Graduate School Form 30
(Revised 08/14)

PURDUE UNIVERSITY
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Thesis/Dissertation Acceptance

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By JIAN-YUAN LI

Entitled
THE MODIFICATION OF BRUCINE DERIVATIVES AS CHIRAL LIGANDS AND ITS APPLICATION IN THE ASYMMETRIC SYNTHESIS

For the degree of Doctor of Philosophy

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THE MODIFICATION OF BRUCINE DERIVATIVES AS CHIRAL LIGANDS AND ITS APPLICATION IN THE ASYMMETRIC SYNTHESIS

A Dissertation

Submitted to the Faculty

of

Purdue University

by

Jian-yuan Li

In Partial Fulfillment of the

Requirements for the Degree

of

Doctor of Philosophy

December 2014

Purdue University

West Lafayette, Indiana

給在天上的祖父母

ACKNOWLEDGEMENTS

First of all, I cannot say anything but thank you so much to my research advisor, Dr. Kyungsoo Oh, for giving me the opportunity to join his group and for a series of interesting projects. I also thank him for his support and guidance in helping me attain my synthetic skills and the way of scientific thinking over the last five years. I would also like to thank my dissertation committee members: Dr. Robert Minto, Dr. Haibo Ge, Dr. Mahdi Abu-omar, Dr. Jonathan Wilker for their time and support in helping me to achieve this millstone. I am also appreciative of Dr. Hun Young Kim from whom I learned about metal-catalyzed asymmetric synthesis. Most of all, she has been my close labmate, helping me a lots when I was in need. Special thanks go out to Dr. Karl Dria, Mr. Cary Pritchard, and Mr. Wai Ping Kam for their generous support with instrumentation and management of chemicals. The staff in the Chemistry department, Ms. Beverly Hewitt and Ms. Kitty O'Doherty, has also offered immeasurable help with all of the documentation for my graduate program. In addition, I especially thank Professor Chao-Hung Lee for helping me writing my thesis. Finally, my gratitude with all my heart goes to my family. I am deeply indebted to my parents and my sister for their endless support. My lovely wife, Katy, must be thanked for her endless love, which seemed to be the only light during my journey through good and hard times. Thanks to all of you, I was able to finish this journey, *safely*. This thesis is for you, *all*!

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LIST OF ABBREVIATION

aq.	Aqueous
conc.	Concentrated
*m*CPBA	*meta*-Chloroperoxybenoic acid
DABCE	1,4-Diazabicyclo[2.2.2]octane
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
DPPA	Diphenylphosphoryl azide
eq.	Equivalent
NMM	*N*-Methylmorpholine
THF	Tetrahydrofuran

ABSTRACT

Li, Jian-Yuan Ph.D., Purdue University, December 2014. The Modification of Brucine Derivatives as Chiral Ligands and Its Application in the Asymmetric Synthesis. Major Professor: Robert Minto.

The modification of brucine derivatives as chiral ligands and the use of a multifaceted chiral ligand, brucine diol, under different reaction conditions to produce various optical isomers is described. In Chapter 1, the generation of a number of brucine derivatives is described. Taking the advantage of brucine-diol's excellent molecular recognition capability for multiple organic functional groups, we focused on the synthetic modifications of brucine-diol and the synthesis of brucine *N*-oxide. We also produced various brucine derivatives with different functional moieties in good yields and selectivities.

In Chapter 2, we described the investigation of brucine *N*-oxide catalyzed Morita-Baylis-Hillman (MBH) reaction of alkyl/aryl ketones. Brucine *N*-oxide was used as a nucleophilic organic catalyst in the MBH reaction of alkyl vinyl ketone. In addition, asymmetric MBH reactions of alkyl vinyl ketones with aldehydes were investigated using a dual catalysis of brucine *N*-oxide and proline. In this dual catalyst system, proline was found to form iminium intermediates with electron-deficient aryl aldehydes, while the *N*-oxide activated vinyl ketones provided enolates through the conjugate addition. Our dual catalysis approach also allowed the development of MBH reaction of aryl vinyl ketones.

In Chapter 3, brucine diol-copper complex catalyzed asymmetric conjugate addition of glycine (ket)imines to nitroalkenes is discussed. Stereodivergent catalytic asymmetric conjugate reactions for glycine (ket)imines with nitroalkenes were achieved using various chiral catalysts derived from a single chiral source, brucine diol. Both *syn*- and *anti*-conjugate addition products were obtained with high diastereoselectivity and enantioselectivity.

In Chapter 4, enantiodivergent production of *endo*-pyrrolidines from glycine (ket)imines using brucine diol-copper complex is described. The [3+2] cycloaddition reaction of glycine imines and activated alkenes was performed to produce *endo*-pyrrolidines. The reversal of enantioselectivity was observed for *endo*-pyrrolidines between concerted and stepwise reaction pathways.

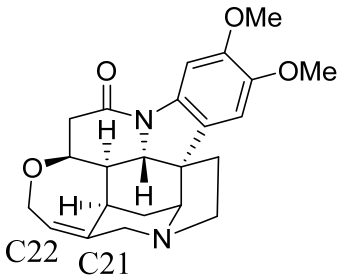
The three new brucine derivatives produced in this study would potentially work as organocatalysts and chiral ligands with metal ion in asymmetric synthesis. The brucine diol-metal complex catalyzed reactions laid a good foundation for catalytic asymmetric reactions, where a single chiral source was used to control the absolute and the relative stereochemical outcomes of reactions. Understanding the molecular-level interactions between catalyst and substrates will provide insightful mechanistic details for the stereodivergent approaches in asymmetric catalysis.

CHAPTER 1. THE MODIFICATION OF BRUCINE AND ITS DERIVATIVES

1.1 Introduction

The objective of this research was to prepare brucine derivatives that function as versatile chiral catalysts in conjunction with a variety of metal salts.

Brucine is a natural product with an intriguing structural complexity (Figure 1). It is known to possess excellent molecular recognition capability, thus widely utilized in chiral resolution of small molecules.[1] Motivated by its wide availability as well as the ability to interact with multiple organic functional groups, we modified its structure and investigated its use in asymmetric catalysis. Our structural modification strategy of brucine was based on the facile functionalization of the alkene moiety at C21-C22.

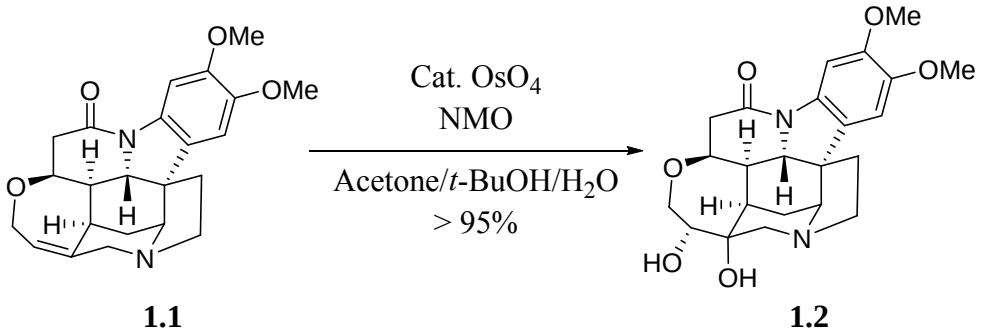


1.1

Figure 1. Brucine **1.1**

Nitrogen-containing ligands are useful in asymmetric catalysis.[2] A great number of amino alcohols have been used as chiral building blocks and chiral auxiliaries in organic

synthesis.[3,4] The nitrogen and oxygen containing functional groups typically allow for multiple types of binding to metals. For example, Wan and Lu described that reverse enantioselectivity could be achieved by adding $Ti(O^iPr)_4$ to the diethylzinc addition to aldehydes in the presence of an *L*-prolinol-backbone ligand.[5] Oh *et al.* modified brucine **1.1** to 1,2-amino alcohol **1.2** by dihydroxylation (Scheme 1) and used it in the 1,3-dipolar cycloaddition reactions of azomethine ylides to produce chiral pyrrolidines with both forms of optical isomers.[6] However, other types of brucine derivatives have not been investigated.



1.1 **1.2**

Scheme 1. Synthesis of **1.2**

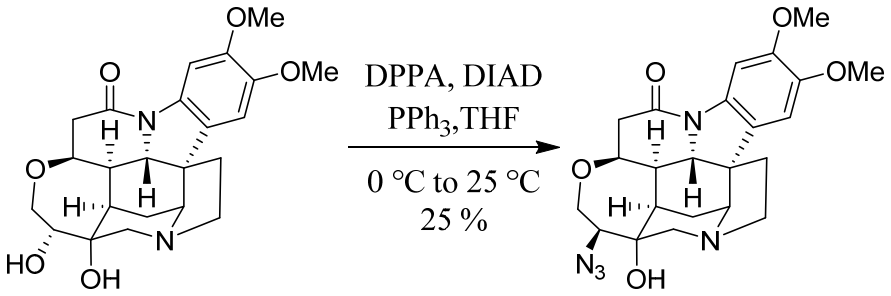
Chiral diamine ligands are also one of the most common types of nitrogen containing ligands that can be used for catalytic asymmetric synthesis.[7,8] Although many types of 1,2-diamine ligands have been investigated in numerous enantioselective reactions,[9,10] the use of 1,3-diamines has not reached the level of stereoselectivity commonly found for 1,2-diamine ligands.

Chiral *N*-oxides have been shown to promote a few synthetic transformations. For instance, in the Sakurai-Hosomi reaction of aldehydes with allyltrichlorosilanes, chiral *N*-oxides are utilized as Lewis base catalysts.[11,12] The application of *N*-oxides as chiral ligands has been reported by Sinn and Carlin with some limited success.[13] In the Oh's

group, brucine *N*-oxide **1.3** was used as an asymmetric oxidant for epoxidation of α,β-unsaturated ketones[14] as well as a dual catalyst component for the Morita-Baylis-Hillman (MBH) reaction.[15]

1.2 Results and Discussion

1.2.1 Synthesis of **1.4**

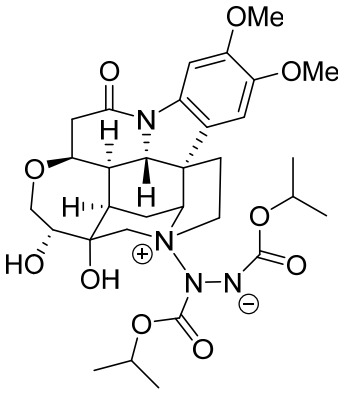


1.2 **1.4**

Scheme 2. Synthesis of **1.4**

Recently, our group reported the use of **1.2** as a chiral ligand for catalytic enantioselective 1,3-dipolar cycloaddition reactions of azomethine ylides to produce both optical forms of pyrrolidines.[6] The tertiary amine and hydroxyl groups on **1.2** provided different binding modes in the presence of metals with different atomic radii, the basis for excellent reversal of enantioselectivity. In order to investigate the binding ability of the tertiary amine in **1.2** and the synthesis of diamine ligand derived from **1.4** to various metal ions, we designed the synthesis of brucine-derived 1,3-diamine ligand by converting the secondary hydroxyl group on **1.2** to an amine group. Inspired by the Staudinger reduction of azides to desired amines, we synthesized **1.4** as a precursor for the desired diamine. Following the protocol of Soos *et al*.,[16] we mixed **1.2** with PPh_3 (1.2 eq.), DIAD (1.2 eq.), and DPPA (1.2 eq.) in THF to produce **1.4** with a 20 % yield after 40 h of reaction at ambient temperature. To improve the yield, the reaction time was increased to 60 h, but the yield of **1.4** only improved to 25% (Scheme 2). To determine whether this incomplete reaction was due to insufficient amount of DPPA, the quantity of DPPA was increased to 2.5 eq., but the yield of **1.4** remained at 25%. While other

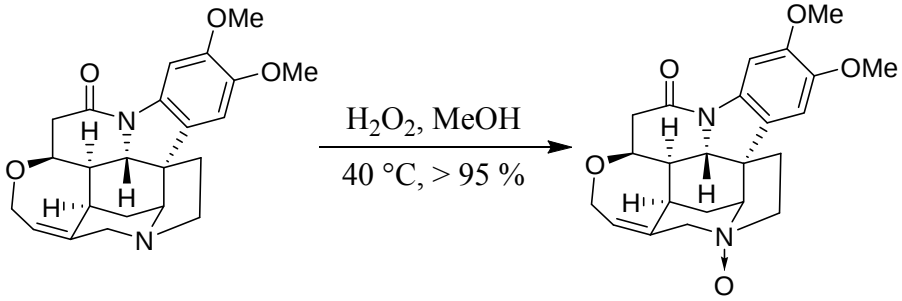
experimental parameters were also investigated, the further optimization of reaction did not yield positive outcomes. Based on our incapability to drive the reaction to completion, it is tempting to speculate that the tertiary amine moiety of brucine might act as a nucleophile, competing for the consumption of DIAD where the salt form of intermediates (Figure 2) releases back brucine diol during the column chromatography purification process.



Proposed Brucine Diol-DIAD Salt

Figure 2. Proposed Structure of Brucine Diol-DIAD Salt

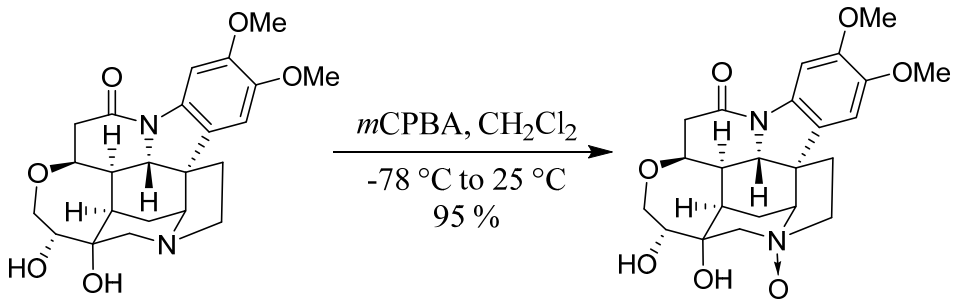
1.2.2 Synthesis of **1.5**



1.1 **1.3**

Scheme 3. Synthesis of **1.3**

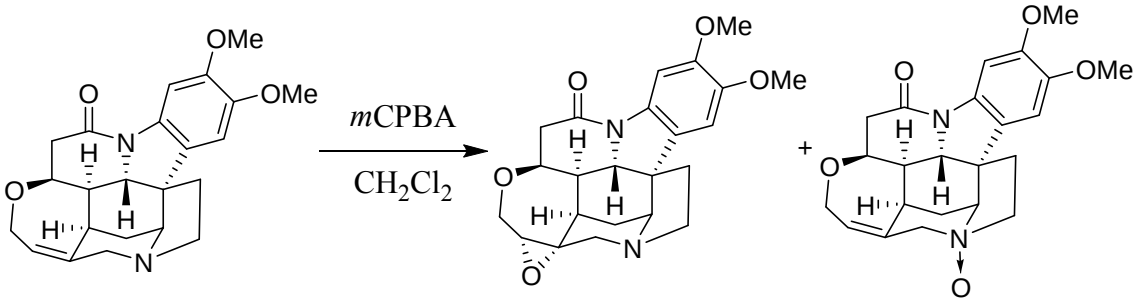
We have previously shown that the MBH reaction of alkyl/aryl vinyl ketone could be enhanced by either **1.3** alone or **1.3** and proline.[15] **1.3** could be easily produced by oxidation of **1.1** with H_2O_2 as shown in Scheme 3.



1.2 **1.5**

Scheme 4. Synthesis of **1.5**

We hypothesized that the synthesis of **1.5** from the oxidation of **1.2** would reveal the nucleophilicity of brucine-derived *N*-oxides that might work as a chiral *N*-oxide ligand in asymmetric reactions (Scheme 4).[17] The one-pot oxidation protocol of **1.1** was investigated using *m*CPBA. While the synthesis of **1.3** as well as brucine epoxide was anticipated upon oxidation, the reaction only yielded **1.3** (Scheme 5) after the addition of 3.0 eq. of *m*CPBA at -78 °C and then at 0 °C for 2 h.



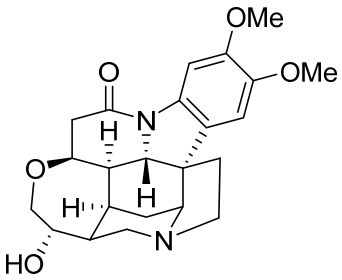
1.1 **Brucine Epoxide**, 0 % **1.3**, 95 %

Scheme 5. Preparation of **Brucine Epoxide** and **1.3**

In an attempt to produce brucine epoxide, we modified the reaction condition from 0 °C to ambient temperature and then to 40 °C for 2 h. However, only **1.3** was produced; the epoxidation of **1.1** to brucine epoxide was not successful. The exact reason to why brucine *N*-oxide **1.3** was not further oxidized was not clear. It was speculated that the nucleophilicity of alkene on **1.3** was not strong enough for attack by *m*CPBA. Upon treatment of **1.2** under this oxidation condition with *m*CPBA in CH_2Cl_2, the formation of **1.5** was achieved at 95 % level (Scheme 4).

1.2.3 Synthesis of **1.6**

In 2009, Oh's group published an approach to the reversal of enantioselectivity by using **1.2** as a chiral ligand in the asymmetric 1,3-dipolar cycloaddition reactions.[6] To investigate the binding modes of this chiral amino alcohol, we envisioned the synthesis of a secondary hydroxyl brucine derivative (Figure 3) under the hydroboration conditions. Difference between the secondary hydroxyl brucine derivative and **1.2**, which was a tertiary hydroxyl brucine derivative, may provide an explanation for the different binding modes of brucine derivatives with metal ions.

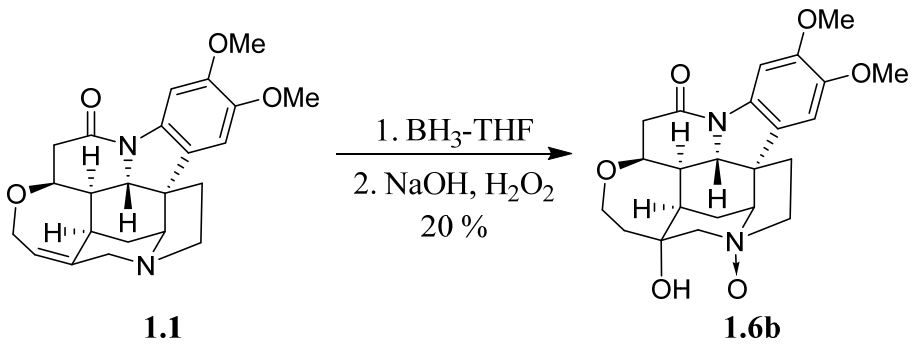


1.6a

Figure 3. Secondary Hydroxyl Brucine Derivative **1.6a**

In practice, **1.1** in dry THF was added to 1.5 eq. of BH_3-THF at 0 °C. The reaction mixture was stirred at room temperature for 18 h. After oxidation with hydrogen peroxide,

the desired product was isolated by silica gel column chromatography at a 10% yield. The structure of **1.6b** was confirmed as a tertiary hydroxyl brucine *N*-oxide derivative by DEPT-135 NMR spectroscopy and mass spectrometry (Scheme 6).



1.1 **1.6b**

Scheme 6. Synthesis of **1.6b**

This type of non-anti-Markovnikov product typically results from the substrate-directed hydroboration. Examples of the substrate-directed hydroboration were first reported in 1967 when Schulte-Elte and Ohloff[18] showed that alcohols could be used as a directing group in the hydroboration of isopulegol with excellent regioselectivity. Evans also showed that phosphinites and amides were useful in substrate-directed hydroboration, while phosphinites and amides induced borane to generate regioselective products.[19,20] Amine directed hydroboration was first reported in 2003 when Vedejs used it as a directing group in the intramolecular hydroboration of allylic amine.[21] After treatment with 5.0 eq. of BH_3-THF, the yield of **1.6b** was increased to 20% (Scheme 6), whereas the yield of **1.6b** was only 16% using 10.0 eq. of BH_3-THF. This low yield of **1.6b** was probably due to the steric hindrance of brucine-borane intermediates as well as the incomplete oxidation of brucine *N*-oxide-borane complex (Figure 4). In the Vedejs's

research, they used iodine to promote the cleavage of the *B*-*N* bond, indicating that iodine might be used in the future as an activating agent to improve the yield of **1.6b**.

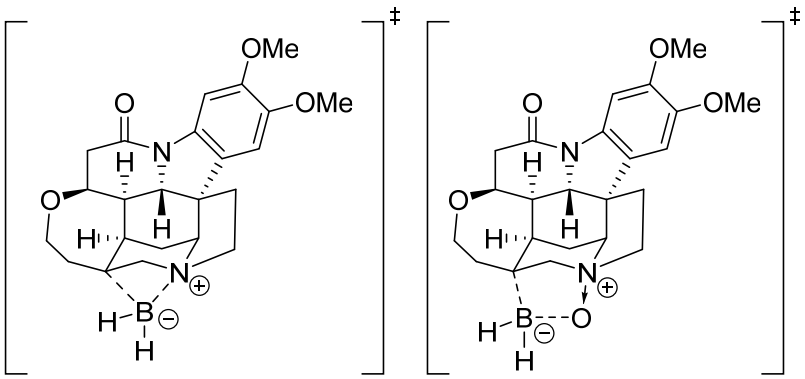
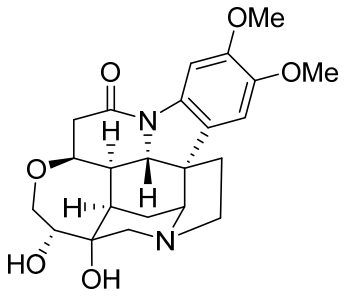


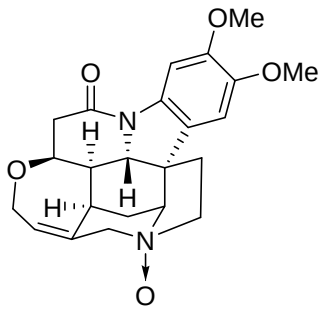
Figure 4. Brucine-Borane Intermediates

1.3 Experimental Section



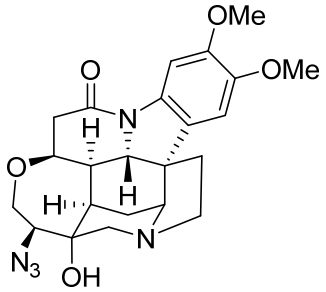
(3*R*,4*R*,4a*R*,4a^1*R*,5a*S*,8a*R*,8a^1*S*,15a*S*)-3,4-Dihydroxy-10,11-dimethoxy-2,3,4,4a,4a^1,5,5a,7,8,8a^1,15,15a-dodecahydro-14*H*-4,6-methanoindolo[3,2,1-*ij*]oxepino[2,3,4-*de*]pyrrolo[2,3-*h*]quinolin-14-one **(1.2)** The dihydroxylation of brucine was performed using modified Upjohn process.[22] To a stirred solution of Brucine dihydrate (5.00 g, 11.6 mmol) in a mixture of acetone (45 mL), *tert*-butanol (2.5 mL), and water (2.5 mL), 4-methylmorpholine *N*-oxide monohydrate (1.73 g, 12.8 mmol) was added, followed by dropwise addition of osmium tetroxide (0.5 mL, 0.07 mmol/4 wt% in water) at ambient temperature. The resulting suspension was stirred at ambient temperature for 24 h after which the resulting solids were collected by filtration. The solids were washed with dichloromethane (80 mL × 2) and dried under vacuum for 24 h to give analytically pure **1.2** (4.74 g, 95%). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.74 (s, 1H), 6.66 (s, 1H), 6.00 (br, *O*H), 4.13 (m, 1H), 4.04 (dd, *J* = 13.0, 3.8 Hz, 1H), 3.99 (d, *J* = 10.7 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.58 (m, 1H), 3.48 (m, 1H), 3.41 (m, 1H), 3.18 (m, 1H), 2.97 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.82 (m, 3H), 2.67 (dd, *J* = 16.0, 5.6 Hz, 1H), 2.51 (d, *J* = 13.0 Hz, 1H), 2.40 (m, 1H), 2.24 (m, 1H), 2.00 (m, 1H), 1.73 (br, *O*H), 1.68 (m, 1H), 1.54 (m, 1H); ^{13}C{1H}NMR ($CDCl_3$, 125 MHz): δ 168.3, 149.2, 146.6, 134.5, 124.2, 105.1, 100.4, 75.3, 74.2, 72.4, 68.8, 67.5, 62.0, 58.7, 56.5, 56.1, 53.2, 51.4, 50.6,

44.9, 40.5, 33.0, 26.4; IR (neat, cm^{-1}): 3563, 3466, 2960, 2937, 2887, 1650, 1501, 1468, 1450, 1414, 1287, 1194, 1132, 1092, 1014, 865; mp throughout: 147-149 °C; HRMS-CI: m/z 429.2016 [$(M+H)^+$; calcd for $C_{23}H_{29}N_2O_6$: 429.2026].



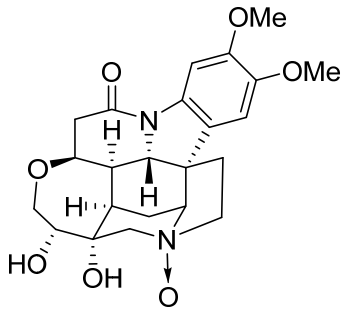
(4a*R*,4a^1*R*,5a*S*,6*R*,8a*S*,8a^1*S*,15a*S*)-10,11-Dimethoxy-14-oxo-2,4a,4a^1,5,5a,7,8,8a^1,15,15a-decahydro-6*H*,14*H*-4,6-methanoindolo[3,2,1-*ij*]oxepino[2,3,4-*de*]pyrrolo[2,3-*h*]quinoline 6-Oxide **(1.3)** The synthesis of *N*-oxides was adopted from the method of Resnati *et al*.[23] To a stirred solution of brucine dihydrate (20.0 g, 46 mmol) in dry methanol (120 ml), H_2O_2 (30% in water, 10.53 ml, 93 mmol) was added drop by drop at ambient temperature. The resulting mixture was stirred at 40 °C for 4 h, after which the solvent was removed under reduced pressure to give a white solid product. The product was further purified using flash column chromatography on silica gel (eluted with ethyl acetate and methanol) as a white solid of brucine *N*-oxide **1.3** (18.0 g, >95%). The spectroscopic data were consistent with those reported in the literature (in $CDCl_3$).[23] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (s, 1H), 6.91 (s, 1H), 6.25 (s, 1H), 4.33 (s, 1H), 4.27 (d, *J* = 8.5 Hz, 1H), 4.19 (dd, *J* = 14.0, 7.0 Hz, 1H), 4.10 (d, *J* = 13.0 Hz, 1H), 4.05-4.01(m, 1H), 3.91-3.80 (m ,2H), 3.85 (s, 3H), 3.82 (s, 3H), 3.68-3.65 (m, 1H), 3.20 (s, 1H), 3.09-3.05 (m, 2H), 2.73 (d, *J* = 15.0 Hz, 1H), 2.68-2.58 (m, 2H), 1.96-1.92 (m, 1H), 1.63 (d, *J* = 15.0 Hz, 1H), 1.32 (d, *J* = 10.0 Hz, 1H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$): δ 168.3, 150.0, 146.5, 135.6, 135.2,

133.5, 119.8, 104.6, 100.8, 83.1, 77.4, 71.8, 68.1, 64.1, 58.6, 56.3, 56.1, 53.2, 47.6, 42.0, 38.8, 30.3, 25.0. In DMSO, the ^{1}H NMR (500 MHz, DMSO) spectroscopic data were the following:[24] δ 7.58 (s, 1H), 7.03 (s, 1H), 6.22 (s, 1H), 4.25-3.76 (m, 8H), 3.73 (s, 3H), 3.68 (s, 3H), 3.35-3.31 (m, 1H), 3.13 (s, 1H), 2.85-2.82(m, 1H), 2.56-2.46 (m, 2H), 2.34-2.28 (m, 1H), 1.84-1.82 (m, 1H), 1.46 (d, J = 14.4 Hz, 1H), 1.28 (d, J = 10.4 Hz, 1H); ^{13}C {1H} NMR (125 MHz, DMSO): δ 169.3, 150.1, 147.0, 137.0, 136.1, 133.6, 122.3, 107.4, 101.4, 82.9, 77.4, 71.5, 68.5, 64.4, 59.2, 56.9, 56.6, 53.5, 49.4, 42.2, 39.2, 30.5, 25.3.



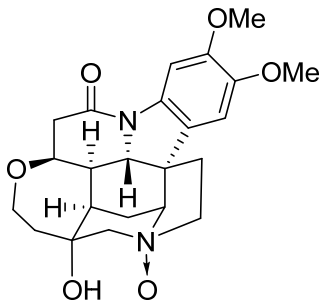
(3*S*,4*R*,4a*R*,4a^{1}*R*,5a*S*,8a*R*,8a^{1}*S*,15a*S*)-3-Azido-4-hydroxy-10,11-dimethoxy-2,3,4,4a,4a^{1},5,5a,7,8,8a^{1},15,15a-dodecahydro-14*H*-4,6-methanoindolo[3,2,1-*ij*]oxepino[2,3,4-*de*]pyrrolo[2,3-*h*]quinolin-14-one **(1.4)** brucine diol **1.2** (214mg, 0.5 mmol) and triphenylphosphine (157 mg, 0.6 mmol) were dissolved in 5.0 mL of dry THF, and the solution was cooled to 0 °C. Diisopropyl azodicarboxylate (0.12 mL, 0.6 mmol) was then added, followed by addition of diphenyl phosphoryl azide (0.13 mL, 0.6 mmol) in 1.0 mL of dry THF at 0 °C. The mixture was allowed to warm up to room temperature. After being stirred for 40 h, the solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel (CH_2Cl_2 / MeOH / conc. aq. NH_4OH = 90 / 9 / 1 as eluant) as a brown powder (57 mg, 25%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (s, 1H), 6.68 (s, 1H), 4.31-4.27 (m, 1H), 4.14 (d, J = 11.0 Hz, 1H), 3.91 (d, J = 12.0

Hz, 1H), 3.82 (s, 6H), 3.82 – 3.73 (m, 2H), 3.53 (d, 1H), 3.27 (d, *J* = 9.5 Hz, 1H), 2.90-2.84 (m, 3H), 2.73-2.69 (m, 1H), 2.51-2.47 (m, 3H), 2.40-2.34 (m, 1H), 1.96 (t, *J* = 11.0 Hz, 1H), 1.76-1.72 (m, 1H), 1.60 (d, *J* = 13.5 Hz, 1H); $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$): δ 168.2, 149.3, 146.7, 134.5, 123.6, 105.3, 100.4, 75.2, 72.5, 67.6, 67.0, 66.7, 61.4, 56.5, 56.1, 53.8, 53.3, 51.3, 49.8, 44.3, 40.5, 29.3, 26.2; IR (neat, cm^{-1}): 3395, 3000, 2933, 2096, 1668, 1499, 1468, 1464, 1444, 1411, 1283, 1223, 1194, 1140, 1117, 1091, 1042, 1009, 947, 857, 758; mp: 260-264 °C; HRMS-CI: m/z 454.2054 [$(M+H)^+$; calcd for $C_{23}H_{28}N_5O_5$: 454.2090].



(3*R*,4*R*,4a*R*,4a^1*R*,5a*S*,6*R*,8a*S*,8a^1*S*,15a*S*)-3,4-Dihydroxy-10,11-dimethoxy-14-oxo-2,3,4,4a,4a^1,5,5a,7,8,8a^1,15,15a-dodecahydro-6*H*,14*H*-4,6-methanoindolo[3,2,1-*ij*]oxepino[2,3,4-*de*]pyrrolo[2,3-*h*]quinoline 6-Oxide **(1.5)** To a stirred solution of brucine diol **1.2** (214 mg, 0.5 mmol) in 5.0 mL of CH_2Cl_2, *m*CPBA (259 mg, 1.5 mmol) was added at 0 °C. The solution was warmed up to room temperature for 18 h. After the solvent was removed under reduced pressure, the residue was purified using flash column chromatography on silica gel (eluent ethyl acetate then methanol) to the title compound **1.5** (212 mg, >95%) as a white solid. ^1H NMR (500 MHz, $CDCl_3$): δ 7.68 (s, 1H), 6.72 (s, 1H), 4.21 (dd, *J* = 13.0, 6.0 Hz, 1H), 4.11-4.06 (m, 2H), 3.99 (s, 1H), 3.88 (s, 3H), 3.86(s, 3H), 3.81 – 3.77 (m, 1H), 3.70-3.66 (m, 1H), 3.65-3.59 (m, 2H), 3.51 (dd, *J* = 13.0, 8.0

Hz, 1H), 3.36 (d, *J* = 13.0 Hz, 1H), 3.19-3.16 (m, 1H), 3.06 (dd, *J* = 17.0, 8.5 Hz, 1H), 2.60 (dd, *J* = 17.0, 4.0 Hz, 1H), 2.51 – 2.50 (m, 1H), 2.39 (d, *J* = 5.5 Hz, 1H), 2.37 (d, *J* = 6.0 Hz, 1H), 1.74-1.71 (m, 1H), 1.56 (d, *J* = 15.0 Hz, 1H); $^{13}C\{1H\}$ NMR (125 MHz, $CDCl_3$): δ 168.0, 150.3, 147.1, 134.7, 121.5, 104.7, 100.5, 76.6, 75.6, 73.1, 71.9, 71.9, 69.0, 67.4, 65.4, 56.4, 56.3, 51.5, 48.6, 41.3, 39.9, 32.7, 22.8; IR (neat, cm^{-1}): 3404, 2971, 1655, 1503, 1454, 1416, 1334, 1293, 1223, 1198, 1143, 1103, 1066, 1010, 989, 847; mp: 208-212 °C; HRMS-CI: m/z 445.1954 [$(M+H)^+$; calcd for $C_{23}H_{29}N_2O_7$: 445.1975].



(4*R*,4a*R*,4a^1*R*,5a*S*,6*R*,8a*S*,8a^1*S*,15a*S*)-4-Hydroxy-10,11-dimethoxy-14-oxo-2,3,4,4a,4a^1,5,5a,7,8,8a^1,15,15a-dodecahydro-6*H*,14*H*-4,6-methanoindolo[3,2,1-*ij*]oxepino[2,3,4-*de*]pyrrolo[2,3-*h*]quinoline 6-Oxide **(1.6b)** To a stirred solution of Brucine **1.1** (215 mg, 0.5 mmol) in 4.0 mL of dry THF, BH_3-THF (2.5 mL, 2.5 mmol) was added at 0 °C. The mixture was allowed to warm up to room temperature for 18 hours and then cooled to 0 °C. 2.0 mL of 1.0 M NaOH (aq.) was then added dropwise, followed by addition of 4.0 mL of H_2O_2 (35% wt in water). The mixture was further stirred at 0 °C for 2 h and diluted to 8.0 mL with hexanes / CH_2Cl_2 = 6 / 2. The aqueous layer was extracted 3 times with 10 mL of CH_2Cl_2. The combined organic layers were dried over $MgSO_4$. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel (CH_2Cl_2 / MeOH / conc. aq. NH_4OH = 90 / 9 / 1 as

eluant) as a brown powder (57 mg, 20%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (s, 1H), 6.71 (s, 1H), 4.08-4.04 (m, 2H), 3.95-3.91 (m, 2H), 3.87 (s, 3H), 3.85 (s, 3H), 3.76 – 3.63 (m, 3H), 3.55 (d, *J* = 13.0 Hz, 1H), 3.32 (d, *J* = 13.5 Hz, 1H), 3.18 (d, *J* = 15.0 Hz, 1H), 3.02 (q, *J* = 8.5 Hz, 1H), 2.57 (dd, *J* = 16.5, 4.5 Hz, 1H), 2.45 (d, *J* = 2.0 Hz, 1H), 2.37-2.34 (m, 2H), 2.07-2.00 (m, 2H), 1.72-1.68 (m, 1H), 1.52-1.49 (m, 1H); ^{13}C{1H} NMR (125 MHz, $CDCl_3$): δ 168.1, 150.2, 147.0, 134.6, 121.9, 104.6, 100.5, 76.4, 75.4, 71.6, 69.2, 68.9, 66.4, 65.9, 56.4, 56.2, 51.5, 48.6, 42.9, 41.0, 40.2, 36.2, 23.0; IR (neat): 3417, 2918, 2849, 1671, 1504, 1446, 1413, 1333, 1281, 1200, 1138, 1126, 1101, 1023, 1009, 990, 873, 851, 758, 659; mp: 200-204 °C; HRMS-CI: m/z 429.2012 [$(M+H)^+$; calcd for $C_{23}H_{29}N_2O_6$: 429.2026].

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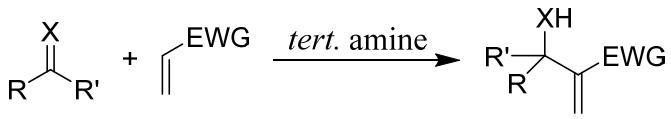
CHAPTER 2. BRUCINE *N*-OXIDE CATALYZED MORITA-BAYLIS-HILLMAN REACTIONS OF ALKYL/ARYL VINYL KETONES

2.1 Introduction

2.1.1 Development of Morita-Baylis-Hillman Reactions

The Morita-Baylis-Hillman (MBH) reaction, first reported by Morita *et al.* in 1968[1] and subsequently by A. B. Baylis and M. E. D. Hillman in 1972,[2] is one of the most important reactions for the carbon-carbon bond formation between electron-deficient alkenes and carbonyl compounds. It is typically catalyzed by a nucleophilic tertiary amine or phosphine to yield α-methylene-β-hydroxyl-carbonyl derivatives (Scheme 7).



R = Aryl, Alkyl, Heteroaryl; R' = H, COOR, Alkyl
X = O, NCOOR, NTs, NSO_2Ph
EWG = Electron Withdrawing Group:
COR, CHO, CN, COOR, $PO(OEt)_2$, SO_2Ph, SO_3Ph, SOPh

Scheme 7. Morita-Baylis-Hillman Reactions

The controlled formation of carbon-carbon bonds is of fundamental importance in organic chemistry. Many research groups have contributed to the development of

asymmetric MBH reactions, using one of the following three essential components in a chiral form: electrophiles, activated alkenes, and catalysts. While the MBH reactions using chiral forms of aldehydes and activated alkenes have been shown to proceed with high diastereoselectivities in some cases,[3] the precise roles of chiral catalysts for the MBH reactions are not well understood.

2.1.2 Catalytic Asymmetric MBH Reactions

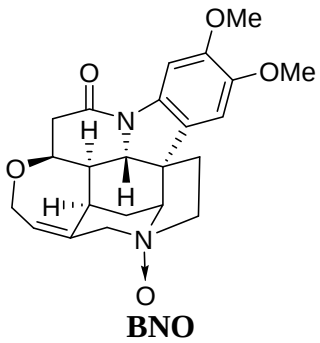
Hirama and Marko had independently reported the use of chiral derivatives of diazabicyclo[2.2.2]octane,[4] quinidine, and cinchonine[5] as asymmetric catalysts. However, only modest levels of enantioselectivity were observed under elevated pressure. Later, Barrett reported the first example of successful asymmetric MBH reactions of ethyl vinyl ketone with aryl aldehydes, where a chiral pyrrolidine catalyst induced up to 72% enantiomeric excess (ee) under normal atmospheric pressure. In 1999, Hatakeyama *et al.* demonstrated a highly enantioselective MBH reaction of 1,1,1,3,3,3-hexafluoroisopropyl acrylate using a catalytic amount of a tricyclic quinidine-derived chiral amine at -55 °C.[6] However, the Hatakeyama's catalyst failed to promote the asymmetric MBH reaction of methyl acrylate, where only 8% ee was observed upon using 4-nitrobenzaldehyde.

2.1.3 Catalytic Asymmetric MBH Reactions Using a Dual Catalyst System

Shi reported the first dual catalyst system for the MBH reaction of methyl vinyl ketone (**MVK**) with arylaldehydes,[7] where the respective catalyst, *L*-proline or imidazole did not promote the MBH reaction regardless of the amount of each catalyst. When the reaction of **MVK** with 4-nitrobenzaldehyde was catalyzed by 10 mol% of both *L*-proline and imidazole, the MHB product was obtained in a 60% yield. A further extension to asymmetric MBH reactions using such dual catalyst systems was investigated by Shi and

Jiang using the Hatakeyama's catalyst and proline as a co-catalyst. In that study, the MBH products with up to 31% ee were achieved using **MVK** as an electron-deficient alkene component.[8] Later, Miller *et al.* reported the development of a new dual catalyst system using proline and peptide-derived phosphine for MBH reaction of **MVK** in 63 – 81% ee's.[9] Nevertheless, the exact roles of co-catalysts used in the studies of Shi and Miller were not well defined.

One possible reaction mechanism of proline/$NaHCO_3$-catalyzed MBH reaction was recently proposed by Gruttadauria *et al.*, where proline acts as a bifunctional catalyst via a bicyclic enaminolactone species.[10] However, it still remains unclear if proline functions as a bifunctional catalyst for the asymmetric MBH reactions under dual catalyst systems. In this chapter, we describe our mechanistic investigation into the dual catalyst system of proline and brucine *N*-oxide (**BNO**) for the asymmetric MBH reactions of vinyl ketones (Figure 5).



BNO

Figure 5. Brucine *N*-Oxide (**BNO**)

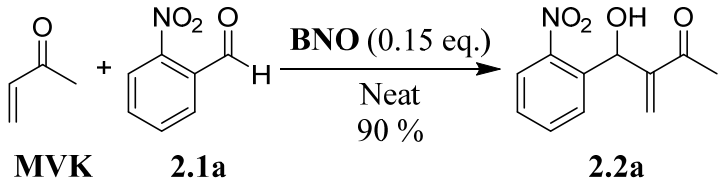
2.2 Results and Discussion

2.2.1 Morita-Baylis-Hillman Reaction with Alkyl Vinyl Ketones

2.2.1.1 Optimization of **BNO**-Catalyzed MBH Reaction

The MBH reaction has been widely used as one of the key carbon-carbon forming processes in synthetic organic chemistry. The reaction features three major components involving the coupling of the α-position of active alkenes with carbon electrophiles under a catalytic amount of tertiary amine. It is a simple and convenient method for the synthesis of densely functionalized molecule.[11] Although the recent development of asymmetric MBH reactions underscores the importance of chiral nucleophilic catalysts, the substrate scope of both reaction partners, alkenes and aldehydes, is rather limited, perhaps due to the complex nature of MBH reactions. In particular, the substrate scope and stereocontrol of the asymmetric MBH reaction of vinyl ketones remain to be further developed.[8, 9, 12, 13] Although Wu *et al.* reported the MBH reaction of **MVK** in the range of 90-94% ee's in the presence of a cyclohexyl aminothiourea, their substrates were limited to electron deficient aromatic aldehydes.[13] Prior to the Wu's work, the enantioselective MBH reaction of **MVK** with electron deficient aromatic aldehydes was in the range of 63-78% ee's where the Miller group utilized a dual catalyst system involving proline as a co-catalyst.[9] The co-catalyst, proline, was first introduced by Shi's group in 2002,[7] however, the exact nature of co-catalyst was not understood. Motivated by the possibility of new mechanistic insight of dual catalyst systems, we investigated a dual catalyst system of **BNO** and proline for the MBH reaction of vinyl ketones with aldehydes.

To study the relative nucleophilicity of both catalysts, we first examined **BNO** in the MBH reaction of **MVK** with 2-nitrobenzaldehyde **2.1a**. As anticipated, **BNO** promoted the MBH reaction of **MVK** with **2.1a** in the presence of 15 mol% of **BNO** (Scheme 8).[14]



Scheme 8. **BNO**-Catalyzed Reaction

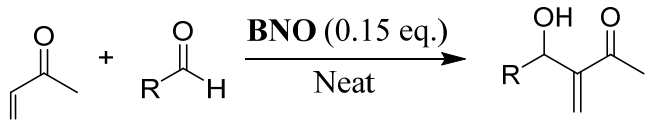
The yield of **2.2a** was less than 10 % after 36 h of reaction, but increased to 41% after a total of 110-120 h of reaction. This low reaction yield was due to the depletion of **MVK** by self-dimerization.[15] After testing various amounts of **MVK**, the optimal use of **MVK** was determined to be 3.0 equivalents, yielding **2.2a** in 90% yield after 120 h of reaction. Interestingly, our investigation into the rate of **BNO**-promoted MBH reaction revealed that while the reaction was influenced by the amount of **BNO** at the beginning of the reaction (*i.e.* 5-10% conversion), the reaction significantly slowed down regardless further additions of **BNO**. While the more precise kinetic data could not be obtained due to the poor solubility of **BNO**, we concluded that our MBH reaction was promoted by **BNO** at the beginning of the reaction and that beyond a reaction conversion of 10% the chemistry involved autocatalysis[16] by the MBH product **2.2a**.

2.2.1.2 Substrate Scope of **BNO**-Promoted MBH Reaction

The MBH reactions are typically very slow requiring days to weeks to complete. In order to reduce the reaction time of **BNO**-catalyzed MBH reaction, we used more reactive aldehydes. Having established the reaction conditions for the **BNO**-promoted

MBH reaction of **MVK** with **2.1a**, we explored the reactivity of other aldehydes under the optimized conditions. As shown in Table 1, electron-deficient aldehydes, in particular nitro group-containing aldehydes, readily reacted to generate MBH products with good to excellent yields (entry 1-6). Halogen-substituted benzaldehydes were less efficient, providing modest yields of MBH products (entry 7-10). Heteroaromatic aldehydes were also suitable substrates for our **BNO**-promoted MBH reactions (entry 11-12), however, the yields were low, possibly due to the degradation of products upon isolation process (entry 12). The MBH reactions with electron-rich aryl aldehydes such as 4-methylbenzaldehyde, 4-methoxybenzaldehyde (entry 14-17), and aliphatic aldehydes such as cyclohexanecarboxyaldehyde and 1-octanal were sluggish leading to low yields of products (entry 18-19). Our attempts to improve the reaction conversion and the reaction time by increasing the amounts of **BNO** were unsuccessful. Surprisingly, varying the amount of **BNO** did not affect reaction yields and time upon using the electron-rich aldehydes, not only at the initial stage but also in the overall reaction, suggesting the lack of autocatalysis.

Table 1. Substrate Scope of **BNO**-Promoted MBH Reactions



MVK **2.1** **2.2**

R = Aryl, Alkyl, Heteroaromatic

Entry	Aldehyde	Reaction time (Day)	**2.2**	Yield (%)
1	2-Nitrobenzaldehyde	5	**2.2a**	90
2	3-Nitrobenzaldehyde	3	**2.2h**	96
3	4-Nitrobenzaldehyde	5	**2.2i**	77
4	1-Nitro-2-naphthaldehyde	5	**2.2b**	61
5	2,4-Dinitrobenzaldehyde	4	**2.2d**	80
6	3-Methoxy-2-nitrobenzaldehyde	4	**2.2c**	82
7	2-Fluorobenzaldehyde	5	**2.2g**	44
8	3-Bromobenzaldehyde	5	**2.2p**	54
9	4-Chlorobenzaldehyde	6	**2.2q**	55
10	2-(Trifluoromethyl)benzaldehyde	6	**2.2f**	14
11	2-Furaldehyde	5	**2.2r**	80
12	2-Thiophenecarboxaldehyde	5	**2.2s**	45
13	Benzaldehyde	6	**2.2j**	47
14	4-Methoxybenzaldehyde	6	**2.2t**	14
15	6-Nitropiperonal	6	**2.2e**	23

Table 1. Continued

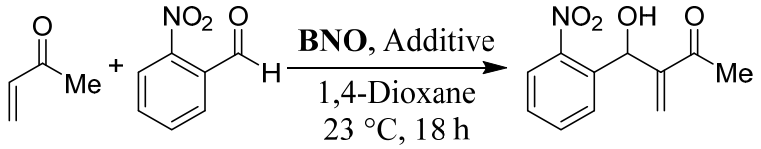
Entry	Aldehyde	Reaction time (Day)	**2.2**	Yield (%)
16	4-Methylbenzaldehyde	6	**2.2u**	16
17	2-Methylbenzaldehyde	6	**2.2v**	13
18	Cyclohexanecarboxaldehyde	8	**2.2x**	6
19	1-Octanal	7	**2.2y**	21

2.2.1.3 Optimization of Asymmetric MBH reaction of Methyl Vinyl Ketone

Although our initial postulation regarding the conjugate addition of amine *N*-oxides to **MVK** was confirmed by the facile MBH reactions with a variety of aldehydes, the asymmetric induction using such intermediate species was not possible using our **BNO**-promoted MBH reactions. We assumed that the poor asymmetric induction was attributed to the slow and non-selective **BNO**-catalyzed MBH reaction, which was the primary reaction pathway at the early stage of reaction in the absence of solvents. In addition, the autocatalysis of MBH product was non-selective, which might be the major reaction pathway beyond 10-20% reaction conversion. Since we have shown that the autocatalysis of MBH product could be slowed down,[24] if not completely shut down, in the presence of solvents, such as 1,4-dioxane, we further examined the possibility of asymmetric induction in the **BNO**-catalyzed MBH reaction (Table 2). The use of **BNO** as a chiral nucleophilic catalyst led to slow formation of MBH product **2.2a** with low ee % (entry 1). Although further effort was made to improve enantioselectivity, our optimization attempts were unsuccessful despite changing the numerous reaction parameters: temperature, solvent, and amounts of **BNO**. We therefore examined the addition of a co-

catalyst, such as imidazole, lithium perchlorate, and (*L*)-proline (entry 2-4). Although imidazole and $LiClO_4$ delivered no significant improvement in enantioselectivity, the presence of co-catalyst (*L*)-proline markedly enhanced the enantioselectivity to 57%. After confirming that (*L*)-proline alone did not catalyze the reaction (entry 5), we made further optimization efforts using various amounts of both **BNO** and (*L*)-proline (entry 6-13).

Table 2. MBH Reaction Using a Dual Catalyst System



MVK **2.1a** **2.2a**

Entry	**BNO** (eq.)	Additive (eq.)	ee (%)
1	0.1	-	8 (*R*)
2	0.1	Imidazole (0.1)	8 (*R*)
3	0.1	$LiClO_4$ (0.1)	NR
4	0.1	(*L*)-Proline (0.1)	57 (*R*)
5	-	(*L*)-Proline (0.1)	NR
6	0.1	(*L*)-Proline (0.2)	40 (*R*)
7	0.1	(*L*)-Proline (0.3)	34 (*R*)
8	0.1	(*L*)-Proline (0.4)	27 (*R*)
9	0.1	(*L*)-Proline (0.5)	32 (*R*)

Table 2. Continued

Entry	**BNO** (eq.)	Additive (eq.)	ee (%)
10	0.2	(*L*)-Proline (0.1)	62 (*R*)
11	0.3	(*L*)-Proline (0.1)	82 (*R*)
12	0.4	(*L*)-Proline (0.1)	83 (*R*)
13	0.5	(*L*)-Proline (0.1)	85 (*R*)

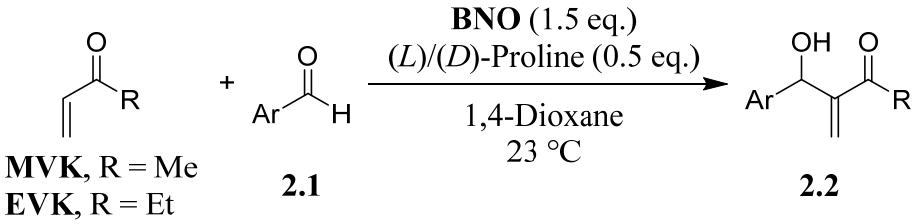
While the increasing amount of (*L*)-proline negatively impacted the observed enantioselectivity, larger amounts of **BNO** led to the further improvement in enantioselectivity up to 85%. Considering a cost-benefit analysis of catalysts used versus the minimal difference in the observed enantioselectivity (entry 11 vs. 13), the optimal catalyst ratio was chosen as a 3:1 between **BNO** and (*L*)-proline. While we further investigated the potential effect of various solvents and molar ratios of the reagents, no further improvement in enantioselectivity was obtained except for increased reaction conversion from 12% to 28% upon using 1.5 eq. of **BNO** and 0.5 eq. of (*L*)-proline.

2.2.1.4 Asymmetric MBH Reaction of Alkyl Vinyl Ketones

Having established the optimal ratio and amount of **BNO** and (*L*)-proline for the MBH reaction of **MVK** and 2-nitrobenzaldehyde **2.1a**, we next examined the scope of aldehyde substrates with different vinyl ketones (Table 3). As expected, the reactivity and enantioselectivity of aldehyde substrates were highly varied at the 24 h mark. For example, 2-nitro-substituted aromatic aldehydes collectively showed good enantioselectivity with reasonable reactivity (entry 1-5), while other less electron-

deficient aldehydes showed significantly diminished reactivity and enantioselectivity (entry 6-10). The substitution pattern on aryl aldehydes also influenced the ee value of MBH products. This may be attributed to the different activation energy barriers for proline-catalyzed and the alcohol-catalyzed (autocatalysis) processes. Diminished enantioselectivity of MBH products was observed after longer reaction times, probably due to the autocatalysis by MBH products. As shown in Table 3, the role of prolines as a chirality-inducing component was confirmed by the formation of both optical isomers of MBH products using (*L*)-proline and (*D*)-proline. Furthermore, the generality of our asymmetric MBH reaction using the dual catalysis of **BNO** and proline was demonstrated with of ethyl vinyl ketone (**EVK**) and 2-nitro-substituted aromatic aldehydes (entry 11-15).

Table 3. Asymmetric MBH Reaction of Alkyl Vinyl Ketones



MVK, R = Me
EVK, R = Et

2.1

2.2

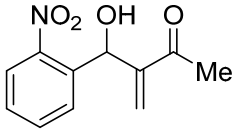
Entry	**2.2**	Co-catalyst	ee (%) at 24 h	Reaction time / d	Yield (%)	ee (%)
1	 **2.2a**	(*L*)-proline	74 (*R*)	4	42	63 (*R*)
		(*D*)-proline	56 (*S*)	5	30	40 (*S*)

Table 3. Continued

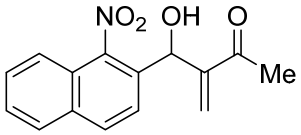
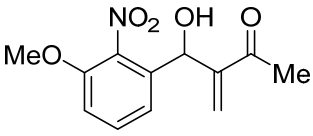
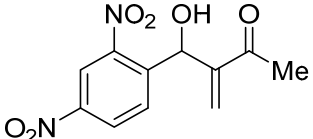
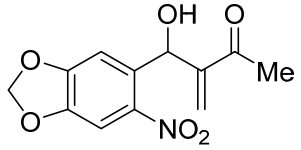
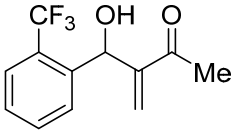
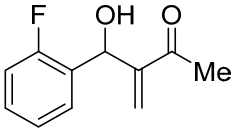
Entry	**2.2**	Additive	ee (%) at 24 h	Reaction time / d	Yield (%)	ee (%)
2	 **2.2b**	(*L*)-proline	78 (*R*)	3	45	44 (*R*)
		(*D*)-proline	81 (*S*)	4	49	39 (*S*)
3	 **2.2c**	(*L*)-proline	75 (*R*)	8	49	49 (*R*)
		(*D*)-proline	45 (*S*)	4	51	21 (*S*)
4	 **2.2d**	(*L*)-proline	35 (*R*)	4	72	55 (*R*)
		(*D*)-proline	44 (*S*)	3	67	32 (*S*)
5	 **2.2e**	(*L*)-proline	81 (*R*)	7	20	45 (*R*)
		(*D*)-proline	81 (*S*)	7	27	43 (*S*)
6	 **2.2f**	(*L*)-proline	60 (*R*)	6	16	59 (*R*)
		(*D*)-proline	84 (*S*)	6	16	37 (*S*)
7	 **2.2g**	(*L*)-proline	44 (*R*)	6	21	50 (*R*)
		(*D*)-proline	33 (*S*)	6	22	29 (*S*)

Table 3. Continued

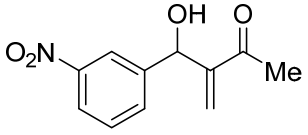
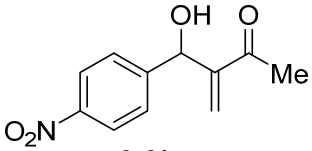
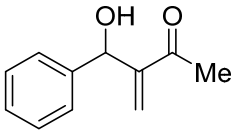
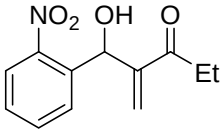
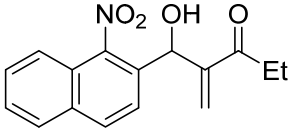
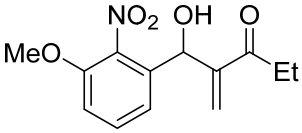
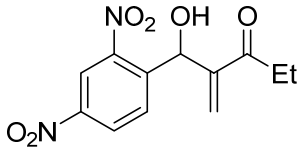
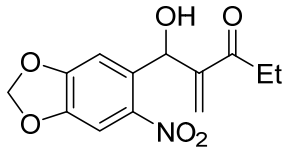
Entry	**2.2**	Additive	ee (%) at 24 h	Reaction time / d	Yield (%)	ee (%)
8	 **2.2h**	(*L*)-proline	29 (*R*)	7	38	48 (*R*)
		(*D*)-proline	36 (*S*)	6	43	16 (*S*)
9	 **2.2i**	(*L*)-proline	20 (*R*)	5	34	26 (*R*)
		(*D*)-proline	49 (*S*)	4	49	42 (*S*)
10	 **2.2j**	(*L*)-proline	10 (*R*)	7	12	8 (*R*)
		(*D*)-proline	19 (*S*)	7	16	11 (*S*)
11	 **2.2k**	(*L*)-proline	74 (*R*)	5	38	58 (*R*)
		(*D*)-proline	74 (*S*)	5	30	54 (*S*)
12	 **2.2l**	(*L*)-proline	79 (*R*)	5	30	54 (*R*)
		(*D*)-proline	82 (*S*)	5	39	61 (*S*)

Table 3. Continued

Entry	**2.2**	Additive	ee (%) at 24 h	Reaction time / d	Yield (%)	ee (%)
13	 **2.2m**	(*L*)-proline	67 (*R*)	5	54	72 (*R*)
		(*D*)-proline	78 (*S*)	5	62	64 (*S*)
14	 **2.2n**	(*L*)-proline	66 (*R*)	3	47	57 (*R*)
		(*D*)-proline	69 (*S*)	3	61	65 (*S*)
15	 **2.2o**	(*L*)-proline	80 (*R*)	8	55	60 (*R*)
		(*D*)-proline	87 (*S*)	8	40	56 (*S*)

2.2.1.5 Mechanistic Study of MBH Reaction Under the Dual Catalysis

McQuade *et al.* investigated the mechanism of MBH reactions using kinetic isotope studies, and revealed that the rate-determining step (RDS) was the elimination of the α-proton by a hemiacetal intermediate (Figure 6 (a)).[17,18] Moreover, the kinetic studies by Aggarwal and Lloyd-Jones revealed that the α-proton-transfer (or RDS) could be facilitated in the presence of protic species (Figure 6 (b)).[16] Thus, the MBH product was a dominant catalyst species for autocatalysis beyond 10-20% conversion. These two mechanistic pathways are consistent with our experiments in which iminium intermediate **2.5** was used to generate *N,O*-hemiacetal intermediate (Figure 6 (c)) and MBH product

with high enantioselectivity after preferential α-H elimination (via H-bridged chair-like transition state of *N*,*O*-acetal **2.7**) at the initial stage of the reaction. The presence of three stereogenic centers in the transition state of *N*,*O*-acetal **2.7** renders 8 possible diastereomeric species. However, considering the most stable chair-like transition state, where proline, two aromatic, and $–CH_2O\text{-}NR_3$ groups occupy equatorial positions, the transition state would effectively discriminate all possible diastereomers for the one shown in Figure 6. Furthermore, the stereochemistry of the iminium intermediate **2.5** would influence the stereochemical outcome of *N*,*O*-acetal **2.7**, possibly through a preferential dissociative ring opening of *exo*-oxazolidinone **2.4**. Thus, it is postulated that the stereoselectivity of the proline-catalyzed MBH reaction was controlled by the proton-transfer step. As shown in Table 3, we observed the product with opposite absolute stereochemistry when (*D*)-proline was utilized as a co-catalyst (rationalized in Figure 6 (d)), and the reaction conversion was promoted by protic species (MBH product **2.2**). However, this autocatalysis by the MBH product was believed to be non-selective as lower enantioselectivities were observed after the addition of enantiomerically enriched MBH products. The role of **BNO** could be two-fold: 1) a nucleophilic promoter to activate **MVK** for the generation of enolate or 2) a stabilizing agent for iminium intermediate **2.5**. Since the synthetic potential of iminium intermediates derived from aryl aldehydes and proline in proline catalysis has been well recognized, it will be interesting to see if our dual catalyst system is applicable to other asymmetric reactions.

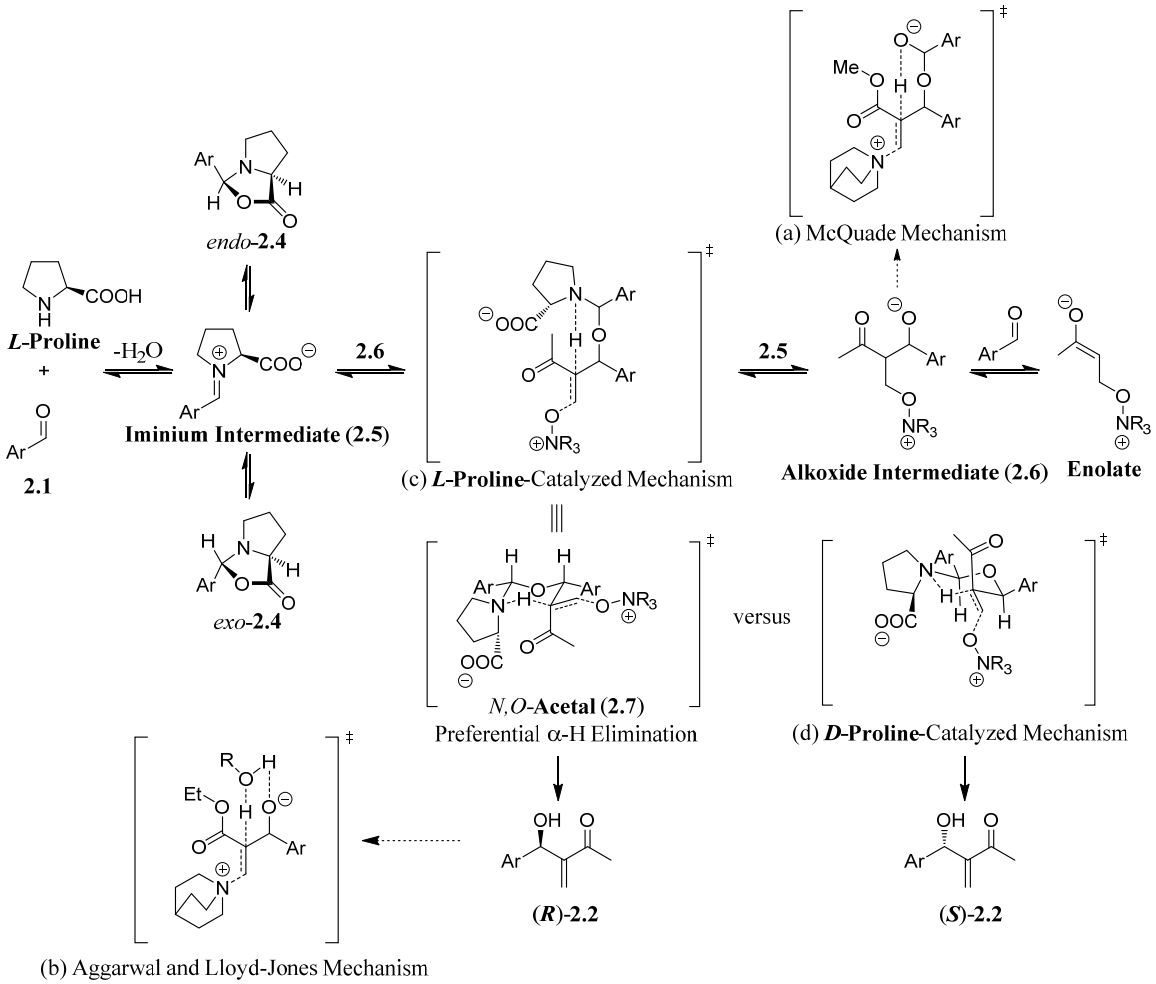


Figure 6. Proposed Mechanism of the MBH Reaction via Dual Catalysis

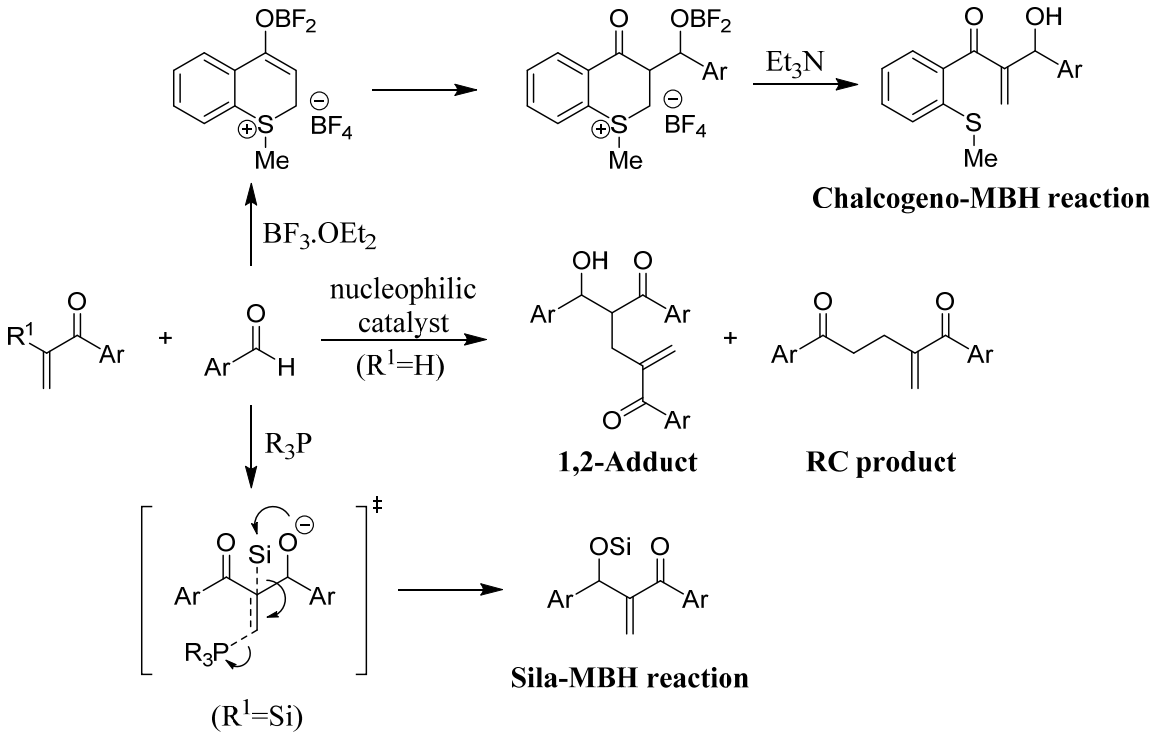
2.2.2 Morita-Baylis-Hillman Reactions with Aryl Vinyl Ketones

2.2.2.1 MBH Reaction of Aryl Vinyl Ketones with Aldehydes

While considerable progress has been made in the development of a variety of catalyst systems for MBH reaction, there are still significant challenges to broaden its substrate scope, especially the MBH reaction for aryl vinyl ketones with aldehydes. As shown in Figure 6, the interactions between the nucleophilic catalyst and its substrates during the MBH reaction are achieved through the following: (1) the preferential α-H

elimination by hemiacetal anions (McQuade mechanism),[17, 18] in which should exhibit second order kinetics for aldehydes occurs at the initial stage of the reaction, and (2) the preferential α-H elimination by MBH products at the later stage of the reaction (Aggarwal/Lloyd-Jones mechanism),[16, 19] in which a rate acceleration occurs in the presence of alcoholic additives or MBH-products.

The interplay between a nucleophilic catalyst and electron-deficient alkenes (or latent enolates) can lead to the coupling of two Michael acceptors, also known as the Rauhut-Currier (RC) reaction.[20, 21] Although the RC reaction can be controlled to some extent by using excess amounts of aldehydes or by employing weak Michael acceptors, self-coupling of Michael acceptors is inevitable under the nucleophilic catalyst systems. Because of the high reactivity of aryl vinyl ketones, the MBH reaction of phenyl vinyl ketone with aldehydes leads to the formation of a mixture of 1:2 adduct and RC product, while the corresponding alkyl vinyl ketones predominantly give rise to normal MBH products. Two indirect approaches have been used to access normal MBH products by the functionalization of aryl vinyl ketones (Scheme 9). Kataoka *et al.* developed a two-step chalcogeno MBH reaction, where 2-(methylchalcogeno)phenyl vinyl ketones were subjected to the Lewis acid-promoted intramolecular Michael reaction, followed by aldol and elimination reactions to provide the normal MBH products.[22] In 2009, Gevorgyan reported the sila-MBH reaction using a silylated aryl vinyl ketone, where a 1,3-Brook rearrangement was exploited to prevent the formation of the 1,2-adduct and RC product in the presence of phosphine catalysts.[23] To date, there is no direct approach to produce MBH product using unfunctionalized aryl vinyl ketones.



Scheme 9. Chalcogeno- and Sila-MBH Reactions of Functionalized Aryl Vinyl Ketones

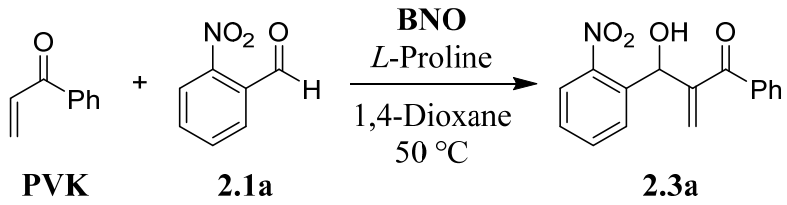
We have previously shown that the asymmetric MBH reaction of alkyl vinyl ketones could be catalyzed by a dual catalyst system of **BNO** and proline.[24] After our study of cooperative catalyst activity between **BNO** and proline, we postulated that our dual catalyst system could promote the normal MBH reaction of aryl vinyl ketones without the formation of 1:2 adducts and RC products.

2.2.2.2 Optimization of MBH Reaction of Aryl Vinyl Ketones

We first examined the MBH reaction of phenyl vinyl ketone (**PVK**) and **2.1a** in the presence of various amounts of catalysts (Table 4). In contrast to the successful MBH reactions of alkyl vinyl ketones, **BNO** did not promote the MBH reaction of **PVK** either in the absence or presence of solvent (entry1). The use of (*L*)-proline as the sole catalyst

also failed to provide the desired MBH product **2.3a** (entry 2). The desired MBH product **2.3a** was obtained in a low yield when the reaction was performed in the presence of both **BNO** and (*L*)-proline (entry 3). When the loading of both catalysts was increased to 100 mol%, the desired normal MBH product was obtained in a 49% yield (entry4-9). While a longer reaction time had a positive effect on the reaction conversion (entry 10), the diminished reaction rate led us to look into alternative reaction parameters. The use of excess **2.1a** resulted in better reaction conversions within 18 h (entry 11), however, a significant deceleration in the reaction rate was observed beyond 18 h (entry 12). To our delight, the use of excess **PVK** improved the reaction rate, providing 86% of **2.3a** in 42 h.

Table 4. Dual Catalysis of **BNO** and *L*-Proline



PVK **2.1a** **2.3a**

Entry	**BNO** (eq.)	*L*-Proline (eq.)	Time (h)	Yield (%)[b]
1[a]	0.15	-	18	0
2[a]	-	0.15	18	0
3[a]	0.15	0.15	18	2
4[a]	0.3	0.15	18	12
5[a]	0.15	0.3	18	9
6[a]	0.3	0.3	18	15

Table 4. Continued

Entry	**BNO** (eq.)	*L*-Proline (eq.)	Time (h)	Yield (%)[b]
7[a]	0.6	0.6	18	34
8[a]	1.0	1.0	18	49
9[a]	1.5	1.5	18	27
10[a]	1.0	1.0	42	69
11[c]	1.0	1.0	18	55
12[c]	1.0	1.0	42	53
13[d]	1.0	1.0	18	51
14[d]	1.0	1.0	42	86

a. Reaction condition: **PVK** (0.33 mmol, 1.0 eq.), **2.1a** (0.33 mmol, 1.0 eq.), 1,4-dioxane (2.5 mL), 50 °C.

b. Isolated yield of **2.3a** after column chromatography. The remaining mass accounts for unreacted starting materials (**PVK** and **2.1a**).

c. Reaction with **2.1a** (3.0 eq.).

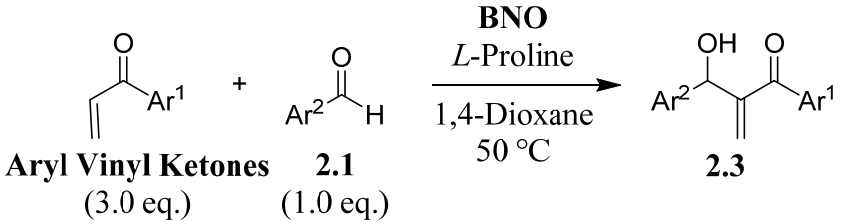
d. Reaction with **PVK** (3.0 eq.)

2.2.2.3 Substrate Scope of MBH Reaction of Aryl Vinyl Ketones

With the optimized conditions established, the scope of the MBH reaction of aryl vinyl ketones was investigated (Table 5). Electron-deficient aldehydes typically provided excellent yields of MBH products within 42 h (entry 1-6), while other electron-neutral and electron-rich aldehydes were less reactive under our dual catalyst conditions (entry 7-10). Studies using other aryl vinyl ketones, 4-chlorophenyl vinyl ketone and 4-

methoxyphenyl vinyl ketone, also revealed a similar reactivity pattern, providing excellent yields of normal MBH products (entry 11-13). The results described above are consistent with our proposed mechanism, where aldehydes are activated by proline to generate proline iminium intermediates that subsequently control the rate-determining step (α-H elimination) of the MBH reaction.

Table 5. Scope of the Morita-Baylis-Hillman Reaction of Aryl Vinyl Ketones



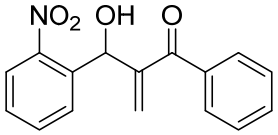
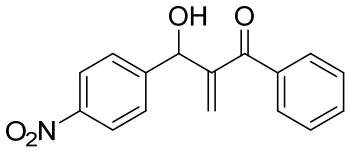
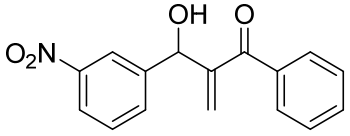
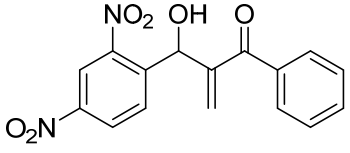
Entry	**2.3**		Time (h)	Yield (%)
1	**2.3a**		42	86
2	**2.3b**		42	86
3	**2.3c**		42	82
4	**2.3d**		18	98

Table 5. Continued

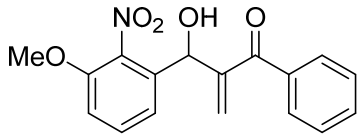
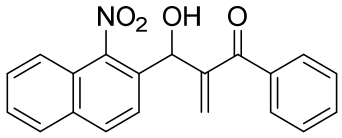
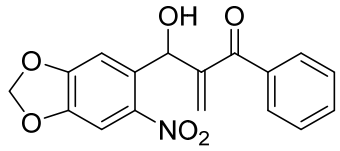
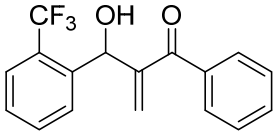
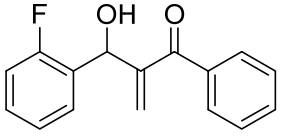
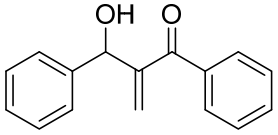
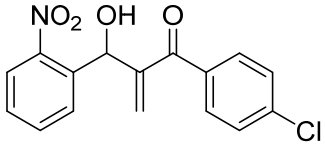
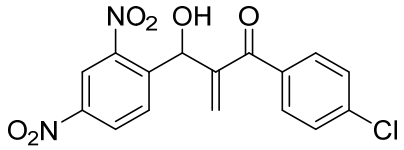
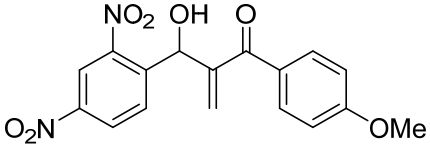
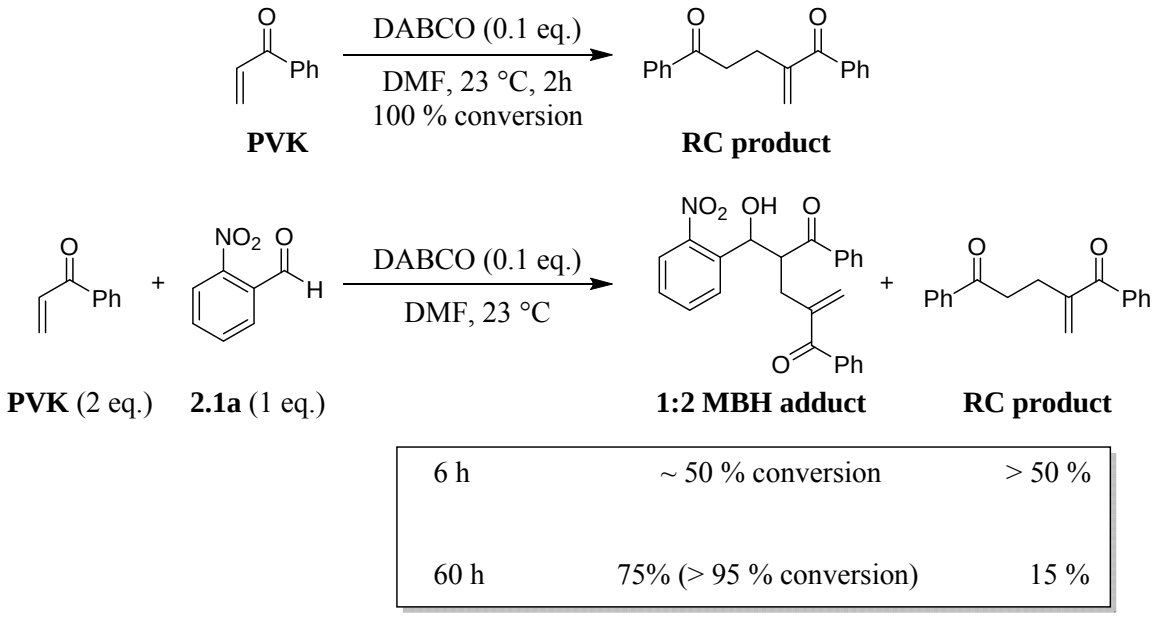
Entry	**2.3**		Time (h)	Yield (%)
5	**2.3e**		42	80
6	**2.3f**		42	90
7	**2.3g**		66	34
8	**2.3h**		42	33
9	**2.3i**		42	15
10	**2.3j**		42	8
11	**2.3k**		42	70

Table 5. Continued

Entry	**2.3**		Time (h)	Yield (%)
12	**2.3l**		18	98
13	**2.3m**		18	98

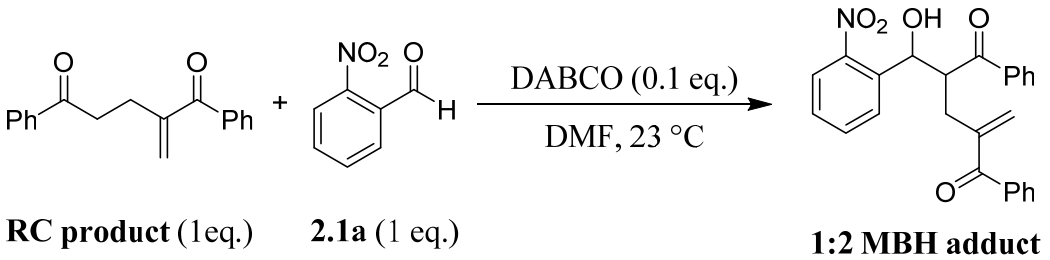
2.2.2.4 Mechanistic Study into the Formation of 1:2 MBH Adduct and RC Product

To shed light on the mechanistic details of the MBH reaction of **PVK**, a series of experiments were conducted to examine the formation of **1:2 MBH adduct** and **RC product**. While the proposed mechanism for the formation of **1:2 MBH adduct** involved a fast second reaction of the transient normal MBH product **2.3a** with **PVK**,[25, 26] our control experiments suggested an alternative mechanism (Scheme 10). We first examined the reaction rate between **PVK** and **RC product**. For 10 mol% DABCO in DMF, **PVK** was completely consumed within 2 h to yield **RC product**. It was also confirmed that depletion of **PVK** was complete less than 6 h of the reaction with **2.1a**, while the formation of **1:2 MBH adduct** continued to increase beyond 6 h. The above control experiments suggested that a major pathway for the formation of **1:2 MBH adduct** at the later stage of the reaction may not involve **PVK**.



Scheme 10. Formation of **1:2 MBH Adduct** and **RC Product**

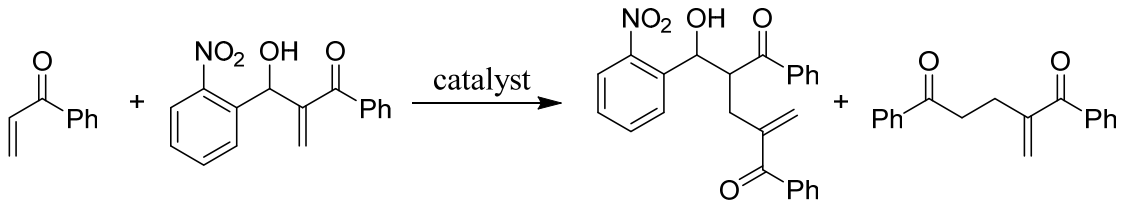
To delineate the role of **RC product** in the formation of **1:2 MBH adduct**, **2.1a** and **RC product** were reacted under the typical MBH reaction conditions (Scheme 11). In agreement with earlier report by Shi *et al.*, the formation of **1:2 MBH adduct** was not observed after 24 h at room temperature. However, we found that the reaction between **2.1a** and **RC product** could be facilitated by the presence of even a small amount of protic additives such as methanol (0.1 eq.) to give **1:2 MBH adduct**. This result clearly demonstrated that the direct aldol reaction of **1:2 MBH adduct** occurred, presumably by using **1:2 MBH adduct** as a protic source.



24 h	0 %
48 h (10 mol% MeOH)	10 % conversion

Scheme 11. Direct Aldol Reaction Pathway of RC Product

To understand the reaction of the normal MBH product **2.3a** with **PVK**, an equal molar ratio of **2.3a** and **PVK** was subjected to the standard reactions. Our results showed that the RC reaction pathway dominated over the reaction of **2.3a** with **PVK** in a ratio of 2:1 (Scheme 12). In addition, we confirmed that the reaction for **2.3a** with **PVK** did not occur under our dual catalyst conditions, implying a unique activation pathway for aldehydes by proline.



PVK (1 eq.) **2.3a** (1 eq.) **1:2 MBH adduct** **RC product**

DABCO (0.1 eq.) DMF, 23 °C	(no **PVK** left)	30 % conversion	> 60 %
BNO/*L*-Proline 1,4-Dioxane 50 °C, 18h	< 5 % conversion (> 95 % **PVK** left)	0 %	0 %

Scheme 12. Reaction of Normal MBH Product **2.3a** with **PVK**

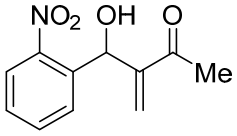
2.3 Conclusion

In summary, our studies showed that brucine *N*-oxide **BNO** is a nucleophilic catalyst for the Morita-Baylis-Hillman reaction of methyl vinyl ketone with aldehydes. In particular, the both catalysts, **BNO** and proline, effected the asymmetric Morita-Baylis-Hillman reactions using electron-deficient aryl aldehydes via the selective formation of iminium intermediates. Although the proline-catalyzed MBH reaction appeared to control the proton-transfer step with high stereoselectivity, the observed enantioselectivity of the products varied depending on the nature of aldehyde substrates. Although our investigation revealed that the alcohol-catalyzed reaction pathway (*i.e.* autocatalysis) negatively affected the observed enantioselectivity of products, various MBH products with modest to good ee's could be obtained for electron-deficient aryl aldehydes. In addition, our studies also demonstrated for the first time the formation of normal MBH products of aryl vinyl ketones under the dual catalysis of **BNO** and proline.

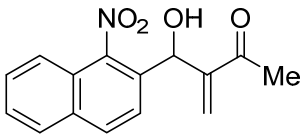
2.4 Experimental Section

General Procedure for Asymmetric Morita-Baylis-Hillman Reaction of Aryl Aldehydes

To a stirred solution of 2-nitroaldehyde **2.1a** (100 mg, 0.65 mmol), brucine *N*-oxide **BNO** (404 mg, 0.98 mmol) and (*L*)-proline (37 mg, 0.32 mmol) in dry 1,4-dioxane (5.0 ml) at ambient temperature were added to methyl vinyl ketone (46 mg, 0.65 mmol). The resulting suspension was stirred at the same temperature for 4-5 days until the aldehyde was completely consumed. The mixture was then directly loaded into a silica gel packed column for flash column chromatography (eluent 33/67 diethyl ether/hexanes) to give the Morita-Baylis-Hillman product **2.2a** (61 mg, 42% with 63% ee).

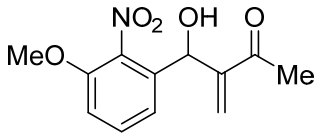


3-(Hydroxy(2-nitrophenyl)methyl)but-3-en-2-one (**2.2a**). The spectroscopic data were consistent with those reported in the literature.[27] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.96 (d, *J* = 8.5 Hz, 1H), 7.77 (d, *J* = 7.5 Hz, 1H), 7.64 (t, *J* = 7.7 Hz, 1H), 7.45 (t, *J* = 7.7 Hz, 1H), 6.21 (d, *J* = 4.0 Hz, 1H), 6.16 (s, 1H), 5.78 (d, *J* = 1.0 Hz, 1H), 3.51 (br, 1H), 2.36 (s, 3H); ^{13}C {^{1}H} NMR ($CDCl_3$, 125MHz): δ 199.8, 148.9, 148.1, 136.4, 133.4, 128.8, 128.5, 126.3, 124.6, 67.6, 25.9.

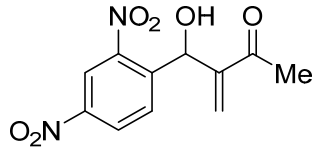


3-(Hydroxy(1-nitronaphthalen-2-yl)methyl)but-3-en-2-one (**2.2b**). The spectroscopic data were consistent with those reported in the literature.[27] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.95 (d, *J* = 8.5 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 1H), 7.74 (d, *J* = 8.5 Hz, 1H), 7.62-7.56

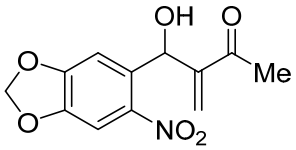
(m, 3H), 6.27 (s, 1H), 6.01 (d, *J* = 1.0 Hz, 1H), 5.87 (s, 1H), 3.66 (br, 1H), 2.33 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 199.7, 147.7, 146.5, 133.3, 131.0, 130.6, 128.6, 127.9, 127.7, 127.4, 124.3, 124.1, 121.8, 68.4, 26.0.



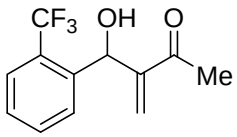
3-(Hydroxy(3-methoxy-2-nitrophenyl)methyl)but-3-en-2-one (**2.2c**). The spectroscopic data were consistent with those reported in the literature.[27] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40 (t, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.5 Hz, 1H), 6.22 (s, 1H), 5.96 (d, *J* = 1.0 Hz, 1H), 5.63 (s, 1H), 3.86 (s, 3H), 3.61 (br, 1H), 2.32 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 199.8, 150.8, 147.5, 140.2, 134.4, 131.1, 127.8, 119.4, 112.0, 68.3, 56.4, 26.0.



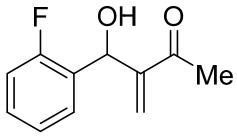
3-((2,4-Dinitrophenyl)(hydroxy)methyl)but-3-en-2-one (**2.2d**). The spectroscopic data were consistent with those reported in the literature.[27] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.76 (d, *J* = 2.5 Hz, 1H), 8.45 (dd, *J* = 8.7, 2.5 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 6.27 (s, 1H), 6.22 (s, 1H), 5.85 (s, 1H), 3.76 (br, 1H), 2.35 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 199.5, 148.1, 147.8, 147.1, 143.3, 130.5, 127.2, 127.1, 120.0, 67.1, 25.8.



3-(Hydroxy(6-nitrobenzo[*d*][1,3]dioxol-5-yl)methyl)but-3-en-2-one (**2.2e**). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.53 (s, 1H), 7.20 (s, 1H), 6.19 (s, 1H), 6.13 (s, 1H), 6.13-6.12 (m, 2H), 5.76 (d, J = 1.0 Hz, 1H), 3.50 (br, 1H), 2.38 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 200.0, 152.3, 149.0, 147.2, 141.8, 134.1, 126.0, 107.7, 105.5, 103.0, 67.5, 26.0; IR (neat, cm^{-1}): 3424, 1675, 1519, 1261; HRMS-CI m/z : 288.0495 [$(M+Na)^{+}$; calcd for $C_{12}H_{11}NO_6Na$: 288.0484].

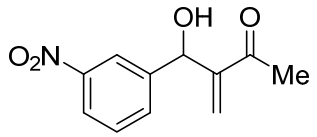


3-(Hydroxy(2-(trifluoromethyl)phenyl)methyl)but-3-en-2-one (**2.2f**). The spectroscopic data were consistent with those reported in the literature.[27] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.69 (d, J = 8.0 Hz 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.58-7.55 (m, 1H), 7.42-7.39 (m, 1H), 6.17 (s, 1H), 6.04 (d, J = 3.0 Hz, 1H), 5.53 (d, J = 1.0 Hz, 1H), 3.46 (br, 1H), 2.37 (s, 3H); $^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz): δ 200.2, 149.9, 139.3, 132.0, 128.6, 127.8, 127.7, 127.3, 125.8, 124.1, 67.4, 26.1.

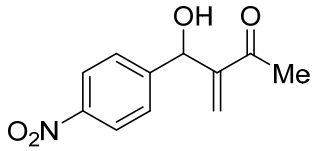


3-((2-Fluorophenyl)hydroxymethyl)but-3-en-2-one (**2.2g**). The spectroscopic data were consistent with those reported in the literature.[27] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.47-7.44 (m, 1H), 7.27-7.23 (m, 1H), 7.15-7.12 (m, 1H), 7.02-6.98 (m, 1H), 6.17 (s, 1H), 5.87 (s,

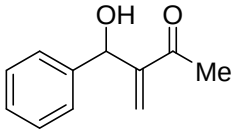
1H), 5.86 (s, 1H), 3.59 (br, 1H), 2.34 (s, 3H); $^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz): δ 200.3, 159.8 (d, J = 245.0 Hz), 148.7, 129.2 (d, J = 8.7 Hz), 128.4 (d, J = 11.2 Hz), 128.1 (d, J = 3.7 Hz), 126.8, 124.1 (d, J = 3.7 Hz), 115.2 (d, J = 21.2 Hz), 66.9 (d, J = 3.7Hz), 26.3.



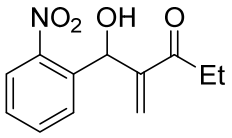
3-(Hydroxy(3-nitrophenyl)methyl)but-3-en-2-one (**2.2h**). The spectroscopic data were consistent with those reported in the literature.[27] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.22 (s, 1H), 8.13-8.11 (m, 1H), 7.73 (d, J = 7.5 Hz, 1H), 7.71 (t, J = 7.7 Hz, 1H), 6.28 (s, 1H), 6.07 (s, 1H), 5.66 (d, J = 5.5 Hz, 1H), 3.28 (d, J = 5.5 Hz, 1H), 2.36 (s, 3H); $^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz): δ 200.0, 149.0, 148.4, 143.9, 132.6, 129.3, 127.5, 122.6, 121.4, 72.2, 26.3.



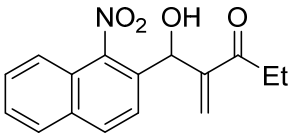
3-(Hydroxy(4-nitrophenyl)methyl)but-3-en-2-one (**2.2i**). The spectroscopic data were consistent with those reported in the literature.[27] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.17 (d, J = 9.0 Hz, 2H), 7.54 (d, J = 8.5 Hz, 2H), 6.26 (s, 1H), 6.03 (d, J = 1.0 Hz, 1H), 5.67 (d, J = 5.0 Hz, 1H), 3.35 (d, J = 5.0 Hz, 1H), 2.34 (s, 3H); $^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz): δ 199.9, 149.1, 148.9, 147.4, 127.5, 127.2, 123.5, 72.1, 26.2.



3-(Hydroxy(phenyl)methyl)but-3-en-2-one (**2.2j**). The spectroscopic data were consistent with those reported in the literature.[27] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34-7.29 (m, 4H), 7.26-7.24 (m, 1H), 6.16 (s, 1H), 5.96 (d, *J* = 1.0 Hz, 1H), 5.58 (d, *J* = 3.0 Hz, 1H), 3.21 (br, 1H), 2.30 (s, 3H); $^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz): δ 200.2, 149.9, 141.4, 128.3, 127.6, 126.5, 126.4, 72.6, 26.4.

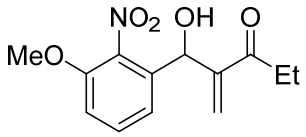


2-[Hydroxy-(2-nitrophenyl)-methyl]-pent-1-en-3-one (**2.2k**).[28] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.95 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.77 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.64 (td, *J* = 7.7, 1.0 Hz, 1H), 7.44 (td, *J* = 7.7, 1.5 Hz, 1H), 6.20 (s, 1H), 6.14 (s, 1H), 5.72 (d, *J* = 1.0 Hz, 1H), 3.61 (br, 1H), 2.77-2.71 (m, 2H), 1.07 (t, *J* = 7.5 Hz, 3H); $^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz): δ 202.7, 148.3, 147.9, 136.4, 133.4, 128.8, 128.4, 125.1, 124.6, 67.7, 31.1, 8.0; IR (neat, cm^{-1}) 3431, 1675, 1525, 1350; HRMS-CI m/z : 258.0729 [$(M+Na)^{+}$; calcd for $C_{12}H_{13}NO_4Na$: 258.0742].

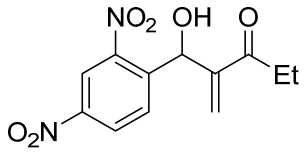


2-[Hydroxy-(1-nitronaphthalen-2-yl)-methyl]-pent-1-en-3-one (**2.2l**). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.96 (d, *J* = 9.0 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.63-7.56 (m, 2H), 6.27 (s, 1H), 5.96 (d, *J* = 1.0 Hz, 1H), 5.87 (s,

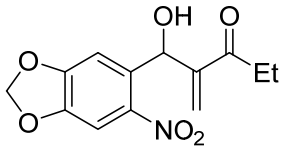
1H), 3.65 (br, 1H), 2.75-2.70 (m, 2H), 1.04 (t, J = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz): δ 202.5, 147.0, 146.5, 133.2, 131.0, 130.6, 128.6, 127.9, 127.4, 126.6, 124.3, 124.0, 121.8, 68.8, 31.2, 7.8; IR (neat, cm^{-1}): 3432, 1676, 1526, 1356; HRMS-CI m/z: 308.0907 [$(M+Na)^+$; calcd for $C_{16}H_{15}NO_4Na$: 308.0899].



2-[Hydroxy-(3-methoxy-2-nitrophenyl)-methyl]-pent-1-en-3-one (**2.2m**). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41 (t, J = 8.2 Hz, 1H), 7.12 (d, J = 7.5 Hz, 1H), 6.97 (dd, J = 4.2, 1.0 Hz, 1H), 6.21 (s, 1H), 5.90 (d, J = 1.0 Hz, 1H), 5.64 (d, J = 4.5 Hz, 1H), 3.87 (s, 3H), 3.54 (d, J = 5.5 Hz, 1H), 2.71 (q, J = 7.0 Hz, 2H), 1.04 (t, J = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz): δ 202.7, 150.8, 146.8, 140.1, 134.4, 131.1, 126.6, 119.3, 111.9, 68.8, 56.4, 31.2, 7.8; IR (neat, cm^{-1}): 3428, 1676, 1606, 1533, 1281; HRMS-CI m/z: 288.0840 [$(M+Na)^+$; calcd for $C_{13}H_{15}NO_5Na$: 288.0848].



2-[(2,4-Dinitrophenyl)hydroxymethyl]-pent-1-en-3-one (**2.2n**). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.78 (d, J = 2.5 Hz, 1H), 8.46 (dd, J = 8.7, 2.0 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 6.28 (s, 1H), 6.21 (s, 1H), 5.78 (s, 1H), 3.52 (br, 1H), 2.77-2.72 (m, 2H), 1.08 (t, J = 7.2 Hz, 3H); $^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz): δ 202.3, 147.8, 147.4, 147.1, 143.3, 130.5, 127.3, 125.8, 120.0, 67.6, 31.0, 7.9; IR (neat, cm^{-1}) 3434, 1675, 1606, 1537, 1348; HRMS-CI m/z: 281.0772 [$(M+H)^+$; calcd for $C_{12}H_{13}N_2O_6$: 281.0768].



2-(Hydroxy(6-nitrobenzo[*d*][1,3]dioxol-5-yl)methyl)pent-1-en-3-one (**2.2o**). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.52 (s, 1H), 7.21 (s, 1H), 6.18 (s, 1H), 6.12 (s, 2H), 6.11 (s, 1H), 5.70 (d, J = 1.0 Hz, 1H), 3.56 (br, 1H), 2.80-2.71 (m, 2H), 1.10 (t, J = 7.2 Hz, 3H); ^{13}C{^{1}H} ($CDCl_3$, 125 MHz): δ 202.8, 152.3, 148.5, 147.2, 141.8, 134.2, 124.7, 107.7, 105.5, 103.0, 67.9, 31.0, 8.0; IR (neat, cm^{-1}): 3440, 1677, 1520, 1259; HRMS-CI m/z: 279.0756 [$(M)^{+}$; calcd for $C_{13}H_{13}NO_6$: 279.0743].

Table 6. HPLC Conditions for MBH Products of Alkyl Vinyl Ketones

2.2	Chiral column	Eluents (Hex: IPA)	Flow rate (ml / min)	Retention time (min)		Ref.
				(*S*)-2.2	**(*R*)-2.2**	
2.2a	CHIRALPAK AD-H	93:7	0.70	20.38	22.52	26
2.2b	CHIRALPAK AD-H	93:7	0.75	29.15	33.45	26
2.2c	CHIRALPAK AD-H	93:7	0.75	38.13	40.51	26
2.2d	CHIRALPAK AD-H	93:7	0.75	28.90	32.48	a
2.2e	CHIRALPAK AD-H	90:10	0.75	27.57	33.48	b
2.2f	CHIRALPAK AD-H	95:5	0.75	11.93	14.28	26
2.2g	CHIRALPAK AD-H	98:2	0.75	26.39	29.26	26
2.2h	CHIRALPAK AD-H	93:7	0.90	37.33	41.95	26
2.2i	CHIRALPAK OD-H	95:5	1.00	25.77	26.45	8, 28
2.2j	CHIRALPAK AD-H	93:7	0.75	22.05	23.87	26

Table 6. Continued

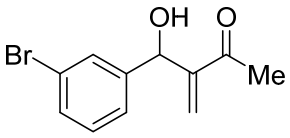
2.2	Chiral column	Eluents (Hex: IPA)	Flow rate (ml / min)	Retention time (min)		Ref.
				(*S*)-2.2	**(*R*)-2.2**	
2.2k	CHIRALPAK OD-H	95:5	0.75	23.60	26.21	b
2.2l	CHIRALPAK OD-H	95:5	0.75	25.79	31.24	b
2.2m	CHIRALPAK AD-H	93:7	0.75	31.03	32.52	b
2.2n	CHIRALPAK AD-H	93:7	0.75	23.70	28.16	b
2.2o	CHIRALPAK AD-H	90:10	0.75	24.85	28.56	b

a. The retention times in the literature were obtained with a different column.[27]

b. New compound.

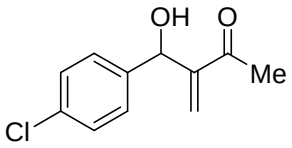
General Procedure for **BNO**-catalyzed Morita-Baylis-Hillman Reaction

To a stirred solution of 2-nitroaldehyde **2.1a** (100 mg, 0.65 mmol), brucine *N*-oxide **BNO** (40 mg, 0.1 mmol) was added to methyl vinyl ketone (138 mg, 1.95 mmol). The resulting suspension was stirred at 23 °C for 5 days, after which the mixture was directly loaded into a silica gel packed column for flash column chromatography (eluent 33/67 diethyl ether/hexanes) to give the Morita-Baylis-Hillman product **2.1a** (130 mg, 90%).

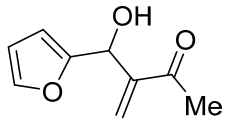


3-((3-Bromophenyl)hydroxymethyl)but-3-en-2-one (**2.2p**). The spectroscopic data were consistent with those reported in the literature.[10] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.49 (t, *J* = 1.7 Hz, 1H), 7.38 (dt, *J* = 7.8, 1.4 Hz, 1H), 7.27 (d, *J* = 7.7 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 6.21 (s, 1H), 6.00 (d, *J* = 1.0 Hz, 1H), 5.44 (d, *J* = 5.3Hz, 1H), 3.30 (d, *J* = 5.4 Hz,

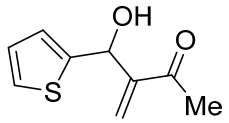
1H), 2.33 (s, 3H); $^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz): δ 200.1, 149.9, 143.3, 130.6, 129.9, 129.5, 127.1, 125.1, 122.5, 72.0, 26.4.



3-((4-Chlorophenyl)hydroxymethyl)but-3-en-2-one (**2.2q**). The spectroscopic data were consistent with those reported in the literature.[8] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.29 (d, *J* = 4.9 Hz, 4H), 6.19 (s, 1H), 5.97 (d, *J* = 1.1 Hz, 1H), 5.57 (d, *J* = 5.1 Hz, 1H), 3.21 (d, *J* = 5.3 Hz, 1H), 2.33 (s, 3H); $^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz): δ 200.2, 149.6, 140.0, 133.4, 128.5, 127.9, 126.9, 72.2, 26.4.

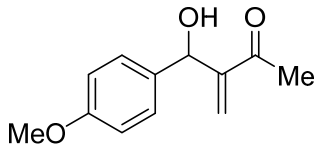


3-((Furan-2-yl)hydroxymethyl)but-3-en-2-one (**2.2r**). The spectroscopic data were consistent with those reported in the literature.[27] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.31 (dd, *J* = 1.8, 0.7 Hz, 1H), 6.28 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.21(s, 1H), 6.18 (d, *J* = 3.3 Hz, 1H), 6.09 (d, *J* = 1.2 Hz, 1H), 5.59 (d, *J* = 6.0 Hz, 1H), 3.56 (d, *J* = 6.1 Hz, 1H), 2.32 (s, 3H); $^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz): δ 199.7, 154.2, 147.3, 142.0, 127.0, 110.2, 107.0, 66.5, 26.1.

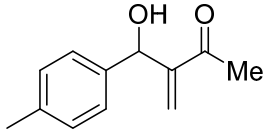


3-(Hydroxy(thiophen-2-yl)methyl)but-3-en-2-one (**2.2s**).[30] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.23 (dd, *J* = 4.5, 1.8 Hz, 1H), 6.95 (t, *J* = 3.2 Hz, 1H), 6.94 (d, *J* = 1.7 Hz, 1H), 6.22 (s, 1H), 6.11 (d, *J* = 1.0 Hz, 1H), 5.81 (d, *J* = 6.0 Hz, 1H), 3.45 (d, *J* = 6.1 Hz, 1H), 2.37 (s,

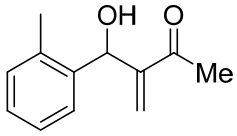
3H); $^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz): δ 200.2, 149.1, 145.8, 126.8, 126.7, 125.1, 124.6, 69.6, 16.5. HRMS-CI m/z: 182.0396 [$(M)^+$; calcd for $C_9H_{10}O_2NS$: 182.0396].



3-(Hydroxy(4-methoxyphenyl)methyl)but-3-en-2-one (**2.2t**). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.28 – 7.26 (m, 2H), 6.87 – 6.85 (m, 2H), 6.18 (s, 1H), 5.99 (d, J = 1.0 Hz, 1H), 5.57 (d, J = 3.5 Hz, 1H), 3.79 (s, 3H), 3.20 (d, J = 4.5 Hz, 1H), 2.33 (s, 3H); $^{13}C\{^{1}H\}$ ($CDCl_3$, 500 MHz): δ 200.4, 159.3, 150.4, 133.9, 128.0, 126.3, 114.0, 72.5, 55.4, 26.7; IR (neat, cm^{-1}): 3440, 3040, 3011, 2962, 2933, 2835, 1674, 1611, 1512, 1366, 1303, 1249, 1175, 1032, 833; HRMS-CI: m/z 205.0874 [$(M-H)^-$; calcd for $C_{12}H_{13}O_3$: 205.0870].

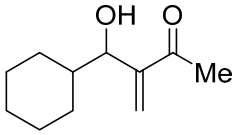


3-(Hydroxy(*p*-tolyl)methyl)but-3-en-2-one (**2.2u**).[31] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.24 (d, J = 8.0 Hz, 2H), 7.14 (d, J = 7.9 Hz, 2H), 6.18 (s, 1H), 5.99 (d, J = 1.2 Hz, 1H), 5.58 (d, J = 4.6 Hz, 1H), 3.03 (d, J = 5.1 Hz, 1H), 2.33 (s, 6H); $^{13}C\{^{1}H\}$ ($CDCl_3$, 125 MHz): δ 200.3, 150.0, 138.6, 137.3, 129.1, 126.4, 126.4, 72.7, 26.5, 21.1.

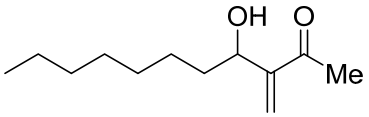


4-Hydroxy-3-methyl-4-(*o*-tolyl)butan-2-one (**2.2v**). ^{1}H NMR ($CDCl_3$, 500 MHz):δ 7.42 - 7.40 (m, 1H), 7.24 - 7.18(m, 2H), 7.16 – 7.14 (m, 1H), 6.17 (s, 1H), 5.86 (d, J = 3.5 Hz, 1H), 5.73 (d, J = 1.0 Hz, 1H), 2.95 (d, J = 4.0 Hz, 1H), 2.39 (s, 3H), 2.28 (s, 3H); $^{13}C\{^{1}H\}$

($CDCl_3$, 500 MHz): δ 200.7, 150.0, 139.1, 135.6, 130.5, 127.8, 126.9, 126.4, 126.3, 68.8, 26.6, 19.3; IR (neat, cm^{-1}): 3417, 3066, 3009, 2965, 2917, 2857, 1679, 1384, 1028, 745; HRMS-CI: m/z 193.1227 [$(M+H)^+$; calcd for $C_{12}H_{17}O_2$: 193.1229].



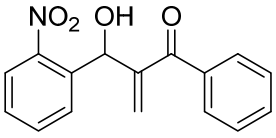
3-(Cyclohexyl(hydroxy)methyl)but-3-en-2-one (**2.2x**). The spectroscopic data were consistent with those reported in the literature.[32] ^1H NMR ($CDCl_3$, 500 MHz): δ 6.12 (s, 1H), 5.91 (s, 1H), 4.06 (t, *J* = 7.5 Hz, 1H), 2.68 (d, *J* = 7.9 Hz, 1H), 2.35 (s, 3H), 1.92 (m, 1H), 1.76-1.16 (m, 3H), 1. 53 (m, 1H), 1.43 (m, 1H), 1.24-1.06 (m, 3H), 0.98-0.89 (m, 2H); $^{13}C\{^1H\}$ ($CDCl_3$, 125 MHz): δ 201.0, 148.8, 126.8, 77.4, 42.4, 30.1, 28.4, 26.6, 26.3, 26.1, 25.9.



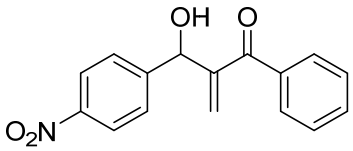
4-Hydroxy-3-methyleneundecan-2-one (**2.2y**). ^1H NMR ($CDCl_3$, 500 MHz): δ 6.08 (s, 1H), 5.98 (d, *J* = 0.9 Hz, 1H), 4.39 (q, *J* = 6.4 Hz, 1H), 2.72 (d, *J* = 6.5 Hz, 1H), 2.33 (s, 3H), 1.59 – 1.54 (m, 2H), 1.43 – 1.36 (m, 1H), 1.30 – 1.24 (m, 9H), 0.85 (t, *J* = 6.95 Hz, 3H); $^{13}C\{^1H\}$ ($CDCl_3$, 125 MHz): δ 200.9, 150.6, 125.6, 71.5, 36.5, 31.9, 29.5, 29.3, 26.6, 26.0, 22.7, 14.2; IR (neat, cm^{-1}): 3447, 3104, 2003, 2952, 2926, 2856, 1675, 1629, 1466, 1429, 1366, 1281, 1107, 1069, 1017, 972, 948, 591; HRMS-CI: m/z 199.1686 [$(M)^+$; calcd for $C_{12}H_{23}O_2$: 199.1698].

General Procedure for Morita-Baylis-Hillman Reaction of Phenyl Vinyl Ketone

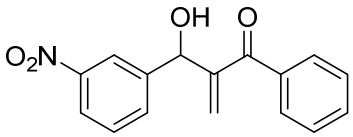
To a stirred solution of **2.1a** (100 mg, 0.65 mmol), **BNO** (269 mg, 0.65 mmol) and *L*-proline (74 mg, 0.65 mmol) in anhydrous 1,4-dioxane (5.0 mL) at ambient temperature were added to **PVK** (0.259 mL, 1.95 mmol). The resulting suspension was stirred at 50 °C for 42 h, and then loaded directly into a silica gel packed column for flash column chromatography (EtOAc–hexanes, 20:80) to give MBH product **2.3a**.



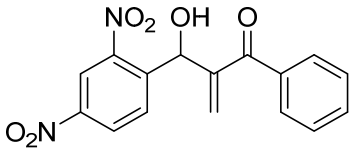
2-(Hydroxy(2-nitrophenyl)methyl)-1-phenylprop-2-en-1-one (**2.3a**). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.01-7.97(m, 2H), 7.73-7.67 (m, 3H), 7.57-7.54 (m, 1H), 7.49-7.42 (m, 3H), 6.31 (s, 1H), 5.82 (d, J = 0.8 Hz, 1H), 5.77(s, 1H), 4.14 (d, J = 1.8 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 198.5, 147.8, 147.6, 136.7, 136.2, 133.6, 133.0, 129.7, 129.0, 128.6, 128.4, 127.7, 124.7, 69.4; IR (neat, cm^{-1}): 3450, 3064, 2920, 2851, 1650, 1524, 1345; HRMS-CI: m/z 283.0845 [(M-H)$^{-}$; calcd for $C_{16}H_{12}NO_4$: 282.0772]; Yellow liquid.



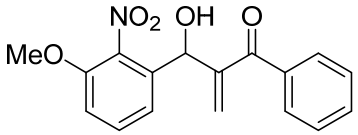
2-(Hydroxy(4-nitrophenyl)methyl)-1-phenylprop-2-en-1-one (**2.3b**). ^{1}H NMR ($CDCl_3$, 500M Hz): δ 8.19 (d, J = 8.75 Hz, 2H), 7.68-7.66 (m, 2H), 7.63 (d, J = 8.5 Hz, 2H), 7.58-7.54 (m, 1H), 7.44-7.41 (m, 2H), 6.12 (s, 1H), 5.88 (s, 1H), 5.84 (s, 1H), 3.74 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 197.9, 148.7, 147.6, 147.4, 136.8, 133.1, 129.5, 128.5, 128.1, 127.2, 123.7, 73.5; IR (neat, cm^{-1}): 3458, 3066, 2925, 1655, 1519, 1347; HRMS-CI: m/z 283.0845 [(M-H)$^{-}$; calcd for $C_{16}H_{12}NO_4$: 282.0772]; Yellow liquid.



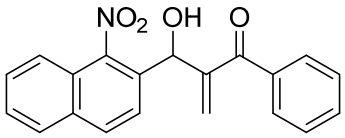
2-(Hydroxy(3-nitrophenyl)methyl)-1-phenylprop-2-en-1-one (**2.3c**). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.34 (s, 1H), 8.15-8.12 (m, 1H), 7.82 (d, *J* = 7.5 Hz, 1H), 7.70-7.68 (m, 2H), 7.58-7.51 (m, 2H), 7.45-7.42 (m, 2H), 6.15 (d, *J* = 1.0 Hz, 1H), 5.92 (s, 1H), 5.84 (d, *J* = 5.5 Hz, 1H), 3.67 (d, *J* = 5.5 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 198.0, 148.4, 147.5, 143.7, 136.9, 133.1, 132.6, 129.5, 129.4, 128.5, 128.4, 122.8, 121.4, 73.6; IR (neat, cm^{-1}): 3451, 3088, 2922, 1654, 1529, 1351; HRMS-CI: m/z 283.0845 [$(M-H)^-$; calcd for $C_{16}H_{12}NO_4$: 282.0772]; Yellow liquid.



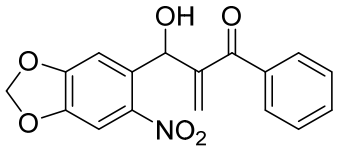
2-((2,4-Dinitrophenyl)(hydroxy)methyl)-1-phenylprop-2-en-1-one (**2.3d**). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.85(d, *J* = 2.0 Hz, 1H), 8.52 (dd, *J* = 8.5 Hz, 2.0 Hz, 1H), 8.26 (d, *J* = 8.5 Hz, 1H), 7.71-7.69 (m, 2H), 7.61-7.58 (m, 1H), 7.48-7.44 (m, 2H), 6.38 (d, *J* = 4.4 Hz, 1H), 5.85 (s, 1H), 5.84 (s, 1H), 4.21 (d, *J* = 4.7 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 198.1, 147.7, 147.3, 146.5, 142.9, 136.2, 133.4, 130.8, 129.7, 128.6, 128.6, 127.5, 120.2, 69.5; IR (neat, cm^{-1}): 3458, 3112, 2926, 1651, 1606, 1535, 1346; HRMS-CI: m/z 328.0695 [$(M+H)^+$; calcd for $C_{16}H_{13}N_2O_6$: 329.0768]; Yellow liquid.



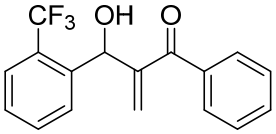
2-(Hydroxy(3-methoxy-2-nitrophenyl)methyl)-1-phenylprop-2-en-1-one (**2.3e**). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.73 (d, *J* = 8.0 Hz, 2H), 7.57-7.54 (m, , 1H), 7.47-7.42 (m, 3H), 7.31 (d, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 8.5 Hz, ,1H), 6.03 (d, *J* = 1.0 Hz, 1H), 5.86 (s, 1H), 5.81 (d, *J* = 5.9 Hz, 1H), 4.09 (d, *J* = 5.9 Hz, 1H), 3.90 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 199.3, 151.0, 145.7, 136.7, 134.1, 133.0, 131.3, 129.7, 129.4, 128.4, 119.5, 112.12, 70.4, 56.5; IR (neat, cm^{-1}): 3440, 2941, 2851, 1653, 1532, 1282; HRMS-CI: m/z 313.0950 [$(M+H)^{+}$; calcd for $C_{17}H_{15}NO_5$: 314.1023]; Yellow liquid.



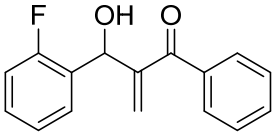
2-(Hydroxy(1-nitronaphthalen-2-yl)methyl)-1-phenylprop-2-en-1-one (**2.3f**). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.02 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 8.5 Hz, 1H), 7.74-7.72 (m, 2H), 7.66-7.52 (m, 3H), 7.44-7.42 (m, 2H), 6.06-6.04 (m, 2H), 5.91 (s, 1H), 4.05 (d, *J* = 4.5 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 198.1, 146.2, 136.8, 133.4, 133.0, 131.2, 130.5, 129.7, 129.1, 129.1, 128.8, 128.4, 128.0, 127.6, 124.4, 124.1, 121.8, 70.2; IR (neat, cm^{-1}): 3434, 3064, 2922, 1654, 1527; HRMS-CI: m/z 333.1001 [$(M-H)^{-}$; calcd for $C_{20}H_{15}NO_4$: 332.0928]; Yellow liquid.



2-(Hydroxy(6-nitrobenzo[*d*][1,3]dioxol-5-yl)methyl)-1-phenylprop-2-en-1-one (**2.3g**). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.74 (d, J = 7.5 Hz, 2H), 7.59-7.56 (m , 2H), 7.46-7.42 (m, 3H), 6.28 (s, 1H), 6.14 (d, J = 4.5 Hz, 2H), 5.80 (s, 1H), 5.73 (s, 1H), 4.12 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 198.8, 152.5, 147.8, 147.3, 141.6, 136.8, 134.1, 133.0, 129.8, 128.4, 127.1, 108.0, 105.7, 103.1, 69.5; IR (neat, cm^{-1}): 3444, 3086, 2919, 1652, 1519, 1262, 1035; HRMS-CI: m/z 327.0743 [$(M-H)^-$; calcd for $C_{17}H_{12}NO_6$: 326.0670]; Yellow liquid.

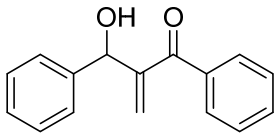


2-(Hydroxy(2-(trifluoromethyl)phenyl)methyl)-1-phenylprop-2-en-1-one (**2.3h**). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.89 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 7.5 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H), 7.59-7.56 (m, 1H), 7.47-7.43 (m, 3H), 6.18 (s, 1H), 5.80 (s, 1H), 5.66 (s, 1H), 3.75 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 198.7, 148.5, 139.1, 137.0, 132.9, 132.2, 129.7, 128.8, 128.4, 125.9, 69.2; IR (neat, cm^{-1}): 3447, 3067, 2920, 1655, 1313, 1160, 1123; HRMS-CI: m/z 306.0868 [$(M+H)^+$; calcd for $C_{17}H_{14}F_3O_2$: 307.0940]; Yellow liquid.

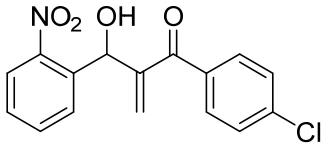


2-((2-Fluorophenyl)hydroxymethyl)-1-phenylprop-2-en-1-one (**2.3i**). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.74-7.72 (m, 2H), 7.60-7.51 (m, 2H), 7.43 (m, 2H), 7.29-7.25 (m, 1H),

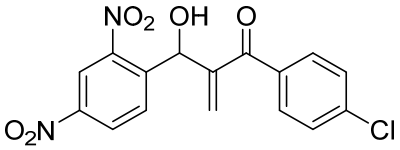
7.19-7.16 (m, 1H), 7.06-7.02 (m, 1H), 6.00 (s, 2H), 5.80 (s, 1H), 3.76 (s, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 198.6, 147.6, 139.6, 136.0, 135.0, 133.8, 131.1, 129.0, 128.8, 128.7, 127.4, 124.9, 69.4; IR (neat, cm^{-1}): 3445, 3065, 2920, 1655, 1489, 1450, 1314, 980, 760; HRMS-CI: m/z 256.0900 [$(M+H)^+$; calcd for $C_{16}H_{14}FO_2$: 257.0972]; Yellow liquid.



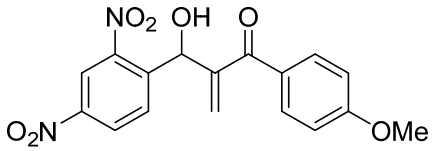
2-(Hydroxy(phenyl)methyl)-1-phenylprop-2-en-1-one (**2.3j**). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.71-7.69 (m, 2H), 7.55-7.52 (m, 1H), 7.47-7.40 (m, 5H), 7.37-7.33 (m, 2H), 6.07 (s, 1H), 5.79 (s, 2H), 3.31 (s, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 198.3, 148.8, 141.3, 137.3, 132.7, 129.6, 128.5, 128.3, 127.8, 126.7, 126.5, 74.2; IR (neat, cm^{-1}): 3467, 3061, 2923, 2852, 1683, 1654, 1449, 979, 700; HRMS-CI: m/z 238.0994 [$(M+H)^+$; calcd for $C_{16}H_{15}O_2$:239.1067]; Colorless liquid.



1-(4-Chlorophenyl)-2-(hydroxy(2-nitrophenyl)methyl)prop-2-en-1-one (**2.3k**). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.03 (dd, J = 8.2 Hz, 1.1Hz, 1H), 7.97 (d, J = 7.6 Hz, 1H), 7.73-7.67 (m, 3H), 7.51-7.48 (m, 1H), 7.43-7.42 (m, 2H), 6.29 (s, 1H), 5.80 (s, 1H), 5.74 (s, 1H), 3.96 (s, 1H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 197.2, 147.6, 139.6, 136.0, 135.0, 133.8, 131.1, 129.0, 128.8, 128.7, 127.4, 124.9, 69.4. IR (neat, cm^{-1}): 3469, 3068, 2924, 2853, 1680, 1658, 1589, 1525, 1346, 1092; HRMS-CI: m/z 317.0455 [$(M+H)^+$; calcd for $C_{16}H_{13}ClNO_4$:318.0528]; Yellow liquid.



1-(4-Chlorophenyl)-2-((2,4-dinitrophenyl)(hydroxy)methyl)prop-2-en-1-one (**2.3l**). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.86 (d, *J* = 2.3 Hz, 1H), 8.53 (dd, *J* = 8.7 Hz, 2.3 Hz, 1H), 8.26 (d, *J* = 8.7 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.44 (d, *J* = 8.5 Hz, 1H), 6.36 (s, 1H), 5.81 (s, 2H), 4.09 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 196.8, 147.6, 147.4, 146.7, 142.8, 140.0, 134.5, 131.1, 130.8, 129.0, 128.3, 127.6, 120.3, 69.3; IR (neat, cm^{-1}): 3458, 3104, 2923, 1655, 1588, 1535, 1346; HRMS-CI: m/z 326.0306 [$(M+H)^+$; calcd for $C_{16}H_{12}ClN_2O_6$:363.0378]; Yellow liquid.



2-((2,4-Dinitrophenyl)(hydroxy)methyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**2.3m**). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.83 (d, *J* = 2.3 Hz, 1H), 8.51 (dd, *J* = 8.7 Hz, 2.3 Hz, 1H), 8.27 (d, *J* = 8.7 Hz, 1H), 7.74-7.72 (m, 2H), 6.95-6.92 (m, 2H), 6.31 (d, *J* = 4.2 Hz, 1H), 5.77 (s, 1H), 5.75 (s, 1H), 4.52 (d, *J* = 4.8 Hz, 1H), 3.87 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 196.9, 164.1, 147.7, 147.3, 146.1, 143.0, 132.3, 130.7, 128.7, 127.4, 127.0, 120.1, 113.9, 70.1, 55.6; IR (neat, cm^{-1}): 3404, 3109, 2923, 2851, 1649, 1599, 1535, 1346; HRMS-CI: m/z 358.0801 [$(M+H)^+$; calcd for $C_{17}H_{15}N_2O_7$:359.0874]; Yellow liquid.

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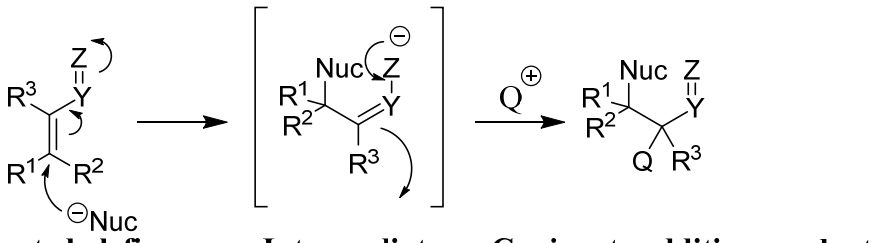
CHAPTER 3. CATALYTIC ASYMMETRIC CONJUGATE ADDITION OF GLYCINE KETIMINE TO NITROALKENES USING BRUCINE DIOL-COPPER COMPLEX

3.1 Introduction

3.1.1 Conjugate Addition

Conjugate addition to α,β-unsaturated carbonyl compounds or electron-deficient alkenes is one of the most useful carbon-carbon bond-forming reactions in organic synthesis.[1] As shown in Scheme 13, nucleophiles attack the β-carbon position of activated alkenes and produce the conjugate addition product.



Activated olefins **Intermediate** **Conjugate addition product**

Y/Z = Carbonyl, Sulfonyl, Nitro

R^1, R^2, R^3 = H, Alkyl, Aryl, Heteroaromatic

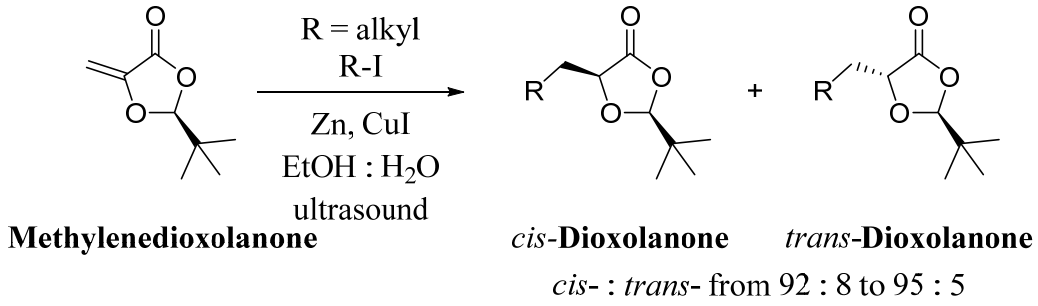
Nuc = Enolate, Nitronate, Organometallic nucleophile, Amine, Alcohol

Q = H

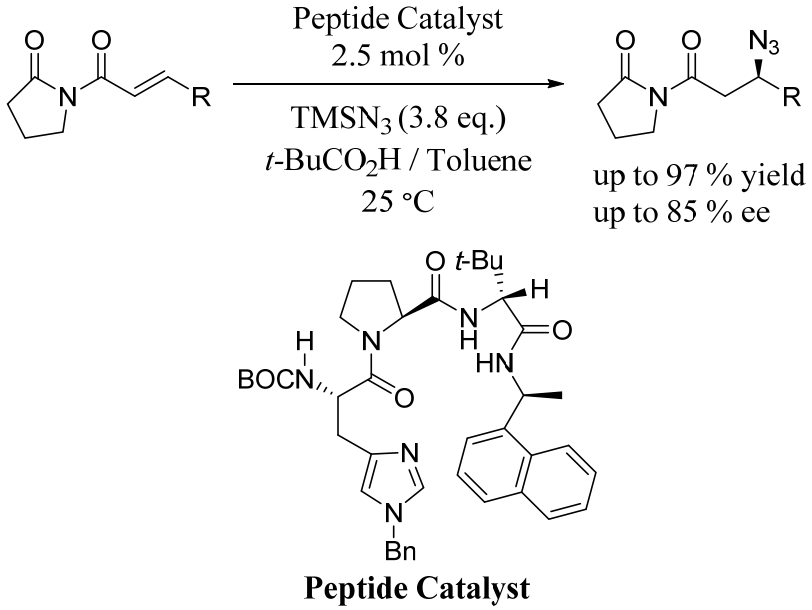
Scheme 13. Conjugate Addition Reaction

Considerable efforts have been devoted to the development of asymmetric conjugate addition reactions.[2-8] Typically, the reaction involves the use of modified chiral reactants

or catalysts in both diastereoselective (Scheme 14) and enantioselective conjugate addition reactions (Scheme 15).



Scheme 14. Diastereoselective Conjugate Addition Reaction[9]

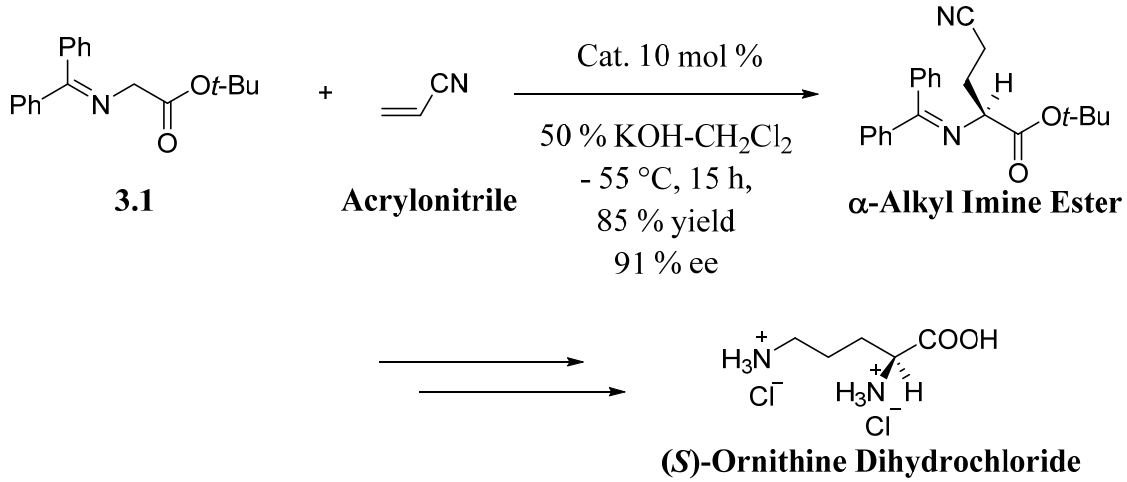


Scheme 15. Enantioselective Conjugate Addition Reaction[10]

3.1.2 Conjugate Addition of Glycine Ester Derivatives to Activated Alkenes

Glycine ester derivatives have been utilized as nucleophiles in catalytic asymmetric carbon-carbon bond-forming reactions to produce optically pure α-amino acid derivatives.

Thus, highly stereoselective reactions have been developed[11-13] since the first report of the asymmetric alkylation of glycine esters using a chiral phase-transfer catalyst by O'Donnell *et al.* in 1978.[14] Among them, the asymmetric conjugate addition of *N*-(diphenylmethylene)glycine *tert*-butyl ester to α,β-unsaturated carbonyl compounds provides an efficient route to optically active α-alkylamino acid derivatives.[15-18] As outlined in Scheme 16, (*S*)-ornithine dihydrochloride could be synthesized from the asymmetric conjugate addition of glycine ketimine **3.1** to acrylonitrile using a chiral catalyst. Furthermore, a variety of activated alkenes have been investigated to expand the scope of substrates such as β-alkyl-α,β-unsaturated esters,[19] β-aryl nitroalkenes,[20] β-aryl-α,β-unsaturated ketones,[21, 22] arylidene malonates,[23, 24] and alkylidene bisphosphonates.[25]



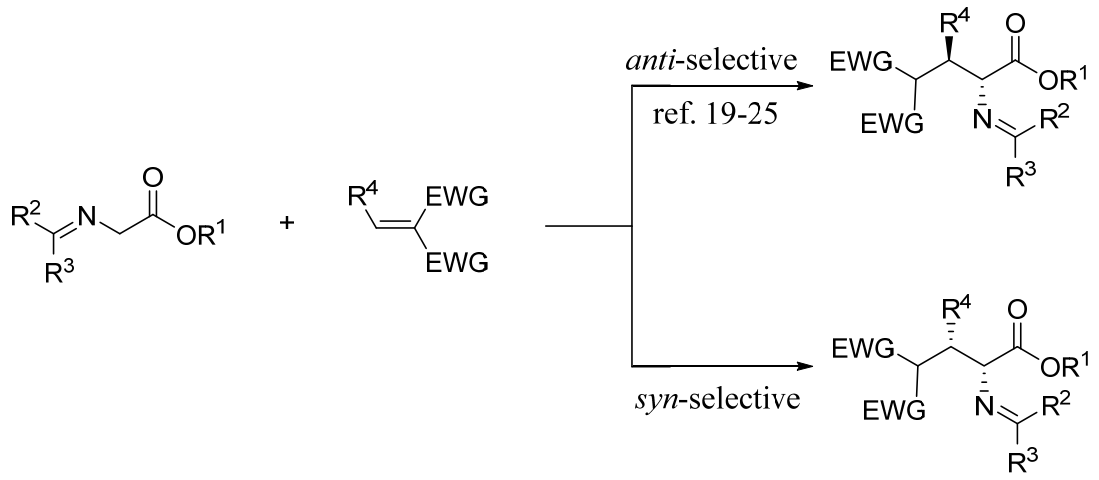
Scheme 16. Synthesis of (*S*)-Ornithine Using Asymmetric Conjugate Addition Reaction

In this chapter, we present our study on the diastereoselective and enantioselective conjugate addition of glycine ketimine **3.1** to nitroalkenes to produce a variety of *anti*-selective conjugate addition products with excellent ee's.

3.2 Results and Discussion

3.2.1 *Anti*-Selective Conjugate Addition Reaction

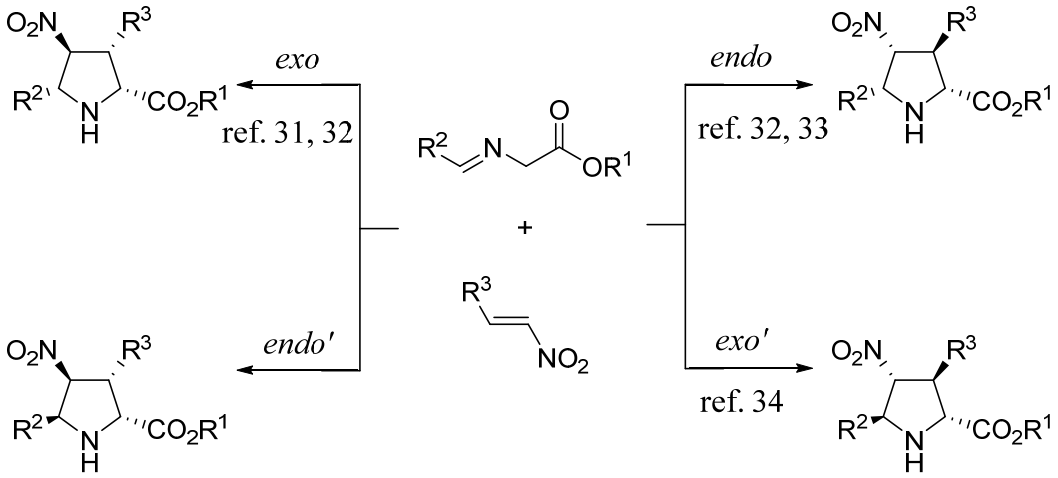
Several research groups have reported the development of catalytic asymmetric conjugate additions of glycine imines to a variety of activated alkenes,[19-25] all leading to *anti*-selective conjugate reaction products (Scheme 17). In contrast, there are no examples of catalytic *enantio*- and *syn*-selective conjugate reactions of glycine imines. As a consequence, there is a clear void in the development of catalytic asymmetric *syn*-selective conjugate reactions.



Scheme 17. *anti*-Selective and *syn*-Selective Conjugate Addition Reactions

In the pursuit of a solution to this stereodivergence issue, we became interested in the stereochemical pathways of [3+2] cycloaddition reactions between glycine imines and electron-deficient alkenes. Since the seminal contribution of Grigg in 1911,[26] significant progress has been made on the catalytic asymmetric [3+2] cycloaddition reactions of *N*-metalated azomethine ylides with alkenes.[27,28] Both concerted and stepwise mechanisms[29,30] have been considered as possible pathways. The stepwise mechanism

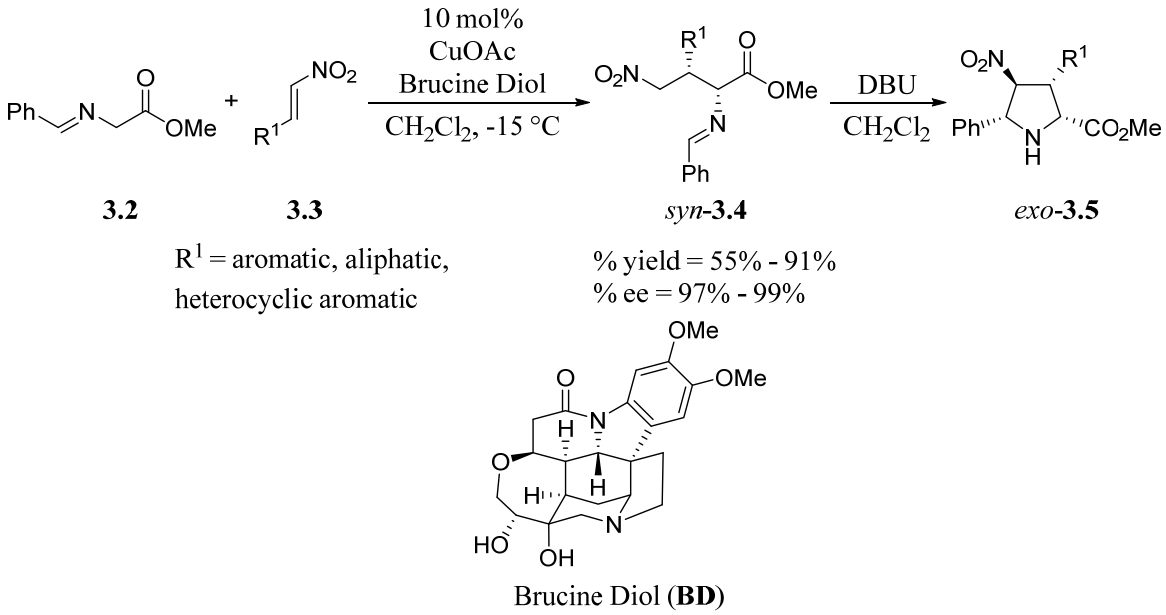
has been suggested in the catalytic asymmetric *exo*-,[31,32] *endo*-,[32,33] and *exo*'-selective[34] [3+2] cycloaddition reactions of *N*-metalated azomethine ylides and nitroalkenes (Scheme 18). This stepwise reaction process in the [3+2] cycloaddition reactions of *N*-metalated azomethine ylides implies the possibility of developing catalytic asymmetric systems for the conjugate reaction pathway.



Scheme 18. Stereochemical Pathway of the [3+2] Cycloaddition Reactions

We have previously reported that the catalyst-substrate arrangements are controlled by multiple binding modes of multidentate amino alcohol, brucine diol (**BD**), through either metal coordination or the hydrogen-binding network.[35,36] When glycine imines were treated with various α,β-unsaturated esters under chiral copper(I) and silver(I) catalysis, the exclusive formation of *endo*-pyrrolidines was observed, possibly through a concerted [3 + 2] cycloaddition pathway.[35] Given the possibility of different preferential interactions between acyclic alkenes and nucleophiles under various chiral catalyst conditions, we used nitroalkenes to develop stereodivergent conjugate addition reactions. We describe herein the first example of such a switch in selectivity to provide respective

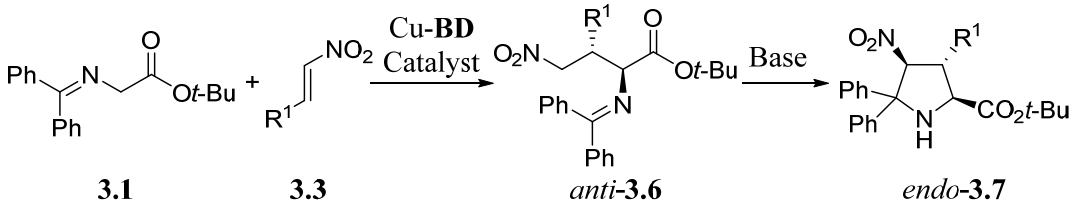
anti- and *syn*-1,4-addition products using the chiral catalyst system derived from a single chiral source.[37,38] In our preliminary study, we produced the *syn*-selective conjugate addition products and further synthesized *exo*-pyrrolidines under basic conditions (Scheme 19).[39]



Scheme 19. Stepwise One-Pot [3+2] Cycloaddition Reaction

After establishing the facile access to chiral *exo*-pyrrolidine through a catalytic *syn*-selective conjugate addition reaction, we investigated *anti*-selective conjugate addition reaction of glycine imines that potentially leads to diastereomeric *endo*-pyrrolidines. In our preliminary studies of the [3+2] cycloaddition reaction, *endo*-**3.5** could be obtained, but the transient nature of the *anti*-selective conjugate addition product was not observed from the reaction of glycine imine **3.2** and nitroalkenes **3.3**. However, the use of glycine ketimine **3.1** turned out to be a key factor in identifying the *anti*-selective conjugate

addition product (Scheme 20). The emergence of *endo*-pyrrolidines **3.7** was attributed to the base-promoted cyclization of *anti*-conjugate product **3.6** under the Cu-**BD** catalyst conditions.



3.1 **3.3** *anti*-**3.6** *endo*-**3.7**

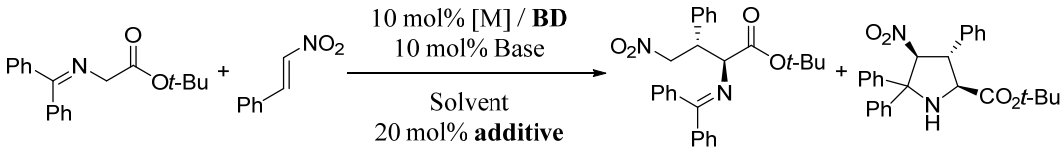
Scheme 20. Stepwise Conjugate Addition Reaction and Cyclization

3.2.2 Optimization of *anti*-Selective Conjugate Addition Reaction

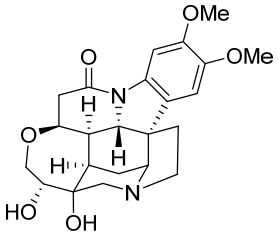
We examined the copper(I)-catalyzed asymmetric conjugate addition of glycine ketimine **3.1** to nitroalkene **3.3a** in the presence of 10 mol % **BD** (Table 7). The use of CuOAc, CuCl, and CuI led to the *end*o-selective formation of **3.7a** with low reactivity and enantioselectivity (entry 1-3). The use of CuOTf was subsequently identified as an *anti*-selective catalyst with 9:1 ratio between *anti*-**3.6a** and *endo*-**3.7a** (entry 4). The $Cu(OTf)_2$ catalyst system was also investigated, however the product ratio between *anti*-**3.6a** and *endo*-**3.7a** was dropped to 1 : 1 (entry 5). To further improve the product ratio and enantioselectivity of *anti*-**3.6a**, we screened a variety of solvents (entry 6-8) and bases (entry 9-14). The coordinating solvent system-THF and the bulky organic base-DBU were identified as an optimal solvent and a base for the asymmetric conjugate addition of glycine ketimine to nitroalkene. The additive effect using protic source, such as H_2O, PhOH, *i*-PrOH, *t*-BuOH, 2,3-dimethyl-2-butanol, 2,2-diphenyl-ethanol, 2-phenyl-2-propanol was also investigated (entry 15-21). While the use of acidic additive, PhOH, and non-bulky protic source, *i*-PrOH, led to lower enantioselectivity (entry 16)

and product ratio (entry 17), *t*-BuOH and 2-phenyl-2-propanol provided improved selectivities (entry 18 and 21). Under our optimized conditions, the combination of CuOTf and DBU in THF in the presence of *t*-BuOH or 2-phenyl-2-propanol, the formation of *anti*-**3.6** was achieved in 89 % yield with 90 and 85 % ee, respectively. Although the exact role of OTf anion was not clear at the present time, the use of coordinating solvent, THF, and bulky base, DBU, were expected to stabilize the complexation between reactants and copper(I)/**BD** complex due to chelating and steric effects. The protic additive, *t*-BuOH, was believed to act as a proton shuttle between the complex intermediates and unbound reactants, thus facilitating the faster catalyst turn-over as evidenced by the improved reaction conversion.

Table 7. Optimization of *anti*-Selective Conjugate Addition Reaction



3.1 **3.3a** *anti*-**3.6a** *endo*-**3.7a**



Brucine Diol (**BD**)

Entry	Metal/Base	Additive	Solvent	Yield (%)[a]	**3.6** : **3.7**[b]	ee (%)[c]
1	CuOAc/no base	-	$CHCl_3$	35	1 : 11	48
2	CuCl/Et_3N	-	$CHCl_3$	45	1 : 6	37
3	CuI/DBU	-	$CHCl_3$	45	1 : 10	34
4	CuOTf/Et_3N	-	$CHCl_3$	90	9 : 1	60
5	$Cu(OTf)_2$/Et_3N	-	$CHCl_3$	89	1 : 1	67
6	CuOTf/Et_3N	-	CH_2Cl_2	99	2 : 1	57
7	CuOTf/Et_3N	-	$PhCH_3$	90	2 : 1	11
8	CuOTf/Et_3N	-	THF	95	15 : 1	68
9	CuOTf/NMM	-	THF	50	1 : 1	71
10	CuOTf/Pyridine	-	THF	50	1 : 1	69
11	CuOTf/DMAP	-	THF	35	2 : 1	59
12	CuOTf/DABCO	-	THF	65	14 : 1	67

Table 7. Continued

Entry	Metal/Base	Additive	Solvent	Yield (%)[a]	**3.6** : **3.7**[b]	ee (%)[c]
13	CuOTf/DBU	-	THF	60	10 : 1	75
14	CuOTf/DBN	-	THF	50	4 : 1	72
15	CuOTf/DBU	H_2O	THF	90	15 : 1	77
16	CuOTf/DBU	PhOH	THF	95	>25 : 1	10
17	CuOTf/DBU	*i*-PrOH	THF	85	5 : 1	83
18	CuOTf/DBU	*t*-BuOH	THF	89	>25 : 1	90
19	CuOTf/DBU	d	THF	93	>25 : 1	71
20	CuOTf/DBU	e	THF	90	>25 : 1	73
21	CuOTf/DBU	f	THF	89	>25 : 1	85

a. Isolated yields.

b. Determined by crude ^{1}H NMR.

c. Determined by HPLC using a chiral column.

d. 2,3-Dimethyl-2-butanol.

e. 2,2-Diphenyl-ethanol.

f. 2-Phenyl-2-propanol.

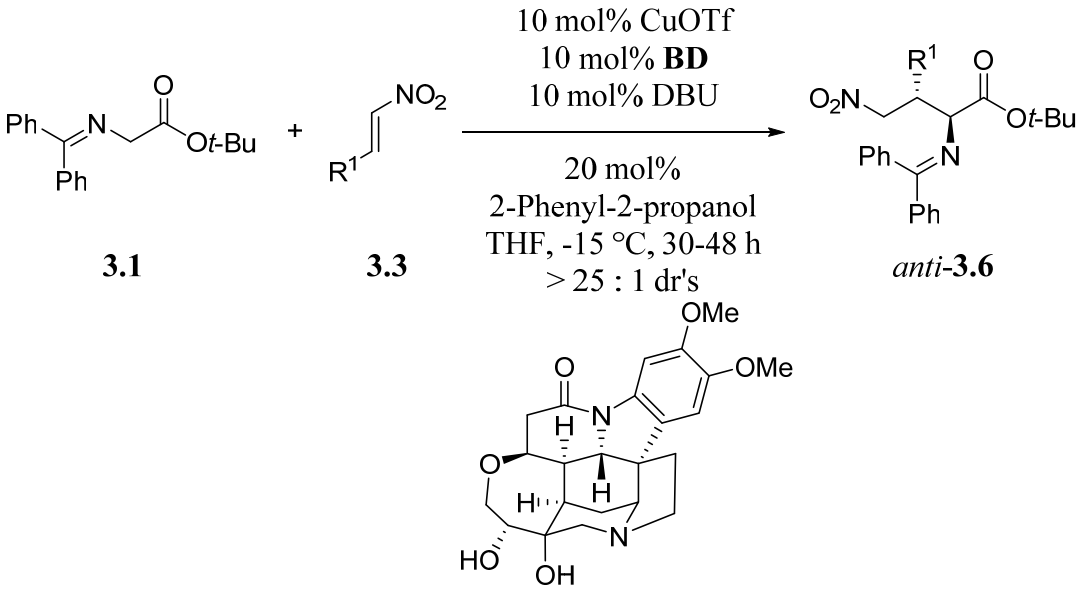
g. CuOTf = $(CuOTf)_2 \bullet C_6H_6$

3.2.3 Substrate Scope of *Anti*-Selective Conjugate Reaction

Table 8 summarizes the scope of the catalytic *anti*-selective conjugate addition of glycine ketimine **3.1**. The formations of *anti*-**3.6** with high enantioselectivities and yields were achieved for various nitroalkene derivatives with different electronic (**3.6a**-**3.6d**)

and steric effects (**3.6e**-**3.6i**). Synthetically satisfactory levels of enantioselectivity (*i.e.* 80-90% ee's) were observed, although sterically demanding substrates proved to be less selective (**3.6g-i**). The use of heteroaromatic nitroalkenes also provided satisfactory selectivities (**3.6j**, **3.6k**) in the absence of protic additives. This result might imply the stronger coordination ability of heteroaromatic nitroalkenes to the catalyst than aryl nitroalkenes. Lower reactivity was observed for aliphatic nitroalkenes (**3.6l**, **3.6m**). While efforts to improve the reaction yields for aliphatic nitroalkenes were made using more than 20 mol % catalyst, due to the facile decomposition of aliphatic nitroalkenes the lower yields of products were obtained. The relative and absolute stereochemistry of *anti*-**3.6** was confirmed to be (2*S*,3*S*) by comparison of its HPLC retention times with those described previously.[20]

Table 8. Scope of the *anti*-Selective Conjugate Addition Reaction



3.1 **3.3** *anti*-**3.6**

Brucine Diol (**BD**)

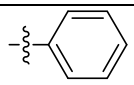
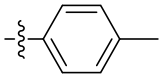
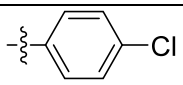
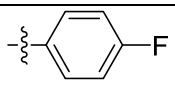
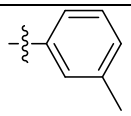
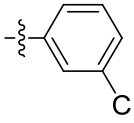
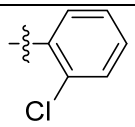
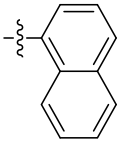
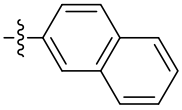
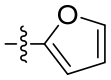
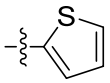
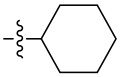
Entry	R^1	*anti*-**3.6**	Yield (%)	ee (%)
1[a]		**3.6a**	89	90
2		**3.6b**	84	88
3		**3.6c**	82	84
4[a]		**3.6d**	68	80
5		**3.6e**	81	88
6		**3.6f**	85	88

Table 8. Continued

Entry	R^1	*anti*-**3.6**	Yield (%)	ee (%)
7		**3.6g**	83	82
8		**3.6h**	73	81
9[b]		**3.6i**	88	80
10[c]		**3.6j**	83	86
11[c]		**3.6k**	83	81
12[b]		**3.6l**	52	80
13[b]		**3.6m**	49	80

a. Reaction used 60 mol % *t*-BuOH.

b. Reaction used 20 mol % catalyst.

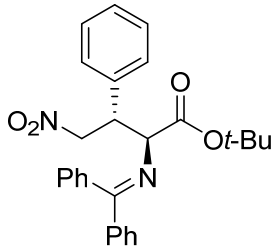
c. No additive was used.

3.3 Conclusion

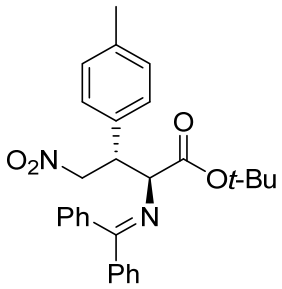
In summary, we have developed a stereodivergent catalytic asymmetric conjugate reaction for glycine (ket)imine with nitroalkenes. Both *syn*- and *anti*-addition products were obtained with high diastereoselectivity and enantioselectivity. The stereoselective formation of *exo*-**3.5** and *endo*-**3.7** was also achieved from *syn*-**3.4** and *anti*-**3.6**, respectively, under the base catalysis. These results clearly demonstrated the stepwise nature of the [3+2] cycloaddition reaction of *N*-metalated azomethine ylides. The preparation of a diverse array of chiral compounds using various chiral catalyst species, particularly those derived from a single chiral source (*i.e.* **BD**), should advance our molecular level understanding of asymmetric catalysis.

3.4 Experimental Section

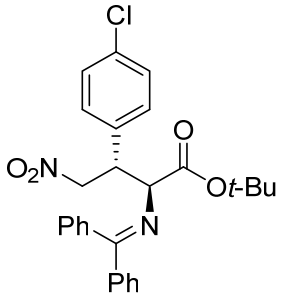
General Procedure A for the Synthesis of *Anti*-Conjugated Products



tert-Butyl (2*S*,3*S*)-2-((Diphenylmethylene)amino)-4-nitro-3-phenylbutanoate (**3.6a**). $(CuOTf)_2 \bullet C_6H_6$ (10 mol %, 25 mg) and brucine diol (**BD**) were added to a 10 mL Schlenk flask. Dry THF (2.0 mL) was then added to the flask at 0 °C, followed by addition of DBU (10 mol %, 7.5 μL). The solution was stirred for 4 h at this temperature. The resulting solution was cooled to -15 °C, and glycine ketimine **3.1** (0.5 mmol, 148 mg) was added and stirred for 10 min. After which, to the resulting solution, 1-((*E*)-2-nitrovinyl)benzene (0.5 mmol, 74 mg) was added followed by the addition of *tert*-butanol additive (60 mol%, 28 μL). The solution was stirred continuously at -15 °C for 48-60 h. The reaction mixture was then subjected to chromatography on a short silica column (5-10 % ethyl acetate in hexanes); the yield of the title compound was 89%. ^{1}H NMR and ^{13}C NMR spectra for this compound are consistent with previously reported data in the literature.[20] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.64-7.63 (m, 2H), 7.45-7.42 (m, 1H), 7.38-7.33 (m, 3H), 7.29-7.26 (m, 2H), 7.25-7.22 (m, 3H), 7.15-7.13 (m, 2H), 6.65 (d, J = 7 Hz, 2H), 5.15-5.07 (m, 2H), 4.29 (dd, J = 9.5, 4.5 Hz, 1H), 4.17 (d, J = 4.5 Hz, 1H), 1.37 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 172.3, 168.9, 138.8, 137.5, 135.6, 130.7, 128.8, 128.6, 128.5, 128.3, 128.2, 128.2, 127.7, 127.4, 82.2, 76.5, 69.2, 46.9, 27.9.

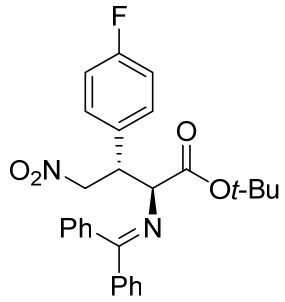


tert-Butyl (2*S*,3*S*)-2-((Diphenylmethylene)amino)-4-nitro-3-(*p*-tolyl)butanoate (**3.6b**). Product was prepared with 1-methyl-4-((*E*)-2-nitrovinyl)benzene (0.5 mmol, 82 mg) by General Procedure A except using 2-phenyl-2-propanol (20 mol%, 14 μL) as an additive. The crude product was subjected to on a short silica column (5-10% ethyl acetate in hexanes); the yield of the title compound was 84%. ^{1}H NMR and ^{13}C NMR spectra for this compound are consistent with previously reported data in the literature.[20] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.66 -7.64 (m, 2H), 7.45-7.41 (m, 1H), 7.37-7.33 (m, 3H), 7.31 - 7.25 (m, 2H), 7.06 - 7.02 (m, 4H), 6.69 (d, J = 7.0 Hz, 2H), 5.12 - 5.05 (m, 2H), 4.29 – 4.26 (m, 1H), 4.18 (d, J = 4.5 Hz, 1H), 2.29 (s, 3H), 1.37 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 172.1, 168.9, 138.8, 137.2, 135.5, 134.3, 130.6, 129.2, 128.8, 128.5, 128.2, 128.1, 127.3, 124.3, 82.0, 76.6, 69.2, 46.5, 27.8, 20.9.



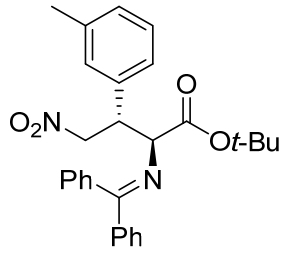
tert-Butyl (2*S*,3*S*)-3-(4-chlorophenyl)-2-((diphenylmethylene)amino)-4-nitrobutanoate (**3.6c**). Product was prepared with 1-chloro-4-((*E*)-2-nitrovinyl)benzene (0.5 mmol, 92

mg) by General Procedure A except that 2-phenyl-2-propanol (20 mol%, 14 μL) was used as an additive. The crude product was subjected to chromatography on a short silica column (5-10% ethyl acetate in hexanes); the yield of the title compound was 82%. ^{1}H NMR and ^{13}C NMR spectra for this compound are consistent with previously reported data in the literature.[20] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.65-7.64 (m, 2H), 7.47-7.43 (m, 1H), 7.39-7.31 (m, 5H), 7.22 (dd, *J* = 7.0, 1.5 Hz, 2H), 7.11 (dd, *J* = 7.0, 1.5 Hz, 2H), 6.73-6.71 (m, 2H), 5.13-5.07 (m, 2H), 4.30-4.26 (m, 1H), 4.17 (d, *J* = 4.5 Hz, 1H), 1.39 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 172.6, 168.6, 138.6, 136.0, 135.4, 133.6, 130.9, 129.7, 128.8, 128.8, 128.7, 128.3, 128.2, 127.3, 82.4, 76.3, 68.9, 46.2, 27.8.

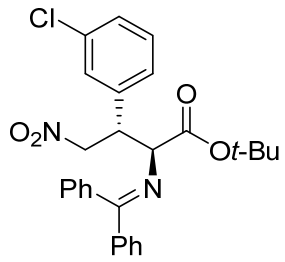


tert-Butyl (2*S*,3*S*)-2-((Diphenylmethylene)amino)-3-(4-fluorophenyl)-4-nitrobutanoate (**3.6d**). Product was prepared with 1-fluoro-4-((*E*)-2-nitrovinyl)benzene (0.5 mmol, 83 mg) by General Procedure A. The crude product was subjected to chromatography on a short silica column (5-10% ethyl acetate in hexanes); the yield of the title compound was 68%. ^{1}H NMR and ^{13}C NMR spectra for this compound are consistent with previously reported data in the literature.[20] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.67 (d, *J* = 8.0 Hz, 2H), 7.46 – 7.32 (m ,6H), 7.16 (dd, *J* = 8.0, 5.5 Hz, 2H), 6.96 (t, *J* = 8.0 Hz, 2H), 6.75 (d, *J* = 7.0 Hz, 2H), 5.10 (d, *J* = 7.5 Hz, 2H), 4.32 (dd, *J* = 12.0, 7.5 Hz, 1H), 4.19 (d, *J* = 4.5 Hz,

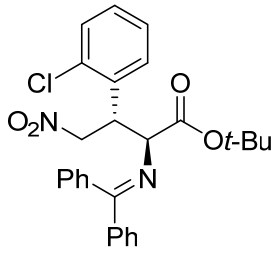
1H), 1.40 (s, 9H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 172.4, 168.6, 162.1 (d, J = 245 Hz), 138.6, 135.4, 133.2(d, J = 2.95 Hz), 130.8, 129.9(d, J = 8.0 Hz), 128.7, 128.6, 128.3, 128.1, 127.2, 115.4 (d, J = 21.1 Hz), 82.2, 76.5, 69.0, 46.1, 27.7.



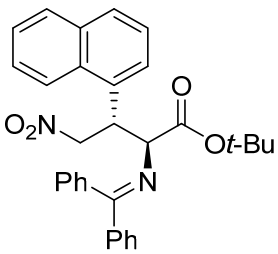
tert-Butyl (2*S*,3*S*)-2-((Diphenylmethylene)amino)-4-nitro-3-(*m*-tolyl)butanoate (**3.6e**). Product was prepared with 1-methyl-3-((*E*)-2-nitrovinyl)benzene (0.5 mmol, 82 mg) by General Procedure A except using 2-phenyl-2-propanol (20 mol%, 14 μL) as an additive. The crude product was subjected to chromatography on a short silica column (5-10% ethyl acetate in hexanes); the yield of the title compound was 81%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.65 - 7.63 (m, 2H), 7.41 - 7.40 (m, 1H), 7.36 – 7.33 (m, 3H), 7.29 – 7.26 (m, 2H), 7.11 (t, J = 7.8 Hz, 1H), 7.03 (d, J = 7.6 Hz, 1H), 6.94 (d, J = 2.0 Hz, 1H), 6.64 (d, J = 1.8 Hz, 1H), 5.15 – 5.07 (m, 2H), 4.29 – 4.25 (m, 1H), 4.17 (d, J = 4.5 Hz, 1H), 2.22 (s, 3H), 1.38 (s, 9H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 172.2, 169.0, 138.9, 138.2, 137.3, 135.7, 130.7, 129.4, 128.8, 128.6, 128.5, 128.4, 128.2, 128.2, 127.4, 125.0, 82.2, 76.5, 69.3, 46.8, 27.9, 21.3; IR (neat, cm^{-1}): 3059, 3025, 2978, 2929, 1732, 1533, 1446, 1150, 701; HRMS-CI m/z: 459.2283 [$(M+H)^{+}$; calcd for $C_{28}H_{31}N_2O_4$: 459.2278].



tert-Butyl (2*S*,3*S*)-3-(3-Chlorophenyl)-2-((diphenylmethylene)amino)-4-nitrobutanoate (**3.6f**). Product was prepared with 1-chloro-3-((E)-2-nitrovinyl)benzene (0.5 mmol, 92 mg) by General Procedure A except using 2-phenyl-2-propanol (20 mol%, 14 μL) as an additive. The crude product was subjected to chromatography on a short silica column (5-10% ethyl acetate in hexanes); the yield of the title compound was 85%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.64 - 7.62 (m, 2H), 7.46 - 7.42 (m, 1H), 7.39 - 7.35 (m, 3H), 7.33 – 7.30 (m, 2H), 7.24 – 7.22 (m, 1H), 7.20 – 7.16 (m, 1H), 7.14 – 7.13 (m, 1H), 7.05 (d, J = 7.6 Hz, 1H), 6.7 (d, J = 6.8 Hz, 2H), 5.09 – 5.08 (m, 2H), 4.28 – 4.24 (m, 1H), 4.15 (d, J = 4.5 Hz, 1H), 1.38 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 172.7, 168.6, 139.6, 138.7, 135.5, 134.5, 130.9, 129.9, 128.8, 128.8, 128.7, 128.3, 128.2, 127.9, 127.3, 126.2, 82.5, 76.1, 68.9, 46.5, 27.9; IR (neat, cm^{-1}): 3060, 2978, 2932, 1733, 1554, 1369, 1151, 696; HRMS-CI m/z: 479.1729 [$(M+H)^+$; calcd for $C_{27}H_{28}ClN_2O_4$: 479.1732].

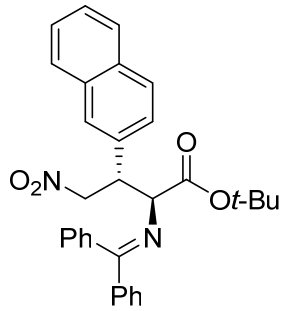


tert-Butyl (2*S*,3*S*)-3-(2-Chlorophenyl)-2-((diphenylmethylene)amino)-4-nitrobutanoate (**3.6g**). Product was prepared with 1-chloro-2-((*E*)-2-nitrovinyl)benzene (0.5 mmol, 92 mg) by General Procedure A except using 2-phenyl-2-propanol (20 mol%, 14 μL) as an additive. The crude product was subjected to chromatography on a short silica column (5-10% ethyl acetate in hexanes); the yield of the title compound was 83%. ^{1}H NMR and ^{13}C NMR spectra for this compound are consistent with previously reported data in the literature.[20] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.68 (d, J = 7.4 Hz, 2H), 7.31 (d, J = 7.3 Hz, 1H), 7.41 – 7.37 (m, 4H), 7.34 - 7.29 (m, 2H), 7.27 – 7.18 (m, 3H), 6.60 (d, J = 6.0 Hz, 2H), 5.36 – 5.21 (m, 2H), 4.97 – 4.93 (m, 1H), 4.37 (d, J = 4.0 Hz, 1H), 1.46 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 172.6, 168.7, 138.6, 135.4, 134.8, 134.4, 130.7, 130.0, 128.7, 128.7, 128.6, 128.2, 128.1, 127.1, 126.7, 124.2, 82.2, 75.0, 66.6, 42.7, 27.8.



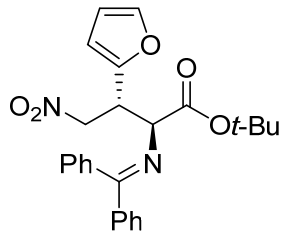
tert-Butyl (2*S*,3*S*)-2-((Diphenylmethylene)amino)-3-(naphthalen-1-yl)-4-nitrobutanoate (**3.6h**). Product was prepared with 1-((*E*)-2-nitrovinyl)naphthalene (0.5 mmol, 99 mg) by

General Procedure A except using 2-Phenyl-2-propanol (20 mol%, 14 μL) as an additive. The crude product was subjected to chromatography on a short silica column (5-10% ethyl acetate in hexanes); the yield of the title compound was 73%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.03 (d, 7.6 Hz, 1H), 7.87 (d, *J* = 8.3 Hz, 1H), 7.78 (dd, *J* = 6.8, 2.4 Hz, 1H), 7.64 (d, *J* = 7.9 Hz, 2H), 7.49 - 7.42 (m, 3H), 7.38 - 7.35 (m, 4H), 7.14 (t, *J* = 7.4 Hz, 1H), 6.97 (t, *J* = 7.3 Hz, 1H), 6.31 (s, 2H), 5.43 (dd, *J* = 12.2, 8.6 Hz, 1H), 5.35 - 5.28 (m, 2H), 4.35 (d, *J* = 2.8 Hz, 1H), 1.38 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 172.4, 169.1, 138.7, 135.1, 134.0, 133.0, 131.4, 130.6, 128.8, 128.7, 128.2, 128.1, 128.0, 127.8, 126.8, 126.5, 125.7, 124.9, 124.3, 122.2, 82.2, 75.6, 67.8, 31.7, 27.8; IR (neat, cm^{-1}): 3058, 2977, 2931, 1733, 1553, 1151, 781, 697; HRMS-CI m/z: 495.2299 [$(M+H)^+$; calcd for $C_{31}H_{31}N_2O_4$: 495.2278].

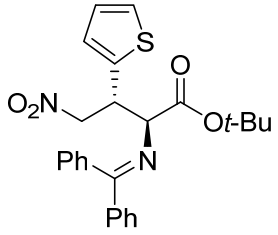


tert-Butyl (2*S*,3*S*)-2-((Diphenylmethylene)amino)-3-(naphthalen-2-yl)-4-nitrobutanoate (**3.6i**). Product was prepared using $(CuOTf)_2 \bullet C_6H_6$ (20 mol%, 50 mg), **BD** (20 mol%, 42 mg), 2-((*E*)-2-nitrovinyl)naphthalene (0.5 mmol, 99 mg) by General Procedure A except using 2-phenyl-2-propanol (20 mol%, 14 μL) as an additive. The crude product was subjected to chromatography on a short silica column (5-10% ethyl acetate in hexanes); the yield of the title compound was 88%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.85 – 7.68 (m,

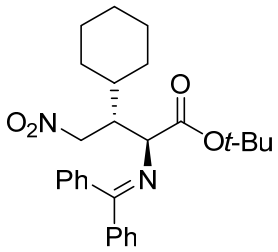
6H), 7.52 – 7.49 (m, 3H), 7.45 – 7.42 (m, 2H), 7.37 - 7.33 (m, 2H), 7.23 (t, J = 7.9 Hz, 2H), 6.64 (d, J = 7.0 Hz, 2H), 5.33 – 5.21 (m, 2H), 4.55 – 4.51 (m, 1H), 4.35 (d, J = 4.6 Hz, 1H), 1.43 (s, 9H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 172.4, 168.9, 138.8, 135.5, 134.9, 133.2, 132.7, 130.8, 128.8, 128.5, 128.3, 128.2, 128.2, 127.8, 127.5, 127.5, 127.3, 126.2, 126.0, 125.9, 82.3, 76.5, 69.2, 47.0, 27.9; IR (neat, cm^{-1}): 3058, 3020, 2978, 2930, 1730, 1553, 1151, 751, 698; HRMS-CI m/z: 495.2291 [$(M+H)^+$; calcd for $C_{31}H_{31}N_2O_4$: 495.2278].



tert-Butyl (2*S*,3*S*)-2-((Diphenylmethylene)amino)-3-(furan-2-yl)-4-nitrobutanoate (**3.6j**). Product was prepared with 2-((*E*)-2-nitrovinyl)furan (0.5 mmol, 69 mg) by General Procedure A without addition of additives. The crude product was subjected to chromatography on a short silica column (5-10% ethyl acetate in hexanes); the yield of the title compound was 83%. ^{1}H NMR and ^{13}C NMR spectra for this compound are consistent with previously reported data in the literature.[20] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.60 (d, J = 8.3 Hz, 2H), 7.45 – 7.33 (m, 6H), 7.27 (dd, J = 2.0, 0.5 Hz, 1H), 6.86 (d, J = 6.9 Hz, 2H), 6.26 (dd, J = 3.0, 1.5 Hz, 1H), 6.12 (d, J = 3.0 Hz, 1H), 5.06 – 5.04 (m, 2H), 4.44 – 4.40 (m, 1H), 4.33 (d, J = 4.0 Hz, 1H), 1.42 (s, 9H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ 172.5, 168.7, 151.1, 142.0, 138.9, 135.6, 130.7, 128.9, 128.7, 128.3, 128.1, 127.6, 110.5, 107.6, 82.4, 75.1, 67.2, 40.9, 27.9.

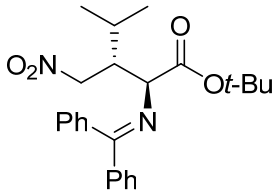


tert-Butyl (2*S*,3*S*)-2-((Diphenylmethylene)amino)-4-nitro-3-(thiophen-2-yl)butanoate (**3.6k**). Product was prepared with 2-((*E*)-2-nitrovinyl)thiophene (0.5 mmol, 78 mg) by General Procedure A without addition of additives. The crude product was subjected to chromatography on a short silica column (5-10% ethyl acetate in hexanes); the yield of the title compound was 83%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.69 (d, *J* = 7.8 Hz, 2H), 7.48 – 7.44 (m, 1H), 7.40 – 7.33 (m, 5H), 7.18 (dd, *J* = 5.0, 0.8 Hz, 1H), 6.91 – 6.88 (m, 2H), 6.84 (d, *J* = 7.0 Hz, 2H), 5.12 (d, *J* = 7.2 Hz, 2H), 4.63 – 4.60 (m, 1H), 4.27 (d, *J* = 3.6 Hz, 1H), 1.45 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 172.9, 168.6, 140.0, 138.8, 135.6, 130.8, 128.9, 128.6, 128.3, 128.1, 127.3, 126.6, 126.1, 125.1, 82.4, 77.8, 69.1, 42.5, 27.8; IR (neat, cm^{-1}): 3061, 3020, 3004, 2979, 2932, 1731, 1554, 1151, 698; HRMS-CI m/z: 451.1685 [$(M+H)^+$; calcd for $C_{25}H_{27}N_2O_4S$: 451.1629].



tert-Butyl (2*S*,3*S*)-3-Cyclohexyl-2-((diphenylmethylene)amino)-4-nitrobutanoate (**3.6l**). Product was prepared using $(CuOTf)_2 \bullet C_6H_6$ (20 mol%, 50 mg), **BD** (20 mol%, 42 mg), ((*E*)-2-nitrovinyl)cyclohexane (0.5 mmol, 78 mg) and *tert*-butanol (20 mol%, 9.0 μL) by General Procedure A. The crude product was subjected to chromatography on a short

silica column (5-10% ethyl acetate in hexanes); the yield of the title compound was 52%. ^{1}H NMR (C_6D_6, 500 MHz): δ 7.77 - 7.75 (m, 2H), 7.14 – 7.05 (m, 8H), 5.03 (dd, *J* = 14.2, 4.1 Hz, 1H), 4.53 (dd, *J* = 9.2, 6.8 Hz, 1H), 4.32 (d, *J* = 2.9 Hz, 1H), 3.12 – 3.08 (m, 1H), 1.52 – 1.42 (m, 5H), 1.33 (s, 9H), 1.29 – 1.20 (m, 1H), 0.97 – 0.84 (m, 3H), 0.80 – 0.68 (m, 2H); ^{13}C{^{1}H} NMR (C_6D_6, 125 MHz): δ 171.3, 170.5, 139.7, 137.0, 130.9, 129.3, 128.9, 128.7, 128.5, 127.9, 81.6, 76.3, 66.1, 46.5, 39.9, 30.5, 30.1, 27.9, 26.6, 26.6, 26.4; IR (neat, cm^{-1}): 3060, 3020, 2977, 2929, 2854, 1732, 1551, 1448, 1368, 1154, 845, 704; HRMS-CI m/z: 451.2594 [(M+H)$^+$; calcd for $C_{27}H_{35}N_2O_4$: 451.2591].



tert-Butyl (2*S*,3*S*)-2-((Diphenylmethylene)amino)-4-methyl-3-(nitromethyl)pentanoate (**3.6m**). Product was prepared using $(CuOTf)_2 \bullet C_6H_6$ (20 mol%, 50 mg), **BD** (20 mol%, 42 mg), (*E*)-3-methyl-1-nitrobut-1-ene (0.5 mmol, 58 mg) and *tert*-butanol (20 mol%, 9.0 μL) by General Procedure A. The crude product was subjected to chromatography on a short silica column (5-10% ethyl acetate in hexanes); the yield of the title compound was 49%. ^{1}H NMR (C_6D_6, 500 MHz): δ 7.75 - 7.74 (m, 2H), 7.12 – 7.04 (m, 8H), 5.01 (dd, *J* = 14.2, 4.2 Hz, 1H), 4.48 (dd, *J* = 14.2, 6.6 Hz, 1H), 4.25 (d, *J* = 3.0 Hz, 1H), 3.08 – 3.04 (m, 1H), 1.60 – 1.53 (m, 1H), 1.31 (s, 9H), 0.68 (d, *J* = 6.8 Hz, 3H), 0.63 (d, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (C_6D_6, 125 MHz): δ 171.3, 170.3, 139.6, 136.9, 130.9, 129.3, 128.8, 128.7, 128.4, 127.9, 81.7, 76.4, 66.3, 47.1, 30.0, 27.8, 20.0, 19.7; IR (neat, cm^{-1}): 3060,

3016, 2967, 2931, 2873, 1731, 1552, 1369, 1152, 697; HRMS-CI m/z: 411.2272 [$(M+H)^+$; calcd for $C_{24}H_{31}N_2O_4$: 411.2278].

Conditions for Determination of Enantiomeric Excess

(1) *tert*-Butyl (2*S*,3*S*)-2-((Diphenylmethylene)amino)-4-nitro-3-phenylbutanoate (**3.6a**): t_{major} =15.96 min t_{minor} = 17.69 min (AD-H Column, hexanes/2-propanol : 99/1, 0.7 mL/min)

(2) *tert*-Butyl (2*S*,3*S*)-2-((Diphenylmethylene)amino)-4-nitro-3-(p-tolyl)butanoate (**3.6b**): t_{major} =13.73 min t_{minor} = 15.28 min (AD-H Column, hexanes/2-propanol : 99/1, 0.7 mL/min)

(3) *tert*-Butyl (2*S*,3*S*)-3-(4-Chlorophenyl)-2-((diphenylmethylene)amino)-4-nitrobutanoate (**3.6c**): t_{major} =14.73 min t_{minor} = 19.60 min (AD-H Column, hexanes/2-propanol : 99/1, 0.7 mL/min)

(4) *tert*-Butyl (2*S*,3*S*)-2-((Diphenylmethylene)amino)-3-(4-fluorophenyl)-4-nitrobutanoate (**3.6d**): t_{major} =6.62 min t_{minor} = 7.97 min (AD-H Column, hexanes/2-propanol : 90/10, 0.7 mL/min)

(5) *tert*-Butyl (2*S*,3*S*)-2-((Diphenylmethylene)amino)-4-nitro-3-(m-tolyl)butanoate (**3.6e**): t_{minor} =13.45 min t_{major} = 14.35 min (AD-H Column, hexanes/2-propanol : 99/1, 0.7 mL/min)

(6) *tert*-Butyl (2*S*,3*S*)-3-(3-Chlorophenyl)-2-((diphenylmethylene)amino)-4-nitrobutanoate (**3.6f**): t_{minor} =14.24 min t_{major} = 15.34 min (AOD-H Column, hexanes/2-propanol : 99/1, 0.7 mL/min)

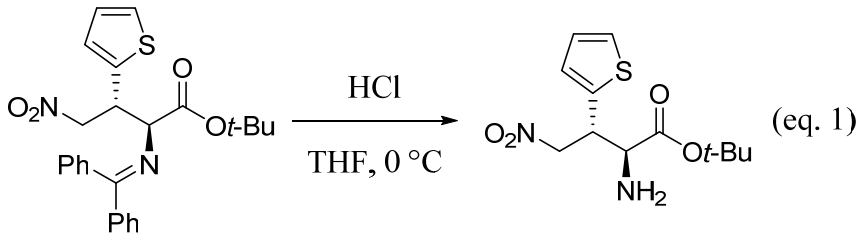
(7) *tert*-Butyl (2*S*,3*S*)-3-(2-Chlorophenyl)-2-((diphenylmethylene)amino)-4-nitrobutanoate (**3.6g**): t_{minor} =9.09 min t_{major} = 11.49 min (AD-H Column, hexanes/2-propanol : 99/1, 0.7 mL/min)

(8) *tert*-Butyl (2*S*,3*S*)-2-((Diphenylmethylene)amino)-3-(naphthalen-1-yl)-4-nitrobutanoate (**3.6h**): t_{minor} =11.63 min t_{major} = 13.21 min (AD-H Column, hexanes/2-propanol : 98/2, 0.5 mL/min)

(9) *tert*-Butyl (2*S*,3*S*)-2-((Diphenylmethylene)amino)-3-(naphthalen-2-yl)-4-nitrobutanoate (**3.6i**): t_{major} = 6.97 min t_{minor} = 9.17 min (AD-H Column, hexanes/2-propanol : 90/10, 0.7 mL/min)

(10) *tert*-Butyl (2*S*,3*S*)-2-((Diphenylmethylene)amino)-3-(furan-2-yl)-4-nitrobutanoate (**3.6j**): t_{minor} = 6.10 min t_{major} = 7.34 min (AD-H Column, hexanes/2-propanol : 90/10, 0.7 mL/min)

(11) *tert*-Butyl (2*S*,3*S*)-2-((Diphenylmethylene)amino)-4-nitro-3-(thiophen-2-yl)butanoate (**3.6k**): Determined with the product by one further transformation in eq. 1. t_{minor} = 11.74 min t_{major} = 13.77 min (AD-H Column, hexanes/2-propanol : 80/20, 0.5 mL/min)



(eq. 1)

tert-Butyl (2*S*,3*S*)-2-Amino-4-nitro-3-(thiophen-2-yl)butanoate (*anti*-**3.6k'**): **3.6k** (22.5 mg, 0.05 mmol) was dissolved in THF (0.5 mL), and 1N HCl (0.5 mL) was added at 0 °C.

After the mixture was stirred at 0 °C for 1h, THF was removed under reduced pressure. The resulting aqueous solution was washed with ether (3 × 10 mL) and neutralized with $NaHCO_3$. The mixture was then extracted three times with 10 ml of CH_2Cl_2 (3 × 10 mL). The organic layers of these three extractions were combined and then dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the desired product **3.6k'** (13.3 mg, 93 % yield, dr > 99 : 1, 81 % ee) was obtained. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.24 (t, *J* = 3.0 Hz, 1H), 6.95 – 6.93 (m, 2H), 4.95 (dd, *J* = 13.0, 5.5 Hz, 1H), 4.71 (dd, *J* = 13.0, 9.0 Hz, 1H), 4.14 – 4.09 (m, 1H), 3.62 (d, *J* = 7.0 Hz, 1H), 1.64 (s, 2H), 1.36 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 172.3, 138.9, 126.8, 126.7, 125.3, 82.3, 78.1, 58.4, 43.5, 27.7; IR (neat, cm^{-1}): 3391, 3324, 3111, 3078, 2978, 2933, 1728, 1554, 1371, 1251, 1155, 844, 704; HRMS-CI m/z: 287.1058 [$(M+H)^+$; calcd for $C_{12}H_{19}N_2O_4S$: 287.1060].

(12) *tert*-Butyl (2*S*,3*S*)-3-Cyclohexyl-2-((diphenylmethylene)amino)-4-nitrobutanoate (**3.6l**): t_{minor} =23.53 min t_{major} = 24.49min (OD-H Column, hexanes/2-propanol : 99/1, 0.2 mL/min)

(13) *tert*-Butyl (2*S*,3*S*)-2-((Diphenylmethylene)amino)-4-methyl-3-(nitromethyl)pentanoate (**3.6m**): t_{minor} =9.81 min t_{major} = 10.17 min (OD-H Column, hexanes/2-propanol : 99/1, 0.5 mL/min)

3.5 References

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CHAPTER 4. ENANTIODIVERGENT APPROACHES TO *ENDO*-PYRROLIDINES USING COPPER-BRUCINE DIOL COMPLEXES

4.1 Introduction

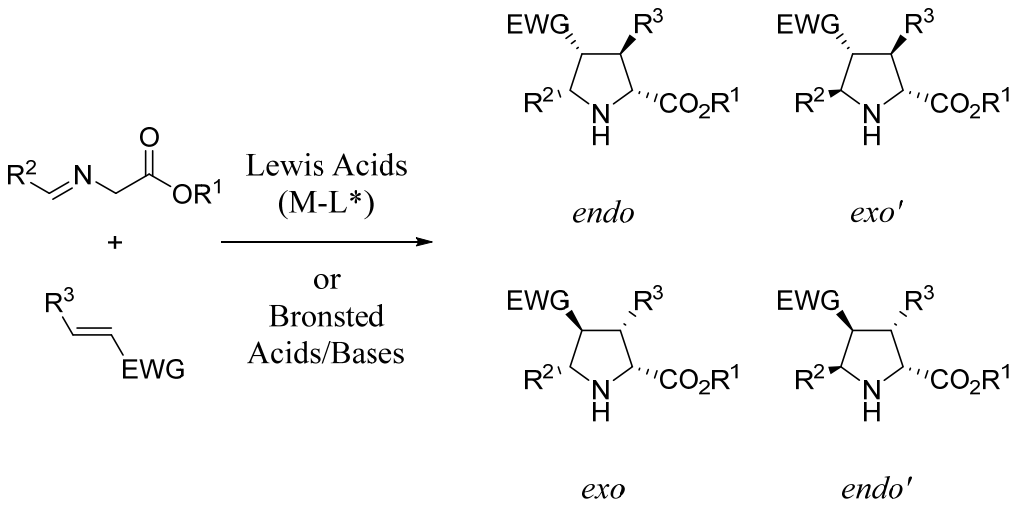
4.1.1 Synthesis of Chiral Pyrrolidine Derivatives

Chiral pyrrolidines are one of the key structural motifs present in many biologically important compounds,[1-4] and they often constitute as the core structure of many organocatalysts.[5-7] Among the synthetic strategies developed for chiral pyrrolidines, the catalytic asymmetric [3+2] cycloaddition reactions of azomethine ylides and activated alkenes directly produce enantiomeric pyrrolidines with a diverse array of functional groups.[8-10] The use of both chiral metal catalysts[10-13] and organocatalysts[14-16] have been extensively investigated for the synthesis of chiral pyrrolidines. Furthermore, intramolecular Mannich reaction, a powerful method for the preparation of azacyclic products from acyclic precursors, has been utilized for the synthesis of pyrrolidine derivatives.[17,18] Although Mannich reaction is commonly used for the synthesis of pyrrolidine derivatives,[19] there exists only few Mannich reaction examples that utilize the asymmetric conjugate addition products of glycine (ket)imines for the preparation of chiral pyrrolidines.[20]

4.1.2 Stereodivergent Synthesis of Pyrrolidine Derivatives

Theoretically, the [3+2] cycloaddition reactions of azomethine ylides with alkenescan provide up to four diastereomers, namely *exo*-, *endo*-, *exo'*-, and *endo'*-

products (Scheme 21). The notation *endo* signifies the "*syn*" relationship between the R^2 of glycine ester and the electron-withdrawing-group (EWG) of alkene. Consequently, the *exo* implies the "*anti*" relationship between the R^2 of glycine ester and the electron-withdrawing-group (EWG) of alkene. The notion *endo'* and *exo'* indicates the "*anti*" relationship between the ester moiety and the R^2 of glycine ester.

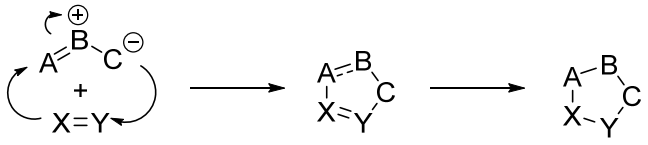


EWG = -COOR, $-NO_2$, -RCO, $-SO_2R$

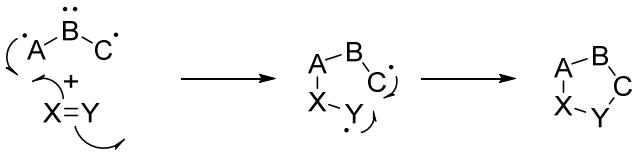
Scheme 21. The [3+2] Cycloaddition Reaction Pathway to Pyrrolidine Derivatives

In 2005, Carretero *et al.* reported the first example of *exo*-selective pyrrolidine synthesis using the catalytic asymmetric [3+2] cycloaddition reaction of azomethine ylides and nitroalkenes.[21] Subsequently, in 2006 Hou *et al.* demonstrated the switch of *endo*/*exo* selectivity by tuning the electron density of a chiral ligand.[12] In 2010, Arai *et al.* reported an *exo'*-selective pyrrolidine synthesis.[22] It is interesting to study the relationship between the stereochemical outcome and the reaction pathway of [3+2] cycloaddition

reactions of glycinates with electron-deficient alkenes since there is not an experimental consensus for either a concerted (Scheme 22) or a stepwise (Scheme 23) reaction pathway.[11,23,24]

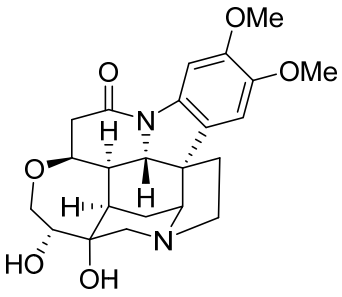


Scheme 22. Concerted Reaction Pathway[25]



Scheme 23. Stepwise Reaction Pathway[26]

In this chapter, we present the copper-brucine diol (**BD**) catalyzed concerted *endo*-selective [3+2] cycloaddition reactions between glycine imines and nitroalkenes, leading to the discovery of the substrate-controlled enantiodivergent [3+2] cycloaddition reactions (Figure 7).



Brucine Diol (**BD**)

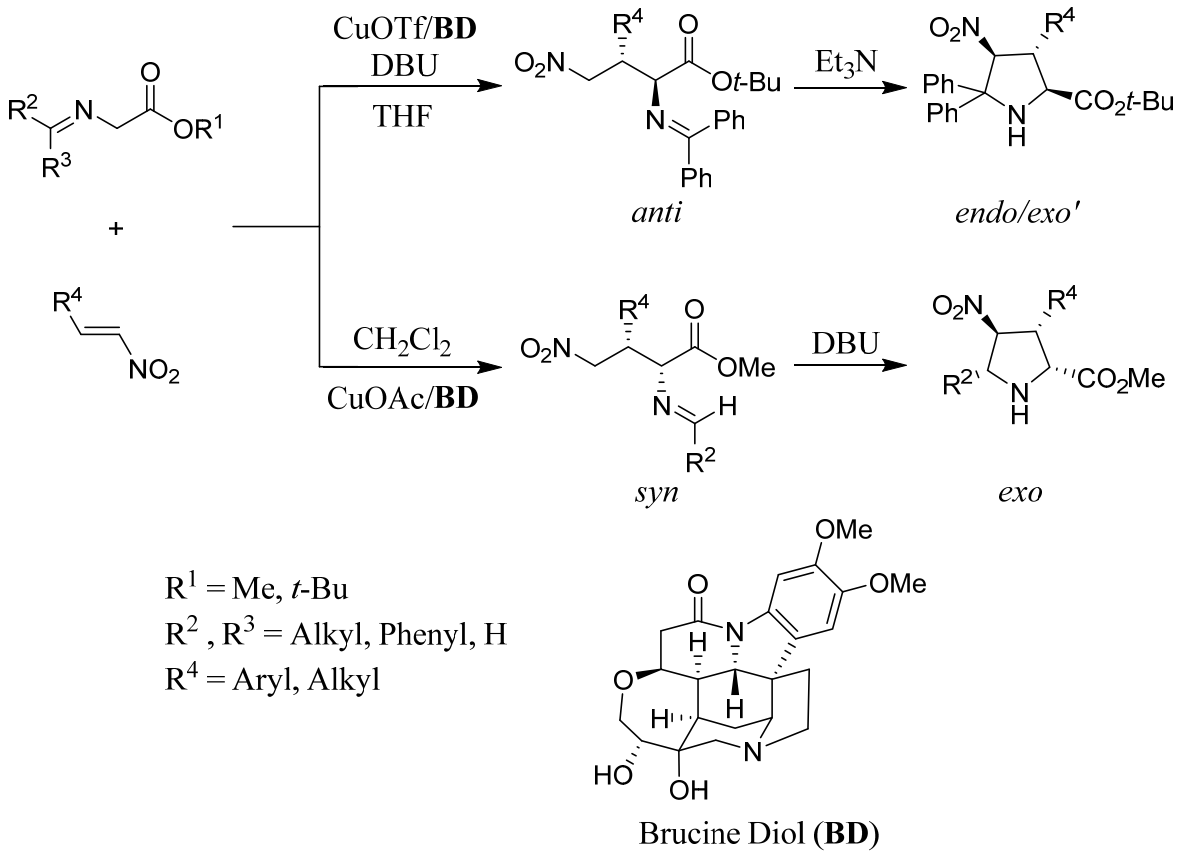
Figure 7. Brucine Diol (**BD**)

4.2 Results and Discussion

4.2.1 The *endo*-Selective [3+2] Cycloaddition Reaction

4.2.1.1 Optimization of *endo*-Selective [3+2] Cycloaddition Reaction

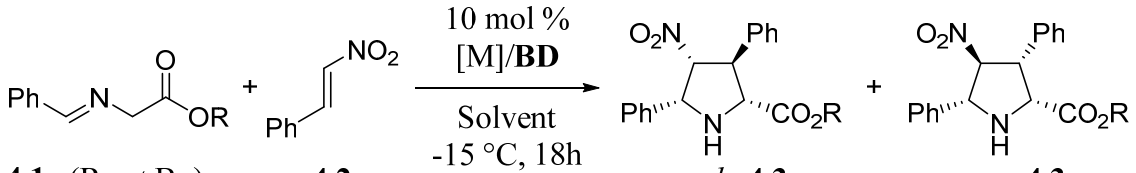
We had previously reported a diastereodivergent catalytic asymmetric conjugate addition reaction (Scheme 24).[27] Results of that study were consistent with the stepwise [3+2] cycloaddition reaction mechanism for *exo*-pyrrolidines. However, because we could not prepare *anti* conjugate addition products from the reaction between glycine imines and nitroalkenes,[28,29] thus, a related mechanistic assertion for *endo*/*exo'*-pyrrolidines required further investigation.



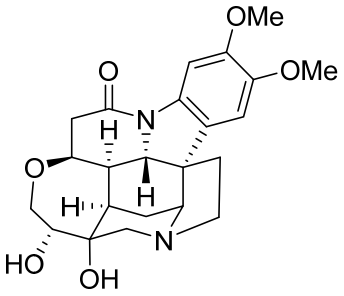
Scheme 24. Stereodivergent Catalytic Asymmetric Conjugate Addition Reactions

From the substrate-controlled diastereoselective conjugate addition reactions, we noted the exclusive formation of *anti*-products from glycine ketimine and *syn*-products from glycine imine. Thus, we investigated the reaction outcome of glycine imines **4.1a-c** under our *anti*-selective conjugate addition reaction conditions (Table 9). Since the ester moiety of glycine imines **4.1** had a great influence on the enantioselectivity of products (Entries 1-3), the use of *tert*-butyl glycine imine **4.1a** produced **4.3Ba** with the lowest enantiomeric excess (ee) of 52%, while the use of methyl glycine imine **4.1c** produced **4.3Ma** at 77% ee (Entry 3) and 72% ee (Entry 4) under another *anti*-selective conjugate addition condition as described previously.[27] In addition, the preferential formation of *endo*-**4.3** instead of *exo*-**4.3** was observed. Thus, glycine imine **4.1c** was chosen for further optimization efforts. Since the effect of protic additives to the observed selectivity was minimal (entry 5), we examined solvent effect in the absence of additives (entries 6-8). No significant advantage in stereoselectivity was observed using other solvent systems; therefore, we screened the effect of base (entries 9-10). Although the use of DBN as base improved the enantioselectivity of *endo*-**4.3Ma** to 82% ee with 13 : 1 ratio of diastereoselectivity (dr) (entry 10), the oxidation state of copper ion did not have much influence to the observed stereoselectivity (entries 11-12). Furthermore, elevated reaction temperatures showed much faster reaction conversions, but with reduced enantioselectivity and diastereoselectivity of *endo*-**4.3Ma** (entry 13). Finally, the catalyst loading was investigated, and the use of 20 mol% of CuOTf and **BD** was identified as the optimal condition to provide the diastereoselective formation of *endo*-**4.3Ma** in 84% ee with > 25 : 1 dr (entry 14).

Table 9. Optimization of *endo*-Selective [3+2] Cycloaddition Reactions



4.1a (R = *t*-Bu) **4.2a** *endo*-**4.3a** *exo*-**4.3a**
4.1b (R = Et)
4.1c (R = Me)



Brucine Diol (**BD**)

Entry	Metal/Base	Solvent	Additive	dr (*endo* : *exo*)[b]	ee (%)[c]
1[d]	CuOTf/DBU	THF	*t*-BuOH	**4.3Ba** (4 : 1)	52
2[d]	CuOTf/DBU	THF	*t*-BuOH	**4.3Ea** (14 : 1)	70
3[d]	CuOTf/DBU	THF	*t*-BuOH	**4.3Ma** (10 : 1)	77
4[e]	CuCl/Et_3N	TCE	EtOH	**4.3Ma** (25 : 1)	72
5	CuOTf/DBU	THF	-	**4.3Ma** (9 : 1)	74
6	CuOTf/DBU	2-MeTHF	-	**4.3Ma** (9 : 1)	66
7	CuOTf/DBU	$PhCH_3$	-	NR[i]	-
8	CuOTf/DBU	$CHCl_3$	-	**4.3Ma** (20 : 1)	77
9	CuOTf/ Et_3N	THF	-	**4.3Ma** (4 : 1)	28
10	CuOTf/DBN	THF	-	**4.3Ma** (13 : 1)	82[f]
11	$Cu(OTf)_2$/DBN	THF	-	**4.3Ma** (7 : 1)	80

Table 9. Continued

Entry	Metal/Base	Solvent	Additive	dr (*endo* : *exo*)[b]	ee (%)[c]
12	$Cu(NTf_2)_2$/DBN	THF	-	**4.3Ma** (10 : 1)	80
13[g]	CuOTf/DBN	THF	-	**4.3Ma** (1 : 1)	26
14[h]	CuOTf/DBN	THF	-	**4.3Ma** (25 : 1)	84

a. Reaction using **4.1** (0.5 mmol) and **4.2** (0.5 mmol) in 0.25 M solution (all reactions have conversion ≥ 50%).

b. Determined by crude ^{1}H NMR.

c. Determined by HPLC using chiral column.

d. 60 mol% *t*-BuOH.

e. 20 mol% EtOH.

f. *exo*-4Ma (45% ee).

g. Reaction at 0 °C for 8 h.

h. 20 mol% of Cu-**BD**.

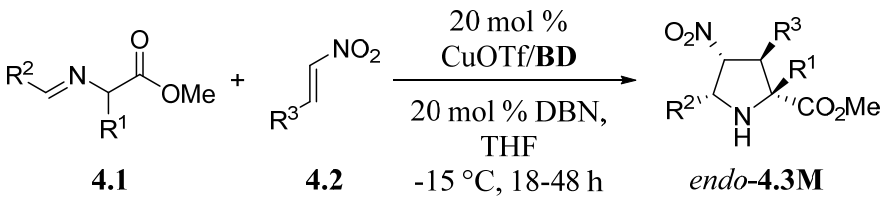
i. NR = No Reaction.

4.2.1.2 Substrate Scope of *endo*-Selective [3+2] Cycloaddition Reactions

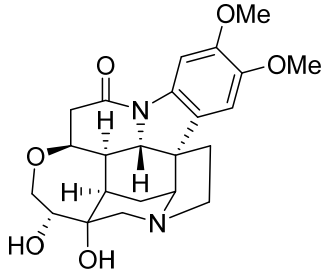
The optimized *endo*-selective [3+2] cycloaddition conditions were further investigated using other glycine imines and nitroalkenes (Table 10). A wide range of imino esters **4.1** with different electronic and steric effect provided the desired *endo*-**4.3Ma-h** in high yields with good to excellent enantio- and diastereoselectivity. The reaction was also applicable to other nitroalkenes with slightly reduced enantioselectivity (*endo*-**4.3Mi-j**). However, a trend in the substrate-selectivity relationship was not found

because the combinations of different substituents on the glycine imines and the nitroalkenes generally provided excellent selectivity (*endo*-**4.3Mk-n**). Although the isolation yield of *endo*-**4.3Mo** from α-methyl glycine imine was reduced to 76%, the enantioselectivity was observed at 94%. Thus, the additional substituent at the α-carbon of glycine imine did not affect the stereoselectivity, implying that the present method could be further utilized to produce chiral pyrrolidines with a quaternary center. The relative and absolute stereochemistry of *endo*-**4.3M** was confirmed to be (2*R*,3*S*,4*R*,5*R*) by comparison of its HPLC retention time with those described previously.[12,13]

Table 10. Scope of *endo*-Selective [3+2] Cycloaddition Reaction



4.1 **4.2** *endo*-**4.3M**



Brucine Diol (**BD**)

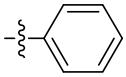
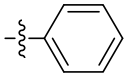
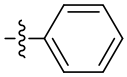
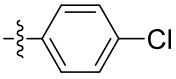
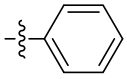
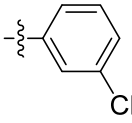
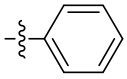
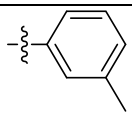
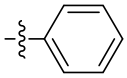
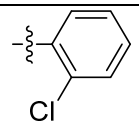
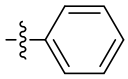
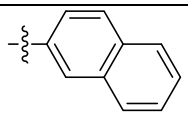
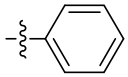
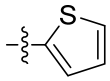
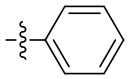
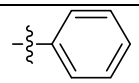
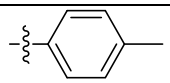
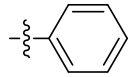
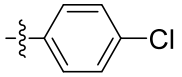
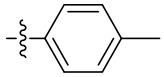
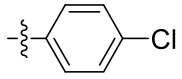
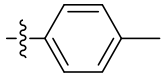
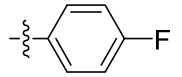
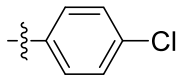
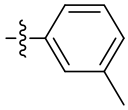
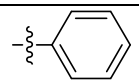
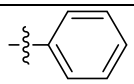
Entry	*endo*-**4.3M**	R^2	R^3	Yield (%)[a]	dr (endo : exo)[d]	ee (%)[e]
1[b]	**4.3Ma**			97	> 25 : 1	84
2[b]	**4.3Mb**			92	> 25 : 1	93
3[b]	**4.3Mc**			92	> 25 : 1	90
4[b]	**4.3Md**			89	10 : 1	81
5[b]	**4.3Me**			99	> 25 : 1	86

Table 10. Continued

Entry	*endo*-**4.3M**	R^2	R^3	Yield (%)[a]	dr (endo : exo)[d]	ee (%)[e]
6[b]	**4.3Mf**			95	20 : 1	81
7[b]	**4.3Mg**			99	> 25 : 1	93
8[b]	**4.3Mh**			94	18 : 1	84
9[b]	**4.3Mi**			92	20 : 1	86
10[b]	**4.3Mj**			95	20 : 1	80
11[b]	**4.3Mk**			89	20 : 1	90
12[b]	**4.3Ml**			92	> 25 : 1	94
13[b]	**4.3Mm**			94	> 25 : 1	93
14[b]	**4.3Mn**			90	20 : 1	94
15[c]	**4.3Mo**			76	> 25 : 1	94

a. Isolated yield of *endo*-**4.3M** after column chromatography.

b. $R^1 = H$

c. R^1 = methyl

d. Determined by crude ^{1}H NMR.

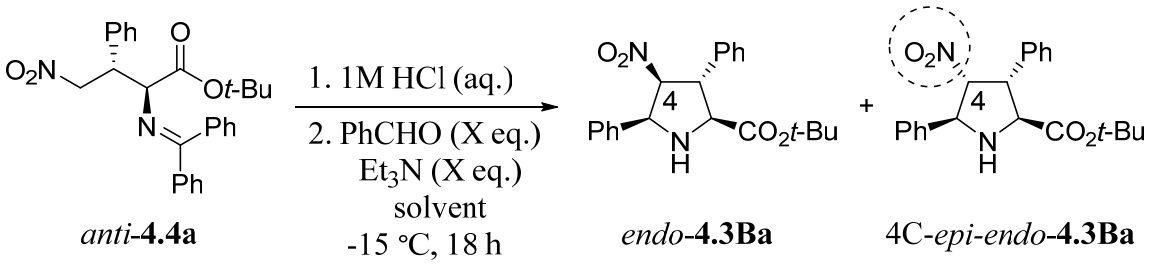
e. Determined by HPLC using chiral column.

4.2.2 Stepwise [3+2] Cycloaddition Pathway

4.2.2.1 Optimization of Intramolecular Mannich Reaction of Conjugate Addition Product *anti*-**4.4**

The stereochemical outcome of the *endo*-selective [3+2] cycloaddition reactions provided insightful mechanistic information. Upon close inspection of various reaction conditions listed in Table 9 and Table 10, we observed the exclusive formation of *endo*-**4.3M** and *exo*-**4.3M** with 50 – 99 % reaction conversions. The absence of other pyrrolidines such as *endo'*-**4.3M**[27] and *exo'*-**4.3M**[22] strongly suggested a concerted [3+2] cycloaddition pathway. Previously, we reported asymmetric *anti*-conjugate addition products with absolute chemistry of (2*S*,3*S*).[27] The results suggested that the *endo*-pyrrolidines derived from the stepwise reaction pathway of our *anti*-conjugate addition products would have opposite absolute chemistry to that of *endo*-**4.3M** from the concerted reaction pathway. To verify this hypothesis, we investigated the intramolecular Mannich reaction of *anti*-**4.4**. We first removed the benzophenone imine moiety of *anti*-**4.4** under acidic conditions,[30] and condensed the primary amine intermediates with aldehydes under basic conditions (Table 11). With different solvents and reaction temperatures, the preferential formation of *endo*-**4.3Ba** was observed with an accompanying by-product, C4-*epi*-*endo*-**4.3Ba** as the only detectable minor product.

Table 11. Optimization of Intramolecular Mannich Reaction for *anti*-**4.4**



anti-**4.4a** *endo*-**4.3Ba** 4C-*epi-endo*-**4.3Ba**

Entry	PhCHO (eq.)	Et_3N (eq.)	Solvent	dr (*endo* : *epi-endo*)[a]	Yield (%)[b]
1	2.0	2.0	CH_2Cl_2	14 : 1	57
2	2.0	2.0	MeOH	14 : 1	99
3	2.0	2.0	EtOH	12 : 1	99
4	2.0	2.0	*i*-PrOH	12 : 1	99
5	1.0	1.0	MeOH	12 : 1	90
6	4.0	2.0	MeOH	13 : 1	99
7	2.0	4.0	MeOH	13 : 1	99
8	4.0	4.0	MeOH	7 : 1	99
9[c]	2.0	2.0	MeOH	1 : 1	99

a. Determined by crude ^{1}H NMR.

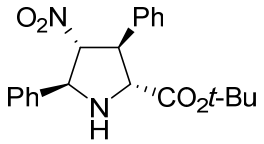
b. Isolated yield of combined *endo*-**4.3Ba** and 4C-*epi-endo*-4.3Ba.

c. Reaction at 23 °C.

4.2.2.2 Substrate Scope of Stepwise [3+2] Cycloaddition Pathway

With the optimized conditions for the intramolecular Mannich reaction of conjugate adducts in hand, we further investigated the synthetic utility of the stepwise [3+2]

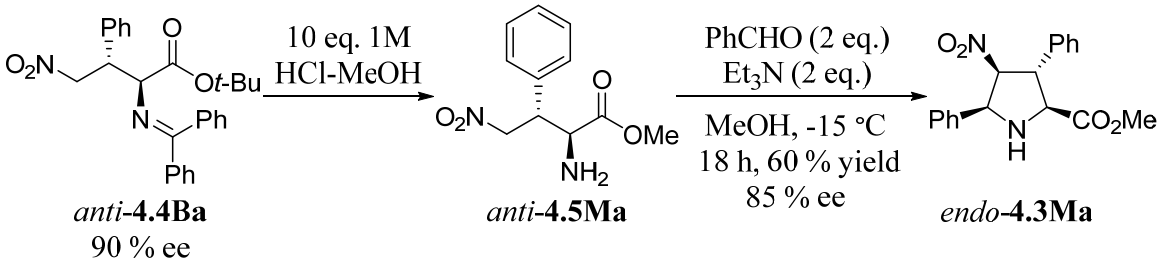
cycloaddition pathway to get access to *endo*-**4.3B**. Results of substrate scope are shown in Table 12. With *anti*-**4.4**, the stereoselective formation of *endo*-**4.3B** was readily achieved with good to excellent yields in three steps. In all cases, the formation of minor products 4C-*epi*-*endo*-**4.3B** was observed, but no other byproducts such as *exo*'-**4.3B** (Figure 8) were detected.[31] While the observed diastereoselectivity of *endo*-**4.3B** varied among substrates (> 25 : 1 to 3 : 1 dr's), a synthetically useful level of enantioselectivity was obtained using various nitroalkenes and aldehydes (80 – 90% ee's).



exo'-**4.3Ba**

Figure 8. *exo'*-**4.3B**

To confirm the opposite stereochemical outcome of *endo*-**4.3M** from the concerted [3+2] cycloaddition reaction pathway, the stepwise synthesis of *endo*-**4.3Ma** from *anti*-**4.4Ba** was performed (Scheme 25). We first removed the benzophenone moiety of *anti*-**4.4Ba**, followed by transesterification to produce *anti*-**4.5Ma**. Finally, *endo*-**4Ma** was obtained by performing the intramolecular Mannich reaction of *anti*-**4.5Ma** with benzaldehyde. By comparison of the retention times of *endo*-**4.3Ma** from both concerted and stepwise reaction pathways, the stereochemistry of *endo*-**4.3B** was confirmed to be (2*S*,3*R*,4*S*,5*S*).



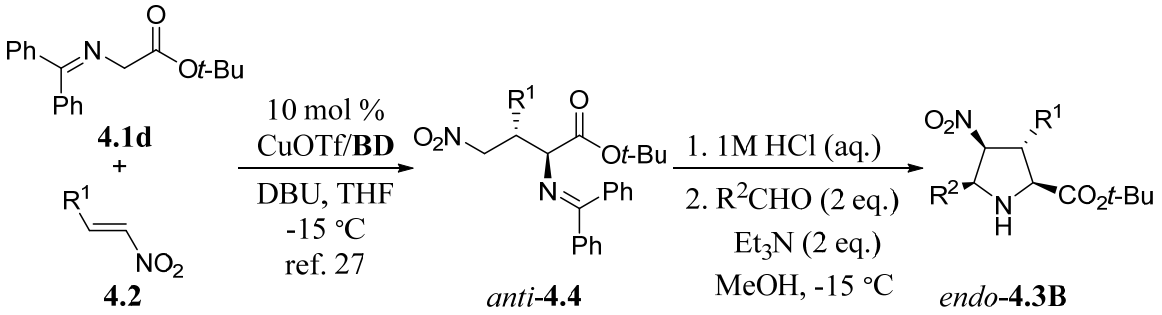
anti-**4.4Ba**
90 % ee

anti-**4.5Ma**

endo-**4.3Ma**

Scheme 25. Synthesis of *endo*-**4.3Ma** from *anti*-**4.4Ba**

Table 12. Scope of Stepwise [3+2] Cycloaddition Reaction



anti-**4.4**

endo-**4.3B**

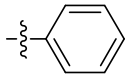
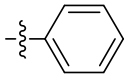
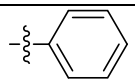
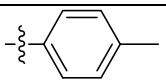
Entry	*endo*-**4.3B**	R^1	R^2	Yield (%)[a]	dr (*endo* : *epi-endo*)[b]	ee (%)[c]
1	**4.3Ba**			57	20 : 1	90
2	**4.3Bb**			74	10 : 1	84

Table 12. Continued

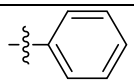
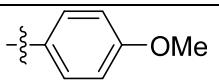
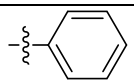
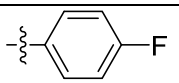
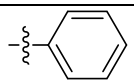
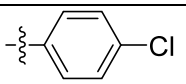
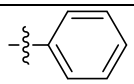
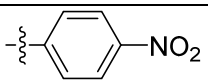
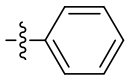
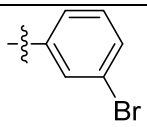
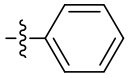
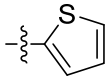
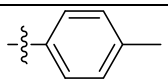
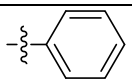
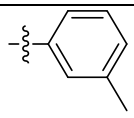
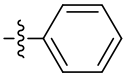
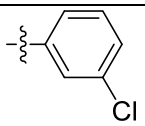
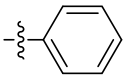
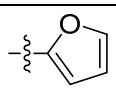
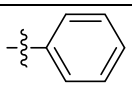
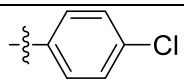
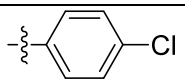
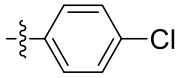
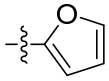
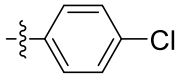
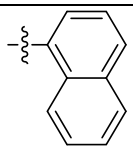
Entry	*endo*-**4.3B**	R^1	R^2	Yield (%)[a]	dr (*endo* : *epi-endo*)[b]	ee (%)[c]
3	**4.3Bc**			79	20 : 1	81
4	**4.3Bd**			48	20 : 1	81
5	**4.3Be**			48	3 : 1	80
6	**4.3Bf**			77	> 25 : 1	80
7	**4.3Bg**			48	> 25 : 1	86
8	**4.3Bh**			44	20 : 1	80
9	**4.3Bi**			48	17 : 1	80
10	**4.3Bj**			73	13 : 1	81
11	**4.3Bk**			67	7 : 1	81
12	**4.3Bl**			47	3 : 1	87

Table 12. Continued

Entry	*endo*-**4.3B**	R^1	R^2	Yield (%)[a]	dr (*endo* : *epi-endo*)[b]	ee (%)[c]
13	**4.3Bm**			71	> 25 : 1	80
14	**4.3Bn**			68	5 : 1	80
15	**4.3Bo**			55	20 : 1	83

a. Isolated yield of *endo*-**4.3B** in three steps from **4.1d** after column chromatography.

b. Determined by crude ^{1}H NMR.

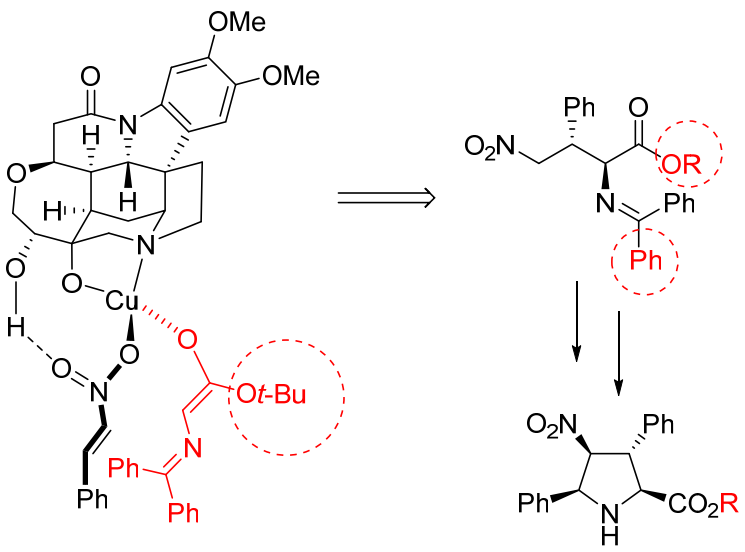
c. Determined by HPLC using chiral column.

4.2.3 Stereomodels for Divergent Reaction Pathways

The stereochemical outcome of the Cu-**BD** catalyzed reactions between glycine (ket)imines and nitroalkenes is likely due to the stereoselective generation of enolates (Scheme 26).[32-35] Thus, the *O*-metallated azomethine ylides of glycine ketimine, **4.1d**, possesses an (*E*)-geometry due to the steric effect of *tert*-butyl ester moiety and the bulky diphenyl groups on **4.1d**. The (*Z*)-geometry is favored for the *N*,*O*-metallated azomethine ylides of glycine imine **4.1c** because of less bulky methyl ester moiety. The geometrical difference in the enolates resulted in the divergent reaction pathways for either conjugate addition or concerted [3+2] cycloaddition products.[36] The proposed stereomodels also explain our *syn*-selective conjugate addition reaction of glycine imine, **4.1c**, via (*E*)-enolates due to more coordinated ligand effect of (-OAc) than (-OTf) at the copper center

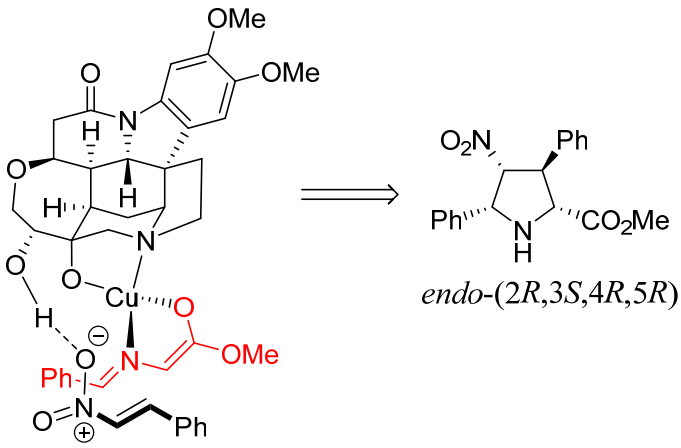
of Cu-**BD** catalyst.[27] The exact difference in the catalyst structure caused by the acetate or triflate ligands is not yet understood. While more work is needed to assert the kinetic/thermodynamic preferences of glycine (ket)imine enolates under metal catalysis, the specific substrate-catalyst interaction is believed to be a crucial diverging factor for the reaction of glycine imines and nitroalkenes for either stereoselective concerted [3+2] cycloaddition pathway (to *endo*-**4.3M**) or *syn*-selective conjugate reaction pathway.

(a) Stepwise Reaction Pathway via (*E*)-enolates



(*E*)-Enolate *endo*-(2*S*,3*R*,4*S*,5*S*)

(b) Concerted Reaction Pathway via (*Z*)-enolates



(*Z*)-Enolate *endo*-(2*R*,3*S*,4*R*,5*R*)

Scheme 26. Stereomodels for Divergent Reaction Pathway

4.3 Conclusion

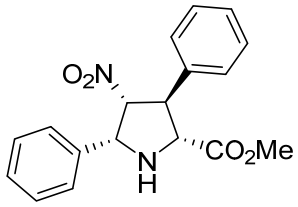
We have developed stereodivergent synthetic approaches to *endo*-pyrrolidines based on different reaction mechanisms (*i.e.* concerted and stepwise reaction pathways). The use of a single chiral source for the stereodivergent catalytic asymmetric reactions is less well developed.[37,38] The implementation of catalytic approaches to multiple synthetic transformations has been challenging because of the nature of specific factors that affect the reversal of stereoselectivity in various reactions and chemotypes. By utilizing the substrate-controlled reaction pathways of glycine ketimine (to *anti*-**4.4**) and glycine imine (to *endo*-**4.3**), we demonstrated the reversal of stereoselectivity using a single chiral ligand, brucine diol (**BD**).

4.4 Experimental Section

General Procedure A for Racemic Synthesis of *Endo*-Selective Cycloaddition Reaction Products

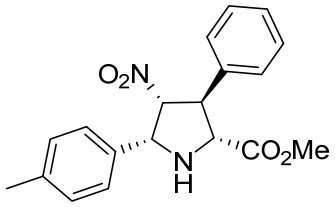
To the solution of methyl (*E*)-2-(benzylideneamino)acetate (0.5 mmol, 89 mg), 1-((*E*)-2-nitrovinyl)benzene (0.5 mmol, 75 mg) and silver(I) acetate (0.5 mmol, 83 mg) in dry DCM (1.0 mL) were added to Et_3N (0.5 mmol) at ambient temperature. The resulting solution was stirred for 18 hours and then concentrated under reduced pressure. The resulting reaction mixture was subjected to chromatography on a short silica column (10-20% ethyl acetate in hexanes), and the yield of the desired *endo*-**4.3Ma** cycloaddition product was 30%.

General Procedure B for the Synthesis of *endo-Selective* [3+2] Cycloaddition Products



(2*R*,3*S*,4*R*,5*R*)-Methyl 4-Nitro-3,5-diphenylpyrrolidine-2-carboxylate (*endo*-**4.3Ma**) $(CuOTf)_2 \bullet C_6H_6$ (20 mol%, 50 mg) and brucine diol (**BD**) (20 mol%, 43 mg) were added to a 10 mL Schlenk flask. Dry THF (2.2 mL) was then added to the flask at 0 °C, followed by addition of DBN (20 mol%, 12 μL). The solution was stirred for 4 h at this temperature. The resulting solution was cooled to -15 °C, and methyl (*E*)-2-(benzylideneamino)acetate **4.1c** (0.5 mmol, 89 mg) was added, with continuous stirring for 10 min after which, 1-((*E*)-2-nitrovinyl)benzene **4.2a** (0.5 mmol, 75 mg) was added. The solution was stirred continuously at -15 °C for 48-60 h. The reaction mixture was

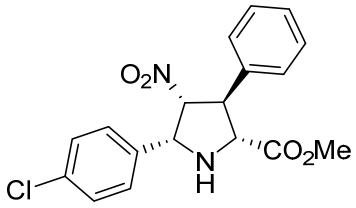
then subjected to chromatography on a short silica column (10-20% ethyl acetate in hexanes); the yield of the title compound was 97%. ^{1}H NMR and ^{13}C NMR spectra of this compound are consistent with previously reported data in the literature.[13] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42−7.29 (m, 10H), 5.28 (dd, *J* = 6.5, 3.5 Hz, 1H), 4.92 (d, *J* = 6.0 Hz, 1H), 4.22 (dd, *J* = 7.5, 3.5 Hz, 1H), 4.15 (d, *J* = 7.5 Hz, 1H), 3.81 (s, 3H), 3.35 (br, *N*H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 171.9, 138.7, 134.5, 129.5, 128.9, 128.9, 128.3, 127.7, 126.6, 97.2, 68.0, 67.6, 55.6, 52.8; IR (neat, cm^{-1}): 3341, 3066, 3031, 2958, 2924, 2854, 1742, 1550, 1497, 1455, 1435, 1367, 1331, 1265, 1211, 1130, 759, 699 cm^{-1}; HRMS-CI m/z 327.1342 [$(M+H)^{+}$; calcd for $C_{18}H_{19}N_2O_4$: 327.1339]. Absolute stereochemistry of this compound was determined by comparison of its HPLC retention time (minor/major peaks) with that of an authentic sample.[13]



(2*R*,3*S*,4*R*,5*R*)-Methyl 4-Nitro-3-phenyl-5-(*p*-tolyl)pyrrolidine-2-carboxylate (*endo*-**4.3Mb**)

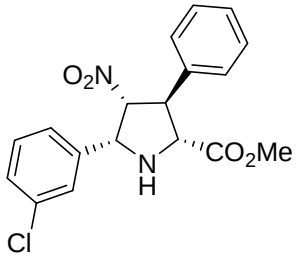
The product *endo*-**4.3Mb** was prepared from methyl (*E*)-2-((4-methylbenzylidene)amino)acetate (0.5 mmol, 96 mg) and 1-((*E*)-2-nitrovinyl)benzene (0.5 mmol, 75 mg) by General Procedure B. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 92%. ^{1}H NMR and ^{13}C NMR spectra of this compound are consistent with previously reported data in the literature.[13] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40 (t, *J* = 7.0 Hz, 2H), 7.35 – 7.31 (m, 1H), 7.30 – 7.28 (m, 2H), 7.25 – 7.22 (m, 2H),

7.16 (d, J = 8.0 Hz, 2H), 5.25 (dd, J = 6.5, 3.5 Hz, 1H), 4.88 (d, J = 6.5 Hz, 1H), 4.20 (dd, J = 7.5, 3.5 Hz, 1H), 4.13 (d, J = 7.5 Hz, 1H), 3.79 (s, 3H), 2.32 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ171.9, 138.8, 138.7, 131.4, 129.6, 129.4, 128.2, 127.6, 126.4, 97.3, 67.9, 67.6, 55.6, 52.8, 21.3; IR (neat, cm^{-1}): 3351, 3063, 3022, 2952, 2917, 2851, 1742, 1550, 1454, 1436, 1367, 1265, 1210, 1130, 823, 758, 701 cm^{-1}; HRMS-CI m/z: 341.1498 $[(M+H)^+$; calcd for $C_{19}H_{21}N_2O_4$: 341.1496].



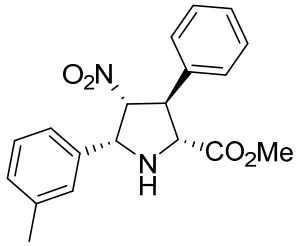
(2*R*,3*S*,4*R*,5*R*)-Methyl 5-(4-Chlorophenyl)-4-nitro-3-phenylpyrrolidine-2-carboxylate (*endo*-**4.3Mc**)

The product *endo*-**4.3Mc** was prepared from methyl (*E*)-2-((4-chlorobenzylidene)amino)acetate (0.5 mmol, 106 mg) and 1-((*E*)-2-nitrovinyl)benzene (0.5 mmol, 75 mg) by General Procedure B. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 92%. ^{1}H NMR and ^{13}C NMR spectra of this compound are consistent with previously reported data in the literature.[13] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42 − 7.39 (m, 2H), 7.36 – 7.28 (m, 7H), 5.26 (dd, J = 6.5, 4.0 Hz, 1H), 4.89 (d, J = 6.5 Hz, 1H), 4.23 (dd, J = 7.5, 4.0 Hz, 1H), 4.15 (d, J = 7.5 Hz, 1H), 3.80 (s, 3H); $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 125 MHz): δ171.8, 138.4, 134.8, 133.3, 129.5, 129.1, 128.3, 128.1, 127.6, 96.8, 67.3, 67.0, 55.1, 52.8; IR (neat, cm^{-1}): 3345, 3072, 3031, 3003, 2958, 2920, 2841, 1741, 1550, 1495, 1366, 1211, 1093, 758, 701 cm^{-1}; HRMS-CI m/z: 361.0945 $[(M+H)^+$; calcd for $C_{18}H_{18}ClN_2O_4$: 361.0950].



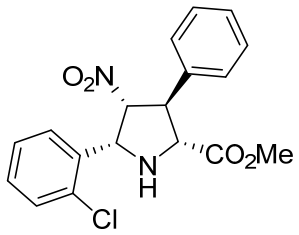
(2*R*,3*S*,4*R*,5*R*)-Methyl 5-(3-Chlorophenyl)-4-nitro-3-phenylpyrrolidine-2-carboxylate (*endo*-**4.3Md**)

The product *endo*-**4.3Md** was prepared from methyl (*E*)-2-((3-chlorobenzylidene)amino)acetate (0.5 mmol, 106 mg) and 1-((*E*)-2-nitrovinyl)benzene (0.5 mmol, 75 mg) by General Procedure B. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 89%. ^{1}H NMR and ^{13}C NMR spectra of this compound are consistent with previously reported data in the literature.[12] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.43 − 7.40 (m, 3H), 7.37 – 7.33 (m, 1H), 7.33 – 7.28 (m, 4H), 7.27 – 7.24 (m, 1H), 5.28 (dd, *J* = 6.5, 4.0 Hz, 1H), 4.88 (d, *J* = 6.5 Hz, 1H), 4.23 (dd, *J* = 7.5, 3.5 Hz, 1H), 4.15 (d, *J* = 7.5 Hz, 1H), 3.81 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ171.7, 138.4, 136.8, 134.9, 130.1, 129.5, 129.1, 128.4, 127.6, 127.2, 124.8, 96.7, 67.3, 67.0, 55.1, 52.9; IR (neat, cm^{-1}): 3383, 3069, 3031, 2952, 2923, 2851, 1740, 1550, 1437, 1369, 1259, 1216, 753, 698 cm^{-1}; HRMS-CI m/z: 361.0952[$(M+H)^+$; calcd for $C_{18}H_{18}ClN_2O_4$: 361.0950].



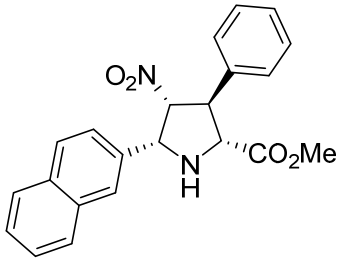
(2*R*,3*S*,4*R*,5*R*)-Methyl 4-Nitro-3-phenyl-5-(*m*-tolyl)pyrrolidine-2-carboxylate (*endo*-**4.3Me**)

The product *endo*-**4.3Me** was prepared from methyl (*E*)-2-((3-methylbenzylidene)amino)acetate (0.5 mmol, 96 mg) and 1-((*E*)-2-nitrovinyl)benzene (0.5 mmol, 75 mg) by General Procedure B. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 99%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42 – 7.39 (m, 2H), 7.36 – 7.29 (m, 3H), 7.26 – 7.23 (m, 1H), 7.16 – 7.13 (m, 3H), 5.27 (dd, *J* = 6.5, 3.5 Hz, 1H), 4.87 (d, *J* = 6.5 Hz, 1H), 4.20 (dd, *J* = 7.0, 3.5 Hz, 1H), 4.14 (d, *J* = 7.0 Hz, 1H), 3.81 (s, 3H), 2.35 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 171.9, 138.8, 138.6, 134.3, 129.7, 129.5, 128.8, 128.2, 127.6, 127.3, 123.6, 97.2, 68.1, 67.7, 55.8, 52.8, 21.6; IR (neat, cm^{-1}): 3341, 3066, 3031, 2952, 2930, 2851, 1742, 1550, 1455, 1436, 1366, 1266, 1212, 1181, 757, 700 cm^{-1}; HRMS-CI m/z: 341.1500 [$(M+H)^+$; calcd for $C_{19}H_{21}N_2O_4$: 341.1496].



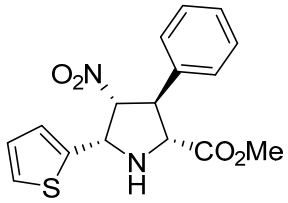
(2*R*,3*S*,4*R*,5*R*)-Methyl 5-(2-Chlorophenyl)-4-nitro-3-phenylpyrrolidine-2-carboxylate (*endo*-**4.3Mf**)

The product *endo*-**4.3Mf** was prepared from methyl (*E*)-2-((2-chlorobenzylidene)amino)acetate (0.5 mmol, 106 mg) and 1-((*E*)-2-nitrovinyl)benzene (0.5 mmol, 75 mg) by General Procedure B. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 95%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.49 − 7.47 (m, 1H), 7.44 – 7.39 (m, 3H), 7.37 – 7.33 (m, 1H), 7.32 – 7.28 (m, 4H), 5.59 (dd, *J* = 6.0, 3.0 Hz, 1H), 5.20 (d, *J* = 6.0 Hz, 1H), 4.24 (dd, *J* = 7.5, 3.0 Hz, 1H), 4.09 (d, *J* = 6.5 Hz, 1H), 3.83 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 171.6, 139.0, 133.3, 132.1, 130.1, 129.7, 129.5, 128.2, 127.6, 127.5, 127.2, 94.9, 67.7, 65.2, 55.3, 52.8; IR (neat, cm^{-1}): 3335, 3066, 3034, 2946, 2917, 2854, 1743, 1551, 1437, 1384, 1365, 1210, 758, 700 cm^{-1}; HRMS-CI m/z: 361.0948 [$(M+H)^+$; calcd for $C_{18}H_{18}ClN_2O_4$: 361.0950].



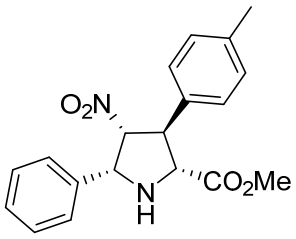
(2*R*,3*S*,4*R*,5*R*)-Methyl 5-(Naphthalen-2-yl)-4-nitro-3-phenylpyrrolidine-2-carboxylate (*endo*-**4.3Mg**)

The product *endo*-**4.3Mg** was prepared from methyl (*E*)-2-((naphthalen-2-ylmethylene)amino)acetate (0.5 mmol, 114 mg) and 1-((*E*)-2-nitrovinyl)benzene (0.5 mmol, 75 mg) by General Procedure B. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 99%. ^{1}H NMR and ^{13}C NMR spectra of this compound are consistent with previously reported data in the literature.[12] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.86 − 7.79 (m, 4H), 7.49 – 7.45 (m, 2H), 7.42 – 7.39 (m, 3H), 7.35 – 7.30 (m, 3H), 5.37 (dd, *J* = 6.5, 3.5 Hz, 1H), 5.05 (d, *J* = 6.5 Hz, 1H), 4.26 (dd, *J* = 7.5, 3.5 Hz, 1H), 4.19 (d, *J* = 7.5 Hz, 1H), 3.81 (s, 3H), 3.48 (br, *N*H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 171.9, 138.7, 133.4, 133.3, 131.9, 129.5, 128.7, 128.3, 128.3, 127.8, 127.7, 126.6, 126.6, 125.9, 124.2, 97.1, 68.0, 67.6, 55.6, 52.8; IR (neat, cm^{-1}): 3335, 3060, 3031, 2949, 2920, 2851, 1741, 1550, 1435, 1365, 1271, 1212, 1180, 754, 700 cm^{-1}; HRMS-CI m/z: 377.1499 [$(M+H)^+$; calcd for $C_{22}H_{21}N_2O_4$: 377.1496].



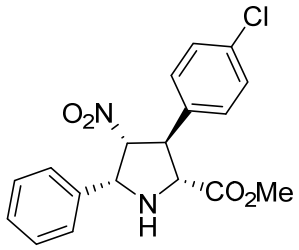
(2*R*,3*S*,4*R*,5*S*)-Methyl 4-Nitro-3-phenyl-5-(thiophen-2-yl)pyrrolidine-2-carboxylate (*endo*-**4.3Mh**)

The product *endo*-**4.3Mh** was prepared from methyl (*E*)-2-((thiophen-2-ylmethylene)amino)acetate (0.5 mmol, 92 mg) and 1-((*E*)-2-nitrovinyl)benzene (0.5 mmol, 75 mg) by General Procedure B. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 94%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.42 – 7.39 (m, 2H), 7.36 – 7.33 (m, 1H), 7.30 – 7.28 (m, 3H), 7.07 (dt, *J* = 3.5, 1.0 Hz, 1H), 7.01 (dd, *J* = 5.5, 3.5 Hz, 1H), 5.27 (dd, *J* = 6.0, 4.5 Hz, 1H), 5.12 (d, *J* = 6.0 Hz, 1H), 4.26 (d, *J* = 7.5, 4.5 Hz, 1H), 4.14 (d, *J* = 7.5 Hz, 1H), 3.80 (s, 3H), 3.37 (br, *N*H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 171.6, 138.3, 137.4, 129.5, 128.3, 127.7, 127.4, 125.9, 125.5, 96.4, 67.2, 63.5, 54.9, 52.9; IR (neat, cm^{-1}): 3338, 3107, 3085, 3063, 3031, 3006, 2952, 2920, 2854, 1741, 1551, 1436, 1384, 1367, 1214, 759, 700 cm^{-1}; HRMS-CI m/z: 333.0906 [(M+H)$^{+}$; calcd for $C_{16}H_{17}N_2O_4S$: 333.0904].



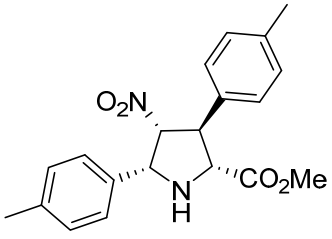
(2*R*,3*S*,4*R*,5*R*)-Methyl 4-Nitro-5-phenyl-3-(*p*-tolyl)pyrrolidine-2-carboxylate (*endo*-**4.3Mi**)

The product *endo*-**4.3Mi** was prepared from methyl (*E*)-2-(benzylideneamino)acetate (0.5 mmol, 89 mg) and (*E*)-1-methyl-4-(2-nitrovinyl)benzene (0.5 mmol, 82 mg) by General Procedure B. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 92%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37 − 7.31 (m, 5H), 7.22 – 7.18 (m, 4H), 5.25 (dd, J = 6.5, 3.5 Hz, 1H), 4.92 – 4.89 (m, 1H), 4.17 (dd, J = 7.5, 3.5 Hz, 1H), 4.13 (t, J = 7.0 Hz, 1H), 3.81 (s, 3H), 3.35 (br, *N*H), 2.37 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 172.0, 138.1, 135.7, 134.6, 130.1, 128.9, 128.9, 127.5, 126.6, 97.3, 67.9, 67.6, 55.4, 52.8, 21.2; IR (neat, cm^{-1}): 3341, 3056, 3025, 2952, 2917, 2847, 1741, 1550, 1435, 1384, 1367, 1208, 1181, 698 cm^{-1}; HRMS-CI m/z: 341.1500 [(M+H)$^{+}$; calcd for $C_{19}H_{21}N_2O_4$: 341.1496].



(2*R*,3*S*,4*R*,5*R*)-Methyl 3-(4-Chlorophenyl)-4-nitro-5-phenylpyrrolidine-2-carboxylate (*endo*-**4.3Mj**)

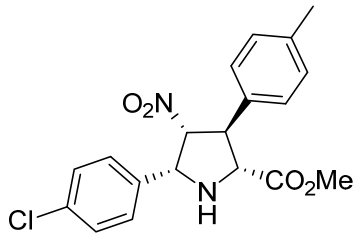
The product *endo*-**4.3Mj** was prepared from methyl (*E*)-2-(benzylideneamino)acetate (0.5 mmol, 89 mg) and (*E*)-1-chloro-4-(2-nitrovinyl)benzene (0.5 mmol, 92 mg) by General Procedure B. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 95%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.39 − 7.32 (m, 7H), 7.24 – 7.23 (m, 2H), 5.23 (dd, *J* = 7.0, 4.0 Hz, 1H), 4.89 (d, *J* = 7.0 Hz, 1H), 4.20 (dd, *J* = 7.5, 4.0 Hz, 1H), 4.08 (d, *J* = 8.0 Hz, 1H), 3.79 (s, 3H), 3.28 (br, *N*H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 171.6, 137.0, 134.5, 134.3, 129.6, 129.1, 129.0, 128.9, 126.7, 96.9, 67.7, 67.4, 54.6, 52.9; IR (neat, cm^{-1}): 3341, 3069, 3025, 2955, 2920, 2854, 1742, 1550, 1494, 1436, 1367, 1213, 1093, 758, 699 cm^{-1}; HRMS-CI m/z 361.0948 [$(M+H)^+$; calcd for $C_{18}H_{18}ClN_2O_4$: 361.0950].



(2*R*,3*S*,4*R*,5*R*)-Methyl 4-Nitro-3,5-di-*p*-tolylpyrrolidine-2-carboxylate (*endo*-**4.3Mk**)

The product *endo*-**4.3Mk** was prepared from methyl (*E*)-2-((4-methylbenzylidene)amino)acetate (0.5 mmol, 96 mg) and (*E*)-1-methyl-4-(2-

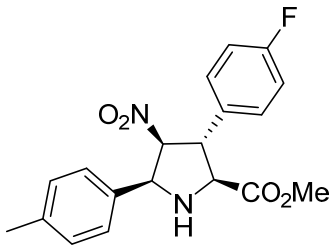
nitrovinyl)benzene (0.5 mmol, 82 mg) by General Procedure B. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 89%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.24 – 7.14 (m, 8H), 5.22 (dd, *J* = 6.5, 4.0 Hz, 1H), 4.86 (d, *J* = 6.5 Hz, 1H), 4.15 (dd, *J* = 7.5, 3.5 Hz, 1H), 4.10 (d, *J* = 7.0 Hz, 1H), 3.79 (s, 3H), 2.35 (s, 3H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 172.0, 138.6, 138.0, 135.8, 131.5, 130.1, 129.6, 127.5, 126.4, 97.4, 67.8, 67.6, 55.3, 52.7, 21.3, 21.2; IR (neat, cm^{-1}): 3335, 3022, 2952, 2920, 2860, 1742, 1550, 1516, 1436, 1366, 1264, 1209, 1180, 1129, 813, 757 cm^{-1}; HRMS-CI m/z: 355.1654 [$(M+H)^{+}$; calcd for $C_{20}H_{23}N_2O_4$: 355.1652].



(2*R*,3*S*,4*R*,5*R*)-Methyl 5-(4-Chlorophenyl)-4-nitro-3-(*p*-tolyl)pyrrolidine-2-carboxylate (*endo*-**4.3Ml**)

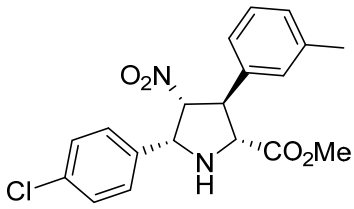
The product *endo*-**4.3Ml** was prepared from methyl (*E*)-2-((4-chlorobenzylidene)amino)acetate (0.5 mmol, 106 mg) and (*E*)-1-methyl-4-(2-nitrovinyl)benzene (0.5 mmol, 82 mg) by General Procedure B. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 92%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33 − 7.30 (m, 4H), 7.22 – 7.16 (m, 4H), 5.24 (dd, *J* = 6.5, 3.5 Hz, 1H), 4.87 (d, *J* = 6.5 Hz, 1H), 4.18 (dd, *J* = 7.5, 4.0 Hz, 1H), 4.12 (d, *J* = 7.5 Hz, 1H), 3.80 (s, 3H), 3.24 (br, *N*H), 2.37 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 171.8, 138.1, 135.4, 134.8, 133.4, 130.1, 129.1,

128.1, 127.5, 96.9, 67.3, 66.9, 54.9, 52.8, 21.2; IR (neat, cm^{-1}): 3345, 3022, 2952, 2917, 2857, 1742, 1550, 1516, 1494, 1436, 1366, 1211, 1181, 1093, 1015, 814, 759 cm^{-1}; HRMS-CI m/z: 375.1109 [$(M+H)^+$; calcd for $C_{19}H_{20}ClN_2O_4$: 375.1106].



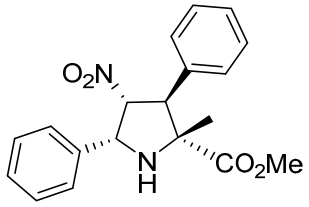
(2*S*,3*R*,4*S*,5*S*)-Methyl 3-(4-Fluorophenyl)-4-nitro-5-(*p*-tolyl)pyrrolidine-2-carboxylate (*endo*-**4.3Mm**)

The product *endo*-**4.3Mm** was prepared from methyl (*E*)-2-((4-methylbenzylidene)amino)acetate (0.5 mmol, 96 mg) and (*E*)-1-fluoro-4-(2-nitrovinyl)benzene (0.5 mmol, 84 mg) by General Procedure B. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 94%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.27 − 7.22 (m, 4H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.10 – 7.06 (m, 2H), 5.21 (dd, *J* = 6.5, 4.0 Hz, 1H), 4.86 (d, *J* = 7.0 Hz, 1H), 4.19 (dd, *J* = 7.5, 3.5 Hz, 1H), 4.07 (d, *J* = 7.5 Hz, 1H), 3.79 (s, 3H), 3.27 (br, *N*H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 171.7, 162.5 (d, *J* = 246.3 Hz), 138.8, 134.4 (d, *J* = 3.8 Hz), 131.5, 129.6, 129.3 (d, *J* = 7.5 Hz), 126.5, 116.4 (d, *J* = 22.5 Hz), 97.2, 67.6, 67.6, 54.6, 52.8, 21.3; IR (neat, cm^{-1}): 3342, 3026, 2954, 2923, 1743, 1607, 1550, 1512, 1436, 1367, 1308, 1227, 1162, 1129, 1101, 1021, 955, 924, 873, 824, 758, 556, 531 cm^{-1}; HRMS-CI m/z: 359.1400 [$(M+H)^+$; calcd for $C_{19}H_{20}FN_2O_4$: 359.1402].



(2*R*,3*S*,4*R*,5*R*)-Methyl 5-(4-Chlorophenyl)-4-nitro-3-(*m*-tolyl)pyrrolidine-2-carboxylate (*endo*-**4.3Mn**)

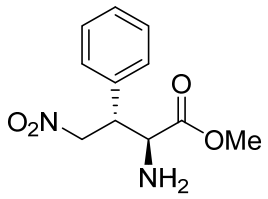
The product *endo*-**4.3Mn** was prepared from methyl (*E*)-2-((4-chlorobenzylidene)amino)acetate (0.5 mmol, 106 mg) and (*E*)-1-methyl-3-(2-nitrovinyl)benzene (0.5 mmol, 82 mg) by General Procedure B. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 90%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33 – 7.24 (m, 5H), 7.14 (d, J = 7.5 Hz, 2H), 7.07 (d, J = 6.5 Hz, 2H), 5.23 (dd, J = 6.5, 3.5 Hz, 1H), 4.87 (d, J = 6.5 Hz, 1H), 4.18 (d, J = 7.5, 3.5 Hz, 1H), 4.13 (d, J = 7.5 Hz, 1H), 3.79 (s, 3H), 3.24 (br, *N*H), 2.37 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 171.8, 139.2, 138.3, 134.7, 133.3, 129.3, 129.0, 129.0, 128.3, 128.1, 124.6, 96.9, 67.2, 67.0, 55.1, 52.8, 21.6; IR (neat, cm^{-1}): 3345, 3025, 2952, 2917, 2866, 1742, 1550, 1492, 1436, 1365, 1211, 1094, 1015, 759 cm^{-1}; HRMS-CI m/z: 375.1107 [$(M+H)^+$; calcd for $C_{19}H_{20}ClN_2O_4$: 375.1106].



(2*R*,3*R*,4*R*,5*R*)-Methyl 2-Methyl-4-nitro-3,5-diphenylpyrrolidine-2-carboxylate (*endo*-**4.3Mo**)

The product *endo*-**4.3Mo** was prepared from methyl (*E*)-2-(benzylideneamino)propanoate (0.5 mmol, 96 mg) and 1-((*E*)-2-nitrovinyl)benzene (0.5 mmol, 75 mg) by General Procedure B. The mixture was stirred at 0 °C for 18 h. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 76%. ^{1}H NMR and ^{13}C NMR spectra of this compound are consistent with previously reported data in the literature.[13] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40 (d, *J* = 7.0 Hz, 2H), 7.37 – 7.29 (m, 6H), 7.25 – 7.24 (m, 2H), 5.65 (t, *J* = 7.0 Hz, 1H), 5.05 (d, *J* = 7.5 Hz, 1H), 4.52 (d, *J* = 6.0 Hz, 1H), 3.85 (s, 3H), 3.42 (br, *N*H), 1.17 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 174.8, 135.7, 135.5, 128.9, 128.9, 128.8, 128.7, 128.1, 127.0, 95.7, 68.8, 65.1, 57.0, 53.0, 22.2; IR (neat, cm^{-1}): 3345, 3091, 3064, 3032, 3002, 2977, 2953, 1734, 1603, 1553, 1498, 1455, 1435, 1370, 1255, 1221, 1141, 1030, 984, 873, 809, 750, 700, 667 cm^{-1}; HRMS-CI m/z: 341.1506 [$(M+H)^+$; calcd for $C_{19}H_{21}N_2O_4$: 341.1496]. Absolute stereochemistry of this compound was determined by comparison of its HPLC retention time (minor/major peaks) with that of an authentic sample.[13]

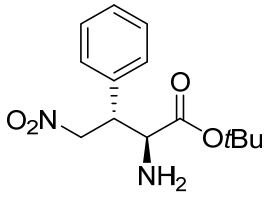
General Procedure C for Transesterification of *anti*-**4.4**



(2*S*, 3*S*)-Methyl 2-Amino-4-nitro-3-phenylbutanoate (*anti*-**4.5Ma**)

anti-4.4**Ba**[27] (0.5 mmol, 222 mg) was dissolved in 1M HCl-MeOH solution (5.0 mmol, 5.0 mL). The mixture was refluxed for 48 hours. HCl and MeOH were then removed under reduced pressure. To the resulting solution, 5.0 mL 1M HCl (aq.) was added. The resulting aqueous solution was washed with ether (2 × 10.0 mL) and neutralized with $NaHCO_3$ (aq.). The mixture was then extracted with CH_2Cl_2 (3 × 10 mL). The organic layers of these three extractions were combined and then dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the desired product (*anti*-**4.5Ma**) was obtained. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34 – 7.28 (m, 3H), 7.21 (d, *J* = 7.5 Hz, 2H), 5.05 (dd, *J* = 13.0, 5.0 Hz, 1H), 4.77 (dd, *J* = 13.0, 9.0 Hz, 1H), 3.82 (d, *J* = 6.5 Hz, 1H), 3.69 (d, *J* = 11.5 Hz, 1H), 3.55 (s, 3H), 1.66 (br, 2*N*H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 174.1, 136.6, 129.1, 128.3, 128.1, 58.0, 52.2, 52.2, 47.9; IR (neat, cm^{-1}): 3389, 3322, 3063, 3028, 3003, 2954, 2923, 2844, 1733, 1552, 1496, 1456, 1436, 1383, 1262, 1203, 1174, 1090, 1019, 702 cm^{-1}; HRMS-CI m/z: 239.1025 [$(M+H)^+$; calcd for $C_{11}H_{15}N_2O_4$: 239.1032].

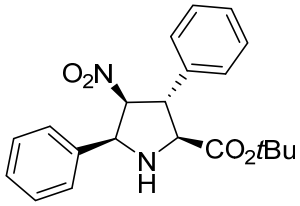
General Procedure D for Hydrolysis of *anti*-**4.5B**



rac-*tert*-Butyl 3-Amino-5-nitro-2-oxo-4-phenylpentanoate (*anti*-**4.5Ba**)

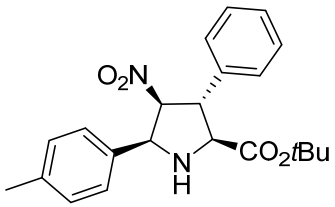
anti-4.4**Ba**[27] (0.5 mmol, 222 mg) was dissolved in 1M HCl-MeOH solution (5.0 mmol, 5.0 mL). The mixture was stirred at 0 °C for 4-6 h. HCl and MeOH were then removed under reduced pressure. To the resulting solution, 5.0 mL 1M HCl (aq.) was added. The resulting aqueous solution was washed with ether (2 × 10 mL) and neutralized with $NaHCO_3$ (aq.). The mixture was then extracted with CH_2Cl_2 (3 × 10 mL). The organic layers of these three extractions were combined and then dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the desired product (*anti*-**4.5Ba**) was obtained. ^{1}H NMR and ^{13}C NMR spectra of this compound are consistent with previously reported data in the literature.[39] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33 − 7.22 (m, 5H), 5.06 (dd, J = 13.0, 5.0 Hz, 1H), 4.72 (dd, J = 13.0, 4.5 Hz, 1H), 3.71 – 3.67 (m, 1H), 3.60 – 3.54 (m, 1H), 1.62 (br, 2*N*H), 1.22 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 173.1, 136.8, 128.9, 128.5, 128.3, 82.0, 78.1, 58.4, 48.4, 27.8.

General Procedure E for the Synthesis of Stepwise [3+2] Cycloaddition Reaction Products



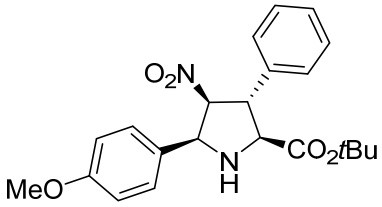
(2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 4-Nitro-3,5-diphenylpyrrolidine-2-carboxylate (*endo*-**4.3Ba**)

The compound *anti*–**4.4Ba** was prepared from glycine ketimine (0.5 mmol, 148 mg) and 1-((*E*)-2-Nitrovinyl)benzene (0.5 mmol, 75 mg) as described previously.[26] The product was then hydrolyzed with 1N HCl in MeOH (5.0 mL) at 0 °C for 4-6 h. HCl and MeOH were then removed under reduced pressure. Et_3N (1.0 mmol) and aldehyde (1.0 mmol) in MeOH (1.0 mL) were then added to the isolated reaction residue at –15 °C. The mixture was stirred continuously at –15 °C for 18 h. The resulting solution was concentrated under reduced pressure and then subjected to chromatography on a short silica column (10 – 20 % Ethyl Acetate in Hexanes); the yield of the title compound was 57 %. ^{1}H NMR ($CDCl_3$, 500 MHz): δ7.40 – 7.27 (m, 10H), 5.29 (dd, *J* = 7.0, 4.0 Hz, 1H), 4.93 (d, *J* = 6.5 Hz, 1H), 4.09 (dd, *J* = 7.5, 4.0 Hz, 1H), 3.99 (d, *J* = 8.0 Hz, 1H), 3.34(br, *N*H), 1.44(s, 9H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 170.6, 138.9, 134.8, 129.3, 128.9, 128.8, 128.1, 127.7, 126.6, 97.2, 82.6, 68.3, 67.9, 56.1, 28.1; IR (neat, cm^{-1}): 3345, 3066, 3031, 3003, 2974, 2936, 1732, 1550, 1455, 1384, 1369, 1155, 759, 699 cm^{-1}; HRMS-CI m/z: 369.1812 [$(M+H)^+$; calcd for $C_{21}H_{25}N_2O_4$: 369.1809].



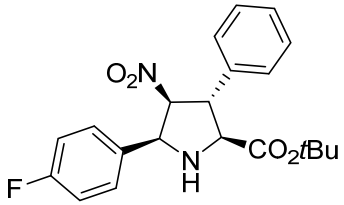
(2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 4-Nitro-3-phenyl-5-(*p*-tolyl)pyrrolidine-2-carboxylate (*endo*-**4.3Bb**)

The product *endo*-**4.3Bb** was prepared from *anti*-**4.4Ba** (0.5 mmol, 222 mg) and 4-methylbenzaldehyde (1.0 mmol, 120 mg) by General Procedure E. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 74%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.39 – 7.36 (m, 2H), 7.32 – 7.22 (m, 5H), 7.15 (d, *J* = 8.0 Hz, 2H), 5.26 (dd, *J* = 7.0, 4.0 Hz, 1H), 4.87 (d, *J* = 6.5 Hz, 1H), 4.08 (dd, *J* = 7.5, 4.0 Hz, 1H), 3.97 (d, *J* = 8.0 Hz, 1H), 3.29 (br, *N*H), 2.31 (s, 3H), 1.43 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 170.6, 138.9, 138.6, 131.8, 129.5, 129.2, 128.0, 127.7, 126.5, 97.3, 82.5, 68.3, 67.8, 56.2, 28.1, 21.2; IR (neat, cm^{-1}): 3304, 3030, 2978, 2926, 1732, 1550, 1518, 1497, 1477, 1455, 1393, 1369, 1330, 1257, 1217, 1157, 844, 825, 797, 759, 700 cm^{-1}; HRMS-CI m/z: 383.1962 [$(M+H)^{+}$; calcd for $C_{22}H_{27}N_2O_4$: 383.1965].



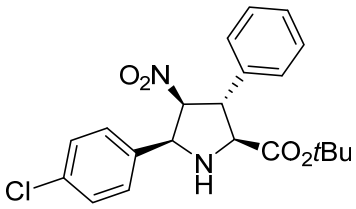
(2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 5-(4-Methoxyphenyl)-4-nitro-3-phenylpyrrolidine-2-carboxylate (*endo*-**4.3Bc**)

The product *endo*-**4.3Bc** was prepared from *anti*-**4.4Ba** (0.5 mmol, 222 mg) and 4-anisaldehyde (1.0 mmol, 136 mg) by General Procedure E. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 79%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.39 – 7.36 (m, 2H), 7.33 – 7.27 (m, 5H), 6.87 (d, J = 9.0 Hz, 2H), 5.25 (dd, J = 6.5, 4.0 Hz, 1H), 4.86 (d, J = 6.5 Hz, 1H), 4.09 (dd, J = 8.0, 4.5 Hz, 1H), 3.97 (d, J = 7.5 Hz, 1H), 3.77 (s, 3H), 3.25 (br, *N*H), 1.43 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 170.7, 160.0, 138.9, 129.2, 128.0, 127.9, 127.7, 126.8, 114.2, 97.3, 82.5, 68.2, 67.5, 56.0, 55.3, 28.1; IR (neat, cm^{-1}): 3339, 3032, 2978, 2932, 2838, 1732, 1613, 1585, 1550, 1517, 1498, 1456, 1369, 1252, 1157, 1033, 837, 761, 701 cm^{-1}; HRMS-CI m/z: 399.1910 [$(M+H)^+$; calcd for $C_{22}H_{27}N_2O_5$: 399.1914].



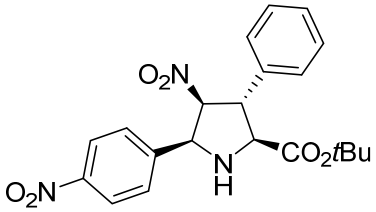
(2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 5-(4-Fluorophenyl)-4-nitro-3-phenylpyrrolidine-2-carboxylate (*endo*-**4.3Bd**)

The product *endo*-**4.3Bd** was prepared from *anti*-**4.4Ba** (0.5 mmol, 222 mg) and 4-fluorobenzaldehyde (1.0 mmol, 124 mg) by General Procedure E. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 48%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.39 − 7.30 (m, 5H), 7.28 – 7.26 (m, 2H), 7.03 (td, *J* = 8.5, 2.0 Hz, 2H), 5.27 (dd, *J* = 7.0, 3.5 Hz, 1H), 4.89 (d, *J* = 6.5 Hz, 1H), 4.10 (dd, *J* = 7.5, 4.5 Hz, 1H), 3.98 (d, *J* = 8.0 Hz, 1H), 3.22 (br, *N*H), 1.43 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 170.6, 162.9 (d, *J* = 246.3 Hz), 138.6, 130.9 (d, *J* = 2.5 Hz), 129.3, 128.5 (d, *J* = 8.8 Hz), 128.1, 127.7, 115.8 (d, *J* = 28.8 Hz), 97.0, 82.6, 68.0, 66.9, 55.7, 28.1; IR (neat, cm^{-1}): 3352, 3032, 2979, 2927, 2853, 1732, 1606, 1551, 1513, 1478, 1455, 1393, 1369, 1230, 1157, 1092, 1015, 950, 841, 800, 760, 700, 539 cm^{-1}; HRMS-CI m/z: 387.1717 [$(M+H)^+$; calcd for $C_{21}H_{24}FN_2O_4$: 387.1715].



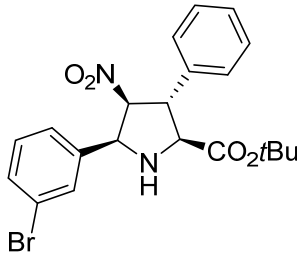
(2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 5-(4-Chlorophenyl)-4-nitro-3-phenylpyrrolidine-2-carboxylate (*endo*-**4.3Be**)

The product *endo*-**4.3Be** was prepared from *anti*-**4.4Ba** (0.5 mmol, 222 mg) and 4-chlorobenzaldehyde (1.0 mmol, 141 mg) by General Procedure E. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 48%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40 − 7.37 (m, 2H), 7.34 – 7.30 (m, 5H), 7.28 – 7.26 (m, 2H), 5.27 (dd, *J* = 7.0, 4.5 Hz, 1H), 4.87 (d, *J* = 6.5 Hz, 1H), 4.09 (dd, *J* = 7.5, 4.5 Hz, 1H), 3.99 (d, *J* = 7.5 Hz, 1H), 3.23 (br, *N*H), 1.43 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 170.5, 138.6, 134.7, 133.6, 129.3, 129.1, 128.2, 128.1, 127.7, 96.9, 82.7, 68.0, 67.0, 55.8, 28.1; IR (neat, cm^{-1}): 3352, 3031, 2979, 2931, 1732, 1602, 1549, 1496, 1455, 1393, 1369, 1299, 1251, 1218, 1157, 1095, 1015, 952, 933, 840, 758, 700, 668, 510 cm^{-1}; HRMS-CI m/z: 403.1412 [$(M+H)^+$; calcd for $C_{21}H_{24}ClN_2O_4$: 403.1419].



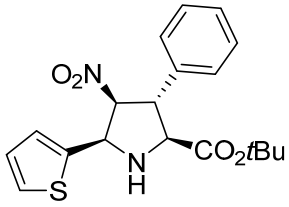
(2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 4-Nitro-5-(4-nitrophenyl)-3-phenylpyrrolidine-2-carboxylate (*endo*-**4.3Bf**)

The product *endo*-**4.3Bf** was prepared from *anti*-**4.4Ba** (0.5 mmol, 222 mg) and 4-nitrobenzaldehyde (1.0 mmol, 151 mg) by General Procedure E. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 77%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.22 (dd, *J* = 7.0, 2.0, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 7.42 – 7.39 (m, 2H), 7.36 – 7.33 (m, 1H), 7.30 – 7.28 (m, 2H), 5.36 (dd, *J* = 7.0, 4.5 Hz, 1H), 5.01 (s, 1H), 4.13 (dd, *J* = 7.5, 4.5 Hz, 1H), 4.05 (s, 1H), 3.25 (br, *N*H), 1.44 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 170.3, 148.2, 142.6, 138.1, 129.4, 128.4, 127.9, 127.7, 124.0, 96.5, 82.9, 67.7, 66.4, 55.4, 28.1; IR (neat, cm^{-1}): 3380, 3031, 2977, 2924, 2853, 1732, 1603, 1553, 1523, 1456, 1369, 1348, 1256, 1156, 856, 757, 700 cm^{-1}; HRMS-CI m/z: 414.1642 [$(M+H)^+$; calcd for $C_{21}H_{24}N_3O_6$: 414.1660].



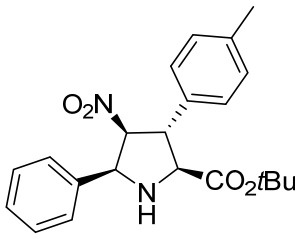
(2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 5-(3-Bromophenyl)-4-nitro-3-phenylpyrrolidine-2-carboxylate (*endo*-**4.3Bg**)

The product *endo*-**4.3Bg** was prepared from *anti*-**4.4Ba** (0.5 mmol, 222 mg) and 3-bromobenzaldehyde (1.0 mmol, 185 mg) by General Procedure E. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 48%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.55 (s, 1H), 7.47 – 7.45 (m, 1H), 7.41 – 7.38 (m, 2H), 7.35 – 7.27 (m, 4H), 7.23 (t, *J* = 7.5 Hz, 1H), 5.29 (dd, *J* = 7.0, 4.0 Hz, 1H), 4.86 (t, *J* = 7.5 Hz, 1H), 4.10 (dd, *J* = 7.5, 4.0 Hz, 1H), 3.99 (t, *J* = 7.0 Hz, 1H), 3.24 (br, *N*H), 1.45 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 170.4, 138.5, 137.4, 132.0, 130.4, 130.1, 129.3, 128.2, 127.7, 125.2, 123.0, 96.7, 82.7, 68.0, 66.9, 55.8, 28.1; IR (neat, cm^{-1}): 3352, 3064, 3031, 2979, 2928, 2854, 1732, 1596, 1552, 1497, 1476, 1455, 1429, 1393, 1369, 1257, 1218, 1155, 1073, 997, 843, 758, 699, 668 cm^{-1}; HRMS-CI m/z: 447.0898 [$(M+H)^+$; calcd for $C_{21}H_{24}BrN_2O_4$: 447.0941].



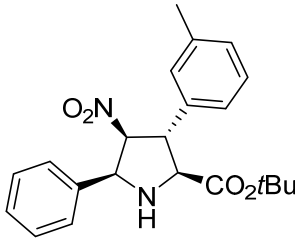
(2*S*,3*R*,4*S*,5*R*)-*tert*-Butyl 4-Nitro-3-phenyl-5-(thiophen-2-yl)pyrrolidine-2-carboxylate (*endo*-**4.3Bh**)

The product *endo*-**4.3Bh** was prepared from *anti*-**4.4Ba** (0.5 mmol, 222 mg) and 2-thiophenecarboxaldehyde (1.0 mmol, 112 mg) by General Procedure E. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 44%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41 − 7.39 (m, 2H), 7.34 – 7.27 (m, 4H), 7.07 (d, *J* = 3.5 Hz, 1H), 7.00 (dd, *J* = 5.0, 3.5 Hz, 1H), 5.29 (dd, *J* = 6.5, 5.0 Hz, 1H), 5.11 (d, *J* = 7.0 Hz, 1H), 4.14 (dd, *J* = 8.0, 5.0 Hz, 1H), 3.99 (d, *J* = 7.5 Hz, 1H), 3.35 (br, *N*H), 1.44 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 170.3, 138.4, 137.9, 129.3, 128.2, 127.8, 127.4, 125.8, 125.5, 96.4, 82.7, 67.8, 63.4, 55.4, 28.1; IR (neat, cm^{-1}): 3355, 3034, 3002, 2978, 2923, 1732, 1552, 1456, 1384, 1369, 1246, 1156, 843, 700 cm^{-1}; HRMS-CI m/z: 375.1373 [$(M+H)^{+}$; calcd for $C_{19}H_{23}N_2O_4S$: 375.1373].



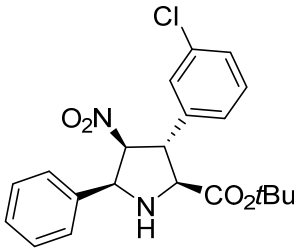
(2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 4-Nitro-5-phenyl-3-(*p*-tolyl)pyrrolidine-2-carboxylate (*endo*-**4.3Bi**)

The product *endo*-**4.3Bi** was prepared from *anti*-**4.4Bi** (0.5 mmol, 229 mg) and benzaldehyde (1.0 mmol, 106 mg) by General Procedure E. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 48%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.36 – 7.32 (m, 2H), 7.20 – 7.16 (m, 4H), 5.26 (dd, *J* = 6.5 Hz, 4.0 Hz, 1H), 4.89 (d, *J* = 6.5 Hz, 1H), 4.06 (dd, J= 7.5 Hz, 4.0 Hz, 1H), 3.98 (d, *J* = 7.5 Hz, 1H), 2.36 (s, 3H), 1.45 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 170.7, 137.8, 136.0, 134.8, 129.9, 128.9, 128.8, 127.6, 126.6, 97.3, 82.6, 68.4, 67.9, 55.9, 28.1, 21.1; IR (neat, cm^{-1}): 3341, 3028, 3003, 2978, 2923, 1733, 1550, 1516, 1456, 1384, 1368, 1320, 1256, 1156, 746, 698 cm^{-1}; HRMS-CI m/z: 383.1969 [$(M+H)^+$; calcd for $C_{22}H_{27}N_2O_4$: 383.1965].



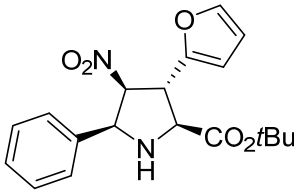
(2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 4-Nitro-5-phenyl-3-(*m*-tolyl)pyrrolidine-2-carboxylate (*endo*-**4.3Bj**)

The product *endo*-**4.3Bj** was prepared from *anti*-**4.4Bj** (0.5 mmol, 229 mg) and benzaldehyde (1.0 mmol, 106 mg) by General Procedure E. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 73%. ^{1}H NMR($CDCl_3$, 500 MHz): δ 7.36 − 7.26 (m, 6H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 2H), 5.29 (dd, *J* = 6.5, 4.0 Hz, 1H), 4.90 (d, *J* = 6.5 Hz, 1H), 4.06 (dd, *J* = 7.5, 3.5 Hz, 1H), 3.99 (d, *J* = 7.5 Hz, 1H), 3.39 (br, *N*H), 2.37 (s, 3H), 1.45 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 170.7, 139.0, 138.9, 134.8, 129.2, 128.9, 128.9, 128.8, 128.5, 126.6, 124.7, 97.2, 82.5, 68.3, 67.9, 56.2, 28.1, 21.6; IR (neat, cm^{-1}): 3338, 3063, 3028, 3006, 2978, 2928, 2870, 1732, 1550, 1456, 1393, 1368, 1250, 1157, 757, 700 cm^{-1}; HRMS-CI m/z: 383.1969 [$(M+H)^{+}$; calcd for $C_{22}H_{27}N_2O_4$: 383.1965].



(2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 3-(3-Chlorophenyl)-4-nitro-5-phenylpyrrolidine-2-carboxylate (*endo*-**4.3Bk**)

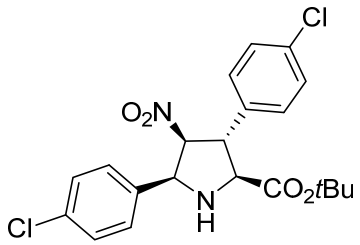
The product *endo*-**4.3Bk** was prepared from *anti*-**4.4Bk** (0.5 mmol, 239 mg) and benzaldehyde (1.0 mmol, 106 mg) by General Procedure E. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 67%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37 – 7.29 (m, 8H), 7.17 (dt, *J* = 6.5, 2.0 Hz, 1H), 5.29 (dd, *J* = 7.0, 4.5 Hz, 1H), 4.89 (d, *J* = 7.0 Hz, 1H), 4.08 (dd, *J* = 7.5, 4.5 Hz, 1H), 3.95 (d, *J* = 7.5 Hz, 1H), 1.45 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 170.2, 140.7, 135.1, 134.7, 130.6, 128.9, 128.9, 128.3, 128.1, 126.7, 125.9, 96.7, 82.9, 68.1, 67.8, 55.4, 28.1; IR (neat, cm^{-1}): 3310, 3056, 3037, 2999, 2979, 2930, 2873, 1732, 1551, 1479, 1456, 1384, 1369, 1250, 1155, 784, 754, 697 cm^{-1}; HRMS-CI m/z: 403.1424 [$(M+H)^+$; calcd for $C_{21}H_{24}ClN_2O_4$: 403.1419].



(2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 3-(Furan-2-yl)-4-nitro-5-phenylpyrrolidine-2-carboxylate (*endo*-**4.3Bl**)

The product *endo*-**4.3Bl** was prepared from *anti*-**4.4Bl** (0.5 mmol, 217 mg) and benzaldehyde (1.0 mmol, 106 mg) by General Procedure E. The crude product was

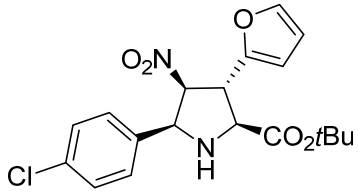
subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 47%. ^{1}H NMR($CDCl_3$, 500 MHz): δ 7.42 – 7.41 (m, 1H), 7.37 – 7.31 (m, 5H), 6.36 (dd, *J* = 3.5, 2.0 Hz, 1H), 6.26 (d, *J* = 3.5 Hz, 1H), 5.34 (dd, *J* = 6.5, 3.5 Hz, 1H), 4.85 (d, *J* = 6.5 Hz, 1H), 4.20 (dd, *J* = 7.0, 3.0 Hz, 1H), 4.06 (d, *J* = 7.0 Hz, 1H), 3.31 (br, *N*H), 1.50 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 170.2, 151.2, 142.9, 134.3, 128.8, 128.8, 126.5, 110.8, 107.8, 94.2, 82.7, 67.8, 65.7, 49.6, 28.1; IR (neat, cm^{-1}): 3303, 3113, 3063, 3037, 2979, 2927, 2841, 1733, 1550, 1456, 1384, 1369, 1251, 1157, 742, 698 cm^{-1}; HRMS-CI m/z: 359.1605 [$(M+H)^+$; calcd for $C_{19}H_{23}N_2O_5$: 359.1601].



(2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 3,5-Bis(4-chlorophenyl)-4-nitropyrrolidine-2-carboxylate (*endo*-**4.3Bm**)

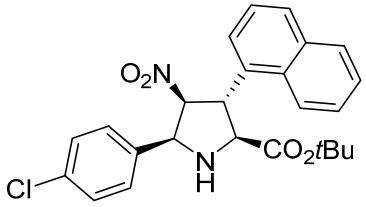
The product *endo*-**4.3Bm** was prepared from *anti*-**4.4Bm** (0.5 mmol, 239 mg) and 4-chlorobenzaldehyde (1.0 mmol, 141 mg) by General Procedure E. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 71%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.37 – 7.35 (m, 2H), 7.34 – 7.29 (m, 4H), 7.21 (dd, *J* = 6.5, 1.5 Hz, 2H), 5.23 (dd, *J* = 7.0, 4.5 Hz, 1H), 4.86 (d, *J* = 7.0 Hz, 1H), 4.08 (dd, *J* = 8.0, 4.5 Hz, 1H), 3.94 (d, *J* = 8.0 Hz, 1H), 1.44 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 170.2, 136.9, 134.9, 134.1, 133.5, 129.5, 129.1, 129.1, 128.1, 96.6, 82.9, 67.8, 66.7, 54.8, 28.1; IR (neat, cm^{-1}): 3355, 3028, 2980, 2926,

1732, 1550, 1494, 1384, 1369, 1250, 1156, 1093, 1015, 822 cm^{-1}; HRMS-CI m/z: 437.1018 [$(M+H)^+$; calcd for $C_{21}H_{23}Cl_2N_2O_4$: 437.1029].



(2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 5-(4-Chlorophenyl)-3-(furan-2-yl)-4-nitropyrrolidine-2-carboxylate (*endo*-**4.3Bn**)

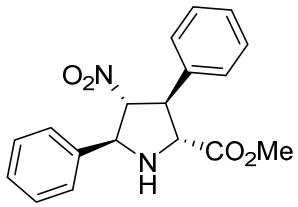
The product *endo*-**4.3Bn** was prepared from *anti*-**4.4Bl** (0.5 mmol, 217 mg) and 4-chlorobenzaldehyde (1.0 mmol, 141 mg) by General Procedure E. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 68%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.41 (t, J = 1.0 Hz, 1H), 7.33 – 7.26 (m, 4H), 6.36 (dd, J = 3.5, 1.5 Hz, 1H), 6.25 (d, J = 3.5 Hz, 1H), 5.32 (dd, J = 6.5, 3.5 Hz, 1H), 4.82 (d, J = 6.0 Hz, 1H), 4.20 (dd, J = 7.0, 3.0 Hz, 1H), 4.04 (d, J = 7.0 Hz, 1H), 3.19 (br, *N*H), 1.49 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 170.1, 151.0, 142.9, 134.7, 133.0, 129.1, 128.0, 110.8, 107.9, 93.9, 82.8, 66.9, 65.5, 49.2, 28.1; IR (neat, cm^{-1}): 3339, 3117, 2979, 2931, 1733, 1550, 1496, 1448, 1384, 1369, 1299, 1251, 1157, 1094, 1015, 841, 741 cm^{-1}; HRMS-CI m/z: 393.1215 [$(M+H)^+$; calcd for $C_{19}H_{22}ClN_2O_5$: 393.1212].



(2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 5-(4-Chlorophenyl)-3-(naphthalen-1-yl)-4-nitropyrrolidine-2-carboxylate (*endo*-**4.3Bo**)

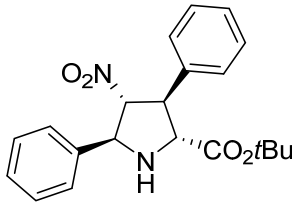
The product *endo*-**4.3Bo** was prepared from *anti*-**4.4Bo** (0.5 mmol, 247 mg) and 4-chlorobenzaldehyde (1.0 mmol, 141 mg) by General Procedure E. The crude product was subjected to chromatography on a short silica column (10 - 20% ethyl acetate in hexanes); the yield of the title compound was 55%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.00 (d, J = 8.5 Hz, 1H), 7.92 – 7.90 (m,1H), 7.85 (dd, J = 7.0, 2.0 Hz, 1H), 7.58 – 7.50 (m, 4H), 7.34 – 7.30 (td, J = 9.5, 2.5 Hz, 4H), 5.22 (dd, J = 6.5, 3.5 Hz, 1H), 5.07 (dd, J = 6.5, 3.5 Hz, 1H), 4.97 (d, J = 6.0 Hz, 1H), 4.28 (d, J = 6.0 Hz, 1H), 3.38 (br, *N*H), 1.32 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 171.0, 135.0, 134.8, 134.2, 133.5, 131.5, 129.3, 129.1, 128.9, 128.1, 127.2, 126.4, 125.6, 124.1, 122.7, 97.1, 82.7, 67.8, 67.2, 50.5, 27.9; IR (neat, cm^{-1}): 3345, 3069, 3044, 3005, 2979, 2930, 1731, 1598, 1550, 1512, 1495, 1456, 1394, 1369, 1332, 1256, 1217, 1157, 1094, 1015, 841, 799, 778, 757 cm^{-1}; HRMS-CI m/z: 453.1591 [$(M+H)^+$; calcd for $C_{25}H_{26}ClN_2O_4$: 453.1576].

General Procedure F for the Synthesis of *exo'*-**4.3M**



rac-Methyl 4-Nitro-3,5-diphenylpyrrolidine-2-carboxylate (*exo'*-**4.3Ma**)

To the solution of methyl (*E*)-2-(benzylideneamino)acetate (0.5 mmol, 89 mg), 1-((*E*)-2-nitrovinyl)benzene (0.5 mmol, 75 mg) in dry acetonitrile (2.5 mL) and nickel(II) acetylacetonate (0.05 mmol) were added at ambient temperature. The resulting solution was stirred for 18 h. The crude product was subjected to chromatography on a short silica column (10% ethyl acetate in hexanes); the yield of the title compound was 30%. ^{1}H NMR and ^{13}C NMR spectra of this compound are consistent with previously reported data in the literature.[21] ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.48 – 7.46 (m, 2H), 7.43 – 7.28 (m, 8H), 4.91 – 4.86 (m, 2H), 4.21 – 4.19 (m, 1H), 4.14 (d, J = 5.0 Hz, 1H), 3.81 (s, 3H), 2.98 (br, *N*H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 173.8, 139.4, 138.6, 129.4, 129.0, 128.9, 128.2, 127.5, 126.9, 98.6, 67.3, 65.9, 54.2, 52.9; IR (neat, cm^{-1}): 3338, 3060, 3031, 3015, 2955, 2911, 2847, 1738, 1552, 1495, 1456, 1436, 1367, 1332, 1220, 1129, 757, 700 cm^{-1}; HRMS-CI m/z: 327.1329 [$(M+H)^+$; calcd for $C_{18}H_{19}N_2O_4$: 327.1339].



rac-*tert*-Butyl 4-Nitro-3,5-diphenylpyrrolidine-2-carboxylate (*exo'*-**4.3Ba**)

The product *exo'*-**4Ba** was prepared from **4.1a** (0.5 mmol, 110 mg) and 1-((*E*)-2-nitrovinyl)benzene (0.5 mmol, 75 mg) by General Procedure F. The crude product was subjected to chromatography on a short silica column (10% ethyl acetate in hexanes); the yield of the title compound was 30%. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.49 (d, *J* = 7.5 Hz, 2H), 7.42 – 7.28 (m, 8H), 4.94 – 4.90 (m, 2H), 4.14 – 4.12 (m, 1H), 4.01 (d, *J* = 6.0 Hz, 1H), 3.01 (br, *N*H), 1.47 (s, 9H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz): δ 172.2, 139.4, 139.2, 129.2, 129.0, 128.7, 128.0, 127.6, 126.8, 98.8, 82.6, 67.2, 66.7, 55.1, 28.1; IR (neat, cm^{-1}): 3335, 3066, 3031, 3006, 2974, 2923, 1729, 1552, 1502, 1456, 1369, 1248, 1157, 758, 700 cm^{-1}; HRMS-CI m/z: 369.1814 [$(M+H)^+$; calcd for $C_{21}H_{25}N_2O_4$: 369.1809].

Conditions for Determination of Enantiomeric Excess

The enantiomeric excess values for the products were determined by chiral HPLC analysis using Chiralcel OD-H, AS-H, and AD-H columns.

(1) (2*R*,3*S*,4*R*,5*R*)-Methyl 4-Nitro-3,5-diphenylpyrrolidine-2-carboxylate (*endo*-**4.3Ma**): t_{minor} = 17.93 min t_{major} = 27.60 min (OD-H Column, hexanes/2-propanol : 80/20, 1.0 mL/min)

(2) (2*R*,3*S*,4*R*,5*R*)-Methyl 4-Nitro-3-phenyl-5-(*p*-tolyl)pyrrolidine-2-carboxylate (*endo*-**4.3Mb**): t_{minor} = 15.13 min t_{major} = 17.64 min (OD-H Column, hexanes/2-propanol : 80/20, 1.0 mL/min)

(3) (2*R*,3*S*,4*R*,5*R*)-Methyl 5-(4-Chlorophenyl)-4-nitro-3-phenylpyrrolidine-2-carboxylate (*endo*-**4.3Mc**): t_{minor} = 21.70 min t_{major} = 25.62 min (OD-H Column, hexanes/2-propanol : 80/20, 1.0 mL/min)

(4) (2*R*,3*S*,4*R*,5*R*)-Methyl 5-(3-Chlorophenyl)-4-nitro-3-phenylpyrrolidine-2-carboxylate (*endo*-**4.3Md**): t_{minor} = 33.76 min t_{major} = 36.69 min (OD-H Column, hexanes/2-propanol : 90/10, 0.8 mL/min)

(5) (2*R*,3*S*,4*R*,5*R*)-Methyl 4-Nitro-3-phenyl-5-(*m*-tolyl)pyrrolidine-2-carboxylate (*endo*-**4.3Me**): t_{minor} = 21.01 min t_{major} = 33.68 min (OD-H Column, hexanes/2-propanol : 85/15, 0.8 mL/min)

(6) (2*R*,3*S*,4*R*,5*R*)-Methyl 5-(2-Chlorophenyl)-4-nitro-3-phenylpyrrolidine-2-carboxylate (*endo*-**4.3Mf**): t_{major} = 19.15 min t_{minor} = 21.47 min (OD-H Column, hexanes/2-propanol : 90/10, 0.8 mL/min)

(7) (2*R*,3*S*,4*R*,5*R*)-Methyl 5-(Naphthalen-2-yl)-4-nitro-3-phenylpyrrolidine-2-carboxylate (*endo*-**4.3Mg**): t_{major} = 41.95 min t_{minor} = 52.73 min (OD-H Column, hexanes/2-propanol : 85/15, 0.8 mL/min)

(8) (2*R*,3*S*,4*R*,5*S*)-Methyl 4-Nitro-3-phenyl-5-(thiophen-2-yl)pyrrolidine-2-carboxylate (*endo*-**4.3Mh**): t_{major} = 29.53 min t_{minor} = 33.84 min (AD-H Column, hexanes/2-propanol : 90/10, 0.7 mL/min)

(9) (2*R*,3*S*,4*R*,5*R*)-Methyl 4-Nitro-5-phenyl-3-(*p*-tolyl)pyrrolidine-2-carboxylate (*endo*-**4.3Mi**): t_{minor} = 16.76 min t_{major} = 26.42 min (OD-H Column, hexanes/2-propanol : 80/20, 1.0 mL/min)

(10) (2*R*,3*S*,4*R*,5*R*)-Methyl 3-(4-Chlorophenyl)-4-nitro-5-phenylpyrrolidine-2-carboxylate (*endo*-**4.3Mj**): t_{major} = 26.12 min t_{minor} = 30.47 min (OD-H Column, hexanes/2-propanol : 80/20, 1.0 mL/min)

(11) (2*R*,3*S*,4*R*,5*R*)-Methyl 4-Nitro-3,5-di-*p*-tolylpyrrolidine-2-carboxylate (*endo*-**4.3Mk**): t_{minor} = 33.03 min t_{major} = 37.56 min (OD-H Column, hexanes/2-propanol : 90/10, 0/8 mL/min)

(12) (2*R*,3*S*,4*R*,5*R*)-Methyl 5-(4-Chlorophenyl)-4-nitro-3-(*p*-tolyl)pyrrolidine-2-carboxylate (*endo*-**4.3Ml**): t_{major} = 12.29 min t_{minor} = 15.90 min (OD-H Column, hexanes/2-propanol : 80/20, 1.0 mL/min)

(13) (2*S*,3*R*,4*S*,5*S*)-Methyl 3-(4-Fluorophenyl)-4-nitro-5-(*p*-tolyl)pyrrolidine-2-carboxylate (*endo*-**4.3Mm**): t_{major} = 18.22 min t_{minor} = 23.94 min (OD-H Column, hexanes/2-propanol : 80/20, 1.0 mL/min)

(14) (2*R*,3*S*,4*R*,5*R*)-Methyl 5-(4-Chlorophenyl)-4-nitro-3-(*m*-tolyl)pyrrolidine-2-carboxylate (*endo*-**4.3Mn**): t_{major} = 22.89 min t_{minor} = 26.17 min (OD-H Column, hexanes/2-propanol : 90/10, 0.8 mL/min)

(15) (2*R*,3*R*,4*R*,5*R*)-Methyl 2-Methyl-4-nitro-3,5-diphenylpyrrolidine-2-carboxylate (*endo*-**4.3Mo**): t_{major} = 10.80 min t_{minor} = 16.02 min (AD-H Column, hexanes/2-propanol : 90/10, 1.0 mL/min)

(16) (2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 4-Nitro-3,5-diphenylpyrrolidine-2-carboxylate (*endo*-**4.3Ba**): t_{minor} = 10.17 min t_{major} = 14.75 min (OD-H Column, hexanes/2-propanol : 90/10, 0.8 mL/min)

(17) (2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 4-Nitro-3-phenyl-5-(*p*-tolyl)pyrrolidine-2-carboxylate (*endo*-**4.3Bb**): t_{minor} = 8.98 min t_{major} = 11.47 min (OD-H Column, hexanes/2-propanol : 90/10, 0.8 mL/min)

(18) (2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 5-(4-Methoxyphenyl)-4-nitro-3-phenylpyrrolidine-2-carboxylate (*endo*-**4.3Bc**): t_{minor} = 13.97 min t_{major} = 24.64 min (OD-H Column, hexanes/2-propanol : 90/10, 0.8 mL/min)

(19) (2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 5-(4-Fluorophenyl)-4-nitro-3-phenylpyrrolidine-2-carboxylate (*endo*-**4.3Bd**): t_{minor} = 10.04 min t_{major} = 11.00 min (OD-H Column, hexanes/2-propanol : 90/10, 0.8 mL/min)

(20) (2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 5-(4-Chlorophenyl)-4-nitro-3-phenylpyrrolidine-2-carboxylate (*endo*-**4.3Be**): t_{minor} = 18.59 min t_{major} = 52.36 min (AD-H Column, hexanes/2-propanol : 90/10, 0.7 mL/min)

(21) (2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 4-Nitro-5-(4-nitrophenyl)-3-phenylpyrrolidine-2-carboxylate (*endo*-**4.3Bf**): t_{major} = 25.12 min t_{minor} = 34.37 min (OD-H Column, hexanes/2-propanol : 90/10, 0.8 mL/min)

(22) (2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 5-(3-Bromophenyl)-4-nitro-3-phenylpyrrolidine-2-carboxylate (*endo*-**4.3Bg**): t_{minor} = 11.48 min t_{major} = 15.82 min (OD-H Column, hexanes/2-propanol : 90/10, 0.8 mL/min)

(23) (2*S*,3*R*,4*S*,5*R*)-*tert*-Butyl 4-Nitro-3-phenyl-5-(thiophen-2-yl)pyrrolidine-2-carboxylate (*endo*-**4.3Bh**): t_{major} = 15.03 min t_{minor} = 24.95 min (AD-H Column, hexanes/2-propanol : 90/10, 0.7 mL/min)

(24) (2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 4-Nitro-5-phenyl-3-(*p*-tolyl)pyrrolidine-2-carboxylate (*endo*-**4.3Bi**): t_{minor} = 9.53 min t_{major} = 14.32 min (OD-H Column, hexanes/2-propanol : 90/10, 0.8 mL/min)

(25) (2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 4-Nitro-5-phenyl-3-(*m*-tolyl)pyrrolidine-2-carboxylate (*endo*-**4.3Bj**): t_{minor} = 8.94 min t_{major} = 12.65 min (OD-H Column, hexanes/2-propanol : 90/10, 0.8 mL/min)

(26) (2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 3-(3-Chlorophenyl)-4-nitro-5-phenylpyrrolidine-2-carboxylate (*endo*-**4.3Bk**): t_{minor} = 10.75 min t_{major} = 17.13 min (OD-H Column, hexanes/2-propanol : 90/10, 0.8 mL/min)

(27) (2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 3-(Furan-2-yl)-4-nitro-5-phenylpyrrolidine-2-carboxylate (*endo*-**4.3Bl**): t_{minor} = 13.16 min t_{major} = 16.41 min (OD-H Column, hexanes/2-propanol : 95/5, 0.8 mL/min)

(28) (2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 3,5-Bis(4-chlorophenyl)-4-nitropyrrolidine-2-carboxylate (*endo*-**4.3Bm**): t_{minor} = 12.78 min t_{major} = 19.63 min (OD-H Column, hexanes/2-propanol : 90/10, 0.8 mL/min)

(29) (2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 5-(4-Chlorophenyl)-3-(furan-2-yl)-4-nitropyrrolidine-2-carboxylate (*endo*-**4.3Bn**): t_{major} = 15.16 min t_{minor} = 28.28 min (AD-H Column, hexanes/2-propanol : 90/10, 1.0 mL/min)

(30) (2*S*,3*R*,4*S*,5*S*)-*tert*-Butyl 5-(4-Chlorophenyl)-3-(naphthalen-1-yl)-4-nitropyrrolidine-2 carboxylate (*endo*-**4.3Bo**): t_{minor} = 14.28 min t_{major} = 17.04 min (OD-H Column, hexanes/2 propanol : 90/10, 0.8 mL/min)

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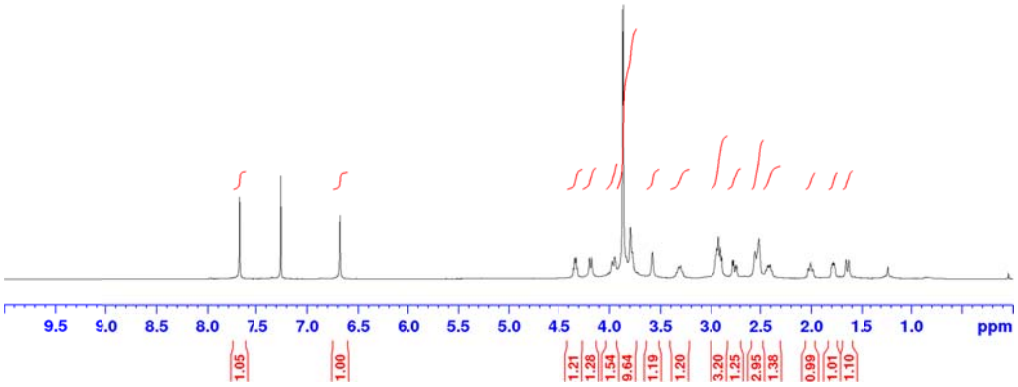
APPENDICES

Appendix A ^{1}H NMR/^{13}C NMR Spectra for Chapter 1

A-1 ^{1}H NMR/^{13}C NMR Spectra

^{1}H NMR and ^{13}C NMR spectra of product **1.2** are published in the literature.[1]

^{1}H NMR and ^{13}C NMR spectra of product **1.3** are published in the literature.[2]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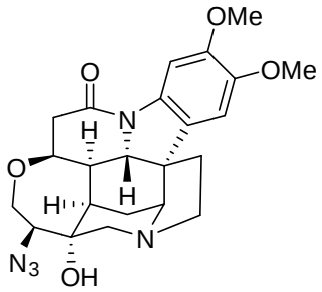
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H
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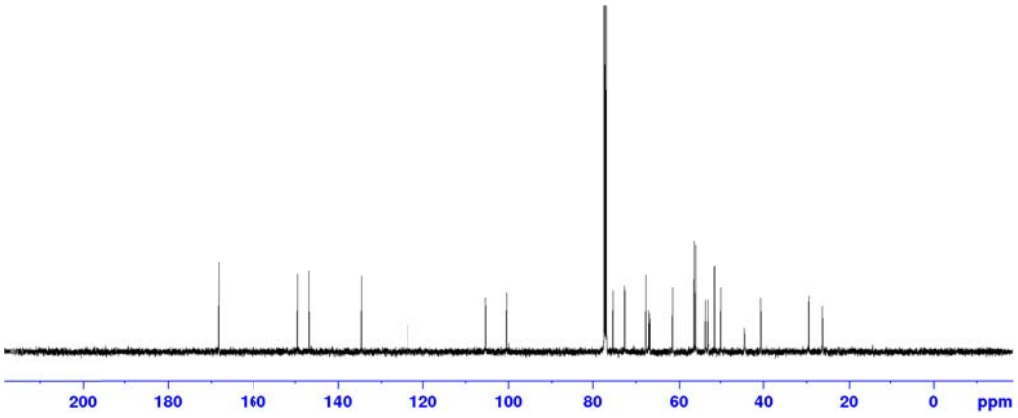
N3
OH

1.4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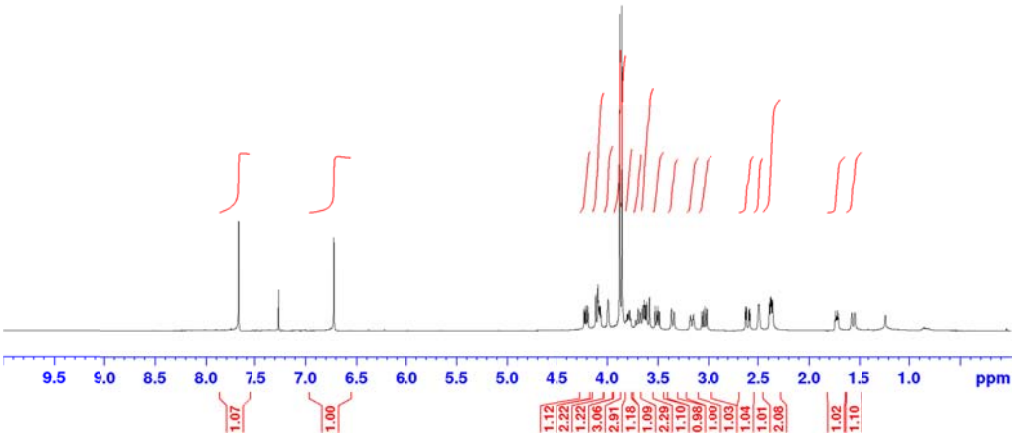
160
140
120
100
80
60
40
20
0
ppm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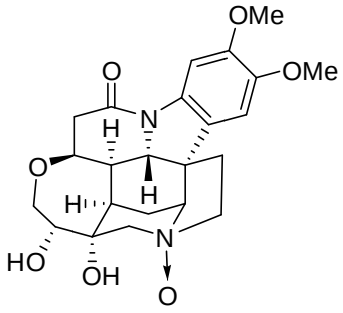
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.07
1.00
1.12
2.22
1.22
3.06
2.91
1.18
1.09
2.29
1.10
0.98
1.00
1.03
1.04
1.01
2.08
1.02
1.10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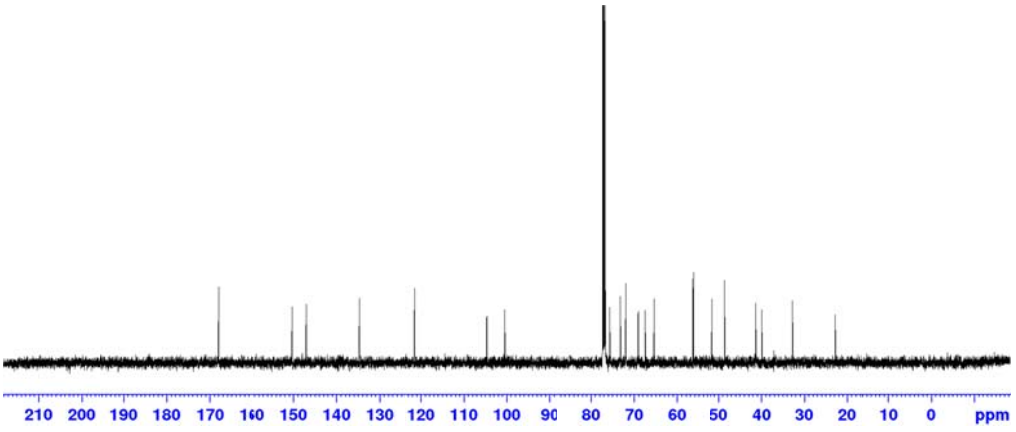
OMe
O
H
N
O
H
H
HO
OH
N
O

1.5


210
200
190
180
170
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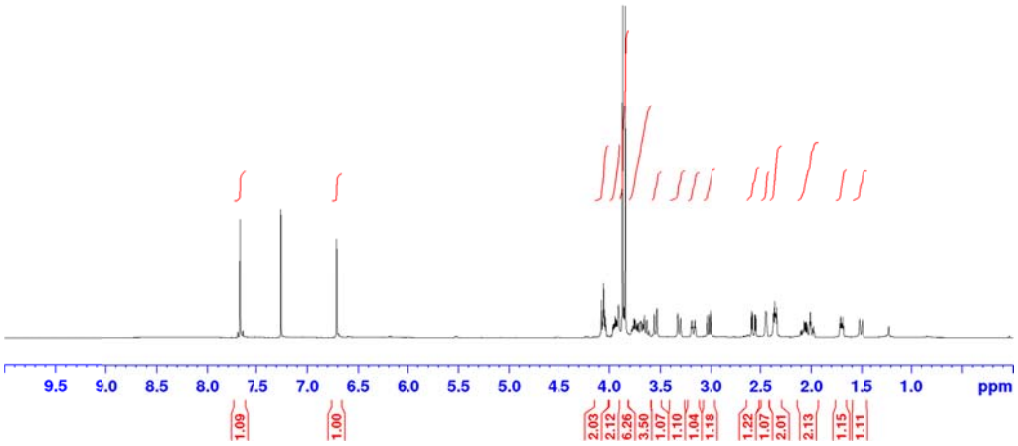
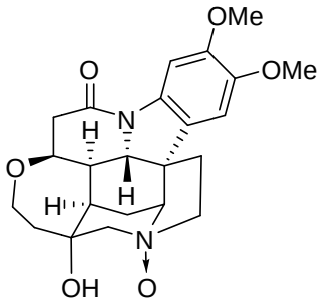
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.09 1.00 2.03 2.12 6.26 3.50 1.07 1.10 1.04 1.18 1.22 1.07 2.01 2.13 1.15 1.11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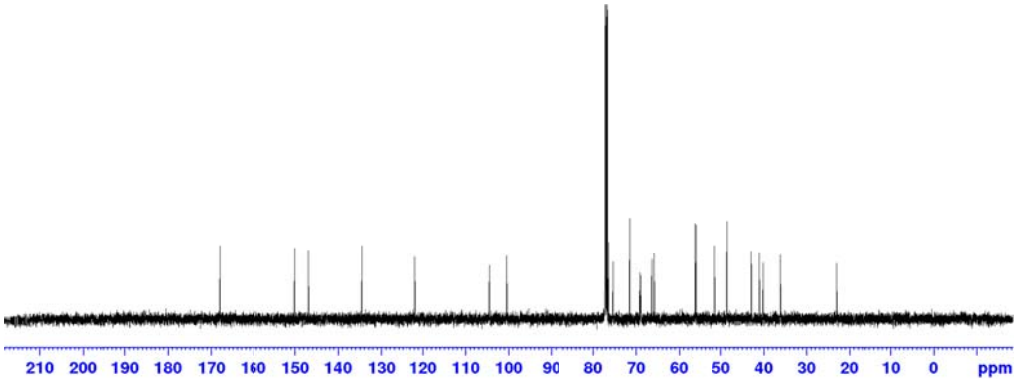
OMe
O
N
H
O
H
H
N
OH
O

1.6b


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

A-2 References

1. Kim, H. Y., Shih, H.-J., Knabe, W. E., & Oh, K. (2009). Reversal of Enantioselectivity between the Copper(I)- and Silver(I)-Catalyzed 1,3-Dipolar Cycloaddition Reactions Using a Brucine-Derived Amino Alcohol Ligand. *Angewandte Chemie International Edition*, *48*(40), 7420-7423.

2. Oh, K., Li, J.-Y., & Ryu, J. (2010). Brucine *N*-Oxide-Catalyzed Morita-Baylis-Hillman Reaction of Vinyl Ketones: a Mechanistic Implication of Dual Catalyst System with Proline. *Organic & Biomolecular Chemistry, 8*(13), 3015-3024.

Appendix B ^{1}H NMR/^{13}C NMR Spectra for Chapter 2

B-1 ^{1}H NMR/^{13}C NMR Spectra

^{1}H NMR and ^{13}C NMR spectra of product **2.2a** are published in the literature.[1]

^{1}H NMR and ^{13}C NMR spectra of product **2.2b** are published in the literature.[1]

^{1}H NMR and ^{13}C NMR spectra of product **2.2c** are published in the literature.[1]

^{1}H NMR and ^{13}C NMR spectra of product **2.2d** are published in the literature.[1]

^{1}H NMR and ^{13}C NMR spectra of product **2.2e** are published in the literature.[1]

^{1}H NMR and ^{13}C NMR spectra of product **2.2f** are published in the literature.[1]

^{1}H NMR and ^{13}C NMR spectra of product **2.2g** are published in the literature.[1]

^{1}H NMR and ^{13}C NMR spectra of product **2.2h** are published in the literature.[1]

^{1}H NMR and ^{13}C NMR spectra of product **2.2i** are published in the literature.[1]

^{1}H NMR and ^{13}C NMR spectra of product **2.2j** are published in the literature.[1]

^{1}H NMR and ^{13}C NMR spectra of product **2.2k** are published in the literature.[1]

^{1}H NMR and ^{13}C NMR spectra of product **2.2l** are published in the literature.[1]

^{1}H NMR and ^{13}C NMR spectra of product **2.2m** are published in the literature.[1]

^{1}H NMR and ^{13}C NMR spectra of product **2.2n** are published in the literature.[1]

^{1}H NMR and ^{13}C NMR spectra of product **2.2o** are published in the literature.[1]

^{1}H NMR and ^{13}C NMR spectra of product **2.2p** are published in the literature.[1]

^{1}H NMR and ^{13}C NMR spectra of product **2.2q** are published in the literature.[1]

^{1}H NMR and ^{13}C NMR spectra of product **2.2r** are published in the literature.[1]

^{1}H NMR and ^{13}C NMR spectra of product **2.2s** are published in the literature.[1]

^{1}H NMR and ^{13}C NMR spectra of product **2.2u** are published in the literature.[1]

^{1}H NMR and ^{13}C NMR spectra of product **2.2x** are published in the literature.[1]

^{1}H NMR and ^{13}C NMR spectra of product **2.3a** are published in the literature.[2]

^{1}H NMR and ^{13}C NMR spectra of product **2.3b** are published in the literature.[2]

^{1}H NMR and ^{13}C NMR spectra of product **2.3c** are published in the literature.[2]

^{1}H NMR and ^{13}C NMR spectra of product **2.3d** are published in the literature.[2]

^{1}H NMR and ^{13}C NMR spectra of product **2.3e** are published in the literature.[2]

^{1}H NMR and ^{13}C NMR spectra of product **2.3f** are published in the literature.[2]

^{1}H NMR and ^{13}C NMR spectra of product **2.3g** are published in the literature.[2]

^{1}H NMR and ^{13}C NMR spectra of product **2.3h** are published in the literature.[2]

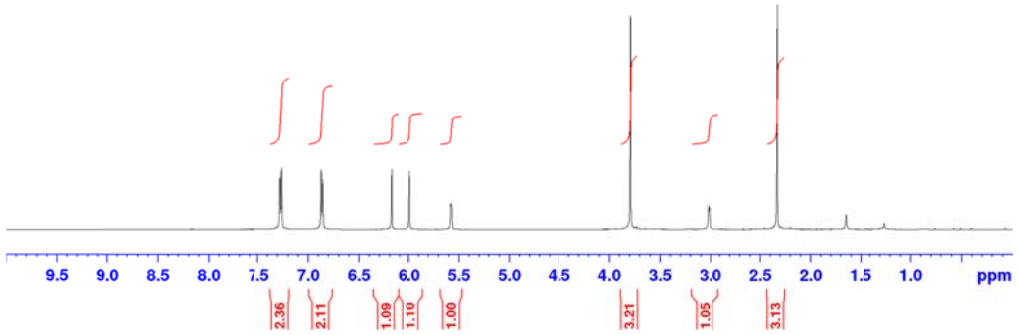
^{1}H NMR and ^{13}C NMR spectra of product **2.3i** are published in the literature.[2]

^{1}H NMR and ^{13}C NMR spectra of product **2.3j** are published in the literature.[2]

^{1}H NMR and ^{13}C NMR spectra of product **2.3k** are published in the literature.[2]

^{1}H NMR and ^{13}C NMR spectra of product **2.3l** are published in the literature.[2]

^{1}H NMR and ^{13}C NMR spectra of product **2.3m** are published in the literature.[2]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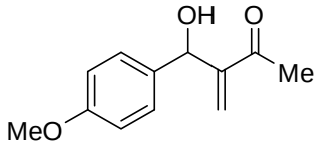
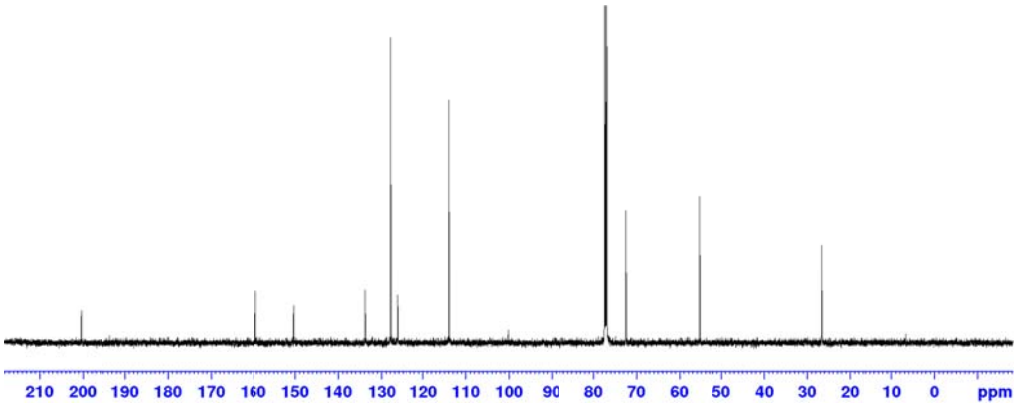
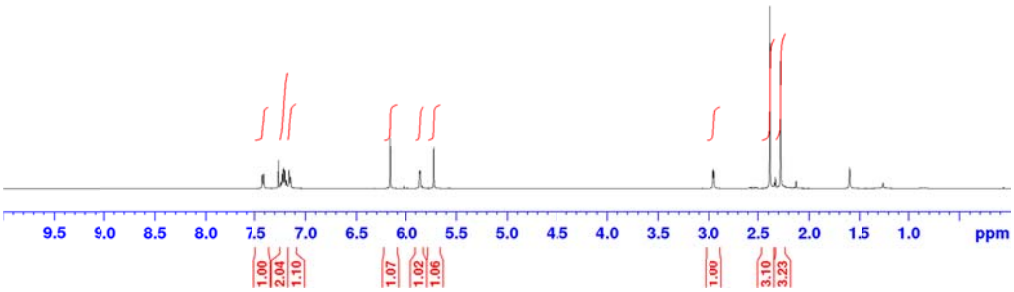
1.09
1.10
1.00
3.21
1.05
3.13


OH
O
Me
MeO

2.2t


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
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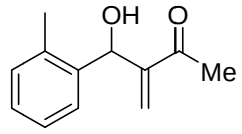
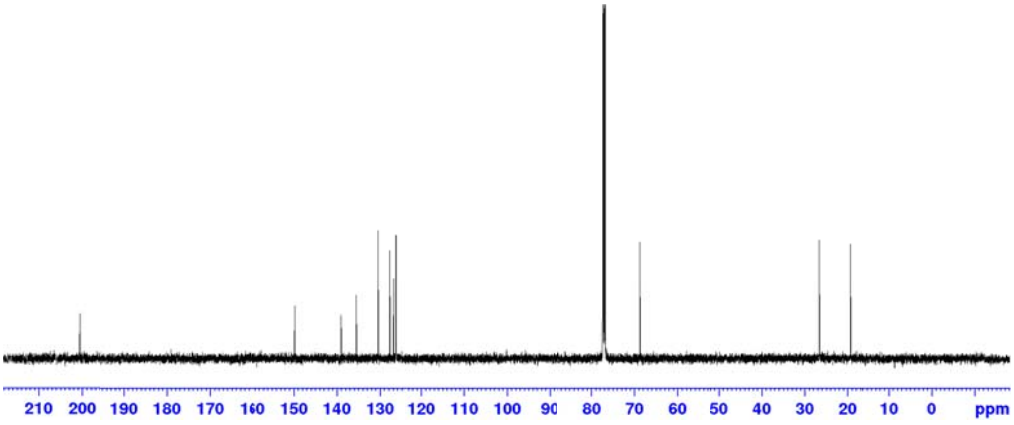
1.02
1.06
1.00
3.10
3.23


OH
O
Me

2.2v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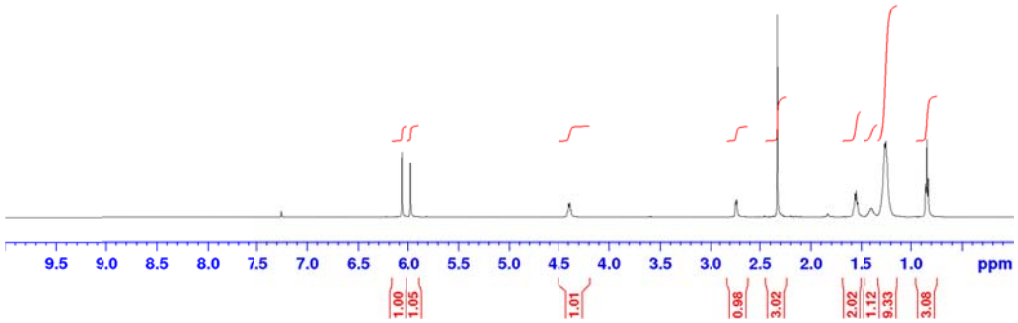
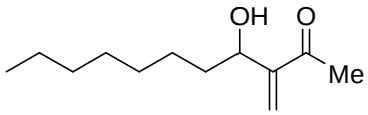
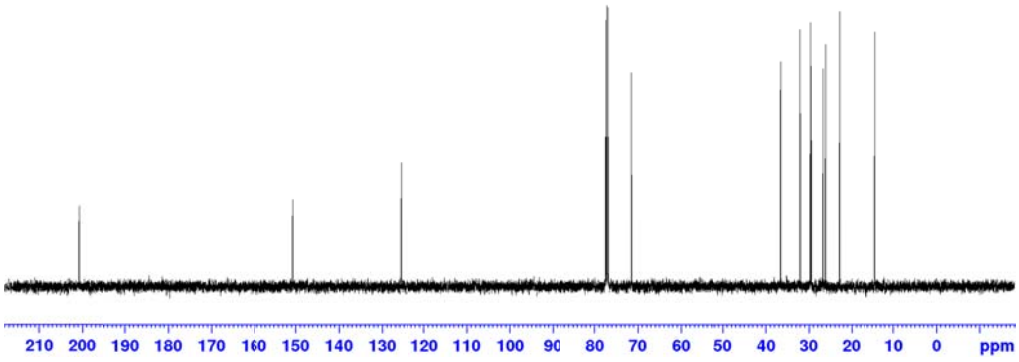

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
1.05
1.01
0.98
3.02
2.02
1.12
9.33
3.08


OH
O
Me

2.2y

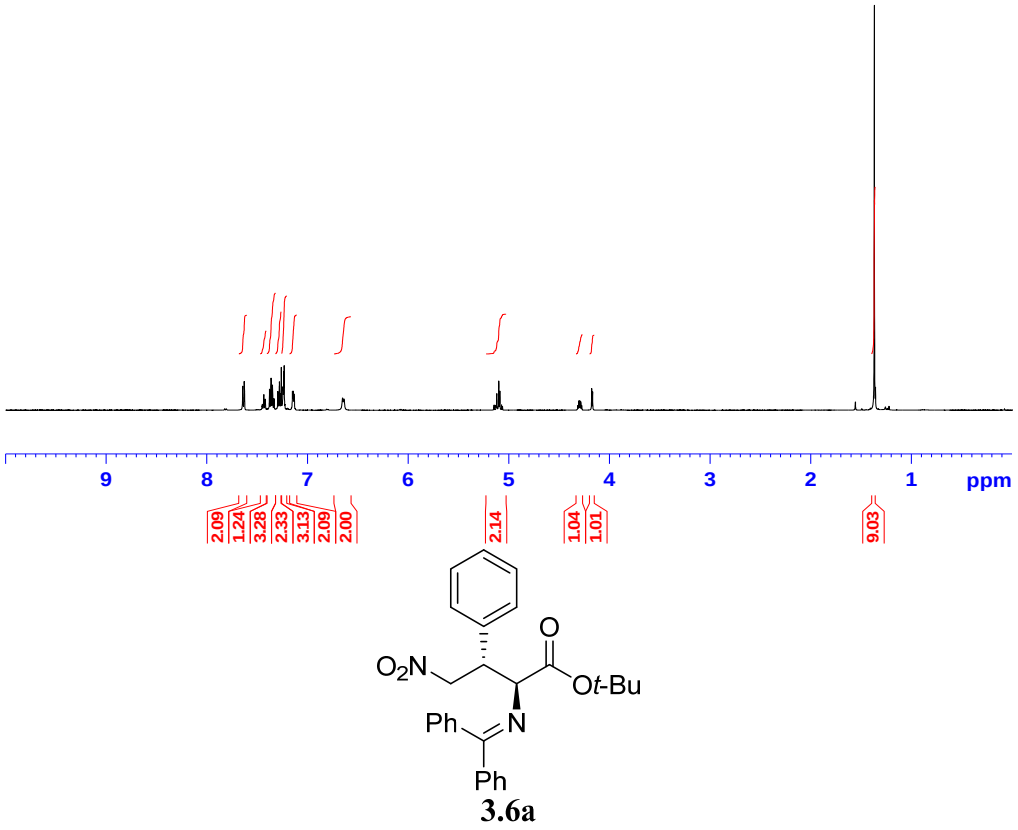

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

B-2 References

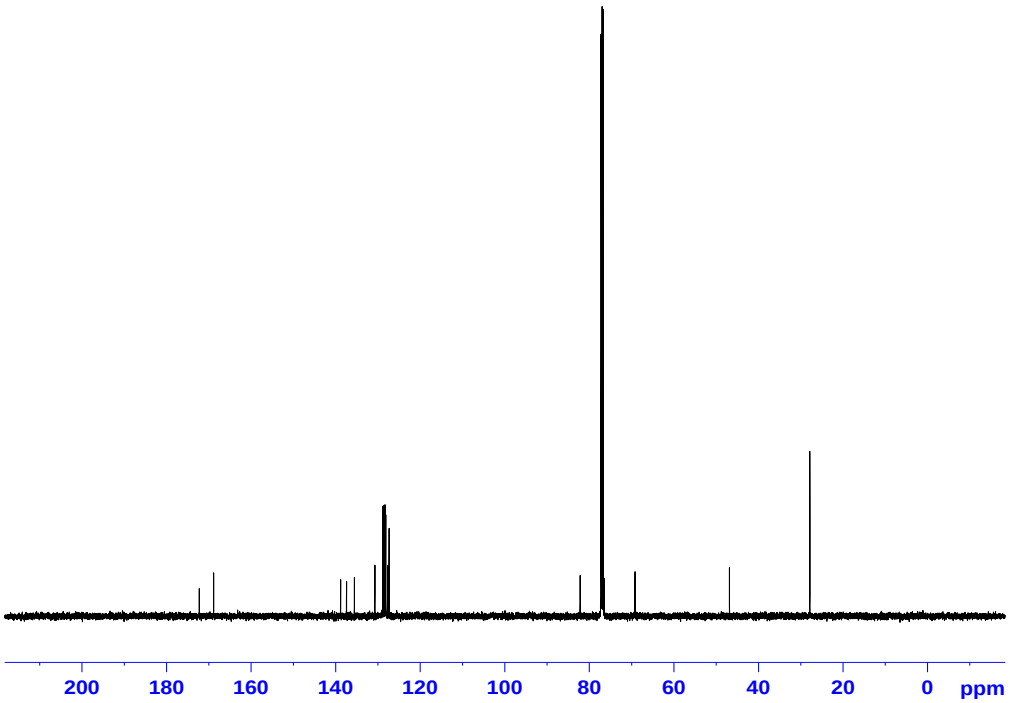
1. Oh, K., Li, J.-Y., & Ryu, J. (2010). Brucine *N*-Oxide-Catalyzed Morita-Baylis-Hillman Reaction of Vinyl Ketones: a Mechanistic Implication of Dual Catalyst System with Proline. *Organic & Biomolecular Chemistry, 8*(13), 3015-3024.

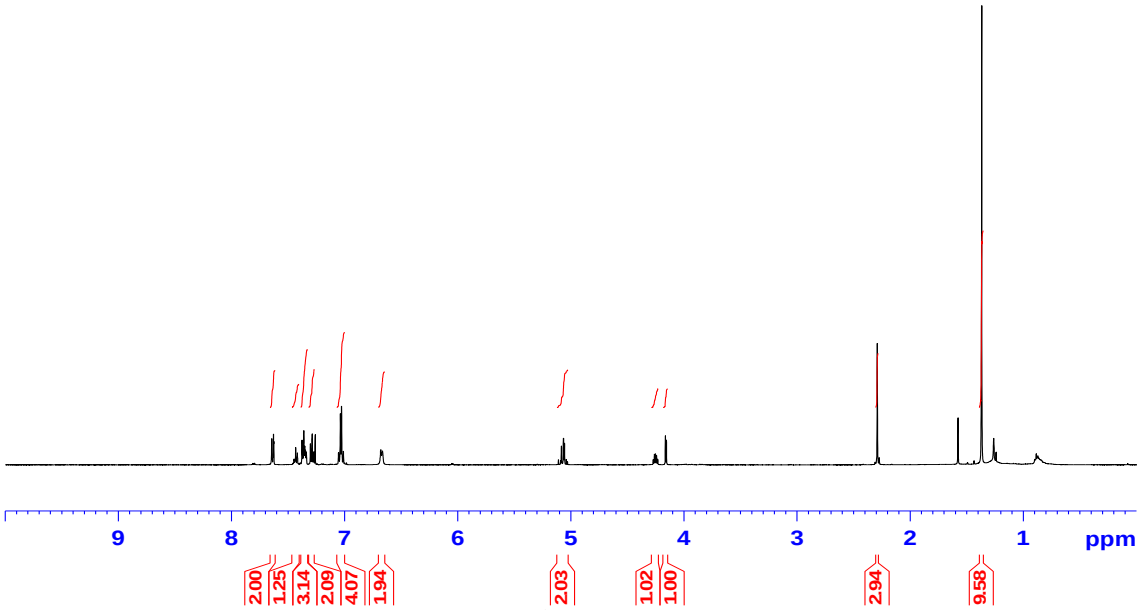
2. Oh, K., & Li, J.-Y. (2011). A Cooperative Catalysis Approach to the Morita-Baylis-Hillman Reaction of Aryl Vinyl Ketones. *Synthesis, 2011*(12), 1960-1967.

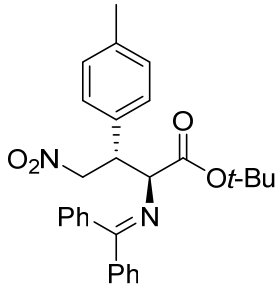
Appendix C ^{1}H NMR/^{13}C NMR Spectra for Chapter 3



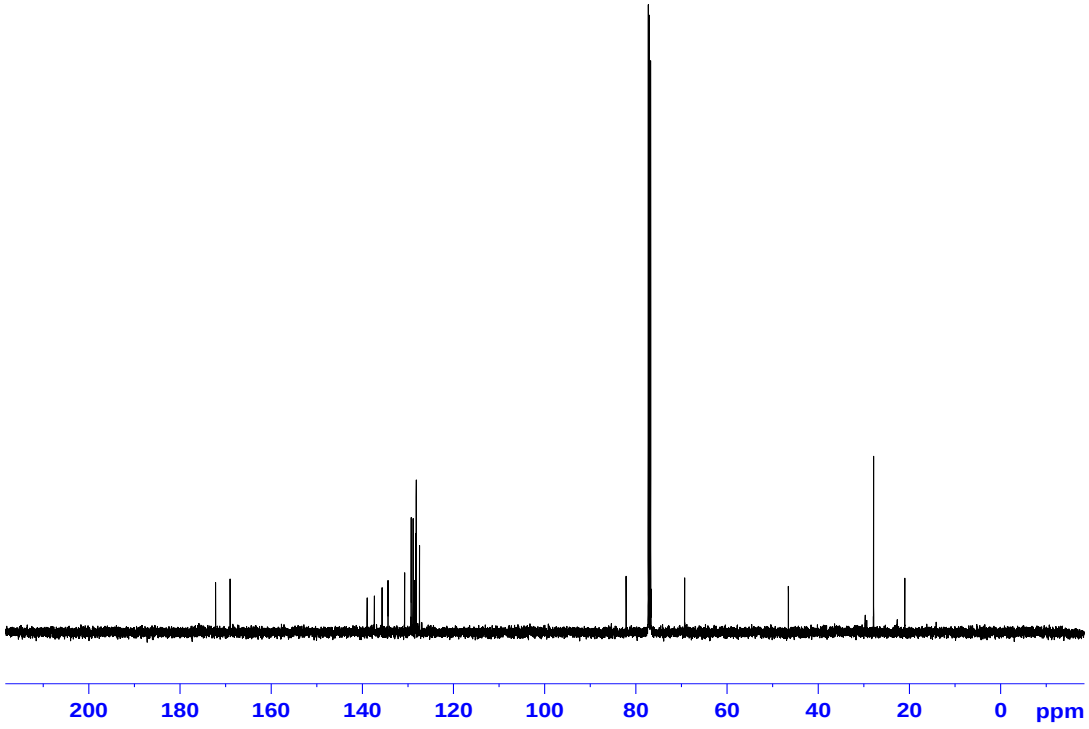
3.6a




9
8
7
6
5
4
3
2
1
ppm
2.00
1.25
3.14
2.09
4.07
1.94
2.03
1.02
1.00
2.94
9.58


O2N
O
Ot-Bu
Ph
N
Ph

3.6b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180
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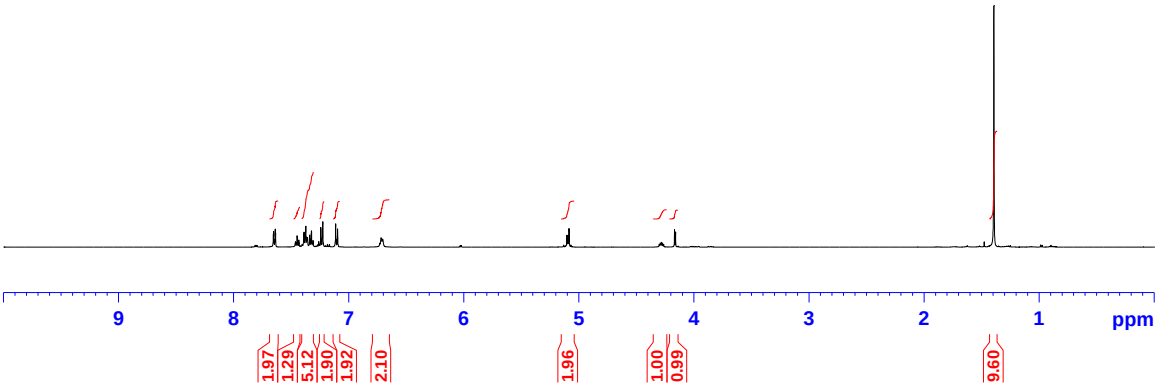
140
120
100
80
60
40
20
0
ppm


9
8
7
6
5
4
3
2
1
ppm
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1.29
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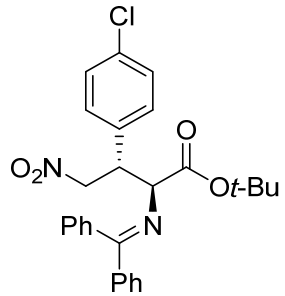
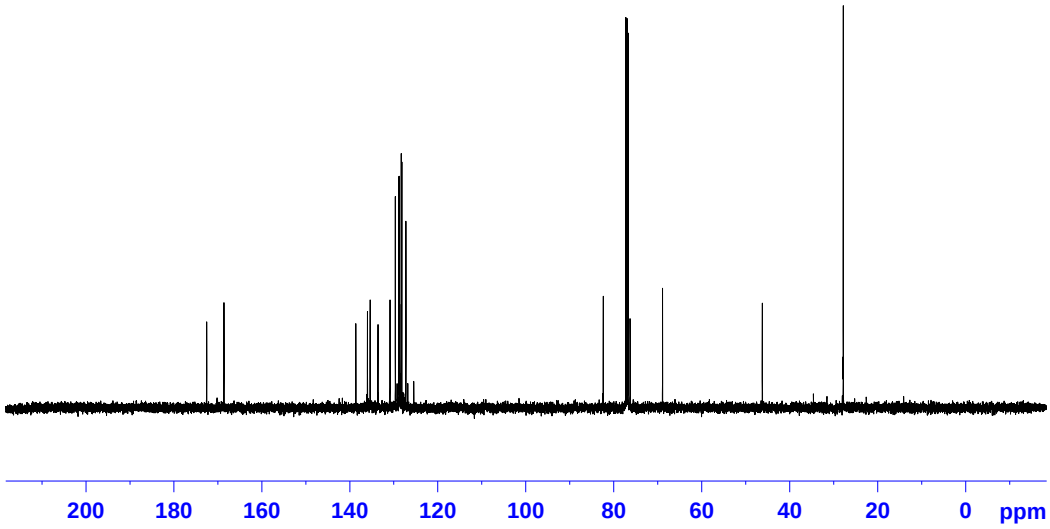
1.90
1.92
2.10
1.96
1.00
0.99
9.60


Cl
O
O2N
Ot-Bu
Ph
N
Ph

3.6c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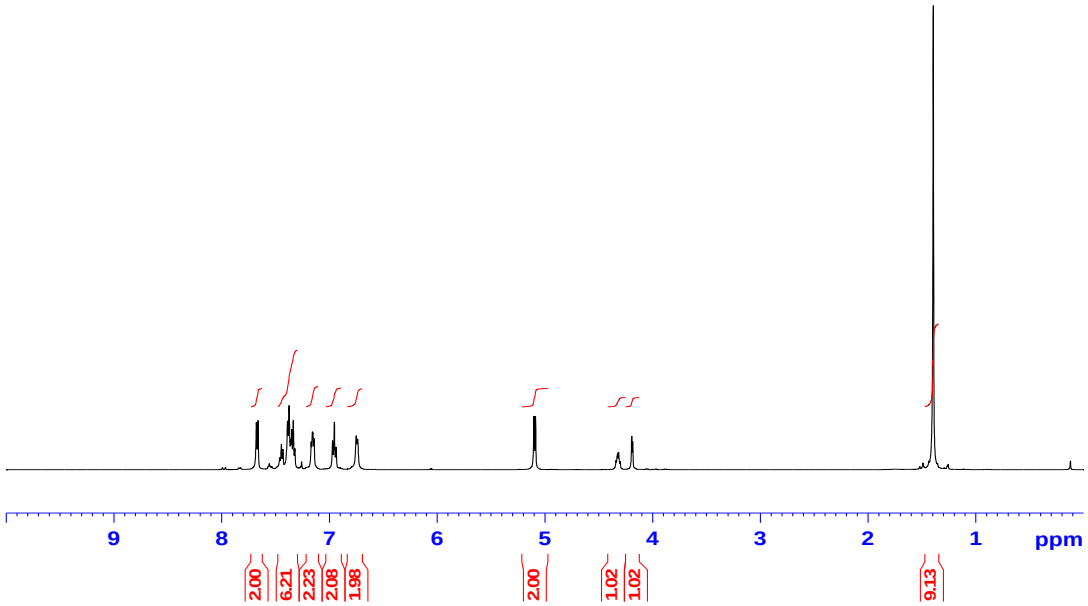
120
100
80
60
40
20
0
ppm


9
8
7
6
5
4
3
2
1
ppm
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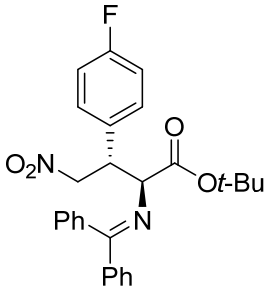
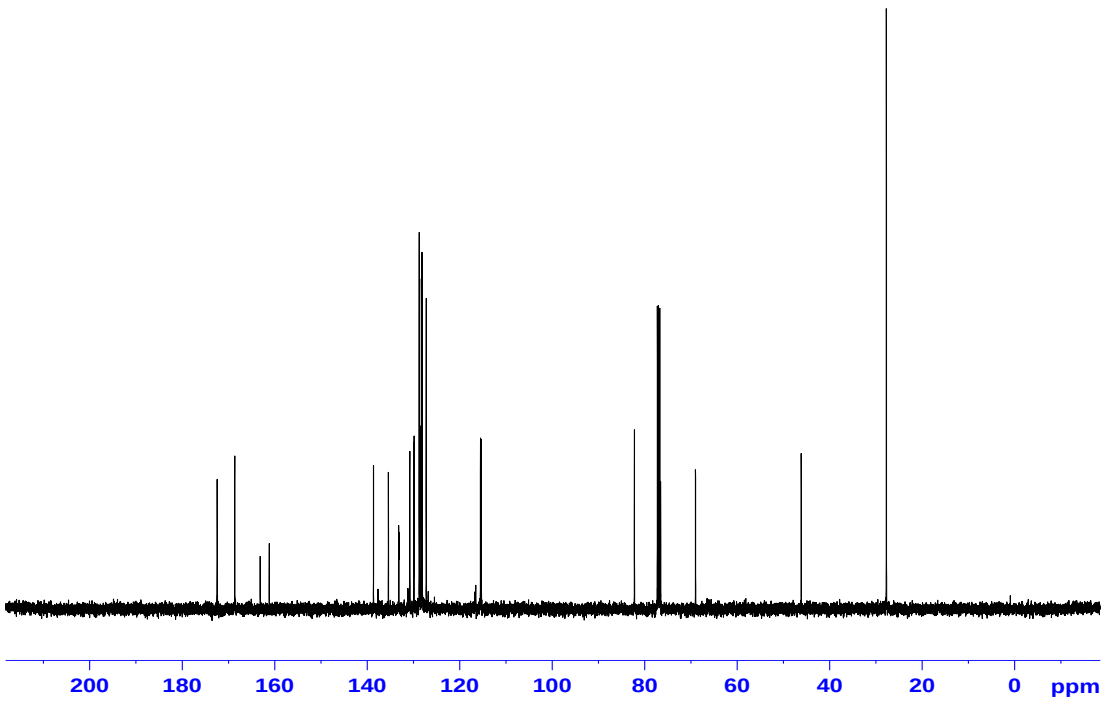
2.00
1.02
1.02
9.13


F
O
O2N
Ot-Bu
Ph
N
Ph

3.6d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140
120
100
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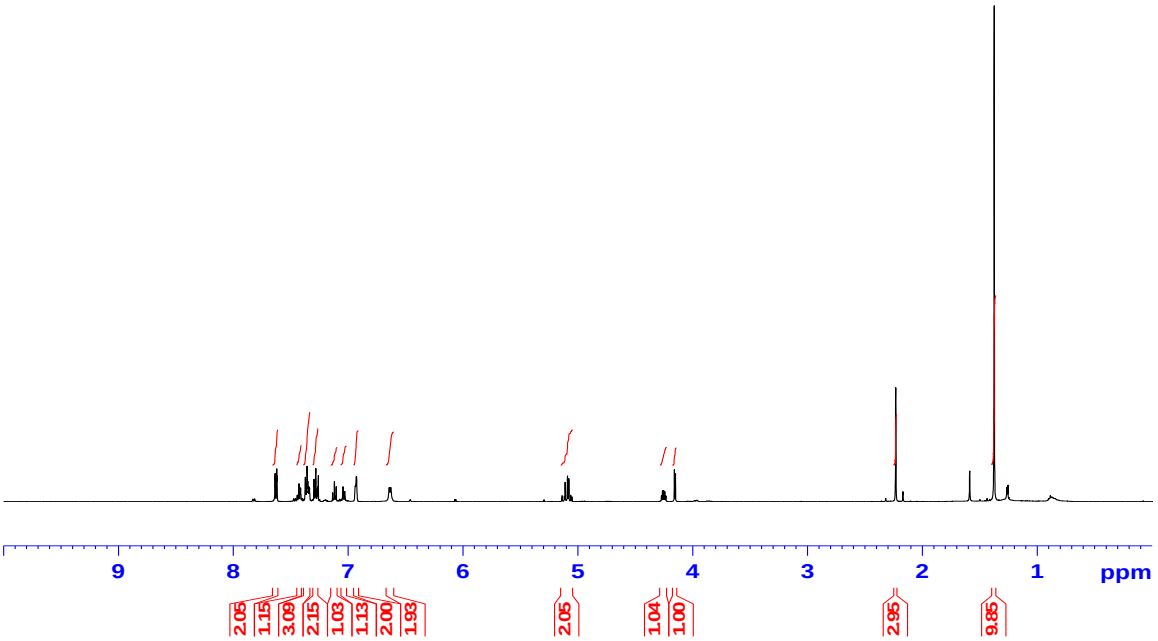
60
40
20
0
ppm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4
3
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1
ppm
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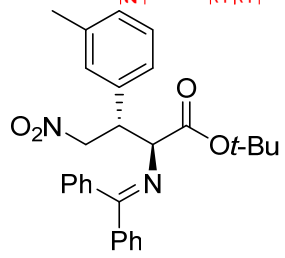
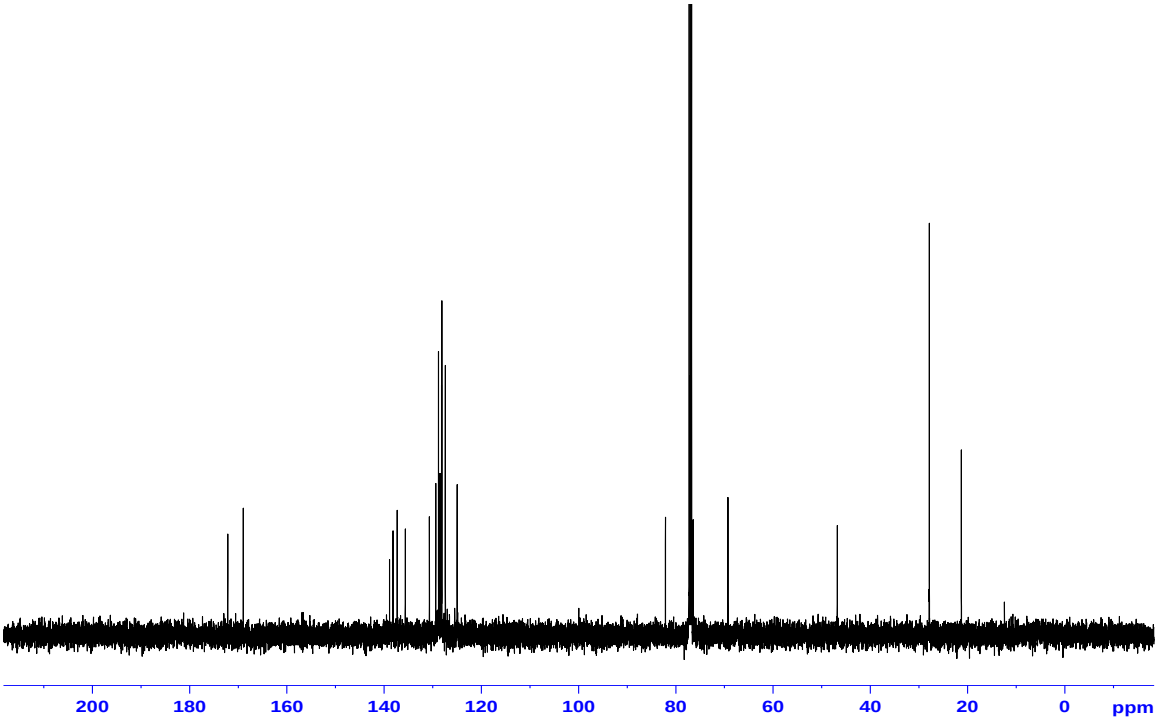
1.93
2.05
1.04
1.00
2.95
9.85


O2N
O
Ot-Bu
Ph
N
Ph

3.6e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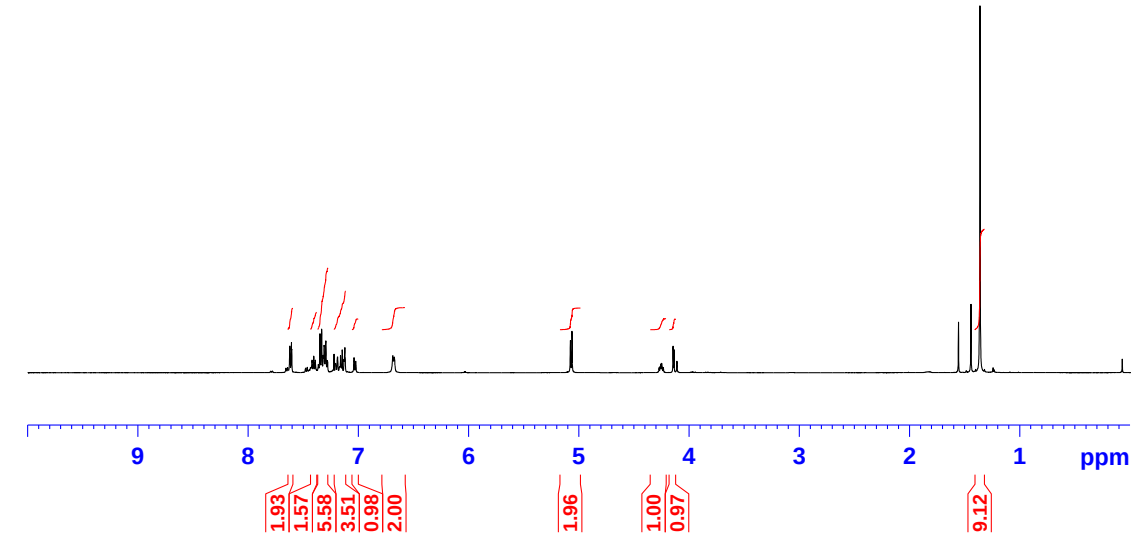
20
0
ppm


9
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5
4
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2
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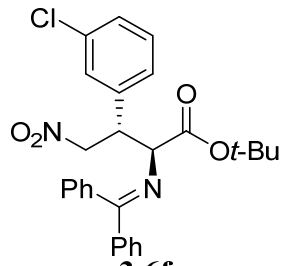
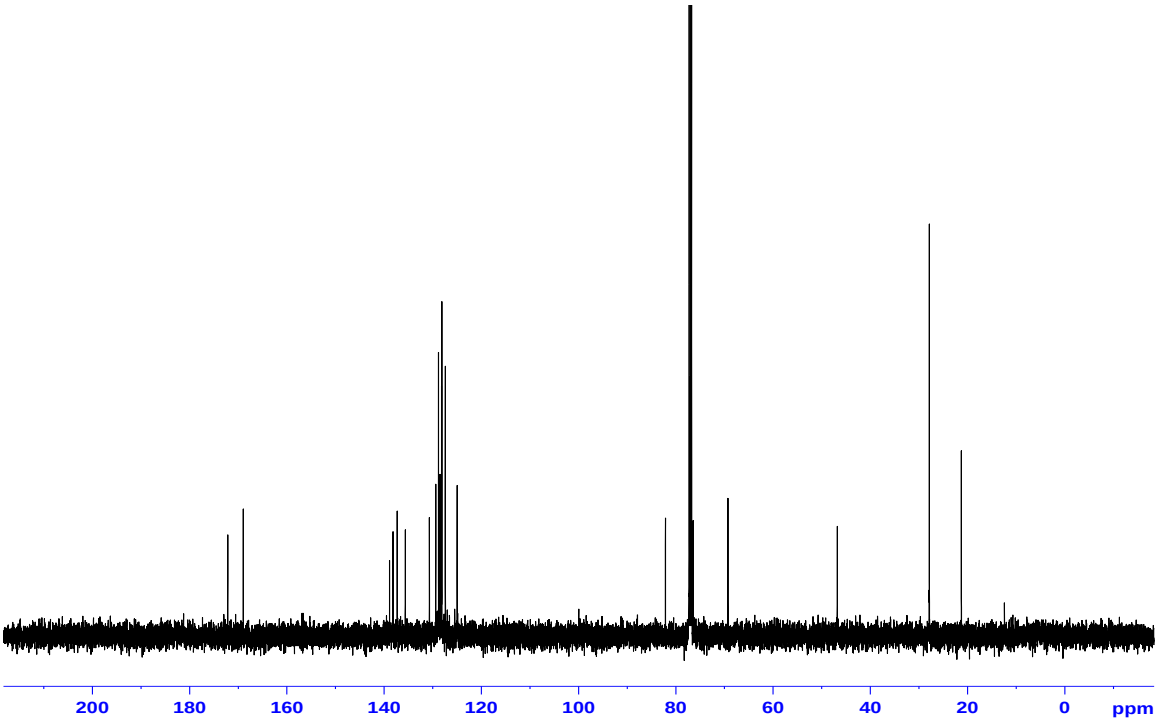
1.96
1.00
0.97
9.12


Cl
O
O2N
Ot-Bu
Ph
N
Ph

3.6f


200
180
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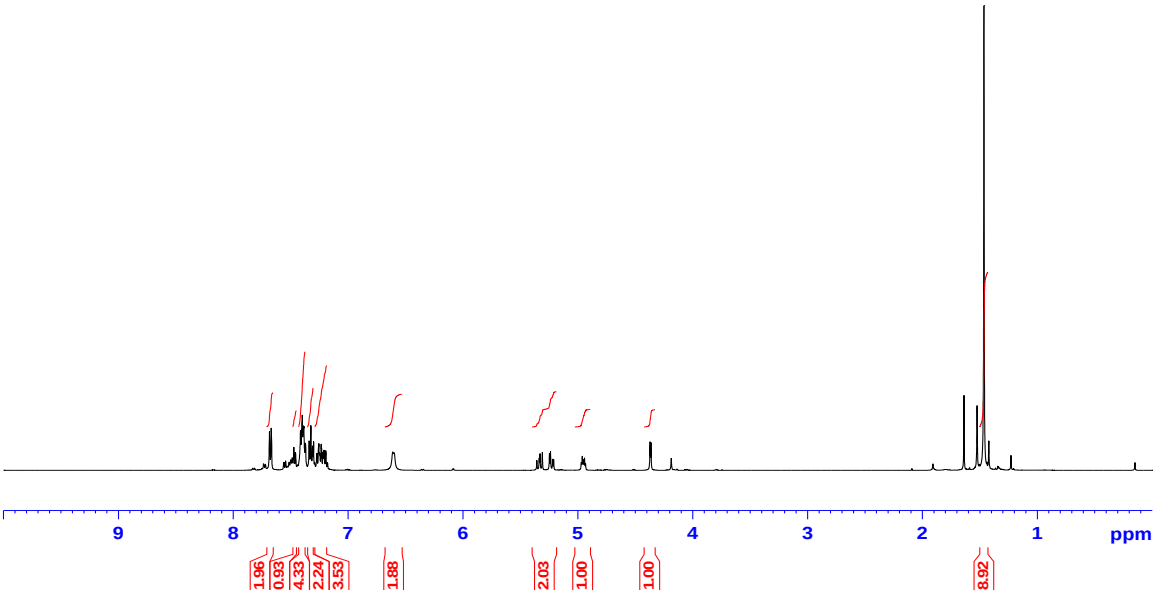
120
100
80
60
40
20
0
ppm


9
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6
5
4
3
2
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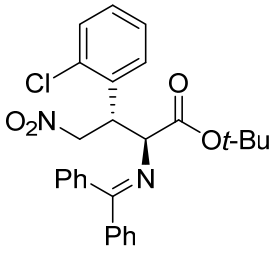
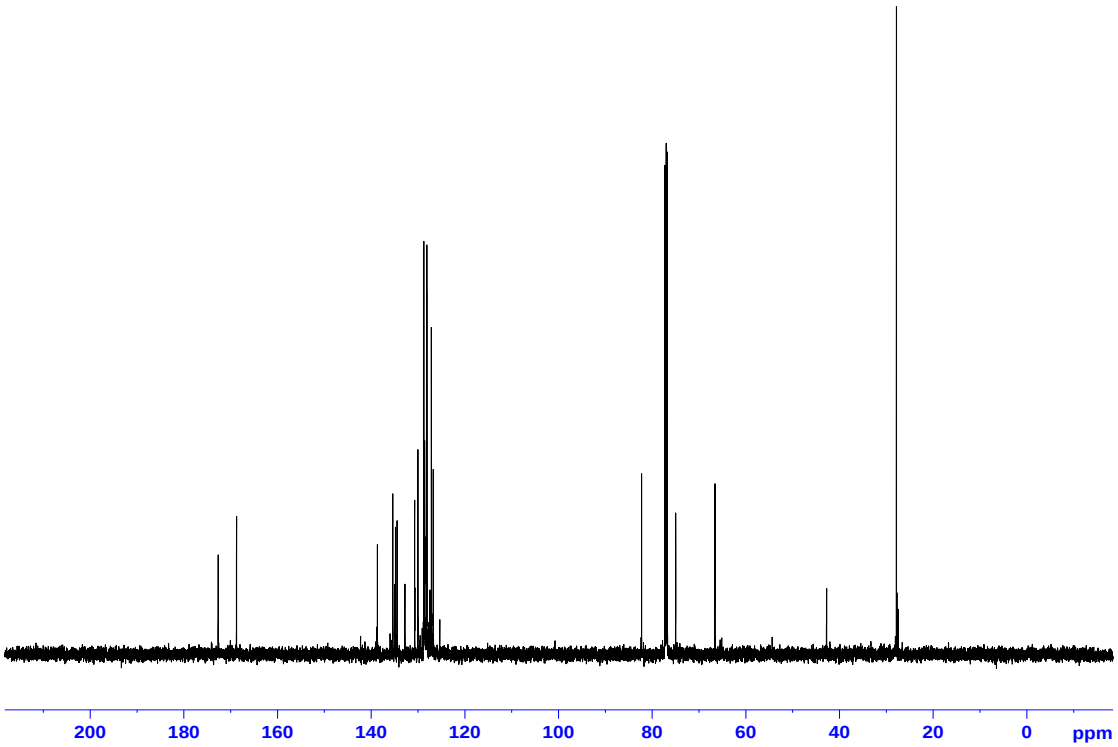
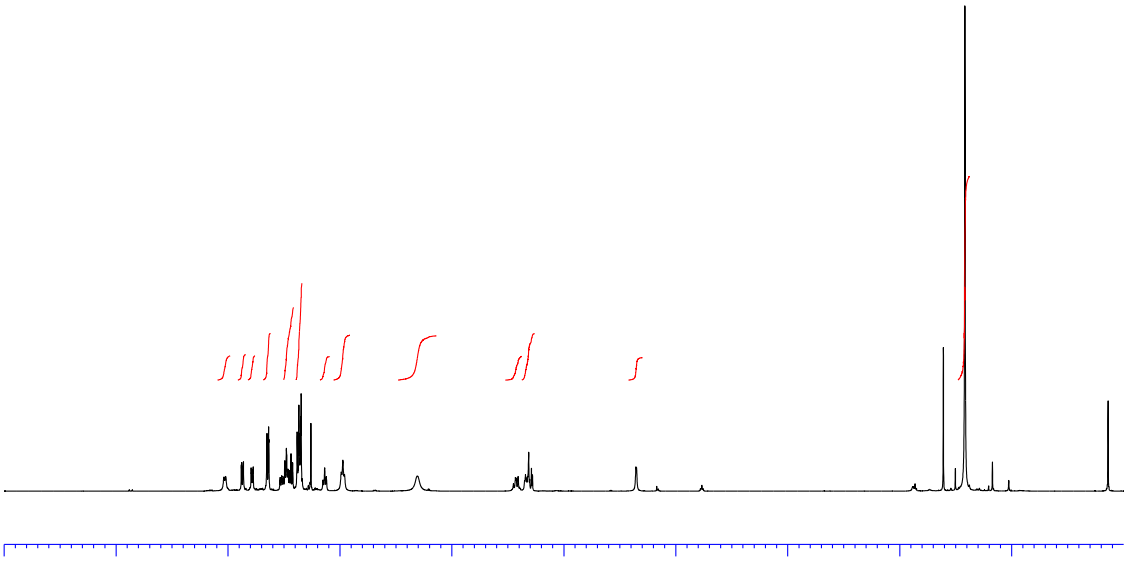
1.00
8.92


Cl
O
O2N
Ot-Bu
Ph
N
Ph

3.6g


200
180
160
140
120
100
80
60
40
20
0
ppm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4
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2
1
ppm
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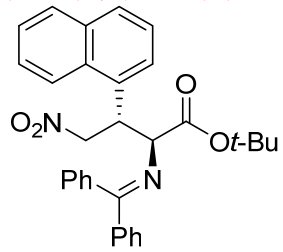
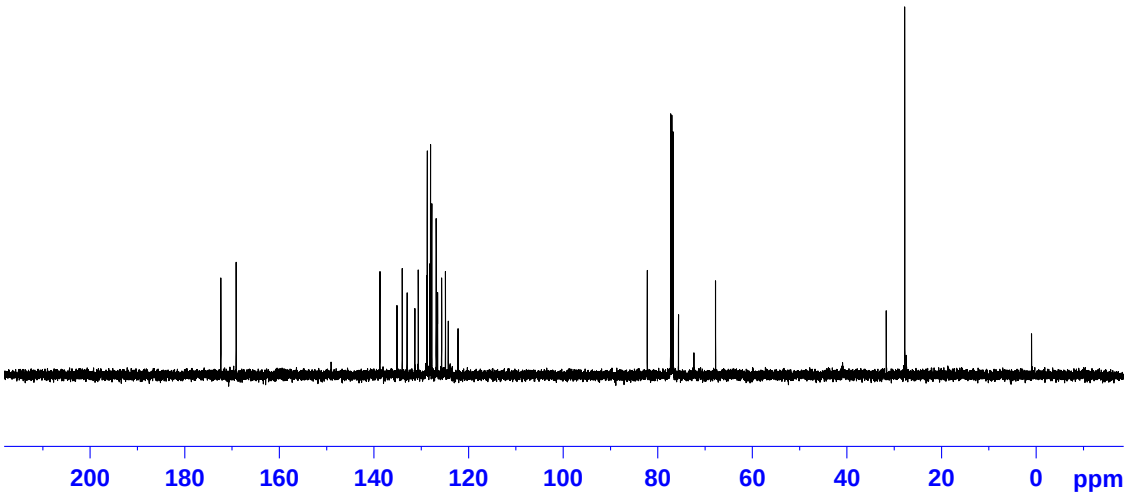
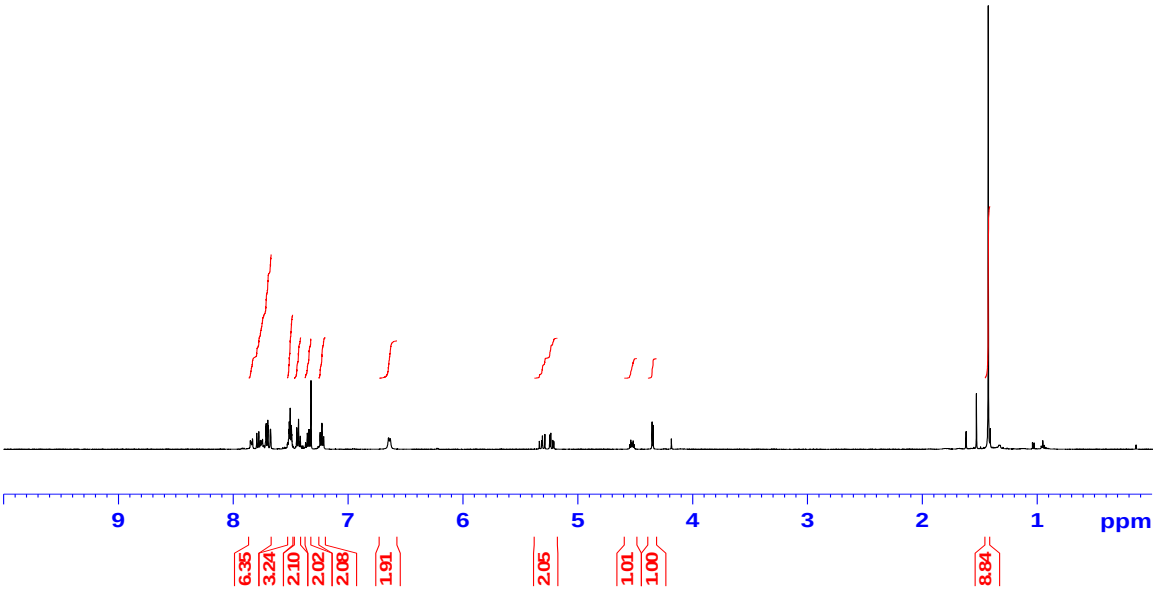
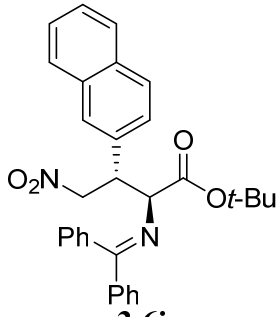
1.14
1.09
2.08
3.24
4.32
1.05
2.00
1.97
1.05
2.07
1.00
9.09


O
O2N
Ot-Bu
Ph
N
Ph

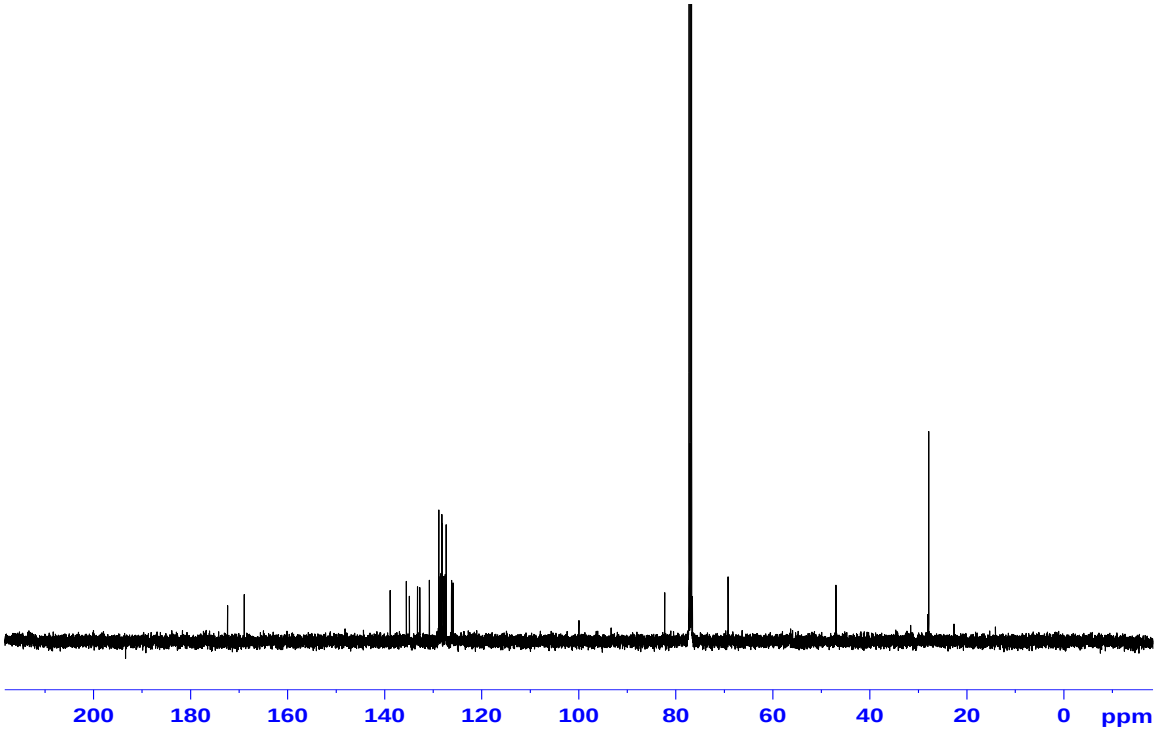
3.6h

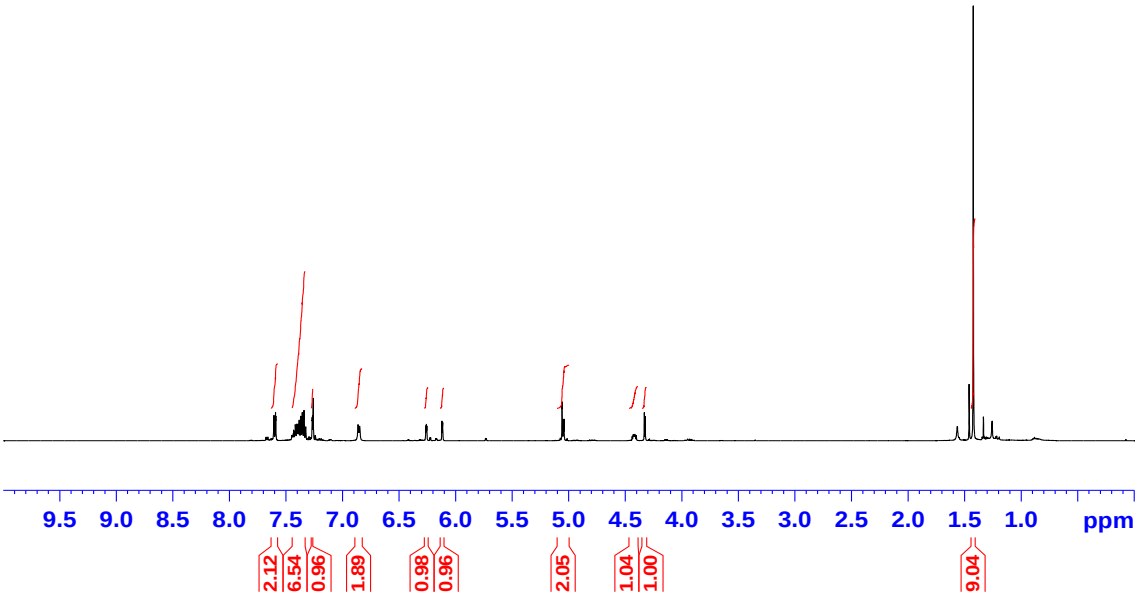

200
180
160
140
120
100
80
60
40
20
0
ppm

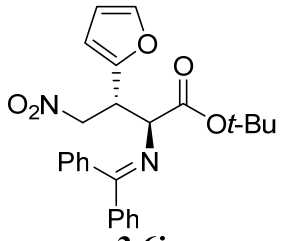

9
8
7
6
5
4
3
2
1
ppm
6.35
3.24
2.10
2.02
2.08
1.91
2.05
1.01
1.00
8.84


O2N
O
Ot-Bu
Ph
N
Ph

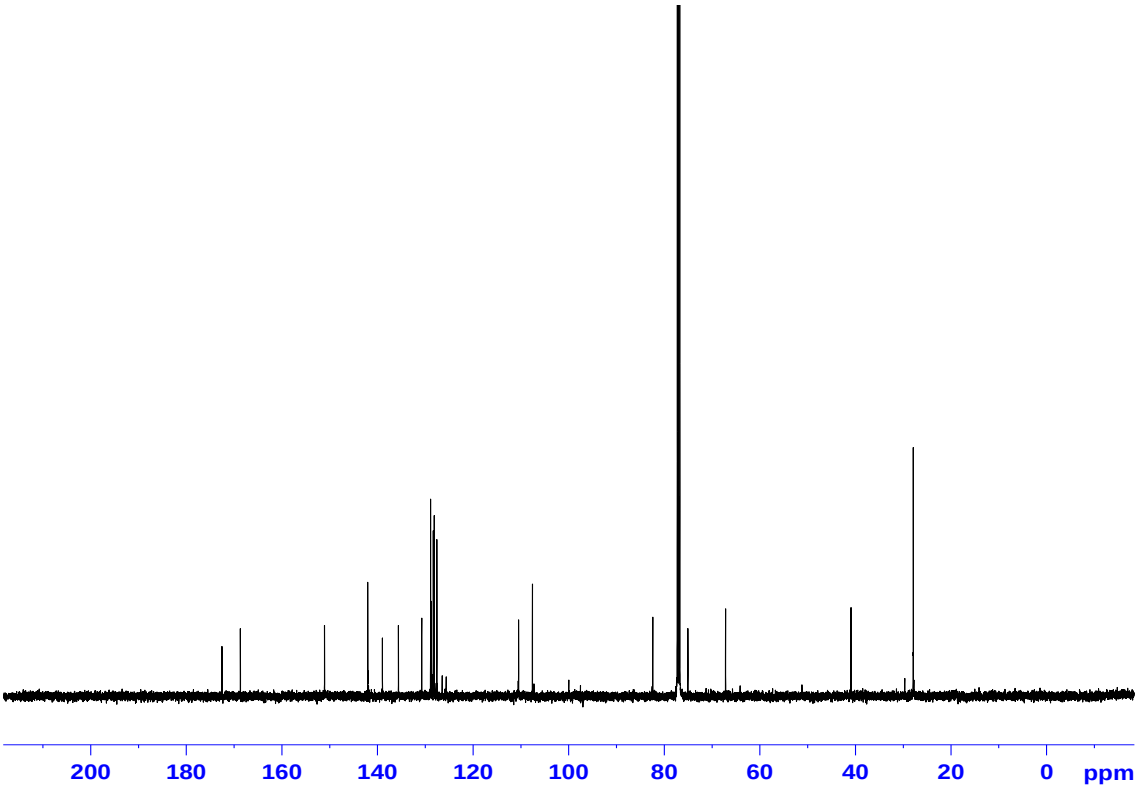
3.6i


200
180
160
140
120
100
80
60
40
20
0
ppm


9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
2.12
6.54
0.96
1.89
0.98
0.96
2.05
1.04
1.00
9.04


O
O
O2N
Ot-Bu
Ph
N
Ph

3.6j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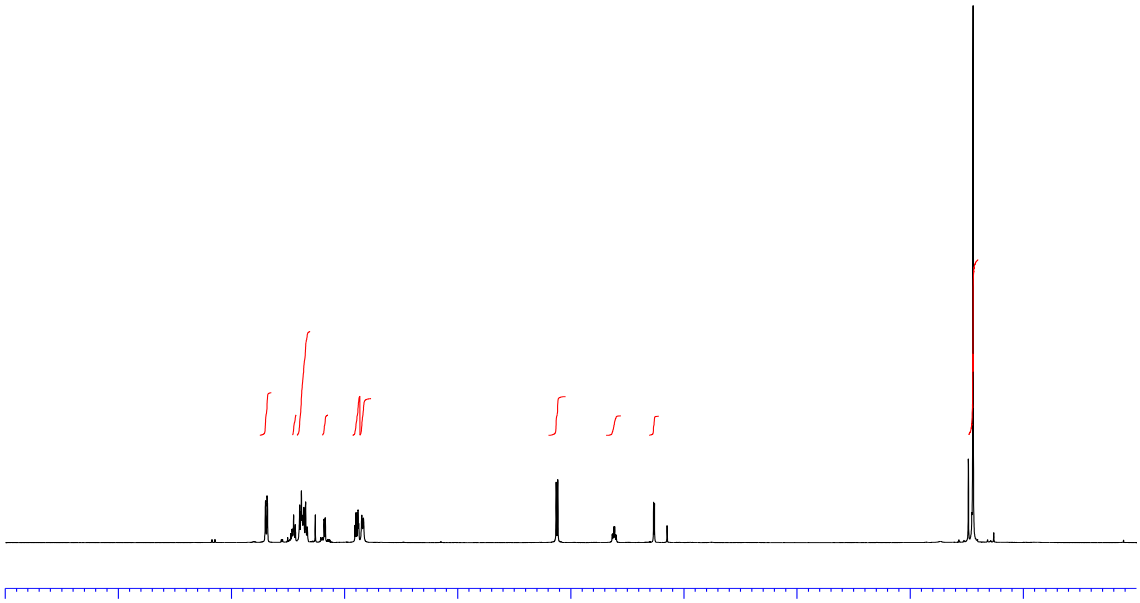
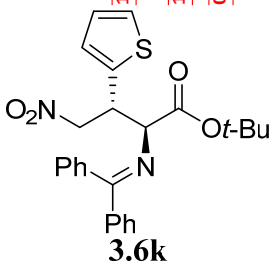
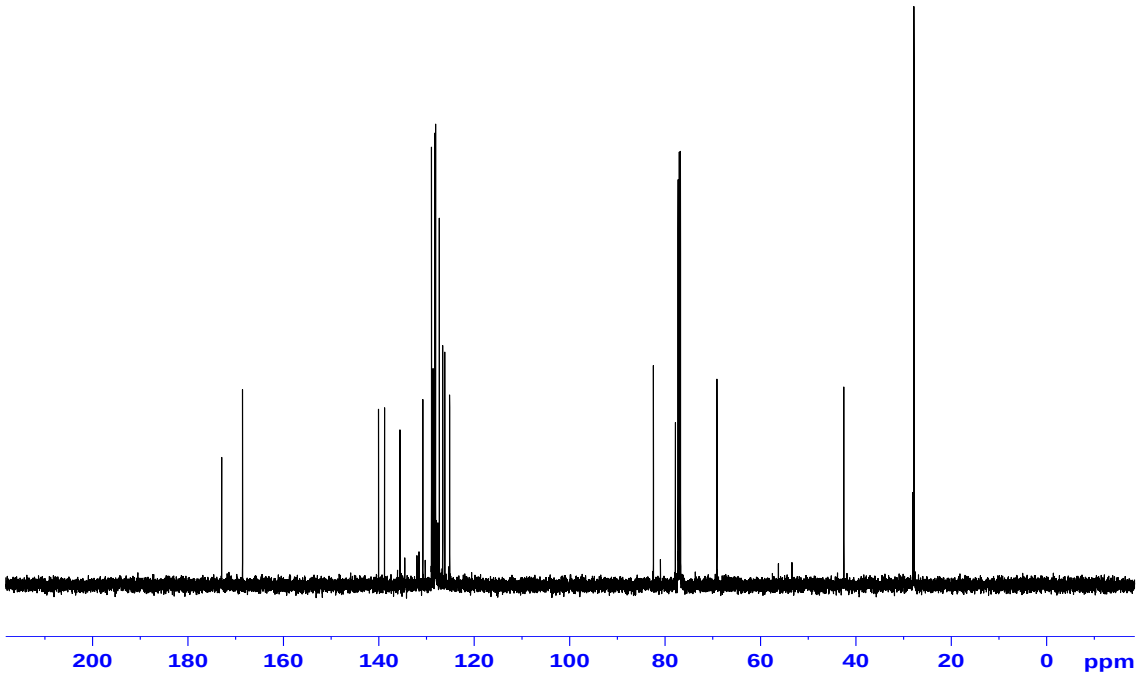
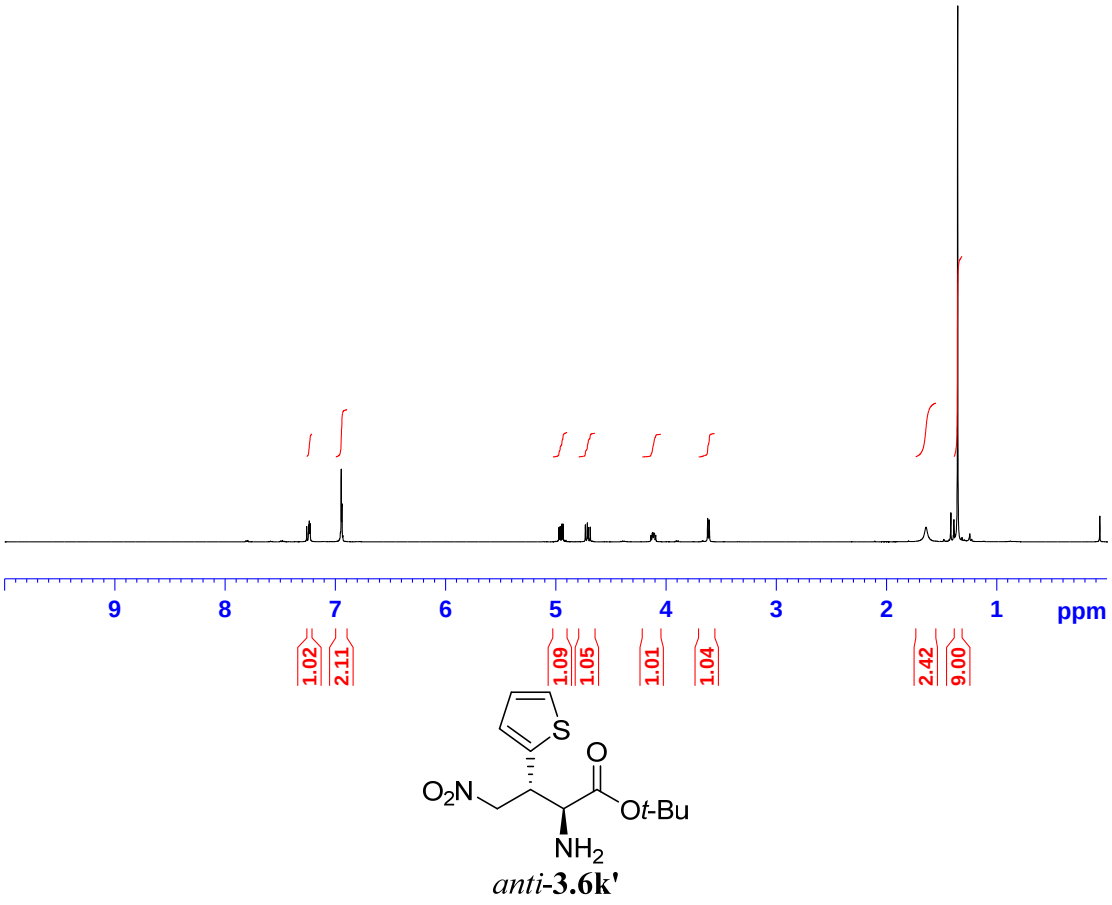

9
8
7
6
5
4
3
2
1
ppm
2.19
1.05
5.34
1.05
2.01
1.89
1.99
1.00
0.99
9.04


S
O
O2N
Ot-Bu
Ph
N
Ph

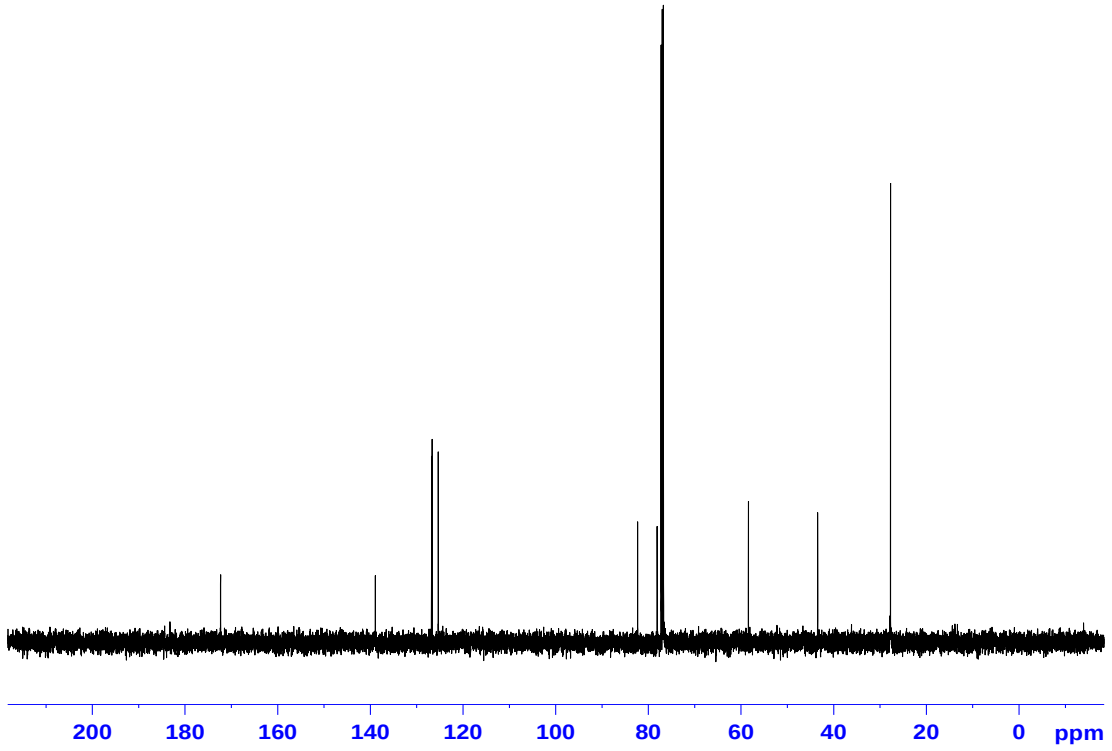
3.6k


200
180
160
140
120
100
80
60
40
20
0
ppm


9
8
7
6
5
4
3
2
1
ppm
1.02
2.11
1.09
1.05
1.01
1.04
2.42
9.00

S
O
O2N
Ot-Bu
NH2

anti-**3.6k'**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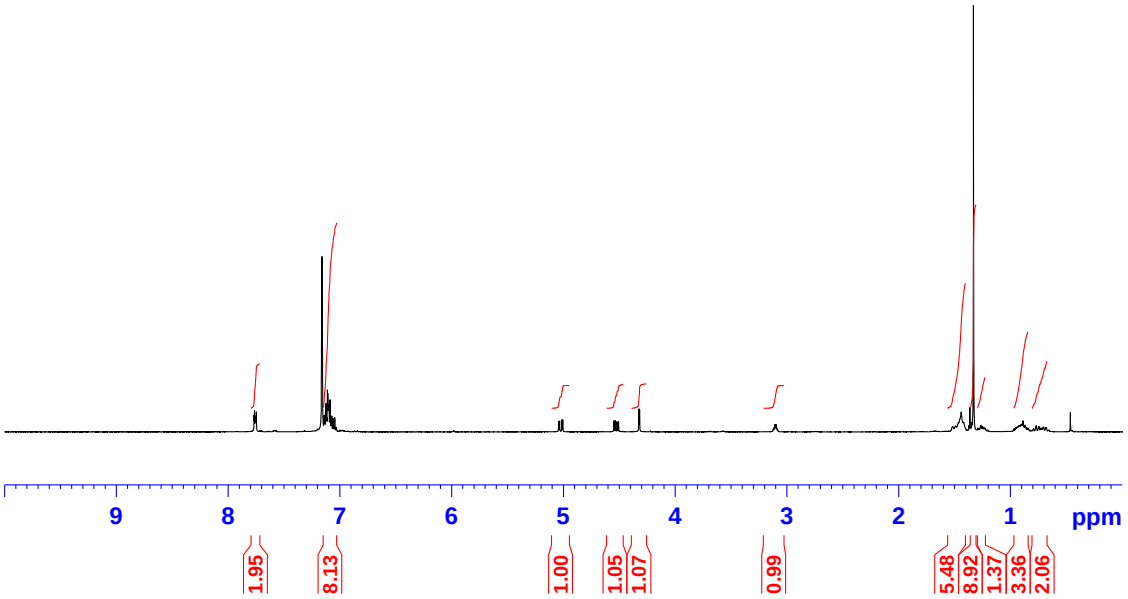
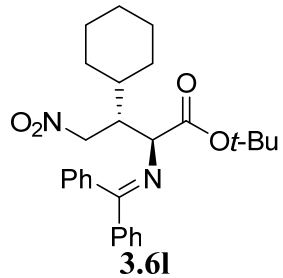
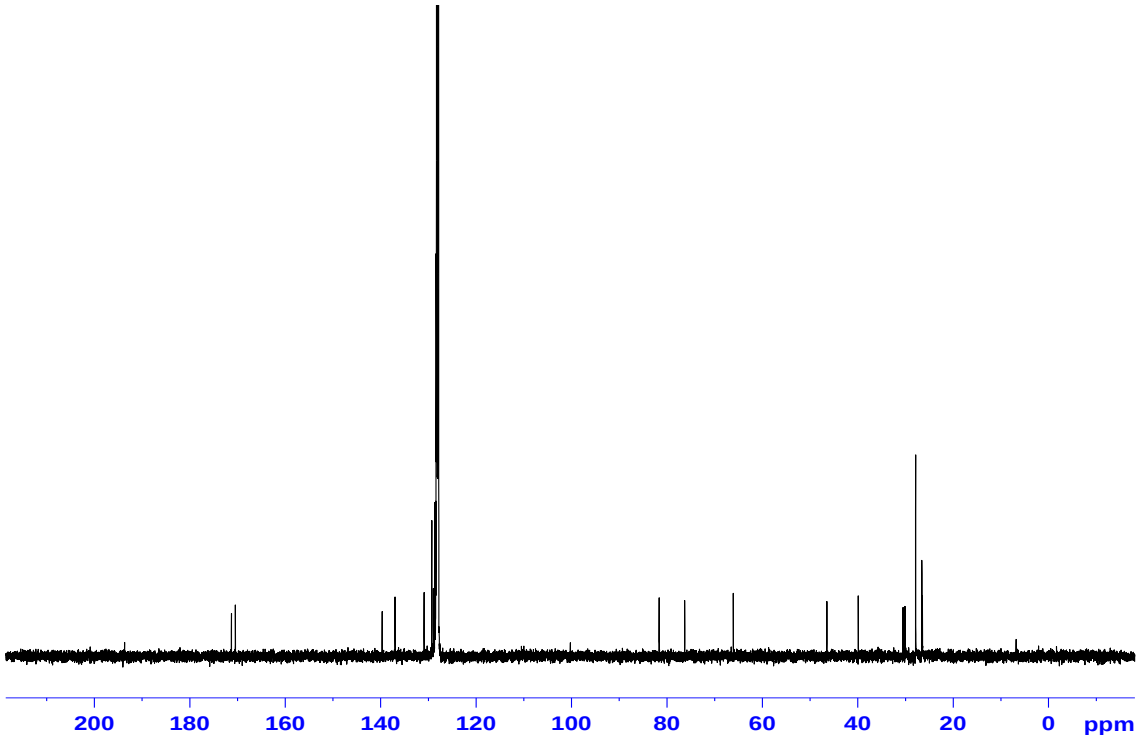
180
160
140
120
100
80
60
40
20
0
ppm


9
8
7
6
5
4
3
2
1
ppm
1.95
8.13
1.00
1.05
1.07
0.99
5.48
8.92
1.37
3.36
2.06


O
O2N
Ot-Bu
Ph
N
Ph

3.6l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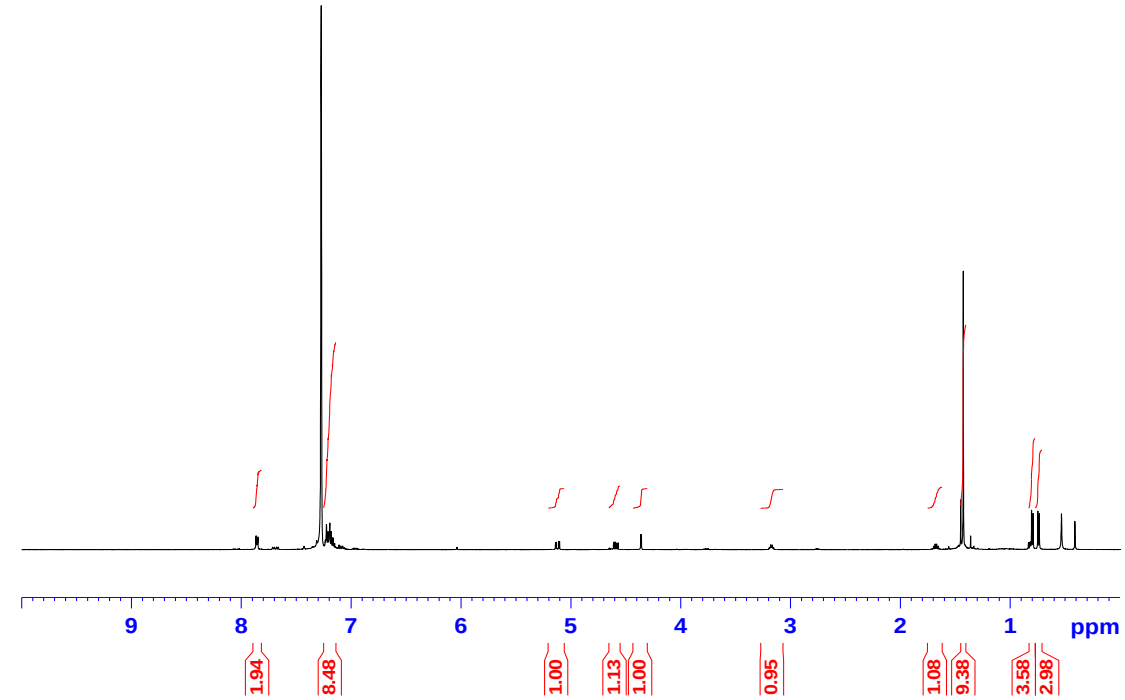
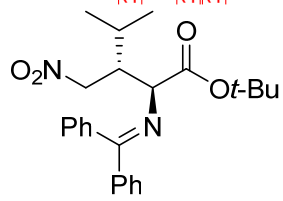
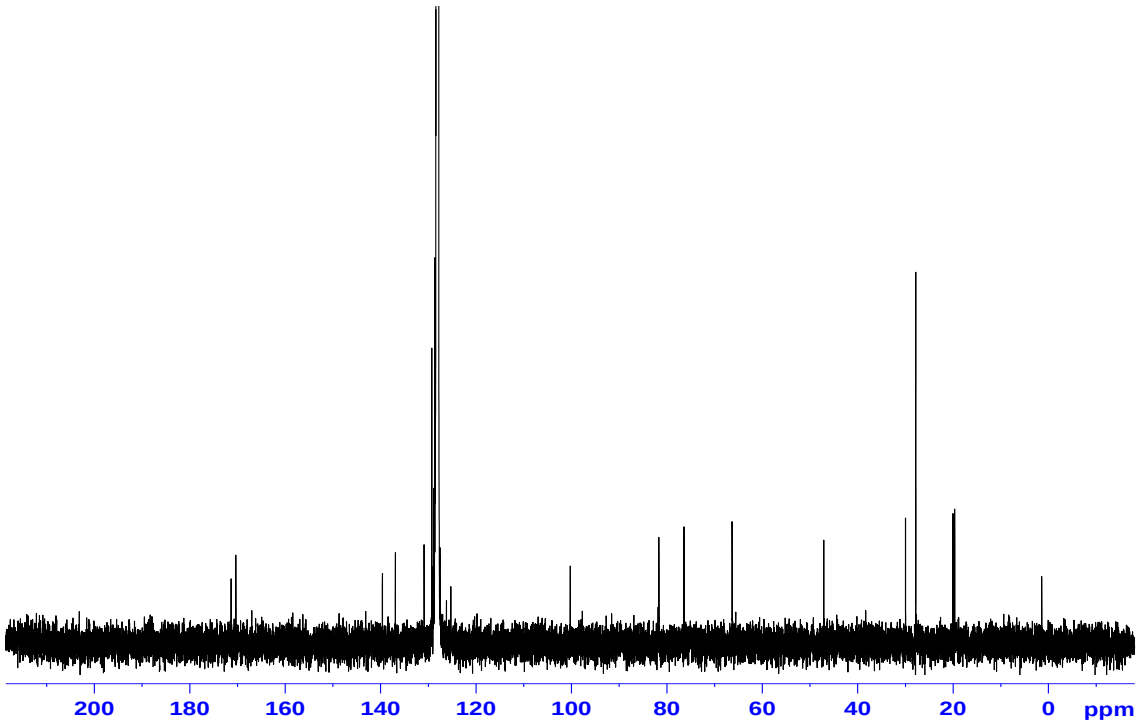
180
160
140
120
100
80
60
40
20
0
ppm

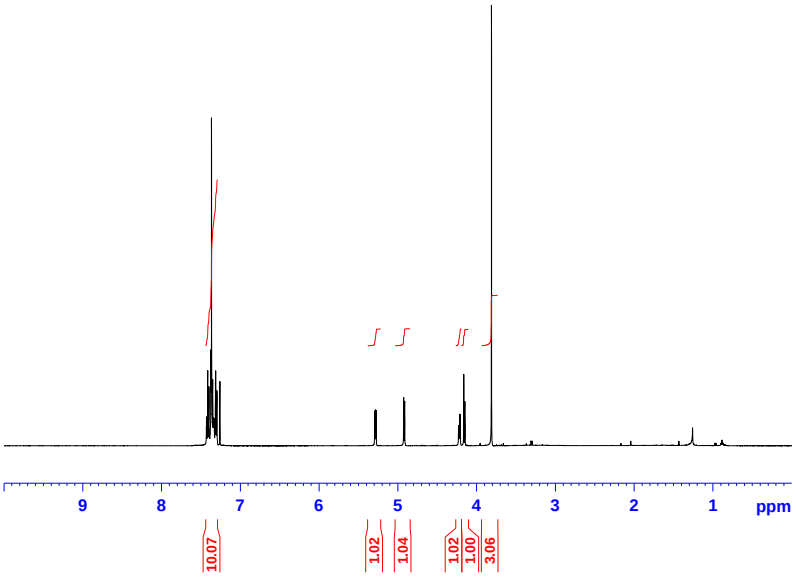

9
8
7
6
5
4
3
2
1
ppm
1.94
8.48
1.00
1.13
1.00
0.95
1.08
9.38
3.58
2.98

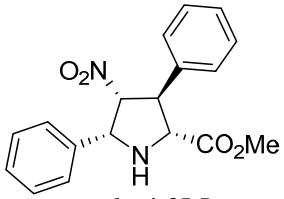

O
O2N
Ot-Bu
Ph
N
Ph

3.6m

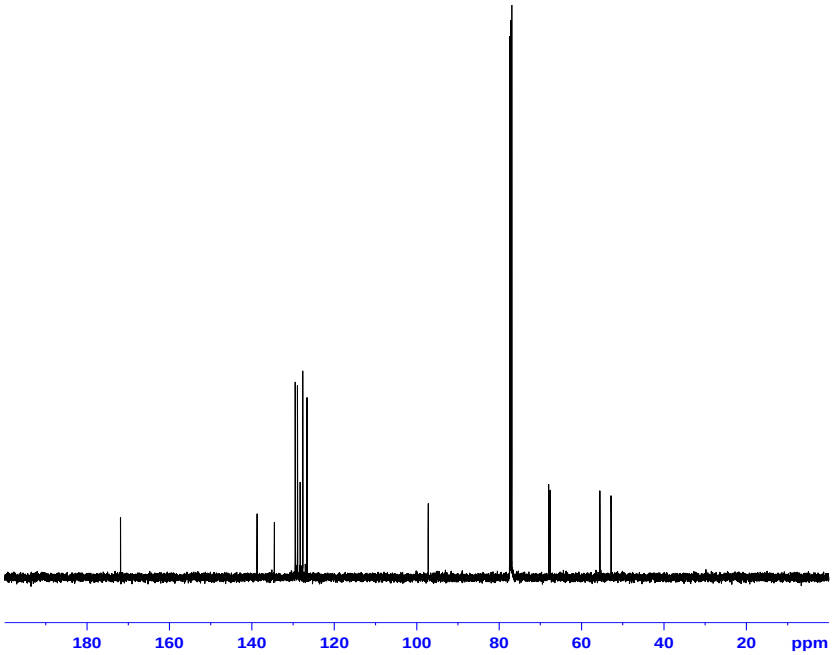

200
180
160
140
120
100
80
60
40
20
0
ppm

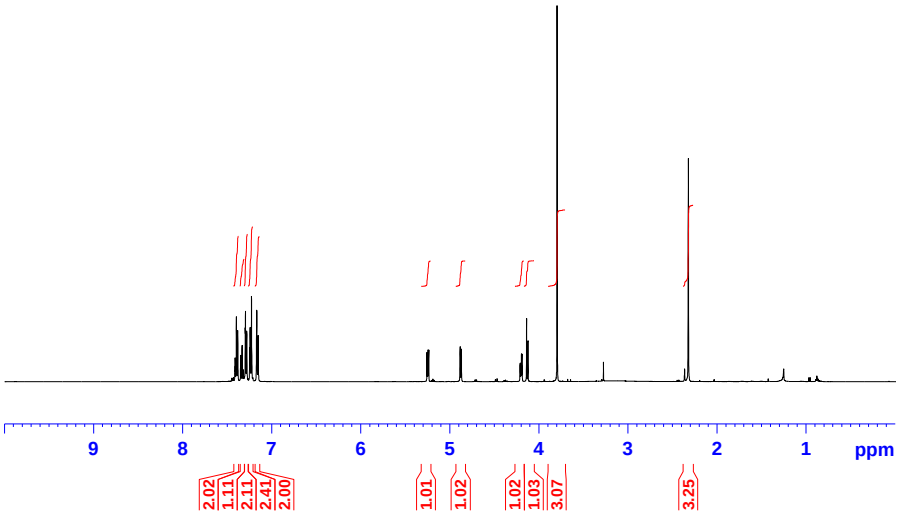
Appendix D ^{1}H NMR/^{13}C NMR Spectra for Chapter 4

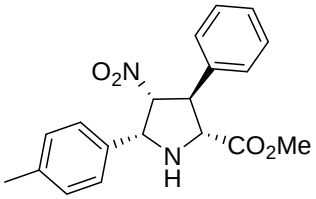




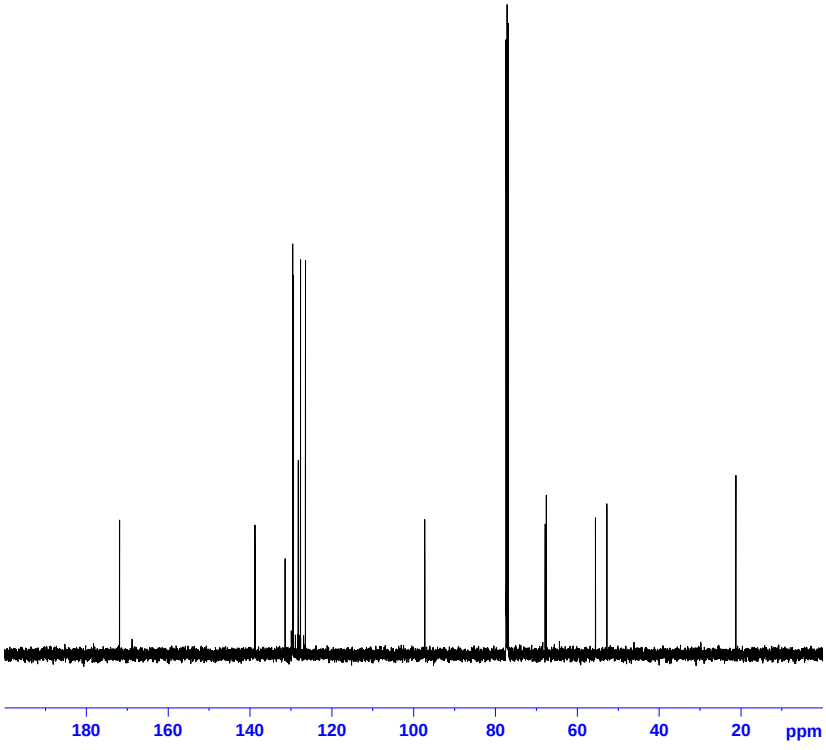
endo-**4.3Ma**

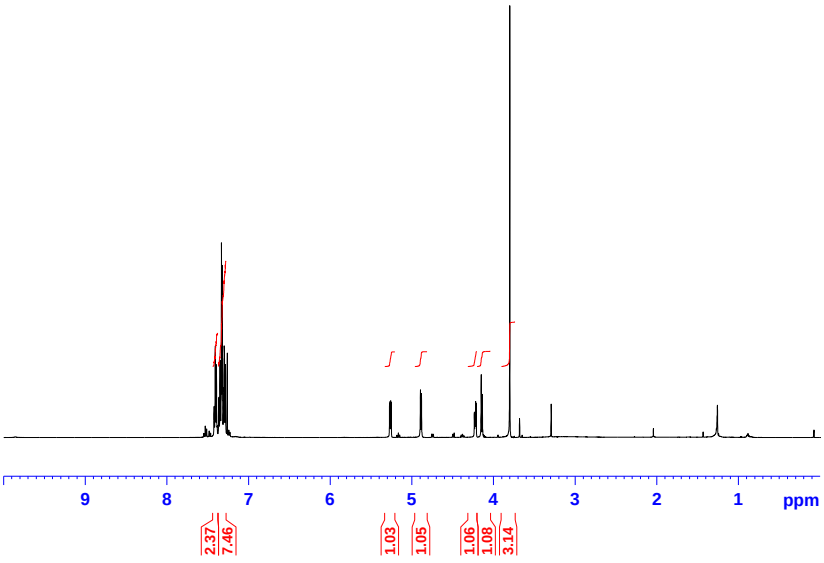


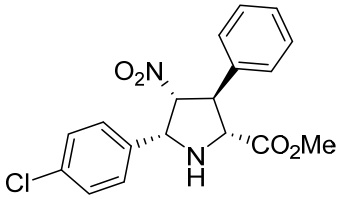

9
8
7
6
5
4
3
2
1
ppm
2.02
1.11
2.11
2.41
2.00
1.01
1.02
1.02
1.03
3.07
3.25


O2N
CO2Me
N
H

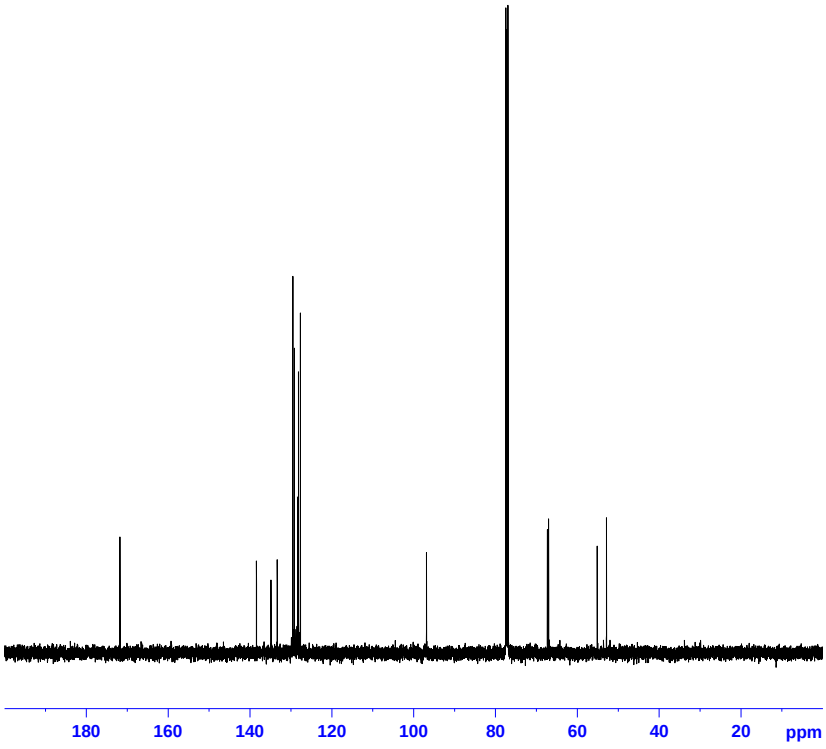
endo-**4.3Mb**

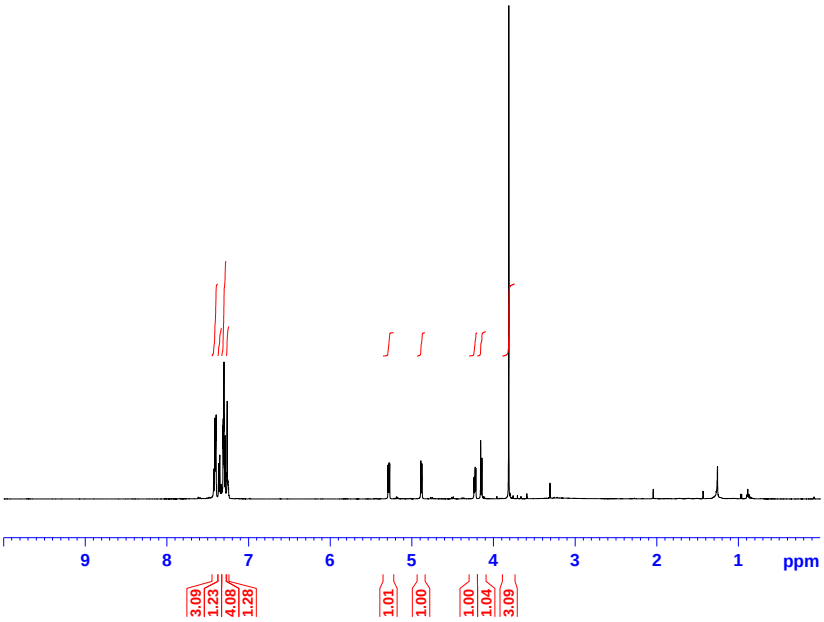

180
160
140
120
100
80
60
40
20
ppm

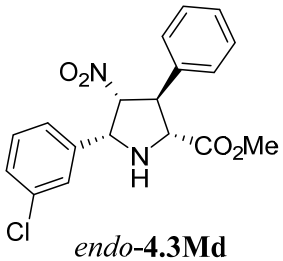

9
8
7
6
5
4
3
2
1
ppm
2.37
7.46
1.03
1.05
1.06
1.08
3.14


O2N
CO2Me
N
H
Cl

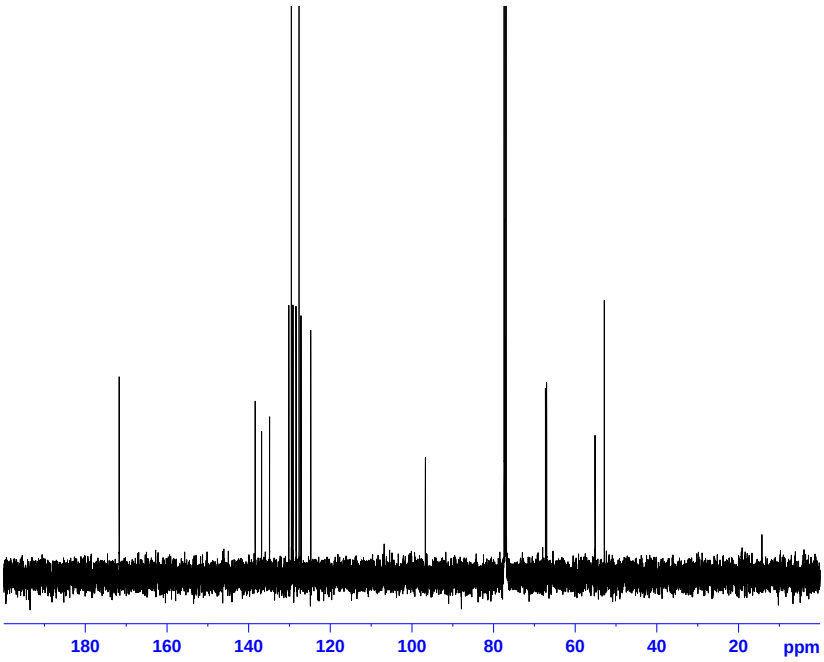
endo-**4.3Mc**

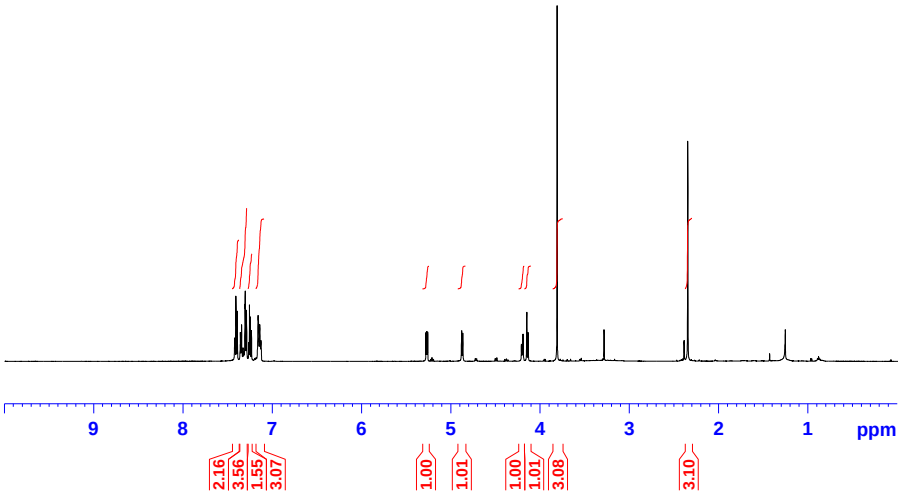

180
160
140
120
100
80
60
40
20
ppm


9
8
7
6
5
4
3
2
1
ppm
3.09
1.23
4.08
1.28
1.01
1.00
1.00
1.04
3.09


O2N
CO2Me
N
H
Cl

endo-**4.3Md**


180
160
140
120
100
80
60
40
20
ppm


9
8
7
6
5
4
3
2
1
ppm
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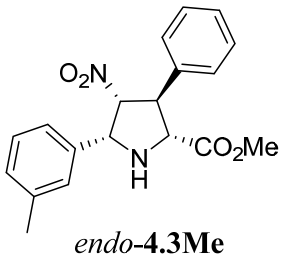
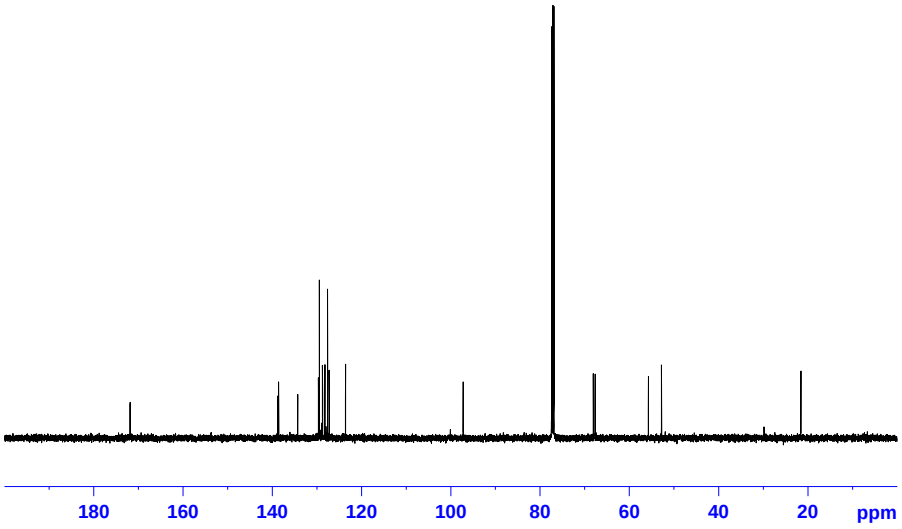
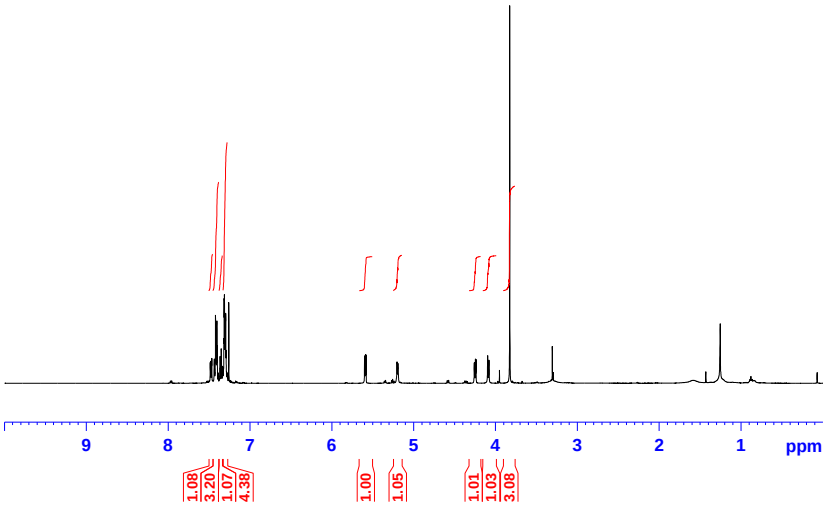
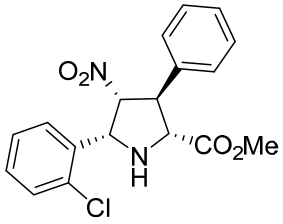
1.55
3.07
1.00
1.01
1.00
1.01
3.08
3.10


O2N
CO2Me
N
H

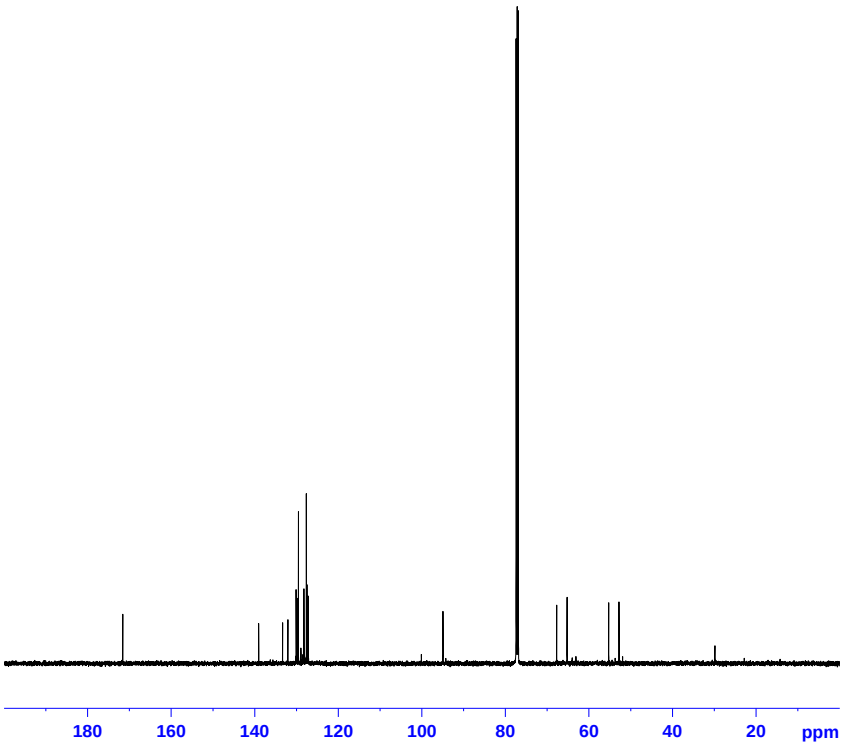
endo-**4.3Me**

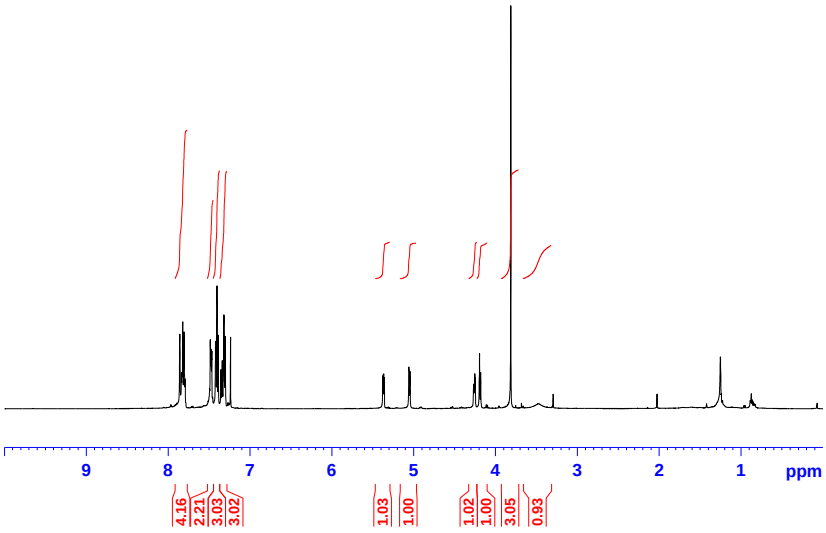

180
160
140
120
100
80
60
40
20
ppm


9
8
7
6
5
4
3
2
1
ppm
1.08
3.20
1.07
4.38
1.00
1.05
1.01
1.03
3.08


O2N
CO2Me
N
H
Cl

endo-**4.3Mf**


180
160
140
120
100
80
60
40
20
ppm


9
8
7
6
5
4
3
2
1
ppm
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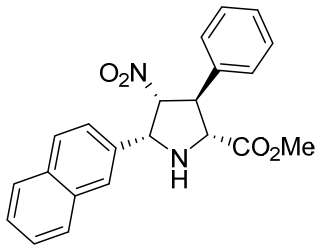
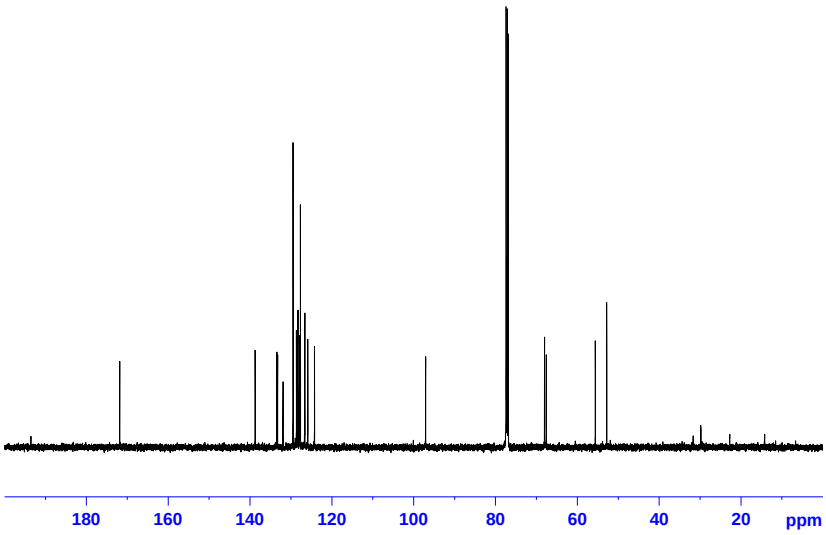
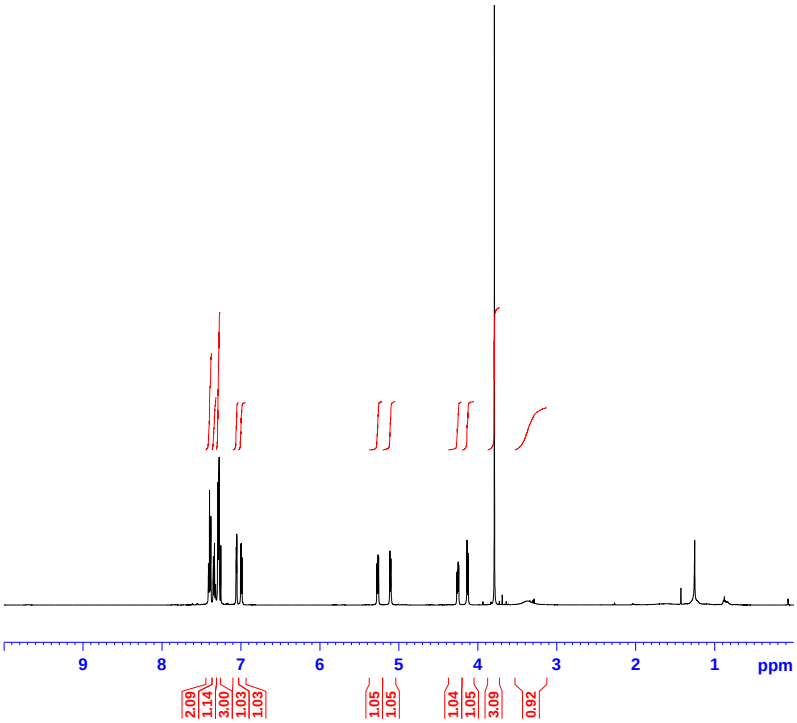
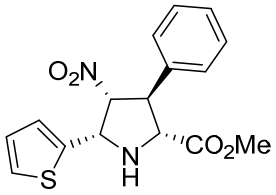
3.02
1.03
1.00
1.02
1.00
3.05
0.93


O2N
CO2Me
N
H

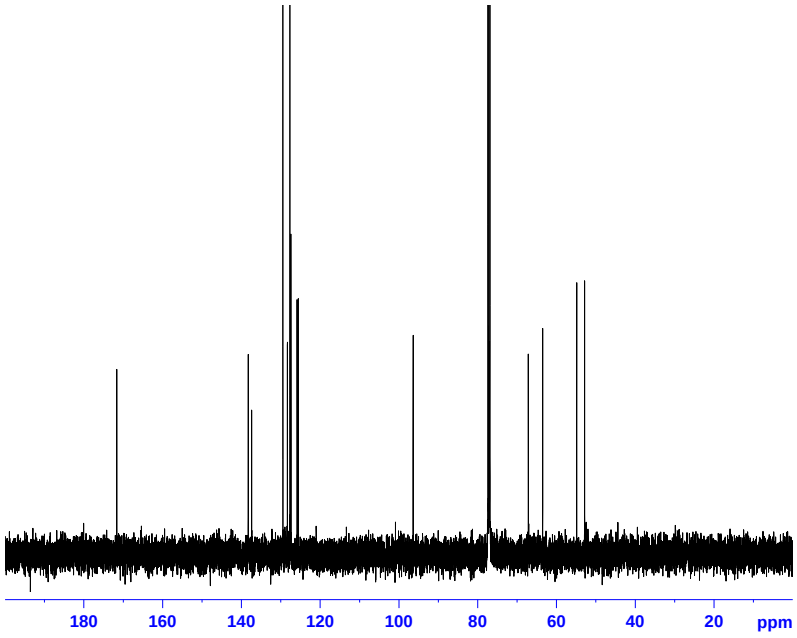
endo-**4.3Mg**

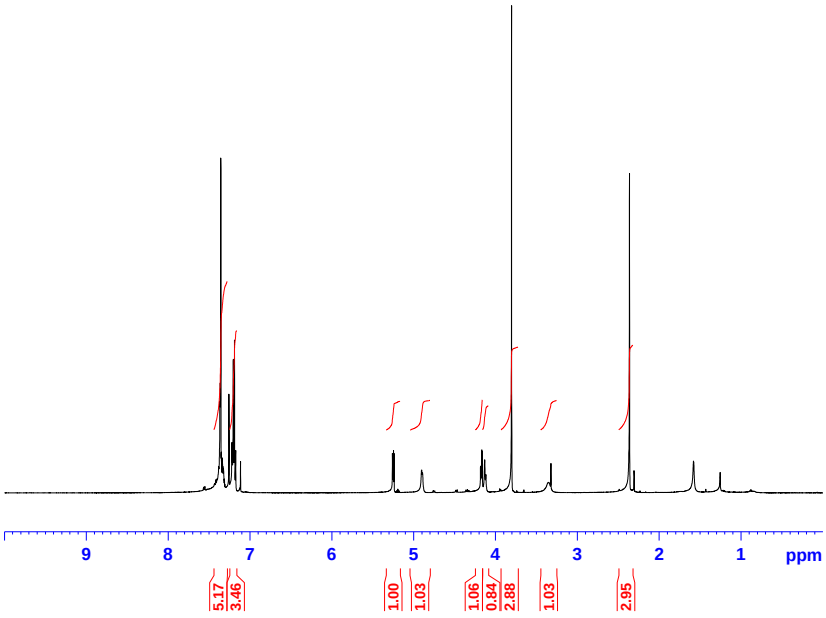

180
160
140
120
100
80
60
40
20
ppm

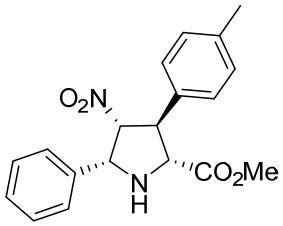

9
8
7
6
5
4
3
2
1
ppm
2.09
1.14
3.00
1.03
1.03
1.05
1.05
1.04
1.05
3.09
0.92


O2N
CO2Me
N
H
S

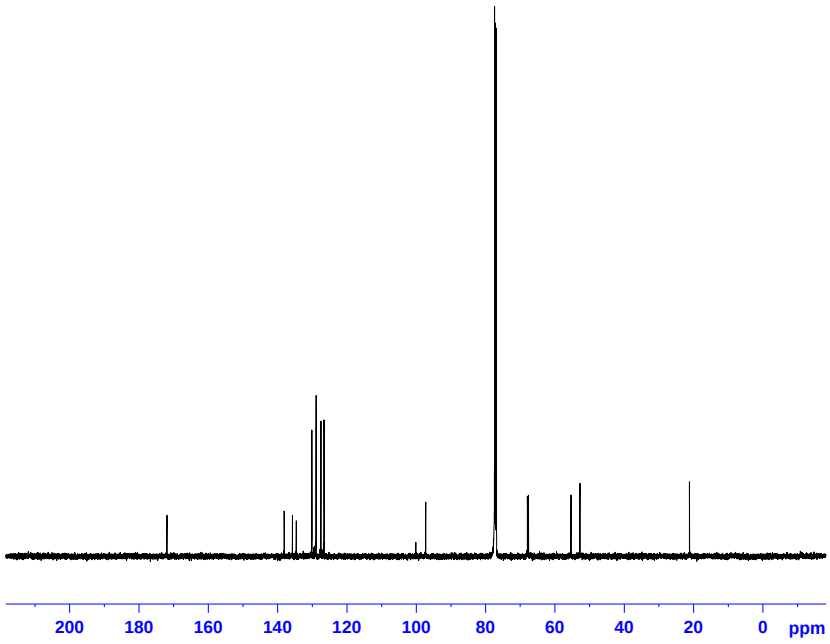
endo-**4.3Mh**

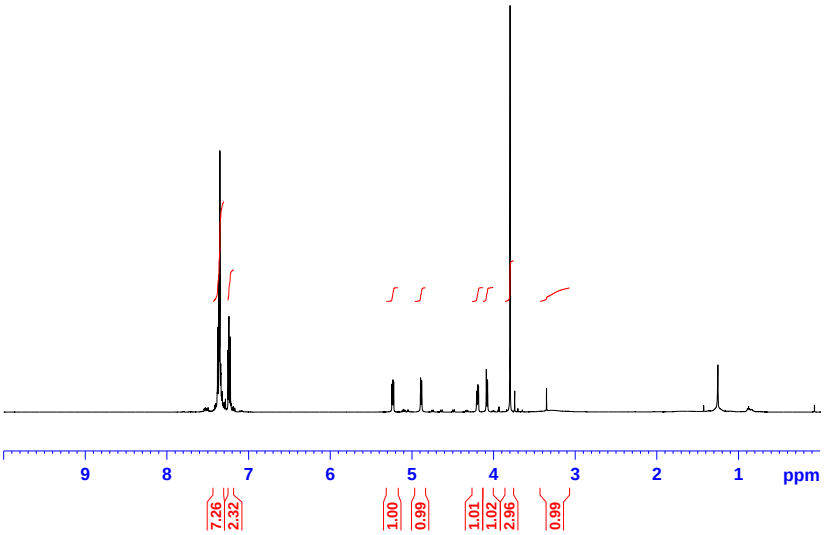

180
160
140
120
100
80
60
40
20
ppm

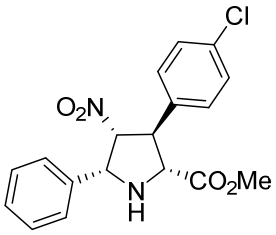

9
8
7
6
5
4
3
2
1
ppm
5.17
3.46
1.00
1.03
1.06
0.84
2.88
1.03
2.95


O2N
CO2Me
N
H

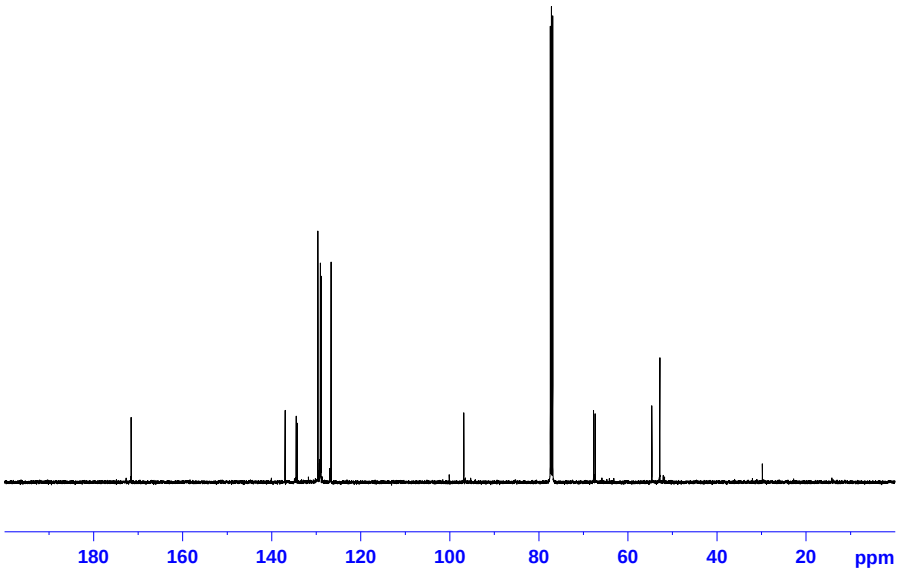
endo-**4.3Mi**

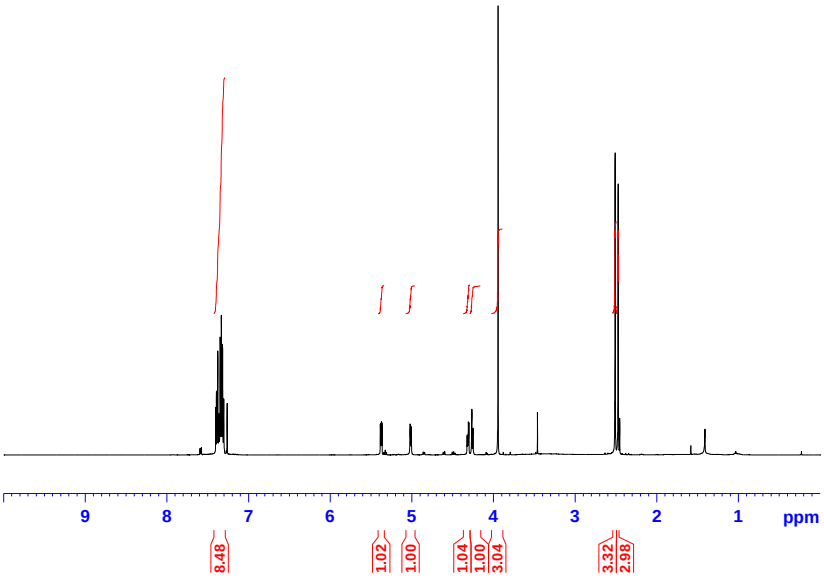

200
180
160
140
120
100
80
60
40
20
0
ppm

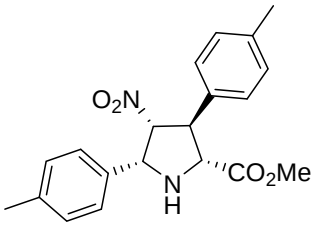

9
8
7
6
5
4
3
2
1
ppm
7.26
2.32
1.00
0.99
1.01
1.02
2.96
0.99


Cl
O2N
CO2Me
N
H

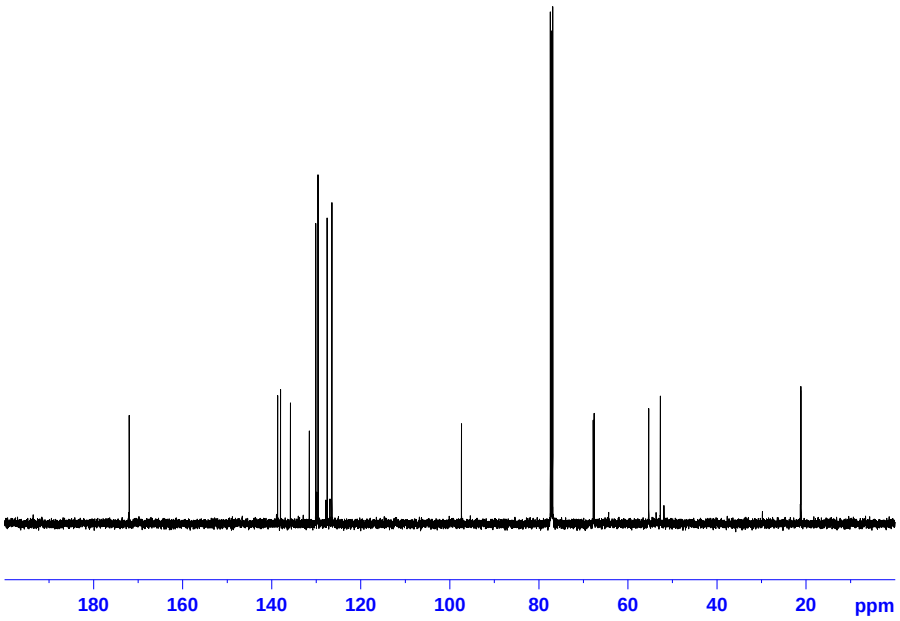
endo-**4.3Mj**


180
160
140
120
100
80
60
40
20
ppm


9
8
7
6
5
4
3
2
1
ppm
8.48
1.02
1.00
1.04
1.00
3.04
3.32
2.98


O2N
CO2Me
N
H

endo-**4.3Mk**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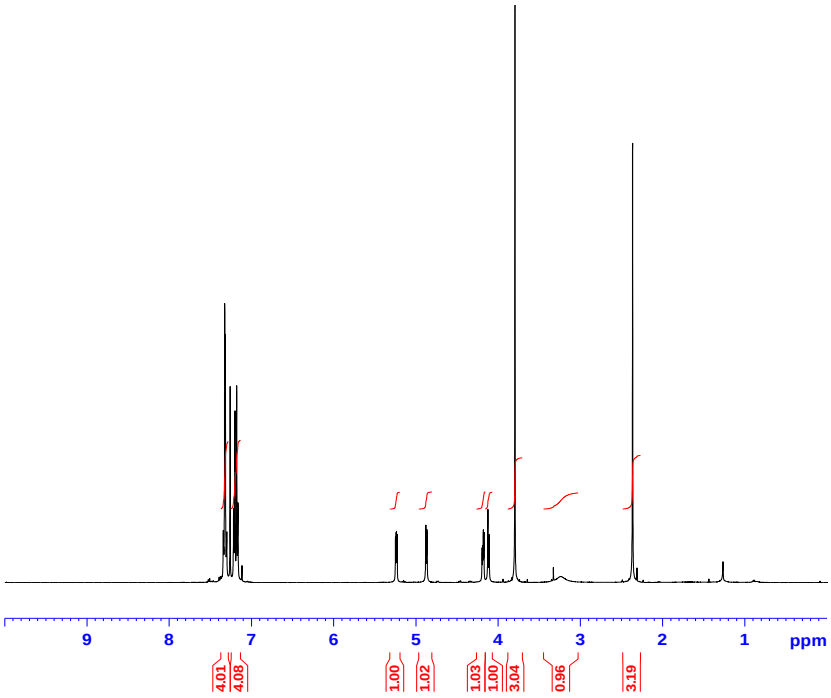
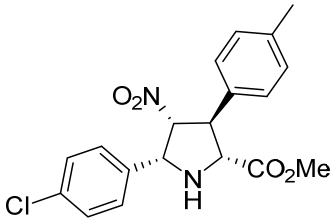
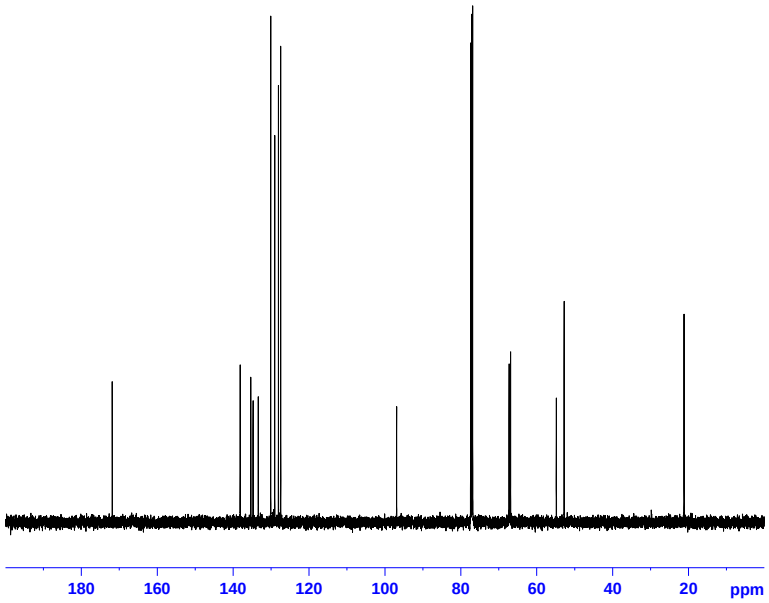
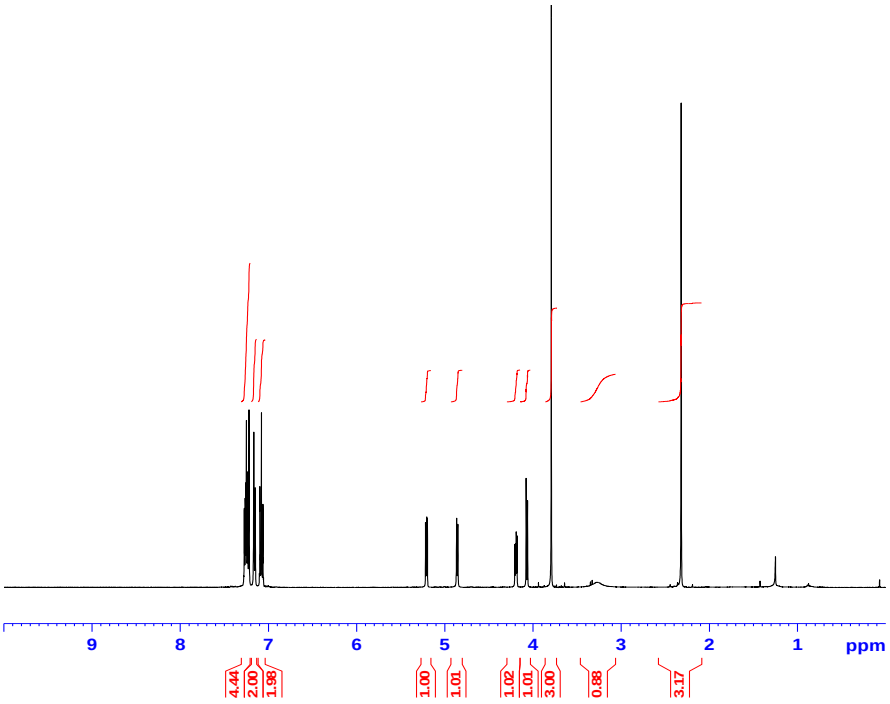
160
140
120
100
80
60
40
20
ppm

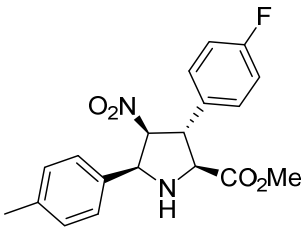

9
8
7
6
5
4
3
2
1
ppm
4.01
4.08
1.00
1.02
1.03
1.00
3.04
0.96
3.19


O2N
CO2Me
N
H
Cl

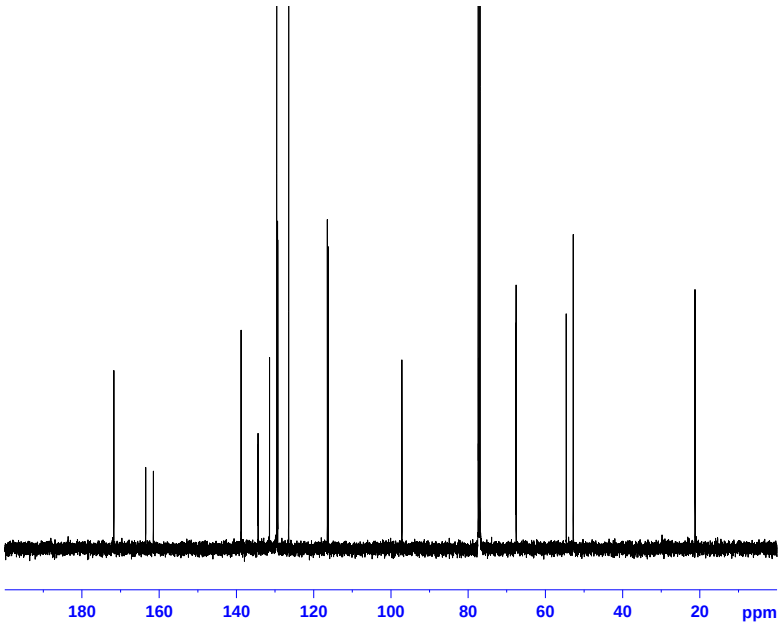
endo-**4.3Ml**


180
160
140
120
100
80
60
40
20
ppm


9
8
7
6
5
4
3
2
1
ppm
4.44
2.00
1.98
1.00
1.01
1.02
1.01
3.00
0.88
3.17


F
O2N
CO2Me
N
H

endo-**4.3Mm**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160
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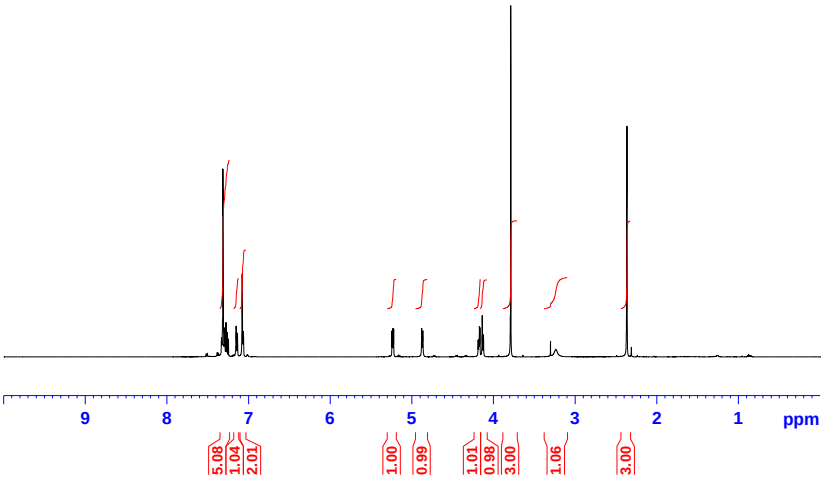
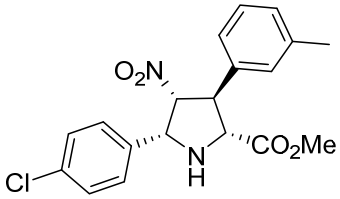
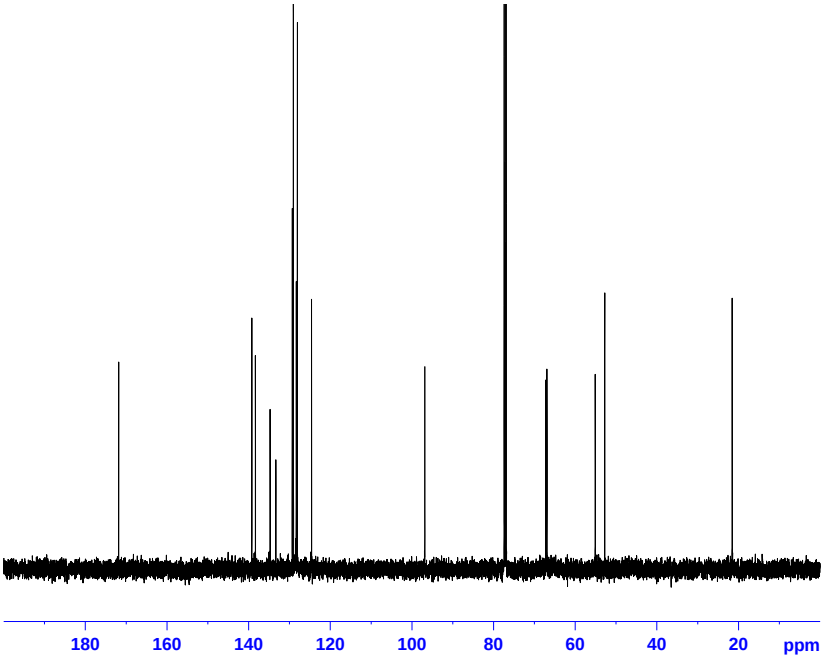
120
100
80
60
40
20
ppm


9
8
7
6
5
4
3
2
1
ppm
5.08
1.04
2.01
1.00
0.99
1.01
0.98
3.00
1.06
3.00


O2N
CO2Me
N
H
Cl

endo-**4.3Mn**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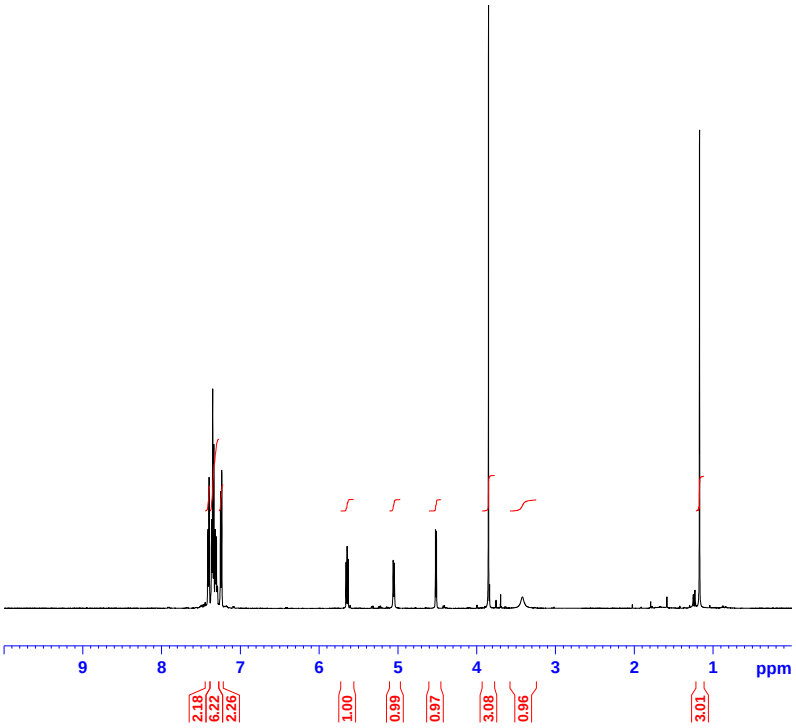
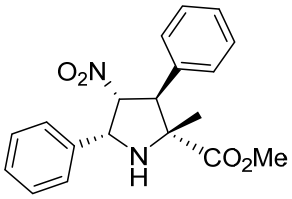
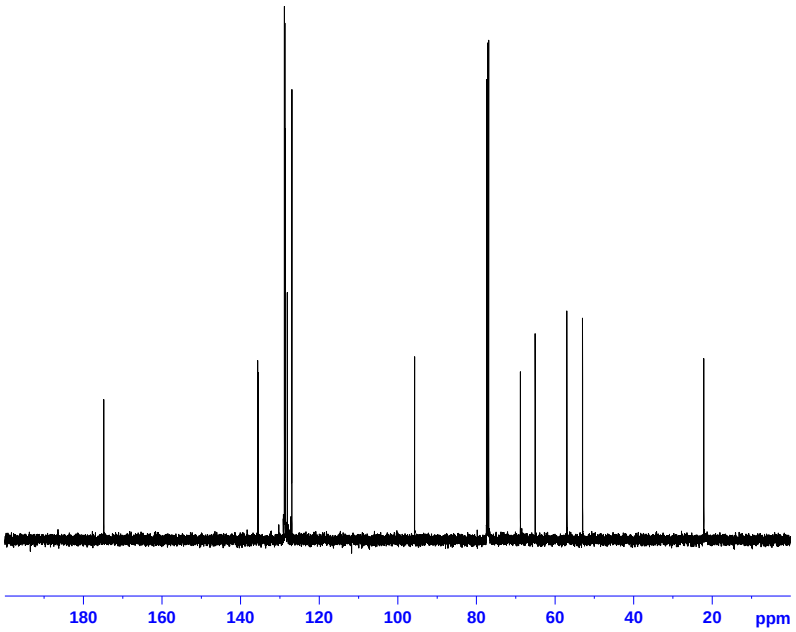
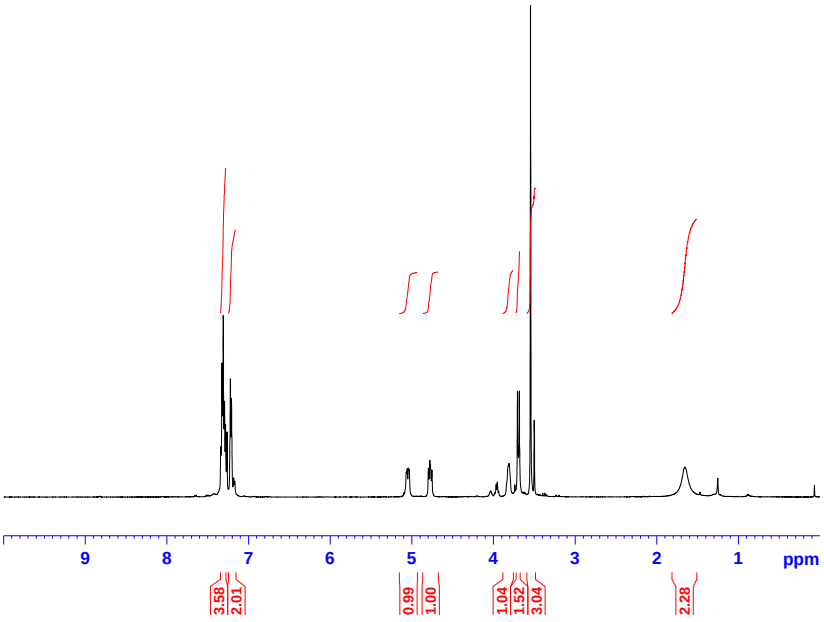
160
140
120
100
80
60
40
20
ppm

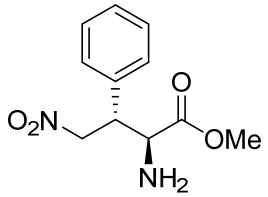

9
8
7
6
5
4
3
2
1
ppm
2.18
6.22
2.26
1.00
0.99
0.97
3.08
0.96
3.01


O2N
N
H
CO2Me

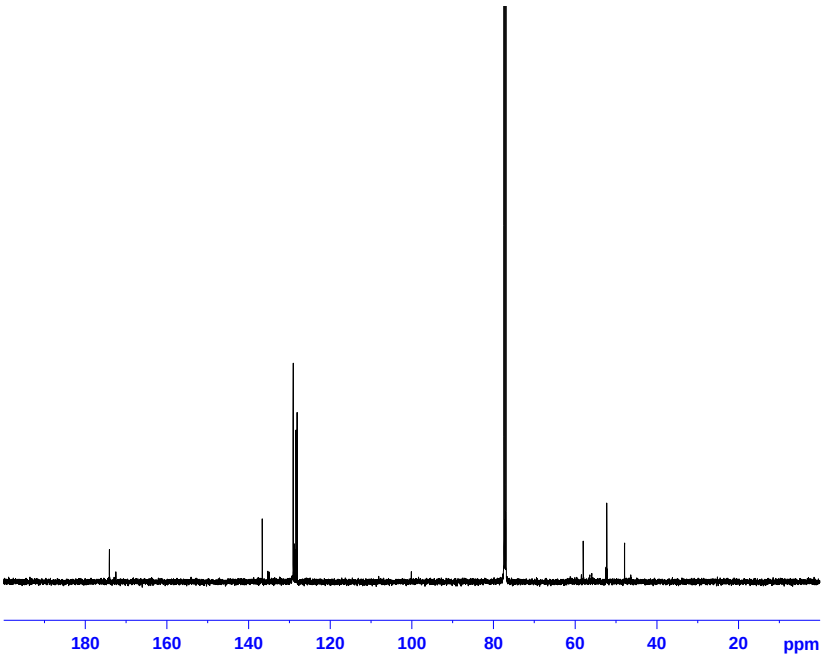
endo-**4.3Mo**

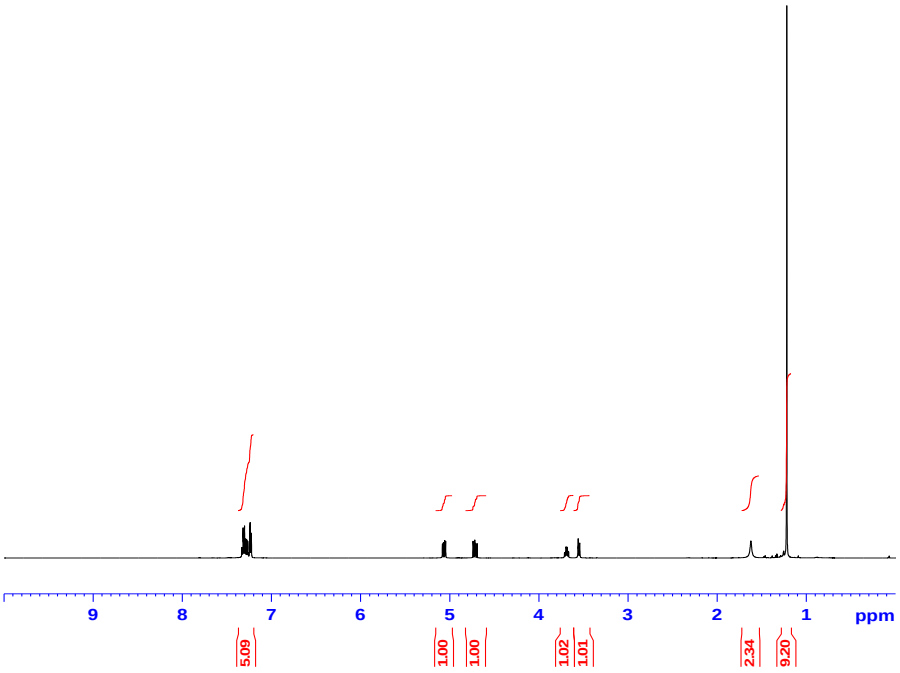

180
160
140
120
100
80
60
40
20
ppm

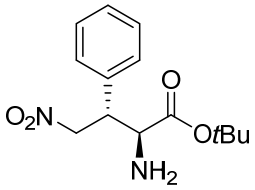

9
8
7
6
5
4
3
2
1
ppm
3.58
2.01
0.99
1.00
1.04
1.52
3.04
2.28


O
O2N
OMe
NH2

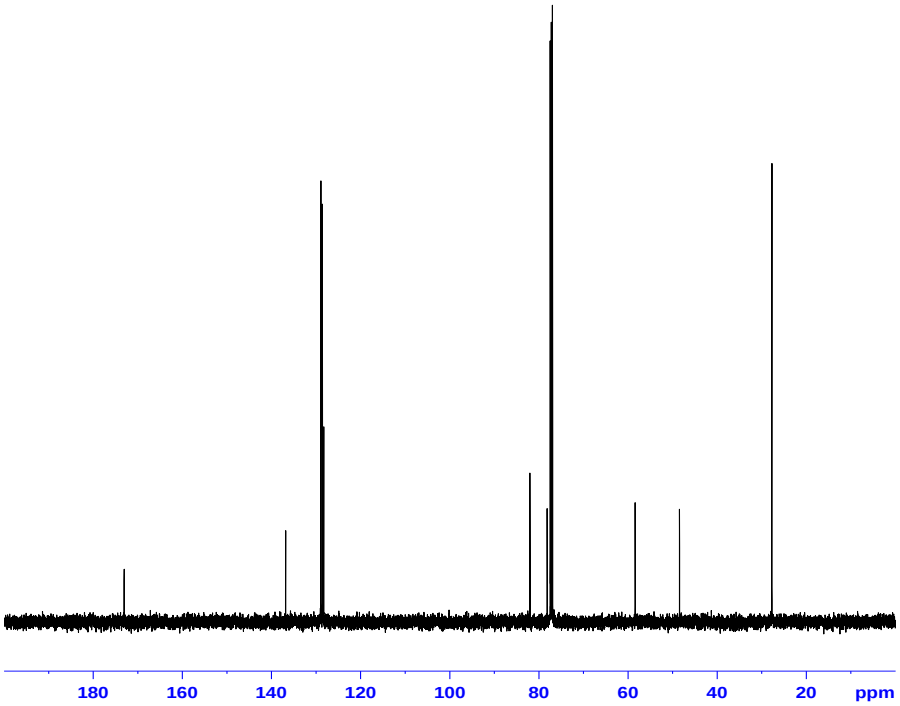
anti-**4.5Ma**

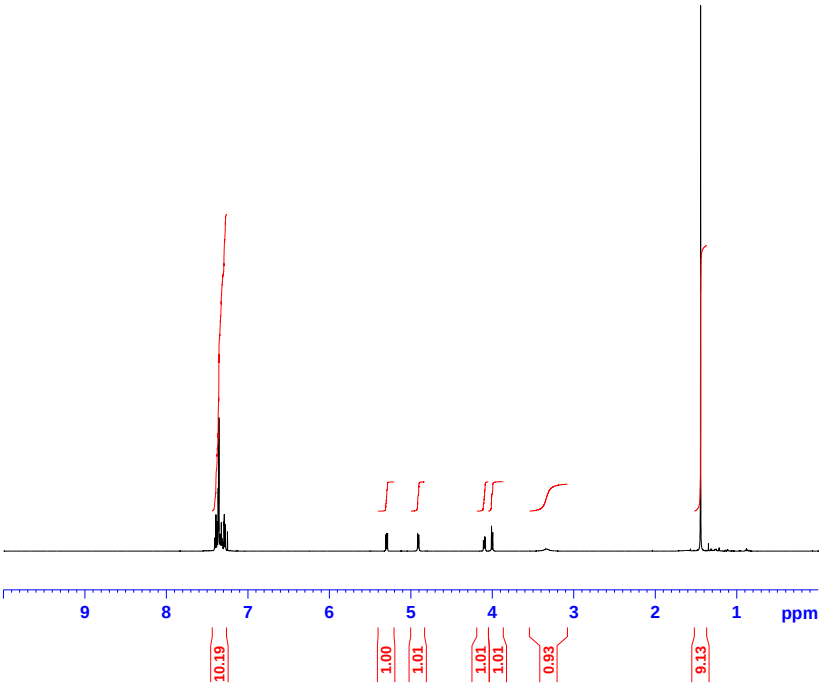

180
160
140
120
100
80
60
40
20
ppm

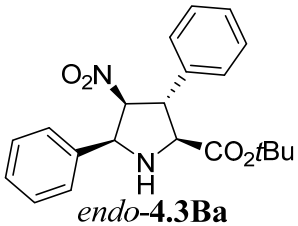

9
8
7
6
5
4
3
2
1
ppm
5.09
1.00
1.00
1.02
1.01
2.34
9.20


O
O2N
OtBu
NH2

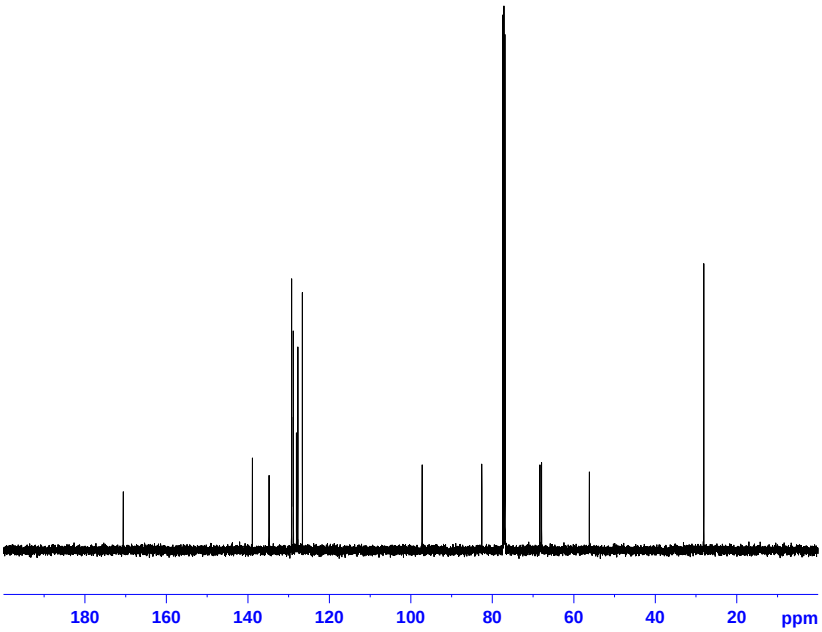
anti-**4.5Ba**


180
160
140
120
100
80
60
40
20
ppm


9
8
7
6
5
4
3
2
1
ppm
10.19
1.00
1.01
1.01
1.01
0.93
9.13


O2N
CO2tBu
N
H

endo-**4.3Ba**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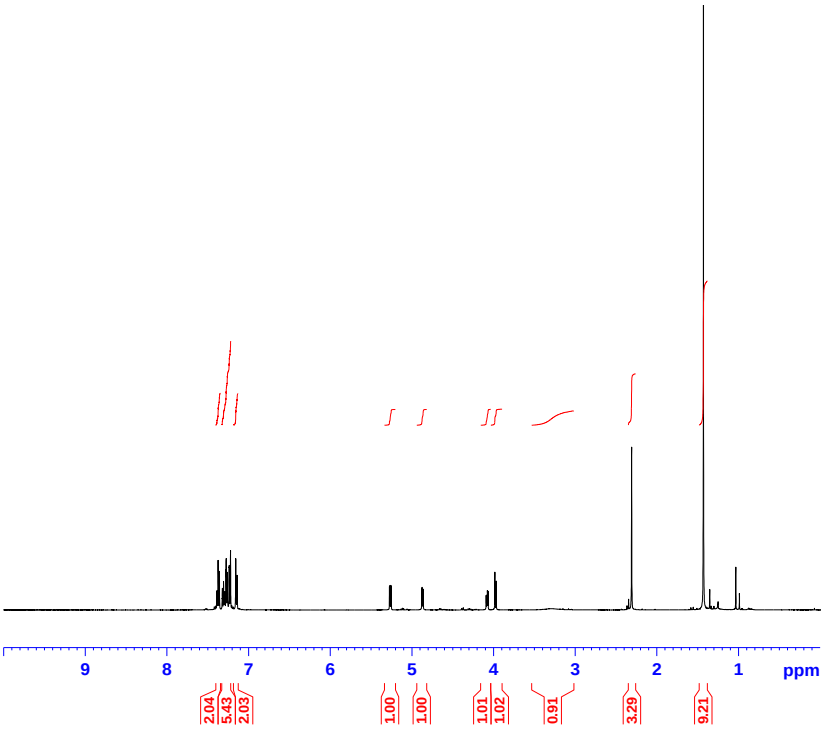
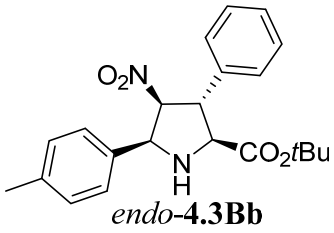
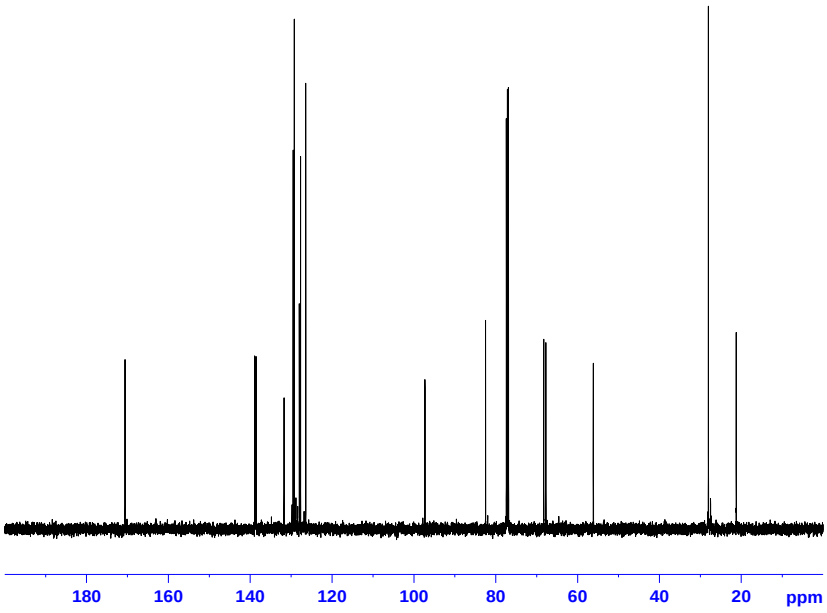
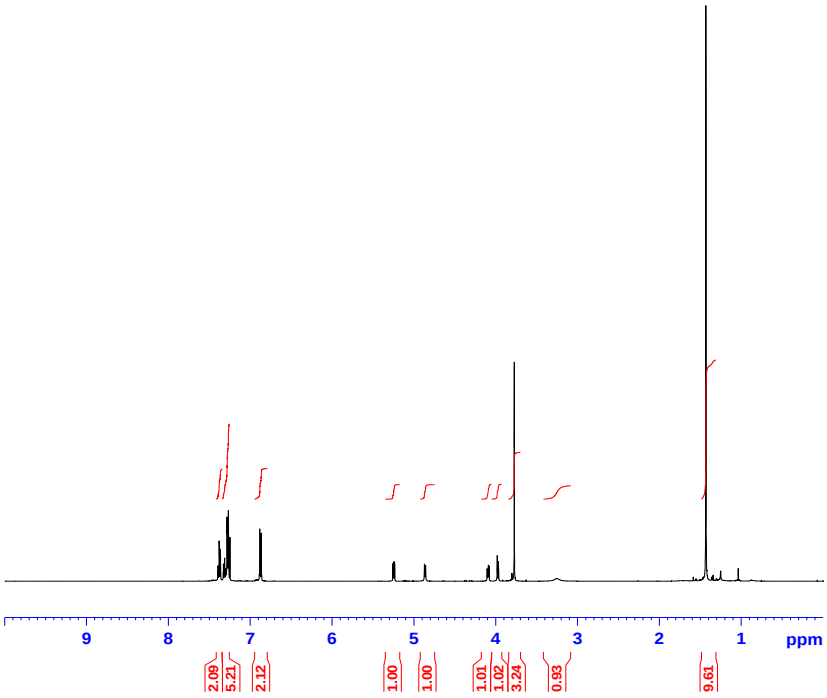
160
140
120
100
80
60
40
20
ppm

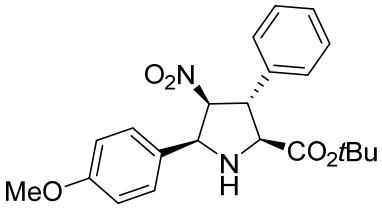

9
8
7
6
5
4
3
2
1
ppm
2.04
5.43
2.03
1.00
1.00
1.01
1.02
0.91
3.29
9.21


O2N
CO2tBu
N
H

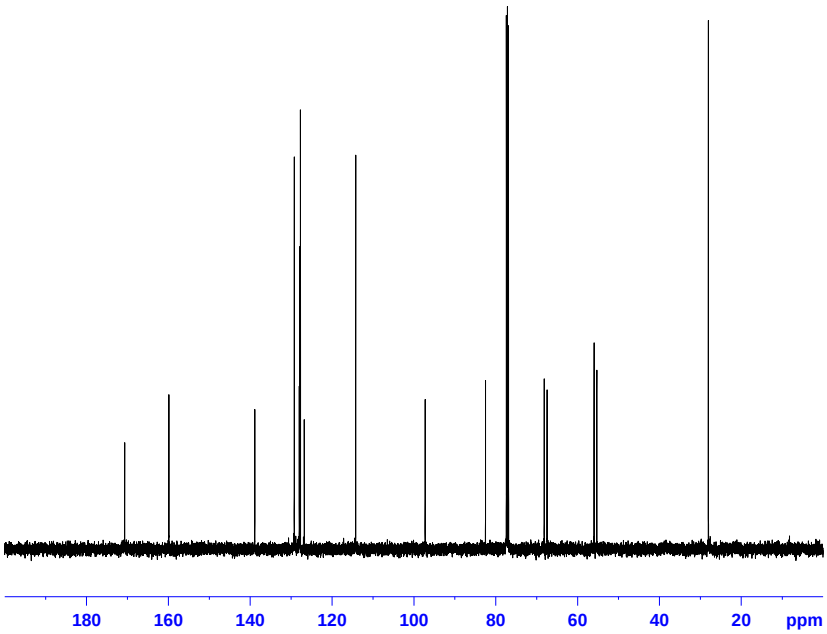
endo-**4.3Bb**

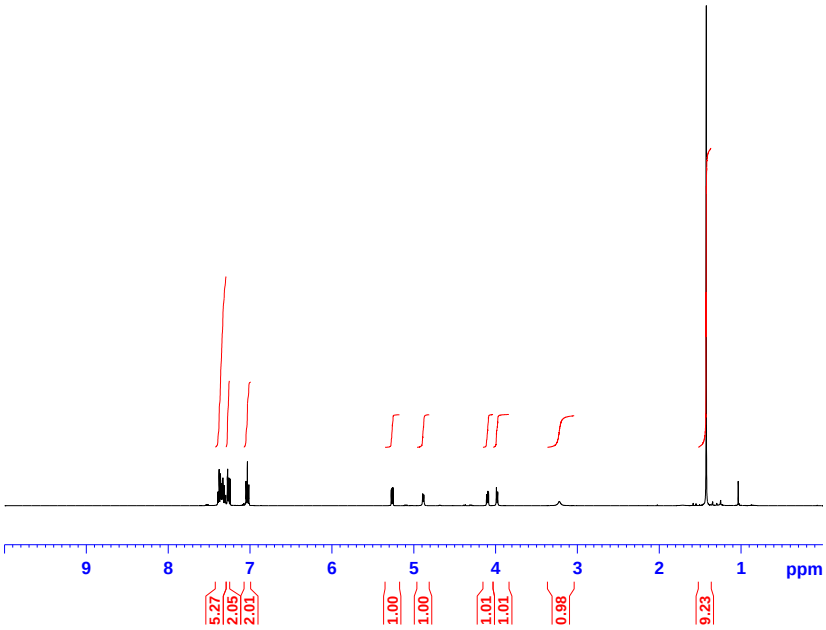

180
160
140
120
100
80
60
40
20
ppm

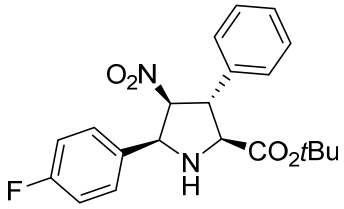

9
8
7
6
5
4
3
2
1
ppm
2.09
5.21
2.12
1.00
1.00
1.01
1.02
3.24
0.93
9.61


O2N
CO2tBu
N
H
MeO

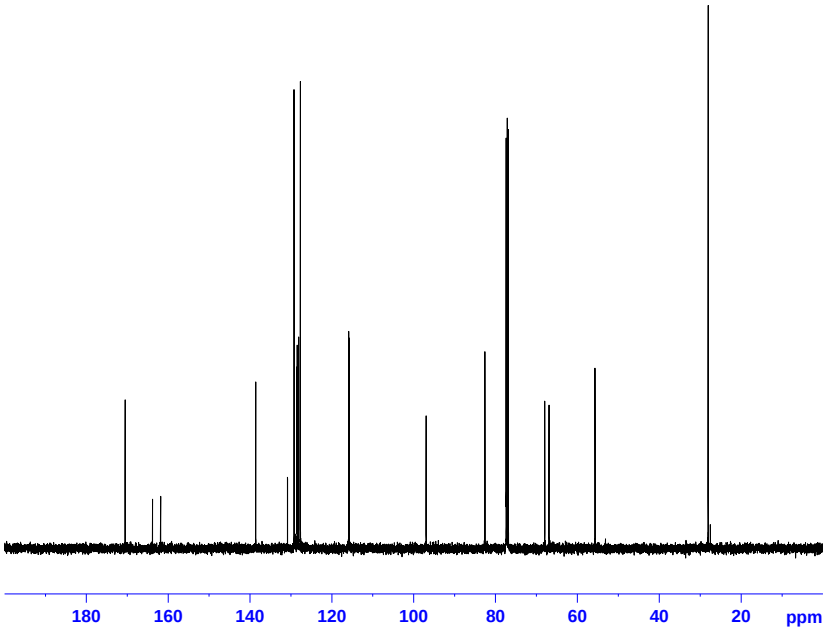
endo-**4.3Bc**

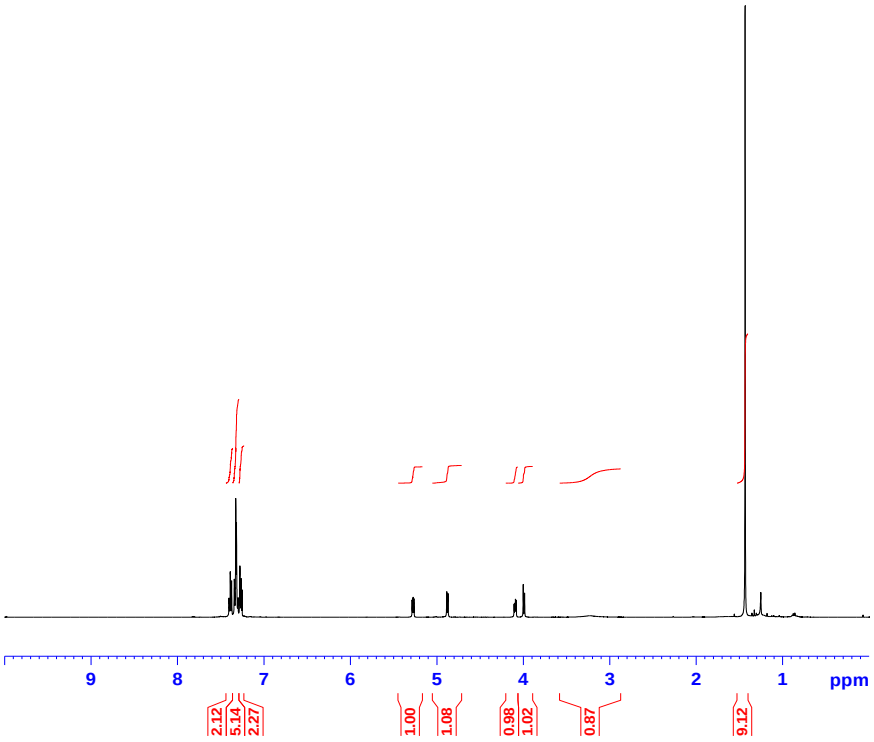

180
160
140
120
100
80
60
40
20
ppm

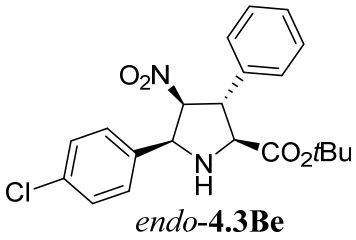

9
8
7
6
5
4
3
2
1
ppm
5.27
2.05
2.01
1.00
1.00
1.01
1.01
0.98
9.23


O2N
CO2tBu
N
H
F

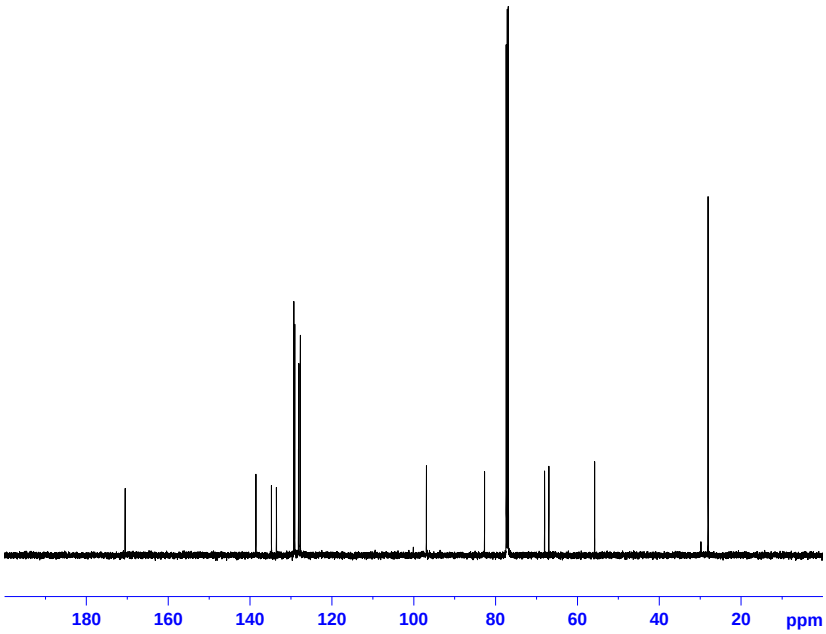
endo-**4.3Bd**

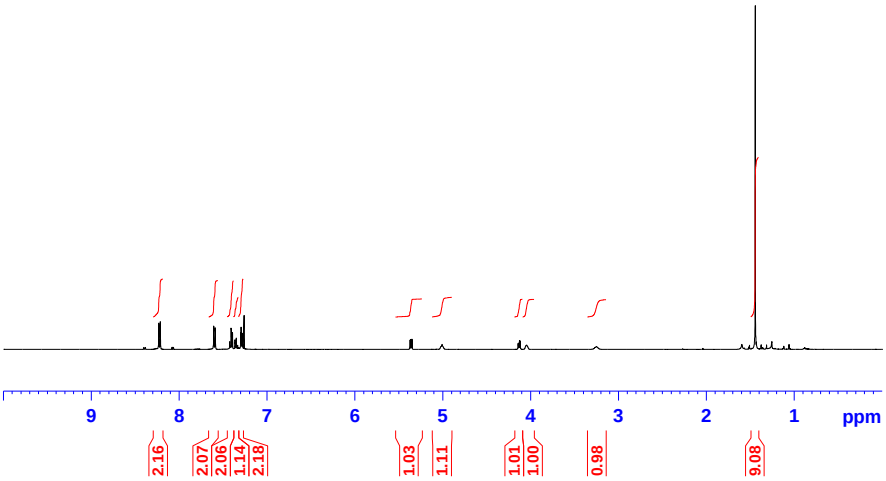

180
160
140
120
100
80
60
40
20
ppm

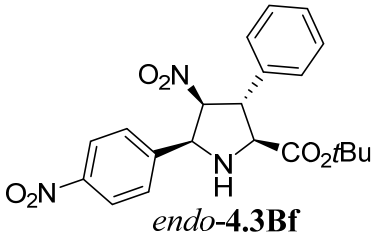

9
8
7
6
5
4
3
2
1
ppm
2.12
5.14
2.27
1.00
1.08
0.98
1.02
0.87
9.12


O2N
CO2tBu
N
H
Cl

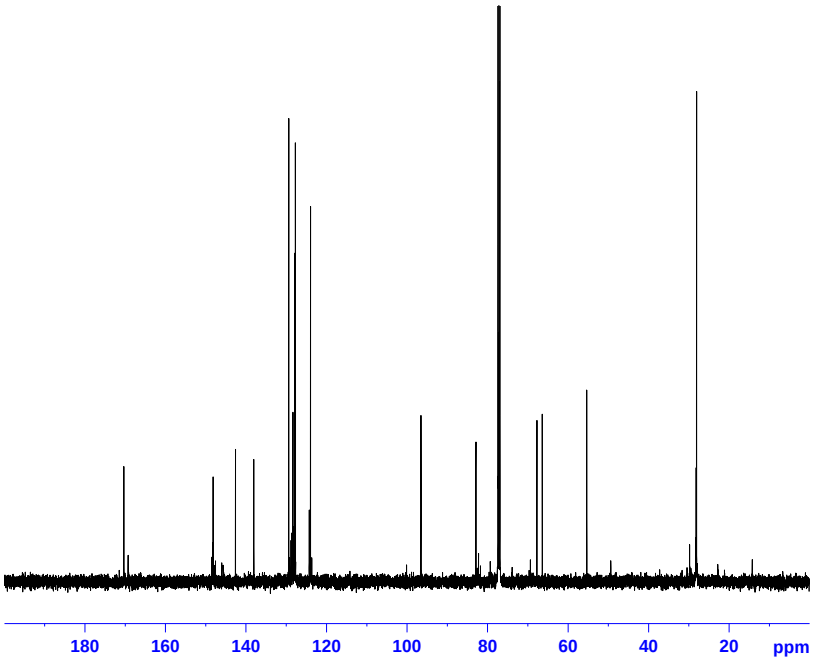
endo-**4.3Be**

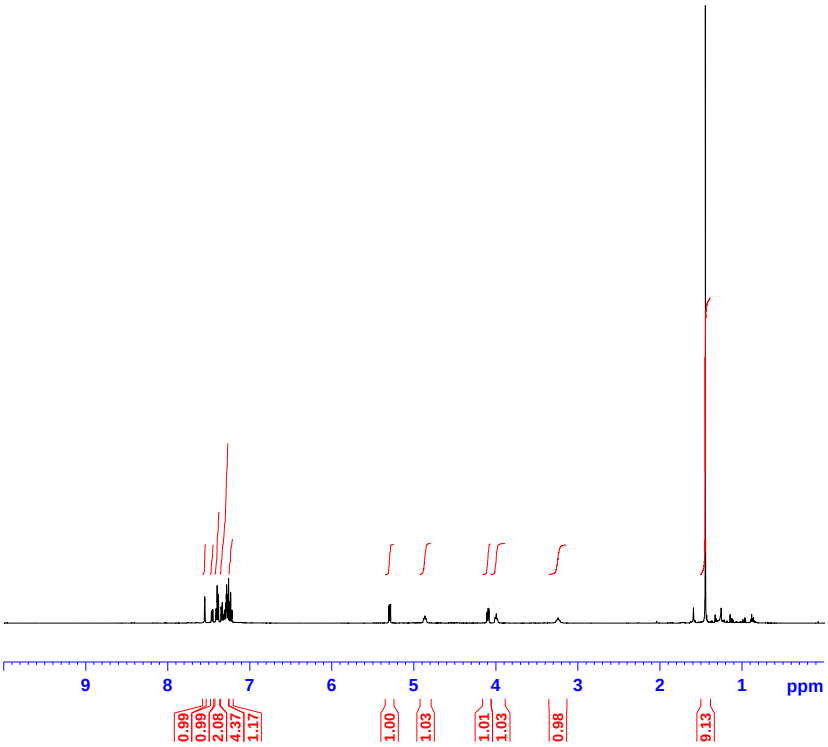

180
160
140
120
100
80
60
40
20
ppm

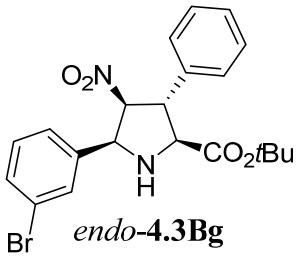

9
8
7
6
5
4
3
2
1
ppm
2.16
2.07
2.06
1.14
2.18
1.03
1.11
1.01
1.00
0.98
9.08


O2N
CO2tBu
N
H
O2N

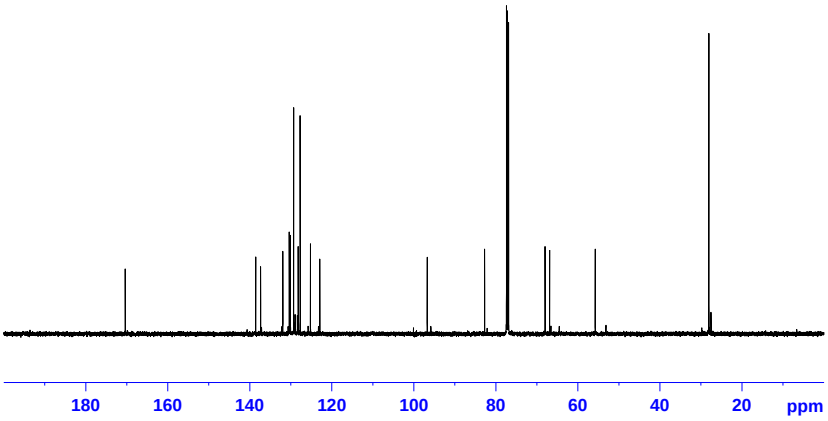
endo-**4.3Bf**

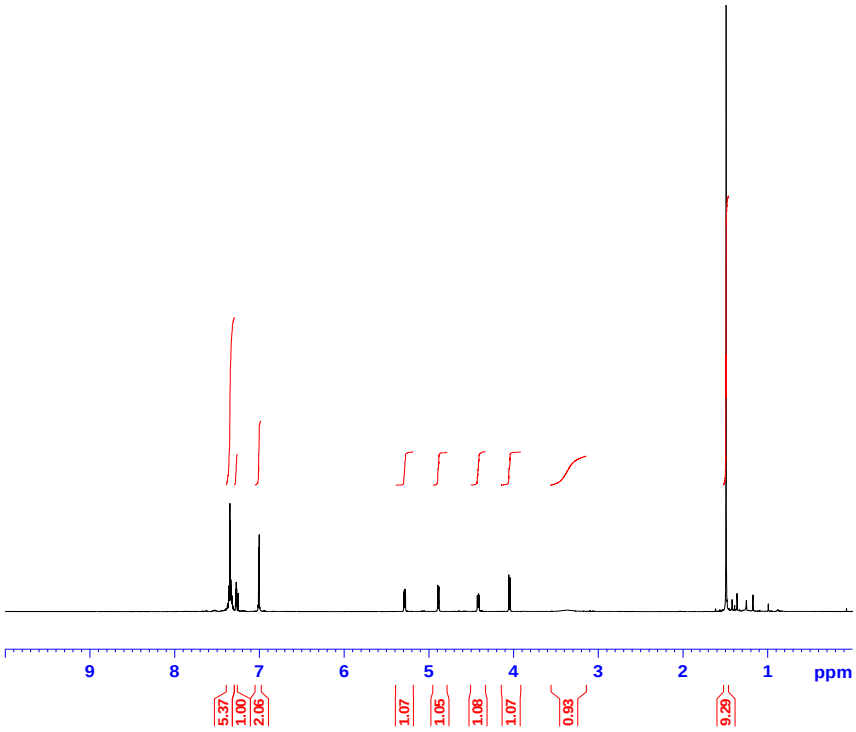

180
160
140
120
100
80
60
40
20
ppm

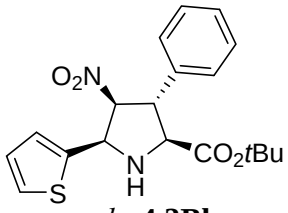

9
8
7
6
5
4
3
2
1
ppm
0.99
0.99
2.08
4.37
1.17
1.00
1.03
1.01
1.03
0.98
9.13


O2N
CO2tBu
N
H
Br

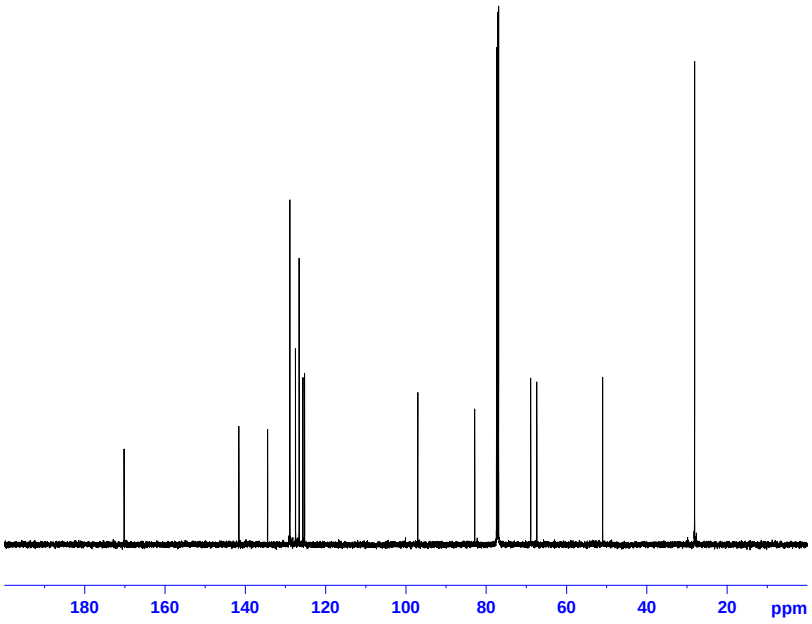
endo-**4.3Bg**


180
160
140
120
100
80
60
40
20
ppm


9
8
7
6
5
4
3
2
1
ppm
5.37
1.00
2.06
1.07
1.05
1.08
1.07
0.93
9.29


O2N
CO2tBu
N
H
S

endo-**4.3Bh**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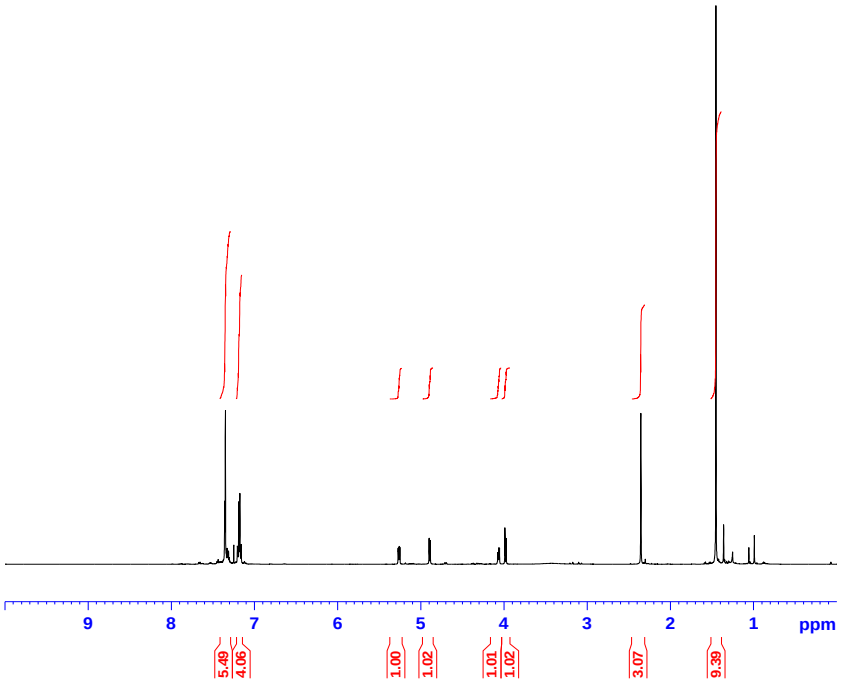
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ppm
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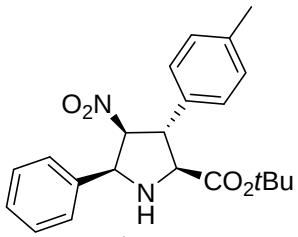
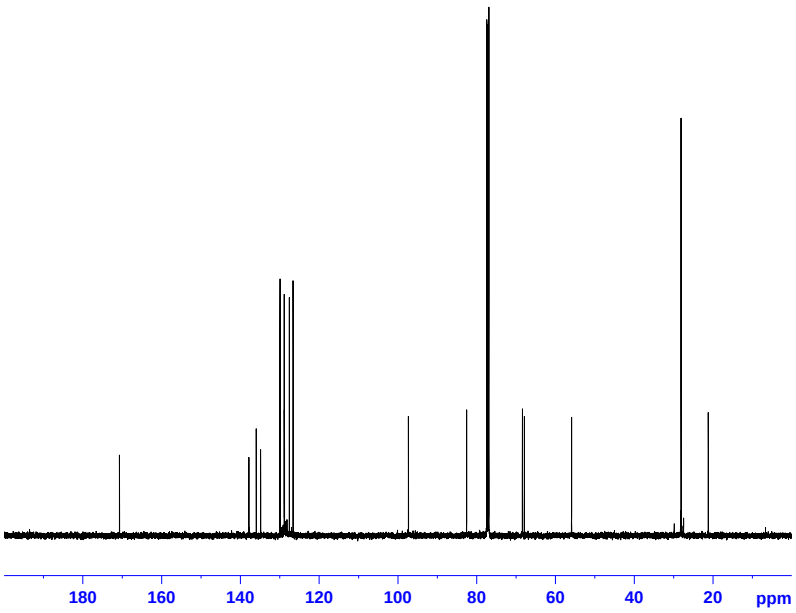
1.02
3.07
9.39


O2N
CO2tBu
N
H

endo-**4.3Bi**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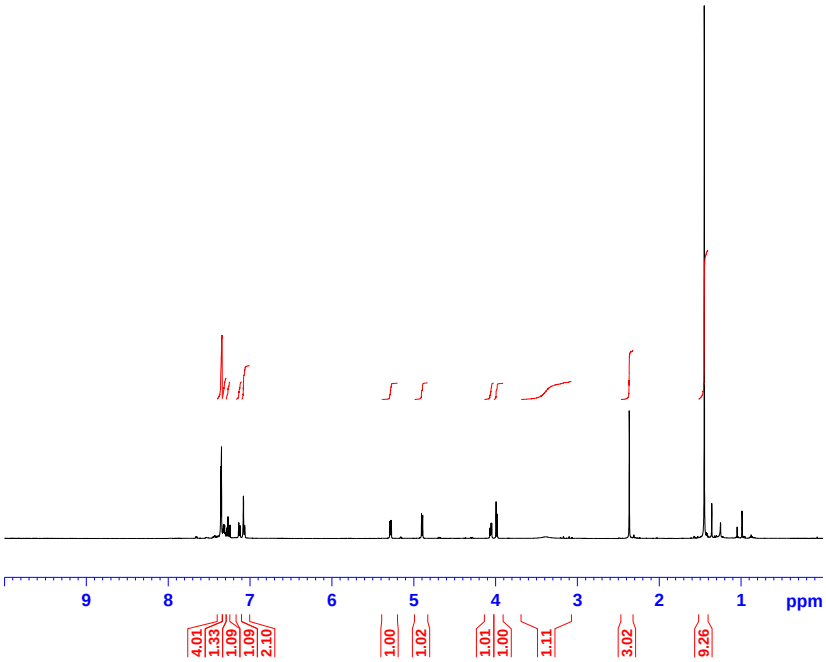
ppm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ppm
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1.01
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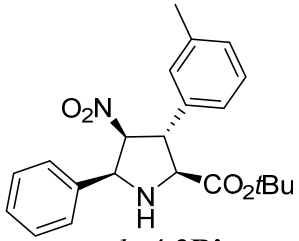
1.11
3.02
9.26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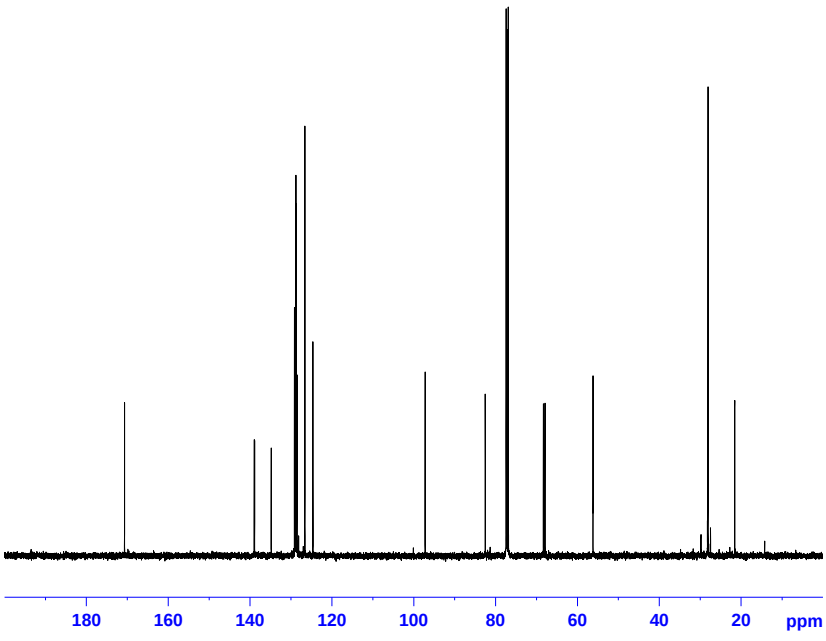
CO2tBu
N
H

endo-**4.3Bj**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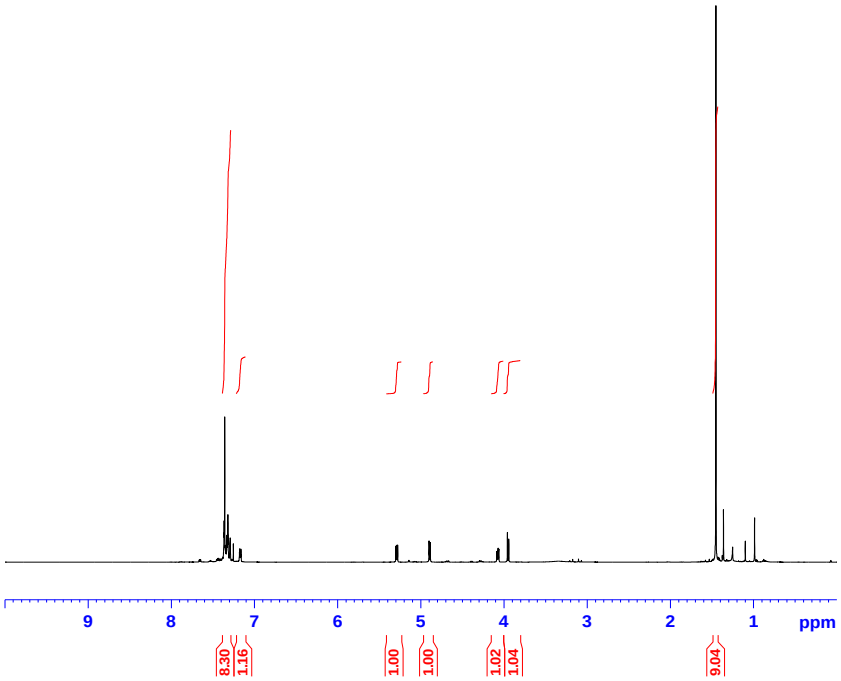
20
ppm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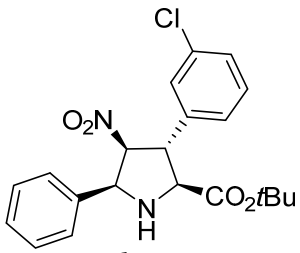
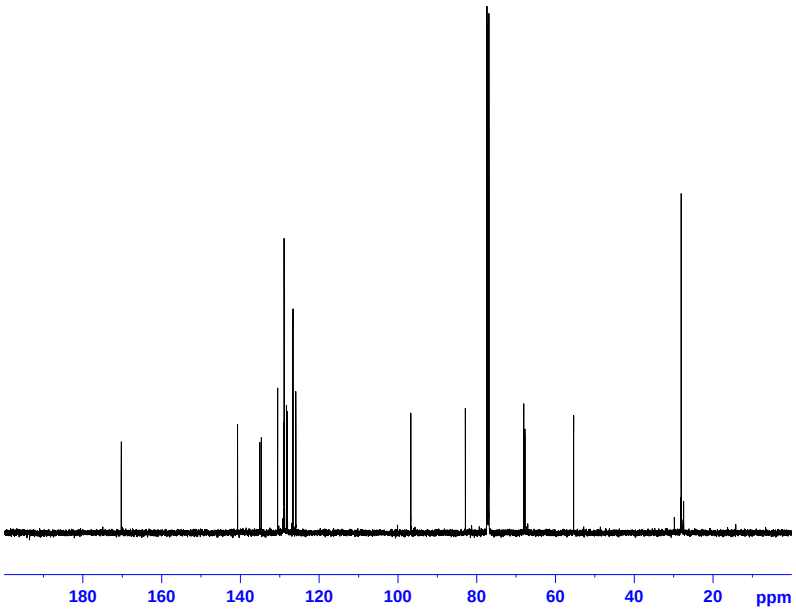
9.04


Cl
O2N
CO2tBu
N
H

endo-**4.3Bk**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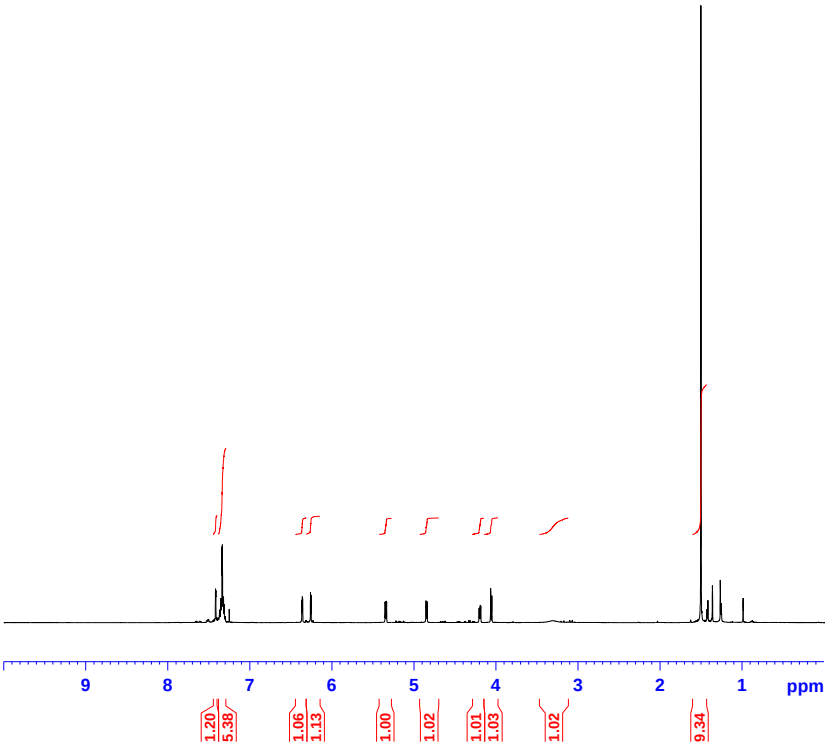
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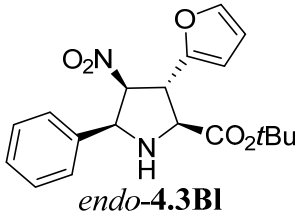
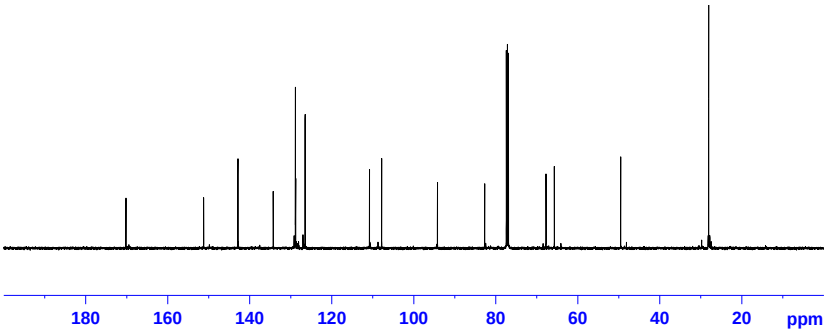
1.02
1.01
1.03
1.02
9.34


O
O2N
CO2tBu
N
H

endo-**4.3Bl**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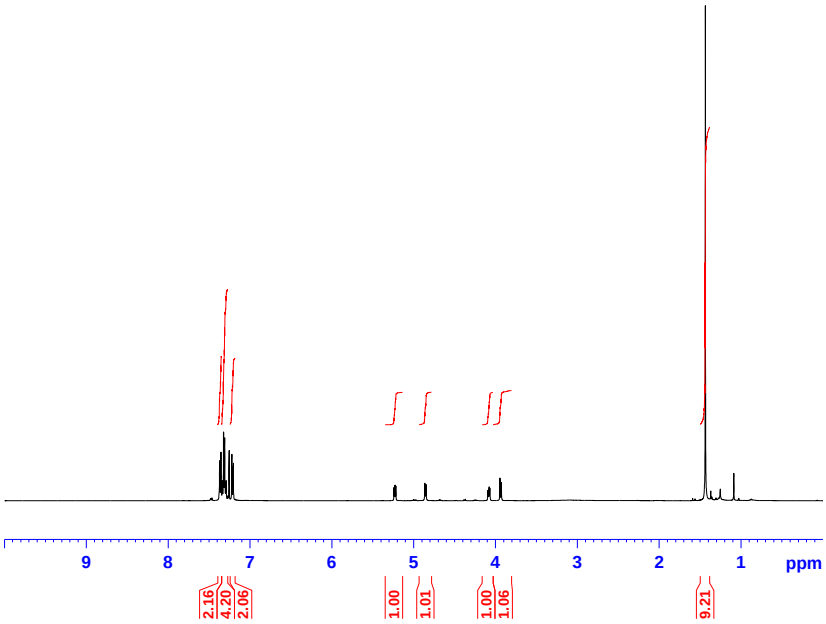
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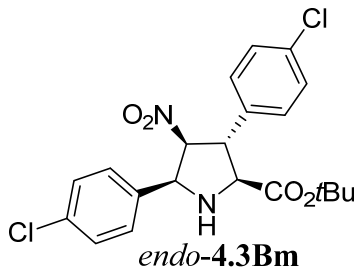
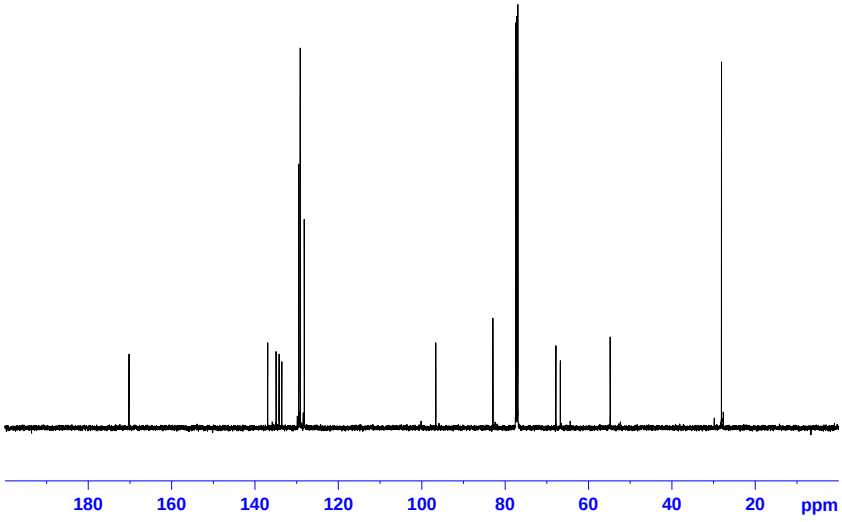
1.06
9.21


Cl
O2N
CO2tBu
N
H
Cl

endo-**4.3Bm**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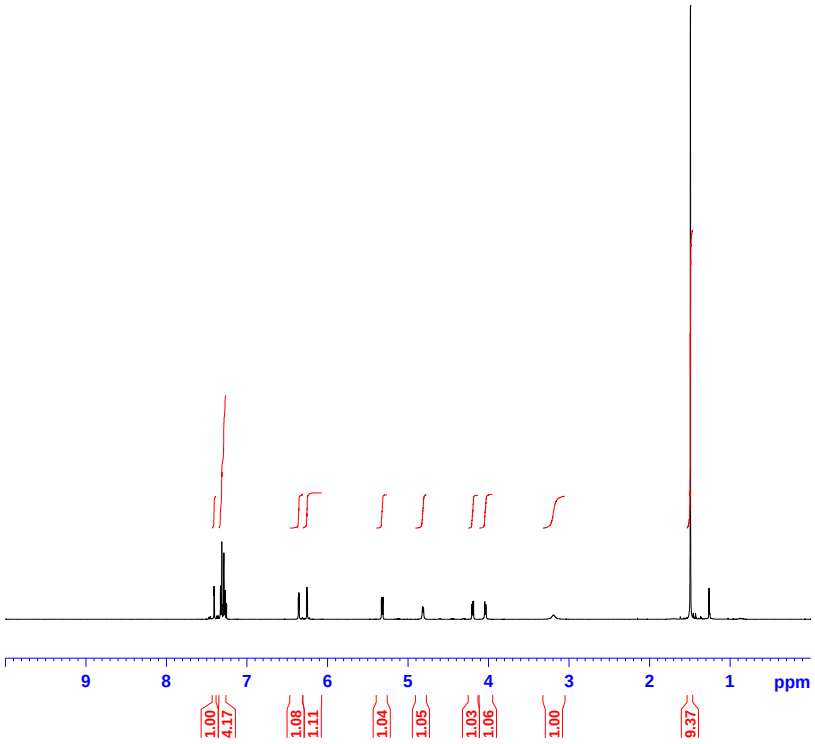
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4
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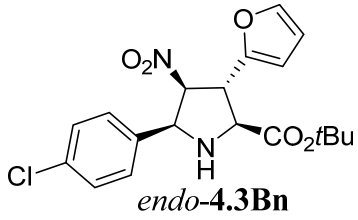
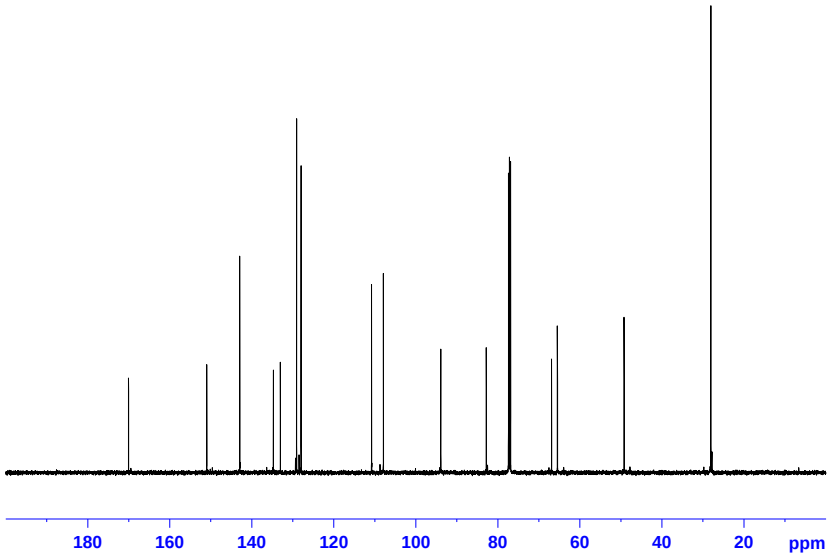
9.37


O
O2N
CO2tBu
N
H
Cl

endo-**4.3Bn**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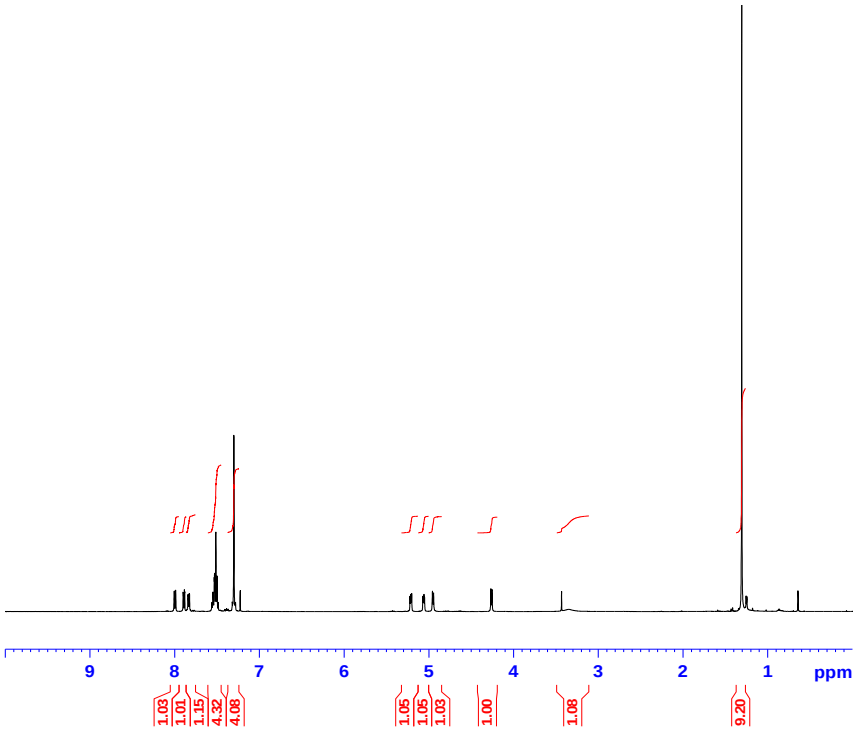
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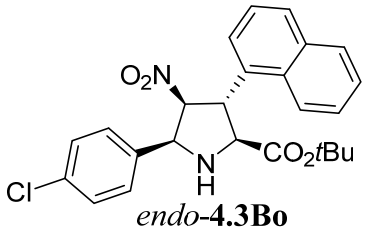
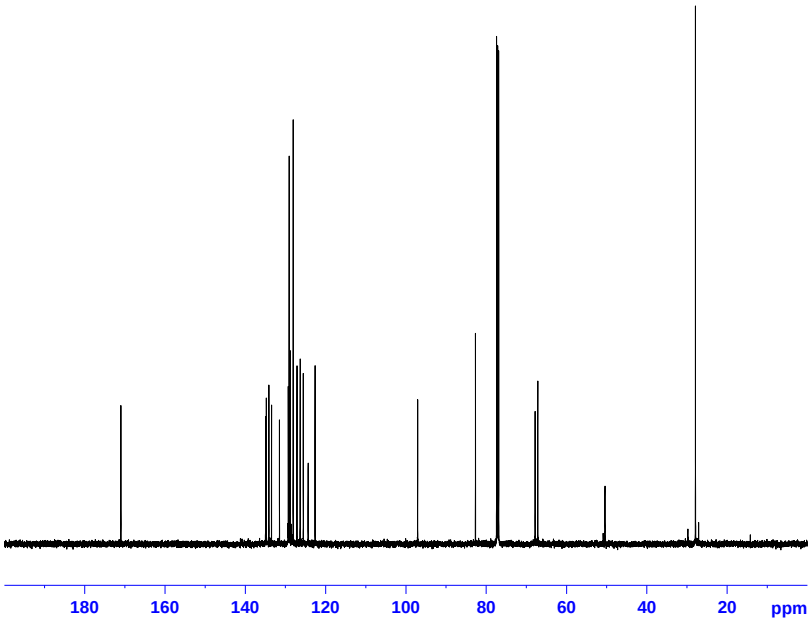
1.08
9.20


O2N
CO2tBu
N
H
Cl

endo-**4.3Bo**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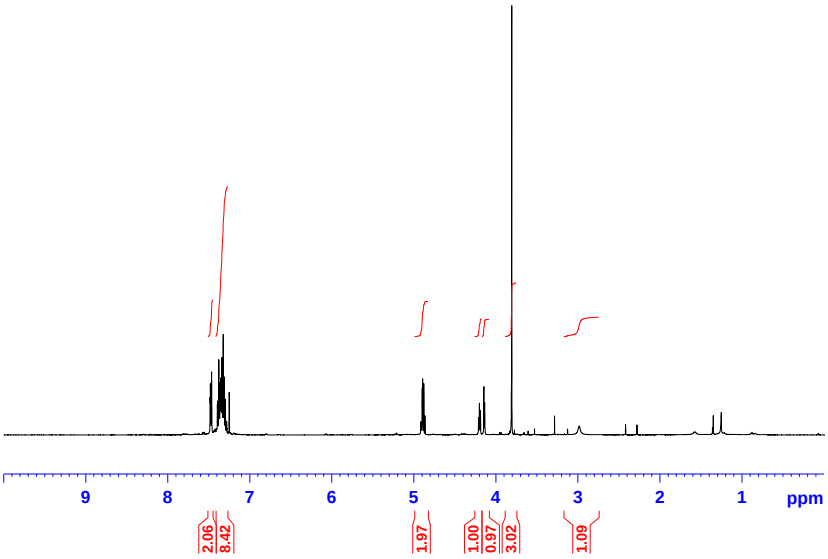
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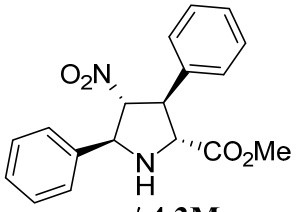
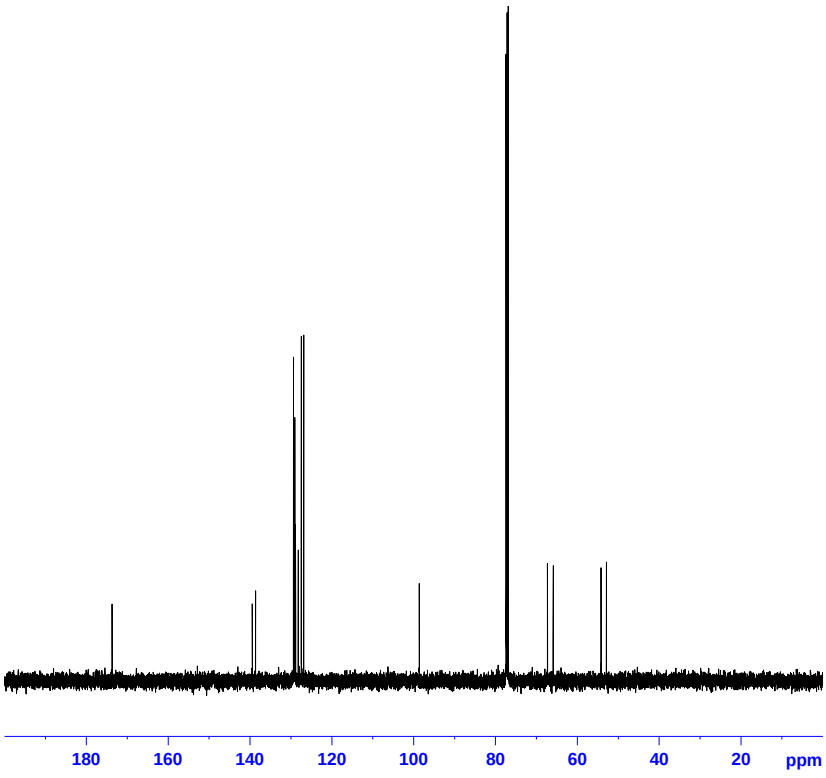
1.09


O2N
CO2Me
N
H

exo'-**4.3Ma**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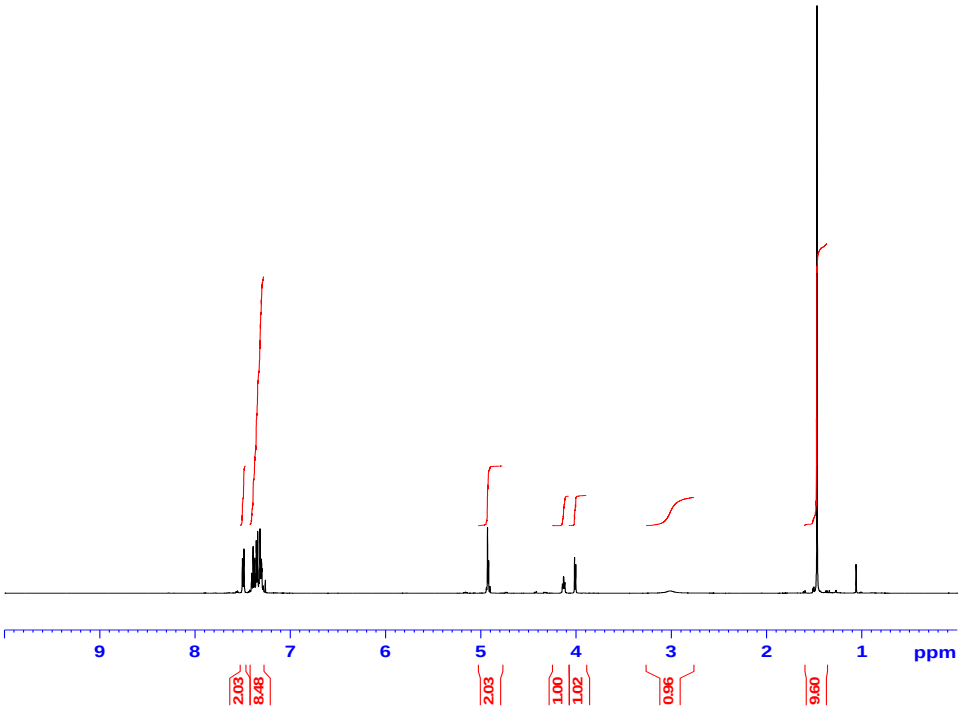
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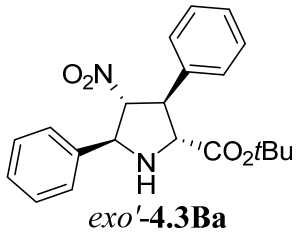
1.00
1.02
0.96
9.60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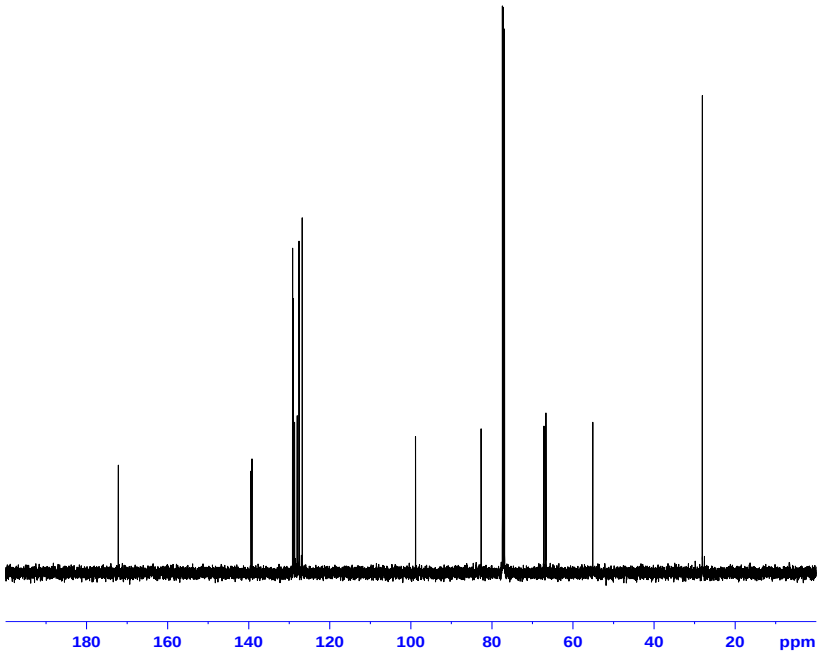
CO2tBu
N
H

exo'-**4.3Ba**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100
80
60
40
20
ppm

VITA

VITA

JIAN-YUAN LI

EDUCATION

- Doctor of Philosophy, Synthetic Organic Chemistry, December 2014

  Purdue University, Indianapolis, Indiana

  Thesis Title: The Modification of Brucine Derivatives as Chiral Ligands and Its Application in the Asymmetric Synthesis

  Research Interest: Synthesis of Natural Products, Catalytic Asymmetric Synthesis
- Bachelor of Science, Chemistry, June 2005

  National Chung Hsing University, Taichung, Taiwan

RESEARCH EXPERIENCE

- Indiana University-Purdue University-Indianapolis, Indianapolis, Indiana (2009-present)

  Advisor: Dr. Kyungsoo Oh

  Explored the modification of brucine derivatives as chiral ligands and their application in the asymmetric synthesis. The major goal of my doctoral research has been to understand the molecular interactions between our brucine-diol

catalyst and substrates, where the stereochemical outcomes of the reactions are substrate controlled through their specific interactions with the molecularities of catalyst. The system that I have investigated used the copper-brucine diol complexes to catalyze the asymmetric conjugate addition reactions of glycine (ket)imines to nitroalkenes and [3+2] cycloaddition reactions between azomethine ylides and activated alkenes.

- National Taiwan University, Taipei, Taiwan (2006-2007)

  Advisor: Dr. Yueh-Hsiung Kuo

  Synthesized and characterized the natural product Salvinal and its derivatives.

- National Chung Hsing University, Taichung Taiwan (2003-2005)

  Advisor: Dr. Tu-Hsin Yan

  Synthesized and characterized the (1*S*)-(+)-ketopinic acid from (1*S*)-(+)-10 camphorsulfonic acid and 2,2-dimethyl-3a,7a-dihydrobenzo[*d*][1,3]dioxole from benzene. Explored the reproducibility of bupropion hydrochloride.

TEACHING EXPERIENCE

- Indiana University-Purdue University-Indianapolis, Indianapolis, Indiana

  Department of Chemistry and Chemical Biology

  Undergraduate Organic Chemistry Laboratory, Teaching Assistant (2010 – present)

  Supervised and instructed students in organic chemistry techniques. Emphasized keeping complete and accurate scientific notes.

- Indiana University-Purdue University-Indianapolis, Indianapolis, Indiana

  Department of Chemistry and Chemical Biology

Tutor at Chemistry Resource Center (2010 – present)

Answered problem sets and assisted laboratory reports of undergraduate level chemistry courses.

- National Taiwan University, Taipei, Taiwan

  Department of Chemistry

  Undergraduate General Chemistry Laboratory, Teaching Assistant (2007 – 2008)

  Supervised instructed students in general chemistry techniques. Emphasized keeping complete and accurate scientific notes.

PUBLICATIONS

- Kim, H. Y., Li, J.-Y., & Oh, K. (2013). A Soft Vinyl Enolization Approach to α-Acylvinyl Anions : Direct Aldol/Aldol Condensation Reactions of (*E*)-β-Chlorovinyl Ketones. *Angewandte Chemie International Edition*, *52*(13), 3736-3740.
- Kim, H. Y., Li, J.-Y., & Oh, K. (2012). Studies on Elimination Pathways of β-Halovinyl Ketones Leading to Allenyl and Propargyl Ketones and Furans under the Action of Mild Bases. *The Journal of Organic Chemistry*, *77*(24), 11132-11145.
- Kim, H. Y., Li, J.-Y., Kim, S., & Oh, K. (2011). Stereodivergency in Catalytic Asymmetric Conjugate Addition Reactions of Glycine (Ket)imines. *Journal of the American Chemical Society, 133*(51), 20750-20753.

- Oh, K., & Li, J.-Y. (2011). A Cooperative Catalysis Approach to the Morita-Baylis-Hillman Reaction of Aryl Vinyl Ketones. *Synthesis, 2011*(12), 1960-1967.

- Oh, K., Li, J.-Y., & Ryu, J. (2010). Brucine *N*-Oxide-Catalyzed Morita-Baylis-Hillman Reaction of Vinyl Ketones: a Mechanistic Implication of Dual Catalyst System with Proline. *Organic & Biomolecular Chemistry, 8*(13), 3015-3024.

PRESENTATIONS

- Enantiodivergent [3+2] Cycloaddition Reactions Between Glycine (Ket)imines and Nitroalkenes

  246th ACS National Meeting, Fall 2013, Indianapolis, Indiana
- Catalytic Asymmetric Synthesis of Pyrrolidines Using a Diverse Chiral Coppor Catalysts Derived from a Single Chiral Source

  243rd ACS National Meeting, Spring 2012, San Diego, California

AWARD

- Chemistry and Chemical Biology Graduate Dissertation Award (2014)

PROFESSIONAL AFFILIATION

- American Chemical Society, Graduate Student Member (2011 – present)

PUBLICATIONS

PUBLICATIONS

1. Kim, H. Y., Li, J.-Y., & Oh, K. (2013). A Soft Vinyl Enolization Approach to α-Acylvinyl Anions : Direct Aldol/Aldol Condensation Reactions of (*E*)-β-Chlorovinyl Ketones. *Angewandte Chemie International Edition*, *52*(13), 3736-3740.

2. Kim, H. Y., Li, J.-Y., & Oh, K. (2012). Studies on Elimination Pathways of β-Halovinyl Ketones Leading to Allenyl and Propargyl Ketones and Furans under the Action of Mild Bases. *The Journal of Organic Chemistry*, *77*(24), 11132-11145.

3. Kim, H. Y., Li, J.-Y., Kim, S., & Oh, K. (2011). Stereodivergency in Catalytic Asymmetric Conjugate Addition Reactions of Glycine (Ket)imines. *Journal of the American Chemical Society, 133*(51), 20750-20753.

4. Oh, K., & Li, J.-Y. (2011). A Cooperative Catalysis Approach to the Morita-Baylis-Hillman Reaction of Aryl Vinyl Ketones. *Synthesis, 2011*(12), 1960-1967.

5. Oh, K., Li, J.-Y., & Ryu, J. (2010). Brucine *N*-Oxide-Catalyzed Morita-Baylis-Hillman Reaction of Vinyl Ketones: a Mechanistic Implication of Dual Catalyst System with Proline. *Organic & Biomolecular Chemistry, 8*(13), 3015-3024.