UNIVERSITY OF CALIFORNIA,
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Palladium-Catalyzed Carbenylative Cross-Coupling and Carbenylative Amination Utilizing Vinylcarbenes

THESIS

submitted in partial satisfaction of the requirements
for the degree of

MASTER OF SCIENCE

in Chemistry

by

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Thesis Committee:
Professor David L. Van Vranken, Chair
Professor Christopher D. Vanderwal
Professor Andrej Luptak

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DEDICATION

To

My mother who I will never be able to repay
for twenty-eight years of unrelenting love and support

and to all my family and friends for all the encouragement, laughs and memories.

Also, Charlie,
nothing is better than coming home after a long day to a wagging tail and slobbery kisses

"Without change, something sleeps inside us, and seldom awakens.
The sleeper must awaken."

-Frank Herbert

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ACKNOWLEDGMENTS

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I also need to thank my high school chemistry teacher, Joanne Overman, who instilled and nurtured my love of chemistry. Similar to Professor Van Vranken, Mrs. Overman has such a passion for chemistry and teaching and I am certain she is the reason why I have such a love for chemistry now. I will never forget the first day I walked into her classroom. She had what looked like a candle burning on the counter in front of her. She did not say a word until everyone was settled in their seats and then finally when everyone was quiet she opened her mouth…and ate the burning "candle". Her goal was to have us question our observations both is science and in life. Eventually she did spill the beans and let us know that the candle was just a simple potato. Her constant view altering demos and quirky energy always had me looking forward to her class. She was a real life Ms. Frizzle without the need for a magic school bus.

I also owe a great deal to my boss and professional mentor, Robert Orr. He has provided me with a job that I love both during my undergraduate career (as a budding intern) and in my graduate career. Even after knowing him for nine years, I find myself still constantly learning new things about chemistry, business and life from him. His understanding and willingness to let me take time off for school (or life) has been invaluable.

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ABSTRACT OF THE THESIS

Palladium-Catalyzed Carbenylative Cross-Coupling and Carbenylative Amination Utilizing Vinylcarbenes

By

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Master of Science in Chemistry

University of California, Irvine, 2017

Professor David L. Van Vranken, Chair

This work focuses on the use of *N*-tosylhydrazones derived from α,β-unsaturated aldehydes – precursors to vinylcarbene ligands – in palladium-catalyzed carbenylative cross-coupling and carbenylative amination reactions. These carbenylative reactions were used to form η^3-allylpalladium intermediates that generate stereogenic centers at the carbene center. An initial acyclic model system was used to intercept a well-known prochiral 1,3-diphenylallyl intermediate to probe the feasibility of enantioselectivity in a palladium-catalyzed carbenylative reaction as a proof of concept for asymmetric carbenylation. Following the proof of concept, the substrate scope was expanded to include aliphatic vinyl hydrazones in order to install prenyl functional groups. Conditions to form isoindolines and tetrahydroisoquinolines, present in many natural products, were developed by employing amine-tethered aryl iodides. The isoindoline model system established that kinetic 5-membered ring formation is preferred over thermodynamic 7-membered ring formation and that under our reaction conditions the cyclization is not reversible. Use of *N*-tosylhydrazones that generate unsymmetrical η^3-allylpalladium intermediates that cannot racemize through η^3-η^1-η^3 isomerization provided evidence consistent with migratory insertion as the step responsible for enantioselection in the

catalytic cycle. Promising ees are demonstrated indicating that selection of the right chiral ligand and reaction conditions could lead to high levels of enantioselection. Finally, formation of 6-membered ring systems proved challenging in comparison to 5-membered and acyclic systems but provided beneficial information about *N*-tosylhydrazone decomposition rates and reactivity effects seen from ortho-substitution on the aryl iodide. These results provide new insights into the mechanism of asymmetric palladium-catalyzed carbenylative cross-coupling and carbenylative amination and provide a foundation for future method development.

Chapter 1

Review of Palladium-Catalyzed Carbenylative Cross-Coupling, Carbenylative Aminations and Carbenylative Alkylations.

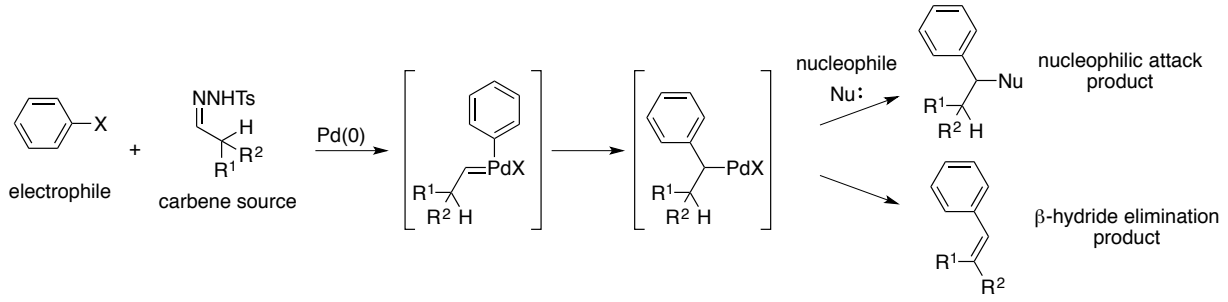
1.1 Introduction

Palladium catalysis has become a fundamental tool in organic synthesis allowing chemists to transform or stitch together complex organic molecules. Of particular note are the palladium-catalyzed cross-coupling reactions developed by Richard F. Heck, Ei-ichi Negishi and Akira Suzuki.[1] The reactions they developed led to their joint award of the Nobel Prize in chemistry in 2010.[2] These palladium-catalyzed carbon-carbon bond-forming reactions combine organic halides with organozinc reagents (Negishi coupling), boronic acids (Suzuki coupling) or alkenes (Heck coupling). Similar transformations can be carried out with other nucleophilic coupling partners for the organic halides: stannanes (Stille coupling), silanes (Hiyama coupling), Grignard reagents (Kumada coupling) alkynyl cuprates (Sonogashira coupling), and amines (Buchwald-Hartwig coupling). Within the past ten years there has been a rising interest in using a carbene source as a third coupling partner in palladium-catalyzed carbenylative cross-coupling processes.

1.2 The Three Components of Palladium-Catalyzed Carbenylative Cross-Coupling, Carbenylative Amination and Carbenylative Alkylation Reactions.

Components that are common to palladium-catalyzed carbenylative cross-coupling, carbenylative amination, and carbenylative alkylation are: an electrophile, a formal carbene source, and a nucleophile (Figure 1.1). When carbene sources or electrophiles are used that contain β-hydrido groups, a nucleophile is not required due to rapid β-hydride elimination.

Figure 1.1 Components Common to Palladium-Catalyzed Carbenylative Reactions



1.2.1 Electrophiles Used in Palladium-Catalyzed Carbenylative Processes

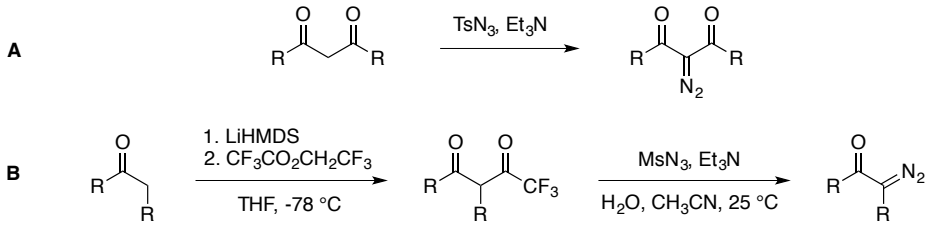
Electrophiles in palladium-catalyzed carbenylative reactions generally undergo oxidative addition, and the rate of the reaction follows the same trend seen in the rates of oxidative additions with palladium(0). Boronic acids[3,4p,q] and azoles,[4m,5] when combined with an oxidant, can also serve in a role equivalent to that of an electrophile. For reactions of vinyl halides, a substituent *syn* to the halide is important for reaction efficiency.[6] Terminal *cis* vinyl halides preform better than *trans* vinyl halides and vinyl iodides produce higher yields than bromides.[7] Aryl iodides are facile electrophiles whereas aryl bromides may require more electron rich palladium ligands (e.g. XPhos vs. PPh_3) in order to aid in the oxidative addition.[8] Allylic bromides and chlorides, which go through highly studied η^3-allylpalladium complexes,[9] have been utilized. Allylic chlorides have been shown to outperform allylic bromides when the allylic halides are substituted.[10] Both benzyl bromides and benzyl chlorides have been used and generate similar yields.[11,12,13] The ability to use aryl triflates instead of aryl halides has been demonstrated allowing for simple reagent synthesis from phenol sources however, vinyl triflates fail to generate any of the desired carbene coupling products.[7,14] Carbonates have also been used for carbenylative transformations and proceed through a palladium promoted decarboxylation.[15]

1.2.2 Carbene Sources and the Formation of Palladium-Carbene Intermediates from Diazo Compounds

The carbene source in palladium-catalyzed carbenylative reactions is generally a stabilized diazo compound or an arenesulfonylhydrazone that generates a diazo compound in situ. There are two classes of bench stable diazo compounds that have been used in palladium-catalyzed carbenylative reactions. The first class of bench stable diazo compounds are sterically stabilized silyl substituted diazomethanes. Trimethylsilydiazomethane is the only silyl stabilized diazo compound utilized in reported palladium-catalyzed carbenylations. This is most likely due to trimethylsilyldiazomethane being the only commercially available silyldiazalkane.

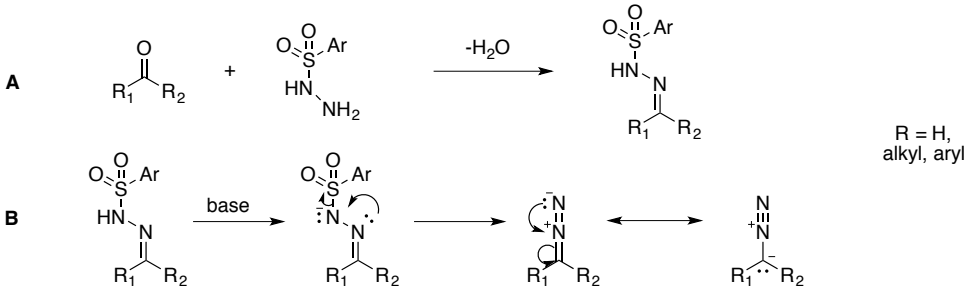
The second class of bench stable diazo compounds are stabilized by π-acceptor groups. α-Diazocarbonyl compounds are the most common carbene precursor with ethyl and *t*-butyl α-diazoacetate being commercially available. Various α-substituted α-diazocarbonyls can be easily synthesized through a diazo-transfer reaction. If a sufficiently acidic carbonyl is used, a simple one-step diazo-transfer can be carried out with a base such as triethylamine and a sulfonylazide diazo donor for instance *p*-acetamidobenzenesulfonyl azide or tosyl azide (Figure 1.2, A).[16] If the carbonyl compound is not acidic enough, the substrate can be converted to a highly reactive 1,3-carbonyl through a Claisen condensation with ethyl formate and alkoxide base or through *C*-trifluoroacetylation of a lithium enolate with trifluoroethyl trifluoroacetate (Figure1.2, B).[16] The 1,3-carbonyl can then be subjected to standard diazo-transfer conditions resulting in α-diazocarbonyl formation and the release of the activating acyl or formyl group as the acylsulfonamide. Diaryldiazomethanes have also been used in palladium-catalyzed carbenylative reactions albeit with less prevalence than other stabilized diazo compounds.[17]

Figure 1.2 Synthesis of Diazo Compounds Through Diazo Transfer



Arenesulfonylhydrazones are used to generate unstable diazo carbene precursors *in situ*, are readily accessible and provide several benefits over stabilized diazo compounds. The most commonly used type of arenesulfonylhydrazone in palladium-catalyzed carbenylations are *N*-tosylhydrazones. Both ketones and aldehydes can be used to quickly generate *N*-tosylhydrazones in high yields by treatment with *N*-tosylhydrazine in a suitable solvent (Figure 1.3, A).[18] Formation of the desired unstable diazo carbene precursor from the bench stable *N*-tosylhydrazone is carried out in situ through a base-promoted Bamford-Stevens reaction (Figure 1.3, B).[19]

Figure 1.3 Synthesis of *N*-Tosylhydrazones and Subsequent Generation of Diazo Compound through a Bamford-Stevens Reaction

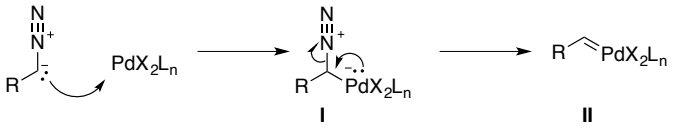


The use of *N*-tosylhydrazones as diazo precursors in palladium-catalyzed carbene reactions provides several benefits over stabilized diazo compounds. Since any aldehyde or ketone can be readily transformed into an *N*-tosylhydrazone, they provide facile access to a large range of carbene donors. Furthermore, metallated *N*-tosylhydrazones are much less prone to

dimerization than their diazo counterparts.[11,20] *N*-tosylhydrazones slowly generate diazo compounds in low concentration in situ eliminating the need to use syringe pumps.[21] The safety profile of *N*-tosylhydrazones is also improved compared to trimethylsilyldiazomethane and α-diazocarbonyls with decreased toxicity and reduced explosive potential.[21] Other less common carbene precursors for metal-catalyzed reactions include diazirines,[22] tethered alkynes,[23] Fischer carbenes,[24] chloroform,[25] and *N*-sulfonyl-1,2,3-triazoles.[26]

Formation of the palladium-carbene is believed to proceed by addition of the anionic carbon center of the diazo compound to palladium(II) to form palladate intermediate **I**, which then goes on to release N_2 forming the reactive palladium-carbene species **II** (Figure 1.4).

Figure 1.4 Formation of Palladium-Carbene from Diazo Compounds



1.2.3 Nucleophiles Used in Palladium-Catalyzed Carbenylative Processes

There are two common types of nucleophiles seen in palladium-catalyzed carbenylative reactions: amines and stabilized enolates. Less frequently used nucleophiles include: stannanes,[11] tethered alkenes,[27,28] hydrides,[29,30] organocopper compounds,[31] and sulfinates[32]. In intermolecular reactions a high concentration of nucleophile, achieved with excess reagent, is typically needed when using *N*-tosylhydrazones in order to outcompete the nucleophilic *N*-tosylhydrazone anions. In contrast, with intramolecular reactions the nucleophile has a high effective concentration because it is tethered to the electrophile.[33]

Amine nucleophiles that are used in palladium-catalyzed carbenylative reactions fall into four categories: alkylamines, anilines, azoles and protected amines. Alkylamines are the most common amine nucleophiles used, as they are the most nucleophilic and tend to give the highest

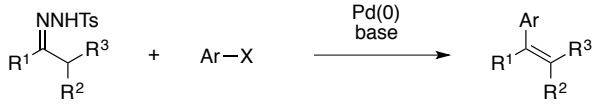
yields. Secondary amines outperform primary amines possibly due to their increased nucleophilicity.[7] Anilines are ineffective nucleophiles in carbenylative reactions,[34] but arylakylamines can be used to generate high yields.[35] Sulfonamide nucleophiles work poorly in palladium-catalyzed carbenylative reactions.[34]

1,3-Dicarbonyls and related compounds such as malonates, beta-ketoesters and malonitriles when used in combination with bases are useful in generating carbon-carbon bonds in carbenylative processes. Typical bases used include sodium hydride and potassium, sodium and lithium tert-butoxides. With simple 1,3-dicarbonyl compounds, the poor solubility of the metal-enolate can make it difficult to achieve a sufficiently high concentration of nucleophile to outcompete the nucleophilic diazo compound.[6]

1.3 Palladium-Catalyzed Carbenylative Cross-Coupling Reactions with β-Hydride Elimination

Palladium-catalyzed carbenylative cross-coupling reactions involving β-hydride elimination can be used to form polysubstituted olefins (Figure 1.5).[3n] The reactions utilize *N*-tosylhydrazones or stabilized diazo compounds as the carbene source and aryl-, benzyl- or allyl-halides or pseudo halides as the electrophile.[4] Surprisingly, there have been no reports of two-component couplings with vinyl halides.

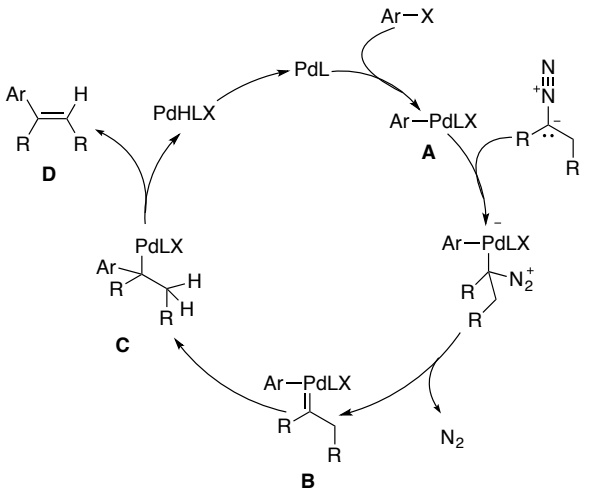
Figure 1.5 Formation of Polysubstituted Olefins Through Palladium-Catalyzed Carbenylative Cross-Coupling



The proposed mechanism is shown in Figure 1.6. Palladium(0) oxidatively adds to the aryl halide to form intermediate **A**. Addition of the diazo compound and loss of nitrogen gas leads to palladium(II)carbene intermediate **B**. Migratory insertion of the aryl group into the

carbene generates intermediate **C**. Finally, β-hydride elimination from the alkylpalladium(II) intermediate **C** forms the olefin product **D** while regenerating the palladium(0) catalyst.

Figure 1.6 Proposed Mechanism of Two-Component Palladium-Catalyzed Carbenylative Cross-Coupling



In these reactions, the carbene precursors serve as an equivalent of a vinylmetal (e.g. vinylboronic acid, vinylstannane, etc.) or alkene. Although this methodology provides an alternate synthetic route to polysubstituted olefins, there isn't an obvious advantage to utilizing this cross-coupling of diazo compounds over the better-known cross-coupling reactions of, for example, alkenes (Heck), vinylboronates (Suzuki), or related compounds.

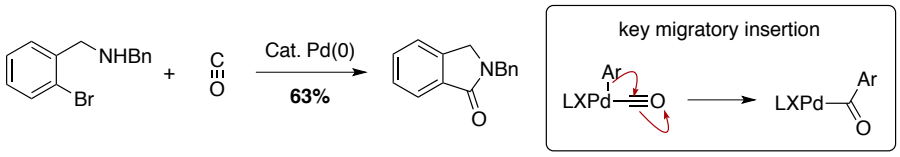
1.4 Palladium-Catalyzed Carbenylative Cross-Coupling Reactions with Nucleophilic Trapping of Migratory Insertion Products

1.4.1 Carbenylative Cross-Coupling is Analogous to Carbonylative Cross-Coupling

Palladium-catalyzed carbenylative cross-coupling reactions are directly analogous to a broad range of palladium-catalyzed carbonylative cross-coupling reactions. Carbonylative cross-coupling of aryl, vinyl, or benzyl halides or triflates has been preformed with numerous nucleophiles: alkoxides, amines and hydrides as well as organoborane, organoaluminum,

organosilane, organoantimony and organozinc compounds.[36] Trapping of the migratory insertion products allows for formation of both new carbon-carbon and new carbon-heteroatom bonds. For example, palladium-catalyzed carbonylative cross-couplings have been used to generate lactams from aryl halides containing an ortho tethered nitrogen group (Figure 1.7).[37] This carbonylative cyclization provides access to five-, six-, and seven-membered ring lactams. While carbonylative cross-couplings are powerful, they do not create new stereogenic centers.

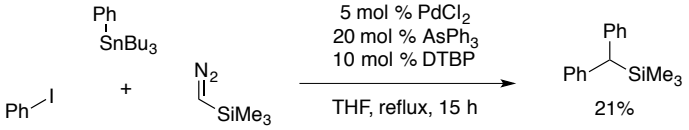
Figure 1.7 Heterocycle Formation Through Carbonylation



1.4.2 Examples of Intermolecular Palladium-Catalyzed Carbenylative Cross-Coupling

1.4.2.1 Formation of Benzhydryls Through Intermolecular Carbenylative Cross-Coupling

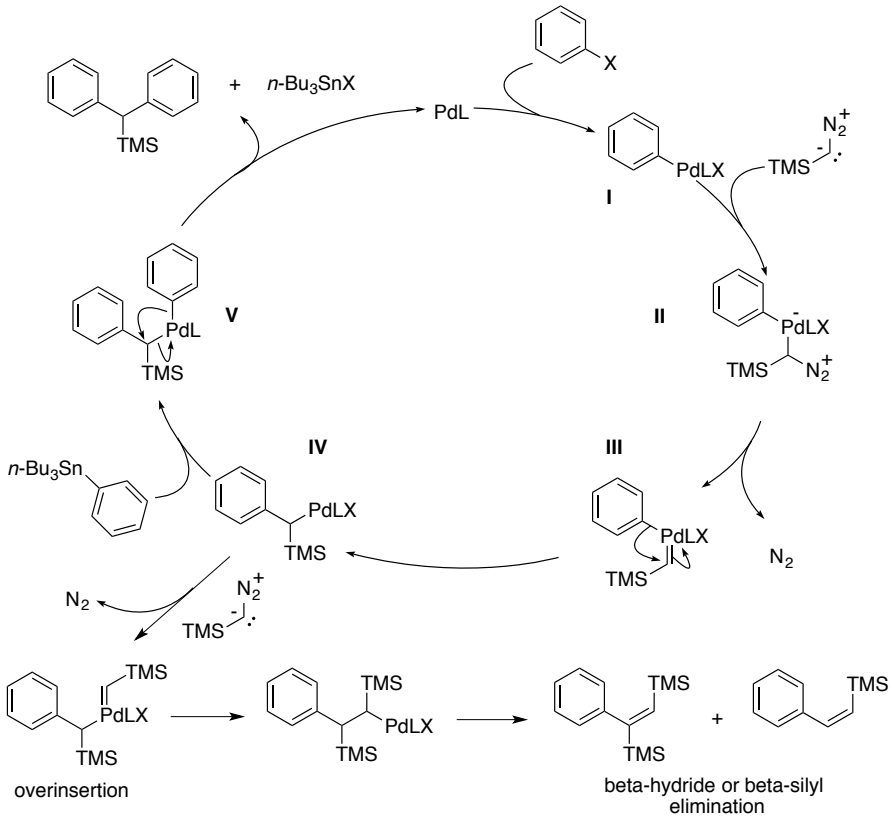
Figure 1.8 Palladium-Catalyzed Carbenylative Cross-Coupling Between Aryl Iodide, Trimethylsilyldiazomethane and Tributylphenyltin



In 2001 Van Vranken and co-workers reported the first example of a palladium-catalyzed carbenylative process: carbenylative cross-coupling of an aryl iodide and an arylstannane. They used aryl halides, trimethylsilyldiazomethane and tris(*n*-butyl)phenylstannane to generate benzhydrylsilanes (Figure 1.8).[11] The catalytic cycle (Figure 1.9) is proposed to go through an initial oxidative addition of palladium into the aryl halide forming intermediate **I**. Trimethylsilyldiazomethane then attacks intermediate **I** to form a zwitterionic palladate intermediate **II** which then extrudes nitrogen gas to generate palladium-carbene intermediate **III**. Migratory insertion forms intermediate **IV**, which undergoes transmetallation with the

arylstannane and reductively eliminates to form the desired product. Similar to carbonylations, intermediate **IV** also has the potential to insert an additional trimethylsilyldiazomethane and β-hydride or β-silyl eliminate to form byproducts.

Figure 1.9 Proposed Catalytic Cycle of Palladium-Catalyzed Carbenylative Cross-Coupling with Nucleophilic Trapping

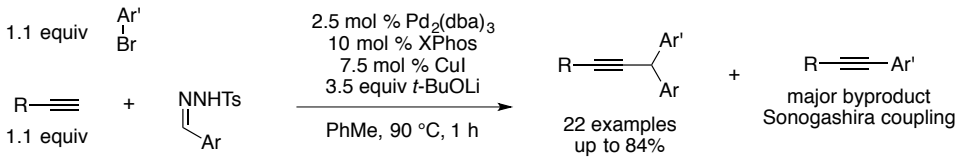


One of the major side reactions was over insertion of the diazo compound followed by β-hydride elimination. The over insertion process is in competition with the desired nucleophilic trapping, which makes it important to control the concentration of the nucleophile and diazo compound in solution. In this particular example it was also important to control the concentration of the nucleophile due to another side reaction of coupling between the aryl halide and tributylphenyltin in a Stille-coupling. Although low yields were obtained due to over insertion of the diazo compound and direct Stille-coupling between aryl halide and arylstannane,

it was an important proof of concept for migratory insertion into palladium-carbene intermediates.

Expanding on the use of organometallics as nucleophiles in palladium-catalyzed carbenylative cross-couplings, Wang and co-workers engaged alkynylcopper species, generated in-situ, with aryl halides and *N*-tosylhydrazones to form benzhydryl acetylenes (Figure 1.10).[31] The Sonogashira coupling product was the major byproduct seen and was theorized to occur due to slow palladium-carbene formation from the low concentrations of diazo substrates generated in situ. Slow addition of alkyne via syringe pump failed to limit the undesired Sonogashira coupling. Switching from an aryl iodide to an aryl bromide to slow down the oxidative addition step helped to reduce the Sonogashira product and increase the yield. Attempts to follow the trend using the aryl chloride failed to generate any desired product.

Figure 1.10 Palladium-Catalyzed Carbenylative Cross-Coupling Between Aryl Bromide, Benzaldehyde *N*-Tosylhydrazone and Alkynylcopper

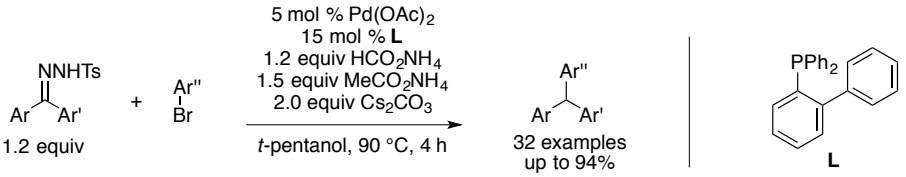


1.4.2.2 Formation of Triarylmethanes with Hydride Nucleophiles Through Intermolecular Carbenylative Cross-Coupling

Wang and co-workers have developed a palladium-catalyzed carbenylative cross-coupling route using benzophenone *N*-tosylhydrazones, aryl bromides and a hydride nucleophile to form triarylmethanes (Figure 1.11).[30] Ammonium formate was employed as a mild hydride source, which forms a hydridopalladium(II) intermediate in situ. Attempts to use other hydride sources such as triethylsilane and isopropanol failed to provide more than trace product. The major side reaction was found to be direct reduction of the aryl halide, which was inhibited by

the addition of ammonium acetate. The authors postulate that the ammonium acetate additive acts in a manner similar to the common-ion effect.

Figure 1.11 Palladium-Catalyzed Carbenylative Cross-Coupling Between Aryl Bromide, Diarylmethanone *N*-Tosylhydrazones and Ammonium Formate

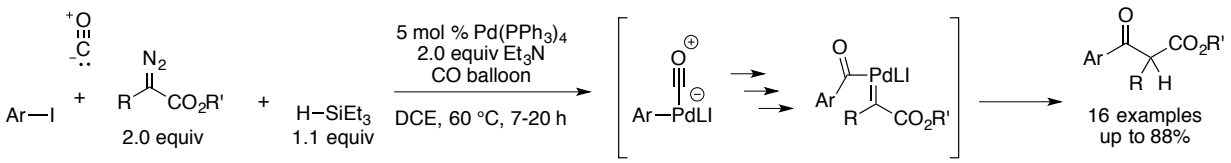


1.4.2.3 Intermolecular Palladium-Catalyzed Four-Component Tandem Carbonylation and Carbenylative Cross-Coupling Utilizing an Acyl Migratory Insertion

In palladium-catalyzed carbenylative transformations, the migratory insertion step typically involves aryl, benzyl, vinyl or allyl groups derived from their respective halides. A palladium-catalyzed four-component tandem carbonylation/carbenylative cross-coupling reaction between an aryl iodide, α-diazocarbonyls or *N*-tosylhydrazones, carbon monoxide and triethylsilane has provided the first example of an acyl migratory insertion into a palladium-carbene (Figure 1.12).[29] The reaction is proposed to proceed through an oxidative addition of palladium(0) to the aryl iodide followed by insertion of carbon monoxide generating an acylpalladium(II) intermediate. Next, the acylpalladium(II) intermediate is thought to form an acylpalladium(II) carbene intermediate by reacting with the diazo compound, which can then undergo a migration of the acyl group onto the carbene carbon. Finally, transmetallation with triethylsilane followed by reductive elimination yields the ketone in competition with β-hydride elimination to produce the enone. When using α-diazocarbonyls, β-hydride elimination side reactions are not observed. The use of *N*-tosylhydrazones does lead to the formation of β-hydride elimination products however two sets of optimized reaction conditions were developed that could provide either the β-hydride elimination product or the transmetallation/reductive

elimination product.

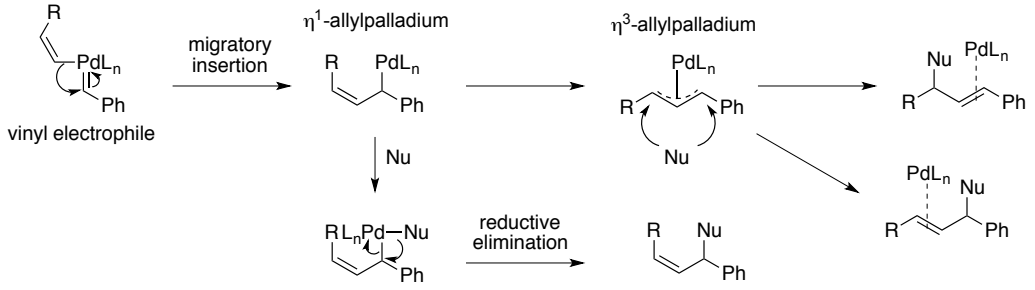
Figure 1.12 Tandem Palladium-Catalyzed Carbonylation and Carbenylative Cross-Coupling Reaction



1.4.2.4 Mechanistic Evidence for an η^3-Allylpalladium Intermediate When Using Vinyl Halides

Of the reactions discussed so far, either no nucleophile is used (reaction proceeds through β-hydride elimination) or a reductive elimination step is involved. When vinyl halides are used the reaction is believed to involve nucleophilic attack of an η^3-allylpalladium intermediate which forms after the migratory insertion step (Figure 1.13). If an η^3-allylpalladium intermediate was not involved there would be only one possible isomer.

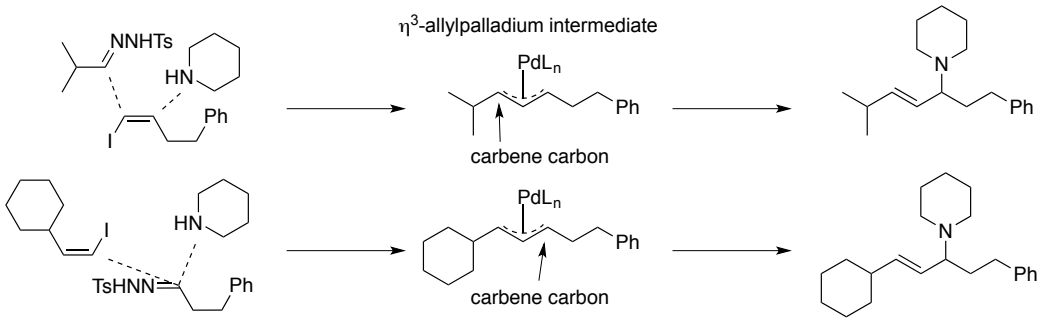
Figure 1.13 Nucleophilic Attack of η^3-Allylpalladium vs. Reductive Elimination



It is well known that sterics can be used to direct the site of nucleophilic attack on η^3-allylpalladium intermediates.[38] In the case of palladium-catalyzed carbenylation the nucleophile can attack the carbene carbon of the η^3-allylpalladium intermediate (cross-coupling) or attack distal to the carbene carbon (amination/alkylation). Van Vranken and co-workers demonstrated that carbenylation with vinyl halides involves an η^3-allylpalladium intermediate by showing that

intermolecular nucleophilic attack will occur at the least hindered side of the substrate regardless of whether the vinyl iodide or the *N*-tosylhydrazone is substituted with a bulky group (Figure 1.14).[33]

Figure 1.14 Sterics Direct Nucleophilic Attack Indicating an η^3-Allylpalladium Intermediate



1.4.3 Examples of Intramolecular Palladium-Catalyzed Carbenylative Cross-Coupling

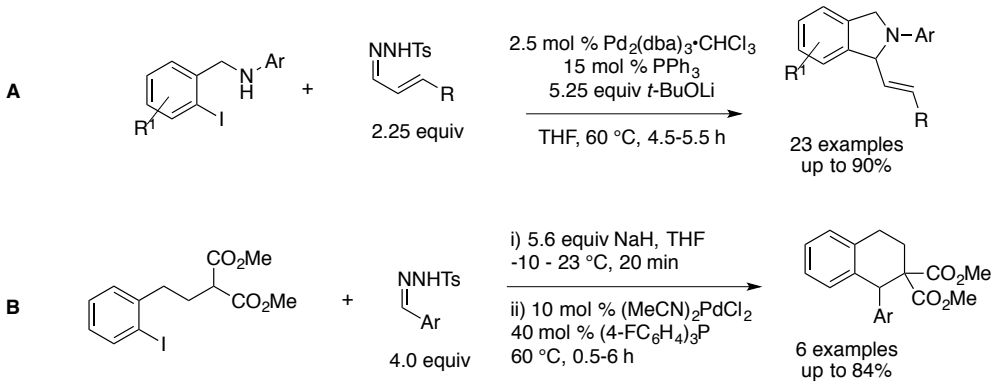
1.4.3.1 Intramolecular Palladium-Catalyzed Carbenylative Cross-Coupling Reactions with Amine and Carbon Nucleophiles

Intramolecular palladium-catalyzed carbenylative cross-coupling reactions utilize electrophiles with tethered nucleophiles to generate five- and six-membered rings. During the course of my research, Liang and co-workers published a paper on palladium-catalyzed carbenylative cross-coupling to form *N*-aniline isoindolines from *N*-(2-iodobenzyl)anilines and α,β-unsaturated *N*-tosylhydrazones (Figure 1.15, A).[35] Although Liang's system is similar to some of the systems presented in this thesis, there are several aspects that were not addressed: *N*-anilines were the only nucleophile used, the cited applications for isoindolines with bioactivity did not contain *N*-arylisoindoline, *N*-aryl groups are difficult to remove; *p*-methoxyphenylamine can be deprotected, but the radical conditions required[39] are not compatible with vinylisoindolines and no examples of 6-member ring formation or asymmetric induction were reported.

Similarly, tethered carbon nucleophiles have produced 1-arylindanes and 1-aryltetralines

from dimethyl (2-iodobenzyl) malonate or dimethyl 2-(2-iodophenethyl)malonate and aryl *N*-tosylhydrazones (Figure 1.15, B).[40] While optimizing the reaction, it was found that using sodium hydride to form both the enolate and *N*-tosylhydrazone salt provided the best results in contrast to carbonate and tert-butoxide salts typically seen in palladium-catalyzed carbenylation reactions.

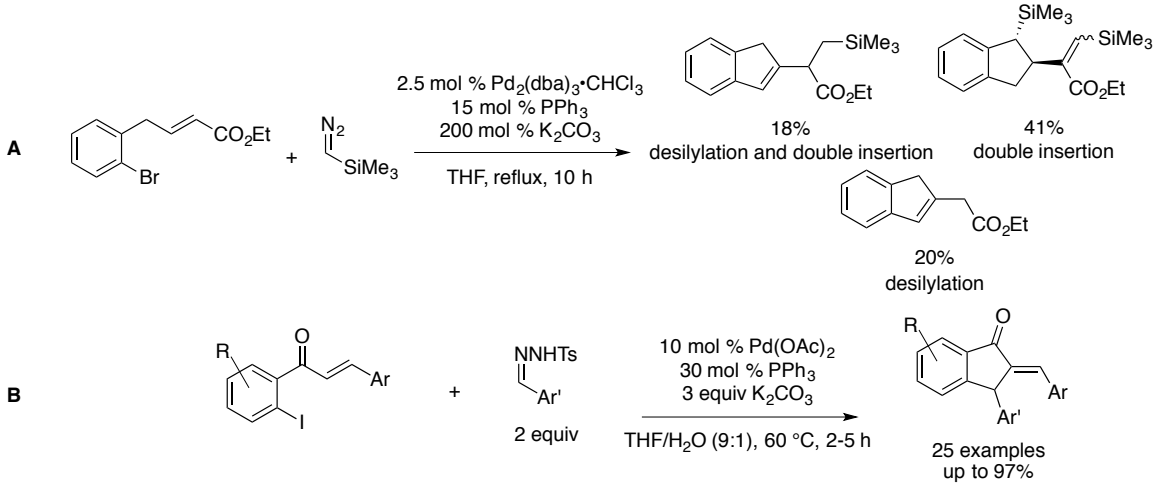
Figure 1.15 Intramolecular Palladium-Catalyzed Carbenylative Cross-Coupling with Amine and Carbon Nucleophiles



1.4.3.2 Intramolecular Palladium-Catalyzed Carbenylative Cross-Coupling Reactions with Alkene Nucleophiles

Palladium-catalyzed carbenylative cross-coupling with alkene nucleophiles is analogous to the Heck reaction. The first attempt to use tethered alkenes as a nucleophile led to poor results from carbene over insertion and protodesilylation, both due to the use of trimethylsilyldiazomethane as the carbene source (Figure 1.16, A).[27] Subsequent use of tethered alkenes with aryl *N*-tosylhydrazones as the carbene source produced high yields of the desired intramolecular carbenylative heck products (Figure 1.16, B).[28]

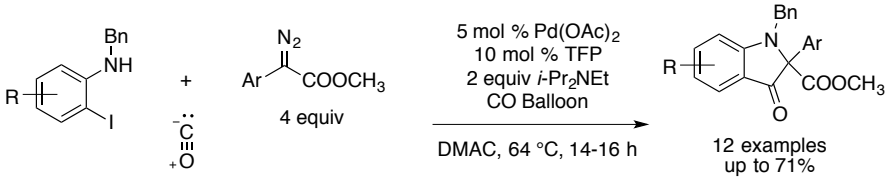
Figure 1.16 Intramolecular Palladium-Catalyzed Carbenylative Cross-Coupling with Alkene Nucleophiles



1.4.3.3 Intramolecular Palladium-Catalyzed Four-Component Tandem Carbonylation and Carbenylative Cross-Coupling

Tandem palladium-catalyzed carbonylation/carbenylative cross-coupling provides a novel method to generate cyclic α,α-disubstituted α-amino esters in modest yields (Figure 1.17).[34] The reaction is believed to go through palladium-catalyzed insertion of aryl iodide into carbon monoxide followed by palladium-carbene formation, migratory insertion of the acyl group into the palladium-carbene and finally nucleophilic attack by the tethered amine.

Figure 1.17 Intramolecular Palladium-Catalyzed Four-Component Tandem Carbonylation and Carbenylative Cross-Coupling



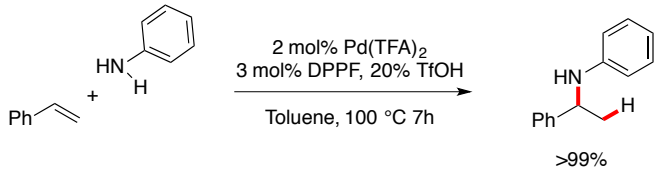
1.5 Palladium-Catalyzed Carbenylative Amination and Alkylation Reactions

1.5.1 Background to Carbenylative Amination: Palladium-Catalyzed Hydroamination and Carboamination

1.5.1.1 Palladium-Catalyzed Hydroamination

The development of palladium-catalyzed amination reactions has generated powerful transformations that chemists can use to piece together amines through non-traditional C-N bond forming reactions. Hydroamination allows for the addition of N-H from a nucleophilic amine across an alkene generating new C-N and C-H bonds in the process. [41] In 2000 Hartwig and Kawatsura reported an efficient palladium-catalyzed hydroamination reaction involving anilines and vinylarenes with the use of an acid co-catalyst (Figure 1.18).[42]

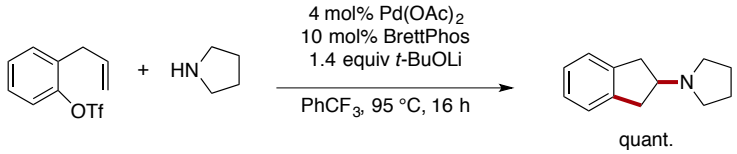
Figure 1.18 Palladium Catalyzed Hydroamination of Vinylarenes with Arylamines



1.5.1.2 Palladium-Catalyzed Carboamination

Di-functionalization of alkenes allows for more complexity to be added to molecules in a single step, compared to hydroamination. In 2004 Wolfe and Ney demonstrated the first catalytic insertion of an alkene into a [Pd(Ar)(NR_2)] complex. [43] The use of tethered alkenes afforded pyrrolidine carboamination products containing both new C-N and C-C bonds. Further expansion of substrates and optimization of reaction conditions has led to a powerful way to generate pyrrolidines as well as nitrogen substituted carbocycles in high yield (Figure 1.19). [44,45]

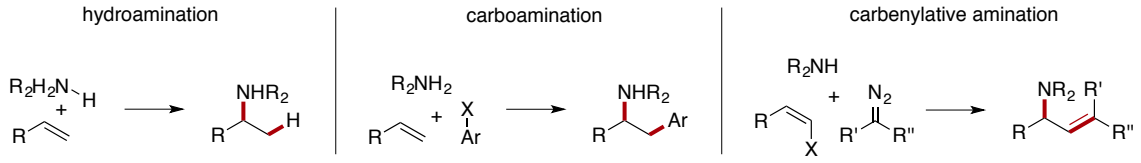
Figure 1.19 Palladium Catalyzed Carboamination to Form Pyrrolidines



1.5.1.3 Comparison of Amination to Carbenylative Amination

The Van Vranken group developed the first palladium-catalyzed carbenylative amination and alkylation reactions.[7,6] In these reactions palladium-carbenes insert into vinyl halides leading to η^3-allylpalladium intermediates that can be efficiently trapped with carbon or nitrogen nucleophiles. In the case of carbenylative amination, the reaction efficiently generates allylamines with new C-N and C-C bonds formed across the vinyl halide. While mechanistically different, the bonds formed in this fashion are analogous to the bonds formed in palladium-catalyzed hydroamination and carboamination (Figure 1.20).

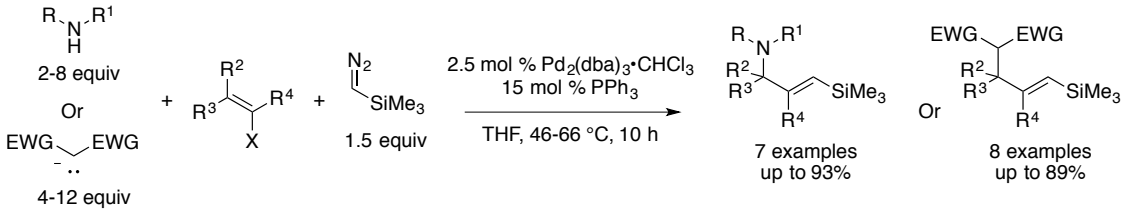
Figure 1.20 Comparison of Palladium-catalyzed Amination Reactions



1.5.2 Examples of Intermolecular Carbenylative Amination and Alkylation Reactions

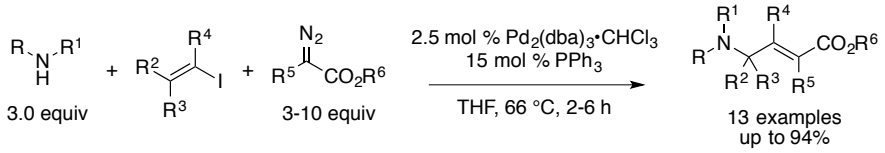
In 2007 Van Vranken and co-workers reported the first example of an intermolecular palladium-catalyzed carbenylative amination of vinyl halides with trimethylsilyldiazomethane and alkyl amines to form vinylsilanes (Figure 1.21).[7] Following on the success of trapping carbene insertion intermediates with amine nucleophiles a set of reaction conditions were optimized replacing amine nucleophiles with carbon nucleophiles.[6] The vinylsilanes formed are useful intermediates for stereospecific electrophilic substitution reactions or can be transformed into terminal alkenes through protodesilation.

Figure 1.21 Intermolecular Palladium-Catalyzed Carbenylation to form Vinylsilanes



Subsequent work led to the use of α-diazoesters instead of trimethylsilyldiazomethane as a carbene source alongside amine nucleophiles in order to generate α,β-unsaturated γ-amino esters (Figure 1.22).[46] Slow addition of the diazo compound is required to prevent inactivation of the palladium catalyst and to inhibit reactions with the enoate products, which were shown to be sensitive to α-diazoesters.

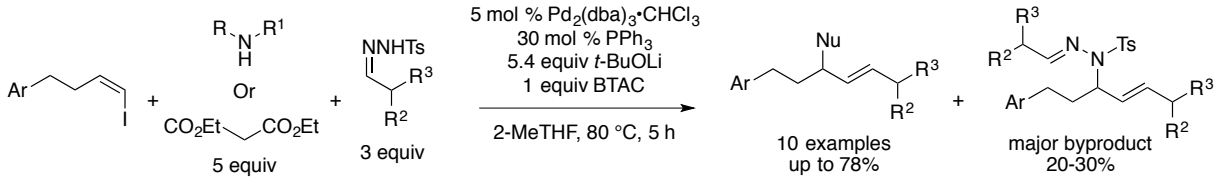
Figure 1.22 Intermolecular Palladium-Catalyzed Carbenylative Amination Generating α,β-Unsaturated γ-Amino Esters



Additional expansion of this methodology has led to conditions suitable for intermolecular carbenylative amination and alkylation with alkylidene precursors (Figure 1.23).[33] Typically alkylidene carbene precursors with α-hydrogens are seen in palladium-catalyzed carbenylative cross-coupling reactions where β-hydride elimination occurs following insertion (vida supra). Van Vranken and co-workers demonstrated that the use of vinyl iodides allowed nucleophilic trapping to outcompete β-hydride elimination. The nucleophiles can outcompete due to the vinyl iodides generating η^3-allylpalladium intermediates, which resist β-hydride elimination. However, under the optimized reaction conditions, lithiated sulfonylhydrazone competes with the desired nucleophile to attack the η^3-allylpalladium intermediate, which leads

to 20-30% of undesired byproduct.

Figure 1.23 Intermolecular Palladium-Catalyzed Carbenylation with Alkylidene Precursors



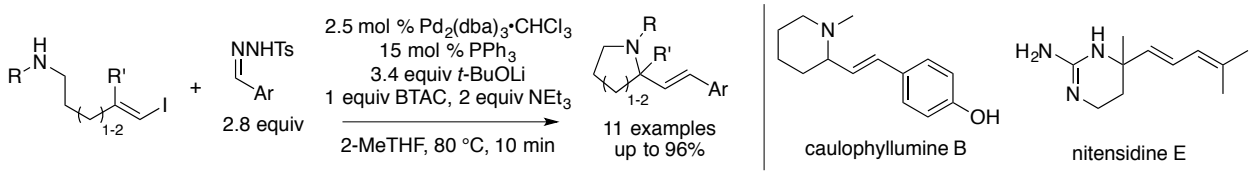
1.5.3 Examples of Intramolecular Carbenylative Amination and Alkylation Reactions

In intramolecular palladium-catalyzed carbenylative amination and alkylation reactions the nucleophile is tethered to the electrophilic component. These reactions have been used to generate cyclopentanes and 5- or 6-membered heterocyclic amines. Due to the speed with which intramolecular nucleophilic attack occurs, compared to intermolecular attack, competition with other nucleophiles such as lithiated sulfonylhydrazone is not observed. Another benefit of using tethered nucleophiles is reagent efficiency; typical intermolecular palladium-catalyzed carbenylative reactions require a large excess of nucleophile, up to twelve equivalents, while intramolecular use one.

Van Vranken and co-workers reported the first intramolecular palladium-catalyzed carbenylative amination reaction using amine-tethered vinyl iodides and aryl or cinnamyl *N*-tosylhydrazones to generate pyrrolidine and piperidine products (Figure 1.24).[47] Utilizing this new reactivity they were able to synthesize the natural product caulophyllumine B through carbenylative amination (70%) followed by nucleophilic deprotection of the methyl ether (68%). The work in this thesis was extended by a coworker in the synthesis of the cyclic guanidine alkaloid natural product nitensidine E.[48] After optimization of reaction conditions for the tethered protected guanidine vinyl iodide and vinyl *N*-tosylhydrazone starting material, the nitensidine E trifluoroacetic acid salt was obtained through palladium-catalyzed carbenylative amination

(76%) and *N*-Boc deprotection (58%).

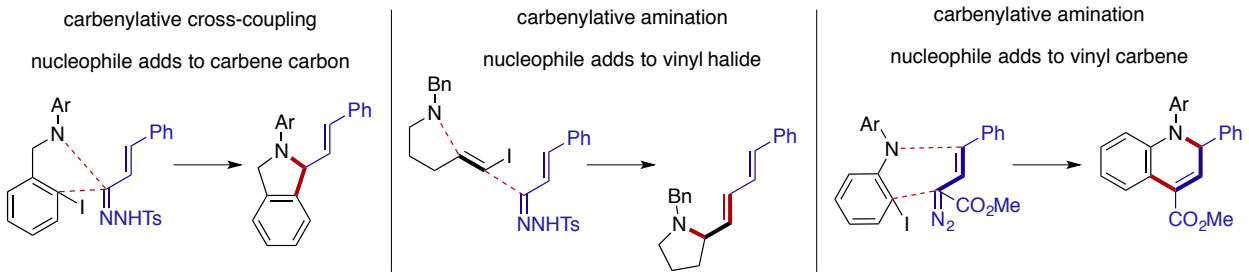
Figure 1.24 Intramolecular Palladium-Catalyzed Carbenylation to Form Pyrrolidines, Piperidines and Cyclic Guanidines



In order to use aliphatic precursors for intramolecular carbenylations it was found that *N*-trisylhydrazones had to be employed instead of *N*-tosylhydrazones to generate the palladium alkylidene intermediates.[33] Initial attempts to use aliphatic *N*-tosylhydrazones led to dimerization and unreacted starting material. The lack of activity seen with *N*-tosylhydrazones was postulated to be due to poor solubility of the lithiated form, which limits concentration. In the reaction conditions, lithiated *N*-trisylhydrazones, which are known to be more reactive than the corresponding *N*-tosylhydrazones,[49] were found to be more soluble and led to product formation.

Substrate design by Liang and co-workers led to an intramolecular palladium-catalyzed carbenylation that provides novel connectivity utilizing aryl vinyl diazoacetates and *N*-substituted-2-iodoanilines.[34] In palladium-catalyzed cross-couplings both the nucleophile and electrophile form bonds to the carbene carbon whereas palladium-catalyzed carbenylative amination typically results in the nucleophile and carbene adding across a vinyl halide (Figure 1.25). The substrates that Liang and co-workers utilize result in a 1,3-addition across the arylvinyldiazoacetate (Figure 1.25) instead of the cross-coupling product due to unfavorable 4-membered ring formation.

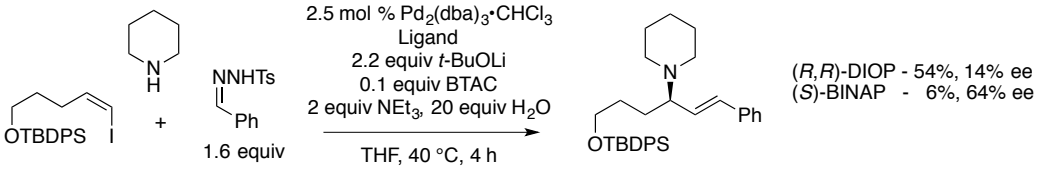
Figure 1.25 Comparison of Palladium-Catalyzed Carbenylation Bond Formation



1.5.4 Enantioselection in Palladium-Catalyzed Carbenylative Reactions

The migratory insertion of a group into the palladium-carbene intermediate typically generates a new chiral center. In the case of reactions involving β-hydride elimination, the newly formed stereochemistry is erased by the β-hydride elimination. Surprisingly, there has been only one published example of using chiral ligands in palladium-catalyzed carbenylative reactions to control enantioselectivity during the migratory insertion step (Figure 1.26).[47] Yields tended to be lower with the chiral bidentate ligands tested compared to triphenylphosphine. Using a (*Z*)-vinyl iodide generated higher enantiomeric excess (ee) than an (*E*)-vinyl iodide indicating that *cis*-substitution may contribute to enantioselection, however the (*E*)-vinyl iodide had a tethered nucleophile so a direct comparison cannot be made. The use of (*S*)-BINAP greatly slowed down the reaction and had a dramatic affect on yield, 6%, but provided a modest 64% ee. Due to the observation that fast reactions and high yields were inversely correlated with ee it was speculated that two catalytic species, a slow chiral palladium complex and a fast achiral palladium complex were in competition. Because the reaction was optimized for triphenylphosphine, an achiral, monodentate ligand, the authors believe that ligand screening and reaction optimization could lead to both high yields and ees.

Figure 1.26 Reported Enantioselection in Palladium-Catalyzed Carbenylative Amination



Chapter 2

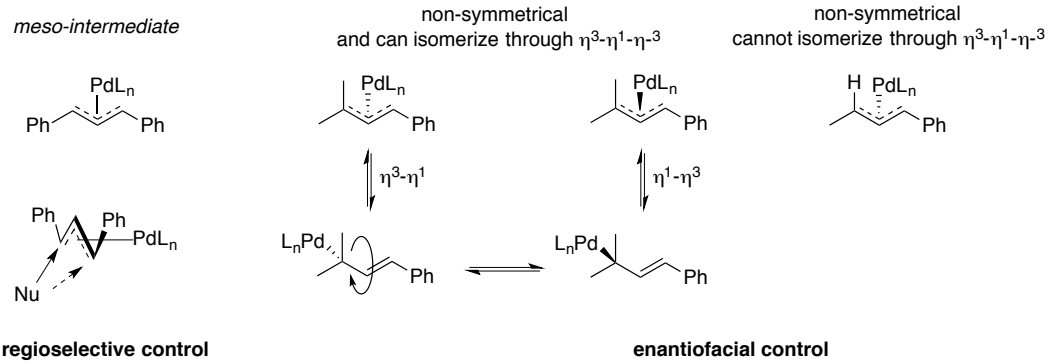
Palladium-Catalyzed Carbenylative Cross-Coupling and Carbenylative Amination with Vinylcarbenes: Progress Towards Asymmetric Carbenylation.

2.1 Introduction

Asymmetric palladium-catalyzed allylic alkylations reactions have been mechanistically studied in detail and extensively used in total synthesis over the past forty years.[9] Within the class of palladium-catalyzed asymmetric allylic alkylations there are two types of η^3-allylpalladium intermediates, symmetrical *meso*-intermediates and non-symmetrical, both of which differ in how stereocontrol in achieved (Figure 2.1). In symmetrical *meso*-intermediates, the chiral palladium species provides regioselective control through steric interactions, which direct the site of nucleophilic attack. In non-symmetrical systems, enantiofacial control generates the enantioselectivity due to the chiral palladium species preferring one face of the olefin to the other. If the substrate has two identical groups on one side, the η^3-allylpalladium intermediate can undergo an η^3-η^1-η^3 isomerization (Figure 2.1) leading to a loss in stereochemical information. In the case of allylic alkylation, this isomerization can erase stereochemistry generated from enantiotopic olefin face coordination or enantiotopic ionization; however, enantiotopic olefin face coordination and enantiotopic ionization are outside of the scope of this work. η^3-Allylpalladium intermediates formed through carbenylative processes can also lose stereochemical information generated from the migratory insertion step through η^3-η^1-η^3 isomerization. Substrates that do not contain two identical substitutions on the same side of the η^3-allylpalladium system can still isomerize by enantioface exchange resulting from addition of palladium(II) to an η^1-allylpalladium(II) intermediate; but the isomerization can be inhibited by using reactive allylic substrates, low palladium concentrations, bidentate ligands and halide ions.

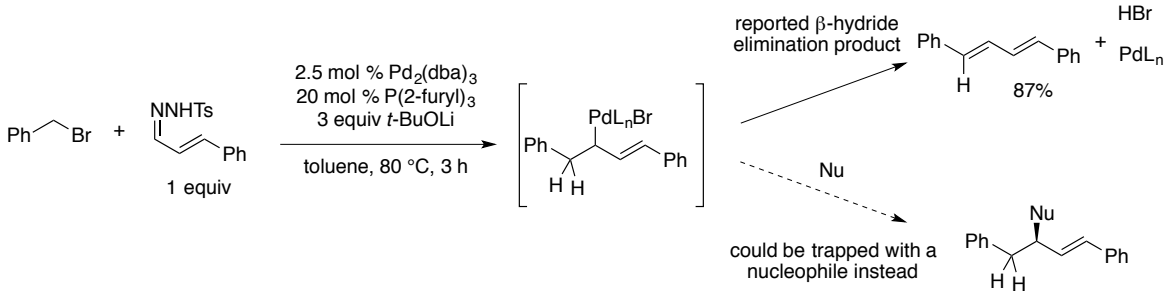
Employing α,β-unsaturated *N*-tosylhydrazones in palladium-catalyzed carbenylative cross-coupling and carbenylative amination reactions would provide access to these well studied symmetrical and non-symmetrical η^3-allylpalladium intermediates. Demonstrating asymmetric induction through a carbenylative process that intercepts a well-known prochiral intermediate is an important first-step proof of concept.

Figure 2.1 Symmetrical and Non-Symmetrical Intermediates in Allylic Alkylations



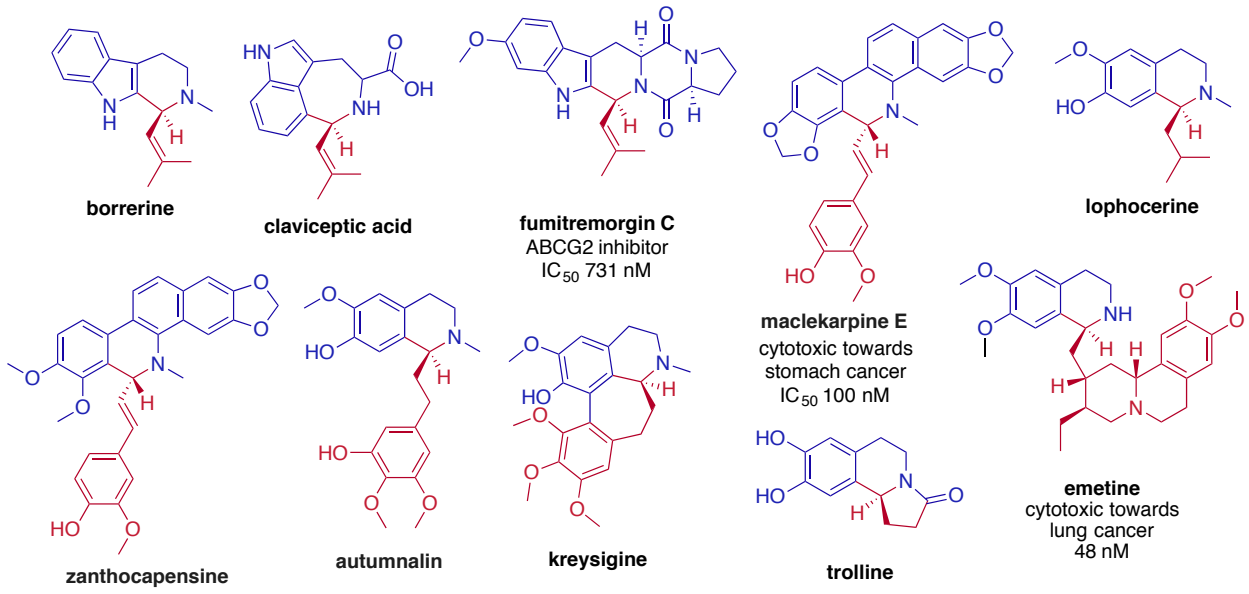
The growing interest in use of a carbene source as a coupling partner in palladium-catalyzed carbenylative cross-coupling and carbenylative amination reactions has led to the development of reactions and conditions to form a diverse range of useful products.[50] The advent of using *N*-tosylhydrazones to generate unstablized diazo compounds in situ allowed for vinyl groups to be introduced through the carbene component. Wang and co-workers first reported the use of an α,β-unsaturated *N*-tosylhydrazone in a two-component palladium-catalyzed carbenylative coupling reaction between cinnamaldehyde-*N*-tosylhydrazone and benzyl bromide.[51] The reaction forms a diene through β-hydride elimination of a palladium-vinylcarbene migratory insertion intermediate (Figure 2.2). Greater utility could be obtained from vinyl carbenes by trapping the migratory insertion intermediate with a nucleophile rather than β-hydride elimination.

Figure 2.2 β-hydride Elimination vs. Nucleophilic Trapping of Palladium-Carbene Insertion Intermediate



Use of a tethered amine nucleophile in palladium-catalyzed carbenylative cross-coupling of aryl halides (mapped in blue) with α,β-unsaturated *N*-tosylhydrazones (mapped in red) would provide access to numerous natural products (Figure 2.3). Additionally, nucleophilic trapping of the insertion intermediate can preserve the chiral center that is typically formed during the migratory insertion step allowing for the possibility of asymmetric induction.

Figure 2.3 Natural Products Accessible Through Palladium-Catalyzed Cross-Coupling with Vinyl *N*-Tosylhydrazones



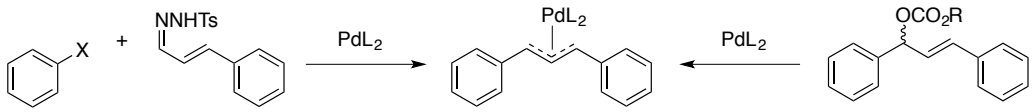
This work focuses on the use of *N*-tosylhydrazones derived from α,β-unsaturated aldehydes – precursors to vinylcarbenes – in palladium-catalyzed carbenylative cross-coupling and carbenylative amination reactions. These carbenylative reactions will be used to form η^3-allylpalladium intermediates that generate stereogenic centers at the carbene center. An initial acyclic model system of iodobenzene, cinnamaldehyde-*N*-tosylhydrazone and piperidine was used to intercept a well-known prochiral 1,3-diphenylallyl intermediate to probe the feasibility of enantioselectivity in a palladium-catalyzed carbenylative reaction as a proof of concept for asymmetric carbenylation. Following the proof of concept, the substrate scope was expanded to include aliphatic vinyl hydrazones in order to install prenyl functional groups. Finally, cyclic systems to form isoindolines and tetrahydroisoquinolines, which could be mapped onto natural products, were developed by employing amine tethered aryl iodides.

2.2 Results and Discussion

2.2.1 Intercepting Symmetrical 1,3-Diphenylallyl, a Known Prochiral Intermediate

2.2.1.1 Introduction

Figure 2.4 η^3-Allylpalladium Intermediate Formation Through Carbenylative Insertion or Allylic Carbonate Ionization



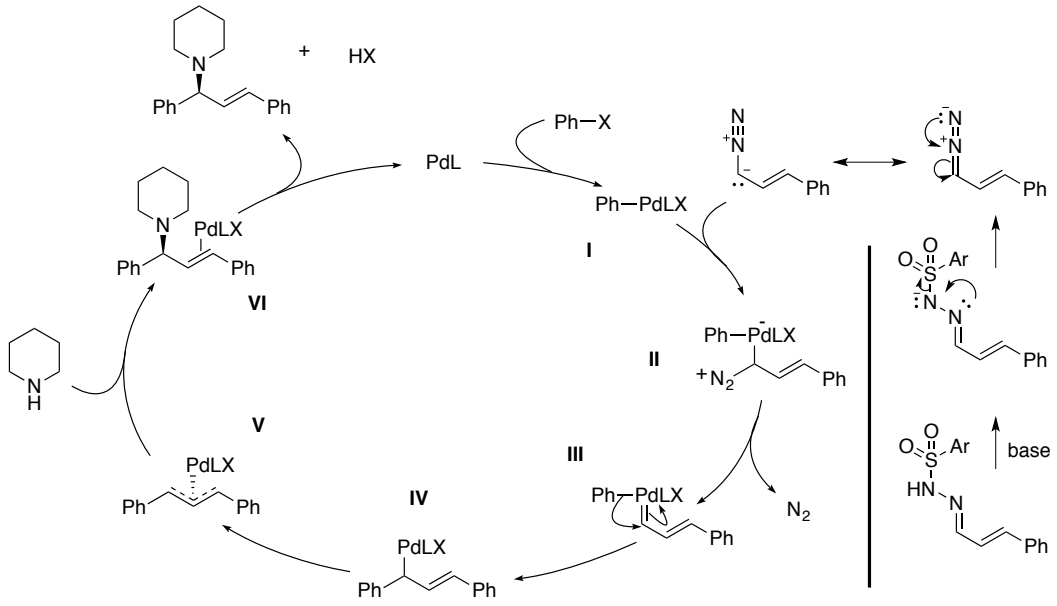
The enantioselective palladium-catalyzed allylic alkylation and amination of symmetrical 1,3-diphenylallyl systems has been studied extensively.[9] The *meso* η^3-1,3-diphenylallyl intermediates give rise to enantioselectivity through regioselective addition to the η^3-allylpalladium species. The same η^3-1,3-diphenylallyl intermediates can be accessed through carbenylative insertion (Figure 2.4) in order to demonstrate that the η^3-diphenylallyl palladium

intermediates generated through carbenylative insertion can generate equivalent enantiomeric excesses (ees) as those generated from ionization of allylic carbonates. As long as the chiral ligands are bound to palladium during the nucleophilic attack, the reaction should generate products with ees that are comparable to values reported for allylic amination with allyic carbonate starting materials. While it is possible that the ees obtained are generated during the migratory insertion, rather than the nucleophilic attack, this system will not provide insight into the source of enantioselectivity, but that topic will be explored later on (*vide infra*). While there are more examples for generating high ees using carbon nucleophiles over amine nucleophiles in these systems, the use of amines is applicable to the work reported herein. As proof of concept, a carbenylative amination was used to access a well-known η^3-1,3-diphenylallylpalladium from *N*-tosylhydrazone **2** and iodobenzene followed by nucleophilic trapping with piperidine to afford a chiral product.

2.2.1.2 Proposed Catalytic Cycle

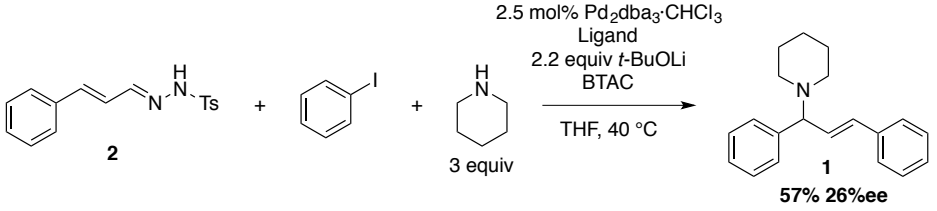
The catalytic cycle (Figure 2.5) is proposed to go through an initial oxidative addition of palladium into the aryl halide forming arylpalladium(II) intermediate **I**. A vinyl diazo compound generated in situ through a Bamford-Stevens reaction then attacks arylpalladium(II) intermediate **I** to form a zwitterionic palladate intermediate **II** which then extrudes nitrogen gas to generate vinylpalladium carbene intermediate **III**. Migratory insertion forms η^1-allylpalldium(II) intermediate **IV**, which goes from η^1 to η^3 forming η^3-allylpalladium(II) intermediate **V**. Nucleophilic attack of η^3-allylpalladium(II) intermediate **V** leads to allylic amine **VI**, which dissociates from palladium to regenerate the catalyst.

Figure 2.5 Proposed Catalytic Cycle for Palladium-Catalyzed Carbenylative Cross-Coupling with Nucleophilic Trapping of η^3-allylpalladium Intermediate



2.2.1.3 Reaction Optimization

Table 2.1 Initial Palladium-Catalyzed Carbenylative Amination Reaction Optimization



Entry	equiv 2	equiv PhI	Ligand	BTAC	Time	Yield (%)
1	1.1	1	15 mol% PPh_3	100 mol%	7 h	32%
2	1.1	1	15 mol% PPh_3	10 mol%	7 h	32%
3	1	1	7.5 mol% (*R,R*)-DIOP	100 mol%	4.5 h	47%[a]
4	1	2	7.5 mol% (*R,R*)-DIOP	100 mol%	4.5 h	57%
5	1	2	7.5 mol% (*R,R*)-DIOP	10 mol%	10 h	59%[a]
6	1	2	5.0 mol% (*R,R*)-DIOP	100 mol%	10 h	33%[a]
7	1	2	15 mol% (*R,R*)-DIOP	100 mol%	21 h	51%
8	1	2	7.5 mol% (*S*)-BINAP(S)	100 mol%	10 h	<5%

[a]NMR yield based on internal standard

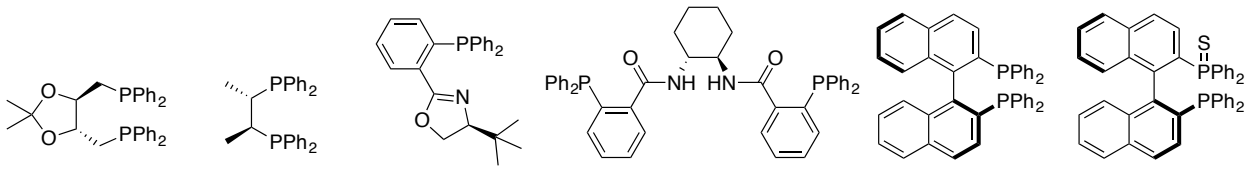
Starting from conditions that had previously been used for arylhydrazones, a set of reaction conditions was screened for the palladium-catalyzed carbenylative amination between

iodobenzene, piperidine and cinnamaldehyde *N*-tosylhydrazone **2**. Initial reaction optimization revealed that the bidentate ligand (*R,R*)-DIOP (Figure 2.6) provided an increase in yield from 32% to 47% compared to triphenylphosphine (Table 2.1, entries 1 and 3). Benzyltriethylammonium chloride (BTAC) was added as a phase-transfer catalyst to solubilize the lithiated *N*-tosylhydrazone salts that form during the reaction. When changing from 100 mol% BTAC to 10 mol% BTAC with triphenylphosphine as a ligand there was no difference in yield or catalyst turnover rate (Table 2.1, entry 1 and 2). When using (*R,R*)-DIOP as a ligand, changing the BTAC concentration from 100 mol% to 10 mol% also had no effect on the yield, however there was a marked decrease in the rate of catalyst turnover as seen by the increase in reaction time from 4.5 h to 10 h (Table 2.1, entry 4 and 5). Iodobenzene could not be monitored by TLC due to its volatility. To ensure that the aryl iodide was not being depleted, the *N*-tosylhydrazone was utilized as the limiting reagent. Increasing the amount of iodobenzene from 1 to 2 equivalents led to an increase in yield from 47% to 57% (Table 2.1, entry 3 and 4). To address concerns of over- or under-ligation of palladium, ligand concentrations were varied. Lowering the amount of ligand to 5 mol % showed a marked decrease in yield while increasing the amount of ligand to 15 mol % did little to affect the yield but quadrupled the reaction time, probably due to over-ligation of the palladium (Table 2.1, entry 4, 6 and 7). In order to deprotonate the *N*-tosylhydrazone and quench the hydroiodic acid formed in the reaction 2.2 equivalents of lithium *t*-butoxide was added. An attempt to use conditions developed by Barluenga and co-workers (XPhos, dioxanes, 70 °C) for two-component carbenylative coupling reactions that proceed through β-hydride elimination[4n] rather than nucleophilic trapping, failed to generate any product. The reaction conditions developed for the 1,3-diphenylallyl system were sufficient to obtain the necessary ees in this proof of concept system and were not optimized

further.

2.2.1.4 Asymmetric Induction Through Regioselective Control

Figure 2.6 Chiral Ligands Screened

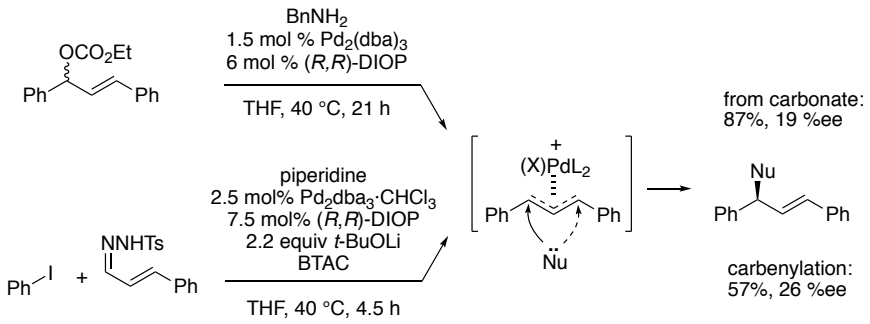


(*R*,*R*)-DIOP (*S*,*S*)-Chiraphos (*S*)-*t*-Bu-PHOX (*R*,*R*)-DACH-phenyl Trost (*S*)-BINAP (*S*)-BINAP(S)

A report by Faller and co-workers employed the use of the mono-sulfide (*S*)-BINAP(S) (Figure 2.6) as a ligand for allylic amination which generated high ees with various amine nucleophiles.[52] Hoping that (*S*)-BINAP(S) would also work well for our reaction, we synthesized the P=S bond of (*S*)-BINAP(S) by addition of elemental sulfur to (*S*)-BINAP followed by separation of bis-phosphine starting material, mono-sulfide and bis-sulfide. Unfortunately, (*S*)-BINAP(S) performed poorly in the carbenylative process yielding <5% product, insufficient to purify and determine ee. Utilizing carbenylative amination conditions published by a co-worker,[47] an additional attempt was made to use (*S*)-BINAP(S), unfortunately no product was detected. Complexes of (*S*)-BINAP and (*R*,*R*)-DACH-phenyl Trost ligand also failed to engage in the carbenylation reaction. Finally, optimized conditions for a 5-membered intramolecular reaction, *vide infra*, failed to generate product with (*S*,*S*)-chiraphos or (*S*)-*t*-Bu-PHOX. We were able to obtain sufficient material using (*R,R*)-DIOP to determine an ee. Hayashi has reported that under conditions similar to our current reaction an ee of 19% was obtained using benzylamine as a nucleophile and (*R,R*)-DIOP as a chiral ligand (Figure 2.7).[53] Previous studies have shown that benzylamine works poorly in carbenylative coupling but utilizing piperidine instead of benzylamine, we obtained an ee of 26% (Table 2.1, entry 4), comparable to Hayashi's result but perhaps higher due to the increased steric demands of a secondary amine nucleophile. Having

shown that palladium-catalyzed carbenylative insertions produce comparable ees when intercepting known 1,3-diphenylallylpalladium intermediates, we were ready to expand substrate scope.

Figure 2.7 Intercepting a Known η^3-1,3-Diphenylallylpalladium(II) Intermediate

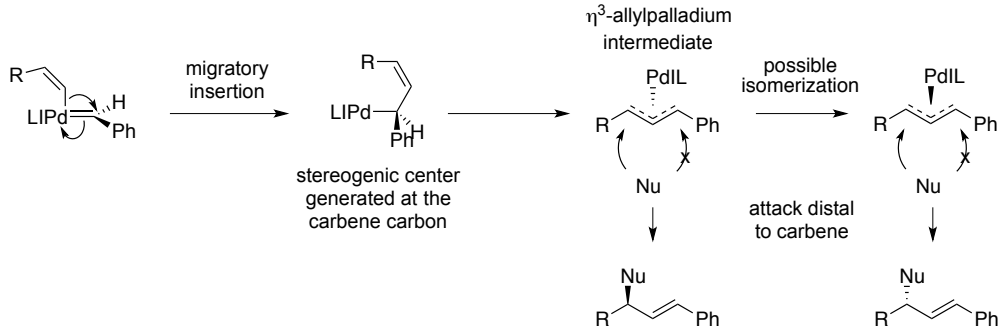


2.2.2 Asymmetric Induction Through Enantiofacial Control in Unsymmetrical η^3-Allylpalladium Systems – Installation of Prenyl Functional Groups

2.2.2.1 Intermolecular Carbenylation with Unsymmetrical η^3-Allylpalladium Systems

Next, we wanted to exploit palladium-catalyzed carbenylative cross-coupling with unsymmetrical η^3-allylpalladium intermediates, which formed new stereogenic centers at the carbene carbon. In previous non-asymmetric examples of palladium-catalyzed carbenylative reactions that intercepted η^3-allylpalladium intermediates the nucleophiles were designed to attack the η^3-allylpalladium intermediate at a site distal from the original carbene center which obscured the carbene center as the potential origin of chirality (Figure 2.8).[46] There are two possible mechanistic sources of asymmetric induction in these reactions, migratory insertion and/or isomerization of the palladium species to a preferred face before nucleophilic trapping (Figure 2.8).

Figure 2.8 Previous Nucleophilic Trapping of η^3-Allylpalladium Intermediates Distal to the Carbene Carbon and Sources of Chirality



We set out to determine if there is a steric or electronic preference for nucleophilic attack when a non-symmetrical η^3-allylpalladium intermediate such as **3** is encountered (Figure 2.9). Regioselectivity can be difficult to predict for alkylation of differentially substituted η^3-allylpalladium intermediates. For example, palladium-catalyzed allylic alkylation with differentially substituted η^3-allylpalladium intermediates generated conjugated product with 1-methyl-3-phenylallyl and non-conjugated product with 1-*t*-butyl-3-phenylallyl (Figure 2.10).[54] Since the available data was insufficient to predict the outcome for the system in Figure 2.9, *N*-tosylhydrazone **4** was synthesized from the corresponding β-methylcrotonaldehyde and *p*-toluenesulfonylhydrazine and used in a carbenylative amination. Electronic preferences would favor nucleophilic attack at the tertiary carbon center of the η^3-allylpalladium intermediate **A** in order to preserve conjugation with the aromatic ring as well as place the palladium, which has an affinity for π-bonds, next to the aromatic ring. Sterics on the other hand would favor attack next to the phenyl ring at the secondary carbon as opposed to the tertiary carbon with two methyl groups. Because it is desired to set the stereocenter at the carbene-carbon, it would be ideal for the sterics to govern the regioselectivity of the reaction. The choice of using *p*-iodoanisole over

iodobenzene was simply for ease of reaction monitoring by TLC. After performing the reaction it was found that the electronic preference is indeed the major factor for determining the regioselectivity producing the achiral conjugated product **5** with a 29% yield; none of the chiral non-conjugated product was observed in the product mixture. The selectivity we found in this intermolecular system was not desirable for our development of an asymmetric palladium-catalyzed carbenylative cross-coupling reaction with nucleophilic attack at the carbene carbon.

Figure 2.9 Determination of the Regioselectivity Preference for Sterics or Conjugation

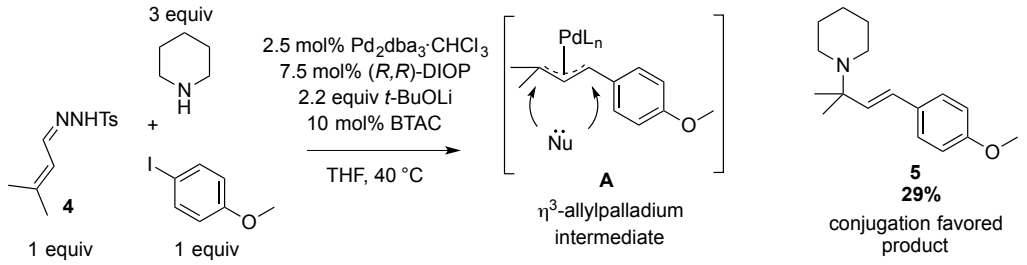
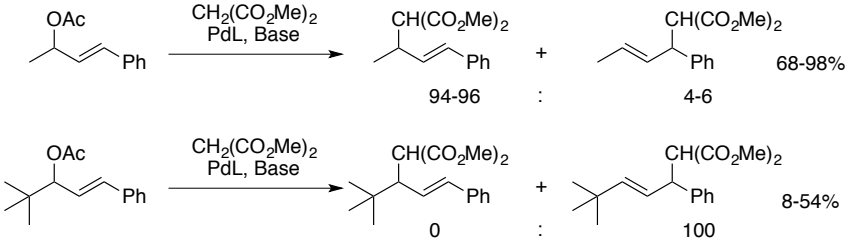


Figure 2.10 Example of Regioselectivity in Allylic Alkylation



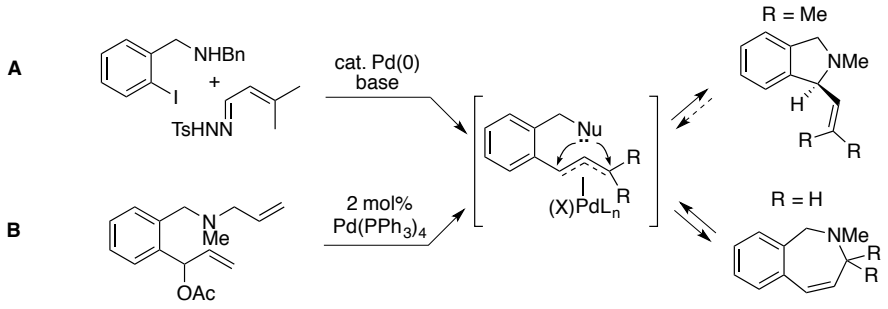
2.2.2.2 Intramolecular Carbenylation with Unsymmetrical η^3-Allylpalladium Systems

2.2.2.2.1 Formation of 5-member Isoindoline Systems with Amine Tethered Aryl Iodides and Prenyl Aldehyde *N*-Tosylhydrazones

In order to control the site of nucleophilic attack after carbene insertion, a model system was designed using a tether to constrain the nucleophile to add kinetically to the end of the η^3-allyl derived from the carbene center, generating a chiral non-conjugated product (Figure 2.11, A). This system does have the potential to form both 5- and 7-membered rings, which could be

detrimental to the desired product yield. Grellier and Pfeffer published work on intramolecular palladium-catalyzed allylic amination on a similar isoindoline system and it was found that the reaction yielded a mixture of both the 5- and 7-membered products (Figure 2.11, B).[55] It was hypothesized, the kinetic 5-membered isoindoline formed and over time isomerization occurred to generate the thermodynamic 7-membered ring product. To confirm the hypothesis Grellier and Pfeffer subjected the pure 5-membered isoindoline product to the reaction conditions and after 9.5 hours 66% had converted to the 7-membered product and after 48 hours 96% was converted. These findings by Grellier and Pfeffer have important mechanistic implications for our model system. Fortuitously only the 5-membered isoindoline was observed in our system. Due to the fact that we do not observe any thermodynamic 7-membered products we can infer that under our reaction conditions, ring opening of the product does not occur, and therefor isomerization and decreases or increases in ee is not possible following nucleophilic cyclization.

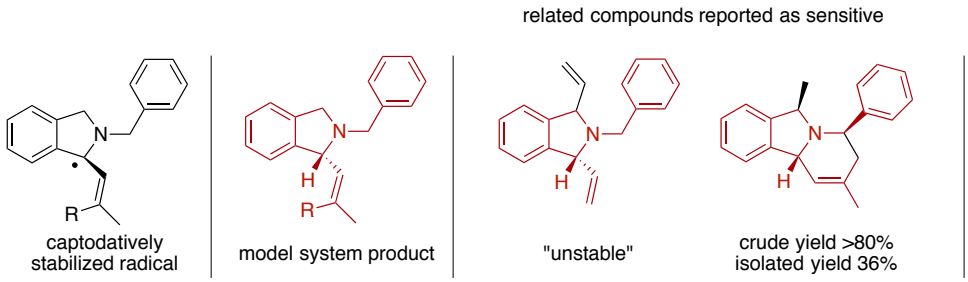
Figure 2.11 The Isoindoline Model System Proceeds Through an η^3-Allylpalladium Intermediate That Has Been Shown to Generate Both Kinetic and Thermodynamic Allylic Alkylation Products



An unanticipated characteristic of the initial model system (Table 2.2) was that the isoindoline product **6** was highly sensitive to molecular oxygen and radical decomposition, which lead to rapid decomposition within minutes if left exposed to air, particularly when dissolved in chlorinated solvents such as $CDCl_3$. The sensitivity to autoxidation is most likely

due to potential for benzylic autoxidation via a captodatively stabilized radical (Figure 2.12). Similar compounds that have been reported in literature (Figure 2.12) are also reported to be highly sensitive.[56,57]

Figure 2.12 Sensitivity of Allylic Isoindoline Systems to Aerobic Decomposition

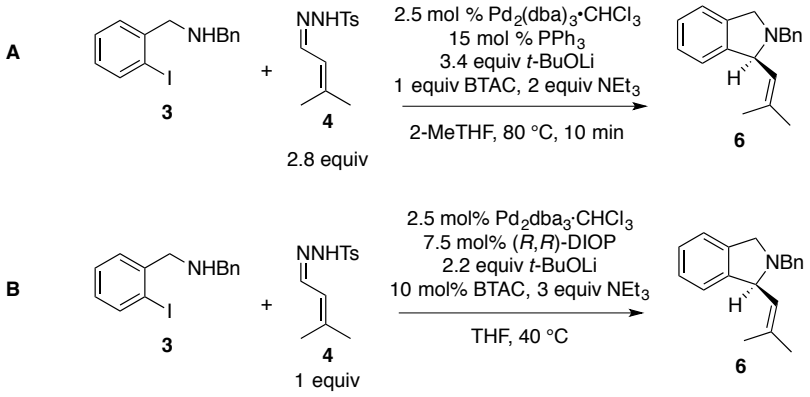


To minimize decomposition of isoindoline **6**, the crude reaction mixtures were passed through a plug of silica instead of an aqueous workup to minimize exposure to air, but isolated yields were variable and much lower than crude yields obtained by ^{1}H NMR against an internal standard. Benzene-d_6 was used instead of $CDCl_3$ for NMR spectroscopy and was compatible with a chiral salt method for determination of enantioselection.[52] An additional aspect that made handling and purification of product **6** challenging was the compound's basic, yet highly hydrophobic properties. Flash column chromatography had to be performed in 99:1 hexane/Et_2O to provide any separation and any attempt to add a TEA modifier to reduce streaking of the amine in product **6** would result in inferior separation due to increased polarity in the mobile phase.

Two sets of conditions were initially tested for the formation of isoindolines through palladium-catalyzed carbenylative cross-coupling. The first set of conditions was developed by a co-worker for carbenylative amination of amine tethered vinyl iodides and aryl hydrazones (Figure 2.13, A)[47] and the second set of conditions were the optimized conditions from the 1,3-diphenylally system (Table 2.1, entry 5) replacing piperidine with TEA and reducing the amount

of aryiodide **3** which can be monitored by TLC in this system (Figure 2.13, B). Yields for these initial reactions were not obtained due to the compound instability, which was not known at the time. Both conditions produced product by crude NMR however the milder 1,3-diphenylallyl conditions produced a much cleaner reaction with a more promising crude NMR. Once it was apparent there was product stability issues the reaction was repeated with the mild conditions and a NMR yield of 27% was obtained. Increasing the temperature to 50 °C improved the yield to 42% by NMR. Finally, removal of TEA and the addition of an extra equivalent of hydrazone **4** and *t*-BuOLi produced a 68% yield by NMR (Table 2.2, entry 1). From this point it was clear this system was not ideal due to the sensitive nature of the products so instead of further optimization it was decided to test asymmetric induction and then move onto a system with more utility.

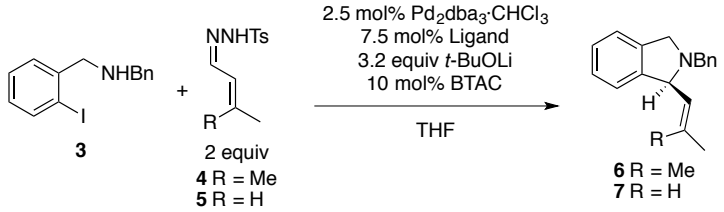
Figure 2.13 Initial Reaction Conditions for Intramolecular Vinylcarbene Insertion



(*R,R*)-DIOP provided the highest yield but it only generated 3% ee (Table 2.2, entry 1). Switching to (*S*)-BINAP greatly increased reaction time and significantly lowered yield but slightly increased ee to 11% (Table 2.2, entry 2). Encouragingly, (*S,S*)-chiraphos provided product with 30% ee (Table 2.2, entry 4). A comparison of (*S,S*)-chiraphos at room temperature, 50 °C and 70 °C demonstrated a noticeable effect on yield and ee (Table 2.2, entries 3,4 and 5). The room temperature reaction was sluggish, producing a 6% yield after 7 days and decomposed

before an ee could be determined. Using a higher temperature, 70 °C, resulted in a 51% yield and 43% ee, an 11% and 13% increase over 50 °C respectively. Unfortunately data was not obtained for (*S,S*)-chiraphos at 50 °C in MeTHF, instead of THF, and therefore the increase in yield and ee seen at 70 °C could also be due in part or in whole to the change in solvent. More importantly though, these results suggest that the right ligand and reaction conditions will be able to control the absolute stereochemistry in palladium-catalyzed carbenylative cross-coupling reactions.

Table 2.2 Results of Isoindoline Formation



Entry	Hydrazone	Ligand	Time	Temperature	NMR Yield	Isolated Yield	%ee
1	4	(*R,R*)-DIOP	5 h	50 °C	68%	43%	3%
2	4	(*S*)-BINAP	12 h	50 °C	15%	15%	11%[c]
3	4	(*S,S*)-chiraphos	7 d	r.t.[a,b]	6%	n.d.	n.d.
4	4	(*S,S*)-chiraphos	12 h	50 °C	40%	37%	30%
5	4	(*S,S*)-chiraphos	4 h	70 °C[a]	51%	29%	43%
6	5	(*S,S*)-chiraphos	19 h	50 °C	n.d.	24%	27%
7	5	(*R,R*)-DIOP	34 h	50 °C[b]	n.d.	11%	4%

[a] Reaction was carried out in MeTHF
[b] An extra equiv of *t*-BuOLi and hydrazone was added
[c] Conservative approximation due to excessive decomposition in chiral shift NMR sample

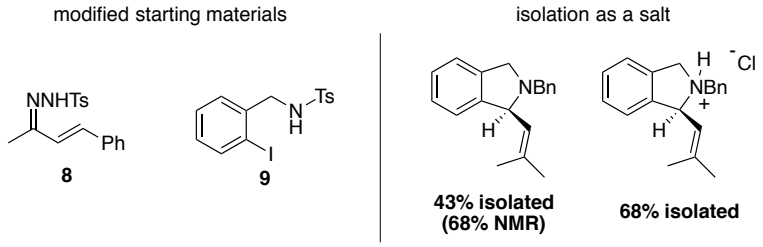
Because hydrazone **4** has a symmetric gem-dimethyl functional group we can not tell whether η^3-η^1-η^3-isomerization of the allylpalladium intermediate is erasing the stereochemistry initially set by the carbene insertion step. In order to eliminate the possibility of isomerization of palladium between enantiopic faces of the allyl fragment, *N*-tosylhydrazone **5** (Table 2.2), which generates an η^3-allylpalladium intermediate that can not isomerize through an η^3-η^1-η^3 mechanism, was synthesized from crotonaldehyde and *p*-toluenesulfonylhydrazide. With *N*-tosylhydrazone **5** the (*S,S*)-chiraphos ligand appears to out-perform the (*R,R*)-DIOP ligand in

catalyst turnover and overall amount of product generated based on reaction monitoring by TLC (Table 2.2, entries 6 and 7). This is a reverse in ligand reactivity compared to the reaction involving hydrazone **4** (Table 2.2, entries 1 and 4). Although the reaction involving the (*S,S*)-chiraphos ligand was mostly product by TLC, it was found that isoindoline product **7**, with only a single methyl substitution, was actually more sensitive to decomposition in comparison to isoindoline product **6**, which contained a gem-dimethyl substitution. With (*S*,*S*)-chiraphos, hydrazones **4** and **5** afforded products with comparable yields and ees (27-29%) consistent with carbene insertion as the origin of enantioselection for both substrates (Table 2.2, entries 4 and 6).

The extraordinary air sensitivity of the *N*-benzyl-2-vinylindoline products led us to vary the carbene precursor and nucleophile in the model reaction. In an attempt to generate products without the sensitive benzylic hydrogen atom, ketohydrazone **8** (Figure 2.14) was synthesized and employed in the carbenylation reaction. However, the ketone hydrazone failed to engage in carbenylation under the reaction conditions probably due to a competitive cyclization of the *N*-tosylhydrazone anion to a pyrazole, which has been reported.[58] Attempting to lower the radical susceptibility of the product by using a sulfonamide **9** (Figure 2.14) also failed to generate any isoindoline product under the reaction conditions. The failure of sulfonamide **9** to generate insertion product may be due to formation of a stable palladacycle.[59] Eventually, we found that addition of the radical inhibitor (BHT) during the workup and use of the solvent toluene prior to column chromatography of the *N*-benzyl-2-vinylindoline **6** minimized decomposition. Addition of ethereal-HCl to the column fractions allowed the isoindoline to be isolated as a stable HCl salt. Formation of the salt allows for isolation of product without resorting to NMR to calculate a reaction yield (Figure 2.14). Unfortunately, the HCl salt of indoline **6** exists as a mixture of diastereomers that exhibit broadened peaks by ^{1}H NMR and the dissolved salt is still sensitive to

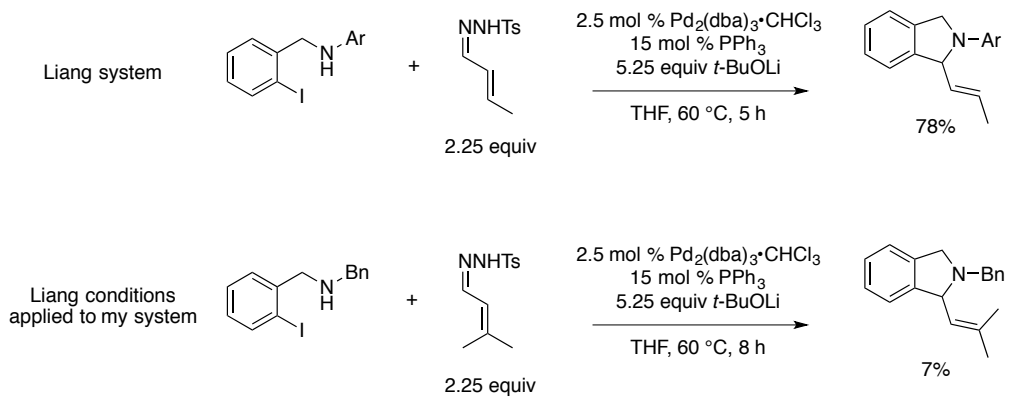
decomposition.

Figure 2.14 Attempted Modification of Starting Materials and Isolation Techniques to Address Product Decomposition



As previously mentioned, during the course of my research, Liang and co-workers published a paper on palladium-catalyzed carbenylative cross-coupling to form *N*-aniline isoindolines (*vide supra*).[35] Due to the similarity between Liang's system and my own it was pertinent to test the robustness of Liang's reaction conditions in my model system (Figure 2.15). With care to minimize decomposition I was only able to obtain a yield of 7% (NMR) with a tethered dialkylamine. It is clear that Liang's methodology cannot be directly applied to non *N*-aniline nucleophiles. Additionally, Liang's system utilizing vinyl hydrazones is shown to only generate 5-membered rings through an intramolecular nucleophilic attack and there are no examples provided for intermolecular nucleophiles or 6-membered ring formation. Furthermore, no attempt is made to control the newly formed stereocenter. My demonstration of intermolecular nucleophilic attack, the ability to control the stereochemistry of carbenylative insertion (*vide supra*), and formation of 6-membered ring systems (*vide infra*) distinguishes my methodology.

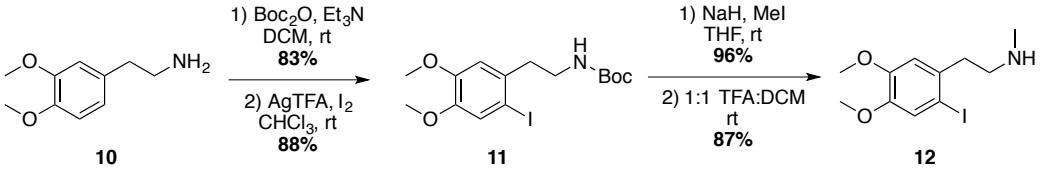
Figure 2.15 Liang's System and an Attempt to Apply it to My Model System



2.2.2.2.2 Formation of 6-member Tetrahydroisoquinoline Systems with Amine Tethered Aryl Iodides and Prenyl Aldehyde *N*-Tosylhydrazones

After demonstrating the potential for asymmetric induction in a sensitive 5-membered isoindoline system we moved on to formation of 6-membered tetrahydroisoquinolines. Tetrahydroisoquinolines are a common synthetic scaffold found frequently in natural products (Figure 2.3). Boc protection of 3,4-dimethoxyphenethylamine **10** followed by iodination with silver trifluoroacetate forms aryl iodide **11** in 88% yield (Figure 2.16). Attempted LAH reduction of Boc protected amine **11** to phenethyl-*N*-methylamine **12** led to deiodination. An alternative route of *N*-methylation of carbamate **11** followed by removal of the Boc group successfully generated aryl iodide **12** in an 87% yield.

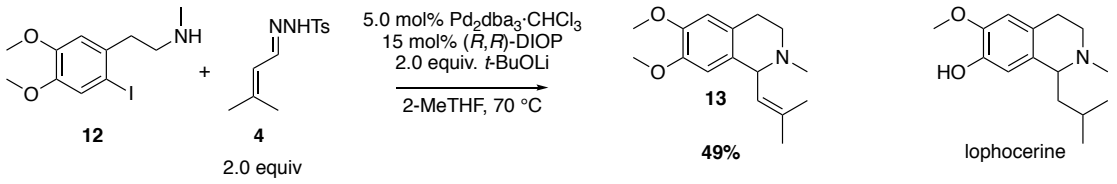
Figure 2.16 Synthesis of Tetrahydroisoquinoline Starting Material



Initially, substrate **12** was subjected to the optimized conditions for substrate **25** (Figure 3.4) *vide infra* (15% yield Boc-borrerine) and generated a chromatographically inseparable mixture of approximately 70% product and 30% of two unknown but structurally similar side

products equating to an approximate 30% yield of 7-*O*-methyl-dehydrolophocerine **13**. To ensure that the inseparable side products were not due to radical decomposition as seen with the isoindoline system, a sample of tetrahydroisoquinoline **13** was analyzed by NMR after storage for a week and no change was seen between the ratio of product and impurity peaks. Although the resulting product couldn't be fully purified, the system was still explored to gain insight into formation of 6-membered ring systems through carbenylation. Using the optimized conditions for the 5-membered cyclization to form isoindolines (Table 2.2, entry 1) without BTAC led to an approximate 40% yield, and slightly outperformed the reaction with BTAC. Increasing the temperature to 70 °C led to rapid decomposition of hydrazone **4** with little change to the aryl iodide starting material. Screening of various bases (*t*-BuOLi, *t*-BuONa, *t*-BuOK, Hünig's and DBU), amounts of base (1-3.2 equivalents) and reaction temperatures (50-110 °C, Dioxanes used instead of MeTHF for high temperatures) in order to try and match the rate of diazo formation with the rate of product formation did little to increase the yields. Switching from bidentate (*R*,*R*)-DIOP to monodentate PPh_3 led to a decrease in yield. Finally, increasing the catalyst loading from 5 mol% palladium to 10 mol% palladium provided an approximate 49% yield which is only a marginal improvement in comparison to 5 mol% (Figure 2.17).

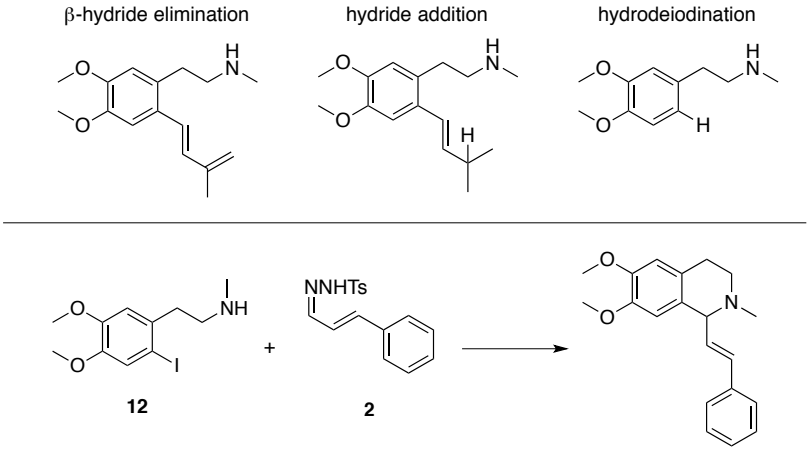
Figure 2.17 Synthesis of 7-*O*-Methyl-Dehydrolophocerine



Based on mass spectrometry and R_f data, several of the main side reactions are believed to stem from β-hydride elimination and hydridopalladium species (Figure 2.18). If the nucleophilic cyclization with the η^3-allylpalladium intermediate is slow, β-hydride elimination

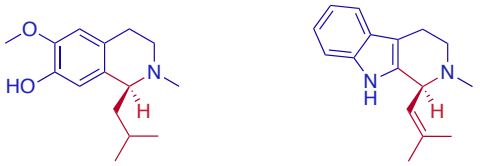
could occur leading to diene formation. Alternatively, if there is a proton source, the η^3-allylpalladium intermediate could pick up a hydride and reductively eliminate leading to a hydride addition product. Having sources of palladium hydride in the reaction would also lead to hydrodeiodination of the starting materials. To eliminate the possibility for β-hydride elimination from the η^3-allylpalladium intermediate and reduce the possible palladium hydride sources, cinnamyl hydrazone **2**, which contains no β-hydrogens, was used (Figure 2.18). The use of a hydrazone without β-hydrogens appeared to curb hydrodeiodination as there was still aryl iodide **12** present at the end of the reaction following consumption of two batches of hydrazone. Unfortunately, cinnamyl hydrazone **12** failed to effectively engage in the reaction generating a minimal amount of product.

Figure 2.18 Suspected Side Products and Attempted Circumvention



Having developed adequate insight and experience with 6-membered ring formation in this tetrahydroisoquinoline model system, which provides access to the skeleton of natural products such as lophocerine, we moved on to a more challenging application towards the synthesis of the natural product borrerine (Figure 2.19).

Figure 2.19 Alkaloids Accessible Through Intramolecular Carbenylative Cross-Coupling



2.3 Conclusion

In conclusion, we have demonstrated that *N*-tosylhydrazones derived from α,β-unsaturated aldehydes – precursors to vinylcarbenes – can be successfully employed in both intermolecular and intramolecular palladium-catalyzed carbenylative cross-coupling and carbenylative amination reactions with aryl iodides to form η^3-allylpalladium intermediates that generate stereogenic centers at the carbene center. By intercepting known 1,3-diphenylallylpalladium intermediates through carbenylative insertion, we were able to produce ees that are comparable to palladium-catalyzed allylic alkylations. With an isoindoline model system we established that kinetic 5-membered ring formation is preferred over thermodynamic 7-membered ring formation and that under our reaction conditions the cyclization is not reversible. Evidence was given for chirality being set during migratory insertion and promising ees were achieved indicating that selection of the right chiral ligand and reaction conditions could lead to high ees. Furthermore, the scope of the reaction was expanded to include 6-member cyclization to generate tetrahydroisoquinolines, which map onto natural products. Though the 6-membered cyclizations proved much more challenging than intermolecular or 5-member cyclization we believe that the reaction could be sufficiently optimized through removal of hydride sources, speeding up the sluggish cyclization and tuning the rate of diazo formation. These results are an important proof of concept for asymmetric palladium-catalyzed carbenylative amination and carbenylative cross-coupling in both inter- and intramolecular

systems. The development of palladium-catalyzed carbenylative cross-coupling and carbenylative amination reactions with α,β-unsaturated *N*-tosylhydrazones and amine nucleophiles presented in this thesis set the stage for further palladium-catalyzed vinyl carbene insertion reactions.[35,47,48,60]

2.4 Experimental

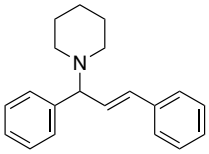
General. NMR spectral data were recorded using either a Bruker 500 or 600 MHz spectrometer. The NMR data are reported as follows: chemical shift in ppm from an internal tetramethylsilane standard on the δ scale, multiplicity (br = broad, app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constants (Hz), and integration. If the tetramethylsilane signal could not be referenced the residual proton found in the NMR solvent was used (^{1}HNMR $CDCl_3$: δ 7.26 ($CHCl_3$), C_6D_6: δ 7.16 (C_6D_5H); ^{13}CNMR $CDCl_3$: δ 77.16 ($CHCl_3$), C_6D_6: δ 128.06 (C_6D_5H)). Analytical thin layer chromatography was performed using EM Reagents 0.25 mm silica gel 60-F plates. When triethylamine was used as a co-eluent for thin layer chromatography, the plates were briefly pre-soaked in the eluent and allowed to dry for a few minutes before spotting with analyte. All reactions were carried out under an atmosphere of nitrogen in glassware that had been flame-dried under a stream of nitrogen or in glassware that had been flame-dried under vacuum. Unless otherwise noted, all reagents were commercially obtained and, where appropriate, purified prior to use. (*S*)-BINAP(S),[61] **2**,[62] **3**,[63] **9**,[64] and **11**[65] were synthesized according to reported literature procedures. (*S*)-BINAP(S),[66] **2**,[62] **3**,[63] **9**,[67] and **11**[65] had spectroscopic data consistent with published values.

Determination of Enantiomeric Excess

Enantiomeric excess (%ee) was determined for compounds **1**, **6**, and **7** by ^{1}H NMR using a chiral shift reagent.[52,68] To purified product (**1**, **6**, or **7**) 1.0 equiv of (*R*)-(+)-MTPA or (*S*)-(–)-MTPA

was added and the mixture was dissolved in C_6D_6. The resulting solution of diastereomeric salts were then analyzed by NMR spectroscopy. Spectra were acquired at elevated temperature (308 K when using the 500 MHz spectrometer and 318 K with the 600 MHz spectrometer) to improve resolution between diagnostic diastereomeric peaks. A diagnostic signal corresponding to the methine proton adjacent nitrogen was used for comparison of integrals. In order to increase the accuracy and reproducibility of integration, both diastereomeric protons were integrated as one integral and software peak deconvolution was used to determine the individual peak contributions. The ratio between the two peak areas was then used to calculate a %ee.

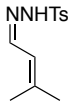
(*E*)-1-(1,3-Diphenylallyl)piperidine, 1.



A 5 mL round-bottom flask was charged with (*R,R*)-DIOP (3.8 mg, 0.0076 mmol, 7.6 mol%), Pd_2dba_3•$CHCl_3$ (2.6 mg, 0.0025 mmol, 2.5 mol%) and THF (0.2 mL). The mixture was stirred under nitrogen for approximately 20 minutes until a clear orange solution was obtained. A separate 5 mL round-bottom flask was charged with *N*-tosylhydrazone **2** (30.5 mg, 0.102 mmol, 100 mol%), iodobenzene (22.4 µL, 0.201 mmol, 197 mol%), *t*-BuOLi (17.9 mg, 0.224 mmol, 220 mol%), BTAC (22.4 mg, 0.0983 mmol, 96.4 mol%) and piperidine (29.6 µL, 0.300 mmol, 294 mol%). The catalyst solution was transferred by syringe into the flask containing **2**; an additional 0.8 mL of THF was used to ensure complete transfer. The reaction mixture was placed into an oil bath at 40 °C and monitored by TLC. After 5 h the reaction was diluted with 1% (w/v) $NaOH_{(aq)}$ and extracted with EtOAc (3×), washed with brine, dried over $MgSO_4$ then concentrated *in vacuo* to obtain a yellow oil (34.9 mg). The crude material was further purified by flash column chromatography using hexanes/EtOAc/AcOH (70:27:3) followed by

hexanes/EtOAc (70:30) and finally hexanes/EtOAC/TEA (70:27:3) to obtain allylamine **1** as a yellow oil (16.0 mg, 0.0577 mmol, 57%). R_f = 0.44 (70:30 hexanes/EtOAc) ^{1}H NMR (600 MHz, C_6D_6) δ 7.50 (d, *J* = 7.6 Hz, 2H), 7.23 (t, *J* = 7.5 Hz, 2H), 7.18 (d, *J* = 7.5 Hz, 2H), 7.10 (t, *J* = 7.3 Hz, 1H), 7.07 (t, *J* = 7.4 Hz, 2H), 7.02 (appt, *J* = 7.2 Hz, 1H), 6.49 (d, *J* = 15.8 Hz, 1H), 6.40 (dd, *J* = 15.8, 8.6 Hz, 1H), 3.80 (d, *J* = 8.5 Hz, 1H), 2.48 (bs, 2H), 2.36 (bs, 2H), 1.52 (bs, 4H), 1.32 (bs, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 141.7, 137.1, 131.61, 131.53, 128.65, 128.63, 128.33, 127.56, 127.31, 126.5, 74.7, 52.6, 25.9, 24.6; MS (ESI) *m* / *z* calcd for $C_{20}H_{23}NH$ $(M + H)^+$ 278.2, found 277.7.

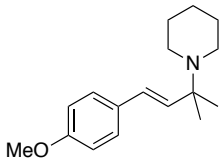
4-Methyl-*N*'-(3-methylbut-2-en-1-ylidene)benzenesulfonohydrazide, 4.[62]



A 100 mL round-bottom flask was charged with *p*-toluenesulfonyl hydrazide (15.4 g, 82.7 mmol, 100 mol%) and MeOH (40 mL). The heterogeneous mixture was stirred vigorously at 40 °C and 3-methyl-2-butenal (7.96 mL, 82.5 mmol, 100 mol%) was added by syringe. The reaction turned clear yellow upon addition. The flask was removed from the oil bath and placed in a -20 °C freezer. After 3 h, a white precipitate had formed. The precipitate was collected by vacuum filtration followed by washing with cold MeOH. The product was recrystallized from hot EtOH, filtered and washed with cold EtOH to obtain an off-white solid. The solid was dissolved in DCM and transferred to a tared recovery flask. Concentration *in vacuo* provided *N*-tosylhydrazone **4** (8.36 g, 33.1 mmol, 40%) of off-white solid. R_f = 0.33 (70:30 hexanes/EtOAc) ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.73 (bs, 1H), 7.70 (d, *J* = 9.7 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 2H), 5.92 (dm, *J* = 9.7, Hz, 1H), 2.42 (s, 3H), 1.83 (s, 3H), 1.79 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.9, 146.1, 144.1, 135.4, 129.7, 127.9, 121.3, 26.5, 21.6, 18.8; IR (thin film) 3053, 2985, 2684, 2305, 1644 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{16}N_2O_2SNa$ (M +

$Na)^+$ 275.0830, found 275.0833.

(*E*)-1-(4-(4-Methoxyphenyl)-2-methylbut-3-en-2-yl)piperidine, 5.



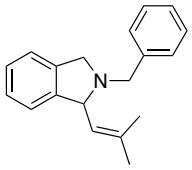
A 5 mL round bottom flask was charged with (*R,R*)-DIOP (7.4 mg, 0.015 mmol, 7.4 mol%), Pd_2dba_3•$CHCl_3$ (5.4 mg, 0.0052 mmol, 2.5 mol%) and THF (1.0 mL). The mixture was stirred under nitrogen for approximately 20 minutes until a clear orange solution was obtained. A separate 5 mL round-bottom flask was charged with *N*-tosylhydrazone **4** (50.2 mg, 0.199 mmol, 100 mol%), 4-iodoanisole (46.5 mg, 0.199 mmol, 100 mol%), *t*-BuOLi (34.8 mg, 0.435 mmol, 219 mol%), BTAC (4.8 mg, 0.021 mmol, 11 mol%) and piperidine (60 μL, 0.61 mmol, 310 mol%). The catalyst solution was transferred by syringe into the flask containing **4**; an additional 1.0 mL of THF was used to ensure complete transfer. The reaction mixture was placed into an oil bath at 40 °C and monitored by TLC. After 4 h the reaction was diluted with 1% (w/v) $NaOH_{(aq)}$ and extracted with EtOAc (3×), washed with brine, dried over $MgSO_4$ then concentrated *in vacuo* to obtain a yellow oil (97.5 mg). The crude material was further purified by flash column chromatography using hexanes/EtOAc (70:30) followed by hexanes/EtOAc/TEA (67:30:3) to obtain allylamine **5** as a yellow oil (14.9 mg, 0.0574 mmol, 29%). R_f = 0.13 (94:5:1 hexanes/EtOAc/TEA) ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 6.30 (d, *J* = 16.4 Hz, 1H), 6.17 (d, *J* = 16.3 Hz, 1H), 3.80 (s, 3H), 2.54 (bs, 4H), 1.58 (quintet, *J* = 5.4 Hz, 4H), 1.41 (bs, 2H) 1.22 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 130.3, 127.4, 126.9, 114.1, 55.3, 47.5, 26.6, 24.8, 23.0; by HMQC it is apparent that one of the alkene carbons is in the baseline of the spectrum at approximately 136 ppm. The quaternary carbon alpha to nitrogen is believed to also be in the baseline around 59 ppm; IR (thin film)

2931, 1607, 1551, 1512, 1247 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{25}NOH$ $(M + H)^+$ 260.2014, found 260.2007.

General procedure to form isoindoline through carbenylative cross-coupling

A round bottom flask containing a magnetic stir bar, $Pd_2(dba)_3$•$CHCl_3$ (2.5 mol%), and bidentate ligand (7.5 mol%) was placed under nitrogen and charged with 200 μL THF. The mixture was stirred at 50 °C until a clear orange solution was obtained (approximately 5 min). A separate round bottom flask, containing a magnetic stir bar, was charged with aryl iodide **3** (0.165 mmol, 100 mol%), *N*-tosylhydrazone (0.330 mmol, 200 mol%), *t*-BuOLi (0.528 mmol, 320 mol%) and BTAC (0.0165 mmol, 10 mol%) under nitrogen. The catalyst solution was transferred by syringe into the flask containing aryl iodide; an additional 0.8 mL of THF was used to ensure complete transfer. The reaction mixture was placed into an oil bath at 50 °C and monitored by TLC. Once finished by TLC the reaction was passed through a plug of silica using EtOAc and concentrated *in vacuo*. Further purification by flash column chromatography using the designated solvent system afforded isoindole product.

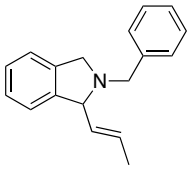
2-Benzyl-1-(2-methylprop-1-en-1-yl)isoindoline, 6.



Isoindoline **6** was synthesized according to the general procedure for isoindoline formation using Pd_2dba_3•$CHCl_3$ (4.0 mg, 0.0039 mmol, 2.4 mol%), (*S,S*)-chiraphos (5.3 mg, 0.012 mmol, 7.8 mol%), **3** (51.5 mg, 0.159 mmol, 100 mol%) and *N*-tosylhydrazone **4** (81.4 mg, 0.323 mmol, 203 mol%). The product was purified by flash chromatography (95:5 hexanes/ethyl ether) to obtain isoindoline **6** as a yellow oil, approximately 95% pure by ^1H NMR (15.3 mg, 0.0581 mmol, 37%). R_f = 0.82 (70:30 hexanes/EtOAc) ^1H NMR (500 MHz, C_6D_6) δ 7.41 (d, *J* = 7.6 Hz, 2H),

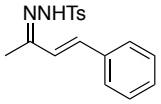
7.22 (t, J = 7.5 Hz, 2H), 7.15–7.06 (m, 4H), 6.93 (d, J = 7.1 Hz, 1H), 5.49 (d, J = 8.9 Hz, 1H), 4.51 (d, J = 8.8 Hz, 1H), 4.19 (d, J = 13.1, Hz 1H), 4.00 (d, J = 12.6 Hz, 1H), 3.37 (d, J = 12.5 Hz, 1H), 3.37 (d, J = 13.2 Hz, 1H), 1.68 (s, 3H) 1.65 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 144.1, 140.5, 140.4, 135.6, 129.1, 128.5, 127.2, 127.1, 126.89, 126.88, 122.8, 122.5, 67.4, 58.0, 57.7, 26.0, 18.2; IR (thin film) 2388, 2279, 1618, 1453 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{21}NH$ $(M + H)^+$ 264.1752, found 264.1754.

(*E*)-2-Benzyl-1-(prop-1-en-1-yl)isoindoline, 7.



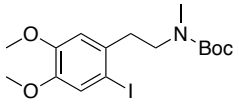
Isoindoline **7** was synthesized according to the general procedure for isoindoline formation using Pd_2dba_3•$CHCl_3$ (4.9 mg, 0.0047 mmol, 2.5 mol%), (*S,S*)-chiraphos (6.0 mg, 0.014 mmol, 7.4 mol%), **3** (61.1 mg, 0.189 mmol, 100 mol%) and *N*-tosylhydrazone **5** (92.0 mg, 0.386 mmol, 204 mol%). The product was purified by flash chromatography (97:3 hexanes/EtOAc) to obtain isoindoline **7** as a yellow oil, approximately 95% pure by ^{1}H NMR (11.5 mg, 0.0581 mmol, 24%). R_f = 0.83 (70:30 hexanes/EtOAc); ^{1}H NMR (500 MHz, C_6D_6) δ 7.40 (d, J = 7.6 Hz, 2H), 7.22 (t, J = 7.5 Hz, 2H), 7.13–7.05 (m, 4H), 6.92 (d, J = 7.2 Hz, 1H), 5.69–5.58 (m, 2H), 4.22 (d, J = 13.2 Hz, 1H), 4.15 (bs, 1H), 3.99 (d, J = 12.7 Hz, 1H), 3.38 (dd, J = 12.9, 2.5 Hz 1H), 3.34 (d, J = 13.2 Hz, 1H), 1.60 (d, J = 4.8 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 143.7, 140.4, 140.1, 132.8, 129.3, 129.0, 128.6, 128.3, 127.3, 127.1, 126.9, 123.0, 122.5, 72.5, 57.7, 57.6, 17.9; IR (thin film) 2293, 2253, 1636, 1443 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{19}NH$ $(M + H)^+$ 250.1596, found 250.1591.

4-Methyl-*N*'-((2*E*,3*E*)-4-phenylbut-3-en-2-ylidene)benzenesulfonohydrazide, 8.



A 100 mL round-bottom flask was charged with *p*-toluenesulfonyl hydrazide (2.55 g, 13.7 mmol, 100 mol%) and MeOH (20 mL). The mixture was stirred vigorously at 40 °C followed by addition of *trans*-4-phenyl-3-buten-2-one (2.00 g, 13.7 mmol, 100 mol%). The reaction turned clear yellow and solids slowly began to precipitate. After one hour an additional batch of *p*-toluenesulfonyl hydrazide (0.0558 g, 0.300 mmol, 2.2 mol%) was added and allowed to react for an additional hour. The reaction was filtered, rinsed with cold MeOH and dried *in vacuo* to obtain solid *N*-tosylhydrazone **8** (4.00 g, 12.7 mmol, 93%). R_f = 0.13 (70:30 hexanes/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.2 Hz, 2H), 7.84 (s, 1H), 7.43 (d, *J* = 7.4 Hz, 2H), 7.35–7.32 (m, 4H), 7.28 (d, *J* = 7.1 Hz, 1H), 6.83 (s, 2H), 2.42 (s, 3H), 1.99 (s, 3H) 1.62 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 144.2, 136.0, 135.3, 134.0, 129.7, 128.8, 128.7, 128.4, 128.0, 127.0, 21.6, 11.3; MS (ESI) *m*/*z* calcd for $C_{17}H_{18}N_2O_2SH$ $(M + H)^+$ 315.1, found 315.1.

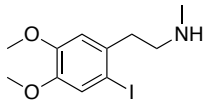
***tert*-Butyl (2-iodo-4,5-dimethoxyphenethyl)(methyl)carbamate, S1.**



A 100 mL pear-shaped flask was charged with aryl iodide **11** (1.52 g, 3.73 mmol, 100 mol%), sodium hydride (60%) (304 mg, 7.60 mmol, 204 mol%) and THF (15 mL). While stirring, methyl iodide (0.70 mL, 11.2 mmol, 300 mol%) was added by syringe. After 9 hours the reaction was quenched by slow addition of H_2O, diluted with brine and extracted with Et_2O (3×). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give 1.66 g of yellow oil. Further purification by flash column chromatography using pentane/EtOAc (85:15) provided *N*-Boc-aryl iodide **S1** as a clear oil (1.51 g, 3.58 mmol, 96%) R_f = 0.26 (80:20 pentane/EtOAc)

Rotamers due to the *N*-Boc group were observed by NMR leading to broad peaks. ^{1}H NMR (600 MHz, 434 K, C_6D_6) δ 7.19 (s, 1H), 6.65 (bs, 1H), 3.44 (s, 3H), 3.39 (bs, 2H), 3.30 (s, 3H), 2.87 (bs, 2H), 2.71 (s, 3H), 1.44 (s, 9H); MS (ESI) *m*/*z* calcd for $C_{16}H_{24}INO_4Na$ $(M + Na)^+$ 444.1, found 443.8.

2-(2-Iodo-4,5-dimethoxyphenyl)-*N*-methylethan-1-amine, 12.



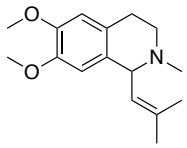
A 200 mL pear-shaped flask was charged with *N*-Boc-aryl iodide **S1** (1.49 g, 3.54 mmol) and DCM (5 mL). While stirring, TFA/DCM (50:50, 17.5 mL) was added by syringe. After 40 minutes the reaction was diluted with toluene and concentrated *in vacuo* (3×). 1 M $NaOH_{(aq)}$ was added to the salt and the solution was extracted with EtOAc (2x). The combined organic layer was washed with brine, dried over anhydrous K_2CO_3 and concentrated *in vacuo* to provide 1.24 g of yellow oil. Flash column chromatography using toluene/MeOH/TEA (90:5:5) provided aryl iodide **12** as a yellow oil that solidified over several days (987.5 mg, 3.07 mmol, 87%). R_f = 0.20 (90:5:5 toluene/MeOH/TEA); ^{1}H NMR (600 MHz, C_6D_6) δ 7.17 (s, 1H), 6.59 (s, 1H), 3.32 (s, 3H), 3.19 (s, 3H), 2.84 (t, *J* = 7.2 Hz, 2H), 2.72 (t, *J* = 7.3 Hz, 2H), 2.26 (s, 3H) 0.65 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.4, 149.2, 135.7, 122.6, 113.8, 88.6, 55.51, 55.49, 52.7, 41.1, 36.6.

General procedure for the carbenylative coupling to form 7-*O*-methyl-dehydrolophocerine, 13

A round bottom flask containing a magnetic stir bar, $Pd_2(dba)_3$•$CHCl_3$ (0.005 mmol, 5 mol%), and bidentate ligand (0.015 mmol, 15 mol%) was placed under nitrogen and charged with 300 µL MeTHF. The mixture was stirred at 70 °C until a clear orange solution was obtained (approximately 5 min). A separate round bottom flask, containing a magnetic stir bar, was

charged with aryl iodide **12** (0.10 mmol, 100 mol%), *N*-tosylhydrazone (0.20 mmol, 200 mol%) and *t*-BuOLi (0.20 mmol, 200 mol%) under nitrogen. The catalyst solution was transferred by syringe into the flask containing aryl iodide; an additional 0.7 mL of THF was used to ensure complete transfer. The reaction mixture was placed into an oil bath at 70 °C and monitored by TLC. Once finished by TLC the reaction mixture was diluted with EtOAc and 1% (w/v) $NaOH_{(aq)}$ followed by extraction with EtOAc (3×). The combined organic layer was sequentially washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography using hexane/EtOAc/TEA (70:25:5) affords an inseparable mixture of product and related substance impurity.

6,7-Dimethoxy-2-methyl-1-(2-methylprop-1-en-1-yl)-1,2,3,4-tetrahydroisoquinoline, (7-*O*-methyl-dehydrolophocerine) 13.



Following the general procedure, (*R,R*)-DIOP (7.5 mg, 0.015 mmol, 15 mol%), Pd_2dba_3•$CHCl_3$ (5.3 mg, 0.0051 mmol, 5 mol%), aryl iodide **12** (32.2 mg, 0.100 mmol, 100 mol%), *t*-BuOLi (16.2 mg, 0.202 mmol, 202 mol%) and *N*-tosylhydrazone **4** (50.7 mg, 0.201 mmol, 200 mol%) were monitored by TLC and at 8 hours an additional batch of *N*-tosylhydrazone **4** (25.7 mg, 0.102 mmol, 100 mol%) and *t*-BuOLi (8.4 mg, 0.105 mmol, 105 mol%) was added. After an additional 2 hours, work-up and purification by flash chromatography resulted in 7-*O*-methyl-dehydrolophocerine **13** as an oil (15.9 mg, 0.0487 mmol, 49%, yield based on the sample being approximately 80% pure by NMR). R_f = 0.15 (80:20:3 hexanes/EtOAc/TEA); ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.57 (s, 1H), 6.49 (s, 1H), 5.15 (d, J = 9.7 Hz, 1H), 3.93 (d, J = 9.6 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.07–2.99 (m, 2H), 2.68–2.64 (m, 1H), 2.54–2.50 (m, 1H), 2.38 (s, 3H),

1.85 (s, 3H) 1.83 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 147.5, 147.1, 134.8, 129.7, 127.1, 126.4, 111.2, 110.6, 63.1, 55.92, 55.86, 52.1, 44.0, 29.0, 25.9, 18.4; MS (ESI) *m* / *z* calcd for $C_{16}H_{23}NO_2H$ $(M + H)^+$ 262.2, found 262.2.

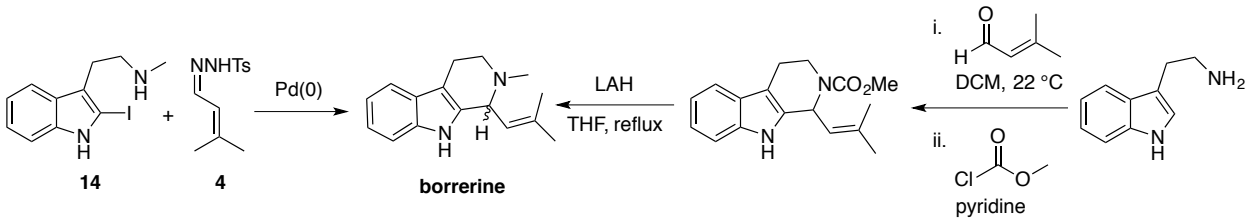
Chapter 3

Palladium-Catalyzed Carbenylative Cross-Coupling and Carbenylative Amination with Vinylcarbenes: Synthesis of *N*-Boc-Borrerine

3.1 Introduction

After gaining experience with palladium-catalyzed carbenylative cross-coupling in several model systems, we set out to apply vinylcarbene insertion directly to a target of interest. Borrerine seemed like a logical target, potentially allowing for an asymmetric alternative to the Pictet-Spengler reaction (Figure 3.1).[69] However, the need to employ a potentially sensitive 2-iodoindole introduced additional risks. Formation of the desired 2-iodo-*N*-methyltryptamine proved exceedingly problematic and only a few of the attempted routes are discussed below. *N*-Protected 2-iodotryrptamines are common in synthesis but unprotected 2-iodotryptamines are rare.

Figure 3.1 Carbenylative Cross-Coupling to Form Borrerine in Comparison to Pictet-Spengler



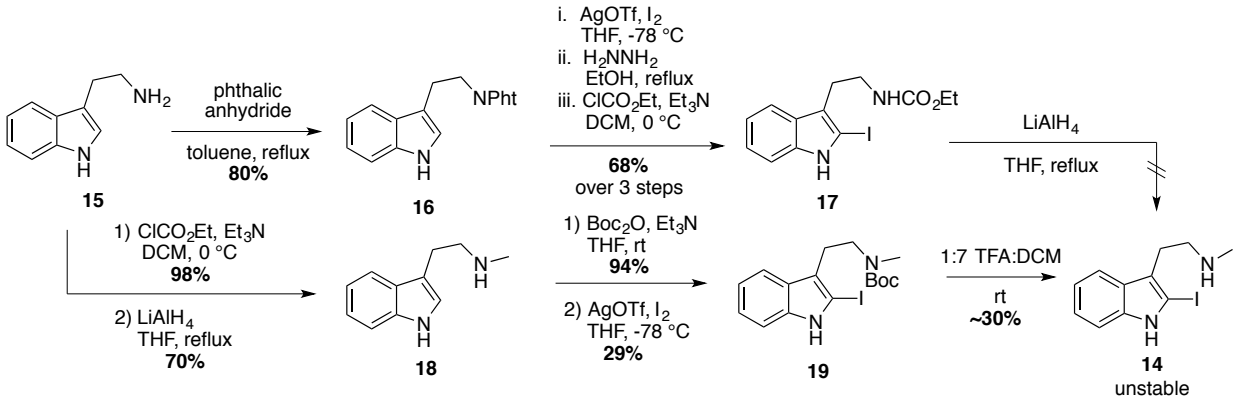
3.2 Results and Discussion

3.2.1 Initial Attempt to Synthesize 2-Iodo-*N*-methyltryptamine

One attempt to synthesize 2-iodo-*N*-methyltryptamine **14** started with the protection of tryptamine **15** as the phthalimide followed by iodination with silver triflate and molecular iodine, the resulting 2-iodotryptamine was deprotected with hydrazine and acylated with ethyl chloroformate to give **17** in 68% yield over 3 steps (Figure 3.2). During the iodination step it was found to be crucial to add sub-stoichiometric amounts of iodine and silver triflate in order to

prevent over-iodination, this is especially important as the mono- and diiodinated products were found to be inseparable by flash chromatography. Attempts to reduce carbamate **17** to the desired *N*-methylamine **14** using $LiAlH_4$ led to complete deiodination. Tosyl protection of the indole nitrogen of **17** before $LiAlH_4$ reduction also led only to deiodinated material. From this it was apparent that methylation needed to be carried out before iodination. A route to **14** that was successful started with the two-step synthesis of *N*-methyltryptamine **18** in a 70% yield. Boc protection of **18** followed by iodination with silver triflate and molecular iodine provided iodoindole **19** in moderate yield due to partial Boc deprotection by the triflic acid by-product. Deprotection of the Boc group on **19** was accompanied by partial proto-deiodination indicating that the product is acid sensitive. Once purified, the unprotected 2-iodo-*N*-methyltryptamine **14** is unstable; decomposition occurs *in vacuo* even when protected from light. The unprotected 2-iodo-*N*-methyltryptamine **14** was too sensitive for use as a substrate in our palladium-catalyzed carbenylation reaction.

Figure 3.2 Synthetic Routes to Sensitive 2-Iodo-*N*-methyltryptamine

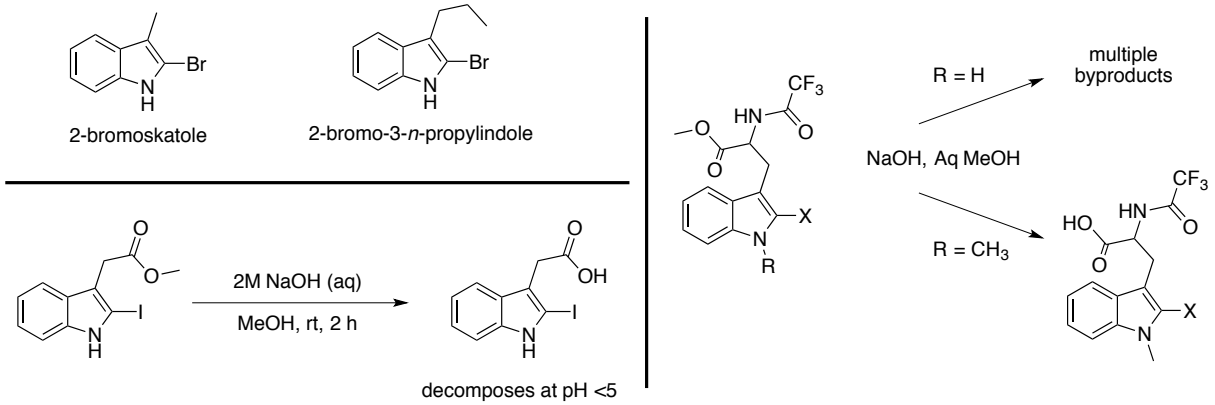


3.2.2 Haloindole Sensitivity

Numerous examples of 2-haloindoles can be found in the literature that discusses the sensitivity and the difficulties encountered during their synthesis. Simple bromoindoles are

reported to be unstable and undergo gradual decomposition on standing which is accelerated by light or acid.[70] Of note, 2-bromoskatole (Figure 3.3) could only be crystallized without decomposition after sublimation and needed to be stored in the dark, under nitrogen at -20 °C. The related 2-bromo-3-*n*-propylindole (Figure 3.3) could not be purified and attempts to distil led to decomposition. Unsworth and co-workers noted that for the workup of 2-iodoindole-3-acetic acid (Figure 3.3) careful control of pH (>5) was needed to prevent acid catalyzed decomposition.[71] In addition to 2-haloindoles being acid sensitive, they are also sensitive to base decomposition. Cohen and co-workers demonstrated that the ability to deprotonate the indole hydrogen of a 2-haloindole greatly increased its susceptibility to base decomposition (Figure 3.3).[72] By replacing the indole *N*-H with a *N*-methyl group they were able to successfully carry out a basic ester hydrolysis on 2-haloindole substrates.

Figure 3.3 Sensitivities of 2-Haloindoles



3.2.3 Route to Stable Boc-Protected 2-Iodo-*N*-methyltryptamine

Recognizing the sensitivity of 2-iodo-*N*-methyltryptamines, a route was formulated to synthesize the Boc-protected indole substrate **22** (Figure 3.4). Although the use of a Boc-indole protected substrate was less than ideal due to increase in sterics so close to the site of palladium reactivity, it was deemed a necessary risk in order to probe the application of carbenylation to

borrerine. Stewart and co-workers had previously carried out a palladium-catalyzed domino Heck-aza-Michael reaction on a Boc-protected 2-bromo-*N*-tosyltryptamine in high yields (Figure 3.5),[73] which is very similar to our target substrate **22** and indicates that a bulky ortho Boc group does not preclude oxidative addition or migratory insertion. Starting from *N*-methyltryptamine **18**, NsCl protection followed by iodination led to **20** in 85% yield. Subsequent protection of the indole nitrogen with Boc anhydride led to **21** in a 99% yield. *N*-Nosyl deprotection of **21** with thiophenol and cesium carbonate led to secondary amine **22** with highly variable yields between 5-40% due to formation of two major byproducts, the oxindole **23** and the protodeiodinated indole **24** (Figure 3.4). These byproducts might be due to the bicarbonate and/or hydroxide arising from the base but alternatives to cesium carbonate were not effective. In an attempt to eliminate both possible sources of byproducts, the reaction was performed by pre-forming the thiolate anion with sodium hydride prior to addition of indole **21**. This combination seemed to generate one product as indicated by thin layer chromatography, but the workup ultimately generated a mixture similar to that obtained with cesium carbonate and thiophenol. Numerous workup conditions were tested however none provided a greater yield of the iodoindole **22**.

Figure 3.4 Synthetic Route to Stable Substrate for Borrerine

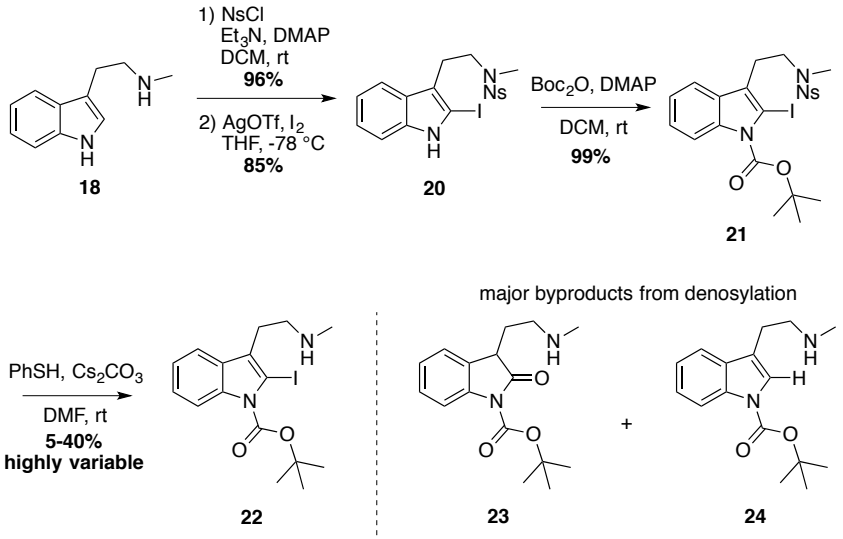
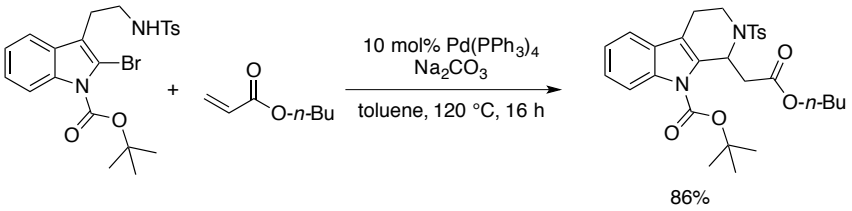


Figure 3.5 Example of Palladium Chemistry Next to a Sterically Demanding Boc Group



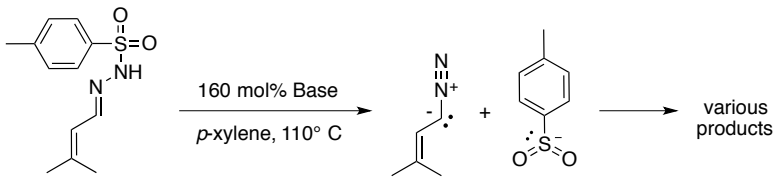
3.2.4 Synthesis of *N*-Boc-Borrerine Through Carbenylative Cross-Coupling

Although the yield for **22** was low, enough material was obtained to perform palladium-catalyzed carbenylative cyclizations (Figure 3.1). Initially the reaction was executed under conditions similar to those optimized for the 5-member ring: 50 °C, MeTHF (instead of THF), 100 mol% BTAC (instead of 10 mol%) (Table 2.2). Under these conditions no significant reaction was seen after four hours at 50 °C. The temperature was increased to 60 °C for another four hours and under these conditions the reaction was not consuming hindered aryl iodide **22** even though hydrazone **4** was being depleted. There are several reasons that the aryl iodide is failing to engage the reaction, sluggish oxidative addition and attack of the palladium by diazo compound, slow 6-membered cyclization and large steric demands due to two ortho groups, one of which is a very bulky Boc group. In an attempt to overcome these barriers the temperature was increased to reflux, 80 °C, and the reaction was complete within 30 min, consuming both of the starting materials. Unfortunately, this led to primarily unproductive pathways that led to only a small amount (<5%) of the desired product, *N*-Boc-borrerine **25** as seen by NMR. We attempted to decrease the amount of BTAC ($BnNEt_3Cl$) to 10 mol% and the temperature to 70 °C in an effort to slow the hydrazone decomposition rate significantly and shut down unproductive diazo side reactions. Slowing down the rate of hydrazone decomposition provided a 13% yield of *N*-Boc-borrerine **25**.

The rate of *N*-tosylhydrazone decomposition via the Bamford-Stevens reaction can be

modified in a variety of ways: changing the concentration of phase transfer catalyst BTAC, altering temperature, using bases with differing solubility or strength and through solvent selection based on polarity. An independent study was carried out to determine the effect of base on *N*-tosylhydrazone decomposition (Table 3.1) in the hopes of being able to fine-tune the rate of diazo formation in our reaction. Using *p*-xylene at 110 °C for this experiment, the *t*-BuOLi, which was slightly soluble, reacted the fastest showing *N*-tosylhydrazone consumption within 15 minutes (Table 3.1, entry 2) potentially due to lithium coordination to the tosyl group stabilizing its ionization. *t*-BuOK which was also slightly soluble was moderately slower (1-2 hours, Table 3.1 entry 3) than the lithium counterpart, possibly due to weaker coordination of the tosyl group. Interestingly, the *t*-BuOK reaction generated a different distribution of byproducts, the majority of which were more polar than the byproducts seen with the other bases. Carbonate bases were all insoluble and a reverse in reaction rates compared to *t*-butoxide was seen with potassium carbonate reacting much faster compared to lithium carbonate (Table 3.1, entries 4 and 7). The reversal in activity can be attributed to solubility, due to not having a solubilizing organic functionality the lithium remains tightly bound to the insoluble carbonate whereas the potassium and cesium ions are more naked allowing for more facile deprotonation. Using a soluble non-nucleophilic amine base, DBU, kept the entire reaction in solution and was equivalent to sodium carbonate (Table 3.1, entries 6 and 8).

Table 3.1 Base Effects on Bamford-Stevens *N*-Tosylhydrazone Decomposition

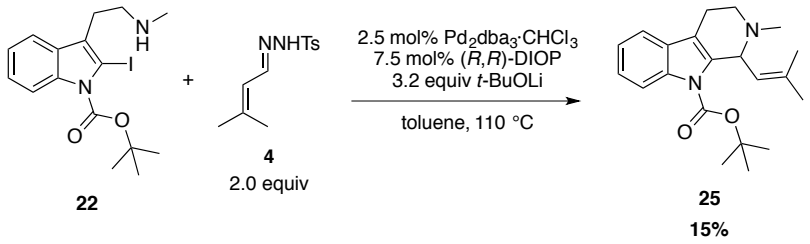


Entry	Base	Solubility of Hydrazone Species	Time Until >90% Consumption
1	None	N/A	>24 h
2	*t*-BuOLi	Slightly Soluble	10-15 min
3	*t*-BuOK[a]	Slightly Soluble	1-2 h
4	K_2CO_3	Insoluble	1 h
5	Cs_2CO_3	Insoluble	1 h
6	Na_2CO_3	Insoluble	>6 h
7	Li_2CO_3	Insoluble	>>6 h
8	Hünig's Base[b]	Soluble	>6 h

Notes
[a] KO*t*-Bu had a noticable different set of byproducts (more polar) then the rest
[b] Hünig's Base kept the entire solution soluble during the reaction

Using what was learned from base effects on *N*-tosylhydrazone decomposition we set out to further optimize the reaction by adjusting the solvent, temperature, BTAC and base. Ultimately we were able to obtain a modest 15% yield of *N*-Boc-borrerine **25** by switching the solvent to toluene, increasing the temperature to 110 °C, removing BTAC and keeping *t*-BuOLi as the base. By adjusting the solvent and temperature, omitting BTAC and utilizing what we learned from base effects on *N*-tosylhydrazone decomposition we were only able to obtained a 15% yield of *N*-Boc-borrerine **25** (Figure 3.6).

Figure 3.6 Synthesis of *N*-Boc-Borrerine



Application of these conditions to the less encumbered aryl iodide **12** generated the six-

membered 7-*O*-methyl-dehydrolophocerine **13** in over twice the yield (36%, Figure 3.7) that we obtained from the 2-iodo-*N*-Boc-indole **22** (*vide supra*). Although the sterically encumbering *N*-Boc group ortho to the halide did little to inhibit Heck chemistry in a similar system (*vide supra*) can inhibit the diazo attack on the arylpalladium(II) intermediate, and raise the energy barrier for both migratory insertion and nucleophilic cyclization due to the sterically hindered environment. The low yields due to an ortho substituent has even been observed by Liang and co-workers with a much less encumbering methyl substituent resulting in a similar drop in yield from 84% to 44% (Figure 3.8).[35]

Figure 3.7 Reaction Conditions with a Less Sterically Hindered Substrate

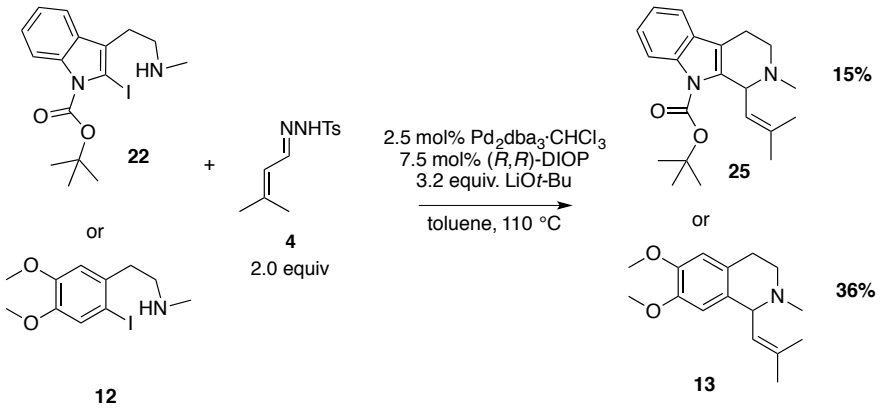
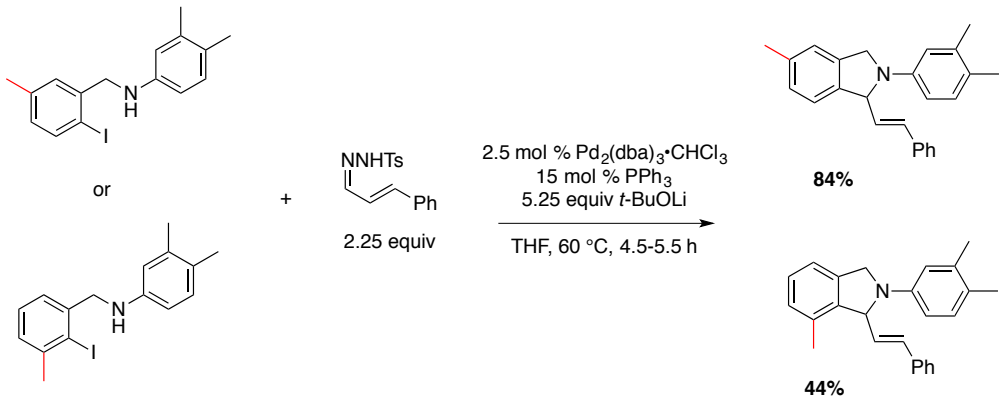


Figure 3.8 Ortho Substituents Have Been Shown to Dramatically Effect the Yield in Carbenylative Cross-Coupling Reactions



3.3 Conclusion

This work demonstrated that vinylcarbene insertion reactions can be used to assemble the heterocyclic rings of alkaloid natural products. It is clear that palladium-catalyzed carbenylative insertion is not superior to Pictet-Spengler approaches to borrerine. This work revealed the complex interplay between rates of diazo generation and the rates of reactions and side reactions in the catalytic cycle. The dramatic effects of ortho substitution on reactivity and methods for controlling of rates of diazo compound formation and decomposition will be invaluable to future method development in palladium-catalyzed carbenylative cross-coupling.

3.4 Experimental

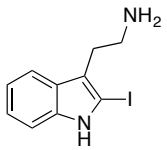
General. NMR spectral data were recorded using either a Bruker 500 or 600 MHz spectrometer. The NMR data are reported as follows: chemical shift in ppm from an internal tetramethylsilane standard on the δ scale, multiplicity (br = broad, app = apparent, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constants (Hz), and integration. If the tetramethylsilane signal could not be referenced the residual proton found in the NMR solvent was used (^{1}HNMR $CDCl_3$: δ 7.26 ($CHCl_3$), C_6D_6: δ 7.16 (C_6D_5H); ^{13}CNMR $CDCl_3$: δ 77.16 ($CHCl_3$), C_6D_6: δ 128.06 (C_6D_5H)). Analytical thin layer chromatography was performed using EM Reagents 0.25 mm silica gel 60-F plates. When triethylamine (TEA) was used as a co-eluent for thin layer chromatography, the plates were briefly pre-soaked in the eluent and allowed to dry for a few minutes before spotting with analyte. All reactions were carried out under an atmosphere of nitrogen in glassware that had been flame-dried under a stream of nitrogen or in glassware that had been flame-dried under vacuum. Unless otherwise noted, all reagents were commercially obtained and, where appropriate, purified prior to use. **16**,[74] **18**,[75] 2-(2-(2-iodo-1*H*-indol-3-yl)ethyl)isoindoline-1,3-dione (**S2**),[76] and *tert*-butyl (2-(1*H*-indol-3-

yl)ethyl)(methyl)carbamate (**S5**),[77] were synthesized according to reported literature procedures. **16**,[74] **18,**[75] **S2**[76] and **S5**[77] had spectroscopic data consistent with published values.

General procedure for the iodination of indoles

A round bottom flask containing a magnetic stir bar, protected indole (100 mol%), iodine (90 – 95 mol%) and THF (0.1 mM) was stirred vigorously at -78 °C while AgOTf (90 - 95 mol%) was added. The reaction turned from deep purple to opaque yellow. The reaction was monitored by TLC, and after completion solid $NaHCO_3$ (200 mol%) was added and the dry ice bath was removed. EtOAc and a 1:1 solution of $Na_2S_2O_{3(sat.\ aq)}$:$NaHCO_{3(sat.\ aq)}$ were added. The crude reaction mixture was filtered through a plug of Celite and washed through with EtOAc. The filtrate was extracted with EtOAc (3×), washed with brine, dried over Na_2SO_4 and then concentrated *in vacuo*. Purification by flash column chromatography in suitable eluent produces 2-iodoindole product.

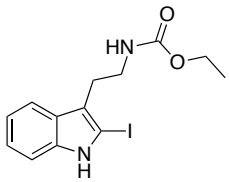
2-(2-Iodo-1*H*-indol-3-yl)ethan-1-amine (2-iodotryptamine), S3.



Starting from a known phthalamide protected 2-iodotryptamine **S2**, a 200 mL pear-shaped flask with condenser was charged with **S2** (1.10 g, 2.64 mmol, 100 mol%) and EtOH (40 mL). The mixture was brought to reflux while stirring and hydrazine hydrate (50%, 0.987 mL, 15.8 mmol, 600 mol%) was added in one portion. After 1 hour a white precipitate formed which was filtered and washed with $CHCl_3$. The filtrate was acidified with 1 mL concentrated HCl, diluted with 100 mL H_2O and extracted with $CHCl_3$. The aqueous layer was neutralized with solid K_2CO_3, extracted with $CHCl_3$ (3×), dried over $MgSO_4$ and concentrated *in vacuo* to obtain 2-iodotryptamine **S3** as a viscous oil (0.63 g, 2.2 mmol, 83%) in sufficient purity to use in further

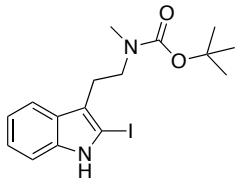
steps. The compound decomposed over several weeks to dark brown oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.79 (br s, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.22 (d, *J* = 7.9 Hz, 1H), 7.08 (t, *J* = 8.1 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H) 3.03 (t, *J* = 6.7 Hz, 2H), 2.87 (t, *J* = 6.7 Hz, 2H), 1.53 (br s, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 139.1, 127.6, 122.1, 119.6, 118.8, 117.9, 110.7, 79.3, 42.3, 31.0.

Ethyl (2-(2-iodo-1*H*-indol-3-yl)ethyl)carbamate, 17.



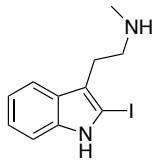
A 50 mL pear-shaped flask was charged with 2-iodotryptamine **S3** (0.55 g, 1.92 mmol, 100 mol%), TEA (0.27 mL, 1.9 mmol, 100 mol%) and DCM (10 mL). The reaction was cooled to 0 °C in an ice bath followed by dropwise addition of ethyl chloroformate (0.18 mL, 1.9 mmol, 100 mol%) while stirring. The reaction was allowed to warm to room temperature. The reaction was washed sequentially with H_2O, 1 M HCl, 5% $NaHCO_3$, H_2O and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* providing 0.67 g of crude material. Further purification by flash column chromatography using toluene/TEA (99:1) provided 2-iodotryptamine **17** (468.9 mg, 1.31 mmol, 68%). R_f = 0.35 (70:30 hexane/EtOAc) A second set of broadened peaks due to a hydrogen bonding species was observed in ^{1}H NMR. ^{1}H NMR (600 MHz, C_6D_6) δ 7.71 (br s, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.11 – 7.04 (m, 3H), 4.26 (br s, 1H), 4.05 (q, *J* = 7.1 Hz, 2H), 3.29 (q, *J* = 6.6 Hz, 2H), 2.80 (t, *J* = 6.8 Hz, 2H), 1.65 (s, 1H), 1.02 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (126 MHz, C_6D_6) δ 156.8, 139.3, 128.0, 122.4, 120.0, 119.0, 118.3, 111.1, 79.0, 60.7, 41.4, 27.5, 14.9.

***tert*-Butyl (2-(2-iodo-1*H*-indol-3-yl)ethyl)(methyl)carbamate, 19.**



Following the general procedure, *N*-Boc-*N*-methyltryptamine **S5** (1.46 g, 5.32 mmol, 100 mol%), iodine (1.23 g, 4.79 mmol, 90 mol%), AgOTf (1.23 g, 4.79 mmol, 90 mol%) $NaHCO_3$ (0.93 g, 10.6 mmol, 200 mol%) and purification by flash chromatography (90:10 hexanes/ethyl acetate) produced 2-iodotryptamine **19** as a yellow solid (0.56 g, 1.40 mmol, 29%). R_f = 0.54 (70:30 hexanes/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.35 (br s, 1H), 7.52 (br s, 1H), 7.27 (d, *J* = 7.9 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 7.05 (t, *J* = 7.3 Hz, 1H), 3.44 (t, *J* = 7.1 Hz, 2H), 2.91 (t, *J* = 6.5 Hz, 2H), 2.88 (br s, 3H), 1.41 (br s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 155.8, 139.2, 127.8, 122.4, 120.0, 119.6, 117.9, 110.6, 79.4, 78.2, 49.3, 34.9, 28.7, 25.9.

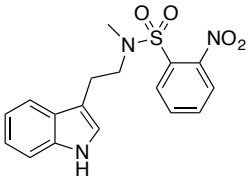
2-(2-Iodo-1*H*-indol-3-yl)-*N*-methylethan-1-amine, 14.



A 20 mL pear-shaped flask was charged with **19** (75.5 mg, 0.189 mmol, 100 mol%) and DCM (2.8 mL). While stirring, TFA (0.45 mL, 5.88 mmol, 3100 mol%) was added dropwise by syringe. After 45 minutes the reaction was neutralized with saturated $NaHCO_{3(aq)}$ and the solution was extracted with EtOAc (3×). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to provide 90.2 mg of crude material. Flash column chromatography using EtOAc/TEA (99:1) provided unstable **14** (32.7 mg, 0.109 mmol, 58%, contaminated by decomposition and grease) which turned from brown to blue-green overnight while under vacuum. Noticeable grease contamination was observed by NMR and was later attributed to the

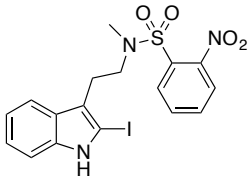
EtOAc used for purification. Decomposition of **14** occurred before repurification could be attempted after attributing the source of contamination and rectifying it. R_f = 0.16 (94:5:1 EtOAc/MeOH/TEA) ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.17 (br s, 1H), 7.55 (d, *J* = 7.7, 1H), 7.26 (d, *J* = 8.2 Hz, 1H), 7.10 (t, *J* = 7.4 Hz, 1H), 7.06 (t, *J* = 7.4 Hz, 1H), 2.96 – 2.91 (m, 4H), 2.48 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 139.2, 127.6, 122.2, 119.8, 119.3, 118.0, 110.6, 78.9, 51.8, 36.3, 27.0.

***N*-(2-(1*H*-Indol-3-yl)ethyl)-*N*-methyl-2-nitrobenzenesulfonamide, S4.**



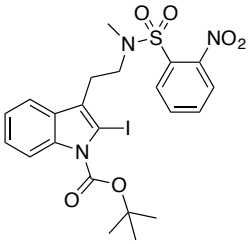
A 50 mL round-bottom flask was charged with *N*-methyltryptamine **18** (1.08 g, 6.18 mmol, 100 mol%), DMAP (76.8 mg, 0.629 mmol, 10.0 mol%), TEA (1.29 mL, 9.27 mmol, 150 mol%) and DCM (22 mL). The reaction was cooled to 0 °C in an ice bath. 2-NsCl (1.52 g, 6.86 mmol, 111 mol%) was added and the reaction vessel was allowed to warm to room temperature. After 30 minutes the reaction mixture was washed sequentially with H_2O, 1 M HCl, 5% (w/v) $NaHCO_{3(aq)}$, H_2O and brine. The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to produce *N*-nosyltryptamine **S4** as a yellow oil (2.11 g, 5.87 mmol, 95%) of sufficient purity to use in further steps. R_f = 0.40 (50:50 hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (br s, 1H), 7.87 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.62 – 7.518 (m, 4H), 7.32 (d, *J* = 8.1 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H) 7.11 (t, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 2.1 Hz, 1H), 3.55 (t, *J* = 7.7 Hz, 2H), 3.07 (t, *J* = 7.6 Hz, 2H), 2.97 (s, 3H), 1.45 (br s, 9H); ^{13}C NMR (151 MHz, C_6D_6) δ 148.0, 136.2, 133.3, 132.5, 131.5, 130.6, 127.1, 124.0, 122.3, 122.1, 119.5, 118.5, 111.9, 111.3, 50.6, 34.8, 24.3; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{17}O_4N_3SNa$ $(M + Na)^+$ 382.0837, found 382.0836.

***N*-(2-(2-Iodo-1*H*-indol-3-yl)ethyl)-*N*-methyl-2-nitrobenzenesulfonamide, 20.**



Following the general procedure, **S4** (4.16 g, 11.6 mmol, 100 mol%), iodine (2.796 g, 11.0 mmol, 95 mol%), AgOTf (2.84 g, 11.0 mmol, 95 mol%), $NaHCO_3$ (1.91 g, 22.7 mmol, 196 mol%) and purification by flash chromatography (80:20 hexanes/ethyl acetate) resulted in 2-iodotryptamine **20** as a yellow oil (4.76 g, 9.81 mmol 85%). R_f = 0.53 (50:50 hexanes/EtOAc); ^{1}H NMR (600 MHz, C_6D_6) δ 7.55 (d, *J* = 7.9 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.47 (s, 1H), 7.09–7.03 (m, 3H), 6.81 (d, *J* = 7.9 Hz, 1H), 6.75 (t, *J* = 7.7 Hz, 1H), 6.69 (t, *J* = 7.6 Hz, 1H), 3.28 (t, *J* = 7.7 Hz, 2H), 2.85 (t, *J* = 7.7 Hz, 2H), 2.69 (s, 3H); ^{13}C NMR (151 MHz, C_6D_6) δ 148.4, 139.3, 133.1, 132.8, 131.2, 130.5, 127.7, 123.9, 122.6, 120.3, 118.2, 118.1, 111.1, 78.9, 50.2, 34.9, 26.4; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{16}O_4SIN_3Na$ $(M + Na)^+$ 507.9804, found 507.9802.

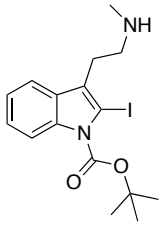
***tert*-Butyl 2-iodo-3-(2-((*N*-methyl-2-nitrophenyl)sulfonamido)ethyl)-1*H*-indole-1-carboxylate, 21.**



A 25 mL pear-shaped flask was charged with **20** (436 mg, 0.898 mmol, 100 mol%), DMAP (19.8 mg, 0.162 mmol, 18.0 mol%), Boc_2O (215.6 mg, 0.988 mmol, 110 mol%) and DCM (5 mL). After mixing for 1 hour the reaction mixture was concentrated *in vacuo*. Flash column chromatography using hexane/EtOAc (70:30) provided Boc-indole **21** as a yellow oil (520 mg,

0.888 mmol, 99%,). R_f = 0.26 (70:30 hexane/EtOAc); ^{1}H NMR (600 MHz, C_6D_6) δ 8.20 (d, *J* = 8.3 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 7.3 Hz, 1H), 7.13 – 7.08 (m, 2H), 6.92 (d, *J* = 7.8 Hz, 1H) 6.89 (t, *J* = 7.7 Hz, 1H), 6.83 (t, *J* = 7.7 Hz, 1H), 3.27 (t, *J* = 7.8 Hz, 2H), 2.87 (t, *J* = 7.8 Hz, 2H), 2.76 (s, 3H), 1.45 (br s, 9H); ^{13}C NMR (151 MHz, C_6D_6) δ 149.2, 148.4, 138.6, 133.3, 132.8, 131.3, 130.5, 129.8, 126.1, 124.8, 124.0, 123.3, 118.5, 116.0, 84.9, 79.7, 49.3, 35.1, 28.1, 27.4; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{24}O_6N_3SINa$ $(M + Na)^+$ 608.0328, found 608.0323.

***tert*-Butyl 2-iodo-3-(2-(methylamino)ethyl)-1*H*-indole-1-carboxylate, 22.**



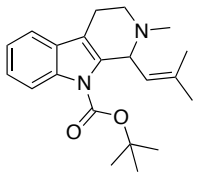
A 500 mL round-bottom flask was charged with **21** (4.56 g, 7.79 mmol, 100 mol%), Cs_2CO_3 (7.63 g, 23.4 mmol, 300 mol%) and DMF (130 mL). The reaction mixture became opaque and slowly turned light pink in color. PhSH (0.957 mL, 9.35 mmol, 120 mol%) was added dropwise to the reaction, which changed the color of the reaction from light pink to orange. The reaction was monitored by TLC and after 3 hours additional PhSH (0.500mL, 4.89 mmol, 63 mol%) was added dropwise and allowed to react for an additional 30 minutes. Upon completion, the reaction was diluted with Et_2O (480 mL) followed by addition of 10% (w/v) $K_2CO_{3(aq)}$ (240 mL). The aqueous layer was extracted with Et_2O (2 × 200 mL) and the combined organic layers were washed with H_2O (2 × 300 mL), brine (300 mL), dried over anhydrous K_2CO_3 and concentrated *in vacuo* to provide 4.12 g of crude material. Flash column chromatography using EtOAc/TEA (95:5) provided *N*-methyltryptamine **22** as an orange solid (493 mg, 1.23 mmol, 16%). R_f = 0.31 (95:5 EtOAc/TEA) ^{1}H NMR (500 MHz, C_6D_6) δ 8.37 (d, *J* = 8.4 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.18 – 7.14 (m, 1H), 7.09 (td, *J* = 7.5, 1.1 Hz, 1H), 2.87 (t, *J* = 7.3 Hz, 2H), 2.7022-H (t, *J* =

7.3 Hz, 2H), 2.21 (s, 3H), 1.41 (s, 9H), 0.73 (s, 1H); ^{13}C NMR (126 MHz, C_6D_6) δ 149.5, 139.0, 130.4, 128.5, 124.7, 122.9, 118.8, 116.1, 84.4, 79.5, 51.6, 36.6, 28.9, 28.1; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{21}O_2N_2INa$ $(M + Na)^+$ 423.0545, found 423.0530.

General procedure for the carbenylative coupling to form Boc-borrerine, 25

A round bottom flask containing a magnetic stir bar, $Pd_2(dba)_3$•$CHCl_3$ (0.0025 mmol, 2.5 mol%), and bidentate ligand (0.0075 mmol, 7.5 mol%) was placed under nitrogen and charged with 500 μL toluene. The purple suspension was stirred at 110 °C until a clear orange solution was obtained (approximately 5 min). A separate round bottom flask, containing a magnetic stir bar, was charged with 2-iodoindole (0.10 mmol, 100 mol%), *N*-tosylhydrazone (0.20 mmol, 200 mol%) and *t*-BuOLi (0.32 mmol, 320 mol%) under nitrogen. The palladium complex solution was then transferred by syringe to the hydrazone containing round bottom flask, washing three times with a total 1.0 mL of toluene. The reaction mixture was then placed into an oil bath at 110 °C and monitored by TLC. The crude reaction mixture was diluted with EtOAc and 1% (w/v) aq. NaOH followed by extraction with EtOAc three times. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash column chromatography using hexane/EtOAc/MeOH (20:80:0 to 0:98:2) affords product.

Boc-borrerine - *tert*-butyl 2-methyl-1-(2-methylprop-1-en-1-yl)-1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-9-carboxylate, 25.



Following the general procedure utilizing the ligand (*R,R*)-DIOP, **22** (40.0 mg, 0.100 mmol, 100 mol%), and *N*-tosylhydrazone **4** (52.9 mg, 0.210 mmol, 210 mol%) were reacted and monitored by TLC. The reaction was complete after 2.5 hours. Purification by flash chromatography

produced Boc-borrerine **25** (5.0 mg, 0.0147 mmol, 15%). R_f = 0.29 (98:2 EtOAc/MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, *J* = 8.1 Hz, 1H), 7.43 (d, *J* = 7.3 Hz, 1H), 7.24 – 7.19 (m, 2H), 5.10 (d, *J* = 9.0 Hz, 1H), 4.89 (d, *J* = 8.9 Hz, 1H), 3.14 – 3.08 (m, 1H), 2.87 – 2.80 (m, 2H), 2.71 – 2.67 (m, 1H), 2.50 (s, 3H), 1.83 (s, 3H), 1.72 (s, 3H), 1.63 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.0, 137.1, 136.9, 136.0, 129.2, 123.6, 122.9, 122.2, 118.0, 114.9, 114.4, 83.2, 57.8, 47.0, 41.9, 28.1, 26.0, 19.8, 18.9; MS (ESI) *m*/*z* calcd for $C_{21}H_{28}N_2O_2H$ $(M + H)^+$ 341.2, found 341.5.

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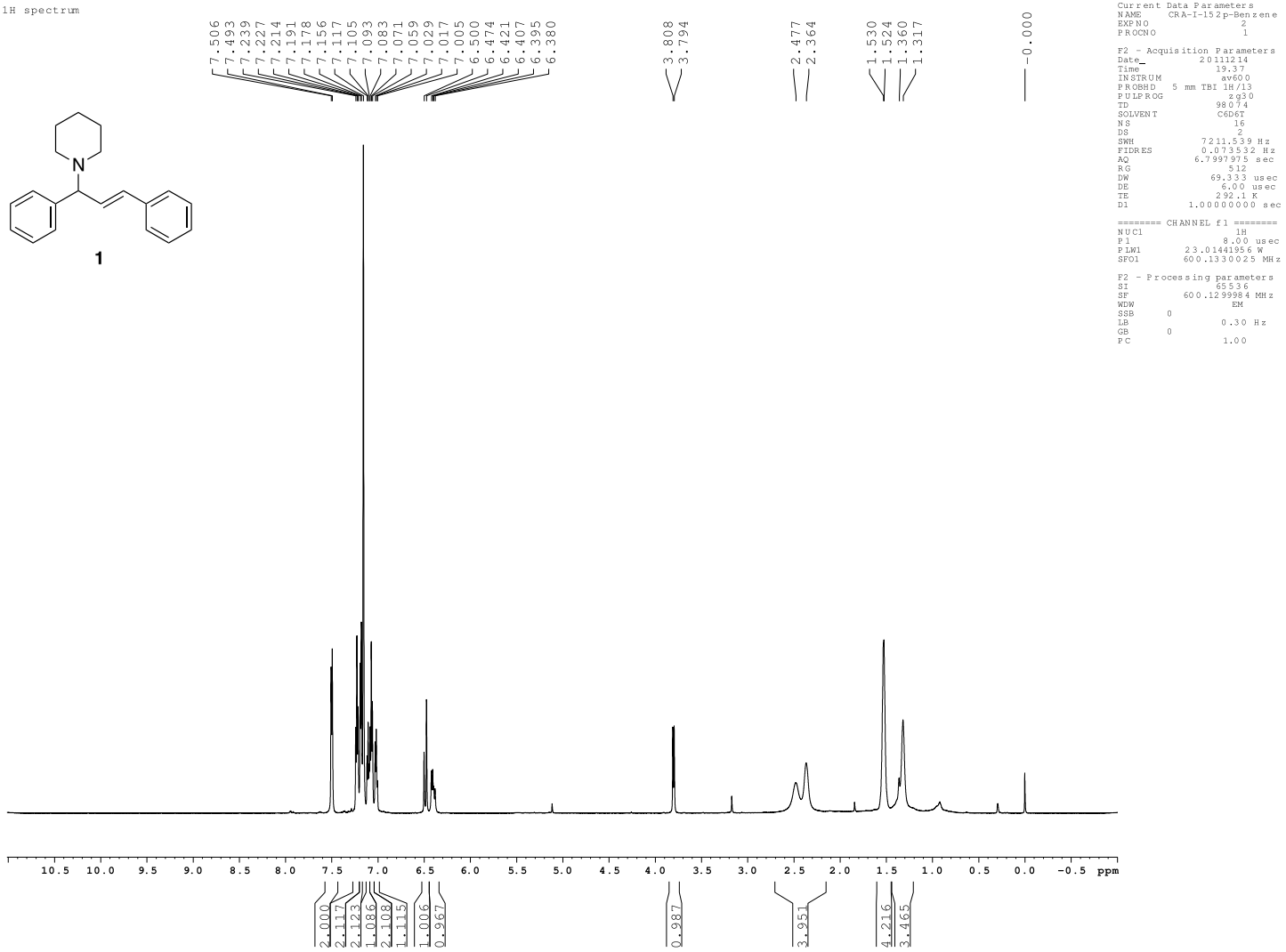

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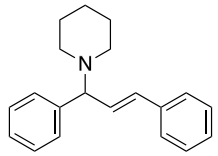
13C spectrum with 1H decoupling



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RG                   2050
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======== CHANNEL f1 ====
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SFO1        150.9194080

======== CHANNEL f2 ====
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PCPD2             70.00
PLW2      0 W
PLW12        0.30199519
SFO2         600.1330010

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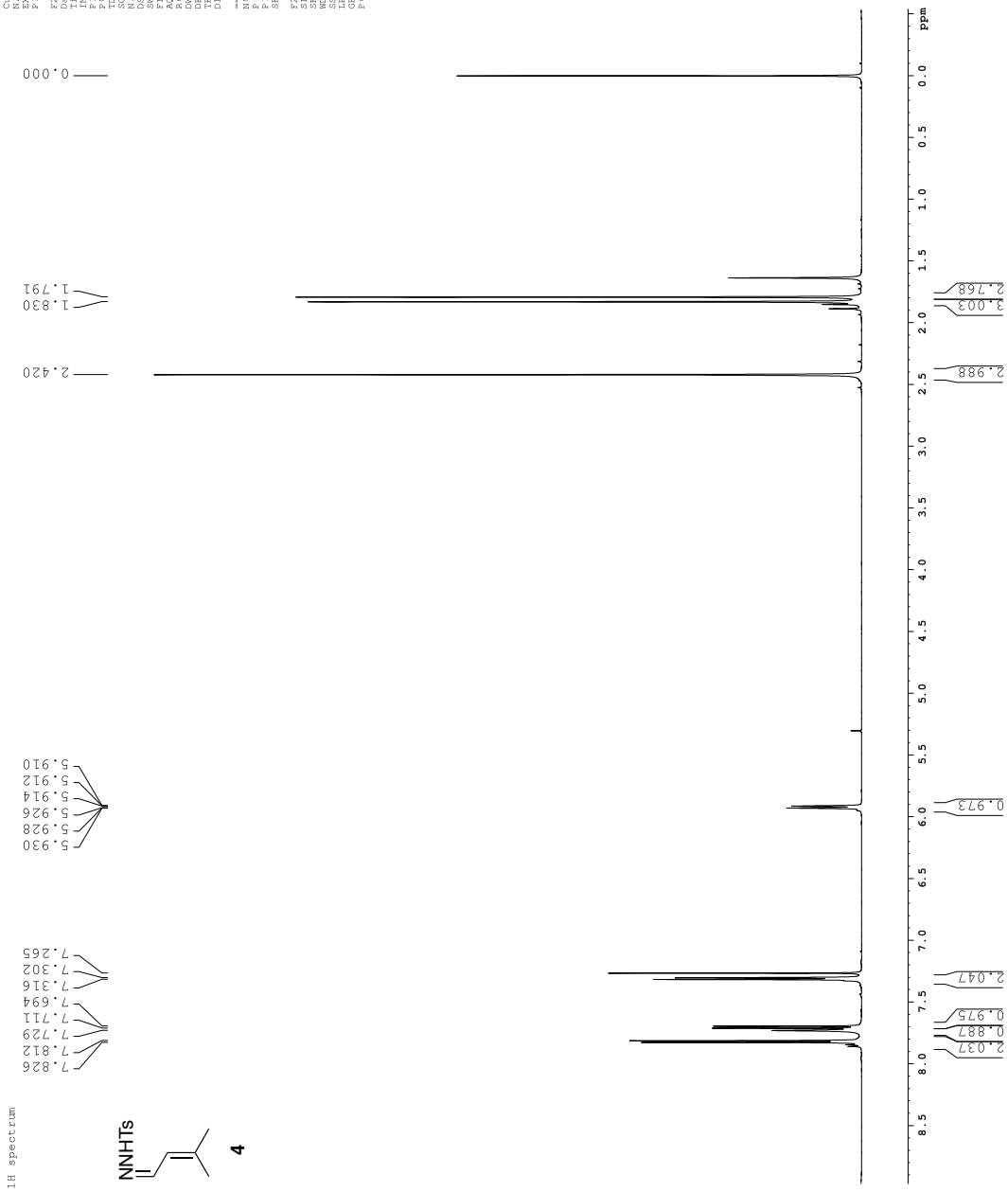
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5.928
5.926
5.914
5.912
5.910
1.830
1.791
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0.000
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0.975
2.047
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2.988
2.003
2.768
ppm

13C spectrum with 1H decoupling

4


```
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RG                          2050
DW                        13.800
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======== CHANNEL f1 ====
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P1                         15.00
PLW1                107.15190125
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PCPD2                      70.00
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PLW12                0.30199519
SFO2                600.1330010

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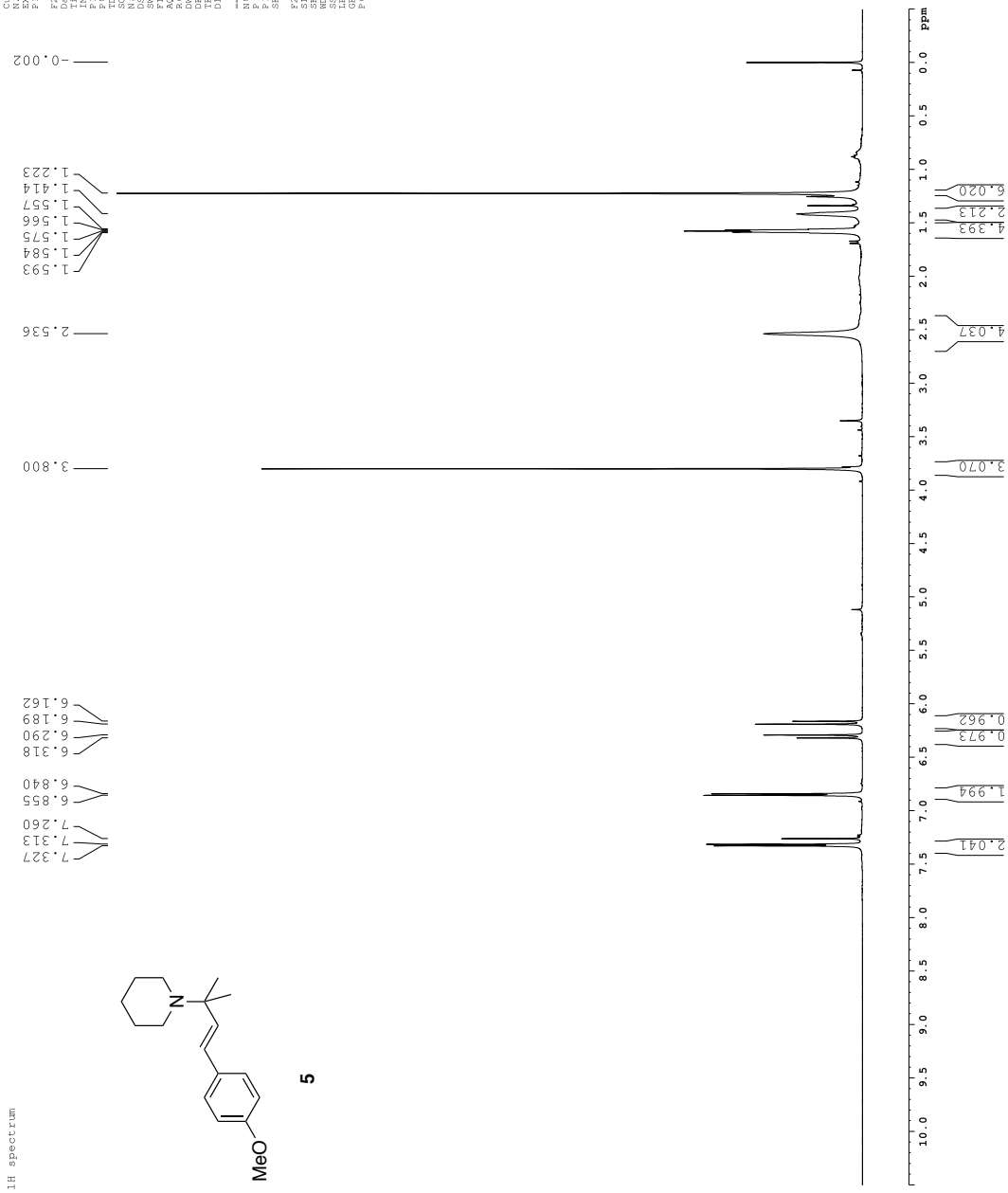
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7.313
7.327
MeO
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ppm
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9.5
9.0
8.5
8.0
7.5
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6.5
6.0
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5.0
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4.0
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3.0
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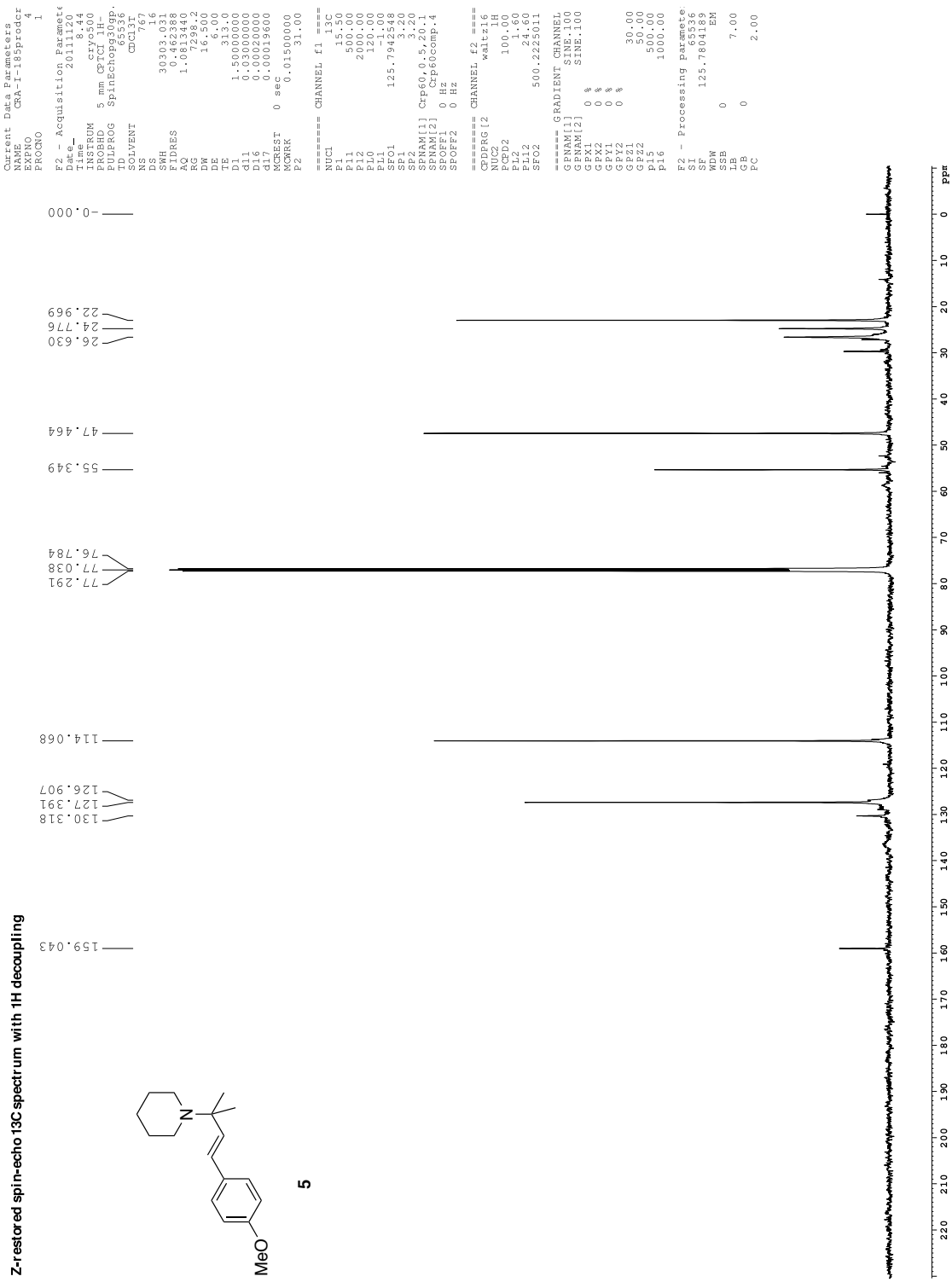
Z-restored spin-echo 13C spectrum with 1H decoupling
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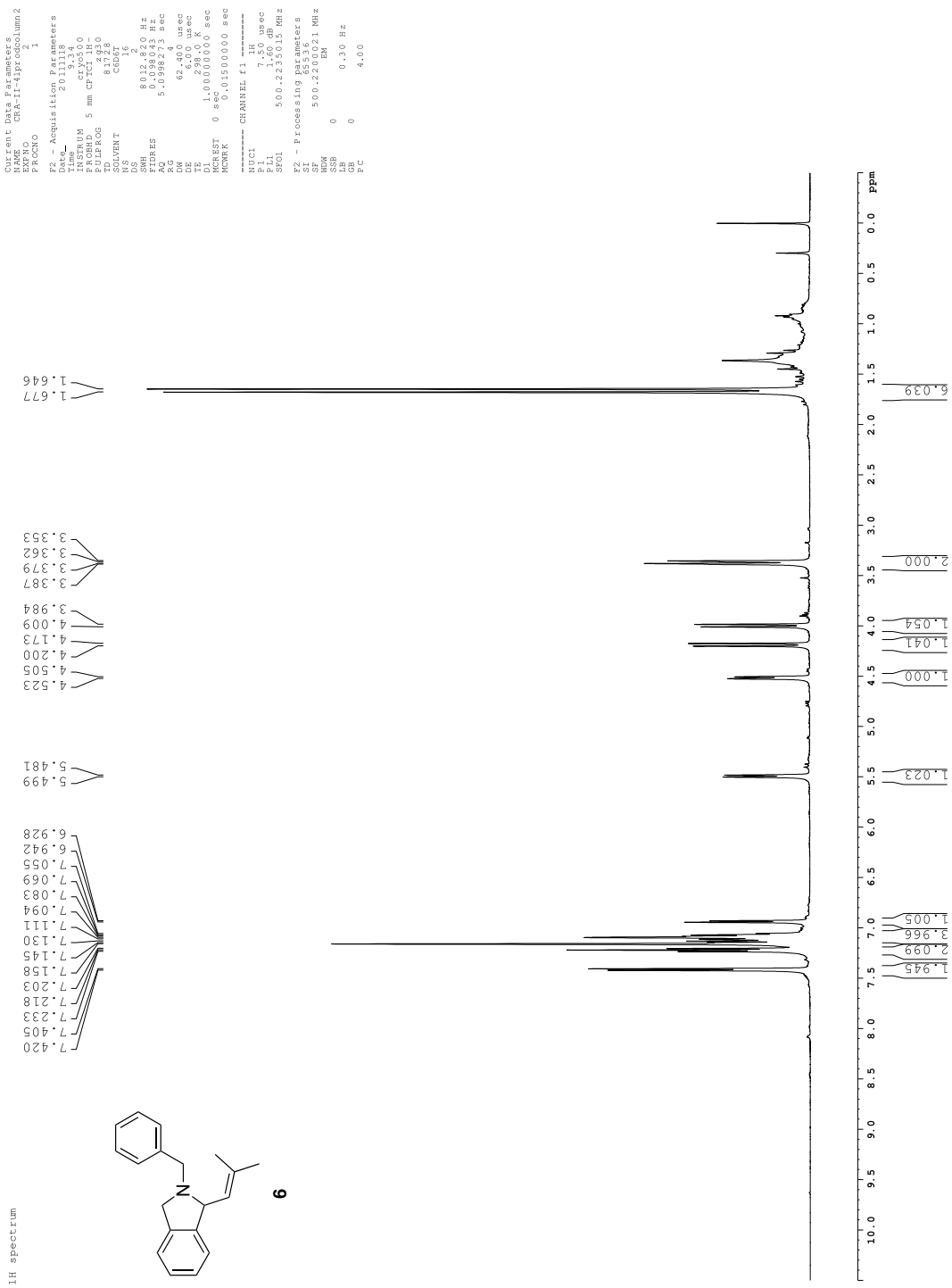
22.969
ppm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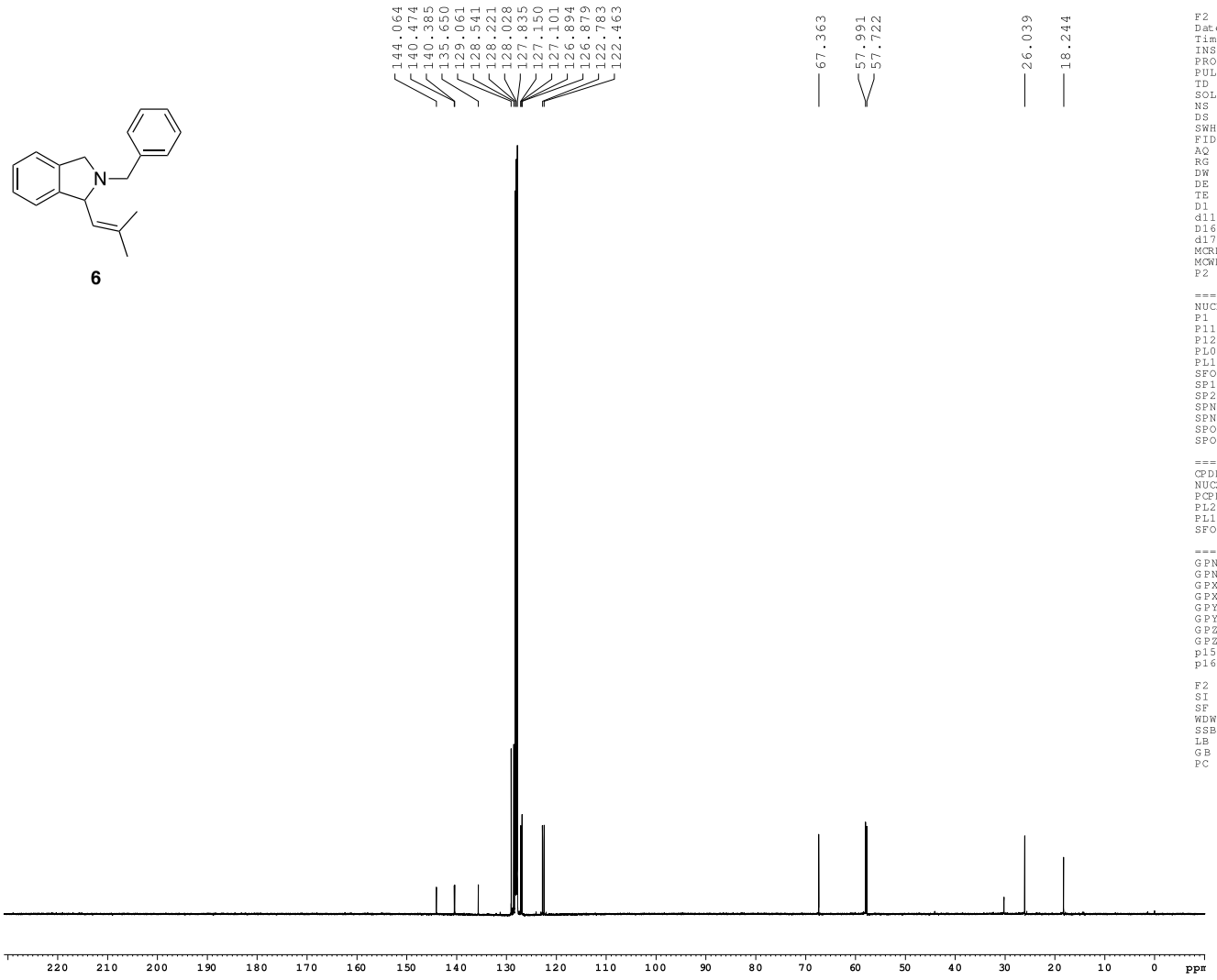
Z-restored spin-echo 13C spectrum with 1H decoupling

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P11               500.00
P12              2000.00
PL0               120.00
PL1                -1.00
SFO1         125.7942548
SP1                 3.20
SP2                 3.20
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SPNAM[2]    Crp60comp.4
SPOFF1    0 Hz
SPOFF2    0 Hz

======== CHANNEL f2 ====
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NUC2                 1H
PCPD2              100.00
PL2                 1.60
PL12               24.60
SFO2         500.2225011

====== GRADIENT CHANNEL
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GPNAM[2]        SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1                30.00
GPZ2                50.00
p15               500.00
p16              1000.00

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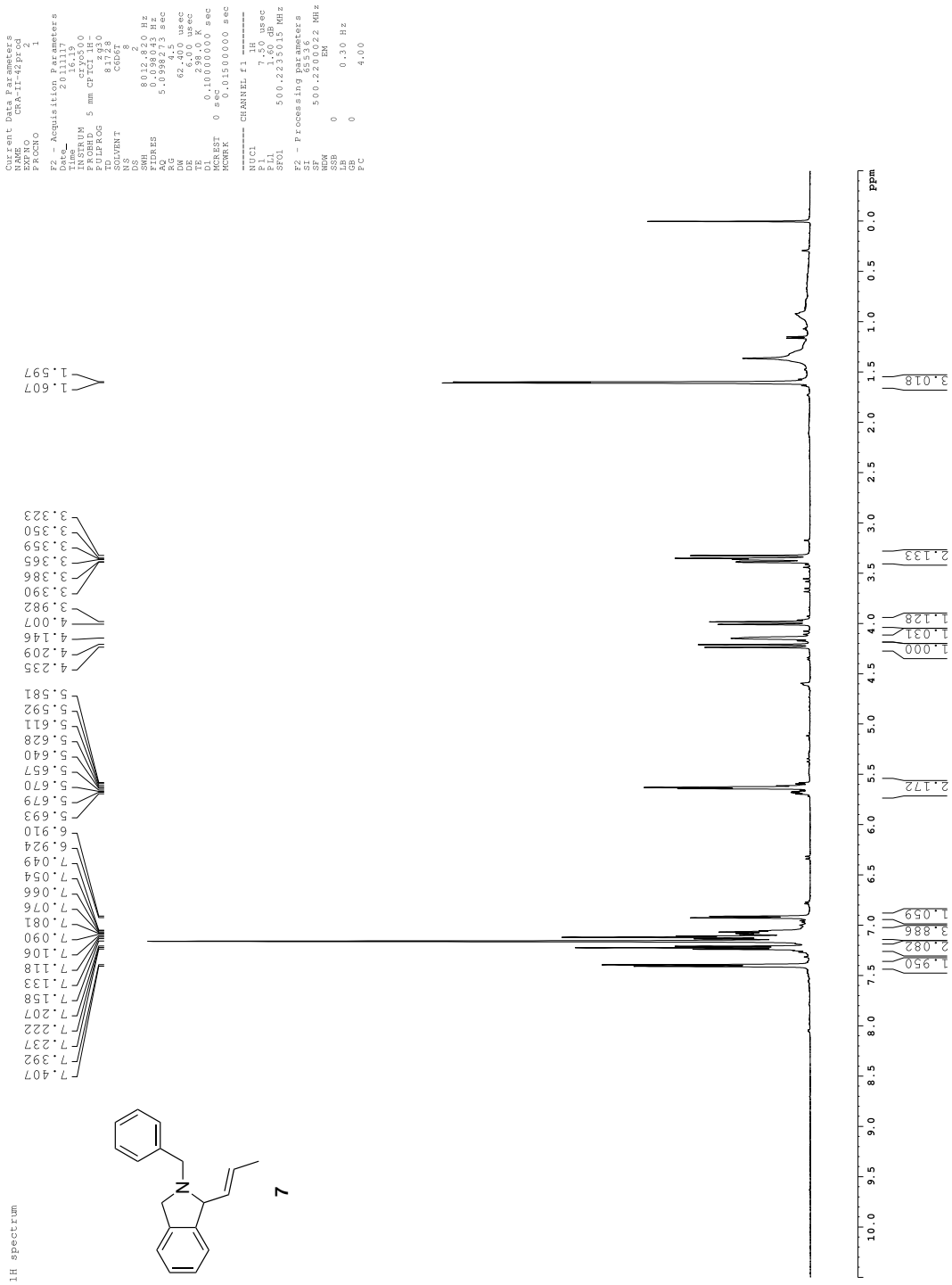
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DE 6.00 usec
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MCREST 0 sec 0.01500000 sec
MCWRK
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7.237
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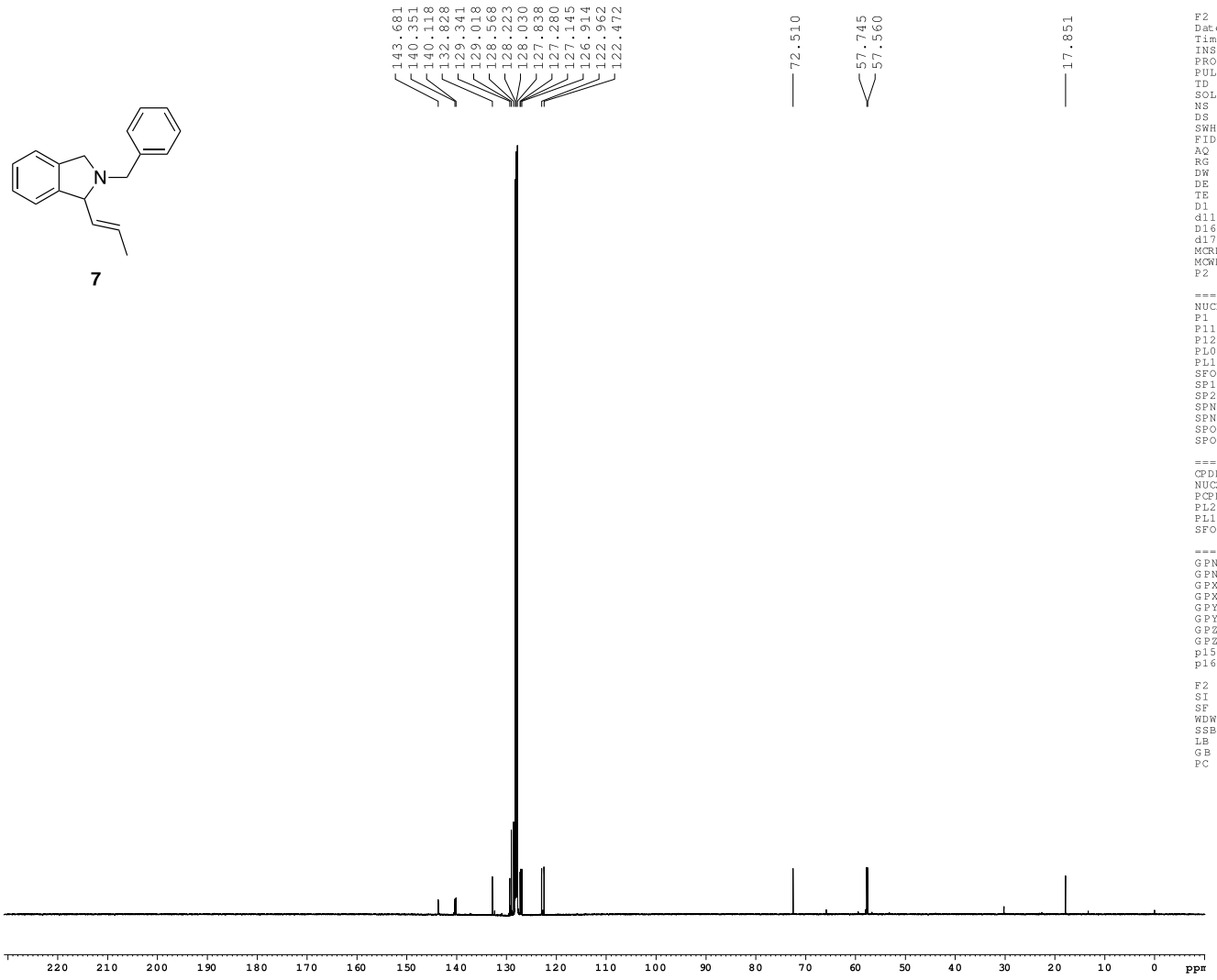
ppm

Z-restored spin-echo 13C spectrum with 1H decoupling

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P2                 31.00

======== CHANNEL f1 ====
NUC1                13C
P1                15.50
P11              500.00
P12             2000.00
PL0              120.00
PL1               -1.00
SFO1         125.7942548
SP1                3.20
SP2                3.20
SPNAM[1] Crp60,0.5,20.1
SPNAM[2]    Crp60comp.4
SPOFF1    0 Hz
SPOFF2    0 Hz

======== CHANNEL f2 ====
CPDPRG[2          waltz16
NUC2                 1H
PCPD2             100.00
PL2                1.60
PL12              24.60
SFO2         500.2225011

====== GRADIENT CHANNEL
GPNAM[1]        SINE.100
GPNAM[2]        SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1               30.00
GPZ2               50.00
p15               500.00
p16              1000.00

F2 - Processing paramete
SI                 65536
SF           125.7803781
WDW                   EM
SSB       0
LB                 1.00
GB        0
PC                 2.00
```
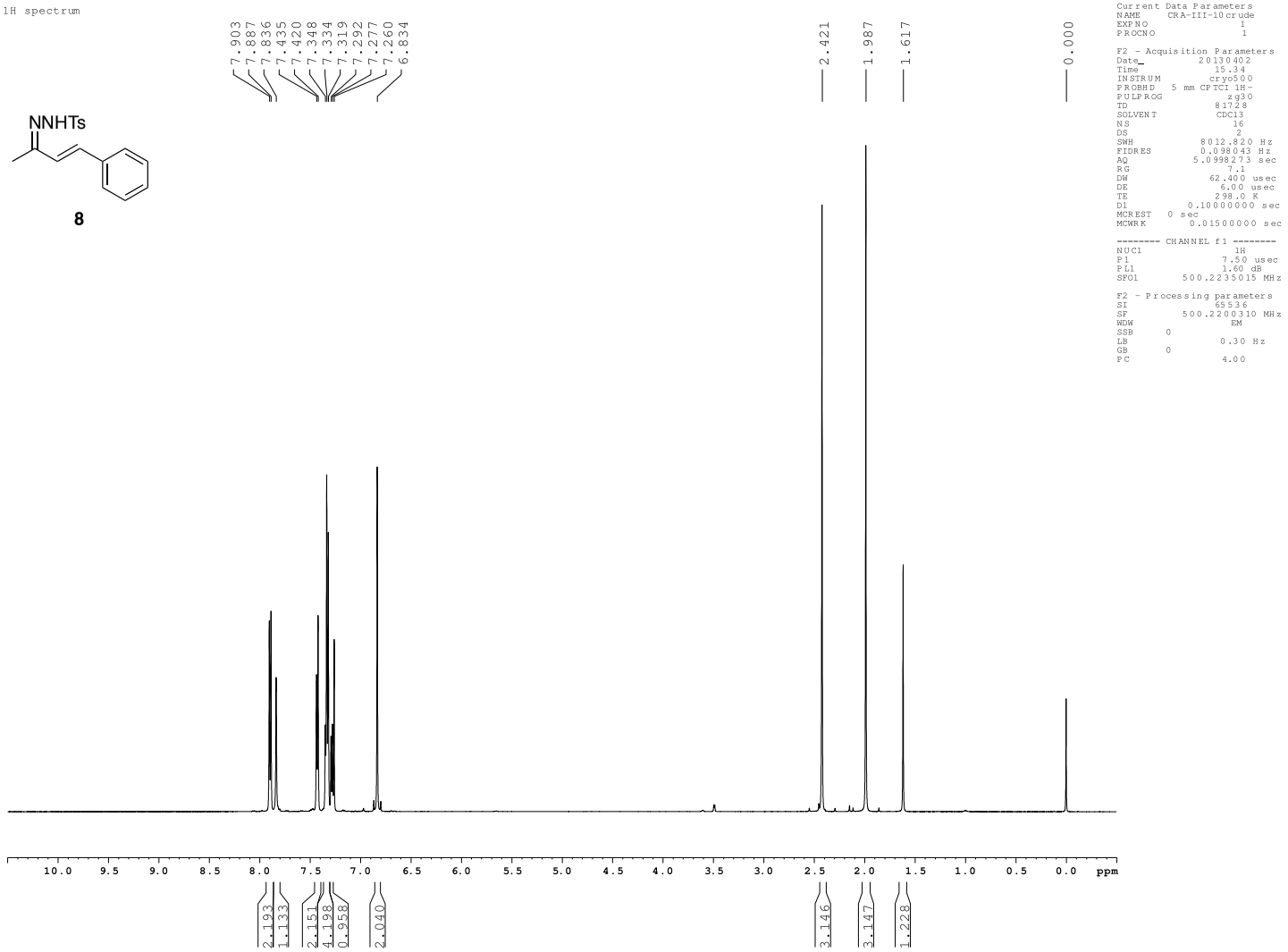
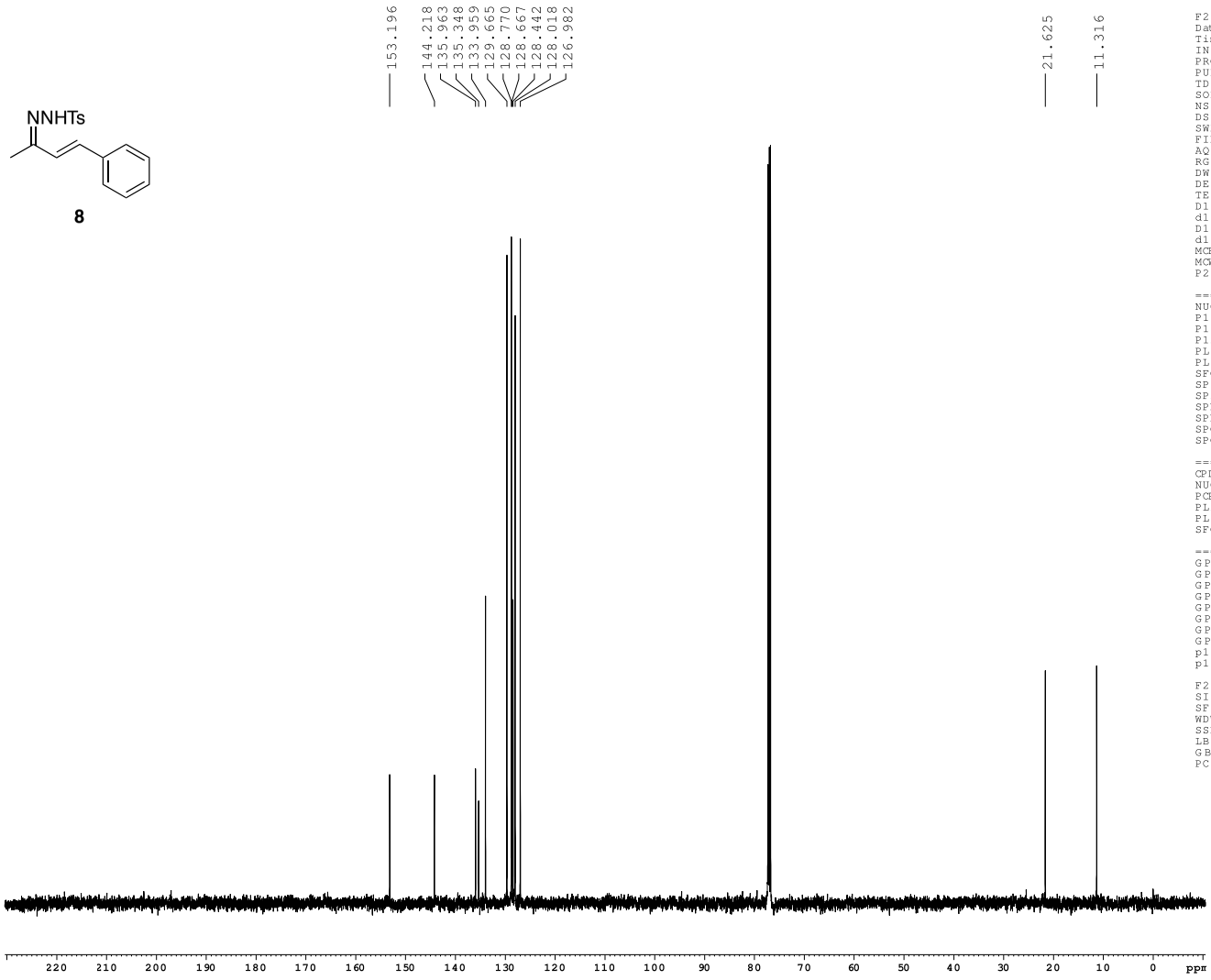
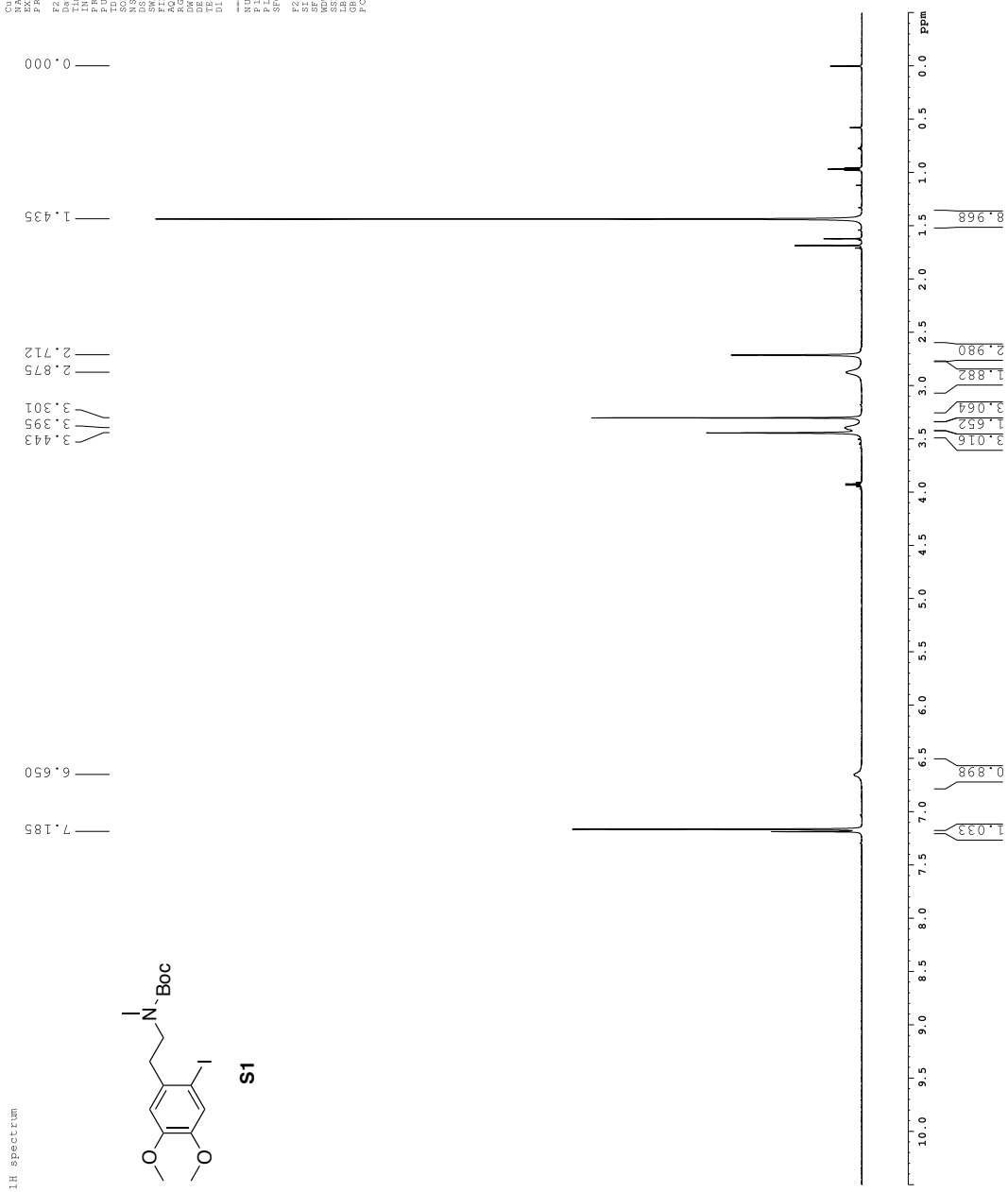
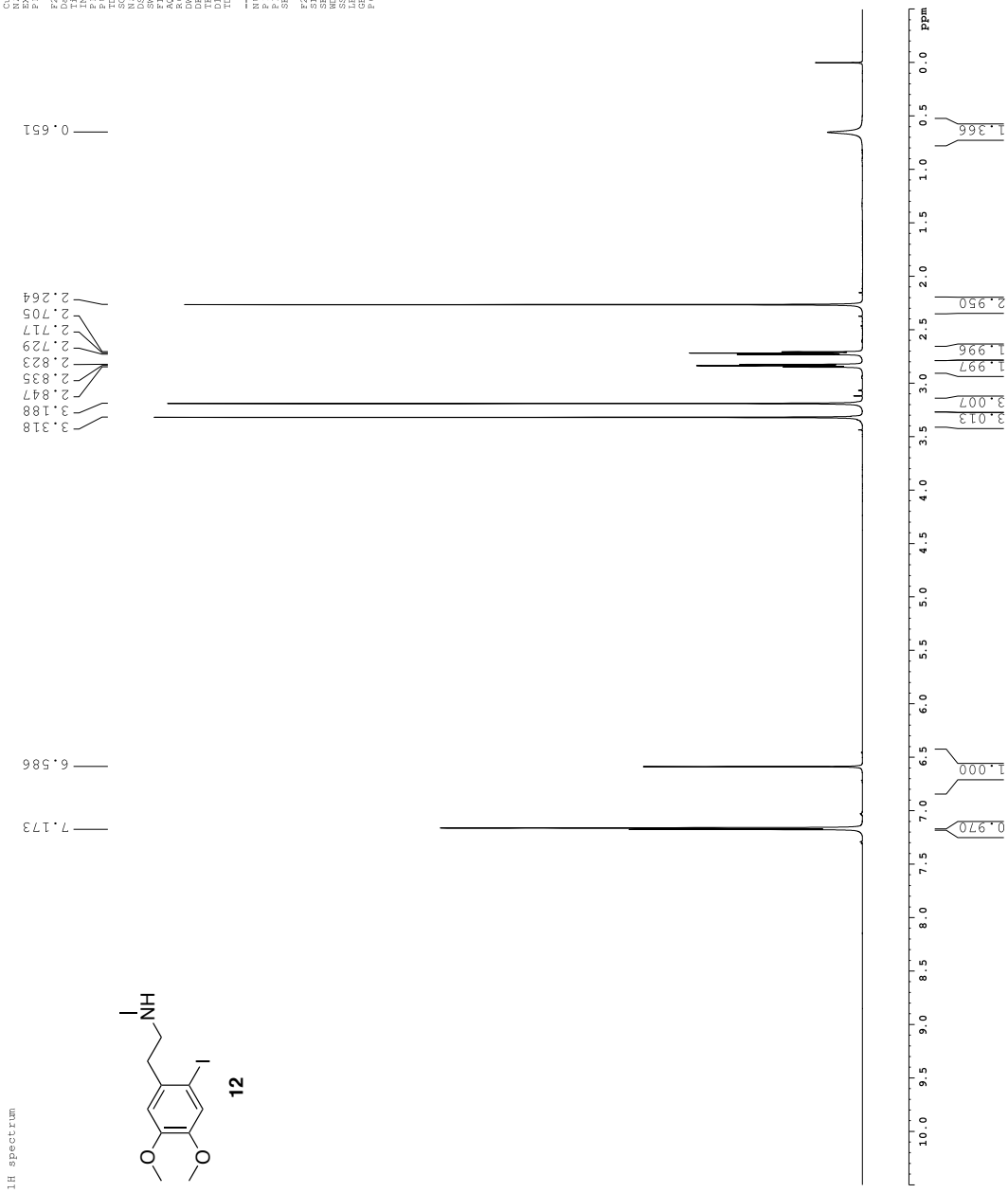


1H spectrum
7.903
7.887
7.836
7.435
7.420
7.348
7.334
7.319
7.292
7.277
7.260
6.834
2.421
1.987
1.617
0.000
NNHTs
8
Current Data Parameters
NAME CRA-III-10crude
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130402
Time 15.34
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 16
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0998273 sec
RG 7.1
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec
MCWRK 0.01500000 sec
-------- CHANNEL f1 --------
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200310 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.193
1.133
2.151
4.198
0.958
2.040
3.146
3.147
1.228

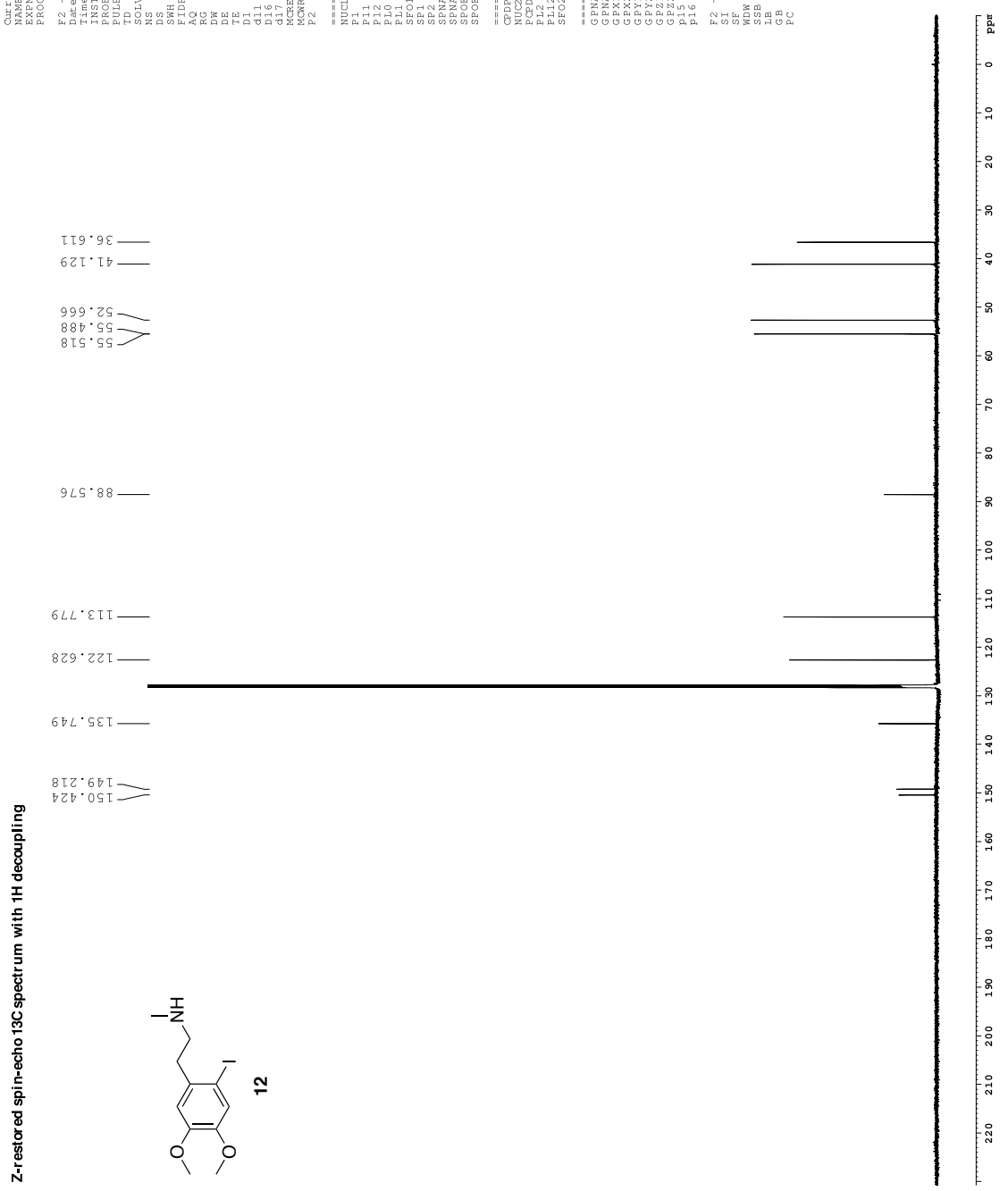
Z-restored spin-echo 13C spectrum with 1H decoupling

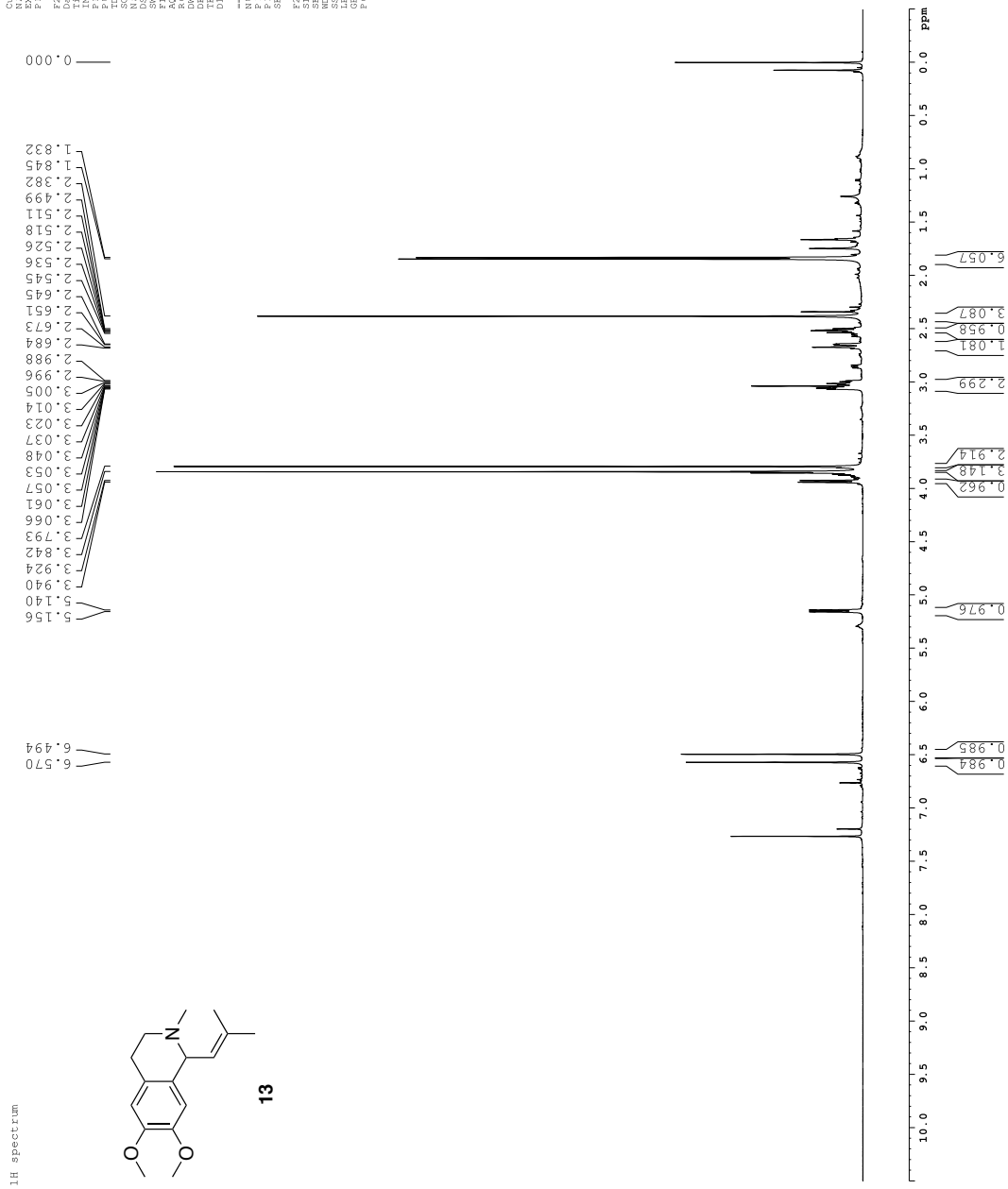



```
Current Data Parameters
NAME      CRA-III-10crude
EXPNO                   2
PROCNO                  1

F2 - Acquisition Paramete
Date_            20130402
Time                15.40
INSTRUM           cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.
TD                  65536
SOLVENT              CDCl3
NS                     400
DS                      16
SWH              30303.031
FIDRES           0.462388
AQ               1.0813440
RG                 11585.2
DW                   16.500
DE                     6.00
TE                   298.0
D1              0.25000000
d11             0.03000000
D16             0.00020000
d17             0.00019600
MCREST    0 sec
MCWRK           0.01500000
P2                    31.00

======== CHANNEL f1 ====
NUC1                   13C
P1                   15.50
P11                 500.00
P12                2000.00
PL0                 120.00
PL1                  -1.00
SFO1          125.7942548
SP1                   3.20
SP2                   3.20
SPNAM[1] Crp60,0.5,20.1
SPNAM[2]    Crp60comp.4
SPOFF1    0 Hz
SPOFF2    0 Hz

======== CHANNEL f2 ====
CPDPRG[2           waltz16
NUC2                   1H
PCPD2                100.00
PL2                    1.60
PL12                  24.60
SFO2          500.2225011

====== GRADIENT CHANNEL
GPNAM[1]         SINE.100
GPNAM[2]         SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1                  30.00
GPZ2                  50.00
p15                  500.00
p16                 1000.00

F2 - Processing paramete
SI                    65536
SF            125.7804273
WDW                     EM
SSB       0
LB                     2.00
GB        0
PC                     2.00
```

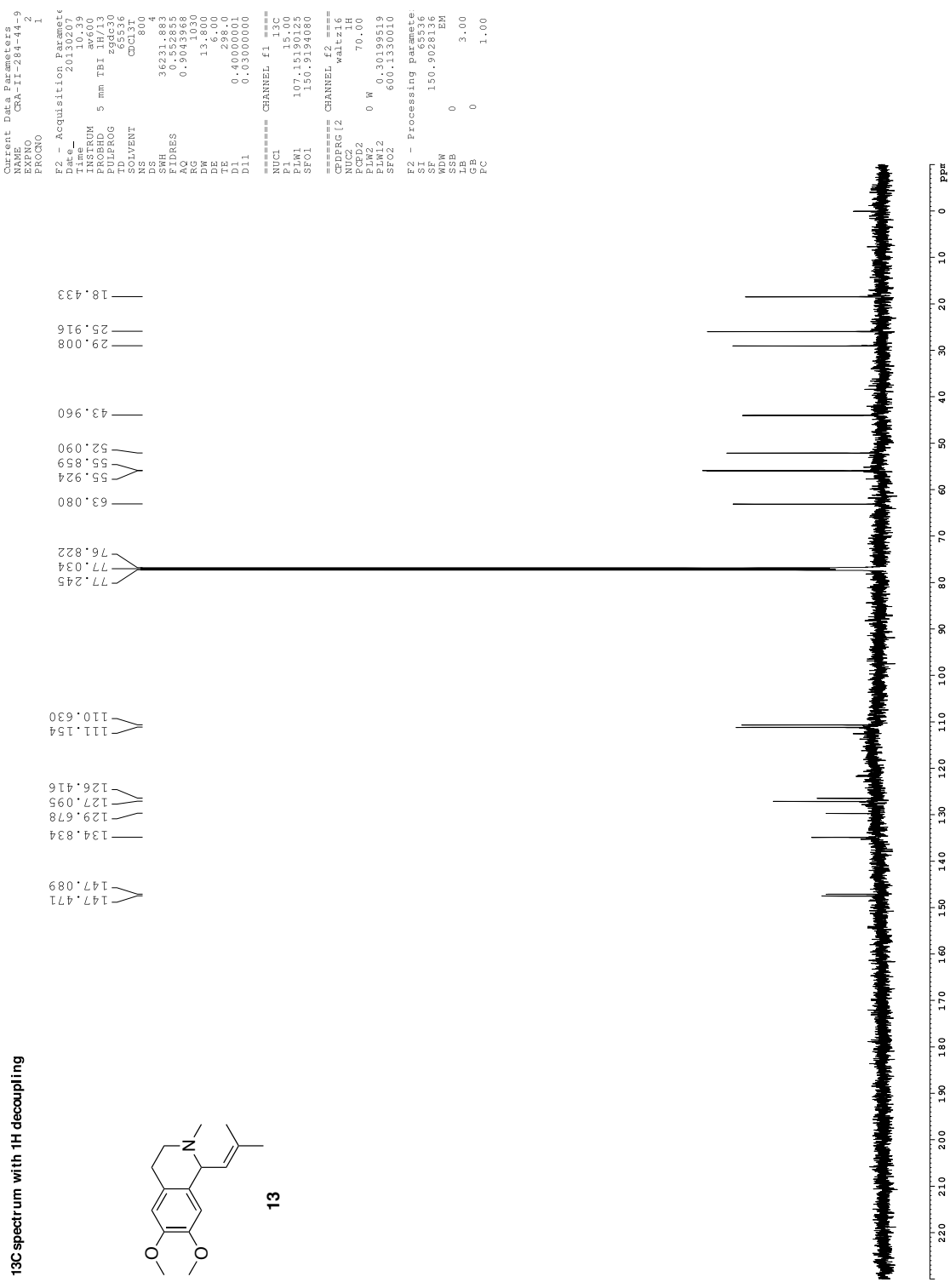

1H spectrum
Boc
N
I
O
O
S1
7.185
6.650
3.443
3.395
3.301
2.875
2.712
1.435
0.000
1.033
0.898
3.016
1.652
3.064
1.882
2.980
8.968
ppm

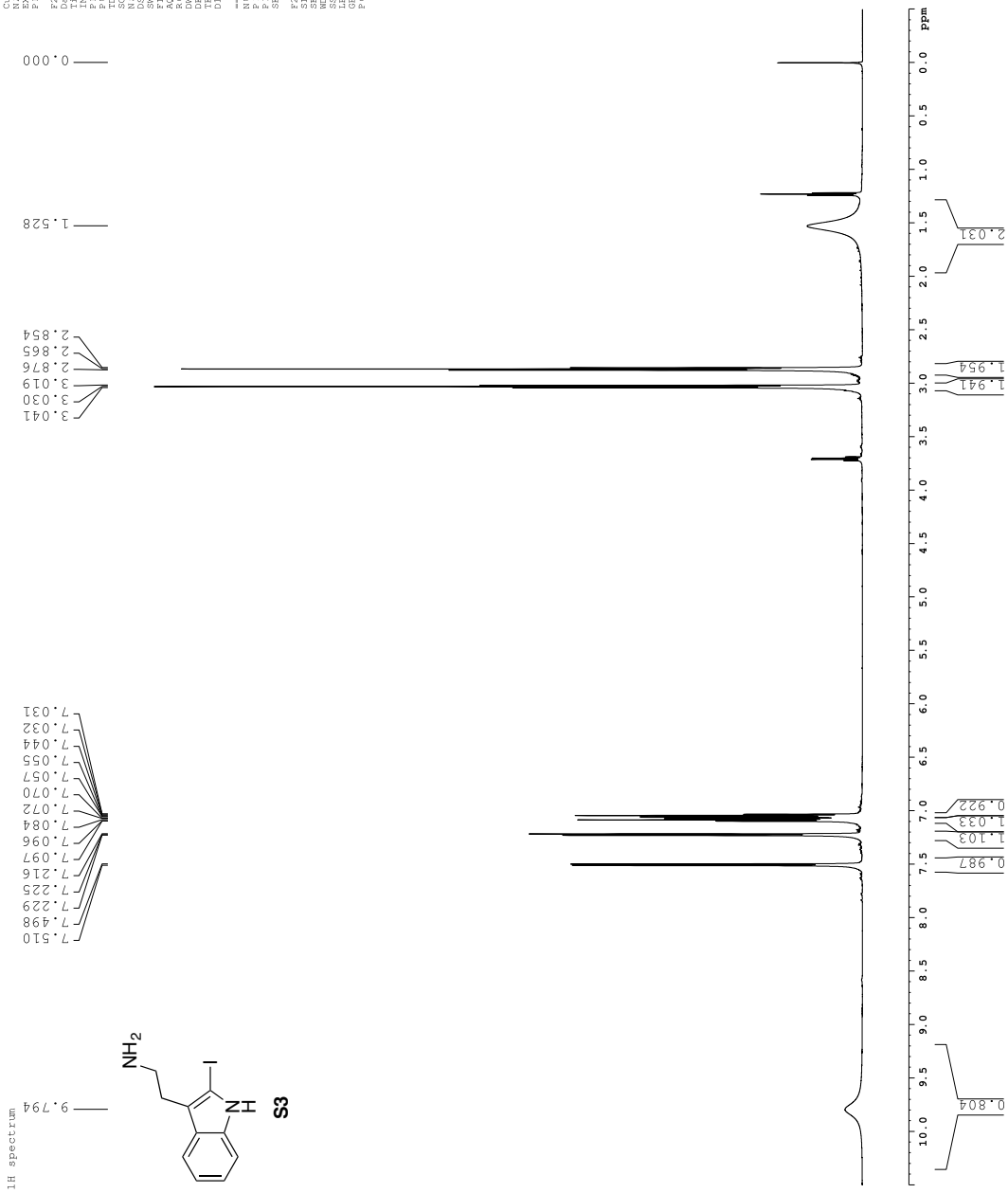

Current Data Parameters
NAME CRA-II-282 col2 copy
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130214
Time 17.05
INSTRUM av600
PROBHD 5 mm TBI 1H/13
PULPROG zg30
TD 98074
SOLVENT C6D6T
NS 16
DS 2
SWH 9615.385 Hz
FIDRES 0.098042 Hz
AQ 5.0998478 sec
RG 84.6
DW 52.000 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
TD0 1
======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PL1 23.01 dB
SFO1 600.1324009 MHz
F2 - Processing parameters
SI 57536
SF 600.1299969 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
0.651
2.264
2.705
2.717
2.729
2.823
2.835
2.847
3.188
3.318
6.586
7.173
1.366
2.950
1.996
1.997
3.007
3.013
1.000
0.970
ppm
12


Z-restored spin-echo 13C spectrum with 1H decoupling
Current Data Parameters
NAME CRA-II-282co12
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130214
Time 17.12
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG spinechop.zg30
TD 65536
SOLVENT CDCl3T
NS 320
DS 16
SWH 30303.031
FIDRES 0.462388
AQ 1.0813440
RG 3649.1
DW 16.500
DE 6.00
TE 298.0
D1 0.25000000
d11 0.03000000
D16 0.00020000
d17 0.00019600
MCREST 0 sec
MCWRK 0.01500000
P2 31.00
======== CHANNEL f1 ========
NUC1 13C
P1 15.50
PL1 500.00
PL12 2000.00
PL0 120.00
PL1 -1.00
SFO1 125.7942548
SP1 3.20
SP2 3.20
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2 0 Hz
======== CHANNEL f2 ========
CPDPRG[2 waltz16
NUC2 1H
PCPD2 100.00
PL2 1.00
PL12 24.60
SFO2 500.2225011
====== GRADIENT CHANNEL
GNAM[1] SINE.100
GNAM[2] SINE.100
GPX1 0 %
GPX2 0 %
GPY1 0 %
GPY2 0 %
GP21 30.00
GP22 50.00
P15 500.00
p16 1000.00
F2 - Processing parameters
SI 65536
SF 125.7803793
WDW EM
SSB 0
LB 1.00
GB 0
PC 2.00
150.424
149.218
135.749
122.628
113.779
88.576
55.518
55.488
52.666
41.129
36.611
12
O
O
NH
I
I
ppm

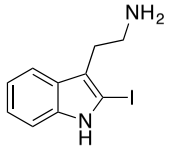

1H spectrum
13
Current Data Parameters
NAME CRA-IT-284-44-9X
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20130207
Time 10.26
INSTRUM av600
PROBHD 5 mm TBI 1H/13
PULPROG zg30
TD 98074
SOLVENT CDCl3T
NS 16
DS 2
SWH 9615.385 Hz
FIDRES 0.098042 Hz
AQ 5.0998478 sec
RG 228.8
DW 52.000 usec
DE 6.00 usec
TE 298.7 K
D1 0.10000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PLW1 23.01441956 W
SFO1 600.1342009 MHz
F2 - Processing parameters
SI 65536
SF 600.1300017 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1.832
1.845
2.382
2.499
2.511
2.518
2.526
2.536
2.545
2.645
2.651
2.673
2.684
2.988
2.996
3.005
3.014
3.023
3.037
3.048
3.053
3.057
3.061
3.066
3.793
3.842
3.924
3.940
5.140
5.156
6.570
6.494
0.000
0.976
0.962
3.148
2.914
2.299
0.958
1.081
3.087
6.057
0.984
0.985
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

13C spectrum with 1H decoupling



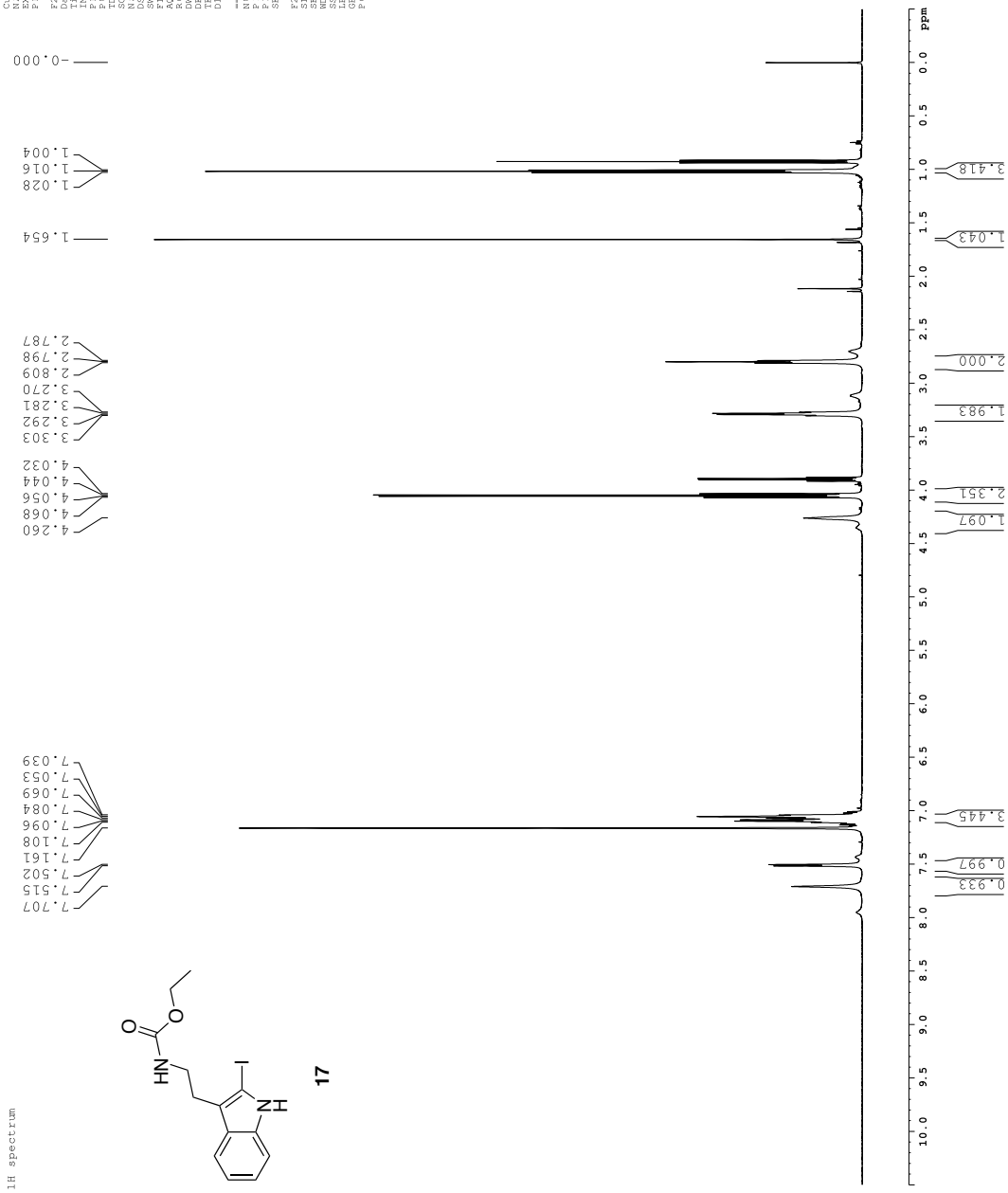

1H spectrum
9.794
7.510
7.498
7.229
7.225
7.216
7.097
7.096
7.084
7.072
7.070
7.057
7.055
7.044
7.032
7.031
3.041
3.030
3.019
2.876
2.865
2.854
1.528
0.000
NH2
NH
S3
Current Data Parameters
NAME CRA-II-117crude
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20120308
Time 13.35
INSTRUM av600
PROBHD 5 mm TBI 1H/13
PULPROG zg30
TD 98074
SOLVENT CDCl3T
NS 16
DS 2
SWH 7812.500 Hz
FIDRES 0.079659 Hz
AQ 6.2767355 sec
RG 406.1
DW 64.000 usec
DE 6.00 usec
TE 298.0 K
D1 1.00000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PLW1 23.01441956 W
SFO1 600.1330594 MHz
F2 - Processing parameters
SI 65536
SF 600.1300055 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
0.804
2.031
1.954
1.941
0.987
1.103
1.033
0.922
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

13C spectrum with 1H decoupling

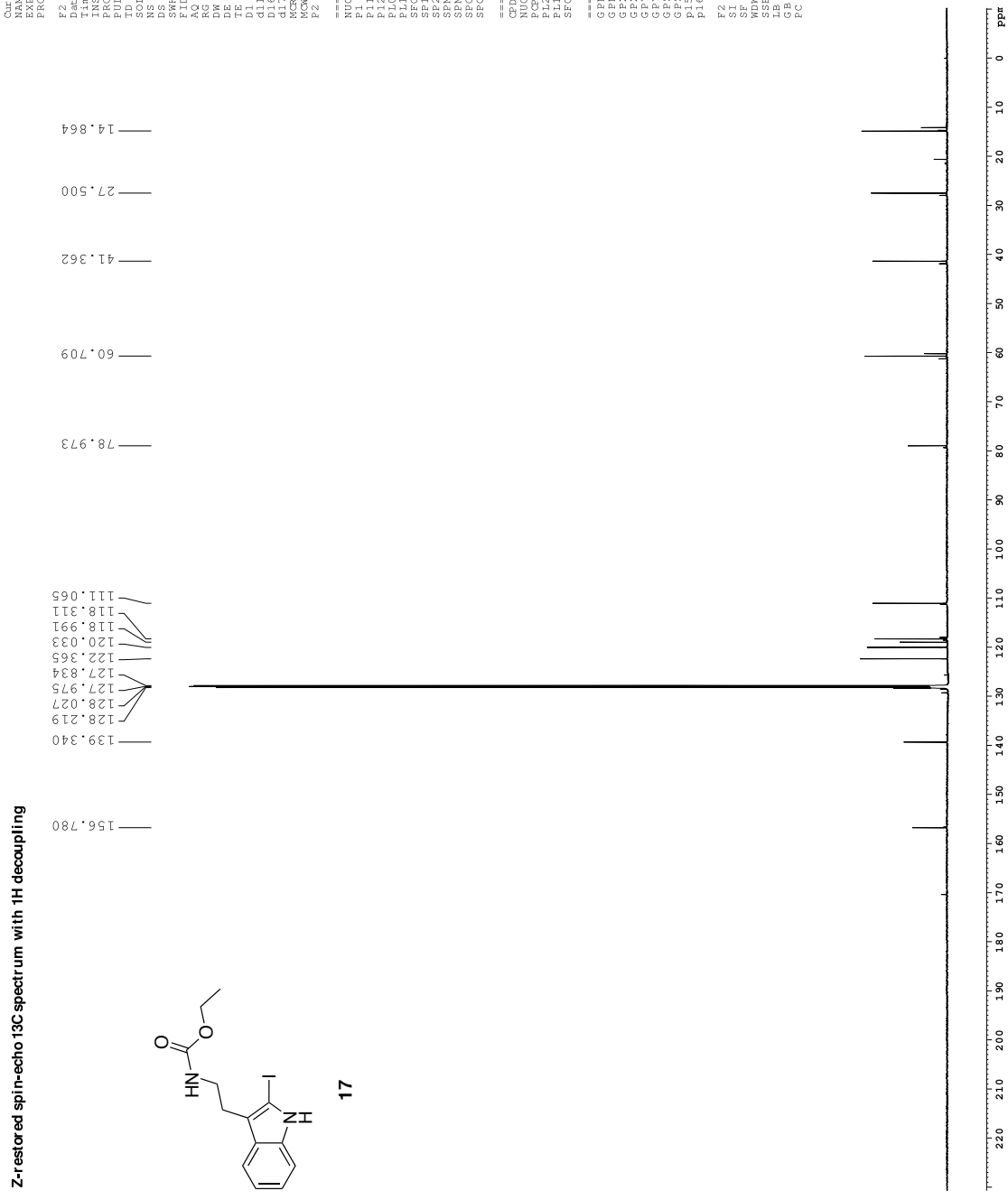


S3


```
Current Data Parameters
NAME      CRA-II-117crude
EXPNO                   3
PROCNO                  1

F2 - Acquisition Paramete
Date_            20120308
Time                3.21
INSTRUM            av600
PROBHD  5 mm TBI 1H/13
PULPROG          zgdc30
TD                65536
SOLVENT           CDCl3T
NS                   240
DS                     4
SWH            36231.883
FIDRES         0.552855
AQ             0.9043968
RG                   362
DW                13.800
DE                 6.00
TE                298.1
D1            0.40000001
D11           0.03000000

======== CHANNEL f1 ====
NUC1                13C
P1                15.00
PLW1       107.15190125
SFO1       150.9194080

======== CHANNEL f2 ====
CPDPRG[2         waltz16
NUC2                1H
PCPD2             70.00
PLW2      0 W
PLW12        0.30199519
SFO2         600.1330010

F2 - Processing paramete
SI                65536
SF           150.9028099
WDW                  EM
SSB       0
LB                 1.00
GB        0
PC                 1.00
```


1H spectrum
Current Data Parameters
NAME CRA-II-110column2-25-3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20120304
Time 8.35
INSTRUM av600
PROBHD 5 mm TBI 1H/13
PULPROG zg30
TD 98074
SOLVENT C6D6T
NS 16
DS 2
SWH 9615.385 Hz
FIDRES 0.098042 Hz
AQ 5.0998478 sec
RG 645.6
DW 52.000 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PLW1 23.0144196 W
SFO1 600.1342009 MHz
F2 - Processing parameters
SI 65536
SF 600.1299556 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
7.707
7.515
7.502
7.161
7.108
7.096
7.084
7.069
7.053
7.039
4.260
4.068
4.056
4.044
4.032
3.303
3.292
3.281
3.270
2.809
2.798
2.787
1.654
1.028
1.016
1.004
-0.000
3.445
0.997
0.933
1.097
2.351
2.000
1.983
1.043
3.418
ppm
17

Z-restored spin-echo 13C spectrum with 1H decoupling



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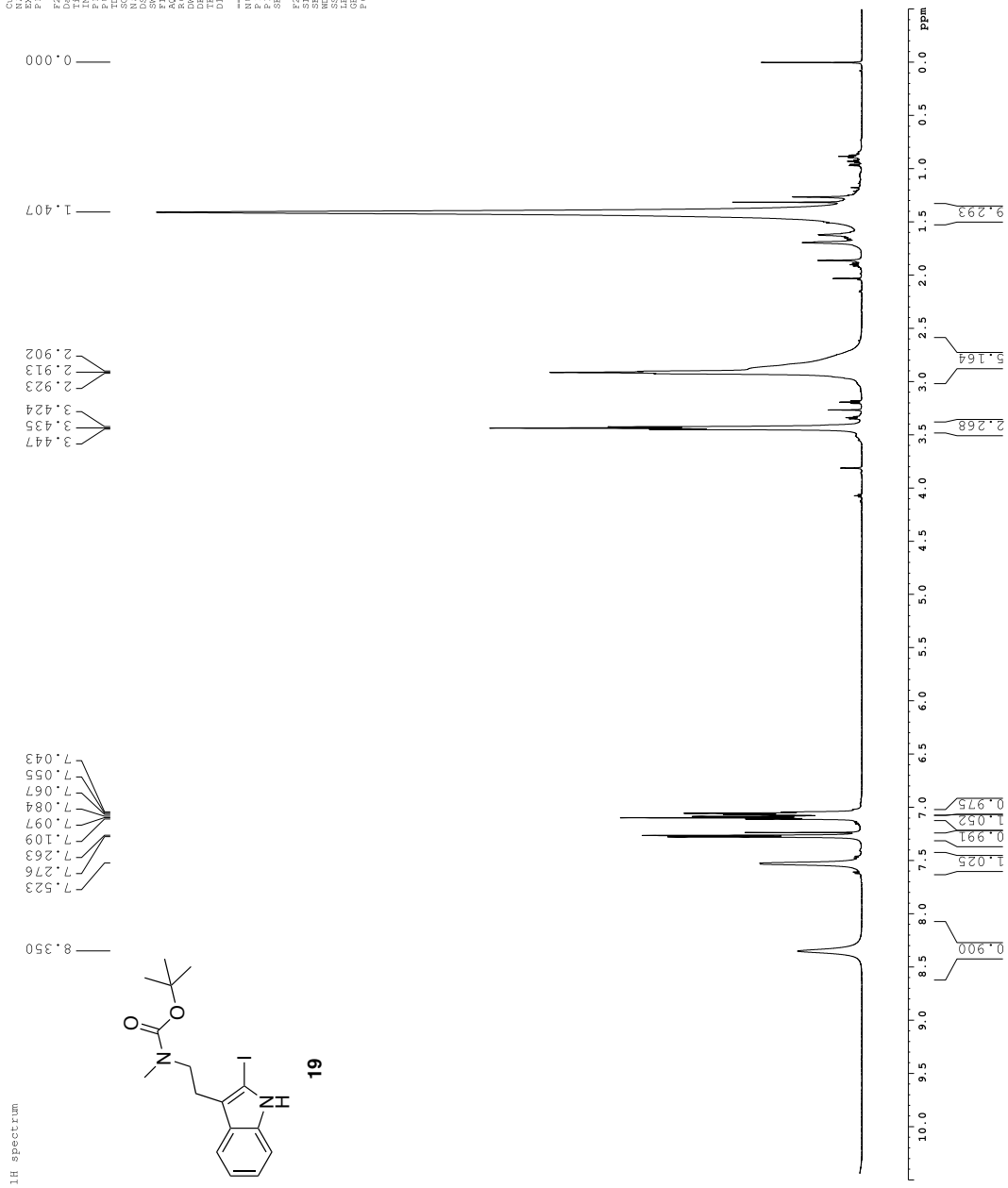
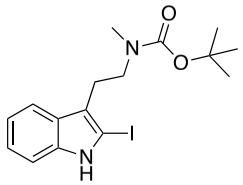
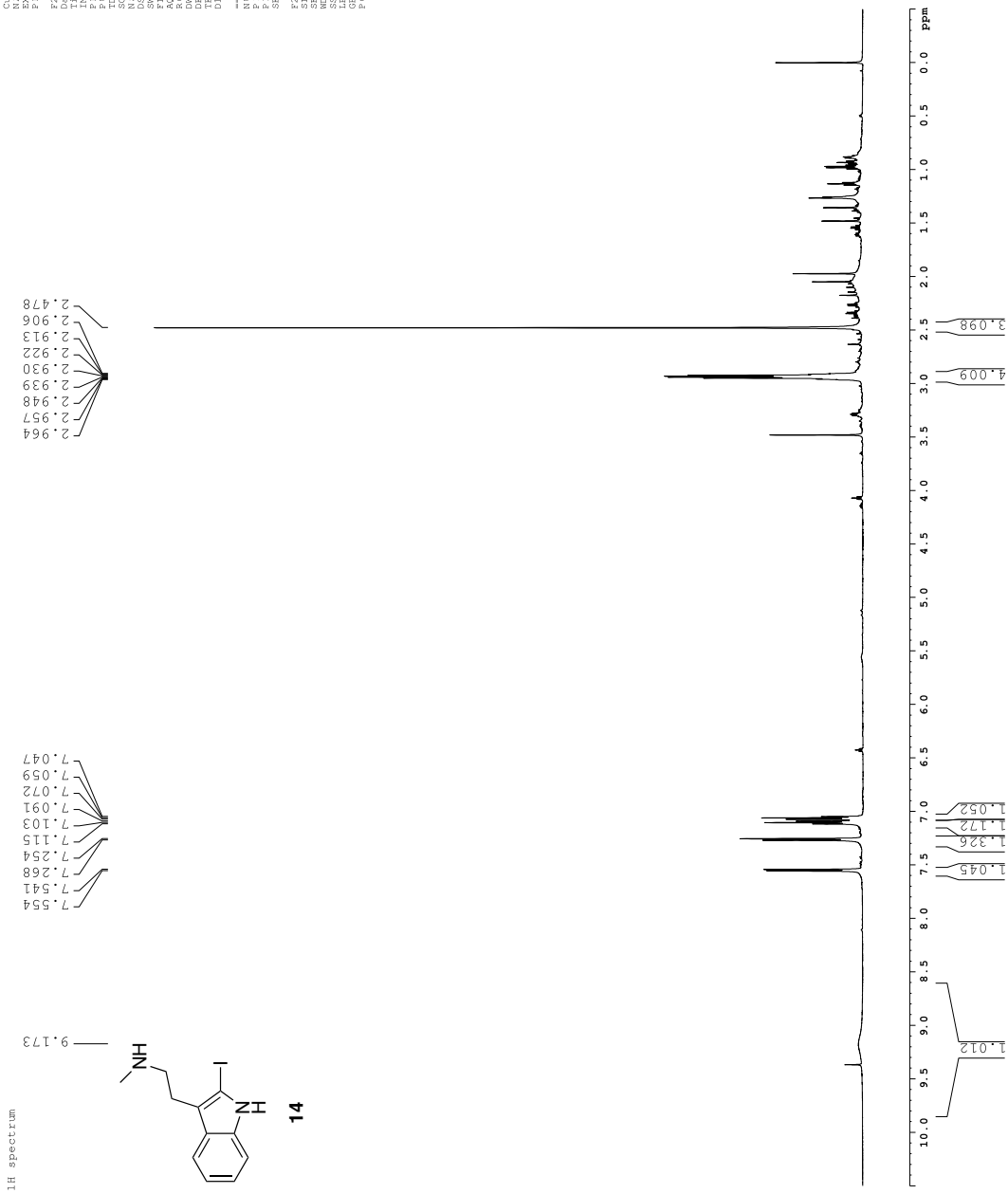

1H spectrum
Current Data Parameters
NAME CRA-II-161col2
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20120512
Time 14.22
INSTRUM av600
PROBHD 5 mm TBI 1H/13
PULPROG zg30
TD 98074
SOLVENT CDCl3
NS 16
DS 2
SWH 6613.757 Hz
FIDRES 0.067436 Hz
AQ 7.4143944 sec
RG 228
DW 75.600 usec
DE 6.00 usec
TE 302.2 K
D1 0.10000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PLW1 23.01441956 W
SFO1 600.1330041 MHz
F2 - Processing parameters
SI 65536
SF 600.1300002 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
0.000
1.407
2.902
2.913
2.923
3.424
3.435
3.447
7.043
7.055
7.067
7.084
7.097
7.109
7.263
7.276
7.523
8.350
0.900
1.025
0.991
1.052
0.975
5.164
2.268
9.293
ppm
19

13C spectrum with 1H decoupling

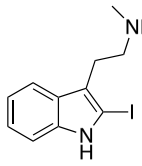


19


```
Current Data Parameters
NAME      CRA-II-161col2
EXPNO                  3
PROCNO                 1

F2 - Acquisition Paramete
Date_           20120512
Time               14.27
INSTRUM            av600
PROBHD  5 mm TBI 1H/13
PULPROG          zgdc30
TD                65536
SOLVENT           CDCl3T
NS                   240
DS                     4
SWH            36231.883
FIDRES         0.552855
AQ             0.9043968
RG                   912
DW                13.800
DE                 6.00
TE                323.0
D1             0.40000001
D11            0.03000000

======== CHANNEL f1 ====
NUC1                13C
P1                15.00
PLW1       107.15190125
SFO1        150.9194080

======== CHANNEL f2 ====
CPDPRG[2          waltz16
NUC2                1H
PCPD2             70.00
PLW2      0 W
PLW12        0.30199519
SFO2         600.1330010

F2 - Processing paramete
SI                 65536
SF            150.9027894
WDW                   EM
SSB       0
LB                 3.00
GB        0
PC                 1.00
```

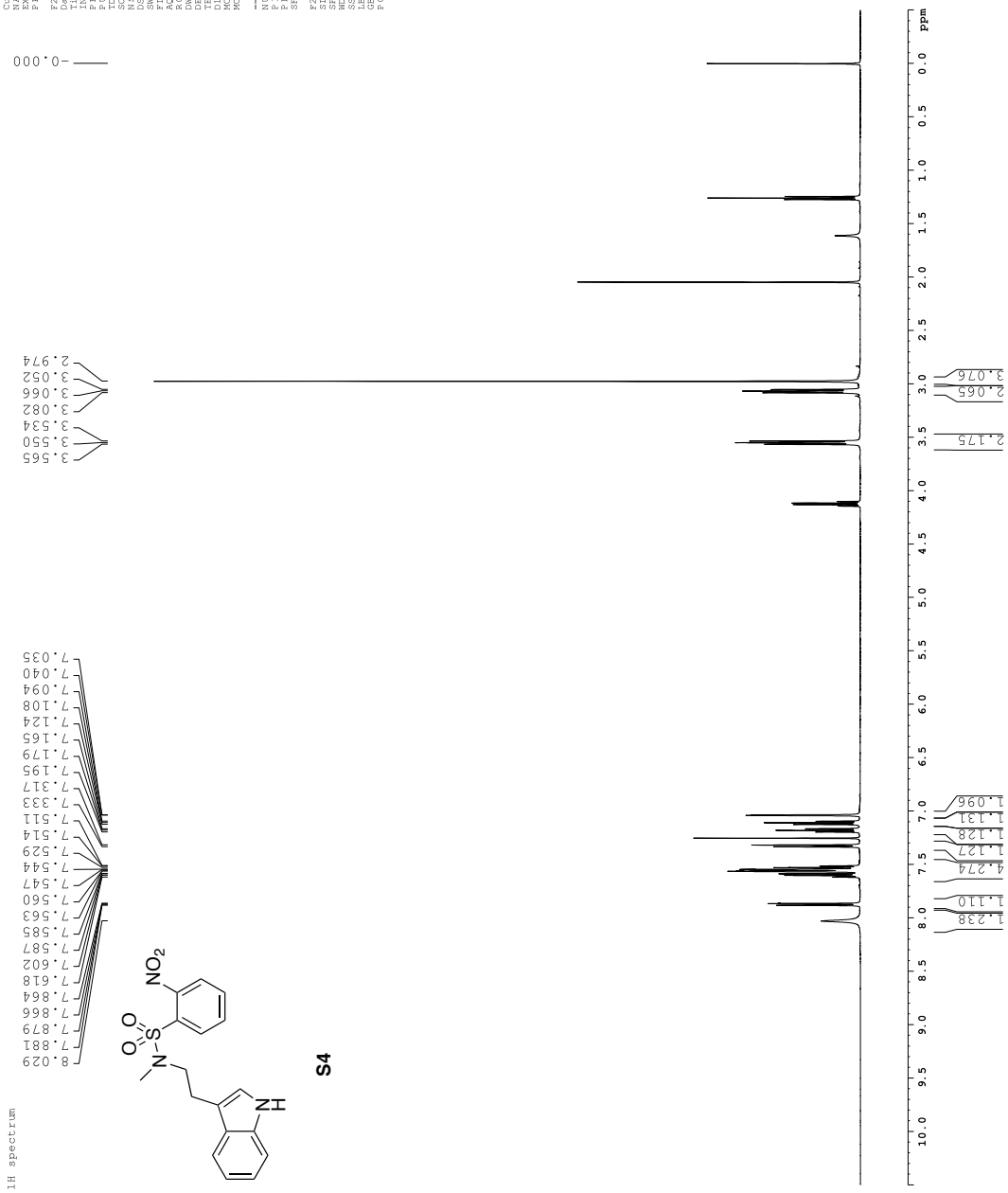

Current Data Parameters
NAME CRA-II-166-30-7-6
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20120518
Time 21.34
INSTRUM av600
PROBHD 5 mm TBI 1H/13
PULPROG zg30
TD 98074
SOLVENT CDCl3T
NS 16
DS 2
SWH 9615.385 Hz
FIDRES 0.098042 Hz
AQ 5.0998478 sec
RG 228.7
DW 52.000 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PLW1 23.01441956 W
SFO1 600.1342009 MHz
F2 - Processing parameters
SI 65536
SF 600.1300098 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1H spectrum
14
9.173
7.554
7.541
7.268
7.254
7.115
7.103
7.091
7.072
7.059
7.047
2.964
2.957
2.948
2.939
2.930
2.922
2.913
2.906
2.478
1.012
1.045
1.326
1.172
1.052
4.009
3.098
ppm

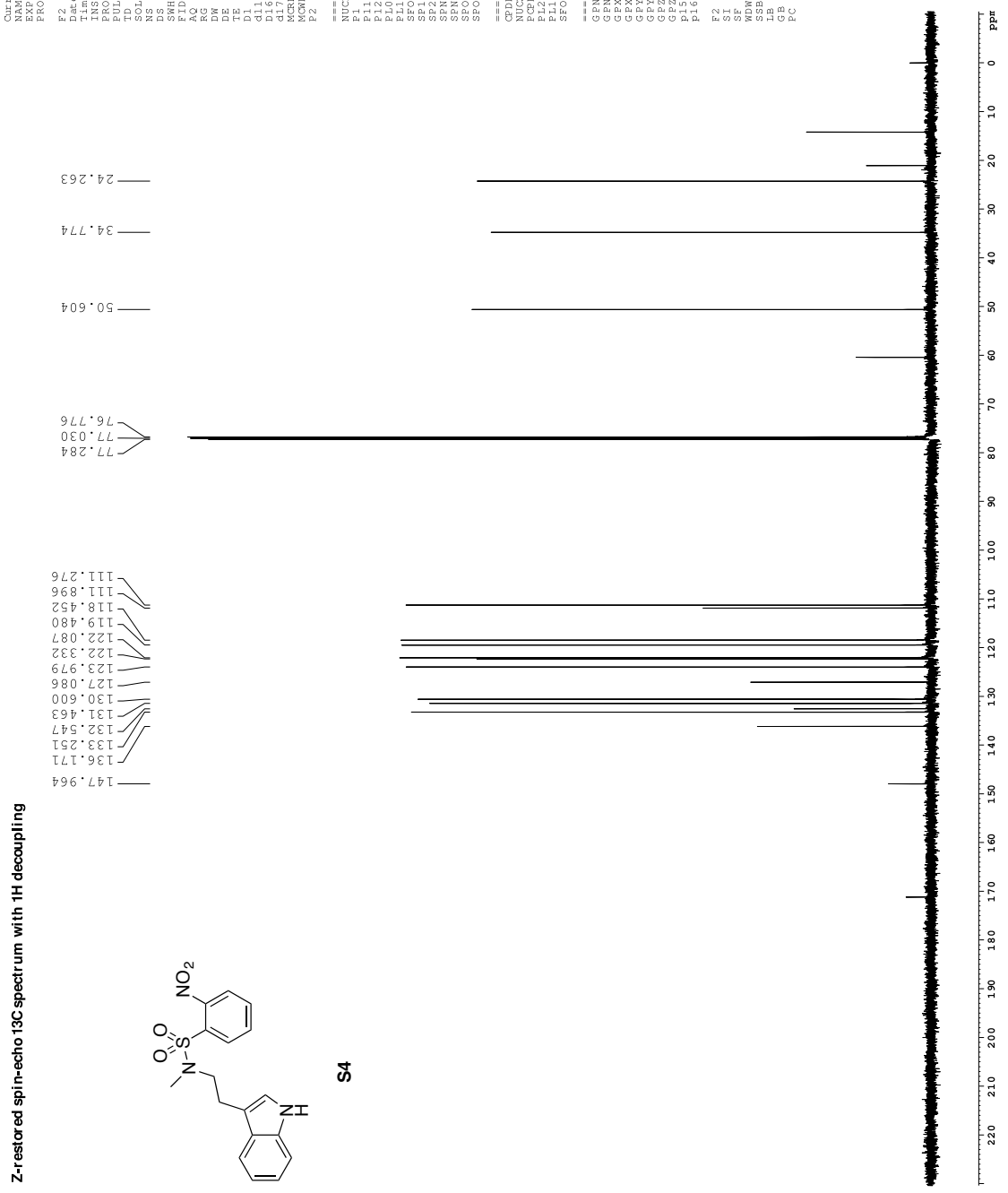
13C spectrum with 1H decoupling



14

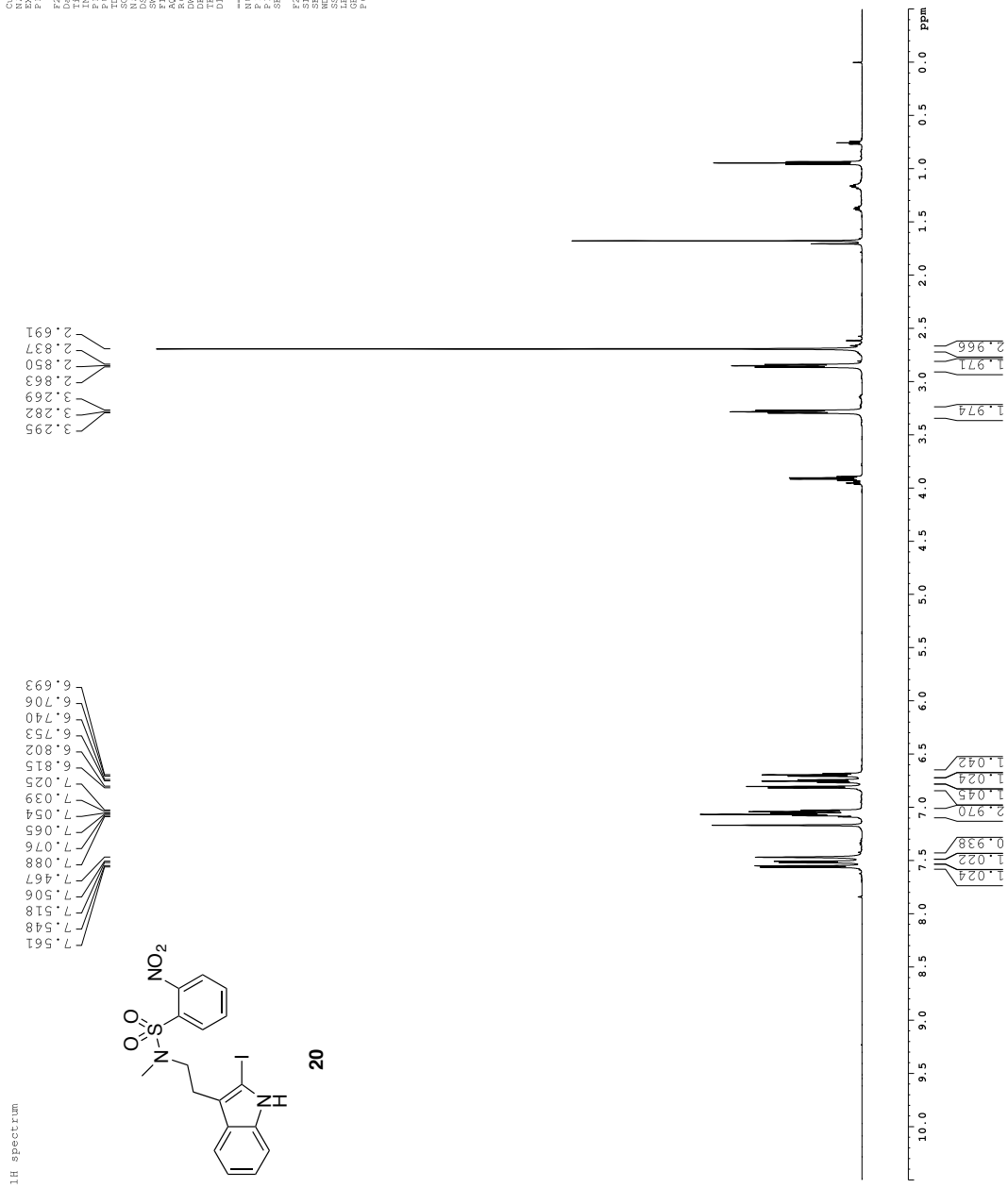

```
Current Data Parameters
NAME      CRA-II-166-30-7
EXPNO                   2
PROCNO                  1

F2 - Acquisition Paramete
Date_            20120518
Time                21.41
INSTRUM             av600
PROBHD  5 mm TBI 1H/13
PULPROG          zgdc30
TD                65536
SOLVENT           CDCl3T
NS                   400
DS                     4
SWH            36231.883
FIDRES         0.552855
AQ             0.9043968
RG                   645
DW                13.800
DE                 6.00
TE                298.1
D1            0.40000001
D11           0.03000000

======== CHANNEL f1 ====
NUC1                13C
P1                15.00
PLW1       107.15190125
SFO1        150.9194080

======== CHANNEL f2 ====
CPDPRG[2          waltz16
NUC2                1H
PCPD2             70.00
PLW2      0 W
PLW12        0.30199519
SFO2         600.1330010

F2 - Processing paramete
SI                  65536
SF           150.9028003
WDW                    EM
SSB       0
LB                  1.00
GB        0
PC                  1.00
```


1H spectrum
S4
8.029
7.881
7.879
7.866
7.864
7.618
7.602
7.587
7.585
7.563
7.560
7.547
7.544
7.529
7.514
7.511
7.333
7.317
7.195
7.179
7.165
7.124
7.108
7.094
7.040
7.035
3.565
3.550
3.534
3.082
3.066
3.052
2.974
-0.000
1.238
1.110
4.274
1.127
1.128
1.131
1.096
2.175
3.076
2.065
ppm

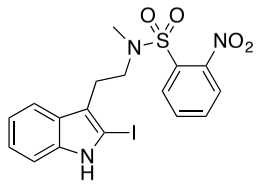


Z-restored spin-echo 13C spectrum with 1H decoupling

S4

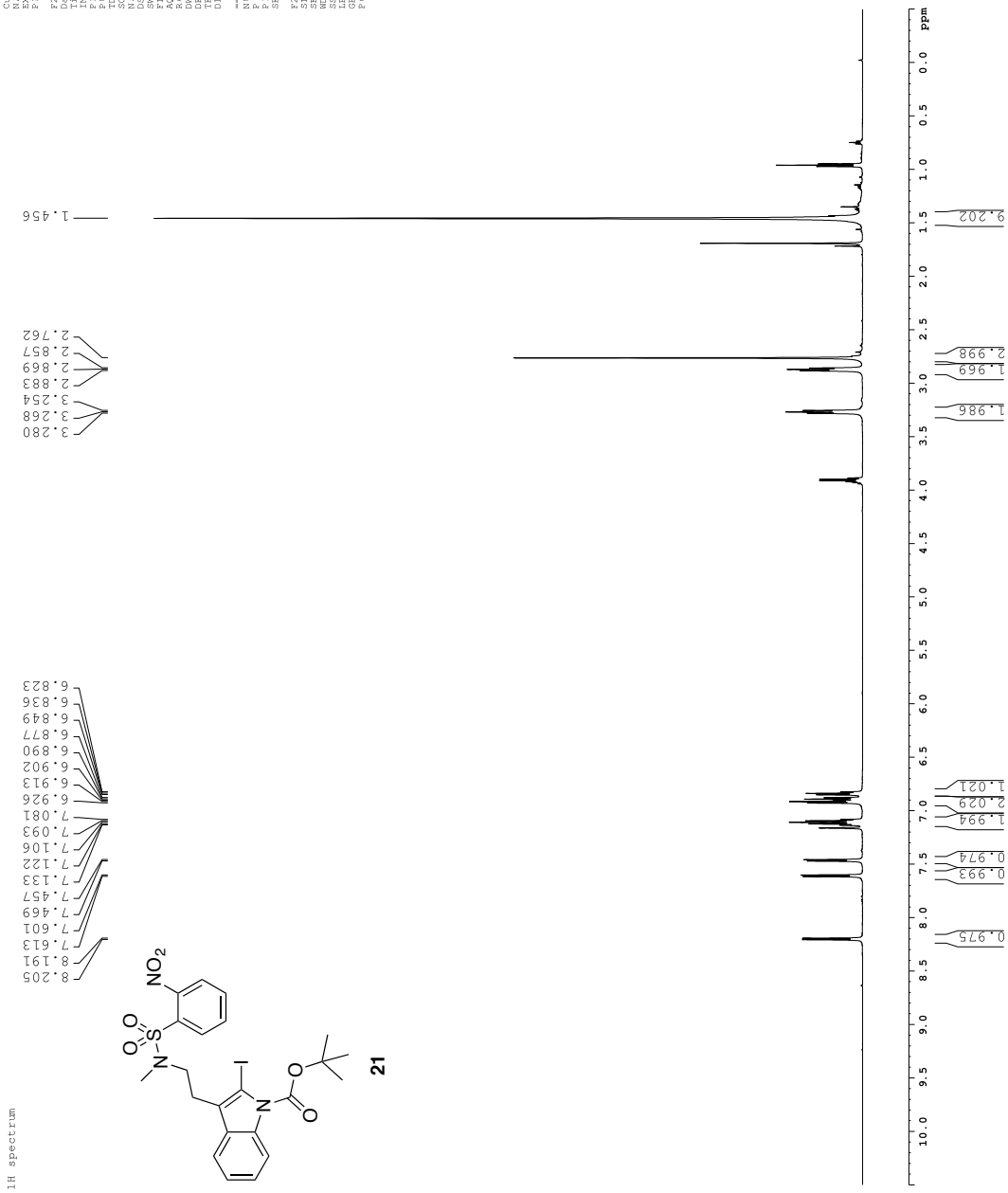

1H spectrum
20
7.561
7.548
7.518
7.506
7.467
7.088
7.076
7.065
7.054
7.039
7.025
6.815
6.802
6.753
6.740
6.706
6.693
3.295
3.282
3.269
2.863
2.850
2.837
2.691
1.974
1.971
2.966
0.938
1.022
1.024
2.970
1.045
1.024
1.042
ppm

13C spectrum with 1H decoupling

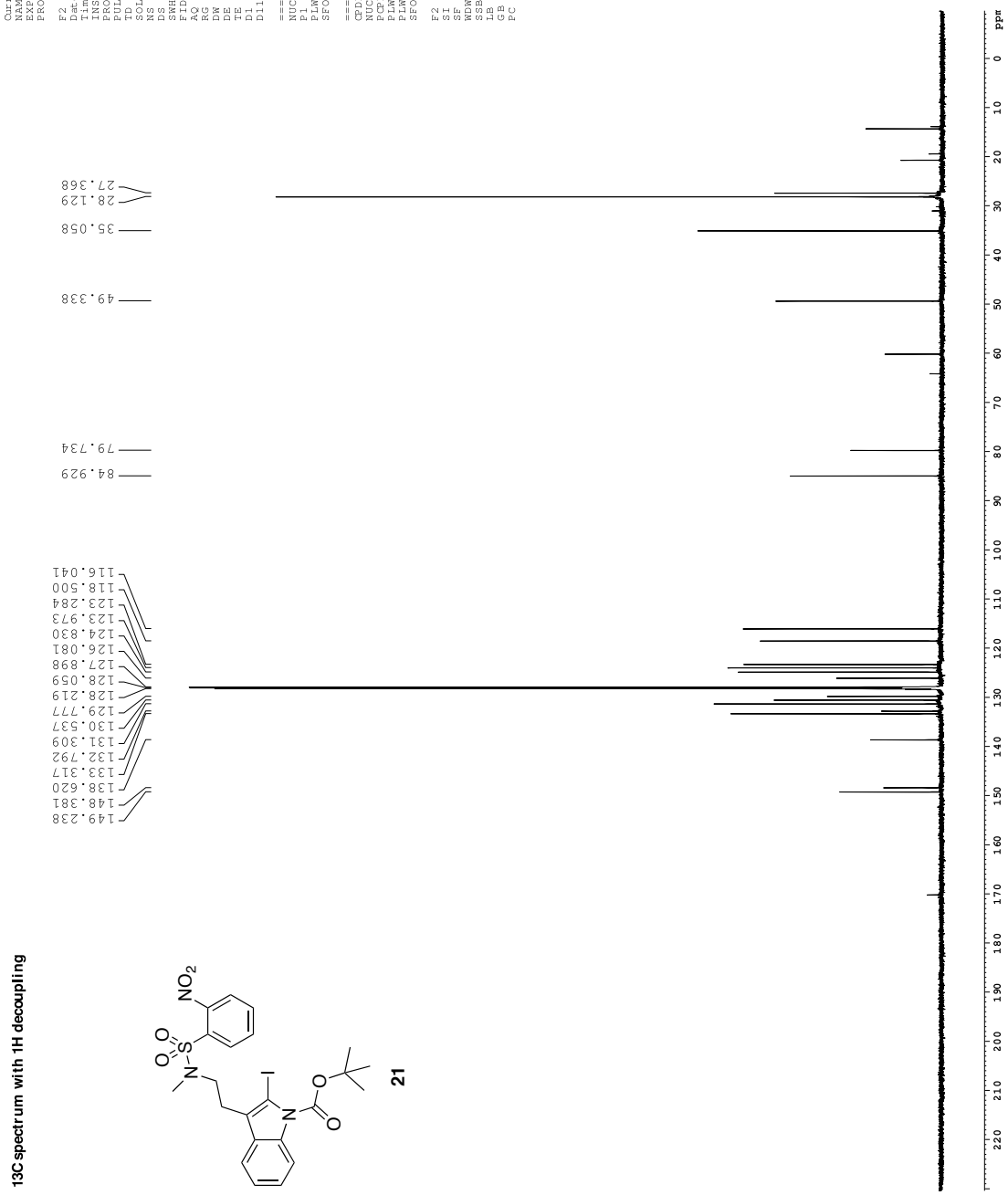


20

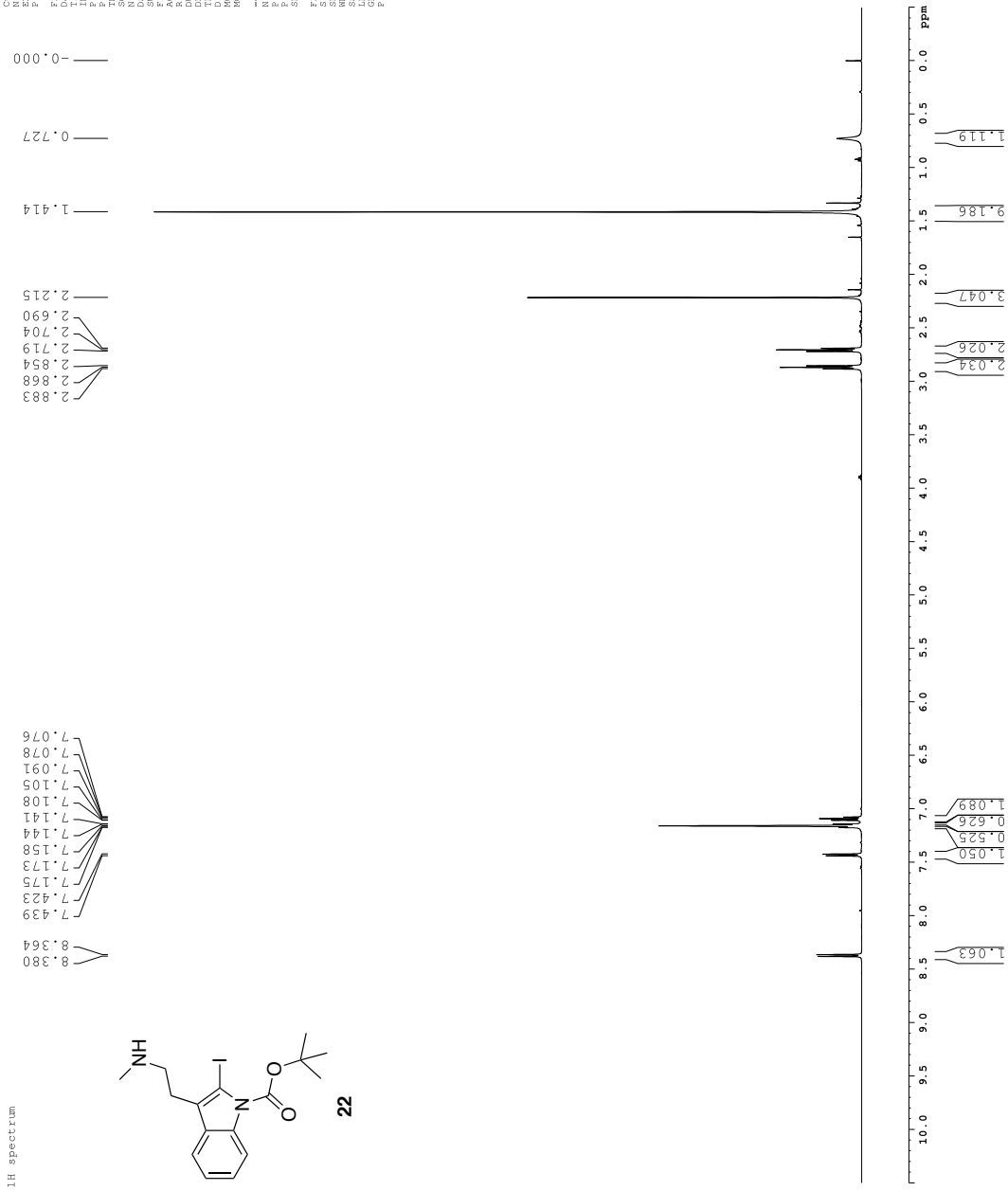

```
Current Data Parameters
NAME      CRA-II-200col2p
EXPNO                   2
PROCNO                  1

F2 - Acquisition Paramete
Date_            20120810
Time                10.21
INSTRUM             av600
PROBHD   5 mm TBI 1H/13
PULPROG          zgdc30
TD                65536
SOLVENT           C6D6T
NS                  512
DS                    4
SWH           36231.883
FIDRES         0.552855
AQ             0.9043968
RG                  101
DW                13.800
DE                 6.00
TE                298.0
D1            0.40000001
D11           0.03000000

======== CHANNEL f1 ====
NUC1                13C
P1                15.00
PLW1       107.15190125
SFO1        150.9194080

======== CHANNEL f2 ====
CPDPRG[2         waltz16
NUC2                1H
PCPD2             70.00
PLW2      0 W
PLW12        0.30199519
SFO2         600.1330010

F2 - Processing paramete
SI                65536
SF           150.9027581
WDW                  EM
SSB       0
LB                 1.00
GB        0
PC                 1.00
```

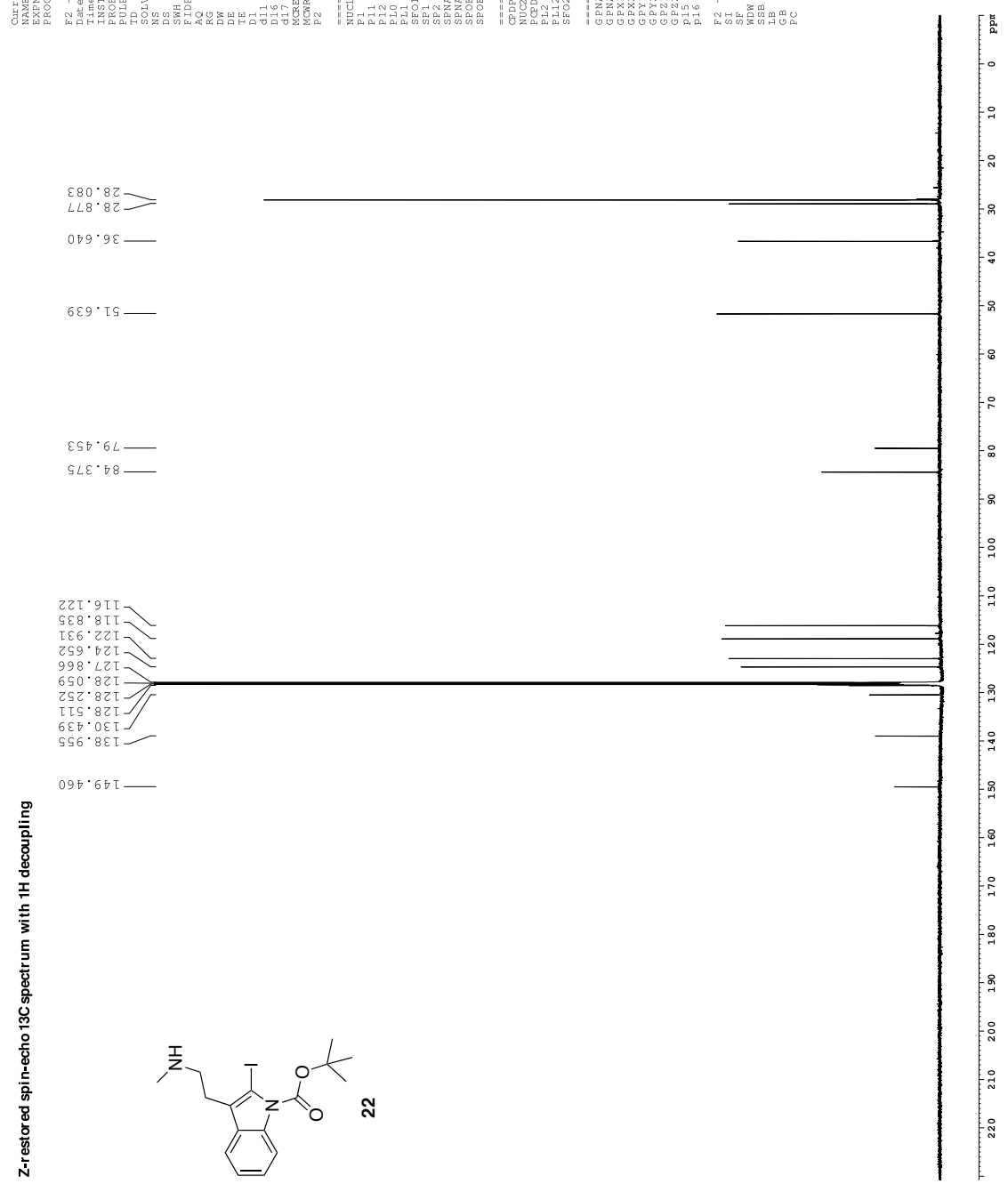

1H spectrum
Current Data Parameters
NAME CRA-II-187prod
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20120709
Time 16.52
INSTRUM av600
PROBHD 5 mm TBI 1H/13
PULPROG zg30
TD 98074
SOLVENT CDCl3
NS 16
DS 2
SWH 9615.385 Hz
FIDRES 0.098042 Hz
AQ 5.0998478 sec
RG 226
DW 52.000 usec
DE 6.00 usec
TE 298.3 K
D1 0.10000000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 8.00 usec
PLW1 23.01441956 W
SFO1 600.1342009 MHz
F2 - Processing parameters
SI 65536
SF 600.1299963 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
8.205
8.191
7.613
7.601
7.469
7.457
7.133
7.122
7.106
7.093
7.081
6.926
6.913
6.902
6.890
6.877
6.849
6.836
6.823
3.280
3.268
3.254
2.883
2.869
2.857
2.762
1.456
9.202
2.998
1.969
1.986
1.021
2.029
1.994
0.974
0.993
0.975
ppm
21

13C spectrum with 1H decoupling

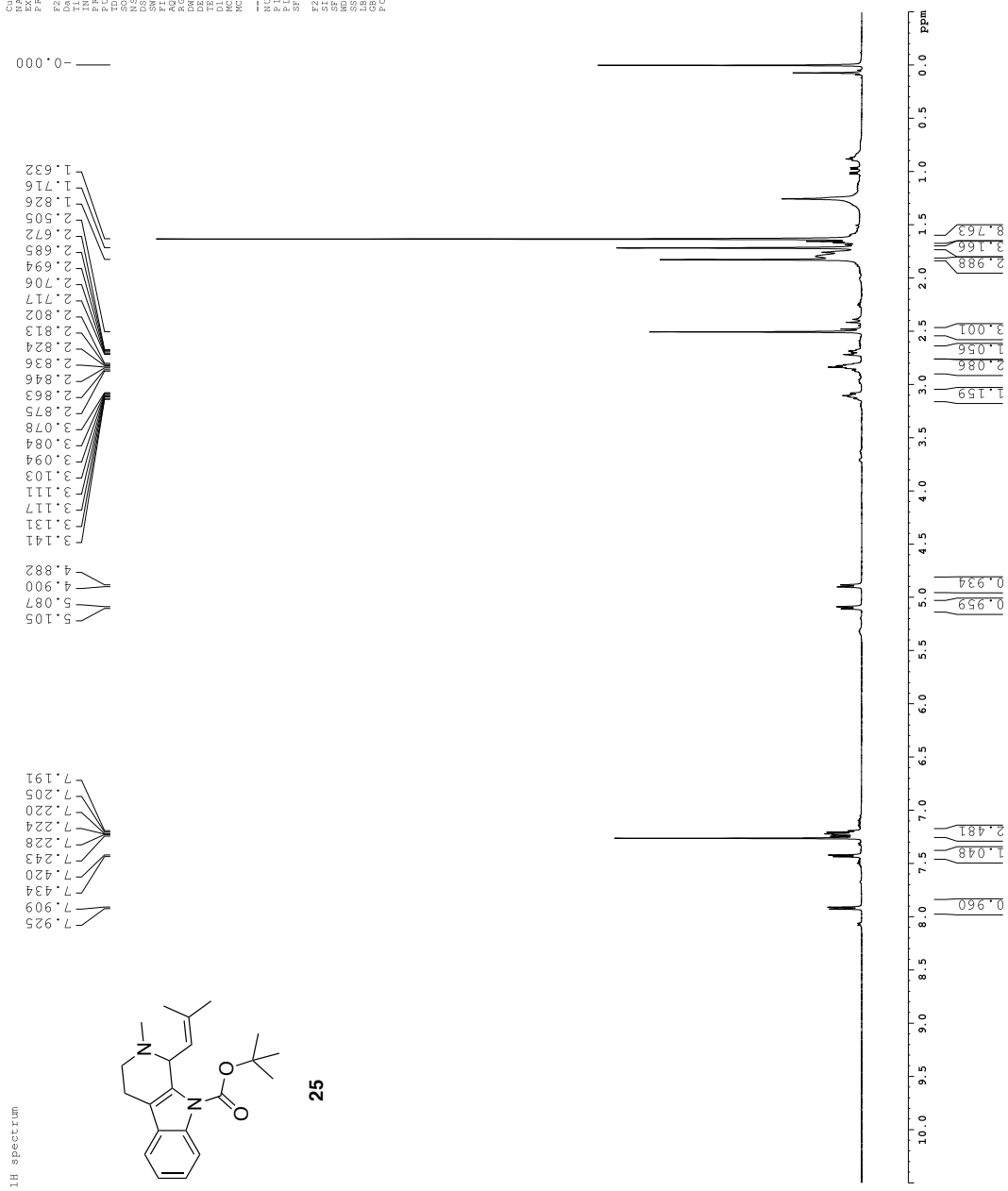


21

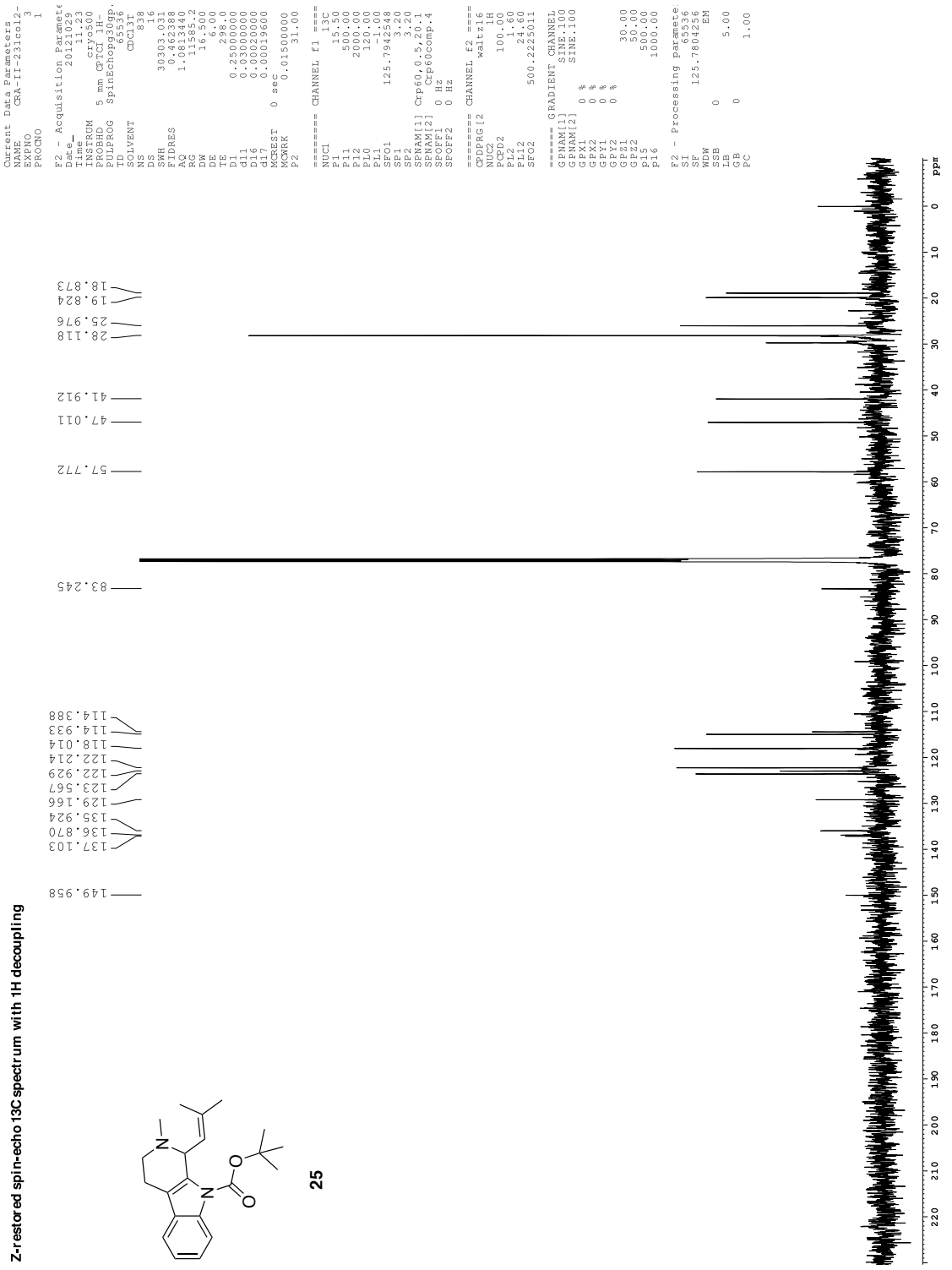

1H spectrum
22
7.076
7.078
7.091
7.105
7.108
7.141
7.144
7.158
7.173
7.175
7.423
7.439
8.364
8.380
2.883
2.868
2.854
2.719
2.704
2.690
2.215
1.414
0.727
-0.000
1.063
1.050
0.525
0.626
1.089
1.119
9.186
3.047
2.026
2.034
ppm



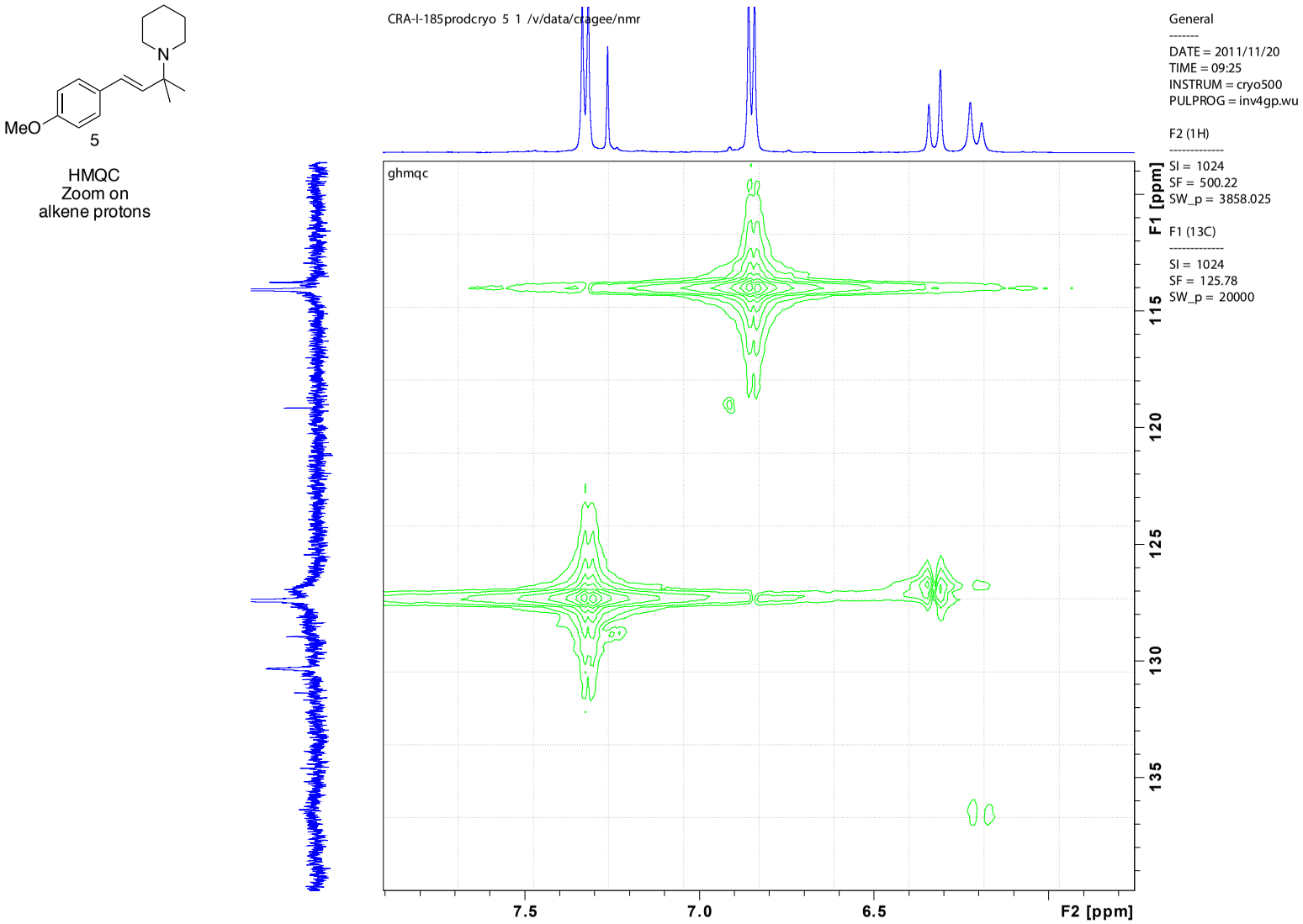
Z-restored spin-echo 13C spectrum with 1H decoupling

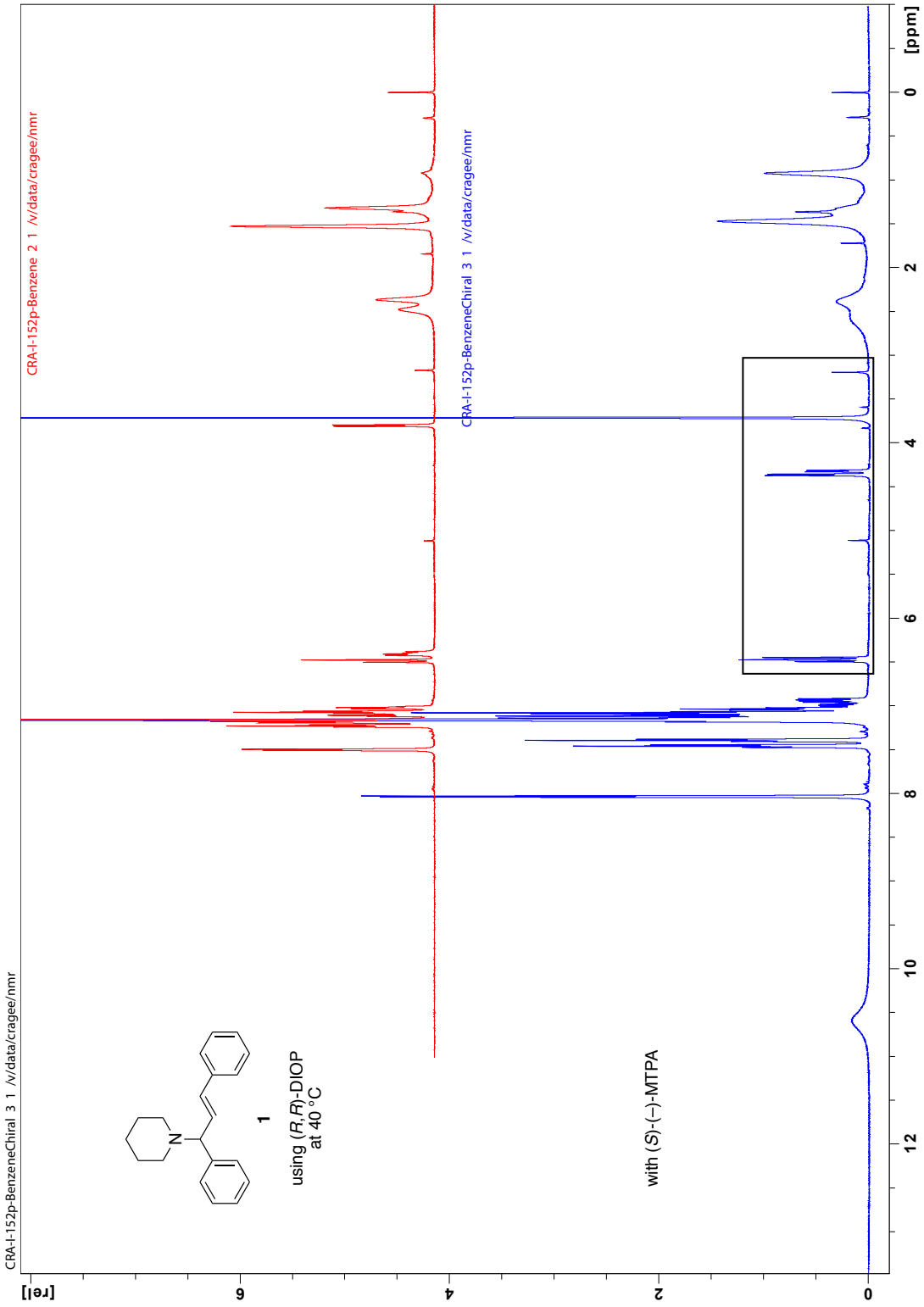

1H spectrum
Current Data Parameters
NAME CRA-II-231col2-11-24 cr
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 20121029
Time 11.17
INSTRUM cry500
PROBHD 5 mm CPTCI 1H-
PULPROG s2pul
TD 81928
SOLVENT CDCl3
NS 32
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0998273 sec
RG 203.11
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec 0.01500000 sec
MCWRK
CHANNEL f1
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200299 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB
PC 4.00
25
ppm
7.925
7.909
7.434
7.420
7.243
7.228
7.224
7.220
7.205
7.191
5.105
5.087
4.900
4.882
3.141
3.131
3.117
3.111
3.103
3.094
3.084
3.078
2.875
2.863
2.846
2.836
2.824
2.813
2.802
2.717
2.706
2.694
2.685
2.672
2.505
1.826
1.716
1.632
0.960
1.048
2.481
2.988
3.166
8.763
3.001
1.056
2.086
1.159
0.959
0.934

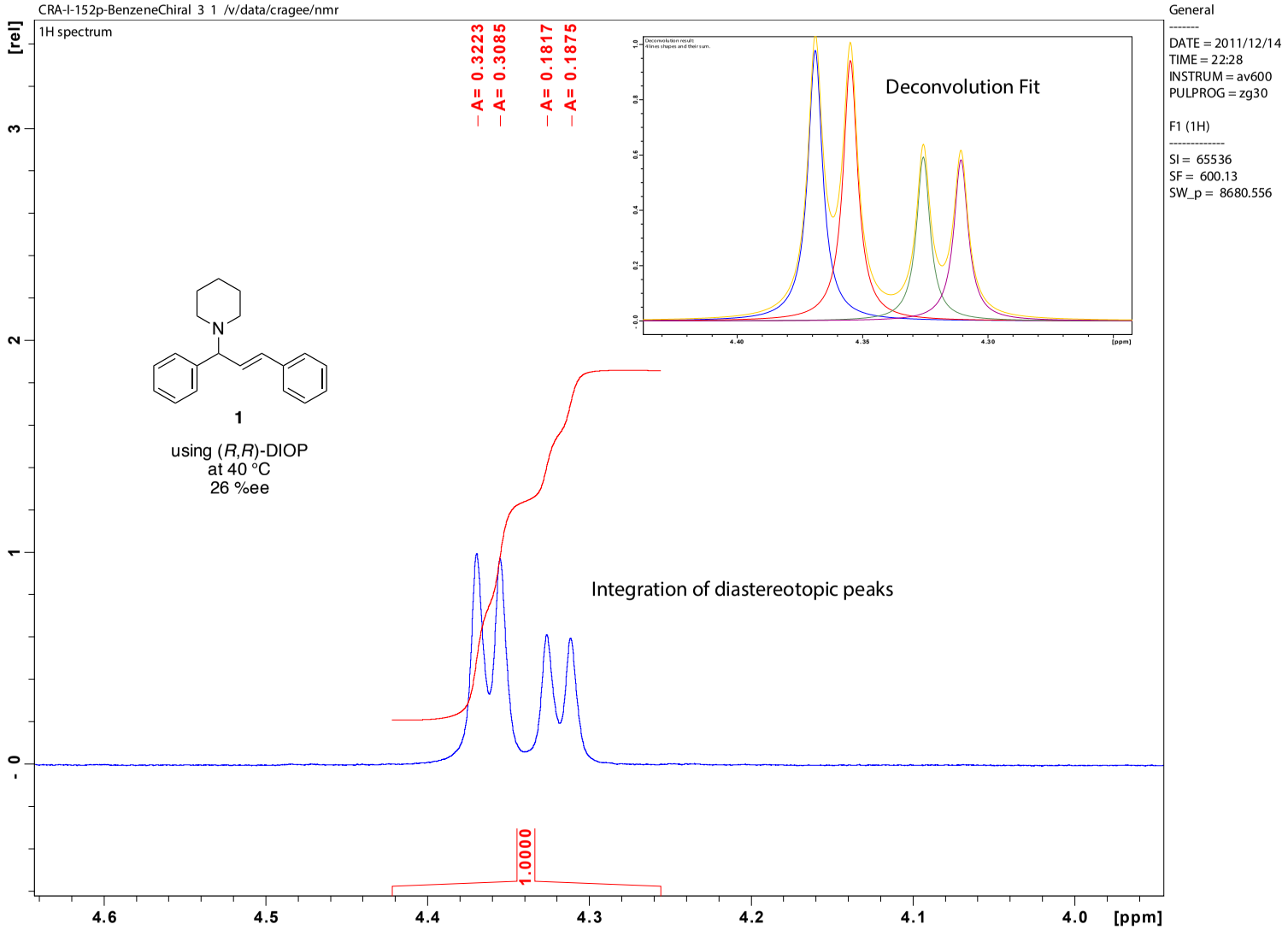
Z-restored spin-echo 13C spectrum with 1H decoupling

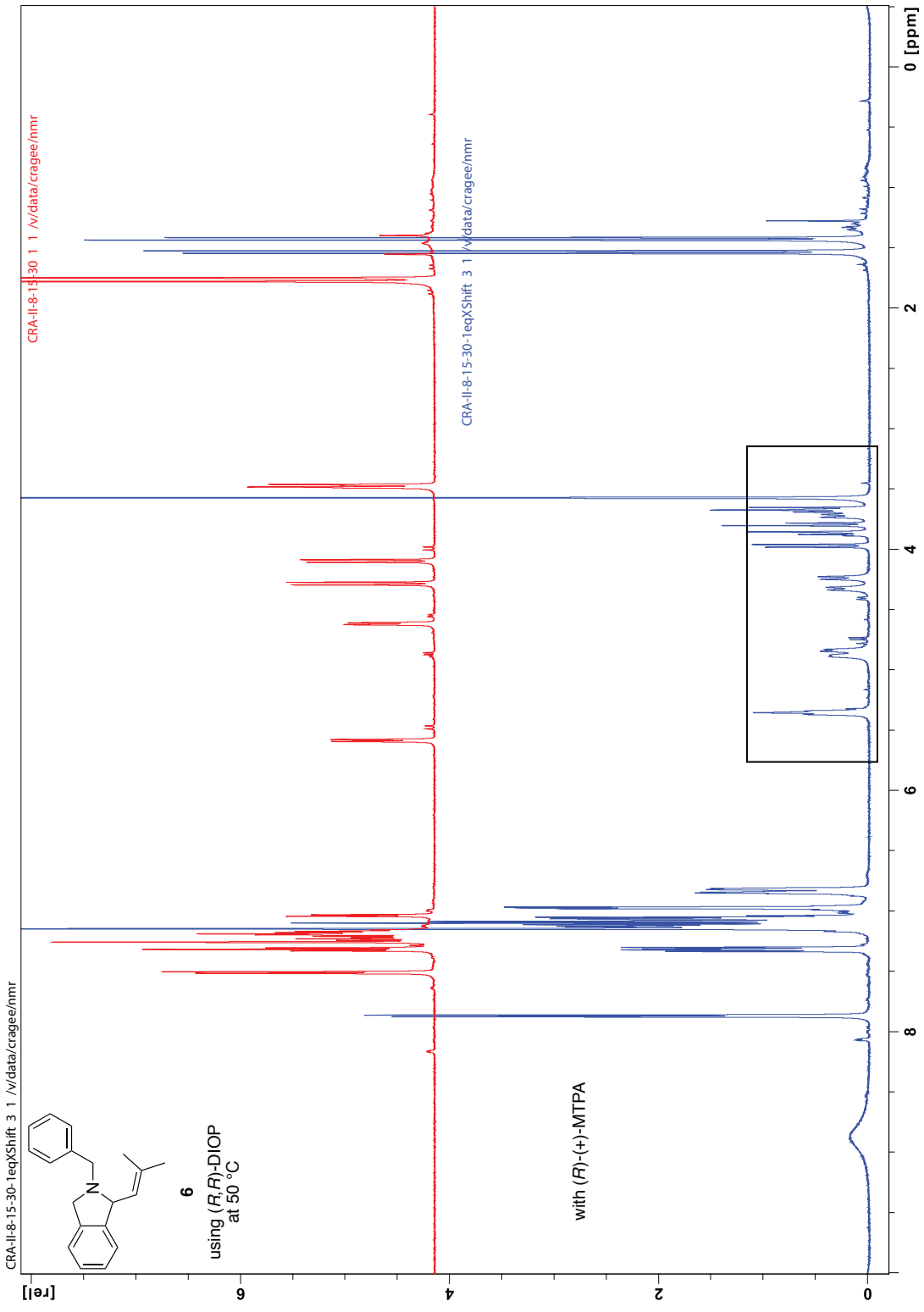


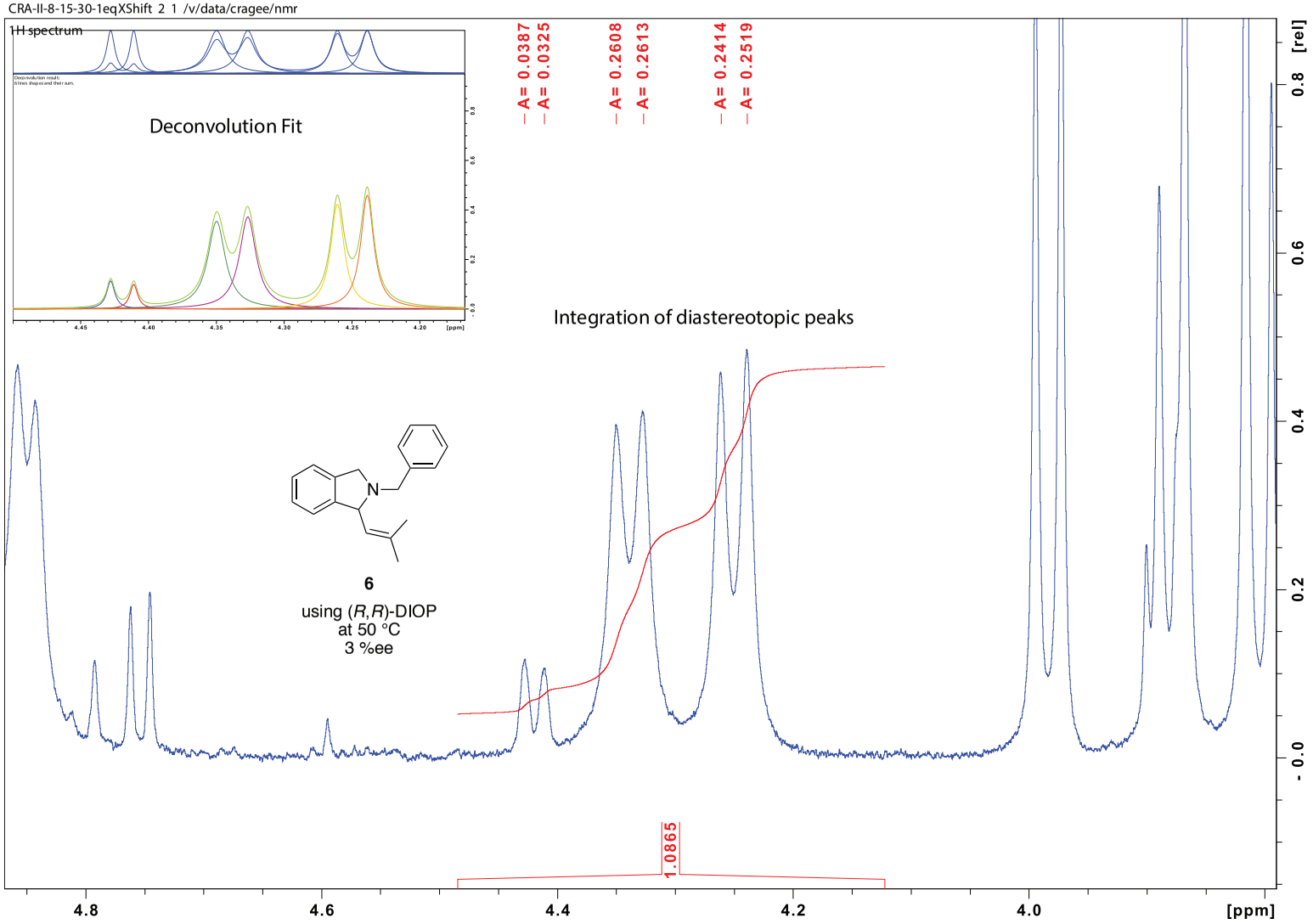
25

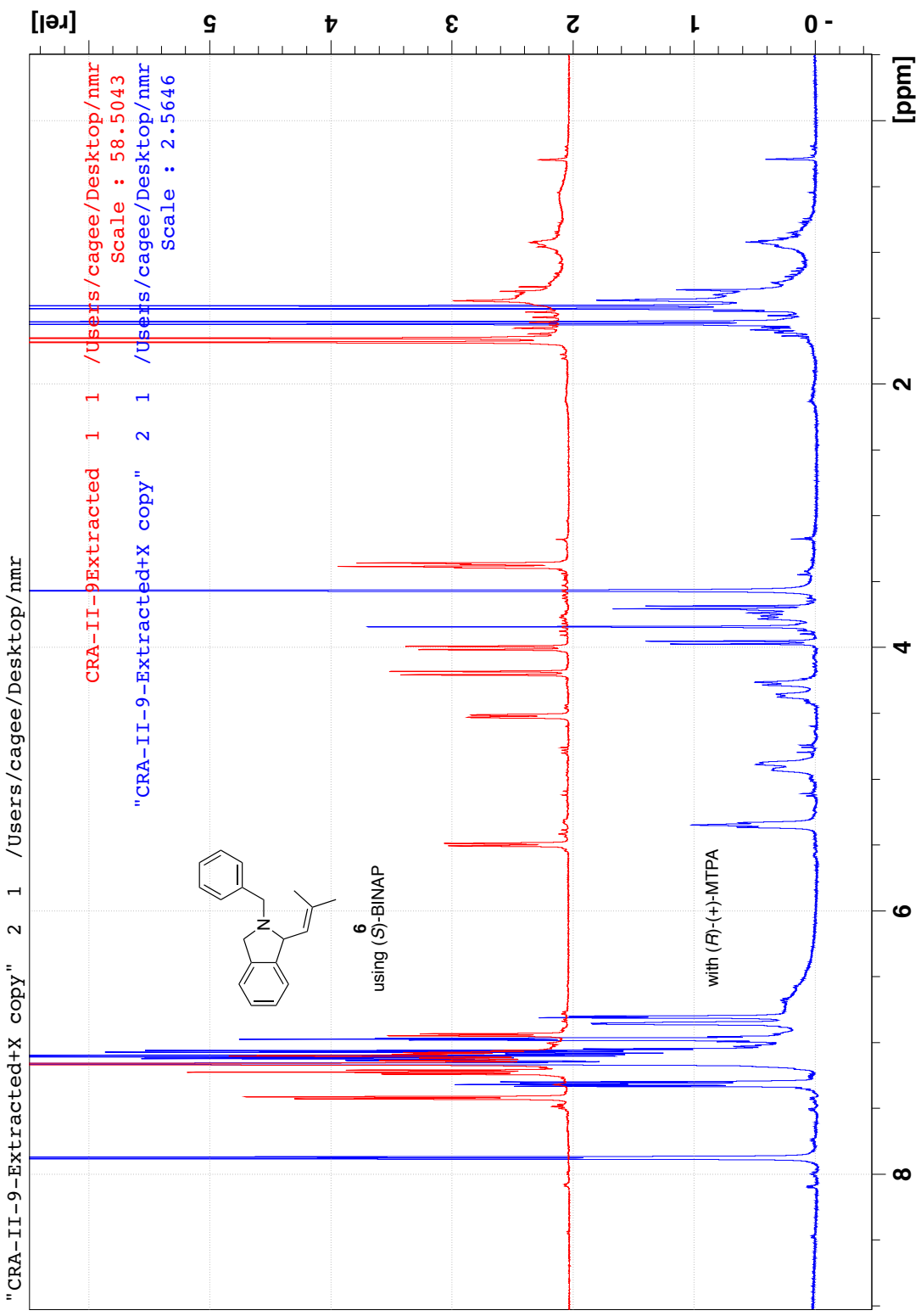

MeO
N
5
HMQC
Zoom on
alkene protons
CRA-I-185prodcryo 5 1 /v/data/cragee/nmr
ghmqc
General
DATE = 2011/11/20
TIME = 09:25
INSTRUM = cryo500
PULPROG = inv4gp.wu
F2 (1H)
SI = 1024
SF = 500.22
SW_p = 3858.025
F1 (13C)
SI = 1024
SF = 125.78
SW_p = 20000
F1 [ppm]
115
120
125
130
135
7.5
7.0
6.5
F2 [ppm]

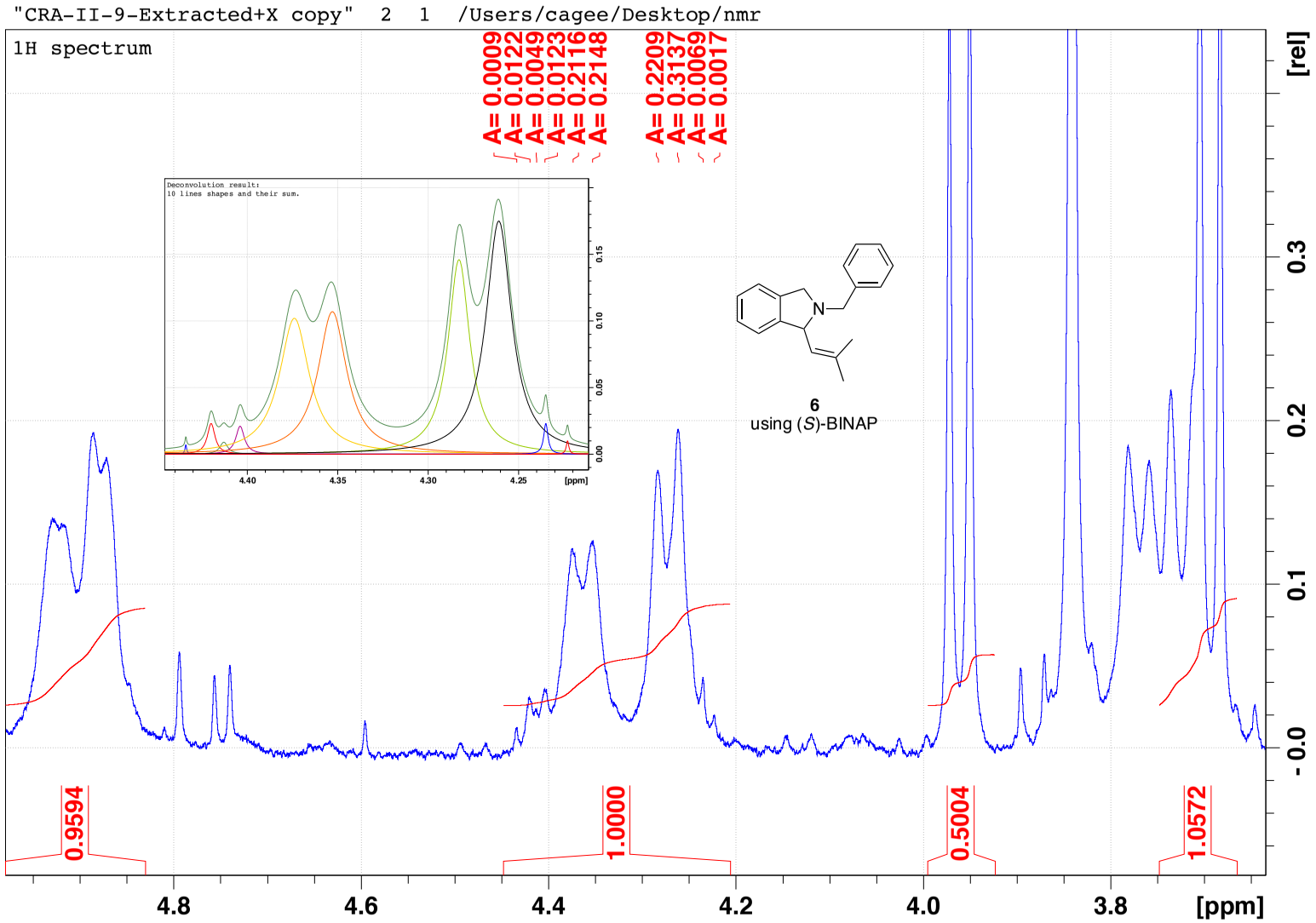

CRA-I-152p-BenzeneChiral 3 1 /v/data/cragee/nmr
CRA-I-152p-Benzene 2 1 /v/data/cragee/nmr
CRA-I-152p-BenzeneChiral 3 1 /v/data/cragee/nmr
[rel]
[ppm]
1
using (R,R)-DIOP
at 40 °C
with (S)-(–)-MTPA

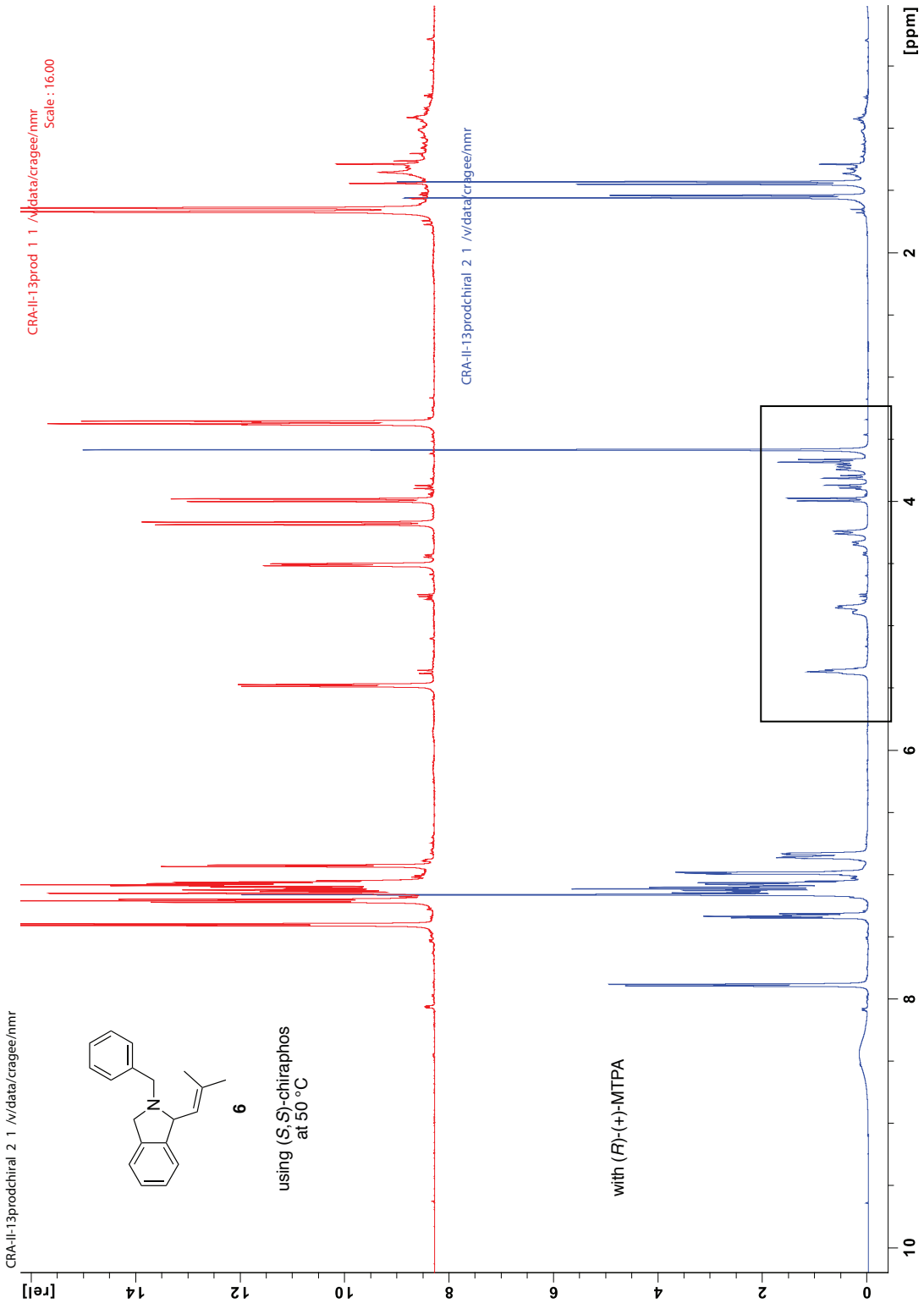

CRA-I-152p-BenzeneChiral 3 1 /v/data/cragee/nmr
1H spectrum
[rel]
3
2
1
- 0
A= 0.3223
A= 0.3085
A= 0.1817
A= 0.1875
Deconvolution Fit
N
1
using (R,R)-DIOP
at 40 °C
26 %ee
Integration of diastereotopic peaks
1.0000
4.6
4.5
4.4
4.3
4.2
4.1
4.0
[ppm]
General
DATE = 2011/12/14
TIME = 22:28
INSTRUM = av600
PULPROG = zg30
F1 (1H)
SI = 65536
SF = 600.13
SW_p = 8680.556

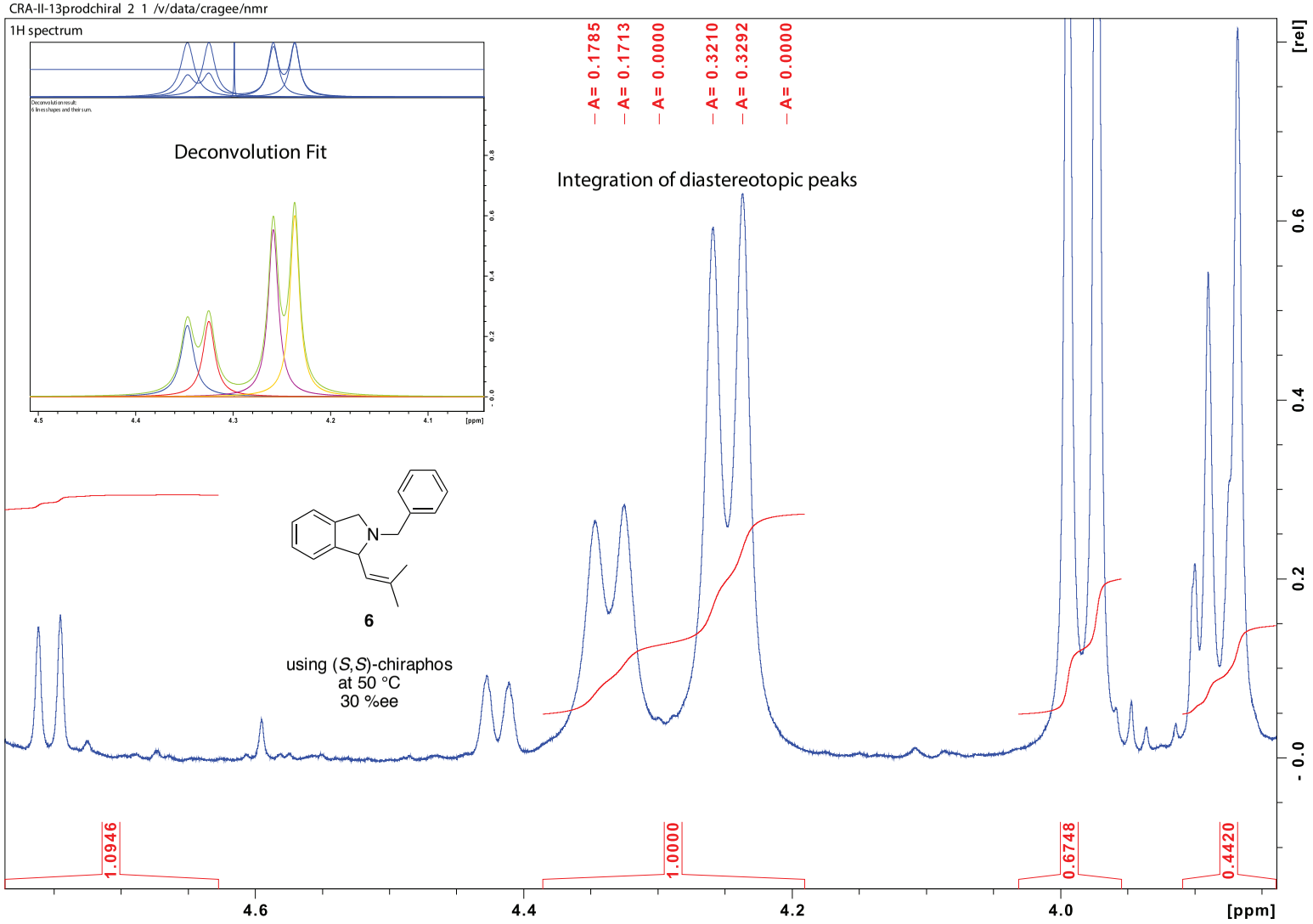

CRA-II-8-15-30-1eqXShift 3 1 /v/data/cragee/nmr
CRA-II-8-15-30 1 1 /v/data/cragee/nmr
CRA-II-8-15-30-1eqXShift 3 1 /v/data/cragee/nmr
9
using (R,R)-DIOP
at 50 °C
with (R)-(+)-MTPA
[rel]
0
2
4
6
8
0 [ppm]
2

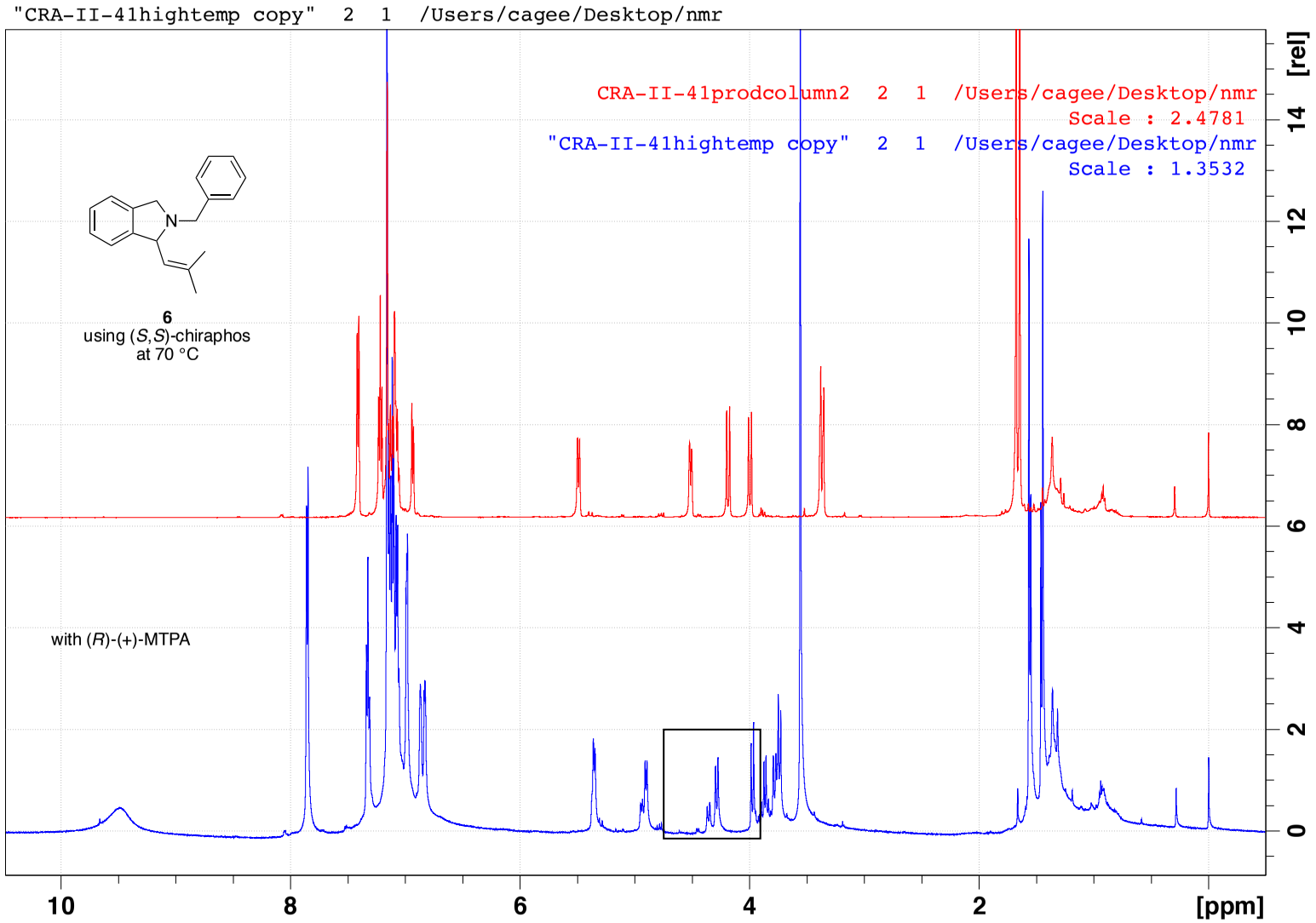

CRA-II-8-15-30-1eqXShift 2 1 /v/data/cragee/nmr
1H spectrum
Deconvolution Fit
Integration of diastereotopic peaks
A= 0.0387
A= 0.0325
A= 0.2608
A= 0.2613
A= 0.2414
A= 0.2519
1.0865
6
using (R,R)-DIOP
at 50 °C
3 %ee
4.8
4.6
4.4
4.2
4.0
[ppm]
[rel]

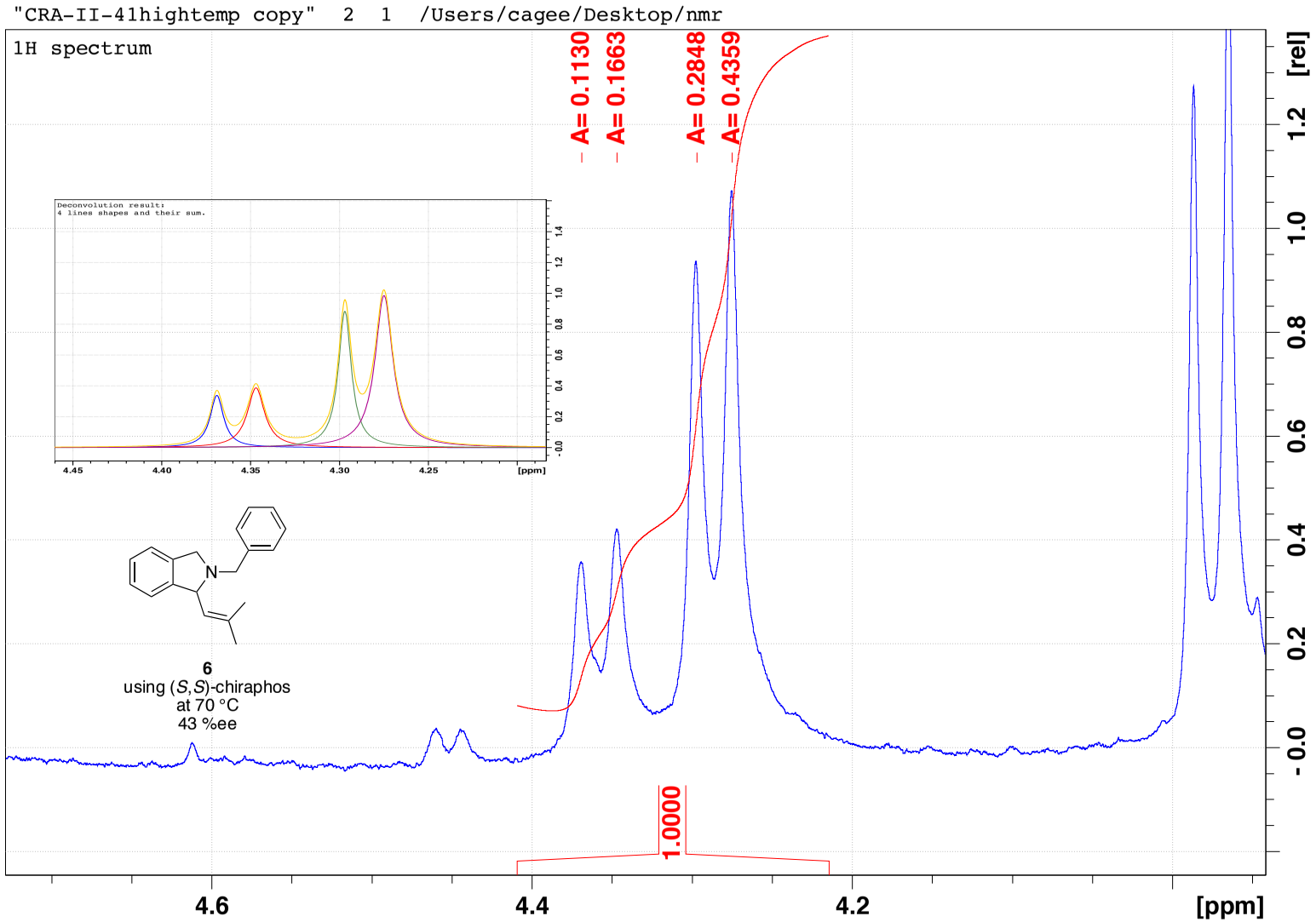

"CRA-II-9-Extracted+X copy" 2 1 /Users/cagee/Desktop/nmr
CRA-II-9Extracted 1 1 /Users/cagee/Desktop/nmr
Scale : 58.5043
"CRA-II-9-Extracted+X copy" 2 1 /Users/cagee/Desktop/nmr
Scale : 2.5646
[rel]
[ppm]
6
using (S)-BINAP
with (R)-(+)-MTPA

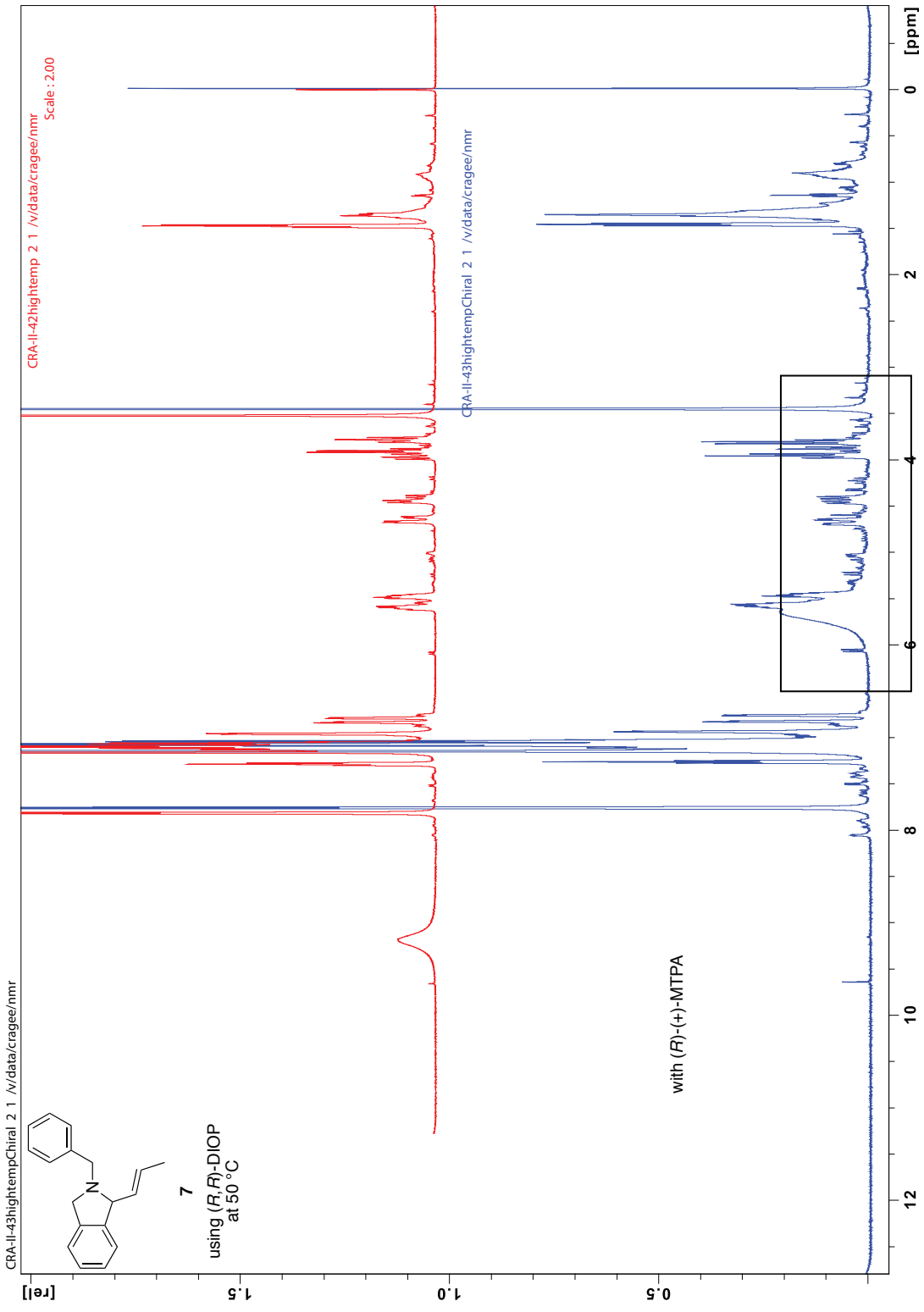

"CRA-II-9-Extracted+X copy" 2 1 /Users/cagee/Desktop/nmr
1H spectrum
A= 0.0009
A= 0.0122
A= 0.0049
A= 0.0123
A= 0.2116
A= 0.2148
A= 0.2209
A= 0.3137
A= 0.0069
A= 0.0017
Deconvolution result:
10 lines shapes and their sum.
4.40
4.35
4.30
4.25
[ppm]
0.15
0.10
0.05
0.00
N
6
using (S)-BINAP
0.9594
1.0000
0.5004
1.0572
4.8
4.6
4.4
4.2
4.0
3.8
[ppm]
[rel]
0.3
0.2
0.1
- 0.0

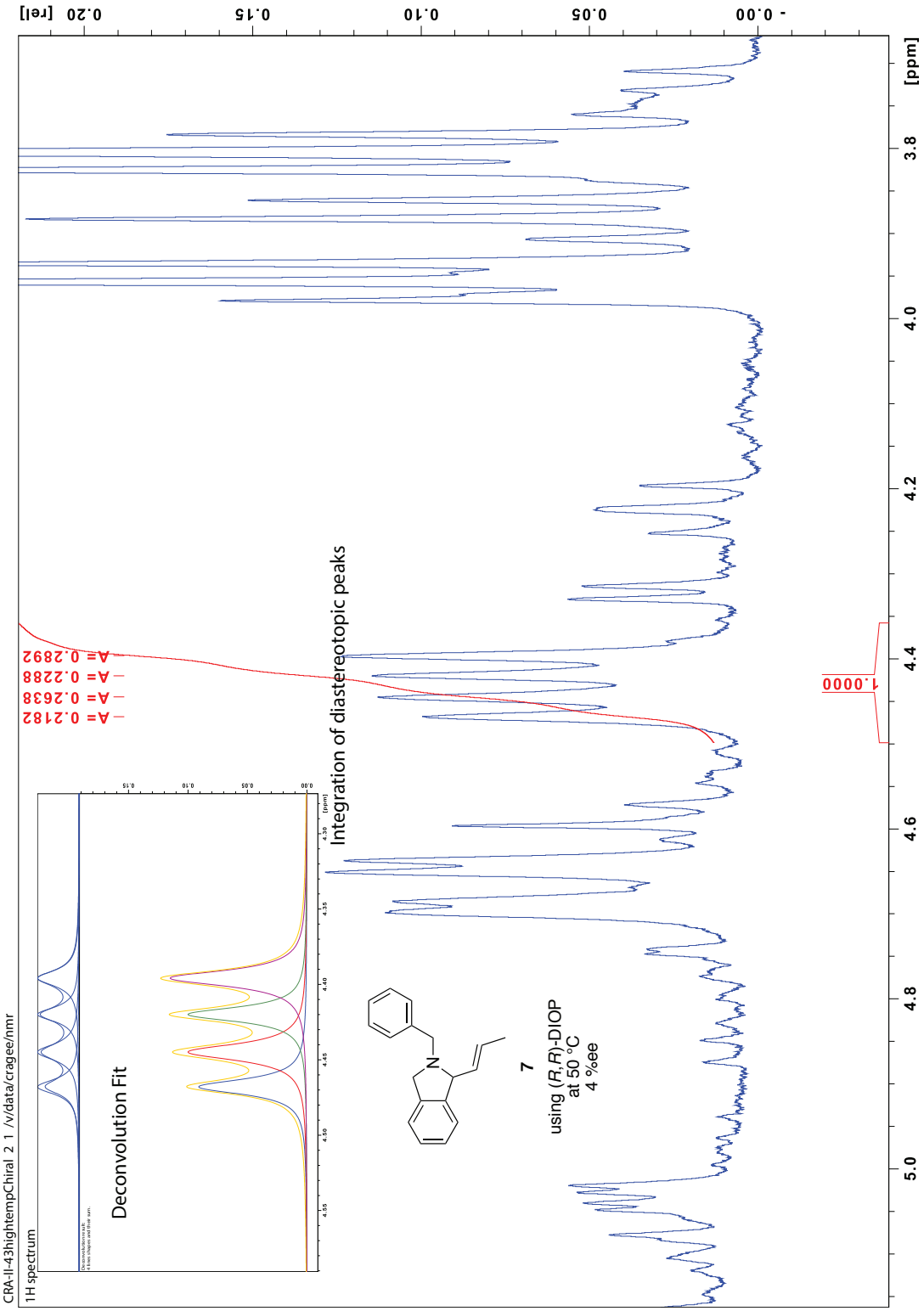

CRA-II-13prodchiral 2 1 /v/data/cragee/nmr
6
using (S,S)-chiraphos
at 50 °C
with (R)-(+)-MTPA
CRA-II-13prod 1 1 /v/data/cragee/nmr
Scale : 16.00
CRA-II-13prodchiral 2 1 /v/data/cragee/nmr
[rel]
[ppm]

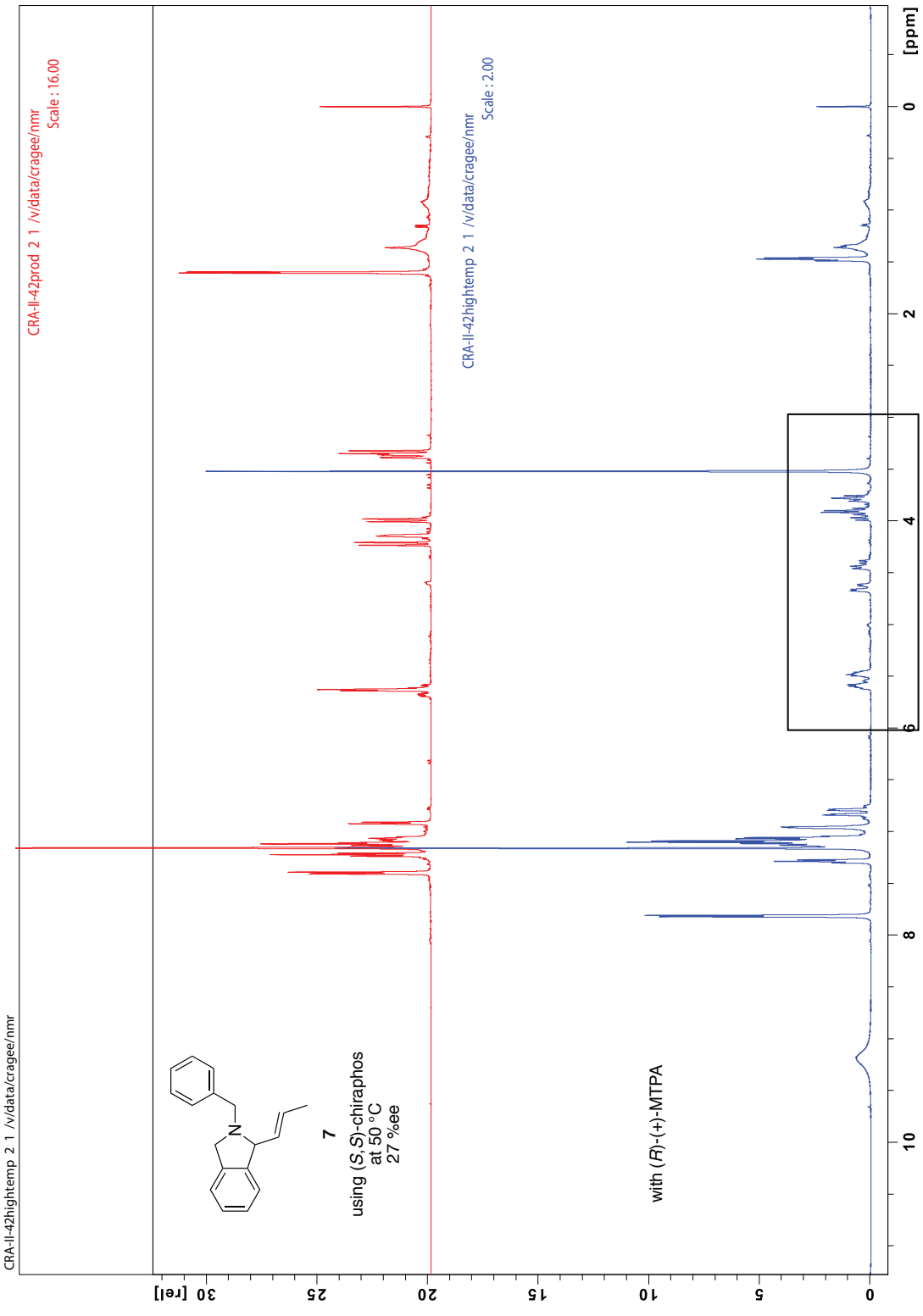

CRA-II-13prodchiral 2 1 /v/data/cragee/nmr
1H spectrum
Deconvolution Fit
Integration of diastereotopic peaks
A= 0.1785
A= 0.1713
A= 0.0000
A= 0.3210
A= 0.3292
A= 0.0000
6
using (S,S)-chiraphos
at 50 °C
30 %ee
1.0946
1.0000
0.6748
0.4420
4.6
4.4
4.2
4.0
[ppm]
[rel]

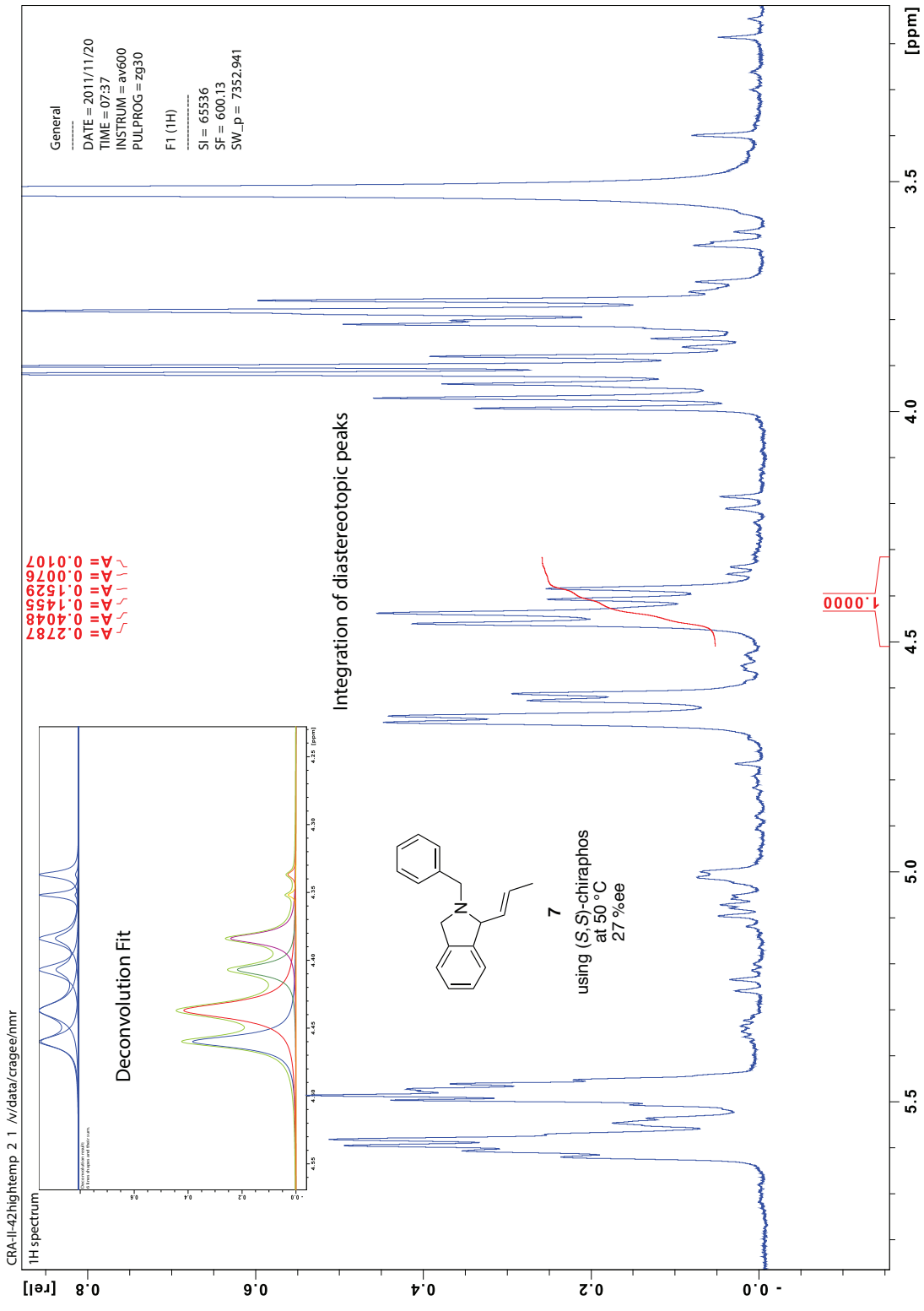

"CRA-II-41hightemp copy" 2 1 /Users/cagee/Desktop/nmr
CRA-II-41prodcolumn2 2 1 /Users/cagee/Desktop/nmr
Scale : 2.4781
"CRA-II-41hightemp copy" 2 1 /Users/cagee/Desktop/nmr
Scale : 1.3532
6
using (S,S)-chiraphos
at 70 °C
with (R)-(+)-MTPA
[rel]
[ppm]


"CRA-II-41hightemp copy" 2 1 /Users/cagee/Desktop/nmr
1H spectrum
A= 0.1130
A= 0.1663
A= 0.2848
A= 0.4359
Deconvolution result:
4 lines shapes and their sum.
4.45
4.40
4.35
4.30
4.25
[ppm]
N
6
using (S,S)-chiraphos
at 70 °C
43 %ee
1.0000
4.6
4.4
4.2
[ppm]
[rel]
1.2
1.0
0.8
0.6
0.4
0.2
-0.0


CRA-II-43hightempChiral 2 1 /v/data/cragee/nmr
7
using (R,R)-DIOP
at 50 °C
with (R)-(+)-MTPA
CRA-II-42hightemp 2 1 /v/data/cragee/nmr
Scale : 2.00
CRA-II-43hightempChiral 2 1 /v/data/cragee/nmr
[rel]
1.5
1.0
0.5
12
10
8
6
4
2
0
[ppm]


CRA-II-43hightempChiral 2 1 /v/data/cragee/nmr
1H spectrum
Deconvolution Fit
Integration of diastereotopic peaks
A= 0.2892
A= 0.2288
A= 0.2638
A= 0.2182
1.0000
7
using (R,R)-DIOP
at 50 °C
4 %ee
[rel]
[ppm]


CRA-II-42hightemp 2 1 /v/data/cragee/nmr
CRA-II-42prod 2 1 /v/data/cragee/nmr
Scale : 16.00
CRA-II-42hightemp 2 1 /v/data/cragee/nmr
Scale : 2.00
7
using (S,S)-chiraphos
at 50 °C
27 %ee
with (R)-(+)-MTPA
[rel]
[ppm]


CRA-II-42hightemp 2 1 /v/data/cragee/nmr
1H spectrum
[rel]
0.8
0.6
0.4
0.2
- 0.0
5.5
5.0
4.5
4.0
3.5
[ppm]
General
DATE = 2011/11/20
TIME = 07:37
INSTRUM = av600
PULPROG = zg30
F1 (1H)
SI = 65536
SF = 600.13
SW_p = 7352.941
Integration of diastereotopic peaks
A= 0.2787
A= 0.4048
A= 0.1455
A= 0.1529
A= 0.0076
A= 0.0107
1.0000
Deconvolution Fit
7
using (S,S)-chiraphos
at 50 °C
27 %ee