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# Part I: Asymmetric Synthesis of α-Allyl-α-Aryl α-Amino Acids Part II: Asymmetric Spirocyclization of Allenyl Ketones Part III: Chemoselective Activation of C(sp3)–h Bond Over C(sp2)–h Bond With Pd(II)

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# Part I: Asymmetric Synthesis of α-Allyl-α-Aryl α-Amino Acids Part II: Asymmetric Spirocyclization of Allenyl Ketones Part III: Chemoselective Activation of C(sp3)–h Bond Over C(sp2)–h Bond With Pd(II)

**Abstract**
Part I. The first asymmetric synthesis of a-allyl-a-aryl a-amino acids by means of a three component coupling of a-iminoesters, Grignard reagents, and cinnamyl acetate is reported. Notably, the enolate from the tandem process provides a much higher level of reactivity and selectivity than the same enolate generated via direct deprotonation, presumably due to differences in the solvation/aggregation state.

A novel method for removal of a homoallylic amine protecting group delivers the free amine congeners. The a-allyl moiety offers a means to generate further valuable a-amino acid structures. Cross-metathesis of the tandem product provided allylic diversity not afforded in the parent reaction. Cyclic a-amino acid derivatives could be accessed by ring closing metathesis presenting a viable strategy to higher ring homologues of enantioenriched a-substituted proline. The 8-member proline analog was successfully converted to the pyrrolizidine natural product backbone.

Part II. The asymmetric spirocyclization of allenyl ketones is reported. High-throughput experimentation by means of a chiral Lewis acid library enabled the determination of a suitable catalyst system. Protecting group manipulation provides an orthogonal route to enantioenriched para-quinone and ortho-quinone spirocycles. This novel technology provides access to the spirocyclic core that is prevalent in many natural products.

Part III. Palladium has been identified as a suitable catalyst for the chemoselective activation of C(sp3)-H bond over C(sp2)-H bond of toluene and tolyl analogs. This technology has been combined with the C(sp3)-H activation of acidic C-H bonds to form new C-C bonds. High-throughput experimentation was used for identifying conditions that reduced toluene loading and engendered catalyst turnover via a suitable oxidant.

The parent reaction has been extended to include the Pd catalyzed alkylation of phenylglycine azlactones with ethylbenzene, 2-ethylnaphthalene, propylbenzene and butylbenzene. Mechanistic studies were initiated to determine whether the process occurs via free radicals or via Pd mediated C(sp3)-H activation. Our studies support a Pd mediated process in which the C(sp3)-H activation of the tolyl analog is the rate determining step. This finding represents a paradigm shift in our understanding of Pd and its selectivity for arene activation vs benzylic activation.

**Degree Type**
Dissertation

**Degree Name**
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**Graduate Group**
Chemistry

# PART I: ASYMMETRIC SYNTHESIS OF α-ALLYL-α-ARYL α-AMINO ACIDS
# PART II: ASYMMETRIC SPIROCYCLIZATION OF ALLENYL KETONES
# PART III: CHEMOSELECTIVE ACTIVATION OF C($sp^3$)–H BOND OVER C($sp^2$)–H BOND WITH Pd(II)

John M. Curto

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in

Chemistry

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in

Partial Fulfillment of the Requirements for the

Degree of Doctor of Philosophy

2014

Supervisor of Dissertation

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Marisa C. Kozlowski, Professor of Chemistry

Graduate Group Chairperson

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Gary A. Molander
Hirschmann-Makineni Professor of Chemistry

Dissertation Committee:

Gary A. Molander, Hirschmann-Makineni Professor of Chemistry
Virgil Percec, Roy Vagelos Professor of Chemistry
Amos B. Smith III, Rhodes-Thompson Professor of Chemistry

*To Barb, your continual love and support made all this possible.*

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Finally I'd like to thank my parents for always believing in me. I am eternally grateful to you for all the sacrifices you have made. I would like to thank my brother, Dan, for being a great role model and raising the bar for our family. I thank my sisters, Sarah and Abby, for not only loving me like second-mothers but also for the sacrifices you have made for your little brother. Thank you to Mr. and Mrs. P for welcoming me into your family and providing me a home away from home. Last, but certainly not least, I need to thank my best friend and wife, Barb. I truly believe that I would not have attained this degree if not for us meeting four years ago. You make me want to be better and I will love you forever.

## ABSTRACT

### PART I: ASYMMETRIC SYNTHESIS OF α-ALLYL-α-ARYL α-AMINO ACIDS

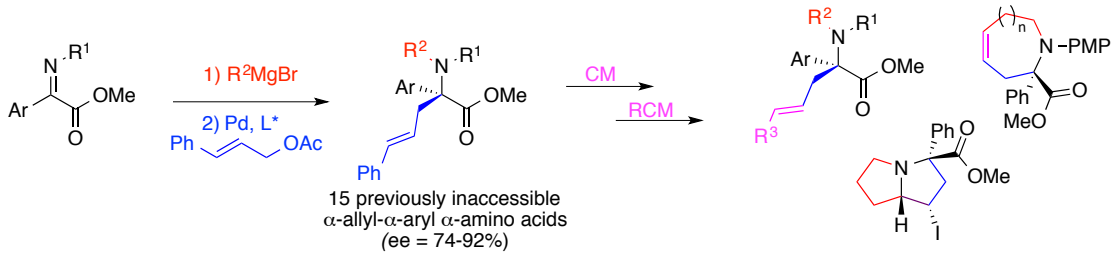
### PART II: ASYMMETRIC SPIROCYCLIZATION OF ALLENYL KETONES

### PART III: CHEMOSELECTIVE ACTIVATION OF C($sp^3$)–H BOND OVER C($sp^2$)–H BOND WITH Pd(II)

John M. Curto

Professor Marisa C. Kozlowski

**Part I.** The first asymmetric synthesis of α-allyl-α-aryl α-amino acids by means of a three component coupling of α-iminoesters, Grignard reagents, and cinnamyl acetate is reported. Notably, the enolate from the tandem process provides a much higher level of reactivity and selectivity than the same enolate generated via direct deprotonation, presumably due to differences in the solvation/aggregation state.

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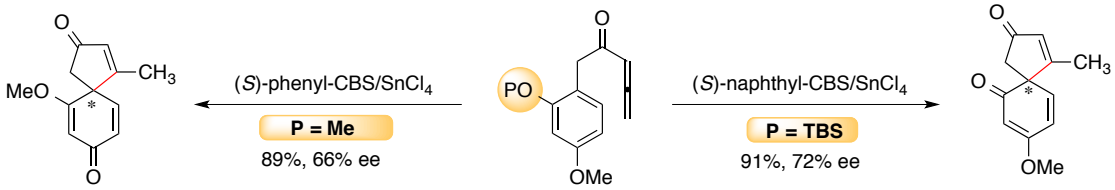
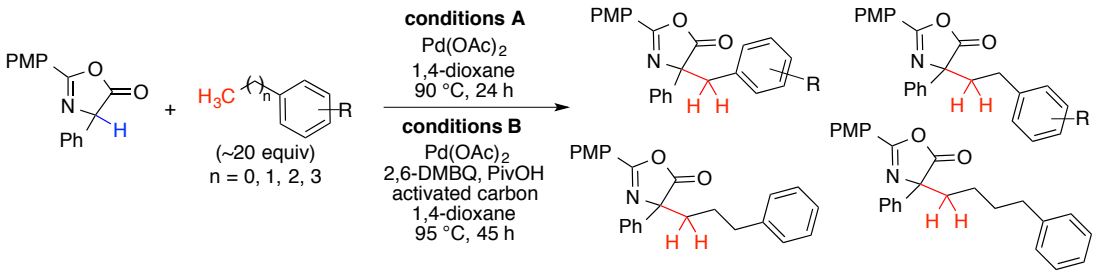



**Part III.** Palladium has been identified as a suitable catalyst for the chemoselective activation of $C(sp^3)$–H bond over $C(sp^2)$–H bond of toluene and tolyl analogs. This technology has been combined with the $C(sp^3)$–H activation of acidic C–H bonds to form new C–C bonds. High-throughput experimentation was used for identifying conditions that reduced toluene loading and engendered catalyst turnover via a suitable oxidant.




The parent reaction has been extended to include the Pd catalyzed alkylation of phenylglycine azlactones with ethylbenzene, 2-ethylnaphthalene, propylbenzene and butylbenzene. Mechanistic studies were initiated to determine whether the process occurs via free radicals or via Pd mediated C($sp^3$)–H activation. Our studies support a Pd mediated process in which the C($sp^3$)–H activation of the tolyl analog is the rate determining step. This finding represents a paradigm shift in our understanding of Pd and its selectivity for arene activation vs benzylic activation.

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# 1. ASYMMETRIC SYNTHEISS OF α-ALLYL-α-ARYL α-AMINO ACIDS BY TANDEM ALKYLATION/π-ALLYLATION OF α-IMINOESTERS

## 1.1. BACKGROUND

### *1.1.1. Significance of α,α-Disubstituted α-Amino Acids*

Enantiomerically pure α,α-disubstituted α-amino acids and their derivatives are vital synthetic building blocks in organic synthesis and play an integral role in pharmaceutical research. The α,α-disubstituted α-amino acid structural motif is found in many natural products.[1] Fumimycin, a natural product related to sorbicillactiones A and B, was discovered in 2007; it is a peptide deformylase inhibitor with antibacterial activity (Figure 1.1).[2] The pharmaceutical industry has demonstrated in numerous examples that incorporation of α,α-disubstituted α-amino acids into biologically active molecules can improve drug properties (Figure 1.1).[3]

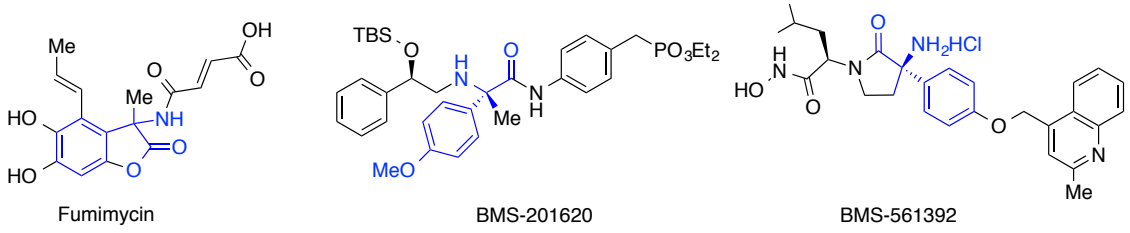


**Figure 1.1** Examples of biologically active α-alkyl-α-aryl α-amino acids.

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1) (a) Kan, T.; Kawamoto, Y.; Asakawa, T.; Furuta, T.; Fukuyama, T. "Synthetic Studies on Altemicidin: Stereocontrolled Construction of the Core Framework" *Org. Lett.* **2008**, *10*, 169-171. (b) Kobayashi, S.; Furuta, T.; Hayashi, T.; Nishijima, M.; Hanada, K. "Catalytic Asmmetric Syntheses of Antifungal Sphingofungins and Their Biological Activity as Potent Inhibitors of Serine Palmitoyltransferase (SPT)" *J. Am. Chem. Soc.* **1998**, *120*, 908-919.
2) Kwon, Y. –J.; Sohn, M. –J.; Zheng, C. –J.; Kim, W. –G. "Fumimycin: A Peptide Deformylase Inhibitor with an Unusual Skeleton Produced by *Aspergillus fumisynnematus*" *Org. Lett.* **2007**, *9*, 2449-2451.
3) (a) Savage, S.A.; Waltermire, R.E.; Campagna, S.; Bordawekar, S.; Toma, J.D.R. "Development and Large-Scale Preparation of an Oral TACE Inhibitor" *Org. Process Res. Dev.* **2009**, *13*, 510 (b) Washburn, W.N. et al., "BMS-201620: a selective beta 3 agonist" *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3525-3529.

Perhaps most notable is the use of α,α-disubstituted α-amino acids for peptidomimetics (Figure 1.2, top).[4] Peptidomimetics are small molecules that exhibit similar properties to peptides and are useful for the study of protein-protein interactions. α-Methyl alanine and α-alkyl alanine are the most well studied modifications to peptides. The incorporation of an alkyl group on the α-position of alanine in a peptide chain restricts the number of potential conformations for higher-order structures and typically induces helical formation with proteins that have >5 and <50 amino acid units.

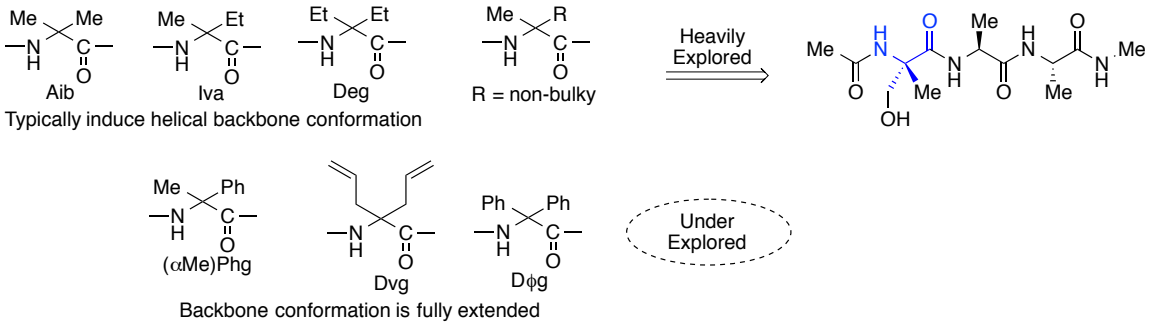



**Figure 1.2** Peptidomimetics: side chain modification.

A less studied system is a sterically bulky groups with alanine, (αMe)Phg, or α,α-disubstituted α-amino acids with two bulky substituents (Figure 1.2, bottom). These types of amino acids are incorporated into peptides to limit the number of potential tertiary structures and typically induce a fully extended backbone conformation.[5]

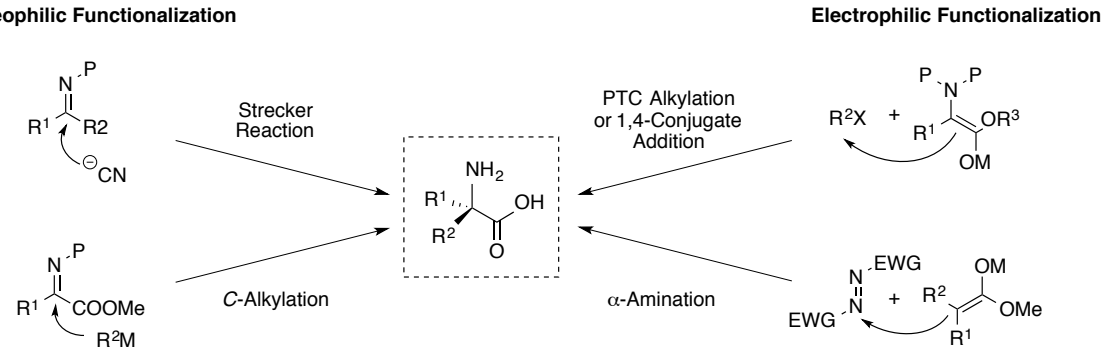
4) (a) Fernandez-Tejada, A.; Corzana, F.; Busto, J. H.; Avenoza, A.; Peregrina, J. M. "Conformational Effects of the Non-natural α-Methylserine on Small Peptides and Glycopeptides" *J. Org. Chem.* **2009**, *74*, 9305-9313. (b) Grauer, A.; Konig, B. "Peptidomimetics – A Versatile Route to Biologically Active Compounds" *Eur. J. Org. Chem.* **2009**, 5099-5111. (c) Venkatraman, J.; Shankaramma, S. C.; Belaram, P. "Design of Folded Peptides" *Chem. Rev.* **2001**, *101*, 3131-3152.

5) Toniolo, C.; Crisma, M.; Formaggio, F.; Peggion, C. "Control of Peptide Conformation by the Thorpe-Ingold Effect (C$^{\alpha}$-Tetrasubstituion)" *Biopolymers* **2001**, *60*, 396-419.

*1.1.2. Previous Synthetic Access to α,α-Disubstituted α-Amino Acids*

Due to the considerable importance of enantioenriched α,α-disubstituted α-amino acids, several methods have been developed for their synthesis.[6] The synthesis of α,α-disubstituted α-amino acids can be accomplished by nucleophilic (Scheme 1.1, left) or electrophilic functionalization (Scheme 1.1, right).

**Scheme 1.1** General enantioselective methods for the synthesis of acyclic α,α-disubstituted α-amino acids.




The Strecker reaction as well as *C*-alkylation of α-iminoesters have been catalyzed by chiral Lewis acids, chiral Brønsted acids and hydrogen bond catalysts. The range of α,α-disubstituted α-amino acids that can be synthesized by the Strecker reaction is limited by the unreactive nature of the ketimine combined with the need for substituents to differ in size.[7] Alternatively, *C*-alkylation of α-iminoesters is limited to

6) (a) Liu, Z.; Mehta, S. J.; Hruby, V. J. "Strategies for Asymmetric Synthesis of Amino Acids with γ,δ-Unsaturation" *Organic Preparations and Procedures International: The New Journal for Organic Synthesis* **2012**, *44*, 222-255. (b) Cativiela, C.; Diaz-De-Villegas, M. D. "Recent progress on the stereoselective synthesis of acyclic quaternary α-amino acids" *Tetrahedron: Asymm.* **2007**, *18*, 569-623. (c) Vogt, H.; Brase, S. "Recent approaches towards the asymmetric synthesis of α,α-disubstituted α-amino acids" *Org. Biomol. Chem.* **2007**, *5*, 406-430.

7) Wang, J.; Liu, X.; Feng, X. "Asymmetric Strecker Reactions" *Chem. Rev.* **2011**, *111*, 6947-6983.

unhindered nucleophiles.[8] Electrophilic functionalization of activated α-amino acids by phase transfer catalysis (PTC) with alkyl halides or α,β-unsaturated carbonyls leads to α,α-disubstituted α-amino acids.[9] Conversely, a disubstituted enolate can undergo α-amination.[4]

A thorough investigation of the methods for synthesizing α,α-disubstituted α-amino acids revealed less common methods such as sigmatropic rearrangements, cycloadditions, aldol type reactions and allylic alkylation.[4] However, a class of compounds that has no general enantioselective synthesis is α-allyl-α-aryl α-amino acids (Figure 1.3).

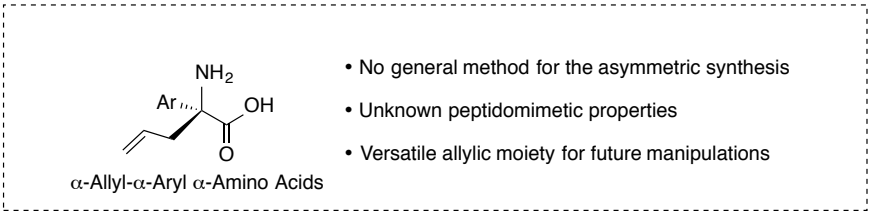



**Figure 1.3** Underexplored class of α,α-disubstituted α-amino acids.

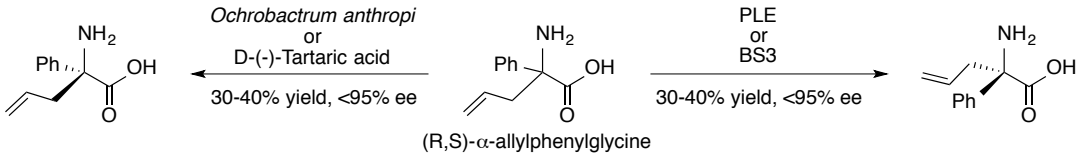
8) (a) Wieland, L. C.; Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. "Ag-Catalyzed Diastereo- and Enantioselective Vinylogous Mannich Reactions of α-Ketoimine Esters. Development of a Method and Investigation of its Mechanism" *J. Am. Chem. Soc.* **2009**, *131*, 570-576. (b) Fu, P.; Snapper, M. L.; Hoveyda, A. H. "Catalytic Asymmetric Alkylations of Ketoimines. Enantioselective Synthesis of *N*-Substituted Quaternary Carbon Stereogenic Centers by Zr-Catalyzed Additions of Dialkylzinc Reagents to Aryl-, Alkyl-, and Trifluoroalkyl-Substituted Ketoimines" *J. Am. Chem. Soc.* **2008**, *130*, 5530-5541. (c) Basra, S.; Fennie, M. W.; Kozlowski, M. C. "Catalytic Asymmetric Addition of Dialkylzinc Reagents to α-Aldiminoesters" *Org. Lett.* **2006**, *8*, 2659-2662. (d) Zhuang, W.; Saaby, S.; Jorgensen, K. A. "Direct Organocatalytic Enantioselective Mannich Reactions of Ketimines: An Approach to Optically Active Quaternary α-Amino Acid Derivatives" *Angew. Chem., Int. Ed.* **2004**, *43,* 4476-4478.

9) Maruoka, K.; Ooi, T. "Enantioselective Amino Acid Synthesis by Chiral Phase-Transfer Catalysis" *Chem. Rev.* **2003**, *103*, 3013-3028.

*1.1.3. Synthesis of Enantioenriched α-Allyl-α-Aryl α-Amino Acids*

To date, synthetic access to enantioenriched α-allyl-α-aryl α-amino acids has remained elusive. The phenylglycine racemate can readily undergo allylation in high yield when the amine is pre-activated as the aldimine. Upon hydrolysis of the aldimine, each enantiomer of α-allylphenylglycine can be kinetically resolved via preferential interaction with a chiral agent (Scheme 1.2). Tourwe and co-workers demonstrated this strategy utilizing pig liver esterase (PLE) to deliver the (*R*)-enantiomer and *Ochrobactrum anthropic* NCIMB 40321 to provide the (*S*)-enantiomer.[10] In 2005, Maeda and co-workers at Merck found that D-(-)-tartaric acid and *Bacillus stearomorphilus* (BS3) could also be used.[11] Kinetic resolutions deliver very high enantioenriched product but a drawback is the theoretical maximum yield of 50%. Tourwe and Maeda each desired the enantioenriched α-allylphenylglycine to deliver novel chemical space through functionalization of the allyl moiety.

**Scheme 1.2** Kinetic resolution of α-allylphenylglycine.



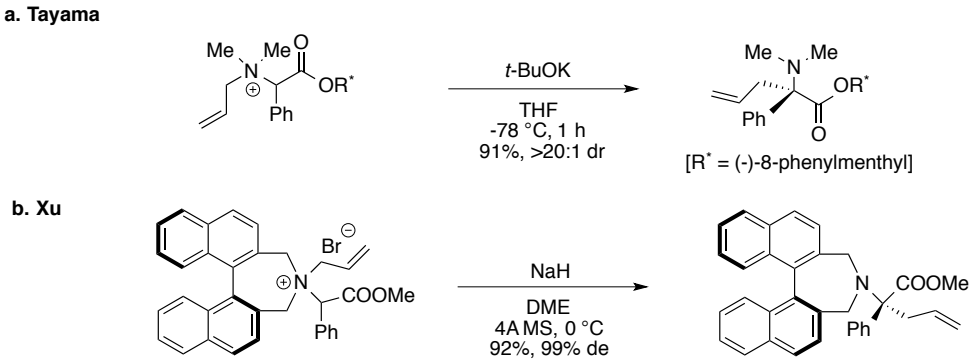

Diastereoselective processes can be powerful tools to deliver enantioenriched product with high yields. Chiral auxiliaries, when low cost and easily accessible, have been utilized successfully to deliver important natural products and active pharmaceutical

10) Van Betsbrugge, J.; Tourwe, D.; Kaptein, B.; Kierkels, H.; Broxterman, R. "A Convenient Synthesis of Protected (*R*)-α-Phenylproline Derivatives Using the Mitsunobu Reaction" *Tetrahedron* **1997**, *53*, 9233-9240.

11) Maeda, K.; Miller, R. A.; Szumigala, R. H., Jr.; Shafiee, A.; Karady, S.; Armstrong, J. D., III "Stereoselective synthesis of 4-hydroxy-2-phenylproline framework" *Tetrahedron Lett.* **2005**, *46*, 1545-1549.

ingredients (API).[12] The synthesis of α-allyl-α-aryl α-amino acids by diastereoselective processes is rare. Tayama and co-workers developed a novel Stevens rearrangement of *N*-allylic α-aryl amino acid derived ammonium salts with good yields and dr (Scheme 1.3, **a**).[13] The chiral auxiliary chosen was derived from menthol, but the necessary salt for reactivity provides the *N*-alkyl α-allylphenylglycine α-amino acid. Xu and co-workers followed up this work by incorporating the chiral auxiliary on the nitrogen, which allows the synthesis of enantioenriched α-allylphenylglycine (Scheme 1.3, **b**).[14] The pincer-like chiral auxiliary is not readily available, involves three steps to incorporate into the α-phenylglycine starting material, and requires harsh conditions to be removed.

**Scheme 1.3** Diastereoselective synthesis of α-allyl-α-aryl α-amino acids by the Stevens rearrangement.




Barrett and co-workers have developed an elegant route to α-allyl-α-aryl α-amino acids with Schollkopf's bislactim ether in good yield and diastereoselectivities (Scheme

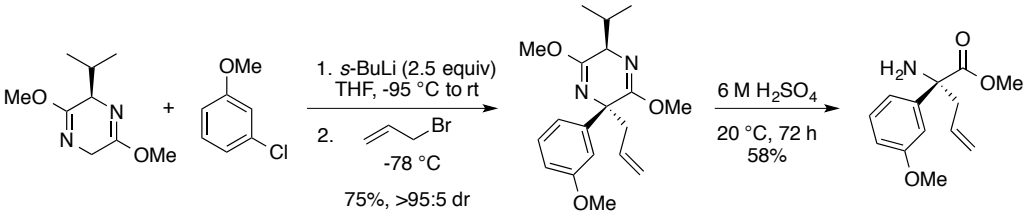
12) Evans, D. A.; Helmchen, G.; Ruping, M. "Chiral Auxiliaries in Asymmetric Synthesis" In *Asymmetric Synthesis – The Essentials*; Christman, M.; Brase, S., Eds.; Wiley: Weinheim, **2007**, 2nd Edition, 3-9.

13) Tayama, E.; Orihara, K.; Kimura, H. "New synthetic routes to optically active α-quaternary α-aryl amino acid derivatives *via* the diastereoselective Stevens and Sommelet–Hauser rearrangements" *Org. Biomol. Chem.* **2008**, *6*, 3673-3680.

14) Zhu, T. –S.; Xu, M. –H. "Efficient synthesis of optically active α-quaternary amino acids by highly diastereoselective [2,3]-rearrangement of allylic ammonium ylides" *Chem. Commun.* **2012**, *48*, 7274-7276.

1.4).[15] The initial step involves the nucleophilic addition of the bislactim ether on a benzyne. The benzyne can only be formed *in situ* when the aromatic ring is substituted with electron-donating substituents. The Schollkopf adduct can be transformed to the α-allyl-α-aryl amino acid by treatment with acid.

**Scheme 1.4** Diastereoselective synthesis of α-allyl-α-aryl α-amino acids with Schollkopf's bislactim.

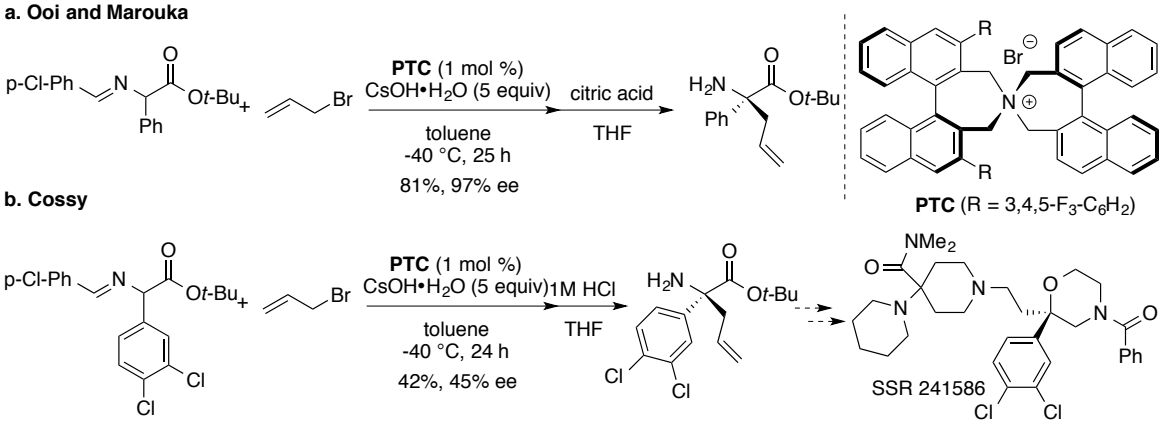



The synthesis of large quantities of enantioenriched compounds from pro-chiral starting materials via a relatively small quantity of chiral catalysts has enormous potential. Ooi and Maruoka have demonstrated that PTC can be used to synthesize enantioenriched α,α-disubstituted α-amino acids.[16a,b] PTC applied to the synthesis of α-allyl-α-aryl α-amino acids has been successful in the synthesis of α-allylphenylglycine (Scheme 1.5, **a**).[16b,c] In 2011, Cossy and co-workers utilized Ooi and Maruoka's method for the synthesis of an analog of α-allylphenylglycine but encountered challenges resulting in low yield and ee (Scheme 1.5, **b**).[16d]

15) Jones, E. P; Jones, P.; White, A. J. P.; Barrett, A. G. M. "Asymmetric synthesis of quaternary aryl amino acid derivatives via a three-component aryne coupling reaction" *Beilstein J. Org. Chem.* **2011**, *7*, 1570-1576.

16) (a) Ooi, T.; Takeuchi, M.; Kameda, M.; Maruoka, K. "Practical Catalytic Enantioselective Synthesis of α,α-Dialkyl-α-amino Acids by Chiral Phase-Transfer Catalysis" *J. Am. Chem. Soc.* **2000**, *122*, 5228-5229. (b) Ooi, T.; Takeuchi, M.; Ohara, D.; Maruoka, K. "Advantage of Anaerobic Conditions in the Highly Enatioselective Synthesis of α,α-Dialkyl-α-amino Acids by Chiral Phase-Transfer Catalysis" *Synlett* **2001**, *7*, 1185-1187. (c) Belokon, Y. N.; Bhave, D.; D'Addario, D.; Groaz, E.; North, M.; Tagliazucca, V. "Copper(II)salen catalysed, asymmetric synthesis of α,α-disubstituted amino acids" *Tetrahedron Lett.* **2004**, *60*, 1849-1861. (d) Metro, T. -X.; Cochi, A.; Pardo, D. G.; Cossy, J. "Asymmetric Synthesis of an Antagonist of Neurokinin Receptors: SSR 241586" *J. Org. Chem.* **2011**, *76*, 2594-2602.

**Scheme 1.5** PTC for the synthesis of α-allyl-α-aryl α-amino acids.

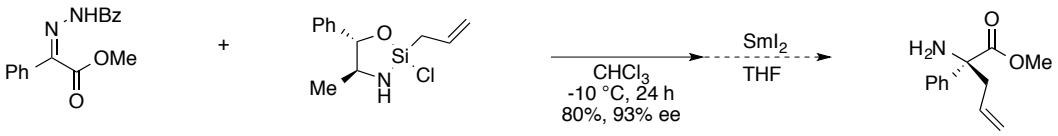



Nucleophilic functionalization of α-iminoesters by *C*-alkylation has seen significant progress over the last 15 years for the synthesis of α,α-disubstituted α-amino acids.[8] Leighton and co-workers have utilized a benzoylhydrazone with a chiral allylsilane reagent to produce α-allylphenylglycine (Scheme 1.6).[17] Similar work has been conducted with chiral sulfoxides and allylation of cyclic imines via rhodium, but in each example, yields and ee were moderate (30-70%, 21-76% ee).[18]

17) Berger, R.; Duff, K.; Leighton, J. L. "Enantioselective Allylation of Ketone-Derived Benzoylhydrazones: Practical Synthesis of Tertiary Carbinamines" *J. Am. Chem. Soc.* **2004**, *126*, 5686-5687.

18) (a) Reyes-Rangel, G.; Bandala, Y.; Garcia-Flores, F.; Juaristi, E. "Asymmetric Allylation of α-Ketoester-Derived *N*-Benzoylhydrazones Promoted by Chiral Sulfoxides/*N*-Oxides Lewis Bases: Highly Enantioselective Synthesis of Quaternary α-Substituted α-Allyl-α-Amino Acids" *Chirality* **2013**, *25*, 529-540. (b) Hepburn, H. B.; Chotsaeng, N.; Luo, Y.; Lam, H. W. "Enantioselective Rhodium-Catalyzed Allylation of Cyclic Imines with Potassium Allyltrifluoroborates" *Synthesis* **2013**, *45*, 2649-2661.

**Scheme 1.6** *C*-Allylation of α-iminoesters to generate α-allyl-α-aryl α-amino acids.




*1.1.4. N-Alkylation of α-Iminoesters with Organometallic Nucleophiles*

α-Iminoesters have played an important role in the synthesis of α-amino acid derivatives. The presence of the adjacent electron-withdrawing ester enhances the electrophilicity of the imine carbon. α-Iminoesters display the expected positive charge buildup at the carbonyl carbons; however, three potential modes of reactivity can be observed (Figure 1.4).[19] Addition to the polarized carbonyl of the imine is the most common mode of reactivity (Figure 1.4, *path a*). Electron-donating or -withdrawing groups on the nitrogen protecting group typically promote *C*-alkylation. Both hard and soft nucleophiles have shown selectivity for the imine carbon. *C*-Alkylation of the ester is viable but less frequent because of the lower electrophilicity of esters compared to imines; however, in some cases organolithiums preferentially add to the ester (Figure 1.4, *path b*).[19]

19) Dickstein, J. S.; Kozlowski, M. C. "Organometal additions to α-iminoesters: *N*-alkylation via umpolung" *Chem. Soc. Rev.* **2008**, *37*, 1166-1173.

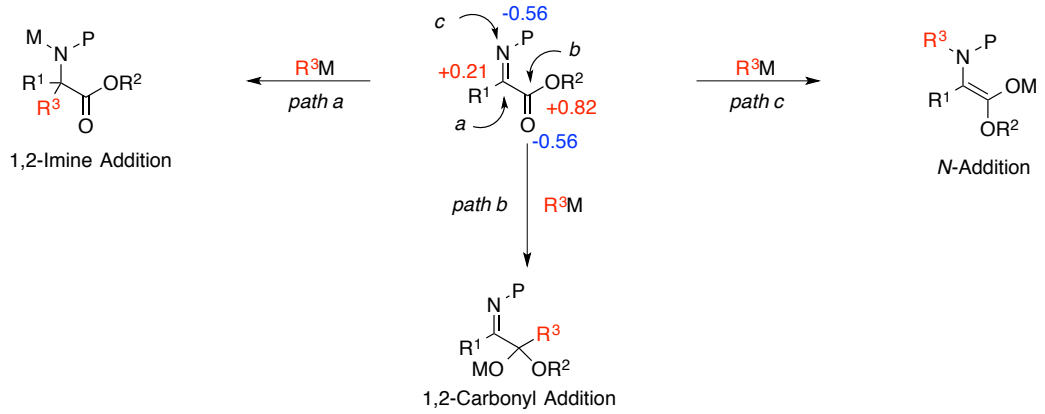



**Figure 1.4** Charge calculations of α-iminoesters and modes of reactivity.

Synthesis of *N*-substituted α-amino acids is an important field of research in chemistry and biology. *N*-Alkylation of α-iminoesters requires a reversal of polarity of the imine group (Figure 1.4, *path c*). Umpolung is any process by which the donor and acceptor reactivity of an atom are interchanged.[20] Nitrogen as an electrophile has been well developed with diazoesters and nitroso compounds but in each case the double bond is composed of two heteroatoms and there is no clear acceptor or donor for addition. *N*-Alkylation of α-iminoesters is proposed to occur by bidentate coordination of the metal species between the nitrogen of the imine and the oxygen of the ester (Figure 1.5). Ostensibly, chelation locks the imine carbon in a more sterically hindered conformation, thus favoring *N*-alkylation.[19]

20) Seebach, D. "Methods of Reactivity Umpolung" *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239-258.

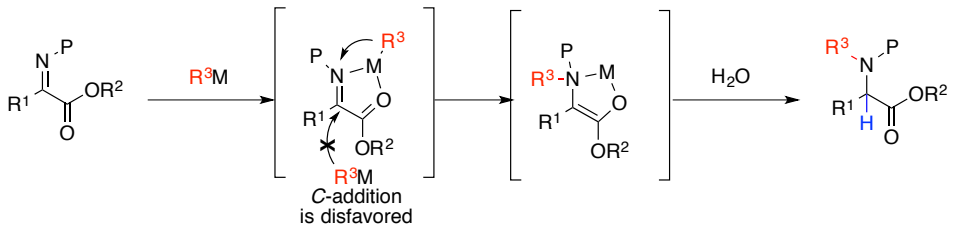
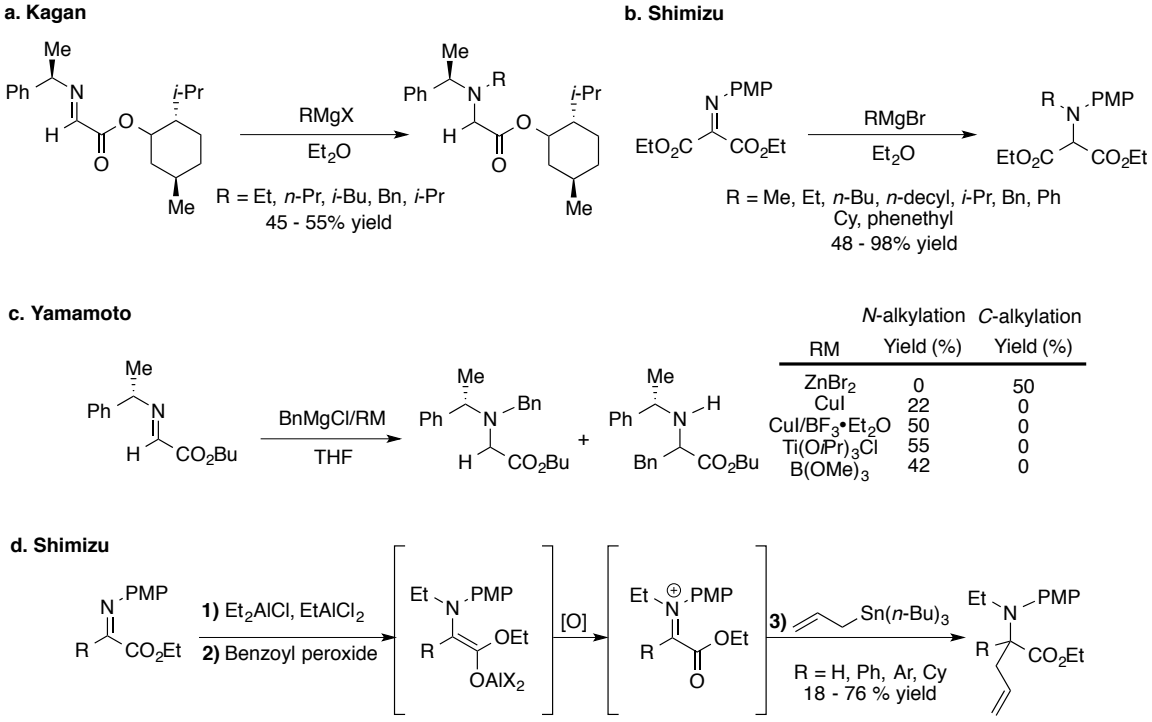



**Figure 1.5** Proposed mechanism for *N*-alkylation.

Magnesium, aluminum, and zinc reagents have been shown to undergo the *N*-alkylation mode with α-iminoesters. *N*-Alkylation was first observed by Kagan and Fiaud in 1970, wherein an α-aldiminoester was reacted with various Grignard reagents (Scheme 1.7, **a**).[21] Kagan observed differing reactivity when primary, secondary and tertiary Grignard reagents were examined. Primary Grignard reagents preferentially produced the *N*-alkylated product. Secondary Grignard reagents produced a 60:40 mixture of *N*-alkylated product to *C*-alkylated product. *tert*-Butylmagnesium bromide provided only *C*-alkylated product at rt but a 55:45 mixture of *N*-alkylated product to *C*-alkylated product at −78 °C. Interestingly, methyl Grignard and allyl Grignard provide exclusively the *C*-alkylated product. Shimizu and co-workers studied the addition of Grignard reagents to iminomalonates (Scheme 1.7, **b**).[22] In contrast to Kagan's observation, secondary, tertiary, methyl and allyl Grignard reagents provided exclusively the *N*-alkylated product; the addition of the second electron-withdrawing group on the imine carbon enhances the electrophilicity of the imine nitrogen.

21) Fiaud, J. C.; Kagan, H. B. "Une nouvelle synthese D'α amino-acides. Synthese asymetrique de l'alaine" *Tetrahedron Lett.* **1970**, *11*, 1813-1816.
22) Niwa, Y.; Takayama, K.; Shimizu, M. "Electrophilic amination with iminomalonate" *Tetrahedron Lett*. **2001**, *42*, 5473-5476.

**Scheme 1.7** Examples of umpolung *N*-alkylation of α-iminoesters with organometals.




Yamamoto and co-workers explored various organometal reagents with α-aldiminoester utilizing benzyl Grignard and transmetallating reagents (Scheme 1.7, **c**).[23] Organo-copper, titanium and boron reagents produced the *N*-alkylated product but were inferior when compared with the selectivity observed by Kagan with Grignard reagents.

Shimizu and co-workers discovered that a mixture of organoaluminum reagents could preferentially produce the *N*-alkylated enolate, which could be oxidized to the imininum and then subjected to nucleophilic addition with allyltin (Scheme 1.7, **d**).[24]

In 2008, our research group demonstrated the first three component coupling of α-iminoesters with alkyl Grignards and electrophiles (Figure 1.6).[25,26] Dickstein and co-

23) Yamamoto, Y.; Ito, W. "Studies on the Reaction of α-Imino Esters with Organometallic Compounds" *Tetrahedron* **1988**, *44*, 5415-5423.

24) Niwa, Y.; Shimizu, M. "Tandem N-Alkylation–C-Allylation Reaction of α-Imino Esters with Organoaluminums and Allyltributyltin" *J. Am. Chem. Soc.* **2003**, *125*, 3720-3721.

workers were able to demonstrate that the enolate generated *in situ* from the initial *N*-alkylation could be trapped with electrophiles. This novel technology provided access to a library of racemic α,α-disubstituted α-amino acids. The diversity of functional groups from the various electrophiles allows the synthesis of other novel compounds.

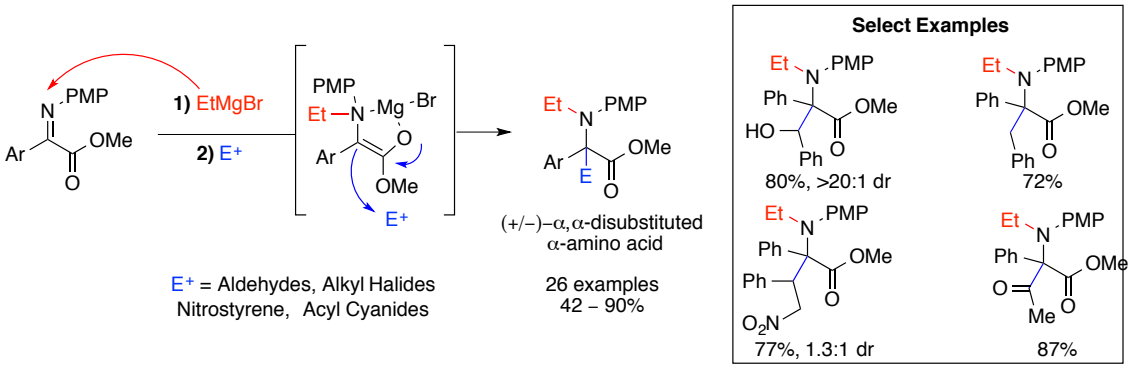



**Figure 1.6** Three component coupling of α-iminoesters via umpolung addition of alkyl Grignards providing α,α-disubstituted α-amino acids.

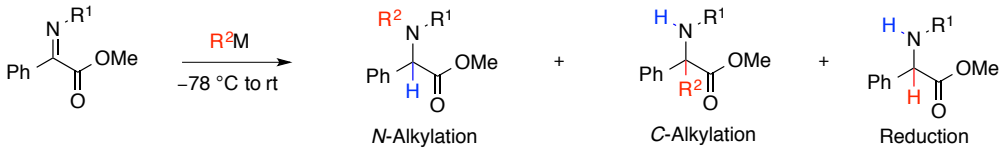
Dr. Dickstein demonstrated that Grignard reagents could preferentially undergo *N*-alkylation with hindered α-iminoesters. Previously, only unhindered (aldimine)[21] and doubly activated (iminomalonates)[22] were shown to be successful. This work also provided insight about the activating group on the imine nitrogen (Table 1.1). An electron-withdrawing activating group such as tosyl or phosphoryl promotes *C*-alkylation

25) Dickstein, J. S.; Fennie, M. W.; Norman, A. L.; Paulose, B. J.; Kozlowski, M. C. "Three Component Coupling of α-Iminoesters via Umpolung Addition of Organometals: Synthesis of α,α-Disubstituted α-Amino Acids" *J. Am. Chem. Soc.* **2008**, *130*, 15794-15795.

26) For tandem reactions of α-iminoesters that followed ref. 25, see: (a) Mizota, I.; Matsuda, Y.; Kamimura, S.; Tanaka, H.; Shimizu, M. "Regioselective Tandem *N*-Alkylation/*C*-Acylation of β,γ-Alkynyl α-Imino Esters" *Org. Lett.* **2013**, *15*, 4206-4209. (b) Shimizu, M.; Kurita, D.; Mizota, I. "Highly Diastereoselective Tandem *N*-Alkylation-Mannich Reaction of α-Imino Esters" *Asian J. Org. Chem.* **2013**, *2*, 208-211. (c) Shimizu, M.; Takao, Y.; Katsurayama, H.; Mizota, I. "Synthesis of Indolin-3-ones and Tetrahydro-4-quinolones from α-Imino Esters" *Asian J. Org. Chem.* **2013**, *2*, 130-134. (d) Mizota, I.; Tanaka, K.; Shimizu, M. "Synthesis of γ,δ–unsaturated quaternary α-alkylamino acids using umpolung reaction and Claisen rearrangement" *Tetrahedron Lett.* **2012**, *53*, 1847-1850.

or reduction via β-hydride elimination. However, hindered α-iminoesters with phenyl or *para*-methoxy phenyl (PMP) activating groups provide entry to the *tetra*-substituted enolate via *N*-alkylation.

**Table 1.1** Regioselectivity of organometals with α-iminoester with various activating groups on the imine nitrogen.




| $R^1$ | $R^2M$ | solvent[a] | *N*-Alkylation[b] | *C*-Alkylation[b] | Reduction[b] |
|---|---|---|---|---|---|
| Ts | EtMgCl | THF | 0 | <15 | 70 |
| $POPh_2$ | $Et_2Zn$ | $CH_2Cl_2$ | 0 | 0 | 100 |
| PMP | $Et_2Zn$ | $PhCH_3$ | 81 | 7 | 12 |
| PMP | EtLi | THF | 0 | 34 | 0 |
| PMP | $Et_2AlCl$ | MeCN | >90 | <5 | <5 |
| PMP | EtMgCl | THF | 79 | 21 | 0 |
| PMP | EtMgBr | THF | >90 | <5 | <5 |

[a]Reaction conditions: 0.19 M of SM, 1.5–3.0 equiv $R^2M$. [b]Conversion by H NMR spectroscopy.

### *1.1.5. Asymmetric Allylic Alkylation for the Synthesis of α,α-Disubstituted α-Amino Acids*

Transition metal-catalyzed allylic substitution with carbon nucleophiles is a powerful tool for the controlled formation of carbon-carbon bonds. Asymmetric allylic alkylation (AAA) has seen considerable progress since Tsuji's seminal work in 1965.[27] However, AAA with α-amino acids is rare. The unreactive nature of α-amino acids as

27) (a) Tsuji, J.; Takahashi, H.; Morikawa, M. "Organic syntheses by means of noble metal and compounds. XVII. Reaction of π-allylpalladium chloride with nucleophiles" *Tetrahedron Lett.* **1965**, 4387-4388. (b) Trost, B. M. "Pd asymmetric allylic alkylation (AAA). A powerful synthetic tool" *Chem. Pharm. Bull.* **2002**, *50*, 1-14. (c) Lu, Z.; Ma, S. "Metal-Catalyzed Enantioselective Allylation in Asymmetric Synthesis" *Angew. Chem., Int. Ed.* **2008**, *47*, 258-297. (d) Rios, I. G.; Rosas-Hernandez, A.; Martin, E. "Recent Advances in the Application of Chiral Phosphine Ligands in Pd-Catalyzed Asymmetric Allylic Alkylation" *Molecules* **2011**, *16*, 970-1010.

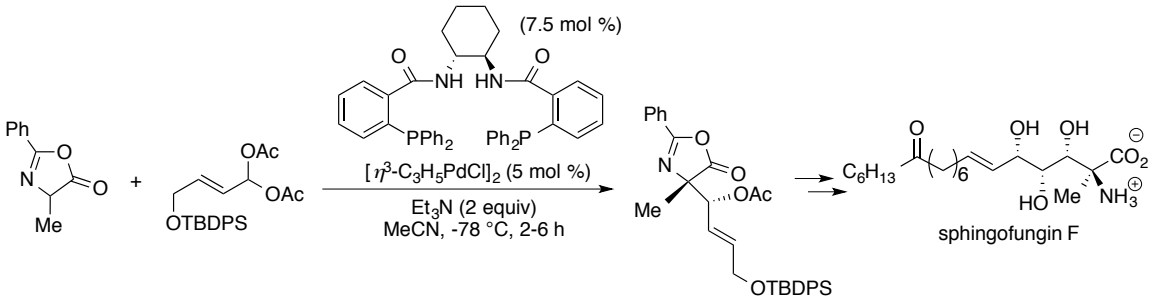
well as the sterically hindered α-carbon requires pre-activation and limits the types of α-amino acid nucleophiles.

Trost and Ariza in 1997 revealed the first AAA for the synthesis of α,α-disubstituted α-amino acids.[28a] Previous work for the synthesis of such compounds was accomplished by the use of a chiral auxiliary or self-reproduction of chirality.[29] AAA is difficult because the attacking nucleophile is very remote from the chiral inducing unit. However, this challenge was overcome by the use of the [(*R,R*)-DACH phenyl Trost ligand], which provides conformational chirality, creating chiral space around the allyl moiety, similar to an enzyme active site. Trost and Lee applied this novel technology for the asymmetric synthesis of Sphingofungin F, a natural product that inhibits the biosynthesis of sphingolipids; all stereochemistry in the final product emanated from the initial AAA (Scheme 1.8).[28b]

28) (a) Trost, B. M.; Ariza, X. "Catalytic Asymmetric Alkylation of Nucleophiles: Asymmetric Synthesis of α-Alkylated Amino Acids" *Angew. Chem., Int. Ed.* **1997**, *36*, 2635-2637. (b) Trost, B. M.; Lee, C. B. "A New Strategy for the Synthesis of Sphingosine Analogues. Sphingofungin F" *J. Am. Chem. Soc.* **1998**, *120*, 6818-6819. (c) Trost, B. M.; Ariza, X. "Enantioselective Allylations of Azlactones with Unsymmetrical Acyclic Allyl Esters" *J. Am. Chem. Soc.* **1999**, *121*, 10727-10737.

29) (a) Seyden-Penne, J. *Chiral Auxiliaries and Ligands in Asymmetric Synthesis*, Wiley, New York, **1995**. (b) Seebach, D.; Sting A. R.; Hoffmann, M. "Self-Regeneration of Stereocenters (SRS)−Applications, Limitations, and Abandonment of a Synthetic Principle" *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2708-2748.

**Scheme 1.8** Pd-catalyzed AAA for the synthesis of α,α-disubstituted α-amino acids and related natural product, Sphingofungin F.



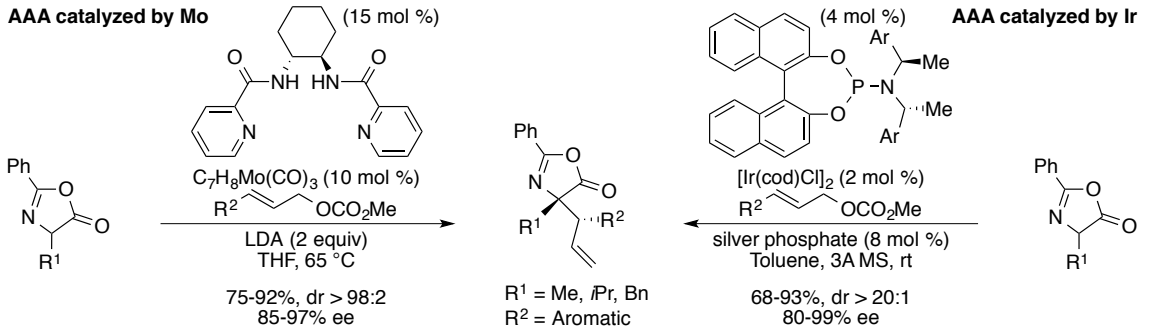

Trost and Dogra, and subsequently Hartwig and Chen, demonstrated that the branched allyl product could be accessed with molybdenum or iridium catalyst with high diastereo- and enantioselectivity (Scheme 1.9).[30,31] The α-amino acid must be converted to the azlactone derivative for reactivity to be observed. Ito and Kuwano have found that acyclic α-amino acids can be utilized when the α-carbon is substituted with an electron-withdrawing group.[32b]

30) Trost, B. M.; Dogra, K. "Synthesis of Novel Quaternary Amino Acids Using Molybdenum-Catalyzed Asymmetric Allylic Alkylation" *J. Am. Chem. Soc.* **2002**, *124*, 7256-7257.

31) Chen, W.; Hartwig, J. F. "Control of Diastereoselectivity for Iridium-Catalyzed Allylation of a Prochiral Nucleophile with a Phosphate Counterion" *J. Am. Chem. Soc.* **2013**, *135*, 2068-2071.

32) For other examples of palladium catalyzed AAA to synthesize α,α-disubstituted α-amino acids, see: (a) Fang, P.; Chaulagain, M. R.; Aron, Z. D. "Catalytic α-Allylation of Unprotected Amino Acid Esters" *Org. Lett.* **2012**, *14*, 2130-2133. (b) Kuwano, R.; Ito, Y. "Catalytic Asymmetric Allylation of Prochiral Nucleophiles, α-Acetamido-β-ketoesters" *J. Am. Chem. Soc.* **1999**, *121*, 3236-3237.

**Scheme 1.9** Mo- or Ir-catalyzed AAA for the synthesis of α,α-disubstituted α-amino acids.




*1.1.6. Proposed Asymmetric N-Alkylation/π-Allylation of α-Iminoesters to Synthesize α-Allyl-a-Aryl α-Amino Acids*

The previous work by our group with the three component coupling of α-iminoesters inspired our interest in the asymmetric synthesis of α,α-disubstitued α-amino acids. A thorough investigation of the literature revealed there is no general method for the synthesis of enantioenriched α-allyl-α-aryl α-amino acids. Considering the previous work of Trost and Hartwig, we proposed the enolate generated *in situ* from *N*-alkylation of α-iminoesters when treated with a Grignard reagent could undergo AAA (Figure 1.7). If this hypothesis proved correct then this novel method would provide access to previously inaccessible α-allyl-α-aryl α-amino acids. This class of compounds is important because of their unknown peptidomimetic properties. Also, the allyl moiety present would allow further reactivity to produce other compounds of interest.

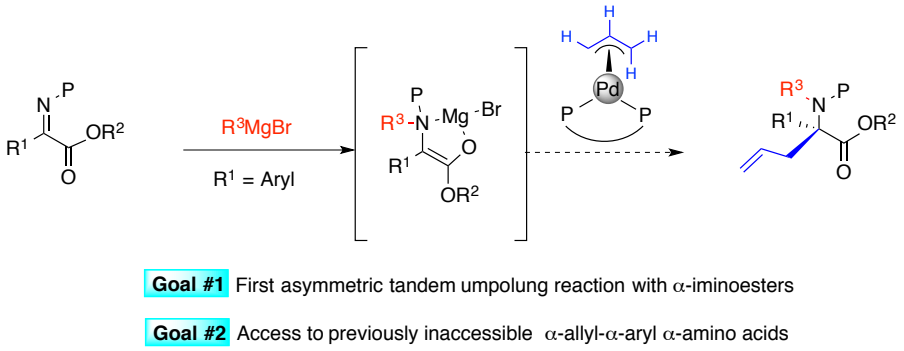


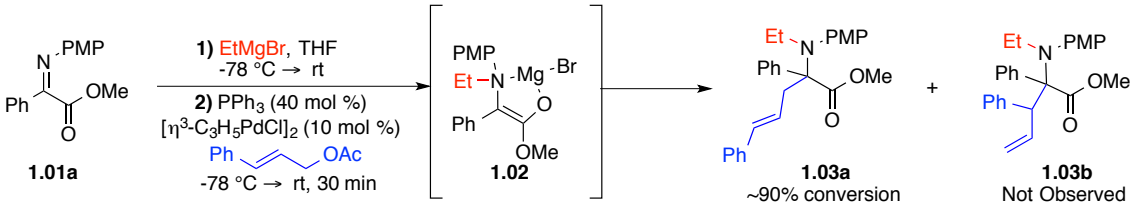

**Figure 1.7** Synthesis of α-allyl-α-aryl α-amino acids and project goals.

## 1.2. RESULTS

### *1.2.1. Initial Studies on the Asymmetric Allylic Alkylation of α-Iminoesters*

Initial studies on the asymmetric three component coupling reaction were conducted by a former group member, Dr. Joshua Dickstein.[33] The proposed trapping of the enolate (**1.02**) generated from *N*-alkylation with an allylmetal complex was investigated. $[\eta^3\text{-}C_3H_5PdCl]_2$ with $PPh_3$ provided the linear product (**1.03a**) in over 90% conversion, while the branched product (**1.03b**) was not observed (Scheme 1.10).

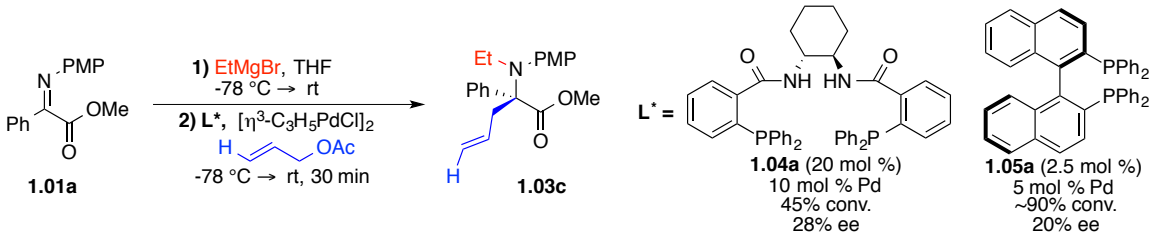
**Scheme 1.10** *N*-Alkylation/π-allylation with Pd and $PPh_3$.




33) Dickstein, J. S. Part I: Palladium-Mediated Aromatic Decarboxylation. Part II: Formation of α,α-Disubstituted α-Amino Acids via Three Component Coupling of α-Iminoesters. Ph.D. Thesis, University of Pennsylvania, Philadelphia, PA, 2009.

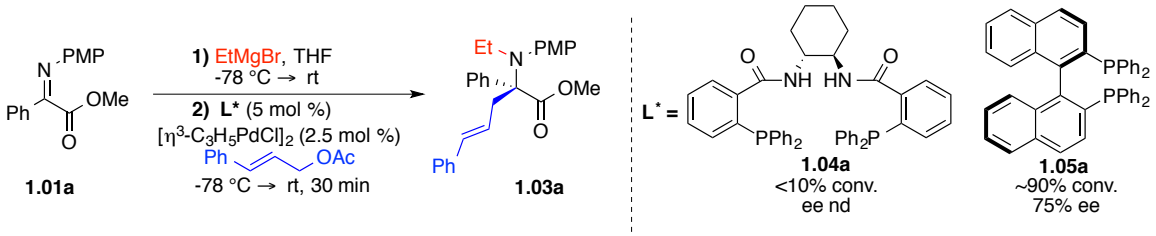
Dr. Dickstein investigated chiral, enantioenriched ligands with allyl acetate (Scheme 1.11). The [(*R*,*R*)-DACH phenyl Trost ligand] (**1.04a**) was superior to (*R*)-BINAP (**1.05a**) in selectivity but inferior in conversion. $Pd_2dba_3$•$CHCl_3$ was also tested with each ligand and provided 10% and 90% conversion to product, respectively; the selectivity for (*R*)-BINAP with $Pd_2dba_3$•$CHCl_3$ was 8% ee.

**Scheme 1.11** Asymmtric *N*-alkylation/π-allylation with allyl acetate.




In an effort to improve the enantioselectivity of the reaction, cinnamyl acetate was substituted for allyl acetate. The mono-substitution of cinnamyl acetate creates an allyl-palladium complex with enhanced definition of termini. Dr. Dickstein found that when cinnamyl acetate was substituted for allyl acetate with (*R*)-BINAP, an increase from 20% to 75% ee was observed without loss of conversion (Scheme 1.12). The Trost ligand was unsuccessful in catalyzing the formation of the tandem product when cinnamyl acetate was substituted for allyl acetate.

**Scheme 1.12** Asymmtric *N*-alkylation/π-allylation with cinnamyl acetate.



*1.2.2. Optimization of the Asymmetric Allylic Alkylation of α-Iminoesters*

Reaction optimization (solvent, temperature, concentration, stoichiometry) was investigated with **1.01a**, EtMgBr, cinnamyl acetate, $[\eta^3\text{-}C_3H_5PdCl]_2$, and (*R*)-BINAP (Figure 1.8). A solvent screen revealed that non-ethereal solvents such as $CH_2Cl_2$, chlorobenzene, trifluorotoluene and toluene all provided lower selectivity than THF; 2-MeTHF and CPME provided the tandem product with comparable selectivity ($Et_2O$ provided lower selectivity). Temperature studies were conducted (-90 °C, -50 °C, -20 °C, 0 °C and rt) and it was found that a temperature profile of -78 °C to 0 °C for each step is optimal. Reaction time was explored, the minimal time for *N*-alkylation was 30 minutes, but similar enantioselectivity was observed when the enolate was aged between 1-3 h. The second step was complete after reaching rt. Concentration has a minimal effect on the reaction. With 1.1 equiv of EtMgBr conversion was reduced to 64% and 24% ee. With 5 equiv of EtMgBr conversion was less than 10%; presumably, the allyl electrophile was consumed by the excess Grignard.

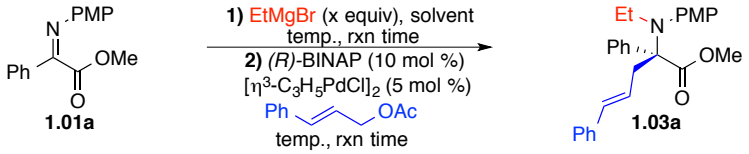



**Figure 1.8** Reaction optimization of **1.01a** with EtMgBr and cinnamyl acetate.

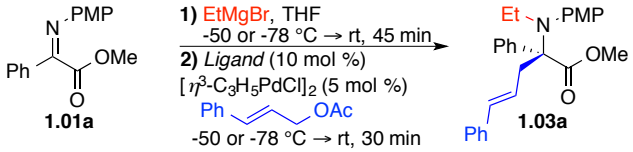
In 2010, our research group began collaborating with Dr. Spencer Dreher of Merck & Co Inc., utilizing the high-throughput experimentation center in Rahway, NJ. Parallel microscale experimentation (PME), a valuable tool for rapidly screening conditions and drawing out trends, was used to optimize the tandem *N*-alkylation/π-

allylation of **1.01a** (Table 1.2).[34] Greater than 190 chiral, enantioenriched ligands were explored with the optimal conditions established with the exception that -50 °C was employed instead of -78 °C due to the limitation with the PME workflow.[35] Nearly all ligands gave minimal conversion and selectivity but axial chiral bisphosphines, such as **1.05a-c**, **1.06a-c** and **1.09-1.12** were most effective in generating **1.03a** as confirmed in larger scale reactions at -78 °C (Table 1.2, right). The Trost ligand (**1.04a-b**) possessing central chirality and the Pfaltz ligand (**1.13**) with planar chirality were unsuccessful, showing both poor reactivity and poor selectivity.

**Table 1.2** Select results from parallel microscale experimentation and scale up reactions.

34) Dreher, S. D.; Dormer, P. G.; Sandrock, D. L.; Molander, G. A. "Efficient Cross-Coupling of Secondary Alkyltrifluoroborates with Aryl Chlorides−Reaction Discovery Using Parallel Microscale Experimentation" *J. Am. Chem. Soc.* **2008**, *130*, 9257-9259.

35) Ir and Mo were explored with cinnamyl acetate. Mo provided the linear product (<30% conv) and the branch product was not observed.

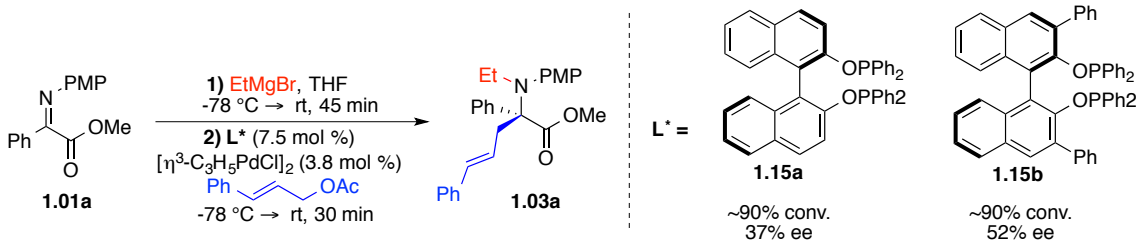



| | | | PME Screen (-50 °C)[a] | | | Bench top Scale Up (-78 °C)[b] | |
|---|---|---|---|---|---|---|---|
| Ligand | | Total Area | Peak 1 | Peak 2 | er (%)[c] | conv. (%)[d] | er (%)[e] |
| S-BINAP | **1.05a** | 3252 | 972 | 2280 | 30:70 | >90 | 90:10 |
| S-H8-BINAP | **1.05b** | 5424 | 3229 | 2195 | 60:40 | >90 | 74:26 |
| (R)-Tol-BINAP | **1.05c** | 5127 | 3264 | 1863 | 64:36 | ~90 | 56:44 |
| (R)-Segphos | **1.06a** | 781 | 550 | 231 | 70:30 | >90 | 70:30 |
| (R)-P3-Segphos | **1.06b** | 5358 | 1681 | 3677 | 31:69 | >90 | 90:10 |
| (R)-Difluorphos | **1.06c** | 456 | 317 | 139 | 70:30 | >90 | 94:6 |
| (R)-Cl,MeO-Biphep | **1.07a** | 5230 | 3530 | 1700 | 68:32 | ~90 | 87:13 |
| SL-A102-1 | **1.08a** | 5126 | 3194 | 1932 | 62:38 | - | - |
| SL-A121-1 | **1.08b** | 5311 | 2119 | 3192 | 40:60 | - | - |
| (S)-C1-Tunephos | **1.09a** | 2574 | 742 | 1832 | 29:71 | ~30 | 64:36 |
| (S)-C2-Tunephos | **1.09b** | 4041 | 1228 | 2813 | 30:70 | - | - |
| (S)-C3-Tunephos | **1.09c** | 5334 | 1675 | 3659 | 31:69 | >90 | 89:11 |
| (S)-C4-Tunephos | **1.09d** | 5248 | 1711 | 3537 | 33:67 | - | - |
| (S)-C5-Tunephos | **1.09e** | 5280 | 1876 | 3404 | 36:64 | - | - |
| (S)-C6-Tunephos | **1.09f** | 4380 | 1475 | 2905 | 34:66 | - | - |
| (S)-Me-Soniphos | **1.10a** | 2297 | 578 | 1719 | 25:75 | >90 | 70:30 |
| (S)-Cyclohex-Soniphos | **1.10b** | 5475 | 1379 | 4096 | 25:75 | >90 | 86:14 |
| (-)-TMBTP | **1.11** | 5512 | 3747 | 1765 | 68:32 | >90 | 70:30 |
| (R)-P-Phos | **1.12a** | 520 | 353 | 167 | 68:32 | >90 | 90:10 |
| (S)-Xylyl-P-Phos | **1.12b** | 964 | 283 | 681 | 29:71 | - | - |
| SL-W001-1 | **1.08c** | 5252 | 2043 | 3209 | 39:61 | - | - |
| SL-W009-1 | **1.08d** | 5356 | 1720 | 3636 | 32:68 | >90 | 74:26 |
| SL-M001-1 | **1.08e** | 3623 | 2421 | 1202 | 69:31 | >90 | 83:17 |
| SL-M003-1 | **1.08f** | 940 | 346 | 594 | 37:63 | - | - |
| (R,R)-DACH-Phenyl Trost | **1.04a** | 0 | 0 | 0 | 50:50 | <10 | ND |
| (R,R)-DACH-Naphthyl | **1.04b** | 499 | 164 | 335 | 33:67 | - | - |
| (R)-Pfaltz(Ph) | **1.13** | 0 | 0 | 0 | 50:50 | ~15 | 57:43 |
| (S)-Xyl-SDP | **1.14** | 5299 | 2023 | 3276 | 38:62 | - | - |

[a] 8.6 µmol of **1.01a**, run at a starting temperature of -50 °C. [b] 0.372 mmol of **1.01a**, run at a starting temperature of -78 °C. [c]Determined by chiral SFC [d]Conv. is determined by amount of **1.03a** to N-alkylated intermediate. [e]Determined by chiral HPLC and when major enantionmer was opposite from PME screen, the opposite enantiomer of ligand was used.

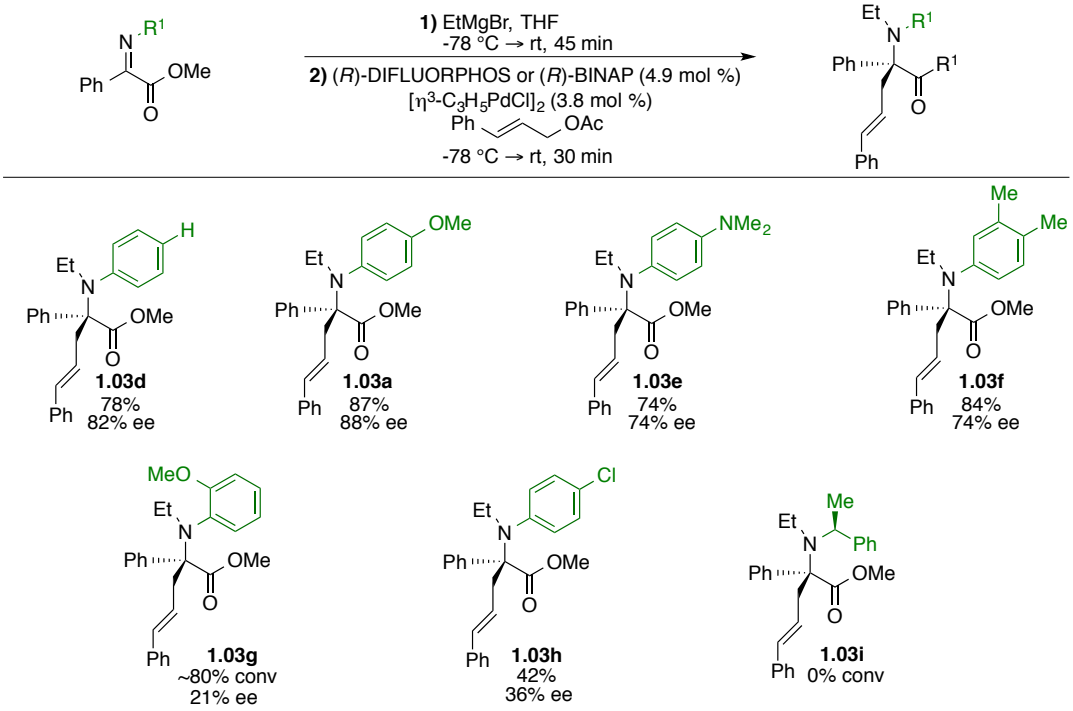
*(R)*-DIFLUORPHOS (**1.06c**) was chosen as the lead ligand after the HTE screen (8.6 µmol) was explored at bench top scale (0.372 mmol). Ethereal solvents (CPME, 2-MeTHF) were investigated but did not improve the reaction. The success of DIFLUORPHOS (**1.06c**) vs SEGPHOS (**1.06a**) suggested that increased π-acidity was important for selectivity. (*R*)-BINAPO (**1.15a**) was investigated along with modification at the C3,C3' position (**1.15b**) but neither showed significant enantioselectivity (Scheme 1.13). Modification of *(R)*-DIFLUORPHOS was not explored because of the multiple synthetic steps required.

**Scheme 1.13** Asymmtric *N*-alkylation/π-allylation with π-acidic ligands.




With optimal conditions established for solvent, temperature, allylating agent, ligand and metal source, the activating agent on the α-iminoester was explored (Table 1.3). Dr. Dickstein and co-workers established that electron donating activating agents were superior to electron withdrawing (phenyl vs tosyl/$POPh_2$, see Table 1.1) for the initial addition of alkyl Grignard reagents to α-iminoesters. Electron-donating phenyl activating agents improved conversion and selectivity (Table 1.3, **1.03a**, **1.03e**-**1.03f**). *para*-Chlorophenyl (**1.03h**) reduced yield and selectivity. To our surprise, when benzyl (**1.03i**) was substituted for phenyl, the tandem product was not formed. This activating group had been successful with less sterically hindered α-iminoesters in past reports (see Scheme 1.7).[21,23]

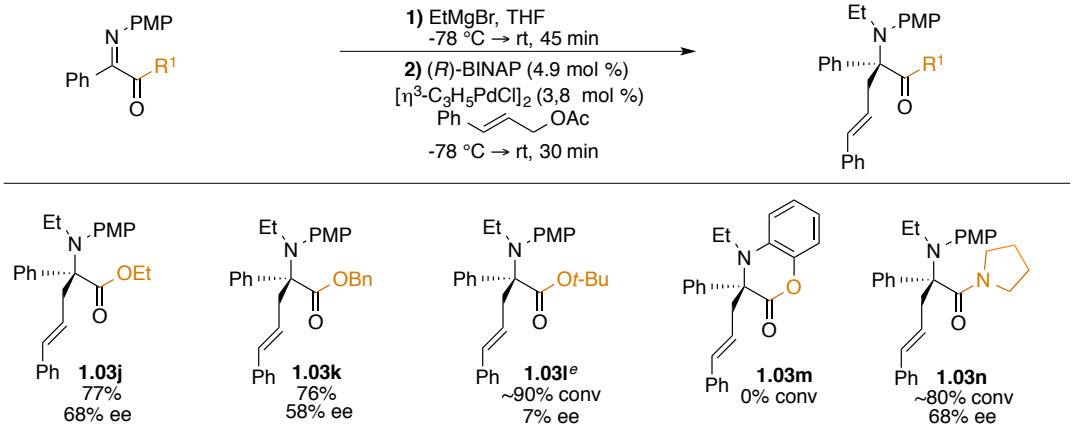
**Table 1.3** Exploration of activating agent on the α-iminoester for the asymmtric *N*-alkylation/π-allylation.[a]




[a]Reaction conditions: α-Iminoester (0.37 mmol), 1.5 equiv EtMgBr, THF (2.0 mL), 1.0 equiv cinnamyl acetate in THF (2.0 mL). [b]Isolated yield unless labeled conversion. [c]Conv. is determined by amount of product to *N*-alkylated intermediate. [d]ee determined by CSP HPLC.

Substitution at the carbonyl was explored once the PMP activating group was determined to be optimal (Table 1.4). As the size of the alkyl ester was increased from ethyl to *tert*-butyl ester, the selectivity of the reaction was reduced. The production of the tandem product was still efficient. Presumably, as the alkyl ester becomes larger, the solvated bridge dimer enolate is less likely to form, and the distinction between the pro-chiral nucleophilic faces is reduced (see Figure 1.10). Compound **1.03m** prevents bidentate coordination of the α-iminoeser with the Grignard reagent (see Figure 1.5) and does not provide the *N*-alkylated product.

**Table 1.4** Exploration of the alkyl ester on the α-iminoester for the asymmtric *N*-alkylation/π-allylation.[a]

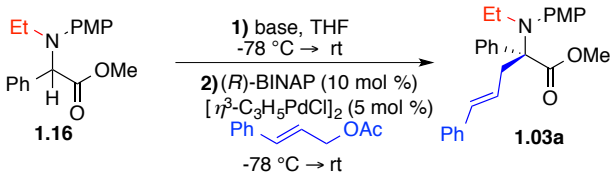



[a]Reaction conditions: α-iminoester (0.37 mmol), 1.5 equiv EtMgBr, THF (2.0 mL), 1.0 equiv cinnamyl acetate in THF (2.0 mL). [b]Isolated yield unless labeled conversion. [c]Conv. is determined by amount of product to N-alkylated intermediate. [d]ee determined by CSP HPLC. [e]Reaction performed by Joshua Dickstein.

Reasoning that the same product **1.03a** ought to be available from racemic α-phenylgylcine, the enolate was generated via deprotonation (Table 1.5). A wide range of bases provided good conversion (>85%), but poor enantioselectivity (ee = 18-34%) compared to the tandem reaction (80% ee) (Table 1.5, entries 1-3). Notably, treatment of **1.16** with EtMgBr should generate the exact same enolate (**1.02**) as in the tandem reaction. However, this enolate provided low conversion and significantly lower selectivity (Table 1.5, entry 4). Enolate aggregation has been shown to play an important role in the asymmetric alkylation of various carbonyls.[36] It was concluded that the exact structural form of the enolate is critical to the outcome. Specifically, the aggregate of **1.21a-c** obtained from **1.01a** differs from that obtained from **1.16** (see Figure 1.10).

36) (a) Kawabata, T.; Kawakami, S. P.; Shimada, S.; Fuji, K. "Control of the Enantioselectivity of Alkylation of Phenylalanine Derivatives by Regulation of the Aggregate Structure of Chiral Enolate Intermediates" *Tetrahedron* **2003**, *59*, 965-974. (b) Kawabata, T.; Kawakami, S.; Fuji, K. "Enantioselective Alpha-Allylation of a Phenylalanine Derivative under the Control of Aggregation of a Chiral Nonracemic Enolate" *Tetrahedron Lett.* **2002**, *43*, 1465-1467.

**Table 1.5** Allylation of the *N*-alkylation product.[a]




| Entry | Base | Conversion (%)[b] | ee (%)[c] |
|---|---|---|---|
| 1 | NaHMDS | ~90 | 19[d] |
| 2 | KHMDS | ~85 | 23[d] |
| 3 | LiHMDS | ~90 | 18[d] |
| 4 | EtMgBr | ~50 | 34 |
| 5 | NaH | No Product | nd |

[a]Reaction conditions: [**1.16**] = 0.19 M, 2.0 equiv base, THF (1.0 mL), rt for 10 min, then cool to -78 °C and add solution of 2.5 mol% [η$^3$-$C_3H_5PdCl]_2$, 5.0 mol% (*R*)-BINAP, 1.0 equiv cinnamyl acetate in THF (1.0 mL) and warm to rt. [b]Determined By $^1$H NMR spectroscopy. [c]Determined by CSP HPLC. [d]Opposite major enantiomer observed.

In order to determine if the enolate aggregate was organizing more than one palladium complex or was selecting for a 2:1 ligand:palladium catalyst, a non-linear effect study was undertaken (Figure 1.9). The observation of a linear trend suggests that 1:1 ligand:palladium complexes are reacting independent of each other with the enolate aggregate.

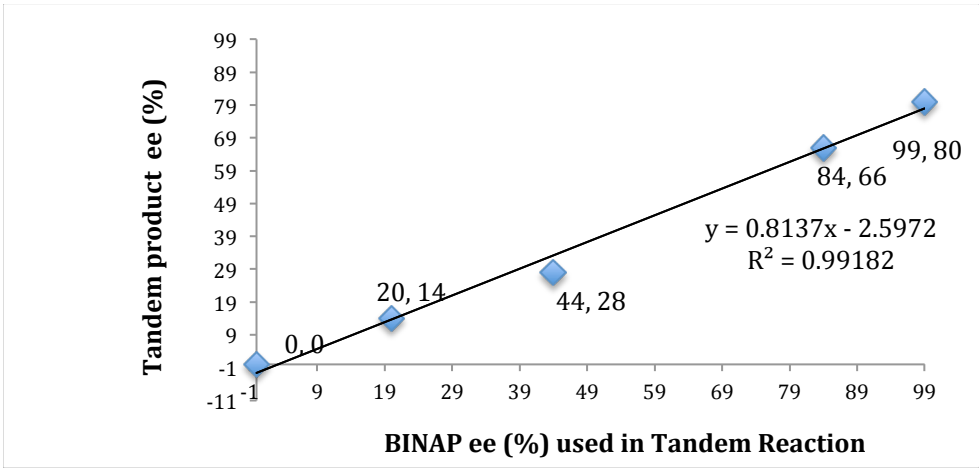
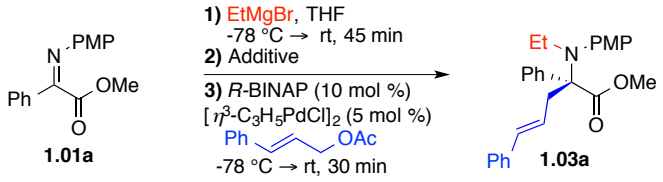



**Figure 1.9** Non-linear effects with BINAP (**Scheme 1.14**).

A number of different types of additives have been shown to affect the selectivity in AAA.[37] Tertiary amines and silver salts should break-up aggregates from enolate formation with magnesium, but each additive explored either had no effect or reduced selectivity (Table 1.6, entry 1-5). It was postulated that transmetallation of the enolate from magnesium to zinc could improve selectivity, but instead it was reduced to 4% ee (Table 1.6, entry 6). Lloyd-Jones and co-workers have proposed ion-pair partitioning on the allyl-Pd complex can improve reaction selectivity.[38] However, treatment of cinnamyl acetate, $[\eta^3\text{-}C_3H_5PdCl]_2$, and (*R*)-BINAP with NaBAr'F did not improve ee (Table 1.6, entry 8)

**Table 1.6** The addition of additives after enolate formation.[a]




| Entry | Additive | Conversion (%)[b] | ee (%)[c] |
|---|---|---|---|
| 1 | $NPh_3$ | ~90 | 79 |
| 2 | $NEt_3$ | ~90 | 34 |
| 3 | DIPA | ~90 | 34 |
| 4 | AgBr | ~90 | 30 |
| 5 | $Ag_2O$ | ~90 | 28 |
| 6 | $ZnCl_2$ | ~50 | 4 |
| 7 | $Me_3SnCl$ | ~80 | 21 |

37) (a) Yan, X. X.; Liang, C. G.; Zhang, Y.; Hong, W.; Cao, B. X.; Dai, L. X.; Hou, X. L. "Highly Enantioselective Pd-Catalyzed Allylic Alkylations of Acyclic Ketones" *Angew. Chem., Int. Ed.* **2005**, *44*, 6544-6546. (b) Negishi, E. I.; John, R. A. "Selective Carbon Carbon Bond Formation Via Transition-Metal Catalysis. 34. Counterion Effects on the Palladium-Catalyzed Allylation of Enolates" *J. Org. Chem.* **1983**, *48*, 4098-4102.

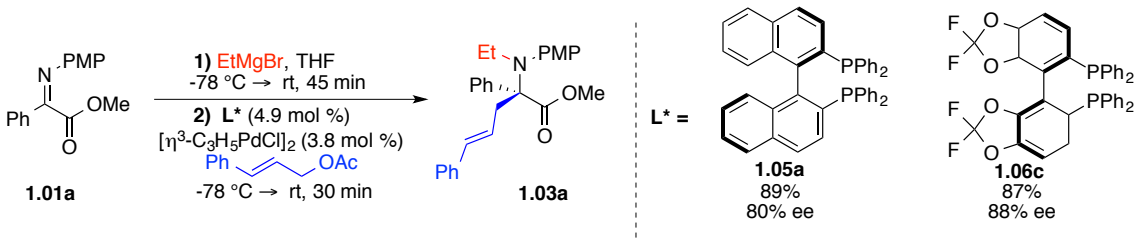
38) Evans, L. A.; Fey, N.; Harvey, J. N.; Hose, D.; Lloyd-Jones, G. C.; Murray, P.; Orpen, A. G.; Osborne, R.; Owen-Smith, G. J. J.; Purdie, M. "Counterintuitive Kinetics in Tsuji-Trost Allylation: Ion-Pair Partitioning and Implications for Asymmetric Catalysis" *J. Am. Chem. Soc.* **2008**, *130*, 14471-14473.

| | | | |
|---|---|---|---|
| 8 | NaBAr'F[d] | ~90 | 28 |

[a]Reaction conditions: 1-2 equiv of additive was added after step 1. [b]Determined by $^1$H NMR spectroscopy with respect to *N*-alkylated intermediate. [c]Determined by CSP HPLC. [d]5 mol % ligand, 2.5 mol % Pd, 5 mol % additive.

In summary, the best activating agent, ester substitution, solvent, ligand and metal source provided the tandem product in 87% yield and 88% ee (Scheme 1.14). This new technology was the first asymmetric three component coupling of α-iminoesters. The next goal was to expand the substrate scope so previously inaccessible enantioenriched α-allyl-α-aryl α-amino acids could be obtained.

**Scheme 1.14** Optimal conditions with **1.01a** and cinnamyl acetate.

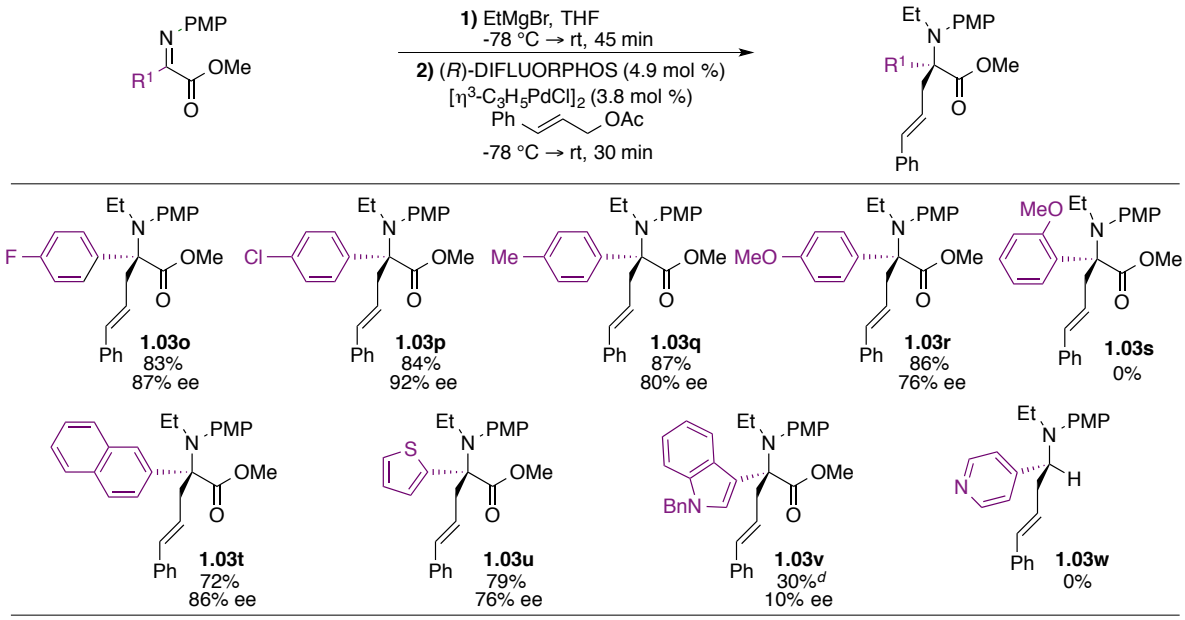



### *1.2.3. Substrate Scope for the Asymmetric Allylic Alkylation of α-Iminoesters*

With the optimal conditions, a range of α-iminoesters reacted with satisfactory yields and enantioselectivity (Table 1.7). Notably, the reaction was equally effective with imine substituents ($R^1$) containing electron-donating and electron-withdrawing aryl groups, while *ortho*-substituted aryl (2-OMe) resulted in lower formation of the desired product. Thiophene could also be employed to good effect but the indole tandem product was not stable. Compound **1.03t** is the only tandem product that is a crystalline solid. Trituration provided >99% ee material and allowed the absolute configuration of the

asymmetric *N*-alkylation/π-allylation products to be determined by X–ray crystallography.

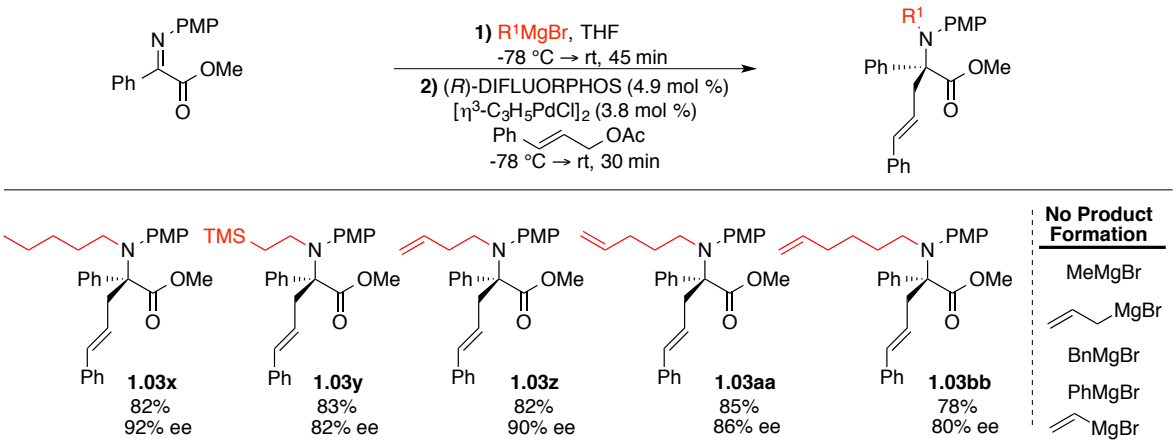
**Table 1.7** Variation of the α-iminoester in the asymmetric *N*-alkylation/π-allylation.[a]




[a] Reaction conditions: α-iminoester (0.37 mmol), 1.5 equiv EtMgBr, THF (2.0 mL), 1.0 equiv cinnamyl acetate in THF (2.0 mL). [b] Isolated yields are shown. [c] ee determined by CSP HPLC. [d] Degrades after isolaton.

In contrast to most other reports of *N*-alkylation of α-iminoesters, a range of Grignard reagents could be employed to provide unique *N*-alkyl α-allyl-α-aryl α-amino acid derivatives (Table 1.8). Notably, more functional Grignards provided terminal silyl and alkenyl derivatives (**1.03y–1.03bb**). For alkenyl substrates, the alkene must be distal to the reacting center as allyl, benzyl, phenyl and vinyl Grignard reagents were not successful. Methyl Grignard would not undergo *N*-alkylation; to date, methyl Grignard has only been successful with the doubly-activated α-iminomalonate (see Scheme 1.7).[22]

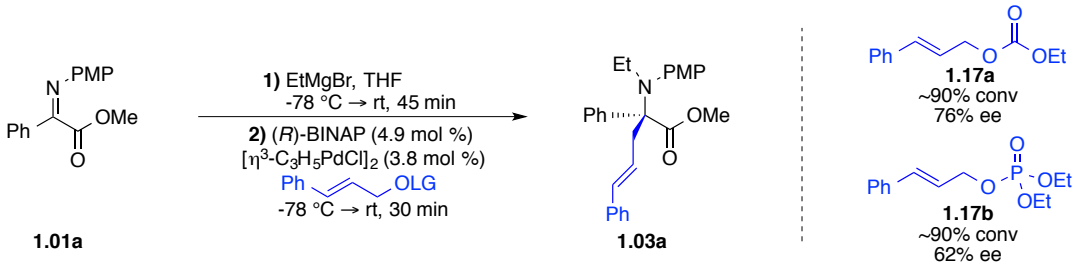
**Table 1.8** Exploration of Grignard Reagents in the asymmetric *N*-alkylation/π-allylation.[a]




[a] Reaction conditions: **1.01a** (0.37 mmol), 1.5 equiv R[1]MgBr, THF (2.0 mL), 1.0 equiv cinnamyl acetate in THF (2.0 mL). [b] Isolated yields are shown. [c] ee determined by CSP HPLC.

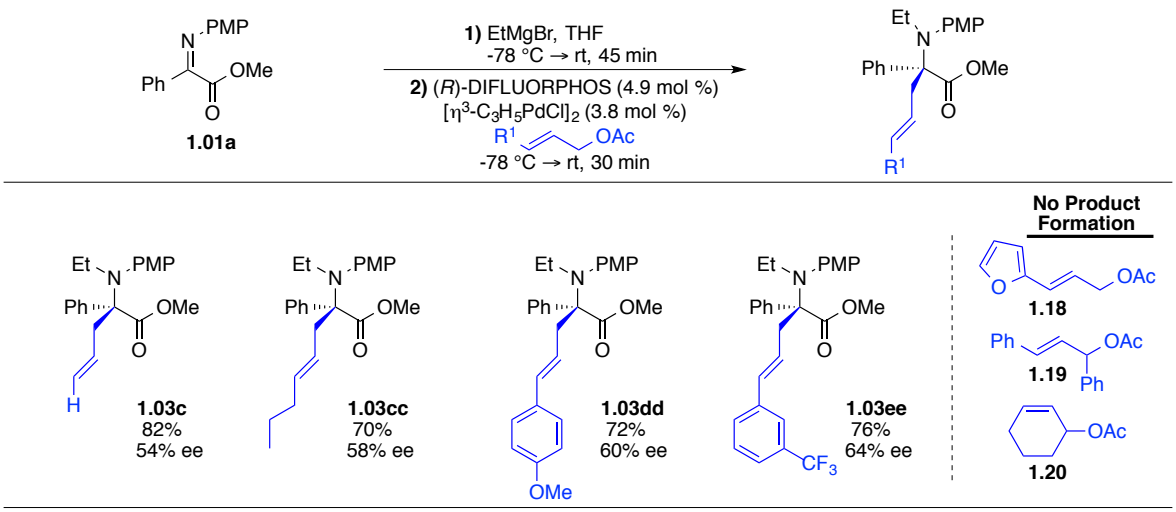
The leaving group on cinnamyl alcohol was explored (Scheme 1.15). The cinnamyl carbonate (**1.17a**) and phosphate (**1.17b**) are better leaving groups than acetate and should form a more reactive allylpalladium-ligand complex. However, cinnamyl acetate gave higher selectivity than cinnamyl carbonate and phosphate. When the π-allylation step was allowed to run at lower temperature for prolonged reaction time with cinnamyl phosphate, no improvement in selectivity was seen.

**Scheme 1.15** Leaving group on cinnamyl alcohol in the asymmetric *N*-alkylation/π-allylation.



Replacing the phenyl ring of cinnamyl acetate with hydrogen reduced selectivity (Table 1.9). This result is in line with phenyl differentiating the termini of the allyl-palladium complex, which is expected to increase selectivity. However, modification of the phenyl group in cinnamyl acetate with either electron-donating or -withdrawing groups did not increase selectivity (**1.03dd** and **1.03ee**). Driven by a desire to generate aspartic/glutamic acid analogs, the corresponding furyl allyl acetate (**1.18**) was surveyed, but no product was observed. Lastly, 1,3-disubstituted allylating agents generated no tandem product (**1.19** and **1.20**).

**Table 1.9** Allylating agents in the asymmetric *N*-alkylation/π-allylation.[a]




[a] Reaction conditions: **1.01a** (0.37 mmol), 1.5 equiv EtMgBr, THF (2.0 mL), 1.0 equiv allylating agent in THF (2.0 mL).
[b] Isolated yields are shown. [c] ee determined by CSP HPLC.

### *1.2.4. Stereochemical Model for the Asymmetric Allylic Alkylation of α-Iminoesters*

Recently, Trost has proposed a stereochemical model for the attack of β-ketoesters onto allyl chloroformate and suggested that lithium aggregates are responsible

for changing the predominant enantiomer obtained.[39] Magnesium enolates, like that generated here, of all but the most hindered ketones are reported to be dimeric in solution.[40] In the development of this technology, a strong solvent dependence was observed, with ethereal solvents being far superior. Depending on the exact structure of the Grignard reagent, subtle differences were seen among the ethereal solvents THF, 2-MeTHF, $Et_2O$, and CPME. On the other hand, non-solvating solvents such as toluene or dichloromethane resulted in minimal addition to the allyl-Pd complex and low selectivity. Amine base additives also reduced the selectivity to less than 30% ee (see Table 1.6). Together, these results suggest a delicate balance where the most selective species is a solvated dimer, such as **1.21a**, that lies in between poorly selective forms including a deaggregated form, such as monomer **1.21c**, and a less solvated form, such as a tetramer or dimer **1.21b** (Figure 1.10).

39) Trost, B. M.; Schaffner, B.; Osipov, M.; Wilton, D. A. A. "Palladium-Catalyzed Decarboxylative Asymmetric Allylic Alkylation of β-ketoesters: An Unusual Counterion Effect" *Angew. Chem., Int. Ed.* **2011**, *50*, 3548-3551.

40) For *X*-ray crystal structure and $^{13}C$ NMR studies of halomagnesium ketone enolates, see: (a) Williard, P. G.; Salvino, J. M. "X-Ray Crystal Structure Determination of a Bromomagnesium Ketone Enolate" *J. Chem. Soc., Chem. Commun.* **1986**, 153-154. (b) Fellman, P.; Dubois, J.–E. "Metal Enolates: Carbon –13 Magnetic Resonance Spectra" *Tetrahedron Lett.* **1977**, *18*, 247-250. (c) Pinkus, A. G.; Lindberg, J. G.; Wu, A.–B. "Structure of Grignard Compound Derived from Mesityl Methyl Ketone" *Chem. Commun.* **1969**, 1350-1351.

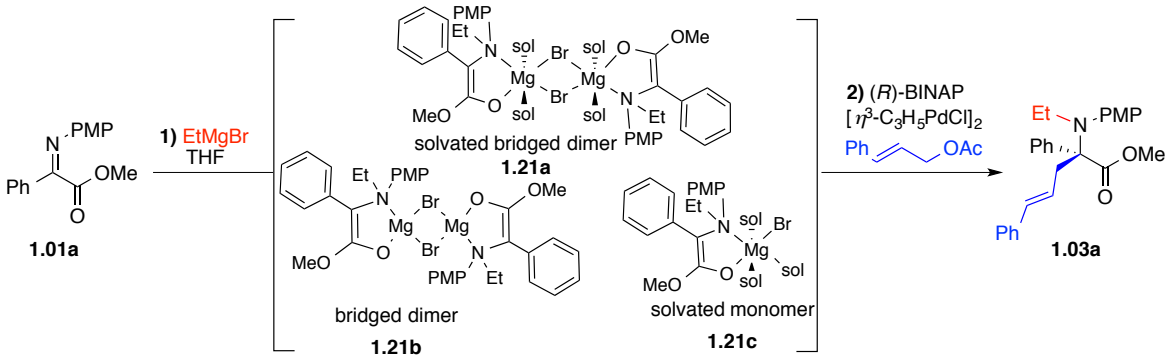



**Figure 1.10** Possible enolate forms of *N*-alkylated intermediate in solution (sol = solvent).

Hypothesizing that a dimeric enolate (**1.21a**) plays a major role in the stereoselectivity of the Pd-catalyzed AAA, a model for the stereochemical outcome can be proposed. Newman projections predict that the enolate dimer should attack via an outer-sphere mechanism with the five-membered enolate chelate ring furthest from the carbon substituent of the allyl (Figure 1.11).

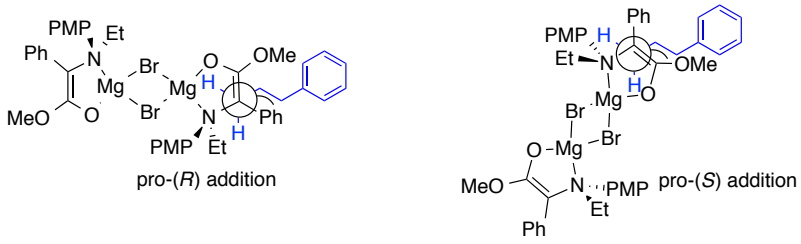



**Figure 1.11** Newman projections of dimeric enolate attack on allyl.

PME revealed that the more common Trost or Pfaltz ligands for AAA, which have central or planar chirality, failed to produce the allylated product (see Table 1.2). Trost has shown elegant examples that the chiral pocket from [(*R,*R)-DACH phenyl]

(**1.04a**) has a flap, wall, flap, wall motif.[41] Helmchen has shown that substituted allyls align their largest group syn to the phosphorus terminus of the Pfaltz ligand (**1.13**), thus creating a pocket from the amine terminus in which nucleophiles can approach.[42] Based on our results, we propose that because of the steric bulk of our α-aryl α-amino acid nucleophile, a pocket type ligand-Pd-allyl reaction site cannot afford nucleophilic addition; this accounts for the poor reactivity observed with these types of ligands. On the other hand, axially chiral ligands gave acceptable enantioselectivity and conversion (see Scheme 1.14).

Ito and Ogasawara have both crystallized and studied BINAP-Pd-allyl complexes.[32b,43] Their X-ray crystal structures show that the largest interaction between a BINAP backbone and a nucleophile undergoing outer sphere attack is through the pseudo-axial phenyl ring on phosphorus near the allyl termini. Inspection of the steric interactions with three-dimensional models reveals sterically unfavorable interactions in the pro-(*R*) approach of the dimeric enolate and the pseudo-axial aryl of (*R*)-BINAP (Figure 1.12, left). On the other hand, the pro-(*S*) approach can minimize interactions with the (*R*)-BINAP phosphorus phenyl rings (Figure 1.12, right). The observed product corresponds to that from this more favorable pro-(*S*) enolate approach. Also, the model predicts that a solvated-monomer enolate with a counterion such as sodium, lithium or

41) Trost, B. M.; Toste, F. D. "Regio- and Enantioselective Allylic Alkylation of an Unsymmetrical Substrate: A Working Model" *J. Am. Chem. Soc.* **1999**, *121*, 4545-4554.

42) Kollmar, M.; Steinhagen, H.; Janssen, J. P.; Goldfuss, B.; Malinovskaya, S. A.; Vazquez, J.; Rominger, F.; Helmchen, G. "($\eta^3$-Phenylallyl)(phosphanyloxazoline)palladium Complexes: X-Ray Crystallographic Studies, NMR Investigations, and Ab Initio/DFT Calculations" *Chem.–Eur. J.* **2002**, *8*, 3103-3114.

43) Ogasawara, M.; Ngo, H. L.; Sakamoto, T.; Takahashi, T.; Lin, W. "Applications of 4,4'-$(Me_3Si)_2$-BINAP in Transition-Metal-Catalyzed Asymmetric Carbon-Carbon Bond-Forming Reactions" *Org. Lett.* **2005**, *7*, 2881-2884.

potassium would favor the opposite enantiomer, in accord with observed results (see Table 1.5).

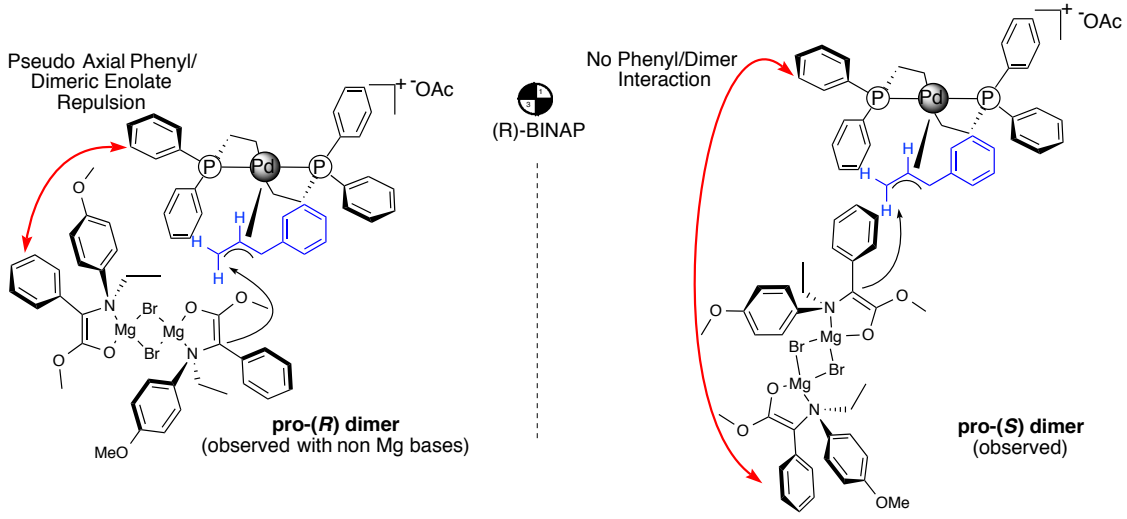



**Figure 1.12** Stereochemical model favoring addition of the pro-(*S*) dimer.

## 1.3. CONCLUSIONS

In summary, we have disclosed the first asymmetric tandem *N*-alkylation/π-allylation of α-iminoesters, which gives rise to complex enantioenriched α-allyl-α-aryl α-amino acids in one step from three commercially available components. This report represents the first enantioselective synthesis of this class of compounds beyond α-allyl-α-phenylglycine. PME was an important element in optimizing this technology, and it showed that the best chiral, enantioenriched ligand was (*R*)-DIFLUORPHOS. The activating group on the imine nitrogen and substitution on the ester were optimized by examining electronic and steric variables. Optimized conditions of ligand, substrate substitution, and solvent allowed the synthesis of >15 α-allyl-α-aryl α-amino acids in good yield and selectivity. The dramatic effect of enolate aggregation demonstrated the

importance of the tandem protocol and provides a cautionary tale for other systems. A stereochemical model was outlined that explains the observed major enantiomer and the importance of ligand screening.

## 1.4. EXPERIMENTAL SECTION

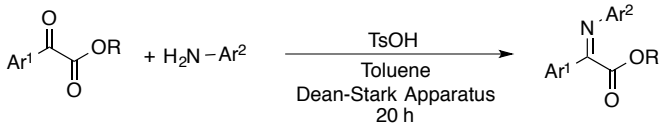
### General Considerations

Unless otherwise stated, all non-aqueous reactions were carried out under an atmosphere of dry argon in dry glassware. All glassware used in three component coupling reactions was base-washed (KOH/*i*-PrOH) prior to use. When necessary, solvents and reagents were dried prior to use. Tetrahydrofuran, diethyl ether, 2-methyltetrahydrofuran, cyclopentyl methyl ether and toluene were distilled from Na/benzophenone prior to use. Organometallic reagents (EtMgBr, *n*-PentylMgBr) were purchased from Aldrich, or made from magnesium turnings/ribbon. Analytical thin layer chromatography (TLC) was performed on Silicycle 250 μm silica-gel F-254 plates.

$^{1}$H NMR and $^{13}$C NMR spectra were recorded on a AM-500 Fourier transform NMR spectrometer at 500 MHz and 125 MHz, respectively. Chemical shifts are reported relative to the solvent resonance peak δ 7.26 ($CDCl_3$) for $^{1}$H and δ 77.16 ($CDCl_3$) for $^{13}$C. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, b = broad singlet, m = multiplet), coupling constants, and number of protons. High resolution mass spectra were obtained using a VG autospec with an ionization mode of either ESI or CI. Infrared spectra are reported in $cm^{-1}$. Melting points were obtained and are uncorrected. Unless otherwise noted, yields refer to isolated

material on the basis of product purity ≥95% by $^1$H NMR following silica gel chromatography with Silica-P flash silica gel (50-63 μm mesh particle size). Enantiomeric excess was determined utilizing chiral stationary phase (CSP) HPLC or SFC on OD [cellulose tris(3,5-dimethylphenylcarbamate) coated on silica gel] 0.46cm x 25 cm or IA [amylose tris(3,5-dimethylphenylcarbamate) immobilized on silica gel] 0.46 cm x 25 cm columns.

**General Procedure A – Synthesis of α-Iminoesters**




To a solution of aniline (20 mmol) in toluene (29 mL), tosic acid monohydrate (350 mg, 2.0 mmol) was added. To this solution was added alkyl arylester (20 mmol). The solution was then heated at reflux with azeotropic removal of water under $N_2$ (Dean-Stark conditions) for 20 h. The mixture was then cooled, passed through $SiO_2$ with 30% EtOAc/Hexanes, and concentrated. The resulting solid was recrystallized from hexanes to afford **x.x.x** (5.0 g) as a mixture of Z:E isomers.

α-Iminoesters **1.01a**[44], **1.01b**[45], **1.01e**[8b], **1.01f**[46], **1.01g**[47], **1.01h**[24], **1.01i**[48], **1.01j**[48], **1.01k**[49], **1.01m**[44], **1.01n**[44], **1.01o**[44], **1.01p**[44], **1.01q**[44], **1.01r**[44], **1.01s**[25], and **1.01t**[50] are

44) Shang, G.; Yang, Q.; Zhang, X. "Rh-Catalyzed Asymmetric Hydrogenation of αAryl Imino Esters: An Efficient Enantioselective Synthesis of Aryl Glycine Derivatives" *Angew. Chem., Int. Ed.* **2006**, *45*, 6360-6362.

45) Huang, H.; Wang, Y.; Chen, Z.; Hu, W. "Rhodium-Catalyzed, Three-Component Reaction of Diazo Compounds with Amines and Azodicarboxylates" *Adv. Synth. Catal.* **2005**, *347*, 531-534.

46) Zhu, C.; Akiyama, T. "Enantioselective Organocatalytic Transfer Hydrogenation of α-Imino Esters by Utilization of Benzothiazoline as Highly Efficient Reducing Agent" *Adv. Synth. Catal.* **2010**, *352*, 1846-1850.

known compounds and their physical and spectroscopic data were in agreement with the reported ones.

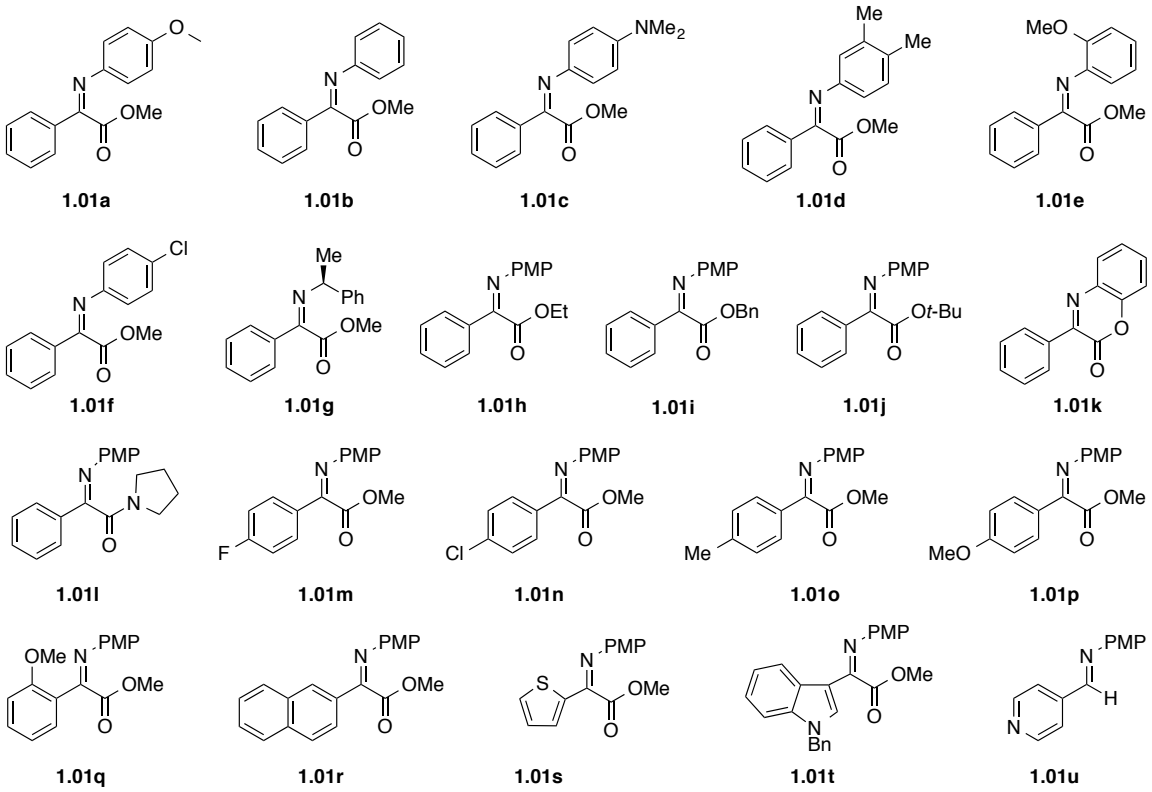
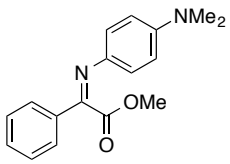



**Figure 1.13** α-Iminoesters explored in *N*-alkylation/π-allylation.



**(Z)-Methyl 2-(4-dimethylaminophenylimino)-2-phenylacetate (1.01c).** Following the

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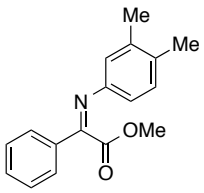
47) Guizzetti, S.; Benaglia, M.; Rossi, S. "Highly Stereoselective Metal-Free Catalytic Reduction of Imines: An Easy Entry to Enantiomerically Pure Amines and Natural and Unnatural α-Amino Esters" *Org. Lett.* **2009**, *11*, 2928-2931.

48) Kang, Q.; Zhao, Z.–A.; You, S.–Li "Highly Enantioselective Transfer Hydrogenation of α-Imino Esters by a Phosphoric Acid" *Adv. Synth. Catal.* **2007**, *349*, 1657-1660.

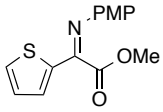
49) Miyabe, H.; Yamaoka, Y.; Takemoto, Y. "Reactive Ketimino Radical Acceptors: Intermolecular Alkyl Radical Addition to Imines with a Phenolic Hydroxyl Group" *J. Org. Chem.* **2006**, *71*, 2099-2106.

50) Jovanovic, B. Z.; Misic-Vukovic, M.; Marinkovic, A. D.; Vajs, V. "Effect of substitution on the $^{13}C$ chemical shifts of the azomethine carbon atom of N-(phenyl substituted) pyridine-4-aldimines" *J. Mol. Structure* **1999**, *482-483*, 375-378.

general procedure A, *N,N*-Dimethyl-*p*-phenylenediamine (1.0 g, 7.3 mmol) was reacted with methyl benzoylformate (1.2 g, 7.3 mmol) and tosic acid monohydrate (260 mg, 1.5 mmol) in toluene (10.4 mL) for 20 h under Dean-Stark conditions. After filtration, concentration and column chromatography (7.5% EtOAc/hexanes) to afford **1.01c** (568 mg) in 28% yield as a 8:1 mixture of Z:E isomers in the form of a brown crystalline solid: mp 66-68 °C; $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 7.8, 1.4 Hz, 2H), 7.49-7.43 (m, 3H), 7.00 (d, *J* = 8.9 Hz, 2H), 6.71 (d, *J* = 7.9 Hz, 2H), 3.74 (s, 3H), 2.97 (s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 170.0, 156.8, 148.9, 139.3, 134.8, 131.1, 128.7, 127.7, 121.9, 112.8, 52.0, 40.7 (minor rotamer peaks: 128.9, 128.5, 125.2, 111.8, 53.1, 40.4).



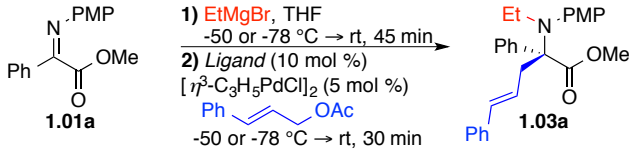

**(Z)-Methyl 2-(3,4-dimethylphenylimino)-2-phenylacetate (1.01d).** Following the general procedure A, 3,4-dimethylaniline (1.0 g, 8.2 mmol) was reacted with methyl benzoylformate (1.35 g, 8.2 mmol) and tosic acid monohydrate (282 mg, 1.5 mmol) in toluene (12 mL) for 20 h under Dean-Stark conditions. After filtration, concentration and column chromatography (7% EtOAc/hexanes) to afford **1.01d** (1.56 g) in 71% yield as a 12:1 mixture of Z:E isomers in the form of a yellow amorphous solid; $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.52-7.44 (m, 3H), 7.08 (d, *J* = 7.9 Hz, 1H), 6.81 (d, *J* = 1.8 Hz, 1H), 6.72 (dd, *J* = 7.9, 1.8 Hz, 1H), 3.69 (s, 3H), 2.25 (s, 3H), 2.24 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 166.0, 159.3, 147.9, 137.3, 134.3, 133.6, 131.7, 130.1, 128.8, 128.0, 121.3, 116.8, 52.0, 20.0, 19.4.




**(Z)-Methyl 2-(4-methoxyphenylimino)-2-(thiophen-2-yl)acetate (1.01s).** Following the general procedure A, *p*-anisidine (362 mg, 2.94 mmol) was reacted with methyl (2-thiophene)formate (417 mg, 2.45 mmol) and TsOH (42 mg, 0.245 mmol) in toluene (5 mL) for 20 h under Dean-Stark conditions. After filtration, concentration and column chromatography (10% EtOAc/hexanes) product **1.01s** (350 mg) was obtained in 52% yield as a 15:1 mixture of Z:E isomers in the form of a dark yellow solid: mp 92-94 °C; $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, $J$ = 5.0 Hz, 1H), 7.39 (d, $J$ = 3.8 Hz, 1H), 7.10 (t, $J$ = 4.2 Hz, 1H), 6.96 (d, $J$ = 8.7 Hz, 2H), 6.87 (d, $J$ = 8.7 Hz, 2H), 3.81 (s, 3H), 3.71 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 165.2, 157.7, 153.1, 142.7, 141.1, 131.2, 131.2, 128.0, 121.7, 114.3, 55.5, 52.4; IR (film) 2952, 1734, 1607, 1500, 1246 cm$^{-1}$; HRMS (ESI) calcd for $C_{14}H_{13}NO_3S$ $[M+H]^+$ $m/z$ = 276.0694; found 276.0692.

**Parallel Microscale Experimentation** (

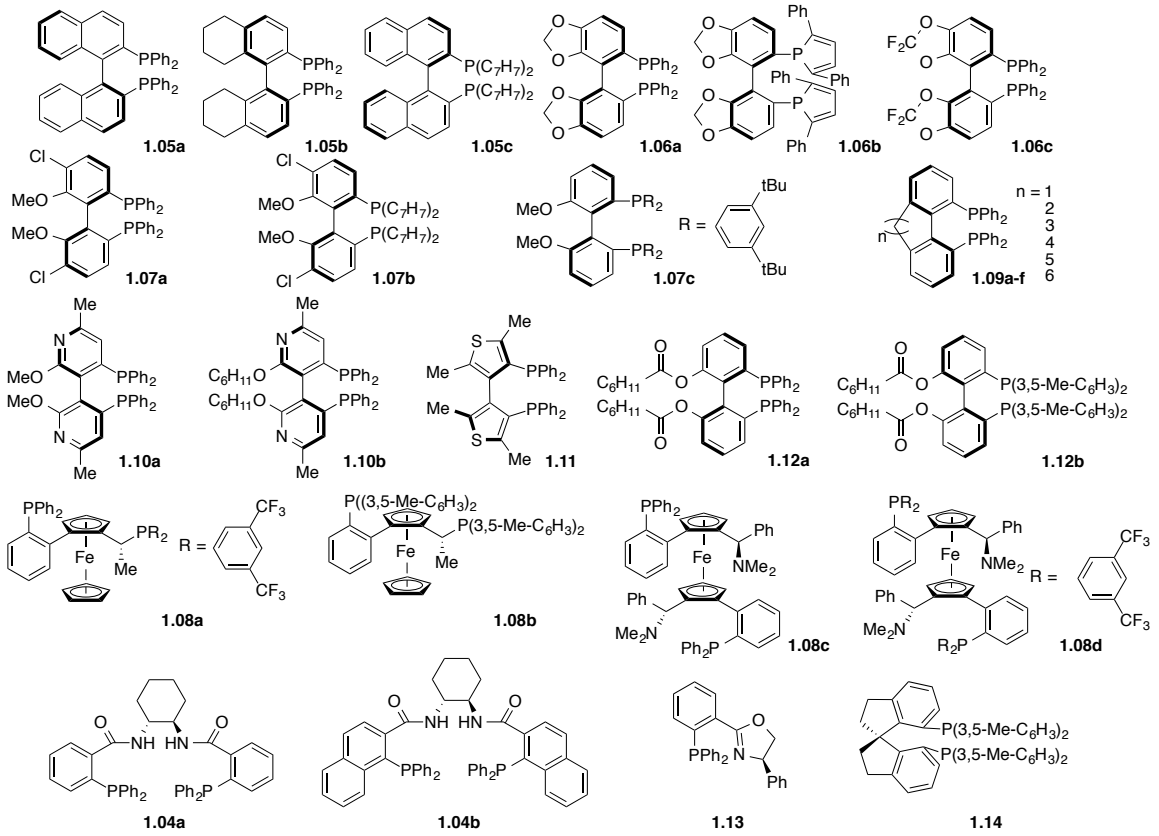
Table 1.2)



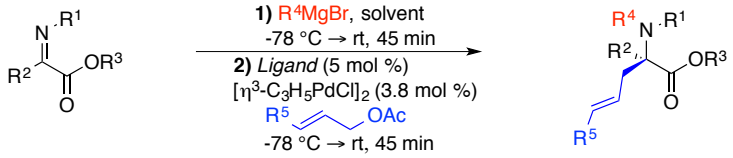

The following procedure is representative of the high-throughput experimentation reactions. The ligands (0.86 μmol) were dosed into the 96-well reactor 1-mL vials as solutions (50 μL of a 0.017 M solution in THF). Plates of these ligands may be plated in advance of the screen; the solvent is removed by evacuation on a Genevac, and the plates

are stored in a glovebox. A solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (0.86 μmol Pd, 50 μL of a 0.017 M solution in THF) was then added to the reaction vials and was evacuated to dryness on a Genevac. A parylene stir-bar was added to each vial. In a separate 20 dram vial, α-iminoester **1.01a** (914 μmol, 246 mg) was dissolved in 4.9 mL THF. The vial was cooled to -50 °C on a Mecour Coolingbox combined with a Julabo temperature controller and 3.0 M EtMgBr in $Et_2O$ (1500 μmol, 0.50 ml) was added. The reaction mixture was warmed to ambient temperature and allowed to react for 45 min and subsequently cooled back to -50 °C. Cinnamyl acetate (8.5 μmol) was dosed into the 96 well reactor 1-mL vials with ligand/catalyst mixture at -50 °C as solutions (50 μL of a 0.17 M solution in THF). The substrate and Grignard mixture was then dosed to the reaction vials at -50 °C (50 μL of a 0.18M solution in THF). The vials were then sealed and allowed to warm to ambient temperature. After stirring for 45 min the residues were diluted with 500 μL of a 5% solution of glacial acetic acid in isopropyl alcohol and the contents were stirred for 30 min. Into a separate 96-well plate LC block was added 750 μL of MeCN per well followed by 20 μL of the diluted reaction mixtures. The 96-well plate LC block was then sealed with a polypropylene 1 mL cap mat. The reactions were analyzed using a CSP SFC (OD-H 250x4.6mm, 5 um, MeOH/$CO_2$, 3 mL/min, 35 C, 200 bar, 215nm, 4% MeOH for 4 min then to 40% at 6 min hold for 5 min, Peak 1 at 6.9 min and Peak 2 at 7.5 min).

Structures of ligands in Table 1.2



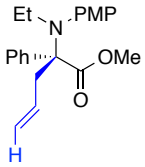

## General Procedure B – Three Component Coupling of α-Iminoesters



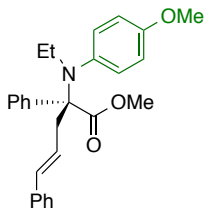

Rigorously anhydrous and air-free conditions are required for optimal results due to the reactivity of the intermediate enolate (see General Considerations). α-Iminoester (0.372 mmol) was added to a flamed dried Schlenk flask that had been charged with a stir bar and was then vacuum-purged three times under argon. The α-iminoester was

dissolved in THF (2.0 mL) and cooled to -78 °C. To this solution was added EtMgBr (3.0 M in $Et_2O$, 198 μL, 0.595 mmol) under argon. The mixture was slowly warmed to room temperature and allowed to stir for an additional 30 min at room temperature. A flame dried round bottom flask equipped with a stir bar was charged with $[\eta^3\text{-}C_3H_5PdCl]_2$ (5.1 mg, 0.0140 mmol) and (*R*)-DIFLUORPHOS (12.7 mg, 0.0186 mmol) and vacuum-purged three times under argon. The mixture was dissolved with THF (2.0 mL) and cinnamyl acetate (66 μL, 0.372 mmol) was added. The second solution was stirred for 5 minutes at ambient temperature under argon, cooled to -78 °C, and added to the cooled (-78 °C) first solution via syringe. The combined mixture was allowed to warm to room temperature and stirred for 45 min. The resultant reaction mixture was quenched with satd $NH_4Cl$ (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The resulting residue was purified by chromatography to afford pure α-allyl-α-aryl α-amino acids.

**Notes:** Typical color after the first step is a translucent yellow and red to orange after the second step. An indicator of the first step not working is when the reaction color turns green or black. Grignard source was important. More than 1 equiv of cinnamyl acetate, or a ligand to palladium ratio greater than 1:1 was detrimental to the enantioselectivity of second step.



**(*S,E*)-Methyl 2-(*N*-ethyl-*N*-(4-methoxyphenyl)amino)-2-phenylpent-4-enoate (1.03c).** Following the general procedure B, 3.0 M EtMgBr (50 μL, 0.15 mmol) was added to **1.01a** (25 mg, 0.093 mmol) in THF (0.5 mL), allowed to react for 45 min and subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (0.85 mg, 0.0023 mmol), (*R)*-DIFLUORPHOS (3.1 mg, 0.0045 mmol) and allyl acetate (11 μL, 0.10 mmol) in THF (0.5 mL) for 45 min. After work-up, concentration and column chromatography (pre-wash $SiO_2$ with 5% $NEt_3$/hexanes, eluent 3% EtOAc/hexanes) product **1.03c** (26 mg) was obtained in 82% yield as a yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.1 Hz, 2H), 7.34 (t, *J* = 7.5 Hz, 2H), 7.28-7.25 (m, 1H), 7.10 (d, *J* = 8.9 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.43-5.35 (m, 1H), 4.72 (d, *J* = 10.3 Hz, 1H), 4.59 (d, *J* = 17.2 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.02-2.88 (m, 2H), 2.48 (dd, *J* = 13.9, 6.8 Hz, 1H), 2.28 (dd, *J* = 13.9, 7.3 Hz, 1H), 0.79 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.3, 157.9, 141.5, 139.2, 134.2, 131.2, 128.0, 127.8, 127.3, 117.7, 113.8, 74.8, 55.5, 51.4, 46.6, 45.3, 14.7; IR (film) 2962, 2929, 1726, 1605, 1507, 1243 $cm^{-1}$; HRMS (ESI) calcd for $C_{21}H_{26}NO_3$ $[M+H]^+$ *m/z* = 340.1913; found 340.1900; $[\alpha]^{25}_D$ = +58.6 (c 0.08, 54% ee, $CH_2Cl_2$); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): $t_R$ of **1.03c**: 4.8 min (major) and 5.2 min (minor).



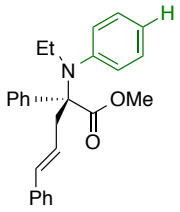

**(*S,E*)-Methyl 2-(ethyl(4-methoxyphenyl)amino)-2,5-diphenylpent-4-enoate (1.03a).** Following the general procedure B, 3.0 M EtMgBr (198 μL, 0.595 mmol) was added to

**1.01a** (100 mg, 0.372 mmol) in THF (2 mL), allowed to react for 45 min and subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (5.1 mg, 0.0140 mmol), *R*-DIFLUORPHOS (12.8 mg, 0.0186 mmol) and cinnamyl acetate (65 mg, 0.372 mmol) in THF (2 mL) for 45 min. After work-up, concentration and column chromatography (pre-wash $SiO_2$ with 5% $NEt_3$/hexanes, eluent 3% EtOAc/hexanes) product **1.03a** (134 mg) was obtained in 87% yield as a yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.7 Hz, 2H), 7.36 (t, *J* = 7.7 Hz, 2H), 7.30-7.27 (m, 1H), 7.21 (t, *J* = 7.4 Hz, 2H), 7.17-7.12 (m, 3H), 7.09 (d, *J* = 7.2 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 5.89 (d, *J* = 16.0 Hz, 1H), 5.73 (dt, *J* = 15.9, 7.5 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.09-3.02 (m, 1H), 2.99-2.92 (m, 1H), 2.63 (ddd, *J* = 13.9, 7.2, 0.5 Hz, 1H), 2.44 (ddd, *J* = 14.0, 7.4, 0.5 Hz, 1H), 0.83 (t, *J* = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.3, 157.8, 141.6, 139.1, 138.0, 133.0, 131.3, 128.4, 127.8 (2), 127.3, 127.0, 126.1 (2), 113.8, 75.1, 55.5, 51.4, 46.7, 44.4, 14.7; IR (film) 3026, 2694, 2836, 1724, 1603, 1507, 1244 $cm^{-1}$; HRMS (ESI) calcd for $C_{27}H_{30}NO_3$ $[M+H]^+$ *m/z* = 416.2226; found 416.2229; $[\alpha]^{24}_D$ = +145.3 (c 0.28, 88% ee, $CH_2Cl_2$); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): $t_R$ of **1.03a**: 6.6 min (major) and 8.0 min (minor).

Ethylmagnesium bromide from Aldrich was batch dependent and was only successful in general procedure A when it was colorless; EtMgBr from Acros was never colorless.

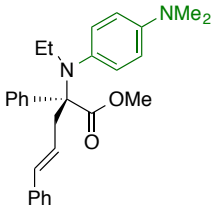
**Ethylmagnesium Bromide**. Magnesium turnings (1.4 g, 58.3 mmol) were stirred in 2.0 M HCl (~15 mL) for ten minutes, filtered, washed with ethanol (~100 mL), $Et_2O$ (~150 mL), collected and dried under vacuum in a 50 °C oil bath for 2 h, and then added to a flame dried 50 mL Schlenk flask charged with a stir bar equipped with a reflux condenser under argon. $Et_2O$ (~3 mL) was added to magnesium. Bromoethane (4.58 mL, 61.4

mmol) and $Et_2O$ (6.14 mL) were added to a second flamed dried round bottom flask under argon. 500 μL of the bromoethane solution was added to magnesium to initiate reflux. $Et_2O$ (5.5 mL) was added to the refluxing magnesium solution, followed by bromoethane solution (500 μL), then $Et_2O$ (5.5 mL). The bromoethane solution was added dropwise while maintaining reflux (~20 min). After addition was complete, the mixture was heated to reflux for 30 min, allowed to cool to rt, and transferred via cannulation into a sealed flask under argon. The 3.0 M ethylmagnesium bromide solution in $Et_2O$ was colorless and would be stored in a refrigerator for up to two weeks with continuous use.



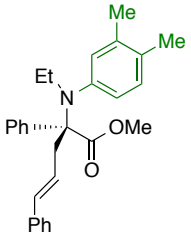

**(*S,E*)-Methyl 2-(*N*-ethyl-*N*-phenylamino)-2,5-diphenylpent-4-enoate (1.03d).** Following the general procedure B, 3.0 M EtMgBr (177 μL, 0.532 mmol) was added to **1.01b** (64 mg, 0.266 mmol) in THF (1.5 mL), allowed to react for 45 min and subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (3.64 mg, 0.0098 mmol), (*R*)-DIFLUORPHOS (9.1 mg, 0.013 mmol) and cinnamyl acetate (46.8 mg, 0.266 mmol) in THF (1.5 mL) for 45 min. After work-up, concentration and column chromatography (pre-wash $SiO_2$ with 5% $NEt_3$/hexanes, eluent 3% EtOAc/hexanes) product **1.03d** (80 mg) was obtained in 78% yield as a yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.0 Hz, 2H), 7.38-7.34 (m, 4H), 7.29 (dt, *J* = 7.3 Hz, 0.4 Hz, 1H), 7.25-7.20 (m, 5H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.10 (d, *J* = 7.7 Hz, 2H), 5.91 (d, *J* = 15.8 Hz, 1H), 5.75 (dt, *J* = 15.8, 7.2 Hz, 1H), 3.87

(s, 3H), 3.16-3.03 (m, 2H), 2.68 (dd, *J* = 13.8, 7.1 Hz, 1H), 2.51 (dd, *J* = 13.7, 7.5 Hz, 1H), 0.87 (t, *J* = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.2, 146.6, 141.5, 137.9, 133.1, 129.9, 128.7, 128.4, 127.9, 127.9, 127.4, 126.9, 126.1, 125.9, 125.9, 75.0, 51.5, 46.4, 44.2, 14.7; IR (film) 3025, 2867, 1725, 1595, 1493, 1215 cm$^{-1}$; HRMS (ESI) calcd for $C_{26}H_{28}NO_2$ $[M+H]^+$ *m/z* = 386.2120; found 386.2132; $[\alpha]^{25}_D$ = +162.9 (c 0.47, 82% ee, $CH_2Cl_2$); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): $t_R$ of **1.03d**: 4.8 min (minor) and 5.1 min (major).

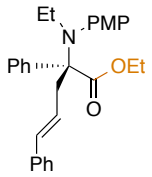



**(*S*,*E*)-Methyl 2-((4-(dimethylamino)phenyl)(ethyl)amino)-2,5-diphenylpent-4-enoate (1.03e).** Following the general procedure B, 3.0 M EtMgBr (100 μL, 0.298 mmol) was added to **1.01c** (53 mg, 0.186 mmol) in THF (1 mL), allowed to react for 45 min and subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (3.7 mg, 0.0093 mmol), (*R*)-BINAP (11.6 mg, 0.0186 mmol) and cinnamyl acetate (34 mg, 0.195 mmol) in THF (1 mL) for 45 min. After work-up, concentration and column chromatography (eluent 7% EtOAc/hexanes) product **1.03e** (62 mg) was obtained in 74% yield as a yellow oil: $^1$H NMR (500 MHz, $(CD_3)_2CO$) δ 7.50 (d, *J* = 7.9 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 1H), 7.18 (t, *J* = 7.4 Hz, 2H), 7.14-7.07 (m, 5H), 6.73 (d, *J* = 8.9 Hz, 2H), 5.88-5.79 (m, 2H), 3.87 (s, 3H), 3.02-2.93 (m, 8H), 2.61 (dd, *J* = 14.2, 6.1 Hz, 1H), 2.43 (dd, *J* = 14.2, 6.1 Hz, 1H), 0.79 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, $(CD_3)_2CO$) δ 173.6, 150.2, 143.0, 138.8, 135.9, 133.2, 131.6, 129.1, 128.6, 128.4, 127.9, 127.6, 127.2, 126.6, 113.2, 75.9,

51.5, 47.2, 45.3, 40.7, 15.0; chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): $t_R$ of **1.03e**: 5.7 min (minor) and 6.4 min (major).

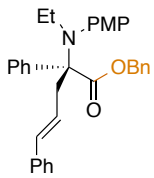



**(*S*,*E*)-Methyl 2-((3,4-dimethylphenyl)(ethyl)amino)-2,5-diphenylpent-4-enoate (1.03f).** Following the general procedure B, 3.0 M EtMgBr (100 μL, 0.298 mmol) was added to **1.01d** (50 mg, 0.186 mmol) in THF (1.3 mL), allowed to react for 45 min and subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (1.72 mg, 0.005 mmol), (*R)*-BINAP (5.9 mg, 0.009 mmol) and cinnamyl acetate (36 mg, 0.195 mmol) in THF (1 mL) for 45 min. After work-up, concentration and column chromatography (eluent 10% acetone/hexanes) product **1.03f** (65 mg) was obtained in 84% yield as a yellow oil: $^1$H NMR (500 MHz, ($CDCl_3$) δ 7.48 (d, *J* = 7.4 Hz, 2H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 2H), 7.14-7.06 (m, 4H), 6.99 (s, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 5.88 (d, *J* = 15.8 Hz, 1H), 5.72 (dt, *J* = 15.8 Hz, 7.3 Hz, 1H), 3.87 (s, 3H), 3.08-2.95 (m, 2H), 2.63 (dd, *J* = 13.7, 7.0 Hz, 1H), 2.45 (dd, *J* = 13.7, 7.4 Hz, 1H), 2.27 (s, 3H), 2.26 (s, 3H), 0.83 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, ($CDCl_3$) δ 173.2, 144.1, 141.7, 138.0, 136.7, 134.5, 132.9, 131.5, 129.8, 128.4, 127.9, 127.8, 127.3, 127.2, 126.9, 126.2, 126.1, 75.1, 51.4, 46.4, 44.4, 20.1, 19.5, 14.8; chiral HPLC (IA, 99:1 hexanes:*i*-PrOH, 0.5 mL/min, 254 nm): $t_R$ of **1.03f**: 8.5 min (minor) and 8.9 min (major).

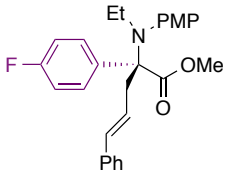



**(*S*,*E*)-Ethyl 2-(ethyl(4-methoxyphenyl)amino)-2,5-diphenylpent-4-enoate (1.03j)**

Following the general procedure B, 3.0 M EtMgBr (85 μL, 0.282 mmol) was added to **1.01h** (50 mg, 0.177 mmol) in THF (1.3 mL), allowed to react for 45 min and subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (1.63 mg, 0.005 mmol), (*R*)-BINAP (5.5 mg, 0.009 mmol) and cinnamyl acetate (34 mg, 0.195 mmol) in THF (1 mL) for 45 min. After work-up, concentration and column chromatography (pre-wash $SiO_2$ with 5% $NEt_3$/hexanes, eluent 7% EtOAc/hexanes) product **1.03j** (62 mg) was obtained in 77% yield as a yellow oil: $^1$H NMR (500 MHz, ($CDCl_3$) δ 7.49 (d, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.7 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.22-7.16 (m, 4H), 7.13 (t, *J* = 7.4 Hz, 1H), 7.08 (d, *J* = 7.3 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.89 (d, *J* = 15.8 Hz, 1H), 5.72 (dt, *J* = 15.9, 7.2 Hz, 1H), 4.42-4.31 (m, 2H), 3.83 (s, 3H), 3.08-2.96 (m, 2H), 2.62 (dd, *J* = 13.9, 7.1 Hz, 1H), 2.42 (dd, *J* = 13.9, 7.2 Hz, 1H), 1.36 (t, *J* = 7.2 Hz, 3H), 0.83 (t, *J* = 6.9 Hz, 3H); $^{13}$C NMR (125 MHz, ($CDCl_3$) δ 172.7, 157.8, 141.8, 139.2, 138.0, 132.9, 131.4, 128.4, 127.9, 127.8, 127.2, 126.9, 126.2, 126.0, 113.8, 74.9, 60.7, 55.5, 46.7, 44.4, 14.7, 14.5; chiral HPLC (OD, 97.5:2.5 hexanes:*i*-PrOH, 1.0 mL/min, 254 nm): $t_R$ of **1.03j**: 4.5 min (major) and 8.3 min (minor).

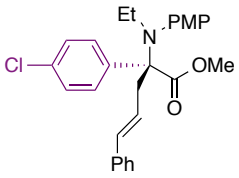


**(*S,E*)-Benzyl 2-(ethyl(4-methoxyphenyl)amino)-2,5-diphenylpent-4-enoate (1.03k)** Following the general procedure B, 3.0 M EtMgBr (193 μL, 0.579 mmol) was added to **1.01i** (100 mg, 0.290 mmol) in THF (2.5 mL), allowed to react for 45 min and subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (3.30 mg, 0.009 mmol), (*R)*-BINAP (11.6 mg, 0.019 mmol) and cinnamyl acetate (56 mg, 0.318 mmol) in THF (2.0 mL) for 45 min. After work-up, concentration and column chromatography (eluent 7% EtOAc/hexanes) product **1.03k** (139 mg) was obtained in 76% yield as a yellow oil: $^1$H NMR (500 MHz, ($CDCl_3$) δ 7.47 (d, *J* = 8.2 Hz, 2H), 7.40 (dd, *J* = 7.5, 4.3 Hz, 2H), 7.37-7.31 (m, 5H), 7.28-7.26 (m, 1H), 7.19 (t, *J* = 7.3 Hz, 2H), 7.14-7.10 (m, 1H), 7.05 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 7.5 Hz, 2H), 6.77 (d, *J* = 8.9 Hz, 2H), 5.83 (d, *J* = 15.9 Hz, 1H), 5.68 (dt, *J* = 15.9, 7.2 Hz, 1H), 5.34 (d, *J* = 12.1 Hz, 1H), 5.29 (d, *J* = 12.1 Hz, 1H), 3.80 (s, 3H), 3.08-3.01 (m, 1H), 2.97-2.91 (m, 1H), 2.62 (dd, *J* = 13.8, 7.2 Hz, 1H), 2.41 (dd, *J* = 13.5, 7.2 Hz, 1H), 0.79 (t, *J* = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, ($CDCl_3$) δ 172.5, 157.8, 141.7, 139.1, 138.0, 135.8, 133.0, 131.4, 129.1, 128.7, 128.5, 128.4, 127.9, 127.8, 127.3, 126.9, 126.1, 126.0, 113.8, 75.1, 66.7, 55.5, 46.7, 44.4, 14.7; chiral HPLC (OD, 97.5:2.5 hexanes:*i*-PrOH, 1.0 mL/min, 254 nm): $t_R$ of **1.03k**: 5.8 min (major) and 9.5 min (minor).



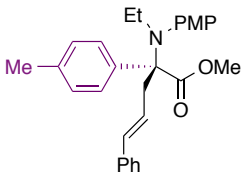

**(*S,E*)-Methyl 2-(*N*-ethyl-*N*-(4-methoxyphenyl)amino)-2-(4-fluorophenyl)-5-phenylpent-4-enoate (1.03o).** Following the general procedure B, 3.0 M EtMgBr (177 μL, 0.532 mmol) was added to **1.01m** (76.3 mg, 0.266 mmol) in THF (1.5 mL), allowed to react for 45 min and subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (3.64 mg, 0.0098

mmol), (*R*)-DIFLUORPHOS (9.1 mg, 0.013 mmol) and cinnamyl acetate (46.8 mg, 0.266 mmol) in THF (1.5 mL) for 45 min. After work-up, concentration and chromatography (pre-wash $SiO_2$ with 5% $NEt_3$/hexanes, eluent 3% EtOAc/hexanes) product **1.03o** (99 mg) was obtained in 86% yield as a yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.48-7.45 (m, 2H), 7.22 (t, *J* = 7.4 Hz, 2H), 7.17-7.13 (m, 3H), 7.10 (d, *J* = 7.3 Hz, 2H), 7.05 (t, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.90 (d, *J* = 15.7 Hz, 1H), 5.71 (dt, *J* = 15.7, 7.6 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.03-2.89 (m, 2H), 2.62 (dd, *J* = 13.7, 7.2 Hz, 1H), 2.39 (dd, *J* = 13.7, 7.6 Hz, 1H), 0.82 (t, *J* = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 172.9, 162.9 (d, *J* = 246 Hz), 157.9, 138.8, 137.8, 137.3 (d, *J* = 3.2 Hz), 133.4, 131.2, 129.6 (d, *J* = 7.6 Hz), 128.5, 127.1, 126.0, 125.6, 114.6 (d, *J* = 21.2 Hz), 113.9, 74.6, 55.5, 51.5, 46.4, 44.4, 14.6; IR (film) 3036, 2965, 2837, 1727, 1606, 1505, 1244 $cm^{-1}$; HRMS (ESI) calcd for $C_{27}H_{29}FNO_3$ $[M+H]^+$ *m/z* =434.2131; found 434.2133; $[\alpha]^{25}_D$ = +128.4 (c 0.48, 86% ee, $CH_2Cl_2$); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): $t_R$ of **1.03o**: 6.6 min (major) and 11.7 min (minor).



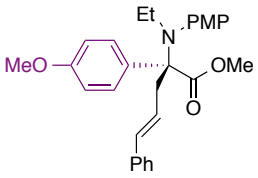

**(*S,E*)-Methyl 2-(*N*-ethyl-*N*-(4-methoxyphenyl)amino)-2-(4-chlorophenyl)-5-phenylpent-4-enoate (1.03p).** Following the general procedure B, 3.0 M EtMgBr (219 μL, 0.658 mmol) was added to **1.01n** (100 mg, 0.329 mmol) in 2-MeTHF (2 mL), allowed to react for 45 min and subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (4.49 mg, 0.0123 mmol), (*R*)-DIFLUORPHOS (11.26 mg, 0.0165 mmol) and cinnamyl acetate (58 mg, 0.329 mmol) in 2-MeTHF (2 mL) for 45 min. After work-up, concentration and

chromatography (pre-wash $SiO_2$ with 5% $NEt_3$/hexanes, eluent 5% EtOAc/hexanes) product **1.03p** (124 mg) was obtained in 84% yield as a yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.6 Hz, 2H), 7.32 (d, *J* = 8.6 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 2H), 7.16-7.08 (m, 5H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.90 (d, *J* = 15.8 Hz, 1H), 5.68 (dt, *J* = 15.6, 7.3 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 2.98-2.87 (m, 2H), 2.60 (dd, *J* = 14.0, 7.0 Hz, 1H), 2.37 (dd, *J* = 14.0, 7.3 Hz, 1H), 0.80 (t, *J* = 7.0 Hz, 3H) ; $^{13}$C NMR (125 MHz, $CDCl_3$) δ 172.7, 158.0, 140.3, 138.7, 137.8, 133.5, 133.0, 131.2, 129.4, 128.5, 128.0, 127.1, 126.1, 125.4, 113.9, 74.7, 55.5, 51.6, 46.5, 44.3, 14.6; IR (film) 2958, 2855, 1725, 1604, 1507, 1244 cm$^{-1}$; HRMS (ESI) calcd for $C_{27}H_{29}ClNO_3$ $[M+H]^+$ *m/z* = 450.1836; found 450.1835; $[\alpha]^{25}_D$ = +117.2 (c 0.37, 92% ee, $CH_2Cl_2$); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): $t_R$ of **1.03p**: 7.2 min (major) and 12.8 min (minor).



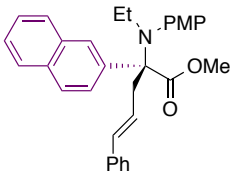

**(*S,E*)-Methyl 2-(*N*-ethyl-*N*-(4-methoxyphenyl)amino)-2-(4-methylphenyl)-5-phenylpent-4-enoate (1.03q).** Following the general procedure B, 3.0 M EtMgBr (177 μL, 0.532 mmol) was added to **1.01o** (75.4 mg, 0.266 mmol) in THF (1.5 mL), allowed to react for 45 min and subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (3.64 mg, 0.0010 mmol), (*R)*-DIFLUORPHOS (9.1 mg, 0.013 mmol) and cinnamyl acetate (46.8 mg, 0.266 mmol) in THF (1.5 mL) for 45 min. After work-up, concentration and chromatography (pre-wash $SiO_2$ with 5% $NEt_3$/hexanes, eluent 3% EtOAc/hexanes) product **1.03q** (99 mg) was obtained in 87% yield as a yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.1 Hz, 2H), 7.22 (t, *J* = 7.6 Hz, 2H), 7.18- 7.13 (m, 5H), 7.11 (d, *J* = 7.9 Hz, 2H), 6.88 (d, *J* =

8.8 Hz, 2H), 5.93 (d, $J$ = 15.7 Hz, 1H), 5.75 (dt, $J$ = 15.8, 7.2 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.09-3.02 (m, 1H), 2.98-2.91 (m, 1H), 2.62 (dd, $J$ = 13.9, 7.0 Hz, 1H), 2.44 (dd, $J$ = 13.9, 7.3 Hz, 1H), 2.37 (s, 3H), 0.83 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.4, 157.8, 139.2, 138.5, 138.1, 136.9, 132.8, 131.3, 128.6, 128.4, 127.7, 126.9, 126.2 126.0, 113.8, 74.8, 55.5, 51.4, 46.6, 44.2, 21.2, 14.7; IR (film) 3026, 2963, 2865, 1724, 1605, 1508, 1244, 1036 cm$^{-1}$; HRMS (ESI) calcd for $C_{28}H_{32}NO_3$ $[M+H]^+$ *m/z* = 430.2382; found 430.2369; $[\alpha]^{25}_D$ = +123.1 (c 0.47, 80% ee, $CH_2Cl_2$); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): $t_R$ of **1.03q**: 7.0 min (major) and 8.1 min (minor).



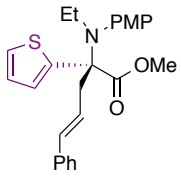

**(*S,E*)-Methyl 2-(*N*-ethyl-*N*-(4-methoxyphenyl)amino)-2-(4-methoxyphenyl)-5-phenylpent-4-enoate (1.03r).** Following the general procedure B, 3.0 M EtMgBr (124 μL, 0.372 mmol) was added to **1.01p** (56 mg, 0.186 mmol) in THF (1 mL), allowed to react for 45 min and subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (1.70 mg, 0.0047 mmol), *R*-BINAP (5.67 mg, 0.0091 mmol) and cinnamyl acetate (32 mg, 0.186 mmol) in THF (1 mL) for 45 min. After work-up, concentration and chromatography (pre-wash $SiO_2$ with 5% $NEt_3$/hexanes, eluent 5% EtOAc/hexanes) product **1.03r** (65 mg) was obtained in 79% yield as a yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, $J$ = 8.7 Hz, 2H), 7.21 (t, $J$ = 7.5 Hz, 2H), 7.15-7.10 (m, 5H), 6.90-6.88 (m, 4H), 5.93 (d, $J$ = 15.9 Hz, 1H), 5.73 (dt, $J$ = 15.8, 7.3 Hz, 1H), 3.86 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.07-3.00 (m, 1H), 2.95-2.89 (m, 1H), 2.61 (dd, $J$ = 13.9, 7.2 Hz, 1H), 2.41 (dd, $J$ = 13.8, 7.3 Hz, 1H), 0.81

(t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.4, 158.7, 157.8, 139.2, 138.0, 133.6, 132.9, 131.3, 129.0, 128.4, 126.9, 126.2, 126.1, 113.8, 113.2, 75.5, 55.5, 55.4, 51.4, 46.4, 44.3, 14.7 ; IR (film) 3035, 2960, 2836, 1724, 1609, 1508, 1245, 1036 cm$^{-1}$; HRMS (ESI) calcd for $C_{28}H_{32}NO_4$ $[M+H]^+$ $m/z$ = 446.2331; found 446.2325; $[\alpha]^{25}_D$ = +126.1 (c 0.32, 74% ee, $CH_2Cl_2$); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): $t_R$ of **1.03r**: 10.4 min (major) and 12.4 min (minor).



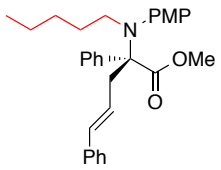

**(*S,E*)-Methyl 2-(*N*-ethyl-*N*-(4-methoxyphenyl)amino)-2-(napthalen-2-yl)-5-phenylpent-4-enoate (1.03t).** Following the general procedure B, 3.0 M EtMgBr (177 μL, 0.532 mmol) was added to **1.01r** (85 mg, 0.266 mmol) in THF (1.5 mL), allowed to react for 45 min and subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (3.64 mg, 0.0010 mmol), (*R)*-DIFLUORPHOS (9.1 mg, 0.013 mmol) and cinnamyl acetate (46.8 mg, 0.266 mmol) in THF (1.5 mL) for 45 min. After work-up, concentration and chromatography (pre-wash $SiO_2$ with 5% $NEt_3$/hexanes, eluent 3% acetone/hexanes) product **1.03t** (89 mg) was obtained in 72% yield as a yellow oil. Absolute configuration was determined by the x-ray structure obtained from >99% ee material by stirring the 84% ee solid in hexanes and then removing the liquid three times, the enhanced ee solid was recrystallized from $Et_2O$ over 24 h of slow evaporation. mp (>99% ee material) = 104 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.91-7.85 (m, 4H), 7.73 (d, $J$ = 8.7 Hz, 1H), 7.51-7.49 (m, 2H), 7.23 (d, $J$ = 8.7 Hz, 2H), 7.18 (t, $J$ = 7.3 Hz, 2H), 7.12 (t, $J$ = 6.9 Hz, 1H), 7.04 (d, $J$ = 7.8 Hz, 2H), 6.92 (d, $J$ = 8.5 Hz, 2H), 5.95 (d, $J$ = 15.8 Hz, 1H), 5.75 (dt, $J$ = 15.8 Hz, 7.1 Hz, 1H),

3.93 (s, 3H), 3.85 (s, 3H), 3.12-2.98 (m, 2H), 2.75 (dd, *J* = 13.8, 7.2 Hz, 1H), 2.59 (dd, *J* = 13.6, 7.3 Hz, 1H), 0.87 (t, *J* = 6.9 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.2, 157.9, 139.2, 139.1, 137.9, 133.1, 133.0, 132.9, 131.4, 128.5, 128.4 (2), 127.6, 127.4, 127.0, 126.9, 126.1 (3), 126.0, 113.9, 75.2, 55.5, 51.5, 46.7, 44.1, 14.7; IR (film) 3056, 2964, 2835, 1724, 1600, 1242, 1036 cm$^{-1}$; HRMS (ESI) calcd for $C_{31}H_{32}NO_3$ $[M+H]^+$ *m/z* = 466.2382; found 466.2371; $[\alpha]^{25}_D$ = +137.5 (c 0.43, 86% ee, $CH_2Cl_2$); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): $t_R$ of **1.03t**: 9.9 min (minor) and 10.7 min (major).



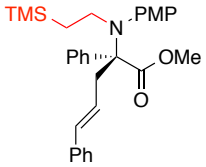

**(*S,E*)-Methyl 2-(*N*-ethyl-*N*-(4-methoxyphenyl)amino)-2-(thiophen-2-yl)-5-phenylpent-4-enoate (1.03u).** Following the general procedure B, 3.0 M EtMgBr (177 μL, 0.532 mmol) was added to **1.01s** (73.2 mg, 0.266 mmol) in THF (1.5 mL), allowed to react for 45 min and subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (3.64 mg, 0.0098 mmol), (*R)*-DIFLUORPHOS (9.1 mg, 0.013 mmol) and cinnamyl acetate (46.8 mg, 0.266 mmol) in THF (1.5 mL) for 45 min. After work-up, concentration and column chromatography (pre-wash $SiO_2$ with 5% $NEt_3$/hexanes, eluent 5% EtOAc/hexanes) product **1.03u** (96 mg) was obtained in 86% yield as a yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.27-7.26 (m, 1H), 7.24-7.19 (m, 4H), 7.17-7.14 (m, 3H), 7.07 (d, *J* = 3.7 Hz, 1H), 6.97-6.95 (m, 1H), 6.87 (d, *J* = 8.5 Hz, 2H), 6.07 (d, *J* = 15.9 Hz, 1H), 5.75 (dt, *J* = 15.9, 7.3 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.17-3.10 (m, 1H), 3.04-2.98 (m, 1H), 2.63 (dd, *J* = 13.4, 7.7 Hz, 1 H), 2.47 (dd, *J* = 13.4, 7.1 Hz, 1H), 0.85 (t, *J* = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz,

$CDCl_3$) δ 172.3, 157.9, 148.1, 138.4, 137.7, 133.4, 131.3, 128.5, 127.2, 126.9, 126.4, 126.2, 125.2, 124.6, 113.7, 72.9, 55.5, 51.8, 46.2, 45.6 14.3; IR (film) 3027, 2970, 2835, 1729, 1605, 1507, 1243 $cm^{-1}$; HRMS (ESI) calcd for $C_{25}H_{28}NO_3$ $[M+H]^+$ *m/z* = 422.1750; found 422.1807; $[\alpha]^{25}_D$ = +120.2 (c 0.34, 76% ee, $CH_2Cl_2$); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): $t_R$ of **1.03u**: 7.2 min (minor) and 7.8 min (major).




**(*S,E*)-Methyl 2-(*N*-pentyl-*N*-(4-methoxyphenyl)amino)-2,5-diphenylpent-4-enoate (1.03x).** Following the general procedure B, 2.0 M pentylMgBr (300 μL, 0.600 mmol) was added to **1.01a** (81 mg, 0.300 mmol) in THF (1.9 mL), allowed to react for 45 min and subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (4.12 mg, 0.0113 mmol), (*R)*-DIFLUORPHOS (10.25 mg, 0.0150 mmol) and cinnamyl acetate (53 mg, 0.300 mmol) in THF (1.9 mL) for 45 min. After work-up, concentration and chromatography (pre-wash $SiO_2$ with 5% $NEt_3$/hexanes, eluent 3% EtOAc/hexanes) product **1.03x** (112 mg) was obtained in 82% yield as a yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 2H), 7.16-7.13 (m, 3H), 7.07 (d, *J* = 7.1 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 5.89 (d, *J* = 15.9 Hz, 1H), 5.70 (dt, *J* = 15.7, 7.3 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 2.97-2.87 (m, 2H), 2.62 (dd, *J* = 13.4, 7.2 Hz, 1H), 2.43 (dd, *J* = 13.4, 7.2 Hz, 1H), 1.17-1.04 (m, 6H), 0.77 (t, *J* = 6.9 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.1, 157.8, 141.5, 139.6, 138.0, 132.9, 131.1, 128.4, 128.0, 127.8, 127.3, 126.9, 126.2, 126.1, 113.8, 75.1, 55.5, 52.2, 51.4, 44.5, 29.3,

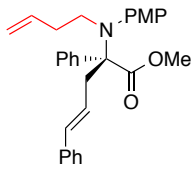
29.0, 22.6, 14.1; IR (film) 3025, 2857, 1725, 1603, 1508, 1245 $cm^{-1}$; HRMS (ESI) calcd for $C_{30}H_{36}NO_3$ $[M+H]^+$ *m/z* = 458.2695; found 458.2704; $[\alpha]^{25}_D$ = +129.1 (c 0.30, 92% ee, $CH_2Cl_2$); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): $t_R$ of **1.03x**: 5.8 min (major) and 7.0 min (minor).




**(*S,E*)-Methyl 2-(*N*-(2-(trimethylsilyl)ethyl)-*N*-(4-methoxyphenyl)amino)-2,5-diphenylpent-4-enoate (1.03y).** Following the general procedure B, 1.38 M 2-(trimethylsilyl)ethylMgBr (269 µL, 0.372 mmol) was added to **1.01a** (50 mg, 0.186 mmol) in THF (1.0 mL), allowed to react for 45 min providing a yellow mixture, which was subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (1.70 mg, 0.00465 mmol), (*R)*-BINAP ( 5.67 mg, 0.00911 mmol) and cinnamyl acetate (32 mg, 0.182 mmol) in THF (1.0 mL) for 45 min, providing an orange mixture. After work-up, concentration and chromatography (pre-wash $SiO_2$ with 5% $NEt_3$/hexanes, eluent 5% EtOAc/hexanes) product **1.03y** (75 mg) was obtained in 83% yield as a yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.9 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 2H), 7.29-7.26 (m, 1H), 7.21 (t, *J* = 7.6 Hz, 2H), 7.15-7.13 (m, 3H), 7.08 (d, *J* = 7.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.89 (d, *J* = 15.9 Hz, 1H), 5.75 (dt, *J* = 15.7, 7.4 Hz, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.06-2.99 (m, 1H), 2.96-2.90 (m, 1H), 2.64 (dd, *J* = 13.8, 7.0 Hz, 1H), 2.46 (*dd, J* = 13.8, 7.5 Hz, 1H), 0.57-0.47 (m, 2H), -0.18 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.3, 157.8, 141.5, 139.3, 138.0, 132.9, 131.4, 128.4, 127.9, 127.8, 127.3, 126.9, 126.2, 126.1, 113.8, 75.2, 55.5, 51.4, 47.9, 44.3, 17.8, -1.6; IR (film) 3026, 2951, 1725, 1602, 1507, 1246 $cm^{-1}$; HRMS (ESI)

calcd for $C_{30}H_{38}NO_3Si$ $[M+H]^+$ *m/z* = 488.2621; found 488.2617; $[\alpha]^{25}_D$ = +118.7 (c 0.25, 82% ee, $CH_2Cl_2$); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): $t_R$ of **1.03y**: 4.9 min (major) and 6.4 min (minor).

**2-(Trimethylsilyl)ethylmagnesium bromide** was prepared by modification of a known procedure[51]: Magnesium ribbon (255 mg, 8.85 mmol) that was scored until shiny was added to a flame dried 10 mL Schlenk flask charged with a stir bar equipped with a reflux condenser under argon. $Et_2O$ (2.95 mL) was added to magnesium. Freshly prepared 2-(trimethylsilyl)ethyl bromide[52] is added dropwise to magnesium at a rate to sustain a slow reflux. After addition is complete, the mixture is heated to reflux for 2 h, allowed to cool to rt and used in preparation of **1.03y**.

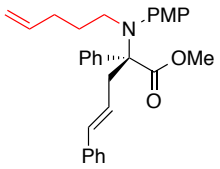



**(*S,E*)-Methyl 2-(*N*-(but-3-en-1-yl)-*N*-(4-methoxyphenyl)amino)-2,5-diphenylpent-4-enoate (1.03z).** Following the general procedure B, 2.7 M butenylmagnesium bromide (222 μL, 0.600 mmol) was added to **1.01a** (81 mg, 0.300 mmol) in THF (1.9 mL), allowed to react for 45 min, providing a yellow/orange mixture, which was subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (4.12 mg, 0.0113 mmol), (*R*)-DIFLUORPHOS (10.25 mg, 0.0150 mmol) and cinnamyl acetate (53 mg, 0.300 mmol) in THF (1.9 mL) for 45 min, providing an orange mixture. After work-up, concentration and chromatography (pre-

51) Wilson, S. R.; Shedrinsky, A. "[β-(Trimethylsilyl)ethyl]lithium: A New Reagent for Carbonyl Reductive Vinylation" *J. Org. Chem.* **1982**, *47*, 1983-1984.
52) Sommer, L.H.; Bailey, D.L.; Goldberg, G.M.; Buck, C.E.; Bye, T.S.; Evans, F.J.; Whitmore, F.C. "Vinylsilanes, Chlorovinylsilanes and β-Styryltrimethylsilane. Further Studies on the α-Silicon Effect and β-Eliminations Involving Silicon" *J. Am. Chem. Soc.* **1954**, *76*, 1613-1618.

wash $SiO_2$ with 5% $NEt_3$/hexanes, eluent 2% acetone/hexanes) product **1.03z** (109 mg) was obtained in 82% yield as a yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.6 Hz, 2H), 7.36-7.33 (m, 2H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.22-7.13 (m, 5H), 7.07 (d, *J* = 7.6 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.89 (d, *J* = 15.8 Hz, 1H), 5.72-5.60 (m, 2H), 4.89-4.83 (m, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 3.06-2.98 (m, 2H), 2.62 (dd, *J* = 13.9, 7.2 Hz, 1H), 2.43 (dd, *J* = 13.9, 7.6 Hz, 1H), 2.05-1.92 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.1, 158.0, 141.3, 139.2, 138.0, 136.8, 133.0, 131.2, 128.4, 128.0, 127.9, 127.8, 127.4, 126.9, 126.1, 115.5, 113.9, 75.1, 55.5 51.8, 51.5, 44.5, 33.9; IR (film) 3025, 2836, 1724, 1604, 1507, 1245 $cm^{-1}$; HRMS (ESI) calcd for $C_{29}H_{32}NO_3$ $[M+H]^+$ *m/z* = 442.2382; found 442.2400; $[\alpha]^{25}_D$ = +137.8 (c 0.42, 90% ee, $CH_2Cl_2$); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): $t_R$ of **1.03z**: 7.3 min (major) and 10.9 min (minor).

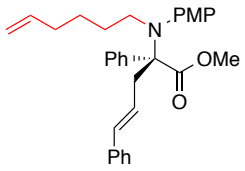
**Butenylmagnesium Bromide.** Magnesium ribbon (255 mg, 8.85 mmol) that was scored until shiny was added to a flame dried 10 mL Schlenk flask charged with a stir bar equipped with a reflux condenser under argon. $Et_2O$ (2.95 mL) was added to the magnesium. Freshly distilled (98 °C, 760 torr) butenyl bromide was added dropwise to the magnesium at a rate to sustain a slow reflux. After addition was complete, the mixture was heated to reflux for 2 h, allowed to cool to rt, and used in preparation of **1.03z**.




**(*S,E*)-Methyl 2-(*N*-(pent-4-en-1-yl)-*N*-(4-methoxyphenyl)amino)-2,5-diphenylpent-4-enoate (1.03aa).** Following the general procedure B, 2.8 M pentenylmagnesium bromide (213 µL, 0.595 mmol) was added to **1.01a** (80 mg, 0.297 mmol) in CPME (1.6 mL),

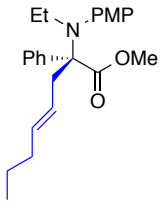
allowed to react for 45 min providing a yellow/orange mixture, which was subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (4.1 mg, 0.0112 mmol), (*R*)-DIFLUORPHOS (10.2 mg, 0.0149 mmol) and cinnamyl acetate (52 mg, 0.299 mmol) in CPME (1.6 mL) for 45 min, providing an orange/red mixture. After work-up, concentration and column chromatography (pre-wash $SiO_2$ with 5% $NEt_3$/hexanes, eluent 3% acetone/hexanes) product **1.03aa** (115 mg) was obtained in 85% yield as a yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.9 Hz, 2H), 7.38-7.06 (m, 10H), 6.88 (d, *J* = 8.9 Hz, 2H), 5.91 (d, *J* = 15.7 Hz, 1H), 5.75-5.58 (m, 2H), 4.90-4.81 (m, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 2.96 (t, *J* = 7.7 Hz, 2H), 2.64 (dd, *J* = 13.5, 6.9 Hz, 1H), 2.44 (dd, *J* = 13.7, 7.1 Hz, 1H), 1.97-1.78 (m, 2H), 1.42-1.22 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.0, 157.9, 141.4, 139.4, 138.8, 138.0, 133.0, 131.1, 128.4, 128.0, 127.9, 127.4, 126.9, 126.1, 126.0, 114.2, 113.9, 75.1, 55.5, 51.9, 51.4, 44.4, 31.3, 28.6; IR (film) 3026, 2856, 1725, 1604, 1508, 1245 cm$^{-1}$; HRMS (ESI) calcd for $C_{30}H_{34}NO_3$ $[M+H]^+$ *m/z* = 456.2539; found 456.2536; $[\alpha]^{24}_D$ = +130.4 (c 0.29, 86% ee, $CH_2Cl_2$); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): $t_R$ of **1.03aa**: 6.2 min (major) and 7.6 min (minor).

**Pentenylmagnesium bromide.** Cut magnesium ribbon (261 mg, 10.9 mmol) that was scored until shiny was added to a flame dried 10 mL Schlenk flask charged with a stir bar equipped with a reflux condenser under argon. $Et_2O$ (3.02 mL) was added to the magnesium. Freshly distilled (124-126 °C, 760 torr) pentenyl bromide was added dropwise to the magnesium at a rate to sustain a slow reflux. After addition was complete, the mixture was heated to reflux for 2 h, allowed to cool to rt, and used in preparation of **1.03aa**.

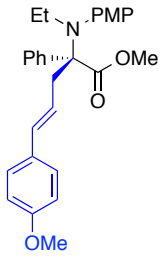



**(*S,E*)-Methyl 2-(*N*-(hex-5-en-1-yl)-*N*-(4-methoxyphenyl)amino)-2,5-diphenylpent-4-enoate (1.03bb).** Following the general procedure B, 1.5 M hexenylmagnesium bromide (355 μL, 0.532 mmol) was added to **1.01a** (72 mg, 0.266 mmol) in 2-MeTHF (1.5 mL), allowed to react for 45 min providing a yellow mixture, which was subjected to a solution of $[\eta^3\text{-}C_3H_5PdCl]_2$ (3.58 mg, 0.0098 mmol), *R*-DIFLUORPHOS (8.09 mg, 0.013 mmol) and cinnamyl acetate (46.8 mg, 0.266 mmol) in 2-MeTHF (1.5 mL) for 45 min, providing an orange mixture. After work-up, concentration and chromatography (pre-wash $SiO_2$ with 5% $NEt_3$/hexanes, eluent 3% EtOAc/hexanes) product **1.03bb** (105 mg) was obtained in 84% yield as a yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, $J$ = 7.6 Hz, 2H), 7.36 (t, $J$ = 7.6 Hz, 2H), 7.30-7.27 (m, 1H), 7.21 (t, $J$ = 7.3 Hz, 2H), 7.17-7.13 (m, 3H), 7.08 (d, $J$ = 7.9 Hz, 2H), 6.88 (d, $J$ = 8.8 Hz, 2H), 5.90 (d, $J$ = 16 Hz, 1H), 5.74-5.65 (m, 2H), 4.91-4.86 (m, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 2.99-2.90 (m, 2H), 2.63 (dd, $J$ = 13.8, 7.1 Hz, 1H), 2.44 (dd, $J$ = 13.5, 7.1 Hz, 1H), 1.89-1.85 (m, 2H), 1.27-1.18 (m, 4H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.0, 157.9, 141.5, 139.5, 139.0, 138.0, 132.9, 131.1, 128.4, 128.0, 127.8, 127.4, 126.9, 126.1, 126.1, 114.3, 113.8, 75.1, 55.5, 52.1, 51.4, 44.5, 33.7, 28.8, 26.3; IR (film) 3025, 2856, 1725, 1604, 1508, 1245, 1036 cm$^{-1}$; HRMS (ESI) calcd for $C_{31}H_{36}NO_3$ $[M+H]^+$ *m/z* = 470.2695; found 470.2693; $[\alpha]^{25}_D$ = +129.0 (c 0.41, 80% ee, $CH_2Cl_2$); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): $t_R$ of **1.03bb**: 6.0 min (major) and 7.5 min (minor).

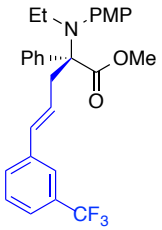
**Hexenylmagnesium bromide.** Magnesium ribbon (144 mg, 6 mmol) that was scored until shiny was added to a flame dried 10 mL Schlenk flask charged with a stir bar equipped with a reflux condenser under argon. THF (3.33 mL) was added to the magnesium. Freshly distilled (25 °C, 0.01 torr) hexenyl bromide was added dropwise to the magnesium at a rate to sustain a slow reflux. After addition was complete, the mixture was heated to reflux for 2 h, allowed to cool to rt, and used in preparation of **1.03bb**.




**(*S*,*E*)-Methyl 2-(*N*-ethyl-*N*-(4-methoxyphenyl)amino)-2-phenyloct-4-enoate (1.03cc).** Following the general procedure B using **1.01a** (50 mg, 0.19 mmol) in THF (1.0 mL), 3.0 M EtMgBr (100 μL, 0.30 mmol), $[\eta^3\text{-}C_3H_5PdCl]_2$ (1.7 mg, 0.0047 mmol), (*R*)-BINAP (5.7 mg, 0.0091 mmol) and hex-2-enyl acetate (31 μL, 0.20 mmol) in THF (1.0 mL). Purification by column chromatography (8% EtOAc/hexanes) provided product **1.03cc** (49 mg) in 70% yield as a yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, $J$ = 7.5 Hz, 2H), 7.32 (t, $J$ = 7.6 Hz, 2H), 7.27-7.22 (m, 1H), 7.10 (d, $J$ = 8.8 Hz, 2H), 6.84 (d, $J$ = 9 Hz, 2H), 5.03-4.88 (m, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 3.03-2.86 (m, 2H), 2.42 (dd, $J$ = 14, 6.3 Hz, 1H), 2.19 (dd, $J$ = 14, 7.0 Hz, 1H), 1.71 (dt, $J$ = 7.6, 6.9 Hz, 2H), 1.16-1.09 (m, 2H), 0.79 (t, $J$ = 7.0 Hz, 3H), 0.71 (t, $J$ = 7.4 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.2, 157.8, 141.7, 139.2, 134.1, 131.2, 128.1, 127.6, 127.0, 125.2, 113.7; IR (film) 2959, 1726, 1508, 1244 cm$^{-1}$; HRMS (ESI) calcd for $C_{24}H_{32}NO_3$ $[M+H]^+$ *m/z* = 382.2382 ; found 382.2388; $[\alpha]^{25}_D$ = +128.75 (c 0.32, 58% ee, $CH_2Cl_2$); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): $t_R$ of **1.03cc**: 4.8 min (major) and 6.8 min (minor).



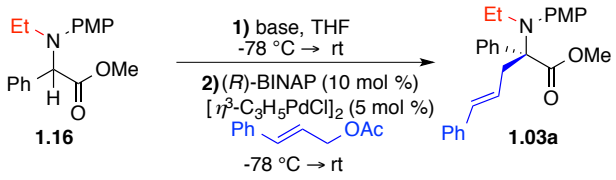

**(*S*,*E*)-Methyl 2-(*N*-ethyl-*N*-(4-methoxyphenyl)amino)-5-(4-methoxyphenyl)-2-phenylpent-4-enoate (1.03dd).** Following general procedure B using **1.01a** (40 mg, 0.15 mmol) in THF (1.0 mL), 3.0 M EtMgBr (80 μL, 0.24 mmol), $[\eta^3\text{-}C_3H_5PdCl]_2$ (1.36 mg, 0.0037 mmol), (*R*)-BINAP (4.6 mg, 0.0073 mmol) and (4-methoxy)cinnamyl acetate (32 mg, 0.16 mmol) in THF (1.0 mL). Purification by column chromatography (pre-wash $SiO_2$ with 5% $NEt_3$/hexanes, eluent 8% EtOAc/hexanes) provided **1.03dd** (48 mg) in 72% yield as a yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 8.4 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 2H), 7.28-7.27 (m, 1H), 7.14 (d, *J* = 8.8 Hz, 2H), 7.01 (m, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.9 Hz, 2H), 6.74 (d, *J* = 8.7 Hz, 2H), 5.82 (d, *J* = 15.8 Hz, 1H), 5.26 (dt, *J* = 15.8, 7.4 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.76 (s, 3H), 3.06-2.99 (m, 1H), 2.97-2.90 (m, 1H), 2.59 (ddd, *J* = 13.7, 7.0, 1.3 Hz, 1H), 2.39 (ddd, *J* = 13.8, 7.5, 1.1 Hz, 1H), 0.81 (t, *J* = 6.9 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.3, 158.7, 157.8, 141.7, 139.2, 132.4, 131.3, 130.9, 127.9, 127.8, 127.3, 127.1, 123.8, 113.9, 113.8, 75.2, 55.5, 55.4, 51.4, 46.6, 44.3, 14.7; IR (film) 2960, 2931, 1724, 1607, 1509, 1246 $cm^{-1}$; HRMS (ESI) calcd for $C_{28}H_{32}NO_4$ $[M+H]^+$ *m/z* = 446.2331; found 446.2322; $[\alpha]^{25}_D$ = +95.3 (c 0.21, 60% ee, $CH_2Cl_2$); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): $t_R$ of **1.03dd**: 9.9 min (major) and 11.8 min (minor).




**(*S*,*E*)-Methyl 2-(*N*-ethyl-*N*-(4-methoxyphenyl)amino)-5-(3-(3-trifluoromethyl)phenyl)-2-phenylpent-4-enoate (1.03ee).** Following general procedure B using **1.01a** (40 mg, 0.149 mmol) in THF (1.0 mL), 3.0 M EtMgBr (80 μL, 0.240 mmol), $[\eta^3\text{-}C_3H_5PdCl]_2$ (1.36 mg, 0.0037 mmol), (*R*)-DIFLUORPHOS (4.98 mg, 0.0073 mmol) and (3-trifluromethyl)cinnamyl acetate (38 mg, 0.156 mmol) in THF (1.0 mL). Purification by column chromatography (pre-wash $SiO_2$ with 5% $NEt_3$/hexanes, eluent 8% EtOAc/hexanes) provided **1.03ee** (55 mg) in 76% yield as a yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.9 Hz, 2H), 7.38-7.34 (m, 3H), 7.30 (t, *J* = 7.9 Hz, 2 H), 7.22 (d, *J* = 7.9, 1H), 7.14 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 5.87 (d, *J* = 15.8 Hz, 1H), 5.80-5.74 (dt, *J* = 15.6, 7.0 Hz, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 3.08-3.01 (m, 1H), 2.98-2.92 (m, 1H), 2.63 (dd, *J* = 13.7, 6.8 Hz, 1H), 2.43 (dd, *J* = 13.7, 7.3 Hz, 1 H), 0.82 (t, *J* = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.3, 158.0, 141.5, 139.1, 138.7, 131.6, 131.3, 130.8 (q, *J* = 32 Hz), 129.0, 128.8, 128.4, 128.0, 127.7, 127.5, 124.4 (q, *J* = 254 Hz), 123.5-123.4 (m), 122.8-122.7 (m), 113.9, 75.1, 55.5, 51.6, 46.8, 44.5, 14.7; IR (film) 3036, 2837, 1725, 1606, 1508, 1328, 1245, 1124 cm$^{-1}$; HRMS (ESI) calcd for $C_{28}H_{29}F_3NO_3$ $[M+H]^+$ *m/z* = 484.2100; found 484.2099; $[\alpha]^{25}_D$ = +99.5 (c 0.26, 64% ee, $CH_2Cl_2$); chiral HPLC (IA, 97.5:2.5 hexanes:*i*-PrOH, 1 mL/min, 254 nm): $t_R$ of **1.03ee**: 6.0 min (major) and 5.6 min (minor).

**(3-Trifluoromethyl)cinnamyl acetate.** Following the modified procedure previously reported.[53] Reaction conditions: 3-iodobenzotrifluoride (577 µL, 4.0 mmol), allyl acetate (1.6 g, 16.0 mmol), $Pd(OAc)_2$ (45 mg, 0.20 mmol), $Ag_2CO_3$ (662 mg, 2.4 mmol), toluene (24 mL). **(3-Trifluoromethyl)cinnamyl acetate** (315 mg) was obtained in 32% yield as a colorless liquid. Spectral data agreed with those reported previously.[54]

**Studies on Allylation of *N*-Alkylated Intermediate (**Table 1.5**)**



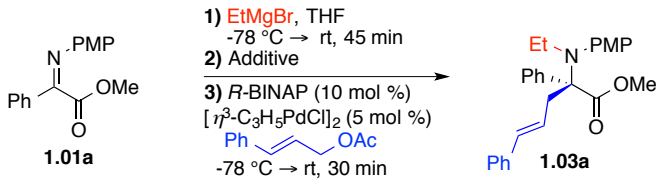

α-Amino ester **1.16** was dissolved in THF in a flame dried 10 mL round bottom flask charged with a stir bar and put under argon. The reaction mixture was cooled to -78 °C and a solution of base in THF was added dropwise. The reaction mixture was warmed to ambient temperature and allowed to react for 10 min and then cooled to -78 °C. A second 10 mL round bottom flask charged with a stir bar was flamed dried under argon, Pd/(*R)*-BINAP/cinnamyl acetate was added, dissolved in THF and cooled to -78 °C. The Pd/(*R)*-BINAP/cinnamyl acetate slurry was added to the reaction mixture, which was allowed to warm to ambient temperature. The resultant reaction mixture was cooled to 0 °C after 45 minutes, quenched with satd $NH_4Cl$ (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$,

53) Pan, D.; Chen, A.; Su, Y.; Zhou, W.; Li, S.; Jia, W.; Xiao, J.; Liu, Q.; Zhang, L.; Jiao, N. "Ligand-Free Pd-Catalyzed Highly Selective Arylation of Allylic Esters with Retention of the Traditional Leaving Group" *Angew. Chem., Int. Ed.* **2008**, *47*, 4729-4732

54) Fleming, S. A.; Renault, L.; Grundy, E. C.; Pincook, J. A. "The Photochemistry of ring-substituted cinnamyl acetates" *Can. J. Chem.* **2006**, *84*, 1146-1154.

filtered and concentrated *in vacuo*. The resulting residue was purified by chromatography to afford pure α-allyl-α-aryl α-amino acid **1.03a.**

**The Addition of Additives after Enolate Formation (**Table 1.6**)**




**1.01a** (40 mg, 0.15 mmol) was added to a flamed dried round bottom flask that had been charged with a stir bar and was put under an argon atmosphere. THF (1.0 mL) was added and the reaction was cooled to -78 °C. To this solution was added EtMgBr (3.0 M in $Et_2O$, 80 µL, 0.24 mmol) under argon. The mixture was slowly warmed to ambient temperature, 1 equiv of respective additive was added (in the case of NaBAr'F, 5 mol % was added to the Pd/L/cinnamyl acetate solution) and allowed to stir for an additional 30 minutes. A flame dried round bottom flask equipped with a stir bar was charged with $[\eta^3\text{-}C_3H_5PdCl]_2$ (1.4 mg, 0.0037 mmol) and (*R*)-BINAP (4.6 mg, 0.0.0073 mmol) and put under an argon atmosphere. The mixture was dissolved with THF (1.0 mL) and cinnamyl acetate (26 µL, 0.15 mmol) was added. The second solution was stirred for 5 minutes at ambient temperature under argon, cooled to -78 °C, and added to the cooled (-78 °C) first solution via syringe. The combined mixture was allowed to warm to ambient temperature and stirred for 45 min. The workup for general procedure A was then followed providing **1.03a**.

# 2. α-ALLYL-α-ARYL α-AMINO ESTERS IN THE ASYMMETRIC SYNTHESIS OF ACYCLIC AND CYCLIC AMINO ACID DERIVATIVES

## 2.1. BACKGROUND

### *2.1.1. Synthesis of α-Allyl-α-Aryl α-Amino Esters*

Recently, we developed an asymmetric method for synthesizing α-allyl-α-aryl α-amino acids, which relies on the formation of a chelated magnesium enolate that is generated *in situ* (Figure 2.1).[55] This was the first example of α-phenylglycine used in asymmetric allylic alkylation (AAA) and represents the only asymmetric method for generating α-allyl-α-aryl α-amino acids that is general for the aryl substituent.[16]

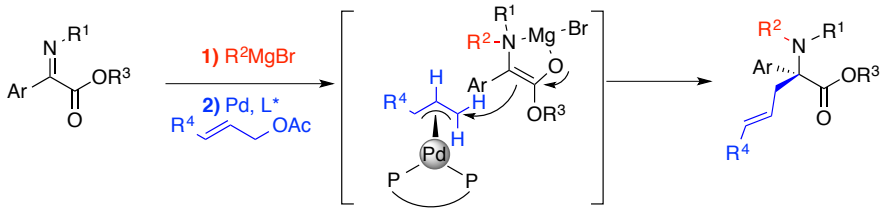



**Figure 2.1** Asymmetric synthesis of α-allyl-α-aryl α-amino acids by *N*-alkylation/π-allylation.

α-Allyl-α-aryl α-amino acids are an interesting class of compounds. The structural properties and biological activities are relatively unknown. The allyl moiety as a side-chain substituent is very attractive. During the course of developing this novel technology for the synthesis of α-allyl-α-aryl α-amino acids, we envisioned that the allyl

55) Curto, J. M.; Dickstein, J. S.; Berritt, S.; Kozlowski, M. C. "Asymmetric Synthesis of α-Allyl-α-Aryl α-Amino Acids by Tandem Alkylation/π-Allylation of α-Iminoesters" *Org. Lett.* **2014**, *16*, 1948-1951.

moiety would undergo various metathesis type reactions, providing access to other new compounds (Figure 2.2).

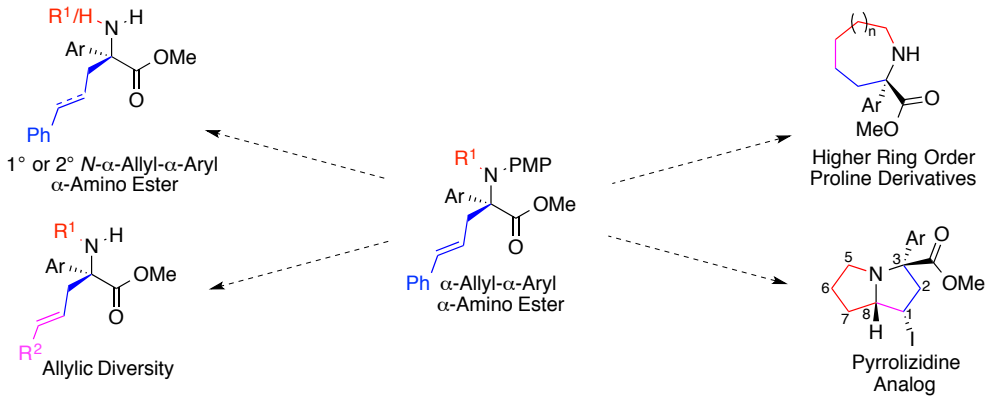
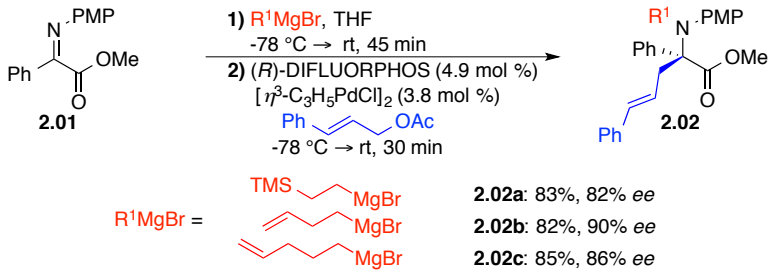



**Figure 2.2** Enantioenriched acyclic and cyclic amino acid derivatives from α-allyl-α-aryl α-amino esters.

In contrast to most other reports on the *N*-alkylation of α-iminoesters, a range of Grignard reagents could be successfully combined with the AAA conditions (Scheme 2.1). Notably, more functional Grignards provided terminal silyl and alkenyl derivatives. These substances proved to be important for generation of other novel α,α-disubstituted α-amino acids.

**Scheme 2.1** Our previous work on the tandem *N*-alkylation/π-allylation of α-iminoesters.



## 2.2. RESULTS

### *2.2.1. Synthesis of Secondary and Primary N-α-Allyl-α-Aryl α-Amino Esters*

The tandem *N*-alkylation/π-allylation method developed readily provides access to *N*-alkyl α-allyl-α-aryl α-amino acids including a number of *N*-alkyl substitutions that would be difficult to generate via reductive amination (see Scheme 2.1). The *para*-methoxyphenyl (PMP) activating group on nitrogen was found to be very important for attaining the best yield and selectivity in this novel technology. We envisioned that the labile PMP group would provide access to secondary *N*-α-allyl-α-aryl α-amino acids (**2.04**) (Figure 2.3, known). The primary *N*-α-allyl-α-aryl α-amino acid (**2.05**) was also desired, but removal of the alkyl group ($R^1$) would be much more challenging (Figure 2.3, unknown).

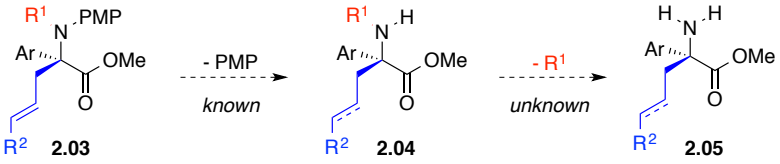


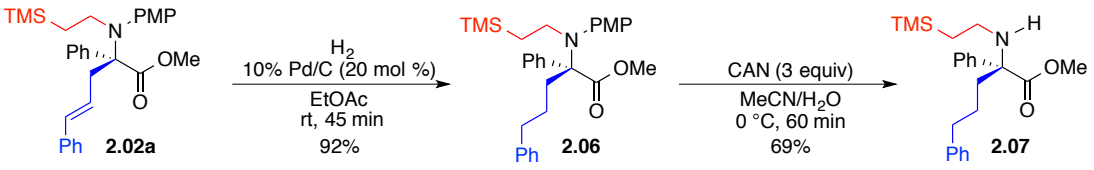

**Figure 2.3** Synthesis of secondary and primary *N*-α-allyl-α-aryl α-amino acids from *N*-alkylation/π-allylation product.

Access to the secondary *N*-α,α-disubstituted α-amino acid was thus pursued with **2.02a** (Scheme 2.2). The PMP group can be removed with strong oxidative conditions.[56] Direct removal of the PMP group on **2.02a** was unsuccessful with ceric ammonium nitrate (CAN), periodic acid or trichloroisocyanuric acid. PMP removal on tertiary amines

56) Verkade, J. M. M.; van Hemert, J. C.; Quaedflieg, P. J. L. M.; Alsters, P. L.; van Delft, F. L.; Rutjes, P. J. T. "Mild and efficient deprotection of the amine protecting *p*-methoxyphenyl (PMP) group" *Tetrahedron Lett.* **2006**, *47*, 8109-8113.

is sluggish, and with **2.02a**, the allyl moiety underwent undesired side reactions before PMP removal. The troublesome olefin was removed by subjecting **2.02a** to $H_2$ and Pd/C. Treatment of the saturated **2.06** with CAN led to the successful removal of the PMP group, providing the desired secondary *N*-α,α-disubstituted α-amino acid (Scheme 2.2, **2.07**).

**Scheme 2.2** Synthesis of secondary *N*-α,α-disubstituted α-amino acid (**2.07**).




We demonstrated in our development of the asymmetric *N*-alkylation/π-allylation of α-iminoesters that the tandem reaction was necessary to achieve high enantioselectivity. This requirement, however, presented an *N*-alkylated α,α-disubstituted α-amino acid that had no known method for C–N bond cleavage (phenyl, benzyl and allyl Grignards were unsuccessful in the *N*-alkylation step). 2-(Trimethylsilyl)ethylmagnesium bromide was a competent nucleophile for the tandem process and precedent in the literature suggested it could be removed (Figure 2.4).

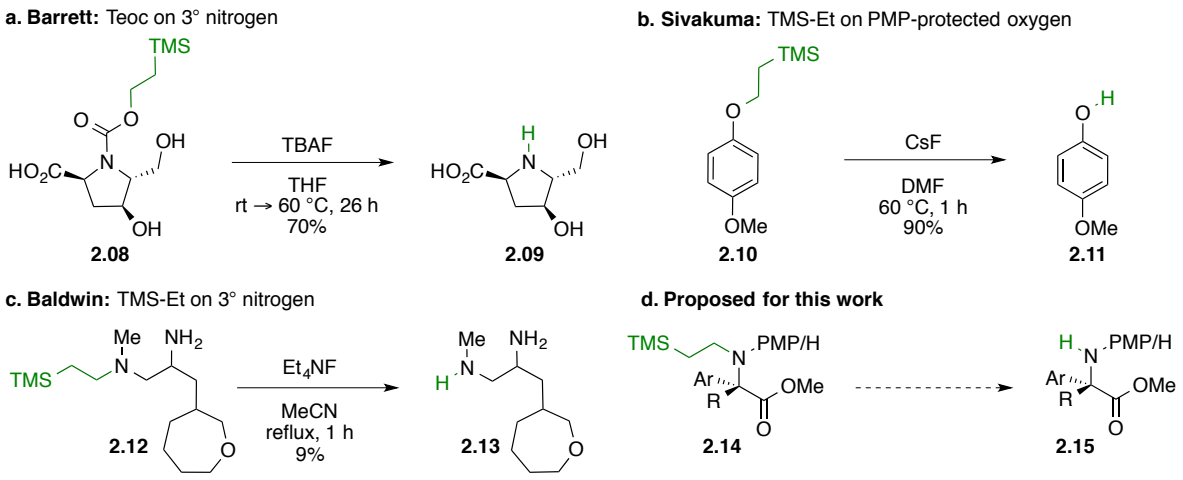


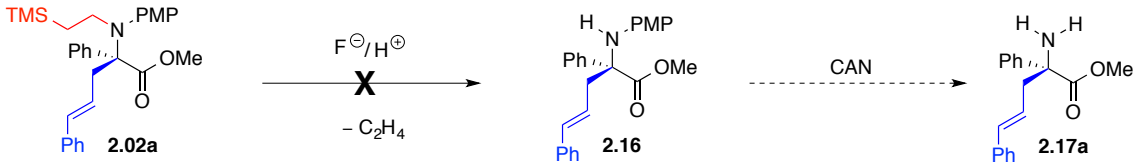

**Figure 2.4** C–N Bond cleavage of 2-(trimethylsilyl)ethyl amine protecting group.

An important protecting group for amines is trimethylsilylethyl carbamate (Teoc). The Teoc protecting group can be used orthogonally with acid labile protecting groups (e.g., Boc and acyl) because it is easily removed with fluoride sources (Figure 2.4, **a**).[57] A variation of the Teoc protecting group is trimethylsilylethyl, which has been shown to be removed with CsF when used to protect *para*-methoxyphenol (Figure 2.4, **b**).[58] Trimethylsilylethyl has been used with moderate success to protect *N,N*-dialkylated amines (Figure 2.4 ,**c**).[59] These examples in the literature prompted us to propose that 2-(trimethylsilyl)ethylamine on **2.14** could be removed with high yields (Figure 2.4, **d**). Putatively, the PMP group and α-$CO_2$Me would increase the leaving group ability of the nitrogen on **2.14** compared to that in **2.12**, which undergoes cleavage in low yield.

57) Barrett, A. G. M.; Pilipauskas, D. "Electrochemical Oxidation of Proline Derivatives: Total Syntheses of Bulgecinine and Bulgecin C" *J. Org. Chem.* **1991**, *56*, 2787-2800.
58) Dibakar, M.; Prakash, A.; Selvakuma, K.; Ruckmani, K.; Sivakuma, M. "2-(Trimethylsilyl)ethanol as a new alcohol equivalent for copper-catalyzed coupling of aryl iodides" *Tetrahedron Lett.* **2011**, *52*, 5338-5341.
59) Baldwin, J. J. et al. Preparation of phenyl[((amino)phenyl)methoxy]ethylcarbamate derivatives and analogs as renin inhibitors. WO 2008-US7662, Dec 24, 2008.

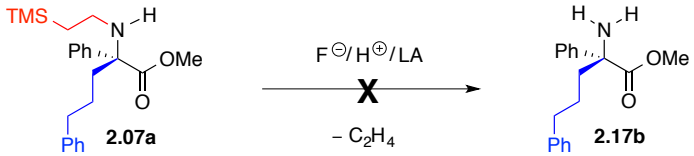
We initiated the investigation of C–N bond cleavage of 2-(trimethylsilyl)ethyl amine on **2.02a** (Scheme 2.3) using TBAF, CsF, HF, KF/18-crown-6, $LiBF_4$ or $LiF/BF_3•Et_2O$. At ambient temperature, as well at elevated temperatures (60–120 °C), for 2–24 h starting material was recovered or decomposition was observed.

**Scheme 2.3** C–N bond cleavage of 2-(trimethylsilyl)ethyl amine (**2.02a**).




In previous studies, the tandem products from the *N*-alkylation/π-allylation method had been subjected to concentrated hydrochloric acid but did not form the ammonium salt. This finding led us to believe that **2.02a** was too sterically hindered for nitrogen to be protonated or to coordinate with a Lewis acid additive to enhance its leaving group potential. The PMP group was removed to investigate the less hindered and more basic amine **2.07a**. The secondary amine was subjected to TBAF, $TBAF/BF_3•Et_2O$, TsOH, TFA, HCl, HF or $TFA/BF_3•Et_2O$ at elevated temperatures (65 °C) and prolonged reaction times (24 h) (Scheme 2.4). In each reaction, only unreacted starting material or unidentified side-products were isolated with no evidence of product (**2.17b**).

**Scheme 2.4** C–N bond cleavage of 2-(trimethylsilyl)ethyl amine (**2.07a**).



The challenges incurred with the C–N bond cleavage of 2-(trimethylsilyl)ethyl amine inspired our investigation of homoallyic amine **2.18**. A survey of the literature suggested that tertiary allylic amines could be reduced to the secondary amines.[61,62,63,64,65] If *N*-butenyl substrate (**2.18**) could be isomerized to the allylic amine (**2.19**), then conditions to either remove the allyl group (*path a)* or generate the enamine, which would undergo subsequent hydrolysis (*path b*), should be achievable (Figure 2.5).

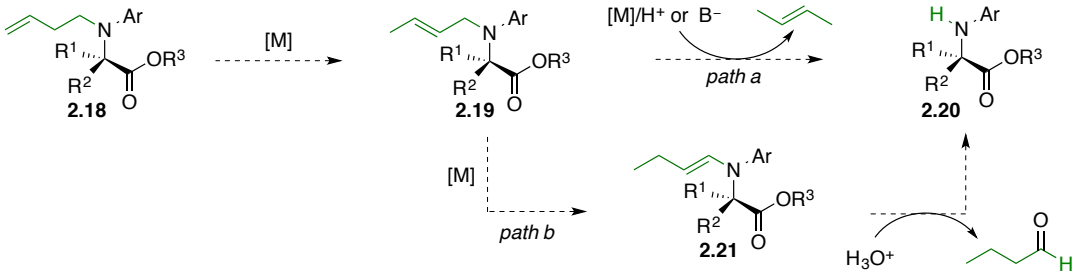



**Figure 2.5** Proposed C–N bond cleavage of allylic amine.

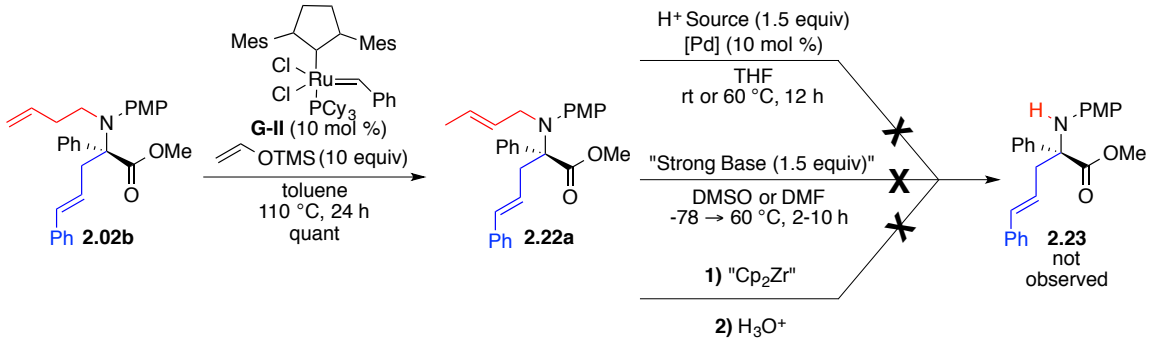
The investigation of the C–N bond cleavage of the allylic amine commenced with **2.01b**. The terminal olefin was isomerized to the internal olefin with conditions developed by Nishida using a ruthenium hydride generated from second generation Grubbs catalyst (G-II) and vinyloxytrimethylsilane at elevated temperatures (Scheme 2.5, left).[60] Previous work by Cossy suggests that similar conditions could also generate the enamine from the allyl *in situ*, but even at elevated temperatures (140 °C) isomerization was not observed.[61] Various conditions for C–N bond cleavage of the allylic amine were investigated (Scheme 2.5, right). Generation of the allylpalladium

60) Arisawa, M.; Terada, Y.; Takahashi, K.; Nakagawa, M.; Nishida, A. "Ruthenium Hydride with *N*-Heterocyclic Carbene and Its Application to the Synthesis of Heterocycles" *J. Org. Chem.* **2006**, *71*, 4255-4261.

61) Cadot, C.; Dalko, P. I.; Cossy, J. "Olefin isomerization by a ruthenium carbenoid complex. Cleavage of allyl and homoallyl groups" *Tetrahedron Lett.* **2002**, *43*, 1839-1841.

complex was unsuccessful.[62] Strong bases including *n*-BuLi, *t*-BuLi, KO*t*-Bu or NaH were explored to form the enamine but in all cases the starting material was recovered unreacted.[63] C–N bond cleavage of allylic amines has been shown to be successful with "$Cp_2Zr$" but when applied to **2.22a**, only unreacted starting material was recovered.[64] $BF_3$•$Et_2O$ can promote C–N bond cleavage via an aza-Cope rearrangement but decomposition of **2.22a** occurred instead.[65]

**Scheme 2.5** Isomerization of homoallylic amine to allylic amine and subsequent studies on the C–N bond cleavage.




Redox isomerizations are examples of atom-economical processes in which one site in an organic substrate is oxidized with concomitant reduction of another site.[66] After the challenges met with C–N bond cleavage of the 2-(trimethylsilyl)ethylamine and

62) (a) Zhao, X.; Liu, D.; Guo, H.; Liu, Y.; Zhang, W. "C–N Bond Cleavage of Allylic Amines via Hydrogen Bond Activation with Alcohol Solvents in Pd-Catalyzed Allylic Alkylation of Carbonyl Compounds" *J. Am. Chem. Soc.* **2011**, *133*, 19354-19357. (b) Garro-Helion, F.: Merzouk, A.; Guibe, F. "Mild and Selective Palladium (0)-Catalyzed Deallylation of Allylic Amines. Allylamine and Diallylamine as Very Convenient Ammonia Equivalents for the Synthesis of Primary Amines" *J. Org. Chem.* **1993**, *58*, 6109-6113.

63) Weisenburger, G. A.; Beak, P. "α-Lithiation of *N*-(*tert*-Butoxycarbonyl)-*N*(*p*-methoxyphenyl)allylamines Mediated by (–)-Sparteine: Enantioselective Syntheses of Either Enantiomer of 3-Substituted Enecarbamates" *J. Am. Chem. Soc.* **1996**, *118*, 12218-12219.

64) Ito, H.; Taguchi, T.; Hanzawa, Y. "Practical Zirconium-Mediated Deprotective Method of Allyl Groups" *J. Org. Chem.* **1993**, *58*, 774-775.

65) Beholz, L. G.; Stille, J. R. "Lewis Acid-Promoted 3-Aza-Cope Rearrangement of *N*-Alkyl-*N*-allylanilines" *J. Org. Chem.* **1993**, *58*, 5095-5100.

66) Trost, B. M. "On Inventing Reactions for Atom Economy" *Acc. Chem. Res.* **2002**, *35*, 695-705.

allylic amines, we began investigating the literature for the isomerization of terminal alkenes to internal alkenes. Ir[67], Fe[68], Zr[69] and Ru[70] have all been shown to be active metals for zipper (>1 carbon) alkene isomerization.

Douglas Grotjahn has published a series of papers detailing the efforts of his research group on redox isomerizations.[71] Grotjahn generously provided us with his catalyst (~50 mg), which was investigated with terminal olefin **2.02b** (Scheme 2.6). When **2.02b** was treated with the Grotjahn catalyst in acetone at rt for 24 h, the mono-isomerized allyl **2.22a** was produced cleanly. Heating **2.02b** to 70 °C for 24 h produced the hydrolyzed product (**2.23**) in 40% yield. Grotjahn and co-workers had demonstrated that the catalyst could be used in combination with $D_2O$ to deuterate allylic C–H bonds selectively.[71b] $H_2O$ and trifluoroacetic acid were thus applied to **2.02b**, which led to exclusive formation of **2.23** resulting from *in situ* hydrolysis of the enamine (Scheme 2.6).

67) Lim, H. J.; Smith, C. R.; RajanBabu, T. V. "Facile Pd(II)- and Ni(II)-Catalyzed Isomerization of Terminal Alkenes into 2-Alkenes" *J. Org. Chem.* **2009**, *74*, 4565-4572.

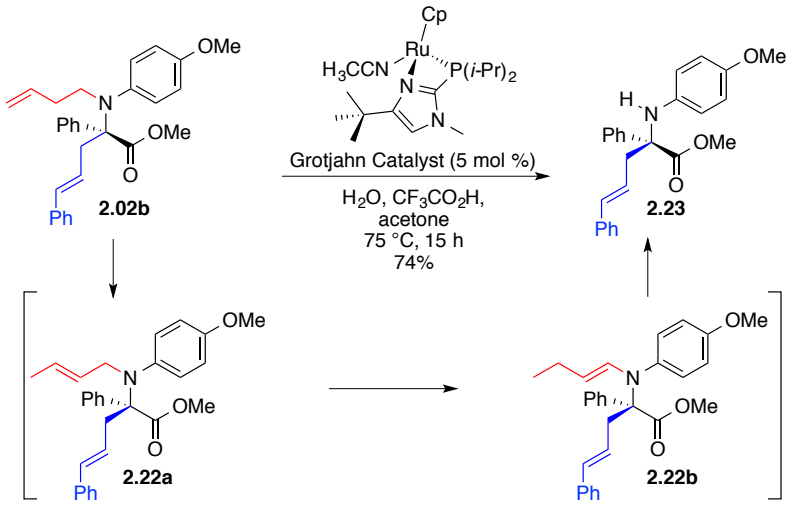
68) Iranpoor, N.; Mottaghinejad, E. "Dodecacarbonyl triiron, an efficient catalyst for photochemical isomerization of unsaturated alcohols, ethers and ester to their carbonyl compounds, enol ethers and esters" *J. Organomet. Chem.* **1992**, *423*, 399-404.

69) Gibson, T.; Tulich, L. "Novel Synthesis of Long-Chain Primary Alkyl Compounds" *J. Org. Chem.* **1981**, *46*, 1821-1823.

70) Ruba, E.; Simanko, W.; Mauthner, K.; Soldouzi, K. M.; Slugovc, C.; Mereiter, K.; Schmid, R.; Kirchner, K. "$[RuCp(PR_3)(CH_3CN)_2]PF_6$ (R = Ph, Me, Cy). Convenient Precursors for Mixed Ruthenium(II) and Ruthenium(IV) Half-Sandwich Complexes" *Organometallics* **1999**, *18*, 3843-3850.

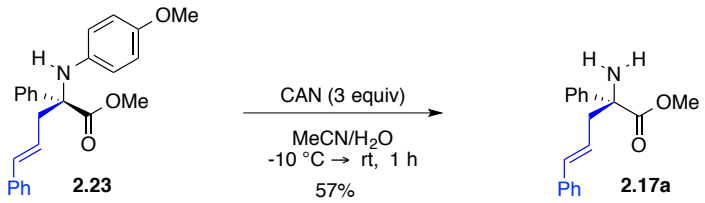
71) (a) Larsen, C. R.; Grotjahn, D. B. "Stereoselective Alkene Isomerization over One Position" *J. Am. Chem. Soc.* **2012**, *134*, 10357-10360. (b) Erdogan, G.; Grotjahn, D. B. "Mild and Selective Deuteration and Isomerization of Alkenes by a Bifunctional Catalyst and Deuterium Oxide" *J. Am. Chem. Soc.* **2009**, *131*, 10354-10355. (c) Grotjahn, D. B.; Larsen, C. R.; Gustafson, J. L.; Nair, R.; Sharma, A. "Extensive Isomerization of Alkenes Using a Bifunctional Catalyst: An Alkene Zipper" *J. Am. Chem. Soc.* **2007**, *129*, 9592-9593.

**Scheme 2.6** C–N bond cleavage by alkene isomerization to enamine followed by *in situ* hydrolysis.




The PMP group was removed from **2.23** with CAN to provide the primary *N*-α-allyl-α-aryl α-amino acid **2.17a** (Scheme 2.7). The successful removal of the PMP group on the secondary amine in the presence of the allylic moiety contrasted our previous efforts with tertiary amines (see Scheme 2.2). Putatively, the secondary amine more effectively coordinates Ce, thus becoming a better leaving group than the corresponding tertiary amine, and side-reactions of the allyl with CAN are minimized.

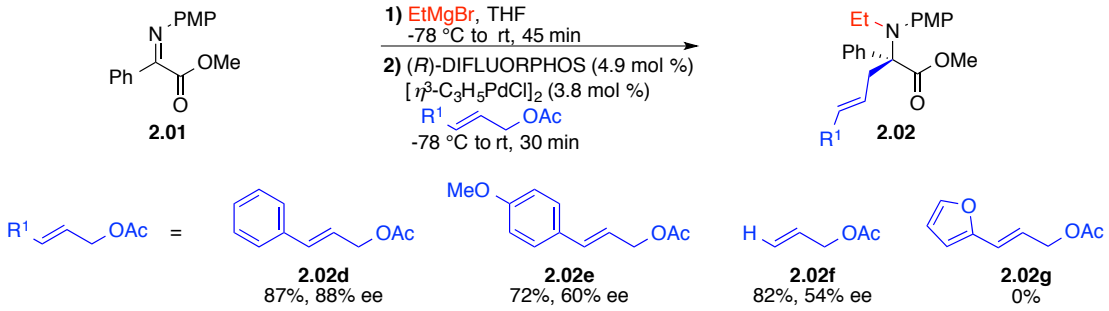
**Scheme 2.7** Synthesis of the primary *N*-α-allyl-α-aryl α-amino acid **2.17a** by removal of the PMP protecting group.



*2.2.2. Asymmetric Synthesis of Acyclic Amino Acid Derivatives by Alkene Metathesis*

α-Aryl homologs of tyrosine and glutamate have been shown to be biologically active.[72] Yet, the inability to use other allylating agents with our previously developed *N*-alkylation/π-allylation of α-iminoesters hindered access to such compounds (Scheme 2.8).

**Scheme 2.8** Our previous work on exploration of allylating agent in *N*-alkylation/π-allylation of α-iminoester.




Olefin cross metathesis (CM) is a convenient route to functionalized olefins from simple alkene precursors. The availability of catalysts with varied activities has increased the prominence of CM, but it is not utilized as often as ring opening metathesis polymerization (ROMP) or ring closing metathesis (RCM). Catalyst activity in CM is low because it has neither a strong enthalpic driving force (ring-strain release in ROMP) nor the entropic advantage of intramolecular reactions (RCM). Also, poor selectivity for the CM product is common because of the many alkylidene intermediates. A seminal paper by Grubbs and co-workers ranked olefins in CM by their ability to homodimerize

72) Wehbe, J.; Rolland, V.; Fruchier, A.; Roumestant, M.; Martinez, J. "Enantioselective synthesis of new 4-substituted glutamic acid derivatives" *Tetrahedron: Asymmetry* **2004**, *15*, 851-858.

(Figure 2.6).[73] Selectivity could be predicted and statistical product distributions could be avoided if two different olefin types were reacted with the correct catalyst.

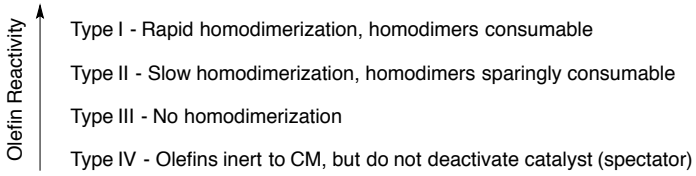



**Figure 2.6** Olefin reactivity in CM (taken from ref 73).

α-Amino acids have been investigated extensively in CM because of their role in biology and myriad applications.[74] α,α-Disubstituted α-amino acids compared to their α-H counterparts when incorporated into peptides typically enhance metabolic stability and possess different folding behavior. On the other hand, CM for the synthesis of α,α-disubstituted α-amino acids is quite rare. Indeed, there are limited methods for the synthesis of enantioenriched α,α-disubstituted α-amino acids with an olefin present. The olefin near a quaternary center is sterically hindered, giving rise to the potential for selective CM.[75] Rutjes and co-workers demonstrated the first example of CM with α,α-disubstituted α-amino acids in the synthesis of α-allyl-α-methyl α-amino acids by 2nd generation, Grubbs catalyst (**G-II**) (Figure 2.7, **a**).[76] Cordero followed this work by

73) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. "A General Model for Selectivity in Olefin Cross Metathesis" *J. Am. Chem. Soc.* **2003**, *125*, 11360-11370.
74) (a) Brik, A. "Metathesis in Peptides and Peptidomimetics" *Adv. Synth. Catal.* **2008**, *350*, 1661-1675. (b) Connon, S. J.; Blechert, S. "Recent Developments in Olefin Cross-Metathesis" *Angew. Chem., Int. Ed.* **2003**, *42*, 1900-1923.
75) Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. "Increased Efficiency in Cross-Metathesis Reactions of Sterically Hindered Olefins" *Org. Lett.* **2008**, *10*, 441-444.
76) Storcken, R. P. M.; Panella, L.; van Delft, F. L.; Kaptein, B.; Broxterman, Q. B.; Schoemaker, H. E.; Rutjes, F. P. J. T. "A Cross-Metathesis Route to Functionalized α-Methyl α-Substituted Amino Acids" *Adv. Synth. Catal.* **2007**, *349*, 161-164.

synthesizing several α-substituted *N*-Boc-protected prolines by CM of *N*-Boc-allylproline (Figure 2.7 ,**b**).[77]

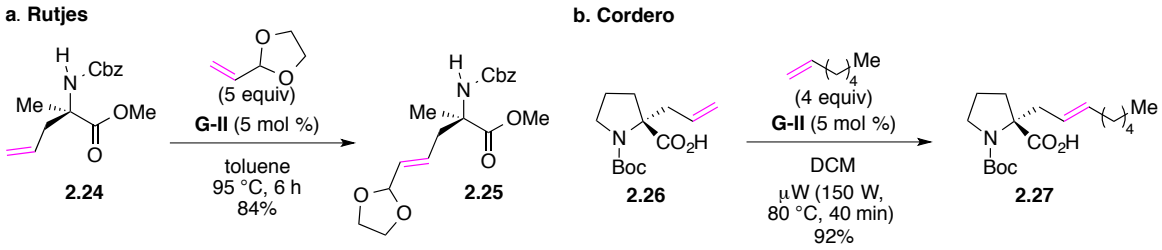



**Figure 2.7** CM of α,α-disubstituted α-amino acids.

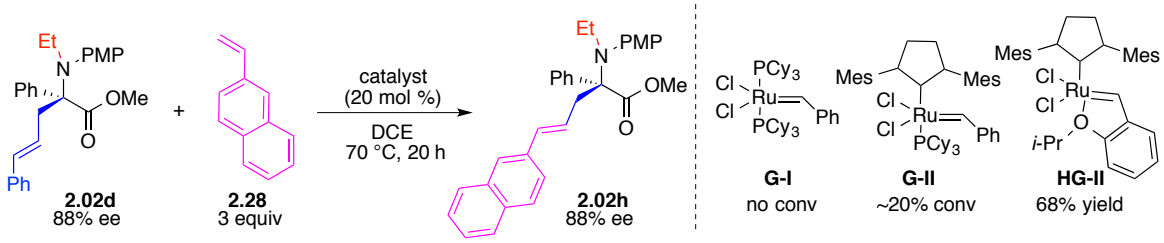
We envisioned that the tandem product from *N*-alkylation/π-allylation of α-iminoesters could be utilized in CM to increase allylic diversity. The tandem product, specifically **2.02d** with high ee (88%), would be a single intermediate that could be combined with a broad range of allyl adducts. A potential limitation to this approach is that tertiary amines need to be deactivated with an electron-withdrawing group (e.g., Boc, Cbz) to prevent catalyst poisoning. However, the tertiary *N*-α-allyl-α-aryl α-amino acids from the tandem chemistry do not behave as expected; ostensibly, the sterics of the α-carbon prevent nitrogen coordination to Brønsted or Lewis acids.

The CM of α-allyl-α-aryl α-amino acids was explored with the tandem product (**2.02d**) and 2-vinylnaphthalene (**2.28**) with various metathesis catalysts (Scheme 2.9). 1st Generation (**G-I**) and 2nd generation (**G-II**), Grubbs catalyst provided zero or minimal CM product, respectively.[78] To our satisfaction, the more active 2nd generation, Hoveyda-Grubbs catalyst (**HG-II**) did successfully generate product in 68% yield. DCM and

77) Lumini, M. Cordero, F. M.; Pisaneschi, F.; Brandi, A. "Straightforward Synthesis of α-Substituted Prolines by Cross-Metathesis" *Eur. J. Org. Chem.* **2008**, 2817-2824.
78) 1st Generation, Hoveyda-Grubbs catalyst also provided minimal CM product.

toluene were also tested but were not as efficient as 1,2-dichloroethane (DCE). Microwave conditions have been shown to increase the efficiency of CM, especially reactions with extended reaction times, but microwave conditions applied to Scheme 2.9 did not improve yield or reaction time.[79]

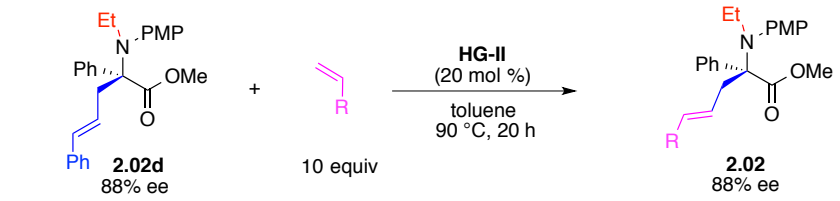
**Scheme 2.9** Screen of metathesis catalysts in the CM of α-allyl-α-aryl α-amino acid.

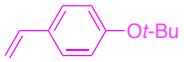
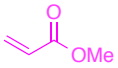



The optimized conditions were successfully applied with the tandem product with high enantioselectivity and 4-*tert*-butoxystyrene, as well as methyl acrylate (Table 2.1). In contrast to 2-vinylnaphthalene, increased temperature did improve yields with these substrates. Sequential addition of catalyst to 4-*tert*-butoxystyrene did not improve the reaction. Ethylene proved recalcitrant, but did afford product **2.02f** with high enantioselectivity, in contrast to direct allylation (see Scheme 2.8), and with high yield based on recovered starting material.

79) Coquerel, Y.; Rodriguez, J. "Microwave-Assisted Olefin Metathesis" *Eur. J. Org. Chem.* **2008**, 1125-1132.

**Table 2.1** CM of high ee tandem product with various type I olefins.




| R = |  |  |  |
|---|---|---|---|
| Product Yield | **2.02i** 74% | **2.02j** 72% | **2.02f** 24% (95% BRSM) |

A range of olefins was explored with the optimized conditions (see Table 2.1) but in nearly all cases only unreacted tandem product and homodimerized type I olefin were isolated (Figure 2.8). Three olefins did provide some product but with a considerable amount of starting material still unreacted; optimization of these compounds was not pursued (Figure 2.8, left).

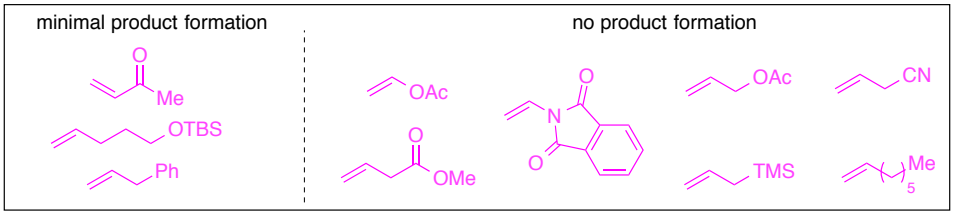
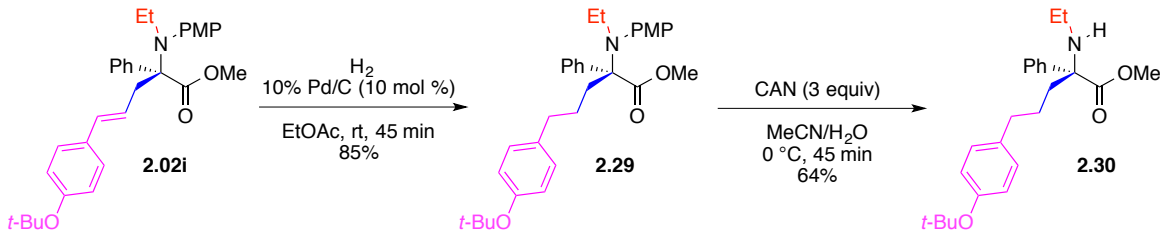



**Figure 2.8** Type I olefins explored that did not provide significant product with **2.02d**.

To further our objective of generating α-amino acid homologs, hydrogenation and PMP-removal was performed on **2.02i** to provide the α-aryl tyrosine homolog **2.30** (Scheme 2.10). Notably, *N*-ethyl amino acids can be difficult to generate due to the difficulty of reductive amination with acetaldehyde.

**Scheme 2.10** Generation of α-aryl tyrosine homolog.




*2.2.3. Asymmetric Synthesis of Cyclic Amino Acid Derivatives by Alkene Metathesis*

Cyclic α-amino acid derivatives are of great synthetic and pharmaceutical interest.[80] Further, α-substituted prolines have been shown to be important as organocatalysts and privileged ligands. Seebach pioneered the asymmetric synthesis of α-substituted prolines in 1983,[81] yet the development of asymmetric methods for the synthesis of higher ring homologues of proline has received little attention.[82]

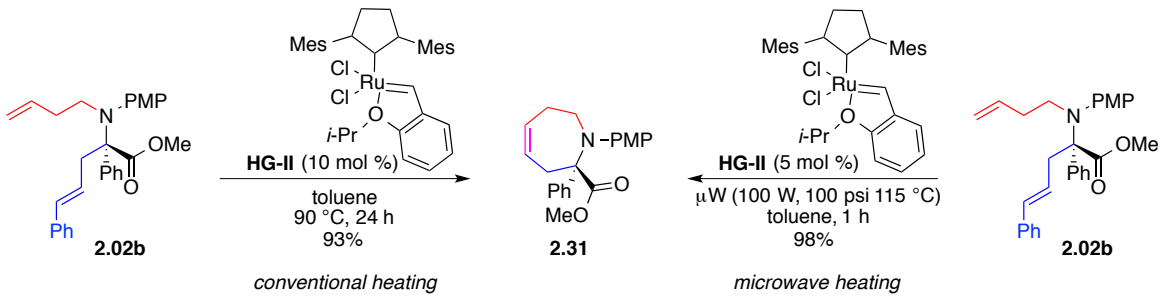
Ring closing metathesis (RCM) has become pervasive in organic synthesis. Even though metathesis originated in polymer chemistry,[83] and the catalysts were developed extensively by organometallic chemists,[84] it has become an important tool for natural

80) Park, K. H.; Kurth, M. J. "Cyclic amino acid derivatives" *Tetrahedron* **2002**, *58*, 8629-8659.
81) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. "Alkylation of Amino Acids without Loss of the Optical Activity: Preparation of α-substituted Proline Derivatives. A Case of Self-Reproduction of Chirality" *J. Am. Chem. Soc.* **1983**, *105*, 5390-5398.
82) For reviews on the asymmetric synthesis of cyclic α,α-disubstituted α-amino acid, see: (a) Cativiela, C.; Ordonez, M. "Recent progress on the stereoselective synthesis of cyclic quaternary α-amino acids" *Tetrahedron: Asymmetry* **2009**, *20*, 1-63. (b) Cativiela, C.; Diaz-De-Villegas, M. D. "Stereoselective synthesis of quaternary α-amino acids. Part 2: Cyclic compounds" *Tetrahedron: Asymmetry* **2000**, *11*, 645-732.
83) Chauvin, Y. "Olefin Metathesis: The Early Days (Nobel Lecture)" *Angew. Chem., Int. Ed.* **2006**, *45*, 3740-3765.
84) Vougioukalakis, G. C.; Grubbs, R. H. "Ruthenium-Based Heterocyclic Carbene-Coordinated Olefin Metathesis Catalysts" *Chem. Rev.* **2010**, *110*, 1746-1787.

product chemists.[85] RCM is driven by entropic forces and is general for 5-membered rings and larger. It has been studied extensively for the formation of α-prolines,[86] spirocyclic α-amino acids[87] and macrocyclization of peptides,[88] but its use for higher-ring order α-substituted prolines is rare.

The *N*-substituents and the α-alkene functional unit present in the α-iminoester addition product described in Scheme 2.1 provide effective precursors for RCM to cyclic analogs. This hypothesis was explored by surveying the various ruthenium based metathesis catalysts (**G-I**, **G-II**, **HG-I**, **HG-II**) with **2.02b**. **HG-II** was found to form the azepine (**2.31**) effectively in 93% yield (Scheme 2.11, left). The catalyst loading and reaction time were relatively high, and microwave conditions were explored (Scheme 2.11, right). Microwave conditions reduced the necessary catalyst loading (10 vs 5 mol %) and shortened reaction time (24 vs 1 h).

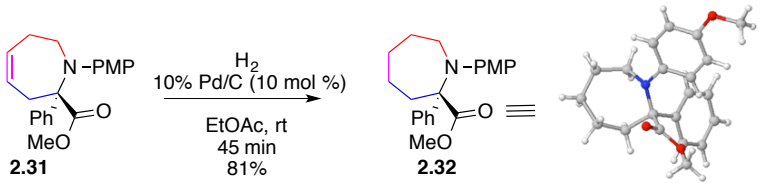
**Scheme 2.11** Synthesis of a higher ring homologue of α-substituted proline.




85) Furstner, A. "Metathesis in total synthesis" *Chem. Commun.* **2011**, *47*, 6505-6511.
86) Calaza, M. I.; Cativiela, C. "Stereoselective Synthesis of Quaternary Proline Analogues" *Eur. J. Org. Chem.* **2008**, 3427-3448.
87) Ple, K.; Haudrechy, A.; Probst, N. P. "Use of the Claisen/metathesis reaction sequence for the synthesis of enantiomerically pure 1-aminocycloalkene-1-carboxylic acids" *Tetrahedron Lett.* **2010**, *66*, 5030-5035.
88) Miller, S. J.; Grubbs, R. H. "Synthesis of Conformationally Restricted Amino Acids and Peptides Employing Olefin Metathesis" *J. Am. Chem. Soc.* **1995**, *117*, 5855-5856.

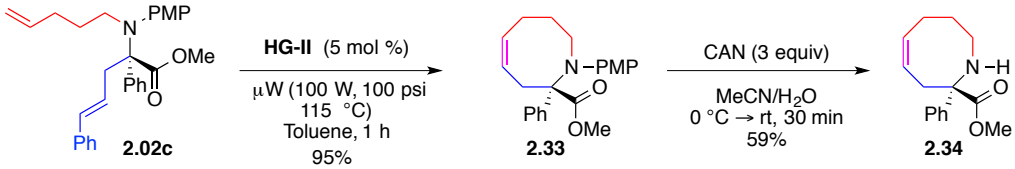
The azepine from RCM was subjected to hydrogenation to generate the higher ring order α-aryl proline **2.32** in 81% yield (Scheme 2.12). This compound was crystalline and could be triturated to produce >95% ee material. X-Ray crystallography was used to determine the absolute configuration of the tandem products from **2.32**.

**Scheme 2.12** Establishing the absolute configuration of tandem products from *N*-alkylation/π-allylation.




The azocine was also desired and formed readily from **HG-II** and microwave conditions (**Scheme 2.13**).[89] The PMP group could be removed in the presence of the alkene, in contrast with the acyclic tertiary *N*-α-allyl-α-aryl α-amino acids (see **Scheme 2.2**). Furthermore, azocine **2.34**, with the alkene moiety, presents an expeditious entry to substituted pyrrolizidines via transannular cyclization.

**Scheme 2.13** RCM to generate azocine.

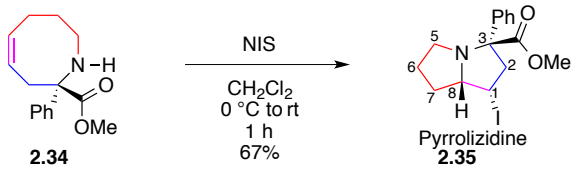



The naturally occurring pyrrolizidine structural motif exists in over 370 natural products, and some molecules in this class have been shown to have toxicity against

89) The corresponding 9-member ring did not form readily.

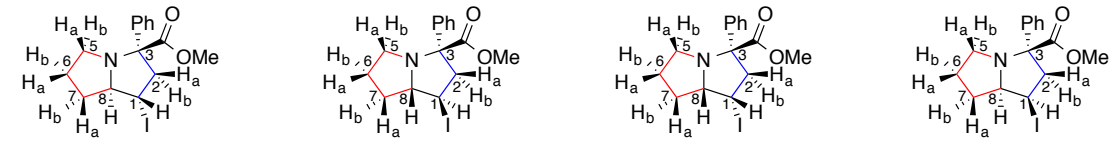
livestock, wildlife and humans.[90] Secondary amine **2.34** is poised to undergo an iodine-induced transannular cyclization,[91] and treatment with NIS led exclusively to cis-iodide **2.35** (Scheme 2.14). Since most naturally occurring pyrrolizidines are substituted at C1, this route offers a labile functional group for further manipulation.[90]

**Scheme 2.14** Transannular cyclization of azocine to α-arly-α-ester pyrrolizidine analogue.




The relative stereochemistry of **2.35** was assigned as (*S,S,S*) by comparing the calculated bond distances and coupling constants of the four potential diasteromers (Figure 2.9) with the NOESY of **2.35** (Figure 2.10). The protons on **2.35** were assigned utilizing the $^{1}$H NMR and 2D NMR (COSY). Splitting of the C1-H (ddd, $J$ = 14, 7.5, 6.5 Hz) matches the predicted cis-iodination products (*S,S,S*) and (*R,S,R*) predicted from our computational studies (Figure 2.9). The NOESY of **2.35** shows that the *ortho*-H of the phenyl ring couples with the C2-$H_a$, C2-$H_b$ and C5-$H_a$ (Figure 2.10, right). The limit for coupling through space is ~3 Å. Comparing (*S,S,S*) and (*R,S,R*) reveals that the observed coupling in the NOESY matches the predicted bond distances for (*S,S,S*). If (*R,S,R*) was produced the *ortho*-H would be expected to couple with C2-$H_b$ and C8-H, which is not observed.

90) Pelletier, S. W. "Alkaloids: Chemical & Biological Perspectives", Vol 9, pp 155-233, Pergamon, New York, **1995**.
91) Wilson, S. R.; Sawicki, R. A. *J. Org. Chem.* **1979**, *44*, 287-291.



(*S,S,R*) (*R,S,S*) (*S,S,S*) (*R,S,R*)

| | Distance | J Value |
|---|---|---|
| C1-H C8-H | 3.109 | 10.3 |
| C1-H C2-$H_a$ | 2.495 | 5.3 |
| C1-H C2-$H_b$ | 3.098 | 11.8 |
| *o*-H-Ph C2-$H_a$ | 2.436 | |
| *o*-H-Ph C2-$H_b$ | 2.886 | |
| *o*-H-Ph C1-H | 4.649 | |
| *o*-H-Ph C5-$H_a$ | 4.048 | |
| *o*-H-Ph C5-$H_b$ | 2.764 | |
| *o*-H-Ph C8-H | 3.647 | |

| | Distance | J Value |
|---|---|---|
| C1-H C8-H | 3.112 | 10.4 |
| C1-H C2-$H_a$ | 3.090 | 11.8 |
| C1-H C2-$H_b$ | 2.520 | 5.2 |
| *o*-H-Ph C2-$H_a$ | 2.730 | |
| *o*-H-Ph C2-$H_b$ | 2.211 | |
| *o*-H-Ph C1-H | 2.244 | |
| *o*-H-Ph C5-$H_a$ | 2.668 | |
| *o*-H-Ph C5-$H_b$ | 3.118 | |
| *o*-H-Ph C8-H | 4.779 | |

| | Distance | J Value |
|---|---|---|
| C1-H C8-H | 2.332 | 7.4 |
| C1-H C2-$H_a$ | 2.471 | 5.2 |
| C1-H C2-$H_b$ | 3.083 | 11.9 |
| *o*-H-Ph C2-$H_a$ | 2.244 | |
| *o*-H-Ph C2-$H_b$ | 2.571 | |
| *o*-H-Ph C1-H | 4.711 | |
| *o*-H-Ph C5-$H_a$ | 2.626 | |
| *o*-H-Ph C5-$H_b$ | 3.263 | |
| *o*-H-Ph C8-H | 4.671 | |

| | Distance | J Value |
|---|---|---|
| C1-H C8-H | 2.330 | 7.4 |
| C1-H C2-$H_a$ | 3.088 | 12.0 |
| C1-H C2-$H_b$ | 2.469 | 5.2 |
| *o*-H-Ph C2-$H_a$ | 3.722 | |
| *o*-H-Ph C2-$H_b$ | 2.385 | |
| *o*-H-Ph C1-H | 3.110 | |
| *o*-H-Ph C5-$H_a$ | 4.582 | |
| *o*-H-Ph C5-$H_b$ | 3.907 | |
| *o*-H-Ph C8-H | 2.586 | |

**Figure 2.9** Calculated bond distances and coupling constants of **2.35**.

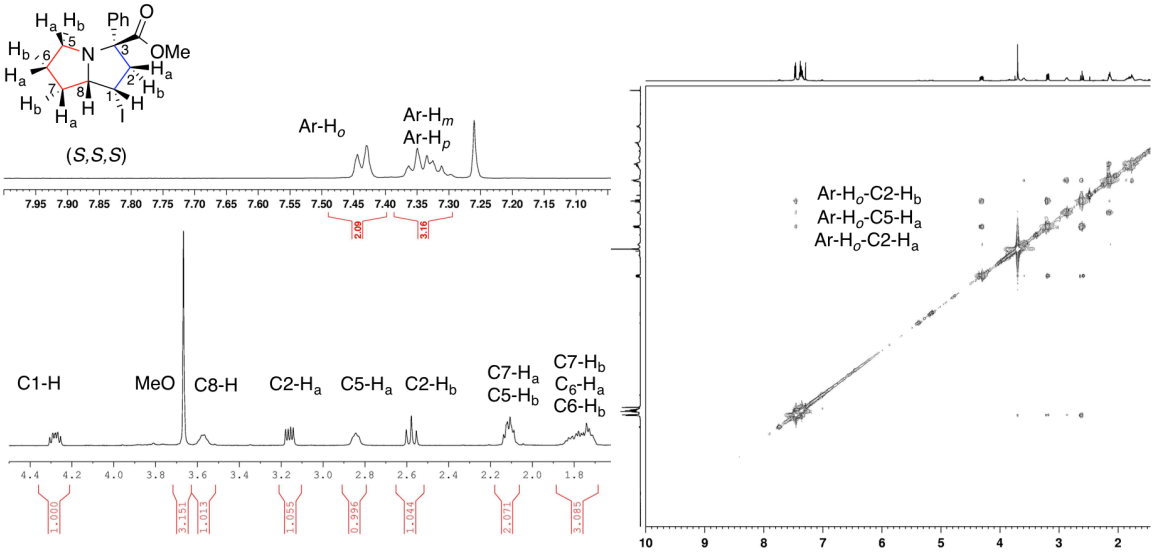



**Figure 2.10** $^1$H NMR and NOESY of **2.35**.

The expected trans-iodide product from formation of the iodonium and transannular cyclization of the amine was not observed (Figure 2.11, *path A*). The cis-iodide is potentially formed from a double inversion type mechanism (*path B* and *path C*), or via a formal syn-addition to the alkene (*path D*).

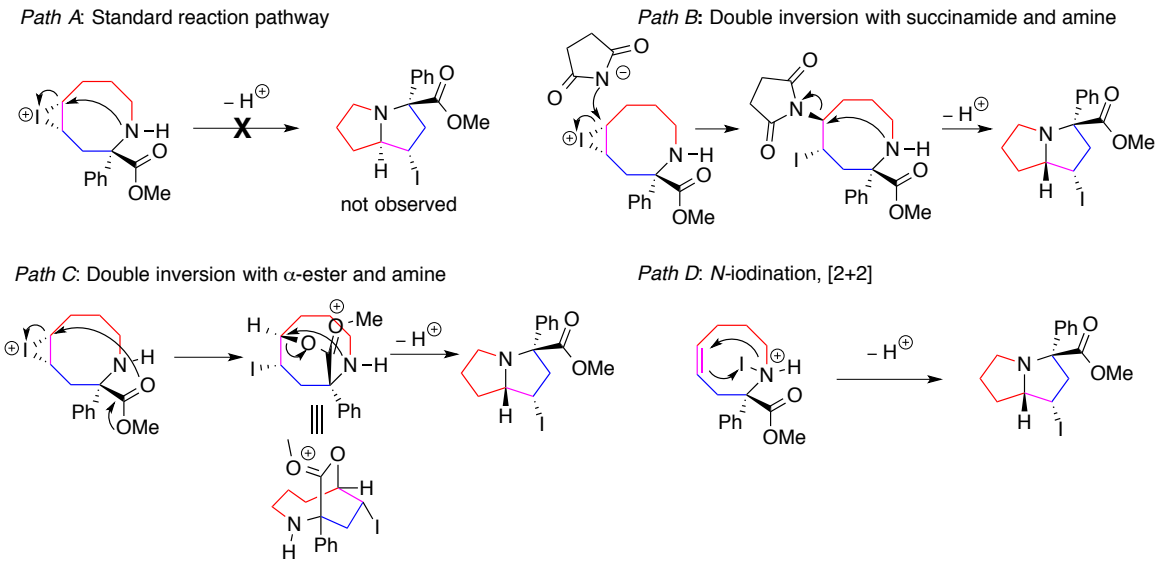



**Figure 2.11** Potential mechanistic pathways for formation of cis-iodide adduct.

The relative stereochemistry of iodine to the β-ester is trans, this configuration is assumed to occur because of steric factors, but the ester could open the iodonium followed by amine displacement (*path C*). The most pragmatic mechanistic proposal is that the azocine undergoes *N*-iodination, followed by a syn addition across the double bond (*path D*).

Carreira and co-workers found that when they treated oxabicyclonorbornene with NIS to form the tricyclic azabicyclononane, the *endo*-iodide was formed exclusively (Figure 2.12).[92] NMR studies of the reaction suggest the oxabicyclonorbornene is transformed immediately to an intermediate with the alkene still present; a tentative assignment of this structure was the *N*-iodo intermediate. It should be noted that the Carreira molecule also has a nearby ester functional group similar to that in our compound (**2.35**).

92) Schindler, C. S.; Stephenson, C. R. J.; Carreira, E. M. "Enantioselective Synthesis of the Core of Banyaside, Suomilide, and Spumigin HKVV" *Angew. Chem., Int. Ed.* **2008**, *47*, 8852-8855.

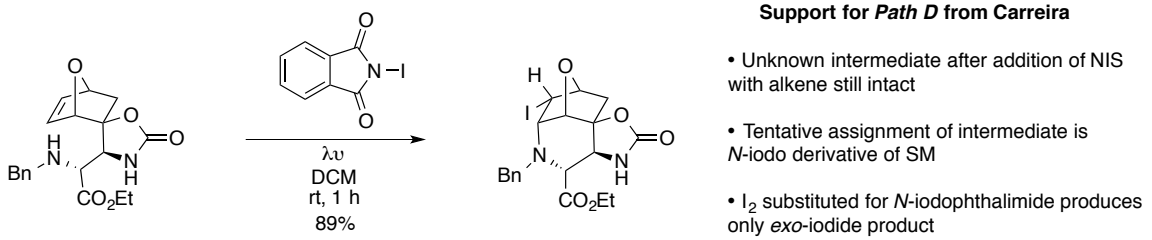



**Figure 2.12** Previous work by Carreira forming *endo*-iodide tricyclic azabicyclononane.

## 2.3. CONCLUSIONS

We demonstrated the tandem α-allyl-α-aryl α-amino acid product from *N*-alkylation/π-allyation could be used to access enantioenriched secondary and primary *N*-α,α-disubstituted α-amino acids. C–N bond cleavage was explored with 2-(trimethylsilyl)ethylamine, allylic amine and homoallylic amine. A novel method for C–N bond cleavage of the homoallyic amine was developed utilizing the Grotjahn catalyst, an alkene zipper, combined with water and acid.

Entry to enantioenriched acylic and cyclic α,α-disubstituted amino acid derivatives by means of cross-metathesis or ring-closing metathesis of the previously disclosed products from asymmetric tandem *N*-alkylation/π-allylation of α-iminoesters was developed. This approach provided rapid entry to homologs of tyrosine and glutamate as well as to higher ring homologues of proline. The eight-membered cyclic α-amino acid was further transformed to the pyrrolizidine natural product backbone in three steps. It was discovered in the synthesis of the pyrrolizidine analog that the transannular cyclization catalyzed by NIS provided a unique cis-iodide product.

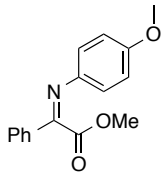
## 2.4. EXPERIMENTAL SECTION

### General Considerations

Unless otherwise stated, all non-aqueous reactions were carried out under an atmosphere of dry argon in dry glassware. All glassware used in three component coupling reactions was base-washed (KOH/i-PrOH) prior to use. When necessary, solvents and reagents were dried prior to use. Tetrahydrofuran, cyclopentyl methyl ether and toluene were distilled from Na/benzophenone prior to use. Organometallic reagents (EtMgBr) were purchased from Aldrich, or made from magnesium turnings/ribbon. Analytical thin layer chromatography (TLC) was performed on Silicycle 250 μm silica-gel F-254 plates.

$^{1}$H NMR and $^{13}$C NMR spectra were recorded on a AM-500 Fourier transform NMR spectrometer at 500 MHz and 125 MHz, respectively. Chemical shifts are reported relative to the solvent resonance peak δ 7.26 ($CDCl_3$) for $^{1}$H and δ 77.16 ($CDCl_3$) for $^{13}$C. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, b = broad singlet, m = multiplet), coupling constants, and number of protons. Time of flight (TOF) high resolution mass spectra were obtained with an ionization mode of either ESI or CI. Infrared spectra are reported in $cm^{-1}$. Melting points were obtained and are uncorrected. Unless otherwise noted, yields refer to isolated material on the basis of product purity ≥95% by $^{1}$H NMR following silica gel chromatography with Silica-P flash silica gel (50-63 μm mesh particle size). Enantiomeric excess was determined utilizing chiral stationary phase (CSP) HPLC or SFC on OD [cellulose tris(3,5-dimethylphenylcarbamate) coated on silica gel] or IA [amylose tris(3,5-dimethylphenylcarbamate) immobilized on silica gel] columns.

Starting materials **2.01** and **2.02a-2.02d** were synthesized following our previous report.[55]

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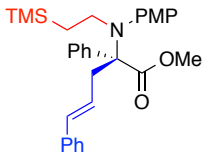
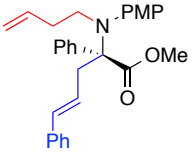
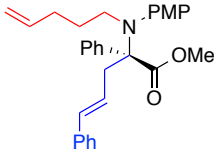


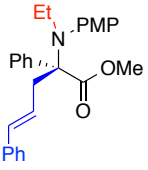

**2.02a**



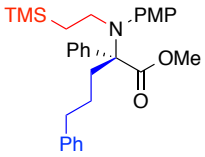

**2.02b**




**2.02c**

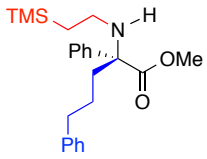



**2.02d**



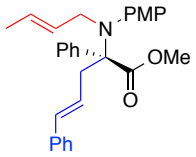

**(*S*)-Methyl 2-((4-methoxyphenyl)(2-(trimethylsilyl)ethyl)amino)-2,5-diphenylpentanoate (2.06). General Procedure A**: A 10 mL round bottom flask was charged with a stir bar and flame dried under vacuum. To the reaction flask was added **2.02a** (50 mg, 0.113 mmol), EtOAc (3.4 mL) and 10% Pd/C (2.4 mg, 0.023 mmol). At ambient temperature the flask was purged with one hydrogen balloon and then subjected to a hydrogen atmosphere with a new hydrogen balloon for 45 min. The flask was opened to air, passed through $SiO_2$ with 30% EtOAc in Hexanes, concentrated *in vacuo* and chromatographed (5% EtOAc in Hexanes) providing **2.06** (46 mg) in 92% yield as an oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, $J$ = 7.4 Hz, 2H), 7.32 (t, $J$ = 7.6 Hz, 2H), 7.28-7.23 (m, 1H), 7.17 (t, $J$ = 7.4 Hz, 2H), 7.11 (d, $J$ = 7.3 Hz, 1H), 7.07 (d, $J$ = 8.9 Hz, 2H), 6.92 (d, $J$ = 7.1 Hz, 2H), 6.85 (d, $J$ = 8.9 Hz, 2H), 3.83 (s, 3H), 3.83 (s, 3H), 2.94 (dt, $J$ = 12.6, 5.4 Hz, 1H), 2.85 (dt, $J$ = 12.5, 5.8 Hz, 1H), 2.31-2.23 (m, 1H), 2.21-2.13 (m, 1H), 1.74 (dt, $J$ = 12.4, 4.8 Hz, 1H), 1.59 (dt, $J$ = 12.2, 4.6 Hz, 1H), 1.29-1.18 (m, 2H), 0.54-0.41 (m, 2H), 0.21 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.7, 157.7, 142.6, 141.7,

139.4, 131.1, 128.4,128.2, 127.8, 127.8, 127.1, 125.6, 113.7, 74.8, 55.5, 51.3, 47.7, 40.1, 36.3, 26.7, 17.9, -1.6; IR (film) 2951, 2925, 1725, 1507, 1246 $cm^{-1}$; HRMS (ESI) calcd for $C_{30}H_{40}NO_3Si$ $[M+H]^+$ *m/z* = 490.2777; found 490.2777; $[\alpha]^{25}_D$ = +103.2 (c 0.25, 82% ee, $CH_2Cl_2$).

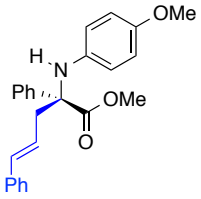



**(*S*)-Methyl 2,5-diphenyl-2-((2-(trimethylsilyl)ethyl)amino)pentanoate (2.07). General Procedure B**: A solution of **2.06** (23 mg, 0.047 mmol) in MeCN (949 µL) was cooled to 0 °C. To this mixture was added a solution of ceric ammonium nitrate (78 mg, 0.141 mmol) in $H_2O$ (475 µL). The mixture went from yellow to purple initially and then brown upon addition. After stirring for 60 min, the mixture was quenched with 5% $NaHCO_3$ until a pH of 9 was obtained (~2 mL). The mixture was diluted with 20% $Na_2SO_3$ (20 mL) and extracted with EtOAc (3 x 25 mL). The combined organic phases were washed with brine (2 x 20 mL), dried over $Na_2SO_4$, and concentrated *in vacuo*. The resulting residue was chromatographed (15% EtOAc in Hexanes). The fractions that stained with $KMnO_4$ ($R_f$ = 0.3) in 20% EtOAc in Hexanes were concentrated to afford product **2.07** (12.5 mg) in 69% yield as an oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.6 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 2H), 7.28-7.20 (m, 3H), 7.15 (t, *J* = 7.4 Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 2H), 3.66 (s, 3H), 2.55 (t, *J* = 7.6, 2H), 2.41-2.25 (m, 2H), 2.13 (dt, *J* = 13.3, 4.5 Hz 1H), 2.00 (dt, *J* = 13.3, 4.5 Hz 1H), 1.72 (b, 1H), 1.59-1.47 (m, 1H), 1.45-1.33 (m, 1H), 0.83-0.68 (m, 2H), -0.013 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 176.0, 142.3, 142.1, 128.5, 128.4, 128.3, 127.4, 126.2, 125.8, 68.6, 52.2, 39.3, 36.0, 34.7, 24.9, 18.8, -1.2; IR (film)

3332, 2951, 1733, 1248 $cm^{-1}$; HRMS (ESI) calcd for $C_{22}H_{34}NO_2Si$ $[M+H]^+$ *m/z* = 384.2359; found 384.2363; $[\alpha]^{25}_D$ = -6.2 (c 0.13, 82% ee, $CH_2Cl_2$).

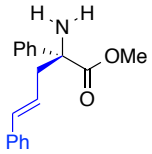



**(*S,E*)-Methyl 2-(((*E*)-but-2-en-1-yl)(4-methoxyphenyl)amino)-2,5-diphenylpent-4-enoate (2.22a).** 2nd Generation, Grubbs catalyst (**G-II**) (6.3 mg, 0.0074 mmol) was added to a flame dried 10 mL round bottom flask equipped with a stir bar and reflux condenser under an argon atmosphere, followed by the addition of vinyloxytrimethylsilane in toluene (0.25 M, 0.742 mmol). After 1 h at 50 °C, **2.02b** in toluene (0.025 M, 0.074 mmol) was added to the reaction mixture. After 15 h at 115 °C, the mixture was cooled, passed through $SiO_2$ with 30% EtOAc in Hexanes, and concentrated *in vacuo*. Purification by column chromatography (pre-wash $SiO_2$ with 5% $NEt_3$ in Hexanes, eluent 5% EtOAc in Hexanes) provided **2.22a.**




**(*S,E*)-Methyl 2-((4-methoxyphenyl)amino)-2,5-diphenylpent-4-enoate (2.23).** Following the modified procedure previously reported by the Grotjahn group for alkene isomerization[71]: An NMR tube equipped with a J Young valve that was kept in an 120 °C oven overnight was brought into the glovebox. **2.02b** (40 mg, 0.09 mmol, 70% ee) was

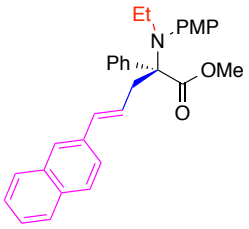
added to the tube via a $d^6$-acetone solution (0.3 M). The Grotjahn catalyst[93] (3 mg, 0.005 mmol) was added via a $d^6$-acetone solution (0.02 M). The NMR tube was sealed and brought out of the glovebox and put under argon via a three-way adapter, allowing for addition of a TFA/$D_2O$ solution in $d^6$-acetone (0.01 mmol of TFA, 0.51 mmol of $D_2O$ in 100 μL $d^6$-acetone, sparged after preparation). The NMR tube was sealed, removed from argon and put in a 70 °C oil bath. The reaction was monitored by $^1$H NMR every 4-5 h. After 24 h no more product was formed, the reaction was transferred with EtOAc, concentrated, passed through Celite with EtOAc and concentrated *in vacuo*. The resultant residue was subjected to chromatography (7% EtOAc in Hexanes) affording **2.23** (26 mg) in 74% yield: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, $J$ = 8.0 Hz, 2H), 7.39 (t, $J$ = 7.5 Hz, 2H), 7.34-7.20 (m, 6H), 6.65 (d, $J$ = 9 Hz, 2H), 6.38 (d, $J$ = 9 Hz, 2H), 6.32 (d, $J$ = 15.9 Hz, 1H), 6.02 (dt, $J$ = 15.8, 7.2 Hz, 1H), 5.00 (b, 1H), 3.70 (s, 3H), 3.69 (s, 3H), 3.36 (d, $J$ = 7.4 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 174.0, 152.5, 140.9, 138.5, 137.3, 134.3, 134.5, 128.8, 128.6, 127.8, 127.5, 127.2, 126.4, 123.9, 117.2, 114.6, 67.2, 55.7, 53.1, 37.6; IR (film) 3403, 1733, 1513, 1447, 1239 $cm^{-1}$; HRMS (ESI) calcd for $C_{25}H_{26}NO_3$ $[M+H]^+$ $m/z$ = 388.1913; found 388.1911; $[\alpha]^{24}_D$ = -61.0 (c 0.67, 70% ee, $CH_2Cl_2$);




**(*S,E*)-Methyl 2-amino-2,5-diphenylpent-4-enoate (2.17a).** General procedure B was followed using **2.23** (22 mg, 0.056 mmol) in MeCN (6.3 mL) and ceric ammonium nitrate (94 mg, 0.17 mmol) in $H_2O$ (3.1 mL). The mixture was allowed to warm to

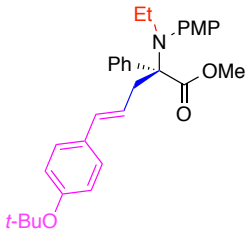
93) The Grotjahn Catalyst, CAS: 930601-66-4, is available from Strem Chemicals, Inc., but was generously provided by the Grotjahn group.

ambient temperature; it went from yellow to blue then purple at rt. The reaction was stirred for 30 min at rt then cooled to 0 °C and quenched. The resulting residue was purified by chromatography (pre-washed $SiO_2$ with 3% $NEt_3$ in Hexanes, eluent 40% EtOAc in Hexanes) providing product **2.17a** (8.7 mg) in 55% yield. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 8 Hz, 2H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.33-7.27 (m, 5H), 7.24-7.20 (m, 1H), 6.54 (d, *J* = 15.9 Hz), 6.12-6.06 (m, 1H), 3.75 (s, 3H), 3.14 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.79 (dd, *J* = 13.8, 8.1 Hz, 1H), 2.00 (b, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 175.8, 142.9, 137.1, 135.1, 128.7, 128.7, 127.8, 127.6, 126.4, 125.5, 124.4, 63.8, 52.8, 44.2; IR (film) 3387, 3323, 3026, 2951, 1731, 1447, 1435, 1214 $cm^{-1}$; HRMS (ESI) calcd for $C_{18}H_{20}NO_2$ $[M+H]^+$ *m/z* = 282.1494; found 282.1493; $[\alpha]^{25}_D$ = -31.3 (c 0.44, 70% ee, $CH_2Cl_2$).



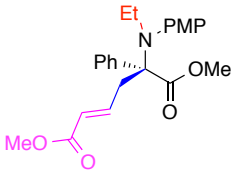

**(*S,E*)-Methyl 2-(*N*-ethyl-*N*-(4-methoxyphenyl)amino)-5-(naphthalene-2-yl)-2-phenylpent-4-enoate (2.02h). General Procedure C:** 2$^{nd}$ Generation, Hoveyda-Grubbs catalyst (**HG-II**) (6.0 mg, 0.0096 mmol) was added to a flame dried 8 mL microwave vial equipped with stir bar in the glove box. 2-Vinylnaphthalene (22 mg, 0.15 mmol) was added followed by **2.02d** (20 mg, 0.048 mmol) in 1,2-dichloroethane (482 µL). The vial was sealed with a Teflon cap, taken out of the glovebox, placed in a 70 °C oil bath and stirred for 20 h. The mixture was cooled, passed through $SiO_2$ with 30% EtOAc in Hexanes, and concentrated *in vacuo*. Purification by column chromatography (pre-wash

$SiO_2$ with 5% $NEt_3$ in hexanes, eluent 7% EtOAc in hexanes) provided **2.02h** (15 mg) in 68% yield as a yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 12.0, 4.0 Hz, 2H), 7.66 (d, *J* = 8.6 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 2H), 7.42-7.33 (m, 5H), 7.29 (t, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.02 (d, *J* = 16.0 Hz, 1H), 5.84 (dt, *J* = 16.0, 7.1 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.08-3.01 (m, 1H), 2.98-2.92 (m, 1H), 2.66 (dd, *J* = 14.0, 7.2 Hz, 1H), 2.47 (dd, *J* = 13.6, 7.5 Hz, 1H), 0.82 (t, *J* = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.4, 157.9, 141.6, 139.2, 135.4, 133.7, 133.1, 132.7, 131.3, 128.0, 127.9 (3), 127.7, 127.4, 126.6, 126.2, 125.6, 125.5, 123.7, 113.9, 75.2, 55.5, 51.5, 46.7, 44.6, 14.7; IR (film) 2924, 2853, 1725, 1507 cm$^{-1}$; HRMS (ESI) calcd for $C_{31}H_{32}NO_3$ $[M+H]^+$ *m/z* = 466.2382; found 466.2399; $[\alpha]^{25}_D$ = +125.5 (c 0.21, 81% ee, $CH_2Cl_2$).



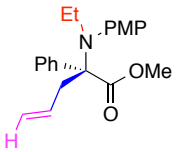

**(*S*,*E*)-Methyl 2-(*N*-ethyl-*N*-(4-methoxyphenyl)amino)-5-(4-(*tert*-butoxy)phenyl)-2-phenylpent-4-enoate (2.02i).** General procedure C was followed using **2.02d** (20 mg, 0.048 mmol, 88% ee), 4-*tert*-butoxystyrene (85 mg, 0.48 mmol) and **HG-II** (6.0 mg, 0.0096 mmol) in toluene (482 μL) at 90 °C for 20 h. Purification by column chromatography (pre-wash $SiO_2$ with 5% $NEt_3$ in hexanes, eluent 3% acetone in hexanes) provided **2.02i** (17 mg) in 74% yield as a yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.4 Hz, 2H), 7.35 (t, *J* = 7.1 Hz, 2H), 7.29 (d, *J* = 7.0 Hz, 1H), 7.14 (d, *J* = 8.8 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.4 Hz, 2H), 5.86 (d,

$J$ = 15.7 Hz, 1H), 5.58 (dt, $J$ = 15.9, 7.3 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.06-2.99 (m, 1H), 2.96-2.91 (m, 1H), 2.60 (dd, $J$ = 13.9, 7.4 Hz, 1H), 2.41 (dd, $J$ = 13.9, 7.4 Hz, 1H), 1.31 (s, 9H), 0.81 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.2, 157.8, 154.5, 141.6, 139.1, 133.2, 132.4, 131.3, 127.9, 127.8, 127.3, 126.5, 124.7, 124.1, 113.8, 78.6, 75.1, 55.5, 51.5, 46.6, 44.3, 29.0, 14.7; IR (film) 2975, 2855, 1725, 1604, 1507, 1241, 1162 cm$^{-1}$; HRMS (ESI) calcd for $C_{31}H_{38}NO_4$ $[M+H]^+$ $m/z$ = 488.2801; found 488.2811; $[\alpha]^{25}_D$ = +170.1 (c 0.13, 88% ee, $CH_2Cl_2$).

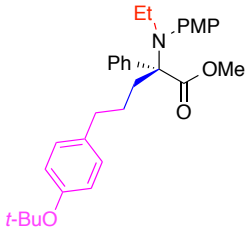



**(*S*,*E*)-Dimethyl 5-(*N*-ethyl-*N*-(4-methoxyphenyl)amino)-5-phenylhex-2-enedioate (2.02j).** General procedure C was followed using **2.02d** (20 mg, 0.048 mmol), methyl acrylate (42 mg, 0.48 mmol) and **HG-II** (6.0 mg, 0.0096 mmol) in toluene (482 μL) at 90 °C for 20 h. Purification by column chromatography (pre-wash $SiO_2$ with 5% $NEt_3$ in hexanes, eluent 3% acetone in hexanes) provided **2.02j** (14 mg) in 72% yield as a yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, $J$ =7.5 Hz, 2H), 7.34 (t, $J$ = 7.4 Hz, 2H), 7.28 (t, $J$ = 7.2 Hz, 1H), 7.10 (d, $J$ = 8.9 Hz, 2H), 6.86 (d, $J$ = 8.9 Hz, 2H), 6.61-6.55 (m, 1H), 5.32 (d, $J$ = 16.5 Hz, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.60 (s, 3H), 3.05-2.98 (m, 1H), 2.95-2.88 (m, 1H), 2.57 (ddd, $J$ = 14.5, 7.3, 0.6 Hz, 1H), 2.43 (ddd, $J$ = 14.4, 7.6, 0.6 Hz, 1H), 0.79 (t, $J$ = 7.0 Hz, 3H);$^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.2, 166.8, 158.1, 145.1, 140.9, 138.9, 131.2, 128.2, 127.7, 127.4, 123.2, 114.0, 74.5, 55.5, 51.7, 51.4, 46.8, 43.7, 14.7; IR (film) 2951, 2855, 1724, 1655, 1508, 1245, 1035 cm$^{-1}$; HRMS (ESI) calcd for

$C_{23}H_{28}NO_5$ $[M+H]^+$ *m/z* = 398.1967; found 398.1963; $[\alpha]^{20}_D$ = +107.2 (c 0.13, 88 % ee, $CH_2Cl_2$).

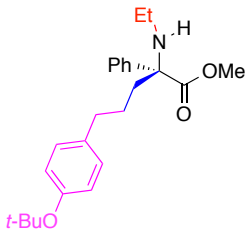



**(*S*,*E*)-Methyl 2-(*N*-ethyl-*N*-(4-methoxyphenyl)amino)-2-phenylpent-4-enoate (2.02f).** General procedure C was followed using **2.02d** (20 mg, 0.0482 mmol) and **HG-II** (8.2 mg, 0.0096 mmol) in dichloroethane (482 µL) and the following modification: ethylene gas was sparged through the flask for 10 min and then subjected to µW (100 W, 100 psi, 90 °C) conditions for 30 min. The mixture was cooled and ethyl vinyl ether (50 µL, 0.523 mmol) was added and stirred for 30 min. The mixture was passed through $SiO_2$ with 30% EtOAc in hexanes and concentrated *in vacuo*. Purification by column chromatography (pre-wash $SiO_2$ with 5% $NEt_3$ in hexanes, eluent 5% EtOAc in hexanes) provided **2.02f** (3.9 mg) in 24% yield (spectral data agreed with our previous report[55]) with unreacted **2.02d** (15 mg, 0.036 mmol) recovered.



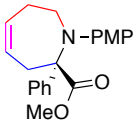

**(*S*)-Methyl 2-(*N*-ethyl-*N*-(4-methoxyphenyl)amino)-5-(4-(*tert*-butoxy)phenyl)-2-phenylpentanoate (2.29).** General procedure A was followed using **2.02i** (17 mg, 0.035 mmol), 10% Pd/C (3.7 mg, 0.0035 mmol) and EtOAc (1.1 mL). Purification by column chromatography (10% EtOAc in Hexanes) provided **2.29** (14.4 mg) in 85% yield as a

colorless oil: $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.7 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.07 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 6.77 (b, 4H), 3.83 (s, 3H), 3.01-2.83 (m, 2H), 2.25-2.19 (m, 1H), 2.15-2.09 (m, 1H), 1.72-1.66 (m, 1H), 1.56-1.50 (m, 1H), 1.29 (s, 9H), 1.28-1.25 (b, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.5, 157.8, 153.1, 141.9, 139.3, 137.3, 131.1, 128.6, 127.9, 127.8, 127.1, 124.0, 113.8, 78.1, 74.5, 55.5, 51.3, 46.6, 40.1, 35.5, 29.0, 26.6, 14.7; IR (film) 3337, 2974, 2930, 1724, 1507, 1241, 1162 $cm^{-1}$; HRMS (ESI) calcd for $C_{31}H_{40}NO_4$ $[M+H]^+$ *m/z* = 490.2957; found 490.2947; $[\alpha]^{25}_D$ = +67.9 (c 0.11, 88% ee, $CH_2Cl_2$).

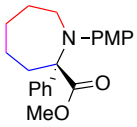



**(*S*)-Methyl 2-(ethylamino)-5-(4-(*tert*-butoxy)phenyl)-2-phenylpentanoate (2.30).** General procedure B was followed using a solution of **2.29** (15 mg, 0.031 mmol) in MeCN (618 μL) and ceric ammonium nitrate (51 mg, 0.092 mmol) in $H_2O$ (309 μL). The mixture was allowed to warm to ambient temperature, stirred for 45 min, cooled to 0 °C and quenched. Purification by column chromatography (5% to 30% EtOAc in Hexanes) provided **2.30** (7.5 mg) in 64% yield as a colorless oil: $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.27-7.25 (m, 1H), 6.99 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 3.66 (s, 3H), 2.52 (t, *J* = 7.5 Hz, 2H), 2.32-2.24 (m, 2H), 2.18-2.12 (m, 1H), 2.06-1.97 (m, 1H), 1.54-1.39 (m, 2H), 1.31 (s, 9H), 1.09 (t, *J* = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 175.8, 153.2, 142.0 (b), 137.3, 128.8, 128.4, 127.4, 126.2, 124.2, 78.2, 68.4, 52.4, 37.6, 35.3, 34.4, 29.0, 25.0, 15.8; IR (film) 2965,

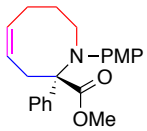
2928, 1733, 1607, 1505, 1234 $cm^{-1}$; HRMS (ESI) calcd for $C_{24}H_{34}NO_3$ $[M+H]^+$ *m/z* = 384.2539; found 384.2547; $[\alpha]^{24}_D$ = -1.5 (c 0.36, 88% ee, $CH_2Cl_2$).




**(*S*)-Methyl 1-(*N*-(4-methoxyphenyl))-2-phenyl-3,6,7-hexahydro-1*H*-azepine-2-carboxylate (2.31). General procedure D**: A 8 mL microwave vial equipped with stir bar was flamed dried under vacuum. The flask was sealed with a septa, put under argon, and catalyst **HG-II** (2.82 mg, 0.003 mmol) and **2.02b** (29 mg, 0.066 mmol, 81% ee) in toluene (6 mL) were added. The septa was replaced with a microwave cap and the vial was subjected to μW (100 W, 100 psi, 115 °C) conditions for 1 h. The mixture was allowed to cool to ambient temperature and ethyl vinyl ether (75 uL, 0.784 mmol) was added and allowed to stir for 30 min to quench catalyst **HG-II.** Upon completion, the mixture was passed through $SiO_2$ with 30% EtOAc in Hexanes, concentrated *in vacuo* and chromatographed (pre-wash $SiO_2$ with 5% $NEt_3$ in Hexanes, eluent 5% EtOAc in Hexanes) to provide **2.31** (23 mg) in >98% yield as a light yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, *J* = 7.6 Hz, 2H), 7.27-7.24 (m, 2H), 7.21-7.18 (m, 1H), 6.63-6.61 (m, 2H), 6.56-6.54 (m, 2H), 5.72-5.68 (m, 1H), 5.41-5.37 (m, 1H), 4.11-4.05 (m, 1H), 3.90-3.85 (m, 1H), 3.68 (s, 3H), 3.63 (s, 3H), 3.23 (dd, *J* = 15.8, 6.2 Hz, 1H), 2.88 (dd, *J* = 16.0, 6.7 Hz, 1H), 2.67-2.55 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 175.2, 152.0, 143.6, 141.3, 131.4, 128.2, 127.8, 126.9, 123.3, 118.0, 113.8, 74.6, 55.6, 52.3, 47.8, 40.6, 32.9; IR (film) 2949, 1729, 1512, 1246, 1037 $cm^{-1}$; HRMS (ESI) calcd for $C_{21}H_{24}NO_3$ $[M+H]^+$ *m/z* = 338.1756; found 338.1755; $[\alpha]^{25}_D$ = +37.9 (c 0.25, 81% ee, $CH_2Cl_2$).

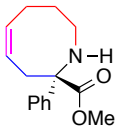



**(*S*)-Methyl 1-(*N*-(4-methoxyphenyl))-2-phenylazepane-2-carboxylate (2.32).** General procedure A was followed using **2.31** (0.033 M ethyl acetate solution, 0.20 mmol) and 10% Pd/C (22 mg, 0.020 mmol). Purification by column chromatography (pre-wash $SiO_2$ with 3% $NEt_3$ in Hexanes, eluent 6% EtOAc in Hexanes) provided **2.32** (55 mg) in 81% yield as a white solid. Trituration of **2.32** in $CH_2Cl_2$ provided undissolved white solid that was close to racemic and liquid that had enhanced ee to 98%. The liquid was concentrated and recrystallized from $Et_2O$ via slow evaporation over 24 h. mp (98% ee material) = 113-110 °C. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, *J* = 7.6 Hz, 2H), 7.29-7.26 (m, 2H), 7.22 (t, *J* = 7.1 Hz, 1H), 6.65-6.63 (m, 2H), 6.54-6.52 (m, 2H), 3.75-3.70 (m, 4H), 3.59 (s, 3H), 3.53 (dd, *J* = 15.6, 8.8 Hz, 1H), 2.61 (dd, *J* = 15.4, 8.9 Hz, 1H), 2.08 (dd, *J* = 15.1, 10 Hz, 1H), 1.96-1.93 (b, 1H), 1.88-1.84 (b, 2H), 1.72-1.69 (b, 1H), 1.63-1.60 (b, 1H), 1.50-1.41 (b, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 175.4, 151.8, 145.1, 141.1, 128.8, 127.9, 126.9, 117.0, 113.8, 72.2, 55.7, 52.4, 51.6, 44.8, 31.0, 29.7, 23.6; IR (film) 2929, 2855, 1731, 1511, 1246, 1222, 1036, 823 cm$^{-1}$; HRMS (ESI) calcd for $C_{21}H_{26}NO_3$ $[M+H]^+$ *m/z* = 340.1913; found 340.1926; $[\alpha]^{25}_D$ = -7.1 (c 0.34, 98% ee, $CH_2Cl_2$).



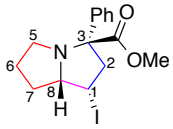

**(*S*,*Z*)-Methyl 1-(*N*-(4-methoxyphenyl))-2-phenyl-3,6,7,8-octahydro-1*H*-azocine-2-carboxylate (2.33).** General procedure D was followed using **2.02c** (30 mg, 0.066 mmol)

and **HG-II** (2.82 mg, 0.003 mmol) in toluene (6 mL). Purification by column chromatography (pre-wash $SiO_2$ with 5% $NEt_3$ in hexanes, eluent 5% EtOAc in Hexanes) provided **2.33** (22 mg) in 95% yield as a light yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.34 Hz, 2H), 7.29-7.26 (m, 2H), 7.20 (t, *J* = 7.0 Hz, 1H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.70 (d, *J* = 8.3 Hz, 2H), 5.92-5.87 (m, 1H), 5.72-5.67 (m, 1H), 3.72 (s, 3H), 3.60-3.50 (m, 1H), 3.43 (s, 3H), 3.35-3.30 (m, 2H), 3.27-3.15 (b, 1H), 2.11-2.03 (m, 1H), 2.03-1.93 (b, 1H), 1.92-1.77 (b, 1H), 1.58-1.44 (b, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 174.2, 152.7, 142.5, 140.7, 132.9, 128.8, 128.0, 127.5, 127.4, 121.1 (b), 113.7, 75.4, 55.5, 52.4, 48.3, 33.6, 29.1, 24.1; IR (film) 3021, 2860, 1728, 1511, 1244, 1038 cm$^{-1}$; HRMS (ESI) calcd for $C_{22}H_{26}NO_3$ $[M+H]^+$ *m/z* = 352.1913; found 352.1923; $[\alpha]^{24}_D$ = -1.03 (c 0.33, 83% ee, $CH_2Cl_2$).




**(*S*,*Z*)-Methyl 2-phenyl-3,6,7,8-octahydro-1*H*-azocine-2-carboxylate (2.34).** General procedure B was followed using **2.33** (10 mg, 0.029 mmol), CAN (50 mg, 0.086 mmol), MeCN (3.2 mL) and $H_2O$ (1.6 mL). The mixture was allowed to stir at ambient temperature for 15 min then cooled to 0 °C and quenched. Purification by column chromatography (pre-wash $SiO_2$ with 3% $NEt_3$ in Hexanes, eluent 5% to 30% EtOAc in Hexanes) provided **2.34** (4 mg) in 59% yield as a yellow oil. The reaction did not scale up well so it was more effective to run multiple reactions with the scale indicated above side-by-side and then combine the material for purification. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.8 Hz, 2H), 7.34 (t, *J* = 7.7 Hz, 2H), 7.28-7.27 (m, 1H), 5.98-5.93 (m, 1H), 5.55-5.50 (m, 1H), 3.67 (s, 3H), 3.06-3.01 (m, 1H), 2.87-2.78 (b, 1H), 2.76-2.72 (m, 1H),

2.69-2.57 (b, 1H), 2.22-2.15 (m, 2H), 1.69-1.63 (m, 1H), 1.60-1.51 (m, 1H), 1.3 (b, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 175.0, 142.3, 134.3, 128.5, 127.6, 126.8, 126.3, 70.0, 52.6, 44.5, 35.0, 32.2, 26.0; IR (film) 3419, 2924, 1731, 1645, 1220, 1032 cm$^{-1}$; HRMS (ESI) calcd for $C_{15}H_{20}NO_2$ $[M+H]^+$ *m/z* = 246.1494; found 246.1497; $[\alpha]^{25}_D$ = -4.8 (c 0.09, 90% ee, $CH_2Cl_2$).




**(*S*)-Methyl 1-iodo-3-phenyloctahydro-1*H*-pyrrolizine-3-carboxylate (2.35).** A solution of **2.34** (23 mg, 0.094 mmol) in $CH_2Cl_2$ (1 mL) open to air was cooled to 0 °C in a flame dried 5 mL round bottom flask equipped with stirbar. NIS (freshly recrystallized from dichloromethane, 42 mg, 0.19 mmol) was added. The mixture was warmed to ambient temperature and stirred for 1.5 h. At 0 °C, the mixture was quenched with 500 μL of 10% aq $Na_2S_2O_3$. The mixture was diluted with $H_2O$ (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (pre-wash $SiO_2$ with 5% $NEt_3$ in hexanes, gradient eluent 5% to 30% EtOAc in hexanes) provided **2.35** (23 mg) in 67% yield as a light yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 7.0 Hz, 2H), 7.36-7.30 (m, 3H), 4.27 (ddd, *J* = 14, 7.5, 6.5 Hz, 1H, C1-H), 3.65 (s, 3H), 3.60-3.52 (b, 1H, C8-H), 3.16 (dd, *J* = 12.3, 6.1 Hz, 1H, C2-$H_a$), 2.88-2.80 (b, 1H, C5-$H_a$), 2.58 (t, *J* = 12.0 Hz, 1H, C2-$H_b$), 2.14-2.09 (m, 2H, C7-$H_a$, C5-$H_b$), 1.87-1.71 (m, 3H, C7-$H_b$, C6-$H_a$, C6-$H_b$); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 173.8, 137.4, 128.6, 128.2, 127.6, 77.2, 66.2, 58.1, 53.2, 52.2, 42.1, 36.7, 25.5; IR (film) 2949, 2868, 1741, 1725, 1448, 1251 cm$^{-1}$;

HRMS (ESI) calcd for $C_{15}H_{19}NO_2I$ $[M+H]^+$ *m/z* = 372.0461; found 372.0450; $[\alpha]^{25}_D$ = +8.2 (c 0.58, 90% ee, $CH_2Cl_2$).

# 3. THE DEVELOPMENT OF THE ASYMMETRIC SPIROCYCLIZATION OF ALLENYL KETONES WITH A CHIRAL LEWIS ACID LIBRARY

## 3.1. REACTION DEVELOPMENT WITH HIGH-THROUGHPUT EXPERIMENTATION

Chemical methods development has increasingly relied on systematic evaluation of catalysts and other variables including solvent, temperature, and supporting ligands. High-throughput experimentation (HTE) is an important tool to expedite this process by quickly screening conditions and identifying important trends. In 2010, the Penn Merck High-Throughput Experimentation Center was established. Our research group has increasingly used the HTE Center to support reaction development (Figure 3.1).[55,94]

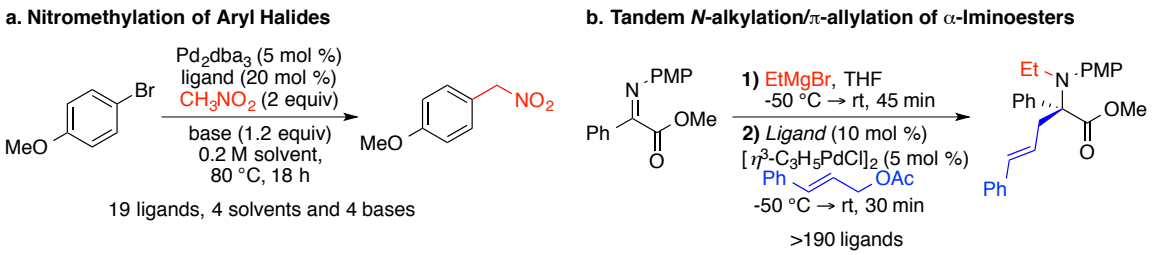



**Figure 3.1** Reaction development with the aid of HTE.

We primarily use HTE when a reaction is established and ligand, temperature, solvent and additives are explored for reaction optimization. An alternative use of HTE would be to identify a class of catalysts and test it on many reactions. This route has been successfully applied for selective-oxidative homo-coupling of phenols by my co-worker

94) Walvoord, R. R.; Berritt, S.; Kozlowski, M. C. "Palladium-Catalyzed Nitromethylation of Aryl Halides: An Orthogonal Formylation Equivalent" *Org. Lett.* **2012**, *14*, 4086-4089.

Young Eun Lee (Figure 3.2).[95] Few non-enzymatic catalytic systems have been reported for the oxidative coupling of phenols but many exist for 2-naphthols. Selective phenol coupling is challenging especially compared to 2-naphthol coupling because phenols are not oxidized as easily and a diverse product mixture is typically seen because of the similar stabilities of the different radical resonance forms.

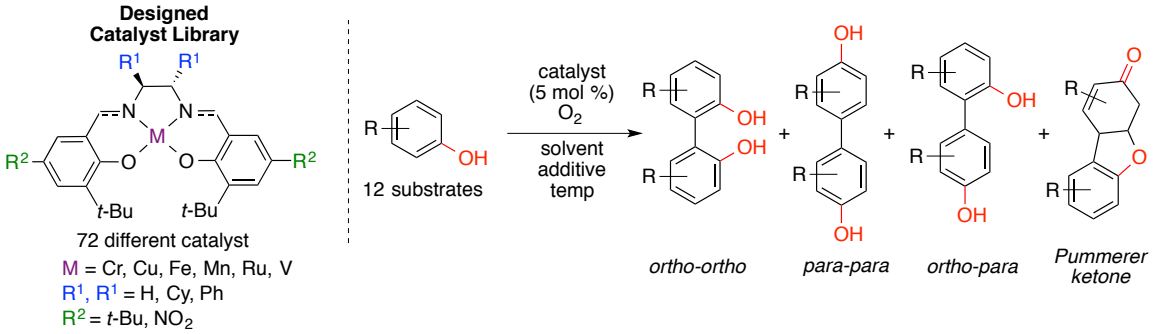



**Figure 3.2** Selective phenol coupling (Ref. 95).

Young and co-workers developed a catalyst library consisting of 72 different catalysts (Figure 3.2, left) and desired to establish conditions for selective formation of each of the four possible homo-coupling isomers (Figure 3.2, right). The additional variables of solvent and additives as well as second-generation catalysts would have resulted in an insurmountable number of reactions to conduct at the bench, but HTE enabled this challenging problem to be solved.

This original work from our group has inspired the exploration of other catalyst libraries to enable reaction development. Ongoing efforts include the high-throughput synthesis of novel, achiral mono-phosphine ligands, and chiral, enantioenriched

95) Lee, Y. E.; Cao, T.; Toruellas, C.; Kozlowski, M. C. "Selective Oxidative Homo- and Cross-Coupling of Phenols with Aerobic Catalysts" *J. Am. Chem. Soc.* **2014**, *136*, 6782-6785.

hydrogen-bond catalysts.[96] A catalyst library of chiral Lewis acids was envisioned that could be synthesized and screened with various reactants.

## 3.2. CHIRAL LEWIS ACIDS

### *3.2.1. Background*

In the *Encyclopedia of Reagents for Organic Synthesis* edited by Paquette, the reagent function index lists the metals in Figure 3.3 as being used as Lewis acid reagents.[97] Since Paquette's publication, Re, Ru, Au, Ga, In, Sc and other lanthanides can be added to this diverse group of elements. Classically, Friedel-Crafts reactions, ene reactions, Diels-Alder reactions, and Mukaiyama-aldol syntheses are catalyzed with Lewis acids such as $AlCl_3$, $TiCl_4$, $BF_3 \bullet OEt_2$ or $SnCl_4$. With the advent of chiral ligands, a Lewis acid can exhibit substantial new reactivity with profound stereoselectivity. Thus, metal ligand tuning is the most essential component in the design of chiral Lewis acid reagents.[98]

96) The phosphine ligand library is being developed by Houng Kang and the hydrogen-bond catalyst library by Alison E. Metz.
97) Paquette, L. A. (ed.) *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, Chichester, New York, Brisbane, Toronto, Singapore, **1995**.
98) Yamamoto, H. (ed.) *Lewis Acid Reagents A Practical Approach*, Oxford University Press Inc., New York, **1999**.

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | | | | | | | | | |
| Li | | | | | | | | | | | | B | | | | | |
| | Mg | | | | | | | | | | | Al | Si | P | S | | |
| | | | Ti | V | | | Fe | Co | Ni | Cu | Zn | | Ge | | | | |
| | | | Zr | | Mo | | | | Pd | Ag | Cd | | Sn | Sb | | | |
| | | La | Hf | | | | | | | | | Tl | | | | | |
| | | | | | | | | | | | | | | | | | |
| | | | | Ce | | | | | Eu | | | | | | | Yb | |

**Figure 3.3** Known Lewis acidic elements (Ref. 97).

Lewis acid reagents can react in two distinct modes (Figure 3.4). *Mode A* involves the complex between substrate and Lewis acid to rearrange to produce the product. An example of *Mode A* is the Claisen rearrangement. *Mode B* involves the formation of a stable complex from Lewis acid and substrate; this complex can react with a variety of reagents from outside the system to form the product. An example of *Mode B* is the intermolecular Diels-Alder reaction.

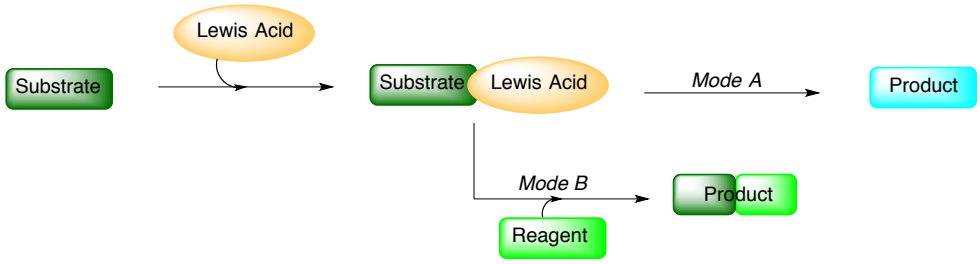



**Figure 3.4** Modes of reactivity for Lewis acid reagents.

An in-depth review of the literature on asymmetric transformations of *Mode B* reveals a considerable amount of work on reactions involving substrates with two Lewis basic sites. Lewis acid reagents that show a preference for two-point binding include Mg, Sc and late-transition metals.

Boron, aluminum and tin complexes with chiral, enantioenriched ligands have demonstrated the most promise for asymmetric transformations on substrates with a single Lewis basic site (Figure 3.5).[99,100,101,102,103,104,105,106,107,108,109] The catalysts shown have been used for Diels-Alder reactions, Mukaiyama-aldols/-1,4-additions, and Morita-Baylis-Hilman reactions.

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99) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. "Asymmetric Hetero-Diels-Alder Reaction Catalyzed by Chiral Organoaluminum Reagent" *J. Am. Chem. Soc.* **1988**, *110*, 310-312.

100) Ketter, A.; Glahsi, G.; Hermann, R. "Asymmetric Diels-Alder reaction of cyclopentadiene and methyl acrylate catalyzed by chiral Lewis acids" *J. Chem. Res. (S)* **1990**, *9*, 278-279.

101) Corey, E. J.; Imwinkerlried, R.; Pikul, S.; Xiang, Y. B. "Practical Enantioselective Diels-Alder and Aldol Reactions Using a New Chiral Controller System" *J. Am. Chem. Soc.* **1989**, *111*, 5493-5495.

102) Maruoka, K.; Saito, S.; Yamamoto, H. "Molecular Design of a Chiral Lewis Acid for the Asymmetric Claisen Rearrangement" *J. Am. Chem. Soc.* **1995**, *117*, 1165-1166.

103) Mukaiyama, T.; Kobayashi, S.; Uchiro, H.; Shiina, I. "Catalytic Asymmetric Aldol Reaction of Silyl Enol Ethers with Aldehydes by the Use of Chiral Diamine Coordinated Tin(II) Triflate" *Chem. Lett.* **1990**, 129-132.

104) Hawkins, J. M.; Loren, S. "Two-Point-Binding Asymmetric Diels-Alder Catalysts: Aromatic Alkyldichloroboranes" *J. Am. Chem. Soc.* **1991**, *113*, 7794-7795.

105) Furuta, K.; Miwa, Y.; Iwanaga, K.; Yamamoto, H. "Acyloxyborane: An Activating Device for Carboxylic Acids" *J. Am. Chem. Soc.* **1988**, *110*, 6254-6255.

106) Corey, E. J.; Cywin, C. L.; Roper, T. D. "Enantioselective Mukaiyama-Aldol and Aldol-Dihydropyrone Annulation Reactions Catalyzed by a Tryptophan-Derived Oxazaborolidine" *Tetrahedron Lett.* **1992**, *33*, 6907-6910.

107) Hayashi, Y.; Rohde, J. J.; Corey, E. J. "A Novel Chiral Super-Lewis Acidic Catalyst for Enantioselective Synthesis" *J. Am. Chem. Soc.* **1996**, *118*, 5502-5503.

108) For Brønsted Acid assisted Lewis Acid (BLA), see: Payette, J. N.; Yamamoto, H. "Regioselective and Asymmetric Diels-Alder Reaction of 1- and 2-Substituted Cyclopentadienes Catalyzed by a Brønsted Acid Activated Chiral Oxazaborolidine" *J. Am. Chem. Soc.* **2007**, *129*, 9536-9537. For Lewis acid assisted Lewis Acid (LLA), see: Futatsugi, K.; Yamamoto, H. "Oxazaborolidine-Derived Lewis Acid Assisted Lewis Acid as a Moisture-Tolerant Catalyst for Enantioselective Diels-Alder Reactions" *Angew. Chem., Int. Ed.* **2005**, *44*, 1484-1487.

109) For BLA, see: Corey, E. J.; Shibata, T.; Lee, T. W. "Asymmetric Diels-Alder Reactions Catalyzed by a Triflic Acid Activated Chiral Oxazaborolidine" *J. Am. Chem. Soc.* **2002**, *124*, 3808-3809. For LLA, see: Liu, D.; Canales, E.; Corey, E. J. "Chiral Oxazaborolidine-Aluminum Bromide Complexes Are Unusually Powerful and Effective Catalysts for Enantioselective Diels-Alder Reactions" *J. Am. Chem. Soc.* **2007**, *129*, 1498-1499.

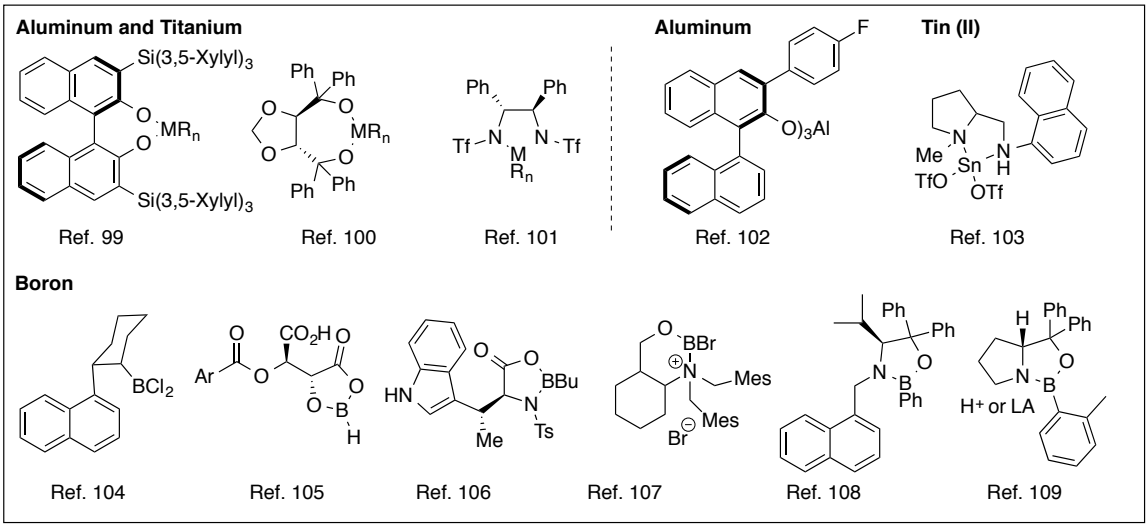



**Figure 3.5** Chiral Lewis acid reagents with affinity for single Lewis basic substrates.

Jacobsen has conducted a significant amount of work with salen ligands with Cr, Co, Al, Mn and Ti, including the enantioselective opening of epoxides and alkylation of tin-enolates.[110] Evans[111] and Franz[112] have demonstrated that PYBOX catalysts can be combined with various lanthanides to catalyze nucleophilic additions to carbonyls. With this significant body of work, we designed a chiral Lewis acid library for monodentate substrates.

110) (a) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. "Highly Selective Hydrolytic Kinetic Resolution of Terminal Epoxides Catalyzed by Chiral (salen)$Co^{III}$ Complexes. Practical Synthesis of Enantioenriched Terminal Epoxides and 1,2-Diols" *J. Am. Chem. Soc.* **2002**, *124*, 1307-1315. (b) Doyle, A. G.; Jacobsen, E. N. "Enantioselective Alkylations of Tributyltin Enolates Catalyzed by Cr(salen)Cl: Access to Enantiomerically Enriched All-Carbon Quaternary Centers" *J. Am. Chem. Soc.* **2004**, *127*, 62-63.

111) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. "Enantioselective Indole Friedel-Crafts Alkylations Catalyzed by Bis(oxazolinyl)pyridine-Scandium(III) Triflate Complexes" *J. Am. Chem. Soc.* **2003**, *125*, 10780-10781.

112) Gutierrez, E. G.; Wong, C. J.; Sahin, A. H.; Franz, A. K. "Enantioselective and Regioselective Indium(III)-Catalyzed Addition of Pyrroles to Isatins" *Org. Lett.* **2011**, *13*, 5754-5757.

*3.2.2. Synthesis of a Chiral Lewis Acid Library*

After a careful survey of the literature (see above), the following library was generated for HTE (Figure 3.6). Seven 24 well plates were obtained from dichloromethane solutions of oxazaborolidine (CBS), TADDOL, STIEN, PYBOX, and salen Lewis acid complexes. The PYBOX catalysts of Al, In, Sc and Yb were generated in the HTE glovebox as solutions of metal and PYBOX. Once all catalysts solutions were distributed onto the 24 well plates, they were concentrated, sealed with plastic mat caps and stored in a zip-lock bag in the glovebox.

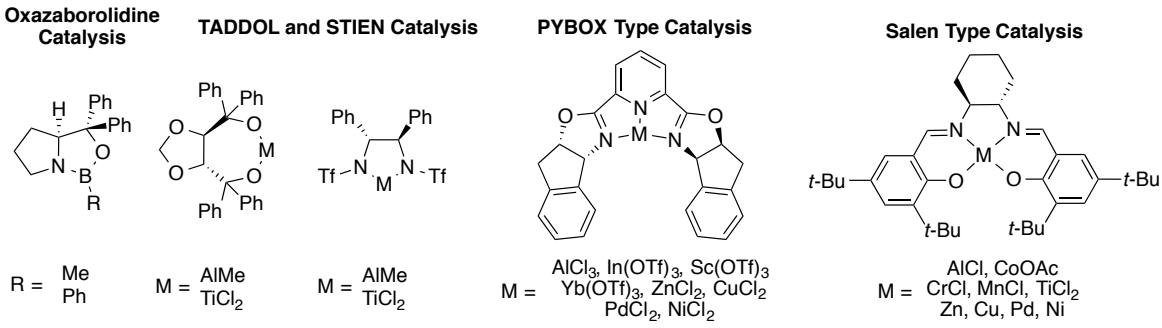



**Figure 3.6** Chiral Lewis acid library for HTE.

*3.2.3. Intramolecular Diels-Alder Reaction of Allenylamides*

Thirty years ago, Himbert discovered the intramolecular Diels-Alder cycloaddition of allenylamides, permitting rapid access to strained polycyclic compounds (Figure 3.7).[113] Ester, thioester, imide, phosphinamide, and phosphinic ester tethers can be used in place of the amide. Himbert published more than 20 studies on this reaction,

113) (a) Himbert, G.; Diehl, K.; Schlindwein, H.–J. "Intramolekulare Diels-Alder-Reaktion bei Allencarboxaniliden; Einbau des 1-Naphthyl-Restes an Stelle monocyclischer Aromatensysteme" *Chem. Ber.* **1986**, *119*, 3227-3235. (b) Himbert, G.; Fink, D. "Intramolekulare Diels-Alder-Reaktion Bei Allencarbonsaure-Arylestern" *Tetrahedron Lett.* **1985**, *26*, 4363-4366.

but not until 2012 was it exploited by other scientists.[114] Our laboratory was interested in developing an asymmetric modification of this reaction because of its ease at providing complex polycycles from readily available starting materials.

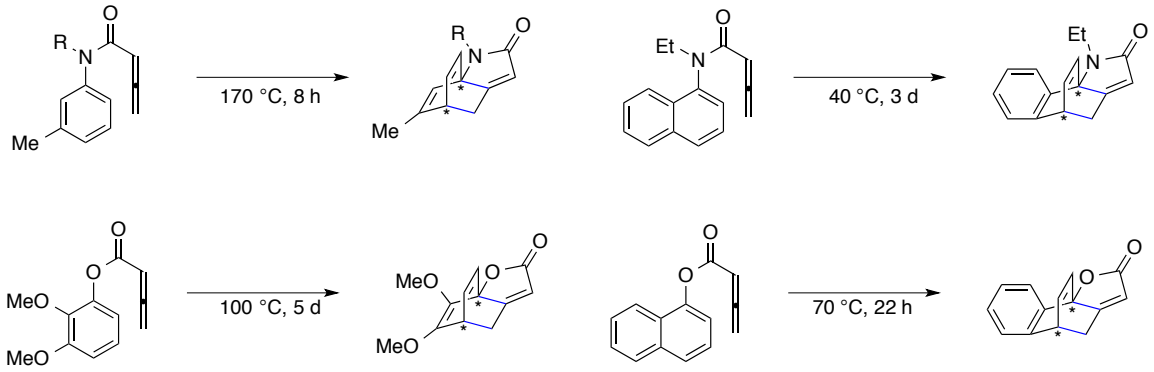
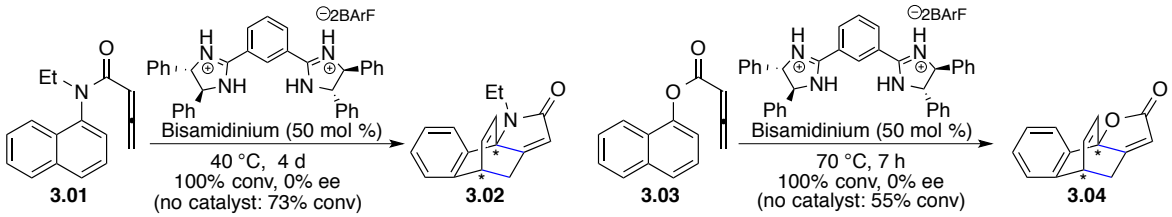



**Figure 3.7** Intramolecular Diels-Alder cycloaddition of allenylamides and allenylesters (Ref. 113).

Ryan Walvoord, a former co-worker, and Claire Gober, a visiting undergraduate, investigated the intramolecular Diels-Alder cycloaddition of allenylamide (**3.01**) and allenylester (**3.03**) with various hydrogen-bonding catalysts. Ryan and Claire found that bisamidinium accelerated the rate of reaction compared to thermal conditions but that no selectivity was observed (Scheme 3.1). This result prompted an investigation of the intramolecular Diels-Alder reaction of allenylamides with our chiral Lewis acid library.

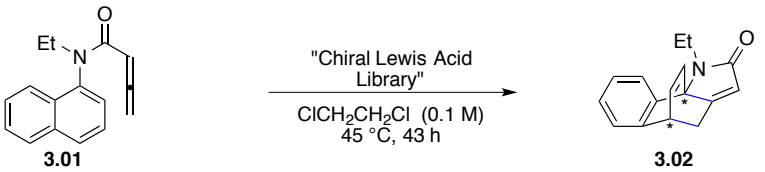
**Scheme 3.1** Intramolecular Diels-Alder cycloaddition of allenylcarbonyls catalyzed by a hydrogen-bond catalyst.

114) Lam, J. K.; Schmidt, Y.; Vanderwal, C. D. "Complex Polycyclic Scaffolds by Metathesis Rearrangement of Himbert Arene/Allene Cycloadducts" *Org. Lett.* **2012**, *14*, 5566-5569.




Allenylamide (**3.01**) was explored with the 23 chiral Lewis acids (40 mol %) at 45 °C for 60 h (Table 3.1). A marginal increase in P/IS was observed with (+)-Cy-salen-CrCl (entry 9) and (-)-PYBOX-Yb(OTf)$_3$ (entry 19) compared to the thermal background reaction (entry 24). (-)-Cl$_2$Ti-TADDOLate (entry 4) and (+)-Cy-salen-CrCl (entry 9) were the only catalysts to provide product with enantiopurity above 5% ee.

**Table 3.1** Studies on allenylamide with the chiral Lewis acid library in HTE.




| entry | catalyst (40 mol %) | P/IS[a] | ee (%)[b] | entry | catalyst (40 mol %) | P/IS[a] | ee (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | (*S*)-Phenyl-CBS | 1.7 | 3 | 13 | (+)-Cy-salen-Cu | 0.8 | 3 |
| 2 | (*S*)-Phenyl-CBS/$SnCl_4$ | 1.5 | 4 | 14 | (+)-Cy-salen-Pd | 2.0 | 2 |
| 3 | (-)-MeAl-TADDOLate | 1.6 | 4 | 15 | (+)-Cy-salen-Ni | 0.6 | 2 |
| 4 | (-)-$Cl_2$Ti-TADDOLate | 1.2 | 10 | 16 | (-)-PYBOX-$AlCl_3$ | 2.4 | 1 |
| 5 | (*R,R*)-STIEN-AlMe | 2.6 | 1 | 17 | (-)-PYBOX-In(OTf)$_3$ | 2.1 | 2 |
| 6 | (*R,R*)-STIEN-$TiCl_2$ | 2.2 | 0 | 18 | (-)-PYBOX-Sc(OTf)$_3$ | 2.4 | 2 |
| 7 | (+)-Cy-salen-AlCl | 2.5 | 4 | 19 | (-)-PYBOX-Yb(OTf)$_3$ | 2.8 | 2 |
| 8 | (+)-Cy-salen-Co(OAc) | 0.1 | 1 | 20 | (-)-PYBOX-$CuCl_2$/$AgSbF_6$ | 1.4 | 2 |
| 9 | (+)-Cy-salen-CrCl | 2.8 | 6 | 21 | (-)-PYBOX-$PdCl_2$/$AgSbF_6$ | 0.2 | 0 |
| 10 | (+)-Cy-salen-MnCl | 0.7 | 1 | 22 | (-)-PYBOX-$NiCl_2$/$AgSbF_6$ | 1.7 | 0 |
| 11 | (+)-Cy-salen-$TiCl_2$ | 0.5 | 2 | 23 | (-)-PYBOX-$ZnCl_2$/$AgSbF_6$ | 2.3 | 1 |
| 12 | (+)-Cy-salen-Zn | 0.5 | 1 | 24 | No Catalyst | 2.7 | 0 |

[a]Determined by HPLC. [b]Determined by CSP-SFC AD column.

Concurrently with our investigation, Christopher Vanderwal and Ken Houk published a mechanistic investigation of a similar Diels-Alder reaction.[115] Their results reveal the concerted [4+2] cycloaddition competes with a stepwise, radical type mechanism (Figure 3.8). In the concerted mechanism, substitution at the α-carbon increases the rate of the reaction; presumably it forces the β,γ-anti-bonding orbitals of the allene to overlap better with the diene in the aromatic ring. The β,γ-anti-bonding orbitals of the allene are nearly unaffected by Lewis acid coordination of the carbonyl oxygen. We reasoned that to induce high stereoselectivity, we would need to design a catalyst that interacts with the allene π-bonds rather than the carbonyl oxygen, such as gold or mercury. This endeavor has not been explored.

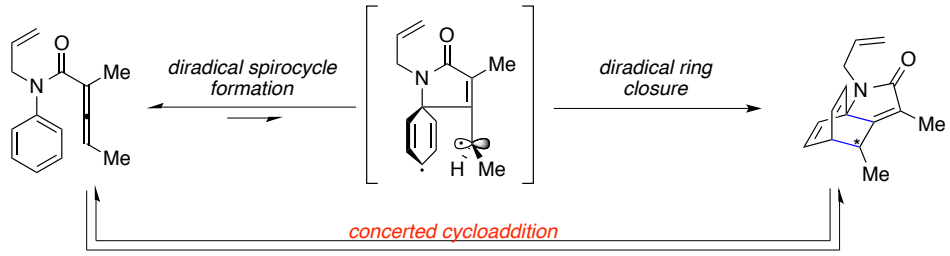



**Figure 3.8** Vanderwal and Houk concerted and stepwise radical mechanism (Ref. 115).

The initial screen of the chiral Lewis acid library for Diels-Alder reactions revealed that allenyl carbonyls were only weakly activated. However, Jacobsen and co-workers have detailed some very elegant work for the synthesis of sesquiterpene skeletons from various acrylates by the use of transannular intramolecular Diels-Alder

115) Schmidt, Y.; Lam, J. K.; Pham, H. V.; Houk, K. N.; Vanderwal, C. D. "Studies on the Himbert Intramolecular Arene/Allene Diels-Alder Cycloaddition. Mechanistic Studies and Expansion of Scope to All-Carbon Tethers" *J. Am. Chem. Soc.* **2013**, *135*, 7339-7348.

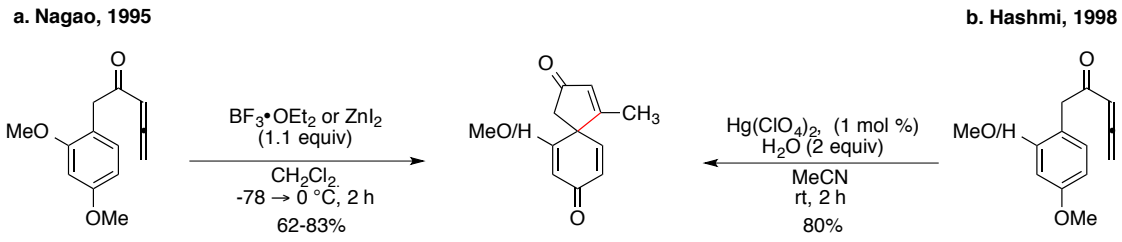
reaction.[116] This information prompted our review of 1,4-additions to allenyl carbonyls and inspired our interest in the spirocyclization of allenyl ketones.

## 3.3. ASYMMETRIC SPIROCYCLIZATION OF ALLENYL KETONES

### *3.3.1. Background on the Intramolecular Spirocyclization of Allenyl ketones*

In 1995, Nagao and co-workers discovered a novel dearomatization spirocyclization of allenyl ketones catalyzed by strong Lewis acids ($BF_3$•$OEt_2$ or $ZnI_2$) (Scheme 3.2, left).[117] The aromatic ring had to be sufficiently rich for the reaction to be successful; the mono-methoxy substrate produced the spirocyclic product in 8% yield. Hashmi and co-workers followed up on this work in 1998 with a catalytic variant using $Hg(ClO_4)_2$ and $H_2O$ (Scheme 3.2, right).[118] The mono-methoxy substrate was successful in forming the spirocycle with these conditions. Hashmi proposed that the soft-nucleophile Hg activates the allene π-bond via a mercurinium intermediate.

**Scheme 3.2** Previous work on the Lewis acid catalyzed spirocyclization of allenyl ketones.




116) Balskus, E. P.; Jacobsen, E. N. "Asymmetric Catalysis of the Transannular Diels-Alder Reaction" *Science* **2007**, *317*, 1736-1740.

117) Nagao, Y.; Lee, W. S.; Jeong, I.–Y.; Shiro, M. "New Intramolecular Spiro-Endo-Mode Ring Closure of Allenyl (Methoxy-Substituted Phenyl)alkyl Ketones" *Tetrahedron Lett.* **1995**, *36*, 2799-2802.

118) Hashmi, A. S. K.; Schwarz, L.; Bolte, M. "Mercury(II)-Catalyzed Synthesis of Spiro[4.5]decatrienediones in the Presence of Water" *Tetrahedron Lett.* **1998**, *39*, 8969-8972.

The spirocycle generated from the work by Nagao and Hashmi is present in many natural products, such as the sesquiterpenes of the vetivone and acorenone classes (Figure 3.9). The challenge in the synthesis of enantioenriched spirocyclic natural products is the efficient assembly of the stereogenic spiro carbon center in a stereoselective manner. The many interesting natural products that exist with the spirocyclic skeleton have led to extensive efforts to solve this synthetic problem.[119]

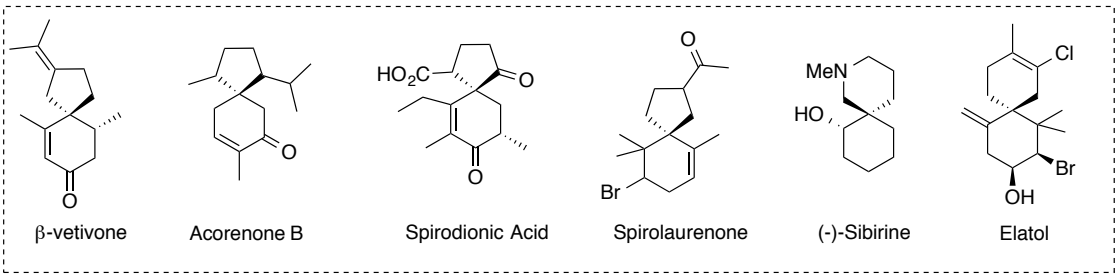



**Figure 3.9** Natural products with a spirocyclic framework.

We envisioned that we could investigate the spirocyclization of allenyl ketones utilizing our chiral Lewis acid library (Figure 3.10).[120] If conditions were found that were successful in generating the spirocycle product in high ee, then we could access various natural products (see above).

119) For reviews on spirocyclization reactions, see: (a) Rios, R. "Enantioselective methodologies for the synthesis of spiro compounds" *Chem. Soc. Rev.* **2012**, *41*, 1060-1074. (b) Pradhan, R.; Patra, M.; Behera, A. K.; Mishra, B. K.; Behera, R. J. "A synthon approach to spiro compounds" *Tetrahedron* **2006**, *62*, 779-828. (c) Sannigrahi, M. "Stereocontrolled Synthesis of Spirocyclics" *Tetrahedron* **1999**, *55*, 9007-9071. (d) Krapcho, A. P. "Synthesis of Carbocyclic Spiro Compounds via Intramolecular Alkylation Routes" *Synthesis* **1974**, 383-419.

120) My co-worker, Alison E. Metz, investigated the spirocyclization reaction with hydrogen-bond catalysts and found that bisamidinum (20 mol %) catalyzed the reaction (81% conv at 50 °C for 5 h) but that no selectivity was observed.

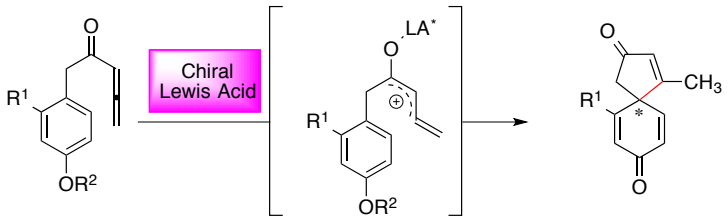
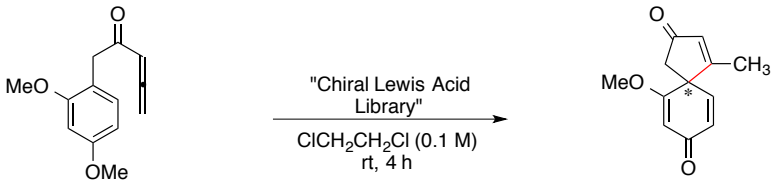



**Figure 3.10** Proposed asymmetric spirocyclization of allenyl ketones by chiral Lewis acid reagents.

*3.3.2. Results on the Spirocyclization of Allenyl Ketones*

High-throughput experimentation (HTE) was used to investigate 2,4-dimethoxy allenyl ketone (**3.05**) with the chiral Lewis acid library (40 mol %) at rt for 4 h (Table 3.2). The activated CBS catalysts, as well as $Sc(OTf)_3$ and $Yb(OTf)_3$ with the PYBOX ligand were the most active catalysts for product formation (entries 1-2 and 18-19). To our surprise, aluminum and titanium catalysts were only weakly active for catalyzing formation of the spiro product (entries 3-7, 11, 16), but (*R*,*R*)-STIEN-AlMe did provide the best selectivity (entry 5). Late-transition metals were not strong enough Lewis acids to catalyze formation of product (entries 12-15, 20-22).

**Table 3.2** HTE on 2,4-dimethoxy allenyl ketone with the chiral Lewis acid library.



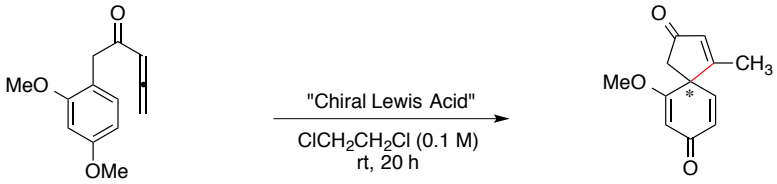

**3.05** **3.06**

| entry | catalyst (40 mol %) | P/IS[a] | ee (%)[b] | entry | catalyst (40 mol %) | P/IS[a] | ee (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | (*S*)-Methyl-CBS/$SnCl_4$ | 4.1 | 14 | 13 | (+)-Cy-salen-Cu | 0.0 | - |
| 2 | (*S*)-Phenyl-CBS/$SnCl_4$ | 22.9 | 76 | 14 | (+)-Cy-salen-Pd | 0.0 | - |
| 3 | (-)-MeAl-TADDOLate | 0.0 | - | 15 | (+)-Cy-salen-Ni | 0.0 | - |
| 4 | (-)-$Cl_2$Ti-TADDOLate | 0.3 | ND[c] | 16 | (-)-PYBOX-$AlCl_3$ | 0.2 | ND |
| 5 | (*R,R*)-STIEN-AlMe | 1.8 | 87 | 17 | (-)-PYBOX-In$(OTf)_3$ | 1.6 | ND |
| 6 | (*R,R*)-STIEN-$TiCl_2$ | 1.5 | ND | 18 | (-)-PYBOX-Sc$(OTf)_3$ | 9.0 | 17 |
| 7 | (+)-Cy-salen-AlCl | 0.0 | - | 19 | (-)-PYBOX-Yb$(OTf)_3$ | 3.8 | 49 |
| 8 | (+)-Cy-salen-Co(OAc) | 0.0 | - | 20 | (-)-PYBOX-$CuCl_2$/$AgSbF_6$ | 0.2 | ND |
| 9 | (+)-Cy-salen-CrCl | 0.0 | - | 21 | (-)-PYBOX-$PdCl_2$/$AgSbF_6$ | 0.0 | - |
| 10 | (+)-Cy-salen-MnCl | 0.0 | - | 22 | (-)-PYBOX-$NiCl_2$/$AgSbF_6$ | 0.0 | - |
| 11 | (+)-Cy-salen-$TiCl_2$ | 0.0 | - | 23 | (-)-PYBOX-$ZnCl_2$/$AgSbF_6$ | 1.7 | 2 |
| 12 | (+)-Cy-salen-Zn | 0.0 | - | 24 | No Catalyst | 0.0 | - |

[a]Determined by HPLC. [b]Determined by CSP-SFC AD column. [c]ND = not determined.

The catalysts that formed the spiro product from the HTE screen with measurable enantioselectivity were validated at bench top scale (Table 3.3). CBS and $Sc(OTf)_3$ were the best catalysts for generating product (entries 1 and 4) but only the CBS catalyst combined good conversion with high selectivity. Disappointingly, (*R,R*)-STIEN-AlMe at bench top scale gave considerably lower selectivity than on the microscale (entry 2). Potentially, the catalyst is not stable and degraded over time, but conversion did remain consistent. The CBS catalyst class was chosen for further exploration.

**Table 3.3** Bench-top scale of the HTE leads.




**3.05** **3.06**

| entry | catalyst (40 mol %) | conv (%)[a] | ee (%)[b] | entry | catalyst (40 mol %) | conv (%)[a] | ee (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | (*S*)-Phenyl-CBS/$SnCl_4$ | 100[c] | 66 | 4 | (-)-PYBOX-Sc(OTf)$_3$ | 50 | 2 |
| 2 | (*R,R*)-STIEN-AlMe | 15 | 18 | 5 | (-)-PYBOX-Yb(OTf)$_3$ | 0 | - |
| 3 | (*R,R*)-STIEN-$TiCl_2$ | 23 | 2 | | | | |

[a]Determined from $^1$H NMR. [b]Determined by CSP-HPLC. [c]Rxn time was 4 h instead of 20 h.

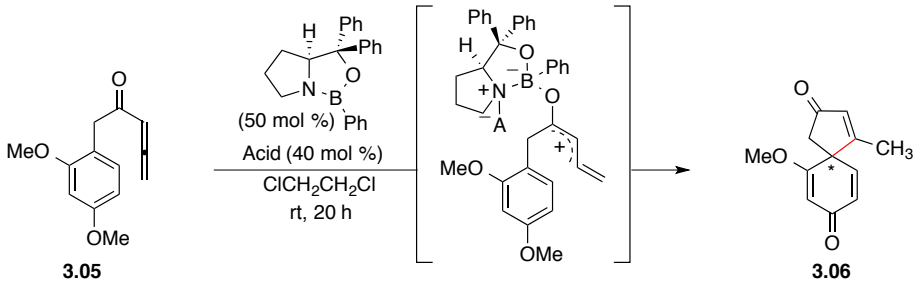
Lewis acid assisted Lewis acids (LLA) with oxazborolidine type catalysts were first discovered by Yamamoto[108b] and Corey.[109b] The Lewis basic nitrogen on the oxazborolidine coordinates to the Lewis acid activator (e.g., $SnCl_4$ or $AlBr_3$), which enhances the Lewis acidity of the boron, enabling coordination to various Lewis bases. A quantum chemical study by Sakata and Fujimoto support this mode of reactivity for oxazborolidine catalysts with $AlBr_3$.[121] This hypothesis was tested experimentally with allenyl ketone (**3.05**); upon removal of $SnCl_4$ from the (*S*)-phenyl-CBS catalyst, no spiro product was observed (Table 3.4, entry 1). Notably, $SnCl_4$ (100 mol %) in the absence of the CBS catalyst provided the spiro product in 95% yield.

Lewis and Brønsted acids were explored with (*S*)-Phenyl-CBS and allenyl ketone (**3.05**) (Table 3.4). In Yamamoto's seminal publication, various Lewis acids ($AlCl_3$, $Et_2AlCl$, $FeCl_3$, $Sc(OTf)_3$, $Sn(Cl_4)$, [$CpTiCl_3$], and $TiCl_4$) were efficient activators for the LLA catalyzed Diels-Alder reaction between cyclopentadiene and methacrolein.[108b] This trend was in contrast to our observations with allenyl ketone (**3.05**); $SnCl_4$, $TiCl_4$ and TMSOTf with (*S*)-phenyl-CBS were the only catalysts that provided spirocyclic product

121) Sakata, K.; Fujimoto, H. "Quantum Chemical Study of Diels-Alder Reactions Catalyzed by Lewis Acid Activated Oxazaborolidines" *J. Org. Chem.* **2013**, *78*, 3095-3103.

**3.06** (Table 3.4, entries 2, 6 and 8). Brønsted acid activation of (*S*)-phenyl-CBS did not provide the spirocycle product; rather, decomposition was observed with no starting material remaining after 4 h (Table 3.4, entries 11-12).

**Table 3.4** Screen of Lewis and Brønsted acid assisted CBS catalysts for spirocyclization.

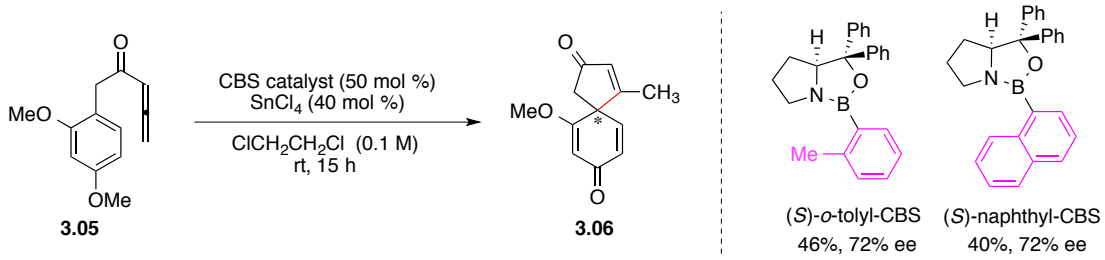



| entry | catalyst activator | conv (%)[a] | ee (%)[b] | entry | catalyst activator | conv (%)[a] | ee (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | none | 0 | - | 7 | $BBr_3$ | 0 | - |
| 2 | $SnCl_4$ | 89% y[c,d] | 66 | 8 | TMSOTf[e] | 47% y[d] | 45 |
| 3 | $AlCl_3$ | 0 | - | 9 | TMSCl[e] | 0 | - |
| 4 | $FeCl_3$ | 0 | - | 10 | MeI[e] | 0 | - |
| 5 | $Sc(OTf)_3$ | >90 | 0 | 11 | TsOH | decomp | - |
| 6 | $TiCl_4$ | >90 | 62 | 12 | $Tf_2NH$ | decomp | - |

[a]Determined from $^1$H NMR. [b]Determined by CSP-HPLC. [c]Rxn time was 4 h instead of 20 h.
[d]isolated by column chromatography. [e]Rxns were performed by Sergei Tcyrulnikov.

The selectivity of the CBS/$SnCl_4$ catalyzed spirocycle formation from allenyl ketone (**3.05**) was enhanced when the boron substituent was changed from methyl to phenyl (see Table 3.2, entries 1-2). (*S*)-*o*-Tolyl-CBS and (*S*)-naphthyl-CBS with $SnCl_4$ both improved the selectivity of the spirocycle product from 66 to 72% but yield was reduced.

**Scheme 3.3** Exploration of (*S*)-aryl-CBS catalyst with $SnCl_4$.




Throughout the development of the asymmetric spirocyclization of allenyl ketone (**3.05**), it was not readily apparent how catalytic turnover was occurring. The catalyst activates the ketone to form an allylic carbocation (**3.07a**), promoting a Friedel-Crafts 1,4-addition to produce **3.07b** (Table 3.5, top). The CBS-enolate complex (**3.07b**) is likely more stable than the CBS-ketone (**3.07a**) and for the CBS/$SnCl_4$ catalyst to be regenerated the enolate would need to undergo protonation (Table 3.5, top). Ostensibly, adventitious water in the solvent permitted the observed catalyst turnover. However, addition of 3 Å molecular sieves with catalyst (50 mol %) still provided similar amounts of product (86% NMR yield, 70% ee).

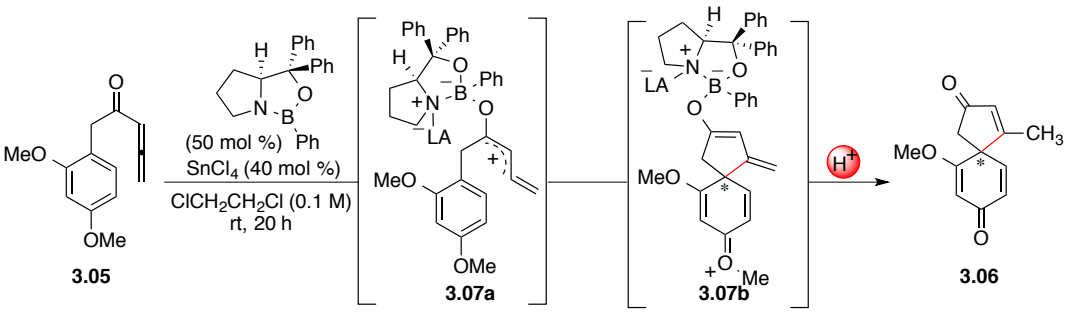
We envisioned that catalyst loading could be reduced from 50 mol % to 10 mol % if a proton source was added to the reaction conditions.[122] In 1999, Evans and co-workers had found the selectivity for the Cu(II) bisoxazoline catalyzed addition of enolsilanes to unsaturated ester derivatives was improved with the addition of *i*-PrOH.[123] In 2002, Harada and co-workers had similar problems with catalyst turnover in a Mukaiyama-1,4-

122) Yamamoto had found in ref. 109b that the oxazaborolidine/$SnCl_4$ complex was relatively stable to wet solvents.

123) Evans, D. A.; Willis, M. C.; Johnston, J. J. "Catalytic Enantioselective Michael Additions to Unsaturated Ester Derivatives Using Chiral Copper(II) Lewis Acid Complexes" *Org. Lett.* **1999**, *1*, 865-868.

addition and found that 2,6-diisopropylphenol was required.[124] Proton sources were explored with the (*S*)-phenyl-CBS/$SnCl_4$ and allenyl ketone (**3.05**) (Table 3.5). $H_2O$, MeOH and *i*-PrOH not only reduced yield, but the spiro product produced was less enantiopure (Table 3.5, entries 1-3). These disappointing results prompted the exploration of oxophilic electrophiles by my co-worker Sergei Tcyrulnikov. Sergei found that TMSOTf, TMSCl and MeI did not improve the reaction yield or selectivity (Table 3.5, entries 4-6).

**Table 3.5** Additives for catalyst turnover.




| entry | proton source (1 equiv) | yield (%)[a] | ee (%)[b] | entry | oxophilic electrophile (1 equiv)[c] | yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|---|---|---|
| 1 | $H_2O$ | 29 | 34 | 4 | TMSOTf | 53 | 57 |
| 2 | MeOH | 37 | 50 | 5 | TMSCl | 33 | 57 |
| 3 | *i*-PrOH[c] | 27 | 5 | 6 | MeI | 32 | 58 |

[a]Isolated by column chromatography. [b]Determined by CSP-HPLC. [c]Rxns were performed by Sergei Tcyrulnikov.

We have utilized a chiral Lewis acid library in HTE to find conditions for the first asymmetric spirocyclization of allenyl ketones. However, the challenges encountered with catalyst turnover prompted us to reexamine our hypothesis that the enantioenriched spirocycle product could be formed from the allenyl ketone (**3.05**) with a sub-stoichiometric amount of a chiral Lewis acid. To date, the only successful formation of

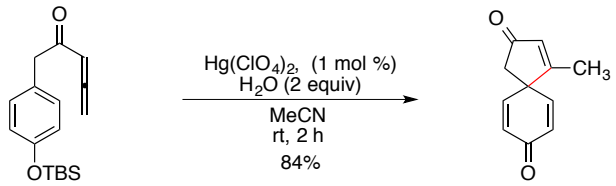
124) Harada, T.; Iwai, H.; Takatsuki, H.; Fujita, K.; Kubo, M.; Oku, A. "Asymmetric Mukaiyama-Michael Addition of Acyclic Enones Catalyzed by *allo*-Threonine-Derived *B*-Aryloxazaborolidinones" *Org. Lett.* **2001**, *3*, 2101-2103.

the spirocycle product with sub-stoichiometric amount of a catalyst was Hashmi and co-workers with $Hg(OCl_4)_2$ and $H_2O$ (see Scheme 3.2). Inspired by the various accounts on Mukaiyama-aldol reactions, we proposed that modification of the phenol protecting group from a methyl to silyl, would permit turnover of the CBS catalyst by means of silyl migration to the newly formed enolate.

*3.3.3. Asymmetric Spirocyclization of 2-TBSO,4-MeO-Allenyl Ketone*

Multiple examples in the literature have demonstrated that Mukaiyama-aldol/-1,4-additions can be catalyzed by oxazaborolidines with high enantioselctivity.[106,124] Notably, the corresponding *para*-TBSO-allenyl ketone (**3.08**) cyclizes to the spiro product in good yield with a mercury catalyst (Scheme 3.4).[118]

**Scheme 3.4** Spirocyclization of 4-TBSO-allenyl ketone with $Hg(ClO_4)_2$ (Ref. 118)




**3.08** **3.09**

The results of the CBS catalyst in the Mukiayama-1,4-addition and the work by Hashmi inspired our proposal for catalyst turnover (Figure 3.11). The CBS/LA complex bound to the enolate (**3.11b**) can be displaced by a silyl migration to provide the enol-silane (**3.12**) and regeneration of the CBS/LA complex. This would be the first example of *ortho*-quinone formation from spirocyclization of an allenyl ketone.

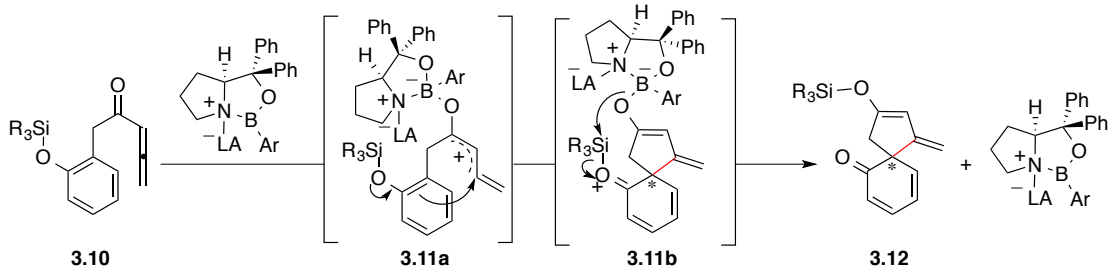
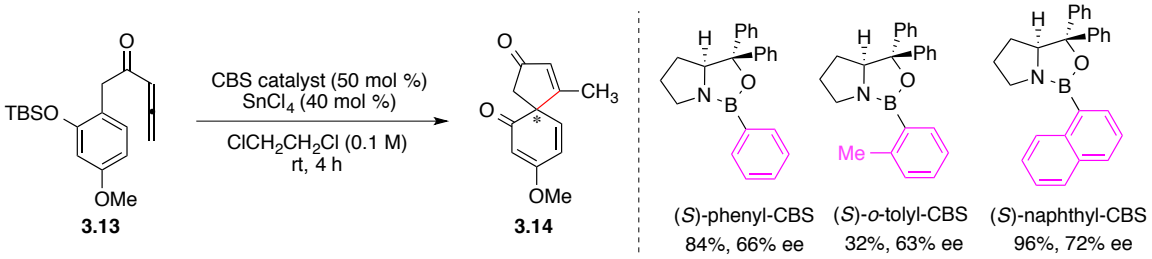



**Figure 3.11** Proposal for *ortho*-quinone formation by pseudo Mukiayama-1,4-addition.

This hypothesis was explored with allenyl ketone (**3.13**) and various CBS catalysts (Scheme 3.5). The yield and selectivity with the *ortho*-TBSO with the (*S*)-phenyl-CBS catalyst was similar to that observed with the 2,4-dimethoxy allenyl ketone (c.f., Table 3.4). The yield and selectivity improved when (*S*)-naphthyl-CBS was used (96%, 72% ee); however, these conditions at cooler temperatures did not result in improved selectivity.

**Scheme 3.5** Exploration of (*S*)-aryl-CBS with $SnCl_4$ to catalyze formation of *ortho*-quinone.




In 1990, Mukaiyama disclosed the first asymmetric addition of enol-silane to aldehydes catalyzed by Sn(II) chiral diamine complexes.[103] They found that slow addition of aldehyde was very important for high yield and selectivity because catalyst turnover was sluggish and TMSOTf generated from the $Sn(OTf)_2$ over the course of the reaction

provided racemic product. Harada observed a similar result; slow addition of the electrophile and a bulky proton source was necessary for high yield and selectivity.[124] These experiments could potentially improve the results observed in Scheme 3.5.

Current efforts in developing catalytic conditions for the asymmetric spirocyclization of 2-TBSO,4-MeO-allenyl ketone are being investigated by my co-worker Sergei Tcyrulnikov. Sergei is exploring computationally the transition states for the CBS-$SnCl_4$ complex catalyzing spirocyclization. These results will hopefully aid in overcoming challenges with catalyst turnover and selectivity.

## 3.4. CONCLUSIONS

In summary, we have synthesized a chiral Lewis acid library to be utilized in HTE for the development of asymmetric transformations. This library was used to explore the intramolecular Diels-Alder reaction of allenylamides and the spirocyclization of allenyl ketones. We have developed the first asymmetric spirocyclization of allenyl ketones using a Lewis acid assisted Lewis acid catalyst system, which was determined from HTE. Through protecting group manipulation on the allenyl ketone, the *para*-quinone and *ortho*-quinone can be accessed. This orthogonality allows access to the spirocyclic core of various natural products. Challenges were incurred with catalyst turnover and future efforts will focus on finding conditions that promote turnover and improve selectivity.

## 3.5. EXPERIMENTAL SECTION

### General Considerations

All non-aqueous reactions were carried out under an atmosphere of dry argon unless otherwise noted. Commercial reagents were used as received without additional purification unless otherwise noted. Dichloromethane and 1,2-dichloroethane were distilled from $CaH_2$, and toluene was distilled from metallic sodium prior to use. Reactions were monitored by thin layer chromatography (TLC) using Silicycle glass-backed TLC plates with 250 μm silica and F254 indicator. Visualization was accomplished by UV light and/or $KMnO_4$.

$^1H$ NMR and $^{13}C$ NMR spectra were recorded on a AM-500 Fourier transform NMR spectrometer at 500 MHz and 125 MHz, respectively. Chemical shifts are reported relative to the solvent resonance peak δ 7.26 ($CDCl_3$) for $^1H$ and δ 77.16 ($CDCl_3$) for $^{13}C$. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, b = broad singlet, m = multiplet), coupling constants, and number of protons. High resolution mass spectra were obtained using a VG autospec with an ionization mode of either ESI or CI. Infrared spectra are reported in $cm^{-1}$. Melting points are uncorrected. Unless otherwise noted, yields refer to isolated material on the basis of product purity (≥95%) by $^1H$ NMR following silica gel chromatography with Silica-P flash silica gel (50-63 μm mesh particle size). Enantiomeric excess was determined utilizing chiral stationary phase (CSP) HPLC or SFC on OD [cellulose tris(3,5-dimethylphenylcarbamate) coated on silica gel] 0.46 cm x 25 cm or IA [amylose tris(3,5-dimethylphenylcarbamate) immobilized on silica gel] 0.46 cm x 25 cm columns.

**Synthesis of chiral Lewis acids:**

CBS catalysts (Figure 3.12, **C2** and **C3**) were purchased from Strem Chemicals Inc. The (-)-IndaPYBOX ligand was synthesized following a known procedure.[112] The following catalysts (Figure 3.12) for the chiral Lewis acid plate were made following known procedures: **A1**[125], **A2**[110a], **A3**[126], **A4**[127], **A5**[128], **A6**[129], **B1**[130], **B2**[131], **B3**[131], **B4**[132], **B5**[132], **B6**[132], **C1**[132], **C4**[133], **C5**[134], **C6**[133], **D1**[134], **D2**[112], **D3**[112], **D4**[112], and **D5**[112].

**Preparation of chiral Lewis acid 24-well plate for HTE:**

Solutions of **A1-D1** (0.04 M solution in 1,2-dichloroethane) were prepared in a glovebox and allowed to stir at ambient temperature for 30 min. The solutions were

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125) Duxbury, J. P.; Warne, J. N. D.; Mushtaq, R.; Ward, C.; Thornton-Pett, M.; Jiang, M.; Greatrex, R.; Kee, T. P. "Phospho-Aldol Catalysis via Chiral Schiff Base Complexes of Aluminum" *Organometallics* **2000**, *19*, 4445-4457.

126) Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. "Highly Enantioselective Ring Opening of Epoxides Catalyzed by (salen)Cr(III) Complexes" *J. Am. Chem. Soc.* **1995**, *117*, 5897-5898.

127) Larrow, J. F.; Jacobsen, E. N. "A Practical Method for the Large-Scale Preparation of [*N,N'*-Bis(3,4-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminato(2-)]manganese(III) Chloride, a Highly Enantioselective Epoxidation Catalyst" *J. Org. Chem.* **1994**, *59*, 1939-1942.

128) Belokon, Y. N.; Caveda-Cepas, S.; Green, B.; Ikonnikov, N. S.; Khrustalev, V. N.; Larichev, V. S.; Moscalenko, M. A.; North, M.; Orizu, C.; Tararov, V. I.; Tasinazzo, M.; Timofeeva, G. I.; Yashkina, L. V. "The Asymmetric Addition of Trimethylsilyl Cyanide to Aldehydes Catalyzed by Chiral (Salen)Titanium Complexes" *J. Am. Chem. Soc.* **1999**, *121*, 3968-3973.

129) Morris, G. A.; Zhou, H.; Stern, C. L.; Nguyen, S. T. "A General High-Yield Route to Bis(salicylaldimine) Zinc(II) Complexes: Application to the Synthesis of Pyridine-Modified Salen-Type Zinc(II) Complexes" *Inorg. Chem.* **2001**, *40*, 3222-3227.

130) Sabarinathan, S.; Vasuki, G.; Rao, P. S. "Chiral Cu(II) salen complexes catalyzed aerobic oxidative biaryl coupling-probing the reaction by EPR" *Eur. J. Chem.* **2010**, *1*, 360-367.

131) Shimazaki, Y.; Yajima, T.; Tani, F.; Karasawa, S.; Fukui, K.; Naruta, Y.; Yamauchi, O. "Syntheses and Electronic Structures of One-Electron-Oxidized Group 10 Metal(II)-(Disalicylidene)diamine Complexes (Metal = Ni, Pd, Pt)" *J. Am. Chem. Soc.* **2007**, *129*, 2559-2568.

132) Jiang, M.; Dalgarno, S.; Kilner, C. A.; Halcrow, M. A.; Kee, T. P. "Chiral bis(oxazoline) complexes. Synthesis, structure and applications in catalytic phosphor-transfer" *Polyhedron* **2001**, *20*, 2151-2162.

133) Corey, E. J.; Sarshar, S. "X-ray Crystallographic and NMR Studies on the Origins of High Enantioselectivity oin Diels-Alder Reactions Catalyzed by a Chiral Diazaaluminolidine" *J. Am. Chem. Soc.* **1992**, *114*, 7938-7939.

134) Seebach, D.; Plattner, D. A.; Beck, A. K.; Wang, Y. M.; Hunziker, D. "161. On the Mechanism of Enantioselective Reactions Using α,α,α',α'-Tetraaryl-1,3-dioxolane-4,5-dimethanol(TADDOL)-Derived Titanates: Differences between $C_2$- and $C_1$-Symmetrical TADDOLs-Facts, Implications and Generalizations)" *Helv. Chim. Acta.* **1992**, *75*, 2171-2209.

transferred to the corresponding vial on a 24-well reactor block (0.004 mmol, 100 μL). Catalysts **D2**-**D5** were prepared *in situ*: $AlCl_3$ (5.3 mg, 0.040 mmol), $In(OTf)_3$ (22.5 mg, 0.040 mmol), $Sc(OTf)_3$ (19.7 mg, 0.040 mmol) or $Yb(OTf)_3$ (24.8 mg, 0.040 mmol) was added to a 20 dram vial equipped with stirbar in the glovebox. (-)-IndaPYBOX (15.7 mg, 0.040 mmol) and 1,2-dichloroethane (960 μL) were added to each vial and stirred for 2 h. 100 μL of each catalyst (0.004 mmol) was added to the 24-well reactor block in locations **D2**-**D5** respectively. 1,2-Dichloroethane was removed on the Genevac and the 24-well reactor block was sealed with a polypropylene 1 mL cap mat. The catalyst library (7 were prepared) was stored in a zip-lock bag in the glovebox

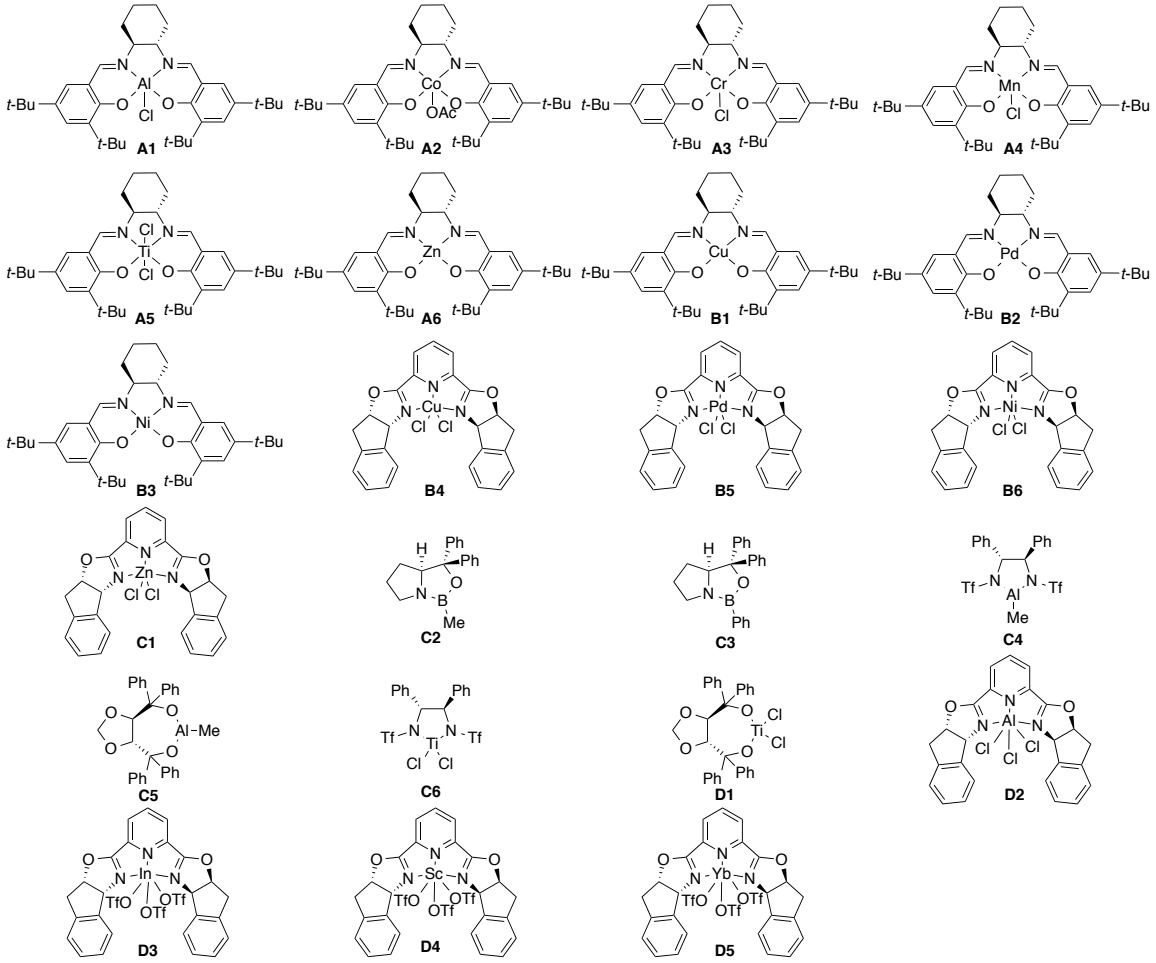
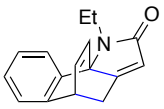


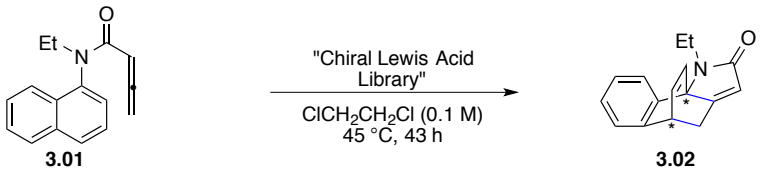
**Figure 3.12** 24 well-plate with chiral Lewis acids.

**Preparation of a racemic sample of 3.02:**




**1-Ethyl-4,5-dihydro-5,9b-ethenobenzo[*g*]indol-2(1*H*)-one (3.02).** Allenyl amide (**3.01)** (7 mg, 0.030 mmol) was added to a flame dried 8 mL microwave vial equipped with stir bar. 1,2-Dichloroethane (300 μL) was added. The vial was backfilled with argon, sealed with a Teflon cap, placed in a 45 °C oil bath and stirred for 65 h. The mixture was allowed to cool to ambient temperature and purified directly by column chromatography (40% EtOAc in Hexanes) providing **3.02** (6.7 mg) in 96% yield: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.29-7.25 (m, 2H), 7.19 (t, *J* = 2.3 Hz, 2H), 6.70 (dd, *J* = 8.3, 6.3 Hz, 1H), 6.53 (d, *J* = 7.8 Hz, 1H), 5.80 (t, *J* = 1.9 Hz, 1H), 4.36-4.29 (m, 1H), 4.20-4.05 (m, 1H), 3.78-3.63 (m, 1H), 2.57 (dt, *J* = 17.2, 2.0 Hz, 1H), 2.41 (dt, *J* = 17.2, 2.0 Hz, 1H), 1.51 (t, *J* = 7.1 Hz, 3H). Spectroscopic data match those reported in the literature.[113a]

**High-Throughput Experimentation with Allenyl Amide (**Table 3.1**)**

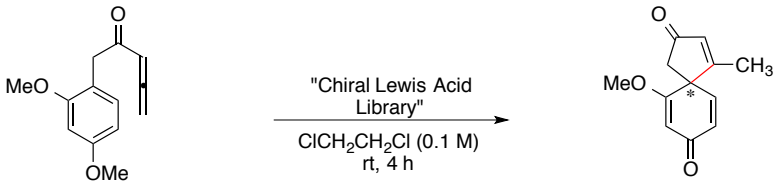



A 24-well reactor equipped with 1 mL vials was pre-dosed with the chiral Lewis acids (0.004 mmol) described above with the following modification: (*S*)-phenyl-CBS was substituted for (*S*)-methyl-CBS in well C2. A solution of $AgSbF_6$ (0.008 mmol, 32

μL of a 0.25 M solution in $CH_2Cl_2$) was added to wells B4-C1. A solution of $SnCl_4$ (0.002 mmol, 16 μL of a 0.13 M solution in $CH_2Cl_2$) was added to well C3. A parylene stir-bar was added to each vial. The reactor block was sealed, removed from the glovebox and heated to 40 °C for 45 minutes on an Alligator tumble stirrer (1000 rpm). The reactor block was brought into the glovebox after cooling to ambient temperature and 1,2-dichloroethane (50 μL) was added to wells A1-D6. A solution of **3.01** (0.010 mmol, 50 μL of a 0.2 M solution in 1,2-dichloroethane) was added to wells A1-D6. The reactor block was sealed, removed from the glove box and heated to 45 °C for 43 h on an Alligator tumble stirrer (1200 rpm). After cooling to ambient temperature, the reactions were quenched *via* dilution with a solution of internal standard in 25% DMSO/MeCN (1.4 μmol, 0.002 M, 700 μL), and the contents were stirred for 15 minutes. Into a separate 96-well plate LC block was added 700 μL of MeCN and 25 μL of the diluted reaction mixtures. The 96-well plate LC block was sealed with a polypropylene 1 mL cap mat. The reaction mixtures were analyzed using an Agilent Technologies 1200 series HPLC with a 96 well-plate auto-sampler. Assay conditions: C18 column with reverse phase eluents (MeCN and 0.1 % $H_3PO_4$ in $H_2O$). 1.8 mL/min; 10% in MeCN to 95% MeCN in 6 min, hold for 2 min. Post time 2 min. Column at 40 °C; 210 nm. The reaction mixtures were analyzed for enantiopurity with supercritical fluid chromatography (SFC) (AD column, 1.8 mL/min, 5% MeOH/$CO_2$, 120 bar, 220 nm): $t_R$ of **3.02**: 6.5 min and 7.7 min.

| entry | catalyst (40 mol %) | SM/IS | P/IS | ee (%) | entry | catalyst (40 mol %) | SM/IS | P/IS | ee (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | (*S*)-phenyl-CBS | 1.3 | 1.7 | 3 | 13 | (+)-Cy-salen-Cu | 1.0 | 0.8 | 3 |
| 2 | (*S*)-phenyl-CBS/$SnCl_4$ | 1.8 | 1.5 | 4 | 14 | (+)-Cy-salen-Pd | 1.0 | 2.0 | 2 |
| 3 | (-)-MeAl-TADDOLate | 2.2 | 1.6 | 4 | 15 | (+)-Cy-salen-Ni | 1.0 | 0.6 | 2 |
| 4 | (-)-$Cl_2$Ti-TADDOLate | 2.4 | 1.2 | 10 | 16 | (-)-PYBOX-$AlCl_3$ | 1.1 | 2.4 | 1 |
| 5 | (*R,R*)-STIEN-AlMe | 1.7 | 2.6 | 1 | 17 | (-)-PYBOX-In$(OTf)_3$ | 1.1 | 2.1 | 2 |
| 6 | (*R,R*)-STIEN-$TiCl_2$ | 1.8 | 2.2 | 0 | 18 | (-)-PYBOX-Sc$(OTf)_3$ | 3.5 | 2.4 | 2 |
| 7 | (+)-Cy-salen-AlCl | 1.0 | 2.5 | 4 | 19 | (-)-PYBOX-Yb$(OTf)_3$ | 4.6 | 2.8 | 2 |
| 8 | (+)-Cy-salen-Co(OAc) | 1.0 | 0.1 | 1 | 20 | (-)-PYBOX-$CuCl_2$/$AgSbF_6$ | 1.3 | 1.4 | 2 |
| 9 | (+)-Cy-salen-CrCl | 1.1 | 2.8 | 6 | 21 | (-)-PYBOX-$PdCl_2$/$AgSbF_6$ | 1.2 | 0.2 | 0 |
| 10 | (+)-Cy-salen-MnCl | 1.0 | 0.7 | 1 | 22 | (-)-PYBOX-$NiCl_2$/$AgSbF_6$ | 1.2 | 1.7 | 0 |
| 11 | (+)-Cy-salen-$TiCl_2$ | 1.3 | 0.5 | 2 | 23 | (-)-PYBOX-$ZnCl_2$/$AgSbF_6$ | 2.0 | 2.3 | 1 |
| 12 | (+)-Cy-salen-Zn | 1.0 | 0.5 | 1 | 24 | No Catalyst | 2.7 | 2.7 | 0 |

**High-Throughput Experimentation with Allenyl Ketone (**Table 3.2**)**

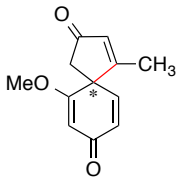



**3.05** **3.06**

A 24-well reactor equipped with 1 mL vials was pre-dosed with the chiral Lewis acids (0.004 mmol) described above. A solution of $AgSbF_6$ (0.008 mmol, 25 μL of a 0.32 M solution in $CH_2Cl_2$) was added to wells B4-C1. A solution of $SnCl_4$ (0.002 mmol, 25 μL of a 0.08 M solution in $CH_2Cl_2$) was added to well C2-C3. A parylene stir-bar was added to each vial. The reactor block was sealed, removed from the glovebox and stirred for 45 minutes on an Alligator tumble stirrer (1000 rpm). The reactor block was brought into the glovebox after cooling to ambient temperature and 1,2-dichloroethane (50 μL) was added to wells A1-D6. A solution of **3.05** (0.010 mmol, 50 μL of a 0.2 M solution in 1,2-dichloroethane) was added to wells A1-D6. The reactor block was sealed, removed

from the glove box and stirred for 43 h on an Alligator tumble stirrer (1200 rpm). The reactions were quenched *via* dilution with a solution of internal standard in 25% DMSO/MeCN (1.0 μmol, 0.002 M, 500 μL), and the contents were stirred for 15 minutes. Into a separate 96-well plate LC block was added 700 μL of MeCN and 25 μL of the diluted reaction mixtures. The 96-well plate LC block was sealed with a polypropylene 1 mL cap mat. The reaction mixtures were analyzed (SM/IS and P/IS) using an Agilent Technologies 1200 series HPLC with a 96 well-plate auto-sampler. Assay conditions: C18 column with reverse phase eluents (MeCN and 0.1 % $H_3PO_4$ in $H_2O$); 1.8 mL/min; 10 % in MeCN to 95 % MeCN in 6 min, hold for 2 min. Post time 2 min. Column at 40 °C; 210 nm. Select reaction mixtures (C1-C4 and D4-D5) were analyzed for enantiopurity with supercritical fluid chromatography (SFC) (AD column, 1.8 mL/min, 5% MeOH/$CO_2$, 120 bar, 220 nm): $t_R$ of **3.06**: 13.0 and 15.5 min.

| entry | catalyst (40 mol %) | SM/IS[b] | P/IS | ee (%) | entry | catalyst (40 mol %) | SM/IS | P/IS | ee (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1 | (*S*)-methyl-CBS/$SnCl_4$ | 0.2 | 4.1 | 14 | 13 | (+)-Cy-salen-Cu | 23.5 | 0.0 | ND |
| 2 | (*S*)-phenyl-CBS/$SnCl_4$ | 0.1 | 22.9 | 76 | 14 | (+)-Cy-salen-Pd | 22.4 | 0.0 | ND |
| 3 | (-)-MeAl-TADDOLate | 20.9 | 0.0 | ND | 15 | (+)-Cy-salen-Ni | 24.8 | 0.0 | ND |
| 4 | (-)-$Cl_2$Ti-TADDOLate | 8.0 | 0.3 | ND | 16 | (-)-PYBOX-$AlCl_3$ | 23.0 | 0.2 | ND |
| 5 | (*R,R*)-STIEN-AlMe | 21.8 | 1.8 | 87 | 17 | (-)-PYBOX-In$(OTf)_3$ | 22.5 | 1.6 | ND |
| 6 | (*R,R*)-STIEN-$TiCl_2$ | 21.6 | 1.5 | ND | 18 | (-)-PYBOX-Sc$(OTf)_3$ | 14.0 | 9.0 | 17 |
| 7 | (+)-Cy-salen-AlCl | 21.0 | 0.0 | ND | 19 | (-)-PYBOX-Yb$(OTf)_3$ | 19.2 | 3.8 | 49 |
| 8 | (+)-Cy-salen-Co(OAc) | 21.1 | 0.0 | ND | 20 | (-)-PYBOX-$CuCl_2$/$AgSbF_6$ | 23.5 | 0.2 | ND |
| 9 | (+)-Cy-salen-CrCl | 22.9 | 0.0 | ND | 21 | (-)-PYBOX-$PdCl_2$/$AgSbF_6$ | 11.1 | 0.0 | ND |
| 10 | (+)-Cy-salen-MnCl | 24.3 | 0.0 | ND | 22 | (-)-PYBOX-$NiCl_2$/$AgSbF_6$ | 32.3 | 0.0 | ND |
| 11 | (+)-Cy-salen-$TiCl_2$ | 10.2 | 0.0 | ND | 23 | (-)-PYBOX-$ZnCl_2$/$AgSbF_6$ | 14.7 | 1.7 | 2 |
| 12 | (+)-Cy-salen-Zn | 21.3 | 0.0 | ND | 24 | No Catalyst | 22.7 | 0.0 | ND |




**6-Methoxy-4-methylspiro[4.5]deca-3,6,9-triene-2,8-dione (3.06**). **General Procedure A:** (*S*)-Phenyl-CBS catalyst (11.7 mg, 0.035 mmol) was added to a flame dried 8 mL microwave vial equipped with stir bar in the glovebox. The vial was sealed with a Teflon cap, taken out of the glovebox, put under an argon atmosphere and dissolved in 1,2-dichloroethane (416 μL). A solution of $SnCl_4$ (0.028 mmol, 100 μL of a 0.28 M solution in $CH_2Cl_2$/1,2-dichloroethane) was added and the mixture was allowed to stir for 30 minutes. Allenyl ketone (**3.05**) (0.069 mmol, 200 μL of a 0.35 M solution in 1,2-dichloroethane) was added to the reaction mixture and stirred for an additional 4 h. The resultant reaction mixture was diluted with $CH_2Cl_2$ (5 mL), quenched with 1 M HCl (5 mL), and extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (20% EtOAc in hexanes to 80% EtOAc in hexanes) provided **3.06** (12.4 mg) in 89% yield: $^1$H NMR (500 MHz, $CDCl_3$) δ 6.37 (d, $J$ = 9.8 Hz, 1H), 6.33 (dd, $J$ = 9.8, 1.0 Hz, 1H), 6.17 (d, $J$ = 1.0 Hz, 1H), 5.75 (s, 1H), 3.73 (s, 3H), 2.84 (d, $J$ = 18.4 Hz, 1H), 2.47 (d, $J$ = 18.4 Hz, 1H), 1.84 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 205.4, 187.5, 176.0, 173.5, 145.6, 133.0, 129.7, 104.3, 56.3, 54.4, 45.2, 15.0; chiral HPLC (OD column, 70:30 hexanes:*i*-PrOH, 0.8 mL/min, 220 nm): $t_R$ of **3.06**: 17.3 min and 20.8 min. Spectroscopic data match those reported in the literature.[117]

**Preparation of a racemic sample of 3.06.**

Allenyl ketone (**3.05)** (0.032 mmol, 320 μL of a 0.1 M solution in $CH_2Cl_2$) was added to a flame dried 8 mL microwave vial equipped with stir bar under argon and placed in a 0 °C ice bath. $SnCl_4$ (0.032 mmol, 32 μL of a 1.0 M solution in $CH_2Cl_2$) was added dropwise. The mixture was allowed to warm to ambient temperature and stirred for 1 h. The resultant reaction mixture was diluted with $CH_2Cl_2$ (5 mL), quenched with 1 M HCl (5 mL), and extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered and concentrated *in vacuo* providing **3.06** (6.8 mg) in 98% yield.

**Bench-top scale of the HTE leads (**Table 3.3**)**

(*R,R*)-STIEN-AlMe (9.5 mg, 0.0184 mmol) or (*R,R*)-STIEN-$TiCl_2$ (10.9 mg, 0.018 mmol) were added to a flame dried 8 mL microwave vial equipped with a stir bar, dissolved in 1,2-dichloroethane (230 μL), sealed with a Teflon cap, removed from the glovebox and put under an argon atmosphere. A solution of **3.05** (0.046 mmol, 230 μL of a 0.2 M solution in 1,2-dichloroethane) was added to the reaction mixture and stirred for 20 h. The products were isolated following general procedure A.

PYBOX-$Sc(OTf)_3$ and PYBOX-$Yb(OTf)_3$ were made *in situ*: indaPYBOX (7.6 mg, 0.019 mmol) and $Sc(OTf)_3$ (9.1 mg, 0.018 mmol) or $Yb(OTf)_3$ (11.4 mg, 0.018 mmol) were added to a flame dried 8 mL microwave vial equipped with stir bar, dissolved in 1,2-dichloroethane (230 μL), sealed with a Teflon cap, removed from the glovebox and placed in a 50 °C oil bath for 10 min, allowed to cool to ambient temperature and stirred for an additional 2 h. A solution of **3.05** (0.046 mmol, 230 μL of

a 0.2 M solution in 1,2-dichloroethane) was added to each reaction mixture and allowed to stir for 20 h. The products were isolated following general procedure A.

**Screen of Lewis and Brønsted acid assisted CBS catalysts for spirocyclization (**Table 3.4**).**

General procedure A was followed using (*S*)-phenyl-CBS (7.8 mg, 0.023 mmol) and designated Lewis/Brønsted acid (0.018 mmol) in 1,2-dichloroethane (230 μL). Addition of **3.05** (0.046 mmol, 20 μL of a 0.2 M solution in 1,2-dichloroethane) was done at 0 °C. The mixture was allowed to warm to ambient temperature and stirred for 20 h. My co-worker Sergei Tcyrulnikov conducted the experiments using TMSOTf, TMSCl and MeI.

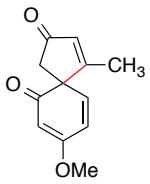
**Exploration of (*S*)-aryl-CBS catalyst with $SnCl_4$ (**Scheme 3.3**).**

(*S*)-*o*-Tolyl-CBS was purchased from Sigma-Aldrich but was impure and not suitable for use. (*S*)-*o*-Tolyl-CBS (0.023 mmol, 451 μL of a 0.05 M solution in toluene) and (*S*)-naphthyl-CBS (0.023 mmol, 230 μL of a 0.1 M solution in toluene) were both synthesized by known procedures[109a,135] General procedure A was followed using $SnCl_4$ (0.018 mmol, 18 μL of a 1 M solution in $CH_2Cl_2$). Addition of **3.05** (0.046 mmol, 110 μL of 0.48 M solution in 1,2-dichloroethane) was done at 0 °C, allowed to warm to ambient temperature and stirred for 16 h.

**Additives for catalyst turnover (**Table 3.5**).**

135) Lee, S. I.; Jang, J. H.; Hwang, G.–S.; Ryu, D. H. "Asymmetric Synthesis of α-Alkylidene-β-hydroxy-γ-butyrolactones via Enantioselectivity Tandem Michael-Aldol Reaction" *J. Org. Chem.* **2013**, *78*, 770-775.

General procedure A was followed using (*S*)-phenyl-CBS (11.5 mg, 0.034 mmol) dissolved in 1,2-dichloroethane (200 μL) and $SnCl_4$ (0.028 mmol, 125 μL of a 0.2 M solution in $CH_2Cl_2$/1,2-dichloroethane). After the reaction mixture stirred for 30 minutes, **3.05** (0.069 mmol, 165 μL 0.4 M solution in 1,2-dichloroethane) was added, followed by the indicated additive (0.069 mmol). The reaction mixture was stirred for 4 h with $H_2O$ and MeOH. My co-worker Sergei Tcyrulnikov conducted the experiments using *i*Pr-OH, TMSOTf, TMSCl and MeI following the above procedure but allowing the reaction mixture to stir for 15 h, 4 h, 1 h and 15 h, respectively.




**8-Methoxy-4-methylspiro[4.5]deca-3,7,9-triene-2,6-dione** (**3.14**). General procedure A was followed using (*S*)-naphthyl-CBS (0.016 mmol, 320 μL of a 0.05 M solution in toluene) and $SnCl_4$ (0.013 mmol, 113 μL of a 0.12 M solution in $CH_2Cl_2$/1,2-dichloroethane). After the reaction mixture stirred for 1 h, **3.13** (0.033 mmol, 150 μL of a 0.22 M solution in 1,2-dichloroethane) was added and allowed to stir for 5 h. Purification by column chromatography (20% EtOAc in Hexanes to 80% EtOAc in Hexanes) provided **3.14** (6.4 mg) in 96% yield: $^1$H NMR (500 MHz, $CDCl_3$) δ 6.31 (dd *J* = 9.9, 2.0 Hz, 1H), 6.21 (d, *J* = 9.8 Hz, 1H), 6.12 (d, *J* = 2.0, 1H), 5.60 (s, 1H), 3.82 (s, 3H), 2.80 (d, *J* = 18.1 Hz, 1H), 2.36 (d, *J* = 18.1 Hz, 1H), 1.86 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 206.8, 198.5, 176.4, 172.3, 143.1, 132.5, 123.3, 100.7, 60.9, 56.3, 47.1, 15.5; IR (film) 2925, 2854, 1721, 1693, 1652, 1622, 1571 cm$^{-1}$; HRMS (ESI) calcd for $C_{12}H_{13}O_3$

$[M+H]^+$ *m/z* = 205.0865; found 205.0873; chiral HPLC (IA, 90:10 hexanes:*i*-PrOH, 0.8 mL/min, 220 nm): $t_R$ of **3.14**: 22.89 min (major) and 24.71 min (minor).

**Preparation of a racemic sample of 3.14:**

Allenyl ketone (**3.13**) (0.021 mmol, 60 μL of a 0.33 M solution in $CH_2Cl_2$) was added to a flame dried 8 mL microwave vial equipped with stir bar under argon and placed in a -10 °C NaCl ice bath. $BF_3$•$OEt_2$ (0.025 mmol, 60 μL of a 0.47 M solution in $CH_2Cl_2$) was added dropwise. The mixture was allowed to warm to 0 °C and stirred for 1 h. The resultant reaction mixture was diluted with $CH_2Cl_2$ (5 mL), quenched with 1 M HCl (5 mL), and extracted with $CH_2Cl_2$ (3 x 10 mL). The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. Purification by column chromatography (20% EtOAc in hexanes to 80% EtOAc in hexanes) provided **3.14** (4.3 mg) in 86% yield.

# 4. CHEMOSELECTIVE ACTIVATION OF C($sp^3$)–H BOND OVER C($sp^2$)–H BOND WITH Pd(II)

## 4.1. BACKGROUND

### *4.1.1. C–H Activation*

The ability of metals, and particularly Pd catalysts, to insert selectively into C–H bonds has provided a host of new, useful methods for the construction of organic structure.[136] C–H Activation is highly significant because additional steps to preactivate a center for a bond construction (e.g., halogenation) can be avoided, thereby increasing efficiency by reducing step-count and decreasing waste streams.

Cross dehydrogenative coupling (CDC) is the ideal reaction where a C–H from each of the two reacting partners is selectively removed, accompanied by an oxidative fragment union, and much progress in this area has been made to date.[137] In this strategy, directing groups commonly play a key role by coordinating substrate to the catalyst, thus lowering the energy barrier for C–H bond functionalization.[138] Although advances with metal catalysts in alkyl C–H activation at unactivated positions have been reported, much

136) (a) Alberico, D.; Scott, M. E.; Lautens, M. "Aryl-Aryl Bond Formation by Transition-Metal-Catalyzed-Direct Arylation" *Chem. Rev.* **2007**, *107*, 174-238. (b) McGlacken, G. P.; Bateman, L. M. "Recent advances in aryl-aryl bond formation by direct arylation" *Chem. Soc. Rev.* **2009**, *38*, 2447-2464. (c) Wencel-Delord, J.; Droge, T.; Liu, F.; Glorius, F. "Towards mild metal-catalyzed C-H bond activation" *Chem. Soc. Rev.* **2011**, *40*, 4740-4761. (d) Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. "Beyond Directing Groups: Transition-Metal-Catalyzed C-H Activation of Simple Arenes" *Angew. Chem., Int. Ed.* **2012**, *51*, 10236-10254.

137) (a) Yeung, C. S.; Dong, V. M. "Catalytic Dehydrogenative Cross-Coupling: Forming Carbon-Carbon Bonds by Oxidizing Two Carbon-Hydrogen Bonds" *Chem. Rev.* **2011***, 111*, 1215-1292. (b) Liu, C.; Zhang, H.; Shi, W.; Lei, A. "Bond Formations between Two Nucleophiles: Transition Metal Catalyzed Oxidative Cross-Coupling Reactions" *Chem. Rev.* **2011**, *111*, 1780-1824.

138) (a) Lyons, T. W.; Sanford, M. S. "Palladium-Catalyzed Ligand-Directed C-H Functionalization Reactions" *Chem. Rev.* **2010**, *110*, 1147-1169. (b) Li, B.; Dixneuf, P. H. "$sp^2$ C-H bond activation in water and catalytic cross-coupling reactions" *Chem. Soc. Rev.* **2013**, *42*, 5744-5767.

progress remains to be made, and the versatility that Pd exhibits in bond formation (C–C, C–N, C–O, C–F, C–F, etc.) renders it appealing for further development.[139]

### *4.1.2. Orthogonal Reactivity of Toluene in C(sp$^2$)–H Activation*

Toluene derivatives are stable, commercially available, and easy to handle and may be potentially used as a benzylation reagents. The benzyl C–H bond in toluene is 20-30 kcal/mol weaker than the arene C–H but palladium displays a remarkable selectivity for C–H insertion into the C(sp$^2$)–H bond (Figure 4.1, left).[140] *In fact, methyl and other alkyl substituents on arenes have been shown to be compatible with Pd-catalyzed C(sp$^2$)–H insertion* (Figure 4.1, right).[141]

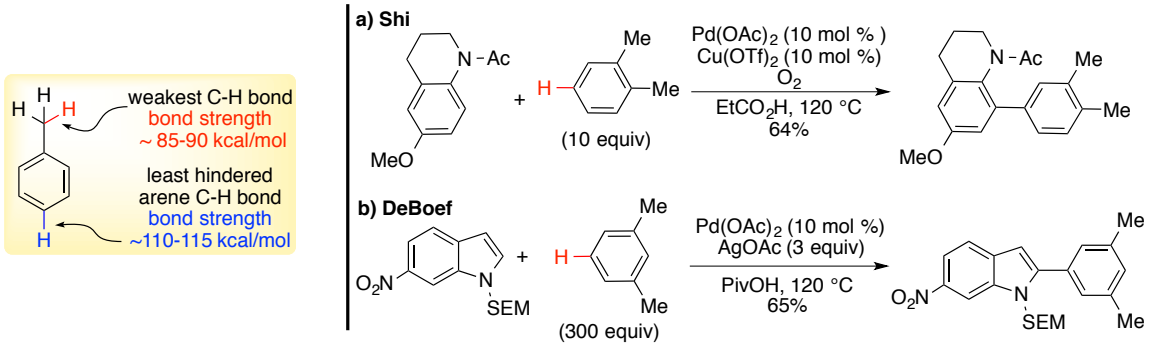



**Figure 4.1** C(sp$^2$)–H activation of toluene with Pd.

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139) For select examples of C-H activation of C(sp$^3$)–H bonds without directing groups or pre-activation, see: (a) Davies, H. M. L.; Hansen, T. "Asymmetric Intermolecular Carbenoid C-H Insertions Catalyzed by Rhodium(II) (S)-*N*-(*p*-Dodecylphenyl)sulfonylprolinate" *J. Am. Chem. Soc.* **1997**, *119*, 9075-9076. (b) Waltz, K. M.; Hartwig, J. F. "Functionalization of Alkanes by Isolated Transition Metal Boryl Complexes" *J. Am. Chem. Soc.* **2000**, *122*, 11358-11369. (c) Chen, M. S.; White, M. C. "A Predictably Selective Aliphatic C-H Oxidation Reaction for Complex Molecule Synthesis" *Science* **2007**, *318*, 783-787.

140) Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255.

141) (a) Li, B.-J.; Tian, S.-L.; Fang, Z.; Shi, Z.-J. "Multiple C–H Activations to Construct Biologically Active Molecules in a Process Completely Free of Organohalogen and Organometallic Components" *Angew. Chem., Int. Ed.* **2008**, *47*, 1115-1118. (b) Potavathri, S.; Pereira, K. C.; Gorelsky, S. I.; Pike, A.; LeBris, A. P.; DeBoef, B. "Regioselective Oxidation Arylation of Indoles Bearing *N*-Alkyl Protecting Groups: Dual C-H Functionalization via a Concerted Metalation-Deprotonation Mechanism" *J. Am. Chem. Soc.* **2010**, *132*, 14676-14681

Presumably, favorable coordination of the palladium catalyst to the π-system of the arene positions the metal carboxylate for a favorable deprotonative insertion (Figure 4.2).[142]

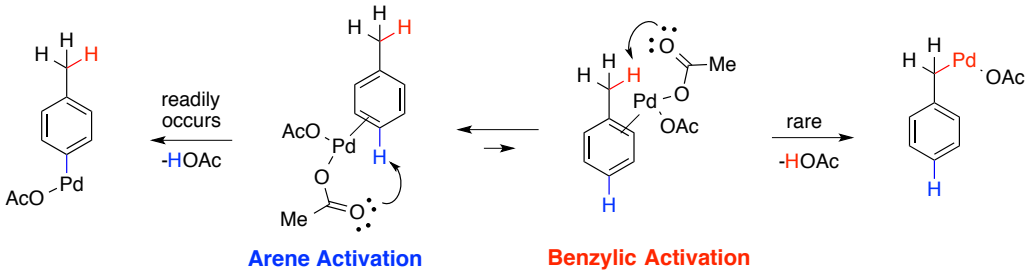


**Figure 4.2** C($sp^2$)–H vs C($sp^3$)–H activation of toluene with Pd.

*4.1.3. C($sp^3$)–H Activation of Toluene via Radical Pathways*

Of late, radical mediated processes for activation of toluene have shown considerable promise in CDC.[143-146] A benzylic radical is easily formed at elevated temperatures with (*t*-BuO)$_2$. Huang and co-workers have demonstrated that the tolyl and heteroatom radical can be transformed to benzylic amides and esters from CO insertion

142) (a) Lapointe, D.; Fagnou, K. "Overview of the Mechanistic Work on the Concerted Metallation-Deprotonation Pathway" *Chem. Lett.* **2010**, *39*, 1118-1126. (b) Balcells, D.; Clot, E.; Eisenstein, O. "C–H Bond Activation in Transition Metal Species from a Computational Perspective" *Chem. Rev.* **2010**, *110*, 749-823.

with Pd (Figure 4.3, top).[143] Powell and co-workers have successfully used Cu to catalyze the formation of benzylic amines (Figure 4.3, bottom).[144]

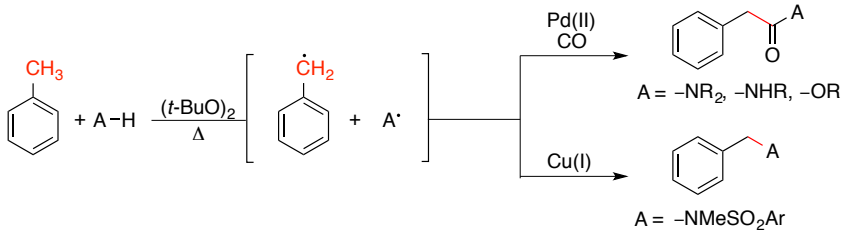


**Figure 4.3** CDC via diradical formation.

CDC can be achieved when a toluene radical is combined with Pd catalyzed C–H activation. The tolyl radical formed from $(t\text{-BuO})_2$ can be transformed to benzaldehyde if exposed to air.[145,146] Yin and Sun pioneered the facile *ortho*-acylation of acetanilides by combining *in situ* acyl radical formation with Pd catalyzed C($sp^2$)-H activation (Figure 4.4).[145] This reaction motif has proven to be general for toluene with various arenes containing directing groups such as carbamate, azoarenes and pyridine.[146]

143) (a) Xie, P.; Xie, Y.; Qian, B.; Zhou, H.; Xia, C.; Huang, H. "Palladium-Catalyzed Oxidative Carbonylation of Benzylic C–H Bonds via Nondirected C($sp^3$)–H Activation" *J. Am. Chem. Soc.* **2012**, *134*, 9902-9905. (b) Xie, P.; Xia, C.; Huang, H. "Palladium-Catalyzed Oxidative Aminocarbonylation: A New Entry to Amides via C–H Activation" *Org. Lett.* **2013**, *15*, 3370-3373. (c) Liu, H.; Laurenczy, G.; Yan, N.; Dyson, P. J. "Amide bond formation *via* C($sp^3$)-H bond functionalization and CO insertion" *Chem. Commun.* **2014**, *50*, 341-343.

144) Powell, D. A.; Fan, H. "Copper-Catalyzed Amination of Primary Benzylic C–H Bonds with Primary and Secondary Sulfonamides" *J. Org. Chem.* **2010**, *75*, 2726-2729.

145) Yin, Z.; Sun, P. "Palladium-Catalyzed Direct *ortho*-Acylation through an Oxidative Coupling of Acetanilides with Toluene Derivatives" *J. Org. Chem.* **2012**, *77*, 11339-11344.

146) (a) Wu, Y.; Choy, P. Y.; Mao, F.; Kwong, F. Y. "Toluene derivatives as simple coupling precursors for cascade palladium-catalyzed oxidative C-H bond acylation of acetanilides" *Chem. Comm.* **2013**, *49*, 689-691. (b) Xiong, F.; Qian, C.; Lin, D.; Zeng, W.; Lu, X. "Palladium-Catalyzed Cascade Oxidation/$sp^2$ C–H Acylation of Azoarenes with Aryl Methanes" *Org. Lett.* **2013**, *15*, 5444-5447. (c) Xu, Z.; Xiang, B.; Sun, P. "Palladium catalyzed direct *ortho* C-H acylation of 2-arylpyridines using toluene derivatives as acylation reagents" *RSC Advances* **2013**, *3*, 1679-1682.

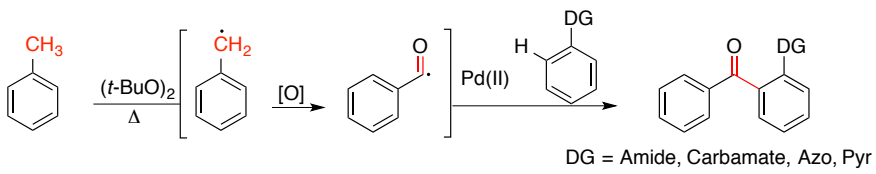


**Figure 4.4** CDC via radical mediated oxidation.

### *4.1.4. C($sp^3$)–H Activation of Toluene via non-Radical Processes*

Palladium catalyzed alkyl C–H activation without radicals or directing groups is rare.[147] In 2008, Shi[148] and White[149] developed the regioselective C–H activation of allylbenzene (Figure 4.5).[150] Each research group found that it was necessary to use the preformed 1,2-bis(benzylsulfinyl)-ethane $Pd(OAc)_2$ complex. However, activation of toluene by non-radical processes is a long-standing challenge. Some success has been seen with *ortho*-directing groups on tolyl analogs.[151,152]

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147) For benzylation from benzyl acetates and Pd, see: (a) Trost, B. M.; Czabaniuk, L. C. "Palladium-Catalyzed Asymmetric Benzylation of 3-Aryl Oxindoles" *J. Am. Chem. Soc.* **2010**, *132*, 15534-15536. (b) Kuwano, R. "Catalytic Transformations of Benzylic Carboxylates and Carbonates" *Synthesis* **2009**, *7*, 1049-1061.

148) Lin, S.; Song, C.-X.; Cai, G.-X.; Wang, W.-H.; Shi, Z.-J. "Intra/Intramolecular Direct Allylic Alkylation via Pd(II)-Catalyzed Allylic C-H Activation" *J. Am. Chem. Soc.* **2008**, *130*, 12901-12903.

149) Young, A. J.; White, M. C. "Catalytic Intermolecular Allylic C–H Alkylation" *J. Am. Chem. Soc.* **2008**, *130*, 14090-14091.

150) Tang, S.; Wu, X.; Liao, W.; Liu, K.; Liu, C.; Luo, S.; Lei, A. "Synergistic Pd/Enamine Catalysis: A Strategy for the C–H/C–H Oxidative Coupling of Allylarenes with Unactivated Ketones" *Org. Lett.* **2014**, *16*, 3584-3587.

151) For seminal work on Pd catalyzed benzylic C-H activation, see: (a) Chen, X.; Goodhue, C.E.; Yu, J.-Q. "Palladium-Catalyzed Alkylation of $sp^2$ and $sp^3$ C-H Bonds with Methylboroxine and Alkylboronic Acids: Two Distinct C-H Activation Pathways" *J. Am. Chem. Soc.* **2006,** *128*, 12634-12635. (b) Campeau, L.-C.; Schipper, D.J.; Fagnou, K. "Site-Selective $sp^2$ and Benzylic $sp^3$ Palladium-Catalyzed Direct Arylation" *J. Am. Chem. Soc.* **2008**, *130*, 3266-3267. (c) Stowers, K.J.; Fortner, K.C.; Sanford, M.S. "Aerobic Pd-Catalyzed $sp^3$ C-H Olefination: A Route to Both N-Heterocyclic Scaffolds and Alkenes" *J. Am. Chem. Soc.* **2011**, *133*, 6541-6544.

152) For reviews on $sp^3$ C-H activation, see: (a) Chen, X.; Engle, K.M.; Wang, D.-H.; Yu J.-Q. "Palladium(II)-Catalyzed C-H Activation/C-C Cross-Coupling Reactions: Versatility and Practicality" *Angew. Chem., Int. Ed.* **2009**, *48*, 5094-5115. (b) Baudoin, O. "Transition metal-catalyzed arylation of unactivated C($sp^3$)-H bonds" *Chem. Soc. Rev.* **2011**, *40*, 4902-4911. (c) Li, H.; Li, B.-J.; Shi, Z.-J.

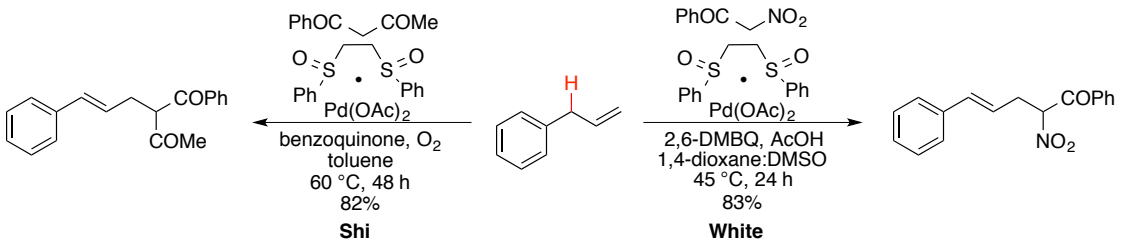



**Figure 4.5** C($sp^3$)–H activation of allylbenzene.

In 2007, Lu and co-workers provided evidence that regioselective C–H activation of toluene was feasible (Figure 4.6).[153] They found when toluene was treated with $Pd(OAc)_2$ at 45 °C for prolonged reaction times that homo-$sp^2$-$sp^3$ coupling and homo-$sp^2$ coupling could be favored with either an excess (7.5 mmol) or minimal amount of TFA (0.5 mmol). Sterics play an important role in the regioselective coupling; substitution of mesitylene for toluene results in only homo-$sp^2$-$sp^3$ coupling. Kinetic isotope effect studies were inconclusive in determining if the C($sp^3$)–H activation was the rate-determining step.

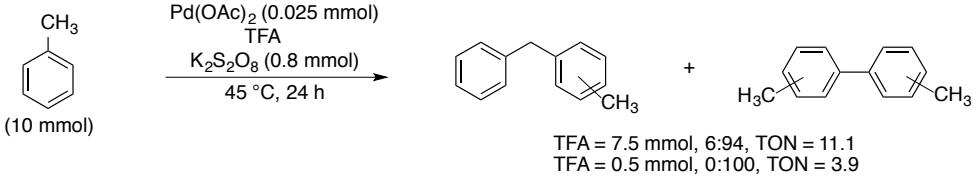



**Figure 4.6** Regioselective C–H activation of toluene with Pd(II).

"Challenges and progress: palladium-catalyzed $sp^3$ C-H activation" *Catal. Sci. Technol.* **2011**, *1*, 191-206.

153) Rong, Y.; Li, R.; Lu, W. "Palladium(II)-Catalyzed Coupling of *p*-Xylene via Regioselective C–H Activation in TFA" *Organometallics* **2007**, *26*, 4376-4378.

The Pd catalyzed acetoxylation of toluene was developed in 1968 by Bryant.[154] In 2013, Zhang and co-workers found that this process could be improved with benzoic acid derivatives (Figure 4.7).[155] Zhang proposes that $Pd(OAc)_2$ can insert into the C–H bond of toluene, generating the Pd-benzyl intermediate and AcOH. An intermolecular attack of the carboxylic acid on the benzyl or reductive elimination from carboxylate ligand exchange on the Pd can provide the observed product. A $k_H/k_D = 2.4$ was observed for toluene vs $d_8$-toluene, suggesting the C–H activation step is the RDS.

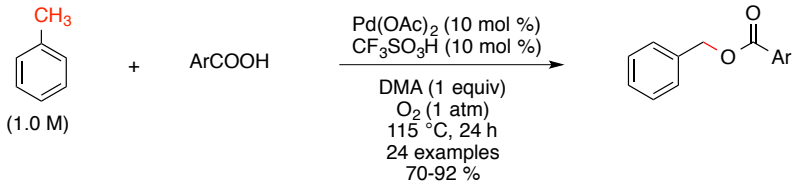



**Figure 4.7** Benzylation of carboxylic acids by Pd catalyzed C–H activation of toluene.

The work by Lu,[153] Bryant[154] and Zhang[155] are rare examples of Pd catalyzed activation of toluene. *In fact, toluene is considered benign in most Pd processes, and is often used as a reaction solvent.* Our longstanding interest[95,156] in metal catalyzed C–H activation prompted our investigation of the Pd catalyzed benzylic activation of toluene.

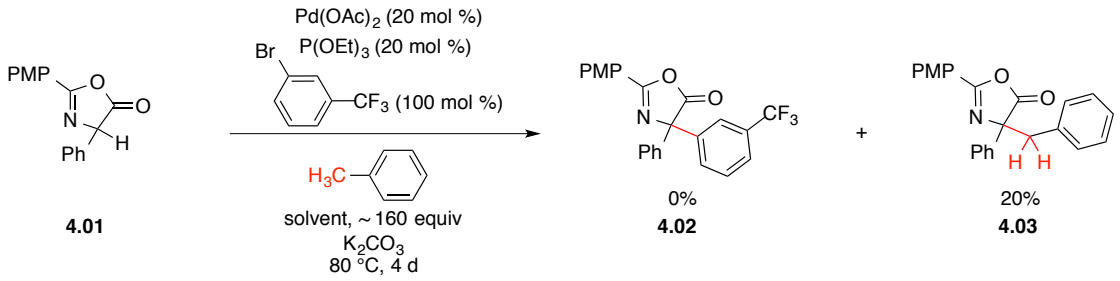
154) Bryant, D. R.; McKeon, J. E.; Ream, B. C. "A Palladium-Catalyzed Synthesis of Benzyl Esters from Methylbenzenes" *J. Org. Chem.* **1968**, *33*, 4123-4127.
155) Liu, H.; Shi, G.; Pan, S.; Jiang, Y.; Zhang, Y. "Palladium-Catalyzed Benzylation of Carboxylic Acids with Toluene via Benzylic C–H Activation" *Org. Lett.* **2013**, *15*, 4098-4101.
156) Li, X.; Yang, J.; Kozlowski, M. C. "Enantioselective Oxidative Biaryl Coupling Reactions Catalyzed by 1,5-Diazadecalin Metal Complexes" *Org. Lett.* **2001**, *3*, 1137-1140.

## 4.2. RESULTS

### *4.2.1. Serendipitous Discovery*

Initial studies on the chemoselective activation of toluene arose from a serendipitous discovery. In 2003, Hartwig and co-workers published the first Pd catalyzed α-arylation of azlactones.[157] We envisioned that an asymmetric variant of this reaction could be achieved with the aid of high-throughput experimentation (HTE). Initial PME screens proved unsuccessful and led to a wider survey of non-traditional ligands such as alkyl phosphites and phosphoramidites. Treatment of phenylglycine azlactone (**4.01**) with the standard arylation conditions [$Pd(OAc)_2$, P(*t*-Bu)$_3$, 3-iodo-benzotrifluoride, $K_2CO_3$ in toluene] developed by Hartwig provided the desired arylated azlactone (**4.02**) in 63% yield. However, when $P(OEt)_3$ was substituted for P(*t*-Bu)$_3$ and 3-bromo-benzotrifluoride for 3-iodo-benzotrifluoride, the arylated product was not observed. After careful examination of the reaction mixture, it was found that the phenylglycine azlactone had undergone benzylation (**4.03**) in 20% yield (Scheme 4.1).

**Scheme 4.1** Unexpected benzylation of phenylglycine azlactone.




This unexpected result from modification of the Hartwig conditions was very intriguing. Benzylation occurred from incorporation of the solvent with the phenylglycine

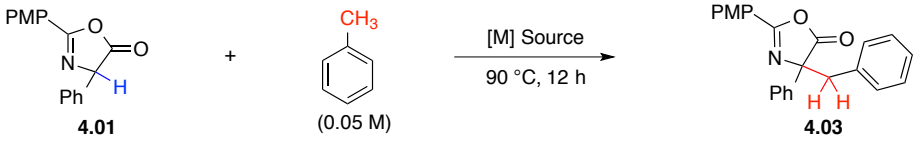
157) Liu, X.; Hartwig, J. F. "Palladium-Catalyzed α-Arylation of Azlactones to Form Quaternary Amino Acid Derivatives" *Org. Lett.* **2003**, *5*, 1915-1918.

azlactone. The conditions used were fairly common but insertion into the C–H bond of toluene is rare (see Sections *4.1.3. – 4.1.4.*). Our initial goals were to determine which components of the reaction mixture were necessary for benzylation, whether the transformation operates with other tolyl analogs, and whether the process occurs via free-radicals or via Pd mediated C($sp^3$)–H activation.

### *4.2.2. Optimization of Stoichiometric Pd Conditions*

Further analysis of the original conditions found for benzylation (see Scheme 4.1), revealed that benzylation occurred when aryl halide, phosphite and base were removed. This result prompted our exploration of various late-transition metals for the selective C($sp^3$)–H activation of toluene (Table 4.1). To our surprise, only Pd(II) provided the benzylated product (Table 4.1, entries 6 and 7). $PdCl_2$ provided the phenylglycine azlactone dimer but all other Pd sources promptly caused decomposition of starting material (Table 4.1, entries 8-12). Palladium carboxylates have been shown to be very successful at C($sp^2$)–H activation when combined with a directing group; the preferential C($sp^3$)–H activation observed in this new technology is novel and without precedent.

**Table 4.1** Metal sources for C–H activation of toluene.

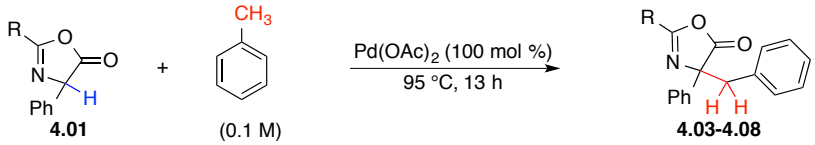



| entry | [M] source (100 mol %) | yield (%)[a] | entry | [M] source (100 mol %) | yield (%)[a] |
|---|---|---|---|---|---|
| 1 | $Au(OAc)_3$[b] | 0 | 7 | $Pd(TFA)_2$ | 81 |
| 2 | $Cu(OAc)_2$[b] | 0 | 8 | $PdCl_2$ | 0 |
| 3 | $Rh_2(OAc)_4$[b] | 0 | 9 | $PdCl_2(MeCN)_2$ | 0 |
| 4 | $Ni(OAc)_2$[b] | 0 | 10 | $PdCl_2(COD)_2$ | 0 |
| 5 | $[Pt_4(OAc)_8]$•HOAc[b] | 0 | 11 | $[Pd(allyl)Cl_2]_2$ | 0 |
| 6 | $Pd(OAc)_2$ | 77 | 12 | $Pd_2dba_3$ | 0 |

[a]Isolated yield. [b]Phenylgylcine azlactone dimer was substituted for **4.03**, 20 mol % metal source was used and reaction time was 5 h.

The protecting group on the phenylglycine azlactone was modified to determine if electronics played an important role in this transformation (Table 4.2). Electron-rich and –poor phenyl protecting groups provided the benzylated product in similar yields (Table 4.2, entries 1-3). However, when alkyl substituents were substituted for the phenyl ring, benzylation was either less efficient or not observed (Table 4.2, entries 4-6). With the $CF_3$ protecting group, the phenylglycine azlactone dimer was not observed (Table 4.2, entry 6). PMP was chosen as the protecting group on phenylglycine azlactone for further studies because it provided the benzylation product in the highest yield and the methoxy substituent was easily observed in the $^1H$ NMR.

**Table 4.2** Modification of the phenylglycine azlactone protecting group.

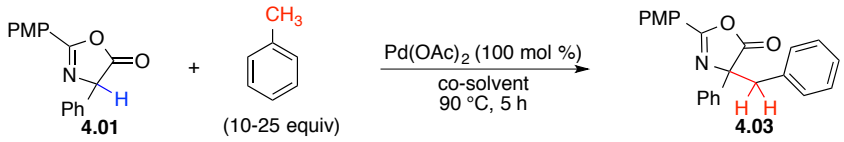



| entry | R = | yield (%)[a] | entry | R = | yield (%)[a] |
|---|---|---|---|---|---|
| 1 | *p*-MeO-$C_6H_4$ (PMP) | 83 | 4 | *t*-Bu | 44 |
| 2 | *p*-Cl-$C_6H_4$ | 69 | 5 | Me | ~20[b] |
| 3 | $C_6H_5$ | 70 | 6 | $CF_3$ | 0 |

[a]Isolated yield. [b]Conversion based on $^1H$ NMR.

With the goal of finding conditions that engendered suitable reactivity while minimizing the amount of toluene, a focused screen of co-solvents was designed (Table 4.3). 1,4-Dioxane was identified as the optimal co-solvent for reducing toluene loading (80 equiv to 25 equiv) while providing the benzylation product in good conversion. Reduction of toluene to 10 equiv reduced the formation of the benzylated product (Table 4.3, entries 5-7). Solvents that are strong Pd coordinators (e.g., DMSO, DMF) prevented benzylation entirely.

**Table 4.3** Survey of co-solvents.




| entry | co-solvent (0.3 M) | toluene (equiv) | conv (%)[a] | entry | co-solvent (0.3 M) | toluene (equiv) | conv (%)[a] |
|---|---|---|---|---|---|---|---|
| 1 | none | 25 | >90 | 5 | none | 10 | ~90 (68)[b] |
| 2 | benzene | 25 | >90 | 6 | benzene | 10 | ~90 (65)[b] |
| 3 | cyclohexane | 25 | >90 | 7 | 1,4-dixoane | 10 | 25[c] |
| 4 | 1,4-dioxane | 25 | >90 | | | | |

[a]Determined by $^1$H NMR. [b]Isolated yield. [c]3:1 mixutre of phenylglycine azlactone and desired product.

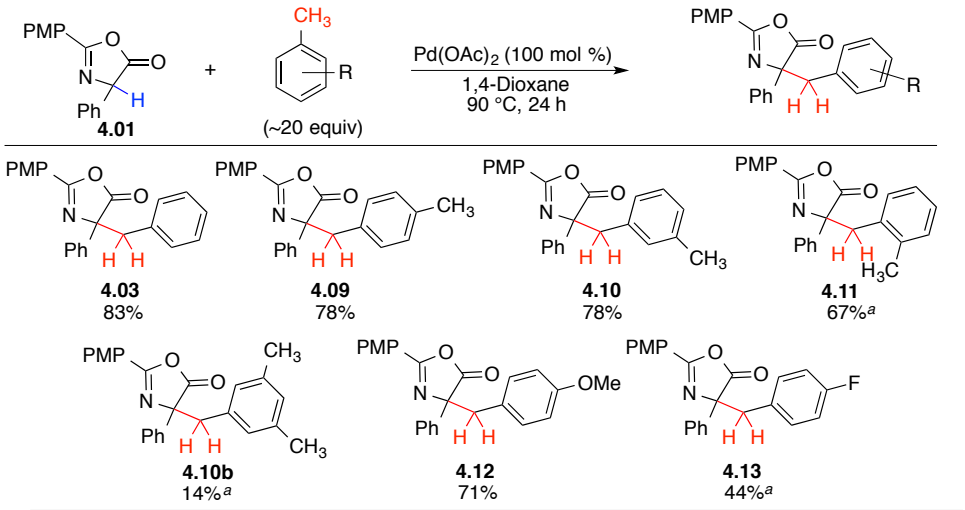
### *4.2.3. Substrate Scope with Stoichiometric Pd*

The benzylation of phenylglycine azlactone with a series of tolyl analogs under the optimal conditions was performed and the results are displayed in Table 4.4.[158] For most substrates, the novel technology developed provided moderate to good yields. In contrast to Bryant's results with acetoxylation of xylene isomers, the mono-benzylated product was the only product observed (Table 4.4, **4.09**-**4.11**).[154] This technology affords

158) Tolyl analogs that did not provide benzylated product are detailed in the supporting information.

complete chemoselectivity for C($sp^3$)–H activation, as no arlyation of the phenylglycine azlactone was observed. Mesitylene only provided the benzylated product in 14% yield; increased temperatures and prolonged reaction times did not improve product formation (Table 4.4, **4.10b**). Electron-rich tolyl analogs were more efficient (Table 4.4, **4.12** vs **4.13**).

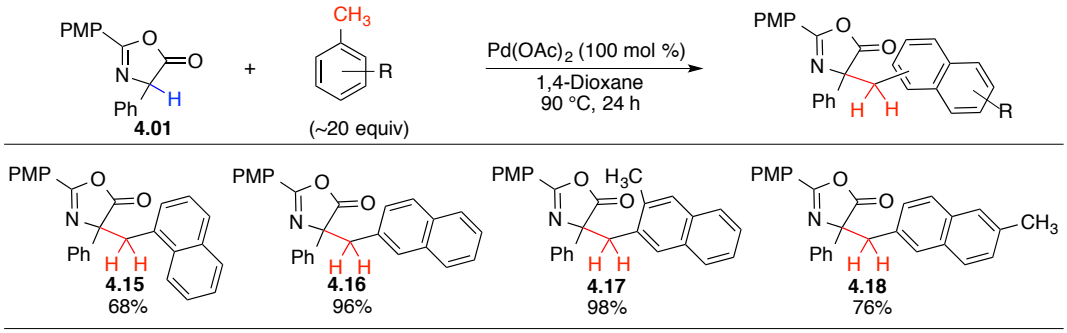
**Table 4.4** C–H Activation of tolyl analogs with phenylglycine azlactone.




[a]Neat reaction solution (0.05 M wrt to tolyl analog) at 120 °C for 14 h.

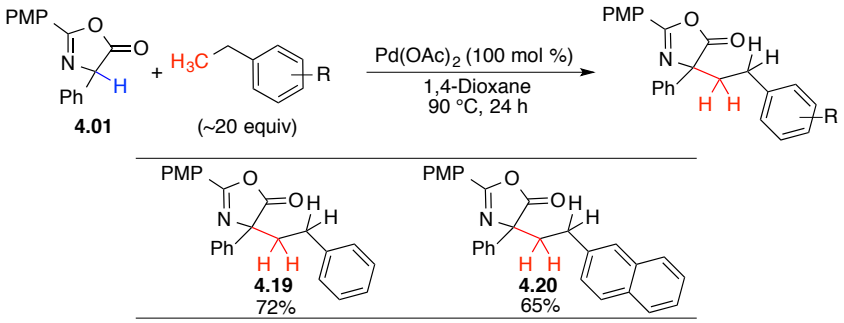
We desired to expand the scope of this technology to naphthalene analogs, because 1- and 2-bromomethylnaphthalene derivatives are relatively unstable for $S_N2$ transformation and are not widely commercially available. The use of 1- and 2-methylnaphthalene in CDC via radical mediated processes is uncommon because the tolyl analog is typically used neat, whereas the naphthyl compounds are typically solids. A series of methylnaphthalenes were explored with the optimal conditions (Table 4.5).

**Table 4.5** C–H Activation of methylnaphthalene analogs with phenylglycine azlactone.




The success with the selective C($sp^3$)–H bond activation of tolyl and methylnaphthyl analogs prompted our exploration of secondary benzylic C–H bonds.[159] The optimal conditions for benzylation of phenylglycine azlactone was studied with ethylbenzene and 2-ethylnaphthalene (Table 4.6). Unexpectedly, the benzyl product was not observed; instead, the ethylated product was formed in good yield (72% and 65%) with both substrates.[160]

**Table 4.6** Alkyl C–H activation with phenylglycine azlactone.



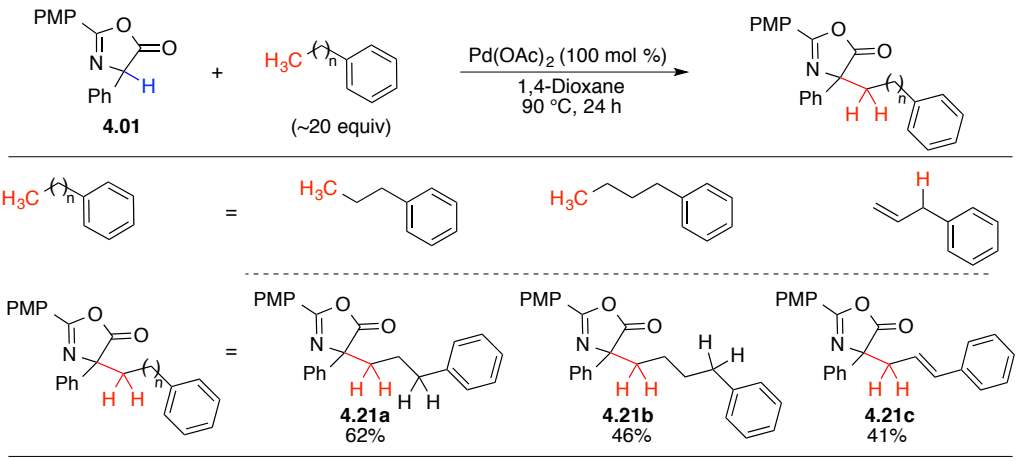

Extension of the alkyl chain on benzene to propyl and butyl most surprisingly gave rise to the alkylated product while <5% of the other insertion isomers were observed

159) Diphenylmethane and cumene were explored with the optimal conditions but did not provide the benzyl product. A chart of various alkyl substrates explored with phenylglycine azlactone has been included in the supporting information.

160) Ethylbenzene was explored by Bryant (ref. 154) and acetoxylation at the terminal methyl was observed as a complex product mixture in 8% isolated yield.

(Scheme 4.2, **4.21a** and **4.21b**). This chemoselectivity provides access to chemical space that would not be feasible via a radical mediated process. Allylbenzene was also explored and **4.21c** was formed in 41% yield; White's catalyst, 1,2-bis(benzylsulfinyl)-ethane $Pd(OAc)_2$ was also explored but the alkylated product was not observed.[149]

**Scheme 4.2** Alkyl vs allylic C–H activation.

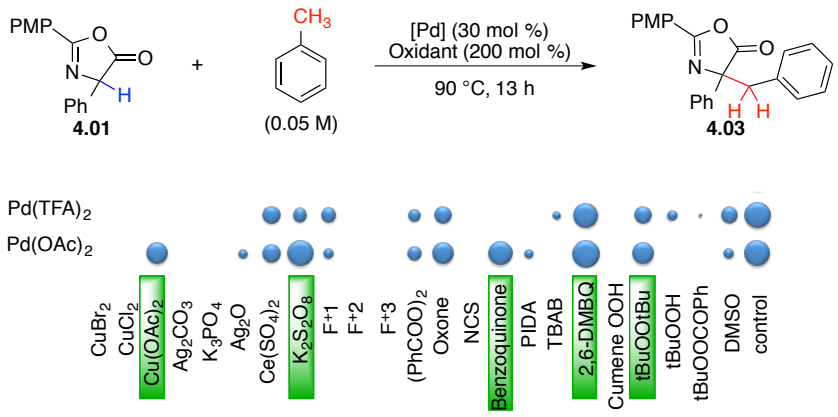



*4.2.4. Optimization of C($sp^3$)–H Activation of Tolyl with Catalytic Pd*

We have successfully discovered a novel C($sp^3$)–H activation of benzylic C–H bonds that can be coupled with phenylglycine azlactone by $Pd(OAc)_2$. We envisioned that if catalytic conditions could be found then this transformation would not only be novel but its utility would be heightened. A parallel microscale experimentation (PME) screen was designed to study 23 diverse oxidants and 2 palladium carboxylates with phenylglycine azlactone and toluene (Table 4.7). Transition metal oxidants that have been used extensively in Pd catalyzed C($sp^2$)–H processes that proceed through a

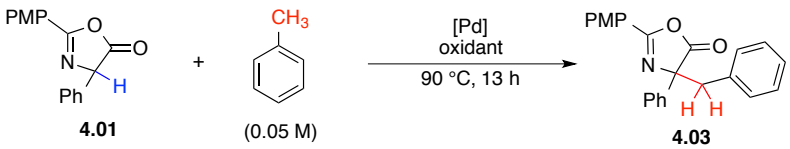
Pd(II)/Pd(0) catalytic cycle proved to be ineffective in this transformation. Peroxides did not stop product formation but were inefficient in turning over Pd.

**Table 4.7** Exploration of oxidant and Pd source via PME




The oxidants highlighted in green in Table 4.7 were targeted as optimal leads to explore on larger scale (Table 4.8). Replication of the PME conditions provided the benzylated product in 73% isolated yield with 2,6-dimethylbenzoquinone (2,6-DMBQ) and $Pd(OAc)_2$ (Table 4.8, entry 4). Reduction of Pd loading, while maintaining high levels of oxidant concentration, caused many unfavorable side reactions and product formation was reduced significantly (Table 4.8, entry 6). However, reduction of 2,6-DMBQ loading (200 vs 100 mol %) provided the benzylated product in 56% isolated yield (Table 4.8, entry 7).

**Table 4.8** Scale up of PME leads.

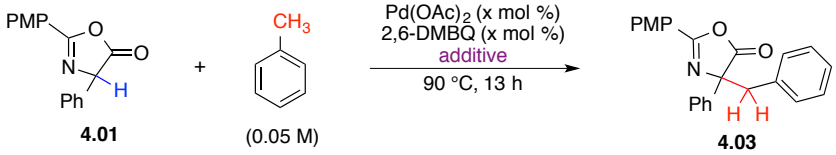



| entry | Pd source (30 mol %) | oxidant (200 mol %) | conv (%)[a] | entry | Pd source (10 mol %) | oxidant | conv (%)[a] |
|---|---|---|---|---|---|---|---|
| 1 | $Pd(OAc)_2$ | $Cu(OAc)_2$ | 17 | 6 | $Pd(OAc)_2$ | 2,6-DMBQ (200 mol %) | 50 |
| 2 | $Pd(OAc)_2$ | $K_2S_2O_8$ | 83 | 7 | $Pd(OAc)_2$ | 2,6-DMBQ (100 mol %) | 80 (56)[c] |
| 3 | $Pd(OAc)_2$ | BQ | decomp.[b] | | | | |
| 4 | $Pd(OAc)_2$ | 2,6-DMBQ | >90 (73)[c] | | | | |
| 5 | $Pd(TFA)_2$ | 2,6-DMBQ | 70 (36)[c] | | | | |

[a]Determined by $^1$H NMR. [b]Product was not obverved, only phenylglycine azlactone dimer was isolated. [c]Isolated yield.

The reduced yield when Pd loading was lowered motivated our exploration of additives with 2,6-DMBQ. Known Pd(0) stabilizers (DMSO, White's sulfoxide ligand,[149] DMA, phenanthroline, BIPY and cyclohexene) were explored without success. However, the addition of AcOH or PivOH enhanced the transformation (Table 4.9, entries 1-2). Presumably, the carboxylic acid additive promotes dissociation of the 1,4-quinone alkoxide from Pd(II). 2,6-DMBQ loading could also be reduced with the addition of the inexpensive co-oxidant, $MnO_2$ (Table 4.9).

**Table 4.9** Additives with catalytic $Pd(OAc)_2$ and 2,6-DMBQ.[a]

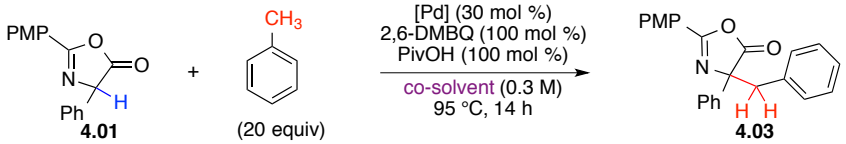



| entry | additive (100 mol %) | yield (%)[b] | entry | additive (100 mol %) | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | AcOH | 75 | 4 | $MnO_2$[c] | 70 |
| 2 | PivOH | 84 | 5 | AcOH, $MnO_2$[c] | 79 |
| 3 | TfOH | 0 | 6 | PivOH, $MnO_2$[c] | mixture[d] |

[a]$Pd(OAc)_2$ (10 mol %) and 2,6-DMBQ (100 mol %). [b]Isolated yield. [c]$Pd(OAc)_2$ (20 mol %) 2,6-DMBQ (20 mol %), $MnO_2$ (200 mol %). [d]50:50 mixture of P and dimer.

With the goal of finding conditions that engendered suitable reactivity while minimizing the amount of toluene, a focused PME screen was designed (Table 4.10). $Pd(OAc)_2$ and $Pd(TFA)_2$ were explored with six high boiling solvents that provided some stabilization to prevent Pd black formation. 1,4-Dioxane was identified as the best co-solvent with both Pd sources (Table 4.10, entries 3 and 9). A PME screen of acid sources was also conducted but proved that our initial acid choices (AcOH and PivOH) were optimal.

**Table 4.10** PME screen of co-solvents with optimal catalytic conditions.



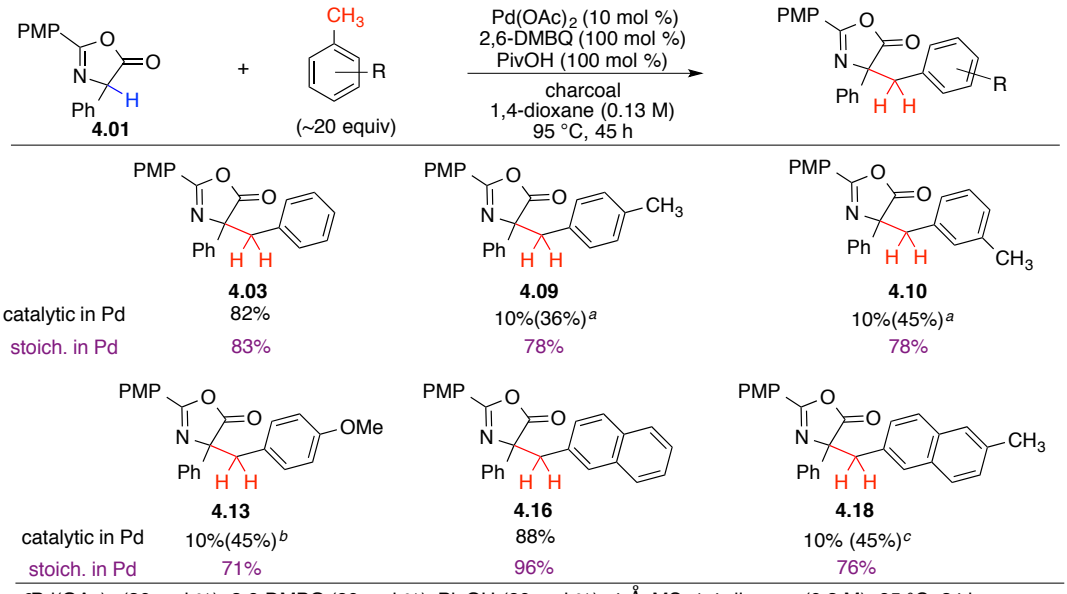

| entry[a] | co-solvent (0.3 M) | P/IS[b] | (P + dimer)/IS[b] | entry[c] | co-solvent (0.3 M) | P/IS[b] | (P + dimer)/IS[b] |
|---|---|---|---|---|---|---|---|
| 1 | DMF | 0.53 | 0.53 | 7 | DMF | 0.20 | 0.79 |
| 2 | NMP | 0.73 | 0.79 | 8 | NMP | 0.61 | 0.81 |
| 3 | 1,4-dioxane | 2.24 | 4.26 | 9 | 1,4-dioxane | 1.87 | 2.92 |
| 4 | 2-butanol | 0.80 | 1.44 | 10 | 2-butanol | 1.12 | 1.12 |
| 5 | diglyme | 0.34 | 2.14 | 11 | diglyme | 0.86 | 2.25 |
| 6 | $MeCO_2i$-Pr | 0.87 | 2.54 | 12 | $MeCO_2i$-Pr | 1.08 | 1.85 |

[a][Pd] = $Pd(OAc)_2$. [b]Determined by HPLC. [c][Pd] = $Pd(TFA)_2$.

The benzylation of phenylglycine azlactone with a series of tolyl and methylnaphthyl derivatives with the optimal conditions for catalytic Pd was performed. However, the transformation proved to not be universal. Further studies on additives were initiated and the addition of charcoal was found to improve upon the initial catalytic findings (Table 4.11). Toluene and 2-methylnaphthalene provided the benzylated product in good yields (Table 4.11, **4.03** and **4.16**). However, tolyl analogs that proved to react slower than toluene were not successful, and decomposition of phenylglycine azlactone

over the course of the reaction was observed. Similar reactivity was not observed with stoichiometric Pd (see Table 4.4 and Table 4.5). Unidentifiable side products that are intense purple and pink colors in solution are formed with the recalcitrant substrates. Presumably, oxidation of the azlactone is occurring in the presence of 2,6-DMBQ. Future work will focus on modifying the protecting group of the azlactone from PMP to phenyl to improve catalytic turnover and minimize side reactions.

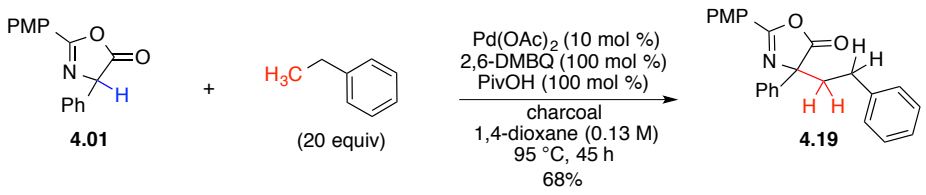
**Table 4.11** C($sp^3$)–H activation catalyzed by $Pd(OAc)_2$.




[a]$Pd(OAc)_2$ (30 mol %), 2,6-DMBQ (80 mol %), PivOH (80 mol %), 4 Å MS, 1,4-dioxane (0.3 M), 95 °C, 24 h.
[b]$Pd(OAc)_2$ (30 mol %), 2,6-DMBQ (80 mol %), PivOH (80 mol %), 4 Å MS, *t*-Amyl-OH (0.3 M), 95 °C, 24 h.
[c]$Pd(OAc)_2$ (100 mol %), 2,6-DMBQ (100 mol %), PivOH (100 mol %), neat, 110 °C, 14 h.

The catalytic conditions were explored with ethylbenzene and provided the ethylated phenylglycine azlactone product in moderate yield (Scheme 4.3). The secondary benzylated product was not observed. This unprecedented C–H activation of the unactivated terminal methyl of ethylbenzene provides access to chemical space that would not be feasible via a radical mediated process.

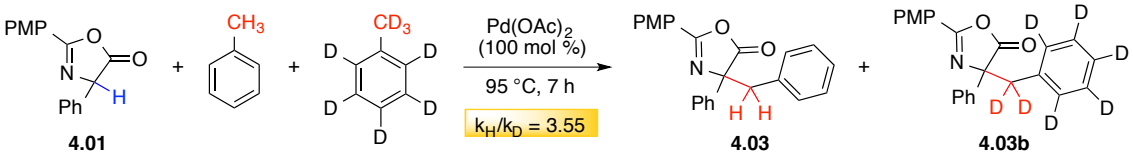
**Scheme 4.3** C($sp^3$)–H activation of ethylbenzene catalyzed by $Pd(OAc)_2$.




*4.2.6. Mechanistic Studies*

These novel findings prompted our interest in elucidating the C–H activation mechanism. Kinetic isotope studies were undertaken with phenylglycine azlactone and $Pd(OAc)_2$. An equimolar mixture of toluene and $d_8$-toluene provided the benzylated product in 3.55/1 $k_H/k_D$, which suggests the C–H activation step is rate-determining (Scheme 4.4).[148,155] Radical mediated processes such as those described in Figure 4.3 typically provide a more significant isotopic effect >5.[143a,161,162]

**Scheme 4.4** Kinetic isotope study of toluene vs $d_8$-toluene.



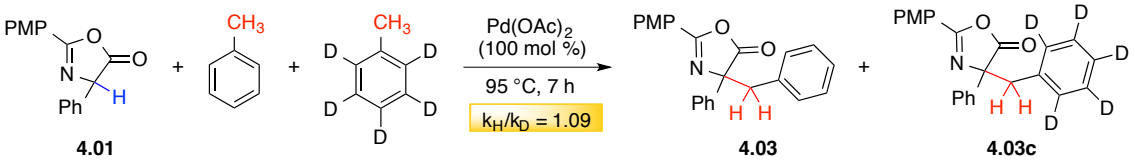

To probe the reaction mechanism further, toluene and $d_5$-toluene were investigated, and in this case isotopic effects were not observed (Scheme 4.5). Based on literature precedence, a mechanism involving arene insertion seemed plausible, but

161) Rout, S. K.; Guin, S.; Banerjee, A.; Khatun, N.; Gogoi, A.; Patel, B. K. "Directing Group Assisted Copper-Catalyzed Chemoselective *O*-Aroylation of Phenols and Enols Using Alkylbenzenes" *Org. Lett.* **2013**, *15*, 4106-4109.

162) ShiGuang, P.; JinHua, L.; YuanMing, L.; ZhiPing, L. "Iron-catalyzed benzylation of 1,3-dicarbonyl compounds by simple toluene derivatives" *Chin. Sci. Bull.* **2012**, *57*, 2382-2386.

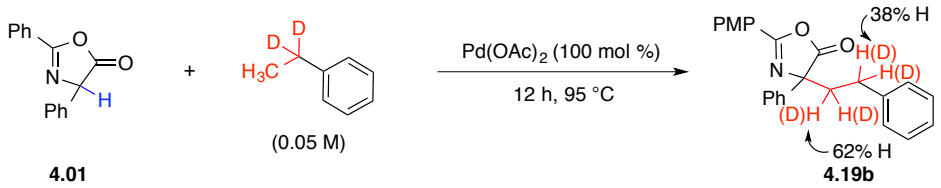
deuterium scrambling and an isotope effect were not observed on the benzylated product (**4.03c**) from $d_5$-toluene. This result suggests this process does not involve Pd insertion into the *ortho*-arene C–H. A stabilized [$\eta^3$-tolyl•Pd complex] is feasible from direct insertion into the benzylic C–H bond.

**Scheme 4.5** Kinetic isotope effect study of toluene vs $d_5$-toluene.




The results observed when phenylglycine was treated with $Pd(OAc)_2$ and ethylbenzene/2-ethylnaphthalene were highly unusual. A deuterium labeling study was therefore conducted with $d_2$-ethylbenzene. The azlactone product from C($sp^3$)–H activation at the terminal methyl of ethylbenzene was a mixture of deuterium/hydrogen at the ethyl carbons (Scheme 4.6). The observation of deuterium scrambling provides evidence that the initial C–H insertion by Pd occurs at the benzylic carbon; β-hydride elimination, insertion of Pd into the terminal carbon and cross-coupling with the phenylglycine azlactone would presumably provide the ethylated product. This result is in agreement with the observed product from propylbenzene (see Scheme 4.2). However, when styrene was introduced with phenylglycine azlactone and $Pd(OAc)_2$, the desired ethylated product (**4.19**) was not observed, but rather styrene polymerization occurred, indicating that the styrene intermediate remains bound to palladium and reacts rapidly.

**Scheme 4.6** Deuterium scrambling study with ethylbenzene.

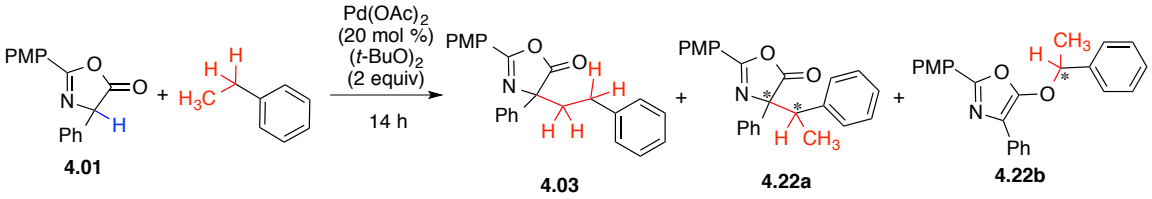



The ethylated product from phenylglycine azlactone and ethylbenzene provided an opportunity to interrogate radical pathways further. It has been shown that $(t\text{-BuO})_2$ undergoes homolysis at 100 °C, providing the oxy-radical.[163] When phenylglycine azlactone was treated with ethylbenzene at 90 °C, below the hemolysis threshold, with $Pd(OAc)_2$ and $(t\text{-BuO})_2$ only the ethylated product (**4.19**) was observed (Table 4.12, entry 1). In the absence of Pd, when the reaction temperature was increased to 125 °C to promote oxy-radical formation, the benzylated products (**4.22a** and **4.22b**) were the only product observed (Table 4.12, entry 2).[164] However, when the reaction temperature was maintained at 125 °C and $Pd(OAc)_2$ was present, a mixture of the ethylated (**4.19**) and benzylated products (**4.22a** and **4.22b**) were observed (Table 4.12, entry 3).

163) Pryor, W. A.; Lee, A.; Witt, C. E. "Reaction of Radicals. IX. *t*-Butyl Peroxide" *J. Am. Chem. Soc.* **1964**, *86*, 4229-4234.

164) A mixture of carbon and oxygen benzylation were observed with six diastereomers. This mixture was separated and identified through collaborative efforts, see: Regalado, E. L.; Kozlowski, M. C.; Curto, J. M.; et al. "Support of Academic Synthetic Chemistry using Advanced Separation Technologies from the Pharmaceutical Industry" *Org. Biomol. Chem.* **2014**, *12*, 2161-2166.

**Table 4.12** Radical studies with ethylbenzene.




| entry | temp (°C) | $Pd(OAc)_2$ (mol %) | observed product |
|---|---|---|---|
| 1 | 90 | 20 | **4.03**[a] |
| 2 | 125 | 0 | **4.22a** and **4.22b**[b] |
| 3 | 125 | 20 | **4.03**, **4.22a** and **4.22b**[c] |

[a]Isolated in 38% yield. [b]9:1 mixture, isolated in 60% yield [c]1:8:1 mixture.

Radical scavengers, such as TEMPO, BHT or 1,1-diphenylethylene, were introduced into the standard reaction with toluene and $Pd(OAc)_2$ and the desired benzylated product was produced in comparable yields.[165] These studies in addition to the information gained from the $(t\text{-BuO})_2$ studies contraindicate a radical process in the C–H alkylation of phenylglycine azlactone.

In the course of developing this technology, the azlactone dimer was observed frequently. Its presence prompted further studies to determine if it was necessary for benzylation or was an unwanted side-product. Dimer formation can be initiated with an oxidant (e.g., $NiO_2$, $MnO_2$), or in a polar solvent (DMSO) and air.[166,167,168] Mild conditions were developed to form the azlactone dimer (**4.23**) from phenylglycine azlactone (**4.01**) in 83% yield with $Pd(OAc)_2$ (5 mol %) and $Ag_2O$ (100 mol %) at rt

165) The benzylated product was provided in 54, 85, and 59% yield with TEMPO, 1,1-diphenylethylene and BHT, respectively. 1,1-Diphenylethylene and BHT were recovered in 58 and 67% yield.

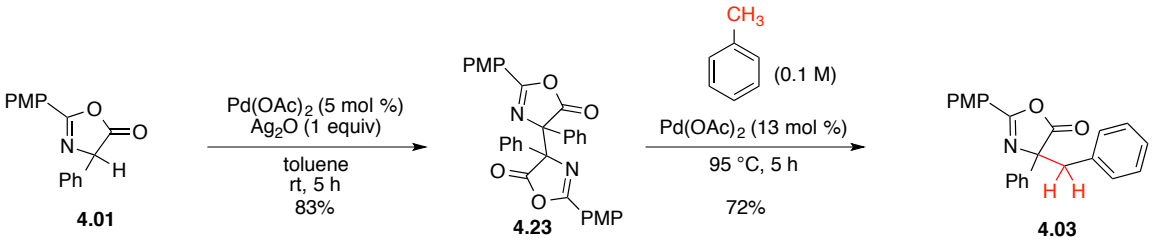
166) Marquez, A.; Chuaqui, C. A.; Rodriquez, H.; Zagal, L. "Generation and Fate of Free Radicals of oxazolin-5-ones" *Tetrahedron* **1985**, *41*, 2341-2346.

167) Rodriguez, H.; Marquez, A.; Chuaqui, C. A.; Gomez, B. "Oxidation of Mesoionic Oxazolones by Oxygen" *Tetrahedron* **1991**, *47*, 5681-5688.

168) Andersen, K. K.; Gloster, D. F.; Bray, D. D.; Shoja, M. "Synthesis of Symmetrical 2,2',4,4'-Tetrasubstituted[4,4'-bioxazole]-5,5'(4H,4'H)-diones and their Reaction with some Nucleophiles" *J. Het. Chem.* **1998**, *35*, 317-324.

(Scheme 4.7). When the dimer was subjected to catalytic $Pd(OAc)_2$ and toluene, the benzylated product was formed in 72% yield (Scheme 4.7).[169] Catalytic turnover of the Pd(II) catalyst without the addition of an oxidant suggests that from the dimer the catalytic cycle is redox neutral. Unfortunately, starting from dimer did not improve the efficiency of the benzylation step with recalcitrant substrates such as mesitylene.

**Scheme 4.7** Benzylation from the phenylglycine azlactone dimer.




The intriguing reactivity of the phenylglycine azlactone dimer (**4.23**) prompted further mechanistic studies. The dimer was exposed to Pd(II) complexes in $d_6$-benzene and monitored by $^1H$ NMR. When the chosen Pd(II) source was $Pd(TFA)_2$, the dimer-Pd complex (**4.24**) was observed (Figure 4.8, top); the *ortho*-hydrogen on the C-4 phenyl ring shifted significantly downfield (7.31 to 9.47 ppm) (Figure 4.8, bottom). The dimer-Pd complex structure was confirmed by X-ray crystallography (Figure 4.8, right).

169) Palladium(0) sources did not provide the benzylated product with dimer and toluene.

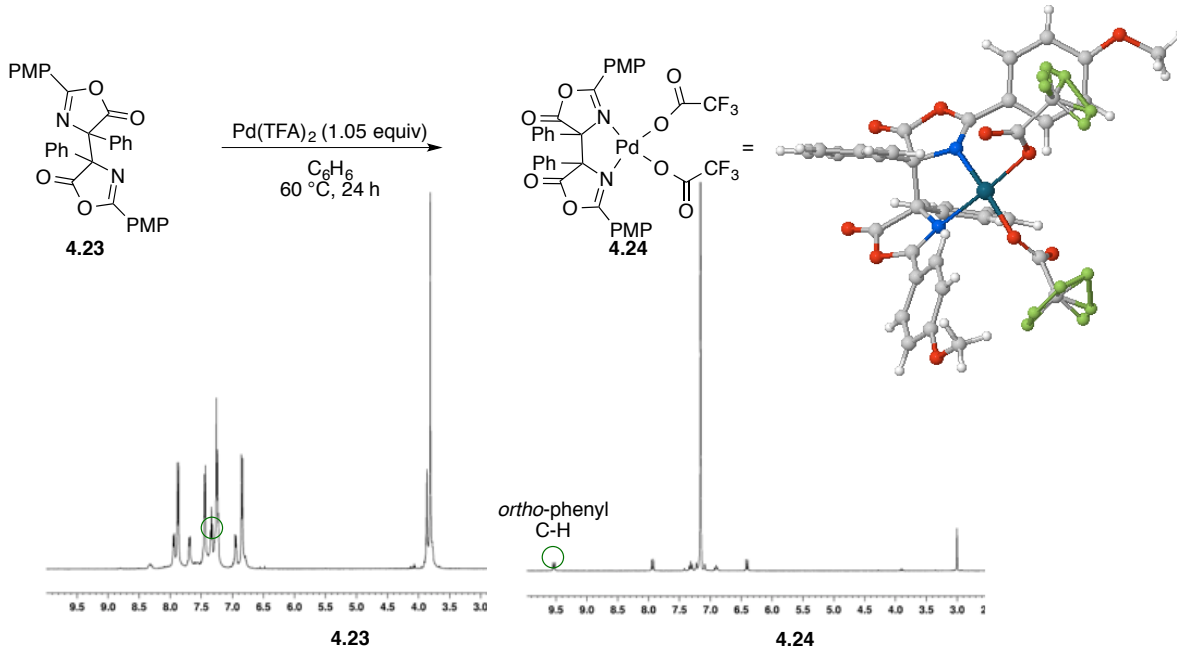
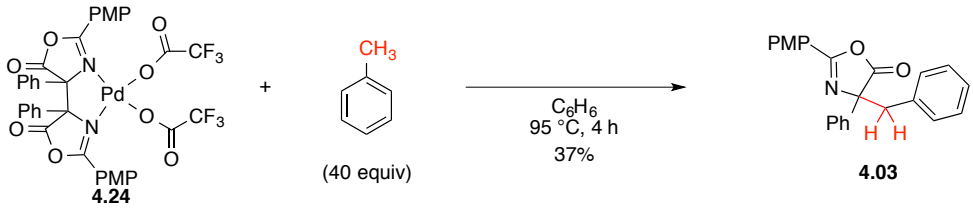



**Figure 4.8** Phenylglycine azlactone dimer-Pd complex.

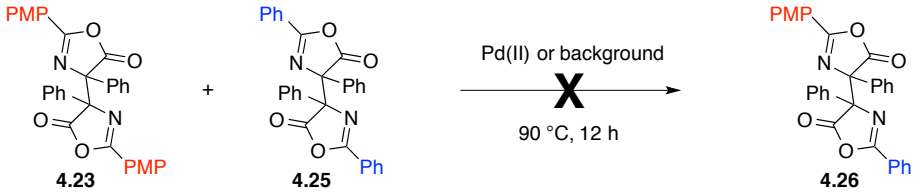
Identification of the dimer-Pd complex prompted us to investigate if its formation was part of the reaction cycle. Treatment of the complex with toluene at elevated temperatures provided the benzyl product (Scheme 4.8), although in reduced yield relative to the monomer and $Pd(TFA)_2$ (see Table 4.1, entry 7). The dimer-Pd complex was monitored in $d_8$-toluene. After thirty minutes at rt the complex had dissociated and the uncomplexed dimer was present. Based on these results, we believe the dimer-Pd complex is not a reactive intermediate.

**Scheme 4.8** Benzylation from the dimer-Pd complex.



Phenylalanine azlactone dimer has been shown to undergo homolytic cleavage at temperatures above 115 °C.[168] Potentially, formation of the azlactone radical from the dimer could be responsible for the observed benzylation with tolyl analogs. However, our studies suggest this is not likely with phenylglycine azlactone. Benzylation is not observed without Pd(II). The ethylated product is not formed under conditions with free radicals present (see Table 4.12, entry 2). Dimer crossover studies have been conducted with the PMP-phenylglycine dimer (**4.23**) and Ph-phenylglycine dimer (**4.25**) at 85-95 °C with and without $Pd(OAc)_2$, and dimer crossover from recombination has not been observed (Scheme 4.9).[170]

**Scheme 4.9** Dimer crossover study.




Although the full mechanistic details of this transformation remain to be elucidated, we tentatively propose the following mechanism (Figure 4.9). $^1$H NMR studies of the reaction reveal that the phenylglycine azlactone is converted to the azlactone dimer in the first 30 minutes when exposed to $Pd(OAc)_2$ and heat. Toluene can undergo C–H activation with $Pd(OAc)_2$ at elevated temperatures in a redox neutral process. The electron-rich benzyl Pd(II) is poised to undergo oxidation with the labile C-C bond of the azlactone dimer, forming a Pd(IV) intermediate. Alternatively, this transformation could occur from two Pd(II) complexes providing a Pd(III) complex.

170) In contrast to ref 168, we did observe dimer mixing from ionization in the MS with a control experiment. Thus, MS cannot be used to track crossover.

Reductive elimination would provide the benzylated azlactone. $Pd(OAc)_2$ can be regenerated in the presence of AcOH. The reformation of the phenylglycine azlactone monomer consumes the remaining $Pd(OAc)_2$ in the production of the azlactone dimer, thus the 72% yield observed in Scheme 4.7 with 13 mol % Pd. Presumably, the resting state of Pd in the active cycle is Pd(II), but in the formation of the dimer, Pd(0) is the resting state. A Pd-black and/or Pd-mirror are evident in these reactions and are consistent with our proposed mechanism.[171]

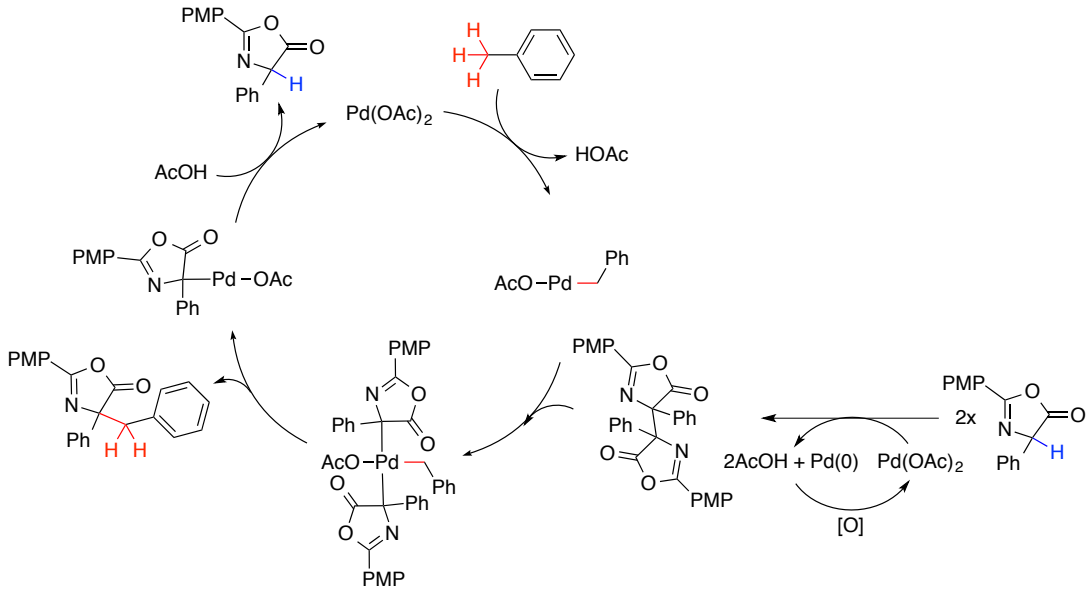



**Figure 4.9** Tentative mechanism.

### *4.2.7. Future Goals*

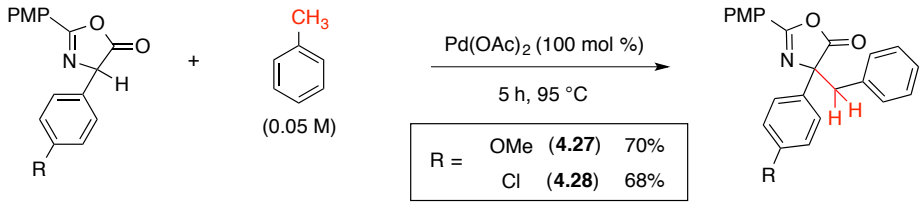
We have successfully discovered a novel C($sp^3$)–H activation of benzylic C–H bonds that can be coupled with phenylglycine azlactone by $Pd(OAc)_2$. Our primary goals

171) Pun, D.; Diao, T.; Stahl, S. S. "Aerobic Dehydrogenation of Cyclohexanone to Phenol Catalyzed by $Pd(TFA)_2$/2-Dimethylaminopyridine: Evidence for the Role of Pd Nanoparticles" *J. Am. Chem. Soc.* **2013**, *135*, 8213-8221.

of optimizing the initial conditions, exploring if the reaction was general for tolyl analogs, and conducting mechanistic studies were successfully completed. Our secondary goal of determining conditions for catalytic Pd were successful but were not universal for all tolyl analogs. Our last goal was to extend the scope of the acidic C–H partner.

Analogs of phenylglycine were explored with toluene and stoichiometric Pd (Scheme 4.10). Electron-donating and –withdrawing substitution at the *para* position provided the benzylated product in yields similar to that of the parent azlactone. Reduced toluene loading with the addition of a co-solvent has not been explored. *ortho*-Substitution reduced the amount of benzylated product, presumably because of sterics.[172] Phenylalanine was also explored and the benzylated product was observed as a 50:50 mixture with starting material after 14 h. Glycine azlactone was unsuccessful and all starting material decomposed under the reaction conditions without providing benzylated product.

**Scheme 4.10** Exploration of phenylglycine azlactone analogs with toluene.

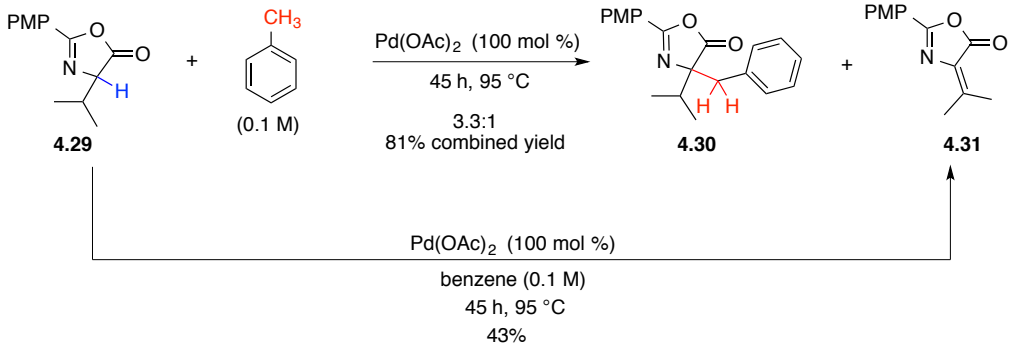



The valine azlactone (**4.29**) was prepared and reacted with toluene and $Pd(OAc)_2$. The benzylated product was observed, but the reaction rate was sufficiently slower than the corresponding phenylglycine azlactone (45 h vs 6 h). Interestingly after complete consumption of starting material, the benzylated product was isolated as a 3:1 mixture

172) *ortho*-Ethoxy phenylglycine azlactone was benzylated in 30% yield.

with the azlactone alkene (**4.31**) in 81% yield (Scheme 4.11). Ostensibly, the alkene is produced from β-hydride elimination with Pd, post C–H insertion. A modification of this "Saegusa" oxidation has been reported by Stammer with phenylalanine azlactone.[173] Treatment of the azlactone with TMSCl and $Et_3N$, followed by stoichiometric $Pd(OAc)_2$, produced the corresponding alkene azlactone in 16% yield. The authors suggest α-alkyl α-amino acids do not undergo this transformation. When toluene was replaced with benzene, the alkene (**4.31**) was produced in 43% yield (Scheme 4.11, bottom).

**Scheme 4.11** Benzylation of valine azlactone.



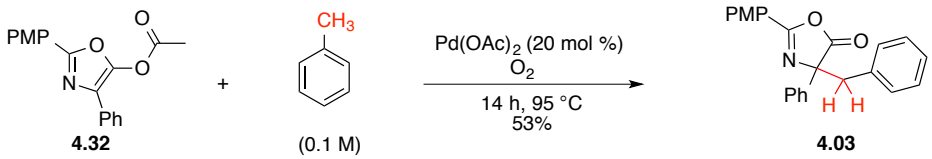

Acyclic α-amino acids were explored, the Schiff base of glycine, valine and phenylglycine were prepared and subject to stoichiometric $Pd(OAc)_2$ and toluene; benzylation was not observed. The Schiff base-Pd complex was formed from insertion of Pd into the *ortho*-phenyl C–H of the ketamine protecting group; this type of reactivity has been observed previously.[174]

173) Lott, R. S.; Breitholle, E. G.; Stammer, C. H. "Azlactone Oxidation" *J. Org. Chem.* **1980**, *45*, 1151-1153.

174) Bohm, A.; Schreiner, B.; Steiner, N.; Urban, R.; Sunkel, K.; Polborn, K.; Beck, W. "Metal Complexes of Biologically Important Ligands, XCVIII [1] Cyclopalladated Schiff Bases of α-Amino Acid and Peptide Esters" *Z. Naturforsch* **1998**, *53 b*, 191-205.

Seidel and co-workers have found that *O*-acylated azlactones can add to isoquinolines in an asymmetric Steglich rearrangement.[175] The *O*-acyl phenylglycine azlactone was prepared (**4.32**) and subject to toluene and $Pd(OAc)_2$ (100 mol %), providing the benzylated product in 81% yield. Catalytic Pd with oxygen as the oxidant was examined and the benzylated product was observed in 53% yield (Scheme 4.12). This catalytic system is currently being explored and we envision the low catalytic loadings combined with the cheap, environmentally friendly $O_2$ could be an important extension to this work.

**Scheme 4.12** Benzylation of the *O*-acylated azlactone with catalytic Pd.




Double C–H activation for C–C bond formations are rare and we hope to extend the scope of this technology beyond cyclic α-amino acids. We are currently exploring acidic C–H partners that have been shown to dimerize in the literature.[176,177,178] Tetralones, oxindoles and arylcyanoacetic esters have been chosen as future targets for

175) De, C. K.; Mittal, N.; Seidel, D. "A Dual-Catalysis Approach to the Asymmetric Steglich Rearrangement and Catalytic Enantioselective Addition of *O*-Acylated Azlactones to Isoquinolines" *J. Am. Chem. Soc.* **2011**, *133*, 16802-16805.

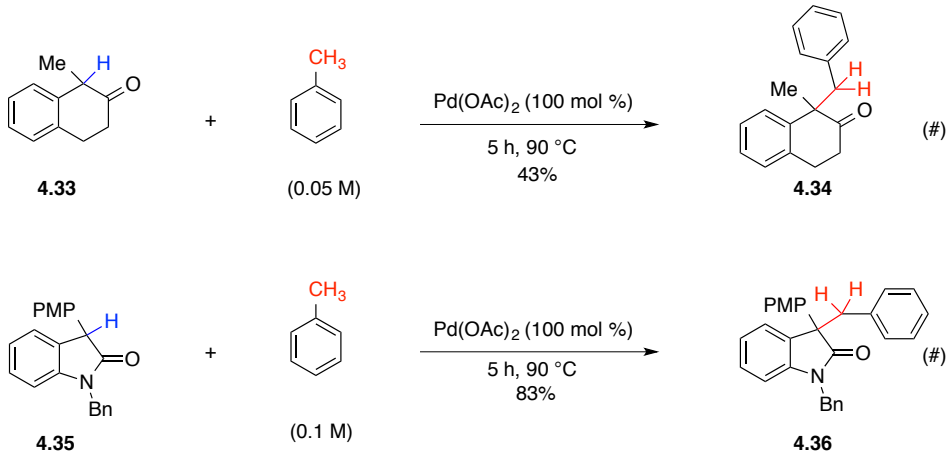
176) Nicolaou, K. C.; Gray, D. L. F. "Total Synthesis of Hybocarpone and Analogues Thereof. A Facile Dimerization of Naphthazarins to Pentacyclic Systems" *J. Am. Chem. Soc.* **2004**, *126*, 607-612.

177) Fang, C.-L.; Horne, S.; Taylor, N.; Rodrigo, R. "Dimerization of a 3-Substituted Oxindole at C-3 and Its Application to the Synthesis of (+/–)-Folicanthine" *J. Am. Chem. Soc.* **1994**, *116*, 9480-9486.

178) De Jongh, H. A. P.; De Jonge, C. R. H. I.; Sinnige, H. J. M.; De Klein, W. J.; Huysman, W. G. B.; Mijs, W. J. "Oxidative Carbon-Carbon Coupling. II. The Effect of Ring Substituents on the Oxidative Carbon-Carbon Coupling of Arylmalonic Esters, Arylmalonodinitriles, and Arylcyanoacetic Esters" *J. Org. Chem.* **1972**, *37*, 1960-1966.

benzylation. Our preliminary work is shown in Scheme 4.13.[179] α-Substituted tetralone and oxindole look like promising substrates. Interestingly, neither has an α-nitrogen for pre-coordination to Pd; the α-nitrogens on the phenylglycine azlactone dimer formed a complex with Pd (see Figure 4.8). Future work will focus on applying the catalytic conditions for Pd with these promising substrates.

**Scheme 4.13** Preliminary work on benzylation of various acidic C–H partners.




## 4.3. CONCLUSIONS

In summary, a novel reactivity mode for alkylarene derivatives has been discovered. With a simple system consisting of $Pd(OAc)_2$ and pivalic acid, CDC with a carbon nucleophile occurs readily for the terminal methyl positions of methyl, ethyl, propyl and butyl arenes. The resultant azlactone products are masked α-amino acids, with hindered a,a-disubstitution patterns that are difficult to achieve via other means. Notably, selective C($sp^3$)–H insertion is observed in benzylic systems even though

179) Various acidic C–H partners that have been explored with toluene and $Pd(OAc)_2$ are listed in the supporting information.

$Pd(OAc)_2$ typically causes arene C–H insertion. Mechanistic studies were initiated, and it was determined that $C(sp^3)$–H activation is the RDS. Studies are ongoing to improve turnover and to extend the scope of the acidic C–H partner in these couplings

## 4.4. EXPERIMENTAL SECTION

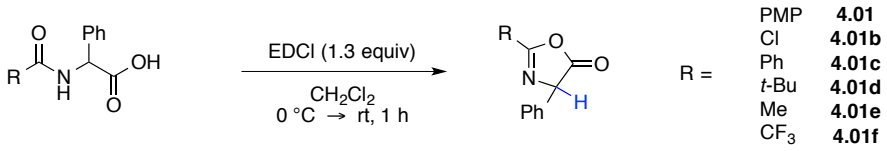
### General Considerations

All non-aqueous reactions were carried out under an atmosphere of dry argon unless otherwise noted. Commercial reagents were used as received without additional purification unless otherwise noted. Dichloromethane was distilled from $CaH_2$, and toluene was distilled from metallic sodium prior to use. Anhydrous 1,4-dioxane was purchased from Sigma Aldrich as 100 mL Sure-Seal bottles and stored in the glovebox. Activated charcoal (Darco G-60) was dried overnight at 80 °C *in vacuo*. Reactions were monitored by thin layer chromatography (TLC) using Silicycle glass-backed TLC plates with 250 μm silica and F254 indicator. Visualization was accomplished by UV light.

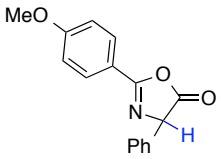
$^1H$ NMR and $^{13}C$ NMR spectra were recorded on a AM-500 Fourier transform NMR spectrometer at 500 MHz and 125 MHz, respectively. Chemical shifts are reported relative to the solvent resonance peak δ 7.26 ($CDCl_3$) for $^1H$ and δ 77.16 ($CDCl_3$) for $^{13}C$. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, b = broad singlet, m = multiplet), coupling constants, and number of protons. High resolution mass spectra were obtained using a VG autospec with an ionization mode of either ESI or CI. Infrared spectra are reported in $cm^{-1}$. Melting points are uncorrected. Unless otherwise noted, yields refer to isolated material on the basis of

product purity (≥95%) by $^1$H NMR following silica gel chromatography with Silica-P flash silica gel (50-63 μm mesh particle size).

**General Procedure A – Synthesis of Azlactones**[180,181,182]




*N*-Protecting group-phenylglycine (0.39 mmol) was added to a flame dried 25 mL round bottom flask equipped with a stir bar under an argon atmosphere. The mixture was dissolved in $CH_2Cl_2$ (6 mL) and cooled to 0 °C. *N*-(3-Dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDCl) (90 mg, 0.47 mmol) was added and the mixture was allowed to warm to ambient temperature. After 1 h at ambient temperature, the mixture was diluted with $CH_2Cl_2$ (10 mL), washed with $H_2O$ (2 x 10 mL), 0.1 M NaOAc (2 x 10 mL), $H_2O$ (10 mL) and brine (15 mL), dried over $Na_2SO_4$, filtered and concentrated *in vacuo* providing the corresponding azlactone.

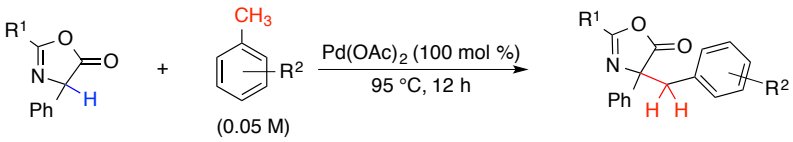


**2-(4-Methoxyphenyl)-4-phenyloxazol-5(4*H*)-one (4.01)**. General procedure A was followed using *N*-*para*-methoxy-phenylglycine (110 mg, 0.39 mmol) and EDCl (90 mg,

180) For R = *p*-Cl-$C_6H_4$, see: Hofle, G.; Steglich, W.; Daniel, H. "Notiz zur Isolierung der 2-Oxazolinon- und Oxazolium-5-olat-Formen bei 2,4-Diaryloxazolin-5-onen" *Chem. Ber.* **1976**, *109*, 2648-2650.
181) For R = Ph, see: Liang, J.; Ruble, J. C.; Fu, G. C. "Dynamic Kinetic Resolutions Catalyzed by a Planar-Chiral Derivative of DMAP: Enantioselective Synthesis of Protected α-Amino Acids from Racemic Azlactones" *J. Org. Chem.* **1998**, *63*, 3154-3155.
182) For R = Me, see: Padwa, A.; Wetmore, Jr. S. I. "Studies on the Photoextrusion of Carbon Dioxide from the $\Delta^3$-Oxazolin-5-one System" *J. Am. Chem. Soc.* **1974**, *96*, 2414-2421.

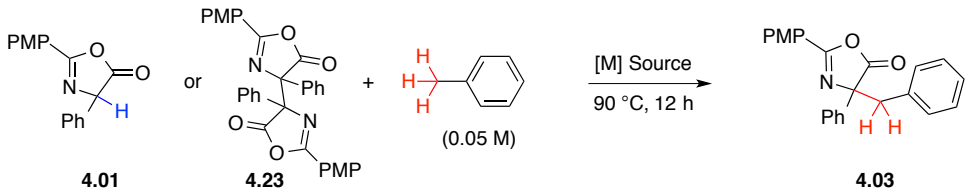
0.47 mmol) in $CH_2Cl$ (6 mL). After work up, **4.01** (15.1 mg) was isolated in 72% yield: $^1$H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.9 Hz, 2H), 7.47-7.33 (m, 5H), 7.01 (d, *J* = 8.9 Hz, 2H), 5.49 (s, 1H), 3.90 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 176.6, 163.6, 162.4, 133.9, 130.2, 129.1, 128.8, 127.0, 118.1, 114.4, 68.3, 55.7; IR (film) 3008, 2935, 2839, 1827, 1648, 1608, 1512, 1260 cm$^{-1}$; HRMS (CI) calcd for $C_{16}H_{13}NO_3$ $[M]^+$ *m/z* = 267.0895; found 267.0895.

**General Procedure B – Benzylation with Stoichiometric Pd**




Phenylglycine azlactone (**4.01**) (0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) were added to a flame dried 8 mL microwave vial equipped with stir bar and brought into the glovebox. The indicated tolyl analog (0.05 M, ~10.5 mmol) was added to the mixture. The microwave vial was sealed with a Teflon cap, removed from the glovebox, and placed in a 95 °C oil bath. After 6 h, the mixture was allowed to cool to ambient temperature, diluted with $CH_2Cl_2$ (1 mL), passed through $SiO_2$ with 30% EtOAc in hexanes, and concentrated *in vacuo*. The resulting residue was purified by column chromatography to afford the alkylated azlactone.

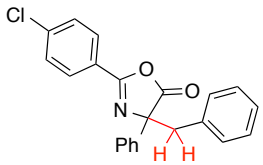
**Metal sources for C–H activation of toluene** (Table 4.1)



For Table 1, entries 1-5: Phenylglycine azlactone dimer (**4.23**) (10 mg, 0.019 mmol) was added to a flame dried 8 mL microwave vial equipped with stir bar and brought into the glovebox. The indicated metal source[183] (0.008 mmol) was added followed by toluene (377 μL). The microwave vial was sealed with a Teflon cap, removed from the glovebox, placed in a 90 °C oil bath. After 5 h, the mixture was allowed to cool to ambient temperature, diluted with $CH_2Cl_2$ (1 mL), passed through $SiO_2$ with 30% EtOAc in hexanes, and concentrated *in vacuo*. The resulting residues were analyzed by $^1H$ NMR spectroscopy and each experiment provided only unreacted phenylglycine azlactone dimer (**4.23**).

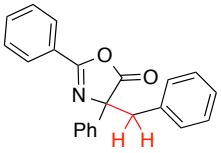
For Table 1, entries 6-12: General procedure B was followed with phenylglycine azlactone (**4.01**) (10 mg, 0.038 mmol), the indicated metal source (0.038 mmol) and toluene (750 μL). After 12 h at 90 °C oil bath, the resulting residues were analyzed by $^1H$ NMR spectroscopy: entries 6 and 7 provided full conversion to benzylated product, entry 8 provided full conversion to phenylglycine azlactone dimer and entries 9-11 provided minimal phenylglycine azlactone dimer (**4.23**) and decomposition of phenylglycine azlactone (**4.01**).

**Modification of the phenylglycine azlactone protecting group (**Table 4.2**).**



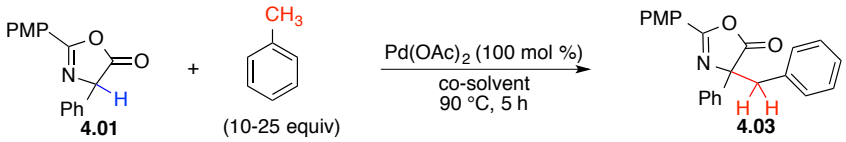

183) $Au(OAc)_3$, $Cu(OAc)_2$, $Rh_2(OAc)_4$ and $Ni(OAc)_2$ were avaialble from commercial sources. $[Pt_4(OAc)_8]$•HOAc was synthesized following a known procedure, see: Basato, M.; Biffis, A.; Martinati, G.; Tubaro, C.; Venzo, A.; Ganis, P.; Benetolo, F. "Reaction of platinum acetate with phosphines and molecular structure of *trans*-$[Pt(OAc)_2(PPh_3)_2]$" *Inorg. Chim. Acta* **2003**, *355*, 399-403.

General procedure B was followed using **4.01b** (10 mg, 0.038 mmol) and $Pd(OAc)_2$ (8.4 mg, 0.038 mmol) in toluene (750 μL) at 90 °C for 3 h. After isolation, concentration and column chromatography (10% EtOAc in hexanes), **4.04** (9.4 mg) was obtained in 69% yield.



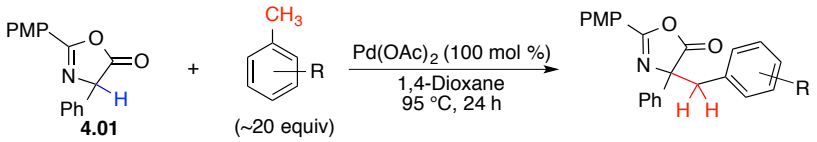

General procedure B was followed using **4.01c** (8.9 mg, 0.038 mmol) and $Pd(OAc)_2$ (8.4 mg, 0.038 mmol) in toluene (750 μL) at 95 °C for 3 h. After isolation, concentration and column chromatography (7% EtOAc in hexanes), **4.05** (8.6 mg) was obtained in 70% yield: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.92 (d, $J$ = 8.0 Hz, 2H), 7.79 (d, $J$ = 8.0 Hz, 2H), 7.54 (t, $J$ = 7.5 Hz, 1H), 7.47-7.38 (m, 4H), 7.35 (t, $J$ = 7.3 Hz, 1H), 7.23-7.12 (m, 5H), 3.53 (d, $J$ = 13.5 Hz, 1H), 3.47 (d, $J$ = 13.5 Hz, 1H). Spectral data agreed with those reported by Hartwig.[157]

**Screen of co-solvents (**Table 4.3**)**

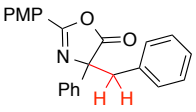



General procedure C was followed using **4.01** (10 mg, 0.037 mmol) and $Pd(OAc)_2$ (8.3 mg, 0.037 mmol) in toluene (0.37 or 0.93 mmol) and co-solvent (133 μL) at 90 °C for 5 h.

**General Procedure C – Alkylation with stoichiometric Pd in 1,4-dioxane**

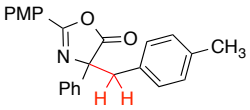



Phenylglycine azlactone (**4.01**) (0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) were added to a flame dried 8 mL microwave vial equipped with stir bar and brought into the glovebox. The indicated tolyl analog (1.12 mmol) and 1,4-dioxane (200 μL) were added to the mixture. The microwave vial was sealed with a Teflon cap, removed from the glovebox and placed in a 90 °C oil bath. After 24 h, the mixture was allowed to cool to ambient temperature, diluted with $CH_2Cl_2$ (1 mL), passed through $SiO_2$ with 30% EtOAc in hexanes, and concentrated *in vacuo*. The resulting residue was purified by column chromatography to afford the alkylated azlactone.

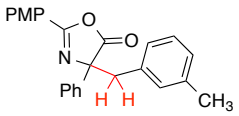



**4-Benzyl-2-(4-methoxyphenyl)-4-phenyloxazol-5(4*H*)-one (4.03).** General procedure C was followed using **4.01** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in toluene (118 μL, 1.12 mmol) and 1,4-dioxane (200 μL) at 90 °C for 24 h. Purification by column chromatography (eluent 7% EtOAc in hexanes) provided **4.03** (16.5 mg) in 83% yield: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, $J$ = 8.8 Hz, 2H), 7.79 (d, $J$ = 8.0 Hz, 2H), 7.41 (t, $J$ = 7.6 Hz, 2H), 7.34 (t, $J$ = 7.4 Hz, 1H), 7.24-7.12 (m, 5H), 6.93 (d, $J$ = 8.8 Hz, 2H), 3.85 (s, 3H), 3.51 (d, $J$ = 13.4 Hz, 1H), 3.44 (d, $J$ = 13.4 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 178.4, 163.2, 159.7, 138.4, 134.4, 130.6, 129.9, 128.8, 128.4, 128.2, 127.4, 126.0, 118.2, 114.2, 75.6, 55.6, 47.4; IR (film) 3031, 2925, 1813, 1653, 1608,

1513, 1260 $cm^{-1}$; HRMS (CI) calcd for $C_{16}H_{12}NO_3$ $[M\text{-}C_7H_7]^+$ *m/z* = 266.0817; found 266.0826.

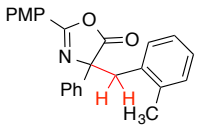



**2-(4-Methoxyphenyl)-4-(4-methylbenzyl)-4-phenyloxazol-5(4*H*)-one (4.09).** General procedure C was followed using **4.01** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in *para*-xylene (140 μL, 1.12 mmol) and 1,4-dioxane (200 μL) at 90 °C for 24 h. Purification by column chromatography (eluent 7% EtOAc in hexanes) provided **4.09** (16.2 mg) in 78% yield: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.88 (d *J* = 8.8 Hz, 2H), 7.78 (d, *J* = 7.9 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 1H), 7.09 (d, *J* = 7.9 Hz, 2H), 6.98 (d, *J* = 7.8 Hz, 2H), 6.94 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 3H), 3.47 (d, *J* = 13.6 Hz, 1H), 3.40 (d, *J* = 13.4 Hz), 2.23 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 178.4, 163.2, 159.7, 138.6, 136.9, 131.3, 130.4, 130.0, 128.9, 128.8, 128.3, 126.0, 118.3, 114.2, 75.7, 55.6, 47.1, 21.2; IR (film) 3007, 2962, 2927, 1813, 1654, 1608, 1512, 1260 $cm^{-1}$; HRMS (ESI) calcd for $C_{24}H_{22}NO_3$ $[M+H]^+$ *m/z* = 372.1600; found 372.1594.




**2-(4-Methoxyphenyl)-4-(3-methylbenzyl)-4-phenyloxazol-5(4*H*)-one (4.10).** General procedure C was followed using **4.01** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in *meta*-xylene (140 μL, 1.12 mmol) and 1,4-dioxane (200 μL) at 90 °C for 24 h. Purification by column chromatography (eluent 7% EtOAc in hexanes) provided **4.10** (16.3 mg) in 78% yield: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.86 (d *J* = 8.9 Hz, 2H), 7.79

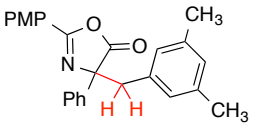
(d, $J$ = 7.8 Hz, 2H), 7.41 (t, $J$ = 7.6 Hz, 2H), 7.34 (t, $J$ = 7.3 Hz, 1H), 7.08-7.00 (m, 3H), 6.96-6.92 (m, 3H), 3.85 (s, 3H), 3.47 (d, $J$ = 13.2 Hz, 1H), 3.40 (d, $J$ = 13.2 Hz), 2.19 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 178.4, 163.2, 159.7, 138.5, 137.6, 134.3, 131.5, 129.9, 128.8, 128.4, 128.1, 128.0, 127.5, 126.0, 118.3, 114.2, 75.6, 55.6, 47.5, 21.4; IR (film) 3062, 2929, 1813, 1653, 1604, 1512, 1257 cm$^{-1}$; HRMS (ESI) calcd for $C_{24}H_{22}NO_3$ $[M+H]^+$ $m/z$ = 372.1600; found 372.1600.



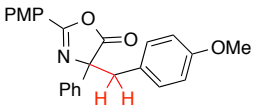

**2-(4-Methoxyphenyl)-4-(2-methylbenzyl)-4-phenyloxazol-5(4*H*)-one (4.11).** General procedure C was followed using **4.01** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in *ortho*-xylene (140 μL, 1.12 mmol) and 1,4-dioxane (200 μL) at 90 °C for 24 h. Purification by column chromatography (eluent 7% EtOAc in hexanes) provided **4.11** (8.4 mg) in 40% yield.

General procedure B was followed with **4.01** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in *ortho*-xylene (1.1 mL, 8.8 mmol). The mixture was allowed to stir at 90 °C for 5 h and purification by column chromatography provided **4.11** (14 mg) in 67% yield: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.84 (d $J$ = 8.8 Hz, 2H), 7.80 (d, $J$ = 8.6 Hz, 2H), 7.42 (t, $J$ = 7.5 Hz, 2H), 7.34 (t, $J$ = 7.4 Hz, 1H), 7.15 (d, $J$ = 7.3 Hz, 1H), 7.04-6.99 (m, 3H), 6.92 (d, $J$ = 8.9 Hz, 2H), 3.85 (s, 3H), 3.55 (d, $J$ = 13.7 Hz, 1H), 3.51 (d, $J$ = 13.7 Hz, 1H), 2.39 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 178.9, 163.2, 159.4, 138.8, 138.1, 133.1, 130.8, 130.5, 129.9, 128.8, 128.3, 127.5, 126.0, 125.7, 118.3, 114.3, 76.2, 55.6,

44.1, 20.2; IR (film) 2963, 2928, 1813, 1653, 1609, 1512, 1260 $cm^{-1}$; HRMS (ESI) calcd for $C_{24}H_{22}NO_3$ $[M+H]^+$ *m/z* = 372.1600; found 372.1588.

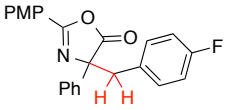



**4-(3,5-Dimethylbenzyl)-2-(4-methoxyphenyl)-4-phenyloxazol-5(4*H*)-one (4.10b).** General procedure B was followed using **4.01** (10 mg, 0.037 mmol ) and $Pd(OAc)_2$ (8.3 mg, 0.037 mmol) in mesitylene (750 μL, 5.4 mmol). The mixture was allowed to stir at 140 °C for 15 h and purification by column chromatography provided **4.10b** (2.0 mg) in 14% yield: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 9.0 Hz, 2H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.34 (d, *J* = 7.4 Hz, 1H), 6.93 (d, *J* = 9.0 Hz, 2H), 6.82 (s, 2H), 6.76 (s, 1H), 3.86 (s, 3H) 3.43 (d, *J* = 13.4 Hz, 1H), 3.37 (d, *J* = 13.4 Hz, 1H), 2.15 (s, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 178.4, 163.2, 159.7, 138.6, 137.5, 134.2, 129.9, 128.9, 128.8, 128.3, 126.0, 118.3, 114.2, 113.9, 75.7, 55.6, 47.5, 21.2; HRMS (ESI) calcd for $C_{25}H_{24}NO_3$ $[M+H]^+$ *m/z* = 386.1756; found 386.1750.



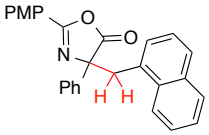

**2-(4-Methoxyphenyl)-4-(4-methoxybenzyl)-4-phenyloxazol-5(4*H*)-one (4.13).** General procedure C was followed using **4.01** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in *para*-methylanisole (140 μL, 1.12 mmol) and 1,4-dioxane (200 μL) at 90 °C for 24 h. Purification by column chromatography (eluent 7% EtOAc in hexanes) provided **4.13** (15.4 mg) in 71% yield: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.0 Hz, 2H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.40 (t, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.12 (d, *J*

= 7.4 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.71 (d, *J* = 8.4 Hz, 2H), 3.86 (s, 3H), 3.71 (s, 3H), 3.45 (d, *J* = 13.6 Hz, 1H), 3.38 (d, *J* = 13.6 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 178.5, 163.3, 159.7, 158.9, 138.5, 131.7, 129.9, 128.8, 128.3, 126.5, 126.0, 118.3, 114.3, 113.6, 75.8, 55.6, 55.3, 46.7; IR (film) 2961, 2926, 2851, 1812, 1760, 1655, 1610, 1513, 1259 cm$^{-1}$; HRMS (ESI) calcd for $C_{24}H_{22}NO_4$ $[M+H]^+$ *m/z* = 388.1549; found 388.1551.



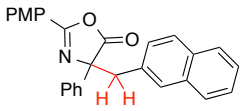

**2-(4-Methoxyphenyl)-4-(4-fluorobenzyl)-4-phenyloxazol-5(4*H*)-one (4.14).** General procedure C was followed using **4.01** (15 mg, 0.056 mmol ) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in *para*-fluorotoluene (123 μL, 1.10 mmol) and 1,4-dioxane (200 μL) at 90 °C for 24 h. The phenylglycine azlactone dimer was isolated with only a minimal amount of the benzylated product observed.

General procedure B was followed with **4.01** (10 mg, 0.037 mmol ) and $Pd(OAc)_2$ (8.3 mg, 0.037 mmol) in *para*-fluorotoluene (750 μL, 6.8 mmol). The mixture was allowed to stir at 120 °C for 14 h and purification by column chromatography provided **4.14**: HRMS (ESI) calcd for $C_{23}H_{19}FNO_3$ $[M+H]^+$ *m/z* = 376.1349; found 376.1352.



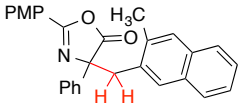

**2-(4-Methoxyphenyl)-4-(naphthalen-1-ylmethyl)-4-phenyloxazol-5(4*H*)-one (4.15)** General procedure C was followed using **4.01** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in 1-methylnaphthalene (159 μL, 1.12 mmol) and 1,4-dioxane (200 μL)

at 90 °C for 24 h. Purification by column chromatography (eluent 7% EtOAc in hexanes) provided **4.15** (15.5 mg) in 68% yield: $^{1}$H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, $J$ = 8.6 Hz, 1H), 7.88 (d, $J$ = 8.1 Hz, 2H), 7.72 (d, $J$ = 8.2 Hz, 1H), 7.67 (d, $J$ = 8.2 Hz, 1H), 7.58 (d, $J$ = 8.8 Hz, 2H), 7.53 (t, $J$ = 7.7 Hz, 1H), 7.46-7.34 (m, 5H), 7.30 (t, $J$ = 7.6 Hz, 1H), 6.78 (d, $J$ = 8.9 Hz, 2H), 4.02 (d, $J$ = 13.7 Hz, 1H), 3.94 (d, $J$ = 13.7 Hz, 1H), 3.78 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 178.7, 163.0, 159.4, 138.7, 133.8, 132.9, 131.0, 129.8, 129.0, 128.9, 128.4, 128.4, 128.4, 126.0, 125.6, 125.5, 125.4, 125.2, 118.0, 114.0, 76.2, 55.5, 43.6; IR (film) 2926, 2051, 1812, 1652, 1609, 1512, 1260 cm$^{-1}$; HRMS (ESI) calcd for $C_{27}H_{22}NO_3$ $[M+H]^+$ $m/z$ = 408.1600; found 408.1612.

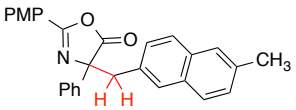



**2-(4-Methoxyphenyl)-4-(naphthalen-2-ylmethyl)-4-phenyloxazol-5(4*H*)-one (4.16)**

General procedure C was followed using **4.01** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in 2-methylnaphthalene (160 mg, 1.12 mmol) and 1,4-dioxane (200 μL) at 95 °C for 24 h. Purification by column chromatography (eluent 8% EtOAc in hexanes) provided **4.16** (22 mg) in 96% yield: $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.87-7.80 (m, 4H), 7.74-7.70 (m, 2H), 7.68 (s, 1H), 7.64 (d, $J$ = 8.4 Hz, 1H), 7.45-7.37 (m, 4H) 7.35 (t, $J$ = 7.8 Hz, 2H), 6.89 (d, $J$ = 8.6 Hz, 2H), 3.83 (s, 3H), 3.68 (d, $J$ = 13.5 Hz, 1H) 3.61 (d, $J$ = 13.5 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 178.4, 163.3, 159.9, 138.6, 133.3, 132.7, 132.2, 130.0, 129.6, 128.8, 128.7, 128.4, 128.0, 127.6, 127.6 126.0, 126.0, 125.8, 118.2, 114.2, 75.7, 55.6, 47.5; IR (film) 3057, 2927, 1813, 1654, 1609, 1511, 1260 cm$^{-1}$; HRMS (ESI) calcd for $C_{27}H_{22}NO_3$ $[M+H]^+$ $m/z$ = 408.1600; found 408.1590.

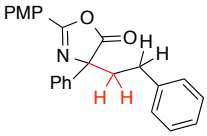



**2-(4-Methoxyphenyl)-4-((3-methylnaphthalen-2-yl)methyl)-4-phenyloxazol-5(4*H*)-one (4.17).** General procedure C was followed using **4.01** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in 2,3-dimethylnaphthalene (175 mg, 1.12 mmol) and 1,4-dioxane (200 μL) at 90 °C for 24 h. Purification by column chromatography (eluent 8% EtOAc in hexanes) provided unreacted 2,3-dimethylnapthalene (~150 mg) and **4.17** (23.4 mg) in 98% yield: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, $J$ = 7.4 Hz, 2H), 7.80 (d, $J$ = 8.5 Hz, 2H), 7.68-7.61 (m, 3H), 7.51 (s, 1H), 7.43 (t, $J$ = 7.8 Hz, 2H), 7.39-7.30 (m, 3H), 6.87 (d, $J$ = 8.6 Hz, 2H), 3.82 (s, 3H), 3.72 (d, $J$ = 13.7 Hz, 1H), 3.67 (d, $J$ = 13.7 Hz, 1H), 2.58 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 178.9, 163.2, 159.5, 144.8, 138.9, 136.1, 133.0, 132.2, 132.0, 129.9, 128.9, 128.4, 128.3, 127.7, 126.8, 126.0, 125.9, 125.1, 118.2, 114.2, 76.4, 55.6, 44.0, 20.8; IR (film) 3057, 2961, 2932, 1813, 1653, 1609, 1512, 1259 cm$^{-1}$; HRMS (ESI) calcd for $C_{28}H_{24}NO_3$ $[M+H]^+$ $m/z$ = 422.1756; found 422.1758.

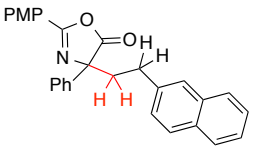



**2-(4-Methoxyphenyl)-4-((6-methylnaphthalen-2-yl)methyl)-4-phenyloxazol-5(4*H*)-one (4.18).** General procedure C was followed using **4.01** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in 2,6-dimethylnaphthalene (175 mg, 1.12 mmol) and 1,4-dioxane (200 μL) at 90 °C for 24 h. Purification by column chromatography (eluent 8% EtOAc in hexanes) provided unreacted 2,6-dimethylnaphthalene (~150 mg) and **4.18** (18.1 mg) in 76% yield: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.87-7.79 (m, 4H), 7.62 (d, $J$ =

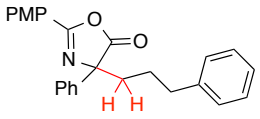
8.1 Hz, 2H), 7.55 (d, *J* = 8.5 Hz, 1H), 7.48 (s, 1H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.35 (t, *J* = 7.2 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 6.89 (d, *J* = 8.8 Hz, 2H), 3.83 (s, 3H), 3.66 (d, *J* = 13.5 Hz, 1H), 3.58 (d, *J* = 13.5 Hz, 1H), 2.45 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 178.5, 163.2, 159.8, 138.6, 135.5, 132.9, 131.6, 131.2, 130.0, 129.3, 128.8, 128.8, 128.4, 128.2, 127.8, 126.9, 126.6, 126.0, 118.2, 114.2, 75.8, 55.6, 47.5, 21.8; IR (film) 3055, 2923, 2852, 1812, 1653, 1609, 1512, 1260 cm$^{-1}$; HRMS (ESI) calcd for $C_{28}H_{24}NO_3$ $[M+H]^+$ *m/z* = 422.1756; found 422.1751.




**2-(4-Methoxyphenyl)-4-phenethyl-4-phenyloxazol-5(4*H*)-one (4.19).** General procedure C was followed using **4.01** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in ethylbenzene (140 μL, 1.12 mmol) and 1,4-dioxane (200 μL) at 90 °C for 24 h. Purification by column chromatography (eluent 7% EtOAc in hexanes) provided **4.19** (15.1 mg) in 72% yield: $^1$H NMR (500 MHz, $CDCl_3$) δ 8.07 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J* = 7.3 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.32 (t, *J* = 7.1 Hz, 1H), 7.24 (t, *J* = 7.6 Hz, 2H), 7.18-7.12 (m, 3H), 7.02 (d, *J* = 8.6 Hz, 2H), 3.90 (s, 3H), 2.66-2.58 (m, 2H), 2.56-2.43 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 179.0, 163.5, 160.3, 140.7, 138.5, 130.2, 128.8, 128.6, 128.5, 128.3, 126.3, 125.8, 118.3, 114.4, 74.2, 55.7, 42.8, 30.8; IR (film) 3027, 2933, 1814, 1652, 1609, 1512, 1260 cm$^{-1}$; HRMS (ESI) calcd for $C_{24}H_{22}NO_3$ $[M+H]^+$ *m/z* = 371.2600; found 372.1613.

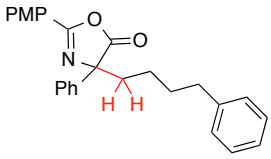


**2-(4-Methoxyphenyl)-4-(2-(naphthalen-2-yl)ethyl)-4-phenyloxazol-5(4*H*)-one (4.20).** General procedure C was followed using **4.01** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in 2-ethylnaphthalene (175 μL, 1.12 mmol) and 1,4-dioxane (200 μL) at 90 °C for 24 h. Purification by column chromatography (eluent 8% EtOAc in hexanes) provided **4.20** (15.3 mg) in 65% yield: $^1$H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.6 Hz, 2H), 7.77 (d, *J* = 7.3 Hz, 1H), 7.75-7.68 (m, 4H), 7.57 (s, 1H), 7.45-7.36 (m, 4H), 7.33 (t, *J* = 7.3 Hz, 1H), 7.28 (d, *J* = 8.6 Hz, 1H), 7.02 (d, *J* = 9.0 Hz, 2H), 3.90 (s, 3H), 2.86-2.74 (m, 2H), 2.65-2.52 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 179.0, 163.5, 160.3, 138.5, 138.1, 133.7, 132.2, 130.2, 128.8, 128.3, 128.1, 127.7, 127.5, 127.2, 126.6, 126.1, 125.8, 125.4, 118.2, 114.4, 74.2, 56.7, 42.6, 30.9; IR (film) 3056, 2930, 1813, 1652, 1608, 1511, 1260 cm$^{-1}$; HRMS (ESI) calcd for $C_{28}H_{23}NO_3Na$ $[M+Na]^+$ *m/z* = 444.1576; found 444.1571.

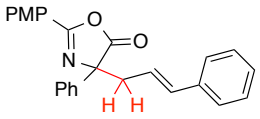



**2-(4-methoxyphenyl)-4-phenyl-4-(3-phenylpropyl)oxazol-5(4*H*)-one (4.21a).** General procedure C was followed using **4.01** (15 mg, 0.056 mmol) and $Pd(OAc)_2$ (12.5 mg, 0.056 mmol) in propylbenzene (140 μL, 1.00 mmol) and 1,4-dioxane (200 μL) at 90 °C for 24 h. Purification by column chromatography (eluent 7% EtOAc in hexanes) provided **4.21a** (15.3 mg) in 62% yield as a yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 9.1 Hz, 2H), 7.66 (d, *J* = 7.9 Hz, 2H), 7.37 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.2 Hz, 1H), 7.24 (d, *J* = 7.7 Hz, 2H), 7.16 (t, *J* = 7.3 Hz, 1H), 7.12 (d, *J* = 7.9 Hz, 2H), 7.00 (d, *J* = 9.0 Hz, 2H), 3.89 (s, 3H), 2.70-2.55 (m, 2H), 2.30-2.18 (m, 2H), 1.71-1.61 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 179.2, 163.4, 160.0, 141.6, 138.7, 130.1, 128.7, 128.5, 128.5,

128.2, 126.0, 125.8, 118.3, 114.4, 74.3, 55.7, 40.8, 35.7, 26.2; IR (film) 2952, 2933, 1815, 1653, 1601, 1512, 1260 $cm^{-1}$; HRMS (ESI) calcd for $C_{25}H_{24}NO_3$ $[M+H]^+$ *m/z* = 386.1756; found 386.1739.




**2-(4-methoxyphenyl)-4-phenyl-4-(4-phenylbutyl)oxazol-5(4*H*)-one (4.21b).** General procedure C was followed using **4.01** (20 mg, 0.075 mmol) and $Pd(OAc)_2$ (16.9 mg, 0.075 mmol) in butylbenzene (190 μL, 1.21 mmol) and 1,4-dioxane (270 μL) at 90 °C for 24 h. Purification by column chromatography (eluent 7% EtOAc in hexanes) provided **4.21b** (13.8 mg) in 46% yield as a yellow oil: $^1H$ NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.1 Hz, 2H), 7.67 (d, *J* = 8.1 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.31 (t, *J* = 7.4 Hz, 1H), 7.23 (t, *J* = 7.5 Hz, 2H), 7.14 (t, *J* = 7.2 Hz, 2H), 7.10 (d, *J* = 7.5 Hz, 2H), 7.01 (d, *J* = 8.1 Hz, 2H), 3.89 (s, 3H), 2.55 (t, *J* = 7.9 Hz, 2H), 2.22 (t, *J* = 8.2 Hz, 2H), 1.61 (m, 2H), 1.37 (m, 2H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 179.3, 163.4, 160.0, 142.4, 138.8, 130.1, 128.8, 128.4, 128.4, 128.2, 125.8, 125.8, 118.4, 114.4, 74.4, 55.7, 41.1, 35.8, 31.4, 24.1; IR (film) 2931, 2856, 1811, 1652, 1609, 1512, 1260 $cm^{-1}$; HRMS (ESI) calcd for $C_{26}H_{26}NO_3$ $[M+H]^+$ *m/z* = 400.1913; found 400.1913.




**4-Cinnamyl-2-(4-methoxyphenyl)-4-phenyloxazol-5(4*H*)-one (4.21c).** General procedure C was followed using **4.01** (20 mg, 0.075 mmol) and $Pd(OAc)_2$ (16.9 mg,

0.075 mmol) in allylbenzene (188 μL, 1.25 mmol) and 1,4-dioxane (270 μL) at 95 °C for 24 h. Purification by column chromatography (eluent 7% EtOAc in hexanes) provided **4.21c** (11.8 mg) in 41% yield as a yellow oil: $^{1}$H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.9 Hz, 2H), 7.74 (d, *J* = 8.3 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.25-7.22 (m, 4H), 7.21-7.15 (m, 1H), 6.98 (d, *J* = 8.9 Hz, 2H), 6.52 (d, *J* = 15.7 Hz, 1H), 6.04 (dt, *J* = 15.7, 7.5 Hz, 1H), 3.88 (s, 3H), 3.09 (d, *J* = 7.5 Hz, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 178.5, 163.4, 160.1, 138.3, 137.0, 135.7, 130.1, 128.8, 128.6, 128.4, 127.6, 126.5, 125.9, 122.2, 118.2, 114.4, 74.8, 55.6, 44.6; IR (film) 3027, 2934, 1815, 1652, 1609, 1512, 1260 cm$^{-1}$; HRMS (ESI) calcd for $C_{25}H_{22}NO_3$ $[M+H]^+$ *m/z* = 384.1600; found 384.1587.

**Chart S4.1** Tolyl analogs explored with phenylglycine azlactone and $Pd(OAc)_2$ at 95 °C for 7 h in neat solution.

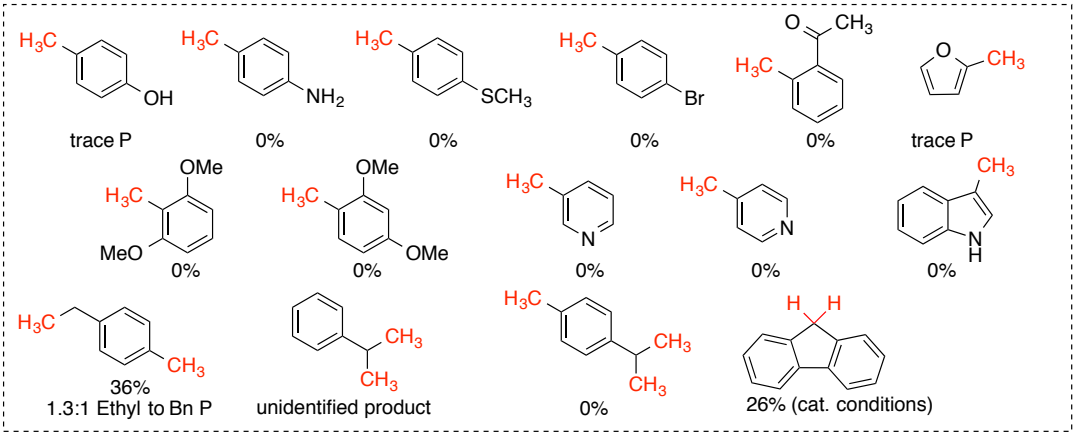
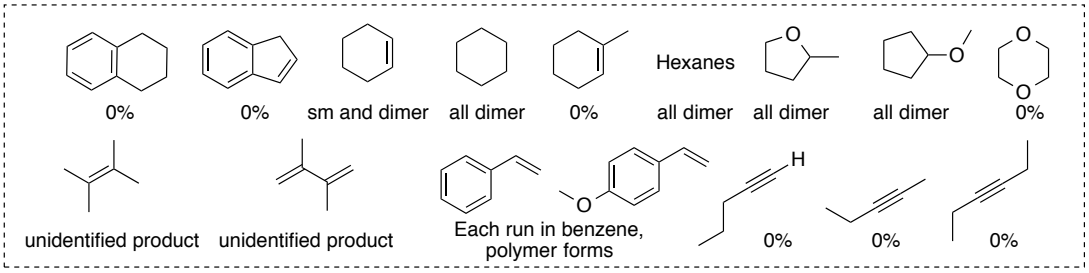
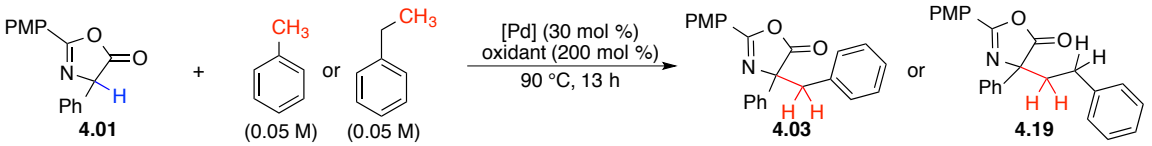



**Chart S4.2** Alkyl analogs explored with phenylglycine azlactone and $Pd(OAc)_2$ at 95 °C for 7 h in neat solution.




**PME studies with 23 oxidants and 2 Pd sources (**Table 4.7**)**



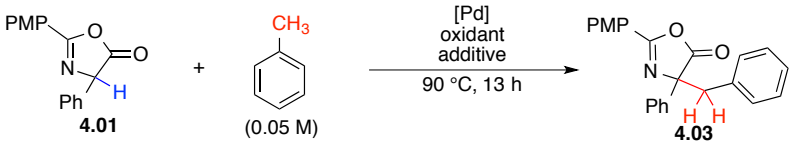

To a 96-well reactor equipped with 1 mL vials was added the indicated oxidant (Table S2, entries 1-18, 0.010 mmol, 50 μL of a 0.2 M solution in toluene, respectively). The solvent was evacuated on a Genevac. To each vial was added **4.01** (0.005 mmol) and the indicated Pd source (0.0015 mmol) (100 μL of a 0.05 M solution in tolyl analog). Oxidants (Table S2, entries 19-23, 0.010 mmol) were added to the respective vial. The control reactions were prepared from a solution of **4.01** (0.005 mmol) and Pd source (0.005 mmol) (100 μL of a 0.05 M solution in tolyl analog) into the respective vial. A parylene stir-bar was added to each vial. The reactor block was sealed, removed from the glovebox and stirred for 13 h on an Alligator tumble stirrer (1000 rpm) at 90 °C. The reactions were quenched *via* dilution with a solution of internal standard in 25% DMSO/MeCN (1.0 μmol, 0.002 M, 500 μL), and the contents were stirred for 15 minutes. Into a separate 96-well plate LC block was added 700 μL of MeCN and 25 μL of the diluted reaction mixtures. The 96-well plate LC block was sealed with a polypropylene 1 mL cap mat. The reaction mixtures were analyzed (P/IS and dimer/IS)

using an Agilent Technologies 1200 series HPLC with a 96 well-plate auto-sampler. Assay conditions: Acquity CORTECS BEH 1.6 μm C18; 50 mm x 2.1 mm; 1 mL/min; MeCN:$H_2O$:$NH_4HCO_2$; gradient: 5% MeCN to 99% in 1.5 min, hold to 2.4 min to 5% MeCN at 2.41 min; ESC pos/neg; nebulizer: 700 L/h; cone gas: 30 L/h; source 150 °C; desolvation 450 °C; 210 nm: $t_R$ of **4.03** = 2.46, **4.19** = 2.73 and **4.23** = 2.73 min.

| | entry | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Toluene** | $Pd(OAc)_2$ P/IS[a] | 0.0 | 0.0 | 4.5 | 0.0 | 0.0 | 0.8 | 3.1 | 6.7 | 0.9 | 0.0 | 0.0 | 1.9 | 4.5 | 0.0 | 5.8 | 0.7 | 0.0 | 7.4 | 0.0 | 4.8 | 0.0 | 0.0 | 0.9 | 6.9 |
| | $Pd(OAc)_2$ Dimer/IS[a] | 0.0 | 0.0 | 1.6 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 1.4 | 0.0 | 0.0 | 0.0 | 1.2 | 0.0 | 0.0 | 0.0 | 0.0 |
| | $Pd(TFA)_2$ P/IS[a] | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 3.0 | 1.8 | 2.1 | 0.0 | 0.0 | 1.5 | 2.7 | 0.0 | 0.0 | 0.0 | 0.5 | 6.2 | 0.0 | 2.7 | 0.0 | 0.1 | 2.5 | 7.0 |
| | $Pd(TFA)_2$ Dimer/IS[a] | 0.0 | 0.0 | 1.3 | 0.0 | 0.0 | 0.0 | 1.4 | 1.7 | 0.0 | 0.0 | 0.0 | 0.8 | 0.0 | 0.0 | 2.1 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.9 | 0.8 |
| **Ethylbenzene** | $Pd(OAc)_2$ P/IS[a] | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 4.1 | 0.0 | 0.0 | 0.0 | 2.1 | 1.6 | 0.0 | 1.7 | 0.0 | 0.0 | 1.6 | 0.5 | 4.5 | 0.0 | 0.4 | 0.0 | 7.1 |
| | $Pd(OAc)_2$ Dimer/IS[a] | 0.0 | 0.0 | 2.1 | 0.0 | 0.7 | 1.0 | 1.8 | 0.0 | 0.0 | 0.0 | 0.0 | 0.9 | 0.0 | 1.0 | 2.7 | 2.8 | 0.7 | 1.0 | 0.0 | 0.8 | 0.0 | 0.0 | 1.6 | 0.0 |
| | $Pd(TFA)_2$ P/IS[a] | 0.7 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 1.1 | 0.0 | 0.7 | 0.0 | 0.0 | 1.3 | 0.0 | 0.0 | 0.0 | 0.0 | 1.4 | 4.1 | 0.3 | 2.0 | 0.0 | 1.9 | 0.0 | 4.2 |
| | $Pd(TFA)_2$ Dimer/IS[a] | 0.0 | 0.0 | 1.7 | 0.0 | 0.0 | 0.0 | 1.5 | 2.2 | 0.0 | 0.0 | 0.0 | 1.9 | 0.7 | 1.2 | 2.3 | 0.9 | 0.0 | 0.0 | 0.4 | 0.0 | 0.0 | 1.0 | 2.8 | 0.7 |
| **Oxidant** | | $CuBr_2$ | $CuCl_2$ | $Cu(OAc)_2$ | $Ag_2CO_3$ | $K_3PO_4$ | $Ag_2O$ | $Ce(SO_4)_2$ | $K_2S_2O_8$ | F+1[b] | F+2[c] | F+3[d] | $(PhCOO)_2$ | Oxone | NCS | Benzoquinone | PIDA | TBAB | 2,6-DMBQ | Cumene OOH | tBuOOtBu | tBuOOH | tBuOOCOPh | DMSO | control |

[a]Determined by UPLC. [b]F+1 = 1-fluoropyridinium tetrafluoroborate. [c]F+2 = 1-fluoro-2,4,6-trimethylpyridinium triflate. [d]F+3 = *N*-fluorobenzenesulfonimide.

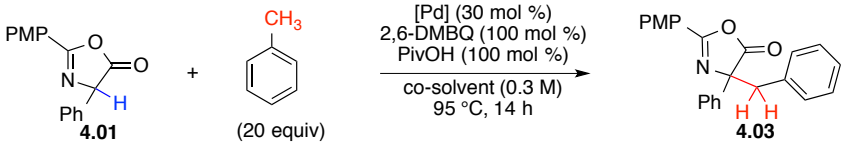
**Optimization of catalytic benzylation (**Table 4.8**,** Table 4.9**)**




Phenylglycine azlactone (**4.01**) (10 mg, 0.038 mmol) was added to a flame dried 8 mL microwave vial equipped with stir bar and brought into the glovebox. Pd carboxylate was added, followed by additive and toluene (750 μL, 0.05 M). The microwave vial was sealed with a Teflon cap, removed from the glovebox and placed in a 95 °C oil bath. After 13 h, the mixture was allowed to cool to ambient temperature, diluted with $CH_2Cl_2$

(1 mL), passed through $SiO_2$ with 30% EtOAc in hexanes, and concentrated *in vacuo*. The resulting residue was analyzed by $^1H$ NMR and if necessary purified by column chromatography to afford **4.03**. See above for characterization.

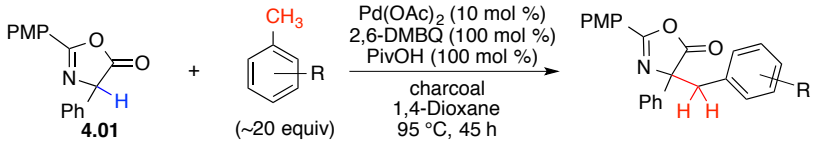
**PME screen of co-solvents with optimal catalytic conditions (**Table 4.10**)**



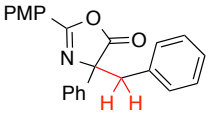

To a 24-well reactor equipped with 1 mL vials was added **4.01** (0.005 mmol) and 2,6-DMBQ (0.005 mmol) in THF (100 μL of a 0.05 M solution). The solvent was evacuated on a Genevac. A solution of Pd carboxylate (0.0015 mmol) and PivOH (0.005 mmol) (40 μL of a 0.038 M solution in co-solvent), respectively, was added to the 24-well reactor. Toluene (22 μL, 0.1 mmol) and a parylene stir-bar were added to each vial. The reactor block was sealed, removed from the glovebox and stirred for 14 h on an Alligator tumble stirrer (1000 rpm) at 95 °C. The reactions were quenched *via* dilution with a solution of internal standard in 25% DMSO/MeCN (1.0 μmol, 0.002 M, 500 μL), and the contents were stirred for 15 minutes. Into a separate 96-well plate LC block was added 700 μL of MeCN and 25 μL of the diluted reaction mixtures. The 96-well plate LC block was sealed with a polypropylene 1 mL cap mat. The reaction mixtures were analyzed (P/IS and dimer/IS) using an Agilent Technologies 1200 series HPLC with a 96 well-plate auto-sampler. Assay conditions: Supeclco Ascentis Express C18 column 100 mm x 4.6 mm, 1.8 μm with reverse phase eluents (MeCN and 0.1 % $H_3PO_4$ in $H_2O$); 1.8

mL/min; 10 % in MeCN to 95 % MeCN in 6 min, hold for 2 min. Post time 2 min. Column at 40 °C; 210 nm: $t_R$ of **4.01** = 4.7, **4.03** = 5.9 and **4.23** = 6.5 min.

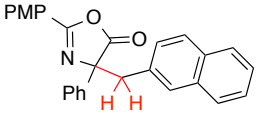
**General Procedure D – Alkylation with catalytic Pd**



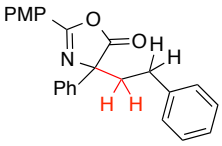

Phenylglycine azlactone (**4.01**) (15 mg, 0.056 mmol), $Pd(OAc)_2$ (1.3 mg, 0.0056 mmol), PivOH (5.7 mg, 0.056 mmol), 2,6-DMBQ (7.6 mg, 0.056 mmol) and charcoal (13 mg, 10x weight of Pd) were added to a flame dried 8 mL microwave vial equipped with stir bar and brought into the glovebox. The indicated tolyl analog (1.12 mmol) was added to the mixture followed by 1,4-dioxane (467 μL, 0.12 M). The microwave vial was sealed with a Teflon cap, removed from the glovebox, and placed in a 95 °C oil bath. After 45 h, the mixture was allowed to cool to ambient temperature, diluted with $CH_2Cl_2$ (1 mL), and purified directly by column chromatography to afford the alkylated azlactone.




**4-Benzyl-2-(4-methoxyphenyl)-4-phenyloxazol-5(4*H*)-one (4.03).** General procedure D was followed using toluene (118 uL, 1.12 mmol). Purification by column chromatography (eluent 8% EtOAc in hexanes) provided **4.03** (16.3 mg) in 82% yield. See above for characterization.

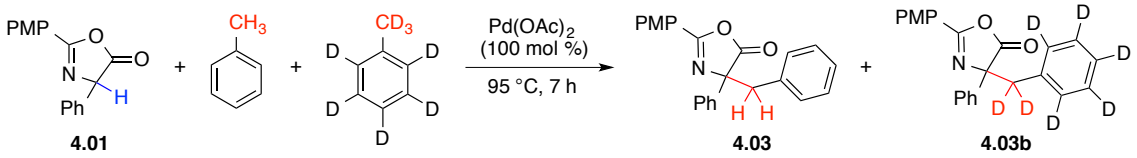


**2-(4-Methoxyphenyl)-4-(naphthalen-2-ylmethyl)-4-phenyloxazol-5(4*H*)-one (4.16).** General procedure D was followed using 2-methylnaphthalene (159 mg, 1.12 mmol). Purification by column chromatography (eluent 8% EtOAc in hexanes) provided **4.16** (20.1 mg) in 88% yield. See above for characterization.




**2-(4-Methoxyphenyl)-4-phenethyl-4-phenyloxazol-5(4*H*)-one (4.19).** General procedure D was followed using ethylbenzene (137 uL, 1.12 mmol). Purification by column chromatography (eluent 8% EtOAc in hexanes) provided **4.19** (14.1 mg) in 68% yield. See above for characterization.

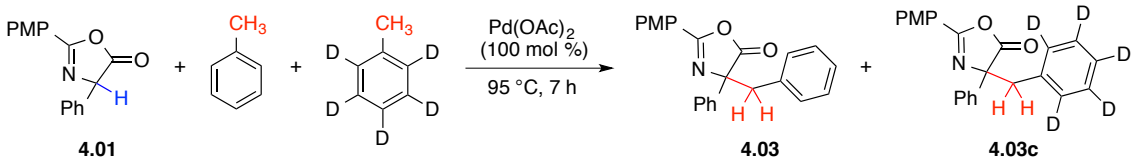
**KIE Studies: $d_8$-toluene (**Scheme 4.5**)**



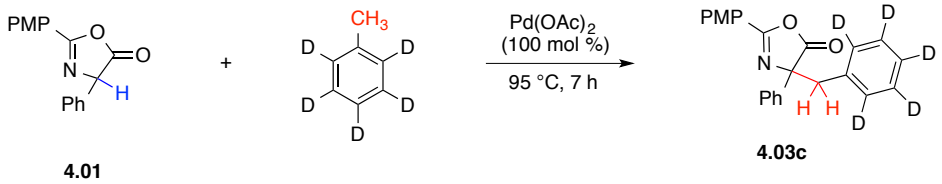

Phenylglycine azlactone (**4.01**) (10 mg, 0.038 mmol) was added to a flame dried 8 mL microwave vial equipped with stir bar and brought into the glovebox. $Pd(OAc)_2$ (8.4 mg, 0.038 mmol) was added followed by toluene (138 μL, 1.5 mmol) and $d_8$-toluene (150 μL, 1.5 mmol). The microwave vial was sealed with a Teflon cap, removed from the glovebox and placed in a 95 °C oil bath. After 7 h, the mixture was allowed to cool to ambient temperature, diluted with $CH_2Cl_2$ (1 mL), passed through $SiO_2$ with 30% EtOAc in hexanes, and concentrated *in vacuo*. The resulting residue was purified by column

chromatography (7% EtOAc in hexanes) to afford a mixture of **4.03** and **4.03b** (12 mg) in 89% yield. Two trials were conducted and the $k_H/k_D$ = 3.4 ± 0.15. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.7 Hz, 2H), 7.78 (d, *J* = 8.0 Hz, 2H), 7.40 (t, *J* = 7.7 Hz, 2H), 7.34 (t, *J* = 7.3 Hz, 1H), 7.22-7.11 (m, 3.8H), 6.93 (d, *J* = 8.9 Hz, 2H), 3.86 (s, 3H), 3.51 (d, *J* = 13.4 Hz, 0.74H), 3.44 (d, *J* = 13.4 Hz, 0.77H).

**KIE Studies: $d_3$-toluene** (Scheme 4.5)

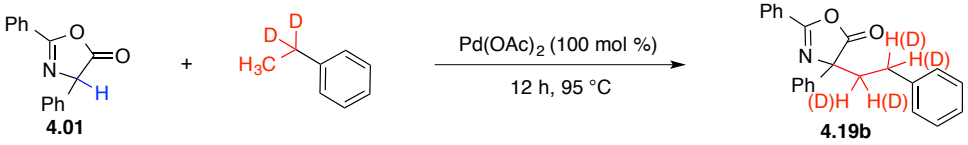



Phenylglycine azlactone (**4.01**) (27 mg, 0.1 mmol) was added to a flame dried 8 mL microwave vial equipped with stir bar and brought into the glovebox. $Pd(OAc)_2$ (23 mg, 0.1 mmol) was added followed by toluene (319 μL, 3.0 mmol) and $d_5$-toluene (336 μL, 3.0 mmol). The microwave vial was sealed with a Teflon cap, removed from the glovebox and placed in a 95 °C oil bath. After 7 h, the mixture was allowed to cool to ambient temperature, diluted with $CH_2Cl_2$ (1 mL), passed through $SiO_2$ with 30% EtOAc in hexanes, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (7% EtOAc in hexanes) to afford a mixture of **4.03** and **4.03c** (19 mg) in 53% yield with $k_H/k_D$ = 1.08. $^1$H NMR (500 MHz, $CDCl_3$) 7.87 (d, *J* = 8.9 Hz, 2H), 7.79 (d, *J* = 7.5 Hz, 2H), 7.41-7.34 (m, 3H), 7.21-7.15 (m, 2.6H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.86 (s, 3H), 3.52 (d, *J* = 13.4 Hz, 1H), 3.45 (d, *J* = 13.4 Hz, 1H).




Phenylglycine azlactone (**4.01**) (7.0 mg, 0.026 mmol) and $Pd(OAc)_2$ (6.0 mg, 0.026 mmol) were added to a flame dried 8 mL microwave vial equipped with stir bar and brought into the glovebox. $d_5$-Toluene (200 μL, 2.0 mmol) was added to the mixture. The microwave vial was sealed with a Teflon cap, removed from the glovebox, and placed in a 95 °C oil bath. After 7 h, the mixture was allowed to cool to ambient temperature, diluted with $CH_2Cl_2$ (1 mL), passed through $SiO_2$ with 30% EtOAc in hexanes, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (7% EtOAc in hexanes) to afford a mixture of **4.03c** (9 mg) in 98% yield. $^1$H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, $J$ = 8.5 Hz, 2H), 7.78 (d, $J$ = 8.1 Hz, 2H), 7.41 (t, $J$ = 7.6 Hz, 2H), 7.34 (t, $J$ = 7.3 Hz, 1H), 6.93 (d, $J$ = 8.5 Hz, 2H), 3.86 (s, 3H), 3.51 (d, $J$ = 13.4 Hz, 1H), 3.44 (d, $J$ = 13.4 Hz, 1H).

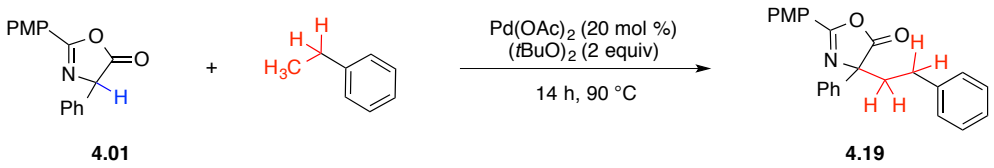
**Deuterium scrambling with ethylbenzene (**Scheme 4.6**)**




Phenylglycine azlactone (**4.01**) (10 mg, 0.038 mmol) and $Pd(OAc)_2$ (9.5 mg, 0.038 mmol) were added to a flame dried 8 mL microwave vial equipped with a stir bar and brought into the glovebox. $d_2$-Ethylbenzene (700 μL, 5.7 mmol) was added to the mixture. The microwave vial was sealed with a Teflon cap, removed from the glovebox

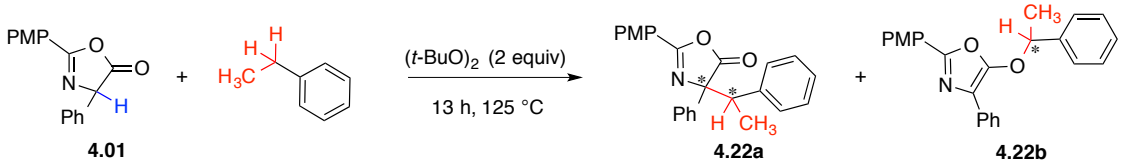
and placed in a 95 °C oil bath. After 12 h, the mixture was allowed to cool to ambient temperature, diluted with $CH_2Cl_2$ (1 mL), passed through $SiO_2$ with 30% EtOAc in hexanes, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (7% EtOAc in hexanes) to afford **4.19b** (3.1 mg) in 22% yield.

**Radical studies with ethylbenzene (**Table 4.12**)**



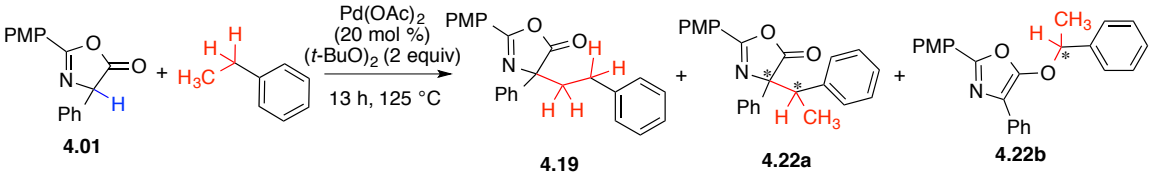

**4.01** **4.19**

Phenylglycine azlactone (**4.01**) (11.2 mg, 0.042 mmol) and $Pd(OAc)_2$ (1.9 mg, 0.008 mmol) were added to a flame dried 8 mL microwave vial equipped with a stir bar and brought into the glovebox. A solution of di-*tert*-butyl peroxide [(*t*-$BuO)_2$] in ethylbenzene (855 μL, 0.1 M) was added to the mixture. The microwave vial was sealed with a Teflon cap, removed from the glovebox and placed in a 90 °C oil bath. After 14 h, the mixture was allowed to cool to ambient temperature, diluted with $CH_2Cl_2$ (1 mL), passed through $SiO_2$ with 30% EtOAc in hexanes, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (7% EtOAc in hexanes) to afford **4.19** (5.9 mg) in 38% yield. The remaining product was phenylglycine azlactone dimer. See above for characterization.



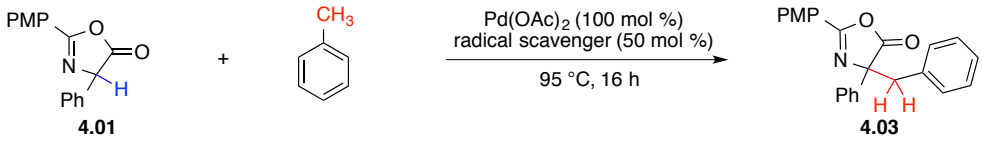

**4.01** **4.22a** **4.22b**

Phenylglycine azlactone (**4.01**) (60 mg, 0.23 mmol) was added to a flame dried 8 mL microwave vial equipped with stir bar, and brought into the glovebox. A solution of (*t*-BuO)$_2$ in ethylbenzene (4.58 mL, 0.1 M) was added. The microwave vial was sealed with a Teflon cap, removed from the glovebox and placed in a 125 °C oil bath. After 13 h, the mixture was allowed to cool to ambient temperature, diluted with $CH_2Cl_2$ (2 mL), passed through $SiO_2$ with 30% EtOAc in hexanes, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (15% EtOAc in hexanes) to afford a 9:1 inseperable mixture of **4.22a** and **4.22b** (50 mg) in 60% yield. This mixture, which consisted of six isomers of **4.22a** and **4.22b**, was further analyzed in a collaboration with Erik Regalado and Christopher Welch at Merck Research Laboratories, Rahway, NJ.[164]



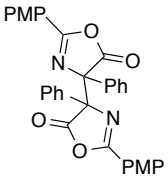

Phenylglycine azlactone (**4.01**) (11.2 mg, 0.042 mmol) and $Pd(OAc)_2$ (1.9 mg, 0.008 mmol) were added to a flame dried 8 mL microwave vial equipped with a stir bar and brought into the glovebox. A solution of (*t*-BuO)$_2$ in ethylbenzene (855 μL, 0.1 M) was added to the mixture. The microwave vial was sealed with a Teflon cap, removed from the glovebox and placed in a 125 °C oil bath. After 13 h, the mixture was allowed to cool to ambient temperature, diluted with $CH_2Cl_2$ (1 mL), passed through $SiO_2$ with 30% EtOAc in hexanes, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (7% EtOAc in hexanes) to afford a 1:8:1 mixture of **4.19**, **4.22b**, and **4.22c**.

**Table 4.13** Radical scavengers study




Phenylglycine azlactone (**4.01**) (10 mg, 0.037 mmol) and radical scavenger (0.019 mmol) were added to a flame dried 8 mL microwave vial equipped with a stir bar and brought into the glovebox. $Pd(OAc)_2$ (8.3 mg, 0.037 mmol) was added followed by toluene (370 μL, 3.7 mmol). The microwave vial was sealed with a Teflon cap, removed from the glovebox, and placed in a 95 °C oil bath. After 16 h, the mixture was allowed to cool to ambient temperature, diluted with $CH_2Cl_2$ (1 mL), passed through $SiO_2$ with 30% EtOAc in hexanes, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (7% EtOAc in hexanes) to afford **4.03**. See above for characterization.

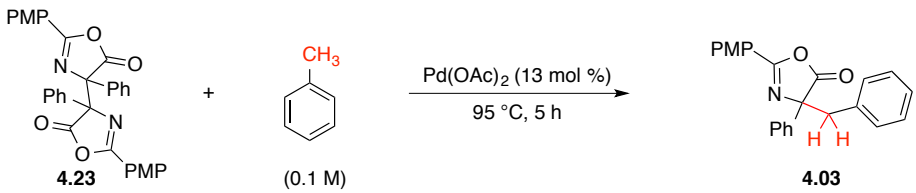
| entry | radical scavenger (50 mol %) | yield (%) | recovered scavenger (%) |
|---|---|---|---|
| 1 | TEMPO | 54 | 0 |
| 2 | 1,1-diphenylethylene | 85 | 58 |
| 3 | BHT | 59 | 67 |
| 4 | none | 83 | - |




**2,2'-bis(4-Methoxyphenyl)-4,4'-diphenyl-[4,4'-bioxazole]-5,5'(4*H*,4'*H*)-dione (4.23).** Phenylglycine azlactone (**4.01**) (60 mg, 0.23 mmol), $Pd(OAc)_2$ (2.5 mg, 0.011 mmol) and $Ag_2O$ (52 mg, 0.23 mmol) were added to a flame dried 8 mL microwave vial equipped with a stir bar and brought into the glovebox. Toluene (2.3 mL, 0.1 M) was added to the

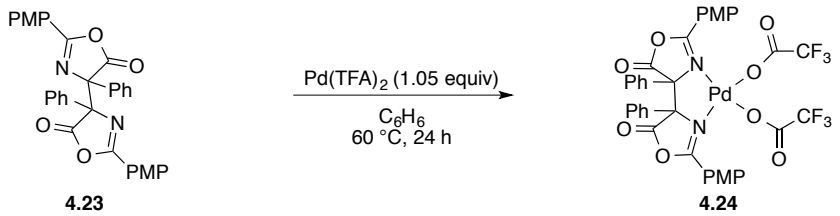
mixture. The microwave vial was sealed with a Teflon cap, removed from the glovebox and allowed to stir at ambient temperature. After 5 h, the mixture was purified directly by column chromatography (20% EtOAc in hexanes) to afford **4.23** (50 mg) in 83% yield. A single crystal for X-ray structural analysis was obtained by slow-evaporation from $CH_2Cl_2$. $^1H$ NMR (500 MHz, $CDCl_3$) δ major: 7.88 (d, $J$ = 8.7 Hz, 2H), 7.44 (d, $J$ = 7.6 Hz, 2H), 7.20 (m, 3H), 6.85 (d, $J$ = 8.7 Hz, 2H), 3.82 (s, 3H); minor: 7.9.4 (d, $J$ = 8.7 Hz, 2H), 7.69 (d, $J$ = 7.6 Hz, 2H), 7.30 (m, 3H), 6.90 (d, $J$ = 8.7 Hz, 2H), 3.87 (s, 3H). Spectral data matched those reported previously by Marquez.[166]

**Dimer with catalytic Pd (**Scheme 4.7**)**



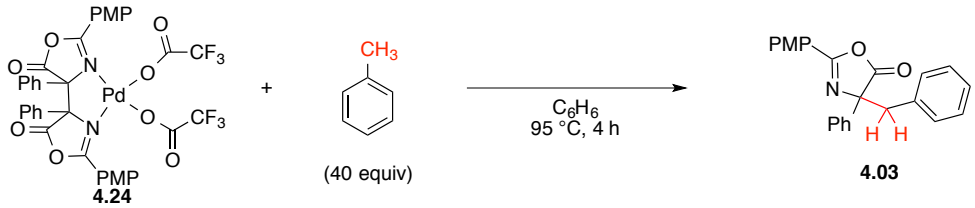

Phenylglycine azlactone dimer (**4.23**) (10.0 mg, 0.019 mmol) and $Pd(OAc)_2$ (1.1 mg, 0.0049 mmol) were added to a flame dried 8 mL microwave vial equipped with a stir bar, and brought into the glovebox. Toluene (375 μL, 0.1 M) was added to the mixture. The microwave vial was sealed with a Teflon cap, removed from the glovebox and placed in a 95 °C oil bath. After 5 h, the mixture was allowed to cool to ambient temperature, diluted with $CH_2Cl_2$ (1 mL), passed through $SiO_2$ with 30% EtOAc in hexanes, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (7% EtOAc in hexanes) to afford **4.03** (9.5 mg) in 72% yield. See above for characterization.

**Dimer with $Pd(TFA)_2$ complex (**Figure 4.8**)**




Phenylglycine azlactone dimer (**4.23**) (25 mg, 0.047 mmol) and $Pd(TFA)_2$ (17.4 mg, 0.0052 mmol) were added to an NMR tube equipped with a J Young valve. The reaction mixture was put under argon and $C_6D_6$ (524 μL, 0.1 M), which had been sparged with argon, was added. The NMR tube was sealed and placed in a 60 °C oil bath. After 24 h, the mixture was allowed to cool to ambient temperature, and subsequently decanted from the black precipitate formed during heating and concentrated *in vacuo*. A single crystal for X-ray structural analysis was obtained by dissolving the resulting residue in THF, layering hexanes on top and storing the mixture in a -8 °C freezer overnight. $^1$H NMR (500 MHz, $CDCl_3$) δ 9.53 (d, $J$ = 7.9 Hz, 2H), 7.94 (d, $J$ = 9.0 Hz, 2H), 7.32 (t, $J$ = 8.0 Hz, 2H), 6.90 (t, $J$ = 7.5 Hz, 1H), 6.41 (d, $J$ = 9.2 Hz, 2H), 3.00 (s, 3H).

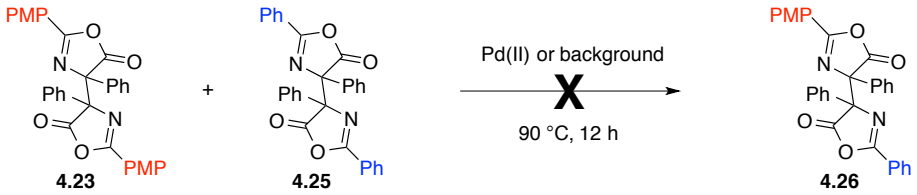
**Dimer-Pd complex with toluene (**Scheme 4.8**)**



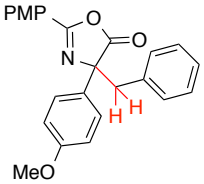

Phenylglycine azlactone dimer (**4.24**) (8 mg, 0.015 mmol) and $Pd(TFA)_2$ (5.5 mg, 0.017 mmol) were added to an NMR tube equipped with a J Young valve. The reaction mixture was put under argon and $C_6D_6$ (524 μL, 0.1 M), that had been sparged with argon, was added. The NMR tube was sealed and placed in a 60 °C oil bath. After 24 h,

the mixture was allowed to cool to ambient temperature. Toluene (165 μL, 0.1 M) was added and the mixture was placed in a 95 °C oil bath. After 4 h, the mixture was allowed to cool to ambient temperature and purified directly by column chromatography (7% EtOAc in hexanes) to afford **4.03** (4.0 mg) in 37% yield. See above for characterization.

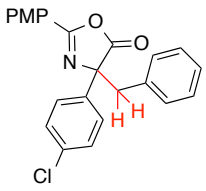
**Dimer crossover experiment (**Scheme 4.9**)**




Phenylglycine azlactone dimer (**4.23**) (6.3 mg, 0.012 mmol), phenylglycine azlactone dimer (**4.25**) (5.6 mg, 0.012 mmol) and additive [$Pd(OAc)_2$ (5.4 mg, 0.024 mmol] or no additive was added to a flame dried 8 mL microwave vial equipped with a stir bar and brought into the glovebox. To each mixture, benzene (240 μL, 0.1 M) was added. The microwave vial was sealed with a Teflon cap, removed from the glovebox and placed in an 90 °C oil bath. After 12 h, each mixture was allowed to cool to ambient temperature, diluted with $CH_2Cl_2$ (1 mL), and purified directly by column chromatography (15% EtOAc in hexanes) to afford only recovered **4.23** and **4.25**. Analysis by UPLC MS suggested dimer mixing, but further investigation with a control (**4.23** and **4.25** mixed together at rt and analyzed) revealed ionization causes mixing during the MS analysis.

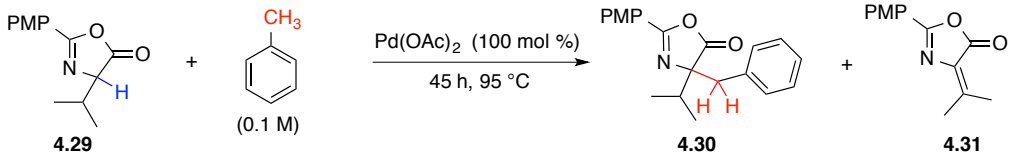


**4-Benzyl-2,4-bis(4-methoxyphenyl)oxazol-5(4*H*)-one (4.27).** General procedure B was followed using *para*-methoxy-phenylglycine azlactone (11.5 mg, 0.037 mmol ) and $Pd(OAc)_2$ (8.3 mg, 0.037 mmol) in toluene (750 μL, 5.4 mmol). The mixture was allowed to stir at 95 °C for 5 h and purification by column chromatography provided **4.27** (9.0 mg) in 70% yield: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, $J$ = 8.9 Hz, 2H), 7.68 (d, $J$ = 9.1 Hz, 2H), 7.22-7.11 (m, 5H), 6.93 (d, $J$ = 8.9 Hz, 4H), 3.86 (s, 3H), 3.82 (s, 3H), 3.49 (d, $J$ = 13.4 Hz, 1H), 3.41 (d, $J$ = 13.4 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 178.7, 163.2, 159.6, 159.6, 134.5, 130.6, 130.5, 129.9, 128.2, 127.3, 127.2, 118.2, 114.2, 114.1, 75.2, 55.6, 55.5, 47.3; IR (film) 2932, 1812, 1653, 1608, 1511, 1255 cm$^{-1}$; HRMS (ESI) calcd for $C_{24}H_{22}NO_4$ $[M+H]^+$ $m/z$ = 388.1549; found 388.1549.

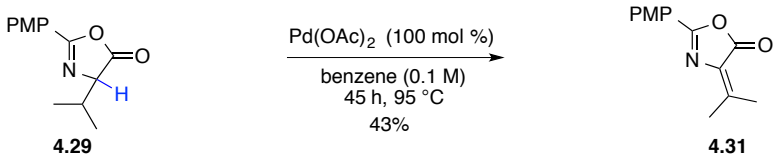



**4-Benzyl-4-(4-chlorophenyl)-2-(4-methoxyphenyl)oxazol-5(4*H*)-one (4.28).** General procedure B was followed using *para*-chloro-phenylglycine azlactone (11.7 mg, 0.037 mmol ) and $Pd(OAc)_2$ (8.3 mg, 0.037 mmol) in toluene (750 μL, 5.4 mmol). The mixture was allowed to stir at 95 °C for 5 h and purification by column chromatography provided **4.28** (9.3 mg) in 68% yield.

**Benzylation of valine azlactone** (Scheme 4.11)



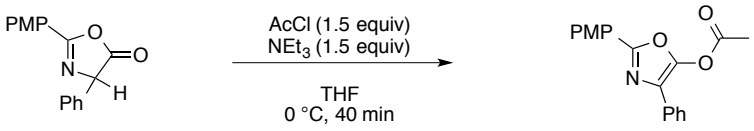
General procedure B was followed using **4.29** (15 mg, 0.064 mmol ) and $Pd(OAc)_2$ (14.5 mg, 0.064 mmol) in toluene (640 μL). The mixture was allowed to stir at 95 °C for 45 h and purification by column chromatography provided an inseparable 3.3:1 mixture **4.30** and **4.31** (15.6 mg) in 81% overall yield.




**4.29** **4.31**

General procedure B was followed using **4.29** (15 mg, 0.064 mmol) and $Pd(OAc)_2$ (14.5 mg, 0.064 mmol) in benzene (640 μL, 0.1 M). The mixture was allowed to stir at 95 °C for 45 h and purification by column chromatography provided **4.31** (6.3 mg) in 43% overall yield as a white solid: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, $J$ = 8.9 Hz, 2H), 6.97 (d, $J$ = 8.9 Hz, 2H), 3.88 (s, 3H), 2.40 (s, 3H), 2.32 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 165.8, 161.2, 159.2, 131.9, 129.7, 118.6, 114.4, 55.6, 22.9, 19.9; (ESI) calcd for $C_{13}H_{14}NO_2$ $[M+H]^+$ $m/z$ = 232.0974; found 232.0973.

**Synthesis of *O*-acyl phenylglycine azlactone**

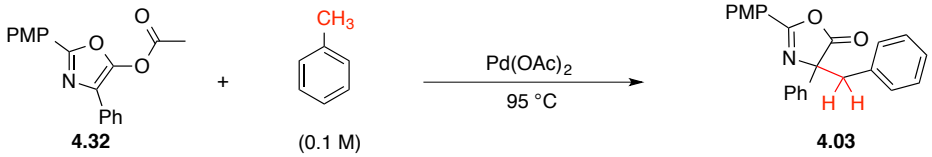



**4.03** **4.32**

**2-(4-Methoxyphenyl)-4-phenyloxazol-5-yl acetate (4.32).** Phenylglycine azlactone (**4.01**) (60 mg, 0.23 mmol) was added to a flame dried 8 mL microwave vial equipped with stir bar, under argon and was dissolved in THF (600 uL, 0.38 M). The mixture was cooled to 0 °C and $NEt_3$ (47 μL, 0.34 mmol) was added and allowed to stir for 5 minutes.

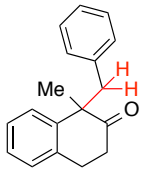
A solution of acyl chloride (0.34 mmol, 325 μL of a 1.0 M solution in THF) was added dropwise to the mixture. After 40 min, the white precipitate was removed by filtration and the solution was concentrated *in vacuo*. The resulting residue was dissolved in EtOAc (10 mL) and washed with 1 M HCl (5 mL), dried over $Na_2SO_4$, filtered and concentrated *in vacuo*. The resulting solid was purified by column chromatography (15% EtOAc in hexanes) to afford **4.32** (42 mg) in 61% yield: $^1$H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, $J$ = 9.0 Hz, 2H), 7.77 (d, $J$ = 7.3 Hz, 2H), 7.43 (t, $J$ = 7.7 Hz, 2H), 7.31 (t, $J$ = 7.4 Hz, 1H), 6.97 (d, $J$ = 8.9 Hz, 2H), 3.87 (s, 3H), 2.44 (s, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 167.3, 161.5, 155.6, 144.9, 130.4, 128.8, 127.9, 127.8, 125.9, 123.7, 120.0, 114.3, 55.5, 20.6; IR (film) 3004, 2932, 2839, 1799, 1645, 1615, 1502, 1256, 1161 cm$^{-1}$; HRMS (ESI) calcd for $C_{18}H_{16}NO_4$ $[M+H]^+$ $m/z$ = 310.1079 ; found 310.1085.

**Benzylation of *O*-acylazlactone (**Scheme 4.12**)**

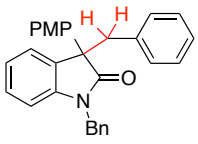



**Stoichiometric conditions**: *O*-Acyl azlactone (**4.32**) (4.2 mg, 0.014 mmol) and $Pd(OAc)_2$ (3.0 mg, 0.014 mmol) were added to a flame dried 8 mL microwave vial equipped with a stir bar and brought into the glovebox. Toluene (135 μL, 0.1 M) was added to the mixture. The microwave vial was sealed with a Teflon cap, removed from the glovebox and placed in a 90 °C oil bath. After 5 h, the reaction mixture was allowed to cool to ambient temperature, diluted with $CH_2Cl_2$ (1 mL), passed through $SiO_2$ with 30% EtOAc in hexanes, and concentrated *in vacuo* to afford **4.03** (4.5 mg) in 94% yield. See above for characterization.

**Catalytic conditions:** *O*-Acyl azlactone (**4.32**) (10 mg, 0.032 mmol) and $Pd(OAc)_2$ (1.5 mg, 0.006 mmol) were added to a flame dried 8 mL microwave vial equipped with a stir bar and brought into the glovebox. Toluene (324 μL, 0.1 M) was added to the mixture. The microwave vial was sealed with a Teflon cap, removed from the glovebox and sparged with an $O_2$ atmosphere for 5 min. The microwave vial was placed in a 95 °C oil bath. After 23 h, the reaction mixture was allowed to cool to ambient temperature, diluted with $CH_2Cl_2$ (1 mL) and purified directly by column chromatography (7% EtOAc in hexanes) to afford **4.03** (6.3 mg) in 53% yield. See above for characterization.




**1-Benzyl-1-methyl-3,4-dihydronaphthalen-2(1*H*)-one (4.34).** General procedure B was followed using 1-methyl-β-tetralone (5.9 mg, 0.038 mmol ) and $Pd(OAc)_2$ (8.4 mg, 0.038 mmol) in toluene (750 μL). The mixture was allowed to stir at 90 °C for 5 h and purification by column chromatography provided **4.34** (4.1 mg) in 43% yield. Spectral data agreed with those reported previously by Miller.[184]

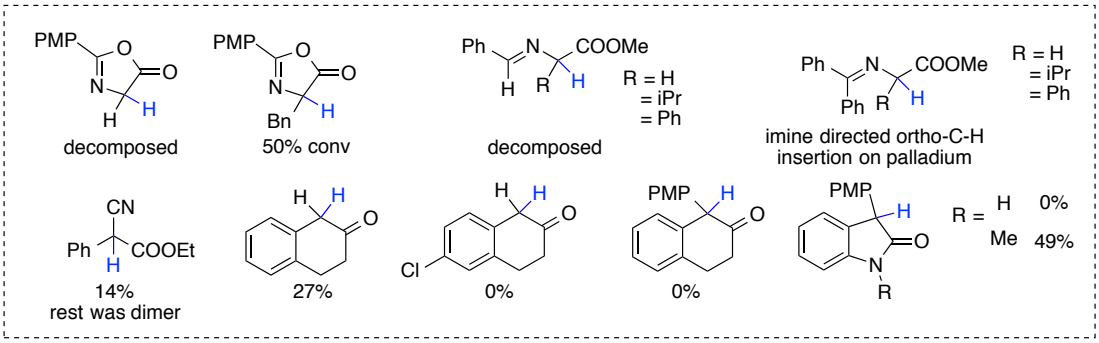



**1,3-Dibenzyl-3-(4-methoxyphenyl)indolin-2-one (4.36).** General procedure B was followed using oxindole (**4.35**) (15 mg, 0.046 mmol) and $Pd(OAc)_2$ (10.4 mg, 0.046

184) Shi, X.; Miller, B. "Cyclization and Rearrangement Processes Resulting from Bromination of 3-Benzylcycloalkenes" *J. Org. Chem.* **1993**, *58*, 2907-2909.

mmol) in toluene (460 μL). The mixture was allowed to stir at 90 °C for 5 h and purification by column chromatography (10% EtOAc in hexanes) provided **4.36** (16 mg) in 83% yield: $^{1}$H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, $J$ = 8.9 Hz, 2H), 7.35-7.31 (m, 1H), 7.20-7.03 (m, 8H), 6.97-6.87 (m, 4H), 6.67 (d, $J$ = 7.3 Hz, 2H), 6.46-6.41 (m, 1H), 4.90 (d, $J$ = 16.1 Hz, 1H), 4.53 (d, $J$ = 15.9 Hz, 1H), 3.84-3.77 (m, 4H), 3.51 (d, $J$ = 12.9 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 178.1, 159.0, 143.1, 136.0, 135.4, 132.4, 131.5, 130.6, 128.7, 128.4, 128.2, 127.9, 127.2, 126.8, 126.7, 125.6, 122.3, 114.1, 109.6, 57.8, 55.4, 44.0, 43.8; IR (film) 2925, 1711, 1610, 1510, 1252, 1182 cm$^{-1}$; HRMS (ESI) calcd for $C_{29}H_{26}NO_2$ $[M+H]^+$ $m/z$ = 420.1964; found 420.1958.

**Chart S4.3** Acidic C–H partners explored in neat toluene solution at 95 °C with $Pd(OAc)_2$ (100 mol %) for 7 h.



## APPENDIX A: SPECTROSCOPIC DATA

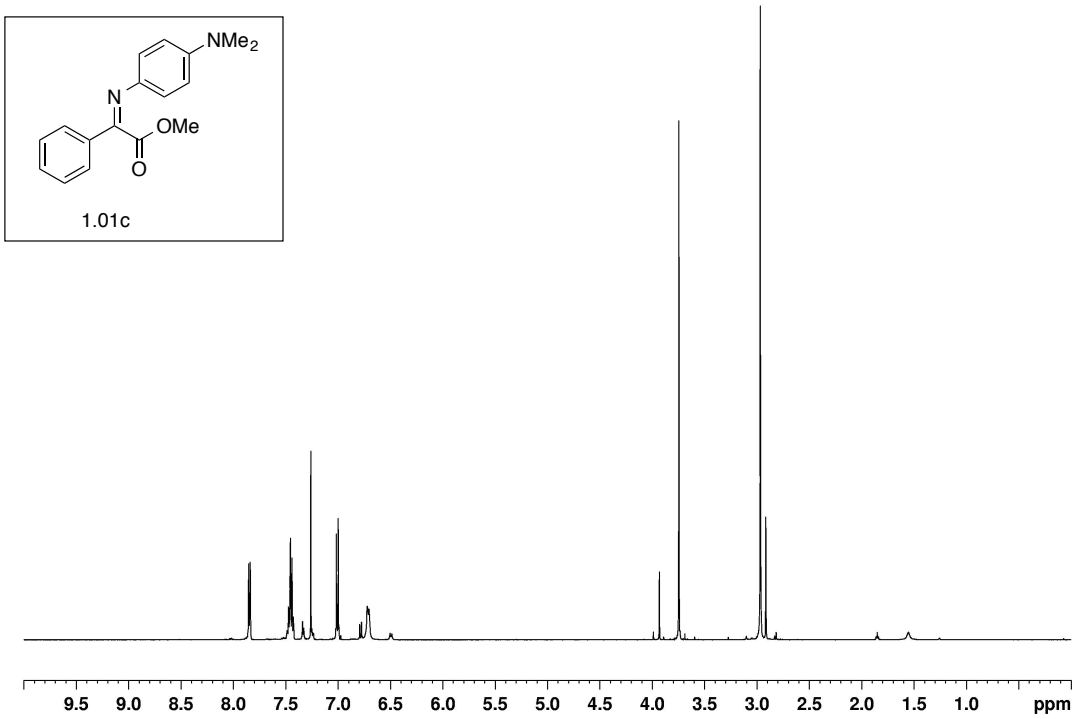



**Figure A. 1.01c_1** $^{1}$H NMR spectrum of compound **1.01c** (500 MHz, $CDCl_3$)

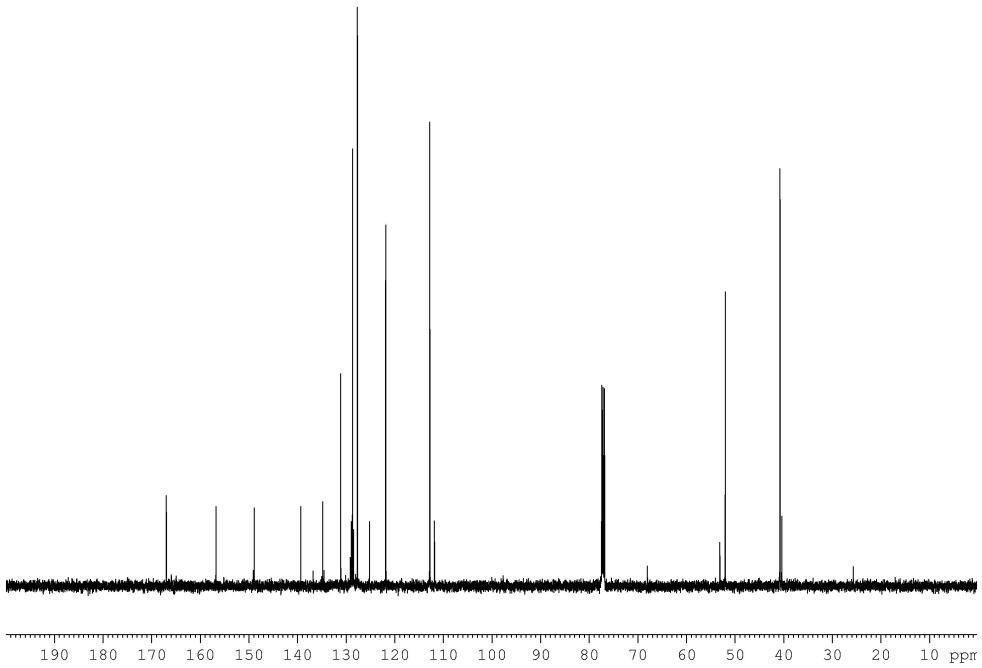



**Figure A. 1.01c_2** $^{13}$C NMR spectrum of compound **1.01c** (125 MHz, $CDCl_3$)

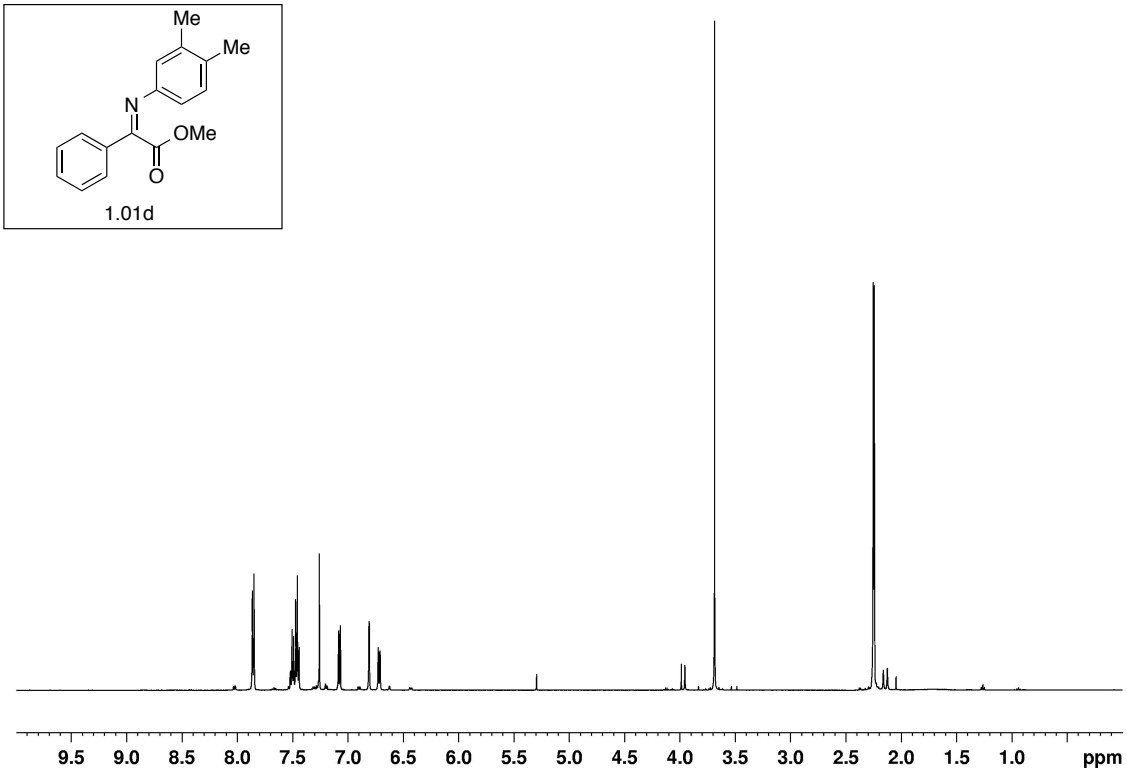



**Figure A. 1.01d_1** $^{1}$H NMR spectrum of compound **1.01d** (500 MHz, $CDCl_3$)

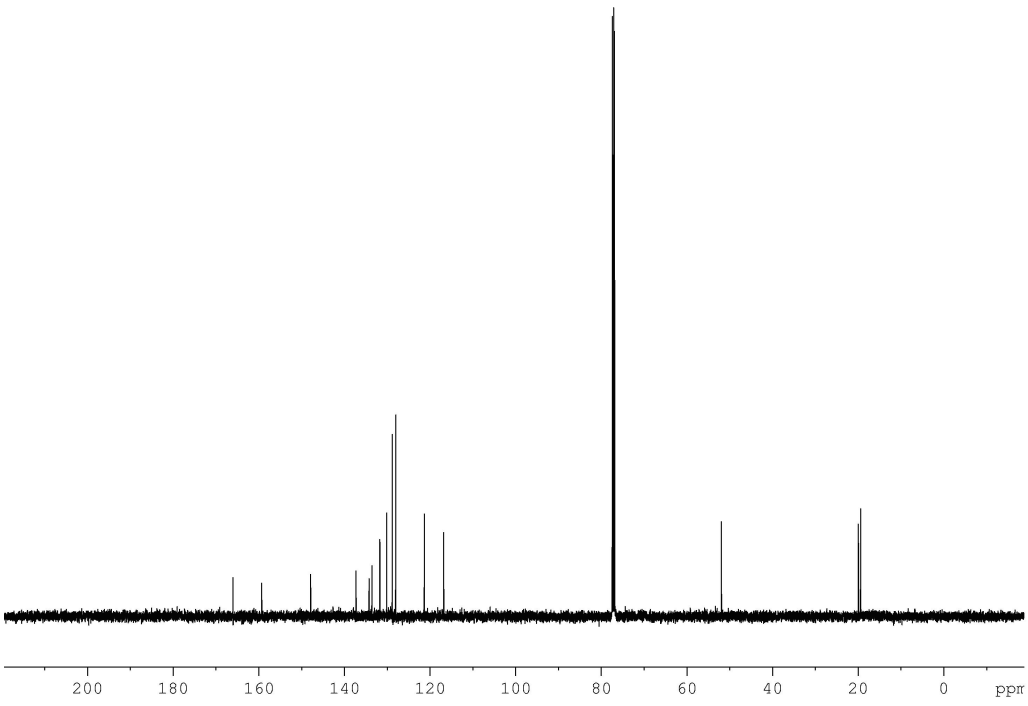



**Figure A. 1.01d_2** $^{13}$C NMR spectrum of compound **1.01d** (125 MHz, $CDCl_3$)

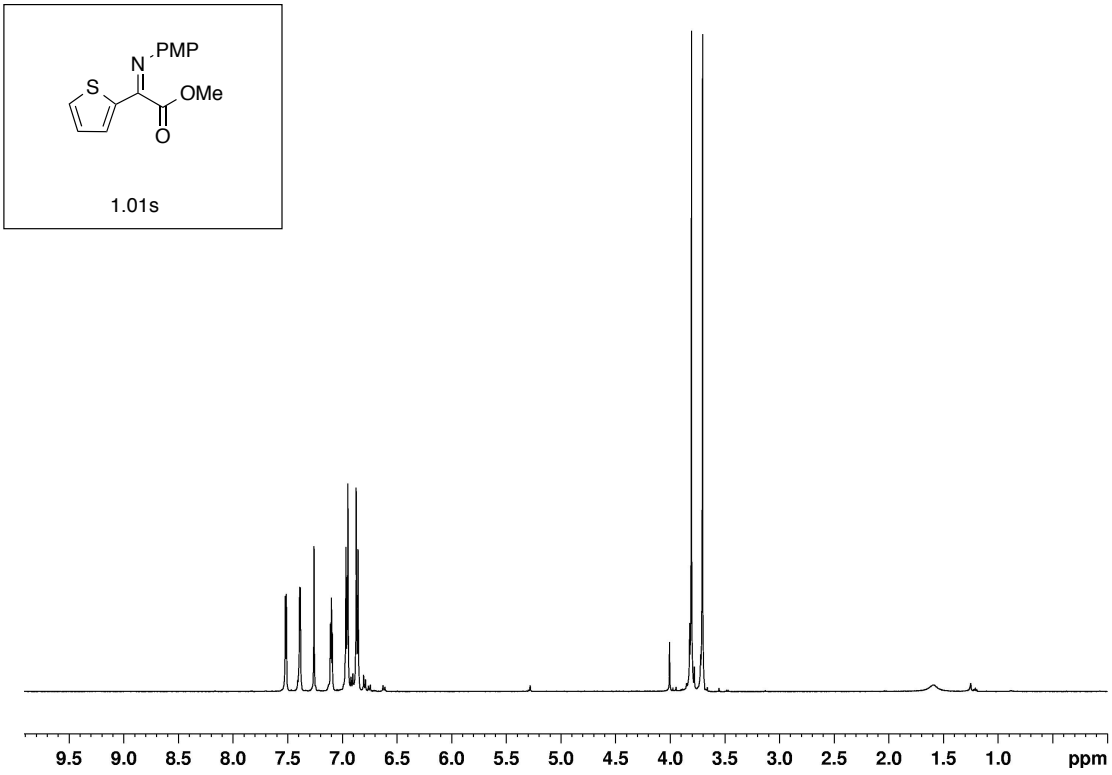



**Figure A. 1.01s_1** $^{1}$H NMR spectrum of compound **1.01s** (500 MHz, $CDCl_3$)

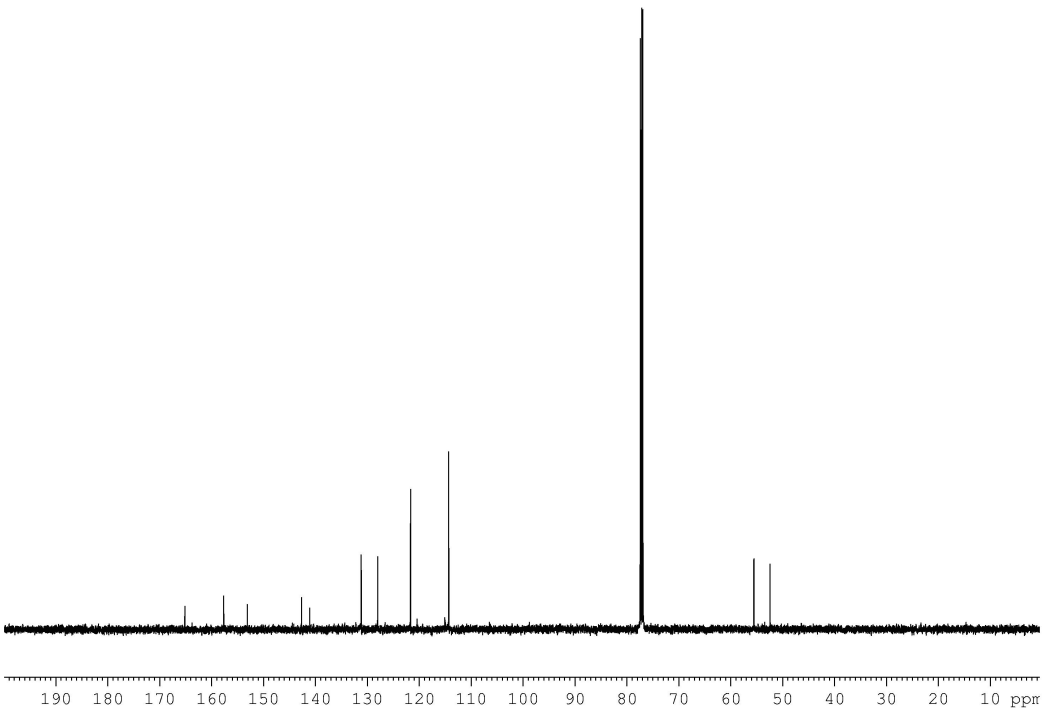



**Figure A. 1.01s_2** $^{13}$C NMR spectrum of compound **1.01s** (125 MHz, $CDCl_3$)

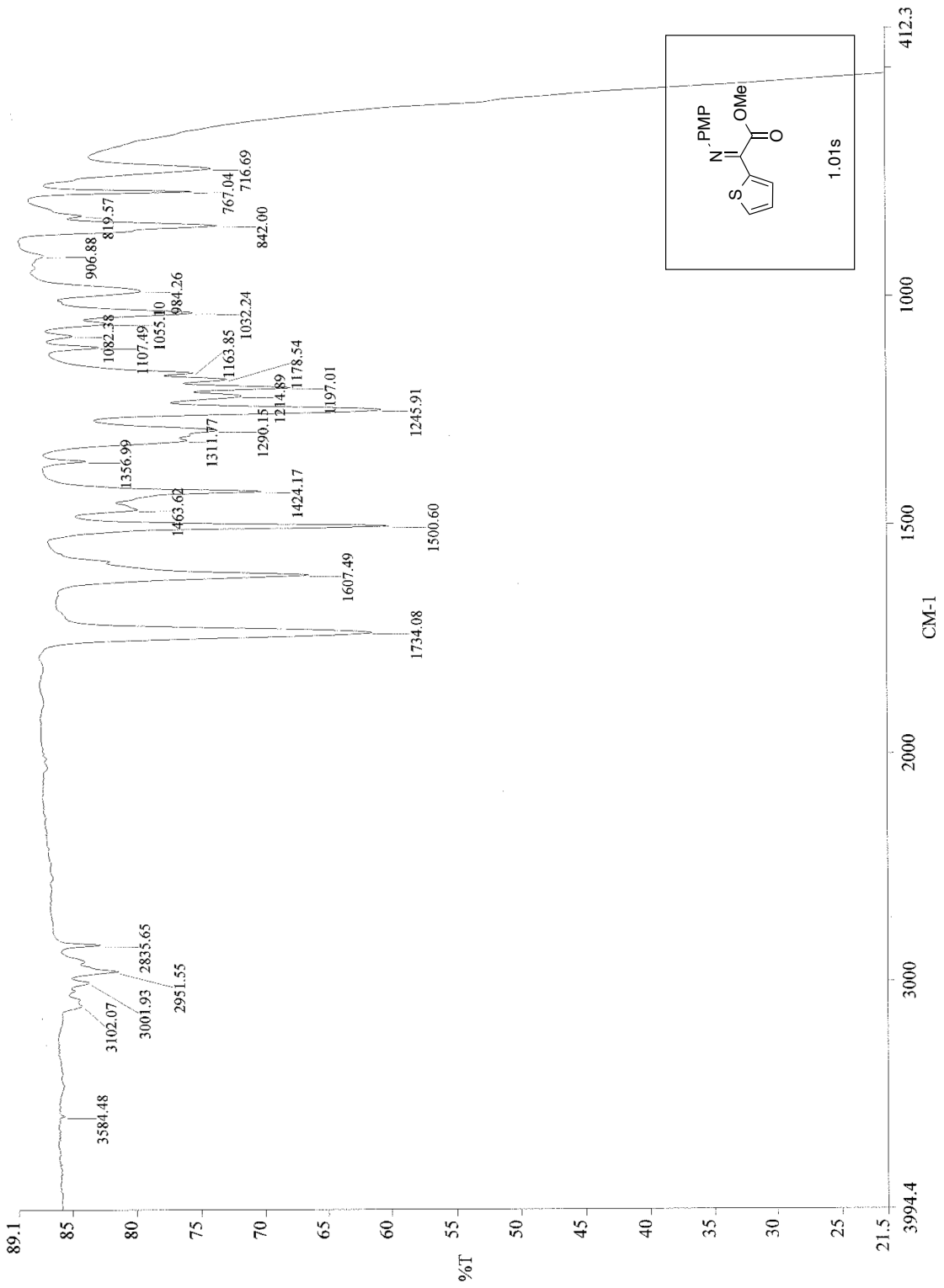



**Figure A.1.01s_3** IR spectrum of compound **1.01s.**

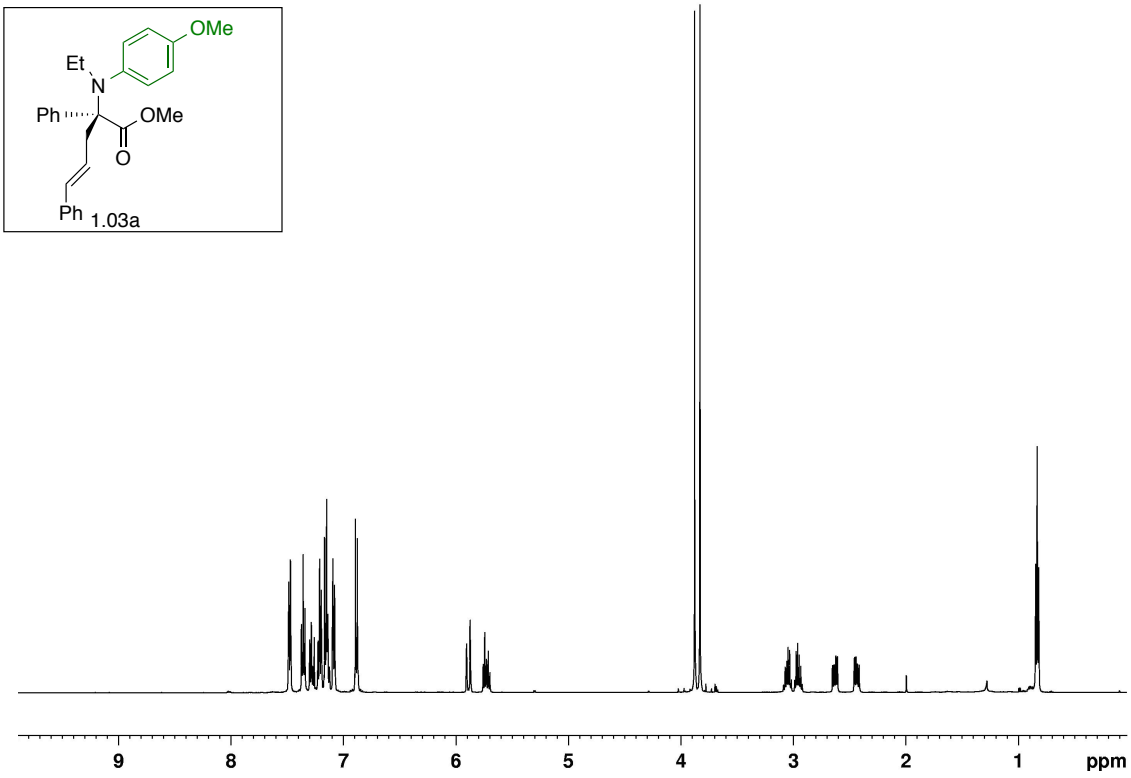



**Figure A. 1.03a_1** $^{1}$H NMR spectrum of compound **1.03a** (500 MHz, $CDCl_3$)

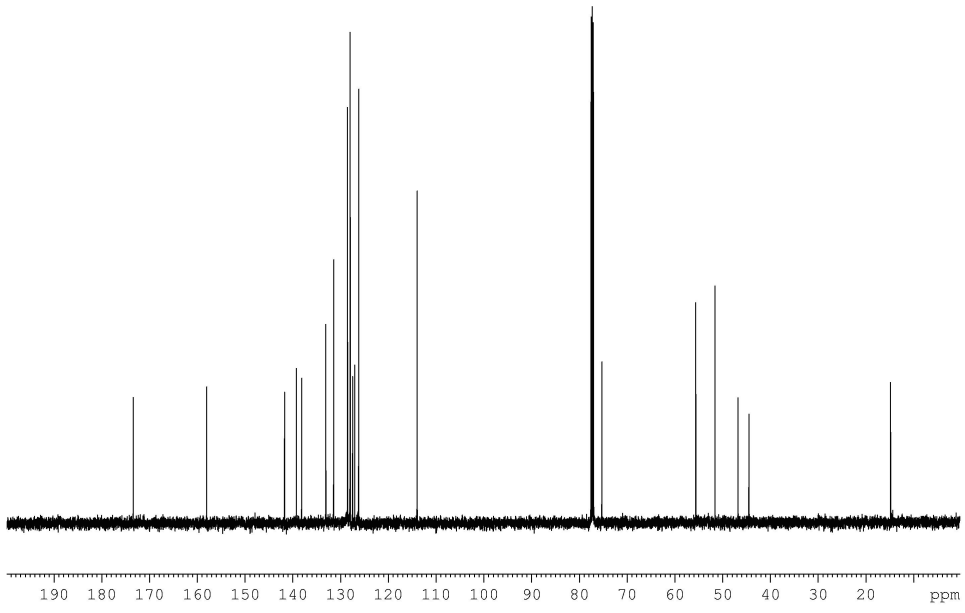



**Figure A. 1.03a_2** $^{13}$C NMR spectrum of compound **1.03a** (125 MHz, $CDCl_3$)

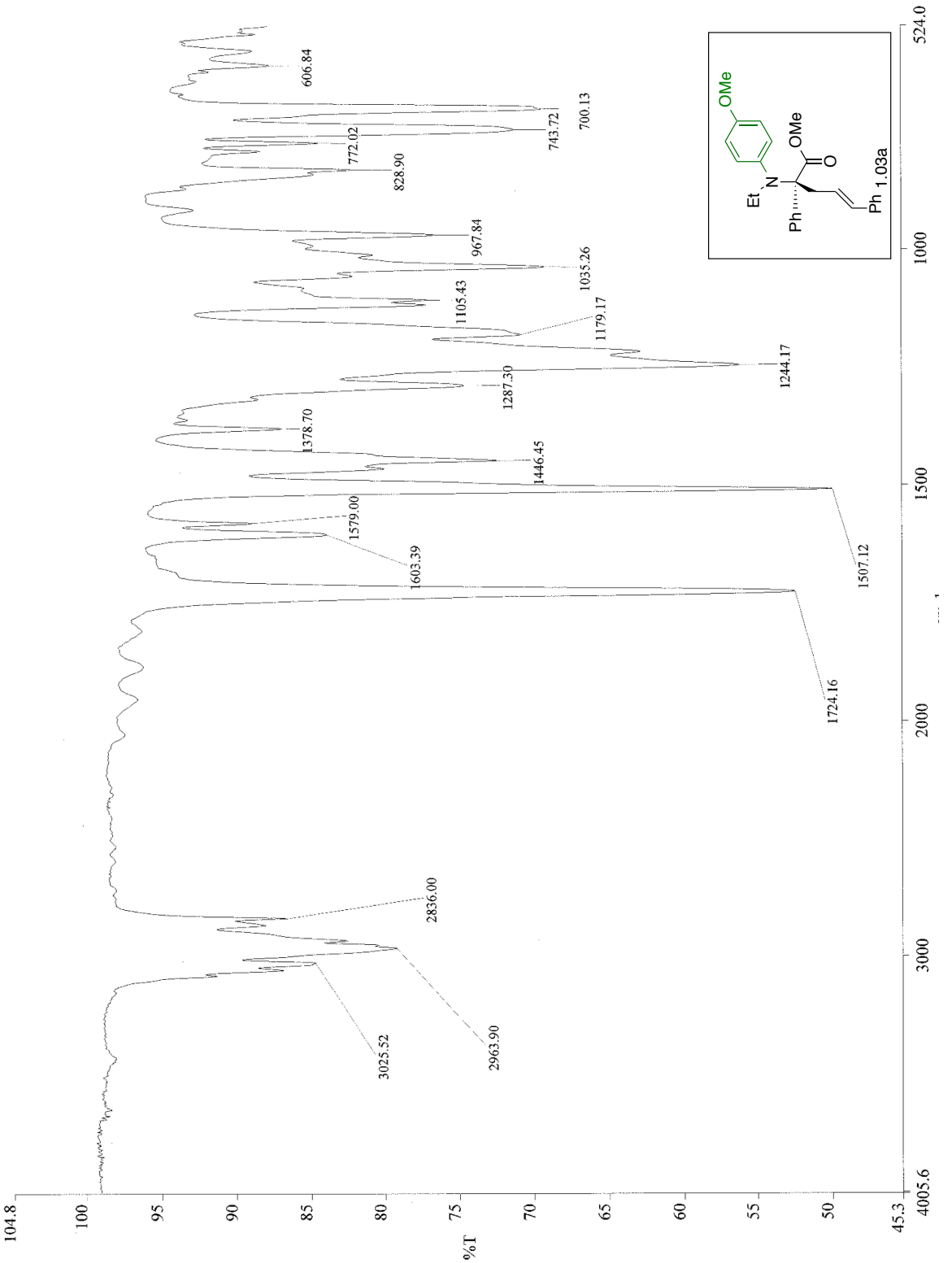



**Figure A.1.03a_3** IR spectrum of compound **1.03a**

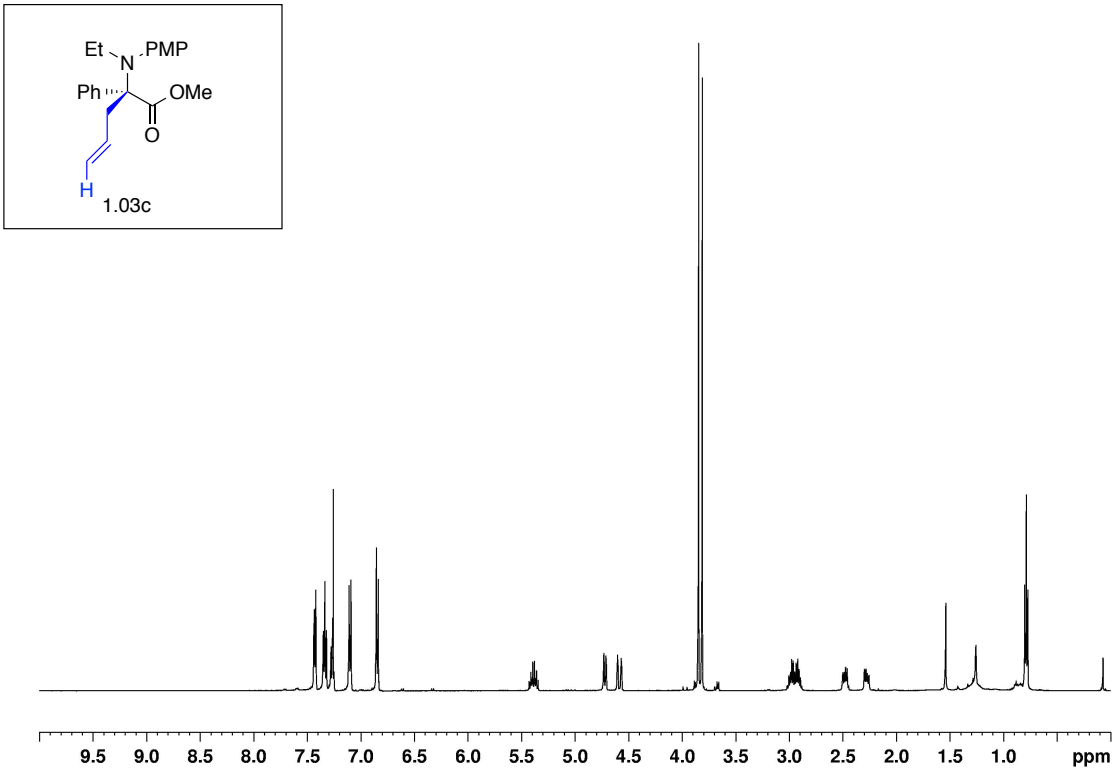



**Figure A. 1.03c_1** $^{1}$H NMR spectrum of compound **1.03c** (500 MHz, $CDCl_3$)

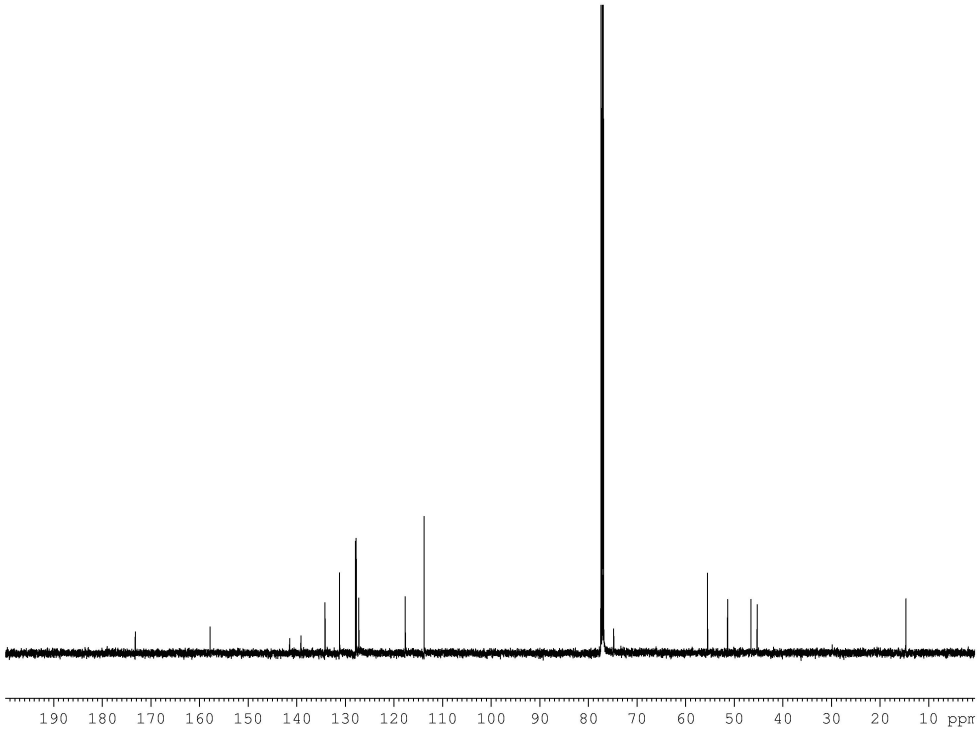



**Figure A. 1.03c_2** $^{13}$C NMR spectrum of compound **1.03c** (125 MHz, $CDCl_3$)

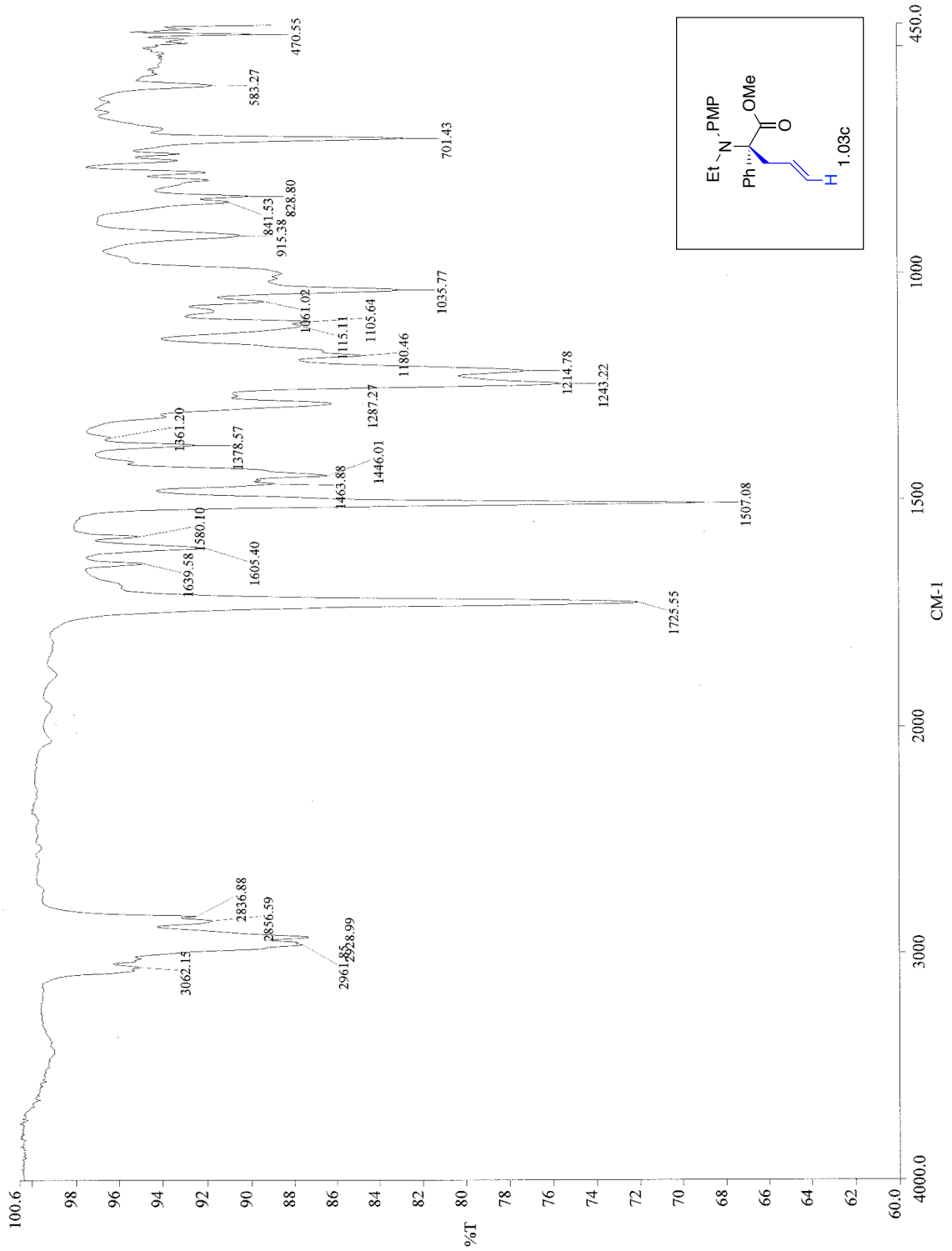



**Figure A.1.03c_3** IR spectrum of compound **1.03c**

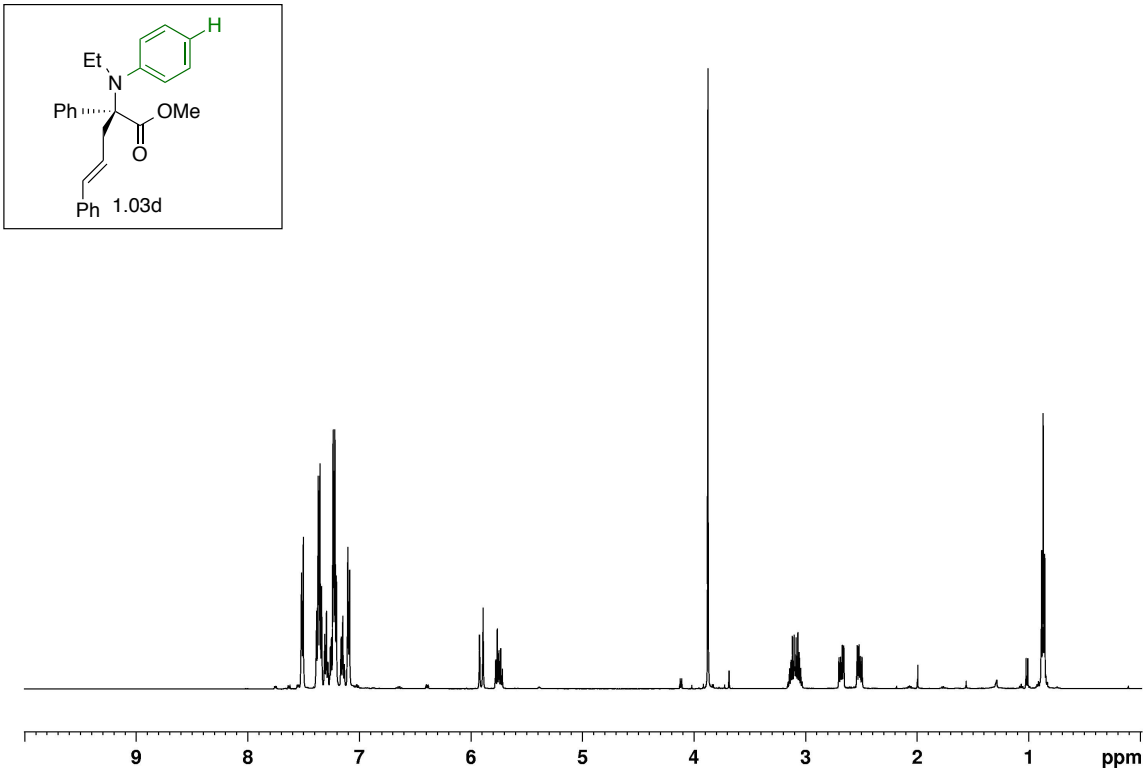



**Figure A. 1.03d_1** $^{1}$H NMR spectrum of compound **1.03d** (500 MHz, $CDCl_3$)

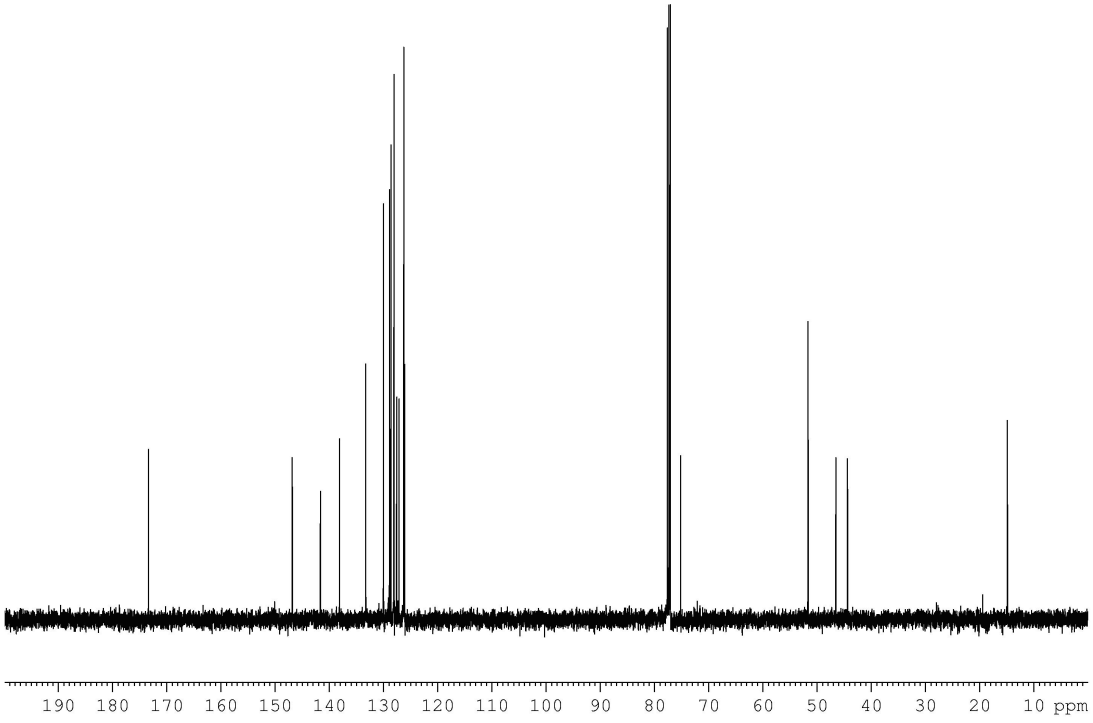



**Figure A. 1.03d_2** $^{13}$C NMR spectrum of compound **1.03d** (125 MHz, $CDCl_3$)

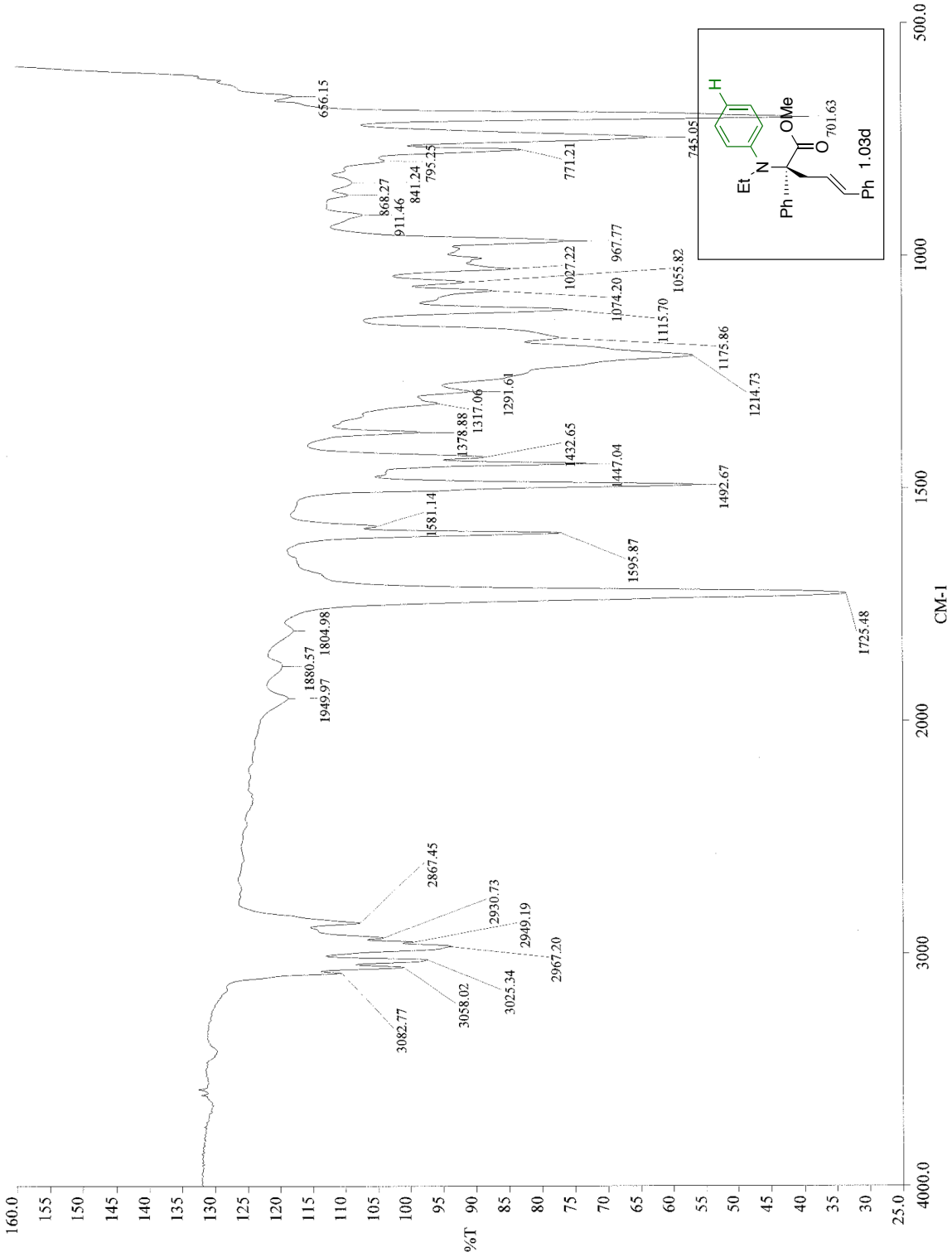



**Figure A.1.03d_3** IR spectrum of compound **1.03d**

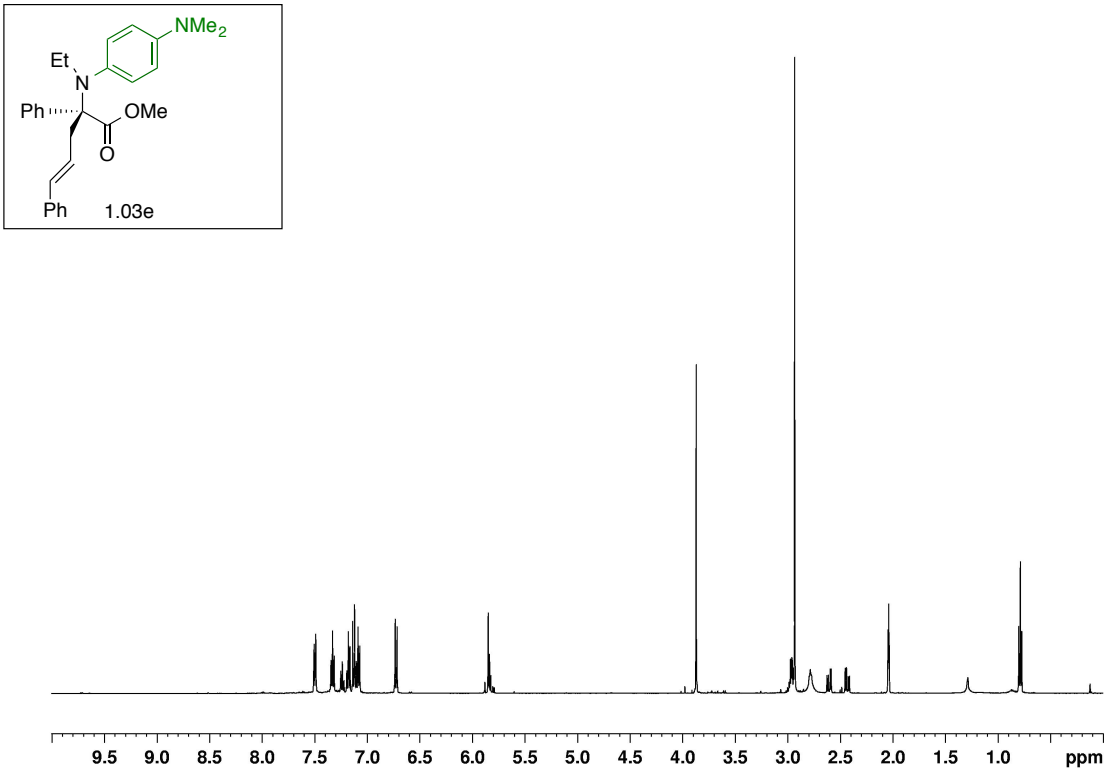



**Figure A. 1.03e_1** $^{1}$H NMR spectrum of compound **1.03e** (500 MHz, $(CD_3)_2O$)

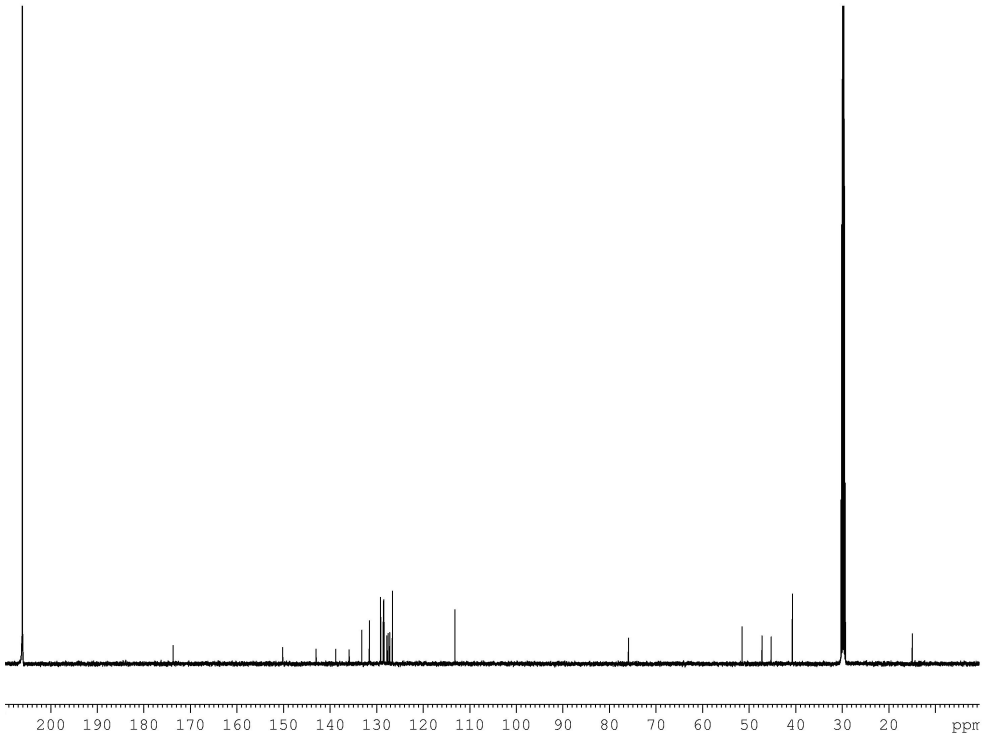



**Figure A. 1.03e_2** $^{13}$C NMR spectrum of compound **1.03e** (125 MHz, $(CD_3)_2O$)

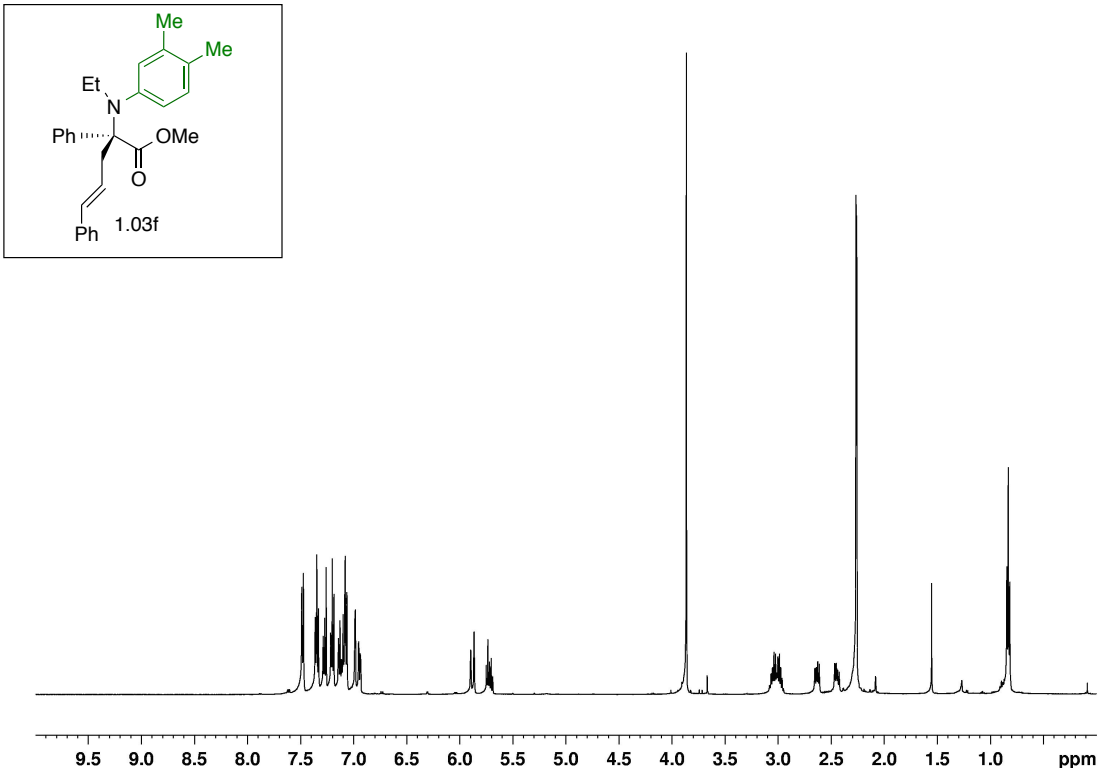



**Figure A. 1.03f_1** $^{1}$H NMR spectrum of compound **1.03f** (500 MHz, $CDCl_3$)

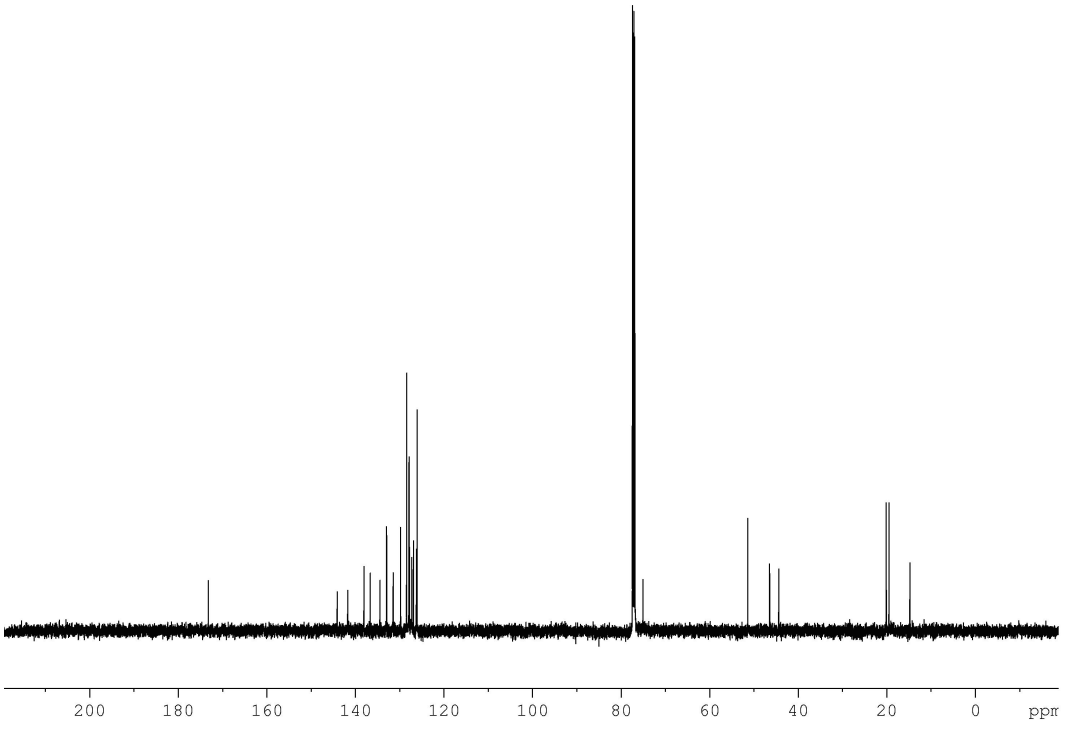



**Figure A. 1.03f_2** $^{13}$C NMR spectrum of compound **1.03f** (125 MHz, $CDCl_3$)

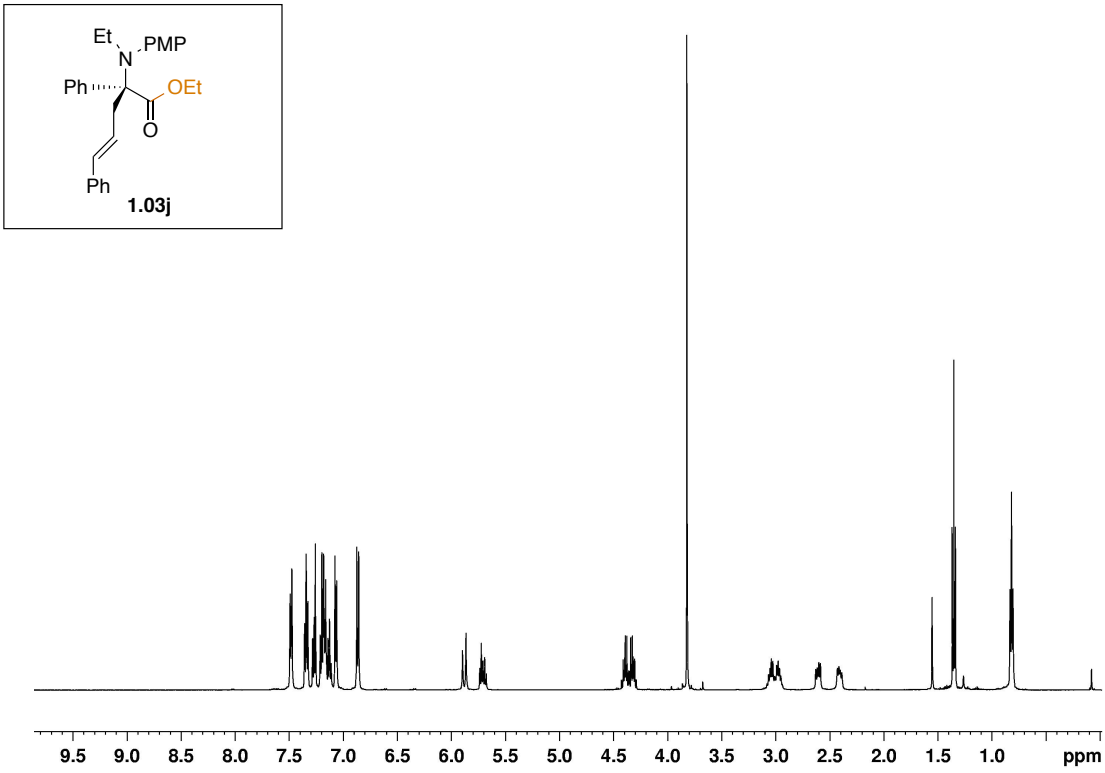



**Figure A. 1.03j_1** $^{1}$H NMR spectrum of compound **1.03j** (500 MHz, $CDCl_3$)

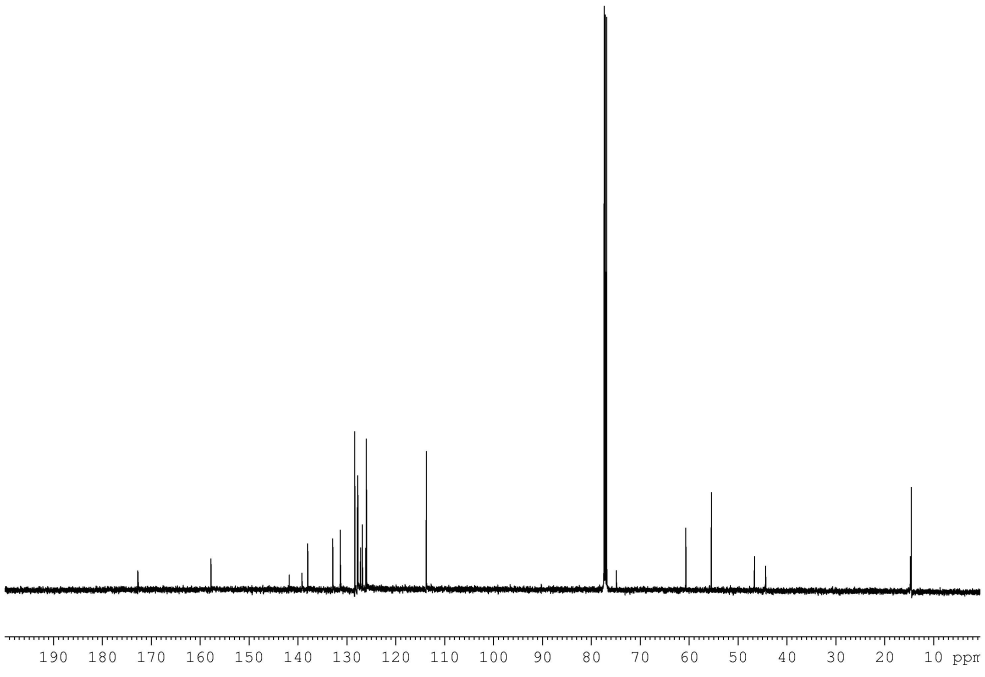



**Figure A. 1.03j_2** $^{13}$C NMR spectrum of compound **1.03j** (125 MHz, $CDCl_3$)

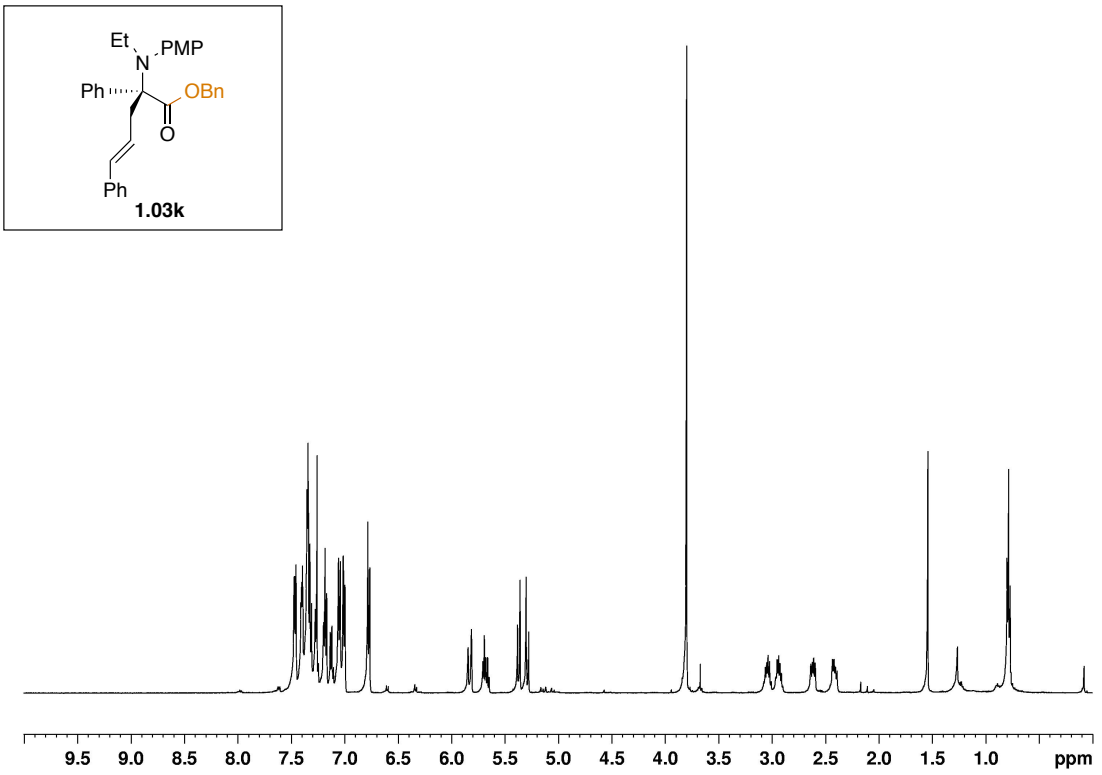



**Figure A. 1.03k_1** $^{1}$H NMR spectrum of compound **1.03k** (500 MHz, $CDCl_3$)

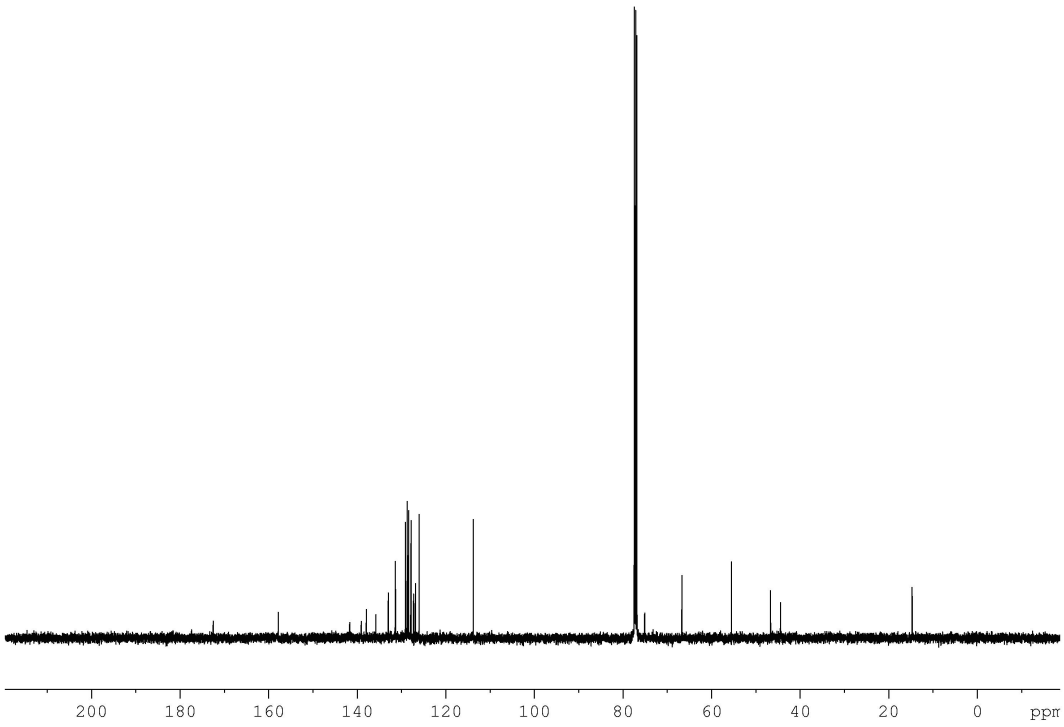



**Figure A. 1.03k_2** $^{13}$C NMR spectrum of compound **1.03k** (125 MHz, $CDCl_3$)

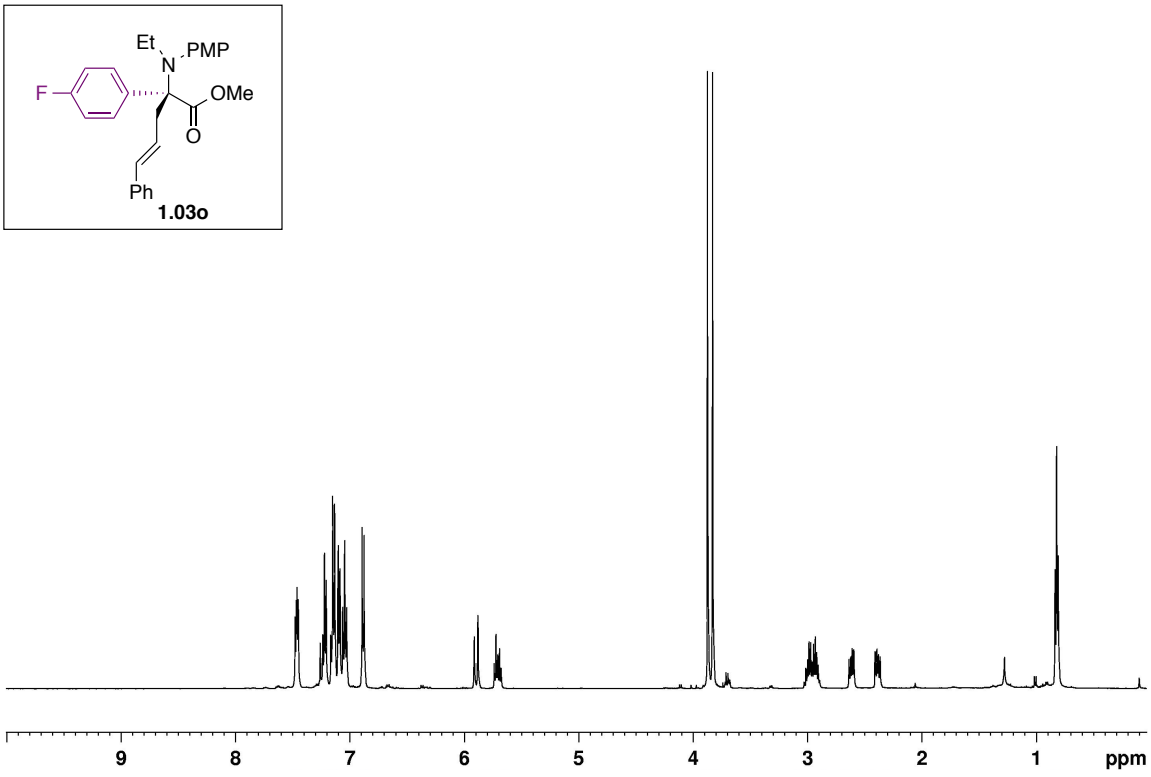



**Figure A. 1.03o_1** $^{1}$H NMR spectrum of compound **1.03o** (500 MHz, $CDCl_3$)

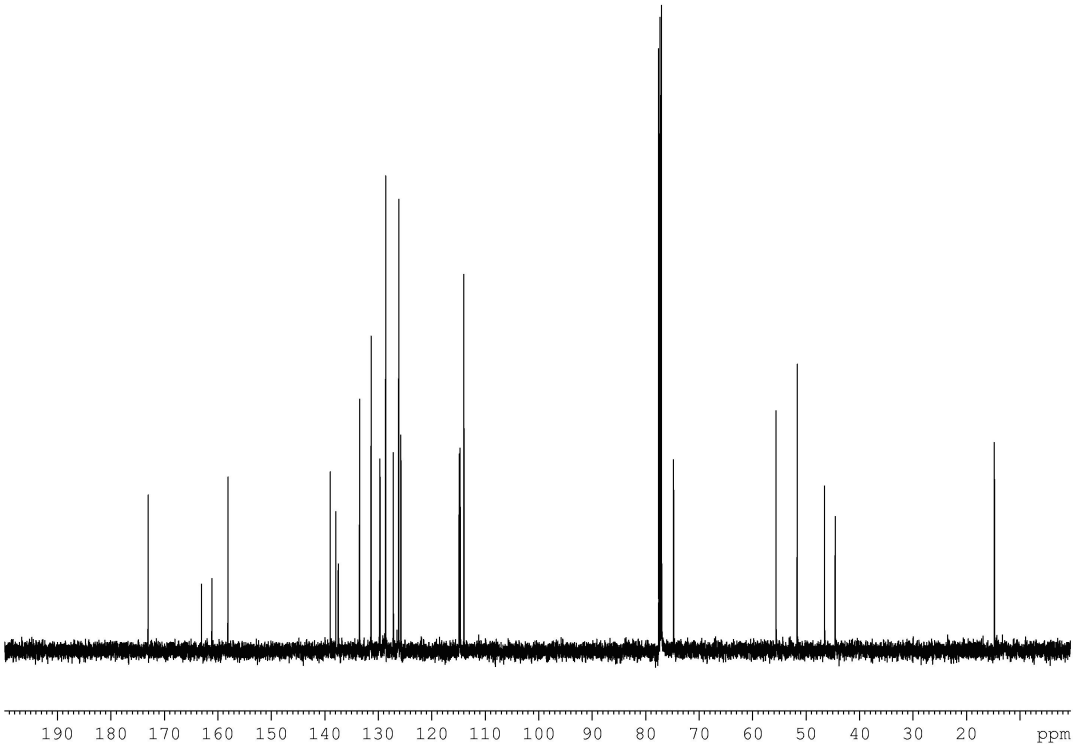



**Figure A. 1.03o_2** $^{13}$C NMR spectrum of compound **1.03o** (125 MHz, $CDCl_3$)

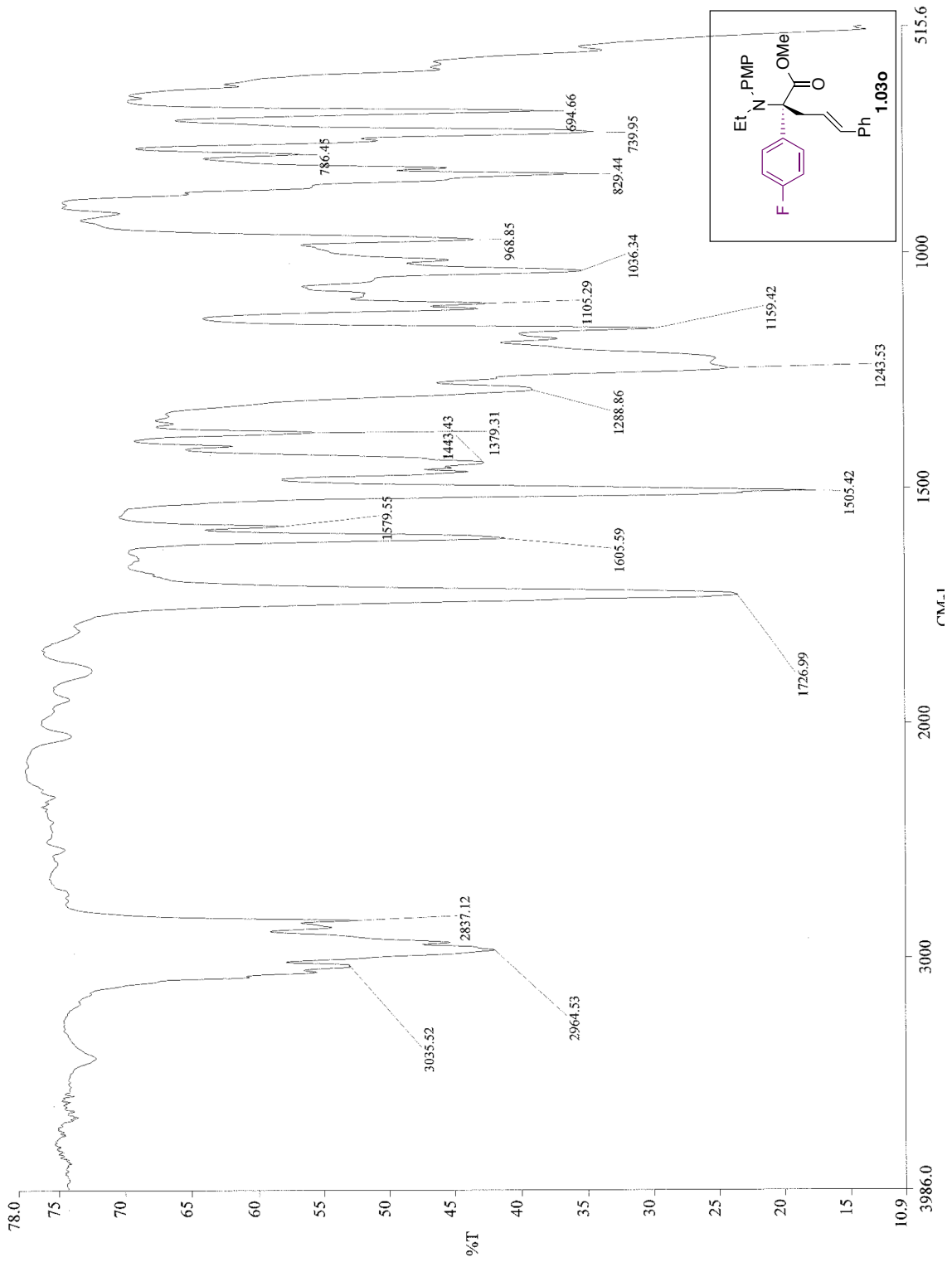



**Figure A.1.03o_3** IR spectrum of compound **1.03o**

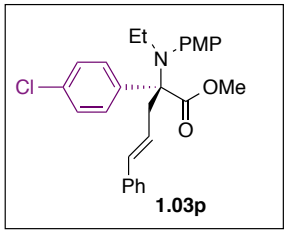






**Figure A. 1.03p_1** $^{1}$H NMR spectrum of compound **1.03p** (500 MHz, $CDCl_3$)

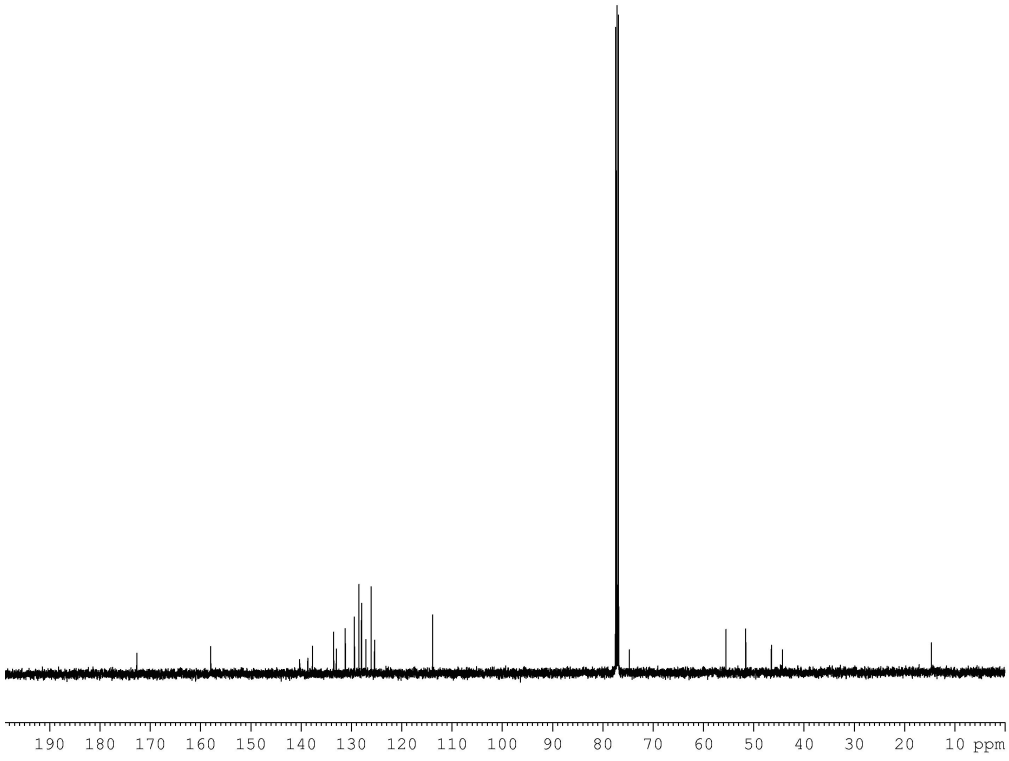



**Figure A. 1.03p_2** $^{13}$C NMR spectrum of compound **1.03p** (125 MHz, $CDCl_3$)

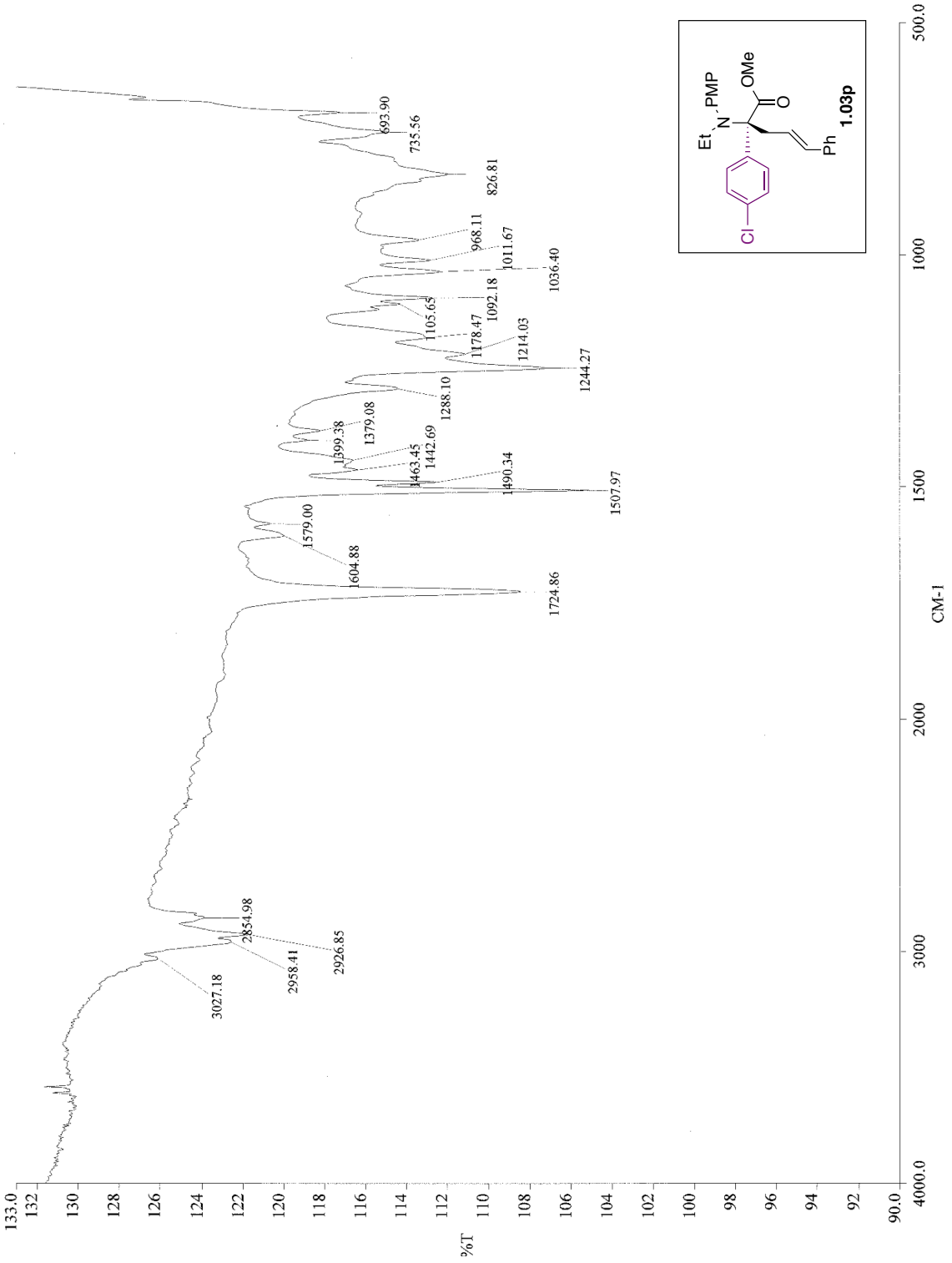



**Figure A.1.03p_3** IR spectrum of compound **1.03p**

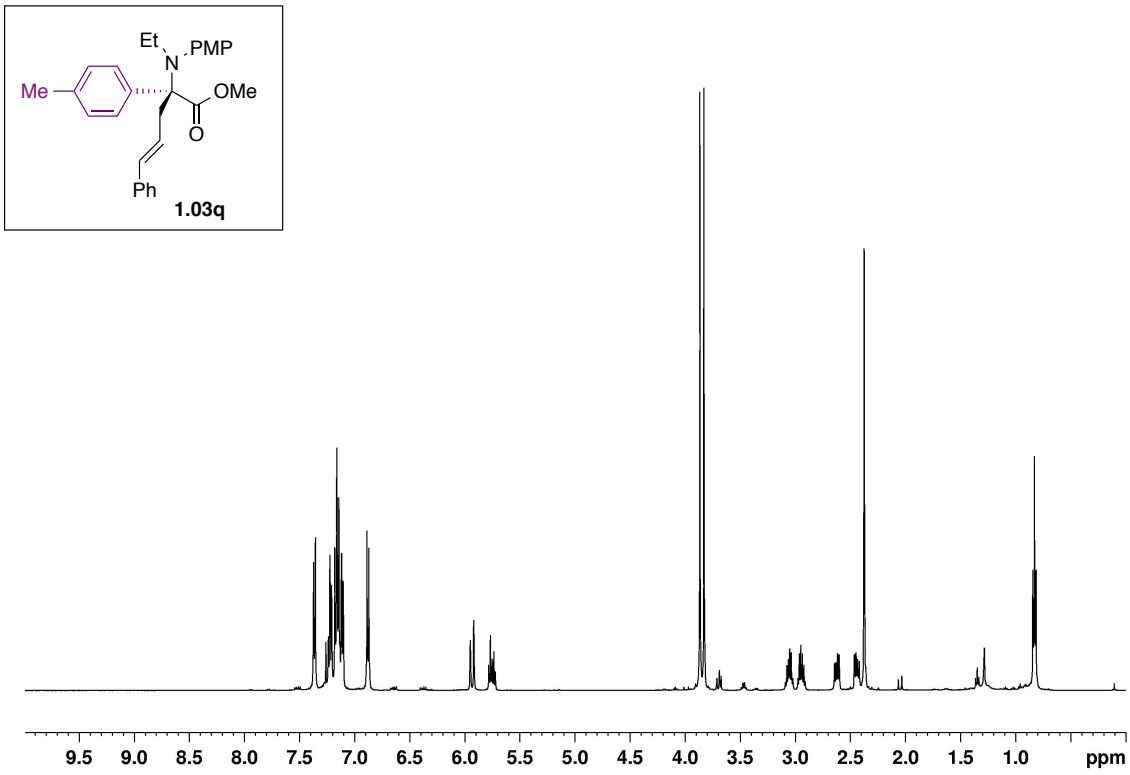



**Figure A. 1.03q_1** $^{1}$H NMR spectrum of compound **1.03q** (500 MHz, $CDCl_3$)

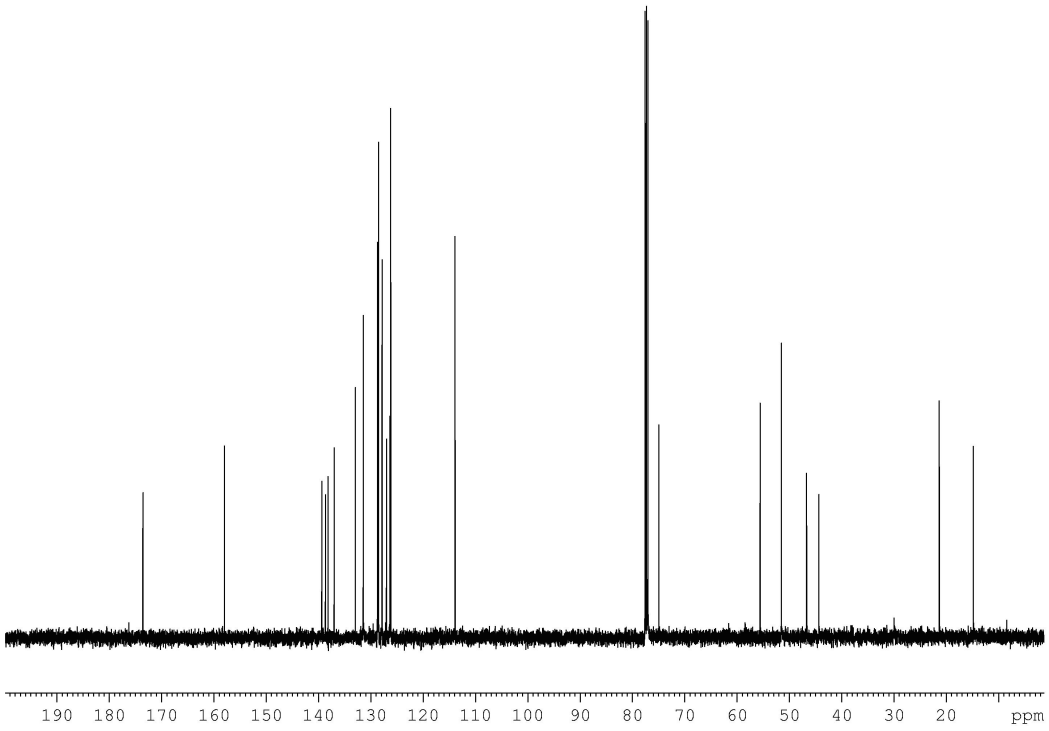



**Figure A. 1.03q_2** $^{13}$C NMR spectrum of compound **1.03q** (125 MHz, $CDCl_3$)

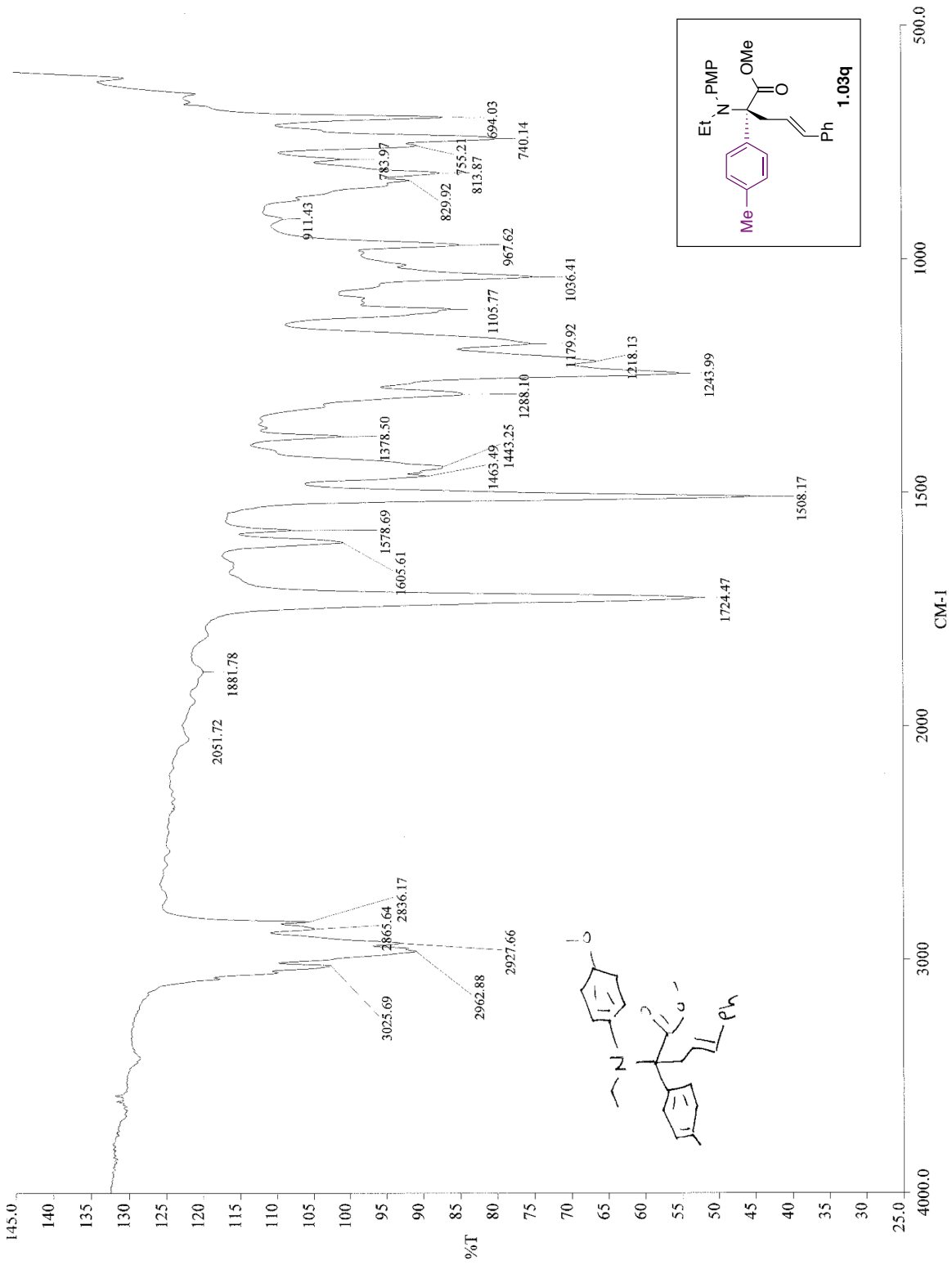



**Figure A.1.03q_3** IR spectrum of compound **1.03q**

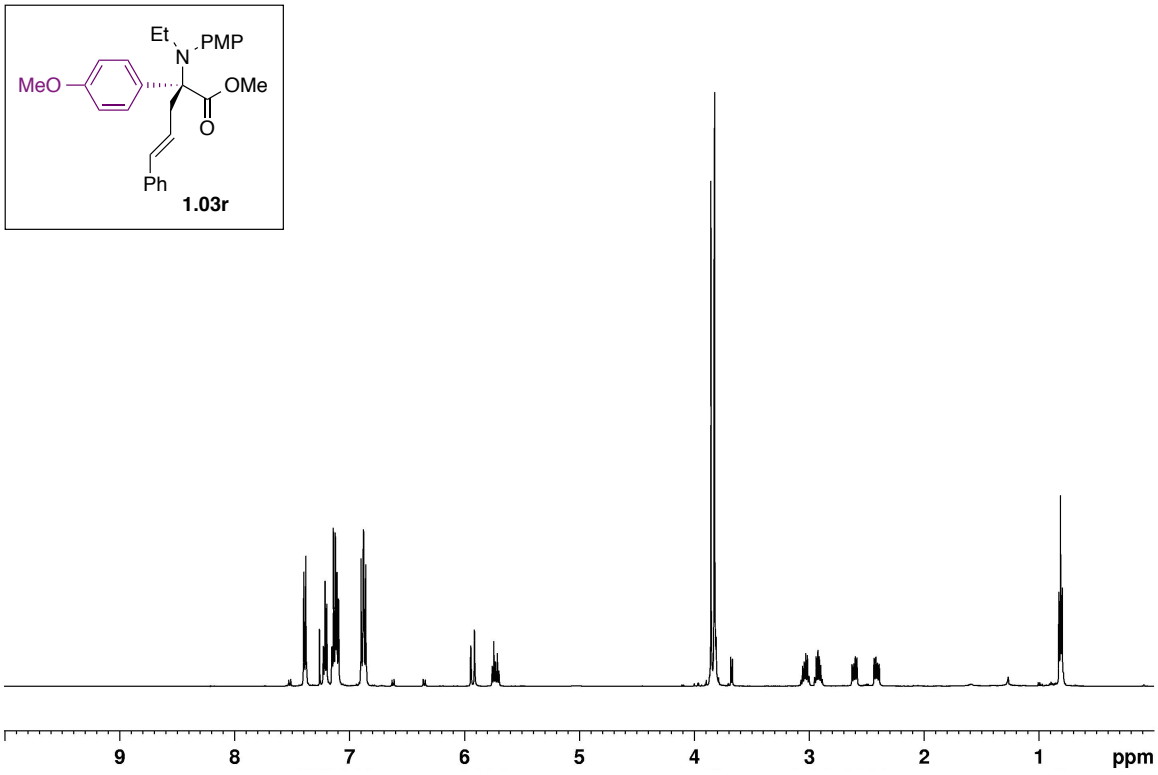



**Figure A. 1.03r_1** $^{1}$H NMR spectrum of compound **1.03r** (500 MHz, $CDCl_3$)

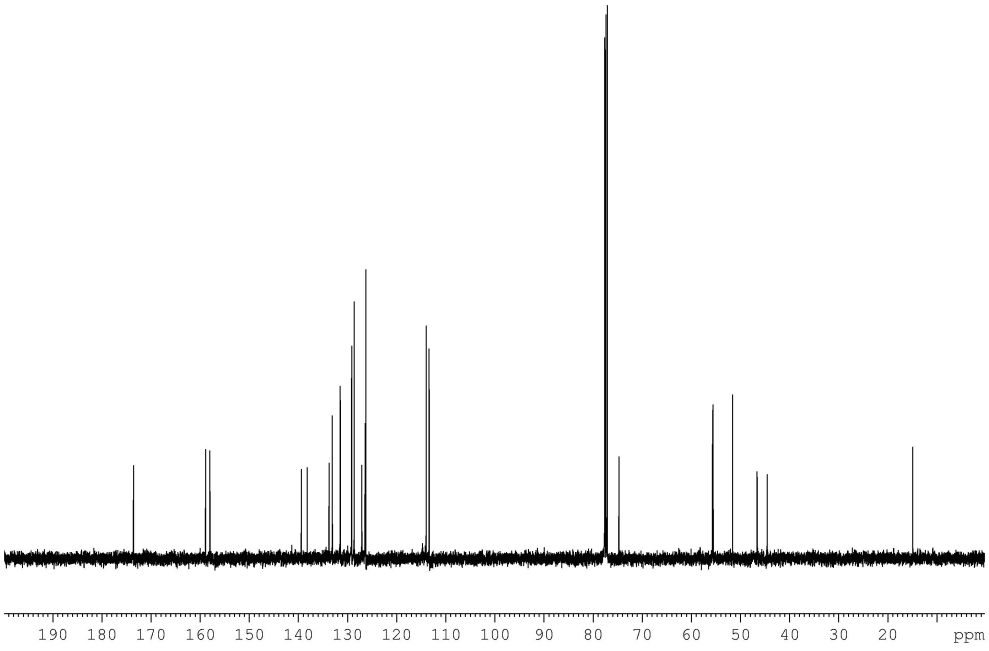



**Figure A. 1.03r_2** $^{13}$C NMR spectrum of compound **1.03r** (125 MHz, $CDCl_3$)

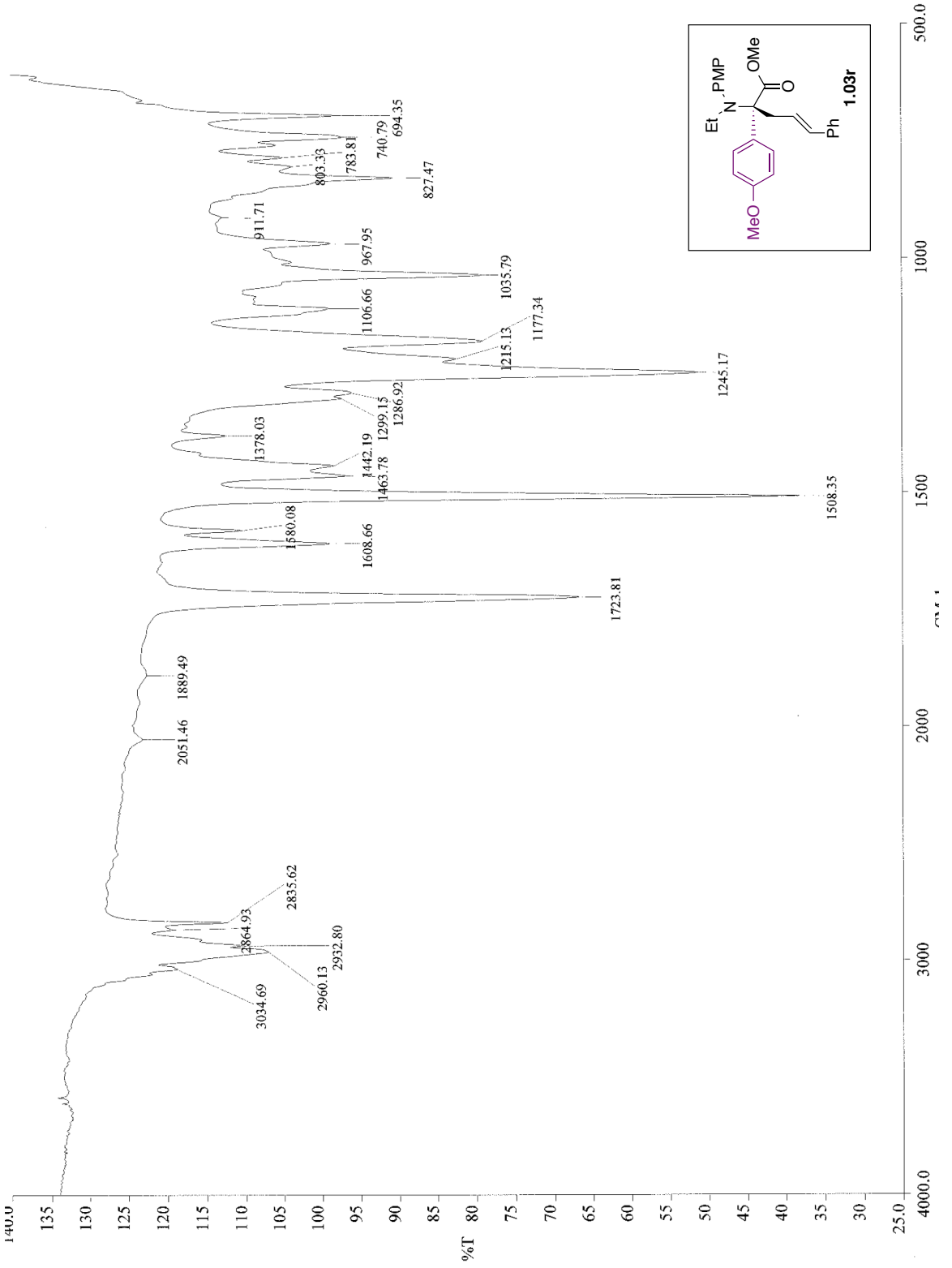



**Figure A.1.03r_3** IR spectrum of compound **1.03r**

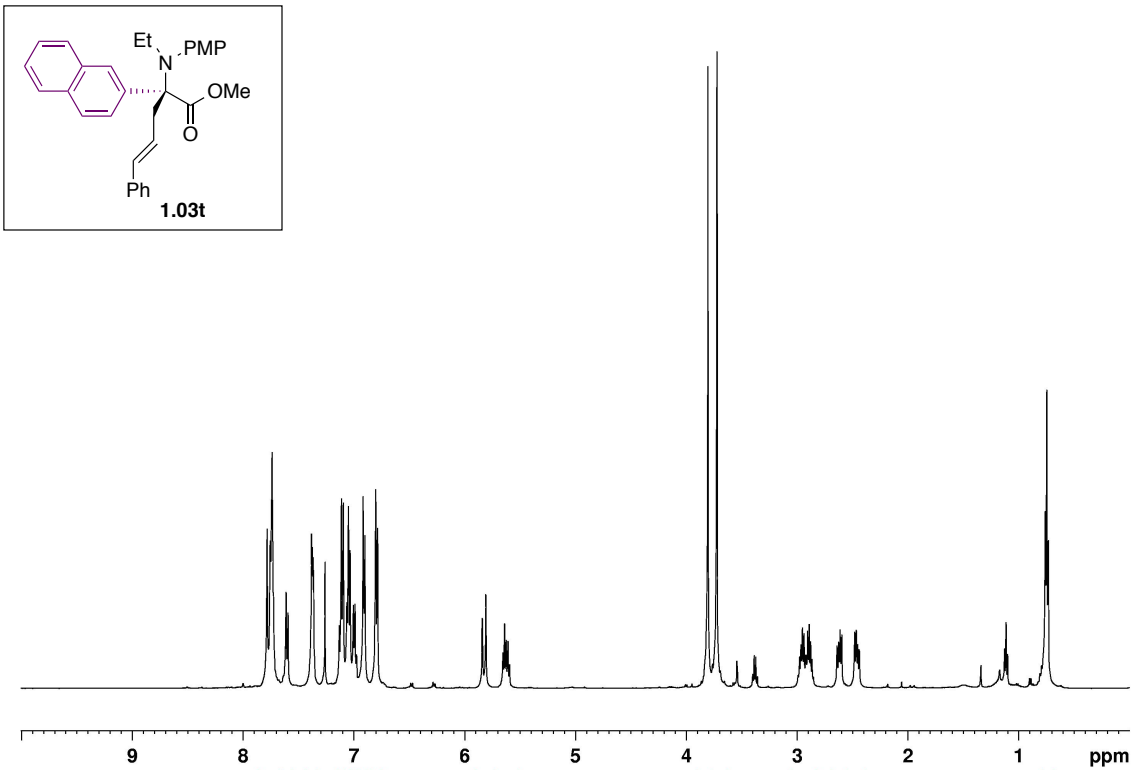



**Figure A. 1.03t_1** $^{1}$H NMR spectrum of compound **1.03t** (500 MHz, $CDCl_3$)

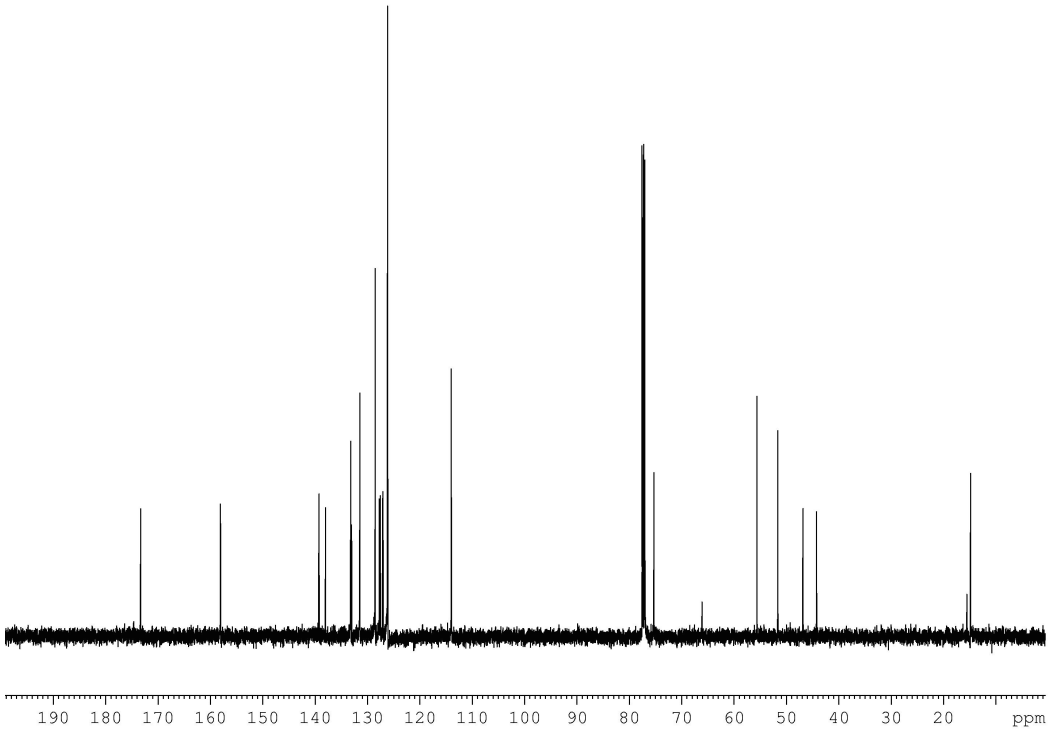



**Figure A. 1.03t_2** $^{13}$C NMR spectrum of compound **1.03t** (125 MHz, $CDCl_3$)

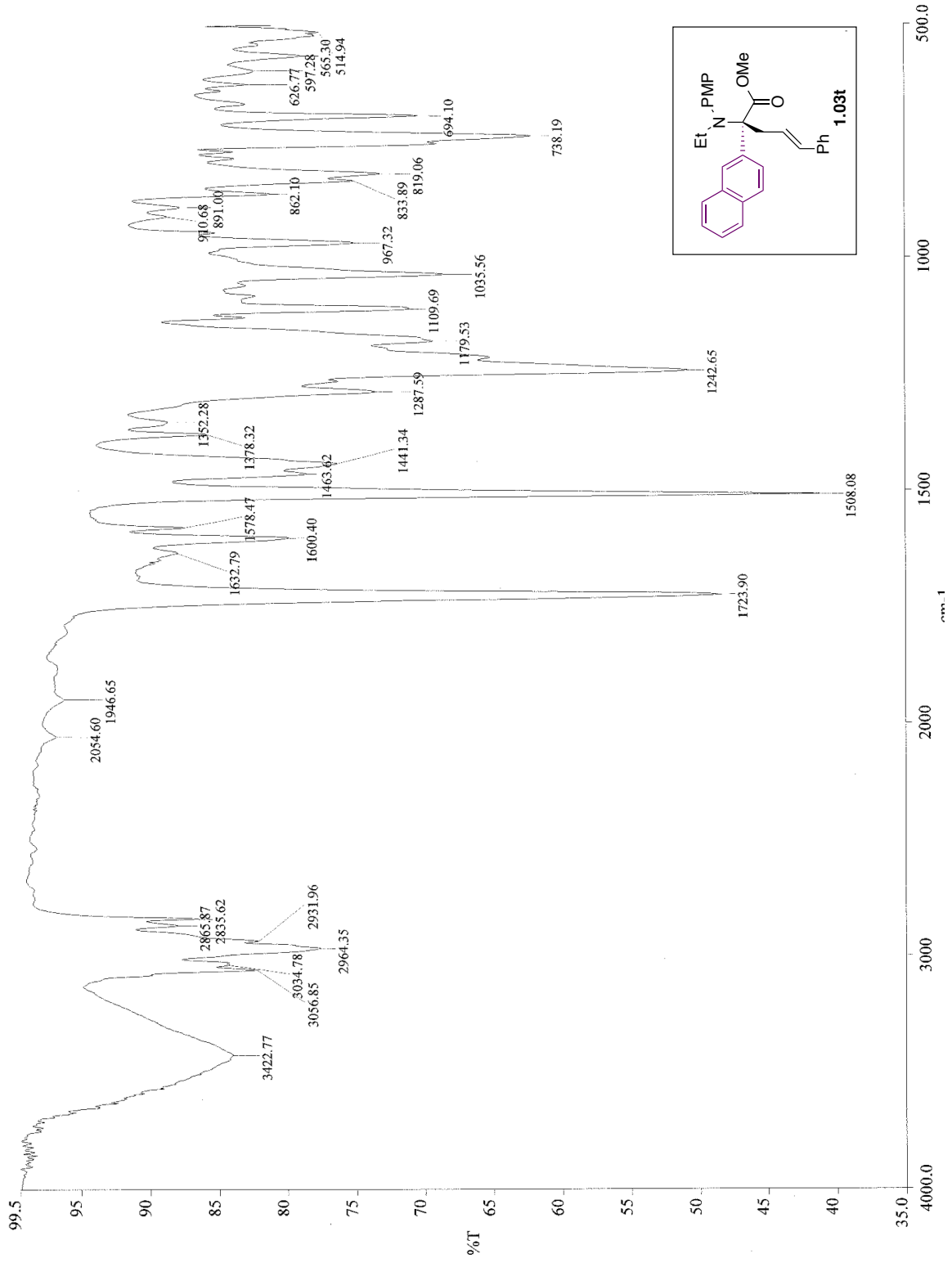
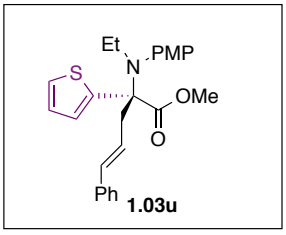



**Figure A.1.03t_3** IR spectrum of compound **1.03t**



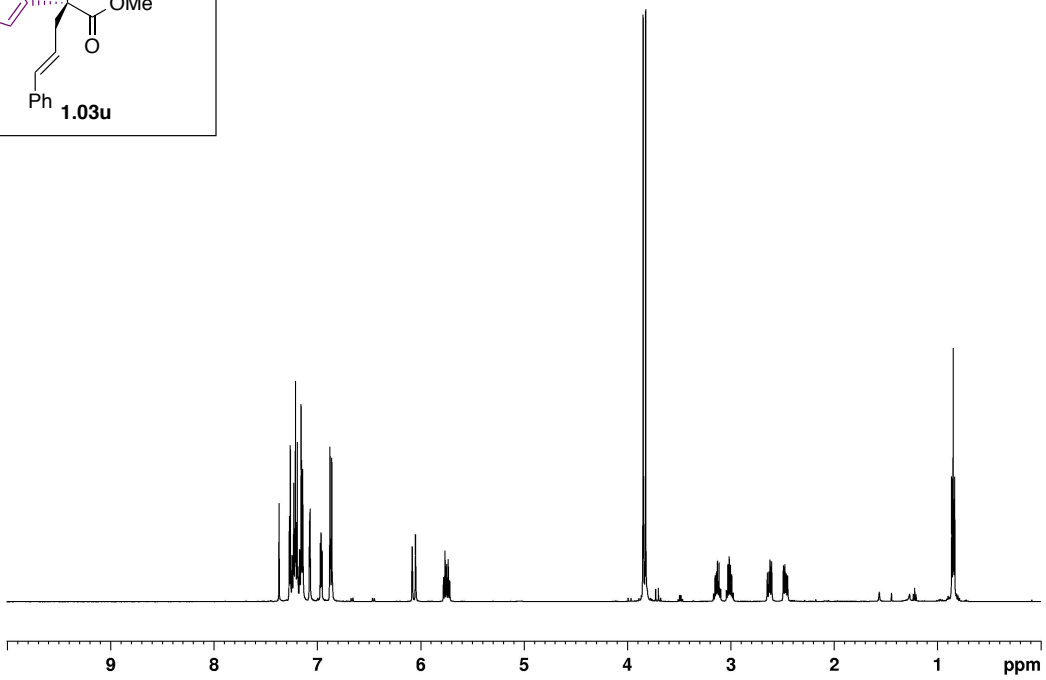




**Figure A. 1.03u_1** $^{1}$H NMR spectrum of compound **1.03u** (500 MHz, $CDCl_3$)

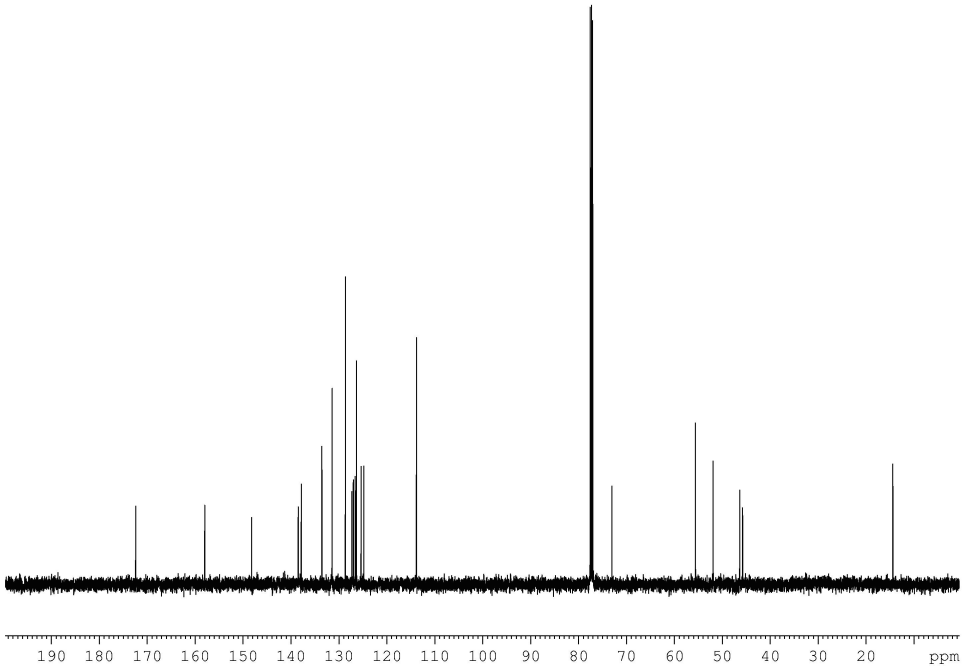



**Figure A. 1.03u_2** $^{13}$C NMR spectrum of compound **1.03u** (125 MHz, $CDCl_3$)

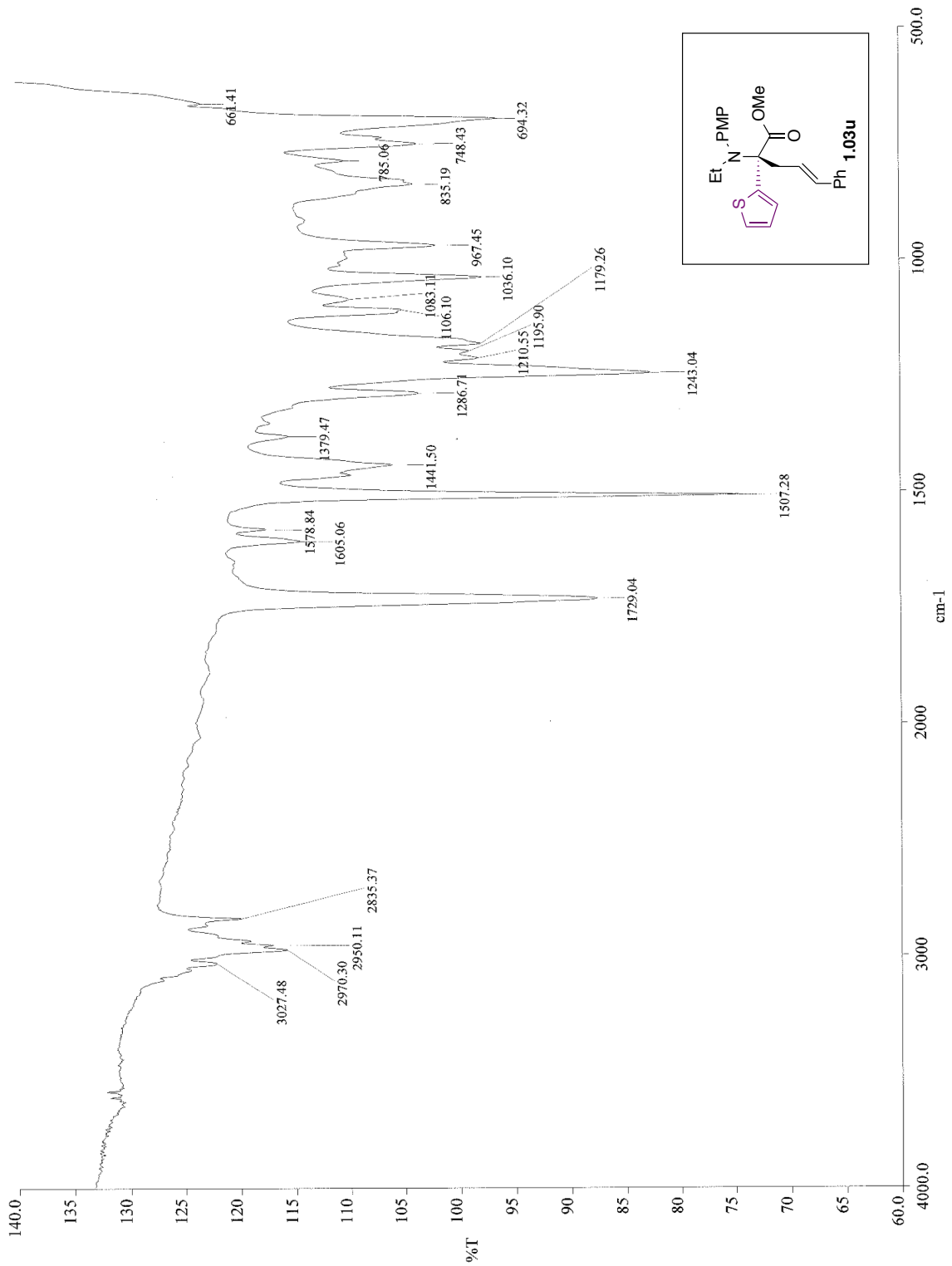



**Figure A.1.03u_3** IR spectrum of compound **1.03qu**

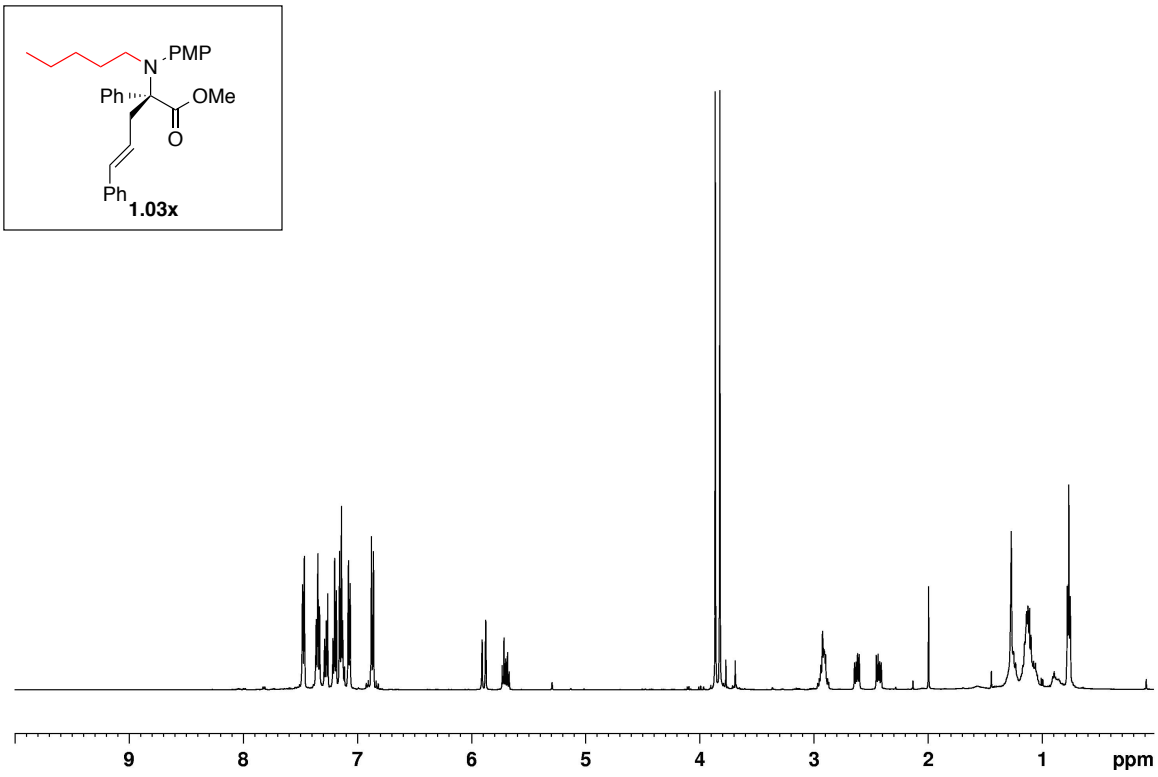



**Figure A. 1.03x_1** $^{1}$H NMR spectrum of compound **1.03x** (500 MHz, $CDCl_3$)

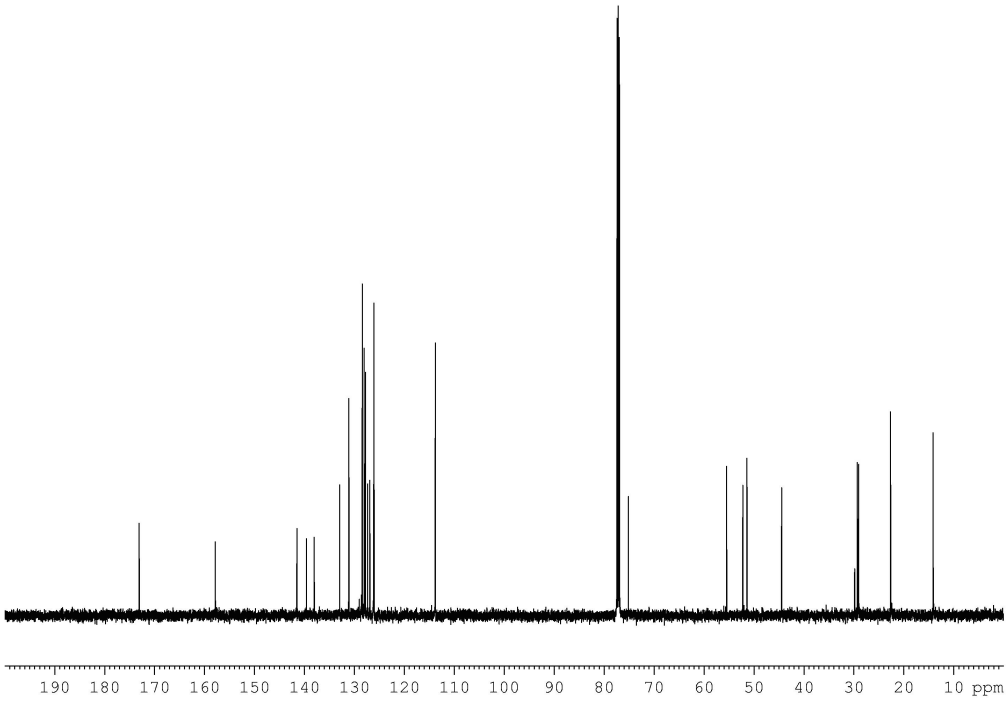



**Figure A. 1.03x_2** $^{13}$C NMR spectrum of compound **1.03x** (125 MHz, $CDCl_3$)

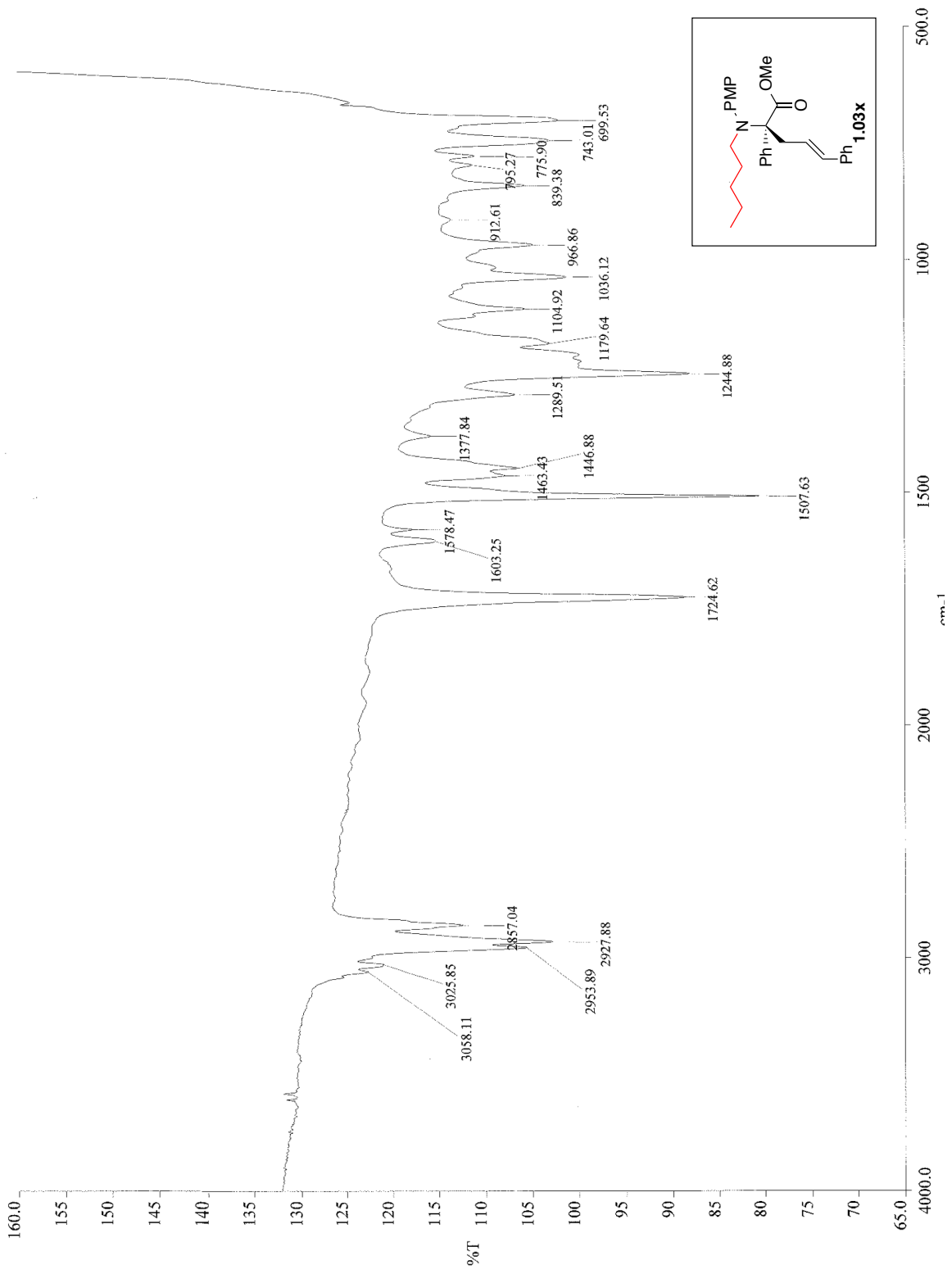



**Figure A.1.03x_3** IR spectrum of compound **1.03x**

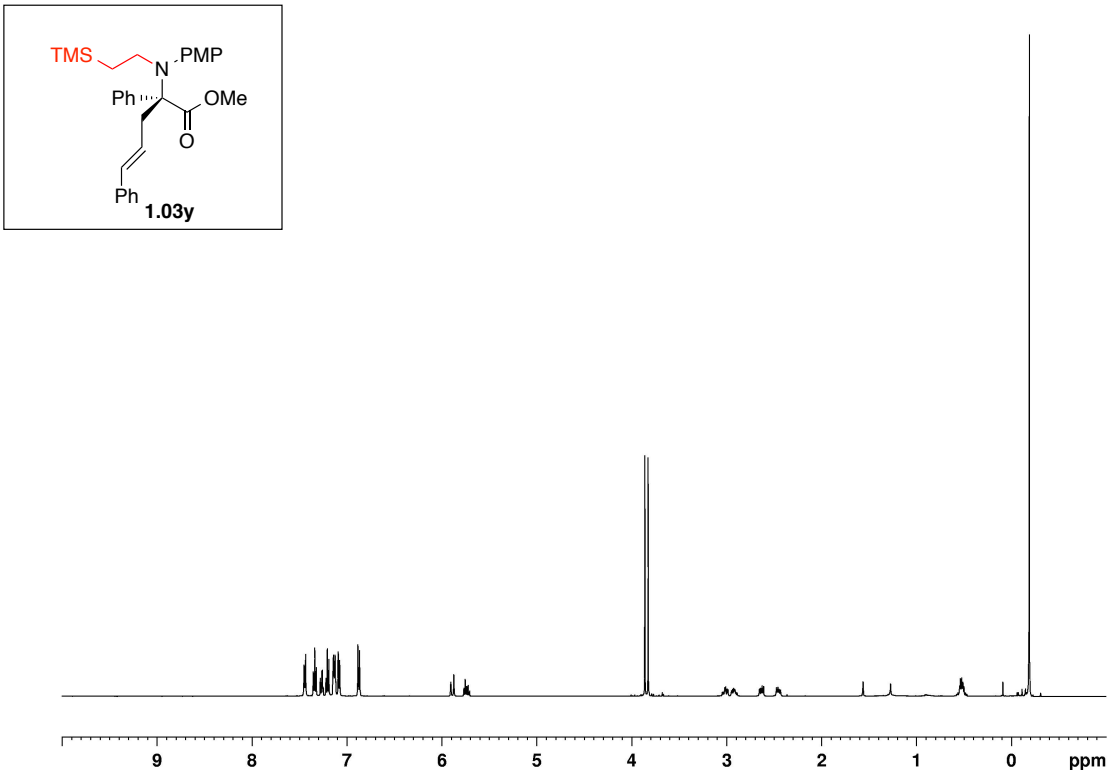



**Figure A. 1.03y_1** $^{1}$H NMR spectrum of compound **1.03y** (500 MHz, $CDCl_3$)

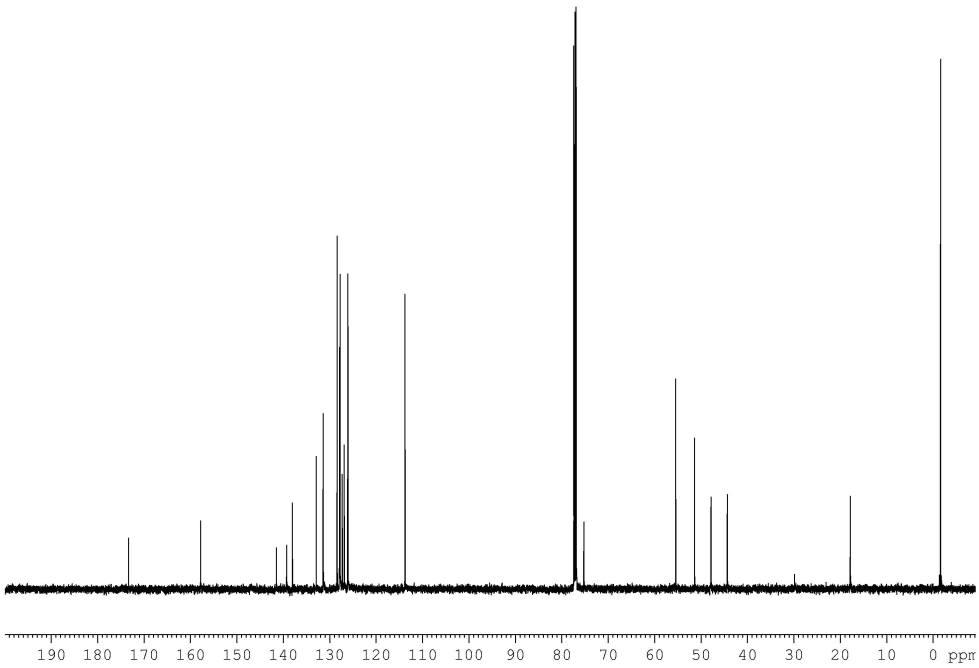



**Figure A. 1.03y_2** $^{13}$C NMR spectrum of compound **1.03y** (125 MHz, $CDCl_3$)

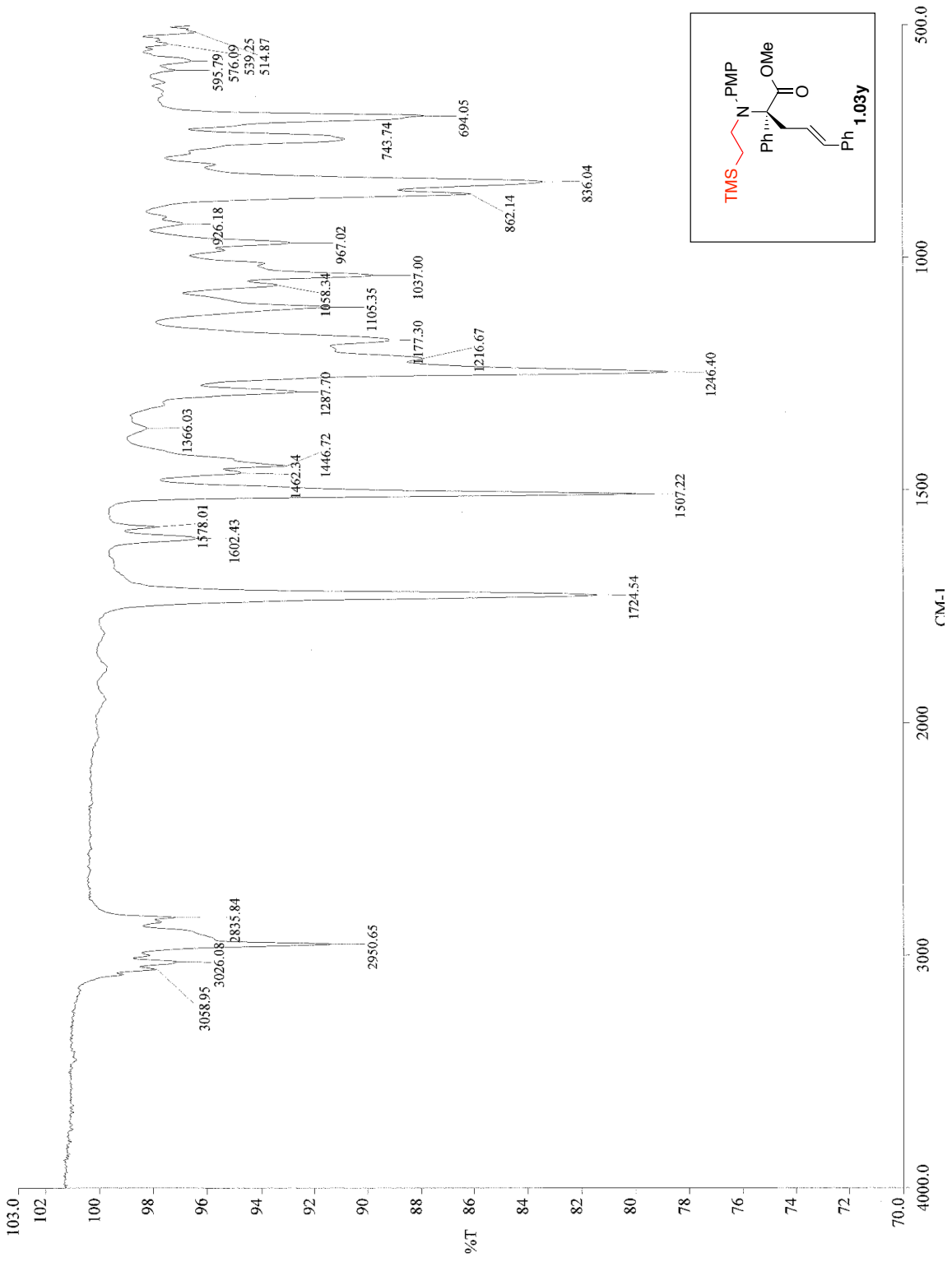
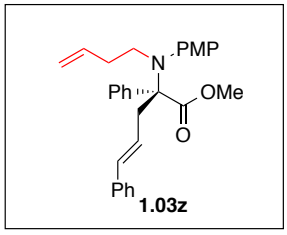



**Figure A.1.03y_3** IR spectrum of compound **1.03y**



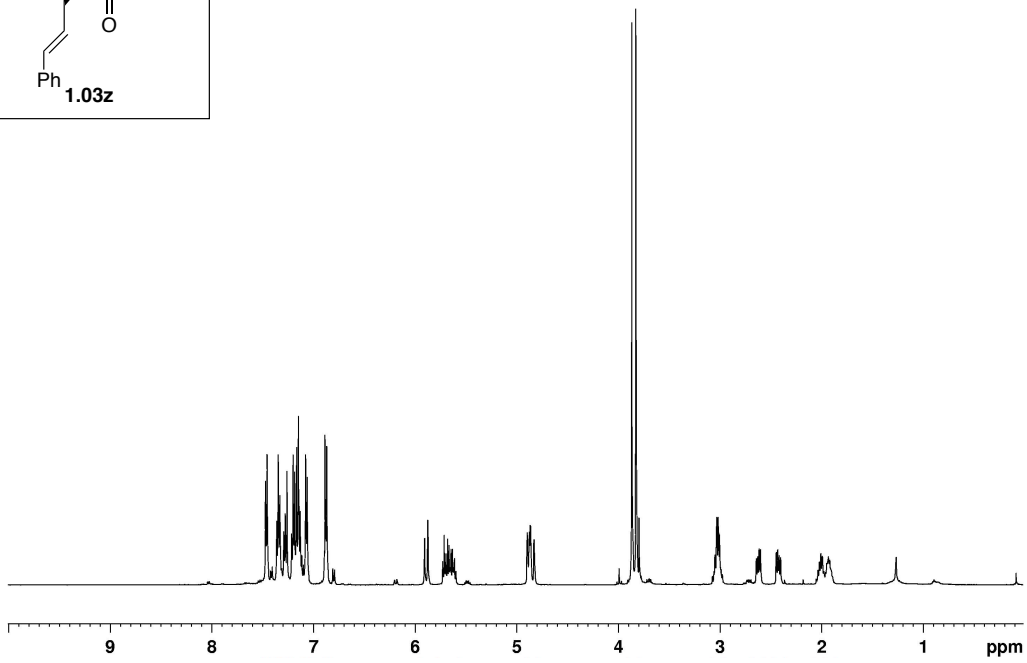




**Figure A. 1.03z_1** $^{1}$H NMR spectrum of compound **1.03z** (500 MHz, $CDCl_3$)

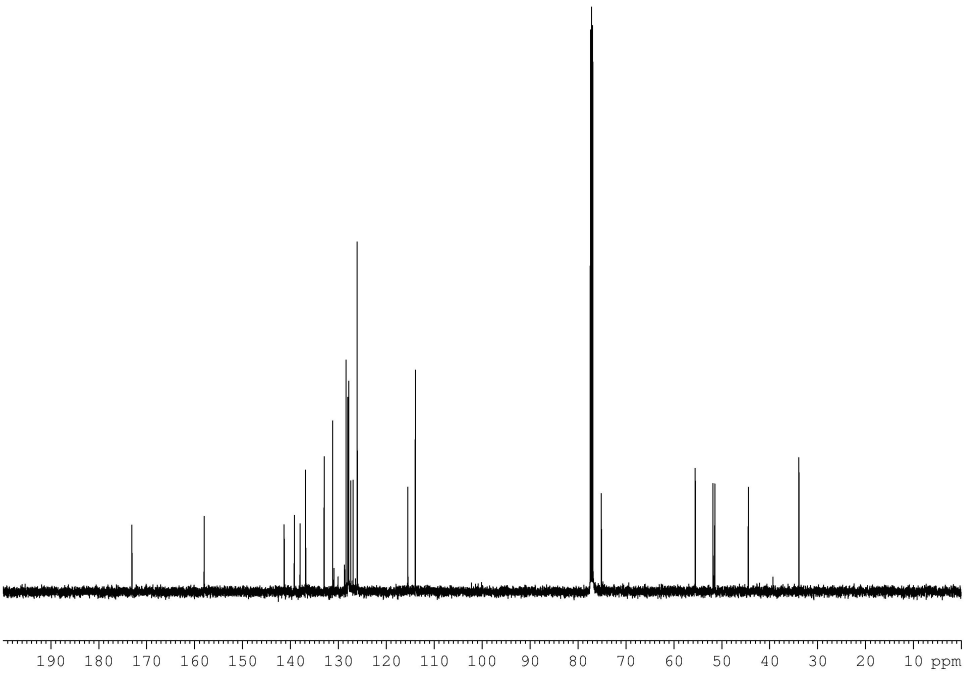



**Figure A. 1.03z_2** $^{13}$C NMR spectrum of compound **1.03z** (125 MHz, $CDCl_3$)

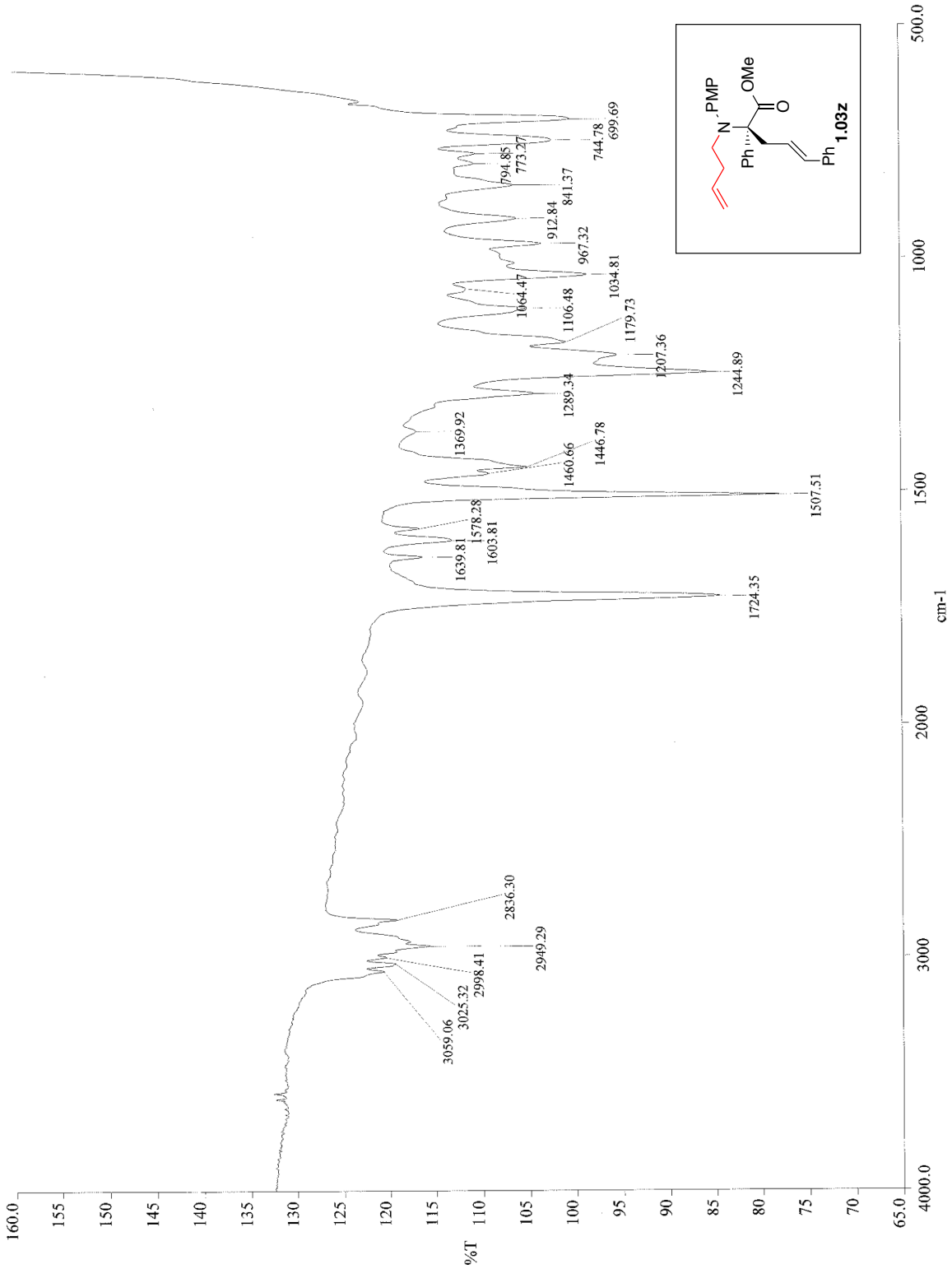



**Figure A.1.03z_3** IR spectrum of compound **1.03z**

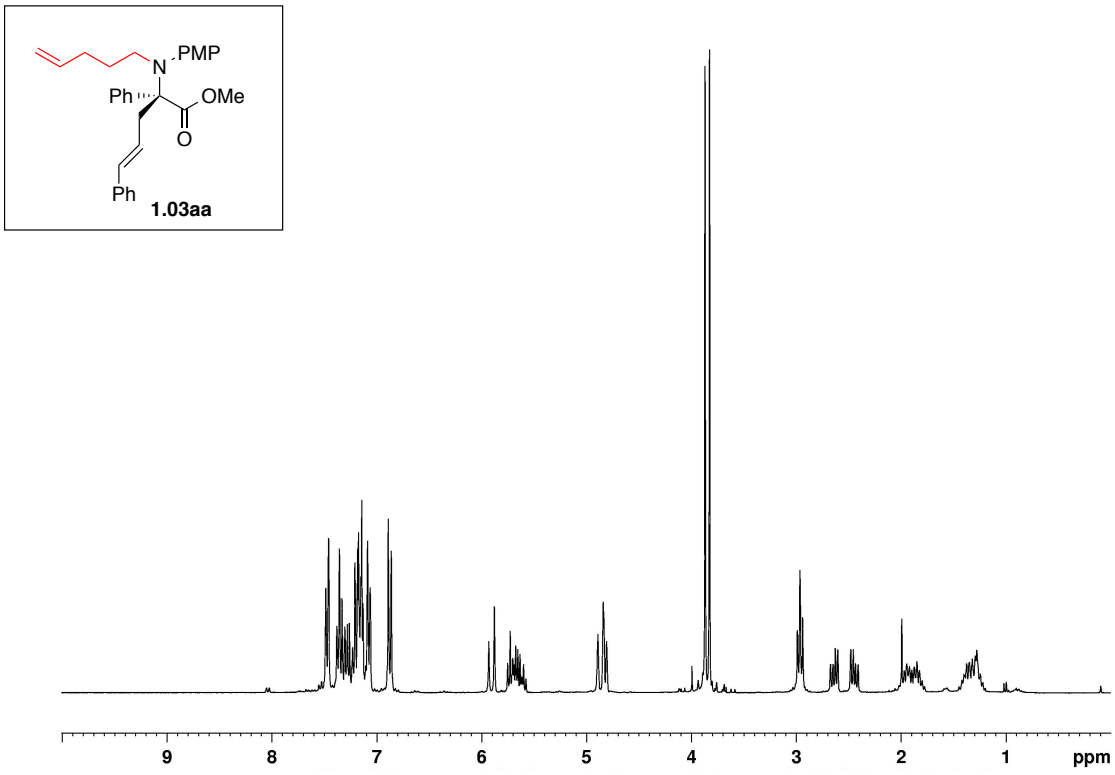



**Figure A. 1.03aa_1** $^{1}$H NMR spectrum of compound **1.03aa** (500 MHz, $CDCl_3$)

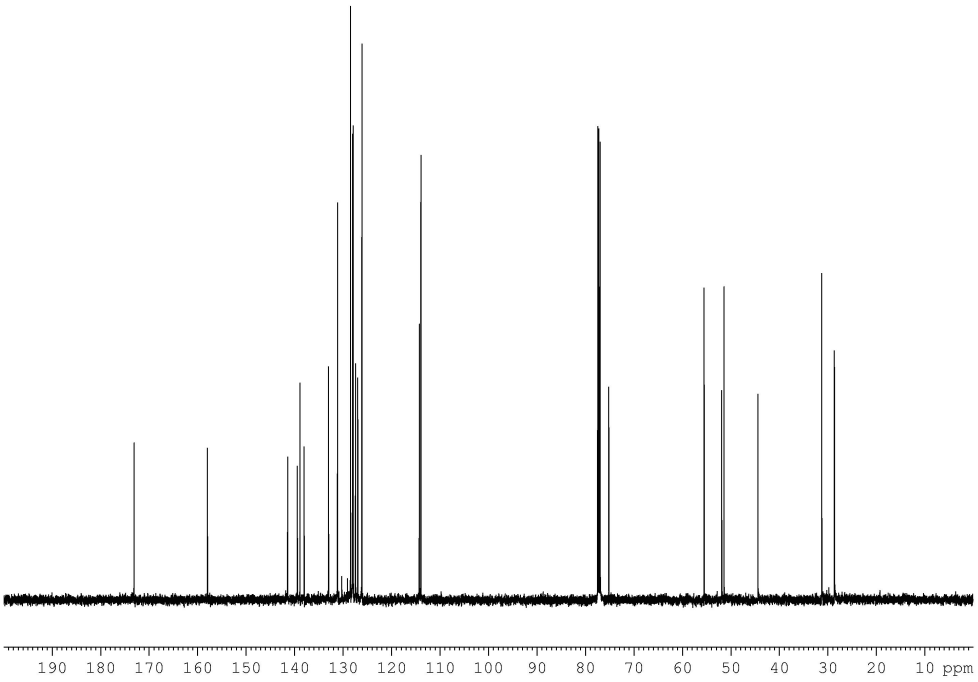



**Figure A. 1.03aa_2** $^{13}$C NMR spectrum of compound **1.03aa** (125 MHz, $CDCl_3$)

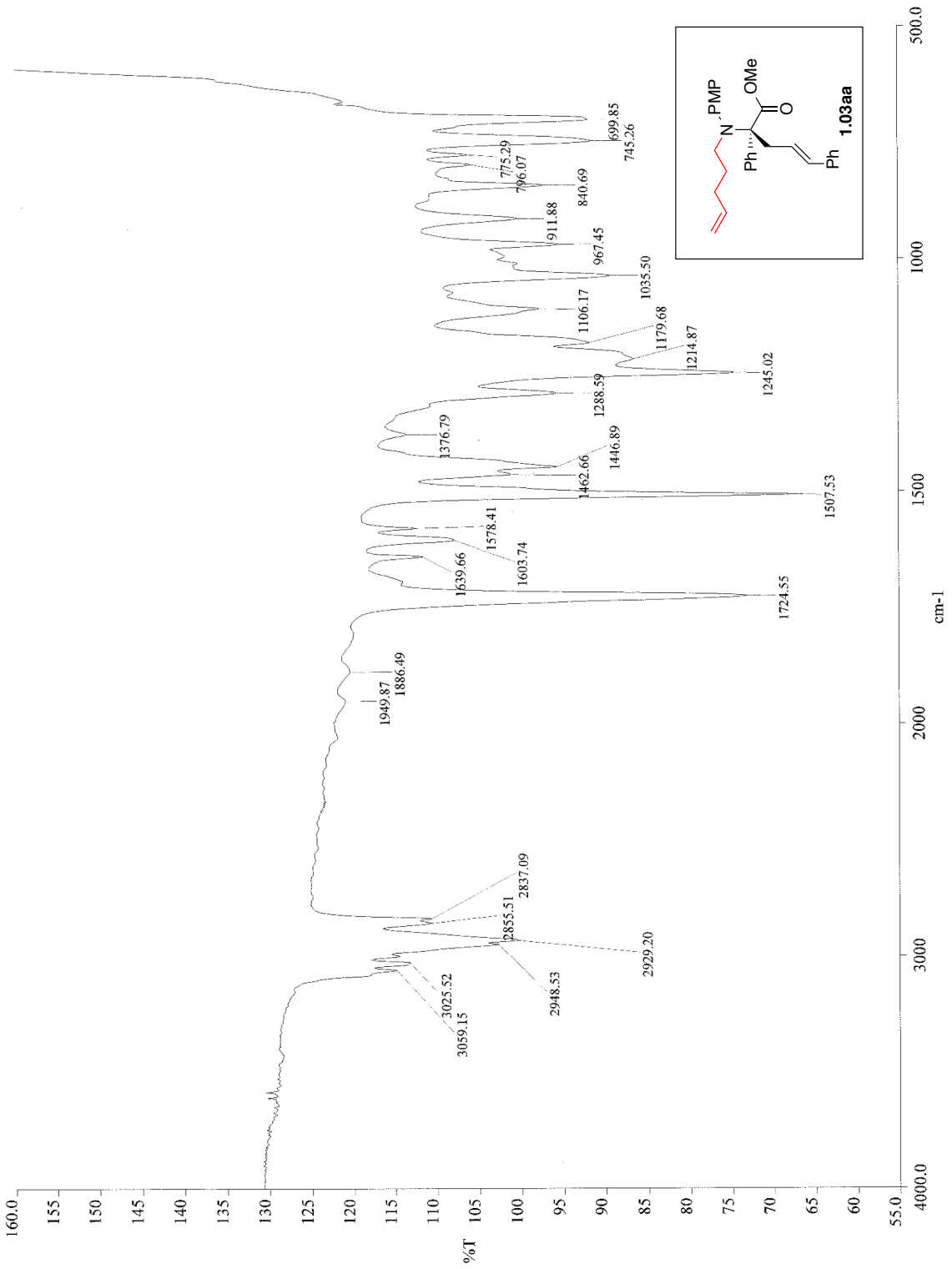



**Figure A.1.03aa_3** IR spectrum of compound **1.03aa**

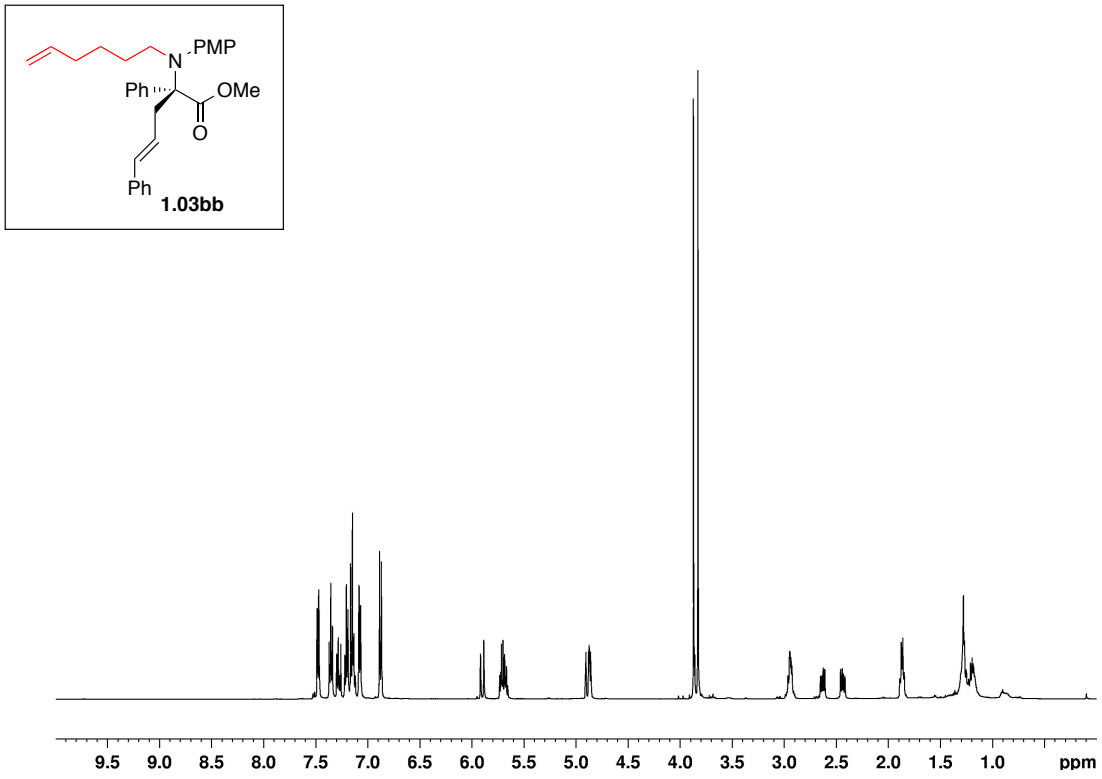



**Figure A. 1.03bb_1** $^{1}$H NMR spectrum of compound **1.03bb** (500 MHz, $CDCl_3$)

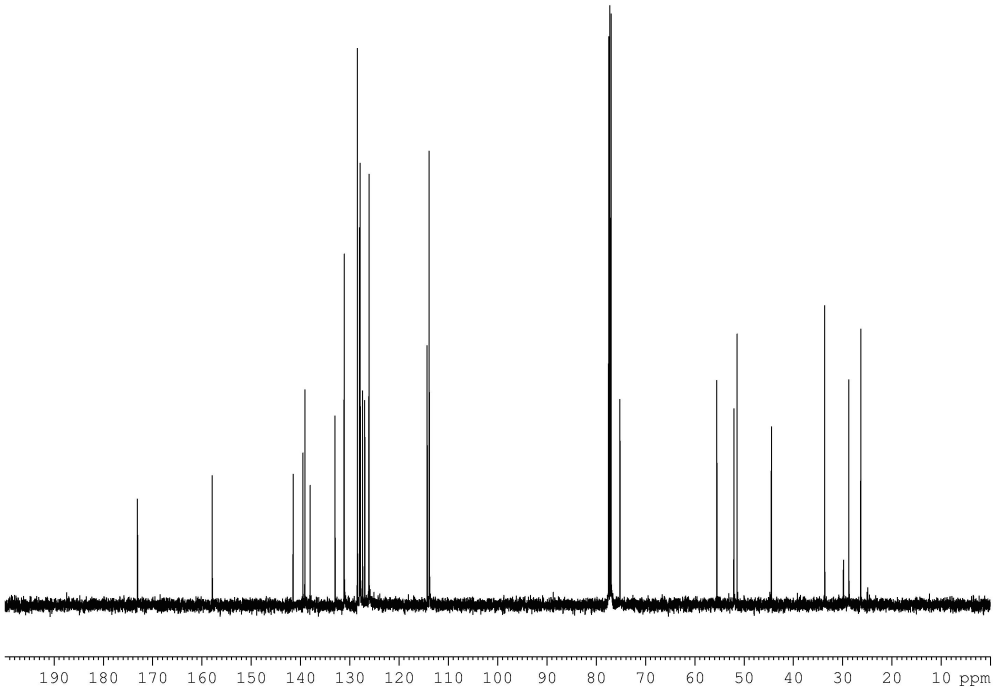



**Figure A. 1.03bb_2** $^{13}$C NMR spectrum of compound **1.03bb** (125 MHz, $CDCl_3$)

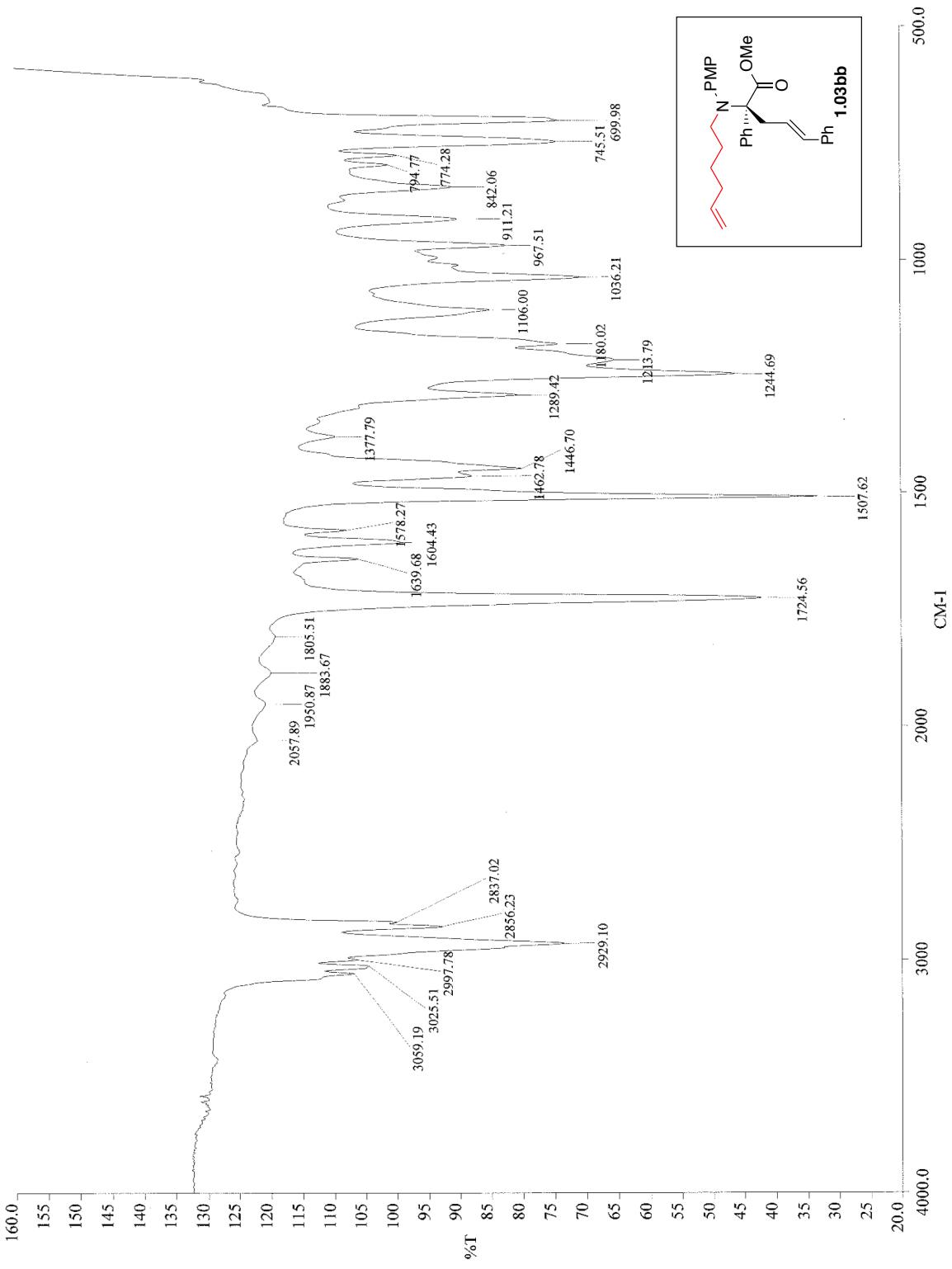



**Figure A.1.03bb_3** IR spectrum of compound **1.03bb**

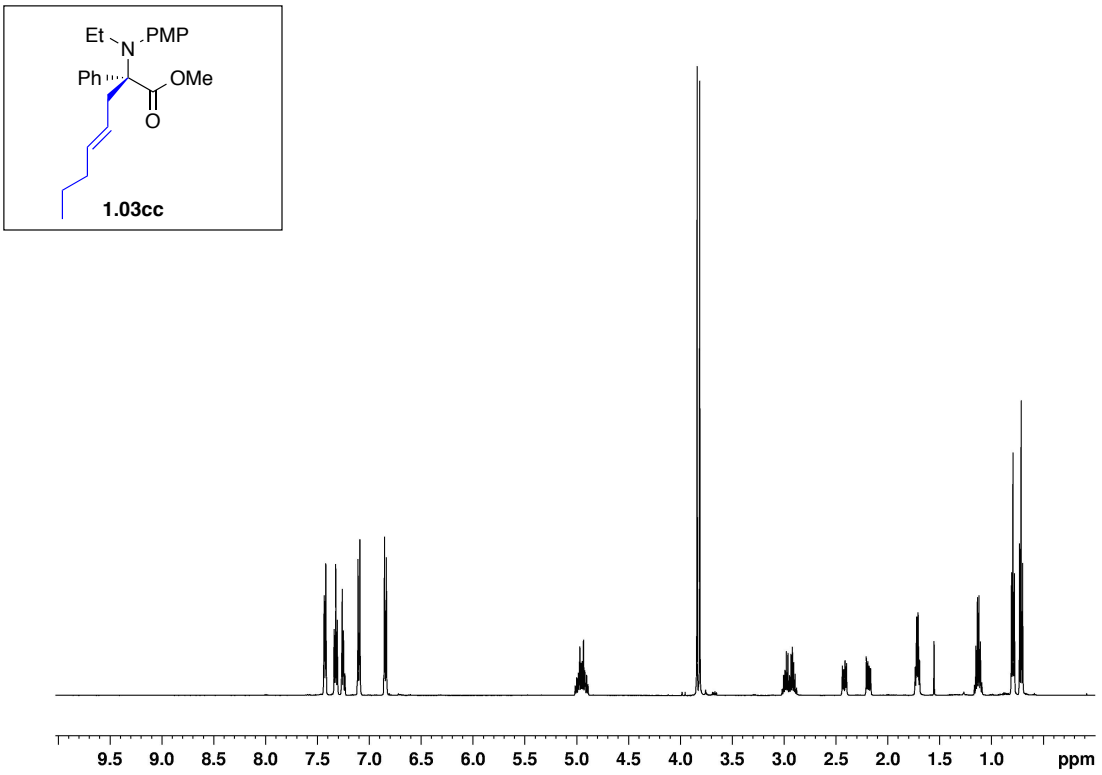



**Figure A. 1.03cc_1** $^{1}$H NMR spectrum of compound **1.03cc** (500 MHz, $CDCl_3$)

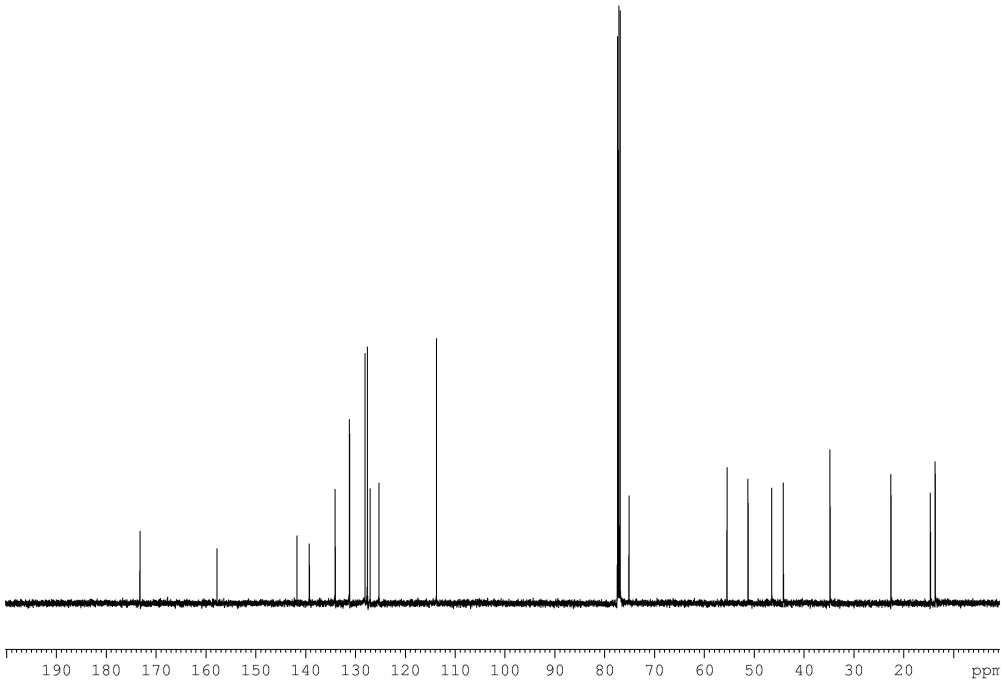



**Figure A. 1.03cc_2** $^{13}$C NMR spectrum of compound **1.03cc** (125 MHz, $CDCl_3$)

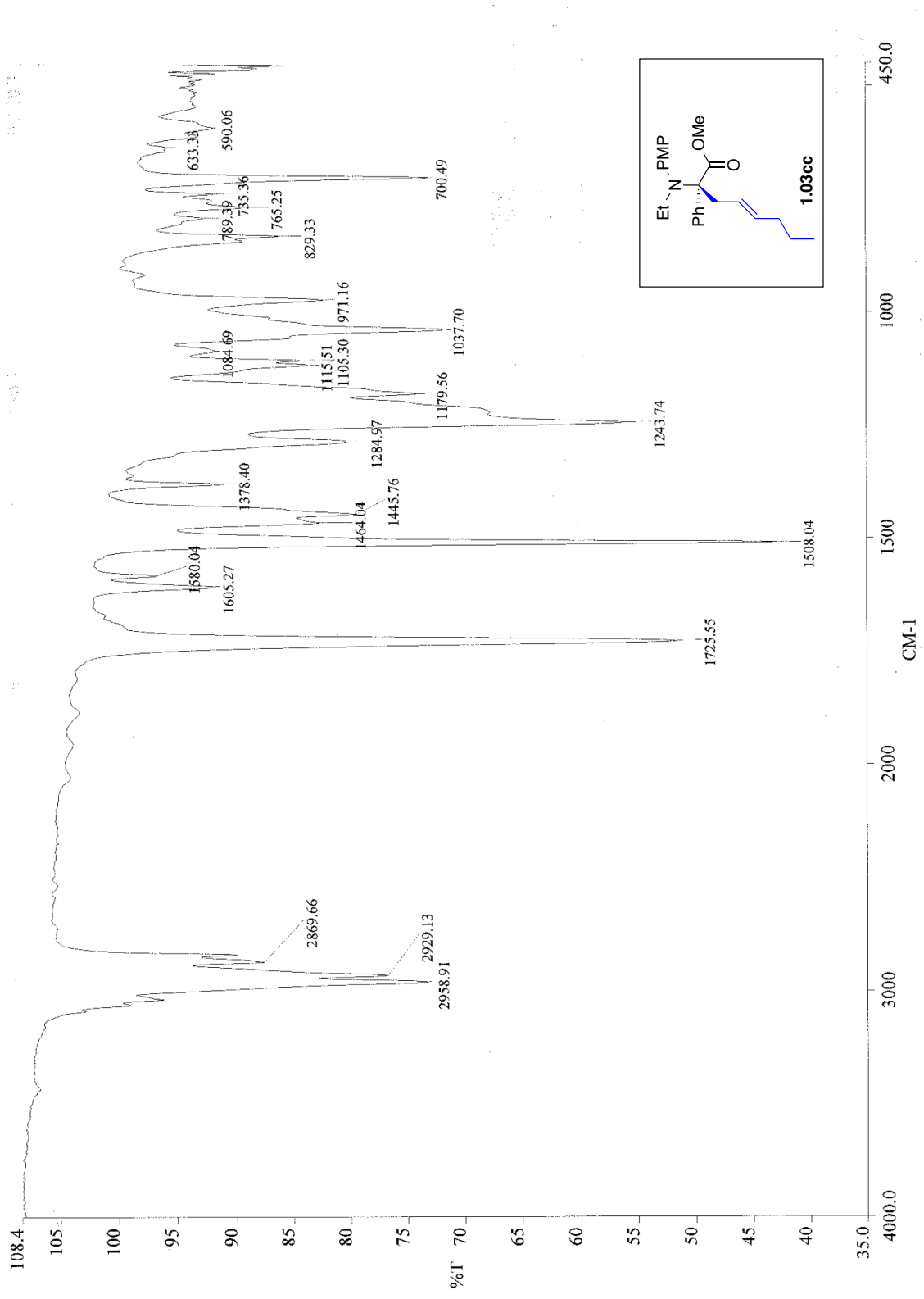



**Figure A.1.03cc_3** IR spectrum of compound **1.03cc**

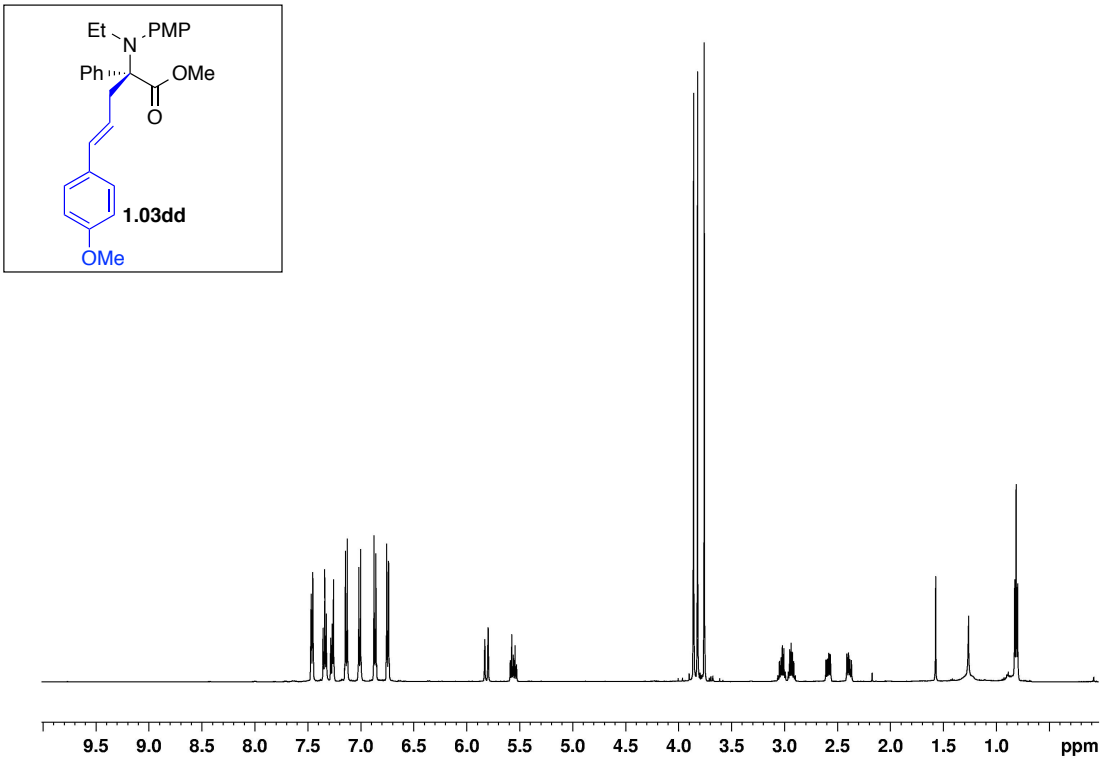



**Figure A. 1.03dd_1** $^{1}$H NMR spectrum of compound **1.03dd** (500 MHz, $CDCl_3$)

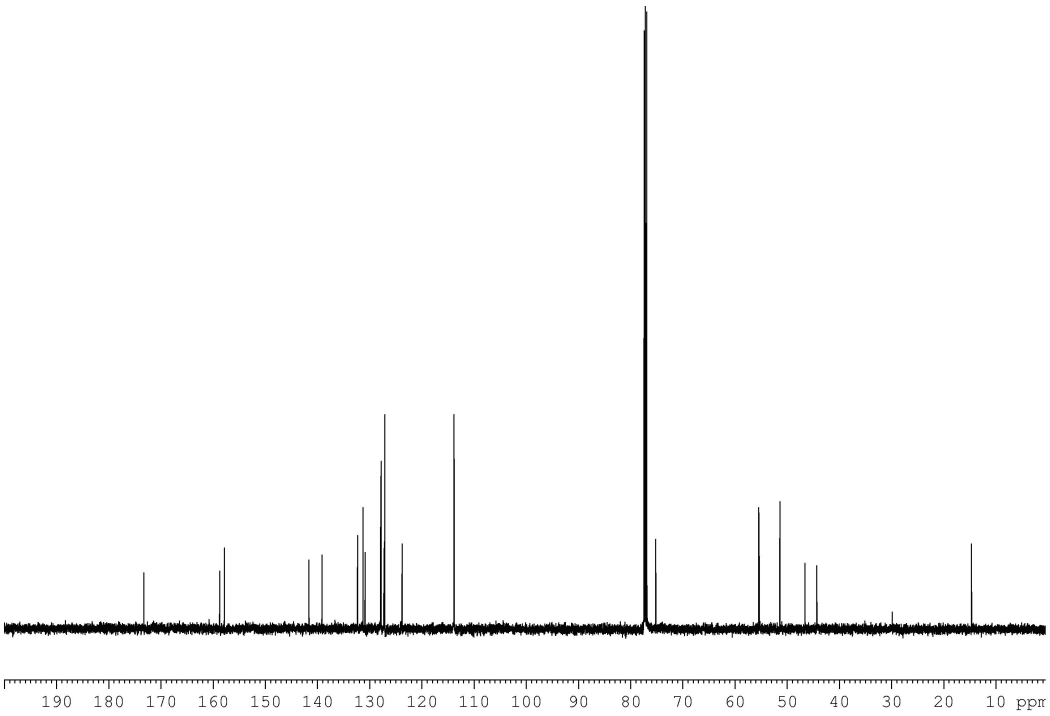



**Figure A. 1.03dd_2** $^{13}$C NMR spectrum of compound **1.03dd** (125 MHz, $CDCl_3$)

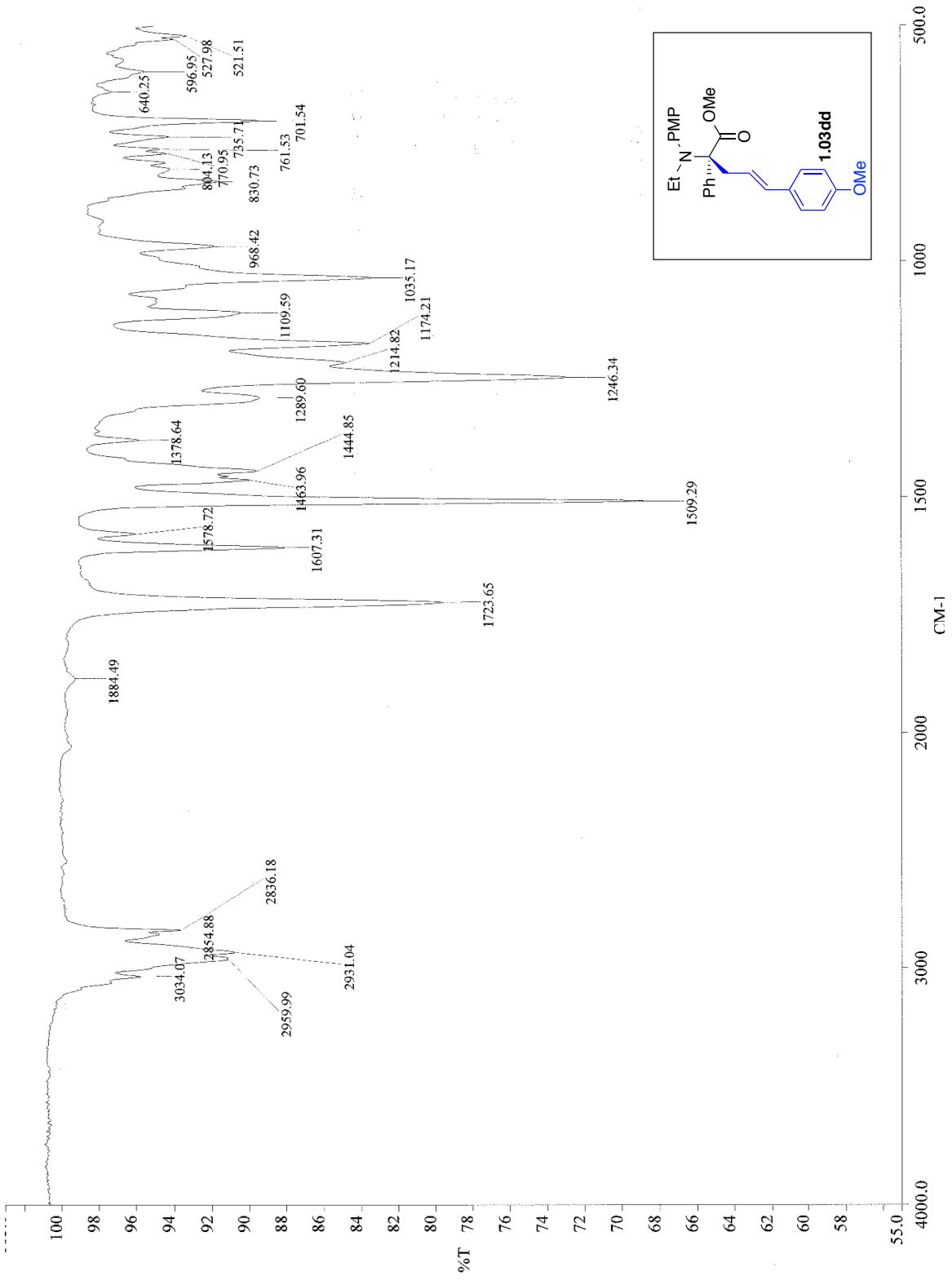



**Figure A.1.03dd_3** IR spectrum of compound **1.03dd**

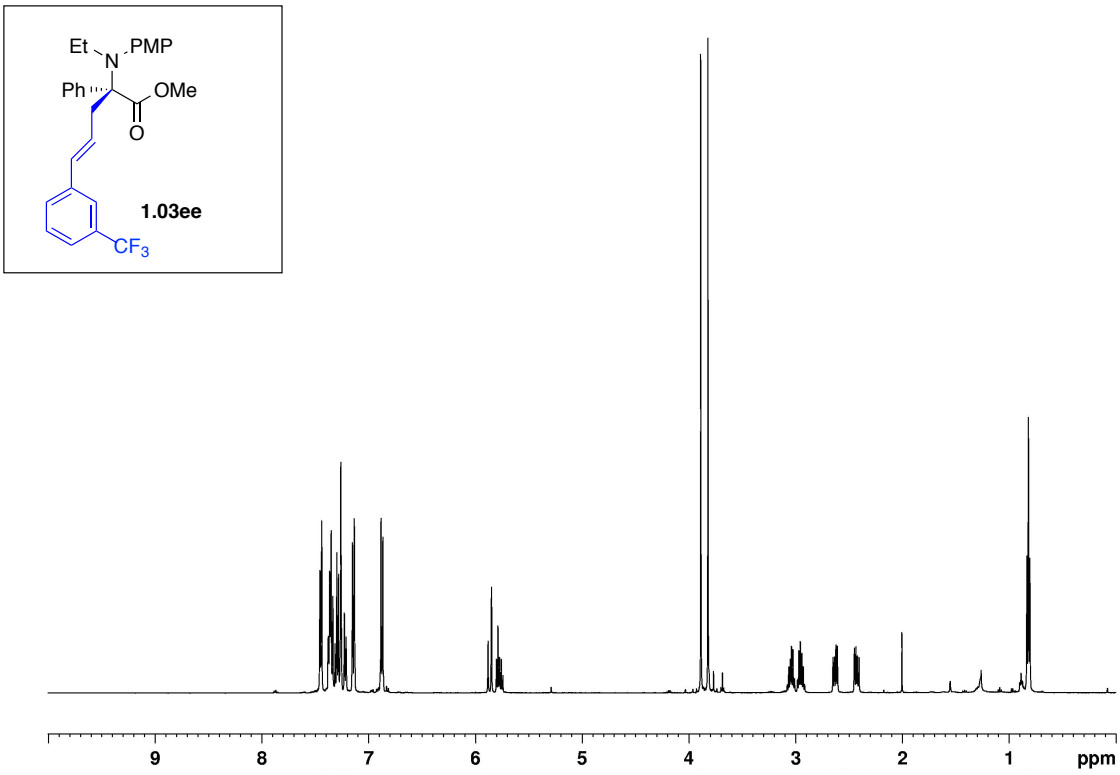



**Figure A. 1.03ee_1** $^{1}$H NMR spectrum of compound **1.03ee** (500 MHz, $CDCl_3$)

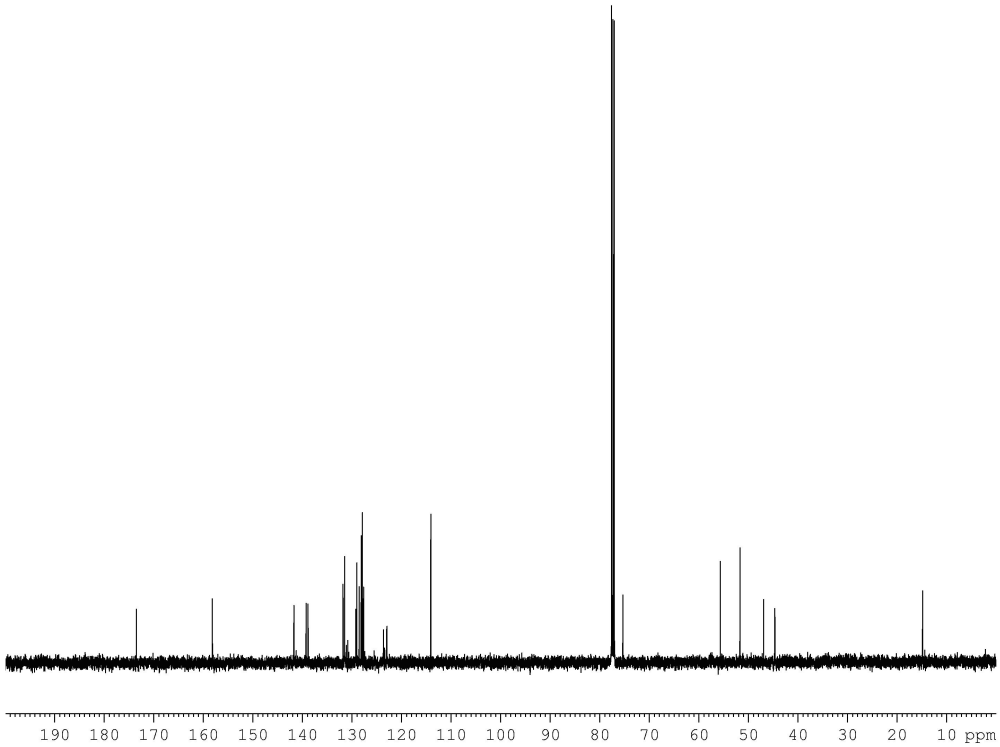



**Figure A. 1.03ee_2** $^{13}$C NMR spectrum of compound **1.03ee** (125 MHz, $CDCl_3$)

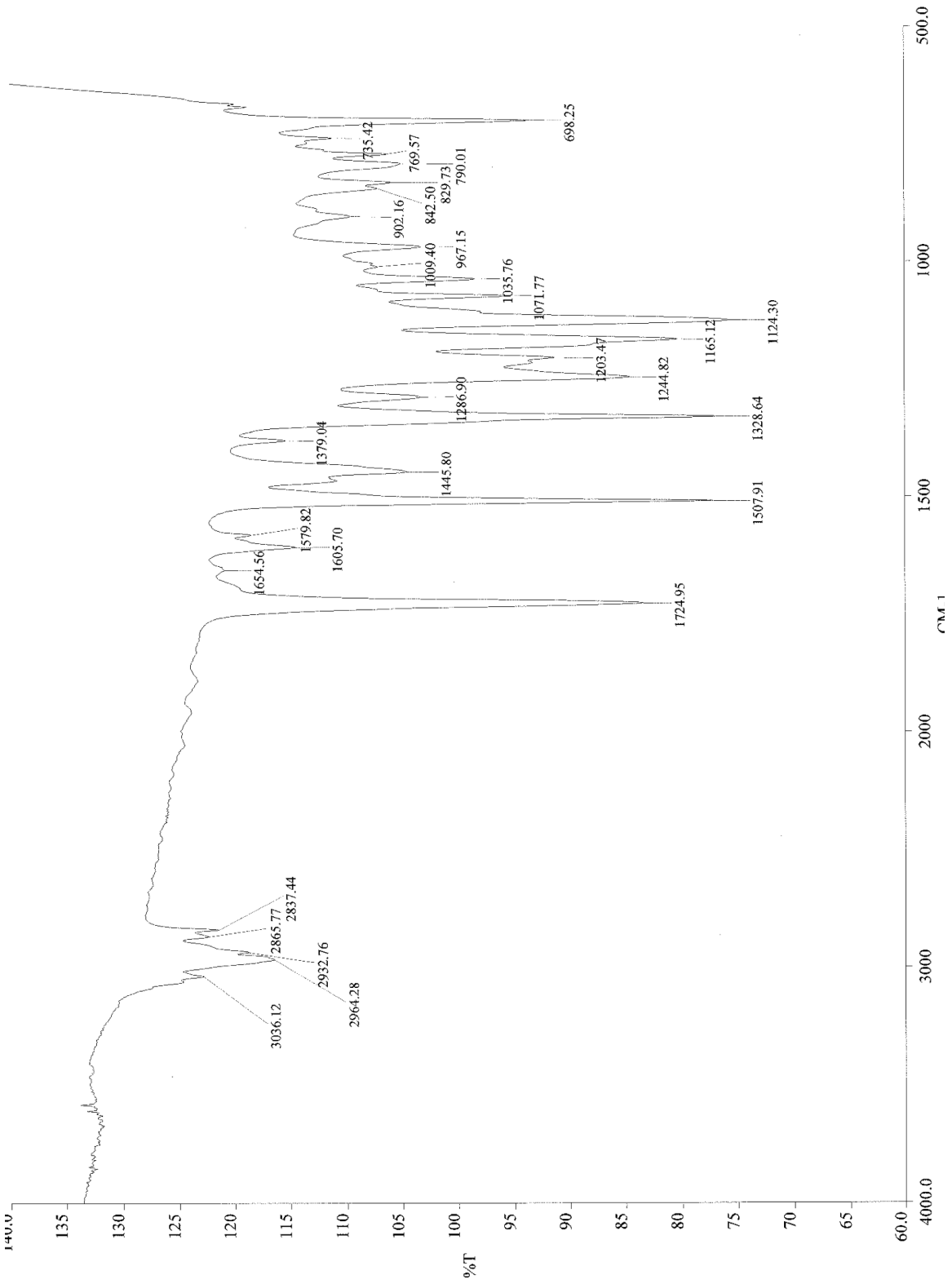



**Figure A.1.03ee_3** IR spectrum of compound **1.03ee**

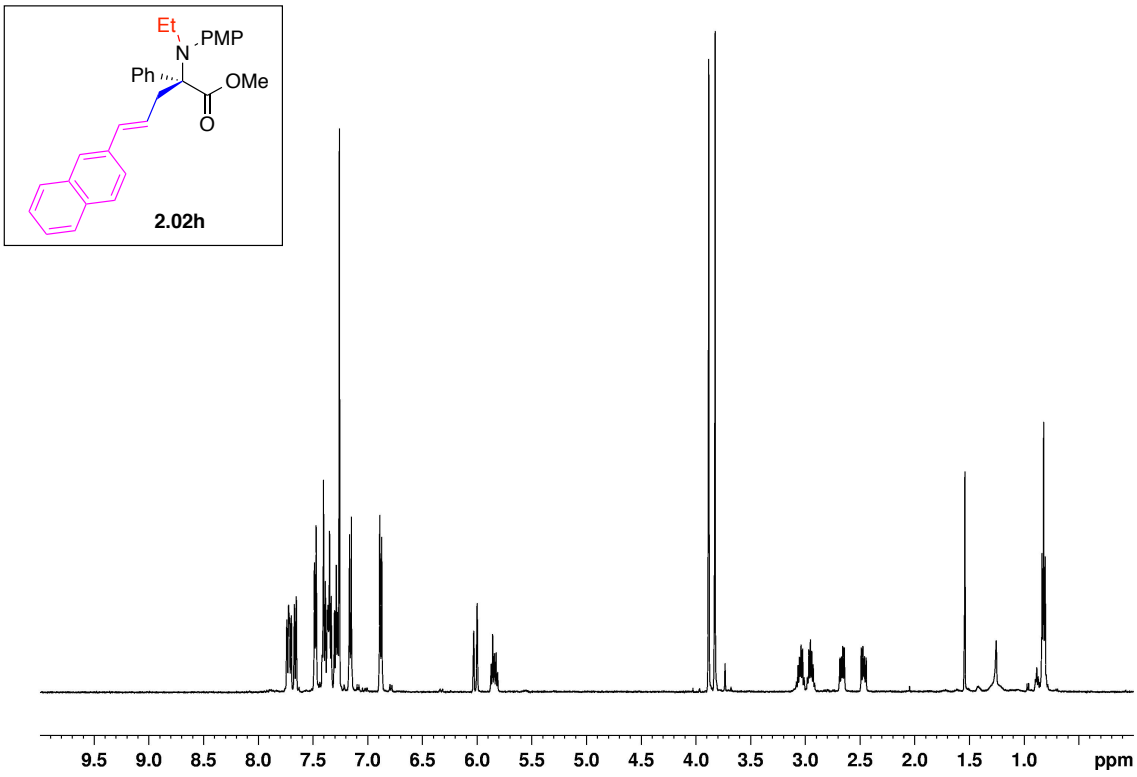



**Figure A. 2.02h_1** $^{1}$H NMR spectrum of compound **2.02h** (500 MHz, $CDCl_3$)

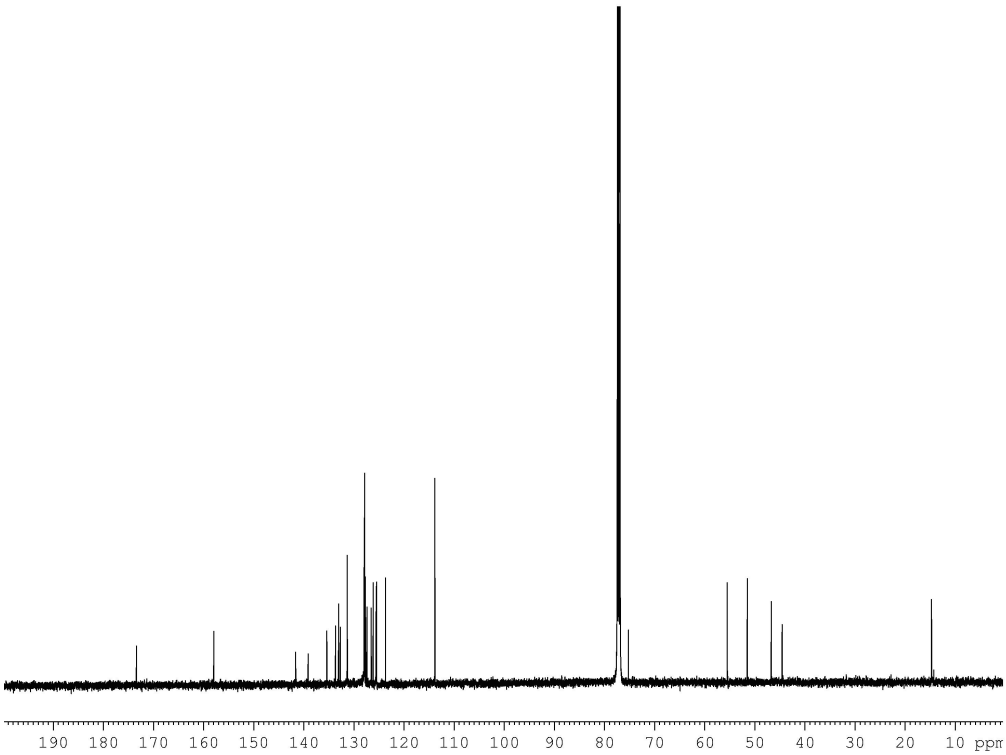



**Figure A. 2.02h _2** $^{13}$C NMR spectrum of compound **2.02h** (125 MHz, $CDCl_3$)

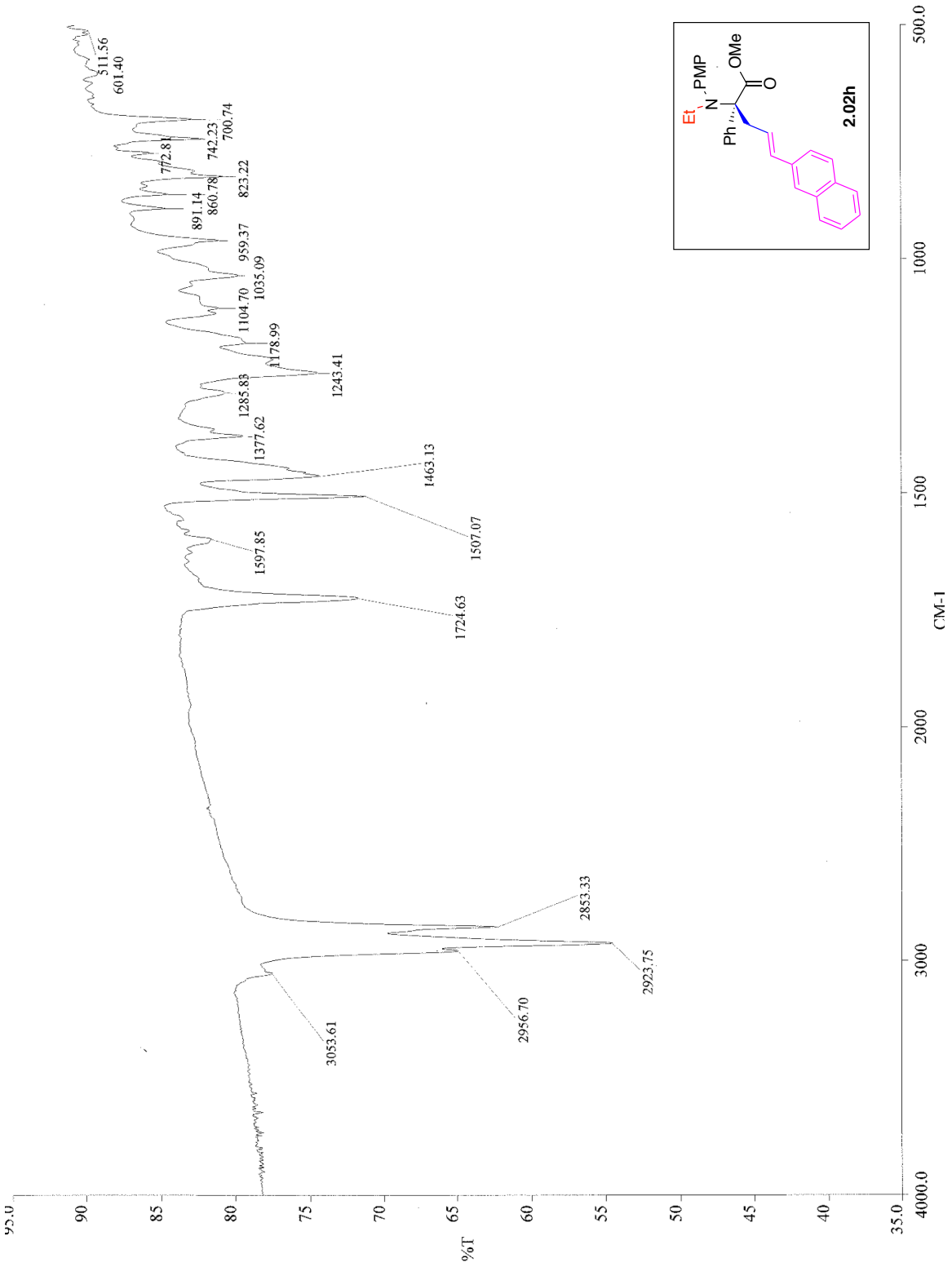



**Figure A. 2.02h _3** IR spectrum of compound **2.02h**

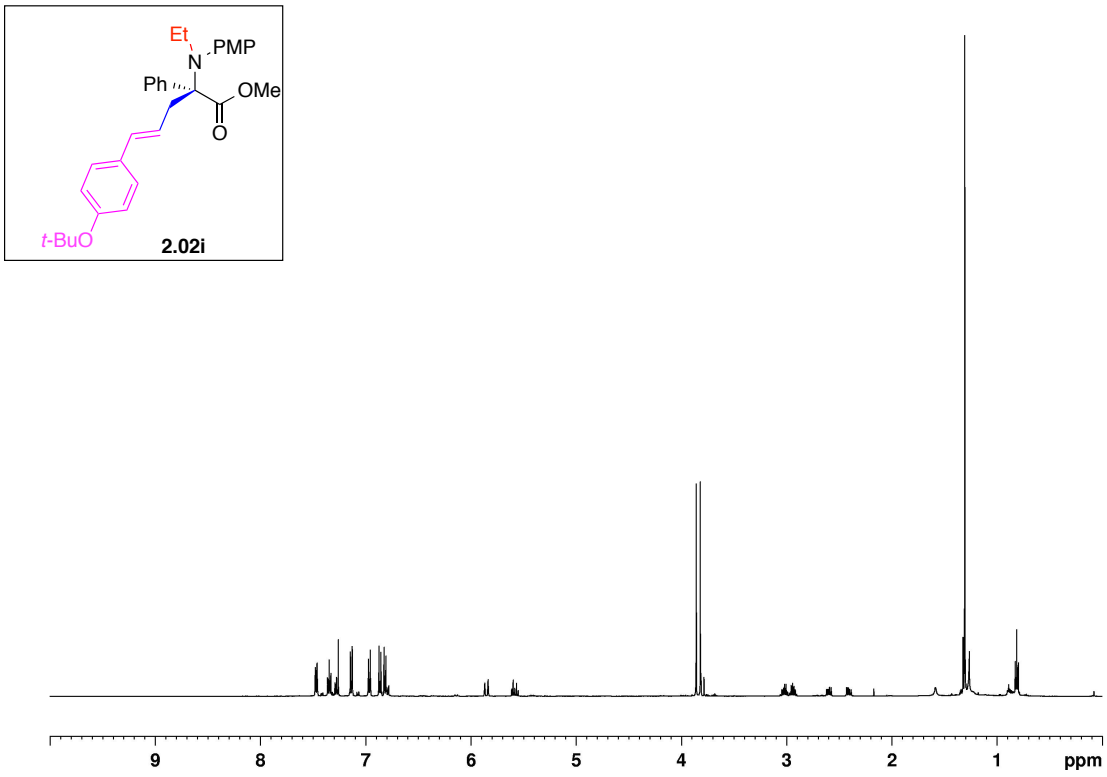



**Figure A. 2.02i_1** $^{1}$H NMR spectrum of compound **2.02i** (500 MHz, $CDCl_3$)

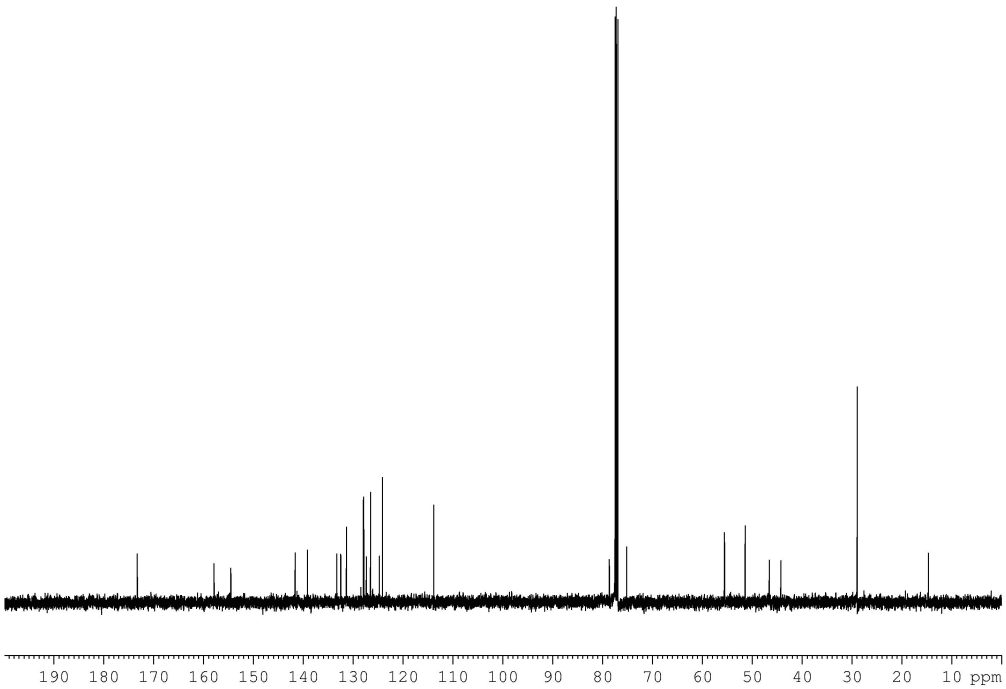



**Figure A. 2.02i _2** $^{13}$C NMR spectrum of compound **2.02i** (125 MHz, $CDCl_3$)

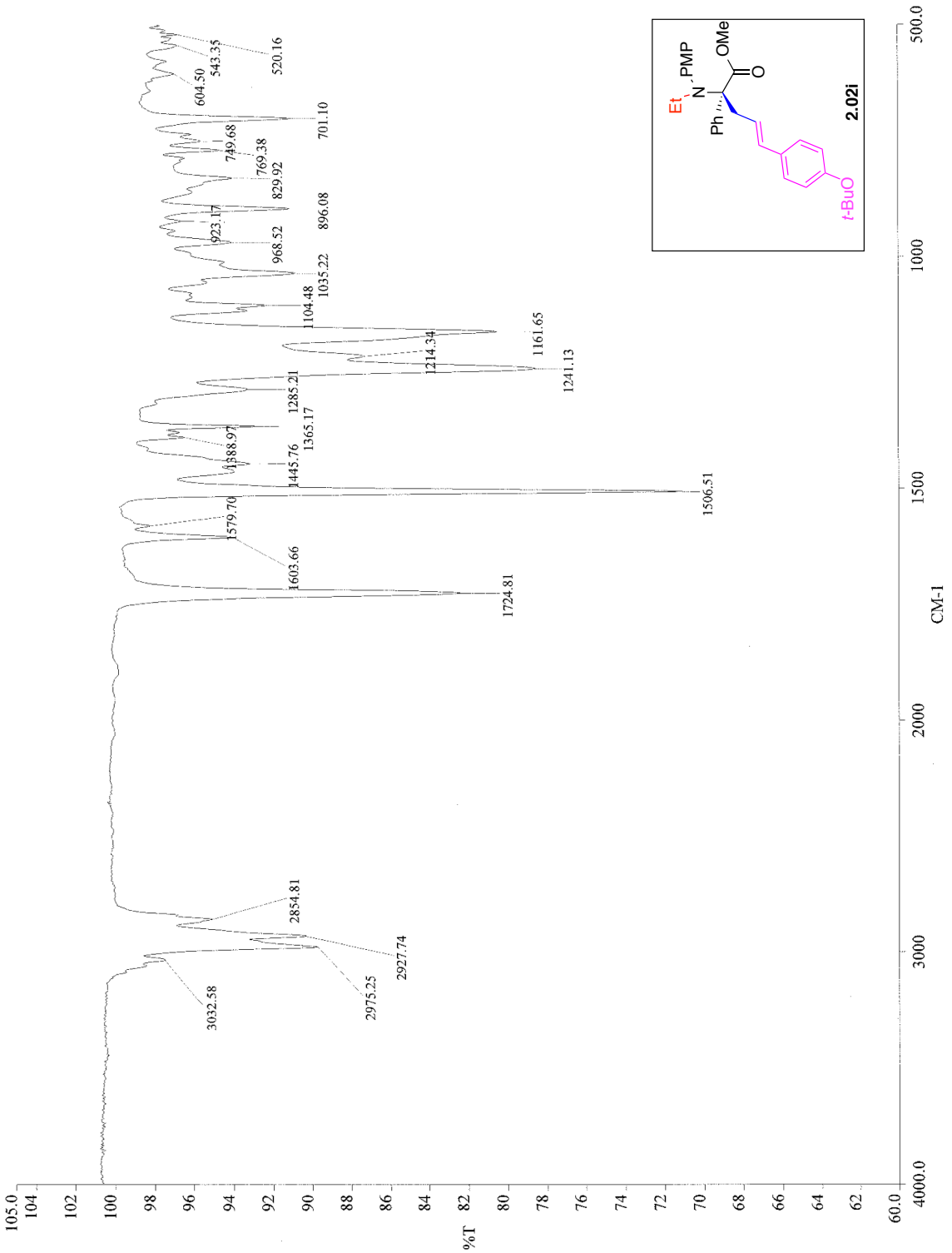



**Figure A. 2.02i_3** IR spectrum of compound **2.02i**

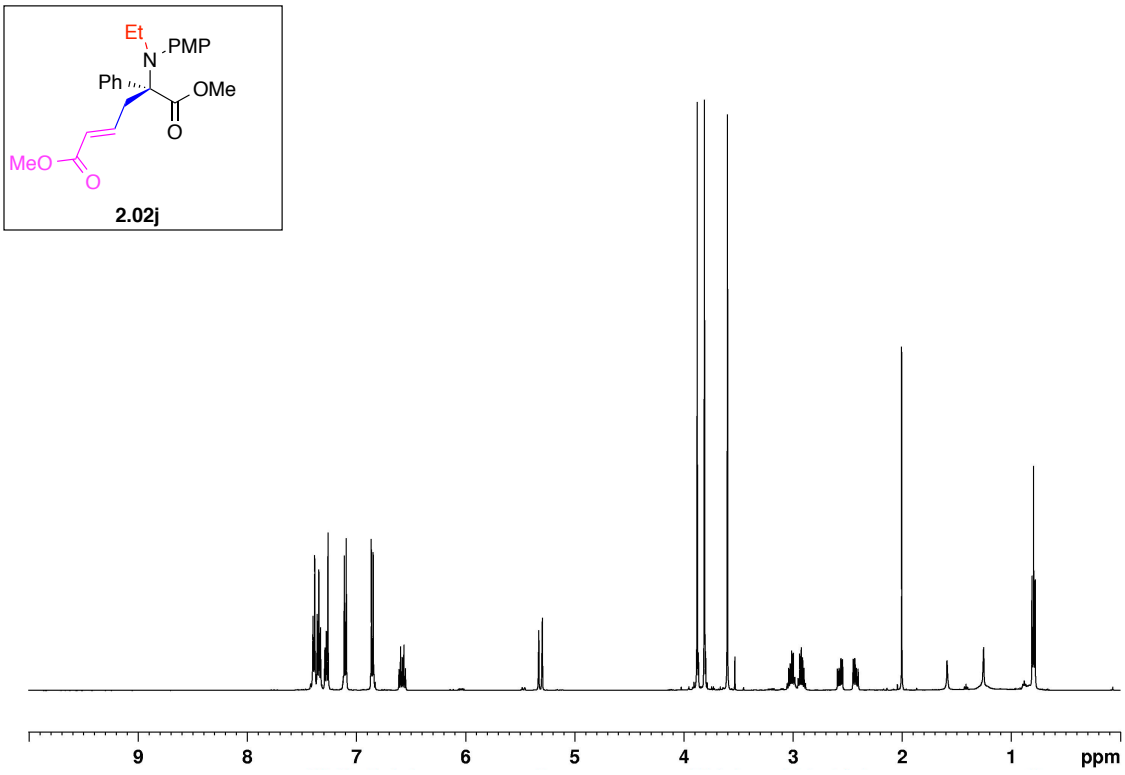



**Figure A. 2.02j_1** $^{1}$H NMR spectrum of compound **2.02j** (500 MHz, $CDCl_3$)

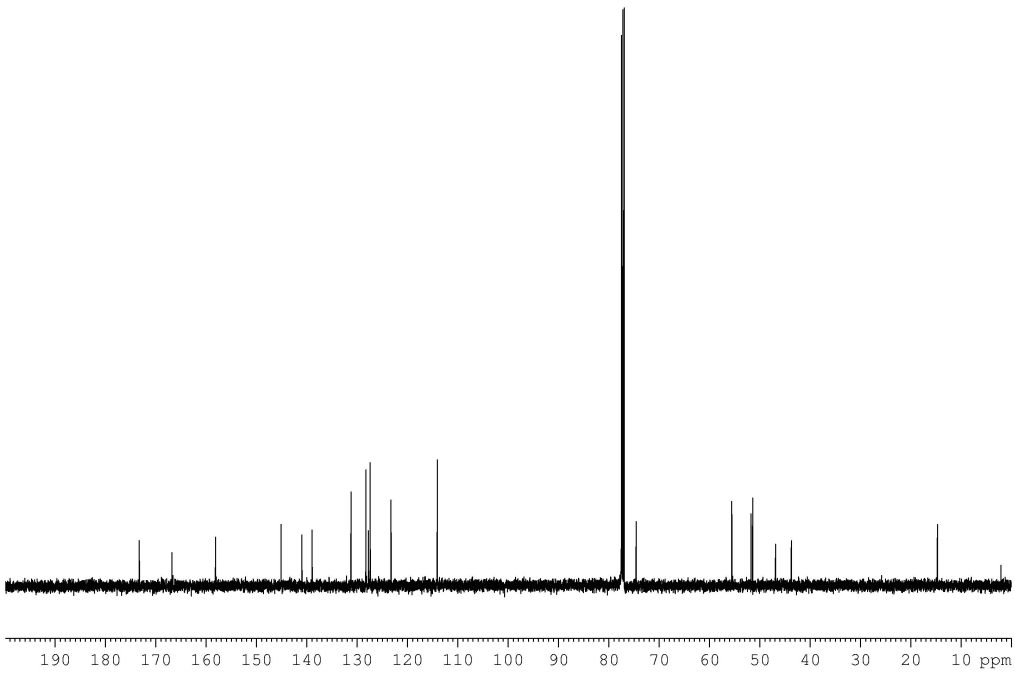



**Figure A. 2.02j_2** $^{13}$C NMR spectrum of compound **2.02j** (125 MHz, $CDCl_3$)

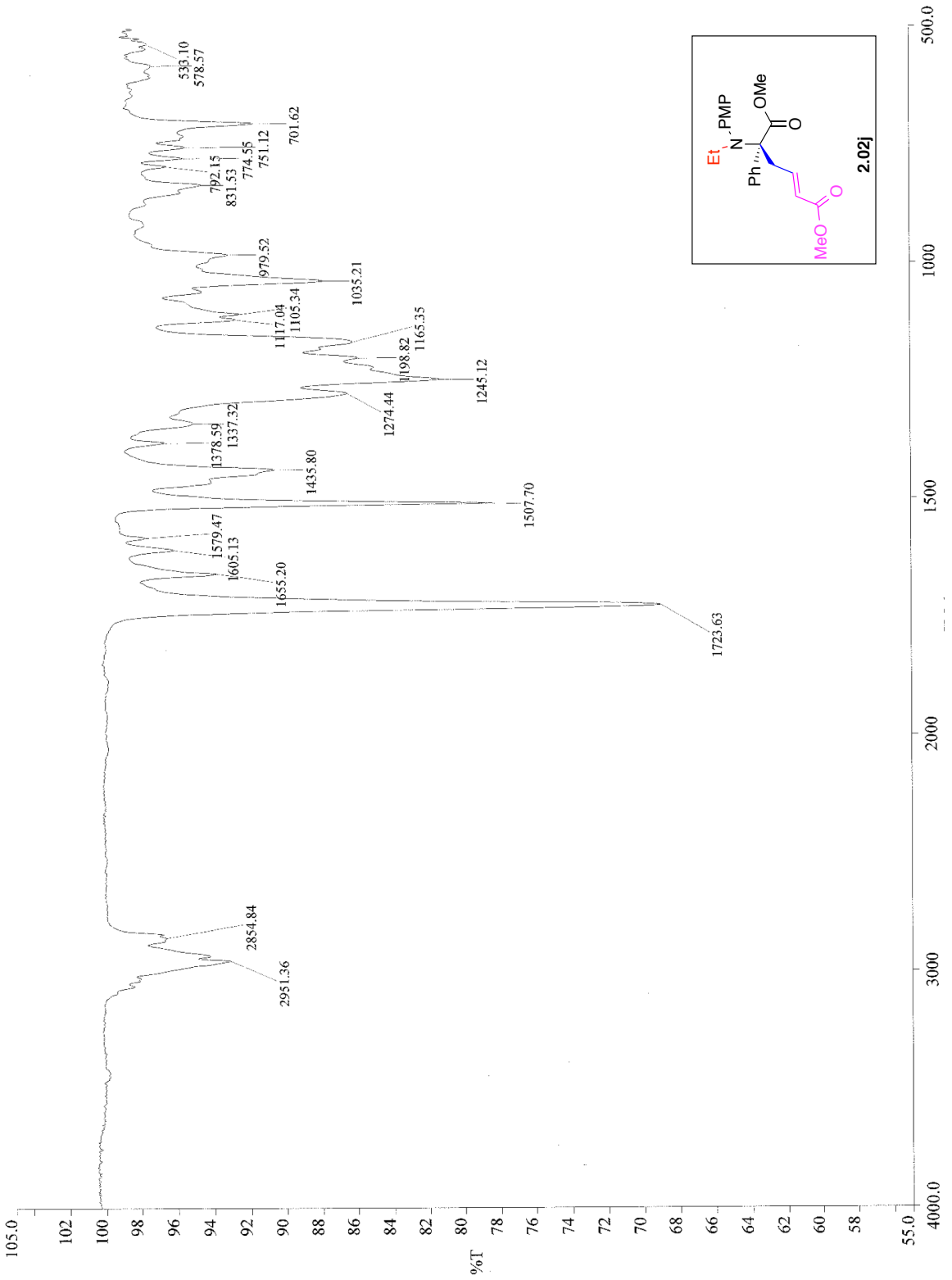



**Figure A. 2.02j _3** IR spectrum of compound **2.02j**

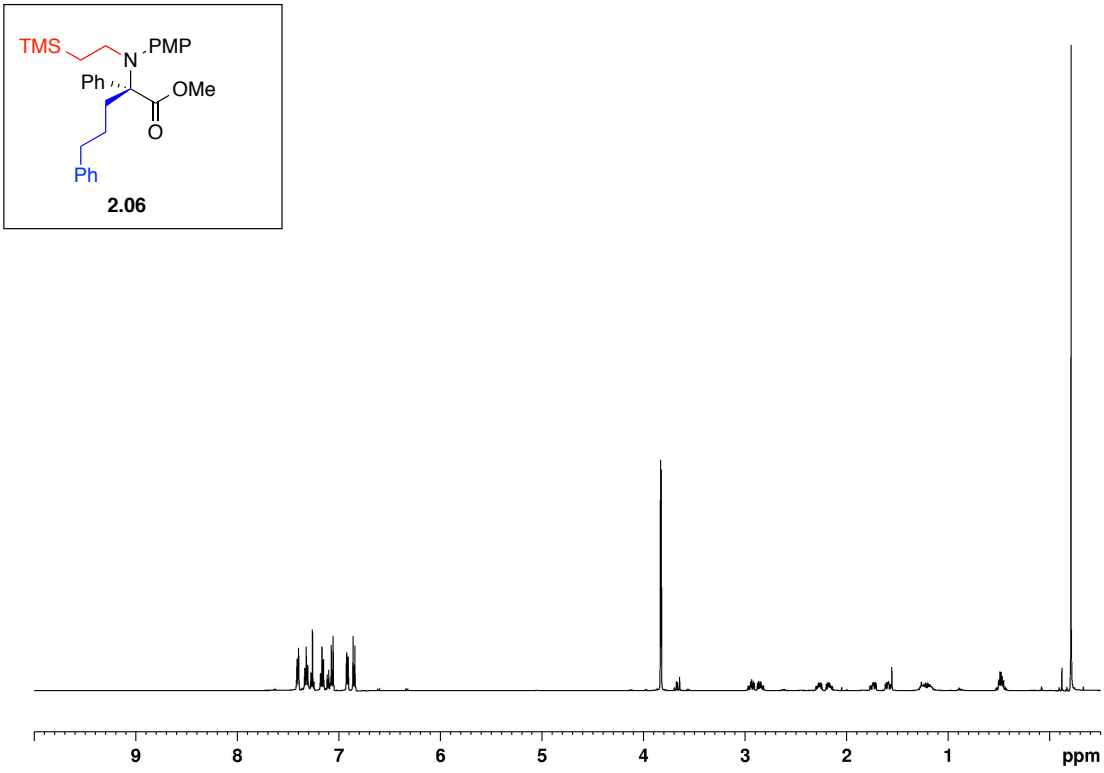



**Figure A. 2.06_1** $^{1}$H NMR spectrum of compound **2.06** (500 MHz, $CDCl_3$)

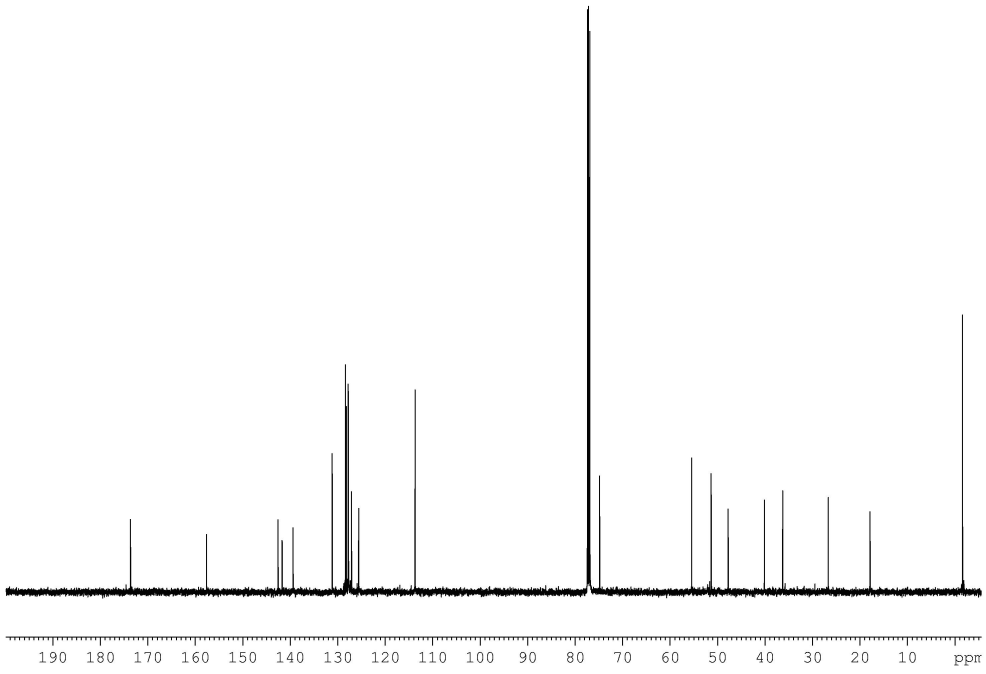



**Figure A. 2.06_2** $^{13}$C NMR spectrum of compound **2.06** (125 MHz, $CDCl_3$)

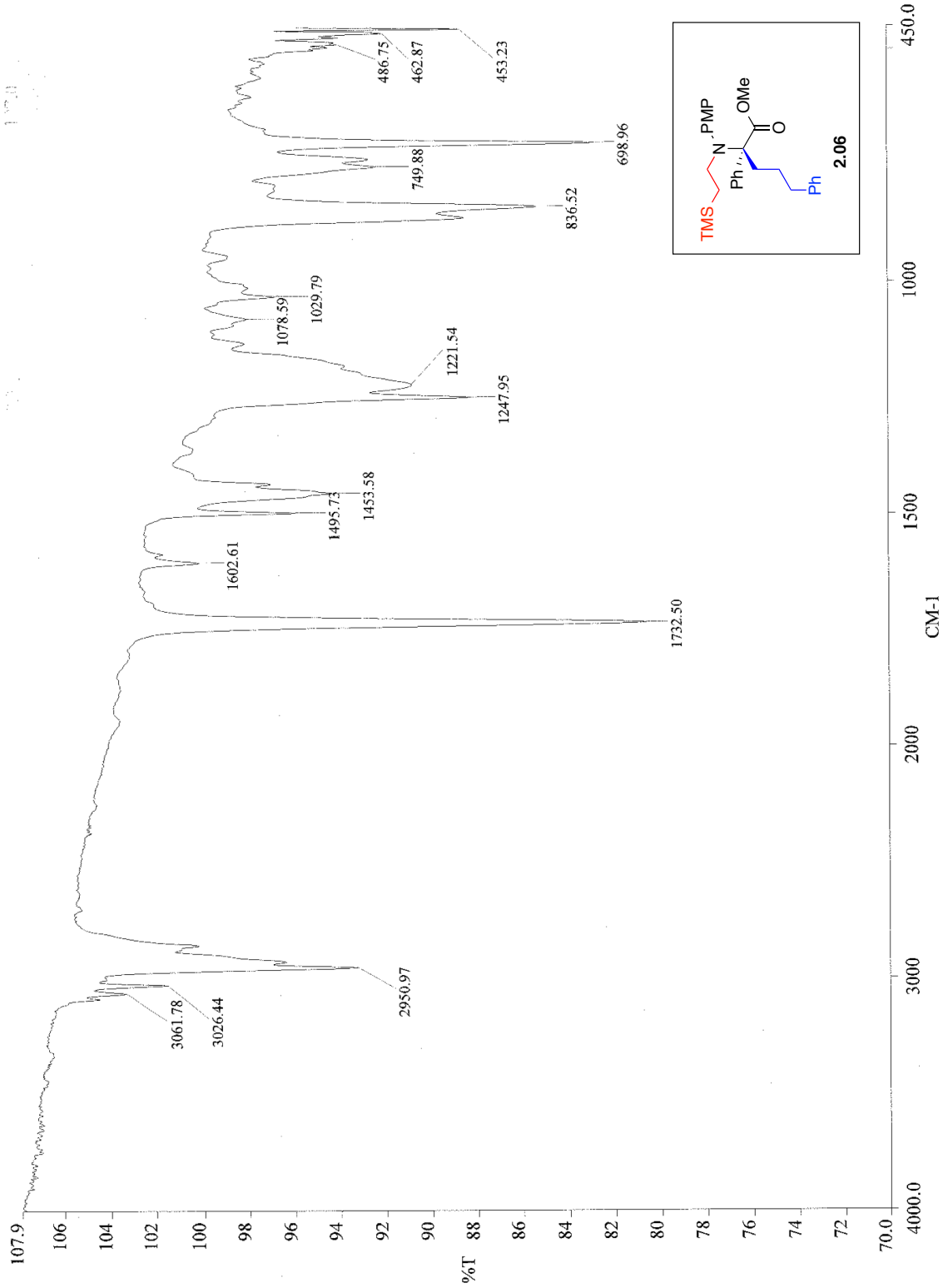



**Figure A. 2.06_3** IR spectrum of compound **2.06**

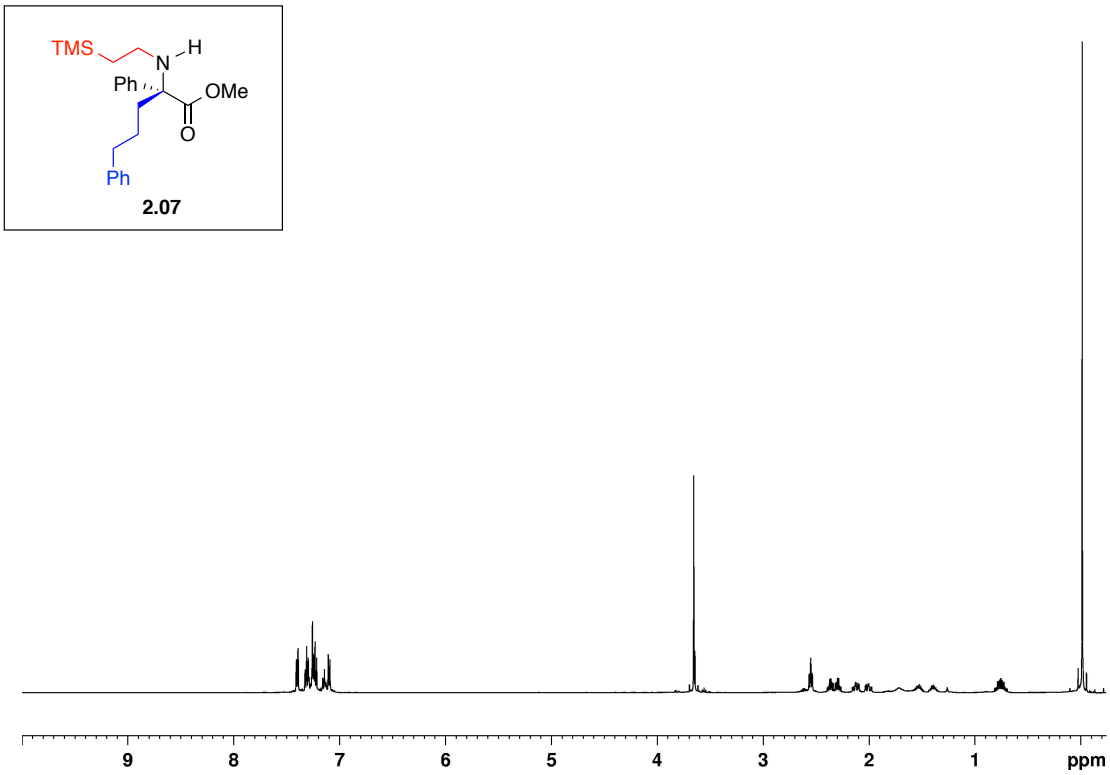



**Figure A. 2.07_1** $^{1}$H NMR spectrum of compound **2.07** (500 MHz, $CDCl_3$)

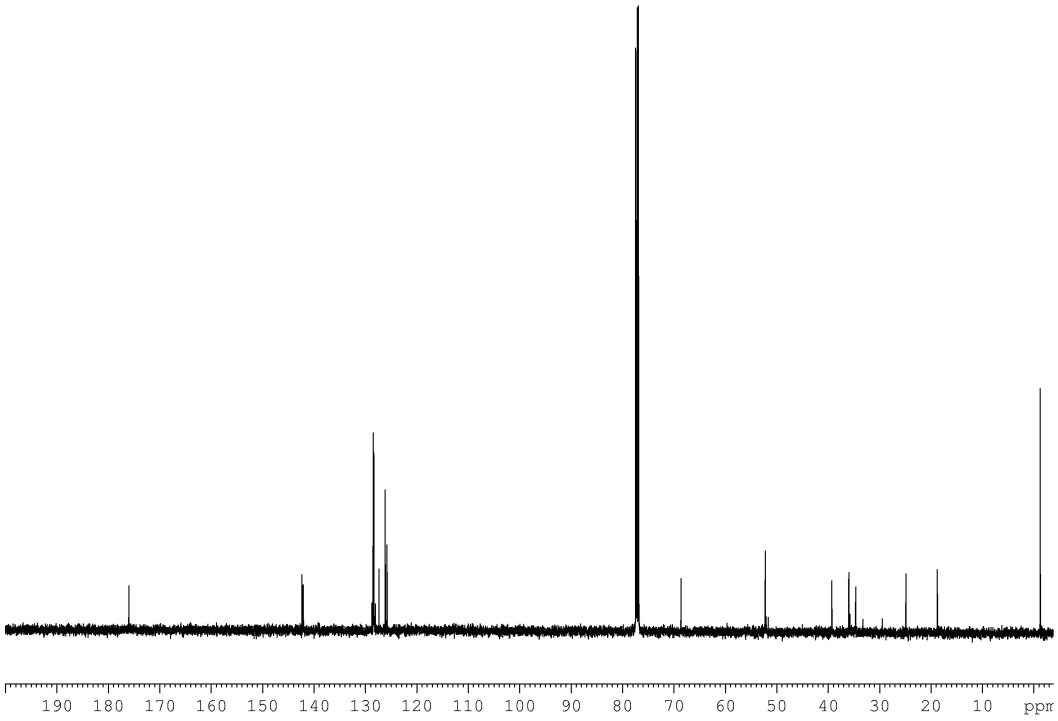



**Figure A. 2.07_2** $^{13}$C NMR spectrum of compound **2.07** (125 MHz, $CDCl_3$)

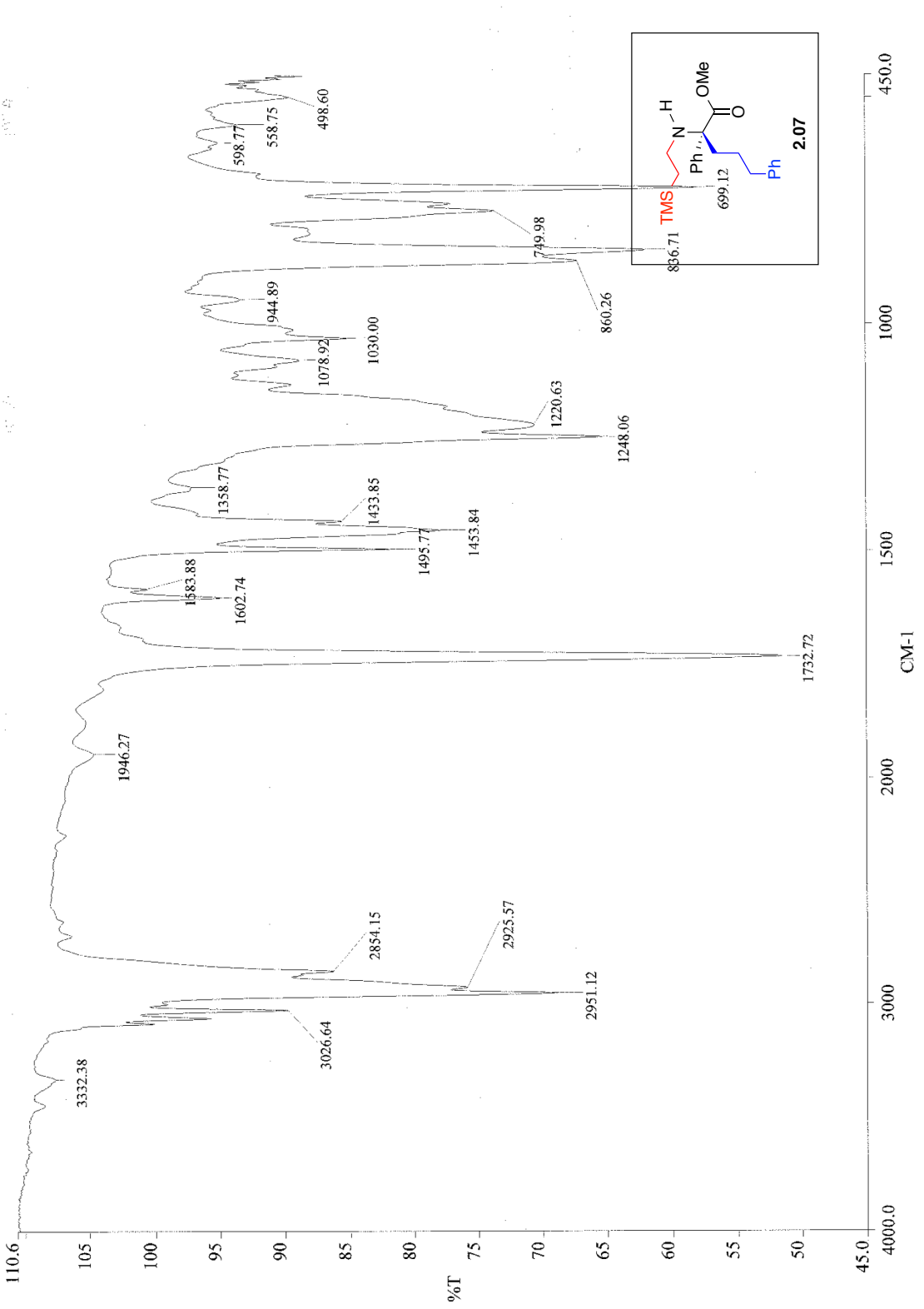



**Figure A. 2.07_3** IR spectrum of compound **2.07**

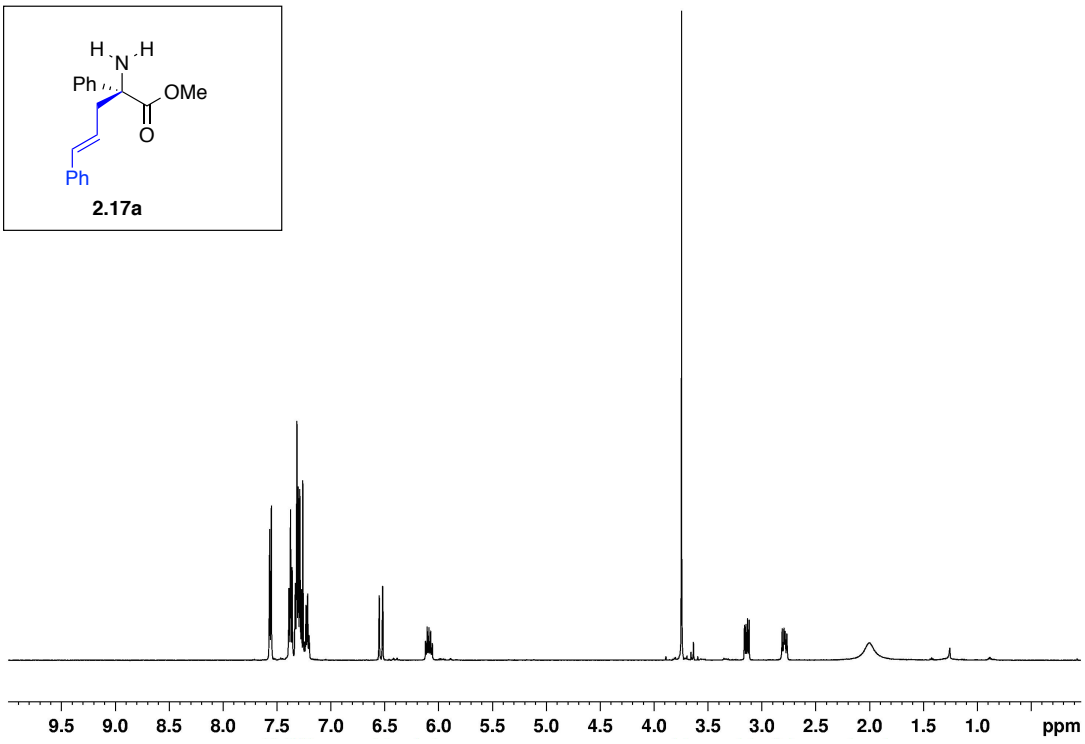



**Figure A. 2.17a_1** $^{1}$H NMR spectrum of compound **2.17a** (500 MHz, $CDCl_3$)

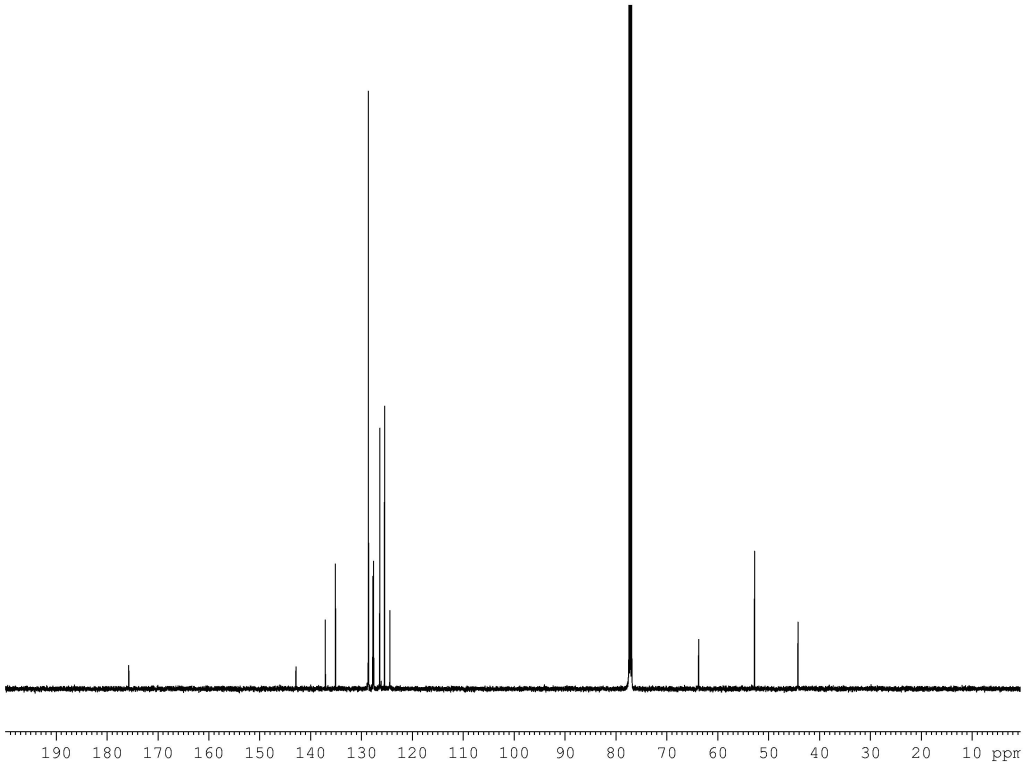



**Figure A. 2.17a_2** $^{13}$C NMR spectrum of compound **2.17a** (125 MHz, $CDCl_3$)

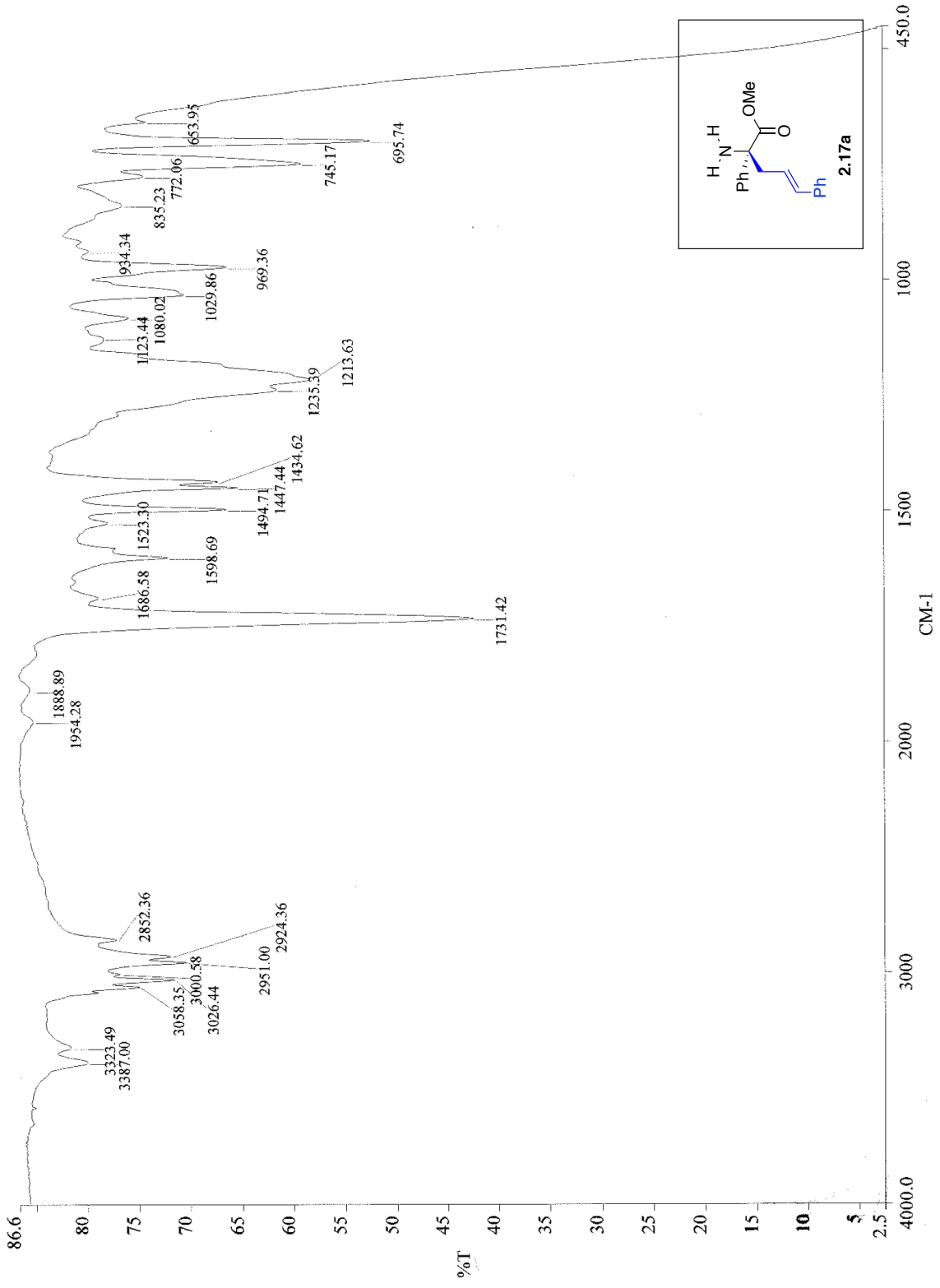



**Figure A. 2.17a_3** IR spectrum of compound **2.17a**

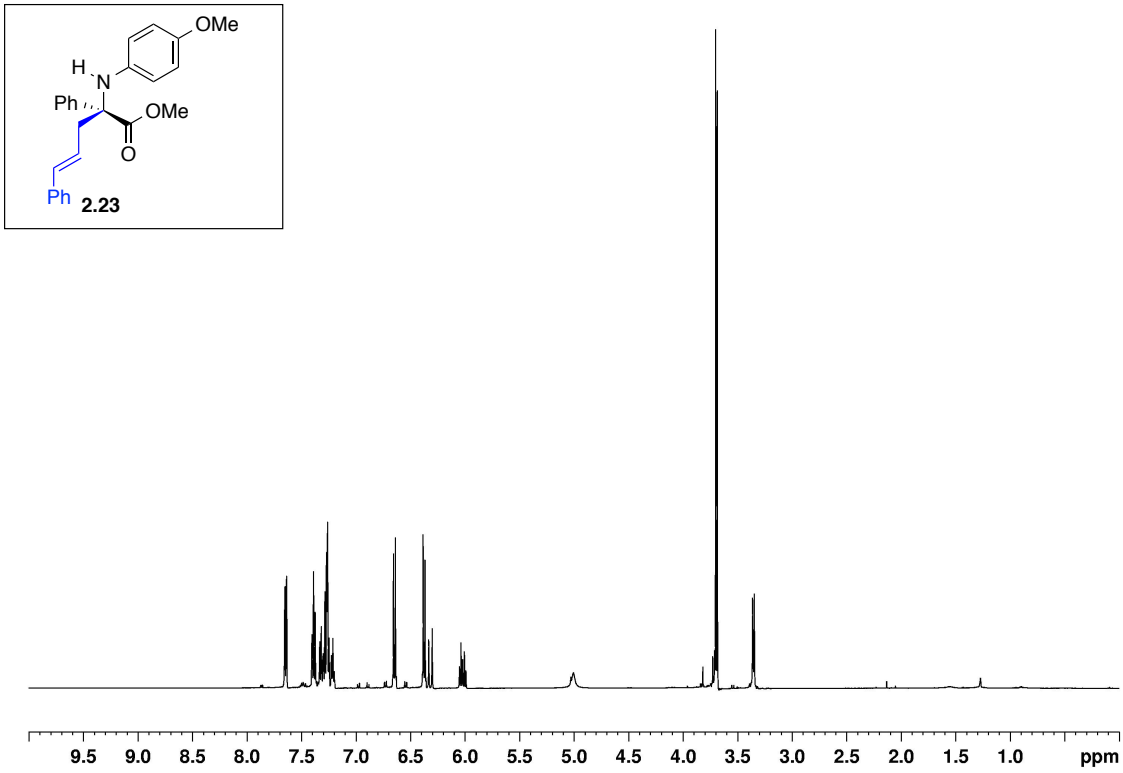



**Figure A. 2.23_1** $^{1}$H NMR spectrum of compound **2.23** (500 MHz, $CDCl_3$)

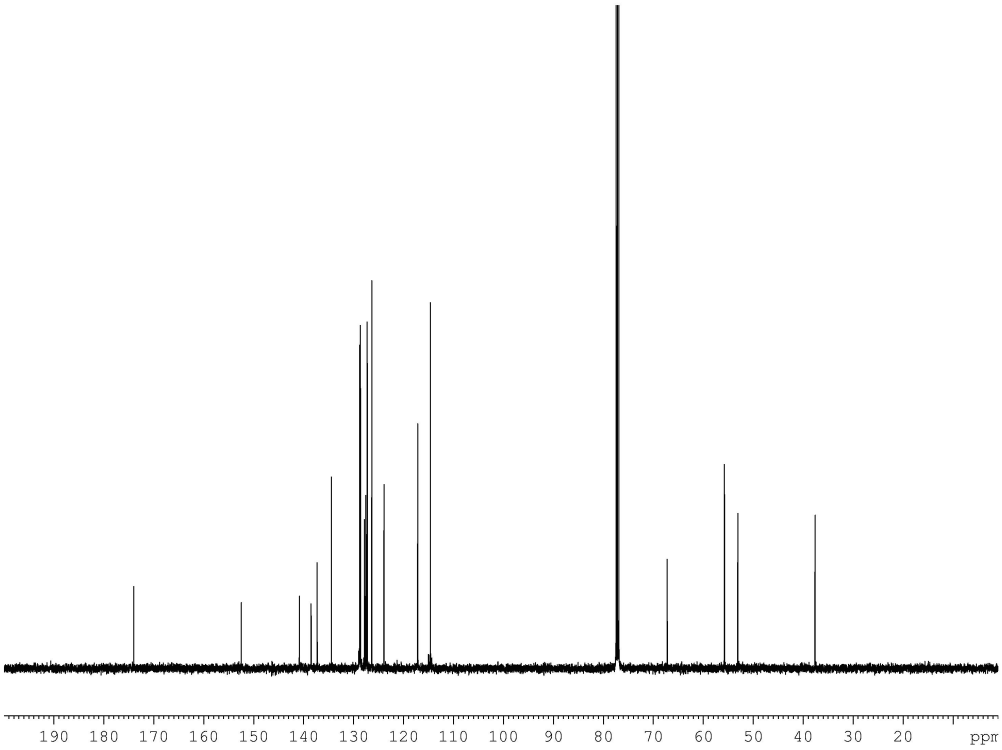



**Figure A. 2.23_2** $^{13}$C NMR spectrum of compound **2.23** (125 MHz, $CDCl_3$)

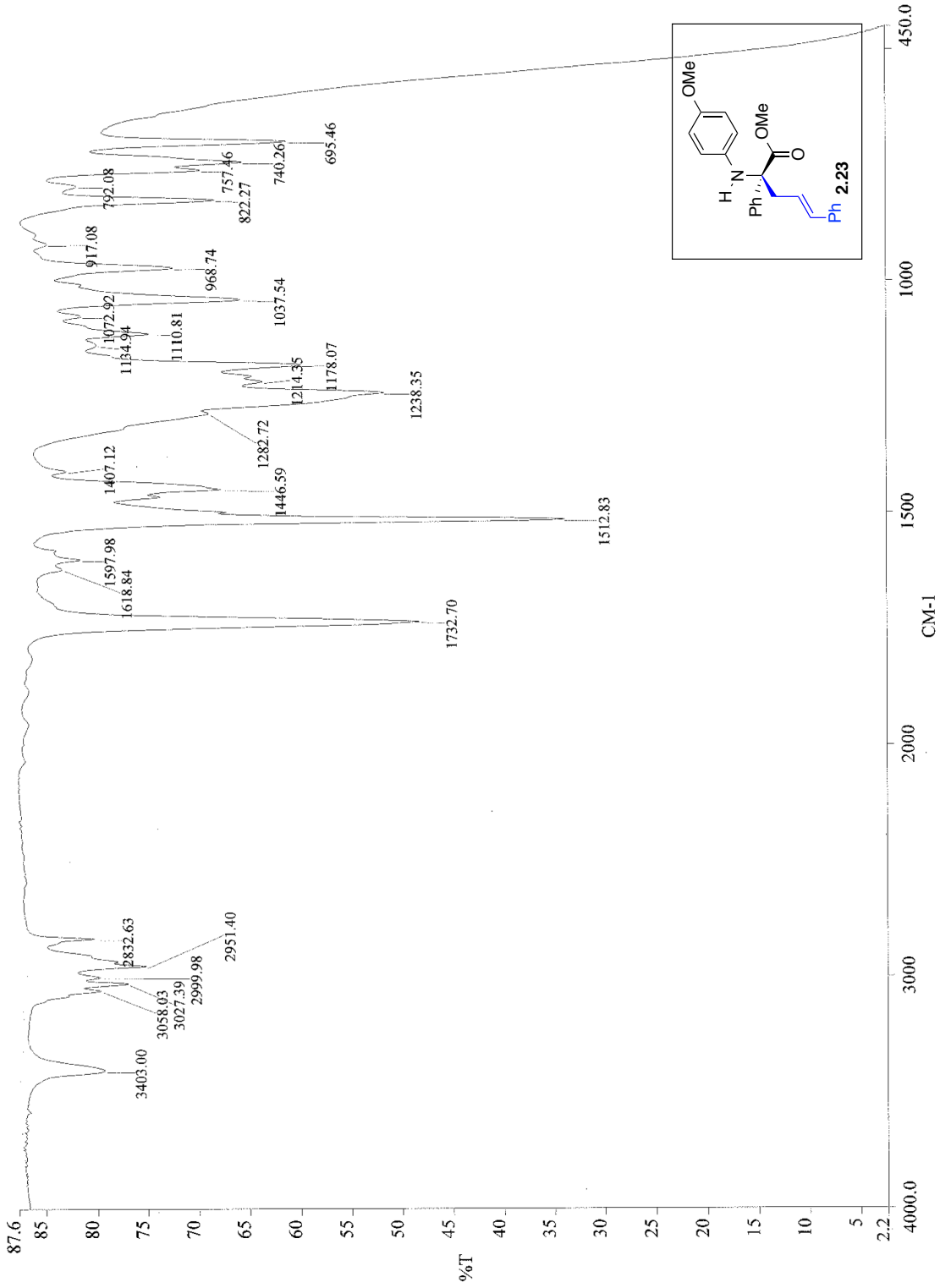



**Figure A. 2.23_3** IR spectrum of compound **2.23**

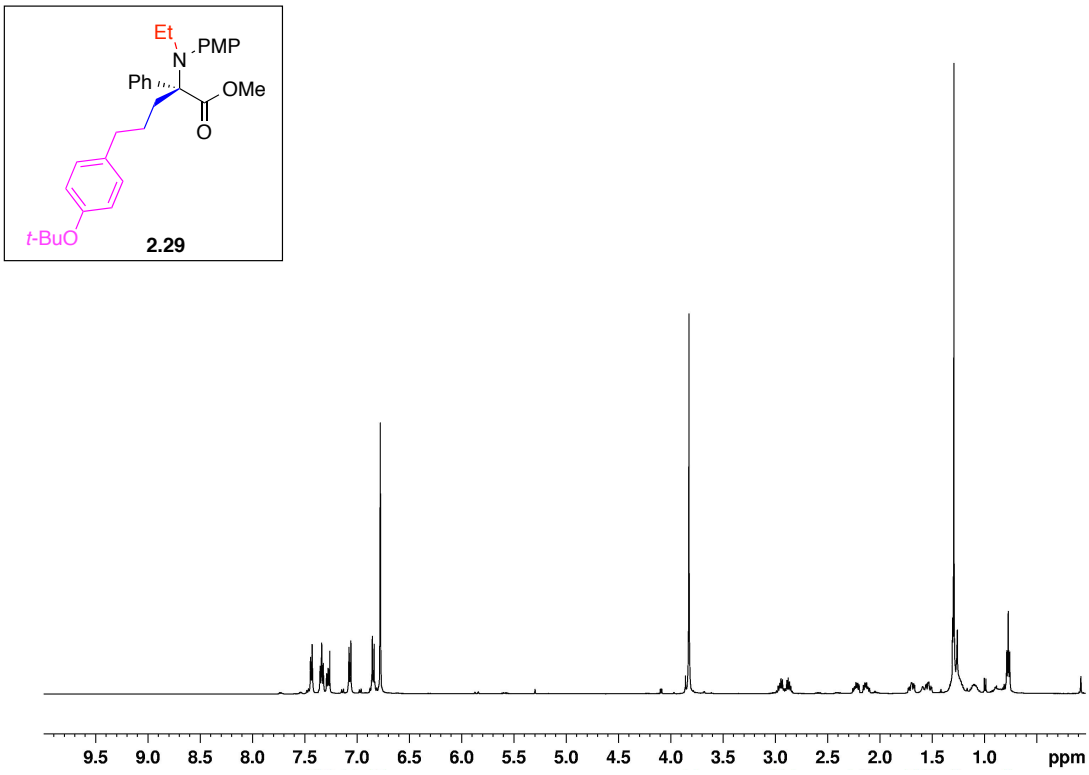



**Figure A. 2.29_1** $^{1}$H NMR spectrum of compound **2.29** (500 MHz, $CDCl_3$)

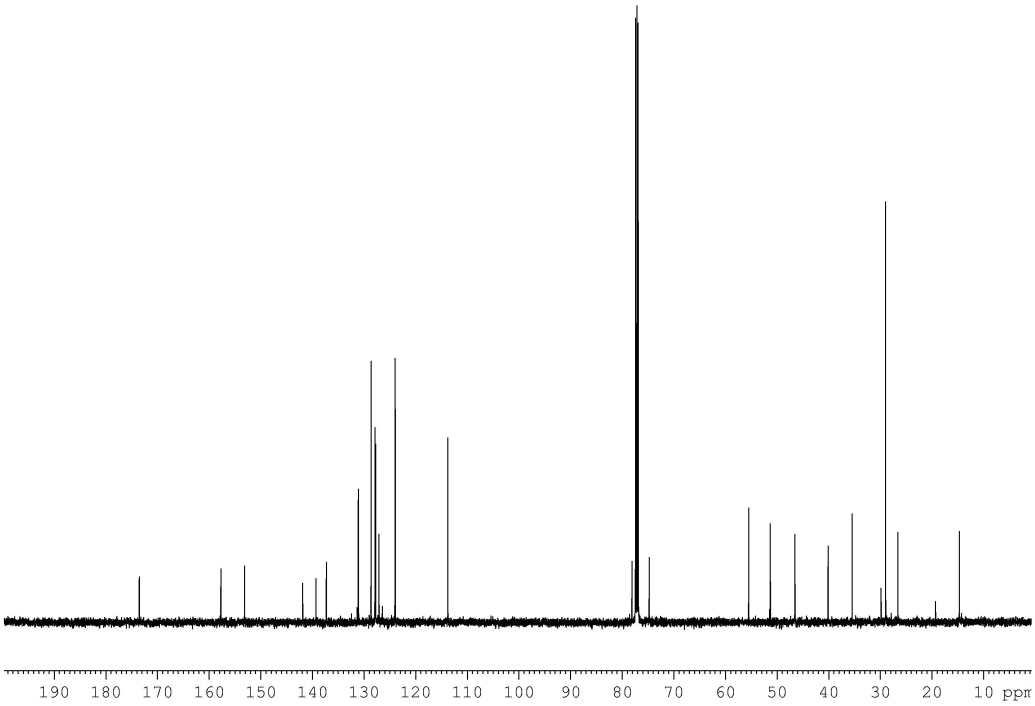



**Figure A. 2.29_2** $^{13}$C NMR spectrum of compound **2.29** (125 MHz, $CDCl_3$)

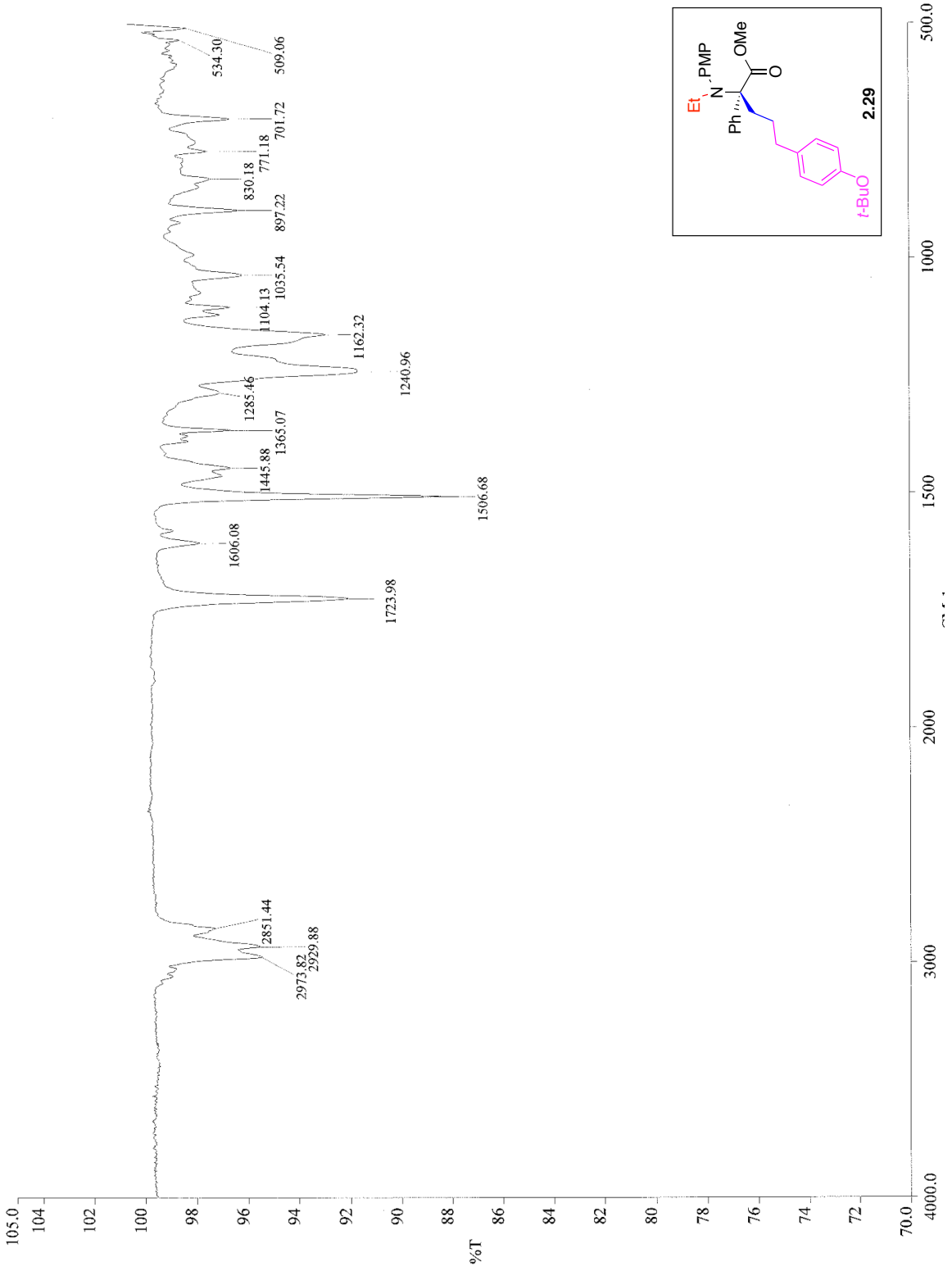



**Figure A. 2.29_3** IR spectrum of compound **2.29**

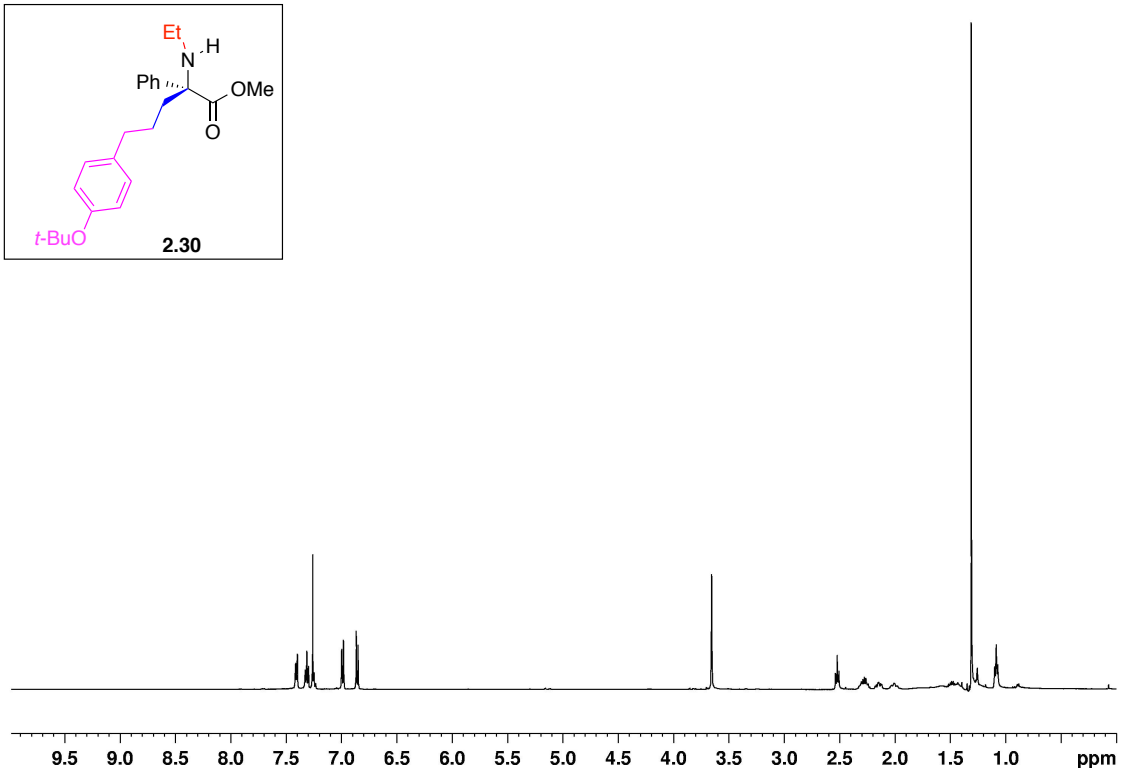



**Figure A. 2.30_1** $^{1}$H NMR spectrum of compound **2.30** (500 MHz, $CDCl_3$)

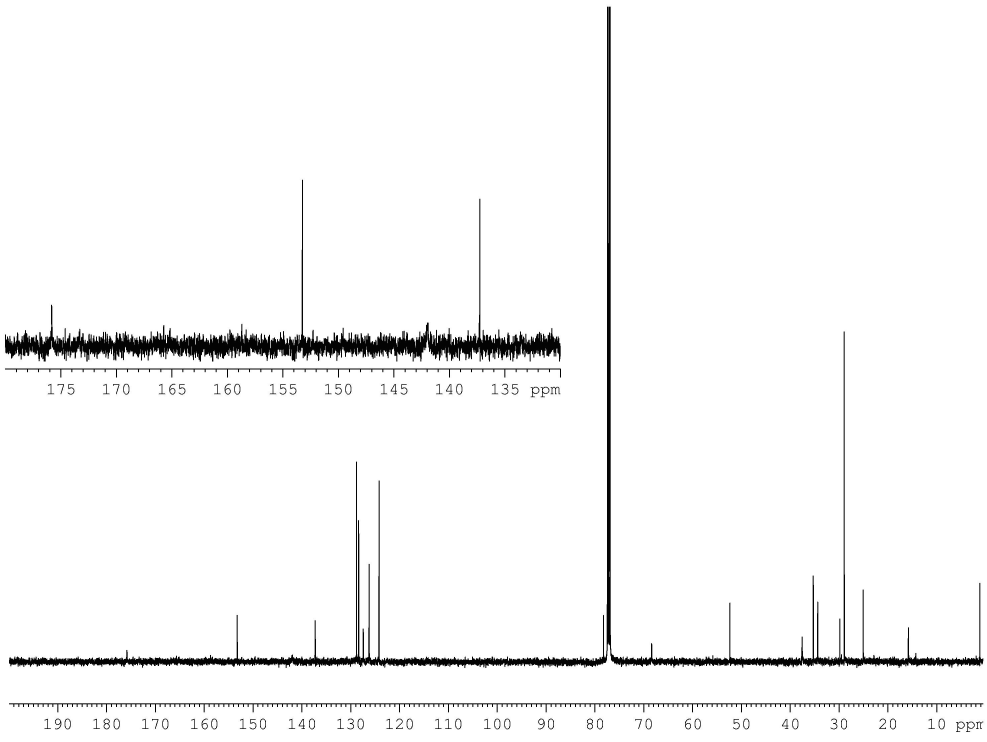



**Figure A. 2.30_2** $^{13}$C NMR spectrum of compound **2.30** (125 MHz, $CDCl_3$)

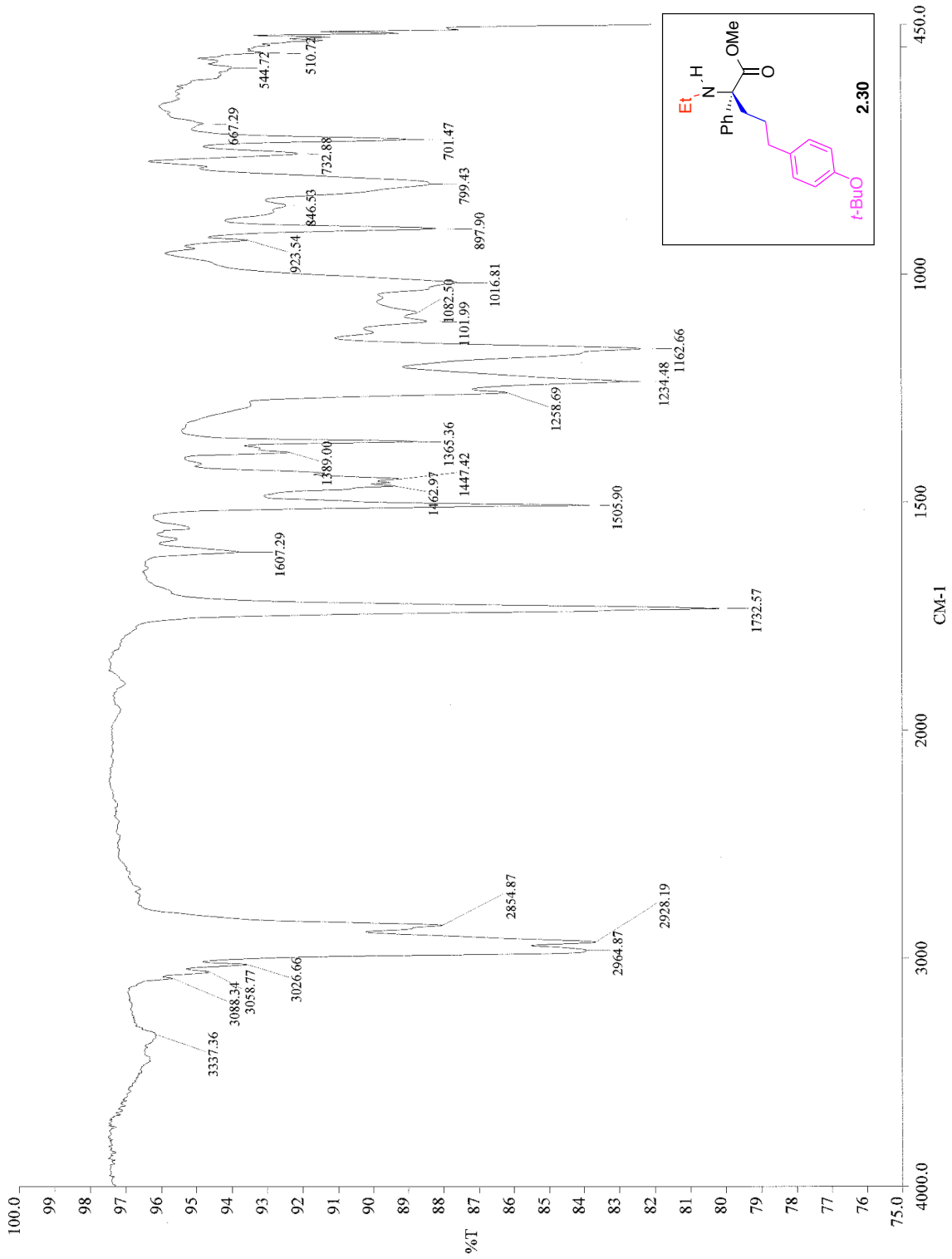



**Figure A. 2.30_3** IR spectrum of compound **2.30**

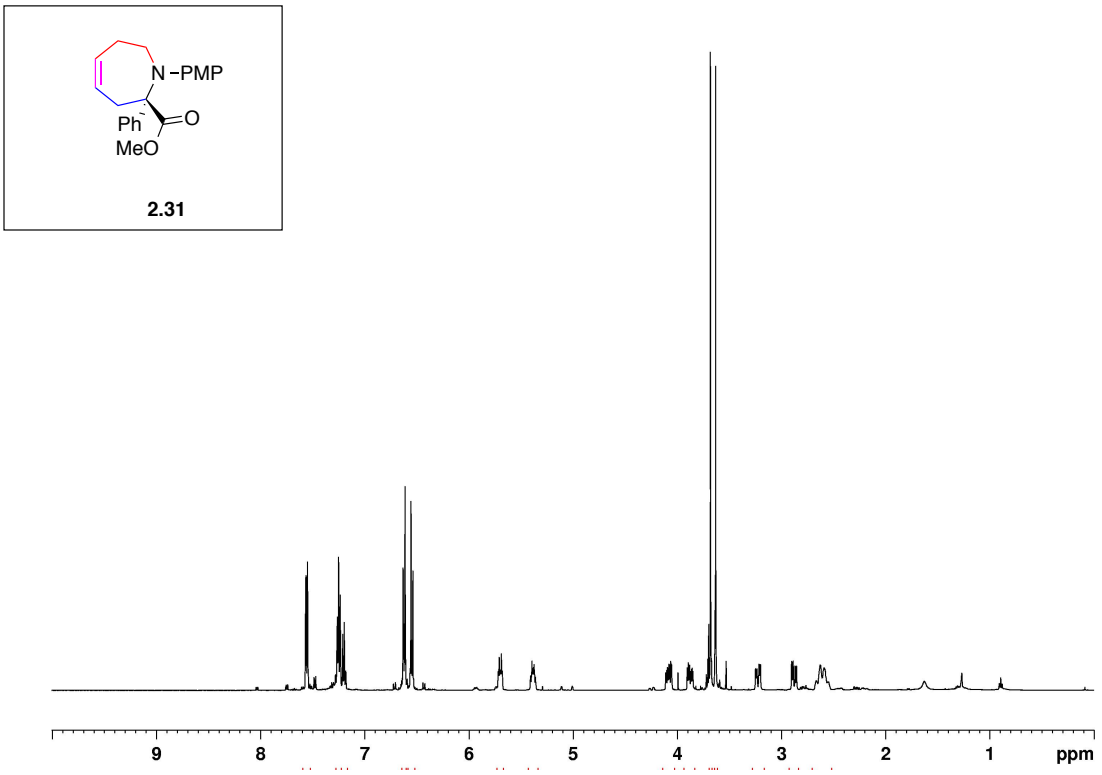



**Figure A. 2.31_1** $^{1}$H NMR spectrum of compound **2.31** (500 MHz, $CDCl_3$)

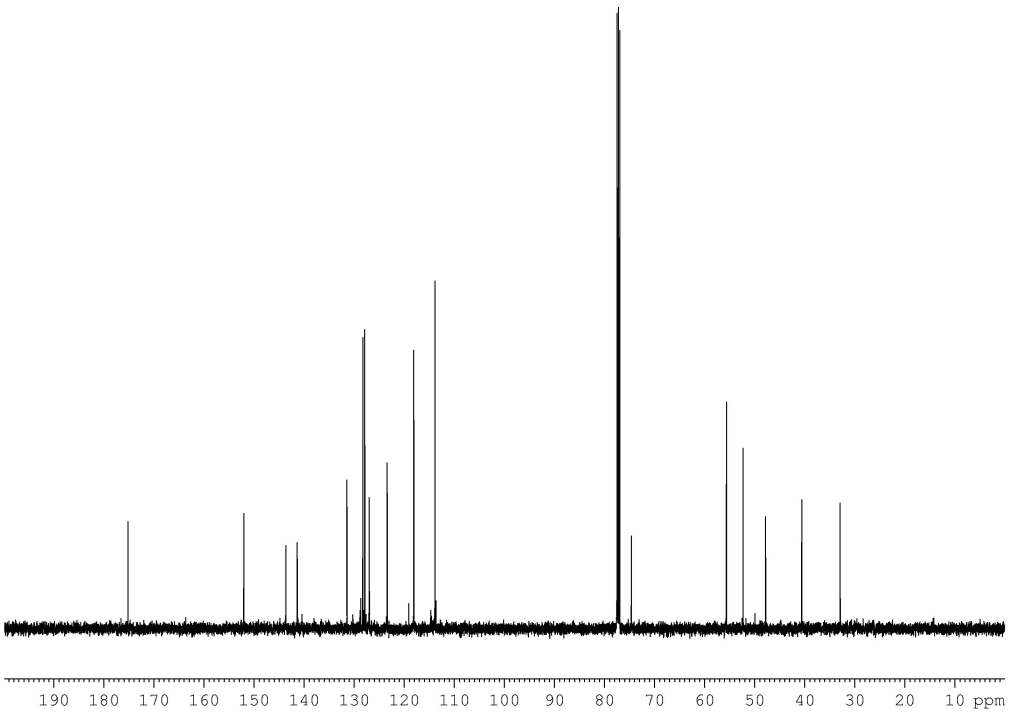



**Figure A. 2.31_2** $^{13}$C NMR spectrum of compound **2.31** (125 MHz, $CDCl_3$)

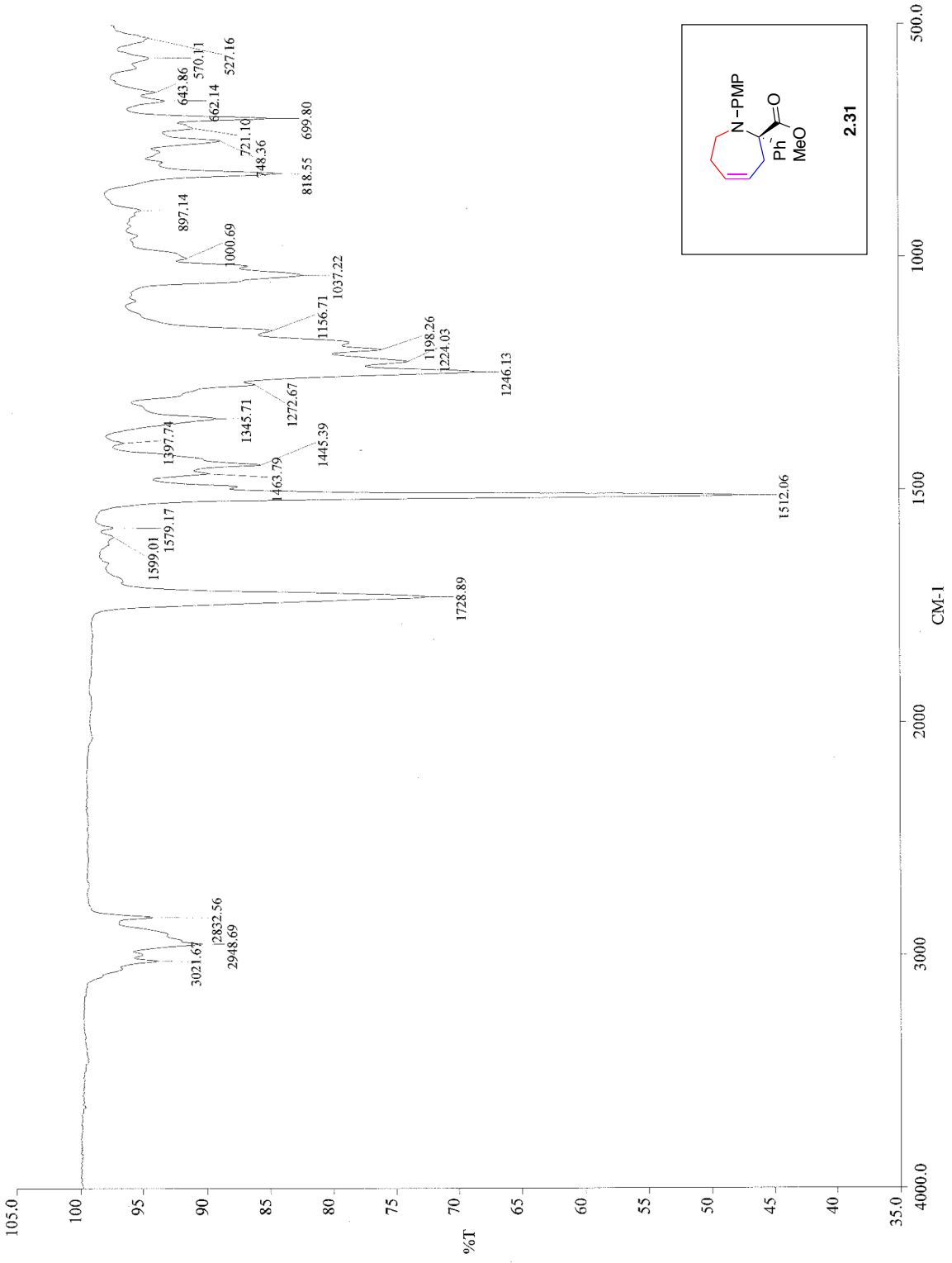



**Figure A. 2.31_3** IR spectrum of compound **2.31**

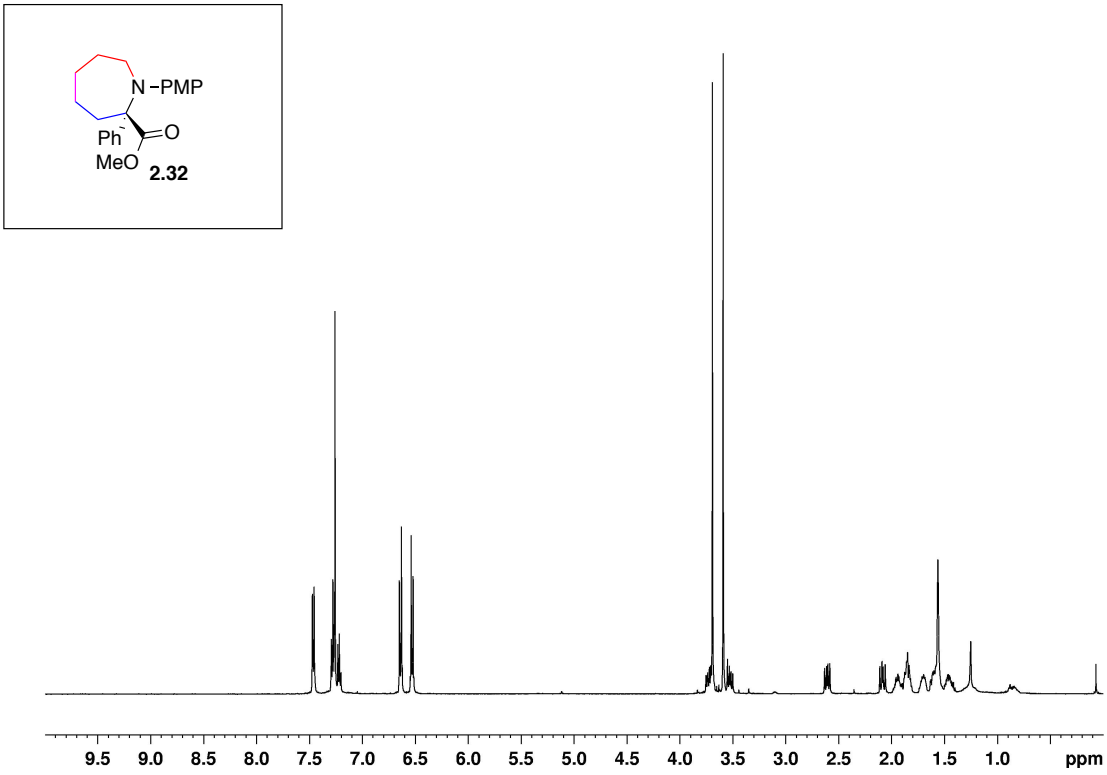



**Figure A. 2.32_1** $^{1}$H NMR spectrum of compound **2.32** (500 MHz, $CDCl_3$)

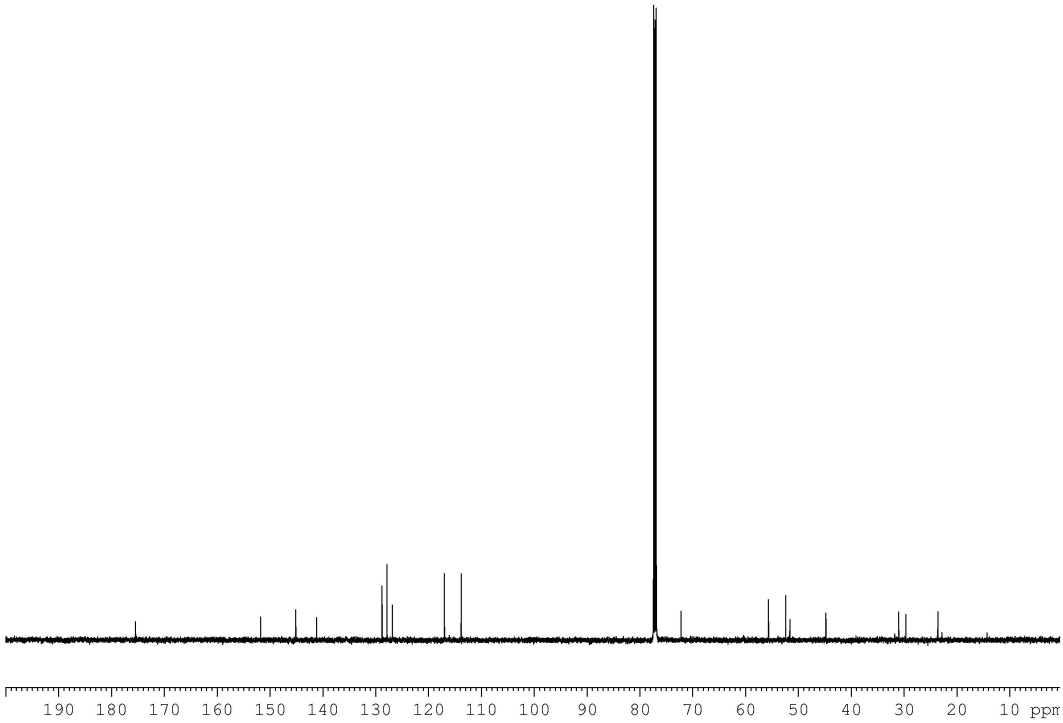



**Figure A. 2.32_2** $^{13}$C NMR spectrum of compound **2.32** (125 MHz, $CDCl_3$)

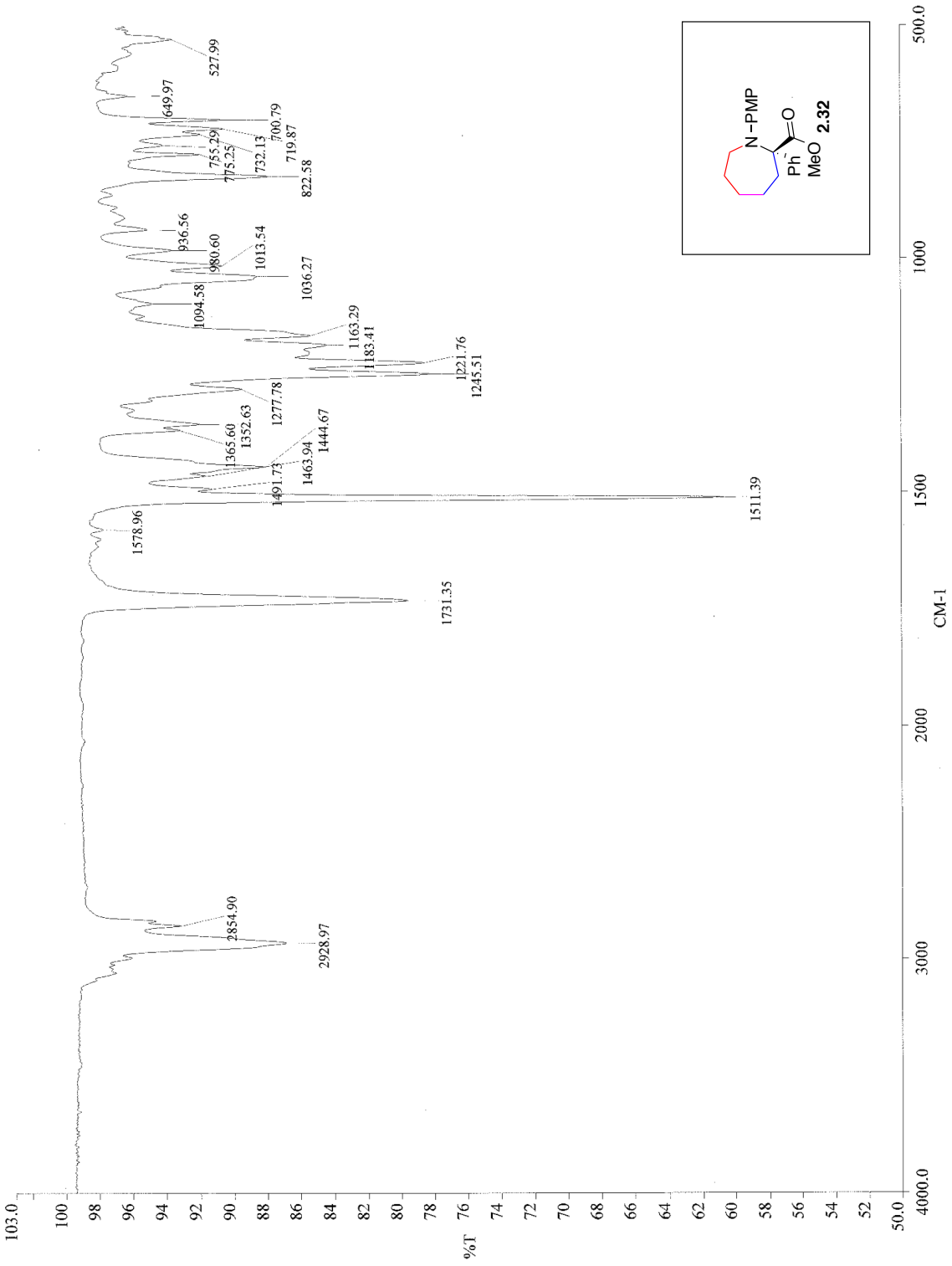



**Figure A. 2.32_3** IR spectrum of compound **2.32**

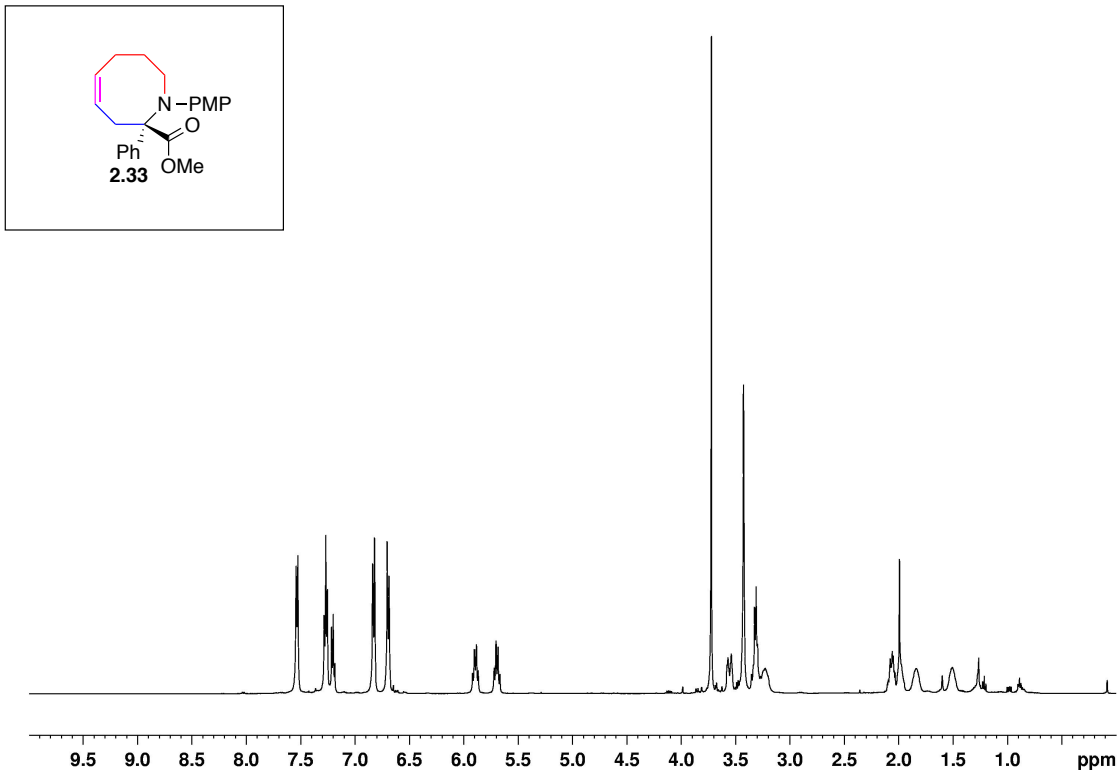



**Figure A. 2.33_1** $^{1}$H NMR spectrum of compound **2.33** (500 MHz, $CDCl_3$)

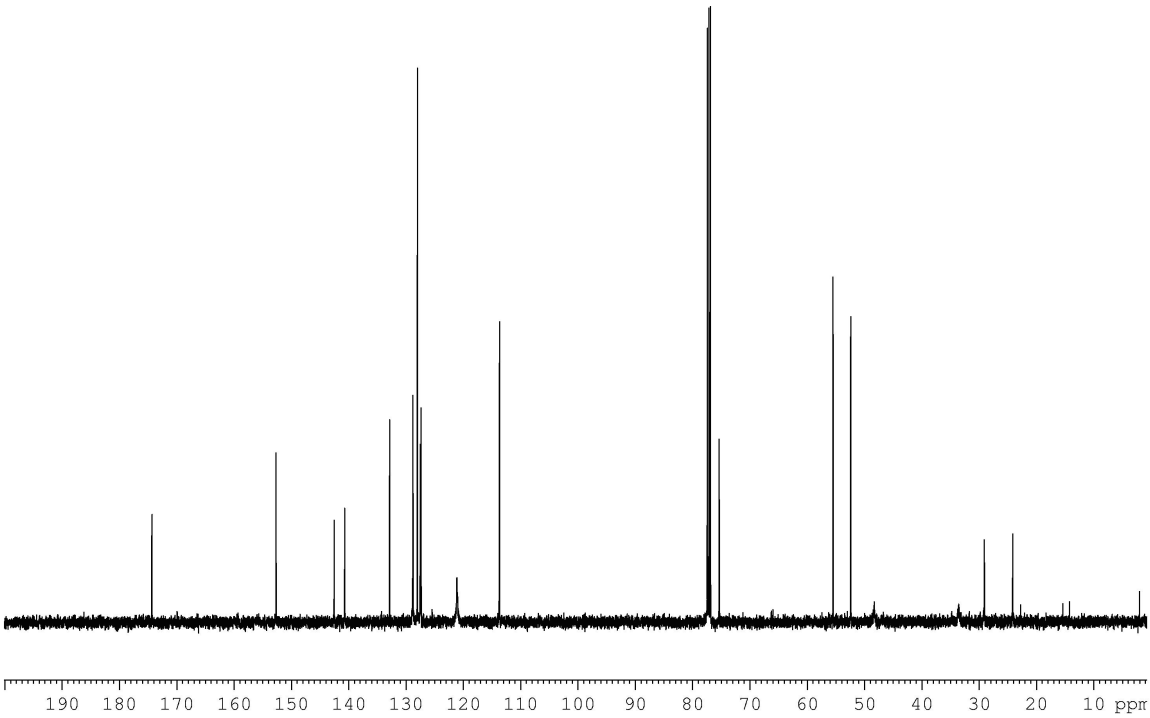



**Figure A. 2.33_2** $^{13}$C NMR spectrum of compound **2.33** (125 MHz, $CDCl_3$)

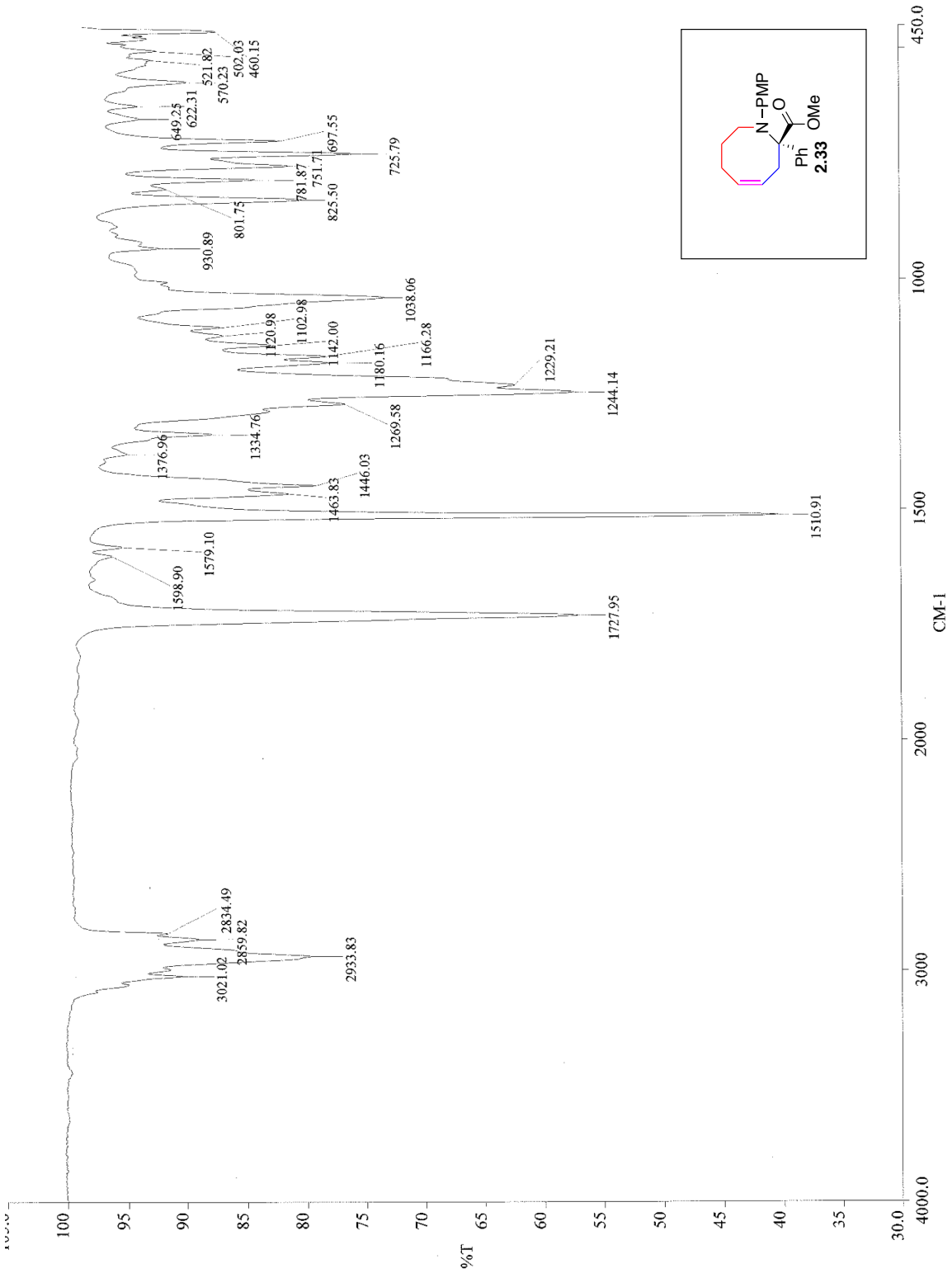



**Figure A. 2.33_3** IR spectrum of compound **2.33**

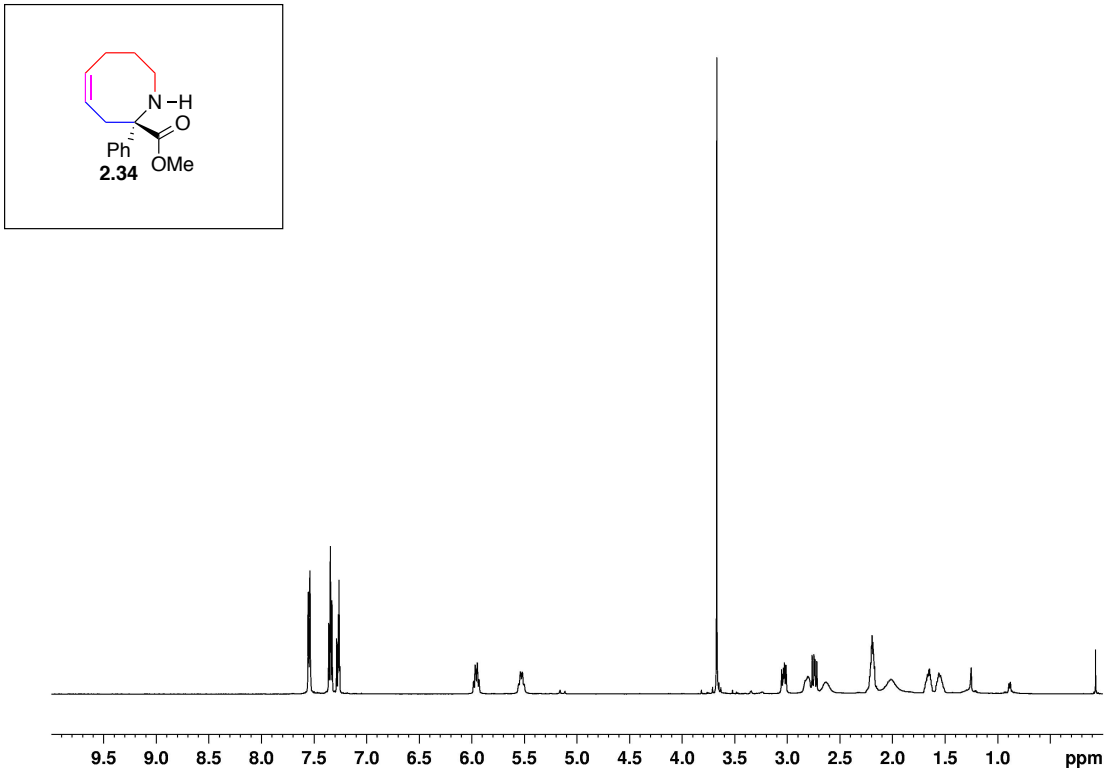



**Figure A. 2.34_1** $^{1}$H NMR spectrum of compound **2.34** (500 MHz, $CDCl_3$)

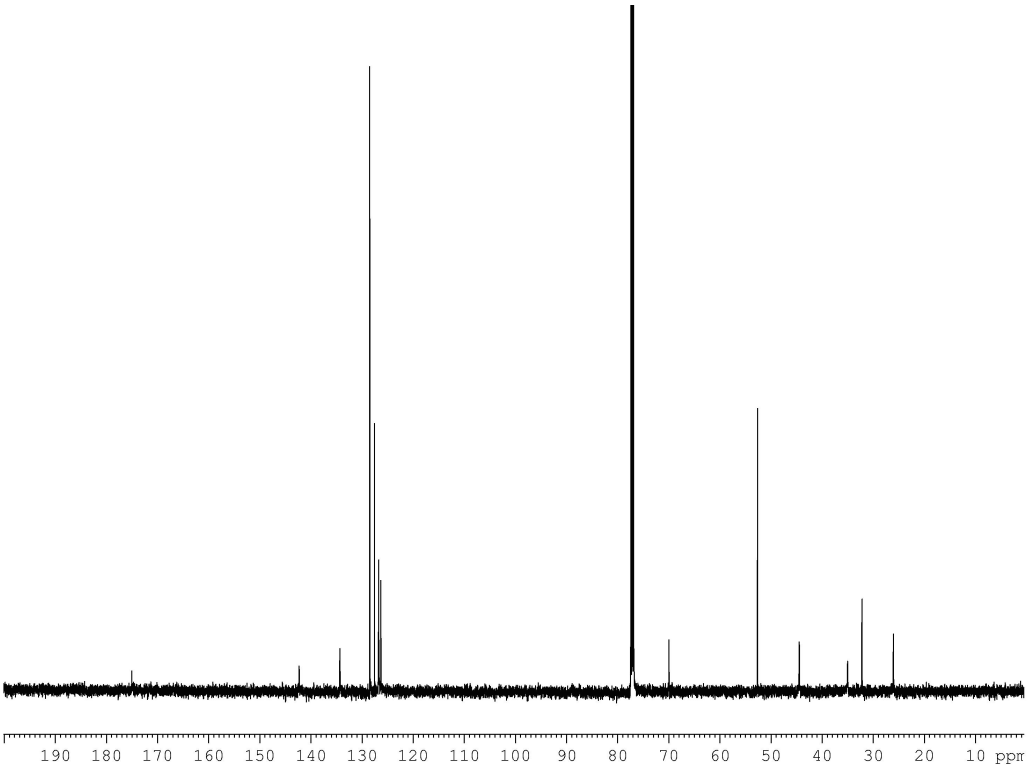



**Figure A. 2.34_2** $^{13}$C NMR spectrum of compound **2.34** (125 MHz, $CDCl_3$)

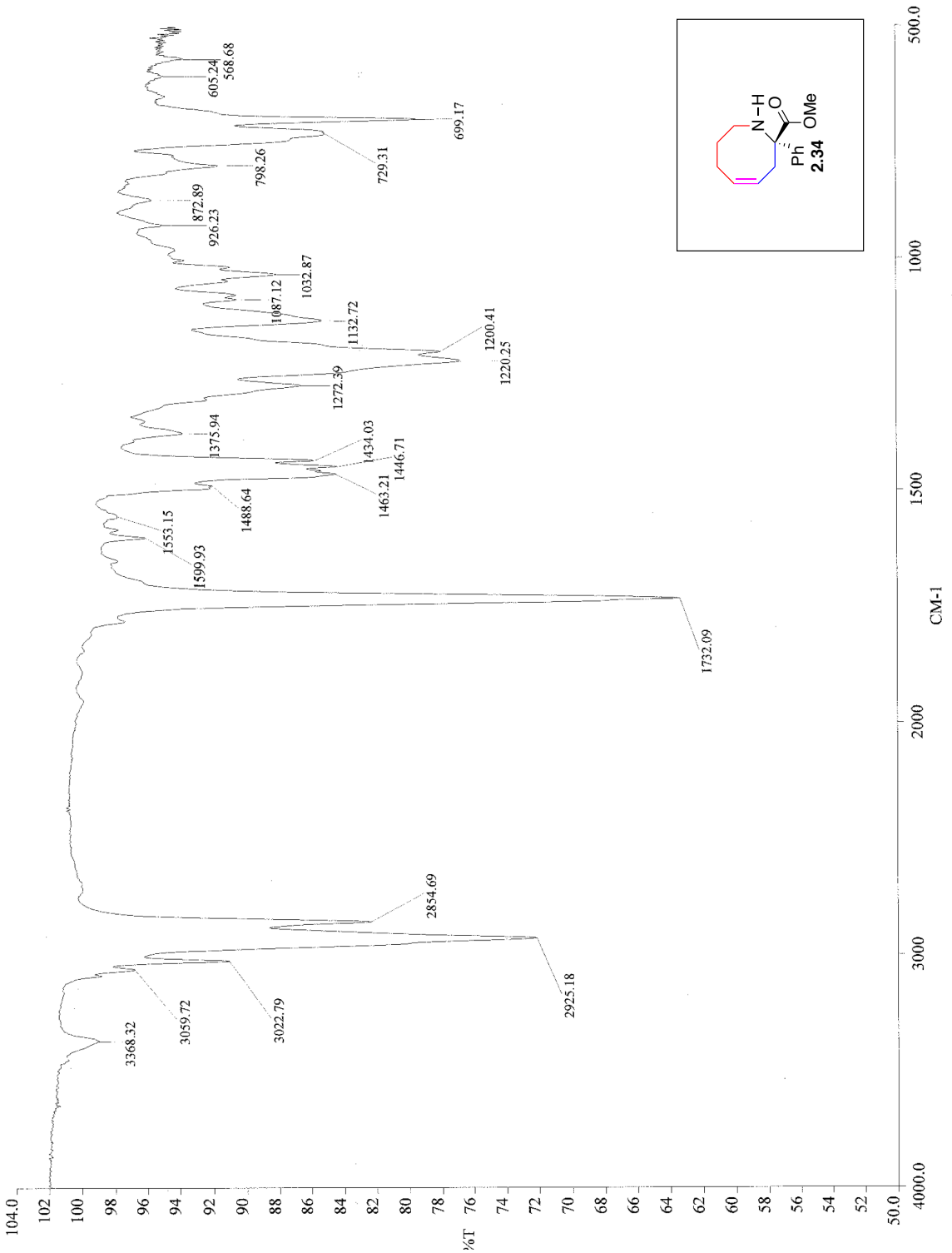



**Figure A. 2.34_3** IR spectrum of compound **2.34**

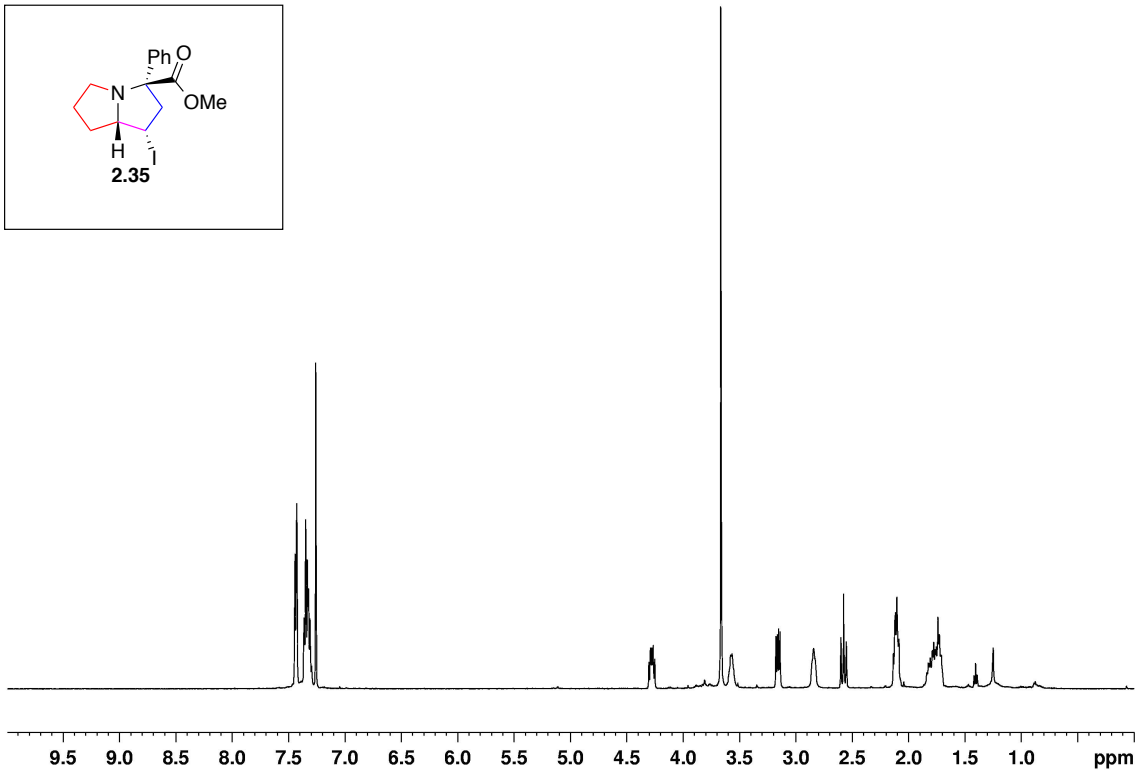



**Figure A. 2.35_1** $^{1}$H NMR spectrum of compound **2.35** (500 MHz, $CDCl_3$)

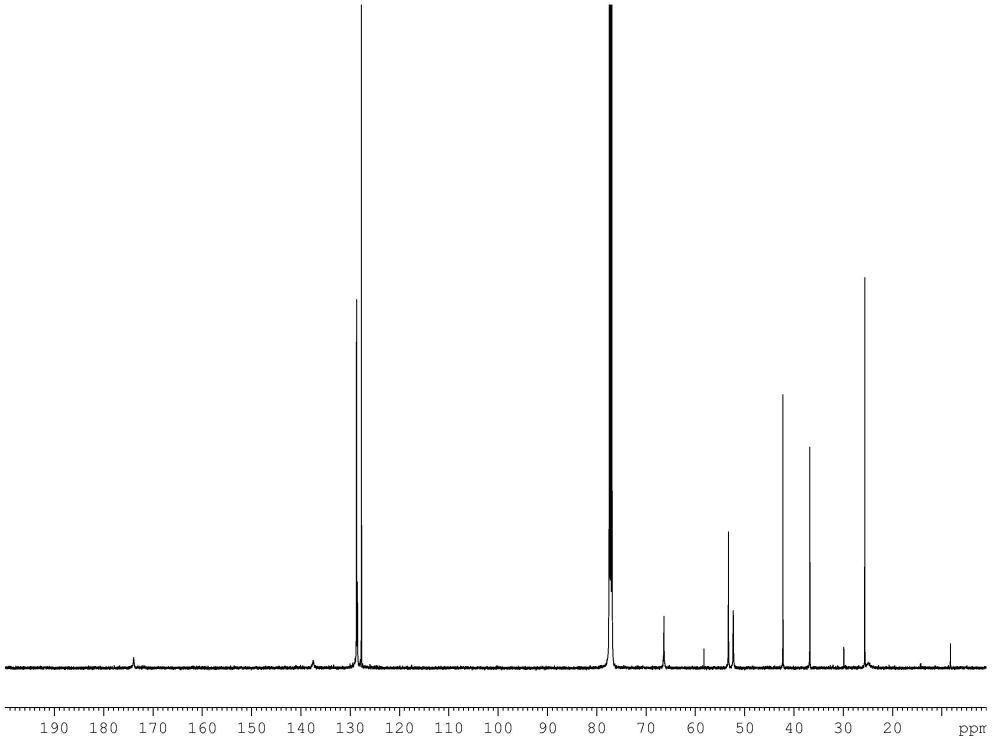



**Figure A. 2.35_2** $^{13}$C NMR spectrum of compound **2.35** (125 MHz, $CDCl_3$)

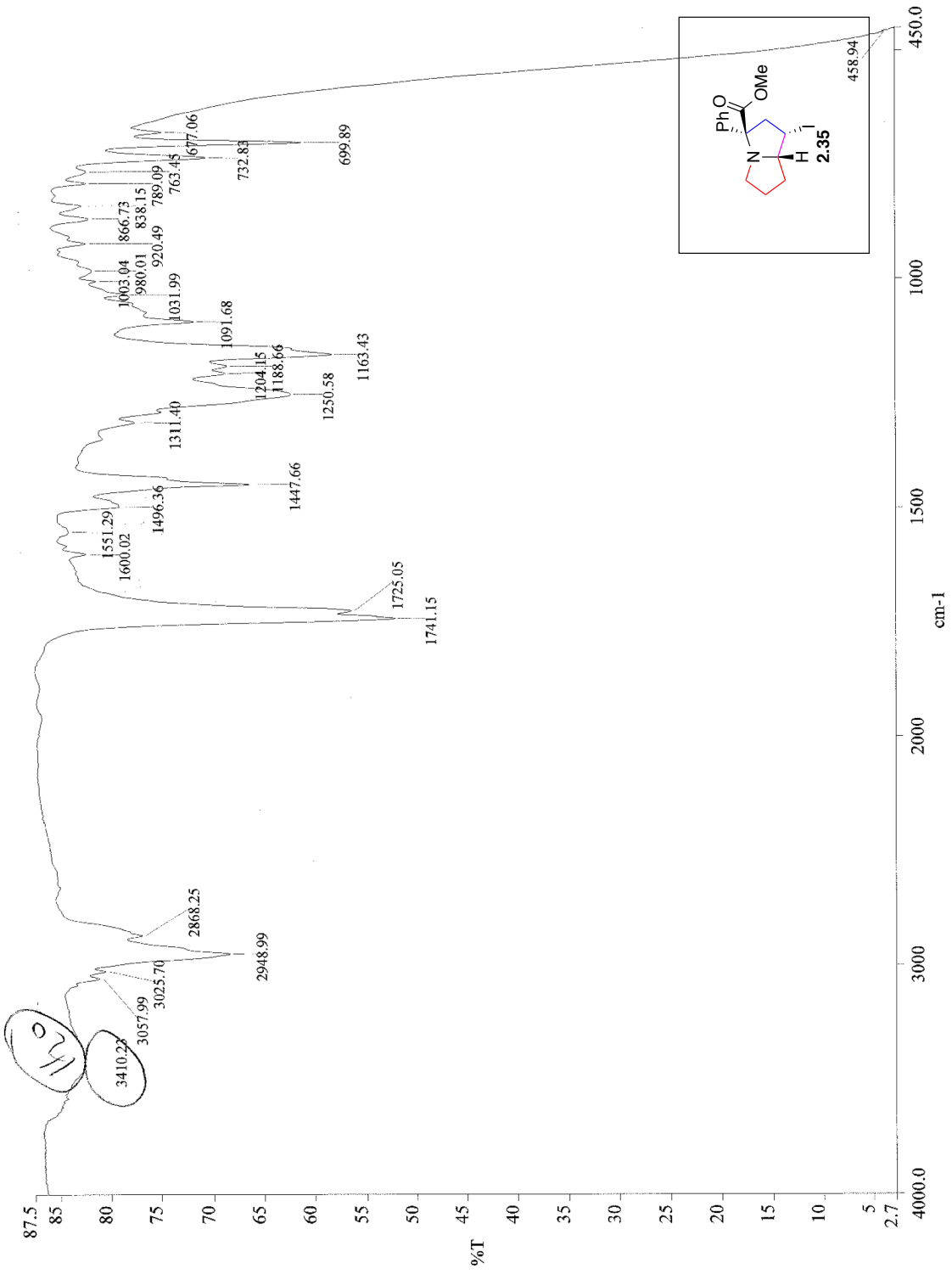



**Figure A. 2.35_3** IR spectrum of compound **2.35**

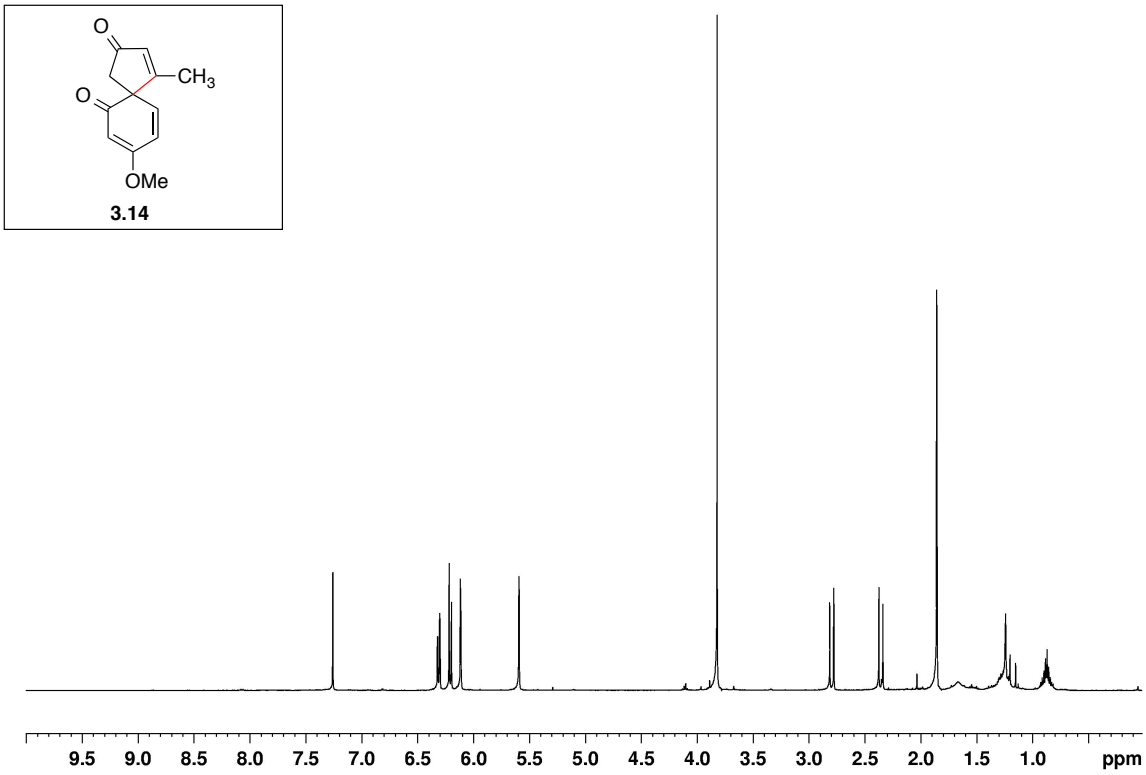



**Figure A. 3.14_1** $^{1}$H NMR spectrum of compound **3.14** (500 MHz, $CDCl_3$)

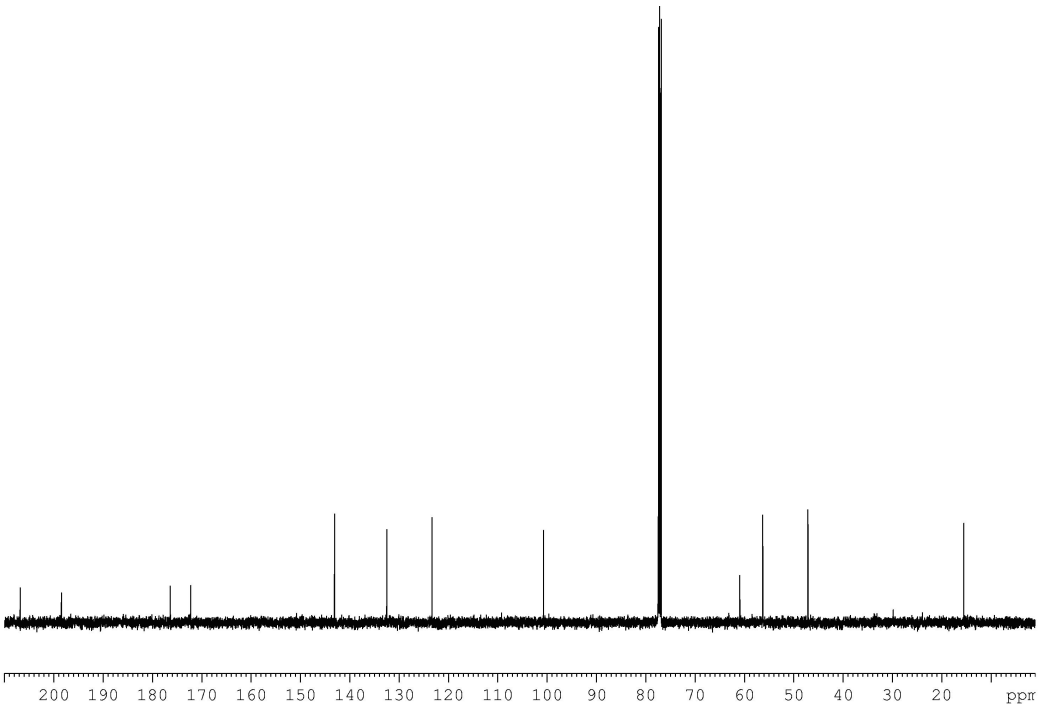



**Figure A. 3.14_2** $^{13}$C NMR spectrum of compound **3.14** (125 MHz, $CDCl_3$)

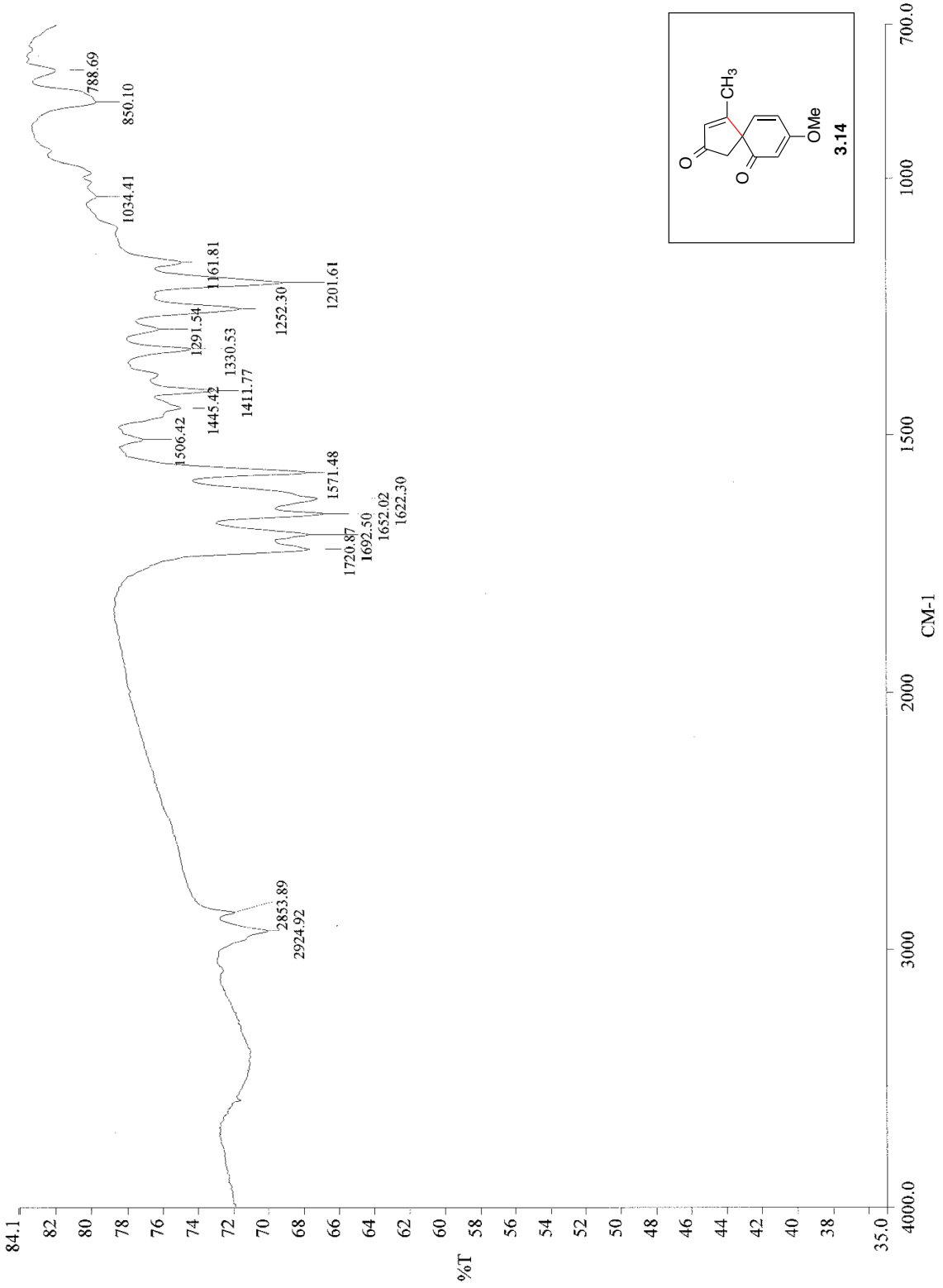



**Figure A. 3.14_3** IR spectrum of compound **3.14**

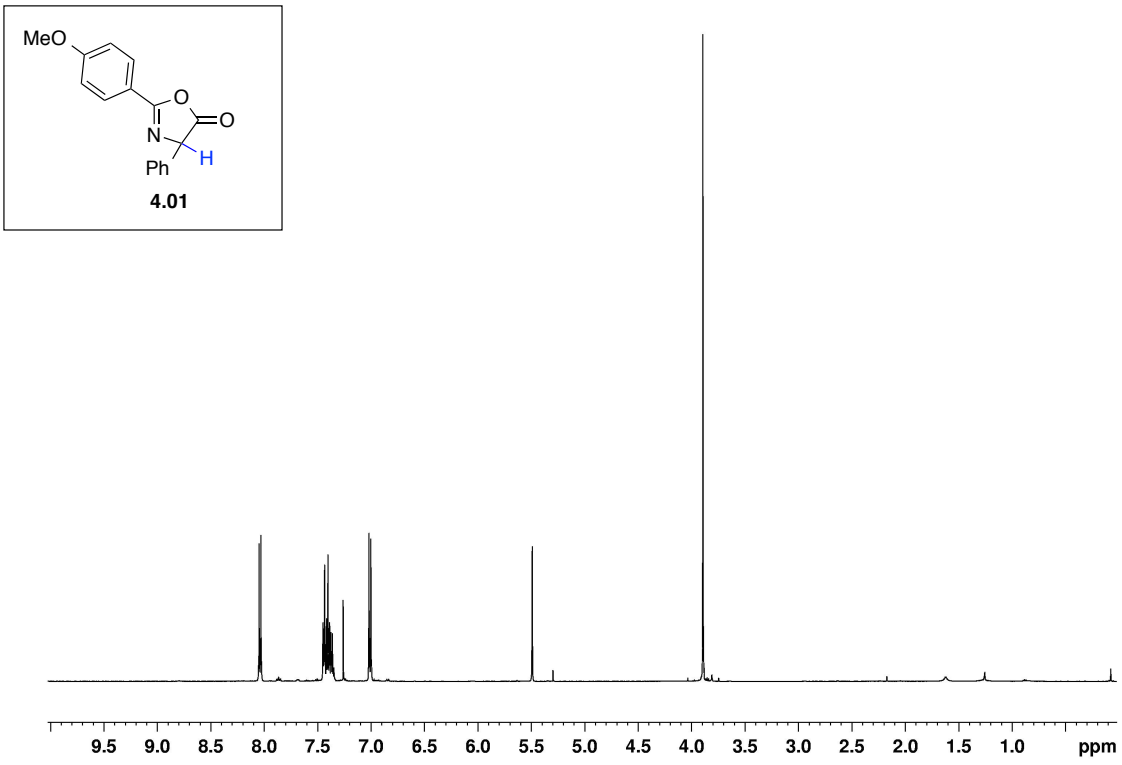



**Figure A. 4.01_1** $^{1}$H NMR spectrum of compound **4.01** (500 MHz, $CDCl_3$)

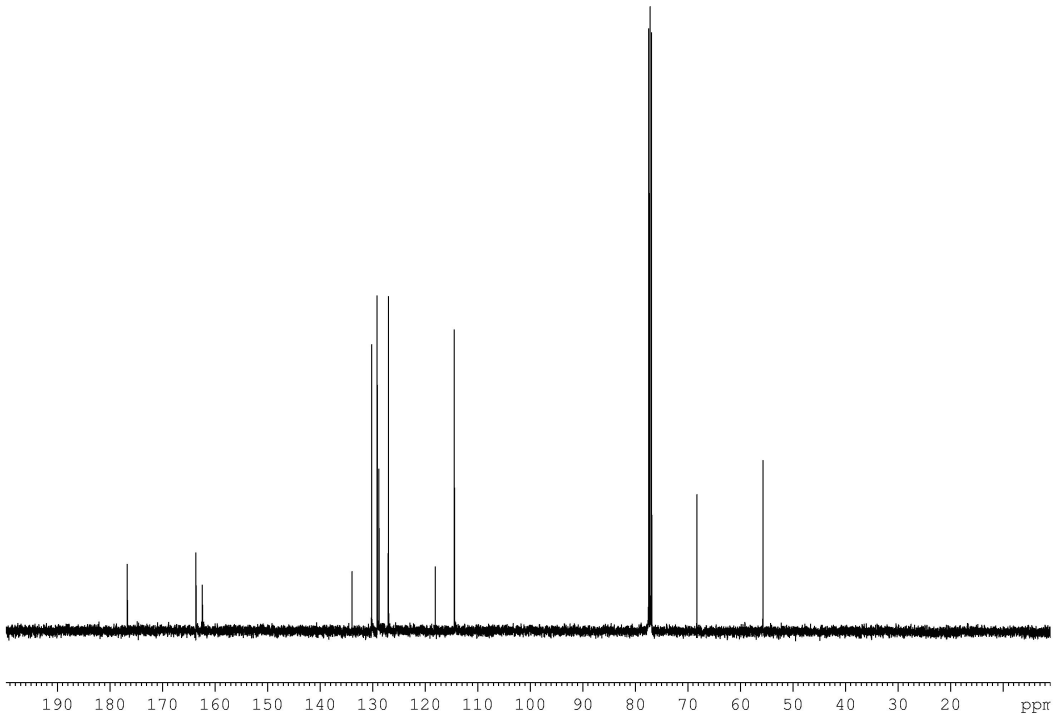



**Figure A. 4.01_2** $^{13}$C NMR spectrum of compound **4.01** (125 MHz, $CDCl_3$)

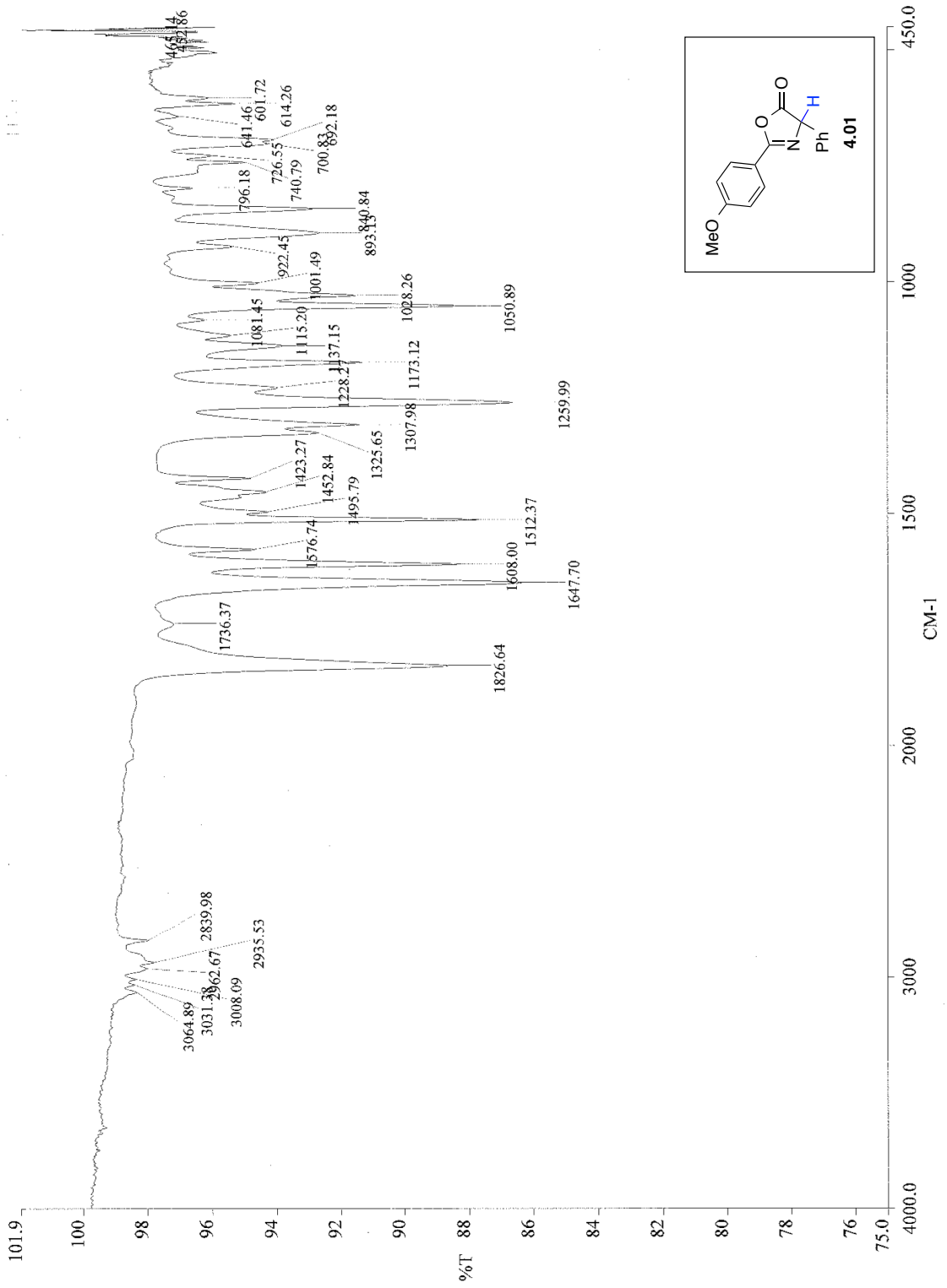



**Figure A. 4.01_3** IR spectrum of compound **4.01**

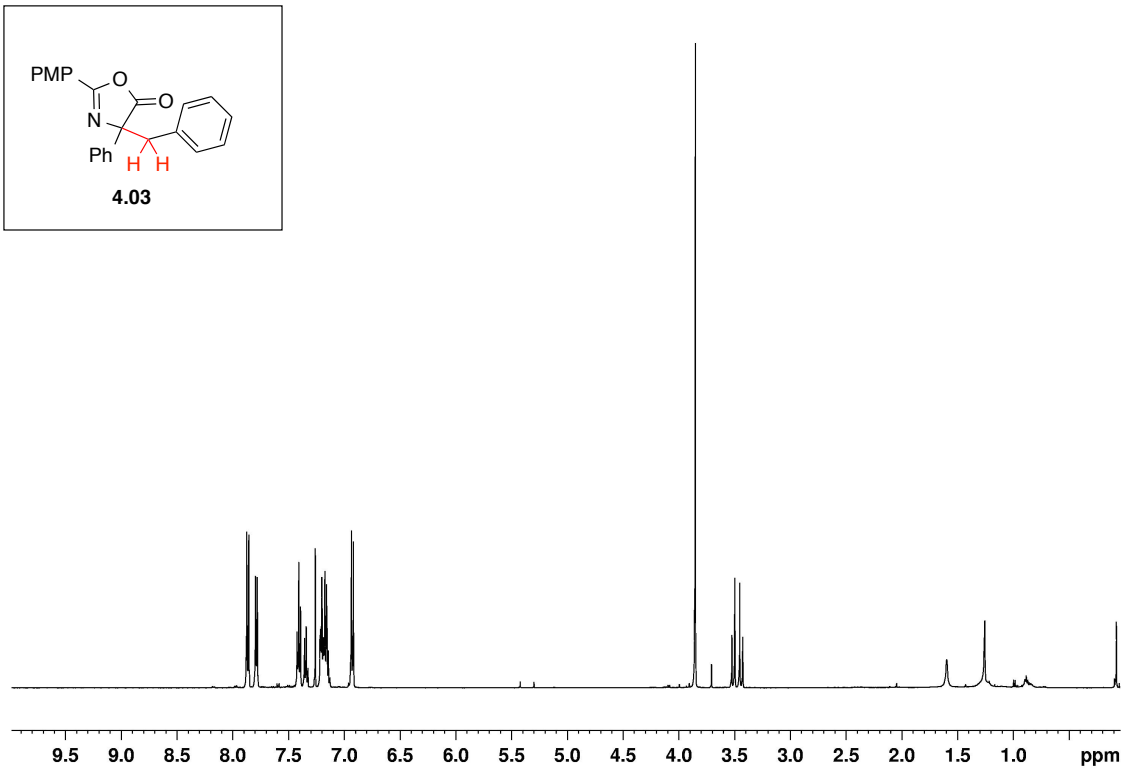



**Figure A. 4.03_1** $^{1}$H NMR spectrum of compound **4.03** (500 MHz, $CDCl_3$)

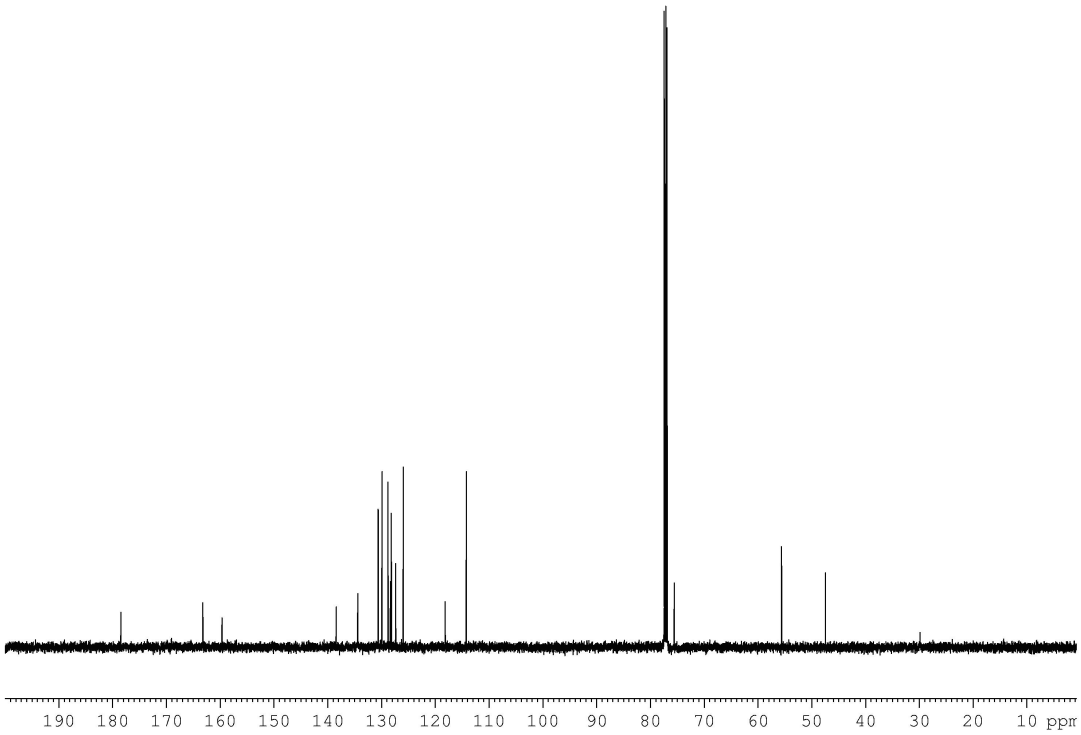



**Figure A. 4.03_2** $^{13}$C NMR spectrum of compound **4.03** (125 MHz, $CDCl_3$)

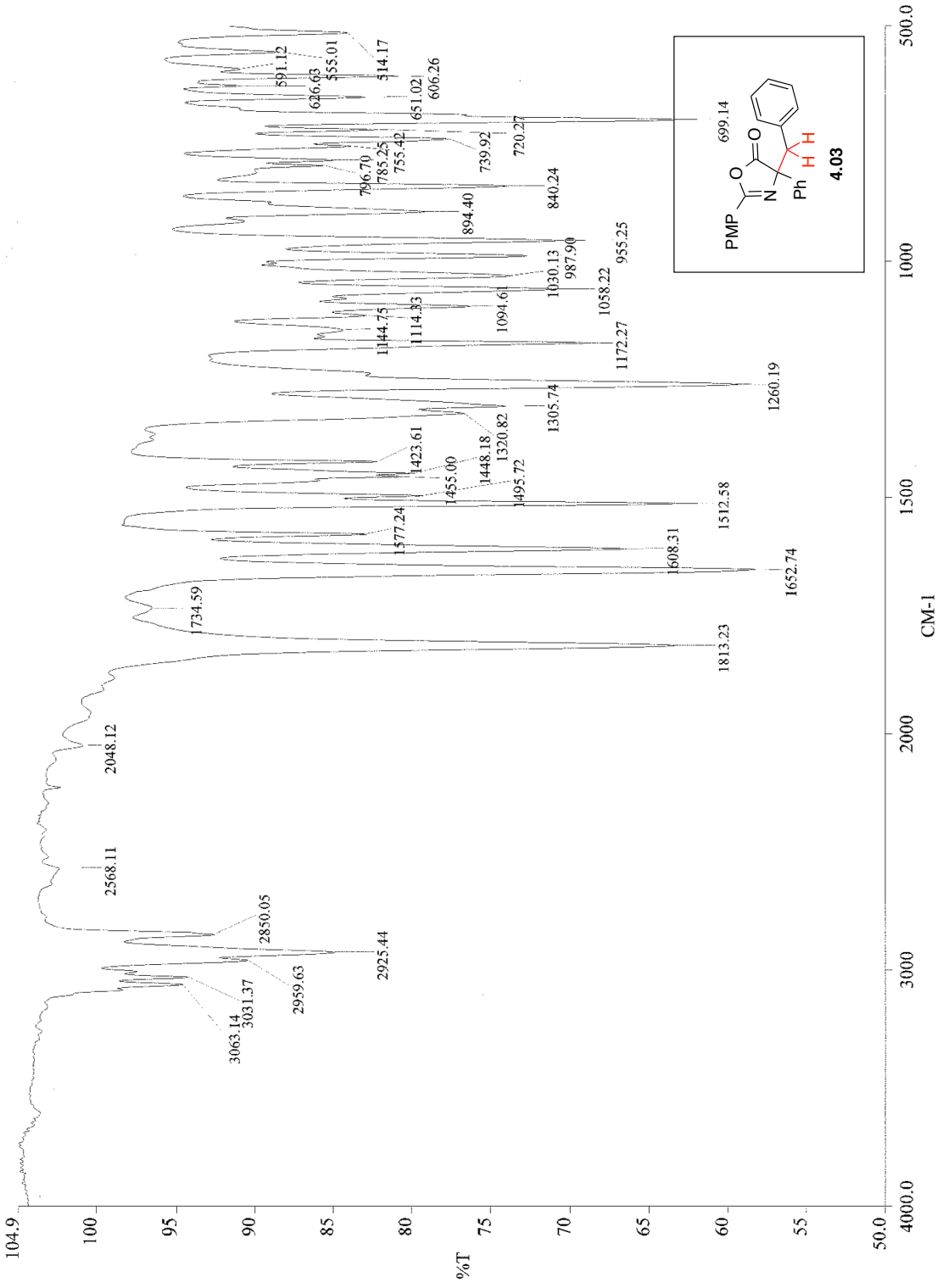



**Figure A. 4.03_3** IR spectrum of compound **4.03**

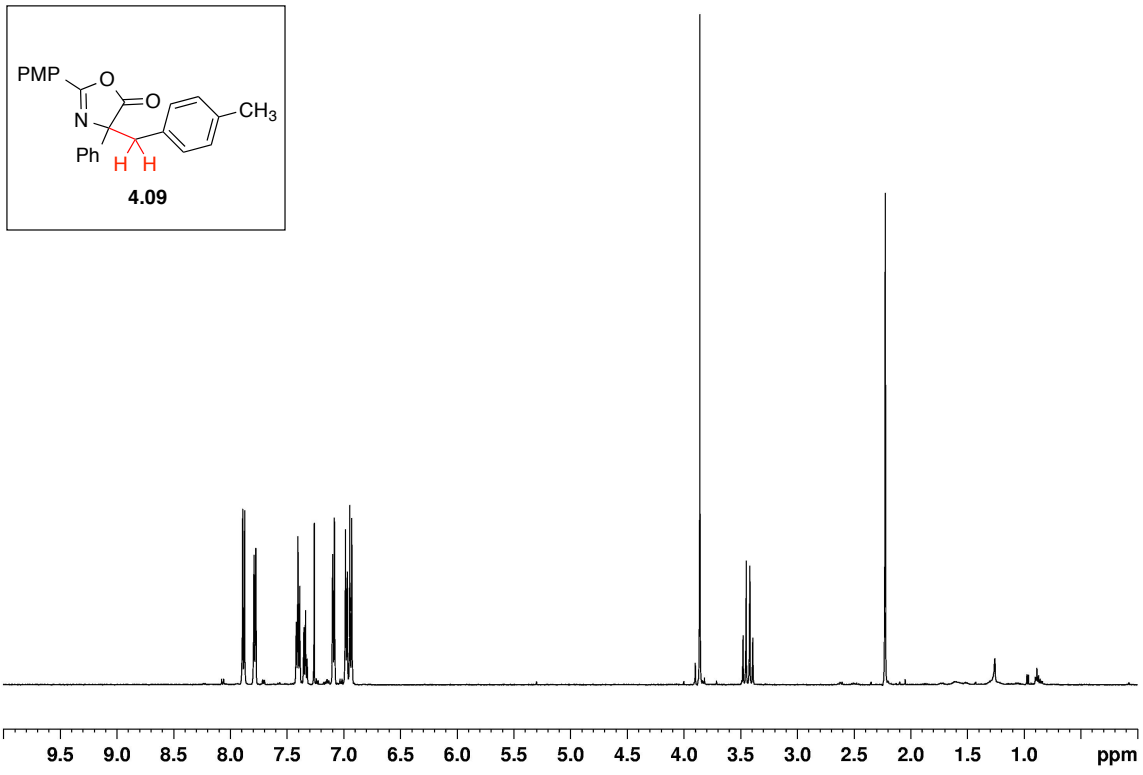



**Figure A. 4.09_1** $^{1}$H NMR spectrum of compound **4.09** (500 MHz, $CDCl_3$)

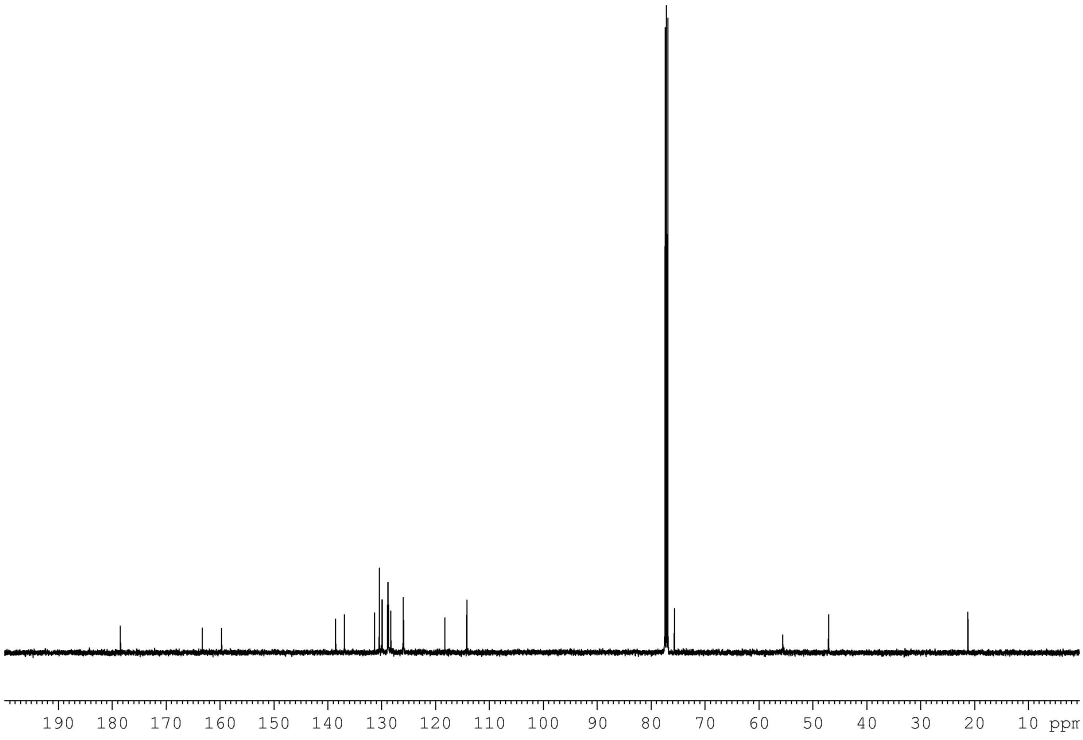



**Figure A. 4.09_2** $^{13}$C NMR spectrum of compound **4.09** (125 MHz, $CDCl_3$)

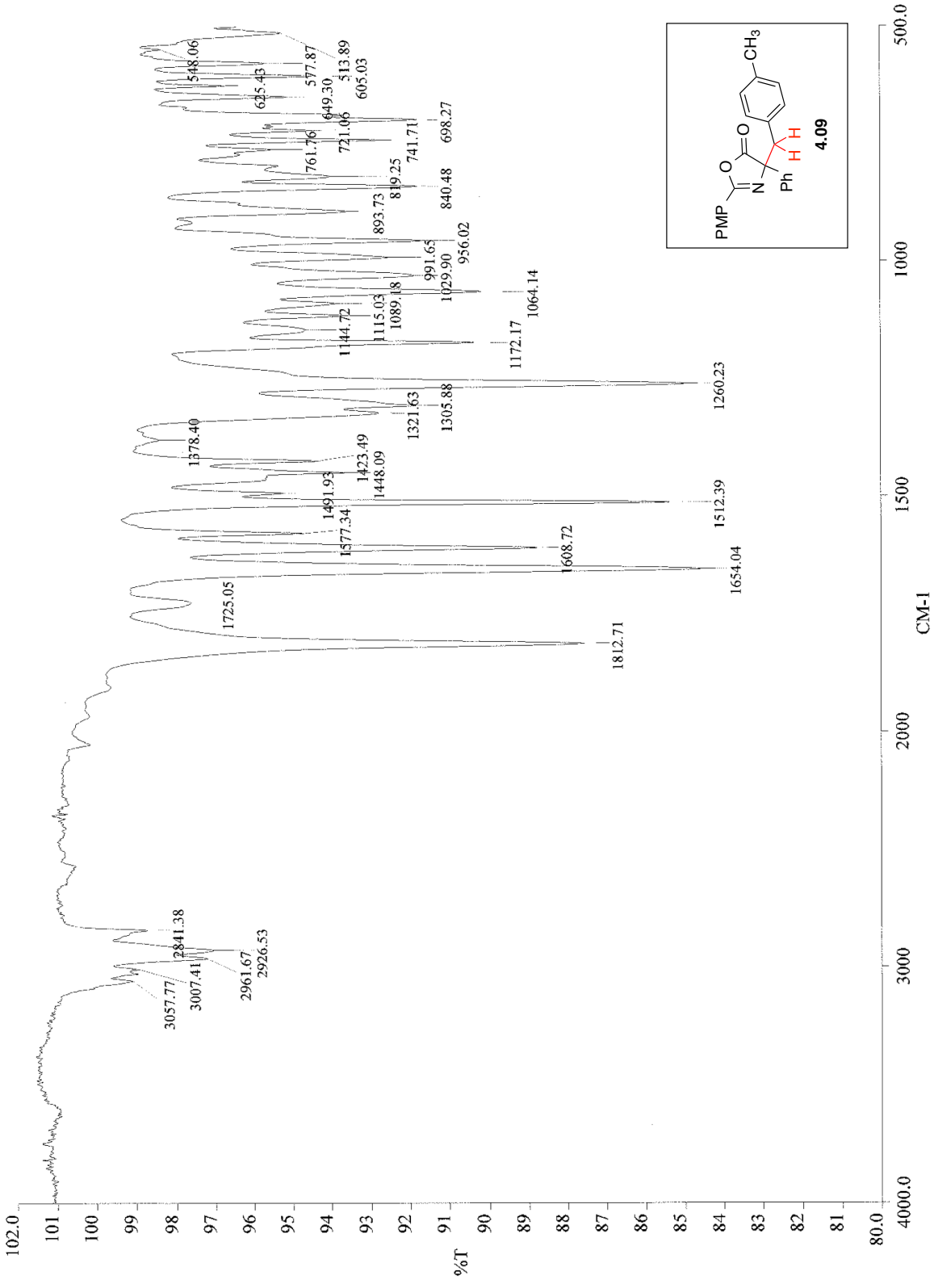



**Figure A. 4.09_3** IR spectrum of compound **4.09**

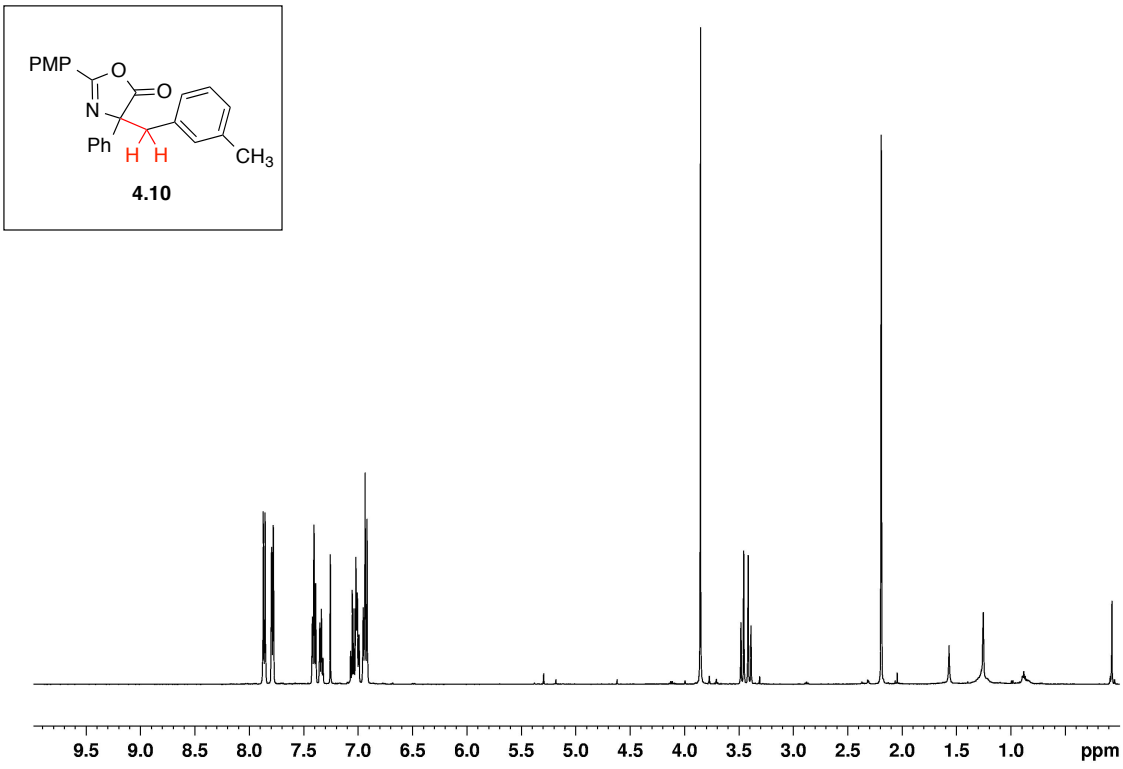



**Figure A. 4.10_1** $^{1}$H NMR spectrum of compound **4.10** (500 MHz, $CDCl_3$)

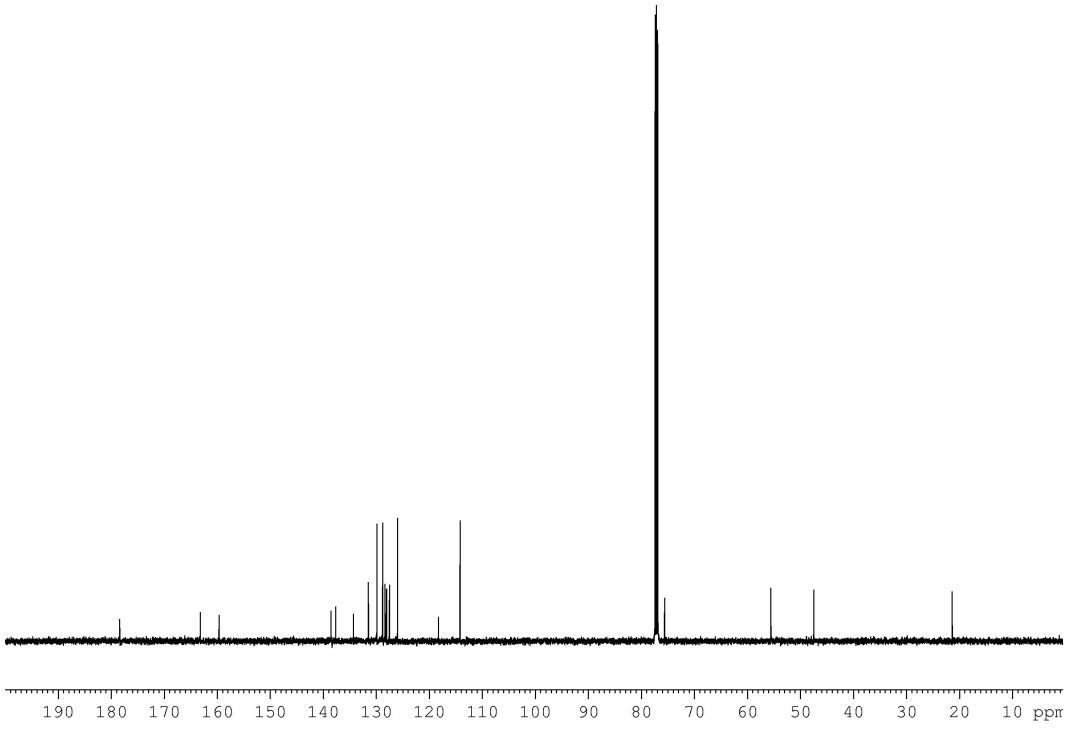



**Figure A. 4.10_2** $^{13}$C NMR spectrum of compound **4.10** (125 MHz, $CDCl_3$)

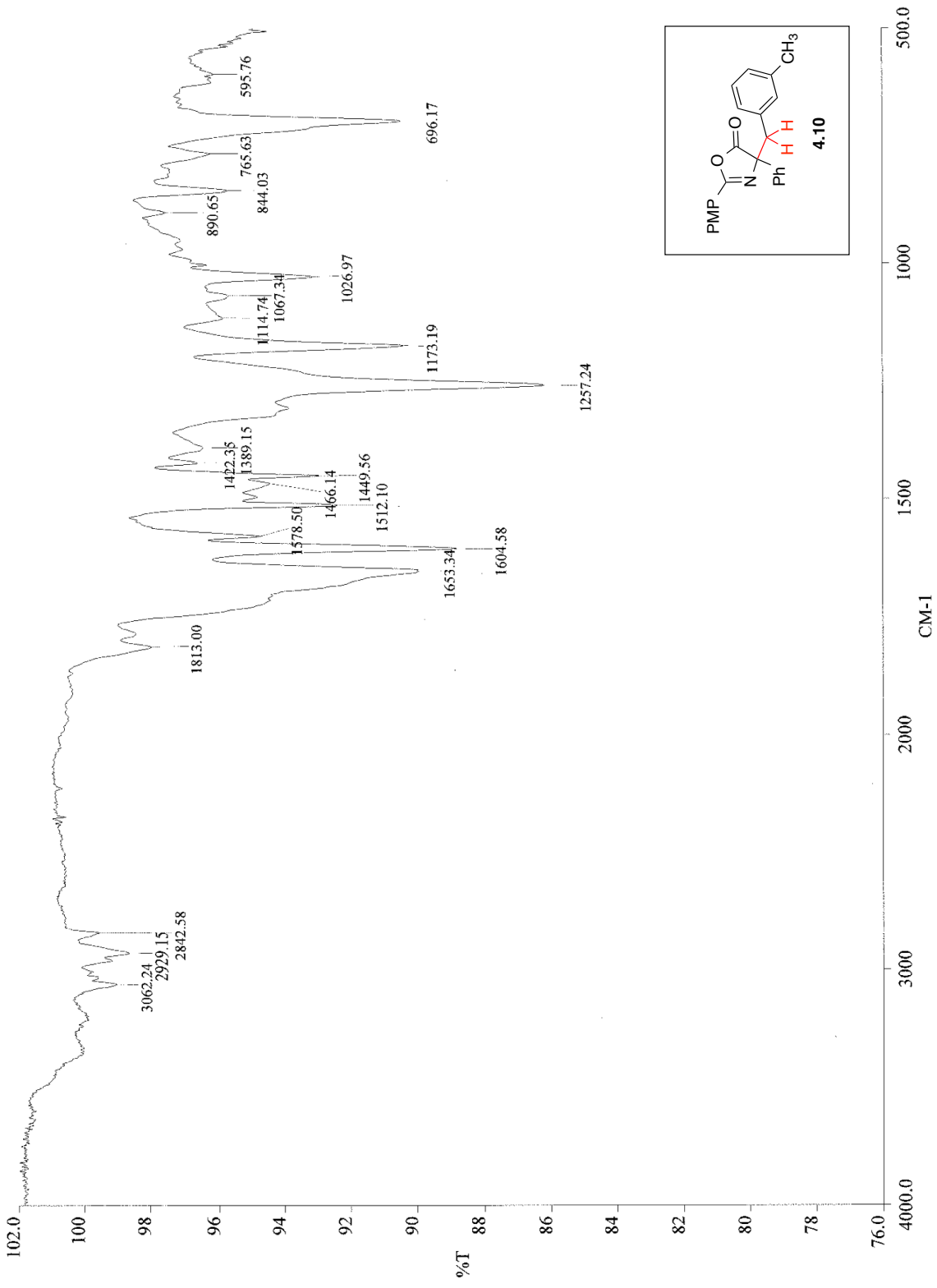



**Figure A. 4.10_3** IR spectrum of compound **4.10**

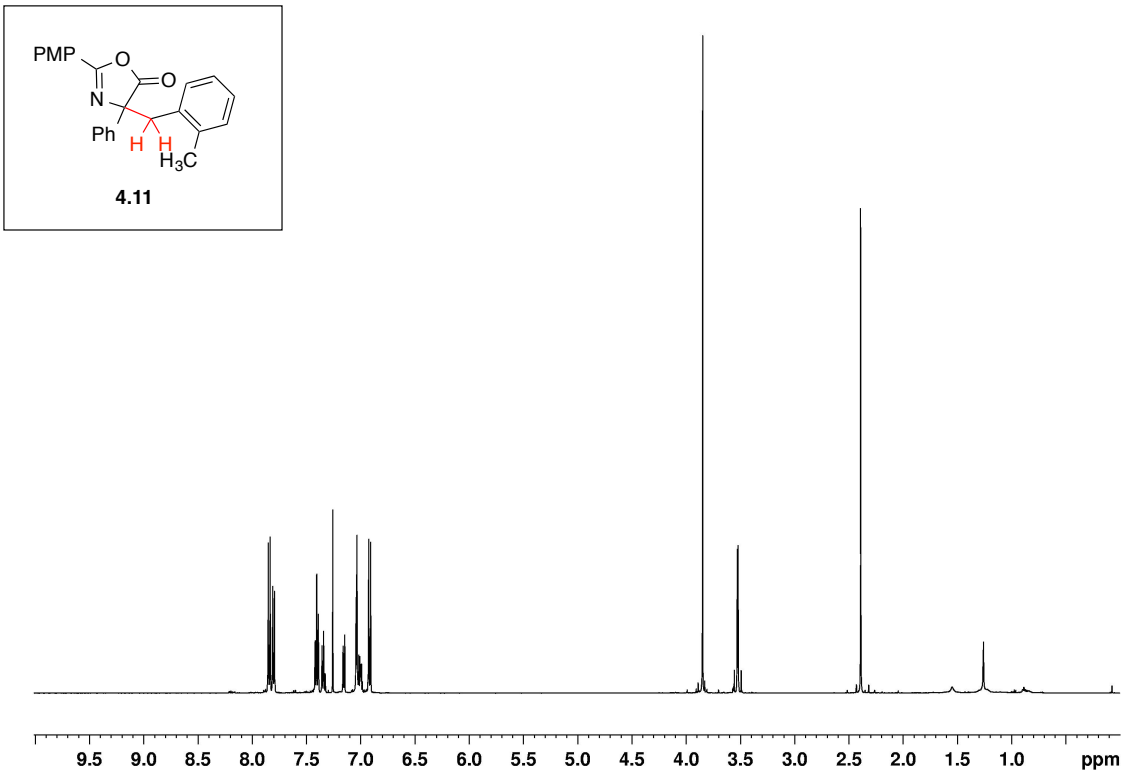



**Figure A. 4.11_1** $^{1}$H NMR spectrum of compound **4.11** (500 MHz, $CDCl_3$)

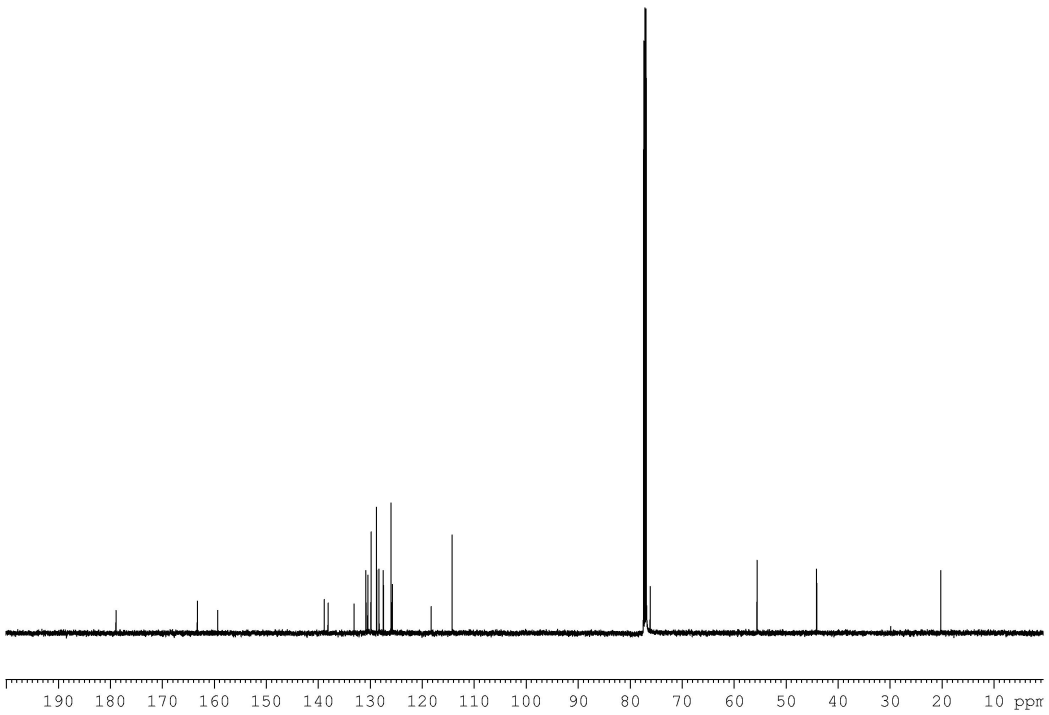



**Figure A. 4.11_2** $^{13}$C NMR spectrum of compound **4.11** (125 MHz, $CDCl_3$)

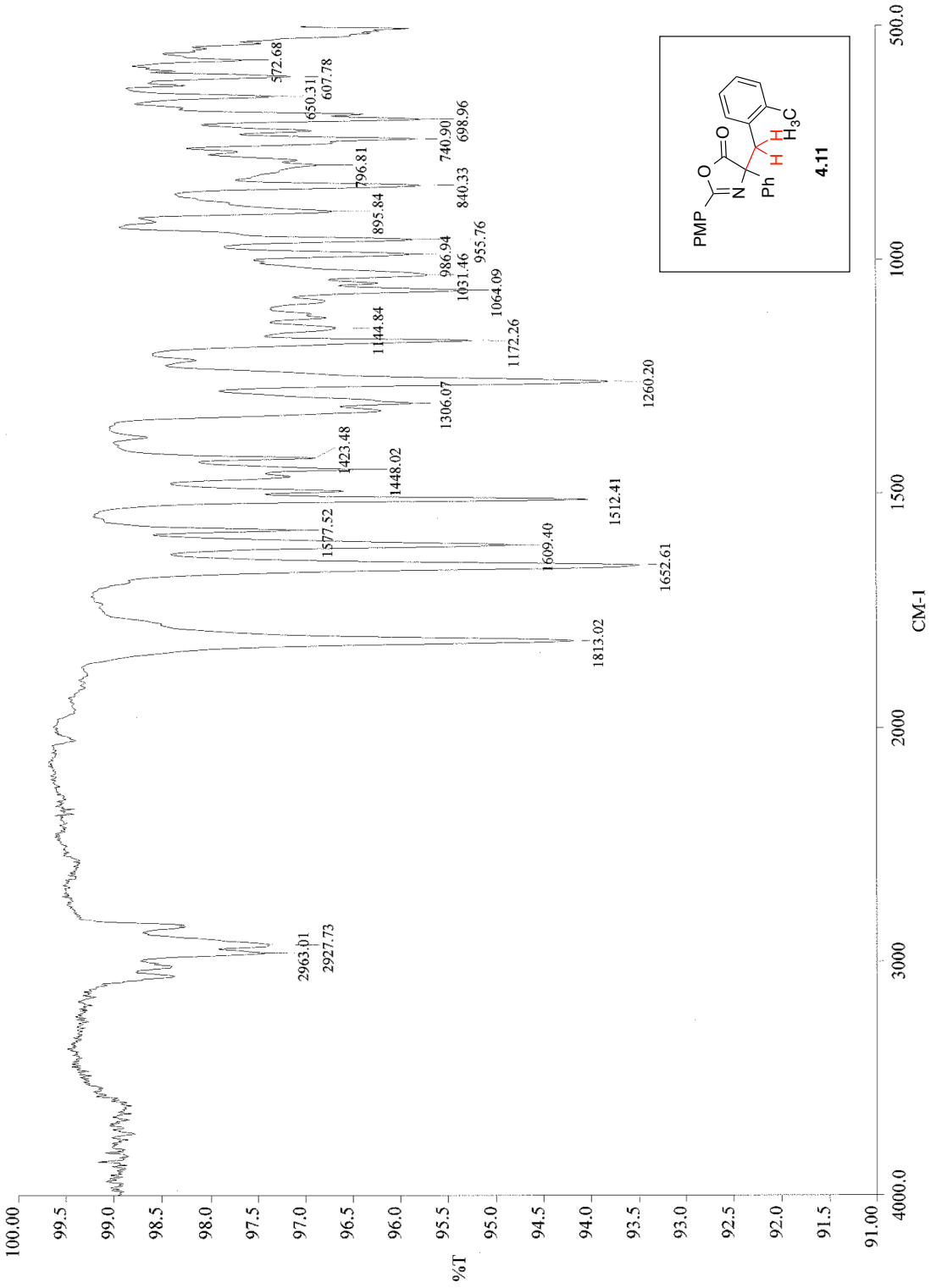



**Figure A. 4.11_3** IR spectrum of compound **4.11**

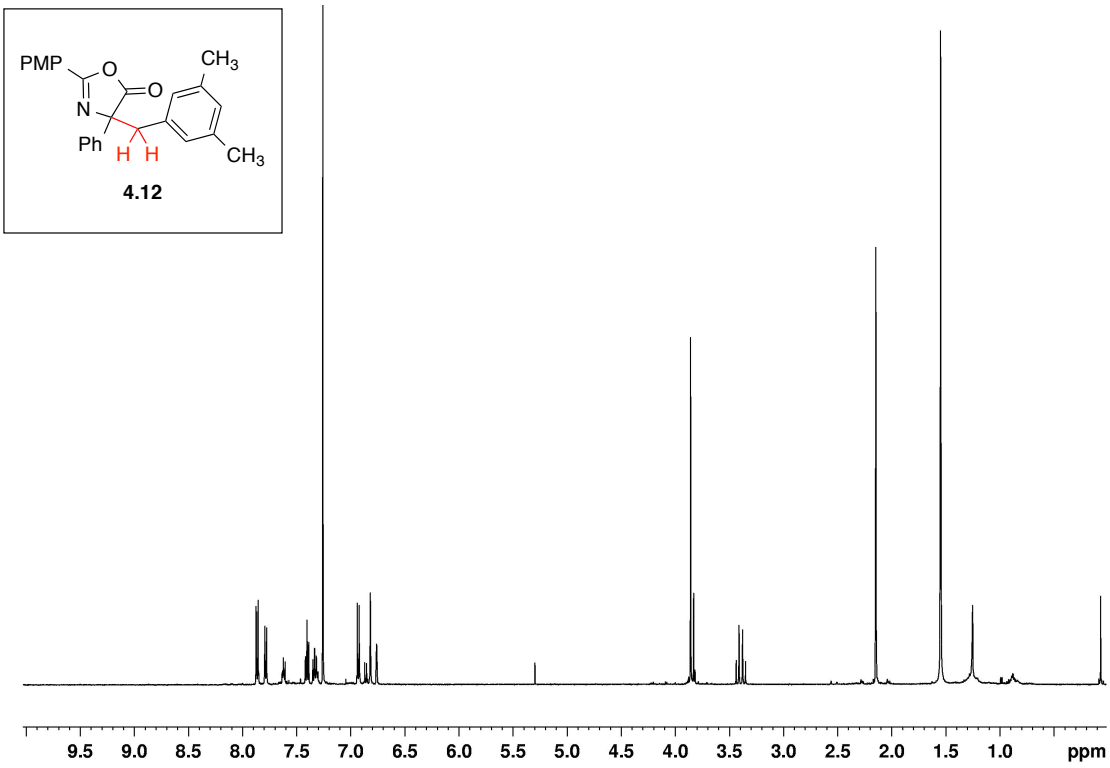



**Figure A. 4.12_1** $^{1}$H NMR spectrum of compound **4.12** (500 MHz, $CDCl_3$)

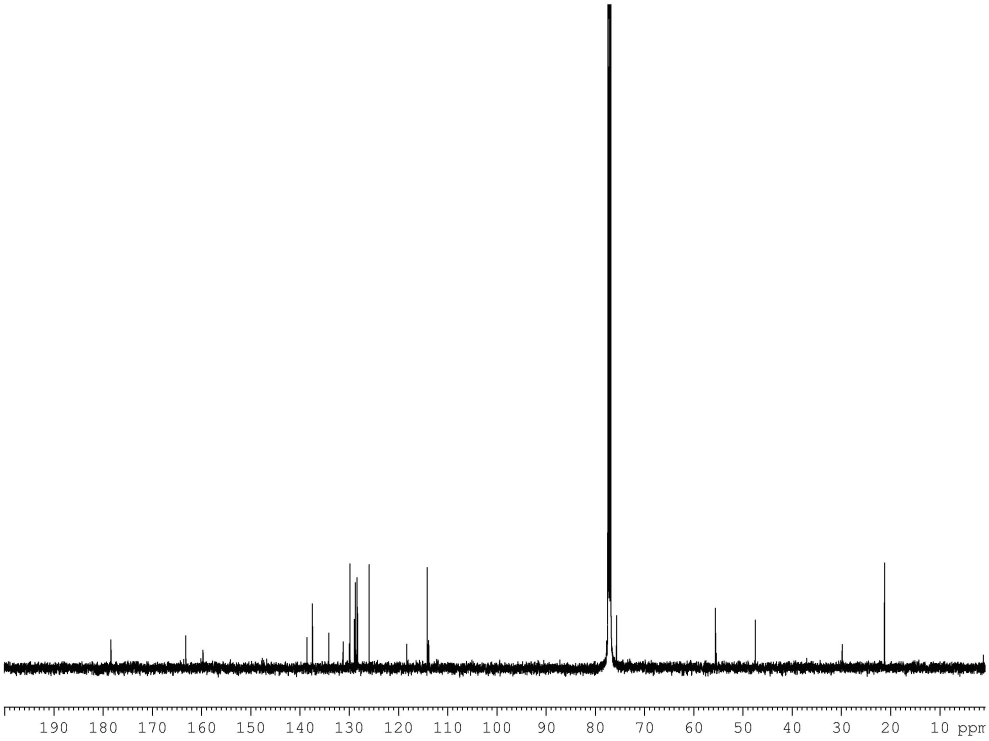



**Figure A. 4.12_2** $^{13}$C NMR spectrum of compound **4.12** (125 MHz, $CDCl_3$)

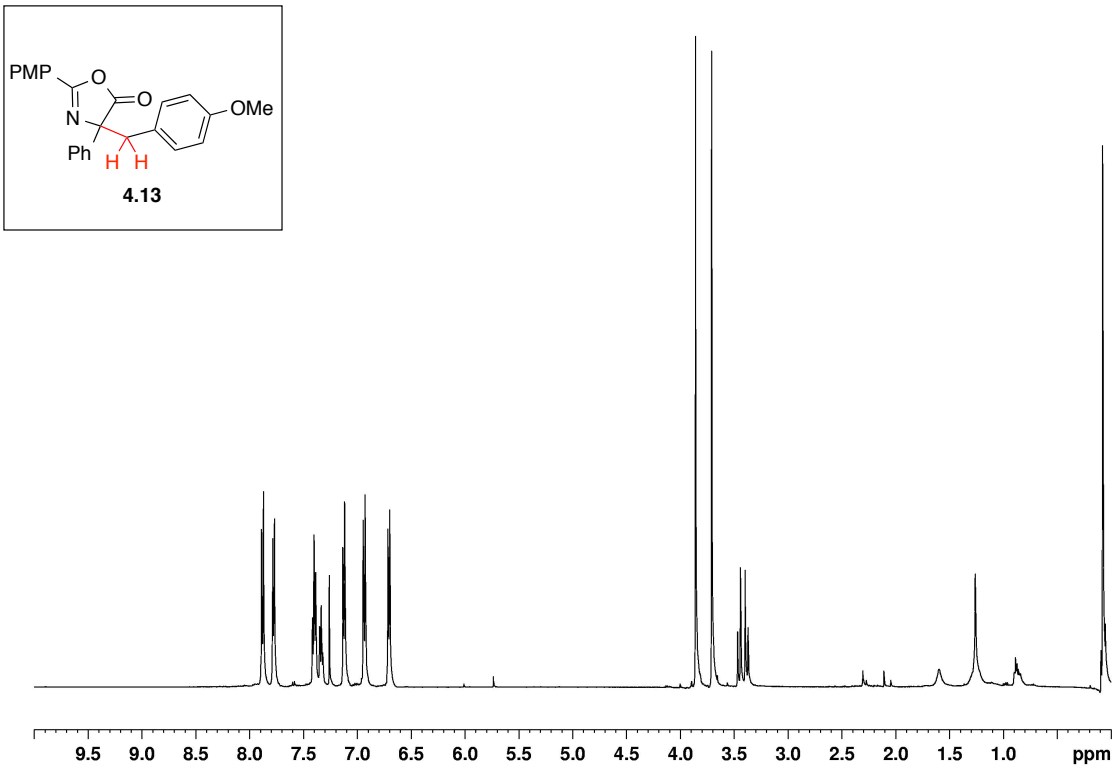



**Figure A. 4.13_1** $^{1}$H NMR spectrum of compound **4.13** (500 MHz, $CDCl_3$)

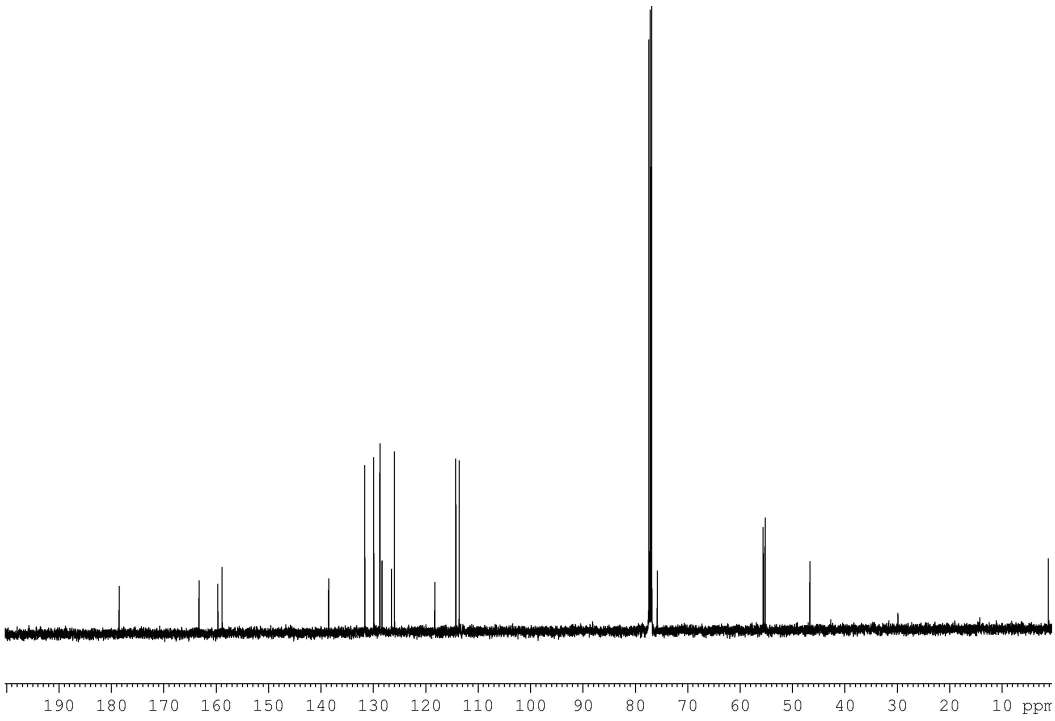



**Figure A. 4.13_2** $^{13}$C NMR spectrum of compound **4.13** (125 MHz, $CDCl_3$)

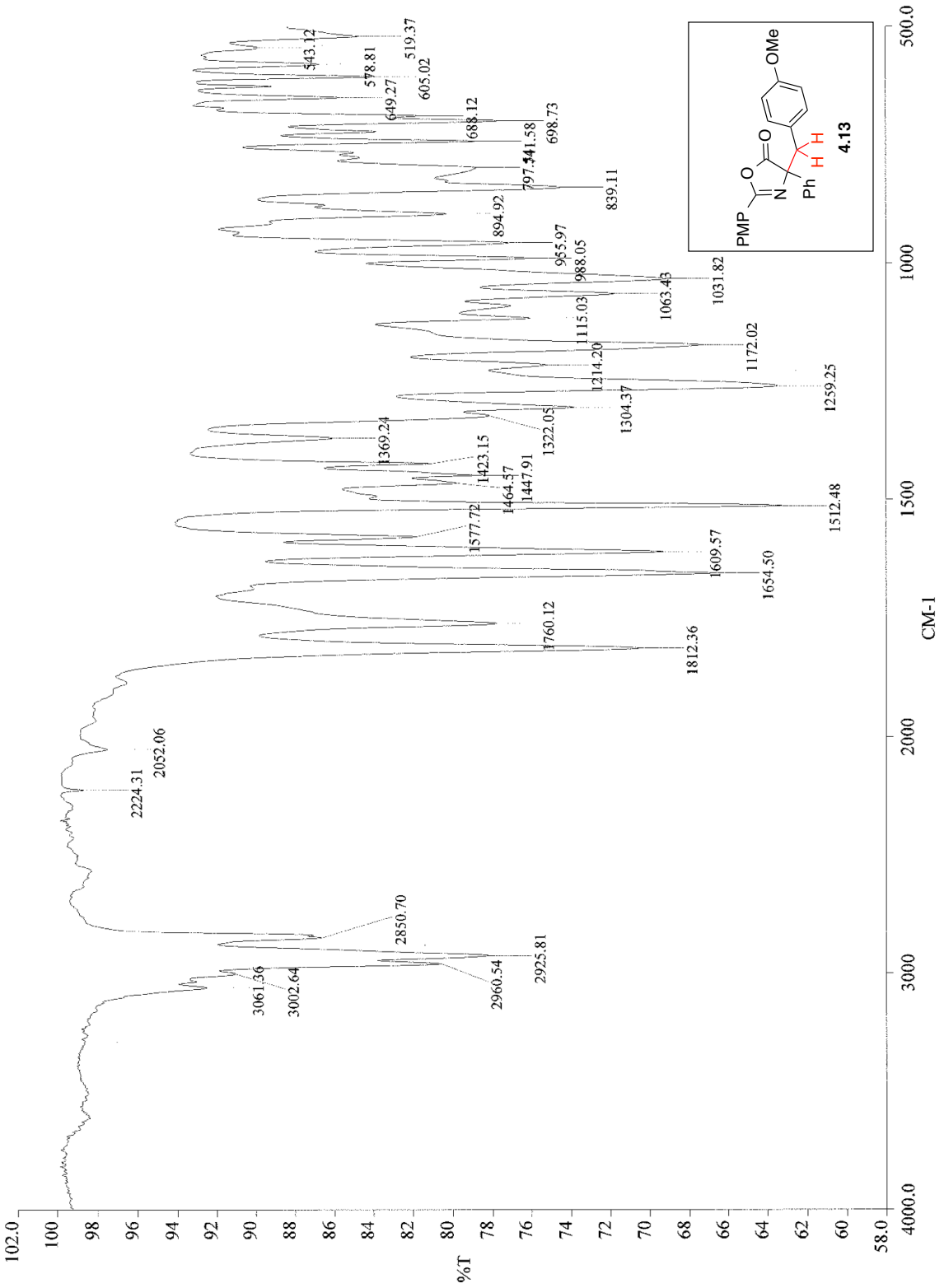



**Figure A. 4.13_3** IR spectrum of compound **4.13**

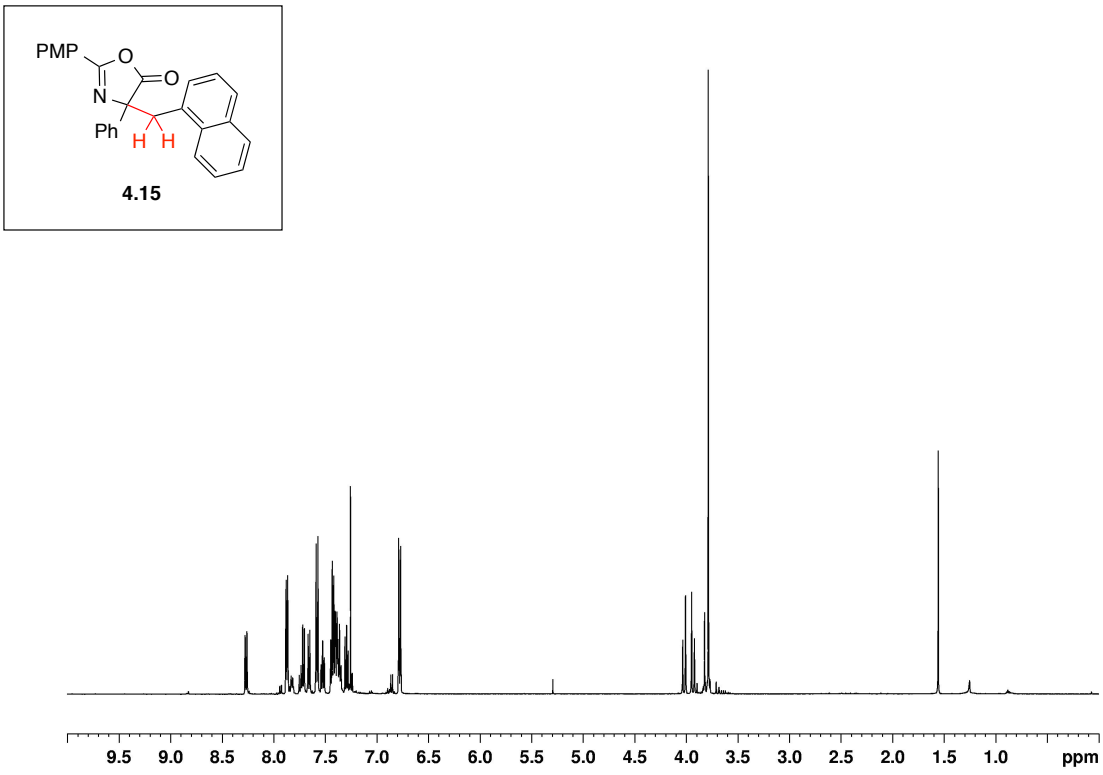



**Figure A. 4.15_1** $^{1}$H NMR spectrum of compound **4.15** (500 MHz, $CDCl_3$)

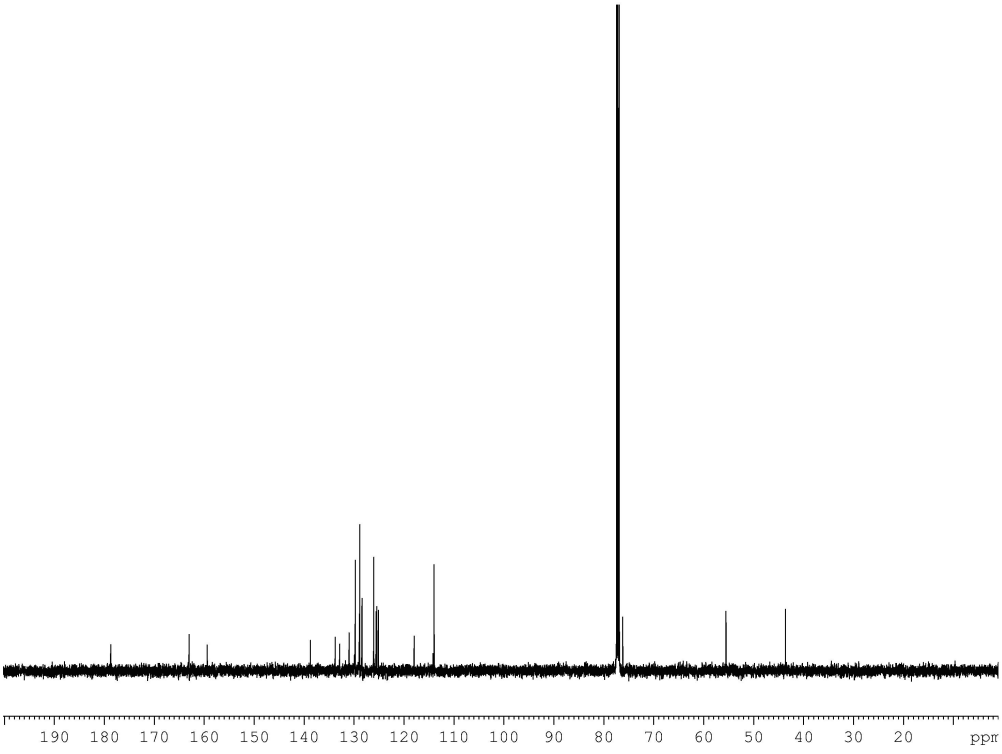



**Figure A. 4.15_2** $^{13}$C NMR spectrum of compound **4.15** (125 MHz, $CDCl_3$)

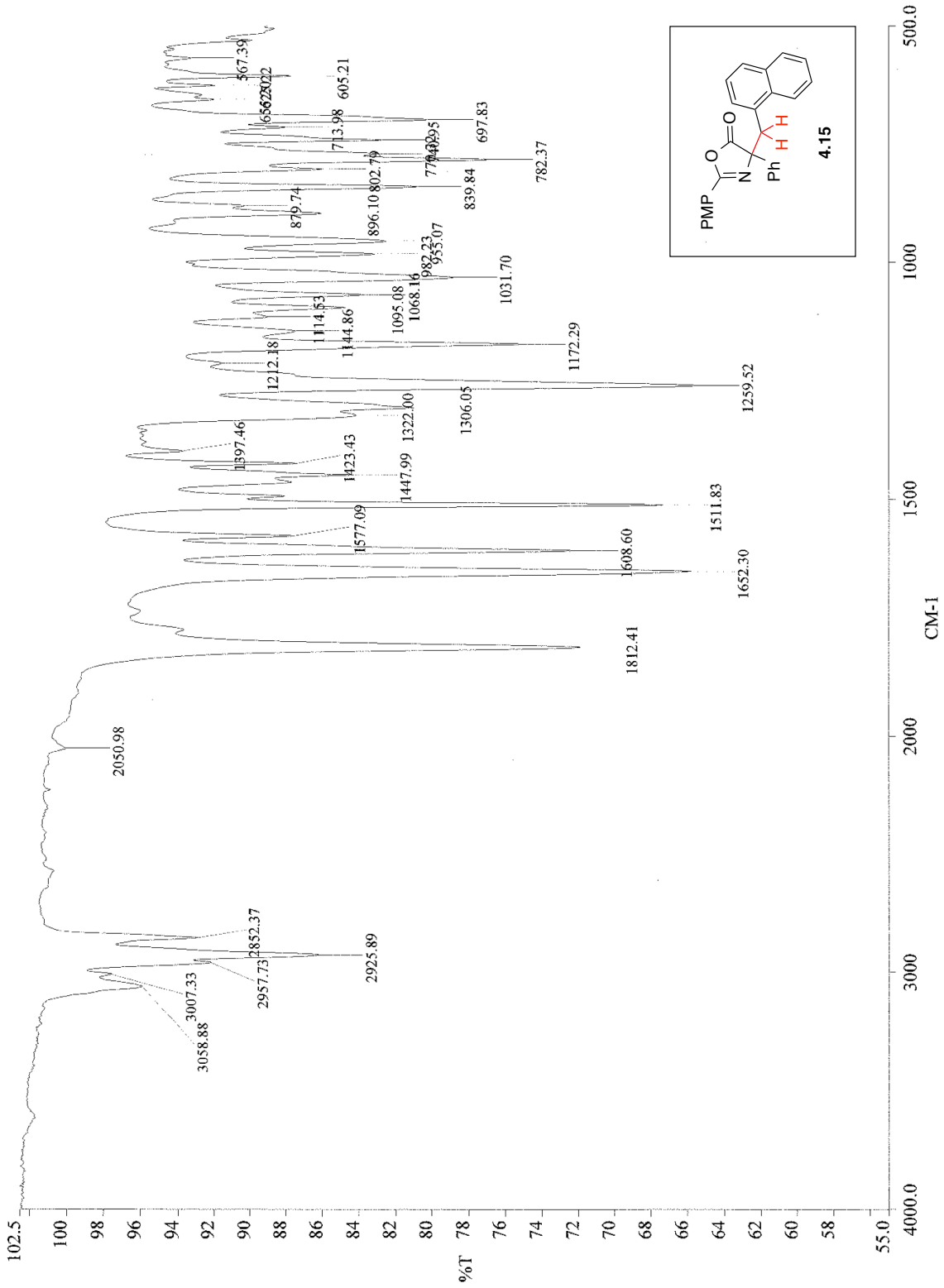



**Figure A. 4.15_3** IR spectrum of compound **4.15**

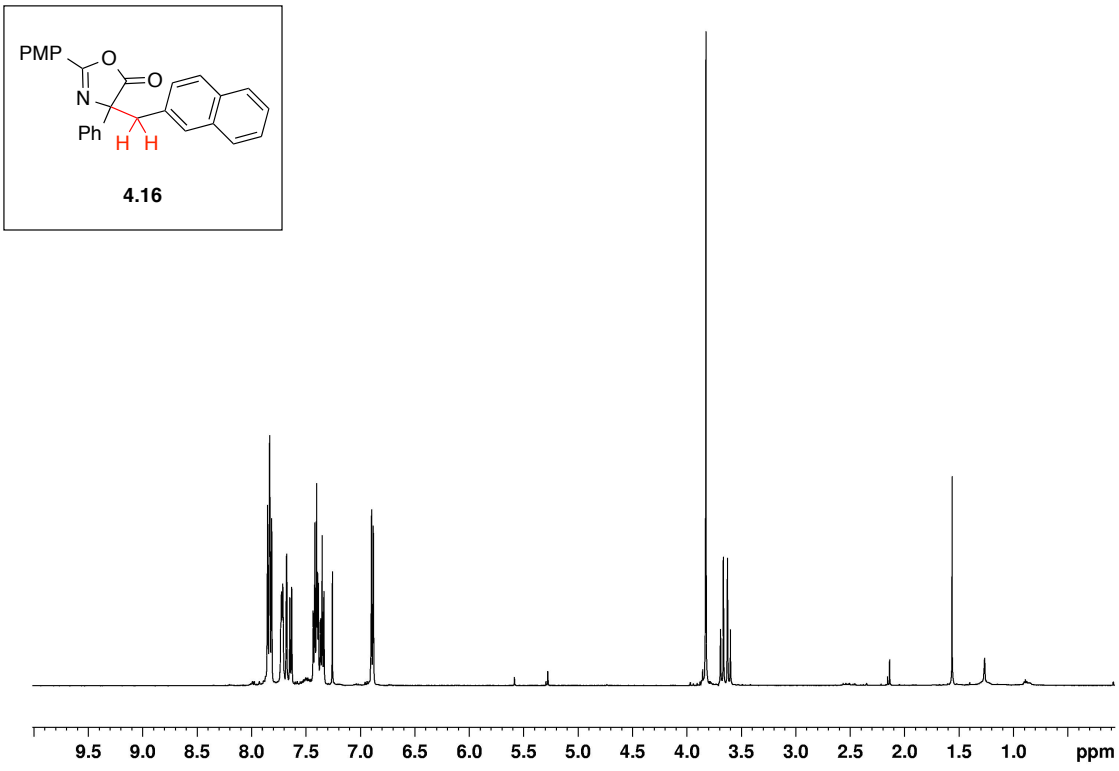



**Figure A. 4.16_1** $^{1}$H NMR spectrum of compound **4.16** (500 MHz, $CDCl_3$)

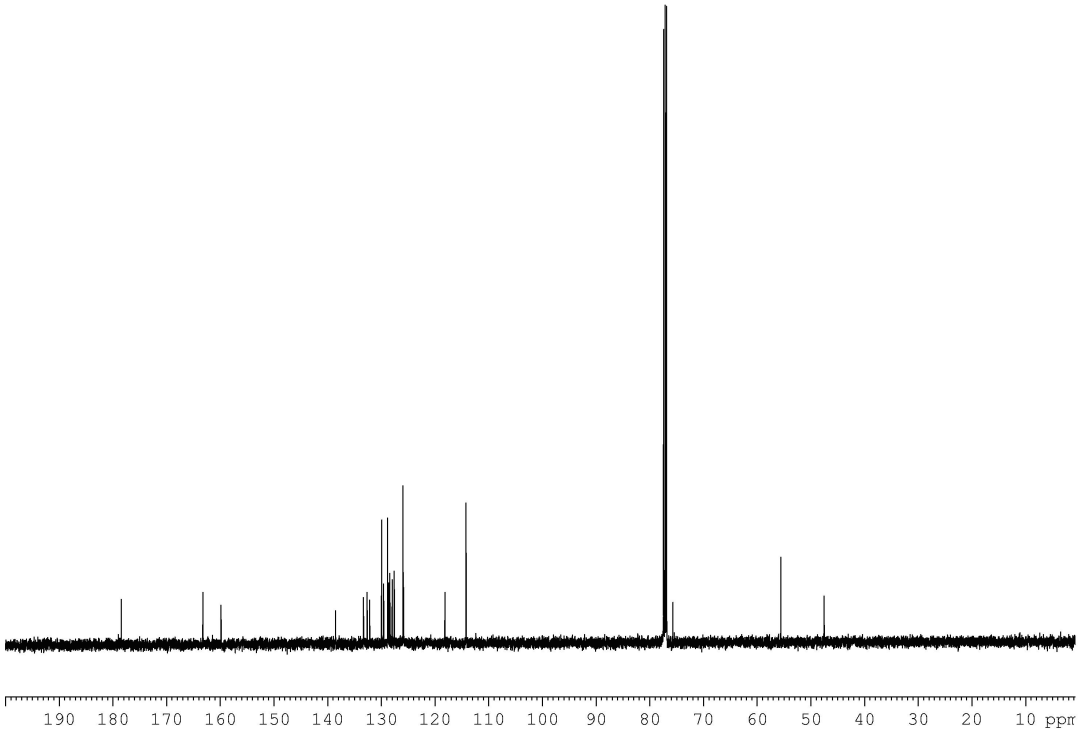



**Figure A. 4.16_2** $^{13}$C NMR spectrum of compound **4.16** (125 MHz, $CDCl_3$)

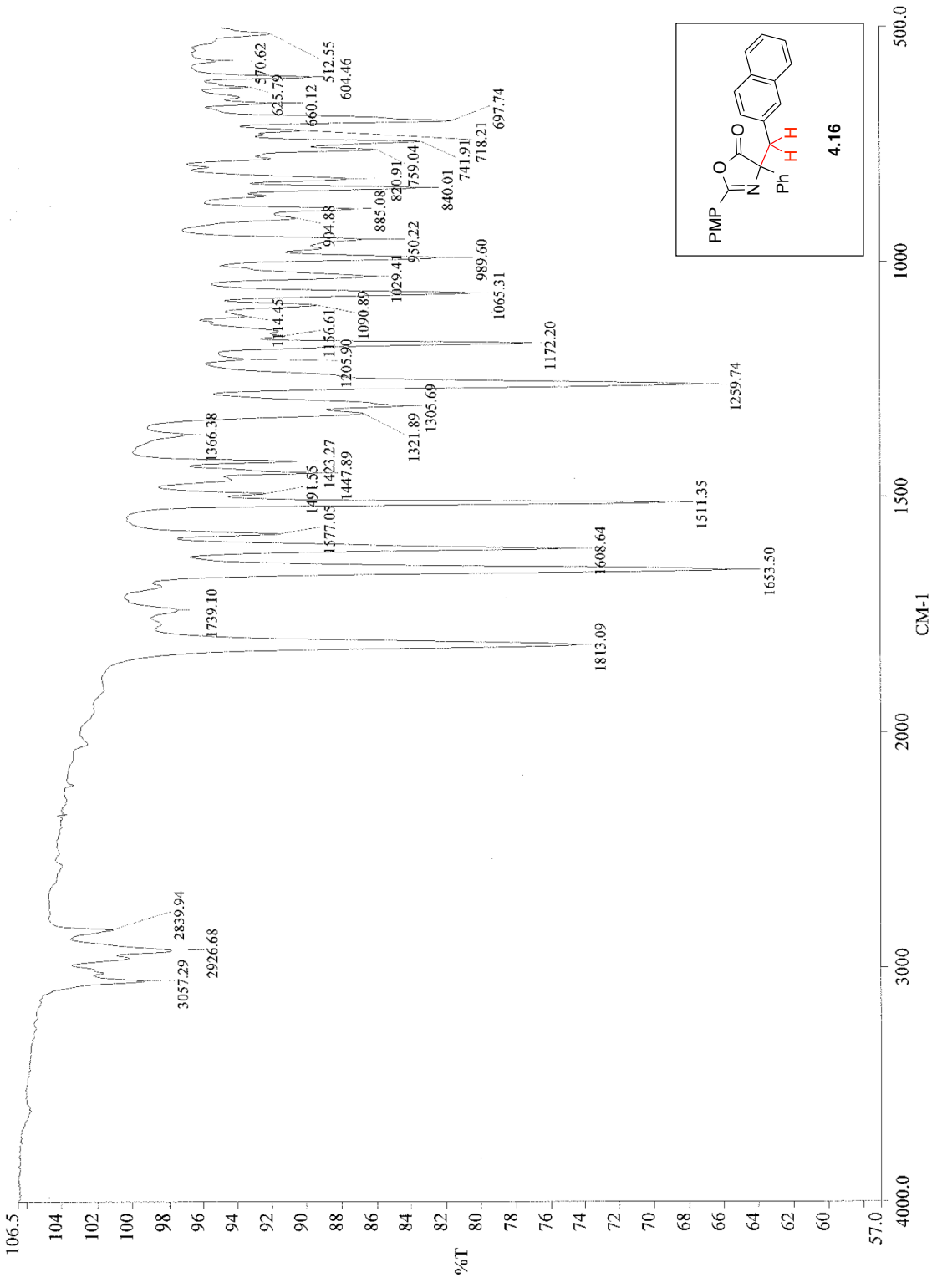



**Figure A. 4.16_3** IR spectrum of compound **4.16**

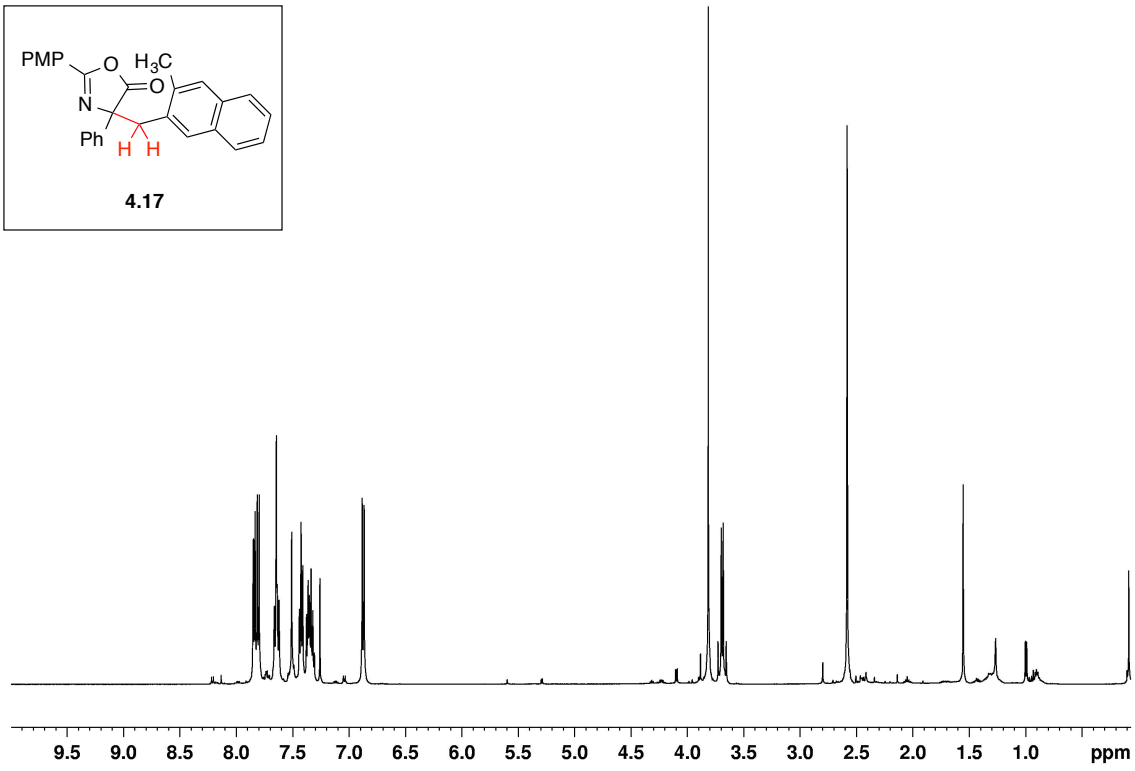



**Figure A. 4.17_1** $^{1}$H NMR spectrum of compound **4.17** (500 MHz, $CDCl_3$)

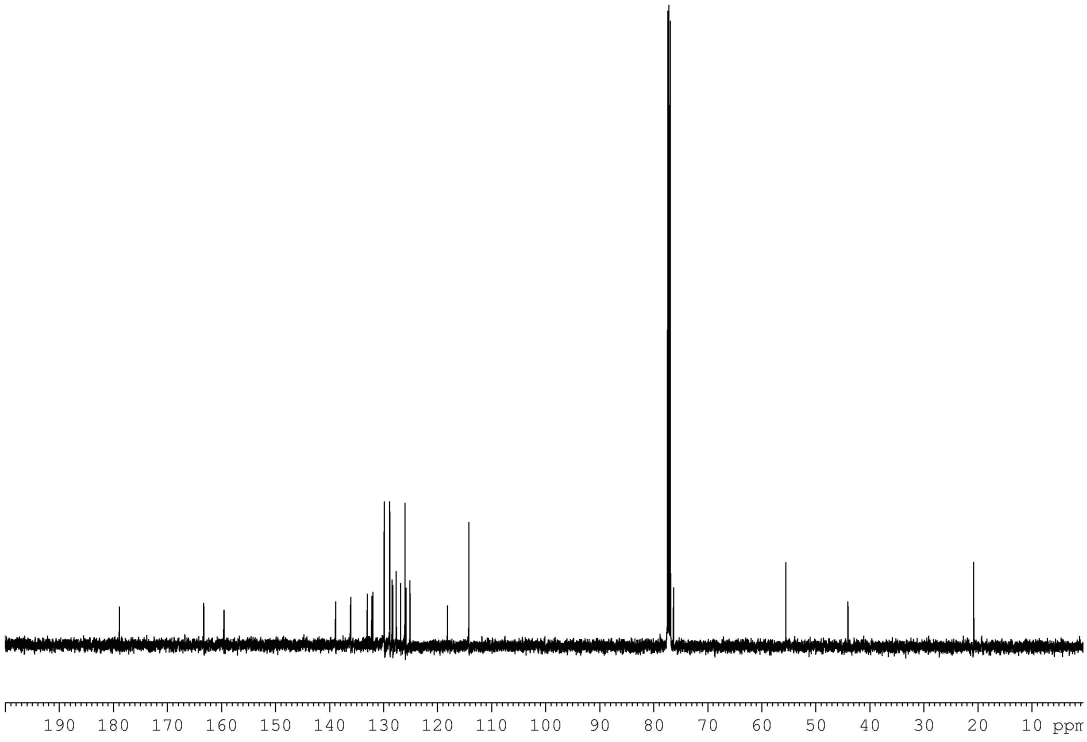



**Figure A. 4.17_2** $^{13}$C NMR spectrum of compound **4.17** (125 MHz, $CDCl_3$)


**Figure A. 4.17_3** IR spectrum of compound **4.17**

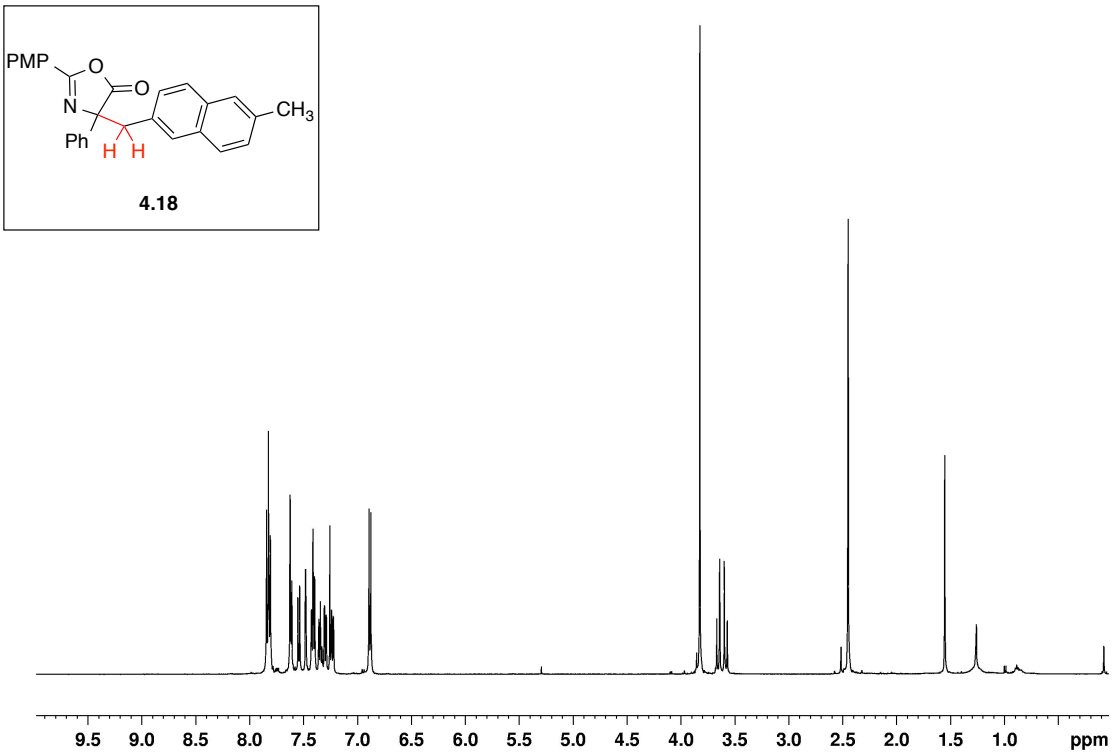



**Figure A. 4.18_1** $^{1}$H NMR spectrum of compound **4.18** (500 MHz, $CDCl_3$)

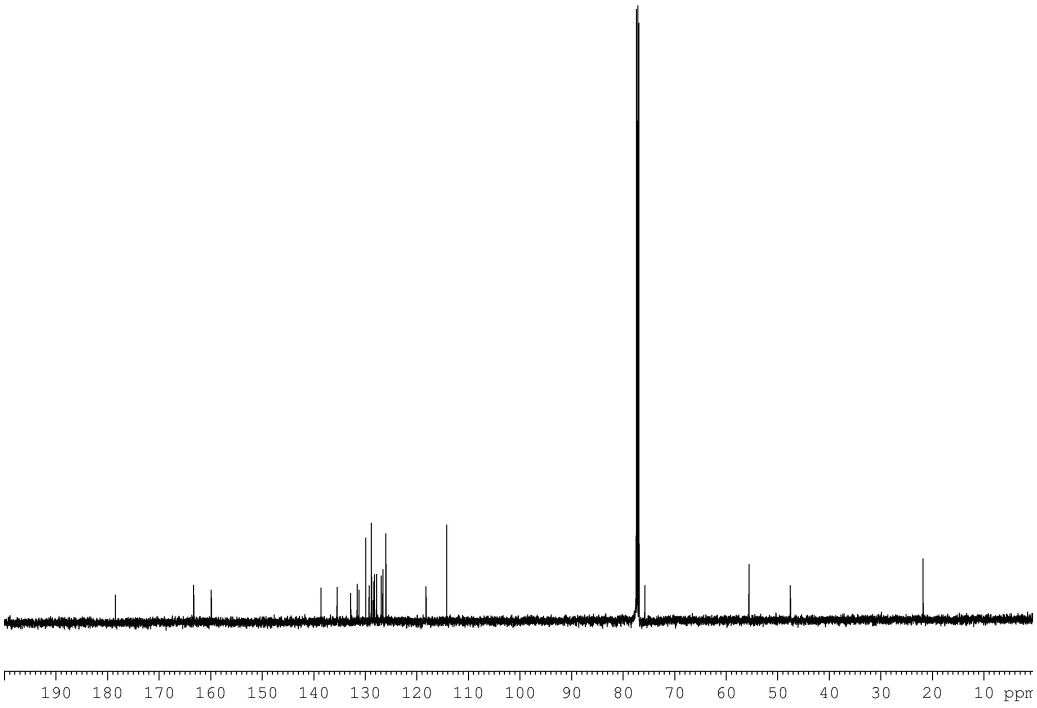



**Figure A. 4.18_2** $^{13}$C NMR spectrum of compound **4.18** (125 MHz, $CDCl_3$)

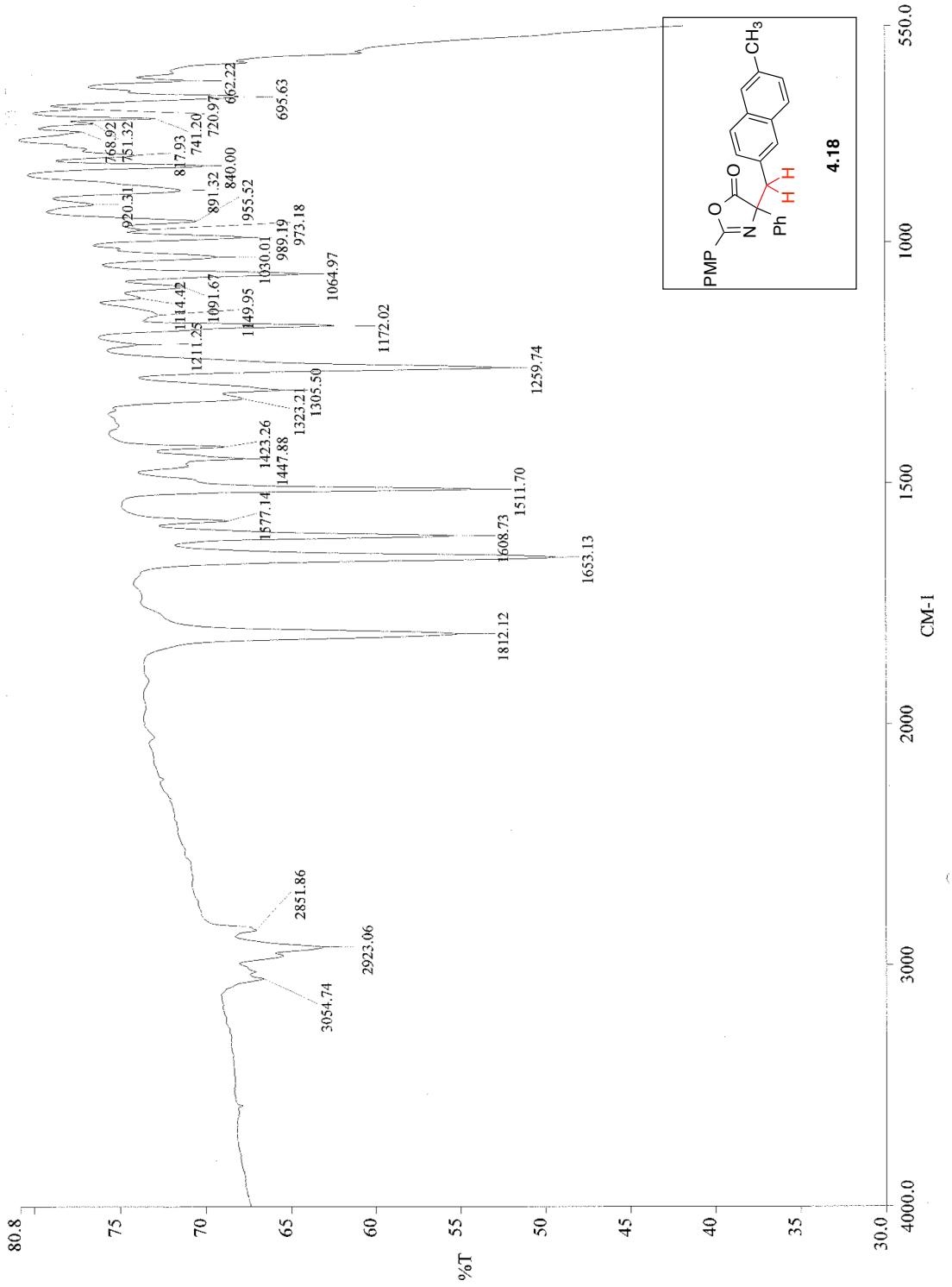



**Figure A. 4.18_3** IR spectrum of compound **4.18**

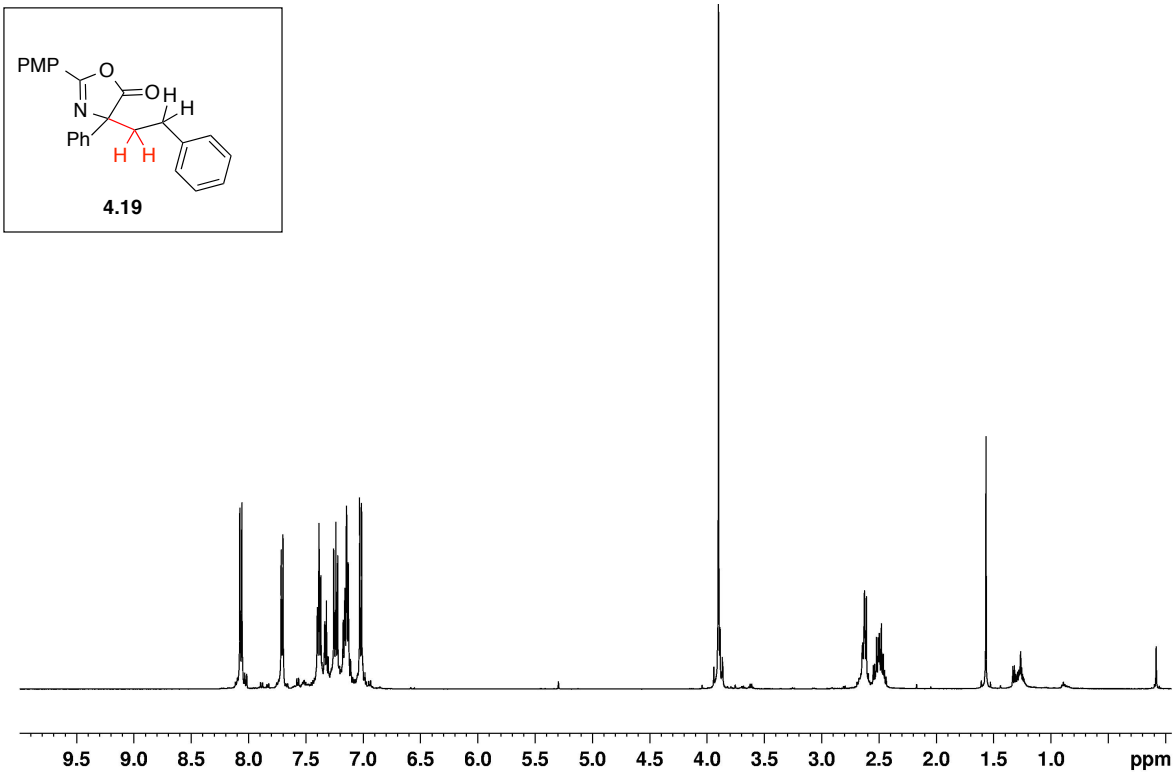



**Figure A. 4.19_1** $^{1}$H NMR spectrum of compound **4.19** (500 MHz, $CDCl_3$)

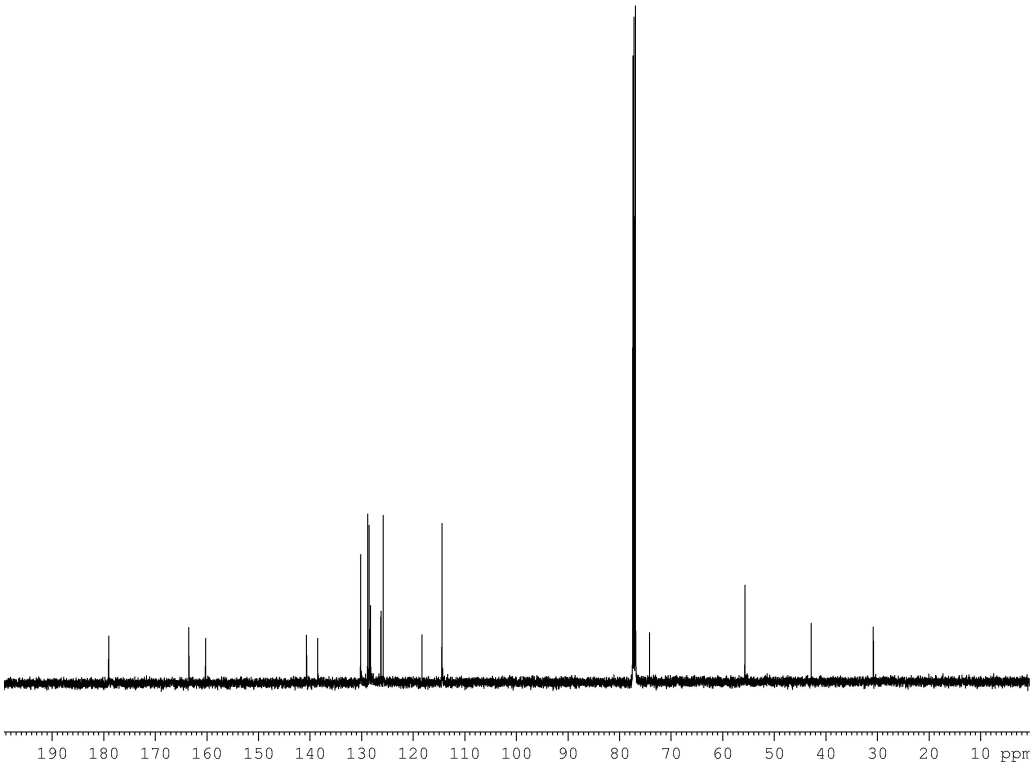



**Figure A. 4.19_2** $^{13}$C NMR spectrum of compound **4.19** (125 MHz, $CDCl_3$)

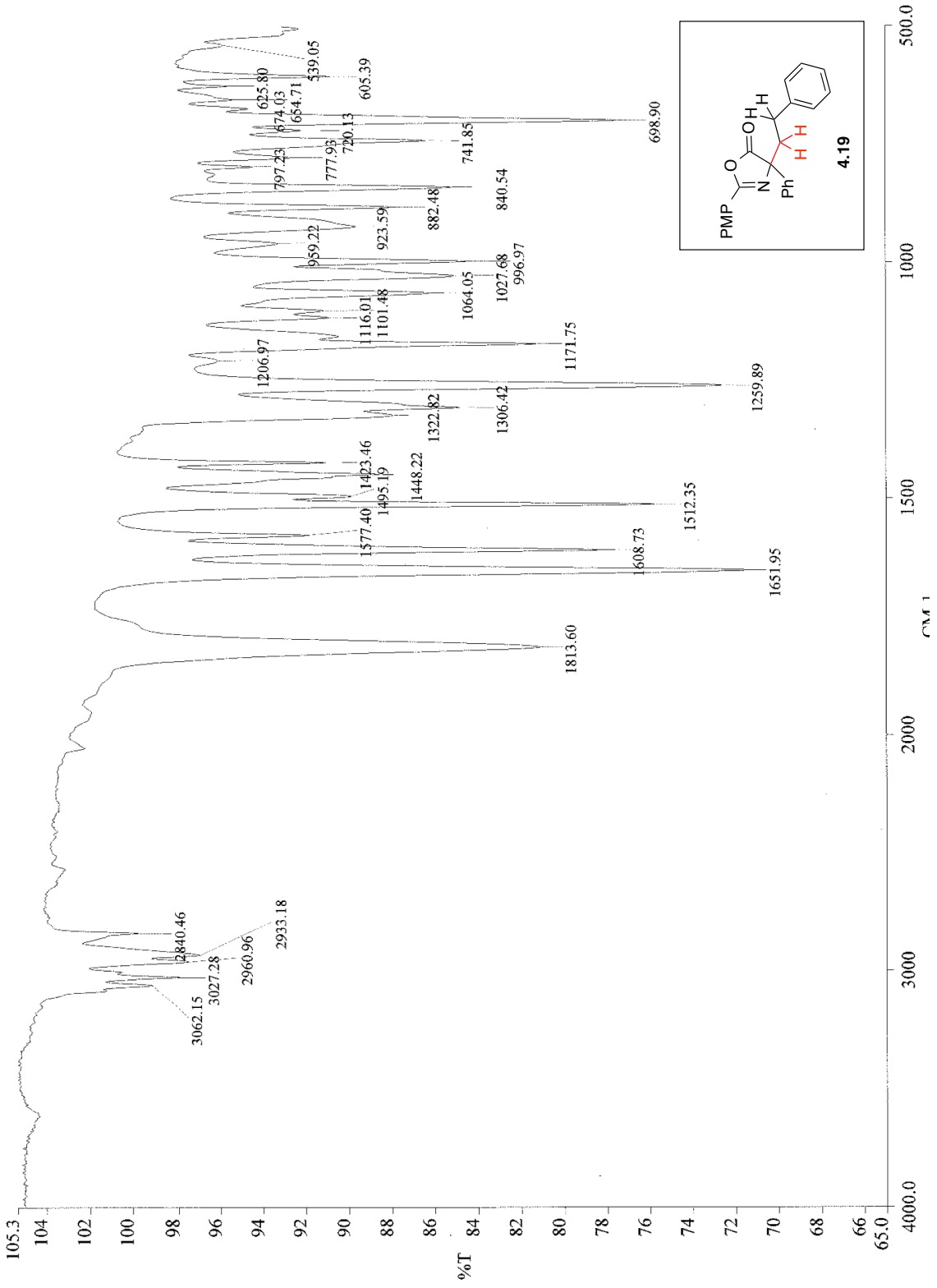



**Figure A. 4.19_3** IR spectrum of compound **4.19**

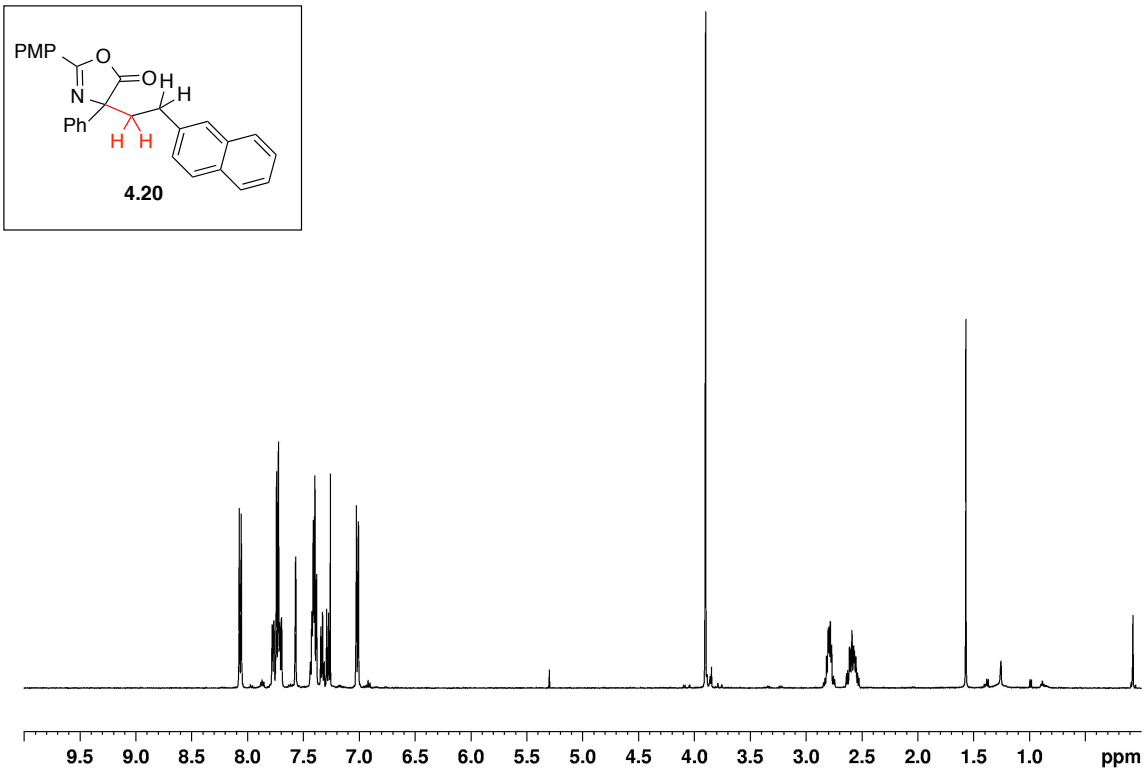



**Figure A. 4.20_1** $^{1}$H NMR spectrum of compound **4.20** (500 MHz, $CDCl_3$)

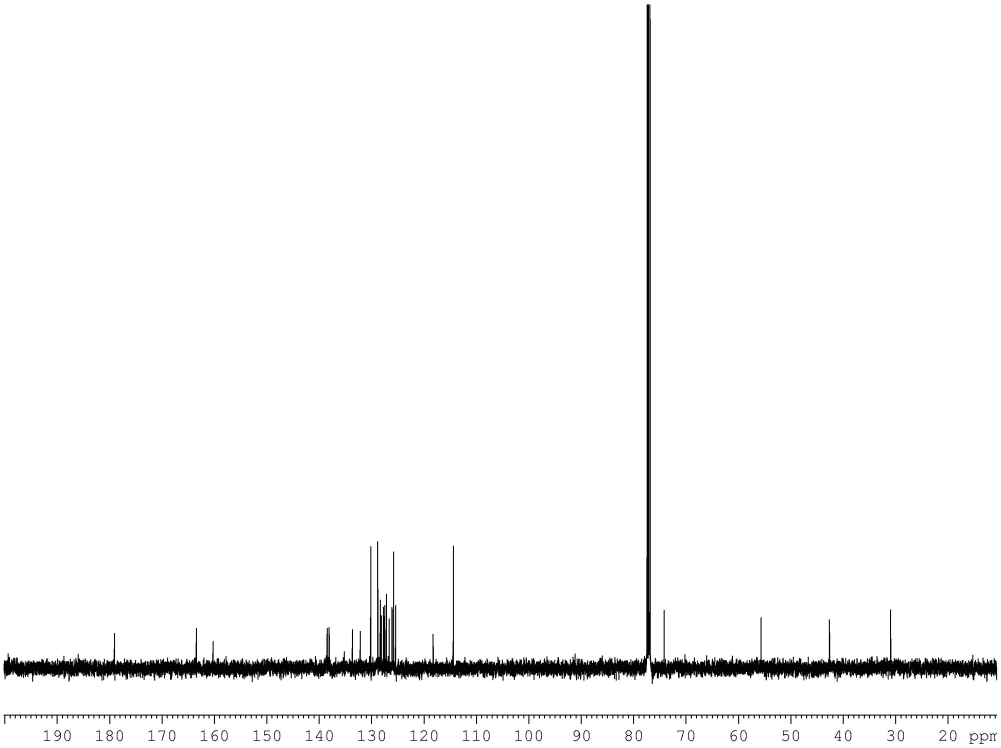



**Figure A. 4.20_2** $^{13}$C NMR spectrum of compound **4.20** (125 MHz, $CDCl_3$)

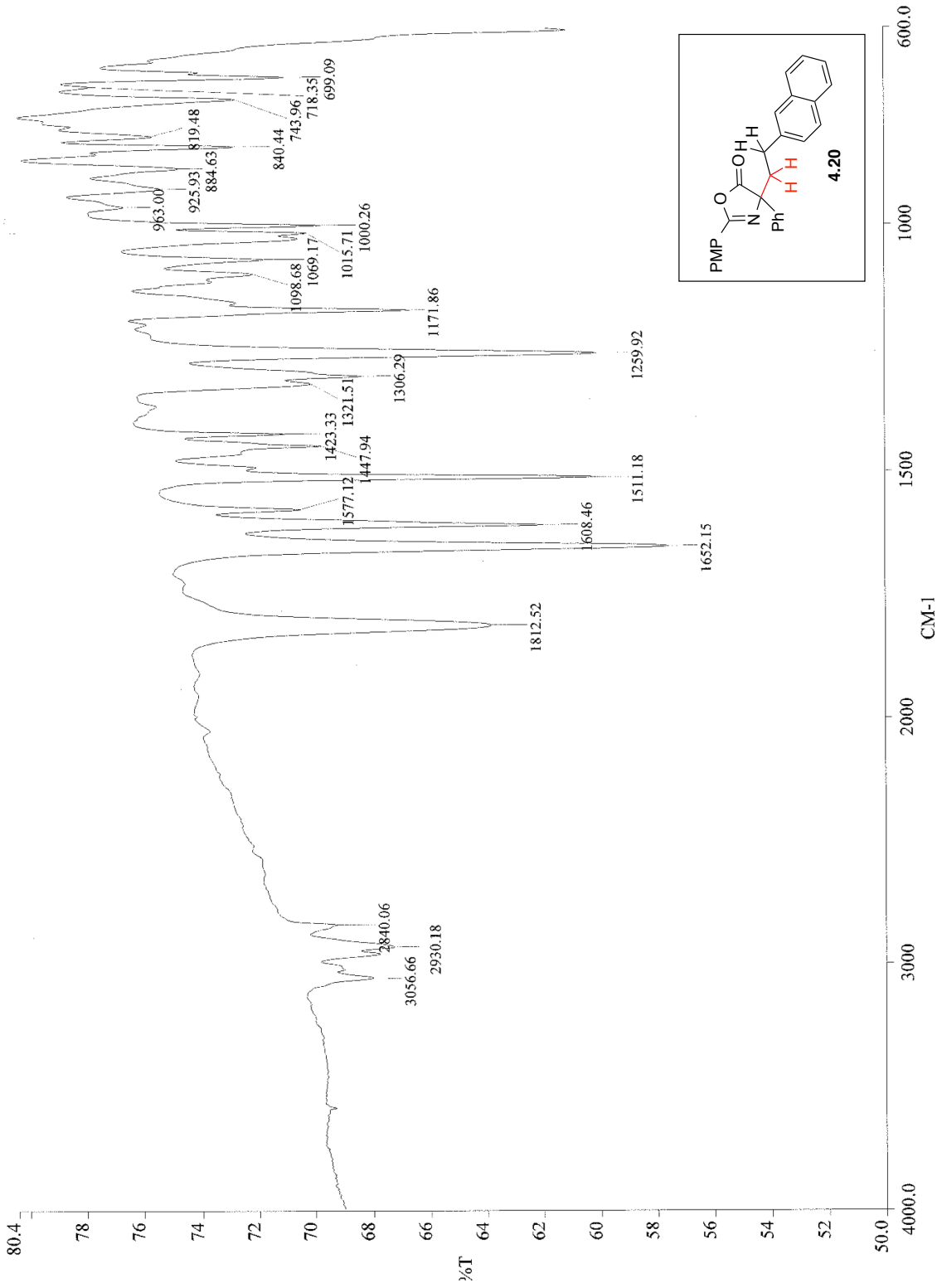



**Figure A. 4.20_3** IR spectrum of compound **4.20**

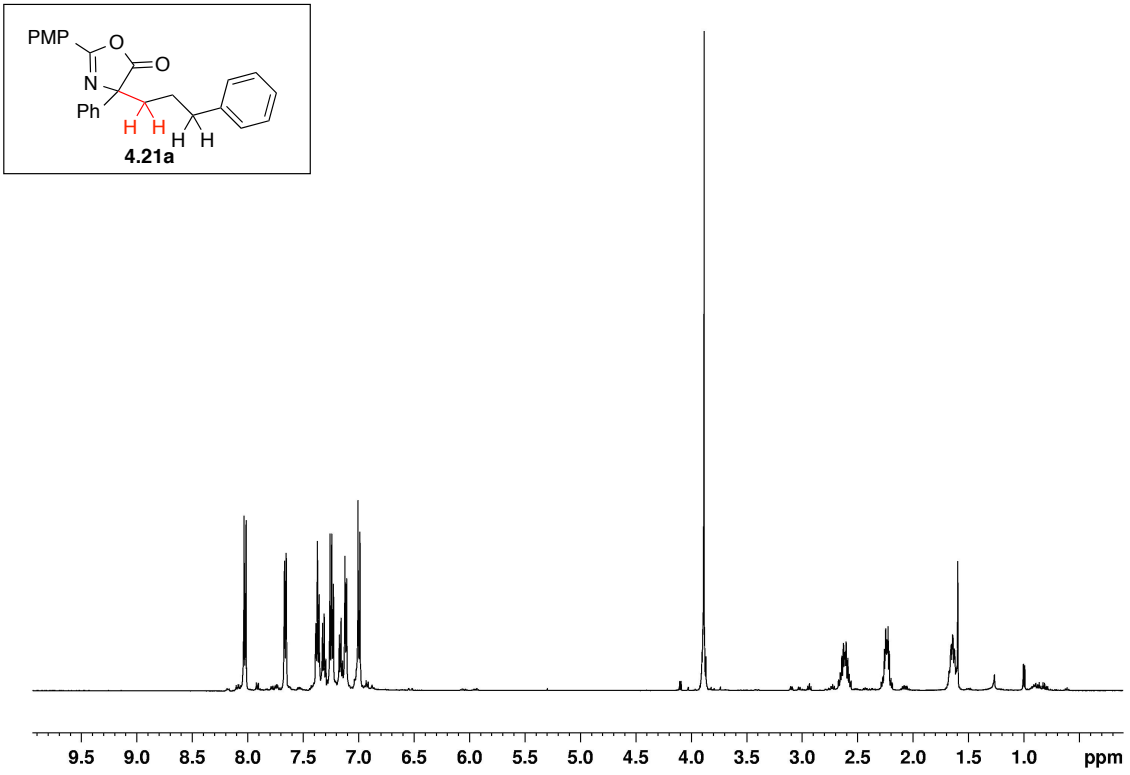



**Figure A. 4.21a_1** $^{1}$H NMR spectrum of compound **4.21a** (500 MHz, $CDCl_3$)

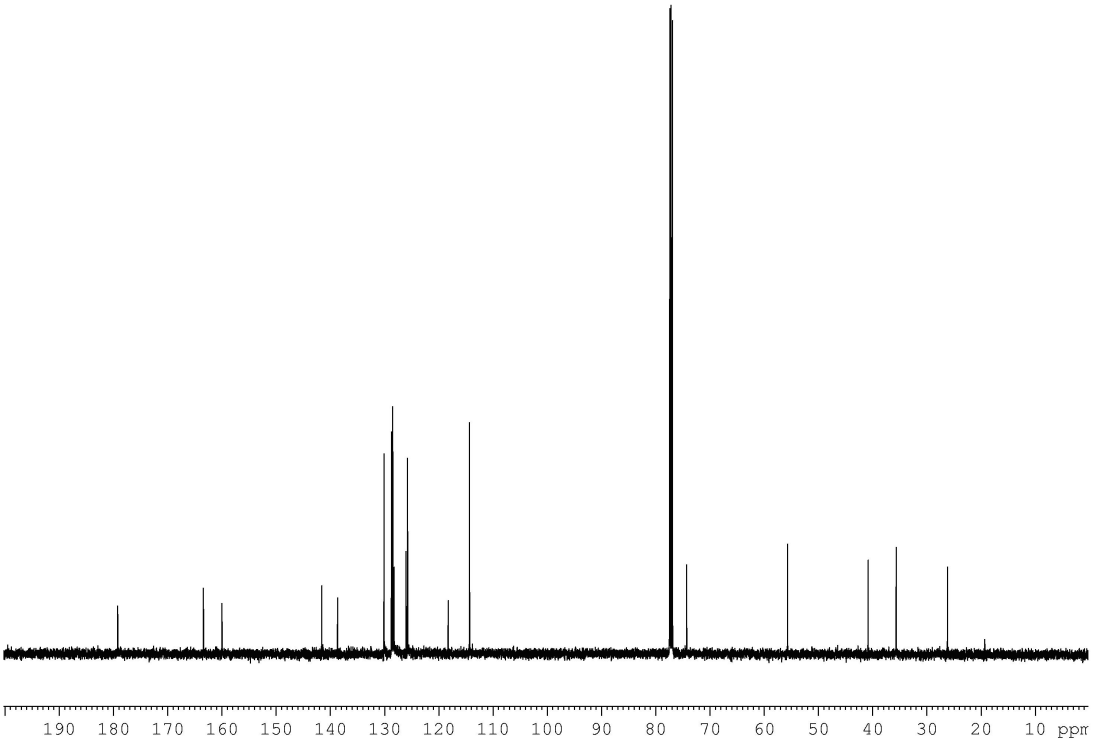



**Figure A. 4.21a_2** $^{13}$C NMR spectrum of compound **4.21a** (125 MHz, $CDCl_3$)

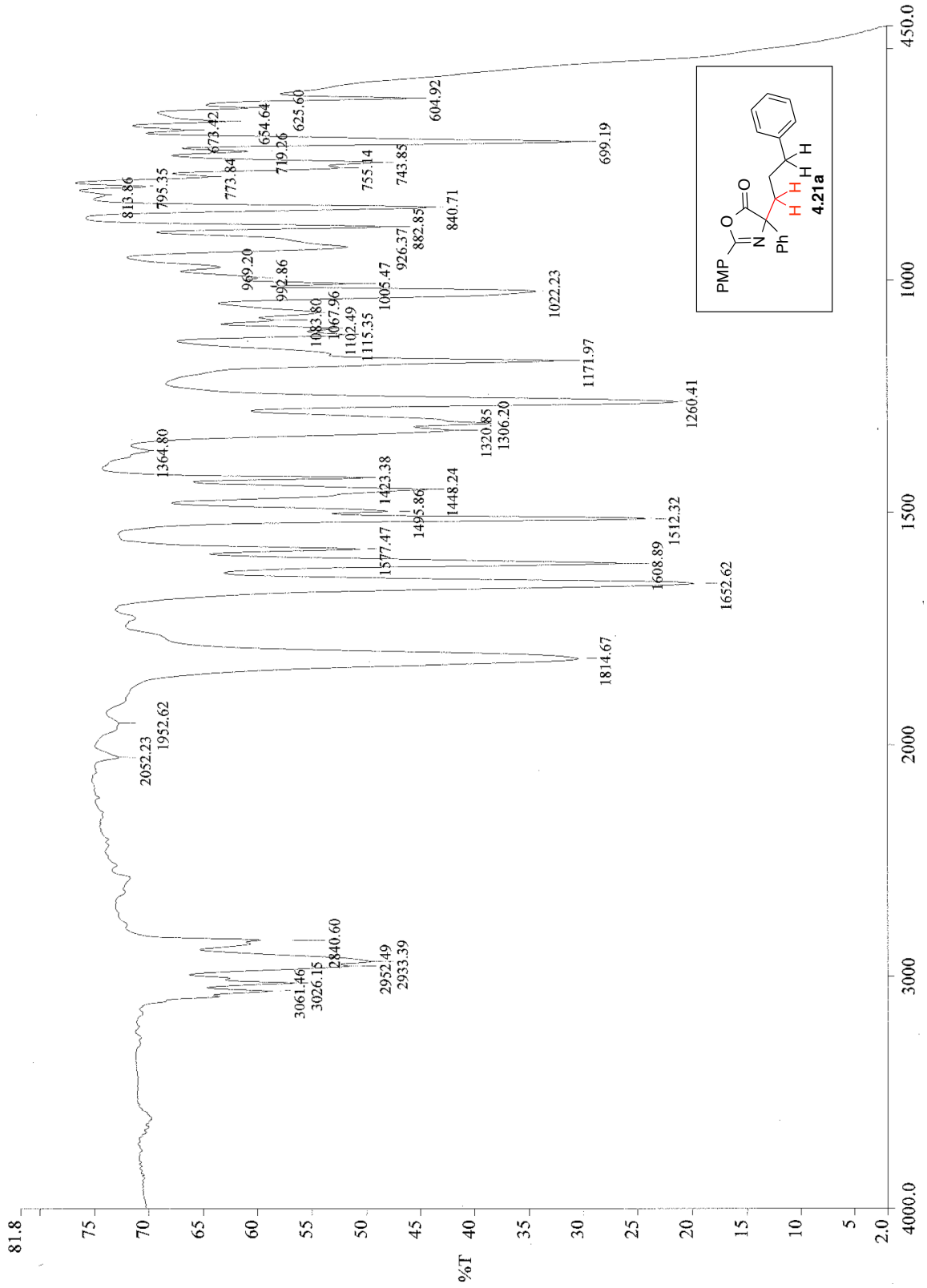



**Figure A. 4.21a_3** IR spectrum of compound **4.21a**

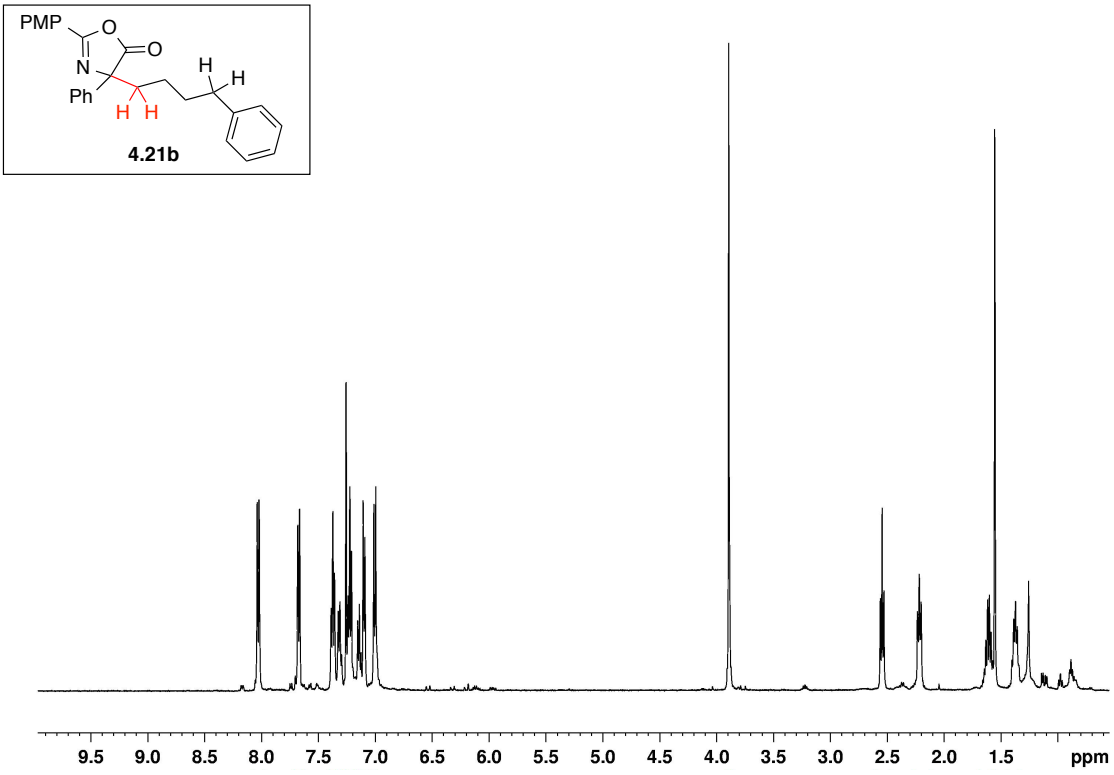



**Figure A. 4.21b_1** $^{1}$H NMR spectrum of compound **4.21b** (500 MHz, $CDCl_3$)

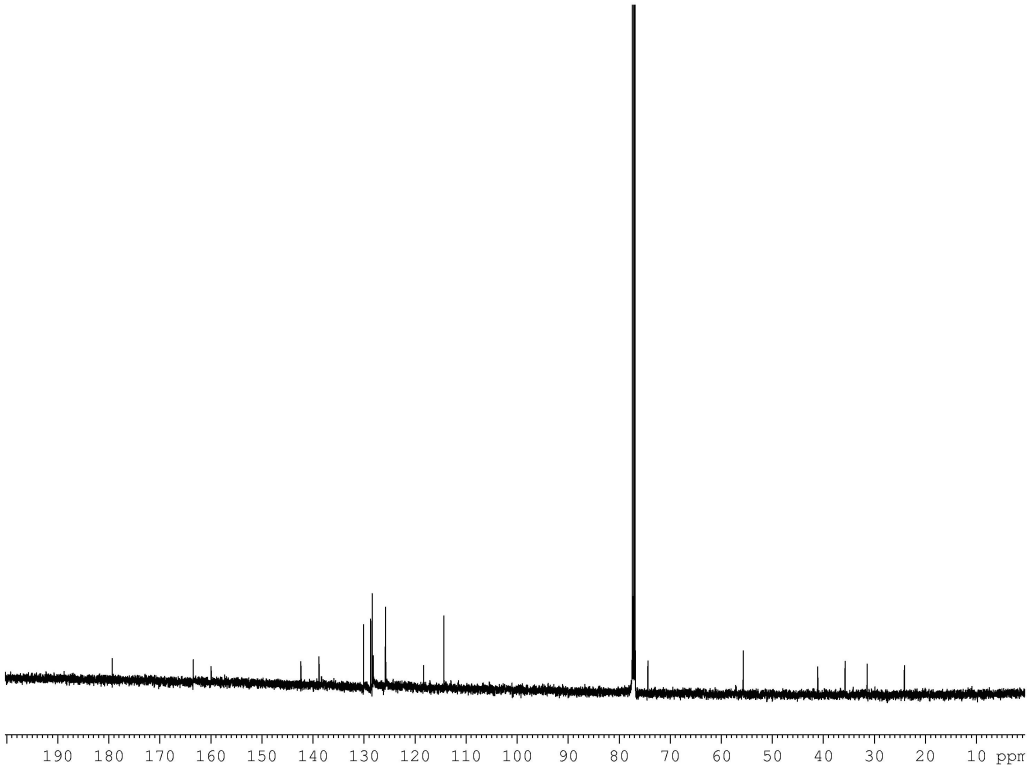



**Figure A. 4.21b_2** $^{13}$C NMR spectrum of compound **4.21b** (125 MHz, $CDCl_3$)

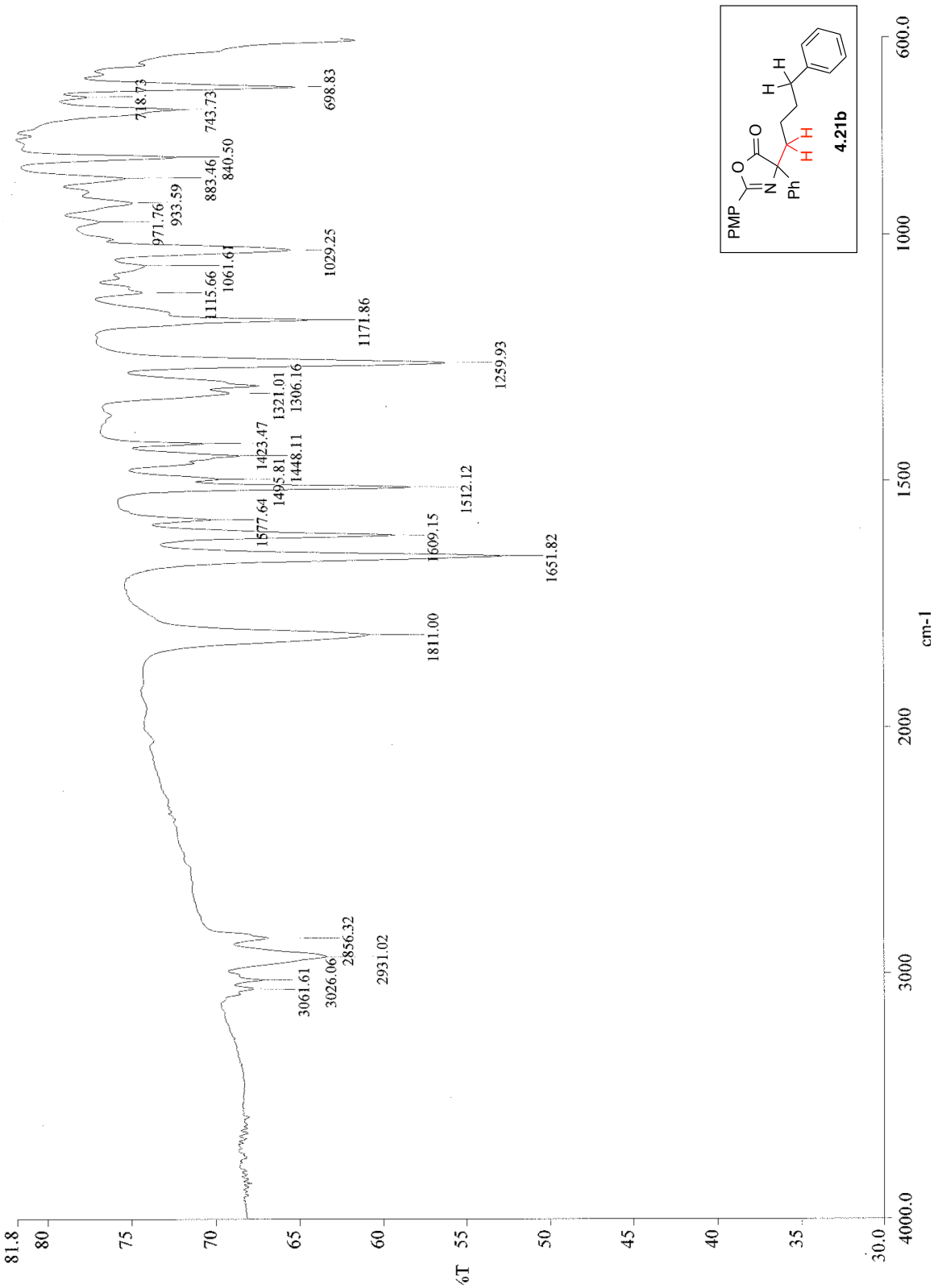



**Figure A. 4.21b_3** IR spectrum of compound **4.21b**

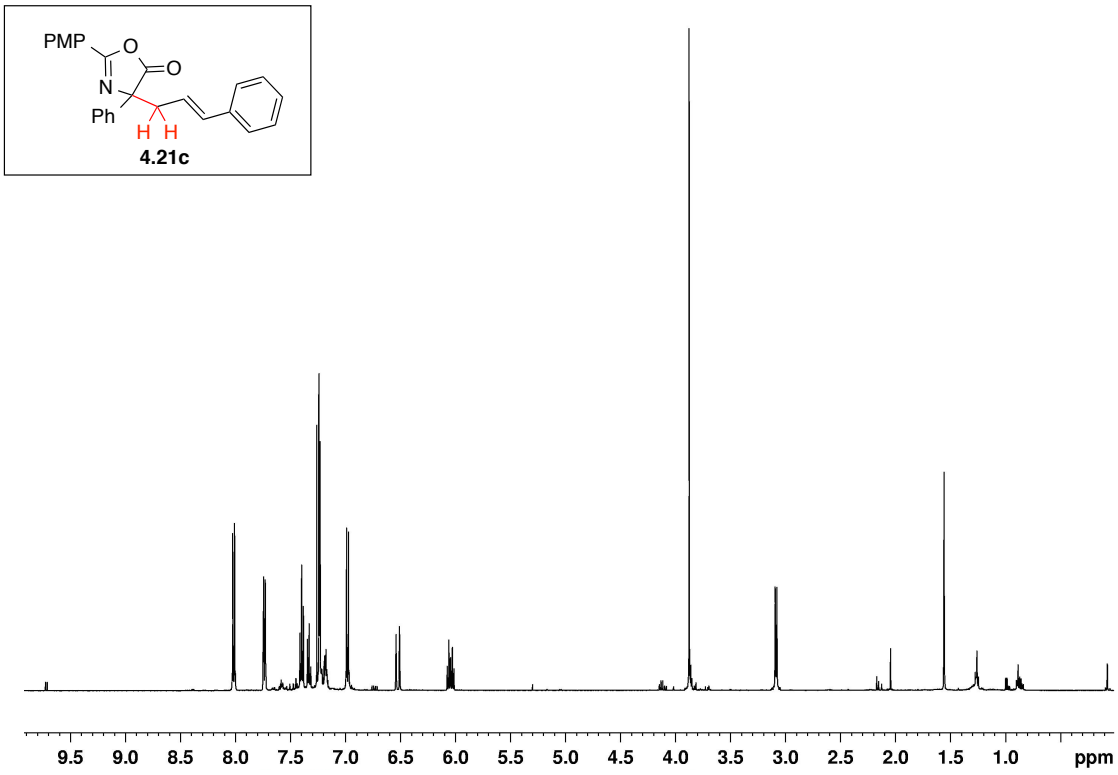



**Figure A. 4.21c_1** $^{1}$H NMR spectrum of compound **4.21c** (500 MHz, $CDCl_3$)

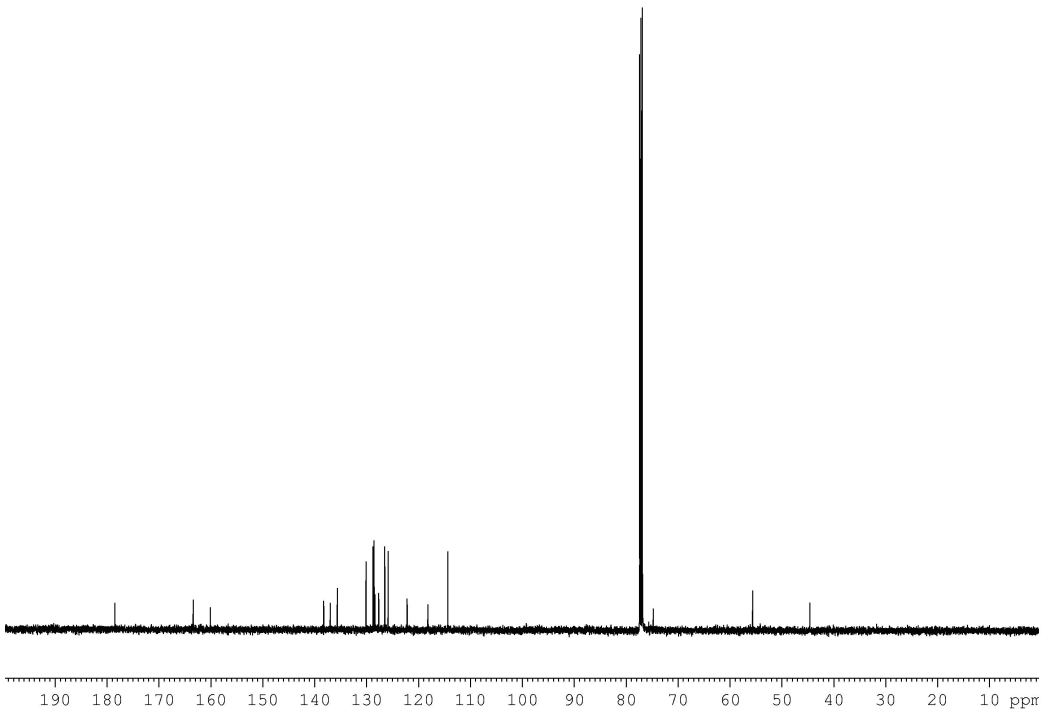



**Figure A. 4.21c_2** $^{13}$C NMR spectrum of compound **4.21c** (125 MHz, $CDCl_3$)

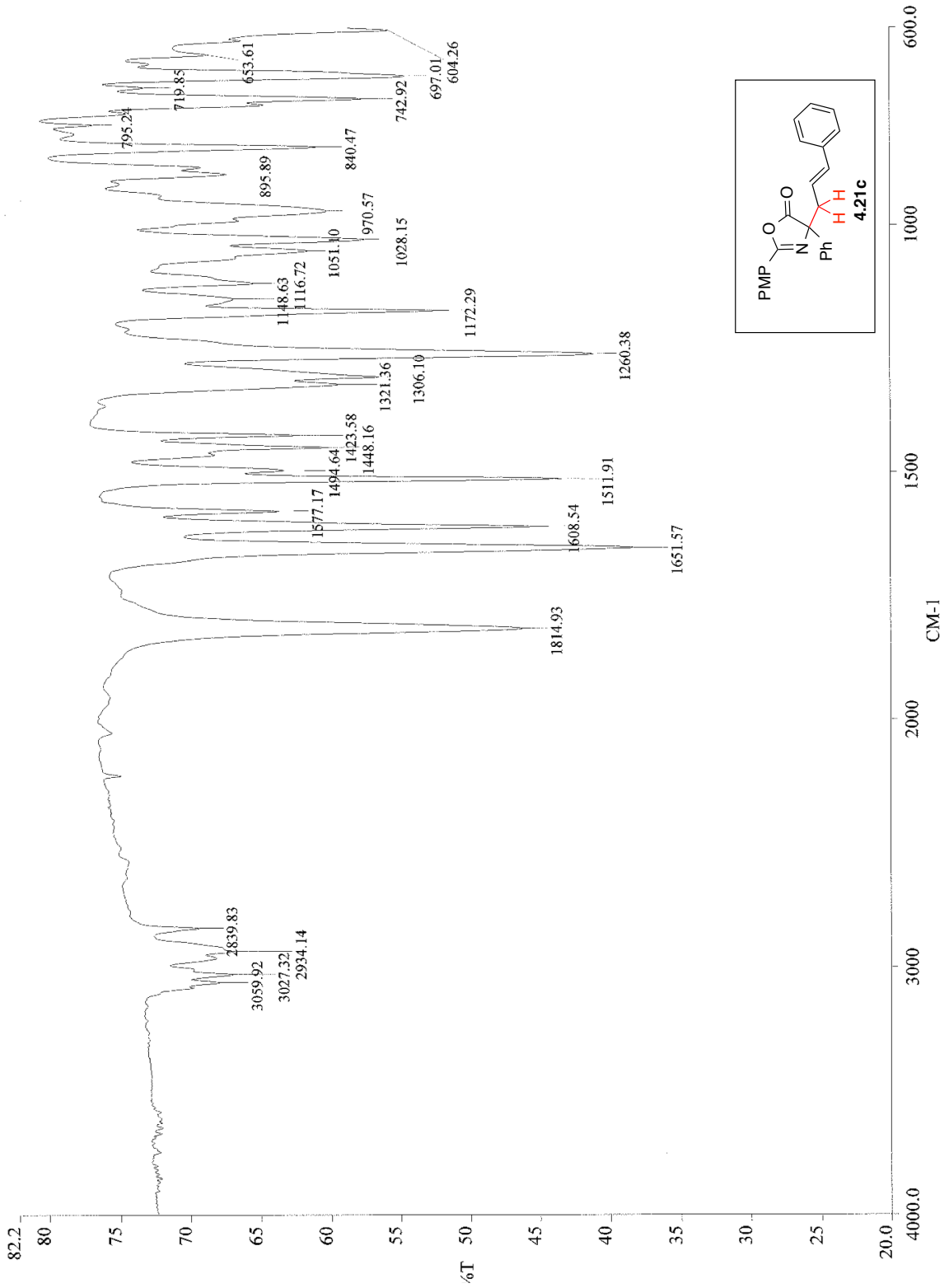



**Figure A. 4.21c_3** IR spectrum of compound **4.21c**

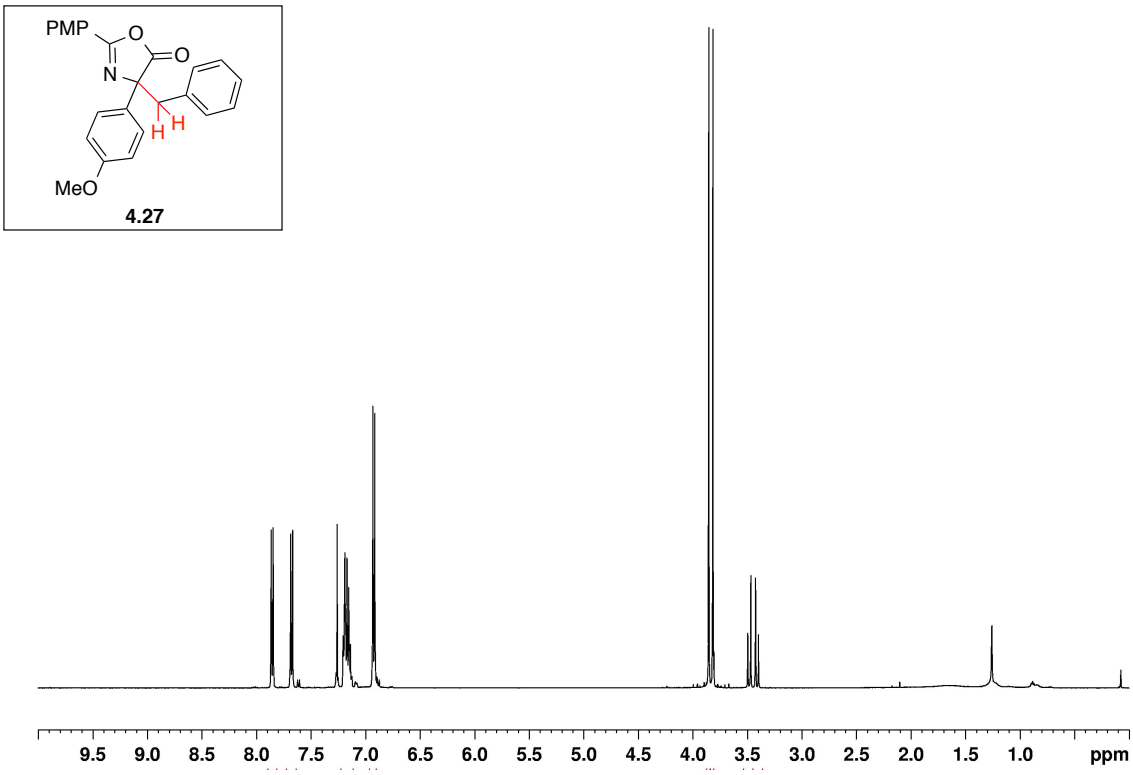



**Figure A. 4.27_1** $^{1}$H NMR spectrum of compound **4.27** (500 MHz, $CDCl_3$)

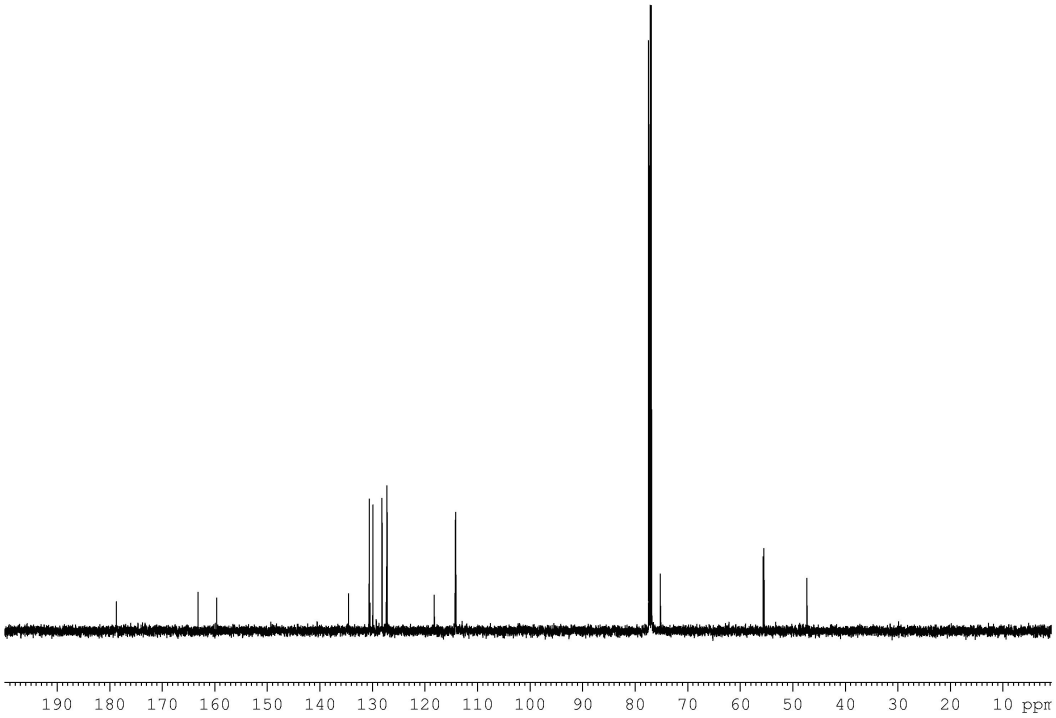
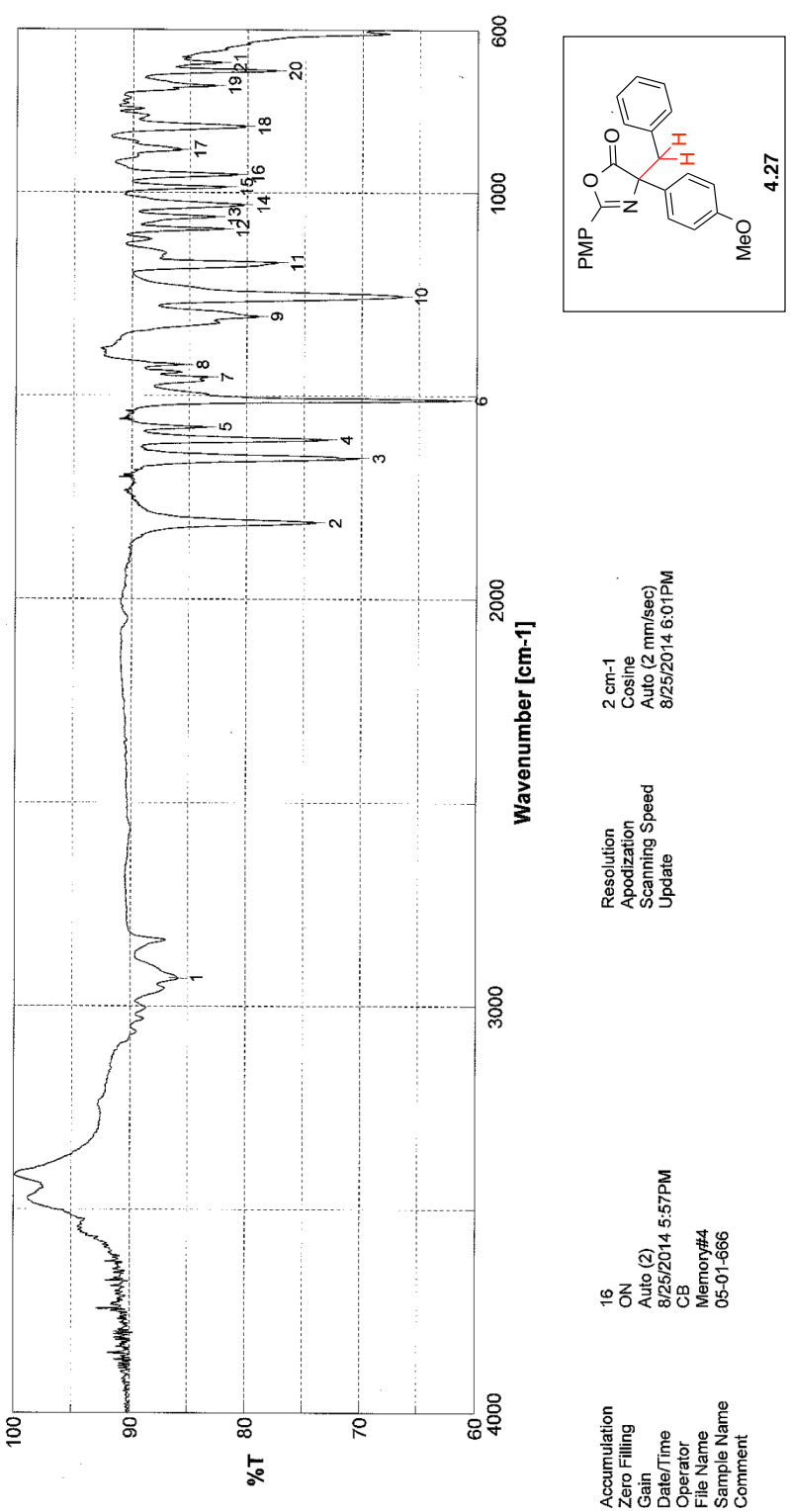



**Figure A. 4.27_2** $^{13}$C NMR spectrum of compound **4.27** (125 MHz, $CDCl_3$)

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| 6 | 1510.95 | 61.2548 | 7 | 1454.55 | 83.2876 | 8 | 1423.69 | 85.4357 | 9 | 1305.09 | 79.0308 | 10 | 1254.95 | 66.4519 |
| 11 | 1172.51 | 77.2719 | 12 | 1089.58 | 81.9971 | 13 | 1060.17 | 82.7466 | 14 | 1030.28 | 80.2636 | 15 | 986.893 | 81.6895 |
| 16 | 956.037 | 80.7482 | 17 | 894.809 | 85.7197 | 18 | 837.437 | 80.1916 | 19 | 738.121 | 82.7394 | 20 | 700.516 | 77.4801 |
| 21 | 681.231 | 82.281 | | | | | | | | | | | | |

**Figure A. 4.27_3** IR spectrum of compound **4.27**

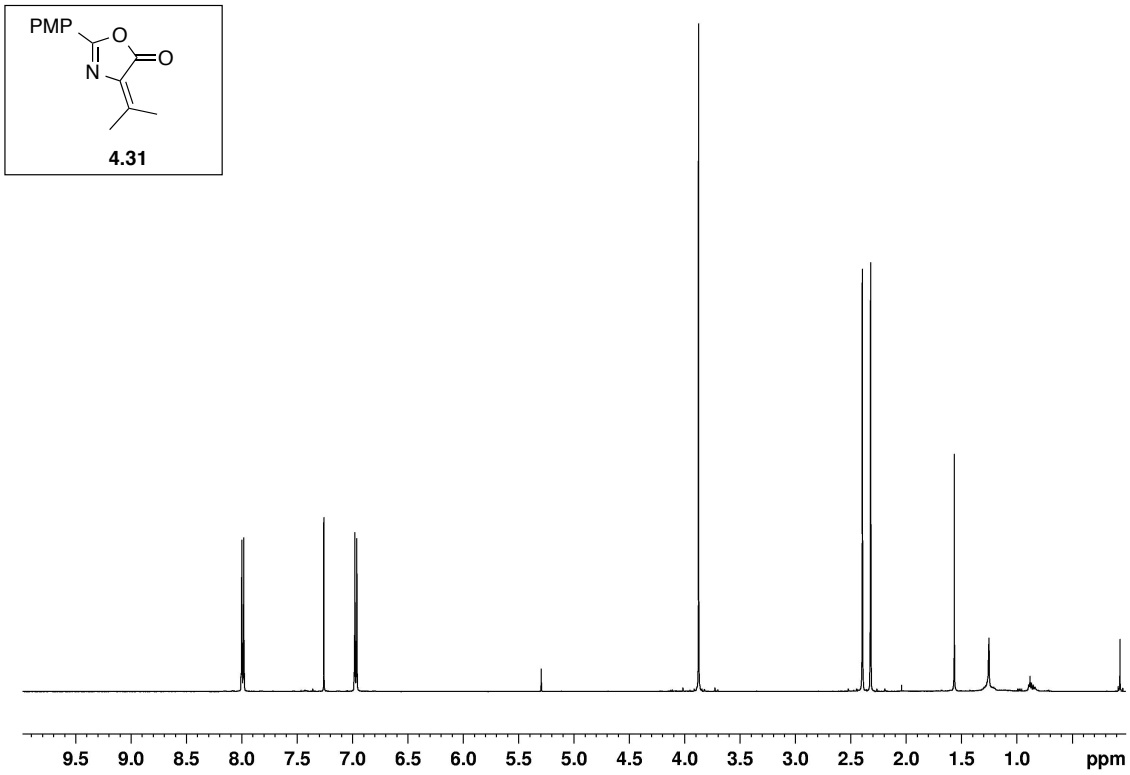



**Figure A. 4.31_1** $^{1}$H NMR spectrum of compound **4.31** (500 MHz, $CDCl_3$)

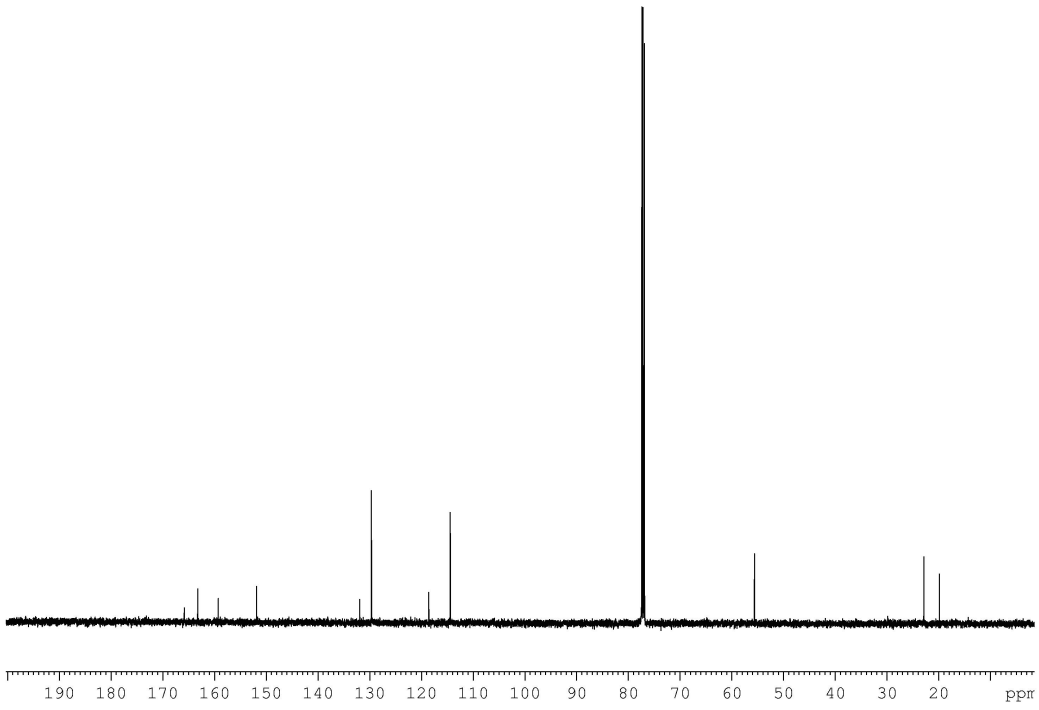



**Figure A. 4.31_2** $^{13}$C NMR spectrum of compound **4.31** (125 MHz, $CDCl_3$)

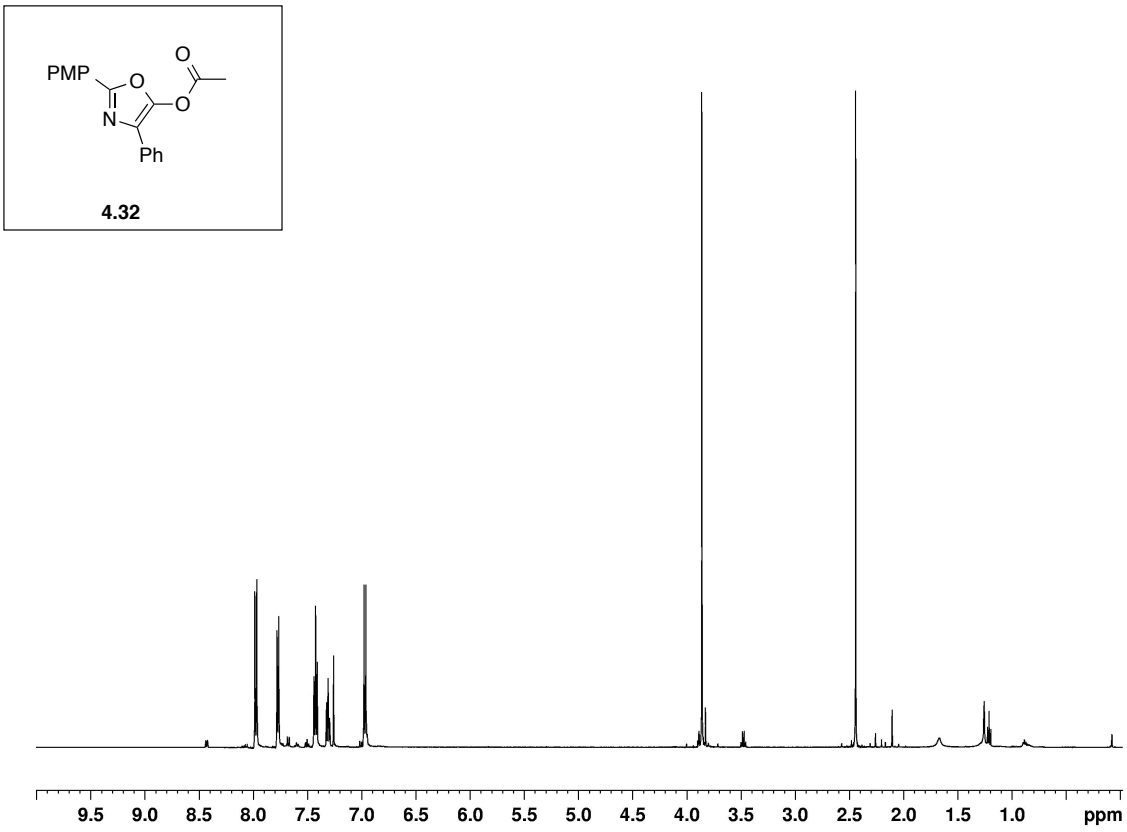



**Figure A. 4.32_1** $^{1}$H NMR spectrum of compound **4.32** (500 MHz, $CDCl_3$)

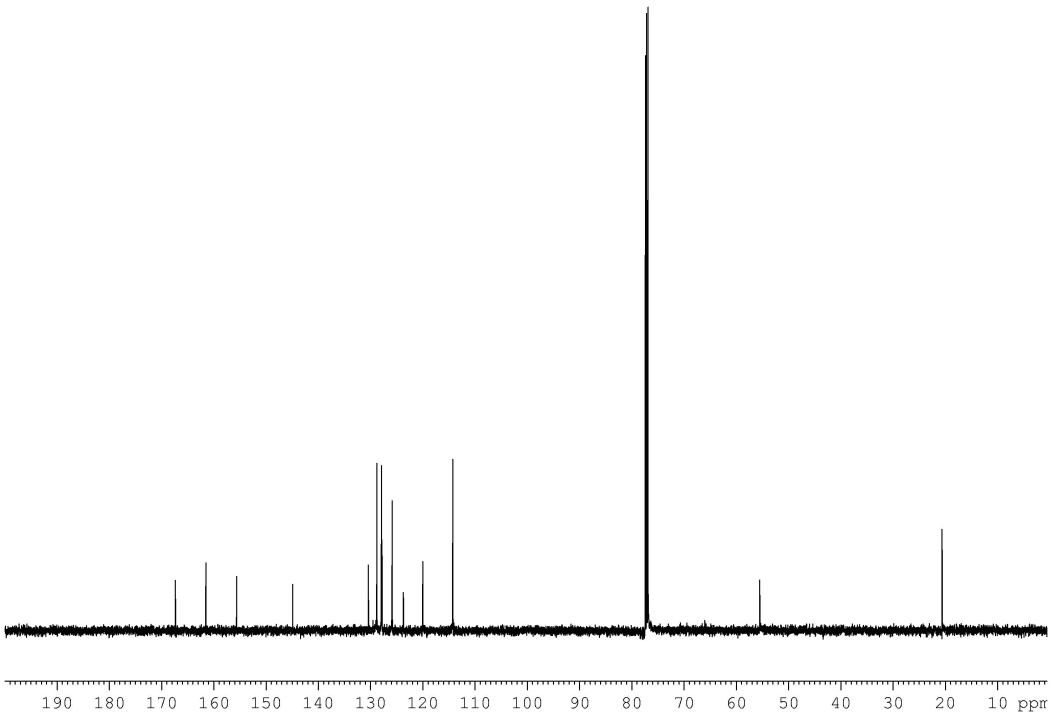


**Figure A. 4.32_2** $^{13}C$ NMR spectrum of compound **4.32** (125 MHz, $CDCl_3$)

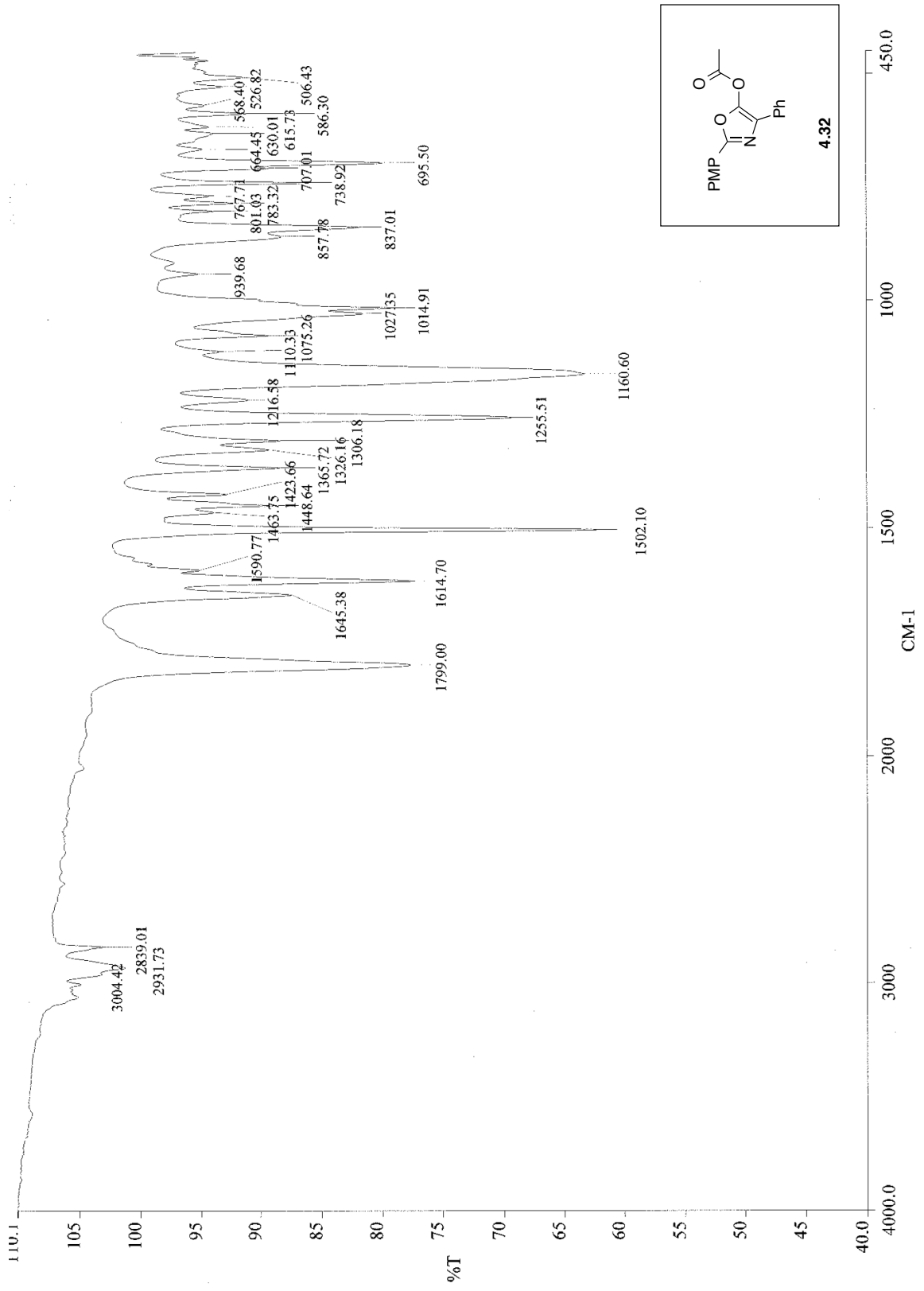


**Figure A. 4.32_3** IR spectrum of compound **4.32**

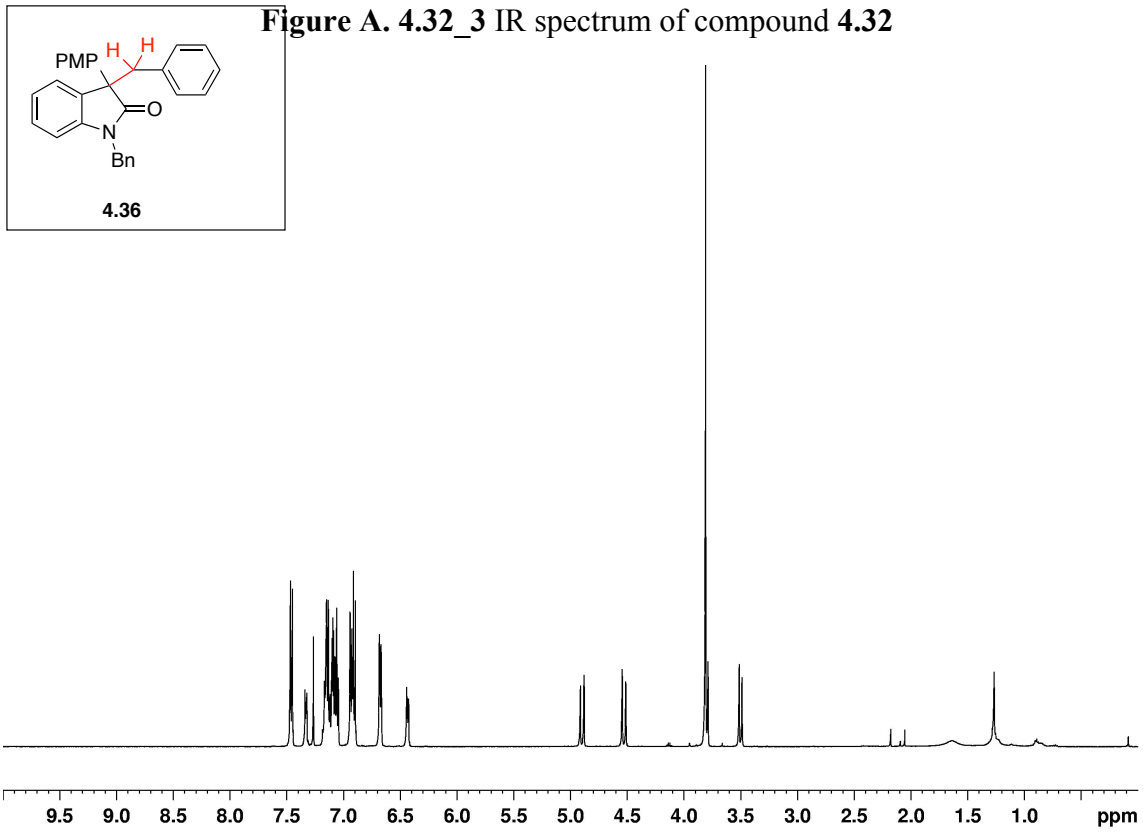



**Figure A. 4.36_1** $^{1}$H NMR spectrum of compound **4.36** (500 MHz, $CDCl_3$)

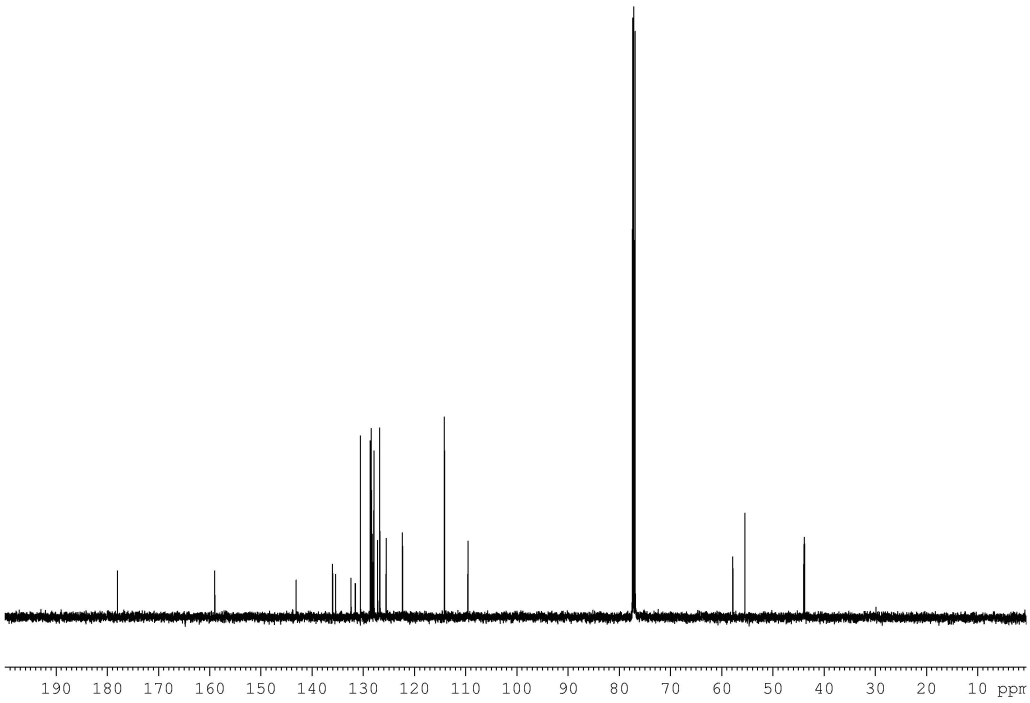


**Figure A. 4.36_2** $^{13}C$ NMR spectrum of compound **4.36** (125 MHz, $CDCl_3$)

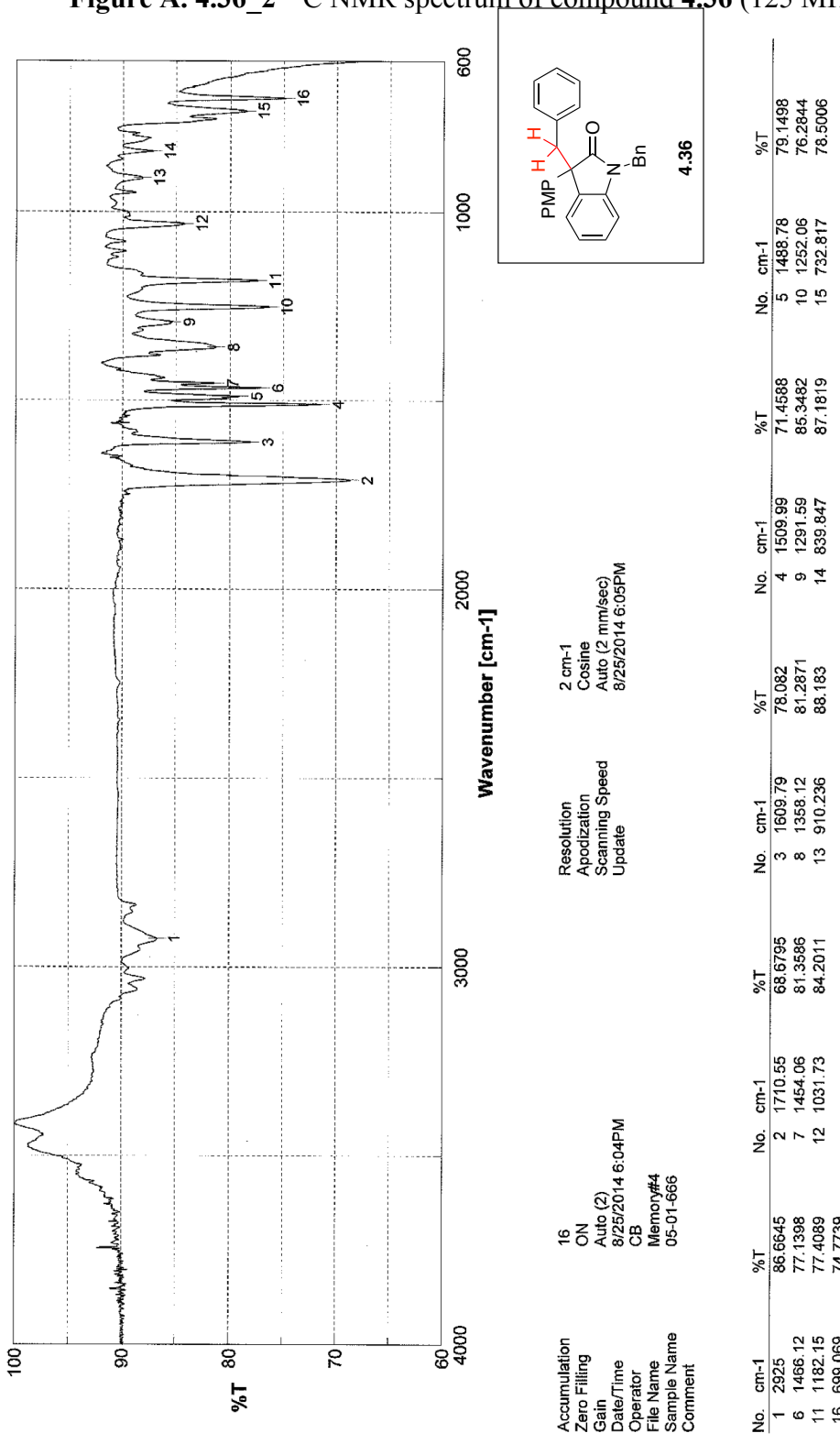
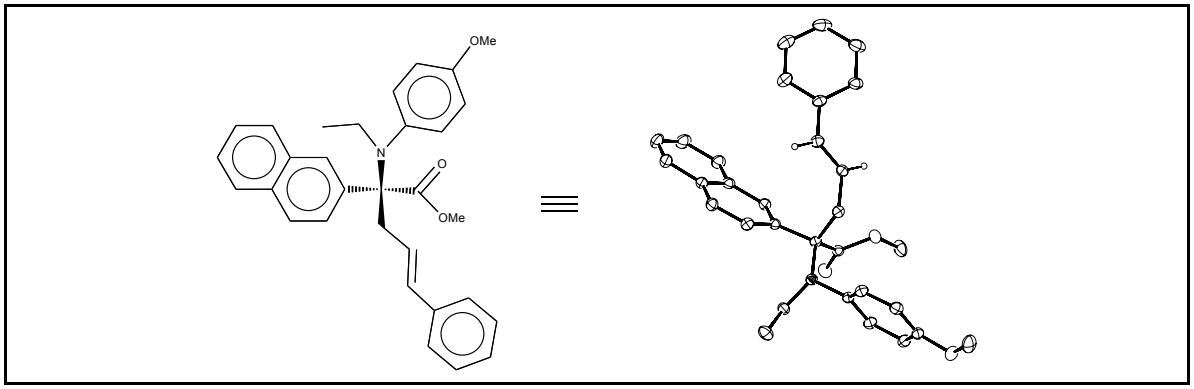



**Figure A. 4.36_3** IR spectrum of compound **4.36**

## Appendix B: X-Ray Crystallographic Data[185]

### B.1. X-Ray Structure Determination of Compound 1.03t




Compound **1.03t**, $C_{31}H_{31}NO_3$, crystallizes in the orthorhombic space group $P2_12_12_1$ (systematic absences h00: h=odd, 0k0: k=odd, and 00l: l=odd) with a=9.1082(8)Å, b=9.9885(8)Å, c=27.957(2)Å, V=2543.5(4)Å$^3$, Z=4, and $d_{calc}$=1.216 g/cm$^3$ . X-ray intensity data were collected on a Bruker APEXII CCD area detector employing graphite-monochromated Cu-K$\alpha$ radiation ($\lambda$=1.54178 Å) at a temperature of 143(1)K. Preliminary indexing was performed from a series of thirty-six 0.5° rotation frames with exposures of 10 seconds. A total of 3210 frames were collected with a crystal to detector distance of 37.6 mm, rotation widths of 0.5° and exposures of 15 seconds:

| scan type | 2θ | ω | ϕ | χ | frames |
|---|---|---|---|---|---|
| ϕ | 92.00 | 88.66 | 348.71 | -26.26 | 739 |
| ϕ | 17.00 | 30.20 | 333.95 | -55.24 | 739 |
| ϕ | 92.00 | 132.53 | 152.05 | -22.49 | 415 |
| ϕ | 17.00 | 346.55 | 43.16 | 65.91 | 79 |
| ω | -23.00 | 331.76 | 256.68 | -41.06 | 211 |
| ϕ | 87.00 | 76.65 | 30.72 | 62.65 | 739 |
| ω | 92.00 | 5.74 | 317.53 | 90.29 | 117 |

185) Dr. Patrick J. Carroll is gratefully acknowledged for solving the crystal structure of each compound.

| | | | | | |
|---|---|---|---|---|---|
| ω | 92.00 | 152.22 | 266.47 | -93.68 | 171 |

Rotation frames were integrated using SAINT[186], producing a listing of unaveraged $F^2$ and $\sigma(F^2)$ values which were then passed to the SHELXTL[187] program package for further processing and structure solution. A total of 15711 reflections were measured over the ranges $3.16 \leq \theta \leq 64.73°$, $-8 \leq h \leq 10$, $-11 \leq k \leq 11$, $-31 \leq l \leq 32$ yielding 4236 unique reflections (Rint = 0.0217). The intensity data were corrected for Lorentz and polarization effects and for absorption using SADABS[188] (minimum and maximum transmission 0.6909, 0.7525).

The structure was solved by direct methods (SHELXS-97[189]). Refinement was by full-matrix least squares based on $F^2$ using SHELXL-97.[190] All reflections were used during refinement. The weighting scheme used was $w=1/[\sigma^2(F_o^2)+ (0.0344P)^2 + 0.3013P]$ where $P = (F_o^2 + 2F_c^2)/3$. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined isotropically. Refinement converged to R1=0.0229 and wR2=0.0576 for 4181 observed reflections for which $F > 4\sigma(F)$ and R1=0.0232 and wR2=0.0579 and GOF =0.997 for all 4236 unique, non-zero reflections and 441 variables.[191] The maximum $\Delta/\sigma$ in the final cycle of least squares was 0.000 and the two most prominent peaks in the final difference Fourier were +0.108 and -0.127 e/Å$^3$. The Hooft absolute structure parameter y[192] was calculated using PLATON[193]. The resulting value was y = 0.07(5) indicating that the absolute structure has been assigned correctly.

Table B. 1 lists cell information, data collection parameters, and refinement data. Final positional and equivalent isotropic thermal parameters are given in Tables B.2 and 3. Anisotropic thermal parameters are in Table B.4. Tables B.5. and 6. list bond distances and bond angles.

186) Bruker (2009) SAINT. Bruker AXS Inc., Madison, Wisconsin, USA.
187) Bruker (2009) SHELXTL. Bruker AXS Inc., Madison, Wisconsin, USA.
188) Sheldrick, G.M. (2007) SADABS. University of Gottingen, Germany.
189) Sheldrick, G.M. (2008) Acta Cryst. A64,112-122.
190) Sheldrick, G.M. (2008) Acta Cryst. A64,112-122.
191) $R1 = S||F_o| - |F_c|| / S |F_o|$; $wR2 = [Sw(F_o^2 - F_c^2)^2/Sw(F_o^2)^2]^{½}$; $GOF = [Sw(F_o^2 - F_c^2)^2/(n - p)]^{½}$; where n = the number of reflections and p = the number of parameters refined.
192) Hooft, R.W.W., Straver, L.H., Spek, A.L. (2008) J. Appl.Cryst., 41, 96-103.
193) Spek, A.L., Acta Cryst., (2009) D65, 148-155.

Figure B.1. is an ORTEP[194] representation of the molecule with 30% probability thermal ellipsoids displayed.

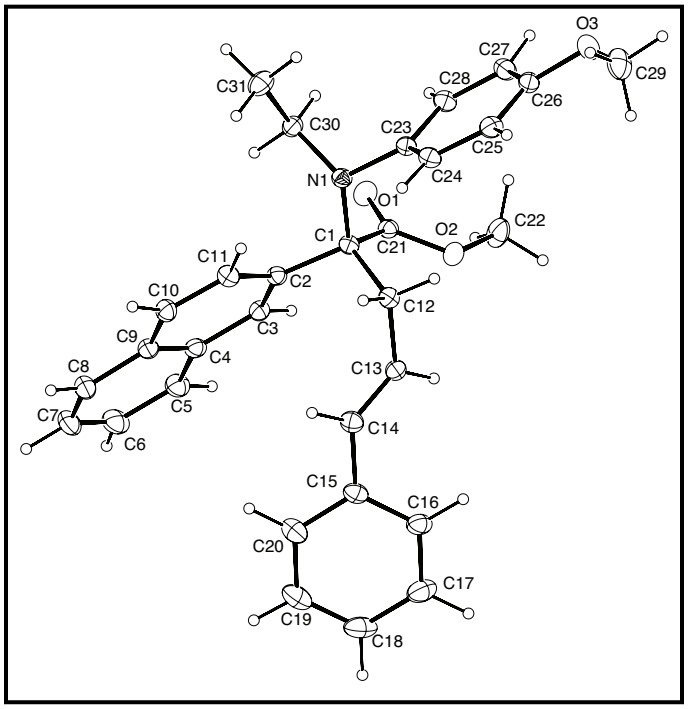



**Figure B. 1** ORTEP drawing of the title compound with 30% probability thermal ellipsoids.

**Table B. 1** Summary of Structure Determination of **1.03t**

| | |
|---|---|
| Empirical formula | $C_{31}H_{31}NO_3$ |
| Formula weight | 465.57 |
| Temperature | 143(1) K |
| Wavelength | 1.54178 Å |
| Crystal system | orthorhombic |
| Space group | $P2_12_12_1$ |

194) "ORTEP-II: A Fortran Thermal Ellipsoid Plot Program for Crystal Structure Illustrations". C.K. Johnson (1976) ORNL-5138.

| | |
|---|---|
| Cell constants: | |
| a | 9.1082(8) Å |
| b | 9.9885(8) Å |
| c | 27.957(2) Å |
| Volume | 2543.5(4) $Å^3$ |
| Z | 4 |
| Density (calculated) | 1.216 $Mg/m^3$ |
| Absorption coefficient | 0.612 $mm^{-1}$ |
| F(000) | 992 |
| Crystal size | 0.46 x 0.24 x 0.22 $mm^3$ |
| Theta range for data collection | 3.16 to 64.73° |
| Index ranges | $-8 \leq h \leq 10$, $-11 \leq k \leq 11$, $-31 \leq l \leq 32$ |
| Reflections collected | 15711 |
| Independent reflections | 4236 [R(int) = 0.0217] |
| Completeness to theta = 64.73° | 99.2 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.7525 and 0.6909 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 4236 / 0 / 441 |
| Goodness-of-fit on $F^2$ | 0.997 |
| Final R indices [I>2sigma(I)] | R1 = 0.0229, wR2 = 0.0576 |
| R indices (all data) | R1 = 0.0232, wR2 = 0.0579 |
| Absolute structure parameter | 0.07(13) |

| | |
|---|---|
| Largest diff. peak and hole | 0.108 and -0.127 e.Å$^{-3}$ |

**Table B. 2** Refined Positional Parameters for **1.03t**

| Atom | x | y | z | $U_{eq}$, Å$^2$ |
|---|---|---|---|---|
| C1 | 0.70625(11) | 0.13558(11) | 0.33358(4) | 0.0237(2) |
| C2 | 0.58884(12) | 0.09598(10) | 0.36990(4) | 0.0246(2) |
| C3 | 0.60282(13) | 0.11924(11) | 0.41793(4) | 0.0267(2) |
| C4 | 0.48283(13) | 0.10002(11) | 0.44969(4) | 0.0288(2) |
| C5 | 0.49489(16) | 0.12586(13) | 0.49937(4) | 0.0370(3) |
| C6 | 0.37594(17) | 0.10776(15) | 0.52875(5) | 0.0457(3) |
| C7 | 0.24080(16) | 0.06406(15) | 0.51047(5) | 0.0458(3) |
| C8 | 0.22518(15) | 0.03806(13) | 0.46292(5) | 0.0395(3) |
| C9 | 0.34642(13) | 0.05417(11) | 0.43143(4) | 0.0301(2) |
| C10 | 0.33568(13) | 0.02671(12) | 0.38197(4) | 0.0313(3) |
| C11 | 0.45188(12) | 0.04807(11) | 0.35213(4) | 0.0292(2) |
| C12 | 0.65416(13) | 0.26935(11) | 0.31062(4) | 0.0265(2) |
| C13 | 0.62886(12) | 0.38211(11) | 0.34505(4) | 0.0264(2) |
| C14 | 0.49860(13) | 0.41081(12) | 0.36376(4) | 0.0310(2) |
| C15 | 0.46910(12) | 0.51849(11) | 0.39839(4) | 0.0304(2) |
| C16 | 0.54879(15) | 0.63732(12) | 0.39813(4) | 0.0373(3) |
| C17 | 0.52180(19) | 0.73625(13) | 0.43173(5) | 0.0470(4) |
| C18 | 0.41485(19) | 0.71749(15) | 0.46638(5) | 0.0495(4) |
| C19 | 0.33551(17) | 0.59990(17) | 0.46714(5) | 0.0505(4) |
| C20 | 0.36132(15) | 0.50159(15) | 0.43336(5) | 0.0421(3) |
| C21 | 0.86021(12) | 0.14710(11) | 0.35629(4) | 0.0246(2) |
| C22 | 1.07987(15) | 0.27307(14) | 0.35763(7) | 0.0466(3) |
| C23 | 0.80837(12) | 0.06319(10) | 0.25533(4) | 0.0255(2) |
| C24 | 0.74910(13) | 0.11831(13) | 0.21416(4) | 0.0291(2) |
| C25 | 0.83615(14) | 0.14806(12) | 0.17459(4) | 0.0313(3) |
| C26 | 0.98553(13) | 0.11816(12) | 0.17592(4) | 0.0306(2) |

| | | | | |
|---|---|---|---|---|
| C27 | 1.04568(13) | 0.06045(13) | 0.21651(4) | 0.0326(3) |
| C28 | 0.95878(13) | 0.03440(12) | 0.25583(4) | 0.0298(2) |
| C29 | 1.0300(2) | 0.20895(17) | 0.09817(5) | 0.0493(4) |
| C30 | 0.73005(13) | -0.10747(11) | 0.31172(4) | 0.0283(2) |
| C31 | 0.65707(18) | -0.20050(14) | 0.27643(5) | 0.0407(3) |
| N1 | 0.71376(10) | 0.03253(9) | 0.29535(3) | 0.0251(2) |
| O1 | 0.91847(9) | 0.05988(8) | 0.37919(3) | 0.03344(19) |
| O2 | 0.92711(9) | 0.26149(8) | 0.34421(3) | 0.03284(19) |
| O3 | 1.08149(10) | 0.13777(9) | 0.13881(3) | 0.0396(2) |

$U_{eq}=^{1}/_{3}[U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*\cos\gamma+2U_{13}aa^*cc^*\cos\beta+2U_{23}bb^*cc^*\cos\alpha]$

**Table B. 3** Positional Parameters for Hydrogens in **1.03t**

| Atom | x | y | z | $U_{iso}$, $A^2$ |
|---|---|---|---|---|
| H3 | 0.6960(14) | 0.1502(13) | 0.4311(4) | 0.027(3) |
| H5 | 0.5925(17) | 0.1611(15) | 0.5128(5) | 0.041(4) |
| H6 | 0.3931(16) | 0.1268(16) | 0.5627(5) | 0.045(4) |
| H7 | 0.1558(19) | 0.0523(17) | 0.5308(6) | 0.058(5) |
| H8 | 0.1297(16) | 0.0077(14) | 0.4530(5) | 0.035(3) |
| H10 | 0.2451(18) | -0.0129(15) | 0.3690(5) | 0.041(4) |
| H11 | 0.4446(15) | 0.0278(14) | 0.3170(5) | 0.037(3) |
| H12a | 0.7228(15) | 0.2952(13) | 0.2859(5) | 0.029(3) |
| H12b | 0.5615(15) | 0.2498(12) | 0.2939(4) | 0.028(3) |
| H13 | 0.7142(16) | 0.4341(14) | 0.3548(5) | 0.037(4) |
| H14 | 0.4149(16) | 0.3550(15) | 0.3559(5) | 0.038(3) |
| H16 | 0.6260(18) | 0.6517(16) | 0.3743(5) | 0.045(4) |
| H17 | 0.578(2) | 0.8231(19) | 0.4303(6) | 0.069(5) |
| H18 | 0.3952(19) | 0.7885(16) | 0.4899(6) | 0.054(4) |
| H19 | 0.2618(19) | 0.5831(16) | 0.4905(6) | 0.055(5) |
| H20 | 0.3056(17) | 0.4165(16) | 0.4339(5) | 0.048(4) |

| | | | | |
|---|---|---|---|---|
| H22a | 1.098(2) | 0.2469(18) | 0.3912(7) | 0.063(5) |
| H22b | 1.109(2) | 0.367(2) | 0.3494(6) | 0.068(5) |
| H22c | 1.138(2) | 0.206(2) | 0.3366(7) | 0.075(6) |
| H24 | 0.6431(15) | 0.1362(14) | 0.2133(4) | 0.031(3) |
| H25 | 0.7922(16) | 0.1849(14) | 0.1455(5) | 0.038(4) |
| H27 | 1.1498(18) | 0.0333(16) | 0.2170(5) | 0.045(4) |
| H28 | 1.0044(16) | -0.0038(14) | 0.2856(5) | 0.037(3) |
| H29a | 0.9533(19) | 0.1634(17) | 0.0818(6) | 0.053(5) |
| H29b | 1.116(2) | 0.2173(19) | 0.0774(7) | 0.067(5) |
| H29c | 0.9913(19) | 0.3007(17) | 0.1070(6) | 0.056(4) |
| H30a | 0.6813(13) | -0.1166(13) | 0.3441(4) | 0.024(3) |
| H30b | 0.8355(15) | -0.1330(14) | 0.3170(5) | 0.035(3) |
| H31a | 0.550(2) | -0.1753(17) | 0.2735(6) | 0.060(5) |
| H31b | 0.6623(17) | -0.2953(17) | 0.2867(6) | 0.048(4) |
| H31c | 0.7007(19) | -0.1948(16) | 0.2445(6) | 0.056(5) |

**Table B. 4** Refined Thermal Parameters (U's) for **1.03t**

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| C1 | 0.0239(5) | 0.0253(5) | 0.0218(5) | -0.0009(4) | -0.0006(4) | 0.0009(5) |
| C2 | 0.0251(5) | 0.0231(5) | 0.0257(5) | 0.0008(4) | 0.0007(4) | 0.0026(4) |
| C3 | 0.0283(6) | 0.0246(5) | 0.0271(5) | 0.0008(4) | -0.0004(4) | 0.0002(5) |
| C4 | 0.0349(6) | 0.0231(5) | 0.0283(5) | 0.0023(4) | 0.0026(5) | 0.0052(5) |
| C5 | 0.0456(7) | 0.0370(6) | 0.0284(6) | 0.0001(5) | 0.0047(5) | 0.0028(6) |
| C6 | 0.0581(9) | 0.0476(8) | 0.0314(7) | 0.0018(6) | 0.0127(6) | 0.0078(7) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C7 | 0.0465(8) | 0.0462(8) | 0.0447(7) | 0.0084(6) | 0.0218(7) | 0.0060(6) |
| C8 | 0.0346(7) | 0.0348(6) | 0.0490(7) | 0.0066(6) | 0.0125(6) | 0.0026(6) |
| C9 | 0.0304(6) | 0.0249(5) | 0.0350(6) | 0.0043(5) | 0.0052(5) | 0.0040(5) |
| C10 | 0.0247(6) | 0.0312(6) | 0.0378(6) | 0.0012(5) | -0.0002(5) | -0.0010(5) |
| C11 | 0.0272(6) | 0.0321(6) | 0.0283(6) | -0.0001(5) | -0.0019(4) | 0.0013(5) |
| C12 | 0.0271(6) | 0.0287(6) | 0.0237(5) | 0.0025(5) | -0.0006(5) | 0.0023(5) |
| C13 | 0.0279(6) | 0.0247(5) | 0.0266(5) | 0.0030(4) | -0.0016(4) | 0.0020(5) |
| C14 | 0.0273(6) | 0.0335(6) | 0.0320(6) | -0.0010(5) | -0.0023(5) | 0.0032(5) |
| C15 | 0.0291(6) | 0.0346(6) | 0.0276(5) | 0.0017(5) | -0.0016(5) | 0.0105(5) |
| C16 | 0.0497(7) | 0.0297(6) | 0.0326(6) | 0.0038(5) | 0.0064(6) | 0.0107(6) |
| C17 | 0.0721(10) | 0.0302(6) | 0.0388(7) | 0.0008(5) | 0.0023(7) | 0.0096(7) |
| C18 | 0.0720(10) | 0.0439(7) | 0.0327(6) | -0.0047(6) | 0.0037(7) | 0.0223(8) |
| C19 | 0.0481(8) | 0.0640(10) | 0.0393(7) | -0.0049(7) | 0.0133(6) | 0.0109(7) |
| C20 | 0.0337(7) | 0.0523(8) | 0.0403(7) | -0.0049(6) | 0.0063(6) | 0.0027(6) |
| C21 | 0.0261(5) | 0.0244(5) | 0.0233(5) | -0.0029(4) | 0.0007(4) | 0.0006(4) |
| C22 | 0.0250(6) | 0.0363(7) | 0.0786(11) | 0.0103(7) | -0.0098(7) | -0.0050(6) |
| C23 | 0.0274(6) | 0.0251(5) | 0.0238(5) | -0.0029(4) | 0.0023(4) | 0.0000(4) |
| C24 | 0.0284(6) | 0.0321(6) | 0.0269(5) | -0.0031(5) | 0.0001(4) | 0.0026(5) |
| C25 | 0.0390(7) | 0.0302(6) | 0.0247(5) | -0.0006(5) | -0.0007(5) | 0.0019(5) |
| C26 | 0.0362(6) | 0.0284(5) | 0.0272(5) | -0.0048(5) | 0.0072(5) | -0.0041(5) |
| C27 | 0.0283(6) | 0.0367(6) | 0.0327(6) | -0.0047(5) | 0.0039(5) | 0.0004(5) |
| C28 | 0.0299(6) | 0.0328(6) | 0.0266(5) | -0.0013(5) | -0.0007(5) | 0.0029(5) |
| C29 | 0.0582(9) | 0.0605(9) | 0.0293(7) | 0.0048(6) | 0.0074(7) | -0.0109(8) |
| C30 | 0.0306(6) | 0.0252(5) | 0.0290(6) | 0.0003(5) | 0.0003(5) | -0.0009(5) |
| C31 | 0.0504(9) | 0.0316(7) | 0.0402(7) | -0.0059(5) | -0.0052(6) | -0.0056(6) |
| N1 | 0.0276(5) | 0.0254(5) | 0.0221(4) | -0.0017(4) | 0.0013(4) | 0.0006(4) |
| O1 | 0.0322(4) | 0.0318(4) | 0.0364(4) | 0.0058(4) | -0.0082(4) | 0.0008(4) |
| O2 | 0.0238(4) | 0.0275(4) | 0.0473(5) | 0.0043(4) | -0.0032(4) | -0.0016(3) |
| O3 | 0.0435(5) | 0.0453(5) | 0.0300(4) | 0.0001(4) | 0.0121(4) | -0.0036(4) |

The form of the anisotropic displacement parameter is:
$\exp[-2\pi^2(a^{*2}U_{11}h^2+b^{*2}U_{22}k^2+c^{*2}U_{33}l^2+2b^*c^*U_{23}kl+2a^*c^*U_{13}hl+2a^*b^*U_{12}hk)]$

**Table B. 5** Bond Distances in **1.03t**, Å

| | | | | | |
|---|---|---|---|---|---|
| C1-N1 | 1.4853(13) | C1-C2 | 1.5268(15) | C1-C21 | 1.5437(15) |
| C1-C12 | 1.5564(15) | C2-C3 | 1.3687(15) | C2-C11 | 1.4254(16) |
| C3-C4 | 1.4212(16) | C3-H3 | 0.975(13) | C4-C5 | 1.4170(16) |
| C4-C9 | 1.4191(17) | C5-C6 | 1.3716(19) | C5-H5 | 1.027(15) |
| C6-C7 | 1.402(2) | C6-H6 | 0.981(15) | C7-C8 | 1.362(2) |
| C7-H7 | 0.968(17) | C8-C9 | 1.4215(17) | C8-H8 | 0.962(15) |
| C9-C10 | 1.4131(17) | C10-C11 | 1.3644(17) | C10-H10 | 0.984(16) |
| C11-H11 | 1.006(14) | C12-C13 | 1.4995(16) | C12-H12a | 0.967(14) |
| C12-H12b | 0.983(14) | C13-C14 | 1.3278(17) | C13-H13 | 0.973(15) |
| C14-C15 | 1.4718(16) | C14-H14 | 0.969(15) | C15-C16 | 1.3913(18) |
| C15-C20 | 1.3958(17) | C16-C17 | 1.3855(18) | C16-H16 | 0.980(16) |
| C17-C18 | 1.387(2) | C17-H17 | 1.010(19) | C18-C19 | 1.379(2) |
| C18-H18 | 0.982(17) | C19-C20 | 1.382(2) | C19-H19 | 0.952(17) |
| C20-H20 | 0.990(17) | C21-O1 | 1.2043(13) | C21-O2 | 1.3383(14) |
| C22-O2 | 1.4457(16) | C22-H22a | 0.988(19) | C22-H22b | 1.01(2) |
| C22-H22c | 1.03(2) | C23-C24 | 1.3853(16) | C23-C28 | 1.3999(16) |
| C23-N1 | 1.4451(14) | C24-C25 | 1.3931(17) | C24-H24 | 0.982(14) |
| C25-C26 | 1.3935(18) | C25-H25 | 0.979(15) | C26-O3 | 1.3706(14) |
| C26-C27 | 1.3858(17) | C27-C28 | 1.3792(17) | C27-H27 | 0.986(16) |
| C28-H28 | 1.006(14) | C29-O3 | 1.4197(17) | C29-H29a | 0.951(18) |
| C29-H29b | 0.98(2) | C29-H29c | 1.012(17) | C30-N1 | 1.4789(14) |
| C30-C31 | 1.5096(17) | C30-H30a | 1.013(12) | C30-H30b | 1.004(14) |
| C31-H31a | 1.013(19) | C31-H31b | 0.991(17) | C31-H31c | 0.980(17) |

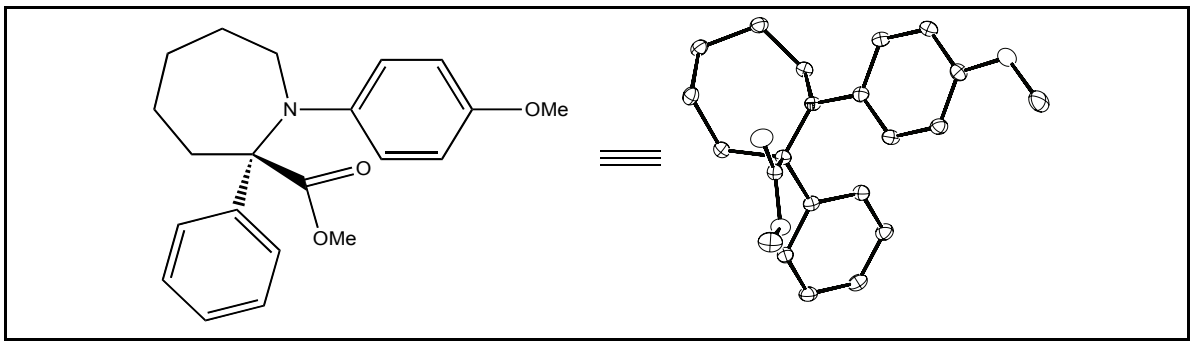
**Table B. 6** Bond Angles in **1.03t**, °

| | | | | | |
|---|---|---|---|---|---|
| N1-C1-C2 | 109.34(8) | N1-C1-C21 | 107.81(8) | C2-C1-C21 | 112.45(8) |
| N1-C1-C12 | 108.20(8) | C2-C1-C12 | 106.45(8) | C21-C1-C12 | 112.49(9) |
| C3-C2-C11 | 118.70(10) | C3-C2-C1 | 122.91(10) | C11-C2-C1 | 117.92(9) |
| C2-C3-C4 | 121.23(11) | C2-C3-H3 | 120.4(7) | C4-C3-H3 | 118.4(7) |

| | | | | | |
|---|---|---|---|---|---|
| C5-C4-C3 | 121.89(11) | C5-C4-C9 | 118.63(11) | C3-C4-C9 | 119.48(10) |
| C6-C5-C4 | 120.12(13) | C6-C5-H5 | 120.7(8) | C4-C5-H5 | 119.1(8) |
| C5-C6-C7 | 121.06(12) | C5-C6-H6 | 115.4(9) | C7-C6-H6 | 123.6(9) |
| C8-C7-C6 | 120.45(12) | C8-C7-H7 | 117.8(10) | C6-C7-H7 | 121.7(10) |
| C7-C8-C9 | 120.12(13) | C7-C8-H8 | 115.9(8) | C9-C8-H8 | 124.0(8) |
| C10-C9-C4 | 118.38(10) | C10-C9-C8 | 122.03(12) | C4-C9-C8 | 119.60(11) |
| C11-C10-C9 | 120.95(11) | C11-C10-H10 | 119.1(8) | C9-C10-H10 | 119.9(8) |
| C10-C11-C2 | 121.22(10) | C10-C11-H11 | 121.0(8) | C2-C11-H11 | 117.8(8) |
| C13-C12-C1 | 115.28(9) | C13-C12-H12a | 111.0(8) | C1-C12-H12a | 109.1(8) |
| C13-C12-H12b | 108.8(7) | C1-C12-H12b | 106.7(7) | H12a-C12-H12b | 105.6(11) |
| C14-C13-C12 | 123.52(11) | C14-C13-H13 | 119.3(8) | C12-C13-H13 | 117.2(8) |
| C13-C14-C15 | 125.44(11) | C13-C14-H14 | 119.3(8) | C15-C14-H14 | 115.2(8) |
| C16-C15-C20 | 118.28(11) | C16-C15-C14 | 121.65(11) | C20-C15-C14 | 120.05(11) |
| C17-C16-C15 | 120.82(13) | C17-C16-H16 | 119.0(9) | C15-C16-H16 | 120.2(9) |
| C16-C17-C18 | 120.14(14) | C16-C17-H17 | 119.7(11) | C18-C17-H17 | 120.2(11) |
| C19-C18-C17 | 119.59(13) | C19-C18-H18 | 120.6(10) | C17-C18-H18 | 119.8(10) |
| C18-C19-C20 | 120.36(13) | C18-C19-H19 | 122.0(10) | C20-C19-H19 | 117.6(10) |
| C19-C20-C15 | 120.81(14) | C19-C20-H20 | 120.8(9) | C15-C20-H20 | 118.4(9) |
| O1-C21-O2 | 123.45(10) | O1-C21-C1 | 124.40(10) | O2-C21-C1 | 111.93(9) |
| O2-C22-H22a | 112.8(11) | O2-C22-H22b | 105.8(10) | H22a-C22-H22b | 114.9(14) |
| O2-C22-H22c | 107.0(11) | H22a-C22-H22c | 106.5(15) | H22b-C22-H22c | 109.5(15) |
| C24-C23-C28 | 118.12(10) | C24-C23-N1 | 119.67(10) | C28-C23-N1 | 122.16(10) |
| C23-C24-C25 | 121.51(11) | C23-C24-H24 | 118.4(7) | C25-C24-H24 | 120.1(7) |

| | | | | | |
|---|---|---|---|---|---|
| C24-C25-C26 | 119.27(11) | C24-C25-H25 | 120.5(9) | C26-C25-H25 | 120.1(9) |
| O3-C26-C27 | 115.30(11) | O3-C26-C25 | 124.88(11) | C27-C26-C25 | 119.79(11) |
| C28-C27-C26 | 120.29(11) | C28-C27-H27 | 119.3(9) | C26-C27-H27 | 120.3(9) |
| C27-C28-C23 | 120.98(11) | C27-C28-H28 | 119.6(8) | C23-C28-H28 | 119.4(8) |
| O3-C29-H29a | 112.8(10) | O3-C29-H29b | 104.6(11) | H29a-C29-H29b | 110.2(14) |
| O3-C29-H29c | 111.9(10) | H29a-C29-H29c | 107.1(14) | H29b-C29-H29c | 110.3(14) |
| N1-C30-C31 | 109.60(10) | N1-C30-H30a | 108.5(7) | C31-C30-H30a | 109.6(7) |
| N1-C30-H30b | 112.4(8) | C31-C30-H30b | 111.1(8) | H30a-C30-H30b | 105.5(10) |
| C30-C31-H31a | 108.9(10) | C30-C31-H31b | 112.2(9) | H31a-C31-H31b | 107.9(13) |
| C30-C31-H31c | 112.4(10) | H31a-C31-H31c | 107.7(14) | H31b-C31-H31c | 107.5(13) |
| C23-N1-C30 | 112.34(8) | C23-N1-C1 | 115.96(8) | C30-N1-C1 | 115.93(8) |
| C21-O2-C22 | 116.17(9) | C26-O3-C29 | 117.83(11) | | |

## B.2. X-Ray Structure Determination of Compound 2.32




Compound **2.32**, $C_{21}H_{25}NO_3$, crystallizes in the orthorhombic space group $P2_12_12_1$ (systematic absences h00: h=odd, 0k0: k=odd, and 00l: l=odd) with a=10.1714(10)Å, b=10.7715(11)Å, c=16.2870(16)Å, V=1784.4(3)Å$^3$, Z=4, and $d_{calc}$=1.263 g/cm$^3$ . X-ray intensity data were collected on a Bruker APEXII CCD area detector employing graphite-monochromated Mo-K$\alpha$ radiation ($\lambda$=1.54178 Å) at a temperature of 143(1)K. Preliminary indexing was performed from a series of thirty-six 0.5° rotation frames with exposures of 10 seconds. A total of 4213 frames were collected with a crystal to detector distance of 37.617 mm, rotation widths of 0.5° and exposures of 20 seconds:

| scan type | 2θ | ω | ϕ | χ | frames |
|---|---|---|---|---|---|
| ϕ | 92.00 | 88.66 | 348.71 | -26.26 | 739 |
| ϕ | -33.00 | 301.93 | 73.64 | 23.24 | 450 |
| ϕ | -28.00 | 282.92 | 258.28 | 59.32 | 267 |
| ω | -23.00 | 8.63 | 319.72 | -61.99 | 111 |
| ω | -43.00 | 310.71 | 275.26 | -33.72 | 128 |
| ϕ | 82.00 | 31.51 | 144.92 | 52.47 | 185 |
| ω | -18.00 | 338.71 | 192.21 | -82.85 | 119 |
| ϕ | 92.00 | 132.53 | 140.50 | -22.49 | 438 |
| ϕ | 87.00 | 76.65 | 32.32 | 62.65 | 724 |
| ω | 92.00 | 152.22 | 266.47 | -93.68 | 171 |
| ϕ | 92.00 | 198.97 | 352.62 | -82.85 | 658 |

| | | | | | |
|---|---|---|---|---|---|
| ω | 92.00 | 9.33 | 317.53 | 90.29 | 109 |
| ϕ | 7.00 | 153.70 | 41.76 | -95.28 | 114 |

Rotation frames were integrated using SAINT[186], producing a listing of unaveraged $F^2$ and $\sigma(F^2)$ values which were then passed to the SHELXTL[187] program package for further processing and structure solution. A total of 12846 reflections were measured over the ranges $4.92 \leq \theta \leq 64.70°$, $-11 \leq h \leq 10$, $-12 \leq k \leq 12$, $-19 \leq l \leq 14$ yielding 2947 unique reflections (Rint = 0.0245). The intensity data were corrected for Lorentz and polarization effects and for absorption using SADABS[188] (minimum and maximum transmission 0.6980, 0.7525).

The structure was solved by direct methods (SHELXS-97[189]). Refinement was by full-matrix least squares based on $F^2$ using SHELXL-97.[190] All reflections were used during refinement. The weighting scheme used was $w=1/[\sigma^2(F_o^2)+ (0.0318P)^2 + 0.2246P]$ where $P = (F_o^2 + 2F_c^2)/3$. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined isotropically. Refinement converged to R1=0.0235 and wR2=0.0589 for 2924 observed reflections for which $F > 4\sigma(F)$ and R1=0.0237 and wR2=0.0591 and GOF =1.110 for all 2947 unique, non-zero reflections and 328 variables.[191] The maximum $\Delta/\sigma$ in the final cycle of least squares was 0.000 and the two most prominent peaks in the final difference Fourier were +0.136 and -0.192 e/Å$^3$. The absolute structure parameter y[192] was calculated using PLATON[193]. The resulting value was y = 0.08(4) indicating that the absolute structure has been assigned correctly.

Table B.7 lists cell information, data collection parameters, and refinement data. Final positional and equivalent isotropic thermal parameters are given in Tables B.8 and B.9 Anisotropic thermal parameters are in Table B.10 Tables B.11 and B.12 list bond distances and bond angles. Figure B.2. is an ORTEP[194] representation of the molecule with 30% probability thermal ellipsoids displayed.

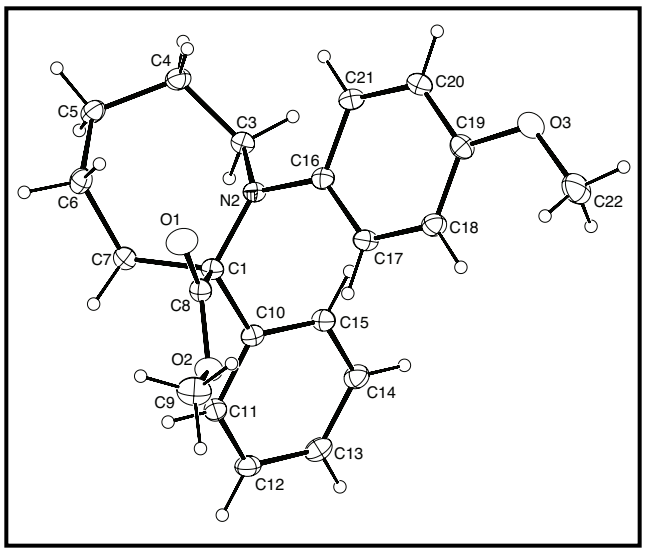



**Figure B. 2** ORTEP drawing of the title compound with 30% probability thermal ellipsoids.

**Table B. 7** Summary of Structure Determination of Compound **2.32**

| | |
|---|---|
| Empirical formula | $C_{21}H_{25}NO_3$ |
| Formula weight | 339.42 |
| Temperature | 143(1) K |
| Wavelength | 1.54178 Å |
| Crystal system | orthorhombic |
| Space group | $P2_12_12_1$ |
| Cell constants: | |
| a | 10.1714(10) Å |
| b | 10.7715(11) Å |
| c | 16.2870(16) Å |
| Volume | 1784.4(3) $Å^3$ |
| Z | 4 |
| Density (calculated) | 1.263 $Mg/m^3$ |

| | |
|---|---|
| Absorption coefficient | 0.670 $mm^{-1}$ |
| F(000) | 728 |
| Crystal size | 0.36 x 0.32 x 0.14 $mm^3$ |
| Theta range for data collection | 4.92 to 64.70° |
| Index ranges | $-11 \leq h \leq 10$, $-12 \leq k \leq 12$, $-19 \leq l \leq 14$ |
| Reflections collected | 12846 |
| Independent reflections | 2947 [R(int) = 0.0245] |
| Completeness to theta = 64.70° | 98.9 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.7525 and 0.6980 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 2947 / 0 / 328 |
| Goodness-of-fit on $F^2$ | 1.110 |
| Final R indices [I>2sigma(I)] | R1 = 0.0235, wR2 = 0.0589 |
| R indices (all data) | R1 = 0.0237, wR2 = 0.0591 |
| Flack Absolute structure parameter | 0.07(14) |
| Hooft Absolute structure parameter | 0.08(4) |
| Largest diff. peak and hole | 0.136 and -0.192 $e.Å^{-3}$ |

**Table B. 8** Refined Positional Parameters for Compound **2.32**

| Atom | x | y | z | $U_{eq}$, $A^2$ |
|---|---|---|---|---|
| C1 | 0.67393(11) | 0.84112(10) | 0.18705(7) | 0.0221(2) |
| C3 | 0.45621(11) | 0.73519(11) | 0.19303(7) | 0.0236(2) |

| | | | | |
|---|---|---|---|---|
| C4 | 0.36427(12) | 0.77281(12) | 0.12381(8) | 0.0289(3) |
| C5 | 0.37164(12) | 0.90932(12) | 0.09967(8) | 0.0293(3) |
| C6 | 0.51132(13) | 0.95541(12) | 0.08524(8) | 0.0287(3) |
| C7 | 0.59375(12) | 0.96054(11) | 0.16396(7) | 0.0247(3) |
| C8 | 0.78905(11) | 0.84253(10) | 0.12545(7) | 0.0241(2) |
| C9 | 1.01040(14) | 0.89110(16) | 0.10046(9) | 0.0404(3) |
| C10 | 0.71291(11) | 0.85258(11) | 0.27865(7) | 0.0227(2) |
| C11 | 0.77221(12) | 0.96008(11) | 0.30928(7) | 0.0253(3) |
| C12 | 0.79499(13) | 0.97437(12) | 0.39305(8) | 0.0292(3) |
| C13 | 0.75966(13) | 0.88166(13) | 0.44783(8) | 0.0312(3) |
| C14 | 0.70275(13) | 0.77416(12) | 0.41834(8) | 0.0300(3) |
| C15 | 0.67929(11) | 0.76025(11) | 0.33437(7) | 0.0259(3) |
| C16 | 0.65550(11) | 0.61440(11) | 0.15995(7) | 0.0228(2) |
| C17 | 0.78478(12) | 0.58977(11) | 0.18383(7) | 0.0264(3) |
| C18 | 0.84080(12) | 0.47234(12) | 0.17430(8) | 0.0284(3) |
| C19 | 0.76760(12) | 0.37642(11) | 0.14151(7) | 0.0272(3) |
| C20 | 0.64007(12) | 0.39951(12) | 0.11557(7) | 0.0273(3) |
| C21 | 0.58497(12) | 0.51561(12) | 0.12446(7) | 0.0255(2) |
| C22 | 0.93934(15) | 0.22968(14) | 0.16175(13) | 0.0492(4) |
| N2 | 0.59554(9) | 0.73100(9) | 0.16961(6) | 0.0222(2) |
| O1 | 0.77765(9) | 0.81587(9) | 0.05423(5) | 0.0354(2) |
| O2 | 0.90219(8) | 0.88333(8) | 0.15839(5) | 0.0292(2) |
| O3 | 0.81126(9) | 0.25561(8) | 0.13287(6) | 0.0354(2) |

$U_{eq}=^{1}/_{3}[U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*\cos\gamma+2U_{13}aa^*cc^*\cos\beta+2U_{23}bb^*cc^*\cos\alpha]$

**Table B. 9** Positional Parameters for Hydrogens in Compound **2.32**

| Atom | x | y | z | $U_{iso}$, $A^2$ |
|---|---|---|---|---|
| H3a | 0.4455(13) | 0.7913(13) | 0.2439(9) | 0.028(3) |
| H3b | 0.4323(13) | 0.6511(12) | 0.2117(7) | 0.020(3) |
| H4a | 0.2700(16) | 0.7530(14) | 0.1432(9) | 0.036(4) |
| H4b | 0.3837(15) | 0.7208(14) | 0.0763(10) | 0.035(4) |
| H5a | 0.3188(16) | 0.9212(14) | 0.0496(10) | 0.037(4) |
| H5b | 0.3329(14) | 0.9638(14) | 0.1449(9) | 0.032(4) |
| H6a | 0.5041(14) | 1.0417(14) | 0.0625(8) | 0.030(3) |
| H6b | 0.5571(14) | 0.9008(13) | 0.0426(8) | 0.025(3) |
| H7a | 0.5352(14) | 0.9783(12) | 0.2122(9) | 0.025(3) |
| H7b | 0.6576(14) | 1.0307(13) | 0.1630(8) | 0.027(3) |
| H9a | 1.0307(17) | 0.8075(17) | 0.0768(10) | 0.049(4) |
| H9b | 1.0860(17) | 0.9260(14) | 0.1322(10) | 0.041(4) |
| H9c | 0.9860(18) | 0.9499(17) | 0.0555(11) | 0.051(5) |
| H11 | 0.7966(13) | 1.0268(13) | 0.2713(8) | 0.024(3) |
| H12 | 0.8377(15) | 1.0528(15) | 0.4134(9) | 0.038(4) |
| H13 | 0.7780(15) | 0.8918(14) | 0.5063(10) | 0.039(4) |
| H14 | 0.6773(15) | 0.7052(14) | 0.4562(9) | 0.033(4) |
| H15 | 0.6359(12) | 0.6830(13) | 0.3149(8) | 0.022(3) |
| H17 | 0.8390(14) | 0.6554(13) | 0.2104(8) | 0.026(3) |
| H18 | 0.9295(16) | 0.4595(13) | 0.1929(8) | 0.031(4) |
| H20 | 0.5915(15) | 0.3308(15) | 0.0933(9) | 0.036(4) |
| H21 | 0.4974(14) | 0.5299(12) | 0.1063(8) | 0.021(3) |
| H22a | 1.008(2) | 0.2770(19) | 0.1285(12) | 0.065(5) |
| H22b | 0.9557(18) | 0.1411(19) | 0.1493(11) | 0.060(5) |
| H22c | 0.9512(19) | 0.2516(18) | 0.2232(12) | 0.063(6) |

**Table B. 10** Refined Thermal Parameters (U's) for Compound **2.32**

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| C1 | 0.0211(6) | 0.0243(6) | 0.0209(5) | -0.0011(5) | 0.0018(5) | -0.0018(5) |
| C3 | 0.0216(6) | 0.0256(6) | 0.0235(6) | -0.0013(5) | 0.0027(5) | -0.0017(5) |
| C4 | 0.0239(6) | 0.0310(6) | 0.0318(6) | -0.0029(6) | -0.0040(5) | -0.0001(5) |
| C5 | 0.0240(6) | 0.0331(7) | 0.0308(7) | 0.0012(5) | -0.0058(5) | 0.0016(5) |
| C6 | 0.0279(7) | 0.0321(7) | 0.0260(6) | 0.0056(6) | 0.0003(5) | 0.0016(5) |
| C7 | 0.0230(6) | 0.0249(6) | 0.0262(6) | -0.0004(5) | 0.0018(5) | -0.0008(5) |
| C8 | 0.0232(6) | 0.0246(6) | 0.0246(6) | 0.0010(5) | 0.0017(5) | 0.0004(5) |
| C9 | 0.0252(7) | 0.0532(9) | 0.0428(8) | -0.0054(8) | 0.0113(6) | -0.0051(6) |
| C10 | 0.0190(6) | 0.0260(6) | 0.0230(6) | -0.0029(5) | 0.0009(5) | 0.0022(5) |
| C11 | 0.0231(6) | 0.0255(6) | 0.0273(6) | 0.0000(5) | -0.0005(5) | -0.0001(5) |
| C12 | 0.0277(6) | 0.0298(6) | 0.0302(6) | -0.0069(5) | -0.0057(5) | 0.0003(5) |
| C13 | 0.0294(6) | 0.0415(7) | 0.0227(6) | -0.0021(6) | -0.0036(5) | 0.0018(5) |
| C14 | 0.0291(6) | 0.0368(7) | 0.0241(6) | 0.0039(5) | -0.0018(5) | -0.0026(5) |
| C15 | 0.0250(6) | 0.0273(6) | 0.0254(6) | -0.0010(5) | -0.0012(5) | -0.0016(5) |
| C16 | 0.0247(6) | 0.0257(6) | 0.0180(5) | -0.0013(5) | 0.0011(5) | -0.0004(4) |
| C17 | 0.0235(6) | 0.0269(6) | 0.0288(6) | -0.0043(5) | -0.0020(5) | -0.0022(5) |
| C18 | 0.0226(6) | 0.0299(6) | 0.0327(6) | -0.0017(5) | -0.0017(5) | 0.0002(5) |
| C19 | 0.0297(6) | 0.0246(6) | 0.0273(6) | -0.0037(5) | 0.0040(5) | 0.0000(5) |
| C20 | 0.0288(6) | 0.0268(6) | 0.0264(6) | -0.0047(5) | 0.0018(5) | -0.0041(5) |
| C21 | 0.0212(6) | 0.0310(6) | 0.0242(6) | -0.0031(5) | -0.0001(5) | -0.0013(5) |
| C22 | 0.0357(8) | 0.0283(7) | 0.0837(13) | -0.0052(8) | -0.0052(8) | 0.0061(6) |
| N2 | 0.0198(5) | 0.0236(5) | 0.0232(5) | -0.0026(4) | -0.0008(4) | -0.0008(4) |
| O1 | 0.0319(5) | 0.0510(6) | 0.0234(5) | -0.0047(4) | 0.0052(4) | -0.0022(4) |
| O2 | 0.0207(4) | 0.0363(5) | 0.0305(4) | -0.0027(4) | 0.0051(4) | -0.0033(3) |

| | | | | | | |
|---|---|---|---|---|---|---|
| O3 | 0.0319(4) | 0.0255(4) | 0.0490(5) | -0.0072(4) | -0.0011(4) | 0.0030(4) |

The form of the anisotropic displacement parameter is:
$\exp[-2\pi^2(a^{*2}U_{11}h^2+b^{*2}U_{22}k^2+c^{*2}U_{33}l^2+2b^*c^*U_{23}kl+2a^*c^*U_{13}hl+2a^*b^*U_{12}hk)]$

**Table B. 11** Bond Distances in Compound **2.32**, Å

| | | | | | |
|---|---|---|---|---|---|
| C1-N2 | 1.4572(14) | C1-C8 | 1.5420(16) | C1-C10 | 1.5486(16) |
| C1-C7 | 1.5688(16) | C3-N2 | 1.4683(15) | C3-C4 | 1.5199(17) |
| C3-H3a | 1.032(14) | C3-H3b | 0.986(13) | C4-C5 | 1.5238(18) |
| C4-H4a | 1.031(16) | C4-H4b | 0.975(16) | C5-C6 | 1.5232(18) |
| C5-H5a | 0.985(16) | C5-H5b | 1.021(15) | C6-C7 | 1.5329(17) |
| C6-H6a | 1.003(15) | C6-H6b | 1.022(14) | C7-H7a | 1.004(14) |
| C7-H7b | 0.997(14) | C8-O1 | 1.2005(15) | C8-O2 | 1.3437(15) |
| C9-O2 | 1.4521(16) | C9-H9a | 1.001(19) | C9-H9b | 1.000(18) |
| C9-H9c | 1.000(18) | C10-C15 | 1.3891(17) | C10-C11 | 1.3977(16) |
| C11-C12 | 1.3925(17) | C11-H11 | 0.980(14) | C12-C13 | 1.3865(19) |
| C12-H12 | 1.007(16) | C13-C14 | 1.3808(19) | C13-H13 | 0.977(16) |
| C14-C15 | 1.3964(17) | C14-H14 | 1.000(16) | C15-H15 | 0.994(14) |
| C16-C17 | 1.3967(17) | C16-N2 | 1.4050(16) | C16-C21 | 1.4076(17) |
| C17-C18 | 1.3959(17) | C17-H17 | 0.996(15) | C18-C19 | 1.3809(18) |
| C18-H18 | 0.962(15) | C19-O3 | 1.3822(15) | C19-C20 | 1.3868(18) |
| C20-C21 | 1.3781(18) | C20-H20 | 0.961(16) | C21-H21 | 0.951(14) |
| C22-O3 | 1.4129(19) | C22-H22a | 1.02(2) | C22-H22b | 0.99(2) |
| C22-H22c | 1.035(19) | | | | |

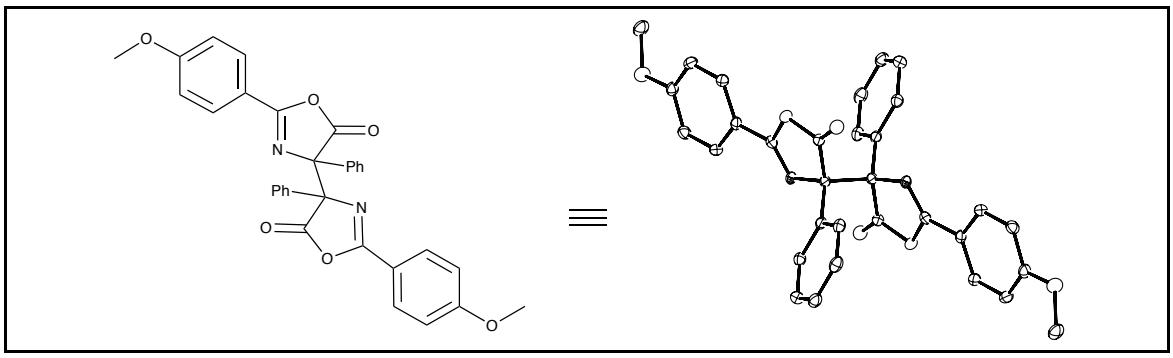
**Table B. 12** Bond Angles in Compound **2.32**, °

| | | | | | |
|---|---|---|---|---|---|
| N2-C1-C8 | 107.26(9) | N2-C1-C10 | 113.13(9) | C8-C1-C10 | 115.57(9) |
| N2-C1-C7 | 109.65(9) | C8-C1-C7 | 103.34(9) | C10-C1-C7 | 107.38(9) |
| N2-C3-C4 | 114.16(10) | N2-C3-H3a | 109.2(8) | C4-C3-H3a | 112.0(7) |
| N2-C3-H3b | 106.9(7) | C4-C3-H3b | 108.8(7) | H3a-C3-H3b | 105.3(10) |

| | | | | | |
|---|---|---|---|---|---|
| C3-C4-C5 | 114.73(10) | C3-C4-H4a | 106.8(8) | C5-C4-H4a | 108.9(8) |
| C3-C4-H4b | 108.1(9) | C5-C4-H4b | 109.9(9) | H4a-C4-H4b | 108.2(12) |
| C6-C5-C4 | 113.59(11) | C6-C5-H5a | 109.8(9) | C4-C5-H5a | 108.2(9) |
| C6-C5-H5b | 106.5(8) | C4-C5-H5b | 110.4(8) | H5a-C5-H5b | 108.2(12) |
| C5-C6-C7 | 113.13(10) | C5-C6-H6a | 106.9(8) | C7-C6-H6a | 108.4(8) |
| C5-C6-H6b | 110.0(8) | C7-C6-H6b | 109.9(8) | H6a-C6-H6b | 108.4(11) |
| C6-C7-C1 | 117.09(10) | C6-C7-H7a | 109.6(8) | C1-C7-H7a | 106.1(8) |
| C6-C7-H7b | 111.7(8) | C1-C7-H7b | 106.6(8) | H7a-C7-H7b | 104.8(11) |
| O1-C8-O2 | 123.14(11) | O1-C8-C1 | 123.57(11) | O2-C8-C1 | 113.19(9) |
| O2-C9-H9a | 110.8(10) | O2-C9-H9b | 105.6(9) | H9a-C9-H9b | 112.2(13) |
| O2-C9-H9c | 108.9(11) | H9a-C9-H9c | 109.8(13) | H9b-C9-H9c | 109.4(14) |
| C15-C10-C11 | 117.79(11) | C15-C10-C1 | 120.62(10) | C11-C10-C1 | 121.36(10) |
| C12-C11-C10 | 120.87(12) | C12-C11-H11 | 119.7(8) | C10-C11-H11 | 119.5(8) |
| C13-C12-C11 | 120.52(12) | C13-C12-H12 | 120.3(8) | C11-C12-H12 | 119.2(8) |
| C14-C13-C12 | 119.26(11) | C14-C13-H13 | 120.9(9) | C12-C13-H13 | 119.9(9) |
| C13-C14-C15 | 120.16(12) | C13-C14-H14 | 121.1(8) | C15-C14-H14 | 118.7(8) |
| C10-C15-C14 | 121.39(11) | C10-C15-H15 | 120.0(8) | C14-C15-H15 | 118.6(8) |
| C17-C16-N2 | 123.18(10) | C17-C16-C21 | 116.79(11) | N2-C16-C21 | 120.03(10) |
| C18-C17-C16 | 121.70(11) | C18-C17-H17 | 117.7(8) | C16-C17-H17 | 120.5(8) |
| C19-C18-C17 | 120.06(11) | C19-C18-H18 | 121.3(8) | C17-C18-H18 | 118.6(8) |
| C18-C19-O3 | 124.79(11) | C18-C19-C20 | 119.21(11) | O3-C19-C20 | 115.99(11) |
| C21-C20-C19 | 120.74(12) | C21-C20-H20 | 121.9(9) | C19-C20-H20 | 117.3(9) |
| C20-C21-C16 | 121.46(11) | C20-C21-H21 | 119.7(8) | C16-C21-H21 | 118.9(8) |
| O3-C22-H22a | 111.0(11) | O3-C22-H22b | 106.1(11) | H22a-C22-H22b | 104.9(15) |
| O3-C22- | 112.6(11) | H22a-C22- | 108.5(16) | H22b-C22- | 113.5(15) |

| | | | | | |
|---|---|---|---|---|---|
| H22c | | H22c | | H22c | |
| C16-N2-C1 | 120.79(9) | C16-N2-C3 | 118.40(10) | C1-N2-C3 | 116.90(9) |
| C8-O2-C9 | 114.12(10) | C19-O3-C22 | 116.64(11) | | |

## B.3. X-Ray Structure Determination of Compound 4.23




Compound **4.23**, $C_{32}H_{24}N_2O_6$, crystallizes in the triclinic space group $P\bar{1}$ with a=6.7034(2)Å, b=10.1139(3)Å, c=19.0350(5)Å, $\alpha$=87.503(2)°, $\beta$=82.219(2)°, $\gamma$=76.2860(10)°, V=1242.10(6)Å$^3$, Z=2, and $d_{calc}$=1.424 g/cm$^3$ . X-ray intensity data were collected on a Bruker APEXII CCD area detector employing graphite-monochromated Mo-K$\alpha$ radiation ($\lambda$=0.71073 Å) at a temperature of 100(1)K. Preliminary indexing was performed from a series of thirty-six 0.5° rotation frames with exposures of 10 seconds. A total of 4619 frames were collected with a crystal to detector distance of 37.5 mm, rotation widths of 0.5° and exposures of 10 seconds:

| scan type | 2$\theta$ | $\omega$ | $\phi$ | $\chi$ | frames |
|---|---|---|---|---|---|
| $\phi$ | -23.00 | 315.83 | 12.48 | 28.88 | 739 |
| $\phi$ | -23.00 | 334.21 | 38.95 | 73.66 | 739 |
| $\phi$ | -15.50 | 258.48 | 13.05 | 19.46 | 704 |
| $\phi$ | 24.50 | 7.41 | 12.48 | 28.88 | 739 |
| $\phi$ | -13.00 | 335.42 | 31.84 | 64.29 | 739 |
| $\phi$ | 19.50 | 59.55 | 348.71 | -26.26 | 739 |
| $\phi$ | -25.50 | 323.22 | 48.36 | 83.36 | 220 |

Rotation frames were integrated using SAINT[186], producing a listing of unaveraged $F^2$ and $\sigma(F^2)$ values which were then passed to the SHELXTL[187] program package for further processing and structure solution. A total of 55649 reflections were measured over the ranges $2.07 \leq \theta \leq 27.50°$, $-8 \leq h \leq 8$, $-13 \leq k \leq 13$, $-24 \leq l \leq 24$ yielding 5551 unique reflections (Rint = 0.0314). The intensity data were corrected for Lorentz and polarization effects and for absorption

using SADABS[188] (minimum and maximum transmission 0.7191, 0.7456).

The structure was solved by direct methods (SHELXS-97[189]). Refinement was by full-matrix least squares based on $F^2$ using SHELXL-97.[190] All reflections were used during refinement. The weighting scheme used was $w=1/[\sigma^2(F_o^2)+ (0.0706P)^2 + 0.3765P]$ where $P = (F_o^2 + 2F_c^2)/3$. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using a riding model. Refinement converged to R1=0.0414 and wR2=0.1115 for 4060 observed reflections for which $F > 4\sigma(F)$ and R1=0.0624 and wR2=0.1270 and GOF =1.022 for all 5551 unique, non-zero reflections and 364 variables.[191] The maximum $\Delta/\sigma$ in the final cycle of least squares was 0.001 and the two most prominent peaks in the final difference Fourier were +0.417 and -0.215 e/Å$^3$.

Table B.13 lists cell information, data collection parameters, and refinement data. Final positional and equivalent isotropic thermal parameters are given in Tables B.14 and B.15. Anisotropic thermal parameters are in Table B.16. Tables B.17 and B.18 list bond distances and bond angles. Figures B3. and B4. are ORTEP[194] representations of the molecule with 50% probability thermal ellipsoids displayed.

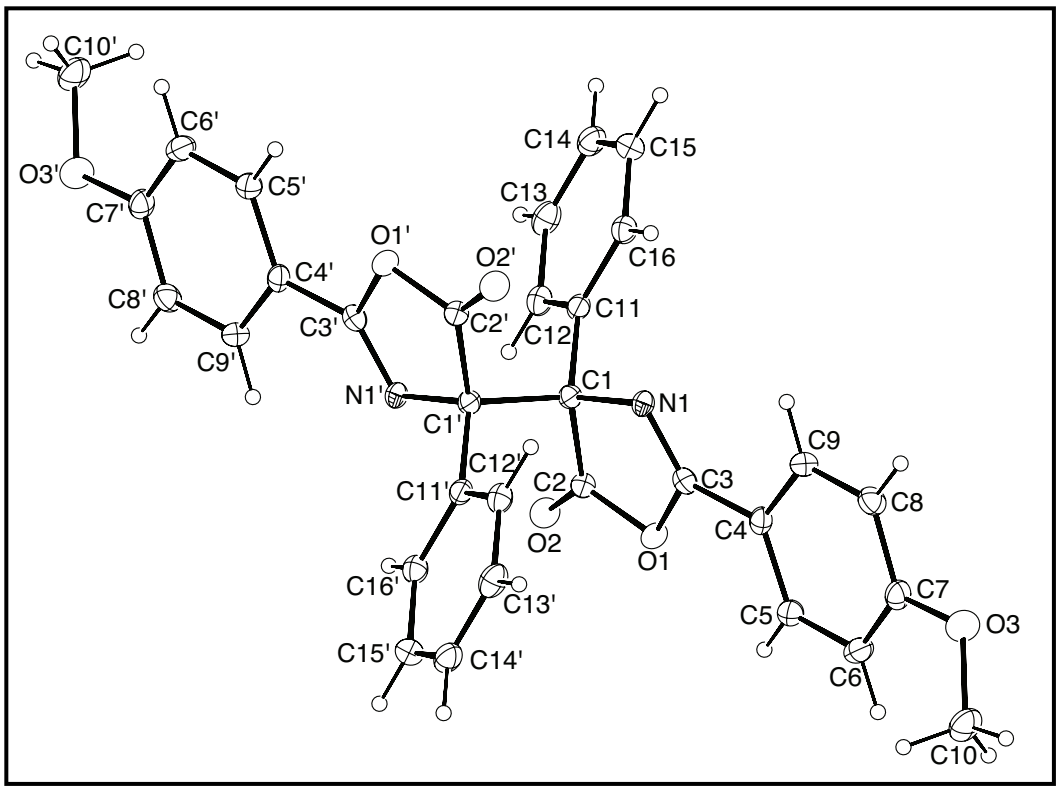



**Figure B. 3** ORTEP drawing of molecule no. 1 of the asymmetric unit with 50% probability thermal ellipsoids.

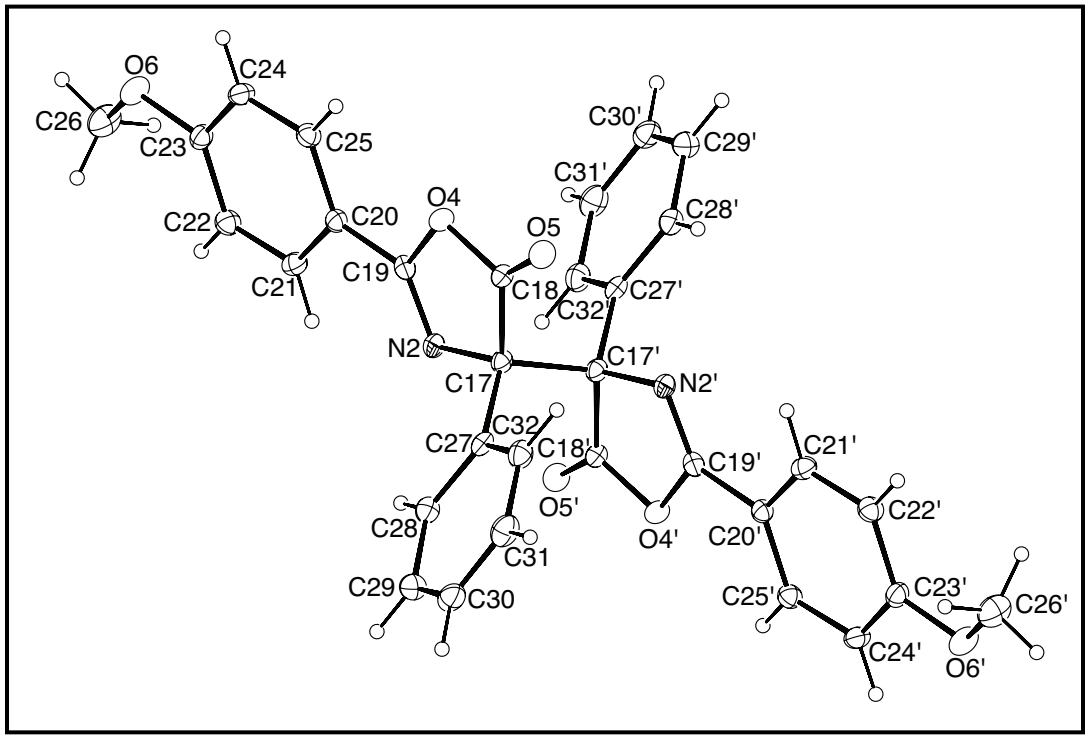


**Figure B. 4** ORTEP drawing of molecule no. 2 of the asymmetric unit with 50% probability thermal ellipsoids.

**Table B. 13** Summary of Structure Determination of Compound **4.23**

| | |
|---|---|
| Empirical formula | $C_{32}H_{24}N_2O_6$ |
| Formula weight | 532.53 |
| Temperature | 100(1) K |
| Wavelength | 0.71073 Å |
| Crystal system | triclinic |
| Space group | $P\bar{1}$ |
| Cell constants: | |
| a | 6.7034(2) Å |
| b | 10.1139(3) Å |
| c | 19.0350(5) Å |
| $\alpha$ | 87.503(2)° |
| $\beta$ | 82.219(2)° |
| $\gamma$ | 76.2860(10)° |
| Volume | 1242.10(6) $Å^3$ |
| Z | 2 |
| Density (calculated) | 1.424 $Mg/m^3$ |
| Absorption coefficient | 0.099 $mm^{-1}$ |
| F(000) | 556 |
| Crystal size | 0.35 x 0.08 x 0.02 $mm^3$ |

| | |
|---|---|
| Theta range for data collection | 2.07 to 27.50° |
| Index ranges | $-8 \leq h \leq 8, -13 \leq k \leq 13, -24 \leq l \leq 24$ |
| Reflections collected | 55649 |
| Independent reflections | 5551 [R(int) = 0.0314] |
| Completeness to theta = 27.50° | 97.3 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.7456 and 0.7191 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 5551 / 0 / 364 |
| Goodness-of-fit on $F^2$ | 1.022 |
| Final R indices [I>2sigma(I)] | R1 = 0.0414, wR2 = 0.1115 |
| R indices (all data) | R1 = 0.0624, wR2 = 0.1270 |
| Largest diff. peak and hole | 0.417 and -0.215 e.$Å^{-3}$ |

**Table B. 14** Refined Positional Parameters for Compound **4.23**

| Atom | x | y | z | $U_{eq}$, $Å^2$ |
|---|---|---|---|---|
| C1 | 0.0709(2) | 0.94160(13) | 0.47411(7) | 0.0124(3) |
| C2 | -0.0549(2) | 0.83529(14) | 0.46534(7) | 0.0138(3) |
| C3 | 0.2170(2) | 0.74664(14) | 0.52120(7) | 0.0137(3) |
| C4 | 0.3459(2) | 0.63542(14) | 0.55799(7) | 0.0139(3) |
| C5 | 0.2825(2) | 0.51623(14) | 0.57875(7) | 0.0155(3) |
| C6 | 0.4024(2) | 0.41636(15) | 0.61775(7) | 0.0176(3) |
| C7 | 0.5882(2) | 0.43562(15) | 0.63579(7) | 0.0173(3) |
| C8 | 0.6578(2) | 0.55183(15) | 0.61219(8) | 0.0176(3) |
| C9 | 0.5376(2) | 0.65099(14) | 0.57367(7) | 0.0156(3) |

| | | | | |
|---|---|---|---|---|
| C10 | 0.6163(3) | 0.25587(16) | 0.72113(8) | 0.0240(3) |
| C11 | 0.1438(2) | 1.00337(13) | 0.40339(7) | 0.0136(3) |
| C12 | 0.0142(2) | 1.03675(14) | 0.35052(7) | 0.0167(3) |
| C13 | 0.0811(2) | 1.09503(15) | 0.28707(8) | 0.0199(3) |
| C14 | 0.2771(2) | 1.12160(15) | 0.27570(8) | 0.0203(3) |
| C15 | 0.4060(2) | 1.08927(15) | 0.32823(8) | 0.0194(3) |
| C16 | 0.3410(2) | 1.02978(14) | 0.39204(7) | 0.0156(3) |
| N1 | 0.24400(17) | 0.86638(11) | 0.50943(6) | 0.0132(2) |
| O1 | 0.04303(15) | 0.71750(9) | 0.49824(5) | 0.0152(2) |
| O2 | -0.20544(16) | 0.84061(10) | 0.43785(5) | 0.0190(2) |
| O3 | 0.71320(17) | 0.34628(11) | 0.67609(6) | 0.0263(3) |
| C17 | 0.9304(2) | 0.56097(13) | 1.02456(7) | 0.0122(3) |
| C18 | 1.0583(2) | 0.66748(13) | 1.02927(7) | 0.0131(3) |
| C19 | 0.7844(2) | 0.75204(14) | 0.97364(7) | 0.0128(3) |
| C20 | 0.6533(2) | 0.86282(14) | 0.93747(7) | 0.0130(3) |
| C21 | 0.4721(2) | 0.84233(14) | 0.91565(7) | 0.0148(3) |
| C22 | 0.3411(2) | 0.94588(14) | 0.88238(7) | 0.0156(3) |
| C23 | 0.3902(2) | 1.07284(14) | 0.87184(7) | 0.0147(3) |
| C24 | 0.5688(2) | 1.09492(14) | 0.89476(7) | 0.0153(3) |
| C25 | 0.6999(2) | 0.99072(14) | 0.92686(7) | 0.0143(3) |
| C26 | 0.1128(3) | 1.16178(16) | 0.80363(9) | 0.0240(3) |
| C27 | 0.8591(2) | 0.50644(13) | 1.09746(7) | 0.0133(3) |
| C28 | 0.6599(2) | 0.48413(14) | 1.11185(7) | 0.0154(3) |
| C29 | 0.5983(2) | 0.42854(15) | 1.17750(8) | 0.0192(3) |
| C30 | 0.7321(2) | 0.39702(15) | 1.22833(8) | 0.0203(3) |
| C31 | 0.9290(2) | 0.42171(15) | 1.21432(8) | 0.0205(3) |
| C32 | 0.9929(2) | 0.47566(14) | 1.14911(8) | 0.0171(3) |
| N2 | 0.75701(17) | 0.63322(11) | 0.98865(6) | 0.0130(2) |
| O4 | 0.96013(15) | 0.78285(9) | 0.99471(5) | 0.0149(2) |
| O5 | 1.21047(15) | 0.66466(10) | 1.05541(5) | 0.0182(2) |
| O6 | 0.27053(16) | 1.18325(10) | 0.84193(6) | 0.0201(2) |

$U_{eq}=^{1}/_{3}[U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*\cos\gamma+2U_{13}aa^*cc^*\cos\beta+2U_{23}bb^*cc^*\cos\alpha]$

**Table B. 15** Positional Parameters for Hydrogens in Compound **4.23**

| Atom | x | y | z | $U_{iso}$, $A^2$ |
|---|---|---|---|---|
| H5 | 0.1588 | 0.5035 | 0.5664 | 0.021 |
| H6 | 0.3592 | 0.3373 | 0.6317 | 0.023 |
| H8 | 0.7849 | 0.5622 | 0.6224 | 0.023 |
| H9 | 0.5837 | 0.7283 | 0.5581 | 0.021 |
| H10a | 0.4944 | 0.3074 | 0.7487 | 0.036 |
| H10b | 0.7111 | 0.2076 | 0.7522 | 0.036 |
| H10c | 0.5787 | 0.1920 | 0.6926 | 0.036 |
| H12 | -0.1175 | 1.0198 | 0.3579 | 0.022 |
| H13 | -0.0057 | 1.1164 | 0.2520 | 0.026 |
| H14 | 0.3215 | 1.1608 | 0.2331 | 0.027 |
| H15 | 0.5370 | 1.1074 | 0.3208 | 0.026 |
| H16 | 0.4286 | 1.0078 | 0.4269 | 0.021 |
| H21 | 0.4390 | 0.7582 | 0.9235 | 0.020 |
| H22 | 0.2220 | 0.9311 | 0.8673 | 0.021 |
| H24 | 0.5995 | 1.1800 | 0.8884 | 0.020 |
| H25 | 0.8196 | 1.0055 | 0.9415 | 0.019 |
| H26a | 0.1726 | 1.0948 | 0.7678 | 0.036 |
| H26b | 0.0496 | 1.2457 | 0.7817 | 0.036 |
| H26c | 0.0099 | 1.1303 | 0.8356 | 0.036 |
| H28 | 0.5688 | 0.5060 | 1.0781 | 0.020 |
| H29 | 0.4662 | 0.4126 | 1.1871 | 0.026 |
| H30 | 0.6904 | 0.3594 | 1.2717 | 0.027 |
| H31 | 1.0183 | 0.4021 | 1.2487 | 0.027 |
| H32 | 1.1252 | 0.4913 | 1.1398 | 0.023 |

**Table B. 16** Refined Thermal Parameters (U's) for Compound **4.23**

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| C1 | 0.0103(6) | 0.0119(6) | 0.0154(6) | 0.0007(5) | -0.0032(5) | -0.0025(5) |
| C2 | 0.0140(7) | 0.0128(7) | 0.0140(6) | 0.0000(5) | -0.0008(5) | -0.0025(5) |
| C3 | 0.0110(6) | 0.0158(7) | 0.0141(6) | -0.0015(5) | -0.0013(5) | -0.0027(5) |
| C4 | 0.0147(7) | 0.0127(6) | 0.0125(6) | -0.0008(5) | -0.0009(5) | 0.0001(5) |
| C5 | 0.0147(7) | 0.0146(7) | 0.0173(7) | 0.0001(5) | -0.0021(5) | -0.0037(5) |
| C6 | 0.0211(8) | 0.0142(7) | 0.0180(7) | 0.0017(5) | -0.0017(6) | -0.0058(6) |
| C7 | 0.0183(7) | 0.0163(7) | 0.0147(7) | 0.0030(5) | -0.0017(6) | 0.0005(6) |
| C8 | 0.0133(7) | 0.0203(7) | 0.0190(7) | 0.0015(6) | -0.0025(6) | -0.0035(6) |
| C9 | 0.0161(7) | 0.0146(7) | 0.0164(7) | 0.0014(5) | -0.0006(5) | -0.0052(5) |
| C10 | 0.0297(9) | 0.0192(7) | 0.0213(8) | 0.0067(6) | -0.0054(6) | -0.0021(6) |
| C11 | 0.0143(7) | 0.0108(6) | 0.0149(6) | 0.0000(5) | -0.0018(5) | -0.0014(5) |
| C12 | 0.0157(7) | 0.0148(7) | 0.0188(7) | -0.0004(5) | -0.0043(6) | -0.0009(5) |
| C13 | 0.0257(8) | 0.0162(7) | 0.0167(7) | 0.0008(6) | -0.0066(6) | -0.0007(6) |
| C14 | 0.0261(8) | 0.0152(7) | 0.0164(7) | 0.0023(6) | 0.0014(6) | -0.0014(6) |
| C15 | 0.0162(7) | 0.0180(7) | 0.0232(7) | 0.0009(6) | 0.0014(6) | -0.0048(6) |
| C16 | 0.0146(7) | 0.0147(7) | 0.0172(7) | -0.0003(5) | -0.0032(5) | -0.0020(5) |
| N1 | 0.0116(6) | 0.0122(5) | 0.0147(6) | 0.0023(4) | -0.0034(5) | -0.0003(4) |
| O1 | 0.0145(5) | 0.0123(5) | 0.0196(5) | 0.0020(4) | -0.0057(4) | -0.0036(4) |
| O2 | 0.0159(5) | 0.0182(5) | 0.0248(5) | 0.0012(4) | -0.0082(4) | -0.0047(4) |
| O3 | 0.0217(6) | 0.0260(6) | 0.0288(6) | 0.0160(5) | -0.0070(5) | -0.0016(5) |
| C17 | 0.0107(6) | 0.0110(6) | 0.0151(6) | 0.0004(5) | -0.0039(5) | -0.0019(5) |
| C18 | 0.0138(7) | 0.0105(6) | 0.0145(6) | -0.0004(5) | -0.0009(5) | -0.0020(5) |
| C19 | 0.0104(6) | 0.0140(7) | 0.0134(6) | -0.0021(5) | -0.0005(5) | -0.0022(5) |
| C20 | 0.0130(7) | 0.0126(6) | 0.0121(6) | 0.0001(5) | 0.0000(5) | -0.0017(5) |
| C21 | 0.0167(7) | 0.0121(6) | 0.0160(7) | -0.0002(5) | -0.0021(5) | -0.0044(5) |
| C22 | 0.0141(7) | 0.0168(7) | 0.0169(7) | 0.0001(5) | -0.0031(5) | -0.0048(5) |
| C23 | 0.0158(7) | 0.0127(6) | 0.0137(6) | 0.0012(5) | -0.0015(5) | -0.0005(5) |
| C24 | 0.0175(7) | 0.0126(6) | 0.0160(7) | 0.0024(5) | -0.0016(5) | -0.0049(5) |
| C25 | 0.0129(7) | 0.0153(7) | 0.0151(7) | 0.0003(5) | -0.0021(5) | -0.0040(5) |
| C26 | 0.0251(8) | 0.0219(8) | 0.0270(8) | 0.0042(6) | -0.0129(7) | -0.0053(6) |
| C27 | 0.0152(7) | 0.0086(6) | 0.0156(7) | -0.0001(5) | -0.0032(5) | -0.0010(5) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C28 | 0.0155(7) | 0.0137(7) | 0.0166(7) | -0.0012(5) | -0.0025(5) | -0.0022(5) |
| C29 | 0.0190(7) | 0.0166(7) | 0.0214(7) | -0.0009(6) | 0.0013(6) | -0.0049(6) |
| C30 | 0.0272(8) | 0.0156(7) | 0.0146(7) | 0.0015(5) | 0.0022(6) | -0.0011(6) |
| C31 | 0.0237(8) | 0.0190(7) | 0.0174(7) | 0.0017(6) | -0.0071(6) | -0.0002(6) |
| C32 | 0.0150(7) | 0.0158(7) | 0.0203(7) | -0.0005(6) | -0.0045(6) | -0.0017(5) |
| N2 | 0.0117(6) | 0.0122(5) | 0.0142(5) | 0.0016(4) | -0.0028(4) | -0.0007(4) |
| O4 | 0.0138(5) | 0.0120(5) | 0.0198(5) | 0.0025(4) | -0.0046(4) | -0.0036(4) |
| O5 | 0.0141(5) | 0.0166(5) | 0.0255(5) | 0.0000(4) | -0.0072(4) | -0.0041(4) |
| O6 | 0.0197(5) | 0.0155(5) | 0.0260(6) | 0.0058(4) | -0.0110(4) | -0.0025(4) |

The form of the anisotropic displacement parameter is:
$\exp[-2\pi^2(a^{*2}U_{11}h^2+b^{*2}U_{22}k^2+c^{*2}U_{33}l^2+2b^*c^*U_{23}kl+2a^*c^*U_{13}hl+2a^*b^*U_{12}hk)]$

**Table B. 17** Bond Distances in Compound **4.23**, Å

| | | | | | |
|---|---|---|---|---|---|
| C1-N1 | 1.4577(17) | C1-C11 | 1.5280(18) | C1-C2 | 1.5425(19) |
| C1-C1#1 | 1.608(3) | C2-O2 | 1.1873(17) | C2-O1 | 1.3849(16) |
| C3-N1 | 1.2723(18) | C3-O1 | 1.3966(16) | C3-C4 | 1.4617(19) |
| C4-C5 | 1.3951(19) | C4-C9 | 1.403(2) | C5-C6 | 1.389(2) |
| C6-C7 | 1.394(2) | C7-O3 | 1.3645(17) | C7-C8 | 1.399(2) |
| C8-C9 | 1.381(2) | C10-O3 | 1.4336(18) | C11-C12 | 1.3961(19) |
| C11-C16 | 1.396(2) | C12-C13 | 1.387(2) | C13-C14 | 1.389(2) |
| C14-C15 | 1.388(2) | C15-C16 | 1.395(2) | C17-N2 | 1.4562(17) |
| C17-C27 | 1.5287(18) | C17-C18 | 1.5401(18) | C17-C17#2 | 1.608(3) |
| C18-O5 | 1.1877(17) | C18-O4 | 1.3834(16) | C19-N2 | 1.2729(18) |
| C19-O4 | 1.3994(16) | C19-C20 | 1.4599(19) | C20-C21 | 1.3978(19) |
| C20-C25 | 1.4011(19) | C21-C22 | 1.3879(19) | C22-C23 | 1.399(2) |
| C23-O6 | 1.3631(16) | C23-C24 | 1.397(2) | C24-C25 | 1.3808(19) |
| C26-O6 | 1.4240(18) | C27-C28 | 1.395(2) | C27-C32 | 1.3957(19) |
| C28-C29 | 1.399(2) | C29-C30 | 1.384(2) | C30-C31 | 1.389(2) |
| C31-C32 | 1.389(2) | | | | |

Symmetry transformations used to generate equivalent atoms:

#1 -x,-y+2,-z+1  #2 -x+2,-y+1,-z+2

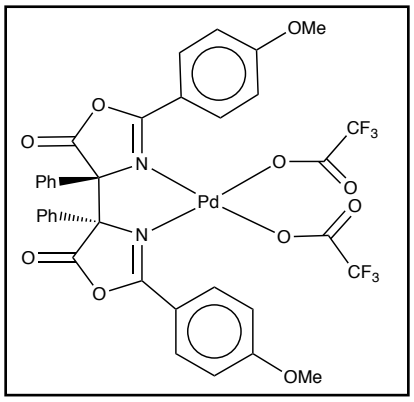
**Table B. 18** Bond Angles in Compound **4.23**, °

| | | | | | |
|---|---|---|---|---|---|
| N1-C1-C11 | 111.99(11) | N1-C1-C2 | 104.04(11) | C11-C1-C2 | 112.65(11) |
| N1-C1-C1#1 | 109.25(13) | C11-C1-C1#1 | 110.52(13) | C2-C1-C1#1 | 108.13(13) |
| O2-C2-O1 | 121.71(12) | O2-C2-C1 | 132.35(13) | O1-C2-C1 | 105.94(11) |
| N1-C3-O1 | 117.23(12) | N1-C3-C4 | 127.19(13) | O1-C3-C4 | 115.57(12) |
| C5-C4-C9 | 119.46(13) | C5-C4-C3 | 122.03(13) | C9-C4-C3 | 118.50(12) |
| C6-C5-C4 | 120.55(13) | C5-C6-C7 | 119.46(13) | O3-C7-C6 | 124.02(13) |
| O3-C7-C8 | 115.68(13) | C6-C7-C8 | 120.30(13) | C9-C8-C7 | 119.93(14) |
| C8-C9-C4 | 120.16(13) | C12-C11-C16 | 119.48(13) | C12-C11-C1 | 120.92(13) |
| C16-C11-C1 | 119.58(12) | C13-C12-C11 | 120.30(14) | C12-C13-C14 | 120.32(14) |
| C15-C14-C13 | 119.60(14) | C14-C15-C16 | 120.57(14) | C15-C16-C11 | 119.73(13) |
| C3-N1-C1 | 106.85(11) | C2-O1-C3 | 105.84(10) | C7-O3-C10 | 116.18(12) |
| N2-C17-C27 | 112.18(11) | N2-C17-C18 | 103.98(10) | C27-C17-C18 | 112.36(11) |
| N2-C17-C17#2 | 109.40(13) | C27-C17-C17#2 | 110.54(13) | C18-C17-C17#2 | 108.11(13) |
| O5-C18-O4 | 121.33(12) | O5-C18-C17 | 132.55(13) | O4-C18-C17 | 106.12(11) |
| N2-C19-O4 | 116.93(12) | N2-C19-C20 | 128.11(13) | O4-C19-C20 | 114.95(11) |
| C21-C20-C25 | 119.25(12) | C21-C20-C19 | 119.03(12) | C25-C20-C19 | 121.66(12) |
| C22-C21-C20 | 120.85(13) | C21-C22-C23 | 119.23(13) | O6-C23-C24 | 115.14(12) |
| O6-C23-C22 | 124.56(13) | C24-C23-C22 | 120.26(13) | C25-C24-C23 | 120.11(13) |
| C24-C25-C20 | 120.28(13) | C28-C27-C32 | 119.73(13) | C28-C27-C17 | 119.61(12) |
| C32-C27-C17 | 120.64(13) | C27-C28-C29 | 119.46(14) | C30-C29-C28 | 120.63(14) |
| C29-C30-C31 | 119.74(14) | C32-C31-C30 | 120.24(14) | C31-C32-C27 | 120.18(14) |
| C19-N2-C17 | 107.07(11) | C18-O4-C19 | 105.82(10) | C23-O6-C26 | 118.05(11) |

Symmetry transformations used to generate equivalent atoms:

#1 -x,-y+2,-z+1  #2 -x+2,-y+1,-z+2

## B.4. X-Ray Structure Determination of Compound 4.24




Compound **4.24**, $C_{36}H_{24}N_2O_{10}F_6Pd$, crystallizes in the monoclinic space group $P2_1$ (systematic absences 0k0: k=odd) with a=17.9656(11)Å, b=9.6793(7)Å, c=21.8956(12)Å, β=91.748(3)°, V=3805.8(4)Å$^3$, Z=4, and $d_{calc}$=1.510 g/cm$^3$ . X-ray intensity data were collected on a Bruker APEXII CCD area detector employing graphite-monochromated Mo-Kα radiation (λ=0.71073 Å) at a temperature of 100(1)K. Preliminary indexing was performed from a series of thirty-six 0.5° rotation frames with exposures of 10 seconds. A total of 36808 frames were collected with a crystal to detector distance of 49.9 mm, rotation widths of 0.5° and exposures of 15 seconds:

| scan type | 2θ | ω | ϕ | χ | frames |
|---|---|---|---|---|---|
| ϕ | 24.50 | 1.93 | 15.97 | 36.30 | 739 |
| ϕ | 27.00 | 19.86 | 76.11 | 69.08 | 335 |
| ϕ | 29.50 | 126.51 | 331.87 | -58.65 | 334 |
| ω | 32.00 | 355.15 | 337.13 | 61.00 | 69 |
| ϕ | -30.50 | 251.25 | 25.81 | 21.36 | 416 |
| ϕ | -30.50 | 5.08 | 330.80 | -60.33 | 739 |
| ϕ | 24.50 | 68.74 | 340.76 | -42.87 | 739 |
| ω | 29.50 | 327.78 | 183.80 | 85.83 | 133 |

| | | | | | |
|---|---|---|---|---|---|
| ω | 32.00 | 123.10 | 101.21 | -99.65 | 176 |

Rotation frames were integrated using SAINT[186], producing a listing of unaveraged $F^2$ and $\sigma(F^2)$ values which were then passed to the SHELXTL[187] program package for further processing and structure solution. A total of 141143 reflections were measured over the ranges $1.44 \leq \theta \leq 27.73°$, $-23 \leq h \leq 23$, $0 \leq k \leq 12$, $0 \leq l \leq 28$ yielding 8803 unique reflections (Rint = 0.0784). The intensity data were corrected for Lorentz and polarization effects and for absorption using SADABS[188] (minimum and maximum transmission 0.5019, 0.7456).

The structure was solved by direct methods (SHELXS-97[189]). There was a region of disordered solvent for which a reliable disorder model could not be devised; the X-ray data were corrected for the presence of disordered solvent using SQUEEZE[195]. Refinement was by full-matrix least squares based on $F^2$ using SHELXL-97.[189] All reflections were used during refinement. The weighting scheme used was $w=1/[\sigma^2(F_o^2)+ (0.0367P)^2 + 87.6152P]$ where $P = (F_o^2 + 2F_c^2)/3$. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were refined using a riding model. Refinement converged to R1=0.1089 and wR2=0.2554 for 7923 observed reflections for which $F > 4\sigma(F)$ and R1=0.1153 and wR2=0.2578 and GOF =1.235 for all 8803 unique, non-zero reflections and 535 variables.[191] The maximum $\Delta/\sigma$ in the final cycle of least squares was 0.007 and the two most prominent peaks in the final difference Fourier were +2.856 and -5.121 e/Å$^3$.

Table B.19 lists cell information, data collection parameters, and refinement data. Final positional and equivalent isotropic thermal parameters are given in Tables B.20 and B.21 Anisotropic thermal parameters are in Table B.22 Tables B.23 and B.24 list bond distances and bond angles. Figure B.5 is an ORTEP[194] representation of the molecule with 50% probability thermal ellipsoids displayed.

195) v.d. Sluis, P. & A.L. Spek (1990). *Acta. Cryst.*, **A46**, 194.

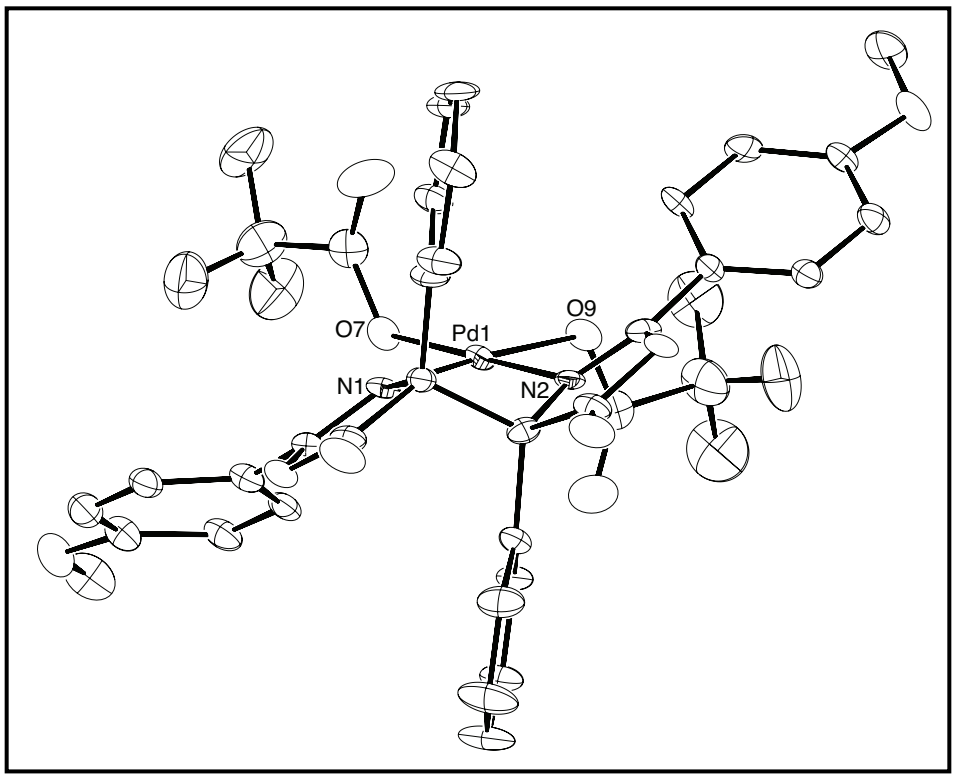



**Figure B. 5** ORTEP drawing of the title compound with 50% probability thermal ellipsoids.

**Table B. 19** Summary of Structure Determination of Compound **4.24**

| | |
|---|---|
| Empirical formula | $C_{36}H_{24}N_2O_{10}F_6Pd$ |
| Formula weight | 864.97 |
| Temperature | 100(1) K |
| Wavelength | 0.71073 Å |
| Crystal system | monoclinic |
| Space group | $P2_1$ |
| Cell constants: | |
| a | 17.9656(11) Å |
| b | 9.6793(7) Å |
| c | 21.8956(12) Å |

| | |
|---|---|
| β | 91.748(3)° |
| Volume | 3805.8(4) $Å^3$ |
| Z | 4 |
| Density (calculated) | 1.510 $Mg/m^3$ |
| Absorption coefficient | 0.574 $mm^{-1}$ |
| F(000) | 1736 |
| Crystal size | 0.46 x 0.08 x 0.06 $mm^3$ |
| Theta range for data collection | 1.44 to 27.73° |
| Index ranges | $-23 \leq h \leq 23, 0 \leq k \leq 12, 0 \leq l \leq 28$ |
| Reflections collected | 141143 |
| Independent reflections | 8803 [R(int) = 0.0784] |
| Completeness to theta = 27.73° | 98.1 % |
| Absorption correction | Semi-empirical from equivalents |
| Max. and min. transmission | 0.7456 and 0.5019 |
| Refinement method | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 8803 / 259 / 535 |
| Goodness-of-fit on $F^2$ | 1.235 |
| Final R indices [I>2sigma(I)] | R1 = 0.1089, wR2 = 0.2554 |
| R indices (all data) | R1 = 0.1153, wR2 = 0.2578 |
| Largest diff. peak and hole | 2.856 and -5.121 $e.Å^{-3}$ |

**Table B. 20** Refined Positional Parameters for Compound **4.24**

| Atom | x | y | z | $U_{eq}$, $A^2$ |
|---|---|---|---|---|
| Pd1 | 0.50083(3) | 0.67733(6) | 0.78290(3) | 0.01680(17) |
| O1 | 0.6159(3) | 0.4903(6) | 0.6416(3) | 0.0202(12) |
| O2 | 0.5786(4) | 0.5921(6) | 0.5525(3) | 0.0271(14) |
| O3 | 0.7514(4) | 0.1523(7) | 0.8614(3) | 0.0308(15) |
| O4 | 0.3765(3) | 0.8586(5) | 0.6385(3) | 0.0190(12) |
| O5 | 0.4054(4) | 0.7509(6) | 0.5515(3) | 0.0260(13) |
| O6 | 0.2533(4) | 1.1953(7) | 0.8589(3) | 0.0290(14) |
| O7 | 0.5754(3) | 0.6283(6) | 0.8494(3) | 0.0204(12) |
| O8 | 0.6304(4) | 0.8381(8) | 0.8414(3) | 0.0428(19) |
| O9 | 0.4306(3) | 0.7261(6) | 0.8492(3) | 0.0206(12) |
| O10 | 0.3807(4) | 0.5119(8) | 0.8468(3) | 0.0349(16) |
| N1 | 0.5641(4) | 0.6236(7) | 0.7121(3) | 0.0161(13) |
| N2 | 0.4316(4) | 0.7283(7) | 0.7113(3) | 0.0157(13) |
| C1 | 0.5401(4) | 0.6845(8) | 0.6528(3) | 0.0161(14) |
| C2 | 0.5779(5) | 0.5897(8) | 0.6061(4) | 0.0199(16) |
| C3 | 0.6039(4) | 0.5131(8) | 0.7015(4) | 0.0181(16) |
| C4 | 0.6371(5) | 0.4150(8) | 0.7437(4) | 0.0215(17) |
| C5 | 0.7090(5) | 0.3645(9) | 0.7309(4) | 0.0235(17) |
| C6 | 0.7443(5) | 0.2760(9) | 0.7707(4) | 0.0267(18) |
| C7 | 0.7097(5) | 0.2344(9) | 0.8245(4) | 0.0262(18) |
| C8 | 0.6369(5) | 0.2771(9) | 0.8358(4) | 0.0246(18) |
| C9 | 0.6010(5) | 0.3676(8) | 0.7952(4) | 0.0232(17) |
| C10 | 0.7201(7) | 0.1096(12) | 0.9192(4) | 0.039(3) |
| C11 | 0.5621(5) | 0.8375(8) | 0.6447(4) | 0.0234(17) |
| C12 | 0.5609(6) | 0.8923(9) | 0.5861(4) | 0.0282(19) |
| C13 | 0.5764(6) | 1.0306(9) | 0.5779(4) | 0.0272(19) |
| C14 | 0.5929(5) | 1.1139(9) | 0.6283(5) | 0.0294(19) |
| C15 | 0.5941(5) | 1.0592(9) | 0.6859(4) | 0.0280(19) |
| C16 | 0.5793(5) | 0.9186(9) | 0.6953(4) | 0.0238(17) |
| C17 | 0.4526(4) | 0.6653(8) | 0.6526(3) | 0.0175(15) |
| C18 | 0.4101(5) | 0.7558(8) | 0.6051(4) | 0.0216(17) |

| | | | | |
|---|---|---|---|---|
| C19 | 0.3922(5) | 0.8391(8) | 0.6990(4) | 0.0196(16) |
| C20 | 0.3603(4) | 0.9379(8) | 0.7403(4) | 0.0185(16) |
| C21 | 0.2890(5) | 0.9846(8) | 0.7275(4) | 0.0211(17) |
| C22 | 0.2549(5) | 1.0730(8) | 0.7675(4) | 0.0213(17) |
| C23 | 0.2931(5) | 1.1142(8) | 0.8219(4) | 0.0195(16) |
| C24 | 0.3663(5) | 1.0722(9) | 0.8328(4) | 0.0217(17) |
| C25 | 0.4003(5) | 0.9850(8) | 0.7930(4) | 0.0215(17) |
| C26 | 0.2884(6) | 1.2364(11) | 0.9157(4) | 0.032(2) |
| C27 | 0.4289(5) | 0.5123(8) | 0.6467(4) | 0.0205(16) |
| C28 | 0.4239(6) | 0.4500(10) | 0.5887(4) | 0.031(2) |
| C29 | 0.4072(7) | 0.3130(11) | 0.5839(5) | 0.043(3) |
| C30 | 0.3963(7) | 0.2315(10) | 0.6339(5) | 0.038(2) |
| C31 | 0.4005(5) | 0.2916(9) | 0.6925(4) | 0.0276(19) |
| C32 | 0.4179(5) | 0.4332(8) | 0.6986(4) | 0.0192(16) |
| C33 | 0.6236(5) | 0.7221(10) | 0.8615(4) | 0.0251(18) |
| C34 | 0.6864(5) | 0.6617(8) | 0.9079(4) | 0.042(2) |
| F1 | 0.7317(7) | 0.5904(13) | 0.8744(5) | 0.055(3) |
| F2 | 0.7218(10) | 0.7685(15) | 0.9314(9) | 0.055(5) |
| F3 | 0.6625(8) | 0.5835(13) | 0.9521(6) | 0.057(4) |
| C35 | 0.3869(5) | 0.6306(10) | 0.8641(4) | 0.0236(17) |
| C36 | 0.3287(5) | 0.6898(8) | 0.9111(4) | 0.044(2) |
| F4 | 0.2761(6) | 0.7498(14) | 0.8780(5) | 0.062(3) |
| F5 | 0.3574(6) | 0.7790(13) | 0.9502(5) | 0.062(3) |
| F6 | 0.3006(10) | 0.5856(14) | 0.9408(8) | 0.072(5) |
| F1' | 0.6458(14) | 0.648(2) | 0.9612(10) | 0.066(5) |
| F2' | 0.7377(15) | 0.759(2) | 0.9252(16) | 0.049(5) |
| F3' | 0.7141(13) | 0.5533(17) | 0.8948(9) | 0.055(4) |
| F4' | 0.3760(9) | 0.678(2) | 0.9680(7) | 0.075(4) |
| F5' | 0.2784(11) | 0.5886(15) | 0.9260(11) | 0.059(4) |
| F6' | 0.3067(11) | 0.7988(13) | 0.9075(8) | 0.064(4) |

$U_{eq}={}^{1}/_{3}[U_{11}(aa^*)^2+U_{22}(bb^*)^2+U_{33}(cc^*)^2+2U_{12}aa^*bb^*\cos\gamma+2U_{13}aa^*cc^*\cos\beta+2U_{23}bb^*cc^*\cos\alpha]$

**Table B. 21** Positional Parameters for Hydrogens in Compound **4.24**

| Atom | x | y | z | $U_{iso}$, $A^2$ |
|---|---|---|---|---|
| H5 | 0.7321 | 0.3916 | 0.6954 | 0.031 |
| H6 | 0.7915 | 0.2430 | 0.7623 | 0.036 |
| H8 | 0.6128 | 0.2454 | 0.8701 | 0.033 |
| H9 | 0.5528 | 0.3967 | 0.8025 | 0.031 |
| H10a | 0.7097 | 0.1898 | 0.9433 | 0.059 |
| H10b | 0.7551 | 0.0517 | 0.9411 | 0.059 |
| H10c | 0.6748 | 0.0592 | 0.9113 | 0.059 |
| H12 | 0.5497 | 0.8362 | 0.5526 | 0.038 |
| H13 | 0.5757 | 1.0680 | 0.5388 | 0.036 |
| H14 | 0.6032 | 1.2071 | 0.6227 | 0.039 |
| H15 | 0.6050 | 1.1159 | 0.7193 | 0.037 |
| H16 | 0.5809 | 0.8810 | 0.7344 | 0.032 |
| H21 | 0.2639 | 0.9564 | 0.6920 | 0.028 |
| H22 | 0.2071 | 1.1054 | 0.7586 | 0.028 |
| H24 | 0.3924 | 1.1036 | 0.8674 | 0.029 |
| H25 | 0.4492 | 0.9570 | 0.8005 | 0.029 |
| H26a | 0.3018 | 1.1557 | 0.9390 | 0.048 |
| H26b | 0.2545 | 1.2918 | 0.9382 | 0.048 |
| H26c | 0.3323 | 1.2890 | 0.9078 | 0.048 |
| H28 | 0.4320 | 0.5020 | 0.5538 | 0.041 |
| H29 | 0.4030 | 0.2734 | 0.5452 | 0.057 |
| H30 | 0.3861 | 0.1378 | 0.6293 | 0.050 |
| H31 | 0.3920 | 0.2383 | 0.7269 | 0.037 |
| H32 | 0.4220 | 0.4734 | 0.7372 | 0.025 |

**Table B. 22** Refined Thermal Parameters (U's) for Compound **4.24**

| Atom | $U_{11}$ | $U_{22}$ | $U_{33}$ | $U_{23}$ | $U_{13}$ | $U_{12}$ |
|---|---|---|---|---|---|---|
| Pd1 | 0.0205(3) | 0.0113(3) | 0.0186(3) | -0.0027(2) | 0.0017(2) | 0.0013(2) |
| O1 | 0.025(3) | 0.013(3) | 0.023(3) | -0.002(2) | 0.004(2) | 0.002(2) |
| O2 | 0.048(4) | 0.021(3) | 0.013(3) | -0.003(2) | 0.007(3) | 0.003(3) |
| O3 | 0.035(4) | 0.028(3) | 0.030(3) | 0.007(3) | 0.004(3) | 0.010(3) |
| O4 | 0.026(3) | 0.009(2) | 0.022(3) | -0.001(2) | -0.002(2) | 0.001(2) |
| O5 | 0.044(4) | 0.020(3) | 0.013(3) | 0.001(2) | -0.001(2) | 0.000(3) |
| O6 | 0.035(4) | 0.026(3) | 0.026(3) | -0.010(3) | -0.003(3) | 0.015(3) |
| O7 | 0.025(3) | 0.020(3) | 0.017(3) | 0.001(2) | -0.001(2) | 0.004(2) |
| O8 | 0.053(5) | 0.040(4) | 0.035(4) | 0.007(3) | -0.006(3) | -0.021(4) |
| O9 | 0.028(3) | 0.019(3) | 0.015(3) | -0.001(2) | 0.005(2) | 0.001(2) |
| O10 | 0.045(4) | 0.035(4) | 0.024(3) | -0.003(3) | 0.003(3) | -0.009(3) |
| N1 | 0.024(3) | 0.010(3) | 0.015(3) | -0.004(2) | 0.001(3) | -0.002(3) |
| N2 | 0.018(3) | 0.010(3) | 0.019(3) | -0.006(2) | 0.002(2) | -0.003(2) |
| C1 | 0.018(4) | 0.013(3) | 0.018(3) | -0.002(3) | 0.002(3) | -0.001(3) |
| C2 | 0.027(4) | 0.016(4) | 0.017(4) | -0.001(3) | 0.006(3) | -0.005(3) |
| C3 | 0.019(4) | 0.012(3) | 0.024(4) | -0.002(3) | 0.000(3) | -0.002(3) |
| C4 | 0.027(4) | 0.014(4) | 0.024(4) | -0.001(3) | 0.003(3) | 0.001(3) |
| C5 | 0.025(4) | 0.016(4) | 0.031(4) | -0.001(3) | 0.008(3) | -0.001(3) |
| C6 | 0.026(4) | 0.022(4) | 0.032(5) | 0.000(4) | 0.006(4) | 0.001(3) |
| C7 | 0.031(5) | 0.021(4) | 0.027(4) | -0.002(4) | 0.003(4) | 0.004(4) |
| C8 | 0.034(5) | 0.017(4) | 0.024(4) | -0.002(3) | 0.009(4) | 0.002(3) |
| C9 | 0.025(4) | 0.014(4) | 0.031(4) | -0.006(3) | 0.007(3) | 0.002(3) |
| C10 | 0.061(7) | 0.037(6) | 0.020(5) | 0.002(4) | 0.001(4) | 0.008(5) |
| C11 | 0.030(4) | 0.011(3) | 0.029(4) | 0.003(3) | 0.004(3) | -0.006(3) |
| C12 | 0.040(5) | 0.017(4) | 0.028(4) | -0.004(3) | 0.007(4) | -0.006(4) |
| C13 | 0.051(6) | 0.021(4) | 0.010(3) | 0.004(3) | 0.006(3) | 0.003(4) |
| C14 | 0.036(5) | 0.013(4) | 0.040(5) | -0.004(3) | 0.001(4) | -0.012(4) |
| C15 | 0.035(5) | 0.015(4) | 0.034(4) | -0.006(3) | 0.000(4) | -0.008(4) |
| C16 | 0.033(5) | 0.017(4) | 0.023(4) | -0.005(3) | 0.008(3) | -0.001(3) |
| C17 | 0.020(4) | 0.015(4) | 0.018(4) | 0.005(3) | 0.003(3) | -0.006(3) |
| C18 | 0.031(5) | 0.015(4) | 0.020(4) | 0.000(3) | 0.009(3) | -0.003(3) |

| | | | | | | |
|---|---|---|---|---|---|---|
| C19 | 0.024(4) | 0.013(4) | 0.022(4) | 0.000(3) | -0.003(3) | -0.005(3) |
| C20 | 0.019(4) | 0.014(4) | 0.023(4) | -0.001(3) | 0.002(3) | 0.002(3) |
| C21 | 0.021(4) | 0.016(4) | 0.026(4) | -0.002(3) | -0.003(3) | 0.001(3) |
| C22 | 0.025(4) | 0.017(4) | 0.021(4) | -0.002(3) | -0.008(3) | 0.006(3) |
| C23 | 0.025(4) | 0.015(4) | 0.019(4) | -0.003(3) | 0.002(3) | 0.004(3) |
| C24 | 0.029(4) | 0.021(4) | 0.015(4) | -0.008(3) | -0.006(3) | -0.003(3) |
| C25 | 0.028(4) | 0.013(4) | 0.024(4) | -0.003(3) | 0.002(3) | 0.007(3) |
| C26 | 0.041(6) | 0.033(5) | 0.022(4) | -0.015(4) | -0.002(4) | 0.005(4) |
| C27 | 0.023(4) | 0.014(4) | 0.025(4) | -0.005(3) | 0.002(3) | 0.001(3) |
| C28 | 0.043(6) | 0.021(4) | 0.029(5) | 0.003(4) | 0.004(4) | -0.009(4) |
| C29 | 0.076(8) | 0.024(5) | 0.029(5) | -0.014(4) | 0.010(5) | -0.009(5) |
| C30 | 0.063(7) | 0.016(4) | 0.034(5) | -0.007(4) | 0.008(5) | -0.014(4) |
| C31 | 0.038(5) | 0.013(4) | 0.032(5) | -0.001(3) | 0.002(4) | -0.005(3) |
| C32 | 0.027(4) | 0.013(4) | 0.018(4) | -0.003(3) | 0.003(3) | -0.005(3) |
| C33 | 0.032(5) | 0.032(5) | 0.011(4) | -0.005(3) | 0.002(3) | 0.001(4) |
| C34 | 0.044(6) | 0.052(5) | 0.030(4) | -0.002(4) | -0.011(4) | -0.007(4) |
| F1 | 0.041(7) | 0.068(9) | 0.055(8) | -0.003(6) | -0.004(5) | 0.008(6) |
| F2 | 0.044(11) | 0.073(9) | 0.048(9) | -0.015(7) | -0.017(7) | -0.015(8) |
| F3 | 0.054(8) | 0.073(9) | 0.043(7) | 0.026(7) | -0.015(5) | -0.001(7) |
| C35 | 0.028(4) | 0.030(4) | 0.013(3) | 0.002(3) | -0.002(3) | 0.003(3) |
| C36 | 0.053(6) | 0.042(5) | 0.038(5) | -0.005(4) | 0.021(4) | 0.003(4) |
| F4 | 0.048(7) | 0.077(9) | 0.063(8) | -0.004(6) | 0.015(5) | 0.026(7) |
| F5 | 0.064(8) | 0.080(8) | 0.045(7) | -0.038(6) | 0.031(5) | -0.002(6) |
| F6 | 0.080(13) | 0.068(8) | 0.070(11) | 0.017(7) | 0.044(7) | -0.005(8) |
| F1' | 0.072(13) | 0.090(14) | 0.034(8) | 0.010(11) | -0.005(7) | -0.010(11) |
| F2' | 0.024(9) | 0.049(8) | 0.072(17) | 0.005(8) | -0.028(7) | 0.008(6) |
| F3' | 0.065(8) | 0.049(6) | 0.051(7) | 0.013(6) | -0.021(5) | 0.012(6) |
| F4' | 0.095(10) | 0.100(11) | 0.031(6) | -0.027(8) | 0.011(6) | 0.016(9) |
| F5' | 0.048(9) | 0.050(7) | 0.081(13) | -0.002(7) | 0.048(7) | 0.011(6) |
| F6' | 0.082(12) | 0.041(6) | 0.070(10) | -0.012(6) | 0.034(6) | 0.015(6) |

The form of the anisotropic displacement parameter is:
$\exp[-2\pi^2(a^{*2}U_{11}h^2+b^{*2}U_{22}k^2+c^{*2}U_{33}l^2+2b^*c^*U_{23}kl+2a^*c^*U_{13}hl+2a^*b^*U_{12}hk)]$

**Table B. 23** Bond Distances in Compound **4.24**, Å

| | | | | | |
|---|---|---|---|---|---|
| Pd1-O7 | 2.005(6) | Pd1-O9 | 2.009(6) | Pd1-N1 | 2.018(7) |
| Pd1-N2 | 2.031(7) | O1-C3 | 1.353(10) | O1-C2 | 1.403(10) |
| O2-C2 | 1.172(10) | O3-C7 | 1.346(11) | O3-C10 | 1.460(12) |
| O4-C19 | 1.358(10) | O4-C18 | 1.384(10) | O5-C18 | 1.176(10) |
| O6-C23 | 1.349(10) | O6-C26 | 1.433(10) | O7-C33 | 1.277(11) |
| O8-C33 | 1.215(12) | O9-C35 | 1.262(11) | O10-C35 | 1.214(11) |
| N1-C3 | 1.311(10) | N1-C1 | 1.477(10) | N2-C19 | 1.309(10) |
| N2-C17 | 1.481(10) | C1-C11 | 1.545(11) | C1-C2 | 1.547(11) |
| C1-C17 | 1.584(10) | C3-C4 | 1.441(11) | C4-C9 | 1.397(12) |
| C4-C5 | 1.417(12) | C5-C6 | 1.365(13) | C6-C7 | 1.406(13) |
| C7-C8 | 1.401(13) | C8-C9 | 1.392(13) | C11-C16 | 1.385(12) |
| C11-C12 | 1.387(12) | C12-C13 | 1.380(12) | C13-C14 | 1.391(12) |
| C14-C15 | 1.368(14) | C15-C16 | 1.403(12) | C17-C18 | 1.544(11) |
| C17-C27 | 1.545(11) | C19-C20 | 1.446(11) | C20-C21 | 1.379(11) |
| C20-C25 | 1.416(12) | C21-C22 | 1.380(12) | C22-C23 | 1.413(11) |
| C23-C24 | 1.389(12) | C24-C25 | 1.370(11) | C27-C32 | 1.390(12) |
| C27-C28 | 1.407(12) | C28-C29 | 1.363(13) | C29-C30 | 1.370(15) |
| C30-C31 | 1.407(13) | C31-C32 | 1.412(11) | C33-C34 | 1.604(12) |
| C34-F3' | 1.20(2) | C34-F2 | 1.3100 | C34-F1 | 1.3100 |
| C34-F3 | 1.3101 | C34-F2' | 1.36(2) | C34-F1' | 1.40(2) |
| F1-F3' | 0.66(2) | F3-F1' | 0.73(2) | F3-F3' | 1.609(19) |
| C35-C36 | 1.596(11) | C36-F6' | 1.128(15) | C36-F5 | 1.3098 |
| C36-F4 | 1.3100 | C36-F6 | 1.3100 | C36-F5' | 1.379(19) |
| C36-F4' | 1.491(16) | F4-F6' | 0.960(18) | F5-F4' | 1.101(19) |
| F5-F6' | 1.300(17) | F6-F5' | 0.51(3) | F6-F4' | 1.71(2) |

**Table B. 24** Bond Angles in Compound **4.24,** °

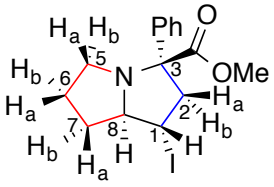
| | | | | | |
|---|---|---|---|---|---|
| O7-Pd1-O9 | 87.2(2) | O7-Pd1-N1 | 96.7(3) | O9-Pd1-N1 | 175.4(3) |
| O7-Pd1-N2 | 175.8(3) | O9-Pd1-N2 | 96.7(3) | N1-Pd1-N2 | 79.4(3) |
| C3-O1-C2 | 109.6(6) | C7-O3-C10 | 117.8(8) | C19-O4-C18 | 109.6(6) |
| C23-O6-C26 | 117.1(7) | C33-O7-Pd1 | 114.7(5) | C35-O9-Pd1 | 115.0(5) |
| C3-N1-C1 | 108.4(6) | C3-N1-Pd1 | 132.0(6) | C1-N1-Pd1 | 114.6(5) |
| C19-N2-C17 | 108.0(7) | C19-N2-Pd1 | 132.3(5) | C17-N2-Pd1 | 113.8(5) |
| N1-C1-C11 | 114.5(6) | N1-C1-C2 | 102.9(6) | C11-C1-C2 | 111.9(6) |
| N1-C1-C17 | 102.6(6) | C11-C1-C17 | 111.7(6) | C2-C1-C17 | 112.5(6) |
| O2-C2-O1 | 123.2(8) | O2-C2-C1 | 132.0(8) | O1-C2-C1 | 104.8(6) |
| N1-C3-O1 | 114.2(7) | N1-C3-C4 | 129.8(8) | O1-C3-C4 | 116.0(7) |
| C9-C4-C5 | 119.7(8) | C9-C4-C3 | 122.8(8) | C5-C4-C3 | 117.6(8) |
| C6-C5-C4 | 119.9(8) | C5-C6-C7 | 120.4(9) | O3-C7-C8 | 125.0(8) |
| O3-C7-C6 | 114.8(8) | C8-C7-C6 | 120.2(8) | C9-C8-C7 | 119.2(8) |
| C8-C9-C4 | 120.4(8) | C16-C11-C12 | 121.3(8) | C16-C11-C1 | 120.2(8) |
| C12-C11-C1 | 118.4(8) | C13-C12-C11 | 119.6(8) | C12-C13-C14 | 119.8(8) |
| C15-C14-C13 | 120.3(8) | C14-C15-C16 | 120.9(8) | C11-C16-C15 | 118.1(8) |
| N2-C17-C18 | 102.5(6) | N2-C17-C27 | 113.1(6) | C18-C17-C27 | 111.0(7) |
| N2-C17-C1 | 103.1(6) | C18-C17-C1 | 113.9(6) | C27-C17-C1 | 112.5(7) |
| O5-C18-O4 | 122.6(8) | O5-C18-C17 | 132.0(8) | O4-C18-C17 | 105.4(6) |
| N2-C19-O4 | 114.2(7) | N2-C19-C20 | 129.4(7) | O4-C19-C20 | 116.3(7) |
| C21-C20-C25 | 120.3(7) | C21-C20-C19 | 118.2(8) | C25-C20-C19 | 121.5(7) |
| C20-C21-C22 | 120.2(8) | C21-C22-C23 | 119.7(8) | O6-C23-C24 | 125.6(7) |
| O6-C23-C22 | 114.7(7) | C24-C23-C22 | 119.7(7) | C25-C24-C23 | 120.6(8) |
| C24-C25-C20 | 119.5(8) | C32-C27-C28 | 119.8(8) | C32-C27-C17 | 120.3(7) |
| C28-C27-C17 | 119.8(8) | C29-C28-C27 | 119.6(9) | C28-C29-C30 | 122.3(9) |
| C29-C30-C31 | 119.1(9) | C30-C31-C32 | 119.6(9) | C27-C32-C31 | 119.5(8) |
| O8-C33-O7 | 131.0(9) | O8-C33-C34 | 119.4(8) | O7-C33-C34 | 109.4(7) |
| F3'-C34-F2 | 125.7(15) | F3'-C34-F1 | 30.2(10) | F2-C34-F1 | 109.4 |
| F3'-C34-F3 | 79.6(10) | F2-C34-F3 | 109.4 | F1-C34-F3 | 109.4 |

| | | | | | |
|---|---|---|---|---|---|
| F3'-C34-F2' | 112.8(18) | F2-C34-F2' | 14.1(17) | F1-C34-F2' | 95.3(17) |
| F3-C34-F2' | 115(2) | F3'-C34-F1' | 110.4(13) | F2-C34-F1' | 90.3(15) |
| F1-C34-F1' | 140.1(10) | F3-C34-F1' | 30.9(10) | F2'-C34-F1' | 101.4(15) |
| F3'-C34-C33 | 117.2(13) | F2-C34-C33 | 106.5(11) | F1-C34-C33 | 105.9(8) |
| F3-C34-C33 | 115.9(9) | F2'-C34-C33 | 112.3(17) | F1'-C34-C33 | 100.8(13) |
| F3'-F1-C34 | 65.7(17) | F1'-F3-C34 | 81(2) | F1'-F3-F3' | 129(2) |
| C34-F3-F3' | 47.2(7) | O10-C35-O9 | 131.7(9) | O10-C35-C36 | 119.1(8) |
| O9-C35-C36 | 109.1(7) | F6'-C36-F5 | 63.9(9) | F6'-C36-F4 | 45.6(9) |
| F5-C36-F4 | 109.4 | F6'-C36-F6 | 127.9(12) | F5-C36-F6 | 109.4 |
| F4-C36-F6 | 109.4 | F6'-C36-F5' | 116.7(15) | F5-C36-F5' | 124.2(17) |
| F4-C36-F5' | 88.7(12) | F6-C36-F5' | 21.6(12) | F6'-C36-F4' | 108.7(10) |
| F5-C36-F4' | 45.7(9) | F4-C36-F4' | 151.7(8) | F6-C36-F4' | 75.2(10) |
| F5'-C36-F4' | 96.3(11) | F6'-C36-C35 | 121.7(12) | F5-C36-C35 | 113.9(8) |
| F4-C36-C35 | 106.2(8) | F6-C36-C35 | 108.3(10) | F5'-C36-C35 | 110.1(12) |
| F4'-C36-C35 | 98.2(8) | F6'-F4-C36 | 57.1(9) | F4'-F5-F6' | 125.7(14) |
| F4'-F5-C36 | 75.8(11) | F6'-F5-C36 | 51.2(7) | F5'-F6-C36 | 87(2) |
| F5'-F6-F4' | 142(2) | C36-F6-F4' | 57.2(7) | F3-F1'-C34 | 67.7(15) |
| F1-F3'-C34 | 84.1(19) | F1-F3'-F3 | 137(2) | C34-F3'-F3 | 53.2(7) |
| F5-F4'-C36 | 58.4(7) | F5-F4'-F6 | 96.4(12) | C36-F4'-F6 | 47.6(6) |
| F6-F5'-C36 | 71(2) | F4-F6'-C36 | 77.2(11) | F4-F6'-F5 | 141.8(15) |
| C36-F6'-F5 | 64.8(8) | | | | |

## Appendix C: Computational Studies on compound 2.35

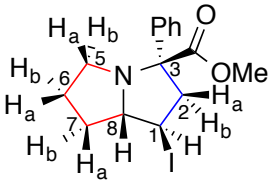
**Calculated Structures**. Structures were calculated using MM2* as implemented in MacroModel 6.5.[1961] Monte Carlo conformational searches were performed of all ground states using a minimum of 1000-5000 steps.[1972] Structures are provided in pdb file format.

MM2* Calculated distances (Å) and coupling constants (Hz) for Pyrrolizidine Products **2.35a-d.**



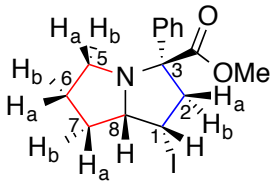
(*S,S,R*) **2.35a**

| | Distance | J Value |
|---|---|---|
| C1-H C8-H | 3.109 | 10.3 |
| C1-H C2-$H_a$ | 2.495 | 5.3 |
| C1-H C2-$H_b$ | 3.098 | 11.8 |
| *o*-H-Ph C2-$H_a$ | 2.436 | |
| *o*-H-Ph C2-$H_b$ | 2.886 | |
| *o*-H-Ph C1-H | 4.649 | |
| *o*-H-Ph C5-$H_a$ | 4.048 | |
| *o*-H-Ph C5-$H_b$ | 2.764 | |
| *o*-H-Ph C8-H | 3.647 | |



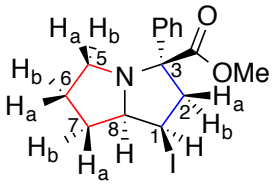
(*R,S,S*) **2.35b**

| | Distance | J Value |
|---|---|---|
| C1-H C8-H | 3.112 | 10.4 |
| C1-H C2-$H_a$ | 3.090 | 11.8 |
| C1-H C2-$H_b$ | 2.520 | 5.2 |
| *o*-H-Ph C2-$H_a$ | 2.730 | |
| *o*-H-Ph C2-$H_b$ | 2.211 | |
| *o*-H-Ph C1-H | 2.244 | |
| *o*-H-Ph C5-$H_a$ | 2.668 | |
| *o*-H-Ph C5-$H_b$ | 3.118 | |
| *o*-H-Ph C8-H | 4.779 | |



(*S,S,S*) **2.35c**

| | Distance | J Value |
|---|---|---|
| C1-H C8-H | 2.332 | 7.4 |
| C1-H C2-$H_a$ | 2.471 | 5.2 |
| C1-H C2-$H_b$ | 3.083 | 11.9 |
| *o*-H-Ph C2-$H_a$ | 2.244 | |
| *o*-H-Ph C2-$H_b$ | 2.571 | |
| *o*-H-Ph C1-H | 4.711 | |
| *o*-H-Ph C5-$H_a$ | 2.626 | |
| *o*-H-Ph C5-$H_b$ | 3.263 | |
| *o*-H-Ph C8-H | 4.671 | |

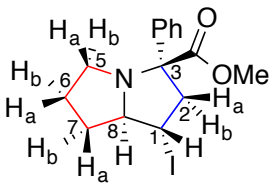


(*R,S,R*) **2.35d**

| | Distance | J Value |
|---|---|---|
| C1-H C8-H | 2.330 | 7.4 |
| C1-H C2-$H_a$ | 3.088 | 12.0 |
| C1-H C2-$H_b$ | 2.469 | 5.2 |
| *o*-H-Ph C2-$H_a$ | 3.722 | |
| *o*-H-Ph C2-$H_b$ | 2.385 | |
| *o*-H-Ph C1-H | 3.110 | |
| *o*-H-Ph C5-$H_a$ | 4.582 | |
| *o*-H-Ph C5-$H_b$ | 3.907 | |
| *o*-H-Ph C8-H | 2.586 | |

196) MacroModel 6.5; W.C. Still, Columbia Univ.

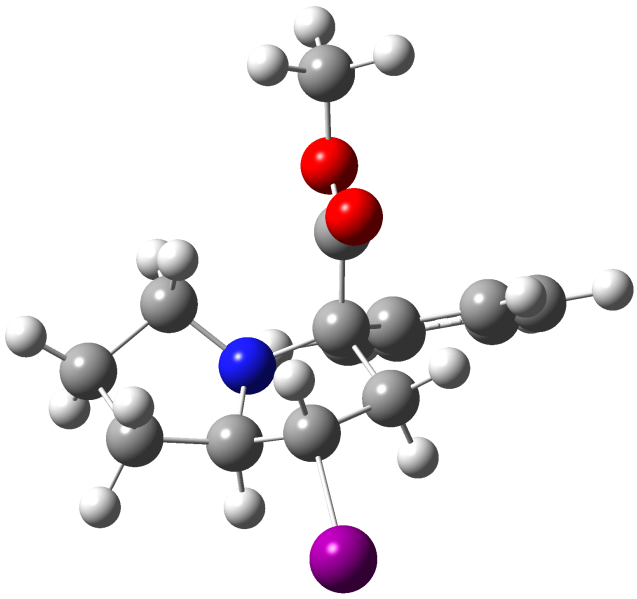
197) Mohamdi, F.; Richards, N.G.; Guida, W.C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, C.; Hendrickson, T.; Still, W.C. *J. Comput. Chem.* **1990**, *11*, 440-467.




(*S,S,R*) **2.35a**

Ground state 36.44 kcal/mol

**Ground State (*S,S,R*) 2.35a**



COMPND John1_PDB

REMARK 1 PDB: 37 38 39 40

REMARK 1 MMOD: 39 40 34 35 /

HETATM 1 C01 UNK 0 -1.049 -1.970 1.004 0.01 0.01 0

HETATM 2 C02 UNK 0 -2.284 -1.902 1.918 0.00 0.00 0

HETATM 3 C03 UNK 0 -1.860 0.215 0.976 0.01 0.01 0

```
HETATM    4  N04 UNK     0      -0.955  -0.698   0.303  0.19  0.19   0
HETATM    5  C05 UNK     0       0.449  -0.312   0.147  0.09  0.09   0
HETATM    6  C06 UNK     0       0.303  -2.158   1.694  0.13  0.13   0
HETATM    7  C07 UNK     0       1.230  -1.565   0.627  0.00  0.00   0
HETATM    8  C08 UNK     0       0.824  -0.031  -1.305 -0.04 -0.04   0
HETATM    9  C09 UNK     0      -0.135   0.132  -2.309  0.00  0.00   0
HETATM   10  C10 UNK     0       0.241   0.401  -3.624  0.00  0.00   0
HETATM   11  C11 UNK     0       1.588   0.519  -3.958  0.00  0.00   0
HETATM   12  C12 UNK     0       2.555   0.370  -2.967  0.00  0.00   0
HETATM   13  C13 UNK     0       2.172   0.100  -1.655  0.00  0.00   0
HETATM   14  C14 UNK     0       0.829   0.900   1.000  0.38  0.38   0
HETATM   15  O15 UNK     0       1.320   0.823   2.109 -0.45 -0.45   0
HETATM   16  O16 UNK     0       0.530   2.052   0.334  0.59  0.59   0
HETATM   17  C17 UNK     0       0.798   3.242   1.045  0.07  0.07   0
HETATM   18  C18 UNK     0      -3.041  -0.686   1.364  0.00  0.00   0
HETATM   19  H19 UNK     0      -1.200  -2.761   0.229  0.00  0.00   0
HETATM   20  H20 UNK     0      -2.897  -2.832   1.893  0.00  0.00   0
HETATM   21  H21 UNK     0      -1.977  -1.695   2.970  0.00  0.00   0
HETATM   22  H22 UNK     0      -1.417   0.618   1.916  0.00  0.00   0
HETATM   23  H23 UNK     0      -2.164   1.055   0.307  0.00  0.00   0
HETATM   24  LP4 UNK     0      -1.174  -0.785  -0.247 -0.21 -0.21   0
HETATM   25  I26 UNK     0       0.749  -4.198   2.208 -0.13 -0.13   0
HETATM   26  H25 UNK     0       0.362  -1.568   2.638  0.00  0.00   0
HETATM   27  H27 UNK     0       1.327  -2.290  -0.216  0.00  0.00   0
HETATM   28  H28 UNK     0       2.249  -1.342   1.021  0.00  0.00   0
HETATM   29  H29 UNK     0      -1.211   0.056  -2.087  0.00  0.00   0
HETATM   30  H30 UNK     0      -0.530   0.525  -4.402  0.00  0.00   0
```

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HETATM   31  H31 UNK     0       1.886   0.733  -4.997  0.00  0.00    0
HETATM   32  H32 UNK     0       3.623   0.467  -3.221  0.00  0.00    0
HETATM   33  H33 UNK     0       2.957  -0.006  -0.889  0.00  0.00    0
HETATM   34  H36 UNK     0       0.505   4.102   0.400  0.00  0.00    0
HETATM   35  H37 UNK     0       0.193   3.263   1.982  0.00  0.00    0
HETATM   36  H38 UNK     0       1.889   3.307   1.272  0.00  0.00    0
HETATM   37  H39 UNK     0      -3.619  -0.971   0.453  0.00  0.00    0
HETATM   38  H40 UNK     0      -3.722  -0.219   2.114  0.00  0.00    0
HETATM   39  LP4 UNK     0       0.922   2.073  -0.127 -0.31 -0.31    0
HETATM   40  LP5 UNK     0      -0.073   2.047   0.281 -0.31 -0.31    0
CONECT    1    2    4    6   19
CONECT    2    1   18   20   21
CONECT    3    4   18   22   23
CONECT    4    3    1    5   24
CONECT    5    4    7    8   14
CONECT    6    1    7   26   25
CONECT    7    5    6   27   28
CONECT    8   13    5
CONECT    8    9
CONECT    8    9
CONECT    9   10   29
CONECT    9    8
CONECT    9    8
CONECT   10    9   30
CONECT   10   11
CONECT   10   11
CONECT   11   12   31
```

CONECT 11 10

CONECT 11 10

CONECT 12 11 32

CONECT 12 13

CONECT 12 13

CONECT 13 8 33

CONECT 13 12

CONECT 13 12

CONECT 14 5 16

CONECT 14 15

CONECT 14 15

CONECT 15 14

CONECT 15 14

CONECT 16 14 17 39 40

CONECT 17 16 34 35 36

CONECT 18 2 3 37 38

CONECT 19 1

CONECT 20 2

CONECT 21 2

CONECT 22 3

CONECT 23 3

CONECT 24 4

CONECT 25 6

CONECT 26 6

CONECT 27 7

CONECT 28 7

CONECT 29 9

CONECT 30 10

CONECT 31 11

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CONECT 35 17

CONECT 36 17

CONECT 37 18

CONECT 38 18

CONECT 39 16

CONECT 40 16

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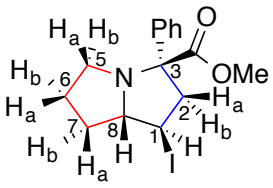
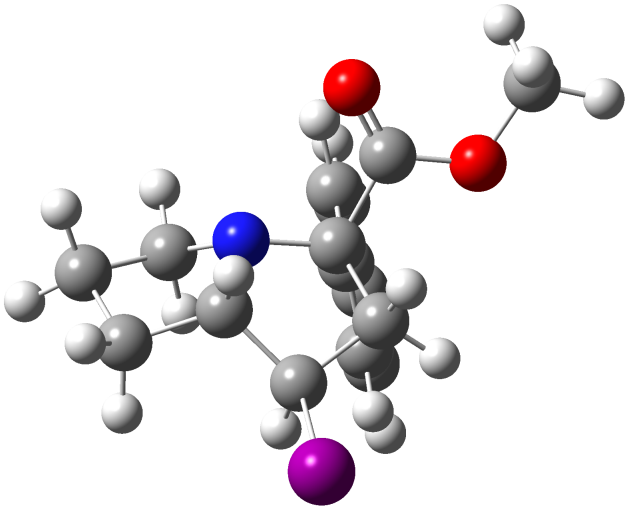



(*R,S,S*) **2.35b**

Ground State 38.21 kcal/mol

**Ground State (*R,S,S*) 2.35b**



COMPND John2_PDB

REMARK 1 PDB: 37 38 39 40

REMARK 1 MMOD: 39 40 34 35 /

HETATM 1 C01 UNK 0 -1.007 -1.993 -0.864 0.01 0.01 0

HETATM 2 C02 UNK 0 -2.215 -2.173 -1.801 0.00 0.00 0

HETATM 3 C03 UNK 0 -1.885 0.110 -1.302 0.01 0.01 0

HETATM 4 N04 UNK 0 -1.024 -0.618 -0.388 0.19 0.19 0

HETATM 5 C05 UNK 0 0.349 -0.142 -0.198 0.09 0.09 0

HETATM 6 C06 UNK 0 0.370 -2.173 -1.508 0.13 0.13 0

HETATM 7 C07 UNK 0 1.230 -1.379 -0.518 0.00 0.00 0

HETATM 8 C08 UNK 0 0.664 1.100 -1.029 -0.04 -0.04 0

HETATM 9 C09 UNK 0 1.358 1.055 -2.242 0.00 0.00 0

HETATM 10 C10 UNK 0 1.618 2.214 -2.971 0.00 0.00 0

HETATM 11 C11 UNK 0 1.186 3.451 -2.501 0.00 0.00 0

HETATM 12 C12 UNK 0 0.489 3.517 -1.298 0.00 0.00 0

HETATM 13 C13 UNK 0 0.233 2.353 -0.576 0.00 0.00 0

HETATM 14 C14 UNK 0 0.596 0.189 1.277 0.38 0.38 0

HETATM 15 O15 UNK 0 -0.248 0.133 2.150 -0.45 -0.45 0

HETATM 16 O16 UNK 0 1.896 0.569 1.443 0.59 0.59 0

HETATM 17 C17 UNK 0 2.250 0.931 2.762 0.07 0.07 0

HETATM 18 C18 UNK 0 -3.021 -0.886 -1.575 0.00 0.00 0

HETATM 19 H19 UNK 0 -1.110 -2.659 0.027 0.00 0.00 0

HETATM 20 H20 UNK 0 -2.809 -3.088 -1.573 0.00 0.00 0

HETATM 21 H21 UNK 0 -1.878 -2.214 -2.863 0.00 0.00 0

HETATM 22 H22 UNK 0 -1.369 0.322 -2.268 0.00 0.00 0

HETATM 23 H23 UNK 0 -2.258 1.057 -0.848 0.00 0.00 0

HETATM 24 LP4 UNK 0 -1.290 -0.615 0.148 -0.21 -0.21 0

HETATM 25 I26 UNK 0 0.972 -4.224 -1.741 -0.13 -0.13 0

HETATM 26 H25 UNK 0 0.403 -1.711 -2.522 0.00 0.00 0

HETATM 27 H27 UNK 0 1.362 -1.996 0.402 0.00 0.00 0

HETATM 28 H28 UNK 0 2.246 -1.131 -0.904 0.00 0.00 0

HETATM 29 H29 UNK 0 1.716 0.103 -2.661 0.00 0.00 0

HETATM 30 H30 UNK 0 2.167 2.153 -3.925 0.00 0.00 0

HETATM 31 H31 UNK 0 1.390 4.368 -3.077 0.00 0.00 0

HETATM 32 H32 UNK 0 0.138 4.490 -0.918 0.00 0.00 0

HETATM 33 H33 UNK 0 -0.328 2.441 0.368 0.00 0.00 0

HETATM 34 H36 UNK 0 3.327 1.219 2.762 0.00 0.00 0

HETATM 35 H37 UNK 0 2.102 0.059 3.443 0.00 0.00 0

HETATM 36 H38 UNK 0 1.636 1.803 3.089 0.00 0.00 0

HETATM 37 H39 UNK 0 -3.661 -0.987 -0.667 0.00 0.00 0

HETATM 38 H40 UNK 0 -3.649 -0.607 -2.452 0.00 0.00 0

HETATM 39 LP4 UNK 0 1.949 1.087 1.134 -0.31 -0.31 0

HETATM 40 LP5 UNK 0 2.219 0.067 1.339 -0.31 -0.31 0

CONECT 1 2 4 6 19

CONECT 2 1 18 20 21

CONECT 3 4 18 22 23

CONECT 4 3 1 5 24

CONECT 5 4 7 8 14

CONECT 6 1 7 26 25

CONECT 7 5 6 27 28

CONECT 8 13 5

CONECT 8 9

CONECT 8 9

CONECT 9 10 29

CONECT 9 8

CONECT 9 8

CONECT 10 9 30

CONECT 10 11

CONECT 10 11

CONECT 11 12 31

CONECT 11 10

CONECT 11 10

CONECT 12 11 32

CONECT 12 13

CONECT 12 13

CONECT 13 8 33

CONECT 13 12

CONECT 13 12

CONECT 14 5 16

CONECT 14 15

CONECT 14 15

CONECT 15 14

CONECT 15 14

CONECT 16 14 17 39 40

CONECT 17 16 34 35 36

CONECT 18 2 3 37 38

CONECT 19 1

CONECT 20 2

CONECT 21 2

CONECT 22 3

CONECT 23 3

CONECT 24 4

CONECT 25 6

CONECT 26 6

CONECT 27 7

CONECT 28 7

CONECT 29 9

CONECT 30 10

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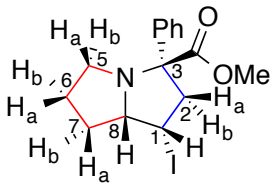
CONECT 37 18

CONECT 38 18

CONECT 39 16

CONECT 40 16

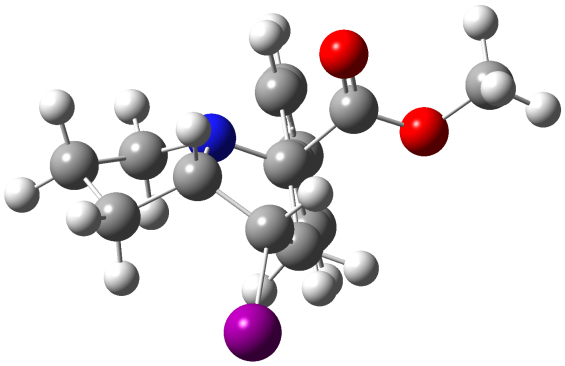
END




(*S,S,S*) **2.35c**

Ground State 39.36 kcal/mol

**Ground State (*S,S,S*) 2.35c**



COMPND John3_PDB

REMARK 1 PDB: 37 38 39 40

REMARK 1 MMOD: 39 40 32 33 /

HETATM 1 C01 UNK 0 -1.361 -1.902 -0.630 0.01 0.01 0

HETATM 2 C02 UNK 0 -2.280 -2.210 -1.827 0.00 0.00 0

HETATM 3 C03 UNK 0 -1.970 0.088 -1.712 0.01 0.01 0

HETATM 4 N04 UNK 0 -1.207 -0.445 -0.593 0.19 0.19 0

HETATM 5 C05 UNK 0 0.220 -0.119 -0.584 0.09 0.09 0

HETATM 6 C06 UNK 0 0.058 -2.491 -0.644 0.13 0.13 0

HETATM 7 C07 UNK 0 0.527 1.231 -1.219 -0.04 -0.04 0

HETATM 8 C08 UNK 0 1.391 1.382 -2.307 0.00 0.00 0

HETATM 9 C09 UNK 0 1.651 2.640 -2.847 0.00 0.00 0

HETATM 10 C10 UNK 0 1.054 3.774 -2.301 0.00 0.00 0

HETATM 11 C11 UNK 0 0.199 3.641 -1.210 0.00 0.00 0

HETATM 12 C12 UNK 0 -0.056 2.380 -0.676 0.00 0.00 0

HETATM 13 C13 UNK 0 0.734 -0.049 0.859 0.38 0.38 0

HETATM 14 O14 UNK 0 0.060 -0.291 1.841 -0.45 -0.45 0

HETATM 15 O15 UNK 0 2.046 0.325 0.861 0.59 0.59 0

HETATM 16 C16 UNK 0 2.638 0.423 2.140 0.07 0.07 0

HETATM 17 C17 UNK 0 -3.101 -0.921 -1.937 0.00 0.00 0

HETATM 18 C18 UNK 0 0.862 -1.347 -1.273 0.00 0.00 0

HETATM 19 H19 UNK 0 -1.889 -2.226 0.299 0.00 0.00 0

HETATM 20 H20 UNK 0 -1.690 -2.337 -2.764 0.00 0.00 0

HETATM 21 H21 UNK 0 -2.919 -3.108 -1.666 0.00 0.00 0

HETATM 22 H22 UNK 0 -2.364 1.107 -1.489 0.00 0.00 0

HETATM 23 H23 UNK 0 -1.349 0.127 -2.638 0.00 0.00 0

HETATM 24 LP4 UNK 0 -1.450 -0.238 -0.086 -0.21 -0.21 0

HETATM 25 I26 UNK 0 0.334 -4.407 -1.583 -0.13 -0.13 0

HETATM 26 H25 UNK 0 0.403 -2.641 0.405 0.00 0.00 0

HETATM 27 H27 UNK 0 1.889 0.513 -2.763 0.00 0.00 0

HETATM 28 H28 UNK 0 2.333 2.740 -3.707 0.00 0.00 0

HETATM 29 H29 UNK 0 1.260 4.769 -2.727 0.00 0.00 0

HETATM 30 H30 UNK 0 -0.274 4.534 -0.769 0.00 0.00 0

HETATM 31 H31 UNK 0 -0.734 2.299 0.190 0.00 0.00 0

HETATM 32 H34 UNK 0 3.702 0.728 2.004 0.00 0.00 0

HETATM 33 H35 UNK 0 2.107 1.199 2.741 0.00 0.00 0

HETATM 34 H36 UNK 0 2.602 -0.570 2.648 0.00 0.00 0

HETATM 35 H37 UNK 0 -3.601 -0.806 -2.926 0.00 0.00 0

HETATM 36 H38 UNK 0 -3.853 -0.858 -1.116 0.00 0.00 0

HETATM 37 H39 UNK 0 1.958 -1.444 -1.097 0.00 0.00 0

HETATM 38 H40 UNK 0 0.666 -1.327 -2.371 0.00 0.00 0

HETATM 39 LP2 UNK 0 2.338 -0.139 0.603 -0.31 -0.31 0

HETATM 40 LP3 UNK 0 2.049 0.895 0.659 -0.31 -0.31 0

CONECT 1 2 4 6 19

CONECT 2 1 17 20 21

CONECT 3 4 17 22 23

CONECT 4 3 1 5 24

CONECT 5 4 18 7 13

CONECT 6 1 18 26 25

CONECT 7 12 5

CONECT 7 8

CONECT 7 8

CONECT 8 9 27

CONECT 8 7

CONECT 8 7

CONECT 9 8 28

CONECT 9 10

CONECT 9 10

CONECT 10 11 29

CONECT 10 9

CONECT 10 9

CONECT 11 10 30

CONECT 11 12

CONECT 11 12

CONECT 12 7 31

CONECT 12 11

CONECT 12 11

CONECT 13 5 15

CONECT 13 14

CONECT 13 14

CONECT 14 13

CONECT 14 13

CONECT 15 13 16 39 40

CONECT 16 15 32 33 34

CONECT 17 2 3 35 36

CONECT 18 6 5 37 38

CONECT 19 1

CONECT 20 2

CONECT 21 2

CONECT 22 3

CONECT 23 3

CONECT 24 4

CONECT 25 6

CONECT 26 6

CONECT 27 8

CONECT 28 9

CONECT 29 10

CONECT 30 11

CONECT 31 12

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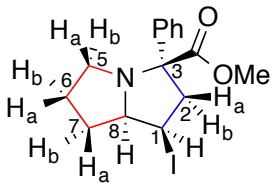
CONECT 37 18

CONECT 38 18

CONECT 39 15

CONECT 40 15

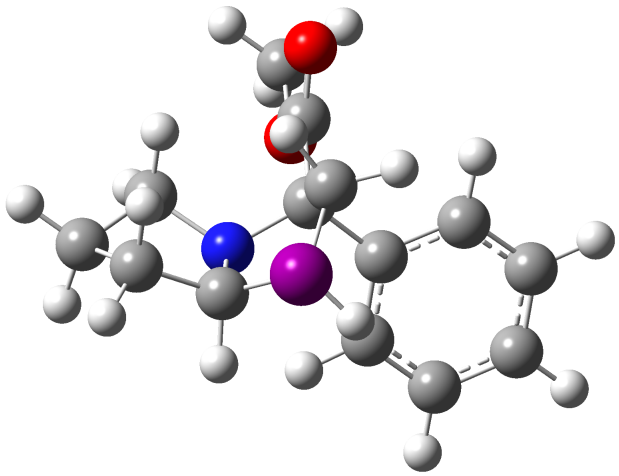
END




(*R,S,R*) **2.35d**

Ground State 38.05 kcal/mol

**Ground State (*R,S,R*) 2.35d**



COMPND John4_PDB

REMARK 1 PDB: 37 38 39 40

REMARK 1 MMOD: 39 40 32 33 /

HETATM 1 C01 UNK 0 -1.391 -1.778 0.671 0.01 0.01 0

HETATM 2 C02 UNK 0 -2.334 -1.951 1.876 0.00 0.00 0

HETATM 3 C03 UNK 0 -1.877 0.311 1.623 0.01 0.01 0

HETATM 4 N04 UNK 0 -1.145 -0.339 0.545 0.19 0.19 0

HETATM 5 C05 UNK 0 0.301 -0.110 0.516 0.09 0.09 0
HETATM 6 C06 UNK 0 -0.012 -2.451 0.729 0.13 0.13 0
HETATM 7 C07 UNK 0 0.863 -0.115 -0.906 -0.04 -0.04 0
HETATM 8 C08 UNK 0 0.060 -0.277 -2.040 0.00 0.00 0
HETATM 9 C09 UNK 0 0.613 -0.269 -3.320 0.00 0.00 0
HETATM 10 C10 UNK 0 1.984 -0.095 -3.491 0.00 0.00 0
HETATM 11 C11 UNK 0 2.796 0.074 -2.373 0.00 0.00 0
HETATM 12 C12 UNK 0 2.237 0.064 -1.097 0.00 0.00 0
HETATM 13 C13 UNK 0 0.702 1.213 1.161 0.38 0.38 0
HETATM 14 O14 UNK 0 1.326 1.304 2.201 -0.45 -0.45 0
HETATM 15 O15 UNK 0 0.257 2.247 0.393 0.59 0.59 0
HETATM 16 C16 UNK 0 0.555 3.534 0.894 0.07 0.07 0
HETATM 17 C17 UNK 0 -3.072 -0.609 1.897 0.00 0.00 0
HETATM 18 C18 UNK 0 0.862 -1.326 1.294 0.00 0.00 0
HETATM 19 H19 UNK 0 -1.937 -2.125 -0.240 0.00 0.00 0
HETATM 20 H20 UNK 0 -3.028 -2.816 1.766 0.00 0.00 0
HETATM 21 H21 UNK 0 -1.757 -2.057 2.825 0.00 0.00 0
HETATM 22 H22 UNK 0 -1.264 0.362 2.554 0.00 0.00 0
HETATM 23 H23 UNK 0 -2.198 1.338 1.334 0.00 0.00 0
HETATM 24 LP4 UNK 0 -1.375 -0.148 0.027 -0.21 -0.21 0
HETATM 25 I25 UNK 0 0.138 -4.323 1.777 -0.13 -0.13 0
HETATM 26 H26 UNK 0 0.325 -2.681 -0.309 0.00 0.00 0
HETATM 27 H27 UNK 0 -1.028 -0.416 -1.955 0.00 0.00 0
HETATM 28 H28 UNK 0 -0.037 -0.401 -4.201 0.00 0.00 0
HETATM 29 H29 UNK 0 2.421 -0.088 -4.502 0.00 0.00 0
HETATM 30 H30 UNK 0 3.882 0.215 -2.498 0.00 0.00 0
HETATM 31 H31 UNK 0 2.904 0.204 -0.231 0.00 0.00 0

HETATM 32 H34 UNK 0 0.139 4.285 0.183 0.00 0.00 0

HETATM 33 H35 UNK 0 0.075 3.668 1.892 0.00 0.00 0

HETATM 34 H36 UNK 0 1.661 3.664 0.961 0.00 0.00 0

HETATM 35 H37 UNK 0 -3.813 -0.550 1.064 0.00 0.00 0

HETATM 36 H38 UNK 0 -3.572 -0.401 2.871 0.00 0.00 0

HETATM 37 H39 UNK 0 0.671 -1.216 2.387 0.00 0.00 0

HETATM 38 H40 UNK 0 1.950 -1.505 1.132 0.00 0.00 0

HETATM 39 LP2 UNK 0 0.582 2.215 -0.117 -0.31 -0.31 0

HETATM 40 LP3 UNK 0 -0.346 2.217 0.426 -0.31 -0.31 0

CONECT 1 2 4 6 19

CONECT 2 1 17 20 21

CONECT 3 4 17 22 23

CONECT 4 3 1 5 24

CONECT 5 4 7 13 18

CONECT 6 1 18 25 26

CONECT 7 12 5

CONECT 7 8

CONECT 7 8

CONECT 8 9 27

CONECT 8 7

CONECT 8 7

CONECT 9 8 28

CONECT 9 10

CONECT 9 10

CONECT 10 11 29

CONECT 10 9

CONECT 10 9

CONECT 11 10 30

CONECT 11 12

CONECT 11 12

CONECT 12 7 31

CONECT 12 11

CONECT 12 11

CONECT 13 5 15

CONECT 13 14

CONECT 13 14

CONECT 14 13

CONECT 14 13

CONECT 15 13 16 39 40

CONECT 16 15 32 33 34

CONECT 17 2 3 35 36

CONECT 18 6 5 37 38

CONECT 19 1

CONECT 20 2

CONECT 21 2

CONECT 22 3

CONECT 23 3

CONECT 24 4

CONECT 25 6

CONECT 26 6

CONECT 27 8

CONECT 28 9

CONECT 29 10

CONECT 30 11

CONECT 31 12

CONECT 32 16

CONECT 33 16

CONECT 34 16

CONECT 35 17

CONECT 36 17

CONECT 37 18

CONECT 38 18

CONECT 39 15

CONECT 40 15

END

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