idea that the coupling appeared to work relatively well. In addition, it was not realized at this point just how air sensitive the coupling was. These initial trials were conducted in capped vials, where the reagents were added, and a stream of argon was used to purge the headspace before capping. This was likely not an effective or reproducible level of degassing. Also, the choice of the 1-bromo-3,5-dimethoxybenzene coupling partner was

completely accidental, but very fortuitous, because in later screening trials and optimization, this bromide turned out to be one of the best coupling partners we ever found, and active at lower catalyst loadings than almost any other substrate. It was very lucky that this bottle happened to be on a nearby shelf, because quite a few other bromides turned out to be unreactive or produced messy reaction mixtures. In hindsight, if the wrong bromide(s) were chosen at this point, this project might have been abandoned. With these preliminary results in hand, and a now optimistic outlook on the future of this project, further studies were conducted.

To further determine the scope of electrophiles, and whether there was a marked preference for EWG or EDG functionality on the aryl bromide, a preliminary substrate scope was developed (Scheme 11). The choice to use Pd(dtbpf)Cl_2 was another fortuitous event, the choice was made because the above trial using this catalyst appeared to give somewhat less byproducts than the other catalysts while giving a good yield, later in the study we screened other catalysts, but failed to find a better one. While the screening could have (and probably should have) continued using Handaphos, we simply didn't have any more. Sachin Handa had left, Bala Takale (who later synthesized this ligand) had not yet arrived, and so rather than performing the lengthy synthesis, I continued with Pd(dtbpf)Cl_2.

Scheme 11: Initial screening of aryl bromides/electrophiles



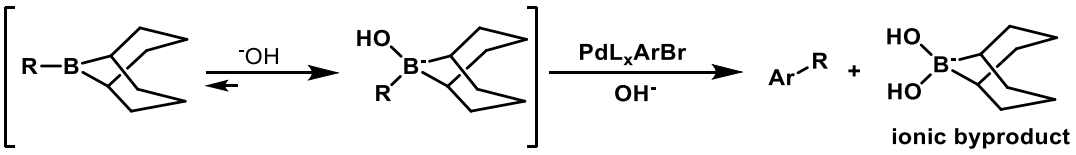
From these initial tests, it appeared that finding cooperative bromides was not going to be a problem. No clear trend was seen in reactivity, and an optimized procedure was still not really developed, so these yield % values must be taken with a grain of salt. A number of substrates however were not receptive, either giving no apparent product, or intractable mixtures of "spots" by TLC. In addition, it was noted that some products were nearly impossible to purify by column chromatography. Though multiple sequential columns could be run on a single sample, and the fractions would appear to contain only one "spot" by TLC, the NMR would show significant amounts of alkyl "fuzz" in the 0.8-2.5

ppm region in the ^{1}H-NMR. It was initially unclear what was happening, and this led to instances of multiple sequential columns being run on a single sample, with increasing frustration, but little to no improvement in purity from column to column.

2.7 Workup Considerations

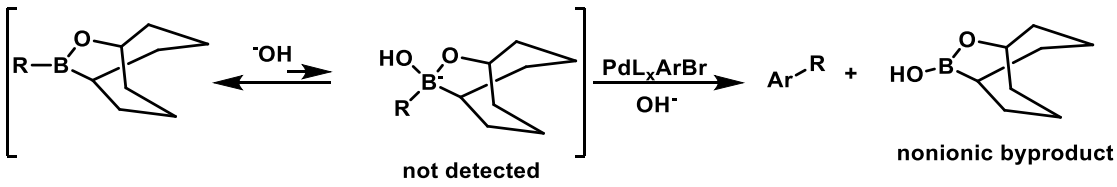
After struggling with these purification-resistant substrates, some trends were noticed. Initial reactions with hydrocarbon-and-oxygen-only containing products were easily purified by column chromatography. However, upon moving on to nitrogenous products, particularly nitrogen containing heterocycles, purification by column chromatography was largely ineffective. The impurities in the alkyl region suspiciously resembled the NMR of the starting OBBD reagents, and it was concluded that the cleaved OBBD "cage" was complexing with these products and co-eluting. Little to no mention of special workup procedures were indicated in the extensive literature on 9-BBN couplings (except for references suggesting to destroying excess borane before workup, presumably out of flammability concern), and the OBBD coupling literature was very scant. The cause of this particularly troublesome issue in the case of OBBD reagents may be related to its reaction with base. It's been shown that the OBBD and 9-BBN reagents behave differently in the presence of base, and evidence exists to show that because of this, the two reagents have different rate determining steps in the Suzuki coupling.

Scheme 11: 9-BBN reagent reaction with base



Alkyl 9-BBN reagents react readily with hydroxide in solution to produce a charged intermediate prior to coupling. While the product of a 9-BBN coupling under basic conditions is drawn as the ionic compound above (Scheme 11), the product of an OBBD coupling is represented as a non-ionic compound below (Scheme 12). We hypothesize that this may be causing the troublesome workup by complexing nitrogenous compounds to the hydroxy OBBD byproduct.

Scheme 12: OBBD reagent reaction with base

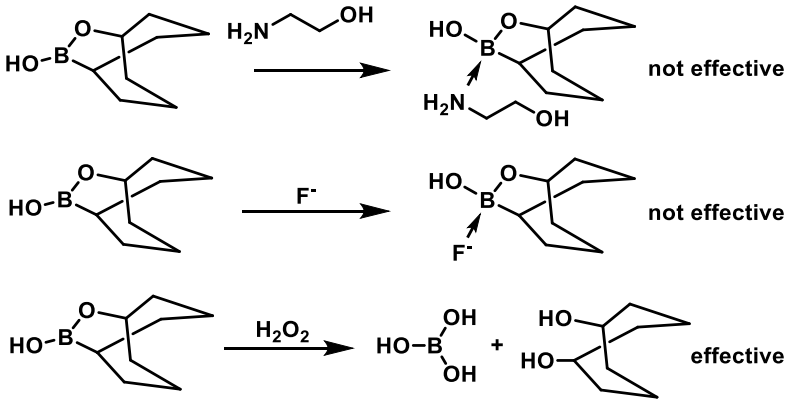


After conducting more than one consecutive column on the same sample, it became clear that a workup procedure was needed, so several workups were screened (Scheme 13). One literature method for 9-BBN workup involved treating with ethanolamine, [63] and the ethanolamine-borane derivative removed by filtration, or by washing the organic extracts with aqueous ethanolamine. Unfortunately, this did not work in our case, the unwanted byproducts persisted. In the second attempt, a wash of the organic extracts with KF solution also failed. However, hydrogen peroxide[64] proved very effective, a small amount of hydrogen peroxide was immediately effective, further oxidizing the troublesome OBBD "cage" to the corresponding diol. Unfortunately, workup with peroxide somewhat limits substrate scope, as compounds susceptible to oxidation proved unhappy with this treatment

[63] Diederich, F.; Stang, P. J. *Metal-Catalyzed Cross-Coupling Reactions*; John Wiley & Sons, 2008. (pg. 87)
[64] (a) Soderquist, J. A.; Santiago, B. *Tetrahedron Lett.* **1990**, *31*, 5541–5542. (b) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Sato, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314–321.

(i.e. benzaldehyde derivatives). Additionally, an H_2O_2 workup is used industrially for workup borane/borohydride reactions for safety/disposal purposes.

Scheme 13: Various workup methods screened to aid in purification

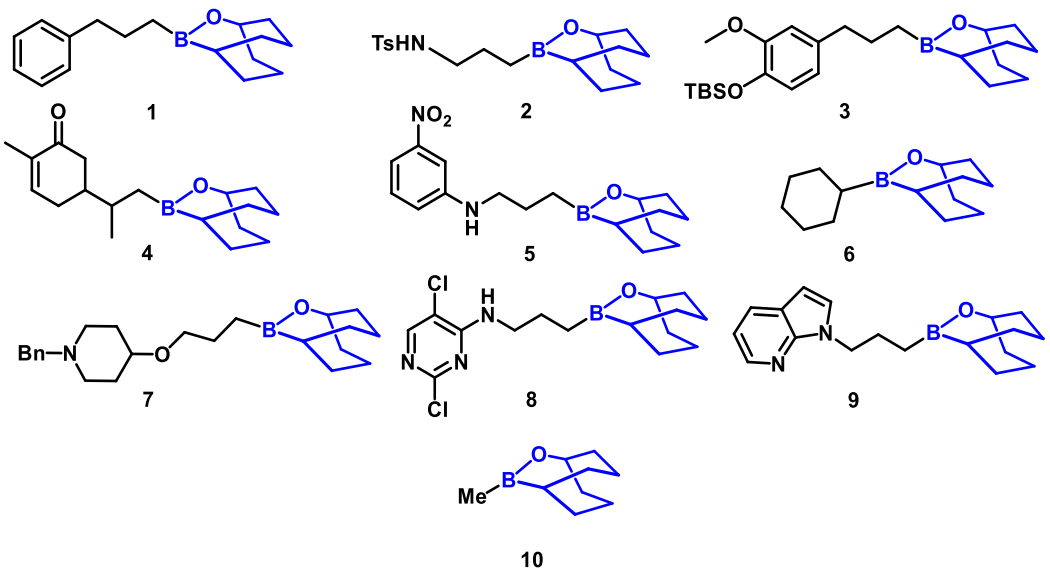


Once this problem of workup/purification was diagnosed and resolved (which consumed more time that it rightfully should have), attention was turned towards expanding the substrate scope. While a number of aryl bromide electrophiles had been found to be suitable, very little testing of other OBBD derivatives had been tested (aside from 2-3 partially decomposed OBBD derivatives donated from the original allenoates coupling project).

2.8 Library of OBBD reagents synthesized

While the screening of aryl bromides showed that most coupling partners worked, the effect of changing the OBBD coupling partner had not yet been explored. For this task, a library of OBBD reagents were synthesized (Scheme 14). Most of the OBBD reagents were synthesized by the hydroboration/selective oxidation route previously outlined. Some interesting functional group compatibilities were possible including the enone carvone, sulfonamides, anilines, nitro groups, and TBS protected alcohols.

Scheme 14: Library of OBBD reagents prepared



A somewhat expected trend in rate of hydroboration was noted (in the form of some incomplete reaction mixtures), where di-substituted alkenes required much longer reaction times (i.e. **1** faster than **4**) prior to adding the oxidizing agent to for the OBBD. This difference in hydroboration rate is very important because if the hydroboration is not complete when the TMANO reagent is added, the result is a messy reaction mixture which decomposes when exposed to air. Because the hydroboration reaction cannot be easily monitored by TLC or GC-MS it was helpful to prepare air-free crude NMR samples to note when the alkene had been consumed.

While literature methods utilizing OBBD reagents mentioned that they were “air stable” there was no particular timeframe given about this stability or how exactly it was tested. Also, the literature OBBD reagents were typically low molecular weight and were usually purified by vacuum distillation. Many of the OBBDs prepared for this study were too high-molecular weight for distillation, so silica gel filtration/chromatography was

cautiously attempted. It was noticed during their preparation that some OBBDs were much more stable than others. In particular, OBBD **8** was very sensitive, decomposing rapidly on silica gel during attempted purification. OBBD **3**, was so stable that it could survive reaction conditions used for coupling, workup (only if H_2O_2 was omitted), column chromatography, and could still be isolated intact (sometimes as an impurity in the desired product). Initially, I was afraid that OBBDs would be too sensitive for column chromatography (which proved partially true in some cases), so these reagents were typically only purified by a quick filtration through pre-wetted silica, this resulted in widely varying purities of the final OBBD products, but nonetheless all OBBDs coupled successfully, except for the 2^o substrate **6** which proved unreactive to all attempts at coupling. One use of the organometallic route was utilized to synthesize the Me-OBBD. Me-OBBD was synthesized by reaction of 9-BBN dimer with MeOH, then methyl lithium, and finally with TMANO largely according to a literature procedure.[65]

2.9 Air Sensitivity Testing

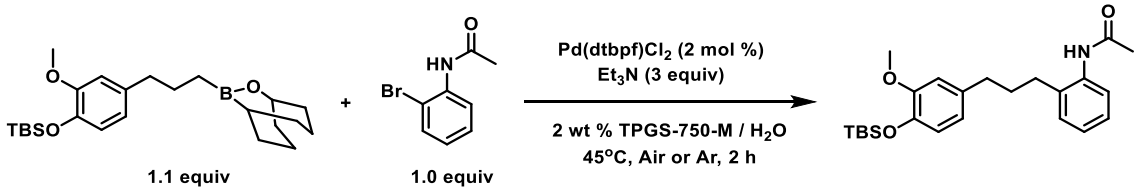
One of the main points of this work was to utilize a convenient, isolable, stable reagent for alkyl Suzuki couplings. During this work, while explaining this concept to fellow labmates, there was some confusion. By saying that the OBBD reagent is air stable, some thought that this implied that the coupling reaction was also air-tolerant. Literature examples of the use of these reagents mentioned that the reagents did not decompose readily under air, but there was no measurement or exact lifetimes for these reagents given, and literature reactions were conducted under nitrogen or argon atmosphere. It was

[65] Soderquist, J. A.; Santiago, B. Methylation via the Suzuki Reaction. *Tetrahedron Letters* **1990**, *31* (39), 5541–5542.

noticed during handling that the OBBD reagents were definitely not indefinitely air stable. Small aliquots (i.e. TLC samples dissolved in EtOAc) would begin to show decomposition after standing overnight, and would often largely decompose after 2 days open to air. Because of the lack of data on both the air sensitivity of the reagent, as well as the air sensitivity of the reaction, several comparison experiments were devised to compare OBBDs with 9-BBN derivatives. The OBBD/9-BBN derivative chosen was probably the most stable compound in the OBBD library, it was the highest purity OBBD prepared, and coupled readily, thus it was chosen for the tests.

As a simple measure of the sensitivity of the reaction to air exposure, the reaction was either run under an atmosphere of argon, or run under air (Table 2). The reactions were run in vials capped with a septum (to prevent evaporation of Et_3N), so the only air present would be the headspace in the vial.

Table 2: OBBD coupling conducted under air vs. argon atmosphere



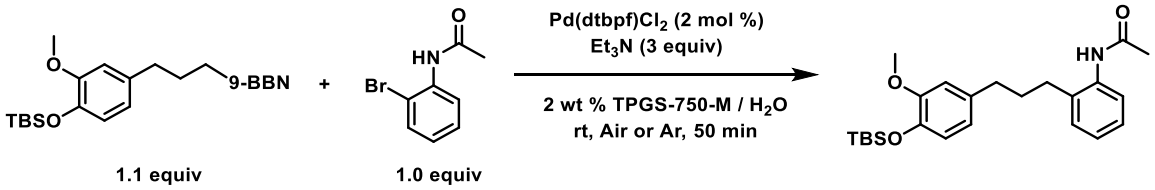
Trial	Air/Argon	Yield
NL-2-183.2	Argon	94%
NL-2-183.3	Air	51%

Failing to exchange the air for argon in the reaction vessel caused >40% decrease in yield even at the relatively high Pd loading of 2 mol % (this coupling will fully reach

completion at 0.25-0.5 mol % Pd). This reaction is typically complete in <45 minutes with this Pd loading, so the reaction was left for 2 h, ample time to reach completion. Overall, it appeared that the palladium catalyst and/or reagent suffered greatly from exposure to air.

The same air exposure test using a 9-BBN reagent gave a similar result as the OBBD coupling, much lower yield if the reaction was not conducted under argon (Table 3). While the 9-BBN derivative is much more reactive in the coupling, it is also more air sensitive. The somewhat lower yield of the "under argon" trial may be due to the difficulty in isolating the 9-BBN without exposure to air, thus the 94% vs 83% yields between OBBD and 9-BBN trials under argon might not be fairly comparable. Once again, it appeared that the palladium catalyst and/or reagent suffered greatly from exposure to air.

Table 3: 9-BBN coupling conducted under air vs. argon atmosphere

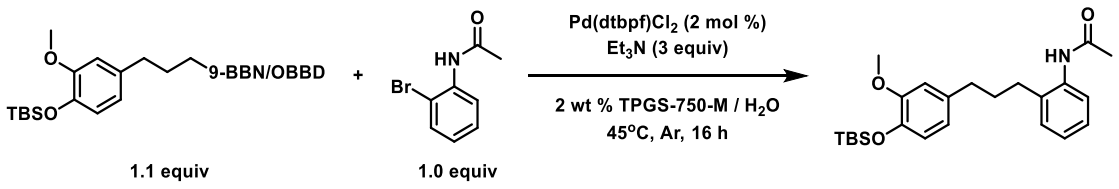


Trial	Air/Argon	Yield
NL-2-184.1	Argon	83%
NL-2-185.1	air	50%

Because it is difficult to separate the air sensitivity of the boron reagent itself from the air sensitivity of the Pd catalyst, a 3rd type of air sensitivity test was devised. The

prepared boron reagent was stirred neat, open to air for 1 h. After 1 h, the coupling reagents were added, and the reaction conducted under argon as per the usual procedure (Table 4).

Table 4: Exposing *B*-alkyl reagent to air for 1 h, then conducting the coupling under argon



Trial	Boron Compound	Yield
NL-2-207	9-BBN	49%
NL-2-208	OBBD	92%

While stirring in air, the 9-BBN reagent turns from a clear oil to a milky white oil, whereas the OBBD reagent remains a clear oil. The result is that the OBBD reagent gives essentially the same yield as typically seen, and the 9-BBN reagent decreases about 40% in yield. Because of this, we feel that the OBBD is a more convenient reagent to use because of the ability to handle under air for periods of time. In addition, as was pointed out by Roscoe, the 9-BBN derivative used in this trial is very high molecular weight and the presence of oxygens on the molecule might serve to complex/shield the 9-BBN from further oxidation by air. During the study on allenoates he attempted to prepare and isolate an *n*-octyl 9-BBN derivative which began angrily fuming and decomposed immediately upon exposure to air. Therefore, this difference between 9-BBN and OBBD

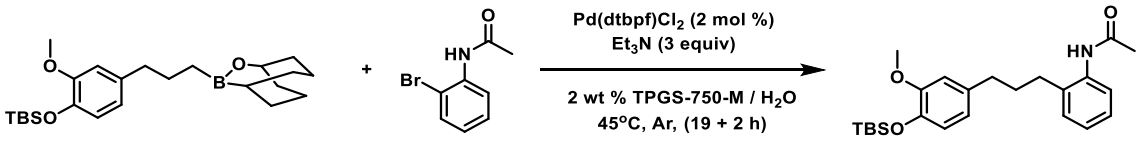
would likely be much more dramatic (potentially igniting) if a lower molecular weight 9-BBN had been used in these trials.

The overall findings from the air sensitivity testing were that care must be taken to remove oxygen from the reaction mixture, but that no particularly special precaution was needed when handling OBBD reagents in air for short periods of time while weighing/syringing/adding to reaction mixtures. Therefore, the OBBD reagent proved very convenient for our purposes in this regard because it could be freely handled, stored, and utilized. Some of these derivatives were successfully stored for >1 year in argon purged, capped vials for over 1 year.

2.10 Reaction Optimization

Because there was no literature precedence for OBBD Suzuki couplings in water, a number of reaction parameters could likely be optimized. While conditions for "typical" Suzuki couplings in water (i.e. common Pd catalysts, triethylamine, argon, etc) had so far produced respectable results, we sought to improve the conditions further. One of the first considerations, especially due to the expensive and specialized nature of this reagent, is the amount of excess boron reagent used. While most SM couplings published in water use a significant excess of boron reagent (i.e. 1.5 equiv), and so far we had been using this 0.5 equivalent excess of boron reagent, this seemed an obvious place to begin. After adding the minimum possible 1.0 equivalents of OBBD reagent, the coupling failed to reach completion, but happily the addition of only 0.1 additional equivalents to the reaction mixture resulted in full conversion (Table 5). This proved to be overly optimistic, because other OBBD derivatives prepared were not as pure as this sample, so additional reagent (i.e. 1.2-1.4 equivalents) was required in many cases.

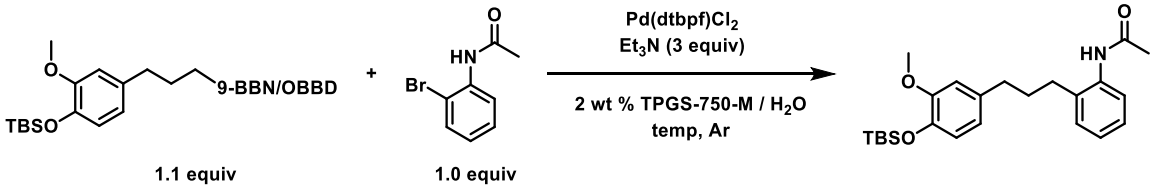
Table 5: Optimizing equivalents of OBBD reagent



Trial	OBBD (equiv)	Result
NL-2-168.2&3	1.0	~90% conversion
NL-2-168.1&4	1.0 + 0.1	Complete (>95% isolated)

Initial attempts to decrease catalyst loading resulted in disappointing results, but increasing temperature from ambient to 45°C improved conversion (Table 6). This was not surprising, as most of the Suzuki couplings published in our group using low catalyst loadings are run at above ambient temperature. Because the OBBD reagents failed to reach reasonable conversion, the analogous 9-BBN derivative was tested and gave a significant amount of conversion at 0.1 mol % Pd (51% isolated), whereas the OBBD reagent gave no conversion whatsoever at this loading. Overall, this confirms the previous assumption that the 9-BBN derivative is more reactive than the OBBD reagent.

Table 6: Attempting lower catalyst loadings

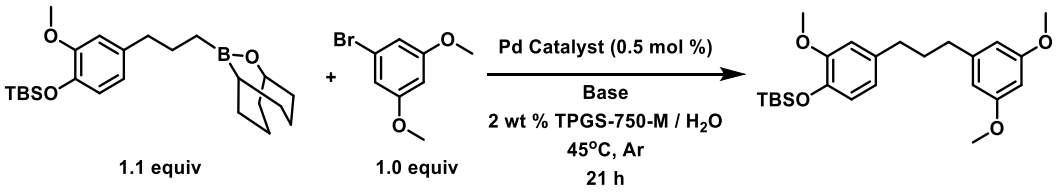


Trial	Catalyst (mol %)	Boron reagent	Time (h)	Temp	Yield (isolated yield %)
NL-2-187.1	1.0	OBBD	48	rt	>50% conversion
NL-2-187.2	**1.0**	**OBBD**	**48**	**45**	**Full conversion (86%)**
NL-2-187.4	0.5	OBBD	48	rt	No rxn
NL-2-187.3	0.5	OBBD	48	45	~50% conversion
NL-2-187.5	0.1	OBBD	48	45	No rxn
NL-2-187.6	0.1	9-BBN	48	45	51% isolated

While the smattering of Pd catalysts (and various mol % Pd loadings) attempted in the discovery trials were largely based on recommendations from Roscoe Linstadt and Dan Lippincott, a more controlled ligand study was needed. DTBPF performed well in the discovery trials, and had previously been found to be a good ligand for Suzuki couplings in water. SPhos has also been found to be a very suitable ligand for Suzuki couplings in water. DPPF appears frequently in the literature in regards to 9-BBN Suzuki couplings, so it was screened as well. Evanphos was a newly created ligand specifically for Suzuki couplings in water, so it was screened as well. Another question of catalyst activation arose, specifically in regards to our efforts to decrease Pd loadings. While most Pd catalysts are available as Pd(II) complexes, the active catalyst for a Suzuki coupling is a Pd(0) species. While the generation of Pd(0) can be achieved in-situ by a number of routes (i.e. β-hydride elimination of Et_3N, homocoupling of boronic acids, etc.), in some

cases it has been found to be beneficial to use a reducing agent such as DIBAL added to the catalyst stock solution (typically in toluene of THF) in order to reduce Pd(II) to Pd(0), prior to addition of the catalyst to the surfactant solution.[66] This catalyst preactivation was found to be especially helpful when using Evanphos for aryl-aryl Suzuki couplings. Screening this selection of ligands, DIBAL activation, and choice of base is shown in Table 7.

Table 7: Screening additional ligands, base, & DIBAL catalyst activation



Entry	Catalyst (mol %)	DIBAL*	Base	Isolated Yield (%)
NL-2-246.1	$Pd(dtbpf)Cl_2$	yes	Et_3N (3)	N/A; poor conv.
NL-2-246.2	SPhos / $Pd(OAc)_2$	yes	Et_3N (3)	N/A; poor conv.
NL-2-246.3	$Pd(dppf)Cl_2$	yes	Et_3N (3)	N/A; poor conv.
NL-2-246.4	EvanPhos / $Pd(OAc)_2$	yes	Et_3N (3)	N/A; poor conv.
NL-2-247.1	$Pd(dtbpf)Cl_2$	no	Et_3N (3)	82
NL-2-247.2	SPhos / $Pd(OAc)_2$	no	Et_3N (3)	58
NL-2-247.3	$Pd(dppf)Cl_2$	no	Et_3N (3)	42
NL-2-247.4	EvanPhos / $Pd(OAc)_2$	no	Et_3N (3)	7
NL-2-249.1	**$Pd(dtbpf)Cl_2$**	**no**	**K_3PO_4 (1.5)**	**94**
NL-2-249.2	SPhos / $Pd(OAc)_2$	no	K_3PO_4 (1.5)	84
NL-2-249.7	EvanPhos / $Pd(OAc)_2$	no	K_3PO_4 (1.5)	49
NL-2-249.8	Evanphos / $Pd(OAc)_2$	yes	K_3PO_4 (1.5)	41

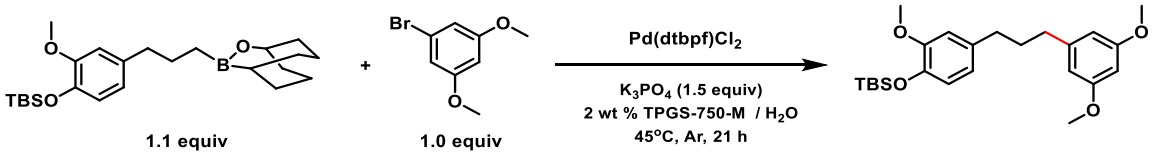
[66] Landstrom, E. B.; Handa, S.; Aue, D. H.; Gallou, F.; Lipshutz, B. H. *Green Chem.* **2018**, *20*, 3436–3443.

*DIBAL was added to the catalyst stock solution for reduction of Pd(II) to Pd(0) using 2.0 equivalents relative to Pd.

While the trials using DIBAL activation showed some conversion after the first ~1 h reaction time, none of them had reached anywhere near full conversion at 21 h. It's not clear why the use of DIBAL would be detrimental in these cases, while being effective in the case of sp^2-sp^2 Suzuki couplings in the same TPGS-750-M reaction medium. One hypothesis put forward involved aluminum salts somehow interfering with the boron reagent, but the DIBAL is used in proportion to the Pd catalyst, so only a very small amount should be present in the reaction mixture. In addition, it is noteworthy that Pd(dppf)Cl_2 and Pd(dtbpf)Cl_2 share a very similar structure, but a marked preference for dtbpf was seen in these reactions. While Et_3N had been the only base screened so far, K_3PO_4 gave significantly better results.

Because of the successful trials at 0.5 mol % Pd and improvement seen with a change of base to K_3PO_4, an attempt to further decrease the loading was made (Table 8). Happily, the reaction proceeded to completion at 0.25 mol % Pd, although the 0.1 mol % Pd trial failed to reach completion, 46% yield was isolated.

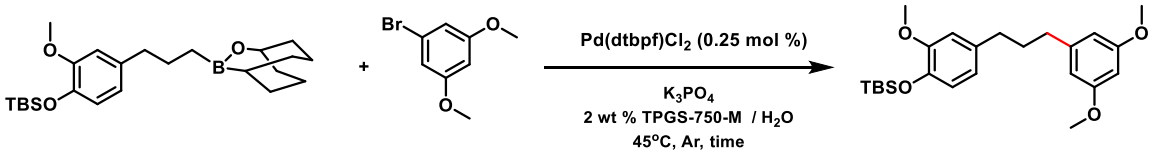
Table 8: Attempting lower catalyst loadings



Entry	Catalyst	Isolated Yield (%)
NL-2-264.3	0.50%	94
NL-2-264.2	0.25%	94
NL-2-264.1	0.10%	46

Up to this point, all trials had been conducted at 0.5 M reaction concentration, which is a typical reaction concentration for running reactions in TPGS-750-M. However, due to a suggestion from Dan Lippincott, who related that he had seen significantly better conversion of some reaction types by using a 0.75 M reaction concentration, the effect of reaction concentration was tested. Because all of these trials should reach completion, in order to see a difference between conditions, the reactions were “stopped short” at 4 or 3 hours to see “who was ahead” (Table 9).

Table 9: Base Equivalents and Concentration Effects



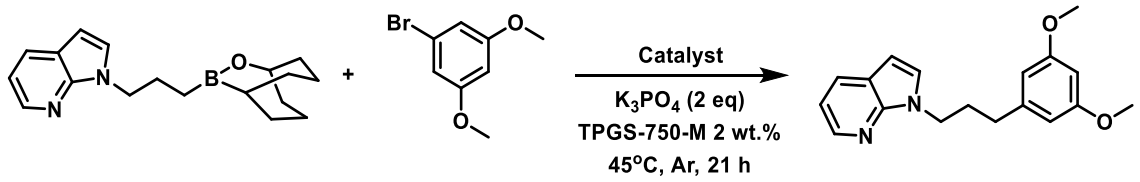
Entry	Reaction conc. (M)	K_3PO_4 (equiv)	Rxn time (h)	Isolated Yield (%)
NL-2-273.4	0.5	1.5	4	62
NL-2-273.1	0.75	1.5	4	85
NL-2-273.2	1.0	1.5	4	89
NL-2-273.3	**0.5**	**2.0**	**4**	**90**
NL-2-276.1	0.75	2.0	3	60
NL-2-276.2	0.75	2.5	3	67
NL-2-276.3	1.0	2.0	3	57
NL-2-276.4	**1.0**	**2.5**	**3**	**73**

Indeed, increasing concentration from 0.5 to 0.75 M gave a significant increase in yield (62 to 85%), and a smaller changed increasing to 1 M (85-89%). To test whether increasing base was relevant, one trial using 2.0 equiv of K_3PO_4 was included, which showed a similar increase in yield, which was comparable to the increase in concentration. A significant increase in "oiling out" was noted at these higher concentrations and higher base loadings as opposed to the 0.5 M and 1.5 equivalents of base originally used.

At the same time this project on alkyl Suzuki couplings was underway, a fellow labmate Bo Jin was working on "*ppm* Pd" Sonogashira couplings. He had found that the Takasago BRIDP family of ligands were very effective as catalysts for Sonogashira couplings in

TPGS-750-M reaction medium, specifically when used with $[(cinnamyl)PdCl]_2$ as Pd source. This family of ligands were screened against $Pd(dtbpf)Cl_2$ on this difficult coupling case (Table 10).

Table 10: Additional ligand screening



Entry	Catalyst	Catalyst (mol %)	OBBD (equiv)	Result
1	cBRIDP / $[(cinnamyl)PdCl]_2$	0.5	1.5	Trace conversion
2	**Cy-cBRIDP / $[(cinnamyl)PdCl]_2$**	**0.5**	**1.5**	**87% isolated**
3	Cy-vBRIDP / $[(cinnamyl)PdCl]_2$	0.5	1.5	<50% conversion
4	**$Pd(dtbpf)Cl_2$**	**0.5**	**1.5**	**88% isolated**
5	Cy-cBRIDP / $[(cinnamyl)PdCl]_2$	0.5	1.2	14% isolated
6	Cy-cBRIDP / $[(cinnamyl)PdCl]_2$	0.25	1.2	<50% conversion
7	Cy-cBRIDP / $[(cinnamyl)PdCl]_2$	0.15	1.2	poor conversion
8	$Pd(dtbpf)Cl_2$	0.5	1.2	81% isolated
9	$Pd(dtbpf)Cl_2$	0.25	1.2	<50% conversion
10	$Pd(dtbpf)Cl_2$	0.15	1.2	<50% conversion

This OBBD/bromide pairing had proved troublesome and had failed to reach completion using the previously optimized conditions using 0.25 mol % $Pd(dtbpf)Cl_2$ and 1.1 equivalents of OBBD. In the initial screening trials, Cy-cBRIDP in conjunction with $[(cinnamyl)PdCl]_2$ reached full conversion similarly to $Pd(dtbpf)Cl_2$, giving similar

isolated yield. Strangely, upon attempting the coupling again using a lesser excess of OBBD reagent, Cy-cBRIDP failed to give good results. This may be due to insufficient time given for complexing in the catalyst stock solution, but overall isn't clear why this failed. Overall, it seemed that $Pd(dtbpf)Cl_2$ and Cy-cBRIDP / $[Pd(cinnamyl)Cl]_2$ were roughly equivalent in performance, but the added layer of complexity of pre-complexing Pd and ligand was possibly problematic, so the choice to continue with $Pd(dtbpf)Cl_2$ was made.

During the above optimization trials, it became evident that there were differences in reaction behavior and appearance depending on which base was used, and at what temperature the reactions were conducted. The use of Et_3N gives much more uniform/homogeneous reaction appearance. The use of K_3PO_4 gives far more oiling-out, but also better conversion than Et_3N (Figure 2). This effect would likely become more important in scale-up trials, though the poor solubility in small scale 0.25-0.5 mmol scale reactions did not seemed to be problematic.

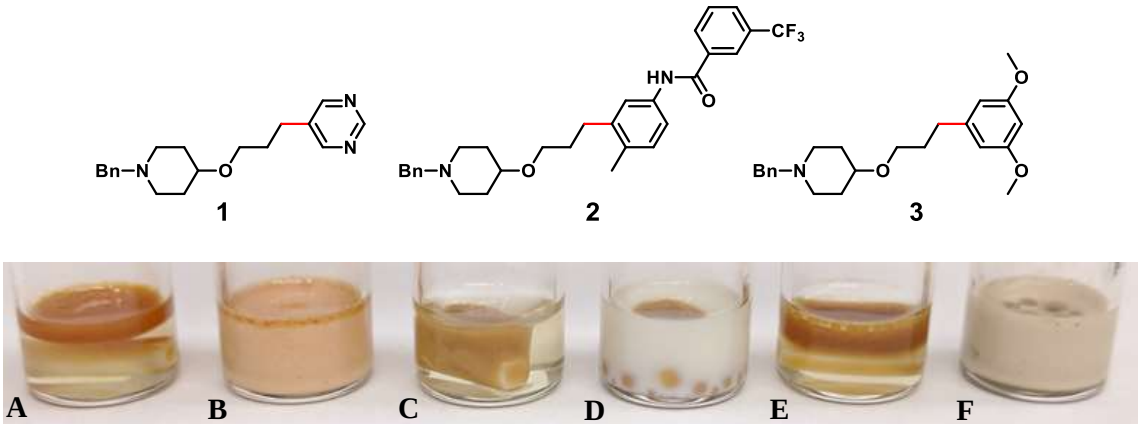


Figure 2: Initial reaction appearance at room temperature using (A) **1** with K_3PO_4, (B) **1** with Et_3N, (C) **2** with K_3PO_4, (D) **2** with Et_3N, (E) **3** with K_3PO_4, (F) **3** with Et_3N.

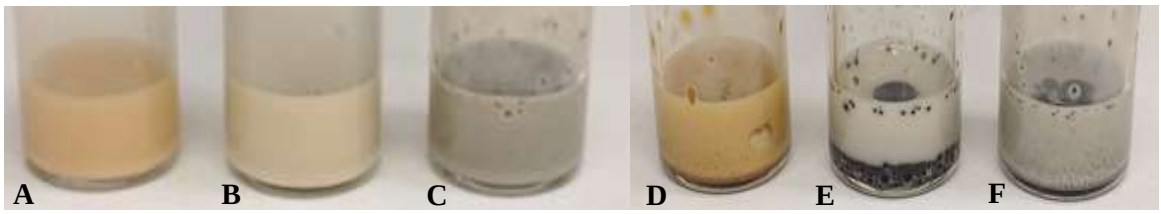


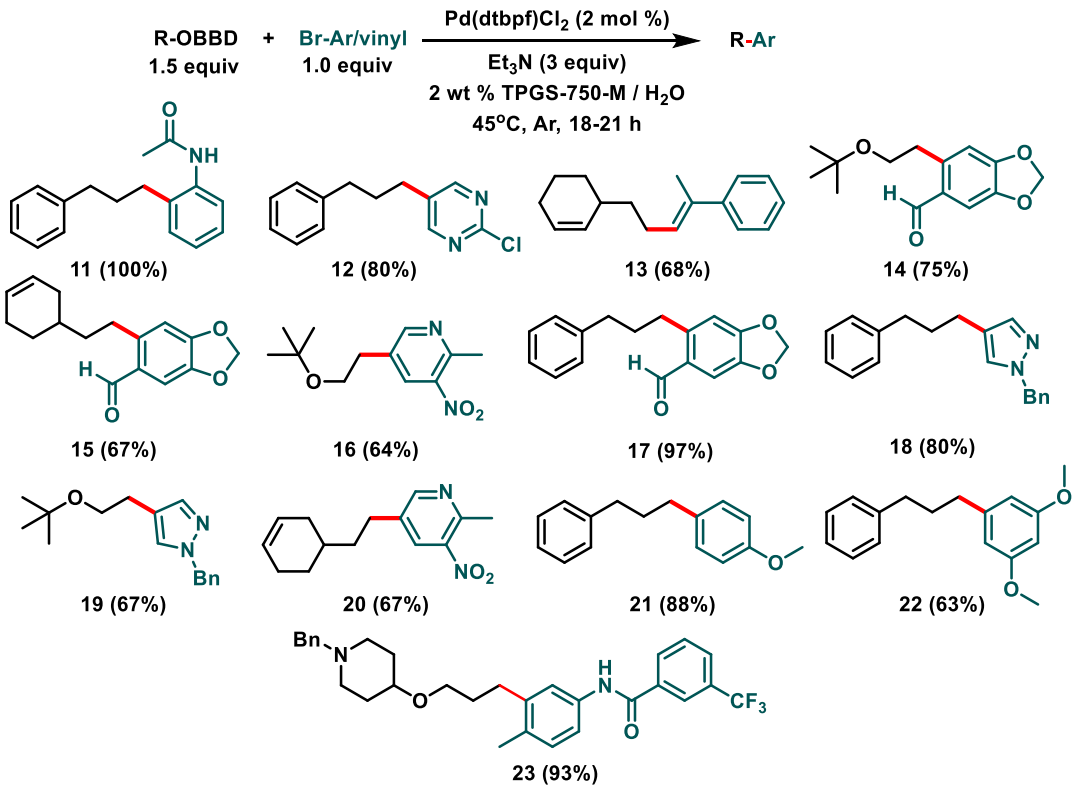
Figure 3: Reaction appearance at completion using Et_3N as base with (A) **1** at rt, (B) **2** at rt, (C) **3** at rt, (D) **1** at 45°C, (E) **2** at 45°C, (F) **3** at 45°C.

In addition, increasing temperature from ambient to 45°C was also correlated to lower solubility of starting materials and products (Figure 3). Once again, though more oiling-out was observed, better conversion was also noted.

2.11 Substrate Scope

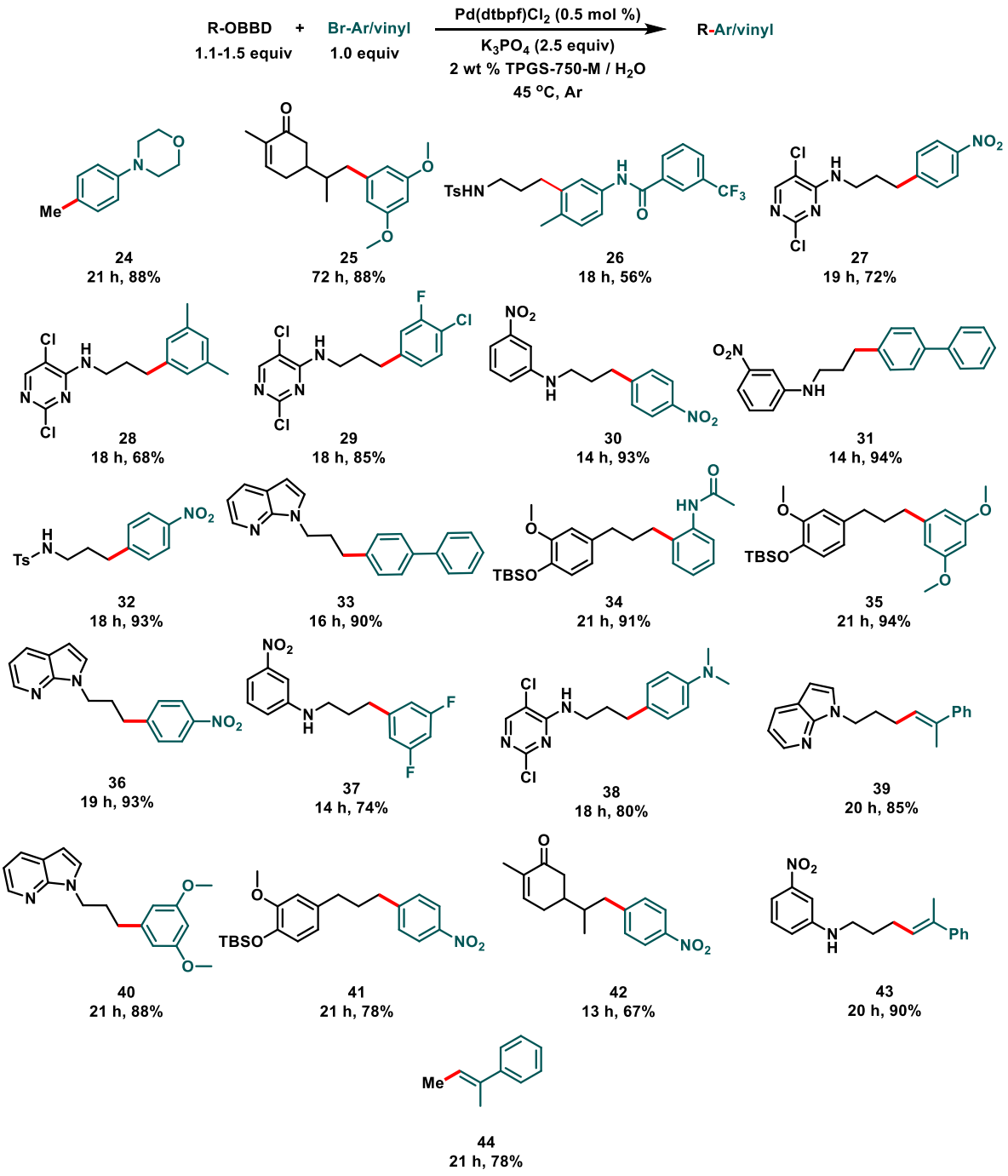
Scheme 15 shows the substrates which were published as the "preliminary substrate scope" run at 2 mol % Pd. Though they were not conducted using the optimized conditions, they added to the scope of the reaction.

Scheme 15: Initial Substrate Scope at 2 mol % Pd loading



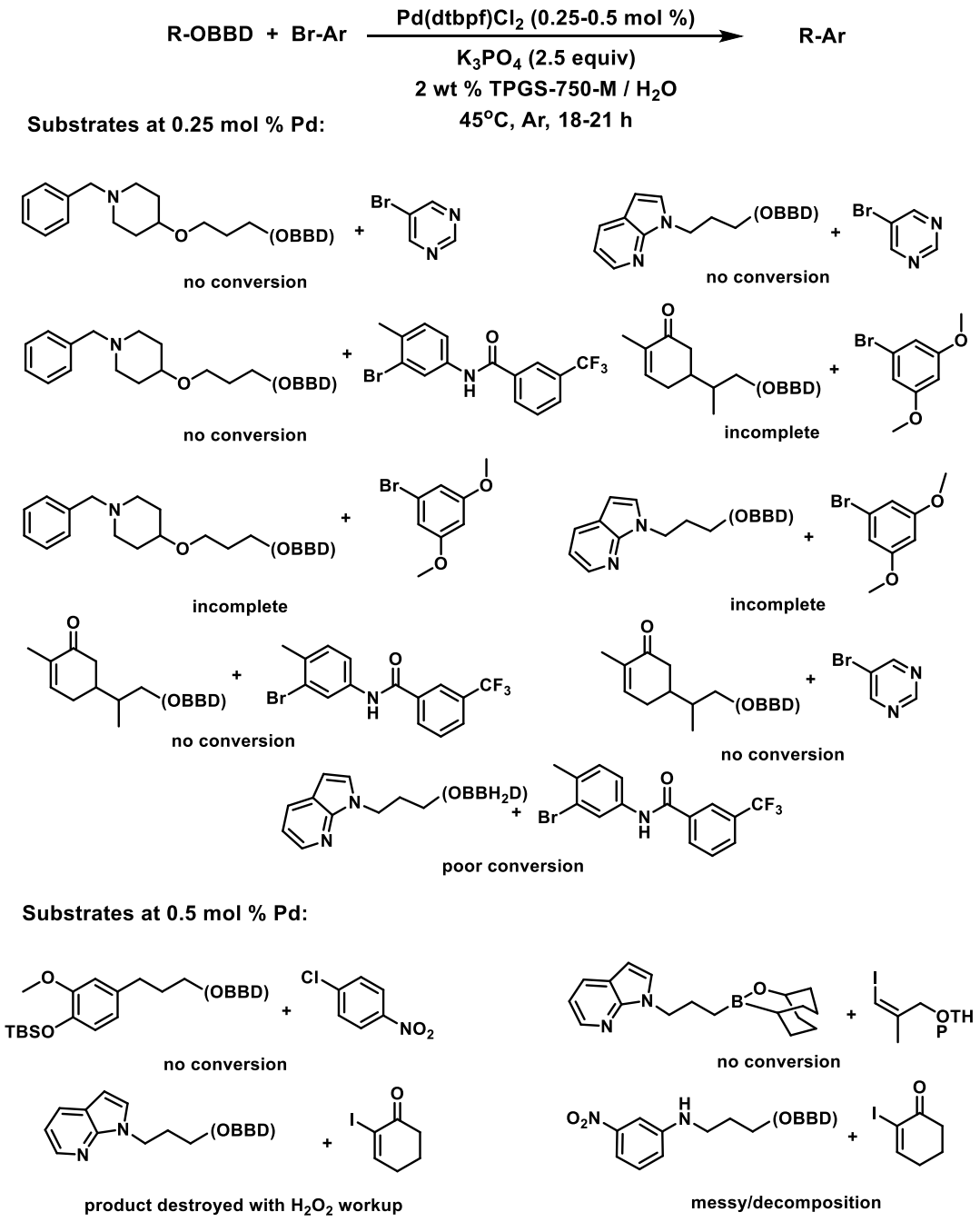
Scheme 16 shows the main substrate scope presented in the publication. Notable examples include methylation substrates **22** and **24**, coupling of a hindered OBBD **25** and **42**, and reaction with a vinyl bromide **39**, **43**, and **44**. No unwanted coupling with aryl chlorides (as would be possible in **29**) was seen, 2-chloropyrimidines are a type of substrate which is typically active for sp^2-sp^2 Suzuki couplings, but did not occur in this case.

Scheme 16: Substrate scope developed at 0.5 mol % after optimization



While the development of a substrate scope was initially attempted at the 0.25 mol % Pd optimized loading, it proved quite difficult. At 0.25 mol % loading, we were encountering an 80+% failure rate of coupling partners to reach full conversion. In order to expedite the process, the loading was increased to 0.5 mol %, which gave a ~50% success rate of coupling partners to reach completion. Scheme 17 shows a collection of substrates which gave insufficient conversion or were problematic.

Scheme 17: Unsuccessful Substrates



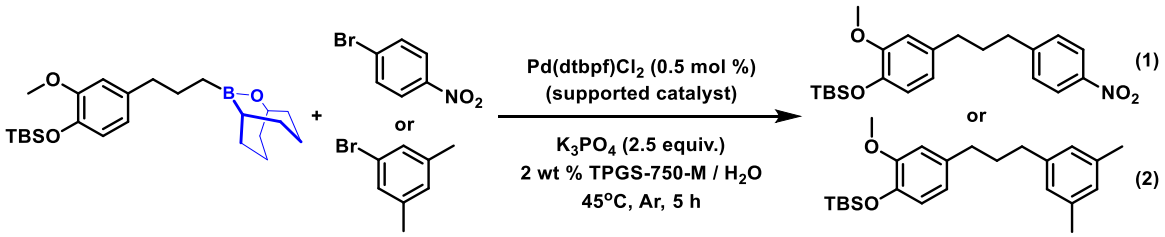
2.12 Recycling, Comparison with Organic Solvents, Tandem Sequence, and Scale-Up

The ability to recycle the reaction medium contributes to the low E Factor of reactions conducted in surfactant medium. In the case of these reactions, the product frequently separates upon standing as a oil, whether on top or on bottom due to density. This makes it an ideal case for recycle, as only a minimum of organic solvent is required to isolate the product (and potentially little/no organic solvent if the scale was large enough to separate this layer). However, several challenges made this a somewhat difficult candidate for recycle studies. The reaction is air-sensitive, so the reaction medium must be degassed at the beginning of each reaction cycle. In a typical recycle study, the reaction vessel is opened, and organic solvent is used to extract. In this case, it was found that the reaction could be extracted while kept under argon, by using a syringe with a long needle to remove the organic phase while keeping the reaction capped with a septum and under a positive pressure of argon. Also, due to the low catalyst loading, the catalyst cannot be directly added as a solid, due to the difficulty in weighing sub-milligram amounts of catalyst.

During recycle studies many sequential reaction trials had to be conducted, and these were often done in triplicate in case of mistakes. The amount of catalyst required for each reaction was too small to weigh accurately, typically ~0.15 mg. It was inconvenient to prepare stock solutions for every recycle attempt, and many catalysts have finite lifetime as stock solutions (some as little as 12 h in the case of Sphos / $Pd(OAc)_2$). To alleviate this problem the adsorption of the catalyst onto a solid support was explored, in order to disperse the catalyst on enough support that it could be weighed

accurately (Table 12). Catalyst was dissolved in DCM (toluene, EtOAc, and acetone were screened but failed to fully dissolve Pd(dtbpf)Cl_2). After addition of a solid support and removal of solvent by rotary evaporation furnished the supported catalyst. While Celite proved ineffective because it decreased catalyst activity significantly, activated carbon worked well, with no decrease in catalyst activity noted in comparison with a freshly prepared catalyst stock solution.

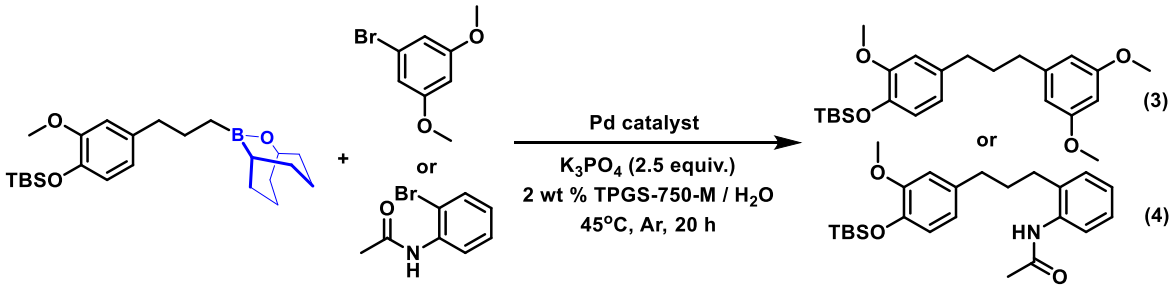
Table 11: Testing supported catalysts



Trial	Cat. Support	Product	Result
DG158.1	Celite	**1**	~50% conversion
DG158.2	Activated carbon	**1**	Full conversion
DG158.3	Celite	**2**	~50% conversion
DG158.4	Activated carbon	**2**	Full conversion

The studies of supported Pd(dtbpf)Cl_2 on carbon was continued at a lower loading of 0.25 mol %, which is the lower limit of catalyst loading necessary to reach full conversion in these reactions (Table 12).

Table 12: Testing catalyst supports



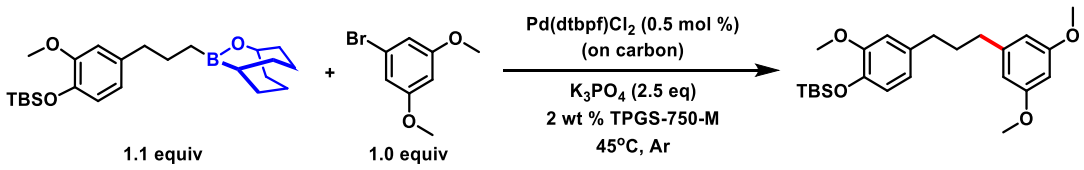
Trial	Catalyst (mol %)	Support or stock solution	Reaction	Result
NL-3-49.1	Pd(dtbpf)Cl_2 (0.25%)	Stock solution	3	Full conversion
NL-3-49.4	Pd(dtbpf)Cl_2 (0.25%)	Carbon	3	Full conversion
NL-3-49.6	Pd(dtbpf)Cl_2 (0.25%)	Carbon	4	Full conversion
NL-3-49.3	Pd/C (0.5%)*	N/A	3	No conv.
NL-3-49.5	Pd/C (0.5%)*	N/A	4	No conv.

*Commercial Pd/C catalyst used as a control

As a control, commercial Pd/C was tested as well, but failed to give any conversion, even at 2x the Pd loading as the Pd(dtbpf)Cl_2 supported on carbon. Therfore, the catalyst appears to retain activity even after being adsorbed onto carbon. This Pd(dtbpf)Cl_2/C was stored under argon for over 1 week, with no decomposition or loss of activity noted.

The recycle of the reaction medium to 3x sequential recycles was found to be feasible, with addition of small amounts of TPGS-750-M solution to reach the original reaction volume (Table 13). After 3x recycles, so much K_3PO_4 had been added that the reaction solubility was extremely poor, and did not stir effectively.

Table 13: Recycle of reaction medium using $Pd(dtbpf)Cl_2$ adsorbed onto carbon

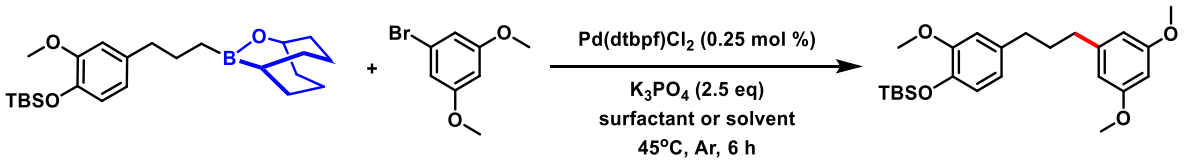


	reaction	1st recycle	2nd recycle	3rd recycle
Isolated yield (%)	81	85	86	88
E factor (organic solvent)	3.2	3.1	3.0	3.9
E factor (including aqueous)	7.8	5.1	3.0	6.0

While this reaction was shown to work at 0.25 mol % Pd, the decision was made to conduct the recycle studies at 0.5 mol % Pd due to the sensitivity of the reaction to air, and to avoid the possibility of stalled reactions. As a side note, while we attempted to recycle the catalyst itself, this proved unsatisfactory. Upon reaction completion, extraction with EtOAc was found to extract all or nearly all of the catalyst from the aqueous phase. This can be visualized as a black colored EtOAc layer, due to the ferrocene based catalyst and Pd black. Extracting with Et_2O or MTBE was found to leave some active catalyst in the aqueous phase, likely due to the very poor solubility of this catalyst in these fairly nonpolar solvents. Attempting to recycle the catalyst (after using Et_2O or MTBE as extraction solvent) gave some conversion, but failed to reach completion.

During this study a very valid question was raised: how do these conditions compare with the reaction conducted in organic solvent? Typical literature examples for 9-BBN or OBBD couplings are run in either aqueous THF or aqueous dioxane.

Table 14: Coupling in TPGS-750-M Versus Organic Solvents

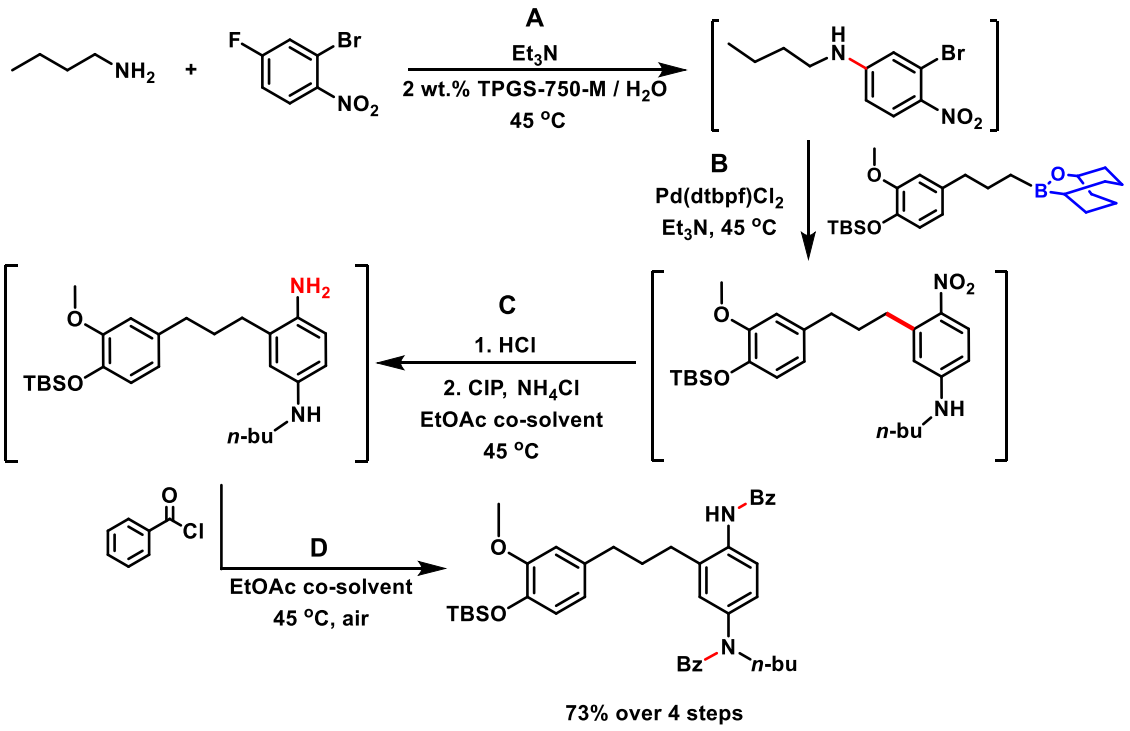


solvent/medium	isolated yield (%)
2 wt % TPGS-750-M / H_2O	94
THF/H_2O (20:1)	44
dioxane/H_2O (20:1)	56

In addition, literature examples run in organic solvent are typically run at significantly more dilute concentrations (i.e. less than the 0.5-1.0 M used in this study, typically 0.1-0.4 M). However, in these literature reports it is doubtful that any consideration was taken as to maximizing reaction concentration. As a comparison against literature conditions, the reactions were run against these two common solvents, and the reactions monitored and halted once the first reaction reached completion. The reaction in 2 wt % TPGS-750-M reached completion significantly faster than the reactions run in organic solvents.

To demonstrate the utility of this method in conjunction with other reaction classes used in in water, a 4-step-1-pot tandem sequence was conducted (Scheme 18). The reaction sequence was planned in order to take advantage of the electronics and functionality presented at each step.

Scheme 18. Tandem 4-step-1-pot sequence using alkyl Suzuki coupling



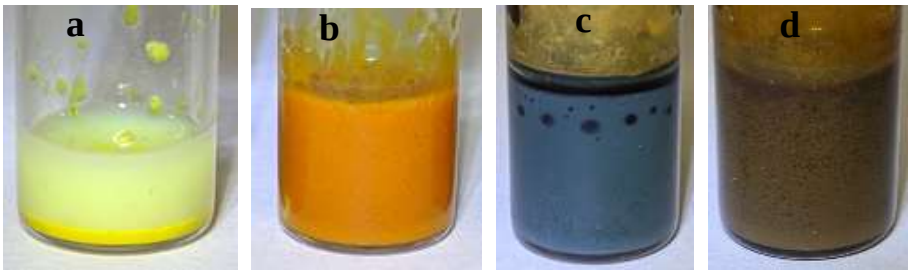
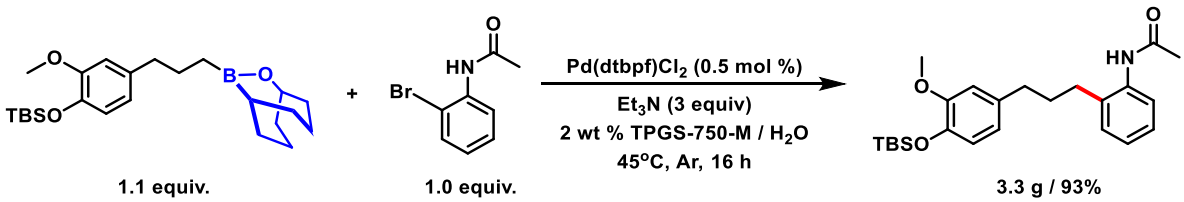


Figure 4: (a) S_NAr upon completion, (b) Suzuki coupling upon completion, (c) nitro reduction upon completion, (d) final product

The S_NAr reaction benefits from the electronics imparted from the nitro and bromide groups. After Suzuki coupling, the nitro product was reduced to the aniline. Initially, isolation of this product was attempted, but the H_2O_2 workup necessary for purification of the OBBD "cage" containing residue resulted in decomposition of the product, presumably the aniline. The sequence was repeated again, and the anilines capped as

amides using benzoyl chloride. It is noteworthy that despite the high molecular weight of the final product, and variety of reagents added, that no major solubility issues were present during this sequence (Figure 4).

The scalability of reactions in aqueous medium is an aspect which is frequently questioned by those unfamiliar with running reactions in water. In some cases, difficulties in solubility at small scale (i.e. 0.5 mmol) can be ignored, but upon scaling these solubility issues become significant problems.



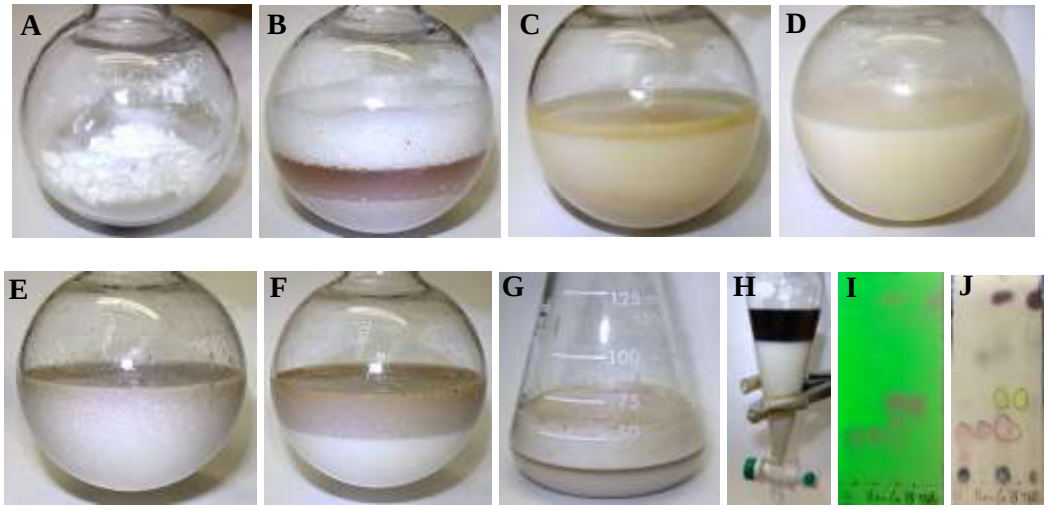


Figure 5: (A) Bromide and Pd(dtbpf)Cl_2 in flask, (B) after addition of TPGS-750-M, (C) after addition of Et_3N, and OBBD, (D) after stirring at 45 ^oC for 20 min, (E) After stirring overnight, (F) Reaction after standing 5 min (G) workup with peroxide, (H) extraction with EtOAc, (I) TLC from left to right: organic layer after workup, reaction mixture, co-spot, bromide, OBBD, (J) TLC stained with vanillin.

Therefore, when scaling a reaction in water, particular emphasis on the nature of the solubility of the reaction mixture must be taken into account. In this scale-up demonstration (Figure 5), due to the "oiling out" frequently presented in these couplings on small scale, the choice was made to run this coupling using Et_3N rather than K_3PO_4. This resulted in a reaction which was somewhat uniform in appearance while stirring, but which separates upon standing. This trial gave similar yield to the initial 0.5 mmol scale trial, and demonstrates that this method is indeed scalable.

2.13 Experimental

2.13.1 General Procedures

General Procedure 1: Couplings at 2 mol % Pd. When untested substrates were attempted for the first time, it was found helpful to first attempt the coupling at a 2 mol % Pd loading, with a large excess of OBBD reagent (i.e 1.5 equivalents) to ensure full conversion and determine the feasibility of the coupling, before attempting lower catalyst loadings such as 0.25-0.5 mol % and attempting to decrease OBBD equivalents (i.e., decreasing from 1.5 to 1.1 equiv).

To a 1 dram (4 mL) vial with magnetic stir bar was added $Pd(dtbpf)Cl_2$ (3.3 mg, 0.005 mmol), K_3PO_4 (133 mg, 0.625 mmol), bromide (0.25 mmol), and OBBD compound if solid (0.275 mmol-0.375 mmol depending on purity). The vial was fitted with a 14/20 septum, wrapped with Parafilm and the septum top cut flush with scissors (see Figure x below). A 22 GA/0.7 mm needle attached to an argon Schlenk line was inserted through the septum

and the vial evacuated/backfilled with argon 3x. TPGS-750-M (2 wt % solution, 0.5 mL) was added via syringe with stirring, then the OBBD reagent if liquid (0.275-0.375 mmol depending on purity), and the needle holes were then sealed with electrical tape. The vial was stirred vigorously (1000 rpm) at 45 ^{o}C until complete consumption of the bromide.

General Procedure 2: Couplings at 0.5 mol % Pd. Due to the sub-milligram amounts of catalyst required for these coupling reactions at 0.5 mol % Pd loading, it was necessary to either prepare (A) a catalyst stock solution, or (B) adsorb the catalyst onto activated carbon in order to ensure accurate catalyst loadings. These procedures were used to deliver 0.5 mol % Pd loading on 0.25 mmol scale reactions, but can be scaled as necessary. Delivery of catalyst via the stock solution method (A) was utilized for substrate scope development, while supported catalyst method (B) was used for couplings associated with recycling studies.

(A) Catalyst stock solution preparation. To a 1 dram (4 mL) vial with a magnetic stir bar was added Pd(dtbpf)Cl_2 (8.2 mg, 0.013 mmol), the vial was fitted with a 14/20 septum and wrapped with Parafilm. A 22 GA/0.7 mm needle attached to an argon Schlenk line was inserted through the septum and the vial evacuated and backfilled with argon 3x cycles. In a separate vial, EtOAc (from solvent keg, with no precaution against moisture) was sparged with argon for 15 minutes before use. Via syringe, 1.00 mL of this degassed EtOAc was added to the vial. This catalyst stock solution was stirred vigorously for 10 minutes before use.

Coupling procedure using catalyst stock solution. To a 1 dram (4 mL) vial with a magnetic stir bar was added K_3PO_4 (133 mg, 0.625 mmol), bromide (0.25 mmol), and OBBD compound if solid (0.275 mmol-0.375 mmol depending on purity). The vial was fitted with

a 14/20 septum, wrapped with Parafilm and the septum top cut flush with scissors (see Figure 6 below). A 22 GA/0.7 mm needle attached to an argon Schlenk line was inserted into the septum and the vial was evacuated/backfilled with argon 3x. Next, catalyst stock solution as prepared above (100 uL, 0.00125 mmol $Pd(dtbpf)Cl_2$) was added via syringe (note: the catalyst stock solution should be stirred vigorously during this transfer to suspend any catalyst particles remaining undissolved), then a 22 GA/0.7 mm needle attached to an argon Schlenk line was inserted through the septum and the solvent removed under vacuum, the vial then backfilled with argon and the needle removed from the septum. Next, TPGS-750-M (2 wt % solution, 0.5 mL) was added via syringe and the vial stirred. OBBD reagent (if oil/liquid) was then added via syringe (0.275-0.375 mmol depending on purity) and the needle holes were then sealed with electrical tape. The vial was placed in an aluminum block reactor and stirred vigorously (1000 rpm) at 45 ^{o}C until bromide had been fully consumed, as determined by TLC.

(B) Catalyst on supported carbon preparation. This procedure was used for recycle studies, as a convenient alternative to preparing a fresh catalyst stock solution for each sequential recycle trial. To a 1 dram (4 mL) vial was added $Pd(dtpbf)Cl_2$ (8.1 mg, 0.0125 mmol), 1.5 mL DCM was added to the vial to dissolve the catalyst (with no special precaution against air or moisture). Next, 16.9 mg of activated carbon was added to the vial and swirled to mix thoroughly. A 19/22 septum with vent needle was fitted to the vial and the solvent removed via rotary evaporator. The vial was dried under vacuum for ~1 h or until constant mass befor use. For each 0.25 mmol scale reaction, 2.5 mg of this supported catalyst is required for 0.5% Pd loading (2.5 mg of supported catalyst contains 0.81 mg $Pd(dtbpf)Cl_2$, or 0.00125 mmol). This supported catalyst was stored under argon up to 1 week without

any noted decomposition or loss of catalytic activity. However, extended shelf life testing was not conducted.

Coupling procedure using the catalyst supported on carbon. To a 1 dram vial with magnetic stir bar was added Pd(dtbpf)Cl_2 supported on carbon (2.5 mg, 0.00125 mmol Pd(dtbpf)Cl_2), K_3PO_4 (133 mg, 0.625 mmol), bromide (0.25 mmol), and OBBD compound if solid (0.275 mmol-0.375 mmol depending on purity). The vial was fitted with a 14/20 septum, wrapped with Parafilm and the septum top cut flush with scissors (see Figure 6 below). A 22 GA/0.7 mm needle attached to an argon Schlenk line was inserted into the septum and the vial was evacuated/backfilled with argon 3x, then TPGS-750-M (2 wt % solution, 0.5 mL) was added via syringe with stirring, then OBBD reagent if liquid (0.275-0.375 mmol depending on purity), and the needle holes were then sealed with electrical tape. The vial was placed in an aluminum block reactor and stirred vigorously (1000 rpm) at 45 ^oC until bromide had been consumed, as determined by TLC.

General procedure 3: Reaction Vial Preparation/Considerations

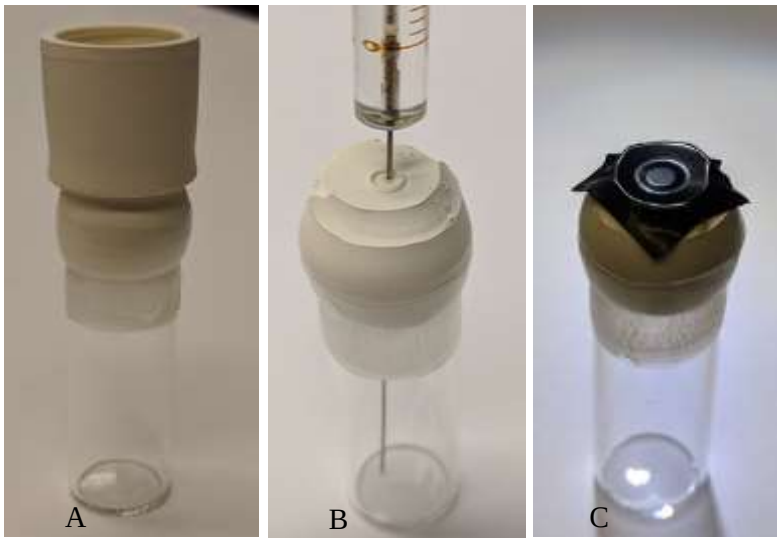


Figure 6: (A) vial with septum, (B) vial with septum clipped, (C) needle holes covered

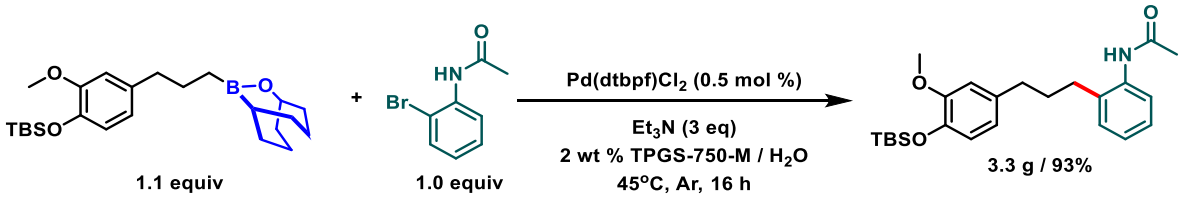
One dram (4 mL) vials capped with 14/20 septa were found to be convenient reaction vessels for these couplings as well as other types of small scale reactions. Several positive attributes make these ideal for this purpose. These vials fit in an aluminum block reactor, allowing multiple trials to be conducted at once, and the use of a septum instead of solid caps allows for convenient reaction monitoring. A microliter syringe can be used to remove aliquots for reaction monitoring opening the reaction. Trials conducted with screw cap vials were found to stall or fail to reach completion if opened midway through the reaction, likely due to air exposure. In the reaction procedures, 22 GA/0.7 mm needles are specified due to their small diameter, larger diameter needle which may "core" the septa should be avoided because they may allow more air exposure to the reaction.

Reaction monitoring: Due to the air sensitive nature of the reaction, the reaction should not be opened while the reaction is in progress. Instead, the electrical tape was removed and while stirring vigorously, 2-3 uL of reaction mixture was removed using a 25 uL syringe, and fresh electrical tape was then used to cover the needle holes. This aliquot was added to a small test tube and mixed with ~25 uL EtOAc, rinsing the syringe into the test tube. The organic layer was used for TLC samples to monitor reaction progress.

Workup and purification. Upon reaction completion the reaction vial was removed from the heated aluminum block reactor. The septum was pierced with a vent needle, and 100 uL of 20% H_2O_2 was added via syringe, and stirred vigorously for 5 minutes. The septum was then removed from the vial and the reaction was extracted with EtOAc (3 x 0.5 mL), the combined organic extracts dried over anhydrous Na_2SO_4 and the crude product adsorbed onto Celite via rotary evaporation. The product was then purified by silica gel column chromatography. Note: attempts to purify products without the use of the H_2O_2

workup resulted in OBBD "cage" co-eluting with product, even if multiple chromatographic purifications were conducted on the same sample. This was particularly a problem with nitrogen containing products such as pyridine and pyrimidine heterocycles. The H_2O_2 workup prior to extraction eliminates this problem and allows for effective purification.

General Procedure 4: Multi-gram Scale-up procedure.

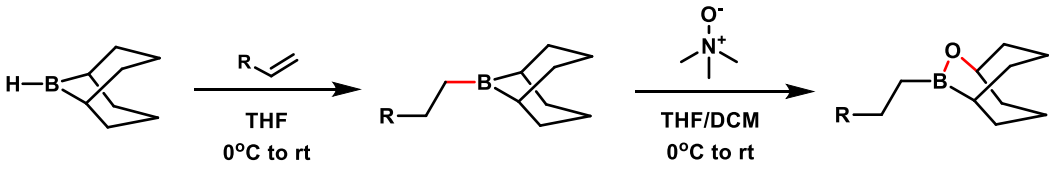


To a 50 mL round bottom flask with 14/20 neck with large oval stir-bar was added; 2-bromoacetanilide (1.82 g, 8.49 mmol), and $Pd(dtbpf)Cl_2$ (27.7 mg, 0.0425 mmol). The flask was fitted with a 14/20 septum and evacuated/backfilled with argon 3x times. Via syringe, 17 mL of degassed 2 wt % TPGS-750-M/H_2O was added and the mixture stirred vigorously for 2 min to disperse the solid bromide. The flask was placed in a 23 ^oC water bath in case of exotherm during addition of base and the OBBD reaction partner. Via syringe, OBBD reagent (3.89 g, 9.34 mmol) was added dropwise. After ~1/3 of OBBD had been added, the bromide and OBBD began to stick together and form clumps, so addition of OBBD was halted. Via syringe, Et_3N (2.83 g, 28.0 mmol, 3.90 mL) was added dropwise, which softened the solids after stirring for 5 min (Note: formation of large solids consisting of unreacted starting materials and/or products has resulted in difficult stirring, sluggish reactions, and byproduct formation in other TPGS-750-M mediated coupling reactions thus the formation of large amounts of solids should be avoided). No warming or exotherm was

noted so the flask was removed from the water bath and placed in a 50 °C oil bath (to maintain 45°C internal temperature) and stirred vigorously while adding the rest of the OBBD coupling partner. After stirring for 20 min at 45 °C, the reaction had become uniformly "milky" in appearance. The reaction was stirred vigorously overnight (16 h total), upon which time it was deemed complete by TLC. The completed reaction mixture was transferred to a 125 mL Erlenmeyer flask containing a stir bar and with stirring, 3 mL of 30% H_2O_2 was added dropwise and stirred for 5 min. The reaction was transferred to a 60 mL separatory funnel and extracted with EtOAc (1 x 15 mL, 2 x 10 mL). These combined extracts were washed with brine (~10 mL), dried with anhydrous Na_2SO_4 and the solvent removed by rotary evaporator. The crude product was purified by silica gel column chromatography using EtOAc/hexanes (20:80 then 40:60), and the product dried under vacuum to constant mass (3.63 g, 93%). Pictures of the reaction setup and workup are shown in Figure 5.

General Procedure 5: Synthesis of OBBD Reagents

All OBBD reagents, except for the methyl-OBBD (**10**), were synthesized via hydroboration with 9-BBN followed by selective oxidation via TMANO.



Hydroboration Procedure. To an oven dried round bottom flask, cooled under vacuum and backfilled with argon, was added 9-BBN (1.00 equiv, 0.5 M in THF), and chilled in an ice bath and stirred. The alkene (1.00 equiv) was added dropwise via syringe if liquid (or if

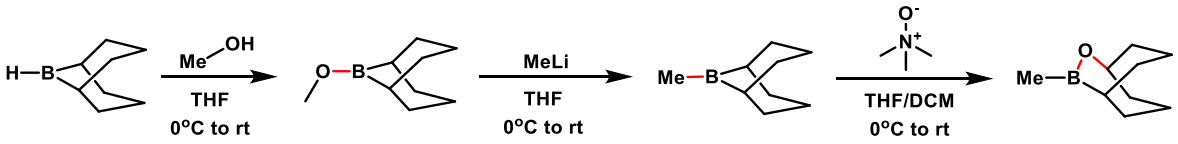
solid, the alkene was dissolved in a minimum of dry, degassed THF before addition). After addition of the alkene, the flask was removed from the ice bath and allowed to warm to room temperature while stirring until hydroboration was complete. For unhindered alkenes (e.g., allyl), the hydroboration was typically complete in <1 h, but for hindered alkenes (e.g., vinyl, or 1,1-disubstituted alkenes, or 1,1,2-trisubstututed alkenes) this was found to require from 1-18 h. It is necessary to ensure that the hydroboration goes to completion before proceeding to the oxidation step. To monitor the reaction progress, it was found very useful to prepare an air-free crude NMR sample to verify the alkene had been consumed. To prepare this sample, an oven dried NMR tube was capped with a septum, and evacuated/backfilled with argon 3x cycles. Next, an aliquot of the reaction mixture was removed via syringe (~150 uL) and injected into a septum-capped, oven dried 1 dram vial under argon. The THF solvent was removed via vacuum and the vial backfilled with argon. A second vial was prepared containing ~1 mL $CDCl_3$, fitted with a septum and sparged with argon for 5 min. Via syringe, through the septum, degassed $CDCl_3$ was transferred to the aliquot vial to dissolve the crude aliquot and then transferred to the argon filled NMR tube via syringe. The septum was quickly removed from the NMR tube, capped and wrapped with Parafilm. The NMR spectrum of this sample should be taken immediately (if allowed to stand or exposed to air, the 9-BBN derivative may decompose) to verify by ^1H NMR the disappearance of the alkene peaks before proceeding to the oxidation step.

Oxidation Procedure. Once the hydroboration was deemed complete, the flask was chilled an ice bath. A solution of anhydrous TMANO in dry DCM was then prepared. Note: TMANO is very hygroscopic so it must be handled quickly. To an oven dried round bottom flask, TMANO (1.25 equiv relative to the 9-BBN derivative) was added, (exact amounts

are not required, if extra TMANO is added it won't adversely affect the reaction outcome as the OBBD product is not easily over oxidized). The flask was capped with a septum, purged with argon and via syringe dry, degassed DCM was added to the flask to dissolve TMANO, which was added dropwise to the reaction flask with stirring. After addition of TMANO, the flask was removed from the ice bath and allowed to stir for ~1 h. The oxidation by TMANO is very rapid; achieving full oxidation was never a problem in this step.

Workup. The reaction mixture was analyzed by TLC to determine R_f of the product, and determine a suitable eluent such that the R_f is ~0.5. The solvent was removed from the reaction mixture via rotary evaporator (we suggest segregating this solvent waste in a separate container due to the noxious odor of the liberated trimethylamine, storing the waste bottle in a fume hood). The crude material was then dissolved in the solvent mixture used for TLC, and quickly filtered through a short column of silica gel which has been packed with the eluent determined above, (i.e., 1.5" x 5" plug of silica for a 5-10 g scale reaction). The OBBD product is eluted using the eluent determined above. Note: most OBBDs are not sensitive to silica gel but others with sensitive groups attached have been found to decompose on silica (e.g., compound **8**). After elution, the solvent was removed via rotary evaporation and the product dried under vacuum and stored under argon in the refrigerator until use. Note: while these compounds have been stored for up to 1 year in the refrigerator, aliquots stored at ambient temperature do not seem to have deteriorated at a noticeably faster rate, therefore refrigeration may not be required.

General Procedure 6: Synthesis of Methyl OBBD



To an oven dried 100 mL round bottom flask which was purged with argon was added 9-BBN in THF (10 mmol, 1.720 g, 20 mL, 0.5 M). The flask was chilled in an ice bath and dry methanol (10 mmol, 0.320 g, 0.405 mL) was added dropwise with stirring. The flask was warmed to 25 ^{o}C and stirred for 1 h, upon which time effervescence had ceased. The flask was again chilled in an ice bath and methyllithium (10 mmol, 0.220 g, 6.25 mL, 1.6 M) in diethyl ether was added dropwise with stirring. The flask was allowed to warm to 25 ^{o}C and stirred for 1 h. The flask was chilled to 0 ^{o}C and trimethylamine *N*-oxide (15 mmol, 1.127 g) dissolved in 15 mL of dry, degassed DCM was added dropwise with stirring. The flask was allowed to warm to 25 ^{o}C and stirred for 30 min. The solvent was then removed via rotary evaporation and the crude material filtered through a pad of silica gel (25 mm x 75 mm), eluting with EtOAc. The solvent was then removed via rotary evaporation and the product dried under high vacuum, yielding 1.32 g (88%) of the desired product as a clear oil. (Note: high vacuum was strong enough to evaporate the product; care must be taken not to lose product under vacuum). Alternatively, this product can be purified by short-path distillation, however this was not necessary to obtain useful purity product.

General Procedure 7: Procedure for Recycle Studies and E Factor Calculations

Recycle Methods.

Initial Reaction. To a 1 dram vial (reaction vial) was added 2.5 mg of Pd(dtbpf)Cl_2 on carbon (see Section: catalyst on supported carbon preparation above), 1-bromo-3,5-dimethoxybenzene (54.3 mg, 0.25 mmol), K_3PO_4 (133 mg, 0.625 mmol), and a magnetic stir bar. The vial was sealed with a septum and evacuated/backfilled with argon 3x cycles. Then, via syringe were added the following with stirring: degassed TPGS-750-M (2 wt %, 0.25 mL), then OBBD reagent (114.5 mg, 0.275 mmol, ~115 uL). The needle holes were then sealed with electrical tape and the vial was stirred vigorously at 45 ^oC at 1000 rpm for 2 h, after which time the reaction was deemed complete by TLC.

Recycle 1. To a 25 mL round bottom flask was added ~10 mL EtOAc (from solvent keg, with no precautions against air or moisture), fitted with a rubber septum and sparged thoroughly with argon for ~30 min and stored under argon. Note: Due to air sensitivity, the extractions were conducted under argon using this degassed EtOAc as extraction solvent and the trials were typically conducted in triplicate in case of mistakes or stalled reactions due to air exposure.

A 22 GA/0.7 mm needle attached to a Schlenk line under argon was inserted through the septum of the completed reaction vial to maintain a positive pressure of argon. Via syringe, 100 uL of degassed EtOAc was added to the vial and stirred briefly and allowed to settle. Using a 1 mL plastic syringe, fitted with 4” x 22 GA/0.7 mm needle, the entire reaction mixture was drawn into the syringe, and the syringe barrel held vertically such that the EtOAc layer forms at the top of the syringe. This layer was carefully pushed into a test tube

and the aqueous layer returned to the reaction vial through the septum. This process was repeated 2x with 100 uL of EtOAc. Upon completion of extraction, the vial was briefly evacuated and purged with argon 2x.

To a separate 1 dram vial (referred to as recycle 1 vial) was added 2.5 mg of the Pd(dtbpf)Cl_2 on carbon catalyst, 1-bromo-3,5-dimethoxybenzene (54.3 mg, 0.25 mmol), K_3PO_4 (133 mg, 0.625 mmol), and a magnetic stir bar. The vial was sealed with a rubber septum in the same manner used for the initial reaction and evacuated/purged with argon 3x. The aqueous medium from the reaction vial was transferred via syringe to the recycle 1 vial with stirring. The reaction vial was rinsed with 50 uL of 2 wt % TPGS-750-M solution and transferred to the recycle 1 vial. Next, OBBD reagent (114.5 mg, 0.275 mmol, ~115 uL) was added via syringe to the recycle 1 vial, the needle holes sealed with electrical tape and the vial stirred vigorously at 1000 rpm and 45 ^oC for 2 h, upon which time the reaction was deemed complete by TLC.

Recycle 2. The same procedure used for Recycle 1 was repeated for Recycle 2.

Recycle 3. The same procedure from recycles 1 and 2 was repeated for Recycle 3. However, upon extraction, the reaction had become very viscous and difficult to extract. Instead of the 100 uL of EtOAc needed for phase separation on the previous trials, 200 uL of EtOAc was required to give phase separation and effective extraction. Because of the difficulty in extraction, this 3rd recycle was deemed to be the practical limit of the recyclability for these trials.

Table 15: Parameters used during recycle trials

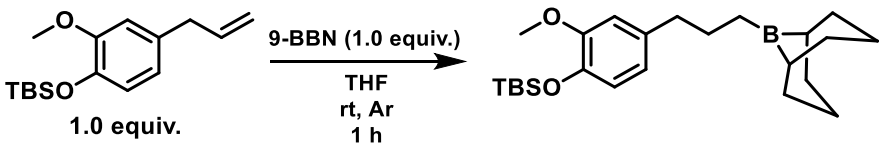
Trial	Rxn Conc. (M)	Rxn Time (h)	Bromide equiv	OBBD equiv	Catalyst loading (%)	K_3PO_4 (equiv)	TPGS vol. (uL)	EtOAc extraction vol. (uL)	Isolated Yield (%)
Reaction	1.0	2	1.0	1.1	0.5	2.5	250	3 x 100	81
Recycle 1	~1.0	2	1.0	1.1	0.5	2.5	50	3 x 100	85
Recycle 2	~1.0	2	1.0	1.1	0.5	2.5	50	3 x 100	86
Recycle 3	~1.0	2	1.0	1.1	0.5	2.5	50	1 x 200 + 2 x 100	88

E Factor Calculations

Table 16: E Factor values and calculations:

E Factor Type	Reaction	Recycle 1	Recycle 2	Recycle 3
organic solvent only	3.2	3.1	3.0	3.9
organic + aqueous + base	7.8	5.1	5.0	6.0

General Procedure 8: Procedures for Air Sensitivity Testing



Preparation of a 9-BBN derivative. An oven dried 1 dram vial with stir bar was capped with a rubber septum and purged with argon. Via syringe, 9-BBN solution in THF (0.55 mL, 0.5 M, 0.275 mmol) was added through the septum, and the vial stirred at rt. TBS-protected eugenol (0.275 mmol/76.6 mg) was added via syringe with stirring. The vial was stirred for 1 h, then THF was removed by gently heating the vial while sparging the solution with argon via a needle through the septum. After most of the solvent was removed, the

product was placed under vacuum via a needle through the septum, leaving the product as a clear oil, the vial was backfilled with argon and used immediately. If this product is exposed to air, the oil will turn to a white paste, indicating decomposition.

Trials run under an air atmosphere.

Used for the coupling of a 9-BBN reagent. A 9-BBN derivative (0.275 mmol, 1.1 equiv) was synthesized according to the above section. To this vial was added $Pd(dtbpf)Cl_2$ (3.3 mg, 0.005 mmol) and the bromide (0.25 mmol, 1.0 equiv). The vial was fitted with a 14/20 septum, wrapped with Parafilm and the septum top cut flush with scissors. TPGS-750-M (2 wt % solution, 0.5 mL) was added via syringe with stirring, then Et_3N (0.75 mmol, 76 mg, 104 uL) and the vial was stirred vigorously at 45 ^oC for 16 h.

Used for the coupling of an OBBD reagent. To a 1 dram vial with magnetic stir bar was added $Pd(dtbpf)Cl_2$ (3.3 mg, 0.005 mmol), bromide (0.25 mmol, 1.0 equiv), and the OBBD compound (0.275 mmol, 1.1 equiv). The vial was fitted with a 14/20 septum, wrapped with Parafilm and the septum top cut flush with scissors. TPGS-750-M (2 wt % solution, 0.5 mL) was added via syringe with stirring, then Et_3N (0.75 mmol, 76 mg, 104 uL), and the vial was stirred vigorously at 45 ^oC for 16 h.

Trials using reagent exposed to air for 1 h before use in a reaction run under argon.

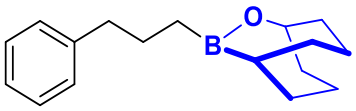
Used for coupling of a 9-BBN reagent. A 9-BBN derivative (0.275 mmol, 1.1 equiv) was synthesized according to section 4.1, and the solvent removed under vacuum. The septum was removed from the vial and the 9-BBN derivative was stirred at 400 rpm, open to air, for 1 h. After 1 h, bromide (0.25 mmol, 1.0 equiv) and $Pd(dtbpf)Cl_2$ (3.26 mg, 0.005 mmol) were added to the vial, the vial capped with a rubber septum, and evacuated/backfilled with

argon 3x cycles, then TPGS-750-M (2 wt % solution, 0.5 mL) was added via syringe, stirred briefly, and then Et_3N (0.75 mmol, 76 mg, 104 uL) added via syringe. The vial was stirred vigorously at 45 ^oC and 1000 rpm for 16 h.

Used for coupling of an OBBD reagent. To a 1 dram vial with stir bar, the OBBD derivative (0.275 mmol, 1.1 equiv) was added via syringe and stirred at 400 rpm, open to air, for 1 h. After 1 h, bromide (0.25 mmol, 1.0 equiv) and $Pd(dtbpf)Cl_2$ (3.26 mg, 0.005 mmol) were added to the vial, the vial capped with septum, and evacuated/backfilled with argon 3x cycles, and then TPGS-750-M (2 wt % solution, 0.5 mL) added via syringe, stirred briefly, then Et_3N (0.75 mmol, 76 mg, 104 uL) added via syringe. The vial was stirred vigorously at 45 ^oC and 1000 rpm for 16 h.

2.13.2 Characterization data

(1s,5s)-10-(3-Phenylpropyl)-9-oxa-10-borabicyclo[3.3.2]decane (**1**)



Synthesized from allylbenzene according to General Procedure 5, to give (**1**) as a colorless oil (6.5 g, 65%).

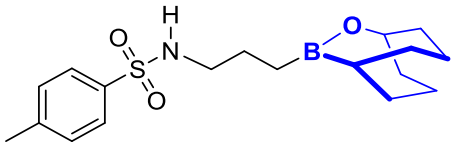
R_f: 0.70 (hexanes)

^1H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.27 (m, 2H), 7.24 – 7.18 (m, 3H), 4.60 (d, *J* = 3.0 Hz, 1H), 2.67 – 2.59 (m, 2H), 1.86 (ddd, *J* = 9.4, 6.5, 2.4 Hz, 5H), 1.78 – 1.63 (m, 6H), 1.63 – 1.54 (m, 2H), 1.43 (ddd, *J* = 8.8, 5.6, 2.7 Hz, 4H), 0.97 – 0.90 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 143.28, 128.62, 128.23, 125.55, 73.41, 42.04, 39.12, 31.92, 27.28, 26.61, 26.34, 26.29, 26.05, 25.77, 22.42, 22.23.

HRMS: (EI, [$C_{17}H_{25}BO$]) calcd, 256.2002; found *m/z*: 256.2009.

N-(3-((1s,5s)-9-Oxa-10-borabicyclo[3.3.2]decan-10-yl)propyl)-4-methylbenzenesulfonamide (**2**)



Compound was synthesized from N-allyl-4-methylbenzenesulfonamide according to General Procedure 5, to give (**2**) as a yellow oil (3.3 g / quant.).

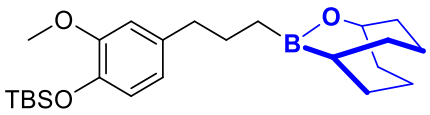
R_f: 0.60 (EtOAc/hexanes 40:60)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.3 Hz, 2H), 7.28 (t, *J* = 7.5 Hz, 2H), 4.82 (s, 1H), 4.62 – 4.50 (m, 1H), 2.88 (dd, *J* = 11.8, 6.5 Hz, 2H), 2.41 (s, 3H), 1.92 – 1.71 (m, 5H), 1.70 – 1.58 (m, 3H), 1.58 – 1.43 (m, 6H), 1.43 – 1.28 (m, 5H), 0.83 (t, *J* = 7.5 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.07, 137.07, 129.54, 127.07, 77.32, 77.00, 76.68, 73.57, 45.39, 31.62, 31.56, 25.70, 23.48, 22.63, 22.17, 21.95, 21.48, 14.11.

HRMS: (ESI, [$C_{18}H_{28}BNO_3S$ + Na]) calcd, 372.1784; found *m/z*: 372.1767.

(4-(3-((1s,5s)-9-Oxa-10-borabicyclo[3.3.2]decan-10-yl)propyl)-2-methoxyphenoxy)(*t*-butyl)di-methylsilane (**3**)



Compound was synthesized from (4-allyl-2-methoxyphenoxy)(*t*-butyl)dimethylsilane according to General Procedure 5, to give (**3**) as a colorless oil (13.5 g / 90%).

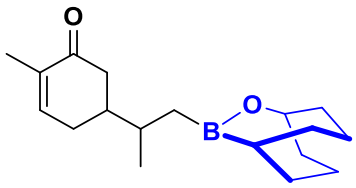
R_f: 0.20 (Et_2O/hexanes 20:80)

^1H NMR (500 MHz, $CDCl_3$) δ 6.74 (d, *J* = 8.0 Hz, 2H), 6.67 (d, *J* = 1.8 Hz, 2H), 6.62 (dd, *J* = 8.0, 1.7 Hz, 2H), 4.57 (d, *J* = 2.9 Hz, 2H), 3.79 (s, 6H), 2.56 – 2.46 (m, 4H), 1.83 (ddd, *J* = 12.9, 6.7, 2.6 Hz, 8H), 1.71 – 1.60 (m, 10H), 1.60 – 1.52 (m, 5H), 1.46 – 1.34 (m, 8H), 1.03 – 0.95 (m, 18H), 0.92 – 0.83 (m, 4H), 0.18 – 0.09 (m, 11H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 150.65, 142.90, 136.86, 120.69, 120.60, 112.84, 73.47, 55.64, 38.85, 31.97, 26.41, 26.10, 25.92, 22.46, 18.59, -4.48.

HRMS: (EI, [$C_{24}H_{41}BO_3Si$]) calcd, 416.2923; found *m/z*: 416.2942.

5-(1-((1s,5s)-9-Oxa-10-borabicyclo[3.3.2]decan-10-yl)propan-2-yl)-2-methylcyclohex-2-en-1-one (**4**)



Compound was synthesized from carvone according to General Procedure 5. The crude product was subjected to Kugelrohr distillation conditions to strip off unreacted carvone and low boiling compounds, leaving (**4**) as a pale yellow oil (3.0 g / 60%).

R_f: 0.70 (Et_2O/hexanes 30:70)

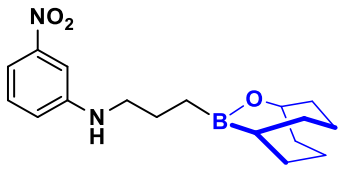
^1H NMR (500 MHz, $CDCl_3$) δ 6.73 (d, *J* = 5.5 Hz, 1H), 4.55 (d, *J* = 2.7 Hz, 1H), 2.53 – 2.43 (m, 1H), 2.36 – 2.26 (m, 1H), 2.18 – 1.99 (m, 2H), 1.93 – 1.77 (m, 7H), 1.74 (qd, *J* =

2.4, 1.1 Hz, 4H), 1.70 – 1.49 (m, 9H), 1.49 – 1.32 (m, 7H), 0.98 – 0.80 (m, 5H), 0.68 (ddd, *J* = 15.9, 9.7, 6.5 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 201.20, 145.73, 145.69, 135.34, 135.30, 73.52, 42.81, 42.68, 42.58, 41.81, 33.30, 33.27, 32.21, 31.95, 31.86, 30.33, 29.42, 26.37, 26.33, 25.87, 22.45, 22.36, 22.15, 19.47, 19.33, 15.82.

HRMS: (EI, [$C_{18}H_{29}BO_2$]) calcd, 288.2264; found *m/z*: 288.2277.

N-(3-((1s,5s)-9-Oxa-10-borabicyclo[3.3.2]decan-10-yl)propyl)-3-nitroaniline (**5**)



Compound was synthesized from N-allyl-3-nitroaniline according to General Procedure 5 to give (**5**) as an orange solid (2.2 g / 83%).

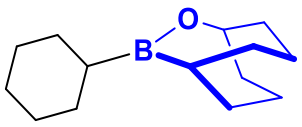
R_f: 0.60 (Et_2O/hexanes 30:70)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.37 (t, *J* = 2.2 Hz, 1H), 7.24 (t, *J* = 8.1 Hz, 1H), 6.83 (dd, *J* = 8.0, 2.1 Hz, 1H), 4.69 – 4.60 (m, 1H), 4.37 (s, 1H), 3.11 (t, *J* = 7.0 Hz, 2H), 1.85 (ddd, *J* = 12.5, 6.7, 4.4 Hz, 6H), 1.76 – 1.50 (m, 10H), 1.48 – 1.34 (m, 6H), 0.98 (t, *J* = 7.4 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.62, 149.39, 129.68, 118.72, 111.48, 106.19, 73.73, 46.39, 32.38, 32.20, 31.95, 26.64, 26.36, 26.00, 23.42, 22.42, 22.24, 22.15.

HRMS: (EI, [$C_{17}H_{25}BN_2O_3$]) calcd, 316.1961; found *m/z*: 316.1975.

(1s,5s)-10-Cyclohexyl-9-oxa-10-borabicyclo[3.3.2]decane (**6**)



Compound was synthesized from cyclohexene according to General Procedure 5, to give (**6**) as an colorless oil (5.0 g / quant).

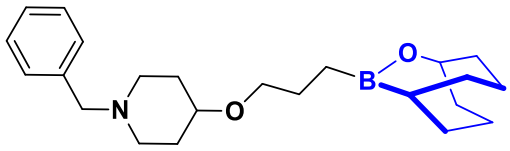
R_f: 0.80 (hexanes)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.54 (s, 2H), 1.80 (dt, *J* = 7.9, 5.6 Hz, 16H), 1.75 – 1.69 (m, 3H), 1.63 (dd, *J* = 10.8, 2.6 Hz, 23H), 1.56 – 1.46 (m, 9H), 1.38 (dt, *J* = 12.1, 10.5 Hz, 17H), 1.20 (dd, *J* = 28.0, 8.8 Hz, 13H), 0.94 – 0.87 (m, 2H), 0.83 (td, *J* = 11.2, 2.4 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 73.19, 71.09, 70.96, 62.36, 34.81, 33.82, 32.39, 32.37, 32.19, 32.05, 31.93, 27.76, 27.70, 27.21, 26.63, 26.37, 26.21, 22.43, 22.27, 22.23, 22.14, 19.16, 13.99.

HRMS: (EI, [$C_{14}H_{25}BO$]) calcd, 220.2001; found *m/z*: 220.1999.

4-(3-((1s,5s)-9-Oxa-10-borabicyclo[3.3.2]decan-10-yl)propoxy)-1-benzylpiperidine (**7**)



Compound was synthesized from 4-(allyloxy)-1-benzylpiperidine according to General Procedure 5, to give (**7**) as an pale yellow oil (5.0 g / quant).

R_f: 0.50 (MeOH/DCM 10:90)

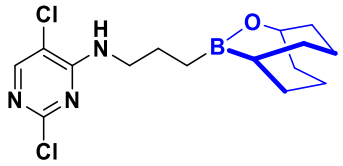
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 4.7, 1.5 Hz, 3H), 7.87 (dd, *J* = 7.8, 1.5 Hz, 3H), 7.23 (d, *J* = 3.4 Hz, 4H), 7.01 (dd, *J* = 7.8, 4.7 Hz, 4H), 6.41 (t, *J* = 3.1 Hz, 3H), 4.53

(d, *J* = 2.8 Hz, 4H), 4.28 – 4.22 (m, 8H), 1.97 – 1.86 (m, 9H), 1.85 – 1.71 (m, 22H), 1.68 – 1.55 (m, 18H), 1.51 (ddd, *J* = 20.3, 13.5, 10.7 Hz, 11H), 1.45 – 1.29 (m, 23H), 0.91 – 0.85 (m, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.53, 142.60, 128.65, 128.25, 120.68, 115.44, 99.07, 73.50, 46.95, 32.35, 32.22, 31.87, 26.61, 25.93, 25.14, 22.38, 22.21, 22.15.

HRMS: (EI, [$C_{23}H_{36}BNO_2$]) calcd, 369.2843; found *m/z*: 369.2855.

N-(3-((1s,5s)-9-Oxa-10-borabicyclo[3.3.2]decan-10-yl)propyl)-2,5-dichloropyrimidin-4-amine (**8**)



Compound was synthesized from *N*-allyl-2,5-dichloropyrimidin-4-amine according to General Procedure 5. Crude product was purified by silica gel column chromatography to give (**8**) as an pale yellow oil (2.9 g / 58%). Note: compound decomposes rapidly on silica gel, chromatography must be conducted quickly.

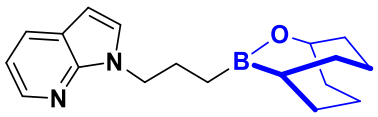
R_f: 0.40 (EtOAc/hexanes 15:85) (decomposes rapidly on silica, leaving a baseline spot)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (s, 1H), 5.93 (s, 2H), 4.60 (d, *J* = 3.0 Hz, 2H), 3.43 (td, *J* = 6.9, 5.5 Hz, 4H), 1.82 (dt, *J* = 16.6, 8.2 Hz, 13H), 1.70 (dd, *J* = 14.3, 7.1 Hz, 4H), 1.68 – 1.46 (m, 18H), 1.37 (ddd, *J* = 15.7, 8.6, 4.8 Hz, 14H), 0.97 (t, *J* = 7.4 Hz, 4H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.93, 158.58, 153.12, 113.09, 73.87, 70.99, 70.92, 62.34, 44.00, 33.78, 32.33, 32.16, 31.84, 26.59, 26.34, 25.92, 23.14, 22.36, 22.19, 22.11, 19.12, 13.98.

HRMS: (EI, [$C_{15}H_{22}BCl_2N_3O$]) calcd, 341.1236; found *m/z*: 341.1248.

1-(3-((1s,5s)-9-Oxa-10-borabicyclo[3.3.2]decan-10-yl)propyl)-1H-pyrrolo[2,3-b]pyridine (**9**)



Compound was synthesized from 1-allyl-1H-pyrrolo[2,3-b]pyridine according to General Procedure 5, to give (**9**) as an pale yellow oil (4.0 g / quant.).

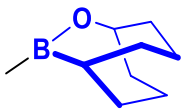
R_f: 0.50 (EtOAc/hexanes 20:80)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (dd, *J* = 4.7, 1.5 Hz, 3H), 7.87 (dd, *J* = 7.8, 1.5 Hz, 3H), 7.23 (d, *J* = 3.4 Hz, 4H), 7.01 (dd, *J* = 7.8, 4.7 Hz, 4H), 6.41 (t, *J* = 3.1 Hz, 3H), 4.53 (d, *J* = 2.8 Hz, 4H), 4.28 – 4.22 (m, 8H), 1.97 – 1.86 (m, 9H), 1.85 – 1.71 (m, 22H), 1.68 – 1.55 (m, 18H), 1.51 (ddd, *J* = 20.3, 13.5, 10.7 Hz, 11H), 1.45 – 1.29 (m, 23H), 0.91 – 0.85 (m, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.53, 142.60, 128.65, 128.25, 120.68, 115.44, 99.07, 73.50, 46.95, 32.35, 32.22, 31.87, 26.61, 25.93, 25.14, 22.38, 22.21, 22.15.

HRMS: (EI, [$C_{18}H_{25}BN_2O$]) calcd, 296.2060; found *m/z*: 296.2062.

(1s,5s)-10-Methyl-9-oxa-10-borabicyclo[3.3.2]decane (**10**)



Compound was synthesized according to General Procedure 6, to give (**10**) as colorless oil, (1.3 g / 85%).

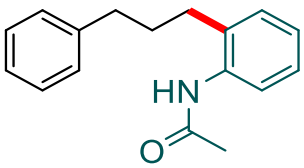
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.55 (s, 1H), 1.91 – 1.75 (m, 6H), 1.69 – 1.54 (m, 7H), 1.47 – 1.33 (m, 6H), 0.36 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 73.50, 33.83, 32.38, 31.95, 26.64, 26.34, 25.81, 22.43, 22.23, 19.16.

HRMS: (EI, [$C_9H_{17}BO$]) calcd, 152.1374; found *m/z*: 152.1378.

Scope of Coupling Reactions

N-(2-(3-Phenylpropyl)phenyl)acetamide (**11**)



Coupling was conducted on a 0.25 mmol scale using General Procedure 1 to give (**11**) as a white solid, 64 mg (quant)

R_f: 0.40 (EtOAc/hexanes 60:40)

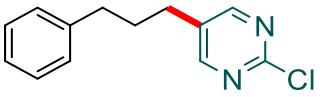
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.8 Hz, 3H), 7.32 (t, *J* = 7.4 Hz, 8H), 7.23 – 7.16 (m, 18H), 7.15 – 7.09 (m, 4H), 6.87 (s, 3H), 2.68 (t, *J* = 7.1 Hz, 9H), 2.60 – 2.51 (m, 7H), 2.00 (s, 11H), 1.91 (d, *J* = 7.7 Hz, 8H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.92, 141.87, 134.98, 133.94, 129.61, 128.63, 128.61, 126.89, 126.16, 125.80, 124.59, 35.27, 31.42, 30.28, 24.14.

mp: 114-117 ^{o}C

HRMS: (ESI, [$C_{17}H_{19}NO$ + H]) calcd, 254.1545; found *m/z*: 254.1547.

2-Chloro-5-(3-phenylpropyl)pyrimidine (**12**)



Coupling was conducted at 0.25 mmol scale using General Procedure 1 to give (**12**) as a clear oil, 47 mg (80%).

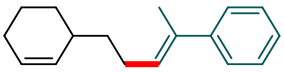
R_f: 0.30 (Et_2O/hexanes 30:70)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 2H), 7.30 (t, *J* = 7.3 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 7.16 (d, *J* = 7.0 Hz, 2H), 2.68 (t, *J* = 7.5 Hz, 2H), 2.65 – 2.58 (m, 2H), 2.03 – 1.92 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.48, 159.20, 140.91, 133.81, 128.67, 128.48, 126.34, 35.17, 32.06, 29.04.

HRMS: (EI, [$C_{13}H_{13}ClN_2$]) calcd, 232.0767, found *m/z*: 232.0774.

(*E*)-(5-(Cyclohex-2-en-1-yl)pent-2-en-2-yl)benzene (**13**)



Coupling was conducted at 0.25 mmol scale using General Procedure 1 to give (**13**) as a clear oil, 38 mg (68%)

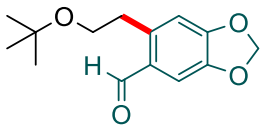
R_f : 0.55 (hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, *J* = 7.6 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.22 (t, *J* = 11.2 Hz, 1H), 5.80 (s, 1H), 5.69 (s, 2H), 2.31 – 2.21 (m, 2H), 2.21 – 2.10 (m, 1H), 2.04 (d, *J* = 14.6 Hz, 5H), 1.80 (d, *J* = 11.9 Hz, 1H), 1.76 – 1.58 (m, 2H), 1.53 – 1.38 (m, 2H), 1.37 – 1.15 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.12, 134.59, 128.87, 128.26, 127.21, 126.72, 126.57, 125.71, 36.62, 33.33, 32.02, 29.05, 26.29, 25.43, 15.88.

HRMS: (ESI, [$C_{17}H_{22}$ + H]) calcd, 226.1721; found *m/z*: 226.1715.

6-(2-(*t*-Butoxy)ethyl)benzo[d][1,3]dioxole-5-carbaldehyde (**14**)



Coupling was conducted at 0.25 mmol scale using General Procedure 1 to give (**14**) as a yellow oil, 47 mg (75%)

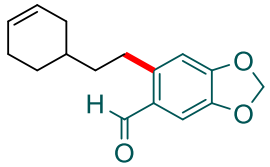
R_f : 0.25 (Et_2O/hexanes 15:85)

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.16 (s, 1H), 7.32 (s, 1H), 6.73 (s, 1H), 6.01 (s, 2H), 3.52 (t, *J* = 6.7 Hz, 2H), 3.12 (t, *J* = 6.7 Hz, 2H), 1.09 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 189.99, 152.32, 147.00, 140.03, 129.35, 110.96, 107.87, 101.92, 77.48, 76.84, 73.28, 62.83, 33.34, 27.50.

HRMS: (EI, [$C_{14}H_{18}O_4$ + H]) calcd, 250.1205; found *m/z*: 250.1208.

6-(2-(Cyclohex-3-en-1-yl)ethyl)benzo[d][1,3]dioxole-5-carbaldehyde (**15**)



Coupling was conducted at 0.25 mmol scale using General Procedure 1 to give (**15**) as a yellow oil, 43 mg (67%).

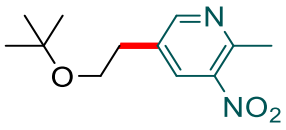
R_f : 0.40 (Et_2O/hexanes 5:95)

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.16 (s, 1H), 7.39 – 7.21 (m, 1H), 6.70 (s, 1H), 6.01 (s, 2H), 5.72 – 5.58 (m, 2H), 3.03 – 2.92 (m, 2H), 2.16 (d, *J* = 16.3 Hz, 1H), 2.05 (s, 2H), 1.84 – 1.60 (m, 3H), 1.61 – 1.51 (m, 2H), 1.28 (dt, *J* = 18.9, 7.8 Hz, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 189.40, 152.55, 146.74, 143.85, 128.09, 127.22, 126.33, 110.38, 108.45, 101.93, 77.48, 76.84, 40.22, 33.57, 31.86, 29.68, 28.86, 25.22.

HRMS: (EI, [$C_{16}H_{18}O_3$]) calcd, 258.1256; found *m/z*: 258.1255.

5-(2-(*t*-Butoxy)ethyl)-2-methyl-3-nitropyridine (**16**)



Coupling was conducted at 0.25 mmol scale using General Procedure 1 to give (**16**) as a faintly yellow oil, 48 mg (80%)

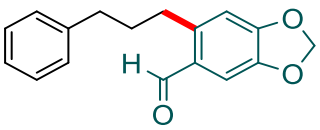
R_f : 0.30 (Et_2O/hexanes 30:70)

^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.19 (s, 1H), 3.58 (t, *J* = 6.1 Hz, 2H), 2.87 (dd, *J* = 8.0, 4.1 Hz, 2H), 2.81 (s, 3H), 1.13 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 152.58, 150.26, 144.47, 133.69, 131.90, 72.30, 60.26, 32.32, 26.54, 22.59.

HRMS: (EI, [$C_{12}H_{18}N_2O_3$ + CH_3]) calcd, 223.1083; found *m/z*: 223.1075.

6-(3-Phenylpropyl)benzo[d][1,3]dioxole-5-carbaldehyde (**17**)



Coupling was conducted at 0.25 mmol scale using General Procedure 1 to give (**17**) as a pale yellow oil, 65 mg (97%)

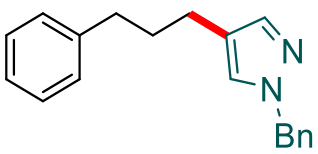
R_f : 0.30 (Et_2O/hexanes 10:90)

^1H NMR (500 MHz, $CDCl_3$) δ 10.08 (s, 1H), 7.34 – 7.27 (m, 3H), 7.20 (dd, *J* = 9.3, 8.2 Hz, 3H), 6.69 (s, 1H), 6.02 (s, 2H), 3.01 – 2.94 (m, 2H), 2.70 (t, *J* = 7.6 Hz, 2H), 2.00 – 1.90 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 189.38, 152.52, 146.83, 143.04, 141.67, 128.54, 128.48, 128.29, 126.10, 110.42, 108.57, 101.95, 35.59, 34.44, 31.61.

HRMS: (EI, [$C_{17}H_{16}O_3$]) calcd, 268.11; found *m/z*: 268.1092.

1-Benzyl-4-(3-phenylpropyl)-1H-pyrazole (**18**)



Coupling was conducted at 0.25 mmol scale using General Procedure 1 to give (**18**) as a clear oil, 55 mg (80%).

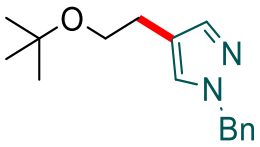
R_f : 0.35 (Et_2O/hexanes 30:70)

^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (s, 3H), 7.37 – 7.25 (m, 20H), 7.24 – 7.17 (m, 14H), 7.16 (s, 5H), 5.27 (s, 7H), 2.70 – 2.59 (m, 6H), 2.53 – 2.43 (m, 6H), 1.94 – 1.82 (m, 7H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 142.15, 138.94, 136.79, 128.76, 128.42, 128.30, 127.94, 127.60, 127.53, 125.74, 121.91, 77.35, 77.03, 76.72, 55.87, 35.39, 32.50, 23.73.

HRMS: (EI, [$C_{19}H_{20}N_2$ + Na]) calcd, 299.1524; found *m/z*: 299.1524.

1-Benzyl-4-(2-(*t*-butoxy)ethyl)-1H-pyrazole (**19**)



Coupling was conducted at 0.25 mmol scale using General Procedure 1 to give (**19**) as a light yellow oil, 41 mg (67%).

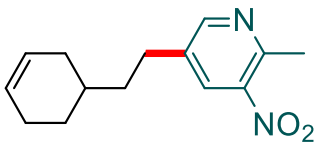
R_f : 0.25 (Et_2O/hexanes 30:70)

^1H NMR (400 MHz, cdcl$_3$) δ 7.41 (s, 1H), 7.37 – 7.30 (m, 2H), 7.29 (d, *J* = 6.9 Hz, 1H), 7.23 (s, 1H), 7.20 (d, *J* = 6.8 Hz, 2H), 5.25 (s, 2H), 3.45 (t, *J* = 7.0 Hz, 2H), 2.65 (t, *J* = 7.0 Hz, 2H), 1.16 (s, 9H).

^{13}C NMR (101 MHz, cdcl$_3$) δ 139.50, 136.97, 128.84, 128.22, 128.01, 127.75, 119.16, 72.87, 62.45, 56.02, 27.67, 25.97.

HRMS: (EI, [$C_{16}H_{22}N_2O$]) calcd, 281.1630; found *m/z*: 281.1623.

5-(2-(Cyclohex-3-en-1-yl)ethyl)-2-methyl-3-nitropyridine (**20**)



Coupling was conducted at 0.25 mmol scale using General Procedure 1 to give (**20**) as a pale yellow oil, 41 mg (67%).

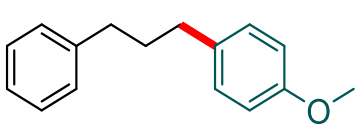
R_f : 0.30 (Et_2O/hexanes 15:85)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (s, 5H), 8.08 (s, 5H), 5.65 (s, 11H), 2.81 (s, 17H), 2.77 – 2.66 (m, 11H), 2.16 (s, 7H), 2.05 (d, *J* = 3.6 Hz, 11H), 1.75 (t, *J* = 18.7 Hz, 14H), 1.67 – 1.49 (m, 19H), 1.27 (dd, *J* = 18.8, 6.3 Hz, 7H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.03, 151.04, 145.65, 137.21, 131.94, 127.22, 126.12, 37.74, 33.10, 31.72, 29.58, 28.75, 25.12, 23.54.

HRMS: (EI, [$C_{14}H_{18}N_2O_2$]) calcd, 246.1368; found *m/z*: 246.1378.

1-Methoxy-4-(3-phenylpropyl)benzene (**21**)



Coupling was conducted at 0.25 mmol scale using General Procedure 1 to give (**21**) as a pale yellow oil, 50 mg (88%).

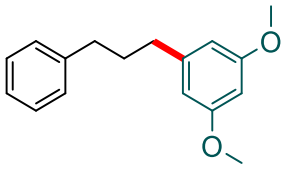
R_f : 0.42 (hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (dd, *J* = 14.0, 6.7 Hz, 5H), 7.23 (dd, *J* = 5.2, 2.6 Hz, 6H), 7.16 (t, *J* = 5.7 Hz, 4H), 6.90 – 6.85 (m, 4H), 3.84 (s, 7H), 2.73 – 2.55 (m, 9H), 1.97 (tt, *J* = 9.1, 6.9 Hz, 5H).

^{13}C NMR: ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.79, 142.49, 134.49, 129.43, 128.57, 128.41, 125.83, 113.82, 55.39, 35.50, 34.63, 33.35.

HRMS: (EI, [$C_{16}H_{18}O$]) calcd, 226.1358; found *m/z*: 226.1360.

1,3-Dimethoxy-5-(3-phenylpropyl)benzene (**22**)



Coupling was conducted at 0.25 mmol scale using General Procedure 1 to give (**23**) as a pale yellow oil, 40 mg (63%).

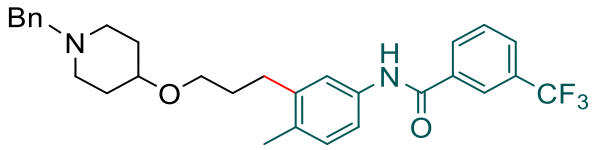
R_f : 0.54 (Et_2O/hexanes 4:96

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.4 Hz, 2H), 7.22 (d, *J* = 6.8 Hz, 3H), 6.38 (s, 2H), 6.34 (s, 1H), 3.80 (s, 7H), 2.68 (t, *J* = 7.7 Hz, 2H), 2.62 (t, *J* = 7.7 Hz, 2H), 2.05 – 1.90 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 160.83, 144.83, 142.35, 128.57, 128.42, 125.86, 106.60, 97.82, 55.35, 35.85, 35.53, 32.82.

HRMS: (EI, [$C_{17}H_{20}O_2$]) calcd, 256.1463, found *m/z*: 256.1467.

N-(3-(3-((1-Benzylpiperidin-4-yl)oxy)propyl)-4-methylphenyl)-3-(trifluoromethyl)-benzamide (**23**)



Coupling was conducted at 0.25 mmol scale using General Procedure 1 to give (**22**) as a brown semi-solid, 119 mg (93%).

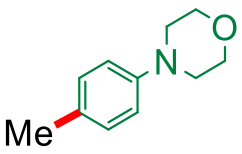
R_f : 0.25 (Et_2O/hexanes 50:50)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (s, 1H), 8.06 (d, *J* = 7.6 Hz, 1H), 8.01 (s, 1H), 7.78 (d, *J* = 7.6 Hz, 1H), 7.60 (t, *J* = 7.7 Hz, 1H), 7.45 (s, 1H), 7.41 – 7.27 (m, 6H), 7.12 (d, *J* = 8.1 Hz, 1H), 3.67 – 3.60 (m, 3H), 3.57 (s, 2H), 3.46 (t, *J* = 6.3 Hz, 2H), 3.36 (d, *J* = 6.8 Hz, 1H), 2.79 (d, *J* = 6.3 Hz, 2H), 2.72 – 2.62 (m, 2H), 2.34 – 2.22 (m, 5H), 1.94 (d, *J* = 11.5 Hz, 2H), 1.90 – 1.78 (m, 3H), 1.66 (d, *J* = 8.9 Hz, 2H), 1.24 (d, *J* = 11.2 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.35, 141.25, 136.06, 135.51, 132.95, 130.74, 130.50, 129.42, 129.31, 128.31, 127.18, 124.22, 124.19, 121.16, 118.32, 70.63, 67.16, 63.00, 51.16, 31.33, 30.50, 29.94, 29.38, 18.92.

HRMS: (ESI, [$C_{30}H_{33}F_3N_2O_2$ + H]) calcd, 511.2572, found *m/z*: 511.2574.

4-(*p*-Tolyl)morpholine (**24**)



Coupling was conducted at 0.25 mmol scale using General Procedure 2 to give (**24**) as a yellow oil 39 mg (88%).

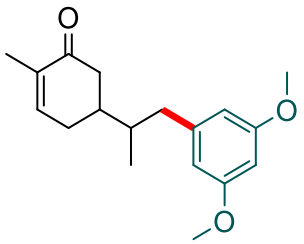
R_f: 0.25 (Et_2O/hexanes 30:70)

^1H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.2 Hz, 2H), 6.90 – 6.78 (m, 2H), 3.91 – 3.79 (m, 4H), 3.17 – 3.06 (m, 4H), 2.29 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.32, 129.82, 129.67, 116.15, 67.10, 50.05, 20.54.

[x]Jiang, D.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2007**, *72*, 672.

5-(1-(3,5-Dimethoxyphenyl)propan-2-yl)-2-methylcyclohex-2-en-1-one (**25**)



Coupling was conducted at 0.25 mmol scale using General Procedure 2 to give (**25**) as a pale yellow oil 63 mg (88%).

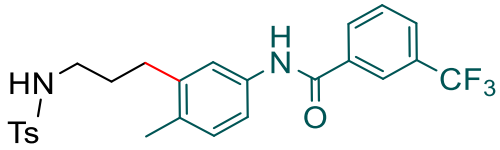
R_f : 0.30 (Et_2O/hexanes 2:8)

^1H NMR (400 MHz, $CDCl_3$) δ 6.74 (s, 1H), 6.29 (s, 3H), 3.77 (s, 6H), 2.68 (t, *J* = 15.8 Hz, 1H), 2.59 – 2.44 (m, 1H), 2.28 (d, *J* = 13.5 Hz, 4H), 2.11 – 1.99 (m, 1H), 1.76 (s, 4H), 0.85 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 200.66, 160.79, 145.46, 145.33, 143.37, 143.32, 135.50, 107.25, 107.20, 97.81, 97.74, 55.38, 42.85, 40.79, 40.70, 40.68, 39.94, 39.87, 38.89, 38.86, 30.68, 28.51, 15.85, 15.83, 15.74.

HRMS: (CI, [$C_{18}H_{24}O_3$ + H]) calcd, 289.1804, found *m/z*: 289.1797.

N-(4-Methyl-3-(3-((4-methylphenyl)sulfonamido)propyl)phenyl)-3-(trifluoromethyl)-benzamide (**26**)



Coupling was conducted at 0.25 mmol scale using General Procedure 2 to give (**26**) as a white solid, 68 mg (56%).

R_f: 0.28 (EtOAc/hexanes 40:60)

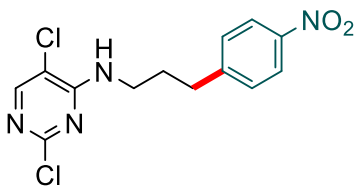
^{1}H NMR (500 MHz, DMSO-d_6) δ 10.29 (s, 2H), 8.26 (s, 2H), 8.23 (d, *J* = 7.9 Hz, 2H), 7.93 (d, *J* = 7.8 Hz, 2H), 7.75 (t, *J* = 7.8 Hz, 2H), 7.65 (d, *J* = 8.2 Hz, 4H), 7.57 (t, *J* = 5.8 Hz, 2H), 7.48 (s, 1H), 7.46 (s, 3H), 7.35 (d, *J* = 8.3 Hz, 4H), 7.08 (d, *J* = 8.0 Hz, 2H), 2.79 (dd, *J* = 13.0, 6.7 Hz, 4H), 2.47 (s, 5H), 2.33 (s, 6H), 2.15 (s, 6H), 1.65 – 1.51 (m, 4H).

^{13}C NMR (101 MHz, DMSO-d_6) δ 163.68, 142.53, 139.90, 137.67, 136.61, 135.84, 131.79, 131.26, 130.08, 129.72, 129.64, 129.32, 129.00, 128.06, 126.53, 125.37, 124.22, 124.18, 124.14, 120.86, 118.30, 42.49, 39.52, 29.95, 29.67, 20.94, 18.33.

mp: 159-160^{o}C

HRMS: (EI, [$C_{25}H_{25}F_3N_2O_3S$ + Na]) calcd, 513.1436; found *m/z*: 513.1447.

2,5-Dichloro-*N*-(3-(4-nitrophenyl)propyl)pyrimidin-4-amine (**27**)



Coupling was conducted at 0.25 mmol scale using General Procedure 2 to give (**27**) as a white solid, 59 mg (72%).

R_f: 0.18 (DCM)

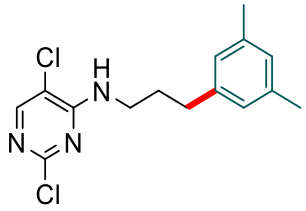
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 6.35 (d, *J* = 2.1 Hz, 2H), 6.31 (t, *J* = 2.1 Hz, 1H), 5.47 (s, 1H), 3.78 (s, 6H), 3.56 (dd, *J* = 13.0, 6.8 Hz, 2H), 2.67 (t, *J* = 7.4 Hz, 2H), 1.99 (p, *J* = 7.2 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 161.07, 158.84, 158.58, 153.42, 143.48, 113.24, 106.51, 98.12, 55.41, 41.01, 33.63, 30.28.

mp: 107.5-108.5 ºC

HRMS: (EI, [$C_{13}H_{12}Cl_2N_4O_2$ + Na]) calcd, 349.0235; found *m/z*: 349.0237.

2,5-Dichloro-*N*-(3-(3,5-dimethylphenyl)propyl)pyrimidin-4-amine (**28**)



Coupling was conducted at 0.25 mmol scale using General Procedure 2 to give (**28**) as a pale yellow oil, 53 mg (68%).

R_f : 0.4 (Et_2O/Hex 30:70)

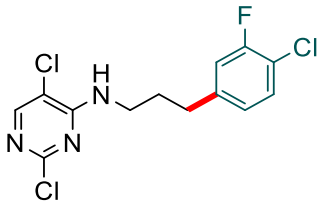
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 1H), 6.85 (s, 1H), 6.82 (s, 2H), 5.46 (s, 1H), 3.56 (dd, *J* = 12.8, 6.9 Hz, 2H), 2.66 (t, *J* = 7.4 Hz, 2H), 2.29 (s, 6H), 2.03 – 1.94 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.85, 158.61, 153.38, 140.96, 138.22, 127.95, 126.28, 113.21,

41.08, 33.15, 30.52, 21.38.

HRMS: (EI, [$C_{15}H_{17}Cl_2N_3$ + Na]) calcd, 332.0697; found *m/z*: 332.0686.

2,5-Dichloro-*N*-(3-(4-chloro-3-fluorophenyl)propyl)pyrimidin-4-amine (**29**)



Coupling was conducted at 0.25 mmol scale using General Procedure 2 to give (**29**) as a white powder, 71 mg (85%).

R_f : 0.50 (Et_2O/hexanes 50:50)

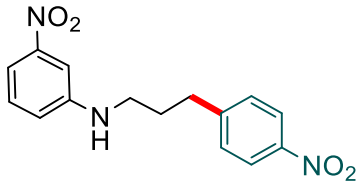
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (s, 1H), 7.29 (t, *J* = 7.9 Hz, 1H), 6.99 (dd, *J* = 10.0, 1.9 Hz, 1H), 6.93 (dd, *J* = 8.2, 1.5 Hz, 1H), 5.50 (s, 1H), 3.56 (dt, *J* = 13.2, 6.6 Hz, 2H), 2.69 (t, *J* = 7.6 Hz, 2H), 2.05 – 1.86 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.15, 158.89, 158.60, 157.17, 153.57, 142.06, 142.00, 130.65, 124.92, 124.89, 118.74, 118.60, 116.64, 116.47, 113.27, 40.74, 32.53, 32.52, 30.33.

mp: 61-63 ^{o}C

HRMS: (EI, [$C_{13}H_{11}Cl_3FN_3$ + H]) calcd, 334.0081; found *m/z*: 334.0077.

3-Nitro-*N*-(3-(4-nitrophenyl)propyl)aniline (**30**)



Coupling was conducted at 0.25 mmol scale using General Procedure 2 to give (**30**) as an orange solid, 70 mg (93%).

R_f: 0.40 (Et_2O/hexanes 30:70)

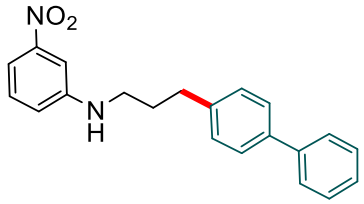
^1H NMR (600 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.6 Hz, 2H), 7.48 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.34 (d, *J* = 8.8 Hz, 3H), 7.24 (t, *J* = 8.1 Hz, 1H), 6.82 (dd, *J* = 8.1, 1.8 Hz, 1H), 4.08 (s, 1H), 3.21 (t, *J* = 7.0 Hz, 2H), 2.85 (t, *J* = 7.7 Hz, 2H), 2.06 – 1.94 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 149.53, 149.24, 148.91, 146.63, 129.88, 129.28, 123.91, 118.84, 112.08, 106.22, 43.07, 33.23, 30.35.

mp: 112-115 °C

HRMS: (EI, [$C_{15}H_{15}N_3O_4$+Na]) calcd, 324.0960; found *m/z*: 324.0973.

N-(3-([1,1'-Biphenyl]-4-yl)propyl)-3-nitroaniline (**31**)



Coupling was conducted at 0.25 mmol scale using General Procedure 2 to give (**31**) as an orange solid, 78 mg (94%).

R_f : 0.4 (Et_2O/hexanes 30:70)

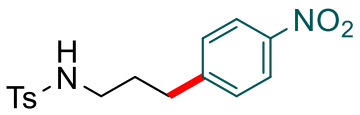
^1H NMR (600 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.6 Hz, 2H), 7.55 (d, *J* = 7.9 Hz, 2H), 7.51 (d, *J* = 7.4 Hz, 1H), 7.44 (t, *J* = 7.6 Hz, 2H), 7.37 (s, 1H), 7.34 (t, *J* = 7.3 Hz, 1H), 7.28 (d, *J* = 7.9 Hz, 2H), 7.25 (t, *J* = 8.1 Hz, 1H), 6.82 (dd, *J* = 8.1, 1.6 Hz, 1H), 4.42 – 3.89 (m, 1H), 3.22 (t, *J* = 7.0 Hz, 2H), 2.79 (t, *J* = 7.5 Hz, 2H), 2.01 (p, *J* = 7.2 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 149.53, 148.97, 140.99, 140.39, 139.22, 129.78, 128.90, 128.87, 127.36, 127.25, 127.08, 118.86, 111.95, 106.39, 43.36, 32.97, 30.63.

mp: 100-112 ^{o}C

HRMS: (EI, [$C_{21}H_{20}N_2O_2$+Na]) calcd, 355.1422; found *m/z*: 355.1414.

4-Methyl-*N*-(3-(4-nitrophenyl)propyl)benzenesulfonamide (**32**)



Coupling was conducted at 0.25 mmol scale using General Procedure 2 to give (**32**) as an off-white solid, 78 mg (93%).

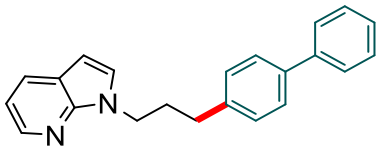
R_f: 0.17 (EtOAc/hexanes 30:70)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.7 Hz, 2H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.24 (d, *J* = 8.7 Hz, 2H), 5.17 (t, *J* = 5.9 Hz, 1H), 2.95 (q, *J* = 6.5 Hz, 2H), 2.77 – 2.68 (m, 2H), 2.41 (s, 3H), 1.88 – 1.74 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.03, 146.52, 143.72, 136.82, 129.87, 129.31, 127.16, 123.75, 77.41, 76.91, 42.36, 32.53, 30.75, 21.60.

HRMS: (EI, [$C_{16}H_{18}N_2O_4S$+Na]) calcd, 357.0885; found *m/z*: 357.0876.

1-(3-([1,1'-biphenyl]-4-yl)propyl)-1H-pyrrolo[2,3-b]pyridine (**33**)



Coupling was conducted at 0.25 mmol scale using General Procedure 2 to give (**33**) as a pale yellow oil, 71 mg (90%).

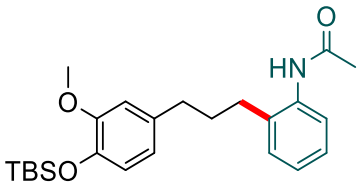
R_f : 0.6 (Et_2O/hexanes 50:50)

^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.96 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.62 (dd, *J* = 8.1, 0.9 Hz, 2H), 7.55 (d, *J* = 8.1 Hz, 2H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.3 Hz, 1H), 7.27 (dd, *J* = 11.7, 5.3 Hz, 3H), 7.11 (dd, *J* = 7.8, 4.7 Hz, 1H), 6.51 (d, *J* = 3.5 Hz, 1H), 4.41 (t, *J* = 7.1 Hz, 2H), 2.82 – 2.65 (m, 2H), 2.30 (dt, *J* = 14.8, 7.5 Hz, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.39, 142.64, 141.05, 140.39, 139.02, 129.01, 128.89, 128.82, 128.10, 127.24, 127.16, 127.07, 120.83, 115.70, 99.60, 77.36, 44.32, 32.73, 31.91.

HRMS: (EI, [$C_{22}H_{20}N_2$+H]) calcd, 313.1705; found *m/z*: 313.1714.

N-(2-(3-(4-((*t*-Butyldimethylsilyl)oxy)-3-methoxyphenyl)propyl)phenyl)acetamide (**34**)



Coupling was conducted at 0.25 mmol scale using General Procedure 2 to give (**34**) as a pale yellow oil, 95 mg (91%).

R_f : 0.48 (Et_2O/hexanes 75:25)

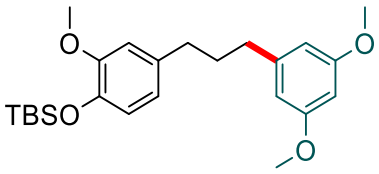
^1H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.9 Hz, 3H), 7.19 (d, *J* = 7.5 Hz, 7H), 7.12 (d, *J* = 6.8 Hz, 4H), 6.90 (s, 3H), 6.78 (d, *J* = 7.9 Hz, 4H), 6.69 – 6.60 (m, 7H), 3.79 (s,

11H), 2.60 (t, *J* = 7.2 Hz, 8H), 2.58 – 2.48 (m, 7H), 2.04 (s, 10H), 1.89 (t, *J* = 7.6 Hz, 9H), 1.00 (s, 34H), 0.15 (s, 22H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 168.74, 150.89, 143.28, 135.24, 135.09, 133.84, 129.62, 126.86, 125.68, 124.45, 120.84, 120.47, 112.61, 55.59, 34.98, 31.48, 30.37, 25.84, 24.22, 18.54, -4.51.

HRMS: (EI, [$C_{24}H_{35}NO_3Si$+Na]) calcd, 436.2284; found *m/z*: 436.2289.

t-Butyl(4-(3-(3,5-dimethoxyphenyl)propyl)-2-methoxyphenoxy)dimethylsilane (**35**)



Coupling was conducted at 0.25 mmol scale using General Procedure 2 to give (**35**) as a clear oil, 98 mg (94%).

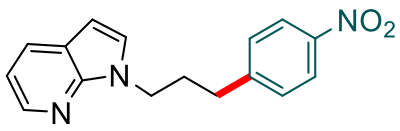
R_f : 0.50 (Et_2O/hexanes 10:90)

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.77 (d, *J* = 7.9 Hz, 1H), 6.68 (s, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 6.35 (s, 2H), 6.32 (d, *J* = 2.0 Hz, 1H), 3.79 (d, *J* = 4.1 Hz, 9H), 2.59 (t, *J* = 7.6 Hz, 4H), 1.99 – 1.87 (m, 2H), 1.00 (s, 9H), 0.16 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.86, 150.79, 144.96, 143.10, 135.84, 120.74, 120.61, 112.66, 106.68, 97.82, 55.63, 55.37, 35.88, 35.23, 32.98, 25.90, 18.58, -4.50.

HRMS: (EI, [$C_{24}H_{36}O_4Si$+H]) calcd, 417.2461; found *m/z*: 417.2452.

1-(3-(4-Nitrophenyl)propyl)-1H-pyrrolo[2,3-b]pyridine (**36**)



Coupling was conducted at 0.25 mmol scale using General Procedure 2 to give (**36**) as yellow oil, 65 mg (93%).

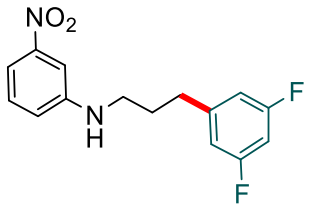
R_f : 0.40 (Et_2O/hexanes 50:50)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 – 8.28 (m, 1H), 8.09 (d, *J* = 8.6 Hz, 2H), 7.90 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.28 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 3.4 Hz, 1H), 7.06 (dd, *J* = 7.8, 4.7 Hz, 1H), 6.46 (d, *J* = 3.4 Hz, 1H), 4.36 (t, *J* = 7.0 Hz, 2H), 2.79 – 2.68 (m, 2H), 2.32 – 2.20 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.12, 147.52, 146.53, 142.81, 129.20, 129.02, 127.79, 123.71, 120.76, 115.85, 99.93, 77.16, 44.07, 33.05, 31.50.

HRMS: (EI, [$C_{16}H_{15}N_3O_2$+H]) calcd, 282.1242; found *m/z*: 282.1242.

N-(3-(3,5-Difluorophenyl)propyl)-3-nitroaniline (**37**)



Coupling was conducted at 0.25 mmol scale using General Procedure 2 to give (**37**) as an orange solid, 54 mg (74%).

R_f : 0.30 (Et_2O/hexanes 30:70)

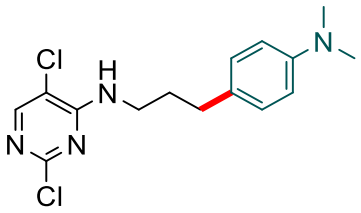
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.37 (t, *J* = 2.2 Hz, 1H), 7.27 (dd, *J* = 10.3, 5.9 Hz, 1H), 6.84 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.75 – 6.69 (m, 2H), 6.66 (tt, *J* = 9.0, 2.2 Hz, 1H), 4.12 (s, 1H), 3.21 (t, *J* = 7.0 Hz, 2H), 2.80 – 2.66 (m, 2H), 2.02 – 1.89 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 164.27, 164.17, 162.30, 162.19, 149.59, 148.85, 145.29, 145.22, 145.15, 129.89, 118.88, 112.20, 111.34, 111.30, 111.19, 111.15, 106.43, 101.99, 101.79, 101.59, 43.16, 33.11, 30.25.

MP: 81-82 ^{o}C

HRMS: (EI, [$C_{15}H_{14}F_2N_2O_2$+Na]) calcd, 315.0921; found *m/z*: 315.0929.

2,5-Dichloro-*N*-(3-(4-(dimethylamino)phenyl)propyl)pyrimidin-4-amine (**38**)



Coupling was conducted at 0.25 mmol scale using General Procedure 2 to give (**38**) as a pink-orange oil 65 mg (80%).

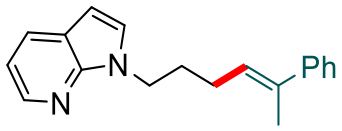
R_f : 0.45 (EtOAc:hexanes 30:70)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (s, 4H), 7.08 (d, *J* = 8.4 Hz, 12H), 6.71 (d, *J* = 7.7 Hz, 12H), 5.45 (s, 6H), 3.54 (dd, *J* = 13.1, 6.5 Hz, 13H), 2.92 (s, 37H), 2.64 (t, *J* = 7.4 Hz, 13H), 1.95 (p, *J* = 7.2 Hz, 13H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.44, 158.72, 158.49, 153.23, 149.26, 128.93, 113.19, 113.09, 77.31, 77.05, 76.80, 40.94, 32.16, 30.63, 29.70.

HRMS: (EI, [$C_{15}H_{18}Cl_2N_4$+H]) calcd, 325.0987; found *m/z*: 325.0973.

€-1-(5-Phenylhex-4-en-1-yl)-1H-pyrrolo[2,3-b]pyridine (**39**)



Coupling was conducted at 0.25 mmol scale using General Procedure 2 to give (**39**) as a tan oil, 59 mg (85%).

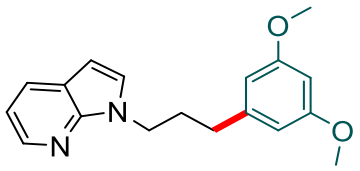
R_f : 0.47 (EtOAc/hexanes 15:85)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 4.7, 1.5 Hz, 1H), 7.92 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.36 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.34 – 7.27 (m, 2H), 7.24 (dd, *J* = 4.7, 2.4 Hz, 2H), 7.06 (dd, *J* = 7.8, 4.7 Hz, 1H), 6.47 (d, *J* = 3.5 Hz, 1H), 5.77 (d, *J* = 1.3 Hz, 1H), 4.38 (t, *J* = 7.1 Hz, 2H), 2.26 (q, *J* = 7.3 Hz, 2H), 2.14 – 2.02 (m, 2H), 1.99 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 147.51, 143.83, 142.72, 135.81, 128.88, 128.42, 128.26, 128.07, 127.06, 126.73, 125.73, 120.79, 115.66, 99.51, 44.37, 30.28, 26.18, 15.98.

HRMS: (EI, [$C_{19}H_{20}N_2$+H]) calcd, 277.1705; found *m/z*: 277.1698.

1-(3-(3,5-Dimethoxyphenyl)propyl)-1H-pyrrolo[2,3-b]pyridine (**40**)



Coupling was conducted at 0.25 mmol scale using General Procedure 2 to give (**40**) as a pale yellow oil, 65 mg (88%).

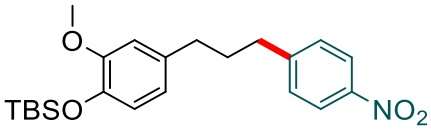
R_f : 0.17 (EtOAc/hexanes 30:70)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, *J* = 5.6 Hz, 1H), 7.91 (d, *J* = 7.3 Hz, 1H), 7.21 (d, *J* = 3.4 Hz, 1H), 7.06 (dd, *J* = 7.8, 4.7 Hz, 1H), 6.46 (d, *J* = 3.4 Hz, 1H), 6.35 (d, *J* = 2.1 Hz, 2H), 6.31 (d, *J* = 2.1 Hz, 1H), 4.34 (t, *J* = 7.1 Hz, 2H), 3.76 (s, 6H), 2.63 – 2.56 (m, 2H), 2.27 – 2.18 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.92, 147.54, 143.71, 142.73, 128.88, 128.06, 120.77, 115.69, 106.56, 99.55, 98.11, 55.36, 44.21, 33.40, 31.69.

HRMS: (EI, [$C_{18}H_{20}N_2O_2$+H]) calcd, 297.1603; found *m/z*: 297.1597.

t-Butyl(2-methoxy-4-(3-(4-nitrophenyl)propyl)phenoxy)dimethylsilane (**41**)



Coupling was conducted at 0.1 mmol scale using General Procedure 2 to give (**41**) as a pale yellow oil, 31 mg (78%).

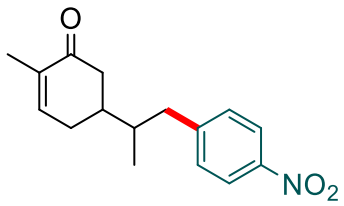
R_f : 0.40 (EtOAc/hexanes 4:96)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 8.6 Hz, 2H), 6.77 (d, *J* = 7.9 Hz, 1H), 6.64 (s, 1H), 6.63 – 6.58 (m, 1H), 3.79 (s, 3H), 2.79 – 2.69 (m, 2H), 2.59 (t, *J* = 7.6 Hz, 2H), 2.03 – 1.90 (m, 2H), 0.99 (s, 9H), 0.15 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.88, 150.46, 146.42, 143.29, 135.08, 129.35, 123.75, 120.86, 120.56, 112.51, 55.63, 35.38, 35.10, 32.76, 25.87, 18.57, -4.51.

HRMS: (EI, [$C_{22}H_{31}NO_4Si$+H]) calcd, 402.2101; found *m/z*: 402.2099.

2-Methyl-5-(1-(4-nitrophenyl)propan-2-yl)cyclohex-2-en-1-one (**42**)



Coupling was conducted at 0.25 mmol scale using General Procedure 2 to give (**42**) as an off-white powder, 46 mg (67%).

R_f : 0.28 (Et_2O/hexanes 30:70)

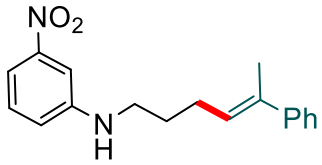
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.4 Hz, 2H), 7.28 (d, *J* = 8.5 Hz, 2H), 6.74 (s, 1H), 2.86 (ddd, *J* = 22.2, 13.5, 5.4 Hz, 1H), 2.52 (dd, *J* = 16.7, 2.6 Hz, 1H), 2.49 – 2.40 (m, 1H), 2.40 – 2.30 (m, 1H), 2.22 (dd, *J* = 30.1, 16.0 Hz, 2H), 2.09 – 1.98 (m, 1H), 1.85 – 1.77 (m, 1H), 1.75 (s, 3H), 0.84 (dd, *J* = 6.8, 2.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 199.95, 148.91, 148.89, 146.59, 144.90, 144.74, 135.68, 135.64, 129.89, 129.88, 123.73, 123.72, 42.67, 40.60, 40.37, 40.26, 40.15, 39.98, 38.99, 38.94, 32.16, 30.55, 28.66, 26.33, 22.11, 15.76, 15.74, 15.64, 15.63.

MP: 55-60 ^{o}C

HRMS: (EI, [$C_{16}H_{19}NO_3$+H]) calcd, 274.1433; found *m/z*: 274.1440.

€-3-Nitro-*N*-(5-phenylhex-4-en-1-yl)aniline (**43**)



Coupling was conducted at 0.25 mmol scale using General Procedure 2 to give (**43**) as a brown-orange oil, 67 mg (90%).

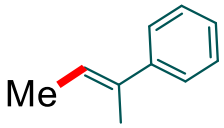
R_f : 0.47 (EtOAc/hexanes 15:85)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.49 (m, 1H), 7.44 – 7.37 (m, 3H), 7.34 (dd, *J* = 10.3, 4.9 Hz, 2H), 7.31 – 7.21 (m, 2H), 6.87 (dd, *J* = 8.1, 2.3 Hz, 1H), 5.81 (td, *J* = 7.2, 1.2 Hz, 1H), 4.13 (s, 1H), 3.24 (t, *J* = 7.1 Hz, 2H), 2.36 (q, *J* = 7.3 Hz, 2H), 2.07 (s, 3H), 1.84 (p, *J* = 7.2 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.53, 149.53, 149.14, 149.14, 143.68, 143.68, 136.01, 129.77, 128.33, 127.07, 126.85, 125.70, 118.75, 111.79, 106.27, 43.51, 29.11, 26.32, 15.99.

HRMS: (EI, [$C_{18}H_{20}N_2O_2$+Na]) calcd, 319.1422; found *m/z*: 319.1429.

(E)-But-2-en-2-ylbenzene (**44**)



Coupling was conducted at 0.25 mmol scale using General Procedure 2 to give (**44**) as a clear oil, 26 mg (78%).

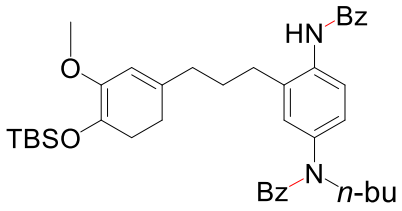
R_f: 0.80 (hexanes)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 5.87 (qd, *J* = 6.8, 0.9 Hz, 1H), 2.04 (s, 3H), 1.81 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.16, 135.62, 128.28, 126.53, 125.65, 122.61, 15.62, 14.50.

Gärtner, D.; Stein, A. L.; Grupe, S.; Arp, J.; Jacobi von Wangelin, A. Iron-Catalyzed Cross-Coupling of Alkenyl Acetates. *Angew. Chem., Int. Ed.* **2015**, *54* , 10545–10549.

N-(4-Benzamido-3-(3-(4-((*t*-butyldimethylsilyl)oxy)-3-methoxyphenyl)propyl)phenyl)-*N*-butylbenzamide (**45**)



Coupling was conducted at 0.5 mmol scale using the procedure in section 2.1.2 to give (**45**) as a yellow semi-solid 237 mg (73%).

R_f : 0.30 (EtOAc/hexanes 30:70)

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.82 (d, *J* = 7.4 Hz, 2H), 7.54 (d, *J* = 2.1 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.43 (s, 1H), 7.42 – 7.37 (m, 3H), 7.22 (d, *J* = 7.2 Hz, 2H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 2H), 7.02 (d, *J* = 8.5 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.65 (d, *J* = 1.7 Hz, 1H), 6.60 (dd, *J* = 8.0, 1.9 Hz,

1H), 4.10 – 3.98 (m, 1H), 3.78 (s, 3H), 3.41 (ddd, *J* = 13.2, 10.3, 5.5 Hz, 1H), 2.62 – 2.48 (m, 3H), 2.36 (dd, *J* = 9.6, 4.9 Hz, 1H), 1.81 (dd, *J* = 12.3, 6.6 Hz, 1H), 1.71 – 1.52 (m, 3H), 1.33 (dt, *J* = 8.6, 7.1 Hz, 2H), 0.99 (s, 11H), 0.92 (t, *J* = 7.3 Hz, 3H), 0.15 (s, 7H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.47, 165.93, 150.80, 143.22, 140.17, 137.72, 137.55, 136.30, 135.28, 134.78, 131.94, 130.08, 129.50, 128.74, 128.35, 127.61, 127.17, 120.77, 120.50, 118.35, 112.59, 55.59, 50.42, 35.87, 31.62, 30.21, 29.50, 25.84, 20.43, 18.51, 13.99, -4.53.

HRMS: (ESI, [$C_{40}H_{50}N_2O_4Si$+Na]) calcd, 673.3438; found *m/z*: 673.3433.

2.13.3 NMR Spectra

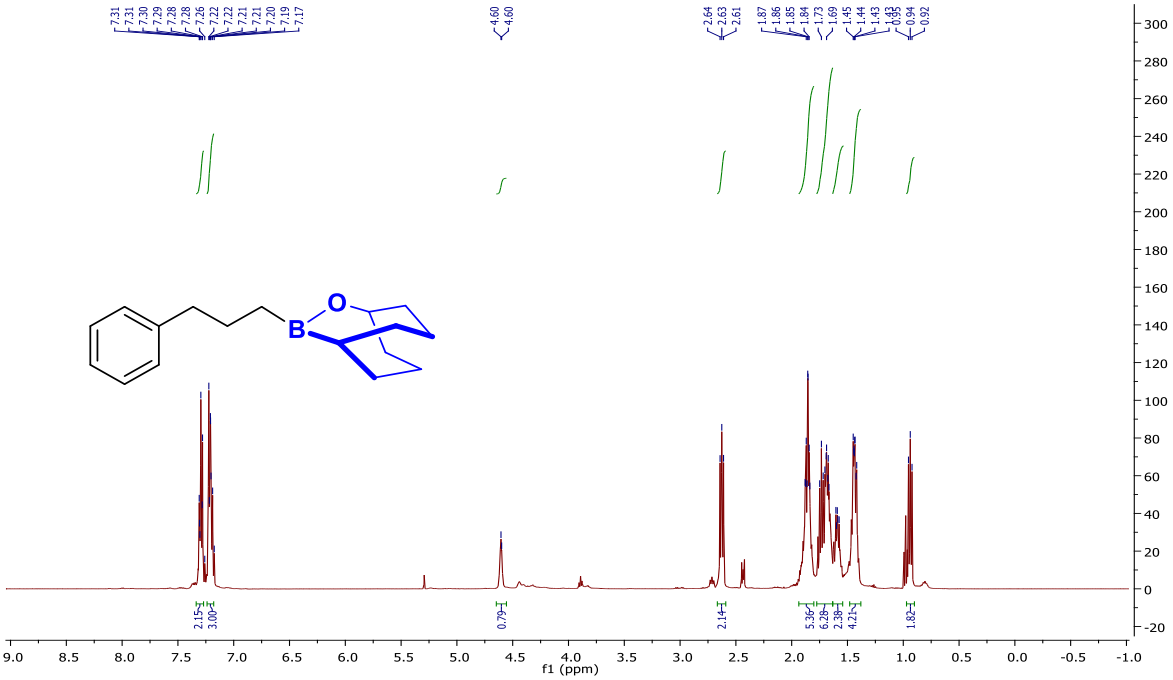


Figure 6: ^{1}H NMR (1s,5s)-10-(3-phenylpropyl)-9-oxa-10-borabicyclo[3.3.2]decane (**1**)

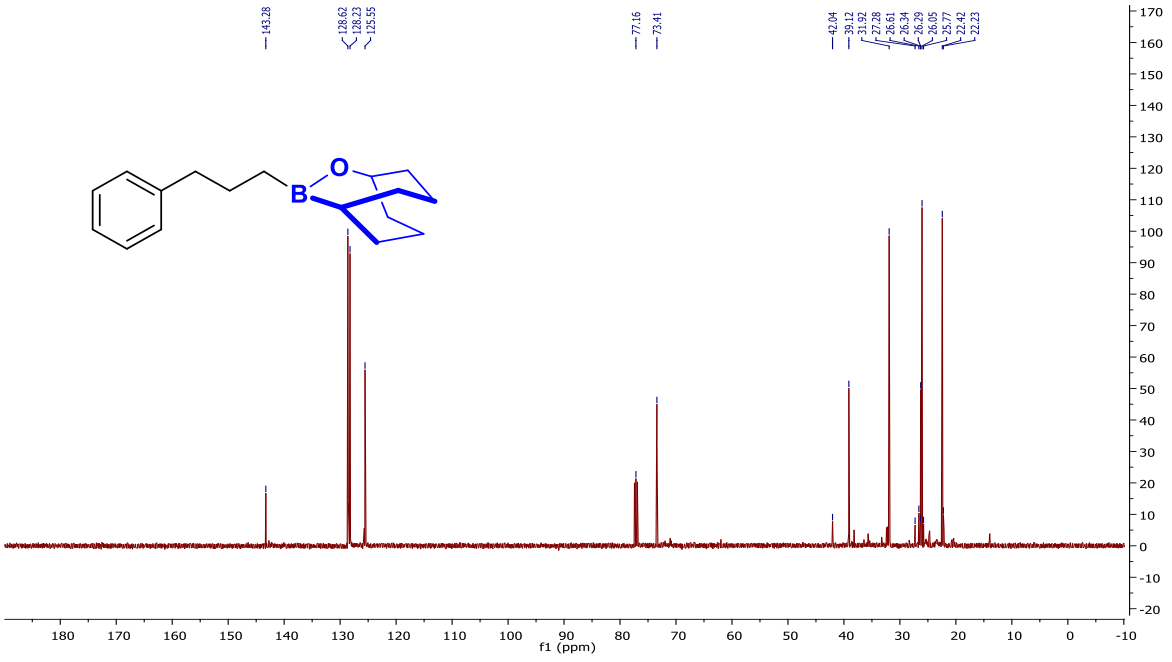


Figure 7: ^{13}C NMR (1s,5s)-10-(3-phenylpropyl)-9-oxa-10-borabicyclo[3.3.2]decane (**1**)

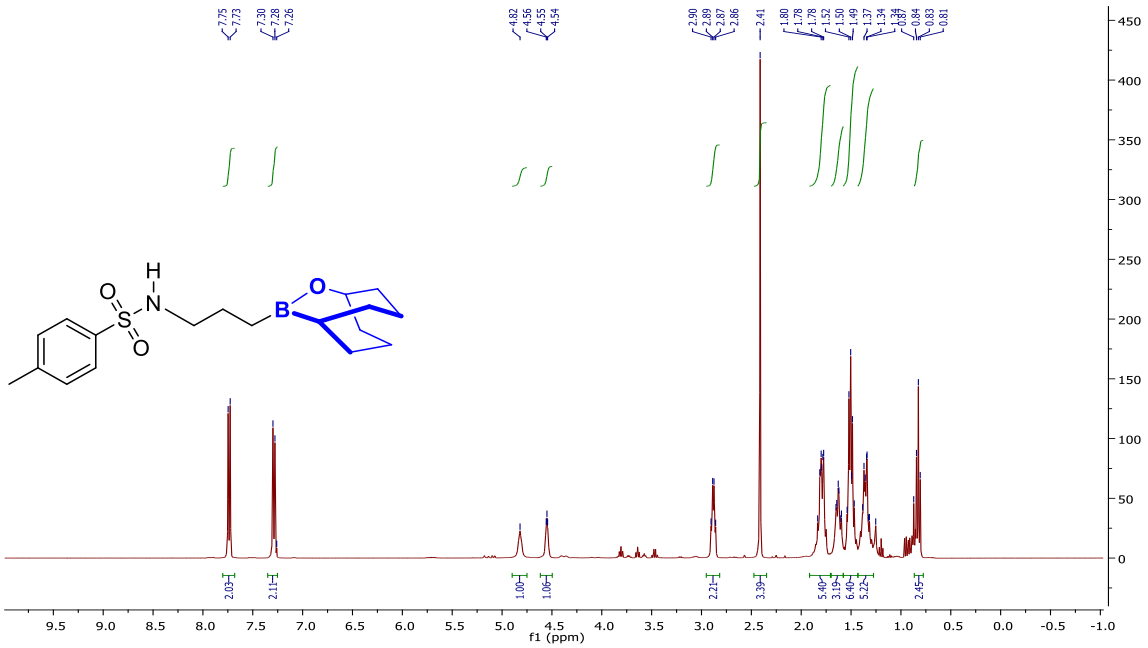


Figure 8: ^{1}H NMR N-(3-((1s,5s)-9-oxa-10-borabicyclo[3.3.2]decan-10-yl)propyl)-4-methylbenzenesulfonamide (**2**)

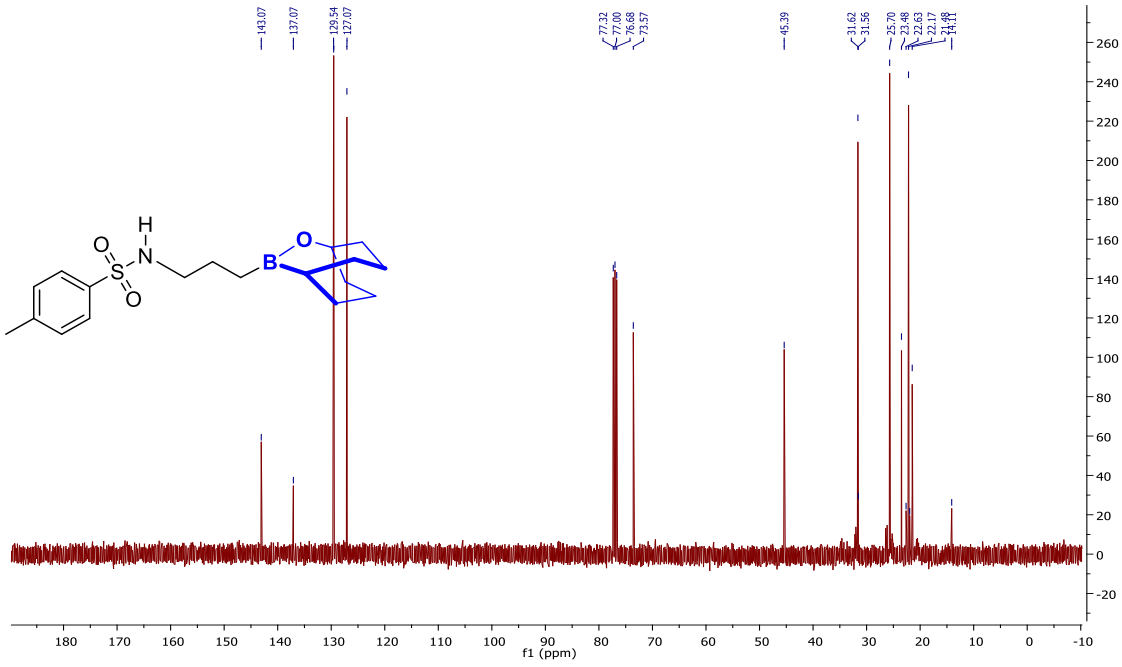


Figure 9: ^{13}C NMR N-(3-((1s,5s)-9-oxa-10-borabicyclo[3.3.2]decan-10-yl)propyl)-4-methylbenzenesulfonamide (**2**)

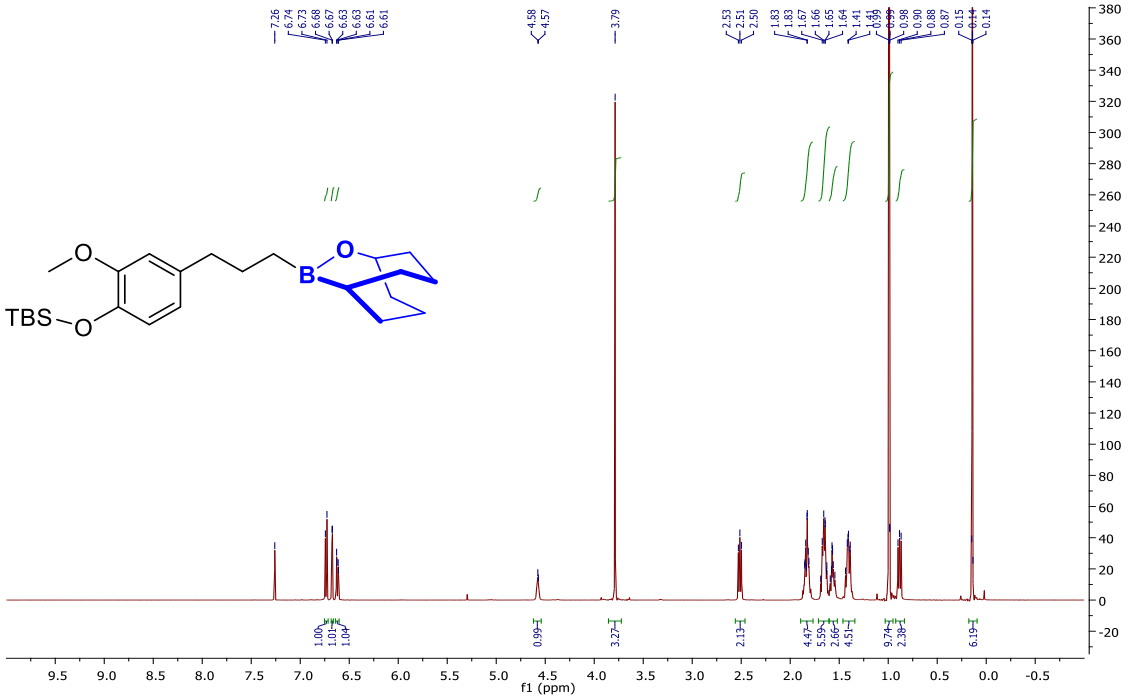


Figure 10: ^{1}H NMR (4-(3-((1s,5s)-9-oxa-10-borabicyclo[3.3.2]decan-10-yl)propyl)-2-methoxyphenoxy)(tert-butyl)dimethylsilane (**3**)

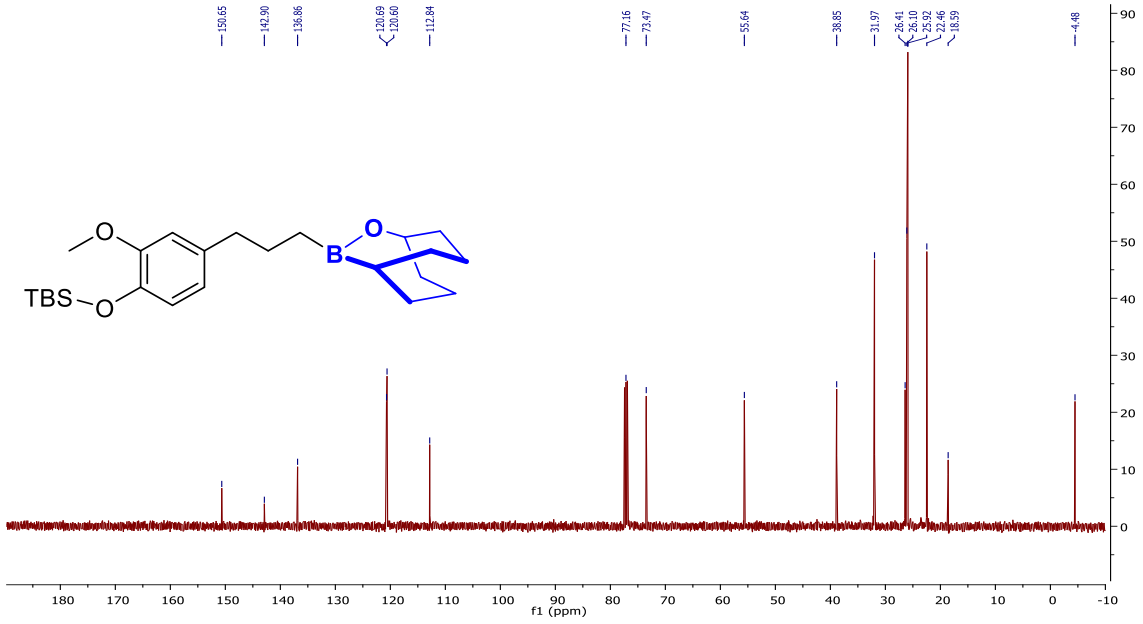


Figure 11: ^{13}C NMR (4-(3-((1s,5s)-9-oxa-10-borabicyclo[3.3.2]decan-10-yl)propyl)-2-methoxyphenoxy)(tert-butyl)dimethylsilane (**3**)

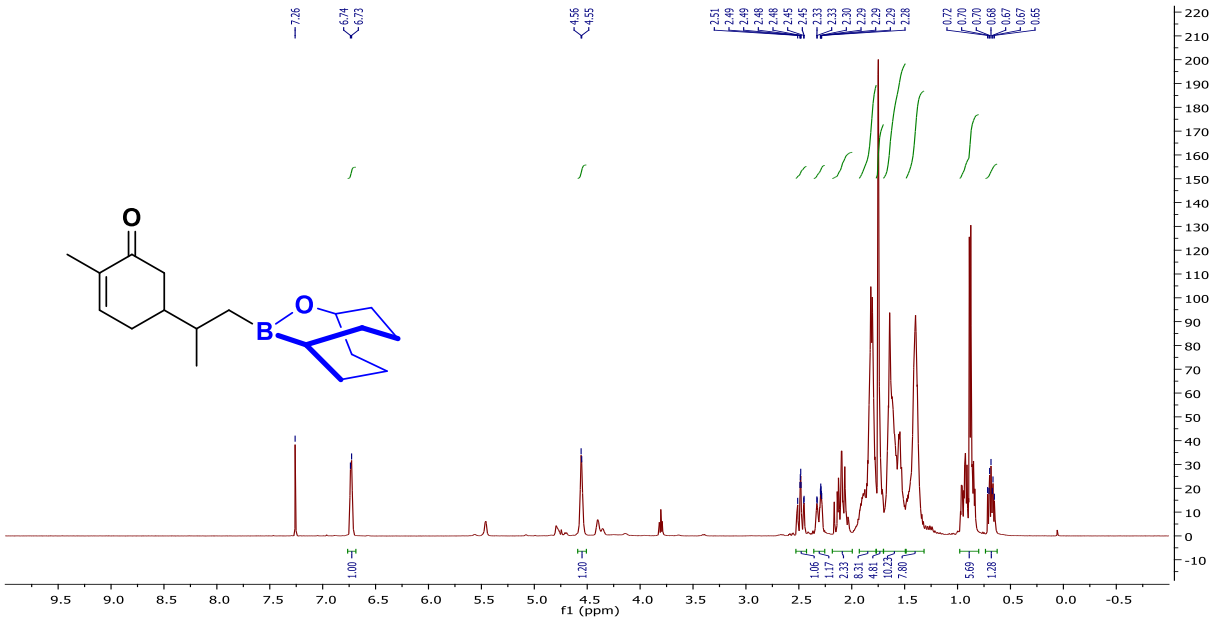


Figure 12: ^{1}H NMR 5-(1-((1s,5s)-9-oxa-10-borabicyclo[3.3.2]decan-10-yl)propan-2-yl)-2-methylcyclohex-2-en-1-one (**4**)

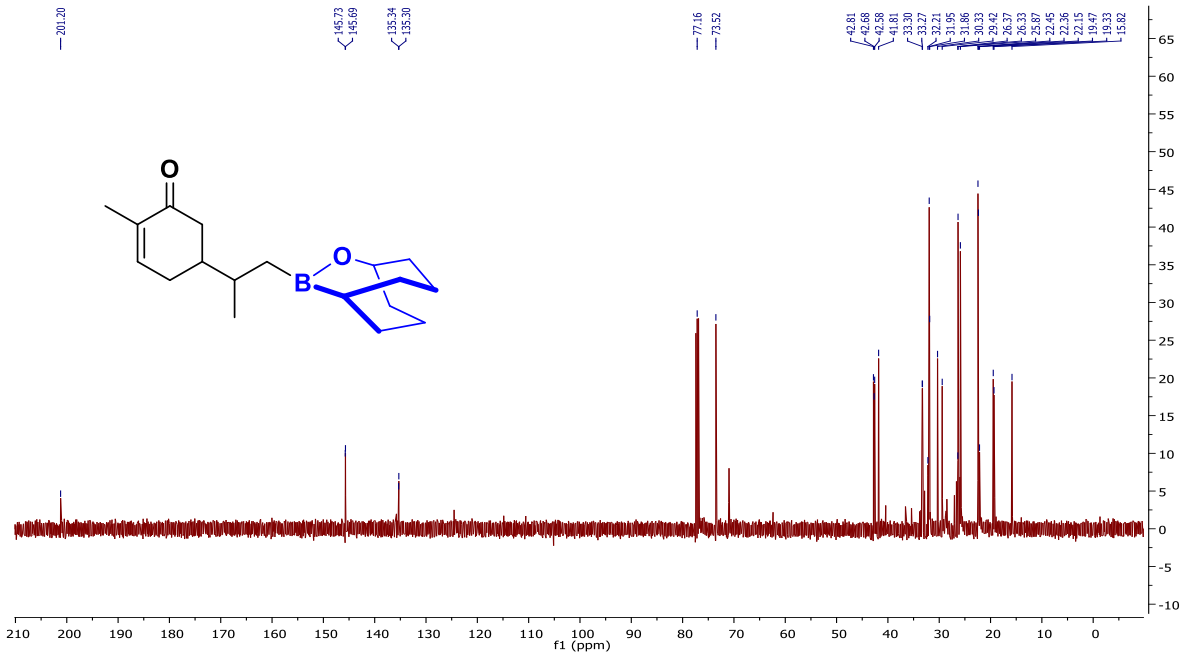


Figure 13: ^{13}C NMR 5-(1-((1s,5s)-9-oxa-10-borabicyclo[3.3.2]decan-10-yl)propan-2-yl)-2-methylcyclohex-2-en-1-one (**4**)

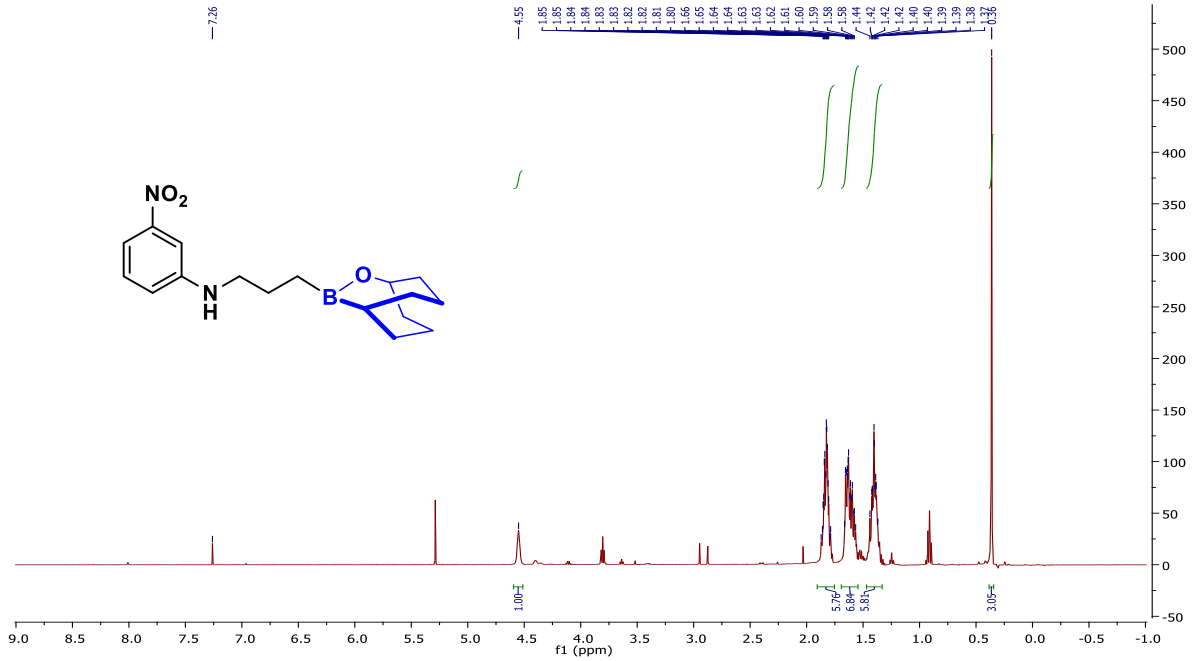


Figure 14: ^{1}H NMR N-(3-((1s,5s)-9-oxa-10-borabicyclo[3.3.2]decan-10-yl)propyl)-3-nitroaniline (**5**)

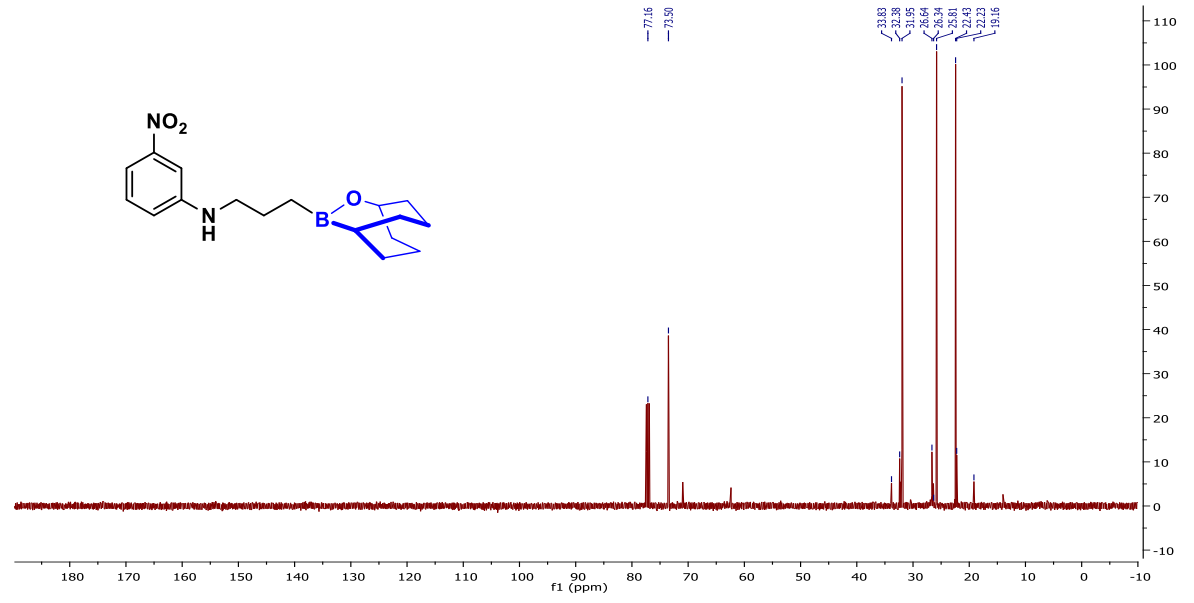


Figure 15: ^{13}C NMR N-(3-((1s,5s)-9-oxa-10-borabicyclo[3.3.2]decan-10-yl)propyl)-3-nitroaniline (**5**)

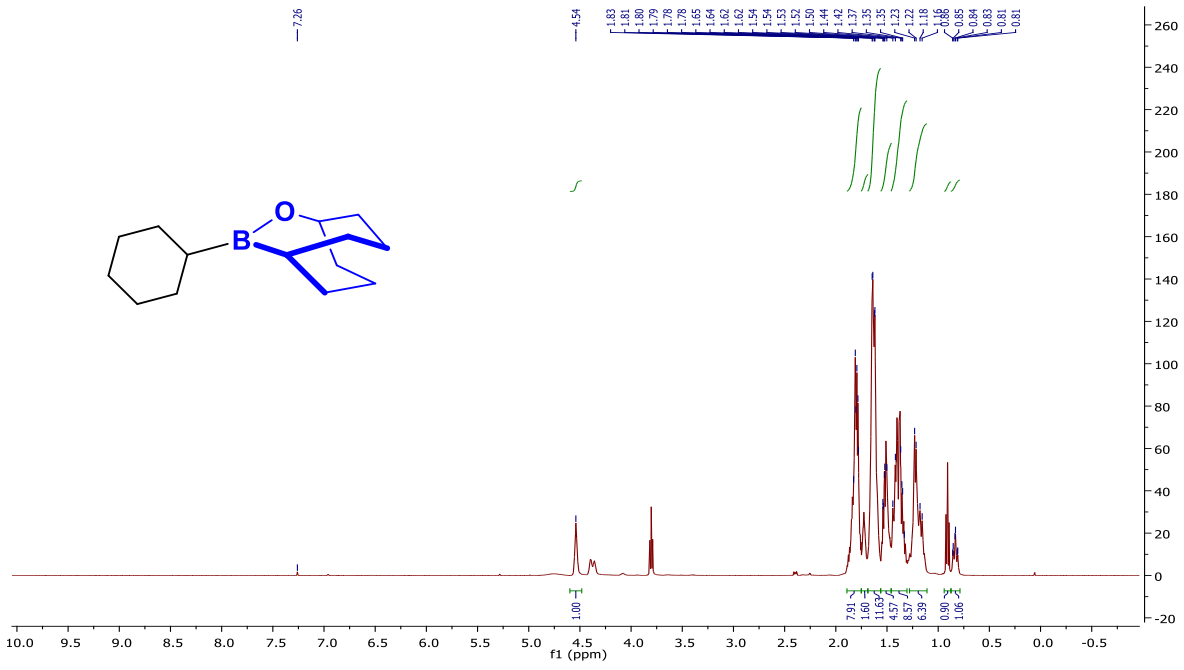


Figure 16: ^{1}H NMR (1s,5s)-10-cyclohexyl-9-oxa-10-borabicyclo[3.3.2]decane (**6**)

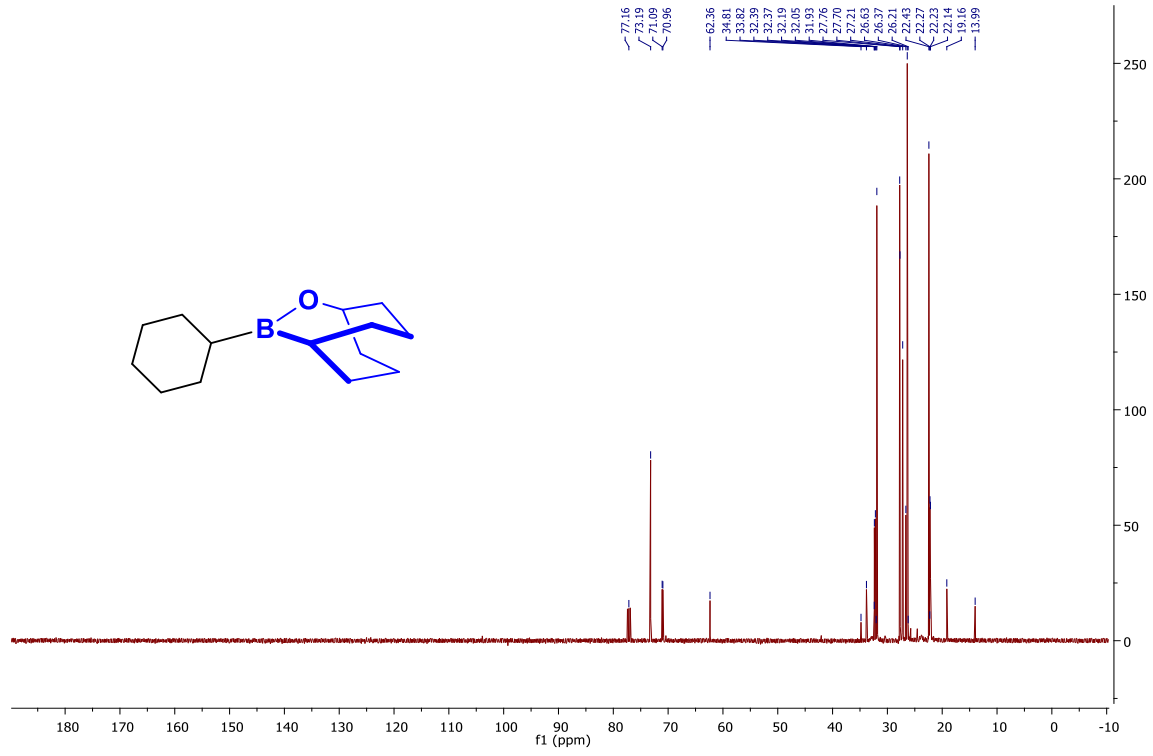


Figure 17: ^{13}C NMR (1s,5s)-10-cyclohexyl-9-oxa-10-borabicyclo[3.3.2]decane (**6**)

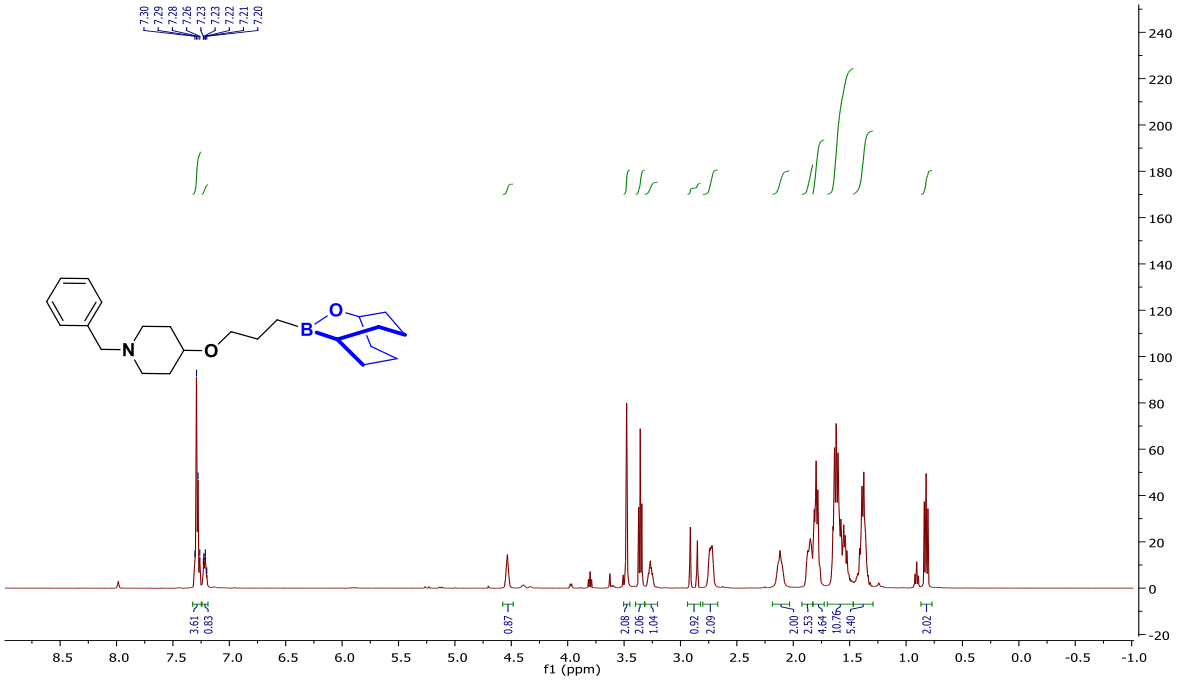


Figure 18: [1] H NMR 4-(3-((1s,5s)-9-oxa-10-borabicyclo[3.3.2]decan-10-yl)propoxy)-1-benzylpiperidine (**7**)

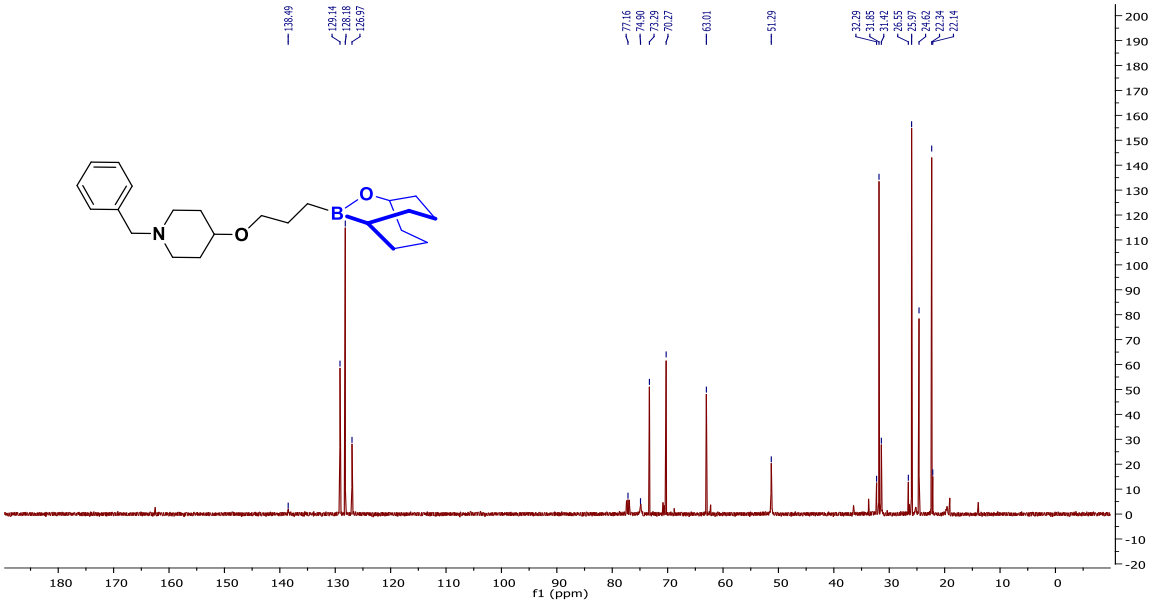


Figure 19: [1] H NMR 4-(3-((1s,5s)-9-oxa-10-borabicyclo[3.3.2]decan-10-yl)propoxy)-1-benzylpiperidine (**7**)

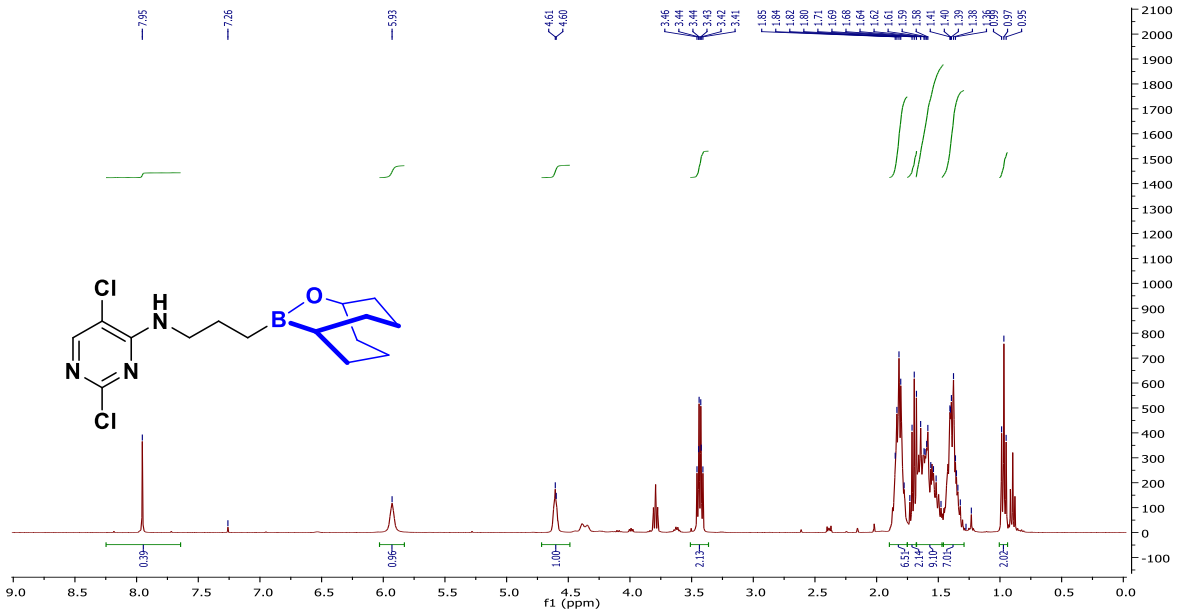


Figure 20: ^{1}H NMR N-(3-((1s,5s)-9-oxa-10-borabicyclo[3.3.2]decan-10-yl)propyl)-2,5-dichloropyrimidin-4-amine (**8**)

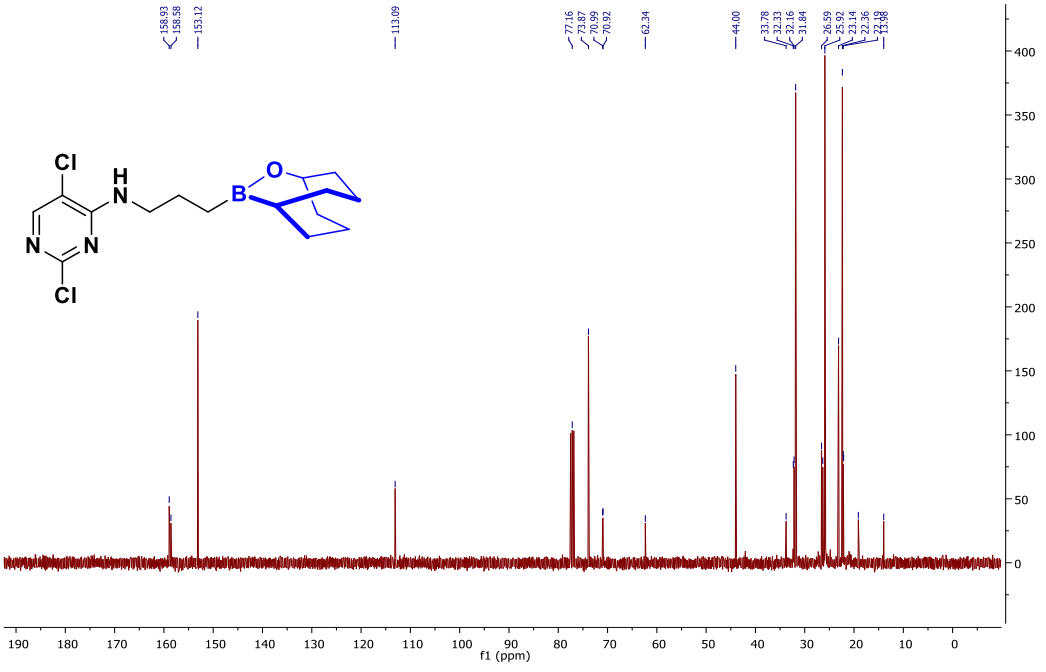


Figure 21: ^{1}H NMR N-(3-((1s,5s)-9-oxa-10-borabicyclo[3.3.2]decan-10-yl)propyl)-2,5-dichloropyrimidin-4-amine (**8**)

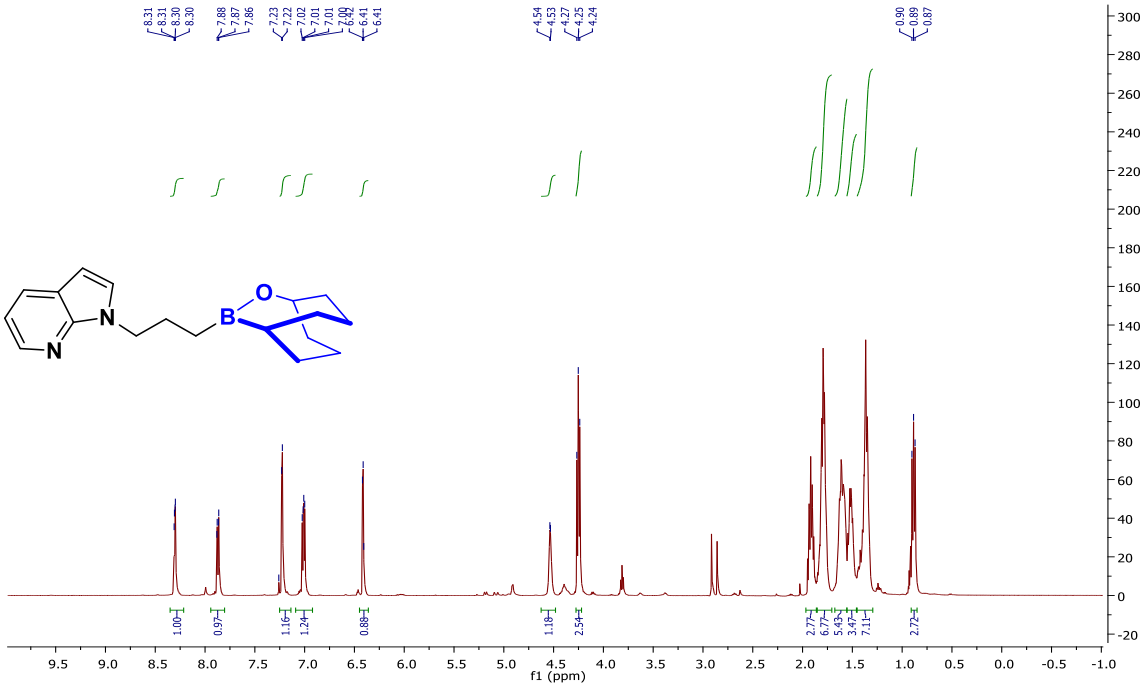


Figure 22: ^{1}H NMR 1-(3-((1s,5s)-9-oxa-10-borabicyclo[3.3.2]decan-10-yl)propyl)-1H-pyrrolo[2,3-b]pyridine (**9**)

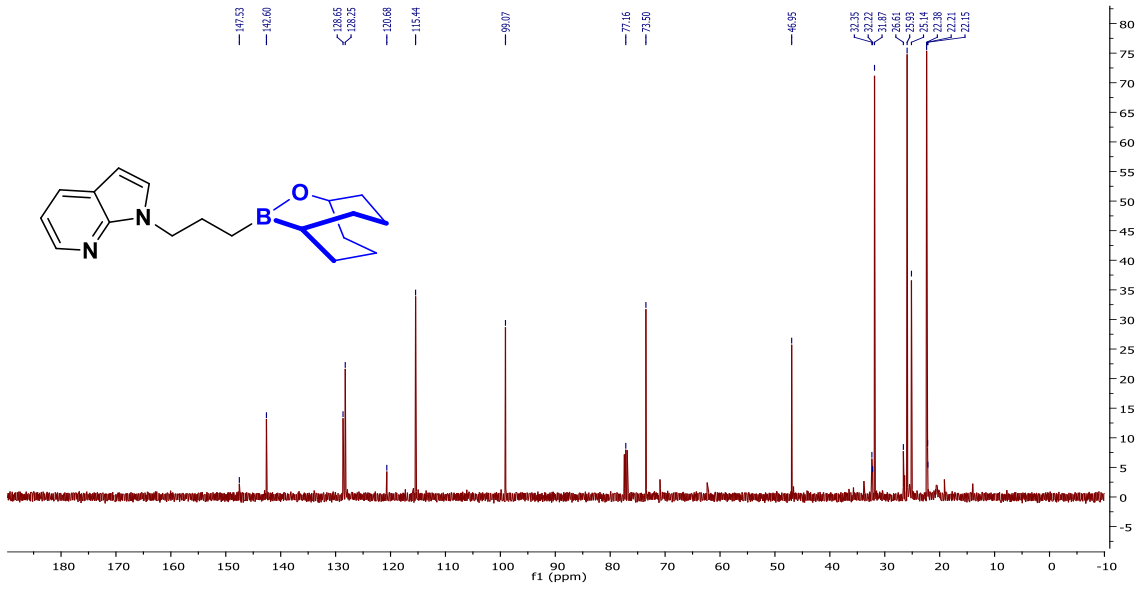


Figure 23: ^{1}H NMR 1-(3-((1s,5s)-9-oxa-10-borabicyclo[3.3.2]decan-10-yl)propyl)-1H-pyrrolo[2,3-b]pyridine (**9**)

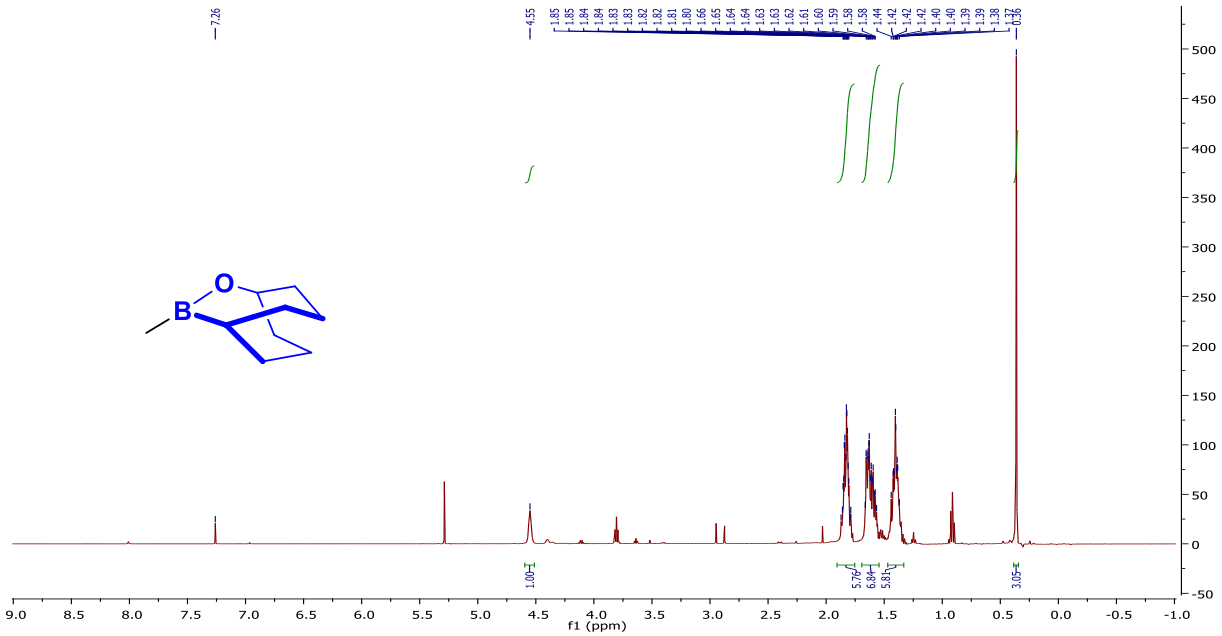


Figure 24: ^{1}H NMR (1s,5s)-10-methyl-9-oxa-10-borabicyclo[3.3.2]decane (**10**)

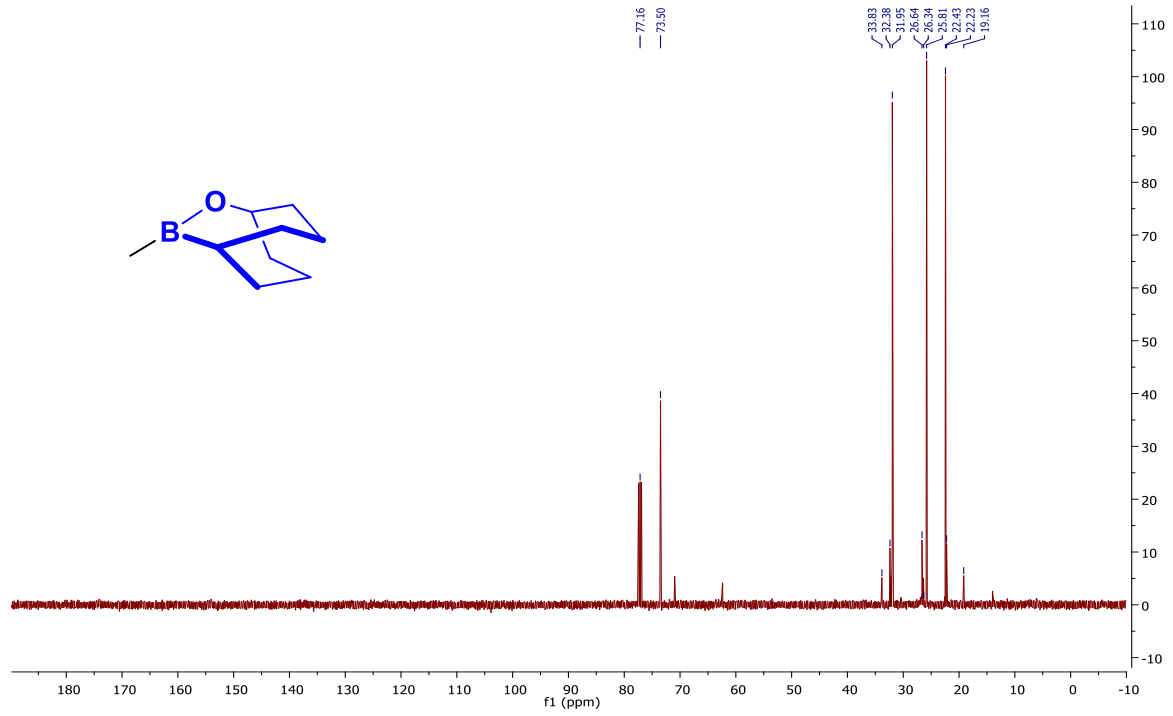


Figure 25: ^{13}C NMR (1s,5s)-10-methyl-9-oxa-10-borabicyclo[3.3.2]decane (**10**)

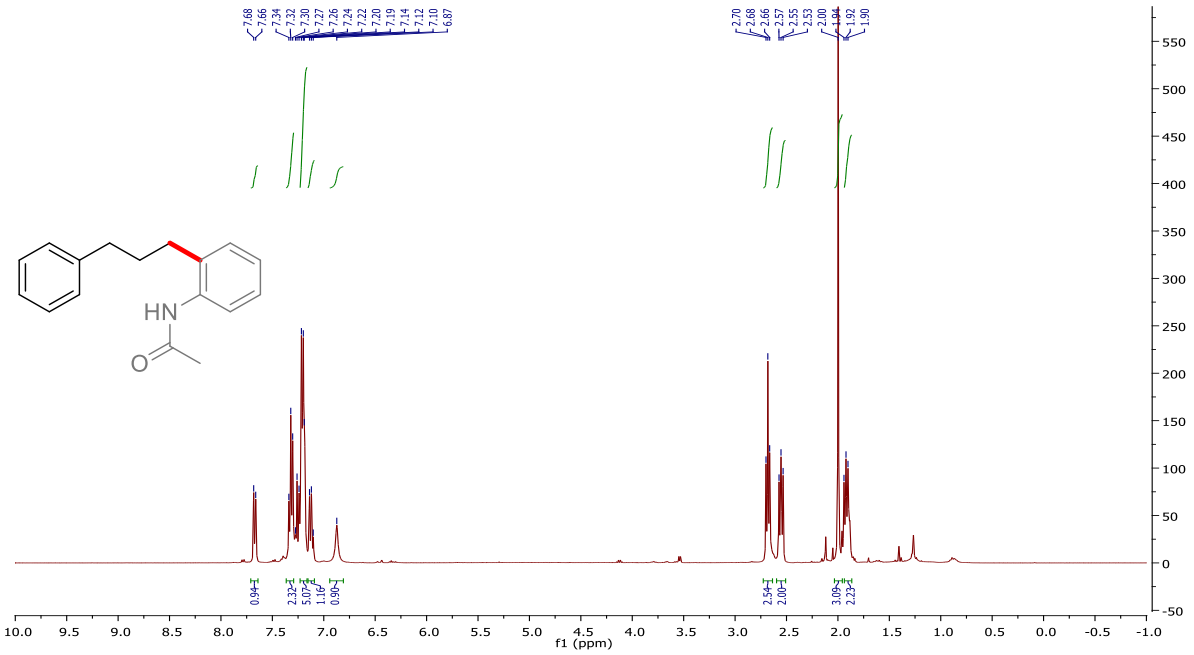


Figure 26: ^{1}H NMR N-(2-(3-phenylpropyl)phenyl)acetamide (**11**)

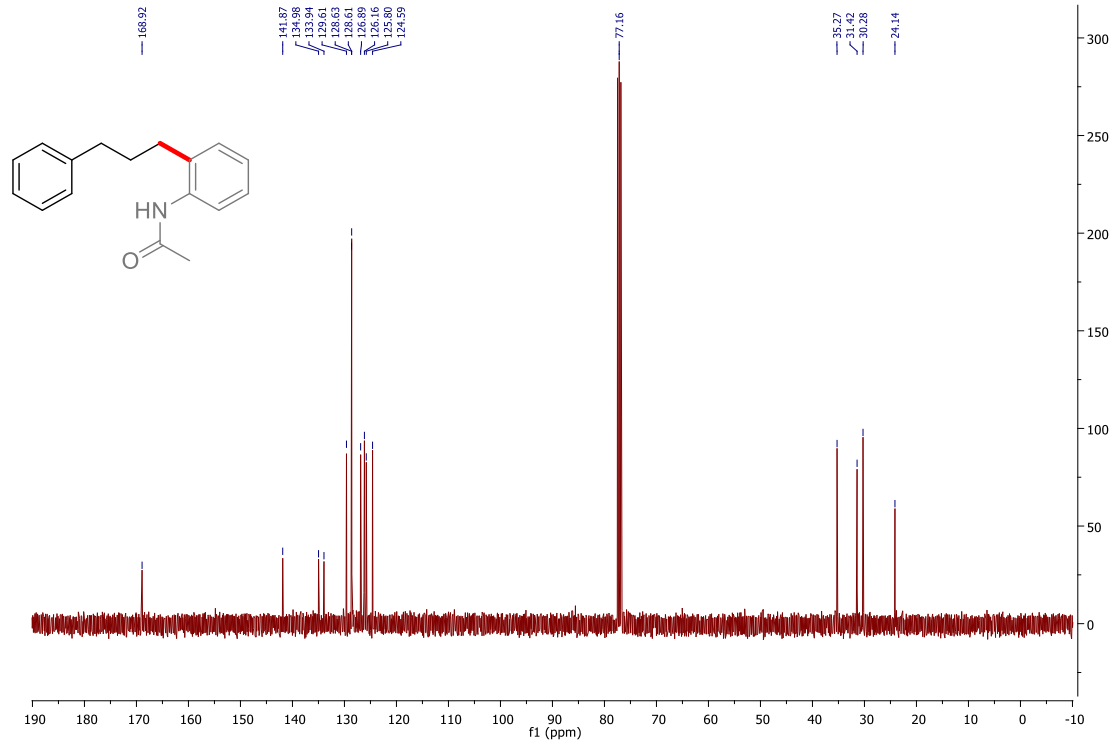


Figure 27: ^{13}C NMR N-(2-(3-phenylpropyl)phenyl)acetamide (**11**)

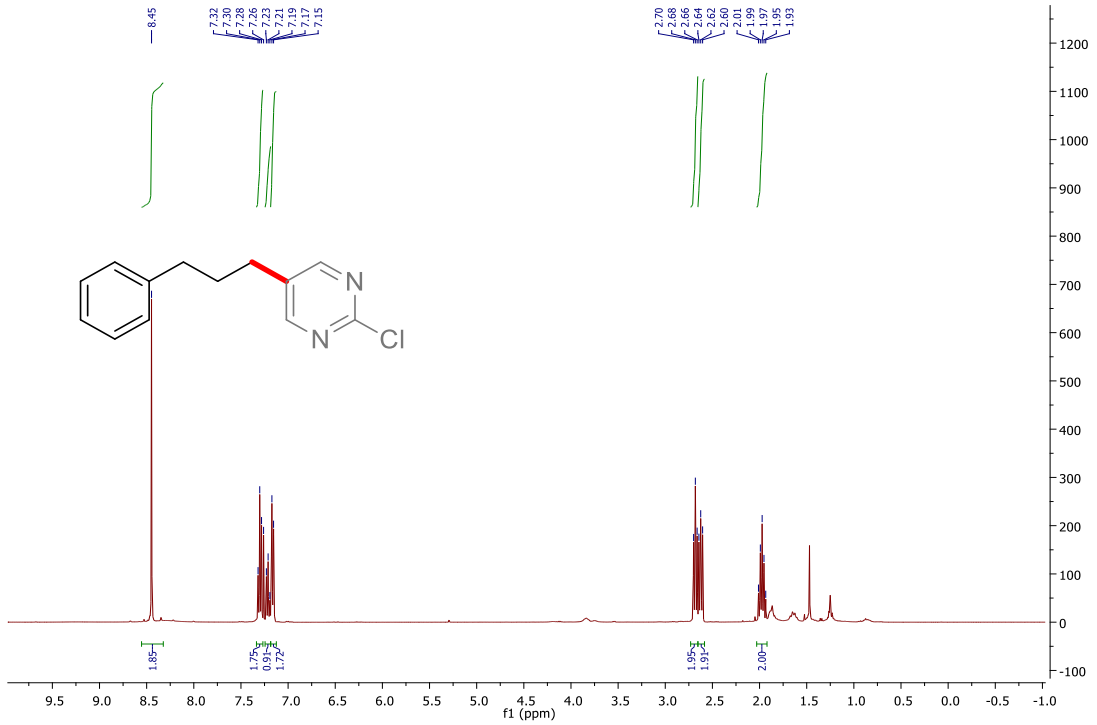


Figure 28: ^{1}H NMR 2-chloro-5-(3-phenylpropyl)pyrimidine (**12**)

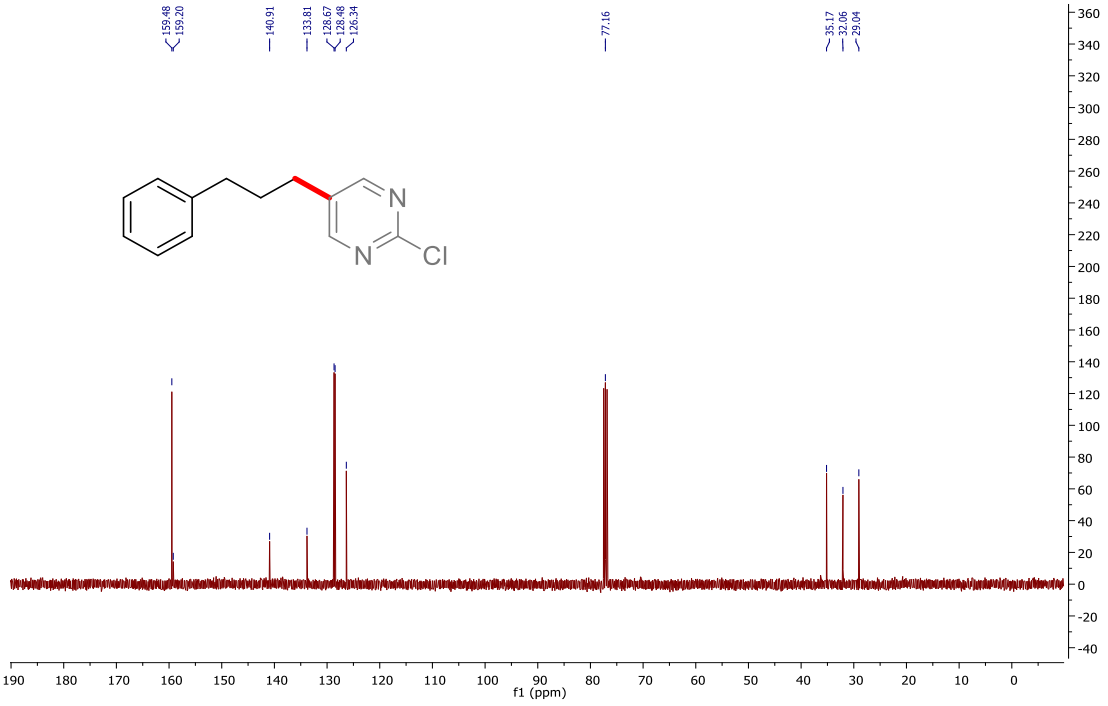


Figure 29: ^{1}H NMR 2-chloro-5-(3-phenylpropyl)pyrimidine (**12**)

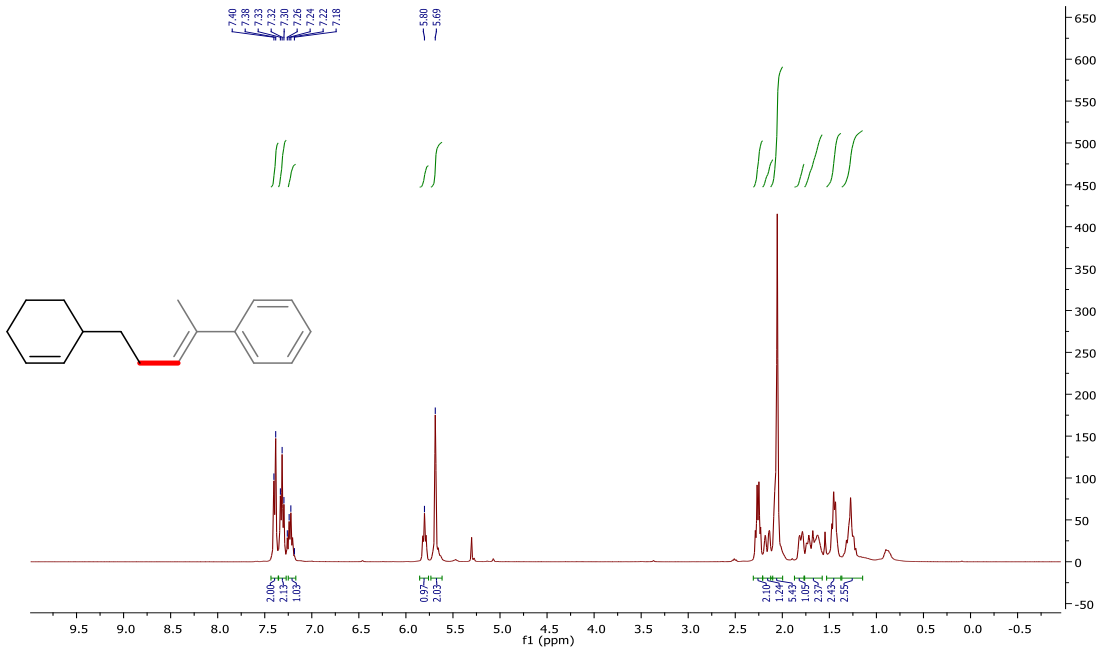


Figure 30: ^{1}H NMR (E)-(5-(cyclohex-2-en-1-yl)pent-2-en-2-yl)benzene (**13**)

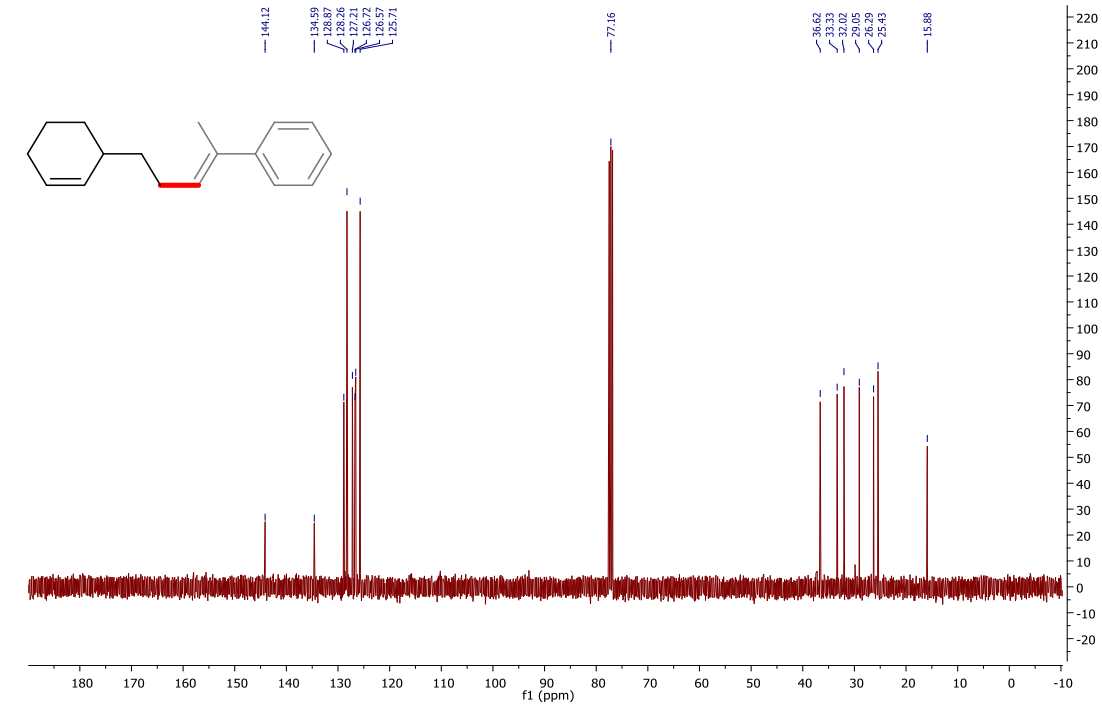


Figure 31: ^{13}C NMR (E)-(5-(cyclohex-2-en-1-yl)pent-2-en-2-yl)benzene (**13**)

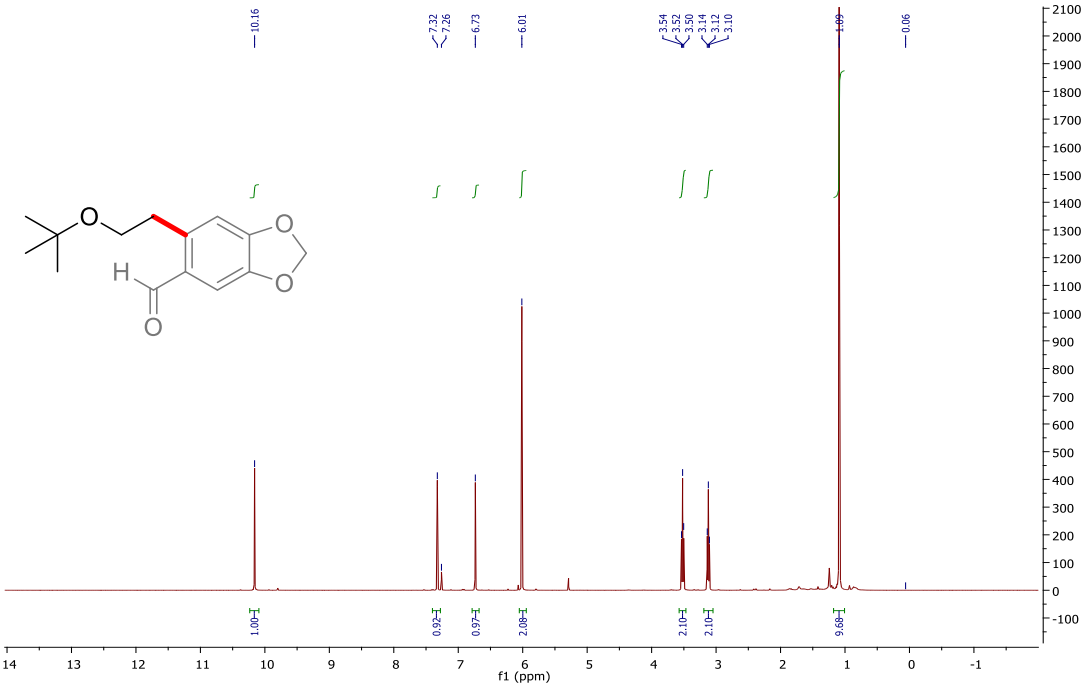


Figure 32: ^{1}H NMR 6-(2-(tert-butoxy)ethyl)benzo[d][1,3]dioxole-5-carbaldehyde (**14**)

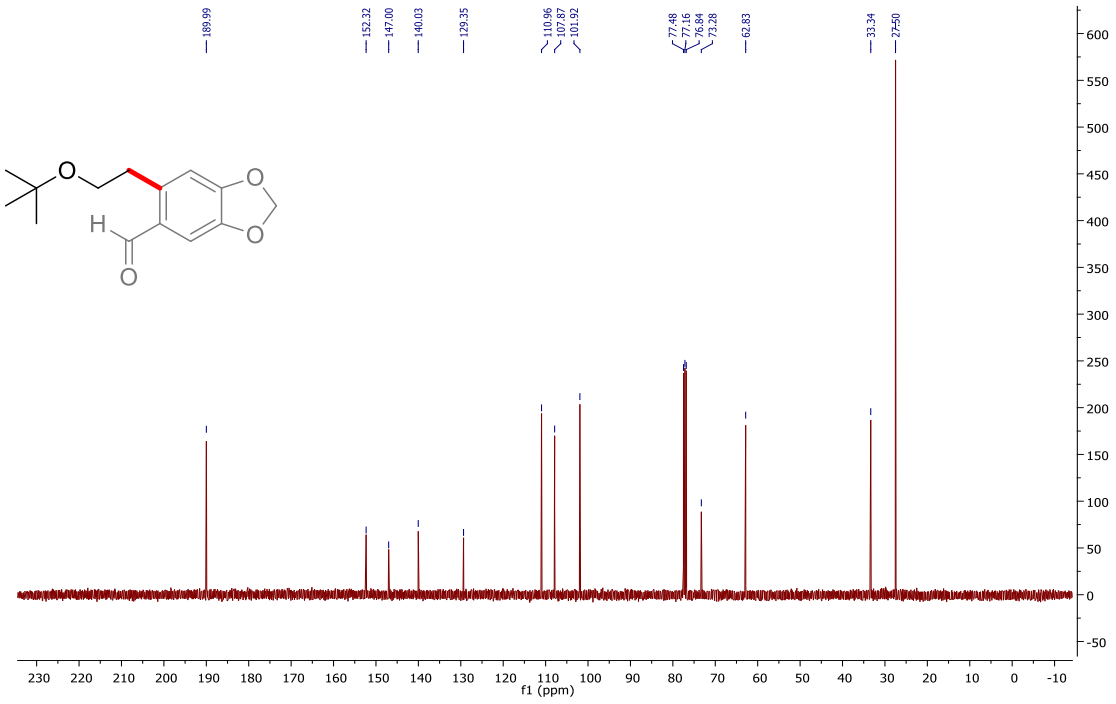


Figure 33: ^{13}C NMR 6-(2-(tert-butoxy)ethyl)benzo[d][1,3]dioxole-5-carbaldehyde (**14**)

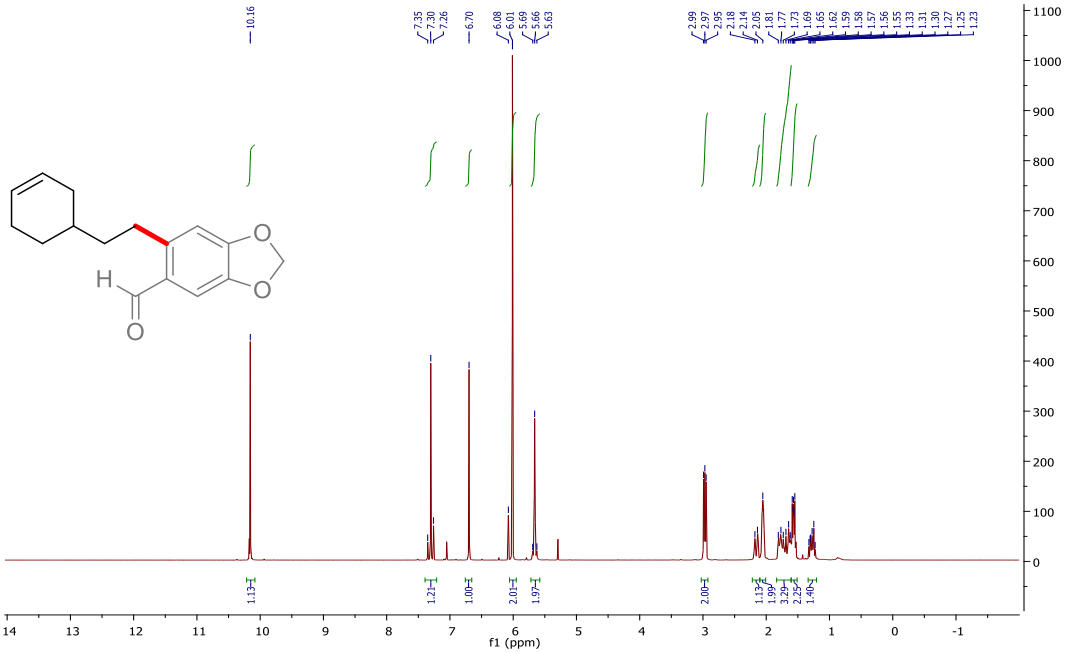


Figure 34: ^{1}H NMR 6-(2-(cyclohex-3-en-1-yl)ethyl)benzo[d][1,3]dioxole-5-carbaldehyde (**15**)

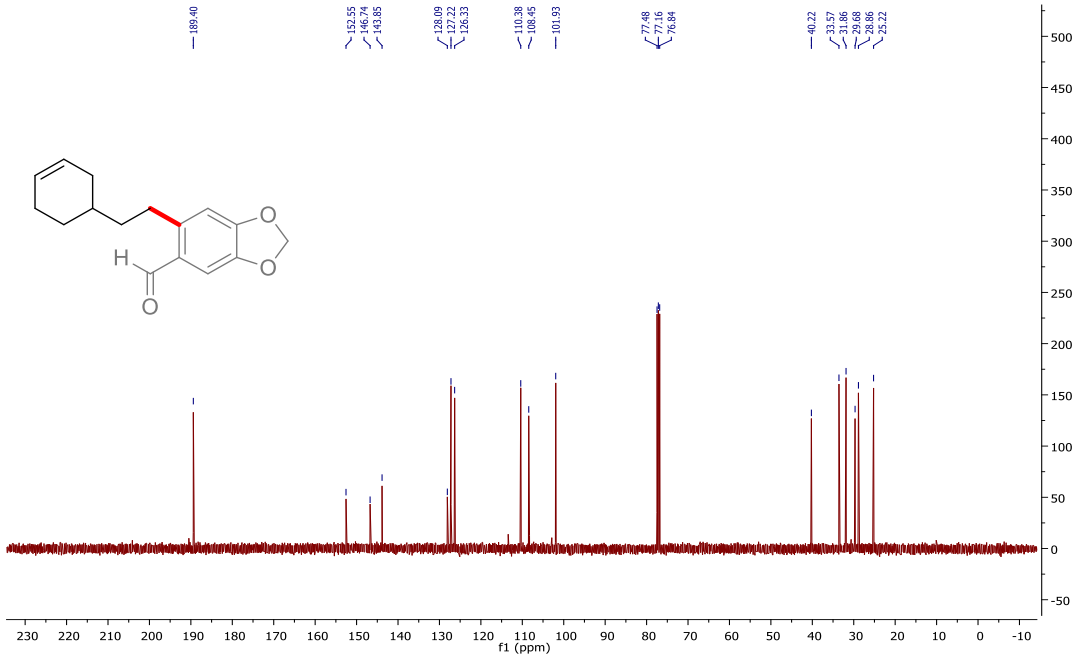


Figure 35: ^{13}C NMR 6-(2-(cyclohex-3-en-1-yl)ethyl)benzo[d][1,3]dioxole-5-carbaldehyde (**15**)

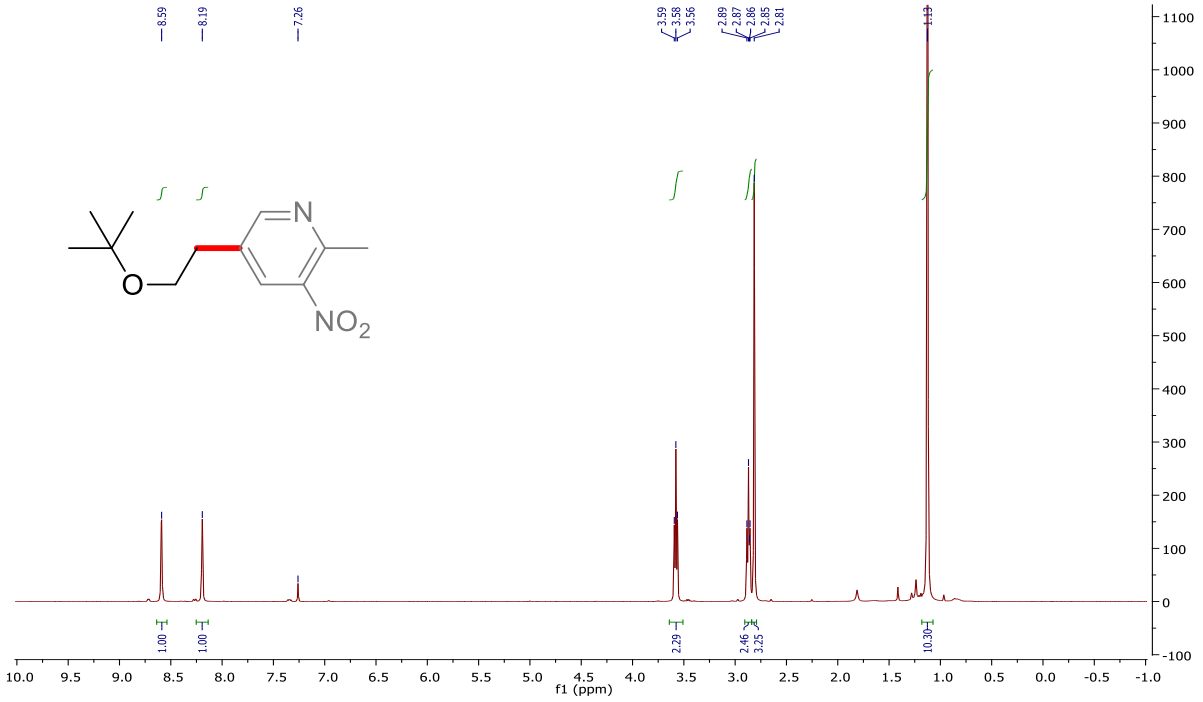


Figure 36: ^{1}H NMR 5-(2-(tert-butoxy)ethyl)-2-methyl-3-nitropyridine (**16**)

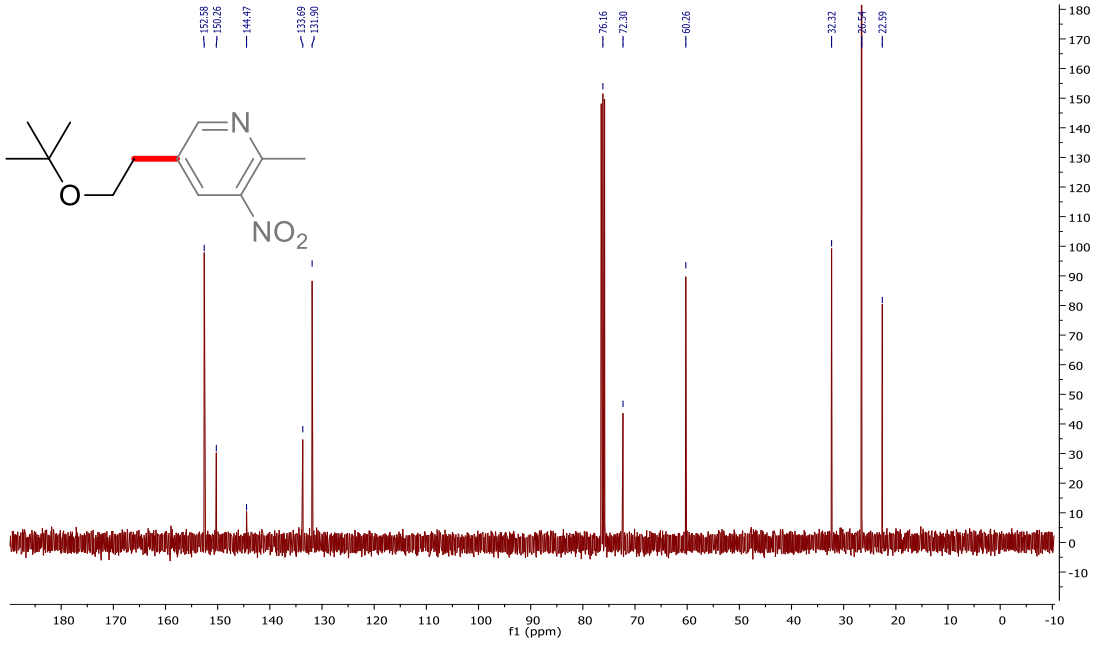


Figure 37: ^{1}H NMR 5-(2-(tert-butoxy)ethyl)-2-methyl-3-nitropyridine (**16**)

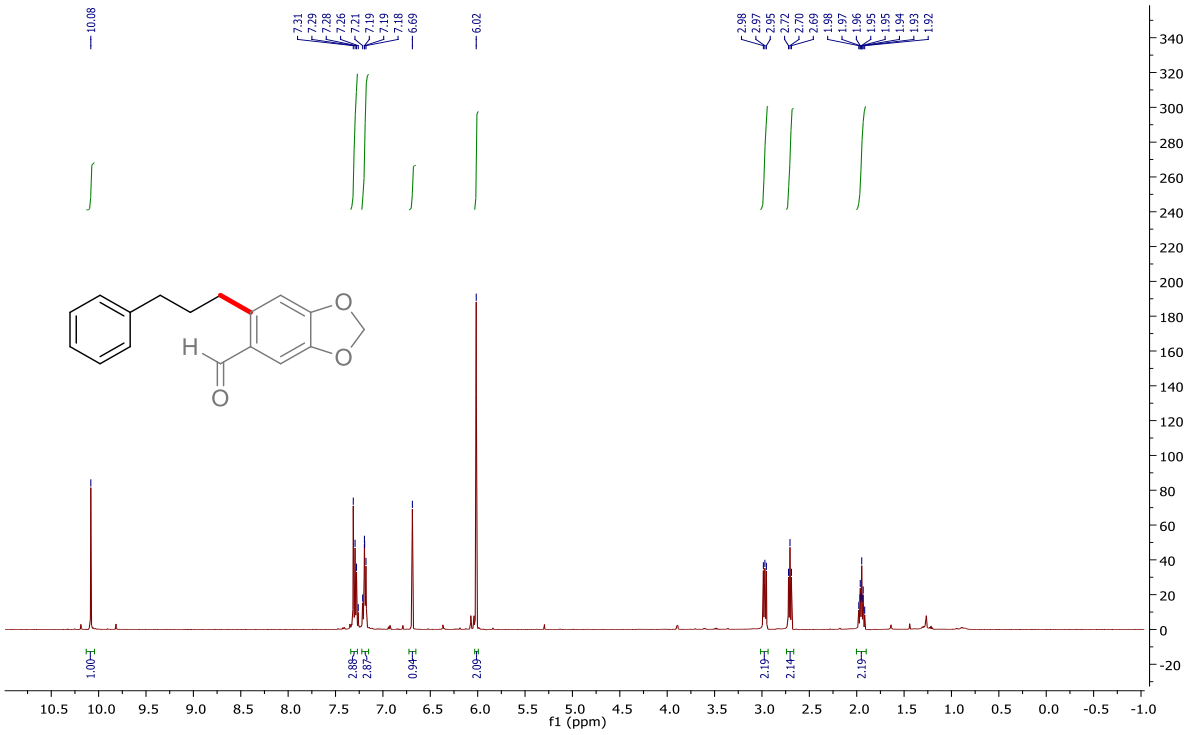


Figure 38: ^{1}H NMR 6-(3-phenylpropyl)benzo[d][1,3]dioxole-5-carbaldehyde (**17**)

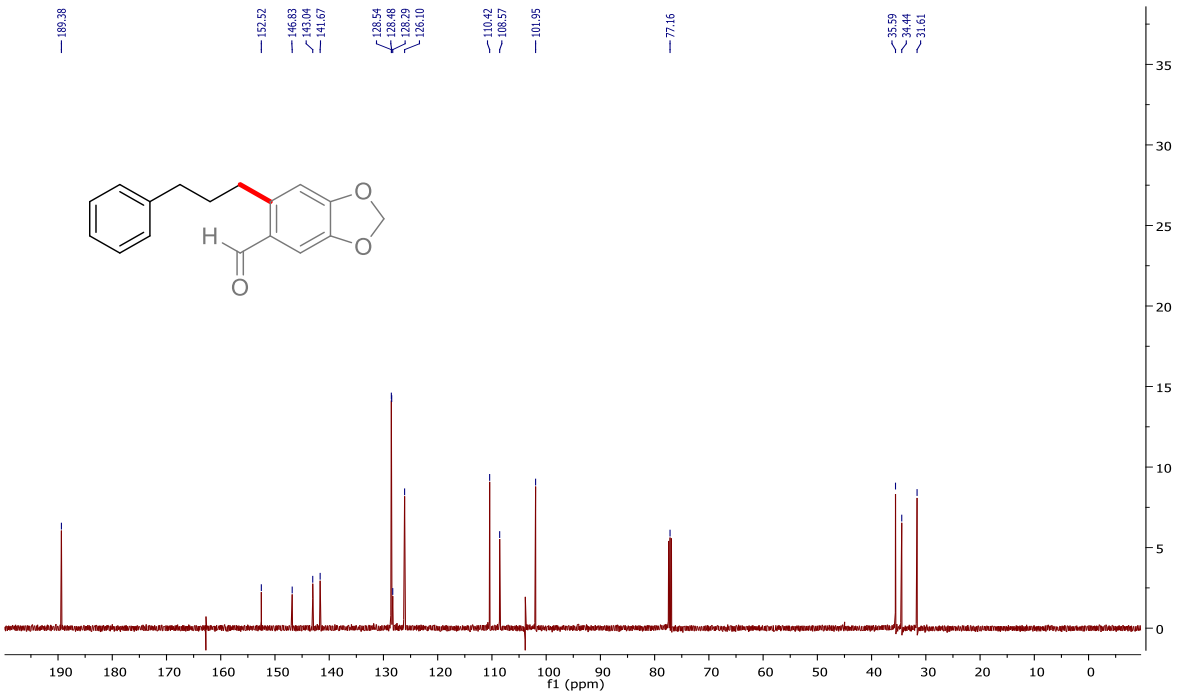


Figure 39: ^{13}C NMR 6-(3-phenylpropyl)benzo[d][1,3]dioxole-5-carbaldehyde (**17**)

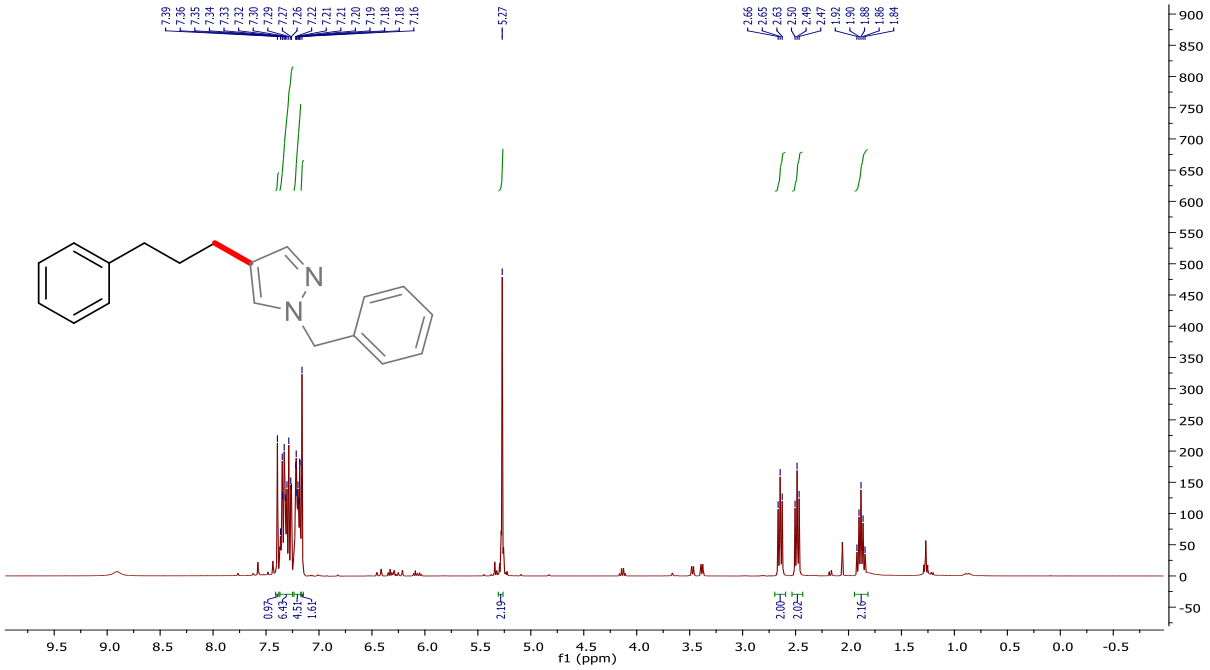


Figure 40: ^{1}H NMR 1-benzyl-4-(3-phenylpropyl)-1H-pyrazole (**18**)

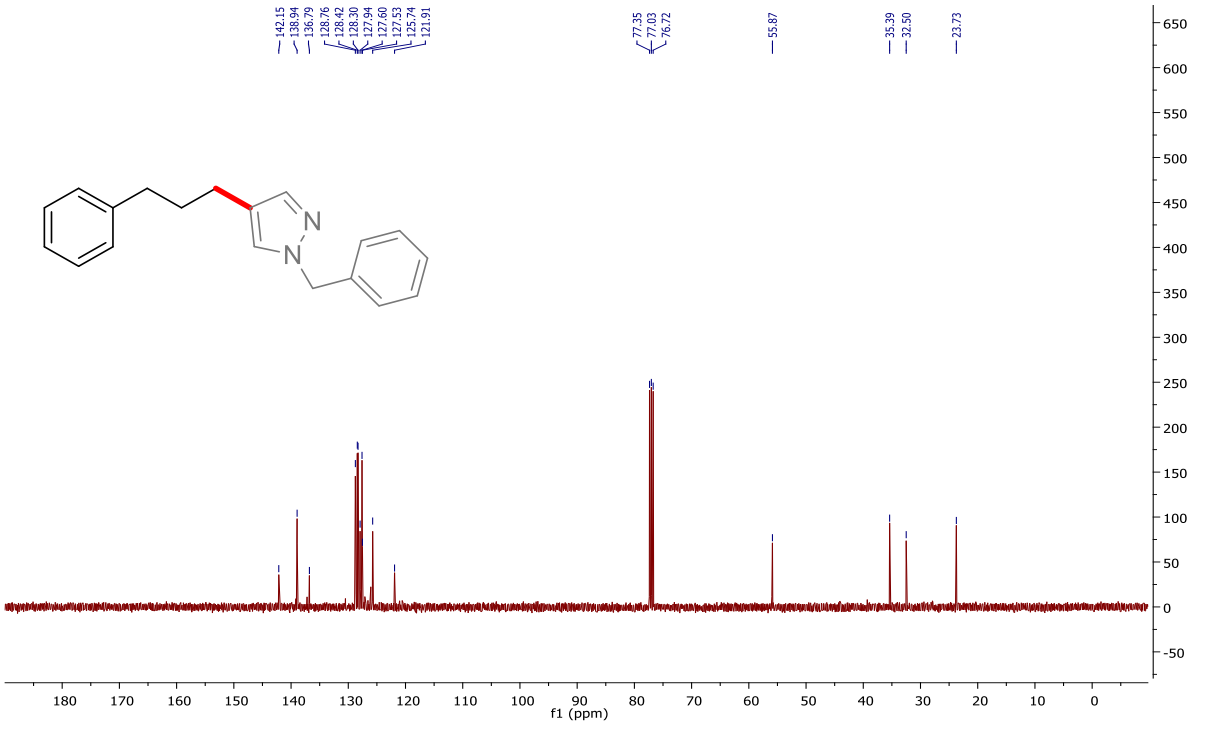


Figure 41: ^{13}C NMR 1-benzyl-4-(3-phenylpropyl)-1H-pyrazole (**18**)

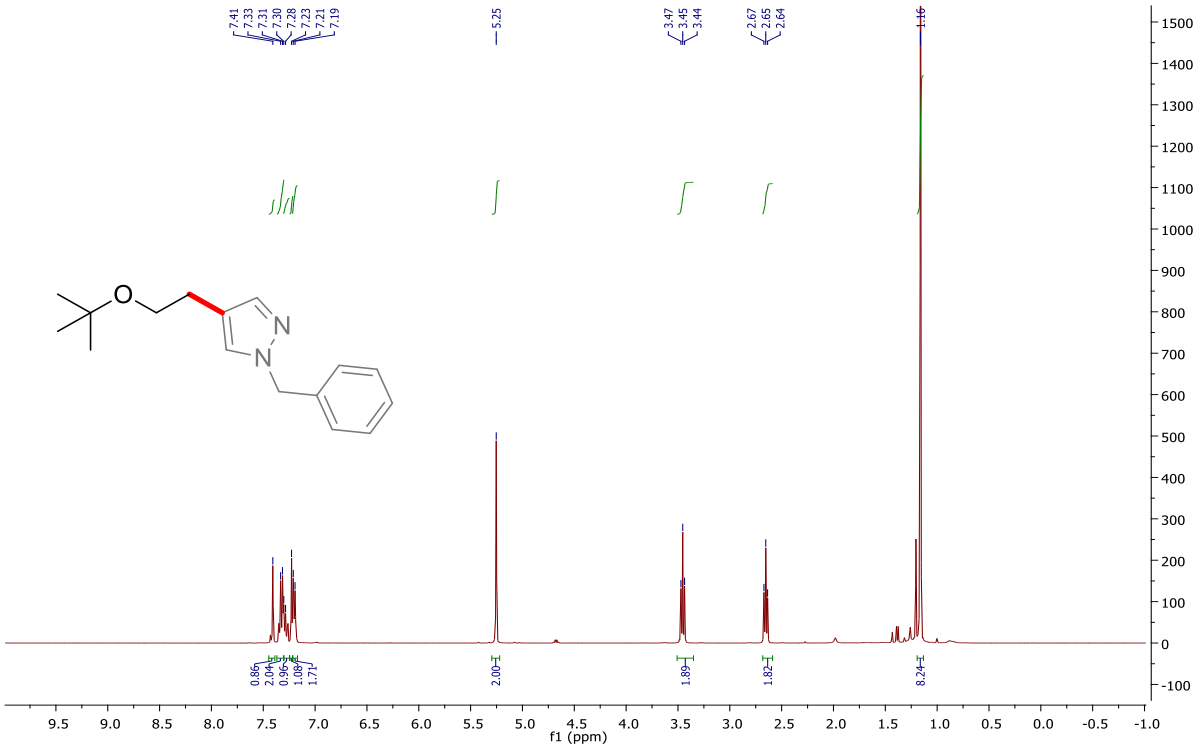


Figure 42: ^{1}H NMR 1-benzyl-4-(2-(tert-butoxy)ethyl)-1H-pyrazole (**19**)

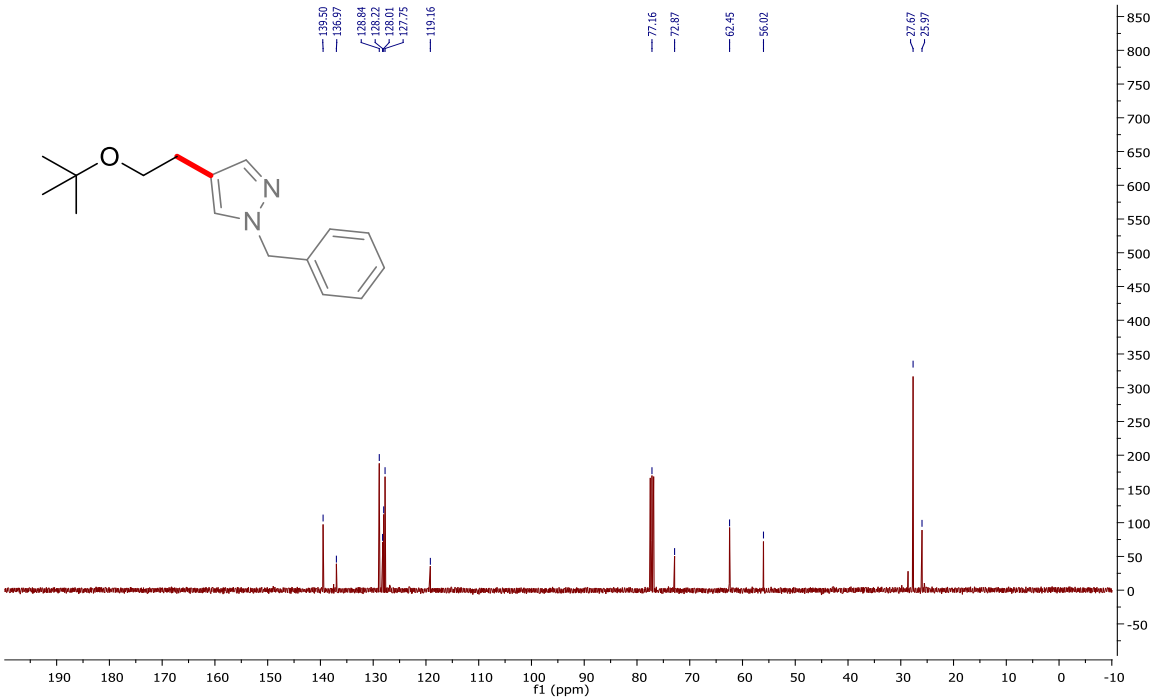


Figure 43: ^{13}C NMR 1-benzyl-4-(2-(tert-butoxy)ethyl)-1H-pyrazole (**19**)

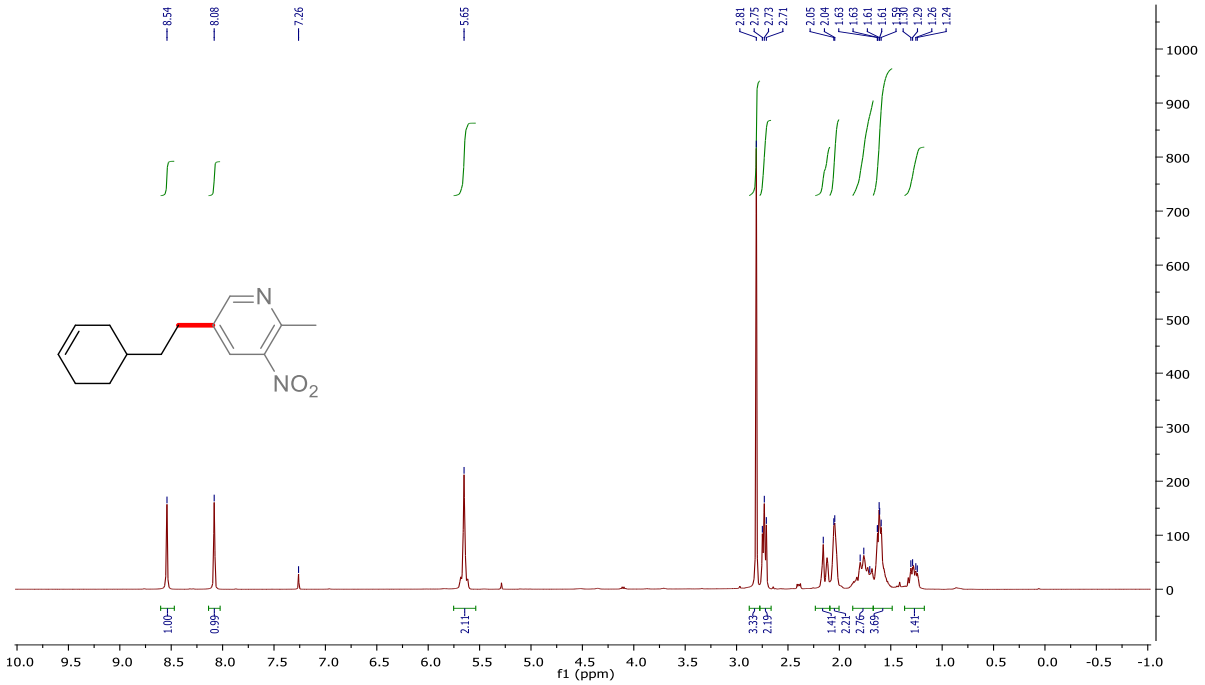


Figure 44: ^{1}H NMR 5-(2-(cyclohex-3-en-1-yl)ethyl)-2-methyl-3-nitropyridine (**20**)

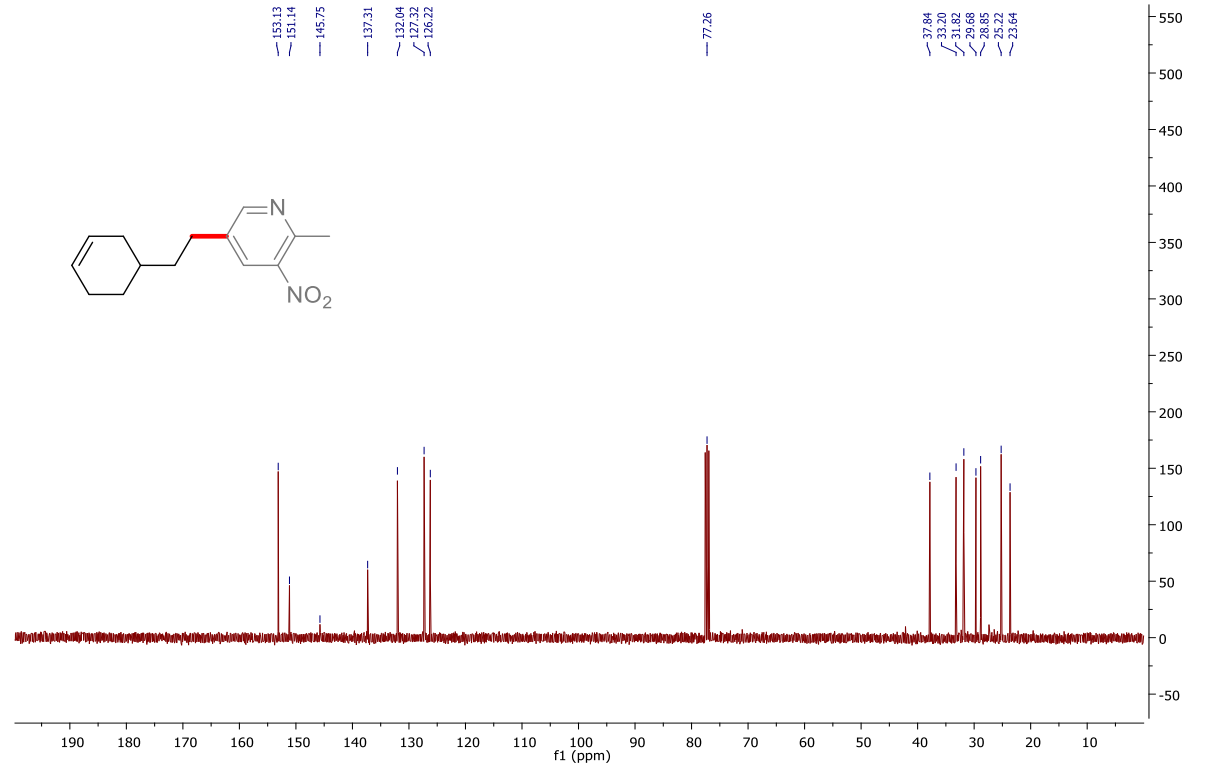


Figure 45: ^{13}C NMR 5-(2-(cyclohex-3-en-1-yl)ethyl)-2-methyl-3-nitropyridine (**20**)

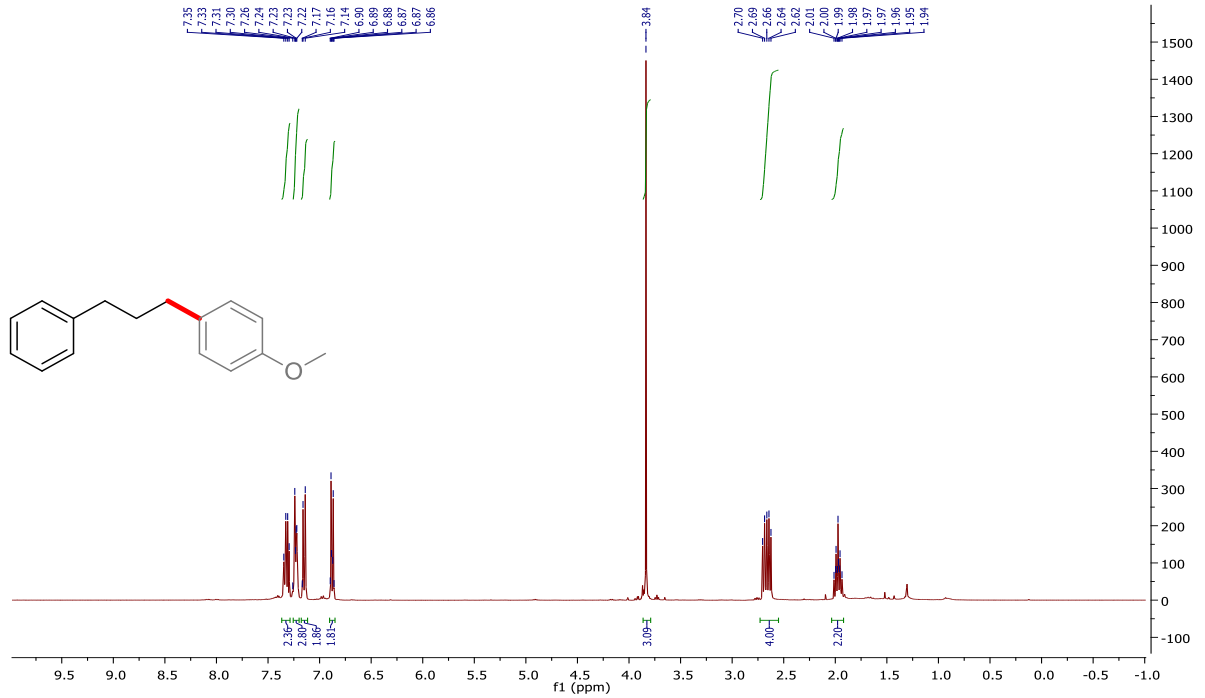


Figure 46: ^{1}H NMR 1-methoxy-4-(3-phenylpropyl)benzene (**21**)

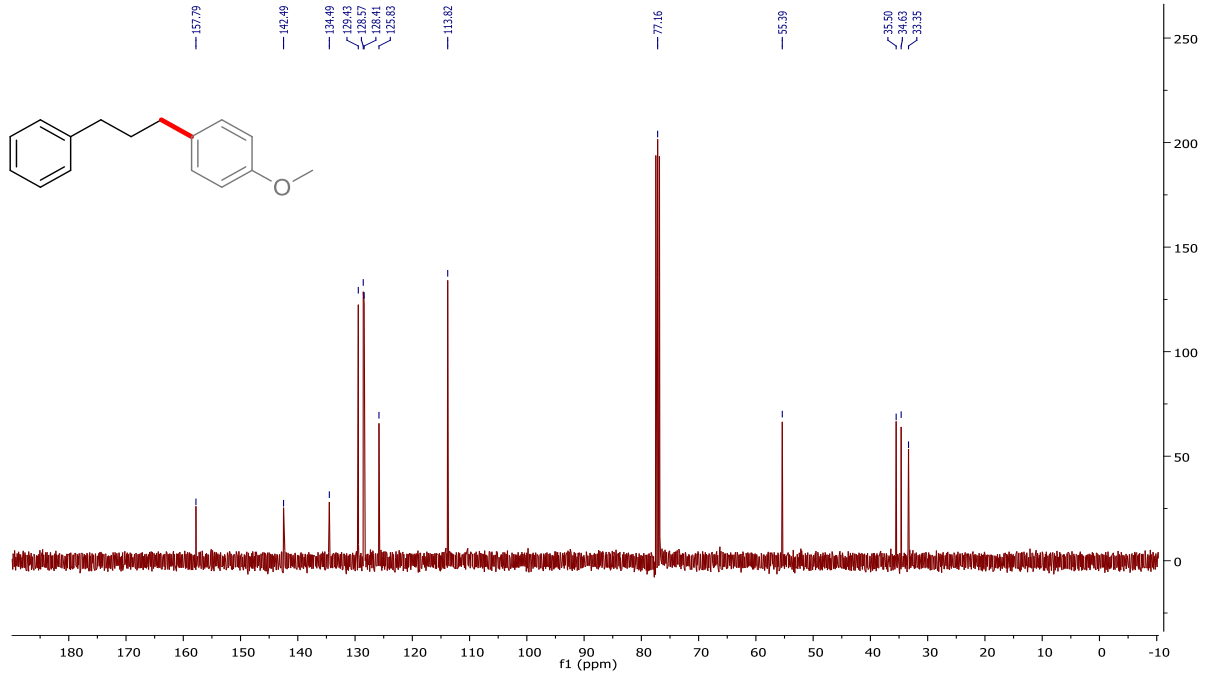


Figure 47: ^{13}C NMR 1-methoxy-4-(3-phenylpropyl)benzene (**21**)

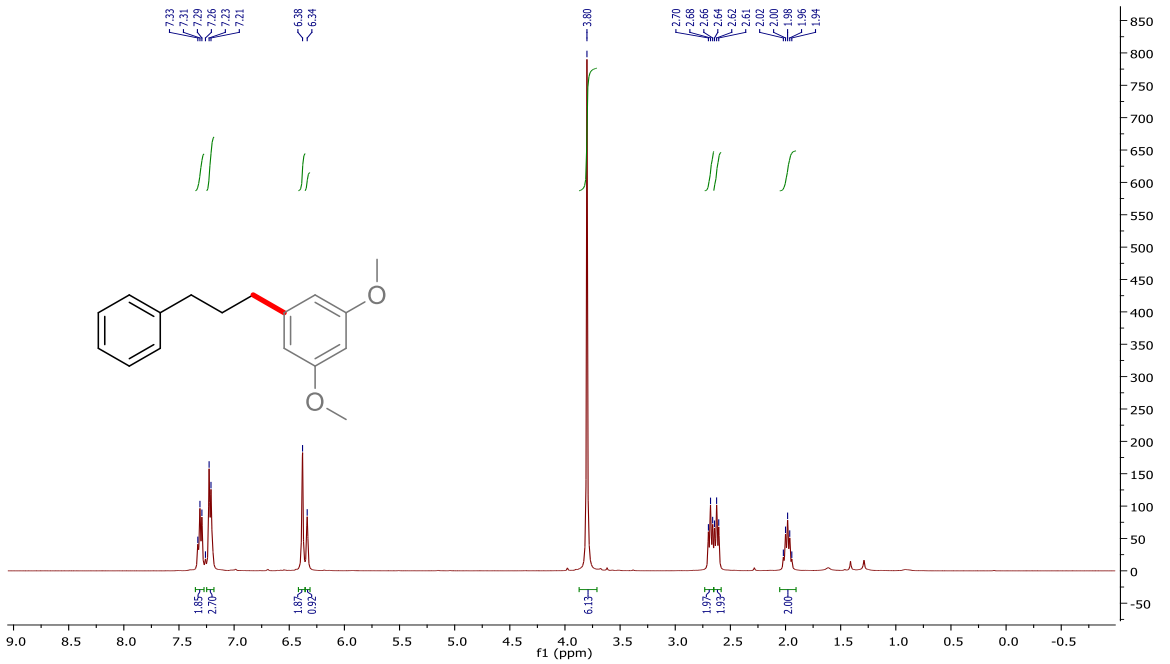


Figure 48: ^{1}H NMR 1,3-dimethoxy-5-(3-phenylpropyl)benzene (**22**)

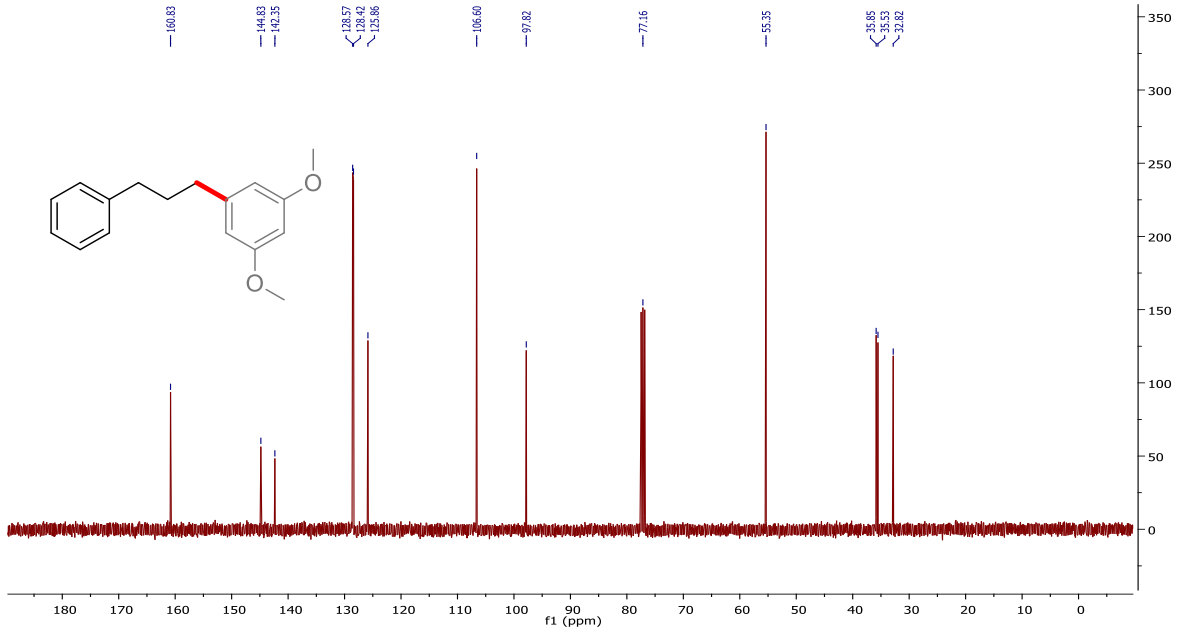


Figure 49: ^{13}C NMR 1,3-dimethoxy-5-(3-phenylpropyl)benzene (**22**)

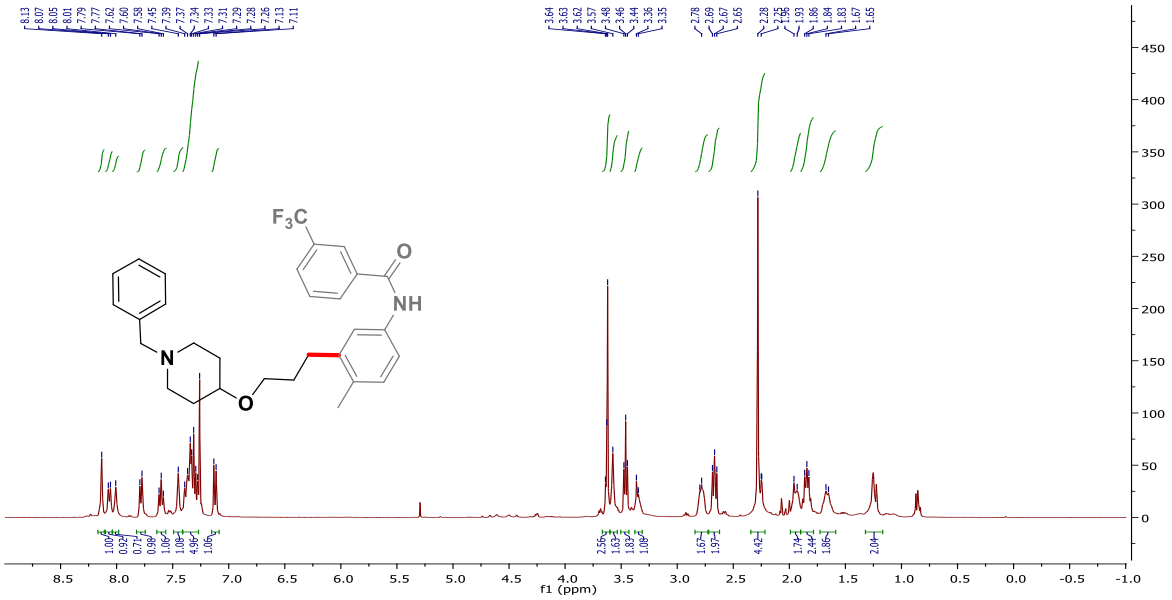


Figure 50: ^{1}H NMR N-(3-(3-((1-benzylpiperidin-4-yl)oxy)propyl)-4-methylphenyl)-3-(trifluoromethyl)benzamide (**23**)

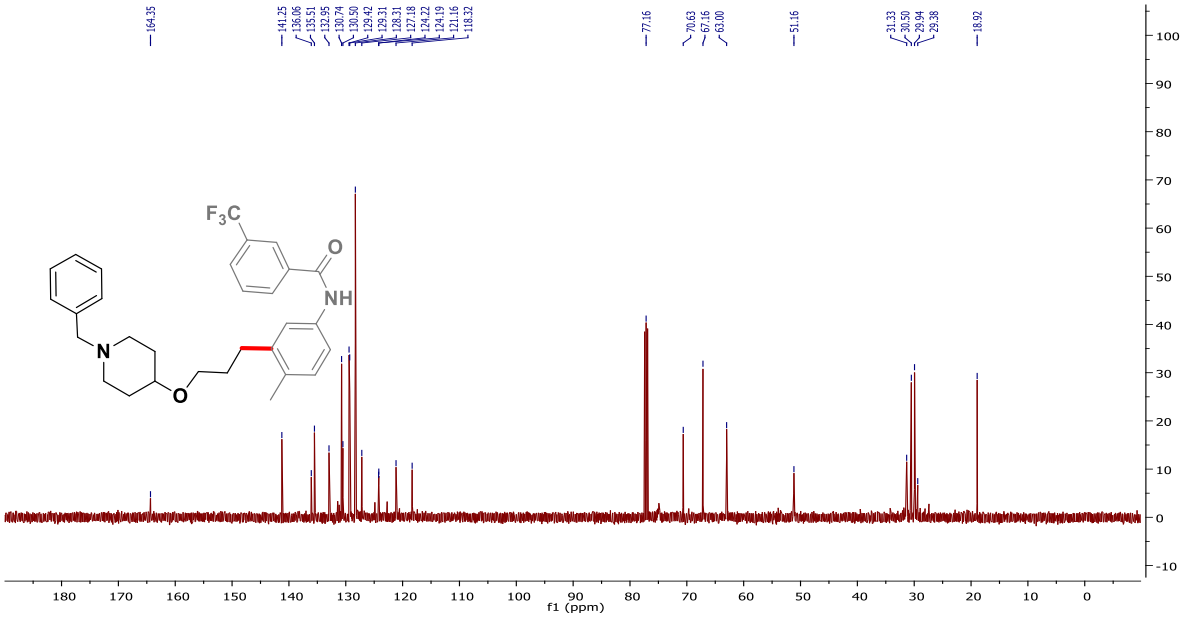


Figure 51: ^{13}C NMR N-(3-(3-((1-benzylpiperidin-4-yl)oxy)propyl)-4-methylphenyl)-3-(trifluoromethyl)benzamide (**23**)

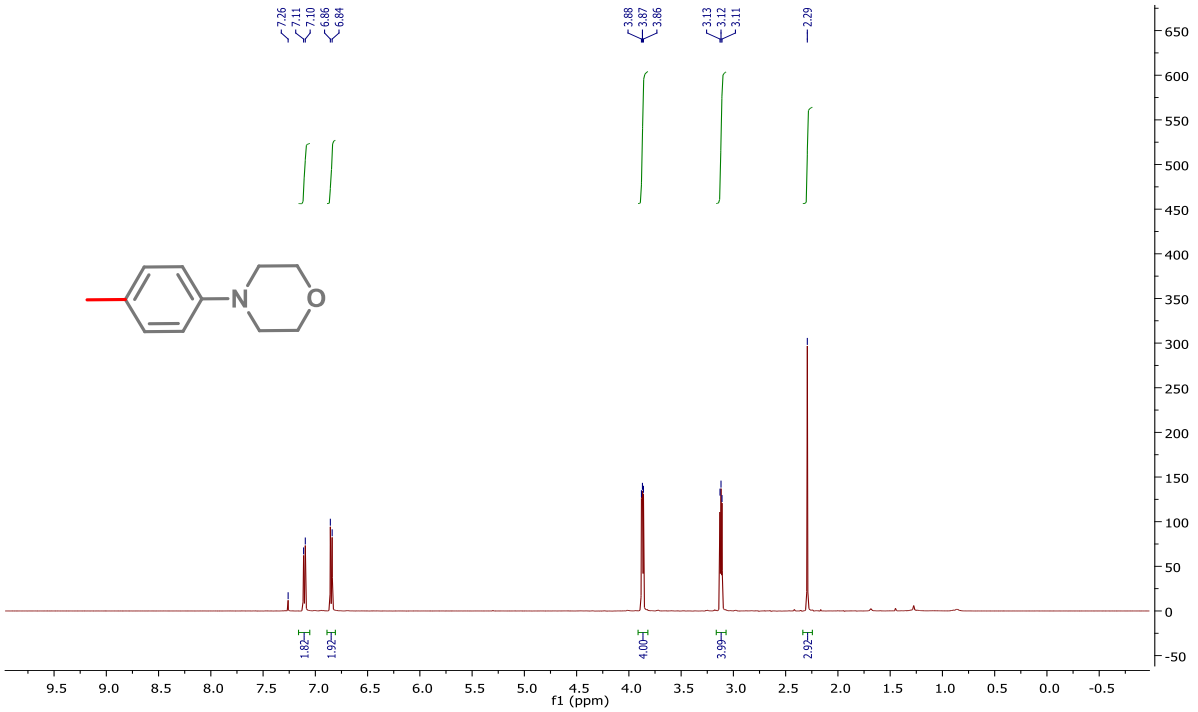


Figure 52: ^{1}H NMR 4-(p-tolyl)morpholine (**24**)

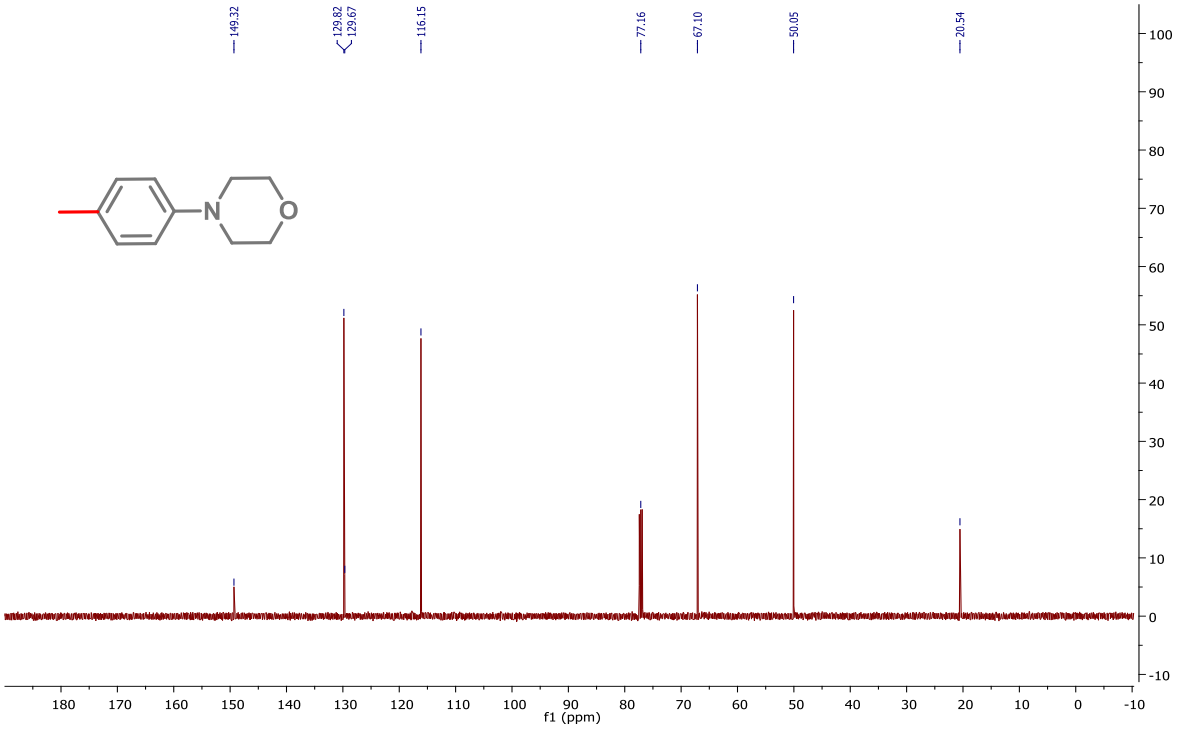


Figure 53: ^{1}H NMR 4-(p-tolyl)morpholine (**24**)

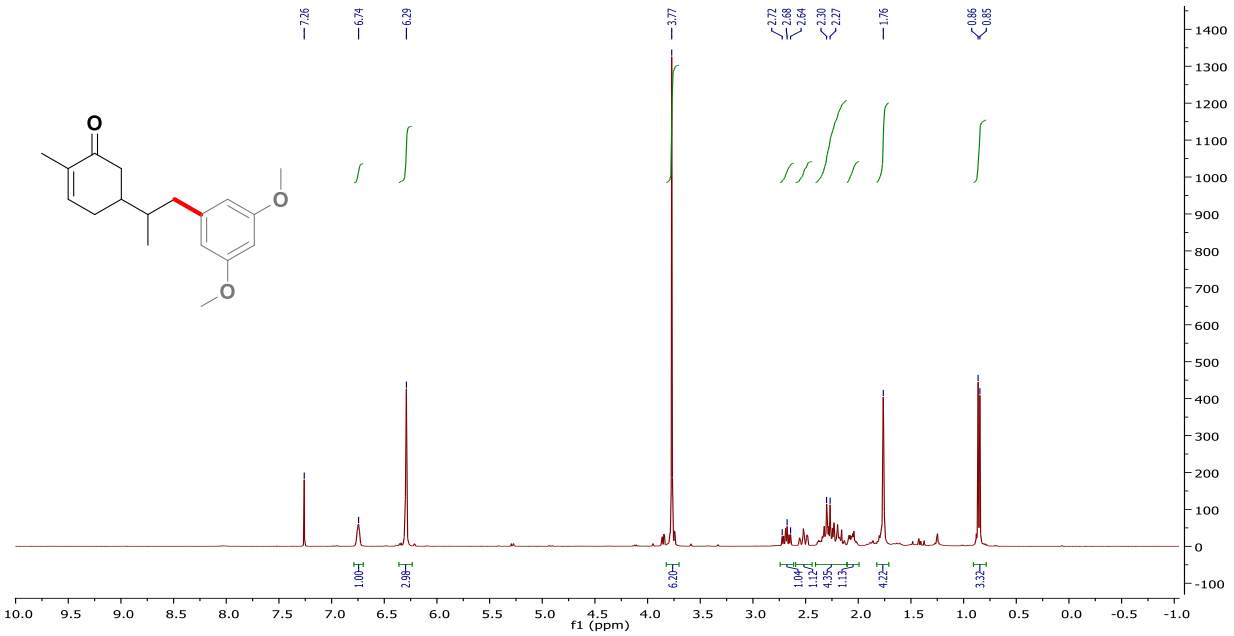


Figure 54: ^{1}H NMR 5-(1-(3,5-dimethoxyphenyl)propan-2-yl)-2-methylcyclohex-2-en-1-one (**25**)

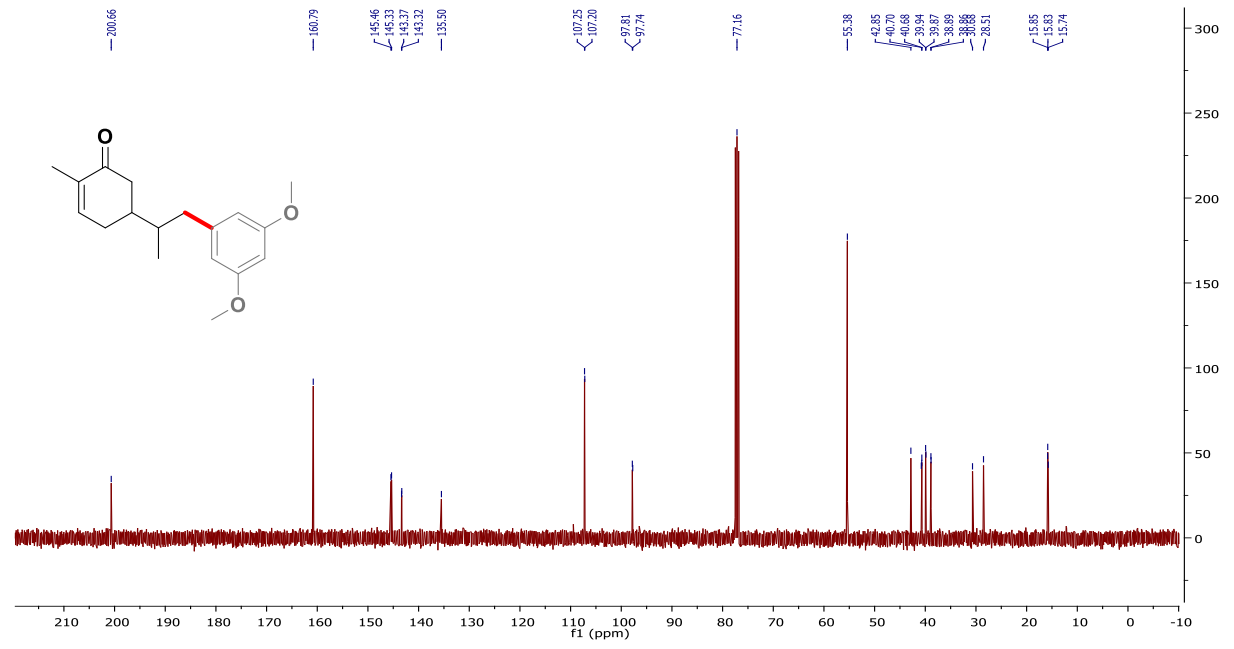


Figure 55: ^{13}C NMR 5-(1-(3,5-dimethoxyphenyl)propan-2-yl)-2-methylcyclohex-2-en-1-one (**25**)

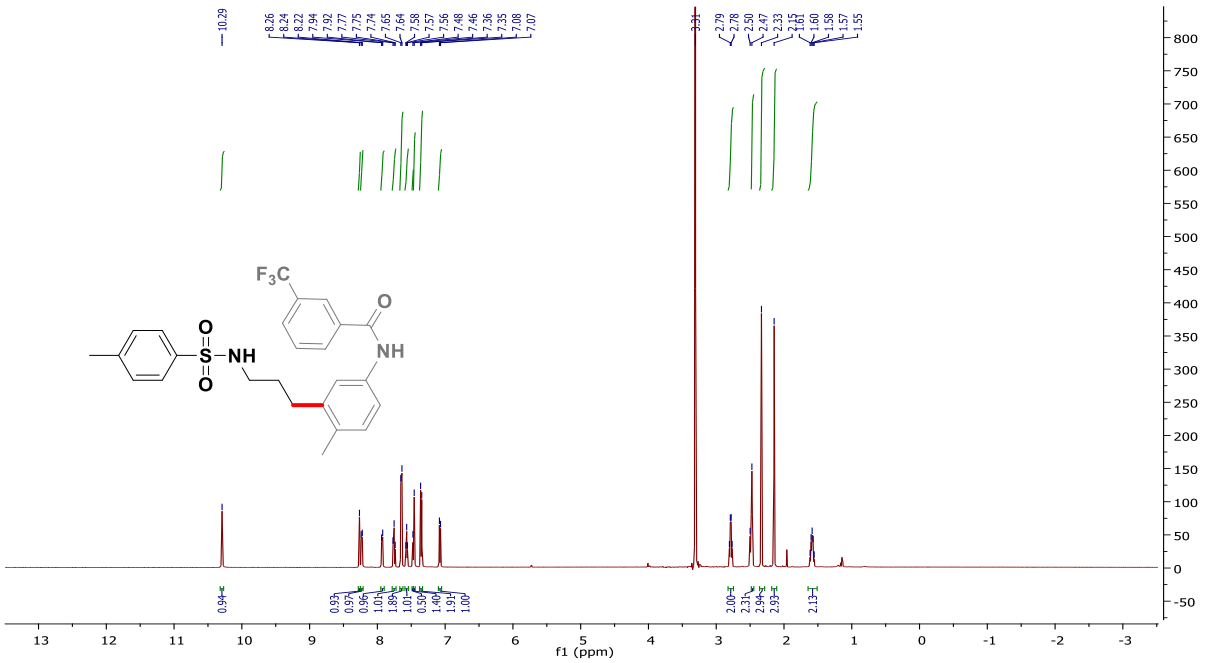


Figure 56: ^{1}H NMR N-(4-methyl-3-(3-((4-methylphenyl)sulfonamido)propyl)phenyl)-3-(trifluoromethyl)benzamide (**26**)

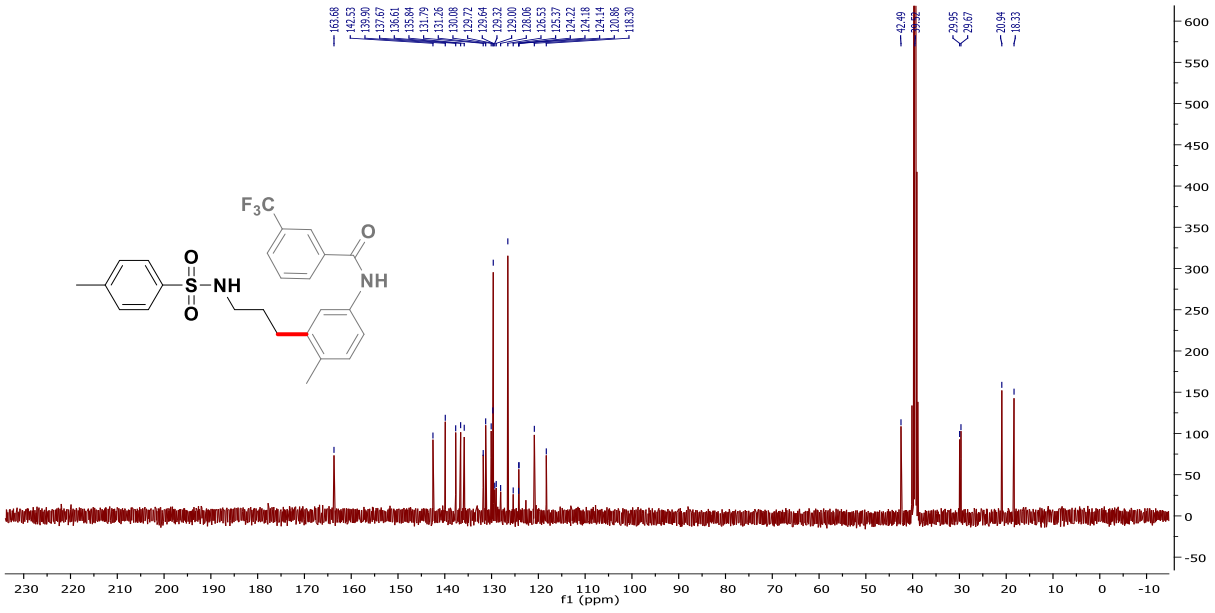


Figure 57: ^{13}C NMR N-(4-methyl-3-(3-((4-methylphenyl)sulfonamido)propyl)phenyl)-3-(trifluoromethyl)benzamide (**26**)

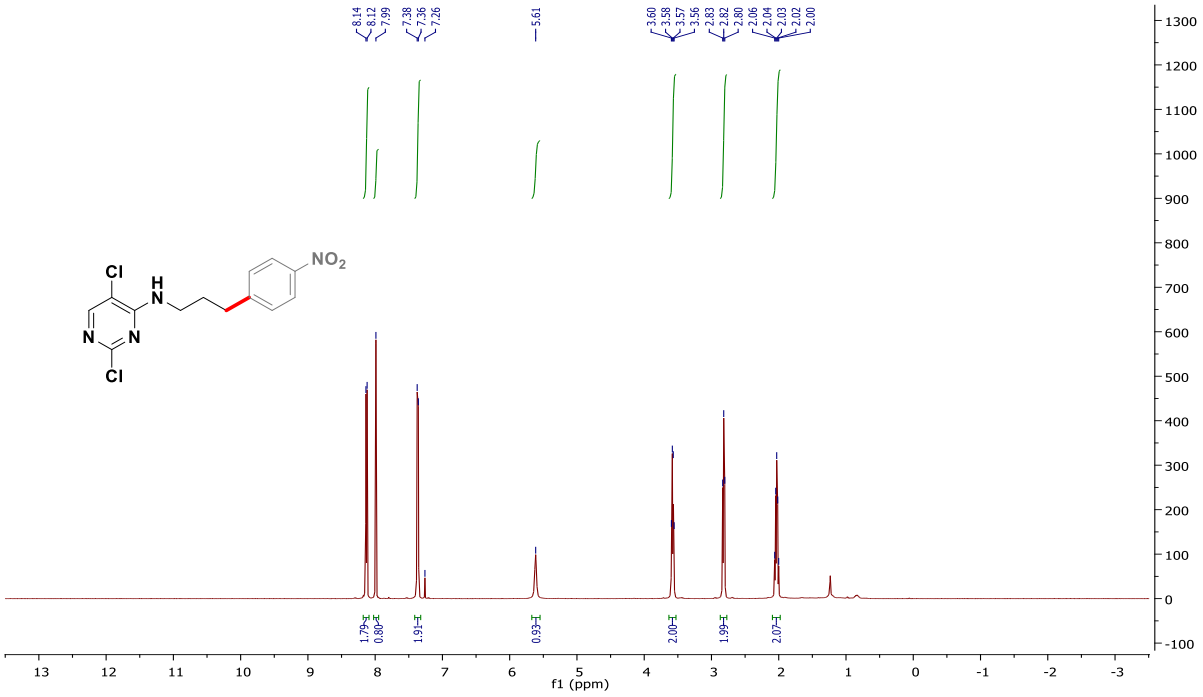


Figure 58: ^{1}H NMR 2,5-dichloro-N-(3-(4-nitrophenyl)propyl)pyrimidin-4-amine (**27**)

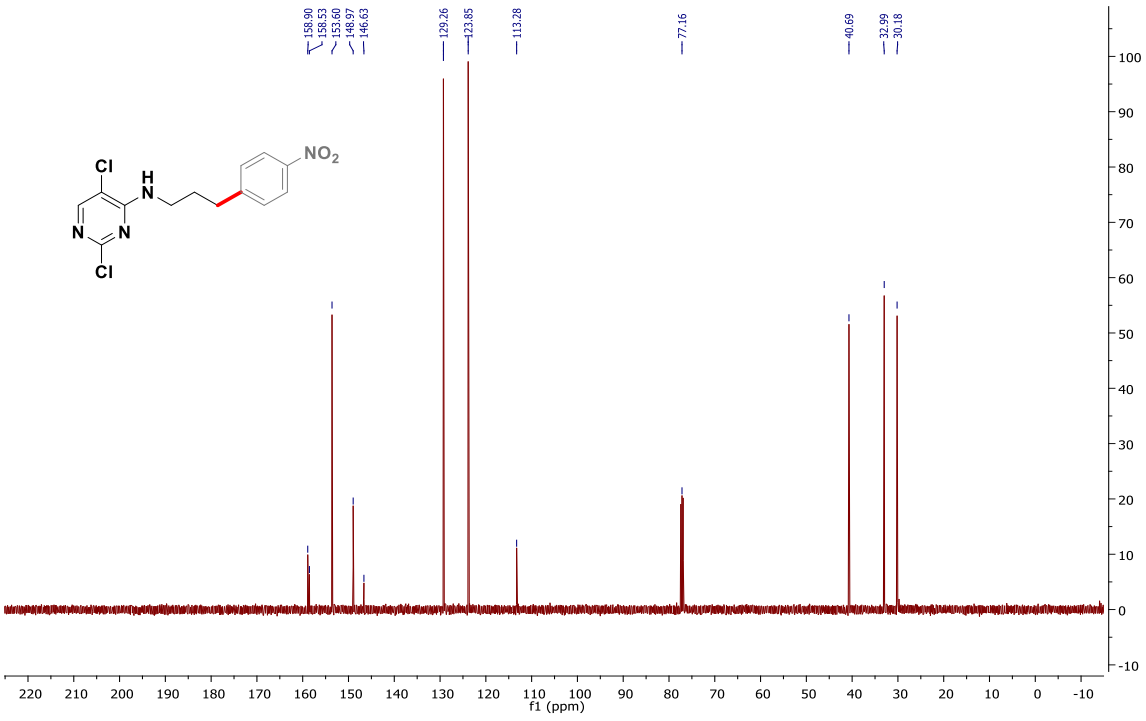


Figure 59: ^{1}H NMR 2,5-dichloro-N-(3-(4-nitrophenyl)propyl)pyrimidin-4-amine (**27**)

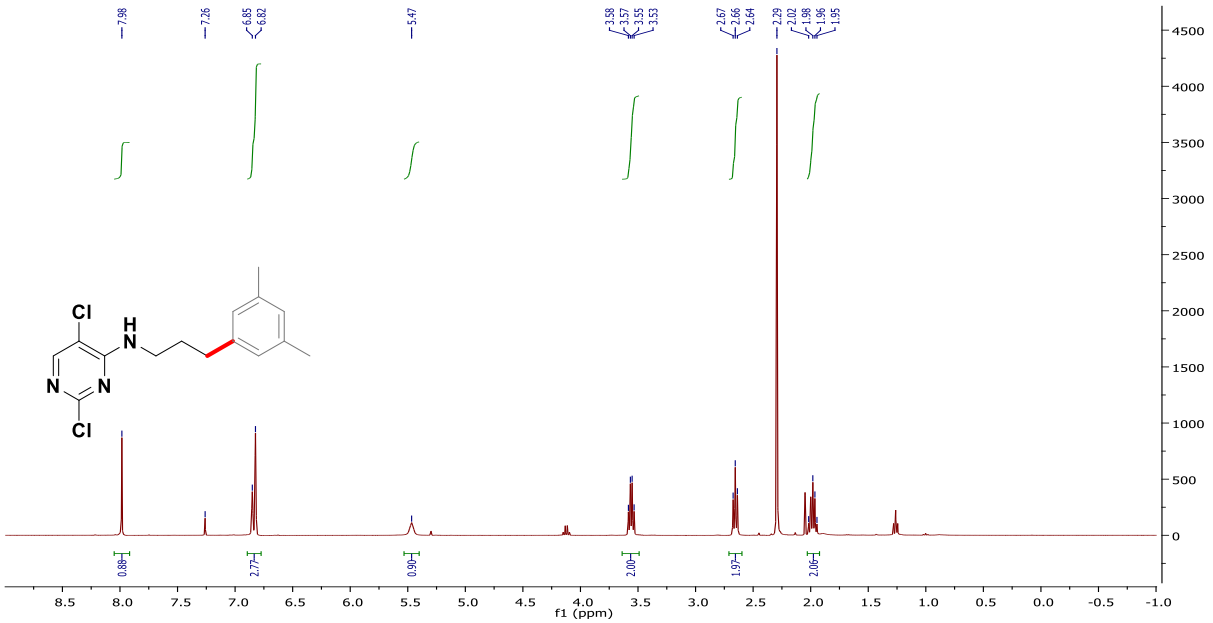


Figure 60: ^{1}H NMR 2,5-dichloro-N-(3-(3,5-dimethylphenyl)propyl)pyrimidin-4-amine (**28**)

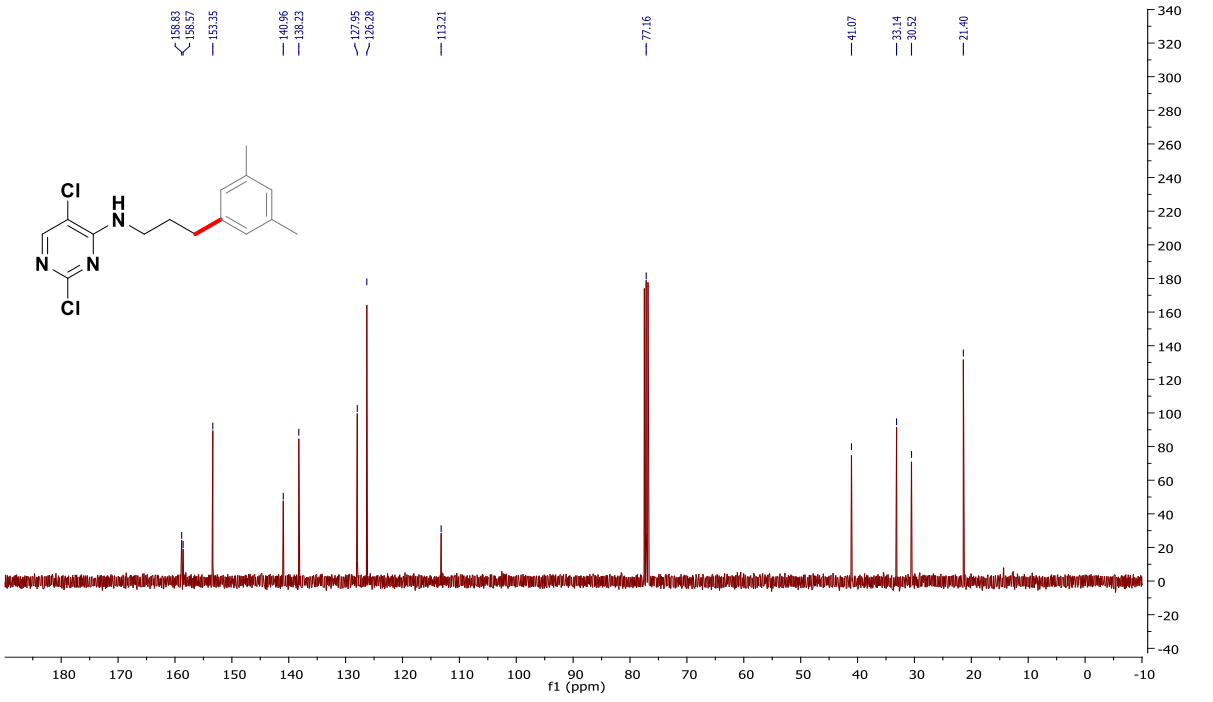


Figure 61: ^{13}C NMR 2,5-dichloro-N-(3-(3,5-dimethylphenyl)propyl)pyrimidin-4-amine (**28**)

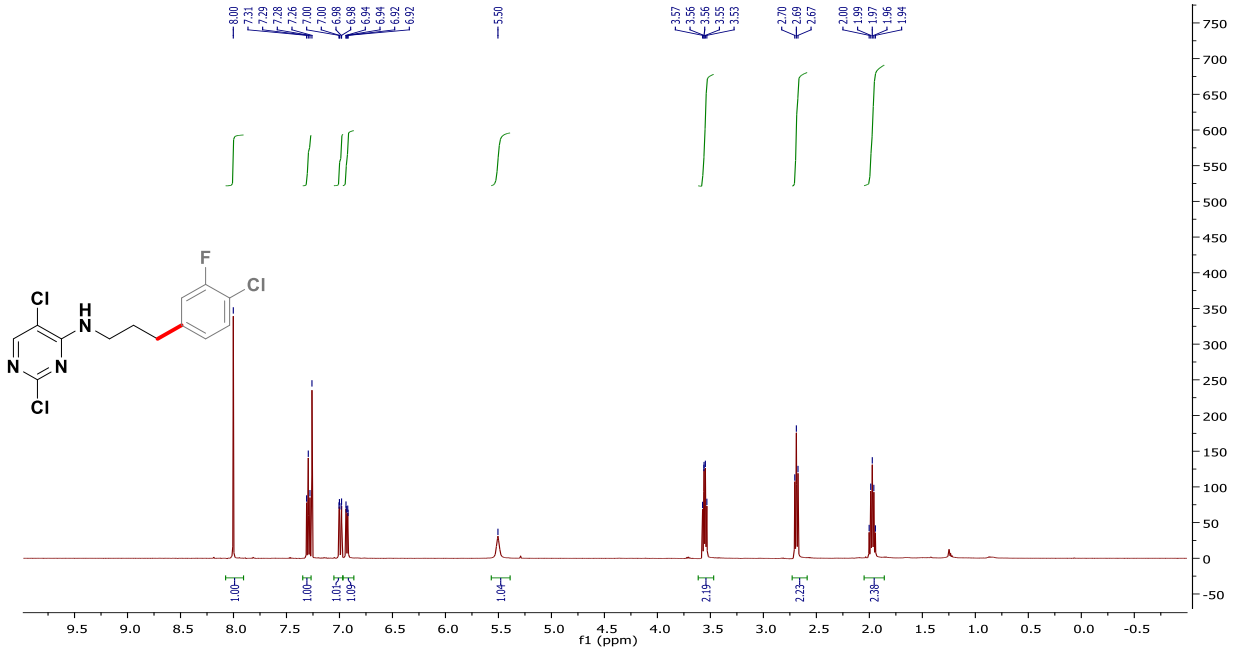


Figure 62: ^{1}H NMR 2,5-dichloro-N-(3-(4-chloro-3-fluorophenyl)propyl)pyrimidin-4-amine (**29**)

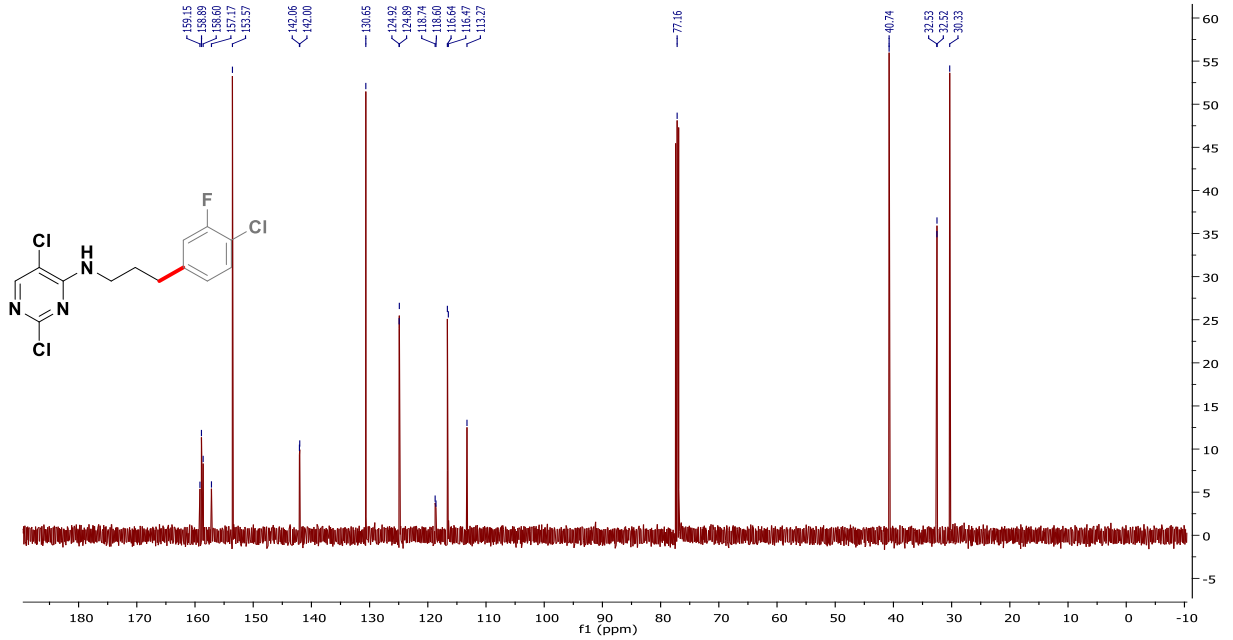


Figure 63: ^{13}C NMR 2,5-dichloro-N-(3-(4-chloro-3-fluorophenyl)propyl)pyrimidin-4-amine (**29**)

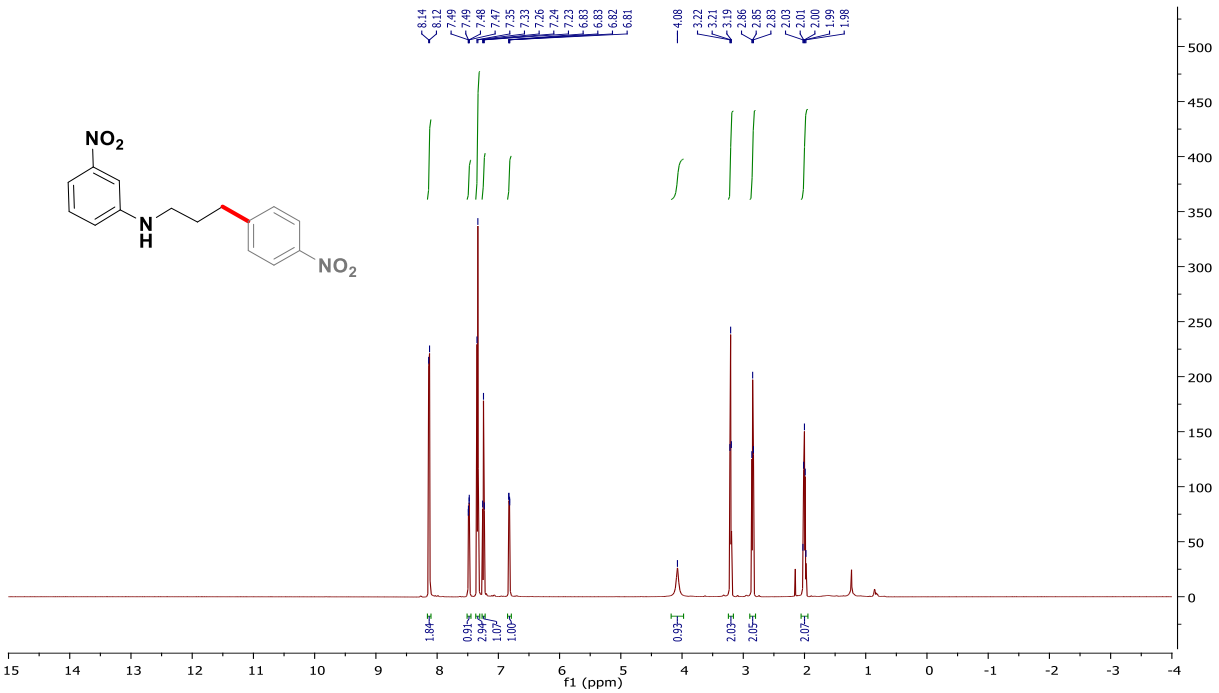


Figure 64: ^{1}H NMR 3-nitro-N-(3-(4-nitrophenyl)propyl)aniline (**30**)

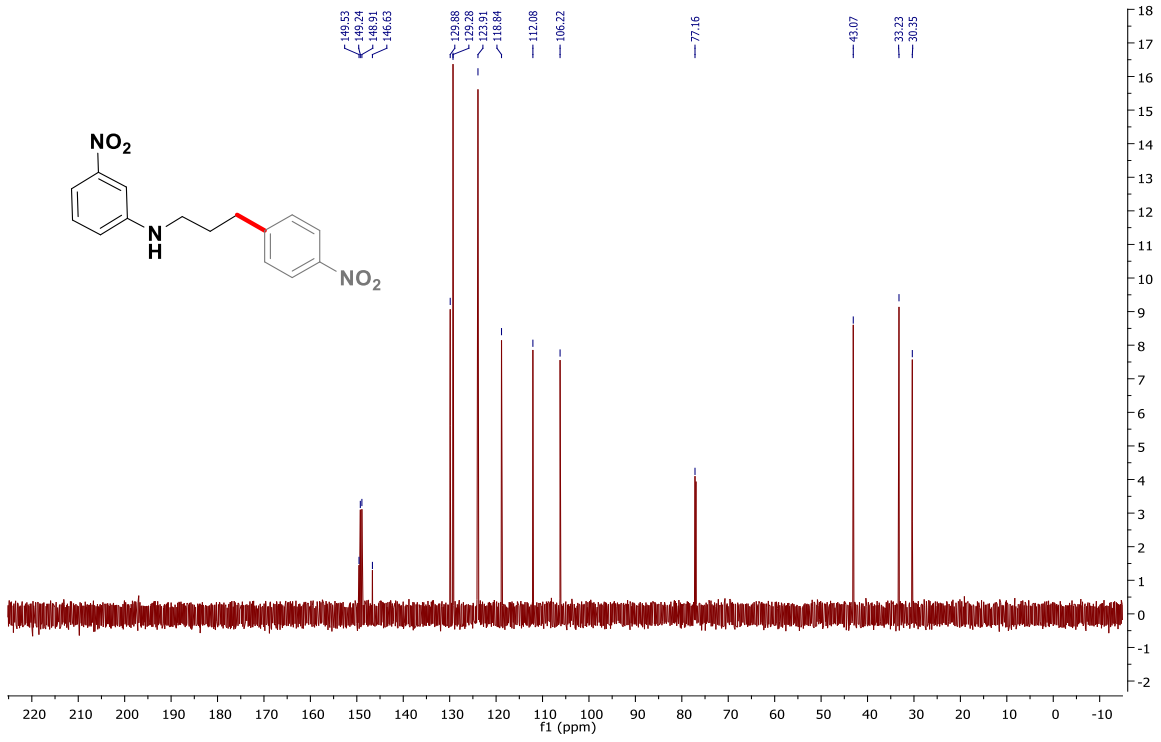


Figure 65: ^{13}C NMR 3-nitro-N-(3-(4-nitrophenyl)propyl)aniline (**30**)

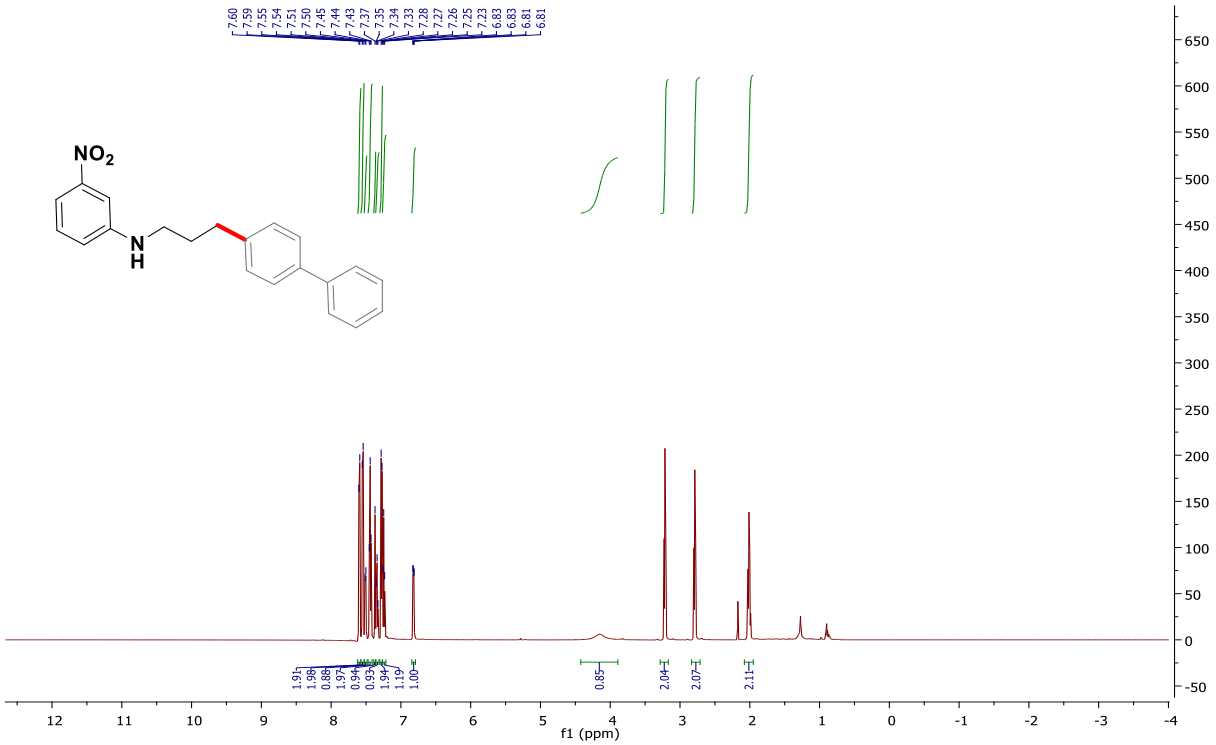


Figure 66: ^{1}H NMR N-(3-([1,1'-biphenyl]-4-yl)propyl)-3-nitroaniline (**31**)

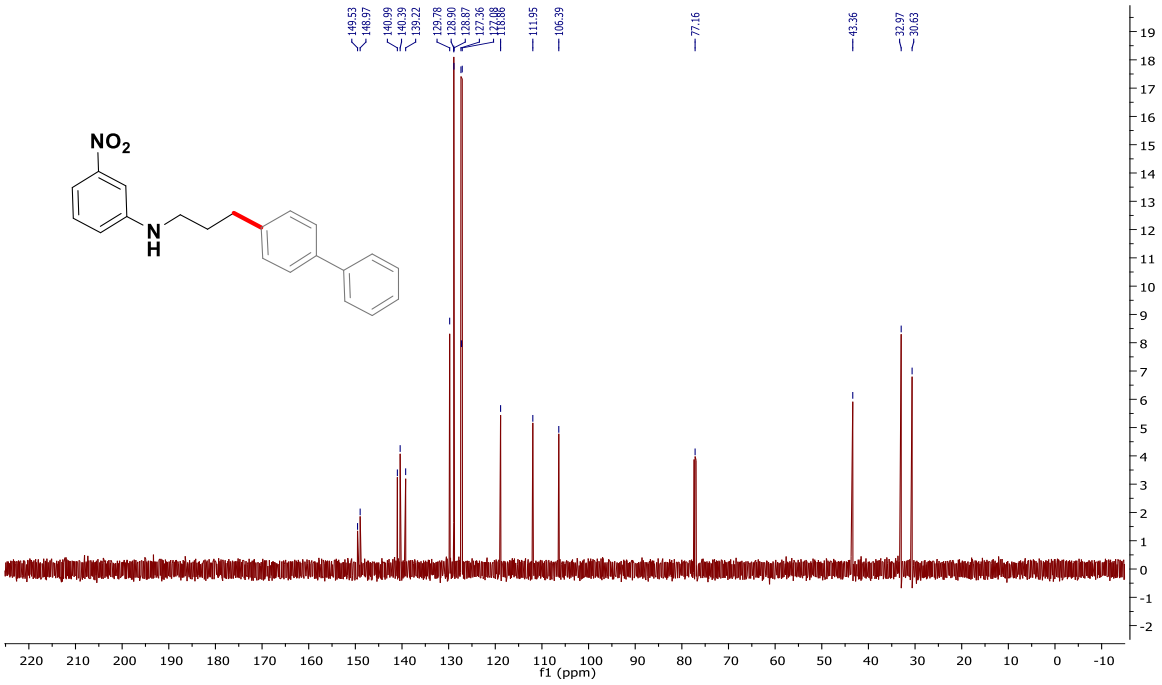


Figure 67: ^{13}C NMR N-(3-([1,1'-biphenyl]-4-yl)propyl)-3-nitroaniline (**31**)

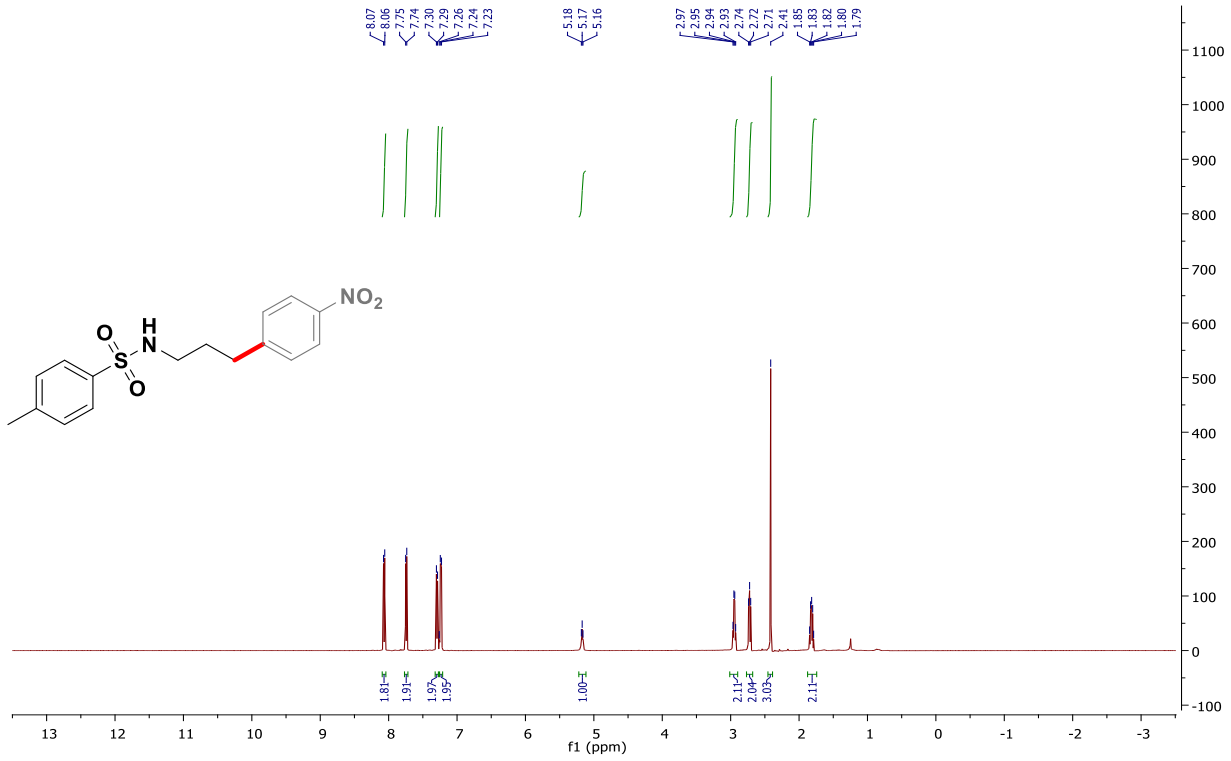


Figure 68: ^{1}H NMR 4-methyl-N-(3-(4-nitrophenyl)propyl)benzenesulfonamide (**32**)

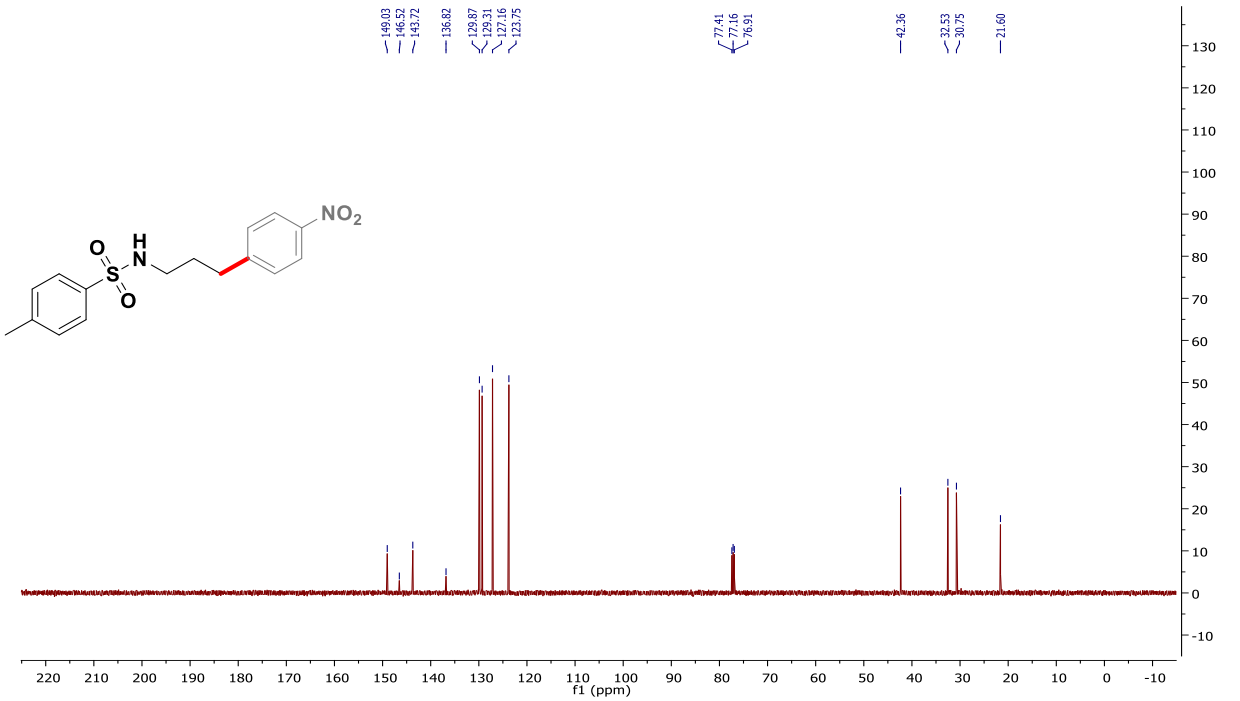


Figure 69: ^{13}C NMR 4-methyl-N-(3-(4-nitrophenyl)propyl)benzenesulfonamide (**32**)

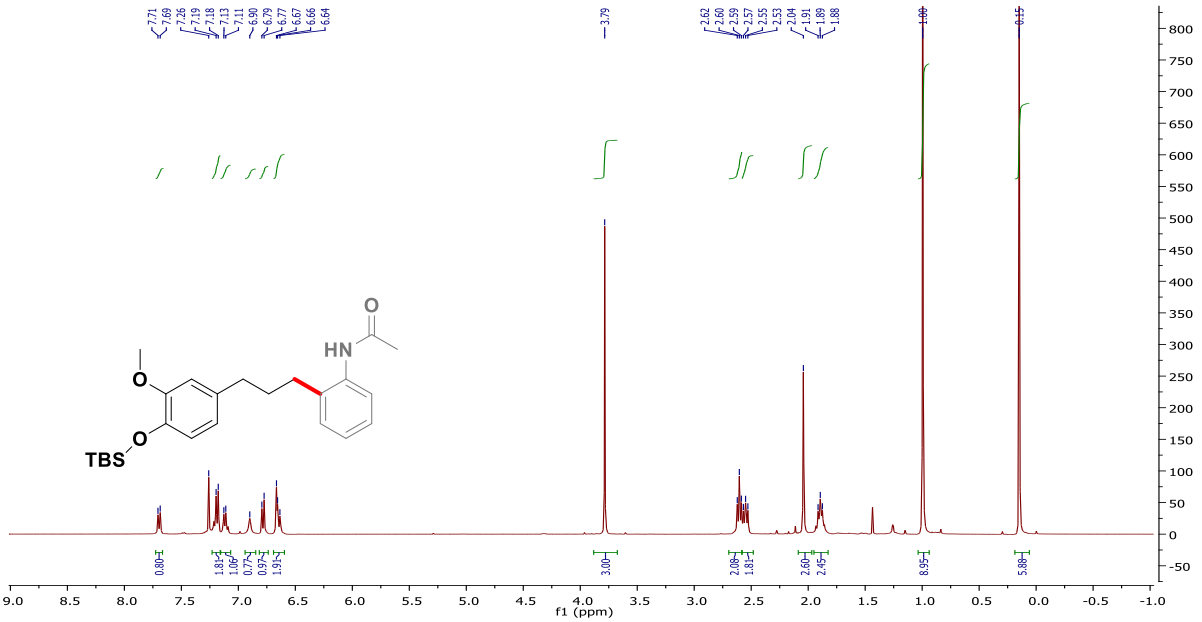


Figure 70: ^{1}H NMR N-(2-(3-(4-((tert-butyldimethylsilyl)oxy)-3-methoxyphenyl)propyl)phenyl)acetamide (**34**)

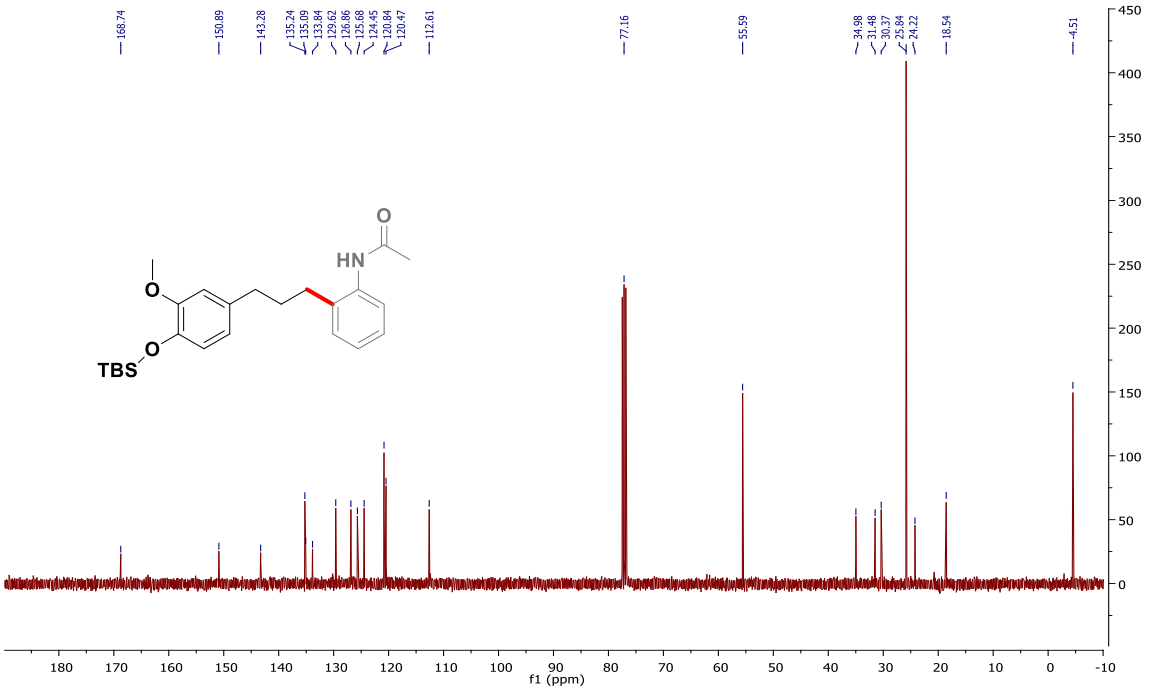


Figure 71: ^{13}C NMR N-(2-(3-(4-((tert-butyldimethylsilyl)oxy)-3-methoxyphenyl)propyl)phenyl)acetamide (**34**)

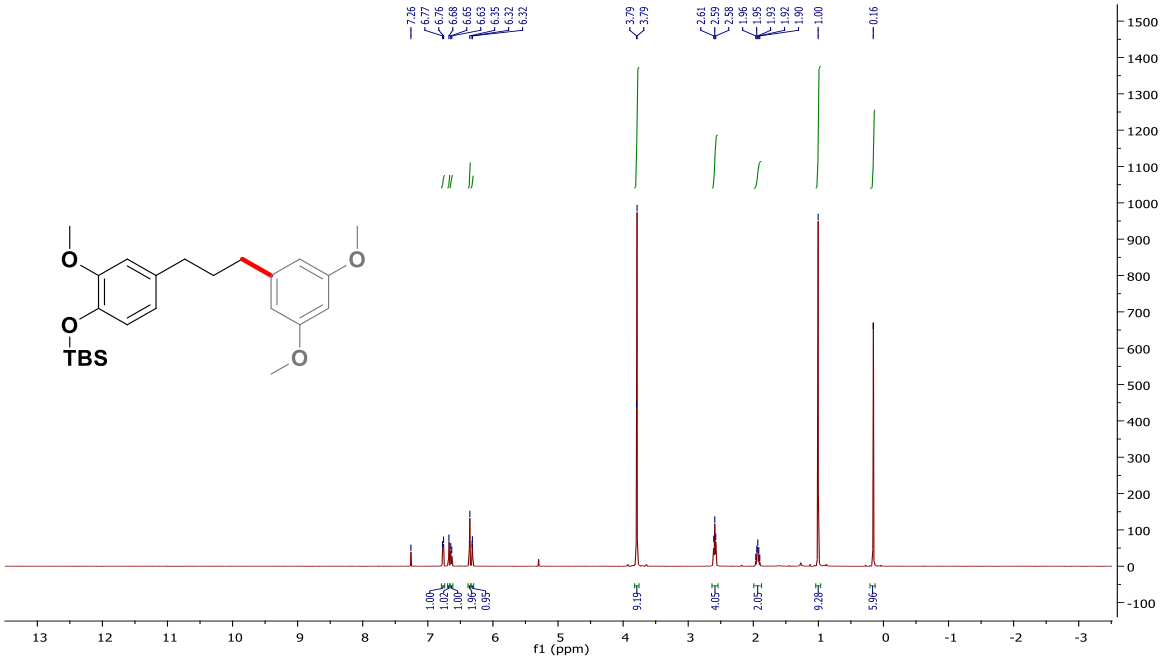


Figure 72: ^{1}H NMR tert-butyl(4-(3-(3,5-dimethoxyphenyl)propyl)-2-methoxyphenoxy)dimethylsilane (**35**)

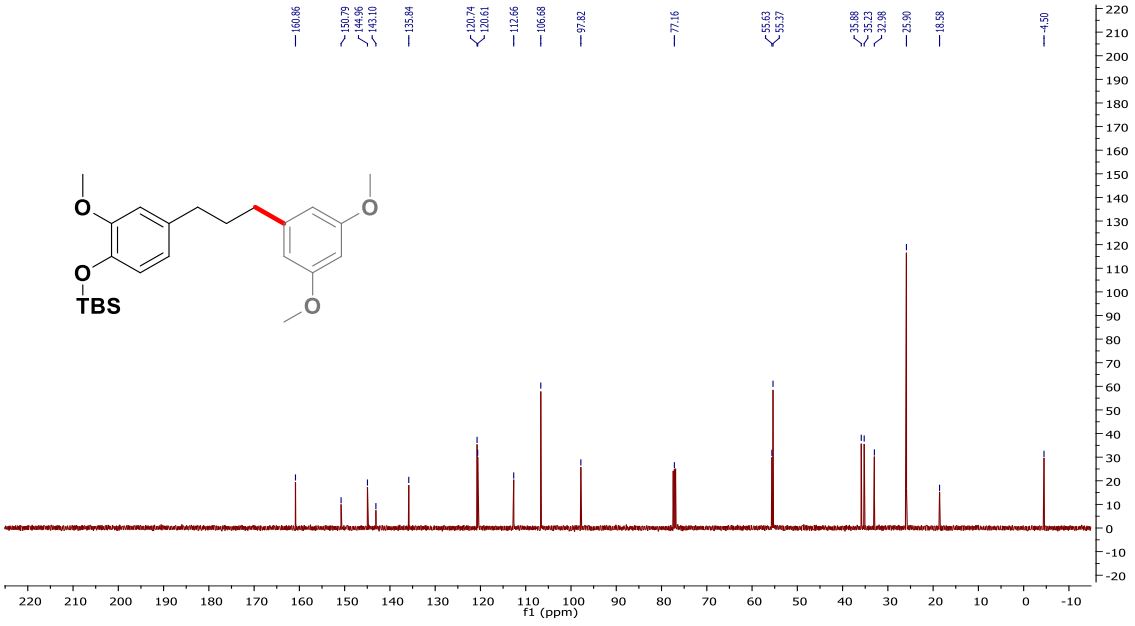


Figure 73: ^{13}C NMR tert-butyl(4-(3-(3,5-dimethoxyphenyl)propyl)-2-methoxyphenoxy)dimethylsilane (**35**)

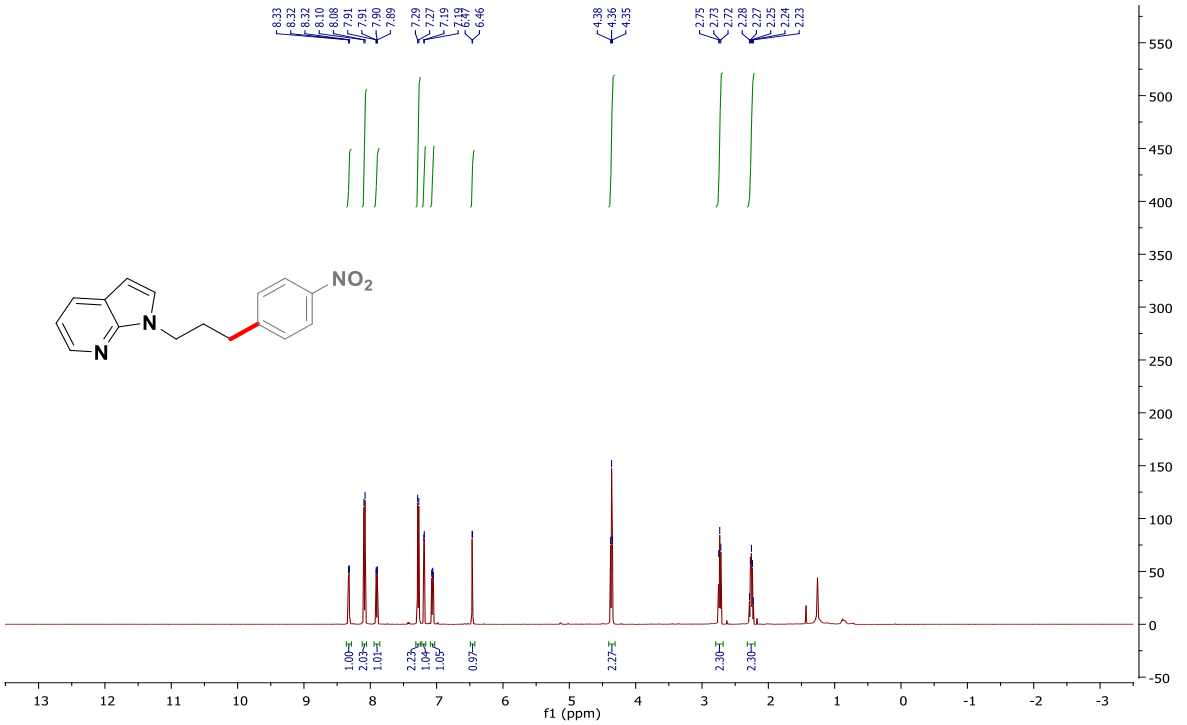


Figure 74: ^{1}H NMR 1-(3-(4-nitrophenyl)propyl)-1H-pyrrolo[2,3-b]pyridine(**36**)

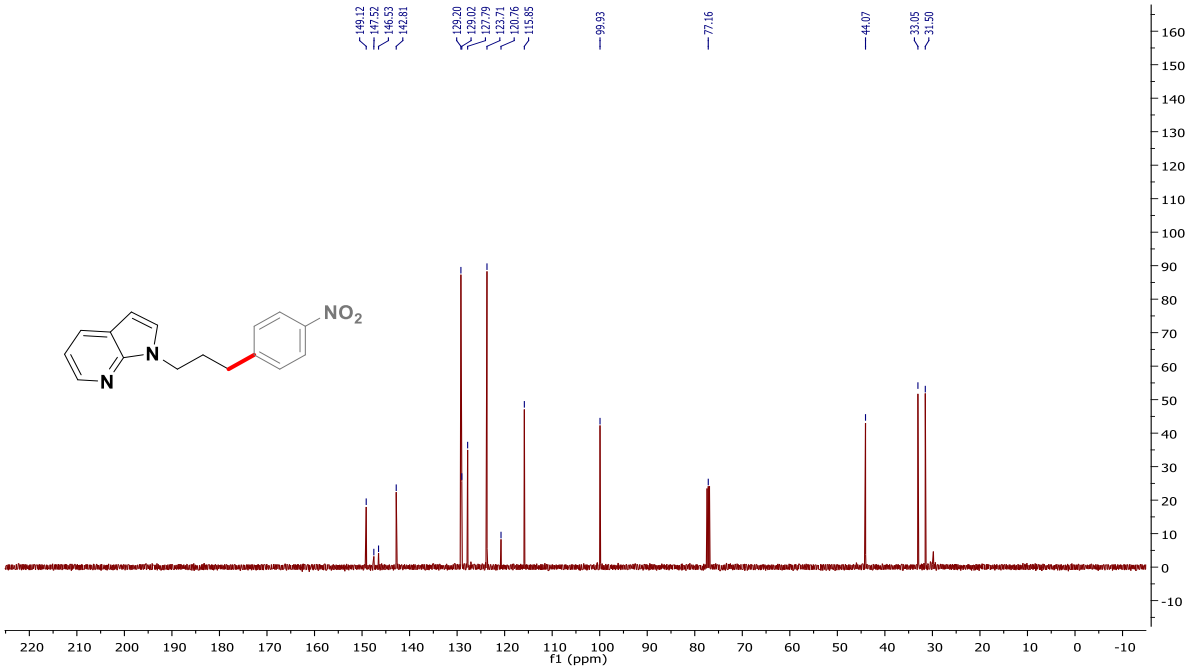


Figure 75: ^{13}C NMR 1-(3-(4-nitrophenyl)propyl)-1H-pyrrolo[2,3-b]pyridine(**36**)

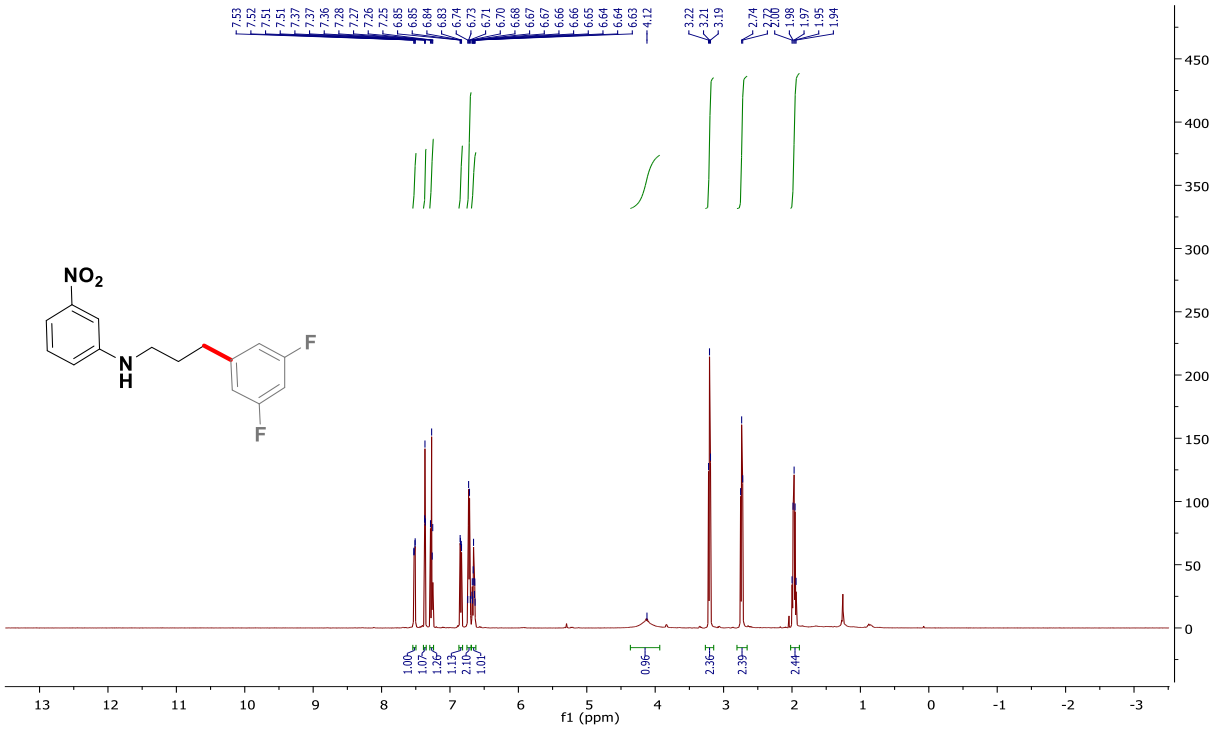


Figure 76: ^{1}H NMR N-(3-(3,5-difluorophenyl)propyl)-3-nitroaniline (**37**)

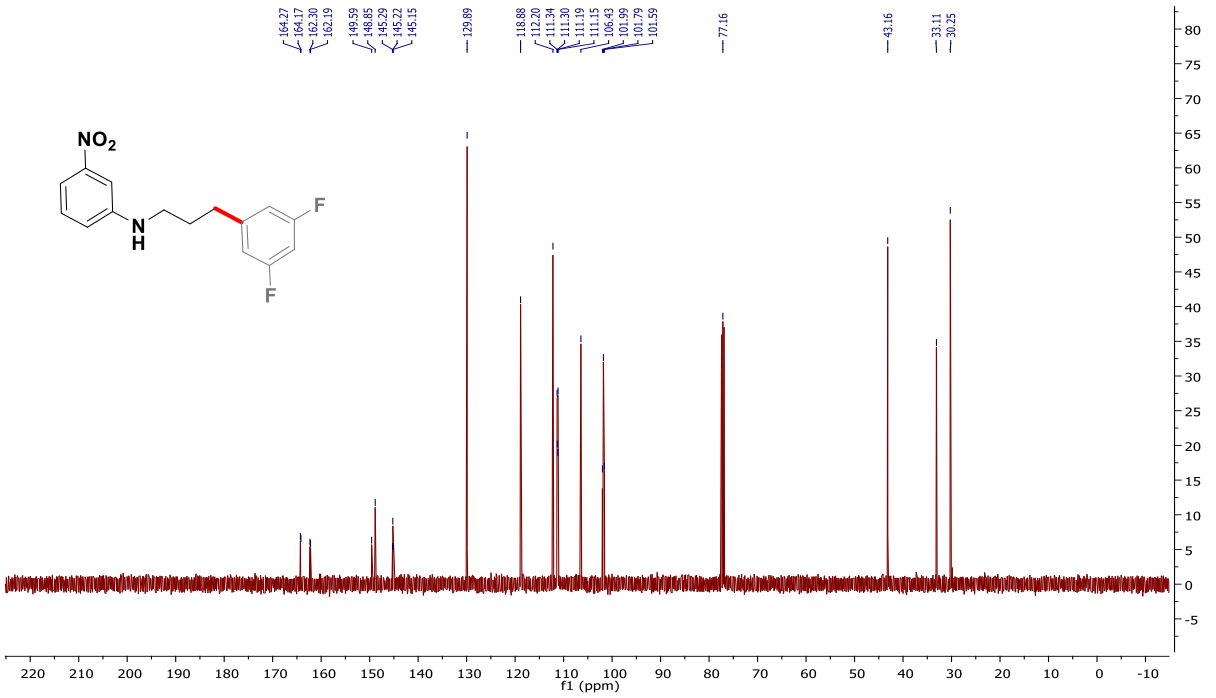


Figure 77: ^{13}C NMR N-(3-(3,5-difluorophenyl)propyl)-3-nitroaniline (**37**)

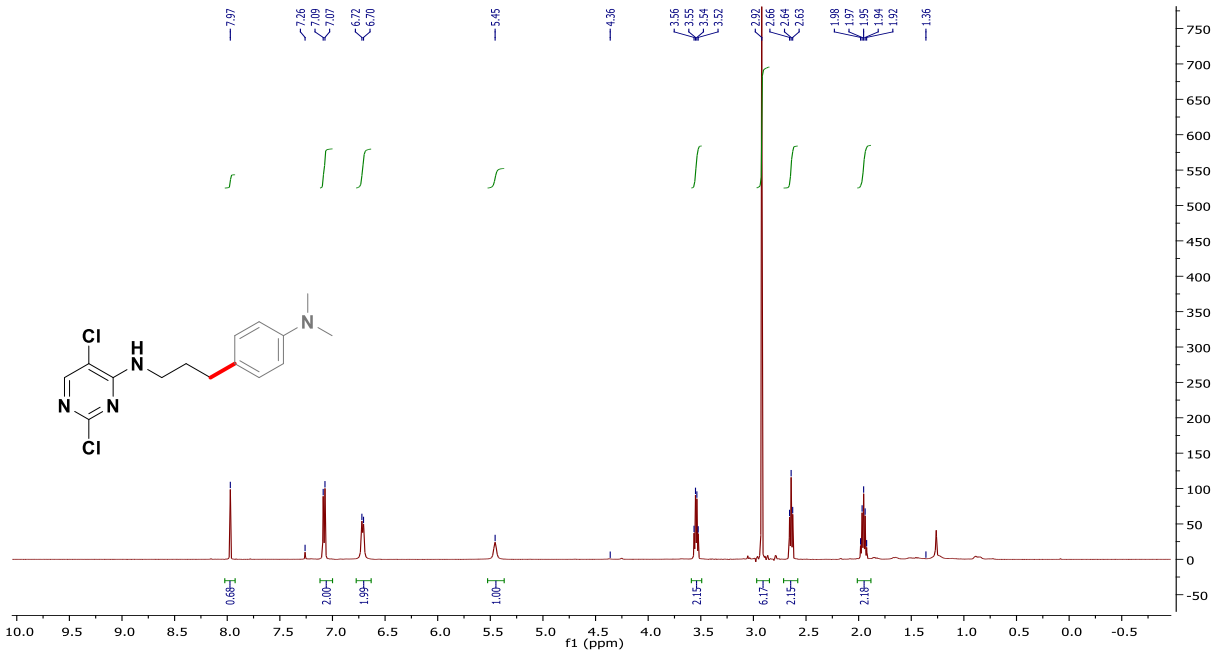


Figure 78: ^{1}H NMR 2,5-dichloro-N-(3-(4-(dimethylamino)phenyl)propyl)pyrimidin-4-amine (**38**)

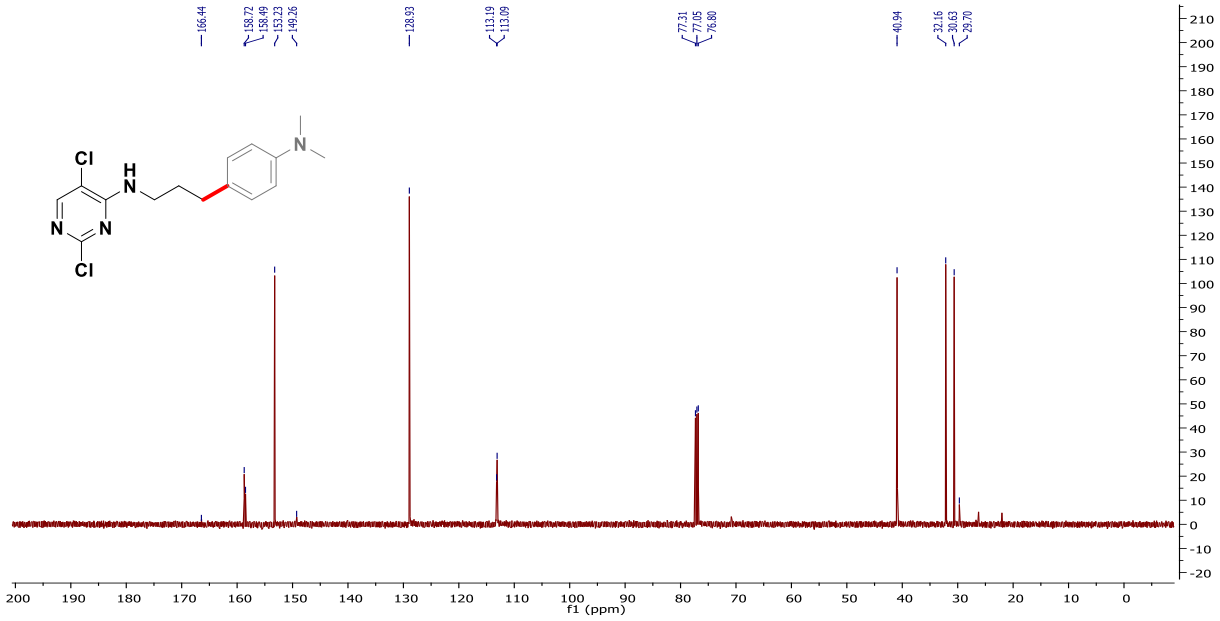


Figure 79: ^{13}C NMR 2,5-dichloro-N-(3-(4-(dimethylamino)phenyl)propyl)pyrimidin-4-amine (**38**)

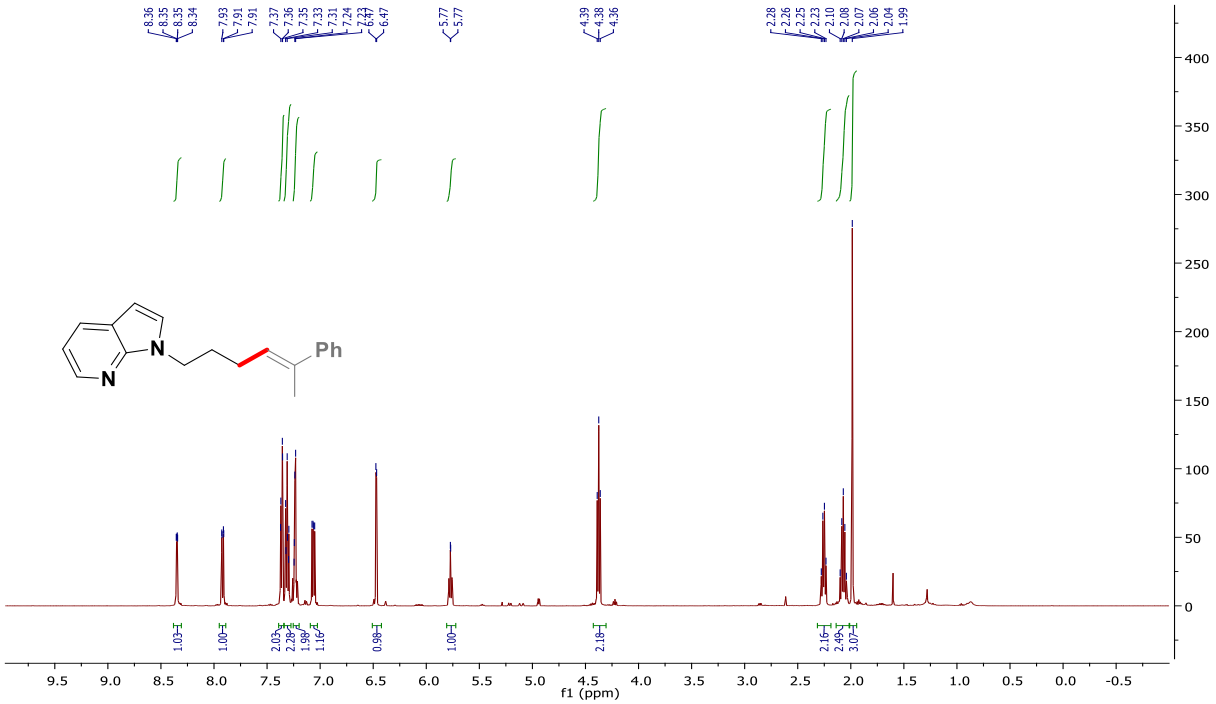


Figure 80: ^{1}H NMR (E)-1-(5-phenylhex-4-en-1-yl)-1H-pyrrolo[2,3-b]pyridine (**39**)

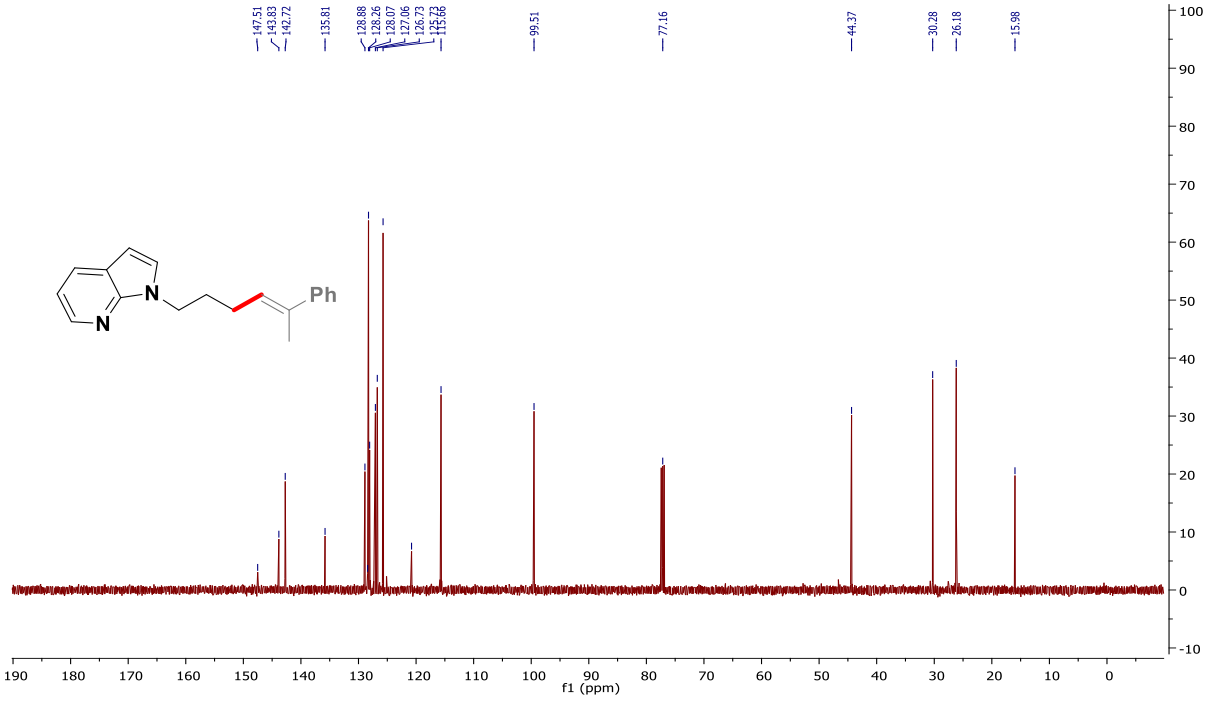


Figure 81: ^{13}C NMR (E)-1-(5-phenylhex-4-en-1-yl)-1H-pyrrolo[2,3-b]pyridine (**39**)

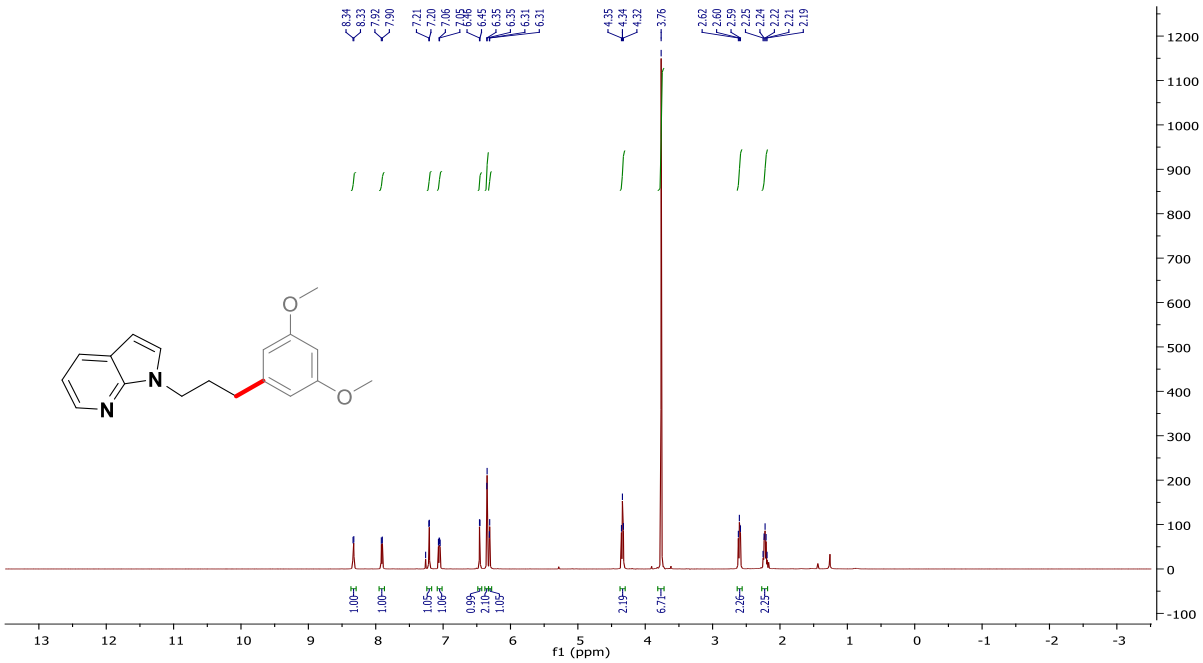


Figure 82: ^{1}H NMR 1-(3-(3,5-dimethoxyphenyl)propyl)-1H-pyrrolo[2,3-b]pyridine (**40**)

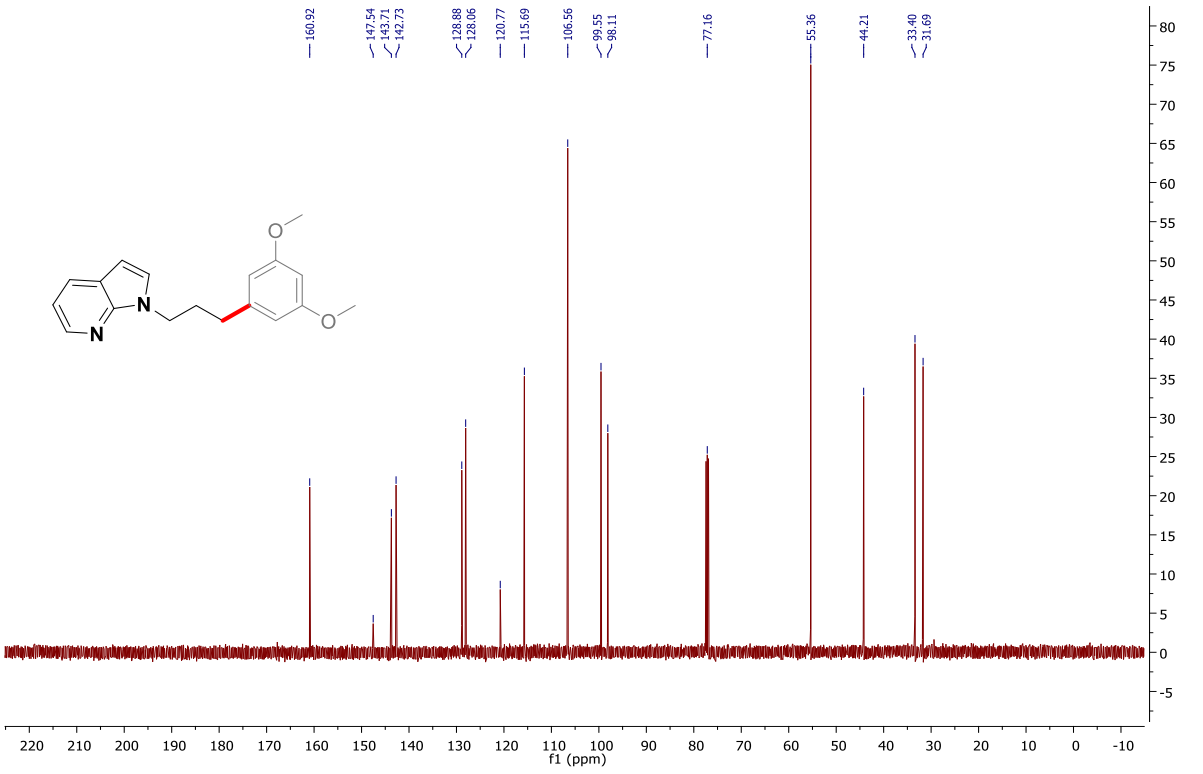


Figure 83: ^{13}C NMR 1-(3-(3,5-dimethoxyphenyl)propyl)-1H-pyrrolo[2,3-b]pyridine (**40**)

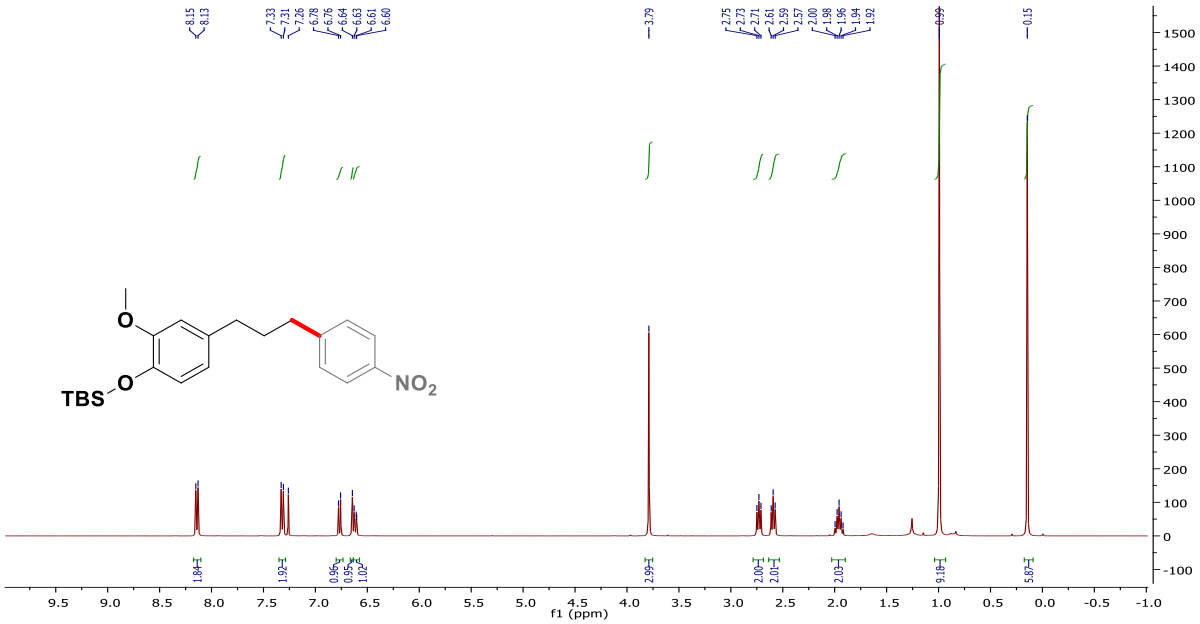


Figure 84: ^{1}H NMR tert-butyl(2-methoxy-4-(3-(4-nitrophenyl)propyl)phenoxy)dimethylsilane (**41**)

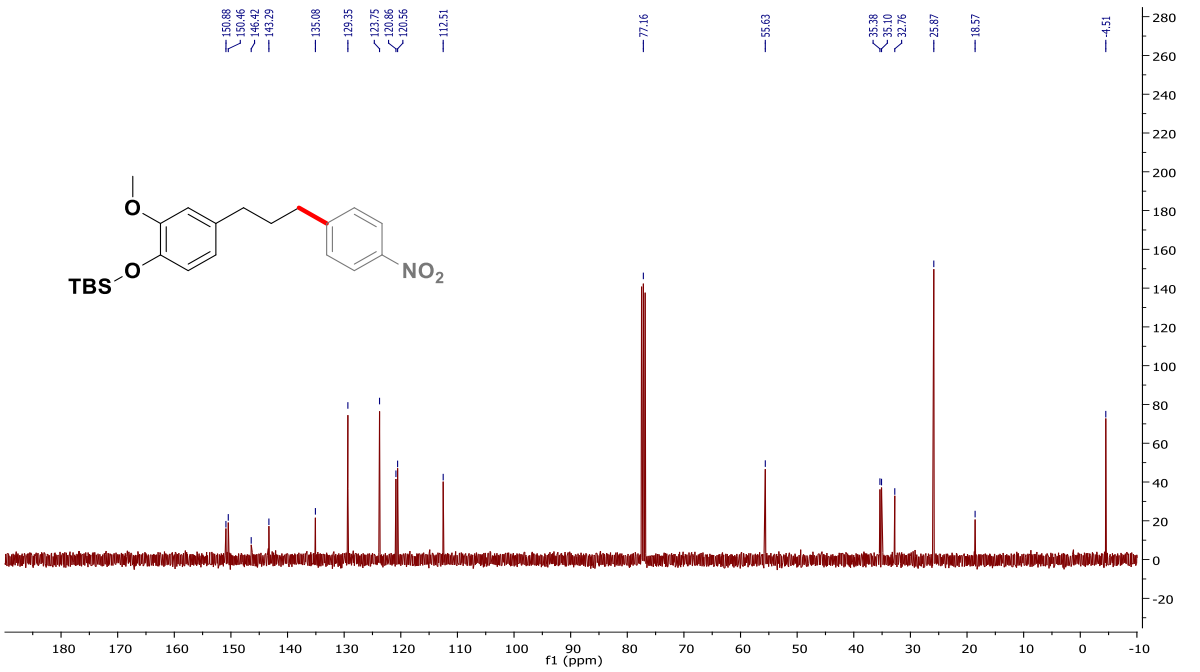


Figure 85: ^{13}C NMR tert-butyl(2-methoxy-4-(3-(4-nitrophenyl)propyl)phenoxy)dimethylsilane (**41**)

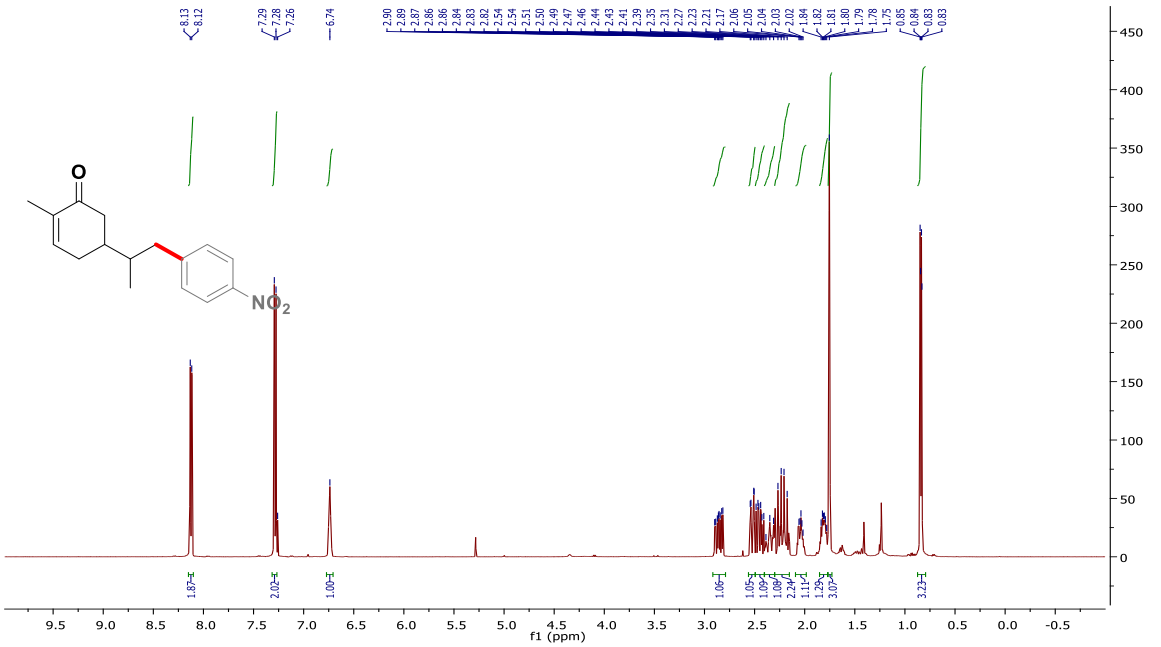


Figure 86: ^{1}H NMR 2-methyl-5-(1-(4-nitrophenyl)propan-2-yl)cyclohex-2-en-1-one (**42**)

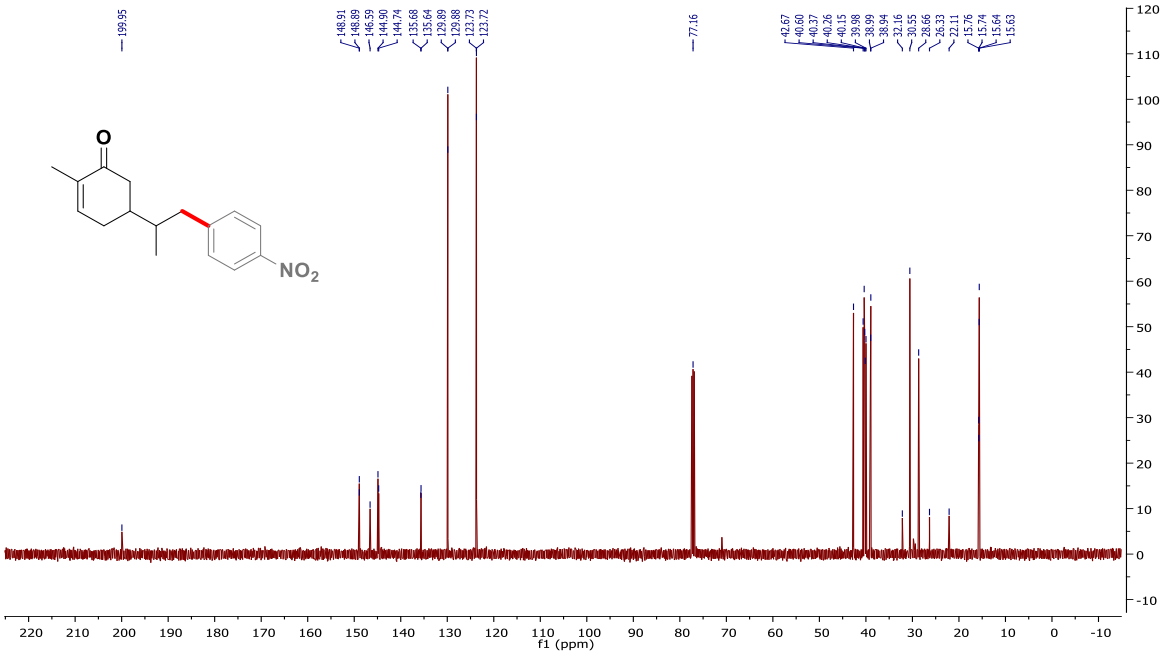


Figure 87: ^{13}C NMR 2-methyl-5-(1-(4-nitrophenyl)propan-2-yl)cyclohex-2-en-1-one (**42**)

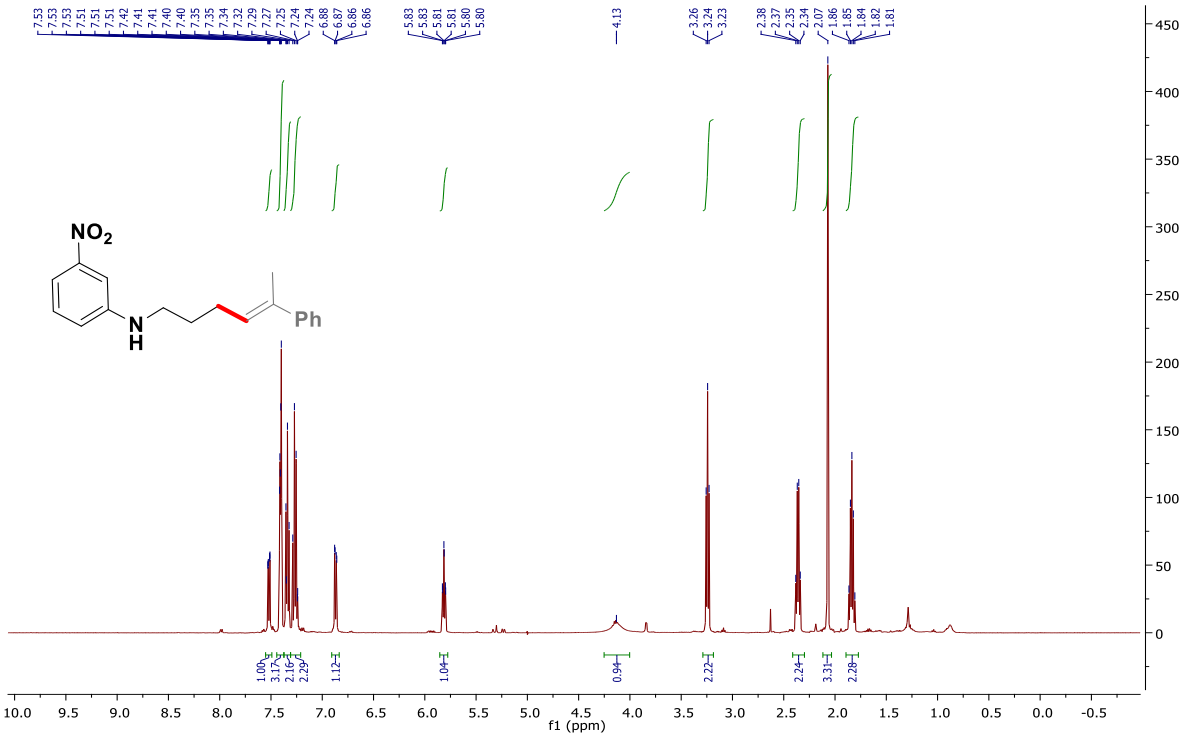


Figure 88: [1] H NMR (E)-3-nitro-N-(5-phenylhex-4-en-1-yl)aniline (**43**)

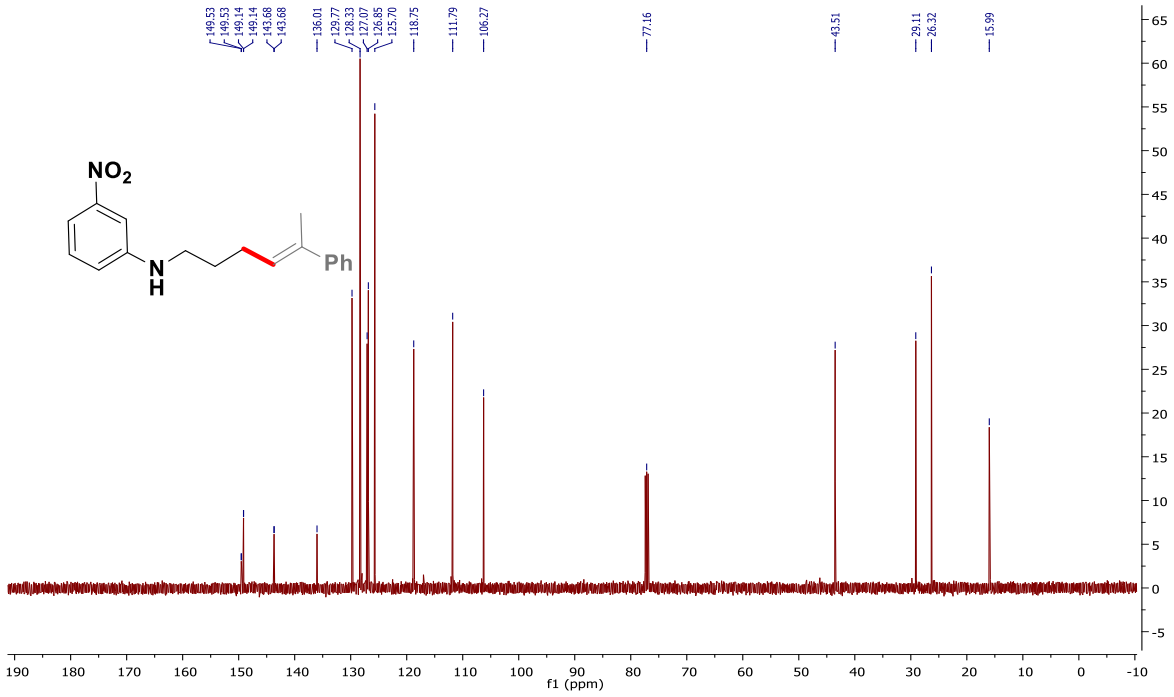


Figure 89: [1] H NMR (E)-3-nitro-N-(5-phenylhex-4-en-1-yl)aniline (**43**)

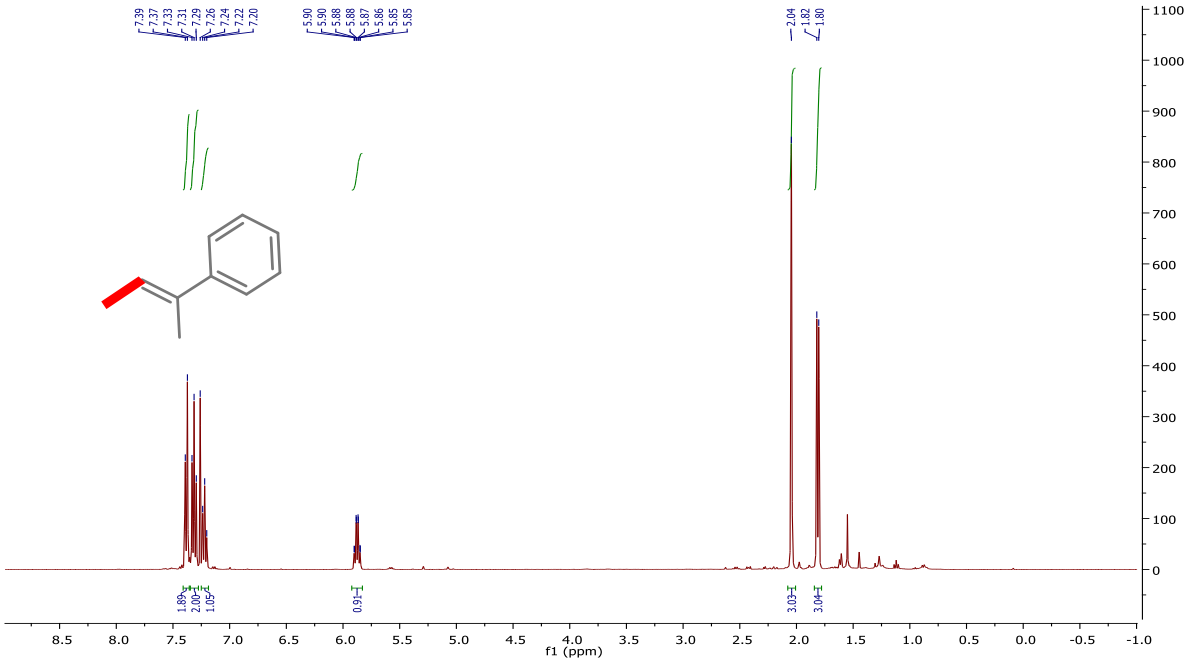


Figure 90: ^{1}H NMR (E)-but-2-en-2-ylbenzene (**44**)

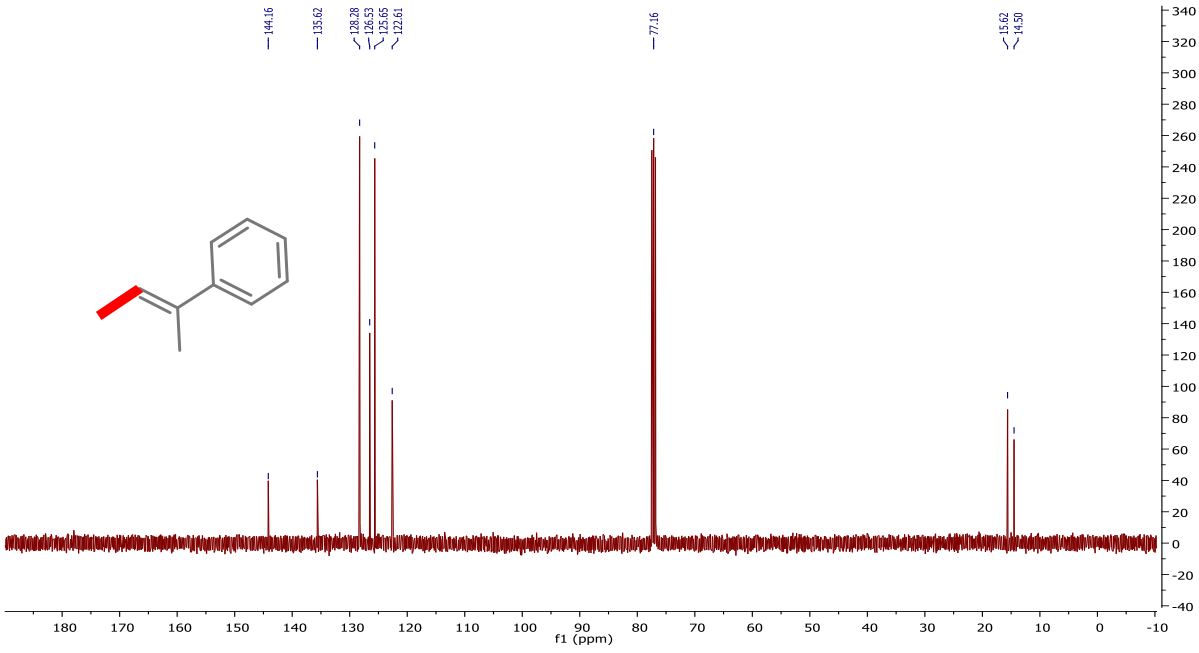


Figure 91: ^{13}C NMR (E)-but-2-en-2-ylbenzene (**44**)

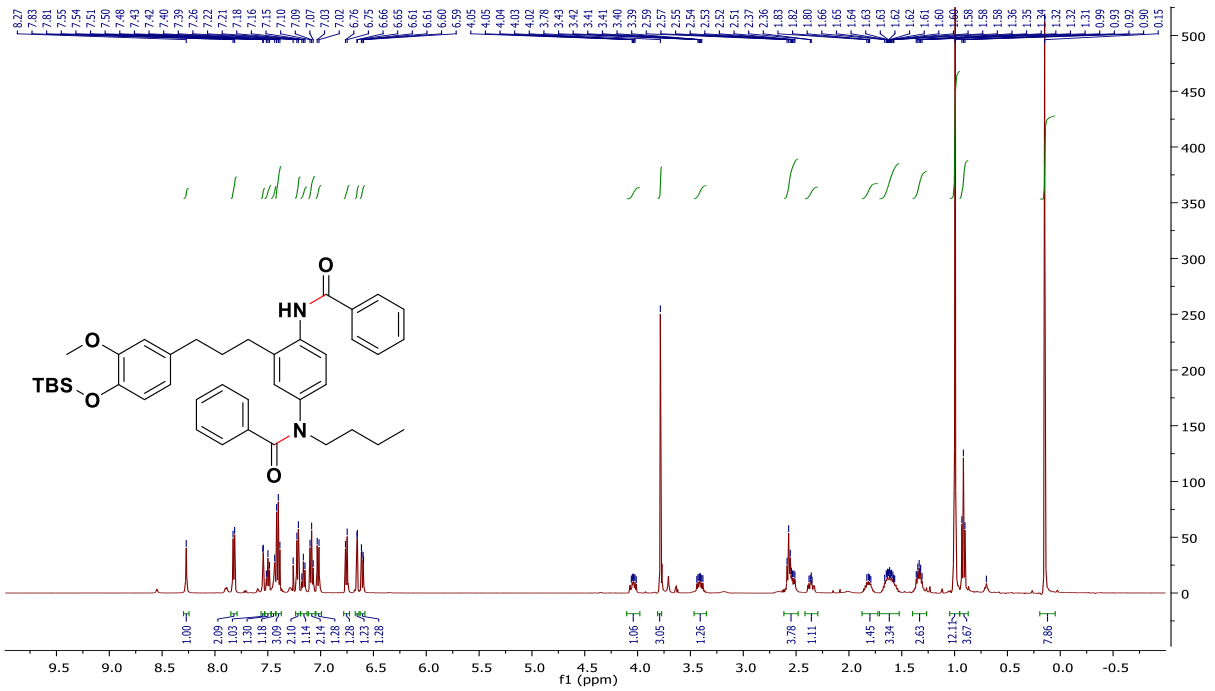


Figure 92: ^{1}H N-(4-benzamido-3-(3-(4-((tert-butyldimethylsilyl)oxy)-3-methoxyphenyl)propyl)phenyl)-N-butylbenzamide (**45**)

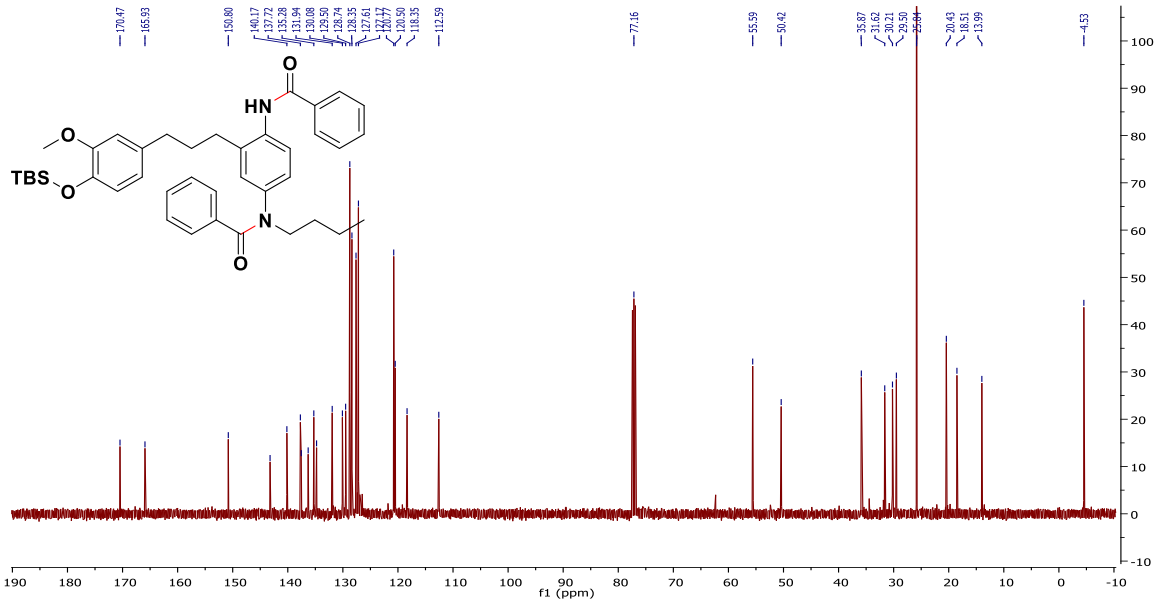


Figure 93: ^{13}C N-(4-benzamido-3-(3-(4-((tert-butyldimethylsilyl)oxy)-3-methoxyphenyl)propyl)phenyl)-N-butylbenzamide (**45**)

III. Development of a Low-Foaming Surfactant for Organic Synthesis in Water

3.1 Personal Accounts

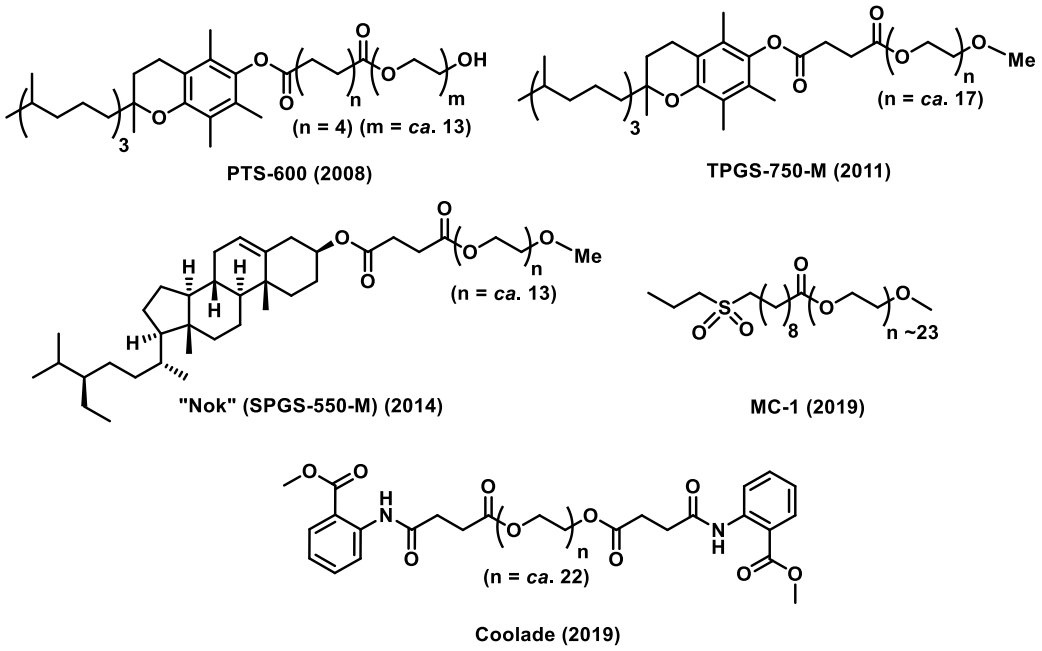
After I joined the group in January 2016, I worked on two scale-up examples of S_NAr reactions in water, producing two examples on 10 g scale. This experience turned out to be extremely useful in learning what can happen when trying to scale reactions in water. And more specifically what the problems and solutions might be to these issues. This was a crash course in solubility, co-solvent selection, and particle size. Somewhere around June I announced to Bruce that I had finished the two examples (in this I was mistaken, the lab work for this project was not over yet), so the obvious thing to do was to start a new project. "So what are we going to do next?" or something to this effect was what I was asked, to which I could only think that as a 1st year grad student I had no idea how to plan a new project. So I was given the task of developing a new generation of surfactant(s) for synthesis in water. The only real directive I was given was to somehow incorporate an amide or "DMF-like" or sulfoxide or "DMSO-like" moiety into the surfactant in hopes of improving solubility of reagents and catalysts. And with that, I sat at my desk for the first 2 weeks of summer and thought about what to do. After asking 3 different lab mates for ideas about how to proceed and given 3 completely different directions, I opted to try several very different approaches and hope that one of them was successful.

3.2 Introduction

This concept of designing surfactants specifically for synthesis in water was not new at this point. And in the years since this project began, several new additions have been made as well. Several "designer surfactants" specifically meant for organic synthesis in water have been published by our group. At various points, some other lab mates have dipped their toes in the area of new surfactant synthesis as well, some of these efforts

remaining unpublished. As an overall history of these efforts (Scheme 1) in 2008, the surfactant PTS[67] as applied to organic reactions in water,[68] TPGS-750-M was published in 2011,[69] and SPGS-550-M (Nok)[70], and two new surfactants in 2019 MC-1[71] and Coolade.[72]

Scheme 1: Surfactants published by Lipshutz group for organic synthesis in water



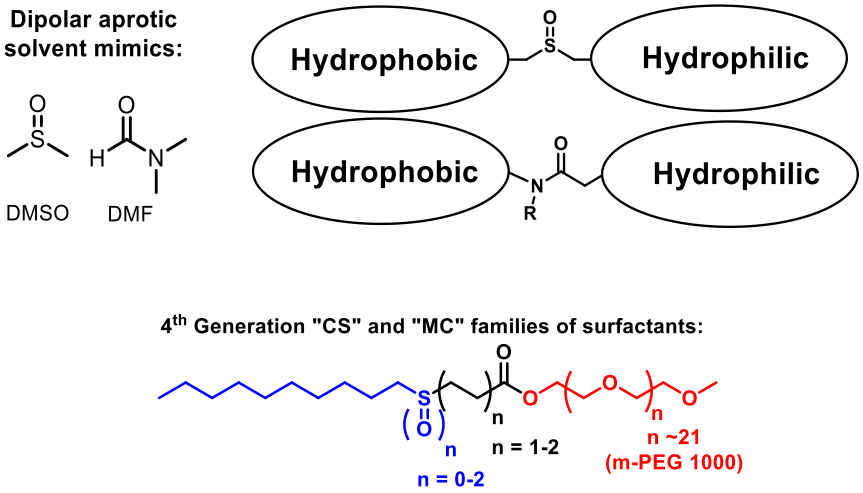
PTS-600, TPGS-750-M, and SPGS-550-M ("Nok") can be considered "multi-purpose" surfactants meant for various types of reactions, in order to accommodate as many classes

[67] H. Borowy-Borowski, M. Sikorska-Walker, P. R. Walker, Water-Soluble Compositions of Bioactive Lipophilic Compounds, US6045826A, 2000.
[68] Lipshutz, B. H.; Ghorai, S. *Aldrichimica Acta* **2008**, 41, 59-86.
[69] Lipshutz, B. H.; Ghorai, S.; Abela, A. R.; Moser, R.; Nishikata, T.; Duplais, C.; Krasovskiy, A.; Gaston, R. D.; Gadwood, R. C. *J. Org. Chem.* **2011**, *76*, 4379–4391.
[70] Klumphu, P.; Lipshutz, B. H. *J. Org. Chem.* **2014**, *79*, 888–900.
[71] Cortes-Clerget, M.; Spink, S. E.; Gallagher, G. P.; Chaisemartin, L.; Filaire, E.; Berthon, J.-Y.; Lipshutz, B. H. *Green Chem.* **2019**, *21*, 2610–2614.
[72] Lee, N. R.; Cortes-Clerget, M.; Wood, A. B.; Lippincott, D. J.; Pang, H.; Moghadam, F. A.; Gallou, F.; Lipshutz, B. H. *ChemSusChem* **2019**, *12*, 3159–3165.

of reactions as possible. However, the two newer surfactants MC-1 and Coolade were both published as special-purpose surfactants. MC-1 was designed for the application of amide bond coupling or more specifically peptide coupling. Coolade was published as a low-foaming surfactant in response to a need identified in several new methodologies in micellar media, and the first "gemini" type surfactant developed in Lipshutz group specifically for synthesis in water. However, the beginnings of this project had nothing to do with foaming, it was later identified as an issue, which resulted in the development of this surfactant.

The initial goal of this surfactant development project was to impart greater solubilizing properties to the surfactant itself, by mimicking dipolar aprotic solvents. I was not the first person to work on the "dipolar-aprotic moiety" surfactant project, two previous visiting students had worked on this project. As a starting place I was given the master's thesis of Gregory Peter Ghallager, who had developed a family of six variants of sulfoxide-containing surfactants known as the "CS" surfactants. The basis of this approach was to change both the oxidation state of sulfur as well as the linker length to alter the solubilizing properties as well as depth into the micellar core of the sulfur.

Scheme 2: Project directive and prior work



Ghallager's work was successful in that he developed one or two surfactants which gave higher yields in test coupling reactions than the competitor TPGS-750-M. This work was not pursued further until years later, when Margery Cortes began work on this idea again, specifically for use in peptide couplings. However, as of 2016 when the project which would result in Coolade began, this effort on sulfur surfactants was not currently in development anymore. So, this work was considered, and a new plan was hatched. Some of the drawbacks identified were that these surfactants involved a 3-step synthesis (Michael addition, esterification, oxidation) to produce the final surfactant. This is unfortunate, because the competitors TPGS-750-M and Nok can both be made in 2 steps, therefore making a 3-step synthesis a significant disadvantage. In addition, synthesis of the "CS/MC" surfactants required esterification using EDC or DCC as coupling reagent. The use of coupling reagents greatly increases the cost and waste generation of the method, and typically requires the use of DCM as solvent, all things we are trying to avoid by using surfactants. In addition, while acrylic acid and MPEG are relatively

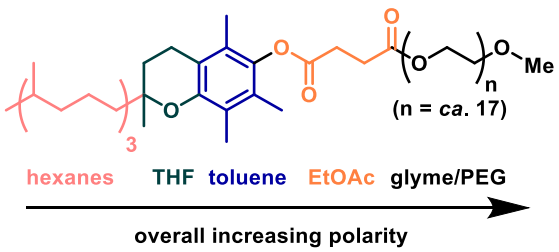
inexpensive, decanethiol is quite expensive. Taking these considerations into account, it seemed reasonable to first draw up a set of synthetic guidelines and requirements before beginning any actual synthesis work. These were assembled in such a manner as to give the final product a good chance of being competitive with TPGS-750-M and Nok surfactants which were currently the standard to beat in our group. In addition, while it is very tempting for the synthetic chemist to begin drawing all sorts of routes, reactions, reagents, and structures and embarking on a complicated synthesis pathway, extensive efforts were made to eliminate complexity in this synthesis project. Namely, rather than building the entire surfactant, I searched for applicable families of molecules with synthetic handles present and preferably with an amide or sulfur present, such that these functionalities did not have to be incorporated. In this search, it became evident that such possible "cores" with sulfur present were not available in any common and inexpensive sources, so the decision was made to pursue amides as the potential "core."

Table 1: Ideal design requirements and considerations

Ideal design requirements	Families of molecules considered for micellar "core"
Inexpensive reagents	Vitamins
Amide present or easily incorporated	Amino Acids
No coupling reagents required	Preservatives
No protection/deprotection sequences	Dietary Supplements
No pyrophoric or toxic reagents	Flavorings
High atom economy in all steps	Lipids
Biodegradable or non-toxic components	Cosmetics ingredients
2-step synthesis at most	Petroleum derivatives/byproducts

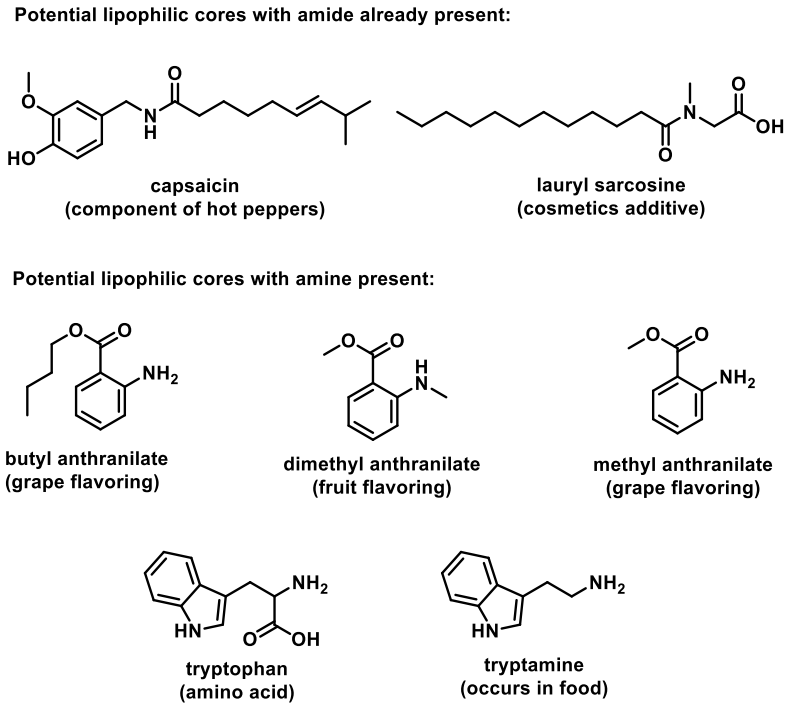
A list of possible "cores" was assembled, looking to the previous successes with PTS-600 and TPGS-750-M. It was hypothesized that vitamin E was a particularly good core because of the presence of a long hydrocarbon tail which mimics hexanes, an oxygen containing ring which mimics THF, a benzene ring which mimics toluene, a linker which looks a lot like ethyl acetate and of course PEG looking like PEG or perhaps diglyme (Scheme 3). While this may be an oversimplification, and supramolecular organization into micelles effects the properties, it is a helpful representation to view the surfactant this way. Because few of the compounds we work with are soluble in hexanes, it was reasoned that the hydrocarbon tail might not be particularly useful. However, many compounds are soluble in toluene and ethyl acetate, so an emphasis was placed on compounds containing aromatic rings and potentially esters or ethers.

Scheme 3: Regions of TPGS-750-M which could act like solvents

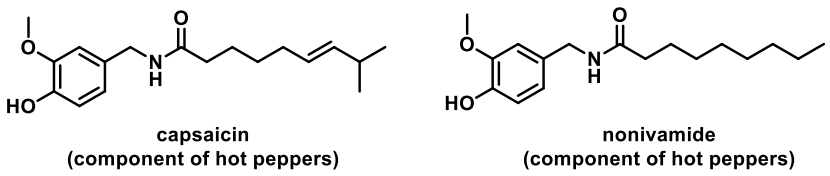


Several potential lipophilic "cores" were identified from food components, preservatives, and flavorings, and amino acid derivatives. All cases had a synthetic "handle" present with which to further functionalize and eventually incorporate PEG. These were deliberately picked from widely varying sources, and with widely varying appearances in order to cover as much ground as possible (Scheme 4). While two of these contained amides already present, it was reasoned that a simple way to produce an amide would be to react an amine with succinic anhydride in order to furnish the amide without requiring expensive and waste-producing coupling reagents.

Scheme 4: Potential lipophilic "cores" identified

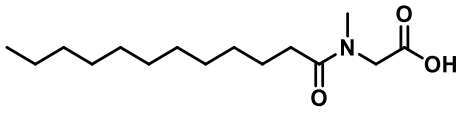


Brief description of various potential "cores" and reasoning for use



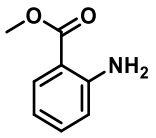
Capsaicinoids are a family of compounds responsible for the spicy flavor of chili peppers. Capsaicin itself is typically extracted from peppers as a mixture of capsaicinoids in ~60% capsaicin purity. Nonivamide is another naturally occurring capsaicinoid, but is also produced synthetically and sold as "synthetic capsaicin." This core is attractive due to the presence of alkyl chain, amide, aromatic, and a phenolic handle. Therefore, the same synthetic sequence/conditions used for TPGS-750-M were applied to this case, which worked well. Unfortunately, though small amounts (i.e. 20 g) could be obtained relatively

inexpensively ($30), bulk quotes for multi-kilo amounts still were unreasonably expensive (i.e. ~200$/kg). While testing the resulting surfactant in the study was useful for gauging how variation on the hydrophobic core would influence the surfactant, this was ultimately deemed too expensive to be a reasonable alternative to tocopherol as a core. And as a final note, possessing 9,200,000 SHU on the Scoville scale makes this a potent irritant and somewhat hinders lab use due to the tendency to produce a pepper-spray like aroma/effect when handling and using in reactions. One can only imagine what factory scale productions of this material must entail to avoid exposure.

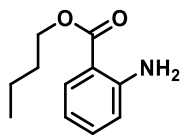


Lauryl Sarcosine
(cosmetics ingredient)

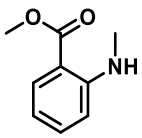
Sodium lauryl sarcosinate is an anionic surfactant which is widely incorporated in cosmetics including toothpaste. As a rough measure of toxicity, this indicates that it should have a very low probability of human toxicity. In addition, because it is a commodity chemical, it is extremely cheap (<10$/Kg). This core is desirable because it has an amide present as well as a "linker" and carboxylic acid already present. This enables a 1-step synthesis of a surfactant, which is far better than a 2-step synthesis required for other surfactants.



methyl anthranilate
(grape flavoring)



butyl anthranilate
(grape/fruit flavoring)



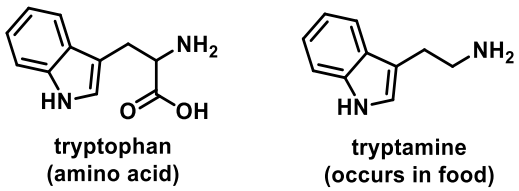
dimethyl anthranilate
(grape/fruit flavoring)

While perusing various food, flavoring, and perfuming ingredients, the anthranilic acid-based family of flavorings and fragrance ingredients stood out. These compounds fit a number of the requirements including being cheap, non-toxic, possessing functional handles, and aromatic rings. However, both methyl anthranilate as well as dimethyl anthranilate both lack any substantial hydrocarbon tail, so would be very unconventional and possibly ineffective for use as a surfactant core. Butyl anthranilate was the only commercially available member which possessed anything resembling a non-polar "tail". These family of molecules were considered mostly as a "what if" possibility, just to see if they would actually be useful as a surfactant core and thus be able to support micelle formation. It was also reasoned that while the presence of an extensive hydrocarbon tail likely helps form a micelle, these hexanes-like tails might not actually be all that beneficial to solubility of reagents and catalysts. Many of the substrates and catalysts used in our reactions are poorly soluble in hexanes, so perhaps this hydrocarbon tail isn't really all that beneficial. While all surfactants synthesized in the group to date have incorporated some sort of extensive hydrocarbon tail, the idea of testing a surfactant with a far less lipophilic component is interesting from several perspectives. Using a less lipophilic portion would test several items: whether a micelle would even form, what the effect would be on solubilization and reaction of substrates, and various properties related to its HLB; this last consideration became extremely important during this study. It is worth a further description of these compounds:

Methyl anthranilate is a naturally occurring component of grapes.[73] It is produced in huge quantities synthetically and is very inexpensive (<5$/kg). This molecule finds diverse

[73] Moio, L.; Etievant, P. X. *Am J Enol Vitic.* **1995**, *46*, 392–398.

uses in the food industry as grape scent/flavoring[74] (an indication of its low toxicity), as well as the surprising application as the active ingredient in bird repellants used to deter nuisance birds such as Canadian geese and crows from places like golf courses and food crops. Butyl anthranilate is used as a food flavoring similar to methyl anthranilate. It is 3-5x as expensive as methyl anthranilate, which puts it in the realm of tocopherol in terms of price (25-30$/kg). This core was included to test the effect of increasing the lipophilicity of the core relative to methyl anthranilate. While anthranilic acid could be used to synthesize an ester of any length tail desirable, it was decided to stick to only commercially available cores in order to keep the synthesis to 2 steps or less. Dimethyl anthranilate is another food flavoring/scent agent in the anthranilate family, and similar to butyl anthranilate it is 3-5x as expensive as methyl anthranilate. This was included in the study to test the effect of having a tertiary amide or "DMF moiety" (after reaction with succinic anhydride) rather than an amide with a free NH. Unfortunately, this compound was not well behaved in its reaction with succinic anhydride and surprisingly gave an unresolvable tarry mixture of products and was never fully incorporated into a surfactant for testing.



Both tryptophan and tryptamine are naturally occurring in foods and hence of low toxicity. Both have the option of additional functionality and "tuning" because of the

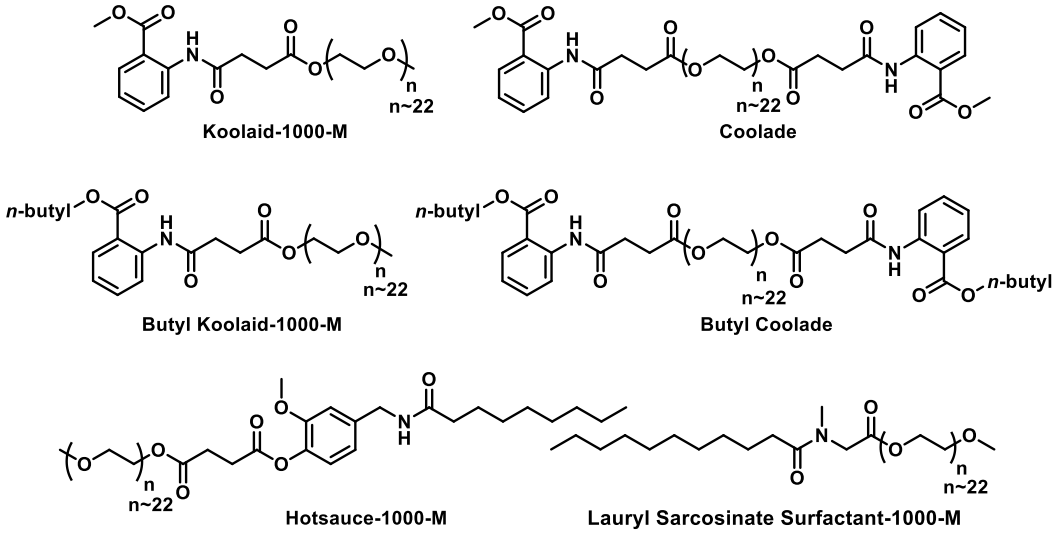
[74] Scientific Opinion on the safety and efficacy of anthranilate derivatives (chemical group 27) when used as flavourings for all animal species. European Food Safety Authority (EFSA), EFSA Journal 2008, 6, 856.

presence of two or more synthetic handles. The initial concept was to further alkylate the indole NH and amino functionalities of tryptophan to obtain a desired hydrophobicity followed by esterification to produce the final surfactant. Tryptophan proved difficult to work with, and functionalization and isolation was not convenient due to its acid/base properties. To eliminate its zwitterionic nature, tryptamine was screened as an alternative to tryptophan. While reaction with succinic anhydride proved effective, esterification of the resulting carboxylic acid with MPEG derivatives was very messy and difficult to handle, and was thus abandoned.

3.3 New surfactants synthesized

In all, about ten new surfactants were synthesized, based on several "cores." These surfactants were synthesized over the course of approximately one year, and were tested to varying degrees. The six new surfactants studied in some depth are shown in Scheme 5 below. The naming of these went through various phases, but they will be referred to using the designations in Scheme 5 below.

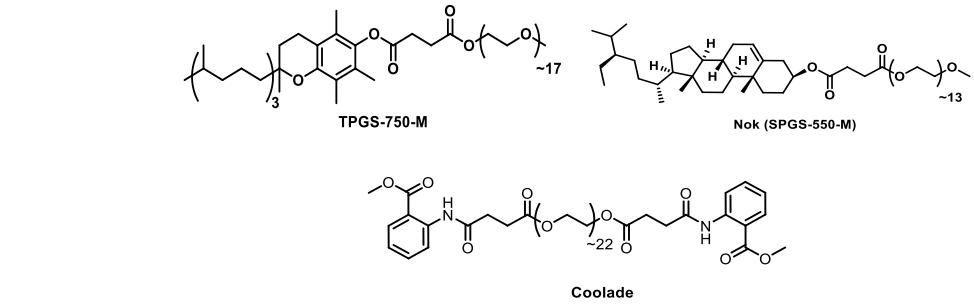
Scheme 5: Library of new surfactants synthesized



While the initial purpose of the project was to produce a new generation, multi-purpose surfactant to potentially replace TPGS-750-M and Nok, this direction changed somewhat. Out of this collection of different surfactants, Coolade became the most promising and was studied in the most depth. An explanation of the choice of this surfactant and its study is best started with a discussion of some of the physical properties noted of this surfactant.

3.4 Physical properties

During the development of the new surfactants, attention was paid to a number of aspects of surfactant behavior. Koolaid-1000-M and Hotsauce-1000-M were the first two to be analyzed for the presence of micelles in aqueous solution by dynamic light scattering (DLS), and indeed, both produced micelles. The DLS measurements of Koolaid-1000-M showed micelle formation, but the micelle size was very much not conclusive, giving micelle sizes of 60-300 nm based on the conditions used for DLS. Later, Coolade was synthesized, and analyzed by TEM to get a better idea of micelle size and appearance. The results of this are interesting in that using three different surfactants resulted in three completely different appearances or morphologies (Figure 1).



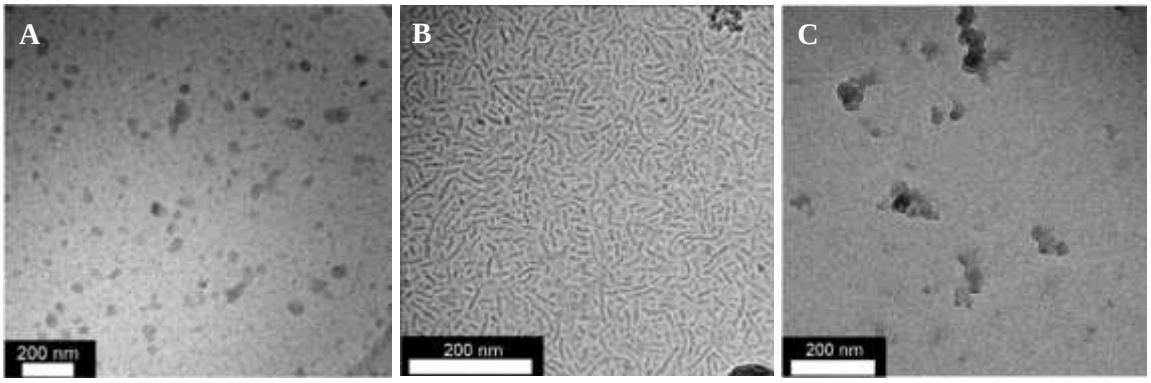


Figure 1: Cryo-TEM of surfactant-derived micelles (A) TPGS-750-M, (B) SPGS-550-M, (C) Coolade

Micelles formed from each of these three surfactants have dramatically different morphologies. While TPGS-750-M appears to form spherical micelles, SPGS-550-M produces “worm-like” structures, and Coolade produces aggregates of spherical micelles.

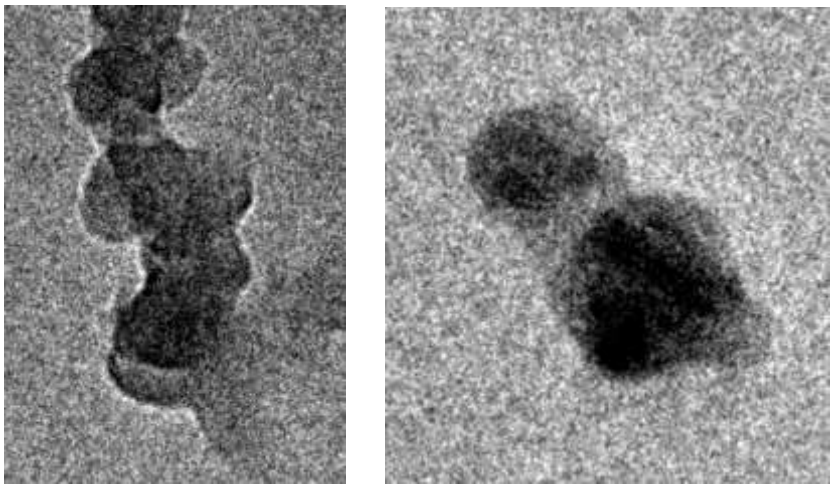
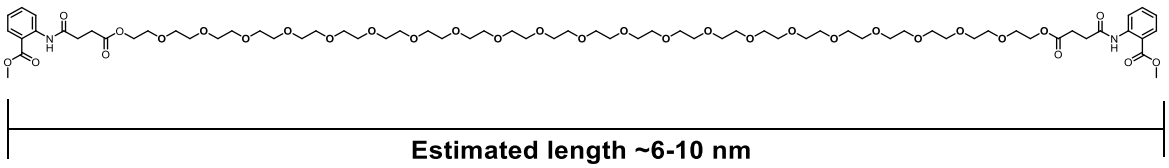


Figure 2: Magnified images of surfactant micelles derived from Coolade

In magnifying these images, it appears that aggregates of somewhat spherical micelles seem to have formed. The TEM aqueous solution is at 1/100th the concentration (0.02 wt % vs. 2 wt %) actually used in a reaction. Because aggregation is seen at this low concentration, it is possible that at 2 wt % the whole solution might be "cross-linked" with these aggregates, making a "micelle-network." An explanation of the clumping/aggregation behavior might be explained by considering the surfactant structure and length (Figure 2).

Scheme 6: Estimation of total length of surfactant



An attempt was made to estimate the total length of the Coolade surfactant. Estimating the length of PEG is not necessarily a trivial affair due to the typically non-linear conformation that PEG is believed to assume in solution. Various looping, coiling, twisting phenomena have been attributed to PEG derivatives in water, which is complicated even further when other additives like salts or when other organics are involved. Based on the length of the ethylene oxide unit gives something in the range of 6-10 nm of the surfactant length if fully extended. This is an overly simplified representation, and in reality, few or none of the actual molecules are likely to exist in solution in a linear fashion as shown.

However, it is interesting to note that in the magnified images, it appears that bridging between micelles is occurring, likely due to the “double-ended” or “gemini” type of structure present.

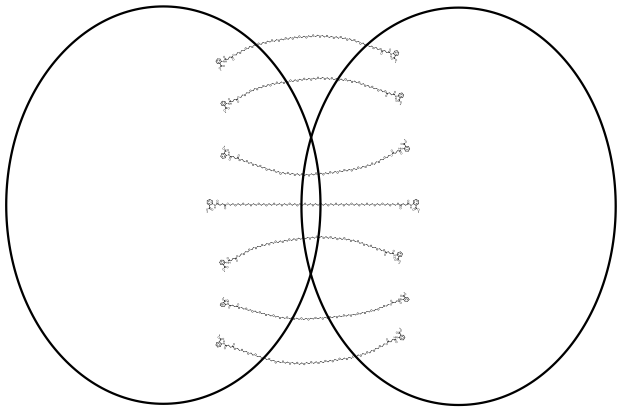


Figure 3: Possible explanation for aggregate formation using Coolade

However, some of this apparent bridging looks like it may be larger than the 6-10 nm longest possible length of surfactant. In the case of the synthesis of this surfactant by Fisher esterification, a number of byproducts were also noted, which were attributed to trans-esterified mixtures. These trans-esterified mixtures have the possibility to produce larger surfactant molecules, this might contribute to the bridging effect.

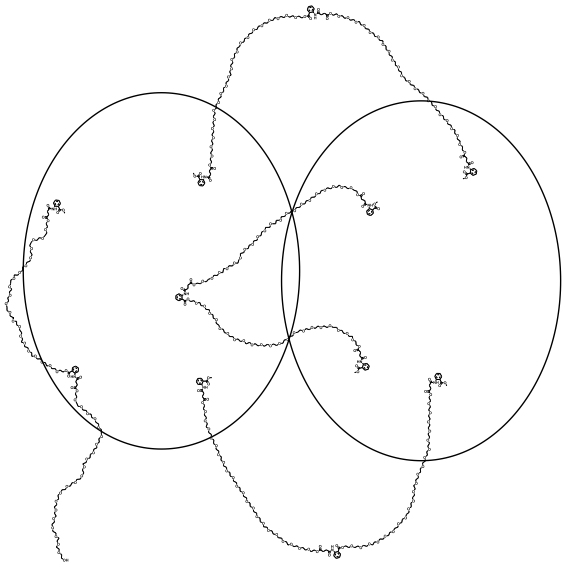


Figure 4: Possible explanation for aggregate formation using trans-esterified mixtures of Coolade

3.5 Surfactant foaming behavior

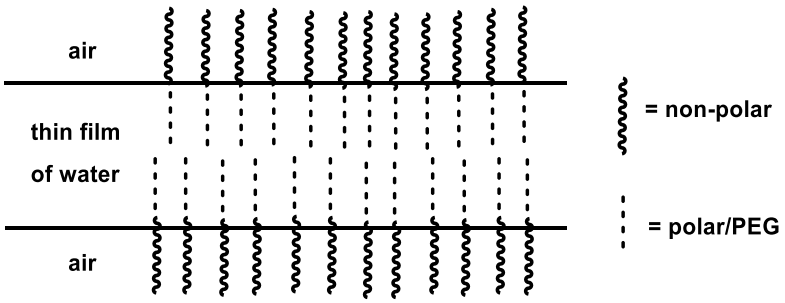
Foaming is an extremely well-studied field in surfactant chemistry. Entire textbooks are available which are dedicated specifically to this topic, such as the >400 page volume entitled "*Bubble and Foam Chemistry*".[75] The *Journal of Surfactants and Detergents* is a peer reviewed journal where new surfactants and their applications are published, one of the most common topics addressed in their articles aside from the surfactant's synthesis and surface tension is the foaming properties of new surfactants. In our use of surfactants, in most synthetic methods utilized, little-to-no thought is dedicated to the foaming properties. However, during my studies of the effect of co-solvent on reaction performance and simultaneous project involving the development of new surfactants for organic synthesis, this aspect of surfactants became very relevant. It was found that

[75] Pugh, R. J. *Bubble and Foam Chemistry*; Cambridge University Press, 2016.

particularly in the case of reactions using $NaBH_4$ as a reducing agent in combination with various NP catalysts, the H_2 produced frequently led to very unruly amounts of foam associated with the aqueous surfactant solution. After instances of cleaning up $NaBH_4$/NP nitro reduction reaction mixtures from hot plates, out of Schlenk manifold lines, off the walls of my fume hood, a solution to this problem was found. Of the ~10 new surfactants prepared, Coolade had the curious property that it produced almost no lasting foam. While these new surfactants were prepared in the hopes of developing an improved surfactant relative to PTS, SPGS-550-M, and TPGS-750-M, this project was instead directed towards the remediation of this problem of excess foaming.

The degree of surfactant foaming is most simply correlated to the alkyl chain or non-polar chain length of the surfactant. This effect has been studied by synthesizing analogs varying only in the length of their non-polar tails.[76] A longer alkyl chain corresponds to higher foam volume and longevity. Foam or bubbles can be envisioned as a bilayer where a thin film of water is coated with surfactant.

Scheme 7: Representation of bilayer nature of thin films present in bubbles and foaming



[76] Zhou, Y.; Wang, S.; Lv, M.; Niu, J.; Xu, B. *Journal of Surfactants and Detergents* **2017**, *20*, 623–630.

Multiple phenomena govern the commonly observed and measured aspects of foam such as volume, longevity, and bubble size/shape. Surface tension, elasticity, drainage rate, Ostwalt ripening, intermolecular interactions between nonpolar "tails" etc. are some of the most commonly invoked processes to account for this.[77] To further complicate this issue, in our usual applications we are not studying the surfactant solution alone, but rather complex mixtures of starting materials, various salts, products, catalysts, as well as soluble, insoluble, and in-between materials as well as frequently observing bi-and-tri-phasic mixtures in reactions. While various standardized methods of measuring foaming exist, such as the Ross-Miles,[78] Winding, and Waring, and Foam Scan tests,[79] these are almost always performed on dilute solutions of the surfactant in water, without additives. While a version of the Ross-Miles test was attempted as a comparison between Coolade and TPGS-750-M, the foam in the Coolade trial collapsed too rapidly and therefore the test criteria wasn't fulfilled. Therefore, without deliberately trying to ignore the established methods of surfactant foaming measurement, this work was conducted using a more "hands-on" approach, where foaming was characterized qualitatively in solutions and reaction mixtures in the same concentrations and proportions of reagents characteristic of the reaction mixtures in which these reactions are typically run.

[77] Sporck, C. R. *J. Am. Oil Chem. Soc.* **1953**, *30*, 190–193.
[78] (a) Miles, G. D. *Oil and Soap* **1941**, *18*, 99–102. (b) Rosen, M. J.; Solash, J. *Journal of the American Oil Chemists' Society* **1969**, *46*, 399–402.
[79] Pugh, R. J. *Bubble and Foam Chemistry*; Cambridge University Press, **2016**, pg 401.

Figure 5: Shaken samples of 2 wt % surfactant aqueous solutions: (A) SDS, (B) PTS, (C) Nok, (D) TPGS-750-M, (E) Coolade

As a simple qualitative test of surfactant foaming, by either vigorously vortexing or shaking surfactant solutions to introduce air and produce foaming, the extent of foam generated can be observed. Several relevant surfactants were tested, including the common surfactant SDS, as well as several generations of "designer" nonionic surfactants PTS, SPGS-550-M ("Nok"), TPGS-750-M, and the new surfactant Coolade. In these trials only Coolade produced no lasting foam; however, some interesting notes were made about the others. Each of the other surfactants produce markedly different foam volume and appearance. The size of bubbles produced are different in each case. Overall, due to lack of an extensive hydrocarbon tail, Coolade produces no lasting foam.

While the foaming of the surfactant solution itself is somewhat important during the preparation of degassed solutions of surfactants for air-sensitive reactions, the main concern of surfactant foaming for our purposes is in active reaction mixtures themselves. Therefore, foam-producing reagent combinations were mixed to observe foaming behavior in each surfactant. In these cases, reagents and surfactant solutions were mixed

in the same amounts and proportions used for an actual reaction, but without adding the substrate itself.

Scheme 8: Foaming test using Fe/ppm Pd/Ni NPs used for aromatic nitro reduction

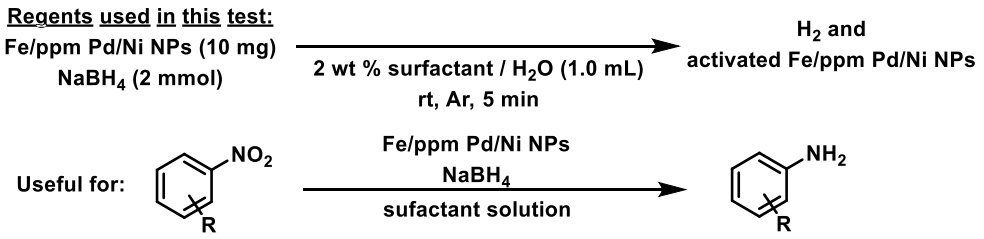


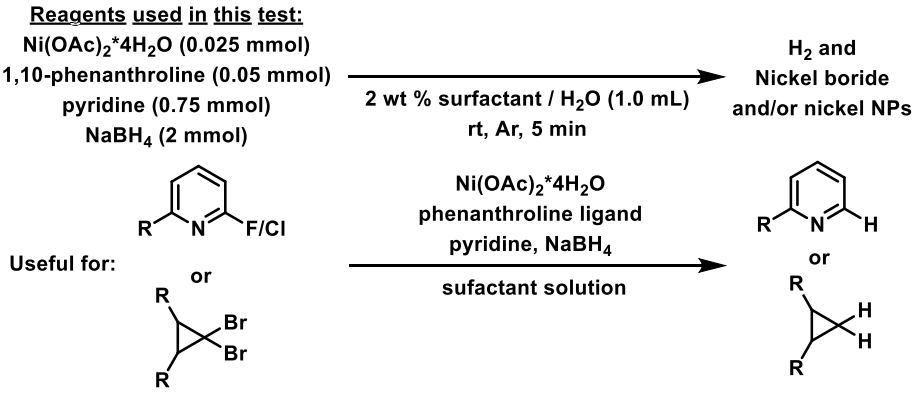
Figure 6: Foaming test using Fe/ppm Pd/Ni NPs using (A) SDS, (B) PTS-600, (C) TPGS-750-M, (D) SPGS-550-E (E) Coolade.

Fe/ppm Pd/Ni nanoparticles (NPs) in conjunction with $NaBH_4$ has been developed as method for aromatic nitro group reduction in a surfactant medium.[80] Upon addition of

[80] (a) Pang, H.; Gallou, F.; Sohn, H.; Camacho-Bunquin, J.; Delferro, M.; Lipshutz, B. H. *Green Chem.* **2018**, *20*, 130–135. (b) Gabriel, C. M.; Parmentier, M.; Riegert, C.; Lanz, M.; Handa, S.; Lipshutz, B. H.; Gallou, F. *Org. Process Res. Dev.* **2017**, *21*, 247–252.

$NaBH_4$ and NPs, a large volume of H_2 is released which causes foaming. As a qualitative test, the typical reagents for a 0.5 mmol scale trial were combined in a large test tube, and the extent of foaming observed. While all surfactants produced foaming (the high-water mark on even the Coolade trial can be seen approximately 1/3 of the way up the test tube), Coolade produces far less and shorter-lived foaming.

Scheme 9: Surfactant foaming test using Ni NP/$NaBH_4$ dehalogenation conditions



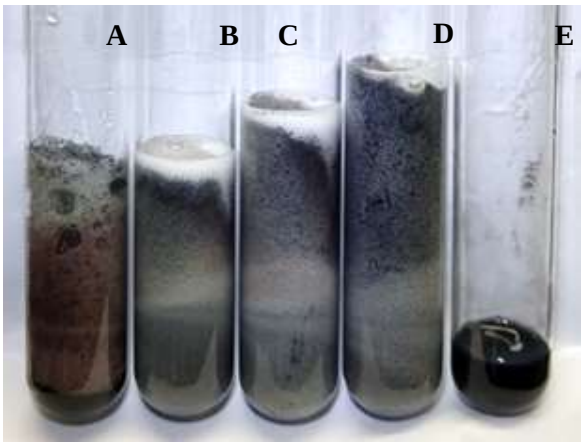


Figure 7: Dehalogenation conditions in: (A) SDS, (B) PTS, (C) TPGS-750-M, (D) SPGS-550-M "Nok" (E) Coolade

The combination of $Ni(OAc)_2$, $NaBH_4$, phenanthroline ligand, and pyridine is used for dehalogenation of 2-chloro and fluoro-pyridine substrates,[81] as well as reduction of *gem*-dibromocyclopropanes.[82] This combination of borohydride with nickel salts produces a nickel boride species.[83] This reaction releases a large amount of hydrogen gas, and subsequent foaming in some surfactant solution. In Scheme 9 above, the reagents for a typical 0.5 mmol scale reduction trial were combined in test tubes and monitored as a qualitative evaluation of foaming produced. While all trials produced some foam during initial gas evolution, Coolade produced the least foam, and the level of foaming decreased almost immediately.

3.6 Temperature & salinity effects

In addition to the relative foam volume produced in each type of surfactant, some other interesting properties were noted. Surfactant solubility is highly temperature dependent, the cloud point and Kraft point are examples of measurements of these phenomena.[84] At temperatures significantly above ambient temperature, surfactant molecules tend to aggregate, producing a cloudy solution and in some cases precipitating from solution.

[81] Isley, N. A.; Wang, Y.; Gallou, F.; Handa, S.; Aue, D. H.; Lipshutz, B. H. *ACS Catal.* **2017**, *7*, 8331–8337.
[82] Wood, A. B.; Cortes-Clerget, M.; Kincaid, J. R. A.; Akkachairin, B.; Singhania, V.; Gallou, F.; Lipshutz, B. H. *Angew. Chem. Int. Ed.* **2020**, *59*, 17587-17593.
[83] (a) Khurana, J. M.; Gogia, A.. *Organic Preparations and Procedures International* **1997**, *29*, 1–32. (b) Hofer, L. J. E.; Shultz, J. F.; Panson, R. D.; Anderson, R. B. *Inorg. Chem.* **1964**, *3* , 1783–1785. (c) Paul, R.; Buisson, P.; Joseph, N. Catalytic Activity of Nickel Borides. *Ind. Eng. Chem.* **1952**, *44*, 1006–1010.
[84] For discussion of cloud and krafft points: Practical Surfactants Science Prof by Steven Abbott https://www.stevenabbott.co.uk/practical-surfactants/cloud-krafft.php (accessed Jun 12, 2020).

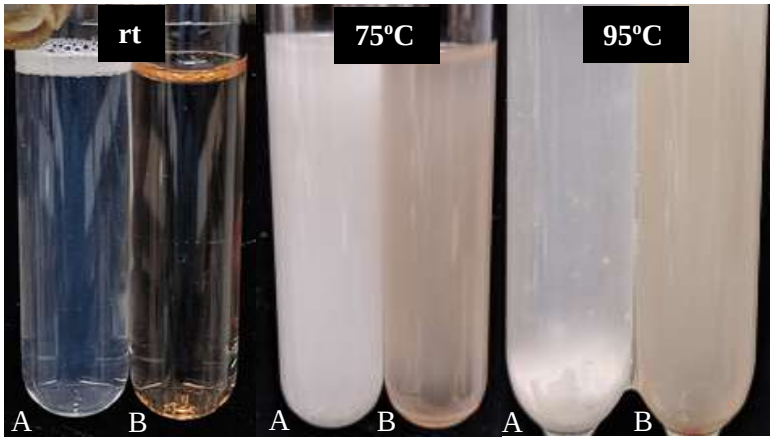


Figure 8: Effect of temperature on surfactant solutions (A) TPGS-750-M, (B) Coolade

While both of these surfactants have a similar cloud point around 70°C, their response to higher temperatures is dramatically different. While TPGS-750-M precipitates out of solution when exposed to high temperatures, Coolade produces only some "oiling out".

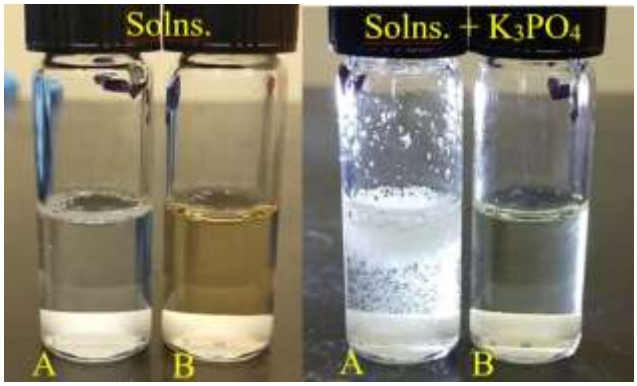


Figure 9: Effect of salinity from K_3PO_4 on surfactant solutions using (A) TPGS-750-M, (B) Coolade

Salinity dependent solubility of surfactants in aqueous solution is also a well-studied topic. The presence of salts is thought to cause increasing or decreasing ordering of water molecules and thus affect how the water molecules interact with the surfactant, in turn affecting the solubility of the surfactant. This effect can be different for ionic versus

nonionic surfactants (and mixtures thereof), and dependent on the nature of the salt ions whereby some ions are responsible for salting-in and some for salting-out of the surfactant. This salinity dependent solubility is utilized in micellar extraction, where compounds occurring in trace quantities can be concentrated and isolated while trapped in the precipitated surfactant.[85] The degree of ethoxylation of PEG-derived surfactants is correlated to this effect, whereby a greater degree of ethoxylation gives the surfactant greater solubility in higher salinity environments. [86] This can also be viewed from the other direction, by stating that the greater the lipophilic portion of the surfactant, the less soluble the surfactant will be at high salinity. In these tests, conditions were utilized which are typical for Suzuki couplings, S_NAr reactions, and S_N2 displacements in proportions typically used for those reactions. K_3PO_4 (0.5 mmol) was added to 2 wt % surfactant solutions (1.0 mL) and stirred vigorously. While TPGS-750-M precipitates with addition of salts, Coolade remains solubilized. This effect is extremely important in cases of reactions where the product is isolated by filtration. At various times, reactions in surfactant solution produced precipitated products which lend themselves to isolation by filtration rather than extraction with solvent. If the product is filtered and dried, it was always found to contain a large amount of surfactant (visible by the large PEG peak(s) in the NMR). The product typically must be suspended in fresh water and stirred, macerated, ground etc, and filtered again in order to remove residual surfactant. It was noted that Coolade was significantly easier to remove from filter cakes of products than

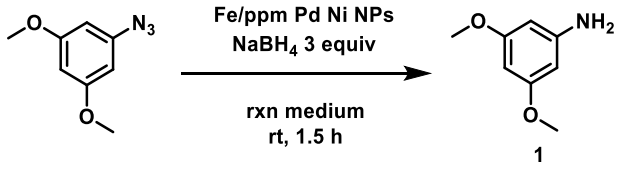
[85] Kiszkiel-Taudul, I.; Starczewska, B.; Karpińska, J.; Kasabuła, M. *J Surfact Deterg* **2017**, *20*, 1401–1409.
[86] (a) Stankova, A. V.; Elokhov, A. M.; Kudryashova, O. S.. *Russ. J. Phys. Chem.* **2018**, *92*, 1386–1391. (b) Amante, J. C.; Scamehorn, J. F.; Harwell, J. H. *J. Colloid Interface Sci.* **1991**, *144*, 243–253. (c) Holtzscherer, C.; Candau, F. *J. Colloid Interface Sci.* **1988**, *125*, 97–110.

TPGS-750-M, likely due to less of the surfactant being precipitated in the product from the start, and the higher solubility at high salinity.

3.7 Surfactant comparison trials: gas producing reactions

The main focus of the publication based on this project was specifically on the application of the new surfactant to reactions which were troublesome due to foaming. During the course of this study, a number of reaction types were screened, some of them were not previously published in this surfactant medium, but the need for as many examples as possible necessitated their development in order to have as many examples as possible. Overall, these reactions are all reduction reactions of some sort, with foaming resulting from the evolution of H_2 gas from the decomposition of $NaBH_4$ over metal catalysts. In addition, reduction of azide compounds using metals like zinc or iron produces gas as well, presumably N_2 and/or H_2.

Table 2: Reduction of an aryl azide in varying reaction medium



Trial	Surfactant/medium	Isolated Yield
NL-3-243.1	2 wt % TPGS-750-M / H_2O	>95%
NL-3-243.2	2 wt % Coolade / H_2O	>95%
NL-3-243.3	H_2O	35%
NL-3-243.4	2 wt % PEG / H_2O	56%

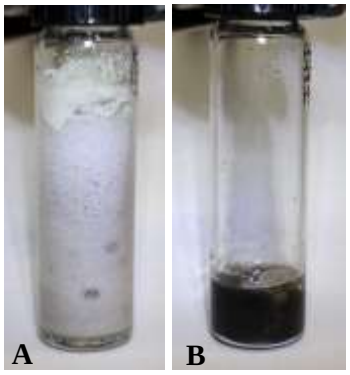
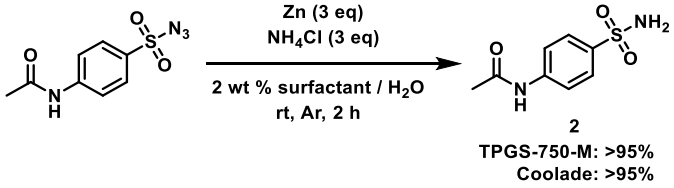
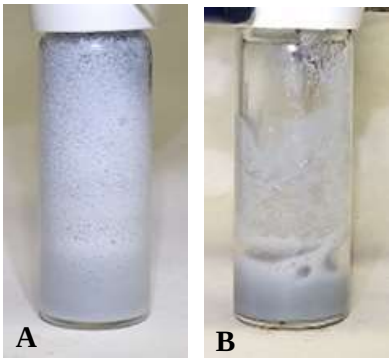


Figure 10: Reaction appearance (A) TPGS-750-M, (B) Coolade

The reduction of an aryl azide (Table 2 and Figure 10) was used as a model gas-evolving reaction. Both TPGS-750-M and Coolade gave essentially quantitative conversion to the desired product. Water alone gave only a small amount of conversion (35% isolated yield) and water + 2 wt % PEG 200 gave slightly more conversion (56%) but failed to reach completion. TPGS-750-M produced a large volume of foam, while the other three trials remained "under control" and did not threaten to escape the reaction vial. Similar results were obtained for sulfonyl azide reduction (Scheme 10 below).

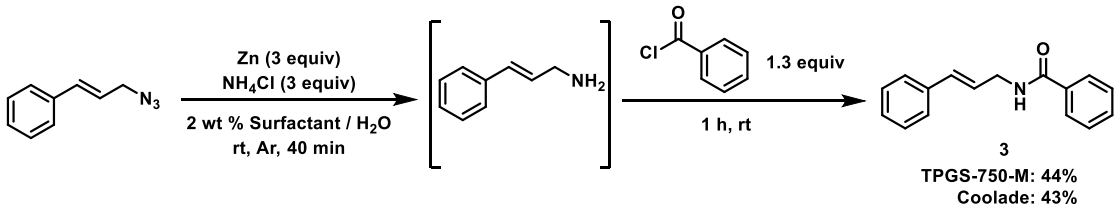
Scheme 10: Comparison trials using sulfonyl azide reduction (A) TPGS-750-M, (B) Coolade





Alkyl/allylic azides are somewhat more challenging to reduce than aryl or sulfonyl azides. The cinnamyl amine product was extremely polar and somewhat volatile, so upon completion of the reduction, benzoyl chloride was added to "cap" the amine as the benzamide. Foaming in this case results presumably from the release of N_2 gas rather than H_2 as in the cases using $NaBH_4$.

Scheme 11: Reduction of an allylic azide in (A) TPGS-750-M, (B) Coolade



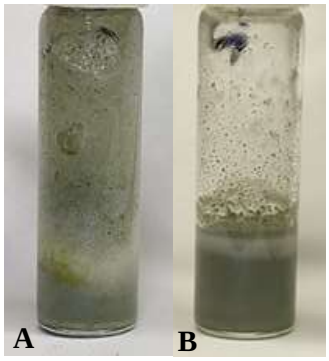


Figure 11: Reduction of cinnamyl azide in (**A**) TPGS-750-M and (**B**) Coolade

A small comparison substrate scope of aryl nitro group reduction reactions was also conducted to compare TPGS-750-M and Coolade. Most cases gave similar results in terms of yields with both surfactants, with product **9** being a notable exception where Coolade performed significantly worse than did TPGS-750-M. Similar to the reduction of aryl azides, the conditions used for reduction of aryl nitro group compounds using $NaBH_4$ and Fe/ppm Pd/Ni NPs produces large volumes of gas and resulting foaming (Figure 12)

Scheme 12: Reduction of aryl nitro compounds via Fe/ppm Pd/Ni NPs and $NaBH_4$

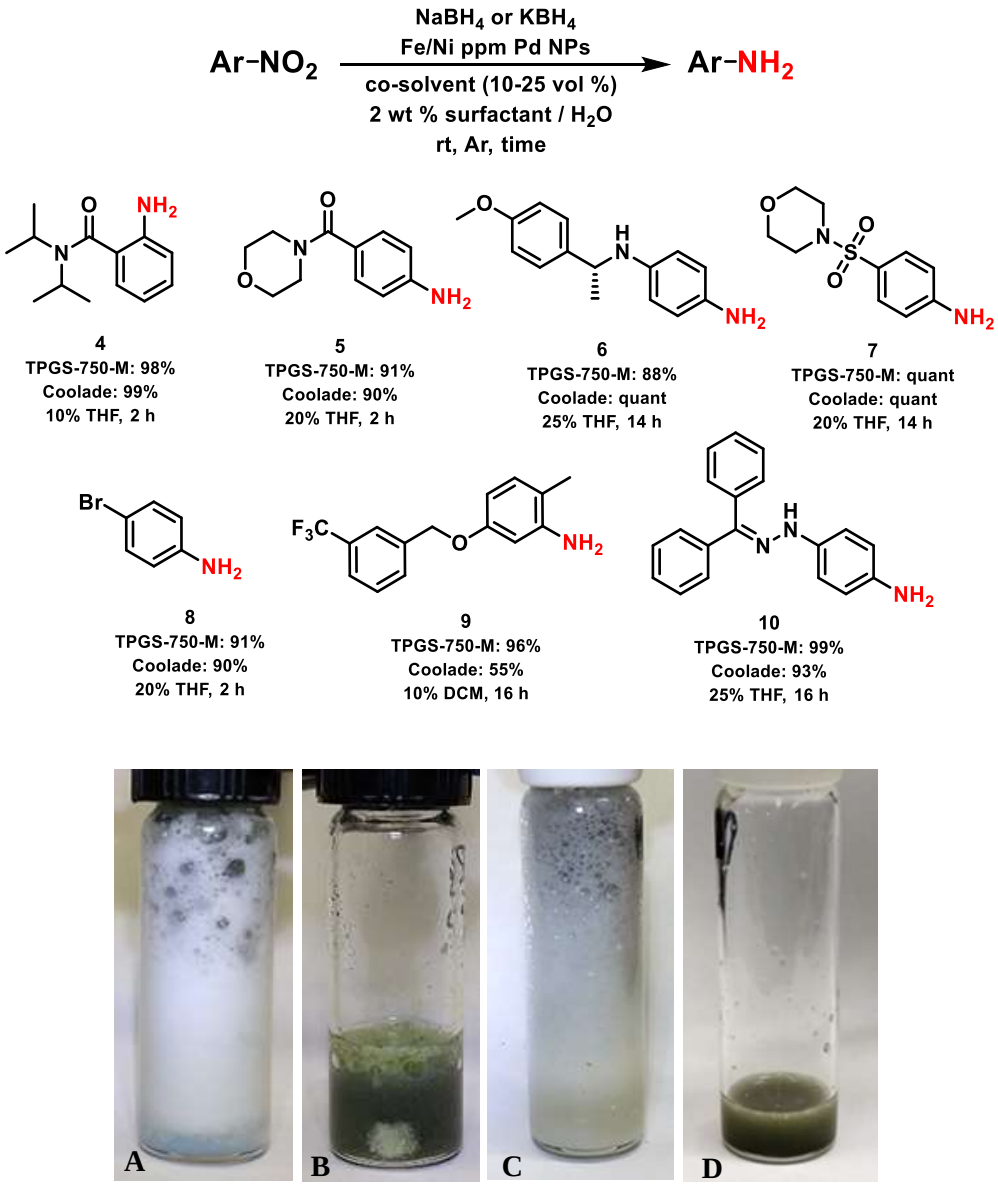
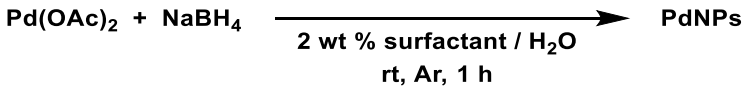


Figure 12: Nitro reduction reaction appearance using 1-chloro-4-nitrobenzene in (A) in TPGS-750-M, (B) Coolade. Nitro reduction appearance using morpholino(4-nitrophenyl)methanone in (C) TPGS-750-M, (D) Coolade.

Scheme 13: Synthesis of Pd NPs for alkyne hydrogenation



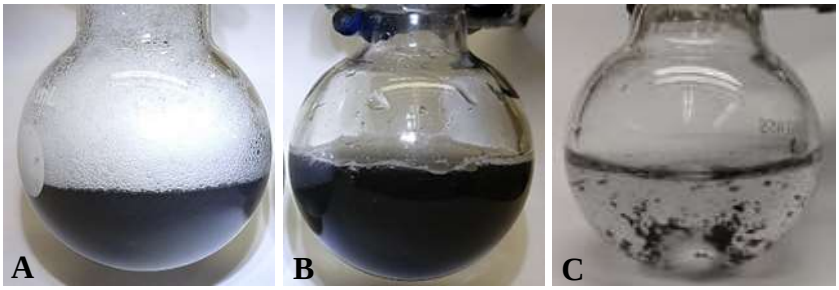


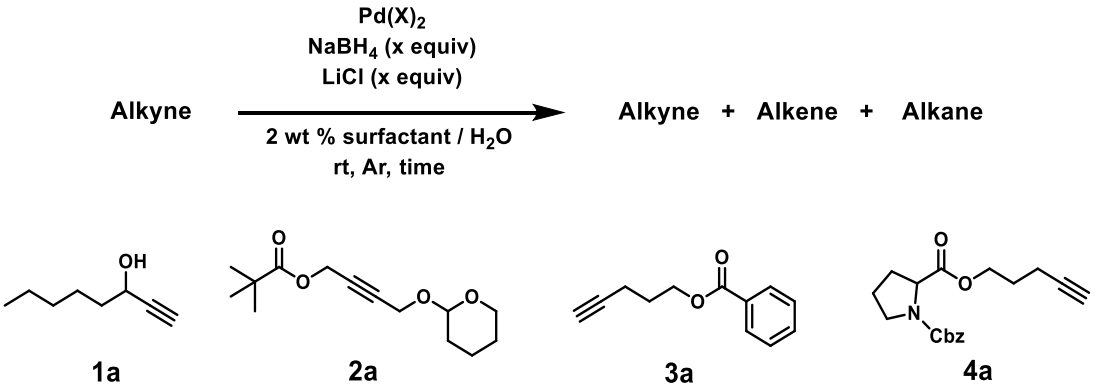
Figure 13: Prepared PdNP solutions using (A) TPGS-750-M, (B) Coolade, (C) water

The action of $NaBH_4$ on $Pd(OAc)_2$ leads to nanoparticles used for semi-hydrogenation of alkynes.[87] A significant amount of foaming results from the preparation of these NPs. In addition, the surfactant appears to help disperse the NP material, as the use of water alone produces a material with a tendency to clump together rapidly (Figure 13 (C)). Some difficulties were seen in obtaining sufficiently disperse NP solutions, where the suspension will remain dispersed for some time after extensive sonication, but always observed was its tendency to "clump" into larger aggregates which cannot be transferred via syringe. Table 3 shows the results of the comparison trials between TPGS-750-M and Coolade as well as water as a control. None of the trials was successful in giving exclusively alkene, possibly due to the above mentioned "clumping" issue. Conditions for semi-hydrogenation (using $Pd(OAc)_2$ in conjunction with LiCl and $NaBH_4$) as well as

[87]Slack, E. D.; Gabriel, C. M.; Lipshutz, B. H. *Angew. Chem. Int. Ed.* **2014**, *53*, 14051–14054.

full-hydrogenation ($PdCl_2$ in conjunction with $NaBH_4$) were taken from procedures in Section 2.2 in the original publication.[21]

Table 3: Surfactant comparison trials using a NP alkyne hydrogenation reaction

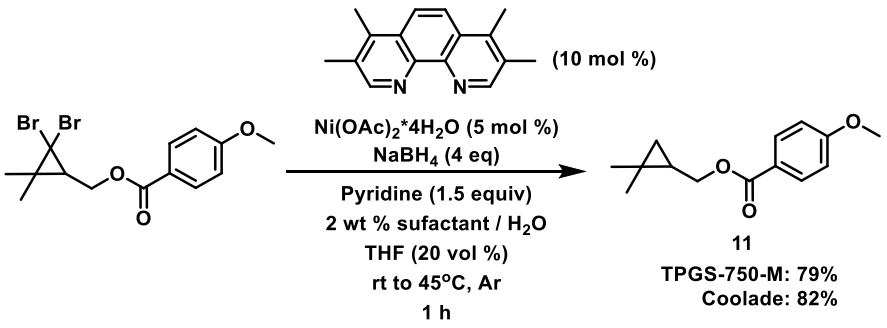


Reaction Conditions							Ratio determined by NMR		
Trial	Alkyne	Surfactant	Catalyst Prep.	Pd source	LiCl (equiv)	$NaBH_4$ (equiv)	Alkyne	Alkene	Alkane
NL-3-206	**1a**	TPGS-750-M	In-situ	$Pd(OAc)_2$	2.2	0.5	0	20	80
NL-3-207	**2a**	TPGS-750-M	In-situ	$Pd(OAc)_2$	2.2	0.5	50	50	0
NL-3-208	**2a**	TPGS-750-M	Bulk soln.	$Pd(OAc)_2$	2.2	0.5	90	10	0
NL-3-209.1	**2a**	TPGS-750-M	In-situ	$PdCl_2$	0	1.0	55	45	0
NL-3-209.2	**2a**	Coolade	In-situ	$PdCl_2$	0	1.0	0	50	50
NL-3-210.1	**2a**	TPGS-750-M	Bulk soln.	$Pd(OAc)_2$	0	0.5	85	15	0
NL-3-210.2	**2a**	Coolade	Bulk soln.	$Pd(OAc)_2$	0	0.5	35	65	0
NL-3-213.1	**3a**	TPGS-750-M	Bulk soln.	$Pd(OAc)_2$	2.0	0.5	50	50	0
NL-3-213.2	**3a**	Coolade	Bulk soln.	$Pd(OAc)_2$	2.0	0.5	0	80	20
NL-3-274.1	**4a**	TPGS-750-M	Bulk soln.	$Pd(OAc)_2$	2.2	0.5	70	20	10
NL-3-274.2	**4a**	Coolade	Bulk soln.	$Pd(OAc)_2$	2.2	0.5	0	75	25
NL-3-274.3	**4a**	TPGS-750-M*	Bulk soln.	$Pd(OAc)_2$	2.2	0.5	60	40	0
NL-3-274.4	**4a**	Coolade	Bulk soln.	$Pd(OAc)_2$	2.2	0.5	10	80	10
NL-3-274.5	**4a**	Water	Bulk soln.	$Pd(OAc)_2$	2.2	0.5	65	35	0
NL-3-280.1	**4a**	TPGS-750-M	In-situ	$Pd(OAc)_2$	2.2	0.5	35	60	5
NL-3-280.2	**4a**	Coolade	In-situ	$Pd(OAc)_2$	2.2	0.5	0	60	40
NL-3-284.1	**2a**	TPGS-750-M	In-situ	$PdCl_2$*	0	3.0	0	85	15
NL-3-284.2	**2a**	Coolade	In-situ	$PdCl_2$*	0	3.0	0	60	40
NL-3-284.3	**4a**	TPGS-750-M	In-situ	$PdCl_2$*	0	3.0	0	80	20
NL-3-284.4	**4a**	Coolade	In-situ	$PdCl_2$*	0	3.0	0	80	20

*trial conducted using freshly synthesized TPGS-750-M. **2 h reaction time

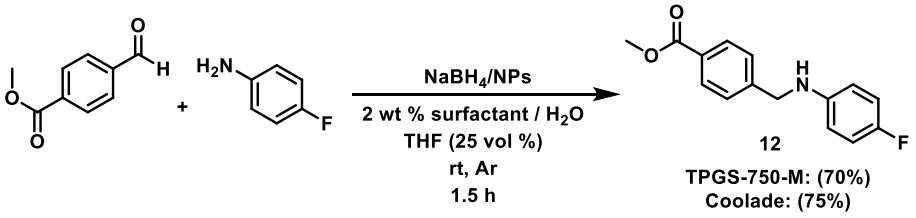
Overall, the trend appears that greater conversion is seen in trials using Coolade versus those using TPGS-750-M, and the trial using water alone giving less conversion that either surfactant.

Scheme 14: *gem*-Dibromocyclopropane reduction surfactant comparison trials



Work on the double-dehalogenation of *gem*-dibromocyclopropanes has been ongoing in our group for several years, and was not published until after the time of the publication on the surfactant Coolade.[88] It was noticed that the combination of $NaBH_4$ and nickel salts produces an immediate release of hydrogen, which causes foaming. Addition of 20 vol % THF serves to decrease the extent of foaming, and to better solubilize the starting material and product.

Scheme 15: Surfactant comparison using reductive amination



[88] Wood, A. B.; Cortes-Clerget, M.; Kincaid, J. R. A.; Akkachairin, B.; Singhania, V.; Gallou, F.; Lipshutz, B. H. *Angew. Chem. Int. Ed.* **2020**, *59*, 17587–17593.

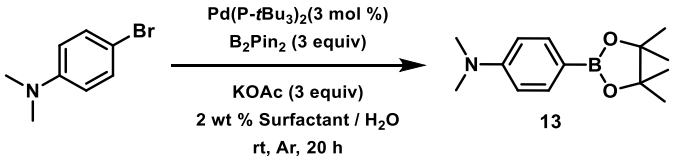
Reductive amination in surfactant solutions is possible in some select cases. This reaction is challenging because of the very insoluble imine intermediate, necessitating the addition of co-solvent. After imine formation, a NP hydrogenation catalyst is added as well as $NaBH_4$, causing rapid gas evolution and foaming, though this is tempered significantly by the THF co-solvent.

3.8 Surfactant comparison trials: non gas-producing reactions

The initial goal of this project was to develop a surfactant which incorporated an amide or "DMF-like" functionality, with the ultimate goal of "beating" TPGS-750-M and Nok. The emphasis on foaming or rather the elimination of foaming came much later and was altogether an accident, and not planned whatsoever. The focus on anti-foaming properties didn't come until at least 2 years deep into this project. Therefore, before any major focus or emphasis for publication was solidified, a number of other reaction types were screened. For most of the duration of this project, all types of reactions known to work in surfactant solution were "fair game" and were tested. While none of these examples were included in the final publication, I personally feel that they are valuable in that they show how the new surfactant(s) perform against TPGS-750-M, as well as constituting a large expenditure of effort, funds, and valuable learning based on the observations obtained thereof. While initially it was planned to test all new surfactants against all reaction types, this became an unreasonably large number of trials. I was very new to organic synthesis and this group, the GC-MS was wholly unreliable and chronically broken. Nobody knew how to operate any of the GC-FID instruments. I was not aware that HPLC was a means of screening reaction conditions. Overall, this project began with an ignorance of all instrumental methods of screening crude reaction mixtures, and instead relied exclusively

on isolated yields of products after column chromatography. Because of this, while early comparison tests were conducted with several new surfactants, later tests were focused on only Coolade vs. TPGS-750-M because Coolade had by this point been identified as a low-foaming surfactant so would be the new surfactant published.

Table 4: Miyaura Borylation

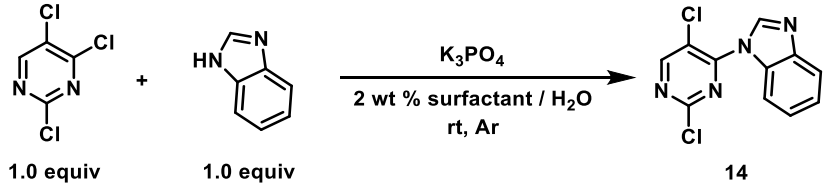


Entry	Surfactant	Isolated Yield (%)
NL249.1	TPGS-750-M	90
NL249.2	Koolaid-1000-M	65
NL249.3	Coolade	87
NL-281.2	Lauryl sarcosine-1000-M	77
NL-281.3	Butyl Coolade	76
NL-281.4	Butyl Koolaid-1000-M	18

After synthesizing several new surfactants, Miyaura borylation was one of the first reaction types screened. Quite a bit of difference was seen between the surfactants in terms of conversion, with TPGS-750-M giving the highest yield. These trials were one of the main reasons for utilizing the symmetrical surfactant Coolade versus its linear predecessor Koolaid-1000-M (87% vs. 65% isolated yield). The same trend of symmetrical > linear surfactant was seen with the two butyl anthranilate-based surfactants, where the symmetrical or “double-ended” surfactant performed better than the linear MPEG derivative. Unfortunately, the symmetrical analog of lauryl sarcosine-

1000-M was not prepared at this point, it would be interesting to see if the trend held for this surfactant as well, especially considering that it gave the highest yield of any of the three new linear surfactants.

Table 5: Screening surfactants for an S_NAr reaction



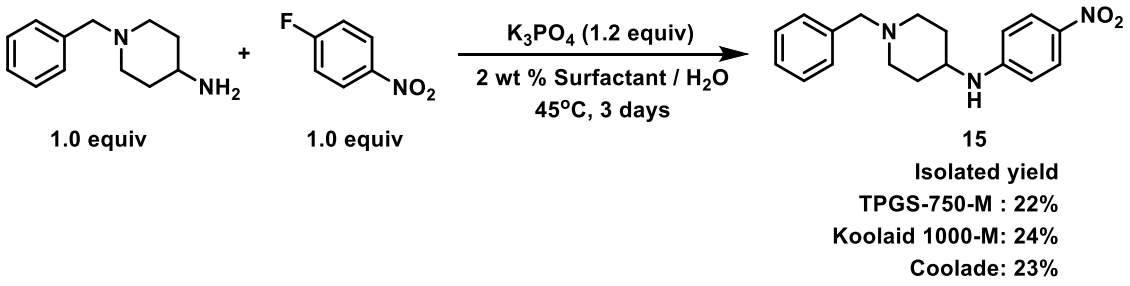
Trial	Surfactant	K_3PO_4 equiv	Rxn time (h)	Isolated yield (%)
NL95A	TPGS-750-M	1.0	22	76
NL95C	Hotsauce-1000-M	1.0	22	80
NL95D	Koolaid-1000-M	1.0	22	77
NL242.1	TPGS-750-M	1.2	4.5	64
NL242.2	Koolaid-1000-M	1.2	4.5	73
NL246.1	TPGS-750-M	1.2	21	80
NL246.2	Koolaid-1000-M	1.2	21	80
NL246.3	Coolade	1.2	21	83

Figure 14: Dispersion of solids in (A) NL246.1, (B) NL246.2, (C) NL246.3

This substrate was used during our co-solvent studies because the product forms an insoluble white ball of product very reproducibly, and because it was an intermediate

yielding reaction so differences in surfactant choice could possibly result in higher or lower yields. While all trials (regardless of surfactant choice) initially produce gummy solids then a solid ball of material, after stirring for prolonged periods of time the solids take on differing characteristics. The trials in TPGS-750-M lead to a solid ball throughout, while reactions in either Koolaid-1000-M or Coolade produce solids which break down into very fine particulates. The behavior of solids is very important for scale-up because the presence of large insoluble materials can result in trapped starting material leading to incomplete reactions, as well as byproduct formation. Overall, little difference in yield was noted between the different surfactants.

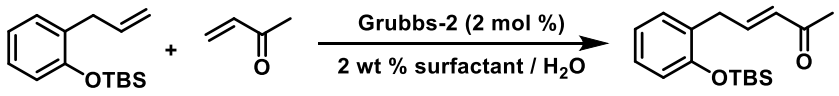
Scheme 16: Testing for rate enhancement using a kinetically slow S_NAr reaction



This reaction had previously been conducted on a ~5 g scale to synthesize starting material for another project. The reaction proceeded extremely slowly, ~5 days reaction time at 65°C was necessary to isolate ~50% yield of product, with the remainder being unreacted starting material. This seemed to be an ideal case to test whether any rate difference existed between surfactants. Overall, essentially the same isolated yield was recovered from all three reactions, suggesting that the nature of the surfactant has little effect on this reaction. Much later, I found an interesting study on the effect of ionic surfactants versus non-ionic surfactant on the rate of S_NAr reactions in micellar media.

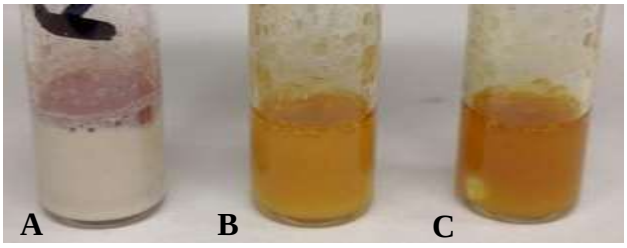
This report was from Bunton, so it seems I was testing the same thing which had been tested in the same hallway decades ago. A case where a careful literature search would have saved time and resulted in potentially better results, the study showed that while nonionic surfactants have a small catalytic effect, cationic surfactants have a much larger catalytic effect on S_NAr rate.[89]

Table 6: Comparison trials on an olefin metathesis reaction



1 equiv. 3 equiv. 16

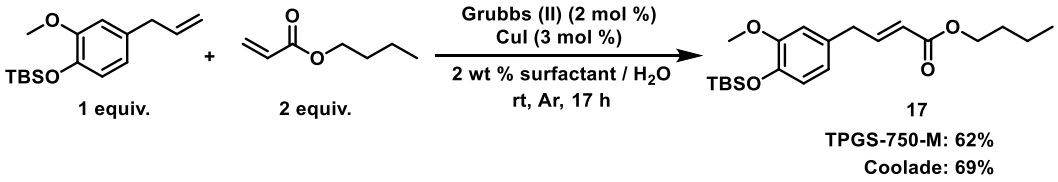
Entry	Surfactant	Rxn Time (h)	Isolated Yield
NL216.1	TPGS-750-M	3.5	31
NL216.2	Hot Sauce-1000-M	3.5	42
NL216.3	Koolaid-1000-M	3.5	44
NL266.1	TPGS-750-M	24	47
NL266.2	Koolaid-1000-M	24	48
NL266.3	Coolade	24	54



[89]Bunton, C. A.; Robinson, L. *J. Am. Chem. Soc.* **1970**, *92*, 356–361.

Figure 17: Reaction appearance using (A) TPGS-750-M, (B) Koolaid-1000-M, (C) Coolade.

While a notable tendency for the starting materials/products to oil out was seen with the methyl anthranilate-based surfactants, this did not seem to harm conversion.



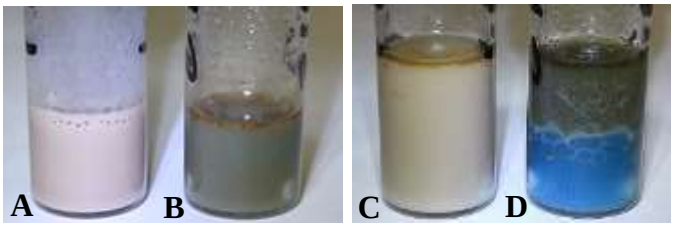
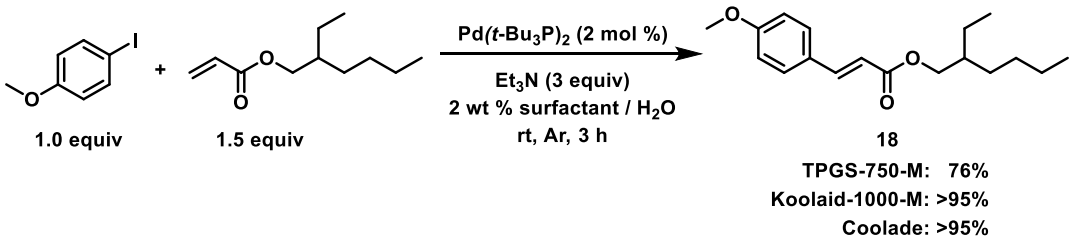


Figure 18 Reaction appearance in (**A**) TPGS-750-M, (**B**) Coolade, extraction of reaction mixture with EtOAc in (**C**) TPGS-750-M, (**D**) Coolade

While the less greasy methyl anthranilate-based surfactants caused more oiling-out (as mentioned above), it was also noted that they caused far less problems during extraction. TPGS-750-M is very difficult to extract when using “greasy” substrates such as this one.

Scheme 19: Comparison trials using Heck coupling



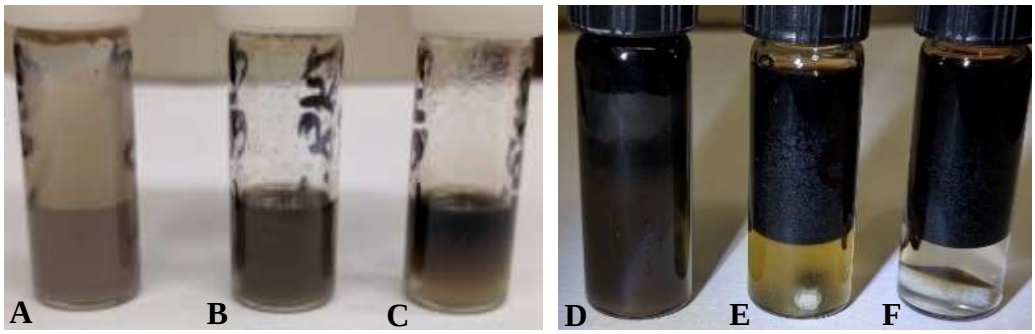
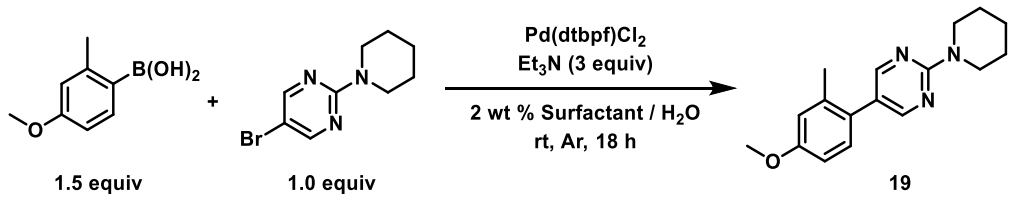


Figure 18: Heck couplings at completion (A) TPGS-750-M, (B) Koolaid-1000-M, (C) Coolade. Reactions during extraction (D) TPGS-750-M, (E) Koolaid-1000-M, (F) Coolade

Similar to the Grubbs metathesis example above, a Heck coupling gives a difficult emulsion in TPGS-750-M during extraction, whereas the less greasy methyl anthranilate surfactants give a cleaner phase separation. The lower yield in the TPGS-750-M trial is likely due to incomplete extraction rather than incomplete conversion

Table 7: Comparison trials using sp^2-sp^2 Suzuki Miyaura coupling



Trial	Surfactant	Pd(dtbpf)Cl_2 (mol %)	Isolated Yield
NL-3-189.1	TPGS-750-M	0.25	91%
NL-3-189.2	Coolade	0.25	90%
NL-3-192.3	TPGS-750-M	0.10	92%
NL-3-192.4	Coolade	0.10	93%

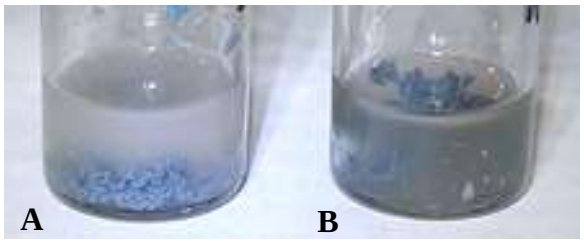


Figure 19: Reaction appearance in (A) TPGS-750-M and (B) Coolade

Suzuki coupling of these compounds was first attempted at 0.25-0.5 mol % Pd, but both surfactants produced a similar yield, so the Pd loading was lowered to 0.1 mol %. Once again, similar yield was seen between the two surfactants. Overall solubility appears better at the beginning of the reaction using TPGS-750-M, but the product is very insoluble, so both reactions produce solids.

Table 8: Comparison using *B*-alkyl Suzuki coupling

Trial	Surfactant	Catalyst (mol %)	Base (equiv)	Rxn Time (h)	Isolated yield (%)
NL-2-226.1	TPGS-750-M	2.0	Et_3N (3)	1	90
NL-2-226.2	Coolade	2.0	Et_3N (3)	1	96
NL-2-267.2	TPGS-750-M	0.25	K_3PO_4 (1.5)	21	94
NL-2-267.3	Coolade	0.25	K_3PO_4 (1.5)	21	97
NL-2-272.2	TPGS-750-M	0.25	K_3PO_4 (1.5)	3	66
NL-2-272.3	Coolade	0.25	K_3PO_4 (1.5)	3	63

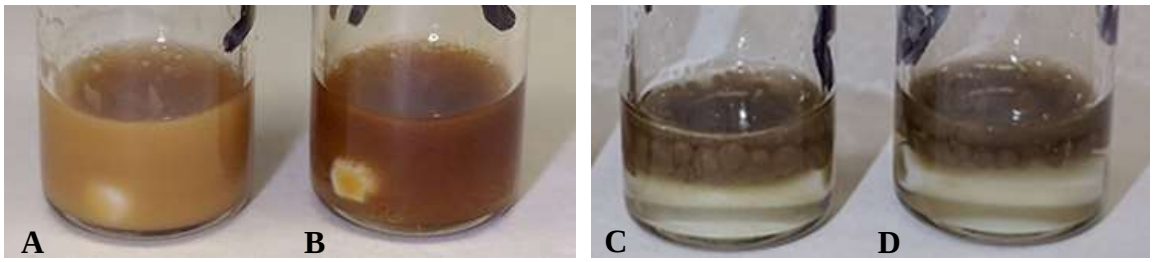
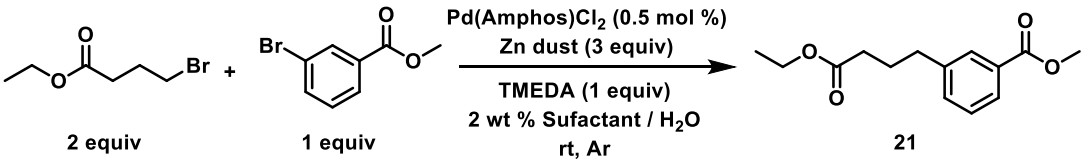


Figure 20: Appearance of reactions using Et_3N as base and K_3PO_4 with (**A**) TPGS-750-M with Et_3N, (**B**) Coolade with Et_3N, (**C**) TPGS-750-M with K_3PO_4, (**D**) Coolade with K_3PO_4.

Similar yields were obtained for both surfactants, even when changing catalyst loadings and base. TPGS-750-M produces a more uniform reaction appearance, whereas Coolade once again showed somewhat more oiling-out though this did not seem to hinder conversion. Both surfactants produced large amounts of oiling-out using K_3PO_4 as base.

Table 9: Comparison trials using a Negishi coupling



Trial	Surfactant	Rxn Time (h)	Isolated Yield (%)
NL-2-229.1	TPGS-750-M	24	46
NL-2-236.2	TPGS-750-M	48	43
NL-2-236.3	Coolade	48	46

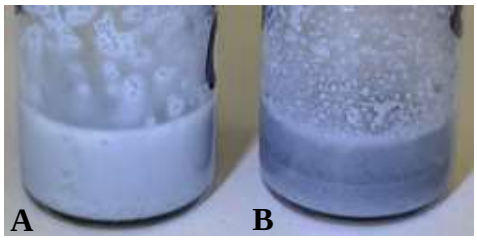
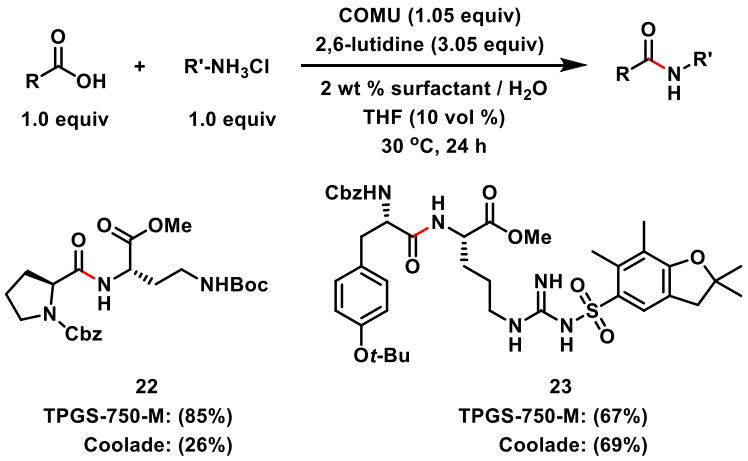


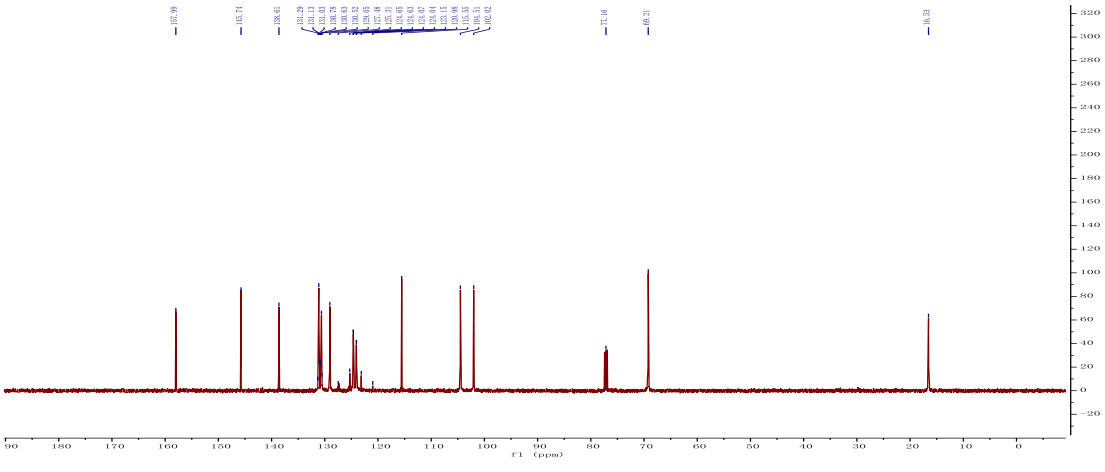
Figure 21: Negishi coupling reaction appearance (A) TPGS-750-M and (B) Coolade

Scheme 20: Comparison trials using peptide couplings



During the development of the MC-1 surfactant, a number of other surfactants were screened for amide coupling including Coolade.

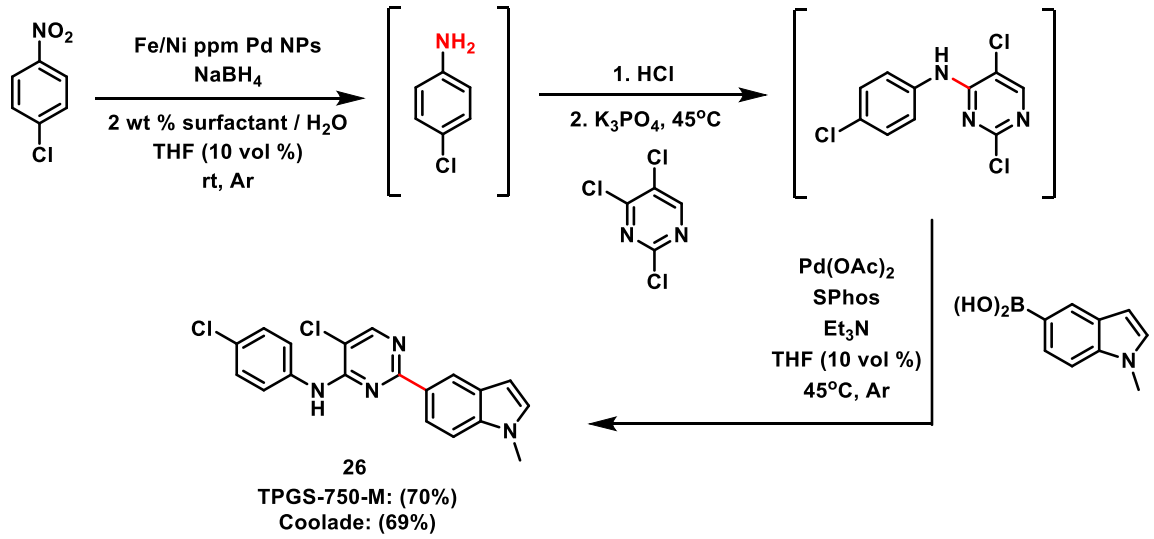
Scheme 21: Comparison trials using 2-step-1-pot deprotection-peptide coupling



Interestingly, while the peptide coupling alone gave varying results for the comparison, both of these 2-step, 1-pot trials gave somewhat better yields for Coolade than TPGS-750-M. Whether this was an effect of the hydrogenation/Cbz deprotection or in the coupling step itself is unclear.

3.9 3-step, 1-pot tandem sequence

Scheme 22: Tandem 3-step, 1-pot sequence

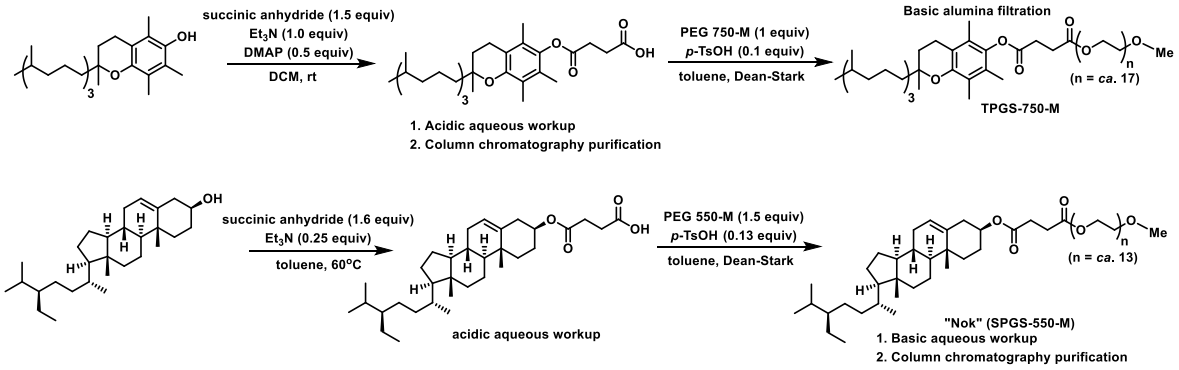


A 3-step, 1-pot sequence was conducted to show the compatibility of various reaction types (Scheme 22). Beginning with a nitro group reduction furnishes the aniline intermediate. After adding aqueous HCl to destroy remaining $NaBH_4$, the reaction mixture is basified with K_3PO_4 and 2,4,5-trichloropyrimidine added as electrophile for S_NAr. After completion of the S_NAr reaction, addition of Et_3N and THF co-solvent helped to dissolve the S_NAr intermediate. Adding boronic acid and Pd catalyst resulted in the final Suzuki product, isolated in both cases in essentially identical yield.

3.10 Synthesis of designer surfactants TPGS-750-M and SPGS-550-M (Nok)

The synthesis of the new surfactant was largely patterned after the published procedure for the synthesis of TPGS-750-M. As a reference, the synthesis of both TPGS-750-M and SPGS-550-M "Nok" are show below (Scheme 23).

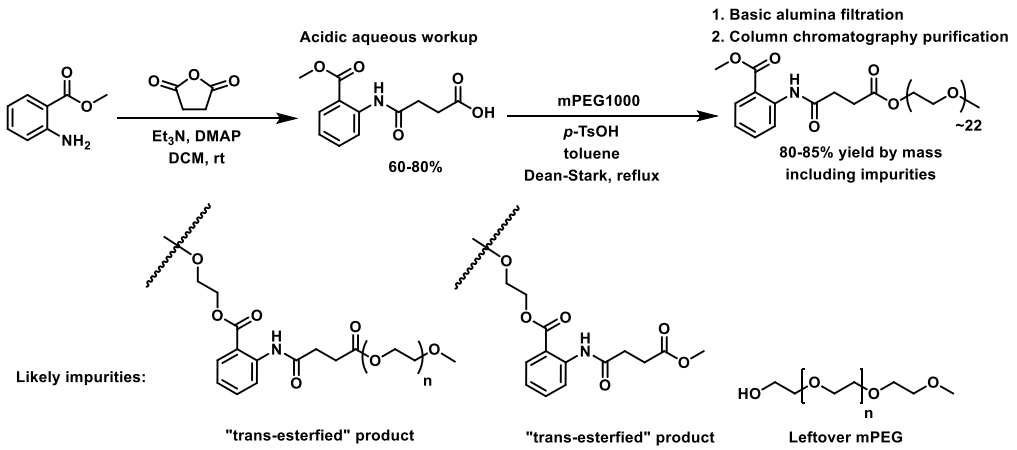
Scheme 23: Synthesis of TPGS-750-M and Nok



The conditions from the TPGS-750-M synthesis were applied to methyl anthranilate as nucleophile instead of tocopherol. This initial route was used to make variations including Koolaid-550-M and Koolaid-1000-M, and used for test reactions above. This material was also analyzed by DLS to confirm the presence of micelles, which was not necessarily guaranteed given that this material lacks the extensive hydrocarbon tail that is present in all of the surfactants we've employed so far. In addition, the NMR of the product was never totally pure (and PEG integration was always significantly greater than theoretical), even after column chromatography, the likely impurities are listed below.

3.11 Initial synthesis of methyl anthranilate derived surfactants

Scheme 24: Initial synthesis of Koolaid-1000-M



The same reaction conditions utilized for the synthesis of TPGS-750-M were applied to the synthesis of Koolaid-1000-M (as well as the analog using butyl anthranilate).

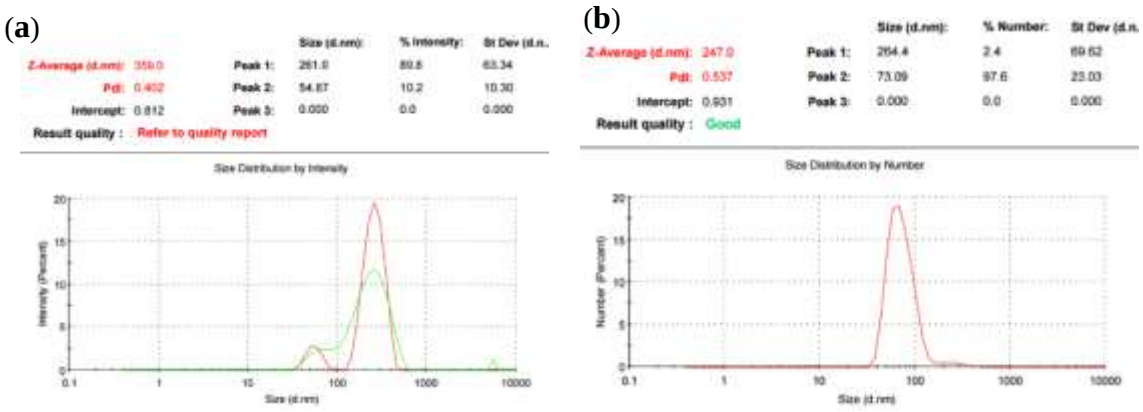


Figure 22: Dynamic light scattering of micelles derived from Koolaid-1000-M synthesized by the above route, (a) intensity percent plot, (b) number percent plot.

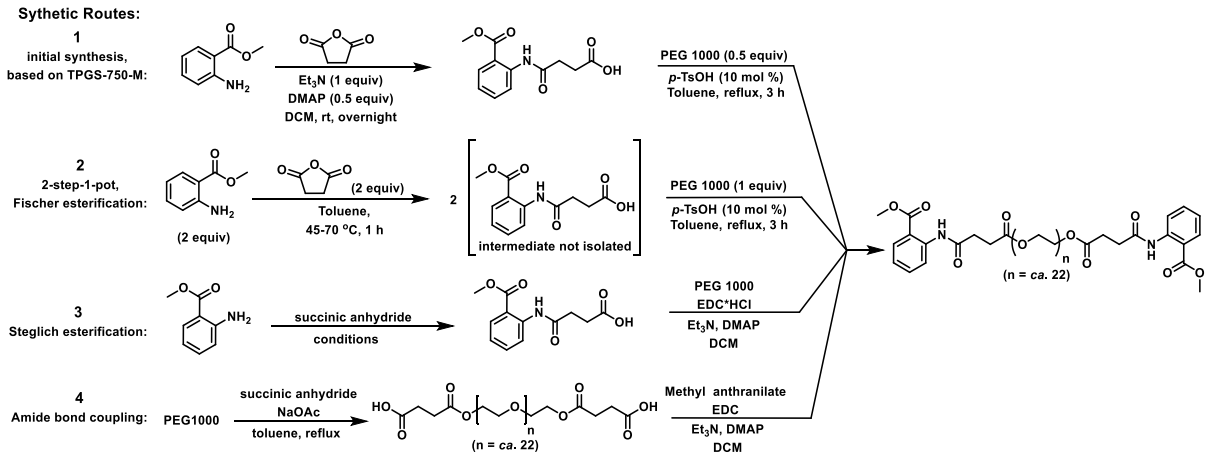
This was my first experience with DLS of surfactant solutions, and overall the results certainly showed that this material would form a micelle, but determining exactly what size micelles was another matter. Previous DLS measurements taken by group members used the intensity (percent) plot to determine micelle size. However, the number percent

curve shows a completely different micelle size, so overall while micelles are present, it is inconclusive as to their size.

3.12 Various routes explored for the synthesis of Coolade

The symmetrical surfactant Coolade came about because of several shortcomings associated with surfactant Koolaid-1000-M. The initial route to anthranilate based surfactants always resulted in a greater than theoretical integration of PEG in the ^{1}H NMR of Koolaid-100-M, suggesting incomplete functionalization of PEG and/or transesterified materials. Also, this surfactant led to relatively poor solubilization of crystalline/solid organic compounds. Thirdly, MPEG is significantly more expensive than PEG. The theory was that by using PEG instead of MPEG these shortcomings could be mitigated. Because PEG has two nucleophilic hydroxyl groups, attempting to esterify both should result in a larger proportion of the total mass of the surfactant resulting from the hydrophobic methyl anthranilate succinate. Increasing the lipophilic proportion of the surfactant should also help with the poor solubilizing properties. And finally, PEG being much cheaper than MPEG should bring the overall price of the surfactant down. In total, four routes were tested towards making this double-ended material that would later be named “Coolade.”

Scheme 25: Routes to Coolade explored



Four separate routes emerged out of a desire for a highly efficient and rapid synthesis on one hand, and very high purity material on the other. No single route was found that can fulfill both of these requirements at the same time. Table 10 shows the overall pros & cons of each route studied.

Table 10: Pros & cons of each synthetic route

Route	Pros	cons
1	No coupling reagents	Excessive waste, isolation and purification in both steps, halogenated waste, low purity product
2	No coupling reagents, No isolation of intermediate, no column chromatography, very small waste stream, very fast procedure	Low purity product
3	High purity product	Coupling reagents required, extreme emulsions, column chromatography, excessive waste, halogenated solvents
4	High to very-high purity product	Coupling reagents required, extreme emulsions, column chromatography, excessive waste, halogenated solvents

Equation 1: E Factor Calculation

$$E\ Factor = \frac{kg\ (waste)}{kg\ (product)}$$

Table 11: E Factor Comparison of Surfactant Synthesis

	TPGS-750-M	SPGS-550-M	Coolade*
Lipophilic core	∝-tocopherol	phytosterols	methyl anthranilate
Price ($/kg)	~30	~25	~4
Organic Waste (mL/g product)	62	>>11	6.5, 3**
Aqueous Waste (mL/g product)	5	68	1, 1**
Total Waste (mL/g product)	67	>>79	7.5, 4**

*When synthesized by 2-step, 1-pot procedure (route **2**)

**with recycle of toluene

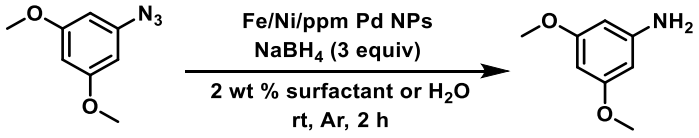
Accounting for the total solvent and aqueous waste in the published syntheses for TPGS-750-M and SPGS-550-M, the bulk of the waste is generated during chromatographic purification. Due to the 2-step, 1-pot synthesis of Coolade, and elimination of chromatographic purification, the E Factor value compares very favorably to syntheses of the existing surfactants.

3.13 Testing various purities of Coolade

In the course of developing several different methods for the synthesis of this surfactant, there were now several samples of differing purities at our disposal. In our group, the surfactant TPGS-750-M is typically synthesized by group members. There is somewhat of a debate about exactly how pure we need to make the surfactant. Typically, everyone

strives for material as pure as possible, this means column chromatography of the intermediate succinate and workup of the final product with basic alumina to remove *p*-TsOH as well as removing some "caramel" colored material typically present in the reaction mixture after an extended azeotropic distillation in toluene. Aside from some sample bottles which have been sent by companies manufacturing TPGS-750-M, which we have tested and never found a problem, these have always been >90% or 95%, overall high purity. To test the impact of purity (in the form of PEG integration %) on reaction outcome, two reactions were attempted with varying purities of surfactant. Three grades were selected for this task. The ~60% purity material was from the 2-step, 1-pot procedure, and the 80 and >95% purity samples were column chromatography purified from EDC coupled product.

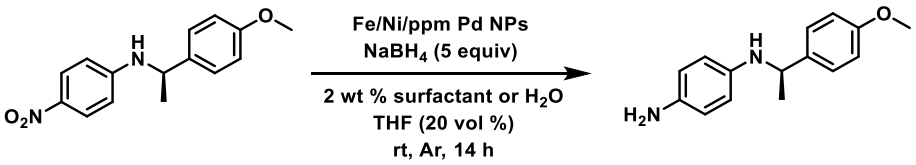
Table 12: Testing varying Coolade purities with azide reduction as a test reaction



Trial	Reaction medium	Isolated yield
NL-5-133.1	H_2O	29.2 mg / 38%
NL-5-133.2	TPGS-750-M (>95% purity)	64.2 mg / 84%
NL-5-133.3	Coolade batch NL-4-302 (~60% purity)	69.1 mg / 90%
NL-5-133.4	Coolade batch NL-5-128 (~80% purity)	69.9 mg / 91%
NL-5-133.5	Coolade batch NL-5-132 (>95% purity)	68.8 mg / 90%

Using the azide reduction as a test, the purity of Coolade looks to have little effect.

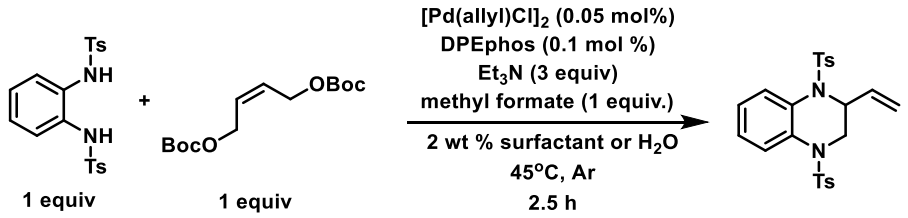
Table 13: Testing varying Coolade purities with nitro reduction as a test reaction



Trial	Reaction medium (all using 20 vol % THF co-solvent)	Isolated yield (%)
NL-5-135.1	H_2O	67%
NL-5-135.2	TPGS-750-M (>95% purity)	73%
NL-5-135.3	Coolade batch NL-4-302 (~60% purity)	65 %
NL-5-135.4	Coolade batch NL-5-128 (~80% purity)	88%
NL-5-135.5	Coolade batch NL-5-132 (>95% purity)	79%

This nitro compound is extremely insoluble in water even in the presence of surfactant. THF co-solvent was added to help with solubilization. Surprisingly, the intermediate purity (80% PEG incorporation) gave the highest yield of the trials.

Table 14: Testing various surfactants and purities of Coolade using a Tsuji-Trost test reaction



Trial	Reaction medium	Isolated yield (%)	Notes
NL-5-153.1	H_2O	90	Poor solubility
NL-5-153.2	TPGS-750-M	89	Good solubility*
NL-5-153.3	Brij 30	94	Poor solubility
NL-5-153.4	Triton-X-100	93	Poor solubility
NL-5-153.5	PTS-600	87	Good solubility*
NL-5-153.6	Coolade (~60% purity, NL-4-302)	94	Poor solubility
NL-5-153.7	Coolade (~80% purity, NL-5-128)	94	Poor solubility
NL-5-153.8	Coolade (>95% purity, NL-5-132)	94	Poor solubility

*emulsion upon extraction

Figure 23: Phase separation upon extraction

All trials gave similar isolated yields, however, some differences in solubility were noticed. The “greasier” surfactants TPGS-750-M and PTS-600 gave much better reaction solubility than the other trials, however they also produced difficult-to-extract emulsions upon workup.

3.14 Experimental

3.14.1 General Information

All commercially obtained reagents and solvents were used without further purification unless otherwise noted. Thin layer chromatography (TLC) was performed using Silica Gel 60 F254 plates (Merck, 0.25 mm thick). Flash chromatography conducted using Silica Gel 60 (EMD, 40-63 μm). ^{1}H and ^{13}C NMR were recorded at 25 °C on a Varian Unity Inova 400 MHz, a Varian Unity Inova 500 MHz or on a Varian Unity Inova 600 MHz spectrometer in in $CDCl_3$ with residual $CHCl_3$ (^{1}H = 7.26 ppm, ^{13}C = 77.20 ppm), in $(CD_3)_2SO$ with residual $(CH_3)_2SO$ (^{1}H = 2.50 ppm, ^{13}C = 39.52 ppm) or in MeOD with residual MeOH (^{1}H = 4.78 ppm, ^{13}C = 49.00 ppm) as internal standards. Chemical shifts are reported in parts per million (ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, bs = broad singlet, d = doublet, dd = doublet of doublets, ddd= doublet of doublet of doublets, t = triplet, td = triplet of doublets, q = quartet, sept = septet, m = multiplet), coupling constant (if applicable) and integration. Polyethylene glycol Mn 1000 was purchased from Sigma Aldrich, catalog # 81190. Methyl anthranilate was purchased from HiMedia, product # GRM10269-500ML. Succinic anhydride was purchased from Sigma Aldrich catalog # 239690. Toluene sulfonic acid was purchased from Lancaster Synthesis Inc catalog # 5446. TPGS-750-M[1] and SPGS-550-M "Nok"[2] were synthesized according to literature procedures. Surfactant solutions (2 wt % surfactant /H_2O) were prepared using degassed HPLC grade water and stored under positive pressure of an argon atmosphere until used.

3.14.2 General Procedures and Consideration for use of Surfactants for Synthesis

Preparation of 2 wt % Coolade solution from wax

A 100 mL cylindrical flask/bottle with magnetic stir bar was filled with 49 mL of HPLC grade water. An aliquot of Coolade wax was heated until fully melted (~70 ^{o}C) in a 1 dram (4 mL) vial and 1.0 g was added to the flask via syringe (1 mL plastic syringe without needle). The flask was capped with a 14/20 rubber septum and shaken vigorously for ~1 min to fully dissolve. The flask was attached to an argon Schlenk line via a 18 ga (1.27 mm) x 6" (152 mm) needle. The flask was stirred on a magnetic stir plate, the needle inserted to the bottom of the flask, and an 18 ga (1.27 mm) vent needle was inserted through the septum to allow argon to escape. The solution was sparged with argon for ~3 h to fully degas. The flask was wrapped in aluminum foil and stored connected to an argon line until use.

Preparation of 2 wt % TPGS-750-M solution from wax

A 250 mL round bottom flask with magnetic stir bar was placed horizontally on a top-loading balance. TPGS-750-M wax was melted in a 20 mL scintillation vial using gentle heating with a heat gun. TPGS-750 M (3.0 g) was added to the flask via syringe (1 mL plastic syringe without needle) such that the wax collected in a pool on the size of the flask. The flask was placed on ice for 10 min such that the surfactant solidified to the side of the flask. To the flask was added 147 mL of HPLC grade water and the flask was capped with a 14/20 rubber septum. The flask was attached to an argon Schlenk line via an 18 ga (1.27 mm) x 6" (152 mm) needle, and placed at a 45^{O} angle over top of a magnetic stir plate such that the TPGS-750-M remained adhered to the glass, above the water level. The argon needle was inserted to the bottom of the flask and an 18 ga (1.27 mm) vent needle was

inserted through the septum. The water was sparged with argon for ~3 h to fully degas while stirring the water. The flask was then rotated such that the TPGS-750-M wax was immersed in the water, and stirred untill fully dissolved (typically overnight ~12 h). The solution was stored under argon, connected to an argon Schlenk line until use.

General notes about de-gassing:

Due to the different amounts of foam produced during sparging with different surfactants, it was found difficult to de-gas TPGS-750-M, Nok, PTS, and SDS surfactants via sparging the prepared solution, Coolade, however, produces little-to-no foaming during sparging and, therefore, the prepared surfactant solution can be sparged easily, provided some headspace is left in the flask to accommodate bubbling.

The exact amounts of dissolved oxygen in the surfactant solution have not been fully established. A good project for a new student might be to prepare surfactant solutions with varying amounts of dissolved oxygen and to run known air sensitive reactions and see the effect. It would be nice to know if a simple exchange of the headspace followed by some mixing and perhaps another headspace exchange would be sufficient to give good results.

Surfactant storage considerations

In general, surfactant solutions (i.e., 2 wt % surfactant/H_2O) are stable when stored under an argon atmosphere. Notable decomposition has been seen in surfactant solutions which were stored under air for prolonged periods of time. For instance, below is a solution of freshly prepared Coolade 2 wt % solution, and a similar flask which had been stored on a shelf, capped with a rubber septum for six months, during which time oxygen had caused significant decomposition of the surfactant.

Figure 24: Left: Coolade 2 wt % solution stored under argon, Right: Coolade 2 wt % solution stored under air, showing decomposition

In similar flasks which were carefully stored under argon, little color change and decomposition was noted. This effect occurs in other surfactant solutions as well, PTS surfactant was found to completely decompose over time if not stored carefully, and TPGS-750-M has shown similar breakdown. A general rule of thumb which has proved amenable is to store surfactant solutions no more than six months after being prepared, and to keep the flask under argon at all times. Following this guideline has caused no problems as of yet. Surfactant wax has been effectively stored in sealed vials, purged with argon, in the refrigerator for years without notable decomposition.

Reaction considerations

A frequent cause of low yields or failure to reproduce results when users familiar with synthesis in typical organic solvents attempt reactions in water/surfactant is due to insufficient stirring. In many reaction classes it is absolutely imperative to "vigorously" stir a reaction, which means maintaining a strong vortex to blend the reaction thoroughly. These reactions frequently "oil out" or sometimes produce solids that can and will still react, but require vigorous stirring to obtain good results. We have seen a number of cases where the starting materials and product are nearly completely insoluble in water or surfactant solution, but because of good mixing the reaction can be pushed to completion.

3.14.3 General Procedures for Comparison Trials

Shaking Test

To each 1 dram (4 mL) vial was added 1 mL of the respective 2 wt % surfactant/H_2O solution and the vial capped with a screw cap. The vials were shaken vigorously for approximately 10 seconds and surfactant foaming behavior observed.

Fe/Ni ppm Pd NPs foam test

This test was used to replicate the foaming observed in NP type nitro group reductions for comparison purposes between various surfactants. Oven dried 16 x 150 mm test tubes were brought into an argon filled glovebox. Each test tube was loaded with $NaBH_4$ (76 mg, 2 mmol) and Fe/Ni ppm Pd NPs (10 mg), and a magnetic stir bar. The top of each test tube was sealed with parafilm and removed from the glovebox. The test tubes were tapped gently on the bench to push all reagents to the bottom of the tube. The test tubes were taped to a sheet of paper using clear tape, and clamped above a magnetic stir plate. The parafilm was removed from the top of each test tube and 1 mL of the respective 2 wt % surfactant/H_2O solution was quickly added to each test tube via syringe and the solutions stirred vigorously with the test tubes left uncapped. The test tubes were stirred until foaming had reached a maximum height (~5-10 min) and pictures were taken.

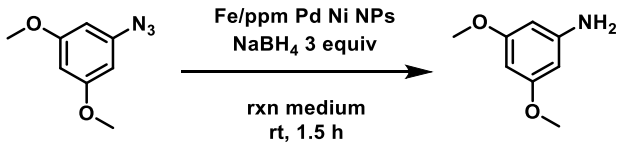
Ni/Phenanthroline/pyridine NPs foam test

This test was used to replicate the foaming observed in NP type reductions including *gem*-dibromocyclopropane reductions and a 2-halopyridyl dehalogenation.[3] Oven dried 16 x 150 mm test tubes were brought into an argon filled glovebox. Each test tube was loaded with $NaBH_4$ (76 mg, 2 mmol), the top of each test tube was sealed with parafilm and removed from the glovebox. The test tubes were tapped gently on the bench to push all reagents to the bottom of the tube. The test tubes were taped to a sheet of paper using clear tape, and clamped above a magnetic stir plate. To 1 dram (4 mL) vials were added sequentially the following: $Ni(OAc)_2 \bullet 4H_2O$ (6.2 mg, 0.025 mmol), 1,10-phenanthroline (9.1 mg, 0.05 mmol), a magnetic stir bar, 1 mL of the respective 2 wt % surfactant/H_2O solution, and pyridine (56 mg, 0.75 mmol, 58 uL) with all operations carried out open to air with no special precautions. The vials were capped with screw caps and placed in an aluminum block reactor and stirred vigorously for 5 min to complex nickel and ligand (slightly pink color). The parafilm was removed from each test tube, and the contents of each 1 dram (4 mL) vial including the stir bar was quickly poured into each respective test tube and the test tubes stirred vigorously with the test tubes left uncapped. The test tubes were stirred until foaming had reached a maximum height (several minutes) and pictures were taken.

General procedures for reaction comparison trials

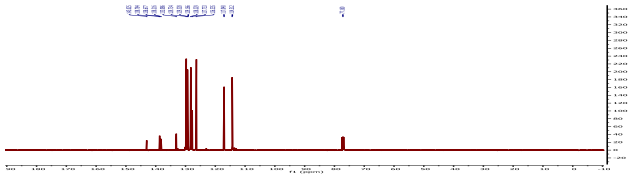
A survey of synthetic methodologies using aqueous surfactant media was used to compare the effect of changing the surfactant on the reaction behavior and outcome. In each case, the same reaction procedure and conditions were used, the only difference being the surfactant utilized in the reaction.

Aryl azide reduction



To a 1 dram (4 mL) vial was added 1-azido-3,5-dimethoxybenzene (89.6 mg, 0.5 mmol, 1.0 equiv), Fe/ppm Pd Ni NPs (5 mg), $NaBH_4$ (56.7 mg, 1.5 mmol, 3 equiv), a magnetic stir bar, and the vial capped with a screw cap. The screw cap was opened slightly and the vial briefly purged with argon using a needle attached to a Schlenk manifold, and 2 wt % surfactant/H_2O solution (1.0 mL) was quickly added via syringe and the cap closed. The reaction was placed in an aluminum block reactor at rt and stirred vigorously, occasionally opening the cap to vent pressure produced in the reaction, and occasionally tapping the vial on the benchtop to knock down the foam level to prevent it from escaping through the cap. After 1.5 h reaction time, the vial was opened and an aliquot of reaction mixture was removed and used for TLC analysis (40:60 EtOAc/Hexanes). The reaction was extracted with EtOAc, dried over anhydrous Na_2SO_4 and purified via column chromatography.

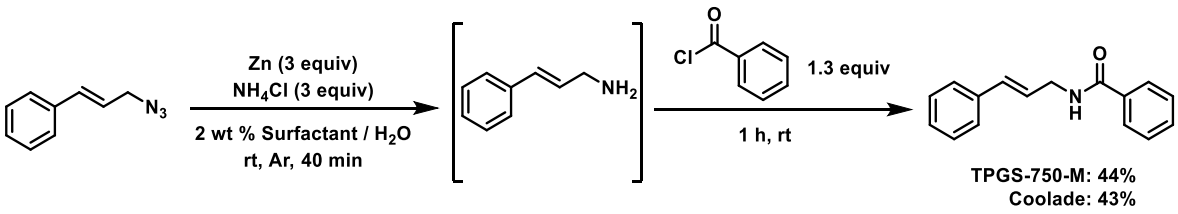
Sulfonyl Azide Reduction



To a 1 dram (4 mL) vial with magnetic stir bar was added 4-acetamidobenzenesulfonyl azide (60.1 mg, 0.25 mmol, 1.0 equiv), zinc dust (49 mg, 0.75 mmol, 3 equiv), and NH_4Cl (40 mg, 0.75 mmol, 3 equiv). The vial was capped with a 14/20 rubber septum and the vial connected to an argon Schlenk manifold via a needle through the septum. The vial was evacuated/backfilled with argon for three cycles and placed in an aluminum block reactor

at rt. Next, 2 wt % surfactant/H_2O solution (0.5 mL) was added via syringe through the septum and the reaction stirred vigorously until completion (~2 h). Reaction completion was determined by TLC analysis (20:80 MeOH/DCM). Upon completion, the reaction mixture was diluted with MeOH and the reaction mixture adsorbed onto Celite via rotary evaporator. The crude material was purified by silica gel column chromatography using 20:80 (MeOH/DCM).

Allylic Azide Reduction



To a 2 dram vial with stir bar was added zinc dust (98.1 mg, 1.5 mmol, 3 equiv) and ammonium chloride (80.2 mg, 1.5 mmol, 3 equiv). The vial was capped with a septum and evacuated/backfilled with argon 3x cycles. Via syringe was added 2 wt % surfactant/H_2O solution and then (*E*)-(3-azidoprop-1-en-1-yl)benzene (79.6 mg, 0.5 mmol, 1 equiv). The reaction was stirred at rt for 40 min, at which point the (*E*)-(3-azidoprop-1-en-1-yl)benzene had been consumed. Via syringe with stirring was added benzoyl chloride (91.4 mg, 0.65 mmol, 75.5 uL, 1.3 equiv) and the reaction stirred for 1 h at which time the contents of the reaction had clumped into a sticky ball. The reaction mixture was extracted with EtOAc, the combined organic phases dried over anhydrous Na_2SO_4 and the solvent removed via rotary evaporation. The crude product was purified by column chromatography using hexanes then 40/60 (EtOAc/hexanes) to give *N*-cinnamylbenzamide as a white solild. (NL-3-287)

Nitro Reduction:

Fe/ppm Pd Ni NP catalyst material was synthesized according to a literature procedure.[4]

Procedure A (used for compound **5**): To a 3 dram vial with magnetic stir bar was added Fe/Ni ppm Pd nanoparticles (10 mg) and morpholino(4-nitrophenyl)methanone (118.0 mg, 0.5 mmol, 1 equiv) and the vial capped with a 19/22 rubber septum. The vial was connected to an argon Schlenk line via a 22 ga (0.7 mm) needle through the septum, and then evacuated and backfilled with argon three times. Via syringe was added THF (0.3 mL) and the vial placed on a magnetic stir plate and stirred vigorously for ~2 min to partially dissolve the nitro compound. Next, 1.2 mL surfactant solution (2 wt % in HPLC grade water) was added via syringe through the septum and the vial stirred vigorously. To an oven dried 1 dram vial was weighed $NaBH_4$ (113.5 mg, 3.0 mmol, 6 equiv), the septum was then quickly removed from the reaction vial and the $NaBH_4$ added to the reaction, and the reaction vial quickly re-capped with the septum, leaving the septum still attached to the Schlenk line. The reaction was stirred vigorously at rt (note: it is necessary to periodically remove the Schlenk line needle and vigorously shake/tap the reaction vial to prevent the foaming from escaping into the Schlenk line). After 1 h, an aliquot was removed via syringe, mixed with EtOAc and analyzed by TLC, the reaction was not complete. To an oven dried 1 dram vial was added Fe/Ni ppm Pd nanoparticles (5 mg) and $NaBH_4$ (25 mg, 0.66 mmol, 1.3 equiv), the septum was removed from the reaction vial and the Fe/Ni ppm Pd nanoparticles and $NaBH_4$ was quickly added to the reaction and the reaction vial re-capped. The reaction was stirred vigorously for an additional 1 h upon which time the reaction was deemed complete by TLC using MeOH/DCM (10/90) R_f ~0.5. The reaction mixture was extracted with EtOAc, dried over anhydrous Na_2SO_4 and the crude product

adsorbed onto Celite. The product was purified by column chromatography using DCM then MeOH/DCM (5/95).

Procedure B (used for all substrates, except **5**): To a 1 dram (4 mL) screwcap vial with stir bar was added Fe/Ni ppm Pd NPs (6 mg), $NaBH_4$ (47.3 mg, 1.25 mmol, 5 equiv) and nitro compound (0.25 mmol). The vial was capped with a screwcap, the screwcap was then opened slightly and the vial purged with argon using a needle attached to an argon Schlenk manifold and then recapped. The cap was opened slightly and co-solvent (amount for respective substrate, i.e. 0.15 mL THF for 20 vol % co-solvent) was added via syringe and the vial capped. The vial was stirred at rt for ~2 min on a magnetic stir plate to partially dissolve the nitro compound. The cap was opened slightly and 2 wt % surfactant/H_2O solution (0.60 mL) was added via syringe and the vial quickly capped to avoid allowing any foaming from escaping the vial. The vial was placed in an aluminum block reactor at rt and stirred vigorously, with a protective blast shield placed in front of the block reactor. *Note: the capped reaction is under pressure, the use of protective eyewear is absolutely necessary and the use of a blast shield is highly recommended.* We also recommend the pressurized vials should only be handled behind the blast shield, while wearing leather gloves. No vials exploded during these reaction tests, but other $NaBH_4$/NP reaction types in surfactant solution have caused vials to explode, especially when heated, so we recommend exercising extreme caution when running/handling these reactions. In addition, these reactions must not be opened before completion is reached or the reaction may stall. Reaction completion time was determined empirically by running multiple trials and opening each at different reaction times. Upon reaction completion, the vial was uncapped to release pressure, and the reaction progress analyzed by TLC. The contents of

the vial were extracted with EtOAc, dried over anhydrous Na_2SO_4, adsorbed onto Celite and purified by silica gel column chromatography.

Preparation of Pd NPs for alkyne hydrogenation

An oven dried 25 mL round bottom flask was brought into an argon filled glove box, to the flask was added $Pd(OAc)_2$ (12.8 mg, 0.057 mmol), $NaBH_4$ (10.8 mg, 0.29 mmol), a oval magnetic stir bar and the vial capped with a 14/20 rubber septum. The flask was removed from the glove box, taking care to keep all reagents centered in the bottom of the flask (i.e., do not spread the reagents around the interior of the flask) and an argon balloon with needle was inserted through the septum and the flask gently tapped on the benchtop to center all reagents in a small pile on the bottom of the flask. The flask was placed in a sonicator bath and sonicated for 60 min. Occasionally the flask was removed from the sonicator bath and a magnet placed against the bottom of the flask and used to uniformly disperse the black material if clumps formed. The flask was removed from the sonicator bath and placed on a magnetic stir plate and stirred. Via syringe, 2 wt % surfactant/H_2O solution (11.4 mL) was added to the flask, resulting in gas evolution and foaming. The flask was removed from the stir plate and placed back in the sonicator bath and sonicated for 15 min. The flask was then placed back on the stir plate and stirred vigorously, additionally sonication/stirring cycles were sometimes necessary to produce finely dispersed nanoparticle material.

General procedure for alkyne semi-hydrogenation

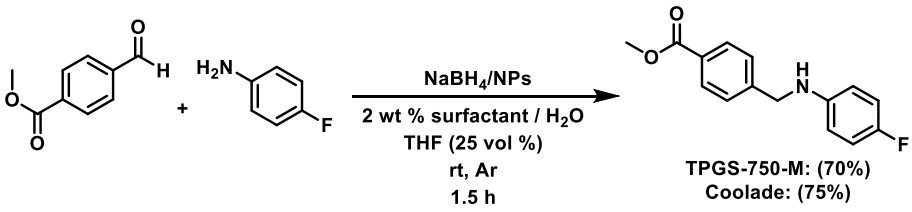
These hydrogenation trials were conducted according to the procedures in the original publication.

***gem*-Dibromocyclopropane double reduction**

To a 1 dram (4 mL) vial was added $Ni(OAc)_2 \cdot 4H_2O$ (3.7 mg, 0.015 mmol), then 3,4,7,8-tetramethyl-1,10-phenanthroline (7.1 mg, 0.03 mmol), (2,2-dibromo-3,3-dimethylcyclopropyl)methyl 4-methoxybenzoate (117.0 mg, 0.3 mmol) and a magnetic stir bar. The vial was capped with a 14/20 rubber septum and connected to an argon Schlenk manifold via a needle through the septum. The vial was evacuated/backfilled with argon for three cycles. Next, THF was added (0.12 mL) via syringe through the septum, followed by degassed 2 wt % surfactant/H_2O solution (0.48 mL) via syringe through the septum, followed by pyridine (34 mg, 0.45 mmol, 34.5 uL) via syringe through the septum. The vial was placed in an aluminum block reactor and stirred vigorously for ~5 min to disperse the substrate and allow for some ligation of the nickel, a slight pink color was noted. To a still warm, oven dried ½ dram (2 mL) vial was quickly weighed $NaBH_4$ (45 mg, 1.2 mmol) and the vial capped to prevent moisture from caking the $NaBH_4$. (Note: good quality $NaBH_4$ is necessary for the reaction, $NaBH_4$ was stored in an argon glovebox and only small aliquots were removed for use at a time, caked/clumpy $NaBH_4$ has resulted in poor reaction conversion). The argon needle was removed from the reaction vial septum, the septum was quickly removed from the reaction vial, and the $NaBH_4$ vial poured into the reaction vial, and the septum replaced immediately, then the argon needle was replaced through the septum. The reaction was stirred vigorously at rt for ~2 min, then placed in an aluminum block reactor at 45 ^oC and stirred vigorously until completion (1 h). During the reaction, foaming may rise in the vial, if foam began to reach the top of the vial, the argon needle was briefly removed and the vial tapped on the benchtop to decrease the foam level, then the argon needle re-inserted and the reaction placed back in the block reactor and stirred

vigorously. Reaction completion was determined by TLC analysis. A 50 uL syringe was inserted through the septum and ~5 uL of reaction mixture was removed from the vial and placed in a small test tube, rinsing with ~75 uL of Et_2O into the test tube. The Et_2O layer was used for TLC analysis, the product spot appearing slightly above the starting material spot (10:90 Et_2O/hexanes). Upon completion, the septum was removed from the vial, and the reaction mixture extracted with EtOAc, dried over anhydrous Na_2SO_4, and the organic layer adsorbed onto Celite. The crude product was purified by silica gel column chromatography using hexanes then 10:90 Et_2O/hexanes.

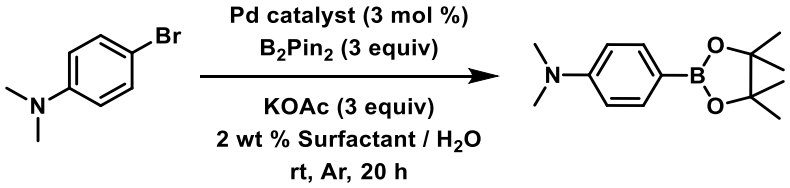
Reductive amination



To a 2 dram vial with stir bar was added Fe/ppm Pd/Ni NPs (5 mg), methyl-4-formylbenzoate (82.1 mg, 0.5 mmol, 1.0 equiv) and the vial capped with a septum. The vial was evacuated/backfilled with argon 3x cycles, then via syringe was added THF (0.2 mL) and 4-fluoroaniline (55.6 mg, 0.5 mmol, 47.4 uL, 1.0 equiv). The mixture was stirred for 2 min, then via syringe was added 2 wt % surfactant/H_2O solution (0.8 mL) and the reaction stirred an additional 15 min at which point the somewhat insoluble imine intermediate had formed. The vial was opened and $NaBH_4$ (37.8 mg, 1.0 mmol, 2 equiv) was quickly added and the vial re-capped with the septum. The reaction mixture was poorly soluble, so an additional 100 uL of THF was added. After stirring for 30 minutes, the reaction was still incomplete, so the vial was opened an addition 1.0 mmol of $NaBH_4$ was

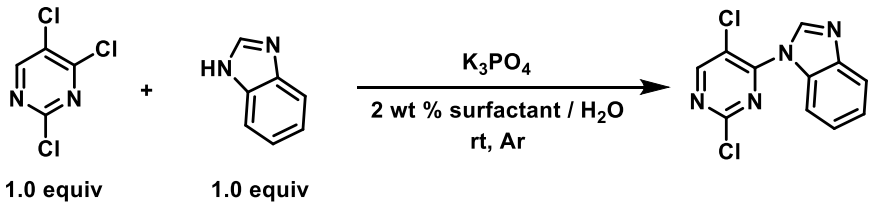
added. After stirring another 30 min, the reaction was complete by TLC using 30/70 (Et_2O/hexanes) and staining with ninhydrin. The reaction mixture was basified using 1 M KOH solution, extracted with EtOAc, the combined organic phase dried over anhydrous Na_2SO_4 and the solvent removed via rotary evaporation. The product was purified by column chromatography using 30/70 (Et_2O/hexanes) to give methyl 4-(((4-fluorophenyl)amino)-methyl)benzoate as a colorless oil which darkens upon exposure to air. (NL-3-179)

Miyaura borylation



To a 1 dram vial inside an argon filled glovebox was added Pd(*t*-$Bu_3P)_2$ (7.7 mg, 0.015 mmol, 3 mol %), potassium acetate (147 mg, 1.5 mmol, 3 equiv), B_2Pin_2 (139.7 mg, 0.55 mmol, 1.1 equiv), and 4-bromo-*N*,*N*-dimethylaniline (100 mg, 0.5 mmol, 1.0 equiv). The vial was capped with a septum and removed from the glovebox. Via syringe was added 2 wt % surfactant / H_2O solution (1.0 mL) and the reaction stirred overnight (20 h) at rt. The reaction was extracted with EtOAc, the combined organic phases dried over anhydrous Na_2SO_4 and the solvent removed via rotary evaporation. The crude product was purified by column chromatography using hexanes then 7/93 (EtOAc/hexanes) to give *N*,*N*-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline as a white solid. (NL249)

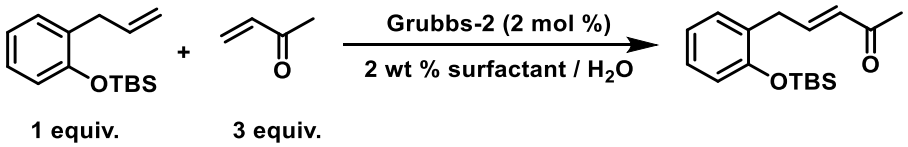
Procedure for S_NAr reactions



To a 2 dram vial with stir bar was added K_3PO_4 (254 mg, 1.2 mmol, 1.2 equiv) and benzimidazole (118.1 mg, 1 mmol, 1.0 equiv). Via syringe was added 2 wt % surfactant/H_2O solution (2 mL) and then 2,4,5-trichloropyrimidine (183.4 mg, 1.0 mmol, 1.0 equiv). The reaction mixture was stirred at rt overnight (typically 21-22 h). The reaction mixture was extracted with EtOAc, the combined organic phase dried over anhydrous Na_2SO_4 and the crude product adsorbed onto Celite. The crude product was purified by column chromatography using 20/80 (EtOAc/hexanes) then 40/60 (EtOAc/hexanes) to give 1-(2,5-dichloropyrimidin-4-yl)-1H-benzo[d]imidazole as a white crystalline solid.

The same procedure was utilized for the other S_NAr reaction, with the only changes being the increase of temperature from ambient to 45 ^oC and longer reaction time.

Grubbs olefin metathesis procedure

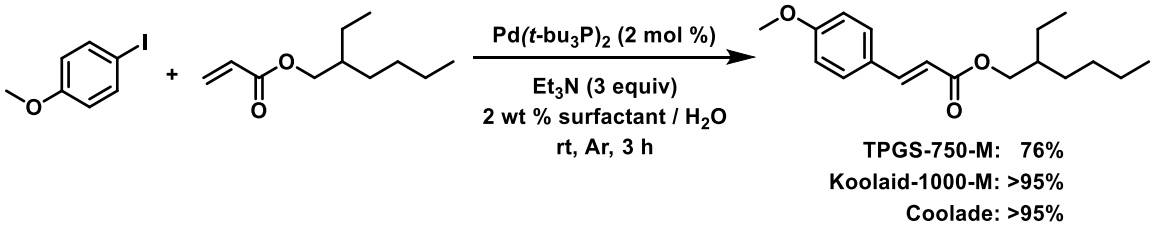


To a 1 dram vial with stir bar was added Grubbs-2 catalyst (8.5 mg, 0.010 mmol, 2 mol %) and (2-allylphenoxy)(tert-butyl)dimethylsilane (124.2 mg, 0.5 mmol, 134 uL, 1.0 equiv). The vial was capped with a rubber septum and evacuated/backfilled with argon 3x cycles. Via syringe was added 2 wt % surfactant/H_2O solution (1.0 mL) and methyl vinyl ketone

(105.1 mg, 1.5 mmol, 121 uL, 3 equiv) and the reaction stirred at rt until completion. The reaction mixture was extracted with EtOAc, the organic phase dried over anhydrous Na_2SO_4 and the crude product adsorbed onto Celite. The crude product was purified by column chromatography using hexanes then 20/80 (EtOAc/hexanes) to give (*E*)-5-(2-((tert-butyldimethylsilyl)oxy)phenyl)pent-3-en-2-one as a colorless oil.

The second Grubbs metathesis example was conducted using the same procedure, but with the following changes: CuI (3 mol %) was added at the beginning of the reaction and 2 equiv of butyl acrylate (as opposed to 3 equiv of methyl ethyl ketone in the previous example).

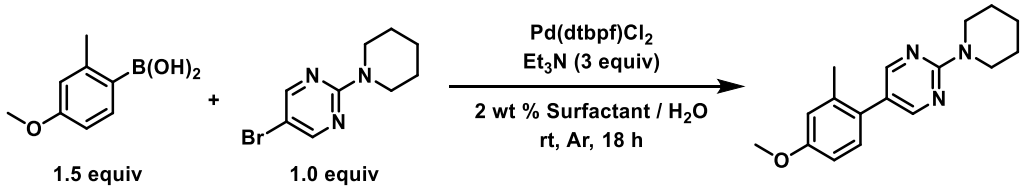
Heck coupling procedure



A 1 dram vial with stir bar was brought into an argon filled glovebox. To the vial was added Pd(*t*-$Bu_3P)_2$ (5.1 mg, 0.01 mmol, 2 mol %) and 4-methoxyiodobenzene (117.0 mg, 0.5 mmol, 1.0 equiv). The vial was capped with a rubber septum and removed from the glovebox. Via syringe was added 2 wt % surfactant / H_2O solution (1.0 mL), then Et_3N (152 mg, 1.5 mmol, 192 uL, 3 equiv), and ethylhexyl acrylate (184.2 mg, 1.0 mmol, 208 uL, 2 equiv). The reaction mixture was stirred vigorously at rt for 3 h. The reaction mixture was extracted with EtOAc and the organic layer dried over anhydrous Na_2SO_4 and the crude product adsorbed onto Celite. Note: a difficult to resolve emulsion was noted in the extraction of the trial using TPGS-750-M, this likely contributed to the lower yield for this

trial. The crude product was purified by column chromatography using hexanes then 5/95 (EtOAc/hexanes) to give 2-ethylhexyl (*E*)-3-(4-methoxyphenyl)acrylate as a colorless oil.

Procedure for ppm Pd Suzuki coupling

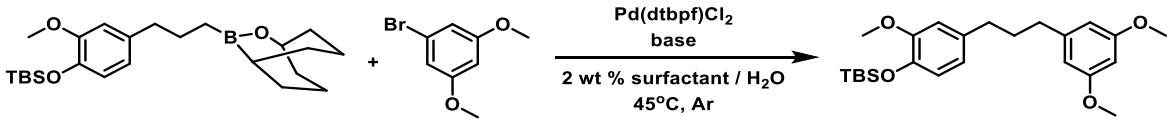


Catalyst stock solution preparation: An oven dried vial with stir bar was capped with a septum and cooled under vacuum. The vial was opened and Pd(dtbpf)Cl_2 (3.1 mg, 0.00476 mmol) was added and the vial re-capped with a septum and evacuated/backfilled with argon 3x cycles. Via syringe, degassed EtOAc (750 uL) was added and the mixture stirred vigorously for 10 min before use. Note: 40 uL of this stock solution is equivalent to 0.1 mol % Pd for a 0.25 mmol scale reaction.

Reaction procedure: To a 1 dram vial with stir bar was added 5-bromo-2-(piperidin-1-yl)pyrimidine (60.5 mg, 0.25 mmol, 1 equiv) and 4-methhoxy-2-methylphenylboronic acid (62.3 mg, 0.375 mmol, 1.5 equiv). The vial was capped with a septum and evacuated/backfilled with argon 3x cycles. Via syringe was added catalyst stock solution from the above procedure (40 uL for 0.1 mol % and 100 uL for 0.25 mol % Pd), and the vial again placed under vacuum to evaporate off the solvent. Via syringe was added degassed 2 wt % surfactant/H_2O solution (0.5 mL) and degassed Et_3N (76 mg, 0.75 mmol, 105 uL, 3 equiv). The reaction mixture was then stirred at rt overnight (18 h). The reaction

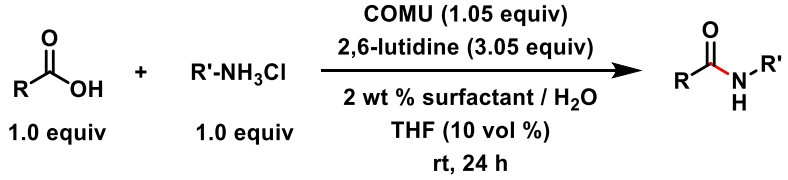
mixture was extracted with EtOAc, the organic phase dried over anhydrous Na_2SO_4, and the crude product adsorbed onto Celite. The crude product was purified by column chromatography using hexanes then 15/85 (EtOAc:hexanes) to afford 5-(4-methoxy-2-methylphenyl)-2-(piperidin-1-yl)pyrimidine as a white solid.

Procedure for *B*-alkyl Suzuki coupling



The coupling reactions were conducted according to the procedures described in the previous section on *B*-alkyl Suzuki couplings.

Procedure for peptide coupling and 2-step-1-pot deprotection-coupling



Coupling procedure: To a 1 dram vial was added *N*-Cbz-protected amino acid (1.0 equiv) and amino ester (1.0 equiv) in 2 wt % surfactant/H_2O [0.5 M] solution, followed by 2,6-lutidine (3.05 equiv). After stirring for 5 min, COMU (1.05 equiv) was added. The reaction was then stirred vigorously at rt (20-25 °C) until completion. The product was extracted with methyl *t*-butyl ether (MTBE; 10 mL) or a 1:1 mixture of hexanes/EtOAc. The organic layer was washed with a solution of HCl (1 M; 2 x 5 mL), with a saturated solution of sodium carbonate (2 x 5 mL) and finally brine (1 x 5 mL). The solution was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to yield the desired peptide. These

peptides can be used without further purification but yields were determined after flash chromatography on silica with a gradient of hexanes/EtOAc: 100:0 / 90:10 / 75:25 / 50:50 (100 mL each).

2-step, 1-pot deprotection-coupling procedure:

To a 1 dram vial was added the Cbz-protected dipeptide (1.1 equiv) followed by a solution of HCl (12 M; 1.0 equiv) in a 2 wt % surfactant/H_2O solution (overall [0.5 M] concentration). After dissolution, $Pd/C_{10\%}$ (10 wt %) was added. The vial was purged twice with hydrogen gas (balloon) and kept under H_2 atmosphere for 2 h at rt (20-25 °C) while stirring vigorously. The reaction was monitored by TLC (1:1 mixture of hexanes/EtOAc – UV and ninhydrin). After completion, the vial was purged with argon for 0.5 h. The vial was opened and *N*-protected amino acid (1.0 equiv) and COMU (3.05 equiv) were added. After 5 min, 2,6-lutidine (3.05 equiv) was added and the reaction was stirred for 2 h at rt (20-25 °C). The product was filtered through a pad of Celite® rinsing with MTBE and then extracted with MTBE or a 1:1 mixture of hexanes/EtOAc (10 mL). The organic layer was washed with a solution of HCl (1 M; 2 x 5 mL), with a saturated solution of sodium carbonate (2 x 5 mL) and brine (1 x 5 mL). The solution was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to yield the desired peptide, which can be used without further purification. Yields were determined after flash chromatography with a gradient of hexanes/EtOAc: 100 / 90:10 / 75:25 / 50:50 / 25:75 / 0:100 (100 mL each).

Procedure for Negishi-like coupling

Catalyst stock solution preparation: An oven dried 1 dram vial with stir bar was capped

with a septum and cooled under vacuum. The vial was opened and Pd(Amphos)Cl_2 (5.3 mg, 0.0075 mmol) was added. The vial was re-capped with a septum and evacuated/backfilled with argon 3x cycles. Via syringe was added degassed THF (150 uL) and the solution stirred for 5 min before use.

Reaction procedure. To a 1 dram vial with stir bar was added methyl-3-bromobenzoate (53.8 mg, 0.25 mmol, 1.0 equiv) and zinc dust (49.0 mg, 0.75 mmol, 3 equiv). The vial was capped with a septum and evacuated/backfilled with argon 3x cycles. Via syringe was added catalyst stock solution (0.00125 mmol, 25 uL, 0.5 mol % Pd), and the vial placed under vacuum to remove the solvent, then backfilled with argon. Via syringe was added 2 wt % surfactant/H_2O solution (0.5 mL), degassed TMEDA (29.1 mg, 0.25 mmol, 37.4 uL, 1.0 equiv), and 4-bromobutryic acid ethyl ester (97.5 mg, 0.5 mmol, 71.6 uL, 2 equiv). The reaction mixture was stirred vigorously at room temperature until completion. The reaction mixture was extracted with EtOAc, the organic phase dried over Na_2SO_4 and the crude product adsorbed onto Celite. The crude product was purified by column chromatography using hexanes then 5/95 (Et_2O/hexanes), then 10/90 (Et_2O/hexanes) to give methyl 3-(4-ethoxy-4-oxobutyl)benzoate as a colorless oil.

Tandem 3-step reaction sequence

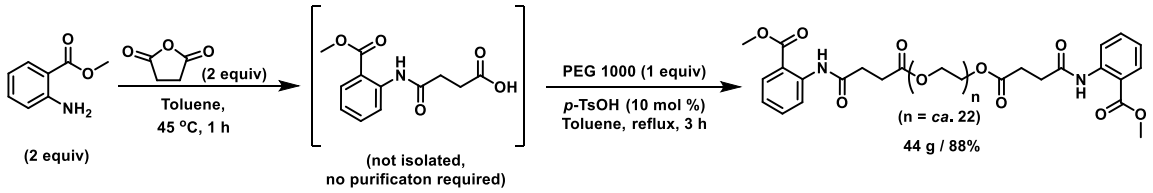
To a 1 dram (4 mL) vial was added 1-chloro-4-nitrobenzene (78.8 mg, 0.5 mmol, 1.0 equiv), Fe/ppm Pd Ni NPs (5 mg), $NaBH_4$ (56.7 mg, 1.5 mmol, 3 equiv), a magnetic stir bar, and the vial was capped with a screwcap. The cap was opened slightly and the vial was briefly purged with argon using a needle attached to an argon Schlenk line and the vial capped. The vial was opened slightly and via syringe THF (0.1 mL) was added and the vial re-capped and placed in an aluminum block reactor at rt and stirred for 2 min to partially

dissolve the nitro compound. The vial was opened slightly and 2 wt % surfactant/H_2O solution (0.9 mL) was added via syringe and the vial capped and stirred vigorously for 1.5 h. The vial was opened and an aliquot of reaction mixture removed, mixed with Et_2O and used for TLC analysis using (30:70 EtOAc/hexanes), showing all nitro compound had been consumed and product had formed which stained red with ninhydrin. The vial was stirred vigorously while concentrated HCl was very slowly added (~100 uL) to neutralize to pH 5-7 and destroy remaining borohydride. Next, K_3PO_4 (159 mg, 0.75 mmol, 1.5 equiv) and via syringe 2,4,5-trichloropyrimidine (91.7 mg, 57.3 uL, 1.0 equiv) were added and the vial capped and placed in an aluminum block reactor set to 45 ^oC and stirred vigorously overnight (18 h). The vial was opened and an aliquot of reaction mixture was removed for TLC analysis (30:70 EtOAc/hexanes) showing the reaction had reached completion. The vial was removed from the block reactor, opened and *N*-methylindole-5-boronic acid (131.2 mg, 0.75 mmol, 1.5 equiv), $Pd(OAc)_2$ (2.2 mg, 0.01 mmol, 0.02 equiv), and SPhos (8.2 mg, 0.01 mmol, 0.02 equiv) were added and the vial capped with a 14/20 rubber septum. The vial was connected to an argon Schlenk line via a needle through the septum and vacuum was applied to the reaction mixture and backfilled with argon for three cycles, allowing bubbling/boiling to occur briefly during each cycle. Via syringe, Et_3N (152 mg, 1.5 mmol, 3 equiv) was added and the vial returned to the aluminum block reactor at 45 ^oC and stirred vigorously overnight (17 h). The vial was opened and an aliquot of reaction mixture was removed for TLC analysis (30:70 EtOAc/hexanes), staining with vanillin (product R_f same as S_NAr product, but staining red with vanillin). The reaction mixture was extracted with EtOAc, dried over anhydrous Na_2SO_4, and purified by column

chromatography (20:80 EtOAc/hexanes) and the product then recrystallized by dissolving in a minimum of hot EtOAc and adding hot hexanes and allowing to cool.

3.14.4 Synthesis of Coolade

Scheme 26: 2-step, 1-pot procedure using Route 2



To an oven dried 250 mL round bottom flask with large oval magnetic stir bar was added 150 mL dry toluene, succinic anhydride (6.82 g, 68.2 mmol), and methyl anthranilate (10.34 g, 68.2 mmol). The flask was capped with a 14/20 septum, placed in a 50 °C oil bath (to maintain in internal temperature of 45 °C), attached to an argon Schlenk line via a needle and stirred vigorously for 1 h (note: argon atmosphere is not necessary for this reaction; attaching to a Schlenk line was merely a precaution against moisture). During this time, the reaction turns to a "slurry" and can become somewhat viscous if the reaction is not stirring effectively, and it may be necessary to remove the flask from the oil bath and shake the flask briefly and return it to the oil bath. After 1 h, an aliquot of the reaction mixture was removed and dissolved in methanol for analysis by TLC using MeOH/DCM (10/90), staining with bromocresol green. Note: some methyl anthranilate will remain after 1 h; this reaction may not go to completion.

Next, PEG 1000 was melted in a 50 mL beaker using a heat gun until fully melted (~70 °C). The reaction flask was removed from the oil bath, uncapped and placed on a top loading balance. PEG 1000 (34.1 g, 34.1 mmol) was added to the flask via pouring and

syringe (syringe the last ~1-2 g using a plastic 1 mL syringe without needle) into the flask. The flask was placed in a 140 ^{o}C (or whatever temperature needed to maintain reflux) oil bath and stirred briefly, then *p*-TsOH·H_2O (1.29 g, 6.82 mmol) was added. A Dean-Stark apparatus and condenser were fitted to the flask, the top of the condenser closed with a 14/20 rubber septum, attached to an argon Schlenk line via a needle and the apparatus purged with argon briefly. The reaction was refluxed until disappearance of methyl anthranilate succinate (typically about 3 h if a brisk reflux is maintained in the Dean-Stark apparatus). Note: do not allow the reaction to reflux significantly longer than necessary, i.e., do not reflux overnight as this has resulted in increased impurities in the reaction mixture. An aliquot of the reaction mixture was removed via pipette, diluted with DCM and used for TLC analysis using first Et_2O/DCM (50:50) then eluting the same plate with MeOH/DCM (10:90).

Upon reaction completion, the flask was removed from the oil bath and allowed to cool, then basic aluminum oxide (7.5 g) was added and it was stirred for ~10 min. The mixture was filtered via a Buchner funnel with filter paper after which the flask and basic alumina were rinsed with warm toluene (~25 mL). The solvent was removed via rotary evaporator (this recovered toluene can be re-used, see section 2.2). The crude product was briefly dried under vacuum while stirring at 60 ^{o}C to remove residual toluene. The crude mass was determined and a 50 wt % aqueous solution was prepared (i.e., 50 g crude product + 50 mL HPLC grade H_2O). This solution was poured into a separatory funnel (it helps to first make a ~60 wt % solution, and keep some water in reserve to rinse the flask into the separatory funnel). The 50 wt % solution was extracted with Et_2O (3 x 50 mL) (note: while EtOAc was originally used for this step, it extracts a significant amount of

surfactant; Et_2O is used here because it extracts far less). Extract with ether until the aqueous layer produces a clean TLC. Note: the 50 wt % solution appears as a milky white emulsion initially, but turns to an opaque red color and the layers separate after shaking and allowing to settle. After extraction, the 50 wt % solution can either be diluted to the desired concentration (i.e., 2 wt %) for immediate use, or if wax is desired, the water can be removed via rotary evaporator and the product dried under vacuum to obtain a reddish colored solid. Note: if the material will be stored for a period of time, remove the water and store the product as a wax. See supporting information for general procedures on surfactant solution preparation and comparison reaction trials.

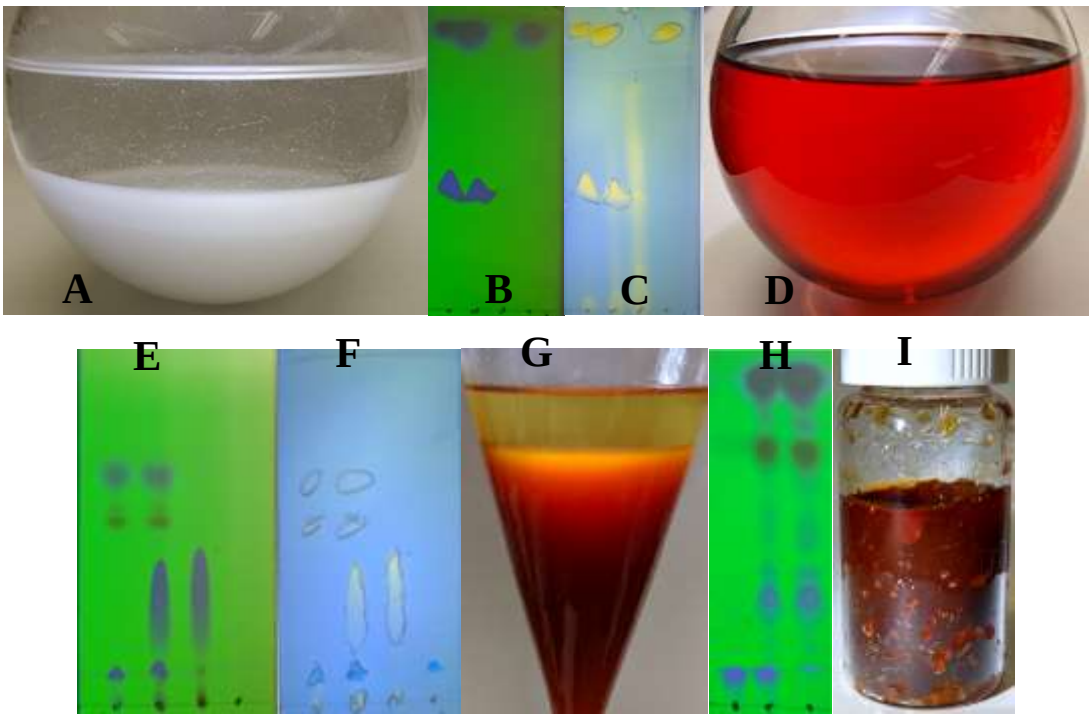


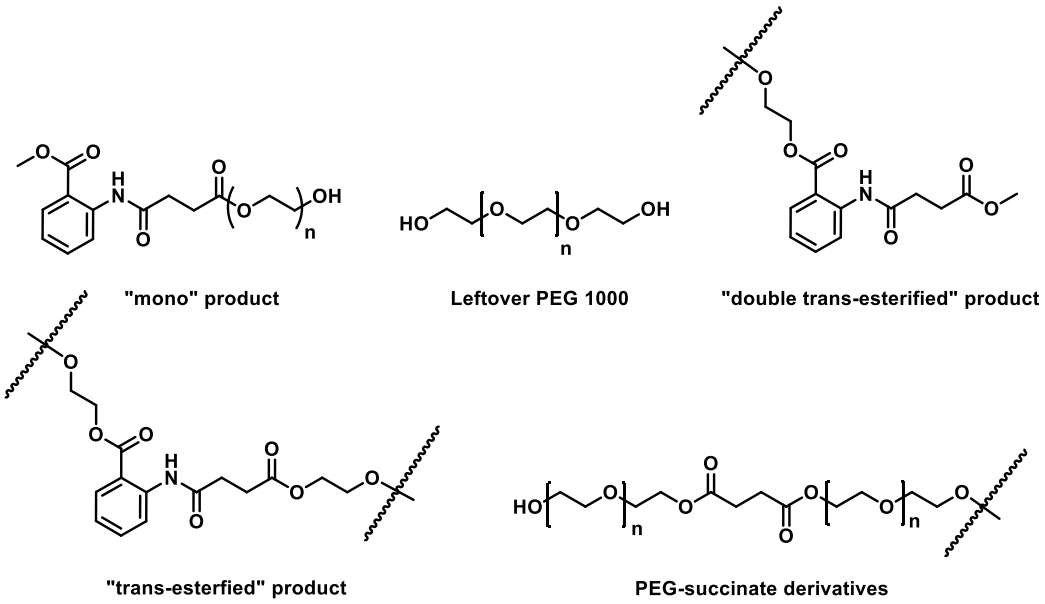
Figure 25: The reaction sequence and purification: (A) reaction after 1 h, (B) TLC of reaction (L to R: reaction mixture, co-spot, succinic anhydride, methyl anthranilate) (C) TLC stained with bromocresol green (D) reflux to completion (3 h) (E) TLC of reaction (L

to R: reaction mixture, co-spot, methyl anthranilate succinate, PEG 1000) (F) TLC stained with bromocresol green (G) removal of impurities by Et_2O extraction (H) TLC of purification (L to R: aqueous layer, co, Et_2O layer) (I) Coolade wax.

Synthesis of Coolade using toluene recycle

After reaction completion, treatment with basic alumina, and then filtration (see synthesis of Coolade in Experimental Section), the solvent was removed via rotary evaporation. The toluene recovered in the receiver flask was then dried using anhydrous Na_2SO_4 and then molecular sieves. This solvent (~140-160 mL) was utilized in the synthesis from section 2.1 above with no other changes to the procedure.

Scheme 27: Possible impurities arising in 2-step-1-pot procedure



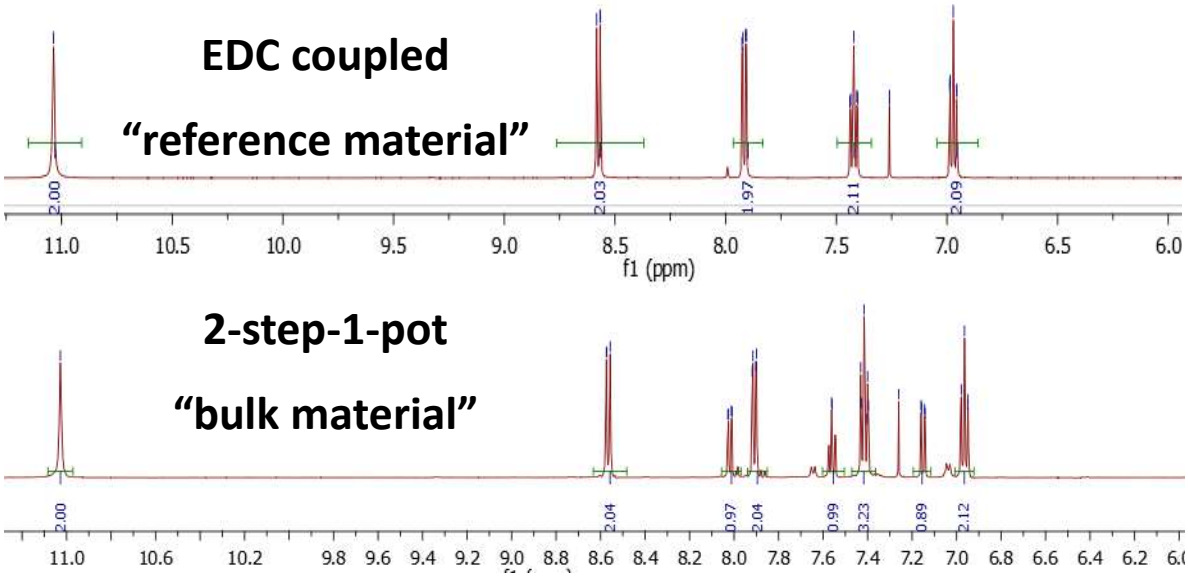


Figure 26: ^{1}H NMR of Coolade synthesized by Route 3 (top) and Route 2 (bottom).

Calculation of E Factors for the synthesis of Coolade using Route 2

E Factor calculation for reaction and purification:

In reaction: $150\ mL\ toluene \times \frac{0.867g}{ml} = 130\ g$

Rinsing flask + basic alumina: $25\ mL\ toluene \times \frac{0.867\ g}{mL} = 22\ g$

Preparing 50 wt % aqueous solution: $50\ mL\ water \times \frac{1\ g}{mL} = 50\ g$

Diethyl ether extraction: $150\ mL\ ether \times \frac{0.713g}{mL} = 107\ g$

E Factor: $130\ g + 22\ g + 50\ g + 107\ g = 309\ g \div 44\ g\ product = 7.0\ \frac{g\ waste}{g\ product}$

E Factor calculation for reaction using toluene recycle:

In reaction: (toluene recycled from previous reaction)

Rinsing flask + basic alumina: $25\ mL\ toluene \times \frac{0.867\ g}{mL} = 22\ g$

Preparing 50 wt % solution: $50\ mL\ water \times \frac{1\ g}{mL} = 50\ g$

Diethyl ether extraction: $150\ mL\ ether \times \frac{0.713g}{mL} = 107\ g$

E Factor: $22\ g + 50\ g + 107\ g = 179\ g \div 42\ g\ product = 4.3\ \frac{g\ waste}{g\ product}$

Synthesis of Coolade via EDC coupling (to make reference material)

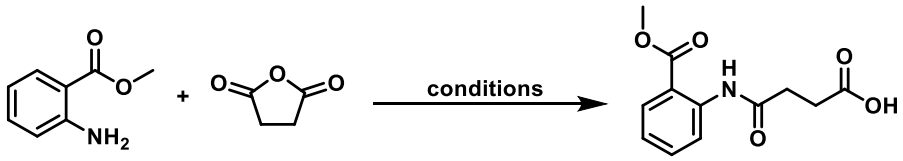
This procedure was used to synthesize pure reference material, not for making bulk material for reactions.

Route 1 optimization

The initial route used to synthesize Coolade was a 2-step, 2-pot procedure where both the intermediate as well as product were isolated and purified. This method was used to synthesize the material for the initial trials, but later Method 2 was developed to make bulk material with a 2-step, 1-pot procedure.

Synthesis of methyl anthranilate succinate:

Table 15: Various reaction conditions used to synthesize methyl anthranilate succinate



Trial	Solvent (M)	Succinic anhydride (equiv)	Et_3N (equiv)	DMAP (equiv)	temp	Time (h)	Result / Yield
NL69	DCM (0.7)	1.5	1	0.5	rt	24	5.3 g / 64%
NL232	DCM (0.6)	1.05	1.05	0.1	rt	8	8.3 g / 77%
NL243	DCM (1.3)	1.	1.05	0.	rt	48	25.5 g / 85%
NL-2-98.1	MTBE (2)	1.1	1.05	0.1	rt	24	2.4 g / 81%
NL-2-98.2	Acetone (2)	1.1	1.05	0.1	rt	24	Trace conversion
NL-2-209	DCM (0.5)	1.5	1.0	0.5	rt	21	62 g / 93%
NL-2-211.1	None (neat)	2	1.0	0.25	rt	17	0.83 g / 83%
NL-2-211.2	None (neat)	1.0	None	0.25	rt	17	Good conversion, not isolated
NL-2-211.3	None (neat)	1.0	None	None	rt	17	Good conversion, not isolated
NL-2-211.4	None (neat)	1.0	none	0.25	rt	17	Good conversion, not isolated
NL-2-211.5	None (neat)	1.0	none	none	rt	17	0.80g / 80%

NL-2-252	Toluene (1.6)	1.0	none	none	rt to 55ºC	24	Good conversion, not isolated
NL-5-127	DCM (1.2)	1.5	1.1	0.1	0ºC to rt	21	98 g / 65%*

*This large-scale reaction turned from purple to black overnight, with some baseline material, which did not happen in any other trials. The product was recrystallized from EtOH, which eliminated the impurities at the loss of some yield. It is unclear why this happened.

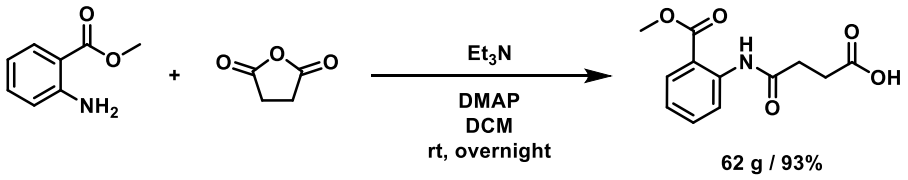
Note: while the "neat" reactions gave very fast conversion, the reaction mixture turns from slurry to solid within minutes, stopping stirring. This method may be useful for small scale (i.e. <10 g), but is likely to be very problematic when scaling so it was not used for larger scale reactions.

Methyl anthranilate was reacted with succinic anhydride using a number of different conditions. The reaction was initially conducted with the same procedure as that for making tocopherol succinate for the TPGS-750-M synthesis. In attempting to improve this process and eliminate the need for halogenated solvents, the reaction was found to proceed in other solvents such as toluene and MTBE. Also, the reaction was found to occur when the reaction was run "neat" in the absence of solvent, however the product is very crystalline and is very difficult to stir, and thus was considered unsuitable for scale-up.

Figure 27: Reaction at completion, crystals filtered after precipitating with HCl

For reactions in solvent, upon reaction completion, almost all of the product is solubilized, with a small amount of succinic anhydride remaining undissolved. Upon addition of aqueous HCl, the product precipitates and can be isolated by filtration. The second step was

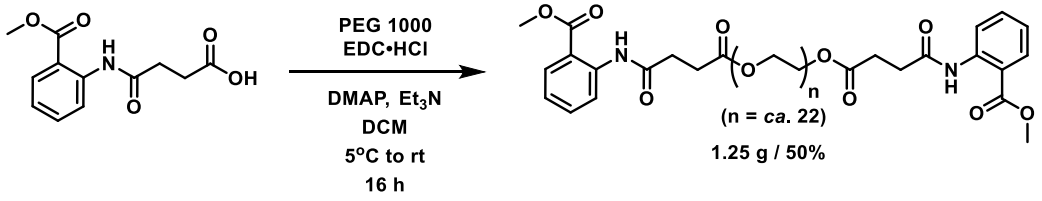
4-((2-(Methoxycarbonyl)phenyl)amino)-4-oxobutanoic acid



To an oven dried 1 L round bottom flask was added dry DCM (500 mL), a large oval magnetic stir bar, succinic anhydride (39.7 g, 397 mmol, 1.5 eq), DMAP (16.2 g, 132 mmol, 0.5 equiv), and triethylamine (26.8 g, 265 mmol, 1.0 equiv) the flask capped with a 24/40 rubber septum and placed in a water bath at rt and stirred vigorously. Via syringe was added methyl anthranilate (40.0 g, 265 mmol, 1 equiv) over ~5 min, during which the succinic anhydride slowly dissolved and a slight exotherm was noted. The flask was stirred overnight at rt upon which time the reaction had taken on a purple color and was homogeneous, except for some flakes of undissolved succinic anhydride. An aliquot of the

reaction mixture was removed via pipette and analyzed by TLC using MeOH/DCM (10/90), product R_f ~0.5 (UV active spot purple in color), showing that methyl anthranilate had been consumed. To the reaction flask was added 2 M HCl solution (~300 mL) and the flask stirred vigorously for ~2 min and allowed to settle, upon which time the product crystallized, forming a "slurry." The flask was transferred to an ice bath and allowed to cool for ~15 min. Product was recovered by filtration in a large Buchner funnel with filter paper, and the DCM layer separated using a separatory funnel. The filter cake was added to an Erlenmeyer flask, and stirred with 1 M HCl, then recovered via filtration in a large Buchner funnel and rinsed with hexanes then dried under vacuum to yield 55 g of off-white crystals (83%). The DCM layer was concentrated to ~150 mL via rotary evaporator, chilled, and an additional 7 g of product were recovered by filtration using the same method as above, overall yield 62 g (93%).

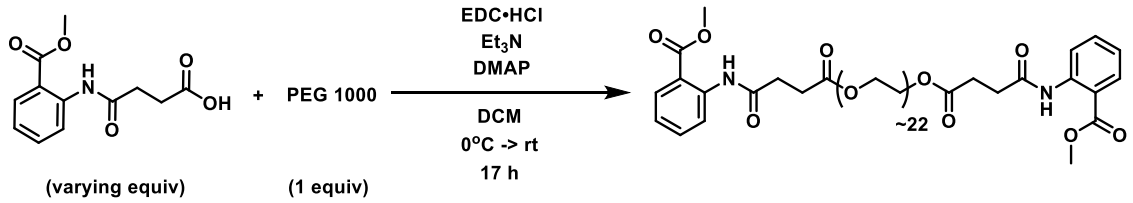
bis(4-((2-(Methoxycarbonyl)phenyl)amino)-4-oxobutanoic acid)polyethylene glycol 1000



To an oven dried 50 mL round bottom flask with magnetic stir bar was added PEG 1000 (1.71 g, 1.71 mmol, 1.0 equiv), 4-((2-(methoxycarbonyl)phenyl)amino)-4-oxobutanoic acid (1.29 g, 5.13 mmol, 3 equiv), DMAP (98 mg, 0.8 mmol, 0.47 equiv), EDC•HCl (1.48 g, 7.70 mmol, 4.5 equiv), the flask was capped with a 14/20 rubber septum and

evacuated/backfilled with argon. Via syringe was added dry DCM (20 mL), the reaction stirred vigorously and upon dissolution of solids the flask was placed in an ice bath. Via syringe was added triethylamine (1.56 g, 15.4 mmol, 9 equiv), the reaction stirred for 10 min before removal of the flask from the ice bath and allowed to return to rt. The reaction was stirred overnight (14 h). An aliquot from the reaction mixture was removed via pipette and used for TLC analysis using Et_2O/DCM (50/50) then MeOH/DCM (10/90) showing that both the PEG 1000 and methyl anthranilate had been consumed, product R_f ~0.6, staining with bromocresol green. The organic layer was washed with 1.5 M HCl (2 x 20 mL) then saturated $NaHCO_3$ aqueous solution (1 x 20 mL) a strong emulsion resulted, the $NaHCO_3$ layer was separated and then extracted with DCM (1 x 15 mL), the combined organic phase was washed with saturated NaCl brine solution, dried over anhydrous Na_2SO_4 and the solvent removed via rotary evaporator. The crude oil was purified by column chromatography using DCM then MeOH/DCM (5:95) to give a tan oil (1.25 g / 50%).

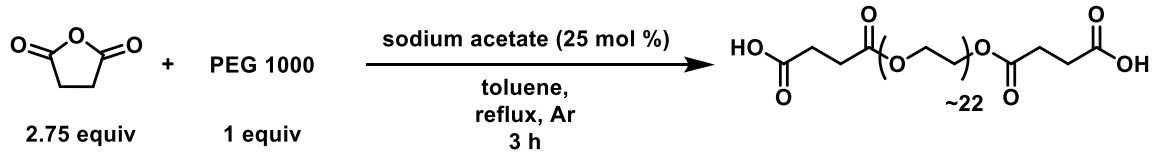
Table 16: Additional couplings using Route 3



Trial	Methyl anthranilate succinate (equiv)	EDC (equiv)	DMAP (equiv)	Et_3N (equiv)	% functionalization of PEG	Yield
NL-5-99	2.2	3.4	0.05	6	71%	39 g / 81%
NL-5-128	2.4 + 0.15	4 + 0.1	0.2	6	80%	20 g / 42%*

*only best fractions kept

Table 17: Synthesis of PEG 1000 di-succinate for using in Route 4



Trial	Succinic anhydride (equiv)	PEG functionalization (%)	Yield
NL-5-131	2.75	>95%	30 g / >95%
NL-5-134	2.75	>95%	238 g / 95%

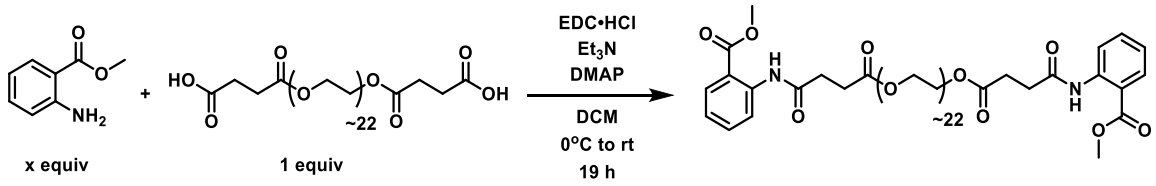
Procedure for PEG di-succinate

To a 1 L round bottom flask with large oval stir bar was added PEG 1000 (208 g, 208 mmol, 1.0 equiv), sodium acetate (4.27 g, 52 mmol, 0.25 equiv), and toluene (300 mL). The flask was fitted with a Dean-Stark trap and condenser and heated to reflux. The

mixture was refluxed for 30 min, occasionally draining off wet toluene. The flask was removed from the oil bath and allowed to cool slightly. The flask was opened and succinic anhydride (57.24 g, 572 mmol, 2.75 equiv) was added. The flask was fitted with a condenser and heated to reflux for 2 h upon which time the reaction was deemed complete by TLC (R_f = 0.50 with 10/90 (MeOH:DCM), staining with bromocresol green. The reaction was cooled to room temperature and the toluene removed via rotary evaporator. The crude product was dissolved in 200 mL of saturated $NaHCO_3$ and stirred for 30 min. Note: Reaction mixture had to be transferred to a 2 L flask due to excessive foaming. The reaction mixture was then acidified to pH ~2 with 2 M HCl and extracted with DCM. Note: This extraction causes a significant emulsion which requires a significant amount of time to resolve. The combined organic phase was dried with anhydrous $MgSO_4$, filtered, and the solvent removed via rotary evaporation. The product was dried under vacuum with stirring at 75°C, to give the product (238 g, ~95%) which contained traces of DCM and acetic acid.

In an attempt to utilize a better nucleophile, the synthesis was rerouted to use methyl anthranilate as the nucleophile. This was only partially successful, as numerous byproducts plagued the reaction and extreme emulsions resulted during attempts at aqueous acidic and basic workup. Some very high purity material was however obtained. Only the best chromatography fractions were kept for these products.

Table 18: Amide coupling for Coolade synthesis using Route 4



Trial	Methyl anthranilate (equiv)	EDC (equiv)	DMAP equiv	Et_3N (equiv)	% functionalization of PEG	Yield
NL-5-132	3.0	4	0.2	6	>95%	23%
NL-5-138	2.2	2.4	0.1	4	69%	40%

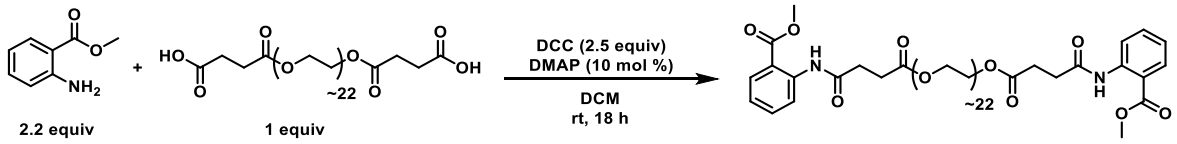
General procedure for amide coupling reaction:

To a 250 mL oven dried round bottom flask with stir bar was added PEG 1000-di-succinate (30 g, 25 mmol, 1.0 equiv) and dry DCM (125 mL). The flask was cooled in an ice bath for 10 min before adding sequentially; methyl anthranilate (11.3 g, 75 mmol, 9.71 mL, 3 equiv), EDC*HCl (19.2 g, 100 mmol, 4 equiv), DMAP (611 mg, 5 mmol, 0.2 equiv), and Et_3N (15.2 g, 150 mmol, 20.9 mL, 6 equiv). After stirring for 20 min, the flask was removed from the ice bath and allowed to warm to rt. The reaction mixture was stirred overnight (19 h), and an aliquot removed for analysis. The aliquot was washed with 1 M HCl and saturated $NaHCO_3$ which produced a slight emulsion. The aliquot showed full consumption of the PEG-di-succinate, with predominantly one product and some small impurities. The reaction mixture was poured into a separatory funnel with 1 M HCl, and gently shaken, which produced an intractable emulsion which only partially resolved after ~2 h. The contents of the separatory funnel were poured into a round bottom flask and the DCM removed via rotary evaporation. The contents of the flask

were placed back in the separatory funnel and extracted with EtOAc, which produced far less emulsion than DCM had produced. The aqueous layer was extracted 2x more times, however persistent emulsion resulted in incomplete phase separation on each extraction. The combined organic extracts were washed with brine, then dried over anhydrous $MgSO_4$, filtered, and the solvent removed via rotary evaporator. The crude material was purified by filtration over a short plug of silica (~3" x 6"), eluting with EtOAc then 10/90 (MeOH:DCM), collecting several fractions. Only one fraction was free of impurities by TLC (8.5 g / 23%).

To eliminate the need for acid/base workup required with EDC coupling, DCC was tested as a coupling reagent. Unfortunately, the resulting DCU byproduct was found to be extremely difficult to remove completely. DCU is fairly soluble in DCM, so it cannot be removed by filtration. While DCU is almost insoluble in Et_2O, the surfactant itself is not soluble in Et_2O. Attempts to remove DCU by precipitation followed by filtration were not successful.

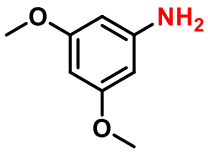
Table 19: Synthesis of Coolade via DCC coupling



Trial	Methyl anthranilate (equiv)	DCC (equiv)	% functionalization of PEG	Yield
NL-5-139.1	2.2	2.5	N/A	N/A
NL-5-139.2	2.2	2.5	84%	60%

3.14.5 Characterization Data

3,5-Dimethoxyaniline (**1**)



Reduction was conducted according to the procedure in section 3.17 to give (**1**) as a white solid. Spectroscopic data matched that reported in the literature.[90]

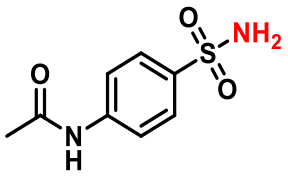
R_f = 0.30 (EtOAc/hexanes 40:60).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (t, *J* = 2.2 Hz, 1H), 5.87 (d, *J* = 2.2 Hz, 2H), 3.73 (s, 7H), 3.62 (s, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 161.74, 148.51, 93.80, 90.98, 77.16, 55.17.

[90] Y. Hoshino, N. Ohtsuka, T. Okada, K. Honda, *Tetrahedron Lett.* **2016**, *57*, 5304–5307.

N-(4-Sulfamoylphenyl)acetamide (**2**)



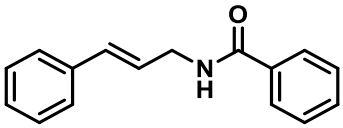
Reduction was conducted according to the procedure in section 3.17 to give (**2**) as a white solid. Spectroscopic data matched that reported in the literature.[91]

R_f = 0.40 (MeOH/DCM 20:80).

^{1}H NMR (500 MHz, DMSO) δ 10.29 (s, 3H), 7.75 (d, *J* = 9.3 Hz, 12H), 7.23 (s, 6H), 3.51 (s, 4H), 2.08 (s, 9H).

^{13}C NMR (126 MHz, DMSO) δ 168.90, 142.20, 138.07, 126.67, 118.43, 69.79, 39.52, 24.12.

N-Cinnamylbenzamide (**3**)



Reaction was conducted according to the procedure in section 3.17, to give (**3**) as a white solid.

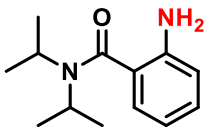
[91] F. J. Lundevall, V. Elumalai, A. Drageset, C. Totland, H.-R. Bjørsvik, *Eur. J. Org. Chem.* **2018**, *83*, 3416–3425.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 – 7.79 (m, 2H), 7.54 – 7.47 (m, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.37 (d, *J* = 7.7 Hz, 2H), 7.32 (dd, *J* = 8.6, 6.7 Hz, 2H), 7.29 – 7.23 (m, 1H), 6.60 (s, 1H), 6.57 (s, 1H), 6.28 (ddd, *J* = 16.0, 7.3, 5.2 Hz, 1H), 4.24 (t, *J* = 6.0 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.5, 136.6, 134.5, 132.5, 131.6, 128.7, 128.7, 127.8, 127.1, 126.5, 125.6, 42.2.

Spectra matches those previously reported[92]

2-Amino-*N*,*N*-diisopropylbenzamide (**4**)



Synthesized according to the procedure in section 3.17 (procedure B) using THF co-solvent (10 vol %) and 3 equiv $NaBH_4$ to give (**4**) as a colorless oil. Spectroscopic data matched that reported in the literature.[93]

R_f = 0.50 (EtOAc/hexanes 20:80)

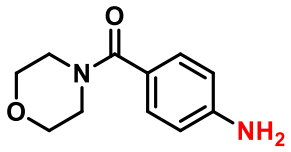
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.14 – 7.10 (m, 1H), 6.99 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.74 – 6.68 (m, 2H), 4.03 (s, 2H), 3.74 (s, 2H), 1.35 (s, 12H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.42, 144.33, 129.56, 126.03, 123.95, 117.82, 116.62, 48.28, 20.99.

[92] Theodorou, A.; Triandafillidi, I.; Kokotos, C. G. Organocatalytic Synthesis of Oxazolines and Dihydrooxazines from Allyl-Amides: Bypassing the Inherent Regioselectivity of the Cyclization. *Adv. Synth. & Catal.* **2018**, *360*, 951–957.

[93] H. Pang, F. Gallou, H. Sohn, J. Camacho-Bunquin, M. Delferro, B. H. Lipshutz, *Green Chem.* **2018**, *20*, 130–135.

(4-Aminophenyl)(morpholino)methanone (**5**)



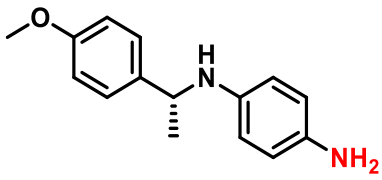
Synthesized according to the procedure in section 3.17 (procedure A) using THF co-solvent (20 vol %) to give (**5**) as a white solid. Spectroscopic data matched that reported in the literature.[94]

R_f = 0.50 (MeOH/DCM 10:90)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.16 (m, 1H), 6.63 – 6.53 (m, 1H), 3.99 (s, 1H), 3.66 – 3.55 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.95, 148.63, 129.33, 124.13, 114.07, 77.16, 70.45, 66.90.

Spectroscopic data matched that reported in the literature.[4d]

(*R*)-*N*^{1}-(1-(4-Methoxyphenyl)ethyl)benzene-1,4-diamine (**6**)



Synthesized according to the procedure in section 3.17 (procedure B) using THF co-solvent (25 vol %) and 5 equiv $NaBH_4$ to give (**6**) as a yellow oil.

[94] C. M. Gabriel, N. R. Lee, F. Bigorne, P. Klumphu, M. Parmentier, F. Gallou, B. H. Lipshutz, *Org. Lett.* **2017**, *19*, 194–197.

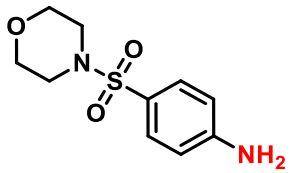
R_f = 0.30 (EtOAc/hexanes 40:60).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.27 (m, 2H), 6.89 – 6.84 (m, 2H), 6.53 (d, *J* = 8.6 Hz, 2H), 6.43 (d, *J* = 8.6 Hz, 2H), 4.37 (q, *J* = 6.6 Hz, 1H), 3.79 (s, 3H), 3.37 (s, 3H), 1.48 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 158.45, 140.56, 137.74, 137.62, 127.05, 116.85, 115.21, 113.99, 77.16, 55.30, 53.86, 25.09.

Spectroscopic data matched that reported in the literature.[95]

4-(Morpholinosulfonyl)aniline (**7**)



Synthesized according to the procedure in section 3.17 (procedure B) using THF co-solvent (20 vol %) and 5 equiv $NaBH_4$ to give (**7**) as a white solid.

R_f = 0.30 (EtOAc/hexanes 40:60).

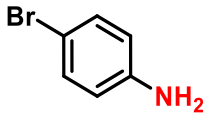
^{1}H NMR (500 MHz, DMSO) δ 7.35 (d, *J* = 8.6 Hz, 1H), 6.66 (d, *J* = 8.7 Hz, 1H), 6.11 (s, 1H), 3.67 – 3.54 (m, 2H), 2.83 – 2.68 (m, 2H).

^{13}C NMR (126 MHz, DMSO) δ 153.34, 129.68, 118.69, 112.69, 65.26, 45.90, 39.52.

[95] N. R. Lee, A. A. Bikovtseva, M. Cortes-Clerget, F. Gallou, B. H. Lipshutz, *Org. Lett.* **2017**, *19*, 6518–6521.

Spectroscopic data matched that reported in the literature.[96]

4-Bromoaniline (**8**).



Synthesized according to the procedure in section 3.17 (procedure B) using THF co-solvent (20 vol %) and 5 equiv of $NaBH_4$ to give (**8**) as a tan oil.

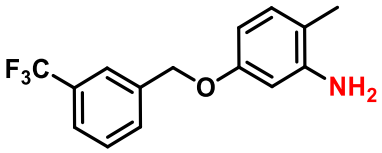
R_f = 0.3 (EtOAc/hexanes 20:80).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 8.6 Hz, 1H), 6.56 (d, J = 8.6 Hz, 1H), 3.57 (s, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 145.47, 132.12, 116.84, 110.33, 77.16.

Spectroscopic data matched that reported in the literature.[97]

2-Methyl-5-((3-(trifluoromethyl)benzyl)oxy)aniline (**9**).



[96] T. R. Jones, M. D. Varney, S. E. Webber, K. K. Lewis, G. P. Marzoni, C. L. Palmer, V. Kathardekar, K. M. Welsh, S. Webber, D. A. Matthews, et al., *J. Med. Chem.* **1996**, *39*, 904–917.
[97] N. R. Lee, A. A. Bikovtseva, M. Cortes-Clerget, F. Gallou, B. H. Lipshutz, *Org. Lett.* **2017**, *19*, 6518–6521.

Synthesized according to the procedure in section 3.17 (procedure B) using DCM co-solvent (10 vol %) and 5 equiv of $NaBH_4$ to give (**9**) as a pale yellow solid.

R_f = 0.30 (EtOAc/ hexanes 20:80).

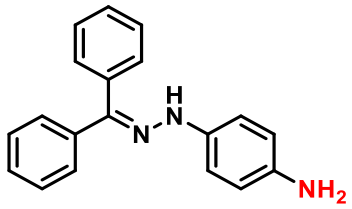
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.61 (s, 2H), 7.50 (s, 1H), 6.97 (d, *J* = 8.9 Hz, 1H), 6.35 (s, 2H), 5.06 (s, 2H), 3.64 (s, 2H), 2.12 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 157.99, 145.74, 138.62, 131.29 (q, $^1J_{(C-F)}$ = 32.5 Hz), 131.13, 130.63, 129.05, 127.48 (q, $^1J_{(C-F)}$ = 271 Hz), 124.65 (q, $^1J_{(C-F)}$ = 3.75 Hz), 124.04 (q, $^1J_{(C-F)}$ = 3.75 Hz), 115.55, 104.51, 102.02, 69.21, 16.54;

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.58

Spectroscopic data matched that reported in the literature.[98]

4-(2-(Diphenylmethylene)hydrazinyl)aniline (**10**).



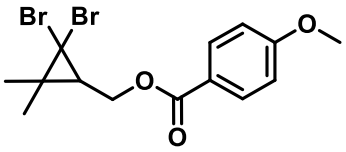
Synthesized according to the procedure in section 3.17 (procedure B) using THF co-solvent (25 vol %) and KBH_4 (6 equiv) to give (**10**) as a dark brown solid. Spectroscopic data matched that reported in the literature.[32] R_f = 0.3 (EtOAc/hexanes 30:70).

[98] H. Pang, F. Gallou, H. Sohn, J. Camacho-Bunquin, M. Delferro, B. H. Lipshutz, *Green Chem.* **2018**, *20*, 130–135.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (t, *J* = 7.6 Hz, 4H), 7.52 (t, *J* = 7.2 Hz, 1H), 7.37 – 7.30 (m, 5H), 7.27 (dd, *J* = 7.9, 5.8 Hz, 1H), 6.96 (d, *J* = 8.6 Hz, 2H), 6.70 (d, *J* = 8.6 Hz, 2H), 3.83 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 142.93, 138.68, 138.58, 138.12, 132.99, 129.63, 129.23, 129.07, 128.13, 127.63, 126.24, 116.94, 114.21.

(2,2-Dibromo-3,3-dimethylcyclopropyl)methyl 4-methoxy-benzoate (**11a**).



Synthesized from (2,2-dibromo-3,3-dimethylcyclopropyl)methanol and 4-methoxybenzoyl chloride. To an oven dried 50 mL round bottom flask was added (2,2-dibromo-3,3-dimethylcyclopropyl)methanol (2.315 g, 8.975 mmol, 1.0 equiv) and DMAP (110 mg, 0.90 mmol, 0.1 equiv) and a magnetic stir bar. The flask was capped with a 14/20 septum and evacuated/backfilled with argon over three cycles. Via syringe was added pyridine (25 mL) and the flask was stirred for 2 min, then the septum removed and *p*-methoxybenzoyl chloride (1.68 g, 9.87 mmol, 1.1 equiv) added portion-wise as a solid over 2 min. The flask was stirred at rt for 1 h, and an aliquot was removed for TLC analysis (20/80 Et_2O:hexanes) showing some (2,2-dibromo-3,3-dimethylcyclopropyl)methanol remaining. An additional 0.4 equiv of *p*-methoxybenzoyl chloride was added as a solid and the reaction stirred an additional 1 h. The reaction mixture was poured into a separatory funnel with 1 M aqueous HCl solution and

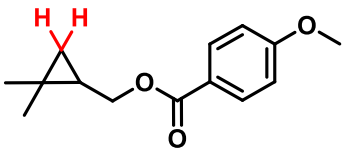
extracted with Et_2O. Several HCl washes were necessary to fully remove pyridine from the organic phase. The organic phase was dried over anhydrous Na_2SO_4 and the organic phase adsorbed onto Celite. The product was purified by column chromatography using hexanes then 10/90 Et_2O: hexanes to give (**11a**) as a white solid, 2.69 g (77%). R_f = 0.60 (Et_2O/hexanes 20:80).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 – 7.98 (m, 2H), 6.96 – 6.90 (m, 2H), 4.45 – 4.32 (m, 2H), 3.85 (s, 3H), 1.78 (t, *J* = 7.3 Hz, 1H), 1.45 (s, 3H), 1.33 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.18, 163.61, 131.82, 122.39, 113.78, 77.16, 63.66, 55.55, 43.68, 37.32, 29.16, 27.27, 19.85.

HRMS: (TOF ESI, [$C_{14}H_{16}Br_2O_2$+Na]) calcd, 414.9344 , found *m/z*: 414.9337.

(2,2-Dimethylcyclopropyl)methyl 4-methoxybenzoate (**11**)



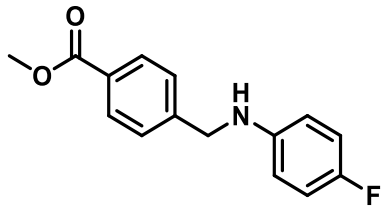
Reduction conducted according to the procedure in section 3.17 to give (**11**) as a pale-yellow oil. R_f = 0.60 (Et_2O/hexanes 10:90).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 7.8 Hz, 2H), 6.92 (d, *J* = 7.9 Hz, 2H), 4.46 (dd, *J* = 11.7, 6.8 Hz, 1H), 4.15 – 4.06 (m, 1H), 3.85 (d, *J* = 1.0 Hz, 3H), 1.15 (s, 3H), 1.10 (s, 3H), 1.09 – 1.03 (m, 1H), 0.58 (dd, *J* = 8.6, 4.5 Hz, 1H), 0.27 (t, *J* = 4.8 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.60, 163.34, 131.67, 123.21, 113.66, 77.16, 66.45, 55.51, 27.22, 22.80, 20.17, 18.90, 16.42.

HRMS: (TOF ESI, [$C_{14}H_{18}O_3$+Na]) calcd, 257.1154 , found *m/z*: 257.1155.

Methyl 4-(((4-fluorophenyl)amino)methyl)benzoate (**12**)



Product was synthesized according to the procedure in section 3.17, to give (**12**) as a pale yellow oil.

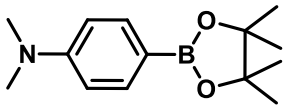
^{1}H NMR (500 MHz, $cdcl_3$) δ 8.01 (d, *J* = 8.2 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 6.87 (t, *J* = 8.7 Hz, 2H), 6.53 (dd, *J* = 8.9, 4.4 Hz, 2H), 4.36 (s, 2H), 4.11 (s, 1H), 3.91 (s, 3H).

^{13}C NMR (126 MHz, $cdcl_3$) δ 167.0, 157.0, 155.1, 144.9, 144.2, 144.2, 130.1, 129.2, 127.2, 115.9, 115.7, 113.8, 113.8, 52.2, 48.6.

Spectra matches those previously reported[99]

N,*N*-Dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**13**)

[99] WO2014086852A1

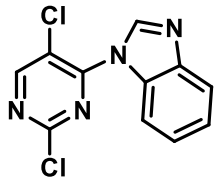


The product was synthesized according to the procedure in section 3.17, to give the (**13**) as a white solid. Spectrascopic data matches those previously reported in the literature.[100]

^{1}H NMR (500 MHz, cdcl$_3$) δ 7.72 (d, *J* = 8.2 Hz, 2H), 6.71 (d, *J* = 8.2 Hz, 2H), 3.00 (s, 6H), 1.35 (s, 12H).

^{13}C NMR (126 MHz, cdcl$_3$) δ 152.6, 136.2, 111.3, 83.2, 40.2, 24.9.

1-(2,5-Dichloropyrimidin-4-yl)-1H-benzo[*d*]imidazole (**14**)



The compound was synthesized according to the procedure in section 3.17, to give (**14**) as a white solid.

R_f 0.27 (4:6 EtOAc/hexanes)

mp 150-152 ^{o}C

^{1}H NMR (500 MHz, CDCl3) δ 8.78 (s, 1H), 8.76 (s, 1H), 8.01 (m, 1H), 7.87 (m, 1H), 7.44 (m, 2H);

[100] Yin, Q.; Klare, H. F. T.; Oestreich, M. *Angew. Chem., Int. Ed.* **2017**, *56*, 3712–3717.

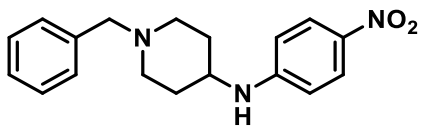
^{13}C NMR (101 MHz, CDCl3) δ 161.50, 158.78, 153.65, 143.41, 140.90, 131.83, 125.27, 124.77, 120.80, 119.74, 114.22.

IR (neat) N = 3145 (w), 3126 (w), 1528 (m), 1425 (m), 1365 (m), 1150 (s), 1133 (s), 748 (s).

HRMS (EI, [C11H6Cl2N4]) Calcd 263.997, Found m/z 263.996.

Spectra matches those previously reported.[101]

1-Benzyl-*N*-(4-nitrophenyl)piperidin-4-amine (**15**)



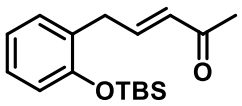
The compound was synthesized according to the procedure in section 3.17 to give (**15**) as a yellow solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 – 8.05 (m, 2H), 7.36 – 7.30 (m, 4H), 7.30 – 7.25 (m, 1H), 6.53 – 6.48 (m, 2H), 4.39 (d, *J* = 7.8 Hz, 1H), 3.54 (s, 2H), 3.40 (dddd, *J* = 14.4, 10.1, 8.1, 4.1 Hz, 1H), 2.87 (dd, *J* = 11.4, 4.8 Hz, 2H), 2.18 (td, *J* = 11.5, 2.6 Hz, 2H), 2.10 – 1.99 (m, 2H), 1.55 (dtd, *J* = 14.1, 10.7, 3.7 Hz, 2H).

Spectra matches those previously reported.[102]

[101] C. M. Gabriel, M. Parmentier, C. Riegert, M. Lanz, S. Handa, B. H. Lipshutz, F. Gallou, *Org. Process Res. Dev.* **2017**, *21*, 247–252.
[102] Lee, N. R.; Bikovtseva, A. A.; Cortes-Clerget, M.; Gallou, F.; Lipshutz, B. H. *Org. Lett.* **2017**, *19*, 6518–6521.

(*E*)-5-(2-((*t*-Butyldimethylsilyl)oxy)phenyl)pent-3-en-2-one (**16**)



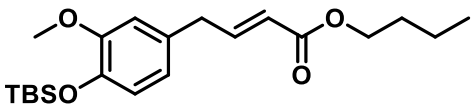
The compound was synthesized according to the procedure in section 3.17 to give (**16**) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.03 (td, *J* = 7.7, 1.8 Hz, 1H), 6.99 (dd, *J* = 7.5, 1.8 Hz, 1H), 6.88 – 6.78 (m, 2H), 6.72 (dd, *J* = 8.1, 1.2 Hz, 1H), 5.92 (dt, *J* = 16.0, 1.7 Hz, 1H), 3.43 (dd, *J* = 6.5, 1.7 Hz, 2H), 2.12 (s, 3H), 0.90 (s, 10H), 0.15 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 198.7, 153.6, 146.7, 132.0, 130.6, 128.4, 128.0, 121.4, 118.6, 33.6, 26.8, 25.9, 18.3, -4.0.

Spectra matches those previously reported.[103]

Butyl (*E*)-4-(4-((tert-butyldimethylsilyl)oxy)-3-methoxyphenyl)but-2-enoate (**17**)



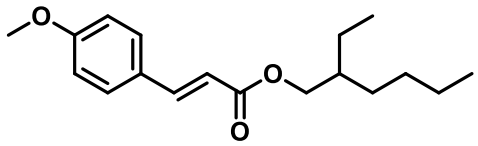
The compound was synthesized according to the procedure in section 3.17 to give (**17**) as a pale yellow oil.

[103] Lipshutz, B. H.; Ghorai, S.; Abela, A. R.; Moser, R.; Nishikata, T.; Duplais, C.; Krasovskiy, A.; Gaston, R. D.; Gadwood, R. C. *J. Org. Chem.* **2011**, *76*, 4379–4391.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (dt, *J* = 15.5, 6.7 Hz, 1H), 6.78 (d, *J* = 7.9 Hz, 1H), 6.66 – 6.59 (m, 2H), 5.80 (dt, *J* = 15.5, 1.6 Hz, 1H), 4.13 (t, *J* = 6.7 Hz, 2H), 3.78 (s, 3H), 3.44 (dd, *J* = 6.8, 1.7 Hz, 2H), 1.68 – 1.59 (m, 2H), 1.44 – 1.33 (m, 2H), 1.00 (s, 9H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.15 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 166.8, 151.1, 147.7, 143.9, 131.1, 122.2, 121.1, 121.0, 112.8, 64.3, 55.6, 38.3, 30.8, 25.8, 19.3, 18.5, 13.8, -4.6.

2-Ethylhexyl (*E*)-3-(4-methoxyphenyl)acrylate (**18**)



The compound was synthesized according to the procedure in section 3.17 to give (**18**) as a pale yellow oil

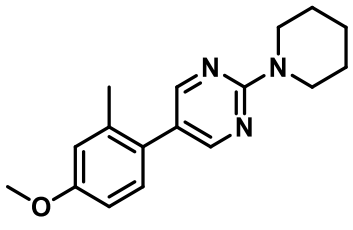
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 15.9 Hz, 1H), 7.49 – 7.43 (m, 2H), 6.91 – 6.85 (m, 2H), 6.31 (d, *J* = 16.0 Hz, 1H), 4.16 – 4.04 (m, 2H), 3.81 (d, *J* = 1.7 Hz, 3H), 1.64 (p, *J* = 6.1 Hz, 1H), 1.40 (dtd, *J* = 13.5, 7.5, 6.1 Hz, 2H), 1.32 (qd, *J* = 8.8, 7.4, 4.5 Hz, 6H), 0.91 (dt, *J* = 8.6, 7.1 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.6, 161.4, 144.2, 129.7, 127.3, 115.9, 114.4, 66.9, 55.4, 39.0, 30.6, 29.0, 23.9, 23.1, 14.1, 11.1.

Spectra matches those previously reported.[104]

[104] Klumphu, P.; Lipshutz, B. H. *J. Org. Chem.* **2014**, *79*, 888–900.

5-(4-Methoxy-2-methylphenyl)-2-(piperidin-1-yl)pyrimidine (**19**)

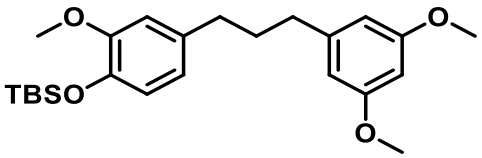


The compound was synthesized according to the procedure in section 3.17 to give (**19**) as a white solid

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 1.1 Hz, 2H), 7.09 (d, *J* = 8.2 Hz, 1H), 6.83 (d, *J* = 2.7 Hz, 1H), 6.79 (dd, *J* = 8.3, 2.8 Hz, 1H), 3.85 – 3.79 (m, 7H), 2.29 (s, 3H), 1.74 – 1.67 (m, 2H), 1.65 (q, *J* = 6.0 Hz, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.7, 159.2, 157.7, 137.5, 130.9, 128.4, 122.6, 116.1, 111.6, 55.4, 45.0, 25.9, 25.0, 20.9.

t-Butyl(4-(3-(3,5-dimethoxyphenyl)propyl)-2-methoxyphenoxy)dimethylsilane (**20**)



Coupling was conducted at 0.25 mmol scale using the procedure in section 3.17 to give (**20**) as a clear oil, 98 mg (94%).

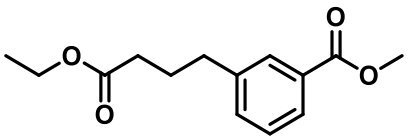
R_f : 0.50 (Et_2O/hexanes 10:90)

^1H NMR (500 MHz, $CDCl_3$) δ 6.77 (d, *J* = 7.9 Hz, 1H), 6.68 (s, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 6.35 (s, 2H), 6.32 (d, *J* = 2.0 Hz, 1H), 3.79 (d, *J* = 4.1 Hz, 9H), 2.59 (t, *J* = 7.6 Hz, 4H), 1.99 – 1.87 (m, 2H), 1.00 (s, 9H), 0.16 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 160.86, 150.79, 144.96, 143.10, 135.84, 120.74, 120.61, 112.66, 106.68, 97.82, 55.63, 55.37, 35.88, 35.23, 32.98, 25.90, 18.58, -4.50.

HRMS: (EI, [$C_{24}H_{36}O_4Si$+H]) calcd, 417.2461; found *m/z*: 417.2452.

methyl 3-(4-ethoxy-4-oxobutyl)benzoate (**21**)



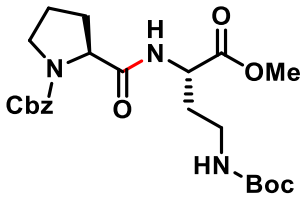
The compound was synthesized according to the procedure in section 3.17 to give (**21**) as a colorless oil

R_f: 0.20 (5:95 Et2O/hexanes)

1H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, J = 4.9, 2.7 Hz, 2H), 7.42 – 7.30 (m, 2H), 4.12 (q, J = 7.1 Hz, 2H), 3.90 (s, 3H), 2.70 (t, J = 7.6 Hz, 2H), 2.31 (t, J = 7.4 Hz, 2H), 1.97 (p, J = 7.5 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 167.3, 141.9, 133.3, 130.4, 129.7, 128.6, 127.5, 60.5, 52.2, 35.0, 33.7, 26.5, 14.4.

Cbz-L-Pro-L-But(Boc)-OMe (**22**)



The compound was synthesized according to the procedure in section 3.17 to give (**22**) as a yellow crystalline solid.

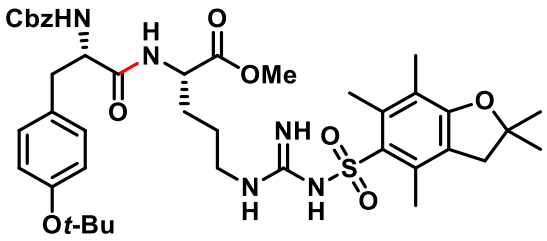
0.7 mmol – 0.27g (83 %)

Rf = 0.67 (100% EtOAc) – Cerium Ammonium Molybdate stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.29 (m, 5H), 7.13 (s, 1H), 6.77 (s, 1H), 5.17 (s, 2H), 5.03 (s, 1H), 4.62 (s, 1H), 4.33 (s, 1H), 3.75 (s, 3H), 3.59 (s, 1H), 3.48 (s, 0.5H), 3.35 (d, J = 11.3 Hz, 0.5H), 2.84 (d, J = 81.9 Hz, 1H), 2.23 (s, 1H), 2.18 – 1.84 (m, 3H), 1.64 (s, 3H), 1.44 (s, 9H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 210.2, 172.7, 156.1, 128.6, 128.1, 128.0, 79.3, 67.4, 60.8, 52.6, 49.9, 47.1, 36.4, 33.1, 29.1, 28.5, 24.7.

Cbz-Tyr(tBu)-L-Arg(Pbf)-OMe (**23**)



The compound was synthesized according to the procedure in section 3.17 to give (**23**) as a white solid.

methyl N2-((S)-2-(((benzyloxy)carbonyl)amino)-3-(4-(tert-butoxy)phenyl)propanoyl)-Nw-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)-L-argininate (**23**).

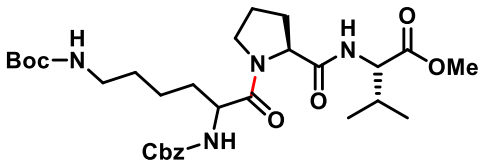
0.25 mmol – 0.137g (69 %) – *off-white powder*

Rf= 0.64 (100% AcOEt) - CAM blue spot

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.30 (m, 5H), 7.07 (d, *J* = 7.0 Hz, 2H), 6.88 (d, *J* = 8.1 Hz, 2H), 6.79 (bs, 1H), 6.09 (bs, 2H), 5.46 (bs, 1H), 5.03 (s, 2H), 4.59 – 4.35 (m, 2H), 3.71 (s, 3H), 3.14 (s, 2H), 3.08 – 2.97 (m, 2H), 2.95 (s, 2H), 2.58 (s, 3H), 2.52 (s, 3H), 2.09 (s, 2H), 2.09 – 2.03 (m, 1H), 1.90 – 1.74 (m, 1H), 1.74 – 1.60 (m, 1H), 1.46 (s, 6H), 1.40 (bs, 2H), 1.32 (d, *J* = 1.6 Hz, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 172.2, 158.9, 156.7, 156.4, 154.2, 138.5, 136.2, 133.0, 132.4, 130.0, 128.6, 128.2, 127.8, 127.8, 124.8, 124.2, 117.7, 86.5, 67.0, 60.5, 56.3, 52.5, 43.4, 38.1, 29.2, 28.9, 28.8, 28.7, 25.1, 19.4, 18.1, 14.3, 12.6.

Cbz-L-Lys-L-Pro-L-Val-OMe (**24**)



The compound was synthesized according to the procedure in section 3.17 to give (**24**) as a pale yellow oil.

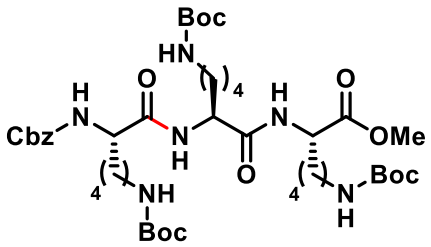
0.27 mmol – (0.20 g - 74%) - *pale yellow syrup*

Rf = 0.36 (1:1 Hexanes/AcOEt) – Cerium Ammonium Molybdate stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.27 (m, 10H), 6.95 (d, J = 8.7 Hz, 1H), 5.64 (d, J = 8.6 Hz, 1H), 5.27 (t, J = 6.2 Hz, 1H), 5.09 (d, J = 6.3 Hz, 4H), 4.61 – 4.45 (m, 2H), 3.71 (s, 3H), 3.77 – 3.53 (m, 1H), 3.27 – 3.11 (m, 2H), 2.28 (dt, J = 11.5, 3.8 Hz, 1H), 2.21 – 2.08 (m, 2H), 1.98 (ddd, J = 15.8, 11.3, 6.9 Hz, 2H), 1.81 – 1.20 (m, 9H), 0.88 (dd, J = 9.7, 6.8 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4, 172.0, 171.1, 156.7, 156.2, 136.9, 136.4, 128.6, 128.6, 128.3, 128.2, 128.1, 67.1, 66.7, 60.2, 57.4, 52.3, 52.2, 47.6, 40.6, 32.6, 31.3, 29.8, 29.4, 27.8, 25.3, 22.0, 19.1, 17.7.

Z-L-Lys(Boc)-L-Lys(Boc)-L-Lys(Boc)-OMe (**25**)



The compound was synthesized according to the procedure in section 3.17 to give (**25**) as a white solid.

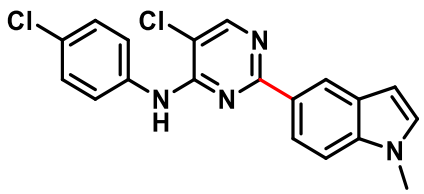
0.18 mmol – (93.3 mg - 61%) - *White powder*

Rf= 0.77 (100% EtOAc) – CAM Stain

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 6.88 (bs, 2H), 5.77 (bs, 1H), 5.10 (s, 2H), 4.90 (bd, *J* = 48.2 Hz, 2H), 4.53 (bs, 1H), 4.40 (bd, *J* = 7.2 Hz, 1H), 4.15 (bs, 1H), 3.73 (s, 3H), 3.07 (m, 6H), 1.84 (m, 4H), 1.76 – 1.58 (m, 3H), 1.42 (m, 40H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 172.5, 171.7, 156.6, 156.4, 156.3, 136.2, 128.6, 128.2, 79.2, 67.1, 55.0, 53.3, 52.5, 52.2, 40.1, 39.8, 32.0, 31.6, 31.5, 29.5, 28.5, 22.6, 22.4.

5-Chloro-*N*-(4-chlorophenyl)-2-(1-methyl-1*H*-indol-5-yl)pyrimidin-4-amine (**26**).



The compound was synthesized according to the procedure in section 3.17 to give (**26**) as a white crystalline solid.

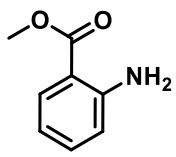
R_f = 0.40 (EtOAc/hexanes 30:70).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, *J* = 1.2 Hz, 1H), 8.39 (s, 1H), 8.24 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.76 – 7.66 (m, 2H), 7.40 – 7.37 (m, 2H), 7.35 (d, *J* = 8.7 Hz, 1H), 7.09 (s, 1H), 7.07 (d, *J* = 3.1 Hz, 1H), 6.59 (dd, *J* = 3.1, 0.5 Hz, 1H), 3.79 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 163.46, 154.91, 153.95, 138.45, 136.95, 129.87, 128.99, 128.82, 128.63, 128.63, 122.11, 122.06, 121.96, 112.04, 109.17, 102.52, 33.04.

HRMS: (TOF ESI, [C+19+$H_{14}Cl_2N_4$+H]) calcd, 369.0674 , found *m/z*: 369.0666.

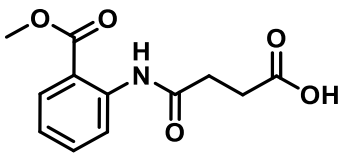
Methyl 2-aminobenzoate



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 – 7.83 (m, 1H), 7.29 – 7.22 (m, 1H), 6.64 (dd, *J* = 8.1, 7.1 Hz, 2H), 5.68 (s, 2H), 3.86 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.61, 150.50, 134.11, 131.24, 116.71, 116.27, 110.74, 77.16, 51.53.

4-((2-(Methoxycarbonyl)phenyl)amino)-4-oxobutanoic acid



Synthesized according to the the procedure in section 3.18 to give the product as an off-white crystalline solid, 62 g (93%).

R_f = 0.40 (MeOH/DCM 10:90)

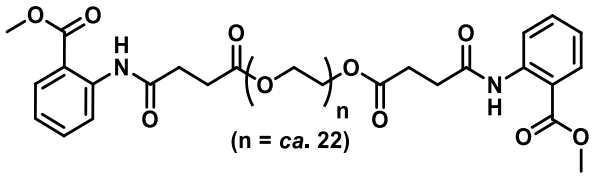
^{1}H NMR (500 MHz, DMSO) δ 12.20 (s, 1H), 10.64 (s, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 7.90 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.65 – 7.50 (m, 1H), 7.21 – 7.09 (m, 1H), 3.85 (s, 3H), 2.63 (dd, J = 3.6 Hz, 2H), 2.55 (dd, *J* = 9.7, 3.6 Hz, 2H).

^{1}H NMR (500 MHz, $CDCl_3$) δ 11.19 (s, 1H), 8.67 (dd, *J* = 8.5, 1.0 Hz, 1H), 8.03 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.54 (ddd, *J* = 8.7, 7.4, 1.6 Hz, 1H), 7.09 (ddd, *J* = 8.3, 7.4, 1.2 Hz, 1H), 3.93 (s, 3H), 2.80 (s, 4H).

^{13}C NMR (126 MHz, DMSO) δ 173.64, 170.31, 167.65, 139.77, 133.97, 130.52, 123.01, 120.90, 117.37, 52.41, 39.52, 31.86, 28.77.

Spectroscopic data matched that reported in the literature.

bis(4-((2-(Methoxycarbonyl)phenyl)amino)-4-oxobutanoic acid)polyethylene glycol 1000 (Coolade).



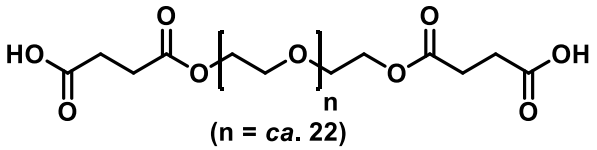
Synthesized according to the procedure in section 3.18 to give the product as either a reddish-brown wax (when synthesized according to Route 2) or a brown oil (when synthesized according to Route 3 or 4), 43.9 g; 88% (Route 2), or 1.25 g, 50% (Route 3).

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.99 (s, 2H), 8.53 (d, *J* = 8.5 Hz, 2H), 7.87 (dd, *J* = 8.0, 1.6 Hz, 2H), 7.41 – 7.34 (m, 2H), 6.97 – 6.88 (m, 2H), 4.14 – 4.09 (m, 4H), 3.78 (s, 6H), 3.55 (dd, *J* = 11.3, 6.5 Hz, 5H), 3.50 (d, *J* = 4.7 Hz, 85H), 2.63 (s, 8H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.13, 169.82, 168.31, 141.14, 134.29, 130.48, 122.13, 119.99, 114.51, 70.30, 70.27, 68.74, 63.54, 52.08, 32.36, 28.82.

HRMS: (TOF ES+, $[C_{64}H_{104}N_2O_{29}Na_2]2+$]) calcd, 705.3260, found *m/z*: 705.3254. (PEG-20 derivative).

Polyethylene glycol 1000-bis succinate.



Synthesized according to the procedure in section 3.18, to give the product as an off-white wax.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.28 – 4.20 (m, 4H), 3.65 (d, *J* = 13.7 Hz, 88H), 2.68 – 2.58 (m, 8H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5, 171.8, 70.2, 70.1, 68.6, 63.4, 28.7, 28.4.

Spectra matches those previously reported[105]

[105] Linker Compound for Imaging Application. KR20190030527A, March 22, 2019.

3.14.6 NMR Spectra

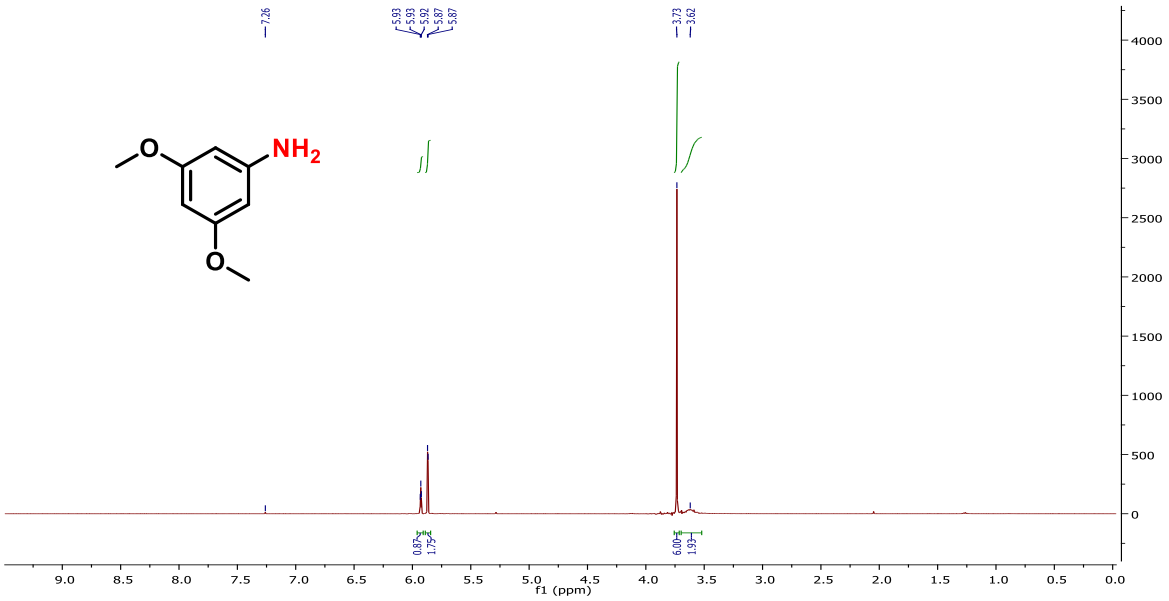


Figure 28: ^{1}H NMR 3,5-Dimethoxyaniline (**14**)

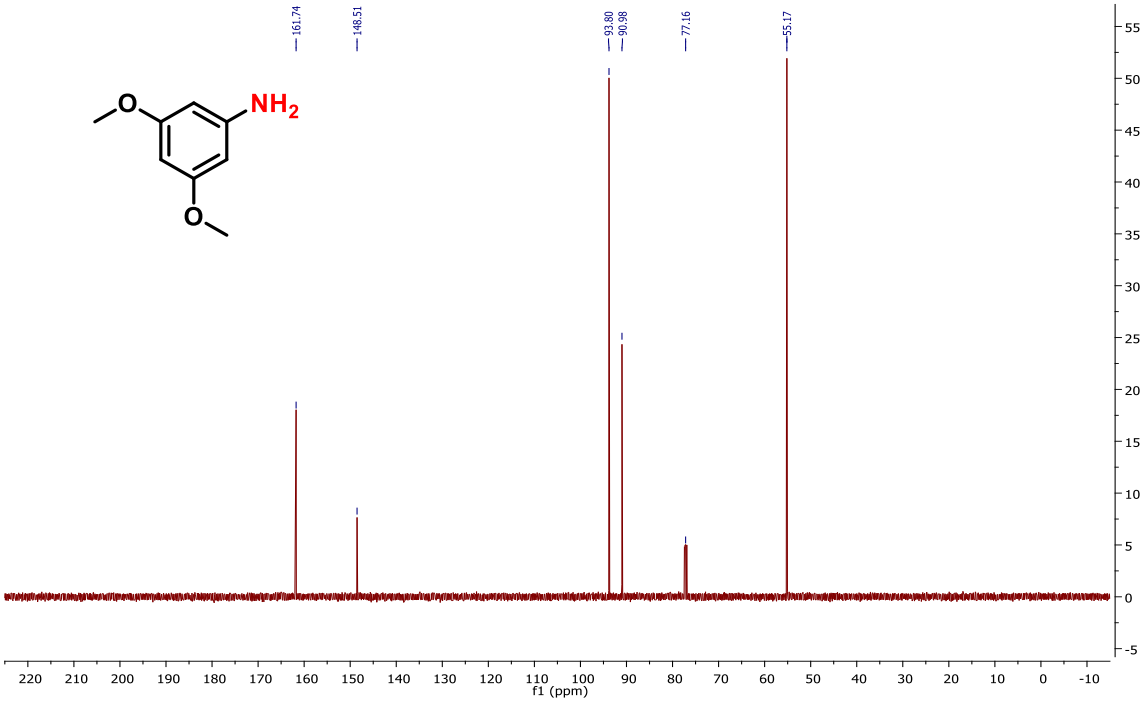


Figure 29: ^{13}C NMR 3,5-Dimethoxyaniline (**14**)

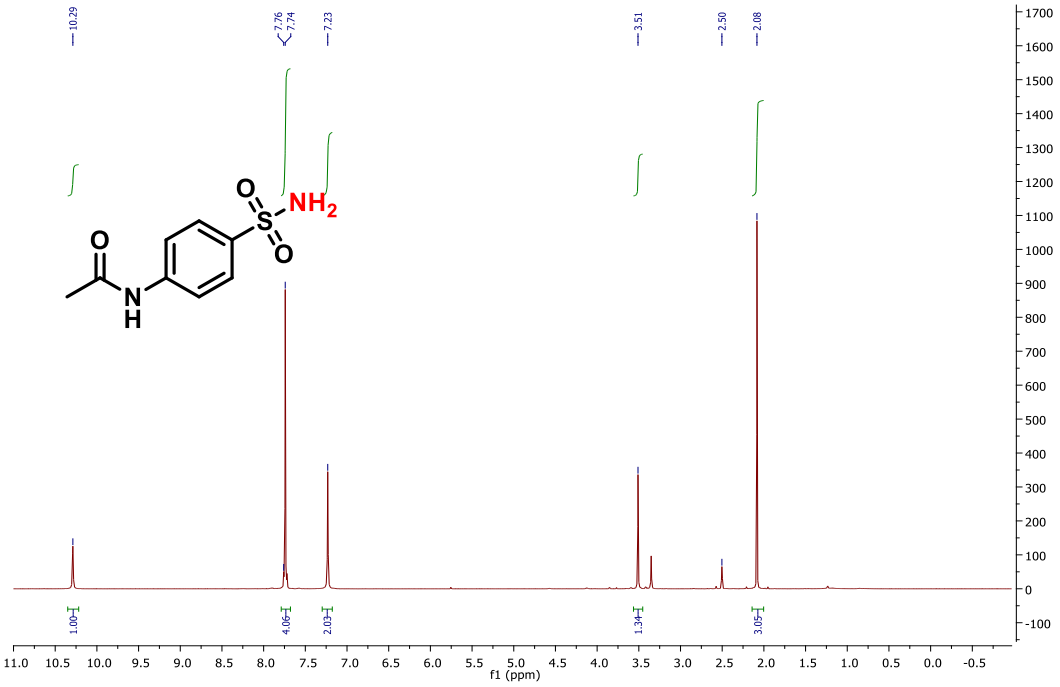


Figure 30: ^{1}H NMR *N*-(4-Sulfamoylphenyl)acetamide (**13**)

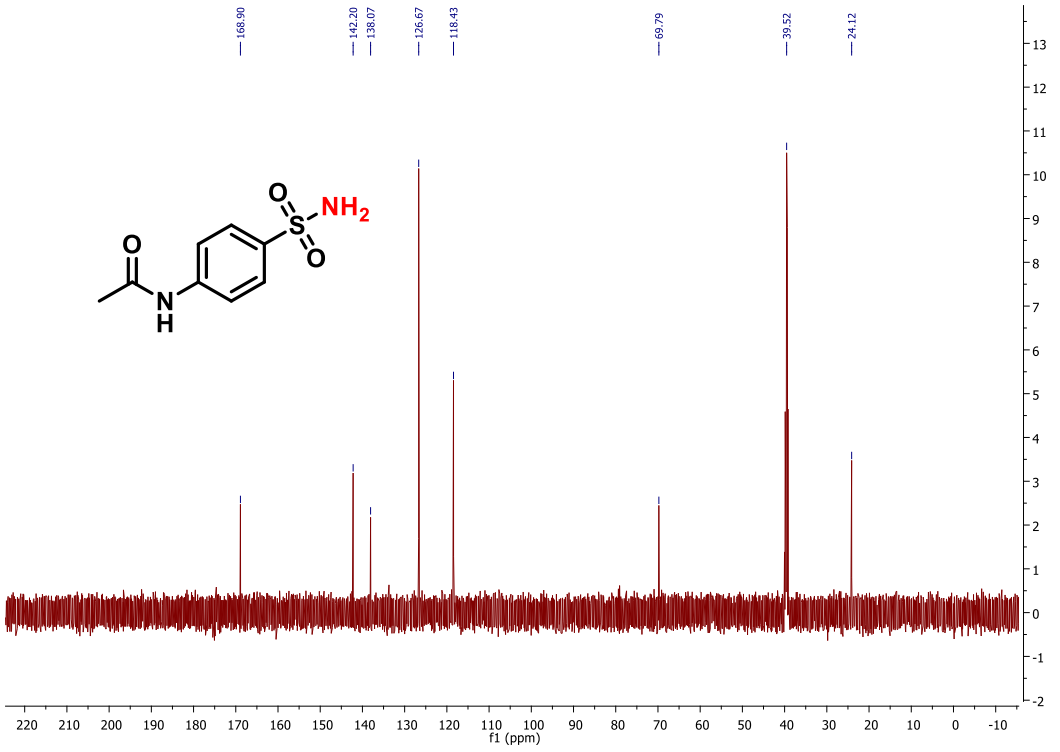


Figure 31: ^{13}C NMR *N*-(4-Sulfamoylphenyl)acetamide (**13**)

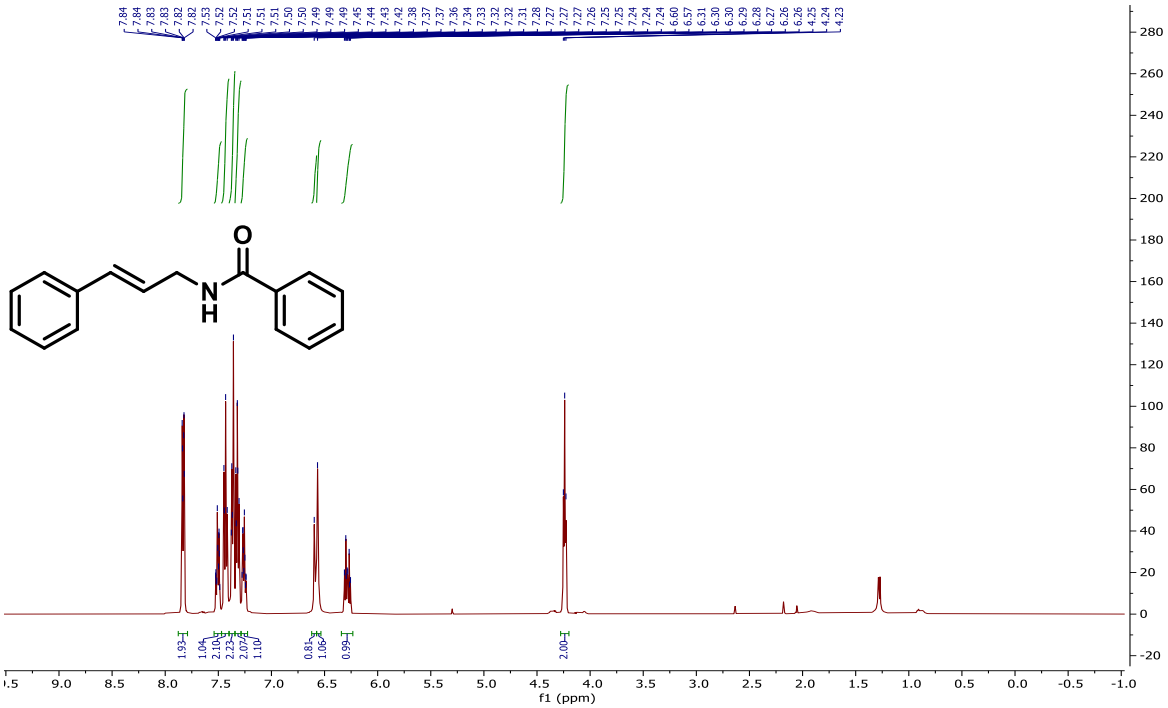


Figure 32: ^{1}H NMR cinnamyl benzamide

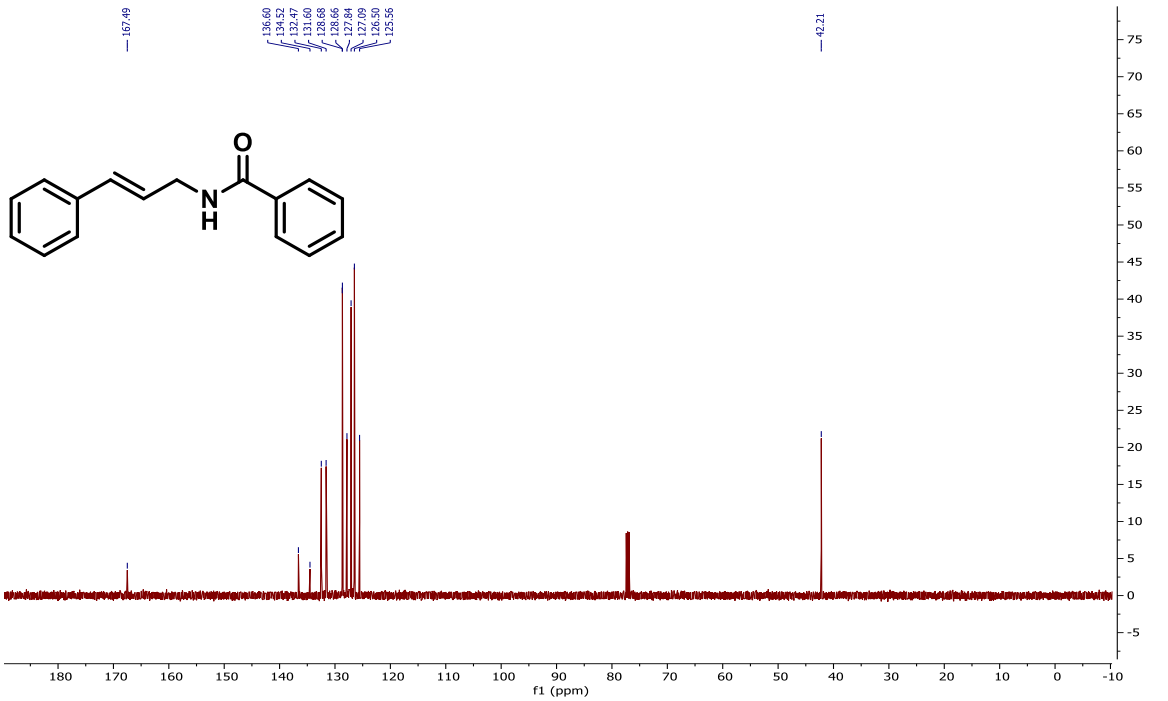


Figure 33: ^{13}C NMR cinnamyl benzamide

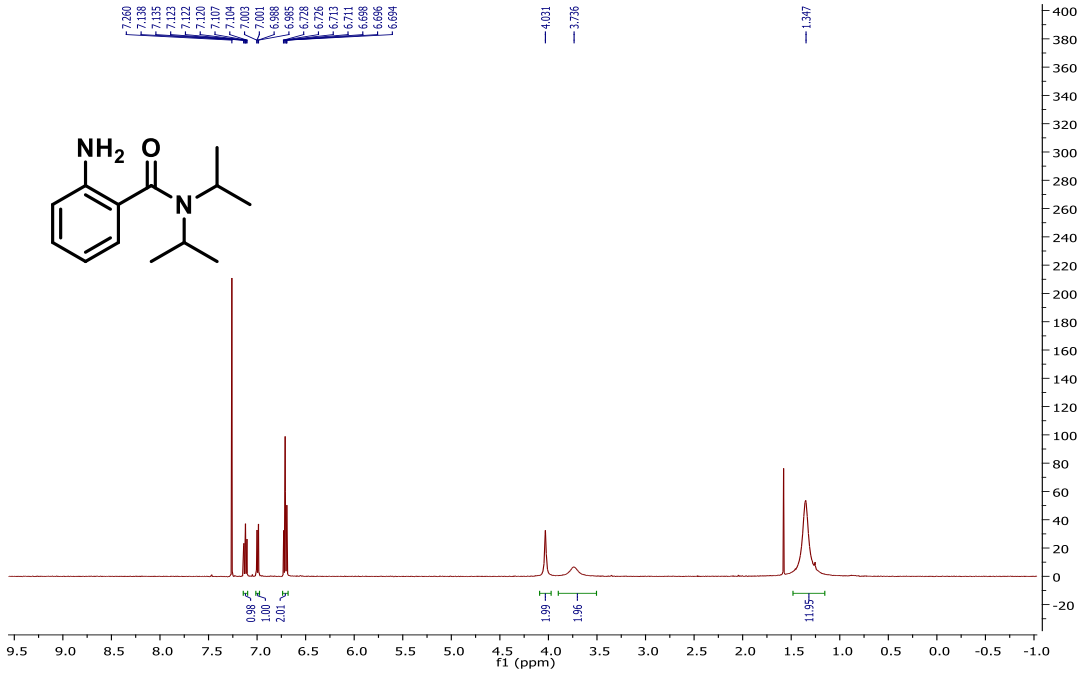


Figure 34: ^{1}H NMR 2-Amino-*N*,*N*-diisopropylbenzamide (**4**)

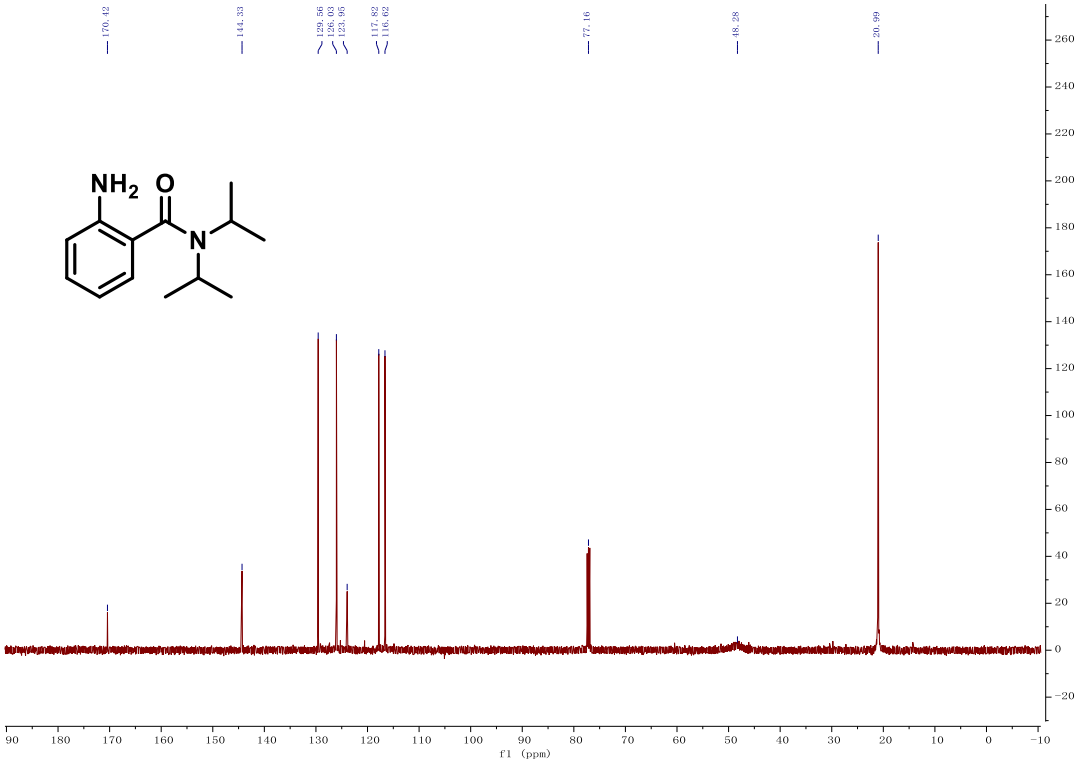


Figure 35: ^{13}C NMR 2-Amino-*N*,*N*-diisopropylbenzamide (**4**)

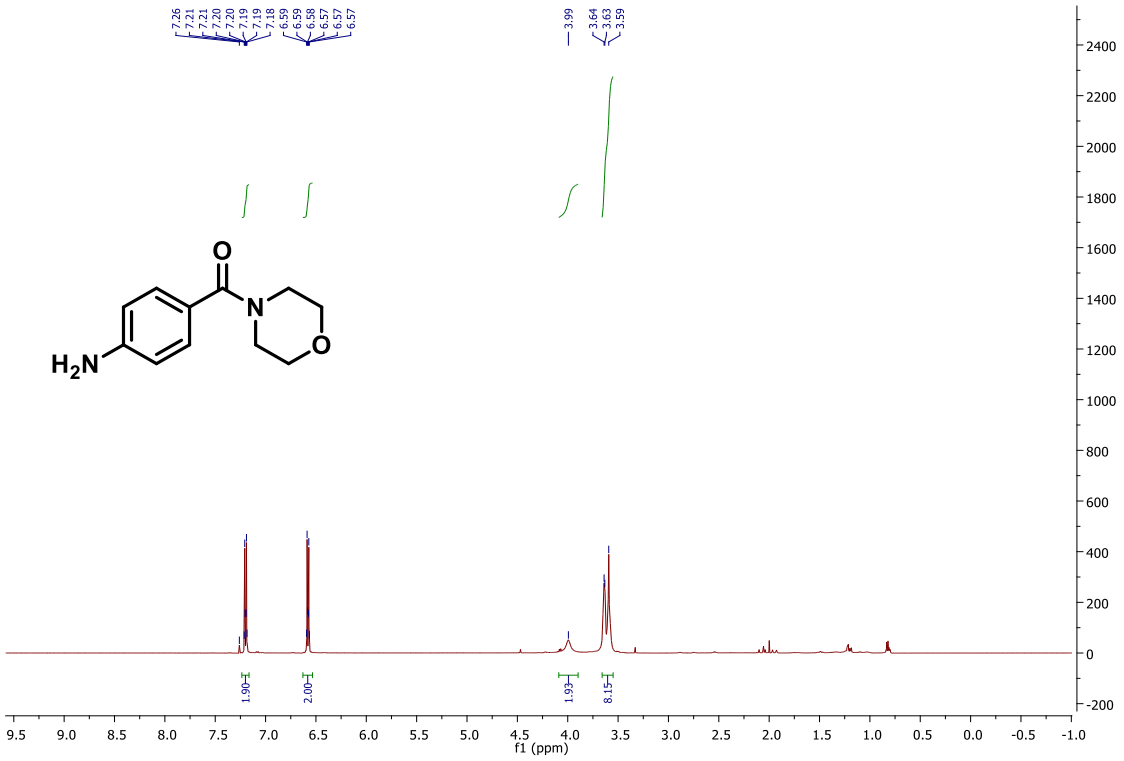


Figure 36: ^{1}H NMR (4-Aminophenyl)(morpholino)methanone (**5**)

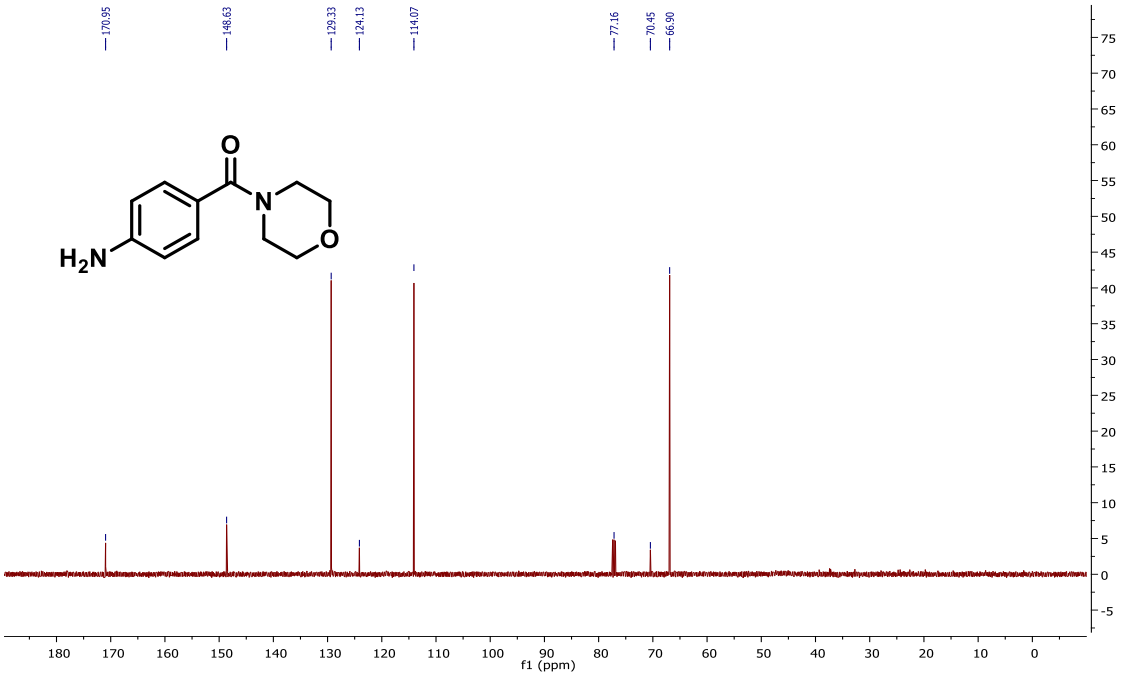


Figure 37: ^{13}C NMR (4-Aminophenyl)(morpholino)methanone (**5**)

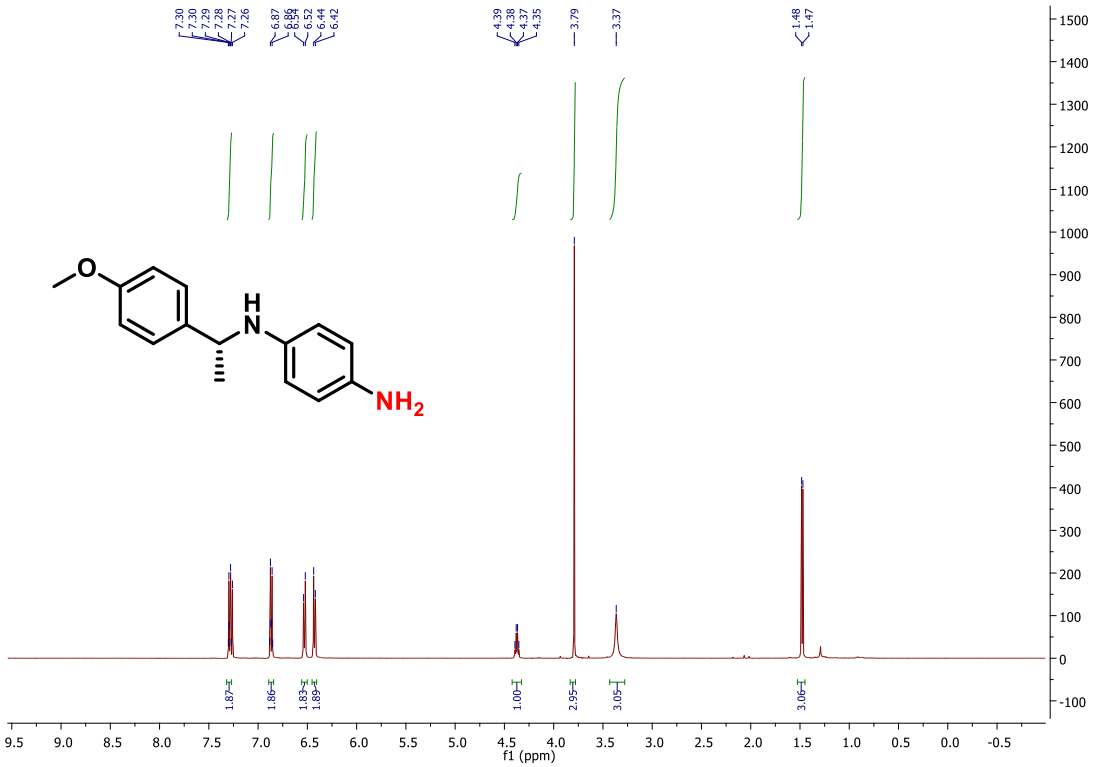


Figure 38: ^{1}H NMR (*R*)-*N*1-(1-(4-Ethoxyphenyl)ethyl)benzene-1,4-diamine (**6**)

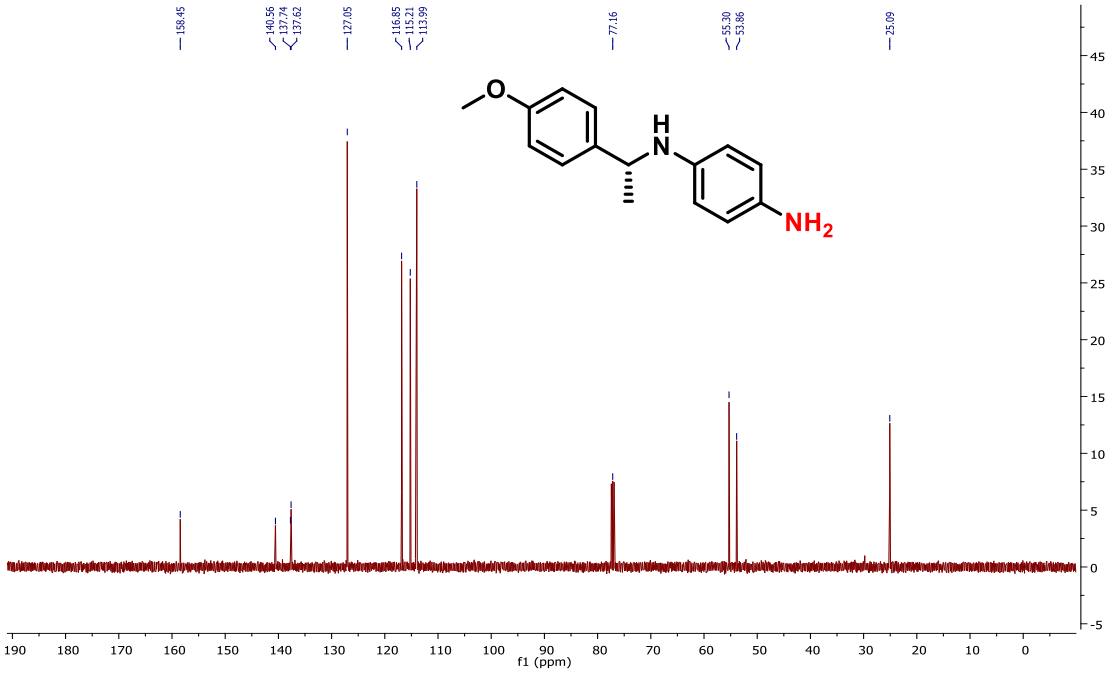


Figure 39: ^{13}C NMR (*R*)-*N*1-(1-(4-Methoxyphenyl)ethyl)benzene-1,4-diamine (**6**)

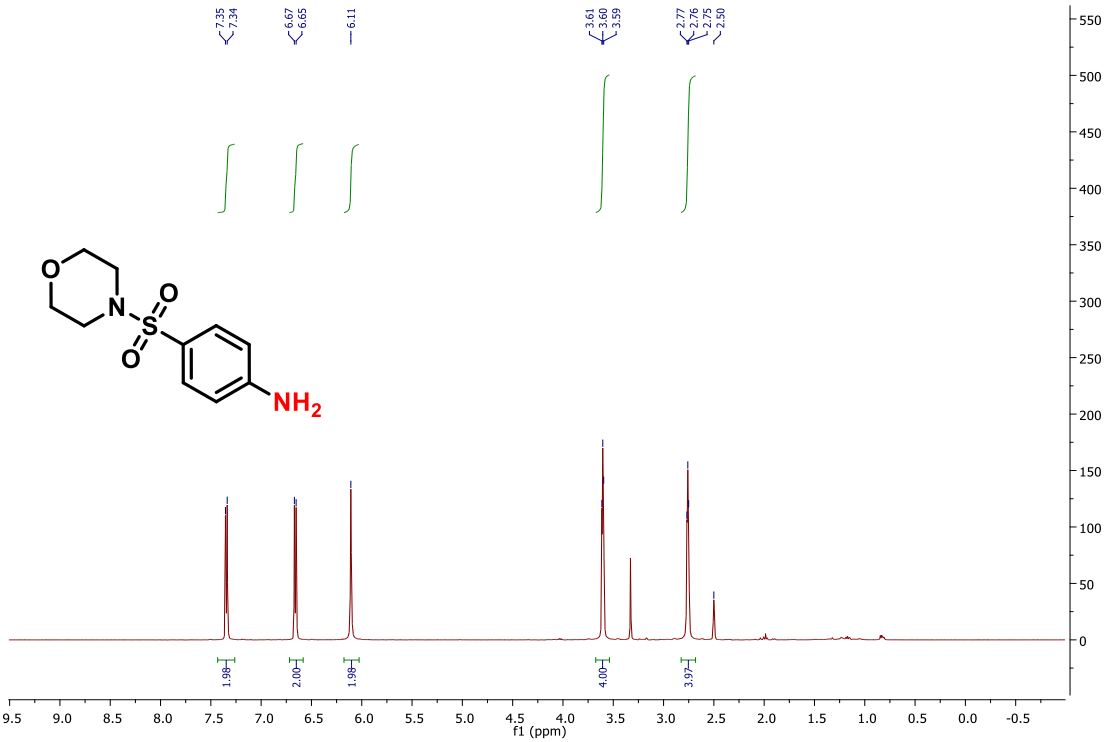


Figure 40: ^{1}H NMR 4-(Morpholinosulfonyl)aniline (**7**)

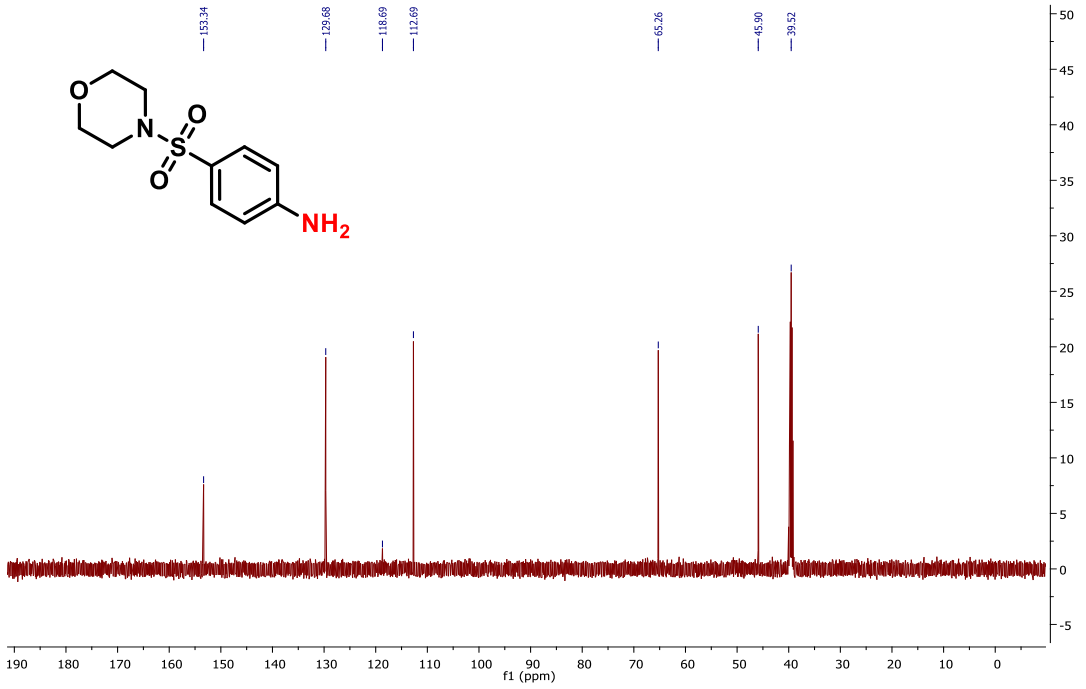


Figure 41: ^{13}C NMR 4-(Morpholinosulfonyl)aniline (**7**)

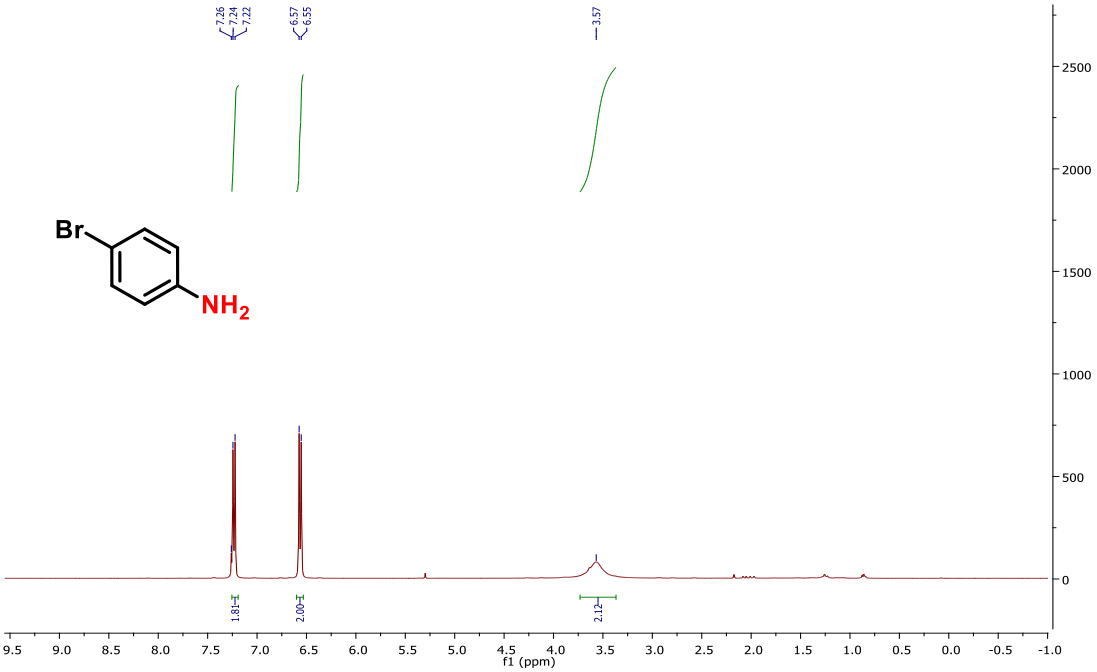


Figure 42: ^{1}H NMR 4-Bromoaniline (**8**)

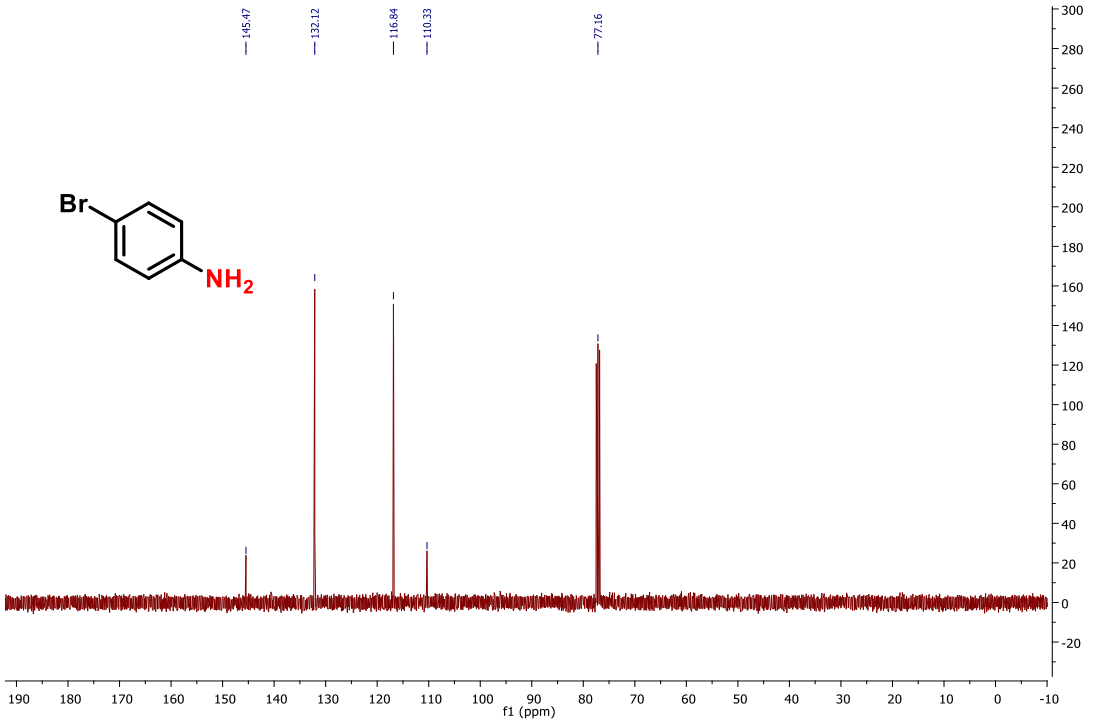


Figure 43: ^{13}C NMR 4-Bromoaniline (**8**)

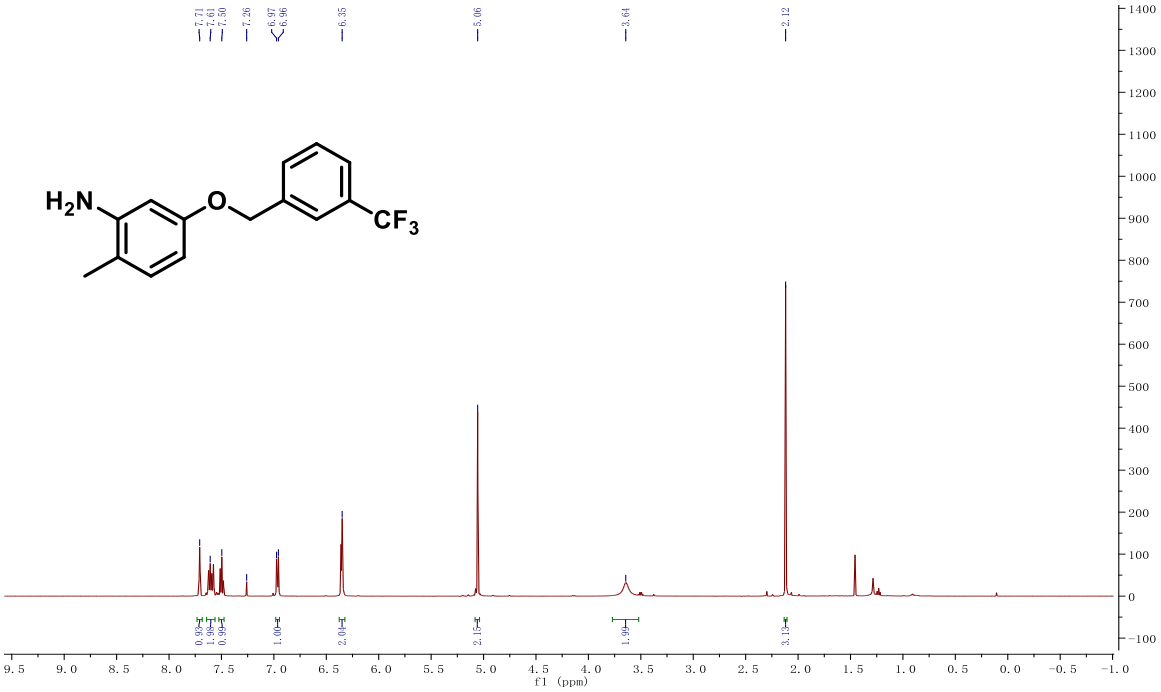


Figure 43: [1]H NMR 2-Methyl-5-((3-(trifluoromethyl)benzyl)oxy)aniline (**9**)

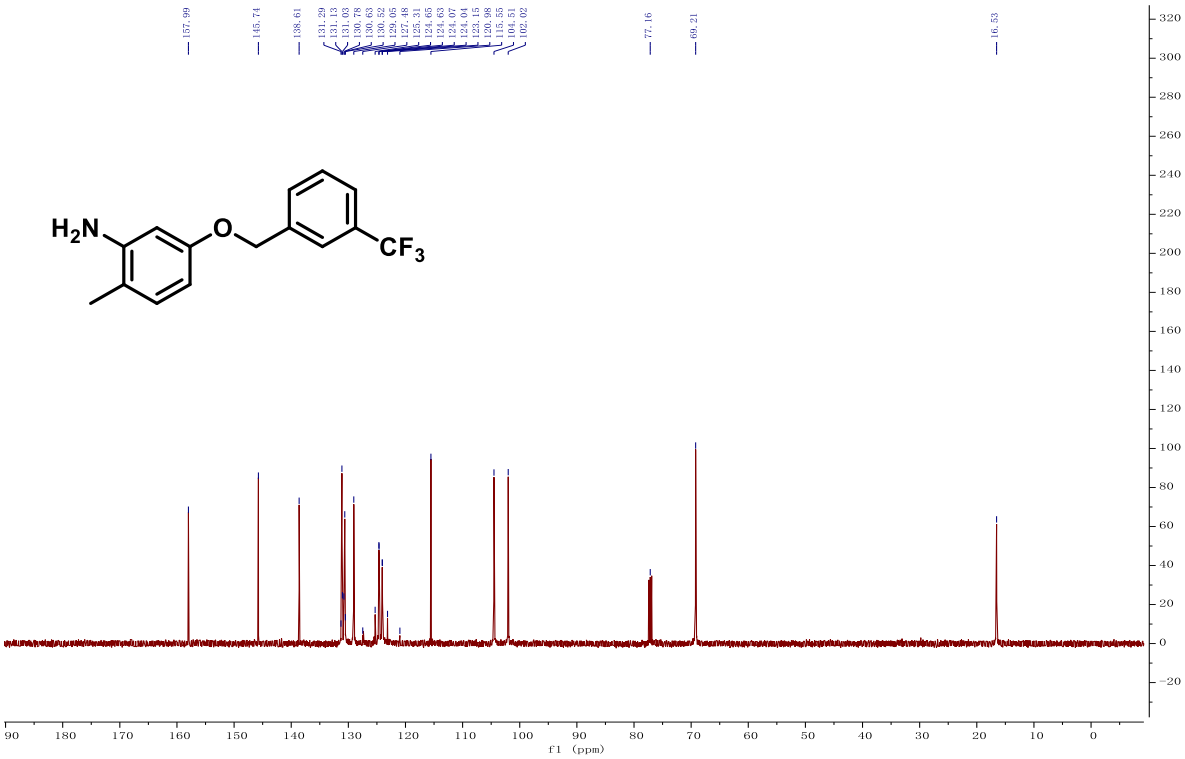


Figure 44: [13]C NMR 2-Methyl-5-((3-(trifluoromethyl)benzyl)oxy)aniline (**9**)

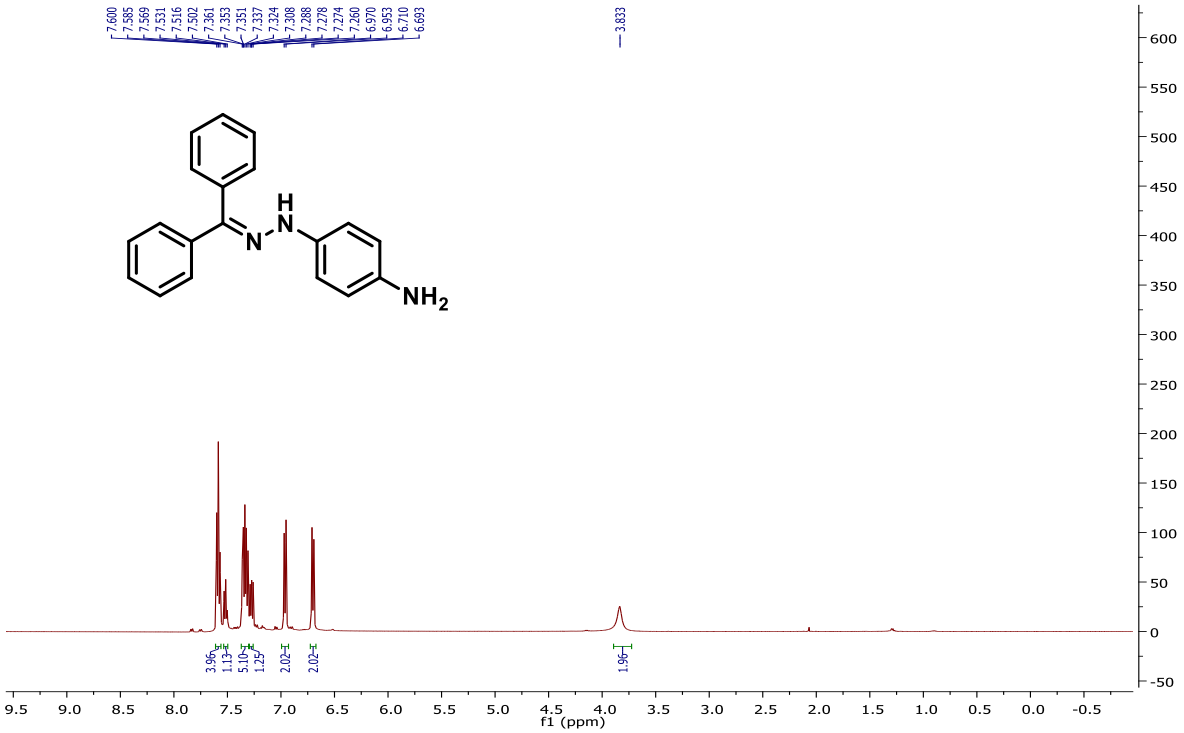


Figure 45: [1]H NMR 4-(2-(Diphenylmethylene)hydrazinyl)aniline (**10**)

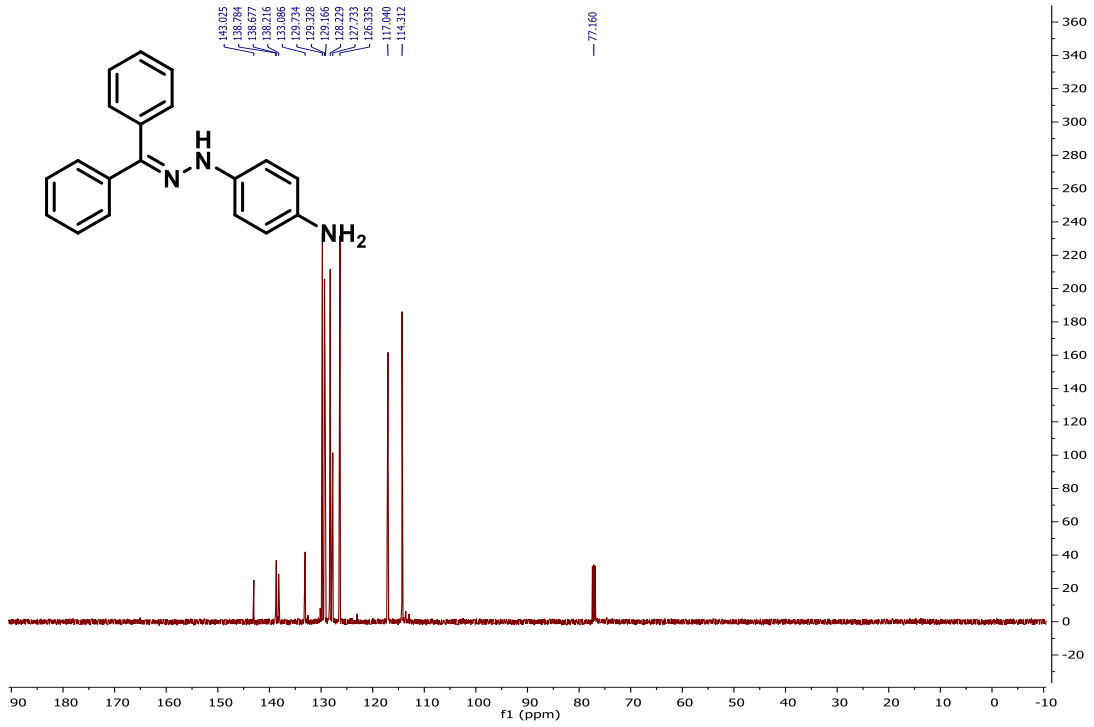


Figure 46: [13]C NMR 4-(2-(Diphenylmethylene)hydrazinyl)aniline (**10**)

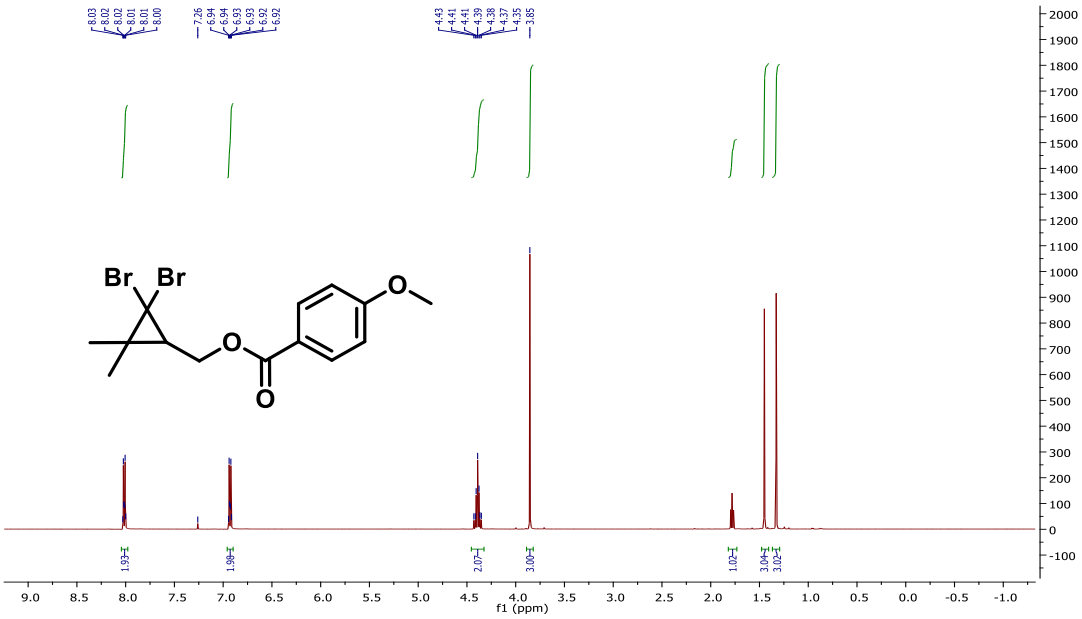


Figure 47: ^{1}H NMR (2,2-Dibromo-3,3-dimethylcyclopropyl)methyl 4-methoxybenzoate (**11a**)

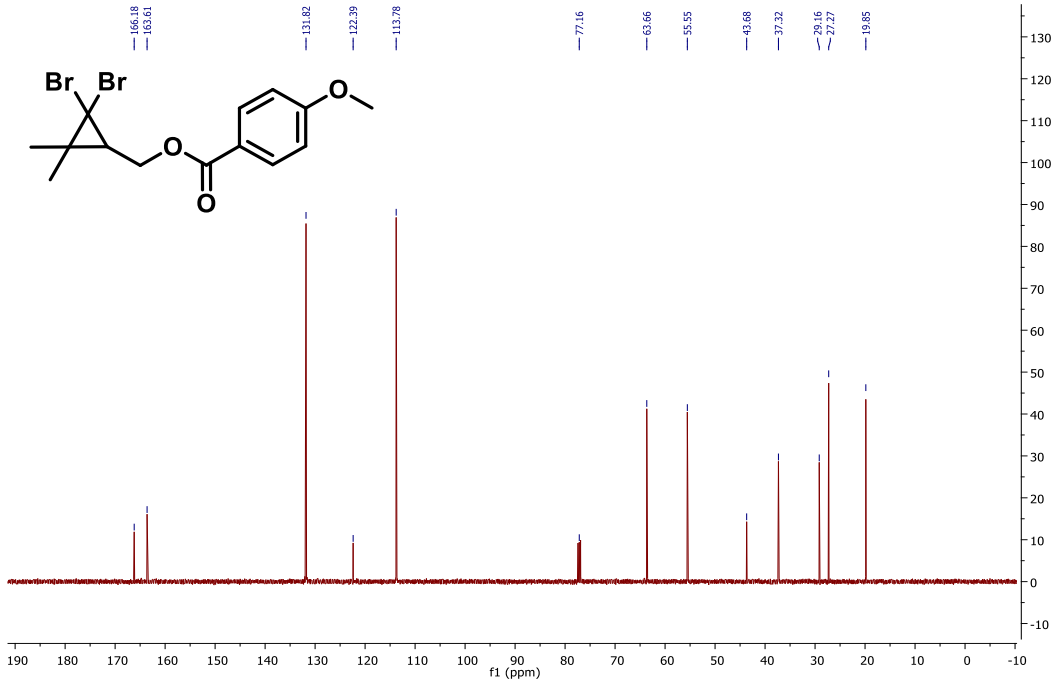


Figure 48: ^{13}C NMR (2,2-Bibromo-3,3-dimethylcyclopropyl)methyl 4-methoxybenzoate (**11a**)

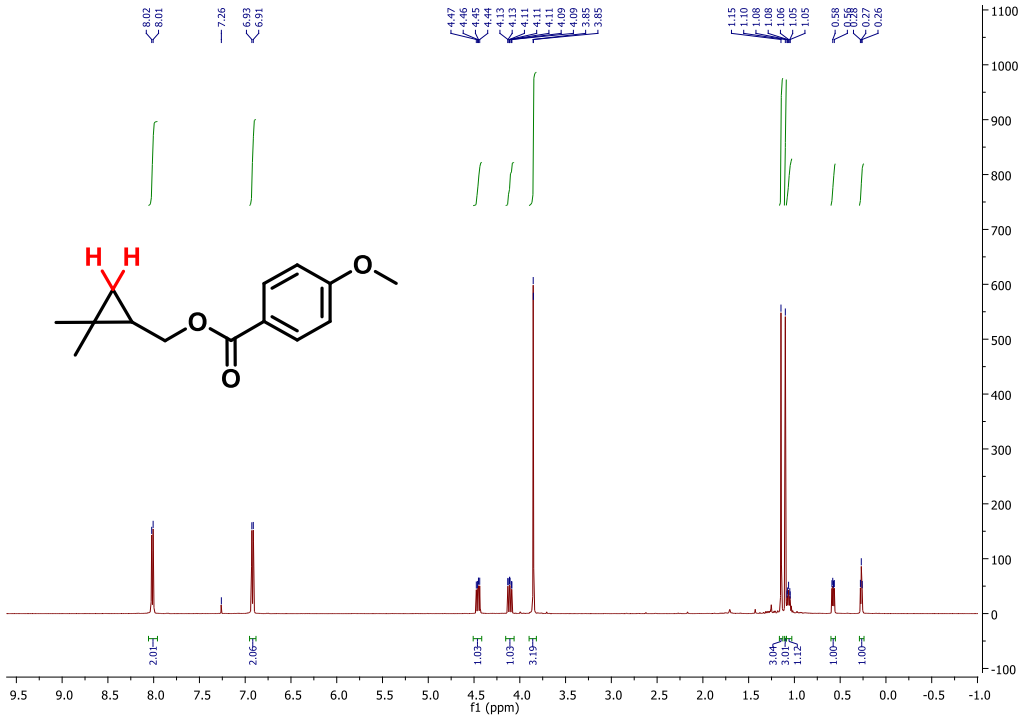


Figure 49: ^{1}H NMR (2,2-Dimethylcyclopropyl)methyl 4-methoxybenzoate (**11**)

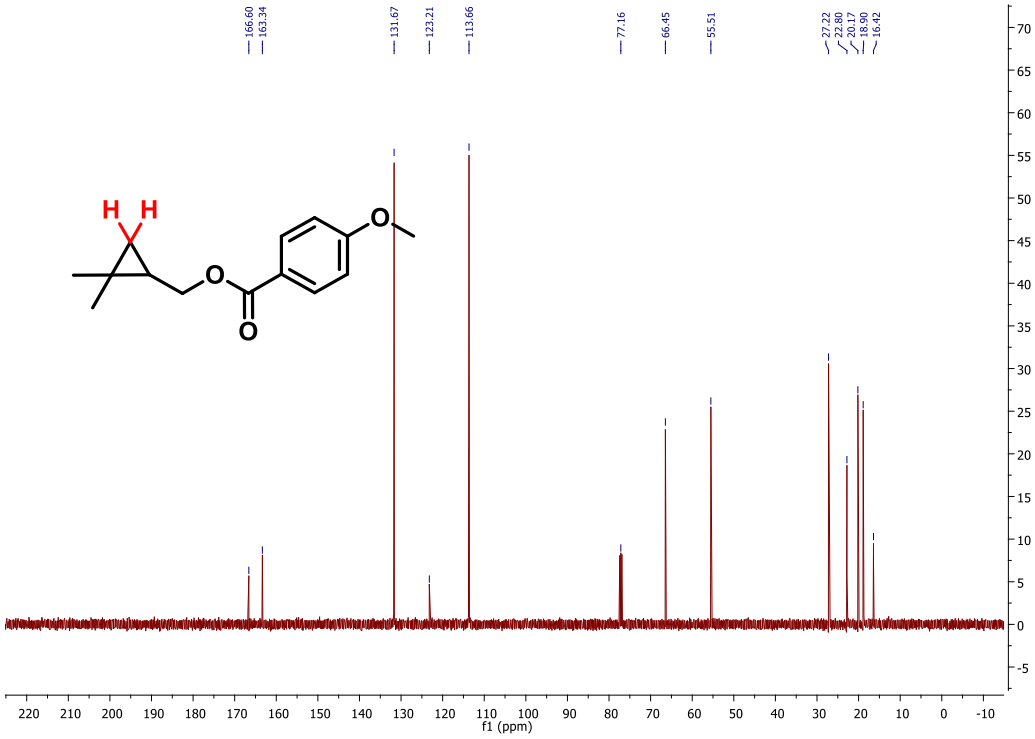


Figure 50: ^{13}C NMR (2,2-Dimethylcyclopropyl)methyl 4-methoxybenzoate (**11**)

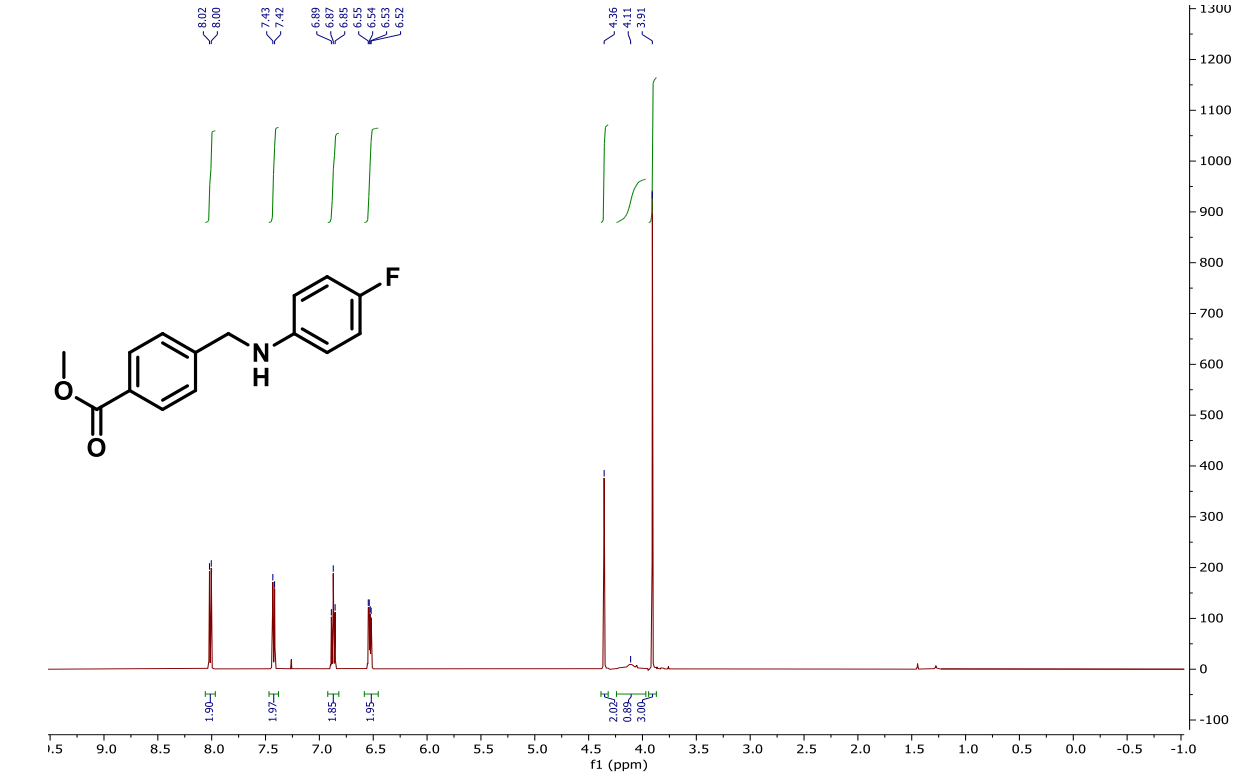


Figure 51: methyl 4-(((4-fluorophenyl)amino)methyl)benzoate Reductive amination (**12**)

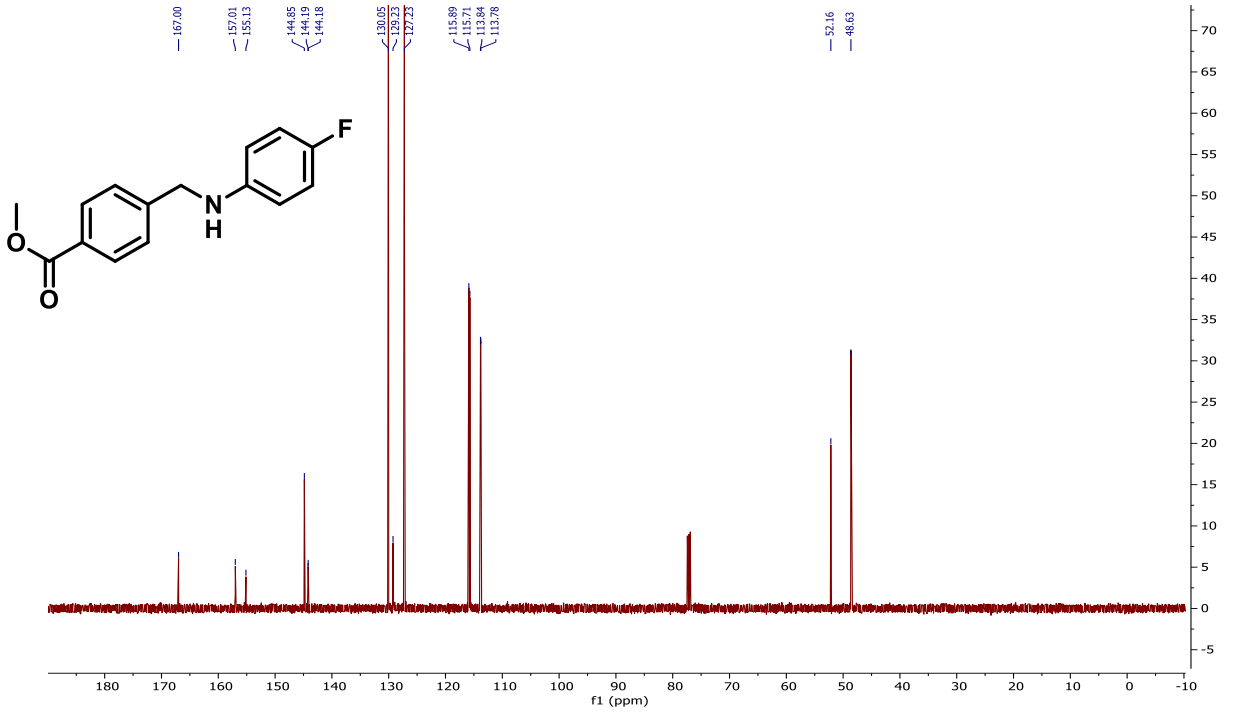


Figure 52: methyl 4-(((4-fluorophenyl)amino)methyl)benzoate Reductive amination (**12**)

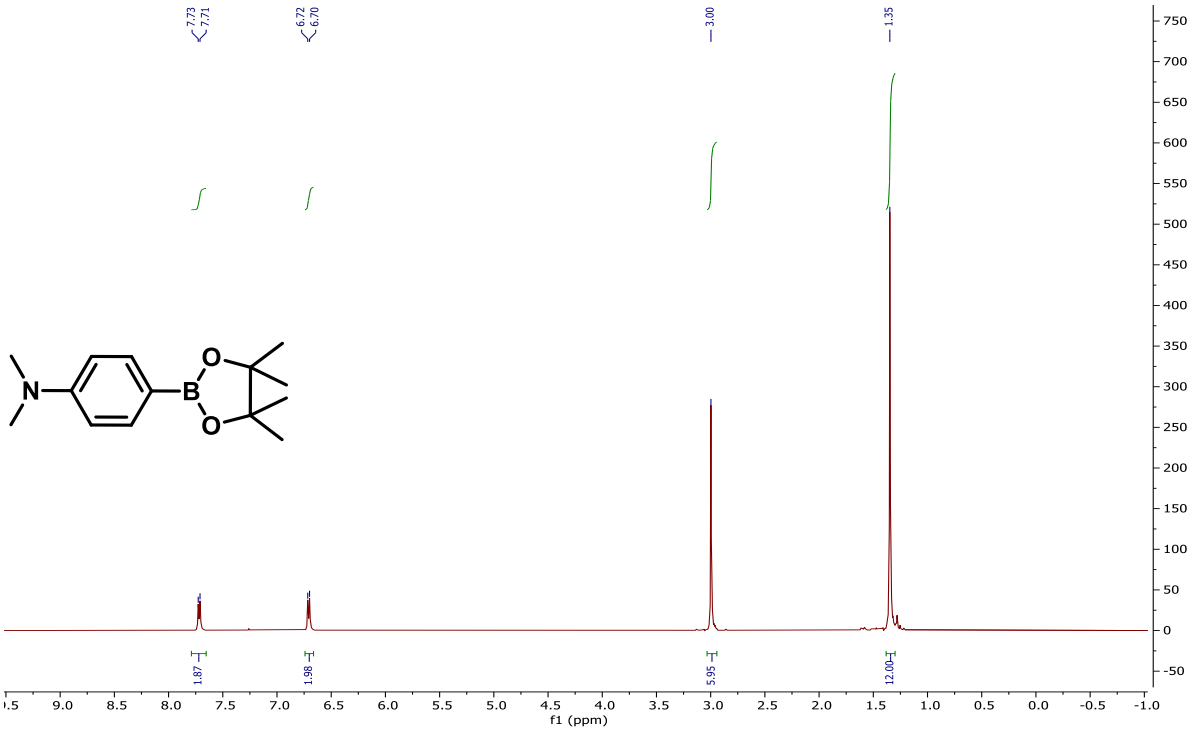


Figure 53: N,N-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**13**)

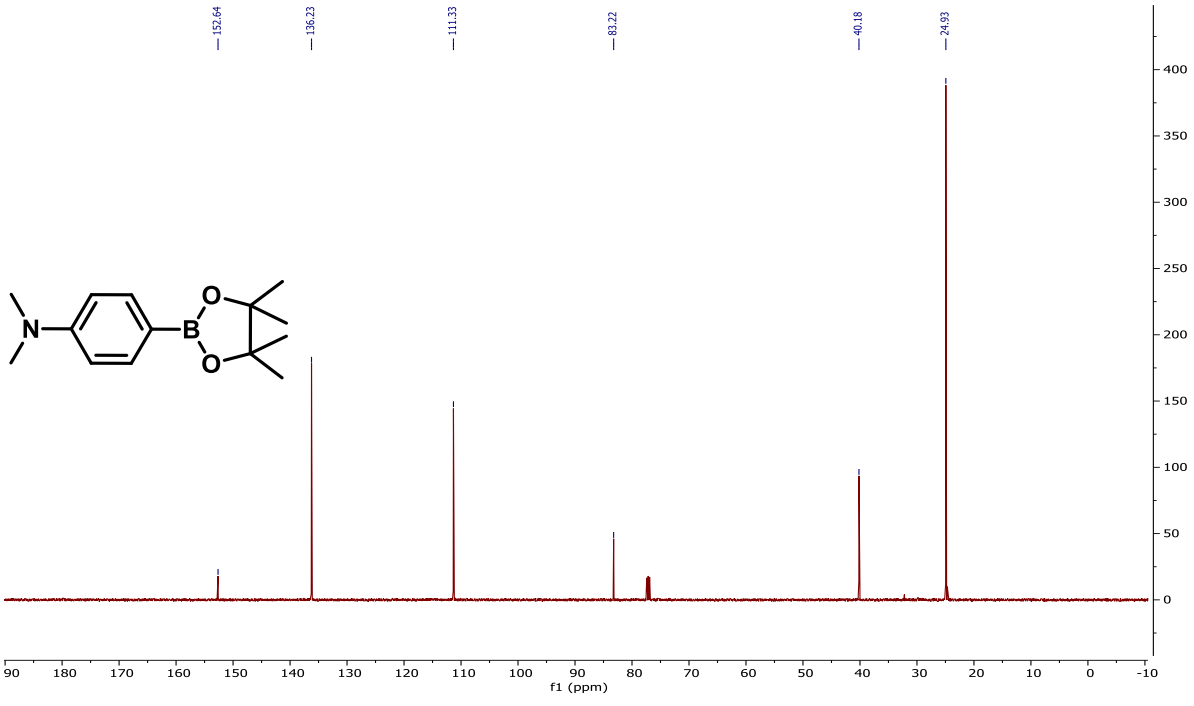


Figure 54: N,N-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**13**)

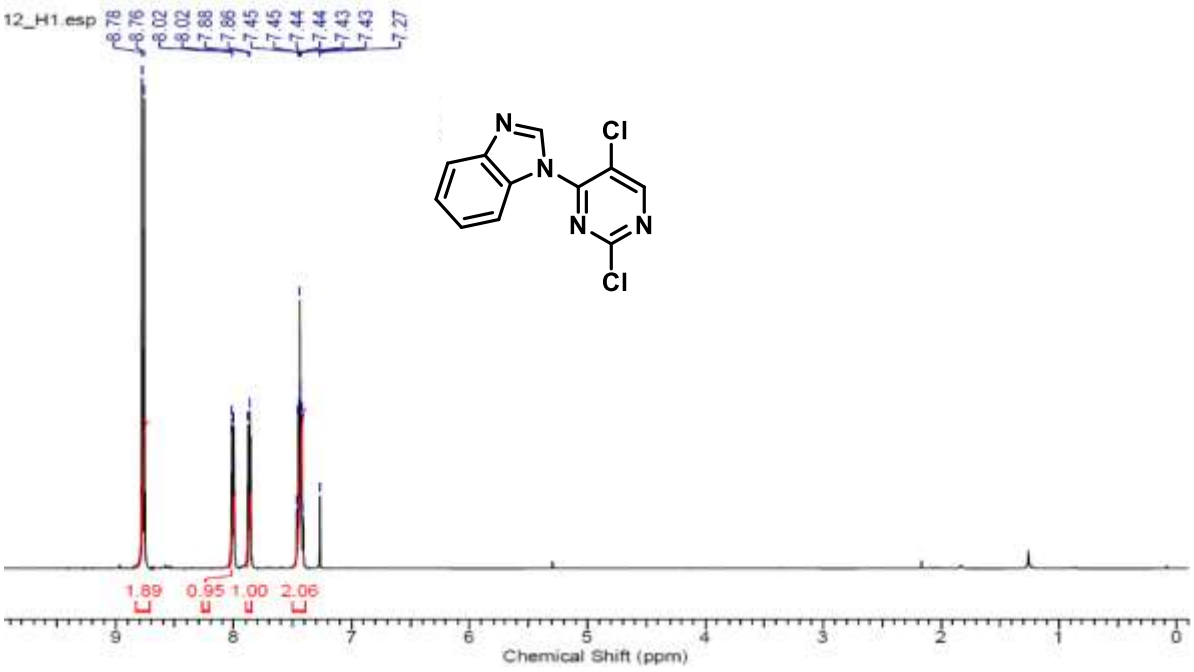


Figure 55: 1-(2,5-dichloropyrimidin-4-yl)-1H-benzo[d]imidazole (**14**)

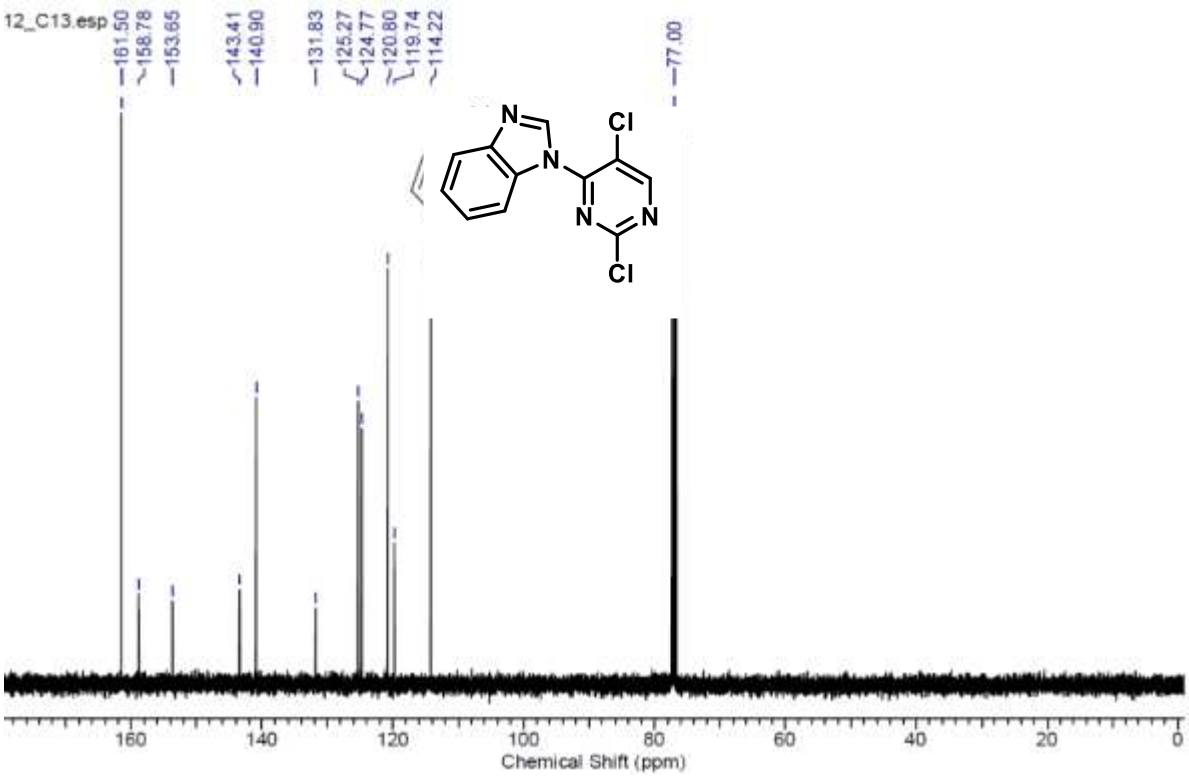


Figure 56: 1-(2,5-dichloropyrimidin-4-yl)-1H-benzo[d]imidazole (**14**)

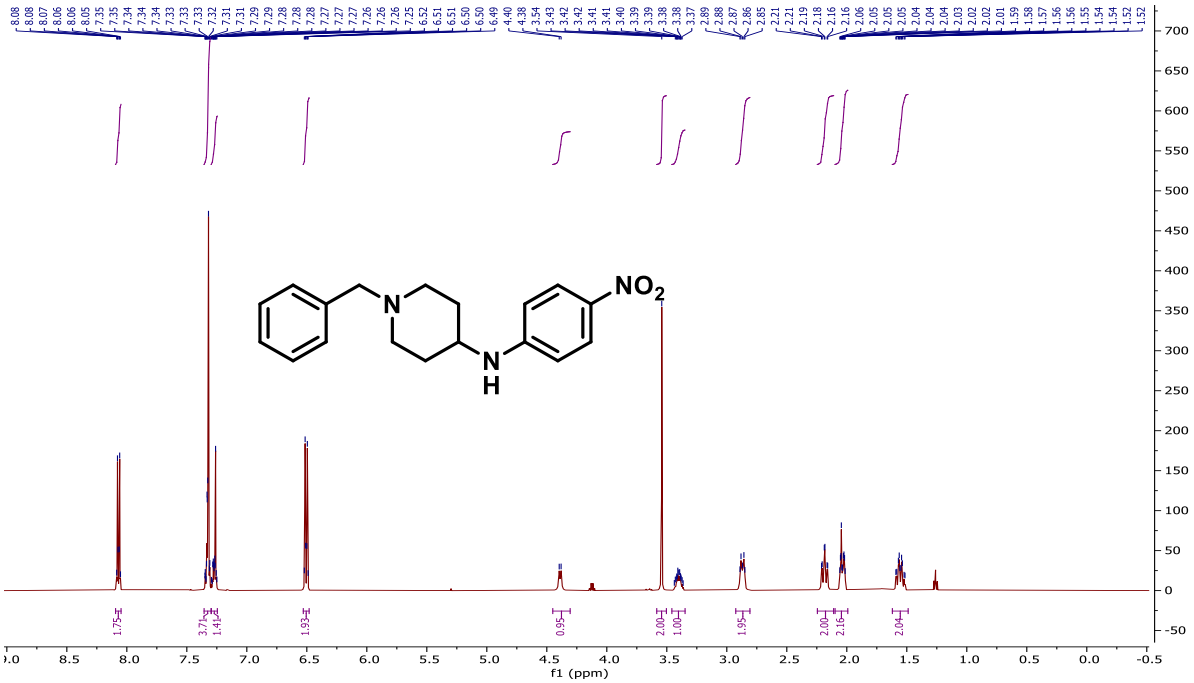


Figure 57: 1-benzyl-N-(4-nitrophenyl)piperidin-4-amine (**15**)

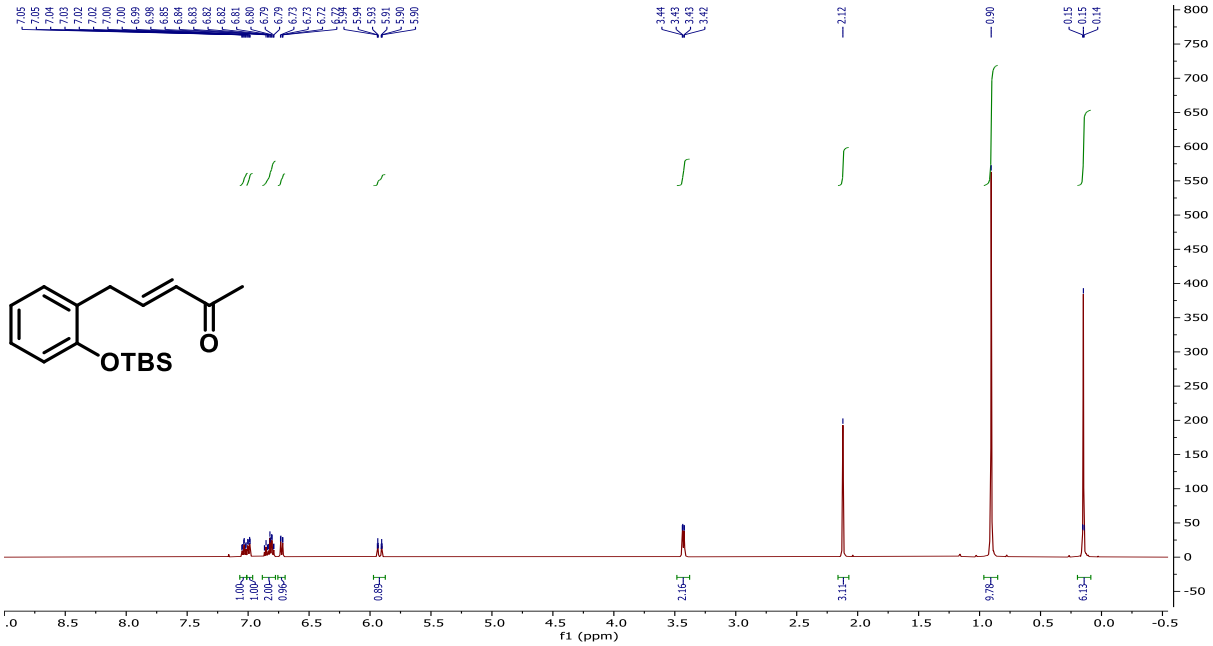


Figure 58: (E)-5-(2-((tert-butyldimethylsilyl)oxy)phenyl)pent-3-en-2-one (**16**)

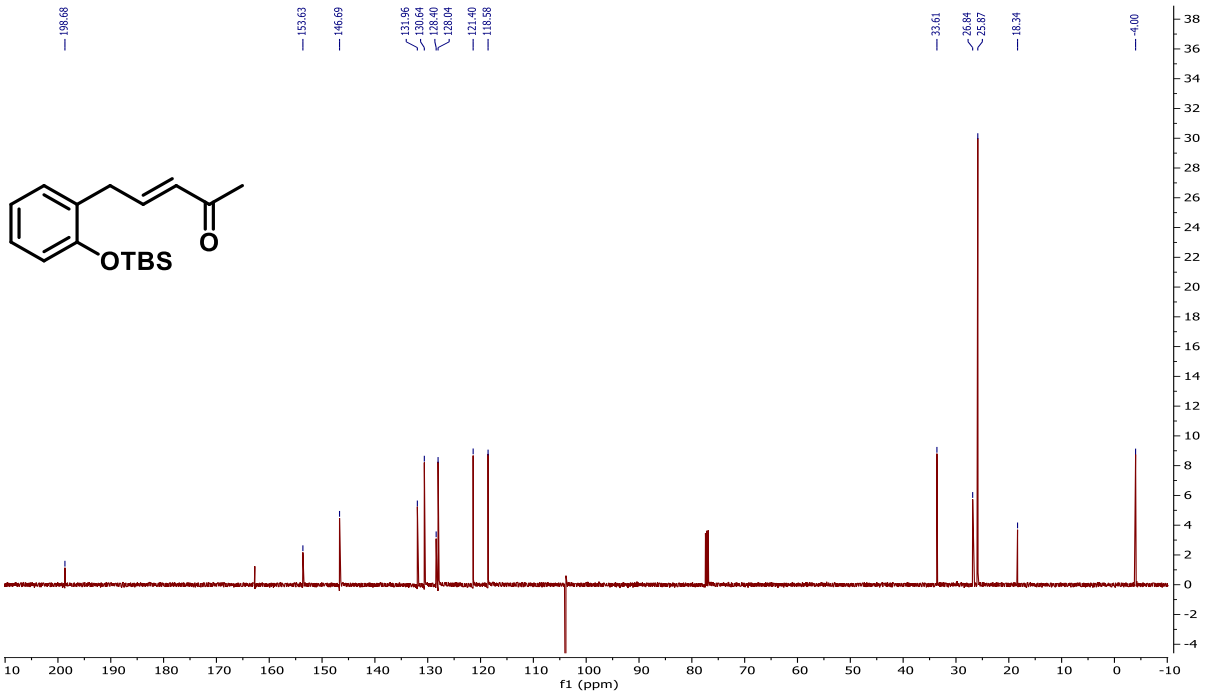


Figure 59: (E)-5-(2-((tert-butyldimethylsilyl)oxy)phenyl)pent-3-en-2-one (**16**)

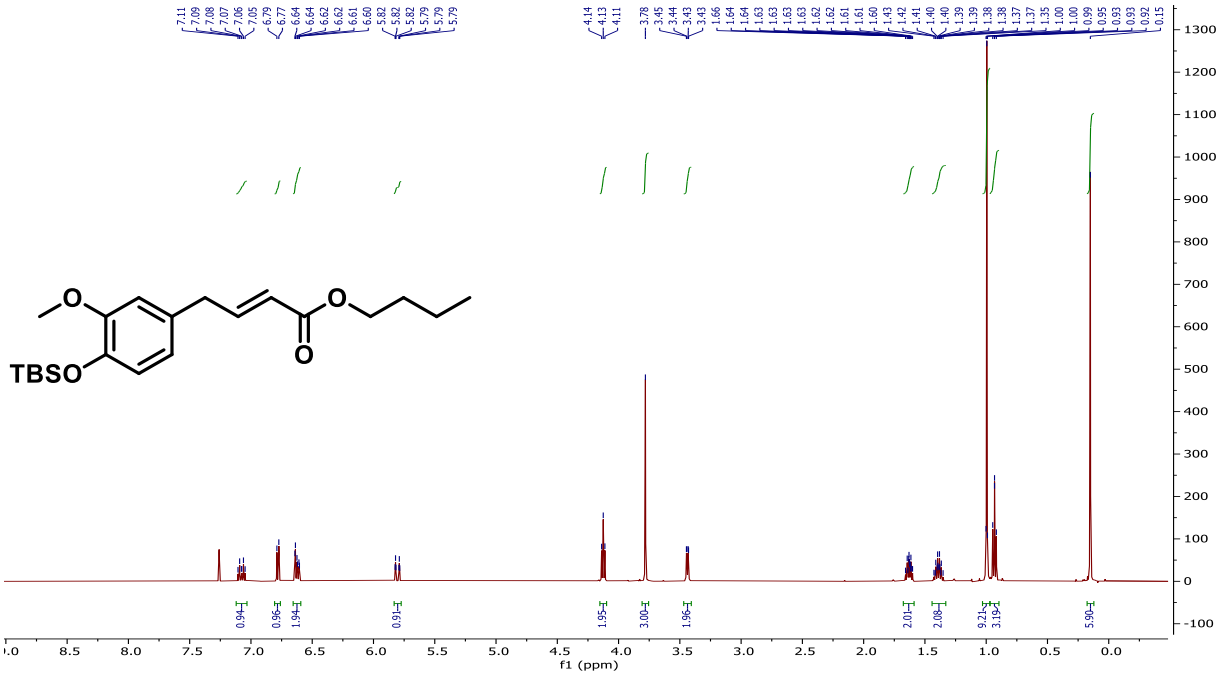


Figure 60: butyl (E)-4-(4-((tert-butyldimethylsilyl)oxy)-3-methoxyphenyl)but-2-enoate (**17**)

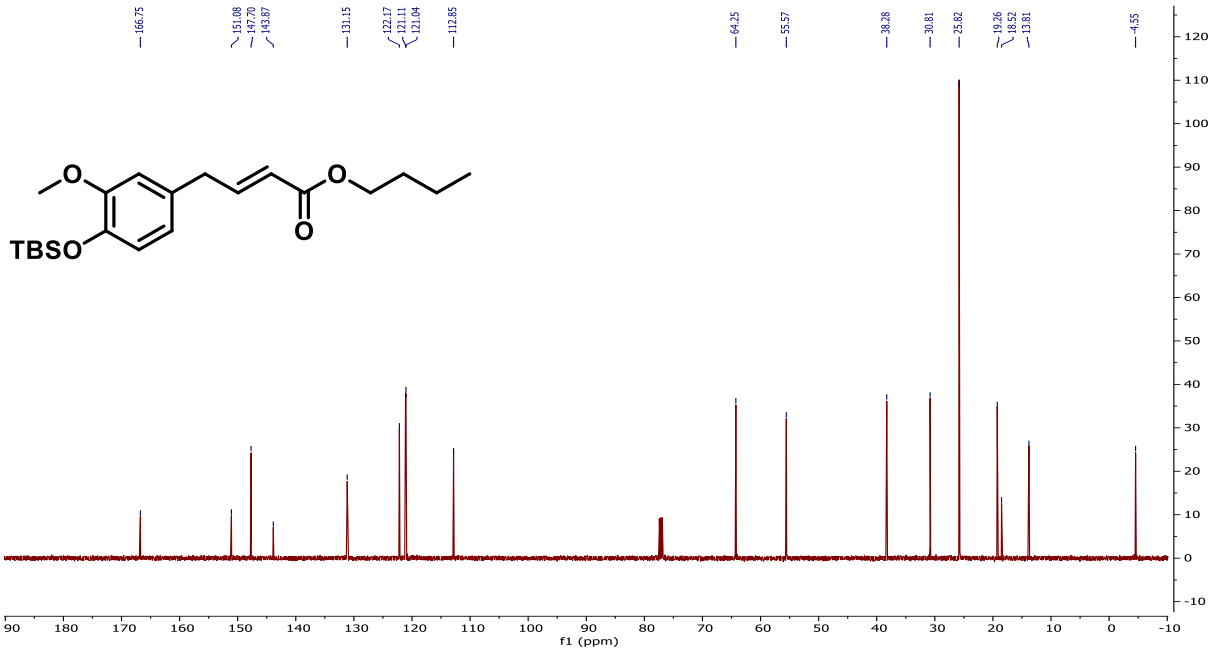


Figure 61: butyl (E)-4-(4-((tert-butyldimethylsilyl)oxy)-3-methoxyphenyl)but-2-enoate (**17**)

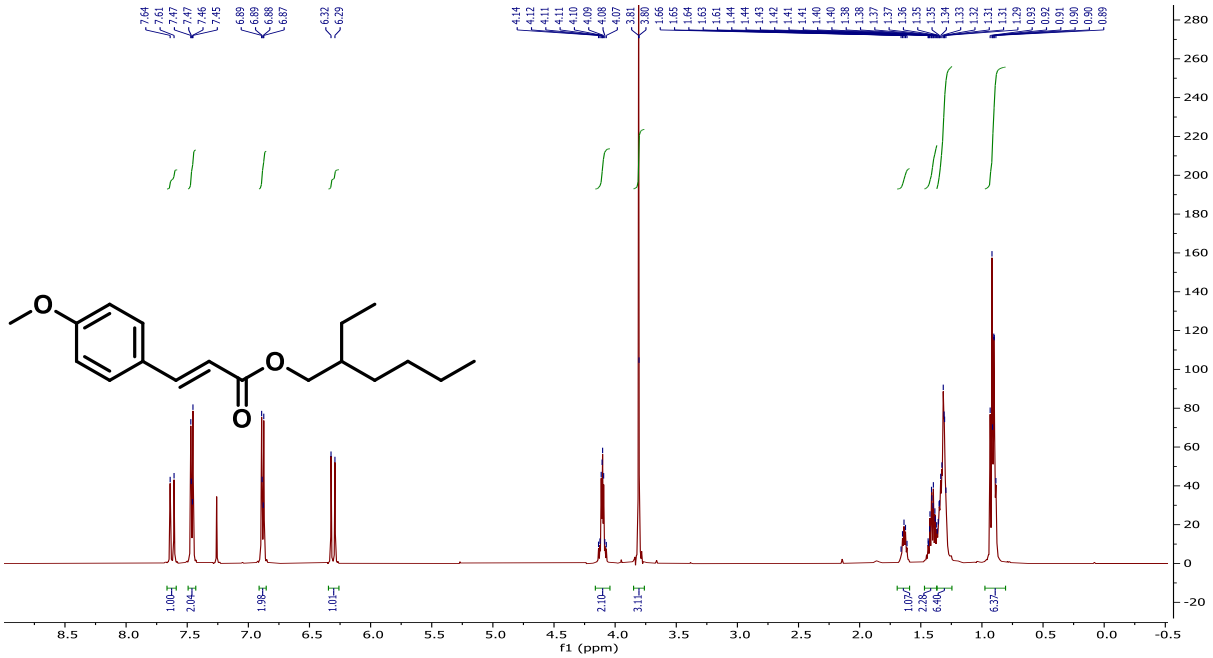


Figure 62: 2-ethylhexyl (E)-3-(4-methoxyphenyl)acrylate (**18**)

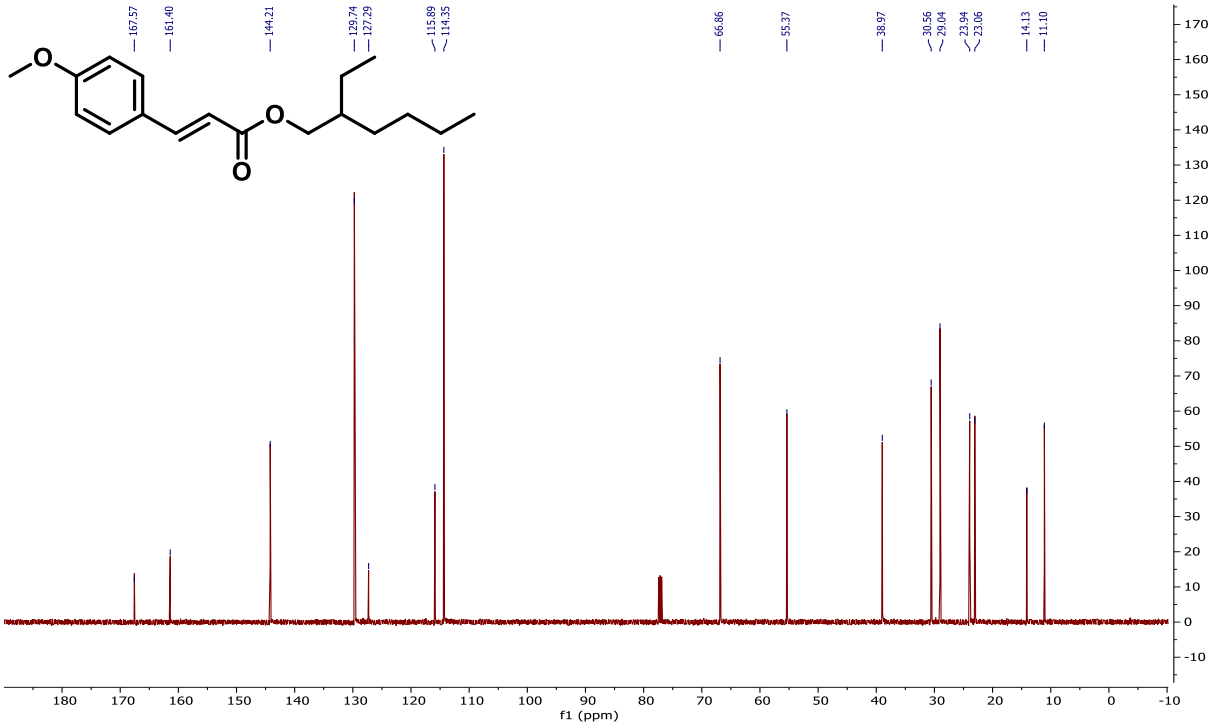


Figure 63: 2-ethylhexyl (E)-3-(4-methoxyphenyl)acrylate (**18**)

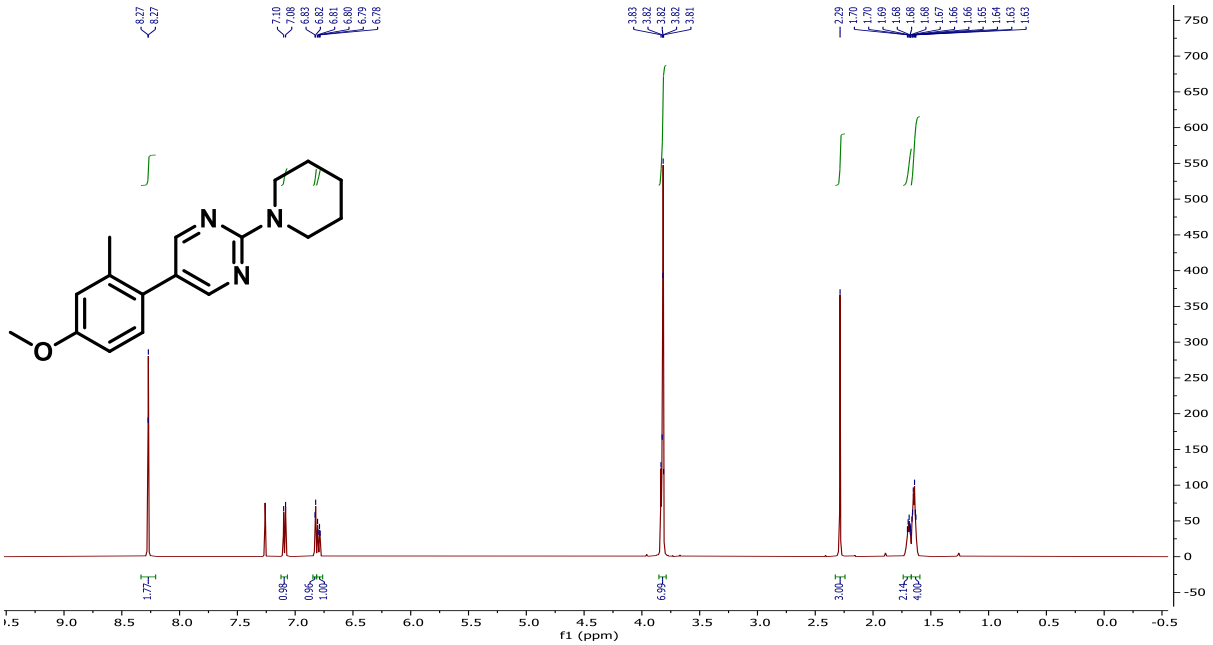


Figure 64: 5-(4-methoxy-2-methylphenyl)-2-(piperidin-1-yl)pyrimidine (**19**)

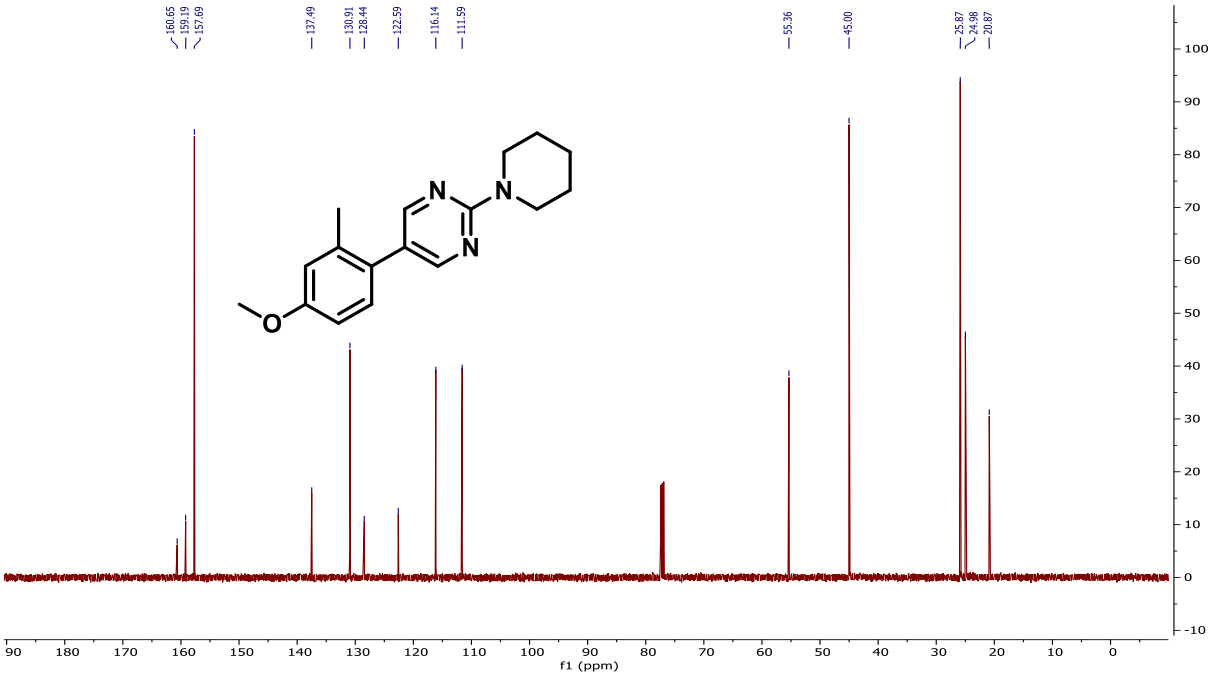


Figure 65: 5-(4-methoxy-2-methylphenyl)-2-(piperidin-1-yl)pyrimidine (**19**)

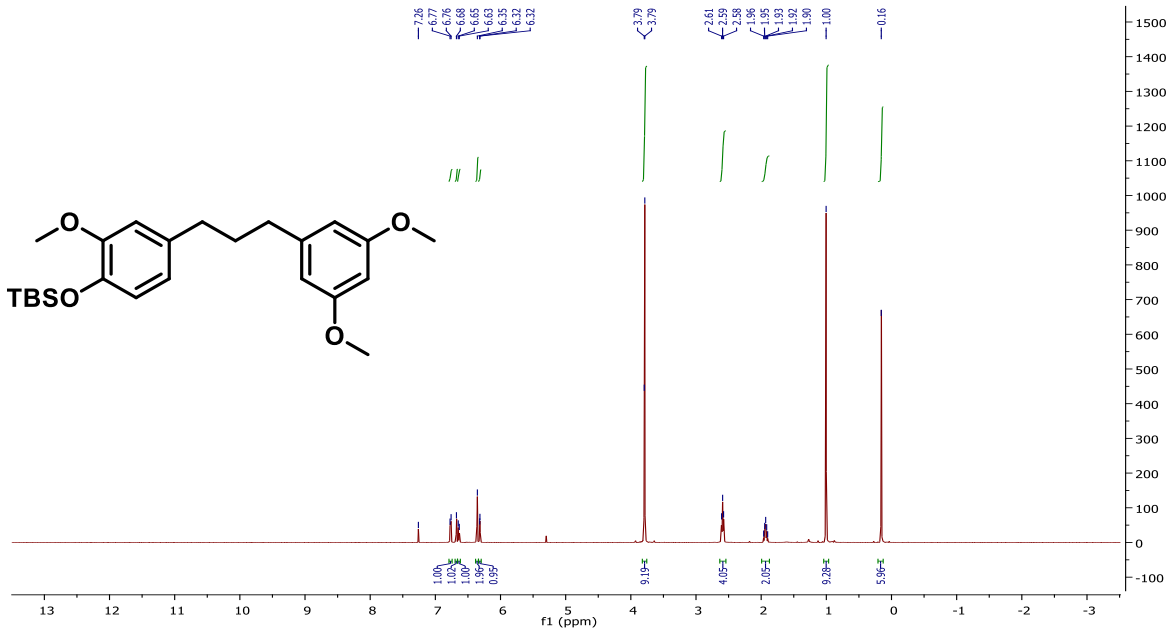


Figure 66: ^{1}H NMR tert-butyl(4-(3-(3,5-dimethoxyphenyl)propyl)-2-methoxyphenoxy)dimethylsilane (**20**)

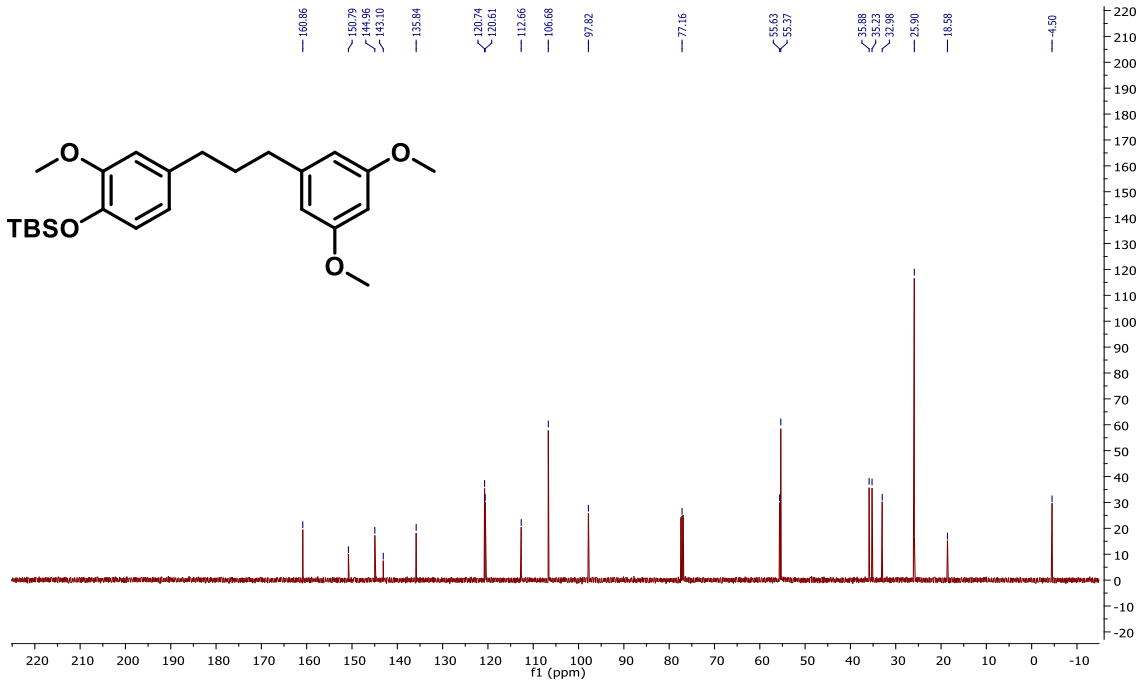


Figure 67: ^{13}C NMR tert-butyl(4-(3-(3,5-dimethoxyphenyl)propyl)-2-methoxyphenoxy)dimethylsilane (**20**)

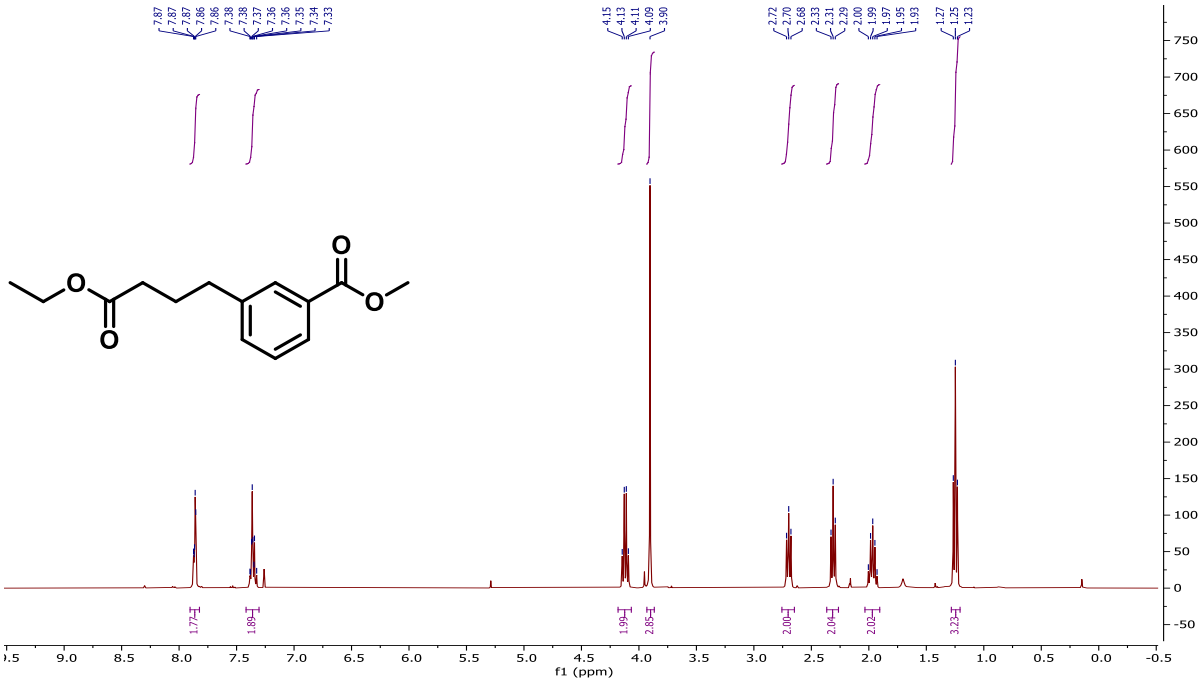


Figure 68: ^{1}H NMR methyl 3-(4-ethoxy-4-oxobutyl)benzoate (**21**)

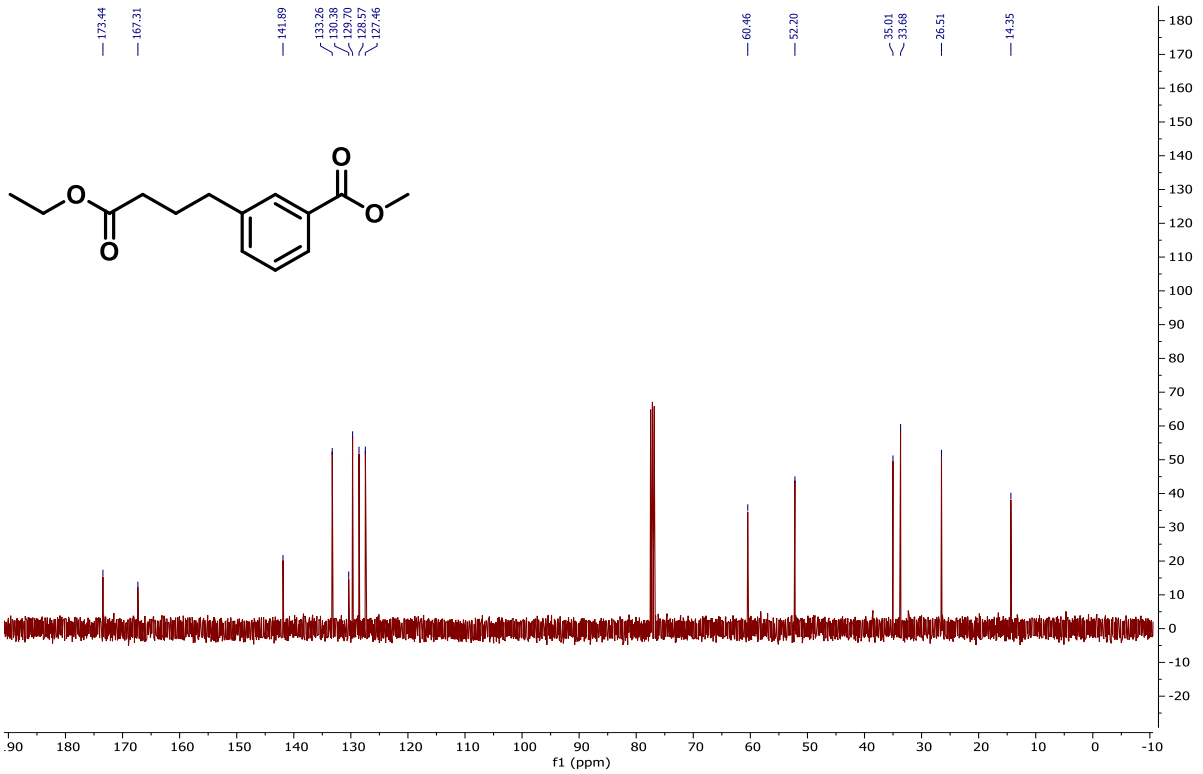


Figure 69: ^{13}C NMR methyl 3-(4-ethoxy-4-oxobutyl)benzoate (**21**)

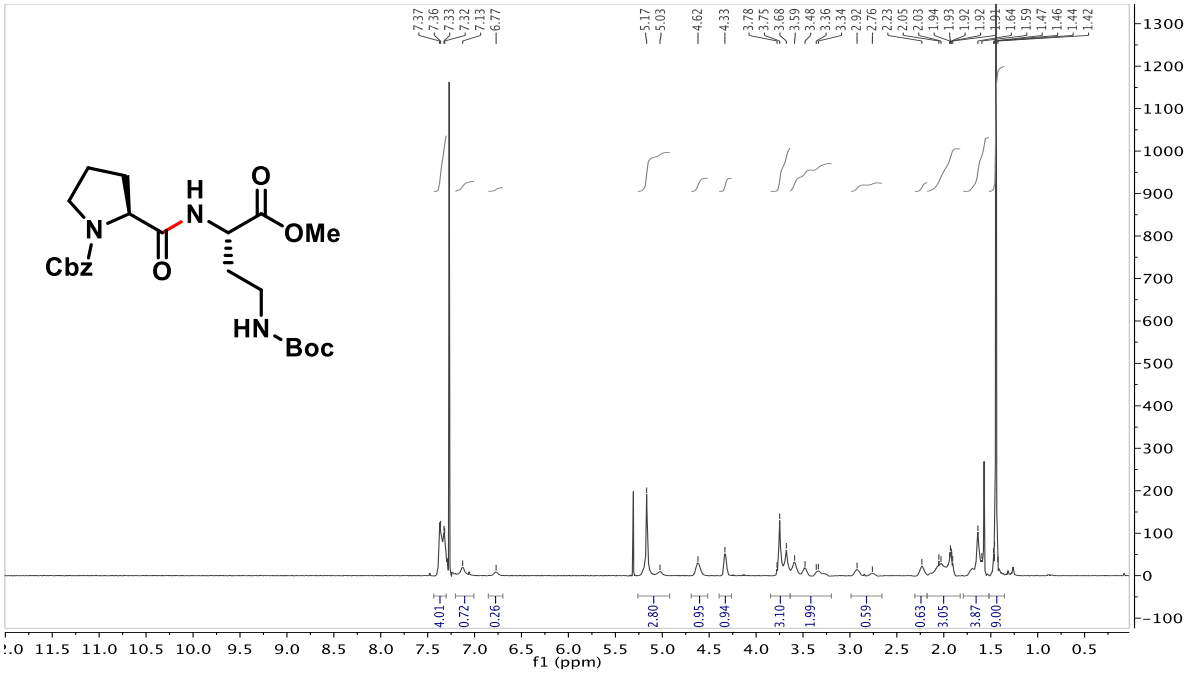


Figure 70: ^{1}H NMR of Cbz-Pro-But(Boc)-OMe (**22**)

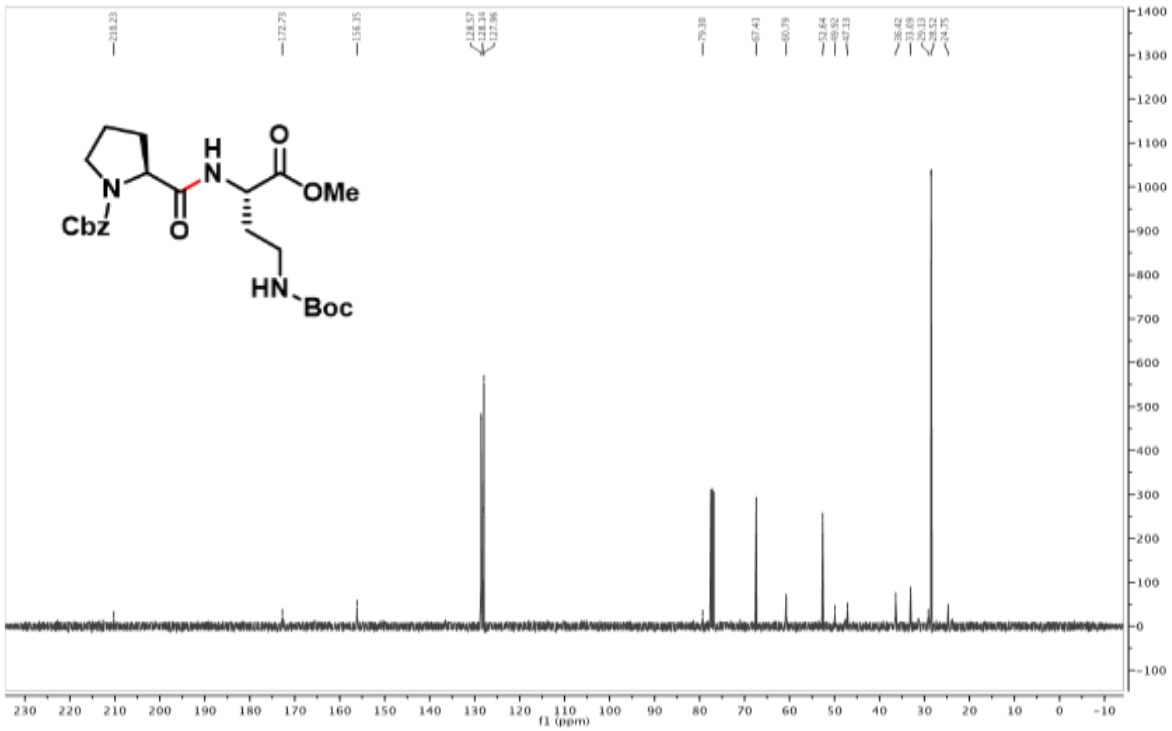


Figure 71: ^{13}C NMR of Cbz-Pro-But(Boc)-OMe (**22**)

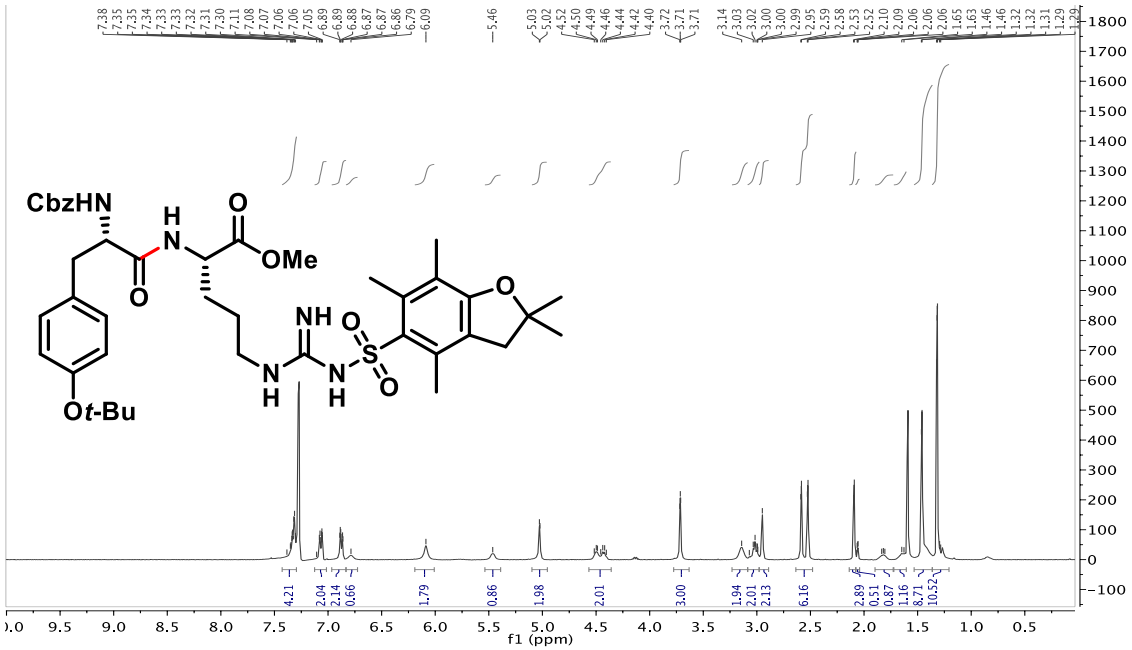


Figure 72: ^{1}H NMR of Cbz-Tyr(tBu)-Arg(Pbf)-OMe (**23**)

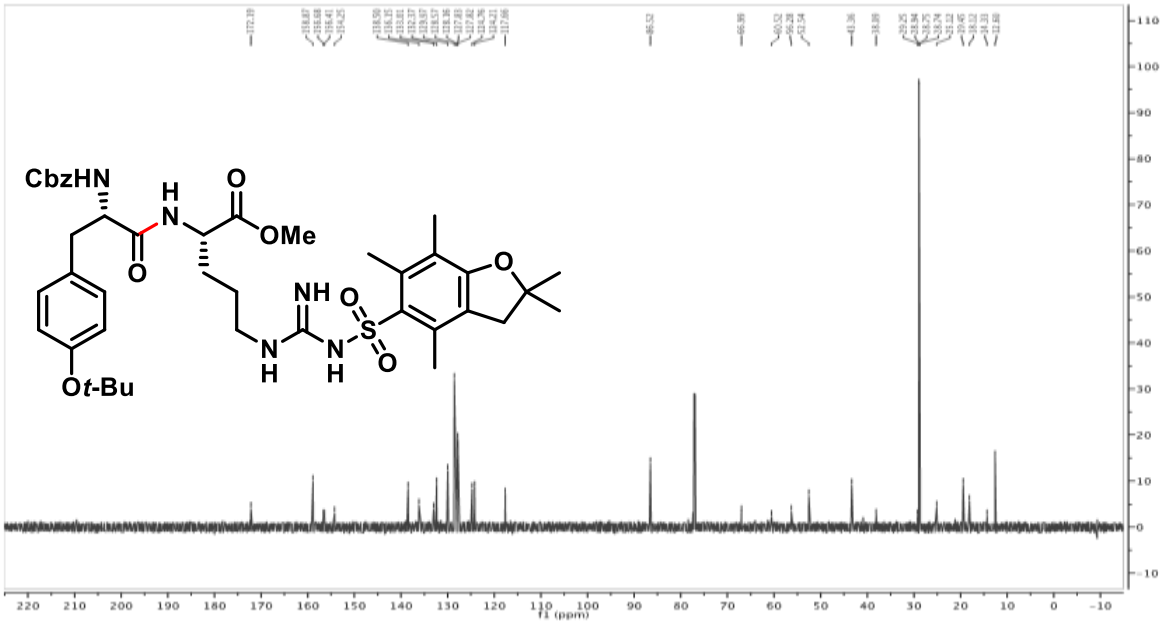


Figure 73: ^{13}C NMR spectra of Cbz-Tyr(tBu)-Arg(Pbf)-OMe (**23**)

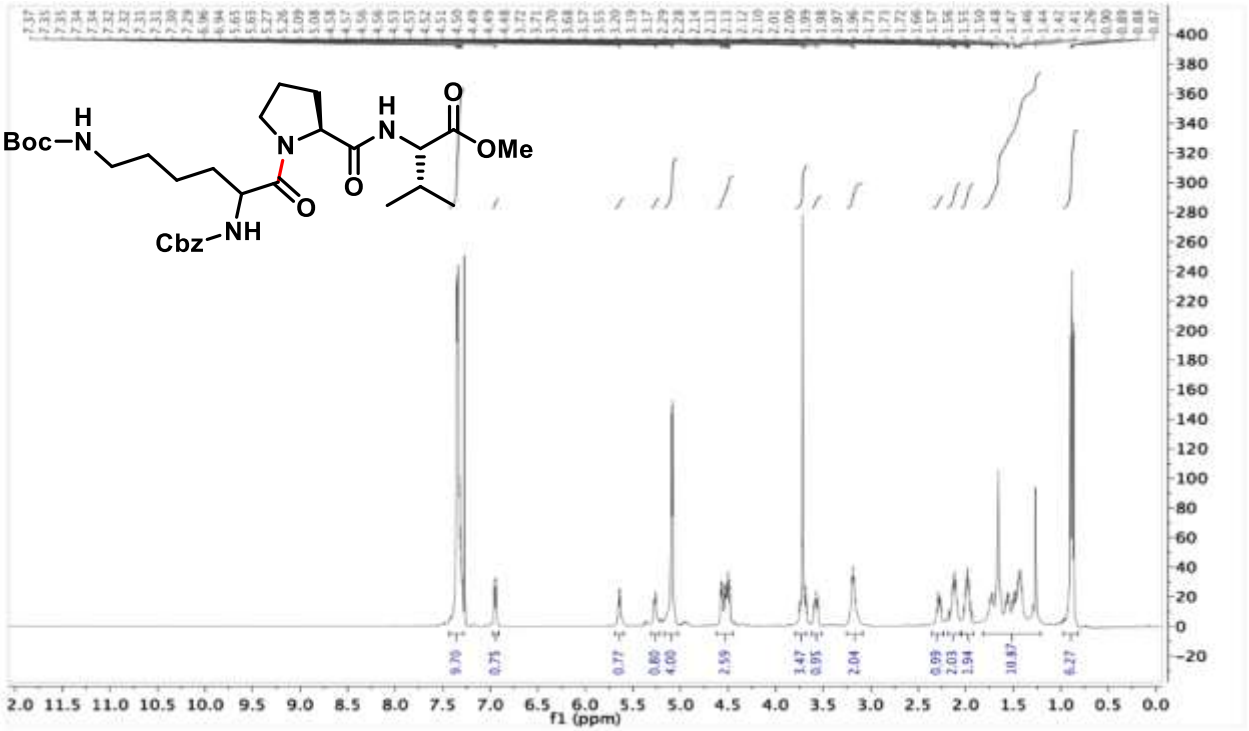


Figure 74: ^{1}H NMR spectra of Cbz-L-Lys(Cbz)-L-Pro-L-Val-OMe (**24**)

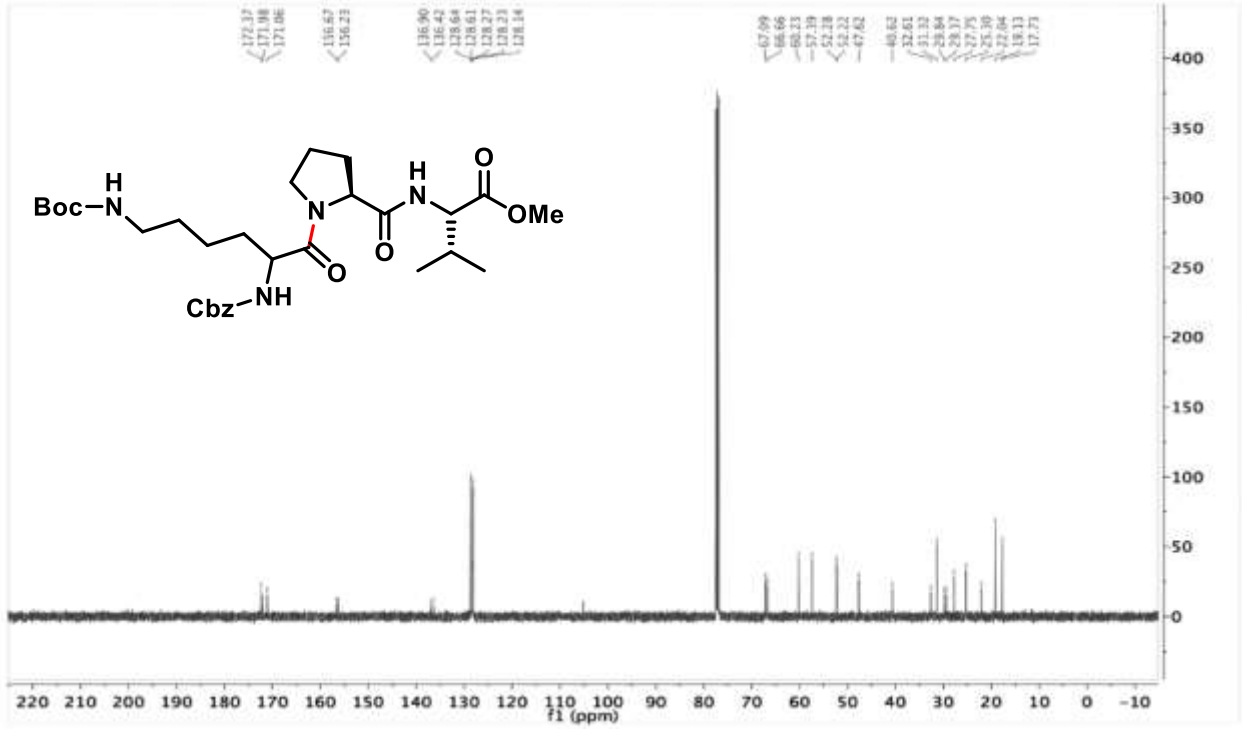


Figure 75: 13C NMR spectra of Cbz-L-Lys(Cbz)-L-Pro-L-Val-OMe (**24**)

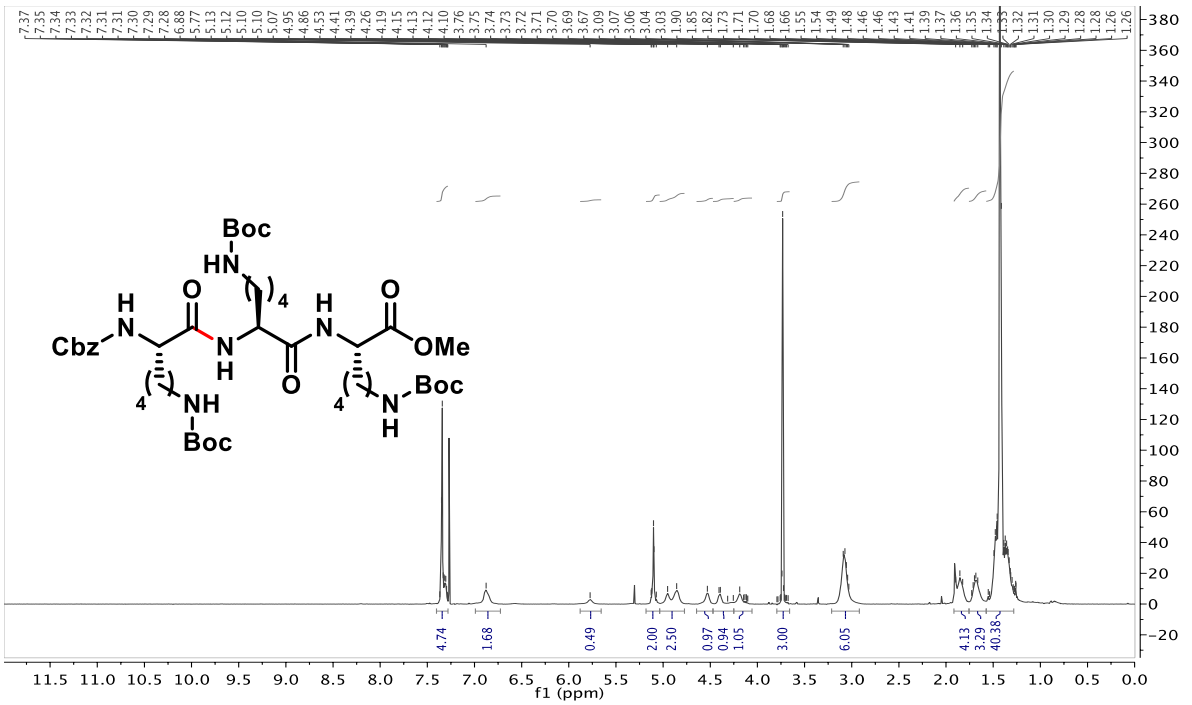


Figure 76: H NMR Cbz-Lys(Boc-Lys(Boc)-Lys(Boc)-OMe (**25**)

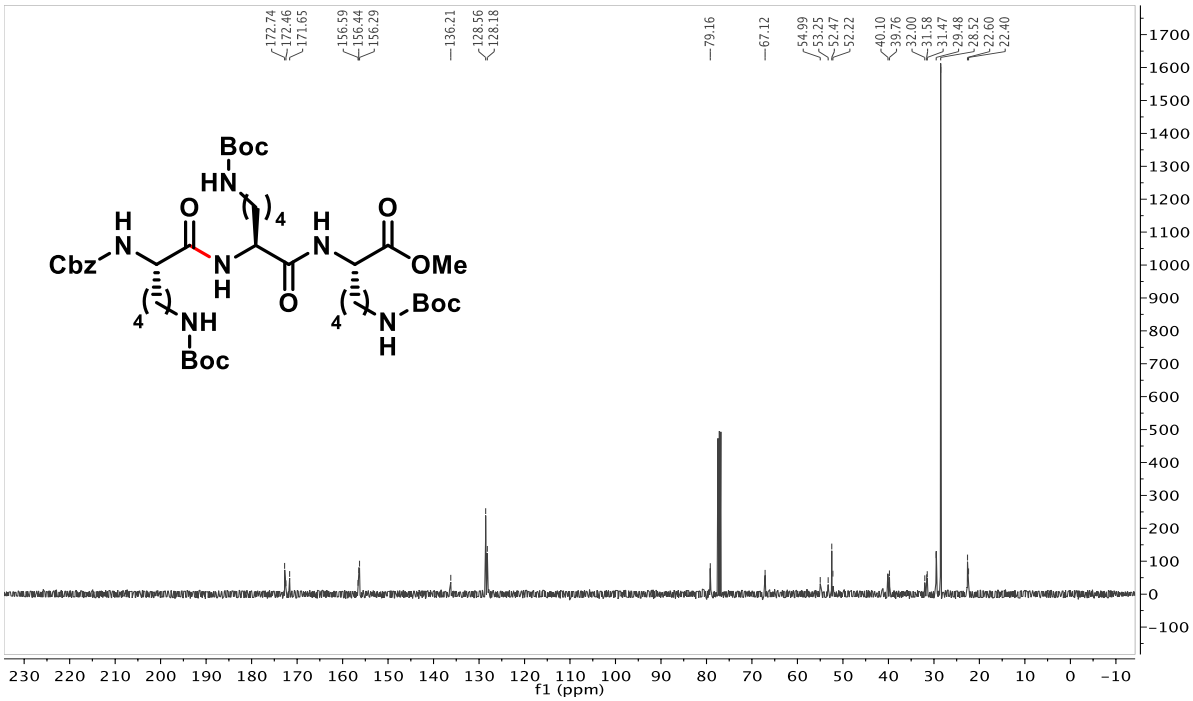


Figure 77: 13C NMR Cbz-Lys(Boc)-Lys(Boc)Lys(Boc)-OMe (**25**)

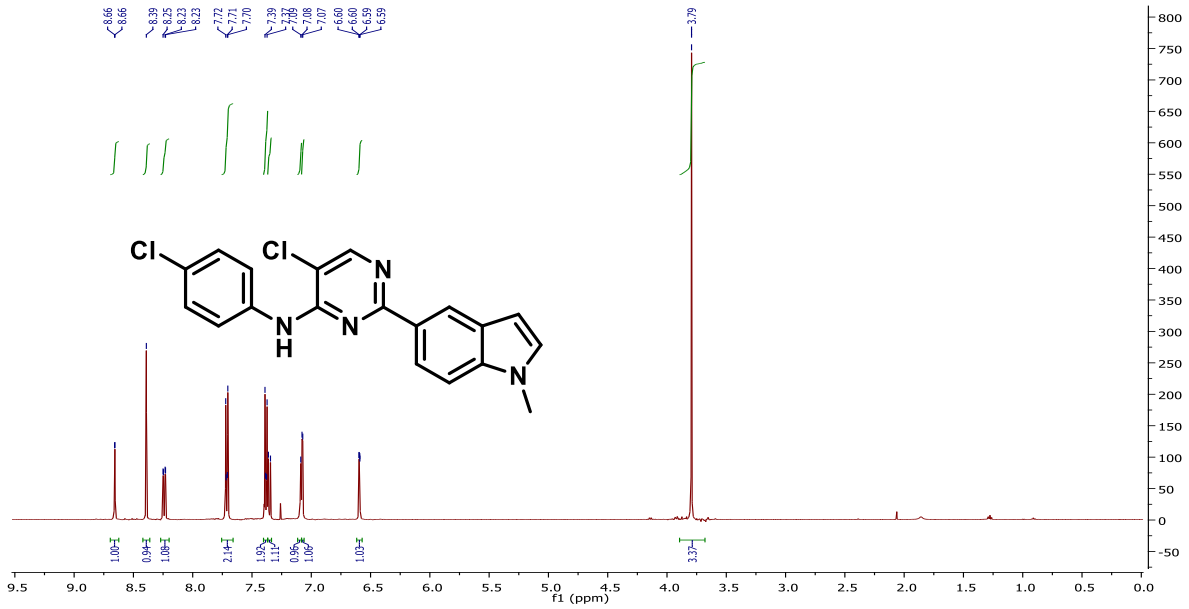


Figure 78: ^{1}H NMR 5-Chloro-*N*-(4-chlorophenyl)-2-(1-methyl-1H-indol-5-yl)pyrimidin-4-amine (**26**)

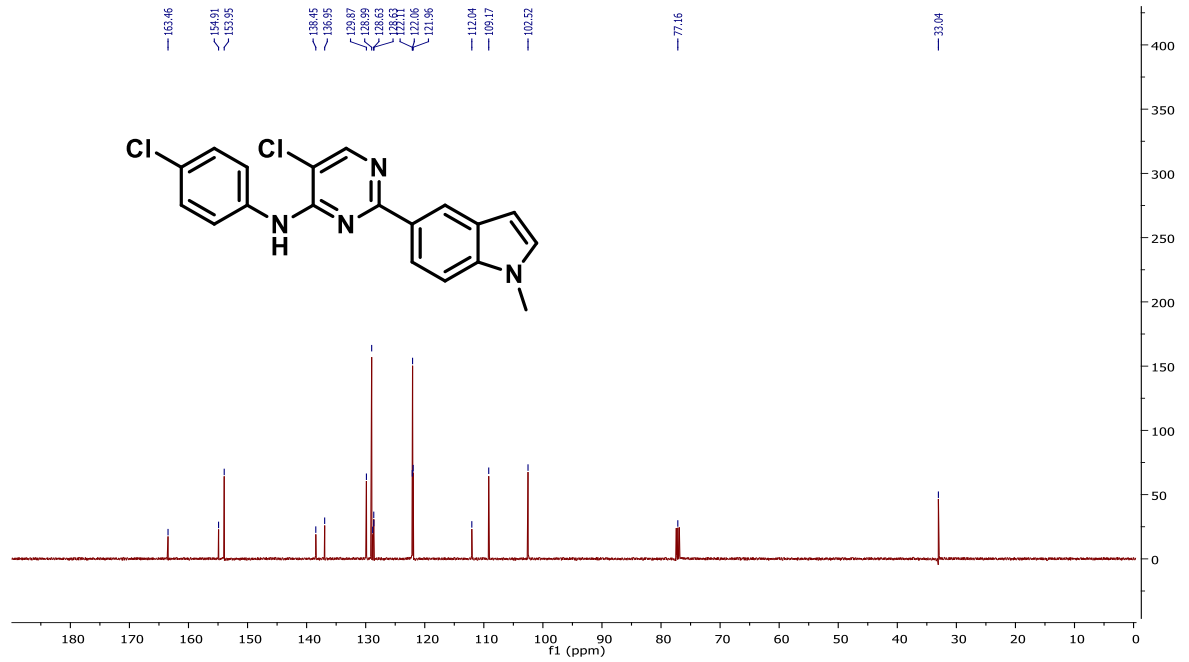


Figure 79: ^{13}C NMR 5-Chloro-*N*-(4-chlorophenyl)-2-(1-methyl-1H-indol-5-yl)pyrimidin-4-amine (**26**)

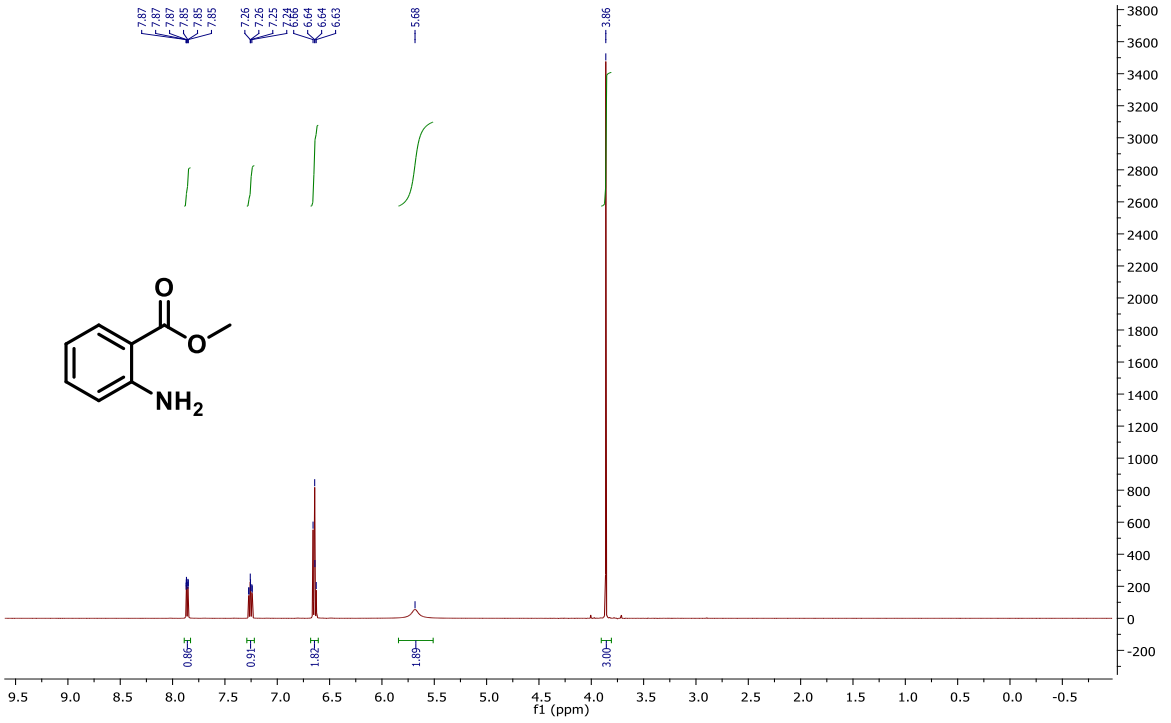


Figure 80: ^{1}H NMR Methyl 2-aminobenzoate

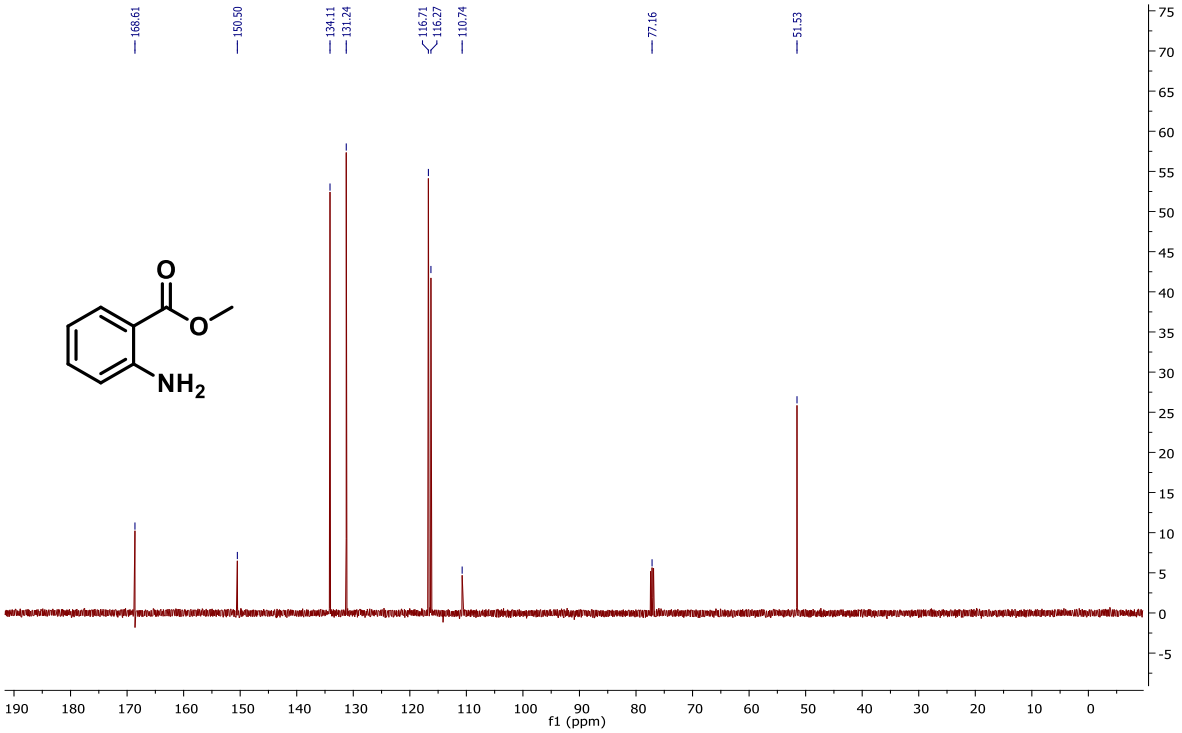


Figure 81: ^{13}C NMR Methyl 2-aminobenzoate

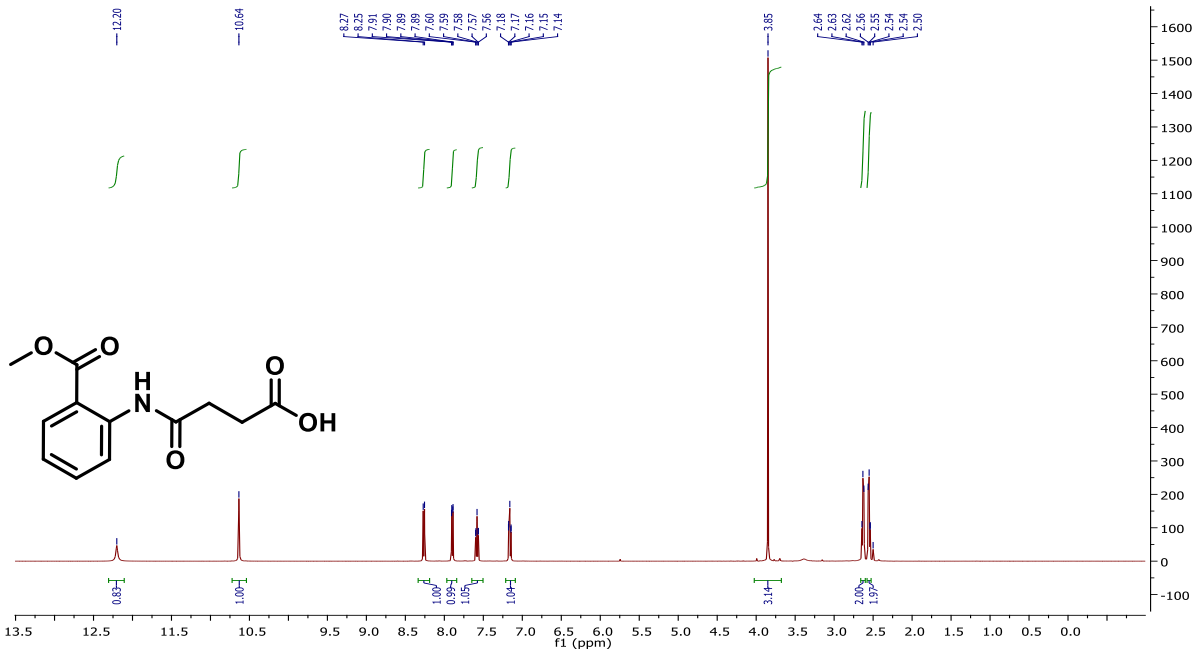


Figure 82: ^{1}H 4-((2-(Methoxycarbonyl)phenyl)amino)-4-oxobutanoic acid

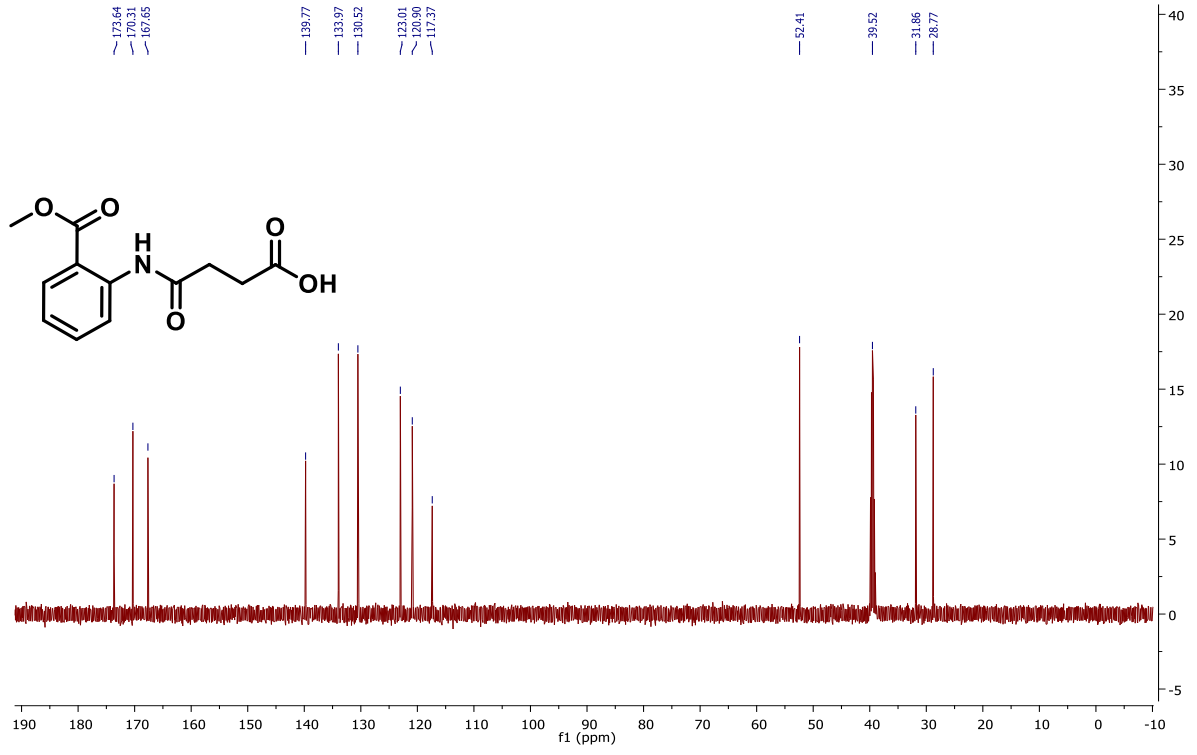


Figure 83: ^{13}C 4-((2-(Methoxycarbonyl)phenyl)amino)-4-oxobutanoic acid

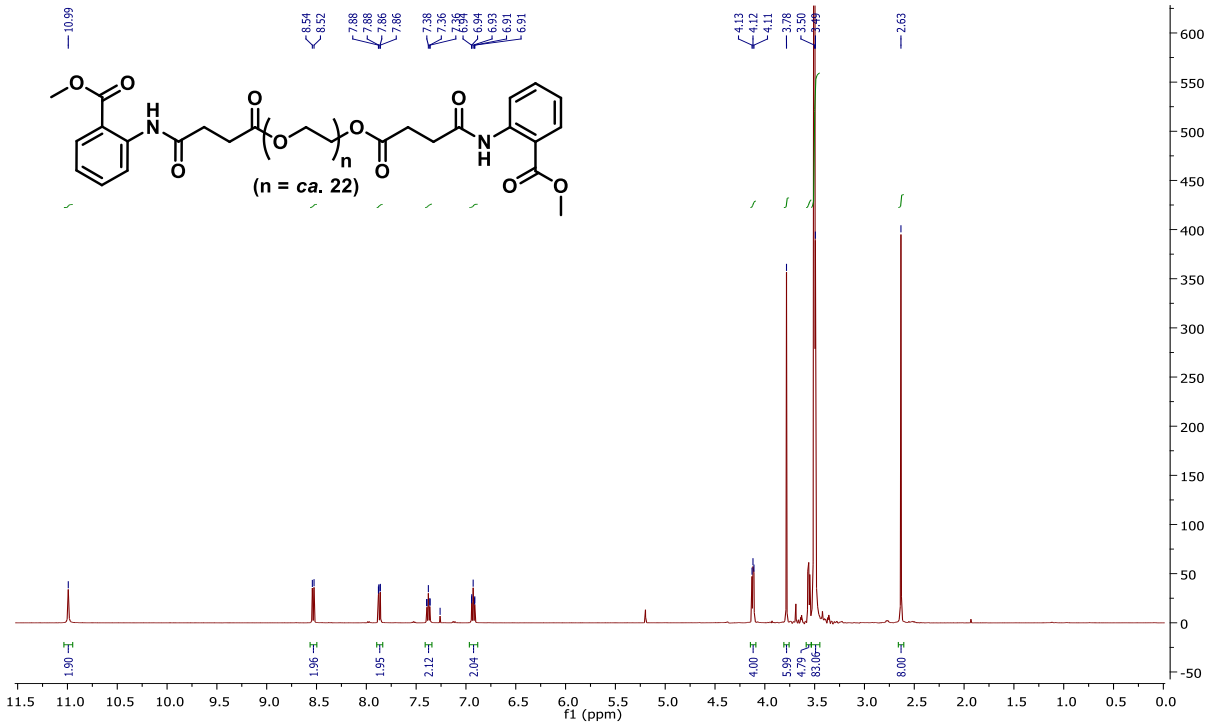


Figure 84: ^{1}H NMR Coolade (Synthesized using Route 3)

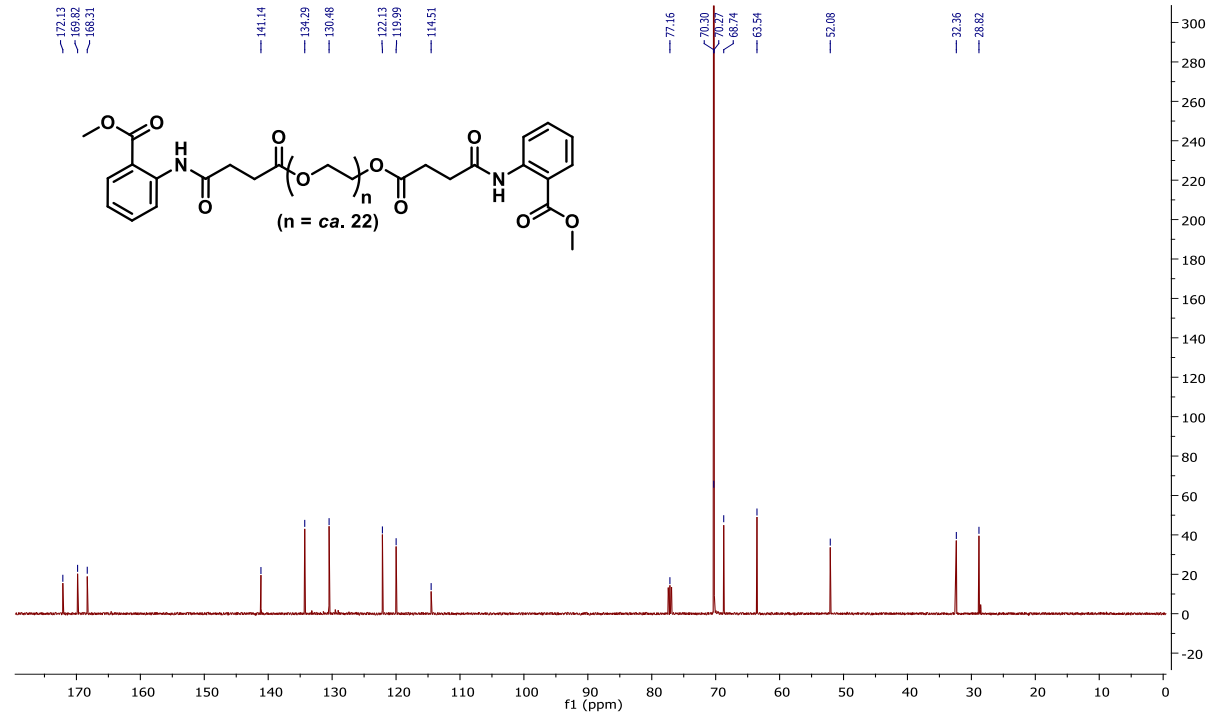


Figure 85: ^{13}C NMR Coolade (Synthesized using Route 3)

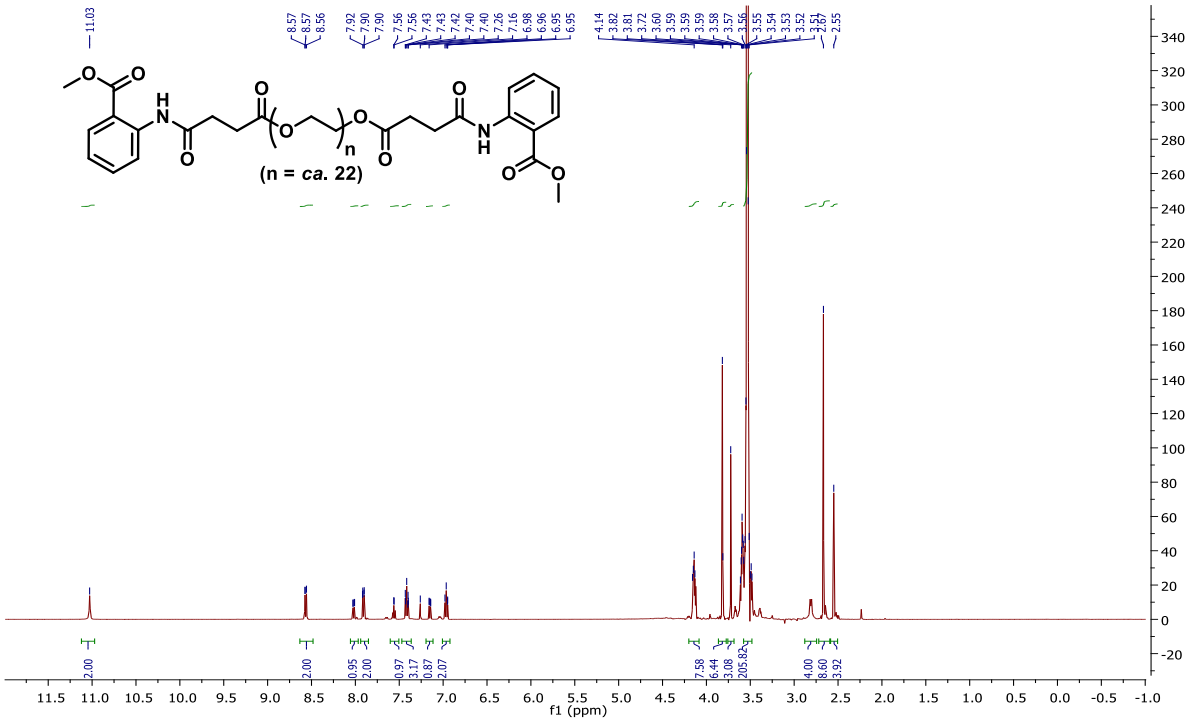


Figure 86: ^{1}H NMR Coolade (Synthesized using Route 2)

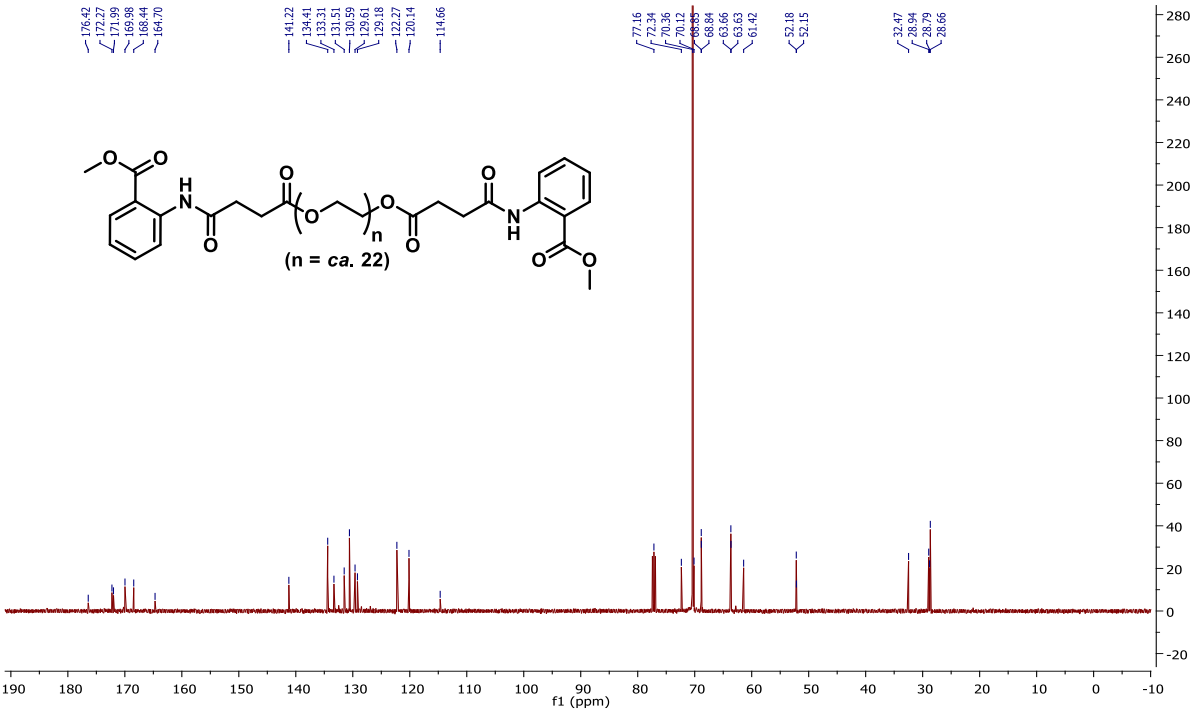


Figure 87: ^{13}C NMR Coolade (Synthesized using Route 2)

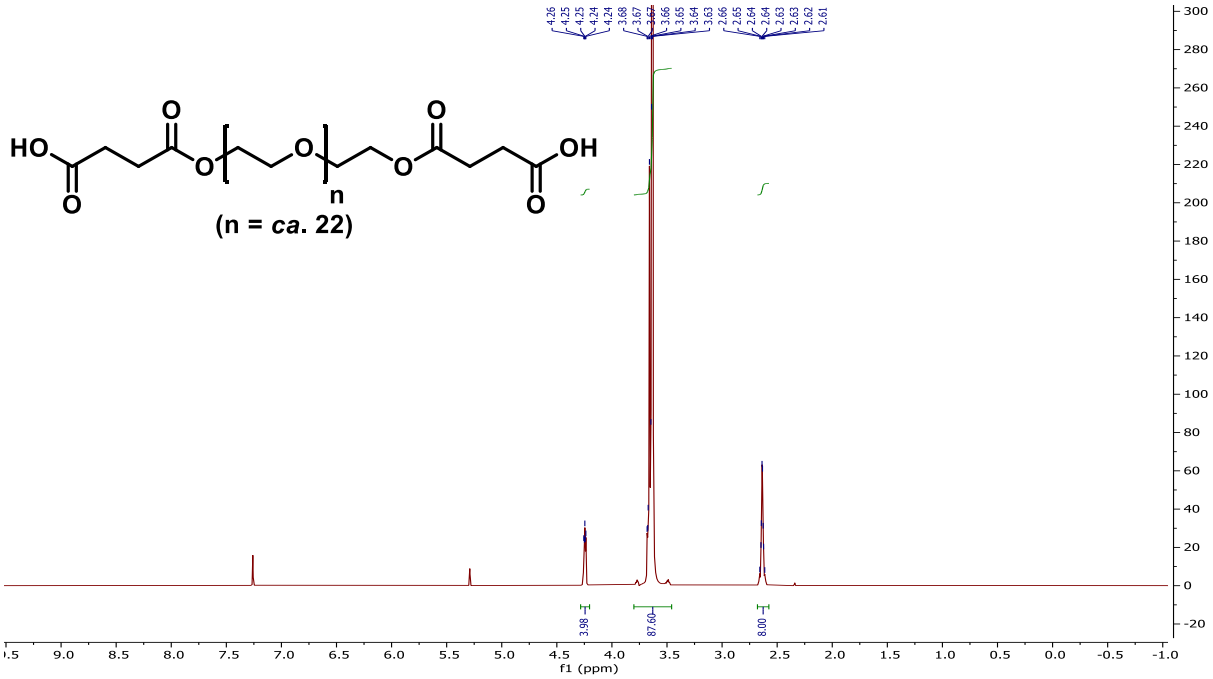


Figure 88: PEG-1000 di-succinate

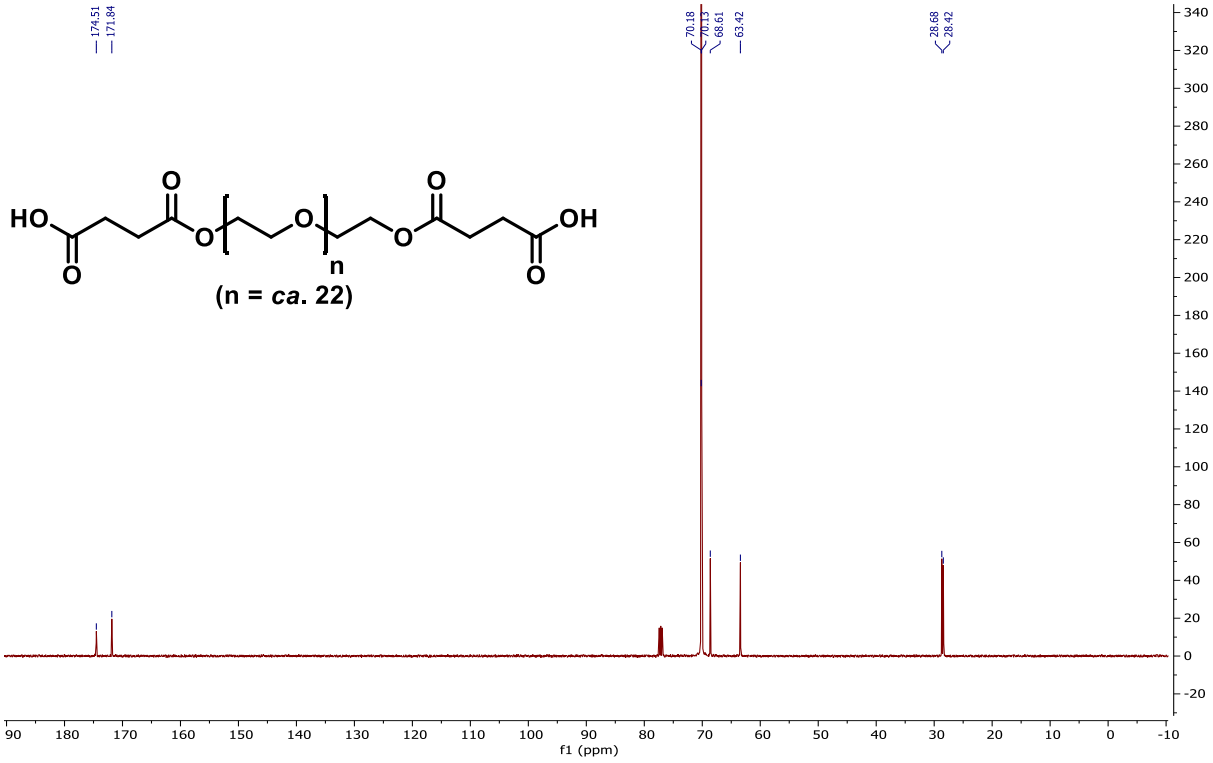


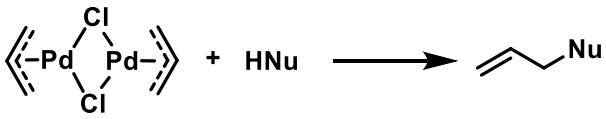
Figure 89: PEG-1000 di-succinate

IV. ppm Pd Tsuji-Trost Allylations in Water

4.1 Introduction & background

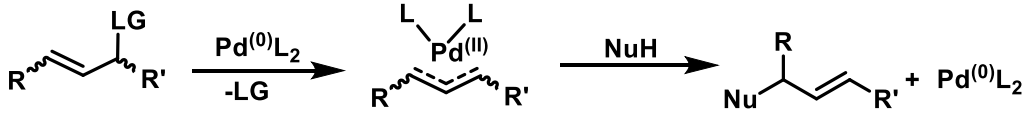
Palladium-catalyzed allylic substitution reactions were first identified by Jiro Tsuji (Scheme 1). This first publication was deduced from the action of a ß-diketone with Pd(allyl)Cl complex, wherein the methylene position was allylated.[106] Trost later expanded on this reaction but these initial discoveries relied on stoichiometric palladium, and no catalytic method had yet been developed.[107]

Scheme 1: Initial discovery of palladium allylic substitution



Eventually, the capability for a catalytic method (Scheme 2), wherein the palladium catalyst is regenerated was defined. Since then, there have been a myriad of custom ligands, asymmetric applications, and approaches utilizing this method.[108] Due to the options for further derivatization of an allylic substituent, this method is particularly useful in synthesis.

Scheme 2: General reaction of Pd-catalyzed allylic substitution



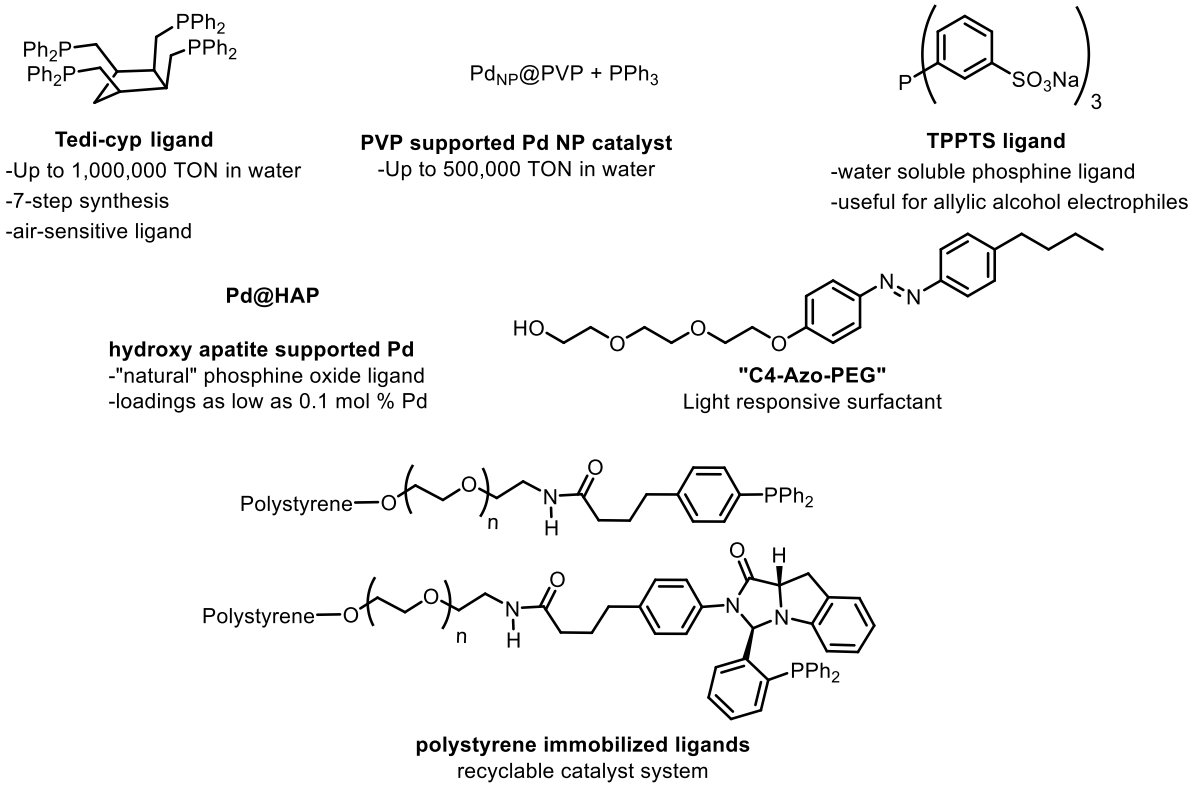
[106] Tsuji, J.; Takahashi, H.; Morikawa, M. Tetrahedron Lett. **1965**, 6, 4387−4388.
[107] Trost, B. M.; Fullerton, T. J. J. Am. Chem. Soc. **1973**, 95, 292−294.
[108] (a) Trost, B. M. Tetrahedron **2015**, 71, 5708−5733. (b) Trost, B. M.; Crawley, M. L. Chem. Rev. **2003**, 103, 2921−2944. (c) Mori, M. 4.5 C−C Bond Formation by Metal-Catalyzed Asymmetric Allylic Alkylation. In Comprehensive Chirality; Carreira, E. M., Yamamoto, H., Eds.; Elsevier: Amsterdam, **2012**; Vol. 4, pp 74−99. (d) Trost, B. M.; Schultz, J. E. Synthesis **2019**, 51, 1−30.

The majority of methodologies developed for this reaction are conducted in traditional organic solvents, such as THF, DCM, DME, etc., and in general, use Pd loadings that are typically in the 1-5 mol % range, which is clearly unsustainable. However, in recent years a number of approaches to this reaction type conducted in water have been published.

4.2 Literature precedence for Tsuji-Trost reactions in water

A number of publications have appeared that conduct the Tsuji-Trost reaction in water, with varying approaches to facilitating the unique challenges associated with this choice of medium (Scheme 3).

Scheme 3: Selected recent approaches to Tsuji-Trost reactions in aqueous reaction medium

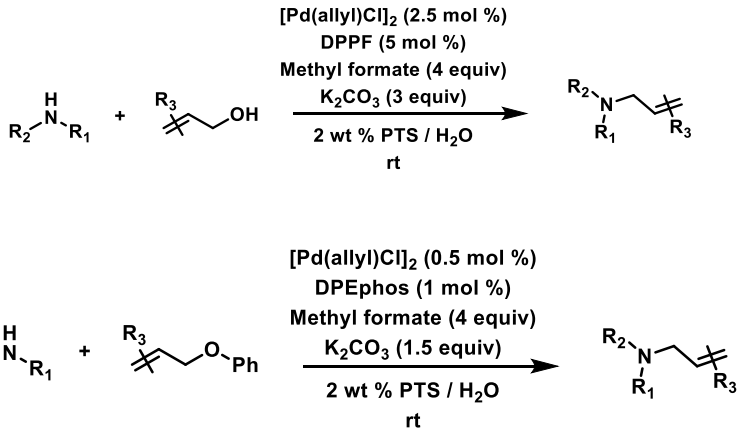


Use of "custom" ligands, such as the *tetra*-tertiary phosphine Tedi-cyp,[109] have achieved very high catalytic activity (up to TON of 680,000 and 1,000,000 in THF and water, respectively), albeit requiring a lengthy synthesis for this air-sensitive ligand's preparation.[3b] Nanoparticle catalysts such as Pd_{NP}@PVP[110] also have produced high turnover numbers (up to 537,000) in water. Tppts has been employed as a water-soluble phosphine ligand, utilized for substitution of allylic alcohols,[111] albeit at high Pd loading (i.e., 5 mol %). Immobilized Pd catalysts, such as Pd on hydroxyapatite (Pd@HAP),[112] and asymmetric ligands attached to polystyrene beads[113] have also been employed with good results. Of the publications utilizing water[114] as the actual solvent or bulk reaction medium, few have utilized surfactants.[115] Some of the noteworthy drawbacks of these approaches include the need for non-commercially available materials or high catalyst loadings.

[109] (a) Feuerstein, M.; Laurenti, D.; Doucet, H.; Santelli, M. *Tetrahedron Lett.* **2001**, *42*, 2313–2315. (b) Doucet, H.; Santelli, M. Phosphine [(1R,2R,3S,4S)-1,2,3,4-Cyclopentanetetrakis(Methylene)]Tetrakis[Diphenyl]. In *Encyclopedia of Reagents for Organic Synthesis*; American Cancer Society, 2004.
[110] Llevot, A.; Monney, B.; Sehlinger, A.; Behrens, S.; R. Meier, M. A. *Chem. Commun.* **2017**, *53*, 5175–5178.
[111] Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2004**, *6*, 4085–4088.
[112] Masuyama, Y.; Nakajima, Y.; Okabe, J. *Appl. Catal., A.* **2010**, *387*, 107–112.
[113] Use of supported catalysts for asymmetric reactions: (a) Uozumi, Y.; Tanaka, H.; Shibatomi, K. *Org. Lett.* **2004**, *6*, 281–283. (b) Uozumi, Y.; Shibatomi, K. *J. Am. Chem. Soc.* **2001**, *123*, 2919–2920. (c) Uozumi, Y. *Catal. Surv. Asia.* **2005**, *9*, 269–278. (d) Uozumi, Y.; Suzuka, T. *J. Org. Chem.* **2006**, *71*, 8644–8646.
[114] Additional references for allylic substitution in water: (a) Blart, E.; Genet, J. P.; Safi, M.; Savignac, M.; Sinou, D. *Tetrahedron* **1994**, *50*, 505–514. (b) Felpin, F.-X.; Landais, Y. *J. Org. Chem.* **2005**, *70*, 6441–6446. (c) Ghorpade, S. A.; Sawant, D. N.; Makki, A.; Sekar, N.; Eppinger, J. *Green Chem.* **2018**, *20*, 425–430. (d) Hikawa, H.; Yokoyama, Y. *J. Org. Chem.* **2011**, *76*, 8433–8439.
[115] For reviews on micellar catalysis and aqueous reaction medium: (a) Kitanosono, T.; Masuda, K.; Xu, P.; Kobayashi, S. *Chem. Rev.* **2018**, *118*, 679–746. (b) Li, C.-J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68–82. (c) Dwars, T.; Paetzold, E.; Oehme, G. *Angew. Chem., Int. Ed*. **2005**. *44*, 7174–7199. (d) Sorella, G. L.; Strukul, G.; Scarso, A. *Green Chem.* **2015**, *17*, 644–683. (e) Lamblin, M.; Nassar-Hardy, L.; Hierso, J.-C.; Fouquet, E.; Felpin, F.-X. *Adv. Synth. Catal.* **2010**, *352*, 33–79. (f) Lipshutz, B. H. *Curr. Opin. Green and Sustain. Chem.* **2018**, *11*, 1–8. (g) Lipshutz, B. H.; Ghorai, S.; Cortes-Clerget, M. *Chem. Eur. J.* **2018**, *24*, 6672–6695. (h) Kobayashi, S. *Pure Appl. Chem.* **2013**, *85*, 1089–1101. (i) Lipshutz, B. H. *J. Org. Chem.* **2017**, *82*, 2806–2816.

At the start of this project, two previous reports of Tsuji-Trost reactions were published by the Lipshutz group (Scheme 4). These reports focused on use of difficult or uncommon electrophiles such as allylic alcohols or allyl phenyl ethers. [116]

Scheme 4: Previous approaches to Tsuji-Trost reactions in water from the Lipshutz group



With a growing emphasis on sustainable catalysis, and the skyrocketing price of palladium, there is considerable attention being focused on sustainable catalysis. While ideally, sustainable catalysis would involve replacement of a non-precious metal catalyst with an earth-abundant and cheap metal, full replacement of "privileged" metals like Pd and Rh is difficult. Alternatively, "sustainable catalysis" can take the form of using the lowest catalyst loading possible. Because the above previously developed methods used relatively typical/higher catalyst loadings (i.e., 1-5 mol %), lowering the catalyst loading was a primary motive of the current project. Toward this goal, a number of conditions

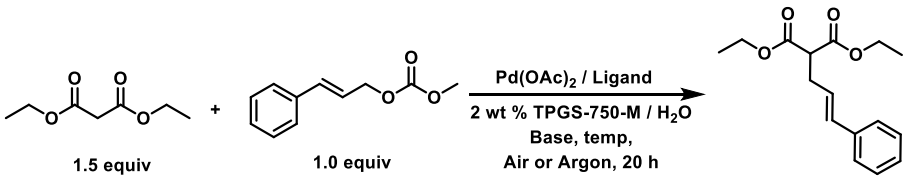
[116] Allylic alcohols as electrophiles: (a) Sundararaju, B.; Achard, M.; Bruneau, C. *Chem. Soc. Rev.* **2012**, *41*, 4467–4483. (b) Butt, N. A.; Zhang, W. *Chem. Soc. Rev.* **2015**, *44*, 7929–7967. (c) Tamaru, Y. *Eur. J. Org. Chem.* **2005**, *2005*, 2647–2656. (d) Yang, S.-C.; Hsu, Y.-C.; Gan, K.-H. *Tetrahedron* **2006**, *62*, 3949–3958. (e) Manabe, K.; Kobayashi, S. *Org. Lett.* **2003**, *5*, 3241–3244. (f) S. Wagh, Y.; N. Sawant, D.; P. Dhake, K.; M. Bhanage, B. *Catal. Sci. Technol.* **2012**, *2*, 835–840. (g) Trillo, P.; Baeza, A.; Nájera, C. *ChemCatChem* **2013**, *5*, 1538–1542. (h) Trillo, P.; Baeza, A.; Nájera, C. *Eur. J. Org. Chem. 2012*, 2929–2934. (i) Akkarasamiyo, S.; Sawadjoon, S.; Orthaber, A.; Samec, J. S. M. *Chem. Eur. J. 24*, 3488–3498.

were screened in hopes of finding conditions amenable to use of very low catalyst loadings. After extensive screening, reasonably "general" conditions were identified which allowed for full conversion at 1000 ppm Pd (0.1 mol %) on a variety of substrates.

4.3 Optimization experiments towards lower catalyst loadings

As an initial "model" substrate, diethyl malonate was treated with cinnamyl-OCO_2Me as electrophile (Table 1). These experiments were very encouraging, since it appeared that full conversion could be reached using simply PPh_3 and $Pd(OAc)_2$. However, the reaction was found to be air sensitive, and Et_3N had to be added to the catalyst stock solution (presumably to encourage reduction of Pd(II) to Pd(0) via ß-hydride elimination).

Table 1: Initial screening studies for the reaction of diethyl malonate with cinnamyl-OCO_2Me at ppm Pd loadings



entry	Pd (mol %)	Ligand	Temp	Air/ Argon	Catalyst Stock solution solvent	Base	Base equiv	conversion[a]
1	0.2	SPhos	rt	Air	THF[b]	Et_3N	1.5	Trace
2	0.2	SPhos	rt	Air	THF[b]	K_2CO_3	1.5	Trace
3	0.2	PPh_3	rt	Air	THF[b]	Et_3N	1.5	Trace
4	0.2	PPh_3	rt	Air	THF[b]	K_2CO_3	1.5	Trace
5	0.1	SPhos	rt	Air	THF[b]	Et_3N	1.5	none
6	0.1	SPhos	rt	Air	THF[b]	K_2CO_3	1.5	none
7	0.1	PPh_3	rt	Air	THF[b]	Et_3N	1.5	none

8	0.1	PPh_3	rt	Air	THF[b]	K_2CO_3	1.5	none
9	0.2	PPh_3	rt	Argon	THF[b]	Et_3N	1.5	Trace[f]
10	0.2	PPh_3	rt	Argon	THF[b]	K_2CO_3	1.5	~50%
11	0.1	PPh_3	rt	Argon	THF[b]	Et_3N	1.5	>50%
12	0.1	PPh_3	rt	Argon	THF[b]	K_2CO_3	1.5	~50%
13	0.05	PPh_3	rt	Argon	THF[b]	Et_3N	1.5	none
14	0.025	PPh_3	rt	Argon	THF[b]	Et_3N	1.5	none
15	0.0125	PPh_3	rt	Argon	THF[b]	Et_3N	1.5	none
16	0.05	SPhos	rt	Argon	THF[b]	Et_3N	1.5	Trace
17	0.025	SPhos	rt	Argon	THF[b]	Et_3N	1.5	Trace
18	0.0125	SPhos	rt	Argon	THF[b]	Et_3N	1.5	none
19	0.05	PPh_3	45°C	Argon	THF[b]	Et_3N	1.5	Trace
20	0.025	PPh_3	45°C	Argon	THF[b]	Et_3N	1.5	none
21	0.0125	PPh_3	45°C	Argon	THF[b]	Et_3N	1.5	none
22	0.05	SPhos	45°C	Argon	THF[b]	Et_3N	1.5	Trace
23	0.025	SPhos	45°C	Argon	THF[b]	Et_3N	1.5	Trace
24	0.0125	SPhos	45°C	Argon	THF[b]	Et_3N	1.5	none
25	0.1	SPhos	rt	Air	Toluene	Et_3N	1.5	Trace
26	0.1	SPhos	rt	Argon	Toluene	Et_3N	1.5	>50%
27	0.1	SPhos	rt	Air	DCM	Et_3N	1.5	Trace
28	0.1	SPhos	rt	Argon	DCM	Et_3N	1.5	~50%
29	0.1	SPhos	rt	Air	THF	Et_3N	1.5	Trace
30	0.1	SPhos	rt	Argon	THF	Et_3N	1.5	~50%
31	0.1	SPhos	rt	Air	Toluene[c]	Et_3N	1.5	Trace
32	0.1	SPhos	rt	Argon	Toluene[c]	Et_3N	1.5	>50%
33	0.1	SPhos	rt	Air	DCM[c]	Et_3N	1.5	Trace
34	0.1	SPhos	rt	Argon	DCM[c]	Et_3N	1.5	~50%
35	0.1	SPhos	rt	Air	THF[c]	Et_3N	1.5	Trace
36	0.1	SPhos	rt	Argon	THF[c]	Et_3N	1.5	~50%
37	**0.1**	**PPh_3**	**rt**	**Argon**	**Toluene[d]**	**Et_3N**	**1.5**	**Full**
38	**0.1**	**PPh_3**	**rt**	**Argon**	**Toluene[d]**	**Et_3N**	**3.0**	**Full**

39	**0.1**	**PPh_3**	**rt**	**Argon**	**Toluene[d]**	**K_2CO_3**	**1.5**	**Full**
40	**0.1**	**PPh_3**	**rt**	**Argon**	**Toluene[d]**	**K_2CO_3**	**3.0**	**Full**
41	0.1	DPEPhos[e]	rt	Argon	**Toluene[d]**	Et_3N	1.5	<50%
42	0.1	DPEPhos[e]	rt	Argon	Toluene[d]	Et_3N	3.0	<50%
43	0.1	DPEPhos[e]	rt	Argon	Toluene[d]	K_2CO_3	1.5	<50%
44	0.1	DPEPhos[e]	rt	Argon	Toluene[d]	K_2CO_3	3.0	<50%
45	0.1	SPhos	rt	Argon	Toluene[d]	Et_3N	1.5	~50%
46	0.1	SPhos	rt	Argon	Toluene[d]	Et_3N	3.0	~50%
47	0.1	SPhos	rt	Argon	Toluene[d]	K_2CO_3	1.5	~50%
48	0.1	SPhos	rt	Argon	Toluene[d]	K_2CO_3	3.0	~50%

[a]Conversion estimated by TLC visualized using UV light.

[b]Very dilute catalyst stock solution, which required addition of 10% of total reaction volume. This later was found to be detrimental to the reaction conversion.

[c]Catalyst stock solution solvent removed via vacuum before adding surfactant solution.

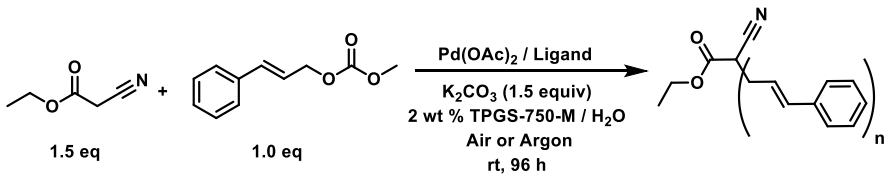
[d]Et_3N added to catalyst stock solution as an activator. (all subsequent catalyst stock solutions using ligand/$Pd(OAc)_2$ were prepared this way).

[e]$Pd(OAc)_2$ is not an optimal Pd source for DPEphos, these trials mistakenly suggest that DPEphos is not an appropriate ligand for this reaction.

[f]This trial was suspected of being exposed to air.

Unfortunately, upon testing the optimized conditions from Table 1 using a different nucleophile (Table 2), none of the reactions gave appreciable conversion at the same 0.1 mol % Pd. Incomplete conversion was seen even at 10x the catalyst loading (1.0%) required for the analogous reaction using diethyl malonate as nucleophile.

Table 2: Applying optimized conditions to a different nucleophile

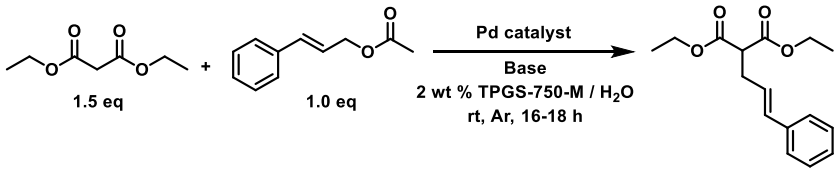


Entry	Pd (mol %)	Ligand	Air/Argon	Catalyst stock solution solvent	Base	Base equiv	Result[a]
1	0.1	PPh_3	Argon	Toluene	K_2CO_3	1.5	Trace conversion
2	1.0	PPh_3	Argon	Toluene	K_2CO_3	1.5	~50% conversion
3	0.1	SPhos	Argon	Toluene	K_2CO_3	1.5	No conversion
4	**1.0**	**SPhos**	**Argon**	Toluene	**K_2CO_3**	**1.5**	**>50% conversion**
5	1.0	PPh_3	Air	Toluene	K_2CO_3	1.5	Trace conversion
6	1.0	Sphos	Air	Toluene	K_2CO_3	1.5	Trace conversion

[a]Conversion estimated by TLC visualized using UV light.

Similar to the results in Table 2, when the leaving group was changed from a methyl carbonate to an acetate (Table 3), once again incomplete conversion was seen at 0.1 mol % Pd. Increasing the Pd loading some 2-2.5x was found to give full conversion.

Table 3: Initial screening studies for the reaction of diethyl malonate with cinnamyl-OAc



entry	Pd (%)	Pd source/Ligand	Catalyst stock solution Solvent	Added toluene as co-solvent	Base	Base equiv	Temp	Rxn conc. (M)	Conversion[a]
1	0.1	$Pd(OAc)_2/PPh_3$	Toluene	none	K_2CO_3	1.5	rt	0.5	~50%
2	0.2	$Pd(OAc)_2/PPh_3$	Toluene	none	K_2CO_3	1.5	rt	0.5	~50%
3	0.5	$Pd(OAc)_2/PPh_3$	Toluene	none	K_2CO_3	1.5	rt	0.5	~50%
4	0.1	$Pd(OAc)_2/PPh_3$	Toluene	none	K_2CO_3	1.5	rt	0.25	~50%
5	0.1	$Pd(OAc)_2/PPh_3$	Toluene	none	K_2CO_3	1.5	rt	0.5	~50%
6	0.1	$Pd(OAc)_2/PPh_3$	Toluene	none	K_2CO_3	1.5	rt	1.0	~50%
7	0.1	$Pd(OAc)_2/PPh_3$	Toluene	none	Et_3N	1.5	rt	0.25	~50%
8	0.1	$Pd(OAc)_2/PPh_3$	Toluene	none	Et_3N	1.5	rt	0.5	~50%
9	0.1	$Pd(OAc)_2/PPh_3$	Toluene	none	Et_3N	1.5	rt	1.0	~50%
10	0.1	$Pd(OAc)_2/PPh_3$	Toluene	none	K_2CO_3	1.5	rt	1.0	~50%
11	0.1	$Pd(OAc)_2/PPh_3$	Toluene	10 vol %	K_2CO_3	1.5	rt	1.0	~50%
12	0.1	$Pd(OAc)_2/PPh_3$	Toluene	20 vol %	K_2CO_3	1.5	rt	1.0	~50%
13	0.1	$Pd(OAc)_2/PPh_3$	Toluene	none	Et_3N	1.5	rt	1.0	~50%
14	0.1	$Pd(OAc)_2/PPh_3$	Toluene	10 vol %	Et_3N	1.5	rt	1.0	~50%
15	0.1	$Pd(OAc)_2/PPh_3$	Toluene	20 vol %	Et_3N	1.5	rt	1.0	~50%
16[c]	0.1	$Pd(PPh_3)Cl_2$	THF	none	Et_3N	1.5	rt	1.0	~50%
17[c]	0.1	$Pd(PPh_3)Cl_2$	THF	none	Et_3N	3.0	rt	1.0	~50%
18[c]	0.1	$Pd(OAc)_2/PPh_3$	DCM	none	Et_3N	1.5	rt	1.0	~50%
19[c]	0.1	$Pd(OAc)_2/PPh_3$	DCM	none	Et_3N + K_2CO_3	1.5 + 3.0	rt	1.0	~50%
20[c]	0.1	$Pd(PPh_3)Cl_2$	THF	none	Et_3N	1.5	rt	1.0	~50%

21[c]	0.1	$Pd(PPh_3)Cl_2$	THF	none	Et_3N + K_2CO_3	1.5 + 3.0	rt	1.0	~50%
22[c]	0.1	$Pd(OAc)_2/PPh_3$	DCM	none	Et_3N	1.5	rt	1.0	~50%
23[c]	0.1	$Pd(OAc)_2/PPh_3$	DCM	none	Et_3N + K_2CO_3	1.5 + 3.0	rt	1.0	~50%
24[c]	0.5	$Pd(OAc)_2/PPh_3$	DCM[b]	none	Et_3N	1.5	rt	1.0	~50%
25[c]	0.5	$Pd(PPh_3)Cl_2$	THF[b]	none	Et_3N	1.5	rt	1.0	~50%
26	0.1	$Pd(OAc)_2$/Sphos	Toluene	none	Et_3N	1.5	rt	1.0	~50%
27	**0.25**	**$Pd(OAc)_2$/Sphos**	**Toluene**	**none**	**Et_3N**	**1.5**	**rt**	**1.0**	**Full**
28	0.5	$Pd(OAc)_2$/Sphos	Toluene	none	Et_3N	1.5	rt	1.0	Full
29	1.0	$Pd(OAc)_2$/Sphos	Toluene	none	Et_3N	1.5	rt	1.0	Full
30	0.5	$Pd(PPh_3)_4$	Toluene	none	Et_3N	1.5	rt	1.0	~50%
31	1.0	$Pd(PPh_3)_4$	Toluene	none	Et_3N	1.5	rt	1.0	~50%
32	0.1	$Pd(OAc)_2$/Sphos	Toluene	none	Et_3N	1.5	45ºC	1.0	~50%
33	**0.2**	**$Pd(OAc)_2$/Sphos**	**Toluene**	none	**Et_3N**	**1.5**	**45ºC**	**1.0**	**Full**
34	0.1	$Pd(OAc)_2/PPh_3$	Toluene	none	Et_3N	1.5	45ºC	1.0	~50%
35	0.2	$Pd(OAc)_2/PPh_3$	Toluene	none	Et_3N	1.5	45ºC	1.0	~50%
36	0.5	$Pd(OAc)_2/PPh_3$	Toluene	none	Et_3N	1.5	45ºC	1.0	~50%

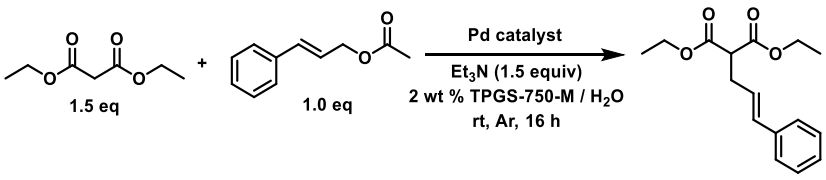
[a]Conversion estimated by TLC visualized using UV light.

[b]Catalyst stock solution solvent removed via vacuum before adding surfactant solution.

[c]Trials have strange combinations of base due to a mistake in setting up trials.

Based on a suggestion from a fellow lab mate that oxygen was possibly seeping into the reaction through the septum and deactivating the catalyst, a study of various methods of keeping the reaction under inert atmosphere were screened (Table 4). Unfortunately, this has no appreciable effect. While previous trials had shown a clear preference for reactions run under argon rather than under air, it appeared that oxygen seepage was not the primary cause of incomplete conversion in our hands.

Table 4: Testing for possible oxygen penetration into reaction vessel during reaction



Trial	Pd (mol %)	Pd source/Ligand	Protection against oxygen	Result[a]
1[b]	0.1	$Pd(OAc)_2$/Sphos	Reaction in vial capped with phenolic cap	~50% conversion
2[b]	0.1	$Pd(OAc)_2$/Sphos	Reaction in vial capped with phenolic cap	~50% conversion
3[b]	0.1	$Pd(OAc)_2$/Sphos	Reaction in vial capped with Teflon lined cap	~50% conversion
4[b]	0.1	$Pd(OAc)_2$/Sphos	Reaction in vial capped with Teflon lined cap	~50% conversion
5[b]	0.1	$Pd(OAc)_2$/Sphos	Reaction in vial capped with rubber septum	~50% conversion
6[b]	0.1	$Pd(OAc)_2$/Sphos	Reaction in vial capped with rubber septum	~50% conversion
7[c]	0.1	$Pd(OAc)_2$/Sphos	Reaction in vial capped with septum, and vial placed in jar purged with argon	<50% conversion
8[c,d]	0.1	$Pd(OAc)_2$/Sphos	Reaction in vial capped with septum, and vial placed in jar purged with argon	<50% conversion

[a]Conversion estimated by TLC visualized using UV light.

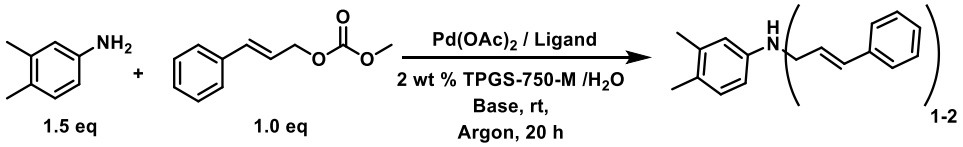
[b]It was discovered that trials run in an aluminum block reactor on a hotplate were heated to 26-28ºC due to the heat generated from the motor, possibly causing better conversion due to the temperature increase.

[c]These trials were run in a jar on top of a hot plate. The lab temperature at the time was 21-23ºC, possibly causing lower conversion that the reactions run in a block reactor.

[d]Trial stopped stirring sometime overnight.

Screening conditions which had proven to be effective in Table 1 were tested on an amine nucleophile; happily, these conditions were also effective at 0.1 mol % Pd (Table 5).

Table 5: Initial screening studies for an allylic amination



Trial	Pd (mol %)	Ligand	Catalyst stock soln. solvent	Base	Base eq.	Result[a]
1	0.1	PPh_3	Toluene	Et_3N	1.5	Full conversion
2	0.1	PPh_3	Toluene	Et_3N	3.0	Full conversion
3	**0.1**	**PPh_3**	**Toluene**	**K_2CO_3**	**1.5**	**Full conversion**
4	0.1	PPh_3	Toluene	K_2CO_3	3.0	Full conversion
5	0.1	DPEPhos[b]	Toluene	Et_3N	1.5	Full conversion
6	0.1	DPEPhos[b]	Toluene	Et_3N	3.0	>50% conversion
7	0.1	DPEPhos[b]	Toluene	K_2CO_3	1.5	>50% conversion
8	0.1	DPEPhos[b]	Toluene	K_2CO_3	3.0	>50% conversion
9	0.1	SPhos	Toluene	Et_3N	1.5	Full conversion
10	0.1	SPhos	Toluene	Et_3N	3.0	Full conversion
11	0.1	SPhos	Toluene	K_2CO_3	1.5	>50% conversion
12	0.1	SPhos	Toluene	K_2CO_3	3.0	Full conversion

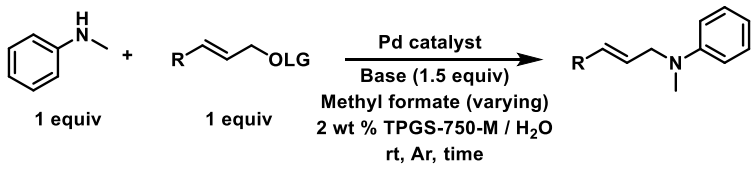
[a]Conversion estimated by TLC visualized using UV light.

[b]$Pd(OAc)_2$ is not an optimal Pd source for DPEphos, these trials mistakenly suggest that DPEphos is not an appropriate ligand for this reaction.

At this point, the mixture of $PPh_3/Pd(OAc)_2$ seemed to be a cost effective and relatively efficient combination. Additional screening at 0.1 mol % and lower catalyst loadings, however, were failing to give full conversion when nucleophile or electrophile was even slightly changed (Table 6). A lab mate mentioned that he had very good success with the DPEphos/$[Pd(allyl)Cl]_2$ combination on certain π-allylic compounds, and that perhaps the reason DPEphos had performed poorly in my trials was because it was not effective when used with $Pd(OAc)_2$. On this tip, DPEphos/$[Pd(allyl)Cl]_2$ was screened, and indeed

proved to be quite effective and did not require the use of Et_3N as base or catalyst activator. Later, PPh_3 was also screened in conjunction with $[Pd(allyl)Cl]_2$ but was not as effective as DPEphos with this Pd source.

Table 6: Screening Pd loading and conditions for allylic amination of *N*-methylaniline with various allylic substrates



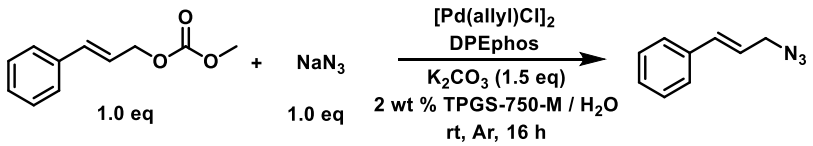
entry	Electrophile	Pd loading (mol %)	Catalyst	Methyl formate (equiv)	Base	Stock soln. solvent	Rxn time (h)	Conversion[a]
1	Cinnamyl-OAc	0.025	$Pd(OAc)_2/PPh_3$	none	Et_3N	Toluene	20	Trace
2	Cinnamyl-OAc	0.05	$Pd(OAc)_2/PPh_3$	none	Et_3N	Toluene	20	Trace
3	Cinnamyl-OAc	0.1	$Pd(OAc)_2/PPh_3$	none	Et_3N	Toluene	20	Trace
4	Cinnamyl-OAc	0.2	$Pd(OAc)_2/PPh_3$	none	Et_3N	Toluene	20	<50%
5	Cinnamyl-OCO_2Me	0.025	$Pd(OAc)_2/PPh_3$	none	Et_3N	Toluene	20	Trace
6	Cinnamyl-OCO_2Me	0.05	$Pd(OAc)_2/PPh_3$	none	Et_3N	Toluene	20	Trace
7	Cinnamyl-OCO_2Me	0.1	$Pd(OAc)_2/PPh_3$	none	Et_3N	Toluene	20	<50%
8	Cinnamyl-OCO_2Me	0.2	$Pd(OAc)_2/PPh_3$	none	Et_3N	Toluene	20	~50%
9	Cinnamyl-OAc	0.4	$[Pd(allyl)Cl]_2$/DPEphos	4	K_2CO_3	Toluene	1.5	Full
10	Cinnamyl-OAc	0.2	$[Pd(allyl)Cl]_2$/DPEphos	4	K_2CO_3	Toluene	1.5	Full
11	Cinnamyl-OAc	0.1	$[Pd(allyl)Cl]_2$/DPEphos	4	K_2CO_3	Toluene	1.5	Full
12	Cinnamyl-OAc	0.05	$[Pd(allyl)Cl]_2$/DPEphos	4	K_2CO_3	Toluene	1.5	Full
13	Allyl alcohol	0.1	$[Pd(allyl)Cl]_2$/DPEphos	4	K_2CO_3	Toluene	18	~50%
14	Allyl alcohol	0.05	$[Pd(allyl)Cl]_2$/DPEphos	4	K_2CO_3	Toluene	18	<50%
15	Allyl acetate	0.1	$[Pd(allyl)Cl]_2$/DPEphos	4	K_2CO_3	Toluene	18	Full

16	Allyl acetate	0.05	$[Pd(allyl)Cl]_2$/DPEphos	4	K_2CO_3	Toluene	18	>50%
17	Allyl-OCO_2Me	0.1	$[Pd(allyl)Cl]_2$/DPEphos	4	K_2CO_3	Toluene	18	Full
18	Allyl-OCO_2Me	0.05	$[Pd(allyl)Cl]_2$/DPEphos	4	K_2CO_3	Toluene	18	Full
19	Cinnamyl-OAc	0.05	$[Pd(allyl)Cl]_2$/DPEphos	3	K_2CO_3	Toluene	48	Full
20	Cinnamyl-OAc	0.05	$[Pd(allyl)Cl]_2$/DPEphos	2	K_2CO_3	Toluene	48	Full
21	Cinnamyl-OAc	0.05	$[Pd(allyl)Cl]_2$/DPEphos	1	K_2CO_3	Toluene	48	Full
22	Cinnamyl-OAc	0.05	$[Pd(allyl)Cl]_2$/DPEphos	0.5	K_2CO_3	Toluene	48	Full
23	Cin-OCO_2Me	0.05	$[Pd(allyl)Cl]_2$/DPEphos	3	K_2CO_3	Toluene	48	Full
24	Cin-OCO_2Me	0.05	$[Pd(allyl)Cl]_2$/DPEphos	2	K_2CO_3	Toluene	48	Full
25	Cin-OCO_2Me	0.05	$[Pd(allyl)Cl]_2$/DPEphos	1	K_2CO_3	Toluene	48	Full
26	Cin-OCO_2Me	0.05	$[Pd(allyl)Cl]_2$/DPEphos	0.5	K_2CO_3	Toluene	48	Full
27	Allyl-OBoc	0.05	$[Pd(allyl)Cl]_2$/DPEphos	3	K_2CO_3	Toluene	48	Full
28	Allyl-OBoc	0.05	$[Pd(allyl)Cl]_2$/DPEphos	2	K_2CO_3	Toluene	48	Full
29	Allyl-OBoc	0.05	$[Pd(allyl)Cl]_2$/DPEphos	1	K_2CO_3	Toluene	48	Full
30	Allyl-OBoc	0.05	$[Pd(allyl)Cl]_2$/DPEphos	0.5	K_2CO_3	Toluene	48	Full
31	Cinnamyl-OAc	0.05	$[Pd(allyl)Cl]_2$/DPEphos	0.5	K_2CO_3	Toluene	48	Full
32	Cinnamyl-OAc	0.025	$[Pd(allyl)Cl]_2$/DPEphos	0.5	K_2CO_3	Toluene	48	~50%
33	Cinnamyl-OAc	0.01	$[Pd(allyl)Cl]_2$/DPEphos	0.5	K_2CO_3	Toluene	48	~50%
34	Cin-OCO_2Me	0.05	$[Pd(allyl)Cl]_2$/DPEphos	0.5	K_2CO_3	Toluene	48	Full
35	**Cin-OCO_2Me**	**0.025**	**$[Pd(allyl)Cl]_2$/DPEphos**	**0.5**	**K_2CO_3**	**Toluene**	**48**	**Full**
36	Cin-OCO_2Me	0.01	$[Pd(allyl)Cl]_2$/DPEphos	0.5	K_2CO_3	Toluene	48	>50%
37	Cin-OBoc	0.05	$[Pd(allyl)Cl]_2$/DPEphos	0.5	K_2CO_3	Toluene	48	Full
38	Cin-OBoc	0.025	$[Pd(allyl)Cl]_2$/DPEphos	0.5	K_2CO_3	Toluene	48	~50%
39	Cin-OBoc	0.01	$[Pd(allyl)Cl]_2$/DPEphos	0.5	K_2CO_3	Toluene	48	<50%
40	Cinnamyl-OAc	0.05	$[Pd(allyl)Cl]_2$/DPEphos	0	K_2CO_3	Toluene	48	Full

[a]Conversion estimated by TLC visualized using UV light.

Once again, upon changing the coupling partners, the previously optimized conditions were found to be ineffective at the desired 0.1 mol % Pd (Table 7). This trend of large changes in catalytic performance each time the coupling partners were changed would become one of the most time consuming and frustrating aspects of this project.

Table 7: Testing optimized amination conditions

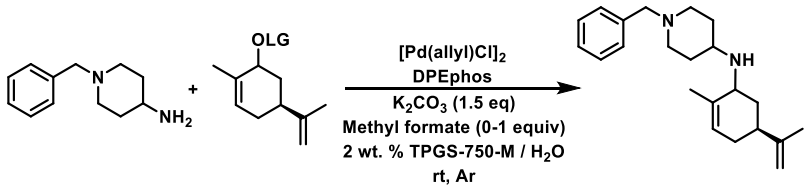


Trial	Pd loading (mol %)	Result[a]
1	0.4	Full conversion
2	**0.2**	**Full conversion**
3	0.1	>50% conversion
4	0.05	~50% conversion

[a]Conversion estimated by TLC visualized using UV light.

Similar to observations listed in Table 7, upon changing the reaction conditions again, in this case increasing the steric bulk around the electrophile, the reaction was found to require significantly more catalyst to give appreciable conversion (Table 8). Previous reports had also used methyl formate as an additive. The use of methyl formate was rationalized as aiding the allylic alcohol as leaving group, but could also possibly be functioning as co-solvent or possibly aiding in catalyst activity.

Table 8: Testing optimized amination conditions on a difficult electrophile

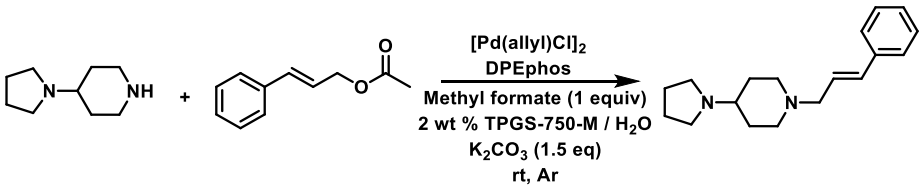


Entry	LG	Pd loading (mol %)	Methyl formate (equiv)	Result[a]
1	**Acetate**	**0.2 mol %**	**1**	**>50% conversion**
2	Acetate	0.2 mol %	0	<50% conversion
3	Alcohol	0.2 mol %	1	Trace conversion
4	Alcohol	0.2 mol %	0	No conversion
5	Acetate	0.1 mol %	1	Trace conversion
6	Acetate	0.1 mol %	0	No conversion

[a]Conversion estimated by TLC visualized using UV light.

Table 9 shows the results of the use of an amine found to be problematic in other previous reaction classes. Presumably this diamine can act as a ligand for metals such as palladium. In this case, this effect appeared to be present. It seemed that >10x as much palladium was required to give conversion remotely comparable to that seen with the same reaction using *N*-methylaniline instead as nucleophile (4000 ppm Pd vs 250 ppm Pd).

Table 9: Testing optimized allylic amination conditions

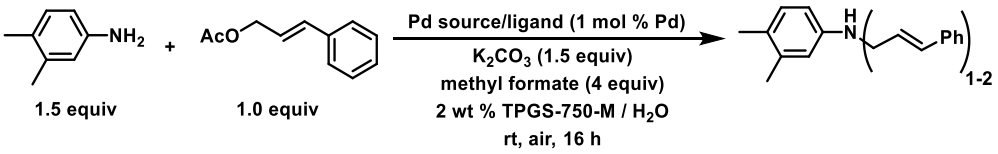


Entry	Pd loading (mol %)	Result[a]
1	0.4	~50% conversion
2	0.2	<50% conversion
3	0.1	Trace conversion
4	0.05	Trace conversion

[a]Conversion estimated by TLC visualized using UV light.

A number of palladium sources/ligands were screened for the reaction shown in Table 10. Regrettably, this data was taken by a previous lab mate, before I was involved in the project and at that time 1 mol % Pd was the current effective catalyst loading for these reactions. This screening would have been much more useful if conducted at perhaps 0.025-0.05 mol % Pd. However, it is included here to give a complete picture of screenings conducted.

Table 10: Screening additional palladium sources and ligands

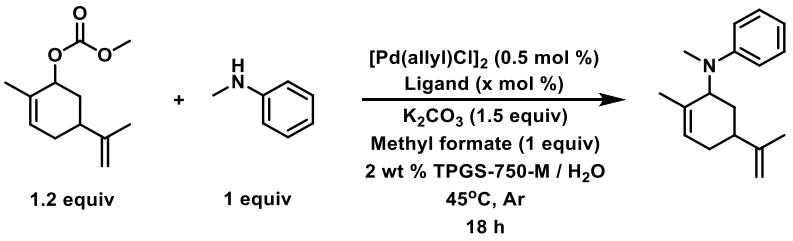


Entry	Pd catalyst	Conversion (%)[a]
1	**[Pd(allyl)Cl]$_2$/DPEphos**	**94**
2	[Pd(cinnamyl)Cl]$_2$/DPEphos	84
3	Pd(MeCN)$_2$Cl$_2$/DPEphos	91
4	Pd(OAc)$_2$/DPEphos	80
5	PdCl$_2$/DPEphos	78
6	Pd$_2$(dba)$_3$/DPEphos	69
7	Pd(DPEphos)Cl$_2$	86
8	Pd(DPPF)Cl$_2$	71
9	Pd(Xantphos)Cl$_2$	80
10	Pd(PPh$_3$)$_2$Cl$_2$	86

[a]Conversion determined by GC-MS.

Later, after it became clear that steric hinderance around the electrophile was an important factor, ligand screening was conducted again using a “difficult” electrophile (Table 11). In this case DPEphos and Xantphos were similarly effective, which isn’t particularly surprising given their similar bidendate structures.

Table 11: Screening additional ligands for allylic amination of a difficult electrophile



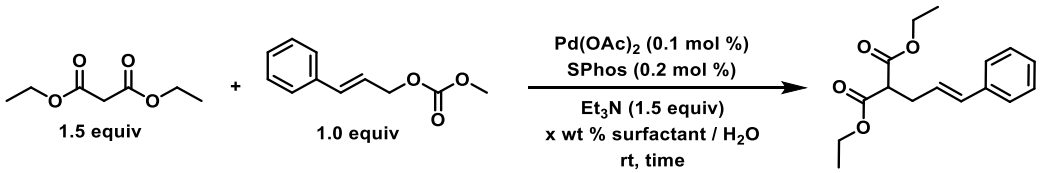
Entry	Ligand	Result[a]
1	**DPEphos (1 mol %)**	**Full conversion (75% isolated)**
2	DPPF (1 mol %)	~50% conversion
3	TDAPP (4 mol %)	<50% conversion
4	$P(OPPh)_3$ (4 mol %)	No conversion
5	**Xantphos (1 mol %)**	**Full conversion (73% isolated)**
6	DTBPF (1 mol %)	~50% conversion
7	PPh_3 (4 mol %)	>50% conversion

TDAPP = tris(4-(dimethylamino)phenyl) phosphite

[a]Conversion estimated by TLC visualized using UV light, isolated yield is of chromatographically purified product

A screening of several commercially available surfactants was also conducted, which showed that TPGS-750-M at 2 wt % solution was the most enabling (Table 12).

Table 12: Surfactant screening

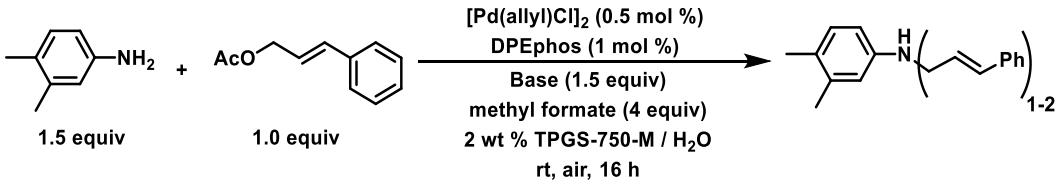


Entry	Surfactant	Surfactant wt %	Conversion[a]
1	TPGS-750-M	1	60
2	**TPGS-750-M**	**2**	**75**
3	TPGS-750-M	3	55
4	SPGS-550-M	3	64
5	Triton X-100	2	50
6	Brij-30	2	40

[a]Conversion determined by GC-MS.

Various carbonate bases were found to be most effective for this reaction in conjuction with $[Pd(allyl)Cl]_2$/DPEphos (Table 13). Little if any cation/counterion effect seems to be present with Na, K, and Cs carbonates, with each performing approximately equally.

Table 13: Base screening

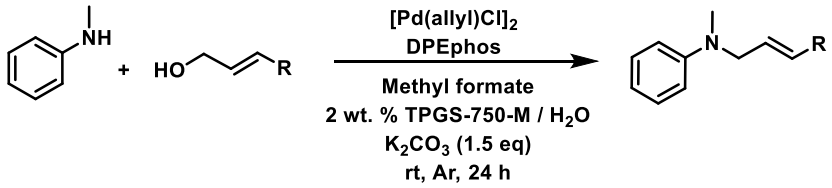


Entry	Base	Conversion (%)[a]
1	Et_3N	71
2	**K_2CO_3**	**94**
3	Na_2CO_3	89
4	Cs_2CO_3	90
5	K_3PO_4	87
6	NaOAc	73
7	KOAc	75
8	KOH	70
9	NaOH	76
10	LiOH	68

[a]Conversion determined by GC-MS.

Some screening of allylic alcohols as electrophiles was conducted (Table 14), though incomplete conversion was seen at ppm Pd catalyst levels. At this point, it was fairly apparent that allylic carbonates were the most effective, followed by acetates, and alcohols as a very distant 3rd.

Table 14: Initial screening of conditions for amination of allylic alcohols at ppm Pd loadings

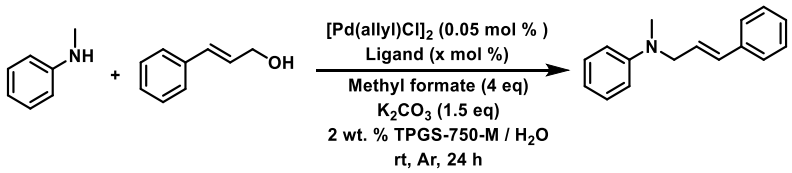


entry	Electrophile	Pd loading (%)	Temp	Methyl formate (equiv)	Rxn time (h)	Result[a]
1	Allyl alcohol	0.1	rt	4	24	~50% conversion
2	Octene-3-ol	0.1	rt	4	24	No conversion
3	Allyl alcohol	0.2	rt	4	24	~50% conversion
4	Octene-3-ol	0.2	rt	4	24	Trace conversion
5	Allyl alcohol	0.1	45°C	4	24	~50% conversion
6	Octene-3-ol	0.1	45°C	4	24	Trace conversion
7	**Allyl alcohol**	**0.2**	**45°C**	**4**	**24**	**>50% conversion**
8	**Octene-3-ol**	**0.2**	**45°C**	**4**	**24**	**~50% conversion**
9	Allyl alcohol	0.1	rt	0	24	Trace conversion
10	Octene-3-ol	0.1	rt	0	24	No conversion

[a]Conversion estimated by TLC visualized using UV light.

Phosphite ligands have appeared in some Tsuji-Trost reactions in organic solvent, specifically for use with allylic alcohol electrophiles. In this case $P(OPPh)_3$ seemed approximately as effective as DPEphos (Table 15), but none of these trials came close to completion. No ref?

Table 15: Screening phosphite ligands against DPEphos for reaction of *N*-methylaniline with cinnamyl alcohol

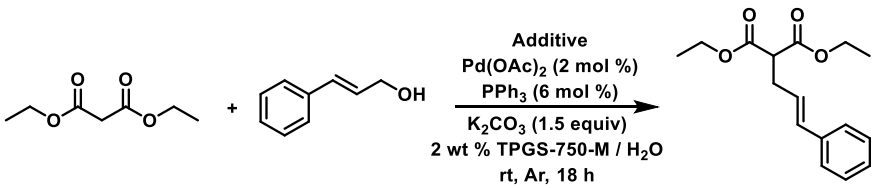


entry	Ligand	Ligand mol %	Result[a]
1	**DPEPhos**	**0.1**	**~50% conversion**
2	**P(OPPh)$_3$**	**0.4**	**~50% conversion**
3	P(O-isooctyl)$_3$	0.4	Trace conversion
4	P(O-2,4-ditertbutylphenyl)$_3$	0.4	No conversion

[a]Conversion estimated by TLC visualized using UV light.

Trialkylboranes have appeared as additives for use with allylic alcohols in Tsuji-Trost reactions in some literature methods conducted in organic solvent. Me-OBBD was screened as a possible additive No refs??? (see previous section II on *B*-alkyl Suzuki couplings for a discussion of OBBD derivatives), however, no improvement was seen. Allylic alcohol electrophiles appeared to be unreactive towards carbon nucleophiles in water.

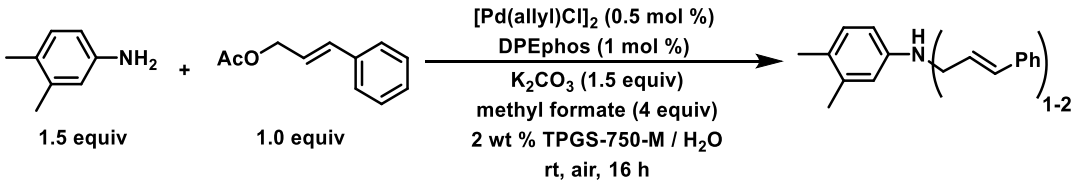
Table 16: Screening additives for use with carbon nucleophiles + an allylic alcohol



entry	Additive	Result
1	None	No conversion
2	Methyl formate (3 equiv)	No conversion
3	Methyl OBBD (0.3 equiv)	No conversion

THF was screened as a co-solvent, but appeared to have the opposite of the intended effect, lowering conversion. Similarly, in Table 10, these data were taken before optimized conditions were reached and lower catalyst loadings found to be effective. Therefore, unfortunately these data are of limited use because the study was conducted at far greater Pd loadings than are necessary, and in the presence of methyl formate, which is not required for this reaction. The same comments on excess Pd and methyl formate can be said for the results in Table 18, below.

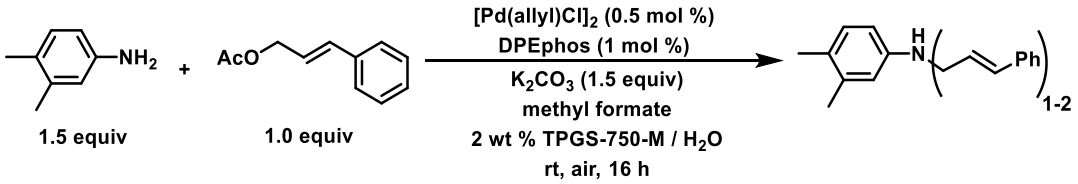
Table 17: Screening added THF as co-solvent



Entry	Added co-solvent	Conversion (%)[a]
1	**None**	**94**
2	10% THF by vol.	87
3	20% THF by vol.	82

[a]Conversion determined by GC-MS.

Table 18: Screening equivalents of methyl formate



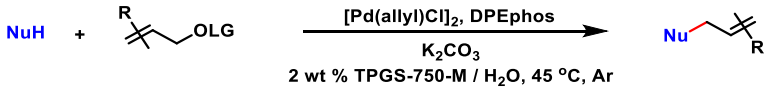
Entry	Methyl formate (equiv)	Conversion (%)[a]
1	none	89
2	**2**	**94**
3	4	94

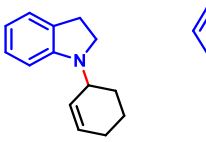
[a]Conversion determined by GC-MS.

4.4. Substrate scope: amine nucleophiles

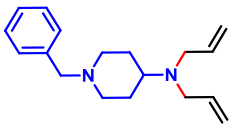
With the above optimization experiments in hand, the substrate scope was next evaluated. A wide variety of amines/NH nucleophiles were found to be suitable for these reactions (Scheme 5).

Scheme 5: Products of Allylic Aminations in Water

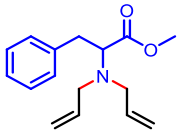




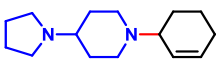
1a
93%[e,h], 19 h
1000 ppm Pd
(from OCO_2Me)



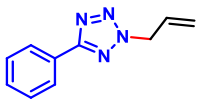
1b
87%[g], 22 h
1000 ppm Pd
(from OAc)



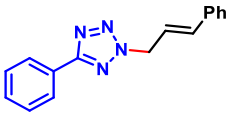
1c
70%[f], 20 h
2000 ppm Pd
(from OAc)



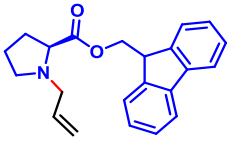
1d
80%[e,h], 19 h
1000 ppm Pd
(from OCO_2Me)



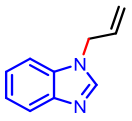
1e
96%, 19 h
1000 ppm Pd
(from OCO_2Me)



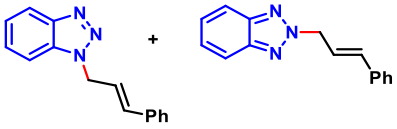
1f
86%, 19 h
1000 ppm Pd
(from OCO_2Me)



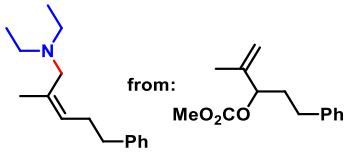
1g
75%[f,k], 20 h
2000 ppm Pd
(from OAc)



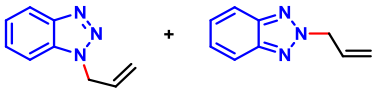
1h
92%, 24 h
1000 ppm Pd
(from OCO_2Me)



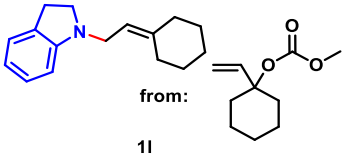
49%
1i
50%
19 h, 1000 ppm Pd
(from OCO_2Me), isomers separated



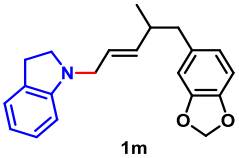
1j
72%[c], 17 h
1000 ppm Pd



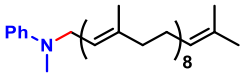
39 %
58 %
1k
19 h, 1000 ppm Pd
(from OCO_2Me), isomers separated



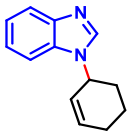
1l
87%[e], 17 h
1000 ppm Pd



1m
90%[e,i], 22 h
1000 ppm Pd
(from OCO_2Me)

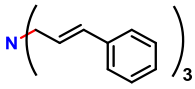


1n
86%[d,i,j,k], 23 h
1 mol % Pd
(from OCO_2Me)

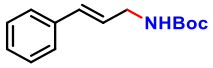


1o
91%[e,h,j], 18 h
1 mol % Pd
(From OCO_2Me)

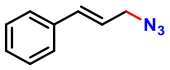
Ammonia Equivalents



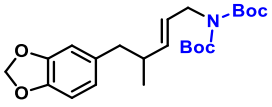
1p
90%[l,j], 1 h
1 mol % Pd
(from OAc)
NH_4OH (conc)



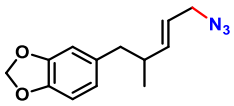
no product seen
$BocNH_2$



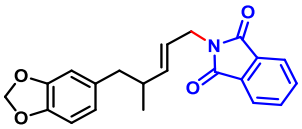
1q
90%[b,d], 16 h
2000 ppm Pd
(from OCO_2Me)
NaN_3



1r
18 h, 2500 ppm Pd
84%[b,d,h] (from OCOOMe)
82%[b,d,h] (from OBoc)
Boc_2NH



non-resolvable mixture
18 h, 2500 ppm Pd[b,d,h]
NaN_3



non-resolvable mixture
1000 ppm Pd[b,d,h]
(from OCO_2Me)
phthalimide

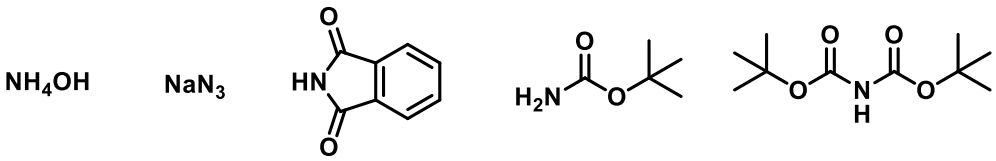
[a] Reaction conditions: nucleophile (1.0 equiv, [b] 1.1 equiv, [c] 1.4 equiv), electrophile (1.1 equiv, [d] 1.0 equiv, [e] 1.2 equiv, [f] 1.5 equiv, [g] 2.2 equiv), K_2CO_3 (1.5 equiv), 2 wt % TPGS-750-M / H_2O (1.0 M reaction concentration), catalyst stock solution prepared in toluene, 45 °C, argon. [h] Methyl formate (1 equiv) added, [i] Et_3N (3 equiv) instead of K_2CO_3, [j] $[Pd(allyl)Cl]_2$/ligand added as solids, [k] 0.5 M reaction concentration instead of 1.0 M, [l] NH_4OH (5 equiv) as base and nucleophile.

4.5 Studies in ammonia equivalents

The incorporation of an ammonia equivalent was explored using a variety of nucleophiles. While some publications in water have used sodium azide[117] and phthalimide as ammonia equivalents in aqueous/organic mixtures or pure water, no studies where found which screened a wide variety of ammonia equivalents. Table 19 below shows some general trends seen in this study of the use of ammonia equivalents for Tsuji-Trost reactions in aqueous TPGS-750-M.

[117] Blart, E.; Geneˆt, J. P.; Safi, M.; Savignac, M.; Sinou, D. *Tetrahedron* **1994**, *50*, 505–514.

Table 19: Pros and cons to various ammonia equivalents studied



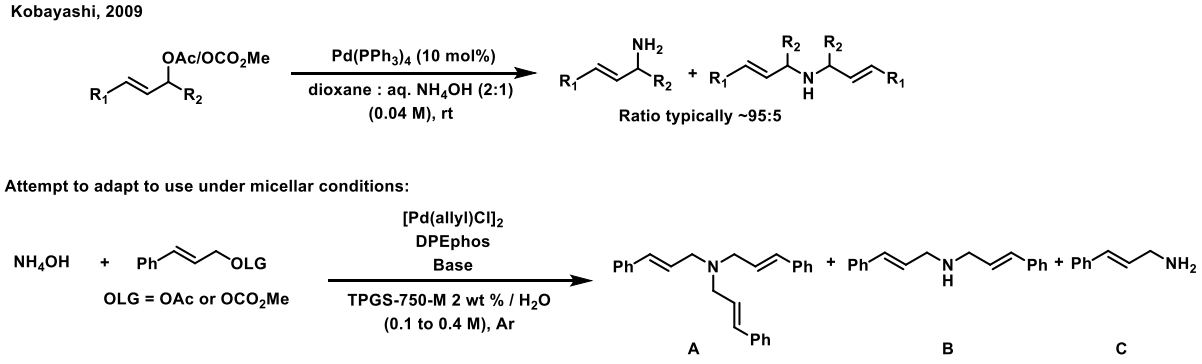
Ammonia equivalent	Ammonium hydroxide	Sodium azide	Phthalimide	Boc-NH_2	Boc_2-NH
Positive attributes	Inexpensive, good atom economy	Inexpensive, no risk of over addition, good atom economy	No risk of over addition, good nucleophilicity in water	Potential for removal with simple acidic conditions	Potential for removal with simple acidic conditions
Negative attributes	Over addition unavoidable	Toxic, potentially explosive, requires strong reducing conditions to form amine	Solubility problems common in products, requires harsh conditions to deprotect	Not an effective nucleophile for allylic substitution in water	Somewhat poor atom economy

The first ammonia equivalent screened was the use of aqueous ammonia. The idea to use ammonia directly was taken from a paper by Kobayashi.[118] Their approach was made successful by the use of very large excesses of aqueous ammonia (solvent : aqueous ammonia (2:1)) under very dilute conditions (0.04 M), with high catalyst loadings (10 mol % Pd). Furthermore, the approach was limited to only 2º allylic substrates due to the tendency for over addition. Unfortunately, in our system, aqueous ammonia was found to

[118] Nagano, T.; Kobayashi, S. *J. Am. Chem. Soc.* **2009**, *131*, 4200–4201.

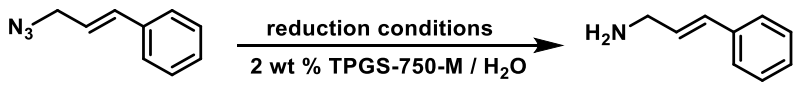
give over addition (Scheme 6), even when using large excess of ammonia (5-10 equivalents) and was not explored in depth due to this problem.

Scheme 6: NH_4OH as nucleophile in literature vs us in water as bulk reaction medium



Under micellar conditions at relatively high Pd loadings of 1 mol%, **A** was seen as the exclusive product. Upon decreasing the Pd loading to 0.1-0.25 mol %, a mixture of **A**, **B**, and **C** was obtained. Overall, this limited the usefulness of this approach. The second approach attempted was the use of sodium azide as nucleophile. This route doesn't suffer from the over-addition problem seen with ammonium hydroxide, and was found to work well on a simple cinnamyl model substrate. However, if the amine is desired, the azide must be reduced. This proved somewhat difficult. Table 20 below shows the various approaches investigated.

Table 20: Azide reduction methods screened

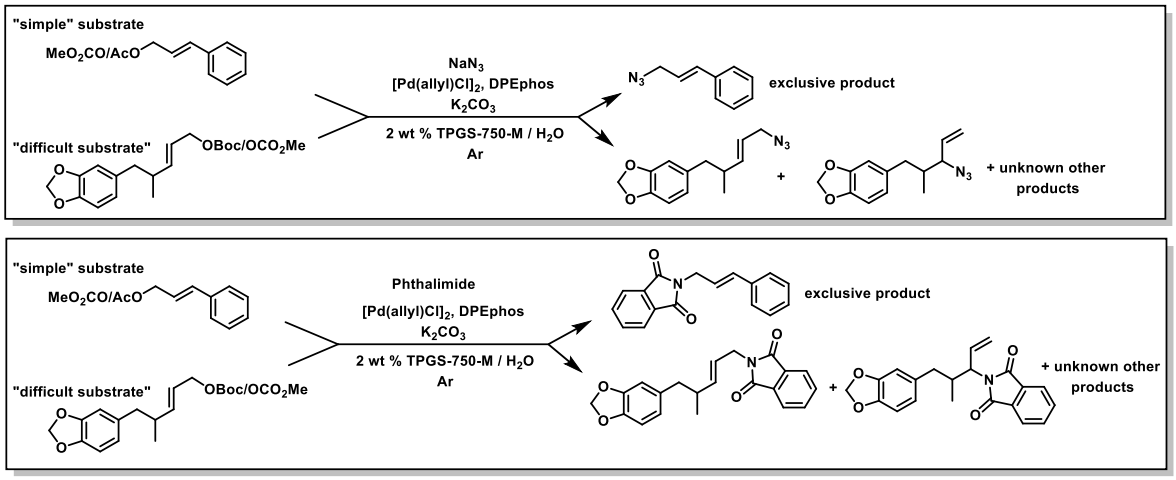


Reagent/approach	Result
PPh_3	No product seen
$NaBH_4$	No conversion
Fe/ppm Pd/Ni NPs + $NaBH_4$	Full conversion, amine + byproducts seen
Fe/NH_4Cl/HCl (CIP reduction)	Some conversion to amine, incomplete
Zn/NH_4Cl	Full conversion to amine

Upon addition of PPh_3 (i.e., Staudinger type reduction), gas was immediately produced and a thick yellow precipitate formed, possibly the iminophosphorane. But despite stirring and attempting acidic hydrolysis of this largely insoluble paste, the desired amine product wasn't produced. $NaBH_4$ alone gave none of the desired product, but $NaBH_4$ in conjunction with Fe/ppm Pd/Ni NPs (typically used for nitro group reduction) gave full conversion with some of the desired amine produced along with some unidentified byproducts. CIP/NH_4Cl (typically used for aromatic nitro group reduction) gave very little conversion. After addition of HCl, the amine was produced, but the reaction was typically incomplete. A slightly stronger reducing agent, Zn dust/NH_4Cl was found to give full conversion to the amine product (see section III for isolated yield). While this approach to using sodium azide as an ammonia equivalent was somewhat successful, the relatively "messy" reduction conditions using several equivalents of Zn dust (or CIP) made this a somewhat impractical approach. Furthermore, while the cinnamyl model case gave exclusively linear product, upon attempting use of NaN_3 as nucleophile on a more

complicated electrophile, a mixture of products was obtained (Scheme 7). Even after careful column chromatography, the linear:branched products could not be cleanly separated from one another.

Scheme 7: "Model" vs "difficult" substrates results using NaN_3 or phthalimide as nucleophile

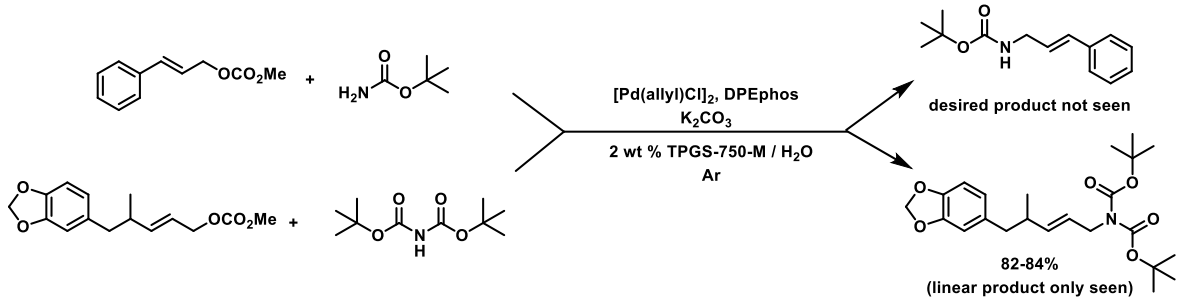


Next, phthalimide was screened as a nucleophile. Similar to the cases using NaN_3, while phthalimide gave exclusively the linear product in the cinnamyl model case, upon testing it upon a more complicated electrophile, once again a complicated mixture of products was obtained including a number of unidentified byproducts. This mixture could likewise not be effectively separated satisfactorily purified.

Because of the shortcomings of aqueous ammonia, sodium azide, and phthalimide as ammonia equivalents, the final family of ammonia equivalents tested was Boc-protected ammonia derivatives. Initially Boc-NH_2 (*t*-butyl carbamate) was tested, and while it has been effective in Pd-catalyzed Buchwald-Hartwig amidation type reactions in

water,[119] it was not found to give the desired product even in the simple cinnamyl model case (Scheme 8).

Scheme 8: "model" vs "difficult" substrates using Boc-amine derivatives



The use of di-*t*-butyl iminodicarboxylate[120] was found to be particularly useful for this difficult substrate and is the only ammonia equivalent nucleophile screened capable of giving a single product. While it's use has been previously reported for Tsuji-Trost reactions,[121] no use of this reagent for reactions in water could be found in the literature.

4.6 Substrate scope: carbon nucleophiles

With a sufficient scope of amine/NH nucleophiles developed, we turned our attention to carbon nucleophiles. A variety of carbon nucleophiles, such as doubly activated cases including 1,3-dicarbonyl-containing compounds such as □-nitro ketones, malonates, etc. readily participated (Scheme 9). In addition, one asymmetric example using a carbon nucleophile (**2h**) was explored and found to give moderate ee%. However, extensive screening was not conducted. It is noteworthy that initially amine nucleophiles (such as

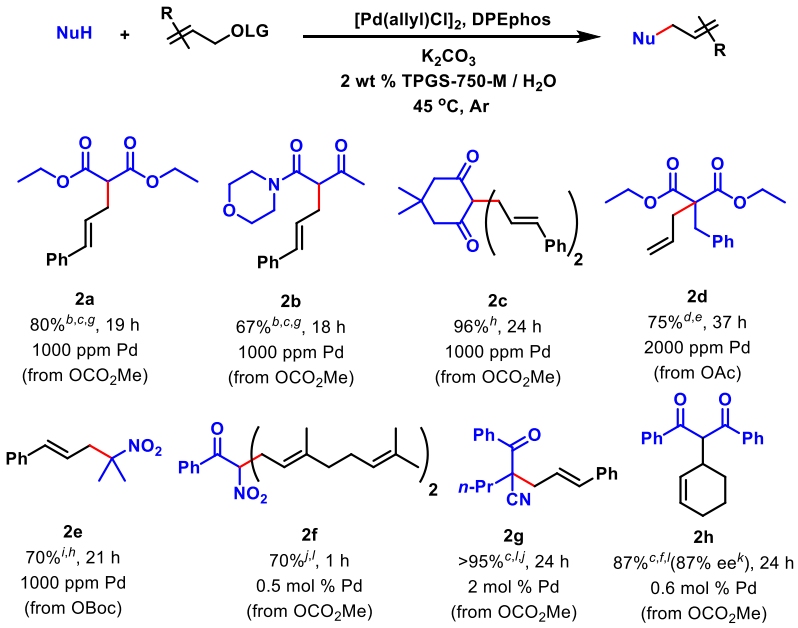
[119] Isley, N. A.; Dobarco, S.; Lipshutz, B. H. *Green Chem.* **2014**, *16*, 1480–1488.

[120] Neelamkavil, S. Di-Tert-Butyl-Imidocarbonate. In *Encyclopedia of Reagents for Organic Synthesis*; American Cancer Society, 2004.

[121] Connell, R. D.; Rein, T.; Aakermark, B.; Helquist, P. *J. Org. Chem.* **1988**, *53*, 3845–3849.

indoline and dibenzylamine) were tried using the same electrophile, but no appreciable ee% was seen.

Scheme 9: Reactions of Carbon Nucleophiles[a]



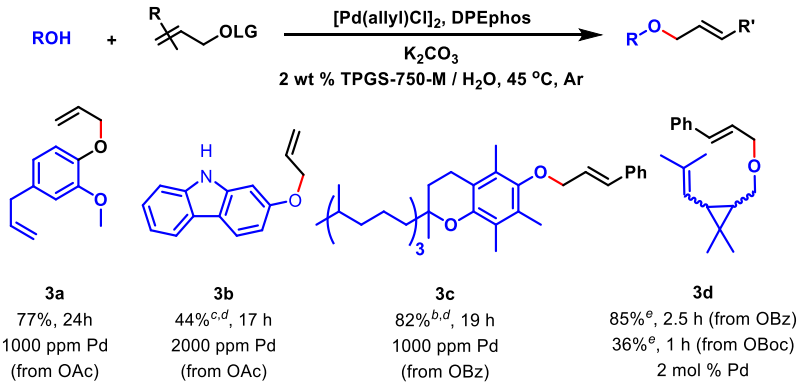
[a] Reaction conditions: nucleophile (1.0 equiv, [b] 1.1 equiv), electrophile (1.1 equiv, [c] 1.0 equiv, [d] 1.5 equiv), K_2CO_3 (1.5 equiv, [e] 1.0 equiv, [f] 2.5 equiv), 2 wt % TPGS-750-M / H_2O (1.0 M reaction concentration) catalyst stock solution prepared in toluene, 45 °C, argon. [g] $Pd(OAc)_2/PPh_3$ used as Pd catalyst, [h] 1.0 equiv of methyl formate added, [I] Et_3N (3.0 equiv) instead of K_2CO_3, [j] $[Pd(allyl)Cl]_2$/ligand added as solids, [k] (*S*,*S*)-DACH-Naphthyl used as ligand instead of DPEphos, [l] 0.5 M (reaction concentration).

4.7 Substrate scope: oxygen nucleophiles

Phenols proved to be competent nucleophiles at ppm levels of Pd in some cases, but alcohols with higher pKa's (e.g., chrysanthemyl alcohol) failed to reach completion at less than 1-2 mol % Pd. In general, however, phenols proved to be somewhat less reactive than

their amine or carbon nucleophile counterparts, resulting in a smaller effective substrate scope (Scheme 10).

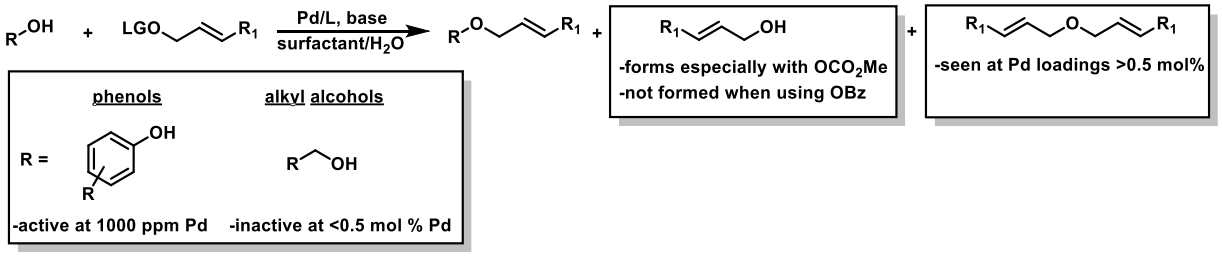
Scheme 10: Products of O-allylation Reactions[a]



[a] Reaction conditions: nucleophile (1.0 equiv), electrophile (1.1 equiv, [b]1.2 equiv, [c]1.5 equiv), K_2CO_3 (1.5 equiv, [d]1.0 equiv), 2 wt % TPGS-750-M / H_2O (1.0 M reaction concentration), catalyst stock solution prepared in toluene, 45 °C, argon. [d] Methyl formate (1 equiv) added, [e] $[Pd(allyl)Cl]_2$/DPEphos added as solids.

During the study of oxygen/alcohol nucleophiles, the nature of the leaving group became particularly important. Allylic carbonates were found to be prone to hydrolysis, and then to react with an allylic-O-LG, producing the symmetrical allylic-O-allylic dimer (Scheme 11). Therefore, in such cases, it became necessary to diversify leaving groups beyond the more typically seen acetates and methyl carbonates. Allylic-OBz derivatives were ultimately found to give greatly enhanced yields without dimerization, but at somewhat of a cost in terms of slightly lower reactivity at low catalyst loadings than their carbonate analogs.

Scheme 11: Trends seen when using oxygen nucleophiles

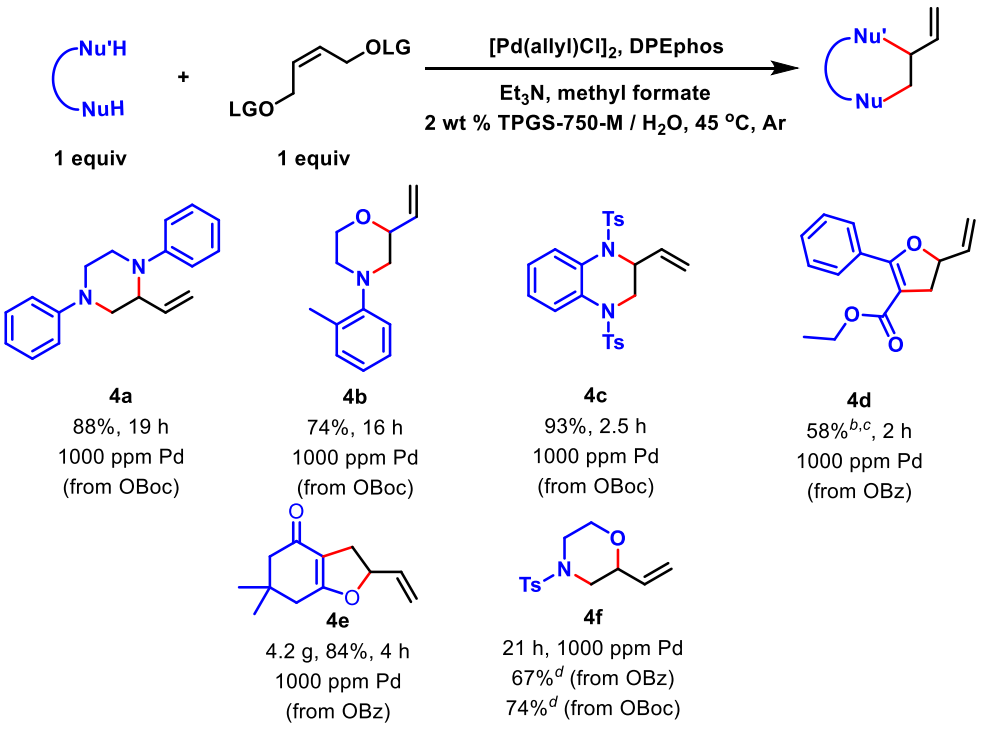


4.8 Substrate scope: intramolecular cyclizations

While many intramolecular variations of this reaction have been reported in organic solvents, they have been conspicuously absent from reports on Tsuji-Trost reactions in water. Because of this, I decided to test several intramolecular cyclizations to form heterocycles via this method. A number of classes of intramolecular cyclization were found to work well, each of these based on literature precedent in organic solvent (Scheme 12).[122]

[122] (a) Aubineau, T.; Cossy, J. *Org. Lett.* **2018**, *20*, 7419–7423. (b) Uozumi, Y.; Tanahashi, A.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 6826–6832. (c) Nakano, H.; Yokoyama, J.; Fujita, R.; Hongo, H. *Tetrahedron Lett.* **2002**, 43, 7761-7764. (d) Ito, K.; Imahayashi, Y.; Kuroda, T.; Eno, S.; Saito, B.; Katsuki, T. *Tetrahedron Lett.* **2004**, *45*, 7277–7281. (e) Tanimori, S.; Kato, Y.; Kirihata, M. *Synthesis* **2006**, *2006*, 865–869. (f) Massacret, M.; Lhoste, P.; Sinou, D. *Eur. J. Org. Chem.* **1999**, *1999*, 129–134.

Scheme 12: Intramolecular cyclization reactions[a]



[a] Reaction conditions: nucleophile (1.0 equiv), electrophile (1.0 equiv), Et_3N (3 equiv, [b] 2.0 equiv), methyl formate (1 equiv), 2 wt % TPGS-750-M / H_2O (0.33 M, [c] 0.25 M, [d] 0.4 M reaction concentration), catalyst stock solution prepared in toluene, 45 °C, argon.

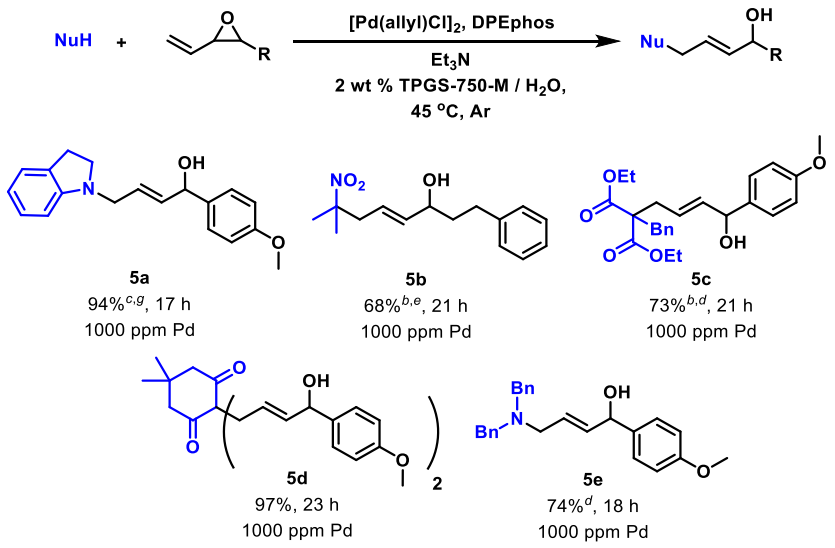
Vinyl-substituted heterocycles such as piperazine, morpholine, dihydrofuran, and tetrahydrovinylquinoxaline-containing rings (Scheme 12) were synthesized in favorable yields. It was particularly noteworthy that use of Et_3N rather than K_2CO_3 as base was very beneficial for solubility, and to avoid aggregation of solids. Initial attempts using K_2CO_3 as base, specifically with substrates **4a** and **4b** resulted in the formation of a "ball" of nearly-completely insoluble material, inside which were localized byproducts. Not only were yields very low (~20% vs. ~90% with optimized conditions), but in the case of **4b** there was poor regioselectivity between oxygen and nitrogen nucleophiles, as to which would be the initial nucleophile to attack the π-allyl intermediate. Upon switching

to Et_3N as base and diluting the reaction mixture, these intramolecular cyclizations were very effective and relatively clean. However, these cyclizations would have the most impact if done under asymmetric conditions. There is to our knowledge no literature on these types of reactions done under asymmetric conditions in water, and it would be an excellent future project to study this under aqueous conditions.

4.9 Substrate scope: vinyl epoxides

In an effort to expand on Pd catalyzed allylic substitution in water, vinyl epoxides were synthesized and tested as potentially useful electrophiles. These reagents proved to be very reactive under ppm Pd conditions with various nucleophiles. In cases where higher loadings were used (such as 1 mol % Pd), large amounts of dimerized/polymerized material were seen, with products/byproducts too numerous to attempt to identify. In addition, the purified and isolated products of these reactions frequently were found to be quite unstable in storage, decomposing to numerous unidentified byproducts after ~1 month (frustratingly, even when stored under argon). It isn't clear exactly why these products were so unruly, perhaps elimination or oxidation by air.

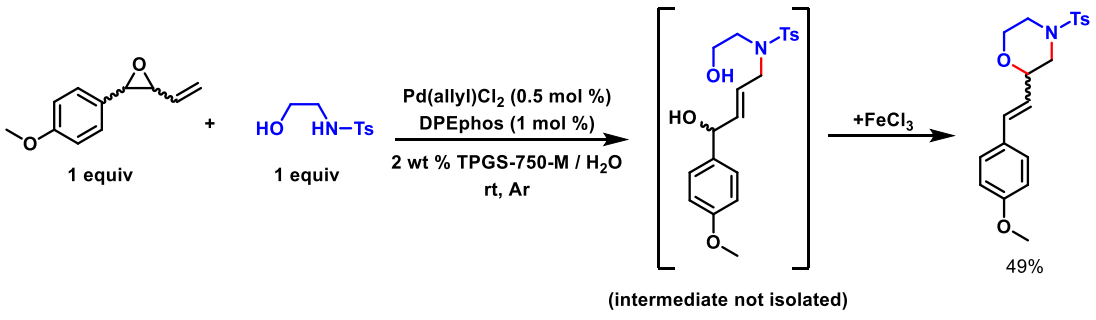
Scheme 13: Vinyl epoxides as electrophiles[a]



[a]Reaction conditions: nucleophile (1.0 equiv), electrophile (1.0 equiv, [b] 1.1 equiv [c] 1.2 equiv), Et_3N (3 equiv, [d] 2.0 equiv), methyl formate (1 equiv), 2 wt % TPGS-750-M / H_2O (0.5 M, [e] 1.0 M reaction concentration), catalyst stock solution prepared in toluene, 45 °C, argon. [f] no methyl formate, [g] K_2CO_3 (2.0 equiv) instead of Et_3N.

Inspired by work of Cossy and co-workers, a tandem sequence was conducted to form a functionalized vinyl/cinnamyl epoxide based on their work in organic solvents (Scheme 14).

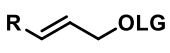
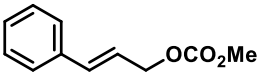
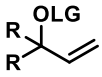
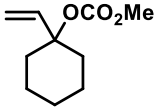
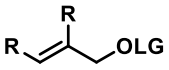
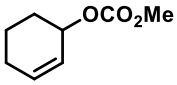
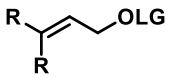
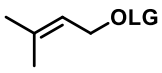
Scheme 14: Tandem 2-step-1-pot synthesis of a vinyl morpholine



4.10 Trends in substitution pattern and required catalyst loading

It was noticed that during substrate scope development that the degree of substitution on the allylic electrophile had a significant influence on catalyst loading required for reaction. While optimization trials showed that complete conversion could be achieved with 0.025-0.05 mol % Pd using substrates such as cinnamyl methyl carbonate and nucleophiles such as *N*-methyl aniline, these conditions were found to be extremely substrate specific. Additional substitution on the electrophile was very much correlated with failure of the catalytic system and frequently required 10-20x as much catalyst loading compared to the optimization substrates. Scheme 15 attempts to capture the variability of catalyst loading as a function of substitution, with examples of each.

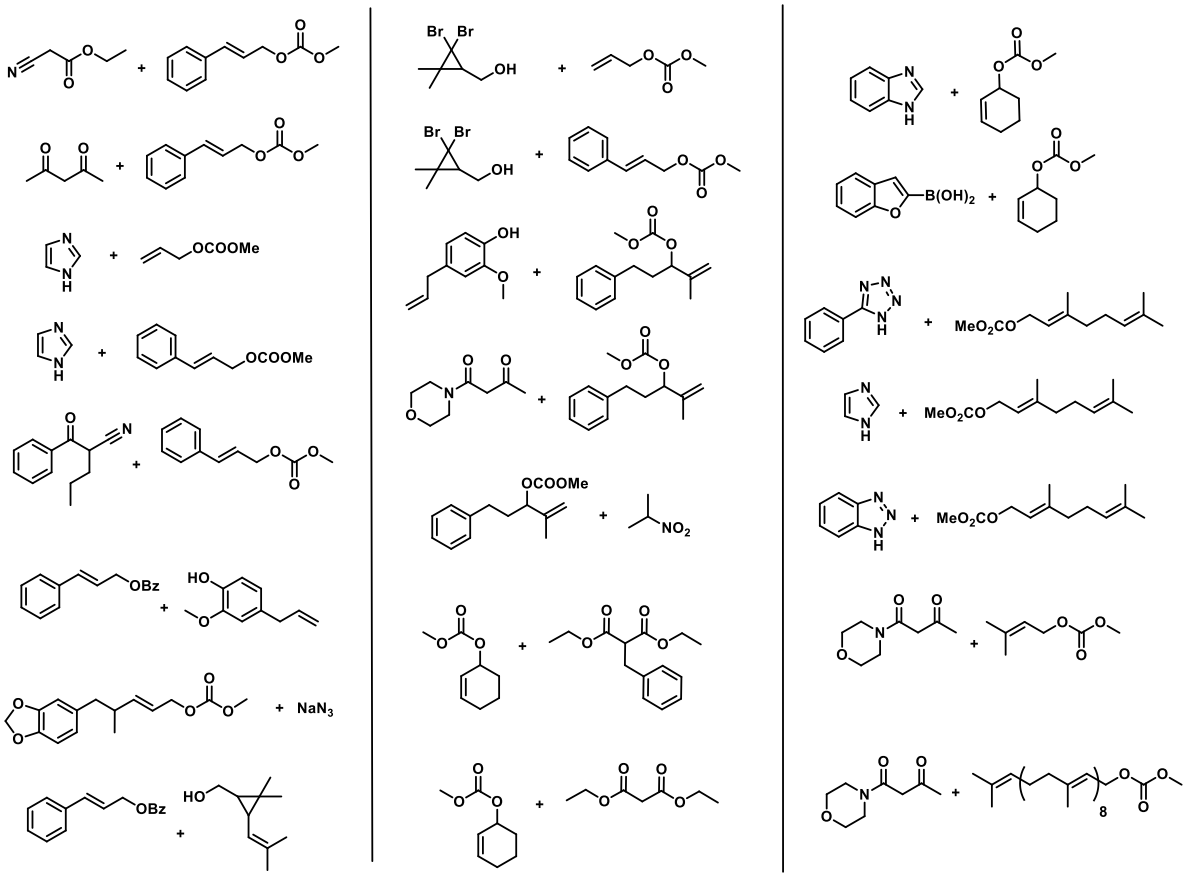
Scheme 15: substitution pattern versus required catalyst loading

Substitution pattern:	Example substrate:	Trends in catalyst loading necessary:
		reactive at >0.025 mol% Pd using amine nucleophiles reactive at >0.05 mol% Pd using carbon/oxygen nucleophiles
		reactive at 0.1 mol% Pd using amine nucelphiles reactive at >0.5 mol% using carbon/oxygen nucleophiles
		reactive at 0.1-0.5 mol% Pd using amine nucelphiles reactive at >0.5 mol% using carbon/oxygen nucleophiles
		reactive at ~0.5-1.0 mol% Pd using amine nucelphiles reactive at >1.0 mol% using carbon/oxygen nucleophiles prone to mixures of linear/branched products

As a follow-up to the data given in Scheme 15, examples of substrate combinations which gave either no detectable conversion or insufficient conversion to warrant isolation

are also shown. These trials were conducted on typically 0.1 mol % Pd loading as had at this point been set as a general “benchmark” (Scheme 16).

Scheme 16: Substrate combinations which gave unsatisfactory conversion at ppm Pd levels



4.11 ß-Lactam antibiotics

The ß-lactam antibiotics have been a mainstay of antimicrobial medications for decades. Several common classes such as penicillins, carbapenems, and cephalosporins are the

most prevalent. As a generic structure, the following figure shows the essential core of the cephalosporin class (Figure 1).

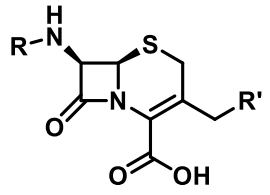
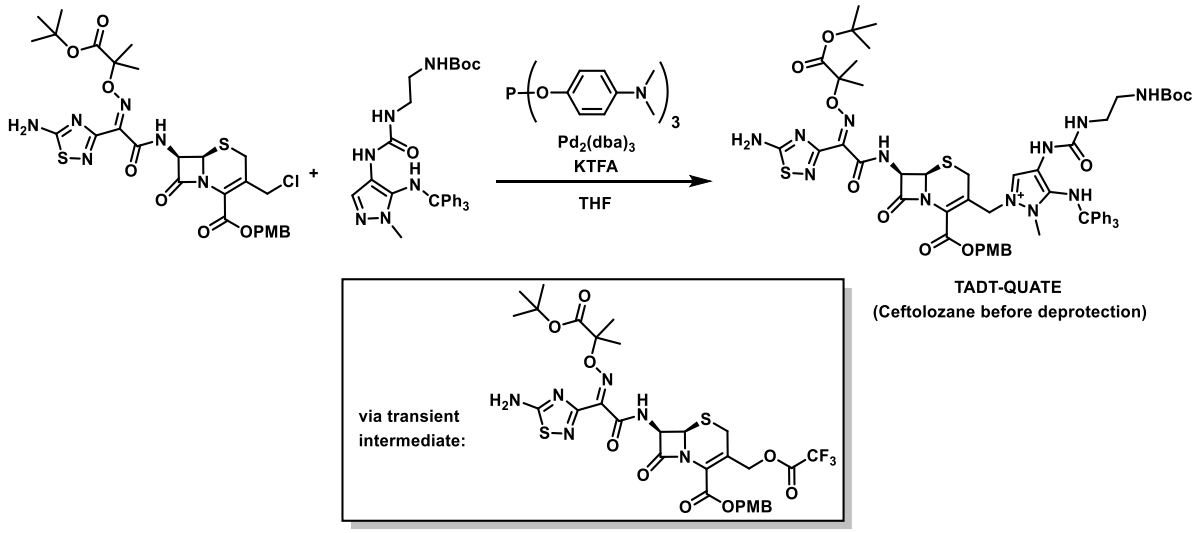


Figure 1: Generic core of cephalosporin antibiotics

Our interest in these drugs originated in a particular palladium catalyzed reaction published in a patent from Merck Sharp & Dohme.[123] It is fair to say that innumerable and nearly every conceivable variation on R and R' have been synthesized and screened by medicinal chemists over the last 40-50 years. Of particular note here is the nature of the R' group. In our case of interest, the R' group is a pyrazolium salt. This moiety can be incorporated through either an S_N2 type substitution or palladium-catalyzed allylic substitution reaction. The S_N2 reaction on these type compounds using a functionalized pyrazole as nucleophile requires very high temperatures, and is very low yielding. The Pd catalyzed route is purported in the patent literature to give much higher yields and occurs under much milder conditions, seemingly a much better approach.

[123] Waller, D.; Gazda, G.; Minden, Z.; Barton, L.; Leigh, C. WO2016025839A1, February 18, 2016.

Scheme 17: Patent literature synthesis of TADT-QUATE (protected Ceftolozane)



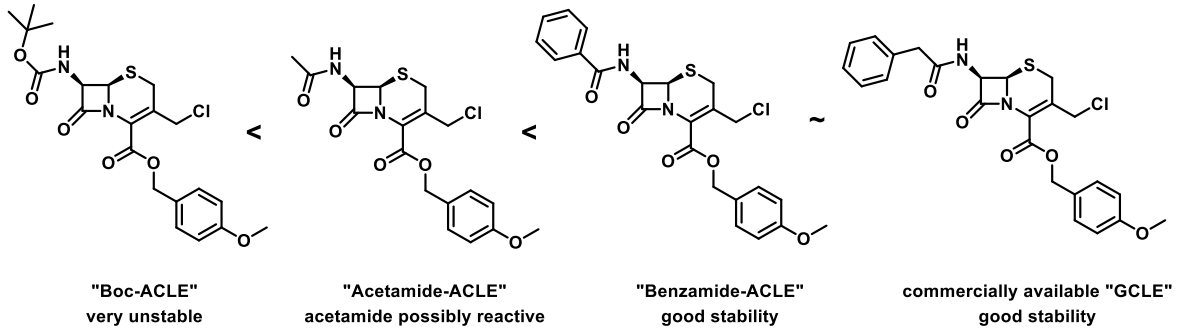
The goal of this project was to adapt this coupling reaction to water, and to decrease the palladium loading below the reported 2 mol % Pd catalyst. While this was the initial goal, this reaction turned out to be extremely difficult. While the goal of a "ppm Pd" method for this synthesis was not accomplished, the journey was quite educational, and I gained experience in areas ranging from analyzing patent literature, to the synthesis of semi-reverse phase silica, and handling of quaternary ammonium/pyridinium type organic compounds.

While there have been a number of approaches to transition metal catalyzed functionalization of cephalosporins, most of these rely on Stille type couplings.[124] The literature on Π-allyl Pd electrophiles is very scant. One aspect that became immediately clear was that cephalosporin compounds are unforgivingly sensitive to reaction conditions. Everything from "unknown" byproducts to apparent "complete decomposition" were observed when attempting to functionalize the compounds under

[124] Topics Organomet Chem (2004) 6: 247–262.

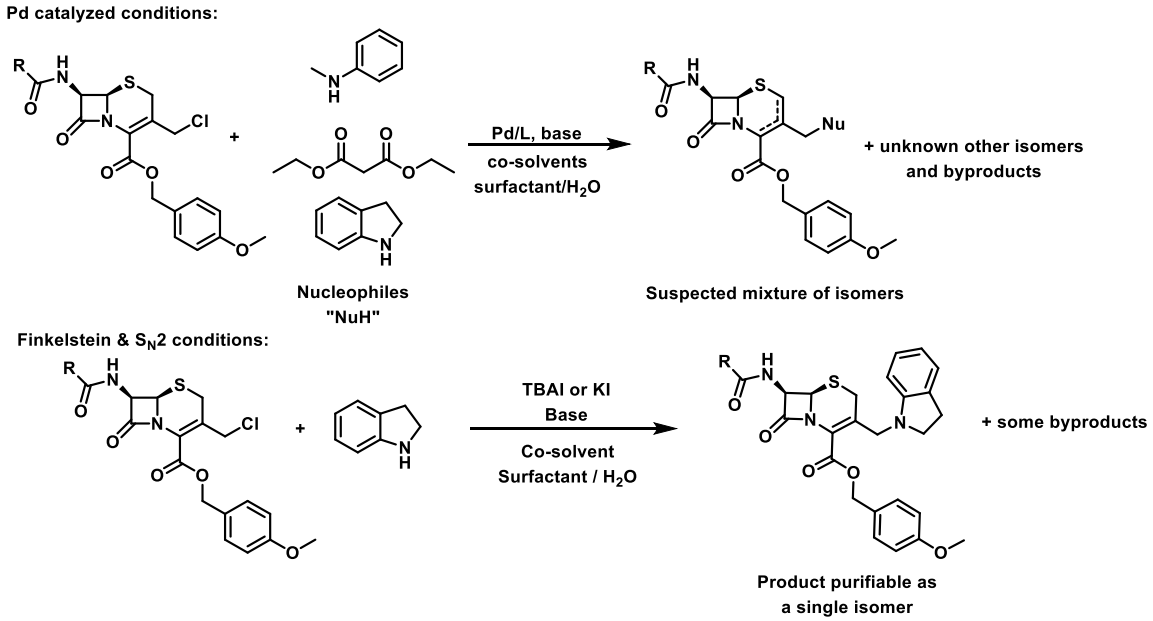
aqueous conditions. After attempting Pd catalyzed nucleophilic substitution on some ACLE derived substrates (Scheme 18), the following trends in stability were loosely derived.

Scheme 18: General trend in stability of derivatives of ACLE synthesized & screened



After screening numerous nucleophiles with several electrophiles, these nucleophiles were found to be at least in-part successful (Scheme 19). After many attempts, a much simpler halide exchange (Finkelstein conditions) was found to make a suitable electrophile for S_N2 substitution by a quite aggressive nucleophile: indoline. While the palladium-catalyzed reactions gave complete conversion, the product mixture could not be successfully purified by column chromatography. The halide “swap” followed by S_N2 gave reasonably pure material after column chromatography.

Scheme 19: Nucleophiles which proved at least partially successful



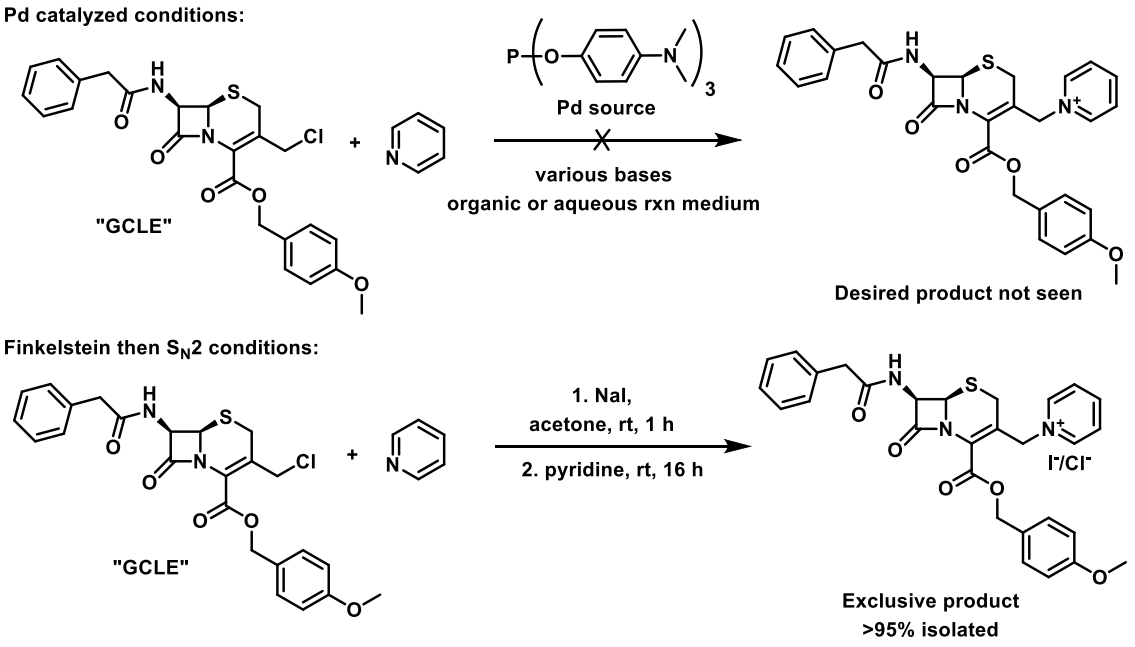
While it appeared that in Pd-catalyzed reactions in water that some of the desired product was obtained, it was unclear what the undesired products were. The characterization was made exceptionally difficult; even starting materials which appeared acceptably "clean" by NMR were found to be unstable to mass spectrum analysis, even using ESI/MS analysis, where MeOH used as solvent was found to add to the allylic chloride and the only MS detected fragments were due to addition of methoxide in the ionization process. After many Pd-catalyzed reactions attempted in both aqueous TPGS-750-M micellar conditions as well as THF as bulk solvent, no acceptably pure material could be obtained. Due to these difficulties, additives such as TBAI (tetrabutyl-ammonium iodide) were used in hopes of isolating purified product(s). The use of the very activated nucleophile indoline was found to be useful in producing reasonably pure product in the case of GCLE electrophile, in the absence of palladium. After discovering that the cephem-allyl chloride substrates could be substituted to some degree of purity using highly

nucleophilic amines in the presence of TBAI as a presumably "in-situ" generating of allylic iodide, it became clear that Pd was not necessary in these cases.

While use of Pd catalysis was not required for couplings in cases of very nucleophilic amines/anilines, it also was apparent that the patent literature had resorted to Pd catalysis out of a dire need to eliminate prominent and seemingly unavoidable decomposition. Pyridine as a nucleophile in the Pd-catalyzed case in at least partially aqueous medium gave what appeared to be successfully quaternized product, however, it appeared by NMR studies that more than one product persisted, even after extensive semi-reverse phase chromatography. In order to identify which NMR peaks corresponded to the correct product, a literature study ensued. Due to the difficulty in determining the products of the Pd catalyzed reactions, alternative methods were explored. A patent for producing pyridinium functionalized cephalosporins[125] was found, and their procedure was applied to GCLE. While the method was found to work extremely well, producing exclusively one product, this material unfortunately did not match any of the NMR spectra produced via the Pd catalyzed coupling in aqueous/partially aqueous reaction media (Scheme 20).

[125] Marquess, D.; Linsell, M. S.; Turner, D. S.; Trapp, S. G.; Long, D. D.; Fatheree, P. WO03099858 (A1), December 4, 2003.

Scheme 20: Quaternization of pyridine using Pd catalyzed conditions or Finkelstein then S_N2 conditions



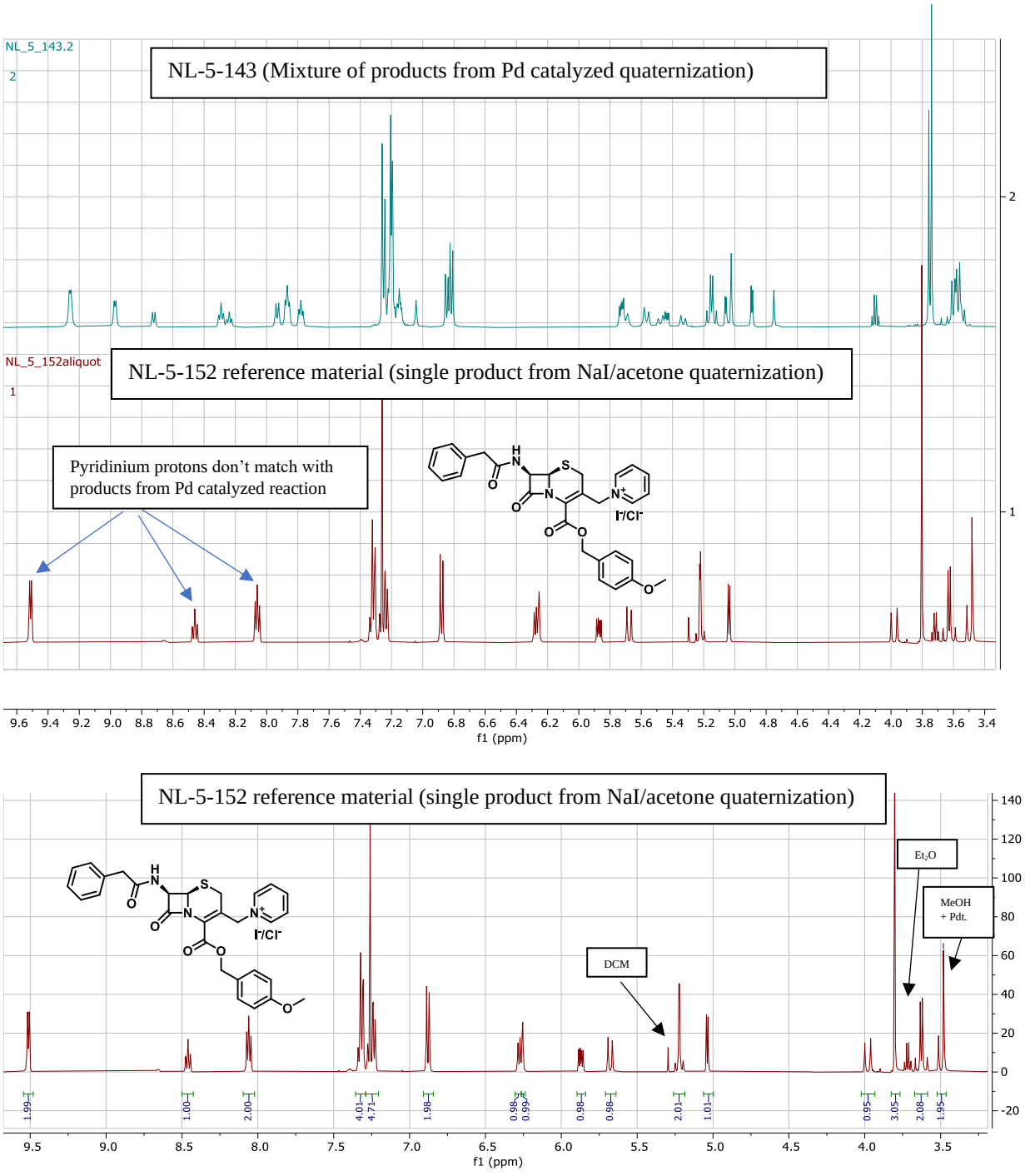
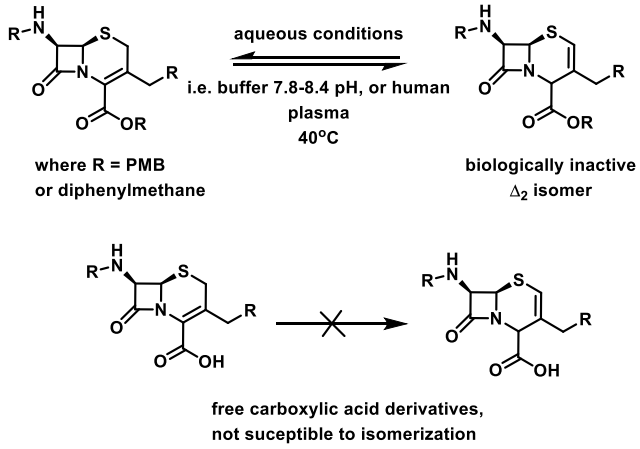


Figure 2: Comparison of products resulting from Pd catalyzed quaternization versus Finkelstein then S_N2 quaternization

It appeared that at least an isomerization of the C-C double bond had occurred, referred to as "Δ_2-Δ_3" isomerization[126] in the cephalosporin literature. This phenomenon has been particularly noted in cases attempting to utilize η^3-allylpalladium intermediates derived from chloromethyl cephem derivatives. Strangely, no mention of this issue is to be found in the patent literature on Ceftolozane published by Merck.

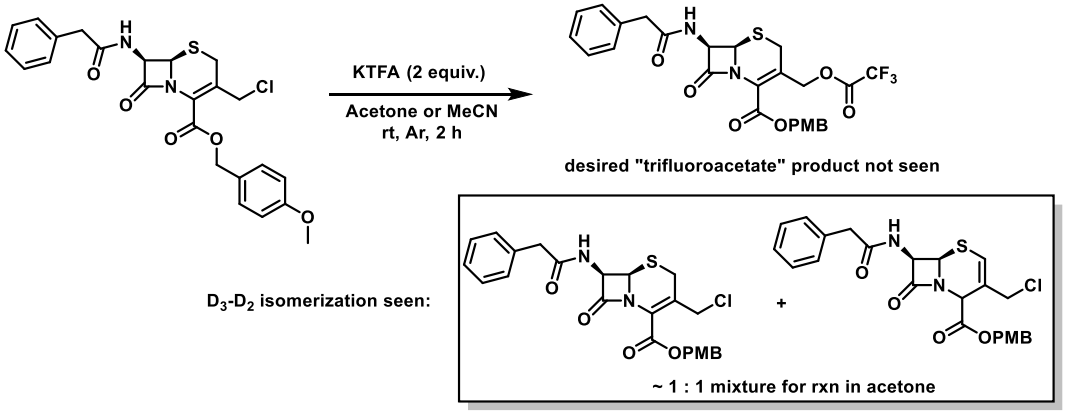
Scheme 21: Δ_3-Δ_2 isomerization of cephalosporin derivatives under aqueous conditions

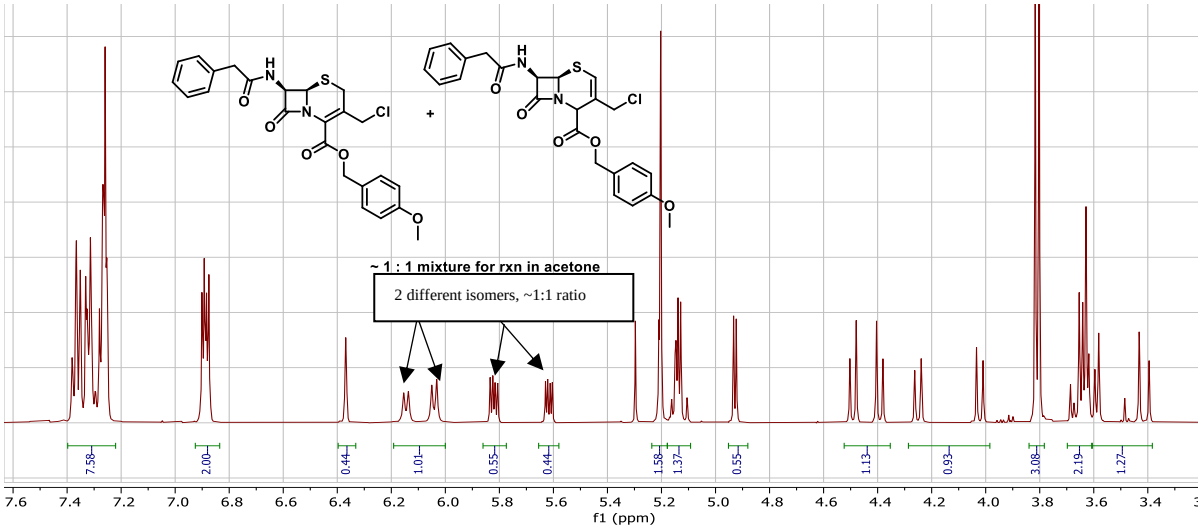


Because it seemed that this isomerization was at least one of the complications leading to our failure in Pd-catalyzed couplings, a simple experiment was devised. GCLE (the most stable of the cephalosporin compounds at my disposal) was mixed with potassium trifluoroacetate in either acetone or acetonitrile. This mixture was stirred at room temperature, and aliquots were removed for analysis by NMR (Scheme 22). It was hoped that a halogen exchange or "Finkelstein" reaction would occur, but rather an isomerization was observed.

[126] (a) Saab, A. N.; Dittert, L. W.; Hussain, A. A. *J. Pharm Sci.* **1988**, *77*, 906–907. (b) Keltjens, R.; Vadivel, S. K.; Vroom, E. de; Klunder, A. J. H.; Zwanenburg, B. *Eur. J. Org. Chem.* **2001**, 2001, 2529-2534.

Scheme 22: Attempting to synthesize allylic-TFA electrophile, resulting in Δ_2-Δ_3 isomerization of GCLE





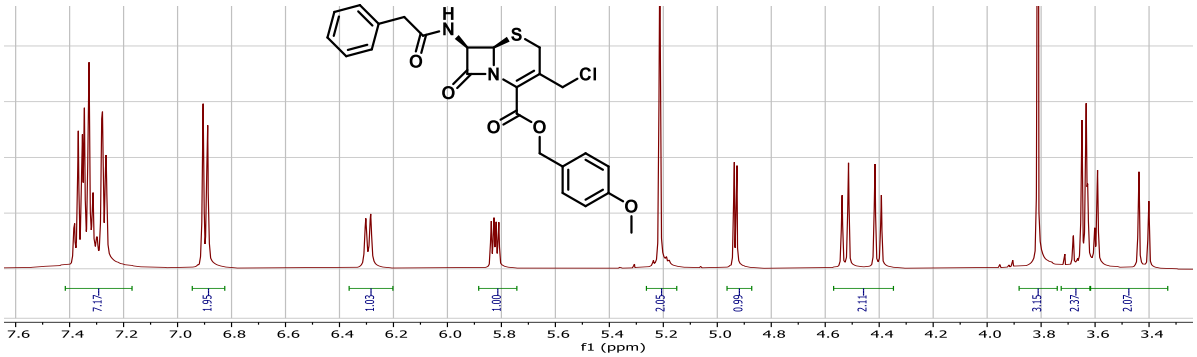


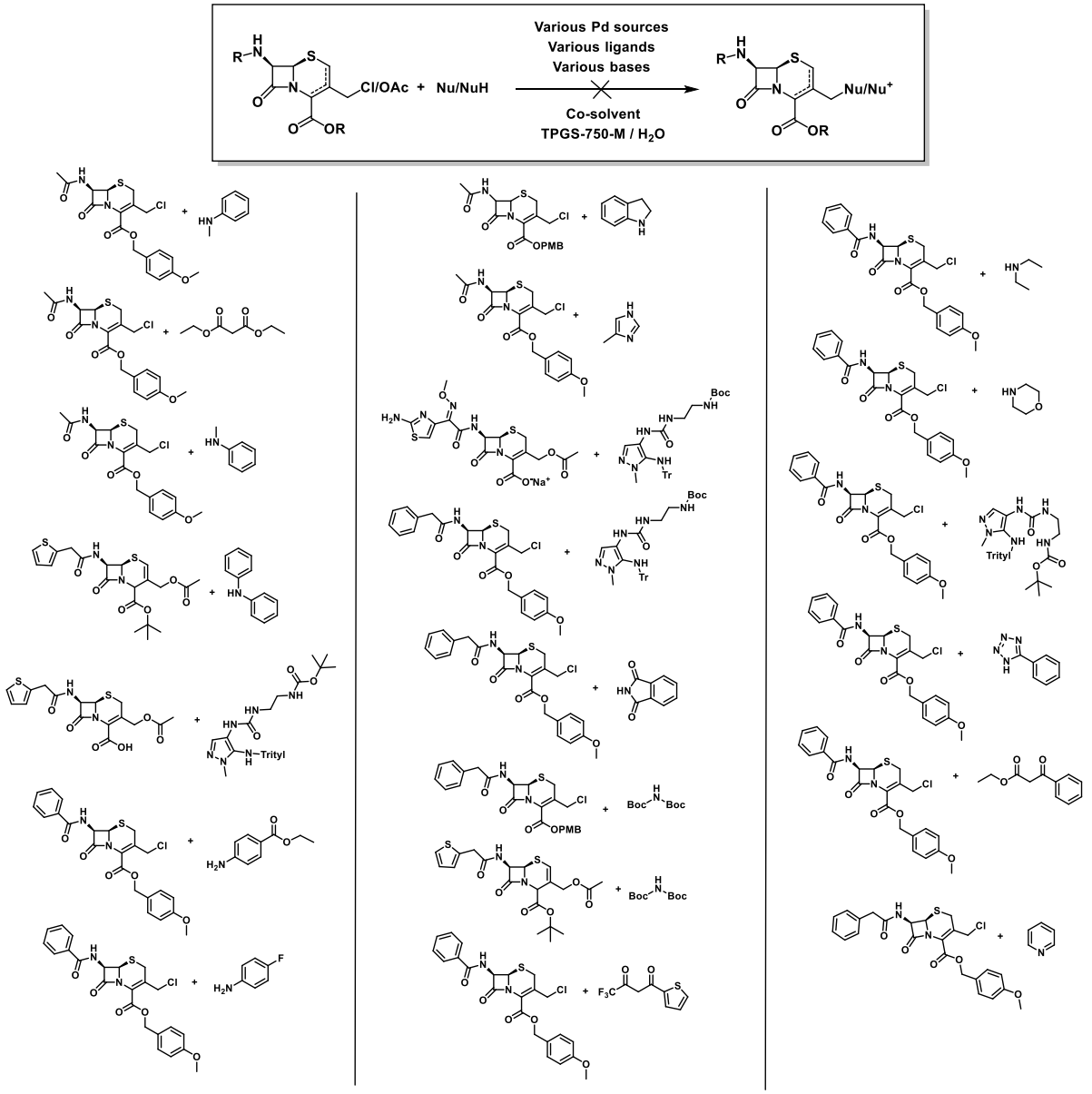
Figure 3: Suspected mixture of Δ_3- Δ_2 products arising from isomerization (top), Δ_3 starting material (bottom)

There exists in the literature related to functionalization of cephalosporins, methods to deal with this particular issue of Δ_3-Δ_2 isomerization. The process is quite involved, and typically results in many decomposition products and loss of the majority of the carefully prepared material (yields of 5-15% are reported overall). The only method to my knowledge for isomerizing the Δ_2 back to the Δ_3 material involves oxidizing the sulfide to the sulfoxide/sulfone to drive the C-C double bond back to the desired Δ_3 position, followed by reduction back to the sulfide using PCl_3. No mention of this problem was made in the Merck patent on the subject of Pd-catalyzed quaternization of this TADT-QUATE product of interest. Overall, in my evaluation, it doesn't seem clear how this base could be used without this isomerization happening. One aspect of this study which was later considered was the possibility that in deprotecting the PMB group under strongly acidic conditions (conducted with TFA in anisole/toluene mixture in the relevant patent), that this might promote isomerization of the C=C double bond back to the desired Δ_3 position. This would be a literature-unprecedented isomerization, however, it might be fitting with the previously reported literature that PCl_3 (likely to be highly acidic conditions) is suitable for reducing sulfones/sulfoxides back to the sulfide and the resulting product being the correct isomer. However, it seems that the literature indicates that the isomerization back to the biologically active Δ_3 isomer occurs in the MCPBA oxidation of the sulfide to sulfoxide & sulfone (obtained as a mixture).

Conclusions of Pd-catalyzed functionalization of cephalosporins

Overall, while this pursuit consumed 3-4 months of effort, no satisfactory method was achieved for palladium-catalyzed functionalization of chloromethyl derivatives of cephalosporins under aqueous, organic, or solvent mixtures of both. During this investigation into cephalosporin functionalization, a number of derivatives were either synthesized or purchased. They were treated with a variety of nucleophiles under aqueous palladium catalyzed conditions. Without exception, these resulted in very disappointing results, none of the desired products could be isolated under these conditions.

Scheme 23: Unsuccessful combinations of cephalosporins electrophile & various nucleophiles attempted under Pd-catalyzed conditions in water



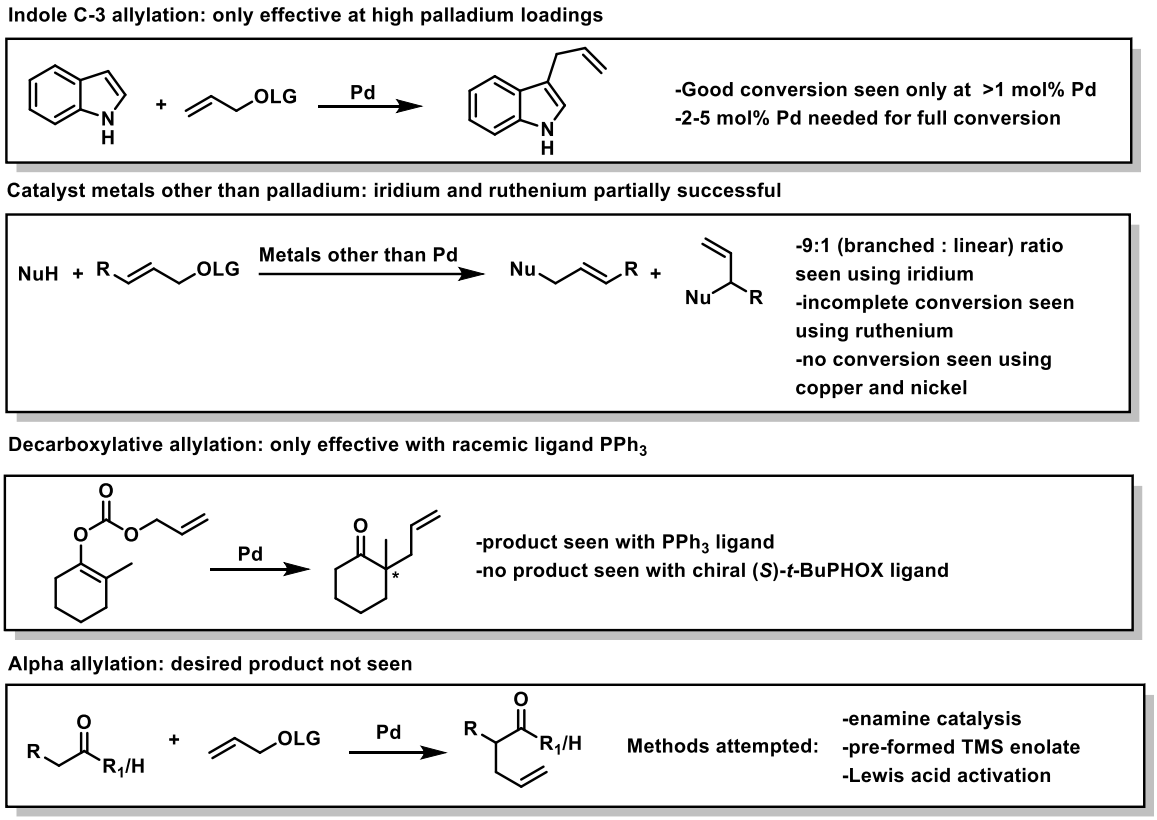
During the many trials attempting to successfully functionalize cephalosporin 3' chlorides with nucleophiles, more than a few nucleophile/electrophile combinations were examined. None of these produced acceptably pure products. In most cases, no conversion was seen, and after increasing the "harshness" of the conditions such as

increasing temperature, base, and Pd loading, typically the only results obtained were a wide variety of impurities. Very few of these impurities could be identified, even after careful chromatography. Of note were the following impurities: deprotected trityl group (evident by the fractions containing “trityl” aromatic groups from the Merck provided pyrazole “UBT”), and various “messes” containing characteristic “PMB” groups. These suggest that both the pyrazole nucleophile and cephalosporin electrophile were decomposing due to different mechanisms.

4.12 Additional classes of metal catalyzed allylic substitution explored in water

The original goal of these allylic substitution reactions using palladium catalysis seemed somewhat “reoccurring” based on the previous literature on this topic. As an attempt to make these reactions somewhat more interesting to the synthetic chemistry community, a variety of other types of reactions were screened and trialed. Some of these were successful, and some were not. These studies are summarized in Scheme 24 below.

Scheme 24: Summary of additional classes of metal catalyzed allylic substitution explored in water



In addition to palladium-catalyzed allylation of "typical" nucleophile + electrophile pairs, a number of other varieties of allylation reactions were screened. Based on several publications detailing indole C-3 allylation in organic solvent, a number of approaches were attempted in water. The reaction was found to be effective under some conditions, but relatively high Pd loadings were required (>1 mol % for reasonable conversion). The synthesis of chiral *N*-allylic indoles has received a large amount of attention in recent years (see Scheme 26 below for references). Because of the tendency for Pd to form linear products, iridium was also screened as an alternative metal due to its tendency to form branched products. Iridium was found to work as a catalyst in water, and gave a reasonable

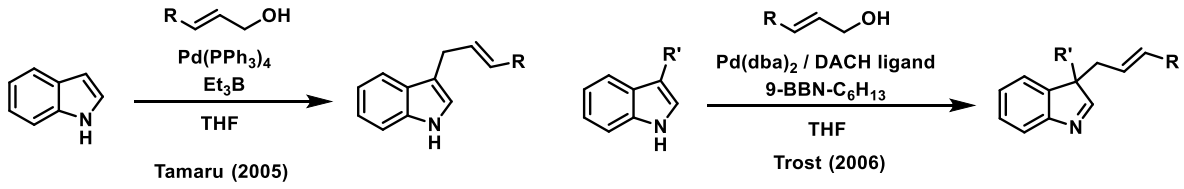
10:1 (branched:linear) ratio in model substrates. Other metals known to catalyze allylic substitution such as nickel and copper were screened, but gave no conversion to the desired product. A small amount of conversion was seen when using ruthenium in a model substrate. Decarboxylative allylation is another class of allylic substitution which has also received a large amount of attention, the Stoltz group being probably the most prolific in this area.[127] This approach, too, was found to work in water, but only when using PPh_3 as ligand, and unfortunately no conversion was seen when using a chiral catalyst. Alpha-allylation of ketones and aldehydes was tested using a variety of approaches including: enamine catalysis, TMS-enolate as nucleophile, and various Lewis acids as activators. These approaches were tested in water based on their precedence in organic solvents, but the desired product was not seen when the reaction was run in water.

One other class of reactions to which the Tsuji-Trost reaction is applied is in the C-3 allylation of indoles. Inspired by a number of publications on this topic, this reaction type was considered for use in water (See Scheme 25 below for the most significant literature examples). No literature precedent for Pd-catalyzed C3 allylation in water existed. However, some other types of C3-functionalization have been documented in water.[128]

[127] (a) Alexy, E. J.; Fulton, T. J.; Zhang, H.; Stoltz, B. M. *Chem. Sci.* **2019**, *10*, 5996–6000. (b) Marziale, A. N.; Duquette, D. C.; Craig, R. A.; Kim, K. E.; Liniger, M.; Numajiri, Y.; Stoltz, B. M. *Adv. Synth. & Catal. 357*, 2238–2245. (c) Keith, J. A.; Behenna, D. C.; Sherden, N.; Mohr, J. T.; Ma, S.; Marinescu, S. C.; Nielsen, R. J.; Oxgaard, J.; Stoltz, B. M.; Goddard, W. A. *J. Am. Chem. Soc.* **2012**, *134*, 19050–19060. (d) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045. (e) Craig, R. A.; Loskot, S. A.; Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Org. Lett.* **2015**, *17*, 5160–5163. (f) Alexy, E. J.; Virgil, S. C.; Bartberger, M. D.; Stoltz, B. M. *Org. Lett.* **2017**, *19*, 5007–5009.
(g) Starkov, P.; Moore, J. T.; Duquette, D. C.; Stoltz, B. M.; Marek, I. *J. Am. Chem. Soc.* **2017**, *139*, 9615–9620. (h) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem. Int. Ed.* **2005**, *44*, 6924–6927.
[128] (a) Kitanosono, T.; Miyo, M.; Kobayashi, S. *ACS Sustainable Chem. Eng.* **2016**, *4*, 6101–6106. (b) Westermaier, M.; Mayr, H. *Org. Lett.* **2006**, *8*, 4791–4794.

Two relevant approaches to C-3 indole allylation by Tamaru[129] and also Trost[130] (Scheme 25), but number of other varying approaches have been developed.[131]

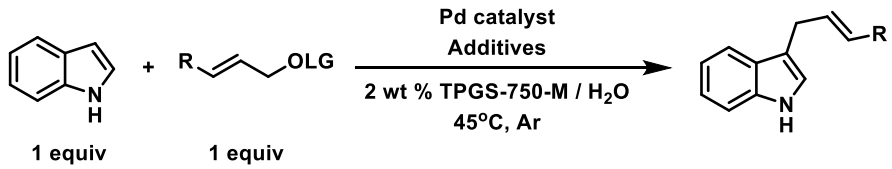
Scheme 25: Literature methods for selective indole C-3 allylation



Similar to the use of trialkylboranes in the literature cases, Me-OBBD (see section II for details on these reagents) was found to be a suitable "activator" of Pd catalysis for these reactions (Table 21). It was notable that Pd(II) salts such as $Pd(OAc)_2$ were completely inactive for these reactions, and only Pd(0) species, or various methods to achieve this oxidation state, were in any reasonable way effective for achieving conversion in these reactions. Other than using a direct Pd(0) source such as $Pd(PPh_3)_4$, the only effective method of Pd(II) to Pd(0) reduction method was the use of wet dioxane as catalyst stock solution which promoted sacrificial oxidation of phosphine ligand to enable reduction of Pd(II) to Pd(0) (superscript [c], reference in footnote of Table 21).

[129] Kimura, M.; Futamata, M.; Mukai, R.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 4592–4593.
[130] Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314–6315.
[131] (a) Peng, B.-J.; Wu, W.-T.; Yang, S.-C. Platinum-Catalyzed Allylation of 2,3-Disubstituted Indoles with Allylic Acetates. *Molecules* **2017**, *22*, 2097. (b) Montgomery, T. D.; Nibbs, A. E.; Zhu, Y.; Rawal, V. H. *Org. Lett.* **2014**, *16*, 3480-3483. (c) Montgomery, T. D.; Zhu, Y.; Kagawa, N.; Rawal, V. H. *Org. Lett.* **2013**, *15*, 1140–1143.

Table 21: Conditions screened for indole C-3 allylation in water



Trial	OLG =	R =	Pd catalyst (mol % Pd)	MeOBBD (equiv)	Additive (equiv)	Time (h)	Result
NL-3-112.1	OH	Ph	$Pd(PPh_3)_4$ (5.0)	0.3	none	16	>50% conversion
NL-3-112.2	OCO_2Me	Ph	$Pd(PPh_3)_4$ (5.0)	0.3	none	16	Full conversion
NL-3-112.3	OAc	Ph	$Pd(PPh_3)_4$ (5.0)	0.3	none	16	<50% conversion
NL-3-112.4	OH	H	$Pd(PPh_3)_4$ (5.0)	0.3	none	16	>50% conversion
NL-3-115.1	OH	Ph	$Pd(OAc)_2/PPh_3$ (5.0)	0.3	none	16	Trace conversion
NL-3-115.2	OCO_2Me	Ph	$Pd(OAc)_2/PPh_3$ (5.0)	0.3	none	16	Full conversion
NL-3-117	OH	Ph	$Pd(PPh_3)_4$ (5.0)	0.3	none	16	64% isolated
NL-3-122	OH	Ph	$Pd(dtbpf)Cl_2$ (5.0)	0.3	None	16	No conversion
NL-3-123.1	OH	Ph	$Pd(OAc)_2/PPh_3$ (5.0)	0.3	None[a]	24	No conversion
NL-3-123.2	OH	Ph	$Pd(OAc)_2/PPh_3$ (5.0)	0.3	$PhB(OH)_2$ (0.1)[a]	24	No conversion
NL-3-123.3	OH	Ph	$Pd(OAc)_2/PPh_3$ (5.0)	0.3	Et_3N (0.1)[a]	24	No conversion
NL-3-124.1	OH	Ph	$Pd(OAc)_2/PPh_3$ (5.0)[c]	0.3	None[b]	24	>50% conversion
NL-3-124.2	OH	Ph	$Pd(OAc)_2/PPh_3$ (5.0)[c]	0.3	$PhB(OH)_2$ (0.1)[b]	24	>50% conversion
NL-3-124.3	OH	Ph	$Pd(OAc)_2/PPh_3$ (5.0)[c]	0.3	Et_3N (0.1)[b]	24	>50% conversion
NL-3-125.1	OH	Ph	$Pd(OAc)_2/PPh_3$ (5.0)[c]	0.3	None	24	>50% conversion
NL-3-125.2	OH	Ph	$Pd(OAc)_2/PPh_3$ (5.0)[c]	none	none	24	No conversion
NL-3-129.1	OH	Ph	$Pd_2(dba)_3/PPh_3$ (5.0)[d]	0.3	None	24	No conversion
NL-3-129.2	OH	Ph	$Pd_2(dba)_3/P(o\text{-tolyl})_3$ (5.0)[d]	0.3	None	24	No conversion
NL-3-129.3	OH	Ph	$Pd_2(dba)_3/PPh_3$ (5.0)	0.3	None	24	No conversion
NL-3-129.4	OH	Ph	$Pd_2(dba)_3/P(o\text{-tolyl})_3$ (5.0)	0.3	None	24	No conversion
NL-3-131.1	OH	Ph	$Pd(OAc)_2/PPh_3$ (5.0)	0.3	DIBAL (0.1)	24	>50% conversion
NL-3-131.2	OH	Ph	$Pd(OAc)_2$/Sphos (5.0)	0.3	DIBAL (0.1)	24	No conversion
NL-3-131.3	OH	Ph	$Pd(dtbpf)Cl_2$ (5.0)	0.3	DIBAL (0.1)	24	No conversion
NL-3-221.1	OCO_2Me	Ph	$Pd(OAc)_2/PPh_3$ (2.0)	0.25	none	24	<50% conversion
NL-3-221.2	OCO_2Me	Ph	$[Pd(allyl)Cl]_2/PPh_3$ (2.0)	0.25	None	24	<50% conversion
NL-3-221.3	OCO_2Me	Ph	$Pd(OAc)_2$/DPEphos (2.0)	0.25	none	24	<50% conversion

NL-3-221.4	OCO_2Me	Ph	$[Pd(allyl)Cl]_2$/DPEphos (2.0)	0.25	none	24	<50% conversion
NL-3-223.1	OCO_2Me	Ph	$Pd(OAc)_2/PPh_3$ (5.0)[c]	0.25	None	16	Full conversion
NL-3-223.2	OCO_2Me	Ph	$[Pd(allyl)Cl]_2/PPh_3$ (5.0)[c]	0.25	None	16	Full conversion
NL-3-223.3	OCO_2Me	Ph	$Pd(OAc)_2/PPh_3$ (2.0)[c]	0.25	None	16	Full conversion
NL-3-223.4	OCO_2Me	Ph	$[Pd(allyl)Cl]_2/PPh_3$ (2.0)[c]	0.25	None	16	Full conversion
NL-3-223.5	OCO_2Me	Ph	$Pd(OAc)_2/PPh_3$ (1.0)[c]	0.25	None	16	>50% conversion
NL-3-223.6	OCO_2Me	Ph	$[Pd(allyl)Cl]_2/PPh_3$ (1.0)[c]	0.25	None	16	>50% conversion
NL-3-268.1	OCO_2Me	Ph	$[Pd(allyl)Cl]_2$/DPEphos (2.0)	none	K_2CO_3 (1.5)	2	Mixture of prods.[e]
NL-3-270	OH	Ph	$[Pd(allyl)Cl]_2$/DPEphos (2.0)	none	K_2CO_3 (1.5)	2	No conversion

[a] Catalyst added as a stock solution in toluene. Additive added to catalyst stock solution as catalyst activator prior to adding to the reaction.

[b] Additional catalyst added to failed NL-3-123 trials.

[c] Catalyst activated by heating $Pd(OAc)_2/PPh_3$ in wet dioxane at 80 °C according to a modified version of a literature procedure.[132]

[d] $Pd_2(dba)_3$/ligand pre-complexed in toluene catalyst stock solution prior to use

[e] Mixture of *N*-allylated, C3-allylated, di-allylated indole products as well as di-cinnamyl ether seen as products

After reviewing the literature on indole C-3 allylation, it became clear that some more "highly regarded" transformations using indoles were the *N*-allylations of indoles, particularly in the case of chiral transformations. Some of these reactions include the following (in Scheme 26): hydrazine + allene, then oxidation to indoles.[133] Hartwig approached this with iridium allylation of indoles,[134] and You approached this using iridium-catalyzed allylation of indolines followed by dehydrogenation to indoles.[135]

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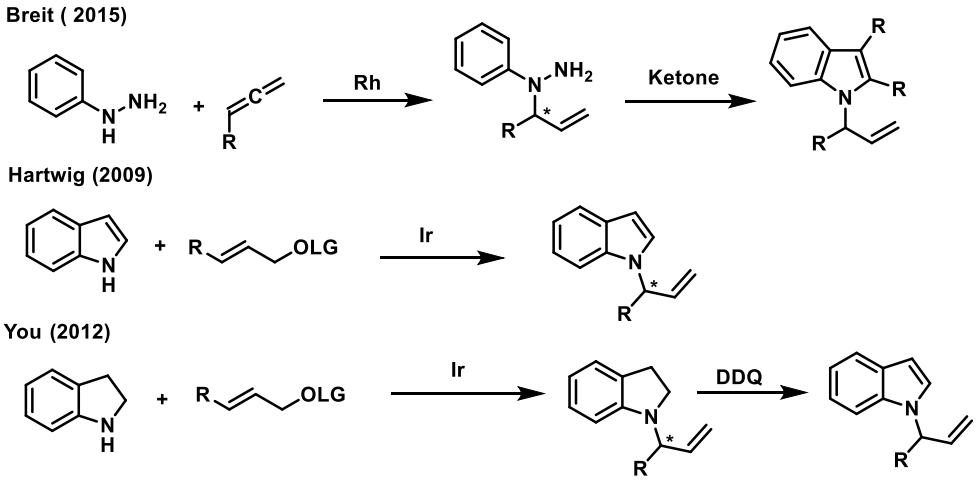
[132] Fors, B. P.; Krattiger, P.; Strieter, E.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 3505–3508.
[133] Xu, K.; Gilles, T.; Breit, B. *Nat. Comm.* **2015**, *6*, 7616.
[134] Stanley, L. M. & Hartwig, J. F. *Angew. Chem. Int. Ed*. 2009, 48, 7841.
[135] Liu, W., Zhang, X., Dai, L. & You, S. *Angew. Chem. Int. Ed*. **2012**, 51, 5183.

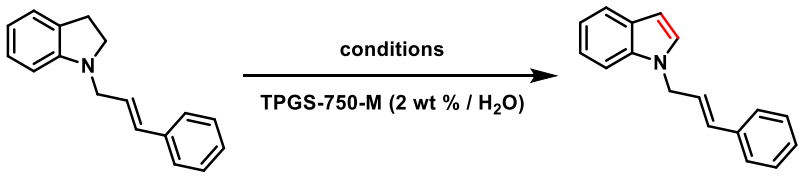
following (in Scheme 26): hydrazine + allene, then oxidation to indoles.[136] Hartwig approached this with iridium allylation of indoles,[137] and You approached this using iridium-catalyzed allylation of indolines followed by dehydrogenation to indoles.[138]

Scheme 26: Literature approaches to *N*-allyl indoles



Due to these methods involving dehydrogenation of *N*-allylic indolines to the corresponding indoles, I sought to develop a method for indoline dehydrogenation in water (Table 22). A number of methods were attempted based on their literature precedent in organic solvents.

Table 22: Various methods screened for dehydrogenation of *N*-cinnamyl indoline

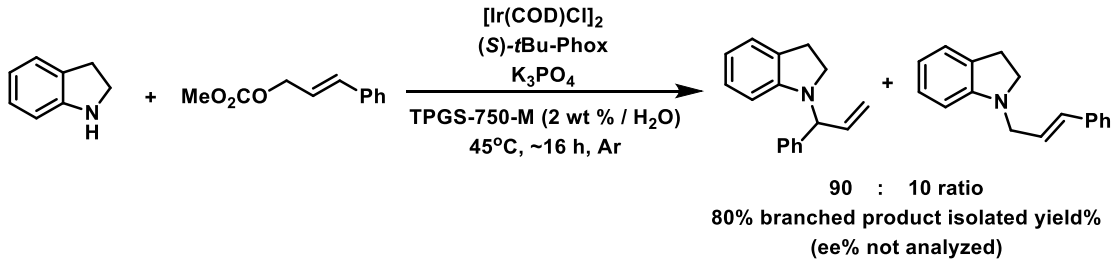


[136] Xu, K.; Gilles, T.; Breit, B. *Nat. Comm.* **2015**, *6*, 7616.
[137] Stanley, L. M. & Hartwig, J. F. *Angew. Chem. Int. Ed*. 2009, 48, 7841.
[138] Liu, W., Zhang, X., Dai, L. & You, S. *Angew. Chem. Int. Ed*. **2012**, 51, 5183.

Method/conditions	Result
MnO_2 (freshly prepared)	No conversion
Pd on hydroxyapatite	No conversion
$CuCl_2$ + TBHP	Full conversion
Co salen + TBHP	Full conversion
Co salen + O_2 balloon	Little/trace conversion

Encouraged by these results using this model substrate, showing that *N*-cinnamyl indoline could be effectively dehydrogenated to the corresponding indole, I turned my attention to the iridium-catalyzed allylation. Cinnamyl methyl carbonate was found to react well with indoline in the presence of an iridium catalyst to give a 9:1 mixture of branched:linear products (Scheme 27). This reaction was also attempted with other types of nucleophiles. No conversion was seen in the case of diethyl malonate, moderate conversion was seen with a phenolic nucleophile, and good conversion was observed with *N*-methylaniline. Also, a carbonate leaving group appeared necessary for these reactions, as no conversion was seen when using the analogous allylic alcohol or acetate electrophiles.

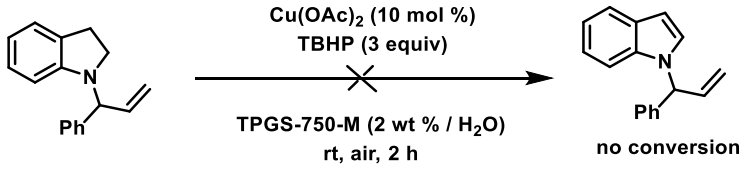
Scheme 27: Studies in iridium-catalyzed allylation in water:



This branched product was then used in an attempted dehydrogenation. Unfortunately, the conditions which gave full conversion with the linear *N*-cinnamyl indoline (~50% isolated yield), gave no conversion using this branched material. It's not clear why the

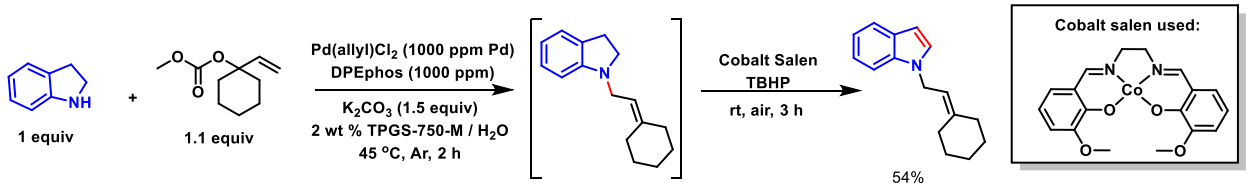
reaction would work on the linear material but fail on the branched material, possibly sterics are at play.

Scheme 28: Attempted dehydrogenation of branched *N*-allylic indole substrate in water



This wasn't explored further, and rather than continue on that path, I decided to use the indoline oxidation in a 2-step, 1 pot example using Pd catalysis instead. It seemed likely that the cinnamyl or styrene-type moiety on the previous case might have contributed to the proliferation of byproducts. This cyclic allylic carbonate was used instead, which did indeed appear to give somewhat fewer byproducts. This sequence concluded the exploration into indole allylation (Scheme 29).

Scheme 29: Tandem 2-step-1-pot synthesis of an *N*-allylic indole



4.13 Conclusions

Notwithstanding the fundamental nature of Pd-catalyzed Tsuji-Trost reactions, their use under aqueous conditions remains both underdeveloped and under-utilized. Reactions occurring in water, especially within nanoparticles derived from enabling surfactants,

have great potential to expand the attractiveness of these efficient catalytic reactions. Many of the Tsuji-Trost couplings conducted under these micellar conditions were found to work well using ppm levels of endangered Pd complexed by DPEPhos as catalyst. Nucleophiles not previously reported were also found to work well, including several *N*-heterocycles. Other notable nucleophilic partners include sulfonamide, azide, and primary alcohols. Several approaches to delivering ammonia equivalents were pursued, with di-Boc-protected ammonia being the most effective. Also described for the first time are intramolecular allylic substitutions, likewise performed in water at ppm levels of Pd. The prognosis for this new technology to be run on a multi-gram scale reaction was also evaluated, as was the recyclability of the entire reaction medium. These features, taken in their entirety, further highlight the sustainable nature of such chemistry in water.

4.14 Experimental

4.14.1 General Information

All commercial reagents were used without further purification unless otherwise noted. Organic solvents specified as "dry" and/or "degassed" such as THF, toluene, and DCM were taken from a solvent purification system (Innovative Technology, Inc.). All other solvents were used as received, such as EtOAc, Et_2O, hexanes, MeOH unless otherwise noted, purchased in 20 L drums from Fisher Scientific. TPGS-750-M was synthesized according to a literature procedure,[1] but can also be purchased from Sigma-Aldrich (now Millipore-Sigma), catalog number 763896. Thin layer chromatography (TLC) was performed using silica gel 60 F_{254} plates (Merck, 0.25 mm thickness) and analyzed by UV lamp (254 nm) and stains as noted. Silica gel column chromatography was conducted in

glass columns with compressed air using SiliaFlash® F60 40-63 μm silica gel purchased from Silicycle. Argon used for inert gas/vacuum manifold was industrial grade purchased from Praxair, and passed through a column of anhydrous $CaSO_4$ (Drierite brand) before entering the manifold. The pump attached to the argon/vacuum manifold, used to evacuate reaction vessels and remove solvent from purified products was a Welch® 1400 DuoSeal® vacuum pump. Reactions were stirred and heated using IKA® Labortechnik brand stirring hotplates with temperature control probe. Vial-scale reactions were conducted in 1 dram (3.7 mL) screwcap glass vials (VWR #66011-041) capped with 14/20 rubber septa (VWR #89097-554), and stirred with 1/2" x 1/8" Teflon® coated magnetic stir bars (VWR #58947-140) with the ends clipped using scissors to fit inside the vial to allow them to spin without becoming stuck. Vial-scale reactions specified as heated (e.g., 45 °C) were placed in a Chemglass® (#CG-1991-04) aluminum block reactor in either of the two inner rings of holes, but never in the outermost ring, to ensure efficient stirring. The aluminum block reactor was placed on top of the previously mentioned stirring hotplate, with temperature probe, and the reactions stirred vigorously (i.e., 800-1200 rpm) to maintain efficient mixing. Glassware specified as "oven-dried" was dried for at least 4 h in an oven at 100 °C before use. ^{1}H and ^{13}C NMR spectra were taken using either 400 MHz Agilent® Technologies, 500 MHz Varian Unity Inova® or 600 MHz Varian Unity Inova® spectrometers, with either $CDCl_3$, CD_3OD, or DMSO-d_6 as noted. ^{1}H NMR spectra were referenced to 7.26 ppm ($CDCl_3$), 3.31 ppm (CD_3OD), or 2.50 ppm (DMSO-d_6). ^{13}C NMR spectra were referenced to 77.16 ppm ($CDCl_3$), 49.00 ppm (CD_3OD), or 29.84 ppm (DMSO-d_6). NMR spectra was processed using MestReNova software version 14.0.0-

23239. Exact mass measurements were taken on a Waters GCT Premier high-resolution Time-of-flight mass spectrometer, with ionization method as noted.

[1] Lipshutz, B. H.; Ghorai, S.; Abela, A. R.; Moser, R.; Nishikata, T.; Duplais, C.; Krasovskiy, A.; Gaston, R. D.; Gadwood, R. C., TPGS-750-M: A Second-Generation Amphiphile for Metal-Catalyzed Cross-Couplings in Water at Room Temperature. *J. Org. Chem.* **2011**, *76*, 4379–4391.

4.14.2 General Procedures

Surfactant solution preparation and storage considerations

2 wt % TPGS-750-M / H_2O solution was typically prepared on a 100 mL scale, but this procedure can be scaled as necessary (see Figure 2 below). TPGS-750-M wax was melted by placing the vial/container in a hot water bath at 70-80 ^oC until fully melted. A 250 mL 14/20 necked round bottom flask (with no precautions against air or moisture) was placed horizontally on a top loading balance, and tared. Using a 1 mL syringe without needle, melted TPGS-750-M (2.0 g) was added to the flask, such that it forms a pool on the side of the flask (Figure 2A). The flask was removed from the balance and placed on ice until the TPGS-750-M fully solidified (Figure 2B). The flask was placed on a top loading balance and HPLC grade water was added such that the total mass of TPGS-750-M and water was 100 g, taking no special precautions against oxygen. A stir bar was added to the flask, and capped with a 14/20 septum. The flask was suspended above a magnetic stir plate at a 60^o angle, such that the TPGS-750-M remained above the water line. A long needle attached to an argon Schlenk manifold was placed through the septum, to the bottom

of the flask and a vent needle inserted through the septum. The flask was stirred while argon was sparged through the water for ~2 h (Figure 2C), or in the event that the solution began to foam significantly, the sparging was stopped before 2 h. The flask was then rotated such that the TPGS-750-M was below the water line (Figure 2D), the vent needle removed, and stirred until fully dissolved (~4-14 h). Vacuum was applied to the flask and backfilled with argon 3x. This solution was stored attached to an argon manifold. Typically, surfactant solutions were stored for no more that 3-4 months and discarded if discolored (e.g., if yellow or milky in appearance).

Figure 2: Preparation of a 2 wt % TPGS-750-M / H_2O. (A) adding melted TPGS-750-M to flask, (B) TPGS-750-M solidified after cooling, (C) sparging the water with argon while keeping TPGS-750-M wax above water line, (D) flask rotated after sparging, ready to be stirred to dissolve.

Note: TPGS-750-M solutions tend to foam vigorously if gas is introduced to the prepared solution (e.g., through sparging or gas-evolving reactions). Because of this, it is difficult to sparge prepared solutions. If the solution has been exposed to air, or is suspected to contain significant amounts of oxygen, vacuum can be applied to the flask and backfilled with argon, repeating several cycles, removing the flask from the manifold and shaking vigorously between vacuum/backfill cycles. While this is not as effective as degassing

methods such as freeze-pump-thaw or prolonged sparging, this has been found to be a sufficient amount of degassing to enable even very sensitive "ppm" Pd catalyzed reactions.

Reaction vessel considerations

Catalyst stock solutions as well as reaction trials were conducted in 1-dram (3.7 mL) screw-top vials capped with a 14/20 rubber septum (see Figure 1a-b; see General Information above for supplier and part number). They are convenient for these reactions for several reasons. Multiple trials can be conducted at the same time because these vials fit in an aluminum block reactor. The flat bottom allows for vigorous stirring (whereas conical tubes and culture tubes do not seem to stir as efficiently), and the small amount of headspace prevents excessive evaporation of low-boiling reagents like triethylamine, methyl formate, ammonia, etc., which can be a problem with larger vials and culture tubes frequently used for methodology studies. The use of larger vessels can be problematic in cases where solids or viscous reaction mixtures are present due to the tendency for material to be trapped on the glass, above the water line. In addition, reaction progress can be easily monitored without opening the vial by removing a small amount (~2-3 μL) of reaction mixture for analysis by TLC or other means, without exposing the reaction to oxygen (which is a problem when using screw-caps). Disposable ½" x 1/8" stir bars are inexpensive and available in packs of 100, however, they are slightly too long to lay flat in a 1-dram vial (c), and frequently wedge/lodge in the vial, halting stirring. To remedy this, a small amount of material can be trimmed from the ends using scissors, so they lay flat in the vial (d). Only a small amount of material should be removed (d) to avoid exposing metal. Note: only small diameter needles should be used to add reagents or remove aliquots

of reaction mixture, as large diameter needles tend to “core” the septum, potentially allowing oxygen to enter the reaction mixture.

Figure 1: (a) reaction vial with stir bar and capped with a septum, (b) microliter syringe used to add liquid reagents, (c) ½” x 1/8” stir bar as received in vial, (d) ½” x 1/8” in vial after trimming the ends (e) untrimmed stir bar on left, trimmed stir bar on right.

Catalyst stock solution preparation

Due to the difficulty in accurately weighing sub-milligram quantities of Pd catalyst needed for “ppm” level catalyst loadings, it was necessary to prepare a catalyst stock solution. The preferred solvent for this stock solution was found to be toluene; other solvents such as THF, acetone, MeOH, and EtOAc were tested but were found to give inferior results. In addition, it is preferred to fully ligate the palladium prior to adding it to the reaction mixture, as quick and full ligation is difficult to achieve in the aqueous reaction medium, especially in the presence of substrates such as amines, sulfonamides, *N*-heterocycles, etc., which may interfere with in-situ ligation in the reaction medium. In

addition, use of pre-ligated palladium, (e.g., Pd(DPEphosCl_2)) was found to give inferior results to a freshly prepared stock solution made from [Pd(allyl)Cl]$_2$ and DPEphos. A 1-dram (~4 mL) scintillation vial with magnetic stir bar was oven dried (minimum 4 h at 100 ^oC). The vial was removed from the oven and capped with a 14/20 septum (see Figure 1 above) and attached to an argon Schlenk manifold via a 22G (0.7 mm) diameter needle and vacuum was applied until the vial had cooled to rt, then the vial was backfilled with dry argon. The vial was opened and quickly added was [Pd(allyl)Cl]$_2$ (9.14 mg, 0.025 mmol) and DPEphos (26.9 mg, 0.050 mmol) and the vial was then capped with a 14/20 septum. Note: [Pd(allyl)Cl]$_2$ was typically weighed on a microgram balance to ensure as close to intended mass of Pd, due to difficulty in weighing small (mg) amounts of Pd on some balances, this stock solution may be scaled. We recommend keeping the same concentrations of reagents and toluene. The vial was re-attached to the Schlenk manifold and evacuated and backfilled with argon 3x. To the vial was added through the septum via syringe 2000 μL of dry, degassed toluene taken from a solvent purification system, with the vial still attached to the Schlenk line. The vial was stirred vigorously at rt, removing the needle and shaking the vial occasionally to rinse any material stuck above the liquid line. A fine yellow precipitate of ligated palladium formed and the vial is allowed to stir for a minimum of 10 min, but no more than 1 h before use. 20 μL of this stock solution is equivalent to 0.1 mol % Pd (1000 ppm) for a 0.5 mmol scale reaction. When transferring stock solution to a reaction mixture, it is necessary to continually stir the stock solution to prevent settling of the yellow suspension, and transfer the stock solution quickly to prevent it from settling in the microliter syringe used to transfer it. Note: some catalyst stock solutions (prepared under various concentrations during optimization) changed from a fine

yellow suspension to a black color with material adhering to the glass, particularly if the stock solution is allowed to stir for >1 h. It was unclear if this was indicative of decomposition due to the presence of water, oxygen, or due to stock solution concentration. Test reactions using this blackened solution/material showed usable catalytic activity, but in the interest of utmost care, these solutions were not used for any important trials. Extensive testing, however, of the effect of this phenomenon was not conducted. Most stock solutions prepared according to the above procedure remained a fine yellow suspension even after standing overnight, suggesting that the shelf life of this stock solution is likely at least 24 h, but extensive shelf life testing was not conducted.

General procedure for intermolecular reactions

To a 1-dram (~4 mL) scintillation vial was added all solids (including solid starting materials and base, but not catalyst except in cases where >0.25 mol % Pd was used, in which case Pd and ligand were added as a solid at this point), then a Teflon coated magnetic stir bar (trimmed to fit vial, see Figure 1 (a)) and the vial capped with a 14/20 septum (see Figure 1). This was done with no special precautions against moisture or oxygen. The vial was attached to an argon manifold/Schlenk line via a 22G / 0.7 mm diameter needle. Vacuum was applied to the vial, and backfilled with argon (industrial grade), making no special attempt to prevent reagents from being sprayed around the inside of the vial during backfilling. The evacuation/backfill was repeated 3x, with several seconds of vacuum and refill allowed during each cycle to fully purge the vial. The argon needle was removed from the vial. Via syringe, was added through the septum a degassed 2 wt % TPGS-750-M / H_2O solution (0.5 mL), taking care to prevent introducing air/oxygen during the transfer.

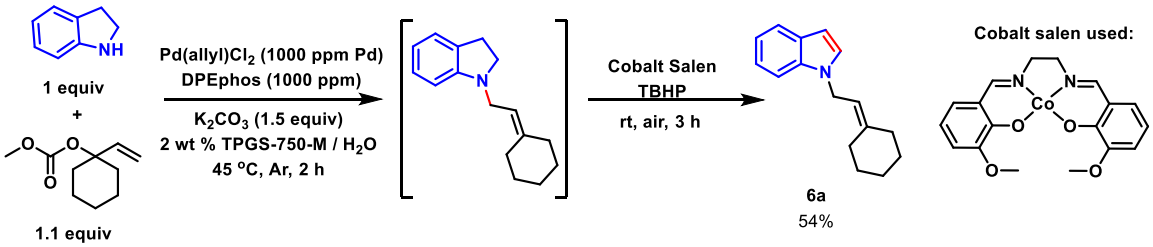
The vial was placed in an aluminum block reactor heated to 50 ^{o}C (to maintain an internal temperature of 45 ^{o}C) and stirred vigorously (~800-1000 rpm). Next, liquid reagents were added via syringe (i.e., allylic carbonate, Et_3N, methyl formate) in no particular order (Note: Et_3N and methyl formate were degassed by sparging ~2-3 mL portions with industrial grade argon for ~5-10 min before use). Lastly was added catalyst stock solution via syringe (20 uL for 0.1 mol % / 1000 ppm Pd) typically using a 50 uL or 100 uL microliter syringe with Teflon plunger to avoid introducing air (Note: many microliter syringes tend to leak air, the syringe used was selected because it does not leak), see above catalyst stock solution procedure for catalyst stock solution preparation.

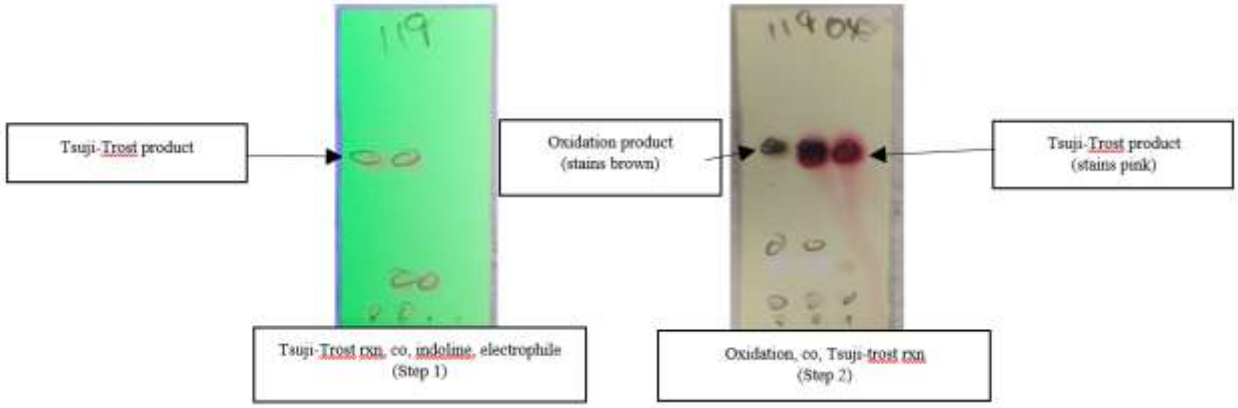
Note: While most reactions can be run at relatively high concentration (i.e., 0.5 mL of surfactant for a 0.5 mmol scale reaction), some particularly high molecular weight or crystalline substrates/products exhibit poor solubility at this concentration, and benefit from a more dilute reaction mixture (e.g., 1.0 mL surfactant solution rather than 0.5 mL). Reaction concentrations from 0.25 to 1.0 M (relative to limiting coupling partner to surfactant solution) were screened, no significant difference was seen, thus a more concentrated reaction mixture contributes to a lower E Factor. In addition, while significant oiling out/precipitate formation may occur when using K_2CO_3 as base, the use of triethylamine as base produces a much more uniform/homogeneous appearing reaction mixture.

General procedure for intramolecular reactions

The same catalyst stock solution and reaction conditions were used. However, the intramolecular reactions benefit from a lower reaction concentration to decrease byproduct formation. Therefore, a reaction concentration of 0.33 to 0.4 M (relative to surfactant solution, i.e., 1.25 mL surfactant solution for a 0.5 mmol scale trial for a concentration of 0.4 M) was typically used. Reactions run at 1.0 M as in intermolecular trials resulted in significantly decreased yields. In addition, Et_3N is the preferred base for intramolecular reactions as it decreases oiling out / precipitate formation which was associated with decreased yields and increased by-products when K_2CO_3 was used as base. Font changes again in next paragraph

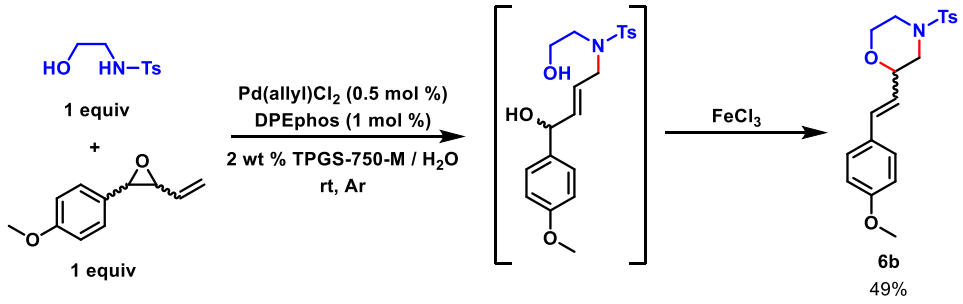
Procedures for 2-step,1 pot reactions





To a 1-dram (~4 mL) scintillation vial with magnetic stir bar was added K_2CO_3 (103.7 mg, 0.75 mmol, 1.5 equiv), with no special precautions against air or moisture. The vial was capped with a 14/20 septum, and attached to an argon Schlenk line via a 22G / 0.7mm diameter needle, and the vial was evacuated and back filled with argon 3x, then the needle removed. Via syringe was added 1.0 mL of degassed 2 wt % TPGS-750-M / H_2O solution and stirred briefly. Next, via microliter syringe was added indoline (59.6 mg, 0.5 mmol, 56.2 uL, 1 equiv) then allylic carbonate (101.3 mg, 0.55 mmol, 99.3 uL, 1.1 equiv) and the vial placed in an aluminum block reactor heated to 50 ^oC to maintain an internal temperature of 45 ^oC, and stirred vigorously (~800-1000 rpm). Catalyst stock solution (as prepared above) was added via microliter syringe (20 uL, 0.0005 mmol Pd, 0.1 mol %). After 2 h, an aliquot of the reaction mixture (~2-4 uL) was removed via microliter syringe and diluted Et_2O (~50 uL), rinsing the syringe into a test tube. The test tube was swirled and the organic layer used for TLC analysis using 7:93 (Et_2O/hexanes) which showed full consumption of indoline starting material. The vial was removed from the block reactor, allowed to cool to rt, uncapped and cobalt salen (9.6 mg, 0.025 mmol, 5 mol %) was added, and the vial re-capped (Note: surfactant solution may make the septum slippery, and may need to be wiped dry to prevent the septum from popping off of the vial), taking no precautions against air, and a 22G / 0.7 mm vent needle was placed through the septum to vent any pressure which might develop. Via microliter syringe was added TBHP (70% aqueous solution) (~260 uL, ~2.0 mmol, ~4 equiv) and the vial placed on a hot plate at rt and stirred vigorously for 3 h, upon which time the *N*-allylic indoline had been consumed, giving a new spot slightly higher (*N*-allyl indoline stains pink with Seebach's magic stain, *N*-allylic indole stains brown with this stain), Note: amounts of TBHP and cobalt catalyst

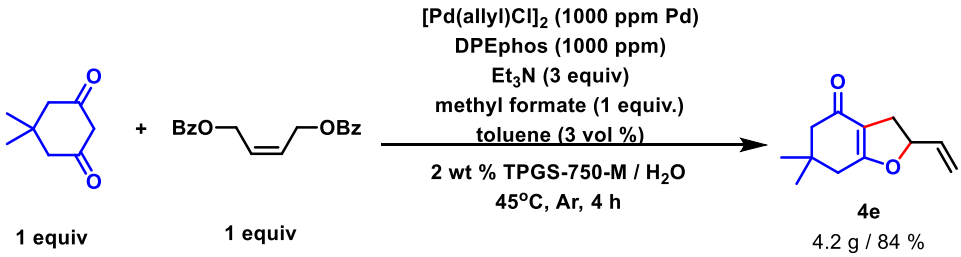
were not optimized. To determine the extent of reaction it was necessary to filter an aliquot through a pipette with a small amount of silica in order to resolve *N*-allylic indoline from the *N*-allylic indole product due to extremely close R_f values. Alternatively, the conversion can be monitored by GC-MS. Note: this oxidation/dehydrogenation must not be allowed to proceed for longer than necessary, as reactions allowed to run overnight produced very little product and large amounts of black tar material. Upon reaction completion (~3 h), the vial was uncapped and extracted with EtOAc, 3 x 1.5 mL. The organic phase was dried over anhydrous Na_2SO_4 and adsorbed onto Celite. Silica gel column chromatography was conducted using hexanes, then 2 : 98 (Et_2O / hexanes) then 5 : 95 (Et_2O / hexanes) to give 61 mg (54%) of 1-(2-cyclohexylideneethyl)-1H-indole as a light yellow oil. See Sections 5 and 6 for characterization data and spectra.

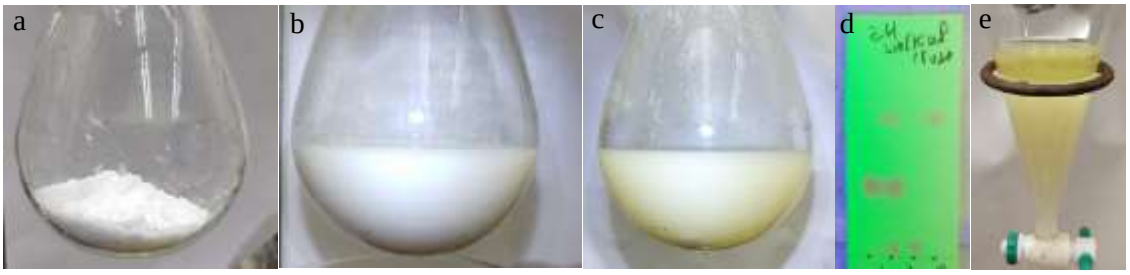


To a 1-dram (~4 mL) vial with magnetic stir bar was added $[Pd(allyl)Cl]_2$ (0.92 mg, 0.005 mmol, 0.5 mol %), DPEphos (2.7 mg, 0.005 mmol, 1.0 mol %), *N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide (107.6 mg, 0.5 mmol, 1.0 equiv), and the was vial capped with a 14/20 septum. The vial was attached to an argon Schlenk line via a 22G / 0.7 mm diameter needle and the vial evacuated and backfilled with argon 3x. Via syringe was added 1.0 mL of degassed 2 wt % TPGS-750-M / H_2O solution and the vial placed in aluminum block reactor at 45 ^oC. With stirring was added 2-(4-

methoxyphenyl)-3-vinyloxirane (88.1 mg, 0.5 mmol, 83.4 uL, 1.0 equiv) via microliter syringe. The reaction was stirred for 3 days, upon which time the vinyl epoxide had been consumed, producing the diol intermediate and a small amount of the vinyl morpholine product. The vial was removed from the reactor and opened. $FeCl_3 \bullet 6H_2O$ (20 mg, 0.074 mmol, 0.15 equiv) was added, the vial capped with a screw cap and placed back in the block reactor at 45 ^oC. The reaction was stirred for 5 h upon which time the diol intermediate was deemed consumed by TLC, diol intermediate $R_f = 0.30$ and vinyl morpholine product $R_f = 0.80$ with 75:25 (EtOAc/hexanes). The reaction was extracted with EtOAc, the organic phase dried with anhydrous Na_2SO_4, and the crude product adsorbed onto Celite. The product was purified via column chromatography with hexanes then 30/70 (EtOAc/hexanes) to give 2-(4-methoxystyryl)-4-tosylmorpholine as a pale-yellow oil (91 mg / 49%). (Note: this sequence was also attempted using Et_3N as base (as per the usual general coupling procedures above), and was found to give additional byproducts and poor conversion of the diol to the vinyl morpholine. Methyl formate was screened as an additive and also failed to improve results. A water stable Lewis acid $Yb(OTf)_3$ was also screened in lieu of $FeCl_3 \bullet 6H_2O$ and it failed to produce a significant amount of the desired product, but did increase the number and amount of unidentified impurities.) See Sections 5 and 6 for characterization data and spectra.

Procedure for scaled-up reaction



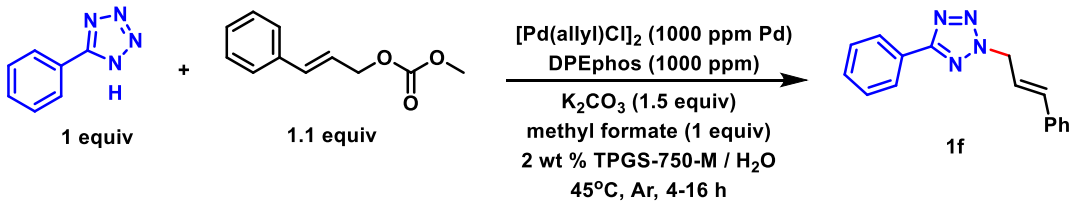


Multi-gram scale reaction: (a) solid reagents in 200 mL flask; (b) reaction mixture at start; (c) reaction upon completion (d) TLC from left to right: reaction mixture, co-spot, dimedone, (Z)-but-2-ene-1,4-diyl dibenzoate; (e) extraction.

To a 200 mL Schlenk flask with 24/40 neck was added a large oval magnetic stir bar (Note: the reaction requires vigorous stirring, so the largest possible stir bar should be used). Next, (*Z*)-but-2-ene-1,4-diyl dibenzoate (7.704 g, 26.0 mmol, 1.0 equiv) and dimedone (3.645 g, 26.0 mmol, 1 equiv) were added and the flask capped with 24/40 rubber septum. The flask was attached to an argon Schlenk manifold via the valve on the flask. The flask was evacuated/backfilled with argon 4x. Next, 60 mL of degassed 2 wt % TPGS-750-M / H_2O solution was added via syringe and the reaction placed in an oil bath at 50 ^oC to maintain an internal temperature of 45 ^oC and stirred vigorously. Via syringe, degassed Et_3N (7.89 g, 78 mmol, 10.87 mL, 3 equiv) was added (Note: Et_3N degassed by sparging with argon for ~20 min, then evacuating/backfilling the flask 3x). Next, catalyst stock solution was

added and the reaction stirred vigorously for 4 h, upon which time the reaction was deemed complete by TLC using 40:60 (EtOAc/hexanes). Catalyst stock solution was prepared by the following procedure: To an oven dried 1 dram (~4 mL) vial with magnetic stir bar, cooled under vacuum, was added $[Pd(allyl)Cl]_2$ (4.76 mg, 0.013 mmol, 0.1 mol % Pd) and DPEphos (14.0 mg, 0.026 mmol, 0.1 mol %) and the vial capped with a 14/20 rubber septum. The vial was attached to an argon Schlenk manifold via a 22G/0.7mm diameter needle and evacuated/backfilled with argon 3x. Dry, degassed toluene (2.0 mL) was added to the vial via syringe, and the stock solution stirred vigorously for 15 min, producing a fine yellow precipitate. The stock solution was transferred via syringe, under argon to the reaction flask. An additional 0.4 mL of toluene was added to the stock solution vial and used to rinse the walls of the vial and syringe, and transferred to the reaction flask. Upon reaction completion, the contents of the flask were poured into a 250 mL round bottom flask, rinsing with EtOAc, and the flask placed on a rotary evaporator to remove Et_3N (Note: extraction of the reaction mixture without removing Et_3N tends to produce a strong emulsion). The aqueous phase was extracted with EtOAc 3x (or until extracts contain no more product). The organic phase was dried over anhydrous Na_2SO_4, and the solvent removed via rotary evaporator. The crude product was purified by silica gel column chromatography using hexanes, then 20:80 (EtOAc/hexanes), then 30:70 (EtOAc/hexanes) to give 6,6-dimethyl-2-vinyl-3,5,6,7-tetrahydrobenzofuran-4(2H)-one, 4.21 g (84%).

Procedure for recycling studies



	Reaction	Recycle 1	Recycle 2	Recycle 3
Yield	**86%**	**79%**	**81%**	**82%**
E Factor (organic)	**0.5**	**0.5**	**0.5**	**0.5**
E Factor (aqueous)	**9**	**7**	**7**	**9**

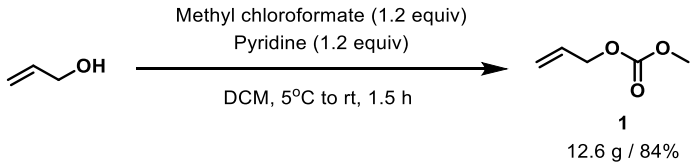
Reagent added	Reaction	Recycle 1	Recycle 2	Recycle 3
5-phenyl-1H-tetrazole	0.5 mmol	0.5 mmol	0.5 mmol	0.5 mmol
cinnamyl methyl carbonate	0.55 mmol	0.55 mmol	0.55 mmol	0.55 mmol
catalyst solution	1000 ppm Pd	1000 ppm Pd	1000 ppm Pd	1000 ppm Pd
K_2CO_3	0.75 mmol	0.75 mmol	0.75 mmol	0.75 mmol
methyl formate	0.5 mmol	0.5 mmol	0.5 mmol	0.5 mmol
2 wt % TPGS-750-M / H_2O	0.5 mL	+ 0.2 mL	+ 0.2 mL	+ 0.25 mL
water used to rinse product	0.5 mL	0.5 mL	0.5 mL	0.75 mL
product mass isolated	113 mg	103 mg	106 mg	107 mg
organic solvents used	47.3 mg	47.3 mg	47.3 mg	47.3 mg
aqueous used	1000 mg	700 mg	700 mg	1000 mg
E Factor (organic)	0.4	0.5	0.5	0.5
E Factor (water)	8.8	6.8	6.6	9.3

To a 1-dram (~4 mL) vial with magnetic stir bar was added 5-phenyl-1-H-tetrazole (73.1 mg, 0.5 mmol, 1.0 equiv) and K_2CO_3 (103.7 mg, 0.75 mmol, 1.5 equiv) and the vial was capped with a 14/20 rubber septum. The vial was attached to an argon Schlenk line via a 22 G / 0.7 mm needle and evacuated/backfilled with argon 3x. Via syringe was added 0.5 mL of degassed 2 wt % TPGS-750-M / H_2O solution and the vial placed in an aluminum block reactor at 50 ^oC to maintain an internal temperature of 45 ^oC, and stirred vigorously. Via syringe was added cinnamyl methyl carbonate (105.7 mg, 0.55 mmol, 1.1 equiv) and methyl formate (30 uL, 0.5 mmol). Next, via microliter syringe was added catalyst stock solution 20 uL (see section 2.2 for preparation). The reaction was stirred overnight (17 h) before removing from the block reactor. Upon cooling the reaction, the product solidified as a fine powder. The vial was opened and liquid was removed via pipette and placed in a second 1-dram vial (~0.3 mL recovered). An additional 0.2 mL of 2 wt % TPGS-750-M / H_2O solution was added to the vial to bring the total volume to 0.5 mL. To the vial was added 5-phenyl-1-H-tetrazole (73.1 mg, 0.5 mmol, 1.0 equiv) and K_2CO_3 (103.7 mg, 0.75 mmol, 1.5 equiv) and the vial was capped with a 14/20 rubber septum. The vial was attached to an argon Schlenk line via a 22G / 0.7 mm needle and evacuated/backfilled with argon 3x, vigorously shaking the reaction mixture in between evacuation/backfill cycles. Next, via microliter syringe was added catalyst stock solution 20 uL (see section 2.2 for preparation). The vial was placed in an aluminum block reactor at 45 ^oC and stirred for 4 h, upon which time the reaction was deemed complete by TLC. The vial was removed from the block reactor and cooled to rt while stirring, the product solidified as a fine powder. The vial was opened and the liquid removed via pipette and placed in a new vial (0.3 mL). This recycle procedure was repeated for a total of 3 recycles. Upon the 3rd recycle, the

solution had become very viscous and the K_2CO_3 was not fully soluble, suggesting that 3x recycles was the extent of practical reuse of the reaction medium.

To the vials containing product was added 0.5 mL of DI water and the vials placed in an aluminum block reactor at 60 ^oC and stirred for 1 h. Upon cooling, the liquid was removed via pipette, leaving the product in the vial, and the product dried under vacuum.

4.14.3 Synthesis of Starting Materials



1
12.6 g / 84%

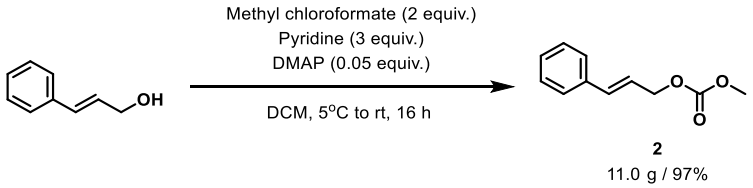
A 24/40 oven dried 500 mL round bottom flask with stir bar was capped with a septum and cooled under vacuum and backfilled with argon. To the flask was added 300 mL of dry DCM, allyl alcohol (10.0 g, 11.7 mL, 172 mmol, 1.0 equiv) and pyridine (16.3 g, 16.6 mL, 1.2 equiv). The flask was placed in an ice bath and stirred for 10 min before dropwise addition of methyl chloroformate (16.3 g, 13.3 mL, 172 mmol, 1.0 equiv.). The flask was stirred for 10 min before removing from the ice bath and allowed to warm to rt, ~1 h. An aliquot was removed and showed some allyl alcohol remaining. Additional methyl chloroformate (3.25 g, 2.7 mL, 34.4 mmol, 0.2 equiv) was added and the mixture was allowed to stir for an additional 30 min, at which time the reaction was deemed complete by NMR. The organic layer was washed with 1 M HCl (3 x 150 mL) then brine, then dried over anhydrous Na_2SO_4, and the bulk of the solvent removed via rotary evaporator. The

crude product was purified by vacuum distillation (bp 83-87 ^{o}C at 97-100 torr) to give 12.6 g (84%) of allyl methyl carbonate as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.97 – 5.83 (m, 1H), 5.32 (ddq, *J* = 17.2, 2.9, 1.5 Hz, 1H), 5.23 (ddq, *J* = 10.4, 3.1, 1.3 Hz, 1H), 4.60 (d, *J* = 5.8 Hz, 2H), 3.76 (d, *J* = 2.1 Hz, 3H).

^{13}C NMR ($CDCl_3$,101 MHz): δ 155.7, 131.6, 118.9, 68.5, 54.8.

Spectra matched those previously reported.[139]



An oven dried 300 mL round bottom flask with stir bar was capped with a septum and cooled under vacuum and backfilled with argon. To the flask was added DCM (150 mL), freshly distilled cinnamyl alcohol (7.68 g, 57.2 mmol, 1.0 equiv), pyridine (13.6 g, 13.8 mL, 171 mmol, 3 equiv) and DMAP (350 mg, 2.6 mmol, 0.05 equiv). The flask was placed in an ice bath and stirred for 10 min before dropwise addition of methyl chloroformate (10.9 g, 115 mmol, 8.9 mL, 2 equiv) The flask was stirred for an additional 15 min before removing from the ice bath and allowed to warm to rt. The flask was stirred overnight (16 h) at rt, at which time the reaction was deemed complete by TLC (R_f 0.50 with 25:75 EtOAc:hexanes), staining with vanillin. The organic phase was washed with 2 M HCl (2 x 200 mL), then brine, and dried over anhydrous Na_2SO_4. The solvent was removed via

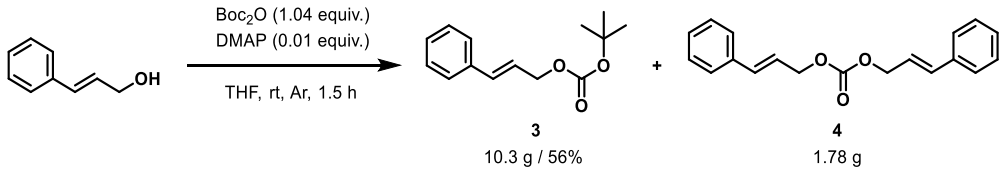
[139] Mutlu, H.; Ruiz, J.; Solleder, S. C.; Meier, M. A. R. *Green Chem.* **2012**, *14*, 1728–1735.

rotary evaporator and the crude product dissolved in EtOAc and filtered through silica and the solvent removed via rotary evaporator. The product was dried under vacuum to afford cinnamyl methyl carbonate (11.0 g, 97%) as a colorless oil which crystallized into white needles upon refrigeration.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 2H), 7.36 – 7.30 (m, 2H), 7.30 – 7.25 (m, 1H), 6.69 (dt, *J* = 15.8, 1.4 Hz, 1H), 6.30 (dt, *J* = 15.9, 6.5 Hz, 1H), 4.80 (dd, *J* = 6.5, 1.4 Hz, 2H), 3.81 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 155.8, 136.1, 134.9, 128.7, 128.3, 126.8, 122.5, 68.5, 54.9.

Spectra matched those previously reported.[140]



A 24/40 oven dried 300 mL round bottom flask with stir bar was capped with a septum and cooled under vacuum and backfilled with argon. Boc anhydride was melted in a water bath at ~60-70 ^oC and added via pipette to the reaction flask. The flask was capped with a septum and evacuated/backfilled with argon 1x. Via cannula was added dry THF (100 mL), and with stirring, via syringe was added freshly distilled, warm cinnamyl alcohol (10 g, 75 mmol, 1.0 equiv). The flask was opened and DMAP (91 mg, 0.75 mmol, 0.01 equiv.) was added, and the flask capped with septum, and the flask stirred at rt. Effervescence began soon after, at which time the reaction flask was placed in a room temperature water bath in case of exotherm. After stirring at rt for 1.5 h, the reaction was deemed complete by TLC

[140] Su, Y.; Jiao, N. *Org. Lett.* **2009**, *11*, 2980–2983.

(R_f = 0.50 with 15:85 Et_2O:hexanes), staining with vanillin. The solvent was removed via rotary evaporator and the crude product dissolved in Et_2O and washed with 2 M HCl (2 x 50 mL), then brine, and dried over anhydrous Na_2SO_4 and the solvent removed via rotary evaporator. The crude product was distilled under vacuum (bp 130 ^oC at 1 torr) in collecting three fractions. Cinnamyl *t*-butyl carbonate was obtained as a viscous colorless oil (10.26 g, 56%), and dicinnamyl carbonate was obtained as a white solid from the distillation flask (1.78 g).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41 (d, *J* = 7.2 Hz, 2H), 7.37 – 7.31 (m, 2H), 7.31 – 7.24 (m, 1H), 6.69 (d, *J* = 15.9 Hz, 1H), 6.32 (dtd, *J* = 15.9, 6.4, 0.9 Hz, 1H), 4.74 (dd, *J* = 6.4, 1.2 Hz, 2H), 1.53 (s, 9H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 153.5, 136.3, 134.5, 128.7, 128.2, 126.8, 123.0, 82.3, 67.6, 27.9.

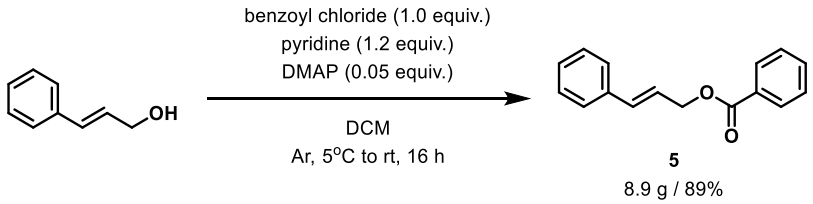
di-cinnamyl carbonate:

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.46 – 7.40 (m, 4H), 7.39 – 7.33 (m, 4H), 7.33 – 7.27 (m, 2H), 6.74 (dt, *J* = 16.0, 1.4 Hz, 2H), 6.35 (dt, *J* = 15.9, 6.4 Hz, 2H), 4.85 (dd, *J* = 6.5, 1.4 Hz, 4H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 155.0, 136.1, 134.9, 128.7, 128.3, 126.8, 122.5, 68.5.

Spectra matched those previously reported.[141]

[141] Trost, B. M.; Luan, X. *J. Am. Chem. Soc.* **2011**, *133*, 1706–1709.

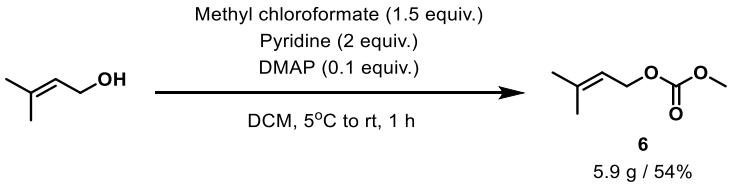


A 500 mL oven dried round bottom flask with stir bar was capped with a septum and cooled under vacuum and backfilled with argon. To the flask was added 170 mL of dry DCM, freshly distilled cinnamyl alcohol (5.63 g, 42.0 mmol, 1.0 equiv), pyridine (4.0 g, 50.4 mmol, 4.1 mL, 1.2 equiv) and DMAP (256 mg, 2.1 mmol, 0.05 equiv). The flask was placed in an ice bath and stirred for 10 min before dropwise addition of benzoyl chloride (5.90 g, 42.0 mmol, 4.87 mL, 1.0 equiv). The flask was stirred for 10 min before removing from the ice bath and allowed to warm to rt. The flask was stirred overnight (16 h), upon which time the reaction was deemed complete by TLC (R_f = 0.70 with 20:80 Et_2O/hexanes). The reaction mixture was washed with 1 M HCl (2 x 100 mL), then brine, and dried over anhydrous Na_2SO_4 and the solvent removed via rotary evaporator. The product was dissolved in Et_2O and filtered through a plug of silica, eluting with 20:80 Et_2O/hexanes, the solvent removed via rotary evaporator and the product dried under vacuum to give cinnamyl benzoate as a viscous colorless oil (8.9 g / 89%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.16 – 8.08 (m, 2H), 7.63 – 7.55 (m, 1H), 7.47 (dd, *J* = 16.4, 8.1 Hz, 4H), 7.36 (t, *J* = 7.5 Hz, 2H), 7.33 – 7.27 (m, 1H), 6.78 (d, *J* = 15.9 Hz, 1H), 6.44 (dt, *J* = 15.9, 6.4 Hz, 1H), 5.02 (dd, *J* = 6.3, 1.5 Hz, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 166.4, 136.3, 134.3, 133.0, 130.3, 129.7, 128.7, 128.4, 128.1, 126.7, 123.3, 65.6.

Spectra matched those previously reported.[142]



6
5.9 g / 54%

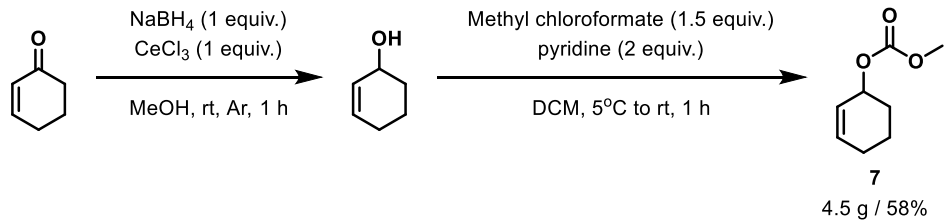
A 300 mL oven dried round bottom flask with stir bar was capped with a septum and cooled under vacuum and backfilled with argon. To the flask was added dry DCM (150 mL), then freshly distilled 3-methyl-2-buten-1-ol (6.46 g, 75 mmol, 7.6 mL, 1.0 equiv), pyridine (11.9 g, 150 mmol, 12.1 mL, 2 equiv.) and DMAP (900 mg, 7.5 mmol, 0.1 equiv). The flask was placed in an ice bath and stirred for 10 min before dropwise addition of methyl chloroformate (10.6 g, 112.5 mmol, 8.7 mL, 1.5 equiv). The flask was stirred for 10 min before removing from the ice bath and allowing to stir for 45 min while warming to rt. The reaction mixture was washed with 2 M HCl (3 x 100 mL), then brine, then dried over anhydrous $MgSO_4$, and the solvent removed via rotary evaporator. The crude product was purified by distillation (bp 110-120 ^oC at 100 torr) to give methyl (3-methylbut-2-en-1-yl) carbonate as a colorless oil (5.85 g / 54%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.23 (dddd, *J* = 7.3, 5.8, 2.9, 1.4 Hz, 1H), 4.47 (d, *J* = 7.3 Hz, 2H), 3.61 (s, 3H), 1.66 – 1.53 (m, 6H).

^{13}C NMR ($CDCl_3$,126 MHz): δ 155.6, 139.4, 118.1, 64.3, 64.3, 54.2, 54.2, 25.4, 25.4, 17.6, 17.6.

[142] Chun, S.; Chung, Y. K. *Org. Lett.* **2017**, *19*, 3787–3790.

Spectra matched those previously reported.[143]



To a 100 mL round bottom flask with stir bar was added 25 mL MeOH (dried over anhydrous Na_2SO_4, then briefly dried over molecular sieves), cyclohexen-1-one (4.90 g, 50.9 mmol, 1.0 equiv) and cerium(III) chloride (12.55 g, 50.9 mmol, 1.0 equiv), and the mixture was stirred for 10 min. Next, $NaBH_4$ was added portion wise over ~20 min, and the reaction mixture stirred at rt for 1 h, with small portions of MeOH added to rinse the sides of the flask periodically. The reaction was deemed complete by TLC (R_f = 0.35 with 30:70 Et_2O/hexanes) staining with vanillin. The reaction mixture was poured into 100 mL of water and extracted with Et_2O, the organic layer was separated and dried over anhydrous $MgSO_4$. Note: the reaction with methyl chloroformate was attempted in this Et_2O solution, but only a small amount of conversion was seen, whether this was due to the choice of solvent or residual methanol and or water is unclear. This failed reaction mixture was washed with HCl, then brine, dried over anhydrous $MgSO_4$ and the solvent removed via rotary evaporation to give crude product, taking care not to distill off the product. The crude product was transferred to a dry 250 mL round bottom flask with stir bar. To the flask was added 150 mL of dry DCM and pyridine (7.91 g, 100 mmol, 8.1 mL, 2 equiv). The flask

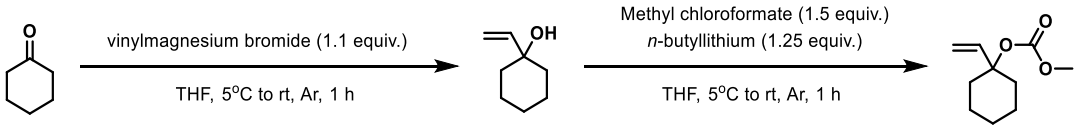
[143] Schlatzer, T.; Kriegesmann, J.; Schröder, H.; Trobe, M.; Lembacher-Fadum, C.; Santner, S.; Kravchuk, A. V.; Becker, C. F. W.; Breinbauer, R. *J. Am. Chem. Soc.* **2019**, *141*, 14931–14937.

was placed in an ice bath and stirred for 10 min before dropwise addition of methyl chloroformate (7.08 g, 75 mmol, 5.8 mL, 1.5 equiv). The flask was removed from the ice bath and stirred for 20 min, upon which time the reaction was deemed complete by TLC (R_f 0.60 with 30:70 EtOAc/hexanes), staining with vanillin. The reaction mixture was washed with 2 M HCl (2 x 100 mL), then brine, and dried over anhydrous Na_2SO_4, and the solvent removed via rotary evaporator. The crude product was purified by Kugelrohr distillation to give cyclohex-2-en-1-yl methyl carbonate as a colorless oil (4.5 g / 58%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.90 – 5.83 (m, 1H), 5.67 (ddt, *J* = 10.1, 4.2, 2.2 Hz, 1H), 5.01 (dt, *J* = 5.3, 1.7 Hz, 1H), 3.66 (s, 3H), 2.04 – 1.94 (m, 1H), 1.94 – 1.84 (m, 1H), 1.79 (dddd, *J* = 13.4, 8.3, 5.8, 2.5 Hz, 1H), 1.75 – 1.59 (m, 2H), 1.59 – 1.47 (m, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 155.5, 133.4, 125.0, 71.9, 54.5, 28.3, 24.9, 18.6.

Spectra matched those previously reported.[144]



8

5.8 g / 63%

An oven dried 250 mL round bottom flask with stir bar was capped with a septum and cooled under vacuum and backfilled with argon. To the flask was added 100 mL of dry THF and freshly distilled cyclohexanone (4.90 g, 50 mmol, 5.17 mL, 1.0 equiv). Note: this reaction was attempted with an "old" bottle of cyclohexanone, and significant amounts of

[144] Hatano, M.; Kamiya, S.; Ishihara, K. *Chem. Commun.* **2012**, *48*, 9465–9467.

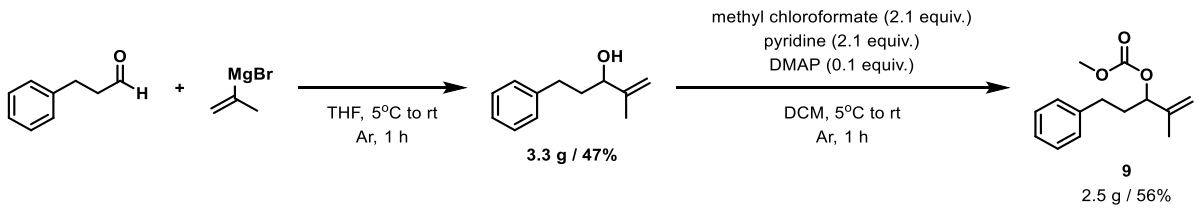
byproducts/decomposition products were noted, therefore we recommend distillation of any "old" samples of cyclohexanone prior to conducting this procedure. The flask was placed in an ice bath and stirred for 15 min before dropwise addition of a 1 M solution of vinylmagnesium bromide (55 mmol, 55 mL, 1.1 equiv). After stirring for 1 h, an aliquot was removed and the reaction deemed complete by TLC (R_f = 0.20 with 7:93 EtOAc/hexanes). Note: we previously attempted to react this magnesium alkoxide with methyl chloroformate as a 2-step, 1-pot reaction (to avoid working up the alcohol intermediate); this gave a mixture of products and was not successful. The reaction was quenched by the addition of water, and the resulting precipitate removed via filtration, rinsing the precipitate with Et_2O. The filtrate was concentrated by rotary evaporation, placed in a separatory funnel with brine solution and Et_2O and shaken vigorously. The Et_2O layer was dried over anhydrous $MgSO_4$ and filtered through a short plug of silica, and the solvent removed via rotary evaporation in a 250 mL round bottom flask (Note: removal of protic compounds is very important in this step, *n*-butyllithium will quench upon contact of water or unwanted alcohols. Drying with anhydrous $MgSO_4$, then filtration through silica is a simple removal of water, but not rigorous or complete). To this flask was added dry THF (100 mL), and a stir bar, and the flask placed in an ice bath. After stirring for 10 min, a 2.5 M solution *n*-butyllithium in hexanes (62.5 mmol, 25 mL, 1.25 equiv) was added. An aliquot was removed and reacted with *o*-phenanthroline in dry THF which failed to show full lithiation. An additional 5 mL of 2.5 M *n*-butyllithium was added to the reaction flask, and another aliquot removed, which reacted with *o*-phenanthroline to give a deep red color, indicating active alkyl lithium remaining in solution. Next, methyl chloroformate (7.09 g, 75 mmol, 5.8 mL, 1.5 equiv) was added dropwise to the reaction

flask. After stirring for 30 min, some allylic alcohol remained in the reaction mixture. An additional ~1 mL of methyl chloroformate was added to the reaction flask, and stirred for an additional 10 min, at which time the reaction was deemed complete via TLC (R_f = 0.60 with 7:93 EtOAc/hexanes). The reaction mixture was quenched with saturated NH_4Cl solution and the bulk of the solvent removed via rotary evaporation. The crude material was taken up in Et_2O and washed with saturated NH_4Cl, then brine, and dried over anhydrous Na_2SO_4. The solvent was removed via rotary evaporation and the product purified by column chromatography with 5:95 Et_2O/hexanes to give methyl (1-vinylcyclohexyl) carbonate as a colorless oil (5.8 g / 63%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.01 (ddq, *J* = 17.0, 11.0, 1.7 Hz, 1H), 5.21 – 5.09 (m, 2H), 3.64 (d, *J* = 2.8 Hz, 3H), 2.12 (dt, *J* = 8.0, 4.2 Hz, 2H), 1.59 – 1.44 (m, 7H), 1.30 – 1.18 (m, 1H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 153.8, 153.7, 141.1, 114.7, 114.6, 83.0, 83.0, 53.9, 53.9, 34.6, 34.6, 25.2, 21.8, 21.7.

Spectra matched those previously reported[145]



A 250 mL oven dried round bottom flask with stir bar was capped with a septum, cooled under vacuum, and backfilled with argon. To the flask was added 50 mL of dry THF and

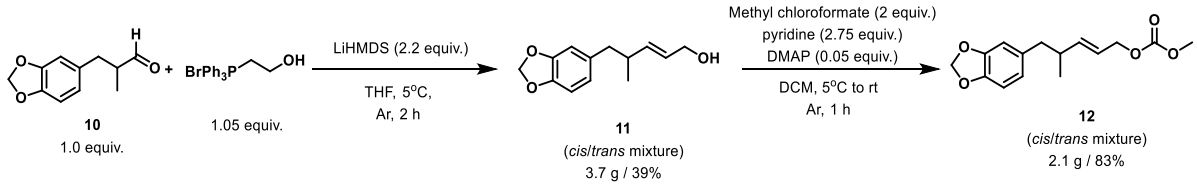
[145] Sun, M.; Chen, J.-F.; Chen, S.; Li, C. *Org. Lett.* **2019**, *21*, 1278–1282.

hydrocinnamaldehyde (5.37 g, 40 mmol, 5.27 mL, 1.0 equiv) and the flask placed in an ice bath. After stirring for 10 min, via dropwise addition was added a 0.5 M isopropenylmagnesium bromide in THF (50 mmol, 100 mL, 1.25 equiv). After stirring for 30 min, the reaction was deemed complete by TLC (R_f = 0.40 with 30:70 Et_2O/hexanes) staining with $KMnO_4$ and vanillin. The reaction was quenched with saturated NH_4Cl and extracted with Et_2O. The organic phase was washed with brine and dried over anhydrous $MgSO_4$ and the solvent removed via rotary evaporation. The crude product showed multiple products, visualized by vanillin and $KMnO_4$ stain. The crude product was purified by Kugelrohr distillation to give 2-methyl-5-phenylpent-1-en-3-ol as a colorless oil (3.3 g / 47%). To a dry 250 mL round bottom flask with stir bar was added 2-methyl-5-phenylpent-1-en-3-ol (3.3 g, 18.7 mmol, 1.0 equiv), pyridine (3.16 g, 40 mol, 3.2 mL, 2.1 equiv) and DMAP (220 mg, 1.8 mmol, 0.1 equiv.). The flask was placed in an ice bath and stirred for 10 min before dropwise addition of methyl chloroformate (3.77 g, 40 mmol, 3.09 mL, 2.1 equiv). The flask was removed from the ice bath after 10 min and allowed to warm to rt. After 1 h, the reaction was incomplete by TLC, an additional aliquot of methyl chloroformate (3.77 g, 40 mmol, 3.09 mL, 2.1 equiv) and pyridine (3.16 g, 40 mol, 3.2 mL, 2.1 equiv) were added to the reaction and stirred an additional 30 min, at which time the reaction was deemed complete by TLC (R_f 0.8 with 30:70 Et_2O/hexanes) staining with vanillin and $KMnO_4$. The organic phase was washed with 2 M HCl, then brine, and dried over anhydrous Na_2SO_4 and the solvent removed via rotary evaporation. The crude product was purified by column chromatography with hexanes then 7:1 Et_2O/hexanes to give methyl (2-methyl-5-phenylpent-1-en-3-yl) carbonate as a colorless oil (2.5 g / 56%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32 – 7.26 (m, 2H), 7.22 – 7.13 (m, 3H), 5.07 – 4.94 (m, 3H), 3.79 (s, 3H), 2.72 – 2.58 (m, 2H), 2.10 – 1.91 (m, 2H), 1.76 (dd, *J* = 1.5, 0.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 155.4, 142.6, 141.3, 128.6, 128.5, 126.2, 113.9, 81.2, 54.8, 34.5, 31.7, 17.9.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calculated for $C_{14}H_{18}O_3Na$ 257.1154; found 257.1154.



An oven dried 24/40 500 mL round bottom flask with stir bar was capped with a septum and cooled under vacuum and backfilled with argon. To the flask was added 100 mL of dry THF and (2-hydroxyethyl)-triphenylphosphonium bromide (17.45 g, 45 mmol, 1.05 equiv) and the flask placed in an ice bath for 10 min. In a separate dry flask, a solution of LiHMDS (15.8 g, 94.5 mmol, 2.2 equiv) was prepared in dry THF (20 mL). The LiHMDS solution was added to the Wittig salt dropwise over 10 min and the flask stirred for 1 h. To the reaction flask was added dropwise freshly distilled 2-methyl-3-(3,4-methylenedioxyphenyl)-propanal (8.22 g, 42.75 mmol, 1.0 equiv) (Note: this aldehyde is also known as helional, or ocean propanal in suppliers of perfuming ingredients) and the reaction was stirred for 2 h. The reaction was deemed complete by TLC (R_f 0.25 with 20:80 EtOAc/hexanes), staining with vanillin and $KMnO_4$, which also showed multiple other byproducts/impurities. The reaction was quenched with saturated NH_4Cl, and the resulting mixture filtered through Celite, rinsing the filter cake with Et_2O. The solvent was removed

from the filtrate via rotary evaporation and the crude product taken up in Et_2O, and the organic phase washed with saturated NH_4Cl, then brine, and dried over anhydrous Na_2SO_4. The organic phase was filtered through a short plug of silica, eluting with 50:50 EtOAc/hexanes, and the solvent removed via rotary evaporator. NMR of this product showed a highly impure mixture, so the product was further purified via column chromatography with 20:80 EtOAc/hexanes to 40:60 EtOAc/hexanes. 5-(benzo[d][1,3]dioxol-5-yl)-4-methylpent-2-en-1-ol was obtained as a colorless oil (3.7 g / 39%).

An oven dried 100 mL round bottom flask with stir bar was capped with a septum, cooled under vacuum and backfilled with argon. To the flask was added dry DCM (45 mL), 5-(benzo[d][1,3]dioxol-5-yl)-4-methylpent-2-en-1-ol (2.0 g, 9.08 mmol, 1.0 equiv), pyridine (1.98 g, 2.0 mL, 2.75 mL), and DMAP (53.4 mg, 53 mg, 0.05 equiv), the flask was placed in an ice bath and stirred for 10 min. Via syringe with dropwise addition was added methyl chloroformate (1.72 g, 18.2 mmol, 1.4 mL, 2.0 equiv) and the reaction stirred for 5 min before removing the flask from the ice bath and allowing to warm to rt. The reaction was stirred for 30 min, at which time the reaction was deemed complete by TLC (R_f = 0.50 with 20:80 EtOAc/hexanes), staining with vanillin. The reaction mixture was washed with 1 M HCl (3 x 50 mL), then brine, and the organic phase dried over anhydrous Na_2SO_4, and the solvent removed via rotary evaporator. The crude product was purified via column chromatography with hexanes then 15:85 EtOAc/hexanes to give 5-(benzo[d][1,3]dioxol-5-yl)-4-methylpent-2-en-1-yl methyl carbonate as a colorless oil (2.1 g / 83%).

Aldehyde (helional)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.69 (d, *J* = 1.6 Hz, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 6.65 (d, *J* = 1.8 Hz, 1H), 6.60 (dd, *J* = 7.9, 1.8 Hz, 1H), 5.91 (s, 2H), 2.98 (dd, *J* = 13.7, 6.1 Hz, 1H), 2.64 – 2.56 (m, 1H), 2.52 (dd, *J* = 13.7, 8.1 Hz, 1H), 1.07 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 204.5, 204.4, 147.8, 146.2, 132.6, 122.0, 109.4, 108.3, 101.0, 48.3, 36.5, 13.2.

Alcohol intermediate

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.71 (dd, *J* = 7.9, 1.4 Hz, 1H), 6.63 (d, *J* = 1.7 Hz, 1H), 6.57 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.91 (d, *J* = 0.7 Hz, 2H), 5.68 – 5.26 (m, 2H), 4.09 – 3.82 (m, 2H), 2.62 – 2.33 (m, 3H), 1.00 (dd, *J* = 18.0, 6.5 Hz, 3H).

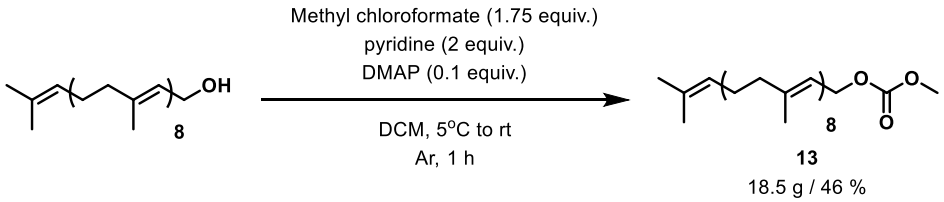
^{13}C NMR ($CDCl_3$, 126 MHz): δ 147.4, 145.6, 138.0, 137.8, 134.4, 127.7, 127.6, 122.0, 121.9, 109.6, 109.5, 107.9, 107.9, 100.8, 100.7, 63.8, 58.6, 43.5, 43.1, 38.1, 34.7, 21.1, 19.5.

Methyl carbonate product

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.70 (d, *J* = 7.9 Hz, 1H), 6.65 – 6.59 (m, 1H), 6.56 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.91 (d, *J* = 1.6 Hz, 2H), 5.79 – 5.43 (m, 2H), 4.58 – 4.33 (m, 2H), 3.76 (d, *J* = 10.9 Hz, 3H), 2.65 – 2.34 (m, 3H), 0.99 (dd, *J* = 11.4, 6.5 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 155.7, 147.5, 145.8, 141.9, 140.6, 134.2, 122.2, 122.1, 122.1, 122.0, 109.7, 109.6, 108.1, 108.0, 100.8, 68.7, 63.8, 54.8, 43.3, 42.9, 38.3, 34.9, 20.7, 19.3.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calculated for $C_{15}H_{18}O_5Na$ 301.1052; found 301.1054.

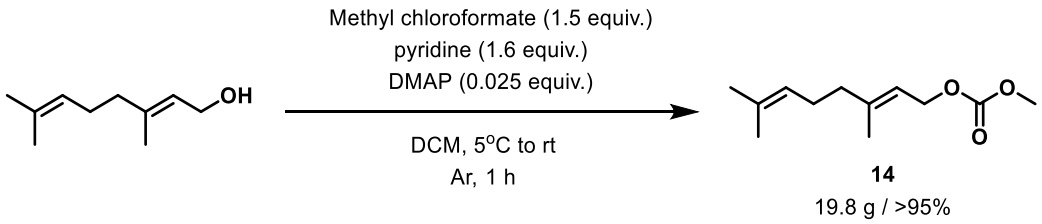


An oven dried 24/40 250 mL round bottom flask with stir bar was capped with a septum and cooled under vacuum and backfilled with argon. To the flask was added solanesol (~95% purity) (25.2 g, 40 mmol, 1.0 equiv.), dry DCM (100 mL) and the flask stirred for 20 min to dissolve. The flask was cooled in an ice bath and to the flask was added pyridine (6.32 g, 80 mmol, 6.43 mL, 2.0 equiv) and DMAP (488 mg, 4.0 mmol, 0.1 equiv). After stirring for 10 min, methyl chloroformate (6.62 g, 70 mmol, 5.4 mL, 1.75 equiv) was added dropwise via syringe. The flask was stirred 10 min before removing from the ice bath and stirring for 1 h, allowing to warm to rt. The reaction was deemed complete via TLC (R_f = 0.60 with 30:70 Et_2O/hexanes) staining with $KMnO_4$. The reaction mixture was washed with 2 M HCl (3 x 50 mL), then brine, and the organic layer dried over anhydrous Na_2SO_4 and the solvent removed via rotary evaporator. The crude product was purified by column chromatography with hexanes then 10:90 Et_2O/hexanes to give solanesyl methyl carbonate as a white solid (18.46 g / 46%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.41 – 5.35 (m, 1H), 5.16 – 5.07 (m, 8H), 4.65 (d, *J* = 7.2 Hz, 2H), 3.76 (s, 3H), 2.08 (q, *J* = 7.1 Hz, 18H), 1.98 (dd, *J* = 9.2, 5.9 Hz, 14H), 1.72 (d, *J* = 1.3 Hz, 3H), 1.68 (d, *J* = 1.5 Hz, 3H), 1.60 (d, *J* = 1.7 Hz, 24H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 155.9, 143.1, 135.5, 134.9, 134.9, 134.8, 134.8, 134.8, 134.8, 131.1, 124.4, 124.3, 124.3, 124.3, 124.2, 123.5, 117.8, 64.7, 54.5, 39.8, 39.7, 39.7, 39.7, 39.5, 29.7, 26.8, 26.7, 26.7, 26.7, 26.2, 25.7, 17.7, 16.5, 16.0, 16.0, 16.0.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{47}H_{76}O_3Na$ 711.5692; found 711.5695.

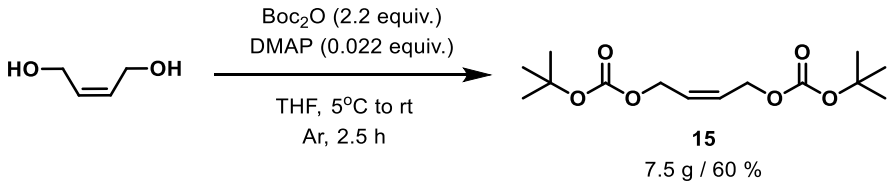


An oven dried 500 mL round bottom flask with stir bar was capped with a septum, cooled under vacuum, and backfilled with argon. To the flask was added dry DCM (250 mL), freshly distilled geraniol (14.53 g, 94.2 mmol, 16.3 mL, 1.0 equiv), pyridine (11.9 g, 150 mmol, 12.1 mL, 1.6 equiv) and DMAP (287 mg, 2.35 mmol, 0.025 equiv). The flask was placed in an ice bath and stirred for 15 min before adding methyl chloroformate (13.4 g, 141 mmol, 10.9 mL, 1.5 equiv) dropwise via syringe. The reaction was stirred for 10 min before removing from the ice bath and allowing to warm to rt. After stirring for 1 h, the reaction was deemed complete by TLC (R_f = 0.60 with 20:80 Et_2O/hexanes), staining with vanillin and $KMnO_4$. The reaction mixture was washed with 2 M HCl (3 x 100 mL), then brine, and the organic phase dried over anhydrous Na_2SO_4 and the solvent removed via rotary evaporation. The product was dissolved in Et_2O and filtered through a 6" x 1.5" column of silica, eluting with 10:90 EtOAc/hexanes. The solvent was removed via rotary evaporator and the product dried under vacuum to give (*E*)-3,7-dimethylocta-2,6-dien-1-yl methyl carbonate as a colorless oil (19.8 g / >95%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.38 – 5.29 (m, 1H), 5.03 (tt, *J* = 5.2, 2.5 Hz, 1H), 4.60 (d, *J* = 7.3 Hz, 2H), 3.72 (s, 3H), 2.09 – 1.97 (m, 4H), 1.67 (d, *J* = 1.8 Hz, 3H), 1.63 (d, *J* = 2.3 Hz, 3H), 1.55 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 155.9, 143.1, 131.8, 123.7, 117.8, 64.6, 54.6, 39.5, 26.2, 25.6, 17.6, 16.4.

Spectra matched those previously reported.[146]



15
7.5 g / 60 %

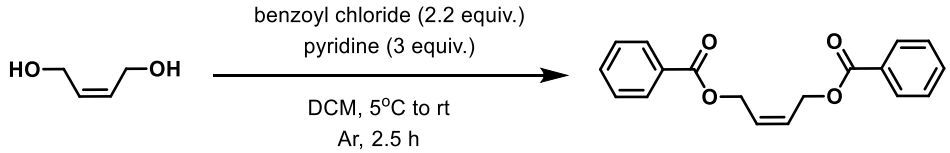
A 250 mL round bottom flask with stir bar was capped with a septum cooled under vacuum, and backfilled with argon. To the flask was added Boc_2O (20.8 g, 95.4 mmol, 2.2 equiv) and dry THF (75 mL). The flask was placed in an ice bath and stirred for 10 min before adding DMAP (117 mg, 0.954 mmol, 0.022 equiv), and (*Z*)-but-2-ene-1,4-diol (3.82 g, 43.4 mmol, 1.0 equiv) dropwise via syringe over ~10 min. The reaction mixture was stirred for 15 min before removing from the ice bath and allowing to warm to rt. After stirring for 2.5 h, the reaction was deemed complete by TLC (R_f = 0.70 with 20:80 EtOAc/hexanes), staining with vanillin and $KMnO_4$. The reaction mixture was washed with 1 M HCl, then 1 M KOH, then brine. The organic layer was dried over anhydrous Na_2SO_4 and the solvent removed via rotary evaporator. The crude product was purified by column chromatography with hexanes then 10:90 Et_2O/hexanes to give (*Z*)-but-2-ene-1,4-diyl di-*t*-butyl bis(carbonate) as a colorless oil (7.5 g / 60%).

[146] Schlatzer, T.; Kriegesmann, J.; Schröder, H.; Trobe, M.; Lembacher-Fadum, C.; Santner, S.; Kravchuk, A. V.; Becker, C. F. W.; Breinbauer, R. *J. Am. Chem. Soc.* **2019**, *141*, 14931–14937.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.76 (ddd, *J* = 5.2, 4.0, 1.2 Hz, 2H), 4.68 – 4.60 (m, 4H), 1.46 (s, 18H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 153.3, 128.1, 82.4, 62.4, 27.8.

Spectra matched those previously reported.[147]



16
10.1 g / 67%

An oven dried 250 mL round bottom flask with stir bar was capped with a septum, cooled under vacuum and backfilled with argon. To the flask was added dry DCM (150 mL), cis-2-butenediol (4.47 g, 50.7 mmol, 1.0 equiv) and pyridine (11.87 g, 150 mmol, 12.1 mL, 3.0 equiv). The flask was placed in an ice bath and stirred for 15 min before dropwise addition of benzoyl chloride (15.7 g, 111.5 mmol, 13.0 mL, 2.2 equiv). The reaction was stirred for 10 min before removing the flask from the ice bath and allowing it to warm to rt. After stirring for 2.5 h, the reaction was deemed complete by TLC (R_f = 0.60 with 1:3 EtOAc/hexanes), showing full consumption of the diol and some benzoyl chloride remaining. To the flask was added ~2 mL of *N*,*N*-dimethylethanolamine, and the reaction stirred for an additional 10 min, at which point TLC showed disappearance of benzoyl chloride. The reaction mixture was washed with 2 M HCl (3 x 100 mL), then brine, and the organic phase dried over anhydrous Na_2SO_4 and the solvent removed via rotary evaporator.

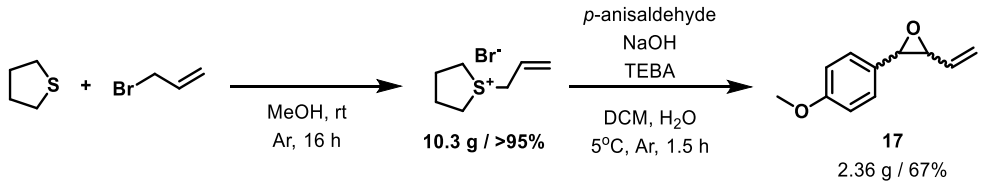
[147] Hassan, A.; Zbieg, J. R.; Krische, M. J. *Angew. Chem., Int. Ed.* **2011**, *50*, 3493–3496.

The crude product was recrystallized from hot hexanes to give (*Z*)-but-2-ene-1,4-diyl dibenzoate as flaky white crystals (10.1 g / 67%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.11 – 8.02 (m, 4H), 7.58 – 7.52 (m, 2H), 7.43 (t, *J* = 7.7 Hz, 4H), 5.99 – 5.90 (m, 2H), 5.01 (d, *J* = 4.5 Hz, 4H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 166.3, 133.1, 130.0, 129.7, 128.4, 128.4, 60.6.

Spectra matched those previously reported.[148]



To a 50 mL round bottom flask with stir bar was added 15 mL of MeOH (dried over anhydrous Na_2SO_4 and briefly dried over molecular sieves). Via syringe was added allyl bromide (6.05 g, 50 mmol, 4.32 mL, 1.0 equiv) and tetrahydrothiophene (5.3 g, 5.3 mL, 60 mmol, 1.2 equiv) and the reaction mixture stirred overnight at rt. The solvent was removed via rotary evaporator and the product dried under vacuum to give 1-allyl-tetrahydrothiophenium bromide as an off white solid (10.3 g / >95%). (Note: tetrahydrothiophene has an extremely unpleasant and strong odor, the waste should be segregated and stored in a fume hood until disposal.)

A 250 mL round bottom flask with a large stir bar (Note: the reaction mixture becomes viscous, efficient stirring is very important) was placed in an ice bath and 40 mL of DCM

[148] Belger, C.; Neisius, N. M.; Plietker, B. *Chem. Eur. J.* **2010**, *16*, 12214–12220.

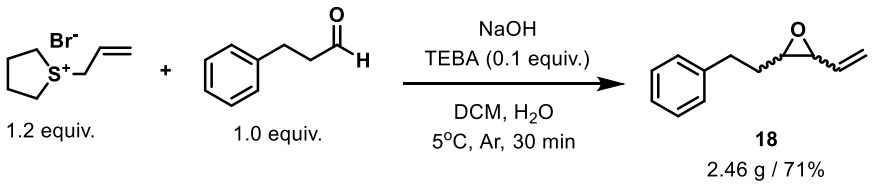
was added with no special precautions against air or moisture. With stirring, was added sequentially benzyltriethylammonium chloride (453 mg, 1.99 mmol, 0.1 equiv), 1-allyl-tetrahydrothiophenium bromide (5.0 g, 23.9 mmol, 1.20 equiv), and *p*-anisaldehyde (2.71 g, 19.9 mmol, 2.42 mL, 1.0 equiv). The flask was capped with a septum and briefly evacuated/backfilled with argon 3x, taking care not to evaporate a significant amount of DCM, then a vent needle was placed through the septum of the flask. In a 100 mL beaker with a stir bar, 31 mL of a 10 M NaOH solution was prepared, and this solution cooled in an ice bath with stirring. Once cold, this NaOH solution was added to the reaction flask over ~5 min while vigorously stirring the reaction flask. After stirring the reaction for 1.5 h, the reaction was deemed complete by TLC (R_f = 0.70 with 3:7 EtOAc/hexanes) staining with $KMnO_4$. While keeping the reaction flask in the ice bath in case of exotherm and with vigorous stirring, the reaction mixture was diluted with water (100 mL). The reaction mixture was then poured into a separatory funnel and extracted with DCM, the organic phase washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed via rotary evaporator and the crude product purified by column chromatography with hexanes then 10:90 EtOAc/hexanes. Note: it is helpful to pack the column with EtOAc and then hexanes, as packing the column with only hexanes caused some decomposition of the vinyl epoxide product during chromatography. 2-(4-Methoxyphenyl)-3-vinyloxirane was obtained as pale-yellow oil (2.36 g / 67%), this material should be stored in the freezer as it slowly decomposes over time, becoming a darker yellow oil.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30 – 7.17 (m, 4H), 6.89 (dd, *J* = 8.9, 2.3 Hz, 4H), 5.73 (ddd, *J* = 17.6, 10.4, 7.4 Hz, 1H), 5.58 – 5.48 (m, 2H), 5.48 – 5.38 (m, 1H), 5.38 – 5.23 (m,

2H), 4.19 (d, *J* = 4.2 Hz, 1H), 3.79 (d, *J* = 0.5 Hz, 6H), 3.72 (d, *J* = 2.0 Hz, 1H), 3.62 (dd, *J* = 8.1, 4.2 Hz, 1H), 3.36 (dd, *J* = 7.4, 2.0 Hz, 1H). (mixture of diastereomers).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 159.7, 159.2, 135.3, 132.3, 129.0, 127.6, 127.1, 126.8, 121.7, 119.3, 114.0, 113.6, 62.7, 60.1, 59.9, 58.6, 55.3, 55.2. (mixture of diastereomers).

Spectra matched those previously reported.[149]



A 250 mL round bottom flask with a large stir bar (Note: the reaction mixture becomes viscous, efficient stirring is very important) was placed in an ice bath and 40 mL of DCM was added with no special precautions against air or moisture. With stirring, was added sequentially benzyltriethylammonium chloride (455 mg, 2.0 mmol, 0.1 equiv), 1-allyl-tetrahydrothiophenium bromide (5.0 g, 23.9 mmol, 1.20 equiv), and hydrocinnamaldehyde (2.68 g, 20.0 mmol, 2.66 mL, 1.0 equiv). The flask was capped with a septum and briefly evacuated/backfilled with argon 3x, taking care not to evaporate a significant amount of DCM, then a vent needle was placed through the septum of the flask. In 100 mL beaker with stir bar, 31 mL of a 10 M NaOH solution was prepared, and this solution cooled in an ice bath with stirring. Once cold, this NaOH solution was added to the reaction flask over ~5 min while vigorously stirring the reaction flask. After stirring the reaction for 1.5 h, the reaction was deemed complete by TLC (R_f = 0.70 with 3:7 E_2O/hexanes) staining with

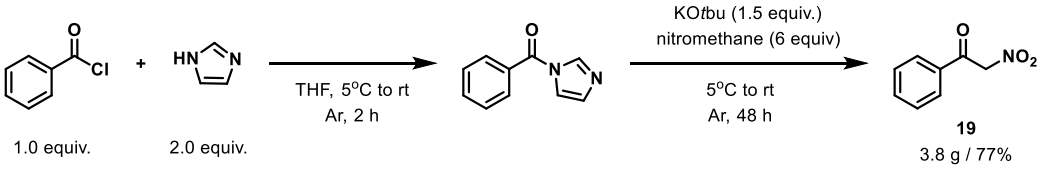
[149] Aubineau, T.; Cossy, J. *Org. Lett.* **2018**, *20*, 7419–7423.

vanillin and $KMnO_4$. While keeping the reaction flask in the ice bath in case of exotherm and with vigorous stirring, the reaction mixture was diluted with water (100 mL). The reaction mixture was then poured into a separatory funnel and extracted with DCM, the organic phase washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed via rotary evaporator and the crude product purified by column chromatography with hexanes then 10:90 EtOAc/hexanes. Note: it is helpful to pack the column with EtOAc and then hexanes, as packing the column with only hexanes caused some decomposition of the vinyl epoxide product during chromatography. 2-Phenethyl-3-vinyloxirane was obtained as colorless oil (2.46 g / 71%), this material should be stored in the freezer as it slowly decomposes over time.

^{1}H NMR ($CDCl_3$, 500 MHz): 7.38 – 7.31 (m, 2H), 7.28 – 7.22 (m, 3H), 5.67 (dddd, *J* = 65.2, 17.6, 10.4, 7.3 Hz, 1H), 5.54 – 5.25 (m, 2H), 3.48 – 3.14 (m, 1H), 3.11 (dd, *J* = 7.5, 2.1 Hz, 1H), 2.93 – 2.83 (m, 2H), 2.79 (dt, *J* = 13.8, 7.7 Hz, 1H), 2.02 – 1.82 (m, 2H) (mixture of diastereomers).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 141.2, 135.7, 132.4, 128.5, 128.5, 128.4, 128.4, 126.1, 120.3, 119.0, 59.7, 58.9, 58.1, 57.2, 33.8, 32.5, 32.2, 29.6 (mixture of diastereomers).

Spectra matched those previously reported.[150]



[150] Aubineau, T.; Cossy, J. *Org. Lett.* **2018**, *20*, 7419–7423.

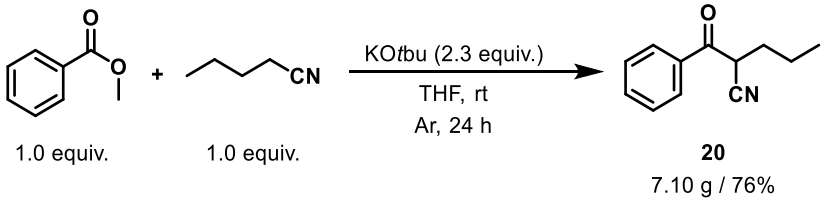
An oven dried 250 mL round bottom flask with stir bar was capped with a septum, cooled under vacuum and backfilled with argon. To the flask was added dry THF (100 mL) and imidazole (4.10 g, 60 mmol, 2.0 equiv). The flask was placed in an ice bath and stirred for 10 min before dropwise addition of benzoyl chloride (4.22 g, 30 mmol, 3.5 mL, 1.0 equiv). The flask was removed from the ice bath and stirred for 2 h before filtering the reaction mixture, rinsing with Et_2O. The solvent was removed from the filtrate to give (1H-imidazol-1-yl)(phenyl)methanone as an oil.

A 250 mL oven dried round bottom flask with stir bar was brought into an argon filled glove box and to it was added KO-*t*-Bu (5.05 g, 45 mmol, 1.5 equiv). The flask was removed from the glovebox and to the flask was added dry THF (60 mL) and the flask placed in an ice bath. After stirring for 10 min, via syringe was added nitromethane (10.9 g, 180 mmol, 9.8 mL, 6 equiv), the reaction became very viscous and an additional 15 mL of THF was added. The flask was removed from the ice bath and stirred for 1 h while allowing to warm to rt. The flask was placed back in the ice bath and stirred for 10 min before adding (1H-imidazol-1-yl)(phenyl)methanone from the previous step as a solution in THF (50 mL). After 30 min, the flask was removed from the ice bath and allowed to stir for 48 h, upon which time the reaction was deemed complete by TLC (R_f = 0.60 with 50:50 EtOAc/hexanes). The crude product was isolated by filtration, the filter cake rinsed with DCM. The filter cake was dissolved in water, acidified with HCl and extracted with DCM. The organic phase was dried over anhydrous Na_2SO_4 and filtered through a short plug of silica gel. The solvent was removed via rotary evaporation and the product dried under vacuum to give 2-nitro-1-phenylethan-1-one as a white solid crystalline solid (3.8 g / 77%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.90 – 7.84 (m, 2H), 7.72 – 7.65 (m, 1H), 7.58 – 7.50 (m, 2H), 5.91 (s, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 186.0, 135.2, 133.5, 129.4, 128.4, 81.5.

Spectra matched those previously reported.[151]



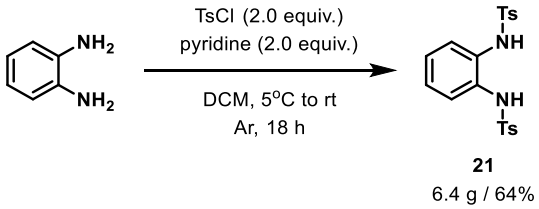
An oven dried 500 mL round bottom flask with a large stir bar was capped with a septum, cooled under vacuum and backfilled with argon. The flask was brought into an argon filled glovebox and KO-*t*-Bu (13.0 g, 116 mmol, 2.3 equiv) was added to the flask and the flask capped with a septum and removed from the glovebox. To the flask was added dry THF (175 mL) and stirred for 5 min before addition of valeronitrile (4.16 g, 50 mmol, 1.0 equiv). The flask was stirred for 10 min at rt before dropwise addition of methyl benzoate (7.49 g, 50 mmol, 1.0 equiv) dropwise via syringe. The reaction was stirred for 24 h at rt upon which time the reaction was deemed complete by TLC (R_f = 0.60 with 20:80 EtOAc/hexanes). The reaction mixture was poured into 1 M HCl (250 mL) and extracted with Et_2O. The organic phase was washed with brine, dried with anhydrous Na_2SO_4 and the solvent removed via rotary evaporator. The crude product was purified by column chromatography with 20:80 EtOAc/hexanes to give 2-benzoylpentanenitrile as a pale-yellow oil (9.36 g / 76%).

[151] Nguyen, H. H.; Kurth, M. J. *Org. Lett.* **2013**, *15*, 362–365.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.96 – 7.90 (m, 2H), 7.61 (td, *J* = 7.4, 1.4 Hz, 1H), 7.48 (t, *J* = 7.9 Hz, 2H), 4.40 (dd, *J* = 8.1, 6.1 Hz, 1H), 2.00 – 1.88 (m, 2H), 1.66 – 1.46 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 191.1, 134.4, 133.9, 129.1, 128.7, 117.5, 39.9, 31.9, 20.4, 13.4.

Spectra matched those previously reported.[152]



21
6.4 g / 64%

An oven dried 250 mL round bottom flask with stir bar was capped with a septum, cooled under vacuum and backfilled with argon. To the flask was added dry DCM (150 mL), *o*-phenylenediamine (2.59 g, 24.0 mmol, 1.0 equiv) and pyridine (3.80 g, 48.0 mmol, 2 equiv), and the flask placed in an ice bath. The flask was stirred for 15 min before addition of tosyl chloride (9.15 g, 48.0 g, 2 equiv) portion wise over 10 min. The flask was stirred for 15 min before removing from the ice bath, and allowed to warm to rt and stirred overnight (18 h). The reaction mixture was reduced to ~75 mL total volume via rotary evaporation, then diluted with water. After stirring for ~10 min the crude product precipitated as a paste, which was recovered via vacuum filtration, the filter cake rinsed with hexanes and dried under vacuum. The crude product was purified by recrystallization

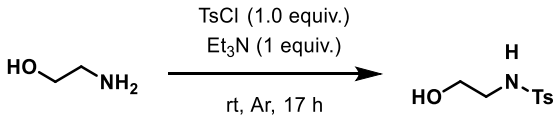
[152] Wang, X.; Studer, A. *J. Am. Chem. Soc.* **2016**, *138*, 2977–2980.

from hot EtOH (~200 mL) to give *N,N'*-(1,2-phenylene)bis(4-methylbenzenesulfonamide) as light purple needles (6.4 g / 64%).

^{1}H NMR (DMSO-d_6, 500 MHz): δ 9.28 (s, 2H), 7.65 – 7.55 (m, 4H), 7.33 (d, *J* = 8.1 Hz, 4H), 7.04 – 6.93 (m, 4H), 2.34 (s, 6H).

^{13}C NMR (DMSO-d_6,126 MHz): δ 143.7, 136.1, 129.7, 129.7, 126.9, 125.9, 123.4, 21.0.

Spectra matched those previously reported.[153]



22
4.4 g / 68%

A 100 mL round bottom flask with stir bar was capped with a septum, cooled under vacuum and backfilled with argon. To the flask was added DCM (50 mL), freshly distilled ethanolamine (1.83 g, 30 mmol, 1.0 equiv) and with stirring was added tosyl chloride (5.72 g, 30 mmol, 1.0 equiv), then Et_3N (3.03 g, 30 mmol, 4.2 mL, 1.0 equiv). The reaction was stirred at rt for 17 h, upon which time the reaction was deemed complete by TLC (R_f = 0.50 with EtOAc). The organic layer was washed with water, then 2 M HCl, then brine, the organic phase dried over anhydrous $MgSO_4$ and the solvent removed via rotary evaporation. Due to the presence of some residual ethanolamine, the crude product was taken up in EtOAc and filtered through a short plug of silica, eluting with 50:50 EtOAc/hexanes. The solvent was removed via rotary evaporation and the product dried

[153] Ramadoss, V.; Alonso-Castro, A. J.; Campos-Xolalpa, N.; Ortiz-Alvarado, R.; Yahuaca-Juárez, B.; Solorio-Alvarado, C. R. *RSC Adv.* **2018**, *8*, 30761–30776.

under vacuum to give *N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide as a white solid (4.4 g / 68 %).

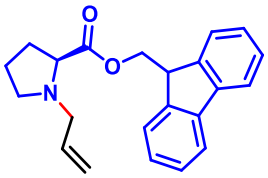
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.74 (d, *J* = 7.9 Hz, 2H), 7.28 (d, *J* = 7.9 Hz, 2H), 5.67 (s, 1H), 3.65 (q, *J* = 4.6 Hz, 2H), 3.03 (p, *J* = 6.8, 5.7 Hz, 3H), 2.40 (s, 3H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 143.67, 136.65, 129.88, 127.19, 61.32, 45.32, 21.60.

Spectra matched those previously reported.[154]

4.14.4 Substrate Scope Characterization Data

(9H-Fluoren-9-yl)methyl allyl-L-prolinate (1a)



The titled compound was obtained according to the procedure in Section 2.2 using the following quantities: (9H-fluoren-9-yl)methyl L-prolinate trifluoroacetate (100.0 mg, 0.25 mmol, 1.0 equiv), allyl acetate (36.0 mg, 0.36 mmol, 38.8 μL, 1.5 equiv), K_2CO_3 (69 mg, 0.5 mmol, 2.0 equiv), 2 wt % TPGS-750-M / H_2O (0.5 mL), 2000 ppm Pd (40 μL of stock solution from Section 4.15). The desired compound was obtained as a colorless oil (62.5 mg / 75%).

TLC: R_f = 0.30 with 20:80 EtOAc/hexanes, UV active, stains with $KMnO_4$.

[154] Aubineau, T.; Cossy, J. *Org. Lett.* **2018**, *20*, 7419–7423.

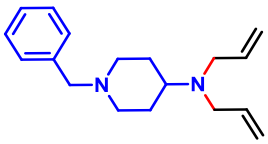
Flash Column chromatography: hexanes then 20:80 EtOAc/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.76 (dt, *J* = 7.6, 0.9 Hz, 2H), 7.61 (dt, *J* = 7.5, 1.0 Hz, 2H), 7.40 (td, *J* = 7.5, 1.0 Hz, 2H), 7.32 (tdd, *J* = 7.4, 2.2, 1.2 Hz, 2H), 5.94 – 5.84 (m, 1H), 5.15 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.07 (ddt, *J* = 10.1, 2.1, 1.1 Hz, 1H), 4.55 – 4.44 (m, 2H), 4.22 (t, *J* = 6.7 Hz, 1H), 3.27 (ddt, *J* = 13.2, 6.3, 1.4 Hz, 1H), 3.23 (dd, *J* = 9.0, 5.5 Hz, 1H), 3.10 – 3.03 (m, 2H), 2.40 (dt, *J* = 9.2, 8.0 Hz, 1H), 2.09 (tt, *J* = 7.9, 3.9 Hz, 1H), 1.89 – 1.81 (m, 2H), 1.81 – 1.73 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 174.2, 143.8, 143.7, 141.4, 141.3, 135.4, 127.7, 127.1, 127.1, 127.0, 125.0, 120.0, 117.3, 66.0, 64.9, 57.4, 53.2, 46.9, 29.4, 23.1.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calculated for $C_{23}H_{23}NO_2$ 334.1807; found 334.1801.

***N,N*-Diallyl-1-benzylpiperidin-4-amine (1b)**



The titled compound was obtained according to the procedure in Section 2.2 using the following quantities: 4-amino-1-benzylpiperidine (95.2 mg, 0.5 mmol, 102.0 µL, 1.0 equiv), allyl acetate (110.0 mg 1.1 mmol, 118.5 µL, 2.2 equiv.), K_2CO_3 (104 mg, 0.75 mmol, 1.5 equiv.), 2 wt % TPGS-750-M / H_2O (0.5 mL), 1000 ppm Pd (20 µL of stock solution from section 4.15). The desired compound was obtained as a pale-yellow oil which blackens upon exposure to air (117.6 mg / 87%).

TLC: R_f = 0.30 with 10:90 MeOH/DCM, faintly UV active, stains with I_2 and $KMnO_4$.

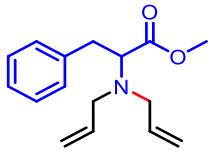
Flash Column chromatography: DCM then 10:90 MeOH/DCM.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30 (d, *J* = 4.4 Hz, 4H), 7.27 – 7.21 (m, 1H), 5.83 (ddt, *J* = 16.6, 10.1, 6.3 Hz, 2H), 5.15 (dq, *J* = 17.2, 1.7 Hz, 2H), 5.08 (dq, *J* = 10.1, 1.4 Hz, 2H), 3.48 (s, 2H), 3.14 (dt, *J* = 6.3, 1.5 Hz, 4H), 2.93 (dt, *J* = 11.3, 2.1 Hz, 2H), 2.56 (tt, *J* = 11.6, 3.9 Hz, 1H), 1.94 (td, *J* = 11.8, 2.5 Hz, 2H), 1.73 – 1.65 (m, 2H), 1.58 (qd, *J* = 12.1, 3.8 Hz, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 138.5, 137.3, 129.2, 128.2, 127.0, 116.5, 63.1, 57.6, 53.5, 53.0, 28.2.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calculated for $C_{18}H_{27}N_2$ 271.2174; found 271.2173.

Methyl diallylphenylalaninate (1c)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: phenylalanine methyl ester hydrochloride (100.0 mg, 0.46 mmol, 1.0 equiv), allyl acetate (69.0 mg, 0.69 mmol, 74.4 µL, 1.5 equiv), K_2CO_3 (127.1 mg, 0.92 mmol, 2.0 equiv), 2 wt % TPGS-750-M / H_2O (0.5 mL), 2000 ppm Pd (40 µL of stock solution from Section 4.15). The desired compound was obtained as a colorless oil (62.6 mg / 70% using allyl acetate as limiting reagent).

TLC: R_f = 0.50 with 10:90 EtOAc/hexanes, UV active, stains with $KMnO_4$.

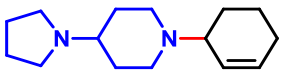
Flash Column chromatography: hexanes then 10:90 EtOAc/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.28 – 7.22 (m, 2H), 7.21 – 7.12 (m, 3H), 5.68 (dddd, *J* = 17.3, 10.1, 7.3, 5.1 Hz, 2H), 5.14 (dq, *J* = 17.2, 1.7 Hz, 2H), 5.07 (dq, *J* = 10.2, 1.5 Hz, 2H), 3.71 (dd, *J* = 8.1, 7.1 Hz, 1H), 3.62 (s, 3H), 3.37 (ddt, *J* = 14.5, 5.1, 1.8 Hz, 2H), 3.12 – 3.07 (m, 2H), 3.07 – 2.86 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.1, 138.6, 136.4, 136.4, 136.4, 129.4, 128.3, 126.3, 117.3, 117.3, 63.9, 53.7, 53.6, 51.2, 51.2, 35.8.

Spectra matched that previously reported.[155]

1-(Cyclohex-2-en-1-yl)-4-(pyrrolidin-1-yl)piperidine (1d)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: 4-(1-pyrrolidinyl)piperidine (77.1 mg, 0.5 mmol, 1.0 equiv), cyclohex-2-en-1-yl methyl carbonate (93.7 mg 0.6 mmol, 88.6 µL, 1.2 equiv), K_2CO_3 (104 mg, 0.75 mmol, 1.5 equiv), methyl formate (30.0 mg, 0.5 mmol, 31 µL, 1.0 equiv), 2 wt % TPGS-750-M / H_2O (0.5 mL), 1000 ppm Pd (20 µL of stock solution from Section 4.15). The desired compound was obtained as a white semi-solid (93.5 mg / 80%).

TLC: R_f = 0.50 with 20:80 MeOH/DCM w/ a drop of Et_3N, stains with I_2 and $KMnO_4$.

[155] Yang, Q.; Xiao, W.-J.; Yu, Z. *Org. Lett.* **2005**, *7*, 871–874.

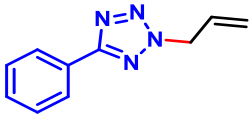
Flash Column chromatography: DCM then 10:90 MeOH/DCM then 15:83:2 MeOH/DCM/Et_3N.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.68 (dt, *J* = 10.1, 3.2 Hz, 1H), 5.58 – 5.48 (m, 1H), 3.18 – 3.08 (m, 1H), 2.81 – 2.70 (m, 2H), 2.54 (td, *J* = 6.3, 5.2, 2.6 Hz, 4H), 2.29 (td, *J* = 11.6, 2.6 Hz, 1H), 2.16 (td, *J* = 11.6, 2.5 Hz, 1H), 2.01 (ddd, *J* = 10.8, 6.9, 3.8 Hz, 1H), 1.83 (dddd, *J* = 25.2, 12.2, 5.7, 2.9 Hz, 4H), 1.75 – 1.62 (m, 6H), 1.56 – 1.36 (m, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 129.7, 129.6, 62.0, 60.2, 51.0, 48.6, 46.5, 31.1, 31.1, 25.2, 23.2, 22.6, 21.5.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calculated for $C_{15}H_{27}N_2$ 235.2174; found 235.2172

2-Allyl-5-phenyl-2H-tetrazole (1e)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: 5-phenyl-1-H-tetrazole (73.1 mg, 0.5 mmol, 1.0 equiv), allyl methyl carbonate (63.9 mg 0.55 mmol, 62.5 μL, 1.1 equiv), K_2CO_3 (104 mg, 0.75 mmol, 1.5 equiv), 2 wt % TPGS-750-M / H_2O (0.5 mL), 1000 ppm Pd (20 μL of stock solution from Section 4.15). The desired compound was obtained as a colorless oil (89 mg / 96%).

TLC: R_f = 0.50 with 30:70 Et_2O/hexanes, UV active.

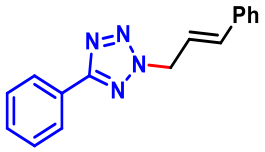
Flash Column chromatography: 20:80 Et_2O/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.14 (ddp, *J* = 6.8, 2.8, 1.3 Hz, 2H), 7.46 (dddd, *J* = 7.0, 5.6, 4.6, 1.3 Hz, 3H), 6.19 – 6.04 (m, 1H), 5.39 (dq, *J* = 3.1, 1.4 Hz, 1H), 5.37 (dq, *J* = 7.3, 1.3 Hz, 1H), 5.23 (ddq, *J* = 5.7, 2.9, 1.4 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3, 130.4, 130.0, 128.9, 127.4, 126.9, 120.9, 55.4.

Spectra matched that previously reported.[156]

2-Cinnamyl-5-phenyl-2H-tetrazole (1f)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: 5-phenyl-1-H-tetrazole (73.1 mg, 0.5 mmol, 1.0 equiv), cinnamyl methyl carbonate (105.7 mg 0.55 mmol, 95.3 µL, 1.1 equiv), K_2CO_3 (104 mg, 0.75 mmol, 1.5 equiv), 2 wt % TPGS-750-M / H_2O (0.5 mL), 1000 ppm Pd (20 µL of stock solution from Section 4.15). The desired compound was obtained as a white solid (mp = 65 ºC) (113.2 mg / 86%).

TLC: R_f = 0.25 with 10:90 Et_2O/hexanes, UV active.

Flash Column chromatography: 10:90 Et_2O/hexanes. Alternatively, the reaction mixture can be filtered and the filter cake recrystallized from hot EtOAc and flooded with hexanes to give white needles.

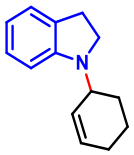
[156] Jia, Y.-H.; Yang, K.-X.; Chen, S.-L.; Huang, M.-H. *J. Phys. Chem. A* **2018**, *122*, 8–15.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.25 – 8.17 (m, 2H), 7.55 – 7.46 (m, 3H), 7.45 – 7.39 (m, 2H), 7.39 – 7.27 (m, 3H), 6.78 (dt, *J* = 15.8, 1.4 Hz, 1H), 6.47 (dt, *J* = 15.8, 6.7 Hz, 1H), 5.42 (dt, *J* = 6.7, 1.9 Hz, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz) δ 165.4, 136.1, 135.5, 130.4, 128.9, 128.8, 128.6, 127.5, 126.9, 126.9, 126.9, 120.7, 55.2.

HRMS (ESI-TOF) *m/z*: $[M + Na + CH_3OH]^+$ calculated for $C_{17}H_{18}N_4ONa$ 317.1378; found 213.1376.

1-(Cyclohex-2-en-1-yl)indoline (1g)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: indoline (59.6 mg, 0.5 mmol, 56.2 µL, 1.0 equiv), cyclohex-2-en-1-yl methyl carbonate (93.7 mg 0.6 mmol, 88.6 µL, 1.2 equiv), K_2CO_3 (104 mg, 0.75 mmol, 1.5 equiv.), methyl formate (30.0 mg, 0.5 mmol, 31 µL, 1.0 equiv), 2 wt % TPGS-750-M / H_2O (0.5 mL), 1000 ppm Pd (20 µL of stock solution from Section 4.15). The desired compound was obtained as a colorless oil which blackens upon exposure to air (93 mg / 93%).

TLC: R_f = 0.60 with 20:80 Et_2O/hexanes, UV active, stains with Seebach's magic stain.

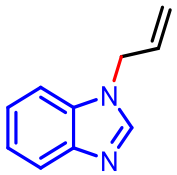
Flash Column chromatography: hexanes then 10:90 Et_2O/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.17 – 7.05 (m, 2H), 6.69 (td, *J* = 7.3, 1.0 Hz, 1H), 6.56 (d, *J* = 7.8 Hz, 1H), 6.02 – 5.91 (m, 1H), 5.71 (ddt, *J* = 10.1, 3.3, 2.2 Hz, 1H), 4.24 (dq, *J* = 6.3, 2.9 Hz, 1H), 3.50 – 3.35 (m, 2H), 3.06 – 2.96 (m, 2H), 2.12 (dtt, *J* = 8.7, 3.3, 1.8 Hz, 2H), 2.04 – 1.87 (m, 2H), 1.80 – 1.68 (m, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 151.3, 130.8, 130.5, 128.7, 127.2, 124.5, 117.1, 107.5, 52.1, 48.1, 28.4, 25.2, 24.9, 21.8.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calculated for $C_{14}H_{18}N$ 200.1439; found 200.1435.

1-Allyl-1H-benzo[d]imidazole (1h)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: benzimidazole (59.1 mg, 0.5 mmol, 1.0 equiv), allyl methyl carbonate (63.8 mg 0.55 mmol, 62.5 μL, 1.1 equiv), K_2CO_3 (104 mg, 0.75 mmol, 1.5 equiv), 2 wt % TPGS-750-M / H_2O (0.5 mL), 1000 ppm Pd (20 μL of stock solution from Section 4.15). The desired compound was obtained as a colorless oil (72.8 mg / 92%).

TLC: R_f = 0.50 with EtOAc, UV active, stains with $KMnO_4$.

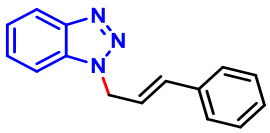
Flash Column chromatography: 50:50 EtOAc/hexanes then EtOAc.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.89 (s, 1H), 7.82 (dt, *J* = 6.7, 2.9 Hz, 1H), 7.40 – 7.33 (m, 1H), 7.32 – 7.25 (m, 2H), 5.99 (ddt, *J* = 17.2, 10.6, 5.5 Hz, 1H), 5.28 (dq, *J* = 10.3, 1.4 Hz, 1H), 5.18 (dq, *J* = 17.0, 1.5 Hz, 1H), 4.75 (dt, *J* = 5.6, 1.7 Hz, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 143.9, 143.0, 133.9, 132.0, 123.0, 122.2, 120.4, 118.7, 110.0, 47.4.

Spectra matched those previously reported.[157]

1-Cinnamyl-1H-benzo[d][1,2,3]triazole (1i)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: benzotriazole (59.6 mg, 0.5 mmol, 1.0 equiv), cinnamyl methyl carbonate (105.7 mg 0.55 mmol, 95.3 µL, 1.1 equiv), K_2CO_3 (104 mg, 0.75 mmol, 1.5 equiv.), 2 wt % TPGS-750-M / H_2O (0.5 mL), 1000 ppm Pd (20 µL of stock solution from section 4.15). The desired compound was obtained as a light yellow solid (57.2 mg / 50%), isolated from the same trial as 2-cinnamyl-2H-benzo[d][1,2,3]triazole, see below, combined yield of >95%).

TLC: R_f = 0.20 with 30:70 Et_2O/hexanes, UV active.

[157] Şahin, N.; Özdemir, N.; Gürbüz, N.; Özdemir, İ. *Appl. Organomet. Chem.* **2019**, *33*, 4704.

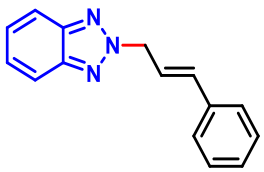
Flash Column chromatography: 10:90 Et_2O/hexanes then 50:50 Et_2O/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.13 – 8.06 (m, 1H), 7.61 – 7.54 (m, 1H), 7.50 – 7.43 (m, 1H), 7.41 – 7.23 (m, 6H), 6.68 (dd, *J* = 16.0, 1.6 Hz, 1H), 6.44 – 6.35 (m, 1H), 5.44 (dd, *J* = 6.3, 1.6 Hz, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 146.3, 135.6, 134.5, 133.0, 128.7, 128.4, 127.4, 126.7, 124.0, 122.2, 120.1, 109.8, 50.6.

Spectra matched those previously reported.[158]

2-Cinnamyl-2H-benzo[d][1,2,3]triazole (1i)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: benzotriazole (59.6 mg, 0.5 mmol, 1.0 equiv), cinnamyl methyl carbonate (105.7 mg 0.55 mmol, 95.3 µL, 1.1 equiv), K_2CO_3 (104 mg, 0.75 mmol, 1.5 equiv), 2 wt % TPGS-750-M / H_2O (0.5 mL), 1000 ppm Pd (20 µL of stock solution from Section 4.15). The desired compound was obtained as a light yellow solid (58.5 mg / 50%), isolated from the same trial as 1-cinnamyl-1H-benzo[d][1,2,3]triazole, see above, combined yield of >95%).

TLC: R_f = 0.50 with 30:70 Et_2O/hexanes, UV active.

[158] Gann, A. W.; Amoroso, J. W.; Einck, V. J.; Rice, W. P.; Chambers, J. J.; Schnarr, N. A. *Org. Lett.* **2014**, *16*, 2003–2005.

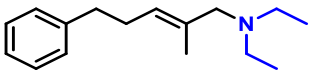
Flash Column chromatography: 10:90 Et_2O/hexanes then 50:50 Et_2O/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.91 (dtd, *J* = 6.5, 3.1, 1.4 Hz, 2H), 7.41 (td, *J* = 6.5, 2.3 Hz, 4H), 7.35 – 7.24 (m, 3H), 6.79 (dd, *J* = 16.1, 1.6 Hz, 1H), 6.56 (dt, *J* = 15.7, 6.7 Hz, 1H), 5.51 (dd, *J* = 6.8, 1.5 Hz, 2H).

^{13}C NMR ($CDCl_3$,126 MHz): δ 144.7, 135.9, 135.5, 128.8, 128.5, 127.0, 126.6, 122.1, 118.2, 58.8.

Spectra matched those previously reported.[159]

***(E)-N,N*-Diethyl-2-methyl-5-phenylpent-2-en-1-amine (1j)**



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: diethylamine (54.6 mg, 0.75 mmol, 77.5 µL, 1.36 equiv), methyl (2-methyl-5-phenylpent-1-en-3-yl) carbonate (117.2 mg 0.55 mmol, 113 µL, 1.0 equiv), K_2CO_3 (138.2 mg, 1.0 mmol, 1.82 equiv), 2 wt % TPGS-750-M / H_2O (0.5 mL), 910 ppm Pd (20 µL of stock solution from section 4.15). The desired compound was obtained as a colorless oil (91.7 mg / 72%).

TLC: R_f = 0.30 with 30:70 Et_2O/hexanes (streaks), stains with I_2 and $KMnO_4$.

Flash Column chromatography: 30:70 Et_2O/hexanes then 50:50 Et_2O/hexanes.

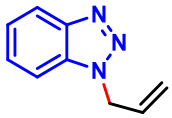
[159] Serra-Muns, A.; Pleixats, R. *J. Organomet. Chem.* **2010**, *695*, 1231–1236.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.28 (dt, *J* = 7.5, 6.1 Hz, 2H), 7.20 (dt, *J* = 8.2, 2.0 Hz, 3H), 5.35 (ddt, *J* = 7.2, 5.8, 1.3 Hz, 1H), 2.88 (d, *J* = 1.2 Hz, 2H), 2.69 (dd, *J* = 8.6, 6.8 Hz, 2H), 2.43 (q, *J* = 7.1 Hz, 4H), 2.38 (q, *J* = 7.5 Hz, 2H), 1.60 (s, 3H), 0.99 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR ($CDCl_3$,126 MHz): δ 142.4, 134.6, 128.6, 128.3, 126.3, 125.8, 62.2, 46.6, 36.1, 29.9, 15.1, 11.7.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calculated for $C_{16}H_{26}N$ 232.2065; found 232.2065.

1-Allyl-1H-benzo[d][1,2,3]triazole (1k)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: benzotriazole (59.6 mg, 0.5 mmol, 1.0 equiv), allyl methyl carbonate (63.9 mg 0.55 mmol, 62.5 μL, 1.1 equiv), K_2CO_3 (104 mg, 0.75 mmol, 1.5 equiv), 2 wt % TPGS-750-M / H_2O (0.5 mL), 1000 ppm Pd (20 μL of stock solution from Section 4.15). The desired compound was obtained as a pale yellow oil (46.2 mg / 58%), isolated from the same trial as 2-allyl-2H-benzo[d][1,2,3]triazole, see below, combined yield of >95%).

TLC: R_f = 0.20 with 30:70 Et_2O/hexanes, UV active.

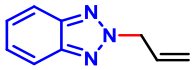
Flash Column chromatography: 10:90 Et_2O/hexanes then 50:50 Et_2O/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.04 (ddt, *J* = 8.3, 2.8, 1.4 Hz, 1H), 7.50 (dq, *J* = 8.3, 1.1 Hz, 1H), 7.47 – 7.42 (m, 1H), 7.37 – 7.31 (m, 1H), 6.09 – 5.98 (m, 1H), 5.30 (ddd, *J* = 10.3, 2.5, 1.3 Hz, 1H), 5.28 – 5.21 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 146.3, 133.0, 131.3, 127.4, 124.0, 120.1, 119.3, 109.8, 50.9.

Spectra matched those previously reported.[160]

2-Allyl-2H-benzo[d][1,2,3]triazole (1k)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: benzotriazole (59.6 mg, 0.5 mmol, 1.0 equiv), allyl methyl carbonate (63.9 mg 0.55 mmol, 62.5 µL, 1.1 equiv.), K_2CO_3 (104 mg, 0.75 mmol, 1.5 equiv), 2 wt % TPGS-750-M / H_2O (0.5 mL), 1000 ppm Pd (20 µL of stock solution from section 4.15). The desired compound was obtained as a pale yellow oil (31.0 mg / 39%), isolated from the same trial as 1-allyl-1H-benzo[d][1,2,3]triazole, see above, combined yield of >95%).

TLC: R_f = 0.50 with 30:70 Et_2O/hexanes, UV active.

Flash Column chromatography: 10:90 Et_2O/hexanes then 50:50 Et_2O/hexanes.

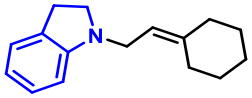
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.86 (dd, *J* = 6.6, 3.2 Hz, 2H), 7.45 – 7.33 (m, 2H), 6.20 (ddt, *J* = 16.6, 10.1, 6.3 Hz, 1H), 5.43 – 5.36 (m, 2H), 5.33 (dt, *J* = 6.3, 1.4 Hz, 2H).

^{13}C NMR ($CDCl_3$, 126 MHz): δ 144.6, 131.2, 126.5, 120.3, 118.1, 59.1.

Spectra matched those previously reported.[161]

[160] Yan, W.; Liao, T.; Tuguldur, O.; Zhong, C.; Petersen, J. L.; Shi, X. *Chem. Asian J.* **2011**, *6*, 2720–2724.
[161] Yan, W.; Liao, T.; Tuguldur, O.; Zhong, C.; Petersen, J. L.; Shi, X. *Chem. Asian J* **2011**, *6*, 2720–2724.

1-(2-Cyclohexylideneethyl)indoline (1l)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: indoline (59.6 mg, 0.5 mmol, 56.2 µL, 1.0 equiv), methyl (1-vinylcyclohexyl) carbonate (110.5 mg 0.6 mmol, 108.3 µL, 1.2 equiv), K_2CO_3 (138.2 mg, 1.0 mmol, 2.0 equiv), 2 wt % TPGS-750-M / H_2O (0.5 mL), 1000 ppm Pd (20 µL of stock solution from Section 4.15). The desired compound was obtained as a colorless oil (98.5 mg / 87%,).

TLC: R_f = 0.70 with 10:90 Et_2O/hexanes, UV active, stains with Seebach's magic stain and $KMnO_4$.

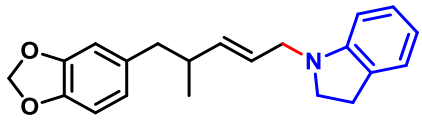
Flash Column chromatography: hexanes then 4:96 Et_2O/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.19 – 7.05 (m, 2H), 6.70 (td, *J* = 7.3, 0.9 Hz, 1H), 6.58 (d, *J* = 7.7 Hz, 1H), 5.31 (td, *J* = 7.0, 3.5 Hz, 1H), 3.76 (d, *J* = 7.0 Hz, 2H), 3.36 (t, *J* = 8.2 Hz, 2H), 2.98 (t, *J* = 8.2 Hz, 2H), 2.29 (t, *J* = 5.5 Hz, 2H), 2.18 (t, *J* = 5.4 Hz, 2H), 1.66 – 1.57 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5, 143.5, 130.5, 127.3, 124.4, 117.6, 116.7, 107.5, 53.0, 45.7, 37.3, 29.0, 28.7, 28.6, 27.8, 26.9.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calculated for $C_{16}H_{22}N$ 228.1752; found 228.1751.

(*E*)-1-(5-(Benzo[d][1,3]dioxol-5-yl)-4-methylpent-2-en-1-yl)indoline (1m)



The titled compound was obtained according to the procedure in section 4.15 using the following quantities: indoline (11.9 mg, 0.1 mmol, 11.2 µL, 1.0 equiv), 5-(benzo[d][1,3]dioxol-5-yl)-4-methylpent-2-en-1-yl methyl carbonate (27.8 mg 0.1 mmol, 24.0 µL, 1.0 equiv), Et_3N (30.3 mg, 0.3 mmol, 3.0 equiv), 2 wt % TPGS-750-M / H_2O (0.2 mL), 1000 ppm Pd (10 µL of stock solution from ection 4.15, but prepared 0.4x as concentrated). The desired compound was obtained as a colorless oil which blackens upon exposure to air (29.0 mg / 90%).

TLC: R_f = 0.70 with 20:80 Et_2O/hexanes, UV active, stains with I_2 and $KMnO_4$.

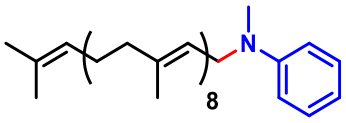
Flash Column chromatography: hexanes then 10:90 Et_2O/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.10 – 7.02 (m, 2H), 6.72 (d, *J* = 7.9 Hz, 1H), 6.68 – 6.62 (m, 2H), 6.57 (dd, *J* = 7.9, 1.7 Hz, 1H), 6.48 (d, *J* = 7.8 Hz, 1H), 5.92 (s, 2H), 5.61 (ddt, *J* = 15.5, 7.4, 1.4 Hz, 1H), 5.48 – 5.39 (m, 1H), 3.71 – 3.55 (m, 2H), 3.21 (td, *J* = 8.4, 3.4 Hz, 2H), 2.92 (t, *J* = 8.2 Hz, 2H), 2.60 – 2.46 (m, 2H), 2.42 (p, *J* = 6.9 Hz, 1H), 1.00 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.4, 147.5, 145.7, 139.0, 134.7, 130.5, 127.3, 124.5, 124.5, 122.1, 117.7, 109.7, 108.0, 107.5, 100.8, 53.1, 51.4, 43.4, 38.7, 28.6, 20.1.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{24}NO_2$ 322.1807; found 322.1810.

***N*-Methyl-*N*-((2E,6E,10E,14E,18E,22E,26E,30E)-3,7,11,15,19,23,27,31,35-nonamethylhexatriaconta-2,6,10,14,18,22,26,30,34-nonaen-1-yl)aniline (1n)**



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: *N*-methylaniline (53.6 mg, 0.5 mmol, 54.1 μL, 1.0 equiv), solanesyl methyl carbonate (344.6 mg, 0.5 mmol, 1.0 equiv), Et_3N (151.6 mg, 1.5 mmol, 209 μL, 3.0 equiv), 2 wt % TPGS-750-M / H_2O (1.0 mL), $[Pd(allyl)Cl]_2$ (0.92 mg, 0.0025 mmol, 0.5 mol %), DPEphos (2.7 mg, 0.005 mmol, 1 mol %). The desired compound was obtained as a white solid (mp 42 ^oC) (310 mg / 86%).

TLC: R_f = 0.70 with 10:90 Et_2O/hexanes, UV active, stains with I_2 and $KMnO_4$.

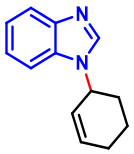
Flash Column chromatography: hexanes then 4:96 Et_2O/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33 – 7.27 (m, 2H), 6.82 (d, *J* = 8.2 Hz, 2H), 6.78 (t, *J* = 7.3 Hz, 1H), 5.32 (td, *J* = 6.4, 1.7 Hz, 1H), 5.26 – 5.16 (m, 8H), 3.98 (d, *J* = 6.3 Hz, 2H), 2.97 (s, 3H), 2.17 (dq, *J* = 16.4, 7.6 Hz, 18H), 2.09 (dd, *J* = 9.5, 5.7 Hz, 15H), 1.82 – 1.76 (m, 6H), 1.69 (d, *J* = 8.5 Hz, 25H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.9, 138.1, 135.2, 134.9, 134.9, 134.9, 134.9, 134.9, 131.2, 129.1, 124.6, 124.4, 124.4, 124.4, 124.3, 124.0, 121.1, 116.6, 113.1, 50.6, 39.9, 39.8, 39.8, 39.7, 37.9, 29.8, 26.9, 26.8, 26.8, 26.5, 25.8, 17.8, 16.3, 16.1, 16.1, 16.1.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{52}H_{82}N$ 720.6447; found 720.6461.

1-(Cyclohex-2-en-1-yl)-1H-benzo[d]imidazole (1o)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: benzimidazole (29.5 mg, 0.25 mmol, 1.0 equiv), cyclohex-2-en-1-yl methyl carbonate (46.8 mg, 0.3 mmol, 44.3 μL, 1.2 equiv), K_2CO_3 (51.8 mg, 0.375 mmol, 1.5 equiv), methyl formate (49 mg, 0.8 mmol, 50 μL, 3.2 equiv), 2 wt % TPGS-750-M / H_2O (0.25 mL), $[Pd(allyl)Cl]_2$ (0.46 mg, 0.00125 mmol, 1 mol % Pd), DPEphos (1.35 mg, 0.0025 mmol, 1 mol %). The desired compound was obtained as a colorless oil (45.2 mg / 91%).

TLC: R_f = 0.50 with EtOAc UV active, stains with I_2 and $KMnO_4$.

Flash Column chromatography: 25:75 EtOAc/hexanes then 40:60 EtOAc/hexanes.

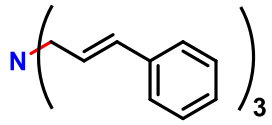
^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.98 (s, 1H), 7.84 – 7.78 (m, 1H), 7.48 – 7.40 (m, 1H), 7.31 – 7.26 (m, 2H), 6.21 (dtd, *J* = 9.8, 3.8, 2.0 Hz, 1H), 5.86 (dq, *J* = 9.9, 2.5 Hz, 1H), 5.01 (dp, *J* = 5.7, 2.8 Hz, 1H), 2.30 – 1.93 (m, 5H), 1.72 (tdd, *J* = 6.3, 4.9, 2.9 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.4, 142.2, 133.9, 133.4, 124.9, 122.7, 122.2, 120.6, 110.3, 51.2, 29.6, 24.9, 19.4.

Spectra matched those previously reported.[162]

[162] Meng, X.; Li, X.; Chen, W.; Zhang, Y.; Wang, W.; Chen, J.; Song, J.; Feng, H.; Feng, B. *J. Hetero. Chem.* **2014**, *51*, 349–356.

(*E*)-Tricinnamylamine (1p)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: conc. ammonium hydroxide (175 mg, 5.0 mmol, 600 μL, 5 equiv), cinnamyl methyl carbonate (192.1 mg, 1.0 mmol, 173.2 μL, 1.0 equiv), 2 wt % TPGS-750-M / H_2O (1.0 mL), $[Pd(allyl)Cl]_2$ (1.83 mg, 0.005 mmol, 0.5 mol %), DPEphos (5.4 mg, 0.01 mmol, 1 mol %). The desired compound was obtained as a white crystalline solid (mp 88-89 ^oC) (109.8 mg / 90.1%).

TLC: R_f = 0.50 with 25:75 EtOAc/hexanes, UV active, stains with $KMnO_4$.

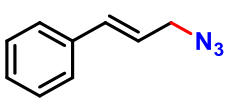
Flash column chromatography: hexanes then 15:85 EtOAc/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.46 (d, *J* = 7.6 Hz, 6H), 7.38 (t, *J* = 7.5 Hz, 6H), 7.34 – 7.27 (m, 3H), 6.63 (d, *J* = 15.8 Hz, 3H), 6.40 (dt, *J* = 15.8, 6.7 Hz, 3H), 3.42 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.2, 133.0, 128.7, 127.5, 127.3, 126.4, 56.2.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calculated for $C_{27}H_{28}N$ 366.2222; found 366.2224.

(*E*)-(3-Azidoprop-1-en-1-yl)benzene (1q)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: sodium azide (71.5 mg, 1.1 mmol, 1.1 equiv), cinnamyl methyl carbonate (192.1 mg, 1.0 mmol, 173.2 μL, 1.0 equiv) K_2CO_3 (207.3 mg, 1.5 mmol, 1.5 equiv), 2 wt % TPGS-750-M / H_2O (1.0 mL), 2000 ppm Pd (40 μL of stock solution from Section 4.15). The desired compound was obtained as a colorless oil (143.9 mg / 90.4%).

TLC: R_f = 0.60 with 10:90 Et_2O/hexanes, UV active, stains with vanillin and $KMnO_4$.

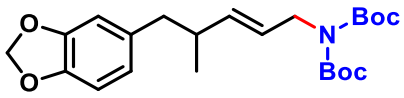
Flash column chromatography: hexanes then 3:97 Et_2O/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.46 – 7.41 (m, 2H), 7.41 – 7.34 (m, 2H), 7.34 – 7.28 (m, 1H), 6.68 (dt, *J* = 15.6, 1.5 Hz, 1H), 6.27 (dt, *J* = 15.7, 6.6 Hz, 1H), 3.96 (dd, *J* = 6.6, 1.5 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.1, 134.6, 128.7, 128.3, 126.7, 122.5, 53.1.

Spectra matched those previously reported.[163]

(*E*)-5-(Benzo[d][1,3]dioxol-5-yl)-4-methylpent-2-en-1-(di-*tert*-butyl iminodicarboxylate) (1r)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: di-*tert*-butyl iminodicarboxylate (23.9 mg, 0.11 mmol, 1.1 equiv), 5-(benzo[d][1,3]dioxol-5-yl)-4-methylpent-2-en-1-yl methyl carbonate (27.8 mg 0.1 mmol,

[163] Barragan, E.; Bugarin, A. *J. Org. Chem.* **2017**, *82*, 1499-1506.

24.0 μL, 1.0 equiv), K_2CO_3 (20.7 mg, 0.15 mmol, 1.5 equiv), methyl formate (6.0 mg, 0.1 mmol, 6.1 μL, 1.0 equiv) 2 wt % TPGS-750-M / H_2O (0.2 mL), 2500 ppm Pd (25 μL of stock solution prepared from $[Pd(allyl)Cl]_2$ (4.57 mg) and DPEphos (13.5 mg) in 2500 μL of toluene). The desired compound was obtained as a colorless viscous oil (35.0 mg / 84%).

TLC: R_f = 0.50 with 20:80 Et_2O/hexanes, UV active, stains with $KMnO_4$.

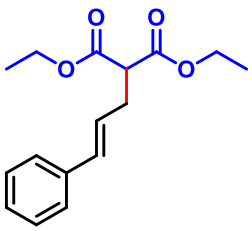
Flash column chromatography: hexanes, then 10:90 Et_2O/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.70 (d, *J* = 7.9 Hz, 1H), 6.62 (d, *J* = 1.7 Hz, 1H), 6.56 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.90 (s, 2H), 5.56 (ddt, *J* = 15.3, 6.8, 1.2 Hz, 1H), 5.40 (dtd, *J* = 15.4, 6.1, 1.0 Hz, 1H), 4.08 (dd, *J* = 6.1, 1.3 Hz, 2H), 2.62 – 2.54 (m, 1H), 2.42 – 2.31 (m, 2H), 1.49 (s, 18H), 0.94 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 152.5, 147.5, 145.7, 138.7, 134.5, 123.9, 122.1, 109.6, 108.0, 100.8, 82.2, 48.1, 43.2, 38.3, 28.2, 19.7.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calculated for $C_{23}H_{33}NO_6Na$ 442.2206; found 442.2205.

Diethyl 2-cinnamylmalonate (2a)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: diethyl malonate (44.1 mg, 0.275 mmol, 42.0 μL, 1.1 equiv), cinnamyl methyl carbonate (48.1 mg 0.25 mmol, 43.3 μL, 1.0 equiv), K_2CO_3 (51.8 mg, 0.375 mmol, 1.5 equiv), 2 wt % TPGS-750-M / H_2O (0.25 mL), 1000 ppm Pd (20 μL of stock solution prepared from $Pd(OAc)_2$ (2.81 mg) and PPh_3 (13.1 mg) in 1.0 mL toluene with 7.0 μL Et_3N. The desired compound was obtained as a colorless oil (55 mg / 80%).

TLC: R_f = 0.25 with 5:95 Et_2O/hexanes, UV active, stains with $KMnO_4$.

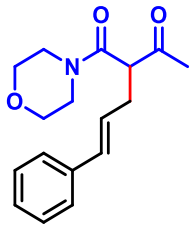
Flash column chromatography: hexanes then 10:90 Et_2O/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32 (dt, *J* = 14.9, 7.4 Hz, 4H), 7.23 (td, *J* = 6.8, 1.6 Hz, 1H), 6.49 (d, *J* = 15.8 Hz, 1H), 6.17 (dt, *J* = 15.7, 7.2 Hz, 1H), 4.22 (qq, *J* = 6.8, 3.7 Hz, 4H), 3.50 (t, *J* = 7.5 Hz, 1H), 2.82 (td, *J* = 7.3, 1.4 Hz, 2H), 1.27 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 137.2, 132.9, 128.6, 127.5, 126.3, 125.8, 61.6, 52.2, 32.4, 14.3.

Spectra matched those previously reported.[164]

2-Cinnamyl-1-morpholinobutane-1,3-dione (2b)



[164] Huang, X.; Fulton, B.; White, K.; Bugarin, A. *Org. Lett.* **2015**, *17*, 2594–2597.

The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: 1-morpholinobutane-1,3-dione (47.1 mg, 0.275 mmol, 1.1 equiv), cinnamyl methyl carbonate (48.1 mg 0.25 mmol, 43.3 μL, 1.0 equiv), K_2CO_3 (51.8 mg, 0.375 mmol, 1.5 equiv), 2 wt % TPGS-750-M / H_2O (0.25 mL), 1000 ppm Pd (20 μL of stock solution prepared from $Pd(OAc)_2$ (2.81 mg) and PPh_3 (13.1 mg) in 1.0 mL toluene with 7.0 μL Et_3N. The desired compound was obtained as a colorless oil (48 mg / 67%).

TLC: R_f = 0.50 with EtOAc, UV active, stains with $KMnO_4$.

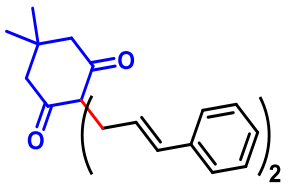
Flash Column chromatography: 10:90 EtOAc/hexanes, then 30:70 EtOAc/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.35 – 7.26 (m, 4H), 7.22 (tdd, *J* = 7.0, 5.0, 2.8 Hz, 1H), 6.47 (dd, *J* = 15.8, 1.5 Hz, 1H), 6.12 (dtd, *J* = 15.7, 7.2, 1.6 Hz, 1H), 3.77 – 3.46 (m, 9H), 2.91 – 2.73 (m, 2H), 2.20 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 204.1, 167.1, 136.9, 132.8, 128.6, 127.6, 126.2, 125.9, 66.9, 66.7, 57.9, 46.5, 42.7, 32.5, 27.2.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calculated for $C_{17}H_{22}NO_3$ 288.1600; found 288.1607.

2,2-Dicinnamyl-5,5-dimethylcyclohexane-1,3-dione (2c)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: dimedone (70.1 mg, 0.5 mmol, 1.0 equiv), cinnamyl methyl carbonate

(105.7 mg, 0.55 mmol, 95.3 µL, 1.1 equiv), K_2CO_3 (103.7 mg, 0.75 mmol, 1.5 equiv.), methyl formate (30.0 mg, 0.5 mmol, 30.6 µL, 1.0 equiv), 2 wt % TPGS-750-M / H_2O (0.5 mL), 1000 ppm Pd (20 µL of stock solution from Section 2.1). The desired compound was obtained as a pale yellow oil (98.8 mg / 96%, using cinnamyl methyl carbonate as limiting reagent).

TLC: R_f = 0.40 with 50:50 Et_2O/hexanes, UV active, stains with $KMnO_4$.

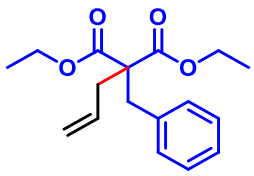
Flash column chromatography: hexanes then 40:60 Et_2O/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33 – 7.26 (m, 8H), 7.24 – 7.18 (m, 2H), 6.45 (d, *J* = 15.7 Hz, 2H), 6.03 (dt, *J* = 15.4, 7.5 Hz, 2H), 2.72 (dd, *J* = 7.5, 1.3 Hz, 4H), 2.58 (s, 4H), 0.96 (s, 6H).

^{13}C NMR ($CDCl_3$) δ 209.0, 137.0, 134.5, 128.5, 127.5, 126.3, 123.9, 68.5, 52.3, 38.4, 30.7, 28.7.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calculated for $C_{26}H_{28}O_2Na$ 395.1987; found 395.1986.

Diethyl 2-allyl-2-benzylmalonate (2d)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: diethyl benzylmalonate (100 mg, 0.40 mmol, 94.0 µL, 1.0 equiv),

allyl acetate (60.1 mg, 0.60 mmol, 64.7 μL, 1.5 equiv), K_2CO_3 (55.3 mg, 0.40 mmol, 1.0 equiv), 2 wt % TPGS-750-M / H_2O (0.4 mL), 2000 ppm Pd (40 μL of stock solution from Section 2.1). The desired compound was obtained as a pale-yellow oil (87.4 mg / 75%).

TLC: R_f = 0.30 with 10:90 EtOAc/hexanes, UV active, stains with $KMnO_4$.

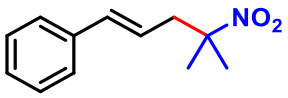
Flash column chromatography: hexanes then 10:90 EtOAc/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30 – 7.22 (m, 3H), 7.16 – 7.10 (m, 2H), 5.85 – 5.73 (m, 1H), 5.18 (q, *J* = 1.2 Hz, 1H), 5.16 (dq, *J* = 3.9, 1.4 Hz, 1H), 4.26 – 4.11 (m, 4H), 3.26 (s, 2H), 2.58 (dt, *J* = 7.3, 1.3 Hz, 2H), 1.25 (t, *J* = 7.1 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 136.2, 132.8, 130.1, 128.3, 127.0, 119.3, 119.3, 61.4, 58.9, 38.2, 36.6, 14.2.

Spectra matched those previously reported.[165]

(*E*)-(4-Methyl-4-nitropent-1-en-1-yl)benzene (2e)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: 2-nitropropane (44.6 mg, 0.5 mmol, 45.4 μL, 1.0 equiv), *t*-butyl cinnamyl carbonate (128.9 mg, 0.55 mmol, 125.8 μL, 1.1 equiv), Et_3N (151.8 mg, 1.5 mmol, 209.2 μL, 3.0 equiv), methyl formate (30.0 mg, 0.5 mmol, 30.6 μL, 1.0 equiv), 2 wt

[165] Shimizu, A.; Hirata, G.; Onodera, G.; Kimura, M. *Adv. Syn. Cat.* **2018**, *360*, 1954–1960.

% TPGS-750-M / H_2O (0.5 mL), 1000 ppm Pd (20 μL of stock solution from Section 2.1). The desired compound was obtained as a colorless oil (72 mg / 70%).

TLC: R_f = 0.50 with plate run 1/8th of the way with Et_2O, dried and then run the rest of the way with hexanes (product difficult to separate from the electrophile starting material). UV active.

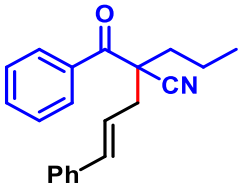
Flash column chromatography: hexanes then 5:95 Et_2O/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.39 – 7.31 (m, 4H), 7.30 – 7.24 (m, 1H), 6.51 (d, *J* = 15.7 Hz, 1H), 6.08 (dt, *J* = 15.4, 7.5 Hz, 1H), 2.81 (dd, *J* = 7.5, 1.3 Hz, 2H), 1.65 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.67, 135.29, 128.61, 127.78, 126.36, 122.41, 88.09, 44.25, 27.82, 25.65.

Spectra matches those previously reported.[166]

(*E*)-2-Benzoyl-5-phenyl-2-propylpent-4-enenitrile (2f)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: 2-benzoylpentanenitrile (93.6 mg, 0.5 mmol, 1.0 equiv), cinnamyl

[166] Wade, P. A.; Morrow, S. D.; Hardinger, S. A. *J. Org. Chem.* **1982**, *47*, 365–367.

methyl carbonate (119.2 mg, 0.50 mmol, 107.5 µL, 1.0 equiv), K_2CO_3 (103.7 mg, 0.75 mmol, 1.5 equiv), 2 wt % TPGS-750-M / H_2O (1.0 mL), $[Pd(allyl)Cl]_2$ (1.8 mg, 0.005 mmol, 1 mol %), DPEphos (5.4 mg, 0.01 mmol, 2 mol %). The desired compound was obtained as a pale-yellow oil (151.7 mg / >95%).

TLC: R_f = 0.30 with 10:90 EtOAc/hexanes. UV active, stains with $KMnO_4$.

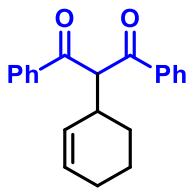
Flash column chromatography: hexanes then 10:90 EtOAc/hexanes.

^{1}H NMR ($CDCl_3$, 600 MHz): δ 8.12 – 8.07 (m, 2H), 7.62 – 7.57 (m, 1H), 7.52 – 7.46 (m, 2H), 7.40 – 7.34 (m, 2H), 7.32 (dd, *J* = 8.5, 6.8 Hz, 2H), 7.27 – 7.23 (m, 1H), 6.58 (dd, *J* = 15.7, 1.5 Hz, 1H), 6.23 (ddd, *J* = 15.4, 7.9, 7.1 Hz, 1H), 2.95 (dddd, *J* = 150.6, 13.9, 7.5, 1.3 Hz, 2H), 2.08 (dddd, *J* = 163.1, 13.6, 12.1, 4.7 Hz, 2H), 1.64 – 1.47 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 195.2, 136.5, 135.8, 135.7, 133.5, 129.0, 128.6, 128.6, 127.9, 126.5, 122.1, 121.2, 52.2, 40.9, 39.3, 18.7, 14.0.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calculated for $C_{21}H_{21}NONa$ 326.1521; found 326.1531.

2-(Cyclohex-2-en-1-yl)-1,3-diphenylpropane-1,3-dione (2g)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities for the racemic product: 1,3-diphenylpropane-1,3-dione (112.2 mg, 0.50 mmol, 1.0 equiv), cyclohex-2-en-1-yl methyl carbonate (78 mg, 0.50 mmol, 1.0 equiv), K_2CO_3 (173 mg, 1.25 mmol, 2.5 equiv), 2 wt % TPGS-750-M / H_2O (1.0 mL), $[Pd(allyl)Cl]_2$ (0.52 mg, 0.0028 mmol Pd, 0.57 mol % Pd), DPEphos (1.7 mg, 0.0032 mmol, 0.63 mol %). The desired compound was obtained as a pale-yellow oil. (125.8 mg / 83%).

The titled compound was obtained according to the procedure in Section 4.15 using the following quantities for the asymmetric example: 1,3-diphenylpropane-1,3-dione (112.2 mg, 0.50 mmol, 1.0 equiv), cyclohex-2-en-1-yl methyl carbonate (78 mg, 0.50 mmol, 1.0 equiv), K_2CO_3 (173 mg, 1.25 mmol, 2.5 equiv), 2 wt % TPGS-750-M / H_2O (1.0 mL), $[Pd(allyl)Cl]_2$ (0.54 mg, 0.0030 mmol Pd, 0.60 mol % Pd), (*S*,*S*)-DACH-naphthyl Trost Ligand (2.8 mg, 0.0035 mmol, 0.7 mol %). The desired compound was obtained as a pale-yellow oil. (132.2 mg / 87%).

TLC: R_f = 0.40 with 10:90 Et_2O/hexanes. UV active, stains with $KMnO_4$.

Flash column chromatography: hexanes then 10:90 Et_2O/hexanes.

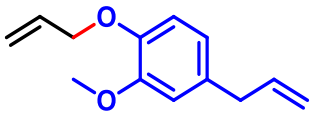
HPLC column conditions: 99:1 hexanes/isopropanol, using Chiral PAK ADH column.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.99 (ddd, *J* = 8.6, 3.6, 1.4 Hz, 4H), 7.59 – 7.47 (m, 2H), 7.42 (td, *J* = 7.8, 1.6 Hz, 4H), 5.72 (ddt, *J* = 9.8, 3.6, 1.9 Hz, 1H), 5.51 (dd, *J* = 10.2, 2.5 Hz, 1H), 5.30 (d, *J* = 10.0 Hz, 1H), 3.49 (dtd, *J* = 10.5, 5.3, 2.6 Hz, 1H), 2.00 (tq, *J* = 5.9, 2.8 Hz, 2H), 1.81 – 1.67 (m, 2H), 1.58 (dddd, *J* = 13.1, 8.1, 6.0, 3.6 Hz, 1H), 1.38 (dddd, *J* = 12.4, 10.0, 8.0, 2.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 195.3, 194.9, 137.2, 137.0, 133.6, 133.5, 129.4, 128.9, 128.8, 128.8, 128.8, 128.6, 62.3, 37.3, 27.4, 25.1, 21.2.

Spectral data matched those previously reported.[167]

4-Allyl-1-(allyloxy)-2-methoxybenzene (3a)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: eugenol (82.1 mg, 0.5 mmol, 77.5 μL, 1.0 equiv), allyl acetate (55.1 mg, 0.55 mmol, 59.3 μL, 1.1 equiv), K_2CO_3 (103.7 mg, 0.75 mmol, 1.5 equiv), 2 wt % TPGS-750-M / H_2O (0.5 mL), 1000 ppm Pd (20 μL of stock solution from Section 2.1). The desired compound was obtained as a colorless oil (78.6 mg / 77%).

TLC: R_f = 0.80 with 20:80 EtOAc/hexanes. UV active, stains with $KMnO_4$

Flash column chromatography: hexanes then 5:95 EtOAc/hexanes.

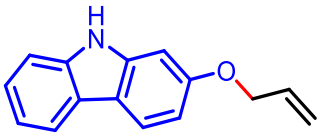
^{1}H NMR ($CDCl_3$, 600 MHz): δ 6.82 (d, *J* = 8.1 Hz, 1H), 6.76 – 6.68 (m, 2H), 6.08 (ddt, *J* = 17.3, 10.7, 5.4 Hz, 1H), 5.96 (ddt, *J* = 16.8, 10.0, 6.7 Hz, 1H), 5.45 – 5.36 (m, 1H), 5.27 (dq, *J* = 10.5, 1.4 Hz, 1H), 5.13 – 5.04 (m, 2H), 4.59 (dt, *J* = 5.4, 1.6 Hz, 2H), 3.86 (s, 3H), 3.34 (d, *J* = 6.7 Hz, 2H).

[167] Zotto, C. D.; Michaux, J.; Zarate-Ruiz, A.; Gayon, E.; Virieux, D.; Campagne, J.-M.; Terrasson, V.; Pieters, G.; Gaucher, A.; Prim, D. *J. Organomet. Chem.* **2011**, *696*, 296–304.

^{13}C NMR (126 MHz, $CDCl_3$) δ 149.5, 146.4, 137.7, 133.6, 133.1, 120.4, 117.8, 115.7, 113.7, 112.3, 70.1, 55.9, 39.9.

Spectra matched those previously reported.[168]

2-(Allyloxy)-9H-carbazole (3b)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: 2-hydroxycarbazole (100 mg, 0.54 mmol, 1.0 equiv), allyl acetate (81.1 mg, 0.81 mmol, 87.4 μL, 1.5 equiv), K_2CO_3 (74.6 mg, 0.54 mmol, 1.0 equiv), 2 wt % TPGS-750-M / H_2O (0.5 mL), 2000 ppm Pd (40 μL of stock solution from Section 2.1). The desired compound was obtained as a yellow solid (mp = 180 ^oC), (53.1 mg / 44%).

TLC: R_f = 0.30 with 20:80 EtOAc/hexanes. UV active, stains with $KMnO_4$

Flash column chromatography: hexanes then 20:80 EtOAc/hexanes.

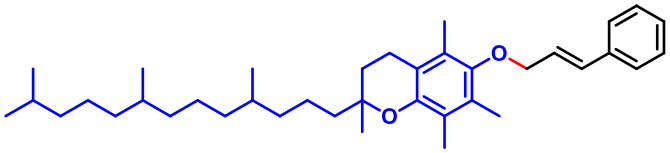
^{1}H NMR (DMSO, 600 MHz): δ 11.20 – 11.06 (m, 1H), 7.99 (ddt, *J* = 24.0, 17.1, 7.8 Hz, 2H), 7.52 – 7.40 (m, 1H), 7.40 – 7.25 (m, 1H), 7.21 – 7.09 (m, 1H), 7.09 – 6.96 (m, 1H), 6.89 – 6.75 (m, 1H), 6.21 – 6.04 (m, 1H), 5.55 – 5.40 (m, 1H), 5.38 – 5.23 (m, 1H), 4.74 – 4.56 (m, 2H).

[168] Llevot, A.; Monney, B.; Sehlinger, A.; Behrens, S.; Meier, M. a. R. *Chem. Commun.* **2017**, *53*, 5175–5178.

^{13}C NMR (151 MHz, DMSO) δ 157.8, 141.4, 140.2, 134.4, 124.6, 123.1, 121.3, 119.7, 119.0, 117.7, 116.8, 111.0, 108.6, 95.9, 95.9, 68.9.

Spectra matched those previously reported.[169]

6-(Cinnamyloxy)-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chromane (3c)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: ∝-tocopherol (racemic synthetic vitamin E) (215.4 mg, 0.5 mmol, 1.0 equiv) (added as though it were a solid due to the high viscosity), cinnamyl benzoate (143.0 mg 0.6 mmol, 129.5 µL, 1.2 equiv), K_2CO_3 (103.7 mg, 0.75 mmol, 1.5 equiv), methyl formate (30.0 mg, 0.5 mmol, 30.6 µL, 1.0 equiv) 2 wt % TPGS-750-M / H_2O (0.5 mL), 1000 ppm Pd (20 µL of stock solution from Section 2.1). The desired compound was obtained as a pale-yellow viscous oil (225.0 mg / 82%).

TLC: R_f = 0.40 with 5:95 Et_2O/hexanes, UV active.

Flash column chromatography: hexanes, then 4:96 Et_2O/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.49 (d, *J* = 7.4 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.30 (t, *J* = 7.4 Hz, 1H), 6.81 (d, *J* = 15.8 Hz, 1H), 6.55 (dt, *J* = 15.9, 5.8 Hz, 1H), 4.43 (dd, *J* = 5.8, 1.5 Hz, 2H), 2.65 (t, *J* = 6.8 Hz, 2H), 2.29 (s, 3H), 2.24 (s, 3H), 2.18 (s, 3H), 1.93 –

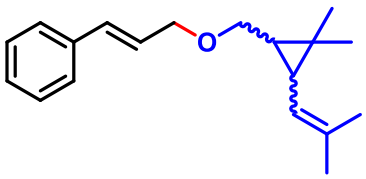
[169] Chattopadhyay, S. K.; Ghosh, D.; Mondal, P.; Ghosh, S. K. *Synthesis* **2012**, 44, 2448-2454.

1.79 (m, 2H), 1.62 (ddt, *J* = 19.7, 13.3, 6.9 Hz, 3H), 1.57 – 1.26 (m, 17H), 1.25 – 1.10 (m, 7H), 0.94 (dd, *J* = 9.9, 6.4 Hz, 13H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 148.4, 147.9, 136.9, 132.0, 128.6, 128.0, 127.7, 126.6, 126.0, 125.8, 122.9, 117.6, 74.9, 74.8, 73.6, 40.2, 40.1, 39.5, 37.7, 37.7, 37.6, 37.6, 37.5, 37.5, 37.5, 37.4, 37.4, 32.9, 32.9, 32.8, 32.8, 31.4, 31.3, 28.1, 24.9, 24.9, 24.5, 24.0, 22.8, 22.7, 21.1, 20.8, 19.9, 19.8, 19.8, 19.7, 19.7, 13.0, 12.2, 11.9.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{38}H_{58}O_2Na$ 569.4335; found 569.4335.

(*E*)-(3-((2,2-Dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl)methoxy)prop-1-en-1-yl)benzene (3d)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: chrysanthemyl alcohol, mixture of *cis* and *trans* (77.1 mg, 0.5 mmol, 86.9 μL, 1.0 equiv), cinnamyl benzoate (131.1 mg, 0.55 mmol, 118.7 μL, 1.1 equiv), K_2CO_3 (103.7 mg, 0.75 mmol, 1.5 equiv), 2 wt % TPGS-750-M / H_2O (0.5 mL), $[Pd(allyl)Cl]_2$ (1.83 mg, 0.005 mmol, 1 mol %), DPEphos (5.4 mg, 0.01 mmol, 2 mol %). The desired compound was obtained as a colorless oil (114.7 mg / 85%).

TLC: R_f = 0.70 with 10:90 Et_2O/hexanes, UV active, stains with $KMnO_4$.

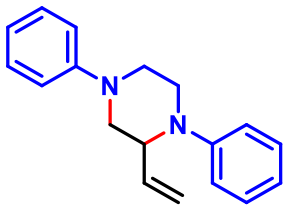
Flash column chromatography: hexanes then 3:97 Et_2O/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42 (dt, *J* = 8.1, 1.6 Hz, 2H), 7.33 (dd, *J* = 8.4, 6.8 Hz, 2H), 7.28 – 7.23 (m, 1H), 6.63 (dt, *J* = 16.0, 1.6 Hz, 1H), 6.33 (dt, *J* = 15.9, 6.0 Hz, 1H), 4.95 (ddt, *J* = 9.6, 6.6, 1.4 Hz, 1H), 4.17 (ddd, *J* = 7.9, 6.2, 1.6 Hz, 2H), 3.62 (ddd, *J* = 71.1, 10.5, 6.4 Hz, 1H), 3.47 (ddd, *J* = 14.2, 10.5, 8.1 Hz, 1H), 1.80 – 1.69 (m, 6H), 1.18 (d, *J* = 1.9 Hz, 3H), 1.17 – 1.13 (m, 1H), 1.11 (s, 2H), 1.06 (s, 1H), 0.88 (d, *J* = 8.2 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.91, 133.05, 132.12, 132.09, 128.60, 127.63, 127.62, 126.77, 126.73, 126.53, 123.70, 119.38, 71.19, 71.01, 70.72, 67.72, 32.45, 28.85, 28.80, 28.22, 26.16, 25.82, 25.72, 22.68, 22.31, 21.58, 20.29, 18.59, 18.36, 15.62.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{19}H_{26}ONa$ 293.1881; found 293.1881.

1,4-Diphenyl-2-vinylpiperazine (4a)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: 1,2-dianilinoethane (106.2 mg, 0.5 mmol, 1.0 equiv), (*Z*)-but-2-ene-1,4-diyl di-*t*-butyl bis(carbonate) (144.17 mg 0.5 mmol, 139.7 µL, 1.0 equiv), Et_3N (151.7 mg, 1.5 mmol, 209.0 µL, 3.0 equiv), methyl formate (30.0 mg, 0.5 mmol, 30.6 µL, 1.0 equiv), 2 wt % TPGS-750-M / H_2O (1.5 mL), 1000 ppm Pd (20 µL of stock solution from Section 2.1). The desired compound was obtained as a white crystalline solid (116.6 mg / 88%).

TLC: R_f = 0.70 with 20:80 Et_2O/hexanes, UV active, stains with $KMnO_4$.

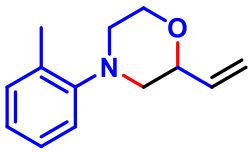
Flash column chromatography: hexanes, then 10:90 Et_2O/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41 (qd, *J* = 7.0, 1.9 Hz, 4H), 7.12 – 7.03 (m, 4H), 7.00 (tt, *J* = 7.3, 1.1 Hz, 2H), 6.09 (ddd, *J* = 17.2, 10.5, 6.6 Hz, 1H), 5.38 – 5.24 (m, 2H), 4.45 – 4.33 (m, 1H), 3.69 – 3.60 (m, 2H), 3.57 – 3.44 (m, 3H), 3.36 – 3.23 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.3, 150.2, 136.4, 129.2, 129.1, 119.9, 119.6, 117.6, 117.3, 115.9, 59.1, 54.2, 48.8, 45.9.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{21}N_2$ 265.1705; found 265.1709.

4-(*o*-Tolyl)-2-vinylmorpholine (4b)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: 2-(*o*-tolylamino)ethan-1-ol (75.6 mg, 0.5 mmol, 1.0 equiv) (added as though it were a solid due to the high viscosity), (*Z*)-but-2-ene-1,4-diyl di-*t*-butyl bis(carbonate) (144.17 mg 0.5 mmol, 139.7 μL, 1.0 equiv), Et_3N (151.7 mg, 1.5 mmol, 209.0 μL, 3.0 equiv), methyl formate (30.0 mg, 0.5 mmol, 30.6 μL, 1.0 equiv), 2 wt % TPGS-750-M / H_2O (1.5 mL), 1000 ppm Pd (20 μL of stock solution from Section 2.1). The desired compound was obtained as a colorless oil (70.4 mg / 74%).

TLC: R_f = 0.80 with 20:80 Et_2O/hexanes, UV active, stains with $KMnO_4$.

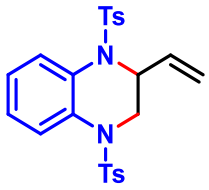
Flash column chromatography: hexanes, then 7:93 Et_2O/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.27 – 7.18 (m, 2H), 7.04 (td, *J* = 7.9, 7.2, 1.4 Hz, 2H), 5.91 (ddd, *J* = 17.1, 10.6, 5.6 Hz, 1H), 5.40 (dt, *J* = 17.4, 1.6 Hz, 1H), 5.24 (dt, *J* = 10.7, 1.4 Hz, 1H), 4.23 (dddd, *J* = 9.9, 5.6, 2.6, 1.3 Hz, 1H), 4.05 (ddd, *J* = 11.1, 3.0, 1.9 Hz, 1H), 3.91 (td, *J* = 10.8, 3.0 Hz, 1H), 3.08 – 2.93 (m, 2H), 2.93 – 2.85 (m, 1H), 2.66 (dd, *J* = 11.6, 9.9 Hz, 1H), 2.36 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.0, 136.3, 132.7, 131.2, 126.7, 123.6, 119.2, 116.6, 76.9, 56.8, 51.7, 17.9.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calculated for $C_{13}H_{18}NO$ 204.1388; found 204.1383.

1,4-Ditosyl-2-vinyl-1,2,3,4-tetrahydroquinoxaline (4c)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: *N*,*N*'-(1,2-phenylene)bis(4-methylbenzenesulfonamide) (208.2 mg, 0.5 mmol, 1.0 equiv), (*Z*)-but-2-ene-1,4-diyl di-*t*-butyl bis(carbonate) (144.17 mg 0.5 mmol, 139.7 μL, 1.0 equiv), Et_3N (151.7 mg, 1.5 mmol, 209.0 μL, 3.0 equiv), methyl formate (30.0 mg, 0.5 mmol, 30.6 μL, 1.0 equiv), 2 wt % TPGS-750-M / H_2O (1.5 mL), 1000 ppm Pd (20 μL of stock solution from Section 2.1). The desired compound was obtained as a white solid (218 mg / 93%).

TLC: R_f = 0.50 with 1:3 EtOAc/hexanes, UV active, stains with $KMnO_4$.

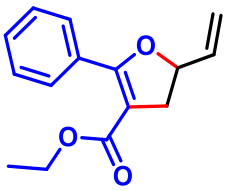
Flash column chromatography: hexanes, then 15:85 EtOAc/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.80 – 7.75 (m, 1H), 7.55 (dd, *J* = 9.2, 3.0 Hz, 3H), 7.46 (d, *J* = 8.1 Hz, 2H), 7.20 (dd, *J* = 13.9, 8.0 Hz, 4H), 7.06 – 6.98 (m, 2H), 5.62 (ddd, *J* = 17.3, 10.4, 4.8 Hz, 1H), 5.33 – 5.23 (m, 1H), 5.10 (dd, *J* = 10.6, 1.8 Hz, 1H), 5.06 (dq, *J* = 4.2, 2.2 Hz, 1H), 4.06 (dd, *J* = 12.8, 4.0 Hz, 1H), 3.27 (dd, *J* = 12.8, 4.4 Hz, 1H), 2.38 (d, *J* = 3.3 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.2, 144.2, 136.4, 135.6, 133.4, 130.6, 129.9, 129.8, 127.2, 127.0, 126.0, 125.9, 125.7, 123.7, 119.5, 118.7, 55.7, 47.8, 21.6, 21.5.

Spectra matched those previously reported.[170]

Ethyl 2-phenyl-5-vinyl-4,5-dihydrofuran-3-carboxylate (4d)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: freshly distilled ethyl benzoylacetate (96.1 mg, 0.5 mmol, 86.6 µL, 1.0 equiv), (*Z*)-but-2-ene-1,4-diyl dibenzoate (148.1 mg 0.5 mmol, 1.0 equiv), Et_3N (101.1 mg, 1.0 mmol, 139 µL, 2.0 equiv), methyl formate (30.0 mg, 0.5 mmol, 30.6 µL, 1.0 equiv),

[170] Massacret, M.; Lhoste, P.; Sinou, D. *Euro. J. Org. Chem.* **1999**, *1999*, 129–134.

2 wt % TPGS-750-M / H_2O (2.0 mL), 1000 ppm Pd (20 µL of stock solution from section 2.1). The desired compound was obtained as a pale-yellow oil (71 mg / 58%).

TLC: R_f = 0.50 with 20:80 Et_2O/hexanes, UV active, stains red with vanillin.

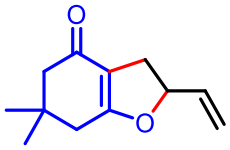
Flash Column chromatography: hexanes, then 5:95 Et_2O/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.84 – 7.76 (m, 2H), 7.45 – 7.35 (m, 3H), 6.03 (ddd, *J* = 17.0, 10.4, 6.5 Hz, 1H), 5.42 – 5.22 (m, 2H), 5.22 – 5.13 (m, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.31 (dd, *J* = 15.0, 10.5 Hz, 1H), 2.93 (dd, *J* = 15.0, 8.2 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.3, 164.7, 137.0, 130.4, 130.1, 129.4, 127.7, 116.9, 102.2, 82.0, 59.8, 37.5, 14.3.

Spectra matched those previously reported.[171]

6,6-Dimethyl-2-vinyl-3,5,6,7-tetrahydrobenzofuran-4(2H)-one (4e)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: dimedone (70.1 mg, 0.5 mmol, 1.0 equiv), (Z)-but-2-ene-1,4-diyl dibenzoate (148.1 mg 0.5 mmol, 1.0 equiv), Et_3N (151.7 mg, 1.5 mmol, 209 µL, 3.0 equiv), methyl formate (30.0 mg, 0.5 mmol, 30.6 µL, 1.0 equiv), 2 wt % TPGS-750-M / H_2O (1.5 mL), 1000 ppm Pd (20 µL of stock solution from section 2.1). The desired compound was

[171] Wang, Y.; Zhang, W.-Y.; You, S.-L. *J. Am. Chem. Soc.* **2019**, *141*, 2228–2232.

obtained as a pale-yellow oil (76.1 mg / 79%). See scale-up example for large scale trial procedure and purification.

TLC: R_f = 0.30 with 40:60 EtOAc/ hexanes, UV active, stains with $KMnO_4$.

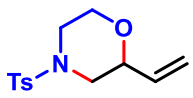
Flash column chromatography: 10:90 EtOAc/hexanes, then 30:70 EtOAc/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.87 (ddd, *J* = 17.1, 10.3, 6.7 Hz, 1H), 5.28 – 5.10 (m, 3H), 3.00 – 2.91 (m, 1H), 2.59 – 2.51 (m, 1H), 2.24 (t, *J* = 1.9 Hz, 2H), 2.16 (s, 2H), 1.04 (d, *J* = 4.0 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 194.6, 175.9, 136.3, 117.1, 111.3, 85.8, 50.9, 37.7, 34.0, 31.6, 28.7, 28.6.

Spectra match those previously reported.[172]

4-*N*-Tosyl-2-vinylmorpholine (4f)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: *N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide (107.6 mg, 0.5 mmol, 1.0 equiv), (*Z*)-but-2-ene-1,4-diyl di-*t*-butyl bis(carbonate) (144.2 mg 0.5 mmol, 139.7 µL, 1.0 equiv), Et_3N (151.7 mg, 1.5 mmol, 209 µL, 3.0 equiv), methyl formate (30.0 mg, 0.5 mmol, 30.6 µL, 1.0 equiv), 2 wt % TPGS-750-M / H_2O (1.2 mL), 1000 ppm Pd (20 µL of stock solution from section 2.1). The desired compound was obtained as a white

[172] Tanimori, S.; Kato, Y.; Kirihata, M. *Synthesis* **2006**, 5, 865 – 869.

solid (99.2 mg / 74%). Using the same ratio of reagents, but with (*Z*)-but-2-ene-1,4-diyl dibenzoate as electrophile gave this compound (89.0 mg / 67%).

TLC: R_f = 0.50, running the plate 1/8th of the way with 10:90 MeOH/DCM, drying, then running the plate all the way with 25:75 EtOAc/hexanes (this separates baseline material from the very polar nucleophile). UV active, stains with $KMnO_4$.

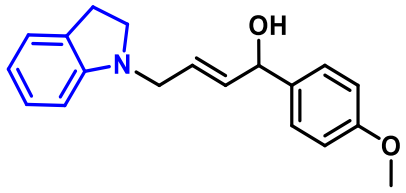
Flash column chromatography: hexanes then 20:80 EtOAc/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.65 – 7.58 (m, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.70 (ddd, *J* = 17.4, 10.7, 5.4 Hz, 1H), 5.31 (dt, *J* = 17.4, 1.4 Hz, 1H), 5.19 (dt, *J* = 10.7, 1.4 Hz, 1H), 4.03 (dddt, *J* = 8.2, 5.4, 2.6, 1.3 Hz, 1H), 3.93 (ddd, *J* = 11.7, 3.4, 1.6 Hz, 1H), 3.69 (td, *J* = 11.5, 2.7 Hz, 1H), 3.54 (ddt, *J* = 39.4, 11.4, 2.2 Hz, 2H), 2.42 (s, 3H), 2.41 – 2.36 (m, 1H), 2.10 (dd, *J* = 11.4, 10.2 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.04, 134.75, 132.15, 129.85, 127.90, 117.74, 75.71, 65.76, 50.05, 45.43, 21.60.

Spectra matched those previously reported.[173]

(*E*)-4-(Indolin-1-yl)-1-(4-methoxyphenyl)but-2-en-1-ol (5a)



[173] Bandini, M.; Monari, M.; Romaniello, A.; Tragni, M. *Chem. Euro. J.* **2010**, *16*, 14272–14277.

The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: indoline (59.6 mg, 0.5 mmol, 56.2 μL, 1.0 equiv), 2-(4-methoxyphenyl)-3-vinyloxirane (105.7 mg, 0.6 mmol, 100.1 μL, 1.2 equiv), K_2CO_3 (138.2 mg, 1.0 mmol, 2.0 equiv), methyl formate (30.0 mg, 0.5 mmol, 30.6 μL, 1.0 equiv), 2 wt % TPGS-750-M / H_2O (1.0 mL), 1000 ppm Pd (20 μL of stock solution from section 2.1). The desired compound was obtained as a pale-yellow oil which darkens upon exposure to air (139.0 mg / 94%). Note: compound is unstable and decomposes in <30 days.

TLC: R_f = 0.50 with 50:50 EtOAc/hexanes, UV active, stains with vanillin and Seebach's magic stain and $KMnO_4$.

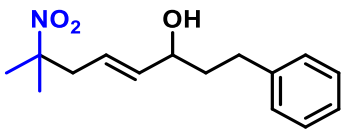
Flash column chromatography: 25:75 EtOAc/hexanes then 50:50 EtOAc/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34 – 7.27 (m, 2H), 7.15 – 7.06 (m, 2H), 6.96 – 6.88 (m, 2H), 6.71 (td, *J* = 7.3, 0.9 Hz, 1H), 6.53 (d, *J* = 7.8 Hz, 1H), 6.00 – 5.82 (m, 2H), 5.18 (d, *J* = 6.0 Hz, 1H), 3.83 (s, 3H), 3.78 – 3.71 (m, 2H), 3.41 – 3.28 (m, 2H), 2.98 (t, *J* = 8.3 Hz, 2H), 2.37 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 152.1, 135.5, 135.3, 130.3, 127.6, 127.4, 127.3, 127.3, 126.7, 124.5, 117.9, 114.1, 114.0, 107.5, 74.1, 55.3, 53.3, 50.9, 28.6.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calculated for $C_{19}H_{22}NO_2$ 296.1650; found 296.1654.

(*E*)-7-Methyl-7-nitro-1-phenyloct-4-en-3-ol (5b)



The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: 2-nitropropane (44.6 mg, 0.5 mmol, 45.4 μL, 1.0 equiv), 2-phenethyl-3-vinyloxirane (95.83 mg, 0.55 mmol, 97.2 μL, 1.1 equiv), Et_3N (151.8 mg, 1.5 mmol, 3.0 equiv), methyl formate (30.0 mg, 0.5 mmol, 30.6 μL, 1.0 equiv), 2 wt % TPGS-750-M / H_2O (0.5 mL), 1000 ppm Pd (20 μL of stock solution from Section 2.1). The desired compound was obtained as a colorless oil (89.0 mg / 68%). Note: compound is unstable and decomposes in <30 days.

TLC: R_f = 0.25 with 25:75 EtOAc/hexanes, UV active, stains blue with vanillin, and also stains with Seebach's magic stain and $KMnO_4$.

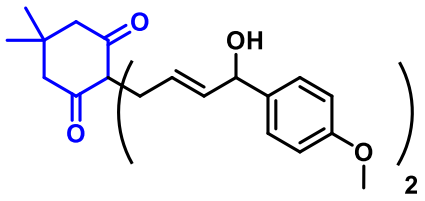
Flash column chromatography: hexanes then 20:80 EtOAc/hexanes.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34 – 7.28 (m, 2H), 7.25 – 7.18 (m, 3H), 5.69 – 5.62 (m, 1H), 5.61 – 5.51 (m, 1H), 4.11 (q, *J* = 6.4 Hz, 1H), 2.70 (tdt, *J* = 13.8, 9.2, 6.7 Hz, 2H), 2.62 (d, *J* = 7.2 Hz, 2H), 2.03 – 1.93 (m, 1H), 1.91 – 1.76 (m, 2H), 1.59 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 141.8, 138.9, 128.5, 128.5, 128.4, 128.4, 128.4, 125.9, 123.6, 88.0, 71.6, 43.5, 38.7, 31.6, 25.6, 25.5.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calculated for $C_{15}H_{21}NO_3Na$ 286.1419; found 286.1417.

2,2-bis((*E*)-4-Hydroxy-4-(4-methoxyphenyl)but-2-en-1-yl)-5,5-dimethylcyclohexane-1,3-dione (5c)



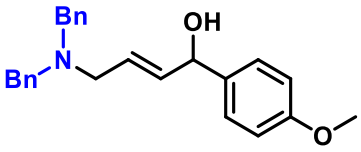
The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: dimedone (70.1 mg, 0.5 mmol, 1.0 equiv), 2-(4-methoxyphenyl)-3-vinyloxirane (88.1 mg, 0.50 mmol, 83.4 μL, 1.0 equiv), Et_3N (152 mg, 1.5 mmol, 210 μL, 3.0 equiv), 2 wt % TPGS-750-M / H_2O (1.0 mL), 1000 ppm Pd (20 μL of stock solution from Section 2.1). The desired compound was obtained as a pale-yellow oil (119.7 mg / 97%, using the electrophile as limiting reagent).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.21 – 7.15 (m, 4H), 6.85 – 6.80 (m, 4H), 5.67 (dd, *J* = 15.3, 6.4 Hz, 2H), 5.52 – 5.43 (m, 2H), 5.00 (d, *J* = 6.3 Hz, 2H), 3.76 (s, 6H), 2.65 – 2.53 (m, 2H), 2.44 (td, *J* = 8.5, 7.9, 2.7 Hz, 8H), 0.86 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 209.07, 208.97, 208.86, 159.05, 137.62, 135.17, 135.16, 127.60, 127.59, 124.85, 124.81, 113.89, 113.86, 74.14, 68.17, 68.14, 55.32, 51.99, 37.21, 37.18, 30.74, 28.69.

HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ calcd for $C_{30}H_{36}O_6Na$ 515.2410; found 515.2408.

(*E*)-4-(Dibenzylamino)-1-(4-methoxyphenyl)but-2-en-1-ol (5d)



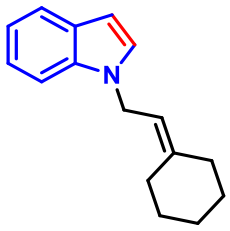
The titled compound was obtained according to the procedure in Section 4.15 using the following quantities: dibenzylamine (98.6 mg, 0.5 mmol, 96.1 µL, 1.0 equiv), 2-(4-methoxyphenyl)-3-vinyloxirane (88.1 mg, 0.5 mmol, 83.4 µL, 1.0 equiv), Et_3N (101.1 mg, 1.0 mmol, 126.5 µL, 2.0 equiv), 2 wt % TPGS-750-M / H_2O (1.0 mL), 1000 ppm Pd (20 µL of stock solution from section 2.1). The desired compound was obtained as a pale-yellow oil (274.4 mg / 74%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.47 – 7.43 (m, 4H), 7.42 – 7.35 (m, 5H), 7.35 – 7.29 (m, 4H), 6.96 – 6.90 (m, 2H), 5.89 (q, *J* = 2.4 Hz, 2H), 5.20 – 5.16 (m, 1H), 3.84 (s, 3H), 3.66 (s, 4H), 3.16 (q, *J* = 1.8 Hz, 2H), 2.23 (s, 1H), 2.10 (s, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.07, 139.64, 135.49, 135.37, 128.85, 128.66, 128.25, 127.58, 126.90, 113.91, 74.21, 58.13, 55.28, 55.19.

HRMS (ESI-TOF) *m/z*: $[M + H]^+$ calculated for $C_{25}H_{27}NO_2H$ 374.2120; found 374.2124.

1-(2-Cyclohexylideneethyl)-1H-indole (6a)



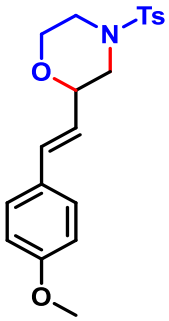
See Section 2.4 for experimental details.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.65 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.16 – 7.08 (m, 2H), 6.50 (d, *J* = 3.1 Hz, 1H), 5.35 (t, *J* = 7.1 Hz, 1H), 4.72 (d, *J* = 7.0 Hz, 2H), 2.36 (s, 2H), 2.14 (s, 2H), 1.67 – 1.57 (m, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 144.3, 136.1, 128.9, 127.4, 121.4, 121.0, 119.3, 116.6, 109.6, 101.0, 43.4, 37.1, 29.1, 28.5, 27.9, 26.8.

HRMS (CI-TOF) *m/z*: $[M]^+$ calculated for $C_{16}H_{19}N$ 225.1517; found 225.1525.

(*E*)-2-(4-Methoxystyryl)-4-tosylmorpholine (6b)



See Section 2.4 for experimental details.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.66 – 7.61 (m, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.30 – 7.24 (m, 2H), 6.86 – 6.80 (m, 2H), 6.59 (dd, *J* = 16.1, 1.2 Hz, 1H), 5.90 (dd, *J* = 16.0, 6.1 Hz, 1H), 4.21 – 4.15 (m, 1H), 3.97 (ddd, *J* = 11.6, 3.6, 1.6 Hz, 1H), 3.78 (s, 3H), 3.77 – 3.72 (m, 1H), 3.65 (dt, *J* = 11.5, 2.3 Hz, 1H), 3.54 (dq, *J* = 11.6, 2.2 Hz, 1H), 2.47 – 2.39 (m, 4H), 2.20 (dd, *J* = 11.5, 10.1 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.7, 144.0, 132.4, 132.2, 129.8, 128.9, 127.9, 127.8, 123.3, 114.1, 75.8, 65.8, 55.3, 50.5, 45.4, 21.6.

Spectra matched those previously reported.[174]

[174] Aubineau, T.; Cossy, J. *Org. Lett.* **2018**, *20*, 7419–7423.

4.14.5 NMR Spectra

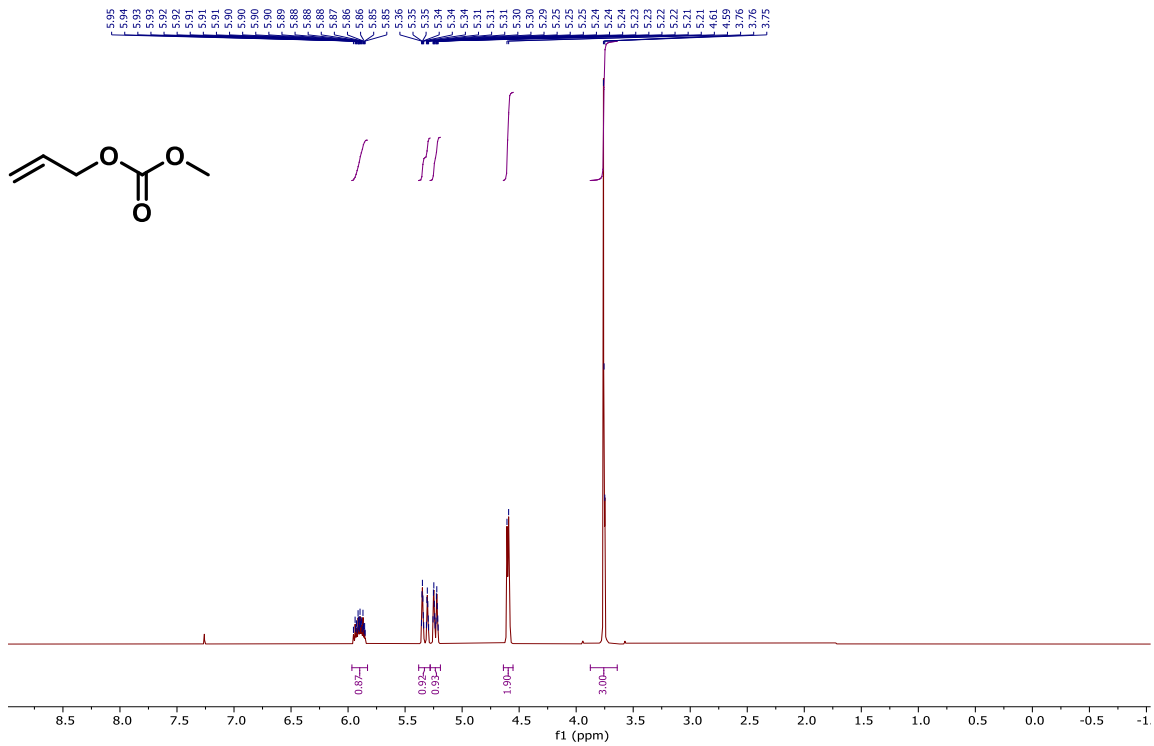


Figure 3: ^{1}H NMR (400 MHz, $CDCl_3$) of allyl methyl carbonate (**1**)

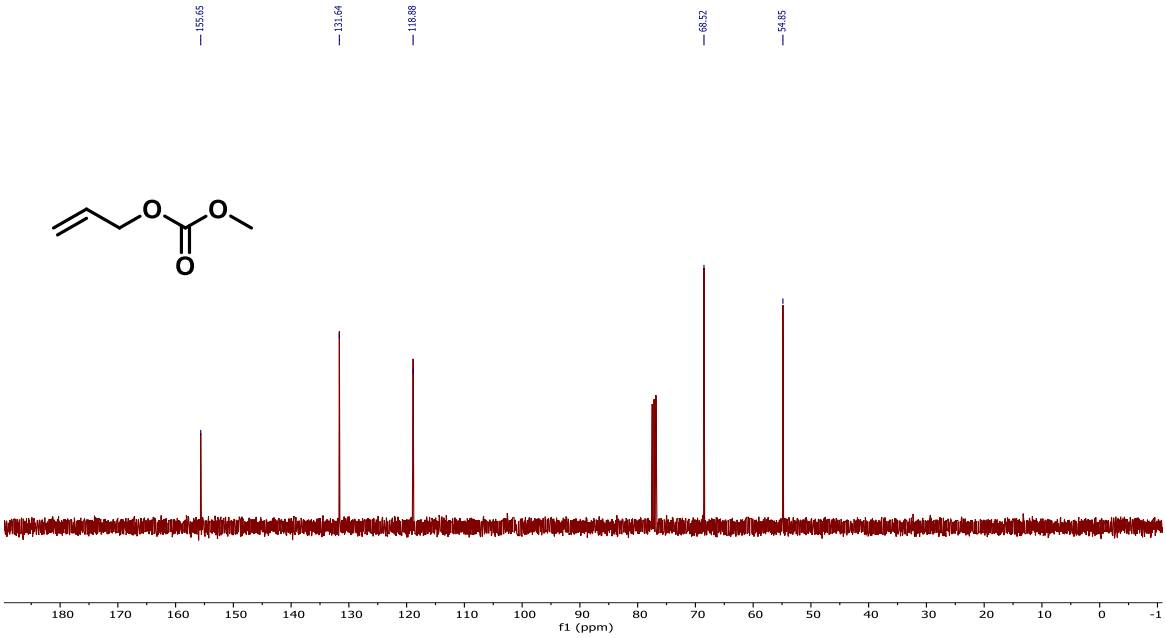


Figure 4: ^{13}C NMR (101 MHz, $CDCl_3$) of allyl methyl carbonate (**1**)

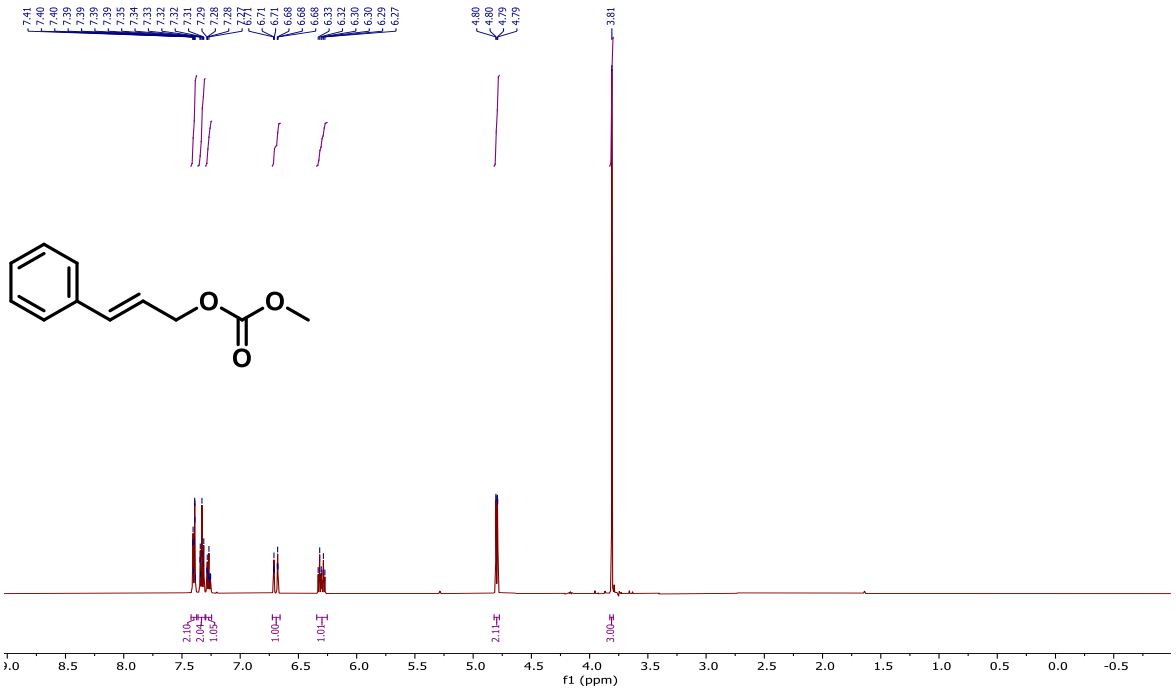


Figure 5: ^{1}H NMR (500 MHz, $CDCl_3$) of cinnamyl methyl carbonate (**2**)

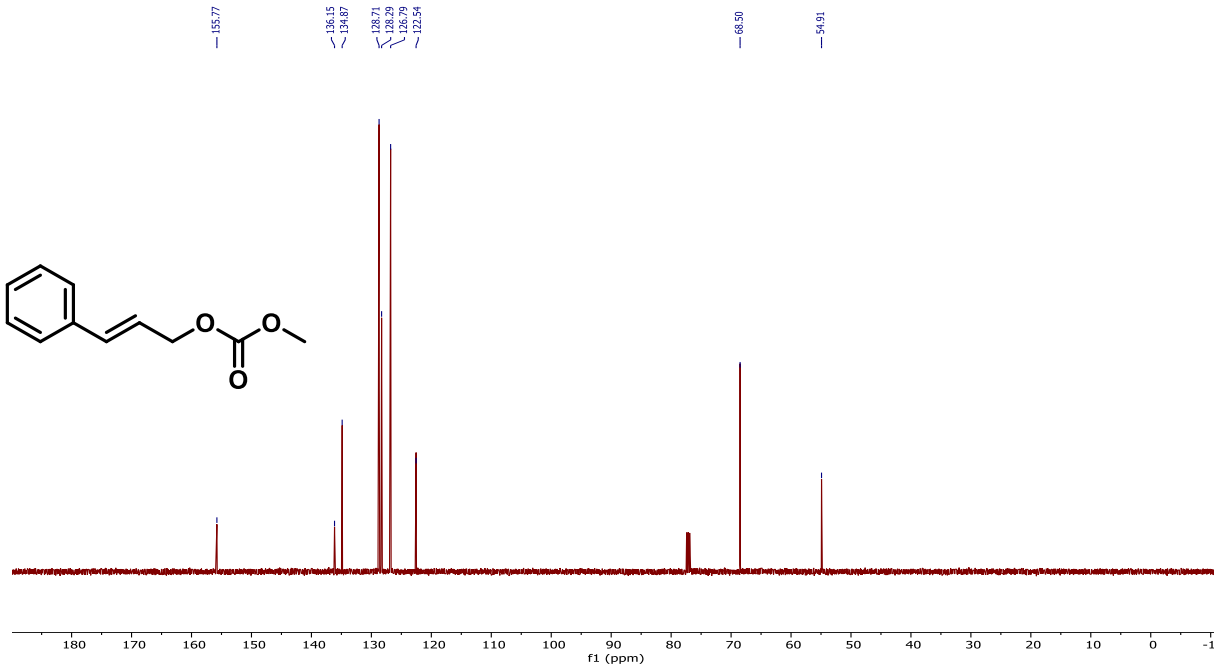


Figure 6: ^{1}H NMR (500 MHz, $CDCl_3$) of cinnamyl methyl carbonate (**2**)

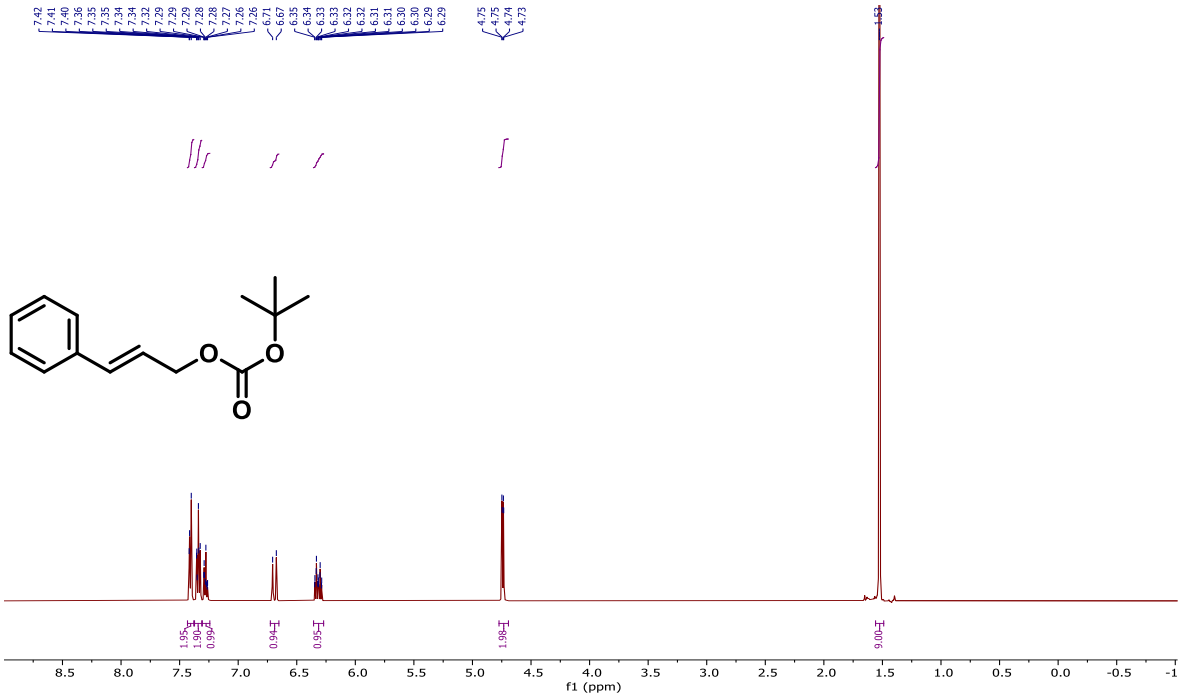


Figure 7: ^{1}H NMR (500 MHz, $CDCl_3$) of Cinnamyl *t*-butyl carbonate (**3**)

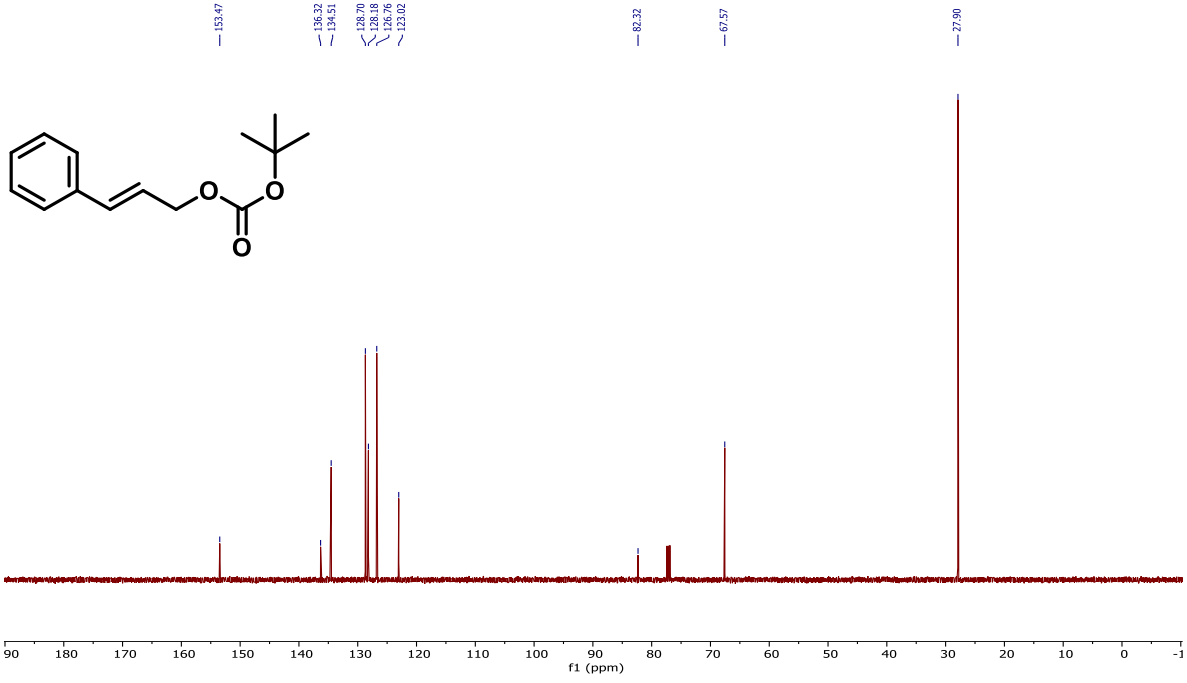


Figure 8: ^{13}C NMR (126 MHz, $CDCl_3$) of Cinnamyl *t*-butyl carbonate (**3**)

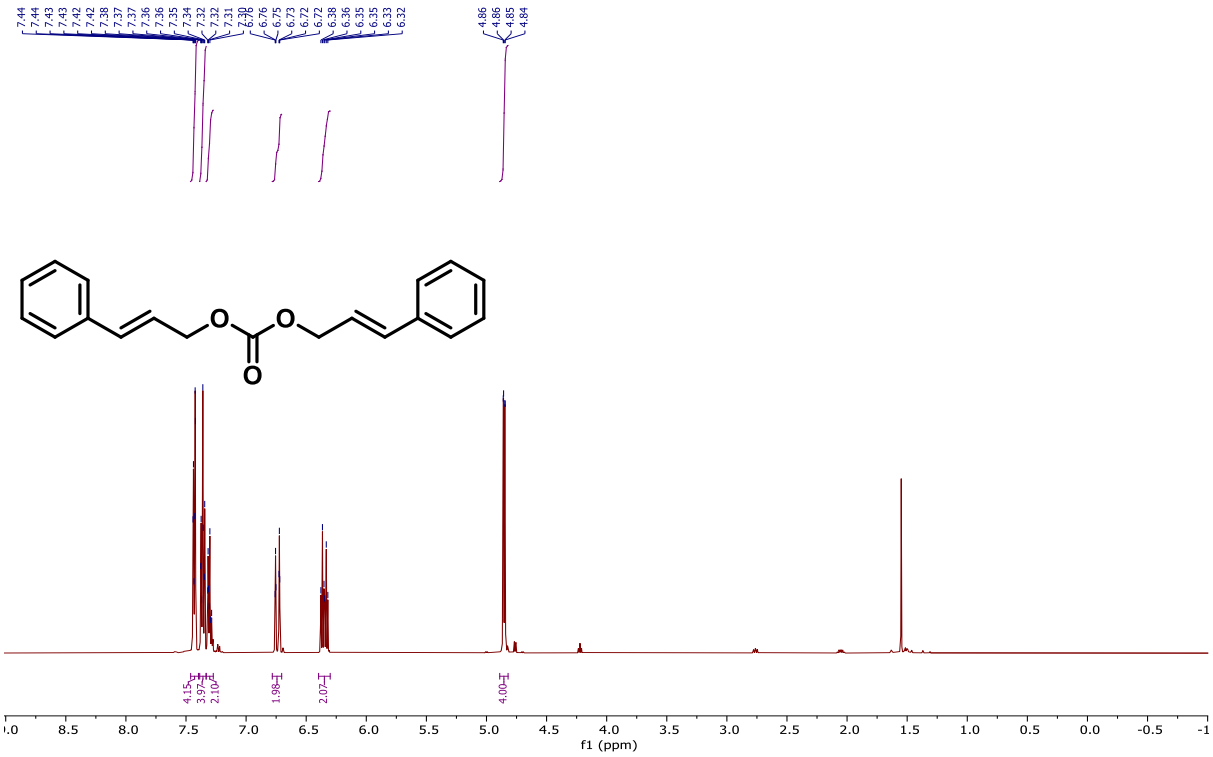


Figure 9: ^{1}H NMR (500 MHz, $CDCl_3$) of dicinnamyl carbonate (**4**)

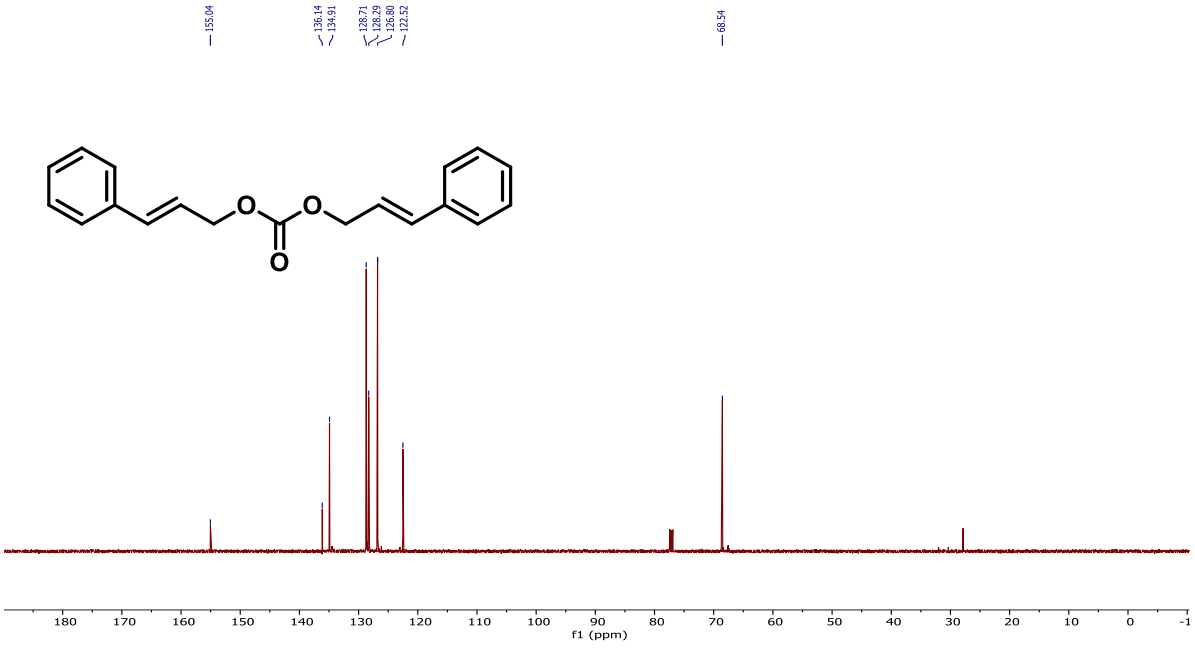


Figure 10: ^{13}C NMR (126 MHz, $CDCl_3$) of dicinnamyl carbonate (**4**)

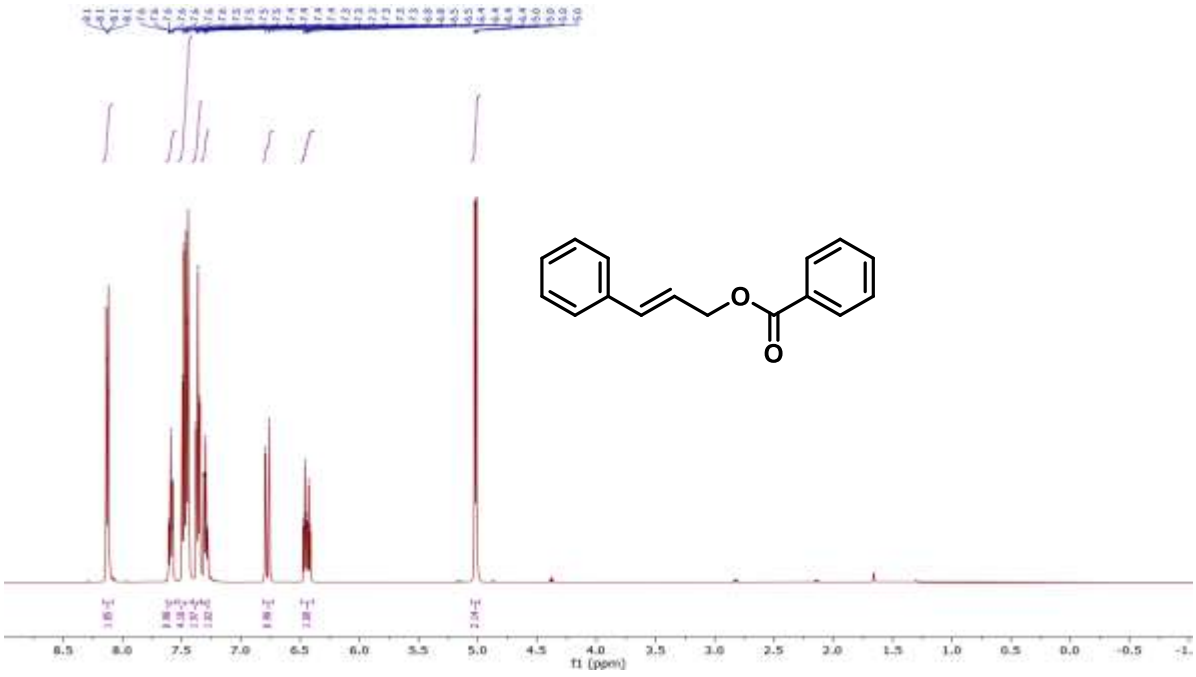


Figure 11: ^{1}H NMR (500 MHz, $CDCl_3$) of cinnamyl benzoate (**5**)

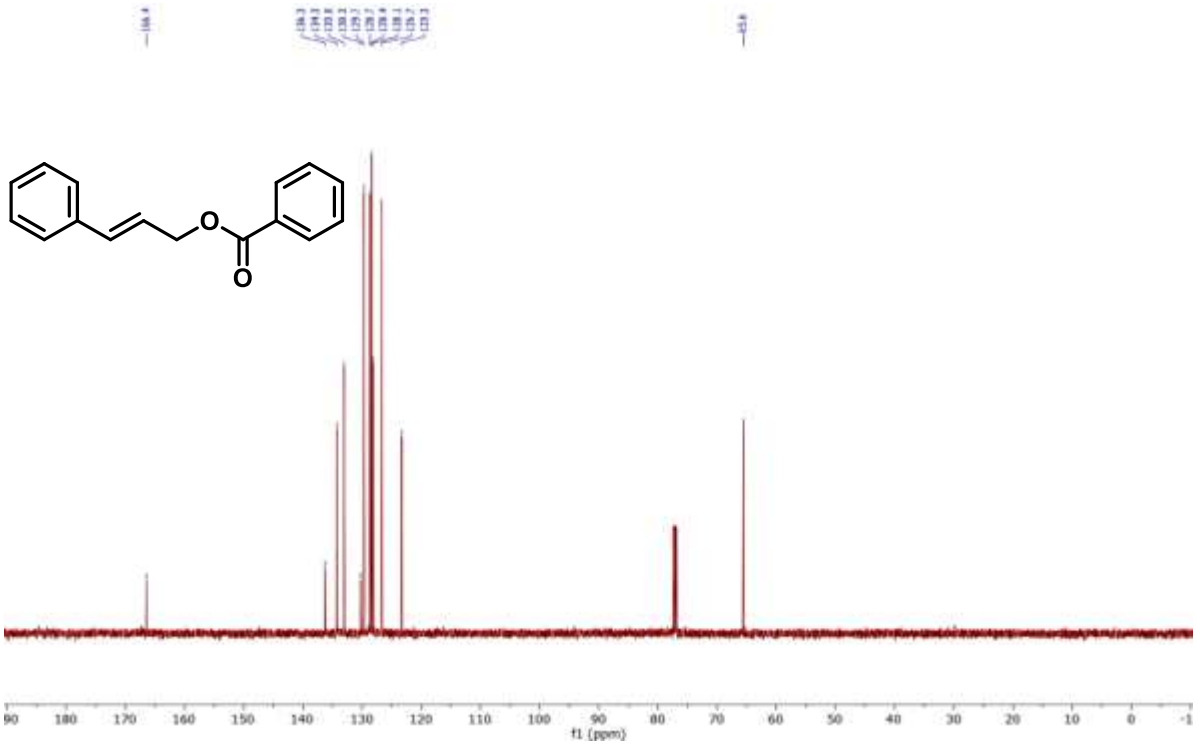


Figure 12: ^{13}C NMR (126 MHz, $CDCl_3$) of cinnamyl benzoate (**5**)

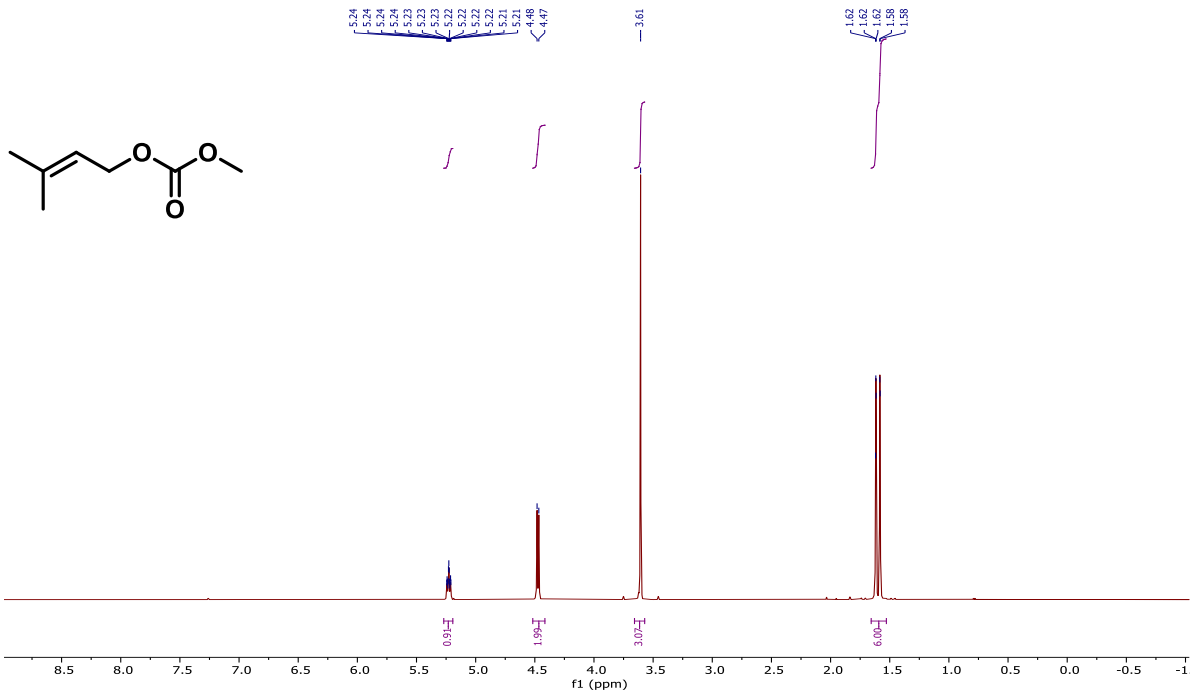


Figure 13: ^{1}H NMR (500 MHz, $CDCl_3$) of methyl (3-methylbut-2-en-1-yl) carbonate (**6**)

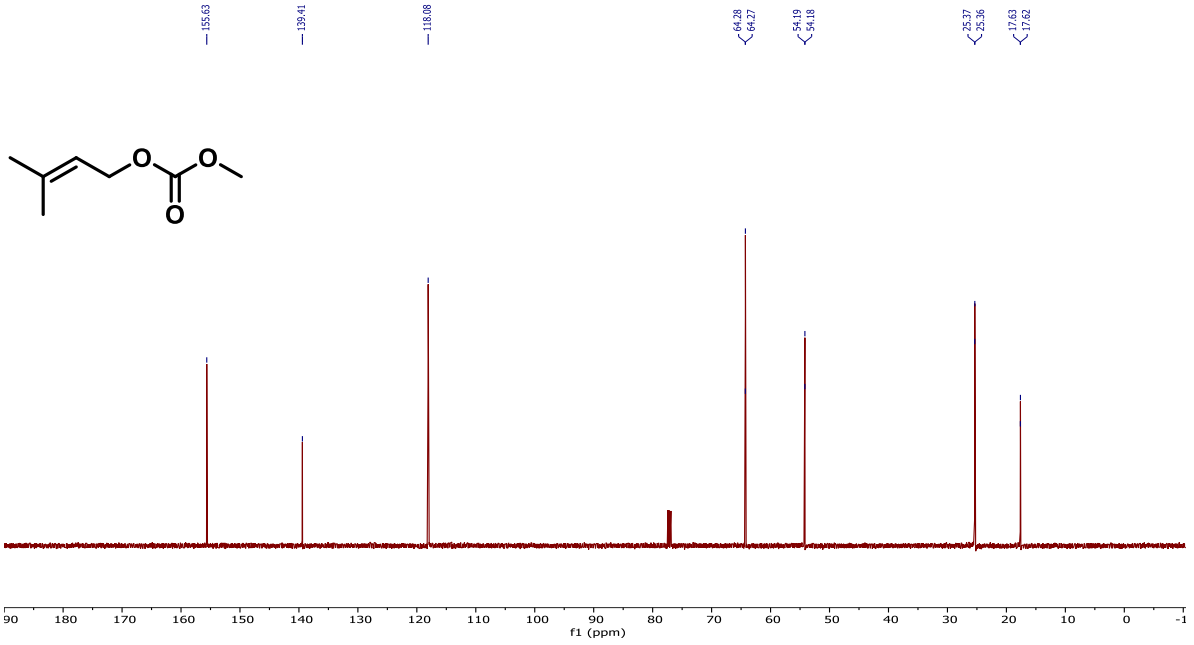


Figure 14: ^{13}C NMR (126 MHz, $CDCl_3$) of methyl (3-methylbut-2-en-1-yl) carbonate (**6**)

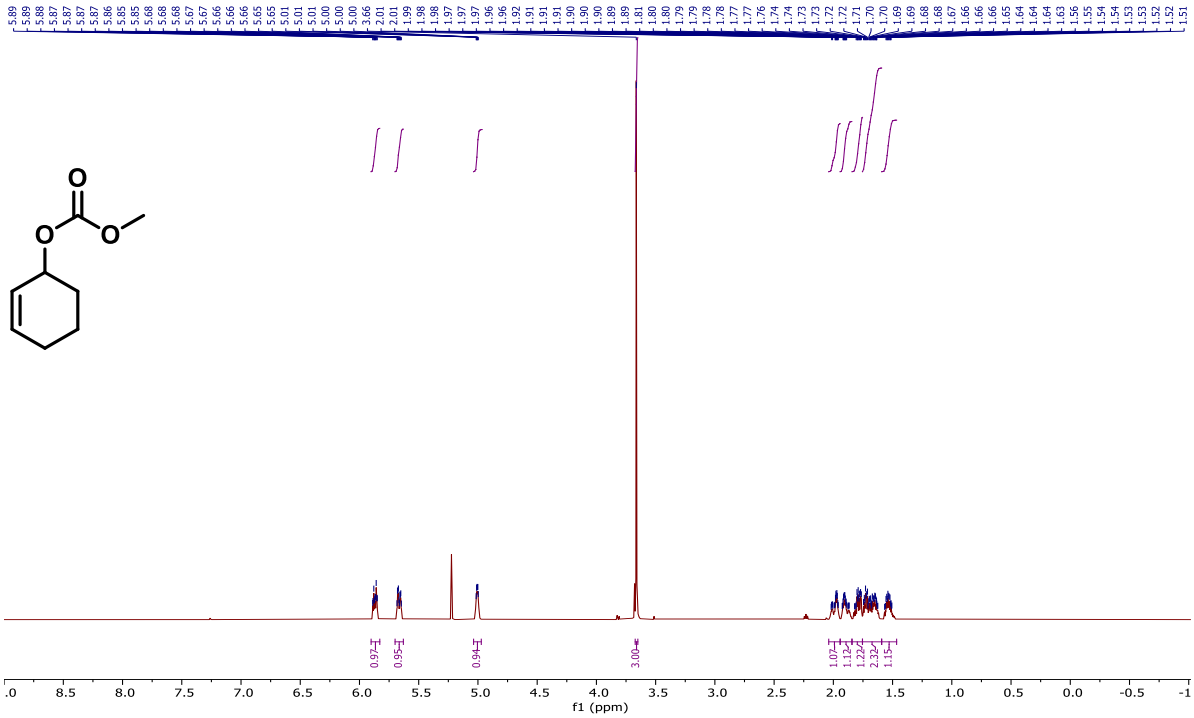


Figure 15: ^{1}H NMR (500 MHz, $CDCl_3$) of cyclohex-2-en-1-yl methyl carbonate (**7**)

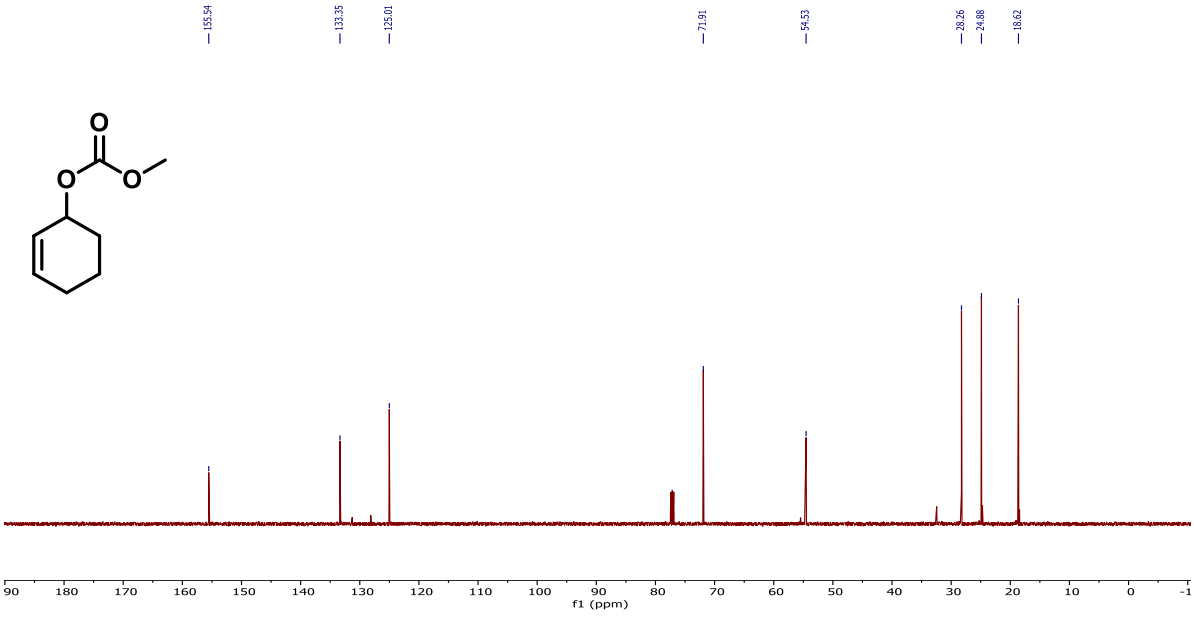


Figure 16: ^{13}C NMR (126 MHz, $CDCl_3$) of cyclohex-2-en-1-yl methyl carbonate (**7**)

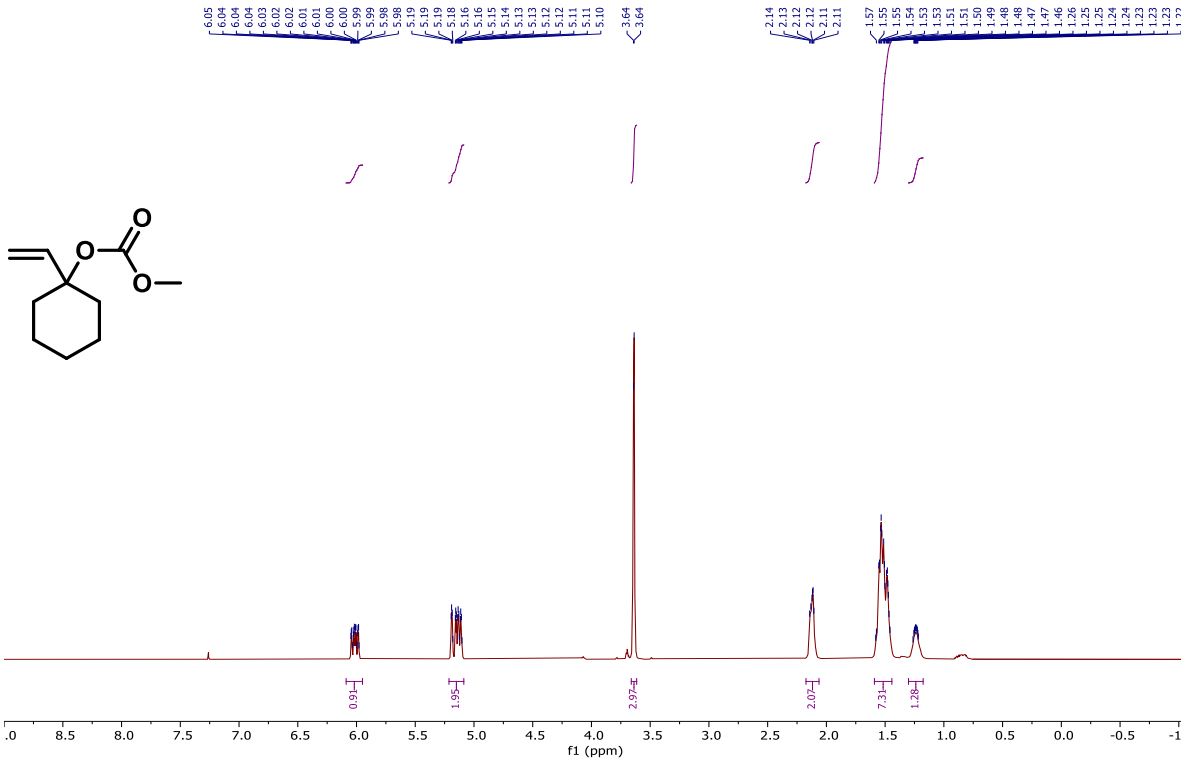


Figure 17: ^{1}H NMR (500 MHz, $CDCl_3$) of methyl (1-vinylcyclohexyl) carbonate (**8**)

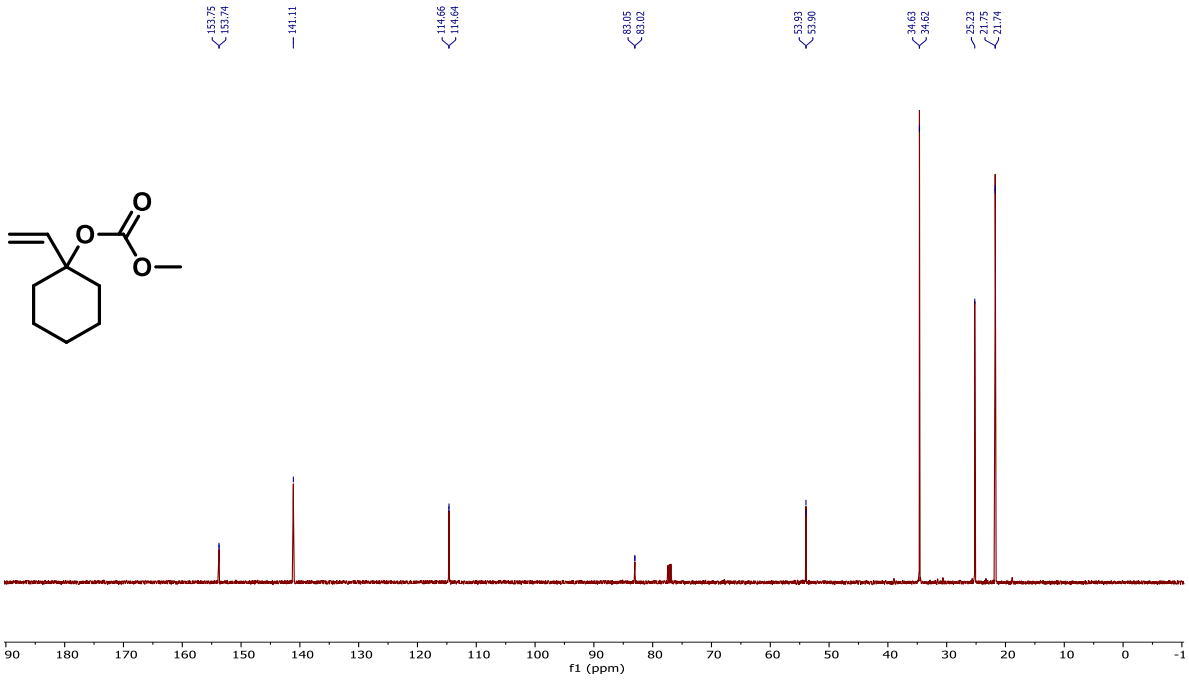


Figure 18: ^{13}C NMR (126 MHz, $CDCl_3$) of methyl (1-vinylcyclohexyl) carbonate (**8**)

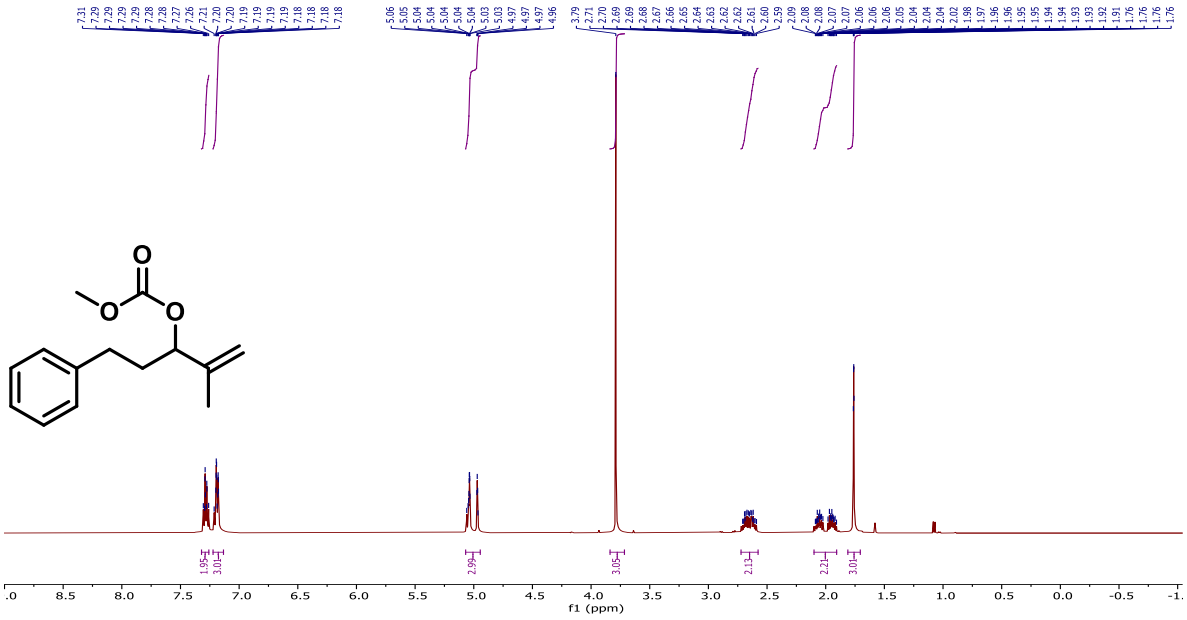


Figure 19: ^{1}H NMR (500 MHz, $CDCl_3$) of methyl (2-methyl-5-phenylpent-1-en-3-yl) carbonate (**9**)

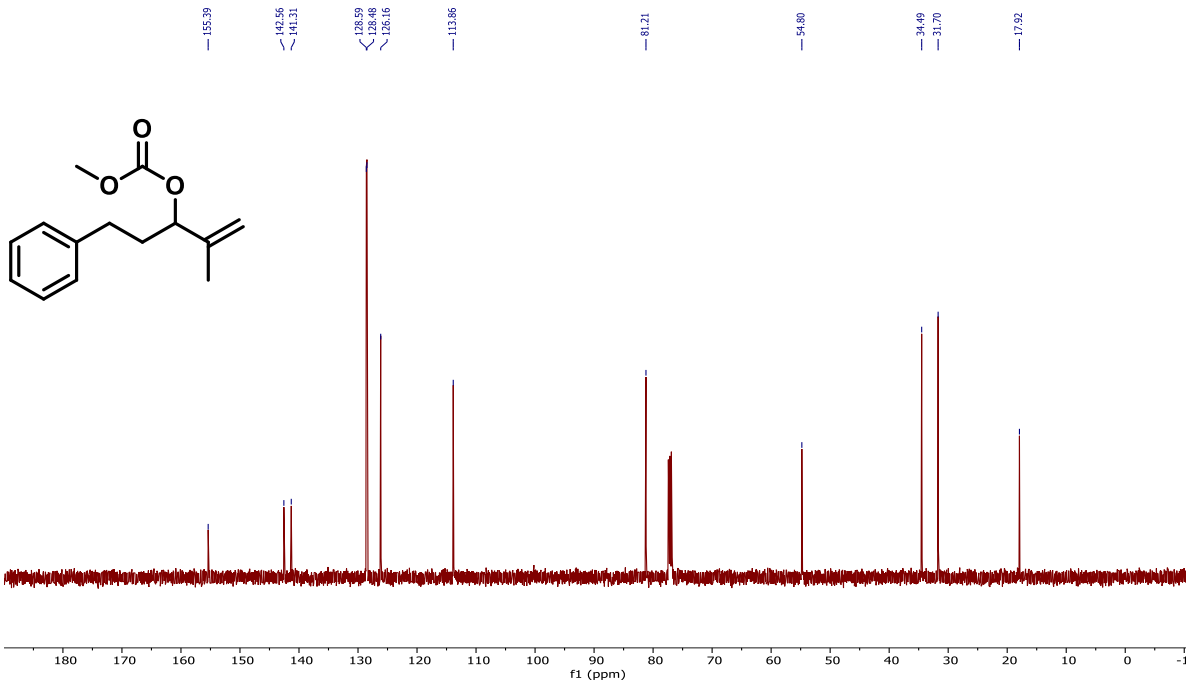


Figure 20: ^{13}C NMR (126 MHz, $CDCl_3$) of methyl (2-methyl-5-phenylpent-1-en-3-yl) carbonate (**9**)

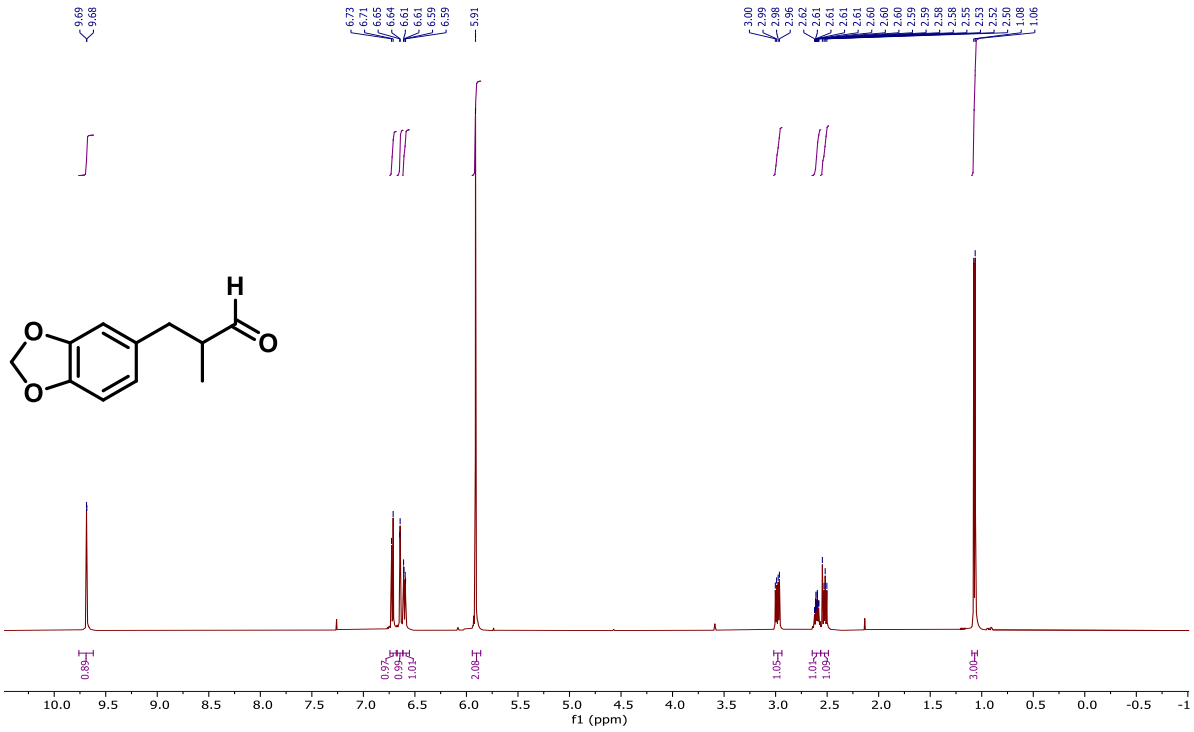


Figure 21: ^{1}H NMR (500 MHz, $CDCl_3$) of helional (**10**)

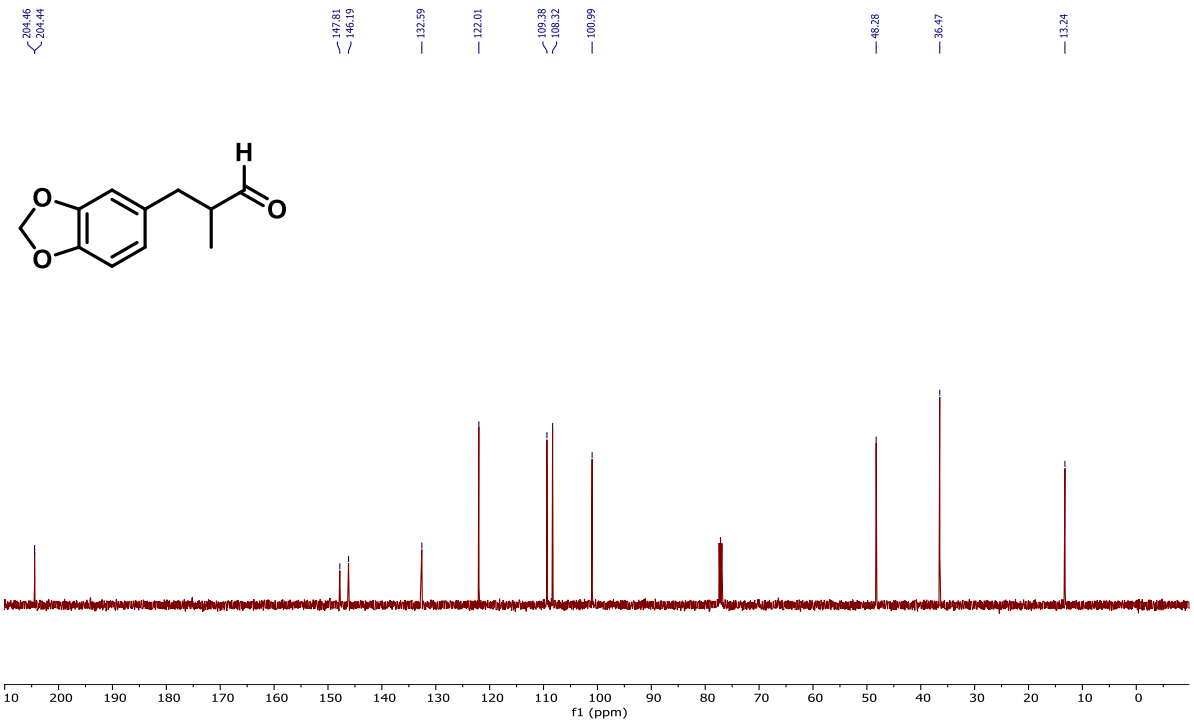


Figure 22: ^{1}H NMR (500 MHz, $CDCl_3$) of helional (**10**)

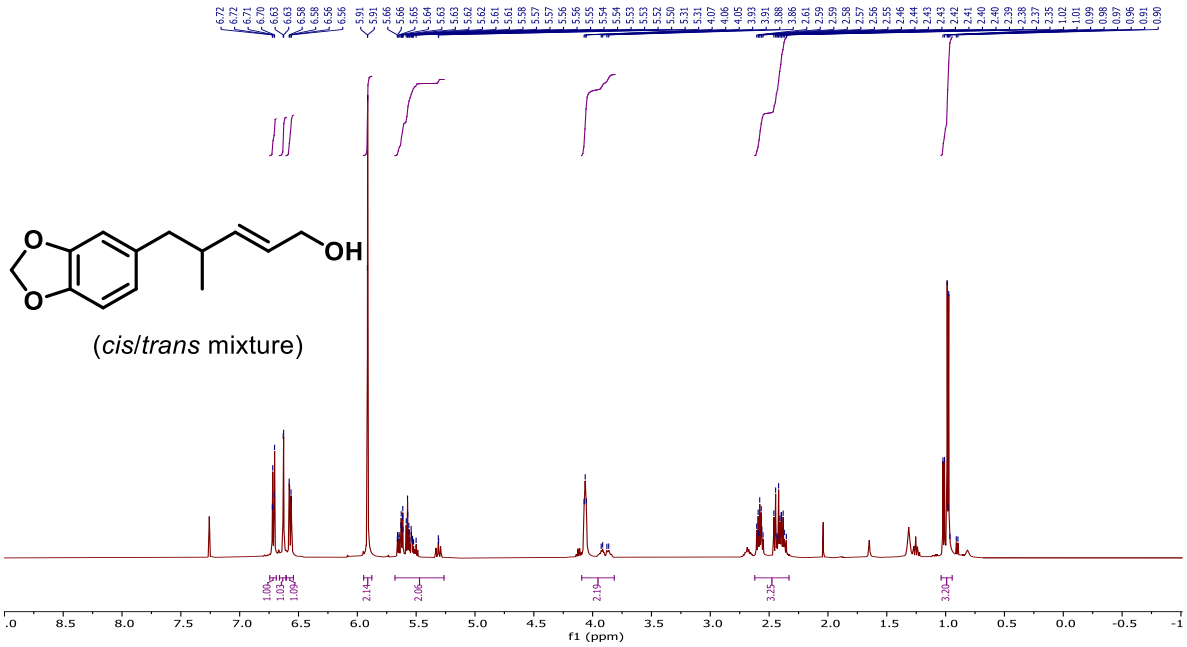


Figure 23: ^{1}H NMR (500 MHz, $CDCl_3$) of alcohol intermediate (**11**)

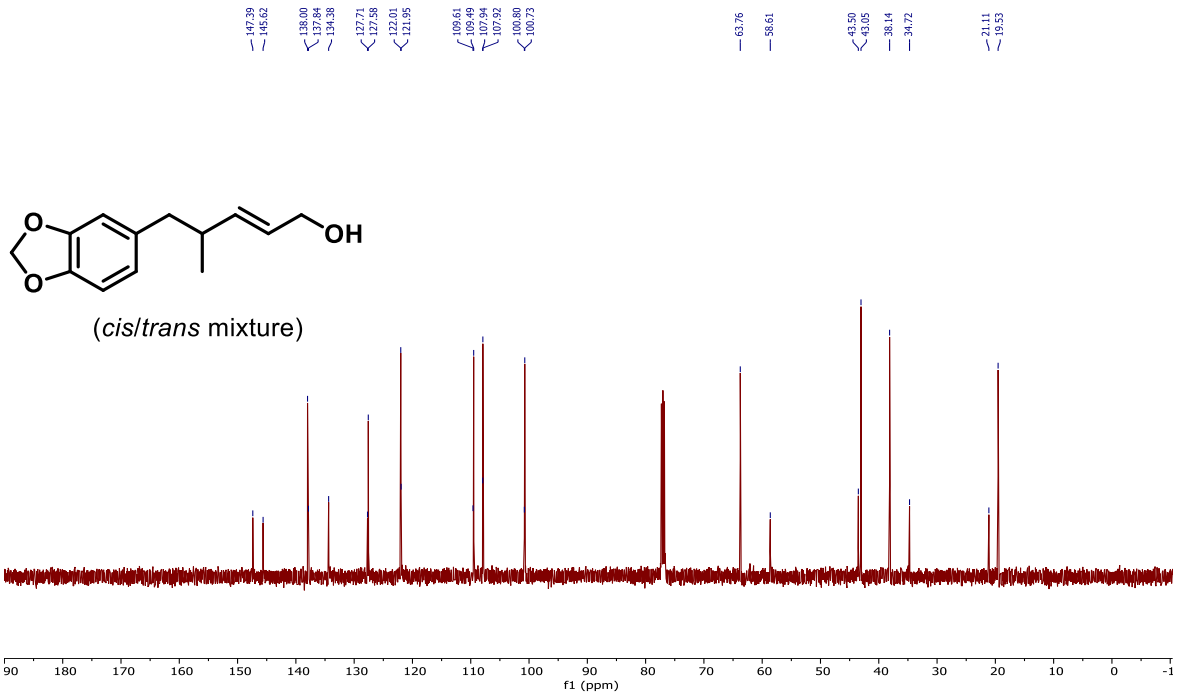


Figure 24: ^{13}C NMR (126 MHz, $CDCl_3$) of alcohol intermediate (**11**)

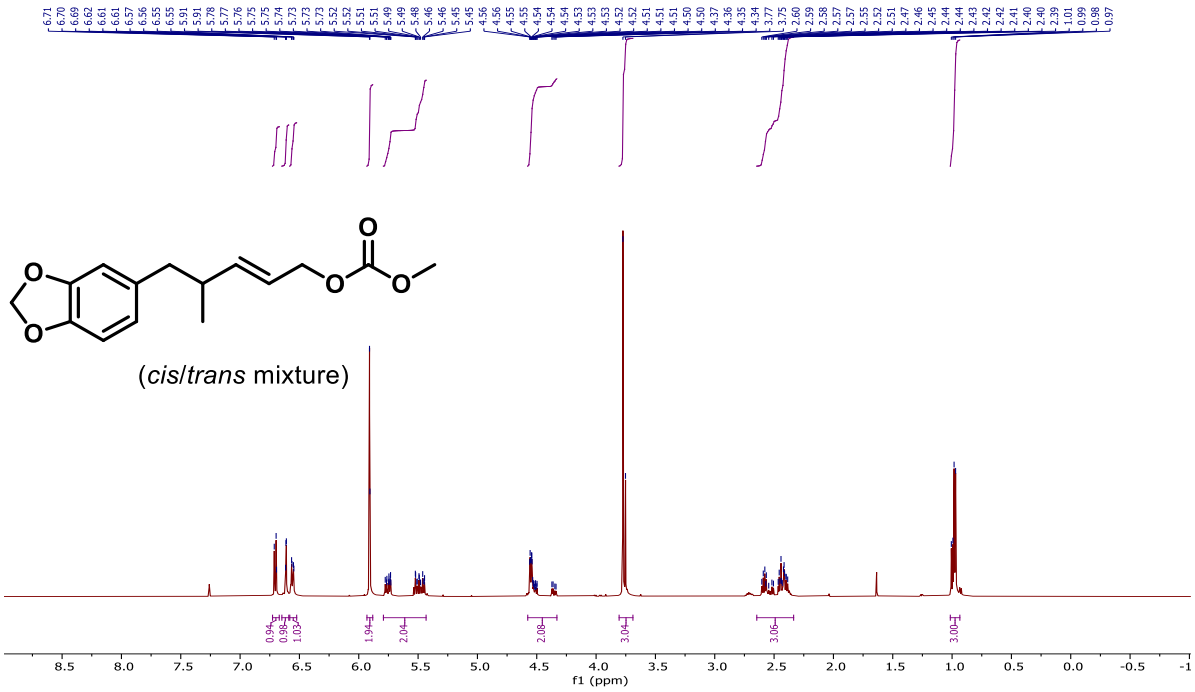


Figure 25: ^{1}H NMR (500 MHz, $CDCl_3$) of 5-(benzo[d][1,3]dioxol-5-yl)-4-methylpent-2-en-1-yl methyl carbonate (**12**)

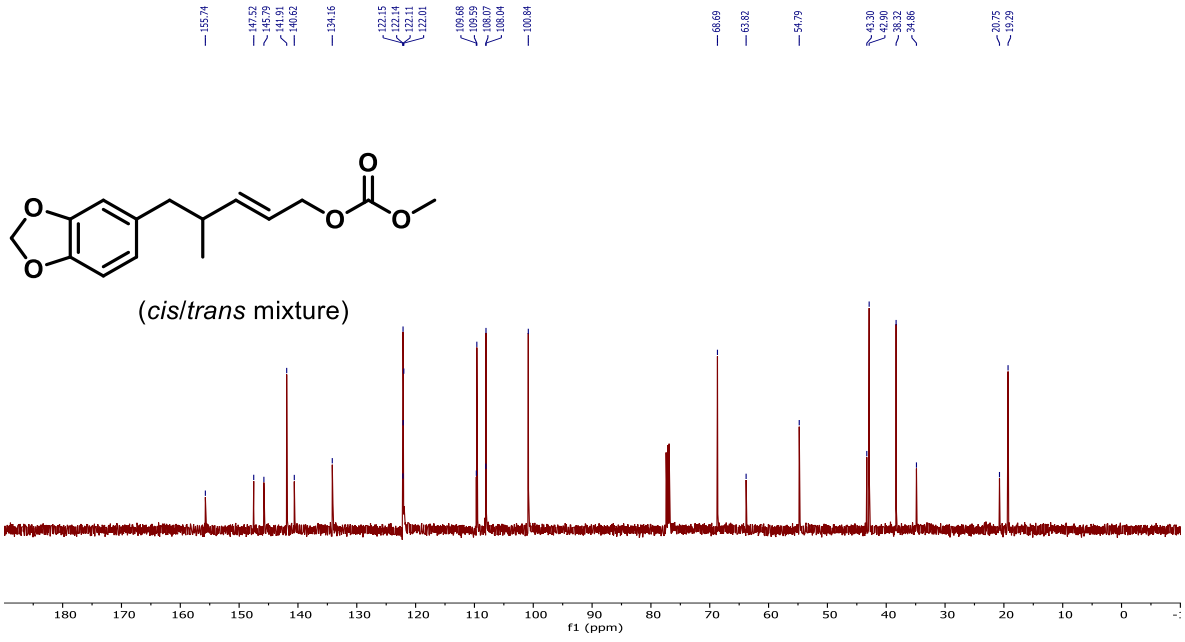


Figure 26: ^{13}C NMR (126 MHz, $CDCl_3$) of 5-(benzo[d][1,3]dioxol-5-yl)-4-methylpent-2-en-1-yl methyl carbonate (**12**)

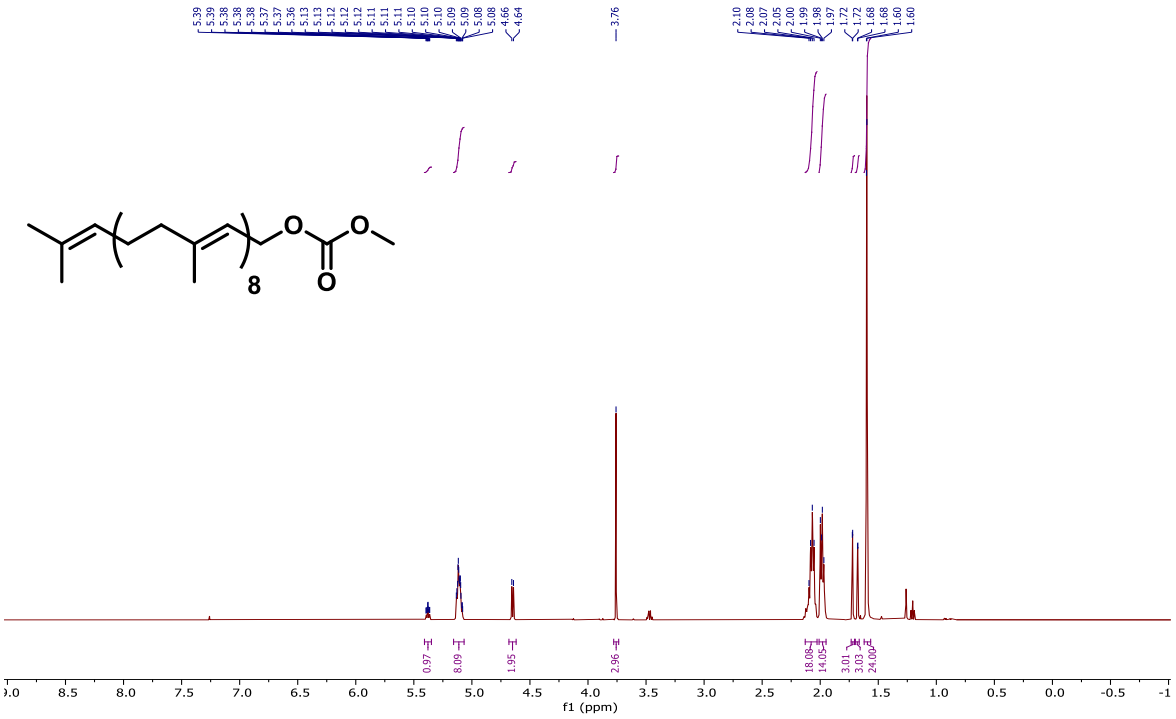


Figure 27: ^{1}H NMR (500 MHz, $CDCl_3$) of solanesyl methyl carbonate (**13**)

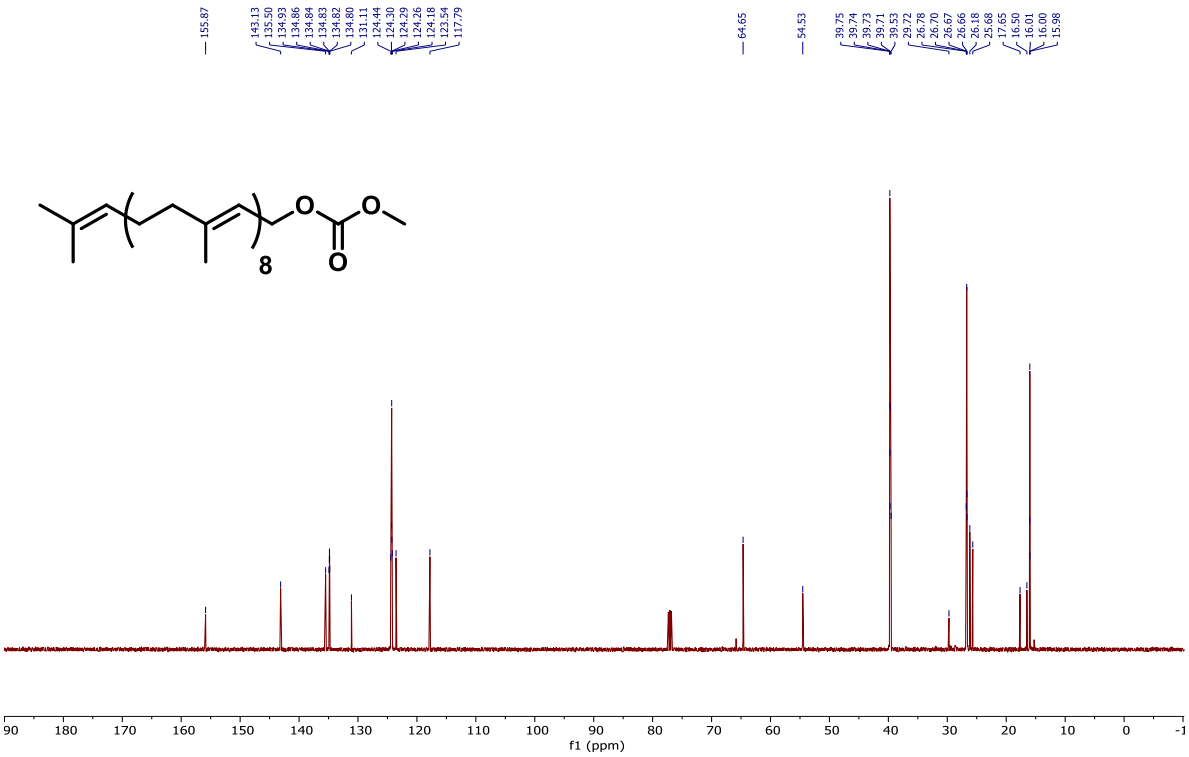


Figure 28: ^{13}C NMR (126 MHz, $CDCl_3$) of solanesyl methyl carbonate (**13**)

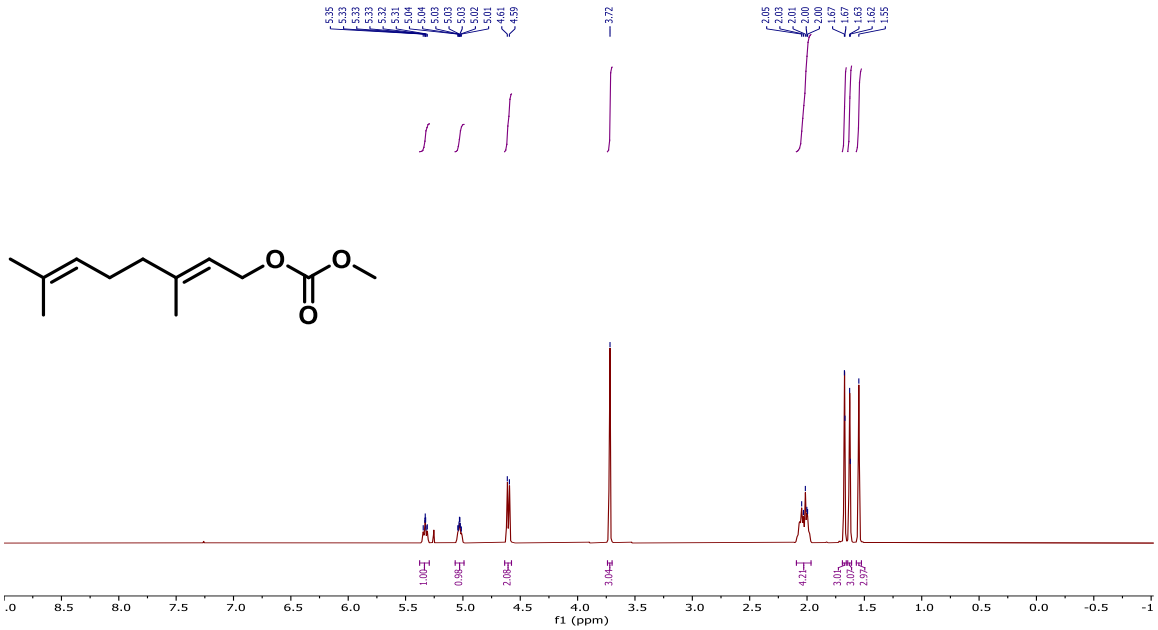


Figure 28: ^{1}H NMR (400 MHz, $CDCl_3$) of (*E*)-3,7-dimethylocta-2,6-dien-1-yl methyl carbonate (**14**)

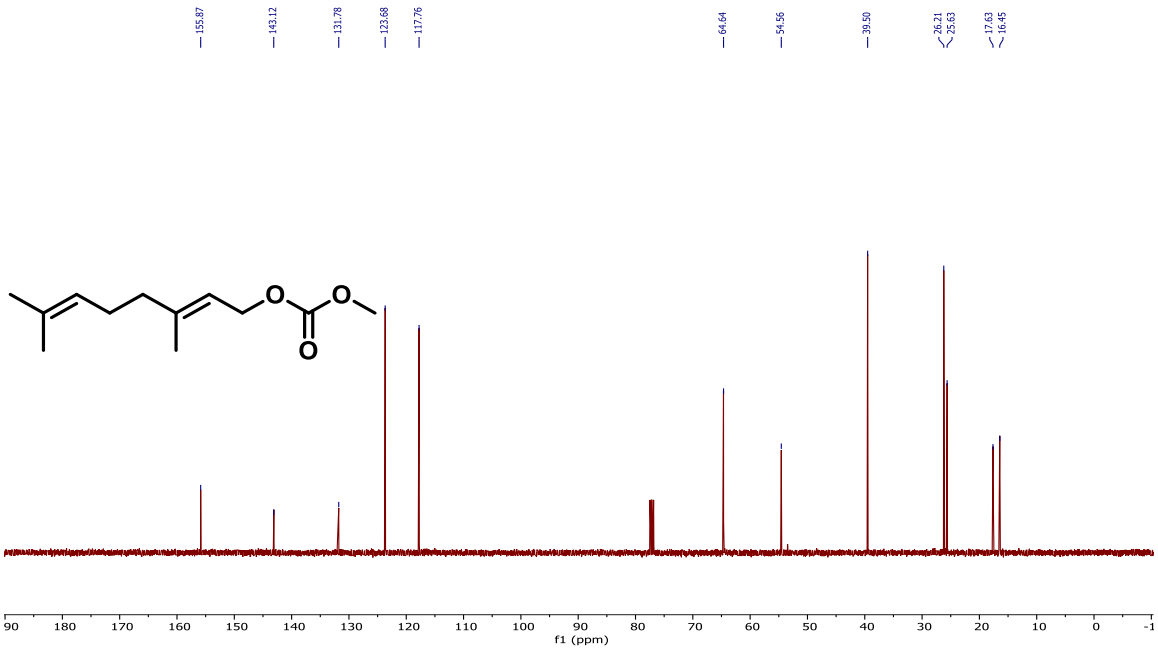


Figure 29: ^{13}C NMR (101 MHz, $CDCl_3$) of (*E*)-3,7-dimethylocta-2,6-dien-1-yl methyl carbonate (**14**)

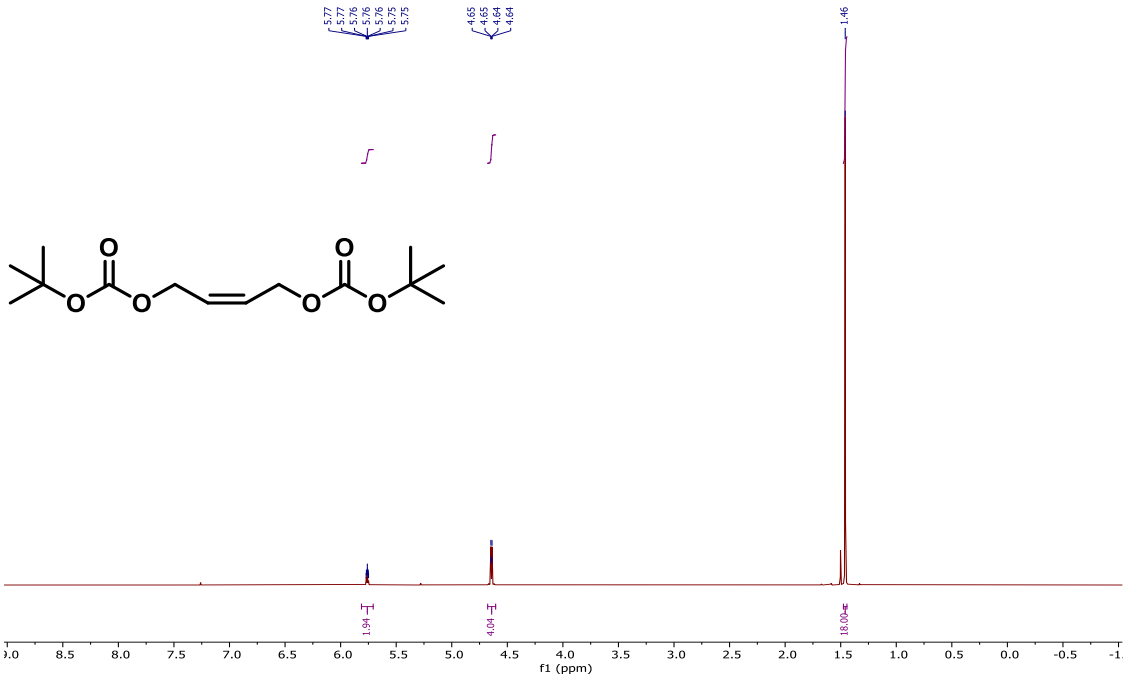


Figure 30: ^{1}H NMR (500 MHz, $CDCl_3$) of (*Z*)-but-2-ene-1,4-diyl di-*t*-butyl bis(carbonate) (**15**)

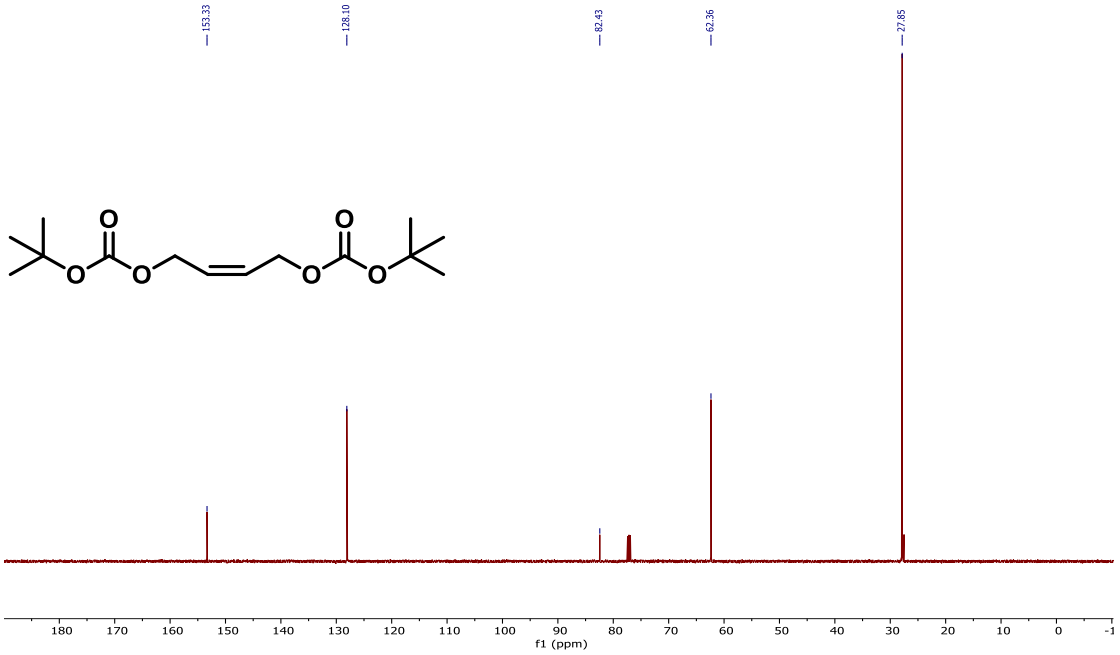


Figure 31: ^{13}C NMR (126 MHz, $CDCl_3$) of (*Z*)-but-2-ene-1,4-diyl di-*t*-butyl bis(carbonate) (**15**)

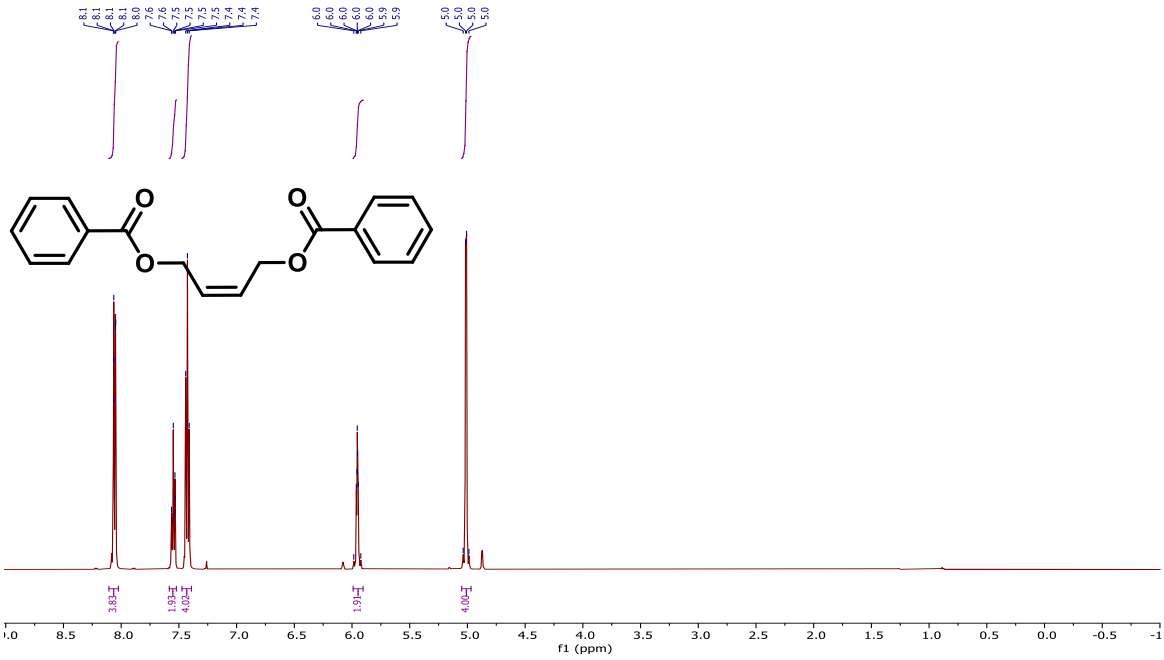


Figure 32: ^{1}H NMR (500 MHz, $CDCl_3$) of (*Z*)-but-2-ene-1,4-diyl dibenzoate (**16**)

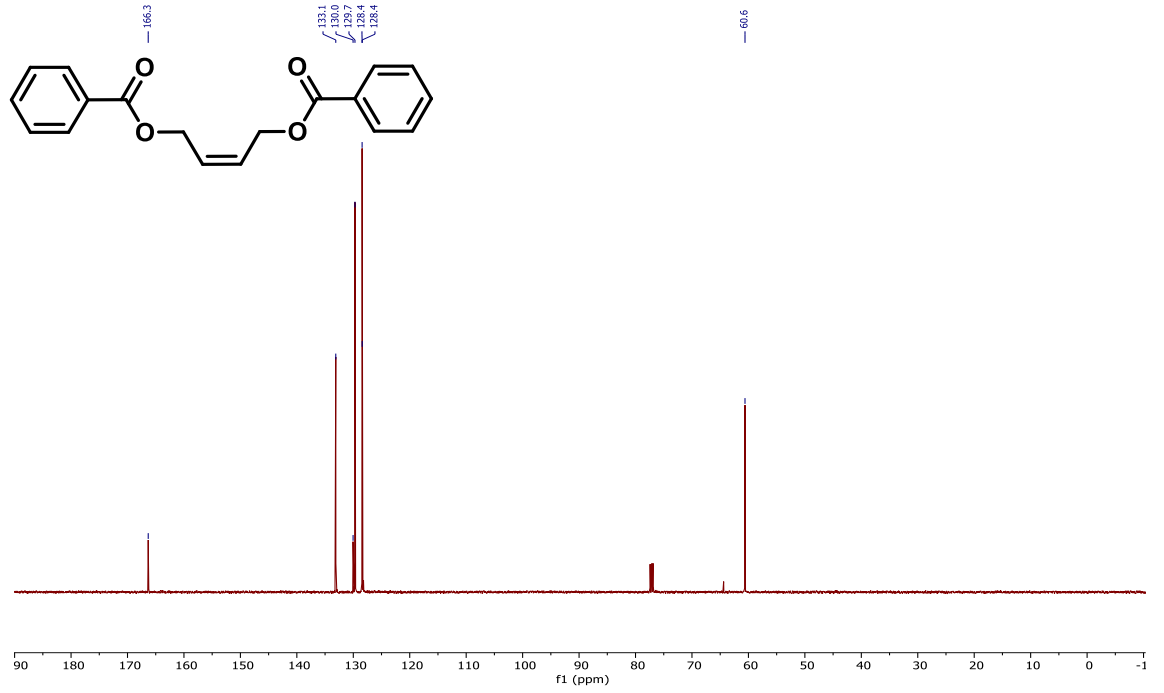


Figure 33: ^{13}C NMR (126 MHz, $CDCl_3$) of (*Z*)-but-2-ene-1,4-diyl dibenzoate (**16**)

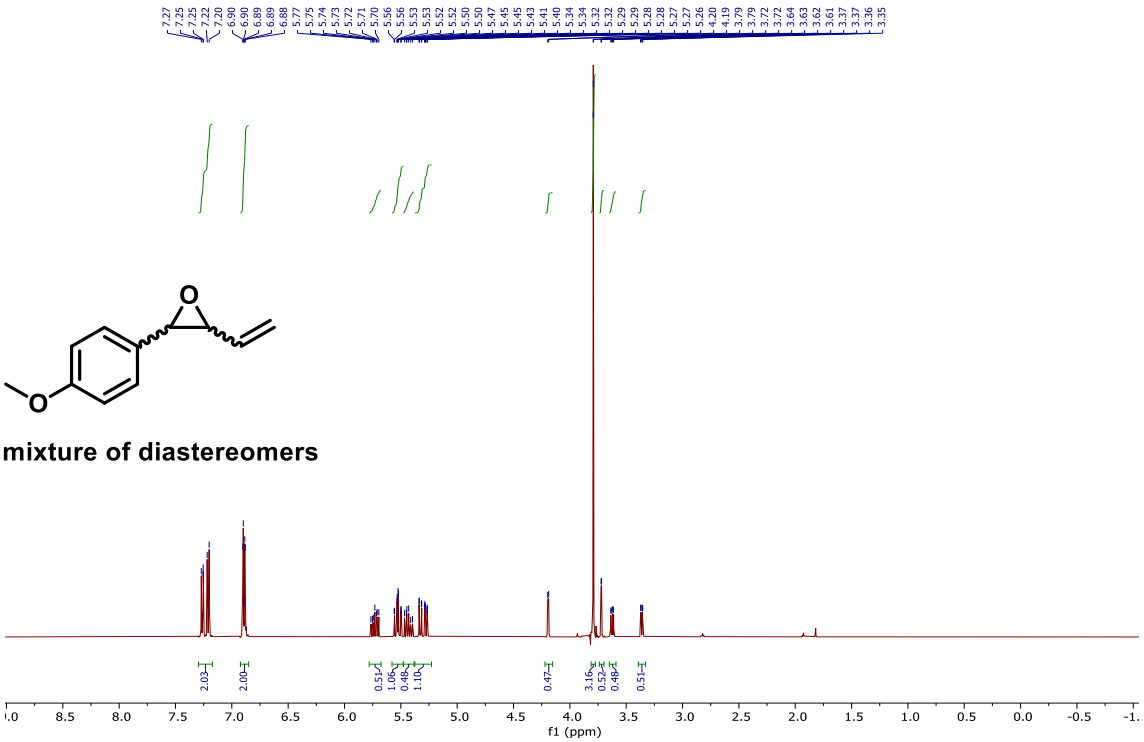


Figure 34: ^{1}H NMR (500 MHz, $CDCl_3$) of 2-(4-Methoxyphenyl)-3-vinyloxirane (**17**)

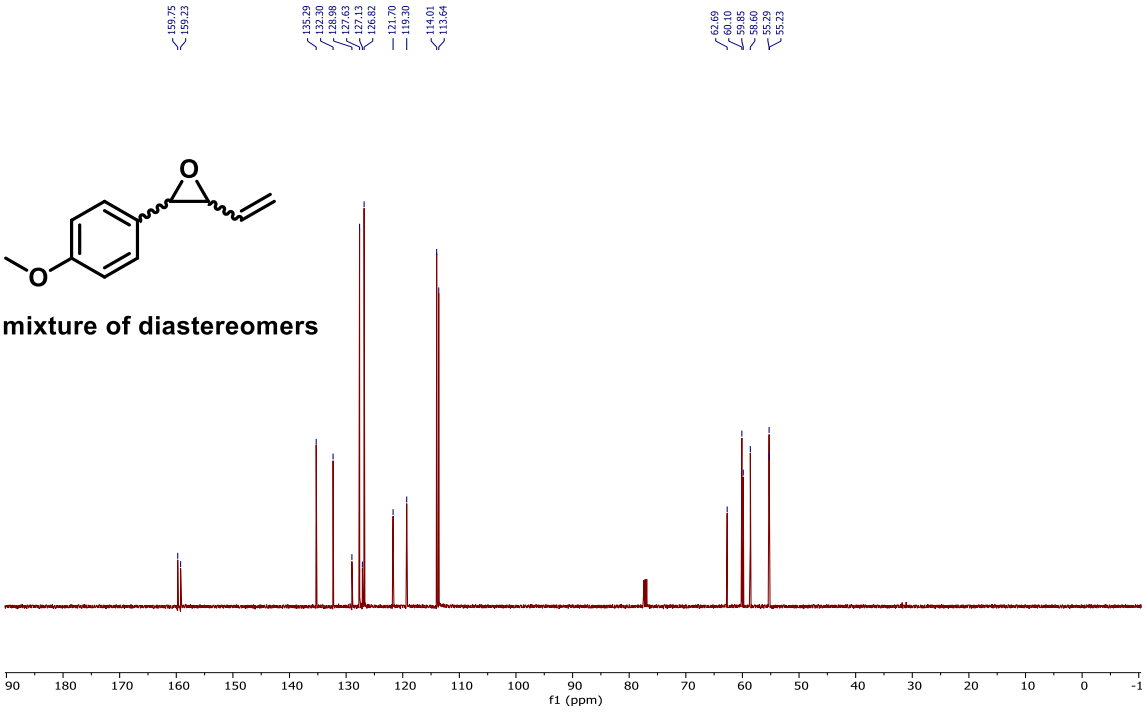


Figure 35: ^{13}C NMR (126 MHz, $CDCl_3$) of 2-(4-Methoxyphenyl)-3-vinyloxirane (**17**)

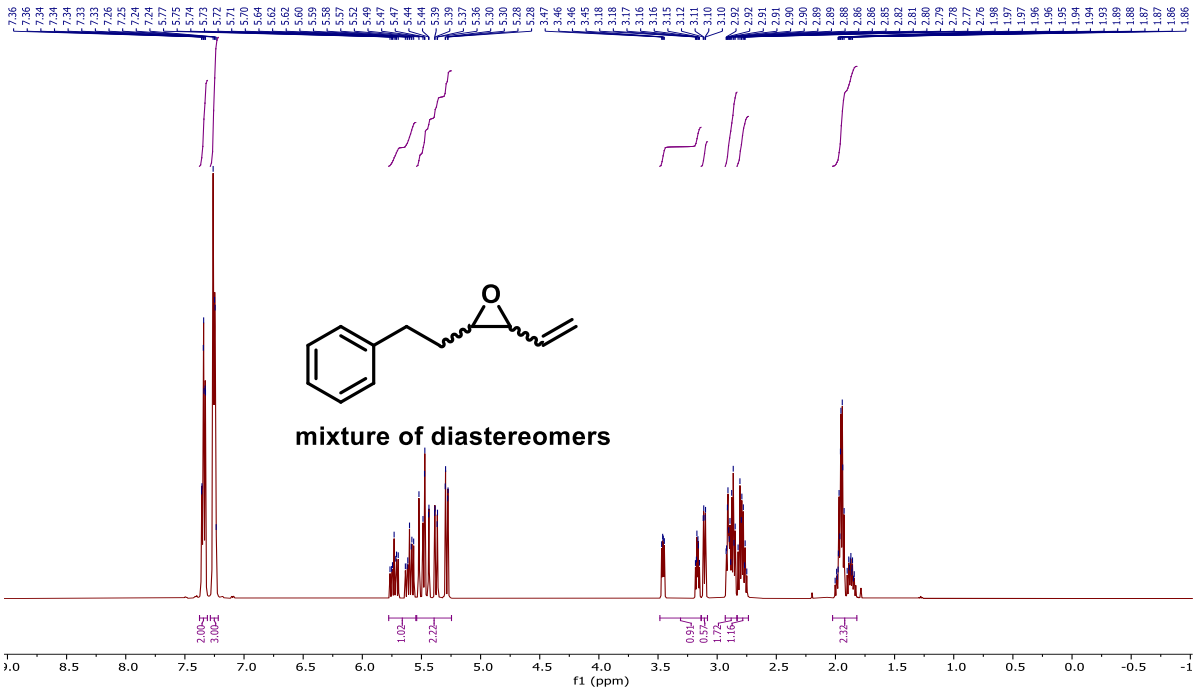


Figure 36: ^{1}H NMR (500 MHz, $CDCl_3$) of 2-Phenethyl-3-vinyloxirane (**18**)

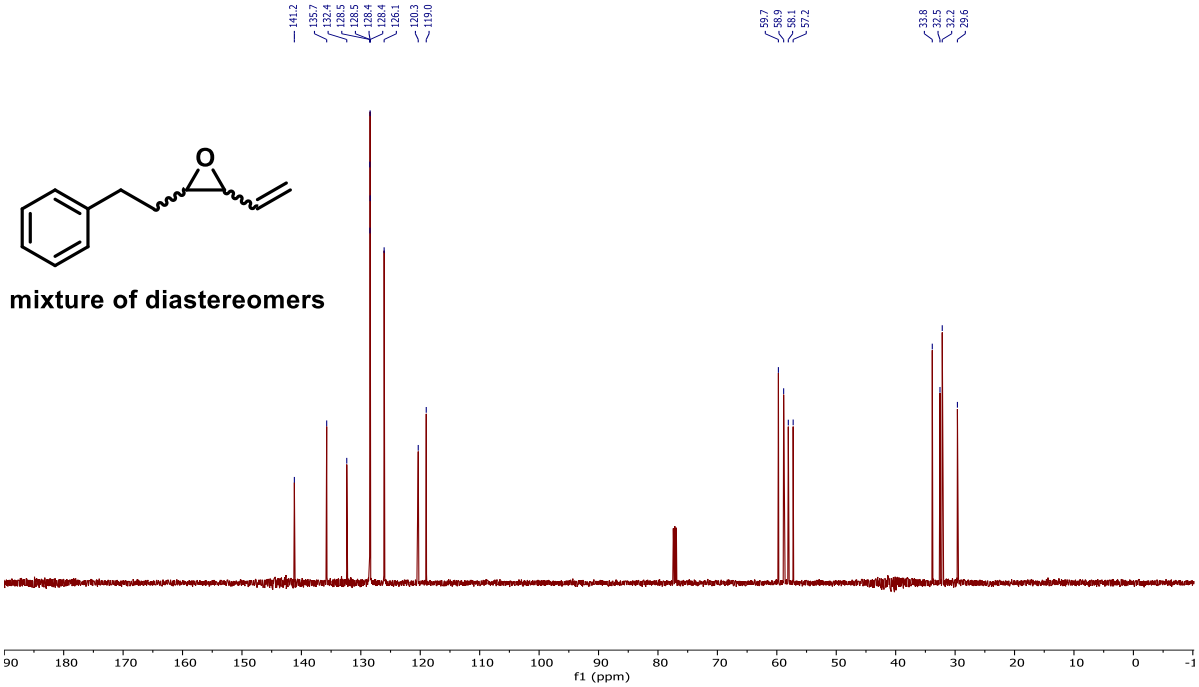


Figure 37: ^{13}C NMR (126 MHz, $CDCl_3$) of 2-Phenethyl-3-vinyloxirane (**18**)

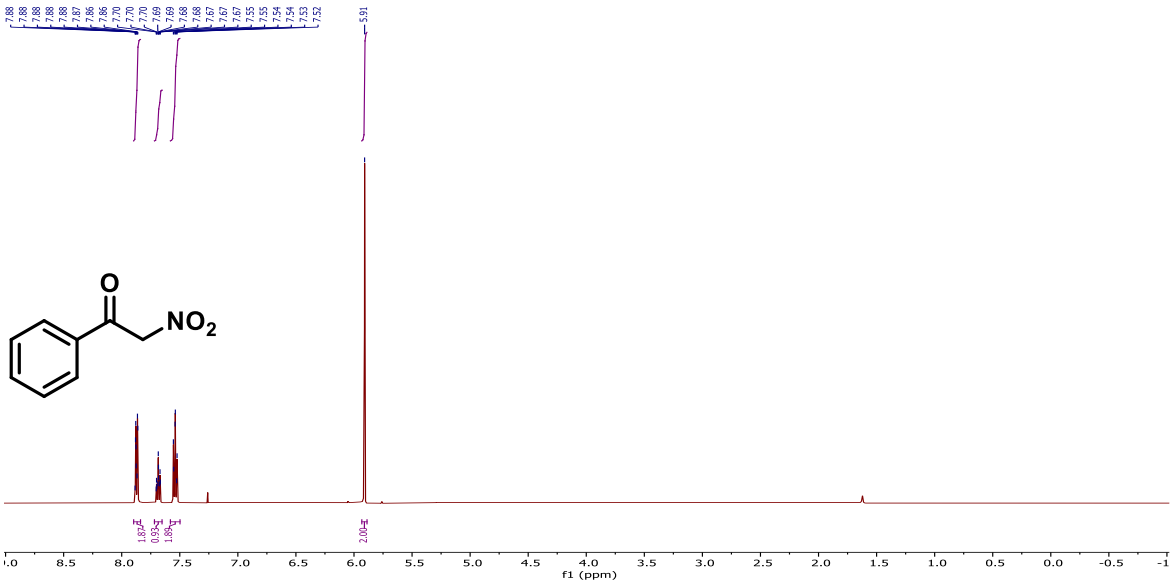


Figure 38: ^{1}H NMR (500 MHz, $CDCl_3$) of 2-nitro-1-phenylethan-1-one (**19**)

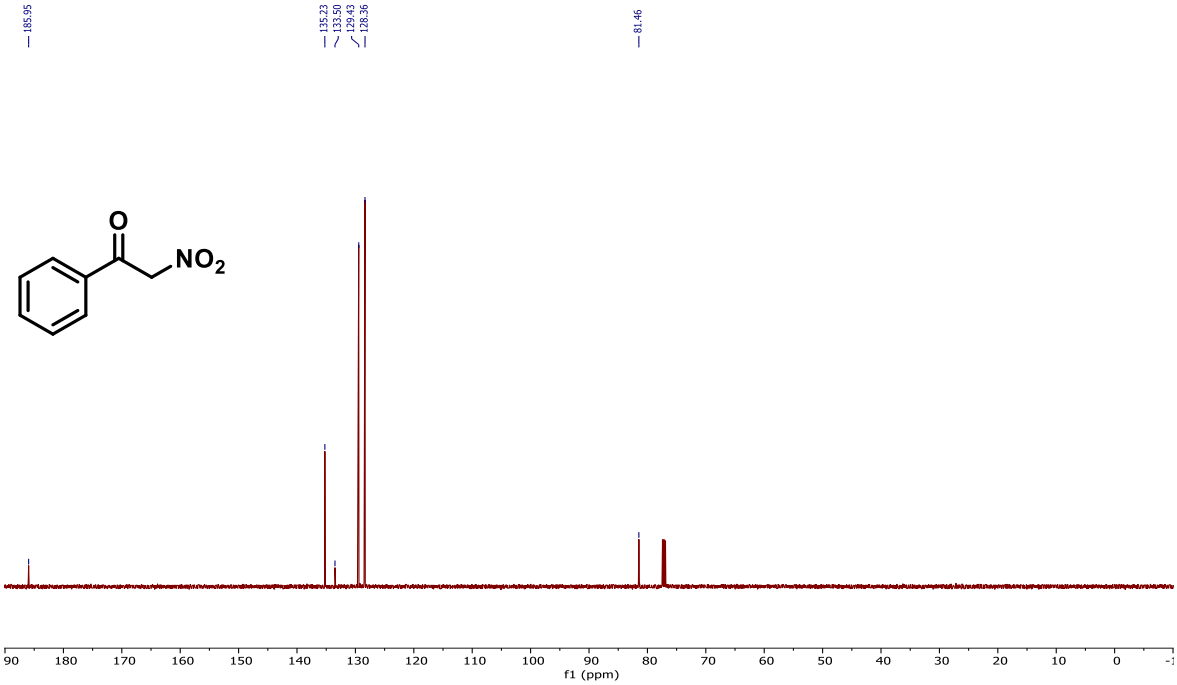


Figure 39: ^{13}C NMR (126 MHz, $CDCl_3$) of 2-nitro-1-phenylethan-1-one (**19**)

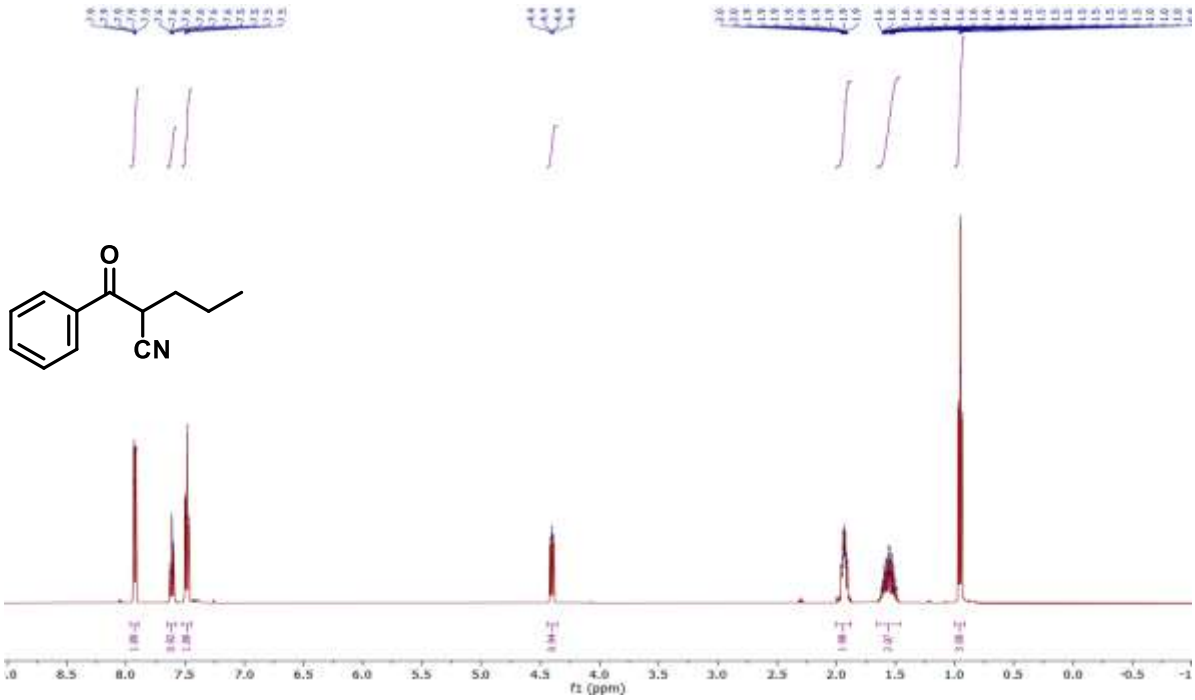


Figure 40: ^{1}H NMR (500 MHz, $CDCl_3$) of 2-benzoylpentanenitrile (**20**)

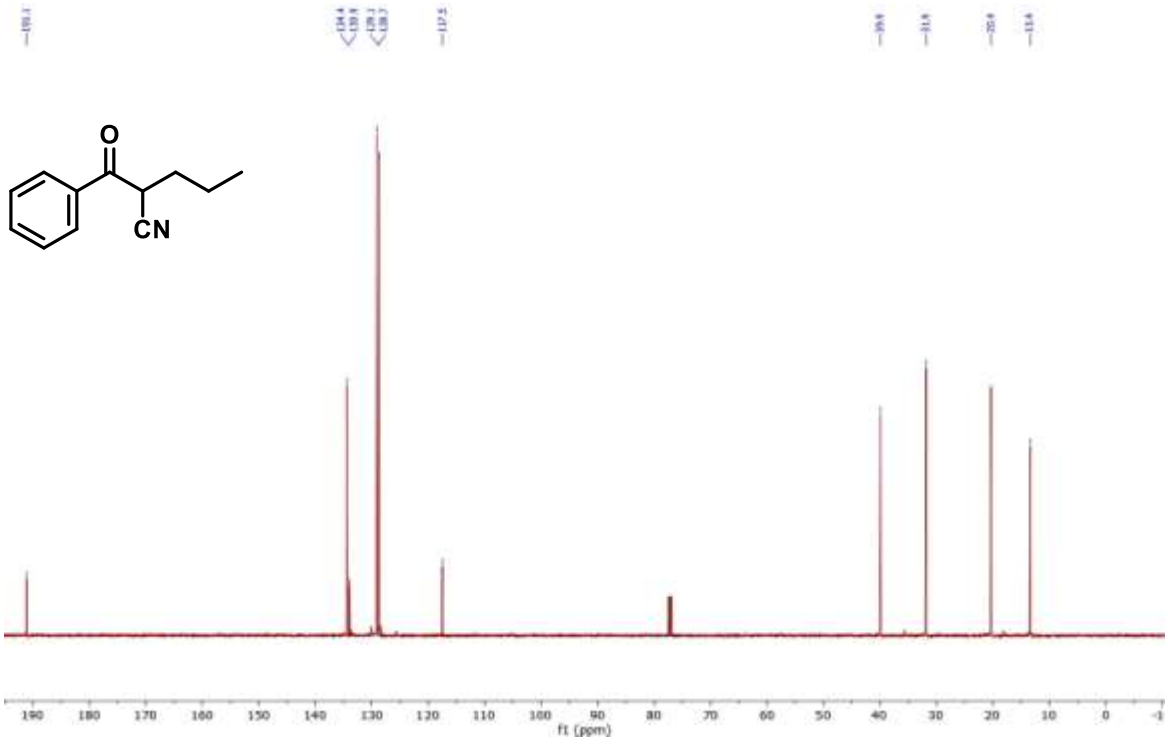


Figure 41: ^{13}C NMR (126 MHz, $CDCl_3$) of 2-benzoylpentanenitrile (**20**)

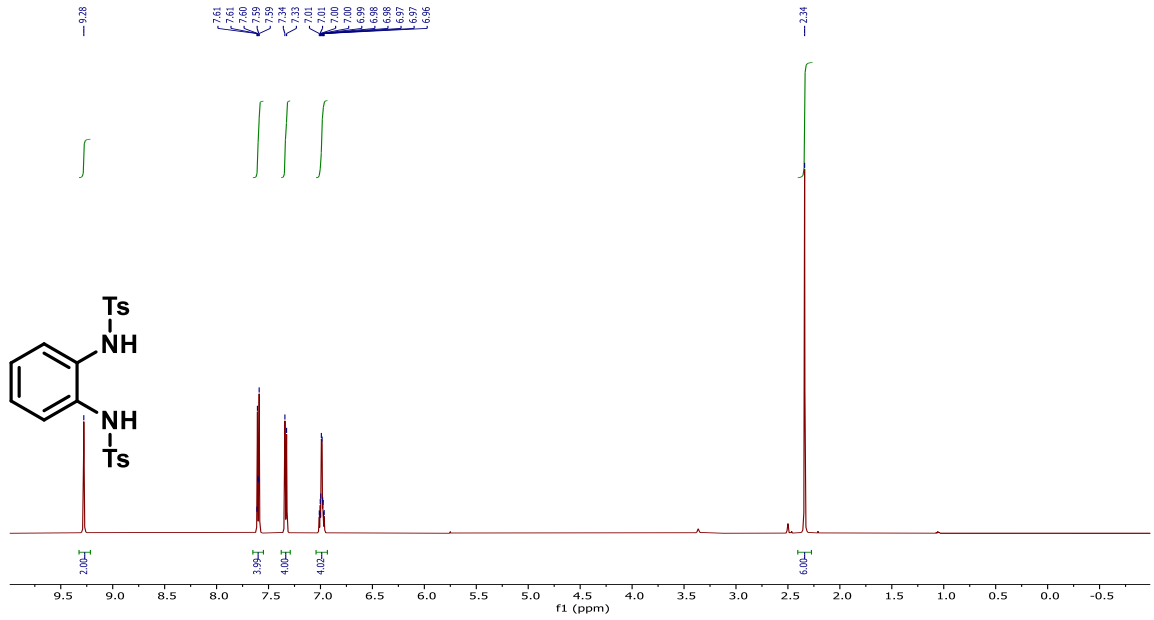


Figure 43: ^{1}H NMR (500 MHz, DMSO-d_6) of *N*,*N*′-(1,2-phenylene)bis(4-methylbenzenesulfonamide) (**21**)

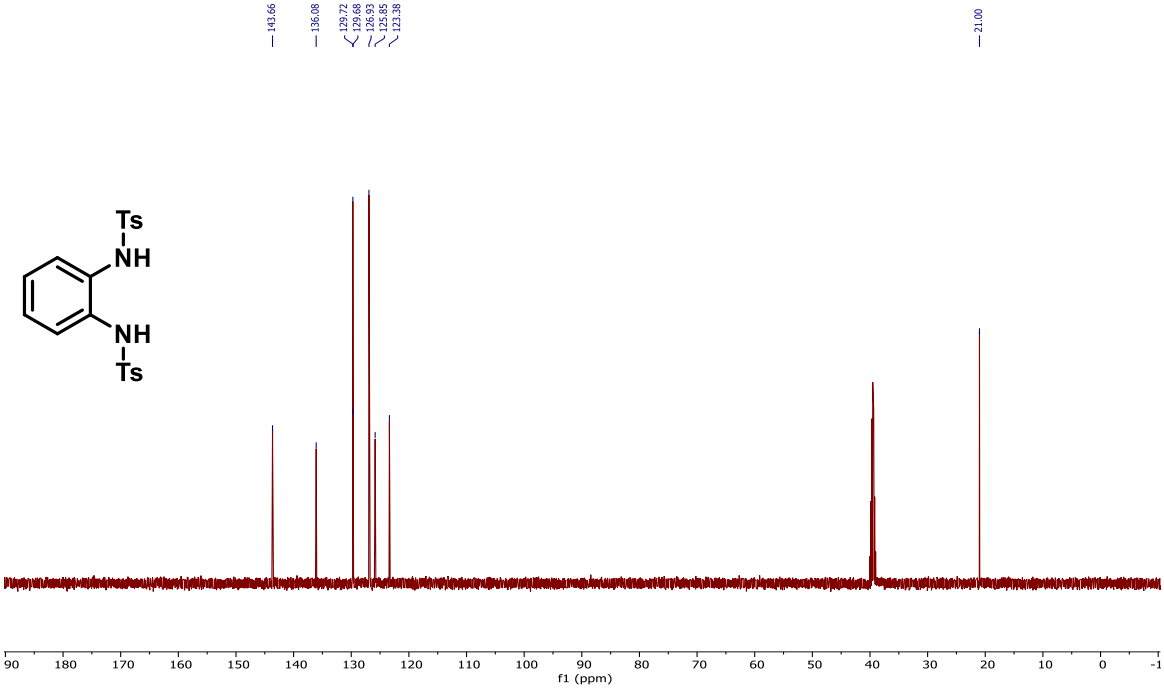


Figure 44: ^{13}C NMR (126 MHz, DMSO-d_6) of *N*,*N*′-(1,2-phenylene)bis(4-methylbenzenesulfonamide) (**21**)

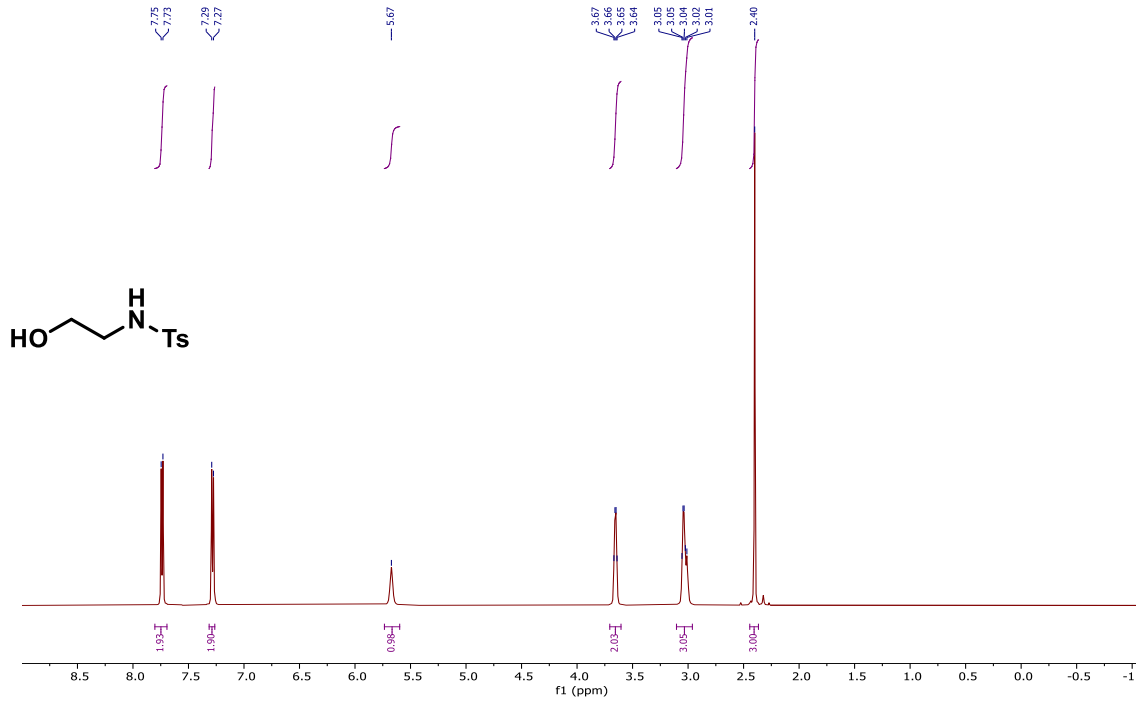


Figure 45: ^{1}H NMR (500 MHz, $CDCl_3$) of *N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide (**22**)

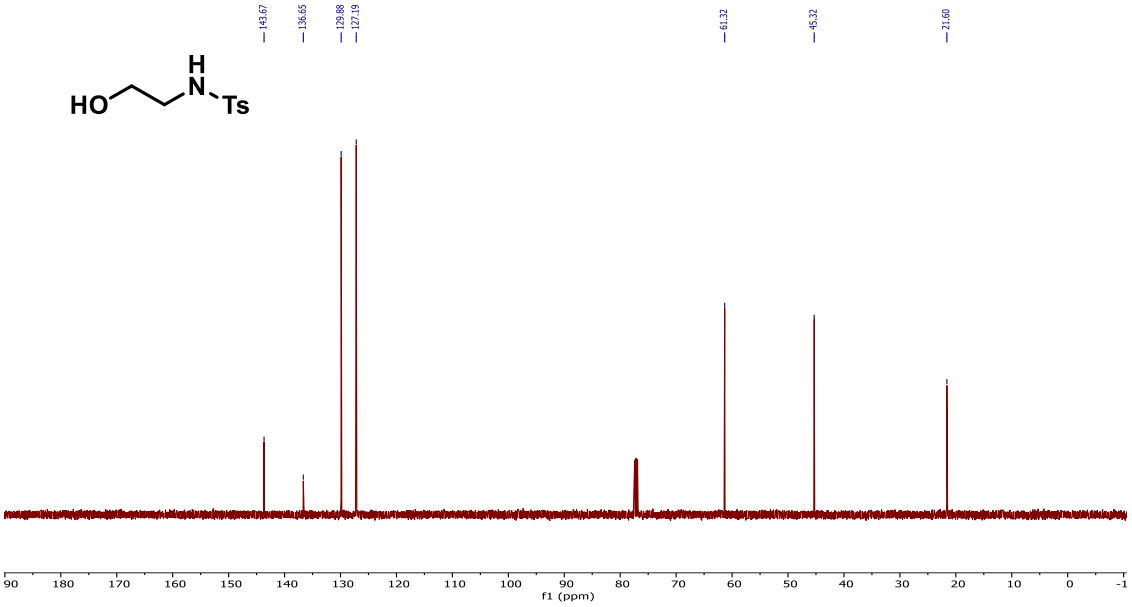


Figure 46: ^{13}C NMR (126 MHz, $CDCl_3$) of *N*-(2-hydroxyethyl)-4-methylbenzenesulfonamide (**22**)

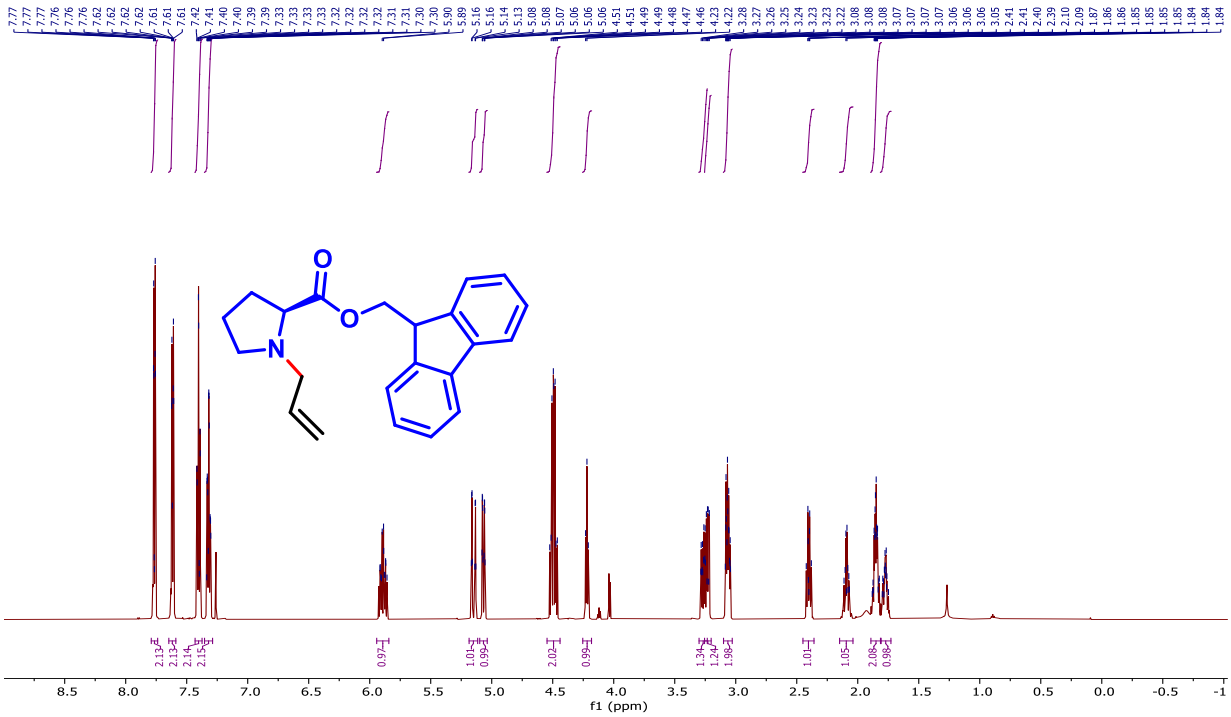


Figure 47: ^{1}H NMR (600 MHz, $CDCl_3$) of (9H-Fluoren-9-yl)methyl allyl-L-prolinate (**1a**)

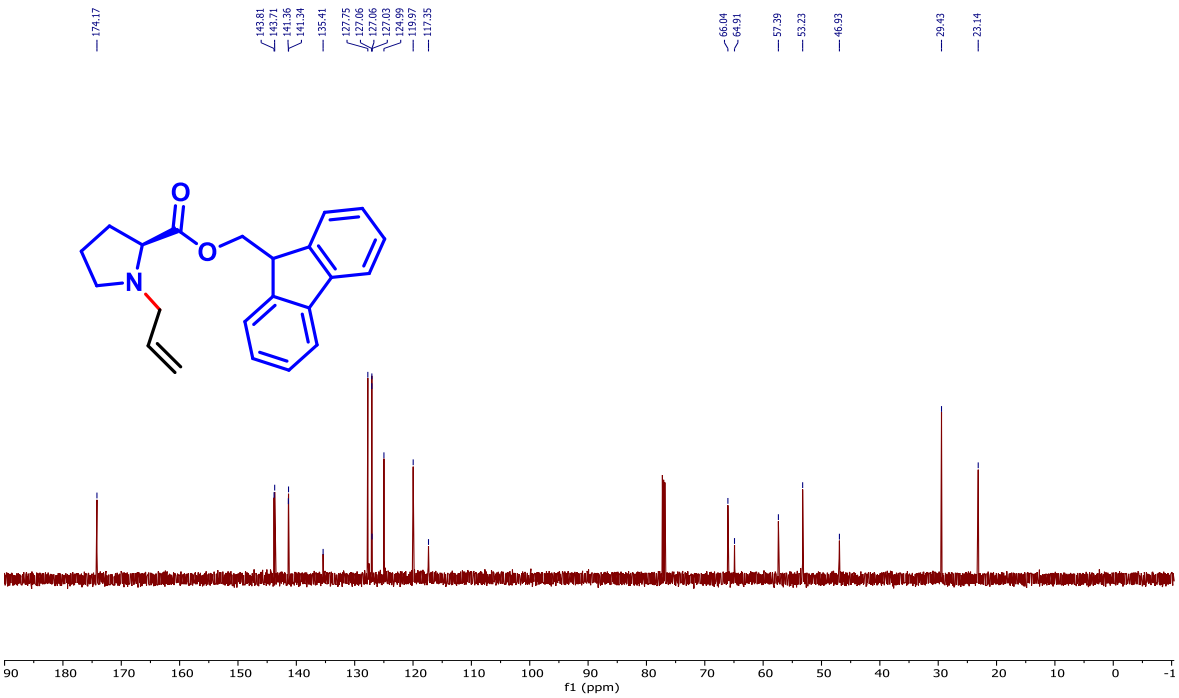


Figure 48: ^{13}C NMR (151 MHz, $CDCl_3$) of (9H-Fluoren-9-yl)methyl allyl-L-prolinate (**1a**)

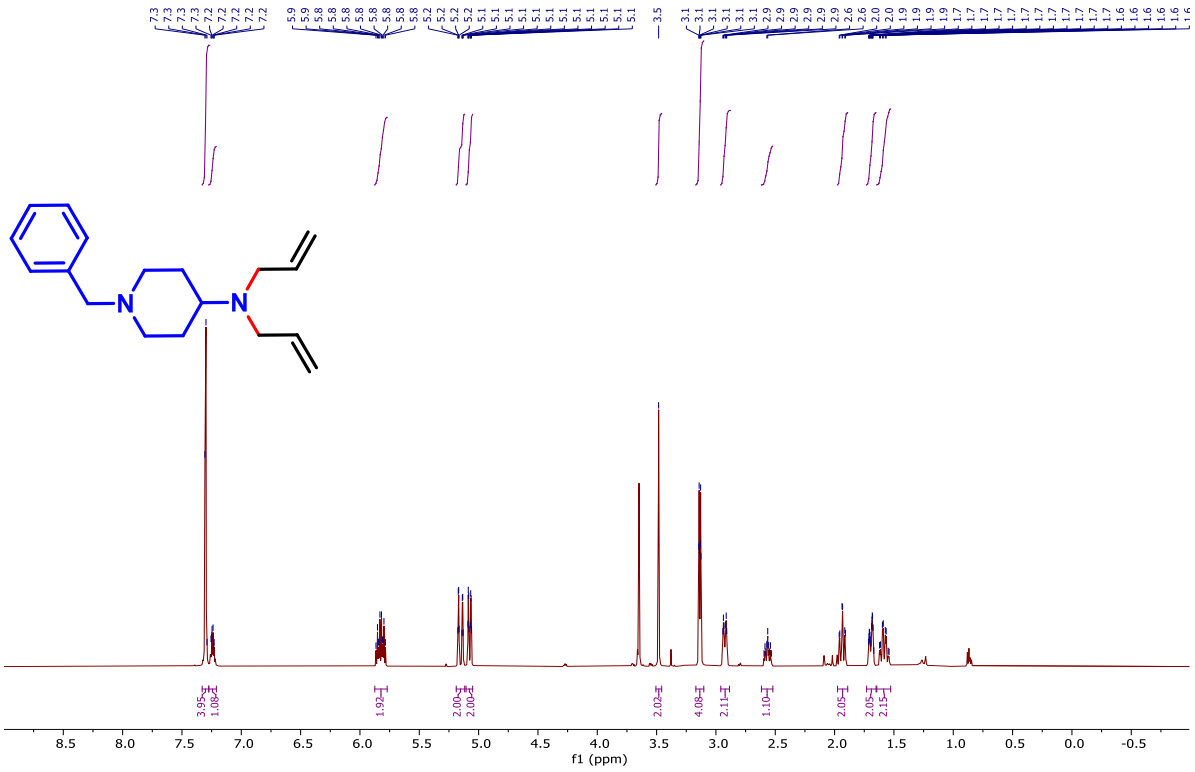


Figure 49: ^{1}H NMR (500 MHz, $CDCl_3$) of *N*,*N*-Diallyl-1-benzylpiperidin-4-amine (**1b**)

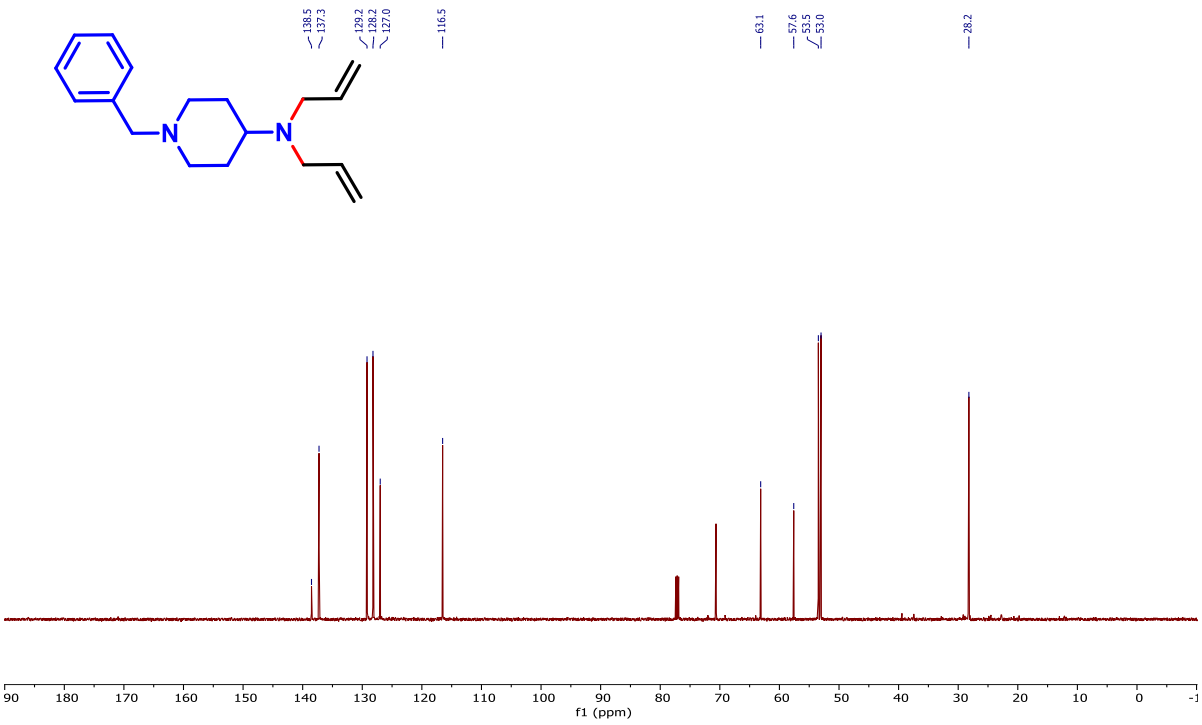


Figure 50: ^{13}C NMR (126 MHz, $CDCl_3$) of *N*,*N*-Diallyl-1-benzylpiperidin-4-amine (**1b**)

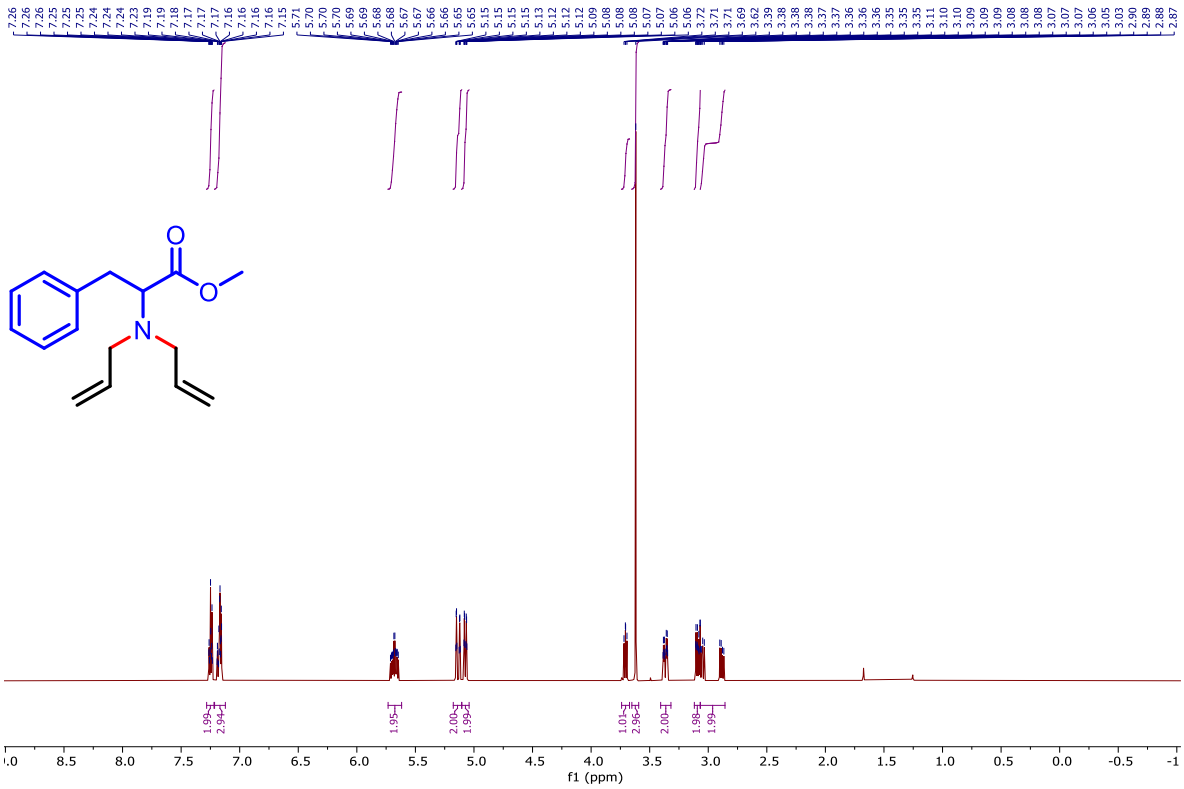


Figure 51: ^{1}H NMR (600 MHz, $CDCl_3$) of Methyl diallylphenylalaninate (**1c**)

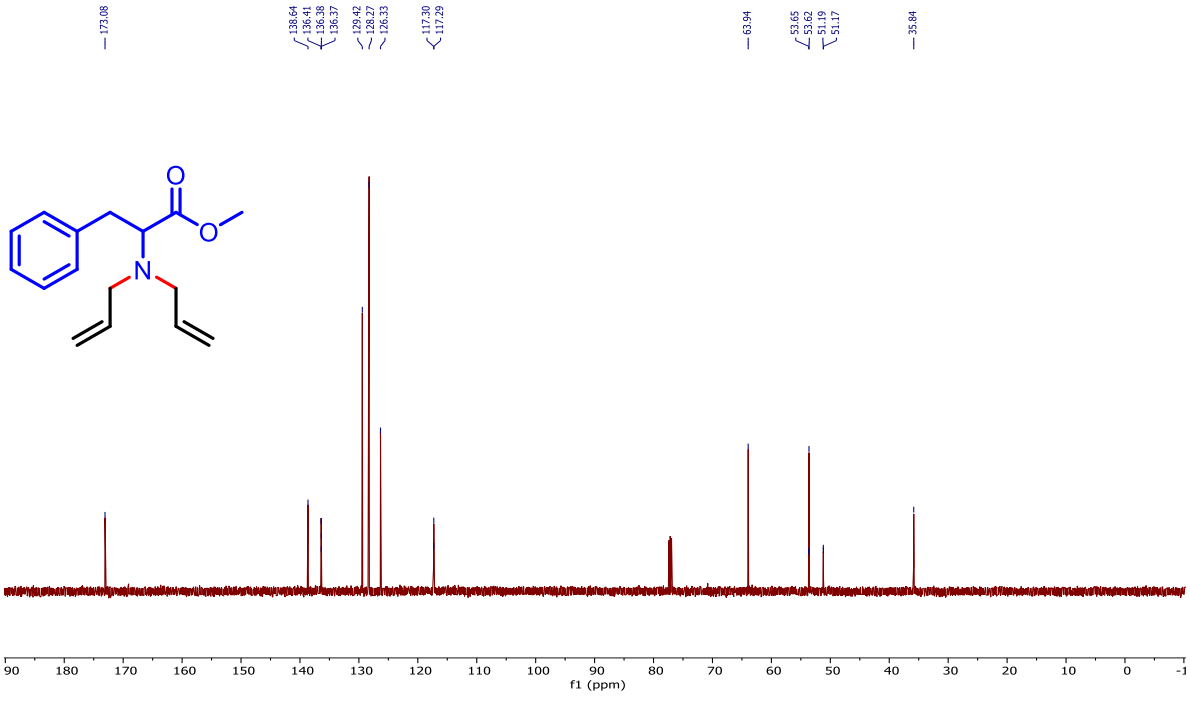


Figure 52: ^{13}C NMR (126 MHz, $CDCl_3$) of Methyl diallylphenylalaninate (**1c**)

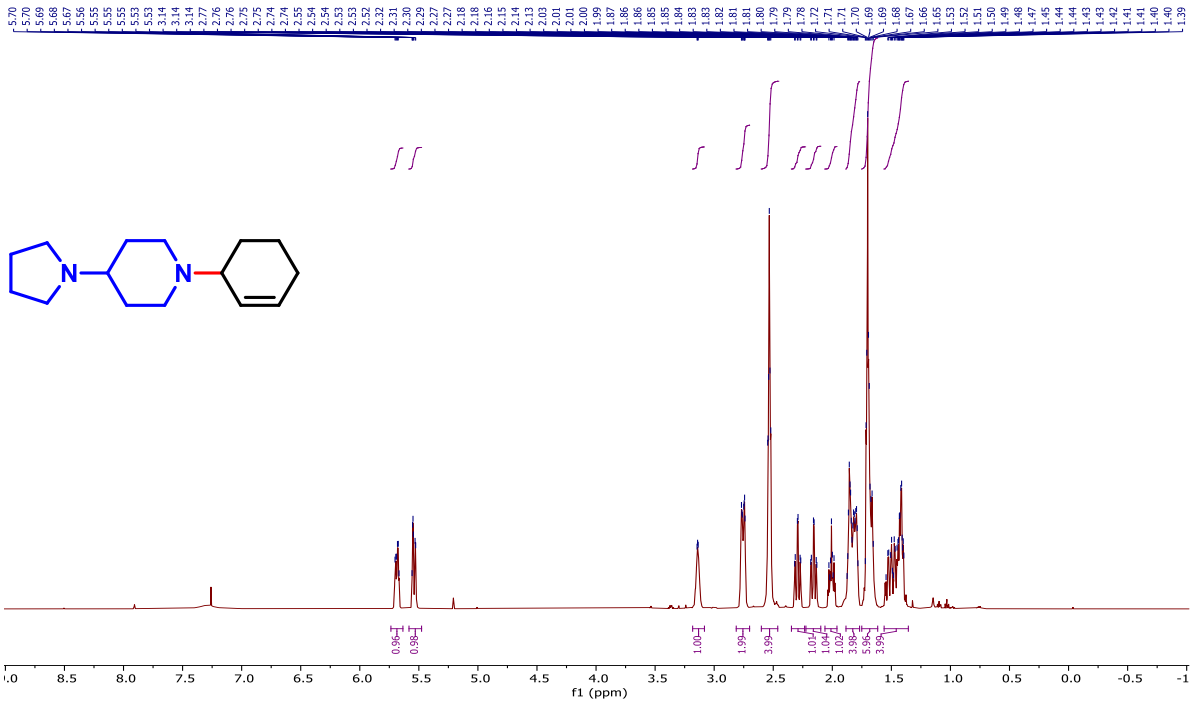


Figure 53: 1-(Cyclohex-2-en-1-yl)-4-(pyrrolidin-1-yl)piperidine (**1d**)

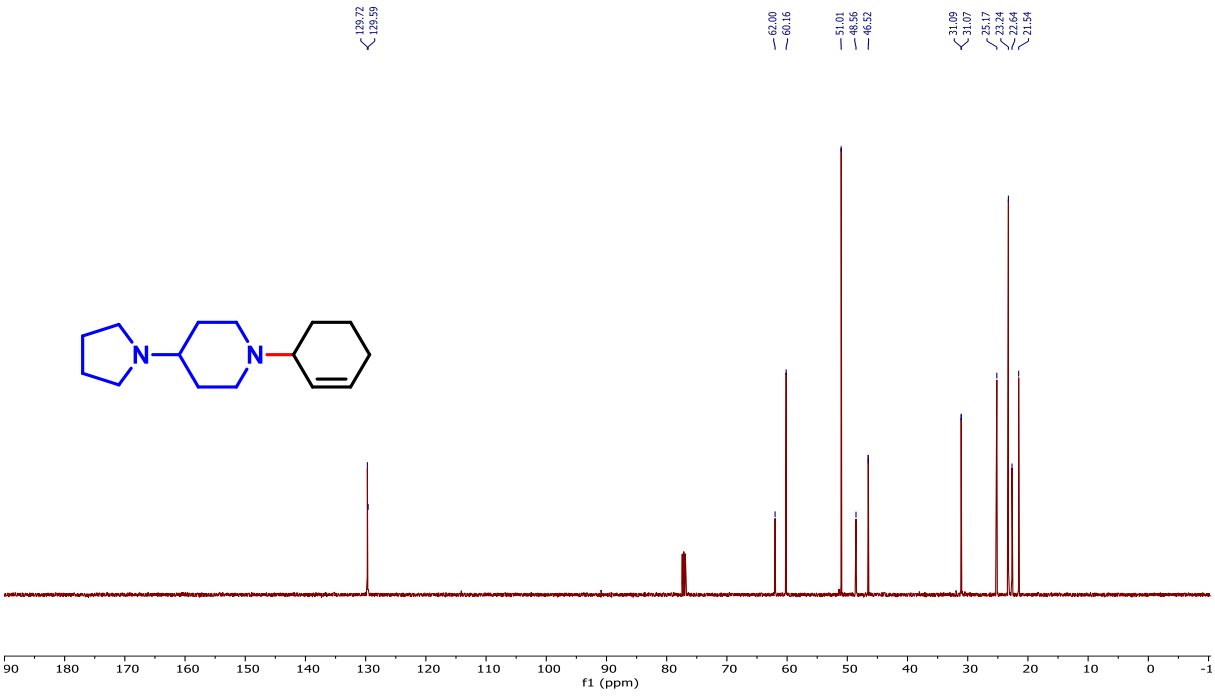


Figure 54: ^{13}C NMR (126 MHz, $CDCl_3$) of 1-(Cyclohex-2-en-1-yl)-4-(pyrrolidin-1-yl)piperidine (**1d**)

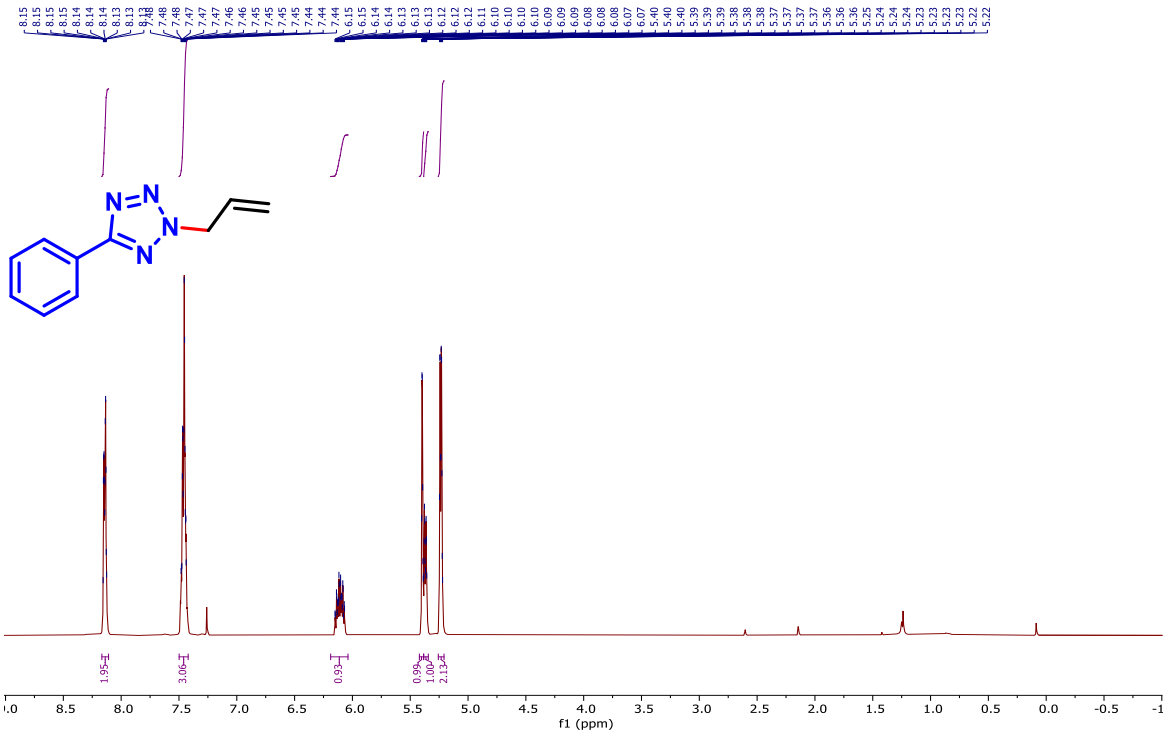


Figure 55: ^{1}H NMR (500 MHz, $CDCl_3$) of 2-Allyl-5-phenyl-2H-tetrazole (**1e**)

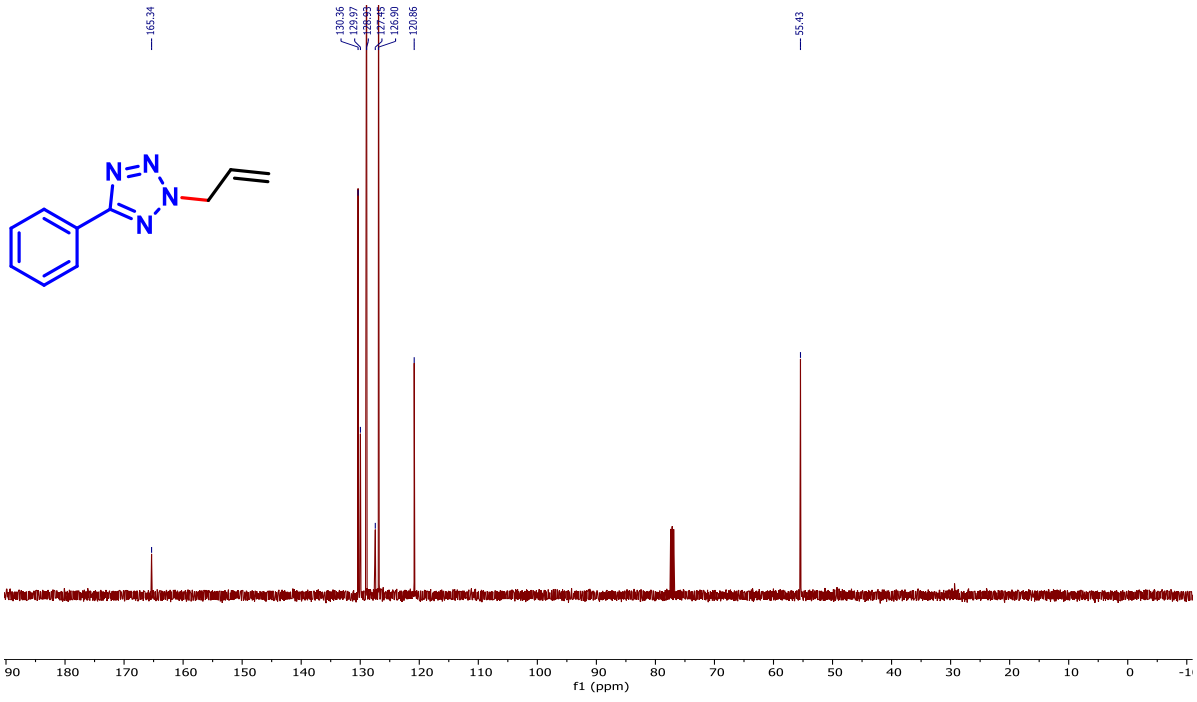


Figure 56: ^{13}C NMR (126 MHz, $CDCl_3$) of 2-Allyl-5-phenyl-2H-tetrazole (**1e**)

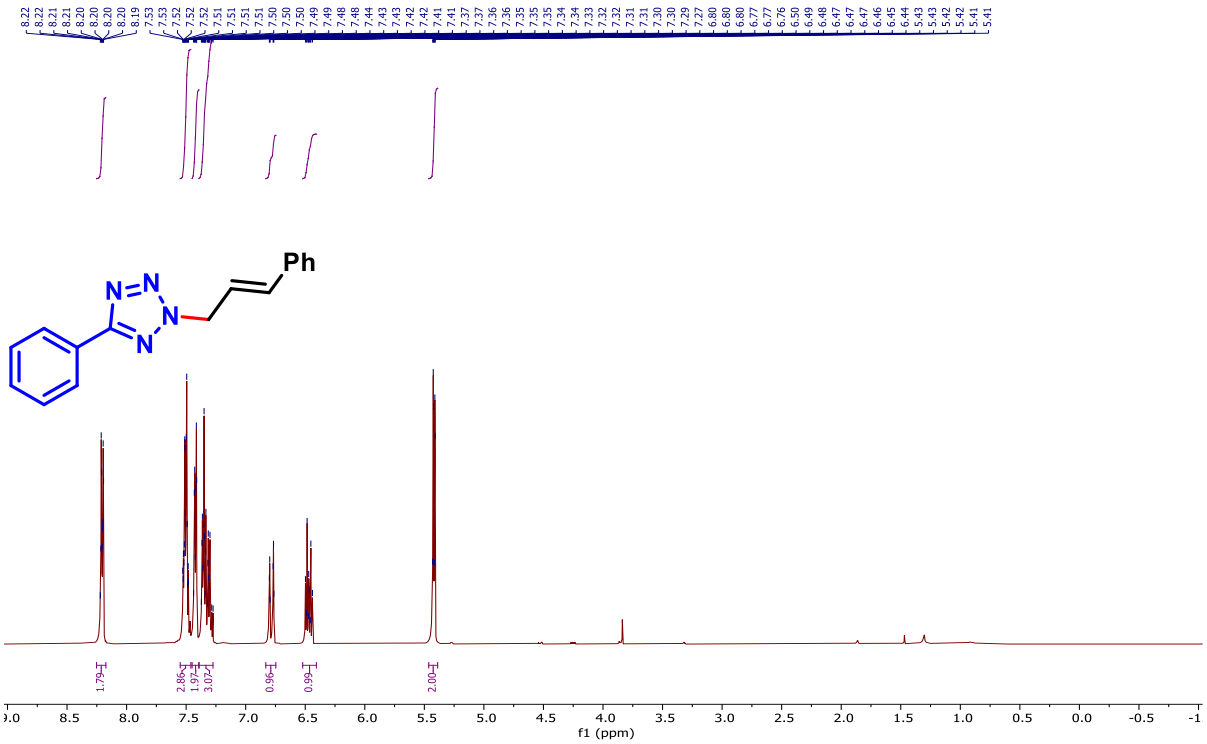


Figure 57: ^{1}H NMR (500 MHz, $CDCl_3$) of 2-Cinnamyl-5-phenyl-2H-tetrazole (**1f**)

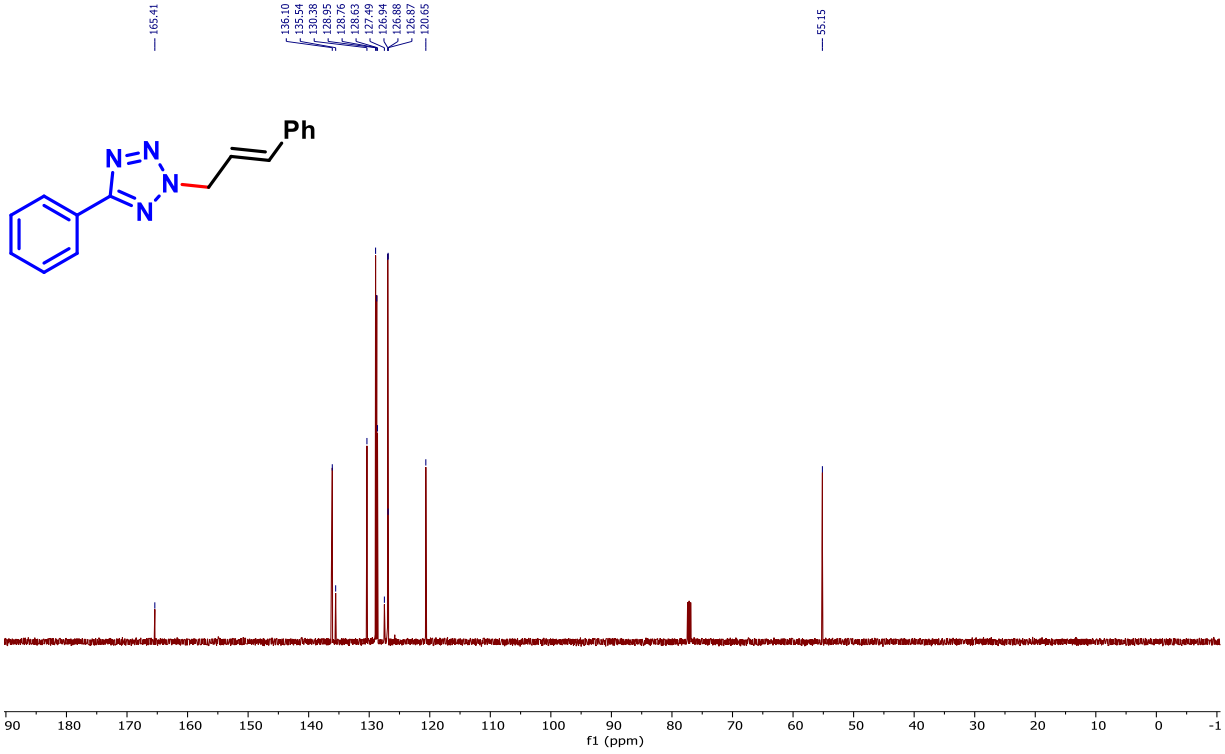


Figure 58: ^{13}C NMR (126 MHz, $CDCl_3$) of 2-Cinnamyl-5-phenyl-2H-tetrazole (**1f**)

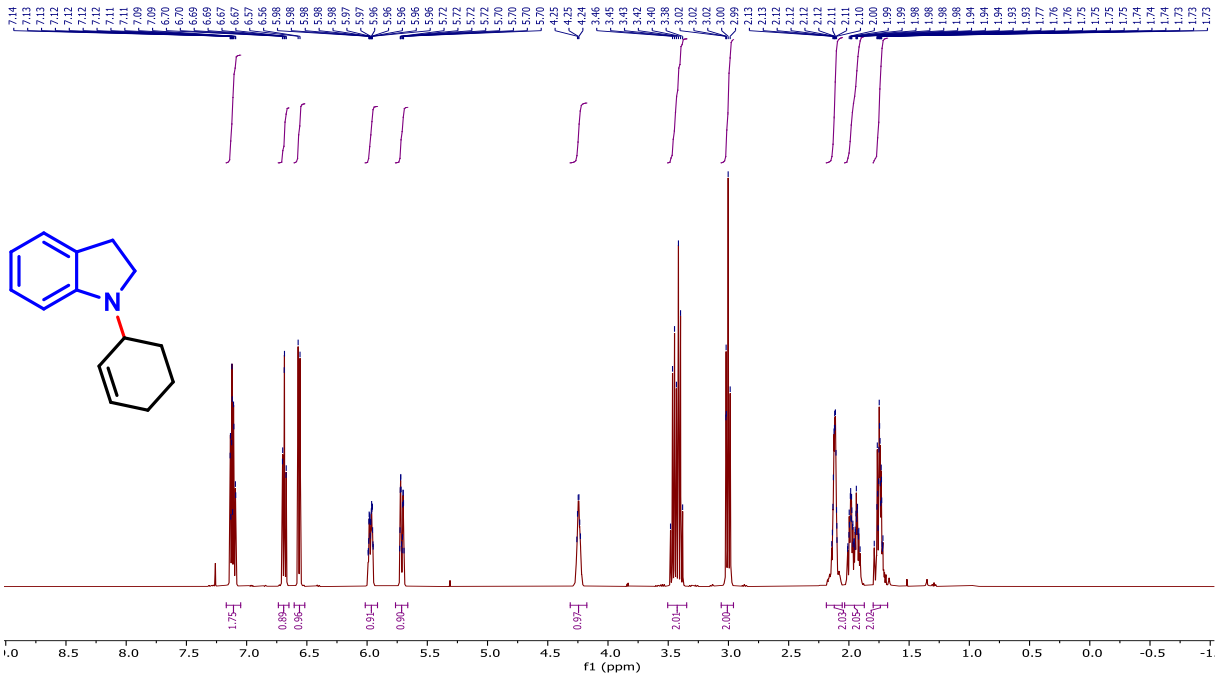


Figure 59: ^{1}H NMR (500 MHz, $CDCl_3$) of 1-(cyclohex-2-en-1-yl)indoline (**1g**)

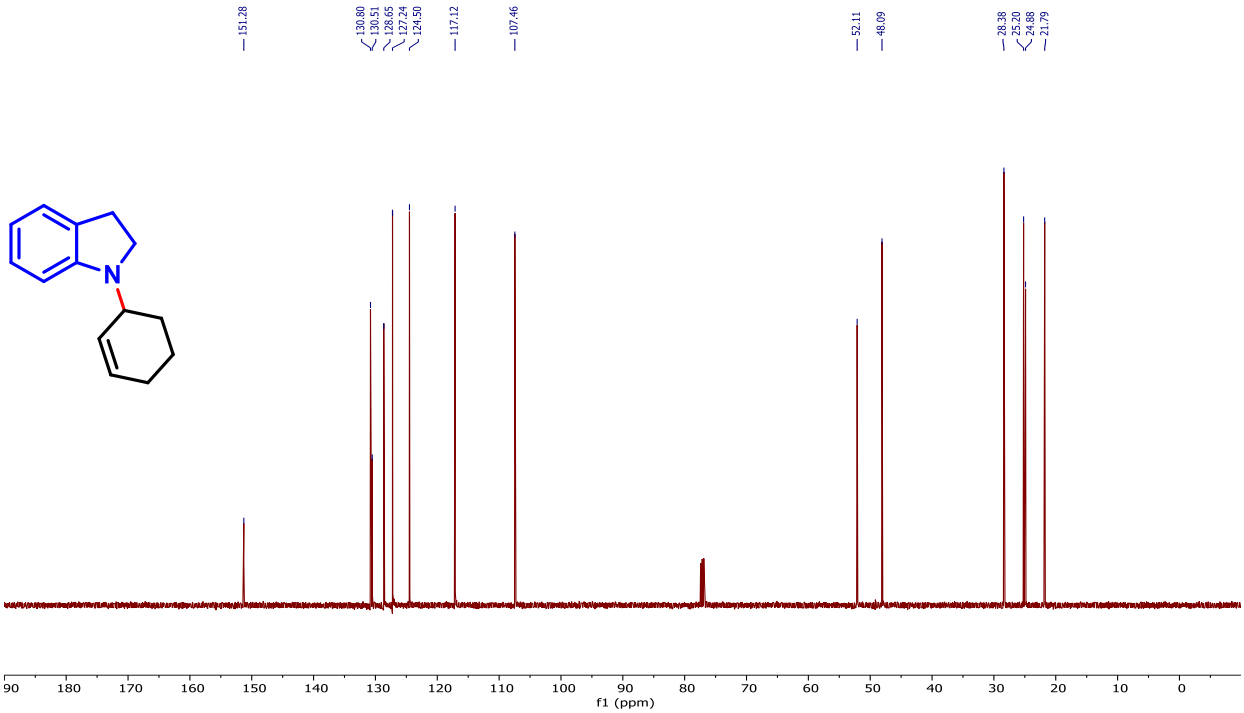


Figure 60: ^{13}C NMR (126 MHz, $CDCl_3$) of 1-(cyclohex-2-en-1-yl)indoline (**1g**)

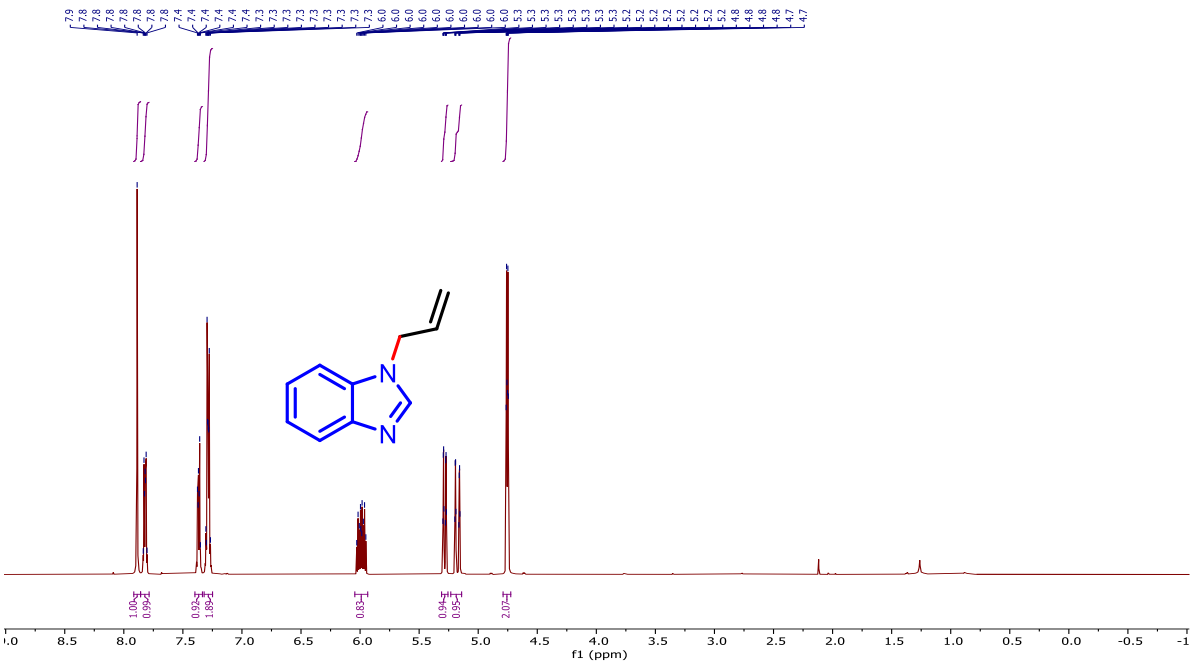


Figure 61: ^{1}H NMR (500 MHz, $CDCl_3$) of 1-Allyl-1H-benzo[d]imidazole (**1h**)

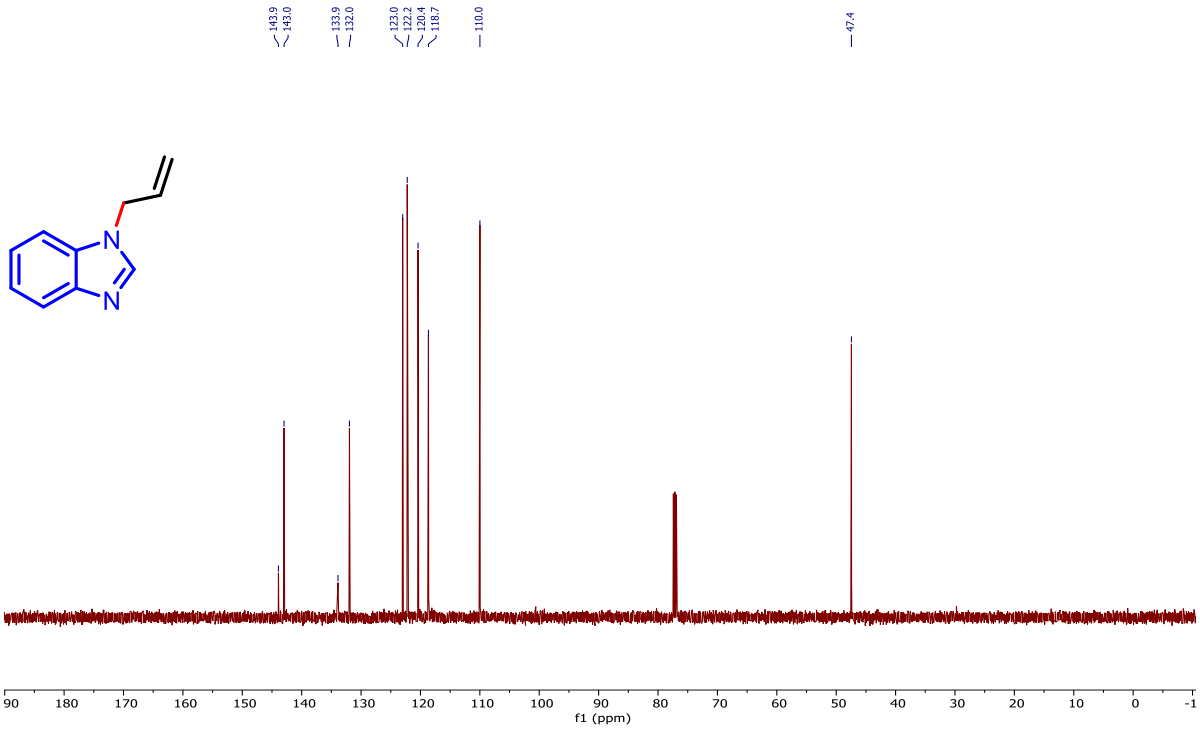


Figure 62: ^{13}C NMR (126 MHz, $CDCl_3$) of 1-Allyl-1H-benzo[d]imidazole (**1h**)

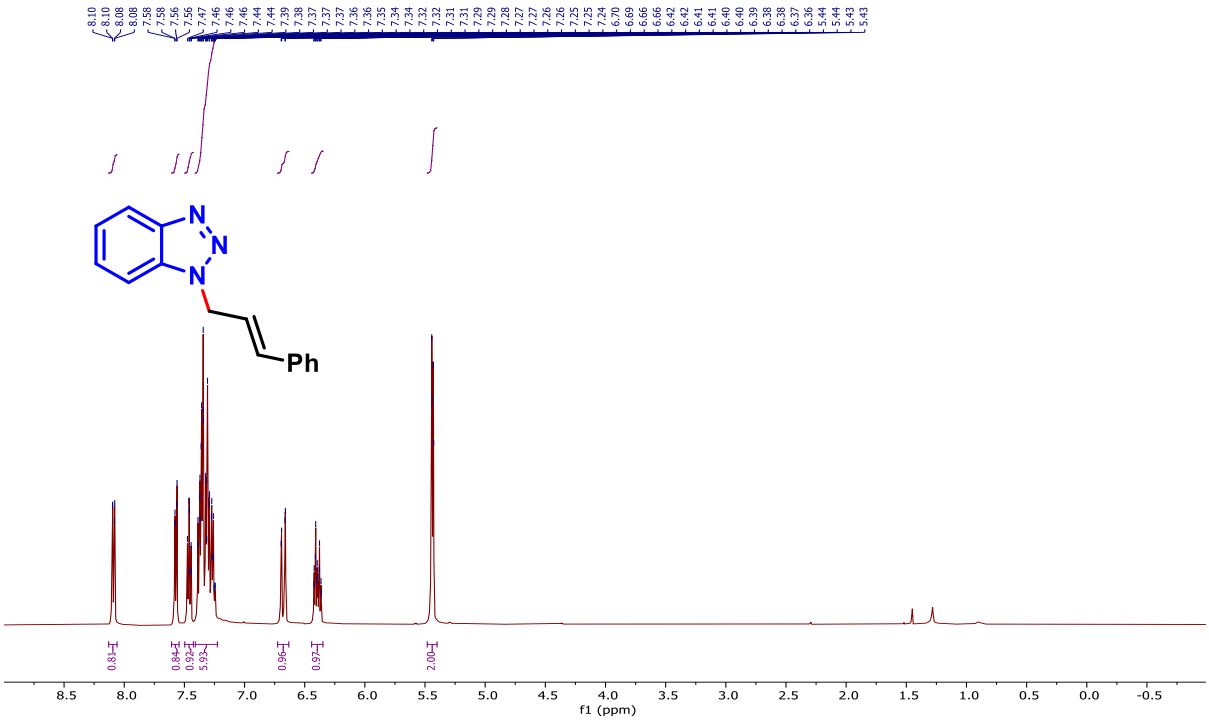


Figure 63: ^{1}H NMR (500 MHz, $CDCl_3$) of 1-Cinnamyl-1H-benzo[d][1,2,3]triazole (**1i**)

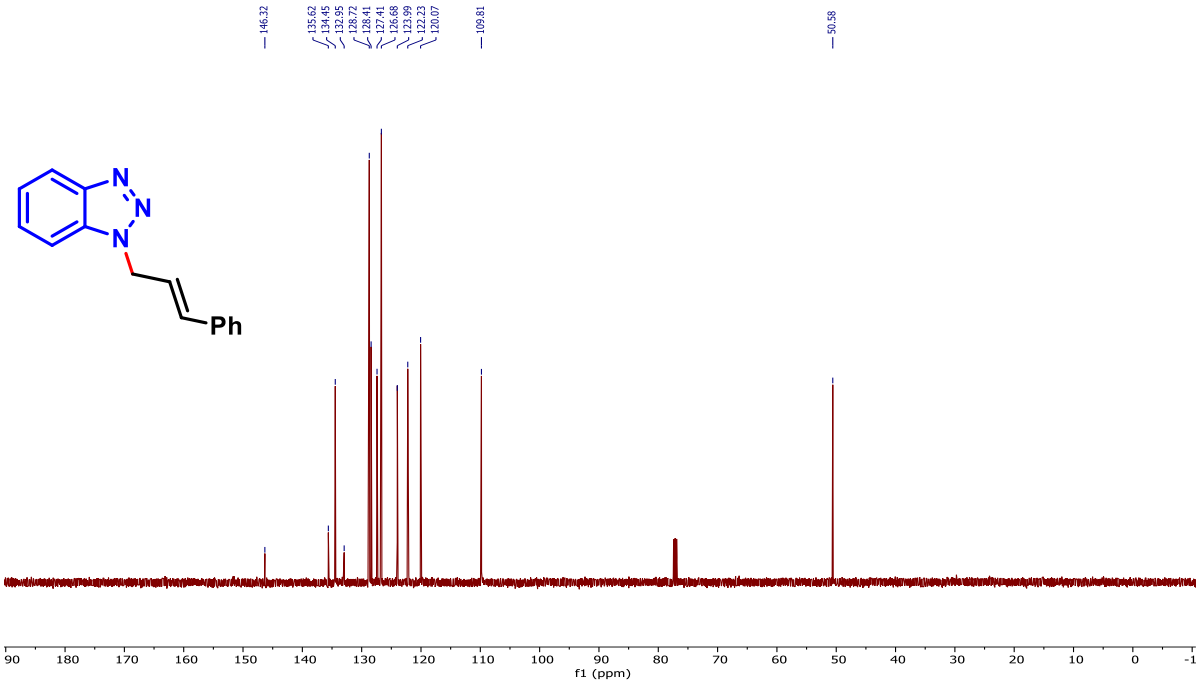


Figure 64: ^{13}C NMR (126 MHz, $CDCl_3$) of 1-Cinnamyl-1H-benzo[d][1,2,3]triazole (**1i**)

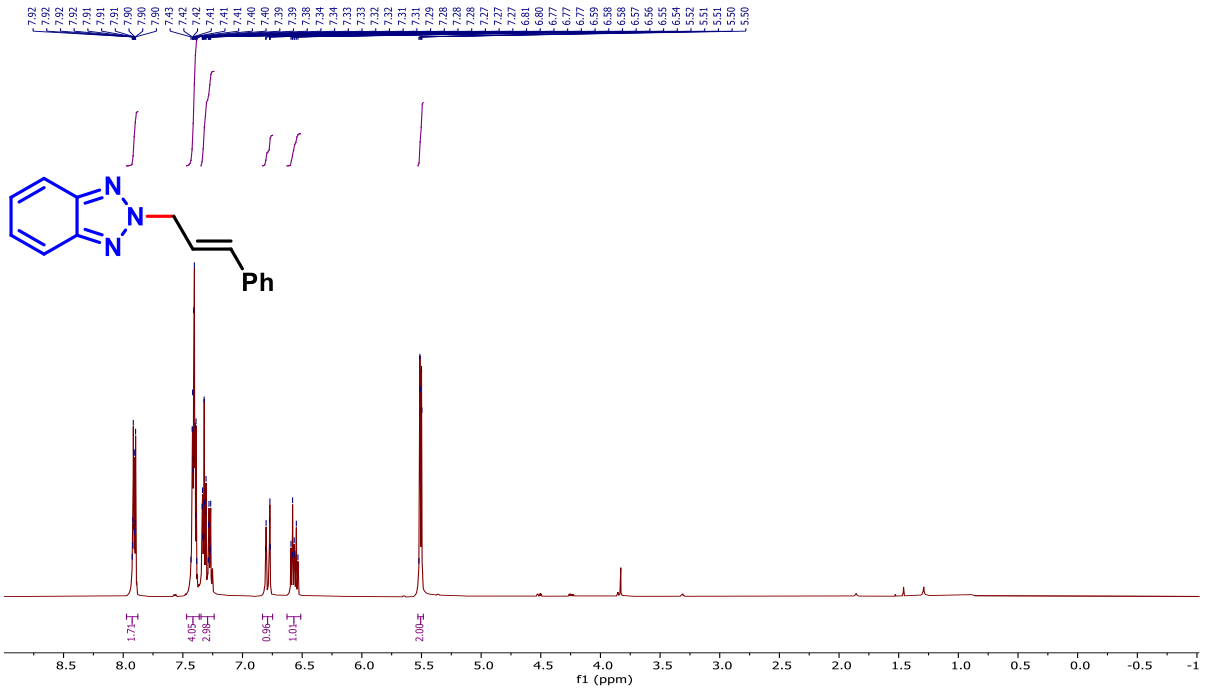


Figure 65: ^{1}H NMR (500 MHz, $CDCl_3$) of 2-Cinnamyl-2H-benzo[d][1,2,3]triazole (**1i**)

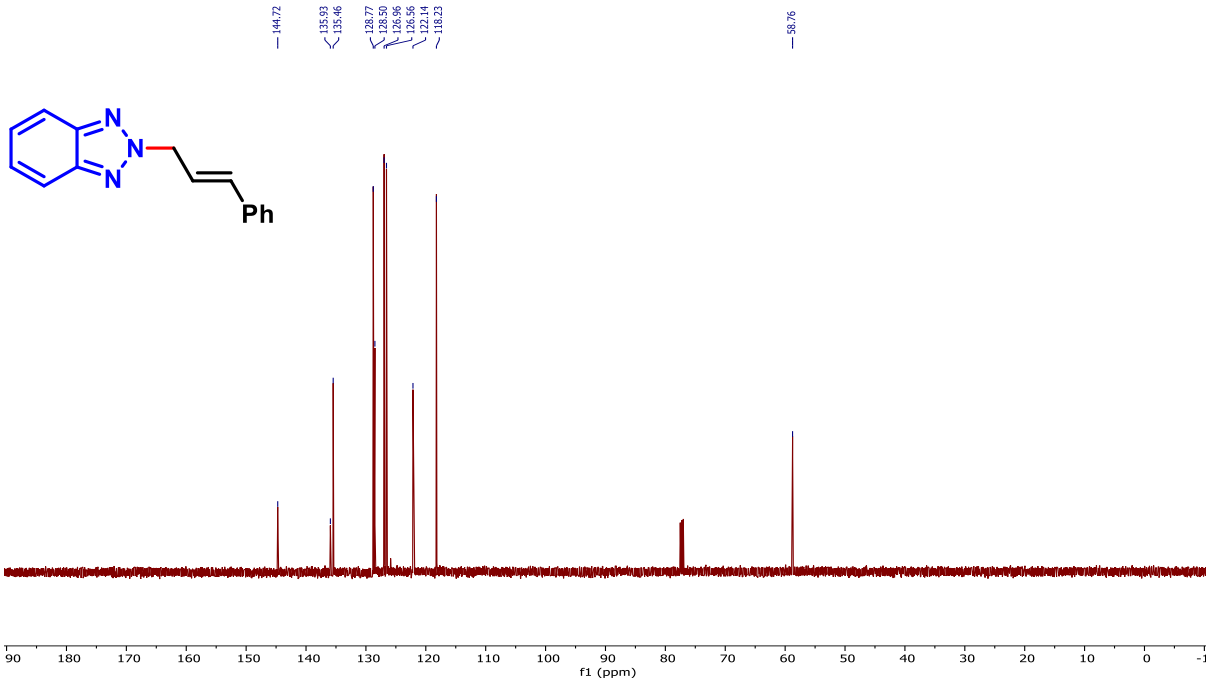


Figure 66: ^{13}C NMR (126 MHz, $CDCl_3$) of 2-Cinnamyl-2H-benzo[d][1,2,3]triazole (**1i**)

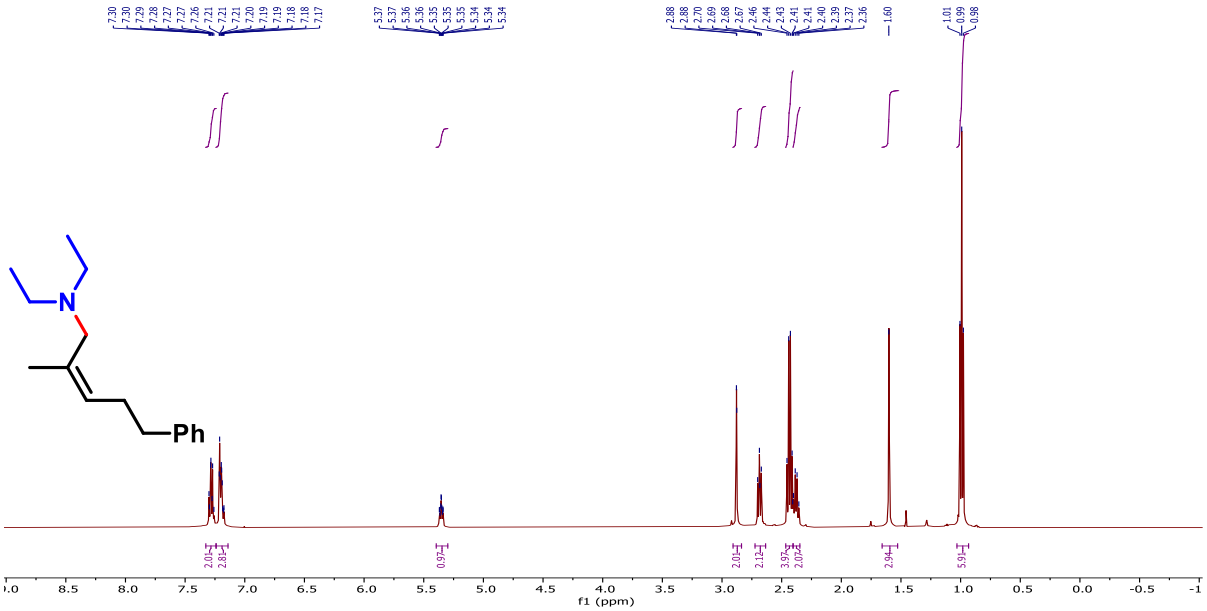


Figure 67: ^{1}H NMR (500 MHz, $CDCl_3$) of *(E)-N,N*-Diethyl-2-methyl-5-phenylpent-2-en-1-amine (**1j**)

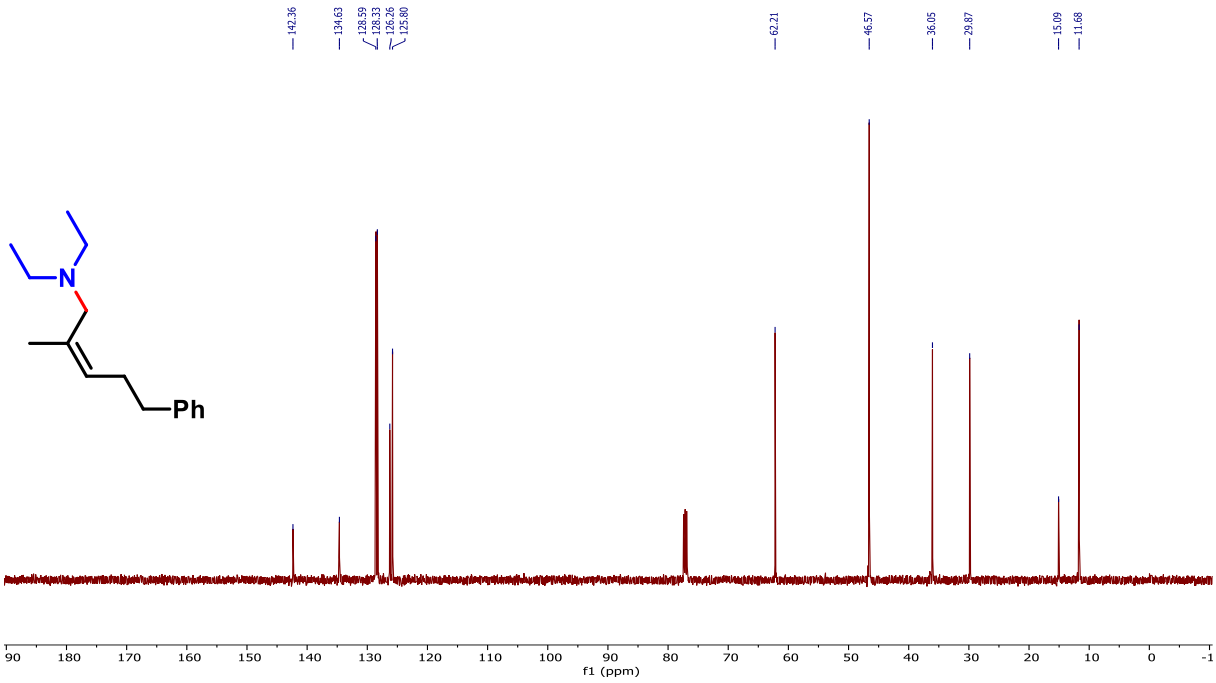


Figure 68: ^{13}C NMR (126 MHz, $CDCl_3$) of *(E)-N,N*-Diethyl-2-methyl-5-phenylpent-2-en-1-amine (**1j**)

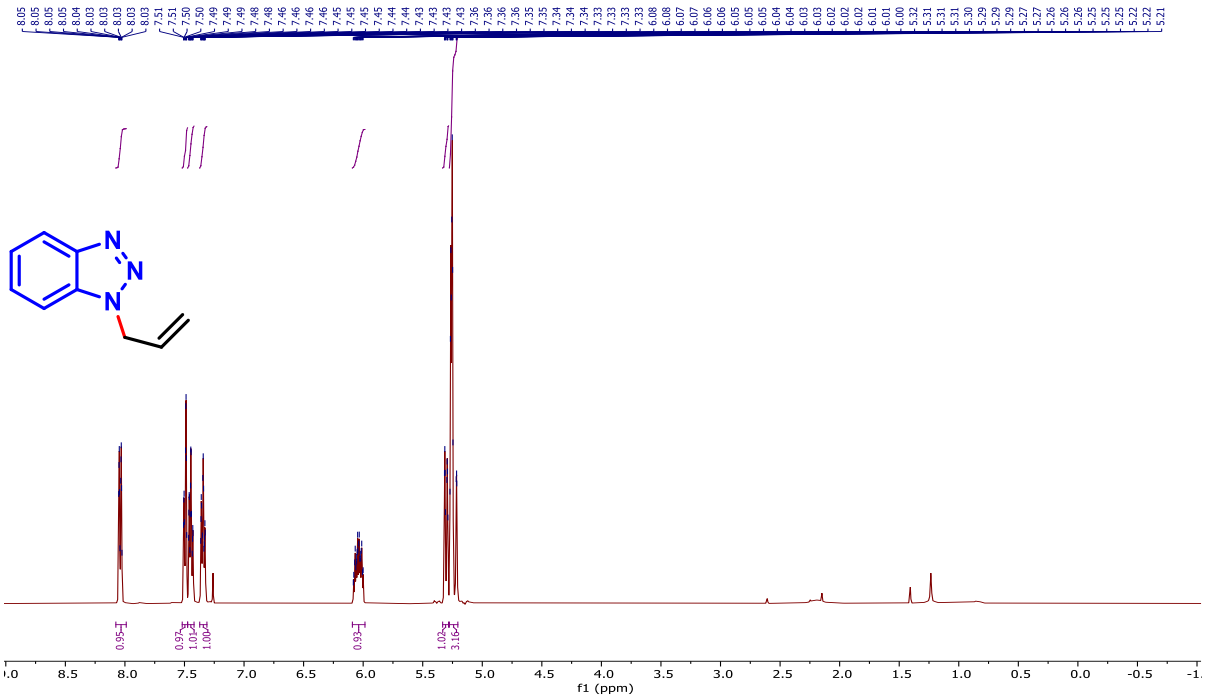


Figure 69: ^{1}H NMR (500 MHz, $CDCl_3$) of 1-Allyl-1H-benzo[d][1,2,3]triazole (**1k**)

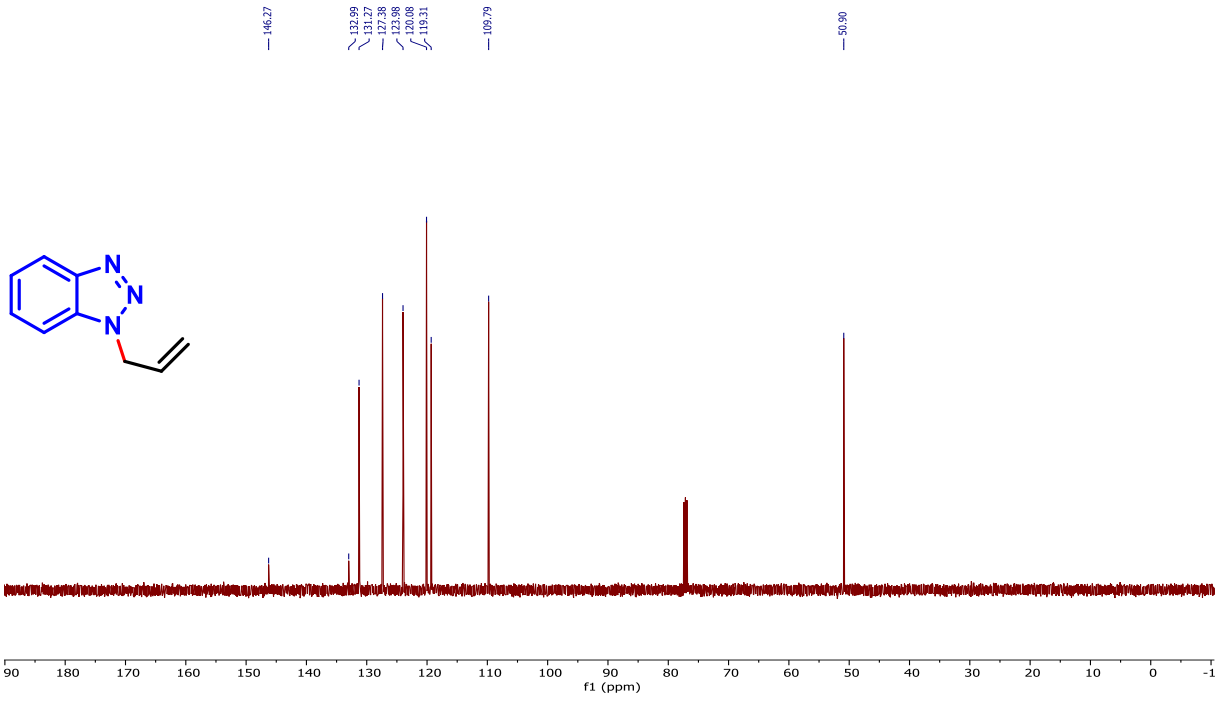


Figure 70: ^{13}C NMR (126 MHz, $CDCl_3$) of 1-Allyl-1H-benzo[d][1,2,3]triazole (**1k**)

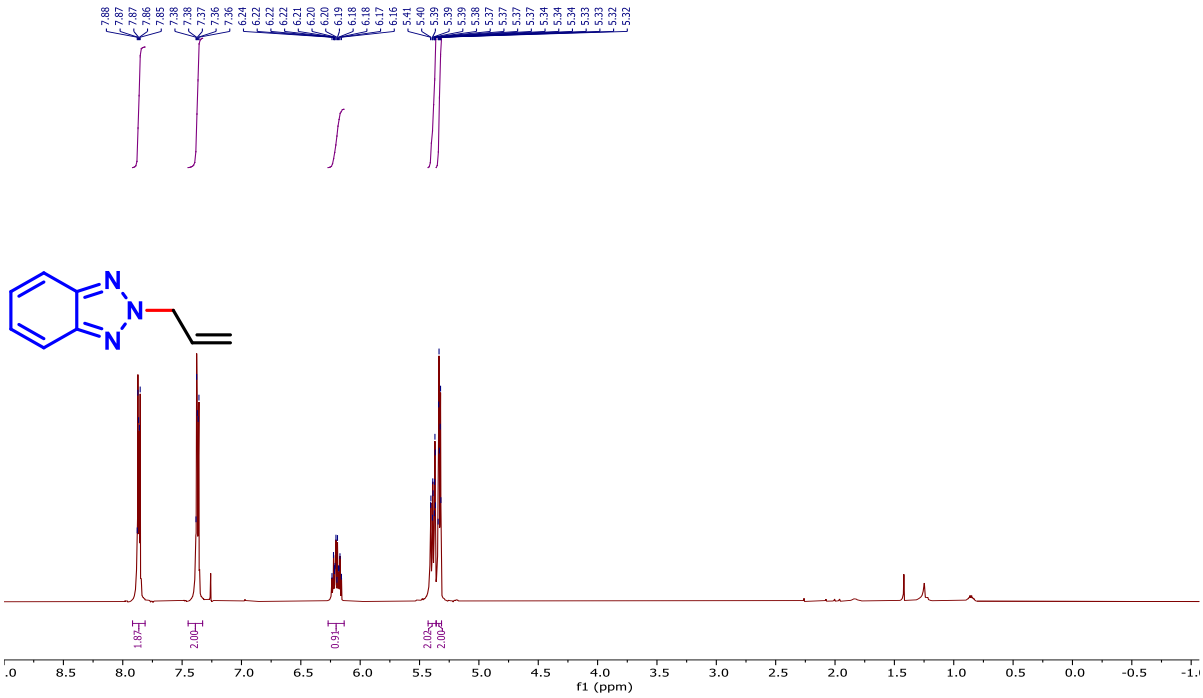


Figure 71: ^{1}H NMR (500 MHz, $CDCl_3$) of 2-Allyl-2H-benzo[d][1,2,3]triazole (**1k**)

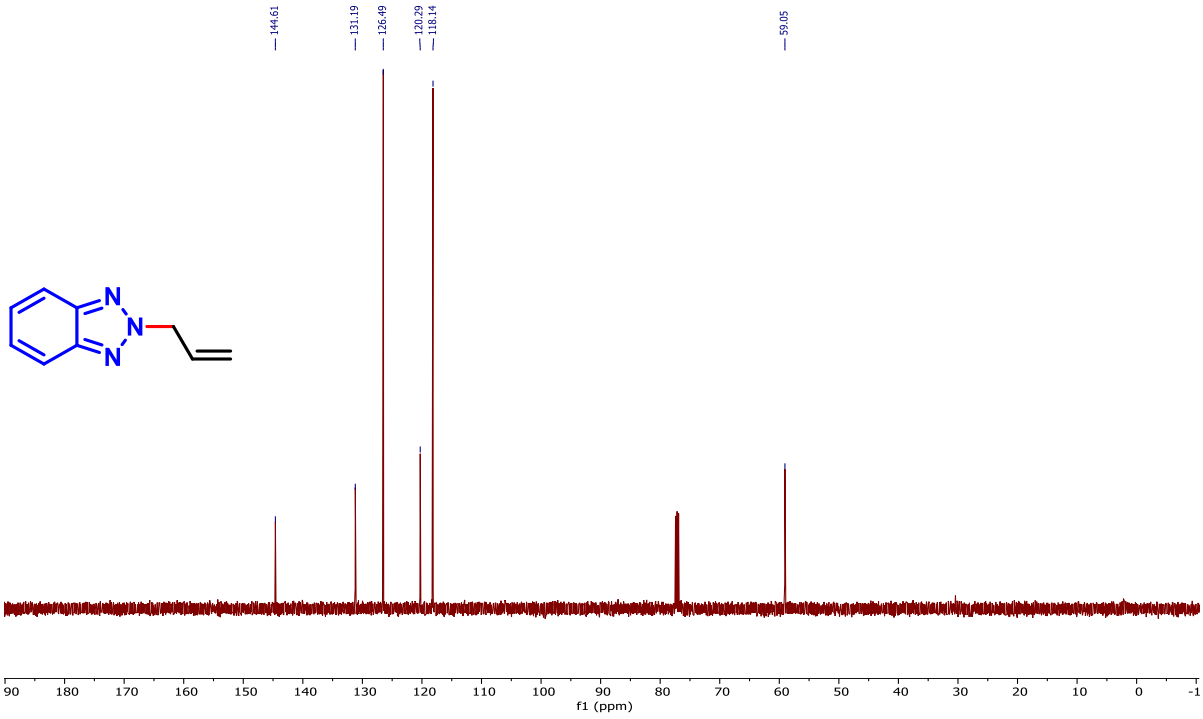


Figure 72: ^{13}C NMR (126 MHz, $CDCl_3$) of 2-Allyl-2H-benzo[d][1,2,3]triazole (**1k**)

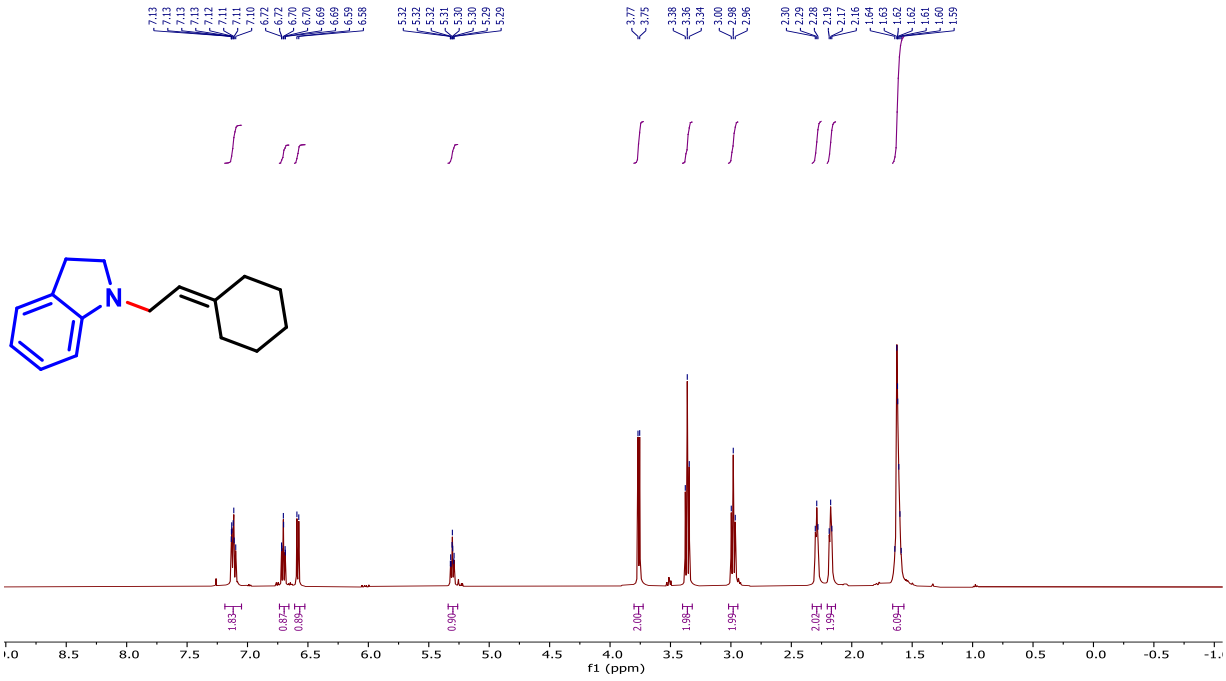


Figure 73: ^{1}H NMR (500 MHz, $CDCl_3$) of 1-(2-Cyclohexylideneethyl)indoline (**1l**)

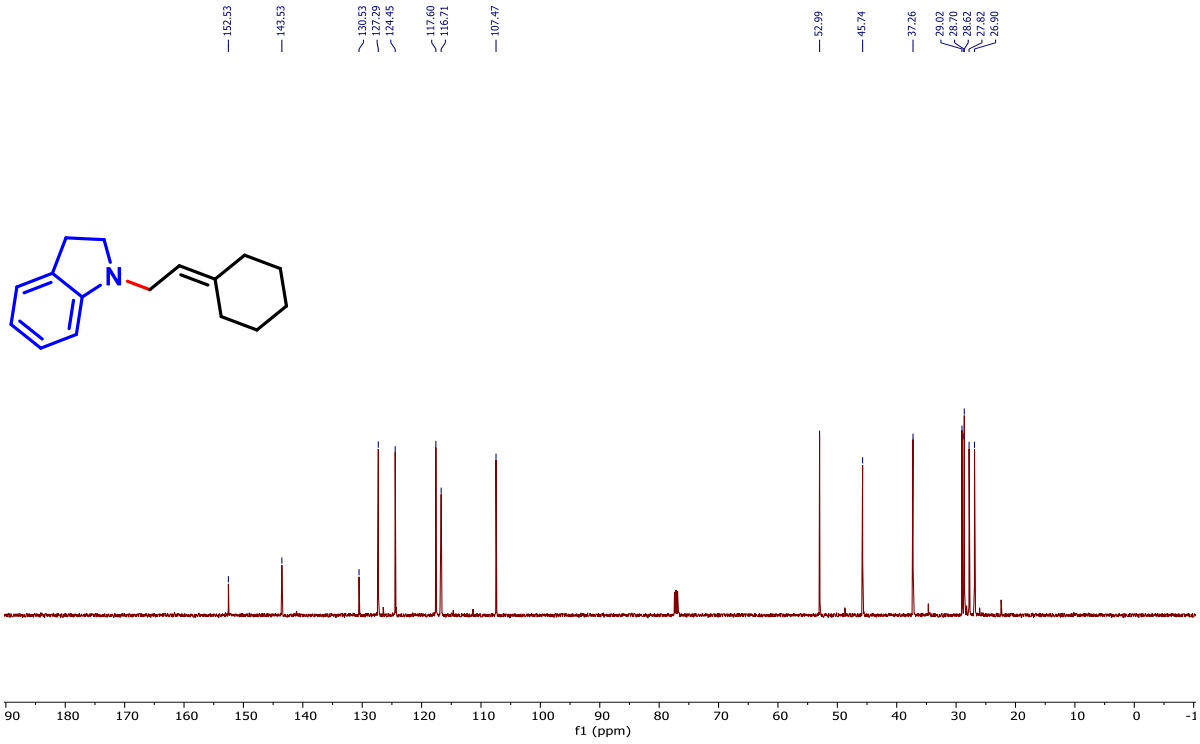


Figure 74: ^{13}C NMR (126 MHz, $CDCl_3$) of 1-(2-Cyclohexylideneethyl)indoline (**1l**)

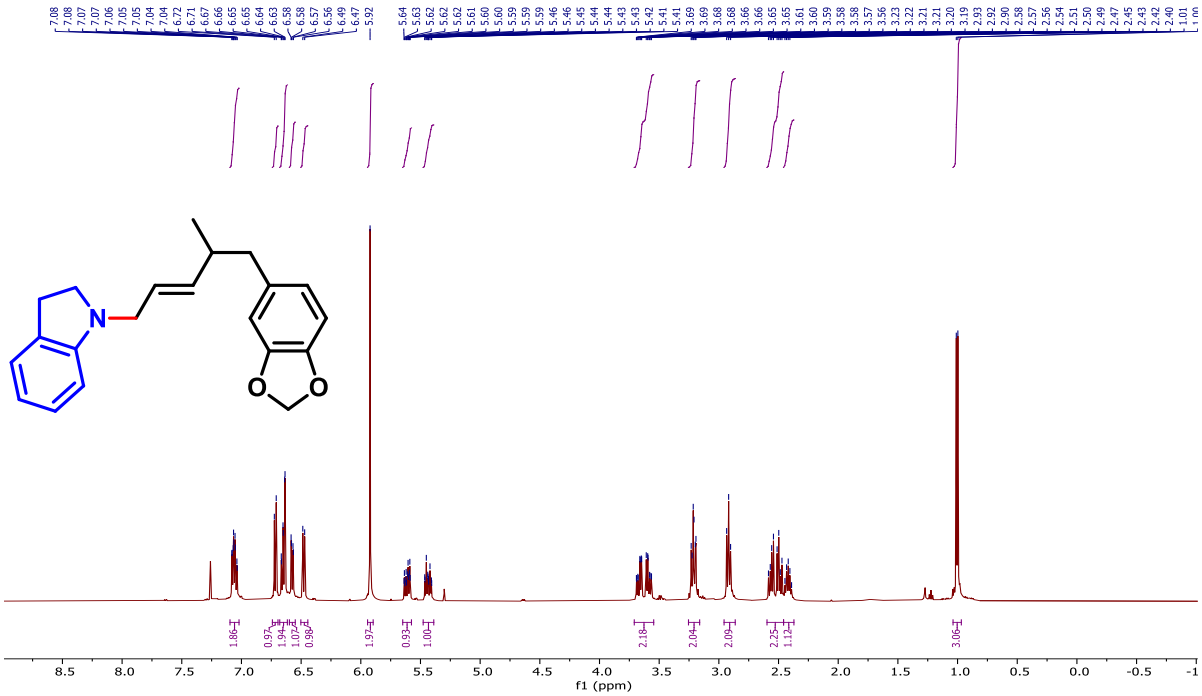


Figure 75: ^{1}H NMR (500 MHz, $CDCl_3$) of (*E*)-1-(5-(Benzo[d][1,3]dioxol-5-yl)-4-methylpent-2-en-1-yl)indoline (**1m**)

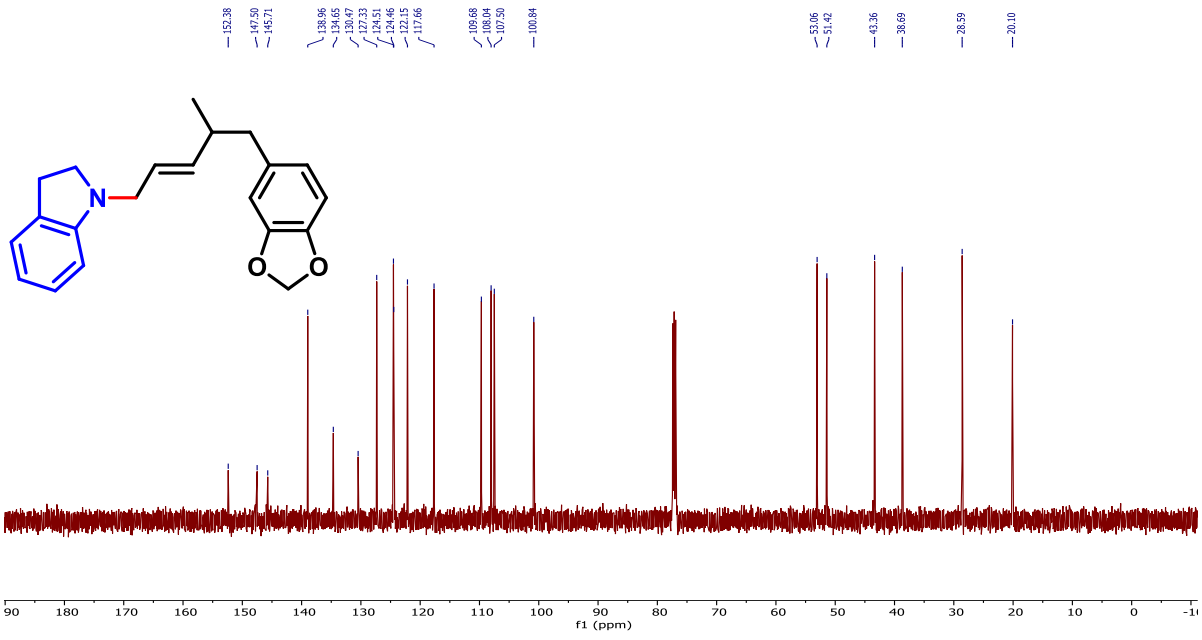


Figure 76: ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-1-(5-(Benzo[d][1,3]dioxol-5-yl)-4-methylpent-2-en-1-yl)indoline (**1m**)

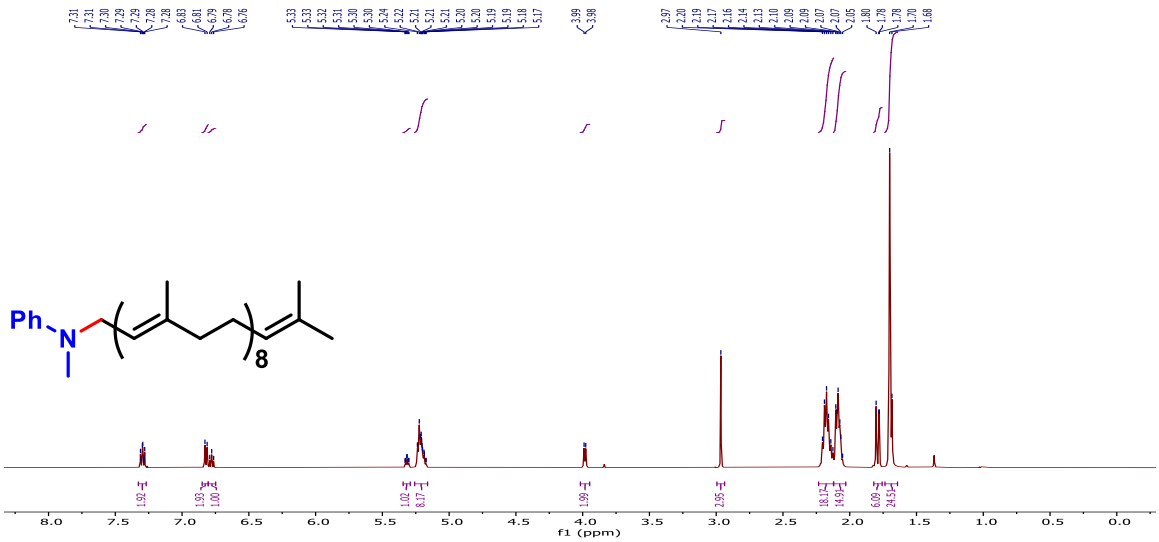


Figure 77: ^{1}H NMR (500 MHz, $CDCl_3$) of *N*-Methyl-*N*-((2E,6E,10E,14E,18E,22E,26E,30E)-3,7,11,15,19,23,27,31,35-nonamethylhexatriaconta-2,6,10,14,18,22,26,30,34-nonaen-1-yl)aniline (**1n**)

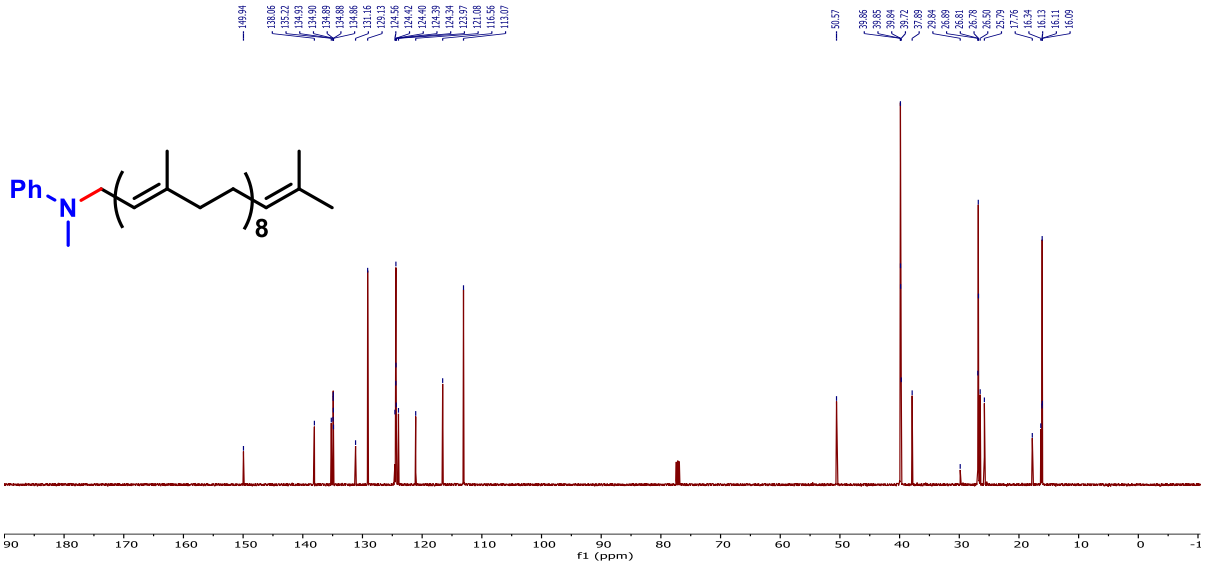


Figure 78: ^{13}C NMR (126 MHz, $CDCl_3$) of *N*-Methyl-*N*-((2E,6E,10E,14E,18E,22E,26E,30E)-3,7,11,15,19,23,27,31,35-nonamethylhexatriaconta-2,6,10,14,18,22,26,30,34-nonaen-1-yl)aniline (**1n**)

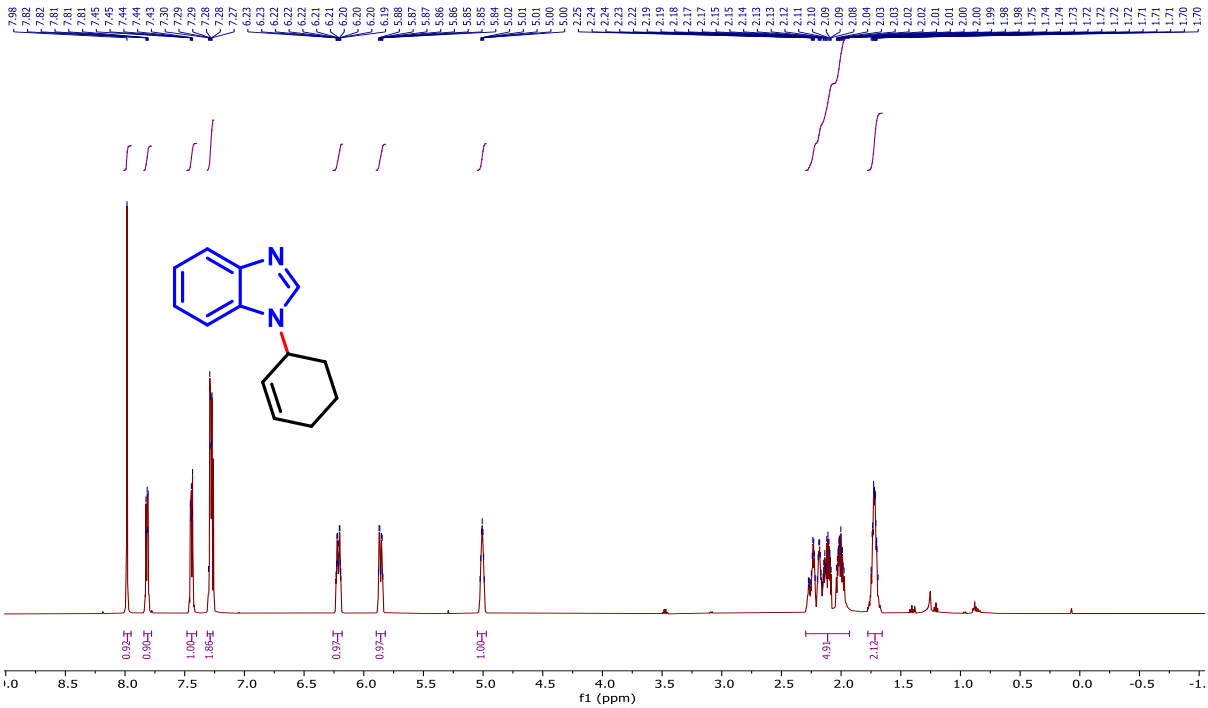


Figure 79: ^{1}H NMR (500 MHz, $CDCl_3$) of 1-(Cyclohex-2-en-1-yl)-1H-benzo[d]imidazole (**1o**)

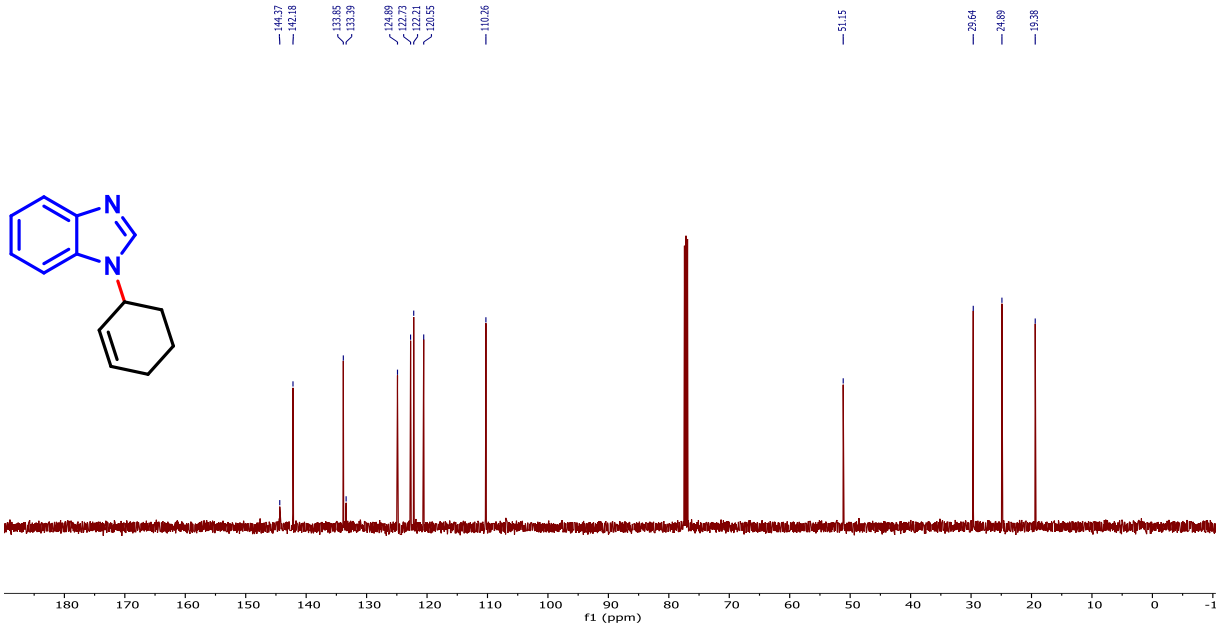


Figure 80: ^{13}C NMR (126 MHz, $CDCl_3$) of 1-(Cyclohex-2-en-1-yl)-1H-benzo[d]imidazole (**1o**)

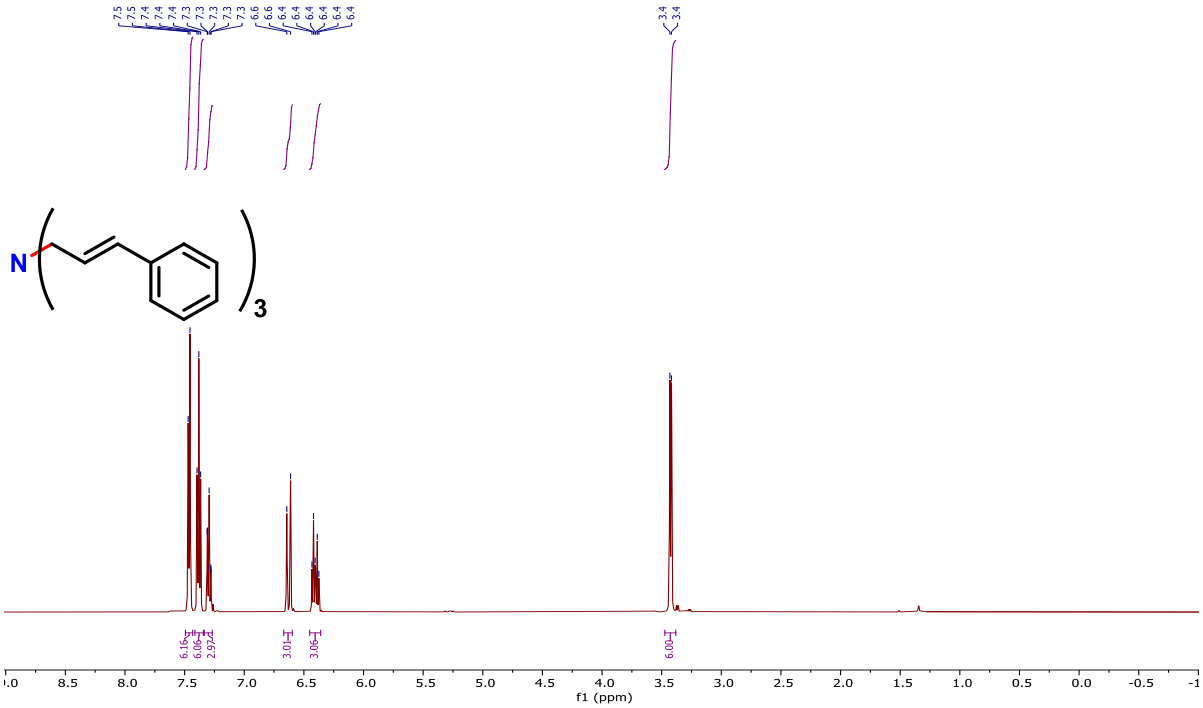


Figure 81: ^{1}H NMR (500 MHz, $CDCl_3$) of (*E*)-Tricinnamylamine (**1p**)

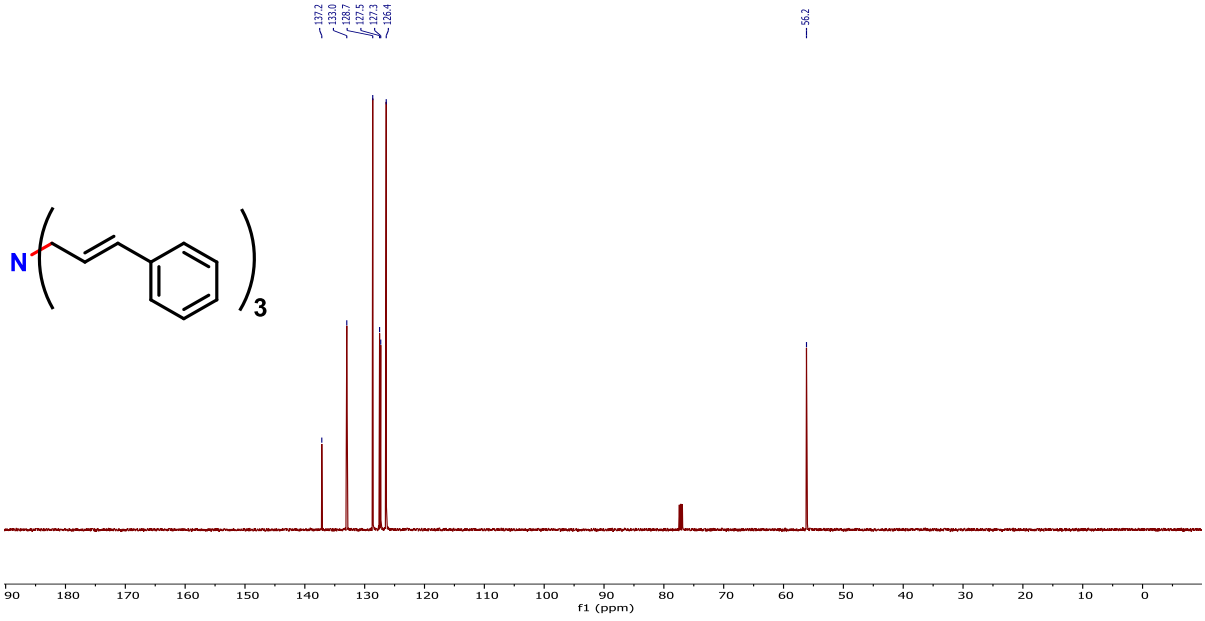


Figure 82: ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-Tricinnamylamine (**1p**)

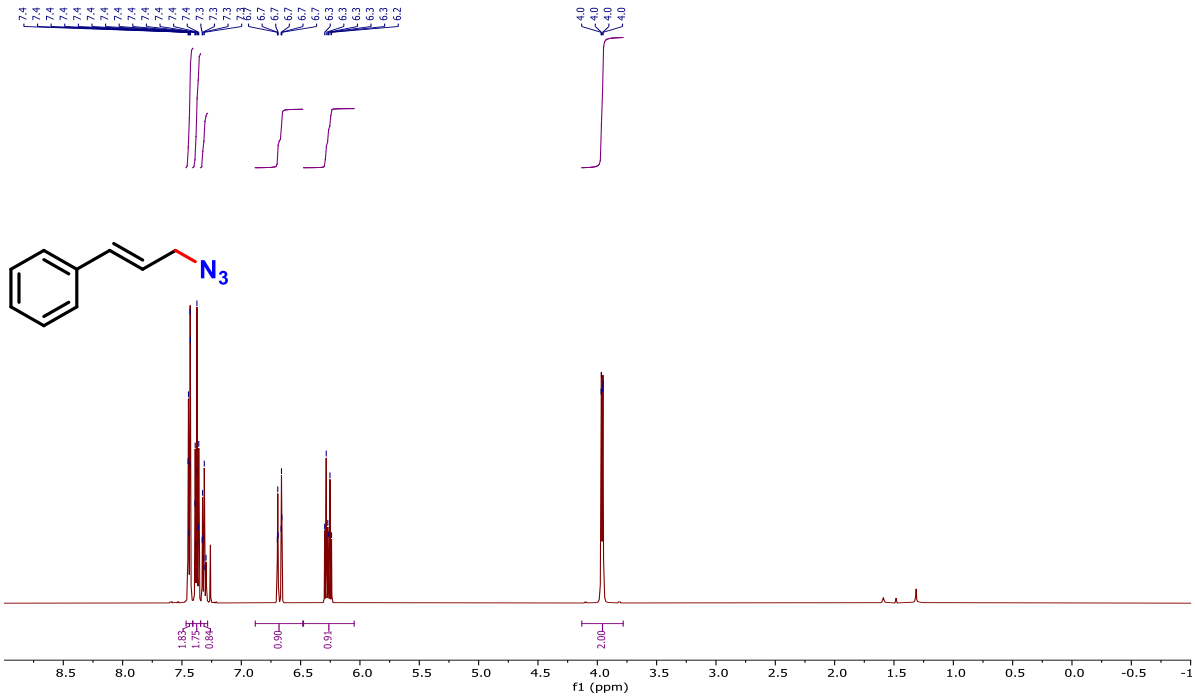


Figure 83: ^{1}H NMR (500 MHz, $CDCl_3$) of (E)-(3-azidoprop-1-en-1-yl)benzene (**1q**)

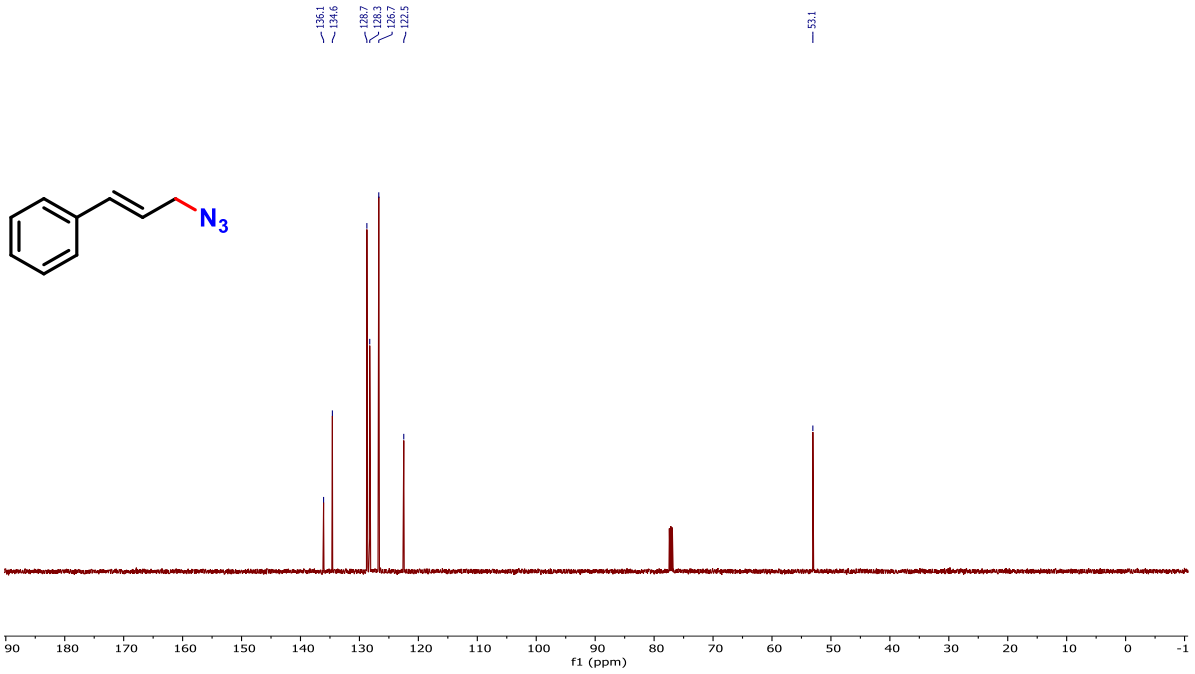


Figure 84: ^{13}C NMR (126 MHz, $CDCl_3$) of (E)-(3-azidoprop-1-en-1-yl)benzene (**1q**)

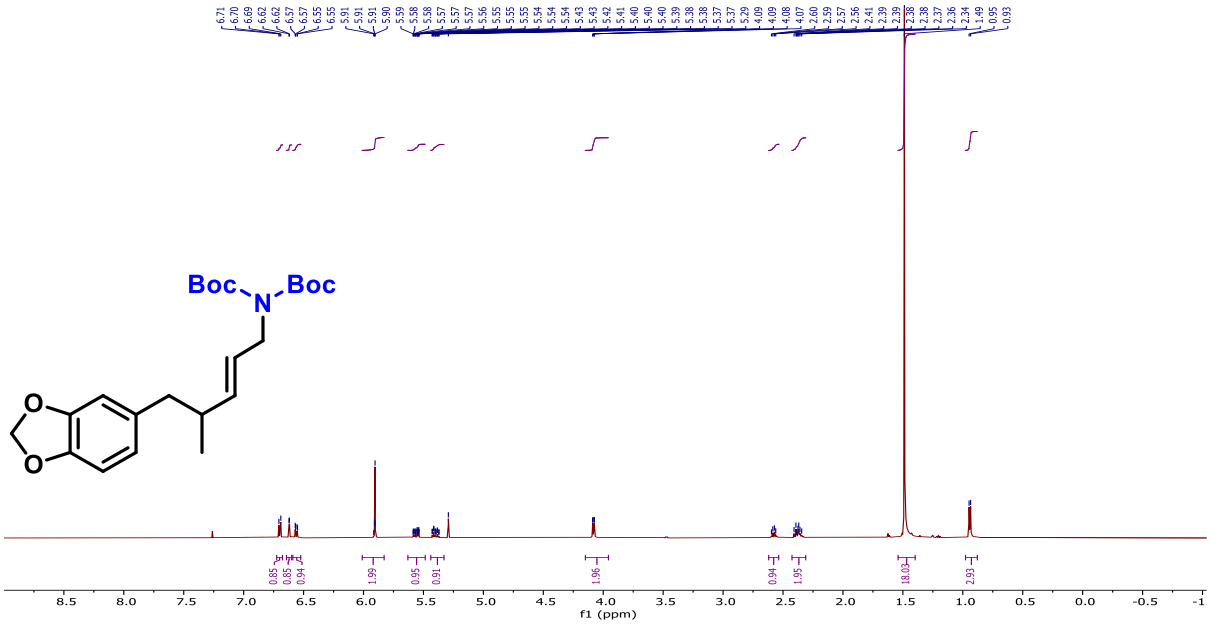


Figure 85: ^{1}H NMR (500 MHz, $CDCl_3$) of (*E*)-5-(Benzo[d][1,3]dioxol-5-yl)-4-methylpent-2-en-1-(di-*tert*-butyl iminodicarboxylate) (**1r**)

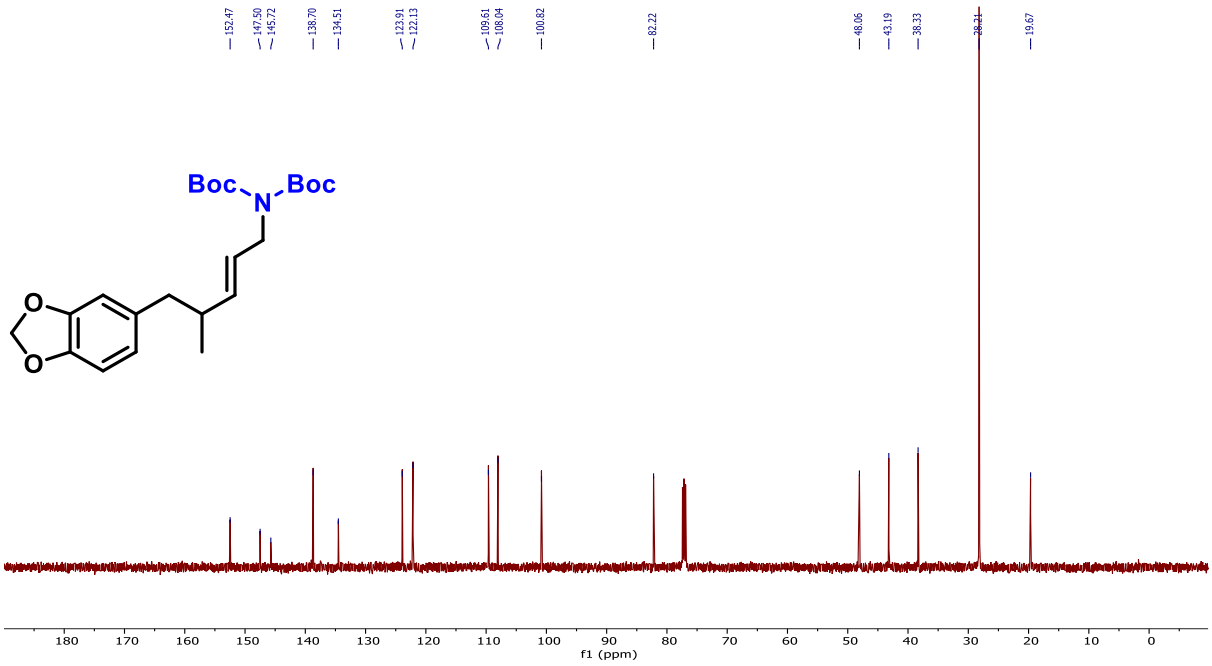


Figure 86: ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-5-(Benzo[d][1,3]dioxol-5-yl)-4-methylpent-2-en-1-(di-*tert*-butyl iminodicarboxylate) **(1r)**

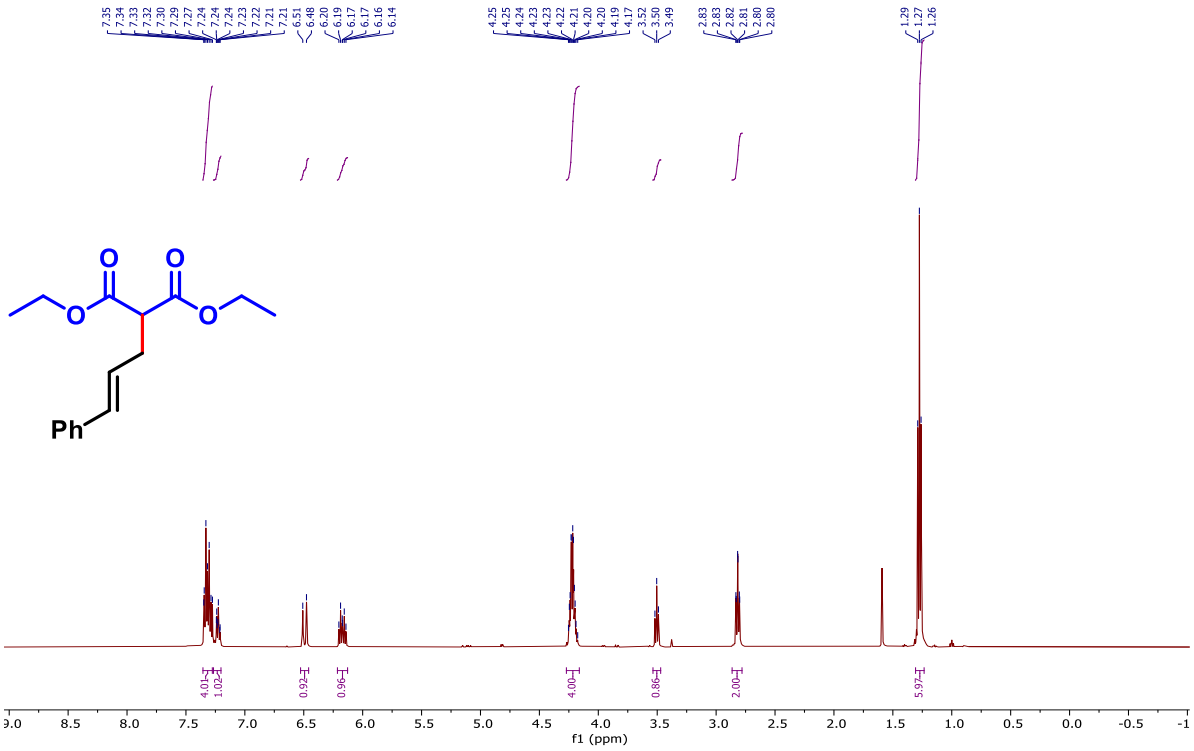


Figure 87: ^{1}H NMR (500 MHz, $CDCl_3$) of Diethyl 2-cinnamylmalonate (**2a**)

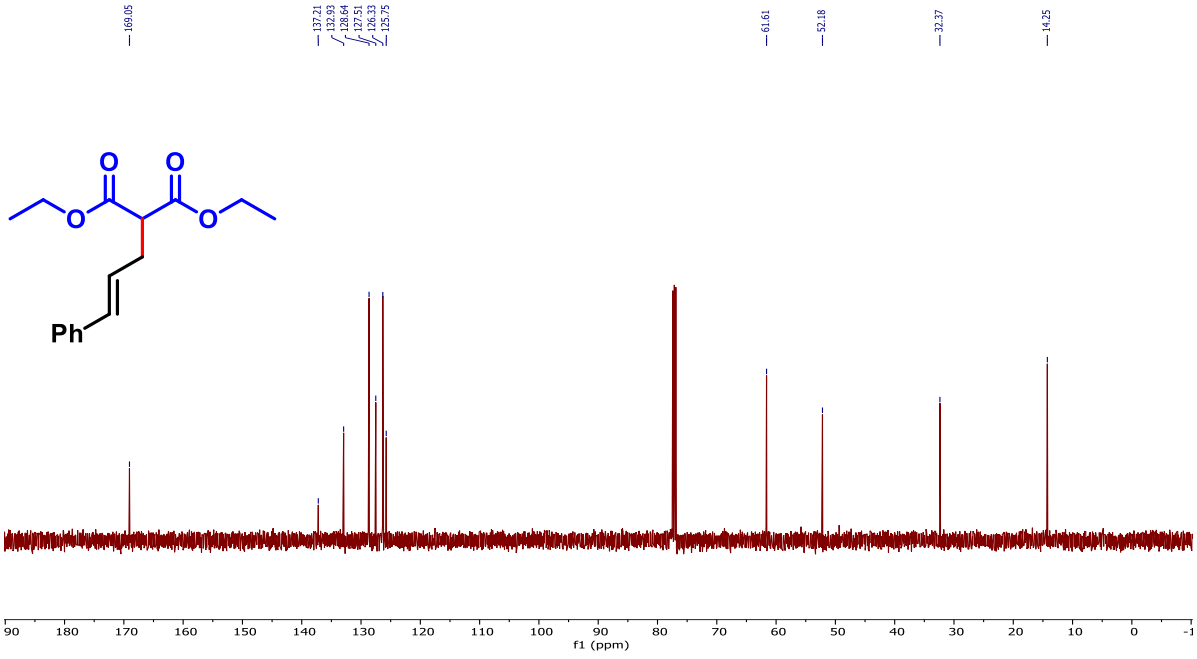


Figure 88: ^{13}C NMR (126 MHz, $CDCl_3$) of Diethyl 2-cinnamylmalonate (**2a**)

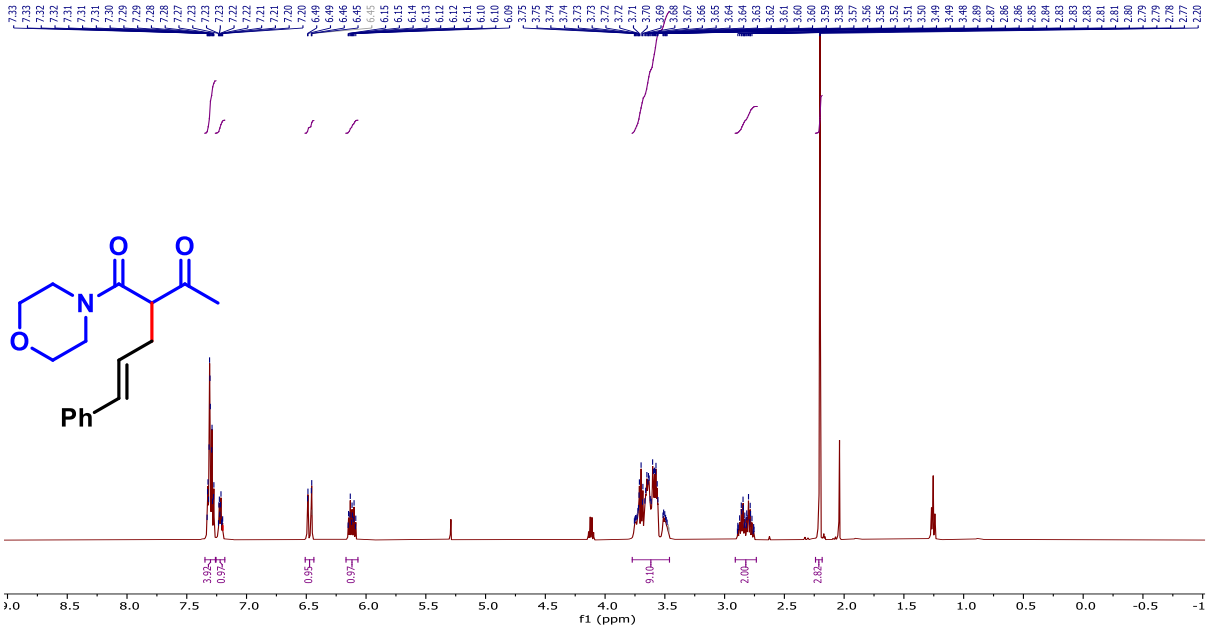


Figure 89: ^{1}H NMR (500 MHz, $CDCl_3$) of 2-Cinnamyl-1-morpholinobutane-1,3-dione (**2b**)

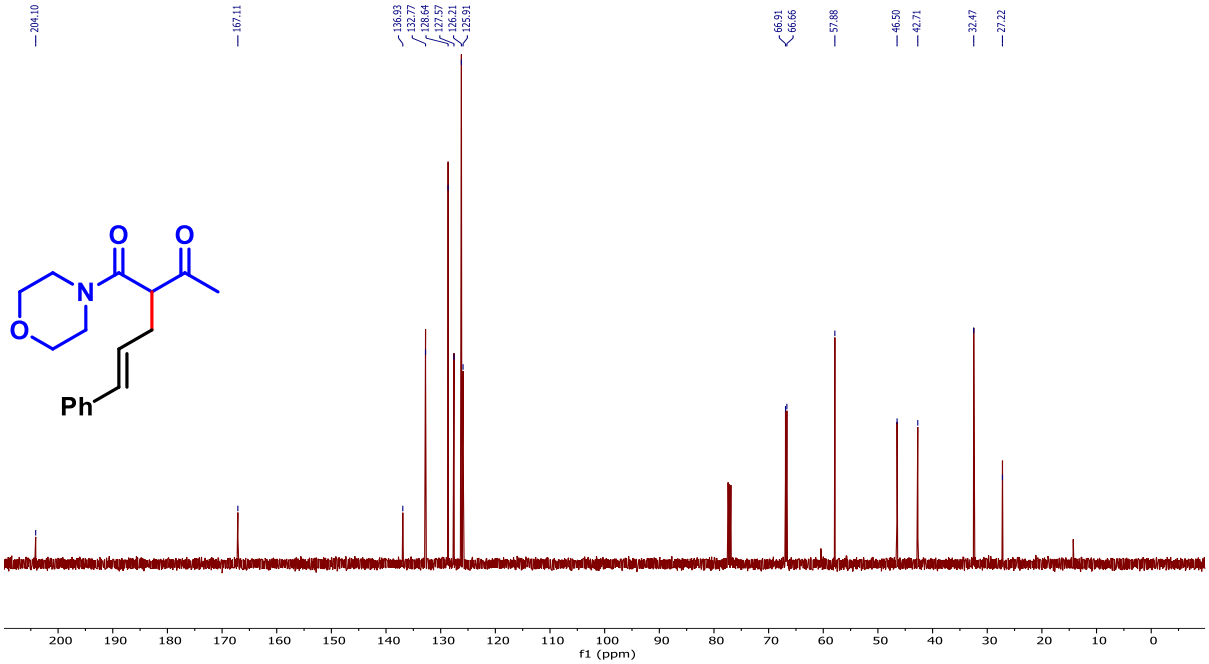


Figure 90: ^{13}C NMR (126 MHz, $CDCl_3$) of 2-Cinnamyl-1-morpholinobutane-1,3-dione (**2b**)

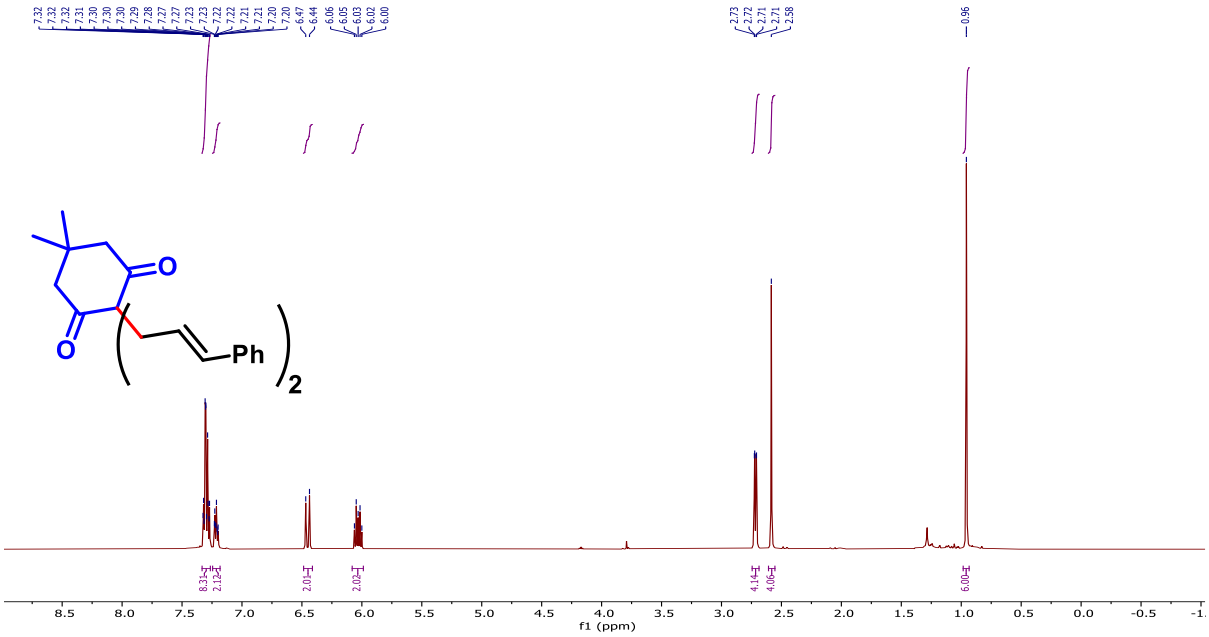


Figure 91: ^{1}H NMR (500 MHz, $CDCl_3$) of 2,2-Dicinnamyl-5,5-dimethylcyclohexane-1,3-dione (**2c**)

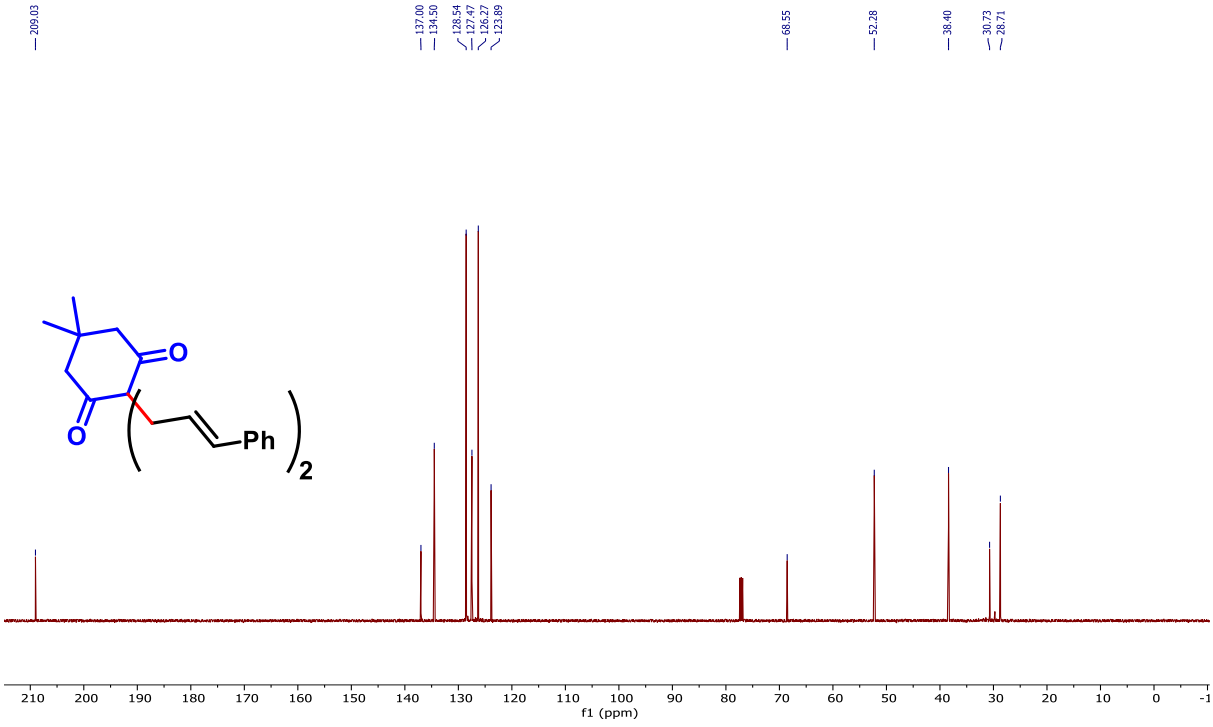


Figure 92: ^{13}C NMR (126 MHz, $CDCl_3$) of 2,2-Dicinnamyl-5,5-dimethylcyclohexane-1,3-dione (**2c**)

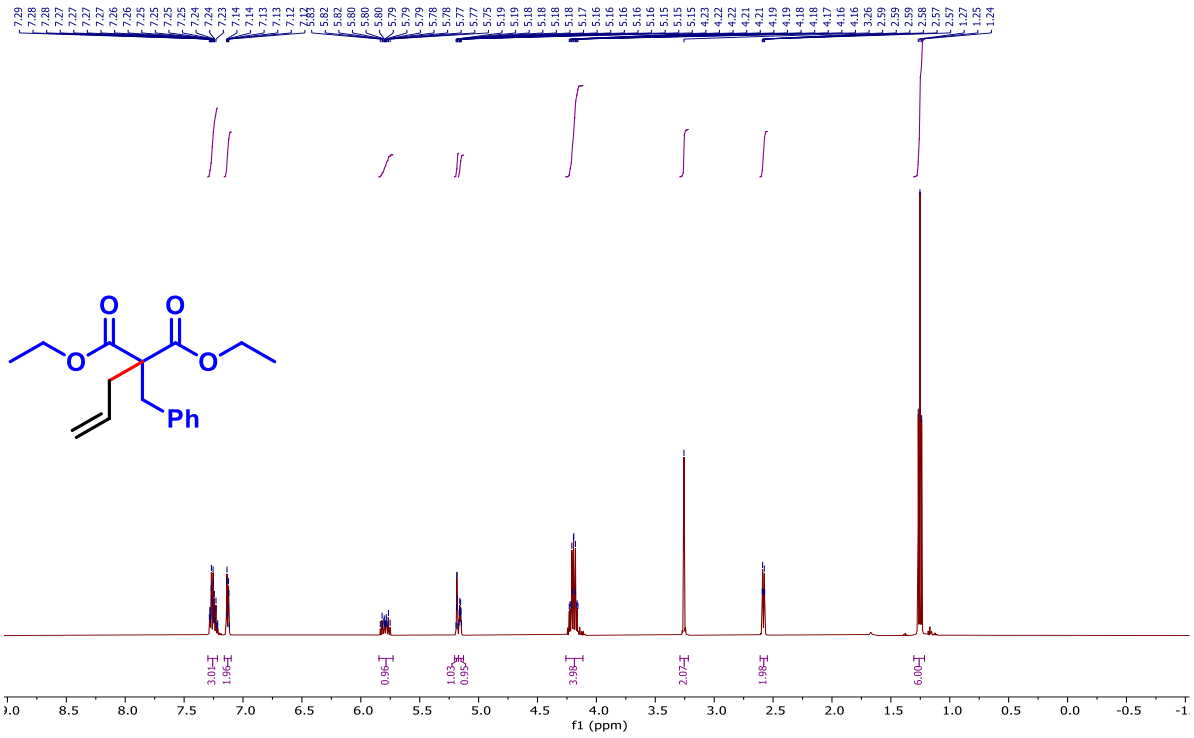


Figure 93: ^{1}H NMR (500 MHz, $CDCl_3$) of Diethyl 2-allyl-2-benzylmalonate (**2d**)

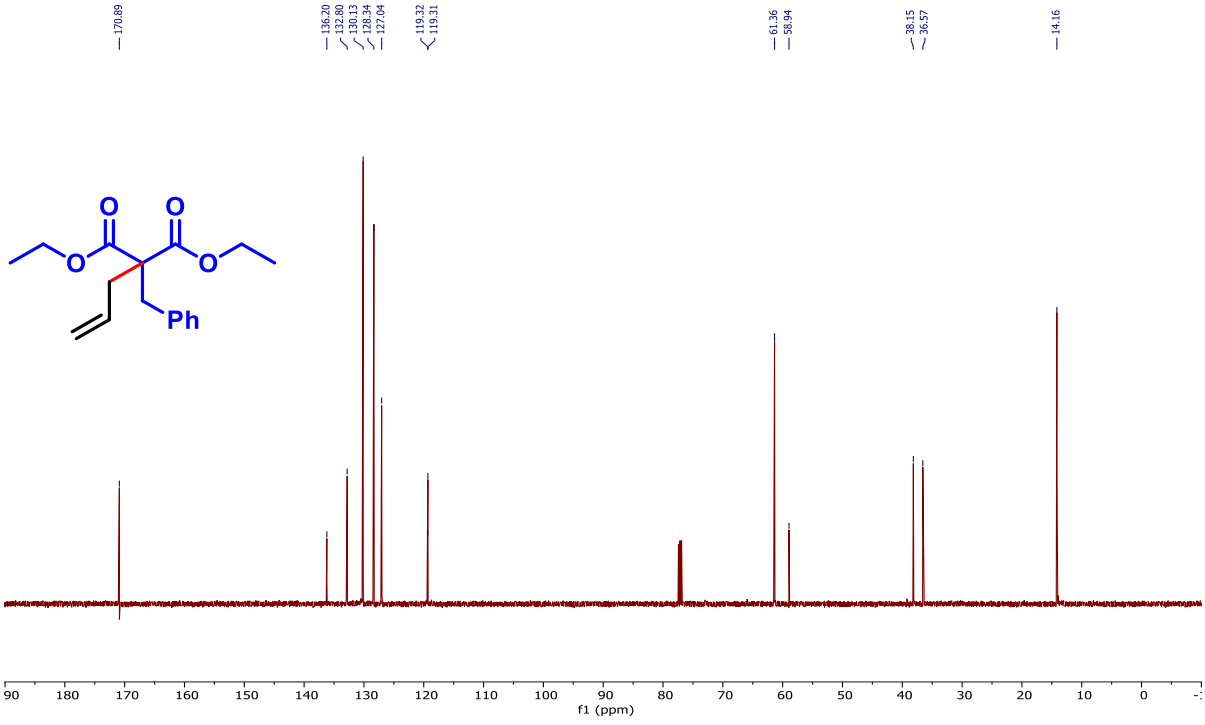


Figure 94: ^{13}C NMR (126 MHz, $CDCl_3$) of Diethyl 2-allyl-2-benzylmalonate (**2d**)

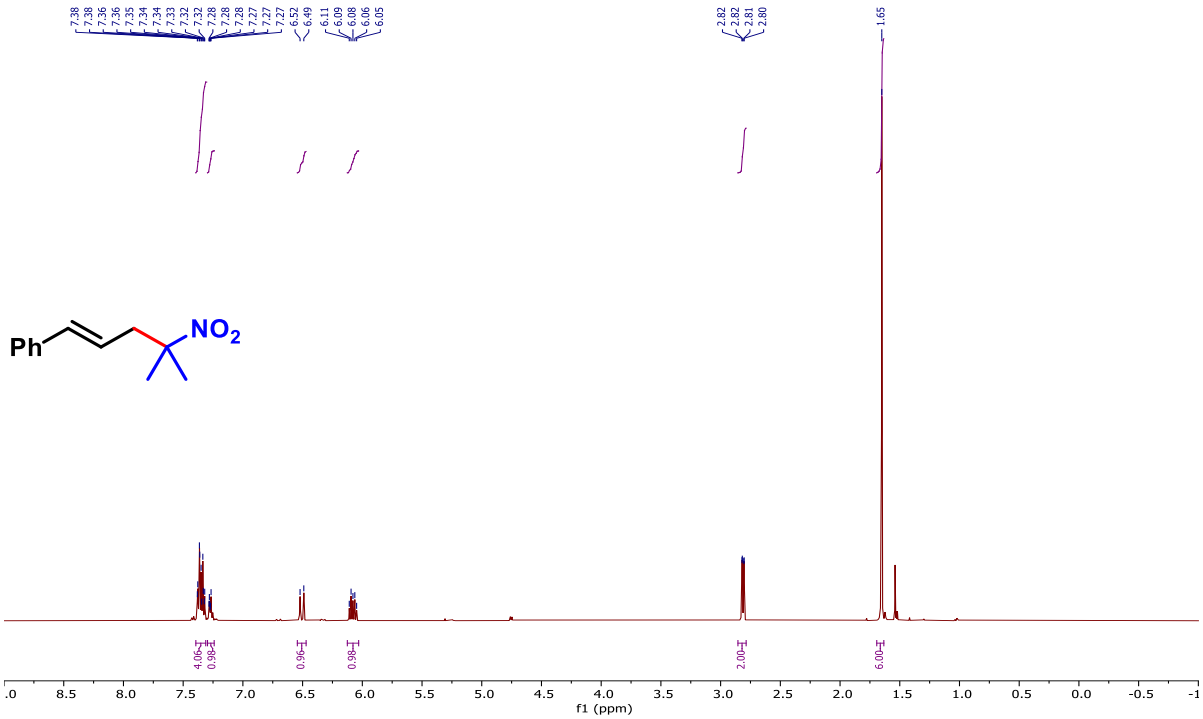


Figure 95: ^{1}H NMR (500 MHz, $CDCl_3$) of (*E*)-(4-Methyl-4-nitropent-1-en-1-yl)benzene (**2e**)

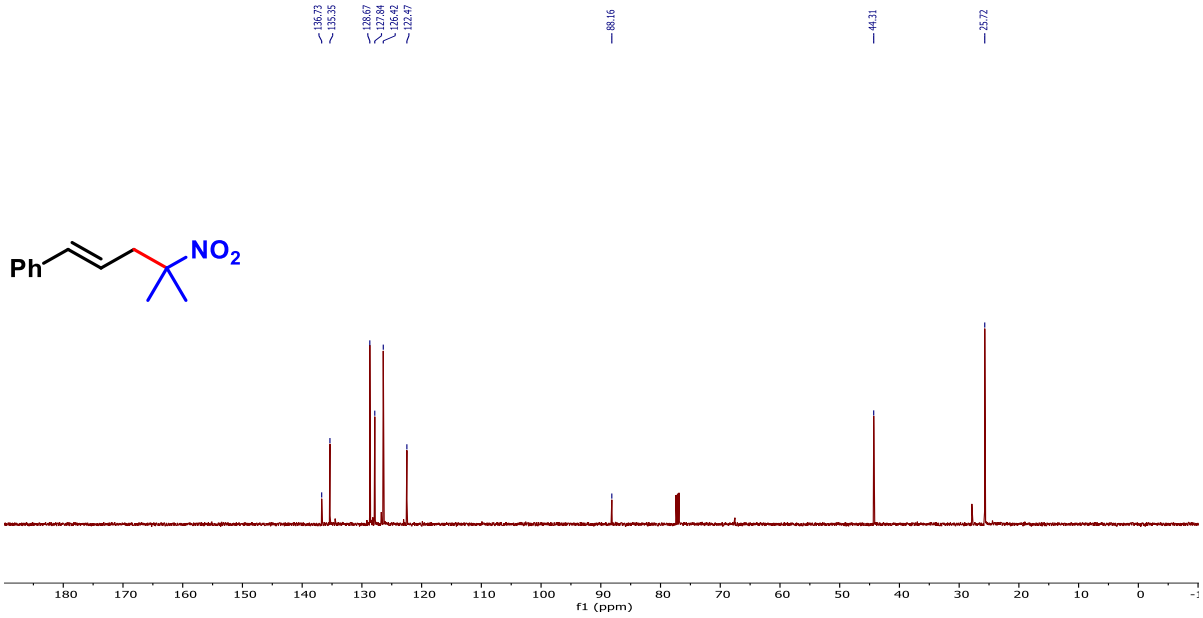


Figure 96: ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-(4-Methyl-4-nitropent-1-en-1-yl)benzene (**2e**)

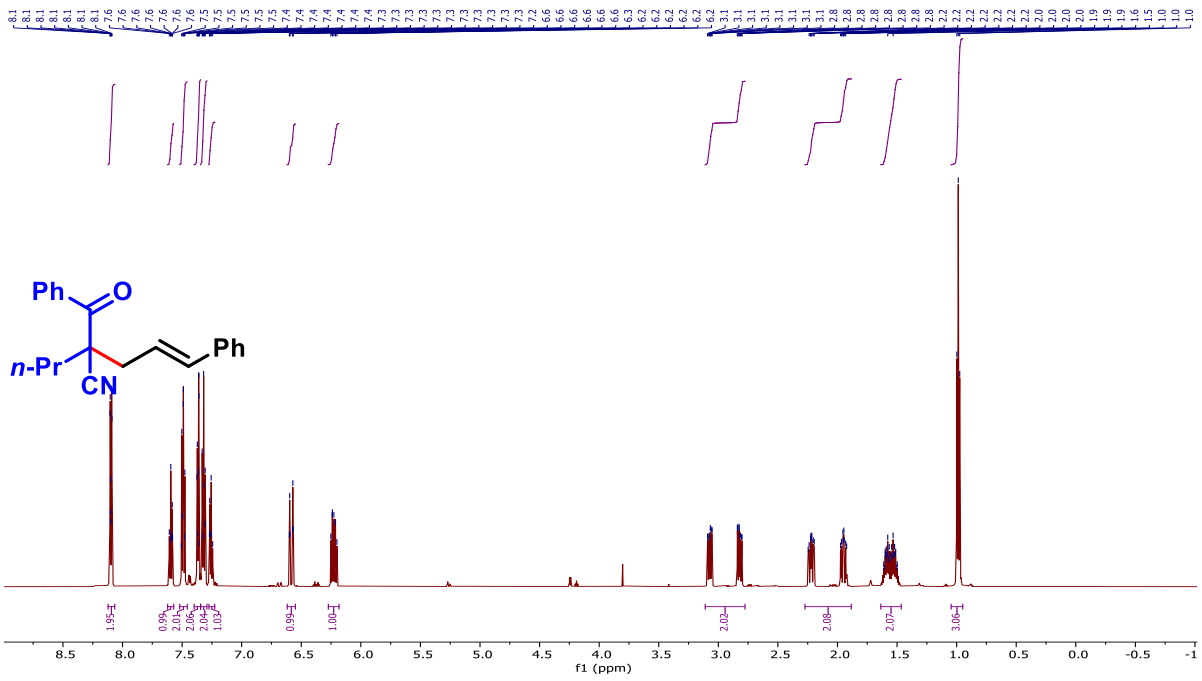


Figure 97: ^{1}H NMR (600 MHz, $CDCl_3$) of (*E*)-2-Benzoyl-5-phenyl-2-propylpent-4-enenitrile (**2f**)

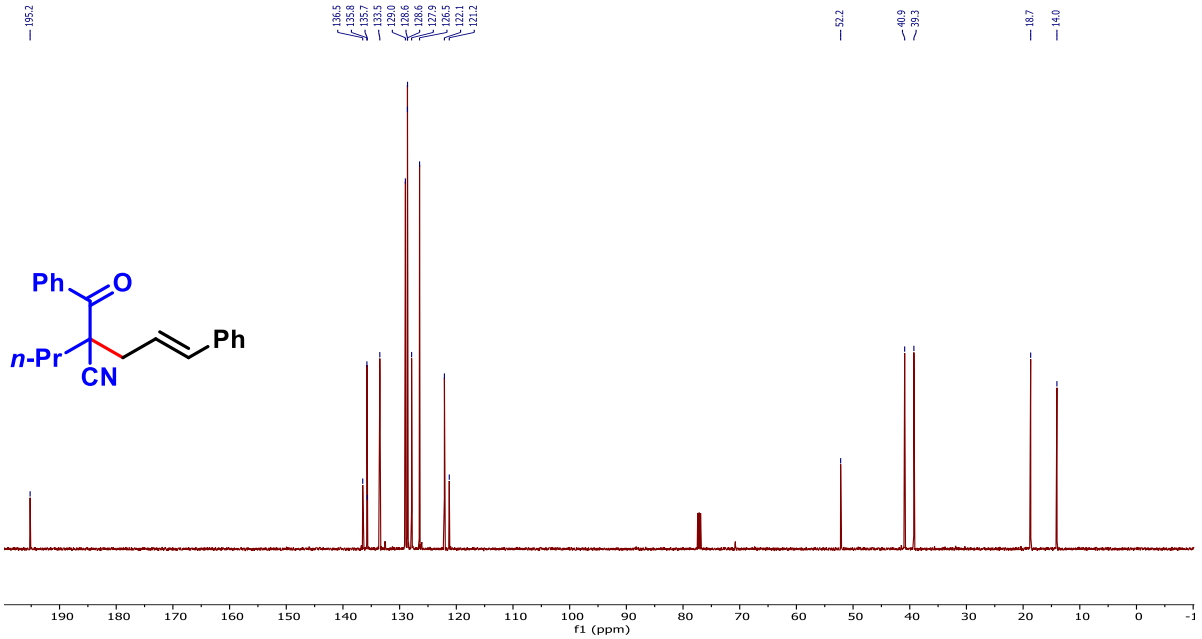


Figure 98: ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-2-Benzoyl-5-phenyl-2-propylpent-4-enenitrile (**2f**)

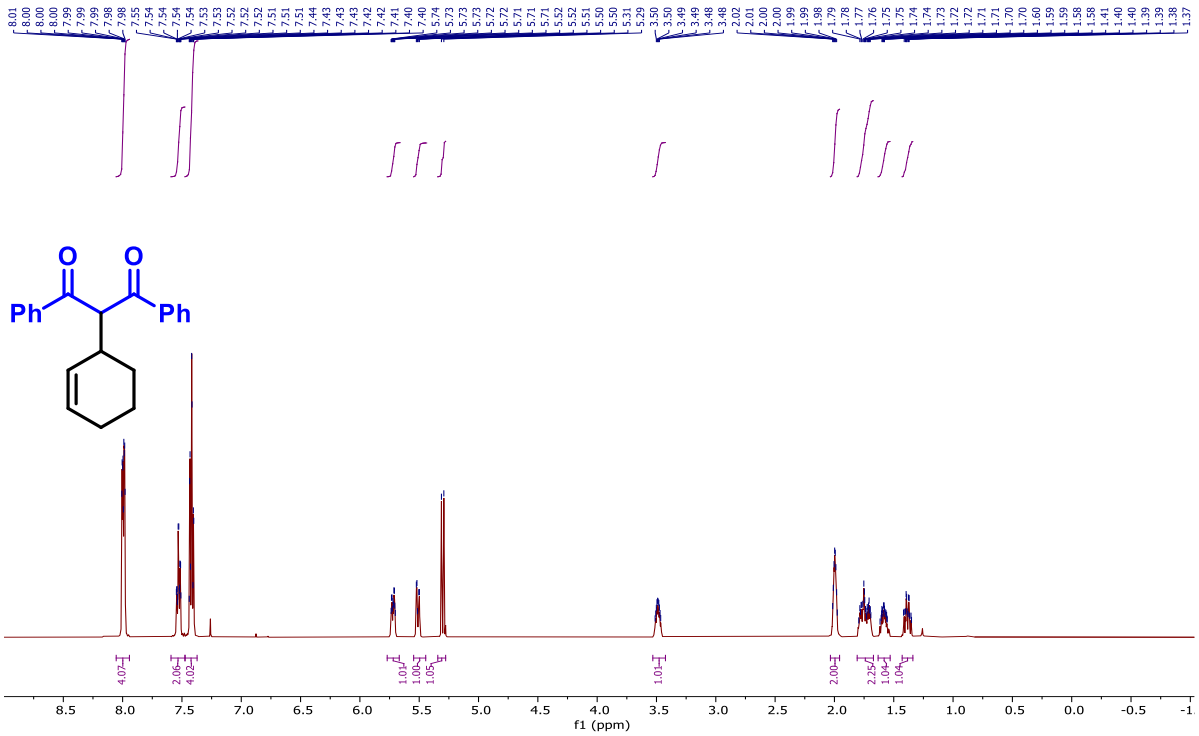


Figure 99: ^{1}H NMR (500 MHz, $CDCl_3$) of 2-(Cyclohex-2-en-1-yl)-1,3-diphenylpropane-1,3-dione (**2g**)

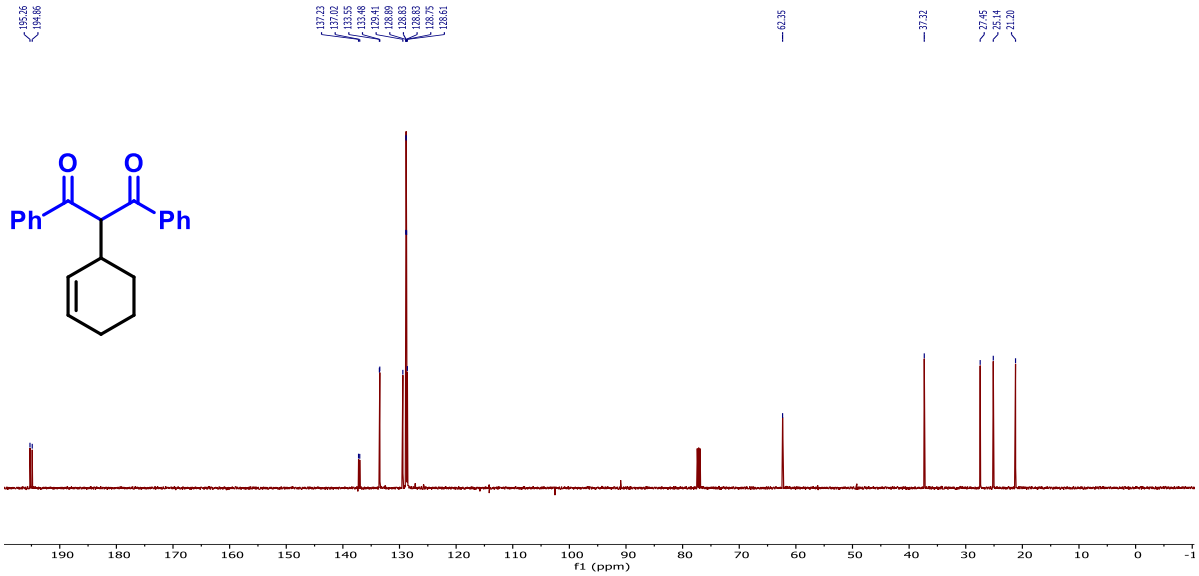


Figure 100: ^{13}C NMR (126 MHz, $CDCl_3$) of 2-(Cyclohex-2-en-1-yl)-1,3-diphenylpropane-1,3-dione (**2g**)

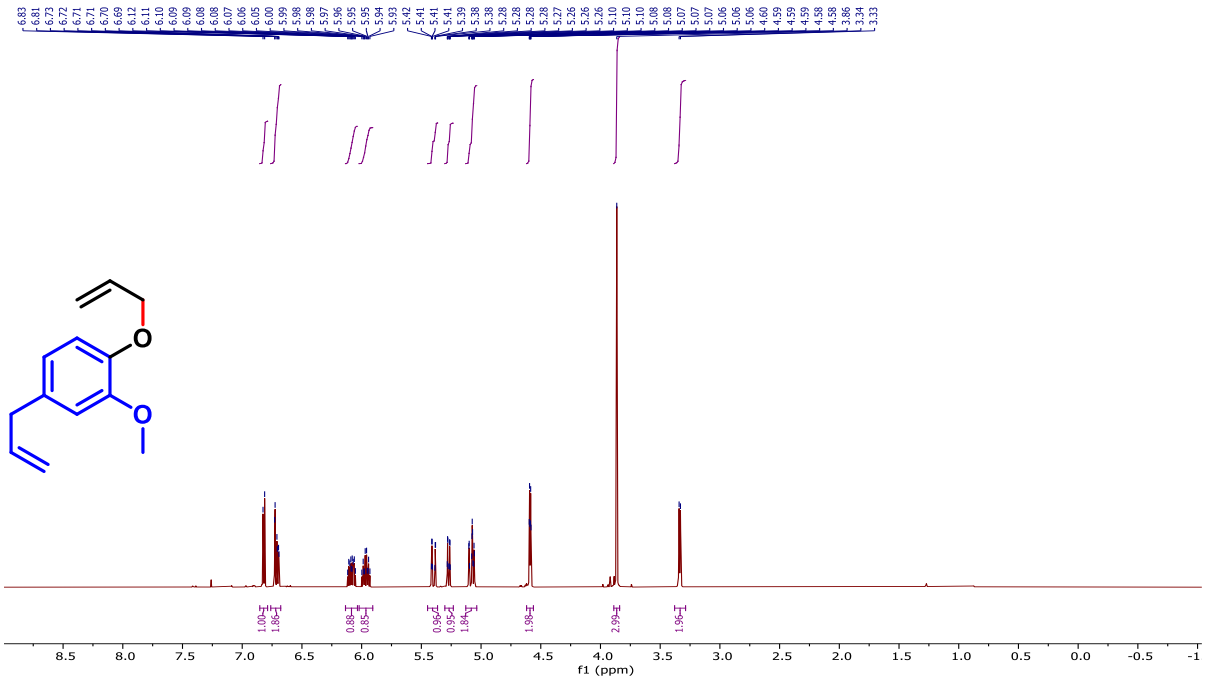


Figure 101: ^{1}H NMR (600 MHz, $CDCl_3$) of 4-Allyl-1-(allyloxy)-2-methoxybenzene (**3a**)

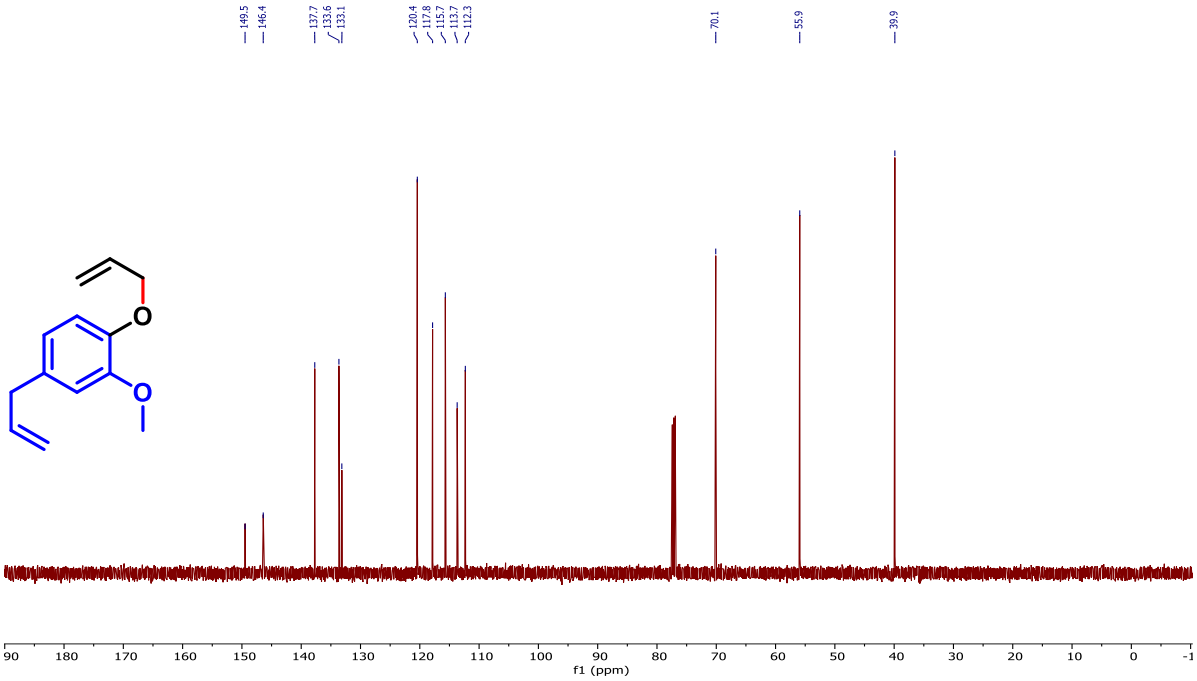


Figure 102: ^{13}C NMR (126 MHz, $CDCl_3$) of 4-Allyl-1-(allyloxy)-2-methoxybenzene (**3a**)

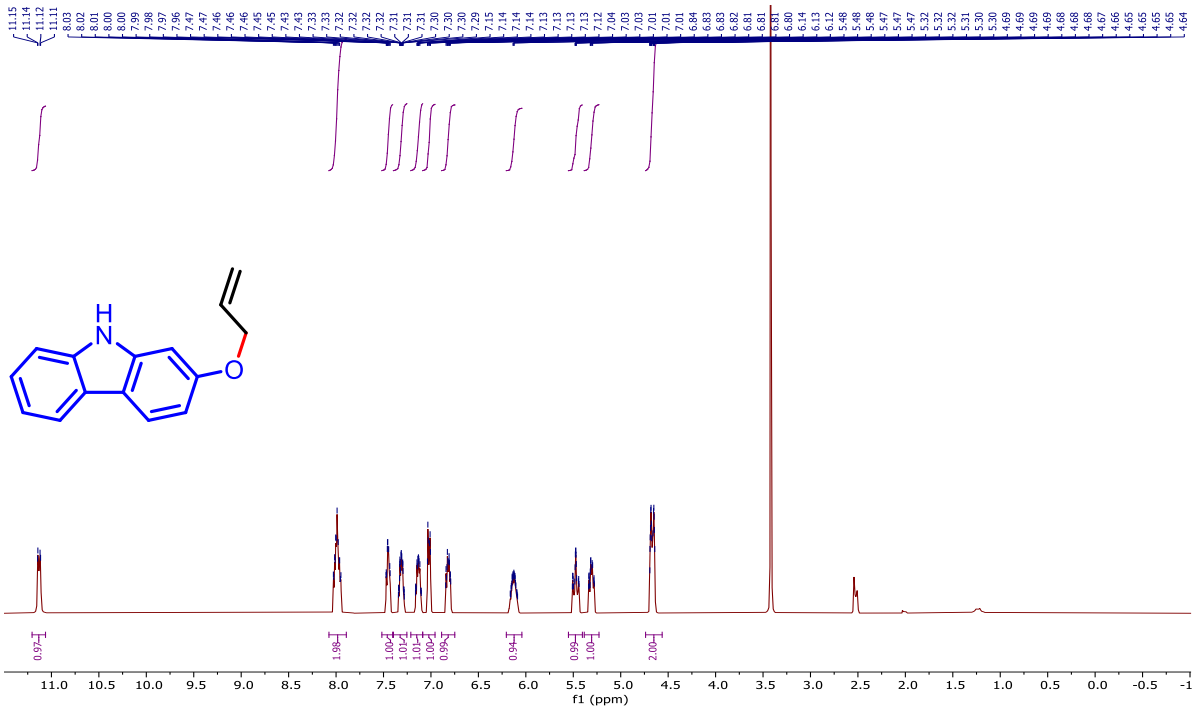


Figure 103: ^{1}H NMR (600 MHz, DMSO) of 2-(Allyloxy)-9H-carbazole (**3b**)

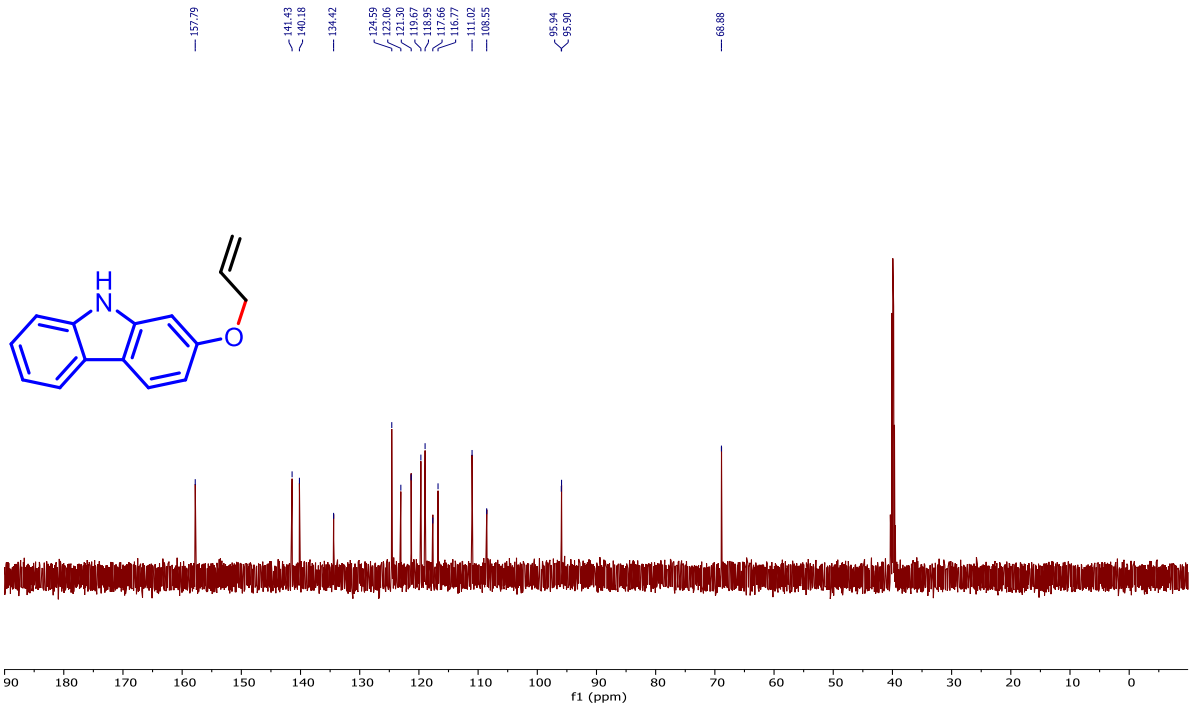


Figure 104: ^{13}C NMR (151 MHz, DMSO) of 2-(Allyloxy)-9H-carbazole (**3b**)

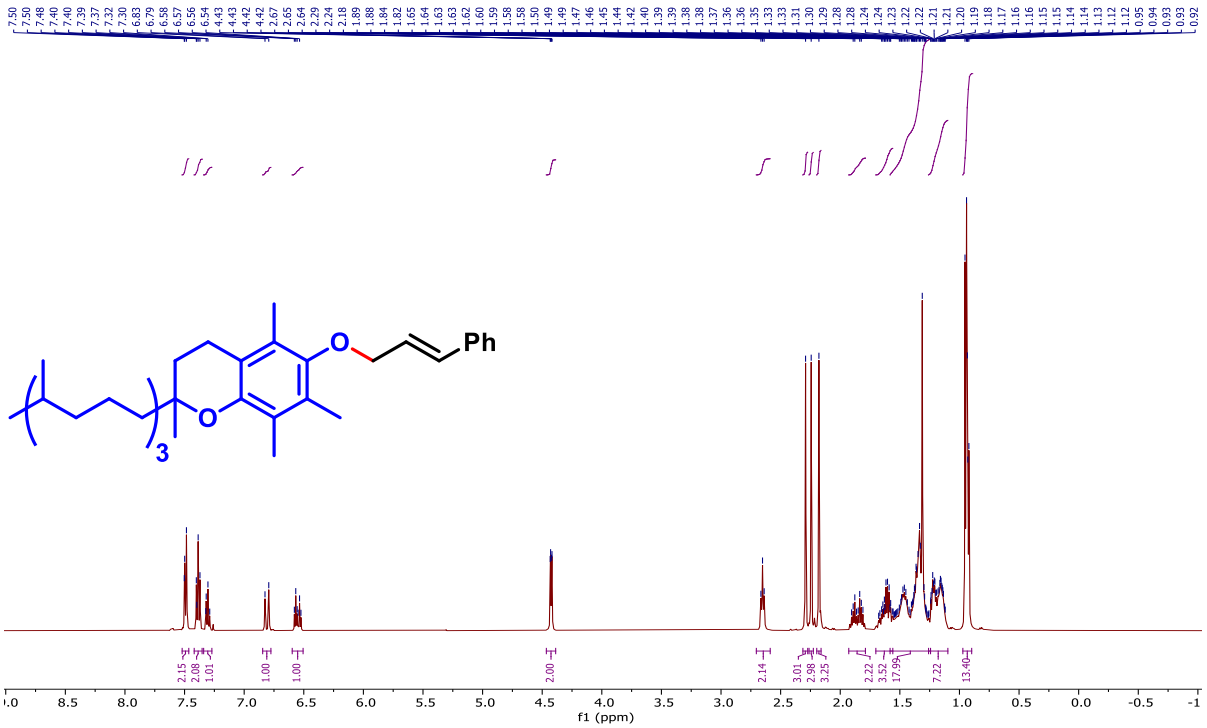


Figure 105: ^{1}H NMR (500 MHz, $CDCl_3$) of 6-(Cinnamyloxy)-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chromane (**3c**)

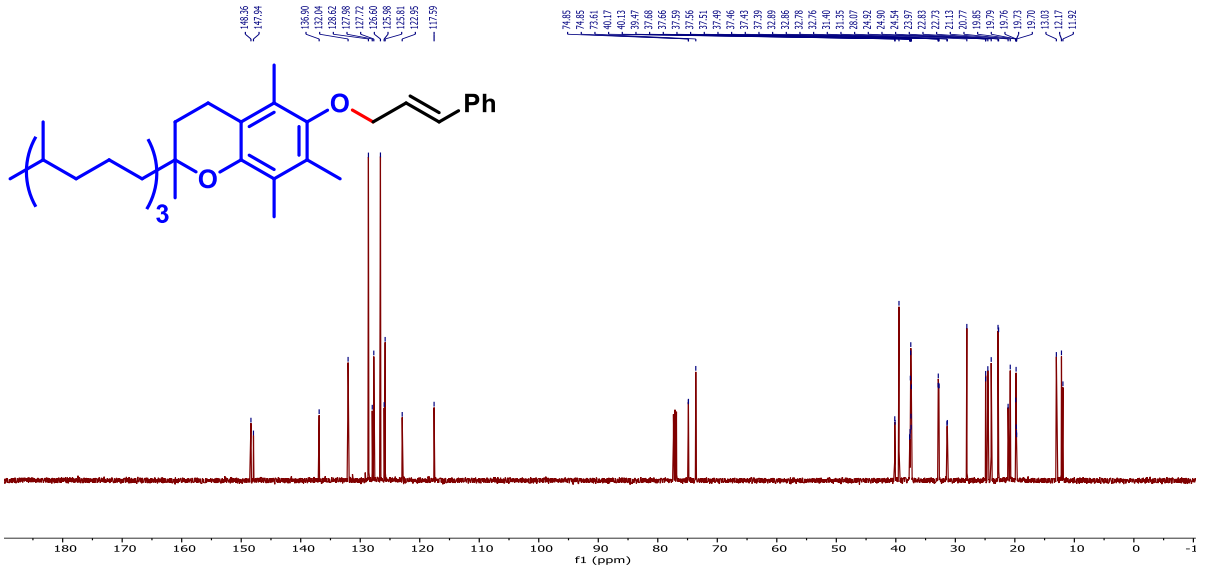


Figure 106: ^{13}C NMR (126 MHz, $CDCl_3$) of 6-(Cinnamyloxy)-2,5,7,8-tetramethyl-2-(4,8,12-trimethyltridecyl)chromane (**3c**)

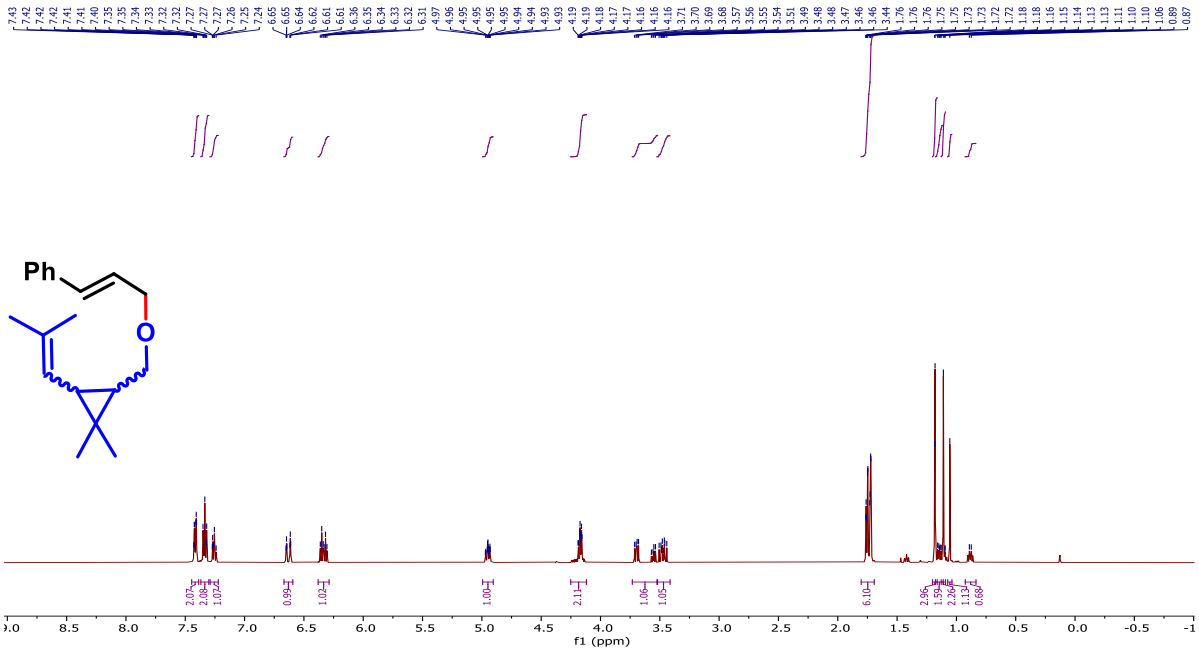


Figure 107: ^{1}H NMR (500 MHz, $CDCl_3$) of (*E*)-(3-((2,2-Dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl)methoxy)prop-1-en-1-yl)benzene (**3d**)

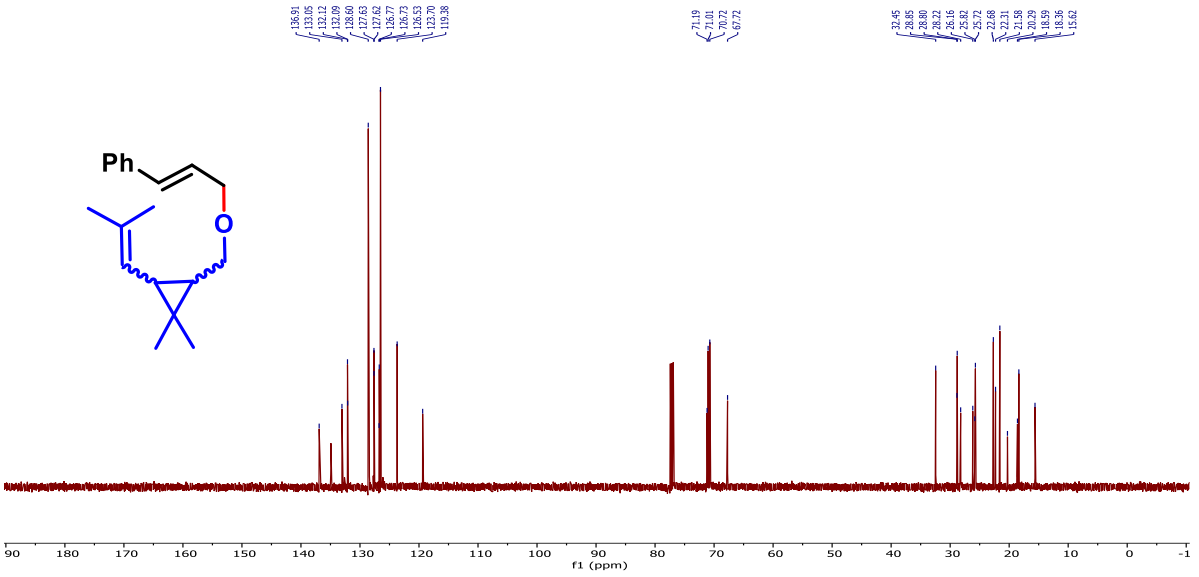


Figure 108: ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-(3-((2,2-Dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropyl)methoxy)prop-1-en-1-yl)benzene (**3d**)

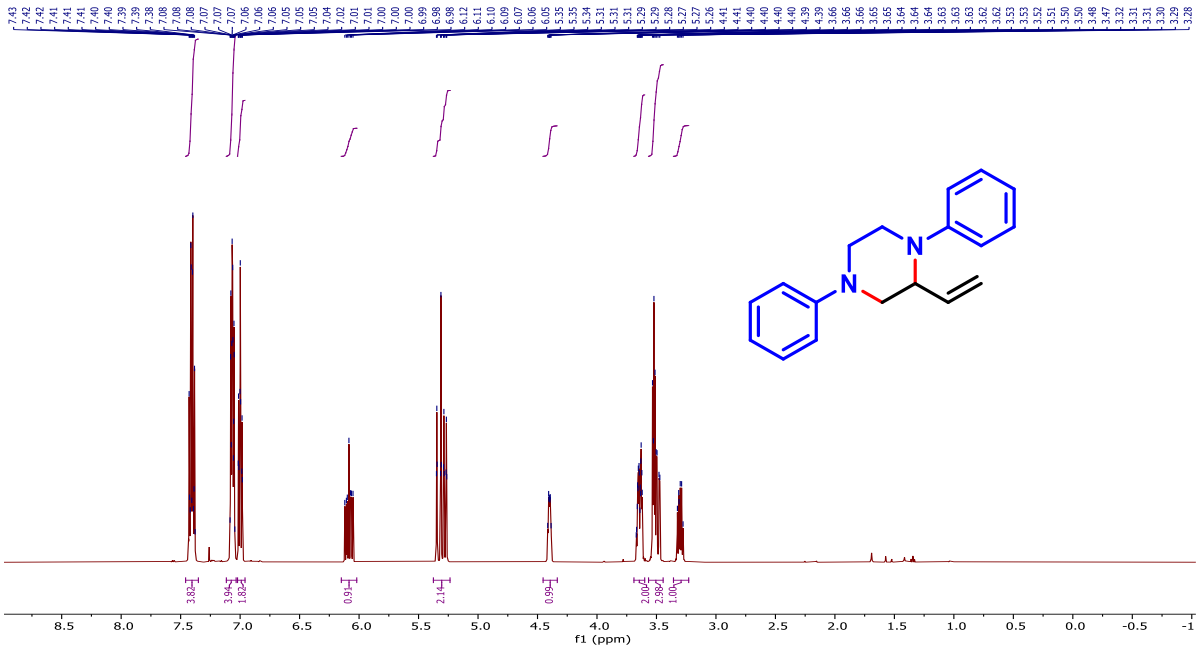


Figure 109: ^{1}H NMR (500 MHz, $CDCl_3$) of 1,4-Diphenyl-2-vinylpiperazine (**4a**)

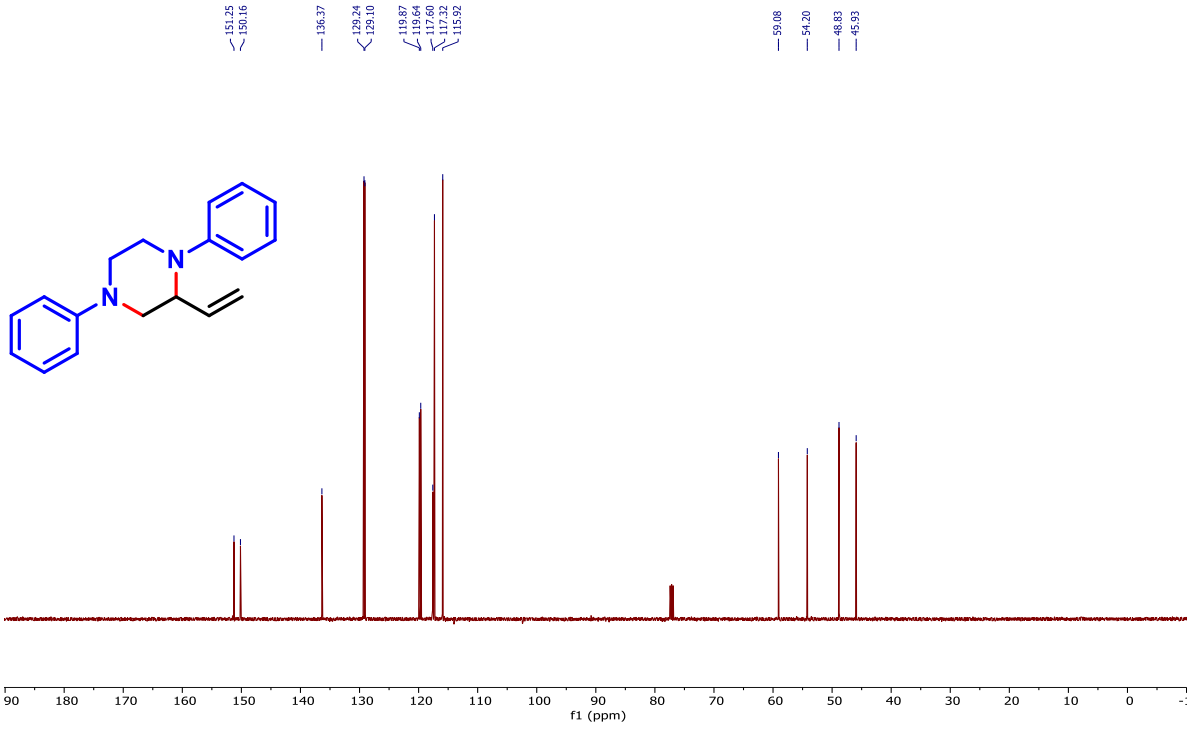


Figure 1110: ^{13}C NMR (126 MHz, $CDCl_3$) of 1,4-Diphenyl-2-vinylpiperazine (**4a**)

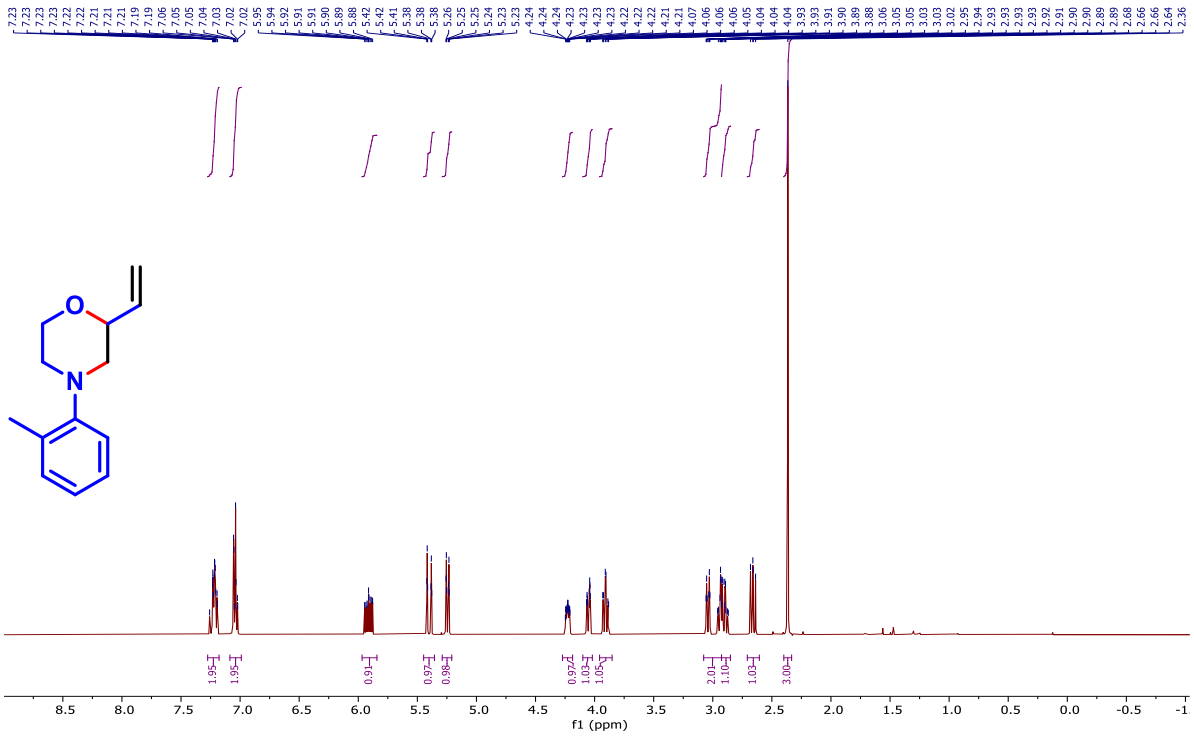


Figure 111: ^{1}H NMR (500 MHz, $CDCl_3$) of 4-(*o*-Tolyl)-2-vinylmorpholine (**4b**)

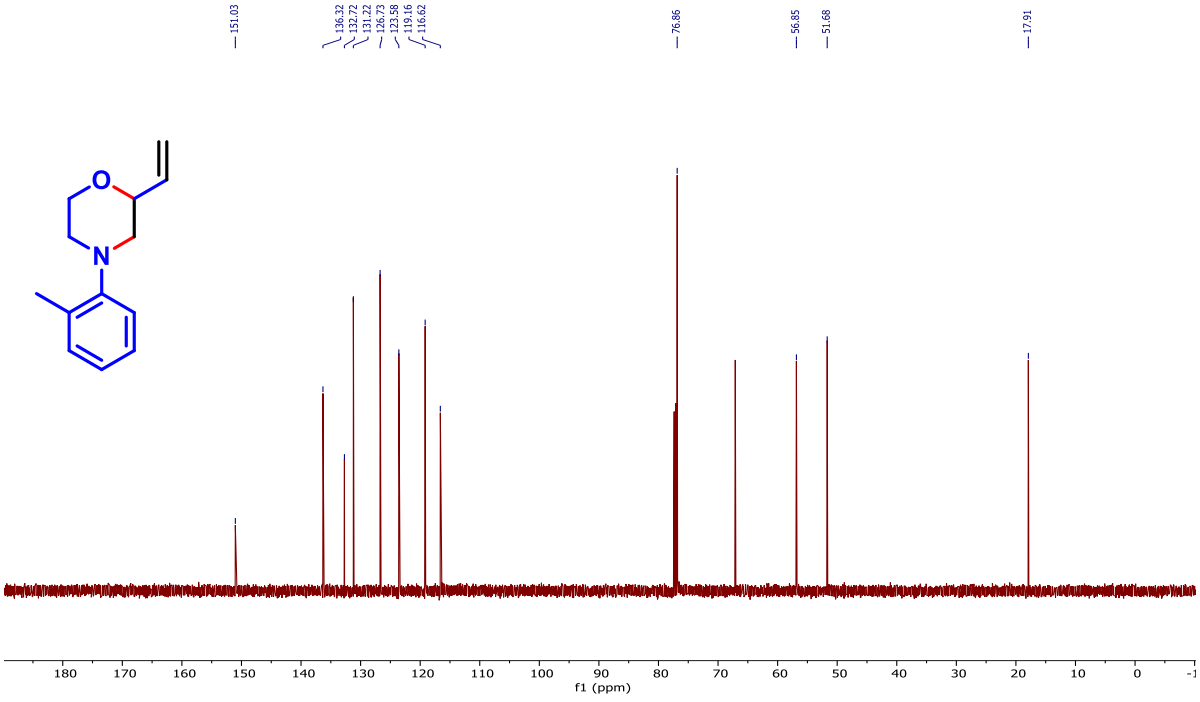


Figure 112: ^{13}C NMR (126 MHz, $CDCl_3$) of 4-(*o*-Tolyl)-2-vinylmorpholine (**4b**)

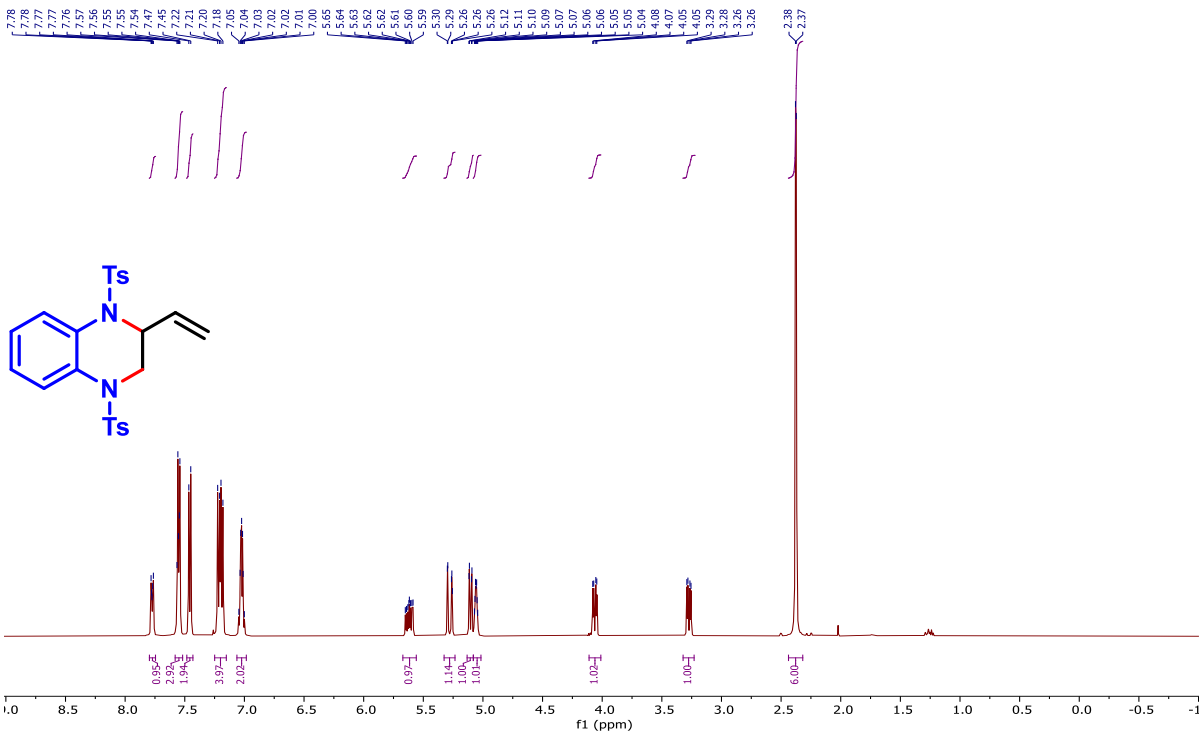


Figure 113: ^{1}H NMR (500 MHz, $CDCl_3$) of 1,4-Ditosyl-2-vinyl-1,2,3,4-tetrahydroquinoxaline (**4c**)

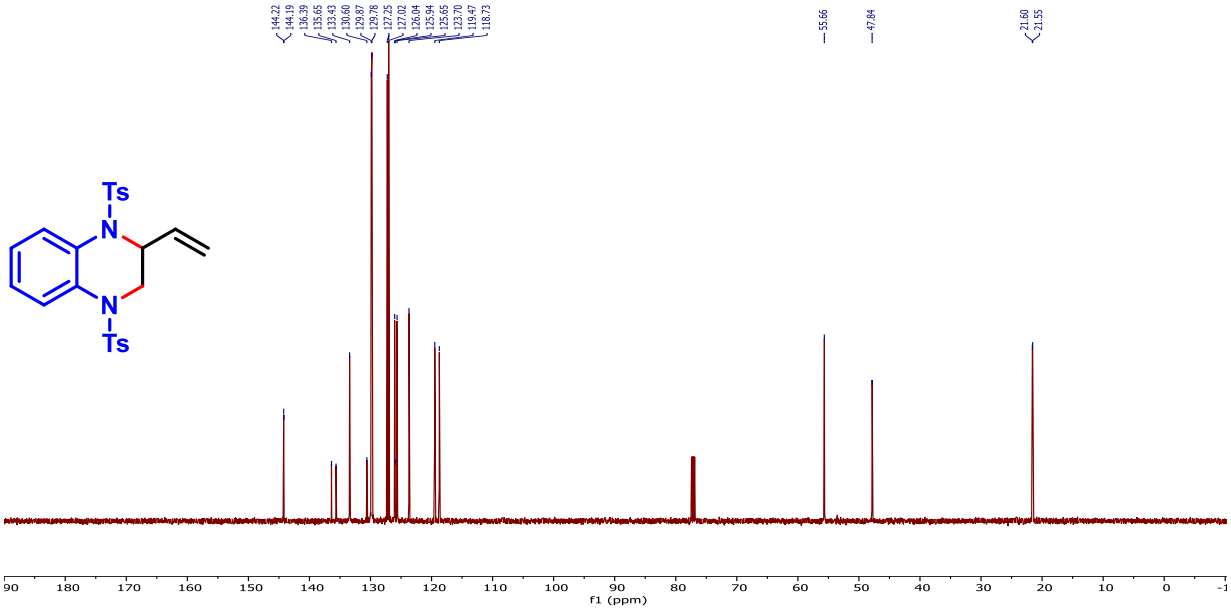


Figure 114: ^{13}C NMR (126 MHz, $CDCl_3$) of 1,4-Ditosyl-2-vinyl-1,2,3,4-tetrahydroquinoxaline (**4c**)

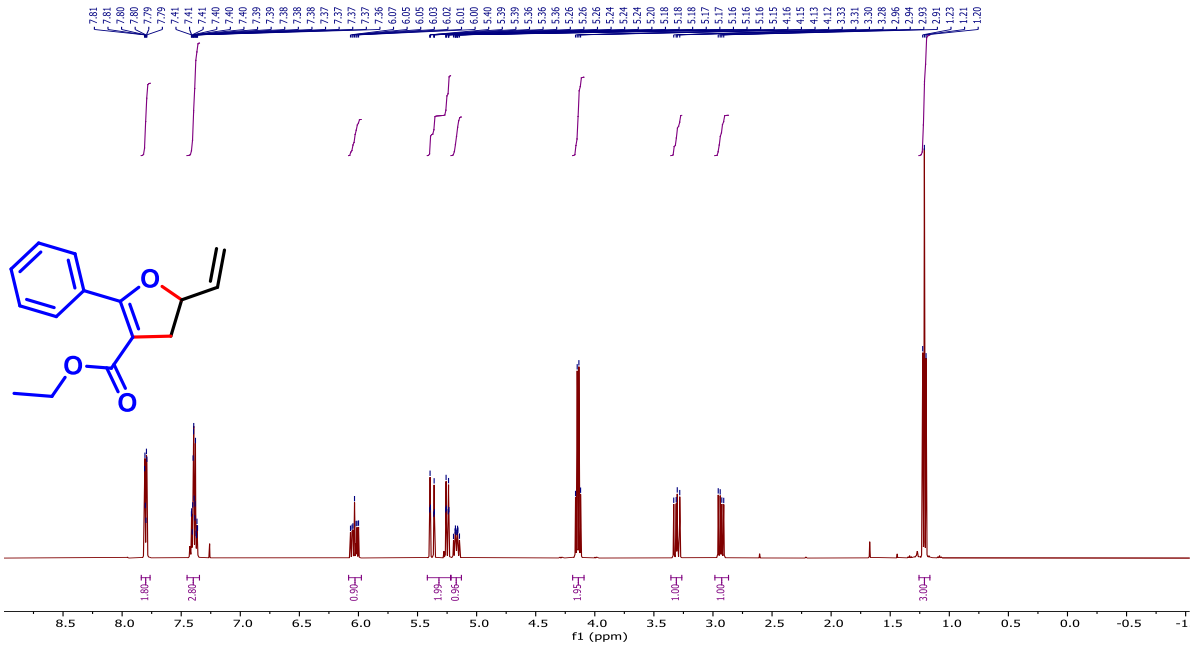


Figure 115: ^{1}H NMR (500 MHz, $CDCl_3$) of Ethyl 2-phenyl-5-vinyl-4,5-dihydrofuran-3-carboxylate (**4d**)

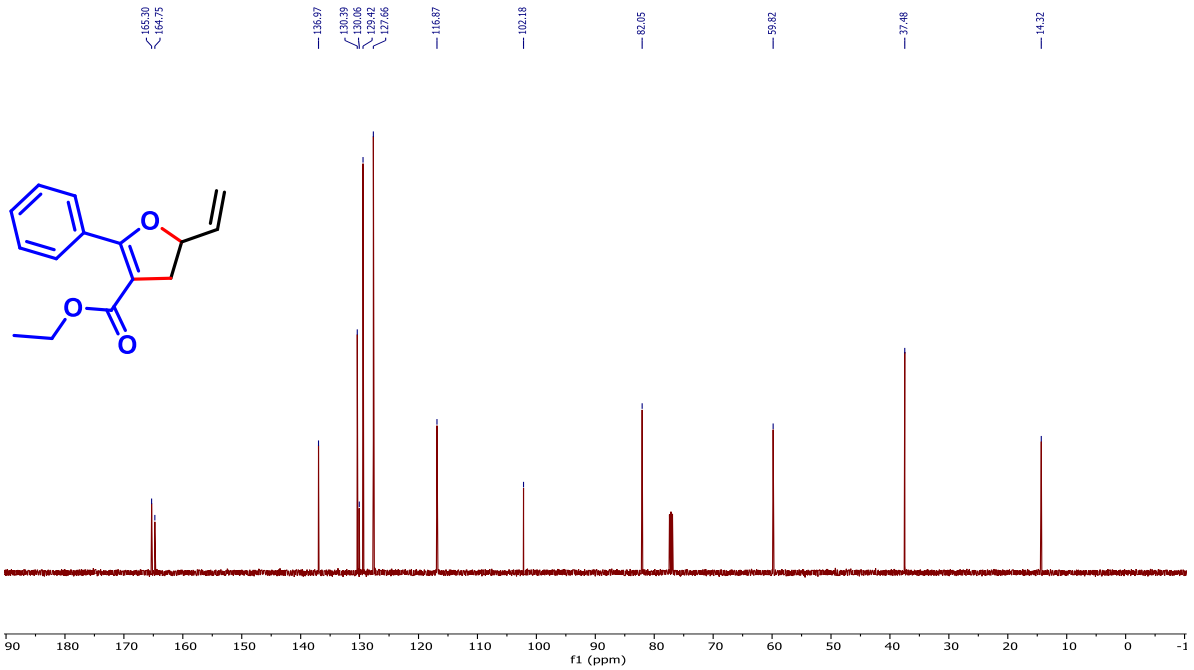


Figure 116: ^{13}C NMR (126 MHz, $CDCl_3$) of Ethyl 2-phenyl-5-vinyl-4,5-dihydrofuran-3-carboxylate (**4d**)

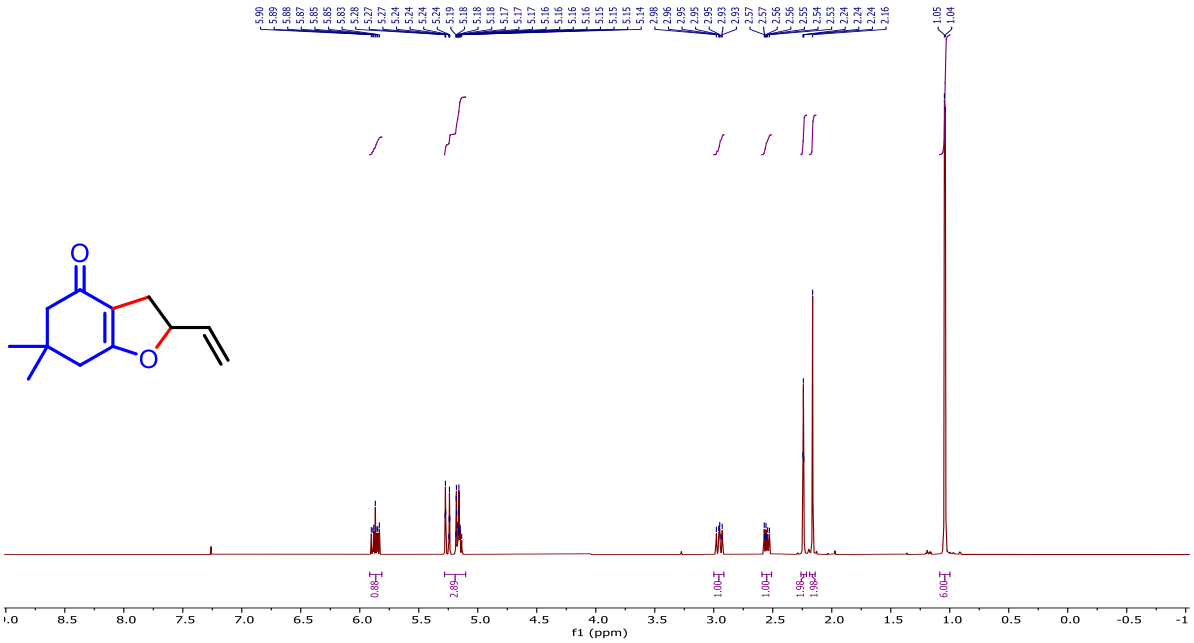


Figure 117: ^{1}H NMR (500 MHz, $CDCl_3$) of 6,6-Dimethyl-2-vinyl-3,5,6,7-tetrahydrobenzofuran-4(2H)-one (**4e**)

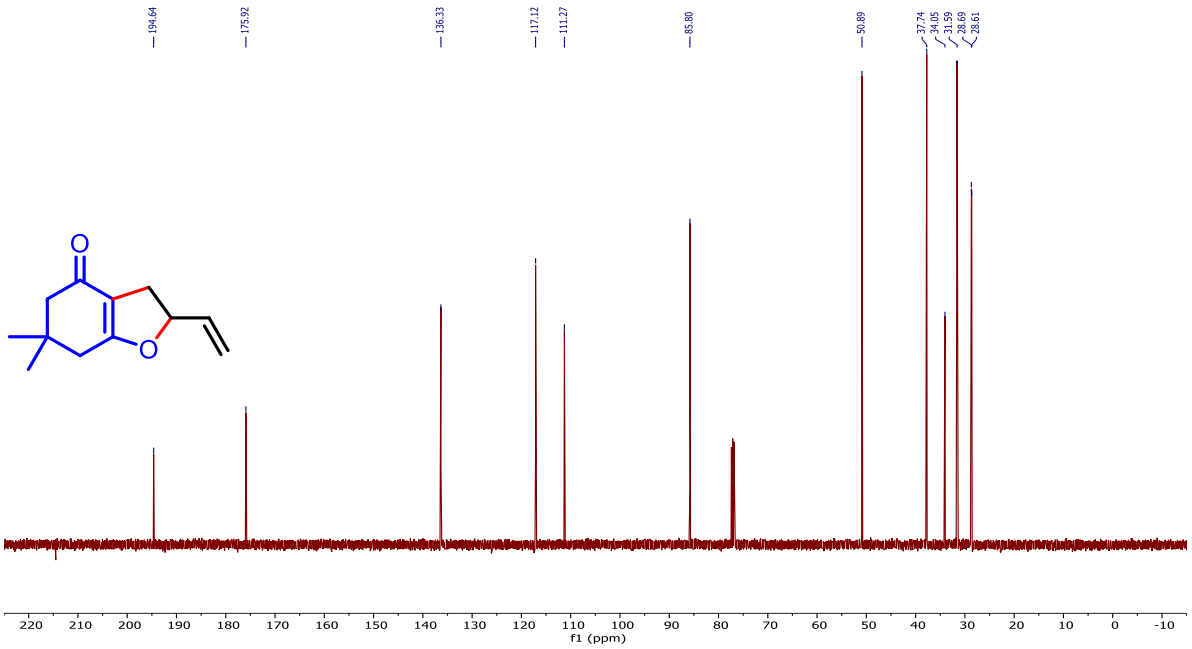


Figure 118: ^{13}C NMR (126 MHz, $CDCl_3$) of 6,6-Dimethyl-2-vinyl-3,5,6,7-tetrahydrobenzofuran-4(2H)-one (**4e**)

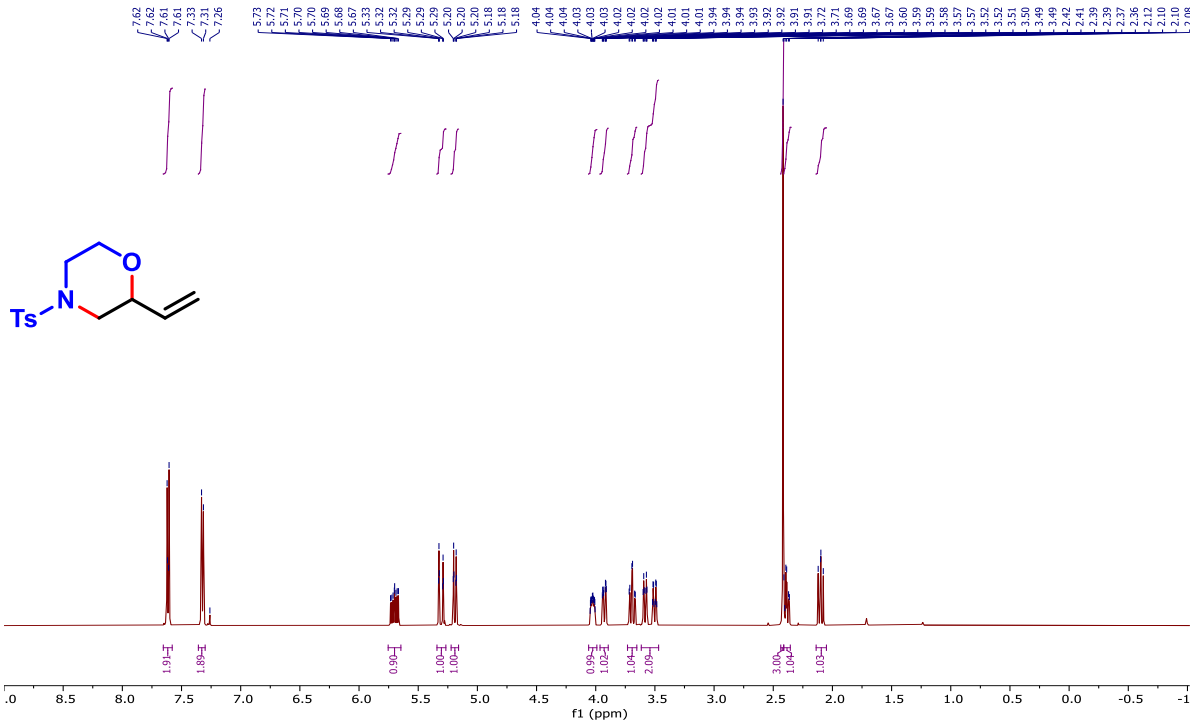


Figure 119: ^{1}H NMR (500 MHz, $CDCl_3$) of 4-*N*-Tosyl-2-vinylmorpholine (**4f**)

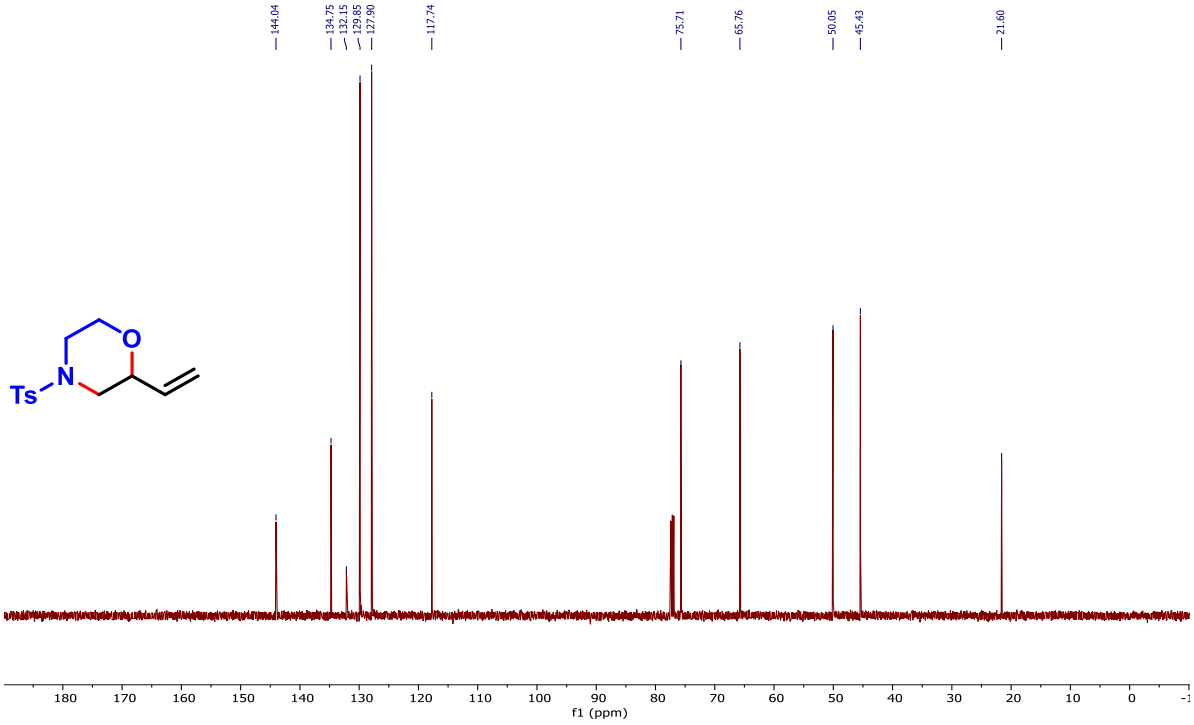


Figure 120: ^{13}C NMR (126 MHz, $CDCl_3$) of 4-*N*-Tosyl-2-vinylmorpholine (**4f**)

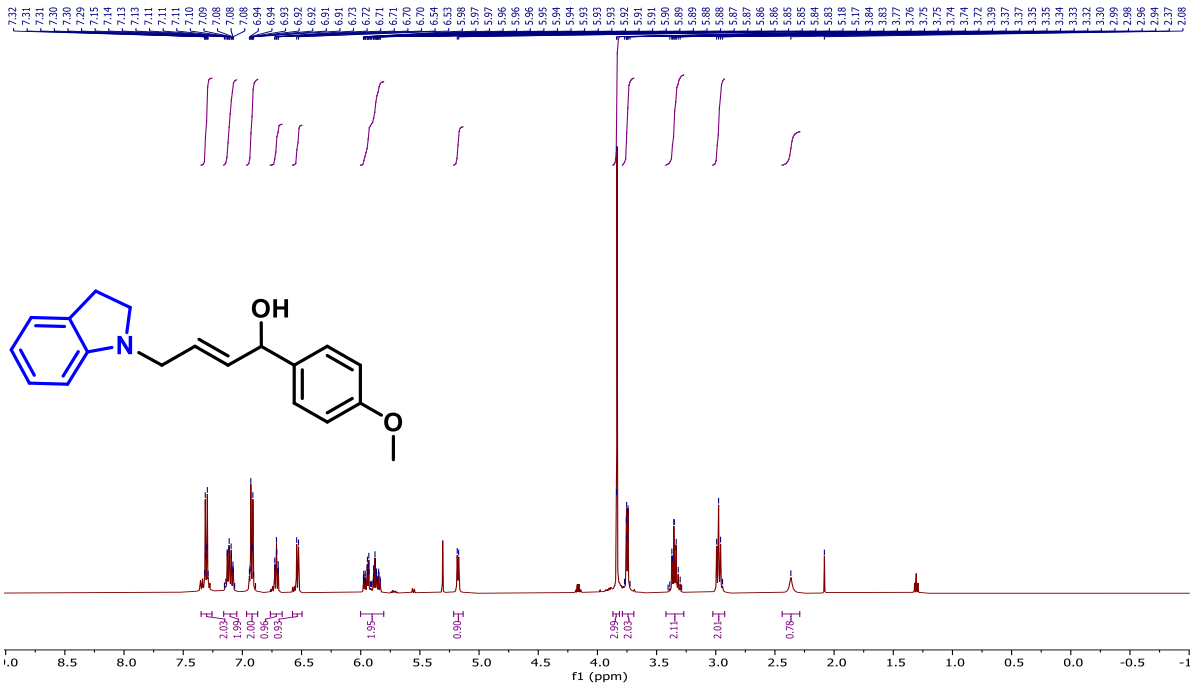


Figure 121: ^{1}H NMR (500 MHz, $CDCl_3$) of (*E*)-4-(Indolin-1-yl)-1-(4-methoxyphenyl)but-2-en-1-ol (**5a**)

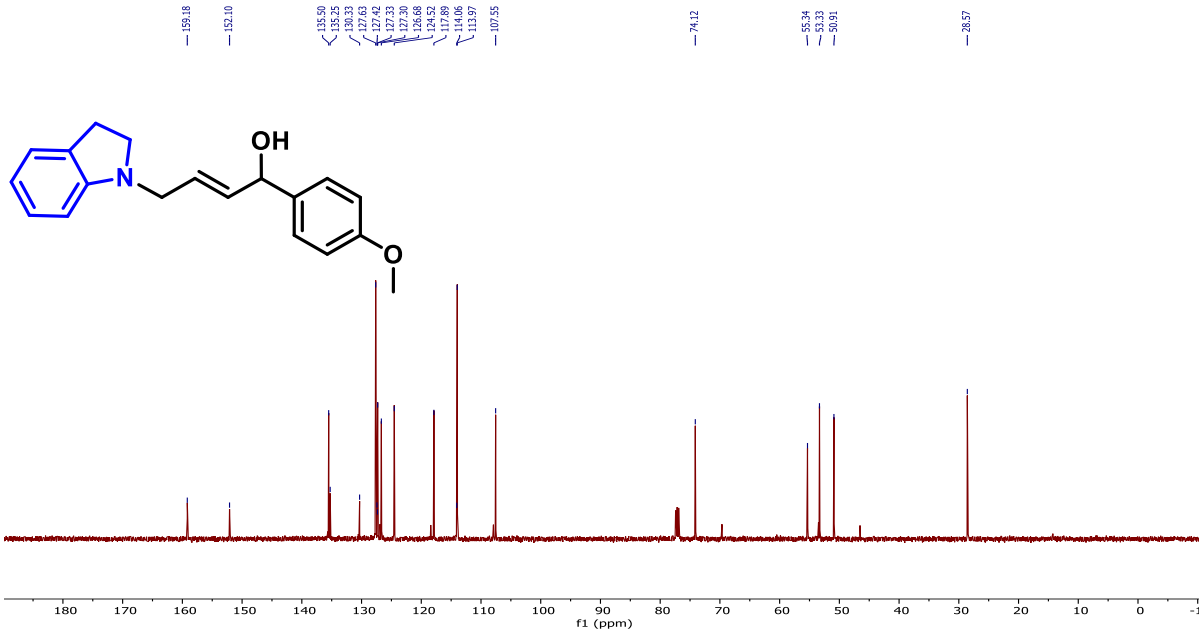


Figure 122: ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-4-(Indolin-1-yl)-1-(4-methoxyphenyl)but-2-en-1-ol (**5a**)

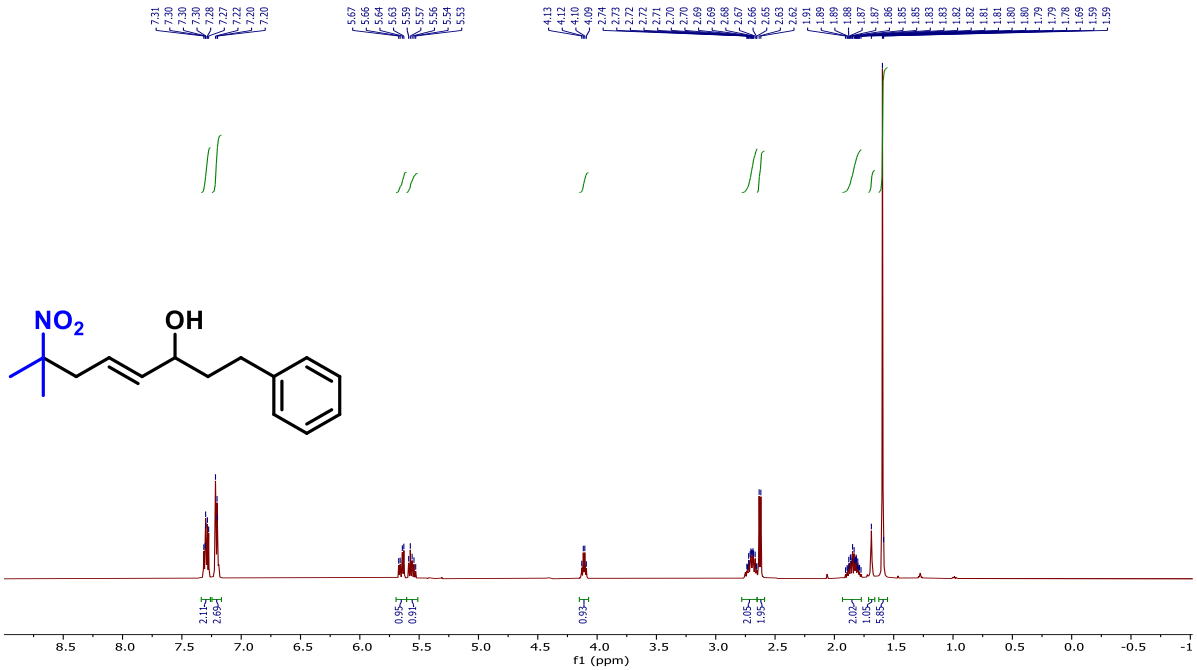


Figure 123: ^{1}H NMR (500 MHz, $CDCl_3$) of (*E*)-7-Methyl-7-nitro-1-phenyloct-4-en-3-ol (**5b**)

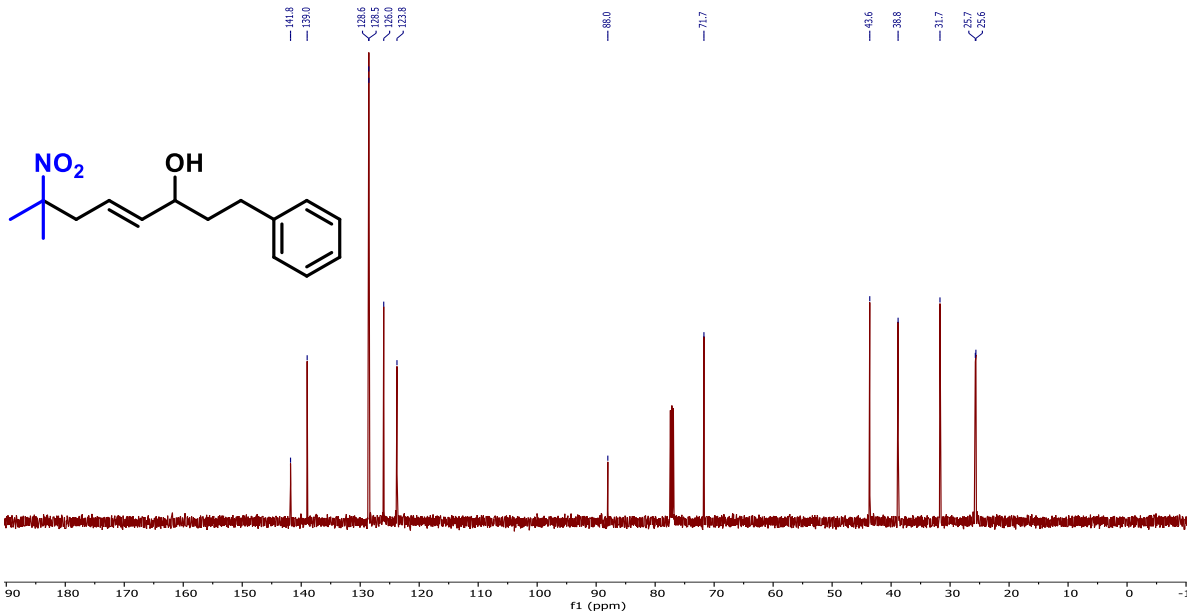


Figure 124: ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-7-Methyl-7-nitro-1-phenyloct-4-en-3-ol (**5b**)

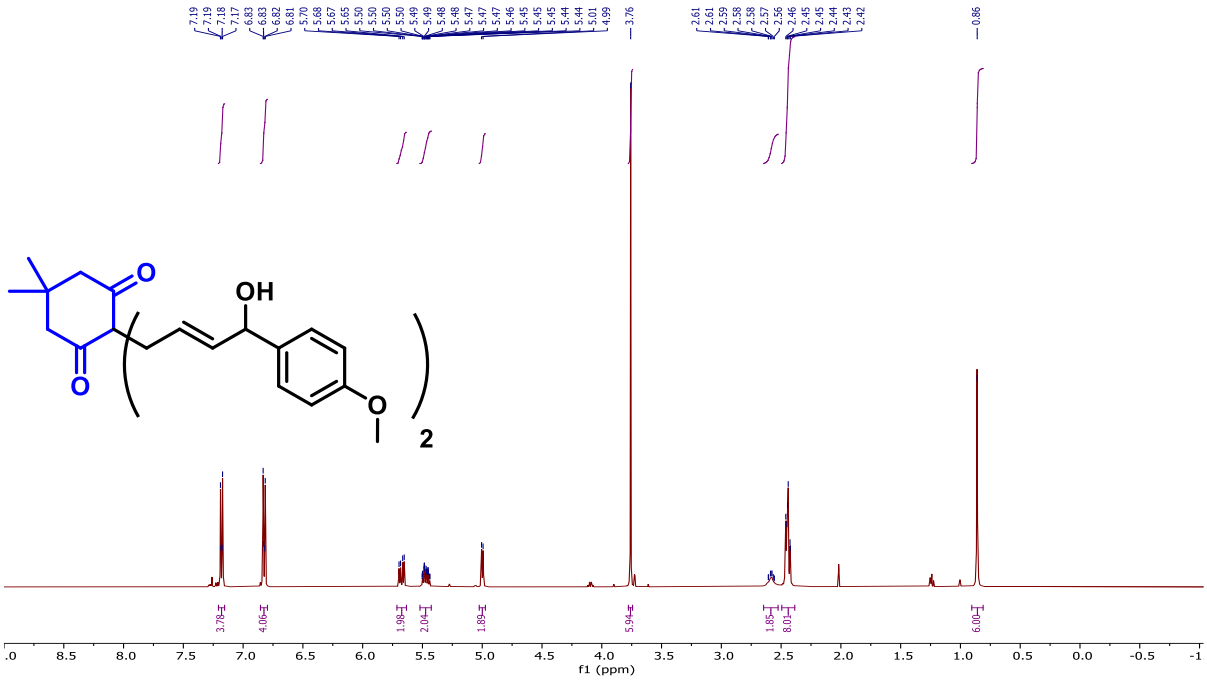


Figure 125: ^{1}H NMR (500 MHz, $CDCl_3$) of 2,2-bis((*E*)-4-Hydroxy-4-(4-methoxyphenyl)but-2-en-1-yl)-5,5-dimethylcyclohexane-1,3-dione (**5c**)

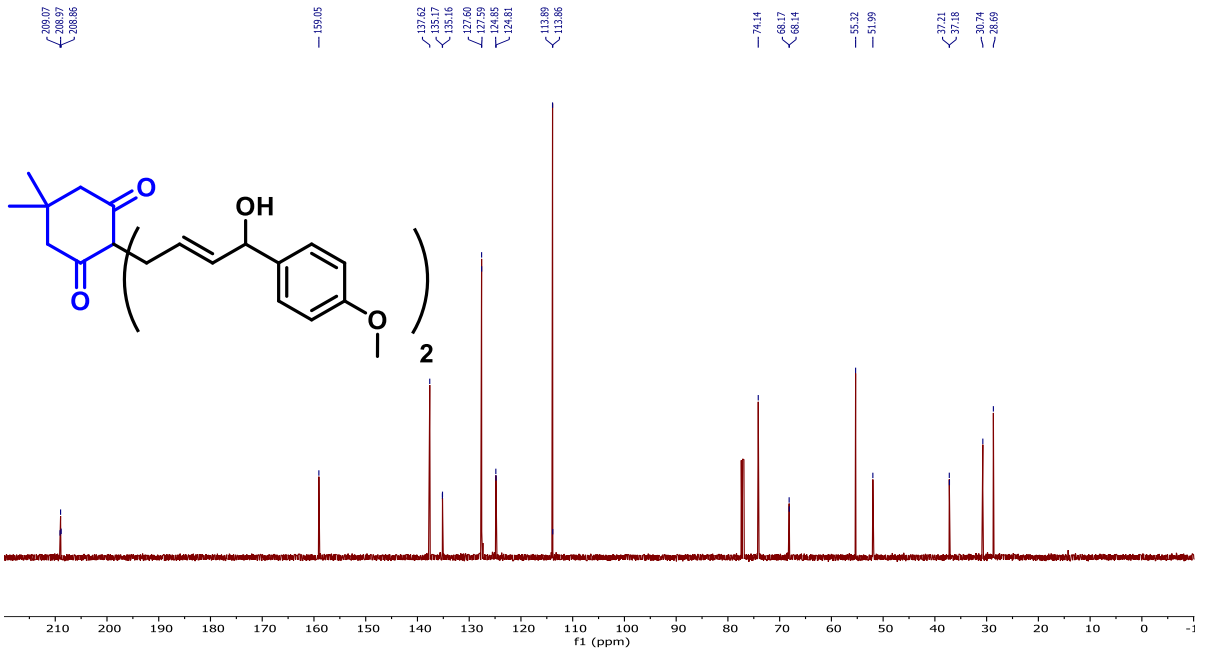


Figure 126: ^{13}C NMR (126 MHz, $CDCl_3$) of 2,2-bis((*E*)-4-Hydroxy-4-(4-methoxyphenyl)but-2-en-1-yl)-5,5-dimethylcyclohexane-1,3-dione (**5c**)

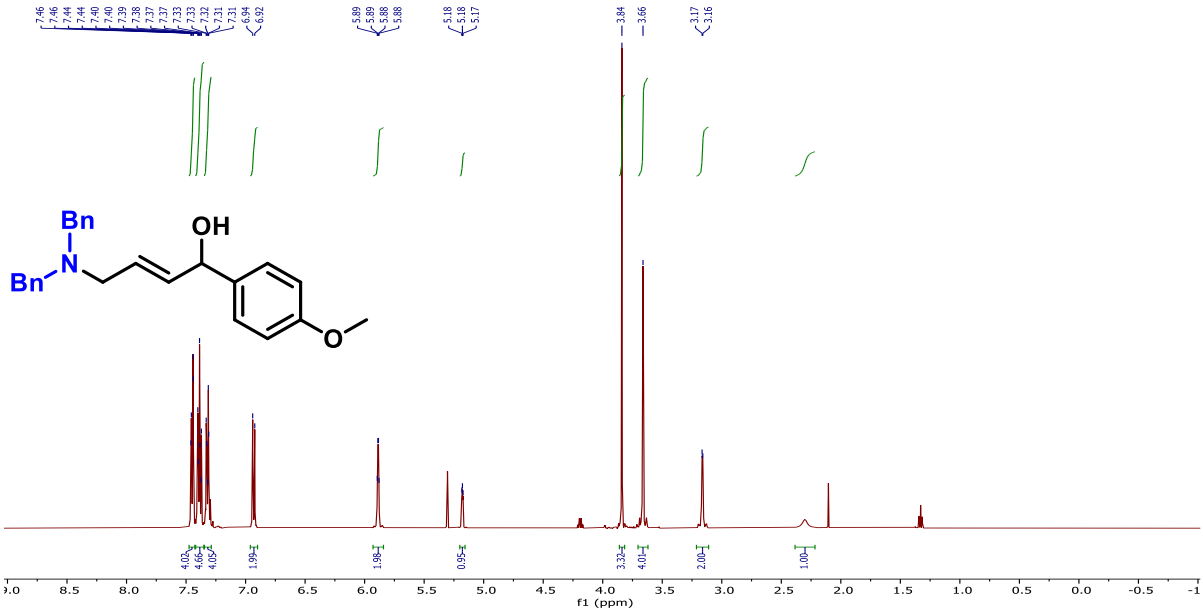


Figure 127: ^{1}H NMR (500 MHz, $CDCl_3$) of (*E*)-4-(Dibenzylamino)-1-(4-methoxyphenyl)but-2-en-1-ol (**5d**)

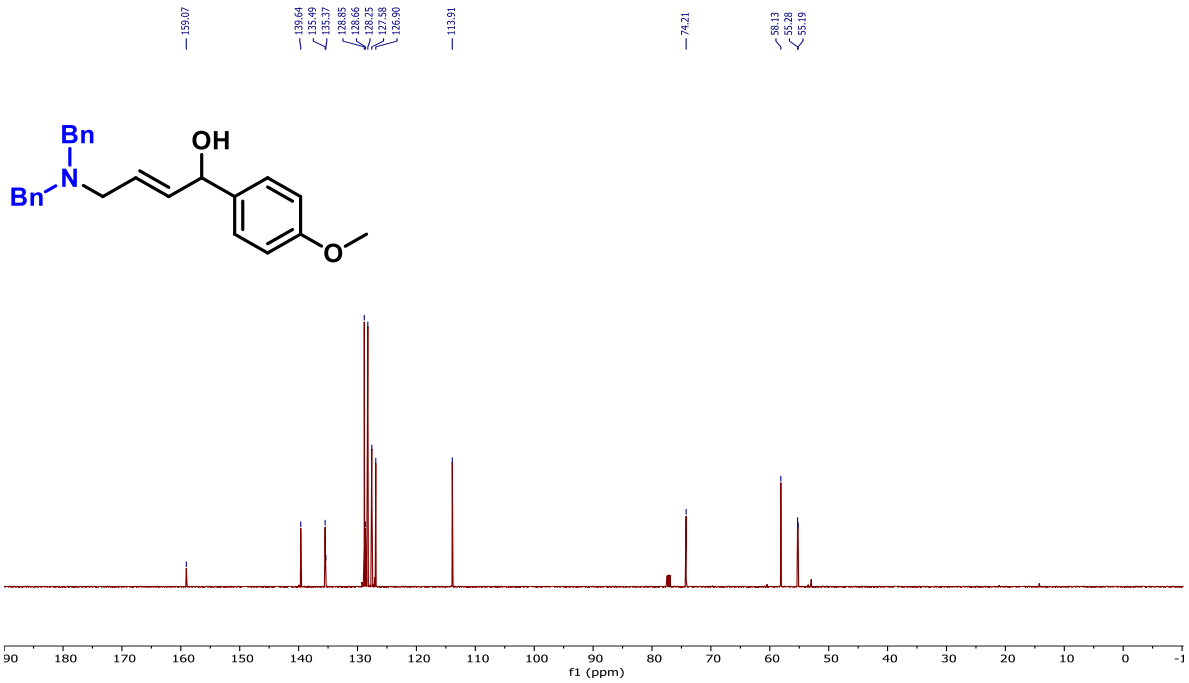


Figure 128: ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-4-(Dibenzylamino)-1-(4-methoxyphenyl)but-2-en-1-ol (**5d**)

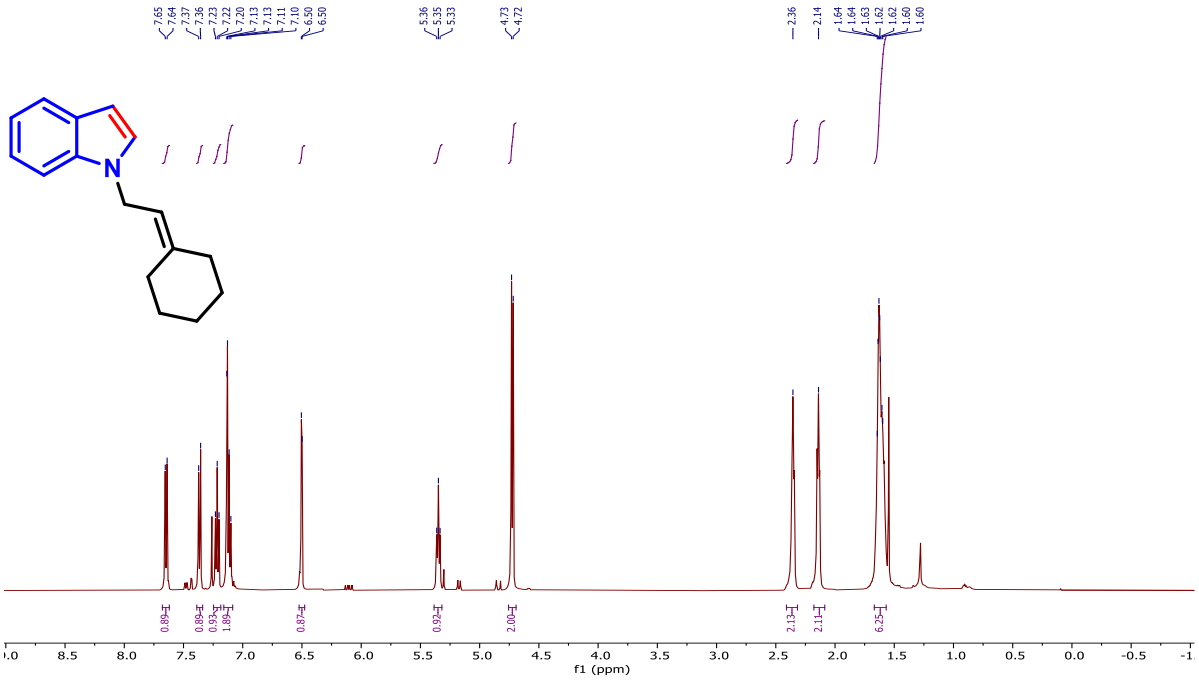


Figure 129: ^{1}H NMR (500 MHz, $CDCl_3$) of 1-(2-Cyclohexylideneethyl)-1H-indole (**6a**)

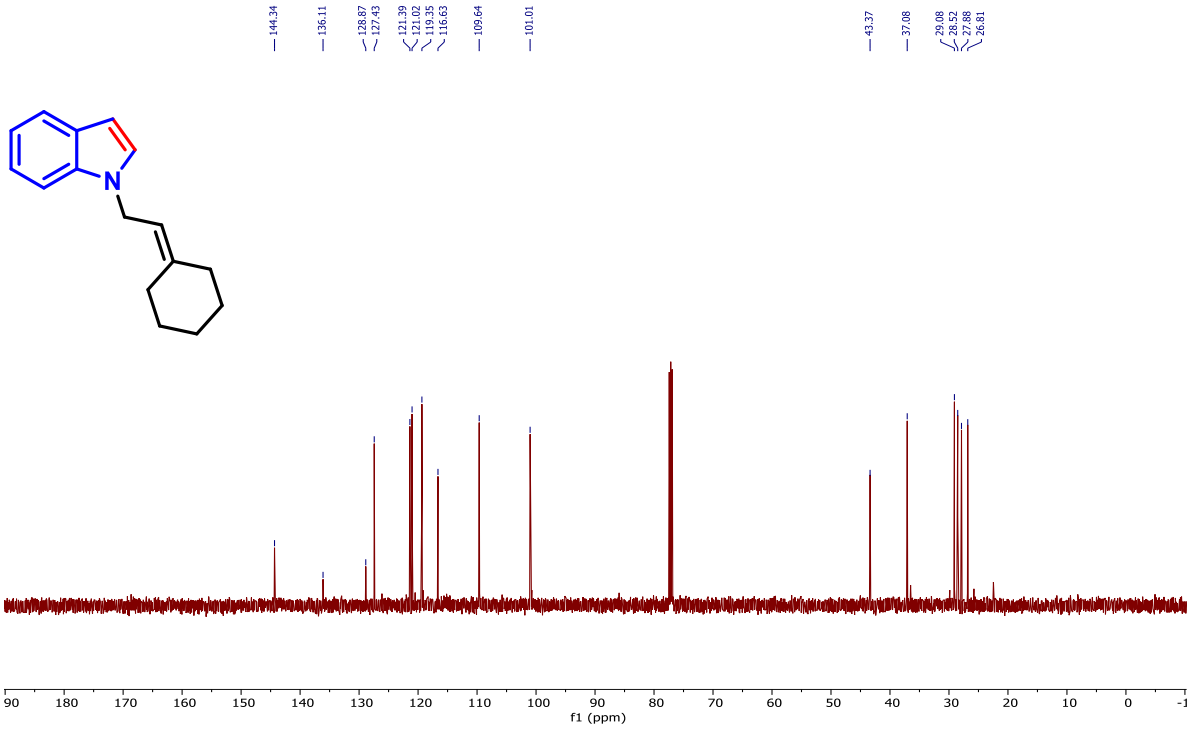


Figure 130: ^{13}C NMR (126 MHz, $CDCl_3$) of 1-(2-Cyclohexylideneethyl)-1H-indole (**6a**)

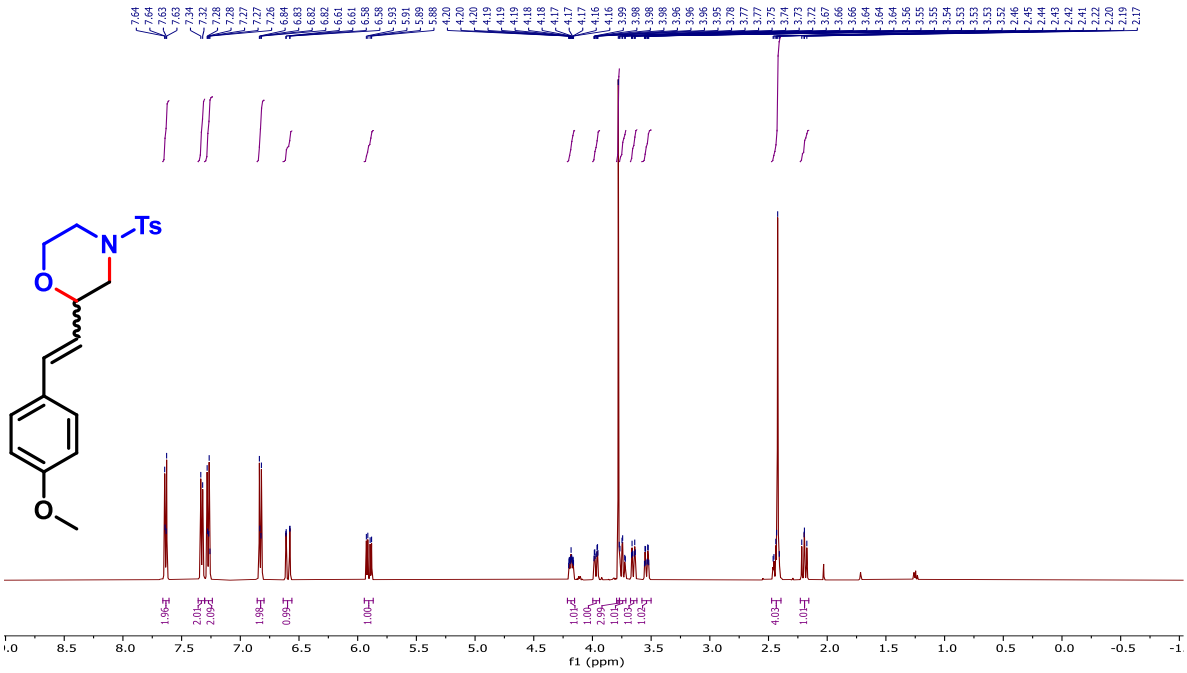


Figure 131: ^{1}H NMR (500 MHz, $CDCl_3$) of (*E*)-2-(4-Methoxystyryl)-4-tosylmorpholine (**6b**)

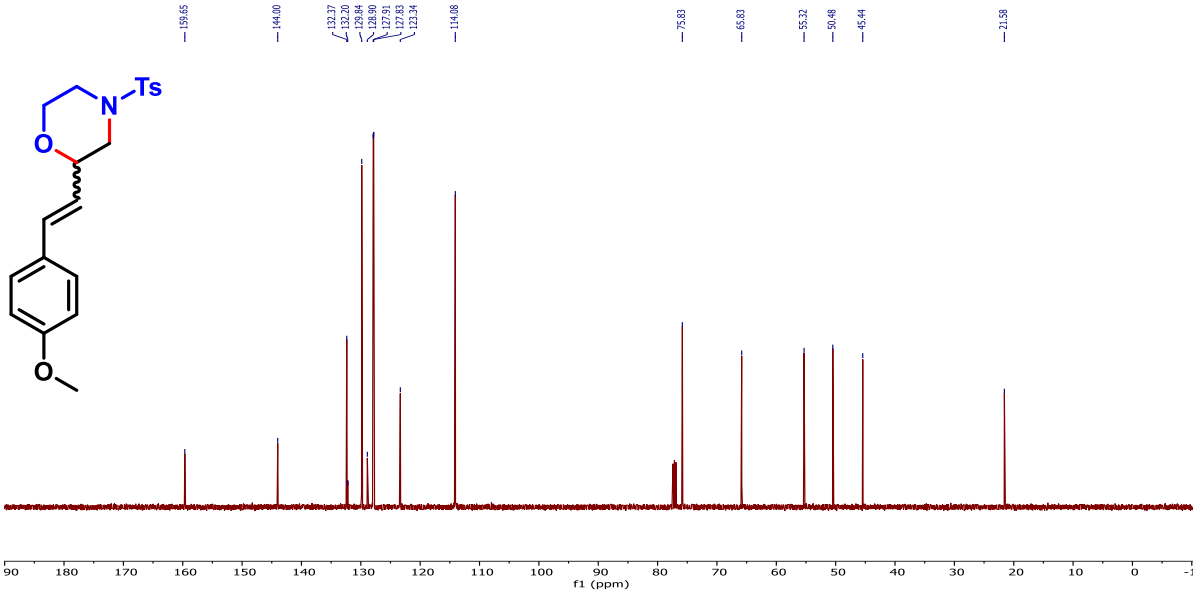


Figure 132: ^{13}C NMR (126 MHz, $CDCl_3$) of (*E*)-2-(4-Methoxystyryl)-4-tosylmorpholine (**6b**)