Stereoselective Cope-Type Hydroamination of Allylic Amines Using Simple Aldehydes as Catalysts

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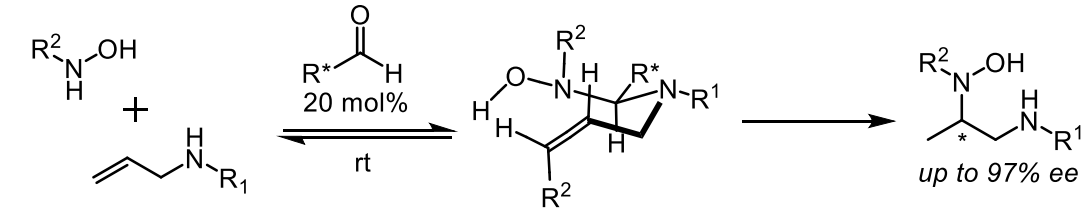
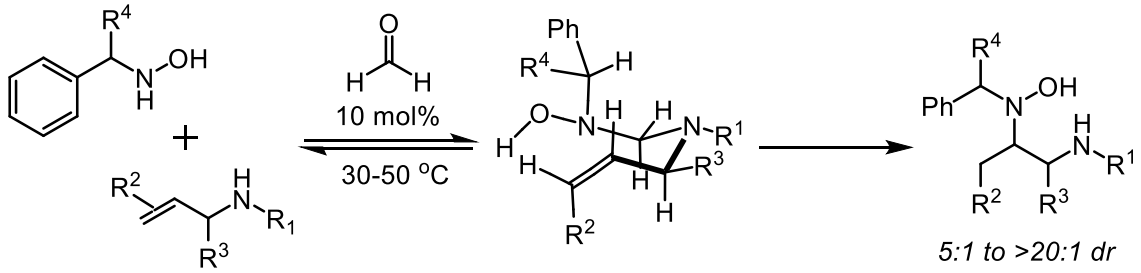
Abstract

Stereoselective hydroaminations of unactivated alkenes are rare as this represents a very challenging synthetic transformation. The most efficient examples occur in biased intramolecular systems and highly enantioselective intermolecular examples are rare, which is consistent with the forcing conditions required to catalyze the reactions. This limited reactivity also accounts for the lack of highly diastereoselective hydroamination variants. Recently our group has shown that intermolecular Cope-Type hydroamination of unactivated alkenes can be achieved using simple aldehydes as catalysts. The aldehyde promotes pre-association of the two reaction partners, inducing temporary intramolecularity resulting in a remarkably facile hydroamination event. This thesis will present the development of two reactions: intermolecular enantioselective Cope-type hydroamination and intermolecular diastereoselective Cope-type hydroamination of allylic amines.



Catalysis and Stereoinduction via Temporary Intramolecularity



Acknowledgements

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List of Abbreviations

Å	angstrom (10^{-10} metres)
Ac	acetyl
anti	against, opposite
aq	aqueous
Ar	aryl
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
Bu	butyl
cat.	catalytic
Cbz	benzyloxycarbonyl
°C	degree Celsius
cis	on the same side
cod	1,5-cyclooctadiene
coe	cyclooctene
conc.	concentrated
Cp (Cp')	cyclopentadienyl (pentamethylcyclopentadienyl)
Cy	cyclohexyl
δ	chemical shift in parts per million
d	deuterium (in NMR solvents)
DMAP	*N*,*N*-4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
EI	electron impact
equiv	equivalent
Et	ethyl

FT	Fourier transform
g	gram
h	hour
h	Planck's constant (6.626×10^{-34} J s)
*h*ν	light; electromagnetic radiation
HRMS	high-resolution mass spectrometry
Hz	Hertz
i	iso
IR	infrared
J	coupling constant
L	litre; ligand
Ln	lanthanide
μL	microlitre
m	meta
M	molar; metal
Me	methyl
mg	milligram
min	minute
mL	millilitre
mmol	millimole
MS	molecular sieves
n	normal
nbd	norbornadiene
Nu	nucleophile
NMR	nuclear magnetic resonance
p	para
PCC	pyridinium chlorochromate
Ph	phenyl
ppm	parts per million
Pr	propyl
py	pyridine

R	carbon-based substituent
rt	room temperature
s	secondary
s	second
sat.	saturated
syn	together, same side
t	tertiary
TBAF	tetra-*n*-butylammonium fluoride
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMANO	trimethylamine *N*-oxide
TMS	trimethylsilyl
TOF	turnover frequency
Ts	*para*-toluenesulfonyl
UV	ultra-violet

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Chapter 1 – Asymmetric Hydroamination of Unactivated Alkenes

1.1 Introduction

Nitrogen-containing molecules are valuable and commercially important bulk chemicals, specialty chemicals, and pharmaceuticals. Classical routes for the formation of carbon-nitrogen bonds usually require refined starting materials containing preactivated functional groups. Transformations such as reductive amination and nucleophilic substitution are commonly used transformations to form carbon-nitrogen bonds. Alkenes represent compelling substrates to functionalize due to their abundance as well as a large number of substitution patterns. Transformations of alkenes leading to the formation of carbon-nitrogen bonds include aziridination, diamination, aminohydroxylation, oxidative amination, aminocarbonylation, and hydroamination (Figure 1.1). While these transformations are very important, a more difficult challenge is the development of highly enantioselective variants. This chapter will focus on various methods that can catalyze enantioselective hydroamination of alkenes[1] as well as perform diastereoselective hydroaminations.

[1] For a recent review on asymmetric hydroamination see: Hannedouche, J. Schulz, E. *Chem. Eur. J.* **2013**, *19*, 4972 and review cited therein.

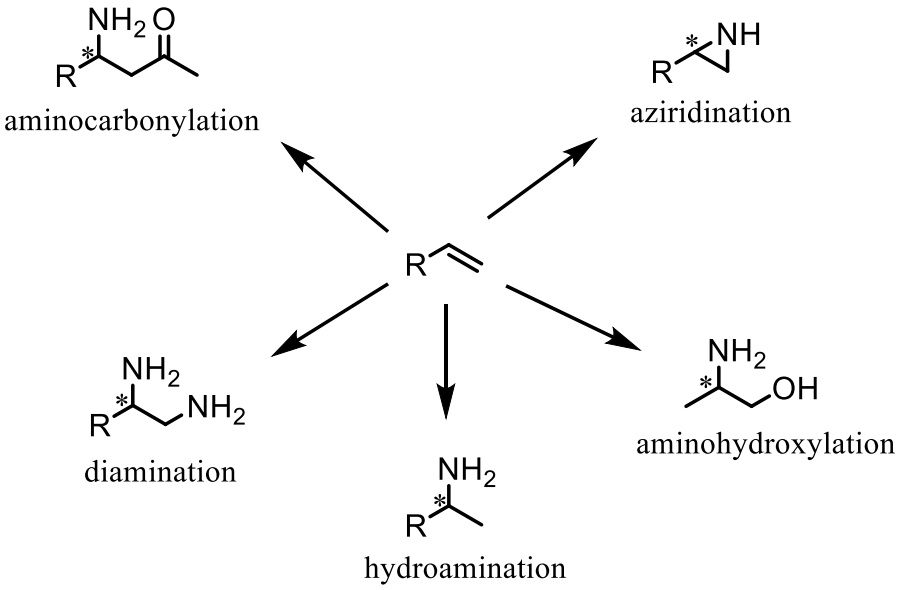


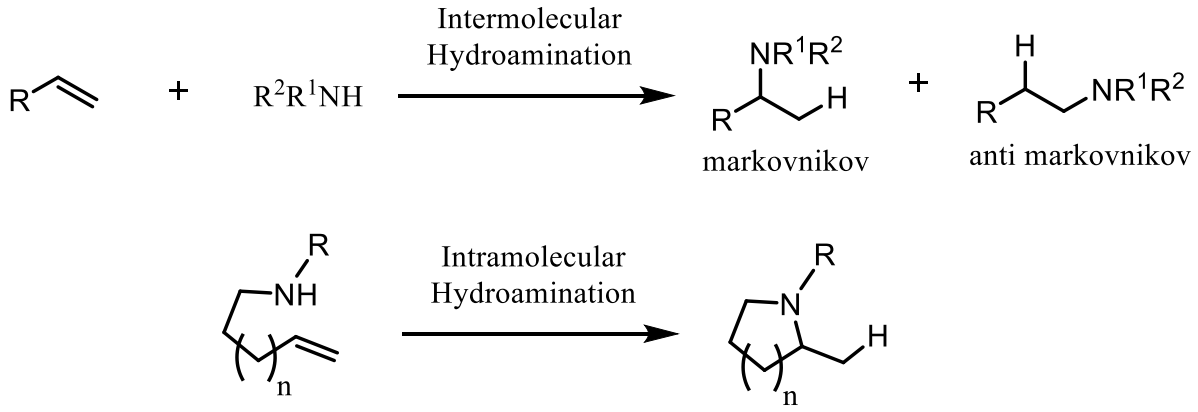
Figure 1.1 Various amination reactivity of alkenes

1.2 Hydroamination of Unactivated Alkenes

Hydroamination, the direct addition of an amine across an unsaturated C-C bond is a very desirable transformation, however, a general solution does not exist.[2] The reaction in theory is 100% atom-efficient, although this is typically not the case since an excess of either the alkene or the amine is required in intermolecular systems. Hydroamination of unactivated alkenes has fundamental issues making it difficult: 1) electrostatic repulsion between the nitrogen lone pair and electron rich double bond, 2) hydroamination is only slightly exothermic or even thermoneutral, and 3) the high negative reaction entropy is causing the process to be less favorable at high temperatures. For these reasons catalysts are typically required, as well as elevated temperatures, to enable hydroamination of unactivated alkenes.

[2] (a) Muller, T. E.; Hultzch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. (b) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367. (c) Muller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98, 675.*

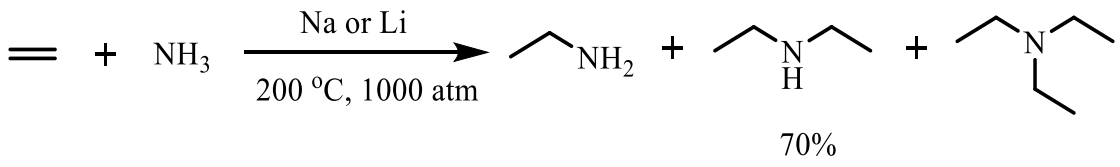
Hydroamination can occur in intermolecular or intramolecular systems (Scheme 1.1). Intramolecular hydroaminations are more common due to the lower entropic penalty associated with the process. Indeed, the development of a general method to catalyze enantioselective hydroamination of alkenes has the potential to simplify chiral amine synthesis, thus enabling an expedient route to enantioenriched amines from alkenes.



Scheme 1.1 Intermolecular and intramolecular hydroamination of alkenes and selectivity

Metal, acid, base, and organo-catalysts are used to enable enantioselective hydroaminations. Intramolecular variants dominate the literature whereas intermolecular examples are rare and high enantioselectivity is strictly limited to biased alkenes. The remainder of this chapter will highlight current methods for stereoselective hydroamination that have been developed using different catalysts and different modes of activation.

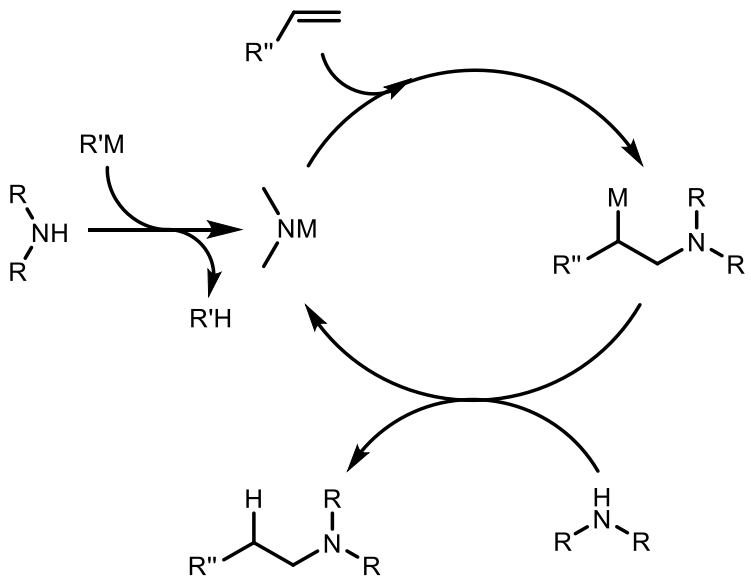
1.3 Base Catalyzed Asymmetric Hydroaminations



Scheme 1.2 Early report of base promoted hydroamination

Base mediated hydroaminations with alkali metals such as sodium and lithium were first reported in 1954.[3] The reaction required both high temperatures and pressures (Scheme 1.2). A simplified mechanism of base catalyzed hydroamination is shown in Scheme 1.3. The catalytic cycle begins with the generation of a metal amide. The metal amide is quite nucleophilic and can add to the olefin to give an alkyl metal species. The alkyl metal species is quickly protonated by another equivalent of amine to give the hydroamination product, and regenerate the metal amide to complete the cycle. The slow step of the cycle has been shown to be the addition of the metal amide to the alkene simply due to the electrostatic repulsion between the metal amide and the electrons of the double bond. The fast step is the protonation of the carbanion with an amine to generate the more stable metal amide.

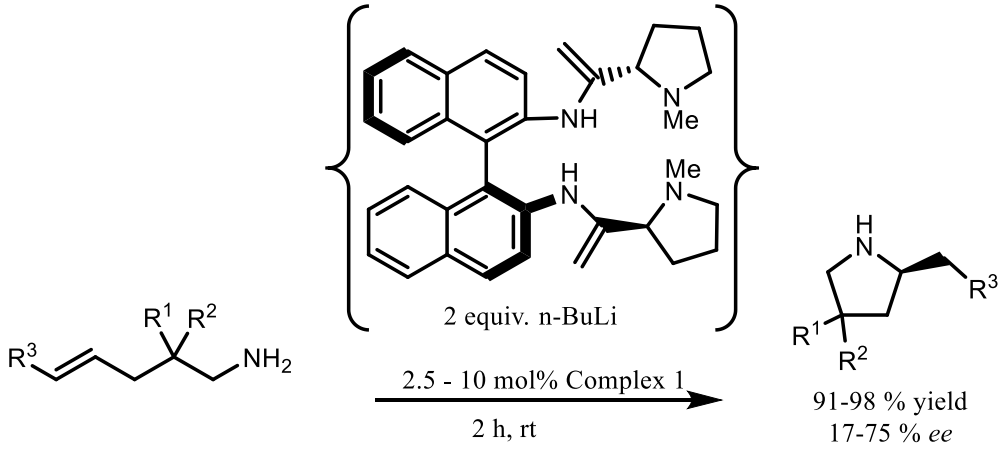
[3] Howk, B. W.; Little, E. L.; Scott, S. L.; Whitman, G. M. *J. Am. Chem. Soc.* **1954**, *76*, 1899.



Scheme 1.3 General mechanism for base catalyzed hydroamination

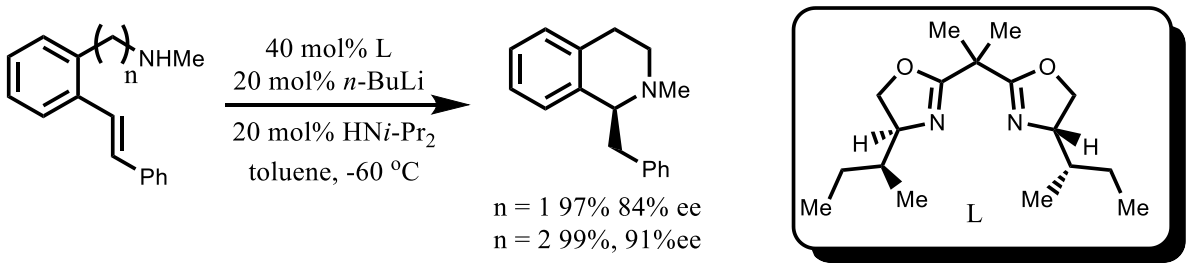
In 2006, the first enantioselective base-catalyzed hydroamination was developed by Hultzsch and coworkers.[4] The method uses a chiral lithiated base prepared by treating a dimeric proline derived diamidobinaphthyl compound with two equivalents of *n*-BuLi (Scheme 1.4). This catalyst was highly reactive enabling high yielding 5-membered cyclizations to enantioenriched pyrrolidines. All substrates contained geminal-disubstitution to accelerate the reaction through the Thorpe-Ingold effect. The enantioselectivities ranged from 17 to 75% *ee* making this a good first attempt at a base-catalyzed enantioselective hydroamination.

[4] Martinez, P. H.; Hultzsch, K. C.; Hampel, F. *Chem. Commun.* **2006**, 2221.



Scheme 1.4 Enantioselective intramolecular hydroamination using an insitu generated chiral base as catalyst

In 2007, Tomioka and co-workers were able to cyclize *N*-methyl amines in both five- and six- membered systems in high yield and high enantiomeric excess using a chiral bisoxazoline ligand (Scheme 1.5).[5] Indeed, base catalyzed enantioselective hydroaminations are rare and the only two examples reported are in biased intramolecular systems. Functional group tolerance is an issue for base catalyzed hydroamination as any functional group that has a hydrogen atom more acidic than the N-H will disrupt the reaction.

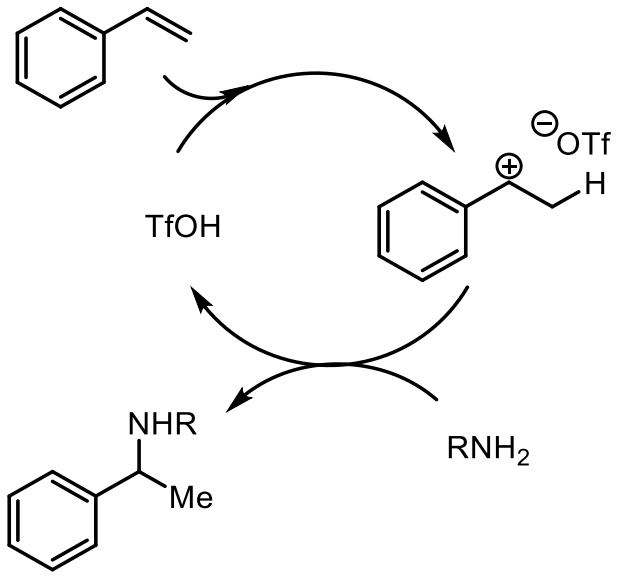


Scheme 1.5 Intramolecular base catalyzed enantioselective hydroamination using a chiral bisoxazoline ligand

[5] Ogata, T.; Ujihara, A.; Tsuchida, S.; Shimizu, T.; Kaneshige, A.; Tomioka, K. *Tetrahedron Lett.* **2007**, *47*, 6648.

1.4 Acid Catalyzed Asymmetric Hydroaminations

In acid-catalyzed hydroaminations the alkene is protonated, generating a carbenium ion, followed by attack of an amine. This approach to hydroamination is limited due to the basic nature of amines. Amines are much more basic than alkenes and protonation consumes the acid catalyst leading to the generation of ammonium salts rendering the amine non-nucleophillic. Despite these inherent challenges hydroamination of alkenes by acid catalysis is possible with amines containing electron-withdrawing substituents. Specifically, employing triflic acid as a catalyst, *N*-tosylamines react well with styrene (Scheme 1.6).[6] The major difficulty in achieving enantioinduction is that while electrostatic forces hold the chiral counterion in close proximity to the carbenium ion, this ion pair lacks rigidity and therefore usually provides no control of facial selectivity.

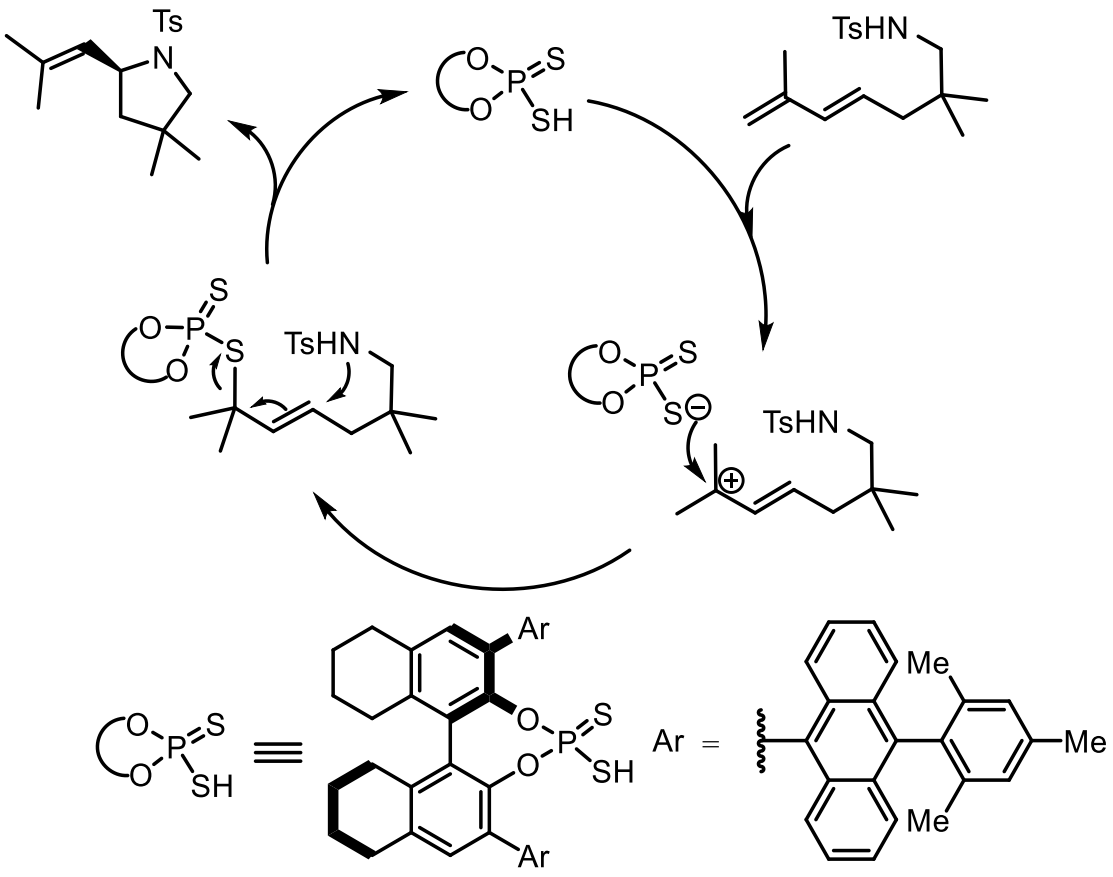


Scheme 1.6 General mechanism for acid catalyzed hydroamination of styrene

[6] Rosenfeld, D. C.; Sekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett*. **2006**, *8*, 4179.

Recently Toste and co-workers reported a unique approach to acid-catalyzed intramolecular hydroamination of 1,3-dienes.[7] A chiral dithiophosphoric acid was used which possessed two key features: 1) strong enough acid to protonate the terminal alkene and 2) the conjugate base was nucleophillic enough to add to the carbocation. By forming a covalent bond to the substrate the chiral information of the acid catalyst could be transferred effectively to the newly forming stereocenter as the nitrogen displaced the conjugate base in an S_N2' fashion. The conjugate base then could deprotonate the hydrogen from the ammonium to give the enantioenriched hydroamination product and regenerate the acid catalyst. This method for the hydroamination of 1,3-dienes was limited to nitrogen atoms bearing electron-withdrawing groups such as tosyl or nosyl and worked best in 5-membered systems with Thorpe-Ingold activation.

[7] Shapiro, N. D.; Rauniyar, V.; Hamilton, G. L.; Wu, J.; Toste, F. D. *Nature* **2011**, *470*, 245.



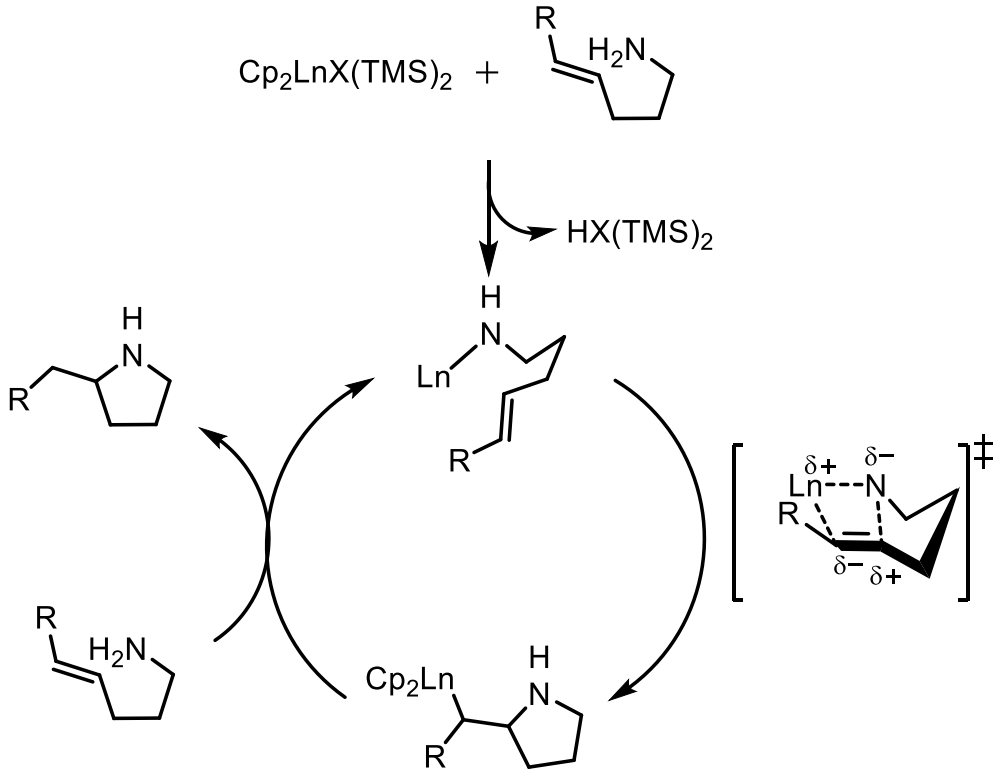
Scheme 1.7 Dithiophosphoric acid catalzyed enantioselective intramolecular hydroamination of 1,3-dienes

1.5 Rare Earth-Metal Catalyzed Asymmetric Hydroaminations

Lanthanide complexes are very effective for intramolecular hydroamination of alkenes most often affording high conversions. Preliminary work by Marks and co-workers in the early 90's set the stage for future development.[8] Initial pre-catalysts contained metallocene ligands and labile $X(TMS)_2$ (X = CH_2 or NH) ligands (Scheme 1.8). In the presence of an amine, the labile ligand is displaced to give an amido complex followed by olefin insertion. Facile insertion of the Ln-N bond into the double bond is what makes these metals so effective.

[8] (a) Gagne, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1989**, *111*, 4108. (b) Gagne, M. R.; Nolan, S. P.; Marks, T. J. **1990**, *9*, 1716. (c) Gagne, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992,** *114***,** 275.

After olefin insertion another equivalent of amine displaces the newly formed Ln-carbon bond to reform the active catalyst and release the hydroamination product.



Scheme 1.8 General mechanism for rare earth metal catalyzed hydroamination

In 1992, preliminary attempts at developing asymmetric hydroaminations were based on C_1-symmetric lanthanide complexes (Figure 1.2).[9] Enantioselectivity of 74% *ee* could be obtained through the use of C_1-symmetric chiral *ansa*-lathanocenes. This design was flawed, as the cyclopentadienyl-based ligands were found to undergo a protonation/deprotonation process under the reaction conditions leading to facile epimerization of the catalyst. Since then, researchers were drawn to axially chiral catalysts that were not prone to epimerization at

[9] Gagné, M. R.; Brard, L.; Conticello, V. P.; Giardello, M. A.; Stern, C. L.; Marks, T. J. *Organometallics* **1992**, *11*, 2003.

high temperatures. Catalysts containing chiral 3,3'-subsitutedbinaphtholate and 3,3'-subsitutedbinaphthamido ligands were found to improve enantioselectivity in intramolecular hydroaminations. The most effective systems with these ligands have been investigated by Marks[9], Hulzsch[10], Scott[11], and Livinghouse[12] (Figure 1.2). The percent yield and enantiomeric excess for each catalyst is reported for the cyclization of the common substrate 2,2-dimethyl-pent-4-ene amine.

[10] Reznichenko, A. L.; Nguyen, H. N.; Hultzsch, K. C. *Angew. Chem. Int. Ed.* **2010**, *49*, 8984.
[11] O'Shaughnessy, P. N.; Scott, P. *Tetrahedron: Asymmetry*, **2003**, *14*, 1979.
[12] Kim, J. Y.; Livinghouse, T. *Org. Lett.* **2005**, *7*, 1737.

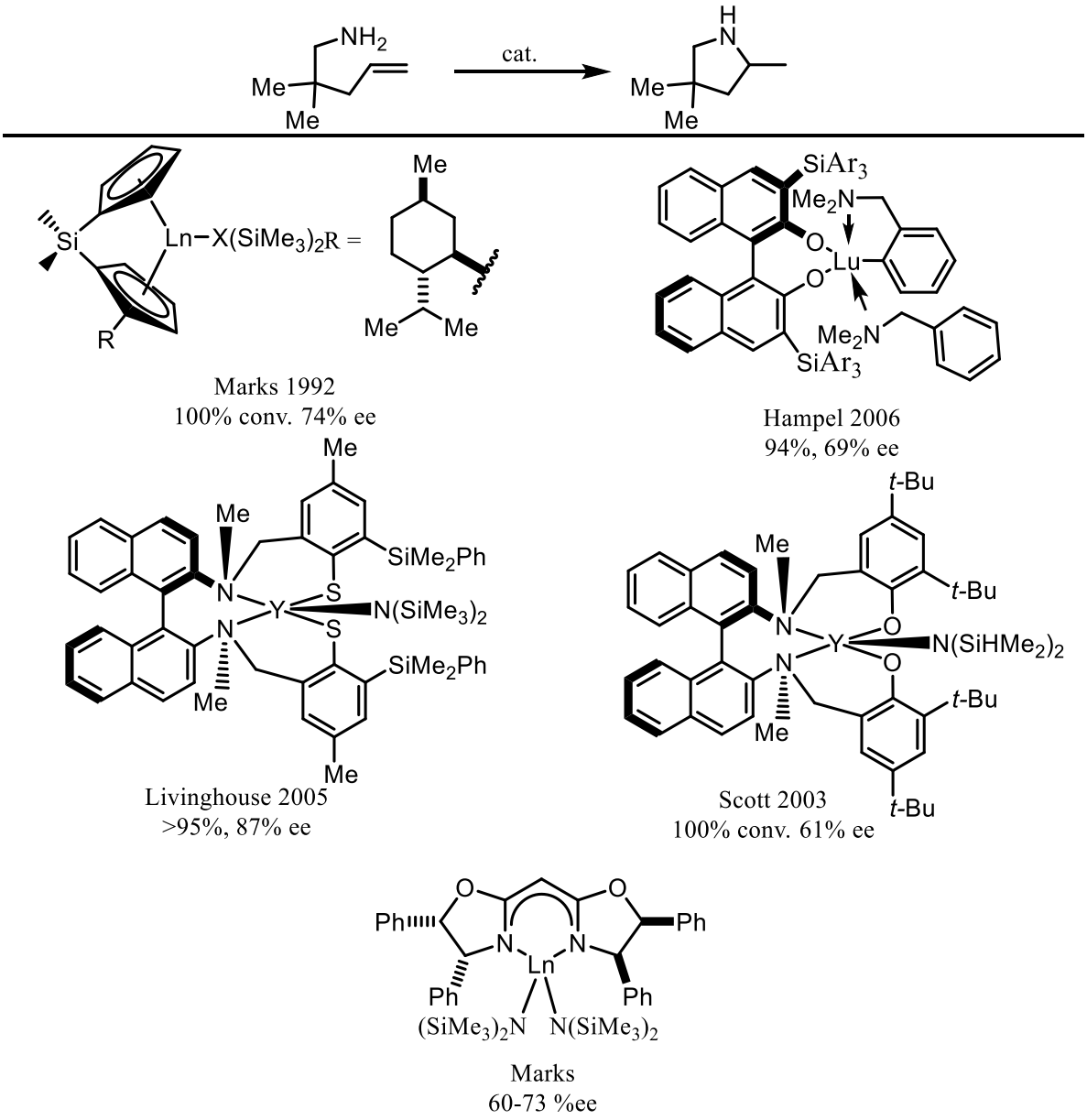
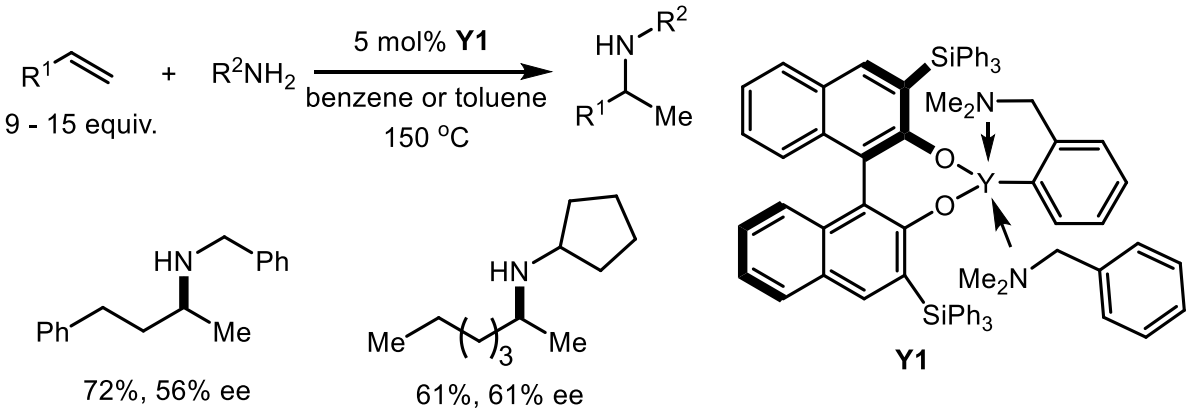


Figure 1.2 Selected examples of rare earth metal complexes as catalysts for intramolecular enantioselective hydroamination of alkenes

Rare earth metal catalyzed intermolecular hydroamination, even from a reactivity standpoint, is much more difficult due to competition between strongly binding amines and weakly binding alkenes for coordination sites on the metal center. Therefore, a large excess of alkene is often required to achieve good levels of reactivity. Hultzsch and coworkers, employing catalyst **Y1**, could only achieve enantioselectivities up to 61% *ee* using 9-15 equiv. of alkene (Scheme 1.9).[10] Currently, this is the best rare earth metal catalyst for intermolecular asymmetric hydroamination of unactivated alkenes.



Scheme 1.9 Best conditions for intermolecular asymmetric hydroamination using rare earth metals

1.6 Group 4 Metal Catalyzed Asymmetric Hydroaminations

Cationic group 4 metals are isoelectronic to the rare earth metals described in section **1.5** and therefore follow a similar catalytic cycle (Figure 1.3, Cycle A). Two different mechanisms for neutral group 4 catalyzed hydroamination of unactivated alkenes have been proposed. The first begins with a reaction between an amine and a neutral group 4 metal affording an imido complex leading to a [2+2] cycloaddition with the olefin generating an azametallacyclobutane. Protonation of the azametallacyclobutane by the substrate regenerates

the imido species and gives the hydroamination product (Figure 1.3, Cycle B).

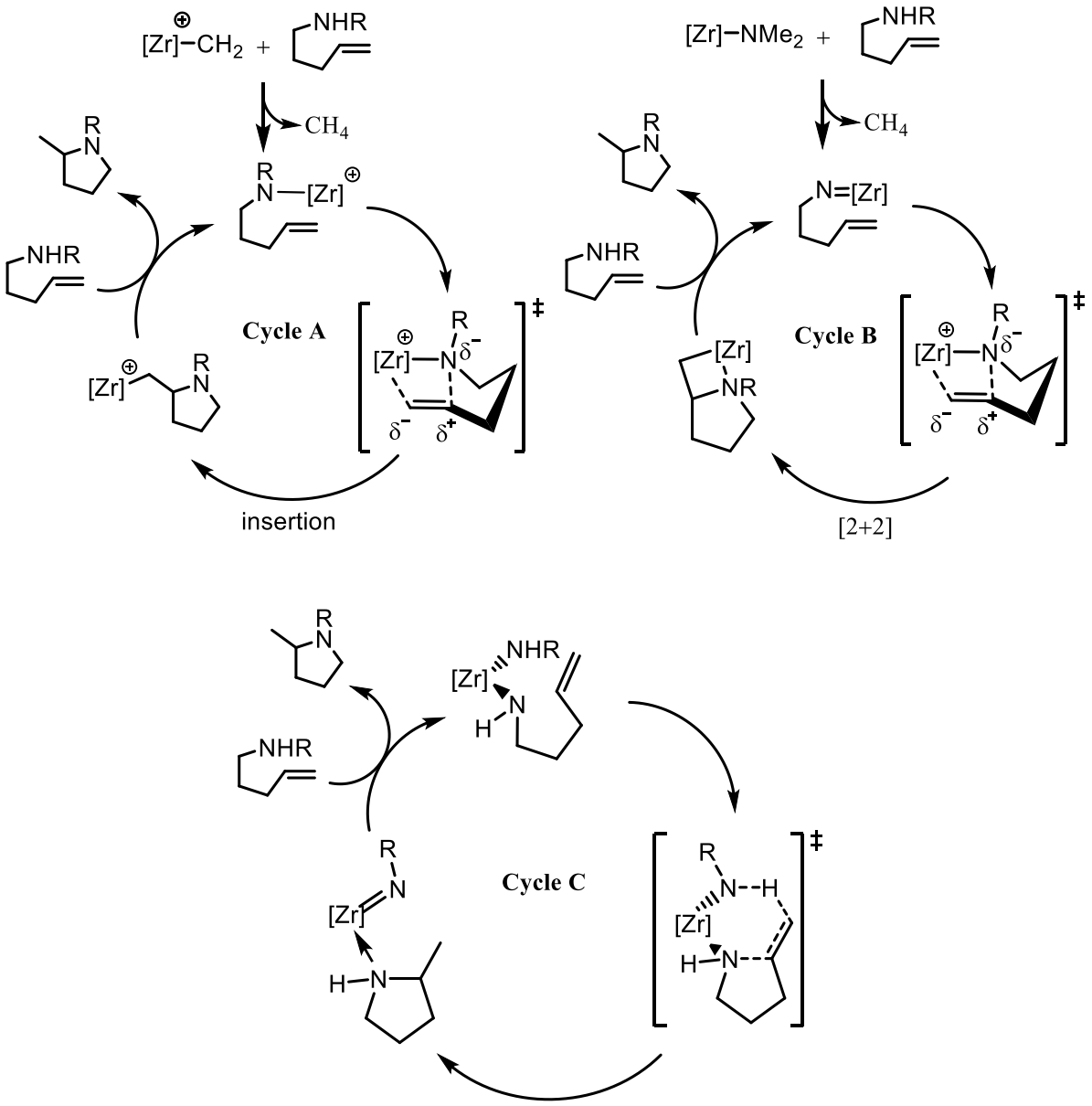


Figure 1.3 Proposed Catalytic cycles of netural and cationic group 4 metal catalyzed hydroamination highlighting mechanistic differences

The second mechanism proposes that the intramolecular hydroamination occurs via a six-membered transition state using a coordinated secondary amine as a source of proton (Figure 1.3, Cycle C).

Chiral zirconium complexes have been shown to induce enantioinduction for intramolecular hydroamination by employing various chiral ligands (Figure 1.3). Key contributors are Bergman[13], Schafer[14], Scott[15], Zhi[16] and Sadow[17]. Catalysts developed by Schafer and Sadow are the best as both are capable of achieving over 90% *ee* in excellent yields. Most substrates however, are limited to alkenes with gem-disubstitution β to the amine providing Thorpe-Ingold activation. One of the biggest limitations for all group 4 catalysts is their inability to enable intermolecular enantioselective hydroaminations as well as functional group tolerance.

[13] Watson, D. A.; Chiu, M.; Bergman, R. G. *Organometallics* **2006**, *25*, 4731.
[14] Wood, M. C.; Leitch, D. C.; Yeung, C. S.; Kozak, J. A.; Schafer, L. L. *Angew. Chem. Int. Ed.* **2007**, *46*, 354.
[15] Gott, A. L.; Clarke, A. J.; Clarkson, G. J.; Scott, P. *Chem. Comm.* **2008**, 1422.
[16] Zi, G.; Liu, X.; Xiang, L.; Song, H. *Organometallics*, **2009**, *28*, 1127.
[17] (a) Manna, K.; Xu, S.; Sadow, A. D. *Angew. Chem. Int. Ed.* **2011**, *50*, 1865. (b) Manna, M.; Everett, W. C.; Schoendorff, G.; Ellern, A.; Windus, T. L.; Sadow, A. D. *J. Am. Chem. Soc.* **2013**, *135*, 7235.

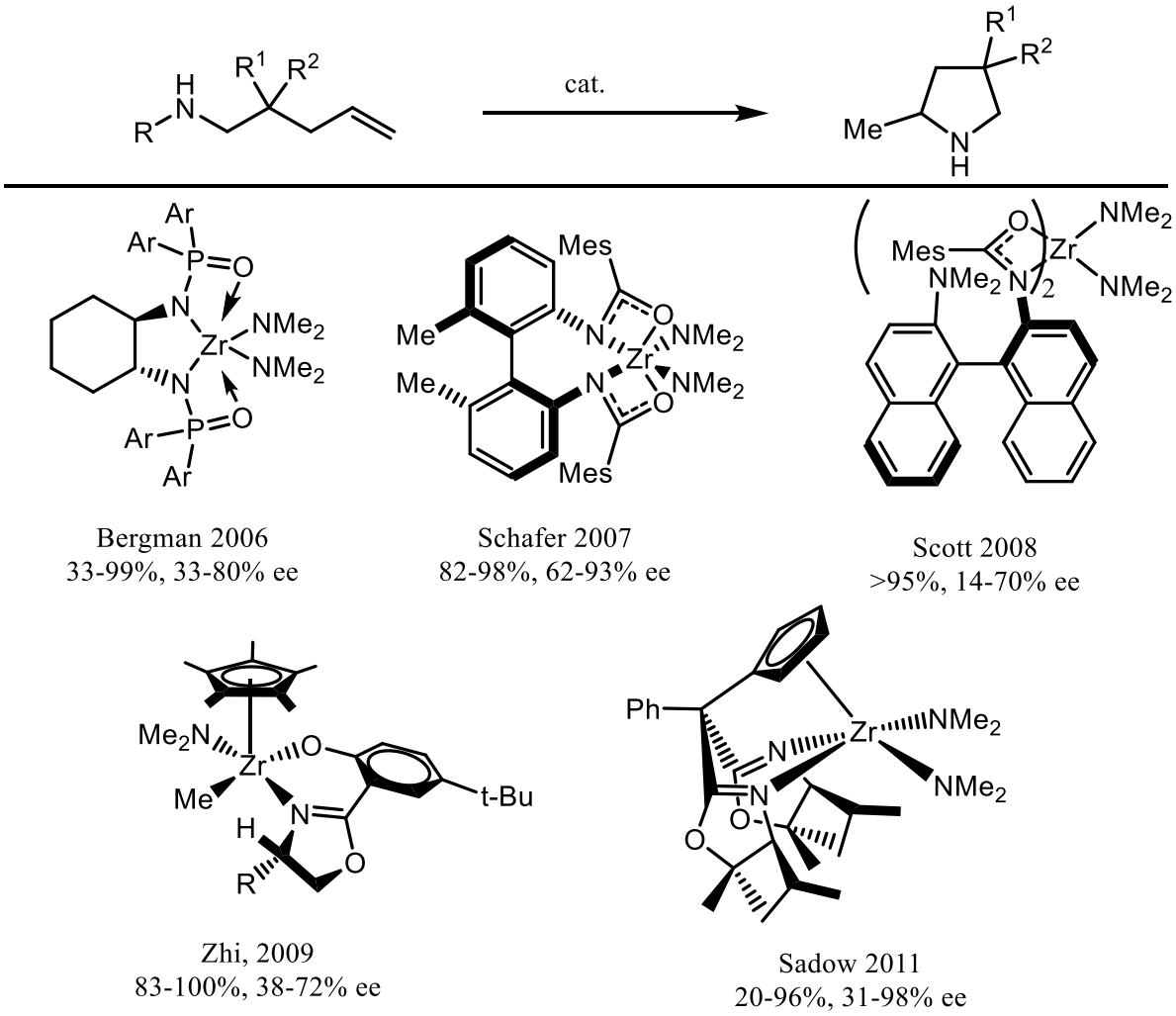


Figure 1.4 Selected examples of group 4 metal catalysts for intramolecular enantioselective hydroamination of alkenes

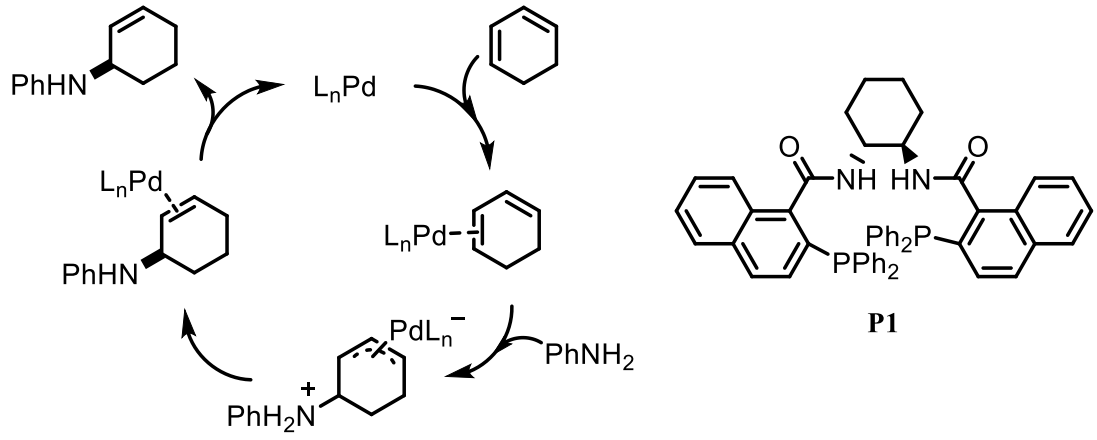
1.7 Late Transition-Metal Catalyzed Asymmetric Hydroamination

Enantioselective hydroamination can be achieved using iridium, palladium, gold, and rhodium transition metals. Hydroamination with transition metal catalysts can proceed through two main mechanisms. The first involves coordination of the alkene to the metal where it is activated towards attack of the amine. The second entails oxidative addition of the

metal into the N-H bond followed by alkene migratory insertion and C-H bond reductive elimination.

1.7.1 Palladium

In 2001, Hartwig and co-workers reported the first asymmetric palladium catalyzed hydroamination of 1,3-cyclohexadiene with aniline derivatives.[18] Using diphosphine ligand **P1** enantioselectivities of up to 99% *ee* could be achieved as well as high yields. The mechanism proceeds through amine addition to a palladium π-allyl species enabling an expedient route to valuable enantioenriched allylic amines from 1,3-cyclohexadiene (Scheme 1.10).

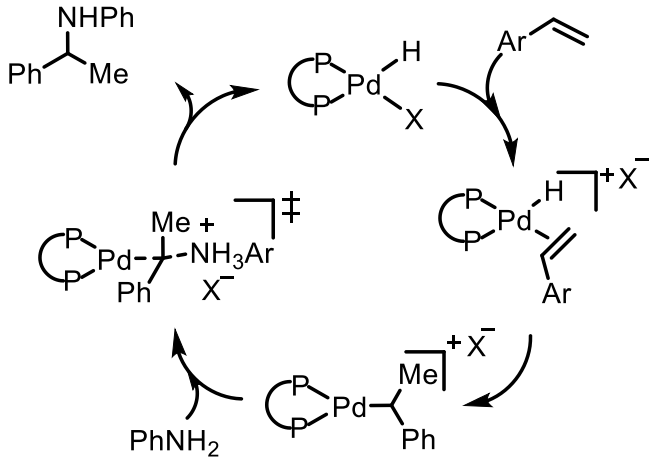


Scheme 1.10 General mechanism for palladium catalyzed hydroamination of 1,3-dienes

In addition, asymmetric intermolecular hydroamination of styrene derivatives has proved to be highly effective with palladium catalysis exhibiting high Markovnikov regioselectivity. The mechanism proceeds by insertion of a Pd(II)-hydride into the alkene followed by nucleophilic attack of the amine (Scheme 1.11). The bulky phosphine ligand

[18] Lober, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366.

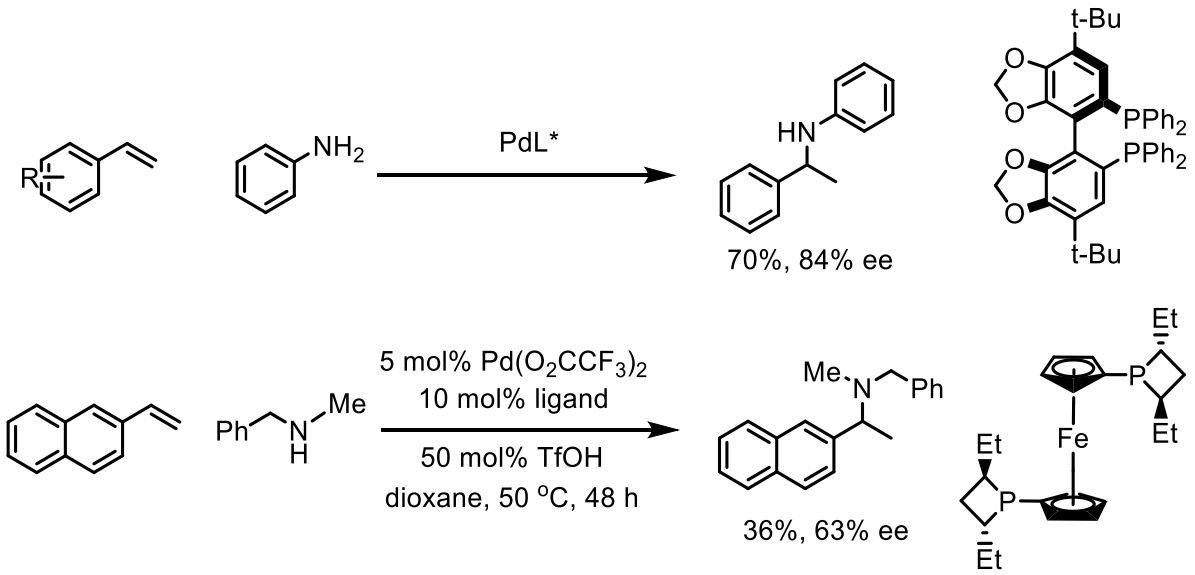
provides enantiocontrol of the amine addition step of the cycle. The best results are obtained with aniline derivatives without substitution on nitrogen.



Scheme 1.11 General mechanism for palladium catalyzed hydroamination of alkenes

In 2003, Hartwig and coworkers discovered conditions to allow hydroamination of dialkylamines.[19] However the only asymmetric example reported afforded poor yield and modest enantioselectivity (Scheme 1.12).

[19] Utsunomiya, M.; Hartwig, J.F. *J. Am. Chem. Soc.* **2003**, *125*, 14286.

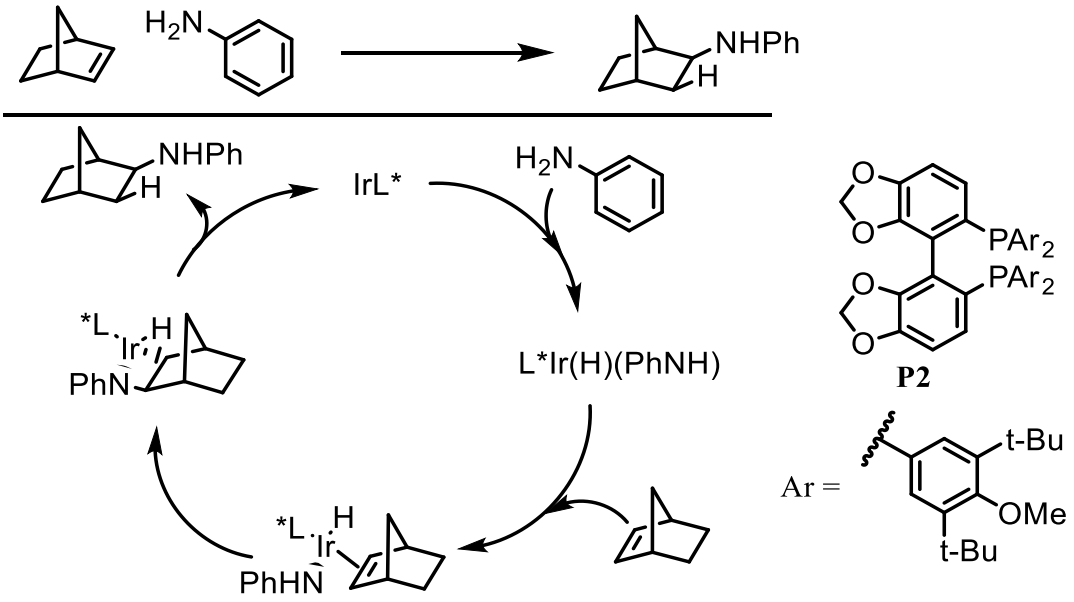


Scheme 1.12 Intermolecular enantioselective palladium catalyzed hydroamination of unactivated alkenes

1.7.2 Iridium

In 1997, Togni and co-workers reported the use of binuclear iridium (I) complexes containing phosphine ligands such as Josiphos and Binap derivatives.[20] This first generation asymmetric system allowed for intermolecular hydroamination of norbornene with aniline derivatives in enantioselectivities up to 95% *ee*. In 2008, Hartwig and co-workers identified a new pre-catalyst and ligand which resulted in higher enantioselectivities and a broader scope of bicyclic alkenes.[21] The mechanism proceeds by oxidative addition of the arylamine to iridium followed by insertion into the alkene (Scheme 1.13). Ligand **P2** resulted in the greatest enantioselectivity affording enantioenriched bicyclic amines in up to 99% *ee*.

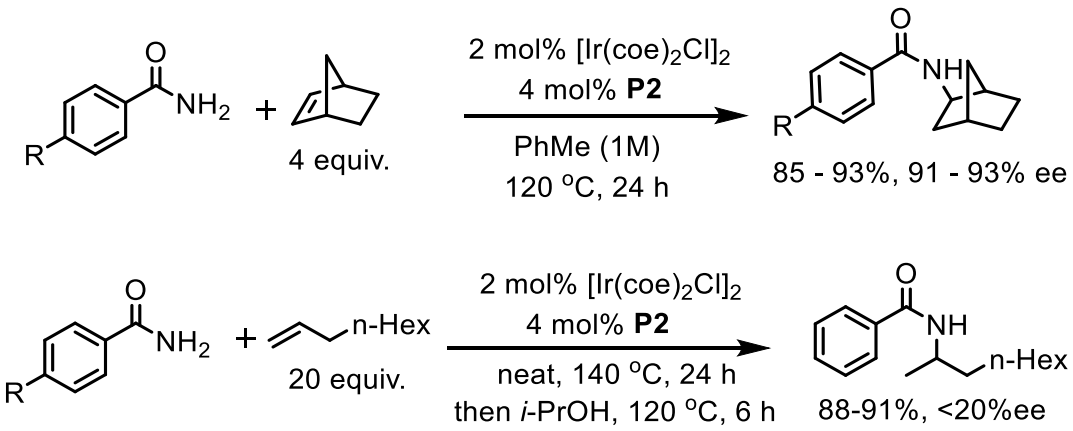
[20] Dorta, R.; Egli, P.; Zurcher, F.; Togni. A. *J. Am. Chem. Soc.* **1997**, *119*, 10857.
[21] Zhou (Steve), J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 12220.



Scheme 1.13 General mechanism of iridium catalyzed hydroamination of alkenes

In 2012, Hartwig and co-workers described the first iridium catalyzed intermolecular hydroamination of bicyclic alkenes and unactivated alkenes with amides and sulfonamides.[22] With bicyclic alkenes amides could be added in high enantioselectivity (up to 93% *ee*) and in high yields. Addition to unactivated alkenes however, required 20 equivalents of alkene and resulted in enantioselectivities only as high as 19% *ee* with the same ligand system used for bicyclic alkenes (Scheme 1.14).

[22] Sevov, C. S.; Zhou (Steve), J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 11960.

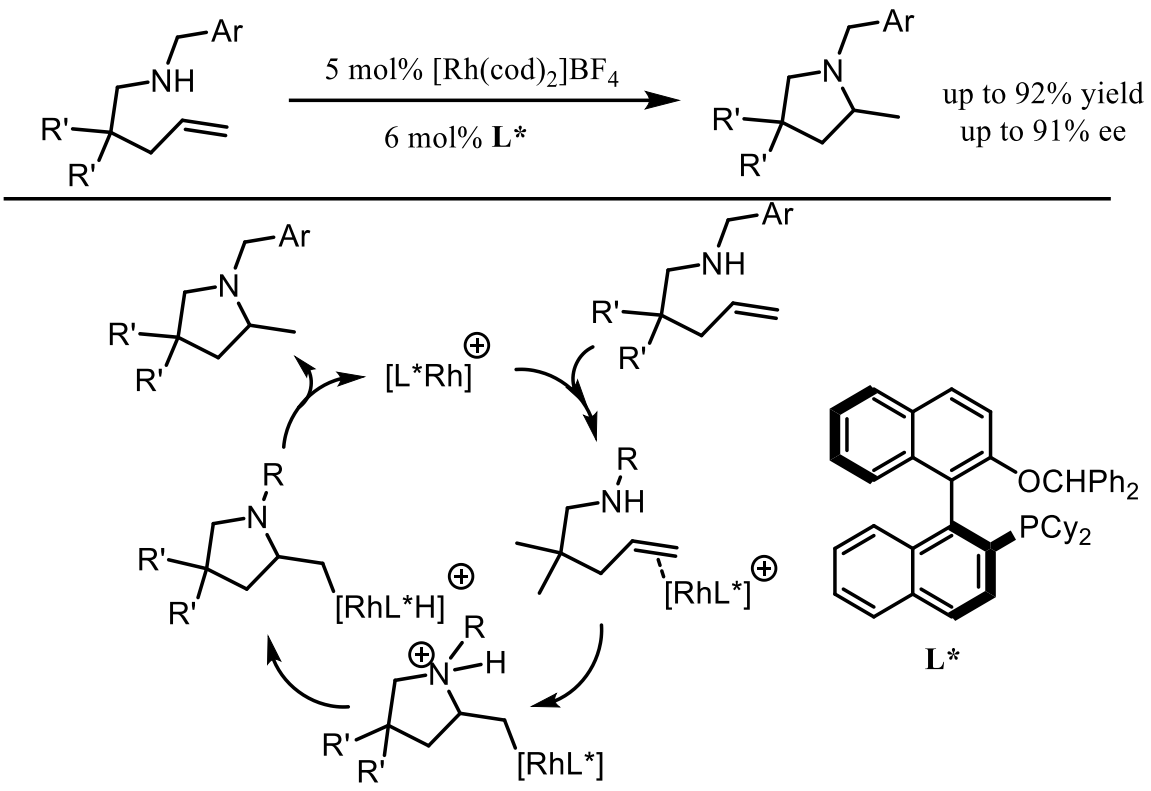


Scheme 1.14 Intermolecular iridium catalyzed hydroamination of norbornene and unactivated alkenes

1.7.3 Rhodium

The first rhodium catalyzed asymmetric hydroamination was reported by Buchwald and co-workers in 2010 (Scheme 1.15).[23] Using binap derived ligand with rhodium(I) precatalyst the intramolecular hydroamination of terminal alkenes with *N*-enzylaminesachieved. Enantioselectivities of 91% *ee* could be achieved in high yields under this protocol.

[23] Shen, X.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2010**, *49*, 564.

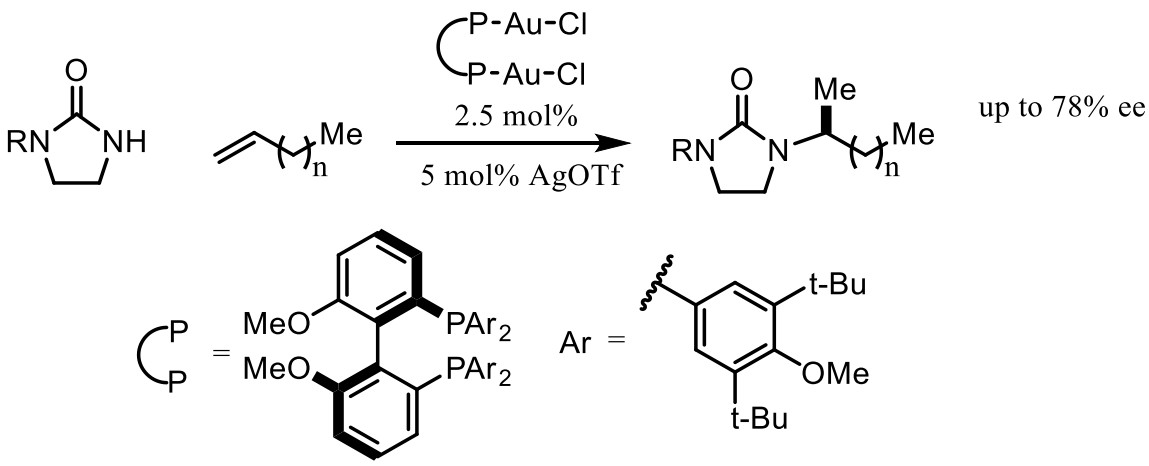


Scheme 1.15 Intramolecular enantioselective rhodium catalyzed hydroamination

1.7.4 Gold

In 2009, the first intermolecular enantioselective hydroamination of unactivated alkenes with cyclic ureas was reported (Scheme 1.16).[24] The use of a dinuclear gold complex bridged by a chiral biarylphosphine ligand allowed unprecedented enantioselective intermolecular hydroaminations in up to 78% *ee*.

[24] Zhang, Z.; Lee, S. D.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 5372.



Scheme 1.16 Enanioselective gold catalyzed hydroamination of unactivated alkenes

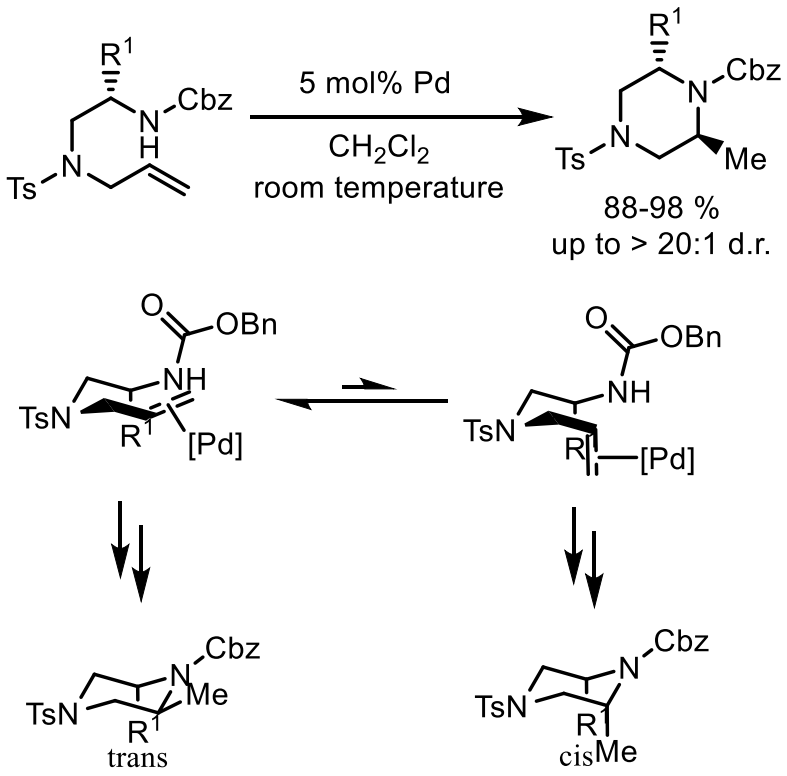
1.8 Diastereoselective Hydroamination of Alkenes

Unlike enantioselective hydroamination there are very few examples of diastereoselective hydroamination in the literature. The most frequently reported examples occur in intramolecular systems, both 5- and 6-membered, containing a stereocenter α to the amine which can control facial attack on the alkene.

In 2008, Michael and co-workers reported a diastereoselective hydroamination approach to generate *trans*-2,6-disubstituted piperazines with orthogonally protected nitrogen atoms (Scheme 1.17).[25] The hydroamination proceeded at room temperature to give the 6-membered heterocycles in >20:1 d.r. In the chair-like transition state for the cyclization, the substituent at the 2-position (R^1) adopts a pseudo-axial orientation to avoid allylic strain with the carbamate group. Cyclization then occurs preferentially with the alkenyl group in a

[25] Cochran, B. M.; Michael, F. E. *Org. Lett.* **2008**, *10*, 329.

pseudo-equatorial orientation rather than in the higher energy pseudo-axial orientation leading to the *trans* isomer as illustrated in Scheme 1.17.

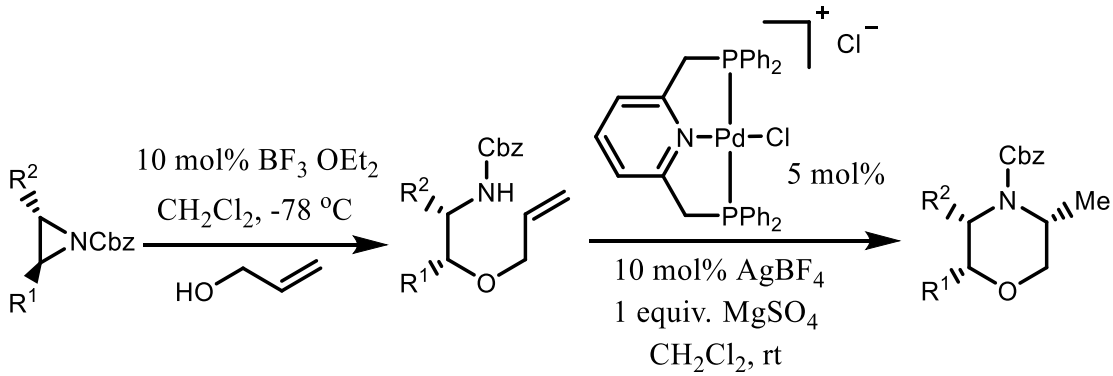


Scheme 1.17 Origin of diastereoselectivity in Michaels Pd-catalyzed synthesis of piperazines

In 2013, Michael and co-workers reported a two-step sequence to access di- and tri-substituted morpholines.[26] The first step is a Lewis acid mediated regioselective ring opening of enantiomerically pure aziridine followed by a palladium-catalyzed diastereoselective hydroamination of the aminoalkene to give the corresponding morpholine as a single diastereomer (Scheme 1.18**)**. Only allyl alcohol was employed in the report, however, if more

[26] McGhee, A.; Cochran, B. M.; Stenmark, T. A.; Michael, F. E. *Chem. Commun.* **2013**, *49*, 6800.

substituted alcohols are tolerated this method would constitute a modular approach to highly substituted morpholines.

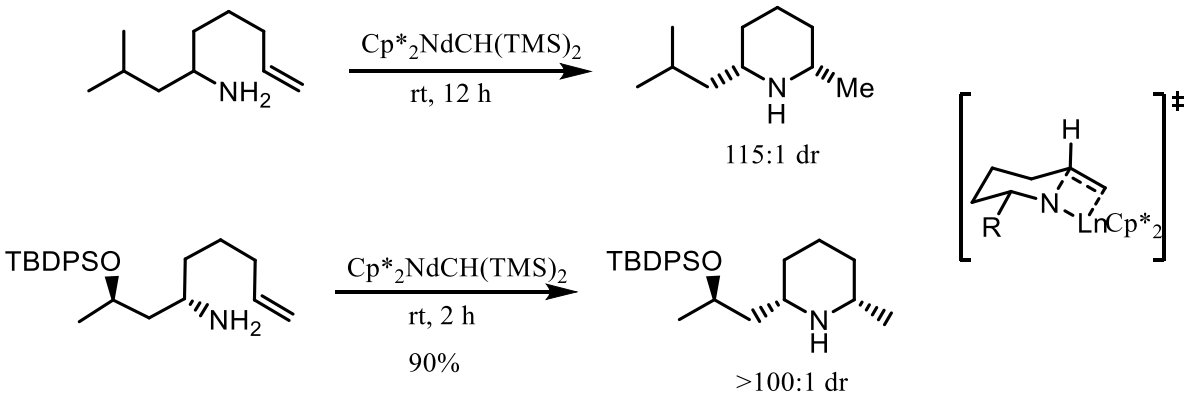


Scheme 1.18 Michael's modular approach to highly substituted highly diastereoselecitve morpholines

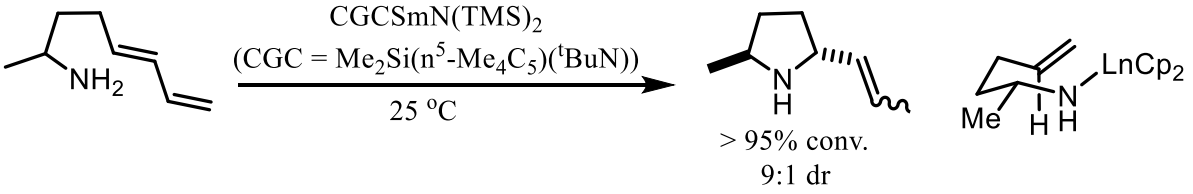
A diastereoselective lanthanocene-catalyzed intramolecular hydroamination reaction was applied to the synthesis of *cis*-2,6-disubstituted piperidines (Scheme 1.19). The diastereoselectivity in this 6-membered hydroamination was extremely high (up to 115:1 d.r.).[27] The model used to rationalize the selectivity employed the chair-like transition state drawn in Scheme 1.19 where the interactions between the 2 and 6 substituents of the pending ring are minimized (both adopt a pseudo-equatorial orientation). This methodology was applied to the synthesis of enantioenriched (+) and (-) pinidinol. In 5-membered systems however the *trans*-diastereoisomer is the favoured product (Scheme 1.20).[28] In this case the

[27] Molander, G. A.; Dowdy, E. D.; Pack, S. K. *J. Org. Chem.* **2001**, *66*, 4344.
[28] Gagne, M. R.; Stern, C. L.; Marks, T. J. *J. Am. Chem. Soc.* **1992**, *114*, 275.

envelope conformation is drawn such that both substituents of the pending 5-membered ring adopt pseudo-equatorial orientations (Scheme 1.20).



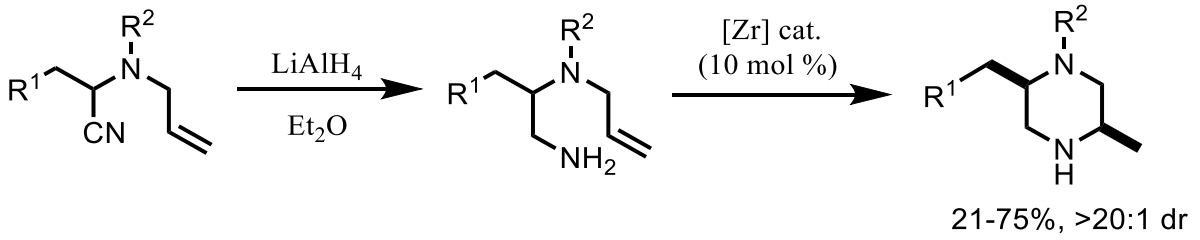
Scheme 1.19 Diastereoselectivity in lanthanide catalyzed hydroamination in 6 membered systems



Scheme 1.20 Diastereoselectivity in lanthanide catalyzed hydroamination in 5 membered systems

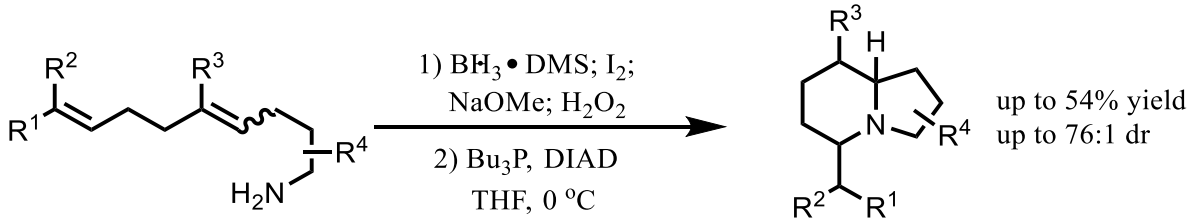
In 2012 Schafer and coworkers reported a highly diastereoselective hydroamination approach to the formation of *cis*-2,5-disubsitutued piperazines from α–aminonitriles (Scheme 1.21).[29] The first step is reduction of the nitrile to the amine using $LiAlH_4$ followed by zirconium catalyzed intramolecular hydroamination to the saturated heterocycle.

[29] Zhai, H.; Borzenko, A.; Lau, Y. Y.; Ahn, S. H.; Schafer, L. L. *Angew. Chem.* **2012**, *124*, 12385.



Scheme 1.21 Schafer's approach to the synthesis of cis-2,5-disubstituted piperazines

In 2012 Shenvi and coworkers reported a diastereoselective hydroamination cascade to access various indolizidines from simple unsaturated amines based on a directed hydroboration/oxidative migration strategy (Scheme 1.22).[30]



Scheme 1.22 Hydroamination cascade developed by Shenvi and coworkers

1.9 Conclusion

In conclusion, both enantioselective and diastereoselective hydroamination of unactivated alkenes have been demonstrated to be highly effective in intramolecular systems. Despite many methods to achieve intermolecular hydroamination, examples that are highly enantioselective and/or diastereoselective are extremely rare for unbiased alkenes. The synthetic potential of intermolecular enantioselective and diastereoselective hydroamination therefore remains virtually untapped (Figure 1.5).

[30] Pronin, S. V.; Tabor, M. G.; Jansen, D. J.; Shenvi, R. A. *J. Am. Chem. Soc.* **2012**, *134*, 2012

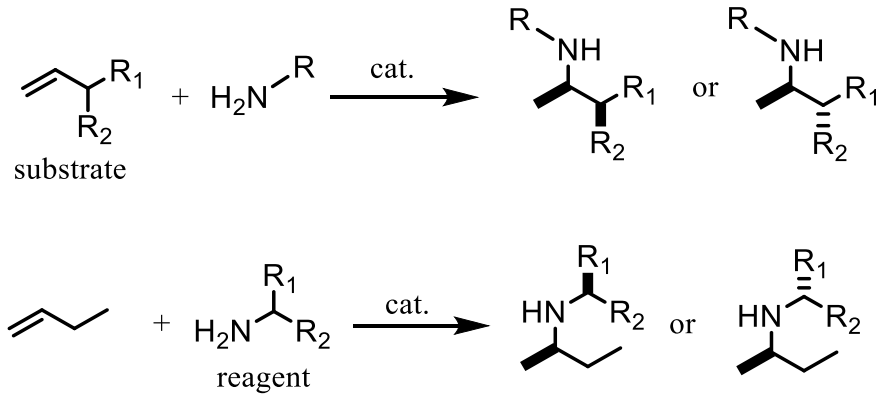


Figure 1.5 Synthetic potential of diastereoselective intermolecular hydroamination

Chapter 2 Aldehyde-Catalyzed Stereoselective Cope-Type Hydroamination of Allylic Amines

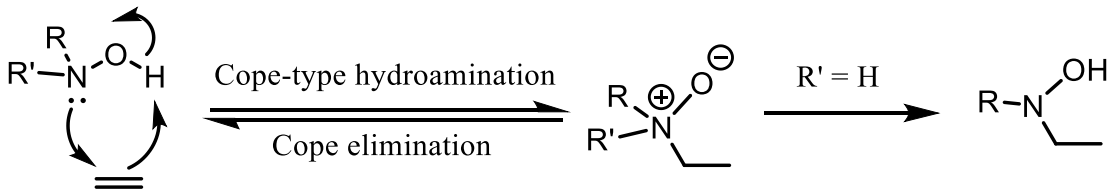
2.1 Introduction

Chapter 1 discussed many catalysts that can promote asymmetric hydroamination of unactivated alkenes and 1,3-dienes. All of the methods discussed followed two types of activation; 1) activation of the amine and/or 2) activation of the alkene. This chapter will introduce an alternative approach that requires none of the aforementioned activation modes by using bifunctional hydroxylamines with a ***tethering*** catalyst. The tethering catalysts' only function is to pre-associate two molecules thus creating a more facile intramolecular reaction but still leading to intermolecular products. This approach has enabled the first intermolecular highly enantioselective Cope-type hydroamination of allylic amines in addition to both reagent- and substrate-controlled diastereoselective hydroaminations.

2.2 Cope-Type Hydroamination

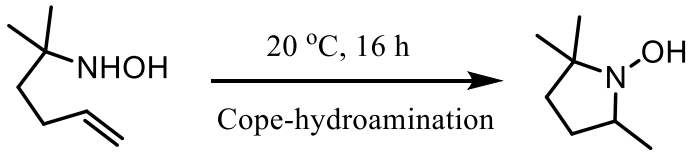
In 1949 Cope and coworkers reported that heating trialkylamine-*N*-oxides possessing a β-hydrogen led to the formation of olefins and *N*, *N*-dialkylhydroxylamines (Scheme 2.1).[31] This reaction is formally named the Cope elimination and can be described as an intramolecular syn- elimination.[32] The nature of the elimination was confirmed by stereochemical[33] and labeling studies.[34]

[31] Cope, A. C.; Foster, T. T.; Towle, P. H. *J. Am. Chem. Soc.* **1949**, *71*, 3929.
[32] DePuy, C. H.; King, R. W. *Chem. Rev.* **1960**, *60*, 431.
[33] Cram, D. J.; McCarty, J. E. *J. Am. Chem. Soc.* **1954**, *76*, 5740.
[34] Bach, R. D.; Andrzejewski, D.; Dusold, L. R. *J. Org. Chem.* **1973**, *38*, 1742.



Scheme 2.1 Cope-type hydroamination and Cope elimination

The microscopic reverse of the Cope-elimination is called the reverse Cope-elimination or Cope-type hydroamination and can occur in both intramolecular and intermolecular systems. In 1976 the intramolecular reaction was reported by House, when he observed Cope-type hydroamination occurring unexpectedly.[35] Following the work by House the majority of studies focused heavily on intramolecular variants in 5 membered cyclizations whereby the hydroamination results in the formation of *N*-hydroxy-pyrrolines or *N*-oxides under very mild conditions (Scheme 2.2).

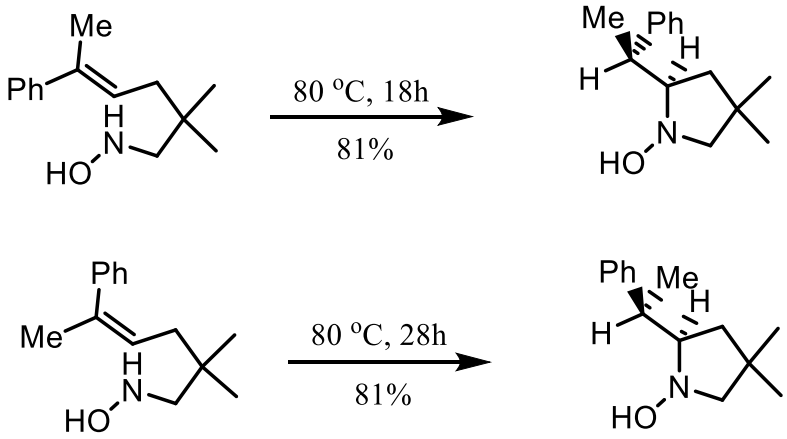


Scheme 2.2 Intramolecular Cope-type hydroamination

Observations by Ciganek in 1990 provided compelling evidence for a concerted mechanism over the radical based mechanism proposed by House.[36] Four key observations were made: (1) only one of two possible *N*-oxides is formed where the newly formed methyl

[35] (a) House, H. O.; Manning, D. T.; Melillo, D. G.; Lee, L. F.; Haynes, O. R.; Wilkes, B. E. *J. Org. Chem.* **1976**, *41*, 855. (b) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863.
[36] (a) Ciganek, E. *J. Org. Chem.* **1990**, *55*, 3007. (b) Ciganek, E.; Read, J. M. Jr.; Calabrese, J. C. *J. Org. Chem.* **1995**, *60*, 5795.

group is *cis* to the *N*-oxide oxygen; (2) the reaction is reversible for certain substrates; (3) the influence of double bond substitution on the rate of cyclization is inconsistent with a radical mechanism; (4) the specific transfer of deuterium is consistent only with a concerted mechanism. Additional experimental evidence by Oppolzer in 1994 provided more evidence for a concerted mechanism (Scheme 2.3).[37] The data confirmed that the cyclization proceeded through suprafacial formation of the new C-N and C-H bonds through a planar five-membered transition state.



Scheme 2.3 Reactions showing *cis* products supporting a *syn*-addition

Reactivity trends of the intramolecular Cope-type hydroamination are summarized in Figure 2.1.[38] The cyclization is sensitive to substitution on the nitrogen of the hydroxylamine and becomes slower as the size of the substituent increases. The cyclization can be accelerated significantly by incorporating geminal-disubstitution on the cycle, taking advantage of the Thorpe – Ingold effect. The cyclization proceeds efficiently to form five-membered cycles,

[37] (a) Oppolzer, W.; Spivey, A. C.; Bochet, C. G. *J. Am. Chem. Soc.* **1994**, *116*, 3139: (b) Oppolzer, W. *Gazz. Chim. Ital*. **1995**, *125*, 207.
[38] Cooper, N. J.; Knight, D. W. *Tetrahedron,* **2004**, *60*, 243.

while six- and seven-membered variants become increasingly difficult. Lastly, the reaction becomes more difficult for alkenes with increased substitution such as di- and tri-substituted alkenes.

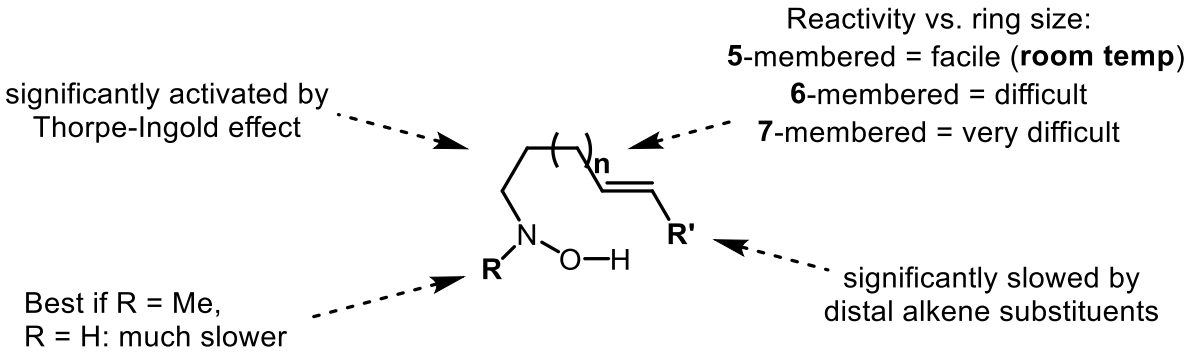


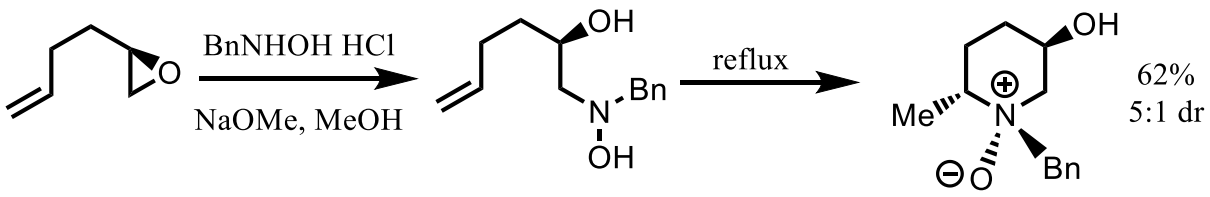
Figure 2.1 Reactivity trends in intramolecular Cope-type hydroamination of alkenes

2.3 Stereoselective Cope-Type Hydroaminations

Attention will now focus on examples of stereoselective Cope-type hydroamination of unactivated alkenes. Diastereoselective Cope-type hydroaminations are most common whereas enantioselective Cope-type hydroaminations are extremely rare and all examples discussed below occur in intramolecular systems.

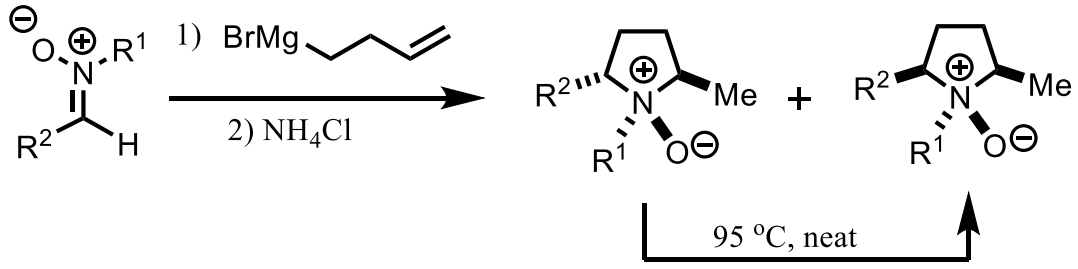
In 2000, O'Neil and coworkers reported the ring opening of an enantiomerically pure epoxide with *N*-benzylhydroxylamine in methanol followed by an intramolecular Cope-type hydroamination to give *trans*-2,5-disubsituted *N*-benzylpiperidine *N*-oxide.[39] Only one example was reported, and diastereoselectivity was found to be solvent dependent and after optimization the best d.r. obtained was 5:1 (Scheme 2.4).

[39]O'Neil, I. A.;Cleator, E;Southern, J. M.;Hone, N.;Tapolczay, D. J.. *Synlett* **2000**, 695.



Scheme 2.4 Diastereoselective Cope-type hydroamination to generate 2,5-disubsituted piperidine N-oxides

In 2001 Bagley and coworkers reported a diastereoselective synthesis of *cis*-2,5-disubstituted pyrrolidine *N*-oxides.[40] Addition of 3-butenylmagnesium bromides to various nitrones gave access to *N*-alkenylhydroxylamines which underwent intramolecular Cope-type hydroamination with low diastereoselectivity. The ratio improved when the mixture was heated under neat conditions as a result of isomerization to the thermodynamically favored *cis*-2,5-disubstituted pyrrolidine *N*-oxide (Scheme 2.5).

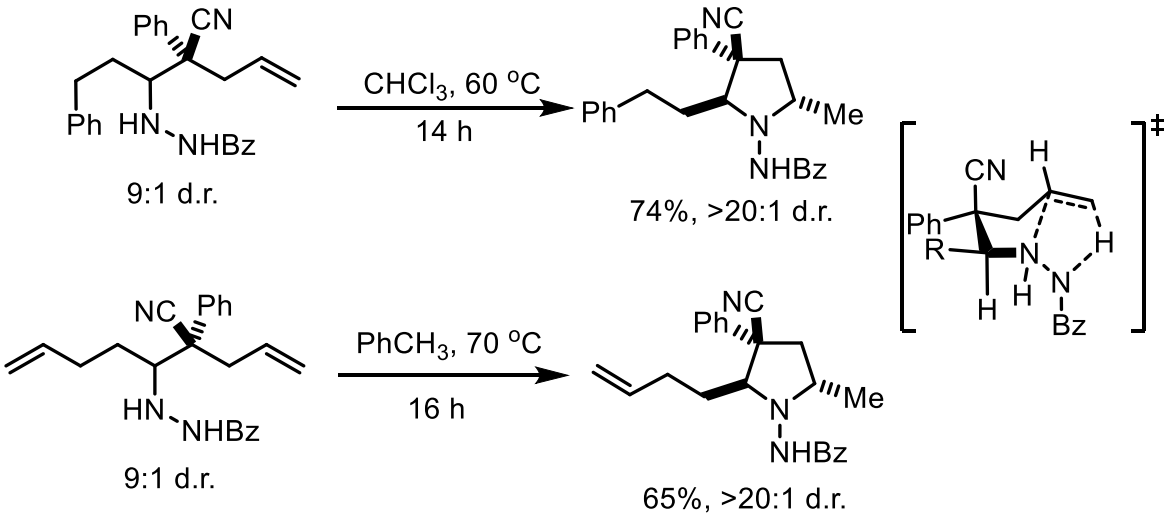


Scheme 2.5 Bagley's two-step sequence to access cis-2,5-disubstiuted pyrrolidin *N*-oxides

In 2011 Leighton reported a reaction sequence to access pyrrolidines in high diastereoselectivity.[41] The first step was a chiral silane Lewis acid promoted enantioselective Mannich reaction of silyl ketene imines with acylhydrazones to form homoallylic benzoic

[40] Bagley, M. C; Tovey, J. *Tetrahedron Lett.* **2001**, *42*, 351.
[41] Baxter, J. M.; Leighton, J. L. *Org. Lett.* **2011**, *15*, 4056.

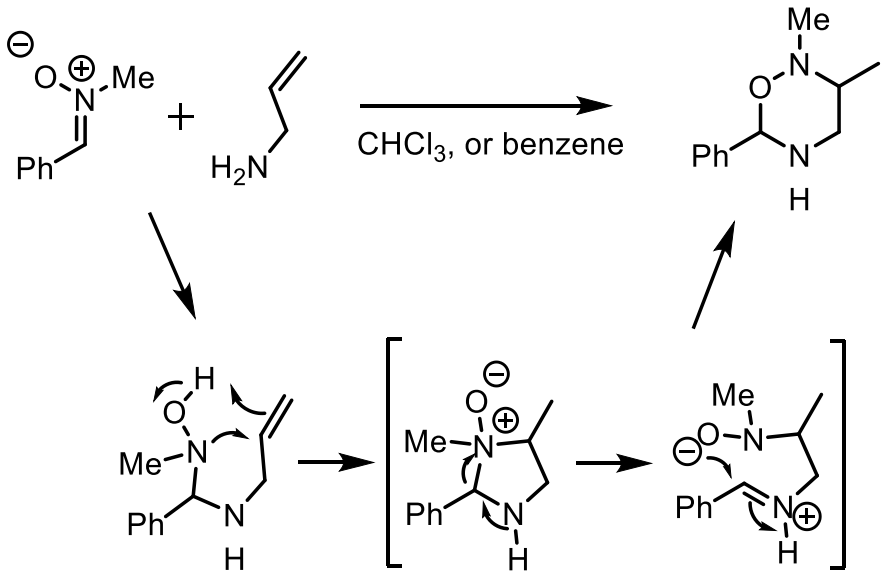
hydrazides, followed by a Cope-type hydroamination developed by Beauchemin in 2009.[42] With the synthesis of enantioenriched homoallylic benzoic hydrazides, Leighton and coworkers were able to achieve mild Cope-type hydroamination to generate highly substituted pyrrolidines in good to excellent diastereoselectivity (Scheme 2.6). No model was proposed to explain the diastereoselectivity, however, it likely originates from the substituent α to the hydrazide and the alkenyl substituent adopting pseudo-equatorial orientations in the 5,5-bicyclic transition state.



Scheme 2.6 Intramolecular diastereoselective hydroamination to afford highly substituted N-pyrrolidines by Leighton

[42] Roveda, J-G.; Clavette, C.; Hunt, A. D.; Gorelsky, S. I.; Whipp, C. J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 8740.

A highly effective system was developed by Knight and coworkers on the Cope-type hydroamination of allylic amines to generate 1,2,5-oxadiazinanes.[43] In this system *N*-alkylhydroxylamines add to nitrones giving an aminal intermediate which is set up for an intramolecular 5-membered Cope-type hydroamination. The *N*-oxide then undergoes a Meisenheimer rearrangement to afford a 1,2,5-oxadiazinane (Scheme 2.7). Nitrones derived from aromatic and aliphatic aldehydes were used as well as various *N*-substituted allylic amines.

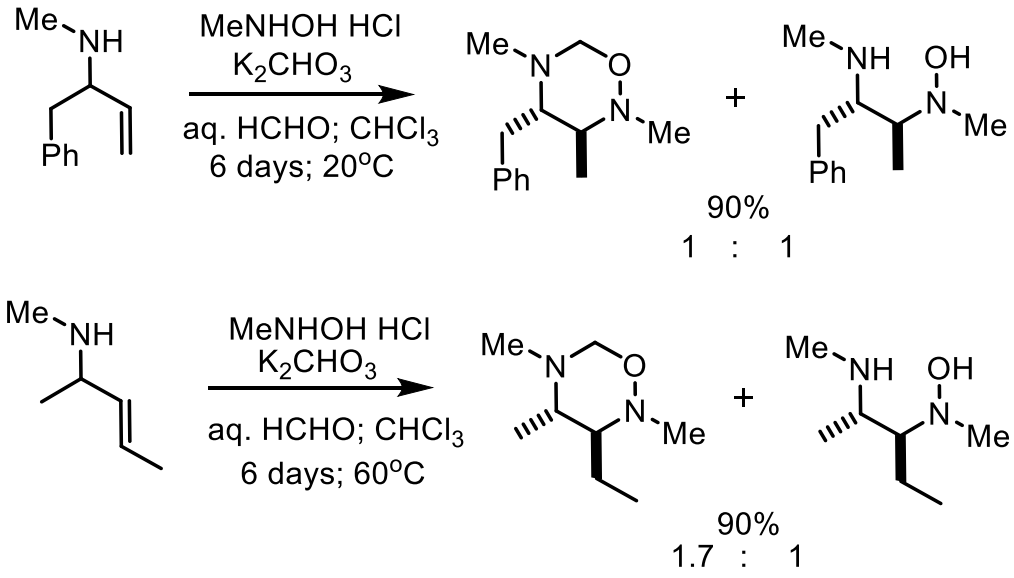


Scheme 2.7 Knight's Approach to the Cope-type hydroamination of allylic amines

In 1997, Knight reported the use of aqueous formaldehyde to generate a less stable nitrone that was more reactive. When using formaldehyde Knight opted to generate the nitrone *in situ* due to its instability. This protocol allowed remarkable room temperature reactivity of

[43] (a) Gravestock, M. B.; Knight, D. W.; Thornton, S. R. *J. Chem. Soc., Chem. Commun.* **1993**, 169. (b) Bell, K. E.; Coogan, M. P.; Gravestock, M. B.; Knight, D. W.; Thornton, S. R. *Tetrahedron Lett.* **1997**, *38*, 8545. (c) Gravestock, M. B.; Knight, D. W.; Malik, K. M. A.; Thornton, S. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3292.

terminal allylic amines as well as improved reactivity of more substituted alkenes at increased temperatures. However, when using formaldehyde a diamine product was isolated, which is the formal intermolecular hydroamination product of the reaction (Scheme 2.8). Its formation was attributed to hydrolysis of the iminium intermediate. Knight extended the scope to α–substituted allylic amines and found that the hydroamination was highly diastereoselective. However, the reactions proceeded very slow requiring several days to reach full conversion (Scheme 2.8).[43]

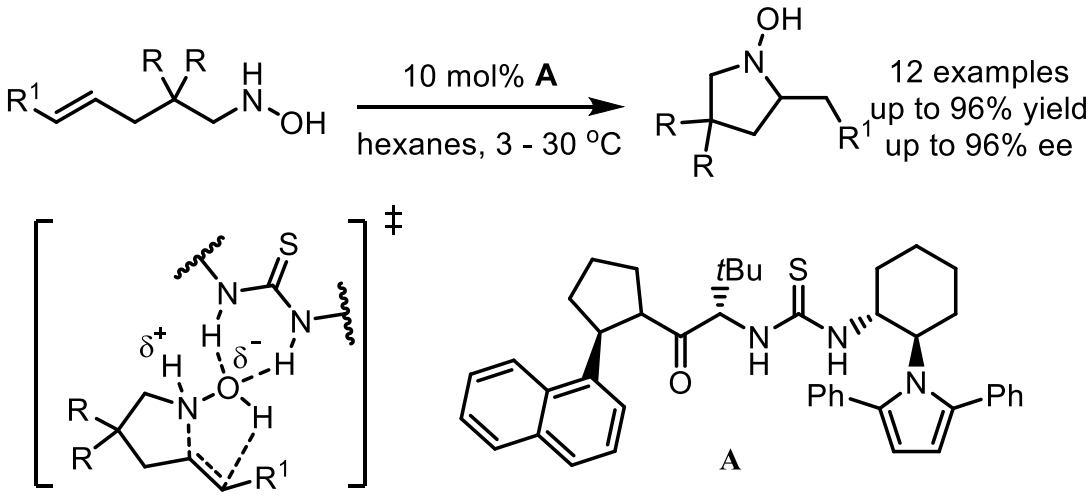


Scheme 2.8 Diastereoselective Cope-type hydroamination of allylic amines by Knight

In 2013, the first enantioselective intramolecular thiourea-catalyzed Cope-type hydroamination was reported by Jacobsen and coworkers.[44] Thiourea catalysts capable of stabilizing the dipolar transition state were found to be most effective to access

[44] Brown, A. R.; Uyeda, C.; Brotherton, C. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2013**, *135*, 6747.

enantioenriched *N*-hydroxy-pyrrolidines (Scheme 2.9). The majority of examples contained geminal-disubstitution to accelerate the reaction through the Thorpe-Ingold effect. This method only worked for mono-substituted hydroxylamines and was strictly limited to 5-membered cyclizations.



Scheme 2.9 Enantioselective thio-urea catalyzed intramolecular Cope-type hydroamination of alkenes by Jacobsen

2.4 Intermolecular Cope-type Hydroamination

The first intermolecular Cope-type hydroamination was reported by Laughlin in 1973 with dialkylhydroxylamines, but afforded mixtures of compounds.[45] In 2008, Beauchemin reported intermolecular Cope-type hydroamination of alkenes with hydroxylamine and *N*-alkylhydroxylamines.[46] Strained alkenes such as norbornene displayed excellent reactivity with both aqueous hydroxylamine and *N*-substituted hydroxylamines. Unbiased alkenes, not

[45] Laughlin, R. G. *J. Am. Chem. Soc.* **1973**, *95*, 3295.
[46] Moran, J.; Gorelsky, S. I.; Dimitrijevic, E.; Lebrun, M-E.; Bédard, A-C.; Séguin, C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 17893.

strained or electronically deficient, however resulted in moderate to poor yields at elevated temperatures (Figure 2.2).

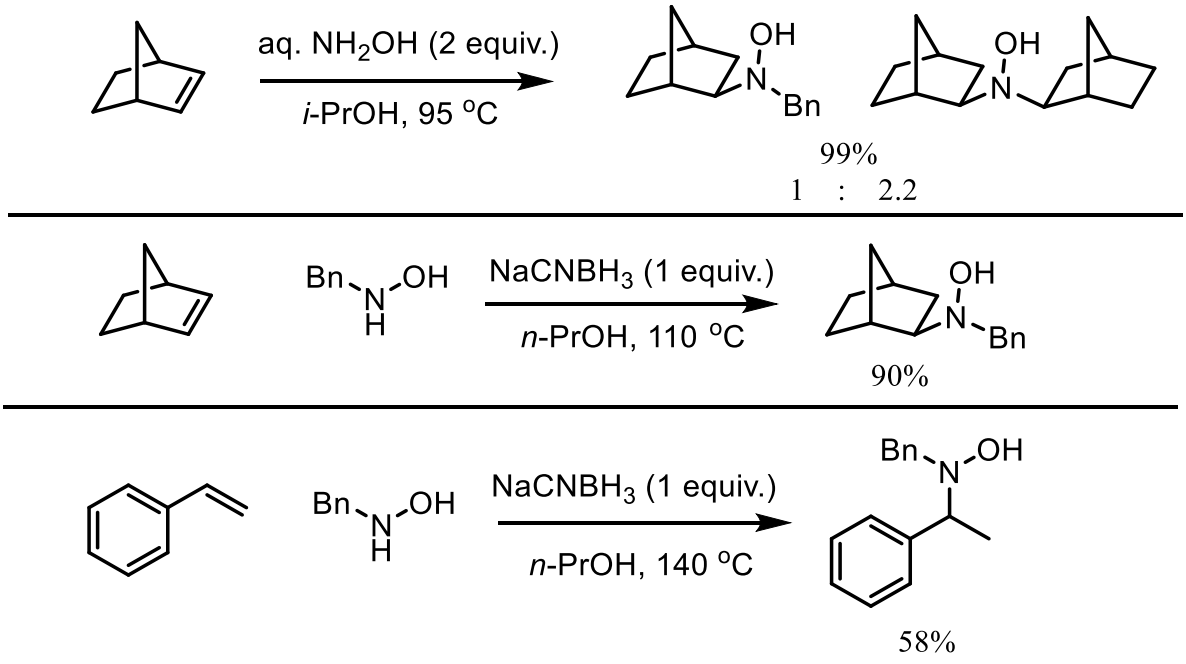
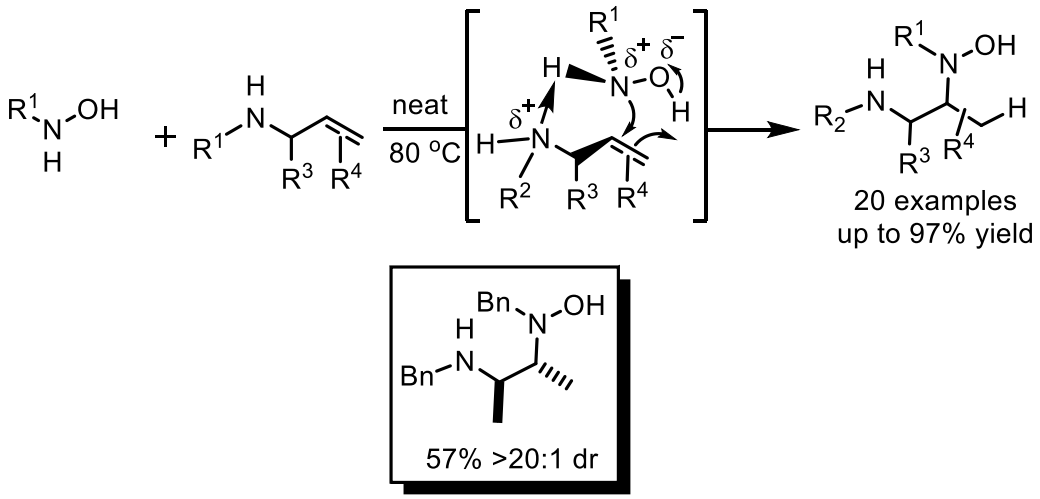


Figure 2.2 Selected examples of intermolecular Cope-type hydroamination of alkenes with aq. hydroxylamine and *N*-alkylhydroxylamines[46]

In 2012 our group showed that heating *N*-alkylhydroxylamines and allylic amines in the absence of solvent afforded intermolecular Cope-type hydroamination products.[47] The yields obtained were high considering allylic amines are unbiased alkenes. The origin of the increased reactivity was attributed to pre-association of the hydroxylamine and allylic amine through hydrogen bonding between the nitrogen lone pair of the allylic amine with the N-H bond of the hydroxylamine (Scheme 2.10). It is worth noting that the reaction performed with

[47] Zhao, S-B.; Bilodeau, E.; Lemieux, V.; Beauchemin, A. M. *Org. Lett.* **2012**, *14*, 5082.

N-benzyl *sec*-butenylamine afforded a single diastereomer and was obtained in 57% yield. The reaction time however, was much greater than other alkenes due to the increased substitution of the amine, requiring two days to achieve a modest yield.



Scheme 2.10 Hydrogen bonding directed intermolecular Cope-type hydroamination of alkenes[47]

2.5 Catalytic Tethering Strategies

The standard Gibbs free energy change determines the spontaneity of a given reaction. The sign and magnitude of the entropy term can be drastically influenced when changing from an intermolecular reaction to an intramolecular reaction. In a typical bimolecular reaction that generates one molecule from two molecules, a significant entropic penalty must be paid. Alternatively, by inducing temporary intramolecularity the entropic term for the difficult intermolecular reaction can be modified increasing the rate of the reaction.[48] However, catalytic tethering systems are complex since first an entropic penalty must be paid to assemble the tether as three molecules must ultimately join to become one molecule. The condensation of *N*-alkylhydroxylamine with an aldehyde leads to formation of two molecules (a nitrone and

[48] For a review see: Tan, K. L. *ACS Catal.* **2011**, *1*,877.

water) from two reagents and is also in rapid equilibrium in favor of the nitrone and is therefore not a major determinant of the reaction. The addition of allylic amine to the nitrone is in equilibrium and the position of this equilibrium is heavily dependent on the structure of the aldehyde precursor. As long as this equilibrium is established and the mixed aminal is able to form then the entropic penalty to bring the nitrone and allylic amine together is minimal compared to the entropic gain in the subsequent intramolecular Cope-Type hydroamination. In addition, increased control over stereoselectivity, regioselectivity, and chemoselectivity can be accompanied by temporary intramolecularity.[49] For these reasons temporary intramolecularity can be a very effective strategy to enable **any** difficult intermolecular reaction. Some enzymes are the best examples of catalysts that induce temporary intramolecularity to enable high reaction efficiency and selectivity. The pre-association of reacting partners accounts for nearly half of the remarkable rate accelerations observed in enzyme catalyzed reactions (up to 10^8 for 1M reactants).[50]

Tethering strategies used by chemists typically involve a stoichiometric approach which can require three to four steps.[48,51] One or two steps are required to assemble the appropriate tethered reactants, one step to perform the desired reaction, and one more step to cleave the tether from the product. Alternatively, the development of a tethering *catalyst* is rather difficult when considering features it must possess (Figure 2.3). Tether assembly must be selective for the mixed species over dimeric species. In addition, two covalent bonds must

[49] Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93,* 1307.
[50] Jencks, W. P. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1975**, *43*, 219.
[51] Si Tethers: (a) Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 6478. (b) Stork, G.; Chan, T. Y.; Breault, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7578. (c) Craig, D.; Reader, J. C. *Tetraedron Lett.* **1990**, *31*, 6585. (d) Gillard, J. W.; Fortin, R.; Grimm, E. L.; Maillard, M.; Tjepkema, M.; Bernstein, M. A.; Glaser, R. *Tetrahedron Lett.* **1991**, *32*, 1145. B Tethers: (a) Narasaka, K.; Shimada, S.; Osoda, K.; Iwasawa, N. *Synthesis*. **1991**, 1171. (b) Batey, R. A.; Thadani, A. N.; Lough, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 450.

be broken in order to regenerate the catalyst after the intramolecular reaction takes place. Examples of metal or organic molecules capable of catalyzing a reaction through temporary intramolecularity are rare. Despite these challenges the group wished to pursue a catalytic tethering approach to enable difficult intermolemolar hydroaminations. Inspiration was acquired from the work of Knight, who employed aldehydes to pre-associate *N*-alkylhydroxylamines and allylic amines (via formation of an aminal) allowing a facile 5-membered Cope-type hydroamination to proceed.

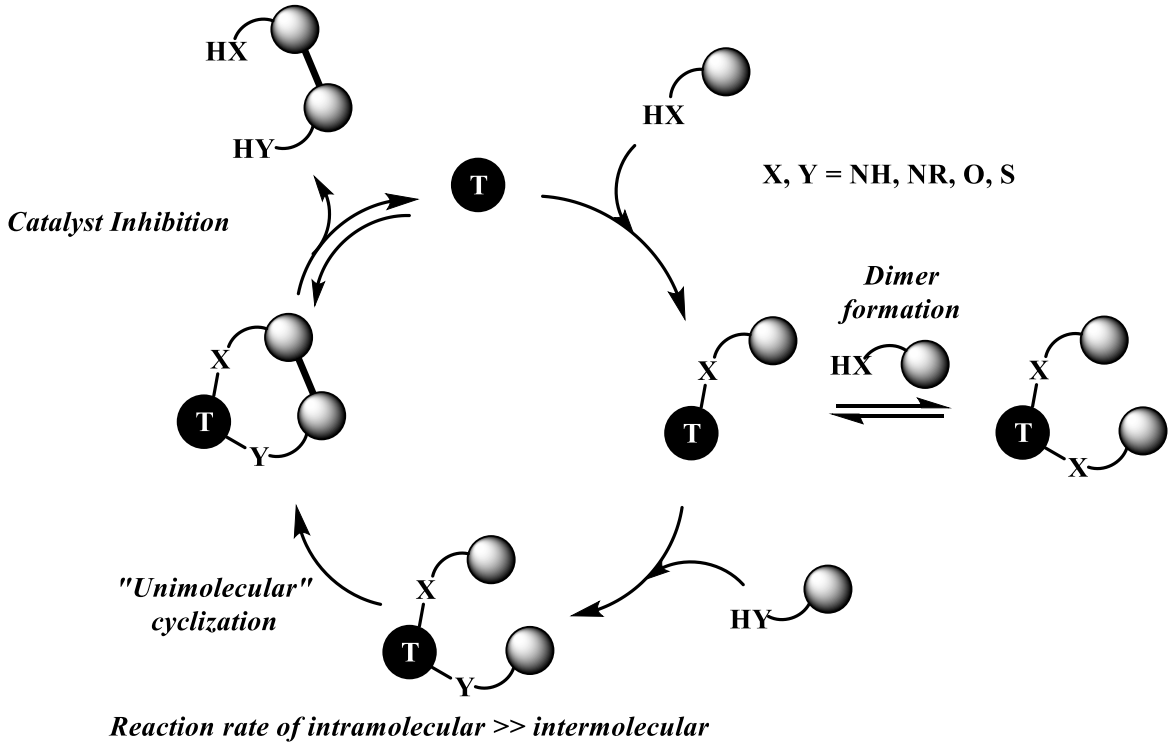


Figure 2.3 General catalytic cycle for a catalyst operating only via temporary intramolecularity

2.6 Aldehyde Catalyzed Cope-type Hydroamination

Our group showed in 2011 and 2012 that using a catalytic tethering approach simple aldehydes can catalyze intermolecular Cope-type hydroamination of allylic amines at room temperature. All of these results are summarized in Figure 2.4 as well as the proposed catalytic cycle.[52] After an exhaustive screening, the aldehyde that displayed the best catalytic activity was found to be α-benzyloxyacetaldehyde. Catalyst loading of 20 mol % with this aldehyde was sufficient for reactivity of terminal allylic amines (13 examples) in respectable yields. In 2012, mechanistic work was conducted on the reaction which resulted in the proposed catalytic cycle and led to the discovery of formaldehyde as a more efficient catalyst.[53] The catalytic cycle begins with condensation of an *N*-substituted hydroxylamine onto an aldehyde to generate a nitrone. Nucleophillic 1,2 addition of an allylic amine to the nitrone generates a mixed aminal, followed by intramolecular Cope-hydroamination. Aminal cleavage and then transamination of the iminium with *N*-benzylhydroxylamine regenerates the nitrone and affords the formal intermolecular hydroamination product.

[52] MacDonald, M. J.; Schipper, D. J.; Ng, P. J.; Moran, J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 20100.
[53] Guimond, N.; MacDonald, M. J.; Lemieux, V.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2012**, *134*, 16571.

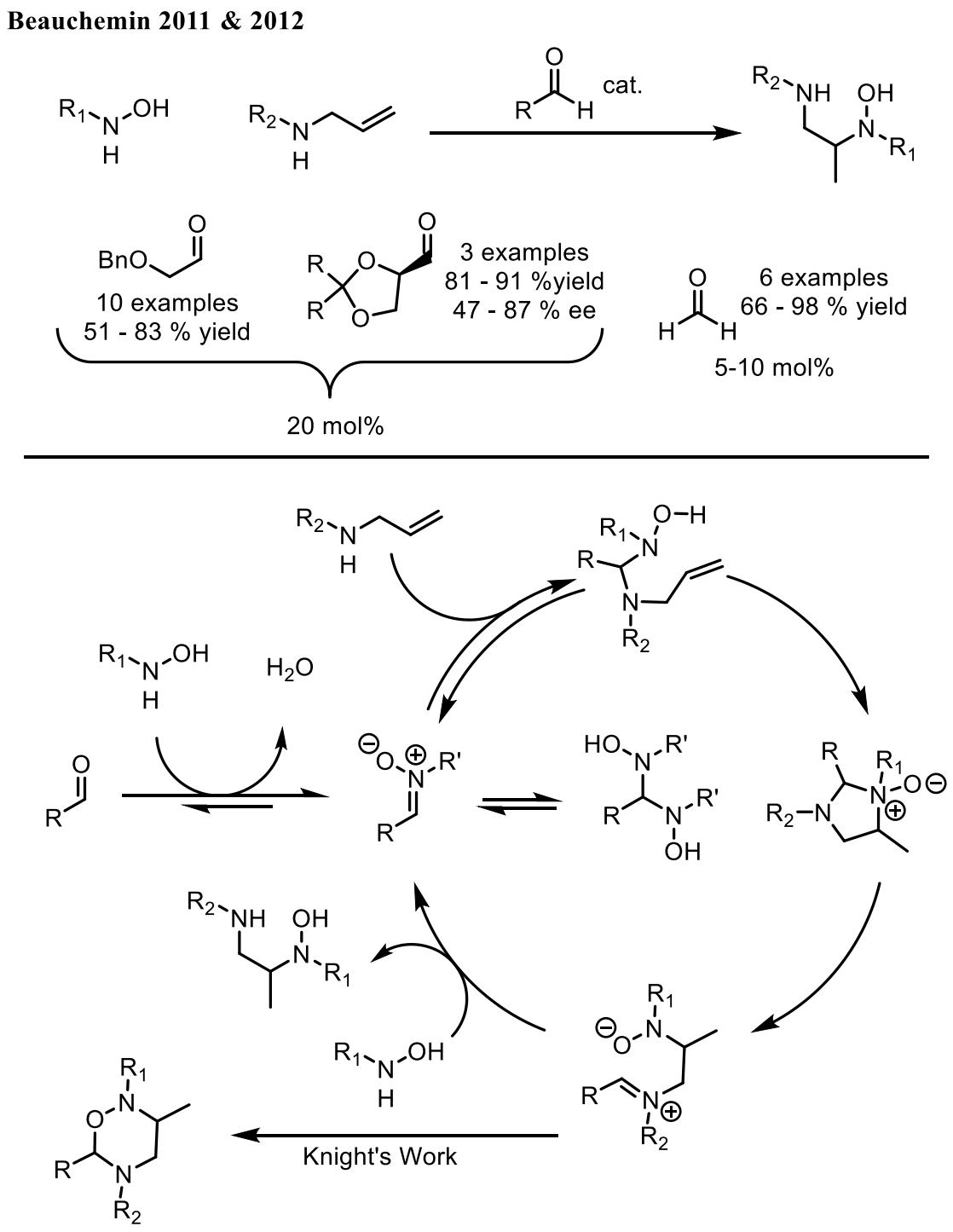
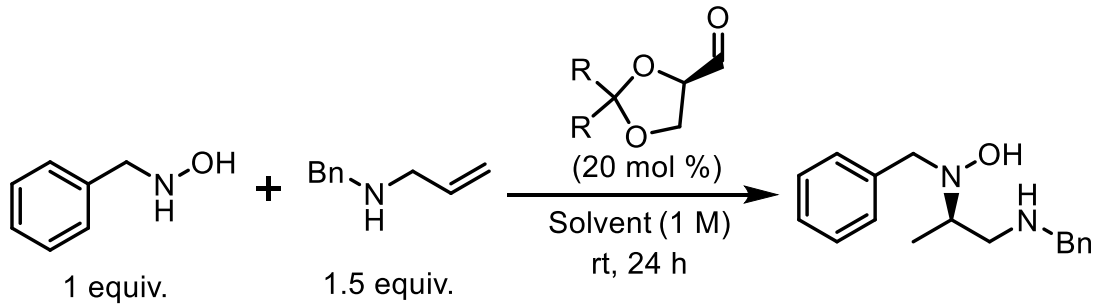


Figure 2.4 Summary of previous work on aldehyde catalyzed Cope-type hydroamination[52,53]

Table 2.1 Preliminary Results for Asymmetric Induction



R	Solvent	Yield	% *ee*
Me	C_6H_6	91	56
Ph	C_6H_6	85	87
Ph	C_6F_6	83	95

Commercially available (*R*)-(+)-2,2-dimethyl-1,3-dioxolane-4-carboxaldehyde was tested to probe whether enantioinduction could be achieved. Initial results exhibited excellent reactivity and good enantioselectivity (75% *ee*). By replacing methyl with phenyl substituents on the dioxolane ring the percent enantiomeric excess increased from 75 to 87 (Table 2.1). The high enantioselectivity achieved validated that simple chiral aldehydes were capable of efficiently inducing enantioinduction in Cope-type hydroamination only through temporary intramolecularity.

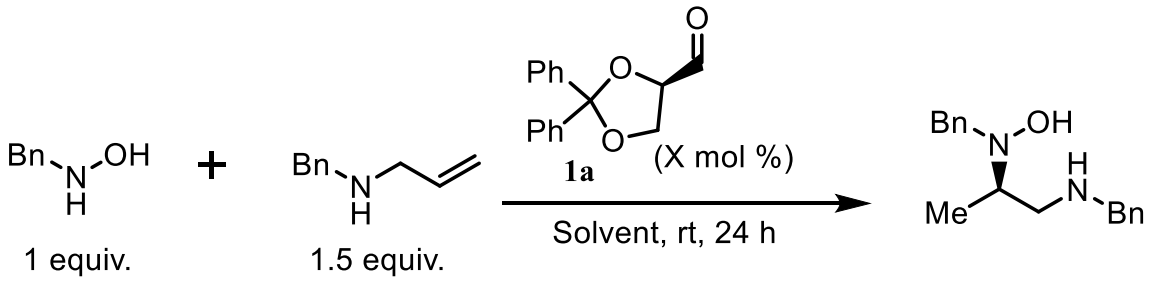
2.7 Results and Discussion for Enantioselective Cope-type hydroamination of allylic amines

2.7.1 Optimization of Aldehyde Catalyzed Cope-type hydroamination

At this point I joined the project working alongside Melissa J. MacDonald. The first task was to conduct a solvent screen to identify the effect of solvent on both the yield and enantioselectivity of the reaction (Table 2.2). The reaction was quite tolerable to most solvents

such as THF, 1,2-DCE and $CHCl_3$ but led to no improvements of the reaction. In *i*-PrOH both yield and enantioselectivity were greatly diminished. In general, benzene and related solvents proved the most effective for both yield and achieving high enantioselectivity. Attempts at reducing the temperature to -10 ^{o}C in toluene retarded the reaction greatly and showed no positive effect on enantioselectivity. The most important development discovered by Melissa J. MacDonald, was the addition of the catalyst last which increased the enantiomeric excess to 97% in hexafluorobenzene. By adding the catalyst last, epimerization of the catalyst before the reaction began was reduced thus leading to improved enantioselectivity. This level of enantioselectivity surpasses any method in the literature for intermolecular hydroamination of unbiased alkenes.[10,19,22,24]

Table 2.2 Optimization of reaction conditions with 1a



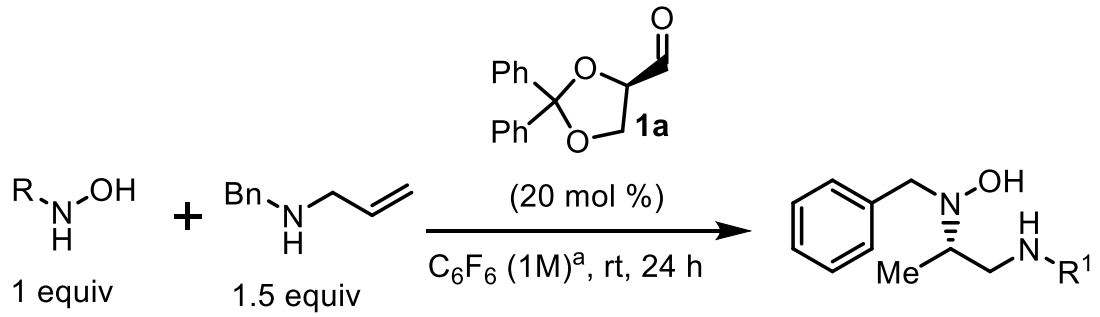
Entry	X	Conc. (M)[a]	Solvent	% NMR Yield	% *ee*[b]
1	20	1	Benzene	91	88[c]
2	20	1	THF	82	83
3	20	1	*i*-PrOH	45	63
4	20	1	$ClCH_2CH_2Cl$	70	81
5	20	1	Toluene	73	85
6	20	1	Toluene	10	82[d]
7	20	1	$CHCl_3$	78	81
8	20	1	C_6F_6	91	97[c]
9	10	1	C_6F_6	60	68

[a] Concentration of BnNHOH; [b] Determined by chiral HPLC;
[c] Addition of catalyst last; [d] Performed at -10 °C

2.7.2 Scope of Chiral Aldehyde Catalyzed Hydroamination

With the optimized conditions the scope of the reaction was examined with respect to substitution of the hydroxylamine component (Table 2.3). Both electron rich and electron poor *N*-benzylic hydroxylamines displayed excellent enantioselectivity with *N*-benzyl-*N*-allylamine. Reduced enantioselectivity and yields were observed for less bulky aliphatic substituted hydroxylamines likely due to decreased stereoselectivity of the 1,2 addition to the chiral nitrone.

Table 2.3 Exploration of hydroxylamine substitution

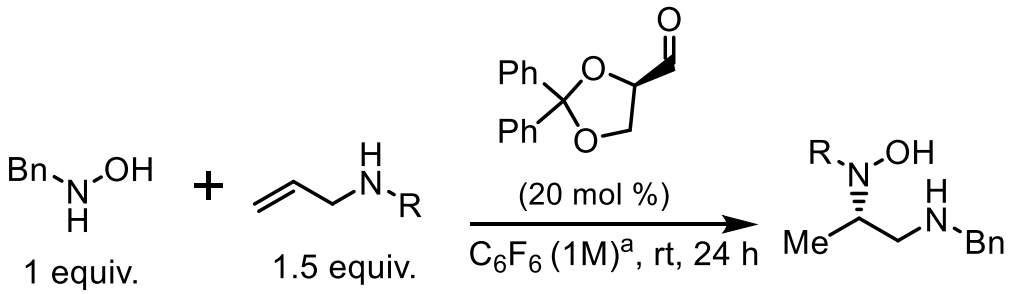


Entry	R	Product	% Yield	% *ee*[b]
1	Bn (**1.1a**)	**2.3a**	91	97
2	*p*-ClBn (**1.1b**)	**2.3b**	81	94
3	*p*-OMeBn (**1.1c**)	**2.3c**	86	92
4	3,5-$(CF_3)_2$Bn (**1.1d**)	**2.3d**	82	82
5	*i*-Pr (**1.1e**)	**2.3e**	60	60
6	$(CH_2)_3$Ph (**1.1f**)	**2.3f**	63	71

[a]Concentration to hydroxylamine. [b]Determined by chiral HPLC

Substitution of the allyl amine was explored (Table 2.4). It was quickly identified that *N*-benzyl substitution of the allylamine was vital to achieve high enantioselectivity. Again the greater enantioselectivity observed for *N*-benzyl substitution can be explained by increased stereoselectivity of the 1,2 addition to the chiral nitrone. For *N*-methyl-*N*-allylamine the enantiomeric excess achieved was 56% whereas for *N*-benzyl-*N*-allylamine derivatives the enantiomeric excess was typically greater than 90%. For allylamines bearing electron withdrawing groups such as esters and acetals the yield was reduced as well as the enantioselectivity. The lower yield observed for allylic amines with electron withdrawing groups is likely due to decreased nucleophilic addition to the nitrone. Work displayed in Tables 2.3 and 2.4 was performed by Melissa MacDonald and I.

Table 2.4 Exploration of scope of *N*-substitution of allylamine

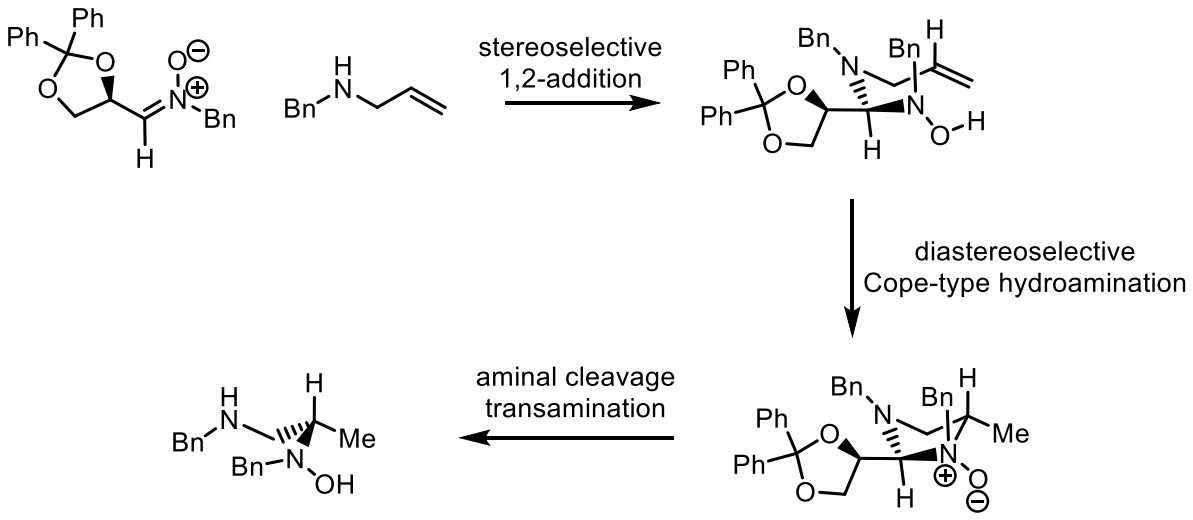


Entry	R	Product	% Yield	% *ee*[b]
1	Me (**1.2a**)	**2.4a**	91	56
2	allyl (**1.2b**)	**2.4b**	85	82
3	*p*-BrBn (**1.2c**)	**2.4c**	81	90
4	*p*-NO_2Bn (**1.2d**)	**2.4d**	83	95
5	$CH_2CH(OEt)_2$ (**1.2e**)	**2.4e**	62	60
6	CH_2CO_2Et (**1.2f**)	**2.4f**	75	72
7	$(CH_2)_2CO_2Me$ (**1.2g**)	**2.4g**	73	82

[a] Concentration to hydroxylamine. [b]Determined by chiral HPLC

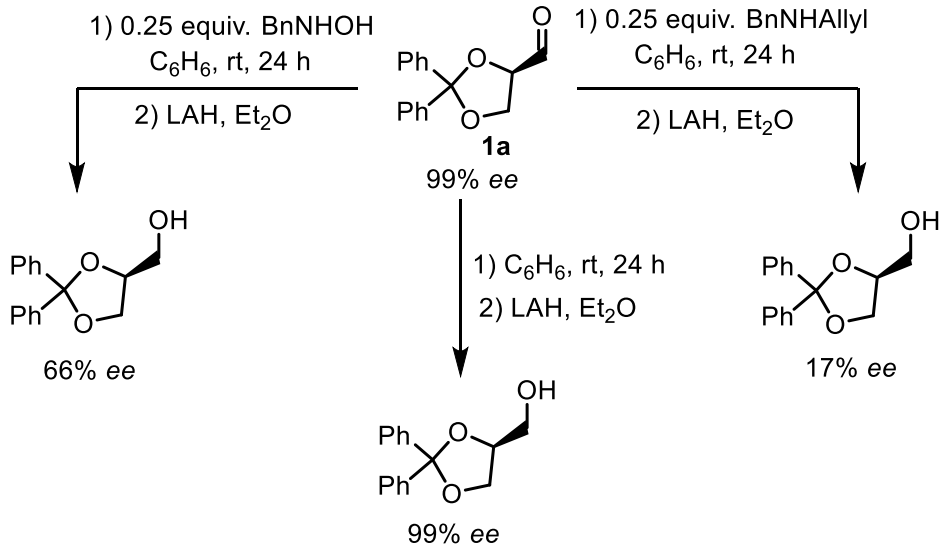
A proposal for the origin of enantioselectivity is illustrated in Scheme 2.11. The chiral nitrone is attacked by an allylic amine to form a transient, chiral mixed aminal most likely with high stereocontrol. The observed sense of induction is consistent with the formation of the temporary stereocenter present in the tether via Felkin-Ahn-controlled addition of the allylamine to the chiral nitrone.[54] In our mechanistic studies, the rate-determining step of the cycle was determined to be the Cope-type hydroamination event.[53] Therefore, it is not clear whether enantioinduction originates from the stereoselective formation of the aminal *or* due to the preference for one of the two diastereomeric transition states for the Cope-type hydroamination, or from the synergy between the two steps.

[54] Merino, P.; Franco, S.; Merchan, F. L.; Tejero, T. *Synlett* **2000**, 442.



Scheme 2.11 Proposed origin of enantioselectivity in aldehyde catalyzed hydroamination of allylic amines

The use of aldehydes containing an α oxygen substituent and a free α hydrogen in the presence of basic amines could lead to epimerization of **1a** under the reactions conditions. The epimerization could lead to erosion of the % *ee* of the catalyst and therefore % *ee* of the hydroamination products. To probe if this was an issue aldehyde **1a** was treated with sub-stoichiometric amounts of either *N*-benzylhydroxylamine or *N*-benzyl-*N*-allylamine. For analysis purposes the aldehyde had to be reduced to the corresponding alcohol after the reactions. The % *ee* of the starting aldehyde was confirmed to be greater than 99%, and stirred by itself the aldehyde in benzene showed no sign of self-epimerization. The reaction run with 25 mol% hydroxylamine for 24 hours resulted in recovered catalyst with 66% *ee* whereas the reaction run with 25 mol% *N*-benzyl-*N*-allylamine gave 17% *ee* (Scheme 2.12). These results provided strong evidence that catalyst epimerization was an issue and could help rationalize the lower % *ee* obtained for some substrates that reacted more slowly using **1a**.



Scheme 2.12 Probing sources of potential catalyst erosion

2.7.3 Screen of Chiral Aldehydes

At this point it was clear that aldehydes bearing a heteroatom substituent at the alpha position displayed the best catalytic activity and the chiral acetonide moiety was effective to induce stereoinduction in Cope-Type hydroamination. However, a catalyst resistant to epimerization would be ideal. A series of chiral aldehydes which contained a heteroatom substituent at the alpha position were synthesized and screened under the optimized conditions in benzene (Figure 2.5 and Table 2.5).

Garner's aldehyde **1c** containing a α Boc protected nitrogen atom displayed poor reactivity and enantioselectivity similar to acyclic aldehyde **1d**. Aldehyde **1e** displayed modest reactivity and good enantioselectivity of the opposite enantiomeric product. Aldehyde **1f** containing a α–quaternary center was a very poor catalyst most likely due to steric hindrance. Ley's aldehyde displayed poor results as well.[55] Bicyclic aldehyde **1h** displayed

[55] Leyva, A.; Blum, F. E.; Hewitt, P. R.; Ley, S. V. *Tetrahedron* **2008**, *10*, 2348.

excellent enantioselectivity of 94% *ee* and reasonable reactivity. Bicyclic aldehyde **1h**, a pseudo-enantiomer of **1a**, was chosen out of the screen for the high enantioselectivity achieved as well as access to the other product enantiomer.

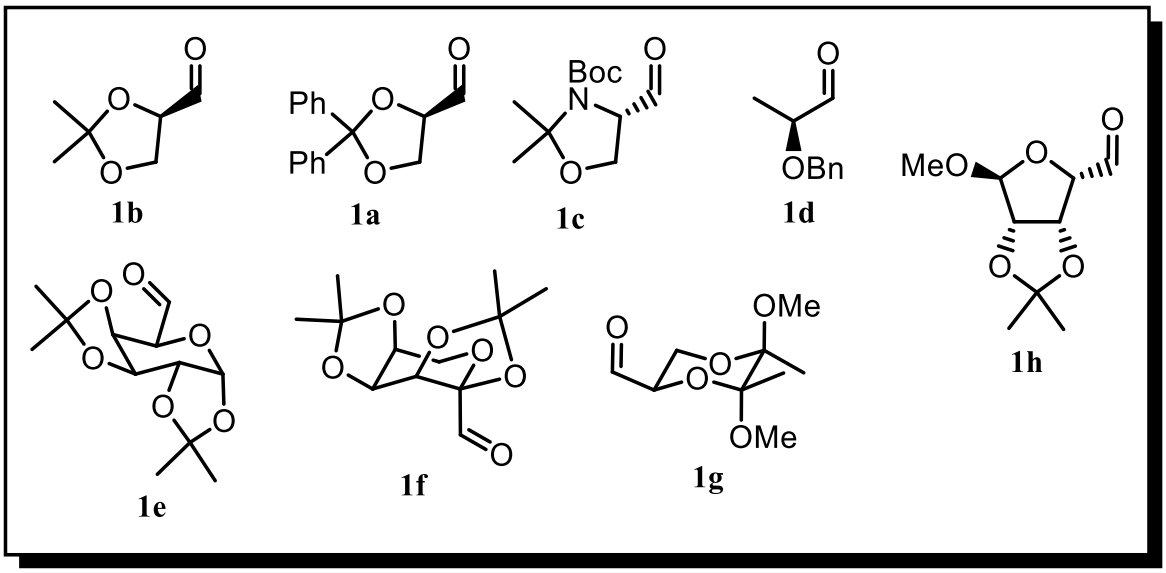
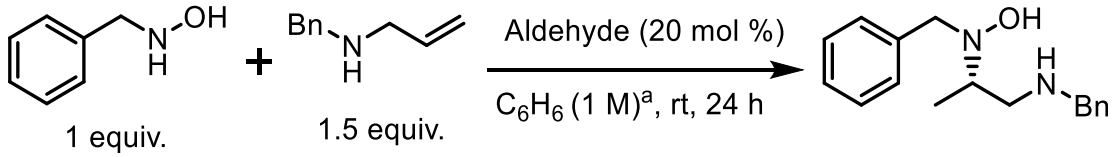


Figure 2.5 List of aldehyde screened for both catalytic activity and enantioinduction capability

Table 2.5 - Results for screening of chiral aldehydes in Figure 2.3



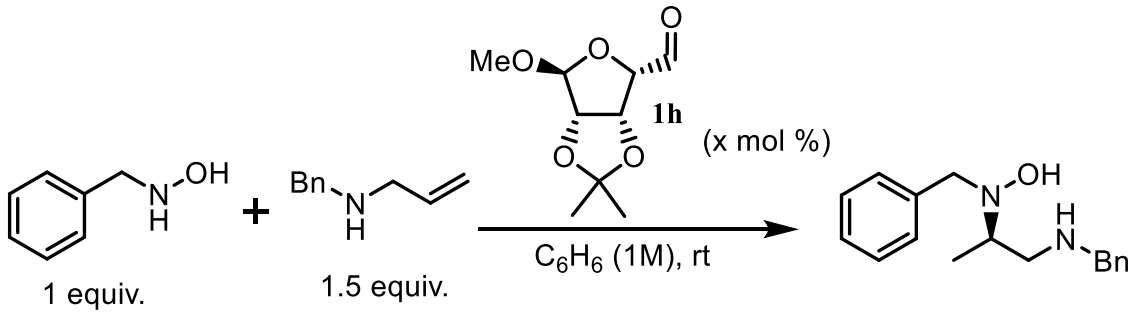
Entry	Aldehyde	% NMR Yield	% ee[b]
1	**1a**	93	75
2[c]	**1b**	91	88
3	**1c**	12	9
4	**1d**	16	9
5	**1e**	51	-85
6	**1f**	5	3
7	**1g**	16	37
8	**1h**	41	-94

[a]Concentration to hydroxylamine. [b] Determined by chiral HPLC
[c] Addition of catalyst last

2.7.4 Optimization and Scope using Aldehyde 1h

Optimization results of the reaction using catalyst **1h** results are summarized in Table 2.6 and began with probing the effect of catalyst loading. In all reactions with low yields the remaining mass balance was unreacted starting material. At 10 mol % the NMR yield dropped by 10%, whereas at 40 mol% the yield increased to 66% while maintaining high enantioselectivity (90% *ee*). The next variable that was probed was time. It was found that keeping the catalyst loading at 20 mol% but lengthening the time of the reaction by a factor of three resulted in good NMR yield of the hydroamination product and enantioselectivity (Table 2.6, Entry 5). Using hexafluorobenzene with this catalyst had no influence on the enantioselectivity as opposed to catalyst **1a**.

Table 2.6 - Optimization of reaction conditions using catalyst 1h

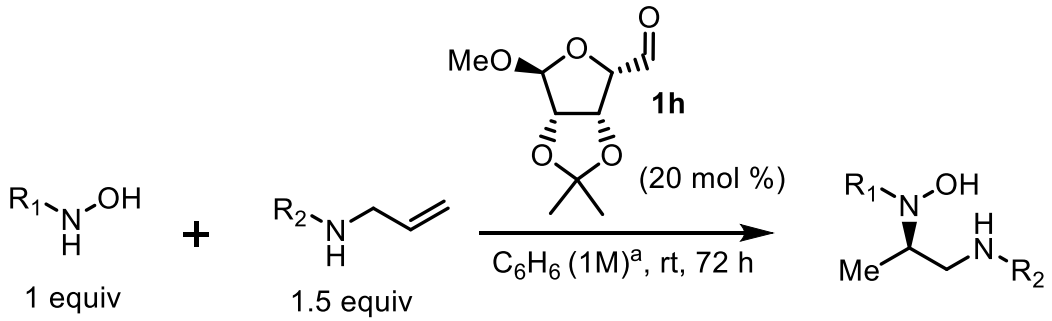


Entry	x	Solvent	Time (h)	NMR Yield	% ee[b]
1	10	C_6H_6	**24**	31	94
2	20	C_6H_6	**24**	41	90
3	40	C_6H_6	**24**	66	88
5	20	C_6H_6	**72**	84	89
6	10	C_6H_6	**72**	43	-
7	20	C_6F_6	**24**	46	93

[b] Determined by chiral HPLC

With the optimized conditions for catalyst **1h** available, entries that gave low enantioselectivities with catalyst **1a** were reexamined. In all entries, except Entry 1, the enantioselectivities were improved using catalyst **1h** relative to catalyst **1a** (Table 2.7 Entries 2-7). The increase in enantioselectivity suggested that catalyst **1h** was less prone to epimerization than catalyst **1a**. In order to verify that this was the case the *N*-benzyl nitrone of catalyst **1h** was prepared and exposed to either stoichiometric *N*-benzylhydroxylamine or *N*-benzyl-*N*-ethylamine. By ^{1}H NMR there was no evidence for epimerization as no peaks were seen that would be resulting from the formation of diastereoisomers.

Table 2.7 - Scope of asymmetric hydroamination with catalyst 1h



Entry	R_1	R_2	Product	Yield	% ee[b]	% ee[b, c]
1	Bn	Bn	**2.7a**	79	88	97
2	3, 5- $(CF_3)_2$Bn (**1.1d**)	Bn	**2.7b**	74	92	82
3	$(CH_2)_3$Ph (**1.1f**)	Bn	**2.7c**	60	77	71
4	Bn	allyl (**1.2b**)	**2.7d**	76	88	82
5	Bn	$(CH_2)CH(OEt)_2$ (**1.2e**)	**2.7e**	51	88	60
6	Bn	CH_2CO_2Et (**1.2f**)	**2.7f**	71	91	72
7	Bn	$(CH_2)_2CO_2Me$ (**1.2g**)	**2.7g**	66	90	82

[a]Concentration to hydroxylamine. [b]Determined by chiral HPLC. [c] % ee of opposite enantiomer obtained using catalyst **1a**

2.7.5 Conclusion for section 2.7

Much improvement was made in the intermolecular enantioselective Cope-type hydroamination of terminal allylic amines with *N*-alkylhydroxylamines catalyzed by simple chiral aldehydes. A new catalyst was identified that gives the opposite enantiomer of the hydroamination products. This catalyst also proved to be more robust by avoiding epimerization and gave consistently higher enantioselectivities. Internal alkenes, however, reacted poorly with both chiral aldehyde catalysts which is a current synthetic limitation to this methodology. The work discussed in this section has been published.[56]

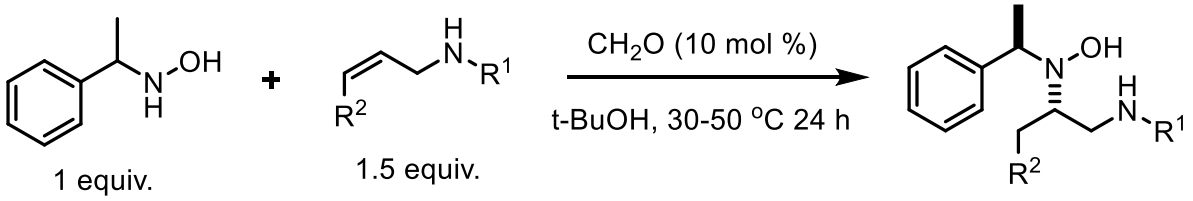
[56] MacDonald, M. J.; Hesp, C. R.; Schipper, D. J.; Pesant, M.; Beauchemin, A. M. *Chem. Eur. J.* **2013**, *19*, 2597

2.8 Results and Discussion for Reagent and Substrate Control Diastereoselective Hydroamination of Allylic Amines

2.8.1 Reagent-Control Diastereoselective Hydroamination of Allylic Amines

The remarkable rate acceleration observed with formaldehyde over α–benzyloxyacetaldehyde in DMSO suggested that more difficult Cope-type hydroamination reactions could be achieved.[53] Reacting *N*-(1-phenylethyl)hydroxylamine and *N*-benzyl-*N*-allylamine with 10 mol% formaldehyde in *t*-BuOH afforded the hydroamination product in 83% isolated yield and 6:1 d.r. Recrystallization of the mixture in hexane/Et_2O resulted in white crystals affording the major diastereomer in >20:1 d.r. The major diastereomer was determined by X-ray crystallography to be that shown in Table 2.8. The product formed from this reaction is a result of an intermolecular *reagent-controlled* diastereoselective Cope-type hydroamination and is - to the best of our knowledge - the first example of a reagent-controlled intermolecular hydroamination reaction. Upon discovery of diastereoselectivity observed in formation of **2.8a** and the crystal structure confirming the relative stereochemistry the scope of the reaction was then conducted by Melissa J. MacDonald. Terminal alkenes gave consistently 5:1 and 6:1 d.r. whereas internal alkenes gave >20:1 d.r. (Table 2.8).

Table 2.8 - Scope of reagent control diastereoselective hydroamination catalyzed by formaldehyde



Entry	R_1	R_2	Product	Temp (^oC)	% Yield	dr[a]
1	Bn	H	**2.8a**	30 ^oC	83	6:1
2	p-OMeBn (**1.1c**)	H	**2.8b**	30 ^oC	47	6:1
3	$(CH_2)CO_2Me$ (**1.1g**)	H	**2.8c**	30 ^oC	50	6:1
4	$(CH_2)_2CONMe_2$ (**1.1h**)	H	**2.8d**	30 ^oC	85	6:1
5	Bn	CH_2OBn (**1.3a**)	**2.8e**	50 ^oC	42	>20:1
6	Bn	$CH_2Oallyl$ (**1.3b**)	**2.8f**	50 ^oC	57	>20:1

[a] Determined by ^1H NMR

The diastereoselectivity likely originates from the stereocenter of the hydroxylamine preferring projection of the phenyl substituent away from the bicyclic transition state as depicted in Figure 2.6.

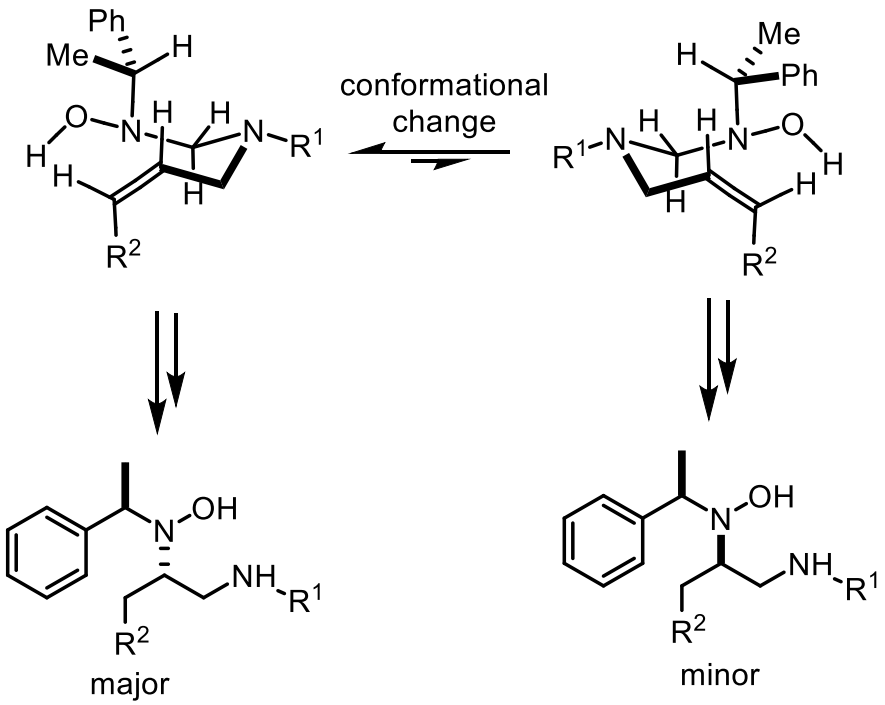


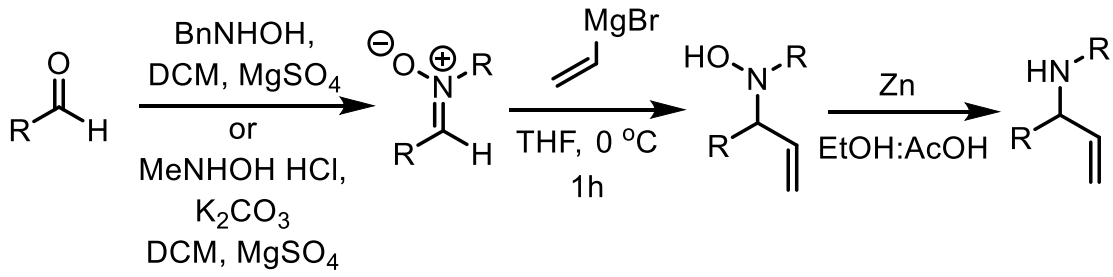
Figure 2.6 Origin of diastereoselectivity under reagent control

2.8.2 Substrate-Controlled Diastereoselective Hydroamination

The excellent diastereoselectivity that Knight and co-workers achieved in the stoichiometric reactivity between *N*-alkylnitrones and allylic amines containing an α–stereocenter suggested that our aldehyde catalysis would be just as selective.[43] A modified three-step procedure reported by Dondoni and coworkers was used to prepare *N*-benzyl and *N*-methyl allylamines, containing a α–stereocenter, from aldehydes (Table 2.9).[57] The first step was condensation of *N*-methyl or *N*-benzyl hydroxylamine onto an aldehyde followed by 1,2-addition of vinyl magnesium bromide. The nitrogen-oxygen bond was then cleaved in the presence of zinc dust and acetic acid to give the substituted allylic amine.

[57] Dondoni, A.; Junquera, F.; Merchan, F. L.; Merino, P.; Terjero, T. *Synthesis* **1994**, 1450.

Table 2.9 - General synthetic route to *N*-methyl and *N*-benzyl allylic amines



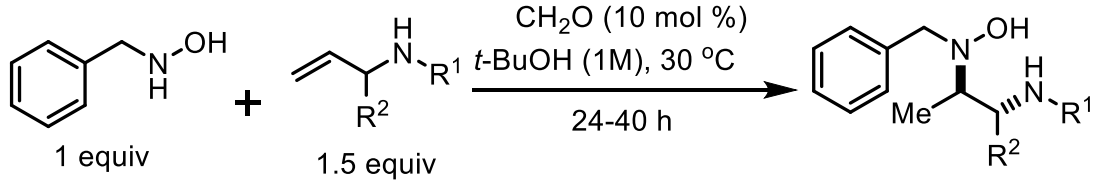
Entry	R	RNHOH	Product	% Yield[a]
1	$(CH_2)_2CH_3$	Bn	**1.4d**	40
2	CH=CHPh (*E*)	Bn	**1.4e**	55
3	Ph	Bn	**1.4f**	50
4	(CH_2)OTBS	Me	**1.4g**	40
5	2-furyl	Me	**1.4h**	51
6	3-pyridyl	Me	**1.4i**	69
7	*i*-Pr	Me	**1.4j**	24

[a]Isolated yield after 3 steps

All substrates synthesized exhibited reactivity as expected for terminal alkenes and the diastereoselectivity obtained in all cases was >20:1 d.r. (Table 2.10). Alkene **1.4b** containing an electron-withdrawing trifluoromethyl substituent displayed no reactivity presumably due to decreased nucleophillcity of the amine. Alkene **1.4c** containing an α phenyl group, reacted very slowly likely due to the bulkiness of the amine, presumably retarding nucleophilic attack onto the nitrone. This could be circumvented by replacing *N*-benzyl with an *N*-methyl group which afforded **3.0e** much more efficiently in 80% yield. The *N*-methyl alkene **1.4f** is more nucleophilic and less bulky than the *N*-benzyl amine. Longer alkyl chains (**1.4d**) and bulky *i*-Pr (**1.4j**) groups were tolerated as well. Heterocyclic substituents were also tolerated such as the furan (**1.4h**) and pyridine (**1.4i**) ring systems. Overall, the results shown in Table 2.10

show that the catalytic procedure developed using formaldehyde results in excellent diastereocontrol, which is similar to what was achieved by Knight under stoichoimetric conditions.[43]

Table 2.10 - Scope of reagent control diastereoselective hydroamination catalyzed by formaldehyde



Entry	R_1	R_2	Product	% Yield	dr[b]
1	Bn	Me (**1.4a**)	**2.10a**	92	>20:1
2	Bn	CF_3 (**1.4b**)	**-**	0	-
3	Bn	Ph (**1.4c**)	**-**	<50[a]	>20:1
4	Bn	$(CH_2)_2CH_3$ (**1.4d**)	**2.10c**	72	>20:1
5	Bn	CHCHPh (**1.4e**)	**2.10d**	71	>20:1
6	Me	Ph (**1.4f**)	**2.10e**	80	>20:1
7	Me	(CH_2)OTBS (**1.4g**)	**2.10f**	70	>20:1
8	Me	2-furan (**1.4h**)	**2.10g**	86	>20:1
9	Me	3-pyridine (**1.4i**)	**2.10h**	81	>20:1
10	Me	i-Pr (**1.4j**)	**2.10i**	76	>20:1

[a] % NMR yield; [b] Determined by ^{1}H NMR

The diastereoselectivity observed is rationalized in Figure 2.7, where the more stable 5,5-bicyclic Cope-type transition state has the α–stereocenter of the allylic amine adopting a pseudo-equatorial orientation to minimize steric interactions. Surprisingly, the Knight group had not proposed a rationale for stereoinduction is this system.

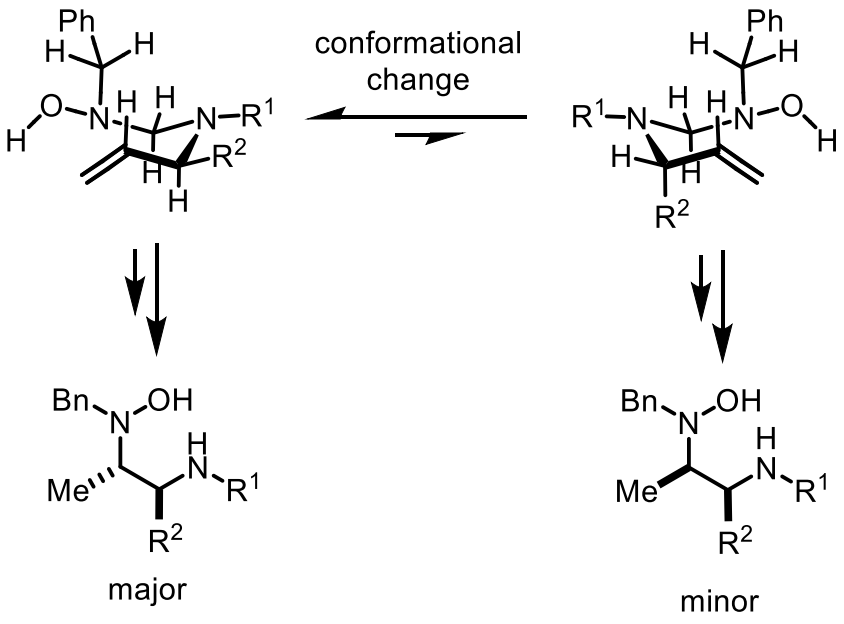
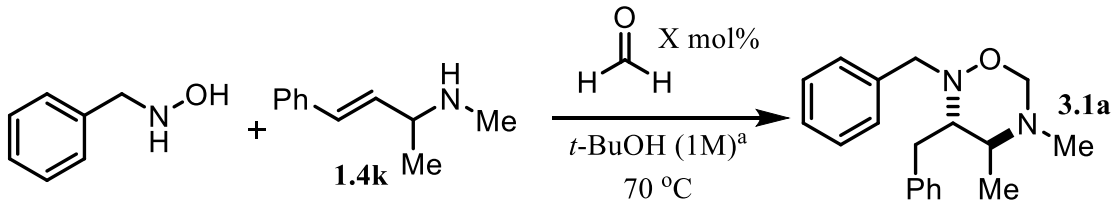


Figure 2.7 Origin of diastereoselectivity under substrate control

The scope of substrate controlled hydroamination of terminal alkenes was tested in Table 2.10 and proved to be quite wide. The next goal was to test allylic amines containing an α stereocenter in addition to internal alkenes. The study began with alkene **1.4k** (Table 2.11). Attempts to perform hydroamination under catalytic conditions were unsuccessful as little turnover was achieved due to formation of 1,2,5-oxadiazinane as observed by Knight in the stoichiometric version. Fortunately, it was found that increasing the catalyst loading of formaldehyde increased the NMR yield of **3.1a**. By using 100 mol % formaldehyde cyclic adduct **3.1a** could be isolated in 72% yield with >20:1 d.r. in only 24 hours. The reactivity in *t*-BuOH was much better in comparison to Knight's system in $CHCl_3$, which usually required several days for difficult substrates to reach completion.[43]

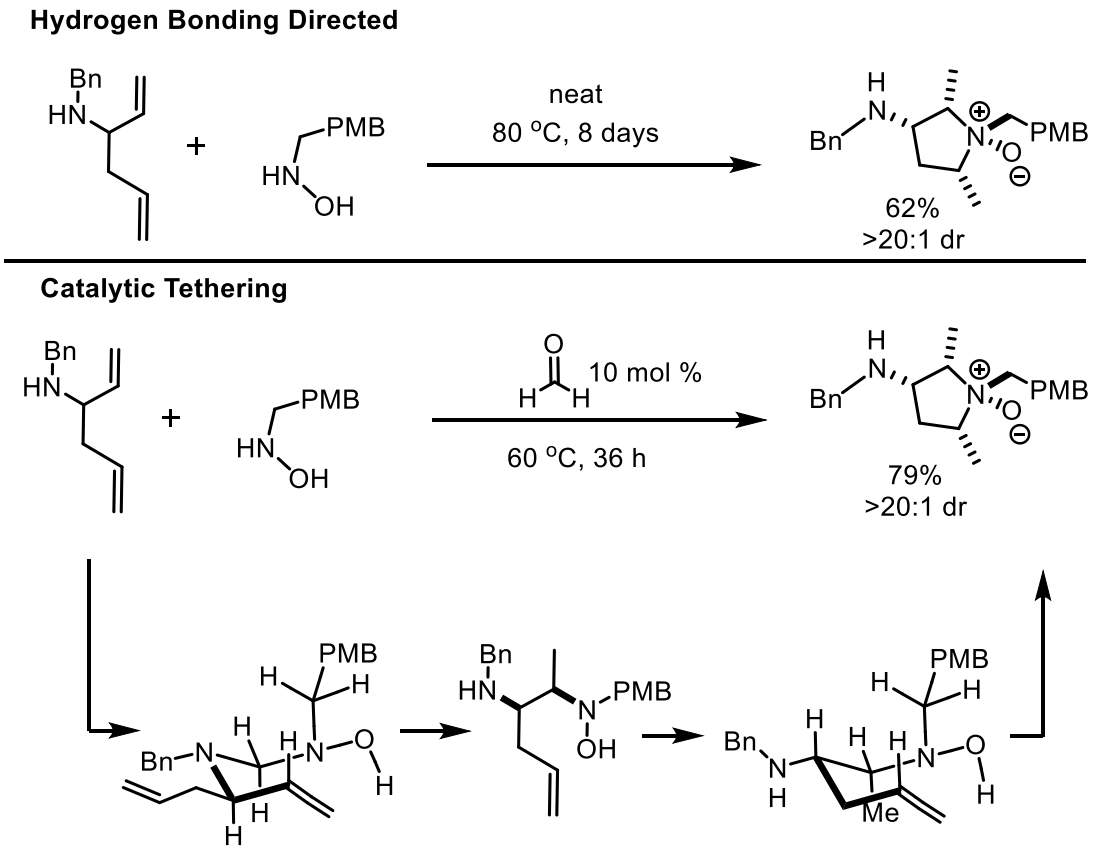
Table 2.11 - Optimization for hydroamination of (±)-Methyl[(3E)-4-phenylbut-3-en-2-yl]amine



Entry	X mol %	Time	NMR Yield (dr[c])
1	20	64 h	28 (>20:1)
2	30	64 h	48 (>20:1)
3	50	64 h	75 (>20:1)
4	100	24 h	72[b] (>20:1)

[a] Concentration to *N*-Benzylhydroxylamine; [b] Isolated Yield;
[c] Determined by ^{1}H NMR

In a 2012 communication the group reported a hydroamination cascade using *N*-benzyl hexa-1,5-dien-3-amine.[47] Using the hydrogen bonding approach the hydroamination cascade afforded the expected pyrolidine *N*-oxide in >20:1 d.r. and 62% yield. However, the reaction was very slow and required 7 days to achieve a 62% yield. Exposing similar substrates to the optimized conditions for formaldehyde catalysis shortened the reaction time to 36 hours (at 60 °C), and the yield increased to 79% with no loss of diastereoselectivity (Scheme 2.13). This reaction was performed by Dr. Shubin Zhao.

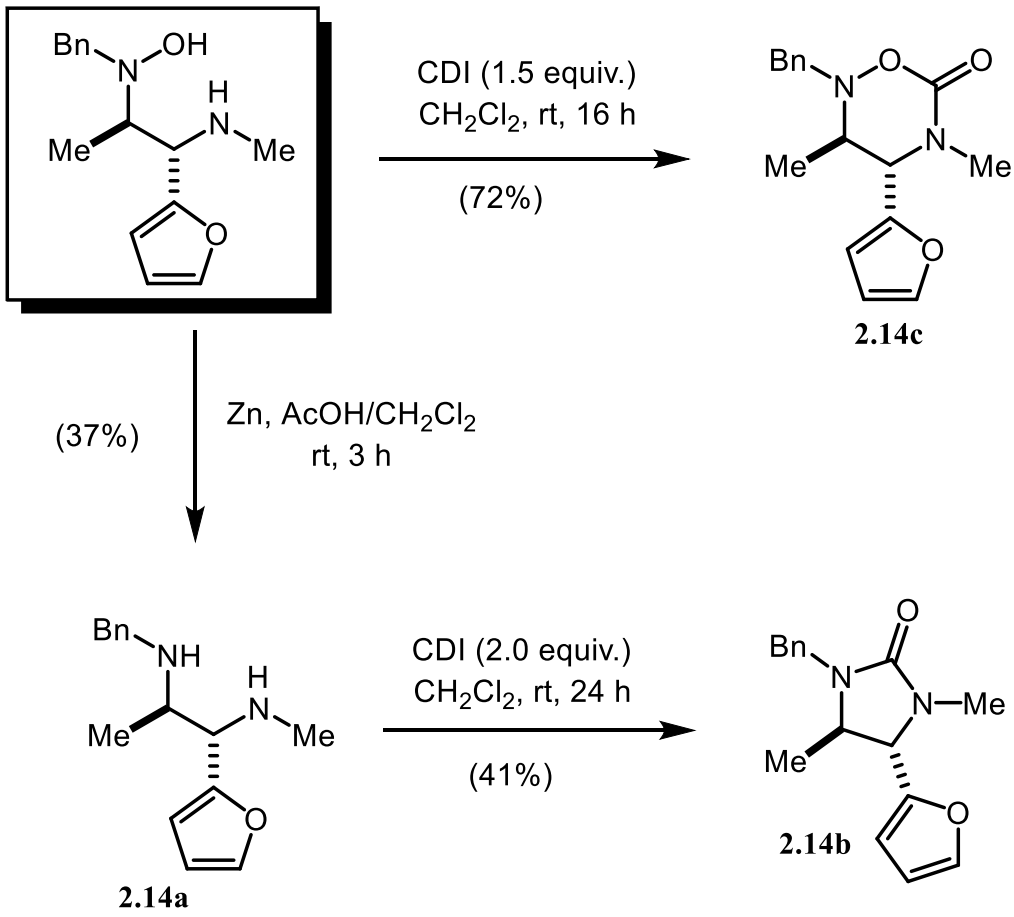


Scheme 2.13 - Hydrogen bonding directed versus catalytic tethering for hydroamination cascade

2.8.4 Derivatization of 1,2 Diamine Products

The hydroamination of allylic amines represents a highly modular approach to the diamine motif. Using aldehyde catalysis, stereoselective hydroamination of allylic amines is now possible and thus many derivatizations can be envisioned (Scheme 2.14). For instance, the hydroamination product can be converted easily to cyclized compound **2.14c** in the presence of 1,1'-carbonyldiimidazole (CDI). In addition, one of the amines has a hydroxyl group that can be removed under a variety of conditions (including zinc dust in AcOH) to give

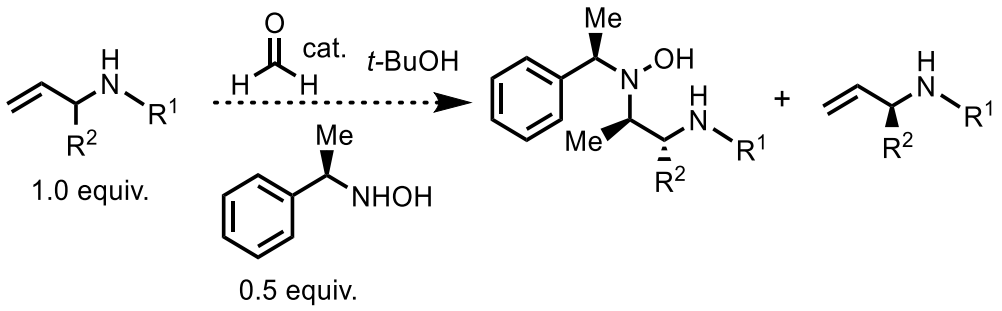
2.14a. A reaction of **2.14a** with CDI can then produce the 5 membered heterocycle **2.14b**. Products **2.14a** and **2.14b** were synthesized by Melissa J. MacDonald.



Scheme 2.14 Derivatization of diamine products

2.8.5 Double Stereodifferentiation

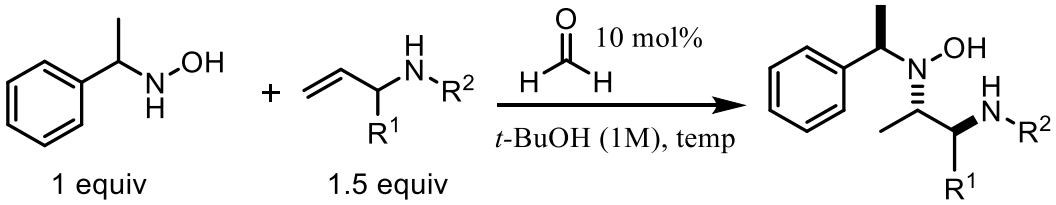
Combining *N*-(1-phenylethyl)hydroxylamine and an allylic amine with an α-stereocenter could allow control over two stereocenters of the diamine products. More interesting is the potential to use enantiopure *N*-(1-phenylethyl)hydroxylamine to perform kinetic resolution of allylic amines or desymmetrization of symmetrical allylic amines (Scheme 2.15).



Scheme 2.15 Potential for kinetic resolution of allylic amines by Cope-type hydroamination

The first attempt employed *N*-(1-phenylethyl)hydroxylamine and *N*-benzylbut-3-en-2-amine in *t*-BuOH with 10 mol% formaldehyde at 80 ^{o}C (Table 2.12). From the crude ^{1}H NMR the d.r. was determined to be 5:1. The major diastereomer from the crude mixture was recrystallized in hexane/ether, and the crystal structure allowed to assign the relative stereochemistry seen in Table 2.12. Unfortunately, lowering the temperature did not have an impact on the d.r. of the reaction. It was hypothesized that having a larger substituent alpha to the allylic amine would increase the d.r. By replacing the methyl group with a phenyl group the d.r. lowered to 1:1.7. In addition, whether the allylic amine was *N*-methyl or *N*-benzyl did impact the d.r. of the hydroamination.

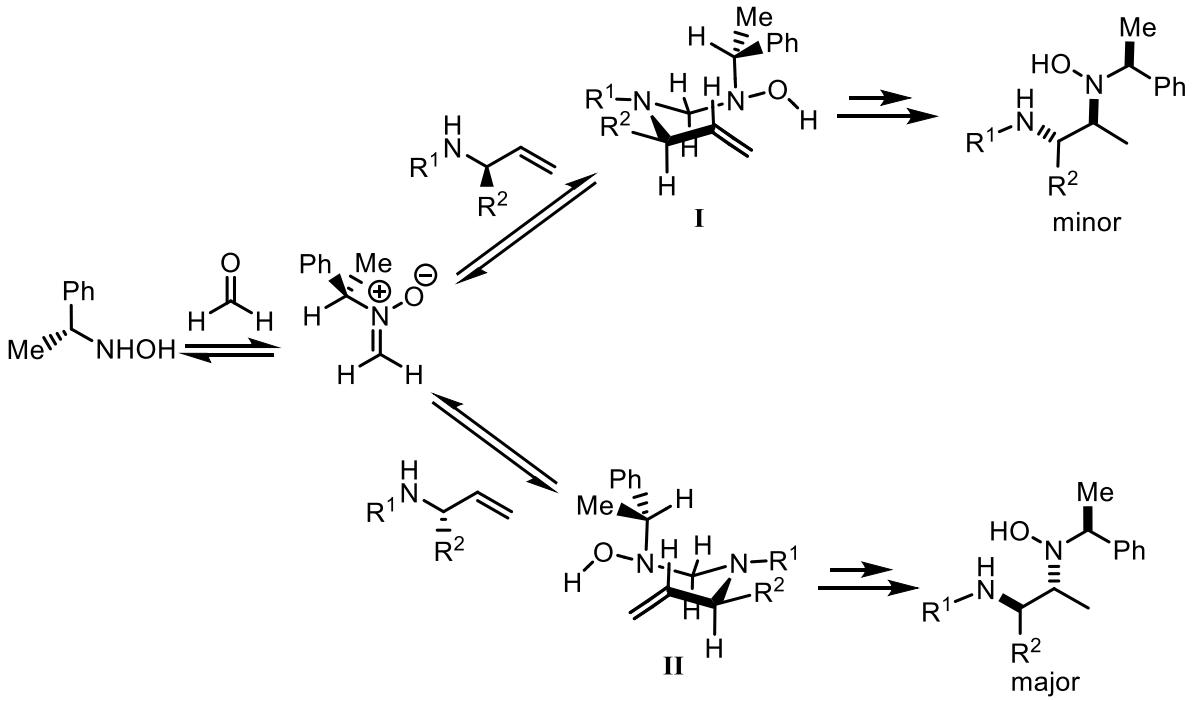
Table 2.12 - Results for double stereodifferentiation of allylic amines using N-(1 phenylethyl)hydroxylamine



Entry	R_1	R_2	Temp (^oC)	dr[b]
1[a]	Me	Bn	80	5:1
2	Me	Bn	50	4:1
4	Ph	Me	50	1:1.7
5	Ph	Bn	50	1:1.4

[a] The crude was recrystallized affording 35% yield and 19:1 d.r;
[b] Determined by ^1H NMR

It was speculated that the poor diastereoselectivity was due to an equal preference for either enantiomer of the chiral allylic amine to undergo 1,2-addition to the formaldehyde nitrone and/or the small differences in the energies required for intermediates I and II to undergo Cope-type hydroamination (Scheme 2.16). Therefore, potential changes to the system that may lead to increased levels of diastereoselectivity are as follows: 1) If a more substituted aldehyde is used, such as α-benzyloxyacetaldehyde, the addition step may become rate determining leading to enhanced diastereoselectivity and/or 2) using a chiral hydroxylamine with a bigger substituent in place of the phenyl substituent to increase the energy difference between Cope-type hydroamination intermediates I and II and/or 3) using internal alkenes.

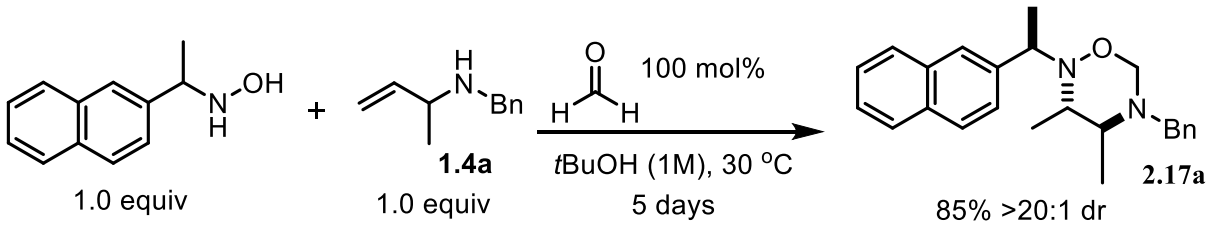


Scheme 2.16 Double stereodifferentiation in formaldehyde catalyzed Cope-type hydroamination

To test the second hypothesis *N*-(2-napthylethyl) hydroxylamine was prepared and reacted with **1.4a** in *t*-BuOH at 30 °C for 5 days using a stoichiometric amount of formaldehyde. A longer reaction time was chosen for this reaction as the hydroxylamine was rather large and because of the low temperature that was selected. The crude 1H NMR spectrum showed complete consumption of **1.4a**, however the crude d.r. was difficult to determine. After column chromatography the 1,2,5-oxadiazinane adduct was isolated in 85% yield and >20:1 dr (Scheme 2.17). This result validated the hypothesis that a larger energy difference in intermediates I and II would increase the diastereoselectivity of the reaction. The next step is to prepare enantiopure *N*-(1-napthylethyl) hydroxylamine from commercially available (*S*) or (*R*)-*N*-(2-napthylethyl)amine[58] to determine if kinetic resolution is possible.

[58] Patel, I; Smith, N. A.; Tyler, S. N. G. *Org. Process Res. Dev.* **2009**, *13*, 49.

It is also worth exploring various substitution patterns on the phenyl substituents, in particular ortho substituents.



Scheme 2.17 Result using *N*-(1-napthylethyl)hydroxylamine

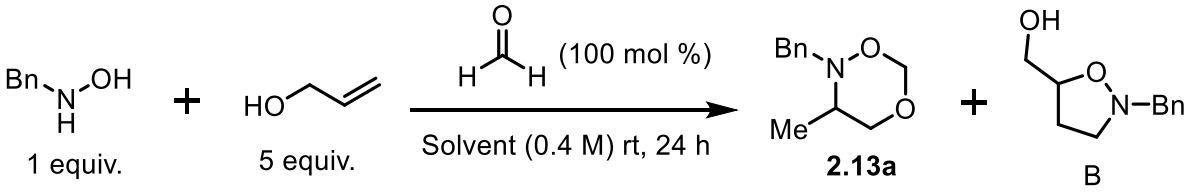
2.8.6 Conclusion for section 2.8

In Chapter 1 no examples of *intermolecular* diastereoselective hydroamination were mentioned owing to the difficulty of such a transformation. However, formaldehyde acting as a tethering catalyst has not only enabled difficult intermolecular hydroaminations to occur under mild conditions but has also allowed highly diastereoselective variants to be developed. Diastereoselectivity was realized for both reagent and substrate controlled systems and the first double stereodifferentiation via Cope-type hydroamination has been achieved.

2.9 Allylic Alcohols

The reactivity described above in principle should be applicable to allylic alcohols and the hydroamination of allylic alcohols would represent an expedient route to 1,2-aminoalcohols. However, because alcohols are less nucleophilic than amines the addition to the nitrone was expected to be much more difficult. Investigation began with employing the best conditions for allylic amines in hopes of similar reactivity patterns. Running the reaction with 5 equivalents of allylic alcohol, 1 equivalent *N*-benzylhydroxylamine with catalytic formaldehyde (25 and 50 mol%) in *t*-BuOH (1M) did not generate any trace of hydroamination product. The reaction conditions were thus modified to employ stoichiometric quantities of formaldehyde and reinvestigate solvent effects on the reaction (Table 2.13).

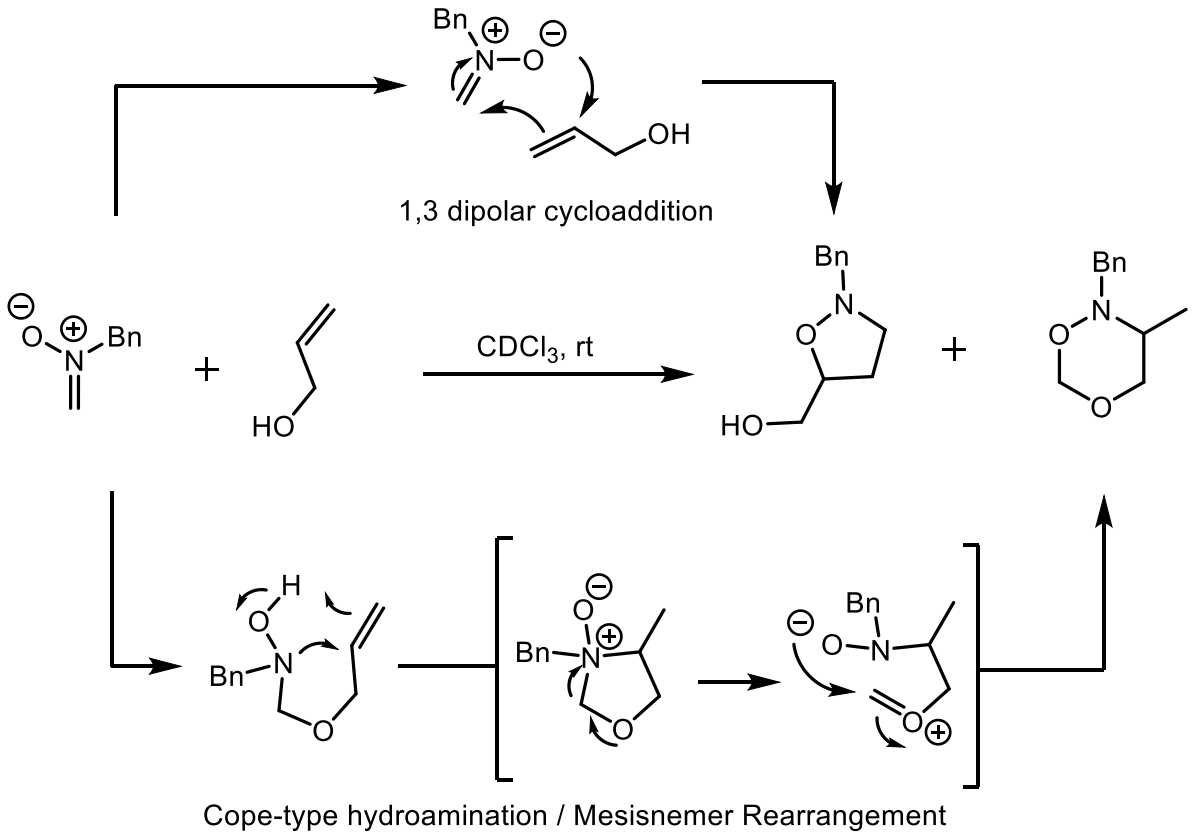
Table 2.13 - Solvent screen for the hydroamination of allylic alcohols



Entry	Solvent	% NMR Yield of 1	Ratio A:B
1	*t*-BuOH	0	-
2	DMSO	0	-
3	$CHCl_3$	13	5:1
4[a]	$CHCl_3$	19	5:1
5	MeCN	8	-
6	EtOAc	2	-
7	$(CH_3)_2CO$	8	-
8	DMF	2	-
9	Dioxane	8	-
10	TFT	15	5:1

[a] Reaction performed at concentration of 1M, Isolated yield of **2.7a** <5%

The crude NMR spectrum in most solvents showed complete consumption of *N*-benzylhydroxylamine with the formation of a cyclic adduct determined to be arising from a 1,3-dipolar cycloaddition.The cycloaddition product was favoured over the hydroamination product in a 5:1 ratio in $CDCl_3$. Efforts toward optimization of the reaction with acids such as para-toluene sulfonic acidor base additives such as DMAP and *t*-BuOK led to no improvements.



Scheme 2.18 Product distribution for the reaction of formaldehyde nitrone with allylic alcohol

2.9.1 Conclusion for section 2.9

Future work towards aldehyde catalyzed hydroamination of allylic alcohols should focus on either of two directions; 1) identifying an aldehyde that will not allow a 1,3-dipolar cycloaddition but permit 1,2 addition with the alcohol or 2) screening of more substituted allylic alcohols that are incapable of undergoing 1,3-dipolar cycloadditions but still can undergo facile intramolecular hydroamination.

Appendix I. Claims to Original Research

Claims to Original Research

1) Development of two aldehyde catalysts for enantioselective Cope-type hydroamination of allylic amines

2) Development of the first example of catalytic *intermolecular* reagent- and substrate-controlled diastereoselective Cope-type hydroamination

3) Development of the first example of double stereodifferentiation through Cope-type hydroamination

Publications from This Work

Highly Enantioselective Intermolecular Hydroamination of Allylic Amines with Chiral Aldehydes as Tethering Catalysts MacDonald, M. J.; Hesp, C. R.; Schipper, D. J.; Peasant, M.; Beauchemin, A. M. *Chem. Eur. J.* **2013**, *8*, 2597-2601.

Formaldehyde as Tethering Organocatalyst: Highly Diastereoselective Substrate and Reagent-Controlled Hydroaminations of Allylic Amines MacDonald, M. J.; Hesp, C. R.; Peasant, M.; Beauchemin, A. M. *Submitted for publication.*

Presentations from This Work

Poster Presentation

Hesp, C. R.; MacDonald, M. J.; Schipper, D. J.; Peasant, M.; Beauchemin, A. M. *Organocatalytic Tether Formation: A Strategy Enabling Enantioselective Intermolecular Amination Reactions.* QOMSBOC, Concordia University, Montreal, Quebec, Canada (2011)

Oral Presentation

Hesp, C. R.; MacDonald, M. J.; Peasant, M.; Beauchemin, A. M. *Aldehyde Catalyzed Stereoselective Cope-Type Hydroamination of Allylic Amines.* CSC National Conference, Quebec City, Quebec, Canada (2013)

Appendix II. Experimental section

Chapter 2 – Section 2.7

General Procedure for Optimization of Catalyst 1a (Table 2.2, Entries 1-9)

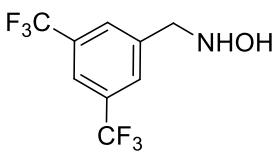
A 5-mL round bottom flask was charged with a stir bar, **1a** (0.2 equiv.), solvent (1 M relative to *N*-benzylhydroxylamine), *N*-benzylhydroxylamine (1 equiv.), and *N*-benzyl-*N*-allylamine (1.5 equiv.). The reaction was stirred at room temperature for 24 hours. An NMR yield was obtained using 1,4-dimethoxybenzene as standard. 1,1'-Carbonyldiimidazole (2-2.5 equiv.) was then added to the mixture. After 2 hours the crude reaction mixture was concentrated under reduced pressure and the cyclic compound purified by column chromatography and the enantiomeric excess determined by chiral HPLC. (See for General Procedure III for derivatization procedures to determine percent enantiomeric excess).

Substrate Synthesis

N-Hydroxylamines (Table 2.3, 1.1a – 1.1f)

N-Alkylhydroxylamines were prepared by reductive amination of the corresponding oximes according to the method of House and Lee.[59] All hydroxylamines prepared have been previously characterized in the literature except **1.1d**.

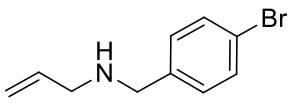
1-[3,5-bis(Trifluoromethyl)phenyl]-*N*-hydroxymethanamine (1.1d)



Prepared by reductive amination of the corresponding oxime according to the method of House and Lee.[59] ^{1}H NMR (400 MHz, $CDCl_3$) 7.87-7.90 (m, 3H), 4.93 (br s, 1H), 4.17 (s, 2H). δ ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5, 131.9, 131.5, 129.0, 128.9, 124.7, 122.0, 121.52, 121.49, 121.45, 121.4, 56.9. IR (film): 3119, 2925, 2857, 1690, 1322, 1067, 784 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{20}N_2O_4$ $[M]^+$: 259.0432 Found: 259.0432.

N-Allylic Amines (Table 2.4, 1.2c & 1.2d)

N-(4-Bromobenzyl)prop-2-en-1-amine (1.2c)

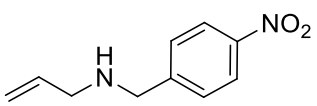


Allylamine (2.00 g, 35 mmol) was added to a 100 mL round-bottom flask equipped with a magnetic stir bar and dissolved in CH_2Cl_2 (25 mL). 4-Bromobenzylbromide (4.37 g, 17.5 mmol) dissolved in CH_2Cl_2 (25 mL) was added dropwise over 3 hours. The reaction was allowed to stir for an additional 2 hours before concentrating the mixture under reduced pressure. Diethyl ether (50 mL) and 2M NaOH (50 mL) were added to the residue. The aqueous layer was extracted twice more with diethyl ether (50 mL). The collected organics

[59] (a) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863

were then washed with water, brine, and dried over Na_2SO_4. After column chromatography (Et_2O) the title compound was obtained as a clear oil (2.57 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 5H), 4.27 (d, J = 14.0 Hz, 1H), 3.89 (d, J = 14.0 Hz, 1H), 3.26-3.10 (m, 3H), 1.20 (d, J = 6.20 Hz, 3H). Spectral data was consistent with literature.[60]

_N_-(4-Nitrobenzyl)prop-2-en-1-amine (1.2 d)



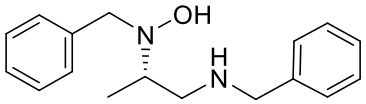
Allylamine (2.00 g, 35.0 mmol) was added to a 100 mL round-bottom flask equipped with a magnetic stir bar and dissolved in CH_2Cl_2 (25 mL). 4-Nitrobenzylbromide (3.78 g, 17.5 mmol) dissolved in CH_2Cl_2 (25 mL) was added dropwise over 3 hours. The reaction was allowed to stir for an additional 2 hours before concentrating the mixture under reduced pressure. Diethyl Ether (50 mL) and 2M NaOH (50 mL) were added to the residue. The aqueous portion was extracted twice more with diethyl ether (50 mL). The collected organics were then washed with water, brine, and dried over Na_2SO_4. The indicated compound was purified by column chromatography (Et_2O) giving a colorless oil (2.05 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 5H), 4.27 (d, J = 14.0 Hz, 1H), 3.89 (d, J = 14.0 Hz, 1H), 3.26-3.10 (m, 3H), 1.20 (d, J = 6.20 Hz, 3H). Spectral data was consistent with literature.[60]

General Procedure I for Tethered Hydroaminations of Allylic Amines with _N_-Alkylhydroxylamines (Table 2.3, Entries 1-6 and Table 2.4, Entries 1-7)

A 5-mL round bottom flask was charged with a stir bar, hydroxylamine (1 equiv.), C_6F_6 (1.0 M to hydroxylamine), amine (1.5 equiv.) and then **1a** (0.2 equiv.). The reaction was stirred at room temperature for 24 hours. The crude reaction mixture was concentrated under reduced pressure and purified by flash column chromatography to give the corresponding *N*,*N*-dialkylhydroxylamine products (See for General Procedure III for derivatization procedures to determine percent enantiomeric excess).

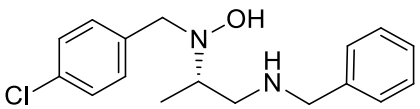
(*S*) - N^1,N^2-Dibenzyl-N^2-hydroxypropane-1,2-diamine – (2.3a) - (Table 2.3, Entry 1)

Following general procedure I using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) the



indicated compound was purified by flash column chromatography on silica gel using (1 % Et_3N/10 % MeOH/CH_2Cl_2) to give a pale yellow oil (0.270 g, 91%). Spectral data was consistent with literature.[52]

(*S*)-N^1-Benzyl-N^2-(4-chlorobenzyl)-N^2-hydroxypropane-1,2-diamine- (2.3b) - (Table 2.3, Entry 2)

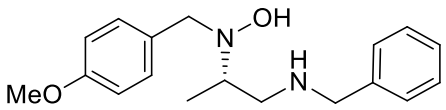


Following general procedure I using *N*-4-chlorobenzylhydroxylamine (0.157 g, 1.27 mmol) the indicated compound was purified by flash column chromatography on silica gel (gradient 1% MeOH/CH_2Cl_2 to 1 % Et_3N/5 % MeOH/CH_2Cl_2). The title compound was obtained as a pale yellow oil (0.314 g, 81%). TLC R_f 0.25 (1 % MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ

[60] Tehrani, K. A.; Van, T. N.; Karikomi, M.; Rottiers, M.; Kimpe, N. D. *Tetrahedron* **2002**, *58*, 7145.

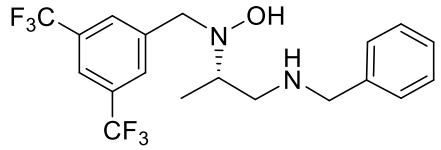
7.36-7.22 (m, 9H), 3.87 (d, J = 16 Hz, 1H), 3.76-3.61 (m, 3H), 3.07-2.96 (m, 1H), 2.85-2.76 (m, 1H), 2.70-2.59 (m, 1H), 1.10 (d, J = 4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 136.9, 132.9, 130.6, 128.5, 128.4, 128.3, 127.3, 59.7, 59.3, 53.3, 52.4, 12.0; IR (film): 2930, 2842, 1491, 1261, 1088, 750 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{17}H_{21}N_2OCl$ $[M]^+$: 304.1342. Found: 304.1347.

(*S*)-*N*^{1}-Benzyl-*N*^{2}-hydroxy-*N*^{2}-(4-methoxybenzyl)propane-1,2-diamine – (2.3c) - (Table 2.3, Entry 3)



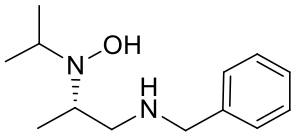
Following general procedure I using *N*-4-methoxybenzylhydroxylamine (0.153 g, 1.00 mmol). The indicated compound was purified by flash column chromatography on silica gel (gradient 1% $MeOH/CH_2Cl_2$ to 1 % Et_3N/5 % $MeOH/CH_2Cl_2$). The title compound was obtained as a pale yellow oil (0.300 g, 86%). TLC R_f 0.18 (10% $MeOH/CH_2Cl_2$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.17 (m, 8H), 6.83 (d, J = 8.4 Hz, 2H), 3.84 (d, J = 12.8 Hz, 1H), 3.76 (s, 3H), 3.68-3.55 (m, 3H), 3.04-2.91 (m, 1H), 2.82-2.71 (m, 1H), 2.59-2.47 (m, 1H), 1.05 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 154.6, 136.2, 130.7, 128.7, 128.1, 127.7, 127.1, 113.8, 58.3, 55.2, 51.5, 51.3, 14.2; IR (film): 1603, 1512, 1451, 1250, 1166, 1098, 1026, 752, 699 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{18}H_{24}N_2O_2$ $[M]^+$: 300.1838. Found: 300.1835.

(*S*) - *N*^{1}-Benzyl-*N*^{2}-[3,5-bis(trifluoromethyl)benzyl]-*N*^{2}-hydroxypropane-1,2-diamine - (2.3d) - (Table 2.3, Entry 4)



Following general procedure I using 1-[3,5-bis(trifluoromethyl)phenyl]-*N*-hydroxymethanamine (0.259 g, 1.00 mmol) the indicated compound was purified by flash column chromatography on silica gel using (1 % Et_3N/10 % $MeOH/CH_2Cl_2$) to give a pale yellow oil (0.406 g, 82%). Following General Procedure II using 1-[3,5-bis(trifluoromethyl)phenyl]-*N*-hydroxymethanamine (0.0687 g, 0.265 mmol) gave (0.0797 g, 74%). TLC R_f 0.17 (10 % $MeOH/CH_2Cl_2$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85-7.74 (4H, m), 7.36-7.25 (m, 4H), 4.12 (s, 1H), 3.98 (d, J = 14, 1H), 3.82-3.68 (m, 3H), 2.88-2.72 (m, 2H), 1.12 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.4, 140.0, 131.3, 129.4, 128.6, 128.3, 127.4, 123.4, 121.1, 60.3, 59.3, 53.4, 52.5, 12.7 ppm; IR (film): 1378, 1276, 1096, 913, 705, 682; HRMS (EI): Exact mass calcd for $C_{19}H_{20}F_6N_2O$ $[M]^+$: 406.1480. Found: 406.1528.

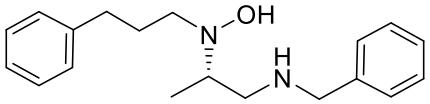
(*S*)-*N*^{1}-Benzyl-*N*^{2}-hydroxy-*N*^{2}-(propan-2-yl)propane-1,2-diamine – (2.3e) - (Table 2.3, Entry 5)



Following general procedure I using *N*-isopropylhydroxylamine (0.0445 g, 0.316 mmol) the indicated compound was purified by flash column chromatography on silica gel (gradient 1% $MeOH/CH_2Cl_2$ to 1 % Et_3N/5 % $MeOH/CH_2Cl_2$). The title compound was obtained as a pale yellow oil (0.0480 g, 60%).TLC R_f 0.22 (5 % $MeOH/CH_2Cl_2$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.20 (m, 5H), 3.85-3.72 (m, 2H), 3.18-3.05 (m, 1H), 3.04-2.93 (m, 1H), 2.88-2.78 (m, 1H), 2.65-2.54 (m, 1H), 1.13 (d, J = 4 Hz, 3H), 0.97 (t, J = 4 Hz, 6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 131.6, 130.0,

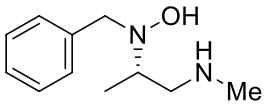
128.4, 127.3, 60.5, 59.3, 52.6, 52.3, 11.7; IR (film): 1444, 1383, 744, 695 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{22}N_2O$ [M^+] 222.1732. Found: 222.1731.

(*S*)-*N*^{1}-Benzyl-*N*^{2}-hydroxy-*N*^{2}-(3-phenylpropyl)propane-1,2-diamine – (2.3f) - (Table 2.3, Entry 6)



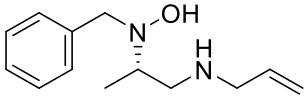
Following general procedure I using *N*-(3-phenylpropyl)hydroxylamine (0.151 g, 1.00 mmol) the indicated compound was purified by flash column chromatography on silica gel using (1 % Et_3N/10 % MeOH/CH_2Cl_2) to give a pale yellow oil (0.188 g, 63%). Following General Procedure II using *N*-(3-phenylpropyl)hydroxylamine (0.0755 g, 0.500 mmol) gave (0.0564 g, 60%). TLC R_f 0.15 (10 % MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.10 (m, 10H), 3.76 (q, *J* = 13.2 Hz, 2H), 2.99-2.87 (m, 1H), 2.87-2.71 (m, 2H), 2.71-2.59 (m, 3H), 2.59-2.45 (m, 1H), 1.98-1.83 (m, 2H), 2.64 (dd, *J* = 12.2, 4.0 Hz, 1H), 1.11 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 128.5, 128.4, 128.3, 128.3, 127.2, 125.7, 60.1, 55.5, 53.6, 52.8, 33.5, 30.9, 28.9; IR (film): 3232, 2897, 1601, 1593, 1408 cm^{-1} ; HRMS (EI): Exact mass calcd for $C_{19}H_{26}N_2O$ [$M]^+$: 298.2045. Found: 298.2010.

(*S*)-*N*^{2}-Benzyl-*N*^{2}-hydroxy-*N*^{1}-methylpropane-1,2-diamine – (2.4a) - (Table 2.4, Entry 1)



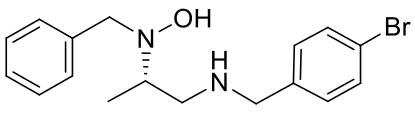
Following general procedure I using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) and **1.2a** the indicated compound was purified by flash column chromatography on silica gel using (1 % Et_3N/10 % MeOH/CH_2Cl_2) to give a pale yellow oil (0.194 g, 91%). Spectral data was consistent with literature.[52]

(*S*)-*N*^{2}-Benzyl-*N*^{2}-hydroxy-*N*^{1}-(prop-2-en-1-yl)propane-1,2-diamine – (2.4b) - (Table 2.4 Entry 2)



Following general procedure I using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) and **1.2b** the indicated compound was purified by flash column chromatography on silica gel (1 % Et_3N/10 % MeOH/CH_2Cl_2) to give a pale yellow oil (0.187 g, 85%). Following General Procedure II using *N*-benzyhydroxlamine (0.123 g, 0.999 mmol) gave (0.167 g, 76%). Spectral data was consistent with literature.[52]

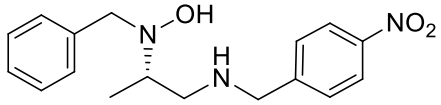
(*S*)-*N*^{2}-Benzyl-*N*^{1}-(4-bromobenzyl)-*N*^{2}-hydroxypropane-1,2-diamine – (2.4c) - (Table 2.4 Entry 3)



Following general procedure I using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) and **1.2c** the indicated compound was purified by flash column chromatography on silica gel (gradient 1% MeOH/CH_2Cl_2 to 1 % Et_3N/5 % MeOH/CH_2Cl_2). The title compound was obtained as a pale yellow oil (0.282 g, 81%). TLC R_f 0.15 (5 % MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (d, *J* = 6 Hz, 2H), 7.34-7.20 (m, 5H), 7.07 (d, *J* = 6 Hz, 2H), 3.90 (d, *J* = 15 Hz, 1H), 3.70 (d, *J* = 15 Hz, 1H), 3.51 (s, 2H), 3.04-2.89 (m, 1H), 2.76-2.64 (m, 1H), 2.53-2.39 (m, 1H), 1.06 (d, *J* = 6.0 Hz, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 131.6, 130.0, 129.3, 128.4, 127.3, 60.5, 59.3,

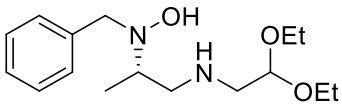
52.6, 52.3, 11.7; IR (film)**:** 1487, 1451, 1071, 1012 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{17}H_{21}N_2OBr$ $[M]^+$: 348.0837. Not found. Exact mass calcd for $C_9H_{12}NO$ $[M\text{-}BnNHCH_2]^+$: 150.0919. Found 150.0929.

(*S*)-*N*^{2}-Benzyl-*N*^{2}-hydroxy-*N*^{1}-(4-nitrobenzyl)propane-1,2-diamine – (2.4d) - (Table 2.4 Entry 4)



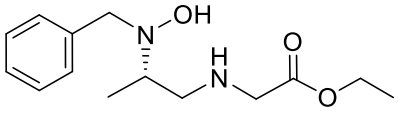
Following general procedure I using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) and **1.2d** the indicated compound was purified by flash column chromatography on silica gel (gradient 1% $MeOH/CH_2Cl_2$ to 1 % Et_3N/5 % $MeOH/CH_2Cl_2$). The title compound was obtained as a pale yellow oil (0.315 g, 83%). TLC R_f 0.19 (1 % $MeOH/CH_2Cl_2$); ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 4.0 Hz, 2H), 7.40-7.25 (m, 5H), 3.98 (d, J = 12 Hz, 1H), 3.88-3.80 (m, 3H), 3.14-3.02 (m, 1H), 2.86-2.75 (m, 1H), 2.67-2.54 (m, 1H), 1.15 (d, J = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 147.1, 138.2, 129.3, 128.7, 128.4, 127.3, 123.7, 60.7, 60.2, 53.1, 53.0, 46.1 IR (film): 1606, 1520, 1347, 1109, 912, 854, 737, 699 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{17}H_{21}N_3O_3$ $[M]^+$: 315.1583 Found: 315.1555

(*S*) - *N*^{2}-Benzyl-*N*^{1}-(2,2-diethoxyethyl)-*N*^{2}-hydroxypropane-1,2-diamine – (2.4e) -(Table 2.4 Entry 5)



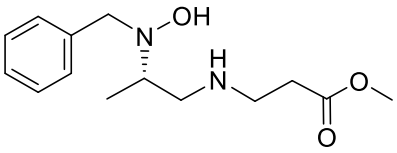
Following general procedure I using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) and **1.2e** the indicated compound was purified by flash column chromatography on silica gel using (1 % Et_3N/10 % $MeOH/CH_2Cl_2$) to give a pale yellow oil (0.183 g, 62%). Following General Procedure II using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) gave (0.150 g, 51%). Spectral data was consistent with literature.[52]

(*S*) - Ethyl ({2-[benzyl(hydroxy)amino]propyl}amino)acetate – (2.4f) -(Table 2.4 Entry 6)



Following general procedure I using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) and **1.2f** the indicated compound was purified by flash column chromatography on silica gel using (1 % Et_3N/10 % $MeOH/CH_2Cl_2$) to give a pale yellow oil (0.199 g, 75%). Following general procedure II using *N*-benzylhydroxylamine (0.123 g, 0.999 mmol) gave (0.188 g, 71%). TLC R_f 0.25 (1 % $MeOH/CH_2Cl_2$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.14 (m, 5H), 4.13 (q, J = 7.2, 6.9 Hz, 2H), 3.97 (d, J = 13.2 Hz, 1H), 3.67 (d, J = 13.2 Hz, 1H), 3.21 (s, 2H), 3.08-2.91 (m, 1H), 2.63 (t, J = 9.6 Hz, 1H), 2.56-2.44 (m, 1H), 1.23 (t, J = 6.9 Hz, 3H), 1.07 (d, J = 6.6 Hz, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 173.1, 138.7, 129.2, 128.1, 126.9, 60.9, 59.7, 59.5, 52.4, 49.8, 14.1, 10.7; IR (film): 2994, 2873, 1739, 1649, 1455, 1200 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{22}N_2O_3$ $[M]^+$: 266.1630. Found: 266.1634.

(*S*) - Methyl 3-({2-[benzyl(hydroxy)amino]propyl}amino)propanoate – (2.4g) - (Table 2.4, Entry 7)

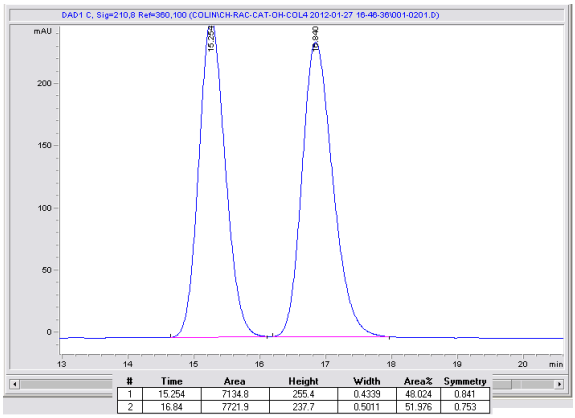


Following general procedure I using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) and **1.2g** the indicated compound was purified by flash column chromatography on silica gel using (1 % Et_3N/10 % MeOH/CH_2Cl_2) to give a pale yellow oil (0.194 g, 73%). Following General Procedure II using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) gave (0.175 g, 66%). TLC R_f 0.25 (1 % MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.21 (m, 5H), 3.94 (d, J = 12.9 Hz, 1H), 3.68 (d, J = 13.5 Hz, 1H), 3.63 (s, 3H), 3.02-2.91 (m, 1H), 2.85-2.68 (m, 3H), 2.55-2.36 (m, 3H), 1.07 (d, J = 6.3 H, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 138.5, 129.3, 128.2, 127.0, 60.5, 59.3, 52.8, 51.6, 44.6, 33.9, 11.4; HRMS (EI): Exact mass calcd for $C_{14}H_{22}N_2O_3$ $[M]^+$: 266.1630. Found: 266.1624

Epimerization of Catalyst 1a (Scheme 2.12)

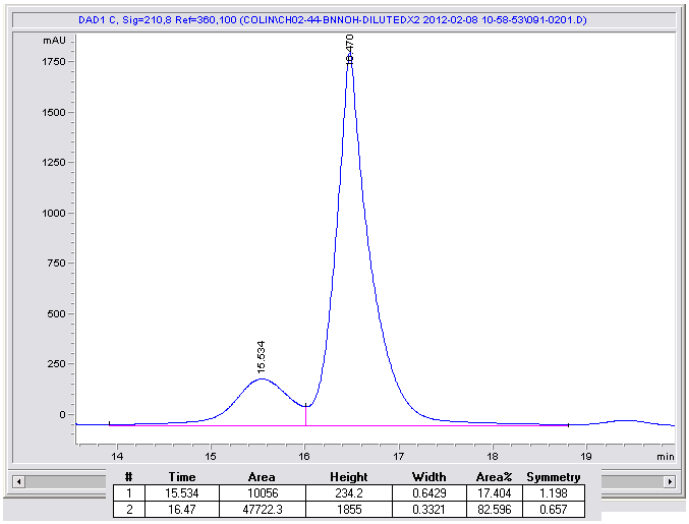
To probe catalyst **1a**'s tendency to epimerize under the reaction conditions, catalyst **1a** (0.064 g, 0.25 mmol, 1 equiv.) was stirred either with (0.0077 g, 0.063 mmol, 0.25 equiv) of *N*-benzylhydroxylamine or *N*-benzylallylamine (9.8 µL, 0.063 mmol, 0.25 equiv) in benzene (1M) for 24 hours. The reaction mixture was then treated with $LiAlH_4$ (1.5 equiv.) and allowed to stir for 30 minutes before drop wise addition of sat. sodium potassium tartrate. The organic was separated with water and extracted three times with Et_2O, washed with water, brine, and dried over sodium sulphate. The solvent was then removed and the percent enantiomeric excess determined by chiral HPLC. Chiral HPLC: ChiralPak OD-H, *i*-PrOH/hexane = 2/98, 1.0 mL/min, 210 nm, Catalyst **1a** t_{major} = 16.8 min, t_{minor} = 15.3 min.

Racemic



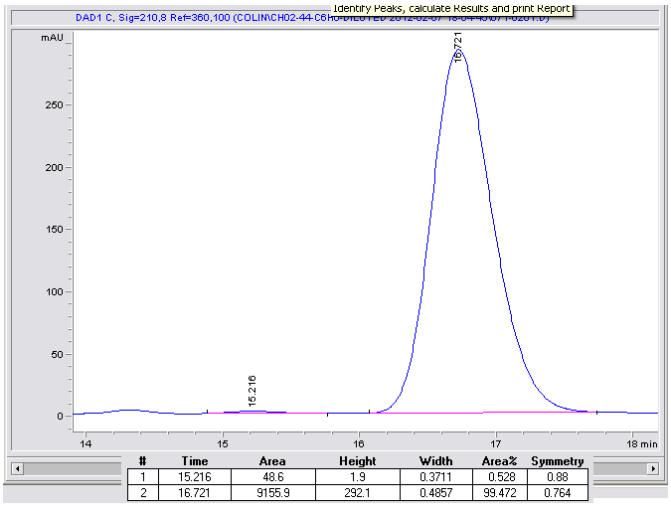
#	Time	Area	Height	Width	Area%	Symmetry
1	15.254	7134.8	255.4	0.4339	48.024	0.841
2	16.84	7721.9	237.7	0.5011	51.976	0.753

24 hours *N*-benzylhydroxylamine



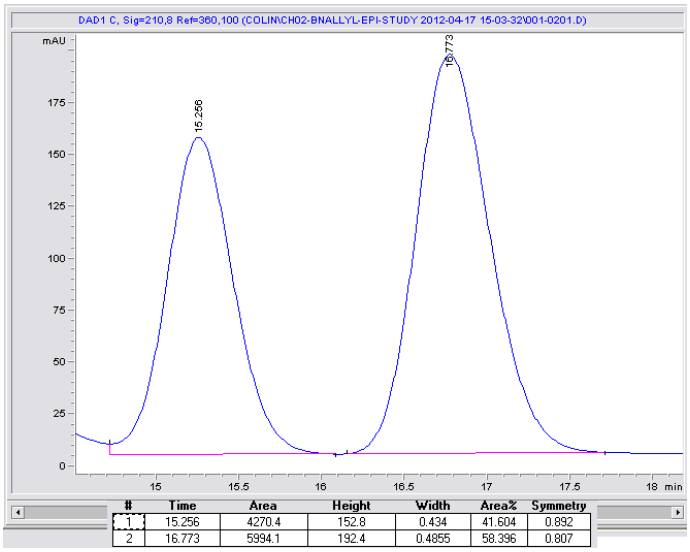
#	Time	Area	Height	Width	Area%	Symmetry
1	15.534	10056	234.2	0.6429	17.404	1.198
2	16.47	47722.3	1855	0.3321	82.596	0.657

24 hours Benzene



#	Time	Area	Height	Width	Area%	Symmetry
1	15.216	48.6	1.9	0.3711	0.528	0.88
2	16.721	9155.9	292.1	0.4857	99.472	0.764

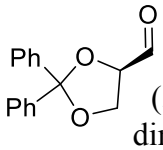
24 hours *N*-benzylallylamine



#	Time	Area	Height	Width	Area%	Symmetry
1	15.256	4270.4	152.8	0.434	41.604	0.892
2	16.773	5994.1	192.4	0.4855	58.396	0.807

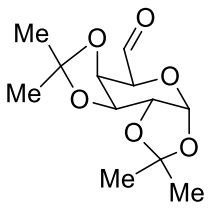
Preparation of Chiral Aldehydes (Figure 2.5)

(*R*)-2,2-Diphenyl-1,3-dioxolane-4-caraldehyde (1a)



Prepared from D-Mannitol according to a modified procedure of Banerjee et al.[61] A solution of the sugar (2.0 g, 10.1 mmol), benzophenone dimethyl acetal (5.01 g, 21.9 mmol) and $SnCl_2$ (0.025g, 0.13 mmol) in freshly distilled dimethoxyethane (50 ml) was heated at reflux for 16 hours. Solvent was evaporated and the product was purified by column chromatography (30% EtOAc/Pet. Ether). The protected diol (0.3074 g, 0.6 mmol) was dissolved in CH2Cl2 and cooled down to 0 ^{o}C. Then $Pb(OAc)_4$ (0.401 g, 0.9 mmol) was added. The mixture was stirred at 0 ^{o}C for 30 min and the resulting mixture was filtered through Celite. The solution was evaporated in vacuo to dryness. The oil was purified by column chromatography (30% EtOAc/Pet. Ether). Spectral data was consistent with literature.[61]

(3a*R*,5*S*,5a*R*,8a*R*,8b*R*)-2,2,7,7-Tetramethyltetrahydro-3a*H*-bis[1,3]dioxolo[4,5-*b*:4',5'-*d*]pyran-5-carbaldehyde (1e)

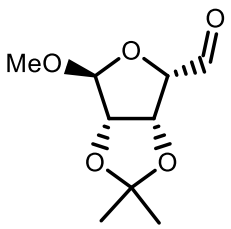


To a 50 mL round bottom flask equipped with a magnetic stirrer is added 1,2:3,4-di-*O*-isopropylidene-beta-D-fructopyranose (1.01 g, 3.84 mmol), CH_2Cl_2 (25 mL). The mixture is then cooled to 0 °C in an ice bath followed by DMSO (2.10 mL, 14.3 mmol), Et_3N (2.56 mL, 17.9 mmol), and SO_3•pyridine (2.27 g, 14.3 mmol). The mixture was stirred at 0 °C for 2 hours before quenching with $NaHCO_3$. The organics were extracted 3 times with CH_2Cl_2 (40 mL), washed with water, brine, and dried over Na_2SO_4 and concentration under reduced pressure. The aldehyde was purified by flash column chromatography on silica gel (30% EtOAc/ Hexane) giving a clear oil (0.605 g, 61%). R_f: 0.17

[61] Banerjee, A.; Schepmann, D.; Kohler, J.; Wurthwein, E.; Wunsch, B. *Bioorg. Med. Chem*. **2010**, *18*, 7855.

(30% EtOAc/ Hexane). Spectral data was consistent with literature.[62] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.63 (s, 1H), 5.68 (d, *J* = 4.8 Hz, 1H), 4.63 (m, 2H), 4.39 (dd, *J* = 2.4 Hz, 1H), 4.19 (d, *J* = 2.0 Hz, 1H), 1.52 (s, 3H), 1.45 (s, 3H), 1.36 (s, 3H), 1.32 (s, 3H).

(3a*S*,4*S*,6*S*,6a*S*)-6-Methoxy-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxole-4-carbaldehyde (1h)



Prepared according to Barton *et al.* from D-Mannose.[63] The aldehyde was purified by flash column chromatography on silica gel using Hexane/EtOAc (40:60). Rf: 0.23 (30% EtOAc/ Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (d, *J* =1.2 Hz, 1H), 5.10-5.04 (m, 2H), 4.61 (d, *J* = 5.6 Hz, 1H), 4.38 (d, *J* = 4 Hz, 1H), 3.36 (s, 3H), 1.43 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 113.5, 107.8, 84.5, 83.9, 80.8, 55.0, 25.8, 24.6. IR (film) 1634, 1379, 1090 cm^{-1}. HRMS (EI): Exact mass calcd for $C_9H_{14}O_5$ $[M]^+$: 202.0841. Found: 202.0839.

Procedures for Screening Chiral Aldehydes (1a-1h) as Potential Catalysts (Table 2.5, Entries 1-8)

A 5 mL round bottom flask was charged with a stir bar, selected aldehyde **(1a-1h)** (0.2 mmol), C_6H_6 or C_6F_6 (1 mL) *N*-benzylhydroxylamine (1 mmol) and *N*-benzyl-*N*-allylamine (1.5 mmol). The reaction was stirred at room temperature for 24 hours. 1,4-dimethoxybezene was added (0.20-0.25 equiv.) as an internal standard, which was used to calculate an NMR yield. 1,1'-Carbonyldiimidazole (0.3 mmol) was then added to the mixture. After 2 hours the crude reaction mixture was concentrated under reduced pressure and the cyclic compound purified by column chromatography and the enantiomeric excess determined by chiral HPLC. Positive enantiomeric excess refers to *S* enantiomer (See General Procedure III for derivatization procedures to determine percent enantiomeric excess).

Optimization using 1h (Table 2.6, Entries 1-7)

A 5 mL round bottom flask was charged with a stir bar, aldehyde **1h** (0.2 mmol), solvent (1 mL) *N*-benzylhydroxylamine (1 mmol) and *N*-benzylallylamine (1.5 mmol). The reaction was stirred at room temperature for various lengths in time and the NMR yield was determined using 1,4-dimethoxybenzene. 1,1'-Carbonyldiimidazole (0.3 mmol) was then added to the mixture. After 2 hours the crude reaction mixture was concentrated under reduced pressure and the cyclic compound purified by column chromatography and the enantiomeric excess determined by chiral HPLC (See General Procedure III for derivatization procedures to determine percent enantiomeric excess).

General Procedure II for Aldehyde Catalysis using 1h (Table 2.7, Entries 1-7)

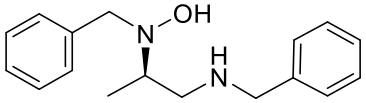
A 5-mL round bottom flask was charged with a stir bar, **1h** (0.2 equiv.), C_6H_6 (1M to hydroxylamine), hydroxylamine (1 equiv.), and amine (1.5 equiv.). The reaction was stirred at room temperature for 72 hours. The crude reaction mixture was concentrated under reduced

[62] Serra, F.; Olszewski, T. K.; Grison, C; Coutrot, P.; Esteve-Quelquejeu, M.; Herson, P. *Eur. J. Org. Chem.* **2011**, *10,* 1841.
[63] Barton, D. H. R.; Gero, S. D.; Quiclet-Sire, B.; Samadi, M. *Tetrahedron: Asymmetry* **1994**, *5*, 2123.

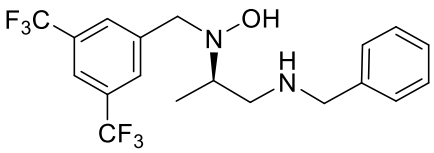
pressure and purified by column chromatography to give the corresponding *N*,*N*-dialkylhydroxylamine products (See General Procedure III for derivatization procedures to determine percent enantiomeric excess).

***(R)* - N^1,N^2-Dibenzyl-N^2-hydroxypropane-1,2-diamine – (2.7a) - (Table 2.7, Entry 1)**

Following General Procedure II using *N*-benzylhydroxylamine (0.0615 g, 0.500 mmol) gave (0.107 g, 79%). Spectral data was consistent with literature.[52]

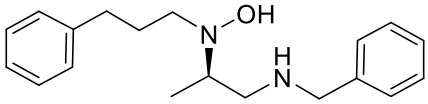


***(R)* - N^1-Benzyl-N^2-[3,5-bis(trifluoromethyl)benzyl]-N^2-hydroxypropane-1,2-diamine – (2.7b) - (Table 2.7, Entry 2)**



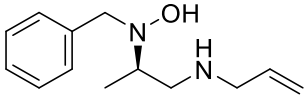
Following General Procedure II using 1-[3,5-bis(trifluoromethyl)phenyl]-*N*-hydroxymethanamine (0.0687 g, 0.265 mmol) gave (0.0797 g, 74%). Spectral data was same as **2.3d**.

***(R)* - N^1-Benzyl-N^2-hydroxy-N^2-(3-phenylpropyl)propane-1,2-diamine – (2.7c) - (Table 2.7, Entry 3)**



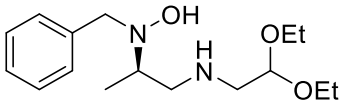
Following General Procedure II using *N*-(3-phenylpropyl)hydroxylamine (0.0755 g, 0.500 mmol) gave (0.0564 g, 60%). Spectral data was same as **2.3f**.

***(R)* - N^2-Benzyl-N^2-hydroxy-N^1-(prop-2-en-1-yl)propane-1,2-diamine (2.7d) - (Table 2.7, Entry 4)**



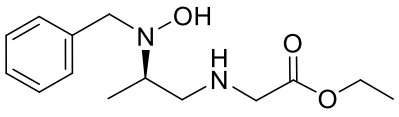
Following General Procedure II using *N*-benzyhydroxylamine (0.123 g, 0.999 mmol) gave (0.167 g, 76%). Spectral data was consistent with literature.[52]

***(R)* - N^2-Benzyl-N^1-(2,2-diethoxyethyl)-N^2-hydroxypropane-1,2-diamine – (2.7e) - (Table 2.7, Entry 5)**



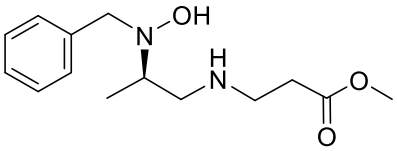
Following General Procedure II using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) gave (0.150 g, 51%). Spectral data was consistent with literature.[52]

***(R)* - Ethyl ({2-[benzyl(hydroxy)amino]propyl}amino)acetate (2.7f) - (Table 2.7, Entry 6)**



Following general procedure II using *N*-benzylhydroxylamine (0.123 g, 0.999 mmol) gave (0.188 g, 71%). Spectral data was same as **2.4f**.

***(R)* - Methyl 3-({2-[benzyl(hydroxy)amino]propyl}amino)propanoate (2.7g) - (Table 2.7, Entry 7)**

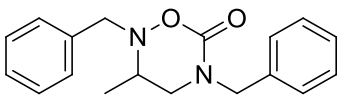


Following General Procedure II using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) gave (0.175 g, 66%). Spectral data was same as **2.4g**.

General Procedure III for Determining the Enantiomeric Excess of Hydroamination Products 2.3a -2.3f (Table 2.3, Entries 1-6), 2.4a – 2.4g (Table 2.4, Entries 1-7), and 2.7a – 2.7g (Table 2.7, Entries 1-7)

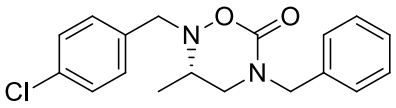
The hydroamination product (1 equiv.) was dissolved in CH_2Cl_2 (0.5 M) then 1,1'-carbonyldiimidazole (CDI) (1.5-2.5 equiv.) was added and the reaction stirred for 3-24 hours. After completion the reaction mixture was concentrated under reduced pressure and purified by column chromatography (reaction yields are unoptimized).

(*R* & *S*) - 2,5-Dibenzyl-3-methyl-1,2,5-oxadiazinan-6-one (3a).



Following General Procedure III using **2a** (0.0861 g, 0.322 mmol) the indicated compound was purified by flash column chromatography on silica gel using (50% EtOAc/Hexane) to give a white solid (0.0868 g, 91%). Enantiomeric ratio of 98.5/1.5 was obtained using **Catalyst 1a** and 94/6 enantiomeric ratio using **Catalyst 1h**. TLC R_f 0.28 (30 % EtOAc/Petroleum Ether). Spectral data was consistent with literature.[52] Chiral HPLC: ChiralPak AD-H, *i*-PrOH/hexane = 5/95, 1.0 mL/min, 210 nm; Catalyst **1b** t_{major} = 43.3 min, t_{minor} = 45.8 min, Catalyst **1h** t_{major} = 43.6 min, t_{minor} = 40.9 min.

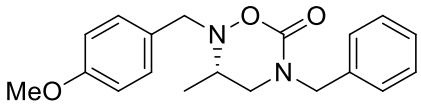
(*S*) - 5-Benzyl-2-(4-chlorobenzyl)-3-methyl-1,2,5-oxadiazinan-6-one (3b).



Following General Procedure III using **2b** (0.0752 g, 0.247 mmol) the indicated compound was purified by flash column chromatography on silica gel using (50% EtOAc/Hexane) to give a white solid (0.0621 g, 76%) and 97/3 enantiomeric ratio. R_f 0.6 (95:5 CH_2Cl_2: MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.22 (m, 10H), 3.87 (d, J = 13 Hz, 1H), 3.76-3.61 (m, 3H), 3.07-2.96 (m, 1H), 2.84-2.75 (m, 1H), 2.69-2.57 (m, 1H), 4.42 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 136.0, 133.9, 133.4, 130.5, 128.7, 128.5, 128.1, 127.8, 58.2, 54.6, 51.5, 51.3, 14.2; IR (film): 2971, 2922, 2849, 1702, 1455, 1087, 752 cm^{-1}; HRMS (EI): $C_{18}H_{19}N_2O_2Cl$ $[M]^+$: 330.1135. Found:

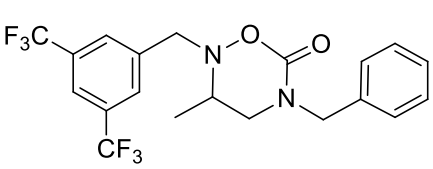
330.1120. Chiral HPLC: ChiralPak OJ-H, *i*-PrOH/hexane = 5/95, 1.0 mL/min, 210 nm, t_{major} = 87.5 min, t_{minor} = 95.8 min.

(*S*)-5-Benzyl-2-(4-methoxybenzyl)-3-methyl-1,2,5-oxadiazinan-6-one (3c).



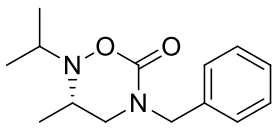
Following General Procedure III using **2c** (0.0643 g, 0.214 mmol) the indicated compound was purified by flash column chromatography on silica gel using (50% EtOAc/Hexane) to give a white solid (0.0510 g, 73%) and 96/4 enantiomeric ratio. R_f 0.6 (95:5 CH_2Cl_2: MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 7H), 6.88 (d, *J* = 8.8 Hz, 2H), 4.73-4.37 (m, 2H), 4.26 (d, *J* = 14 Hz, 1H), 3.88 (d, *J* = 14 Hz, 1H), 3.81 (s, 3H), 3.31-3.09 (m, 1H), 3.09-2.90 (m, 1H), 1.15 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8, 138.9, 130.5, 128.4, 127.2, 113.7, 59.7, 55.2, 53.0, 52.0, 11.4; IR (film): 3059, 2837, 1708, 1613, 1586, 1514, 1485, 1443, 1363, 1248, 1179, 1141, 1123, 1110, 1076, 825 cm^{-1}; HRMS (EI): $C_{19}H_{22}N_2O_3$ $[M]^+$: 326.1630. Found: 326.1629. Chiral HPLC: ChiralPak AD-H, *i*-PrOH/hexane = 5/95, 1.0 mL/min, 210 nm, t_{major} = 62.3 min, t_{minor} = 67.1 min.

(*R* & *S*)-5-Benzyl-2-(3,5-bis(trifluoromethyl)benzyl)-3-methyl-1,2,5-oxadiazinan-6-one (3d)



Following General Procedure III using **2d** (0.0521 g, 0.128 mmol) the indicated compound was purified by flash column chromatography on silica gel using (50% EtOAc/Hexane) to give a white solid (0.0376 g, 68%). Enantiomeric ratio of 91/9 was obtained using **Catalyst 1a** and 96/4 enantiomeric ratio using **Catalyst 1h**. R_f 0.53 (1:1 EtOAc:Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.74 (m, 3H), 7.38-7.25 (m, 5H), 4.62 (d, *J* = 11 Hz, 1H), 4.45 (d, *J* = 11Hz, 1H), 4.29 (d, *J* = 11 Hz, 1H), 3.92 (d, *J* = 11 Hz, 1H), 3.35-3.13 (m, 2H), 3.13-3.02 (m, 1H), 1.19 (d, *J* = 4.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ;154.0, 138.7, 136.0, 132.2, 131.9, 131.6, 131.2,128.8, 128.2, 127.9, 122.0, 121.8, 121.7, 121.6, 58.1, 55.7, 51.6, 51.3. 29.7; IR (film); 2971, 2914, 2816, 1622, 1496, 1455, 1368, 1368, 1280, 1185, 1132, 901, 842. HRMS (EI): $C_{20}H_{18}N_2O_2F_6$ $[M]^+$: 432.1272 Found: 432.1300. Chiral HPLC: ChiralPak AD-H, *i*-PrOH/hexane = 5/95, 1.0 mL/min, 210 nm; Catalyst **1b** t_{major} = 28.1 min, t_{minor} = 37.5 min; Catalyst **1h** t_{major} = 38.5 min, t_{minor} = 31.0 min.

(*S*)-5-Benzyl-2-isopropyl-3-methyl-1,2,5-oxadiazinan-6-one (3e)



Following General Procedure III using **2e** (0.0456 g, 0.205 mmol) the indicated compound was purified by flash column chromatography on silica gel using (50% EtOAc/Hexane) to give a yellow oil (0.0229 g, 45%) and 80/20 enantiomeric ratio using **Catalyst 1b**. R_f 0.6 (1:1 EtOAc:Hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.24 (m, 5H), 4.62 (d, *J* = 14.8 Hz, 1H), 4.42 (d, *J* = 16 Hz, 1H), 3.41-3.01 (m, 3H), 3.01-2.88 (m, 1H), 1.29 (d, *J* = 6.8 Hz, 3H), 1.10-1.01 (m, 6H) . ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 136.3, 128.7, 128.1, 127.7, 52.3, 51.7, 51.5, 20.7, 13.5 ; IR (film): 2978, 2877, 1699, 1487, 1456, 1383, 1371, 1363, 1248, 1198, 1135, 1091, 1072, 947, 750, 704 cm^{-1}; HRMS (EI): $C_{14}H_{20}N_2O_2$ $[M]^+$: 248.1525. Found: 248.1521. Chiral HPLC: ChiralPak OD-H, *i*-PrOH/hexane = 5/95, 1.0 mL/min, 210 nm, t_{major} = 17.9 min, t_{minor} = 14.4 min.

(*R* & S)-5-Benzyl-3-methyl-2-(3-phenylpropyl)-1,2,5-oxadiazinan-6-one (3f).

Following General Procedure III using **2f** (0.0394 g, 0.132 mmol) the indicated compound was purified by flash column chromatography on silica gel using (50% EtOAc/Hexane) to give a white solid (0.0158 g, 37%). Enantiomeric ratio of 85.5/14.5 was obtained using **Catalyst 1a** and 88.5/11.5 enantiomeric ratio using **Catalyst 1h**. R_f 0.6 (95:5 CH_2Cl_2: MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9, 141.6, 136.2, 128.8, 128.5, 128.4, 128.1, 127.8, 125.9, 54.2, 51.5, 33.1, 31.0, 27.3; IR (film): 2924, 1709, 1271 cm^{-1}; HRMS (EI): $C_{20}H_{24}N_2O_2$ $[M]^+$: 324.1838. Found 324.1853. Chiral HPLC: ChiralPak AD-H, *i*-PrOH/hexane = 5/95, 1.0 mL/min, 210 nm, t_{major} = 62.3 min, t_{minor} = 67.1 min.

(*S*)-2-Benzyl-3,5-dimethyl-1,2,5-oxadiazinan-6-one (3g).

Following general procedures III using **2g** (0.142 g, 0.276 mmol) the indicated compound was purified by flash column chromatography on silica gel using (1:1 EtOAc:Hexane) to give a yellow oil (0.0463 g, 76%) and 80/20 enantiomeric ratio using **Catalyst 1a**. Spectral data was consistent with literature.[52] Chiral HPLC: ChiralPak OJ-H, *i*-PrOH/hexane = 10/90, 1.0 mL/min, 210 nm, t_{major} = 28.2 min, t_{minor} = 30.7 min.

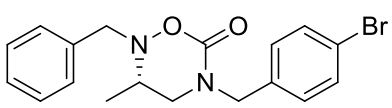
(*R* & *S*)-5-Allyl-2-benzyl-3-methyl-1,2,5-oxadiazinan-6-one (3h).

Following General Procedure III using **2h** (0.270 g, 1.23 mmol) the indicated compound was purified by flash column chromatography on silica gel using (1:1 EtOAc:Hexane) to give a yellow oil (0.226 g, 70%). Enantiomeric ratio of 81/19 was obtained using **Catalyst 1a** and enantiomeric ratio of 94/6 using **Catalyst 1h**. R_f 0.32 (1:1 EtOAc:Petroleum Ether). Spectral data was consistent with literature.[52] Chiral HPLC: ChiralPak AD-H, *i*-PrOH/hexane = 5/95, 1.0 mL/min, 210 nm, t_{major} = 36.8 min, t_{minor} = 32.5 min.

(*S*)-2-Benzyl-3-methyl-5-(4-nitrobenzyl)-1,2,5-oxadiazinan-6-one (3i).

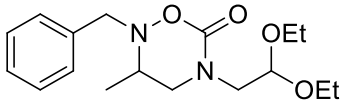
Following General Procedure III using **2i** (0.0845 g, 0.268 mmol) the indicated compound was purified by flash column chromatography on silica gel using (1:1 EtOAc:Hexane) to give an off white solid (0.0856 g, 64%) and 97.5/2.5 enantiomeric ratio using **Catalyst 1a**. R_f 0.58 (1:1 EtOAc:Hexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 12 Hz, 2H), 7.49 (d, *J* = 8 Hz, 2H), 7.44-7..29 (m, 5H), 4.72-4.56 (m, 2H), 4.34 (d, *J* = 12 Hz, 1H), 3.95 (d, *J* = 12 Hz, 1H), 3.33-3.18 (m, 1H), 3.13-3.01 (m, 1H), 1.20 (d, *J* = 8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 147.5, 143.7, 135.0, 129.2, 128.6, 128.4, 127.7, 123.9, 58.9, 52.0, 51.0; IR (film): 2975, 1653, 914, 752; HRMS (EI): $C_{18}H_{19}N_3O_4$ $[M]^+$: 314.1376. Found: 341.1384. Chiral HPLC: ChiralPak OD-H, *i*-PrOH/hexane = 20/80, 1.0 mL/min, 254 nm, t_{major} = 55.2 min, t_{minor} = 38.2 min.

(*S*)-2-Benzyl-5-(4-bromobenzyl)-3-methyl-1,2,5-oxadiazinan-6-one (3j).



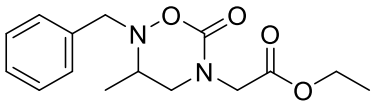
Following General Procedure III using **2j** (0.0328 g, 0.0939 mmol) the indicated compound was purified by flash column chromatography on silica gel using (1:1 EtOAc:Hexane) to give a white solid (0.0243 g, 69%) and 96/4 enantiomeric ratio using **Catalyst 1a.** R_f 0.62 (1:1 Hexane:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 5H), 4.27 (d, J = 14.0 Hz, 1H), 3.89 (d, J = 14.0 Hz, 1H), 3.26-3.10 (m, 3H), 1.20 (d, J = 6.20 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 135.3, 129.3, 128.4, 127.7, 58.9, 54.3; IR (film): 3119, 2925, 2857, 1690, 1322, 1067, 784 cm^{-1}; HRMS (EI): $C_{18}H_{19}N_2O_2Br$ $[M]^+$: 374.0630. Found: 374.0626. Chiral HPLC: ChiralPak OD-H, *i*-PrOH/hexane = 7/93, 1.0 mL/min, 210 nm, t_{major} = 69.6 min, t_{minor} = 58.4 min.

(*R* & S)-2-Benzyl-5-(2,2-diethoxyethyl)-3-methyl-1,2,5-oxadiazinan-6-one (3k)



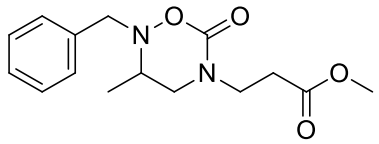
Following General Procedure III using **2k** (0.0148 g, 0.0501mmol) the indicated compound was purified by flash column chromatography on silica gel using (1:1 EtOAc/Hexane) to give a yellow oil (7.73 mg, 49%). Enantiomeric ratio of 80/20 was obtained using **Catalyst 1a** and 94/6 enantiomeric ratio using **Catalyst 1h**. R_f 0.4 (1:1 Hexane/EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) 7.39-7.21 (m, 5H), 4.71 (t, J = 5.6 Hz, 1H), 4.26 (d, J = 13.6 Hz, 1H), 3.89 (d, J = 14 Hz, 1H), 3.78-3.66 (m, 2H), 3.59-3.66 (m, 3H), 3.40-3.13 (m, 4H), 1.22-1.15 (m, 9H); δ ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.3, 135.3, 129.2, 128.4, 127.6, 101.2, 63.7, 58.9, 54.1, 51.4, 15.42, 15.37; HRMS (EI): $C_{12}H_{16}N_2O_4$ $[M]^+$: 322.1893 Found: 322.1908. Chiral HPLC: ChiralPak AD-H, *i*-PrOH/hexane = 5/95, 1.0 mL/min, 210 nm, t_{major} = 62.3 min, t_{minor} = 67.1 min.

(*R* & S)-Ethyl 2-(2-benzyl-3-methyl-6-oxo-1,2,5-oxadiazinan-5-yl)acetate (3l).



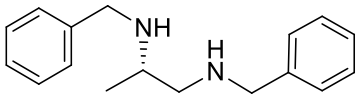
Following General Procedure III using **2l** (0.0654 g, 0.246 mmol) the indicated compound was purified by flash column chromatography on silica gel using (50% EtOAc/Hexane) to give a clear oil (0.0272 g, 38%). Enantiomeric ratio of 86/14 was obtained using **Catalyst 1a** and 95.5/4.5 enantiomeric ratio using **Catalyst 1h**. R_f 0.6 (95:5 CH_2Cl_2: MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.17 (m, 5H), 4.35-4.24 (m, 1H), 4.25-4.13 (m, 2H), 4.12-3.86 (m, 3H), 3.56-3.25 (m, 2H), 3.25-3.09 (m, 1H), 1.33-1.09 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7, 154.4, 135.2, 129.2, 128.4, 127.7, 64.4, 61.4, 58.9, 52.9, 49.1, 30.9, 25.3, 14.1; IR (film): 2912, 2856, 1647, 1274; HRMS (EI): $C_{15}H_{20}N_2O_4$ $[M]^+$: 292.1423. Found 292.1419: Chiral HPLC: ChiralPak AD-H, *i*-PrOH/hexane = 5/95, 1.0 mL/min, 210 nm, Catalyst 1b t_{major} = 35.4 min, t_{minor} = 30.0 min. Catalyst 1h t_{major} = 41.8 min, t_{minor} = 38.9 min.

(*R* & *S*)-Methyl 3-(2-benzyl-3-methyl-6-oxo-1,2,5-oxadiazinan-5-yl)propanoate (3m).



Following General Procedure III using **2m** (0.0432 g, 0.162 mmol) the indicated compound was purified by flash column chromatography on silica gel using (50% EtOAc/Hexane) to give a yellow oil (0.0175 g, 37%). Enantiomeric ratio of 91/9 was obtained using **Catalyst 1a** and 95/5 enantiomeric ratio using **Catalyst 1h**. R_f 0.6 (95:5 CH_2Cl_2: MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36-7.28 (m, 5H), 4.27 (d, J = 14.0 Hz, 1H), 3.89 (d, J = 14.0 Hz, 1H), 3.26-3.10 (m, 3H), 1.20 (d, J = 6.20 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.4, 135.3, 129.3, 128.4, 127.7, 58.9, 54.3; IR (film): 3119, 2925, 2857, 1690, 1322, 1067, 784 cm^{-1}; HRMS (EI): $C_{15}H_{20}N_2O_4$ $[M]^+$: 292.1423. Found: 292.1427. Chiral HPLC: ChiralPak OJ-H, *i*-PrOH/hexane = 10/90, 1.0 mL/min, 210 nm, Catalyst A t_{major} = 297.2 min, t_{minor} = 245.9 min, Catalyst B t_{major} = 249.0 min, t_{minor} = 379.5 min.

Assignment of Absolute Configuration of *N*-Dibenzyl-1,2-diaminopropane



(*S*)-*N*-Dibenzyl-1,2-diaminopropane. Prepared by the method of Goti and coworkers.[64] *N*-Benzyl-1-(benzylamino)-*N*-hydroxypropan-2-amine (0.340 g, 1.27 mmol) was dissolved into a 2:1 solution of EtOH and saturated aqueous NH_4Cl (9 mL) in a 25-mL round-bottomed flask equipped with a Claisen condenser and a magnetic stirring bar. Indium powder (0.18 g, 1.59 mmol) was then added, and the mixture was heated under reflux for 5 hours until the reaction was deemed complete when no starting material remained by TLC analysis (20 % MeOH/CH_2Cl_2). The mixture is cooled to ambient temperature and filtered through a pad of Celite. The Celite is washed with methanol. The washing are combined with the filtrate and concentrated under reduced pressure. A saturated Na_2CO_3 solution (15 mL) is added, and the product is extracted with ethyl acetate (3 ×15 mL). The organic phase is dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The product was purified by silica gel chromatography (5 % MeOH/CH_2Cl_2) afford the titled amine (0.15 g, 45 %). NMR spectra were found to be consistent with the literature.[65]

The optical rotation was determined using a Perkin Elmer Model 141 polarimeter: $[\alpha]_D$ = +39.3° (c = 0.8, EtOH). Literature data for (*R*)-*N*-dibenzyl-1,2-diaminopropane is $[\alpha]_D$ = –37.3°,[66] thus allowing assignment of the absolute configuration of **1c** as *S*.

[64] Cicchi, S.; Bonanni, M.; Cardona, F.; Revuelta, J.; Goti, A. *Org. Lett.* **2003**, *5*, 1773.
[65] Ralambomanana, D. A.; Razafimahefa-Ramilison, D.; Rakotohova, A.; Maugein, J.; Pelinski, L. *Bioorg. Med. Chem.* **2008**, *16*, 9546.
[66] Kurganov, A. A; Davankov, V. A.; Zhuchkova, Y. A.; Ponomaryova, T. M. *Inorg. Chimi. Acta*. **1980**, *39*, 237.

Chapter 2 – Section 2.8

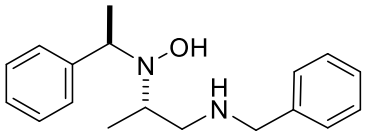
Allylic amines

3-(allylamino)-*N*,*N*-dimethylpropanamide,[67] (*Z*)-*N*-benzyl-4-(benzyloxy)but-2-en-1-amine,[68] and *N*-(4-methoxybenzyl)prop-2-en-1-amine,[67] were prepared according to literature procedures.

General Procedure I

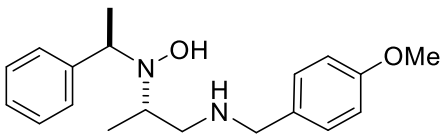
A 2-5 mL microwave flask was charged with a stir bar, amine (1-1.5 equiv.), *t*-BuOH (1.0 M to hydroxylamine), hydroxylamine (1.0 equiv) and formaldehyde (via 0.5 M solution of formalin in *t*-BuOH) (0.1 equiv). The reaction was stirred at 30-50 °C for 24 hours. The crude reaction mixture was concentrated under reduced pressure and purified by flash column chromatography to give the corresponding *N*,*N*-dialkylhydroxylamine products.

(±)-(*S)-*N*-Benzyl-2-(hydroxy((*R**)-1-phenylethyl)amino)propan-1-amine - (2.8a) – (Table 2.8, Entry 1)**



Following general procedure I using *N*-(1-phenylethyl)hydroxylamine (0.137 g, 1.00 mmol) the indicated compound was purified by flash column chromatography on silica gel using (1 % NH_4OH/2 % MeOH/CH_2Cl_2) to give a white solid (0.235 g, 83%). Diagnostic peaks for *d.r.* ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (d, *J* = 6.4, 3H), 1.11 (d, *J* = 6.6, 3H) (6:1 d.r.) **Major Diastereomer**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.25 (m, 10H), 3.93 (q, *J* = 6.4 Hz, 1H), 3.74 (d, *J* = 13.3 Hz, 1H), 3.59 (d, *J* = 13.1, 1H), 2.87-2.76 (m, 2H), 2.50-2.42 (m, 1H), 1.46 (d, *J* = 6.4 Hz, 3H), 0.95 (d, *J* = 6.1 Hz, 3H) ^{13}C NMR (75 MHz, $CDCl_3$) 143.5 (C), 139.9 (C), 128.6 (CH), 128.4 (CH), 128.2 (CH), 127.6 (CH), 127.3 (CH), 127.0 (CH), 63.5 (CH), 54.8 (CH), 53.3 (CH_2), 52.6 (CH_2), 22.2 (CH_3), 9.8 (CH_3); IR (film): 3324, 3070, 3024, 2933, 1595, 1500, 1454, 1321, 1154, 1086, 976 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{18}H_{24}N_2O$ $[M]^+$: 284.1889. Found: 284.1877.

(±)-(*S)-2-(Hydroxy((*R**)-1-phenylethyl)amino)-*N*-(4-methoxybenzyl)propan-1-amine- (2.8b) – (Table 2.8, Entry 2)**

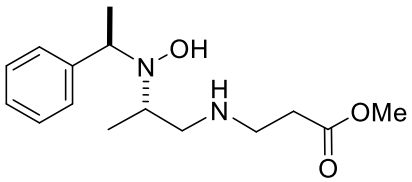


Following general procedure I using *N*-(1-phenylethyl)hydroxylamine (0.137 g, 1.00 mmol) the indicated compound was purified by flash column chromatography on silica gel (1 % NH_4OH/1 % MeOH/CH_2Cl_2). The title compound was obtained as a pale yellow oil (0.148 g, 47%). TLC R_f 0.25 (1 % MeOH/CH_2Cl_2); Diagnostic peaks for *d.r.* ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.42 (d, *J* = 6.4, 3H), 1.10 (d, *J* = 6.6 Hz, 3H) (6:1 d.r.) **Major Diastereomer**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.14 (m, 7H), 6.83-6.81 (m, 2H), 3.92 (q, *J* = 6.4 Hz, 1H), 3.77 (s, 3H), 3.96 (d, *J* = 12.9 Hz, 1H), 3.46 (d, *J* = 12.9, 1H), 2.77 (m, 2H),

[67] A. Leitner, S. Shekhar, M. J. Pouy, J. F. Hartwig, *J. Am. Chem. Soc*. **2005**, *127*, 15506-15514.
[68] D. F. Harvey, D. M. Sigano, *J. Org. Chem.* **1996**, *61,* 2268-2272.

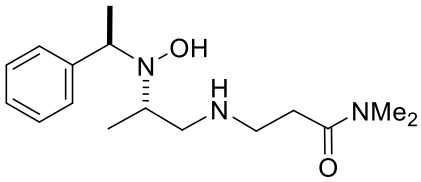
2.39 (m, 1H), 1.42 (d, J = 6.4 Hz, 3H), 0.93 (d, J = 6.0 Hz, 3H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7 (C), 143.6 (C), 131.7 (C), 129.5 (CH), 128.6 (CH), 127.7 (CH), 127.3 (CH), 113.8 (CH), 63.4 (CH), 55.3 (CH), 54.6 (CH_3), 52.4 (CH_2), 52.3 (CH_3), 22.3, 9.8 (CH_3); IR (film): 3324, 3070, 3024, 2933, 1595, 1500, 1454, 1321, 1154, 1086, 976 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{19}H_{26}N_2O_2$ $[M]^+$: 314.1994. Not found. Found Fragment $C_9H_{13}NO$ 151.0997.

(±)-Methyl 3-(((*S)-2-(hydroxy((*R**)-1-phenylethyl)amino)propyl)amino)propanoate- (2.8c) – (Table 2.8, Entry 3)**



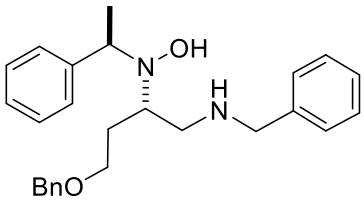
Following general procedure I using *N*-(1-phenylethyl)hydroxylamine (0.137 g, 1.00 mmol) the indicated compound was purified by flash column chromatography on silica gel (1 % NH_4OH/4 % $MeOH/CH_2Cl_2$). The title compound was obtained as a pale yellow oil (0.140 g, 50%). Diagnostic peaks for *d.r.* ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.46 (d, J = 6.4 Hz, 3H), 1.08 (d, J = 6.5 Hz, 3H). (6:1 d.r.) **Major Diastereomer**: TLC R_f 0.18 (4% $MeOH/CH_2Cl_2$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.17 (m, 5H), 3.80 (q, J = 6.4 Hz, 1H), 3.55 (s, 3H), 2.46 (dt, J = 3.7 Hz, 1.4 Hz, 4H), 2.33 (m, 2H), 2.17 (m, 1H), 1.29 (d, J = 6.4 Hz, 3H), 0.78 (d, J = 6.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0 (C), 144.5 (C), 128.8 (CH), 127.8 (CH), 127.4 (CH), 63.0 (CH), 55.0 (CH), 53.4 (CH_3), 51.6 (CH_2), 45.0 (CH_2), 35.0 (CH_2), 23.3 (CH_3), 10.1 (CH_3). IR (film): 3283, 3115, 2956, 2865, 1736, 1454, 1359, 1242, 1181, 922 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{15}H_{24}N_2O_3$ $[M]^+$: 280.1787. Found: 280.1795.

(±)-3-(((*S)-2-(Hydroxy((*R**)-1-phenylethyl)amino)propyl)amino)-*N*,*N*-dimethyl-propanamide- (2.8d) – (Table 2.8, Entry 4)**



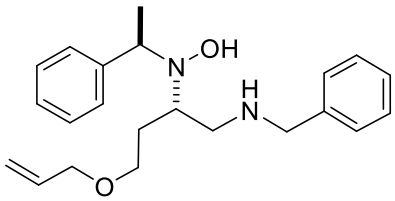
Following general procedure I using *N*-(1-phenylethyl)hydroxylamine (0.137 g, 1.00 mmol) the indicated compound was purified by flash column chromatography on silica gel using (1 % NH_4OH/5 % $MeOH/CH_2Cl_2$) to give a pale yellow oil as a mixture of diastereoisomers (0.249 g, 85%, 6:1 d.r.). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.19 (m,), 3.91 (q, J = 6.4 Hz), 2.94-2.76 (m), 2.55-2.46 (m), 1.45 (d, J = 6.4 Hz), 1.28 (d, J = 6.7 Hz), 1.08 (d, J = 6.5 Hz), 0.94 (d, J = 6.1 Hz) ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.1, 143.5, 129.0, 128.5, 128.3, 127.6, 127.3, 127.2, 126.7, 77.3, 63.3, 63.2, 54.9, 54.8, 53.2, 52.6, 45.2, 45.2, 37.3, 37.2, 35.4, 35.3, 32.7, 32.4, 30.9, 22.5, 20.5, 9.8. IR (film): 3347, 2941, 1637, 1504, 1443, 1405, 1143 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{16}H_{37}N_3O_2$ $[M]^+$: 293.2103. Found: 293.2146.

(±)-(*S)-*N*-Benzyl-4-(benzyloxy)-2-(hydroxy((*R**)-1-phenylethyl)amino)butan-1-amine- (2.8e) – (Table 2.8, Entry 5)**



Following general procedure I using *N*-(1-phenylethyl)hydroxylamine (0.137 g, 1.00 mmol) the indicated compound was purified by flash column chromatography on silica gel using (5 % NH_4OH/1 % MeOH/CH_2Cl_2) to give a pale yellow oil (0.169 g, 42%, 20:1 d.r.) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.18 (m, 15H), 4.37-4.47 (m, 2H), 4.01 (q, *J* = 6.4 Hz, 1H), 3.61 (d, *J* = 13.1, 1H), 3.25-3.49 (m, 3H), 2.80-2.94 (m, 2H), 2.56 (dd, *J* = 12.2 Hz, 3.09 Hz, 1H), 2.06-2.18 (m, 1H), 1.65-1.78 (m, 1H), 1.39 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2 (C), 139.5 (C), 138.5 (C), 128.6 (CH), 128.4 (CH), 128.4 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.2 (CH), 127.1 (CH), 126.0 (CH), 72.9 (CH), 68.0 (CH_2), 63.5 (CH_2), 56.5 (CH), 52.5 (CH_2), 49.0 (CH_2), 26.1 (CH_2), 20.5 (CH_3). IR (film): 3309, 3298, 3032, 2857, 1683, 1477, 1371, 1080, 1033 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{26}H_{32}N_2O_2$ $[M]^+$: 404.2464. Found: 404.2394.

(±)-(*S)-4-(Allyloxy)-*N*-benzyl-2-(hydroxy((*R**)-1-phenylethyl)amino)butan-1-amine- (2.8f) – (Table 2.8, Entry 6)**



Following general procedure I using *N*-(1-phenylethyl)hydroxylamine (0.137 g, 1.00 mmol) the indicated compound was purified by flash column chromatography on silica gel using (1 % NH_4OH/1 % MeOH/CH_2Cl_2) to give a pale yellow oil (0.202 g, 57%, 20:1 d.r.) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.20 (m, 10H), 5.87-5.75 (ddt, *J* = 16.9 Hz, 10.9 and 5.7 Hz, 1H), 5.21-5.10 (m, 2H), 4.01-3.98 (m, 1H), 3.87-3.76 (m, 2H), 3.64 (d, *J* = 13.2 Hz, 1H), 3.47-3.26 (m, 3H), 2.87-2.79 (m, 2H), 2.57 (m, 1H), 2.09-2.00 (m, 1H), 1.69-1.60 (m, 1H), 1.38 (d, *J* = 6.4 Hz, 3H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.1 (C), 139.2 (C), 134.8 (CH), 128.5 (CH), 128.5 (CH), 128.4 (CH), 127.7 (CH), 127.3, (CH), 127.1, (CH), 116.7 (CH_2), 71.8 (CH), 67.9 (CH_2), 63.5 (CH_2), 56.5 (CH), 52.7 (CH_2), 48.9 (CH_2), 26.1 (CH_2), 22.0 (CH_3). IR (film): 3305, 3032, 2937, 2861, 1648, 1443, 1090, 915 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{22}H_{30}N_2O_2$ $[M]^+$: 354.2307. Found: 354.2344.

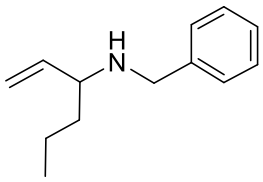
General Procedure IV for the Synthesis of *N*-Benzyl and *N*-Methyl Allylic Amines– (1.4c – 1.4k) – (Table 2.9, Entries 1-7)

Allylic amines were prepared using the method of Dondoni, Merino and co-workers.[69] An oven dried 100 mL round bottom flask was charged with a magnetic stir bar and either *N*-benzylhydroxylamine (1 equiv.) or *N*-methylhydroxylamine hydrochloride (1.2 equiv.) with $NaHCO_3$ (2.2 equiv.). Dichloromethane (0.2 M to hydroxylamine) was then added followed by dropwise addition of the appropriate aldehyde (1.0 equiv) and then $MgSO_4$ (1.0 equiv). The mixture was stirred at room temperature for 18 hours before filtering the mixture through a Celite pad and removing solvents in vacuo. The crude nitrone was dissolved in THF (0.1

[69] Dondoni, A.; Franco, S.; Junquera, F.; Merchan, F. L.; Merino P.; Tejero, T.; Bertolasi, V.; *Chem. Eur. J.* **1995**, *1*, 505-520. (b) Dondoni, A.; Junquera, F.; Merchan, F. L.; Merino, P.; Terjero, T. *Synthesis* **1994**, 1450-1456. (c) Dondoni, A.; Merchan, F. L.; Merino, P.; Tejero, T. *Chem. Commun.* **1994**, 1731-1733.

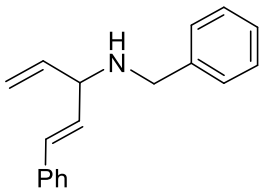
M) and cooled to 0 °C. A Grignard reagent (1.5 equiv.) is added dropwise to the nitrone and the mixture is allowed to stir for 2 hours at 0 °C before quenching with a saturated solution of NH_4Cl followed by dilution with Et_2O and H_2O. The organic layer was separated and the aqueous portion was extracted twice with Et_2O. The combined organic fractions were washed with brine, dried over $MgSO_4$, filtered through a short silica gel plug, washed with Et_2O and concentrated in vacuo. The crude hydroxylamine was taken in EtOH:AcOH (0.5 M) followed by addition of zinc dust (5 equiv.) at room temperature. The reaction was stirred for 18 hours at room temperature before diluting the mixture with Et_2O and filtering over Celite. The solvents were removed in vacuo and the mixture neutralized with saturated aqueous $NaHCO_3$ followed by extracting the organic layer three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The crude amine was then purified by column chromatography over silica gel.

(±)-*N*-Benzylhex-1-en-3-amine – (1.4d) – (Table 2.9, Entry 1)



Synthesized following the general procedure IV using *n*-butyraldehyde (0.851 mL, 9.43 mmol), vinyl magnesium bromide (14.0 mL of a 1M solution in THF, 14.0 mmol) and zinc dust (3.08 g, 47.2 mmol). The title compound was purified by column chromatography over silica gel (4% MeOH/CH_2Cl_2) to give 0.768 g of the desired amine (40% from aldehyde). Spectral data is consistent with literature.[70] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.22 (m, 5H), 5.62 (ddd, *J* = 16.8, 10.4, 7.6, 1H), 5.14 (dd, *J* = 10.4, 1.6 Hz, 1H), 5.10 (dd, *J* = 16.8, 1.6 Hz, 1H), 3.83 (d, *J* = 13.2 Hz, 1H), 3.64 (d, *J* = 13.2 Hz, 1H), 3.03 (dt, *J* = 7.6, 6.0 Hz, 1H), 1.52-1.25 (m, 5H), 0.89 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 140.7, 128.3, 128.2, 126.8, 115.9, 61.0, 51.2, 37.9, 19.1, 14.0.

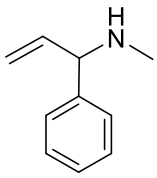
(±)-Benzyl[(4E)-5-phenylpenta-1,4-dien-3-yl]amine – (1.4e) – (Table 2.9, Entry 2)



Synthesized following general procedure IV using cinnamaldehyde (0.926 g, 7.01 mmol) vinyl magnesium bromide (10.5 mL of a 1M solution in THF, 10.5 mmol) and zinc dust (2.29 g, 35.1 mmol). The addition was conducted at –78 °C for 4 hours and allowed to slowly warm to –25 °C before quenching. The title compound was purified by column chromatography over silica gel (5% MeOH in CH_2Cl_2) to give 0.961 g of the desired amine (55 % from aldehyde). Spectral data is consistent with literature.[71] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.16 (m, 10H), 6.53 (d, *J* = 16.0 Hz, 1H), 6.18 (dd, *J* = 16.0 and 7.5 Hz, 1H), 5.88 (ddd, *J* = 17.2, 10.2 and 7.1 Hz, 1H), 5.29-5.16 (m, 2H), 3.90-3.79 (m, 3H), 3.52 (br, 1H) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 139.0, 136.8, 131.4, 128.52, 128.46, 128.3, 127.5, 127.1, 126.4, 116.3, 62.9, 50.8.

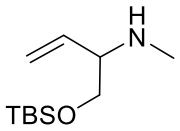
(±)-Methyl(1-phenylprop-2-en-1-yl)amine – (1.4f) – (Table 2.9, Entry 3)

[70] Leitner, A.; Shekhar, S.; Pouy, M. J.; Hartwig, J. F.; *J. Am. Chem. Soc.* **2005**, *127*, 15506-15514.
[71] Zheng, W.; Sun, N.; Hou, X. *Org. Lett.* **2005**, *7,* 5151-5154.



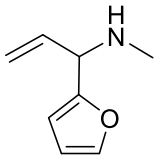
Synthesized following general procedure IV using benzaldehyde (0.956 g, 9.01 mmol), vinyl magnesium bromide (13.5 mL of a 1M solution in THF, 13.5 mmol) and zinc dust (2.94 g, 45.1 mmol). The title compound was purified by column chromatography over silica gel (5% MeOH/CH_2Cl_2) to give 0.663 g of the desired amine (50 % from aldehyde). Spectral data was consistent with literature.[72] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.15 (m, 5H), 5.96-5.77 (m, 1H), 4.03-3.97 (m, 1H), 2.32 (s, 3H), 1.48 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4, 140.5, 128.3, 127.6, 127.0, 114.9, 67.8, 34.1.

(±)-1-((*tert*-Butyldimethylsilyl)oxy)-*N*-methylbut-3-en-2-amine – (1.4g) - (Table 2.9, Entry 4)



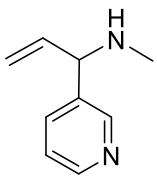
Synthesized following general procedure IV using the TBS-protected aldehyde[73] (1.93 g, 11.1 mmol), vinyl magnesium bromide (22.2 mL of a 1M solution in THF, 22.2 mmol) and zinc dust (3.63 g, 55.6 mmol). The title compound was purified by column chromatography over silica gel (3% MeOH/CH_2Cl_2) to give 0.948 g of the desired amine (40 % from aldehyde). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.61 (ddd, J = 17.3, 10.2 and 8.0 Hz, 1H), 5.28-5.16 (m, 2H), 3.63 (dd, J = 9.9 and 4.1 Hz, 1H), 3.51 (dd, J = 9.9 and 4.2 Hz, 1H), 3.06 (td, J = 8.0 and 4.2 Hz, 1H), 2.39 (s, 3H), 0.901 (s, 9H), 0.066 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 117.9, 66.0, 65.3, 33.9, 25.9, 18.3, 5.4; IR (film): 2956, 2926, 2860, 1511, 1475, 1254, 997, 937, 832, 778 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{11}H_{25}NOSi$ $[M]^+$: 215.1705. Found fragments: $C_9H_{22}NOSi$: 188.1419 and C_2H_3: 27.0245.

(±)-[1-(Furan-2-yl)prop-2-en-1-yl](methyl)amine – (1.4h) - (Table 2.9, Entry 5)



Synthesized following general procedure IV using 2-furaldehyde (1.81 mL, 21.9 mmol*),* vinyl magnesium bromide (33.0 mL of a 1M solution in THF, 33.0 mmol) and zinc dust (7.21 g, 110 mmol). The title compound was purified by column chromatography over silica gel (4% MeOH/CH_2Cl_2) to give 1.49 g of the desired amine (51 % from aldehyde). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (dd, J = 1.9 and 0.8 Hz, 1H), 6.22 (dd, J = 3.2 and 2.0 Hz, 1H), 6.09 (d, J = 3.2 Hz, 1H), 5.83 (ddd, J = 17.2, 10.1 and 7.2 Hz, 1H), 5.20-5.08 (m, 2H), 4.06 (d, J = 7.2 Hz, 1H), 2.29 (s, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 141.4, 137.1, 116.4, 109.7, 105.9, 60.7, 33.6; IR (film): 2915, 2849, 1665, 1466, 1147, 1011, 733 cm^{-1}; HRMS (EI): Exact mass calcd for $C_8H_{11}NO$ $[M]^+$: 137.0841 Found 137.0827.

(±)-Methyl[1-(pyridin-3-yl)prop-2-en-1-yl]amine – (1.4i) - (Table 2.9, Entry 6)

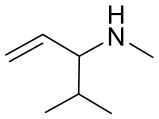


Synthesized following general procedure IV using 3-pyridinecarboxaldehyde (1.82 mL, 15.0 mmol), vinyl magnesium bromide (22.5 mL of a 1M solution in THF, 22.5 mmol) and zinc dust (4.89 g, 75.0 mmol). The title compound was purified by column chromatography over silica gel (6% MeOH/CH_2Cl_2) to give 1.53 g of the desired amine (69% from aldehyde). Spectral data was consistent with literature.[74] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, J = 2.2 Hz, 1H), 8.48

[72] Leitner, A.; Shekhar, S.; Pouy, M. J.; Hartwig, J. F.; *J. Am. Chem. Soc.* **2005**, *127*, 15506-15514.
[73] Lafontaine, J. A.; Provencal, D. P.; Gardelli, C.; Leahy, J. W. *J. Org. Chem.* **2003**, *68*, 4215-4234.
[74] Dübon, P.; Farwick, A.; Helmchen, G. *Synlett* **2009**, 1413.

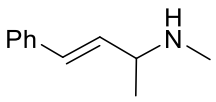
(dd, J = 4.8, 1.7 Hz, 1H), 7.8 (dt, J = 7.8, 1.8 and 1.8 Hz, 1H), 5.86 (ddd, J = 17.2, 10.1 and 7.2 Hz, 1H), 5.19 (m, 2H), 4.08 (d, J = 7.3 Hz, 1H), 3.30 (br s, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 148.6, 139.6, 137.8, 134.9, 123.6, 116.2, 65.5, 34.2.

(±)-Methyl(4-methylpent-1-en-3-yl)amine – (1.4j) - (Table 2.9, Entry 7)



Synthesized following general procedure IV using isobutyraldehyde (0.790 g, 30.0 mmol), vinyl magnesium bromide (45.0 mL of a 1M solution in THF, 45.0 mmol) and zinc dust (9.79 g, 150 mmol). The title compound was purified by column chromatography over silica gel (4% MeOH/CH_2Cl_2) to give 0.805 g of the desired amine (24 % from aldehyde). ^{1}H NMR (400 MHz, $CDCl_3$) δ ; 5.57-5.45 (m, 1H), 5.15-5.00 (m, 2H), 2.58 (dd, J = 8.4 and 5.6 Hz, 1H), 2.31 (s, 3H), 1.71-1.59 (m, 1H), 0.88 (d, J = 6.8 Hz, 3H), 0.83 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7, 116.9, 69.9, 34.4, 32.1, 19.4, 18.1; IR (film): 2965, 2923, 2867, 1711, 1637, 1466, 1380, 1365, 989, 912 cm^{-1}; HRMS (EI): Exact mass calcd for $C_7H_{15}N$ $[M]^+$: 113.1205 Found: 113.1204.

(±)-Methyl[(3E)-4-phenylbut-3-en-2-yl]amine – (1.4k)

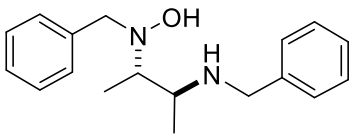


Synthesized following general procedure IV using cinnamaldehyde (4.01 mL, 31.8 mmol) and MeMgBr (15.9 mL of a 3 M solution in Et_2O, 47.7 mmol) and zinc dust (10.4 g, 159 mmol). The addition of MeMgBr was conducted at –78 °C and maintained at –78 °C for 7 hours before allowing the mixture to slowly warm to –25 °C followed by quenching. The title compound was purified by column chromatography over silica gel (5% MeOH/CH_2Cl_2) to give 1.38 g of the desired amine (27% from aldehyde). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.15 (m, 5H), 6.45 (d, J = 15.6 Hz, 1H), 6.03 (dd, J = 15.6, 7.6 Hz, 1H), 3.26-3.16 (m, 1H), 2.39 (s, 3H), 1.22 (d, J =6.4 Hz, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1, 134.0, 129.6, 128.5, 127.2, 126.2, 58.0, 34.2, 21.8; IR (film): 3027, 2970, 2788, 1597, 1495, 1476, 1447, 1368, 1348, 1315, 1135, 1028, 962, 751, 696, 597 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{11}H_{15}N$ $[M]^+$: 161.1205 . Found: 161.1203.

General Procedure (Table 2.10, Entries 1-10)

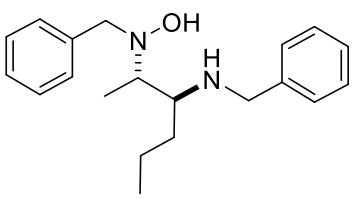
A 2-5 mL microwave flask was charged with a stir bar, amine (1-1.5 equiv.), *t*-BuOH (1.0 M to hydroxylamine), hydroxylamine (1.0 equiv) and formaldehyde (via 0.5 M solution of formalin in *t*-BuOH) (0.1 equiv). The reaction mixture was stirred at 30-50 °C for 24 hours. The crude reaction mixture was concentrated under reduced pressure and purified by flash column chromatography to give the corresponding *N*,*N*-dialkylhydroxylamine products.

(±)-(2*S,3*S**)-*N*-Benzyl-*N*-[3-(benzylamino)butan-2-yl]hydroxylamine - (2.10a) – (Table 2.10, Entry 1)**



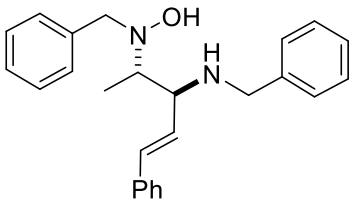
The general procedure II was followed using *N*-benzylhydroxylamine (0.0617 g, 0.501 mmol), and **1.4a** (0.0806 g, 0.501 mmol) and 0.5 mL of catalyst stock solution. The reaction was stirred at 30 °C in a oil bath for 24 hours. The title compound was purified by column chromatography (10% MeOH/CH_2Cl_2) to yield a white solid (0.130 g, 92%, > 20:1 d.r.). Spectral data was consistent with literature.[47]

(±)-(2*S,3*S**)-*N*-Benzyl-*N*-[3-(benzylamino)hexan-2-yl]hydroxylamine- (2.10c) – (Table 2.10, Entry 4)**



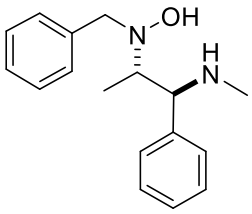
The general procedure II was followed using *N*-benzylhydroxylamine (0.0618 g, 0.501 mmol), and **1.4d** (0.104 g, 0.550 mmol) and 0.5 mL of catalyst stock solution. The reaction was stirred at 30 °C in an oil bath for 24 hours. The title compound was purified by column chromatography (5% MeOH/CH_2Cl_2) to yield a white solid (0.111 g, 71%, 95:5 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.19 (m, 10H), 3.94 (d, *J* = 13.2 Hz, 1H), 3.85 (d, *J* = 12.8 Hz, 1H), 3.75-3.67 (m, 2H), 2.87-2.78 (m, 1H), 2.71-2.64 (m, 1H), 1.68-1.57 (m, 1H), 1.52-1.25 (m, 3H), 1.16 (d, *J* = 6.8 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.3, 138.5, 129.1, 128.4, 128.3, 128.2, 127.0, 61.7, 60.0, 59.7, 51.6, 33.3, 18.4, 14.5, 9,7; IR (film): 3069, 3030, 2964, 2926, 2867, 1494, 1447, 1370, 1211, 1022, 968, 906, 728, 693 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{20}H_{28}N_2O$ $[M]^+$: 312.2202 Found 312.2208.

(±)-(2*S,3*S**)-*N*-Benzyl-*N*-[(4E)-3-(benzylamino)-5-phenylpent-4-en-2-yl]hydroxylamine- (2.10d) – (Table 2.10, Entry 5)**



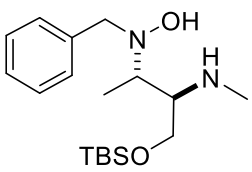
The general procedure II was followed using *N*-benzylhydroxylamine (0.0617 g, 0.501 mmol), and **1.4e** (0.125 g, 0.501 mmol) and 0.5 mL of catalyst stock solution. The reaction was stirred at 30 °C in an oil bath for 24 hours. The title compound was purified by column chromatography (5% MeOH/CH_2Cl_2) to yield a white pasty solid (0.1347 g, 72%, 95:5 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.21 (m, 15H), 6.54 (d, *J* = 16.0 Hz, 1H), 6.03 (dd, *J* = 15.6, 8.8 Hz, 1H), 3.82-3.67 (m, 3H), 3.54 (d, *J* = 13.6 Hz, 1H), 3.26-3.17 (m, 1H), 3.10-3.98 (m, 1H), 1.12 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 138.4, 136.6, 129.2, 128.5, 128.4, 128.3, 128.2, 127.6, 127.09, 127.06, 126.4, 63.8, 62.7, 59.3, 50.0, 9.6. IR (film): 3059, 3021, 1496, 1454, 1149, 1025, 970, 733, 692 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{25}H_{28}NO$ $[M]^+$: 372.2202 Found 372.2205.

(±)-(2*S,3*S**)-*N*-Benzyl-*N*-[1-(methylamino)-1-phenylpropan-2-yl]hydroxylamine - (2.10e) – (Table 2.10, Entry 6)**



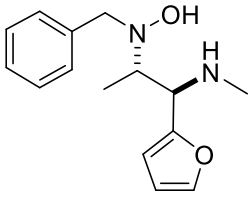
The general procedure II was followed using *N*-benzylhydroxylamine (0.0617 g, 0.501 mmol), and **1.4f** (0.0751 g, 0.510 mmol) and 0.5 mL of catalyst stock solution. The reaction was stirred at 30 °C in an oil bath for 24 hours. The title compound was purified by column chromatography (5% MeOH/CH_2Cl_2) to yield a white solid (0.108 g, 80%, 95:5 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44-7.17 (m, 10H), 3.87 (d, *J* = 13.2 Hz, 1H), 3.68 (d, *J* = 13.2 Hz, 1H), 3.36-3.20 (m, 2H), 1.74 (s, 3H), 0.88 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 139.4, 129.5, 128.4, 128.3, 128.2, 127.4, 127.1, 69.1, 67.0, 57.7, 33.0, 9.3. IR (film): 3059, 3026, 1948, 1600, 1488, 1451, 1372, 1148, 1032, 975, 912, 740, 695 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{17}H_{22}N_2O$ $[M]^+$: 270.1732 Found 270.1737.

(±)-(2*S,3*R**)-*N*-Benzyl-*N*-{4-[(*tert*-butyldimethylsilyl)oxy]-3-(methylamino)butan-2-yl}hydroxylamine- (2.10f) – (Table 2.10, Entry 7)**



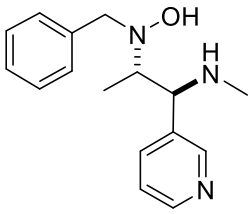
The general procedure II was followed using *N*-benzylhydroxylamine (0.0618 g, 0.501 mmol), and **1.4g** (0.0754 g, 0.55 mmol) and 0.5 mL of catalyst stock solution. The reaction was stirred at 30 °C in an oil bath for 24 hours. The title compound was purified by column chromatography (5% MeOH/CH_2Cl_2) to yield a white solid (0.118 g, 70%, 95:5 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39-7.19 (m, 5H), 3.92 (d, *J* = 13.2 Hz, 1H), 3.75-3.68 (m, 2H), 3.59 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.01-2.92 (m, 1H), 2.60-2.53 (m, 1H), 2.31 (s, 3H), 1.15 (d, *J* = 6.8 Hz, 3H), 0.85 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 129.1, 128.2, 127.0, 64.5, 61.5, 59.7, 33.8, 25.8, 18.1, 10.7, -5.5, -5.6. IR (film): 2960, 2926, 2854, 1470, 1250, 1002, 836, 773, 694 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{18}H_{34}N_2O_2$ $[M]^+$: 338.2390 Not found. Found fragments $C_9H_{22}NOSi$ 188.1471 and $C_9H_{12}NO$ 150.0919.

(±)-(2*S,3*R**)-*N*-Benzyl-*N*-[1-(furan-2-yl)-1-(methylamino)propan-2-yl]hydroxylamine- (2.10g) – (Table 2.10, Entry 8)**



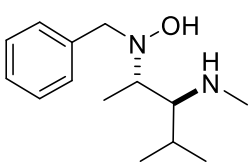
The general procedure II was followed using *N*-benzylhydroxylamine (0.0618 g, 0.501 mmol), and **1.4h** (0.0754 g, 0.55 mmol) and 0.5 mL of catalyst stock solution. The reaction was stirred at 30 °C in an oil bath for 24 hours. The title compound was purified by column chromatography (5% MeOH/CH_2Cl_2) to yield an off-white solid (0.112 g, 86%, 95:5 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.25 (m, 6H), 6.34 (d, *J* = 3.1, 1.9 Hz, 1H), 6.27 (d, *J* = 3.1, 0.7 Hz, 1H), 4.01 (d, *J* = 13.2 Hz, 1H), 3.81 (d, *J* = 13.1 Hz, 1H), 3.68 (d, *J* = 9.6 Hz, 1H), 3.29 (dq, *J* = 9.7 and 6.5 Hz, 1H), 2.25 (s, 3H), 0.95 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 138.3, 129.4, 128.4, 127.3, 110.0, 109.0, 67.9, 63.2, 61.5, 60.4, 33.4, 9.3. IR (film): 1639, 1499, 1456, 1380, 1304, 1023, 972, 757, 732, 692 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{15}H_{20}N_2O_2$ $[M]^+$: 260.1525 Found fragments: C_6H_8NO 110.0608 and $C_9H_{12}NO$ 150.0919.

(±)-(2*S,3*S**)-*N*-Benzyl-*N*-[1-(methylamino)-1-(pyridin-3-yl)propan-2-yl]hydroxylamine- (2.10h) – (Table 2.10, Entry 9)**



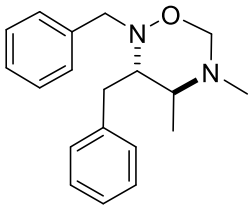
The general procedure II was followed using *N*-benzylhydroxylamine (0.0618 g, 0.501 mmol), and **1.4i** (0.0815 g, 0.55 mmol) and 0.5 mL of catalyst stock solution. The reaction was stirred at 30 °C in an oil bath for 24 hours. The title compound was purified by column chromatography (5% MeOH in CH_2Cl_2) to yield a white solid (0.110 g, 81%, 95:5 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (dd, *J* = 4.8 and 1.6 Hz, 1H), 8.4 (d, *J* = 1.7 Hz, 1H), 7.68 (dt, *J* = 7.9 and 1.9 Hz, 1H), 7.40-7.23 (m, 6H), 3.94 (d, *J* = 13.2 Hz, 1H), 3.71 (d, *J* = 13.1 Hz, 1H), 3.48 (d, *J* = 9.8 Hz, 1H), 3.14-3.03 (m, 1H), 1.94 (s, 3H), 0.869 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 149.1, 138.6, 136.3, 135.7, 129.5, 128.4, 127.4, 123.8, 66.2, 65.8, 33.5, 8.7; IR (film): 1640, 1593, 1580, 1453, 1426, 1379, 1022, 906, 822, 735, 719, 692 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{21}N_3O$ $[M]^+$: 271.1685 Found 271.1688.

(±)-(2*S,3*S**)-*N*-Benzyl-*N*-[4-methyl-3-(methylamino)pentan-2-yl]hydroxylamine-(2.10i) – (Table 2.10, Entry 10)**



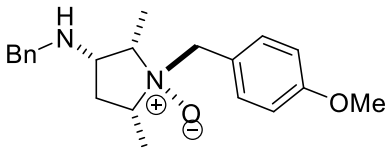
The general procedure II was followed using *N*-benzylhydroxylamine (0.0618 g, 0.501 mmol), and **1.4j** (0.0567 g, 0.55 mmol) and 0.5 mL of catalyst stock solution. The reaction was stirred at 30 °C in an oil bath for 24 hours. The title compound was purified by column chromatography (5% MeOH/CH_2Cl_2) to yield a yellow oil (0.0897 g, 76%, 95:5 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (m, 5H), 3.91 (d, *J* = 13.2 Hz, 1H), 3.65 (d, *J* = 13.2 Hz, 1H), 2.92-2.83 (m, 1H), 2.34 (s, 3H), 2.10-2.04 (m, 1H), 1.98-1.84 (m, 1H), 1.17 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 138.7, 129.3, 128.2, 127.1, 70.6, 60.3, 59.9, 37.7, 30.0, 20.1, 18.5, 10.7; IR (film): 2961, 2866, 1449, 1380, 1304, 1023, 972, 757, 732, 692 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{14}H_{24}N_2O$ $[M]^+$: 236.1889 Found fragments $C_9H_{12}NO$ 150.0920 and $C_5H_{12}N$ 86.0972.

2,3-Dibenzyl-4,5-dimethyl-1,2,5-oxadiazinane – (3.1a) – (Table 2.11 Entry 4)



To a microwave vial is added a magnetic stir bar, *N*-benzylhydroxylamine (0.0618 g, 0.501 mmol), (*E*)-*N*-methyl-4-phenylbut-3-en-2-amine (**1.4k**) (0.0887 g, 0.55 mmol) and *t*-BuOH (0.5 mL). Formaldehyde 37 wt. % formaldehyde in water (0.0407 g, 0.502 mmol) was then added. The reaction was stirred at 70 °C in an oil bath for 24 hours. The title compound was purified by column chromatograph (30% EtOAc in Hexanes) to yield a white solid (0.106 g, 72%, 95:5 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45-7.16 (m, 10H), 4.48-4.35 (m, 2H), 4.28 (d, *J* = 14.5 Hz, 1H), 3.62 (d, *J* = 14.5 Hz, 1H), 3.14-2.96 (m, 2H), 2.89-2.73 (m, 2H), 2.35 (s, 3H), 1.21 (d, *J* = 6.6 Hz, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 128.1, 129.1, 128.5, 128.4, 128.1, 126.8, 126.1, 86.1, 66.1, 59.3, 57.5, 35.9, 34.8, 15.5; IR (film): 3120, 2921, 2857, 1410, 1313, 1322, 1067, 784 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{19}H_{24}N_2O$ $[M]^+$: 296.1889 found 296.1891.

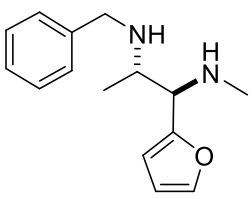
(±)-(1*R,2*S**,3*S**,5*R**)-3-(Benzylamino)-1-(4-methoxybenzyl)-2,5-dimethylpyrrolidine 1-oxide (Scheme 2.13)**



N-(4-methoxybenzyl)hydroxylamine (0.153 g, 1.00 mmol), *N*-benzylbut-3-en-2-amine (0.187 g, 1.10 mmol) and 0.1 M formalin in *t*-BuOH (1.00 mL, 0.100 mmol) were transferred to a sealed microwave vial and heated at 60 °C for 36 hours. Obtained as a single diastereomer as judged by NMR analysis. Isolated 0.269 g (79%) of a light yellow oil after column chromatography (1 % ammonium hydroxide/20% MeOH/Et_2O). TLC *R*f 0.35 (20% MeOH/Et_2O). Spectral data was consistent with literature.[47] NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 7.2 Hz, 2H), 7.29-7.20 (m, 4H), 7.16 (m, 1H), 6.86 (d, *J* = 7.2 Hz, 2H), 4.15 (dd, *J* = 13.9 Hz, 2H), 3.87 (d, *J* = 13.7 Hz, 2H), 3.57 (d, *J* = 13.7 Hz, 2H), 3.18-3.08 (m, 2H), 2.87 (m, 1H), 2.16 (m, 2H), 1.84 (m, 2H), 1.57 (d, *J* = 6.4 Hz, 2H), 1.47 (d, *J* = 6.4 Hz, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.3 (C), 140.5 (C), 132.3 (CH), 128.1 (CH), 128.0 (CH), 126.6 (CH), 123.0 (C), 114.3 (CH), 68.9

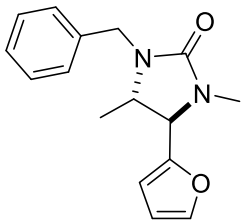
(CH), 65.1 (CH), 64.5 (CH_2), 55.3 (CH), 54.8 (CH), 50.8 (CH_2), 37.4 (CH_2), 13.0 (CH_3), 9.3 (CH_3).

(±)-(1*R,2*S**)-*N*^{2}-Benzyl-1-(furan-2-yl)-*N*^{1}-methylpropane-1,2-diamine - (2.14a) – (Scheme 2.14)**



Prepared by a modified method of Shuto and coworkers,[75] 0.031g of **3.0g** was dissolved in 3 mL of 5:1 CH_2Cl_2:AcOH. 0.075g (10 equiv.) of zinc power was added and the mixture was stirred at room temperature for 16 hours. The reaction was filtered through celite and concentrated under reduced pressure. The oil was washed with sodium bicarbonate and extracted with CH_2Cl_2. The crude was purified by flash column chromatography on silica gel using (1 % NH_4OH/4 % MeOH/CH_2Cl_2) to give a pale yellow oil (0.014 g, 37%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.31 (m, 6H), 6.30 (dd, *J* = 3.1 and 1.8 Hz, 1H), 6.19 (d, *J* = 3.0 Hz, 1H), 3.94 (d, *J* = 13.1 Hz, 1H), 3.72 (d, *J* = 13.0 Hz, 1H), 3.31 (d, *J* = 9.0 Hz, 1H), 2.89 (m, 1H), 2.24 (s, 3H), 2.07 (br, 2H), 0.94 (d, *J* = 6.3 Hz, 3H) ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.9 (C), 141.8 (CH), 140.2 (C), 128.5 (CH), 128.3 (CH), 127.1 (CH), 109.9 (CH), 108.3 (CH), 62.9 (CH), 56.0 (CH), 51.3 (CH_2), 34.2 (CH_3), 17.1 (CH_3). IR (film): 2933, 2865, 1645, 1454, 1082 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{15}H_{20}N_2O$ $[M]^+$: 244.1576. Not found. Exact mass calcd for C_6H_9NO $[M\text{-}C_9H_{13}N]^+$: 111.0684. Found 111.0683.

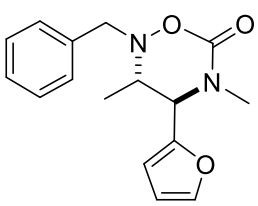
(±)-(4*S,5*R**)-3-Benzyl-1,4-dimethyl-5-(furan-2-yl)imidazolidin-2-one - (2.14b) – (Scheme 2.14)**



N^2-Benzyl-1-(furan-2-yl)-*N*^{1}-methylpropane-1,2-diamine (7.7 mg, 1 equiv.) was dissolved in CH_2Cl_2 (1 mL) and charged with 1,1'-carbonyldiimidazole (8.5 mg, 1.7 equiv.). The reaction was stirred for 16 hours at room temperature and then concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel using (1 % NH_4OH/2 % MeOH/CH_2Cl_2) to give a pale yellow oil (3.4 mg, 41%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.23 (m, 6H), 6.32-6.24 (m, 2H), 4.76 (d, *J* = 15.4 Hz, 1H), 4.14 (d, *J* = 15.4 Hz), 3.93 (d, *J* = 8.5 Hz), 3.44 (m, 1H), 2.70 (s, 3H), 1.57 (br, 2H), 1.15 (d, *J* = 6.2 Hz, 3H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.1 (C), 151.2 (C), 143.5 (CH), 137.3 (C), 128.6 (CH), 128.1 (CH), 127.3 (CH), 110.5 (CH), 108.7 (CH), 61.9 (CH), 54.4 (CH_2), 45.9 (CH), 29.8 (CH_3), 17.6 (CH_3). IR (film): 2975, 2929, 1705, 1443, 1226, 1093, 1006 cm^{-1}. HRMS (EI): Exact mass calcd for $C_{16}H_{18}N_2O_2$ $[M]^+$: 270.1368. Found: 270.1377.

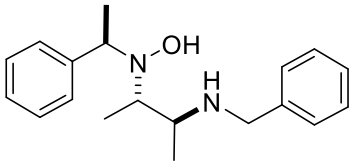
[75] Kazuta, Y.; Abe, H.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2004**, *69*, 9143-9150.

(±)-(3*S,4*R**)-2-Benzyl-4-(furan-2-yl)-3,5-dimethyl-1,2,5-oxadiazinan-6-one - (2.14c) – Scheme 2.14**



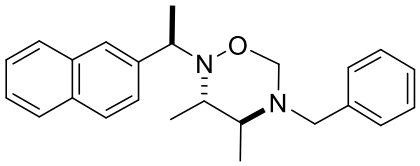
To a 5 mL round bottom flask was added a magnetic stir bar, **3.0g** (0.026 g, 0.10 mmol) and CH_2Cl_2 (2 mL). CDI (0.024 g, 0.15 mmol) is then added and the mixture is stirred at room temperature for 16 hours. The title compound was purified by column chromatograph (4:6 EtOAc/Hexanes) to yield a yellow oil (0.021 g, 72%, 95:5 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 6H), 6.36-6.32 (m, 2H), 4.30 (d, J = 14 Hz, 1H), 4.17 (d, J = 7.0 Hz, 1H), 3.42-3.30 (m, 1H), 2.78 (s, 3H), 2.15 (s, 3H), 1.18 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5 (C), 150.7 (C), 142.8 (CH), 135.2 (C), 129.1 (CH), 128.4 (CH), 127.6 (CH), 110.4 (CH), 109.5 (CH), 62.4 (CH), 59.3 (CH), 58.7 (CH_2), 33.7 (CH_3), 13.7 (CH_3); IR: 2930, 1704, 1497, 1453, 1433, 1401, 1353, 1311, 1261, 1240, 736, 697, 594 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{18}N_2O_3$ $[M]^+$: 286.3310 found 286.3310.

(±) – 5-benzyl-3,4-dimethyl-2-(1-phenylethyl)-1,2,5-oxadiazinane – (Table 2.11, Entry 1)



A 5 mL microwave flask was charged with a stir bar, (*E*)-*N*-methyl-4-phenylbut-3-en-2-amine (**1.4k**) (0.0402 g, 0.250 mmol), *N*-(2-phenylethyl) hydroxylamine (0.0342 g, 0.249 mmol) and formaldehyde (via 0.5 M solution of formalin in *t*-BuOH) (0.25 mL, 0.0250 mmol). The reaction was stirred at 80 °C for 24 hours. The crude reaction mixture was concentrated under reduced pressure and the d.r. determined to be 5:1 by ^{1}H NMR. The crude mixture was recrystallized from Et_2O/Hexane to give the title compound in 35% yield (0.0276 g, 19:1 dr) along with an undesired impurity. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46-7.12 (m, 10H), 3.94-3.76 (m, 2H), 3.58 (d, J = 13.4 Hz, 1H), 2.76-2.60 (m, 1H), 2.47-2.29 (m, 1H), 1.41 (d, J = 6.4 Hz, 3H), 0.98 (d, J = 6.6 Hz, 3H), 0.93 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 128.7, 128.6, 128.4, 128.3, 127.5, 127.4, 127.4, 63.3, 59.9, 54.9, 22.3, 17.1, 7.9; IR: 3280, 3025, 2926, 1598, 1371, 901, 855, 721 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{19}H_{26}N_2O$ 298.2045 Found 298.2027.

(±) – 5-benzyl-3,4-dimethyl-2-(1-napthylethyl)-1,2,5-oxadiazinane - (2.17a) – Scheme 2.17



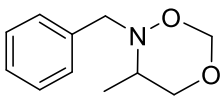
To a microwave vial is added a magnetic stir bar, *N*-(2-napthylethyl) hydroxylamine (0.0470 g, 0.251 mmol), (*E*)-*N*-methyl-4-phenylbut-3-en-2-amine (**1.4k**) (0.0403 g, 0.250 mmol) and *t*-BuOH (0.25 mL). Formaldehyde 37 wt. % formaldehyde in water (0.0204 g, 0.250 mmol) was then added. The reaction was stirred at 30 °C in an oil bath for 5 days. The title compound was purified by column chromatograph (30% EtOAc in Hexanes) to yield a clear oil (0.0765 g, 85%, 95:5 dr). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.75 (m, 4H), 7.67 (d, J = 8.3 Hz, 1H), 7.52-7.43 (m, 2H), 7.35-7.20 (m, 5H), 4.69-4.57 (m, 1H), 4.51 (d, J = 9.7 Hz, 1H), 4.33-4.16 (m, 1H), 3.83-3.58 (m, 2H), 2.98-2.85 (m, 1H), 2.64-2.51 (m, 1H), 1.58 (d, J = 6.7 Hz, 3H), 1.22-1.03 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 133.2, 132.8, 129.0, 128.3, 127.8, 127.7, 127.6, 127.3, 127.0, 125.9, 125.7, 83.2, 61.5, 59.0, 56.9, 21.1, 16.2, 13.7; IR: 3117,

2857, 1405, 1320, 1322, 1061, 777 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{24}H_{28}N_2O$ 360.2202 Found 360.2197.

General Procedure for Optimization of Cope-type hydroamination of allylic alcohol (Table 2.13, Entries 1-10)

In a 5 mL microwave vial is added a magnetic stir bar, *N*-benzylhydroxylamine (1 equiv.), solvent (1M to hydroxylamine), formalin (1 equiv. formaldehyde), allylic alcohol (5 equiv.). The vial was capped and allowed to stir for 24 hours. 1,3,5 trimethoxybenzene was then added as an internal standard and an NMR yield was calculated

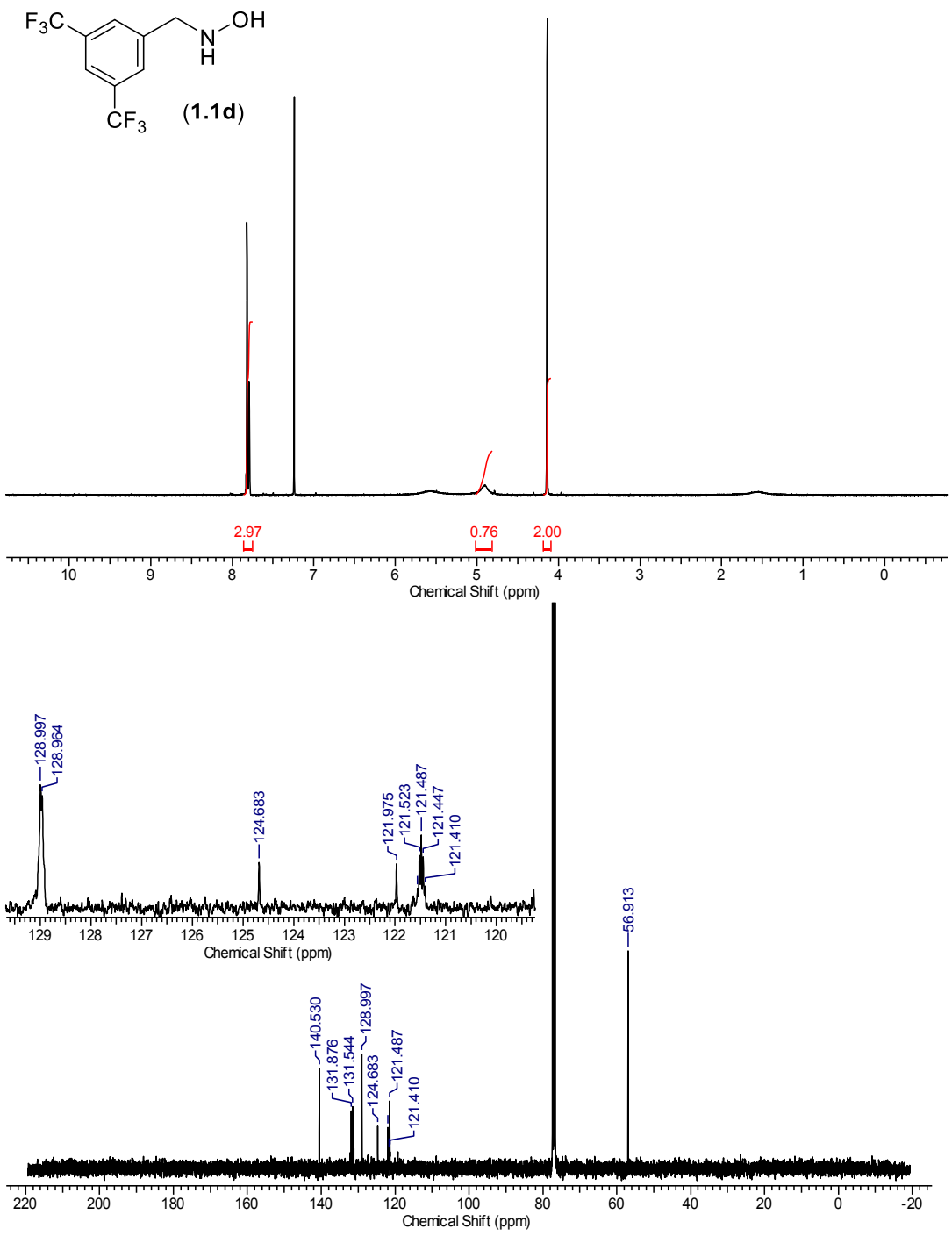
(±) - 2-benzyl-3-methyl-1,5,2-dioxazinane - (2.13a) – (Table 2.13, Entry 4)



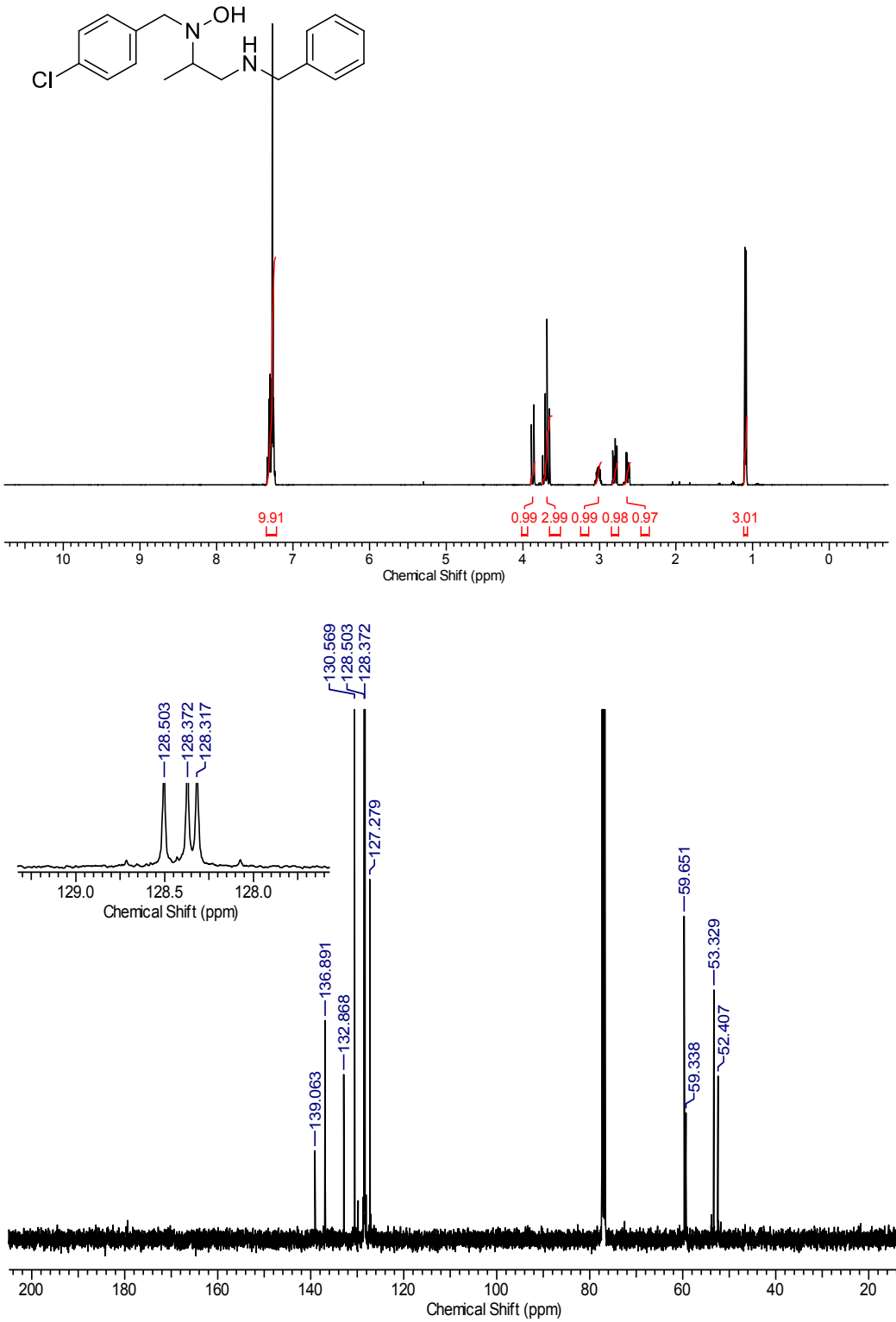
To a 5 mL microwave vial is added *N*-benzylhydroxylamine (0.0308 g, 0.25 mmol), $CDCl_3$ (0.25 mL), formalin (18.6 μL, 0.25 mmol), and allylic alcohol (85.0 μL, 1.25 mmol). The reaction was stirred at room temperature for 24 hours. The reaction mixture was concentrated under reduced pressure and then purified by column chromatography (20% EtOAc/80% Hexane) to give less than 5 mg of the title compound along with an undesired impurity. ^1H NMR (400 MHz, $CDCl_3$) δ 7.58-7.29 (m, 5H), 5.11 (d, J = 5.4 Hz, 1H), 4.76-4.55 (m, 3H), 4.38-4.30 (m, 1H), 3.95-3.82 (m, 2H), 1.27 (d, J = 6.1 Hz, 3H); HRMS (EI): Exact mass calcd for $C_{11}H_{15}NO_2$ 193.1103 Found 193.1103.

Appendix III. NMR and HPLC

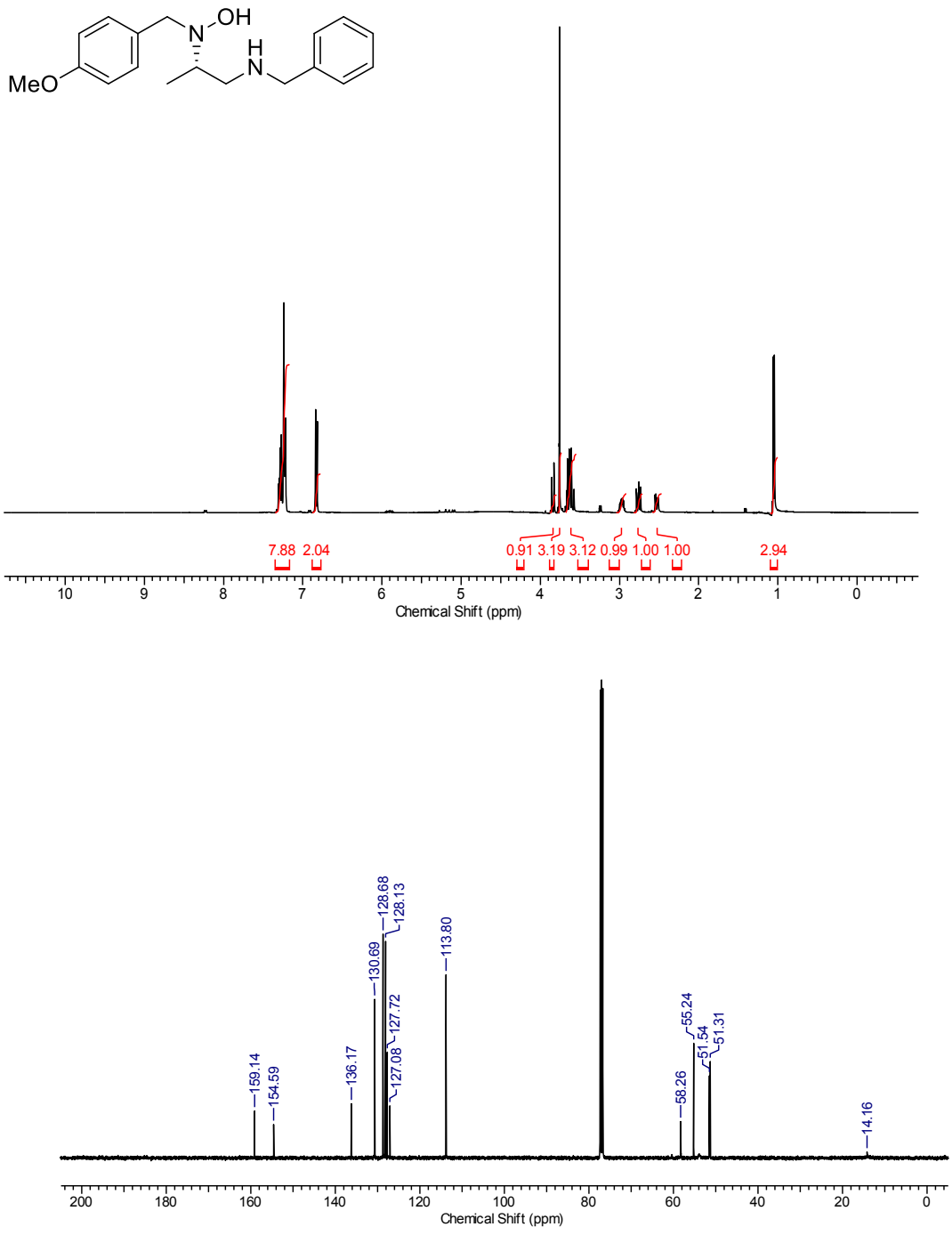
Spectra1.1d (Table 2.3)



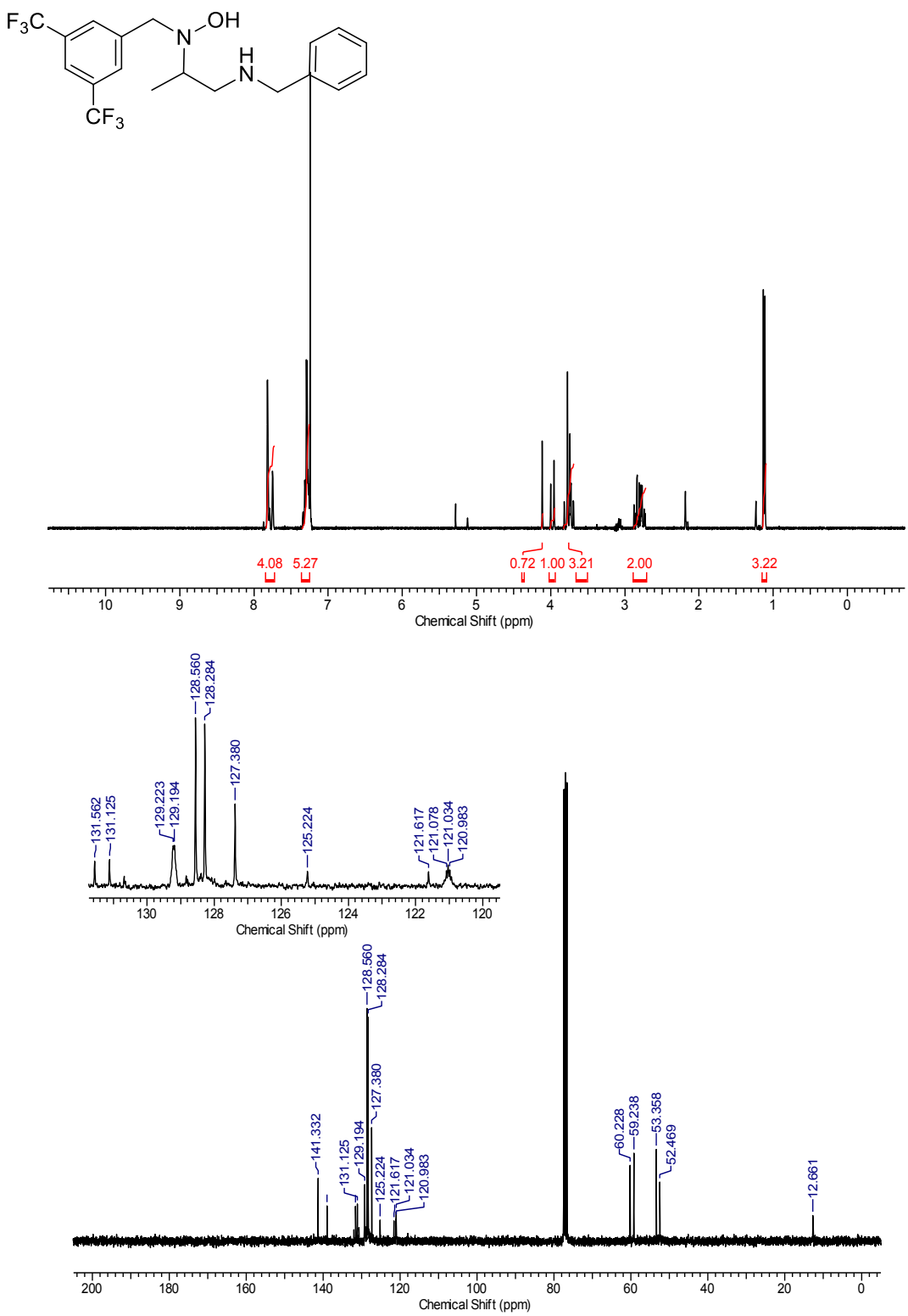
2.3b (Table 2.3 Entry 2)



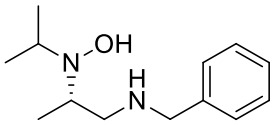
2.3c (Table 2.3 Entry 3)

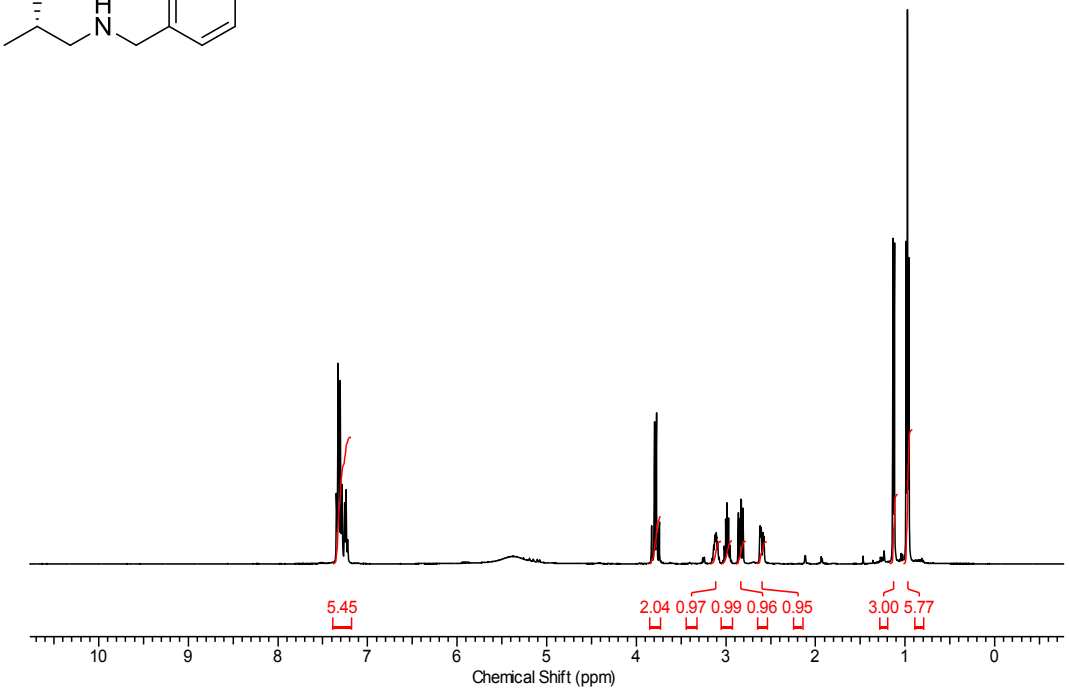


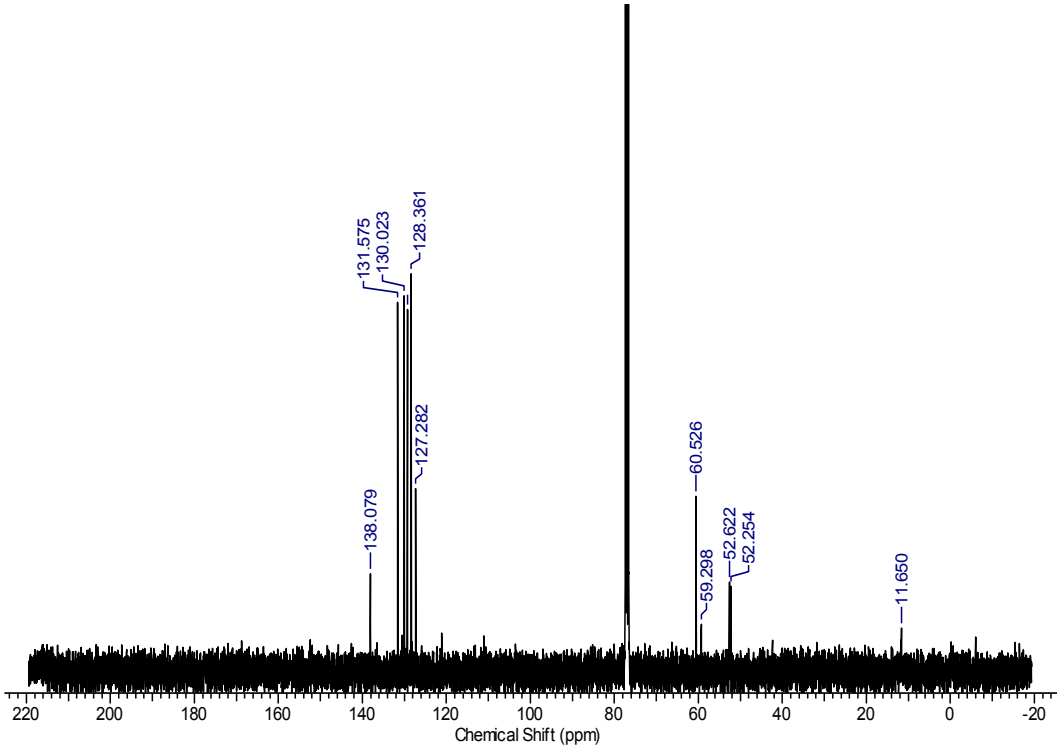
2.3d (*S*) & 2.7b (*R*) - (Table 2.3 Entry 4 and Table 2.8 Entry 2)



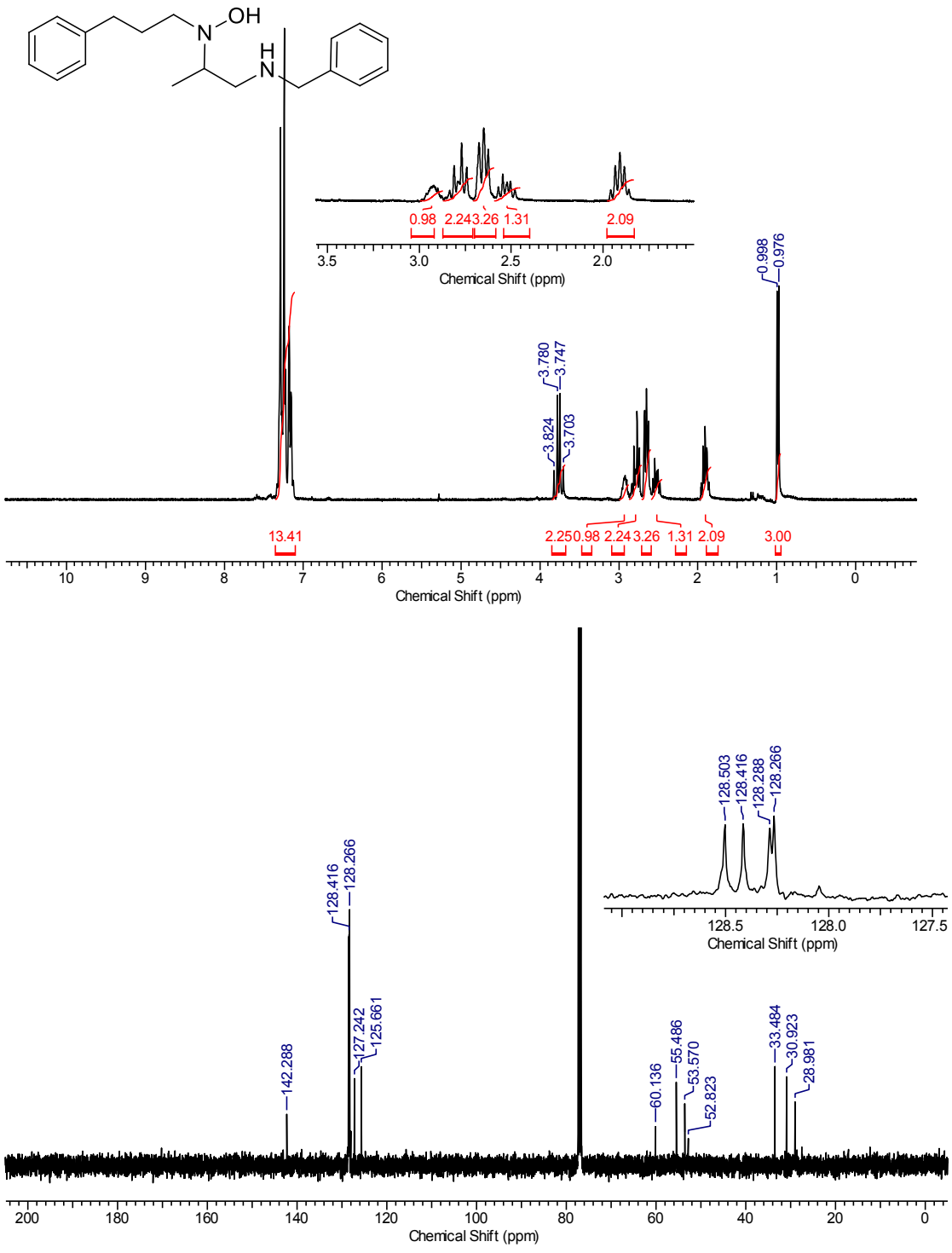
2.3e (Table 2.3 Entry 5)



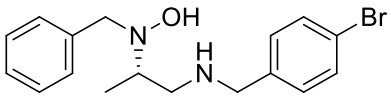


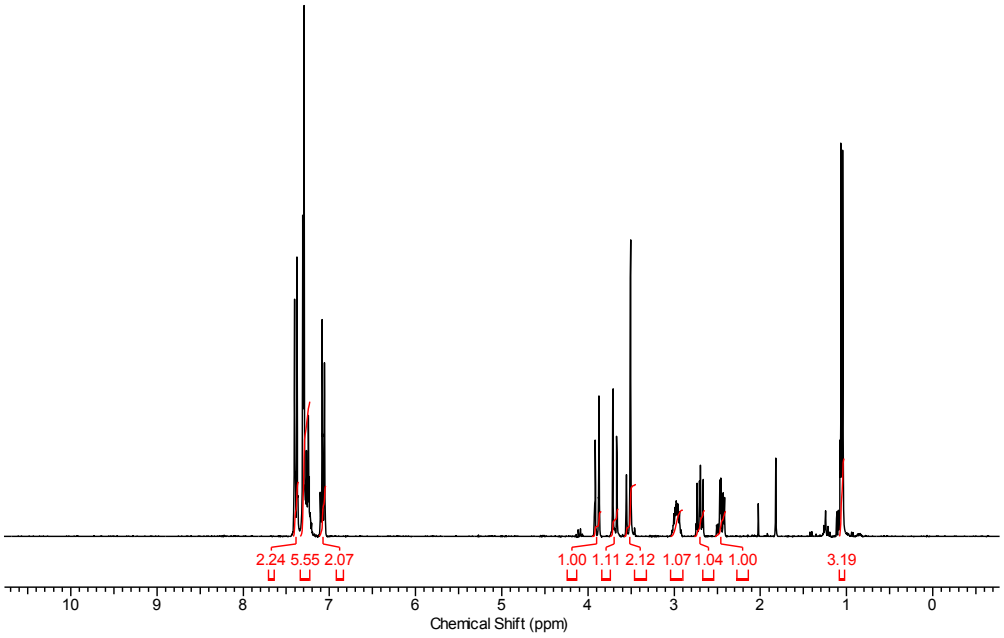


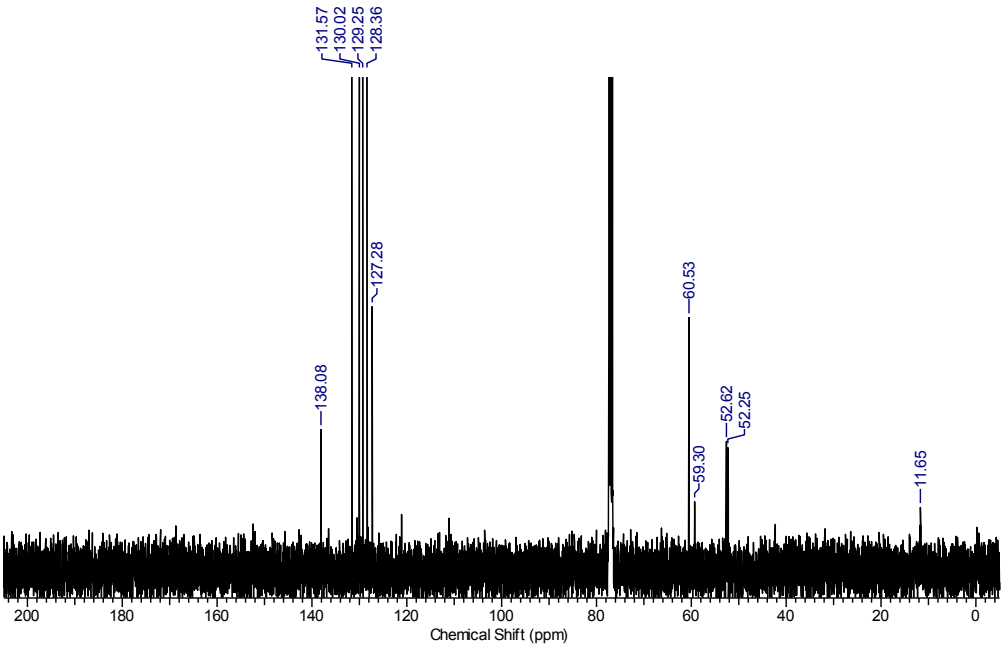
2.3f (*S*) & 2.7c (*R*) - (Table 2.3 Entry 6 and Table 2.7 Entry 3)



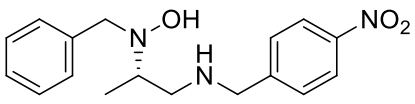
2.4c (Table 2.4 Entry 3)

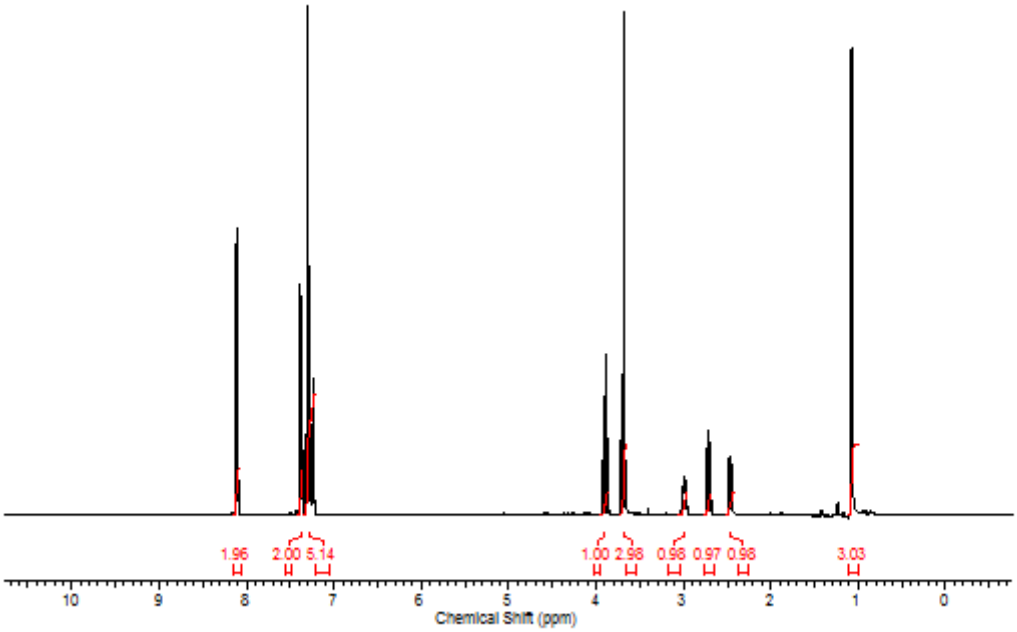


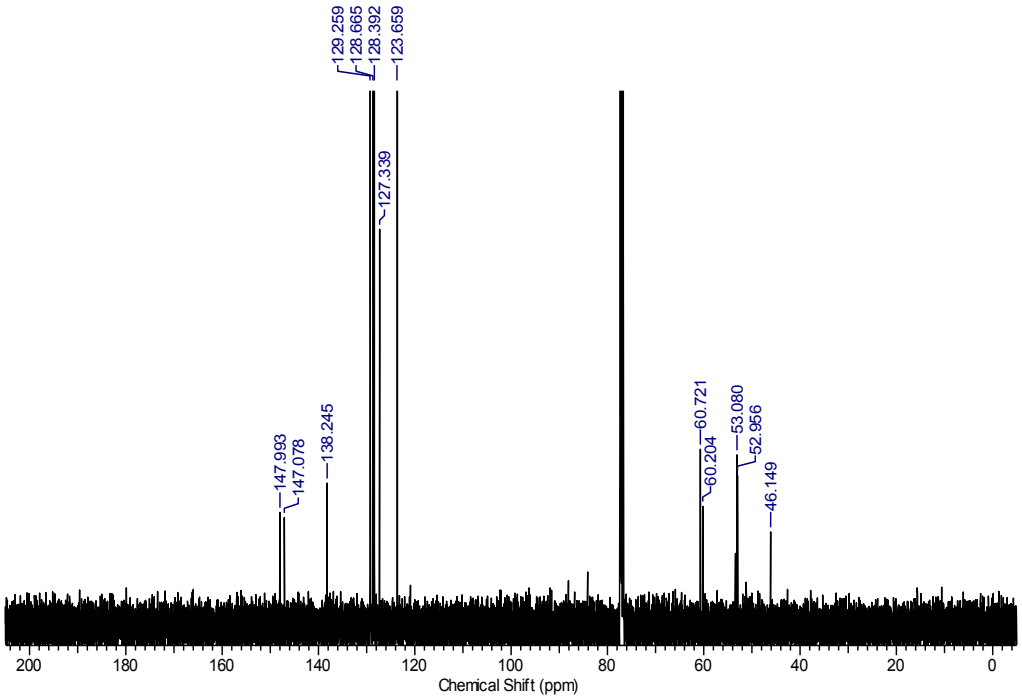




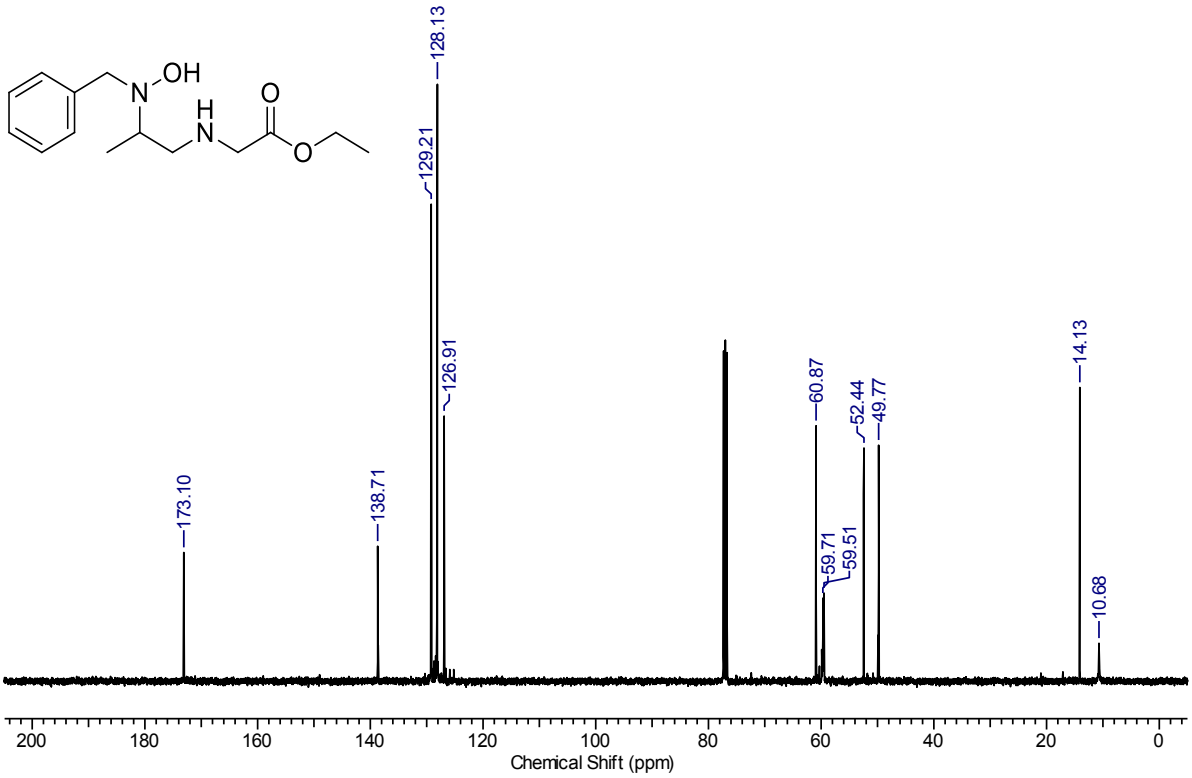
2.4d (Table 2.4 Entry 4)

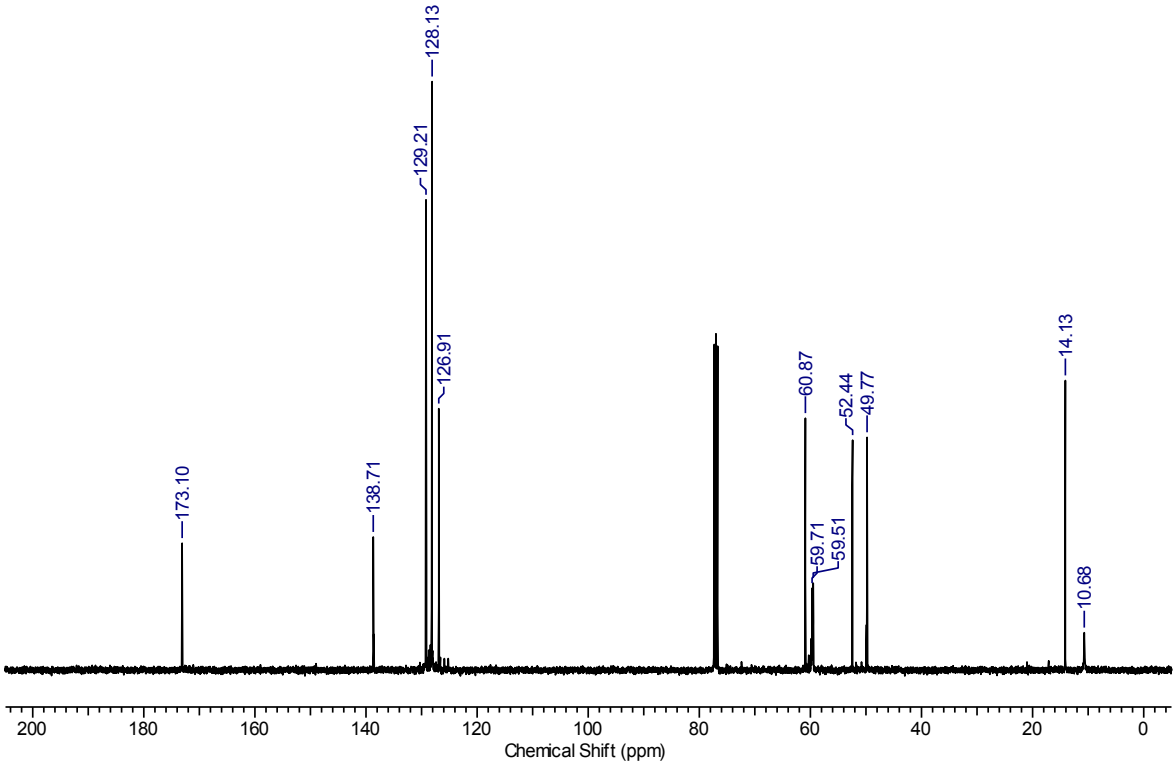




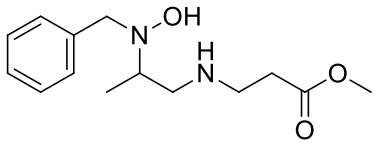


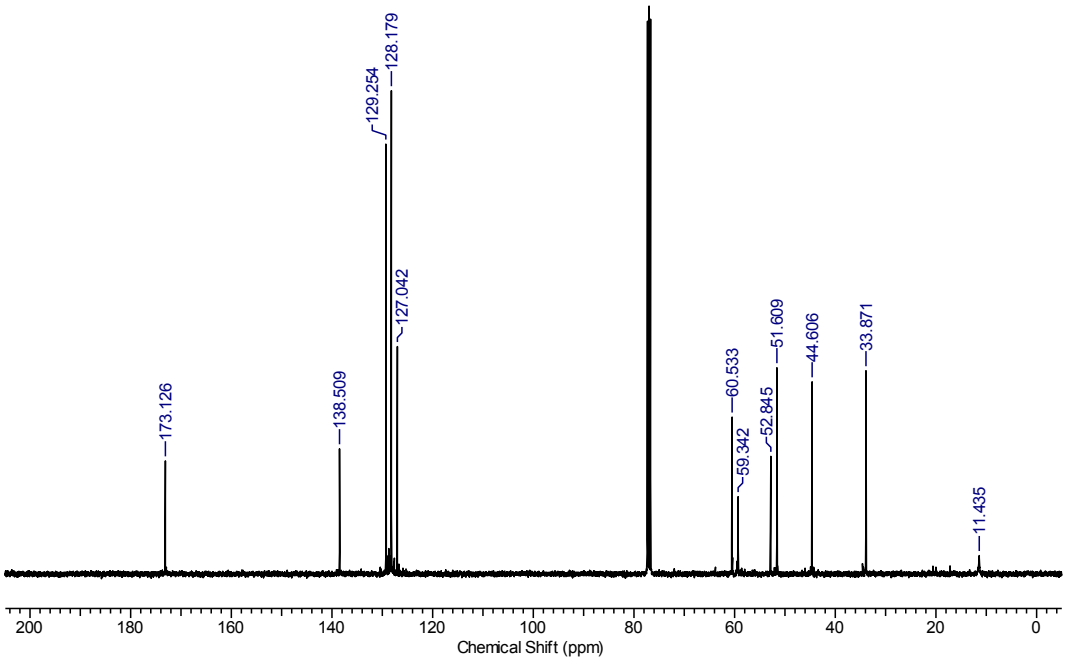
2.4f (*S*) & 2.7f (*R*) - (Table 2.4 Entry 6 and Table 2.7 Entry 6)



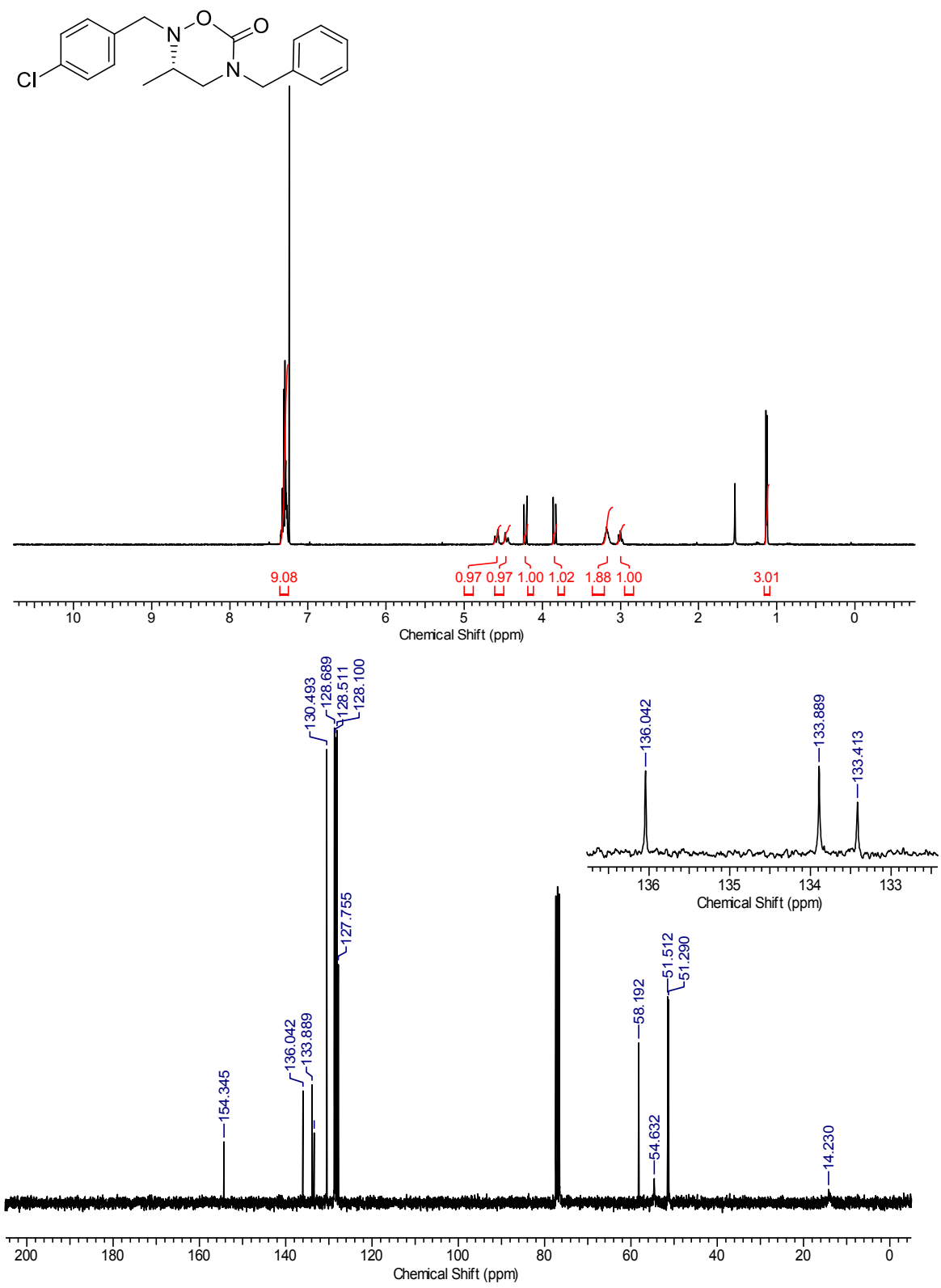


2.4g (*S*) & 2.7g (*R)* - (Table 2.4 Entry 7 and Table 2.7 Entry 7)

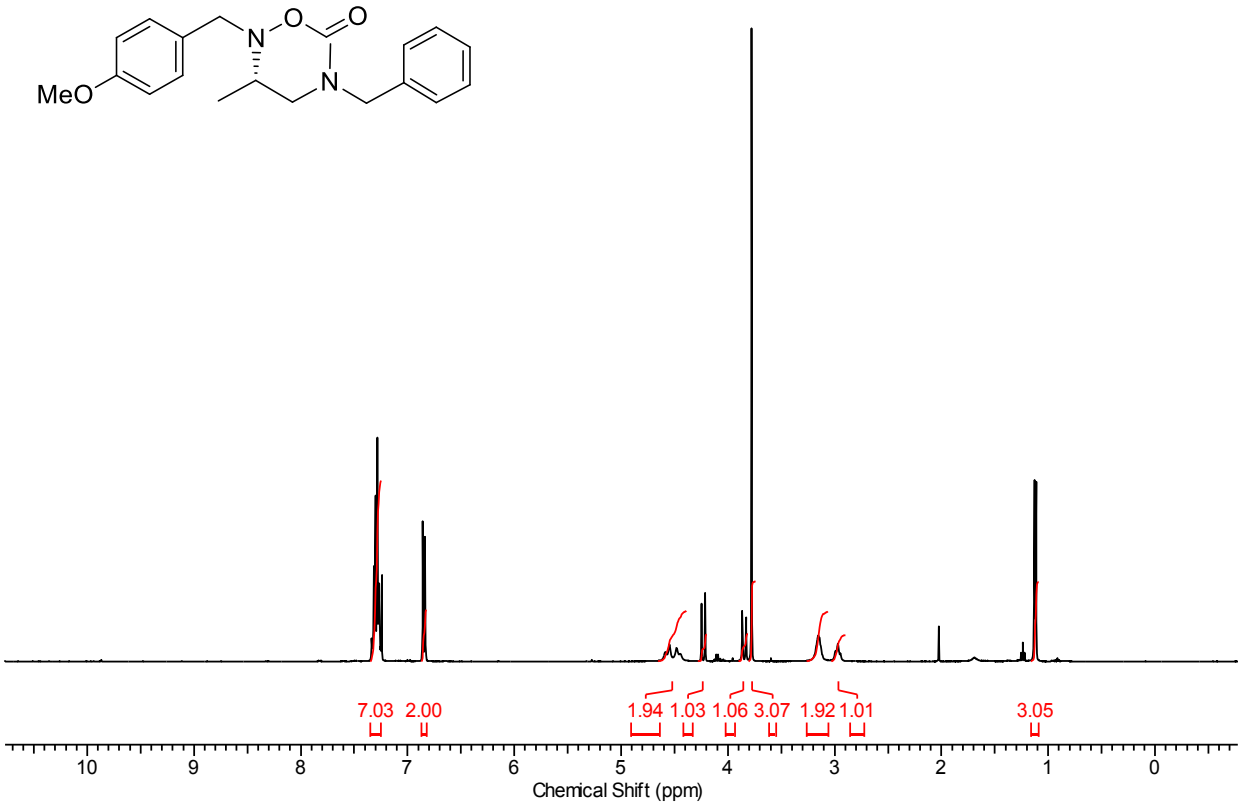


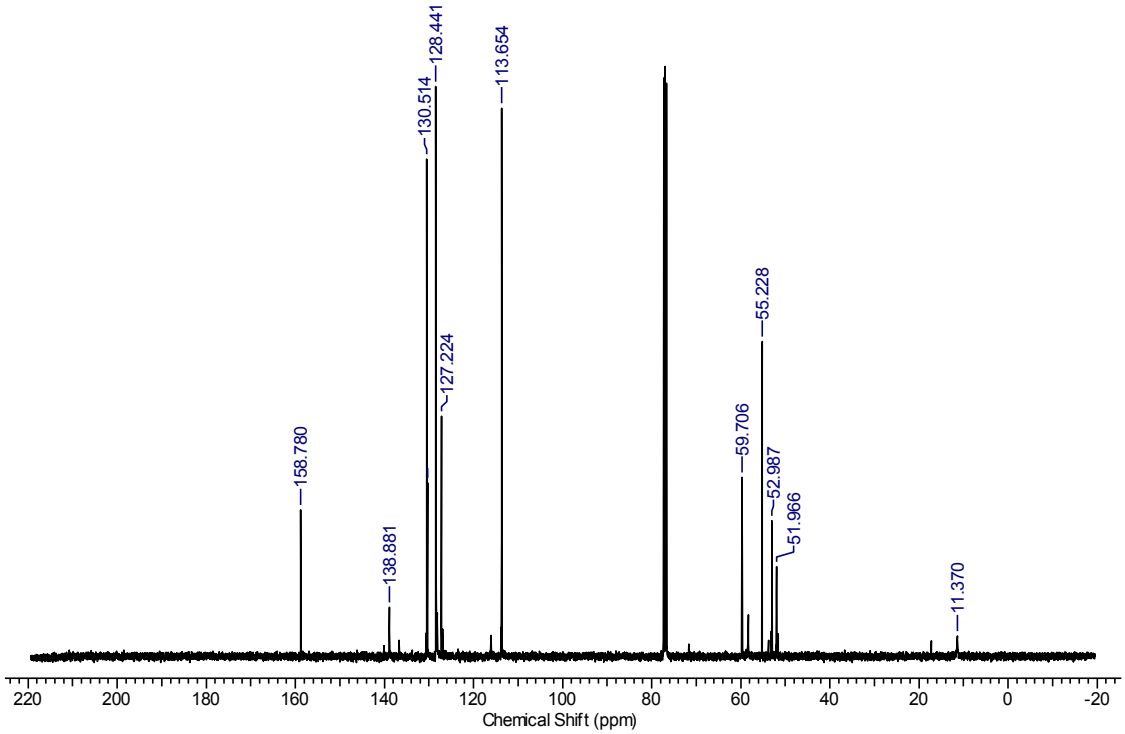


Derivative of 2.3b

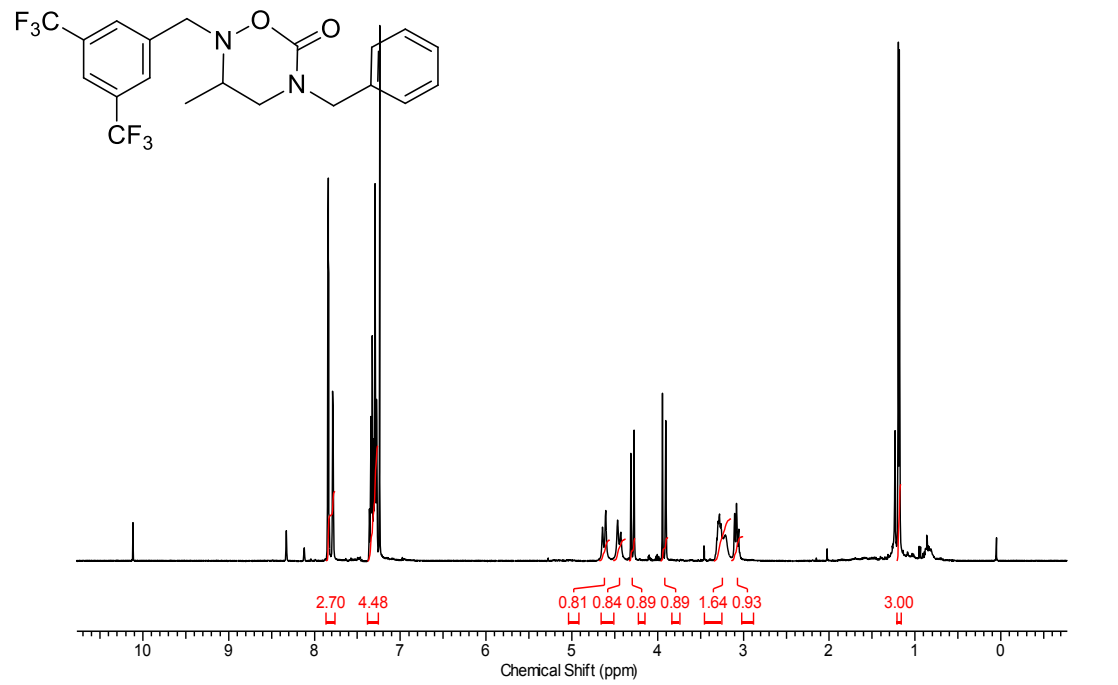


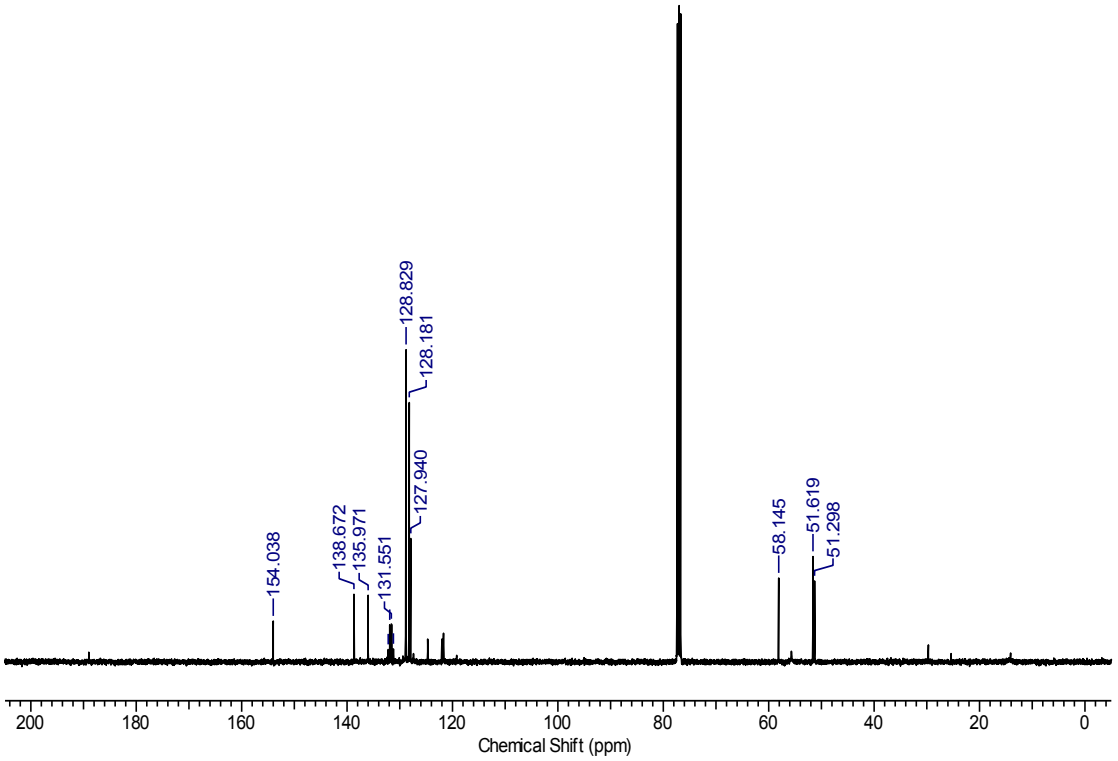
Derivative of 2.3c



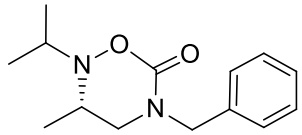


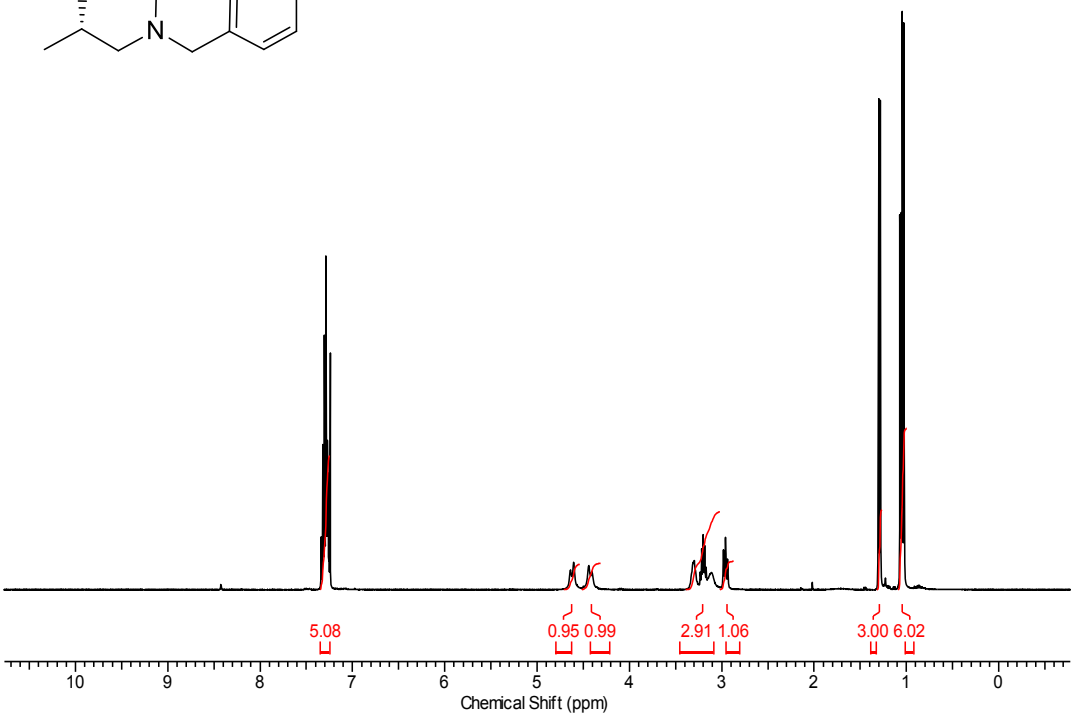
Derivative of 2.3d (*S*) and 2.7b (*R*)

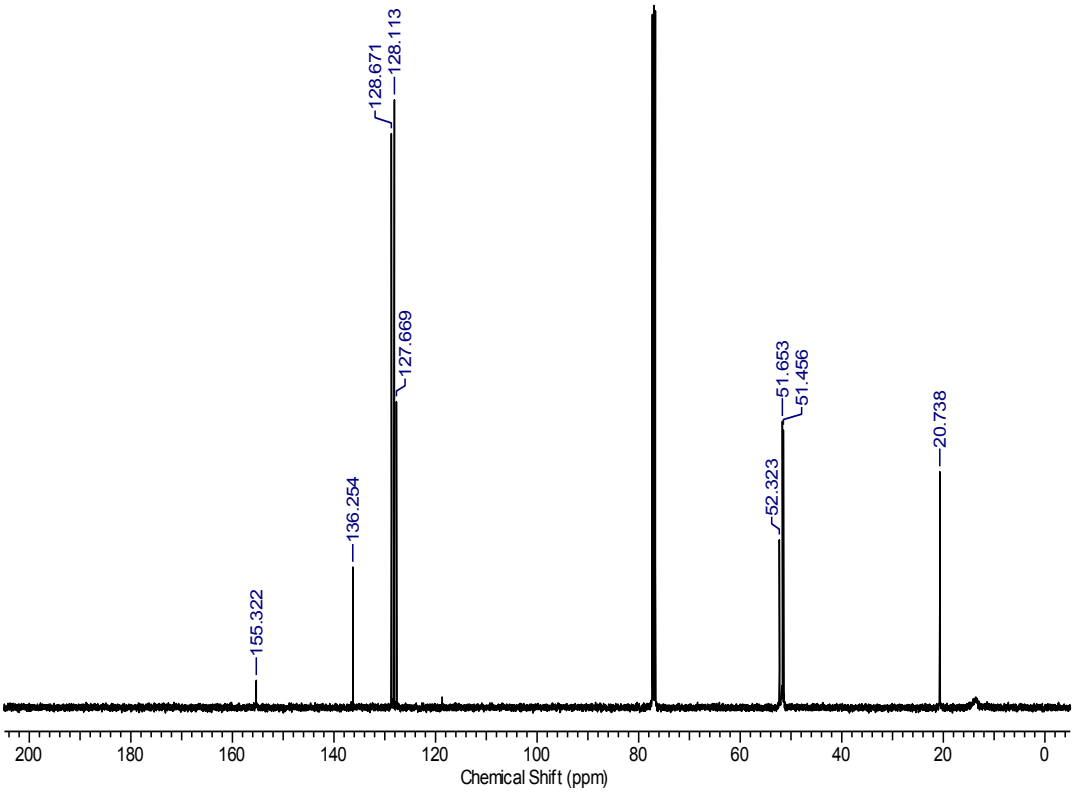




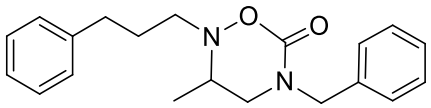
Derivative of 2.3e

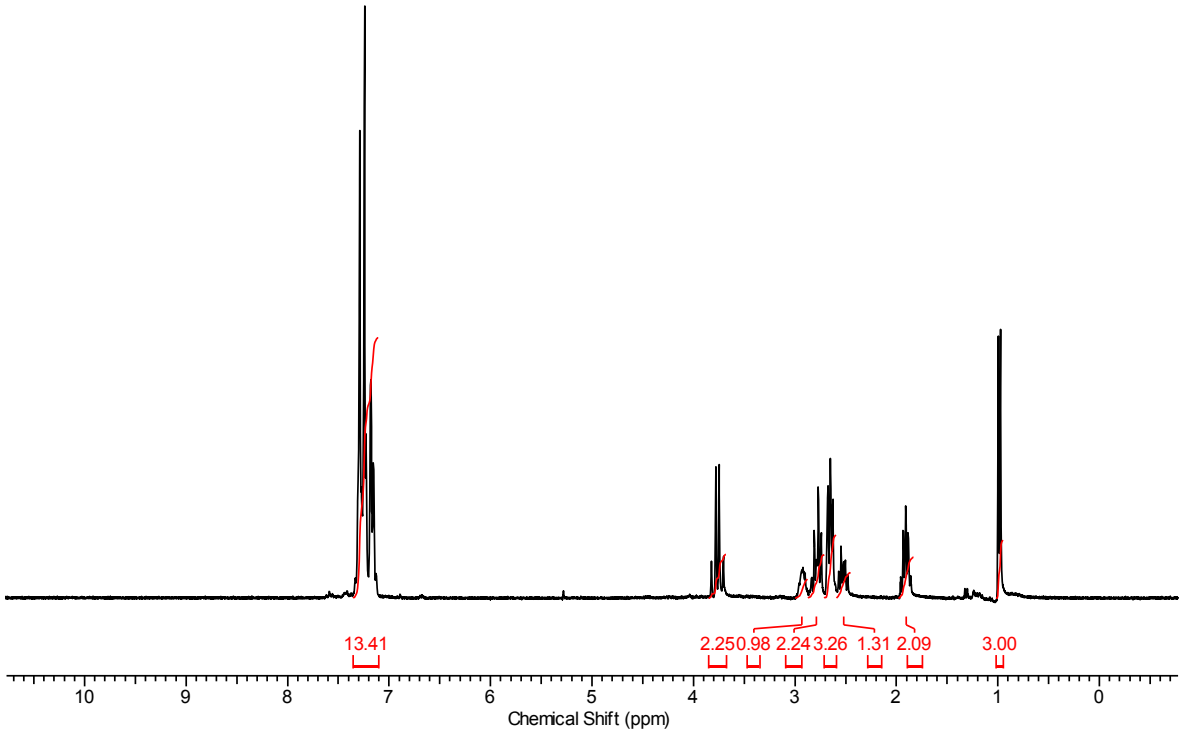


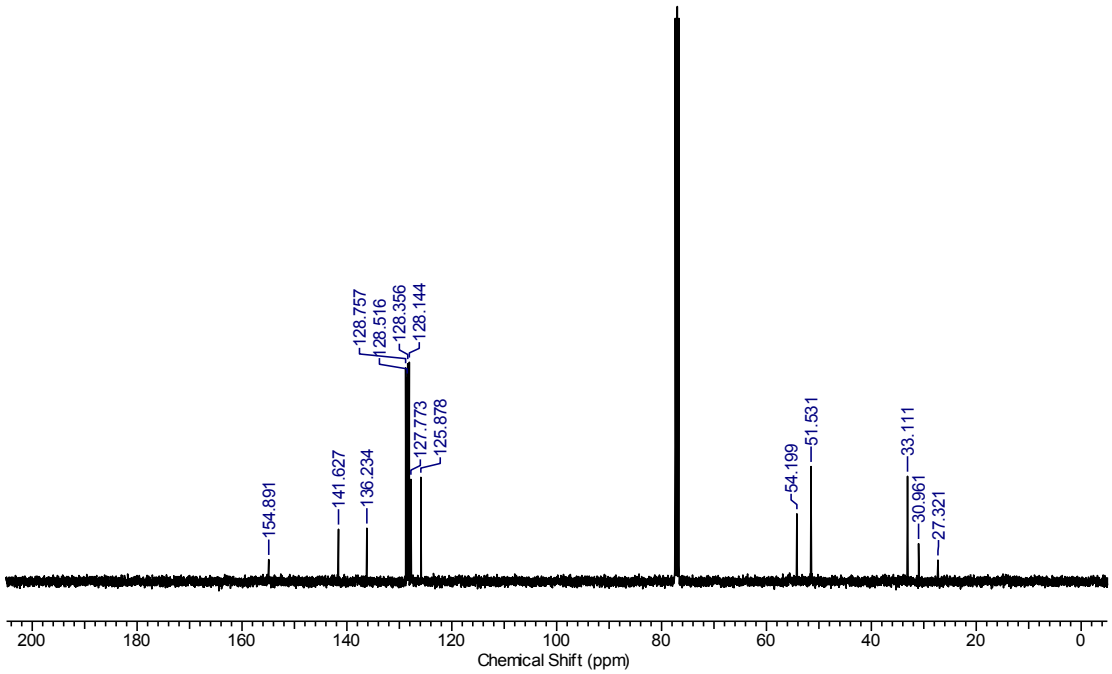




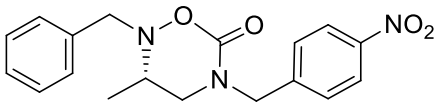
Derivative of 2.3f (*S*) and 2.7c (*R*)

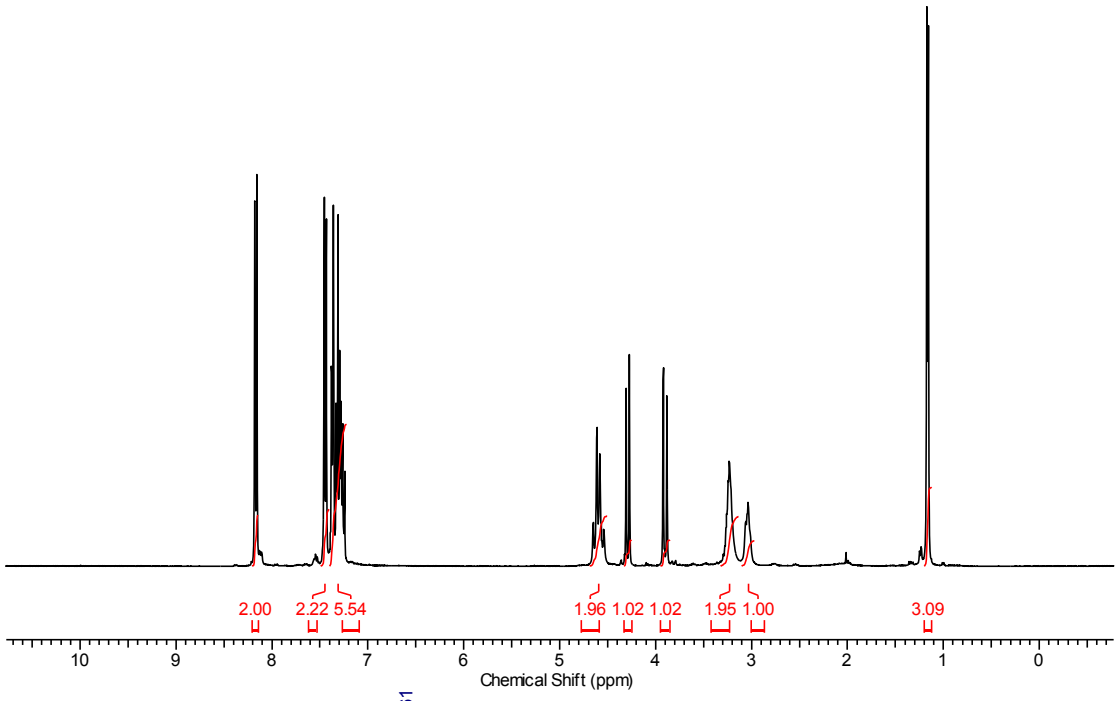


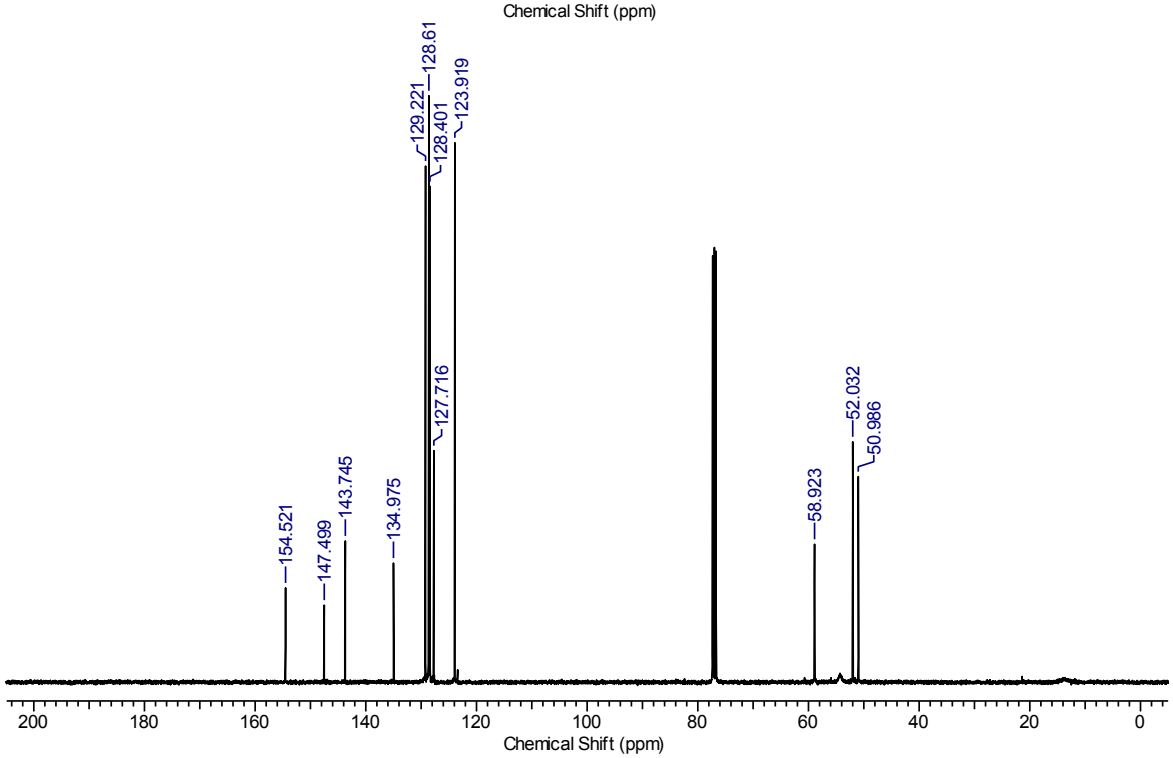




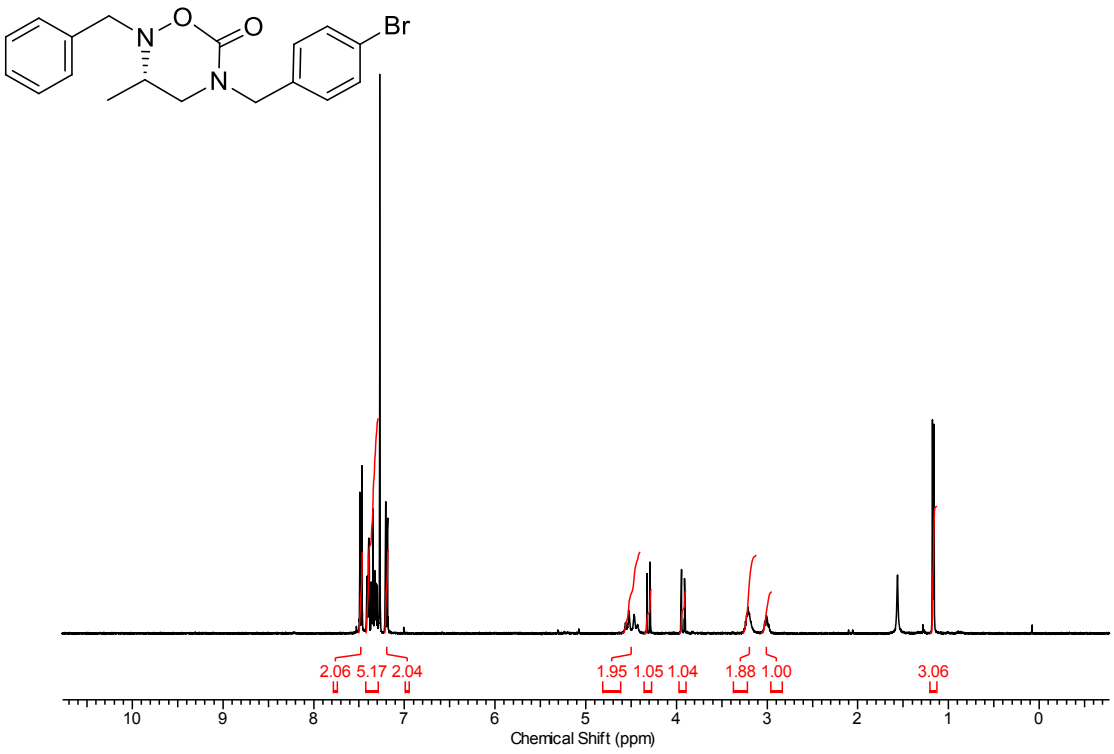
Derivative of 2.4d

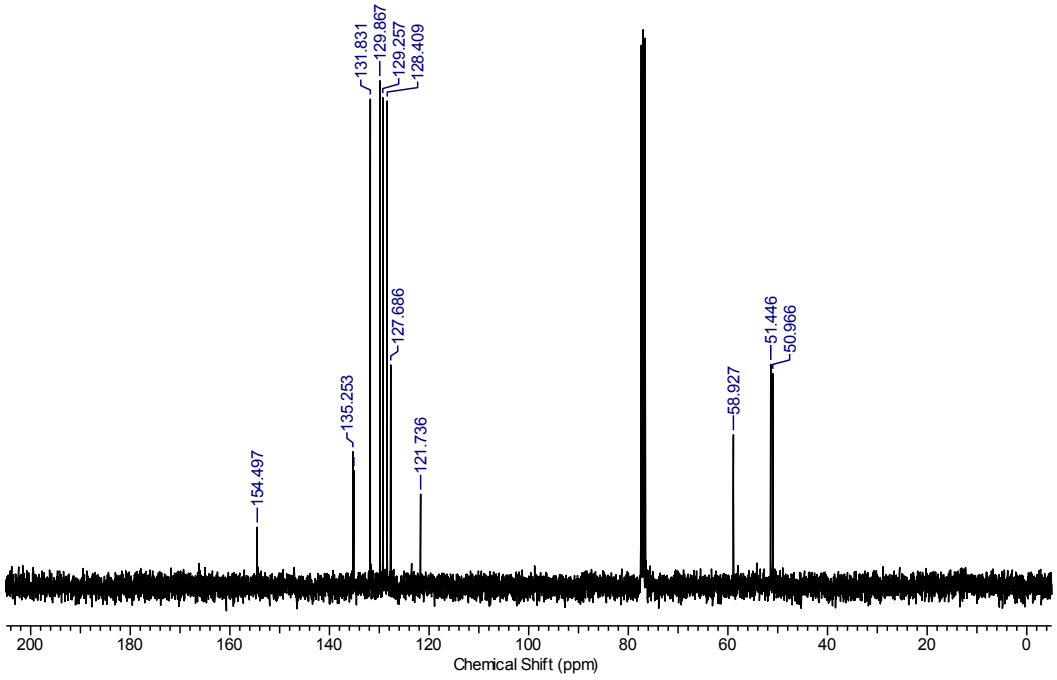




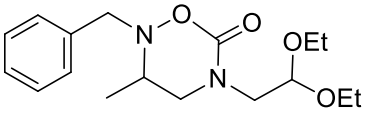


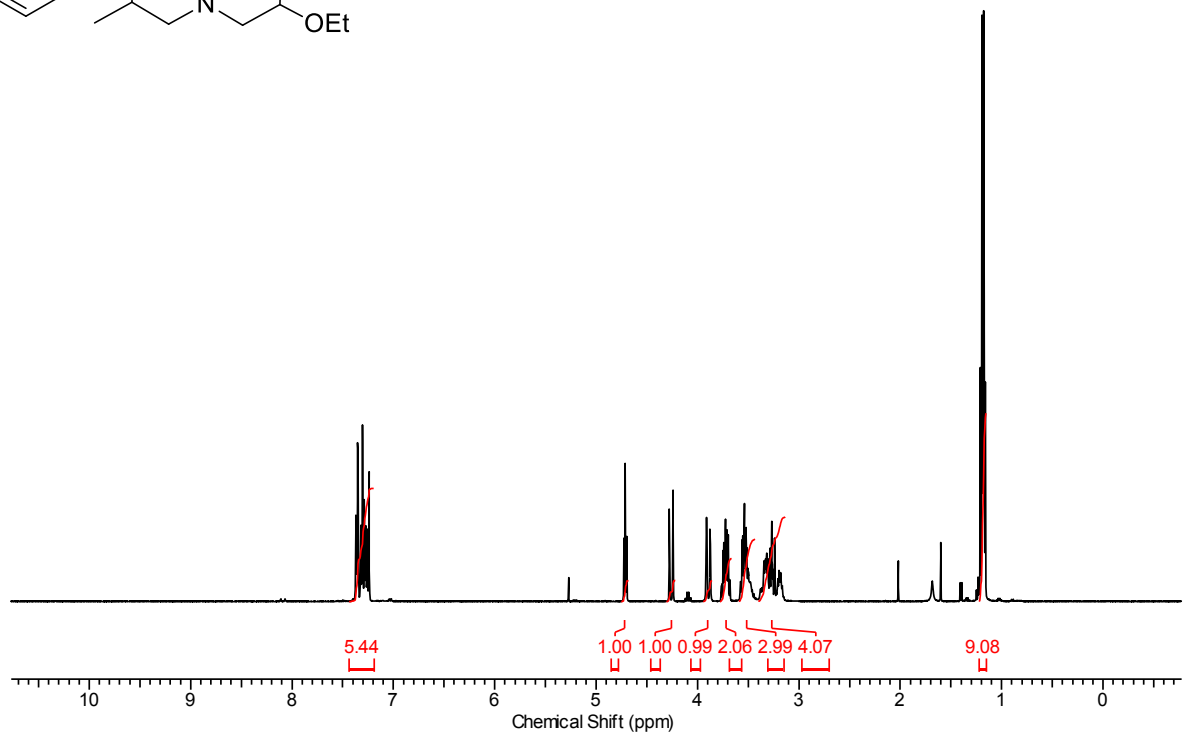
Derivative of 2.4c

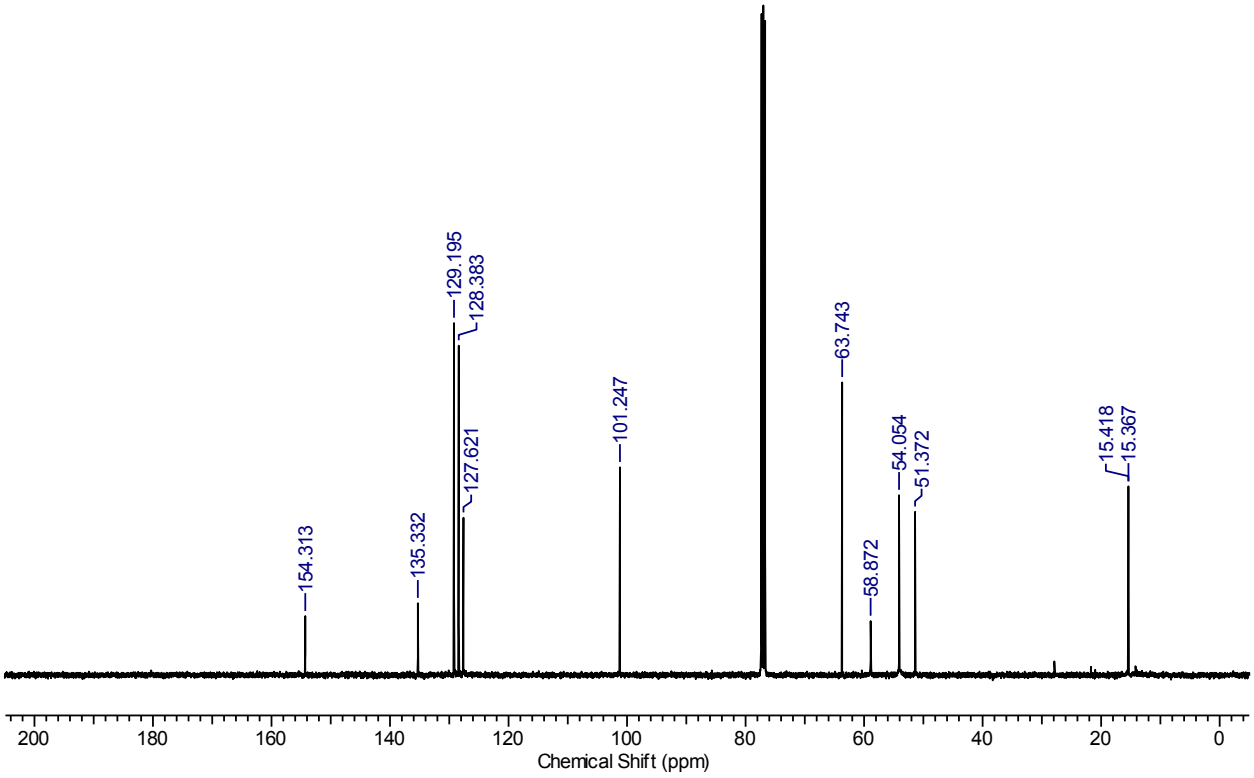




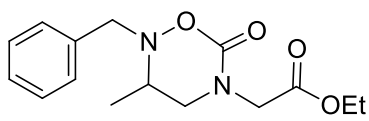
Derivative of 2.4e (*S*) and 2.7e (*R*)

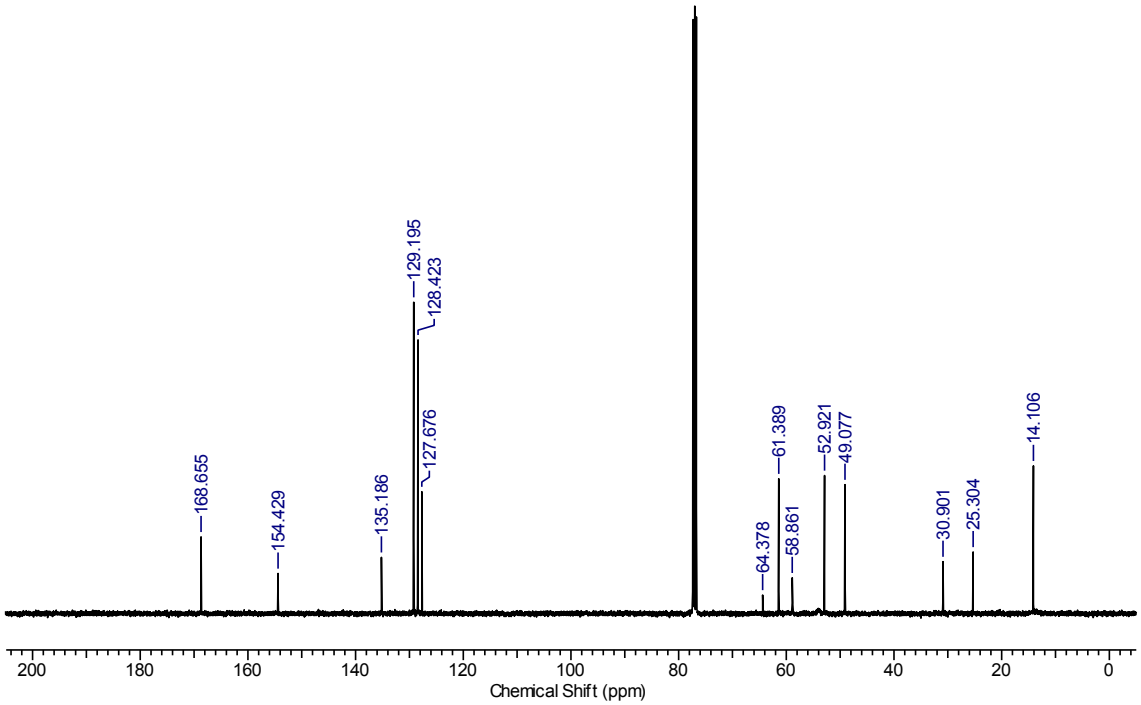




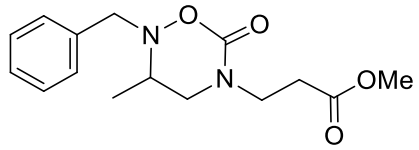


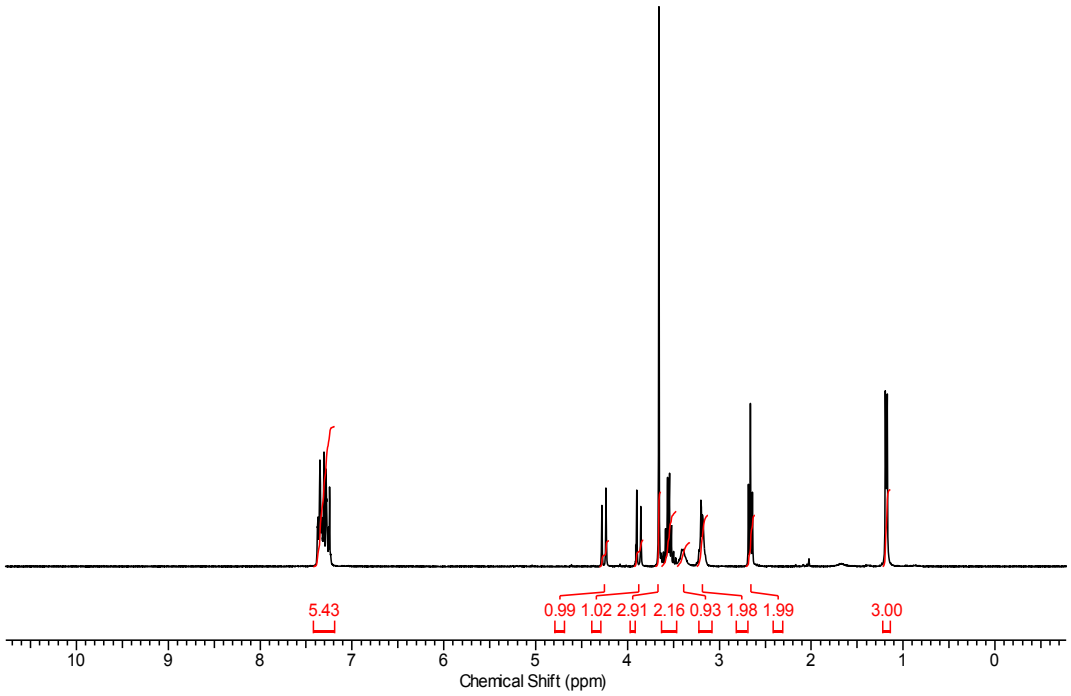
Derivative of 2.4f (*S*) and 2.7f (*R*)

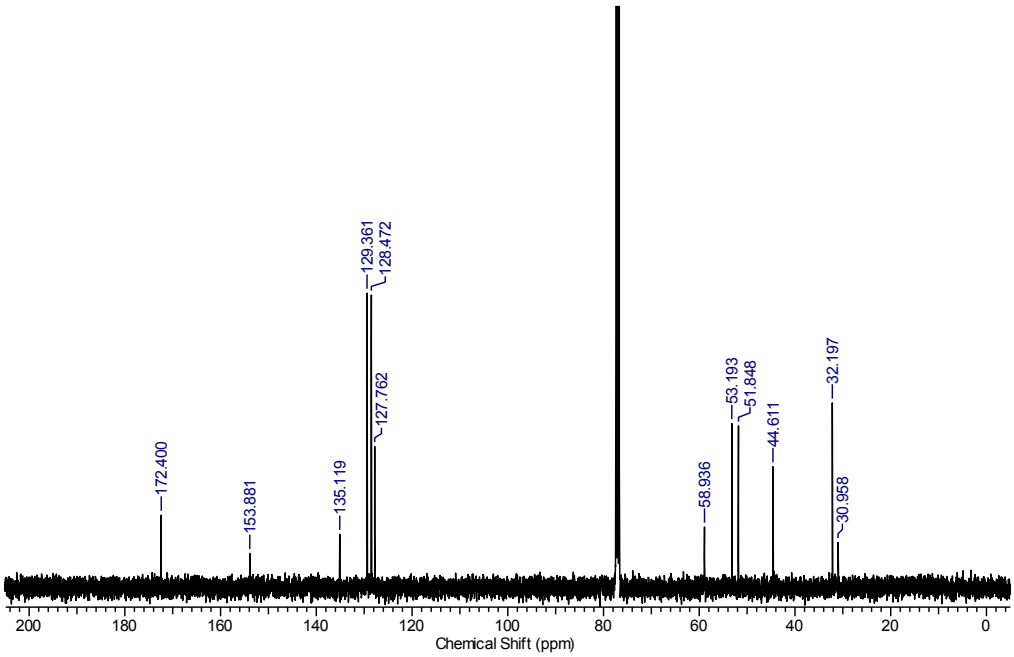




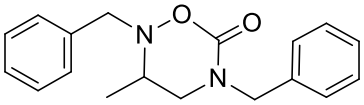
Derivative of 2.4g (*S*) and 2.7g (*R*)



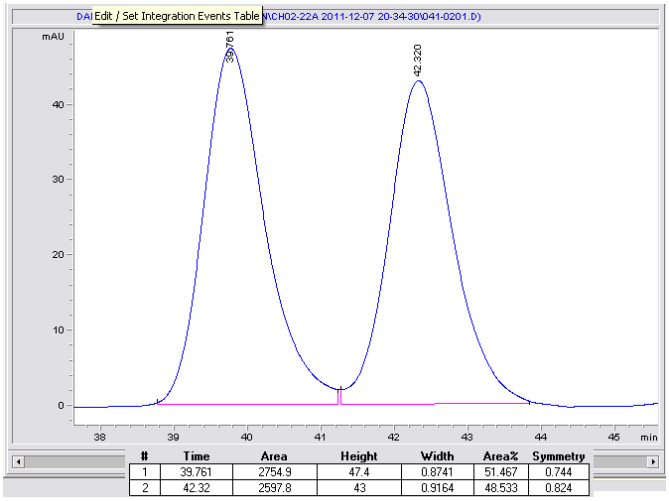




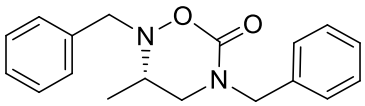
Copies of HPLC Spectra for derivatives for: 2.3a-2.3f (Table 2.3 Entries 1-6), 2.4a-2.4g (Table 2.4 Entries 1-7) and 2.7a-2.7g (Table 2.7 Entries 1-7)



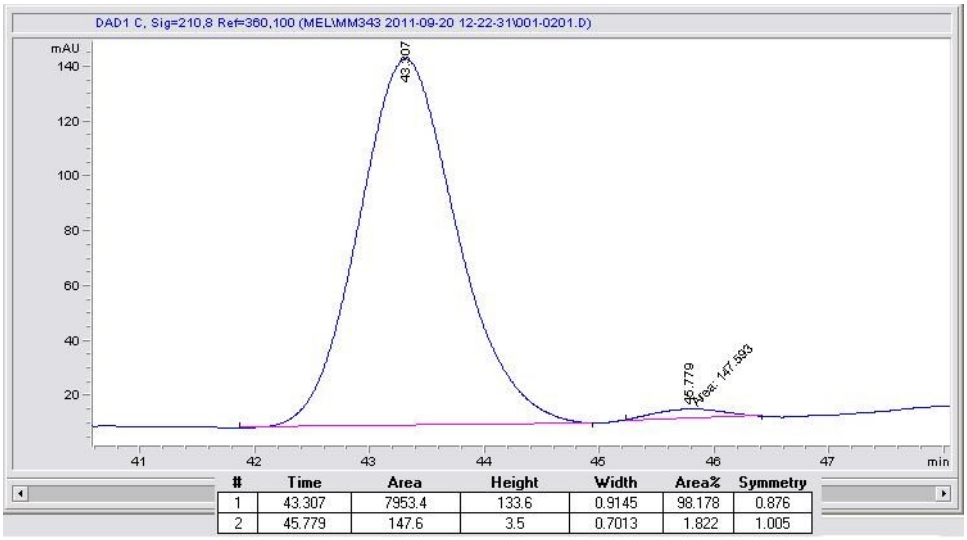
Racemic



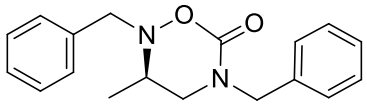
#	Time	Area	Height	Width	Area%	Symmetry
1	39.761	2754.9	47.4	0.8741	51.467	0.744
2	42.32	2597.8	43	0.9164	48.533	0.824



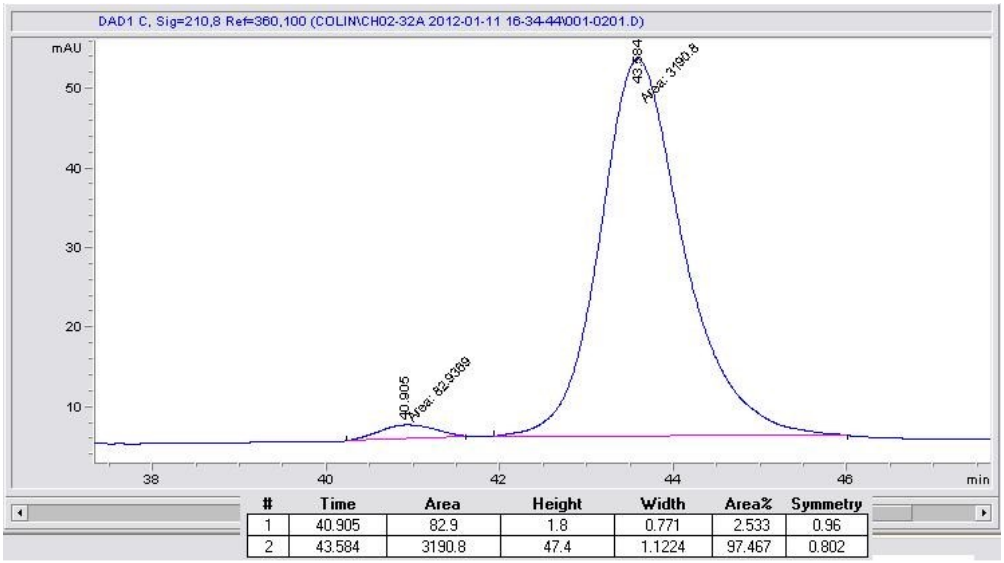
Using Catalyst 1a



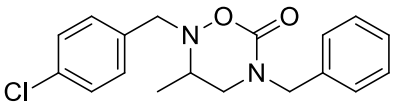
#	Time	Area	Height	Width	Area%	Symmetry
1	43.307	7953.4	133.6	0.9145	98.178	0.876
2	45.779	147.6	3.5	0.7013	1.822	1.005



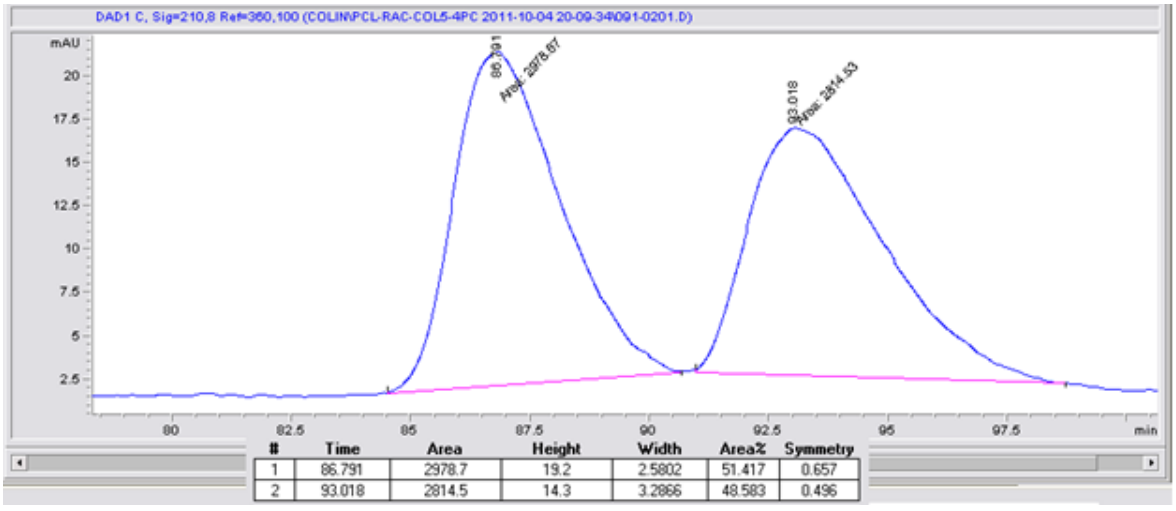
Using Catalyst 1h



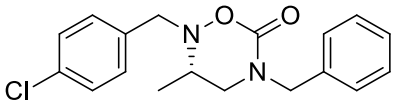
#	Time	Area	Height	Width	Area%	Symmetry
1	40.905	82.9	1.8	0.771	2.533	0.96
2	43.584	3190.8	47.4	1.1224	97.467	0.802



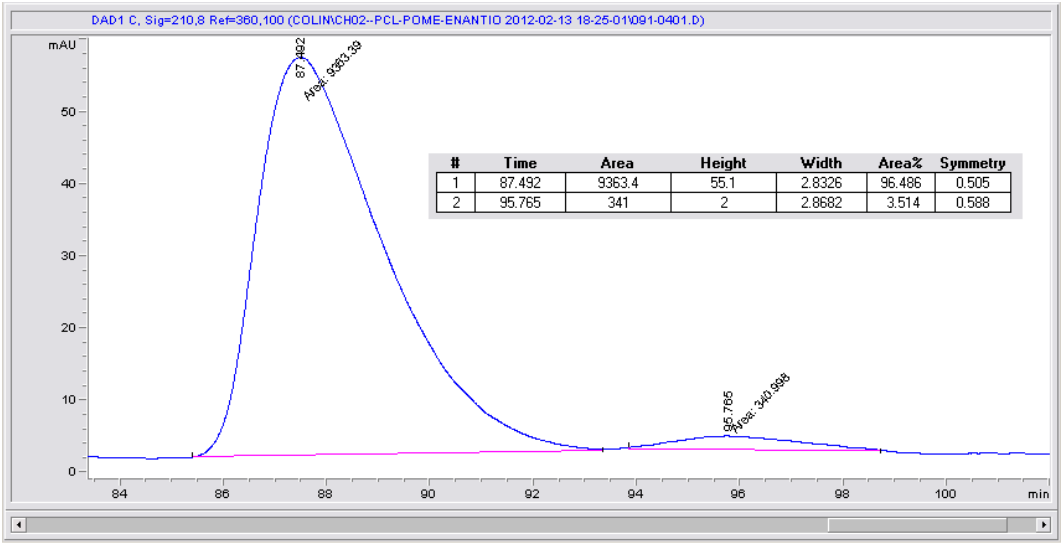
Racemic



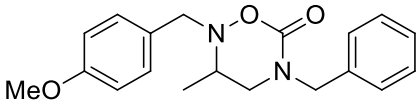
#	Time	Area	Height	Width	Area%	Symmetry
1	86.791	2978.7	19.2	2.5802	51.417	0.657
2	93.018	2814.5	14.3	3.2866	48.583	0.496



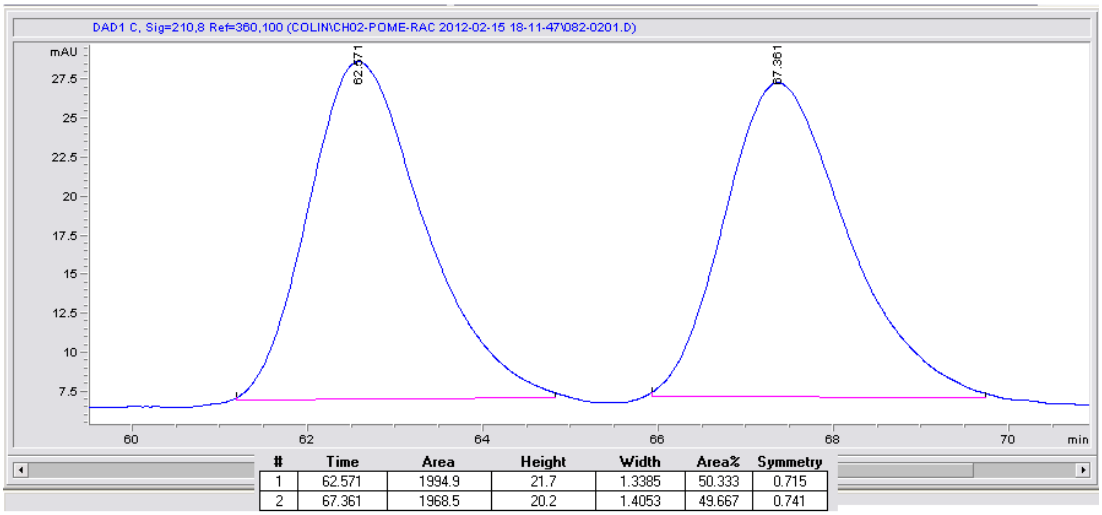
Using Catalyst 1a



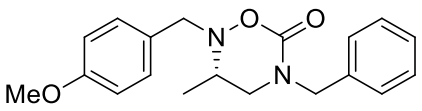
#	Time	Area	Height	Width	Area%	Symmetry
1	87.492	9363.4	55.1	2.8326	96.486	0.505
2	95.765	341	2	2.8682	3.514	0.588



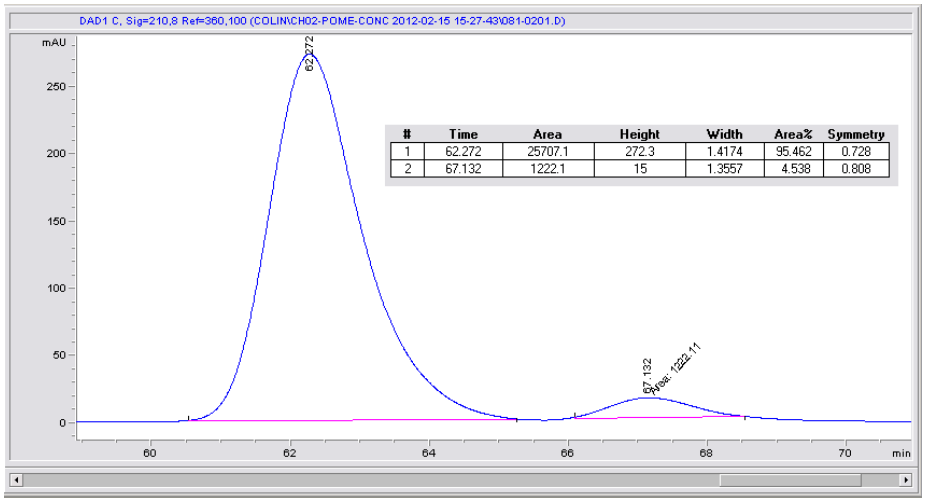
Racemic



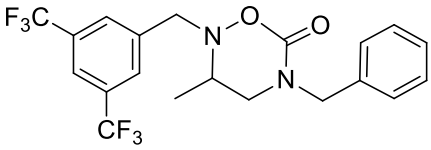
#	Time	Area	Height	Width	Area%	Symmetry
1	62.571	1994.9	21.7	1.3385	50.333	0.715
2	67.361	1968.5	20.2	1.4053	49.667	0.741



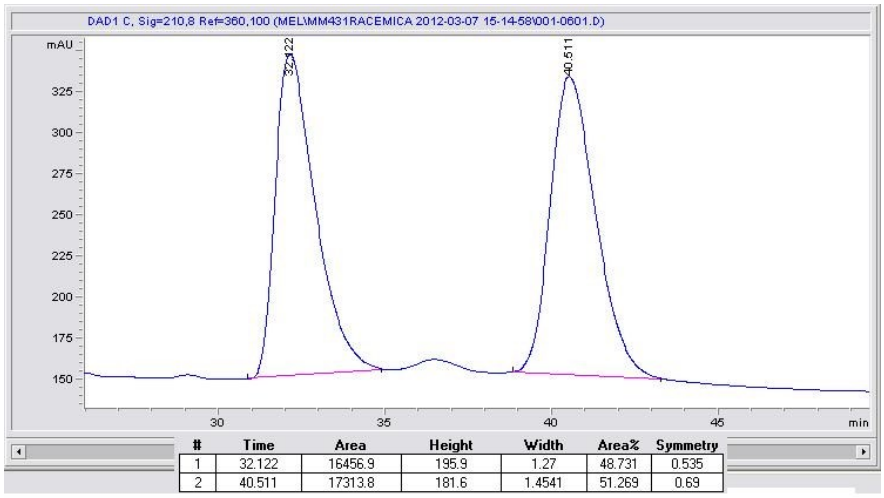
Using Catalyst 1a



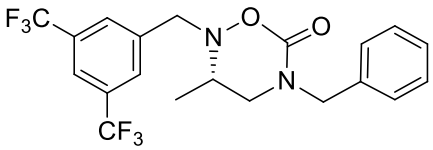
#	Time	Area	Height	Width	Area%	Symmetry
1	62.272	25707.1	272.3	1.4174	95.462	0.728
2	67.132	1222.1	15	1.3557	4.538	0.808



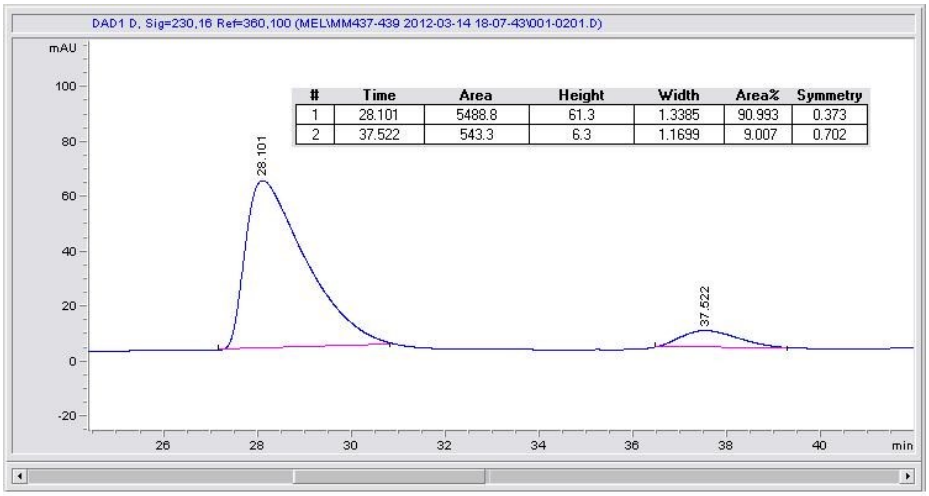
Racemic



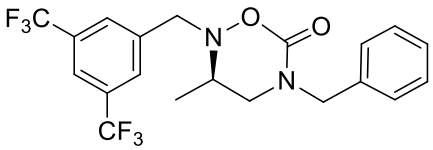
#	Time	Area	Height	Width	Area%	Symmetry
1	32.122	16456.9	195.9	1.27	48.731	0.535
2	40.511	17313.8	181.6	1.4541	51.269	0.69



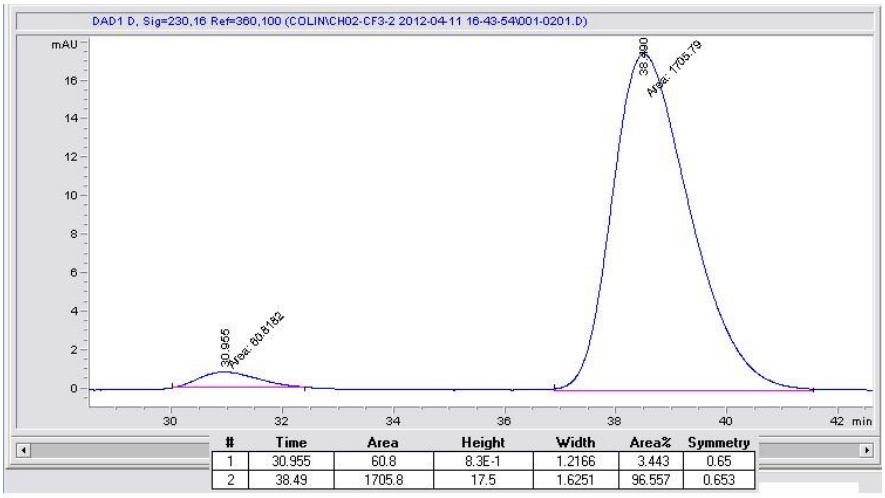
Using Catalyst 1a



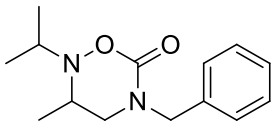
#	Time	Area	Height	Width	Area%	Symmetry
1	28.101	5488.8	61.3	1.3385	90.993	0.373
2	37.522	543.3	6.3	1.1699	9.007	0.702



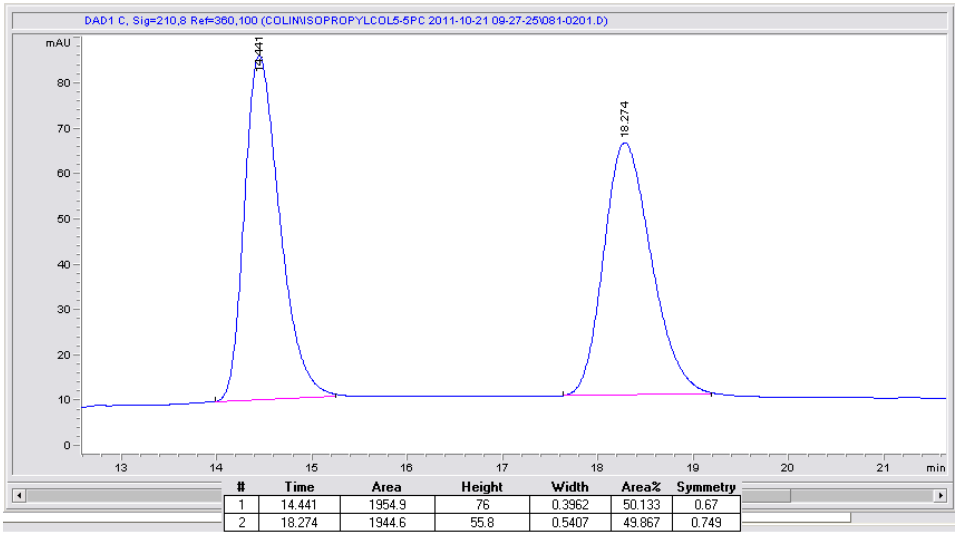
Using Catalyst 1h



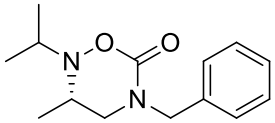
#	Time	Area	Height	Width	Area%	Symmetry
1	30.955	60.8	8.3E-1	1.2166	3.443	0.65
2	38.49	1705.8	17.5	1.6251	96.557	0.653



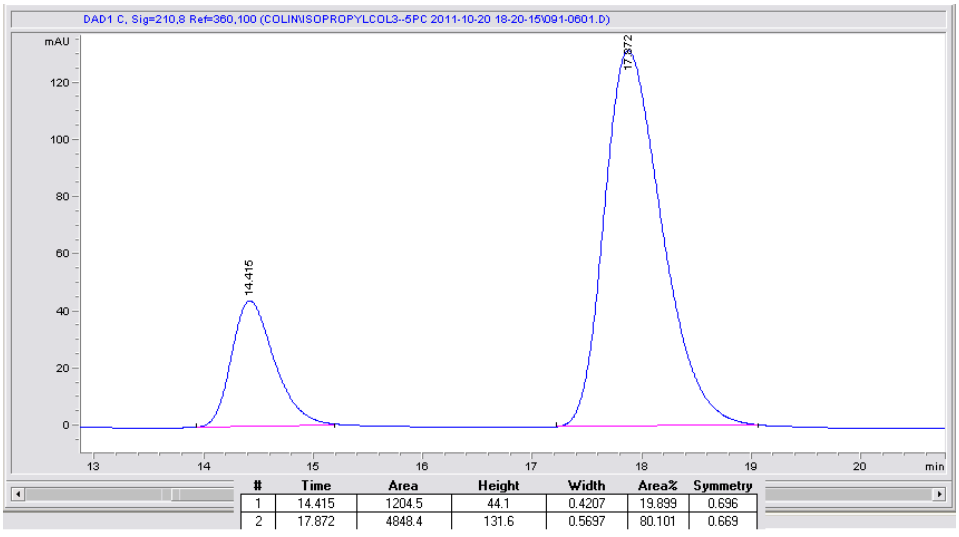
Racemic



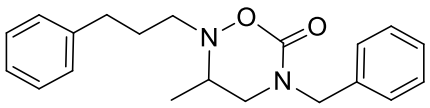
#	Time	Area	Height	Width	Area%	Symmetry
1	14.441	1954.9	76	0.3962	50.133	0.67
2	18.274	1944.6	55.8	0.5407	49.867	0.749



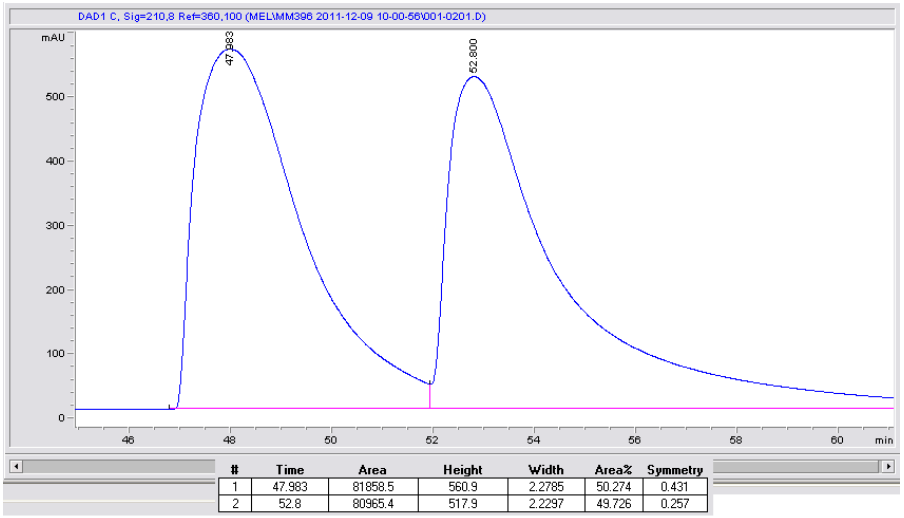
Using Catalyst 1a



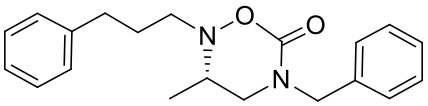
#	Time	Area	Height	Width	Area%	Symmetry
1	14.415	1204.5	44.1	0.4207	19.899	0.696
2	17.872	4848.4	131.6	0.5697	80.101	0.669



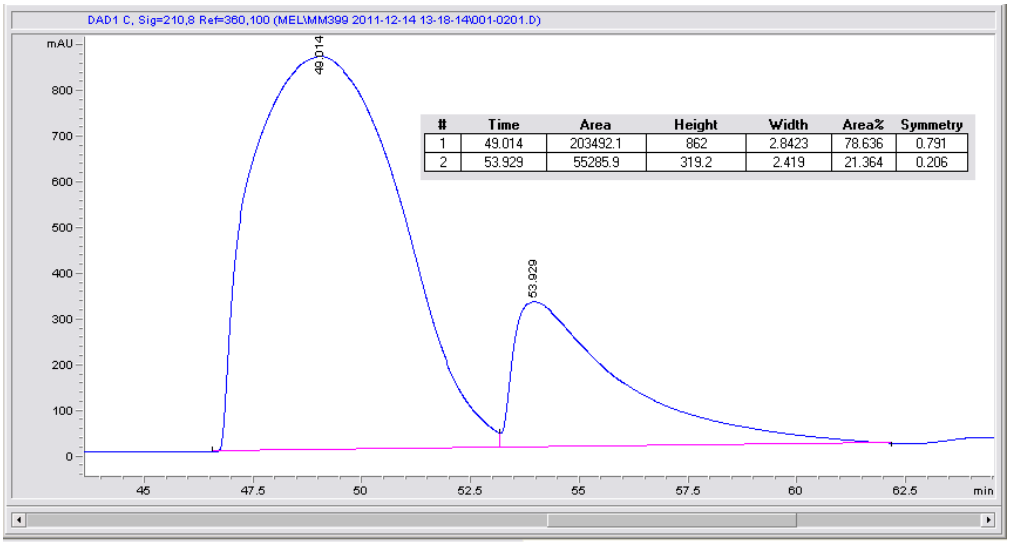
Racemic



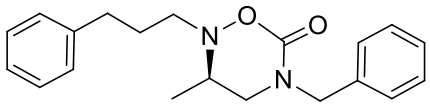
#	Time	Area	Height	Width	Area%	Symmetry
1	47.983	81858.5	560.9	2.2785	50.274	0.431
2	52.8	80965.4	517.9	2.2297	49.726	0.257



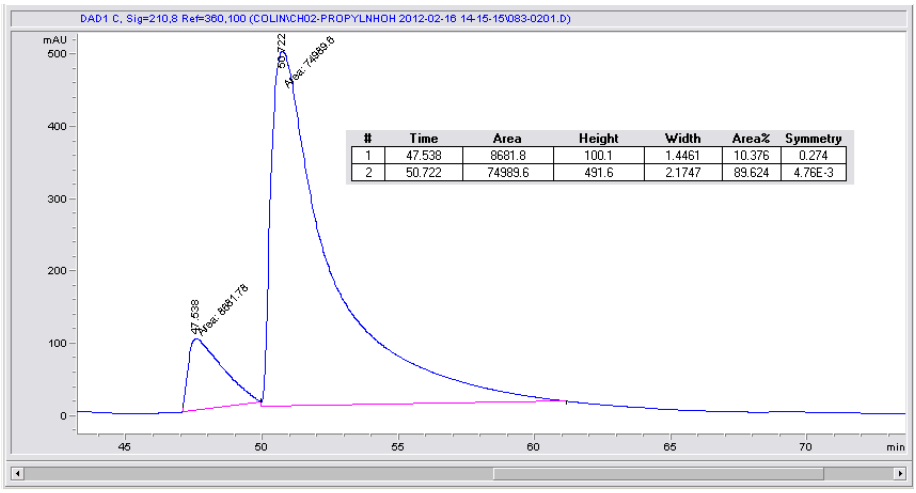
Using Catalyst 1a



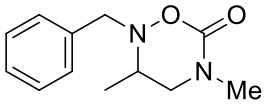
#	Time	Area	Height	Width	Area%	Symmetry
1	49.014	203492.1	862	2.8423	78.636	0.791
2	53.929	55285.9	319.2	2.419	21.364	0.206



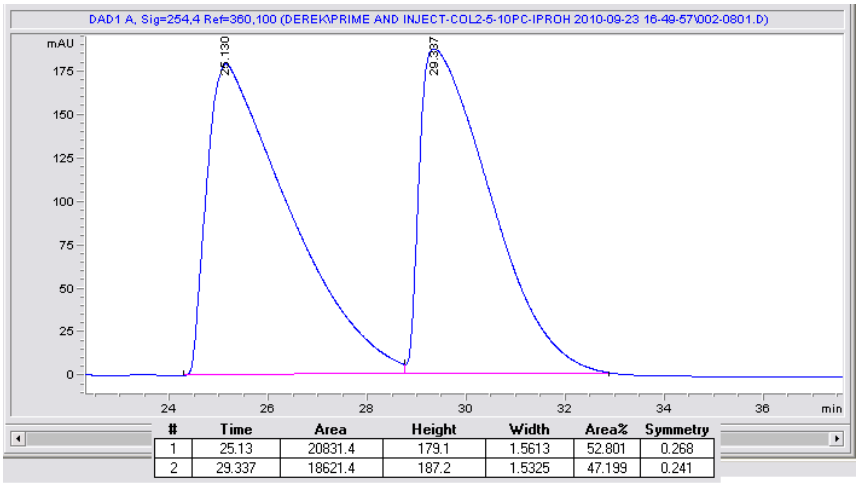
Using Catalyst 1h



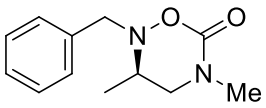
#	Time	Area	Height	Width	Area%	Symmetry
1	47.538	8681.8	100.1	1.4461	10.376	0.274
2	50.722	74989.6	491.6	2.1747	89.624	4.76E-3



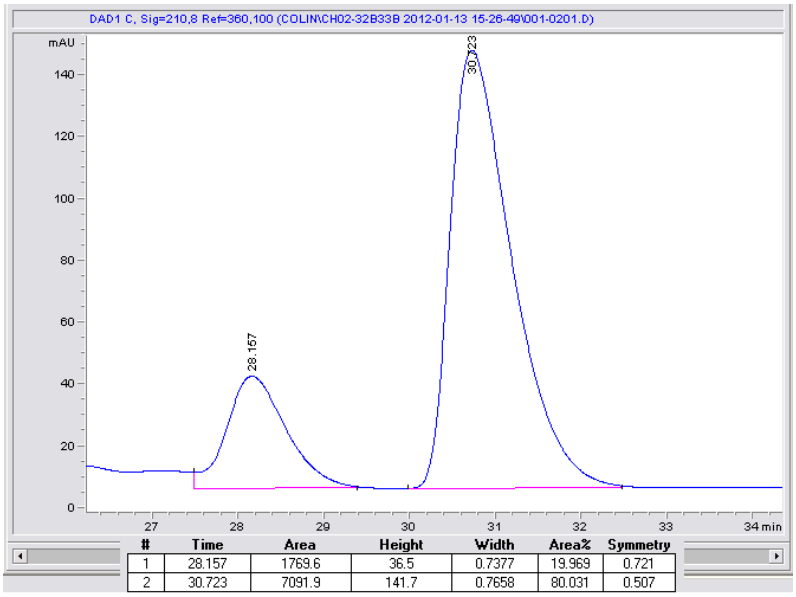
Racemic



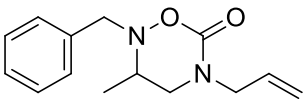
#	Time	Area	Height	Width	Area%	Symmetry
1	25.13	20831.4	179.1	1.5613	52.801	0.268
2	29.337	18621.4	187.2	1.5325	47.199	0.241



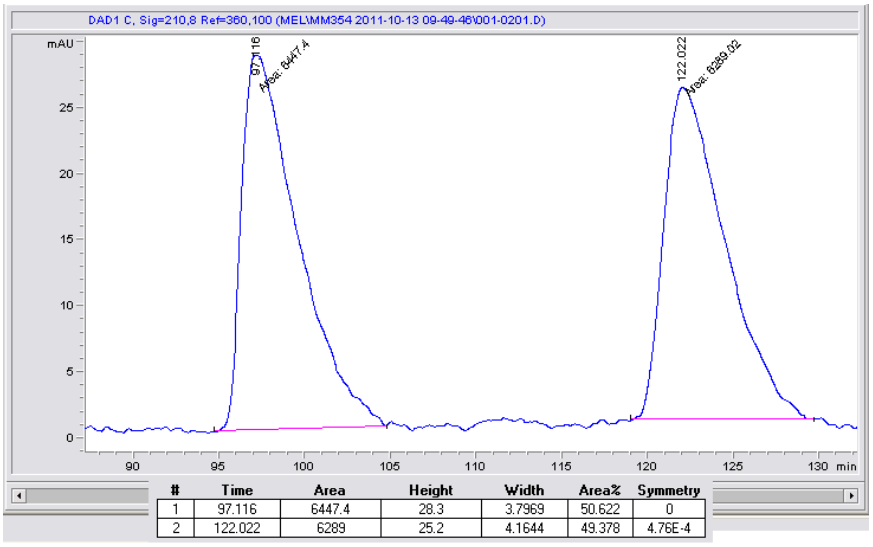
Using Catalyst 1a



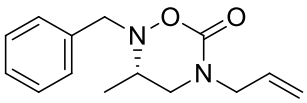
#	Time	Area	Height	Width	Area%	Symmetry
1	28.157	1769.6	36.5	0.7377	19.969	0.721
2	30.723	7091.9	141.7	0.7658	80.031	0.507



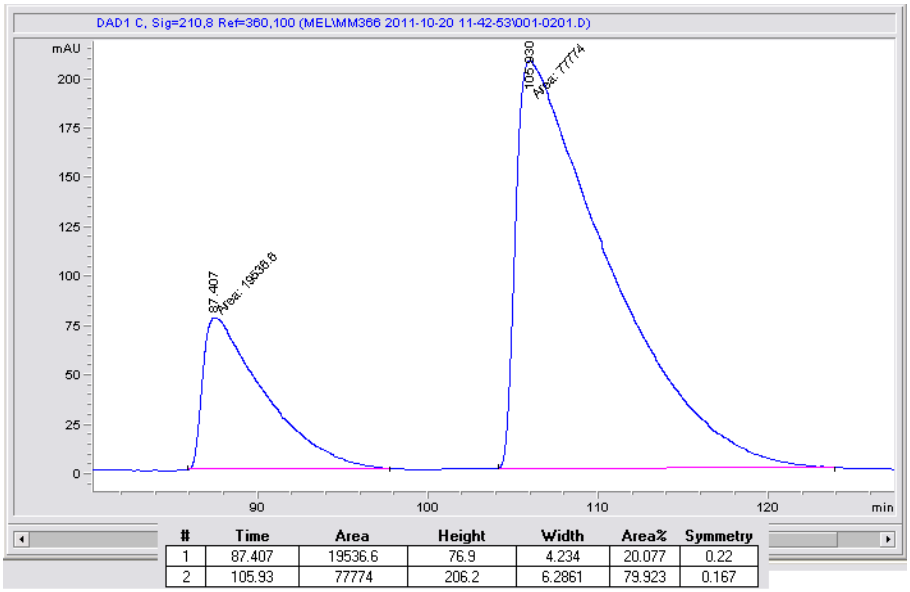
Racemic



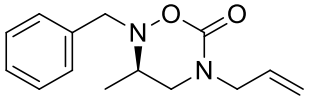
#	Time	Area	Height	Width	Area%	Symmetry
1	97.116	6447.4	28.3	3.7969	50.622	0
2	122.022	6289	25.2	4.1644	49.378	4.76E-4



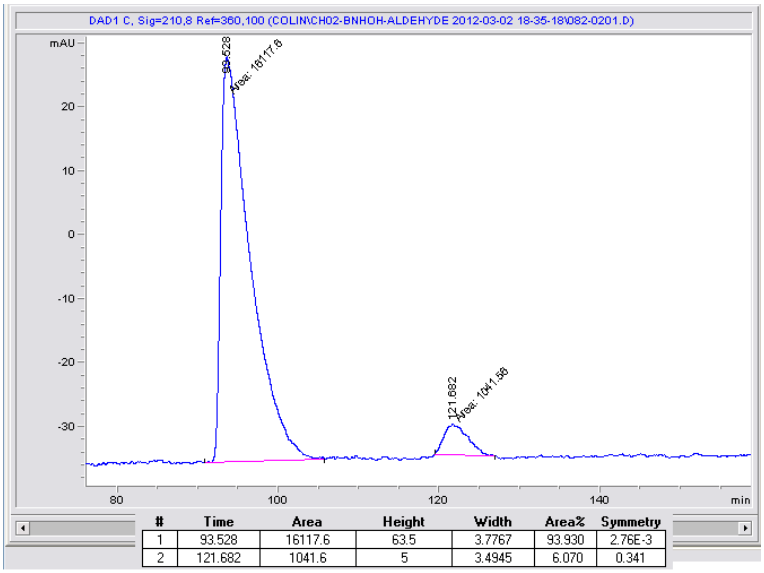
Using Catalyst 1a



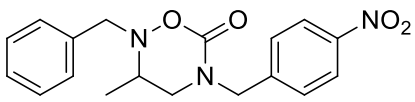
#	Time	Area	Height	Width	Area%	Symmetry
1	87.407	19536.6	76.9	4.234	20.077	0.22
2	105.93	77774	206.2	6.2861	79.923	0.167



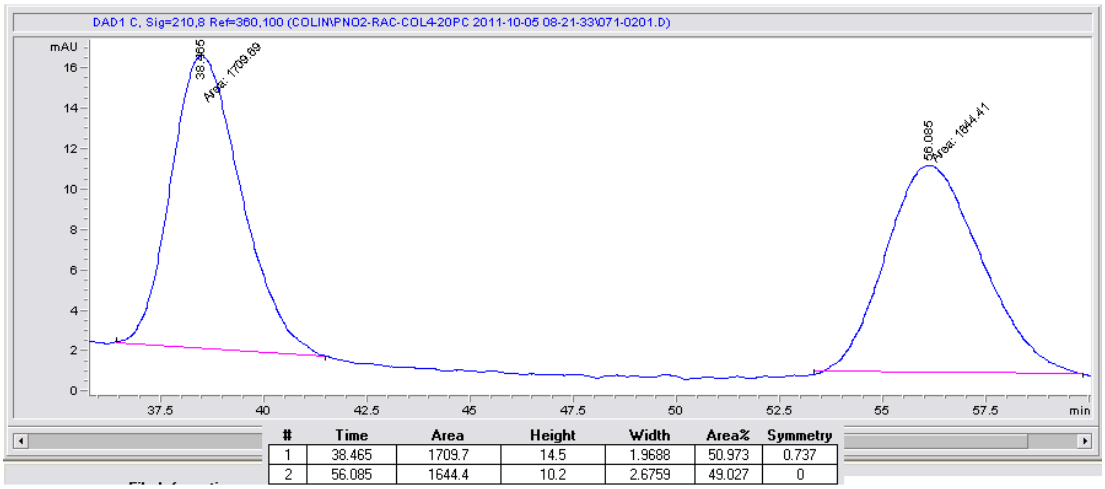
Using Catalyst 1h



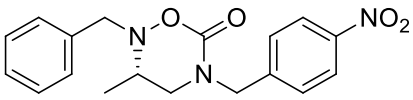
#	Time	Area	Height	Width	Area%	Symmetry
1	93.528	16117.6	63.5	3.7767	93.930	2.76E-3
2	121.682	1041.6	5	3.4945	6.070	0.341



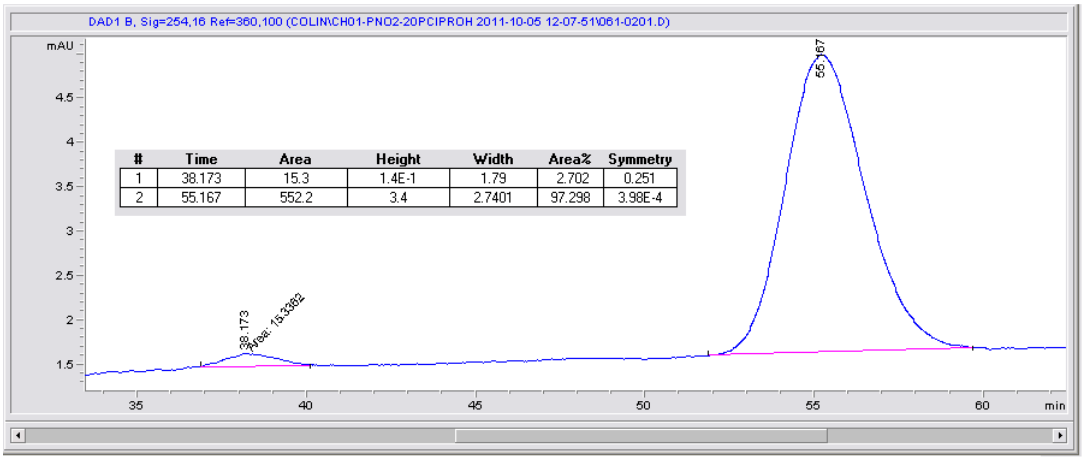
Racemic



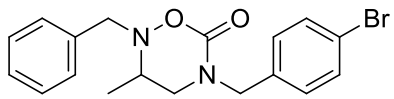
#	Time	Area	Height	Width	Area%	Symmetry
1	38.465	1709.7	14.5	1.9688	50.973	0.737
2	56.085	1644.4	10.2	2.6759	49.027	0



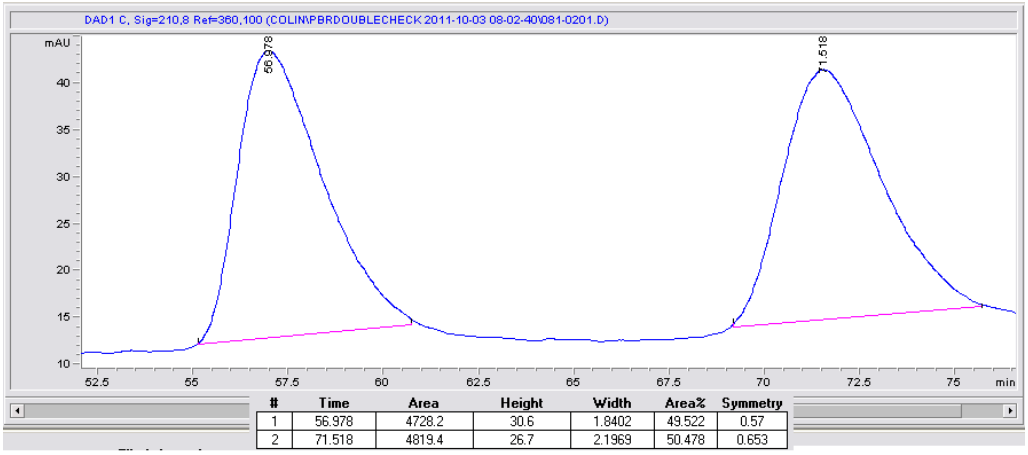
Using Catalyst 1a



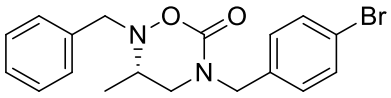
#	Time	Area	Height	Width	Area%	Symmetry
1	38.173	15.3	1.4E-1	1.79	2.702	0.251
2	55.167	552.2	3.4	2.7401	97.298	3.98E-4



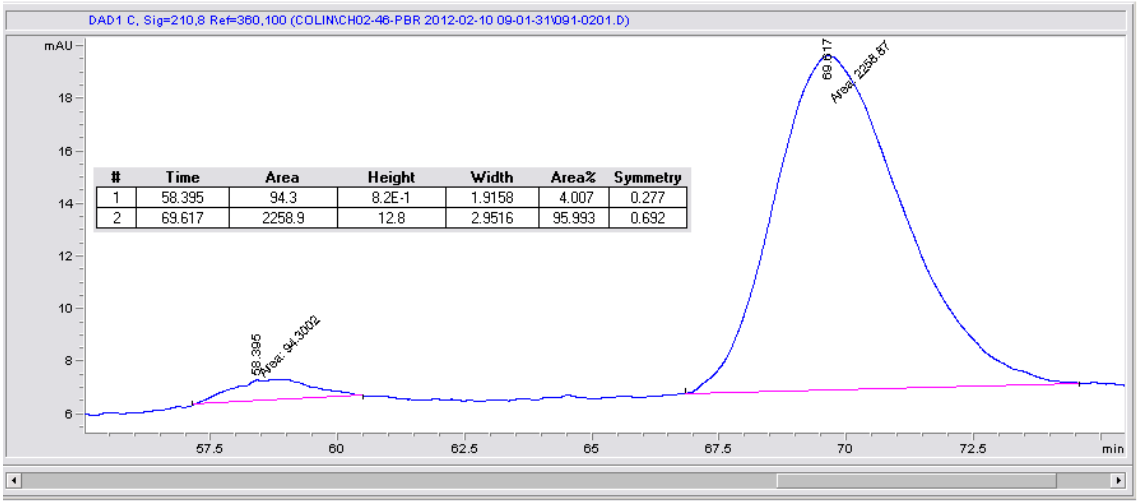
Racemic



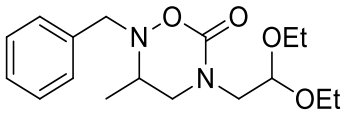
#	Time	Area	Height	Width	Area%	Symmetry
1	56.978	4728.2	30.6	1.8402	49.522	0.57
2	71.518	4819.4	26.7	2.1969	50.478	0.653



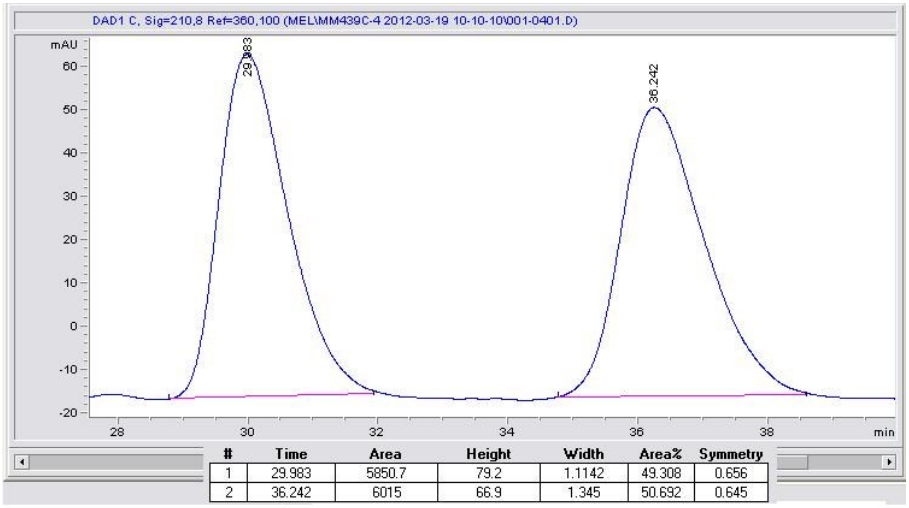
Using Catalyst 1a



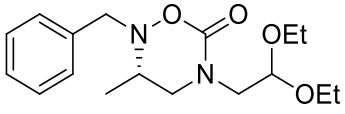
#	Time	Area	Height	Width	Area%	Symmetry
1	58.395	94.3	8.2E-1	1.9158	4.007	0.277
2	69.617	2258.9	12.8	2.9516	95.993	0.692



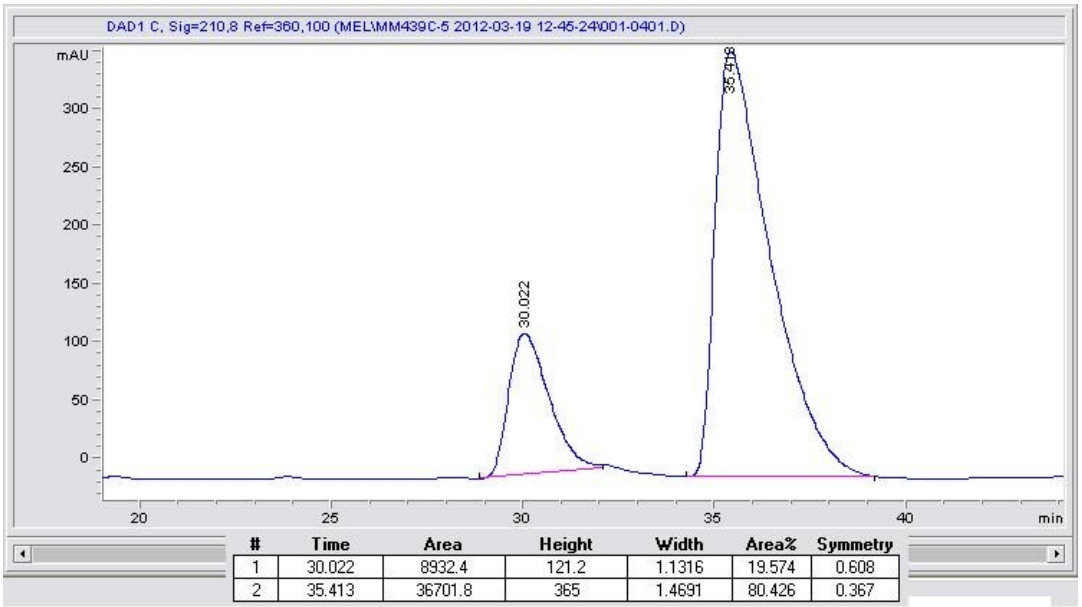
Racemic



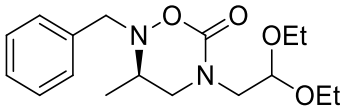
#	Time	Area	Height	Width	Area%	Symmetry
1	29.983	5850.7	79.2	1.1142	49.308	0.656
2	36.242	6015	66.9	1.345	50.692	0.645



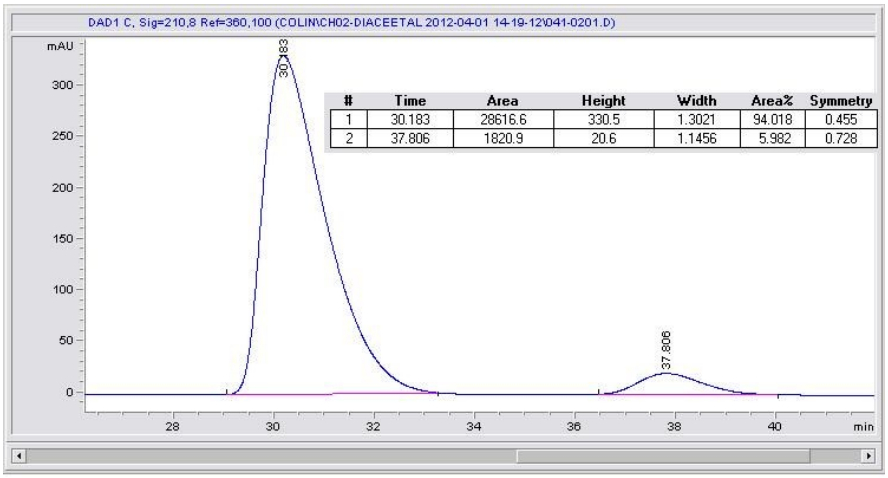
Using Catalyst 1a



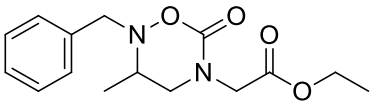
#	Time	Area	Height	Width	Area%	Symmetry
1	30.022	8932.4	121.2	1.1316	19.574	0.608
2	35.413	36701.8	365	1.4691	80.426	0.367



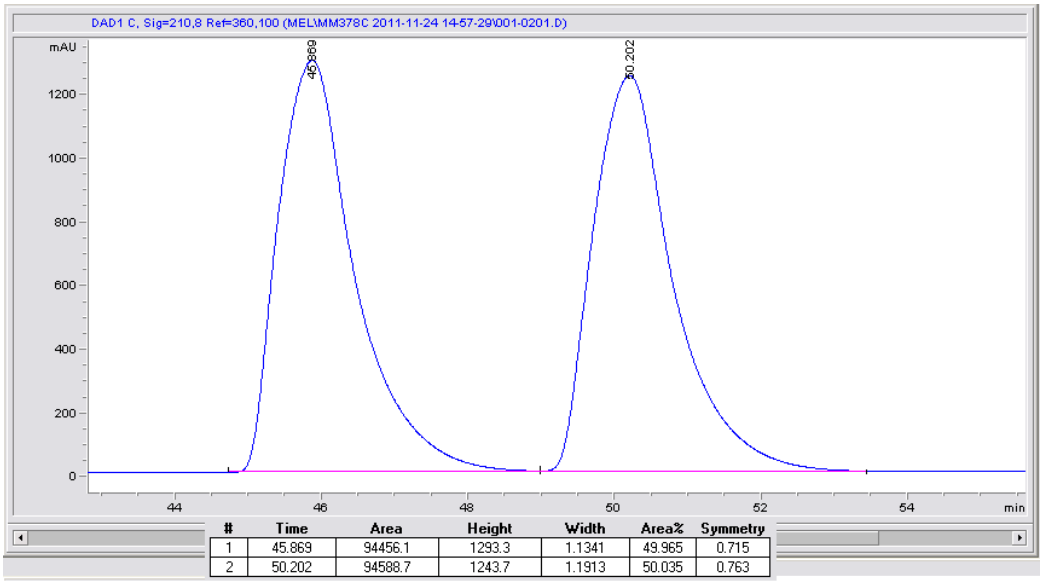
Using Catalyst 1h



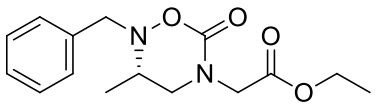
#	Time	Area	Height	Width	Area%	Symmetry
1	30.183	28616.6	330.5	1.3021	94.018	0.455
2	37.806	1820.9	20.6	1.1456	5.982	0.728



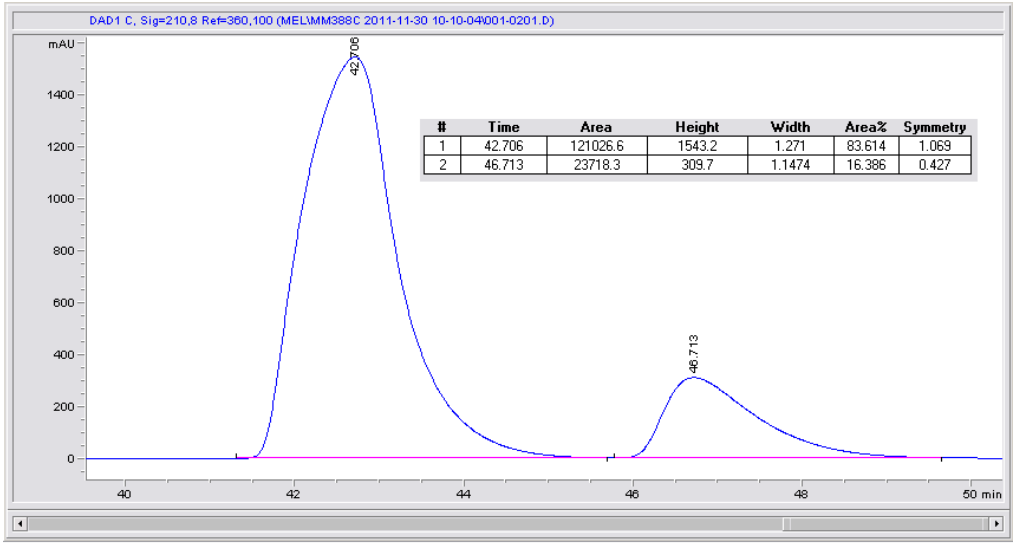
Racemic



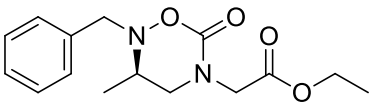
#	Time	Area	Height	Width	Area%	Symmetry
1	45.869	94456.1	1293.3	1.1341	49.965	0.715
2	50.202	94588.7	1243.7	1.1913	50.035	0.763



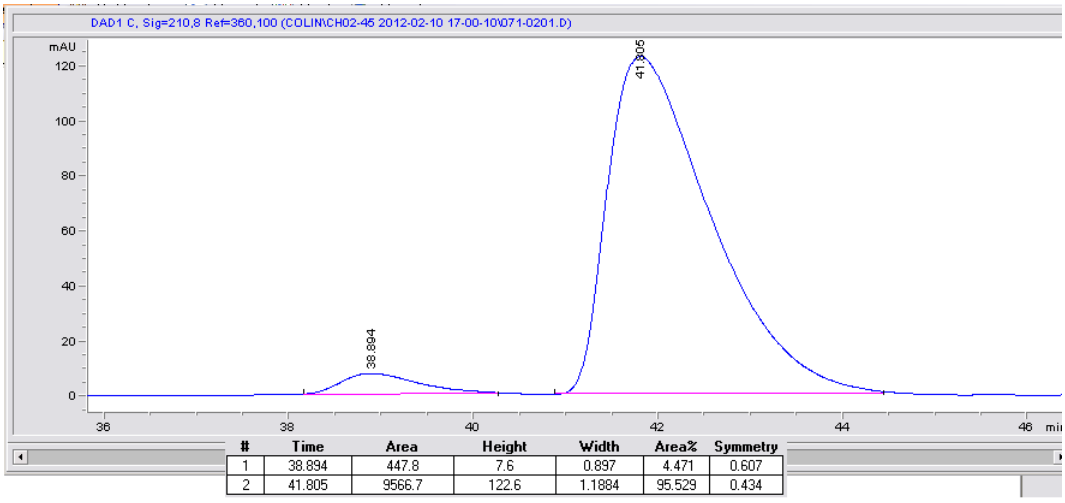
Using Catalyst 1a



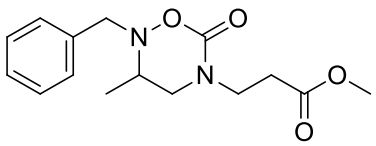
#	Time	Area	Height	Width	Area%	Symmetry
1	42.706	121026.6	1543.2	1.271	83.614	1.069
2	46.713	23718.3	309.7	1.1474	16.386	0.427



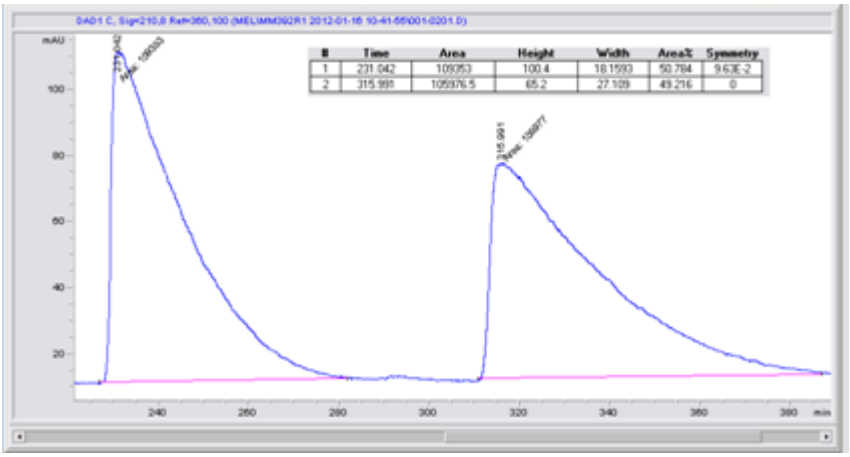
Using Catalyst 1h

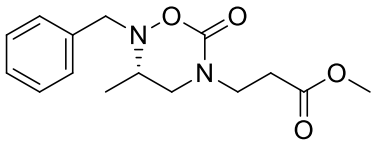


#	Time	Area	Height	Width	Area%	Symmetry
1	38.894	447.8	7.6	0.897	4.471	0.607
2	41.805	9566.7	122.6	1.1884	95.529	0.434

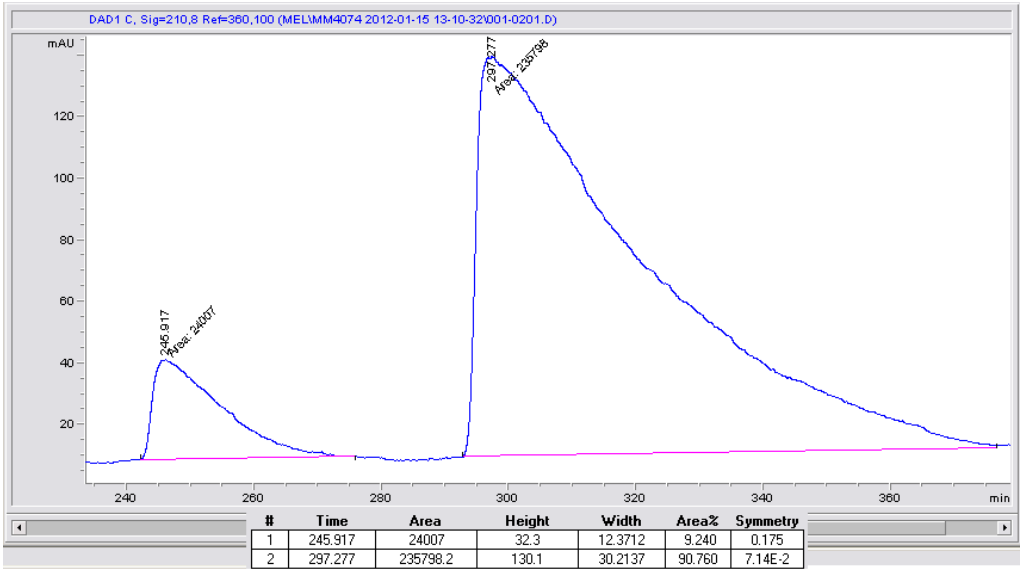


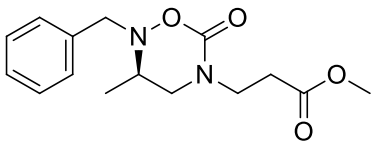
Racemic



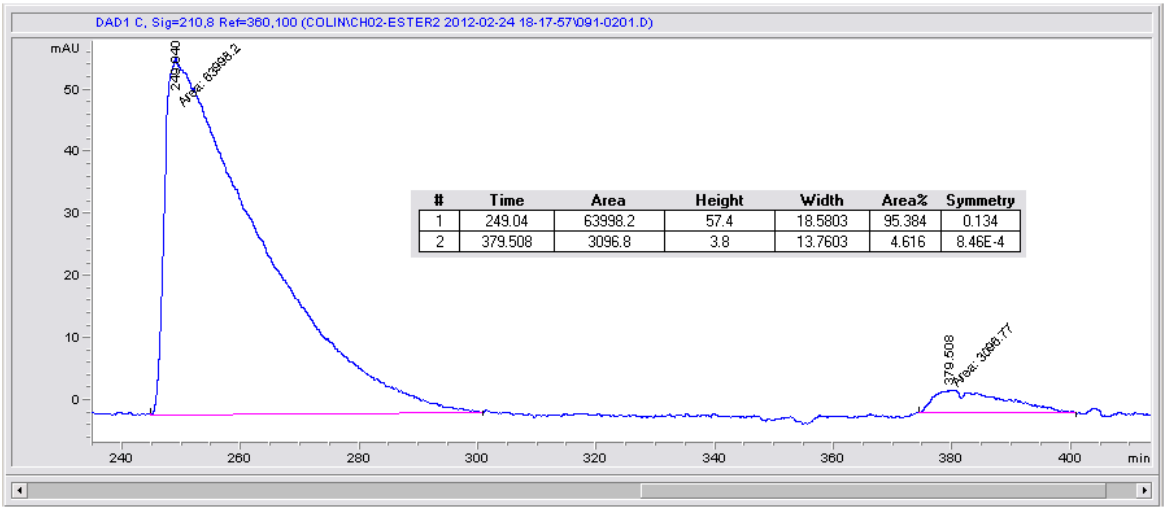


Using Catalyst 1a



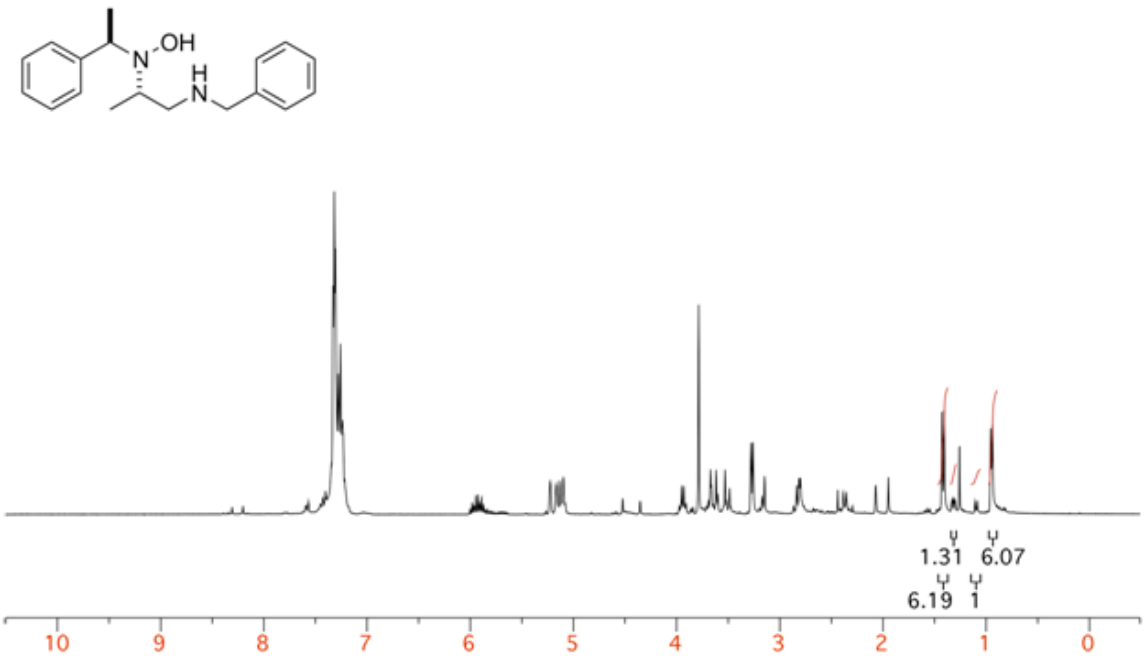


Using Catalyst 1h

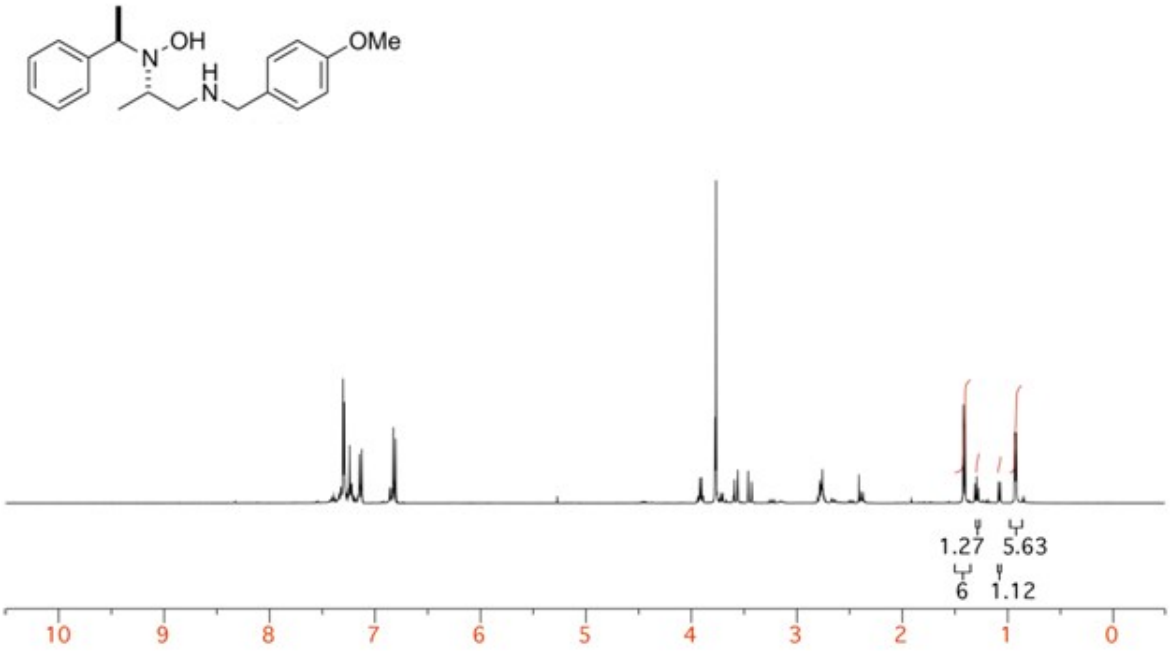


#	Time	Area	Height	Width	Area%	Symmetry
1	249.04	63998.2	57.4	18.5803	95.384	0.134
2	379.508	3096.8	3.8	13.7603	4.616	8.46E-4

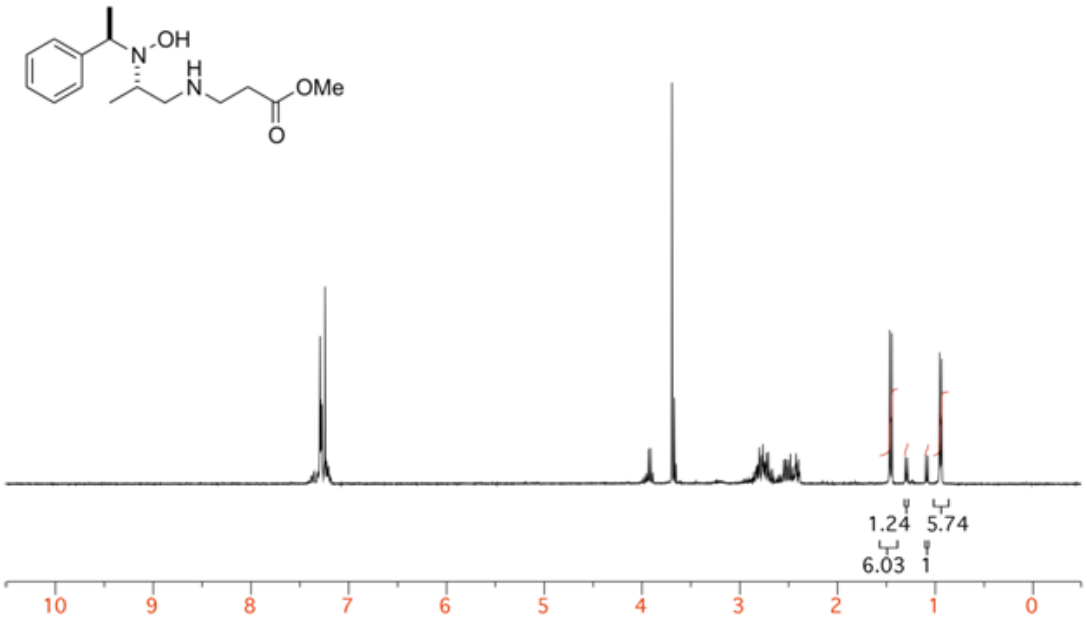
NMR Spectra for (d.r.) Diagnostics: 2.8a (Table 2.8, Entry 1) (6:1 dr)



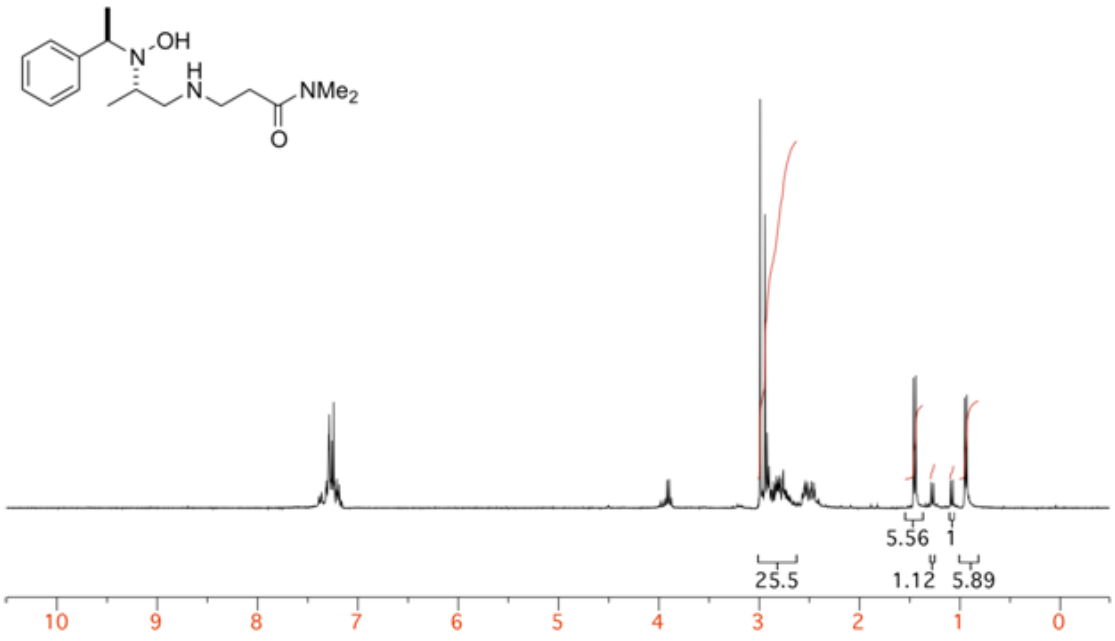
NMR Spectra for (d.r.) Diagnostics: 2.8b (Table 2.8, Entry 2) (6:1 dr)



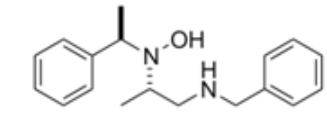
NMR Spectra for (d.r.) Diagnostics: 2.8c (Table 2.8, Entry 3) (6:1 dr)

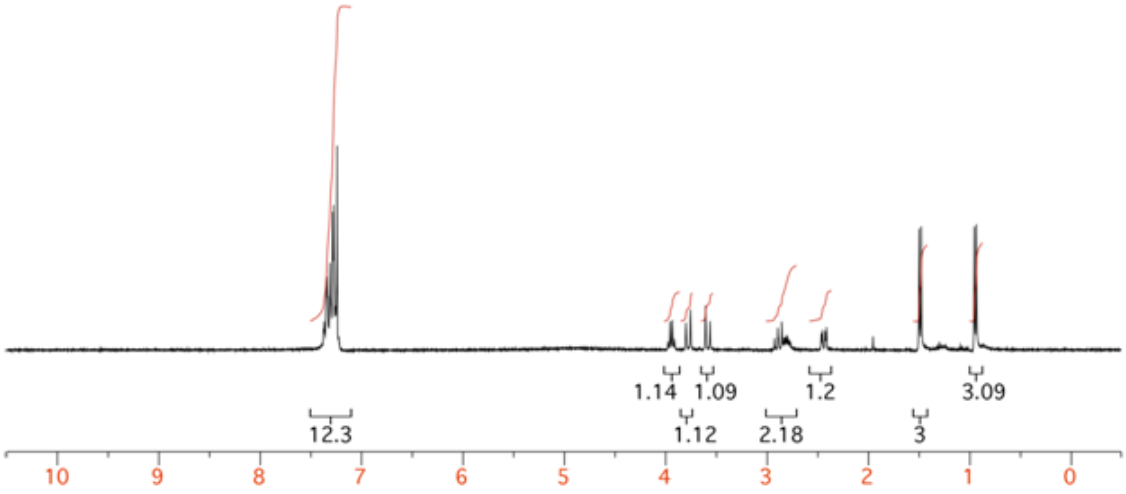


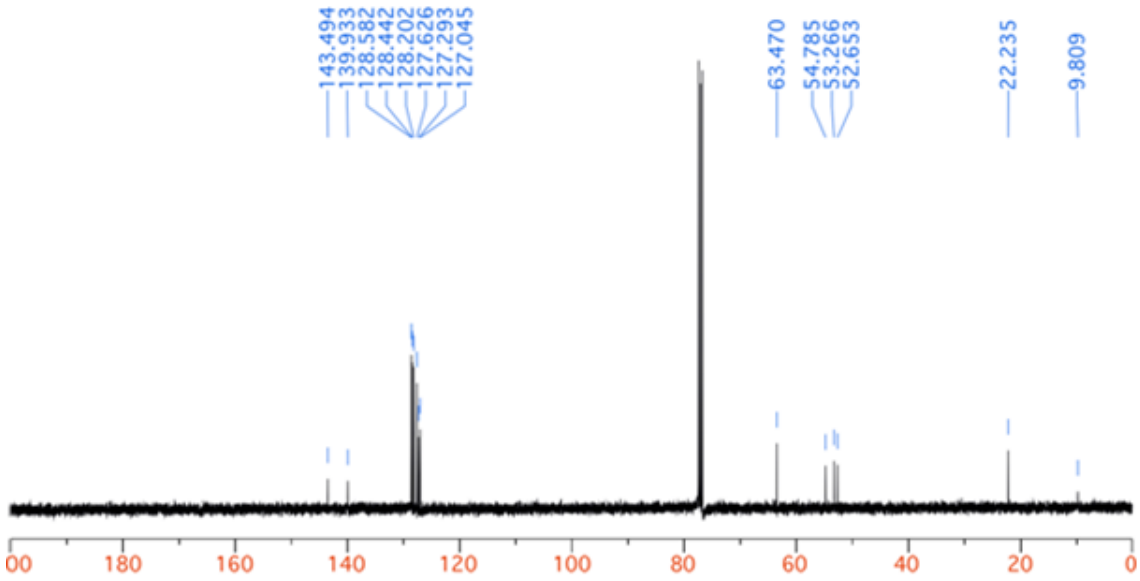
NMR Spectra for (d.r.) Diagnostics: 2.8d (Table 2.8, Entry 4) (6:1 dr)



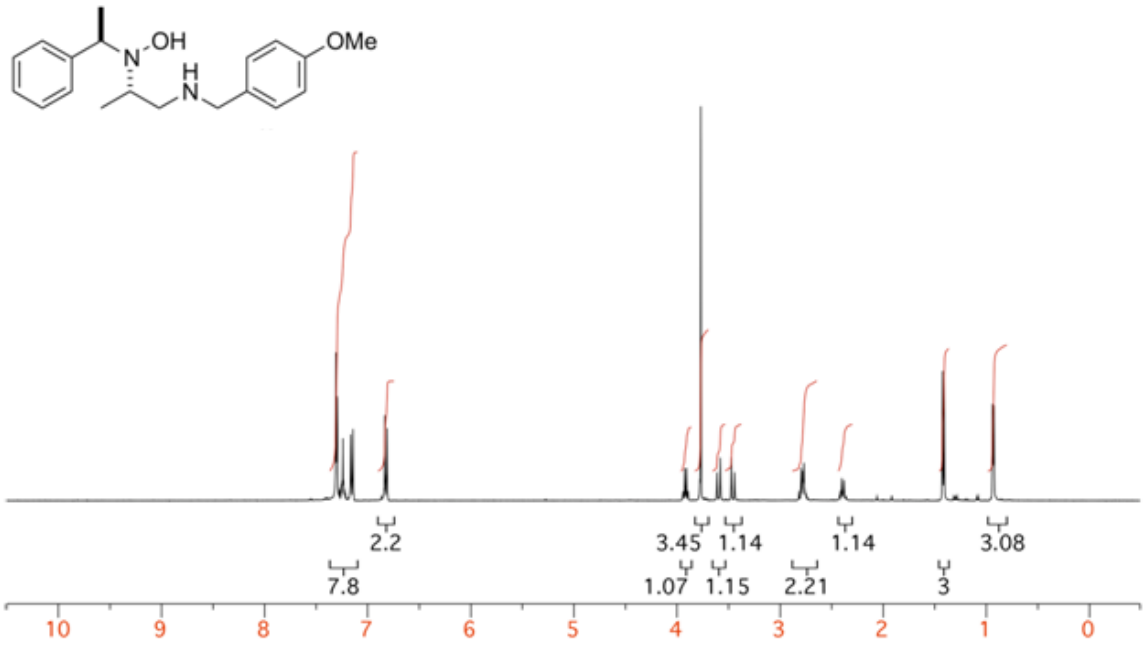
NMR Spectra for Major Diastereomer 2.8a (Table 2.8, Entry 1)

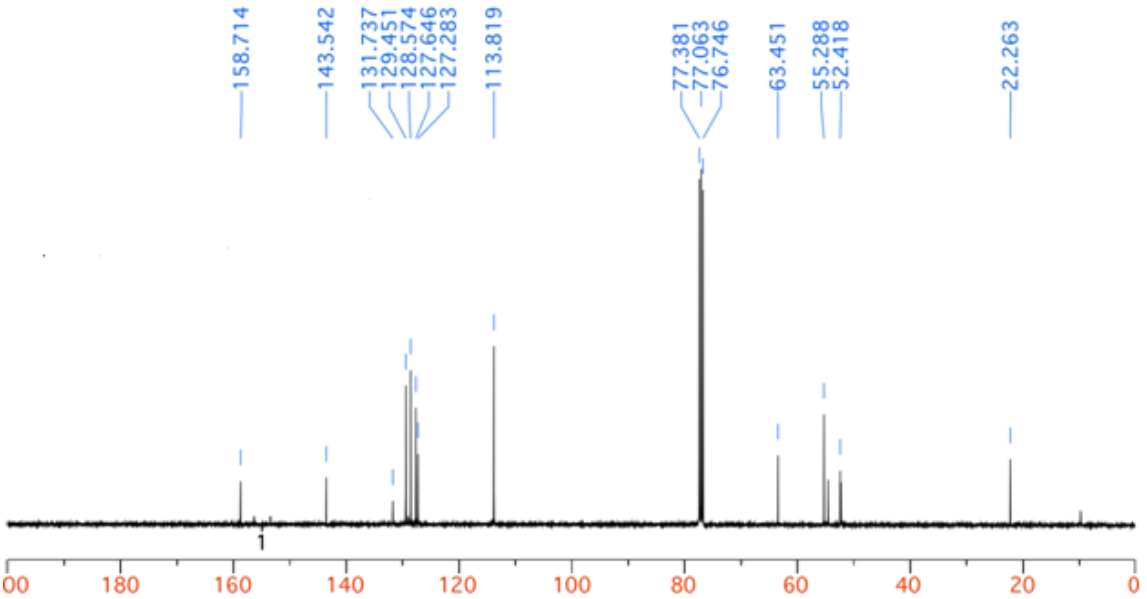




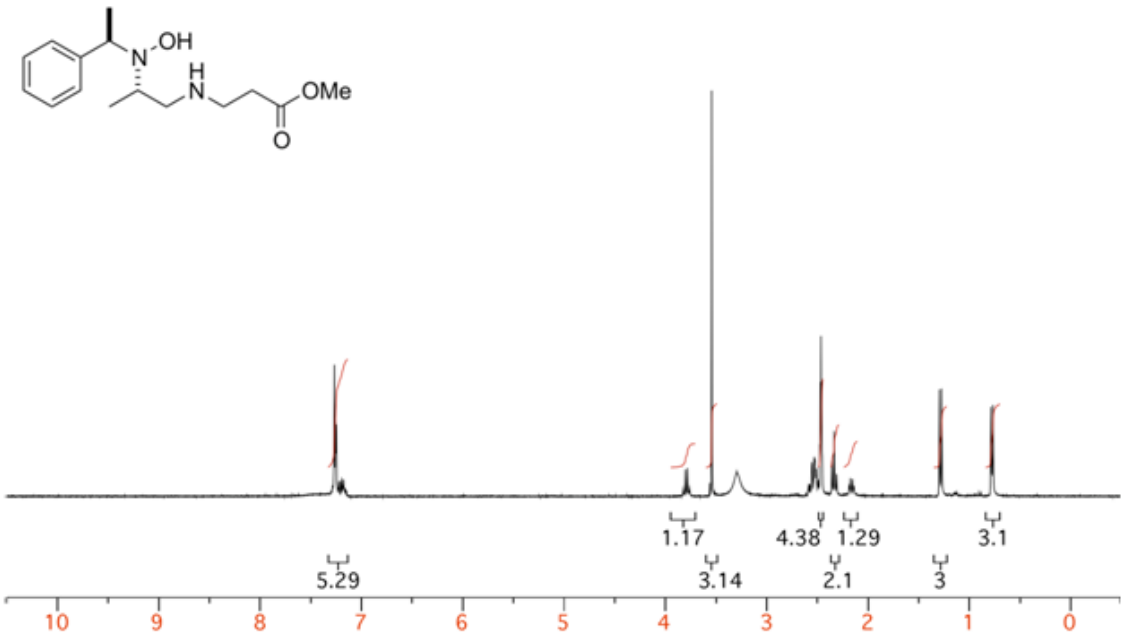


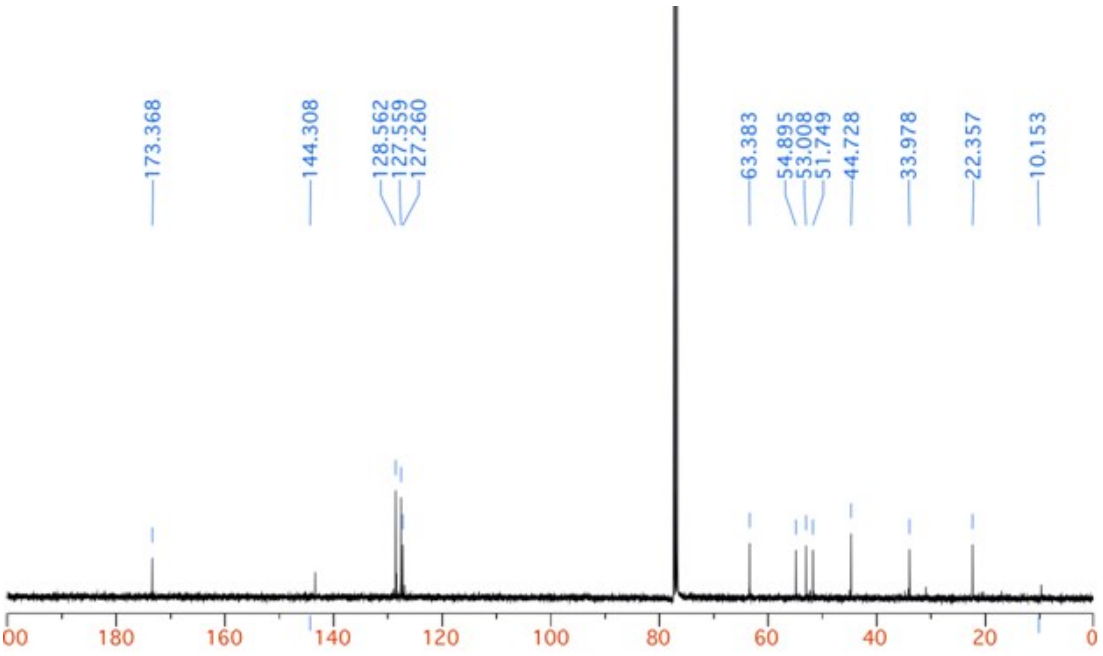
NMR Spectra for Major Diastereomer 2.8b (Table 2.8, Entry 2)



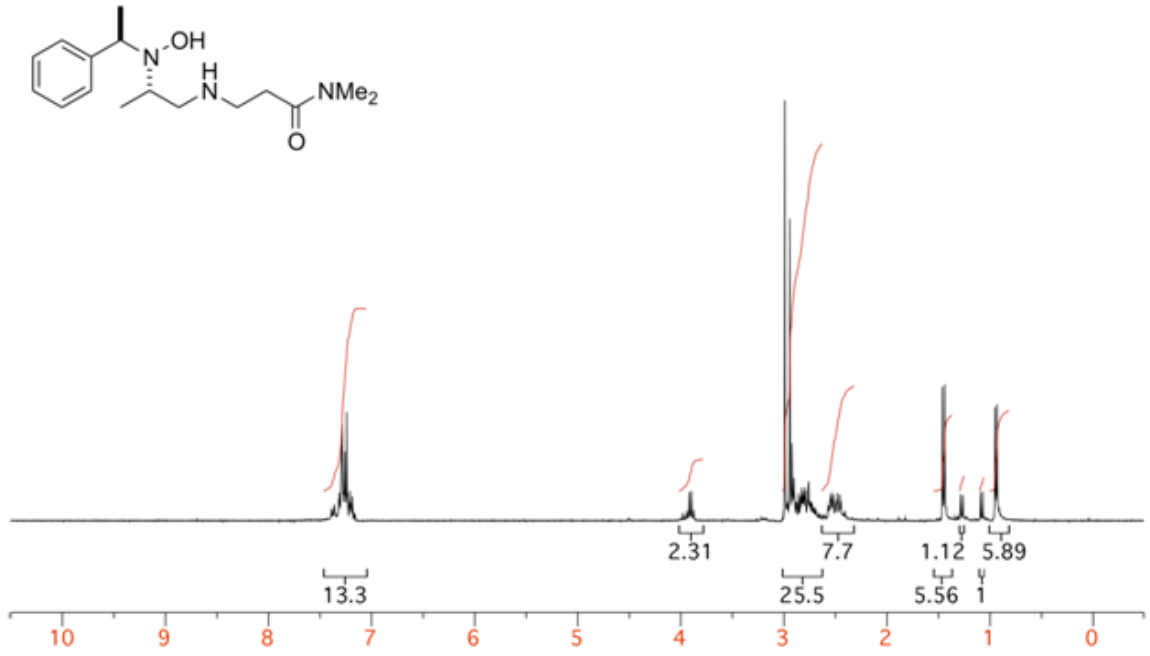


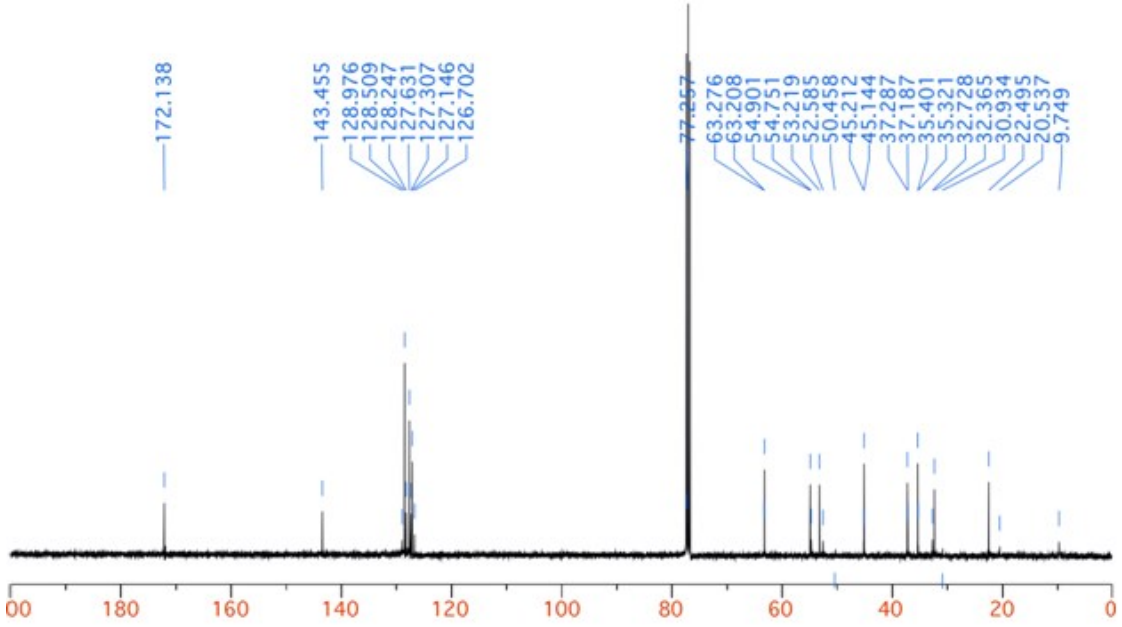
NMR Spectra for Major Diastereomer 2.8c (Table 2.8, Entry 3)



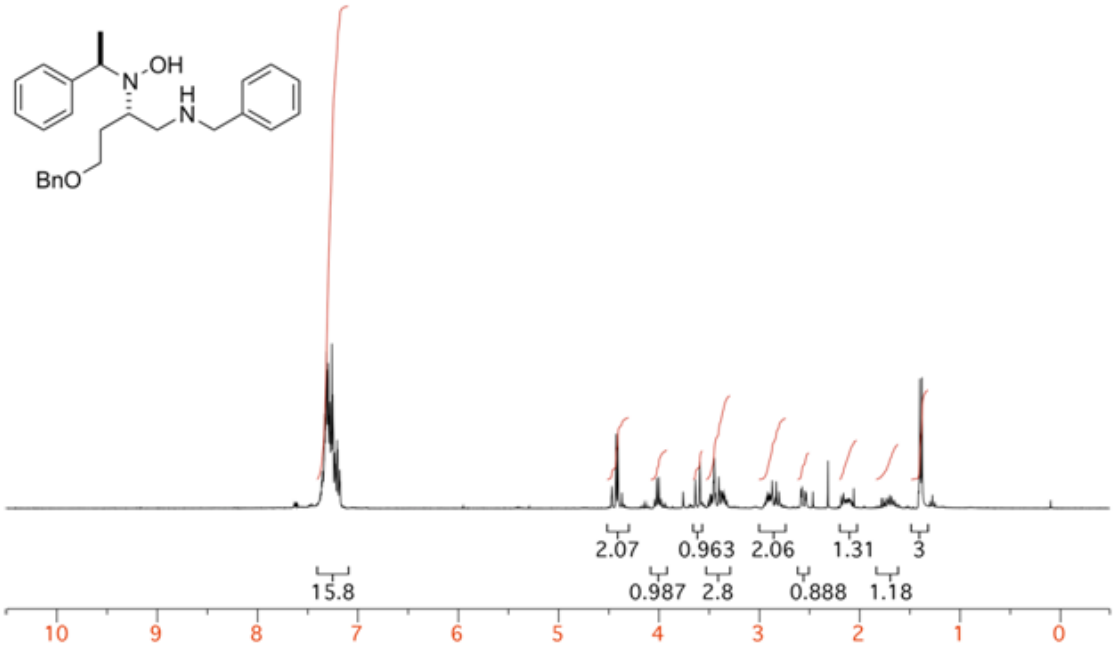


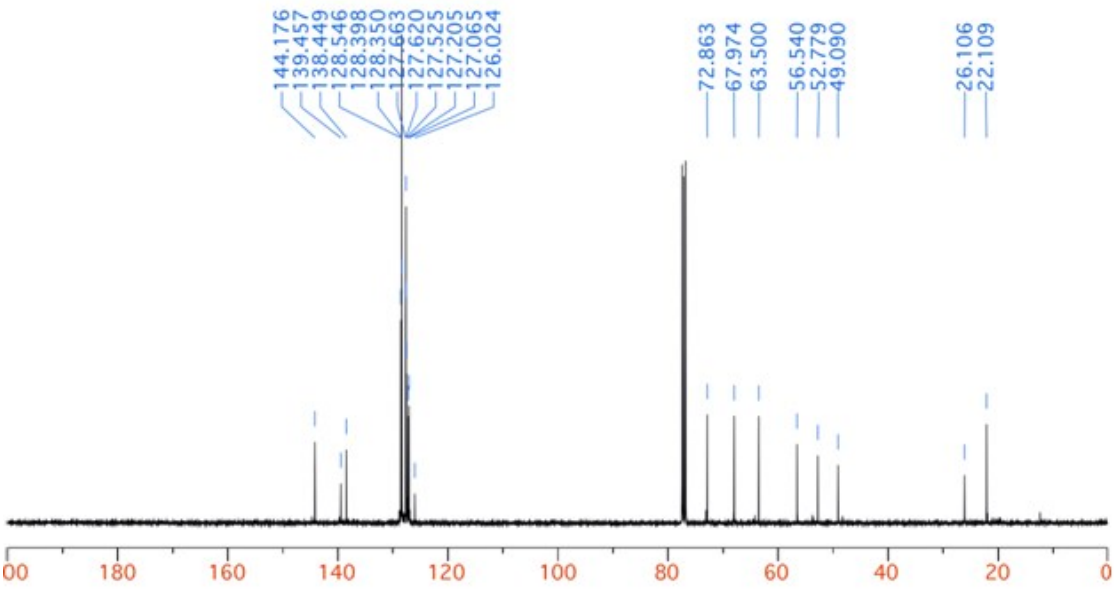
NMR Spectra for Major Diastereomer 2.8d (Table 2.8, Entry 4)



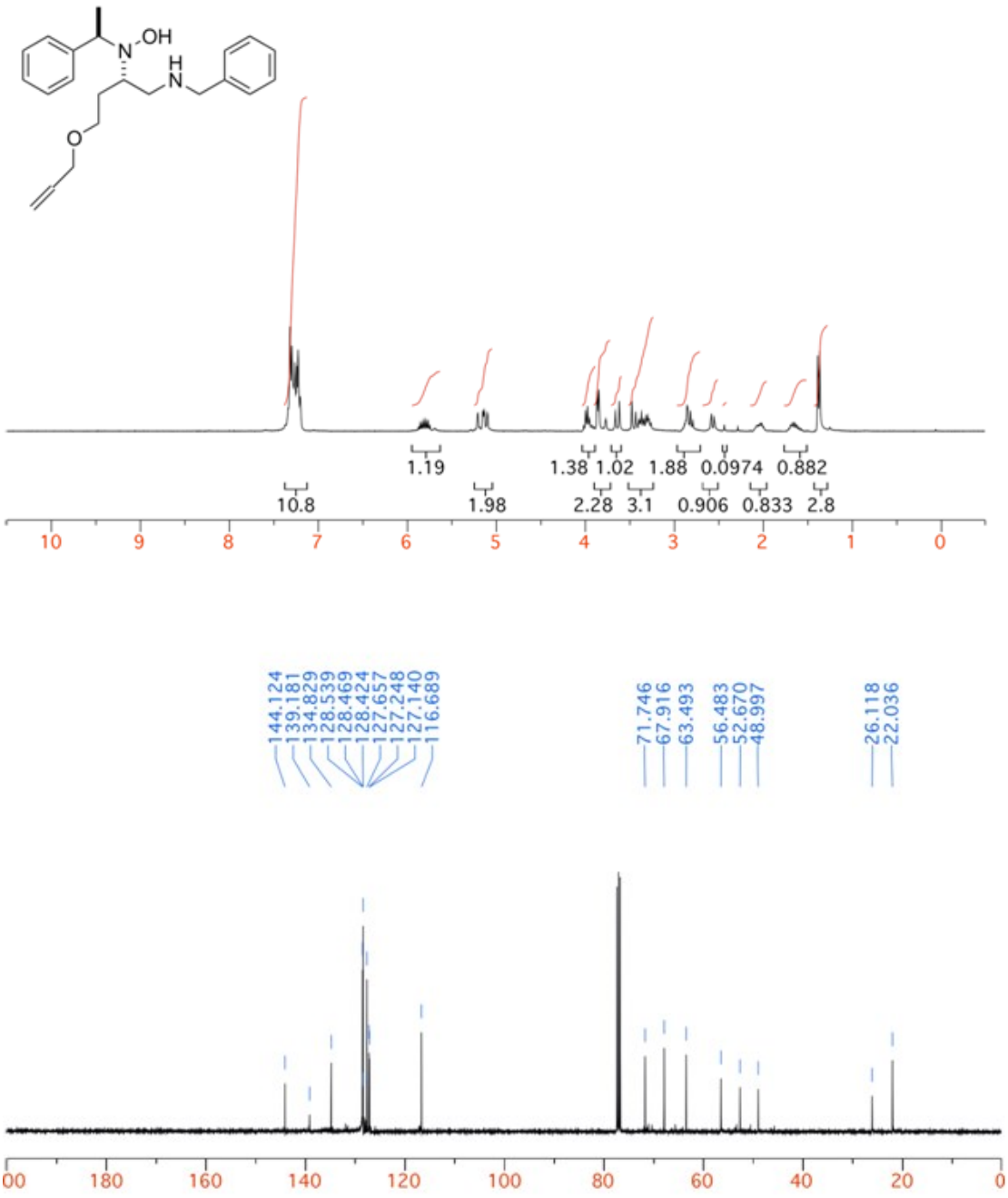


NMR Spectra for Major Diastereomer 2.8e (Table 2.8, Entry 5)

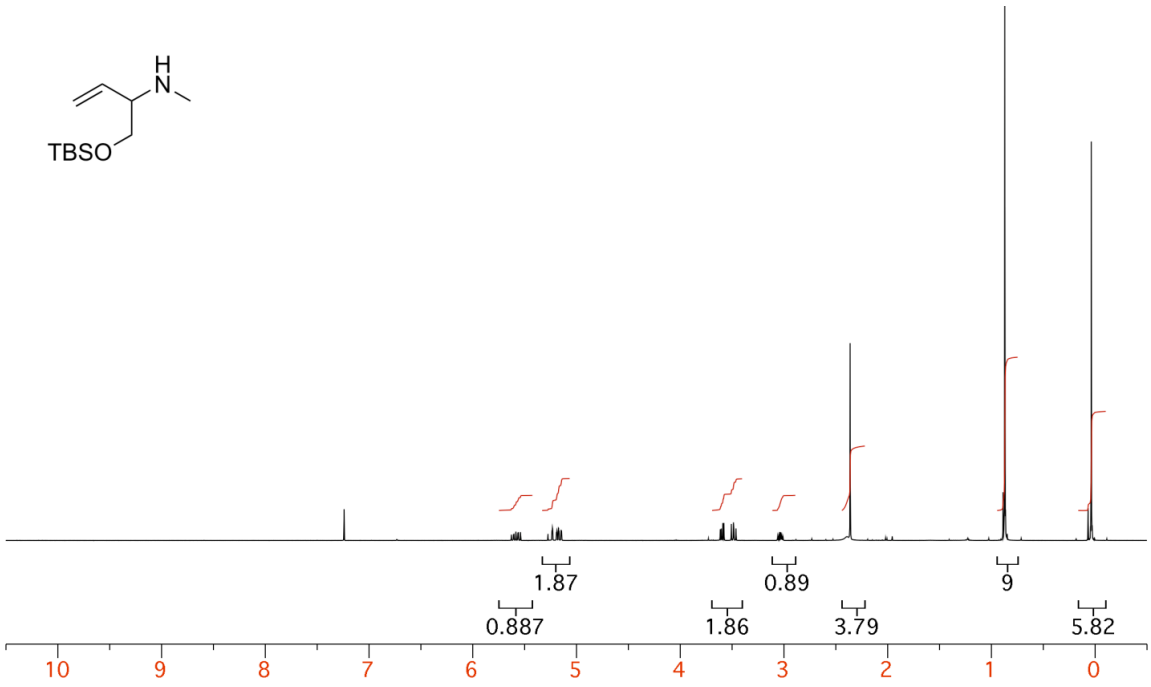


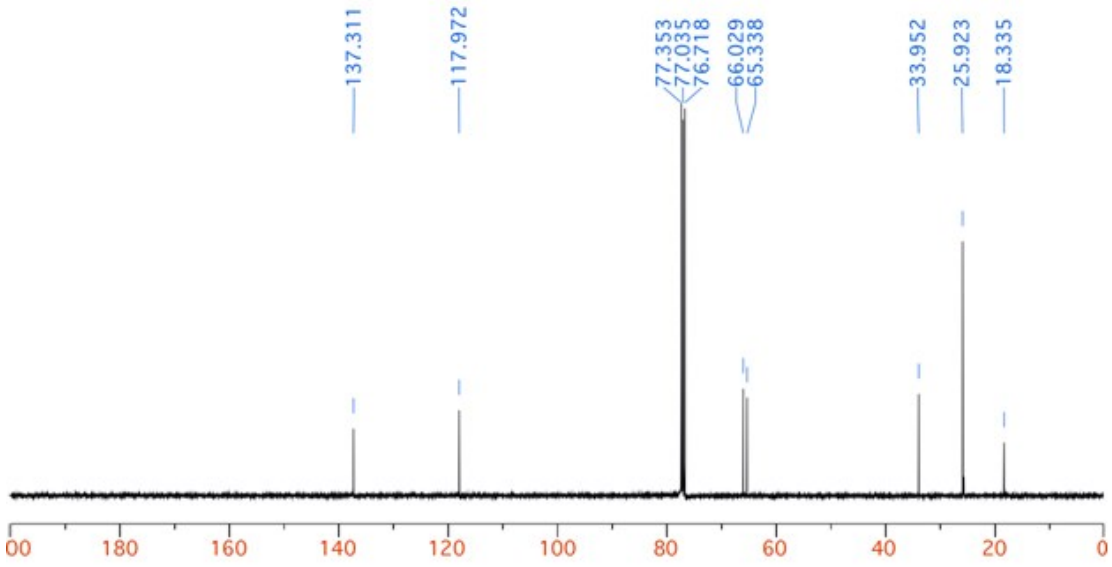


NMR Spectra for Major Diastereomer 2.8f (Table 2.8, Entry 6)

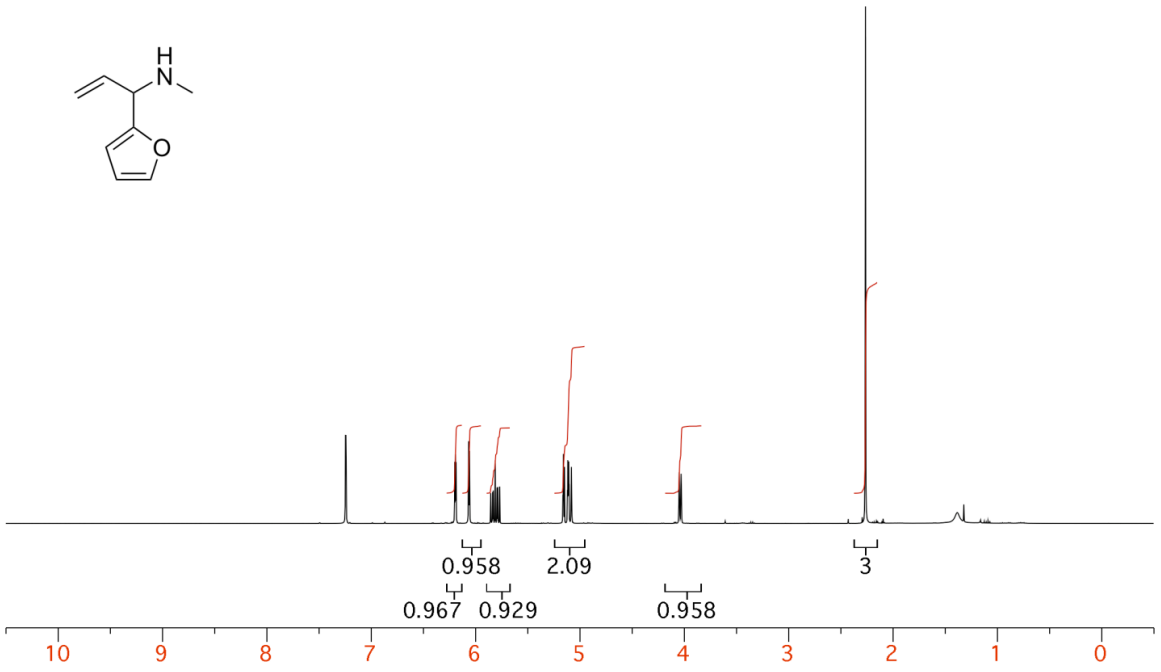


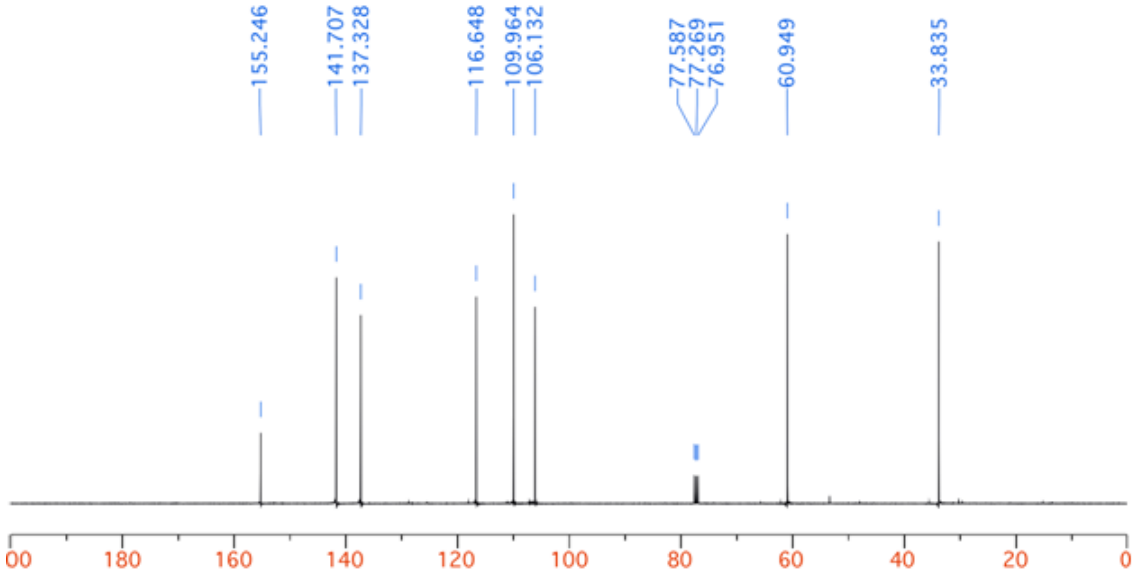
1.4g


H
N
TBSO
1.87
0.89
9
0.887
1.86
3.79
5.82
10
9
8
7
6
5
4
3
2
1
0

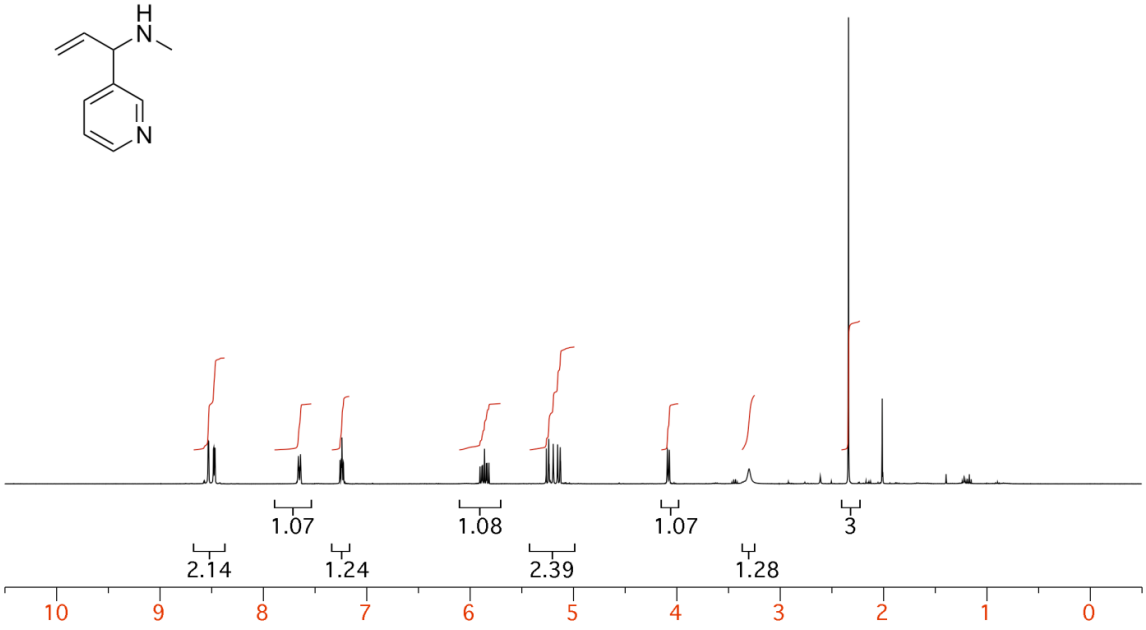

137.311
117.972
77.353
77.035
76.718
66.029
65.338
33.952
25.923
18.335
00
180
160
140
120
100
80
60
40
20
0

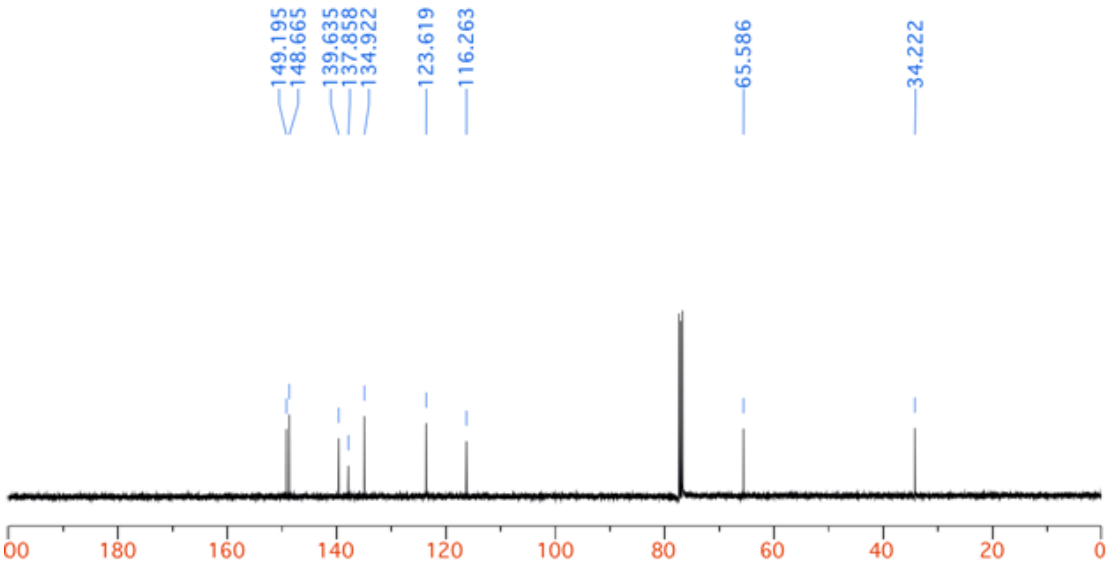
1.4h


H
N
O
0.958
2.09
3
0.967
0.929
0.958
10
9
8
7
6
5
4
3
2
1
0

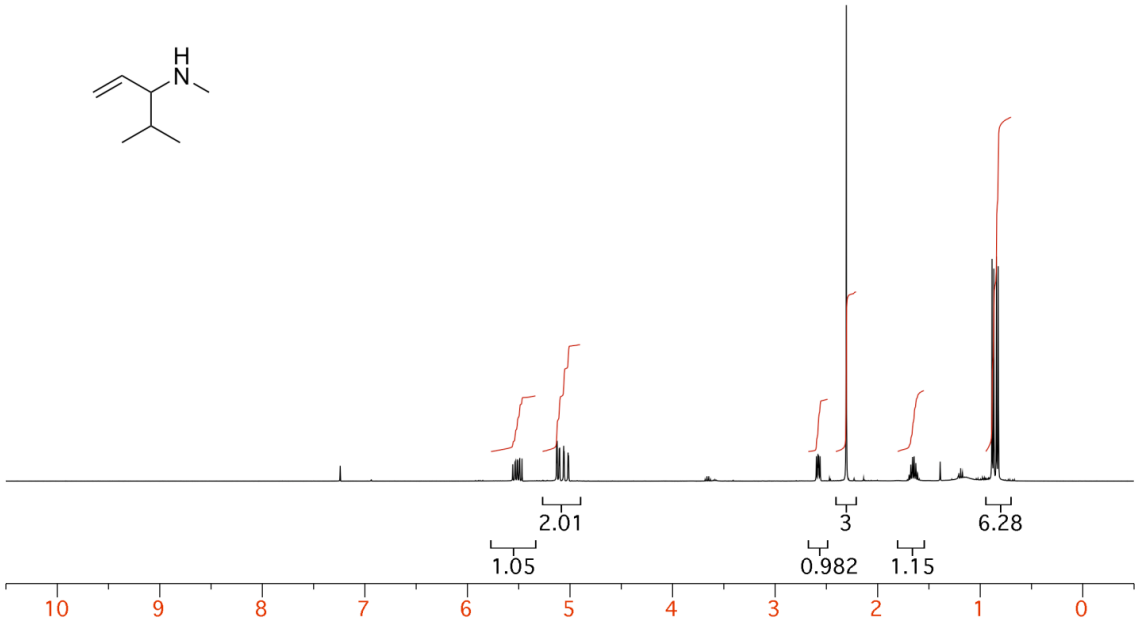

155.246
141.707
137.328
116.648
109.964
106.132
77.587
77.269
76.951
60.949
33.835
00
180
160
140
120
100
80
60
40
20
0

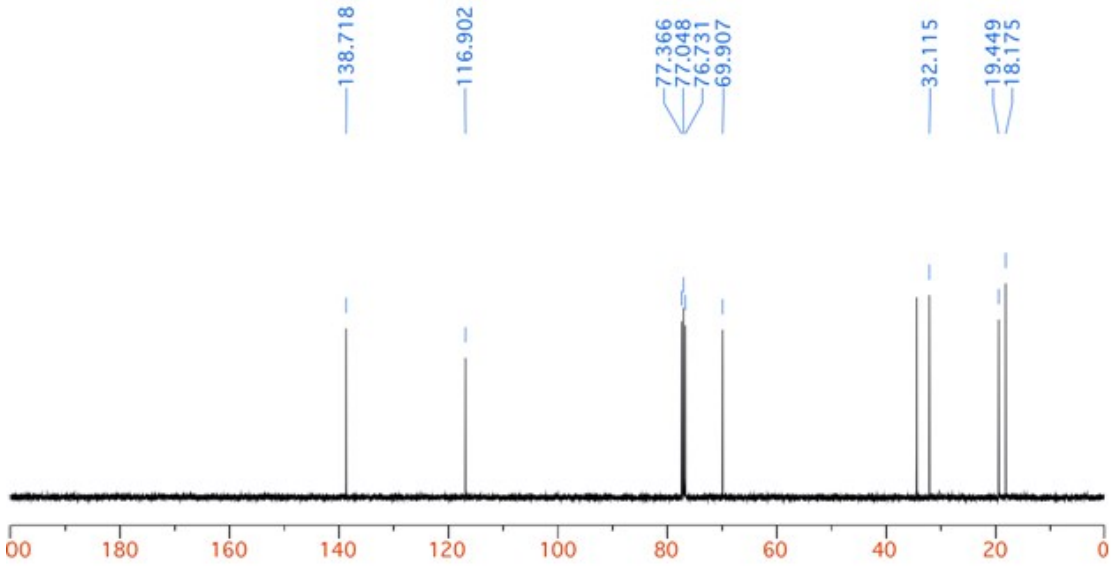
1.4i


1.07
1.08
1.07
3
2.14
1.24
2.39
1.28
10
9
8
7
6
5
4
3
2
1
0


149.195
148.665
139.635
137.858
134.922
123.619
116.263
65.586
34.222
00
180
160
140
120
100
80
60
40
20
0

1.4j


H
N
2.01
3
6.28
1.05
0.982
1.15
10
9
8
7
6
5
4
3
2
1
0


138.718
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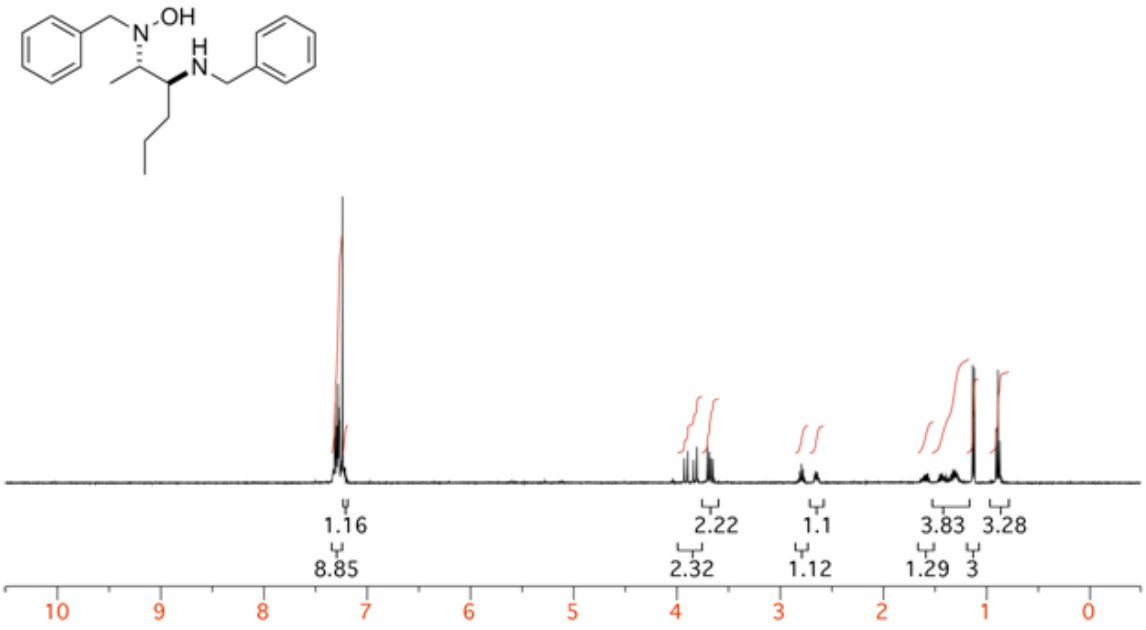
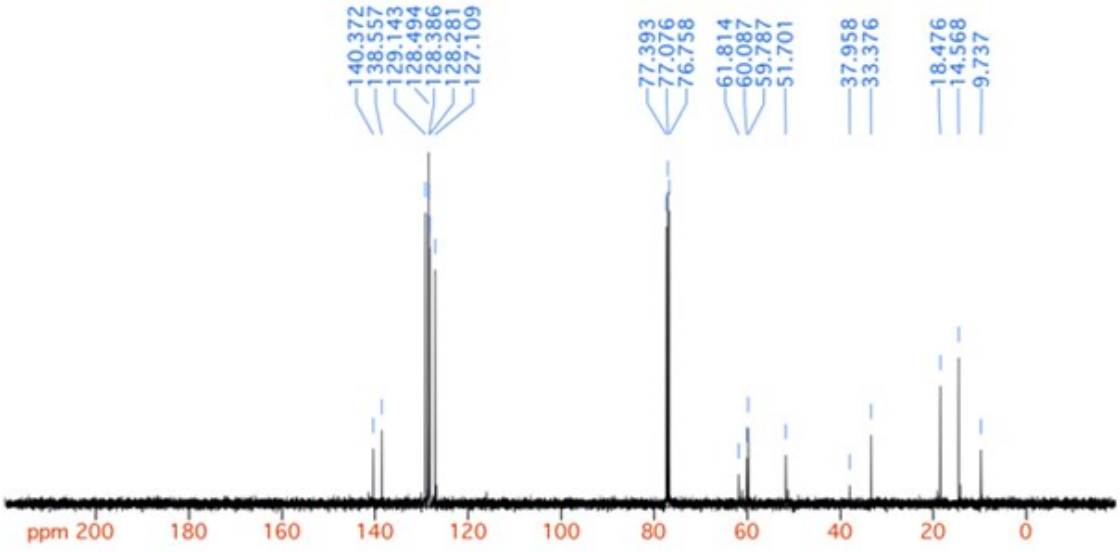
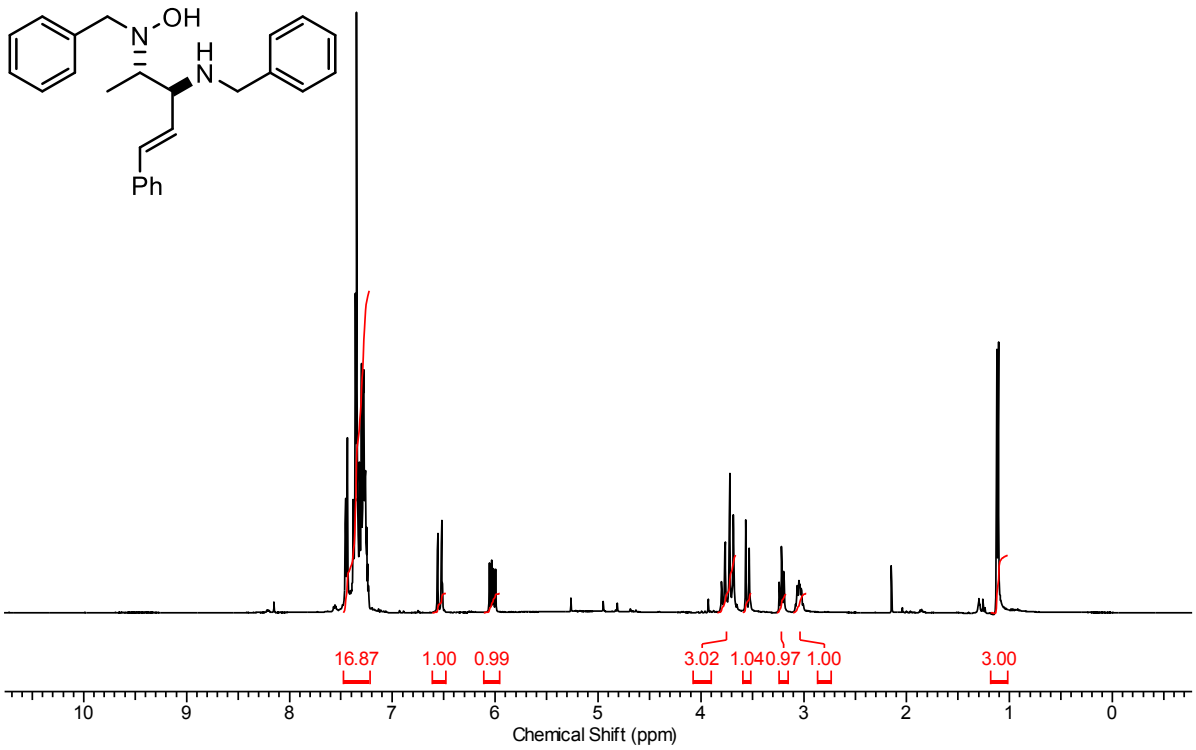
77.366
77.048
76.731
69.907
32.115
19.449
18.175
00
180
160
140
120
100
80
60
40
20
0

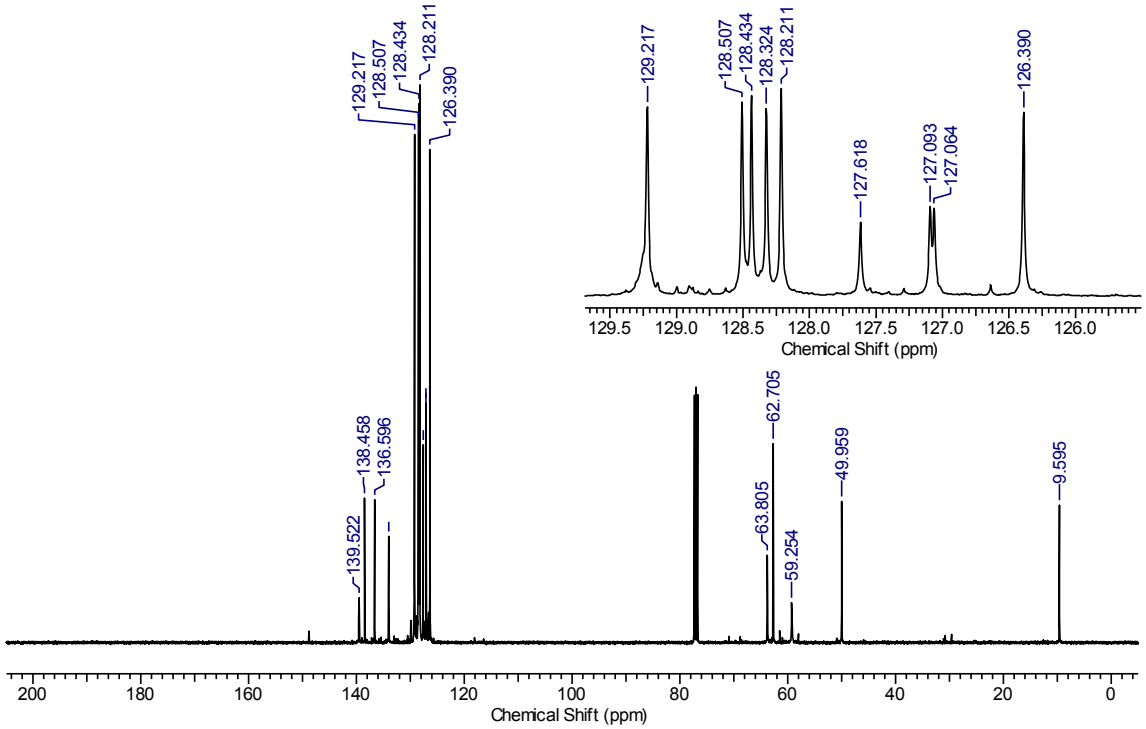
2.10c (Table 2.10 Entry 4)



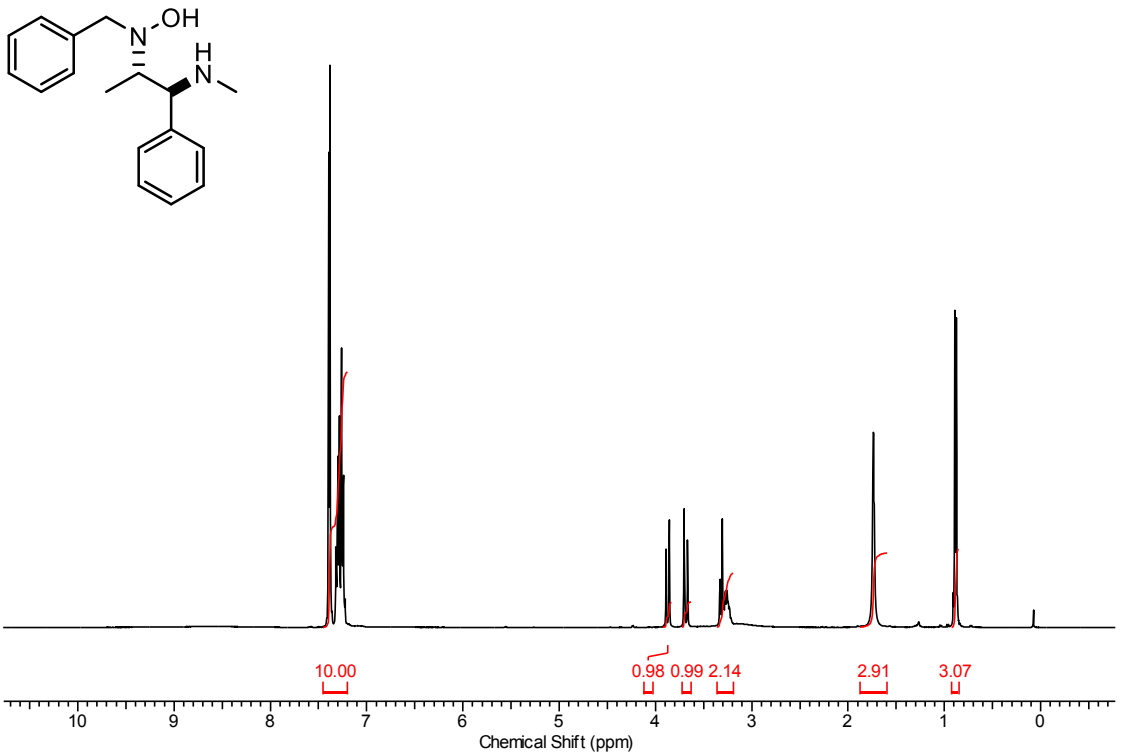


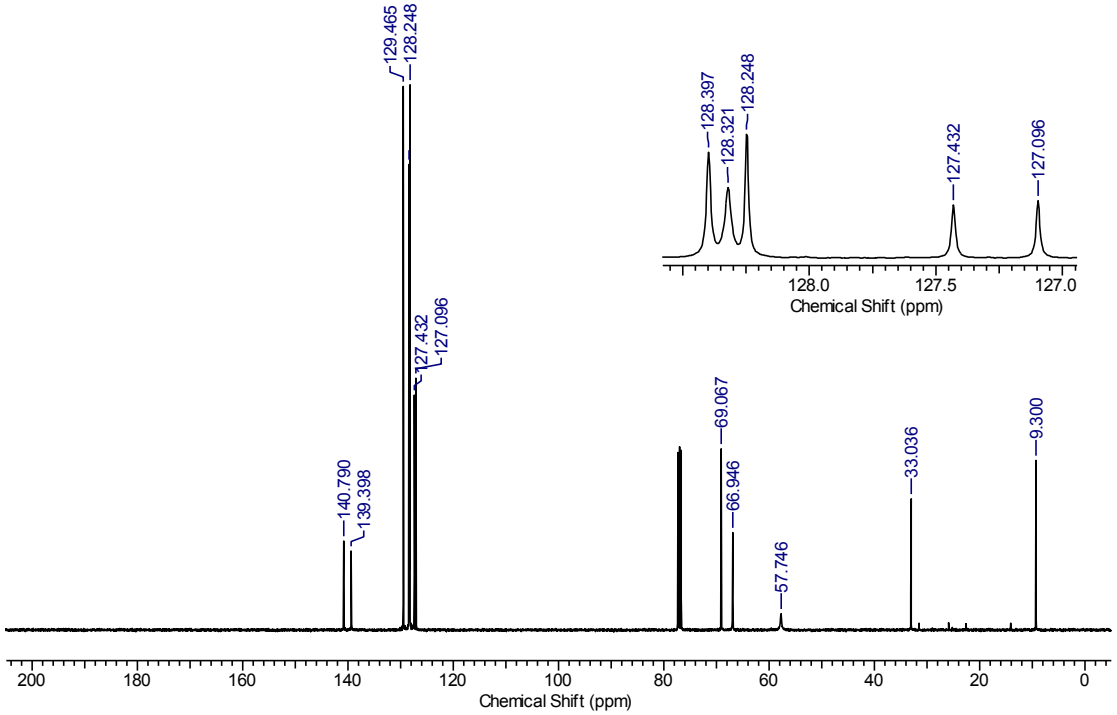
2.10d (Table 2.10 Entry 5)



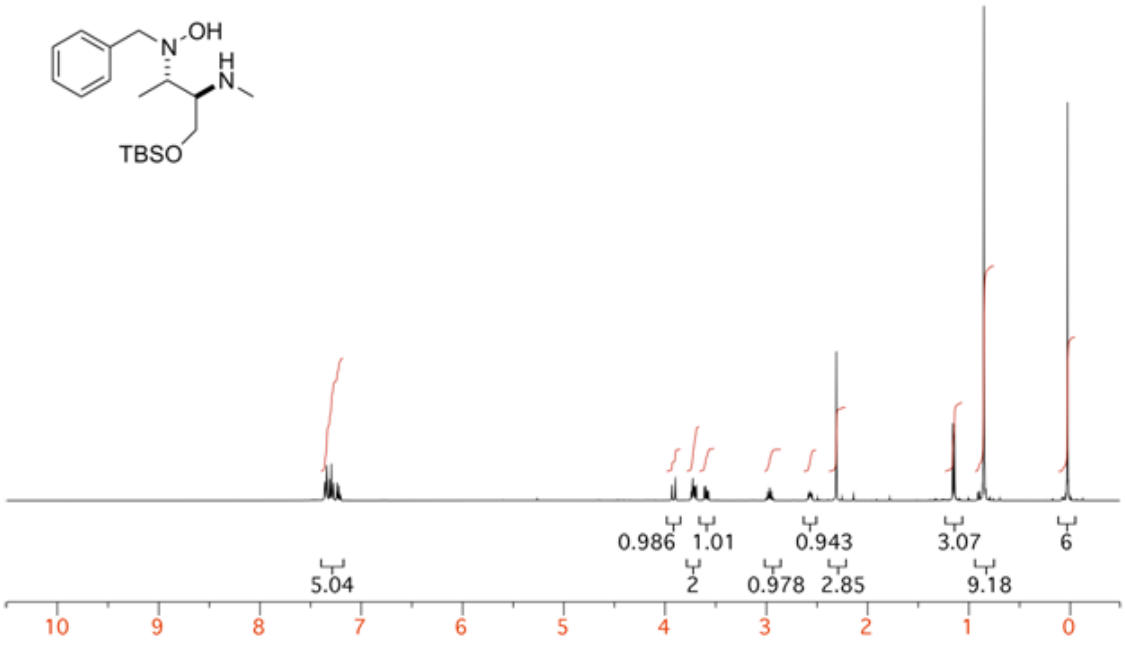


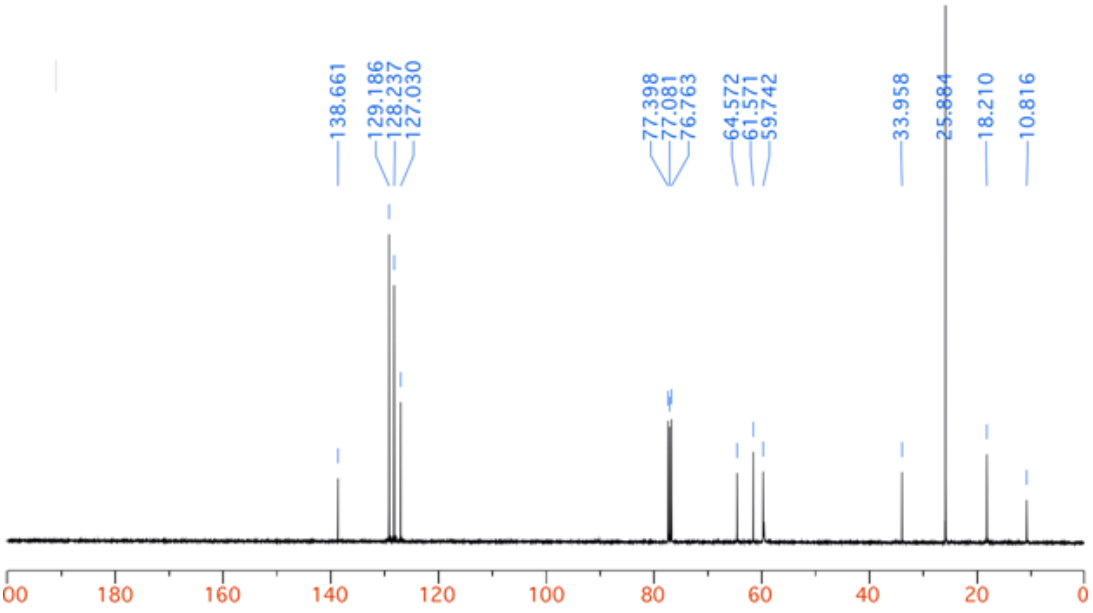
2.10e (Table 2.10 Entry 6)



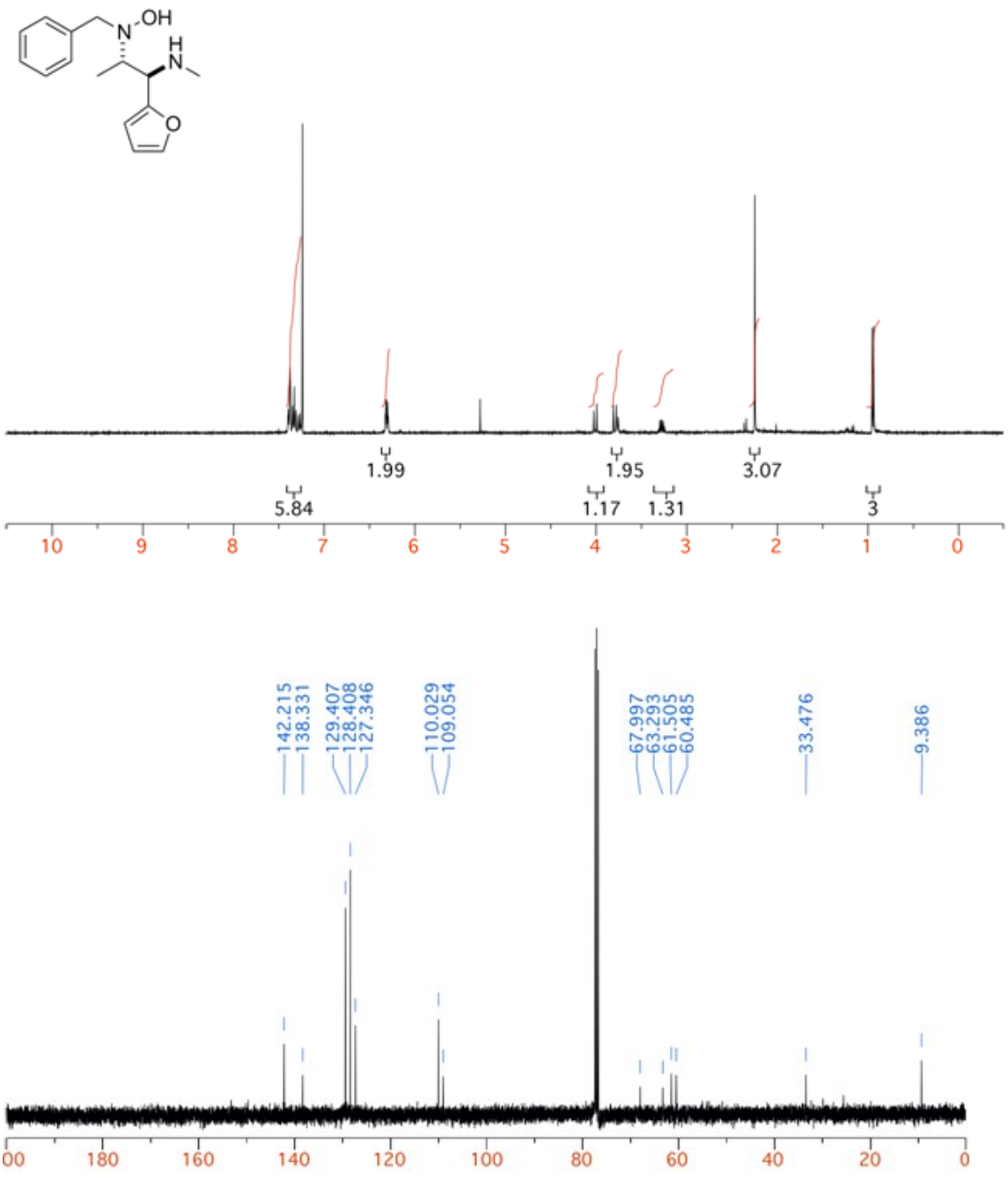


2.10f (Table 2.10, Entry 7)

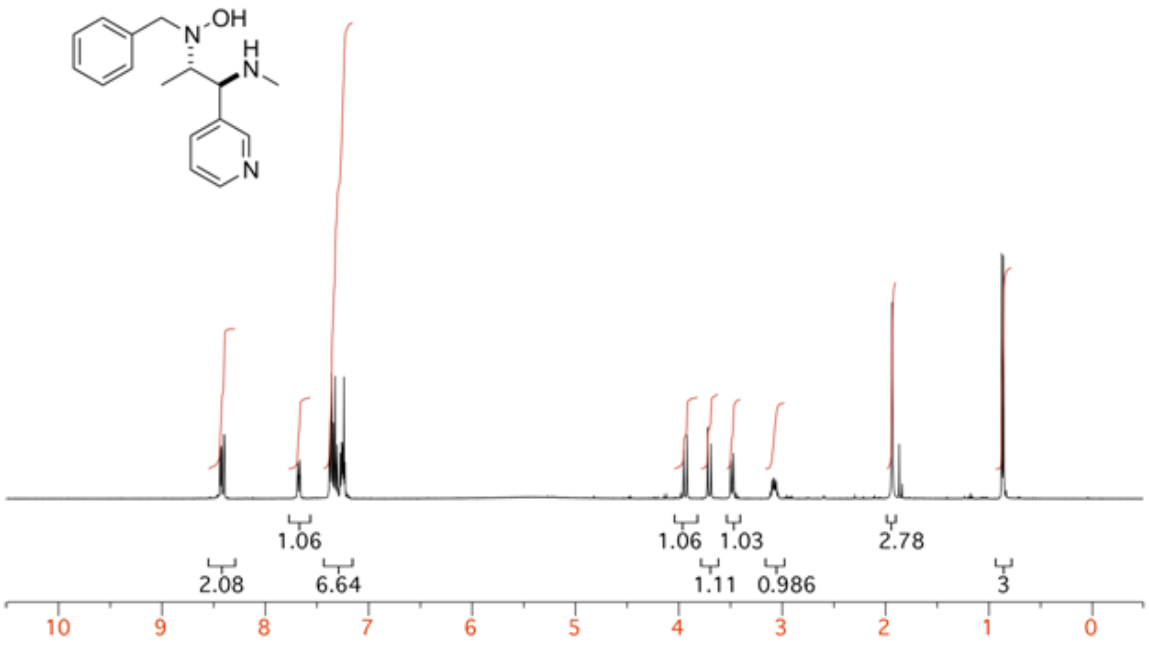


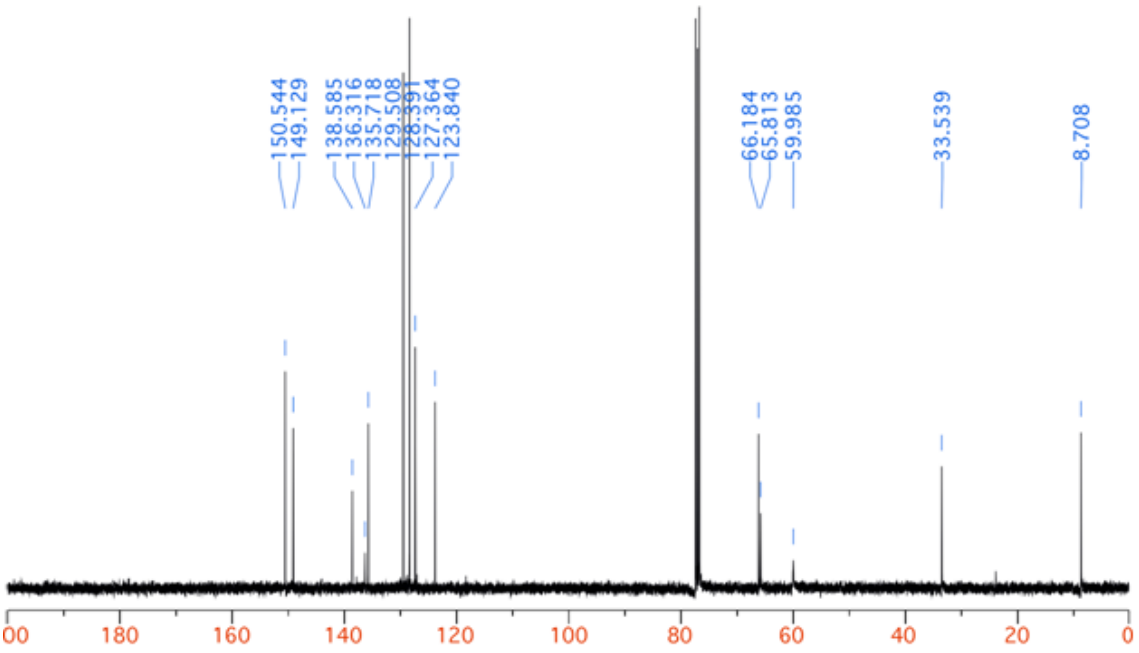


2.10g (Table 2.10 Entry 8)

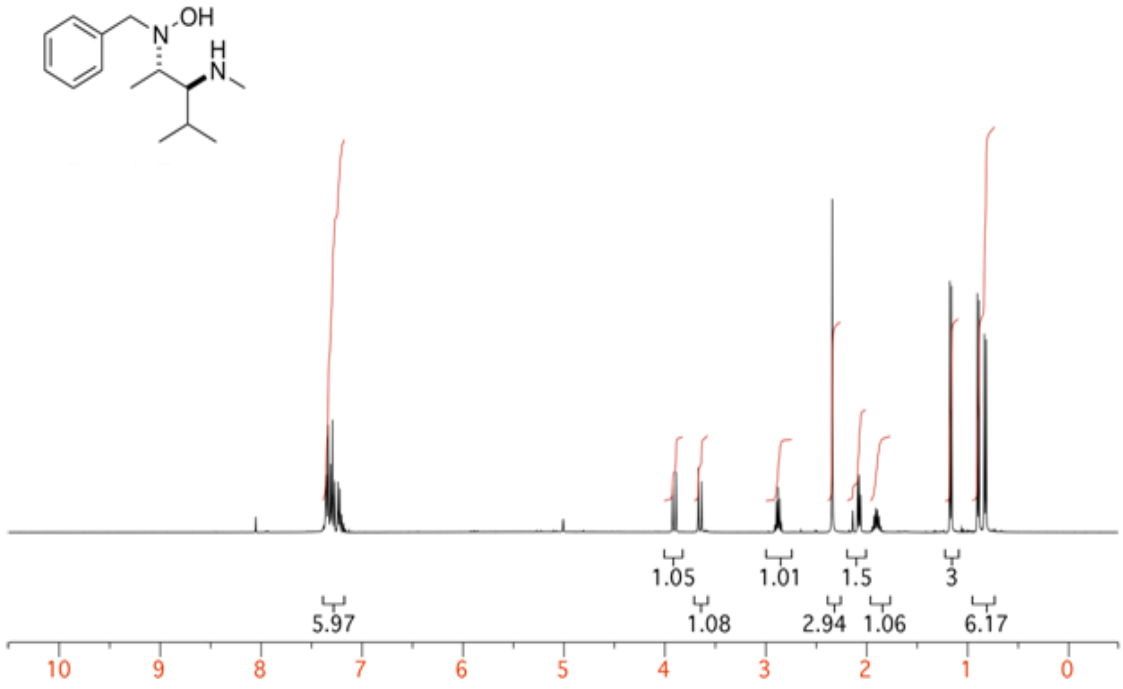


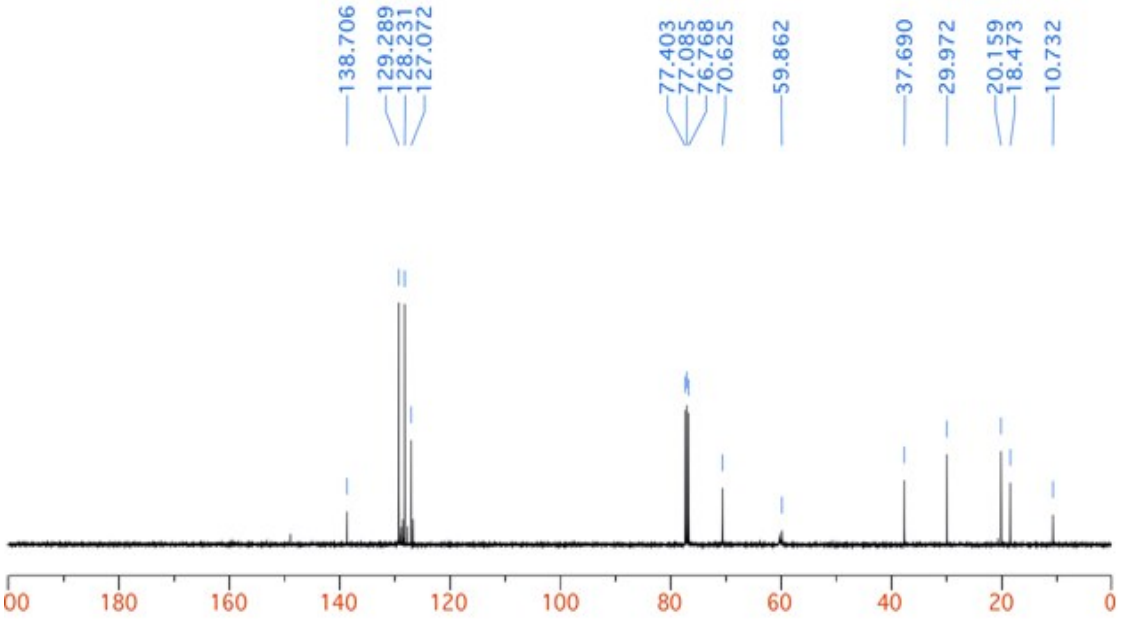
2.10h (Table 2.10 Entry 9)



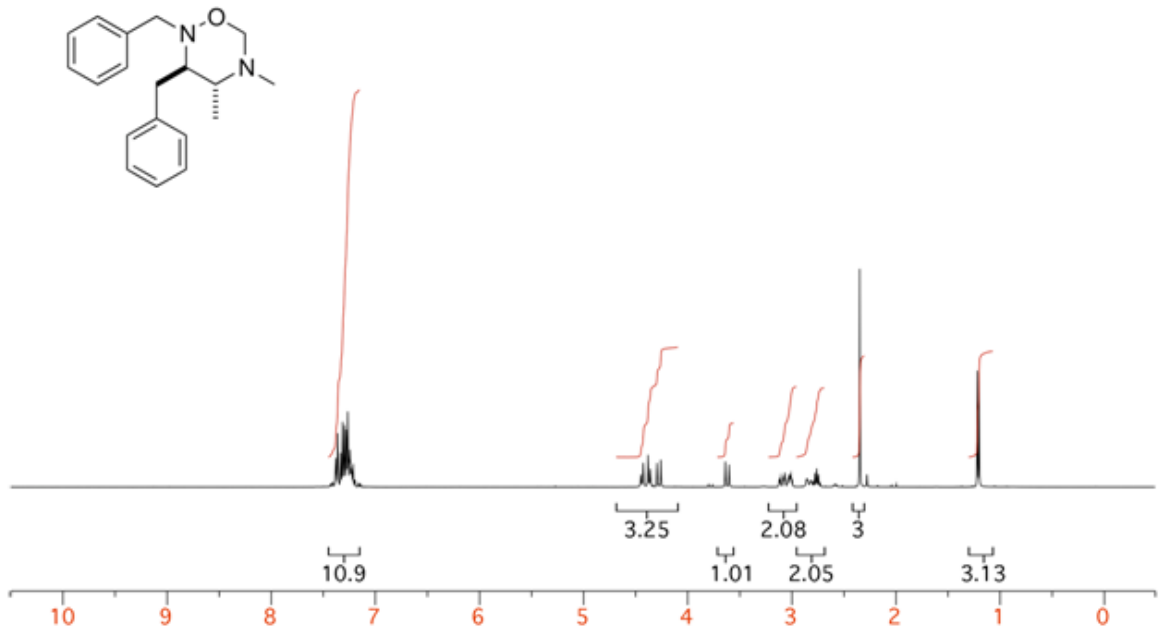


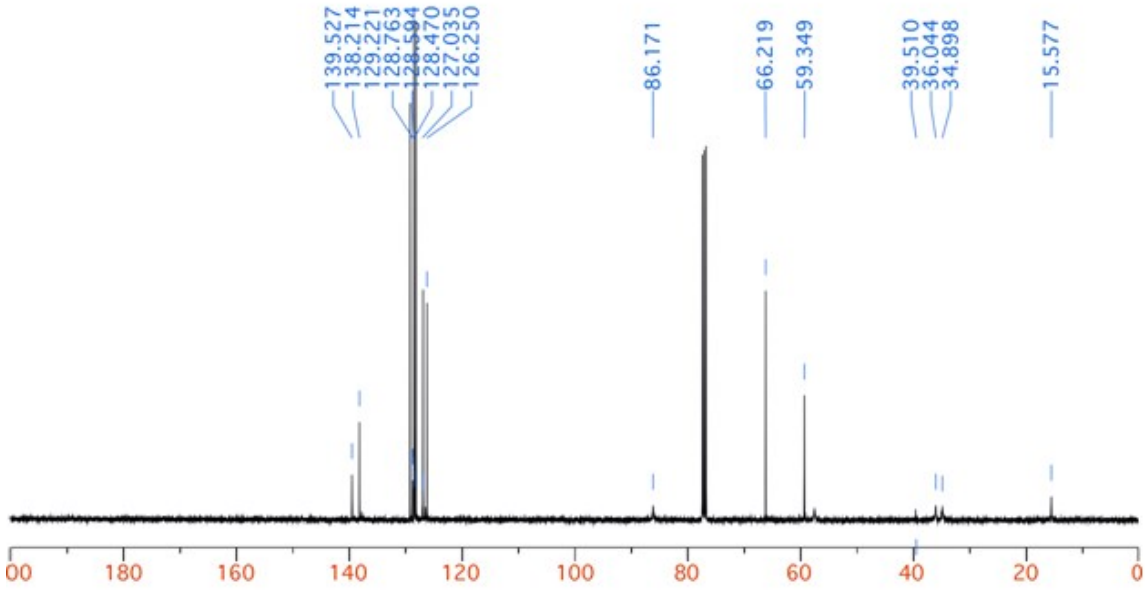
2.10i (Table 2.10 Entry 10)



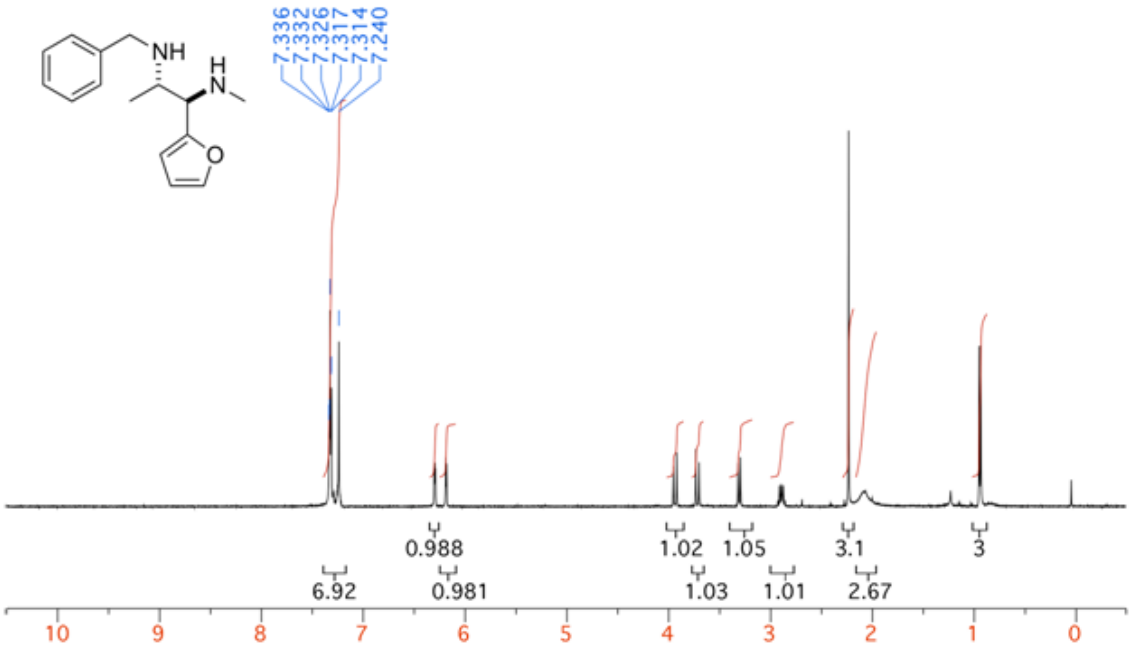


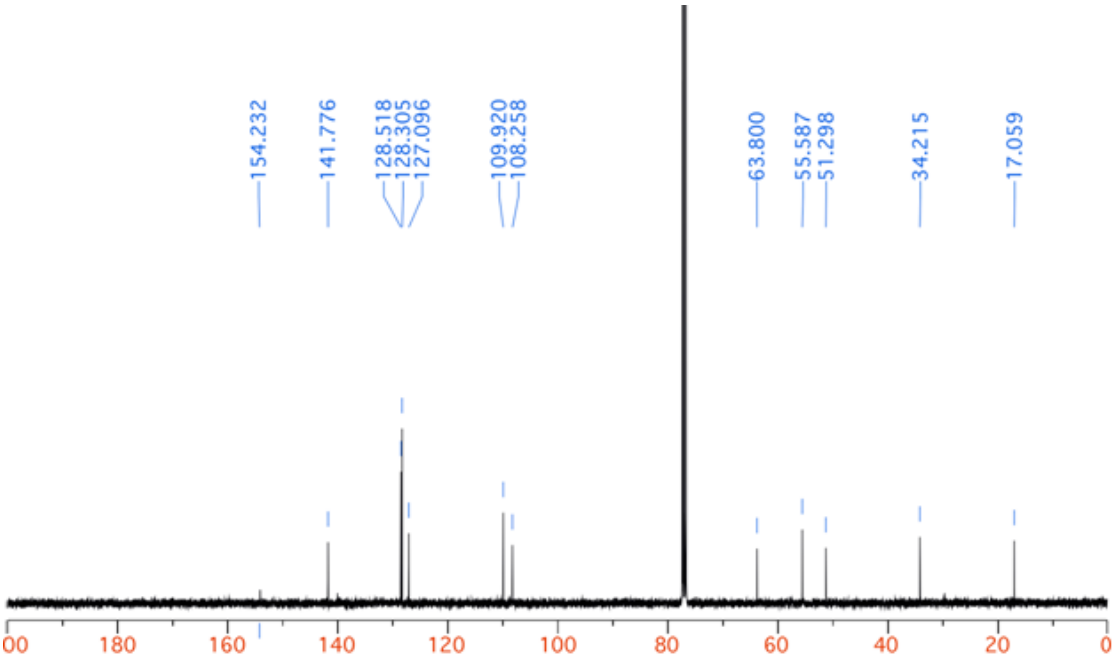
3.1a (Table 2.11 Entry 4)



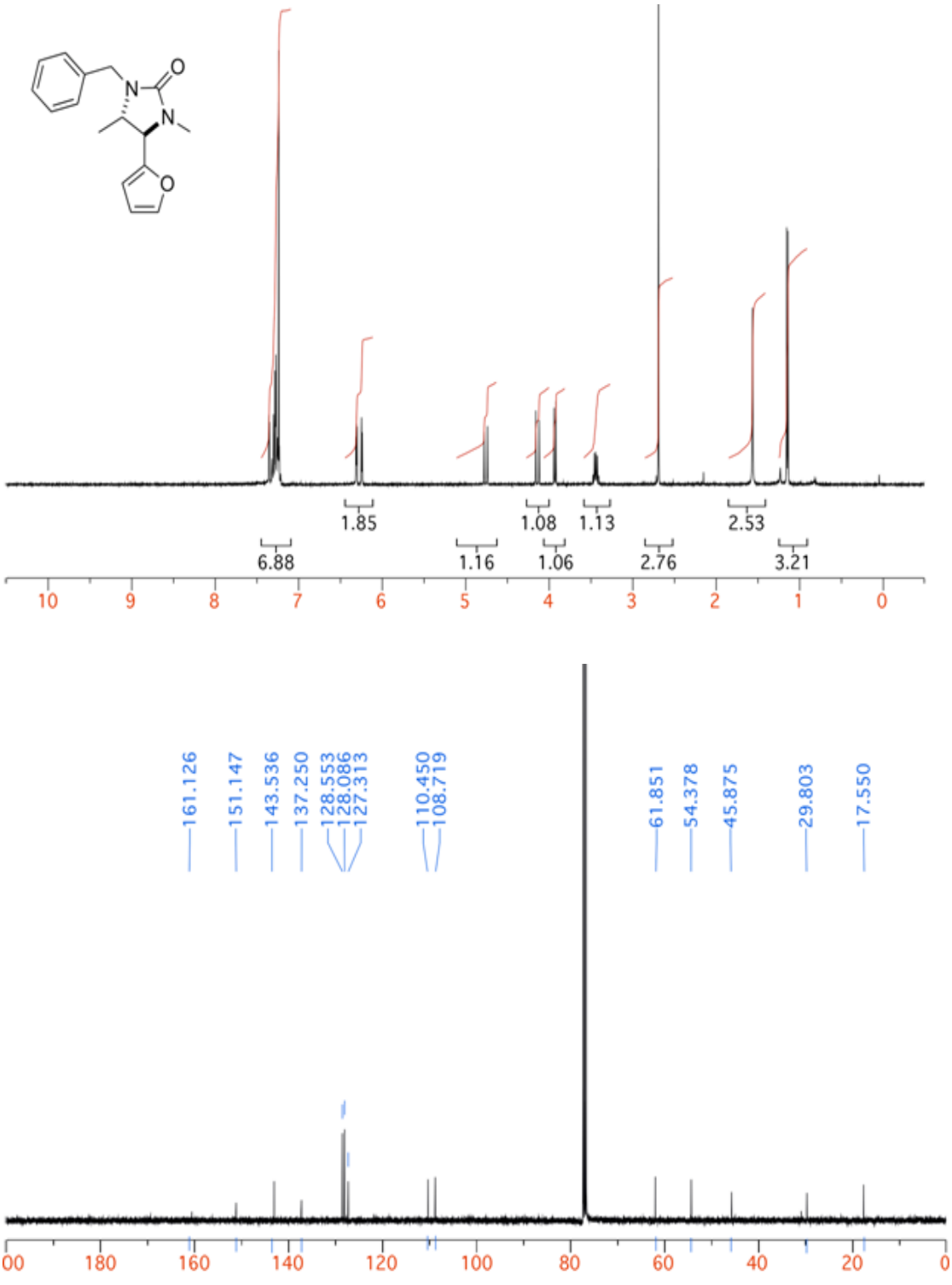


2.14a (Scheme 2.14)

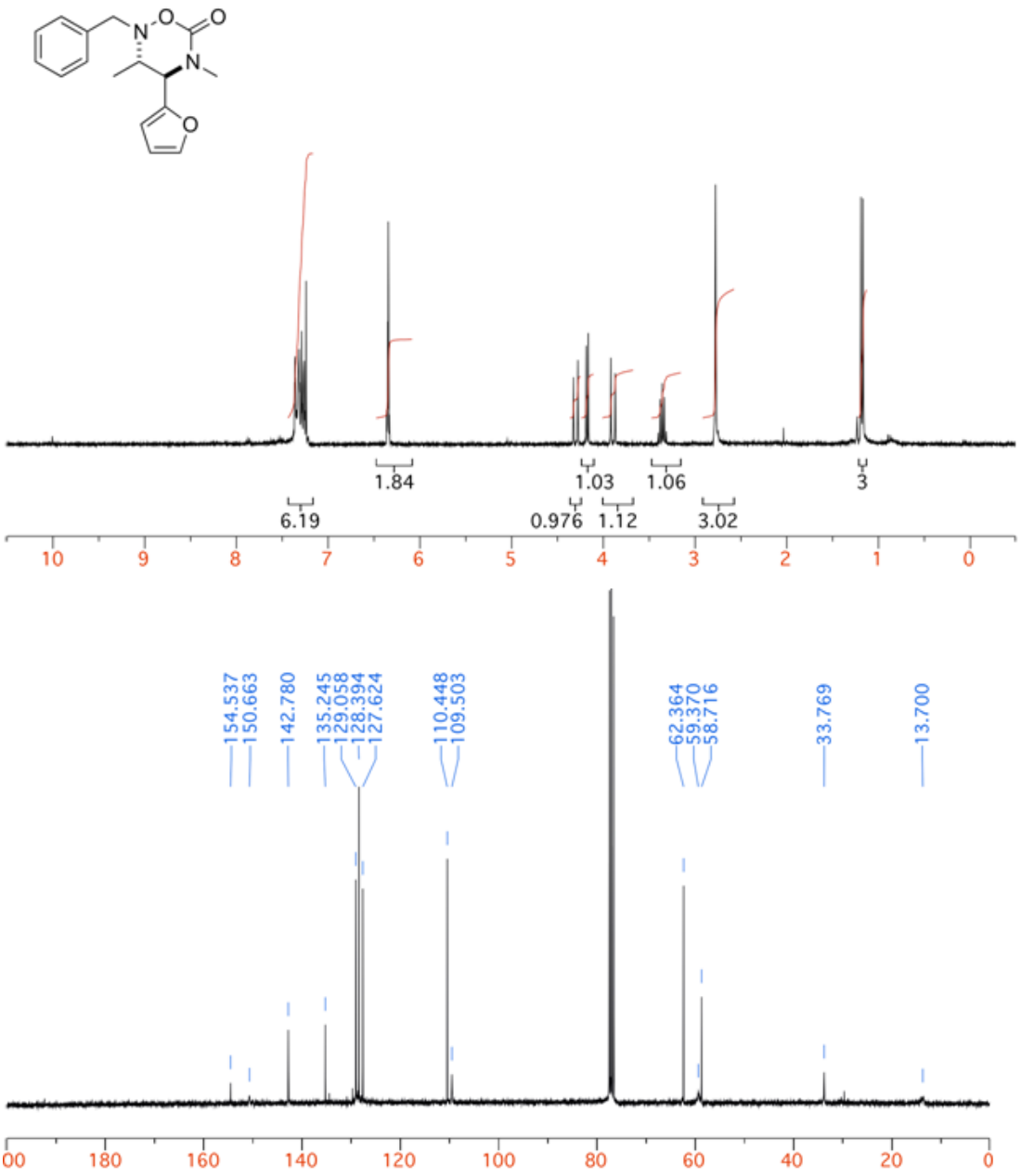




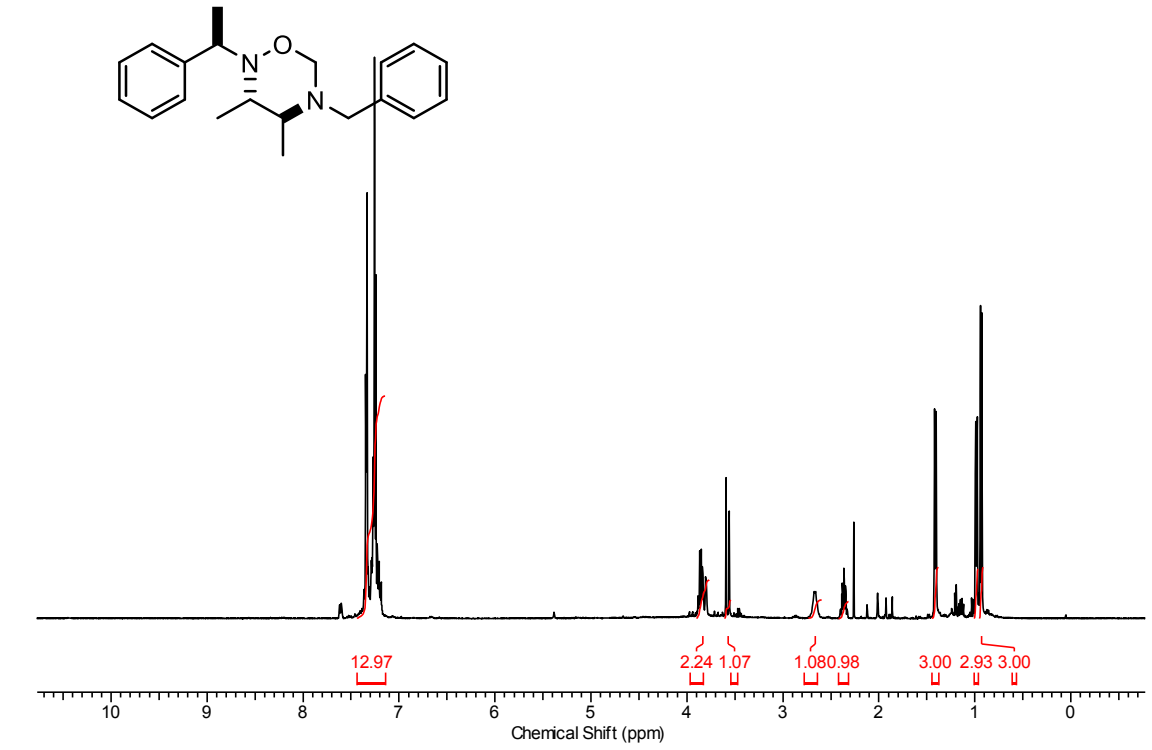
2.14b (Scheme 2.14)

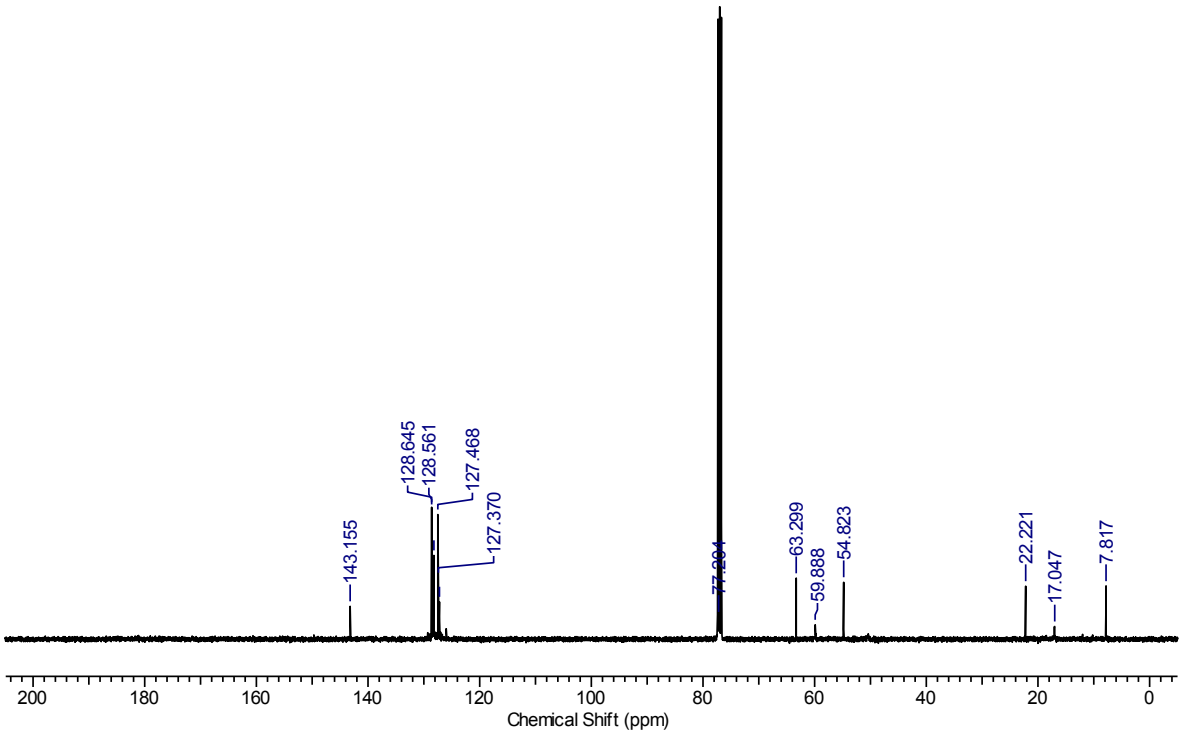


2.14c (Scheme 2.14)

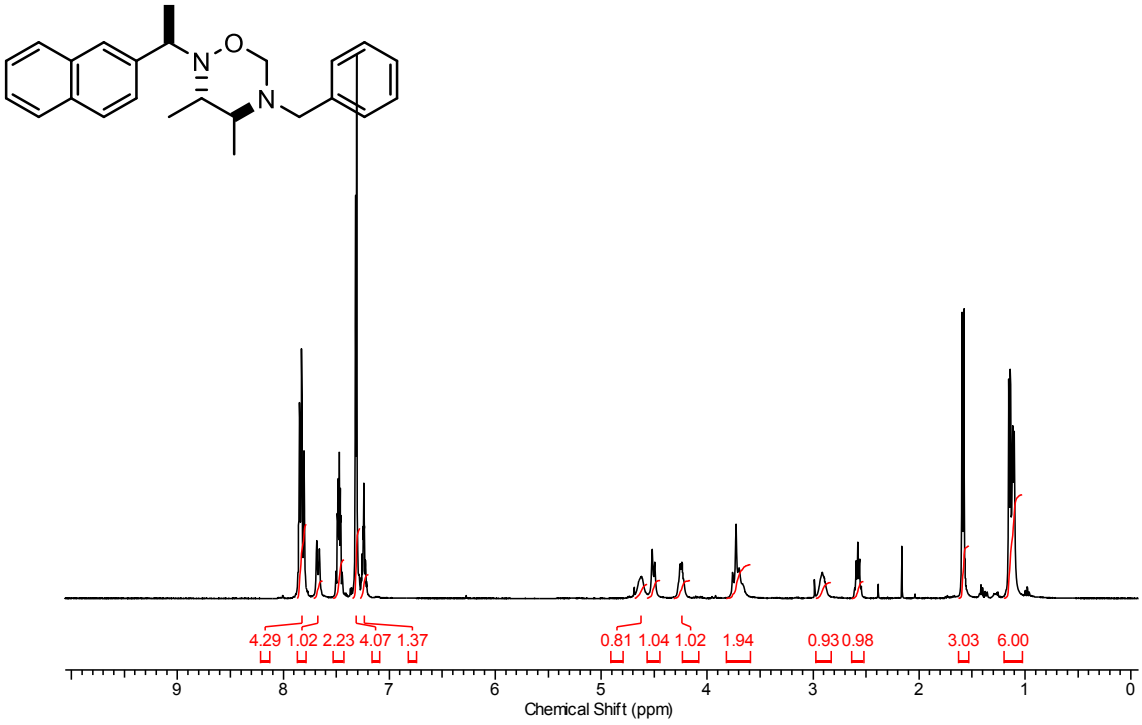


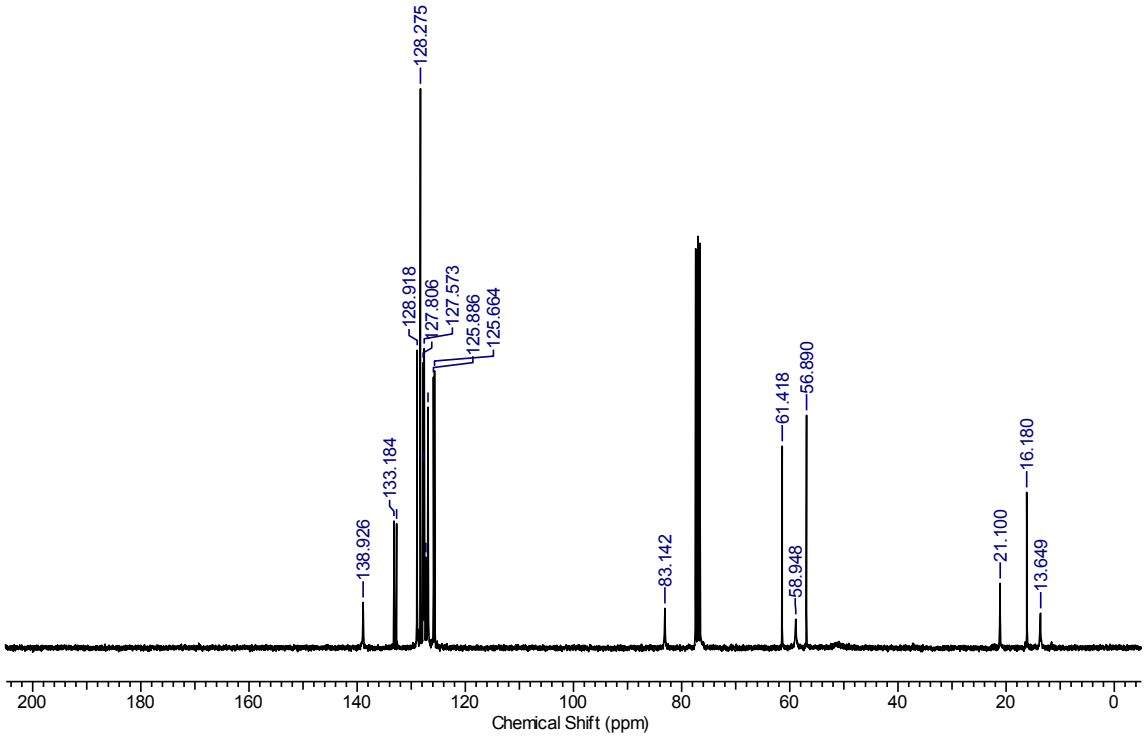
Entry 1 (Table 2.12) 19:1 dr





2.17a – (Scheme 2.17)





2.13a – (Table 2.13, Entry 4)