

**An Organocatalytic Tethering Strategy: Aldehyde-Catalyzed Cope-type
Hydroaminations of Allylic Amines**

By

Melissa MacDonald

B.Sc., University of Western Ontario, 2009

A thesis submitted to the Faculty of Graduate and Postdoctoral Studies In
partial fulfillment of the requirements For the Philosophiae Doctor (Ph.D.)
degree in chemistry

Candidate

Supervisor

Melissa MacDonald

Dr. André Beauchemin

© Melissa MacDonald, Ottawa, Canada, 2014

Abstract

Intermolecular reactions have long been a challenge in organic chemistry due to their high negative entropy and difficult nature, which often includes achieving regioselectivity and stereoselectivity. One strategy that has showed promise in overcoming these obstacles is the use of stoichiometric tethers to effectively *temporarily* make the reaction an intramolecular system. Therefore in several steps, the formation of a temporary tether, performing the desired reaction, and removal of the tether can enable a selective intermolecular reaction. The clear drawbacks to this method are the several steps required for a single transformation, the inherent waste and reduced overall yield for the synthetic sequence. This work aims at creating a catalytic approach to tethering to by-pass the above limitations and showcase how small organic molecules are effective catalysts' and can induce asymmetry simply via temporary intramolecularity.

The first part of this thesis illustrates this organocatalytic tethering approach via the application of the Cope-type hydroamination of alkenes. The intermolecular reaction of this methodology is extremely difficult and the goal of this work was to create a solution for the harsh conditions and low yields. This chapter describes a proof of concept for our approach using allylic amines and hydroxylamines, and a preliminary look at an asymmetric version of this reaction.

The second part of this thesis describes a mechanistic study of our catalytic cycle and provides a detailed look at inhibition and off-cycle pathways. Through this research a second-generation catalyst, formaldehyde, was discovered and an advanced scope is presented.

The final portion of the thesis focuses on an enantioselective and diastereoselective Cope-type hydroamination of alkenes via the organocatalytic tethering strategy. Optimization and substrate scope are presented, along with a discussion of the origins of selectivity. Derivatization of the final products is explored and future applications of the strategy are discussed.

Acknowledgments

A PhD is definitely a mental, emotional and physical roller coaster. It has been an amazing ride but I could not have got to the end without the support and unconditional love from my family and friends.

First of all, I want to thank the Beauchemin lab for welcoming me into the group when I moved to Ottawa. I didn't know a single person in this city and I didn't realize that I was going to meet lifelong friends that I still cherish today. Special thanks to my fumehood and desk labmate Frank, you have been the biggest and best surprise of my PhD. You supported me from day 1, to the end and I will never forget what an amazing friend you are. A huge thanks to my lab brothers Tom and Matt, you made me laugh every day and I will always remember our epic adventures, parties and the cheese! Thanks Nic for your hilarious accent, 50 joe, and inspiring chemistry discussions. I know you will succeed in whatever you decide to do. I want to thank all the undergrads that I had the pleasure of working with, Eric, Val, and Brittney. I wish you all good luck in the future. A big thanks to my first undergrad, and best friend, Alishya. We might have been unlikely friends at first, with very different interests....but somehow we have remained so close and I thank you for all your support! Thanks J.F. for interesting chemistry discussions and being my early morning lab buddy. I want to thank Lyanne and Brittney for making my last year in the Beauchemin lab always exciting, CSC was a blast and good luck with the rest of your graduate/bachelor degrees. To all the other Beauchemin members, thanks for the great discussions and themed parties, good luck in the future! A big thanks also to my friends in other labs, Nathalie, Jennie, Meghan, and Chantelle.

I have to thank André for this amazing opportunity and welcoming this bright eyed and very blonde University of Western graduate to his lab. Thanks for your guidance and support over these four years.

Finally, I have to thank my parents for their unconditional and never wavering love and support. I wouldn't be the person I am today, without your guidance and amazing example of what it means to be family. I love you more than anything and hope that I always make you proud.

Only those who will risk going too far can possibly find out how far one can go.

T. S. Eliot

Table of Contents

Abstract	II
Acknowledgments.....	IV
Table of Contents.....	VII
List of Abbreviations	XII
List of Figures	XVI
List of Schemes	XIX
List of Tables.....	XX
1 Introduction.....	1
1.1.2 Tethered Reactions.....	2
1.1.3 Overview of key Examples in Tethered Reactions.....	3
<i>Diels Alder reaction.....</i>	4
<i>Olefin and enyne metathesis.....</i>	8
<i>Metal-catalyzed reactions.....</i>	10
<i>Radical reactions.....</i>	11
<i>Tethers in total synthesis.....</i>	13
<i>Summary of examples of tethered reactions.....</i>	15
1.1.2 Directed Reactions.....	15
<i>Cyclopropanation.....</i>	17
<i>Epoxidations.....</i>	18
<i>Hydroformylation with a reversibly bound directing group.....</i>	20
<i>Selective activation of diols.....</i>	21
<i>Metal catalyzed ligand directed C-H functionalization reactions.....</i>	22
1.2 Intermolecular Hydroamination of Alkenes.....	24
1.2.1 Overview of Hydroamination.....	24
<i>Acid catalyzed hydroamination.....</i>	26
<i>Base catalyzed hydroamination.....</i>	30
<i>Transition metal-catalyzed hydroamination.....</i>	31
<i>Thermodynamic concerns.....</i>	33
<i>Conclusion.....</i>	34

2	A Catalytic Tethering Strategy: Simple Aldehydes Catalyze Intermolecular Alkene Hydroamination.....	36
2.1	Introduction.....	36
2.1.1	Tethering Strategies.....	36
2.1.2	Cope-type Hydroamination.....	38
2.1.3	Intramolecular/ Intermolecular Cope-type Hydroamination.....	40
2.1.4	Aldehyde Catalysis.....	42
2.2	Initial Approach to an Organocatalytic Tethering Strategy.....	46
2.2.1	Results and Discussion.....	50
	<i>Derivatization and attempts to isolate compound 2a.....</i>	<i>50</i>
	<i>Revised aldehyde scan.....</i>	<i>52</i>
	<i>Scope of the reaction.....</i>	<i>53</i>
	<i>Preliminary asymmetric advances.....</i>	<i>56</i>
	<i>Background reactivity.....</i>	<i>59</i>
2.3	Summary and Outlook.....	60
3	Mechanistic Investigations on Aldehyde-Catalyzed Cope-Type Hydroamination Lead to the Discovery of a More Efficient Tethering Catalyst.....	61
3.1	Introduction.....	61
3.1.1	Carbonyl Catalysis.....	61
3.2	Results and Discussion.....	67
	<i>Equilibrium studies.....</i>	<i>69</i>
	<i>Kinetic Isotope Effect for α-benzyloxyacetaldehyde.....</i>	<i>72</i>
	<i>Proposed catalytic cycle.....</i>	<i>73</i>
3.2.1	Aldehyde Optimizations and Discoveries.....	75
	<i>Ketones as organocatalysts for intermolecular Cope-type hydroamination.....</i>	<i>76</i>
	<i>Destabilized nitrones as competent organocatalysts.....</i>	<i>77</i>
	<i>Scope of formaldehyde catalyzed Cope-type hydroamination.....</i>	<i>81</i>
	<i>Aldehyde scan with consistent conditions.....</i>	<i>82</i>
3.2.2	Role of Aldehydes in Prebiotic Chemistry.....	84

<i>Miller-Urey experiment</i>	85
<i>"Low concentration issue" under prebiotic conditions</i>	87
<i>Aldehyde catalyzed Cope-type hydroamination in water</i>	88
3.3 Summary and Outlook.....	90
4 Using Chiral Aldehydes as Tethering Catalysts to Induce Asymmetry with Applications in Intermolecular Hydroamination and Conjugate Additions	92
4.1 Introduction.....	92
4.1.1 Asymmetric Hydroamination.....	92
4.1.2 Enantioselective Intramolecular Hydroamination.....	93
<i>Metal catalyzed asymmetric hydroamination</i>	93
<i>Metal free asymmetric hydroamination</i>	95
4.1.3 Enantioselective Intermolecular Hydroamination.....	97
<i>Iridium catalysis</i>	98
<i>Palladium catalysis</i>	99
<i>Gold catalysis</i>	100
<i>Rare earth metal-catalysis</i>	101
<i>Copper metal-catalysis</i>	101
4.2 Results and Discussion.....	102
<i>Solvent scan</i>	105
<i>Scope of the asymmetric aldehyde catalyzed Cope-type hydroamination of alkenes</i>	106
<i>Investigation on catalyst epimerization</i>	107
<i>Mechanism and rational of stereoiduction</i>	111
<i>t-BuOH effect</i>	112
<i>Additional applications for chiral aldehydes as tethering catalysts</i>	113
4.3 Summary and Outlook.....	114
5 Formaldehyde as a Tethering Organocatalyst: Highly Diastereoselective Substrate and Reagent-Controlled Hydroaminations of Allylic Amines and Further Attempts at Expanding Substrate Scope	116
5.1 Introduction.....	116
5.1.1 Stereoselective Cope-type Hydroaminations.....	116

5.2 Results and Discussion.....	120
<i>Optimization of reaction conditions</i>	121
<i>Reagent controlled diastereoselective hydroamination</i>	122
<i>Substrate controlled diastereoselective hydroamination</i>	124
<i>Derivatization of hydroaminated compounds</i>	127
5.3 Allylic Alcohols.....	128
5.4 Summary and Outlook.....	133
Appendix I. Claims to Original Research.....	135
Claims to Original Research.....	135
Publications from This Work.....	135
Presentations from This Work.....	136
Appendix II. Experimental Section.....	138
General Information.....	138
Procedures and characterization for Chapter 2.....	140
General procedure for tethered hydroaminations of allylic amines with <i>N</i> -alkylhydroxylamines.....	140
Synthesis of aldehydes used for Cope-type hydroamination.....	141
Synthesis of diamine compounds.....	142
Procedures for determining the enantiomeric excess of substrates (2b.1, 2c.1, 2e.1).....	151
Assignment of absolute configuration of <i>N</i> -dibenzyl-1,2-diaminopropane.....	151
Procedures and characterization for Chapter 3.....	153
Molecules for mechanistic experiments.....	153
Equilibrium experiments.....	154
Paraformaldehyde-catalyzed Cope-type hydroamination of Allylic amines with <i>N</i> -alkylhydroxylamines.....	157

Procedures and characterization for Chapter 4.....	161
Procedure for racemic hydroamination products.....	162
Preparation of aldehydes.....	162
Procedures for screening chiral aldehydes as potential catalysts.....	163
General procedures for tethered hydroaminations of allylic amines with <i>N</i> -alkylhydroxylamines.....	164
General procedure for determining the enantiomeric excess of substrates 4.1-4.13.....	164
Miscellaneous Materials.....	178
Epimerization of catalyst 2.3.....	180
Procedures and characterization for Chapter 5.....	184
Procedure for formaldehyde stock solution.....	185
General procedures for tethered hydroaminations of allylic amines with <i>N</i> -alkylhydroxylamines.....	186
General Procedures for the synthesis of <i>N</i> -benzyl and <i>N</i> -methyl allylic amines.....	186
Formaldehyde catalyzed intermolecular Cope-type hydroamination products...	187
Derivatized diamine products.....	203
X-ray crystallographic proof of structure.....	205
Appendix III. NMR and HPLC spectra.....	207
Appendix IV. Mechanistic paper to support Chapter 3.....	297

List of Abbreviations

Å	angstrom (10^{-10} metre)
Ac	acetyl
AcOH	acetic acid
AIBN	azobisisobutyronitrile
<i>Anti</i>	against, opposite
aq	aqueous
Ar	aryl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bu	butyl
Bz	benzoyl
cat.	catalytic
°C	degree Celsius
<i>cis</i>	<i>Z</i> , on the same side
Cy	cyclohexyl
δ	chemical shift in parts per million
d	deuterium (in NMR solvents); doublet
DCB	1,2-dichlorobenzene
DCE	dichloroethane
ΔG	change in Gibbs-free energy
ΔH	change in enthalpy
ΔS	change in entropy
DMF	dimethylformamide

DMAP	4-dimethylaminopyridine
DMSO	dimethyl sulfoxide
d.r.	diastereomeric ratio
<i>ee</i>	enantiomeric excess
eq	equation
equiv.	equivalent
Et	ethyl
EWG	electron-withdrawing group
g	gram
h	hours
HRMS	high-resolution mass spectroscopy
Hz	Hertz
<i>i</i>	iso
IMDA	intermolecular Diels Alder
IR	Infrared
<i>J</i>	coupling constant
<i>k</i>	rate constant
K	equilibrium constant
KIE	kinetic isotope effect
L	litre; ligand
LA	Lewis Acid
<i>m</i>	meta
M	molar; metal; Markovnikov
<i>m</i> -CPBA	meta-chloroperbenzoic acid

Me	methyl
MeCN	acetonitrile
mg	milligram
min	minute
mL	millitre
MS	molecular sieves
Nu	nucleophile
NMR	nuclear magnetic resonance
<i>o</i>	ortho
<i>p</i>	para
Ph	phenyl
PivOH	pivalic acid
PMB	<i>para</i> -methoxybenzyl
pr	propyl
psi	pounds per square inch
py	pyridine
R (R [#])	carbon-based substituent
RT	room temperature
s	second
sat.	saturated
SM	starting material
<i>syn</i>	together, same side
<i>t</i>	tertiary, <i>tert</i> -

TBAF	tetra- <i>n</i> -butylammonium fluoride
temp.	temperature
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TfOH	triflic acid
TLC	thin layer chromatography
TS ($\ddagger$)	transition state
TFB	trifluorobenzene
TFT	trifluorotoluene
<i>t</i> BuOH	<i>tert</i> -butanol
UV	ultra-violet
X	heteroatom or pseudohalide

List of Figures

Figure 1.1 Intramolecular vs. Intermolecular reactions.....	2
Figure 1.2 Examples of tethers in the literature.....	3
Figure 1.3 Overman's strategy to tether an intramolecular Diels Alder reaction in the total synthesis of (+) Aloperine.....	14
Figure 1.4 Rational for directed epoxidation.....	17
Figure 1.5 Directed control of regioselectivity in the hydroformylation of homo-bis allylic alcohols.....	21
Figure 1.6 Approaches to site-selective functionalization.....	22
Figure 1.7 Selected data on the reactions utilized on large scale for the formation of a carbon-nitrogen bond.....	25
Figure 1.8 Intermolecular hydroamination of alkenes.....	26
Figure 1.9 Mechanism of Pt(OTf) ₂ catalyzed intermolecular hydroamination of alkenes.....	29
Figure 1.10 Thermodynamics of hydroamination.....	33
Figure 2.1 Targeted stepwise approach to tethering for challenging intermolecular reactions and catalytic alternative.....	37
Figure 2.2 Cope elimination of trialkylamine- <i>N</i> -oxides.....	39
Figure 2.3 Reactivity trends of the reverse Cope-cyclization.....	41
Figure 2.4 Key reactivity of the intermolecular Cope-type hydroamination with alkene.....	42
Figure 2.5 General concept of an organocatalytic tethering strategy.....	43
Figure 2.6 A stoichiometric system leading to hydroamination products through a transient hydroxylamine (Knight and co-workers).....	45
Figure 2.7 Proposed catalytic cycle for a catalytic variant in which an aldehyde is used as the tethering precatalyst (this work).....	47
Figure 2.8 Discovery of a catalytic role for CH ₂ Cl ₂	57

Figure 2.9 Hydrogen bonding directed intermolecular Cope-type hydroamination of alkenes.....	58
Figure 3.1 Modes of activation in catalysis of intermolecular reactions.....	62
Figure 3.2 Reports of amide hydrolysis via carbonyl catalysis.....	63
Figure 3.3 Enantioselective hydrolysis of α -aminonitriles.....	64
Figure 3.4 Ester hydrolysis via a carbonyl catalyst	65
Figure 3.5 Sammakia and et al.'s α -hydroxy ester alcoholysis.....	66
Figure 3.6 Competing 1,2-addition on nitron.....	69
Figure 3.7 Equilibrium constants for the addition of <i>N</i> -ethylbenzylamine and <i>N</i> -benzylhydroxylamine to nitron 3.1.....	70
Figure 3.8 Competing 1,2-addition with benzylamine and <i>N</i> -benzylhydroxylamine with benzaldehyde and dihydrocinnamaldehyde.....	71
Figure 3.9 Hydrogen-bonding network with symmetrical aminor formation on aldehyde 2.1 Vs. lack of stabilization on dihydrocinnamaldehyde.....	72
Figure 3.10 Proposed catalytic cycle.....	74
Figure 3.11 Initial rate comparison in DMSO- d_6 using benzylallylamine (1.5 equiv.), <i>N</i> -benzylhydroxylamine (1 equiv.), catalyst 2.1 or 3.4 (20 mol %), DMSO- d_6 (1 M), 25 °C.....	78
Figure 3.12 Advanced aldehyde scan in $CHCl_3$ and <i>t</i> -BuOH.....	83
Figure 3.13 α -Aminonitrile hydrolyses via carbonyl catalysis.....	85
Figure 3.14 Miller-Urey experiment and the possible aldehyde role in the synthesis of amino acids.....	86
Figure 4.1 Thiourea-catalyzed intramolecular Cope-type hydroamination.....	97
Figure 4.2 Probing the source of epimerization for catalyst 4h	110
Figure 4.3 Enantioselective hydroamination originating from a transient stereocentre formed via a stereoselective 1,2-addition.....	111
Figure 4.4 Enantioselective Cope-type hydroamination originating from a transient stereocentre formed via a stereoselective 1,2-addition on favoured nitron.....	112
Figure 4.5 The strategy of a temporary chiral amine performing nucleophilic additions	

on to activated electrophiles.....	114
Figure 5.1 Diastereoselective Cope-type hydroamination.....	118
Figure 5.2 Proposed transition state for reagent controlled Cope-type hydroamination.....	123
Figure 5.3 Proposed transition state for substrate controlled Cope-type hydroamination.....	126
Figure 5.4 Hydroamination under high pressure.....	133

List of Schemes

Scheme 1.1: Tamao's silicon-tethered Diels Alder reaction.....	5
Scheme 1.2 Examples of directed reactions overriding steric effects.....	17
Scheme 1.3 Examples of directed metal catalyzed C-H activation.....	23
Scheme 1.4 Summary of approach's to metal catalyzed hydroamination.....	32
Scheme 2.1 Attempts of catalysis with internal alkenes using catalyst 2.1.....	55
Scheme 3.1 Rate law order of each reagent.....	68
Scheme 3.2 Importance of steric factors with a ketone precatalyst.....	77
Scheme 4.1 Activation of amino functional group to promote hydroamination.....	98
Scheme 4.2 Probing the source of racemization for catalyst 2.3.....	109
Scheme 5.1 Bagley's diastereoselective synthesis of cis-2,5-disubstituted pyrrolidine <i>N</i> -oxides.....	119
Scheme 5.2 Leighton's diastereoselective hydroamination reaction sequence.....	120
Scheme 5.3 Comparison of cascade Cope-type hydroamination via hydrogen bonding directed and tethering organocatalysis.....	126
Scheme 5.4 Diamine motifs: examples of derivatization reactions.....	128

List of Tables

Table 2.1 Aldehyde scan of intermolecular Cope-type hydroamination.....	47
Table 2.2 Optimization of α -benzyloxyacetaldehyde catalyzed Cope-type hydroamination.....	48
Table 2.3 Optimizing protection derivatization.....	50
Table 2.4 Representative reactivity of optimized aldehyde scan.....	52
Table 2.5 Aldehyde catalyzed intermolecular Cope-type hydroamination.....	54
Table 2.6 Aldehyde catalyzed intermolecular Cope-type hydroamination.....	56
Table 2.7 Background reactivity and control experiments.....	59
Table 3.1 Comparative reaction scope for the formaldehyde-catalyzed Cope-type hydroamination.....	80
Table 3.2 Cope-type hydroamination of internal alkenes catalyzed by formaldehyde....	81
Table 3.3 Aldehyde catalyzed Cope-type hydroamination in water.....	89
Table 4.1 Representative results of chiral aldehyde screening.....	104
Table 4.2 Optimization of aldehyde 2.3 reactivity.....	106
Table 4.3 Scope of asymmetric hydroaminations using chiral aldehydes.....	107
Table 5.1 Optimization of formaldehyde-catalyzed asymmetric intermolecular Cope-type hydroamination.....	122
Table 5.2 Reagent controlled diastereoselective hydroamination.....	123
Table 5.3 Substrate controlled diastereoselective hydroamination.....	125
Table 5.4 Attempts of α -benzyloxyacetaldehyde 2.1 to catalyze allylic alcohols and hydroxylamines.....	129
Table 5.5 Effects of Bronsted and Lewis acids on α -benzyloxyacetaldehyde to catalyze the hydroamination of allyl alcohol.....	130
Table 5.6 Solvent effects on formaldehyde's ability to catalyze the hydroamination of allylic alcohol and <i>N</i> -benzylhydroxylamine.....	131

Part A: Tethered and Directed Reactions

1.1 Introduction

Approaches that are capable of efficient and selective intermolecular reactions are at the centre of organic chemistry. A key area that has shown promise in the past is the use of stoichiometric “temporary tethers” to achieve an easier, more controlled, "temporarily" intramolecular version of a difficult intermolecular reaction. As this strategy develops, more catalytic approaches are needed to minimize the amount of steps and waste inherently associated with the stoichiometric approach. This introduction will focus on reviewing strategies to tether and direct reactions in order to improve reactivity and selectivity. A survey of common reactions that are targeted for this approach, along with their advantages and drawbacks, will be discussed in order to gain perspective on the achievements presented in Chapter 2, 3, 4 and 5. Finally, a review of the hydroamination literature will be discussed which, will provide context for our results on a catalytic tethering strategy to facilitate this difficult carbon-nitrogen bond forming reaction.

1.1.2 Tethered Reactions

Intermolecular reactions are at the forefront of organic chemistry and are responsible for a large number of key bond-forming reactions. At the core of most intermolecular reactions is the difficulty of overcoming the negative entropy change seen in Gibbs free energy, ($\Delta G = \Delta H - T\Delta S$). Therefore the free energy of the reaction is higher and control over selectivity more complex (see Figure 1.1). This is in contrast to intramolecular reaction counterparts that typically only result in a minimal entropic penalty and more control over the regio- and stereoselectivity.

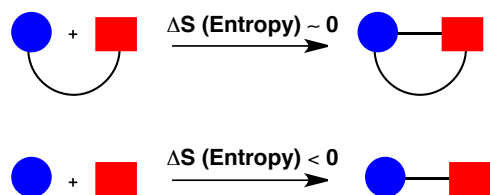


Figure 1.1 Intramolecular vs. Intermolecular reactions in the entropy of a reaction

Therefore a common strategy to overcome the entropic cost of an intermolecular reaction is to temporarily bring together, or “tether”, the two starting materials.¹ As a result the reaction becomes, for a moment, essentially intramolecular and can proceed with a lower activation energy. This approach has flourished over the past few decades with several examples of common tethers including boron or silicon (see Figure 1.2).

¹ For reviews, see: (a) *Templated Organic Synthesis*; Diederich; Stang; Eds; Wiley-VCH, 2000. (b) Gauthier, Jr., D. R.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, 54, 2289-2338. (c) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, 95, 1253-1277. (d) Fensterbank, L.; Malacria, M.; Sieburth, S. M. *Synthesis* **1997**, 813-854. (e) Bracegirdle, S.; Anderson, E. A. *Chem. Soc. Rev.* **2010**, 39, 4114-4129. (f) Cusack, A. *Chem. Eur. J.* **2012**, 18, 5800-5824.

Examples of known tethering strategies

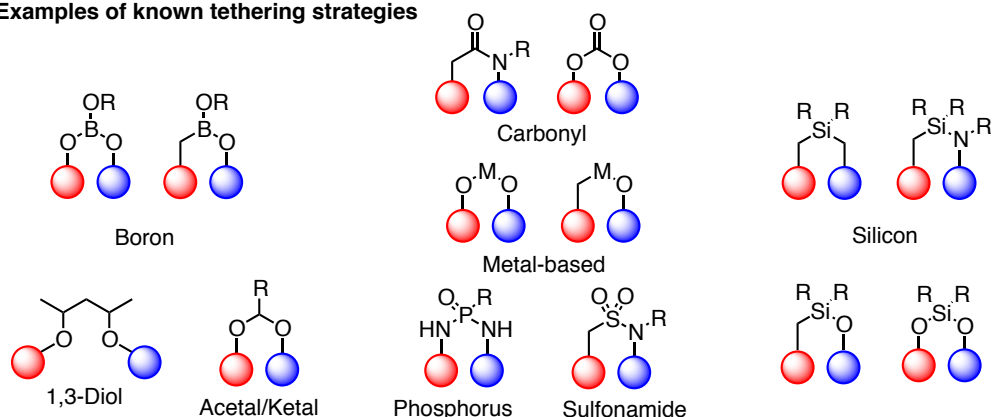


Figure 1.2 Examples of tethers in the literature

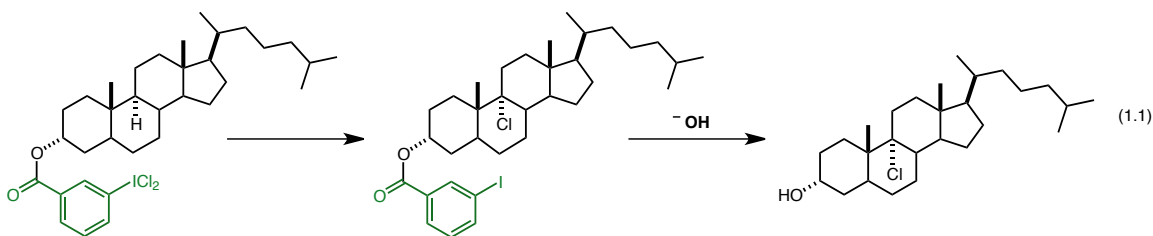
These tethers tend to be installed for use, and then removed at the appropriate time in the synthetic sequence or further derivatized. The main drawbacks common to all these approaches is that these operations inherently require additional steps. In addition, the tether is stoichiometric and catalytic examples are unknown.² Therefore the series involves a lengthier synthesis and a reduced overall yield. The ability to be able to install, use, and remove a tether in *a single operation* would be extremely advantageous.

1.1.3 Overview of Key Examples in Tethered Reactions

One of the pioneers of using temporary intramolecularity was Professor Ronald Breslow. He utilized an ester as a temporary tether to introduce a *meta* iodobenzoate substituent, which could perform a selective chlorination on a steroid in the presence of

² Enzymes can catalyze reactions through "pseudo-intramolecularity." See: (a) Fersht, A. *Enzyme Structure and Mechanism*; W. H. Freeman and Company, 1985. (b) Jencks, W. P. *Catalysis in Chemistry and Enzymology*; McGraw-Hill, 1969. (c) The Ti-atom in the Sharpless asymmetric epoxidation can be thought of as having a tethering role.

phenyliodine dichloride.³ This process showcased a stoichiometric approach with three steps resulting in one overall transformation⁴ (eq. 1.1) and was used to target a variety of difficult intermolecular reactions.



Diels Alder reaction

Since its discovery the Diels Alder reaction has been enormously important in forming a variety of six membered rings with high regioselectivity and stereoselectivity. However, the intermolecular Diels Alder reaction can suffer from poor reactivity, and therefore requires harsh conditions. Consequently, this reaction is a perfect target to apply a tethering strategy. The earliest reports of this application were seen in 1989, when Tamao and co-workers use a silicon tether to perform several intermolecular Diels Alder reactions (see Scheme 1.1).⁵ Through the use of a silicon tether, installed through a substitution reaction, regio- and stereocontrol is gained and the product is isolated in a single isomer, before removal of the tether in a final step. Stork furthered these silicon-tethered cycloadditions with vinyl silanes. The regiocontrol and addition of four new stereocentres is worth noting (eq. 1.2).⁶

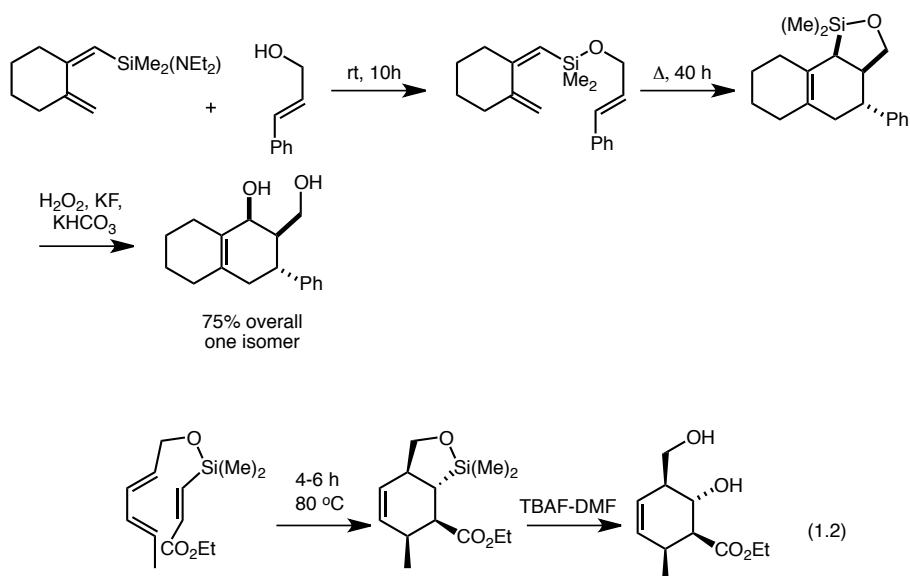
³ Breslow, R.; Corcoran, R.; Dale, J. A.; Liu, S.; Kalicky, P. *J. Am. Chem. Soc.* **1974**, *96*, 1973-1974.

⁴ (a) Breslow, R. *Acc. Chem. Res.* **1980**, *13*, 170-177. (b) Breslow, R. *Acc. Chem. Res.* **1995**, *28*, 146-153.

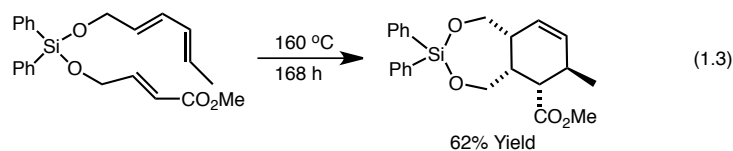
⁵ Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 6478-6479.

⁶ Stork, G.; Chan, T. Y.; Breault, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7578-7579.

Scheme 1.1 Tamao's silicon-tethered Diels Alder reaction



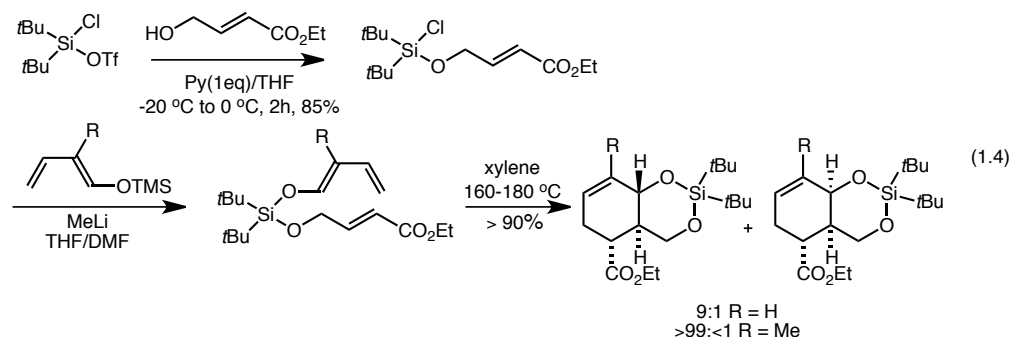
In 1990 Craig and Fortin developed the strategy and synthesis of silicon acetals as competent tethers for the Diels Alder reaction.⁷ Craig, synthesizing the acetals via silyl chlorides, was able to isolate the tethered Diels Alder product in moderate yields as a single stereoisomer (eq. 1.3).



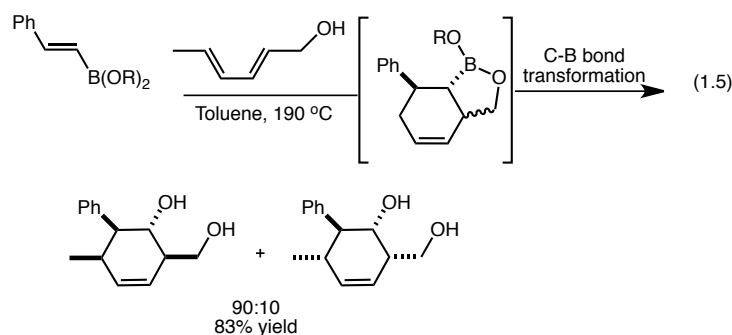
Noting the difficulty in the synthesis of the silicon acetals due to several side products, Fortin was able to develop a sequence using silicon triflates that resulted in an efficient

⁷ (a) Craig, D.; Reader, J. C. *Tetrahedron Lett.* **1990**, 31, 6585-6588. (b) Craig, D.; Reader, J. C. *Tetrahedron Lett.* **1992**, 33, 4073-4076. (c) Craig, D.; Reader, J. C. *Tetrahedron Lett.* **1992**, 33, 6165-6168. (d) Gillard, J. W.; Fortin, R.; Grimm, E. L.; Maillard, M.; Tjepkema, M.; Bernstein, M. A.; Glaser, R. *Tetrahedron Lett.* **1991**, 32, 1145-1148.

synthesis of these starting materials (eq. 1.4). The Diels Alder reaction proceeded with excellent stereoselectivity when R = Me (99:1).

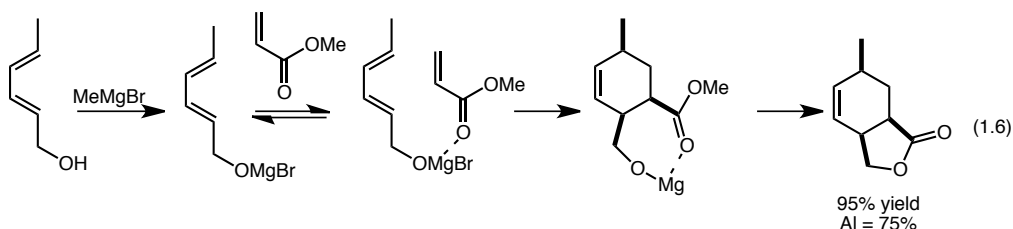


A Boron-tethered approach to the intermolecular Diels Alder (IMDA) was reported by Batey and co-workers in 1999.⁸ They developed a system that tethered alkenyl boronic acids to a diene component, which triggered a C-B-O tethered intramolecular Diels Alder (eq. 1.5). The resulting boracycles were transformed into diols through known organoborane oxidation chemistry. This is an example of not only cleaving a stoichiometric tether but also manipulating the tether with further functionalization.



⁸ Batey, R. A.; Thadani, A. N.; Lough, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 450-451. Other examples of phenyl boronic as tethers for Diels Alder reactions: (a) Narasaka, K.; Shimada, S.; Osoda, K.; Iwasawa, N. *Synthesis* **1991**, 1171-1172. (b) Nicolaou, K. C.; Liu, J. J.; Yang, Z.; Ueno, H.; Sorensen, E. J.; Claiborne, C. F.; Guy, R. K.; Hwang, C. K.; Nakada, M.; Nantermet, P. G. *J. Am. Chem. Soc.* **1995**, *117*, 634- 644. (c) Shimada, S.; Osoda, K.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1254-1257.

Many research groups have also successfully applied metal tethers to the IMDA. Magnesium and aluminum examples were reported by both Stork and Ward and showed excellent regiochemical control when compared to a non-tethering control experiment (eq. 1.6).⁹ Through a series of comparison based experiments, magnesium was found to be the most effective tether allowing the shortest reaction time (1 h, 70°C) and mildest conditions.



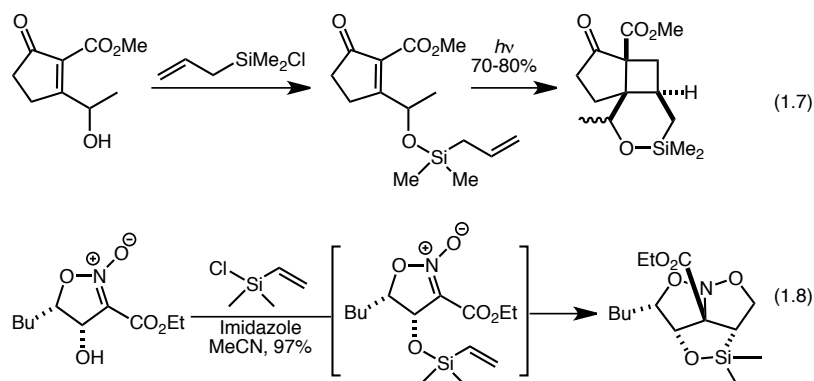
Due to the success of 4+2 cycloadditions, tethering strategies were applied to a variety of 2+2¹⁰, 3+2 cycloadditions¹¹ and *meta* photocycloadditions¹² (1,3-addition of an alkene across the excited state of a benzene derivative) (see eq. 1.7 and 1.8). Several different lengths between the tether and starting material have been explored as well as the chemical nature of the tether.

⁹ (a) Stork, G.; Chan, T. Y. *J. Am. Chem. Soc.* **1995**, *117*, 6595-6596. (b) Ward, D. E.; Abaee, M. S. *Org. Lett.* **2000**, *2*, 3937-3940. (c) Barriault, L.; Thomas, J.D.; Clément, R. *J. Org. Chem.* **2003**, *68*, 2317-2323. For aluminum and magnesium comparison see: Bertozzi, F.; Olsson, R.; Frejd, T. *Org. Lett.* **2000**, *2*, 1283-1286.

¹⁰ (a) Crimmins, M. T.; Guise, L. E. *Tetrahedron Lett.* **1994**, *35*, 1657-1660. (b) Fleming, S. A.; Ward, S. C. *Tetrahedron Lett.* **1992**, *33*, 1013-1016. (c) Ward, S. C.; Fleming, S. A. *J. Org. Chem.* **1994**, *59*, 6476-6479.

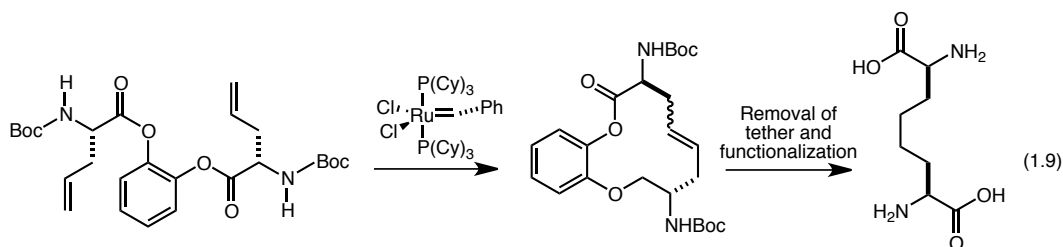
¹¹ (a) Garner, P. P.; Cox, P. B.; Klippenstein, S. J.; Youngs, W. J.; McConville, D. B. *J. Org. Chem.* **1994**, *59*, 6510-6511. (b) Righi, P.; Marotta, E.; Landuzzi, A.; Rosini, G. *J. Am. Chem. Soc.* **1996**, *118*, 9446-9447. (c) Denmark, S. E.; Hurd, A. R.; Sacha, H. J. *J. Org. Chem.* **1997**, *62*, 1668-1674.

¹² (a) Penkett, C. S.; Byrne, P. W.; Teobald, B. J.; Rola, B.; Ozanne, A.; Hitchcock, P. B. *Tetrahedron* **2004**, *60*, 2771-2784. (b) Sugimura, T.; Yamasaki, A.; Okuyama, T. *Tetrahedron: Asymmetry* **2005**, *16*, 675-683. For review: Gauthier, D.R.; Zandi, K. S.; Shea, K. J. *Tetrahedron Lett.* **1998**, *54*, 2289-2338.



Olefin and enyne metathesis

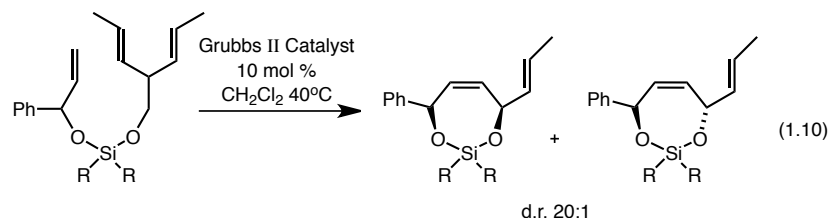
Tethering strategies have garnered a lot of attention for promoting intermolecular olefin and enyne metathesis. The use of tethering atoms has allowed certain reactions that were not suitable with ruthenium intermolecular metathesis to be performed under mild conditions. A representative example in the literature was reported by Grubbs and co-workers in 1997 during the total synthesis of (*S,S*)-2,7-diaminosuberic acid.¹³ Their key step involved BOC-protected *C*-allylglycine methyl ester undergoing an intermolecular metathesis. However, even under forcing conditions the alkene was unreactive. Using catechol as a template the reaction proceeded smoothly in 85 % yield (eq. 1.9).



Shortly after this report several research groups published examples of tethering

¹³ O'Leary, D. J.; Miller, S. J.; Grubbs, R. H. *Tetrahedron Lett.* **1998**, 39, 1689-1690.

approaches to ring closing metathesis using silicon¹⁴ or phosphorus¹⁵ as temporary tether reagents. Evans investigated a noteworthy diastereoselective approach in 2003, which utilized prochiral alcohols to induce long-range asymmetry with excellent diastereoselectivity (eq. 1.10).¹⁶ The silicon tether could be cleaved in the final step to gain access to selective 1,2-diols.



Alkene-alkyne (enyne) metathesis has also been shown to benefit from tethering strategies especially with regards to regiocontrol. In 2001, Yao and co-workers showcased this approach with the synthesis of highly functionalized acyclic dienes, using a silicon tether (eq. 1.11).¹⁷ Several diols were synthesized in excellent yield (up to 87%) with both Grubbs I/II catalysts.

These examples, as mentioned previously, allow certain reactions that were not suitable with ruthenium intermolecular metathesis to be performed under mild conditions in a regiocontrolled manner. The significant limitation with these strategies is the use of a

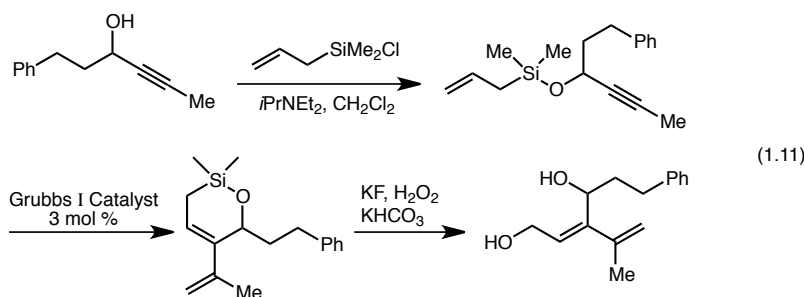
¹⁴ (a) Evans, P. A.; Murthy, V. S. *J. Org. Chem.* **1998**, *63*, 6768-6769. (b) Hoye, T. R.; Promo, M. A. *Tetrahedron Lett.* **1999**, *40*, 1429-1432. (c) Gierasch, T. M.; Chytil, M.; Didiuk, M. T.; Park, J. Y.; Urban, J. J.; Nolan, S. P.; Verdine, G. L. *Org. Lett.* **2000**, *2*, 3999-4002. (d) Lobbel, M.; Köll, P. *Tetrahedron: Asymmetry* **2000**, *11*, 393-396.

¹⁵ Sprott, K. T.; McReynolds, M. D.; Hanson, P. R. *Org. Lett.* **2001**, *3*, 3939-3942.

¹⁶ Evans, P. A.; Cui, J.; Buffone, G. P. *Angew. Chem. Int. Ed.* **2003**, *42*, 1734-1737.

¹⁷ (a) Yao, Q. *Org. Lett.* **2001**, *3*, 2069-2072. (b) Grimm, J. B.; Otte, R. D.; Lee, D. *J. Organomet. Chem.* **2005**, *690*, 5508-5516.

stoichiometric tether and the long synthetic sequence for one desired transformation.



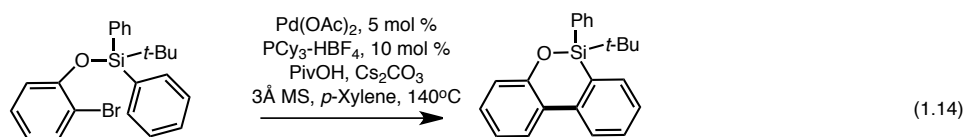
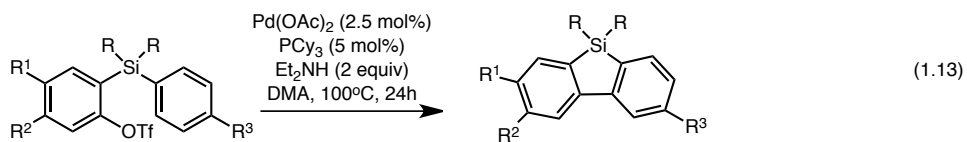
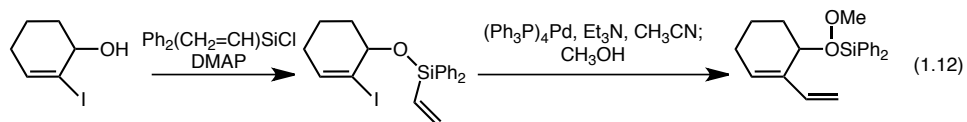
Metal-catalyzed reactions

Some intermolecular metal-catalyzed reactions can also be prone to low reactivity and poor regioselectivity. Directing groups can help overcome these issues but are not without exceptions or their own limitations.¹⁸ Thus mimicking more efficient intramolecular ring forming metal catalyzed reactions would benefit this methodology. In 2001 one of the first metal catalyzed coupling reactions involving a stoichiometric tether was reported on route to the total synthesis of Curcusone A.¹⁹ Young and co-workers developed a silicon-tethered Heck reaction with yields up to 81% (eq. 1.12). These strategies have been further developed by Hiyama and Gevorgyan and applied to aryl triflates and *o*-bromophenols (eq. 1.13 and 1.14).²⁰

¹⁸ Do, H.-Q.; Kashif Khan, R. M.; Daugulis, O. *J. Am. Chem. Soc.* **2008**, *130*, 15185-15192.

¹⁹ Mayasundari, A.; Young, D. G. *J. Tetrahedron Lett.* **2001**, *42*, 203-206.

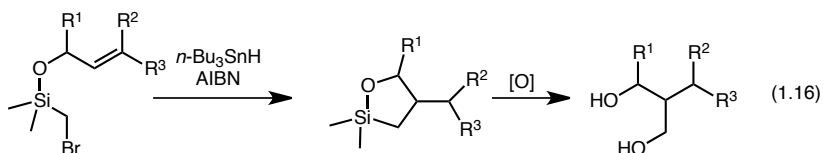
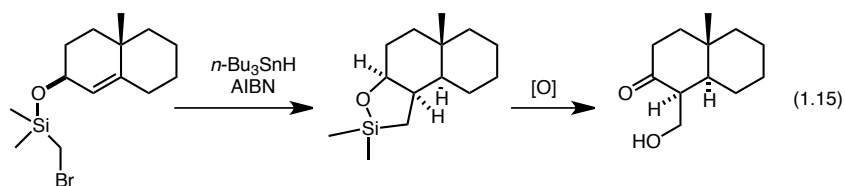
²⁰ (a) Shimizu, M.; Mochida, K.; Hiyama, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 9760-9764. (b) Huang, C.; Gevorgyan, V. *J. Am. Chem. Soc.* **2009**, *131*, 10844-10845. (c) Mochida, K.; Shimizu, M.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 8350-8351.



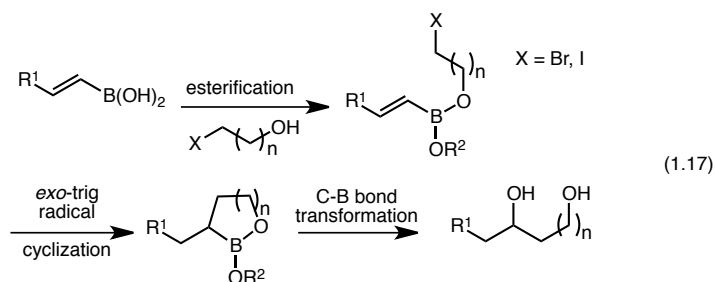
Radical reactions

Intermolecular radical reactions can be inefficient and problematic, notably leading to side products easily with the very small lifetime of the radical species. Thus, radical cyclizations have benefited from tethered reactions as early as the 1980's with reports from both Stork and Nishiyama (eq. 1.15 and 1.16).²¹ Using silicon as their tethering atom, both research groups were able to selectively form 5-membered rings via a radical process. Further functionalization through an oxidative process synthesized the desired alcohols.

²¹ (a) Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298-2300. (b) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500-501.



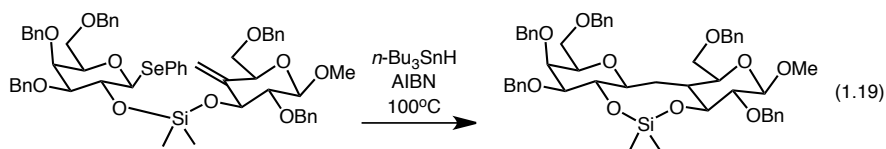
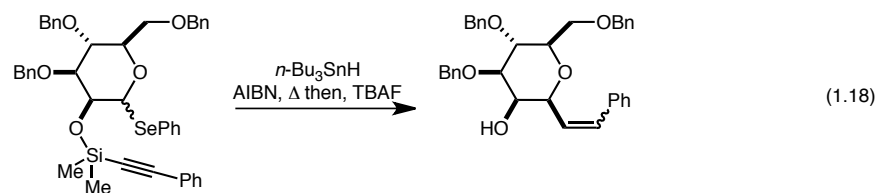
In an extension of the work done with silicon, the first boron-tethered radical cyclization was published in 1999. Batey and co-workers reported yields (up to 83%) for the radical cyclization and provide an alternative to silicon-based tethering strategies (eq. 1.17).²²



Carbohydrate synthesis has benefited from the use of tethers in the synthesis of C-glycosides.²³ Using a selenium radical process the alkene synthesis proceeds with 10:1 E/Z selectivity (eq. 1.18). This approach has also been applied towards the synthesis of C-disaccharides (eq. 1.19).^{23b}

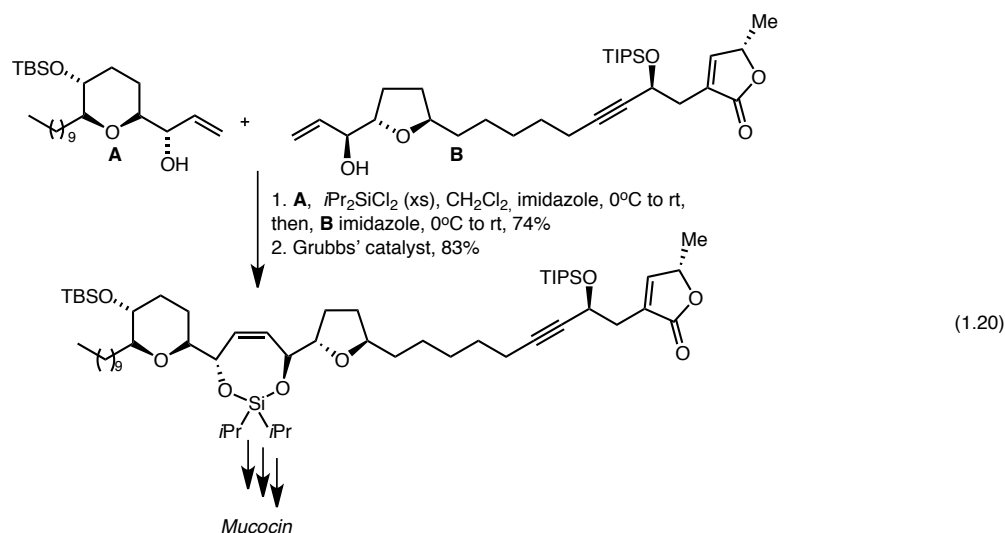
²² Batey, R. A.; Smil, D. V. *Angew. Chem. Int. Ed.* **1999**, 38, 1798-1800.

²³ (a) Stork, G.; Suh, H. S.; Kim, G. *J. Am. Chem. Soc.* **1991**, 113, 7054-7056. (b) Rubinstenn, G.; Mallet, J. M.; Sinay, P. *Tetrahedron Lett.* **1998**, 39, 3697-3700. See also: (b) Rubinstenn, G.; Esnault, J.; Mallet, J. M.; Sinay, P. *Tetrahedron: Asymmetry* **1997**, 8, 1327-1336.



Tethers in total synthesis

The use of tethers to target key reactions in the synthesis of natural products has a long history and shows the significance of this approach in organic methodologies. Evans reported an example that highlights this theory in 2003 on the synthesis of (–)-mucocin through a late stage ring-closing metathesis (eq. 1.20).²⁴



The temporary silicon tethered metathesis was achieved in 83% yield and was the first

²⁴ Evans, P. A.; Cui, J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H. R. *J. Am. Chem. Soc.* **2003**, *125*, 14702-14703.

application of this strategy in the synthesis of this annonaceous acetogenin (a class of new antitumor agents and pesticides).

A tethered intramolecular Diels Alder reaction was showcased in the total synthesis of (+)-aloperine in 1999. Overman used a silicon-tethering atom to overcome the limitations and selectivity issues associated with the original intermolecular reaction (Figure 1.3). The resulting Diels Alder products were synthesized in a 5:1 ratio and converted to a more stable alcohol through a series of experiments as the silicon tether was not stable in an aqueous workup.²⁵

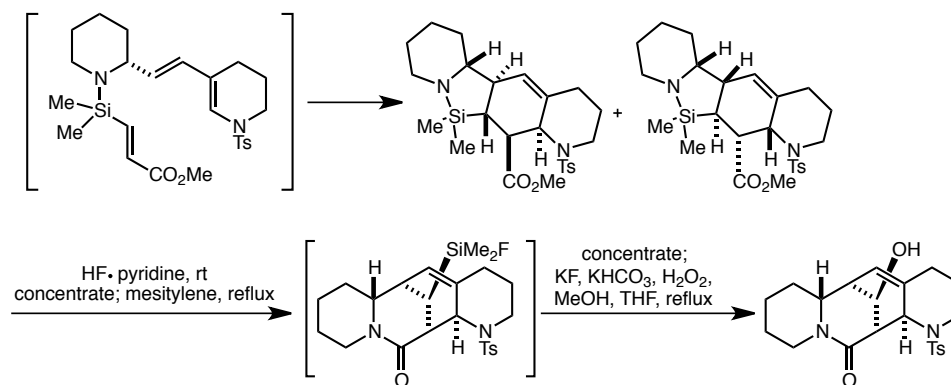
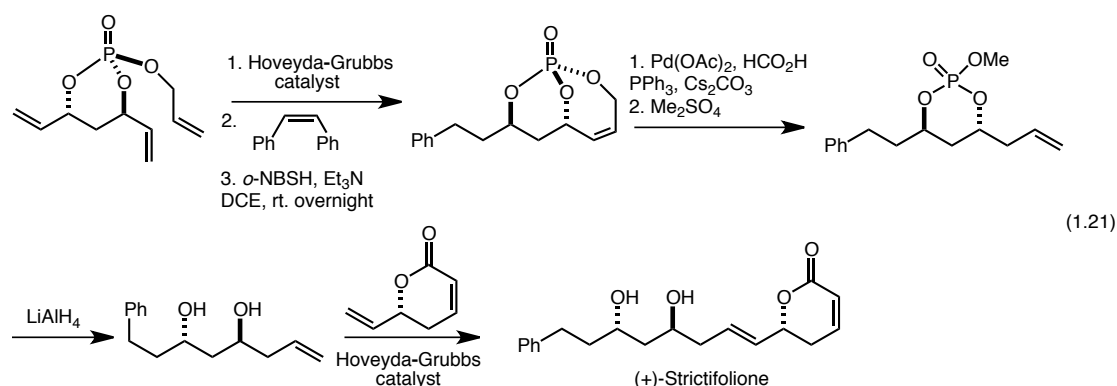


Figure 1.3 Overman's strategy to tether an intramolecular Diels Alder reaction in the total synthesis of (+)-Aloperine

A recent and impressive case of utilizing a tether for applications in natural product synthesis occurred on route to the synthesis (+)-strictifolione in 2014.²⁶ This one pot process features two consecutive phosphate tether-mediated processes, and allows the synthesis of the antifungal product. The phosphate triester's orthogonal protection, and ease of removal creates an effective streamlined synthesis.

²⁵ Brosius, A. D.; Overman, L. E.; Schwink, L. *J. Am. Chem. Soc.* **1999**, *121*, 700-709.

²⁶ Jayasinghe, S.; Venukadasula, P. K. M.; Hanson, P. R. *Org. Lett.* **2014**, *16*, 122-125.



Summary of examples of tethered reactions

As the above examples show, the use of tethers and their benefits toward difficult and non-selective intermolecular reactions have wide applications in organic chemistry. A range of methodologies have benefited from dramatic increases in reaction rates, along with increased regio- and stereoselectivity. The main drawback to all of these strategies is the requirement of several steps, attachment and removal, to perform the desired reaction. As a result, the overall yield of the synthetic sequence is reduced and further functionalization of the resulting compound is needed.

1.1.4 Directed Reactions

As chemists continually try to develop methods for regiospecific and stereospecific reactions the ability to control selectivity is of the utmost importance. The ability to direct a reaction through catalyst and/or substrate interactions has drawn attention over the past decades especially its ability to, in some cases, override steric

effects.²⁷ This approach primarily uses polar functional groups in the vicinity of the reaction centre to direct the outcome of a given system. The preassociation can be effected through a covalent bond or one or more non-covalent associative interactions such as, hydrogen bonding or Lewis acid interactions. Several reactions have benefited from this approach including cyclopropanation,²⁸ hydrogenation,²⁹ reduction,³⁰ cycloaddition,³¹ and orthometalation.³²

The first recognized examples of directed reactions were observed with the stereoselective Henbest epoxidation and Simmons-Smith cyclopropanation²⁷ (see Scheme 1.2). These systems are directed by the allylic alcohol to deliver the reaction to the most sterically hindered side of the molecule. As a result, these examples demonstrated the importance of directed reactions in asymmetric organic methodologies.

²⁷ Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307-1370.

²⁸ (a) Winstein, S.; Sonnenberg, J. *J. Am. Chem. Soc.* **1961**, *83*, 3235-3244. See also: (b) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256-4264.

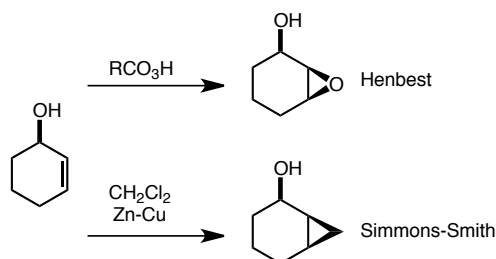
²⁹ (a) Brown, J. M.; Naik, R. G. *J. Chem. Soc., Chem. Commun.* **1982**, 348-350. See also: (b) Brown, J. M.; Cutting, I. *J. Chem. Soc., Chem. Commun.* **1985**, 578-579. (c) Thompson, H. W.; McPherson, E. *J. Am. Chem. Soc.* **1974**, *96*, 6232-6233.

³⁰ (a) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939-5942. For selected examples, see also: (b) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273-276. (c) Turnbull, M. D.; Hatter, G.; Ledgerwood, D. E. *Tetrahedron Lett.* **1984**, *25*, 5449-5452. (d) Hughes, M. J.; Thomas, E. J.; Turnbull, M. D.; Jones, M. D.; Jones, R. H.; Warner, R. E. *J. Chem. Soc., Chem. Commun.* **1985**, 755. (e) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560-3578. (f) Adams, J.; Poupart, M.-A.; Grenier, L. *Tetrahedron Lett.* **1989**, *30*, 1753-1756.

³¹ (a) Barriault, L.; Thomas, J. D. O.; Clément, R. *J. Org. Chem.* **2003**, *68*, 2317-2323. For other examples of directed cycloadditions, see: (b) Krafft, M. E.; *J. Am. Chem. Soc.* **1988**, *110*, 968-970. (c) Krafft, M. E.; Juliano, C. A.; Scott, I. L.; Wright, C.; McEachin, M. D. *J. Am. Chem. Soc.* **1991**, *113*, 1693-1703. (d) Curran, D. P.; Choi, S. M.; Gothe, S. A.; Lin, F. T. *J. Org. Chem.* **1990**, *55*, 3710-3712.

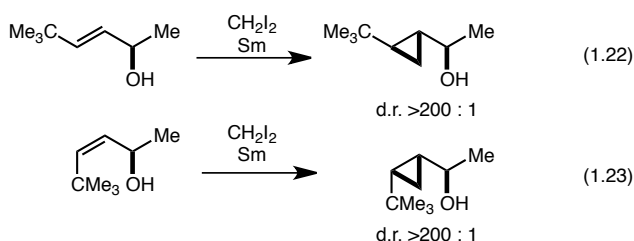
³² (a) Lewis, L. N. *Inorg. Chem.* **1985**, *24*, 4433-4435. See also: (b) Parshall, G. W.; Knoth, W. H.; Schunn, R. A. *J. Am. Chem. Soc.* **1969**, *91*, 4990-4995. (c) Lewis, L. N.; Smith, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 2728-2735. For selected reviews on orthometalations, see: (d) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1-360. (e) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731-1769.

Scheme 1.2 Examples of directed reactions overriding steric effects



Cyclopropanation

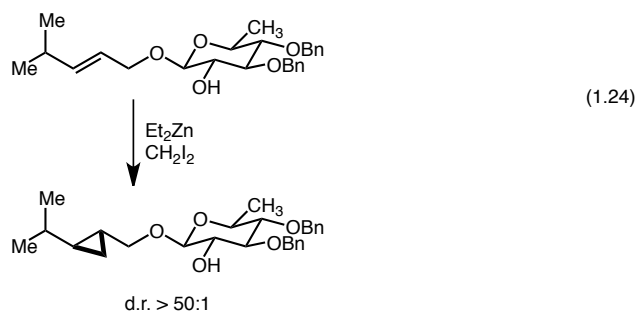
Cyclopropanation is an excellent example of a reaction that has benefited from directing heteroatoms. Several selective directed reactions were reported as well as applications in many natural product syntheses.²⁷ An example of the selectivity achieved is seen with samarium and acyclic allylic alcohols (eq.'s 1.22 and 1.23).³³



Using Simmons-Smith conditions, directed cyclopropanations have also displayed success in carbohydrate synthesis (eq. 1.24).³⁴ Given the ability of a hydroxyl group to direct the attack of the reagent and the abundance of protecting groups to modify the chelation these substrates are excellent candidates for a directed cyclopropanation.

³³ Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1987**, 52, 3944-3946.

³⁴ Charette, A. B.; Cote, B.; Marcoux, J. F. *J. Am. Chem. Soc.* **1991**, 113, 8166-8167.



Epoxidations

Epoxidations have been at the forefront of directed reactions for decades since the 1950's when Henbest discovered that hydroxyl groups, through hydrogen bonding, could direct the peracid oxygen (see Figure 1.4).³⁵ Expanding on this result, several functional groups have been reported to direct epoxidations including amides,³⁶ ureas,³⁷ and silyl ethers³⁸ with great success (eq.'s 1.25, 1.26 and 1.27).

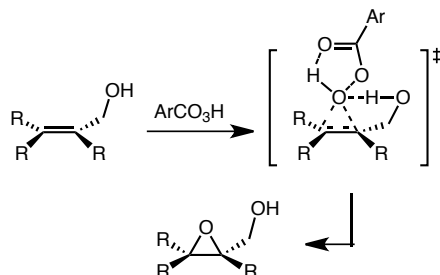


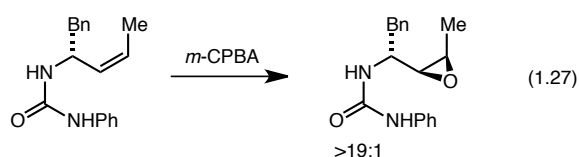
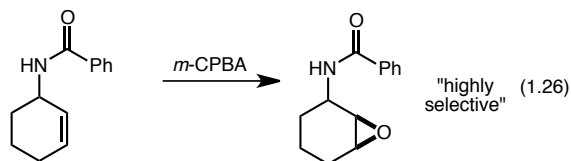
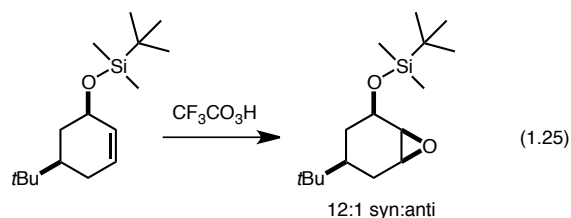
Figure 1.4 Proposed rationale for directed epoxidation

³⁵ Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1957**, 1958-1965.

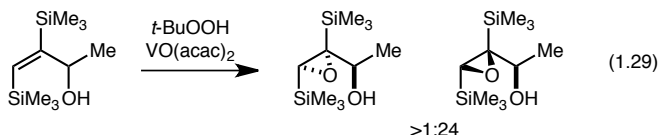
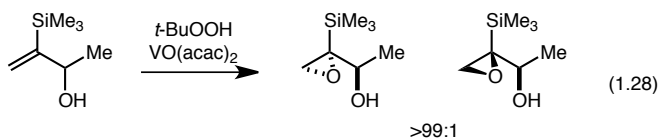
³⁶ (a) Mohamadi, F.; Spees, M. M. *Tetrahedron Lett.* **1989**, 30, 1913-1916. (b) Hasegawa, A.; Sable, H. Z. *J. Org. Chem.* **1966**, 31, 4154-4161. (c) Goodman, L.; Winstein, S.; Boschan, R. *J. Am. Chem. Soc.* **1958**, 80, 4312-4317. (d) Lukacs, G.; Fukushima, D. K. *J. Org. Chem.* **1969**, 34, 2707-2710. (e) Roush, W. R.; Straub, J. A.; Brown, R. J. *J. Org. Chem.* **1987**, 52, 5127-5136. (f) Hauser, F. M.; Ellenberger, S. R.; Glusker, J. P.; Smart, C. J.; Carrell, H. L. *J. Org. Chem.* **1986**, 51, 50-57.

³⁷ Fukushima, D. K.; Smulowitz, M.; Liang, J. S.; Lukacs, G. *J. Org. Chem.* **1969**, 34, 2702-2707.

³⁸ McKittrick, B. A.; Ganem, B. *Tetrahedron Lett.* **1985**, 26, 4895-4898.



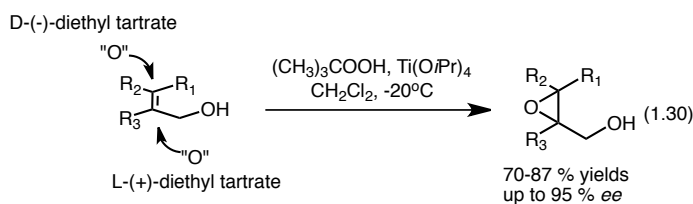
Metals have shown excellent success in catalyzing the epoxidation of alkenes with high selectivity. Sharpless reported that vanadium and molybdenum were both capable of catalyzing the epoxidations of allylic alcohols with excellent syn/anti ratios (eq. 1.28 and 1.29).³⁹ The selectivities of these reactions are dominated by allylic strain. If there is a sizeable amount of A(1,2) strain, as seen in the molecules in equation 1.28, the anti conformation is favoured. However, under conditions where A(1,3) strain is present the syn conformer is the favoured product (eq. 1.29).



One of the most common and effective methods of directed epoxidation was

³⁹ Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136-6137.

published by Sharpless in 1980, and is still used today as one of the most selective and efficient reactions for asymmetric epoxidations.⁴⁰ Using $\text{Ti}(\text{O}i\text{-Pr})_4$ and D(-)/L(+) diethyl tartrate a variety of allylic alcohols were synthesized in high yields (77-92%) and high enantiomeric excesses (eq. 1.30). It has been proposed that the titanium atom can be viewed as playing a tethering role in the proposed transition state, as it interacts with both the allylic alcohol and the peroxide.⁴¹



Hydroformylation with a reversibly bound directing group

To date, development of new directing techniques is key to many new methodologies. As an example, Breit and co-workers recently developed a directed hydroformylation of homoallylic and bishomoallylic alcohols with the use of phosphinites as reversible catalyst-directing groups (see Figure 1.5).⁴² This approach allows a selective hydroformylation of internal alkenes, a method previously unknown. The selectivity was very high for a variety of substrates (up to 99:1) and showcased diastereoselective examples (eq. 1.31). Future efforts will focus on enantioselective examples and applying this method to other catalytic systems. Similar to the Sharpless example, rhodium can be viewed as playing a tethering role in this process.

⁴⁰ Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974-5976.

⁴¹ Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 113-126

⁴² (a) Šmejkal, T.; Breit, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 311-315. (b) Šmejkal, T.; Breit, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 3946-3949. See also: (c) Grünanger, C. U.; Breit, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 7346-7349. (d) Grünanger, C. U.; Breit, B. *Angew. Chem. Int. Ed.* **2010**, *49*, 967-970.

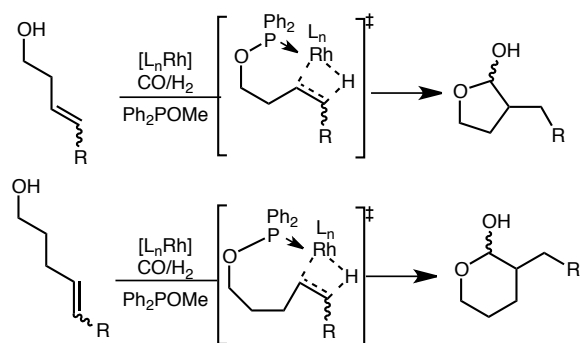
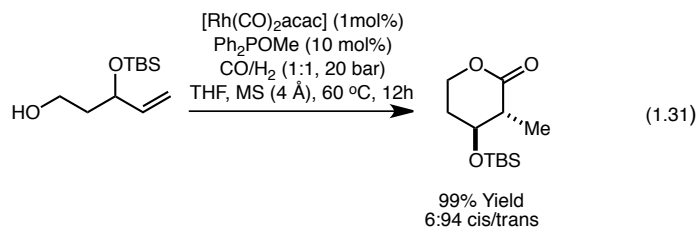


Figure 1.5 Directed control of regioselectivity in the hydroformylation of homo-bis allylic alcohols



Selective activation of diols

A more recent approach in the substrate directing field focuses on the design of synthetic scaffolds that mimic enzyme pockets through key site activation. Tan *et al.* designed scaffolds that can target and/or activate one alcohol from diols or within carbohydrate-based compounds (Figure 1.6).⁴³ Through creating a formal covalent bond with the substrate the less reactive, axial positions within monosaccharides, can be selectively protected. This strategy can be applied to several monosaccharides and natural products.

⁴³ (a) Sun, X.; Worthy, A.D.; Tan, K.L. *Angew. Chem. Int. Ed.* **2011**, *50*, 8167-8171. (b) Worthy, A.D.; Sun, X.; Tan, K.L. *J. Am. Chem. Soc.* **2012**, *134*, 7321-7324. Sun, X.; Lee, H.; Lee S.; Tan, K.L. *Nature Chem.* **2013**, *5*, 790-795.

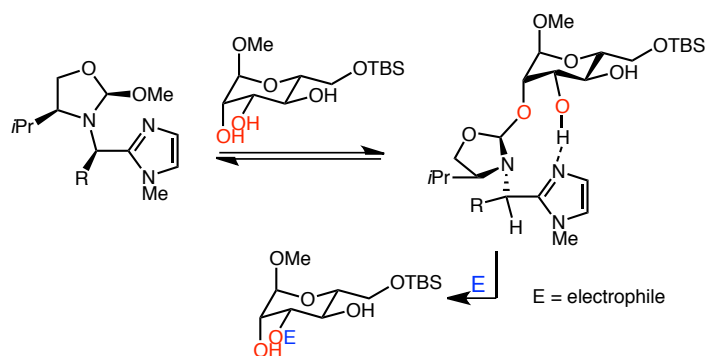


Figure 1.6 Approaches to site-selective functionalization

Metal catalyzed ligand directed C-H functionalization reactions

The direct functionalization of C-H bonds to desired C-X (X = O, N, C, etc.) fragments is an important and difficult transformation in organic chemistry. Previous traditional approaches relied on prefunctionalization of the starting material to achieve this transformation, and therefore resulted in a higher number of chemical steps and/or cost of the procedure. Over the past decade directed C-H activation has flourished, with several metals (Pd, Ru, Rh and Pt) catalyzing this reaction; however, one of the challenges of this strategy is selectively activating one C-H bond in a complex molecule.⁴⁴ An effective method to overcome this conundrum is the use of directing groups on the substrate to bind to the metal centre and selectively deliver the catalyst to a proximal C-H bond.⁴⁵ Several reports of carbon-halogen,⁴⁶ carbon-nitrogen,⁴⁷ and

⁴⁴ (a) Dunina, V. V.; Zalevskaya, O. A.; Potapov, V. M. *Russ. Chem. Rev.* **1988**, *57*, 250-269. (b) Ryabov, A. D. *Chem. Rev.* **1990**, *90*, 403-424. (c) Dyker, G. *Angew. Chem., Int. Ed.* **1999**, *38*, 1698-1712. (d) Dupont, J.; Consorti, C. S.; Spencer, J. *Chem. Rev.* **2005**, *105*, 2527-2571. (e) Cope, A. C.; Siekman, R. W. *J. Am. Chem. Soc.* **1965**, *87*, 3272-3273.

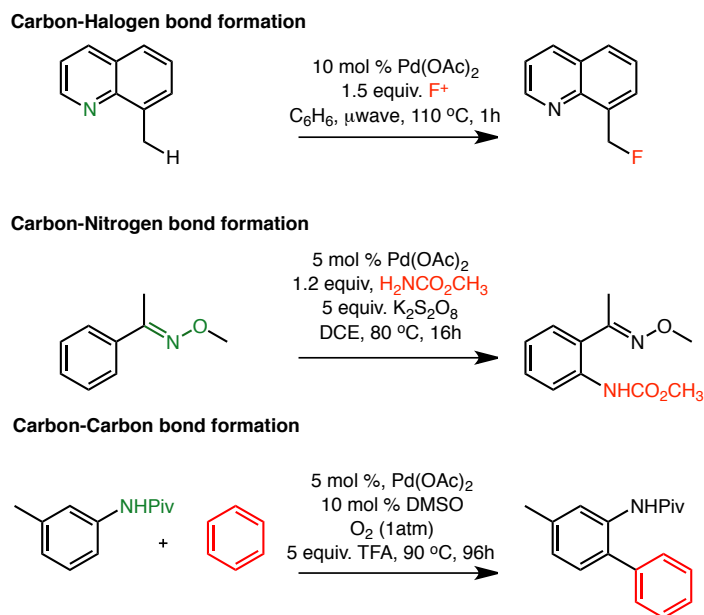
⁴⁵ Recent reviews: (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147-1169. (b) Colby, D. A.; Bergman, R.G.; Ellman, J. A. *Chem. Rev.*, **2010**, *110*, 624-655.

⁴⁶ (a) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134-7135. (b) Wang, X.; Mei, T. S.; Yu, J. Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520-7521.

⁴⁷ Thu, H. Y.; Yu, W. Y.; Che, C. M. *J. Am. Chem. Soc.* **2006**, *128*, 9048-9049.

carbon-carbon,⁴⁸ bond formation have been successful (Scheme 1.3). As this approach is fundamentally different than the previous one where a catalyst is needed to favour the pressociation event, it is still an impressive example of a directed reaction. Challenges that need to be addressed in the future include, effective asymmetric examples, less basic directing groups, and broader substrate scope tolerance.

Scheme 1.3 Examples of directed metal catalyzed C-H activation



As seen above, the role of tethered and directed reactions has been solidified as an excellent approach to regioselective and stereoselective reactions. In the future, the focus will be on more catalytic approaches that do not suffer from the drawbacks of lengthy synthesis and/or stoichiometric conditions. Only in recent examples, such as Kian Tan's approach to selective diol protection, shows the potential of a catalytic and directed

⁴⁸ Brasche, G.; Garcia-Fortanet, J.; Buchwald, S. L. *Org. Lett.* **2008**, *10*, 2207-2210.

reaction.

Part B: Overview of the Hydroamination of Alkenes

1.2 Intermolecular Hydroamination of Alkenes

As will be seen in the next chapters, we have used hydroamination as a key reaction to be used at the centre of a new catalytic tethering strategy. An introduction to hydroamination will serve in establishing the basis of that reaction, to better put in context the achievements described later. This thesis will focus on an organocatalytic tethering approach to the intermolecular Cope-type hydroamination of alkenes. An introduction to this dynamic research area is therefore required to place the results in context.

Nitrogen containing molecules have been used for a variety of significant applications including pharmaceuticals, paints, coatings and agrochemicals. Approximately 90% of all drug candidates in the pharmaceutical industry contain nitrogen atoms.⁴⁹ Therefore, versatile carbon-nitrogen bond forming reactions are in high demand and this insight requires quality research on the reactions that lead to the formation of these bonds. In a study looking at the reactions run on large scale at several pharmaceutical companies between 1985-2002 it was reported that 15% of these reactions involved carbon-nitrogen bond formation (see Figure 1.7).⁴⁹

⁴⁹ (a) Dugger, R. W.; Ragan, J. A.; Brown Ripin, D. H. *Org. Proc. Res. Dev.* **2005**, *9*, 253-258. (b) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337-2347.

Of all the reactions, 15% involved C-N bond formation

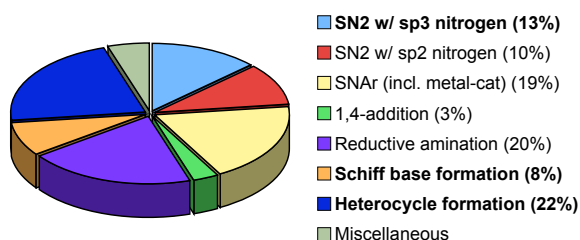


Figure 1.7 Selected data on the reactions utilized on large scale for the formation of a carbon-nitrogen bond

Of these 15%, the common reactions included nucleophilic substitutions, S_NAr and reductive aminations; however, there were no reports of direct amination of a nitrogen atom onto a C-C unsaturation. As a result, there is a significant gap in the literature of accessing these desired carbon-nitrogen bonds from readily commercially available and accessible alkenes and alkynes. Therefore there is potential for hydroamination, the addition of an N-H bond across an alkene or alkyne, to become an extremely useful synthetic tool (Figure 1.8). This reaction has shown promise in the total syntheses of natural products and has the ability to be catalyzed in several different fashions. Amines, enamines, and imines can be formed from different variations of the reaction. Hydroamination can also be expanded into asymmetric processes; however, this is still underdeveloped and faces crucial limitations.⁵⁰ Among those, intermolecular hydroamination suffers from a negative entropy of the reaction and high activation energy. A simple efficient and selective method for this reaction is still unknown.

⁵⁰ For a recent comprehensive review, see: Müller, T.; Hultzs, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795-3892.

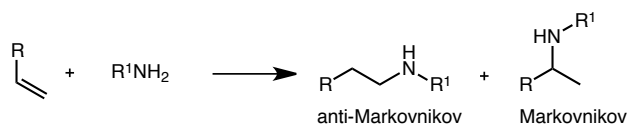


Figure 1.8 Intermolecular hydroamination of alkenes

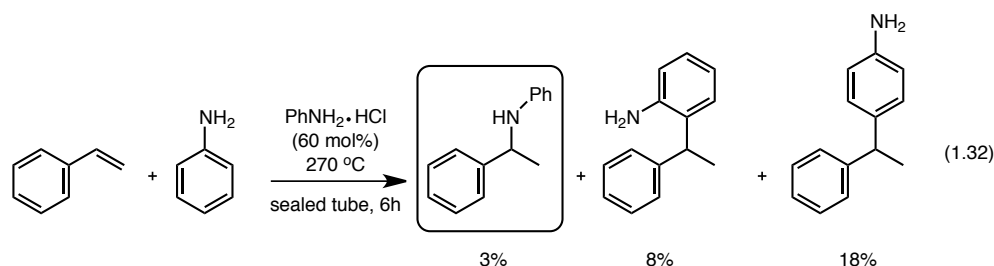
1.2.1 Overview of Hydroamination

Acid catalyzed hydroamination

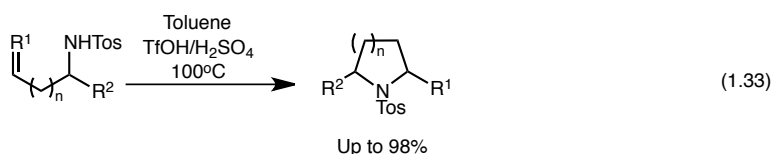
Hydroamination was first reported by Hickinbottom in 1932, when he published his results of acid catalyzed additions of arylamines to alkenes.⁵¹ The approach allowed the formation of a carbocation via protonation of the alkene, followed by addition of the nucleophile, similar to the Ritter reaction.⁵² The Ritter reaction proceeds with an electrophilic addition of a less basic nitrogen nucleophile such as a nitrile. Unfortunately, the results indicated that the reactions required harsh conditions such as high temperatures and long reaction times, and resulted in very low yields of the desired product (eq. 1.32). The key issue with this approach was the amine basicity and its inability to buffer the acidity required for protonation of the alkene. Furthermore, as the nitrogen is protonated under acidic conditions, the nucleophilicity of the atom is removed.

⁵¹ (a) Hickinbottom, W. J. *J. Chem. Soc.* **1932**, 2646-2654. (b) Hickinbottom, W. J. *J. Chem. Soc.* **1934**, 319-323. (c) Hickinbottom, W. J. *J. Chem. Soc.* **1934**, 1981-1984.

⁵² (a) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, 70, 4045-4048. For a review of the Ritter reaction, see: (b) Krimen, L. I.; Cota, D. J. *Org. React.* **1969**, 17, 213-325.



In 2002 Hartwig and co-workers revisited the use of acid to activate intramolecular hydroamination.⁵³ The cyclization of aminoalkenes bearing a protecting group was catalyzed by triflic or sulfuric acid and led to the synthesis of pyrrolidines and piperidines in high yields (up to 98%) (eq. 1.33). Hartwig postulated that the mechanism was more complex than a simple protonation of the alkene by strong acid. As tosylamides were the most effective protecting group Hartwig proposed that the triflic acid was consumed by the protonation of the sulfonamide and this would initiate cyclization by an intramolecular proton transfer. Due to the nature of the mechanism the scope was quite limited and at the time only efficient in intramolecular systems.

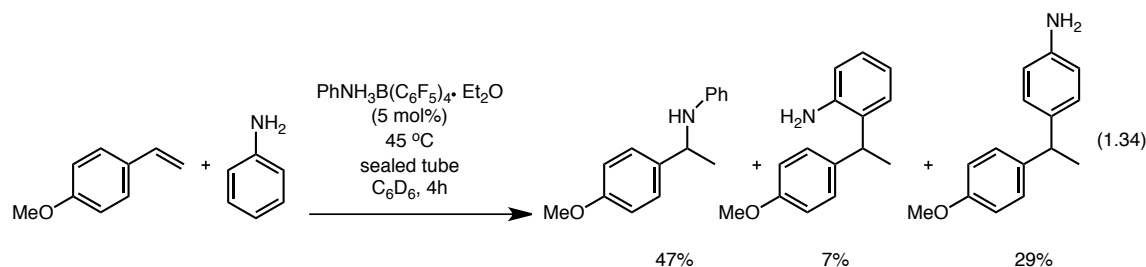


More than 70 years since the first acid catalyzed hydroamination, Anderson, Arnold and Bergman overcame the initial boundaries on acid catalysis by using $\text{PhNH}_3\text{B}(\text{C}_6\text{F}_5)_4 \cdot \text{Et}_2\text{O}$.⁵⁴ Impressive results were shown both with norborene and variations of styrene (eq. 1.34) The majority of the reactions were completed at moderate

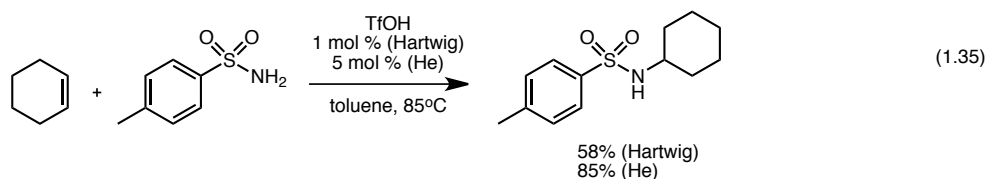
⁵³ Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, 4, 1471-1474.

⁵⁴ (a) Anderson, L. L.; Arnold, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, 127, 14542-14543. (b) Lapis, A. A. M.; DaSilveira Neto, B. A.; Scholten, J. D.; Nachtigall, F. M.; Eberlinb, M. N.; Duponta, J. *Tetrahedron Lett.* **2006**, 47, 6775-6779.

temperatures, within a 24-hour timeline with good to moderate yields, due to a competing hydroarylation process.



The following year both Hartwig and He explored the addition of a protected N-H bond to olefins via triflic acid catalysis.⁵⁵ This advancement led to high yields at moderate temperature; however, there was still a limited substrate scope (eq. 1.35). Their research shed light on whether metal catalyzed triflates truly acted as catalyst precursors or simply generated a protic acid *in situ*.



An abundance of Lewis acids (BiCl_3 , AlCl_3 , FeCl_3 and SnCl_4) have proven effective in catalyzing the hydroamination of alkenes.⁵⁶ It is believed they are operating by a reaction with aniline derivatives to form a strong Bronsted acid. TiCl_4 ,⁵⁷ Au(I) ,⁵⁸

⁵⁵ (a) Li, Z.; Zhang, J.; Brouwer, C.; Yang, C.-G.; Reich, N. W.; He, C. *Org. Lett.* **2006**, 8, 4175-4178. (b) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J. F. *Org. Lett.* **2006**, 8, 4179-4182.

⁵⁶ Wei, H.; Qian, G.; Xia, Y.; Li, K.; Li, Y.; Li, W. *Eur. J. Org. Chem.* **2007**, 4471-4474.

⁵⁷ (a) Ackermann, L.; Kaspar, L. T.; Gschrei, C. J. *Org. Lett.* **2004**, 6, 2515-2518. (b) Kaspar, L. T.; Fingerhut, B.; Ackermann, L. *Angew. Chem., Int. Ed.* **2005**, 44, 5972-5974.

⁵⁸ Zhang, J.; Yang, C. G.; He, C. *J. Am. Chem. Soc.* **2006**, 128, 1798-1799.

Bi(OTf)₃,⁵⁹ and Pt(II)⁶⁰ triflates are also believed to operate in the same fashion through metal-generated acid catalysis (see Figure 1.9). This was supported by mechanistic data published by Tilley and coworkers in their design of a platinum catalyzed intermolecular hydroamination of alkenes.

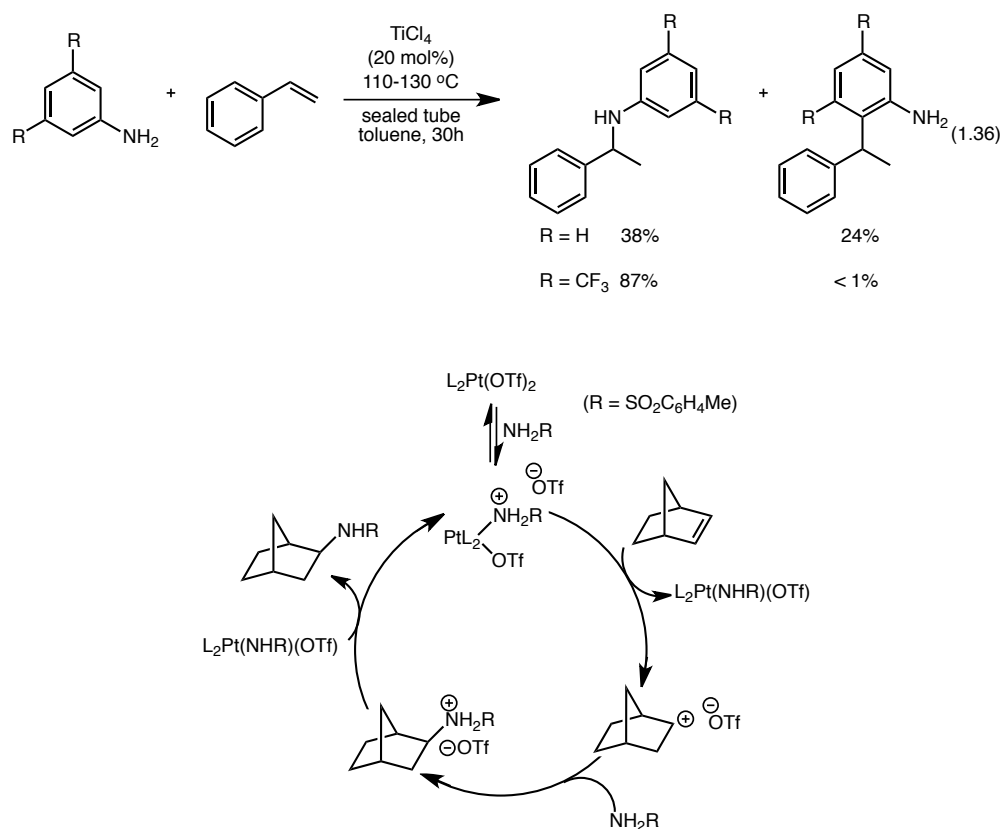


Figure 1.9 Mechanism of Pt(OTf)₂ catalyzed intermolecular hydroamination of alkenes

The main drawback with these approaches is the competitive side reaction of hydroarylation. The side reaction is minimized with the use of electron withdrawing

⁵⁹ (a) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 1611-1614. (b) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Chem. Asian J.* **2007**, *2*, 150-154.

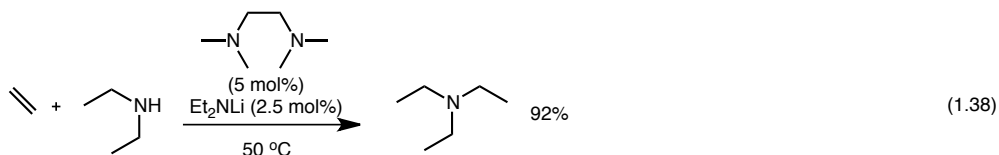
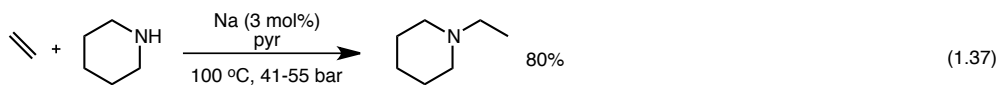
⁶⁰ Karshedt, D.; Bell, A. T.; Tilley, T. D. *J. Am. Chem. Soc.* **2005**, *127*, 12640-12646.

groups on the aniline moiety but presents a limitation to this chemistry (eq. 1.36).

Overall, the main drawbacks to acid catalyzed hydroamination are the limited substrate scope and harsh conditions required. The constant struggle of protonating the amine under these acidic conditions, led to chemists seeking other activation modes.

Base catalyzed hydroamination

In contrast with acid catalysis of hydroamination, base catalyzed hydroamination has the advantage of deprotonating the amine and significantly increasing the nucleophilicity of the nitrogen atom.⁶¹ However, under base catalysis, all functional groups must be less acidic than the amine and the reaction is limited to electron-poor alkenes. Furthermore the conditions are harsh, as they require high temperature and high pressure to be effective (eq. 1.37 and 1.38). It is known that bidentate chelating ligands can improve reactivity and lower the temperature needed for the reaction to proceed.⁶²



⁶¹ For selected examples of intermolecular strong base-catalyzed hydroamination, see: (a) Horrillo-Martinez, P.; Hultsch, K. C.; Gil, A.; Branchadell, V. *Eur. J. Org. Chem.* **2007**, 3311-3325. (b) Pez, G. P.; Galle, J. E. *Pure Appl. Chem.* **1985**, 57, 1917-1926. (c) Lehmkuhl, H.; Reinehr, D. *J. Organomet. Chem.* **1973**, 55, 215-220. (d) Takabe, K.; Katagiri, T.; Tanaka, J. *Bull. Chem. Soc. Jpn.* **1973**, 46, 222-225. (e) Closson, R. D.; Napolitano, J. P.; Ecke, G. G.; Kolka, A. *J. Org. Chem.* **1957**, 22, 646-649.

⁶² Khedkar, V.; Tillack, A.; Benisch, C.; Melder, J. P.; Beller, M. *J. Mol. Catal. A: Chem.* **2005**, 241, 175.

Transition metal-catalyzed hydroamination

Due to previously mentioned restrictions a tremendous amount of research has been focused on metal-catalyzed hydroaminations. The use of metals allows for alkene/alkyne and amine activation, and the opportunity for an asymmetric reaction. Metals that have been applied towards hydroamination predominantly fall under three categories: rare-earth, group 3 and 4, and late stage transition metals. The rare-earth metals, organolanthanides and actinides, have become efficient and selective in catalyzing inter- and intramolecular hydroamination of specific alkenes.⁶³ The metals operate by facilitating the insertion of the Ln-N bond into unsaturated carbon bonds, followed by protonation from the amine. These catalysts have been known to have very high turnover frequencies and the ability to induce asymmetry using enantiopure ligands. The use of vinylarenes notably allows excellent anti-Markovnikov regioselectivity, which is attributed to the interaction between the arene π -system and the electrophilic lanthanide centre. The main drawback of lanthanide catalysis is the limited substrate scope of the alkene, as it is not effective with linear alkenes, and the catalysts are often moisture/air sensitive catalysts.⁶⁴

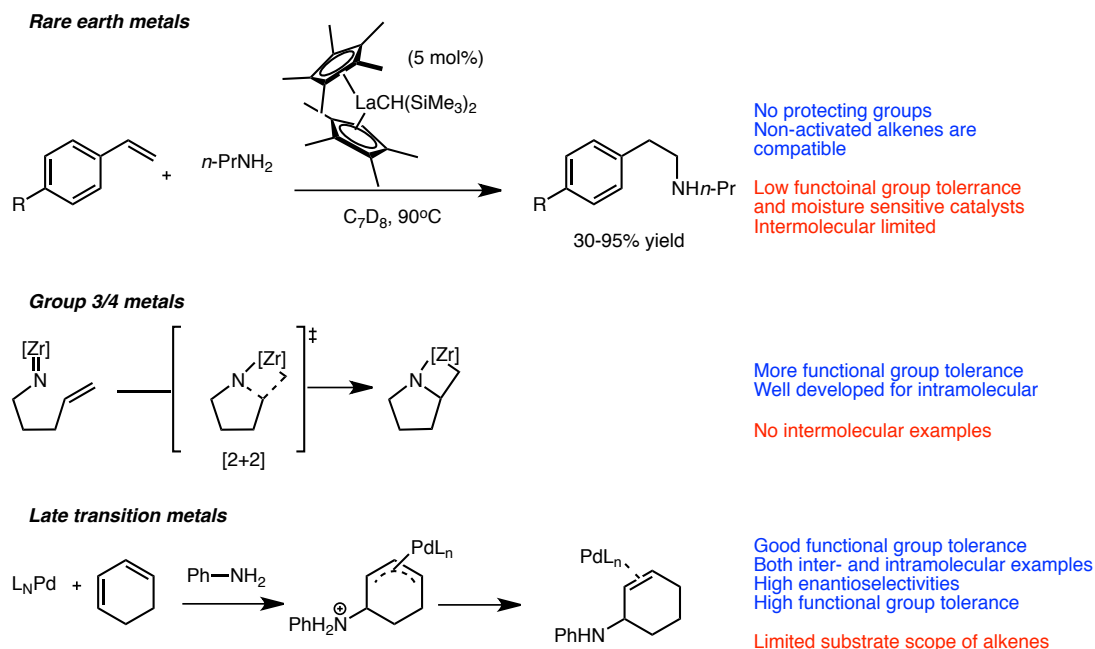
Group 3 and 4 metals (i.e. titanium and zirconium) operate via the formation of different metal complexes including metal imido complexes that can participate in [2+2] cycloadditions with carbon unsaturations to give hydroaminated products.⁶⁵

⁶³ For a review of lanthanide-catalyzed hydroamination, see: Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673-686.

⁶⁴ Ryu, J. S.; Li, G. Y.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 12584-12605.

⁶⁵ Hultsch, K. C. *Org. Biomol. Chem.*, **2005**, *3*, 1819-1824.

Scheme 1.4 Summary of approach's to metal catalyzed hydroamination



Perhaps the most successful in achieving high yields and substrate scope compatibility is the approach of late stage transition metal catalysis in the hydroamination of alkenes. The ability to form metal-stabilized π -allyl or π -benzyl complexes allows activation of the alkene, followed by attack of the amine moiety.⁶⁶ Scheme 1.4 summarizes the types of metal catalysis on the hydroamination of alkenes. This summary shows the advancements of hydroamination while highlighting that intermolecular examples are still rare. The strategies that target intermolecular hydroamination constantly face a negative entropy penalty and as such display a limited substrate scope

⁶⁶ Pd: (a) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546-9547. (b) Lober, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366-4367. (c) Nettekoven, U.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 1166-1167. (d) Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14286-14287. (e) Johns, A. M.; Utsunomiya, M.; Incarrito, C. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 1828-1839. (f) Sakai, N.; Ridder, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 8134-8135. Ni: (g) Pawlas, J.; Nakao, Y.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 3669-3679.

for both the amine and alkene.

Thermodynamic concerns

Several groups prior to 2006 had stated that hydroamination was favoured thermodynamically, however no quantitative data (equilibrium constants, etc.) had been measured. Finally, Hartwig and co-workers published direct measurements of the addition of aniline derivatives on to vinylarenes to provide clear evidence to support previous claims about the thermodynamics of this system. They discovered that the addition of *N*-methylaniline to styrene confirmed that the reaction was exothermic but almost ergoneutral due to the negative entropy associated with this intermolecular addition reaction.⁶⁷ Through the measurement of several equilibrium constants of the addition of aniline derivatives on various alkenes they discovered that the sterics of the amine had a much a greater effect on the equilibrium constant than electronic factors (Figure 1.10).

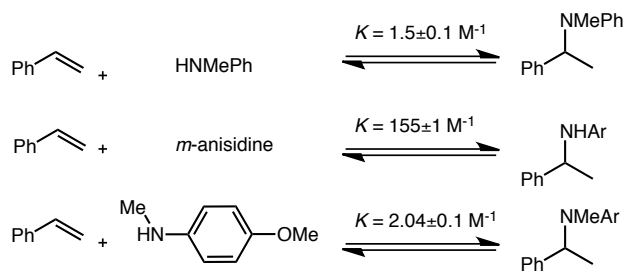


Figure 1.10 Thermodynamics of hydroamination

This is observed as *N*-methylaniline has an equilibrium constant of $K = 1.5 \pm 0.1 \text{ M}^{-1}$ and a

⁶⁷ Johns, A. M.; Sakai, N.; Ridder, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 9306-9307.

less sterically hindered amine, *m*-anisidine, has a much higher value at $K = 155 \pm 1 \text{ M}^{-1}$. Furthermore, substitution of the alkene had a significant impact on the free energy of the reaction as seen in the example of the addition of *m*-anisidine to 1,2-dihydronaphthalene ($1.31 \pm 0.18 \text{ kcal/mol}$) as compared to the more favourable styrene ($-3.54 \pm 0.01 \text{ kcal/mol}$). The results clearly demonstrate the difficulties in designing hydroamination methodologies that are efficient and selective. Minor changes to the alkene or amine moiety have substantial effects on the thermodynamics of the reaction.

Consequently, tethering is an area that has shown promise in targeting difficult intermolecular reactions and has not been applied to hydroamination. Given the challenges mentioned above this approach has an opportunity to make an impact on this field.

Conclusion

There is a great need, as exemplified in the first section, for a tethering strategy that would not be classical (stoichiometric or stepwise), and that could potentially be part of a catalysis event. As will be exemplified in the next chapters, the use of hydroamination will become the starting point, through a tethered process, to the development of an innovative, organocatalytic tethering strategy. The ability to temporarily bring together an alkene and amine moiety would have a significant impact on accelerating a formal intermolecular reaction. Additionally, it would provide a handle on achieving highly stereoselective transformations.

The reaction discussed in this thesis is the intermolecular hydroamination of

alkenes that is mechanistically related to the Cope elimination. This reaction is commonly referred to as Cope-type hydroamination, which takes advantage of a bifunctional reagent to achieve a very similar transformation as mentioned above; this reaction will be discussed in Chapter 2.

A Catalytic Tethering Strategy: Simple Aldehydes Catalyze Intermolecular Alkene Hydroaminations

2.1 Introduction

This chapter will focus on the design of a catalytic tethering strategy via aldehyde catalysis. The challenges and limitations of the hydroamination of alkenes will be discussed, to be followed by the discovery and development of aldehyde-catalyzed Cope-type hydroamination along with a substrate scope of the system. The application to an enantioselective process will be presented. This includes the discovery of a chiral aldehyde capable of inducing asymmetry solely via preassociation (temporary intramolecularity) and an optimization of that catalyst. An early investigation into substrate scope will also be explored.

2.1.1 Tethering Strategies

In the last two decades the use of directed, tethered or templated reactions to perform difficult intermolecular reactions have emerged as general strategies in organic synthesis.⁶⁸ Such strategies are desirable, as the use of temporary tethers allow for an increase in reactivity by lowering the entropic term ($\Delta S^\ddagger$) in Gibbs free energy of

⁶⁸ (a) For a review on substrate-directable chemical reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, 93, 1307–1370. (b) For a recent review on removable or catalytic directing groups, see: Rousseau, G.; Breit, B. *Angew. Chem., Int. Ed.* **2011**, 50, 2450–2494.

activation ($\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$), in many difficult intermolecular reactions.⁶⁹ This approach closely resembles the way nature approaches challenging bimolecular reactivity through the use of enzymes. In many respects, the synthetic catalysts developed so far have attempted to emulate the remarkable efficiency of enzymes in catalyzing intermolecular reactions (with rate accelerations as high as 10^{17}).⁷⁰

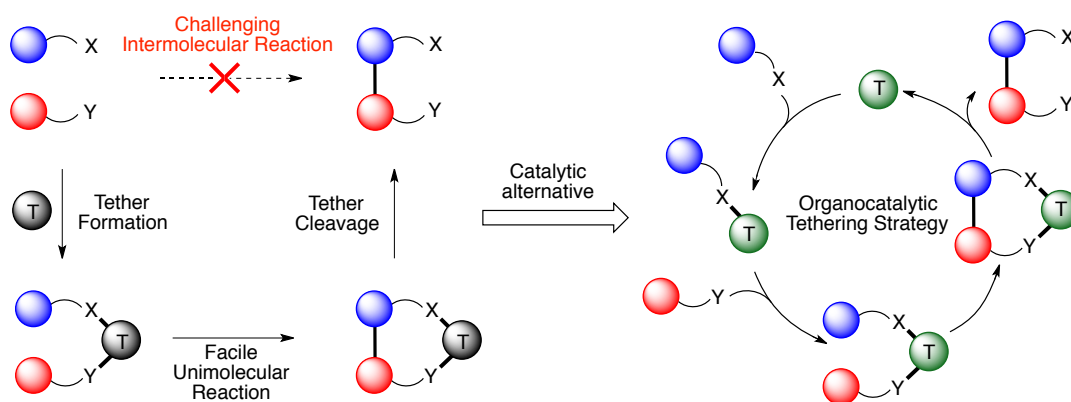


Figure 2.1 Targeted stepwise approach to tethering for challenging intermolecular reactions and catalytic alternative

Enzymes are able to pre-organize substrates through covalent and non-covalent interactions therefore resulting in a preassociation domain that reduces the entropic barrier of the reaction. It is generally accepted that rate accelerations of 10^4 - 10^8 for 1M

⁶⁹ For selected examples in which the catalytic systems operate via preassociation and substrate activation, see: (a) Sammakia, T.; Hurley, T. B. *J. Am. Chem. Soc.* **1996**, *118*, 8967-8968. (b) Sammakia, T.; Hurley, T. B. *J. Org. Chem.* **1999**, *64*, 5652-5653. (c) Sammakia, T.; Hurley, T. B. *J. Org. Chem.* **2000**, *65*, 974-978. (d) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, *42*, 112-114. (e) Lightburn, T. E.; Dombrowski, M. T.; Tan, K. L. *J. Am. Chem. Soc.* **2008**, *130*, 9210-9211. (f) Grünanger, C. U.; Breit, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 7346-7349. (g) Fuchs, D.; Rousseau, G.; Diab, L.; Gellrich, U.; Breit, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 2178-2182. (h) Worthy, A. D.; Joe, C. L.; Lightburn, T. E.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 14757-14759. (i) Sun, X.; Worthy, A. D.; Tan, K. L. *Angew. Chem., Int. Ed.* **2011**, *50*, 8167-8171. (j) Murphy, S. K.; Coulter, M. M.; Dong, V. *Chem. Sci.* **2012**, *3*, 355-358. (k) Worthy, A. D.; Sun, X.; Tan, K. L. *J. Am. Chem. Soc.* **2012**, *134*, 7321-7324. For a review, see: (l) Tan, K. L.; Sun, X.; Worthy, A. D. *Synlett* **2012**, *23*, 321-325.

⁷⁰ Radzicka, A.; Wolfenden, R. *Science* **1995**, *267*, 90-93.

reactants at room temperature can be achieved via temporary intramolecularity.⁷¹ Therefore it is no surprise that synthetic chemists have tried to mimic the remarkable efficiency achieved by enzymes.

As the field of temporary tethers has shown significant promise over the past decades there are still critical limitations in the literature. The majority of tethered reactions suffer from the drawbacks of auxiliary-type approaches: additional steps are required for the formation and cleavage of the "temporary" tether (Figure 2.1).⁷² Catalytic variants are extremely rare and therefore many systems contain lengthy syntheses as well as wasteful by-products. Catalytic methods are needed that would allow the formation of a tether, the key desired reaction and the cleavage of the tether in one-pot. Furthermore, the ability to induce asymmetry via a catalytic tethering strategy has not been demonstrated. The Beauchemin group has shown interest in *a new strategy in aldehyde catalysis* that would be able to reversibly form a tether between two reagents and induce temporary intramolecularity, which led us to speculate that several reactions could benefit not only in reactivity but stereoselectivity from this approach.

2.1.2 Cope-type Hydroamination

The Cope elimination was first discovered by Cope and co-workers in 1949 when they showed that heating trialkylamine-*N*-oxides possessing a β -hydrogen once heated,

⁷¹ Jencks, W. P. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1975**, *43*, 219-410.

⁷² (a) Diederich, F.; Stang, P. J. *Templated Organic Synthesis*; Wiley- VCH: Chichester, U.K., **2000**. (b) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253-1277. (c) Fensterbank, L.; Malacria, M.; Sieburt, S. *Synthesis* **1997**, 813-854. (d) Gauthier, D. R., Jr.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289-2338.

led to the formation of an olefin and a *N,N*-dialkylhydroxylamine (see Figure 2.2).⁷³ This thermally induced *syn* elimination is well documented and has led to many fascinating publications in the literature.^{73, 74}

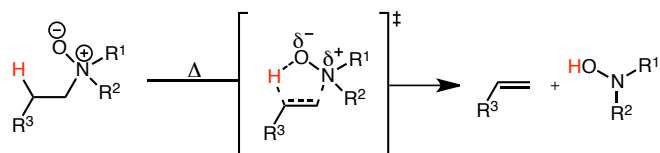


Figure 2.2 Cope elimination of trialkylamine-*N*-oxides

It was reported by House in 1976 that the microscopic reverse of the Cope elimination in a cyclic system could yield cyclic hydroxylamines.⁷⁵ It was a mild reaction that could occur at room temperature and was called the “reverse Cope cyclization” (eq. 2.1). The debate for the proposed mechanism continued for almost 20 years with hypotheses ranging from a radical process to a concerted mechanism.⁷⁶ Eventually, a series of experiments reported in 1994 by Oppolzer showed the reaction proceeds through a stereospecific and suprafacial five-membered transition state (eq. 2.2 and 2.3).⁷⁷ This

⁷³ (a) Cope, A. C.; Foster, T. T.; Towle, P. H. *J. Am. Chem. Soc.* **1949**, *71*, 3929. (b) Cope, A. C.; Pike, R. A.; Spencer, C. *J. Am. Chem. Soc.* **1953**, *75*, 3212. (c) Cope, A. C.; McLean, D. C.; Nelson, N. A. *J. Am. Chem. Soc.* **1955**, *77*, 1628. (d) Cope, A. C.; Bumgardner, C. L. *J. Am. Chem. Soc.* **1957**, *79*, 960. (e) Cope, A. C.; Bumgardner, C. L.; Schweizer, E. E. *J. Am. Chem. Soc.* **1957**, *79*, 4729. (f) Cope, A. C.; Acton, E. M. *J. Am. Chem. Soc.* **1958**, *80*, 355. (g) Cope, A. C.; Ciganek, E.; Howell, C. F.; Schweizer, E. E. **1960**, *82*, 4663. (h) Cope, A. C.; LeBel, N. A. *J. Am. Chem. Soc.* **1960**, *82*, 4656. Reviews: (a) Beauchemin, A. M. *Org. Biomol. Chem.* **2013**, *11*, 7039-7050. (b) Cooper, N. J.; Knight, D. W. *Tetrahedron* **2004**, *60*, 243–269.

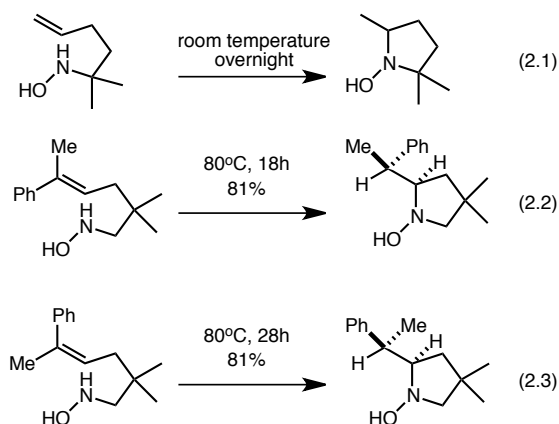
⁷⁴ Cram, D. J.; McCarty, J. E. *J. Am. Chem. Soc.* **1954**, *76*, 5740-5745.

⁷⁵ (a) House, H. O.; Manning, D. T.; Melillo, D. G.; Lee, L. F.; Haynes, O. R.; Wilkes, B. E. *J. Org. Chem.* **1976**, *41*, 855-863. (b) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863-869.

⁷⁶ (a) Black, D. St. C.; Doyle, J. E.; *Aust. J. Chem.* **1978**, *31*, 2317. (b) Ciganek, E. *J. Org. Chem.* **1990**, *55*, 3007-3009. (c) Ciganek, E.; Read, J. M. Jr.; Calabrese, J. C. *J. Org. Chem.* **1995**, *60*, 5795-5802. (d) Ciganek, E. *J. Org. Chem.* **1995**, *60*, 5803-5807.

⁷⁷ (a) Oppolzer, W.; Spivey, A. C.; Bochet, C. G. *J. Am. Chem. Soc.* **1994**, *116*, 3139-3140. See also: (b) Oppolzer, W. *Gazz. Chim. Ital.* **1995**, *125*, 207-213.

finding reinvigorated the field of reverse Cope cyclizations with many publications expanding this methodology with alkynes⁷⁸ and for the synthesis of various saturated heterocycles.⁷⁹



2.1.3 Intramolecular/ Intermolecular Cope-type Hydroamination

As the reverse Cope cyclization experienced an expansion in the literature many key findings were discovered about the reactivity of this cyclization. These results are summarized in Figure 2.3. Due to the transition state being bicyclic 5-membered ring formation is favoured and as the ring size increases, as does the difficulty of the reaction.

⁷⁸ (a) Pradhan, S. K.; Akamanchi, K. G.; Divakaran, P. P.; Pradhan, P. M. *Heterocycles* **1989**, 28, 813-816. (b) Holmes, A. B.; Smith, A. L.; Williams, S. F.; Hughes, L. R.; Lidert, Z.; Swithenbank, C. *J. Org. Chem.* **1991**, 56, 1393-1405. (c) Fox, M. E.; Holmes, A. B.; Forbes, I. T.; Thompson, M. *Tetrahedron Lett.* **1992**, 33, 7421-7424. (d) Fox, M. E.; Holmes, A. B.; Forbes, I. T.; Thompson, M.; Ziller, J. W. *Tetrahedron Lett.* **1992**, 33, 7425-7428. (e) Fox, M. E.; Holmes, A. B.; Forbes, I. T.; Thompson, M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3379-3995. (f) Davison, E. C.; Holmes, A. B.; Forbes, I. T. *Tetrahedron Lett.* **1995**, 36, 9047-9050. (g) Williams, G. M.; Roughley, S. D.; Davies, J. E.; Holmes, A. B.; Adams, J. P. *J. Am. Chem. Soc.* **1999**, 121, 4900-4901. (h) Smith, C. J.; Holmes, A. B.; Press, N. J. *Chem. Commun.* **2002**, 1214-1215.

⁷⁹ (a) Bagley, M. C.; Tovey, J. *Tetrahedron Lett.* **2001**, 42, 351-353. (b) Knight, D. W.; Leese, M. P.; De Kimpe, N. *Tetrahedron Lett.* **2001**, 42, 2597-2600. (c) Knight, D. W.; Leese, M. P. *Tetrahedron Lett.* **2001**, 42, 2593-2597. (d) Yamada, F.; Hasewaga, T.; Wakita, M.; Sugiyama, M.; Somei, M. *Heterocycles* **1986**, 24, 1223-1226. (e) Takano, I.; Yasuda, I.; Nishijima, M.; Hitotsuyanagi, Y.; Takeya, K.; Itokawa, H. *J. Org. Chem.* **1997**, 62, 8251-8254. (f) Coogan, M. P.; Knight, D. W. *Tetrahedron Lett.* **1996**, 37, 6417-6420.

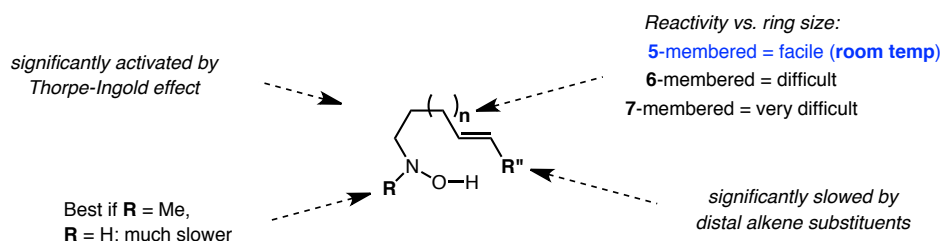


Figure 2.3 Reactivity trends of the reverse Cope-cyclization

The majority of intramolecular cases are activated by the Thorpe-Ingold effect for a faster cyclization. Substitution on the alkene creates a stabilizing affect by donating electron density to the partial positive charge forming in the asynchronous concerted transition state, which results in a slower cyclization.

In direct contrast the challenging intermolecular variant of this reaction, which we refer to as the Cope-type hydroamination,⁸⁰ remained underdeveloped. Reports of intermolecular Cope-type hydroaminations with unbiased alkenes are very rare and enantioselective variants even more scarce.⁸¹ Therefore, in 2008 our research group set out to tackle this problem specifically focussing on the intermolecular Cope-type hydroamination of alkenes and alkynes. Through the discovery that a protic solvent can help mediate a crucial proton transfer step several unsaturated substrates were successfully reacted with aqueous and substituted hydroxylamines (see Figure 2.4).⁸²

⁸⁰ Alternatively, the reaction has been named the reverse-Cope elimination, the reverse-Cope cyclization, or more simply the Cope cyclization. We are strong advocates of the name Cope-type hydroamination for it describes the process and reaction happening, while keeping its mechanistic origin intact, and is applicable to intermolecular processes as well.

⁸¹ For a recent review: Müller, Beller, Yus, Foubelo, Tada *Chem. Rev.* **2008**, *108*, 3795-3892 (and reviews cited therein). Hannedouche, J.; Schulz, E. *Chem. Eur. J.* **2013**, *19*, 4972 – 4985.

⁸² (a) Beauchemin, A. M.; Moran, J.; Lebrun, M. E.; Séguin, C.; Dimitrijevic, E.; Zhang, L.; Gorelsky, S. I. *Angew. Chem., Int. Ed.* **2008**, *47*, 1410-1413. (b) Moran, J.; Gorelsky, S. I.; Dimitrijevic, E.; Lebrun, M. E.; Bédard, A. C.; Seguin, C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2008**, *130*, 17893-17906. (c) Bourgeois,

This achievement allowed access to a variety of amines through an easily cleaved N-O bond.

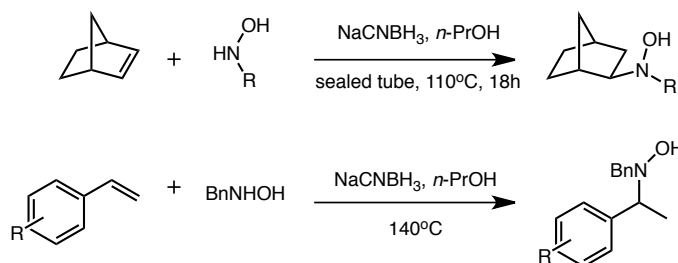


Figure 2.4 Key reactivity of the intermolecular Cope-type hydroamination with alkenes

The limitations of the reaction at this time were the use of biased alkenes and harsh conditions for example: high temperatures and the use of sealed tubes in a microwave. Looking ahead, we wanted to develop a methodology that allowed Cope-type hydroamination under milder conditions and displayed a broader substrate scope.

2.1.4 Aldehyde Catalysis

Aldehydes offer many advantages as temporary tethering catalysts, especially their ability to form aminals and acetals reversibly under mild conditions. However, even with this propensity the capacity to favour preassociation between two *different* substrates as opposed to homodimers can be problematic. Additionally, creating a system that favours catalyst turnover and has a built in driving force to regenerate the aldehyde is also difficult (see Figure 2.5 for example). With all these challenges in mind we sought to

J.; Dion, I.; Cebrowski, P. H.; Loiseau, F.; Bédard, A. C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 874-875.

develop an organocatalytic tethering strategy targeting the difficult reaction of the intermolecular hydroamination of unactivated alkenes.

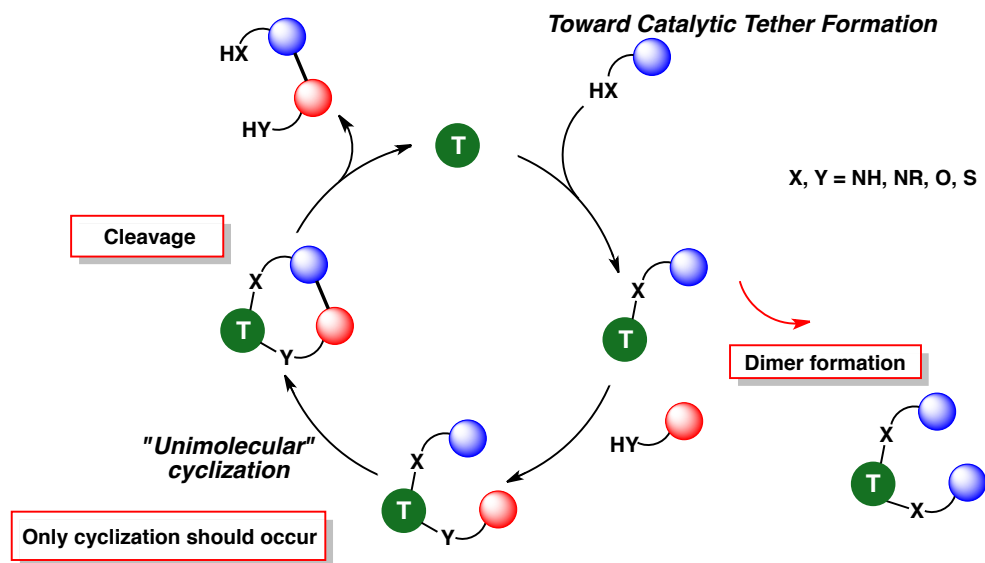


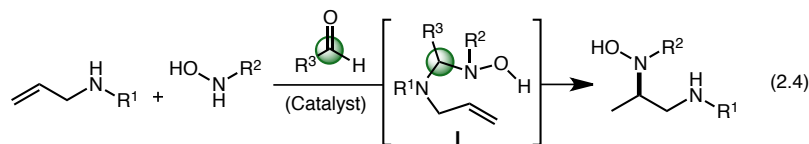
Figure 2.5 General concept of an organocatalytic tethering strategy

The intermolecular hydroamination of alkenes has long been a challenge in the literature with many successful approaches requiring harsh conditions, biased substrates and expensive transition metal catalysts. It has a near thermoneutral profile,⁸³ high activation energy, negative reaction entropy and no simple solution exists to this methodology. Enantioselective variants are even more rare and severely underdeveloped with respect to unbiased alkenes.⁸⁴ To our surprise directed reactions to overcome these

⁸³ Johns, A. M.; Sakai, N.; Ridder, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 9306-9307.

⁸⁴ For examples of enantioselective intermolecular hydroaminations in biased systems, see: (a) Dorta, R.; Egli, P.; Zurcher, F.; Togni, A. *J. Am. Chem. Soc.* **1997**, *119*, 10857-10858. (b) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546-9547. (c) Lober, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366-4367. (d) Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14286-14287. (e) Li, K.; Horton, P. N.; Hursthouse, M. B.; Hii, K. K. *J. Organomet. Chem.* **2003**, *665*, 250-257. (f) Hu, A.; Ogasawara, M.; Sakamoto, T.; Okada, A.; Nakajima, K.; Takahashi, T.; Lin, W. *Adv. Synth. Catal.* **2006**, *348*, 2051-2056. (g) Zhou, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 12220-12221.

challenges have not been reported. However this method is very desirable as the hydroamination of alkenes is conceptually simple and potentially highly efficient way to synthesize carbon nitrogen bonds. The reaction is 100% atom economical and starts from highly diverse and inexpensive starting materials. This is in stark contrast to the intramolecular variant, especially in five-membered ring systems, where the reaction can occur at room temperature. Therefore this reaction proved to be well suitable for the first application of an organocatalytic tethering strategy. We proposed that by temporarily bringing together (via aldehyde catalysis) a hydroxylamine and allylamine we could take advantage of the room temperature reactivity seen in intramolecular Cope-type hydroaminations via aldehyde catalysis (eq. 2.4). The use of aldehydes, to form a one-carbon tether, would allow the most facile favoured 5-membered hydroamination event.



We were confident about the specific reactivity shown due to the inspirational work by Knight on the stoichiometric reaction of nitrones and allylamines.⁸⁵ In his system, Knight used nitrones as reagents and they became incorporated into the product through an amination/formation/hydroamination/ring-opening/ring-closing sequence (see Figure 2.6).

⁸⁵ (a) Gravestock, M. B.; Knight, D. W.; Thornton, S. R. *J. Chem. Soc., Chem. Commun.* **1993**, 169-171. (b) Bell, K. E.; Coogan, M. P.; Gravestock, M. B.; Knight, D. W.; Thornton, S. R. *Tetrahedron Lett.* **1997**, 49, 8545-8548. (c) Gravestock, M. B.; Knight, D. W.; Abdul Malik, K. M.; Thornton, S. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3292-3305.

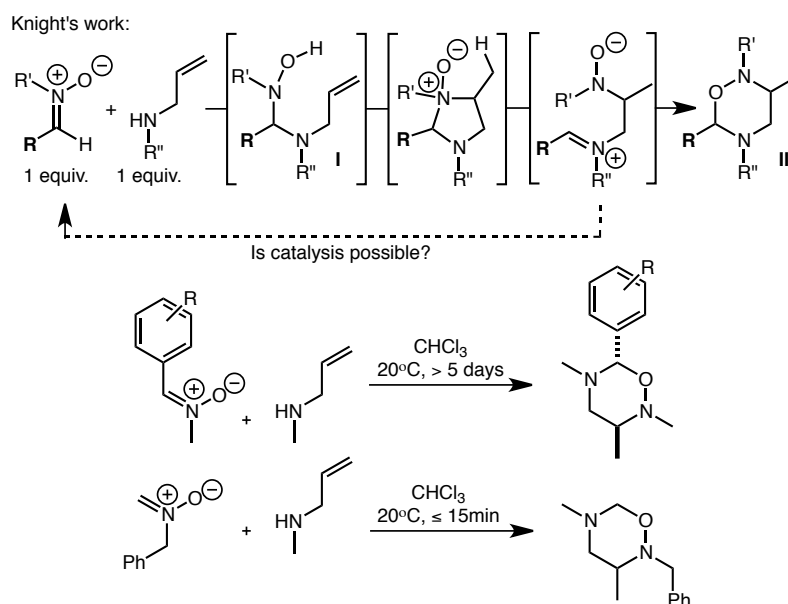


Figure 2.6 A stoichiometric system leading to hydroamination products through a transient hydroxylamine (Knight and co-workers).

Therefore, his research suggested that a catalytic variant could be possible if an aldehyde could be discovered that promoted preassociation and avoided the irreversible formation of the heterocyclic intermediate (**II**). Knight's work also provided useful information on which aldehydes might display good catalytic activity. As seen in Figure 2.6 a benzaldehyde-derived nitronium reacted very slowly with *N*-methylallylamine (5 days) as opposed to a formaldehyde-derived nitronium (15 mins). As a result, our initial catalyst scan focussed on electron-withdrawing aldehydes to create the most destabilized nitrones. Our proposed catalytic cycle begins with the condensation of the aldehyde and hydroxylamine to create a nitronium (see Figure 2.7). This intermediate can then initiate a 1,2-addition with the allylamine to synthesize a mixed amination (**I**). At this time a presumably facile room temperature Cope-type hydroamination would occur followed by amination cleavage and regeneration of the nitronium. In order for this to be successful the specific aldehyde would

have to promote preassociation and avoid the formation of cyclic intermediate (**II**).

Therefore, the project began with a search for the appropriate aldehyde.

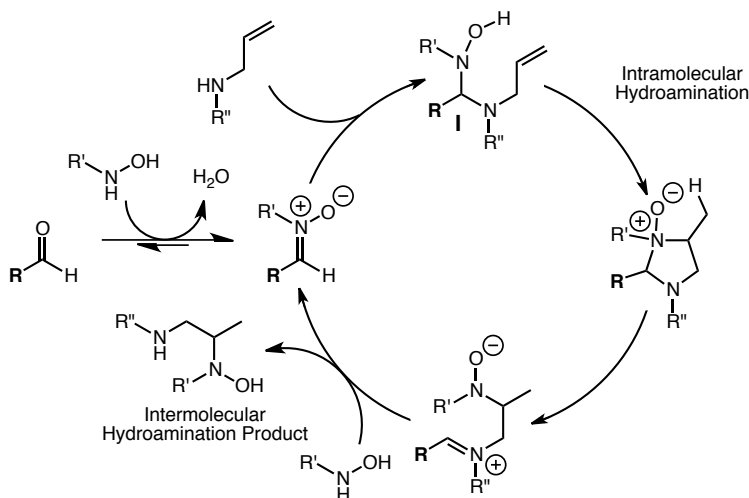
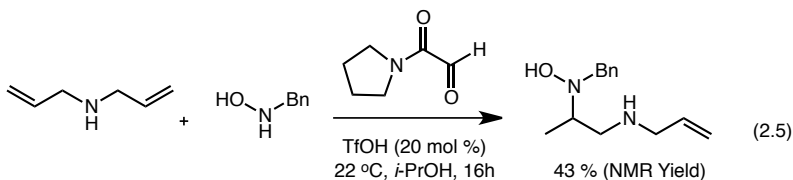


Figure 2.7 Proposed catalytic cycle for a catalytic variant in which an aldehyde is used as the tethering precatalyst (this work).

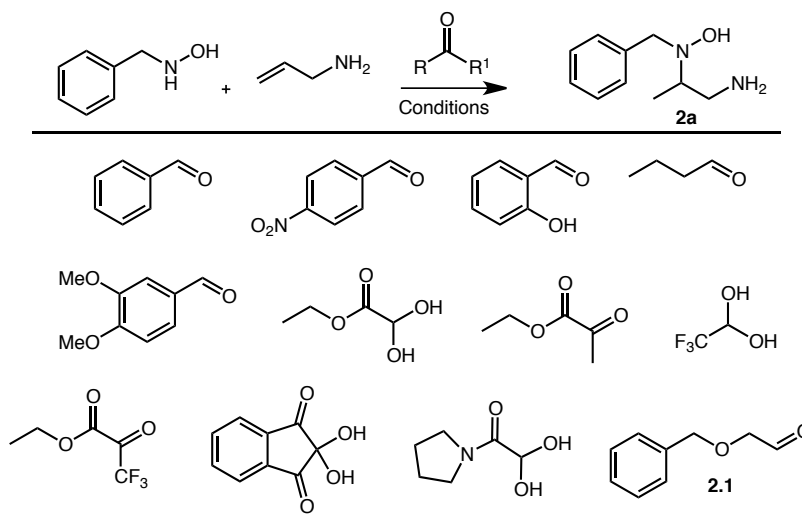
2.2 Initial Approach to an Organocatalytic Tethering Strategy

Dr. Joseph Moran carried out preliminary investigations with several different allylamines and hydroxylamines. Dr. Moran discovered that glyoxamide was capable of catalytic turnover with diallylamine, benzylhydroxylamine and a substoichiometric amount of triflic acid (eq. 2.5). Due to the aldehyde degrading over time and difficulty isolating the product this lead result was given to a new Master's student Mr. Peter Ng, who went on to expand the original scope.



Mr. Peter Ng began re-investigating this project by focussing on different allylamines and attempting to isolate the products. As the yields continued to be low and glyoxamide a constant stability issue, efforts were placed on a thorough aldehyde scan. The goal was always to discover an aldehyde that would promote preassociation between the allylamine and hydroxylamine and therefore allow catalytic turnover with good yield. However, this aldehyde needed to show good stability and consistent results. The initial scan focused on aldehydes that contained electron-withdrawing groups and can be seen in Table 2.1.

Table 2.1 Aldehyde scan of intermolecular Cope-type hydroamination^a



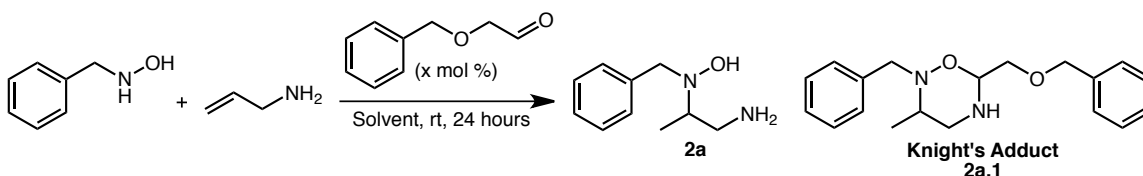
^a Conditions: 1 equiv. hydroxylamine, 1 equiv. allylamine, 1 equiv. aldehyde, CDCl₃, 24 hours

Several carbonyl compounds (and equivalents) were screened for in situ tethering reactivity. Table 2.1 shows selected examples and is not an exhaustive list. In most cases, the nitrone was observed very quickly; however, after 24 hours little or no hydroamination was present, as indicated by NMR. The majority of aldehydes screened under the reaction conditions showed no or less than 10 % of the expected

hydroamination product. Fortunately, the glyoxamide hydrate and α -benzyloxyacetaldehyde **2.1** showed encouraging stoichiometric tethering reactivity, and the latter was selected for further optimization of the catalytic reactivity observed.

Mr. Peter Ng performed solvent and catalyst loading optimization series with α -benzyloxyacetaldehyde **2.1** (Table 2.2). During this study it was discovered that benzene and chloroform were suitable solvents for this transformation. Polar nucleophilic solvents such as H₂O and/or MeOH were thought to compete as nucleophiles in the reaction thus resulting in low yield of the mixed aminal **I** and therefore product. The best catalyst loading was 20 mol %. As the catalyst loading was increased the competition between the formation of either Knight's adduct (**II**), incorporation of catalyst into the product, and the desired diamine would become a critical issue. Mr. Peter Ng also discovered that a 1.0:1.5 ratio of hydroxylamine to allylamine yielded the best results.

Table 2.2 Optimization of α -benzyloxyacetaldehyde catalyzed Cope-type hydroamination^a



Entry	Solvent	Catalyst Loading (mol %)	NMR Yield (%) ^b
1	CDCl ₃	20	83
2	CD ₃ CN	20	75
3	DMSO- <i>d</i> ₆	20	59
4	C ₆ D ₆	20	84
5	CD ₃ OD	20	10
6	(CD ₃) ₂ CO	20	5
7	Acetone- <i>d</i> ₆	20	2
8	D ₂ O	20	5
9	CDCl ₃	10	59
10	CDCl ₃	10	89 (72 h)
11	CDCl ₃	15	77
12	CDCl ₃	20	86
13	CDCl ₃	25	81
14	CDCl ₃	30	76
15	CDCl ₃	0	0
16	CDCl ₃ (0.5 M)	20	76
17	CDCl ₃ (2 M)	20	77

^a Conditions: 1 equiv. hydroxylamine, 1 equiv. allylamine, (x mol %) aldehyde, solvent (1 M). ^b Determined using 1,4-dimethoxybenzene as an internal standard.

With optimized conditions in hand I joined the Beauchemin group to work with Mr. Peter Ng, and started my work on preliminary substrate scope and product isolation studies.

2.2.1 Results and Discussion

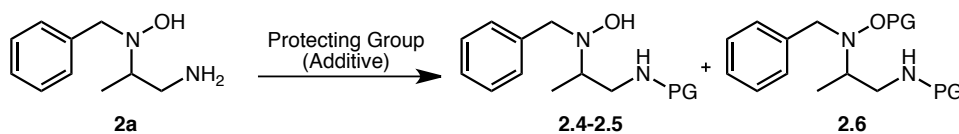
Efforts from Dr. Joseph Moran and Mr. Peter Ng had allowed significant progress on the development of the project prior to my joining the lab. A lead aldehyde had been

discovered and a preliminary optimization was performed. Therefore as I began my graduate studies the goals were to overcome the isolation difficulties, improve the yields of the products, expand the substrate scope and explore an asymmetric variant.

Derivatization and attempts to isolate compound 2a

From the beginning of the project, purification of the aminohydroxylamine (**2a**) had been a constant struggle. Column chromatography was never successful and due to the oily nature of the compound other methods proved useless. Our hypothesis was that by protecting the primary amine one could attempt chromatography from the derivatized product. As a result, several different protecting groups were scanned and the results are shown below (Table 2.3).

Table 2.3 Optimizing protection derivatization^a



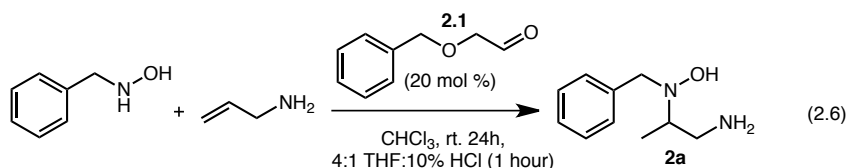
Protecting Group	Additive	Result
Toluene sulfonic acid chloride	NEt ₃	13% yield (2.4) ^b
Di- <i>tert</i> -butyl dicarbonate	No additive	48% yield (2.5) ^b
Benzyl chloroformate	No additive	12% yield ^c
1,1'-Carbonyldiimidazole	No additive	Not reactive

^a Conditions: 1 equiv. of **2a**, equiv of protecting group, 1 equiv additive. ^b Isolated yield. ^c NMR yield (Determined using 1,4-dimethoxybenzene as internal standard).

From this scan of protecting groups the Boc-anhydride was clearly the most suitable for this protection. However, the overall yield was still low due to competition

between the oxygen and nitrogen on the diamine. The bis-protected product could be isolated from the purification process. As a result, excess Boc-anhydride was added hoping to increase the yield of the overall bis-protected compound. After optimization, 81% yield of the desired protected product was obtained (**2.6**). Such an achievement was deemed encouraging, even though product isolation without added derivatization remained optimal and desired.

Previously, our method of organocatalysis had no reaction “work-up” to aid in the purification process. An acidic work-up was designed, with the intention of removing several side products and intermediates. The best conditions were found to be a 4:1 mixture of THF:10 % HCl added to the reaction after 24 hours. The obtained solution from such a wash could be stirred for 1 hour and extracted with ether, sodium carbonate and brine. The results showed an extremely pure crude sample of the desired product. Yields over 90% were obtained based on ^1H NMR analysis of the reaction (eq. 2.6). An isolated yield of 83% was secured, and this work-up was used for yield and stereoselectivity determinations of all primary amines in this methodology.

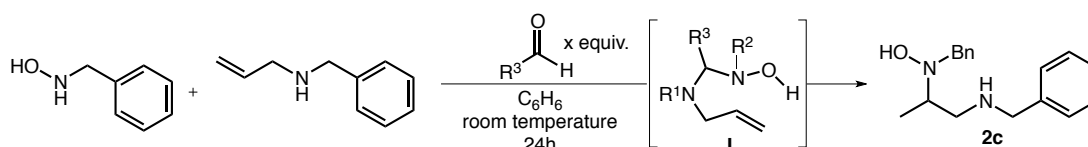


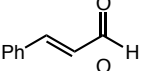
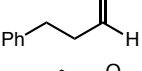
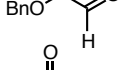
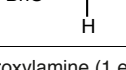
Revised aldehyde scan

As isolation of the compounds was now achievable, efforts turned towards increasing the yields of the reaction. A key discovery was then made: that *degassed* C_6H_6 was the optimal solvent for this methodology resulting in substantial increase of yields

(10-20%). The hypothesis is the absence of oxygen helps prevent degradation of catalyst **2.1**. Therefore a final aldehyde scan was performed with degassed benzene using stoichiometric amounts of key aldehydes (Table 2.4). These results confirm our working theory that destabilized nitrones favour the mixed aminal kinetically and thermodynamically and indeed help offset the negative entropy associated with the formation of mixed aminal **I**. Aldehydes that contain an electron-withdrawing group show better reactivity (Entry 6 and 8). With these results it was demonstrated at this time that catalyst **2.1** was the most reactive aldehyde and the best at promoting catalyst turnover. A substrate scope study was pursued with aldehyde **2.1**.

Table 2.4 Representative reactivity of optimized aldehyde screen^a



Entry	Aldehyde	Quantity	NMR Yield (%) ^b
1	none	–	0
2		100 mol%	1
3		100 mol%	41
4		100 mol%	0
5		100 mol%	22
6		100 mol%	94
7		20 mol%	12
8		20 mol%	77

^a Conditions: Hydroxylamine (1 equiv), allylamine (1.5 equiv), aldehyde (20 mol %), and C₆H₆ (1 mL) were charged into a vial and stirred at room temperature for 24 h.

^b Determined using 1,4-dimethoxybenzene as an internal standard.

Scope of the reaction

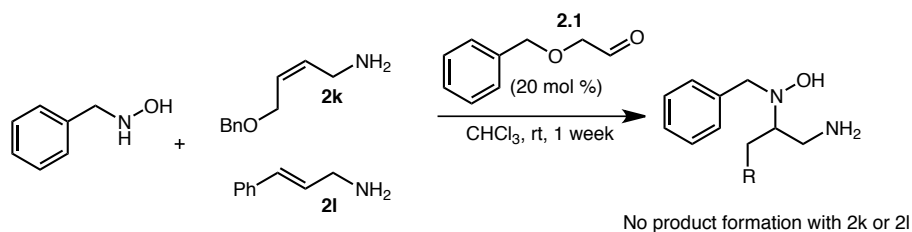
The substrate scope of the Cope-type hydroamination of allylic amines and hydroxylamines catalyzed by α -benzyloxyacetaldehyde **2.1** is presented in Table 2.5. This reaction is compatible with primary allylamines (Entry 1) as well as *N*-substituted allylamines (Entries 2-10). Both benzylic and allylic substituents are tolerated, which in turn allows for orthogonal approaches to vicinal diamines. Benzylic, acyclic and cyclic derivatives of the hydroxylamine (Entries 9 and 10) all yield moderate to good results and are well suited for the reaction. Steric hindrance (Entries 4 and 10) is well tolerated, which is noteworthy especially considering the difficult nitron addition involved. It is also significant that *N*-benzylbut-3-en-2-amine when reacted with benzyl hydroxylamine displayed near perfect diastereoselectivity (20:1) (Entry 4). The majority of these reactions displayed excellent yields for a room temperature intermolecular hydroamination of alkenes. Although catalyst **2.1**'s reactivity is noteworthy it was shown to have severe limitations in its substrate scope due to its instability and incompatibility with high temperatures. Internal alkenes and homoallylic amines were unsuccessful under these standard conditions and further optimization with heat or an additive provided no yields of the hydroamination products (see Scheme 2.1). Due to the difficult synthesis of primary amines **2k** and **2l**, a limited quantity of the amines, allowed few experiments to be run.

Table 2.5 Aldehyde catalyzed intermolecular Cope-type hydroamination^a

Entry	Allylamine	Hydroxylamine	Product	Solvent	Yield (%) ^b
1				CHCl ₃	83
2				C ₆ H ₆	72
3				C ₆ H ₆	75
4				C ₆ H ₆	61 ^c
5				C ₆ H ₆	69
6				C ₆ H ₆	56 ^e
7				CHCl ₃	61
8				C ₆ H ₆	51
9				CHCl ₃	61 ^{d, e}
10				CHCl ₃	57

^a Conditions: Hydroxylamine (1 equiv), allylamine (1.5 equiv), catalyst A (20 mol %), and solvent (1 mL) were charged into a vial and stirred at room temperature for 24 h [except for entries 5 (48 h), 6 (96 h), 7 (46 h), and 10 (29 h)]. ^b Isolated yields. ^c 20:1 mixture of diastereoisomers. ^d 1:1 mixture of diastereoisomers. ^e At 60 °C.

Scheme 2.1 Attempts of catalysis with internal alkenes using catalyst **2.1**



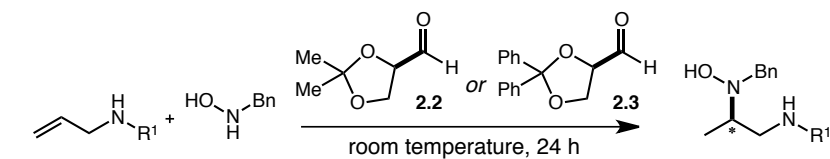
As mentioned previously, catalyst **2.1** was very sensitive under the reaction conditions and was not robust enough to tolerate the higher temperature required for some of these difficult hydroaminations. In order to expand the substrate scope for the proposed reactivity, a more reactive and robust aldehyde would have to be identified.

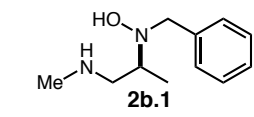
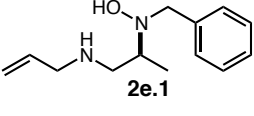
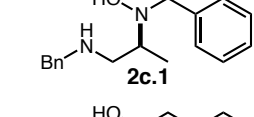
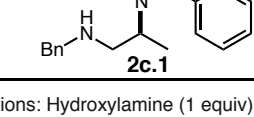
Preliminary asymmetric advances

All new methodologies are measured by their reactivity, general scope and ability to be both regioselective and stereoselective. From the beginning of designing this catalytic approach to tethering the question of whether asymmetry could be induced solely via temporary intramolecularity was of utmost importance. We began by looking at commercially available chiral aldehydes to achieve a selective 1,2-addition and efficient transfer of chirality through a highly ordered 5,5-bicyclic Cope-type hydroamination transition state (Table 2.6). We also developed a derivatization procedure with 1,1'-carbonyldiimidazole to stabilize the compounds for chiral HPLC analyses (see experimental section). Mr. Derek Schipper discovered that (*R*)-glyceraldehyde acetonide (**2.2**) gave very encouraging results with compound **2b.1** resulting in 47 % *ee*. Increasing the steric hindrance on the allylamine increased the selectivity with compounds **2e.1** and

2c.1 both displaying encouraging high enantiomeric excess (78 and 77% ee, entries 2 and 3). It is also noteworthy that catalyst **2.2** resulted in the highest yields at that time.

Table 2.6 Aldehyde catalyzed intermolecular Cope-type hydroamination^a



Entry	Product	Catalyst (20 mol%)	Yield (%) ^b	ee (%) ^c
1	 2b.1	2.2	91	47
2	 2e.1	2.2	81	78
3	 2c.1	2.2	93	77
4	 2c.1	2.3	91	87

^a Conditions: Hydroxylamine (1 equiv), allylamine (1.5 equiv), catalyst (20 mol %), and C₆H₆ (1 mL) were charged into a vial and stirred at room temperature for 24 h.

^b Isolated yields. ^c Determined by chiral HPLC analysis (see the SI).

In order to increase the selectivity it was hypothesized that an increase in the bulk of the gem-dimethyl would make the initial 1,2-addition more selective. A gem-diphenyl aldehyde was synthesized from D-mannitol. This catalyst **2.3** was a solid as opposed to an oil (**2.2**), which in turn was much easier to handle. Using catalyst **2.3** resulted in a 10% *ee* increase for compound **2c.1**. At that time, and to the best of our knowledge this was the highest enantiomeric excess achieved for the intermolecular hydroamination of an unactivated alkene.

As a result, three aldehydes (**2.1**, **2.2** and **2.3**) were found to catalyze the Cope-type hydroamination of allylamines and hydroxylamines via preassociation. Over the course of the project several aldehydes were tested for reactivity and during the substrate scope studies additional aldehydes were evaluated. During these tests it was initially found that D-glucose in dichloromethane (CH_2Cl_2) showed exceptional reactivity and gave almost quantitative yields for product **2b**. As the product was tested for enantiopurity it was found to be racemic; this prompted control experiments to be performed. These tests discovered that it was actually CH_2Cl_2 catalyzing the reactivity and glucose played little to no part in the system. CH_2Cl_2 was undergoing an initial $\text{S}_{\text{N}}2$ displacement by the allylamine component, followed by iminium formation and 2 equivalents of HCl production (Figure 2.8). This discovery was fully investigated by an undergrad working under my supervision (Mrs. Valerie Lemieux) and the results are summarized below.

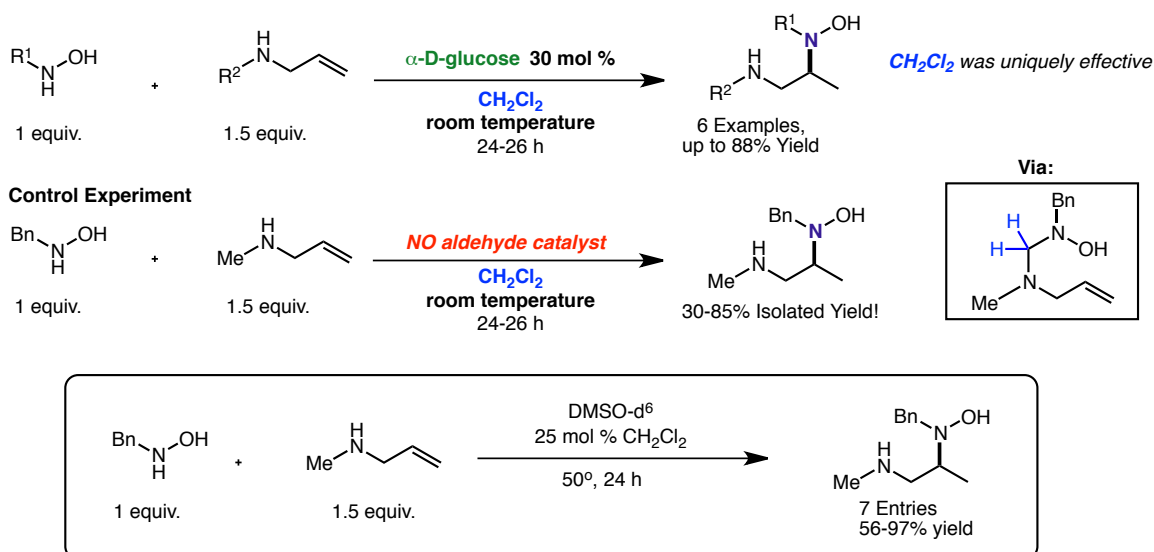


Figure 2.8 Discovery of a catalytic role for CH_2Cl_2

Background reactivity

Throughout the experiments and test reactions performed, as described previously, control experiments were routinely performed to determine if any background reaction was present. The vast majority of experiments showed less than 10 % NMR yield in the absence of an aldehyde catalyst. The only substrate combination for which a significant background reaction was observed is shown below in Table 2.7 (Entry 2). This interesting result was pursued by Dr. Shubin Zhao and resulted in the first hydrogen bond catalyzed intermolecular Cope-type hydroamination (Figure 2.9).⁸⁶ This transformation may be accelerated by the hydrogen bonding of the nitrogen on the allylamine to the N-H bond on the hydroxylamine, which helps decrease the entropy of activation in this intermolecular process. This possibility of a competing H-bonding directed process is thus present in the tethering catalysis. However the high enantiomeric excess observed with the use of chiral aldehydes as catalysts indicate that this pathway is less efficient than the use of covalent catalysis.

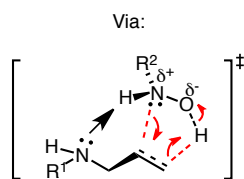


Figure 2.9 Hydrogen bonding directed intermolecular Cope-type hydroamination of alkenes

⁸⁶ Zhao, S.; Bilodeau, E.; Lemieux, V.; Beauchemin, A. M. *Org. Lett.* **2012** *19*, 5082-5085.

Table 2.7 Background reactivity and control experiments^a

Entry	Hydroxylamine	Allylamine	Solvent	Product	NMR Yield (%) ^b
1			CHCl ₃		0
2			C ₆ H ₆		30
3			C ₆ H ₆		0
4			C ₆ H ₆		5
5			CHCl ₃		9

^a Conditions: 1 equiv. hydroxylamine, 1.5 equiv. allylamine, solvent (1 M). ^b Determined using 1,4-dimethoxybenzene as internal standard.

2.3 Summary and Outlook

An organocatalytic tethering strategy was validated and applied towards the intermolecular Cope-type hydroamination of hydroxylamines and allylamines. Typically difficult hydroaminations were carried out under mild and metal free conditions. This resulted in the synthesis of several different desired vicinal 1,2-diamines motifs in moderate to good yield.

This approach was also validated in asymmetric synthesis, as the use of chiral aldehydes resulted in high enantioselectivities. These results strongly supported simple molecules being able to induce asymmetry only via temporary intramolecularity. The

selectivity observed and discussed above was, at the time of publication, the highest obtained for an intermolecular hydroamination of unactivated alkenes, including variants using transition metal catalysis.

In the future, efforts must be made to broaden the scope of the reaction to a variety of alkenes and to discover aldehydes that are more robust and/or reactive. Mr. Bashir Hussain continued this aspect of the project focussing on advanced substrate scope. More optimization is needed for the asymmetric version of this methodology including testing several chiral aldehydes and looking at physical effects such as temperature and solvent. The next chapter will provide an insight into the mechanism of this catalytic cycle.

Mechanistic Investigations on Aldehyde-Catalyzed Cope-Type Hydroamination Lead to the Discovery of a More Efficient Tethering Catalyst

3.1 Introduction

This chapter will elaborate on the details and kinetics of the aldehyde-catalyzed intermolecular Cope-type hydroamination catalytic cycle. A mechanistic investigation will be discussed with a focus on identifying the limitations of the reaction, to assist in the design of an advanced system with a more robust and reactive aldehyde. A more efficient catalyst will be presented along with a comparative study showcasing the abilities of this superior aldehyde. The possible role of aldehydes as catalysts in prebiotic chemistry will be discussed focussing on overcoming the low concentration issue that most likely existed in primitive Earth.

3.1.1 Carbonyl Catalysis

As Chapter 2 highlighted and focused on accelerating bi-molecular reactions that are at the centre of organic chemistry, this chapter will continue to survey the field of carbonyl catalysis.⁸⁷ In order to promote difficult intermolecular reactions and overcome

⁸⁷ For an entry in the literature on bifunctional catalysis, see: (a) Rowlands, G. J. *Tetrahedron* **2001**, 57, 1865-1882. (b) Ma, J. A.; Cahard, D. *Angew. Chem. Int. Ed.* **2004**, 43, 4566-4583. (c) Bhadury, P. S.; Song,

high entropic activation costs catalysis is often the most effective strategy. Catalysts traditionally operate by activating one or both reagents in the system and are therefore essential in the key bond-forming step. However, catalysts that solely focus on bringing reagents closer together via preassociation can be just as effective. This is evident in the rate accelerations enzymes can achieve, which can be up to 10^{17} times faster.⁷⁰ To achieve this efficiency enzymes stabilize the transition state, and help minimize the entropic penalty through a favourable preassociation event that results in a close proximity between the reactants. It is generally accepted that rate enhancements of 10^4 – 10^8 are possible simply via a temporary intramolecularity pathway.⁷¹ In our current organocatalytic tethering strategy we focus on only preassociation without any other activation mode (Figure 3.1). This allows us to ask questions currently not answered in the literature: is preassociation enough to not only significantly accelerate reactions but also induce asymmetry? Are small organic molecules capable of high catalytic efficiencies? This ordered pre-organization should provide a substantial handle on regioselectivity and stereoselectivity via a formal intermolecular reaction operating via an intramolecular pathway.

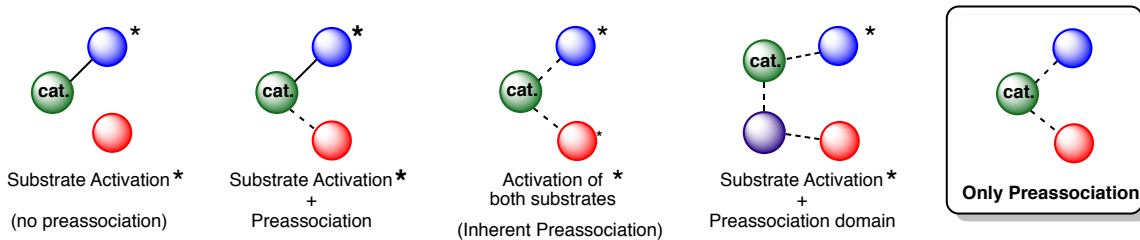


Figure 3.1 Modes of activation in catalysis of intermolecular reactions

B. A.; Yang, S.; Hu, D. Y.; Xue, W. *Curr. Org. Synth.* **2009**, 6, 380-399. (d) Connon, S. J. *Chem. Commun.* **2008**, 2499-2510.

Catalysts that operate solely via temporary intramolecularity are rare and often involve stoichiometric conditions and lengthy syntheses. Highly efficient enantioselective approaches have not been reported.⁸⁸ One area that has shown promise in the field of temporary intramolecularity is carbonyl catalysis.⁸⁸ This area is primarily focussed on hydrolysis (i.e. inherently limited to the use of water as a reactant) and most often, a stoichiometric equivalent of the carbonyl is employed. Commeyras and co-workers were pioneers in this field, and published an approach using formaldehyde to hydrolyze α -aminoamides into amino acids (see Figure 3.2).⁸⁹

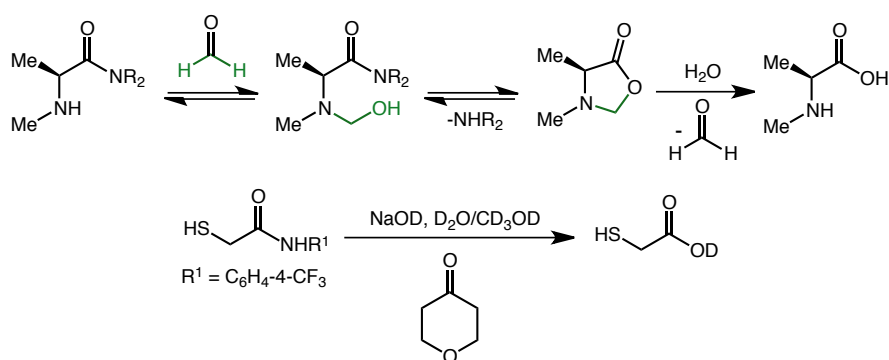


Figure 3.2 Reports of amide hydrolysis via carbonyl catalysis

In this reaction the amine moiety condenses on formaldehyde, followed by an intramolecular attack on the amide by the oxygen atom present in the hemi-aminal. Hydrolysis of the 5-membered heterocycle resulted in the regeneration of formaldehyde and the amino acid. This has been further applied to α -mercaptoamides by Seto *et al.* using various ketones as catalysts. They reported that their carbonyl catalyzed reaction

⁸⁸ For reviews: (a) Tan, K. L. *ACS Catal.* **2011**, *1*, 877-886. (b) Pascal, R. *Eur. J. Org. Chem.* **2003**, 1813-1824.

⁸⁹ Pascal, R.; Lasperas, M.; Taillades, J.; Commeyras, A. *New. J. Chem.* **1987**, *11*, 235-244.

was 15 000 times faster than the background, catalyst-free reaction (Figure 3.2).⁹⁰

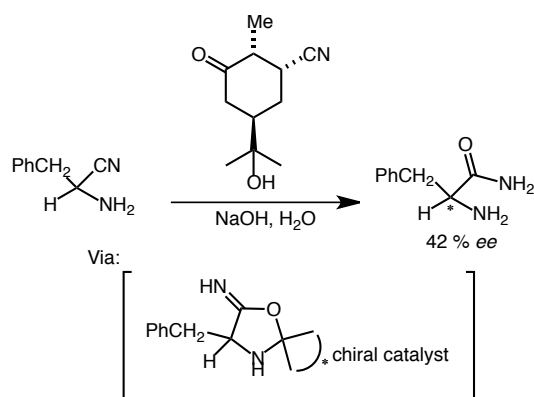


Figure 3.3 Enantioselective hydrolysis of α -aminonitriles

Commeyras is also responsible for one of the rare examples of enantioselective carbonyl catalysis via hydration of α -aminonitriles (Figure 3.3).^{91,92} This process occurs similarly with initial attack of the amine on the carbonyl, followed by attack of the alkoxide on the nitrile. The final step is hydrolysis to release the catalyst and α -aminoamide. The highest enantioselectivity reported in this paper is a modest 42% *ee* and definitely could be revisited for optimization. A key limitation in this strategy thus far is

⁹⁰ Ghosh, M.; Conroy, J. L.; Seto, C. T. *Angew. Chem., Int. Ed.* **1999**, 38, 514-516.

⁹¹ Tadros, Z.; Lagriffoul, P. H.; Mion, L.; Taillades, J.; Commeyras, A. *J. Chem. Soc., Chem. Commun.* **1991**, 1373-1375.

⁹² (a) Pascal, R.; Taillades, J.; Commeyras, A. *Tetrahedron* **1978**, 34, 2275-2281. (b) Pascal, R.; Taillades, J.; Commeyras, A. *Bull. Soc. Chim. Fr.* **1978**, 177. (c) Pascal, R.; Taillades, J.; Commeyras, A. *Tetrahedron* **1980**, 36, 2999-3008. (d) Sola, R.; Brugidou, J.; Taillades, J.; Commeyras, A. *Tetrahedron Lett.* **1983**, 24, 1501-1504. (e) Sola, R.; Brugidou, J.; Taillades, J.; Commeyras, A. *New J. Chem.* **1984**, 8, 459-474. (f) Sola, R.; Taillades, J.; Brugidou, J.; Commeyras, A. *New J. Chem.* **1989**, 13, 881. (g) Taillades, J.; Beuzelin, I.; Gabrel, L.; Tabacik, V.; Bied, C.; Commeyras, A. *Orig. Life Evol. Biosph.* **1996**, 28, 61. For discussion and representative experimental procedures, see: (h) Pascal, R.; Marnier, M. L.; Rousset, A.; Commeyras, A.; Taillades, J.; Mion, L. Process for the Chemical Catalytic Hydrolysis of an α -Aminonitrile or of One of the Salts Thereof. U.S. Patent 4,243,814, Jan 6, 1981. For kinetic resolution using chiral ketones, see: (i) Taillades, J.; Garrel, L.; Lagriffoul, P. H.; Commeyras, A. *Bull. Soc. Chim. Fr.* **1992**, 129, 191-198. (j) Lagriffoul, P. H.; Tadros, Z.; Taillades, J.; Commeyras, A. *J. Chem. Soc. Perkin Trans. 2* **1992**, 1279-1285. (k) Taillades, J.; Garrel, L.; Guillen, F.; Collet, H.; Commeyras, A. *Bull. Soc. Chim. Fr.* **1995**, 132, 119-127. (l) Taillades, J.; Garrel, L.; Guillen, F.; Collet, H.; Commeyras, A. *React. Polym.* **1995**, 24, 261-269.

the critical use of a base, which likely causes epimerization of the chiral catalyst. It should be highlighted that this study follows up their seminal work that showed that several aldehydes and ketones catalyze the hydrolysis of Stecker adducts.⁹²

In other developments, ester hydrolysis has also been accelerated by the use of a carbonyl catalyst. As early as 1956 Wieland reported that bicarbonate, via carbon dioxide, is capable of catalyzing the hydrolysis of *p*-nitrophenyl esters.⁹³ The mechanism is believed to occur through condensation and formation of a cyclic anhydride. Hydrolysis finishes the catalytic cycle and releases an equivalent of carbon dioxide.

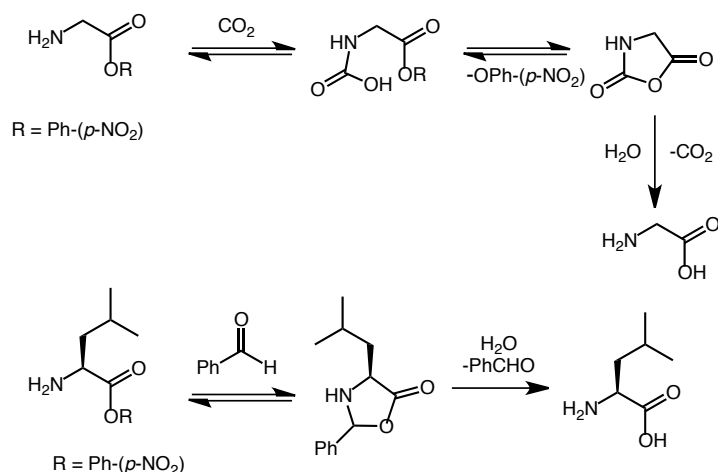


Figure 3.4 Ester hydrolysis via a carbonyl catalyst

After this was published several groups reported that aromatic aldehydes displayed excellent reactivity (Figure 3.4).⁹⁴

⁹³ This reaction is related to the Bucherer–Bergs reaction wherein carbonyls or cyanohydrins react with ammonium carbonate and potassium cyanide to give glycolylureas. (Occurs through an intramolecular attack of a carbonyl on a nitrile.)

⁹⁴ (a) Wieland, V. T.; Lambert, R.; Lang, H. U.; Schramm, G. *Justus Liebigs Ann. Chem.* **1956**, 597, 181. (b) Wieland, V. T.; Jaenicke, F. *Justus Liebigs Ann. Chem.* **1956**, 599, 125. (c) Capon, B.; Capon, R. J.

Sammakia further developed this approach in the intramolecular transesterification of a α -hydroxy ester (Figure 3.5).⁹⁵ Ketones with electron-withdrawing groups were observed to be the most reactive, presumably through promotion of the initial addition. As seen in previous mechanisms of carbonyl catalysis the 5-membered acetal was observed via NMR in the reaction. This further supports the hypothesis that the acceleration is due to temporary intramolecularity.

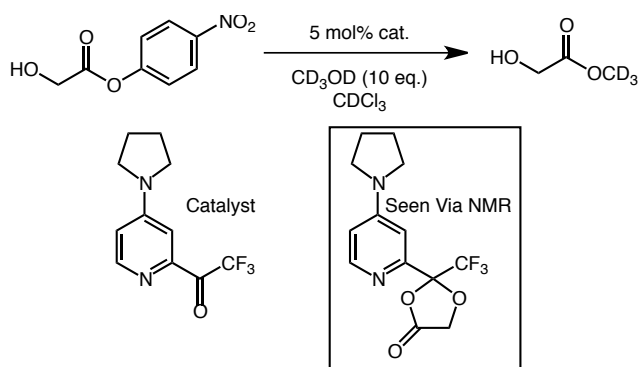


Figure 3.5 Sammakia et al.'s α -hydroxy ester alcoholysis

Common to the majority of the previously mentioned strategies is the use of stoichiometric amounts of carbonyl "catalyst" even though catalysis should be possible. In addition, the examples described above are limited to hydrolyses reactions, and thus are only applicable for simple transformations. This highlights the lack of examples of true tethering catalysts in the literature and the difficulty to induce asymmetry solely via

Chem. Soc., Chem. Commun. **1965**, 20, 502-503. (d) Hay, R.W.; Main, L. *Aust. J. Chem.* **1968**, 21, 155-169.

⁹⁵ (a) Sammakia, T.; Hurley, T. B. *J. Am. Chem. Soc.* **1996**, 118, 8967-8968. (b) Sammakia, T.; Hurley, T. B. *J. Org. Chem.* **1999**, 64, 5652-5653. (c) Sammakia, T.; Hurley, T. B. *J. Org. Chem.* **2000**, 65, 974-978. (d) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, 42, 112-114.

temporary intramolecularity.

As mentioned in Chapter 2 we have validated an organocatalytic tethering strategy and applied this towards the Cope-type hydroamination of alkenes. α -Benzyloxyacetaldehyde **2.1** was discovered to be the best "1st generation" aldehyde to promote preassociation between the two substrates, providing high yields and modest catalyst efficiency. This chapter details mechanistic studies into the catalytic cycle with aldehyde **2.1**.

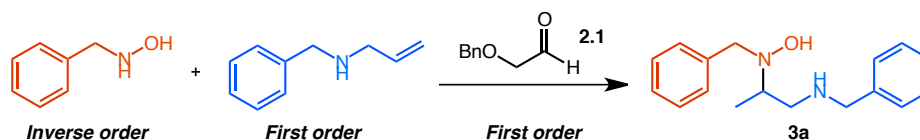
3.2 Results and Discussion

As seen in Chapter 2 α -oxygenated aldehydes are competent catalysts for the Cope-type hydroamination of allylic amines and *N*-alkylhydroxylamines. Unfortunately, the initial reaction scope was limited to unsubstituted alkenes and yields were moderate to good (51-83%). In order to discover a more versatile system a new reactive and stable aldehyde needed to be found. As a result, Mr. Nicolas Guimond and I performed a series of mechanistic experiments relating to the catalytic cycle in the hopes of gaining a better understanding of the reaction that would ultimately lead to better reactivity through a second-generation aldehyde.

We began this approach by using initial rate kinetics to evaluate the reaction order of each reagent. This strategy was taken in order to ensure high concentrations of the starting material and avoid inhibition pathways that could potentially affect the kinetic experiments. Mr. Nicolas Guimond performed these reactions and constructed the linear log plot of initial rate dependence (gathered from previous experiments measuring the

rate of the reaction with varying reagent) versus initial reagent concentration in order to be able to read the reaction orders directly from the slope of these graphs (Scheme 3.1).⁹⁶ As a result, with respect to aldehyde the reaction was first order (1.28)⁹⁶ and this in good agreement with a catalytic cycle where only one molecule of aldehyde is involved prior to or at the rate-determining step. This experiment was subsequently performed varying *N*-allylbenzylamine initial concentrations and the results were consistent with a first order relationship (0.92) in the allylamine component. Finally, the order of *N*-benzylhydroxylamine was probed and a surprising slope of -0.83 was seen, which is indicative of an inverse order relationship in that reagent. Therefore this result confirms that increasing the hydroxylamine concentration leads to a decrease in the rate of the reaction.

Scheme 3.1 Reaction order of each reagent



To better understand this result the equilibria that exists between the nitron and two possible nucleophiles (hydroxylamines and allylic amines) needed to be examined (Figure 3.6). Our proposed catalytic cycle requires formation of the mixed aminal, from addition of the allylic amine on the nitron, to form the Cope-type hydroamination

⁹⁶ (a) Guimond, N.; MacDonald, M. J.; Lemieux, V.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2012**, *134*, 16571 – 16577. (b) Guimond, N. "Part A: Rhodium-Catalyzed Synthesis of Heterocycles Part B: Mechanistic Studies on Tethering Organocatalysis Applied to Cope-Type Alkene Hydroamination", PhD Thesis, University of Ottawa, ON, 2013. (c) See Appendix IV for more information.

precursor. In contrast, addition of the hydroxylamine leads to the formation of a symmetrical aminal, which is a possible source of catalyst inhibition.

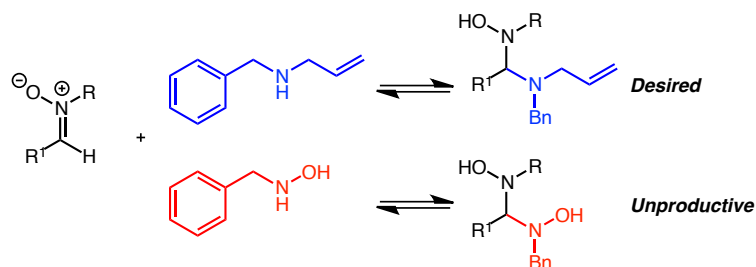


Figure 3.6 Competing 1,2-addition on nitronium

Given the importance of these two competing preassociation equilibria for the development of tethering catalysis, we decided to measure equilibrium constants for several nitrones. *N*-Benzylethylamine was used instead of *N*-allylbenzylamine to form a stable mixed aminal intermediate and avoid Cope-type hydroamination.

Equilibrium studies

The equilibrium studies were performed in deuterated solvents with extreme care taken to ensure accurate measurements. The aldehyde-derived nitrones were synthesized and isolated. The nitrones were then used under conditions similar to the reaction conditions (1 M benzene, room temperature) in order to obtain accurate equilibrium constants (*K*) for the preassociation between each nitronium and its mixed or symmetrical aminals. The equilibrium was reached in approximately 18 hours. The value obtained for the equilibrium constant between the nitronium and benzylamine was $K_A = 0.46 \pm 0.1$, thus showing that the mixed aminal is not favoured thermodynamically (Figure 3.7). The

reaction between the nitrone and *N*-benzylhydroxylamine resulted in an equilibrium constant of $K_B = 1.1 \pm 0.1$. This indicates that formation of the symmetrical aminor is thermodynamically favoured over the desired mixed aminor.⁹⁷ Given the inverse order relationship of hydroxylamine and the thermodynamic preference for the symmetrical aminor it is proposed that this dimer is the resting state of the catalyst (Figure 3.7).

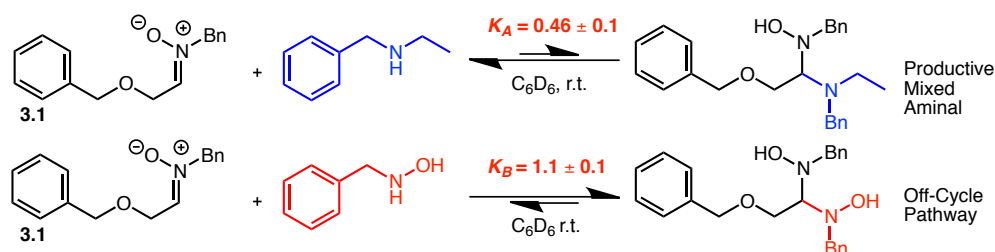


Figure 3.7 Equilibrium constants for the addition of *N*-ethylbenzylamine and *N*-benzylhydroxylamine to nitrone **3.1**

Equilibrium constants were also evaluated for other aldonitrones to gain some perspective on these measurements and to see if these equilibria were indicative of aldehyde reactivity. Equilibrium constants were measured with benzaldehyde- and dihydrocinnamaldehyde-derived nitrones to provide a reference point for α -benzyloxyacetaldehyde **2.1** (Figure 3.8).

⁹⁷ For related hydroxylamine behavior, see: Turega, S. M.; Lorenz, C.; Sadownik, J. W.; Philp, D. *Chem. Commun.* **2008**, 4076–4078.

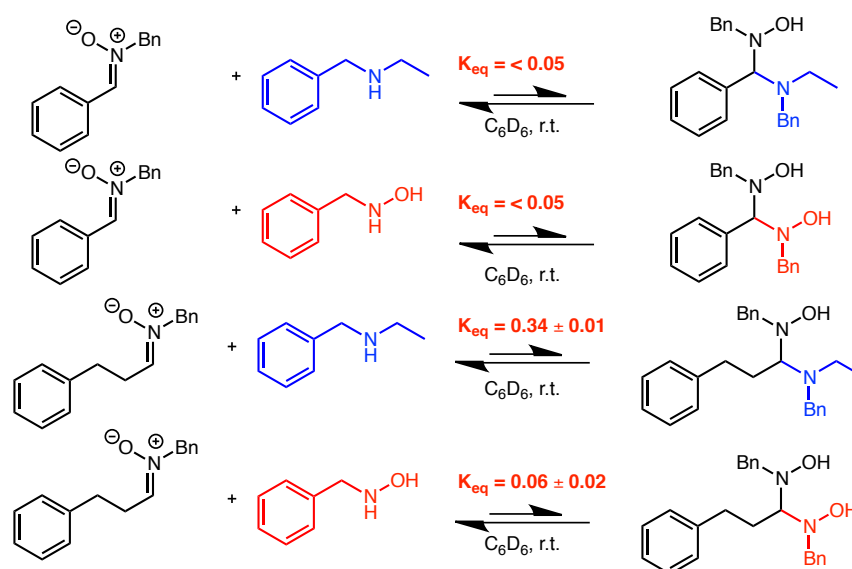


Figure 3.8 Competing 1,2-addition with benzylamine and *N*-benzylhydroxylamine with benzaldehyde and dihydrocinnamaldehyde

The nitron derived from benzaldehyde showed a K_{eq} value of less than < 0.05 for the reaction with each reagent. This nitron is too stable to favour addition from either nucleophilic starting material. Finally, the nitron synthesized from dihydrocinnamaldehyde displayed unique values, as the K_{eq} for the desired mixed aminor was 0.34 ± 0.01 . This result is very similar to α -benzyloxyacetaldehyde **2.1** yet this aldehyde is almost 4 times less reactive when compared to **2.1** (22% compared to 94%, NMR yield, for catalyzing the reaction of *N*-benzylhydroxylamine and *N*-allylbenzylamine).⁹⁸ An even more interesting result is the lack of preference for the equilibrium leading to the symmetrical adduct ($K_{eq} = 0.06 \pm 0.02$). It is postulated that α -benzyloxyacetaldehyde **2.1**, given its β -oxygen, could form an internal hydrogen bond with aminor formation (see Figure 3.9).

⁹⁸ Stoichiometric amount of aldehyde, 1 M Benzene. See Chapter 2 for more analysis.

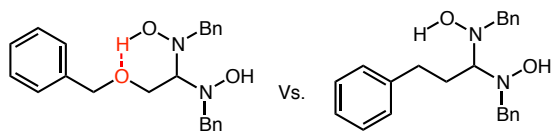


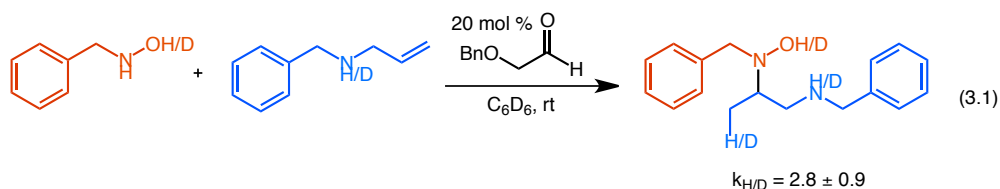
Figure 3.9 Internal hydrogen bond with symmetrical aminal formation on aldehyde **2.1** vs. lack of stabilization on dihydrocinnamaldehyde

This could help stabilize the symmetrical aminal intermediate and thus help explain the thermodynamic preference for this aminal. This added stabilization is simply not present in the hydrocarbon backbone of dihydrocinnamaldehyde. However, the electron-withdrawing nature of the oxygen must be playing a key role in improving catalytic activity via a favoured 1,2-addition and higher K_{eq} for the mixed aminal. These results suggest that the equilibria found here hold critical information on how the nitron would react in the catalytic system. However, more equilibria studies are needed to identify which structural elements of the aldehyde precatalyst could positively impact the catalytic efficiency of the system. This project has been given to Mr. Didier Bilodeau to expand our understanding of these values.

Kinetic Isotope Effect for α -benzyloxyacetaldehyde

Deuterium kinetic isotope effects (DKIE) are measured to help gain an understanding of bond changes during the rate-determining step. Evaluating a hydrogen isotope effect involves comparing the rate of a reaction with a natural abundance of isotope to the rate of a fully deuterated species (k_H/k_D). These values can provide information on whether a hydrogen/deuterium bond (X-H/X-D) is being broken during the turnover-limiting step. Therefore, Mr. Nicolas Guimond conducted DKIE

experiments to probe the nature of the rate-determining step (eq 3.1).⁹⁶ Deuterium was introduced to all exchangeable protons in the starting materials via several washes in MeOD and a kinetic isotope effect of 2.8 ± 0.9 was obtained. Due to this value being reflective of a composition of several steps and the high probability of equilibrium isotope effects in several stages of this catalytic cycle, extreme care must be taken in evaluating the significance of this measurement. Assuming all proton transfer steps have a low energy barrier, the value of this KIE supports a possible theory that a hydrogen/deuterium is being broken during the rate-determining step. Therefore a hypothesis that is consistent with our proposed mechanism would be that hydroamination is the turnover-limiting step of the catalytic cycle. A second hypothesis for the turnover-limiting step would be that the initial 1,2-addition is rate determining. This is supported due to the fact that it takes a long time (approximately 18 hours) for equilibrium to be reached in this system. Further evaluation of how deuterium would affect the reversible steps in our catalytic cycle need to be performed in order to better understand the KIE value and gain further evidence on the nature of the rate-determining step. This can be accomplished by re-evaluating the equilibrium measurements with deuterated substrates.



Proposed catalytic cycle

The final off-cycle pathway that is possible in this system occurs after the

hydroamination event, as there are theoretically two pathways that can take place (see Figure 3.10). The first would be the desirable transamination that can lead to the nitrone and the second is a cyclization that leads to Knight's adduct (V) as presented earlier in Chapter 2. The off-cycle pathway results from a *6-endo-trig* addition of the negatively charged oxygen onto the iminium ion in IV.

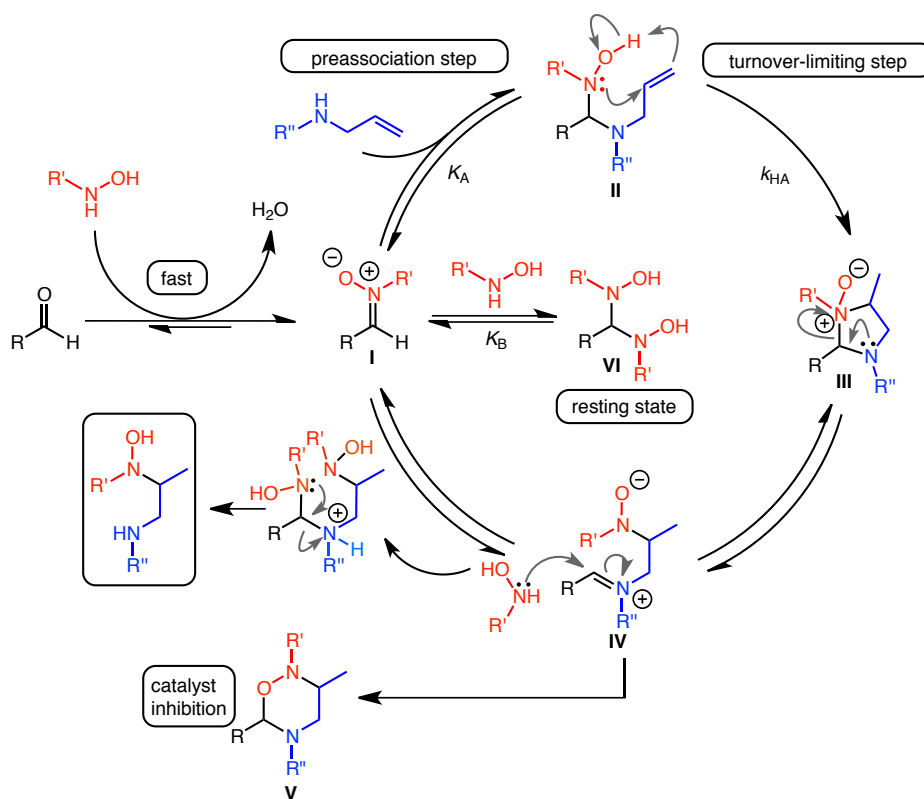


Figure 3.10 Proposed catalytic cycle

This reaction is not fully reversible given the fact that when this adduct is subjected to our reaction conditions as a catalyst, less than 10% product formation is formed.⁹⁶ Therefore this pathway serves as a potential source of catalyst inhibition.

Taking into consideration all of the mechanistic data we proposed and assuming

hydroamination is our rate-determining step a revised catalytic cycle is seen in Figure 3.10. The first proposed step is fast condensation to form the nitron (observed via ^1H NMR), which can either react with another equivalent of the hydroxylamine or react with the allylic amine to form hydroamination precursor **II**. Using α -benzyloxyacetaldehyde **2.1** the favoured equilibrium is towards the symmetrical adduct **VI**. As mentioned previously, given the inverse order relationship of *N*-benzylhydroxylamine and the symmetrical amination being the favoured equilibrium, this dimer is most likely the resting state of the catalyst. Once the desired mixed amination **II** is formed the proposed rate-determining step, hydroamination takes place, and given literature precedence this is likely the only irreversible step (excluding off-cycle pathways) in the catalytic cycle.⁷⁵ Following hydroamination there is a reversible amination ring opening to provide iminium **IV** and this intermediate can either form the 6-membered ring **V** or release the desired product and regenerate the nitron after the addition of the hydroxylamine reagent.

3.2.1 Aldehyde Optimizations and Discoveries

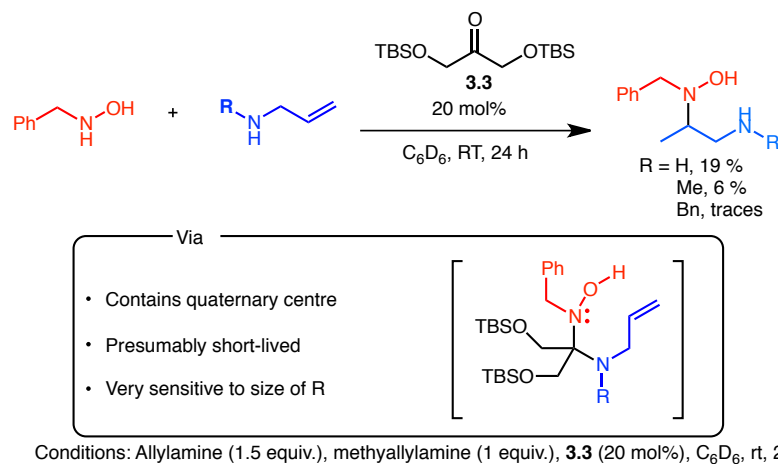
In parallel to these mechanistic studies several strategies were explored to design and identify a more robust, yet reactive aldehyde. Our studies showed that a more reactive aldehyde would have to favour the mixed amination by either generating a higher concentration of the hydroamination precursor (mixed amination) or by accelerating the hydroamination step. These strategies also have to minimize the off-cycle pathways discussed previously.

Ketones as organocatalysts for intermolecular Cope-type hydroamination

The first hypothesis was that a more sterically hindered carbonyl such as a ketone, could improve the reaction efficiency by taking advantage of the Thorpe-Ingold effect to accelerate the hydroamination step. This effect is well known to accelerate intramolecular Cope-type cyclizations.^{78,79} Mr. Nicolas Guimond synthesized and studied several ketones and the reactivity of the best carbonyl **3.3** is seen in Scheme 3.2.⁹⁶ Unfortunately, all ketones displayed limited reactivity and only moderate yields were achieved with primary allylamine (19% yield). This is presumably due to a difficult preassociation step (**I-II**) as the equilibrium for the formation of the mixed aminal (**II**) is unfavourable as a result of the steric destabilization present in this intermediate. Consequently, the benefit of accelerating the hydroamination step is never fully reached. As a result, this observation is related to the concept of tether strain recently discussed by Krenske, Holmes, Houk *et al.* in related Cope-type hydroamination systems. In this investigation they compared tether lengths and alkene/alkyne reactivity in intramolecular Cope-type cyclizations. Using computational methods they were able to evaluate what advantage the tether has on the system and the distortion that results from the tethers' presence.⁹⁹ In summary, the increased stability of ketonitrone relative to aldonitrone likely results in a disfavoured preassociation equilibrium.

⁹⁹ Krenske, E. H.; Davison, E. C.; Forbes, I. T.; Warner, J. A.; Smith, A. L.; Holmes, A. B.; Houk, K. N. *J. Am. Chem. Soc.* **2012**, *134*, 2434-2441.

Scheme 3.2 Importance of steric factors with a ketone precatalyst⁹⁶



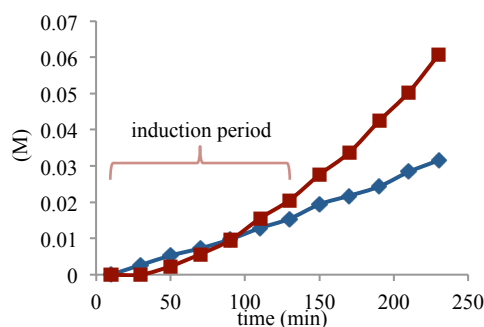
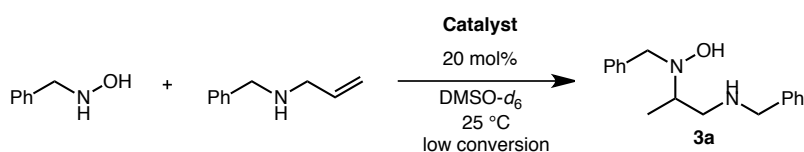
Destabilized nitrones as competent organocatalysts

The second strategy to design a more efficient aldehyde precatalyst focuses on creating the most destabilized nitron that would hopefully favour the desired equilibrium (**I-II**) and create a higher concentration of the desired reactive aminal. Over the course of this project aldehydes with electron-withdrawing groups such as trifluoroacetaldehyde hydrate and 2-(4-nitrophenoxy)acetaldehyde did not display catalytic activity.¹⁰⁰ Therefore, the new approach to create a destabilized nitron was to use an aldehyde with the lowest number of functional groups and/or lowest electron density to provide any stabilization. The only aldehyde that matched this strategy was formaldehyde.

Consequently, paraformaldehyde was tested as an organocatalyst in this reaction. Initial reactions in CHCl₃ and C₆H₆, the solvents initially found to be ideal for our

¹⁰⁰ See Chapter 2 for more information.

catalytic tethering strategy, gave very low conversions. However, this is likely due to the poor solubility of this polymerized aldehyde. In contrast, when paraformaldehyde was tested in *t*-BuOH as a solvent remarkable reactivity was observed.¹⁰¹ As a result, Mr. Nicolas Guimond performed a rate study to compare both aldehydes' performance in DMSO-*d*₆.⁹⁶ Interestingly, the reaction rate at low conversion is lower with paraformaldehyde than with aldehyde **2.1**, but it becomes approx. 3 times faster after an induction period (Figure 3.11).



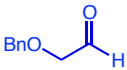
Catalyst	η_0	rel. rate
 (2.1)	2.38×10^{-6} M/s	1
 (3.4)	6.91×10^{-6} M/s ^b	2.9

Figure 3.11 Initial rate comparison in DMSO-*d*₆ using benzylallylamine (1.5 equiv.), *N*-benzylhydroxylamine (1 equiv.), catalyst **2.1** or **3.4** (20 mol%), DMSO-*d*₆ (1 M), 25 °C.^b Value obtained after induction period.⁹⁶

¹⁰¹ The reaction resulted in near quantitative results with methylallylamine (1.5 equiv.), benzylhydroxylamine (1 equiv.), 10 mol % of catalyst in 1 M *t*-BuOH.

Due to the polymeric nature of formaldehyde, the slow depolymerization of the pre-catalyst employed in this reaction was most likely the cause.

The use of paraformaldehyde as a precatalyst led to increased yields of all products relative to the parent reactions catalyzed by α -benzyloxyacetaldehyde **2.1**. As seen in Table 3.1 a comparative study was performed to evaluate the improved reactivity observed using paraformaldehyde. At only 5 mol % catalyst loading, as opposed to 20 mol % for **2.1**, the use of formaldehyde led to higher yields (typically 10-20 %, entries 1-3). With more difficult substrates 10 mol % of paraformaldehyde was used and was associated with a dramatic increase on the reactivity (entries 4-6). In theory lower catalyst loadings should be just as efficient; however, due to the low mass of formaldehyde it is neither practical nor accurate to handle smaller measurements. These results show substantial increases in yield, therefore making the synthesis of the vicinal diamine motifs very efficient. Furthermore, the fact that paraformaldehyde is readily available and inexpensive makes for a more practical approach to this strategy.

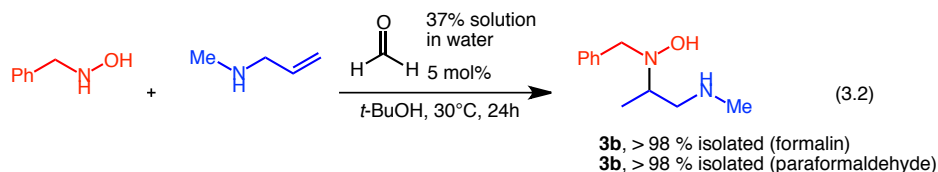
Table 3.1 Comparative reaction scope for the formaldehyde-catalyzed Cope-type hydroamination^a

Entry	Product	Conditions using 2.1	Yields using 2.1	Yield using 3.4
1		C ₆ H ₆ , rt, 24h	75%	85%
2		C ₆ H ₆ , rt, 24h	72%	>98%
3		C ₆ H ₆ , rt, 24h	69%	92%
4		CHCl ₃ , rt, 24h	56%	66% ^b
5		CHCl ₃ , rt, 24h	61%	74% ^b
6		CHCl ₃ , rt, 24h	51%	80% ^b

^a Conditions: 2.1 catalyzed (red): Allylamine (1.5 equiv.), hydroxylamine (1 equiv.), 2.1 (20 mol%), C₆H₆ or CHCl₃ (1 M), 24-96 h. 3.4 (paraformaldehyde) catalyzed (blue): Allylamine (2 equiv.), hydroxylamine (1 equiv.), 3.4 (5 mol%), *t*-BuOH (1 M), 30 °C, 24 h. ^b Using 10 mol% 3.4.

To discover the exact amount of formaldehyde responsible for catalyzing the reaction and to avoid concerns about the depolymerization process, aqueous formalin (37% formaldehyde in water) was tested. Encouragingly, this result was very similar to the result using paraformaldehyde (eq. 3.2) and this finding suggests that the presence of water does not cause significant catalyst inhibition. Formalin was subsequently used as

the source of formaldehyde from this point in studies directed at improving the scope of aldehyde-catalyzed hydroaminations.



Scope of formaldehyde catalyzed Cope-type hydroamination

As formaldehyde was discovered to be a superior catalyst our investigation changed to see if this aldehyde could expand the scope of the reaction and overcome limitations present at this time. A key challenge was the use of internal alkenes as their hydroaminations are notoriously more difficult.⁷⁵

Table 3.2 Cope-type hydroamination of internal alkenes catalyzed by formaldehyde^a

Entry	Allylamine	Product	Yield ^b
1		 3g	80%
2		 3h	97%
3		 3i	83%

^a Conditions: Allylamine (1.5 equiv.), hydroxylamine (1 equiv.), **3.4** (10 mol%)(37% aq. solution in H₂O), *t*-BuOH (1M), 50 °C, 24 h. ^b Isolated yield.

Gratifyingly, formaldehyde was successful in catalyzing the Cope-type hydroamination of internal alkenes with *N*-benzylhydroxylamine in high yields (Table 3.2). *Cis* and/or *trans* alkenes were both well tolerated in this system and led to good reactivity.¹⁰² Given the result reported by Hartwig, that the reaction of styrene and aniline is thermoneutral at 80°C, these examples represent unique results in the hydroamination literature.^{67, 103} This expansion in scope further solidifies this methodology as an efficient way to synthesize vicinal diamines.

Aldehyde scan with consistent conditions

As these mechanistic experiments shed new light on the functionality required for an aldehyde to be effective in our system we thought an aldehyde scan was required to ensure an interesting aldehyde had not been missed. We tested various aldehydes in both CHCl₃ and *t*-BuOH with 25 mol % of aldehyde and a 1:1.5 ratio of *N*-benzylhydroxylamine and *N*-allylbenzylamine. The allylic amine was always in excess due to the inverse order relationship of hydroxylamine observed in the mechanistic studies with α -benzyloxyacetaldehyde (*vide supra*). *N*-Allylbenzylamine was chosen as the substrate, as it is known to have the least amount of background reactivity for this methodology.¹⁰⁴ These experiments would provide a way to compare aldehyde reactivity as most of the aldehydes scans to date were performed under different reaction conditions (solvents and/or amounts of reagents with little consistency), or simply using allylamine rather than a secondary allylic amine. The results were performed by Mr. Didier Bilodeau

¹⁰² MacDonald, M. J.; Hesp, C. R. *Unpublished results*.

¹⁰³ See Chapter 1, Part B: Overview of the Hydroamination of Alkenes, for more information.

¹⁰⁴ See Chapter 2 (Table 2.7) for more information on background activity.

and are summarized in Figure 3.12. This data confirms that formaldehyde (37 wt. % in H₂O) **3.4** and α -benzyloxyacetaldehyde **2.1** are the best aldehydes for this reaction and that *t*-BuOH is critical for formaldehyde activity. Glycolaldehyde and a related α -N-tosyl aldehyde also showed moderate reactivity. This data shows that any aldehyde with an alpha aromatic ring is too stable to display catalytic activity. Furthermore, other aldehydes that are stored as a hydrate (3,3,3-trifluoropropanal and 2,2-dimethoxyacetaldehyde) do not perform well in either solvent and this result has always been difficult to understand. A possible theory for this observation is that these aldehydes may simply be acting as promoters and not catalysts in the reaction.

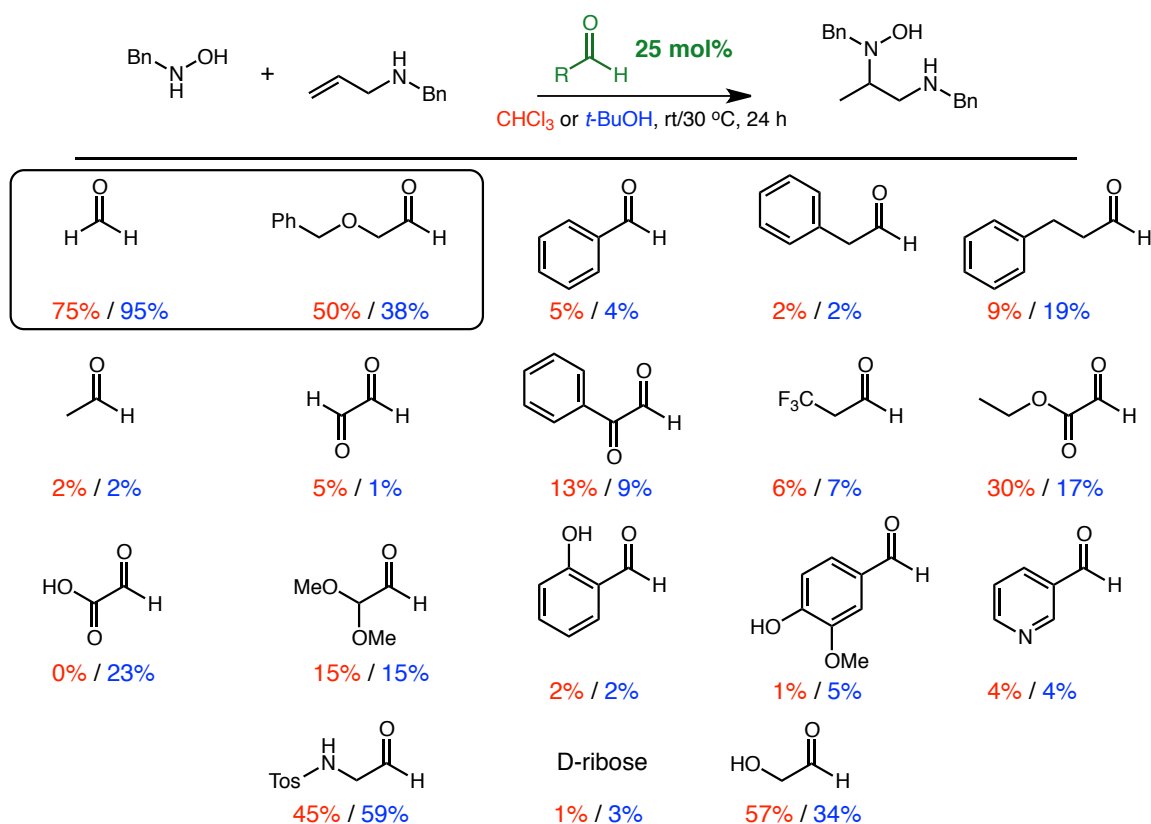


Figure 3.12 Advanced aldehyde scan in CHCl₃ and *t*-BuOH

This aldehyde scan re-confirms the majority of our hypotheses as to which aldehydes can be effective in our catalytic hydroamination strategy.

3.2.2 Role of Aldehydes in Prebiotic Chemistry

Bimolecular reactions are fundamental to chemistry and the role of small organic molecules as catalysts for these complex reactions is still in development.⁸⁸ We have shown that aldehydes are efficient catalysts exploiting temporary intramolecularity in Cope-type hydroamination and began to look at other reactions that could benefit from this strategy. In the literature, reports on the catalysis of hydrolysis reactions are present, and showed significant rate acceleration could be achieved utilizing simple carbonyl compounds.⁸⁸ As most of this work was performed using stoichiometric amounts of catalysts, we became interested in exploring the catalytic efficiency of several carbonyl-containing compounds in the hydrolysis of α -amino nitriles. The underlying hypothesis was to determine if the catalytic activity trends would mirror those observed for hydroaminations. Gratifyingly, the most efficient carbonyl catalysts under conditions using 20 mol % of both catalyst and NaOH were found to be formaldehyde and glycolaldehyde. In addition, these catalysts proved significantly more efficient with hindered substrates (e.g. α -amino nitriles on which the nitrogen atom is substituted; difficult initial addition via preassociation) when compared to other carbonyl compounds. Overall, formaldehyde is a broadly applicable, efficient catalysis for this transformation. A more complete analysis of the project can be found in Mr. Bashir Hussain's thesis

(Figure 3.13).¹⁰⁵

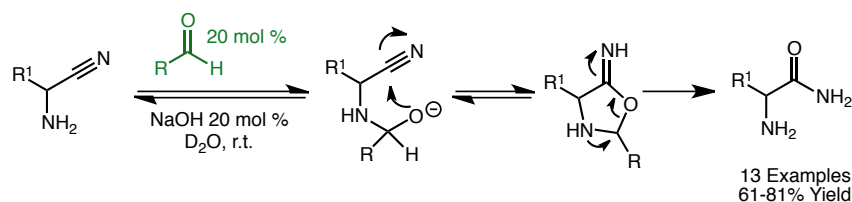


Figure 3.13 α -Aminonitrile hydrolyses via carbonyl catalysis¹⁰⁵

As a result of the success formaldehyde achieved in catalyzing this hydrolysis reaction in water we began to wonder what role aldehydes might have played in the synthesis of amino acids in primitive Earth conditions.¹⁰⁶ Therefore we sought to investigate the reactivity of aldehydes in the context of one of the biggest questions facing scientists: the understanding of the "origin of life" on Earth.

Miller-Urey experiment

One of the most influential and highly discussed experiments in the origin of life debate is the Miller "primordial soup" experiment, reported in 1953.^{107, 108} This experiment was designed to emulate the likely primitive Earth conditions to track and observe any compound synthesis from simple molecules. Using a spark discharge apparatus water was heated with hydrogen (H₂), methane (CH₄) and ammonia (NH₃). After two days, Miller was able to detect the production of glycine and after 2 weeks

¹⁰⁵ Hussain, B. "Catalysis via Induced Intramolecularity: Carbonyl-catalyzed Hydration of α -Amino Nitriles" Submitted MSc. Thesis, University of Ottawa, ON, 2014.

¹⁰⁶ Taillades, J.; Beuzelin, I.; Garrel, L.; Tabacik, V.; Bied, C.; Commeyras, A. *Origins of Life and Evolution of the Biosphere*. **1998**, 28, 61-77. Printed in the Netherlands.

¹⁰⁷ Miller, S. L. *Science* **1953**, 117, 528-529.

¹⁰⁸ Ruiz-Mirazo, K.; Briones, C.; Escosura, A. *Chem. Rev.* **2014**, 114, 285-366.

several other amino acids (e.g. alanine). Given the analytic techniques available at that time, a full analysis of what was formed during the experiment is still debated; however, many decades later the samples were further evaluated to discover that over 20 amino acids were synthesized.¹⁰⁹ Another key discovery was the formation of HCN, formaldehyde, and several carbohydrates presumably from formaldehyde oligomerization (e.g. the formose reaction). Most geoscientists today do not believe the highly reducing conditions of Miller's experiment were present throughout primitive Earth.¹⁰⁹ However, certain volcanic hot spots may have provided isolated systems that would contain the right conditions for these reactions to occur. Given our recent observations on the ability of aldehydes to *efficiently* catalyze the hydrolysis of α -amino nitriles in water we wondered if aldehyde catalysis could help address other questions in the field of origin of life chemistry.

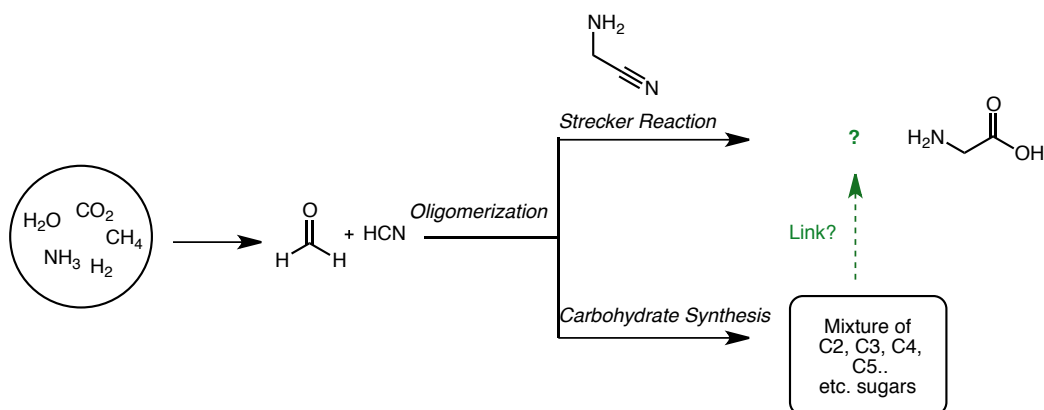


Figure 3.14 Miller-Urey experiment and the possible aldehyde role in the synthesis of amino acids

¹⁰⁹ Bada, J. L. *Earth and Planetary Science Letters* **2004**, 226, 1–15.

Commeyras and co-workers have provided evidence that carbonyl catalysis, either by aldehydes or CO₂, could have helped displacing the equilibrium towards amino acids under primitive earth conditions (Figure 3.14).⁹² Furthermore, could the simplest aldehydes help overcome the low concentration issue inherently associated with the synthesis of complex organic molecules via intermolecular reactions?

"Low concentration issue" under prebiotic conditions

One of the main challenges when discussing the reactions that took place in primitive Earth is trying to explain how they took place under very dilute conditions. There are many theories as to how the key reagents became concentrated enough to initiate the intermolecular reactions necessary for the formation of key amino acids and other critical compounds. The most popular theory focuses on a combination of eutectic brines in shallow ocean water, periodical freezing and evaporation.^{109, 110} Eutectic freezing (combinations of compounds that have a lower freezing point than any other composition of those reagents) has demonstrated that purines, pyrimidines, and amino acids can be concentrated effectively. However it has not been proven that this method is capable of concentrating carbohydrates, even though sugars should be more stable at low temperatures.¹¹¹ Another hypothesis discusses the “frozen clay model”, which focusses on key reactions taking place on a clay-mineral surface. When a clay-water system is frozen, the effect is similar to drying the system, as the water is removed, solutes concentrated and the surface may induce precipitation.¹¹² The remaining hypotheses for

¹¹⁰ (a) Cleaves, H. J. *Precambrian Research*. **2008**, 164, 111–118. (b) Miyakawa, S.; Cleaves, H.; Miller, S. *Orig. Life Evol. Biosph.* **2002**, 32, 209–218. (c) Sanchez, R.; Ferris, J.; Orgel, L. *Science* **1966**, 153, 72–73.

¹¹¹ Larralde, R.; Robertson, M.; Miller, S. *Proc. Natl. Acad. Sci. USA* **1995**, 92, 8158–8160.

¹¹² (a) Lahav, N.; Chang, S. *J. Mol. Evol.* **1976**, 8, 357–380. (b) Lahav, N.; Anderson, D. M. *Clay and Clay*

the concentration problem are more specific for reagents instead of addressing a larger area. For example, it is believed that formaldehyde can dimerize to glycolaldehyde, a less volatile compound, to remain concentrated.¹¹³ A final theory investigates the geochemical process and impact UV and visible light had on dilute solutions of key reagents such as HCN, and formaldehyde. These compounds could have been concentrated under UV and visible light during evaporation or periodical freezing.¹¹⁴

The exact explanation for how these simple molecules became present in concentrations high enough for intermolecular reactions to occur is most likely a combination of all the theories presented. However, even considering the hypotheses mentioned above, the intermolecular reactions necessary for formation of key intermediates must have been extremely difficult under moderately dilute conditions. This is particularly true for challenging reactions, which typically require catalysis at room temperature for moderate efficiency. Therefore we wondered if aldehyde catalysis might have catalyzed intermolecular reactions — through temporary intramolecularity — and thus allowed difficult intermolecular reactions to occur under dilute conditions.

Aldehyde catalyzed Cope-type hydroamination in water

To address this question we became interested in studying intermolecular Cope-type hydroaminations in water, thus using this reaction as a model for difficult prebiotic

Minerals **1973**, *21*, 137-139.

¹¹³ The equilibrium constant for this dimerization is unknown, however Weber and *et al.* published a rudimentary calculation of approximately 40. Weber, A. *Orig. Life Evol. Biosph.* **2002**, *32*, 333–357.

¹¹⁴ Bocclair, J.; Braterman, P.; Brister, B.; Jiang, J.; Lou, S.; Wang, Z.; Yarberry, F. *Orig. Life Evol. Biosph.* **2001**, *31*, 53–69.

reactions. An optimization study was performed for the Cope-type hydroamination of *soluble* allylamine (or *N*-methylallylamine) and *N*-methylhydroxylamine in D₂O (see Table 3.3).¹¹⁵ All of the aldehydes tested showed product formation in 24 hours with either allylamine or *N*-methylallylamine at room temperature or 50 °C. Formaldehyde remained the most successful at overcoming the preassociation between the two starting materials and the 60% NMR yield with allyl amine was noteworthy. Glycolaldehyde (formaldehyde dimer) was quite effective at 30% NMR yield with *N*-methylallylamine.

Table 3.3 Aldehyde catalyzed Cope-type hydroamination in water^a

Reaction scheme: CH2=CH-CH2-NH-R1 + Me-N(OH)H.HCl >> [Aldehyde (x %)] >> Me-N(OH)-CH2-CH2-NH-R1

Aldehyde	R ¹	mol %	Temperature (°C)	NMR Yield (%) ^b
	Me	10	r.t.	37
	H	10	r.t.	60
	Me	20	r.t.	30
	H	20	r.t.	10
	Me	20	r.t.	5
	Me	20	50	17
	H	20	r.t.	8
	Me	20	r.t.	0
	Me	20	50	13
	Me	20	r.t.	2
	H	20	r.t.	2
No aldehyde	Me	–	r.t.	27
No aldehyde	H	–	r.t.	3

^a Conditions: Allylamine (2.5 equiv.), hydroxylamine (1.equiv.), (x mol %) of aldehyde 24 hours, D₂O (1M). ^b Determined by ¹H NMR spectroscopy with 1,4-dimethoxybenzene as internal standard.

Ribose and threose showed less catalytic activity but product formation was still present

¹¹⁵ MacDonald, M.J. *Unpublished results*.

in 24 hours. Control experiments (no aldehyde) were performed with both starting materials at room temperature. *N*-Methylallylamine showed a 27% NMR yield and allylamine was much less at 3%. These results suggest that the aldehyde component in certain entries could be a source of inhibition.

Overall, this experiment shows support that aldehydes may be capable of catalyzing difficult bimolecular reactions in water in modest to good yields. This preliminary study thus constitutes a proof of concept, performed at high concentration (1 M in water), showing that catalytic tethering reactivity is plausible as a hypothesis in chemical evolution. More experiments are needed to study aldehyde catalysis for other bimolecular reactions in water, to study stoichiometric variants, and to expand these studies to reactions performed under more dilute conditions achievable through the other concentration mechanisms discussed above.

3.3 Summary and Outlook

A preliminary mechanistic evaluation of the organocatalytic tethering strategy applied towards the Cope-type hydroamination of hydroxylamine and allylic amines was presented. As a result of experiments performed by Mr. Nicolas Guimond the reaction was found to be first order in catalyst and allylic amine but inverse order in the hydroxylamine reagent. These experiments suggested an off-cycle pathway that led to a symmetrical adduct and the possible resting state of the catalyst. Equilibrium constants between the main nitron and the various possible amins were evaluated and confirmed the thermodynamic preference for the symmetrical adduct. Several other equilibria were also evaluated using different nitrones to provide insight towards a hypothesis on

why certain aldehydes favour preassociation.

As a result of the mechanistic data a new aldehyde was discovered that displayed improved reactivity. A comparative study was performed on six substrates to showcase the yield advancement of formaldehyde as opposed to α -benzyloxyacetaldehyde. Using only 5 mol % catalyst loading of formaldehyde allowed an increase in yield of 10-20 % for each entry compared to catalyst **2.1**. Formaldehyde was also able to expand the scope of this catalytic tethering strategy by allowing the hydroamination of internal allylic amines in high yield.

The discovery of formaldehyde as an effective aldehyde catalyst led to an application in the prebiotic chemistry research area. The Cope-type hydroamination of allylic amines and *N*-methylhydroxylamine in water was catalyzed by several aldehydes. This implies that aldehydes could help overcome the plausible low concentration problem in primitive Earth, by inducing temporary intramolecularity.

In the next chapter, more efforts will be placed on the asymmetric version of this reaction to yield highly enantioenriched diamines. Chiral aldehydes will be synthesized and tested in a variety of conditions to discover the best way to induce asymmetry.

Using Chiral Aldehydes as Tethering Catalysts to Induce Asymmetry with Applications in Intermolecular Hydroamination and Conjugate Additions

4.1. Introduction

This chapter will elaborate on the details of the intermolecular Cope-type hydroamination catalyzed by chiral aldehydes leading to enantioenriched diamines. An aldehyde synthetic design and discovery strategy will be presented, followed by optimization and a substrate scope study. Mechanistic insight into these new catalysts will be discussed along with a detailed study on the source of epimerization. A rationale for stereo-induction will be discussed. Finally, alternative reactions for the application of an aldehyde catalyzed tethering strategy will be explored.

4.1.1 Asymmetric Hydroamination

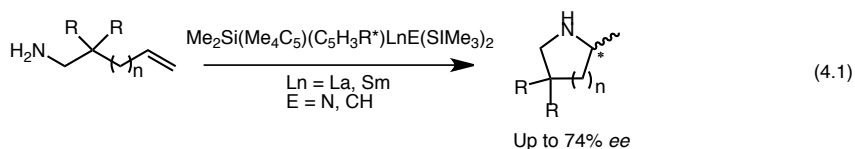
Due to the importance of nitrogen-containing molecules, the development of efficient and selective C-N bond methodologies continues to attract significant research interest by academic and industrial chemists. Hydroamination, given its atom economical nature, simplicity, and readily available starting materials, has garnered much attention over the past two decades. However, as mentioned in Chapters 1 and 2, asymmetric

alkene hydroamination reactions remain severely underdeveloped and intermolecular accounts are very rare.¹¹⁶ The majority of reports have focussed on the use of transition metal catalysts and chiral ligands to overcome the challenges of this reaction, which include a high activation energy, a negative entropy, and a near thermoneutral process.^{81,67}

4.1.2 Enantioselective Intramolecular Hydroamination

Metal catalyzed asymmetric hydroamination

In stark contrast to intermolecular hydroamination, asymmetric intramolecular hydroamination has allowed access to a variety of enantiopure cyclic saturated heterocycles. The first ever report was published in 1992 by Tobin J. Marks and co-workers.¹¹⁷ They showed that chiral organolanthanide complexes were capable of catalysis in the cyclization of amino alkenes with moderate selectivity (up to 74% *ee*) (eq. 4.1). This efficient transformation was the starting point for this methodology and showed promise for this reaction in the future in terms of selectivity.

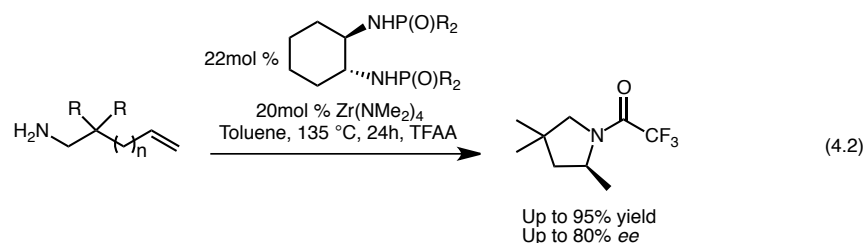


Over the last two decades, several advancements were made towards this methodology regarding reactivity, selectivity and catalyst design. A key discovery was

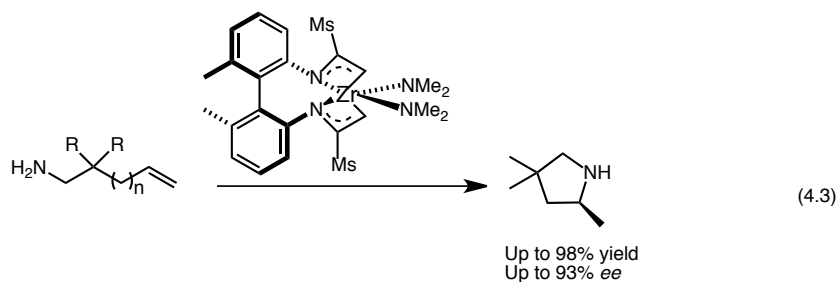
¹¹⁶ Hannedouche, J.; Schulz, E. *Chem. Eur. J.* **2013**, *19*, 4972-4985.

¹¹⁷ Gagne, M. R.; Brard, L.; Conticello, V. P.; Giardello, M. A.; Stern, C. L.; Marks, T. J. *Organometallics* **1992**, *11*, 2003-2005.

group 4 bis(amido) complexes focussing on zirconium and the use of chiral diamine ligand to induce asymmetry (eq. 4.2). Bergman published this concept in 2006, which showed a significant advancement in yields and *ee*'s up to 80%.¹¹⁸



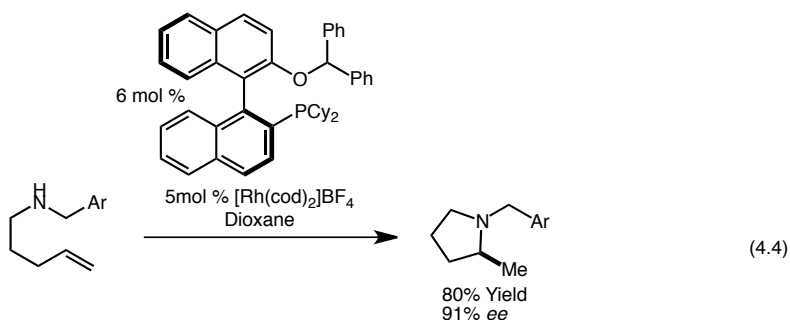
Later that year, using a chiral neutral amidate zirconium complex, Schafer *et al.* set the bar higher at 93% *ee* for the intramolecular hydroamination of an unactivated alkene (eq. 4.3).¹¹⁹ The group was able to synthesize many heterocycles including bicyclic compounds in good selectivity. Despite these reports and other developments in the literature, there was still a limitation on the use of substituted alkenes and mild conditions for these asymmetric cyclizations. Furthermore, functional group tolerance was very low and the majority of high enantioselectivities observed were limited to 5-membered cyclizations.



¹¹⁸ Watson, D.A.; Chiu, M.; Bergman, R.G. *Organometallics* **2006**, 25, 4731-4733.

¹¹⁹ Wood, M. C.; Leitch, D. C.; Yeung, C. S.; Kozak, J. A.; Schafer, L. L. *Angew. Chem. Int. Ed.* **2007**, 46, 354-358.

Buchwald and co-workers published a significant advancement in this field in 2010 with a rhodium-catalyzed intramolecular hydroamination.¹²⁰ This was one of the first cyclizations that reported reactivity without assistance from the Thorpe-Ingold effect. This is a paramount accomplishment as intramolecular Cope-type cyclizations rely heavily on this activation mode. Enantioenriched 2-methylpyrrolidines were synthesized using this approach in up to 91% *ee* with chiral dialkylbiaryl phosphines as ligands (eq. 4.4).



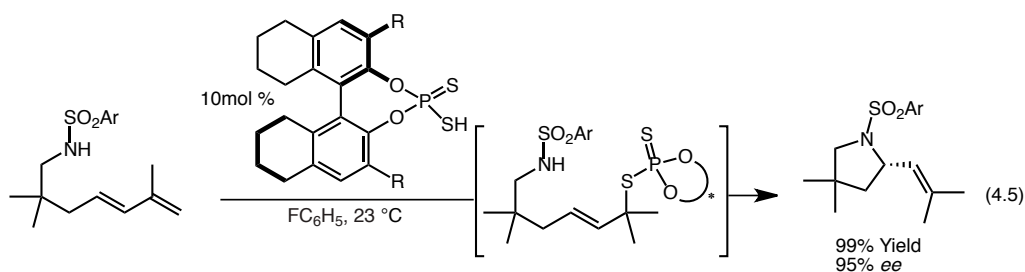
Metal free asymmetric hydroamination

A highly selective, novel metal-free approach to asymmetric diene hydroamination was reported by Toste and showcases a chiral dithiophosphoric acid catalyst.¹²¹ One of the difficulties with selective additions to alkenes catalyzed by chiral acids is the formation of a carbocation and the lack of interactions between that carbocation and the conjugate base. With only electrostatic interactions the lack of proximity of the chiral conjugate base often prevents a selective preference for one face of the molecule. Therefore Toste and coworkers developed a clever strategy to have a

¹²⁰ Shen, X.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2010**, *49*, 564-567.

¹²¹ Shapiro, N. D.; Rauniyar, V.; Hamilton, G. L.; Wu, J.; Toste F. D. *Nature* **2011**, *470*, 245-250.

nucleophilic conjugate base that would attack the diene and form a covalent bond. As a result, the intramolecular cyclization could displace the conjugate base and form an enantiopure heterocycle (eq. 4.5). The results were outstanding with quantitative yields and > 99% *ee* for several substrates. These results were even more impressive as the conditions were metal free and relatively mild.



In 2013 the first enantioselective hydrogen bonding catalyzed Cope-type hydroamination was reported by Jacobsen and co-workers (Figure 4.1).¹²² The group used chiral thiourea derivatives to stabilize the bicyclic dipolar transition state and induce asymmetry. This resulted in enantioenriched α -substituted pyrrolidines in very high enantioselectivity (up to 97% *ee*). However, this method was limited to 5-membered ring cyclizations and the majority of substrates benefited from the presence of a Thorpe-Ingold effect.

¹²² Brown, A. R.; Uyeda, C.; Brotherton, C. A.; Jacobsen E. N. *J. Am. Chem. Soc.* **2013**, *135*, 6747-6749.

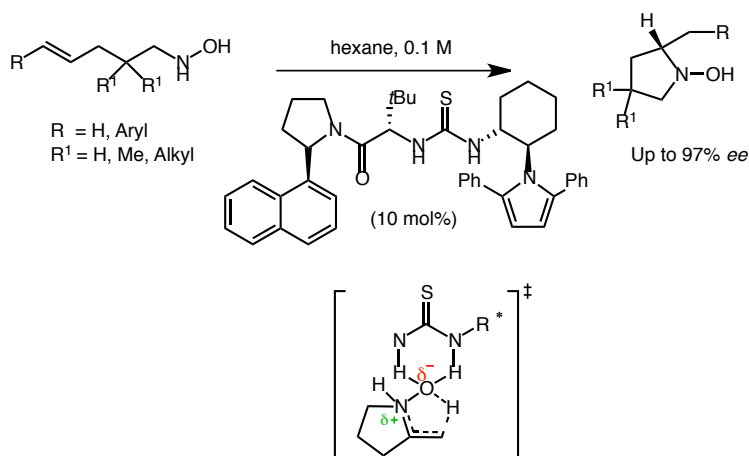


Figure 4.1 Thiourea-catalyzed intramolecular Cope-type hydroamination

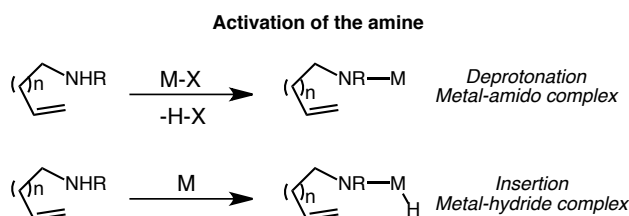
As seen above the enantioselective intramolecular alkene hydroamination has developed dramatically since 1992. Through the use of a variety of transition metal catalysts, dithiophosphoric acids, and hydrogen donors the ability to form enantiopure heterocycles has been reported. However, scope limitation for more difficult substrates such as substituted and internal alkenes still present a challenge. Presently, the enantioselective intramolecular hydroamination of alkenes is approaching a simple solution that is effective and widely applicable. In contrast, enantioselective intermolecular alkene hydroaminations remain very substrate specific, and severely underdeveloped.

4.1.3 Enantioselective Intermolecular Hydroamination

Intermolecular asymmetric hydroamination is extremely rare and suffers from a very high activation energy and lack of directed examples. In the past for intramolecular hydroamination several metals have either activated the amine moiety through a

deprotonation mechanism to form a metal-amido complex, or via an oxidative insertion pathway, which leads to a metal hydride (Scheme 4.1).¹²³ Although effective in achieving cyclizations, these strategies are challenged by the necessity to also overcome the entropic cost associated with intermolecular hydroamination. Attempting to activate the alkene through a Lewis acidic late transition metal or carbocation formation has been limited.¹²⁴

Scheme 4.1 Activation of the amino functional group to promote hydroamination



Iridium catalysis

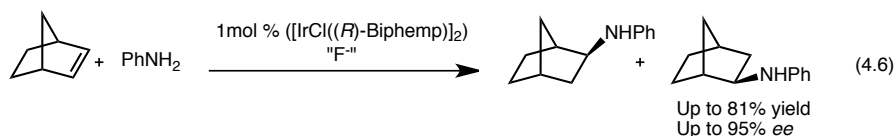
Togni and co-workers published the first report of asymmetric intermolecular hydroamination in 1997.¹²⁵ Recognizing that a fluoride ion could enhance reactivity they were able to react norbornene with aniline using an iridium catalyst in up to 95% *ee* (eq. 4.6). They speculated that the good π -donating properties of fluoride as a ligand and its ability to form hydrogen bridges enhanced the N-H oxidative addition pathway. Despite the high *ee* values, the yields of the reaction were quite low and balancing reactivity and selectivity was a challenge. Nonetheless, this report was key in developing the field of

¹²³ (a) Tobisch, S. *Dalton Trans.* **2012**, 41, 9182-9191. (b) Motta, A.; Lanza, G.; Fragala, I. L.; Marks, T. J. *Organometallics* **2004**, 23, 4097-4104. (c) Sevov, C. S.; Zhou, J. S.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, 134, 11960-11963.

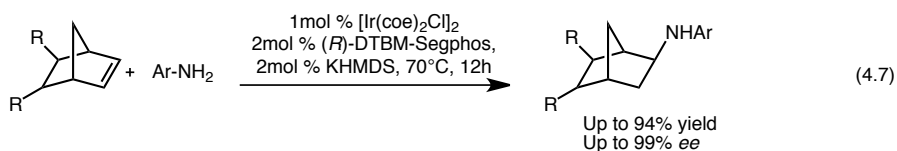
¹²⁴ Hesp, K. D.; Tobisch, S.; Stradiotto, M. *J. Am. Chem. Soc.* **2010**, 132, 413-426.

¹²⁵ Dorta, R.; Egli, P.; Zurcher, F.; Togni, A. *J. Am. Chem. Soc.* **1997**, 119, 10857-10858.

asymmetric intermolecular hydroamination.



Hartwig *et al.* published significant advances with an iridium-catalyzed process by replacing the fluoride ion with an organic base to generate an arylamide in situ.¹²⁶ Hartwig hypothesized that the benefits of the fluoride ion could have come from the species acting as a base and generating small amounts of an arylamide. Therefore the addition of organic bases resulted in a dramatic increase in reactivity while maintaining the selectivity of the reaction. Several variations of 2-norbornylamine were synthesized with high enantioselectivity (eq. 4.7). A limitation in this methodology was the use of biased/strained alkenes, expensive catalysts and harsh conditions.



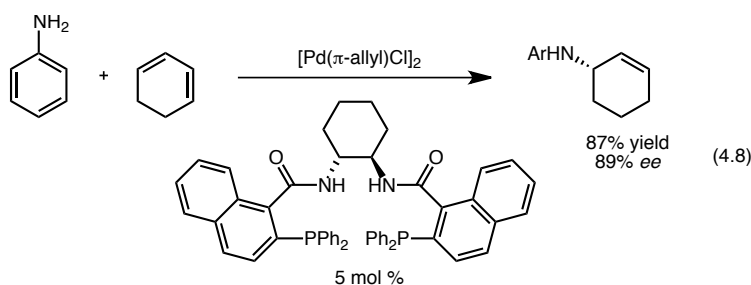
Palladium catalysis

A noteworthy achievement was also reported by Hartwig using palladium to catalyze the hydroamination of 1,3-dienes and aniline derivatives (eq. 4.8).¹²⁷ Utilizing chiral diamines several enantioenriched allylic amines were synthesized in modest yields (59-83%). The scope of allylic amines that were synthesized was very restricted but the

¹²⁶ (a) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546-9547. (b) Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14286-14287. (c) Zhou, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 12220-12221.

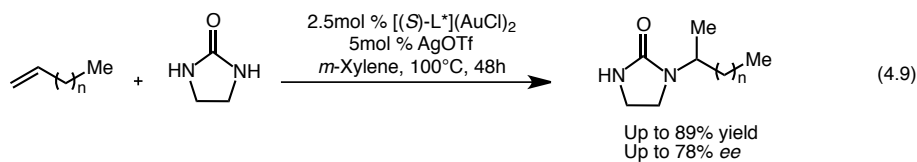
¹²⁷ Löber, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366-4367.

enantioselectivities observed were impressive for this time.



Gold catalysis

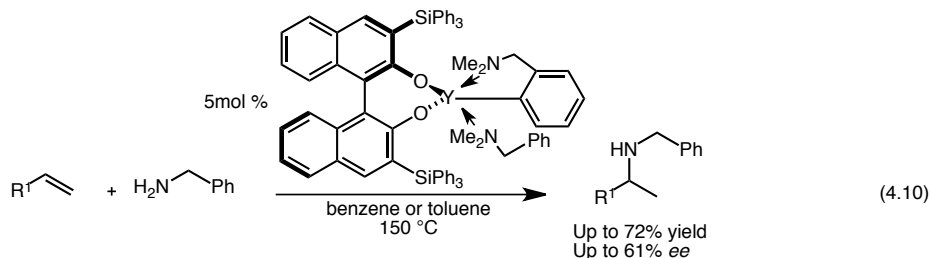
One of the first examples of an enantioselective intermolecular hydroamination on an unactivated alkene was reported in 2009. Widenhoefer and co-workers showed that the reaction of simple alkenes with cyclic ureas could be catalyzed by gold complexes (eq. 4.9).¹²⁸ The ability of gold to activate carbon-carbon multiple bonds makes it an attractive metal for hydroamination. This resulted in excellent yields (76-89%) with moderate enantioselectivities (71-78%). Despite the difficult nature of this reaction on an unactivated alkene, the observed selectivity is very good. The major restriction with this methodology was a very specific substrate scope that only allowed cyclic ureas as the amine moiety.



¹²⁸ Zhang, Z.; Du Lee, S.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 5372-5373.

Rare earth metal-catalysis

The reactivity of alkenes was further developed by Hultzsch *et al.* using rare earth metal catalysts.¹²⁹ This catalysis operates by synthesis of a rare earth metal-amido species, followed by olefin insertion and protonation. This methodology showed a broad substrate scope of alkyl alkenes and a variety of benzyl amines (eq. 4.10). With a substantial excess of alkene (10:1) the reactivity was very good (up to 72%) and displayed moderate *ee* (up to 61%). Utilizing anilines allowed through the use of this method the synthesis of chiral primary aminoalkanes, after the relatively easy removal of the benzyl group through hydrogenation.



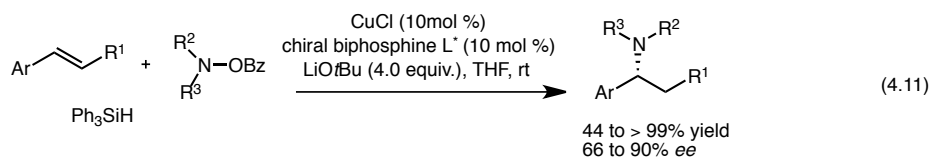
Copper metal-catalysis

Recently, a formal hydroamination of styrenes with polymethylhydrosiloxane (PMHS) and hydroxylamines catalyzed by copper showed excellent selectivity. Miura and co-workers were able to perform this reaction at room temperatures on a variety of styrenes including challenging β -substituted reagents (eq. 4.11).¹³⁰ Using several chiral biphosphine ligands good selectivities were observed (up to 90% *ee*). To-date, the work of Miura is one of the highest reported intermolecular enantioselective hydroaminations

¹²⁹ Reznichenko, A. L.; Nguyen, N. H.; Hultzsch, K. C. *Angew. Chem. Int. Ed.* **2010**, 49, 8984-8987.

¹³⁰ (a) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2013**, 52, 10830-10834. (b) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Org Lett.* DOI: 10.1021/ol5003219.

of a styrene-based alkene.¹³¹



As demonstrated through the above examples, intermolecular enantioselective hydroamination remains a challenge, as the narrow substrate scope, the lack of mild conditions, and low selectivities are still unsolved problems. The Beauchemin group therefore embarked on a challenge to expand the substrate scope of our previously presented hydroamination methodology to perform highly enantioselective Cope-type hydroaminations solely via temporary intramolecularity. Taking advantage of the strongly encouraging results on intermolecular reactivity, and high control associated via an "intramolecular" hydroamination event, our strategy had a significant chance of providing excellent selectivity, using the appropriate catalysts. Expanding on the results explored in Chapter 2 the project began with a screen of chiral aldehydes.

4.2 Results and Discussion

From the early designs of our organocatalytic approach to tethering, the possibility of efficiently inducing selectivity and particularly asymmetry only through temporary intermolecularity was always at the forefront. In Chapter 2 a preliminary investigation was carried out utilizing aldehyde catalysts **2.2** and **2.3**. At the time epimerization of the catalyst was a constant concern and the aldehydes displayed limited

¹³¹ Shortly after this was published, a very similar approach was also reported: Zhu, S.; Nootaree, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 15746–15749.

stability. Therefore, in order to optimize the selectivity a chiral aldehyde scan was performed with the assistance of Mr. Colin Hesp.¹³² Emphasis was placed on synthesizing aldehydes derived from carbohydrates, as they are naturally enantiopure and have a wealth of literature on their functionalization (Table 4.1). This optimization revealed that several aldehydes can be competent organocatalysts. Unfortunately Ley's aldehyde (**4a**) and Garner's aldehyde (**4b**) displayed poor reactivity (Entries 3 and 4). In the hopes of removing the source of epimerization, an aldehyde was synthesized that did not contain an α -proton (**4e**); however, this resulted in presumably too much steric hindrance and showed little reactivity (Entry 5). This suggests that the initial preassociation is very sensitive to steric bulk. Catalyst **4g** was the first aldehyde to provide access to the opposite enantiomer (*R*) of catalyst **2.3** in very high enantiomeric excess (Entry 7). We also explored bi-cyclic aldehydes with multiple stereocentres to avoid suspected epimerization and help ensure a memory of chirality¹³³ (Entry 8). Aldehyde **4h** gave very consistent and excellent results with (-) 94 % *ee* and access to the opposite enantiomer of aldehyde **2.3**. Aldehydes adjacent to 5,6-membered cycles with rigid structures provided the best results. This is in contrast to acyclic aldehydes (**4f**) that have too much rotation and are prone to epimerization via enamine formation. A solvent dependence was also observed, and an increase in enantiomeric excess could be seen in

¹³² Hesp, C. "Submitted" Msc. Thesis, University of Ottawa, ON, 2013.

¹³³ For reviews on asymmetric synthesis via memory of chirality: a) Kawabata, T.; Fuji, K. *Top. Stereochem.* **2003**, *23*, 175-205. b) Zhao, H.; Hsu, D. C.; Carlier, P. R. *Synthesis*, **2005**, *1*, 1-16. c) Kawabata, T, *Asymmetric Synthesis and Application of α -AminoAcids*, ACS Symp. Ser., **2009**, *1009*, 31-56. (d) Seebach, D.; Sting, A. R.; Hoffman, M. *Angew. Chem.* **1996**, *108*, 2881-2921.

hexafluorobenzene presumably due to π -stacking on the catalyst and/or carbohydrate- π interactions¹³⁴ (Entries 10-12).

Table 4.1 Representative results of chiral aldehyde screening^a

Entry	Catalyst	Solvent	Yield (%) ^b	ee (%) ^c
1	2.2	C ₆ H ₆	93	75
2	2.3	C ₆ H ₆	91	88
3	4a	C ₆ H ₆	16	37
4	4b	C ₆ H ₆	12	9
5	4e	C ₆ H ₆	5	3
6	4f	C ₆ H ₆	16	9
7	4g	C ₆ H ₆	51	(-) 85
8	4h	C ₆ H ₆	41	(-) 94
9	4f	C ₆ H ₆	34	8 ^d
10	4g	C ₆ F ₆	54	(-) 94 ^d
11	4h	C ₆ F ₆	46	(-) 93 ^e
12	2.3	C ₆ F ₆	91	97 ^d

^a Conditions: hydroxylamine (1 equiv), allylamine (1.5 equiv), and catalyst **2.2**, **2.3**, **4a–h** (0.2 equiv) in a solvent (1 M) under argon, for 24 h at room temperature. ^b Determined by ¹H NMR spectroscopy with 1,4-dimethoxybenzene as internal standard. ^c Determined by chiral HPLC analysis of derivatized products (see the Supporting Information). ^d Catalyst was added to the reaction mixture last. ^e At 10 mol %, catalyst **4h** gave 89% ee with a 43% NMR yield in 72 h.

¹³⁴ Laughrey, Z. R.; Kiehna, S. E.; Riemen, A. J.; Waters, M. L. *J. Am. Chem. Soc.* **2008**, *130*, 14625-14633.

As epimerization was always a concern an experiment was run, ensuring the addition of the catalyst would be made last. There was a significant chance the longer the aldehyde was in contact with either nucleophilic starting material, the greater chance of epimerization. This result gave the highest *ee* we have seen with any chiral aldehyde with 97 % *ee* (Entry 12). At this time a solvent/temperature scan was performed to ensure optimal conditions were found (Table 4.2).

Solvent scan

During this optimization scan different solvents and conditions were tested, varying both catalyst and substrate concentration (Table 4.2). The reaction was surprisingly robust and many different solvents proved to display moderate to good enantiomeric excess (80-83% *ee*). Maintaining a high concentration of solvent (Entry 8) and room temperature (Entry 14, 16-17) proved to be essential. Not surprisingly the reaction was extremely slow at lower temperatures or under dilute conditions. As seen in Entry 18 adding the catalyst last and using C₆F₆ as the solvent gave the best yield and *ee*, which therefore concluded our tests for optimized conditions. In addition, catalyst **2.3** and **4h** provide access to both enantiomers of the diamines and with these optimized conditions, the substrate scope of each catalyst could then be determined.¹³⁵

¹³⁵ Mr. Colin Hesp assisted with this solvent scan.

Table 4.2 Optimization of aldehyde 2.3 reactivity^a

Entry	Catalyst	Solvent	% <i>ee</i>	Conc	NMR Yield ^f
1	20%	Benzene	83	1 M	83
2	20%	THF	83	1 M	82
3	20%	<i>i</i> PrOH	63	1 M	59
4	30%	THF	81	1 M	82
5	20%	Chloroform	81	1 M	78
6	20%	DCE	81	1 M	70
7	20%	Toluene	85	1 M	73
8	20%	Benzene	81	0.25 M	40
9	20%	C ₆ F ₆	88	1 M	66
10	20%	Benzene	83	1 M	89 ^b
11	10%	C ₆ F ₆	68	1 M	60
12	20%	1,2 - DCB	81	1 M	70
13	20%	1,3,5-TFB	85	1 M	78
14	20%	C ₆ F ₆	81	1 M	71 ^c
15	20%	TFT	82	1 M	68
16	20%	Toluene	80	1 M	10 ^d
17	20%	TFT	66	1 M	7 ^d
18	20%	C ₆ F ₆	97	1 M	85 ^e

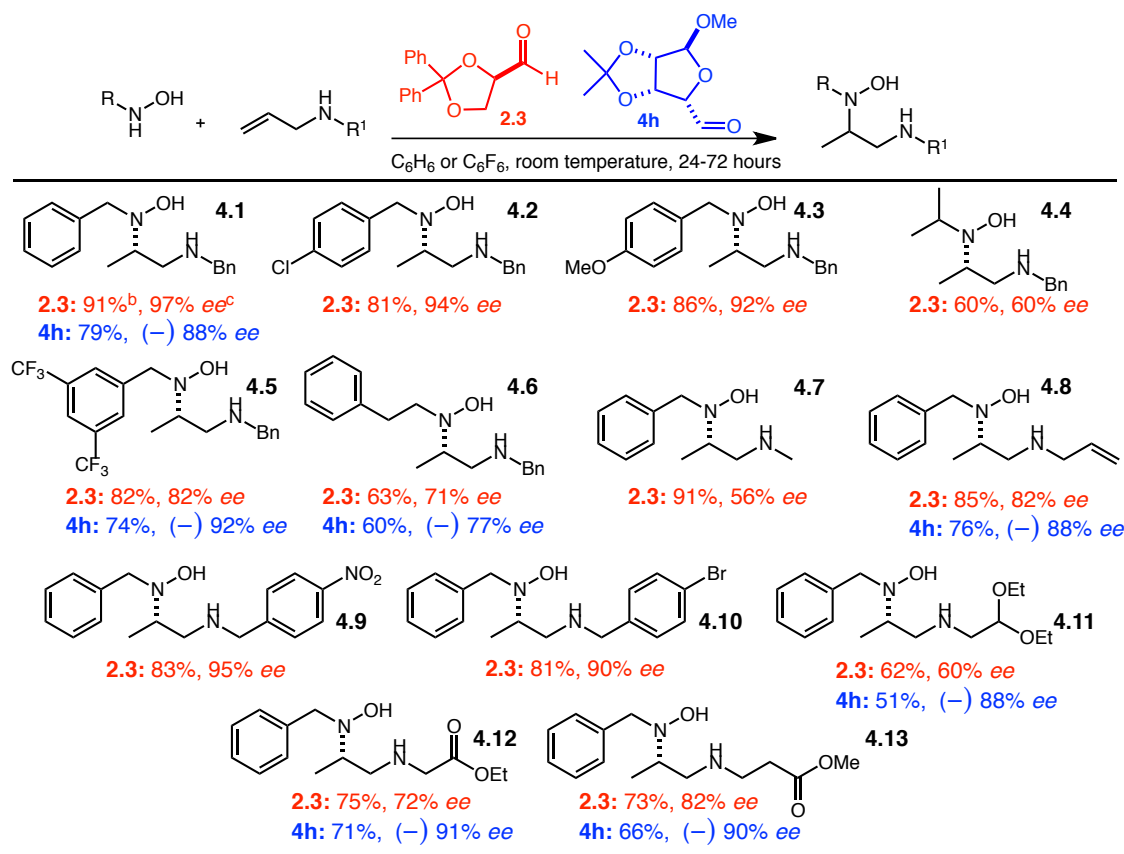
^a Conditions: Hydroxylamine (1 equiv), allylamine (1.5 equiv), catalyst (x mol %), solvent (1 M), room temperature. ^b Reverse order of addition for two starting materials. ^c 50 °C. ^d -20 °C. ^e Added catalyst last. ^f Determined by ¹H NMR spectroscopy with 1,4-dimethoxybenzene as internal standard

Scope of the asymmetric aldehyde catalyzed Cope-type hydroamination of alkenes

The results of the substrate scope study are outlined in Table 4.3.¹³⁶ Electron-poor and electron-rich benzylic hydroxylamines displayed excellent selectivity (82-97% *ee*) when reacted with benzylallylamine (**4.1-4.3** and **4.5**). However, aliphatic hydroxylamines resulted in a reduced product *ee* when reacted with the same allylic

¹³⁶ Mr. Colin Hesp assisted with this substrate scope.

Table 4.3 Scope of asymmetric hydroaminations using chiral aldehydes^a



[a] Performed with 1 equiv. of hydroxylamine, 1.5 equiv. catalyst, in solvent (1M) under argon, for 24 hours with catalyst **2.3** (and 72 hours with **4h**) at room temperature. [b] Isolated yields. [c] Determined using chiral HPLC analysis of derivatized products (see Appendix II).

amine (**4.4** and **4.6**). To test the effect of the nature of the amine on selectivity, methylallylamine was reacted and resulted in excellent product yields but very low enantioselectivity. This provides strong support for the selective initial 1,2-addition being extremely important for high *ee*. Several secondary amines were reacted with both the catalyst derived from D-mannitol (**2.3**) and the aldehyde derived from D-mannose (**4h**) to give a range of selectivities. These results showed that aldehyde **2.3** was very sensitive to the nature of the allylic amine. If the amine was electron-rich the selectivity was high, (**4.1**, 97% *ee*) but lower selectivity was observed for less nucleophilic amines (**4.11**, 60%

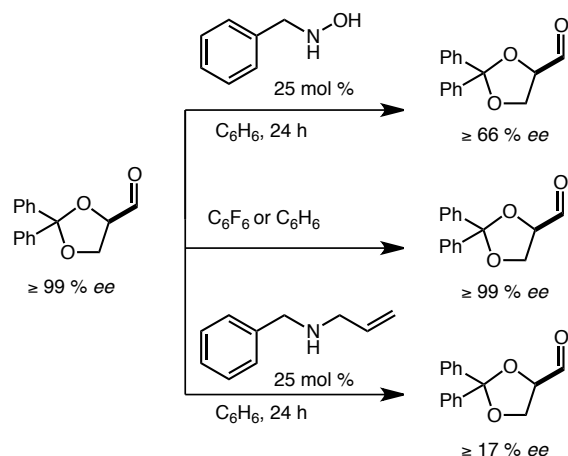
ee). Therefore, the hypothesis is that a more nucleophilic amine leads to a faster hydroamination reaction, relative to catalyst epimerization (or racemization) side reaction. In contrast with aldehyde **4h** the enantioselectivities are more consistent and reliable (77-92% *ee*). Catalyst **4h** is obviously more robust and less prone to epimerization. Overall, the enantioselectivities obtained are, in many cases, the highest reported for intermolecular hydroaminations of unactivated alkenes by any method (including metal-catalyzed reactions). These results confirm this tethering strategy as an effective approach in asymmetric organocatalysis, and are to the best of our knowledge the highest enantioselectivities obtained for an asymmetric reaction catalyzed by an aldehyde.

Investigation on catalyst epimerization

In order to understand the origin of the epimerization process and hopefully discover a way to minimize or prevent a likely cause of erosion of enantioselectivity, several studies were performed (Scheme 4.2). The first focused on aldehyde **2.3** by testing the enantiopurity of the catalyst after interacting with each of the separate reagents in the reaction. We exposed this aldehyde to 25 mol% of each reagent to facilitate recovery of the aldehyde after being exposed to the reaction conditions. The results in scheme 4.2 show that aldehyde **2.3** is very stable in both solvents used in the reaction. However, both the hydroxylamine and allylic amine reagents when mixed with the catalyst separately promoted significant racemization. This confirms the theory that a fast reaction would provide better selectivity with aldehyde **2.3**, by preventing excessive catalyst racemization. However, it should be emphasized that in the presence of an excess

of allylic amine or hydroxylamine, formation of amins could also help minimize aldehyde racemization (or epimerization).

Scheme 4.2 Probing the source of racemization for catalyst **2.3**



To confirm the robustness of the catalyst derived from D-mannose (**4h**) Mr. Colin Hesp synthesized the nitrone and subjected this compound to the same experiments as aldehyde **2.3**. The aldehyde was separately mixed with each species in the reaction, including solely the solvent, and tested for epimerization after 24 hours. As seen in Figure 4.2 the NMR of the nitrone is nearly identical to the experiments with either reagent. There is no sign of diastereoisomers, which would indicate epimerization of the catalyst. Therefore, aldehyde **4h** is more robust presumably due to prevention of enamine formation or through selective protonation after enamine formation, which in both cases could be derived from its bicyclic nature.

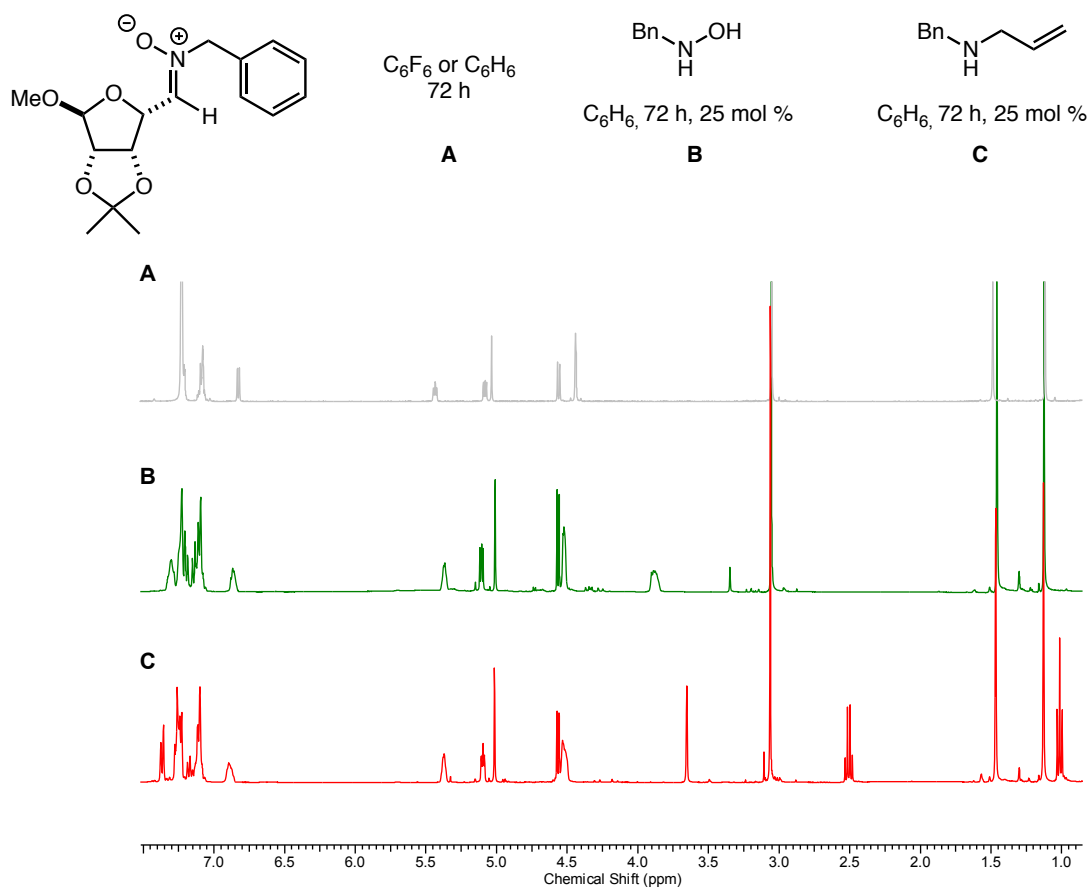


Figure 4.2 Probing the source of epimerization for catalyst **4h**

Mechanism and rational of stereoinduction

The mechanism for the reaction has been fully studied for its racemic counterpart in Chapter 3. Differences for the asymmetric system include the fact that it starts from the condensation between the aldehyde and hydroxylamine to form an aminor, which is then attacked by the allylamine in a likely highly diastereoselective 1,2-addition. This results in the formation of a stereocentre on the tethering carbon atom of the aminor intermediate, which is likely efficiently transferred due to the rigid bicyclic transition state associated with Cope-type hydroaminations (Figure 4.3).

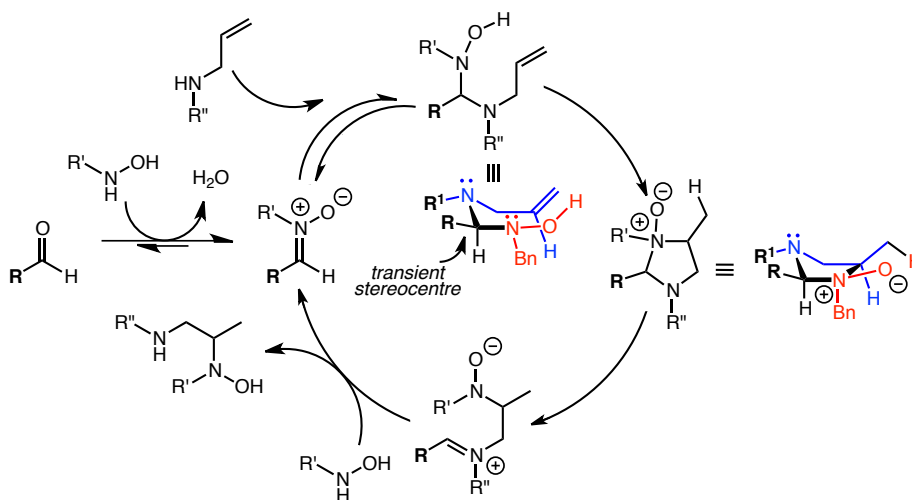


Figure 4.3 *Enantioselective hydroamination originating from a transient stereocentre formed via a stereoselective 1,2-addition*

Considering the hydroamination event was discovered to be rate determining with α -benzyloxyacetaldehyde it is not clear if the selectivity comes from a stereoselective 1,2-addition onto the nitron, or a preference for the cyclization (hydroamination) of one of the two transient aminals, or a combination of the two rate determining steps operating

synergistically.

It is also critical that the hydroxylamine be more nucleophilic than the allylamine to ensure nitron synthesis, as opposed to iminium formation (see Figure 4.4). Iminium formation, condensation of the allylamine on the aldehyde, could lead to mixtures of diastereomers. This occurs through a separate 1,2 addition, and could be a cause of the poor *ee* observed with less reactive aldehydes.

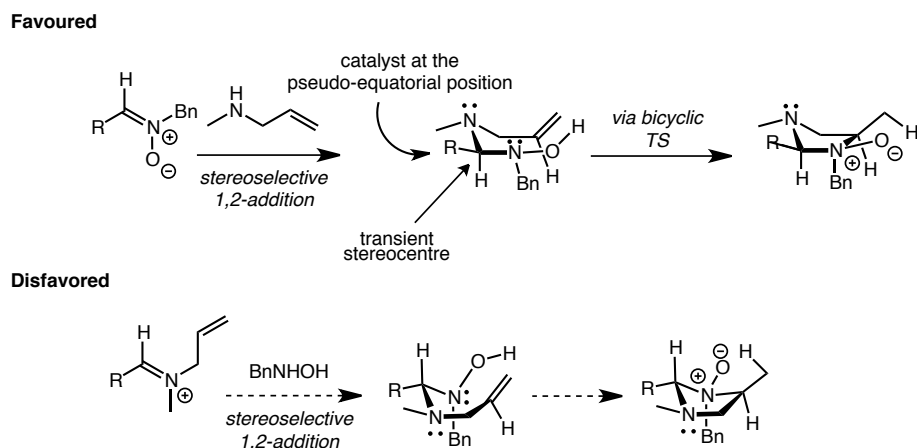
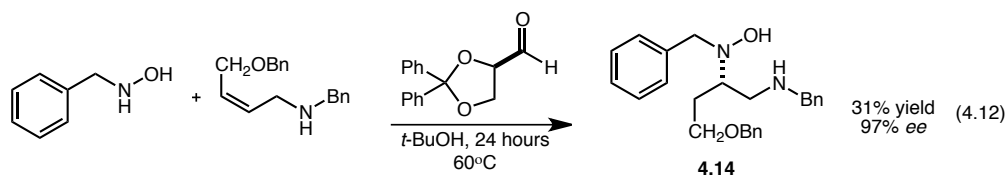


Figure 4.4 Enantioselective Cope-type hydroamination originating from a transient stereocentre formed via a stereoselective 1,2-addition on favoured nitron

t-BuOH effect

Throughout this project a major limitation of this catalytic system was expanding the scope of the allylic amine component to internal alkenes. The chiral aldehydes discovered so far were not compatible with internal alkenes and resulted in no reaction, or decomposition if the conditions were forced. Taking a different approach to tackling this challenge the effect of the solvent upon reaction was studied. *t*-BuOH has displayed unique reactivity in achiral Cope-type hydroamination reactions and was not tested in our

original solvent scan for this asymmetric process.⁹⁶ At 60 °C, with aldehyde **2.3**, (*Z*)-*N*-benzyl-4-(benzyloxy)but-2-en-1-amine was tested for reactivity and selectivity (eq. 4.12). We were pleased to see a 31% isolated yield, and 97% *ee* of product **4.14**. As *t*-BuOH is a good proton donor, this solvent may be stabilizing certain charged intermediates in our catalytic cycle. The full explanation of this effect is unknown at this time. After this result, my time in the Beauchemin lab was complete and the project was given to Mr. Didier Bilodeau.



Additional applications for chiral aldehydes as tethering catalysts

In our ongoing approach to expand the field of aldehyde catalysis, experiments are constantly being performed to find other reactions that could benefit from this strategy. In the aldehyde catalyzed Cope-type hydroamination a temporarily chiral mixed aminal, formed from a selective 1,2-addition, is capable of transferring this chirality through a rigid hydroamination transition state. This result raised questions as to what other reactions a temporarily chiral mixed aminal could play an asymmetry-inducing role. A reaction that seemed suitable for this approach was the conjugate addition of nucleophiles on activated alkenes (Figure 4.5). The idea was to use a simple amine that would form a temporarily chiral mixed aminal, through addition to a chiral aldehyde, followed by attack on an electrophile and hydrolysis.

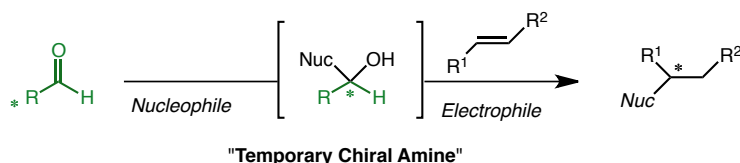
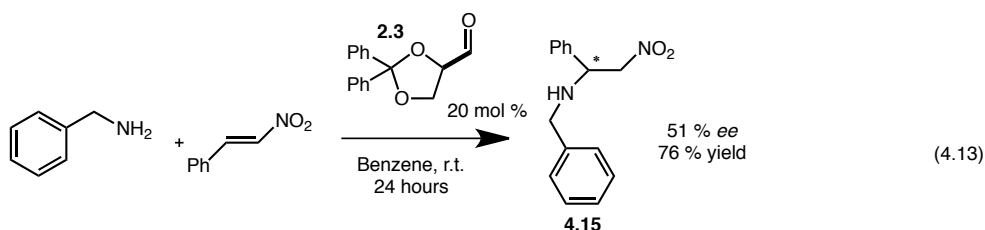


Figure 4.5 The strategy of a temporary chiral amine performing nucleophilic additions on to activated electrophiles

Starting with catalyst **2.3**, benzylamine, and trans- β -nitrostyrene, were reacted in benzene for 24 hours. The final result was very encouraging as the compound was synthesized in 76 % isolated yield and 51 % *ee* (eq. 4.13). The reaction was also attempted with the D-mannose derived aldehyde **4h**; however, there was very little product formation after 24 hours. The background reaction for this system is very quick, and along with catalyst epimerization achieving highly enantioselectivity has many challenges and is an ongoing problem. This achievement does show promise for additional applications of aldehyde catalysis in asymmetric reactions.



4.3 Summary and Outlook

This work confirms that simple organocatalysts are capable of inducing asymmetry solely via preassociation. These chiral aldehydes were able to catalyze the Cope-type hydroamination of various hydroxylamines and allylamines in good yield and very high enantiomeric excess. Presently, these selectivities are still the highest reported

for asymmetric hydroamination on unactivated alkenes. Two different competent organocatalysts were able to give access to both enantiomers of the hydroamination products containing the 1,2-diamine motif in high enantioselectivity. Furthermore, catalyst **2.3** was able to catalyze an asymmetric conjugate addition of benzylamine to trans- β -nitrostyrene showing additional applications of aldehyde catalysis.

The cause of epimerization was studied for both catalyst **2.3** and **4h** through a series of experiments. Aldehyde **2.3** was found to be very prone to epimerization throughout the reaction and achieves the best results using highly reactive starting materials. Catalyst **4h** proved to be remarkably stable and gave very consistent results and high *ee* for all substrates.

Future studies are needed to focus on the expansion of the reaction substrate scope to include more substituted alkenes as well as other nucleophilic allylic amine analogs (i.e, allylic alcohols and thiols). This will likely need further catalyst design and mechanistic insight. Allylic alcohols are less nucleophilic than allylamines, and therefore suffer from a very difficult preassociation step. Allylic thiols, due to poor orbital overlap in a C-S bond, may have difficulty ring-opening the mixed aminated intermediate. Presently, the only aldehyde to effectively catalyze the reaction of internal alkenes in our system is formaldehyde. To induce asymmetry in this reaction chiral hydrogen bonding catalysts could be explored to determine its compatibility with an achiral catalytic tethering strategy, and could constitute a novel approach in dual catalysis.

Formaldehyde as a Tethering Organocatalyst: Highly Diastereoselective Substrate and Reagent-Controlled Hydroaminations of Allylic Amines and Further Attempts at Expanding Substrate Scope

5.1 Introduction

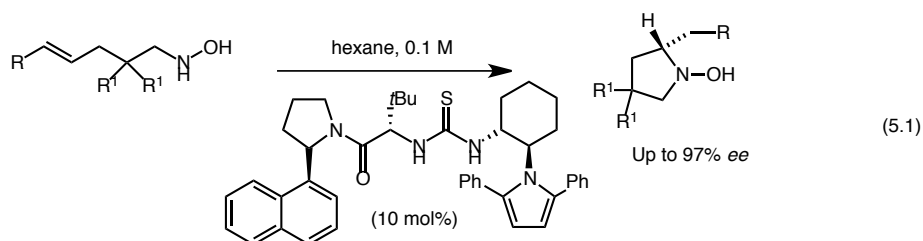
This chapter focuses on the development of a diastereoselective Cope-type hydroamination using formaldehyde as a tethering catalyst with reagent and substrate controlled approaches. Both approaches were optimized and substrate scope was explored focussing on synthesizing a variety of chiral vicinal diamines. Applications of this approach will be discussed leading to a cascade reaction and derivatization of the products. Finally, allylic alcohols were tested under several conditions including a high-pressure experiment.

5.1.1 Stereoselective Cope-type Hydroaminations

Asymmetric Cope-type hydroamination of alkenes is still rare in the literature and often suffers from a specific substrate scope and harsh conditions. In this field,

enantioselective examples are more common than diastereoselective examples, as these reports are all intramolecular and typically use terminal alkenes. These critical limitations indirectly provide evidence on how difficult this reaction is and the need for a simple solution. A survey of the key reports in the literature is discussed below.

As mentioned in Chapter 4 the first enantioselective *intramolecular* Cope-type hydroamination was reported by Jacobsen in 2013.¹²² This system was accelerated by chiral thiourea derivatives and hydrogen bonding stabilization. Combined with our contributions (covered in Chapter 4) these are the only reports of enantioselective Cope-type hydroamination of alkenes (eq. 5.1).



Knight and co-workers were the first to capitalize on the reverse Cope cyclization to produce heterocycles with high diastereoselectivity.⁸⁵ Utilizing stoichiometric amounts of nitrones and allylic amines, oxadiazinanes were synthesized through a sequence initiated by nucleophilic attack of the amine, followed by a Cope-type hydroamination event and a Meisenheimer rearrangement (Figure 5.1). Through the use of several nitrones Knight discovered that destabilized nitrones promoted the initial 1,2-addition and had a dramatic effect on reactivity. As seen in Figure 5.1, the benzaldehyde-derived nitrone took 5 days to react as opposed to the formaldehyde derived-nitrone, which took 18 hours. Knight did observe that using an isolated formaldehyde-derived nitrone resulted

in better reactivity but due to stability issues had to rely on the use of the aqueous aldehyde.^{85b} All of these examples showed excellent selectivity with near perfect diastereoselectivity using a substrate-controlled approach.

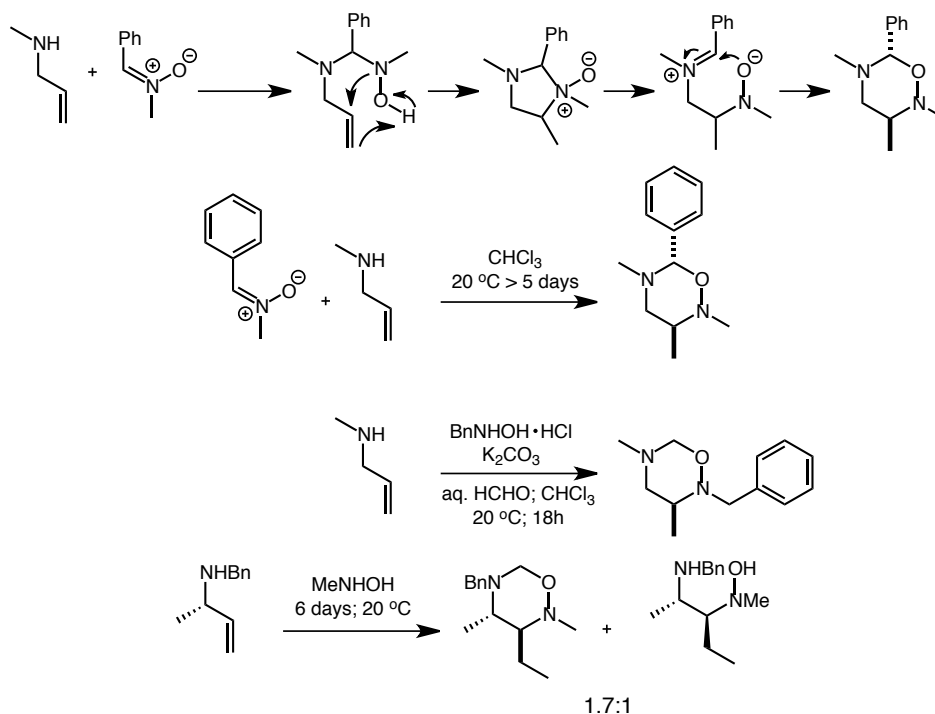
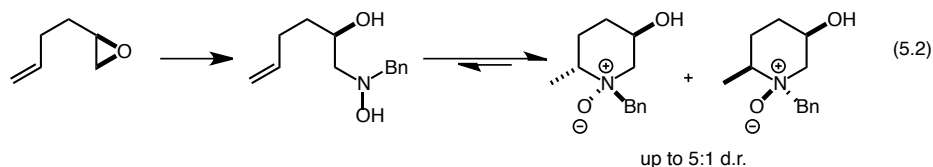


Figure 5.1 Diastereoselective Cope-type hydroamination

In 2001 O’Neil published a diastereoselective reverse-Cope cyclization, initiated via nucleophilic attack on enantiopure epoxides.¹³⁷ Refluxing in methanol resulted in the synthesis of highly functionalized *N*-oxides in up to 5:1 d.r (eq. 5.2). The selectivity was solvent dependent with polar protic solvents such as methanol and ethanol providing the best selectivity. The hypothesis is that a protic solvent can hydrogen bond with the *N*-oxide and therefore shifts the equilibrium to the product. There was only one reported

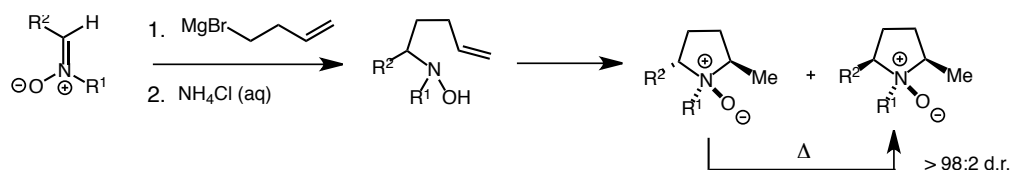
¹³⁷ O’Neil, I. A.; Cleator, E.; Southern, J. M.; Hone, N.; Tapolczay, D. J. *Synlett* **2000**, 695-697.

substrate in this publication.



Bagley in 2001 furthered the methodology of a diastereoselective Cope-type hydroamination by the synthesis of *trans/cis* -2,5-disubstituted pyrrolidine *N*-oxides in high selectivity (Scheme 5.1).¹³⁸ Through Grignard 1,2-additions onto a variety of nitrones, hydroxylamines were made *in situ*, followed by 5-membered ring formation. It was discovered that the selectivity could be improved by heating the resulting products to favour the more thermodynamically stable *cis* -2,5-disubstituted pyrrolidine *N*-oxide.

Scheme 5.1 Bagley's diastereoselective synthesis of *cis*-2,5-disubstituted pyrrolidine *N*-oxides



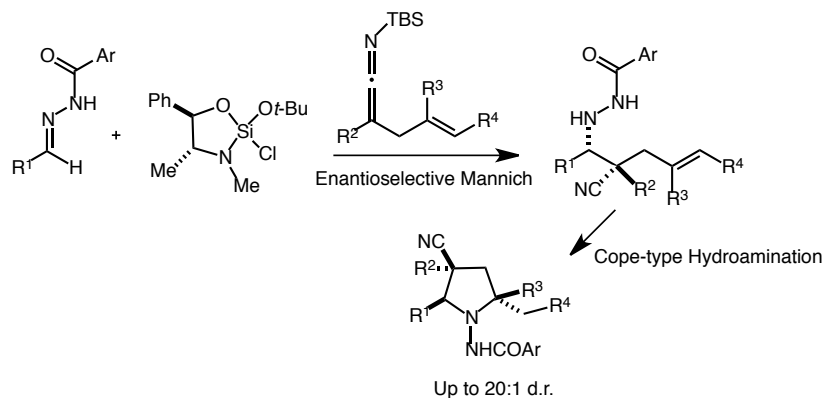
A more recent example of a selective diastereoselective hydroamination was reported by Leighton in 2011 (Scheme 5.2).¹³⁹ This publication featured a two-step process to synthesize highly selective pyrrolidines in greater than 20:1 d.r. The first reaction was a chiral Lewis acid promoted Mannich reaction to synthesize bishomoallylic benzoic hydrazides in good enantiomeric excess, followed by a Cope-type

¹³⁸ Bagley, M. C.; Tovey, J. *Tetrahedron Lett.* **2001**, 42, 351-353.

¹³⁹ Baxter, J. M.; Leighton, J. L. *Org. Lett.* **2011**, 13, 4056-4059.

hydroamination developed by the Beauchemin lab in 2009.¹⁴⁰ The hydroamination provided excellent selectivity and allowed access to valuable nitrogen heterocycles.

Scheme 5.2 Leighton's diastereoselective hydroamination reaction sequence



As seen above there are very few examples of asymmetric diastereoselective Cope-type hydroamination and the examples are often restricted in scope. We planned to use the organocatalytic tethering strategy described previously to create a highly diastereoselective intermolecular Cope-type hydroamination that showed a broad scope under relatively mild conditions.

5.2 Results and Discussion

In Chapter 3 we discovered that formaldehyde was a superior catalyst for promoting preassociation between *N*-benzylhydroxylamines and allylic amines, which resulted in very high yields for the aldehyde catalyzed Cope-type hydroamination of

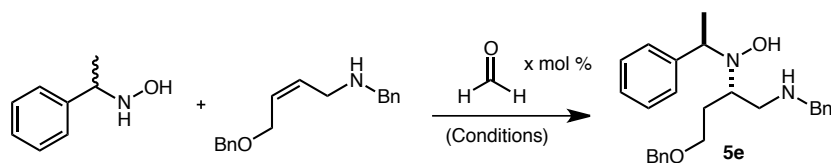
¹⁴⁰ (a) Roveda, J. G.; Clavette, C.; Hunt, A. D.; Gorelsky, S. I.; Whipp, C. J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 8740-8741. (b) Loiseau, F.; Clavette, C.; Raymond, M.; Roveda, J.G.; Burrell, A.; Beauchemin, A. M. *Chem. Comm.* **2011**, *47*, 562-564.

alkenes. Given formaldehyde's high reactivity and small size, we hypothesized that it could tolerate the increased substitution required for the development of a directed diastereoselective variant.

Optimization of reaction conditions

To test and optimize this hypothesis we used an internal alkene and *N*-(1-phenylethyl)-hydroxylamine to induce asymmetry. The optimization initially used *t*-BuOH as solvent and 10 mol % catalyst, as these conditions were found to be the best for aqueous formaldehyde reactivity (Chapter 3). The first reaction was run at 30 °C and gratifyingly led to a high diastereoselectivity (d.r. > 20:1). Unfortunately at 30 °C and after 24 hours the yield of the reaction was quite low at 10%. Increasing the temperature to help overcome the difficult hydroamination step increased the yield of **5e** to 58%. Attempting to further increase the temperature resulted in decomposition and allowing the reaction to run longer resulted in a lower yield. Hydroxylamines are known to decompose at high temperatures, which is presumably why the reaction run at 80 °C did not produce a greater yield. The diastereoselectivity was quite robust and maintained near perfect d.r. for several conditions and no reactivity was seen in the absence of catalyst (Entry 6). With optimized conditions in hand (Entry 2) a substrate scope was explored for both a reagent and substrate controlled diastereoselective Cope-type hydroamination.

Table 5.1 Optimization of formaldehyde-catalyzed asymmetric intermolecular Cope-type hydroamination^a



Entry	Catalyst	T (°C)	Time	Yield (%) ^b	d.r.
1	10	30	24	10	> 20:1
2	10	50	24	58	> 20:1
3	10	50	48	42	> 20:1
4	10	80	24	41	> 20:1
5	5	50	24	39	> 20:1
6	0	50	24	0	---

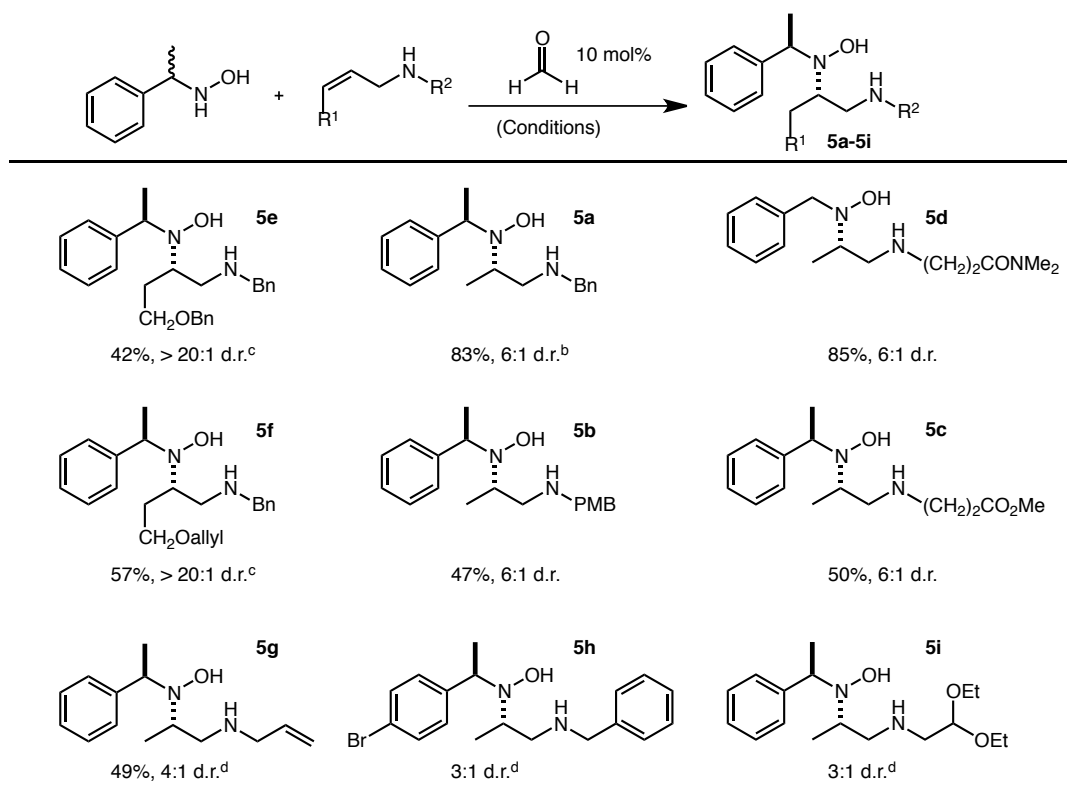
^a Conditions: Hydroxylamine (1.0 equiv.), allylamine (1.0 equiv.), formaldehyde (x mol%), in *t*-BuOH (1 M) under argon. ^b NMR Yield, determined with 1,4-dimethoxybenzene.

Reagent controlled diastereoselective hydroamination

Utilizing the conditions discovered above, substrate scope was explored using *N*-(1-phenylethyl)-hydroxylamine and several secondary allylic amines (Table 5.2). The products of this reaction (**5e** and **5f**) using internal alkenes displayed excellent d.r. with moderate yields. The hydroamination step becomes increasingly difficult with this extra substitution. Unsubstituted alkenes give moderate to excellent yields with good d.r.'s (6:1-3:1). (**5a-5d-5g-5i**). Electron-rich allylamines tend to favour the mixed amination and therefore results in higher yields (**5a**). Separating the diastereomers proved to be fairly facile through recrystallization of the racemic mixture (see Appendix II). The anti orientation of the diamine was confirmed by determining the X-ray structure of product **5a** and is consistent with the proposed orientation in the amination intermediate (see Figure

5.2).

Table 5.2 Reagent controlled diastereoselective hydroamination^a



^a Conditions: Hydroxylamine (1 equiv.), allylamine (1.5 equiv.), catalyst (0.1 equiv.), in *t*-BuOH (1M) under argon, for 24 h at 30 °C, d.r. determined by ¹H NMR of crude mixture. ^b X-ray obtained of major diastereomer. ^c Performed at 50 °C. ^d Unpublished results

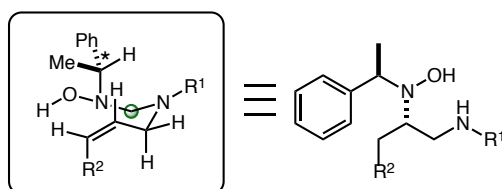


Figure 5.2 Proposed rationale rationale of stereoselection for reagent controlled Cope-type hydroamination

In this proposed model the groups on the stereocentre of the hydroxylamine are oriented to minimize steric interactions between the pseudo-axial substituent and the

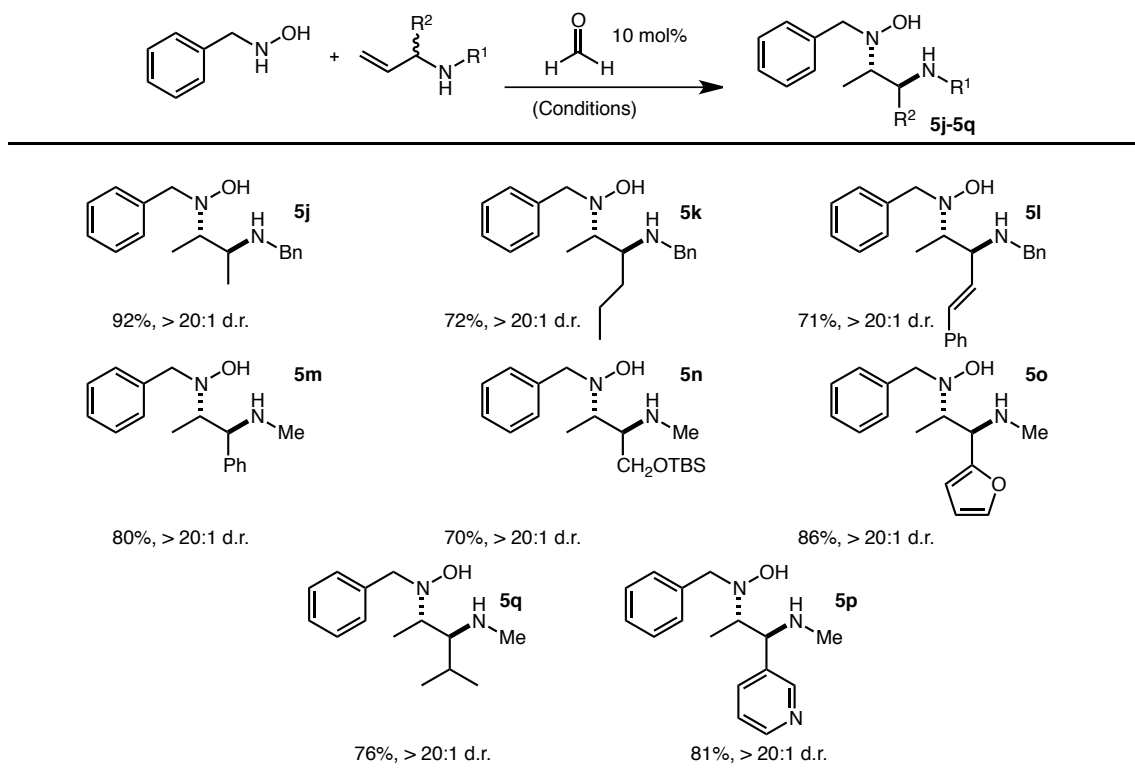
forming 5-membered ring system (Figure 5.2).

Substrate controlled diastereoselective hydroamination

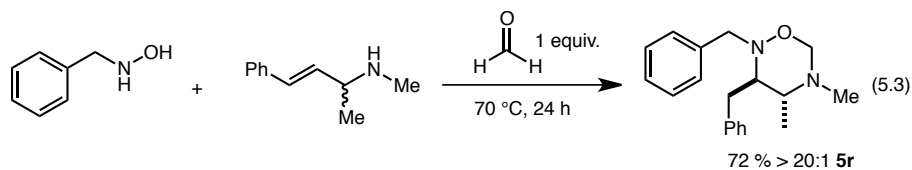
At this time we sought to perform a substrate controlled Cope-type hydroamination with the stereocentre on the allylic amine. A similar approach was taken by Knight and co-workers using stoichiometric amounts of formaldehyde (see introduction). They observed excellent diastereoselectivity and therefore we were quite confident our system could achieve similar results. Mr. Colin Hesp reacted several secondary allylic amines with *N*-benzylhydroxylamine and 10 mol% formaldehyde (Table 5.3). All of the entries displayed near perfect diastereoselectivity (d.r. > 20:1) and excellent yields for intermolecular hydroamination. Good chemoselectivity was observed for **5l**, as well as impressive steric tolerance for all substrates. Aromatic heterocycles were compatible in the reaction (**5o** and **5p**) as well as TBS-protected alcohols (**5n**). Higher yields could be obtained with *N*-methylallyl derivatives instead of *N*-benzyl examples most likely due to the easier initial 1,2-addition on the formaldehyde-derived nitron. Unfortunately, a limitation with this methodology was the degree of substitution on the alkene with catalytic amounts of formaldehyde. If a stoichiometric amount of catalyst is used, these difficult substrates work quite well in forming a 6-membered heterocycle in moderate yield and excellent d.r. (eq. 5.3). An example can be seen in equation 5.3 with (±)-methyl[(3*E*)-4-phenylbut-3-en-2-yl]amine and *N*-benzylhydroxylamine.¹⁴¹

¹⁴¹ This reaction was performed by Mr. Colin Hesp

Table 5.3 Substrate controlled diastereoselective hydroamination^a



^a Conditions: Hydroxylamine (1 equiv.), allylamine (1.5 equiv.), catalyst (0.1 equiv.), in *t*-BuOH (1M) under argon, for 24 h at 30°C, isolated yields, d.r. determined by ¹H NMR.



The origin of selectivity for this transformation originates from R³ adopting a pseudo-equatorial position in the bicyclic 5,5-transition state structure (Figure 5.3).

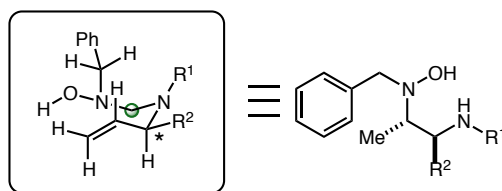
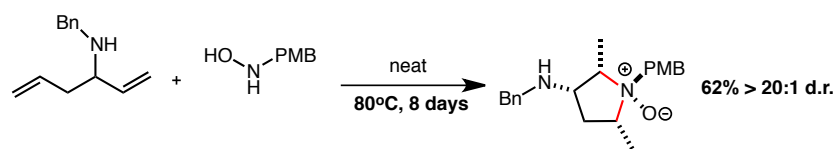


Figure 5.3 Proposed rationale of stereoinduction for substrate controlled Cope-type hydroamination

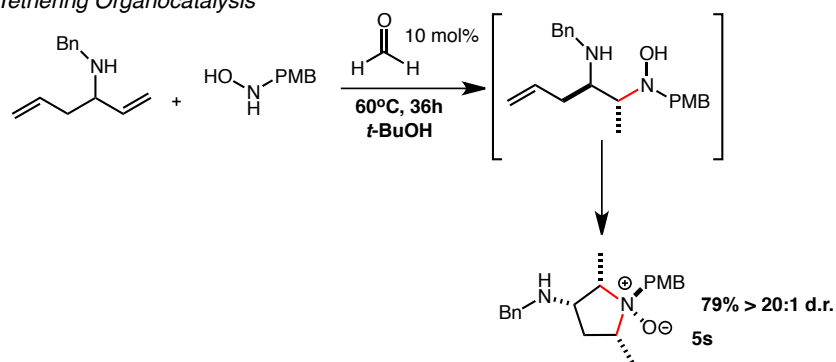
Intrigued by the remarkable reactivity seen with formaldehyde thus far we also sought to perform a double hydroamination cascade with *N*-benzylhexa-1,5-dien-3-amine under our standard conditions. This sequence synthesized highly substituted *N*-oxide **5s** in very high selectivity with low catalyst loading and mild conditions (Scheme 5.3).

Scheme 5.3 Comparison of cascade Cope-type hydroamination via hydrogen bonding directed and tethering organocatalysis

Hydrogen Bonding Activated



Tethering Organocatalysis



This reaction was previously performed using a hydrogen-bonding approach by the Beauchemin group in 2012, which yielded the product in 62 % over 8 days at 80 °C with similar selectivity.⁸⁶ Formaldehyde was able to *catalyze* the reaction in 36 hours at

60 °C, and these improved conditions led to a 79% isolated yield. This showcases the amount of rate acceleration achieved by the tethering catalyst.¹⁴²

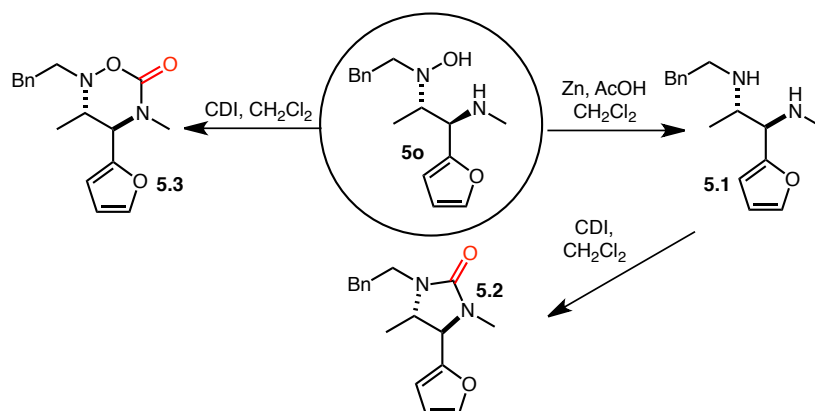
Derivatization of hydroaminated compounds

This diastereoselective Cope-type hydroamination reactivity has the ability to synthesize a variety of vicinal diamine motifs. Such diamines have shown great success as chiral ligands in several aspects of catalysis both transition metal and organocatalysis. In pharmaceutical targets, diamines are often present in biologically active molecules, and can be very difficult to synthesize in a stereoselective fashion.¹⁴³ Keeping this in mind, we sought to derivatize our compounds to display the utility of this transformation. The preliminary experiments are presented in (Scheme 5.4). Compound **5o** was easily converted to a diamine (**5.1**) under mild reductive conditions. The diamine was then cyclized with source of carbonyl (1,1'-carbonyldiimidazole, CDI) to create a cyclic urea **5.2**. Finally **5o** can be derivatized into a rigid 6-membered heterocycle **5.3** with CDI.

¹⁴² These reactions were performed by Dr. Shubin Zhao

¹⁴³ (a) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem. Int. Ed.* **1998**, 37, 2580-2647. (b) Kotti, S. R. S. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, 67, 101-114.

Scheme 5.4 Diamine motifs: examples of derivatization reactions^a



Conditions: [**5.1**] Zn, AcOH, CH₂Cl₂, r.t., 3 h, 37% [**5.2**] 1. Zn, AcOH, CH₂Cl₂, r.t., 3 h, 37% 2. CDI, CH₂Cl₂, r.t., 24 h, 41% [**5.3**] CDI, CH₂Cl₂, r.t., 16 h, 72%.

5.3 Allylic Alcohols

Near the beginning of this organocatalytic tethering project the idea of using allylic alcohols to synthesize 1,2-amino alcohols was always at the forefront of our interests. 1,2-Amino alcohols are a desired functional group in several pharmaceutical targets.¹⁴⁴ The ability to have a facile and possibly selective transformation for this unit would have a significant impact. Therefore both formaldehyde **3.4** and α -benzyloxyacetaldehyde **2.1** were tested with allylic alcohol.

Starting with α -benzyloxyacetaldehyde **2.1** no reaction was seen after 24 hours with allylic alcohol and *N*-benzylhydroxylamine and 20 mol % of catalyst in CDCl₃. Allyl alcohol is less nucleophilic than allylamine and given that only starting material was seen in the NMR the preassociation step was assumed to be very difficult. Several

¹⁴⁴ Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis. Construction of Chiral Molecules Using Amino Acids*, Wiley: New York, 1987.

additives and temperatures were explored in an attempt to promote the initial 1,2-addition. Catalytic amounts of base such as Hunig's base or *t*-BuOK did not result in any improvement and only starting material remained (Entries 1 and 2). Increasing the temperature led to catalyst and hydroxylamine degradation (Entry 3) and trying other hydroxylamines proved unsuccessful (Entries 4-6).

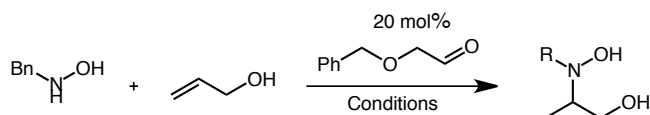
Table 5.4 Attempts of α -benzyloxyacetaldehyde 2.1 to catalyze the reaction of allylic alcohols and hydroxylamines^a

Entry	Hydroxylamine	Additive (x)	Temperature	Result
1	Bn	DIPEA	r.t.	-
2	Bn	<i>t</i> BuOK	r.t.	-
3	Bn	No additive	80°C	-
4	Cy	No additive	r.t.	-
5	Me	No additive	r.t.	-
6	Me	DIPEA	r.t.	-
7	Me	<i>t</i> BuOK	r.t.	-

^a Conditions: (1 equiv.) Hydroxylamine, (1 equiv.) allylic alcohol in CHCl₃ (1M), room temperature for 24 hours

To further test allylic alcohol reactivity several Bronsted and Lewis acids were tried as additives to see if they could activate the nitron and promote preassociation (Table 5.5). Beginning with trifluoroacetic acid and triflic acid no reaction was seen with either acid and only starting material was observed by NMR. Running the reaction in benzene or increasing the temperature proved to be unsuccessful and only led to decomposition. Lewis acids were tried in polar solvents at both room temperature and increased heat. Unfortunately no product was seen with any of these conditions.

Table 5.5 Effects of Bronsted and Lewis acids on α -benzyloxyacetaldehyde to catalyze the hydroamination of allyl alcohol^a



Entry	Additive (x)	Temperature	Solvent (1M)	Result
1	TFA ^b	r.t.	CDCl ₃	-
2	TrOH ^b	r.t.	CDCl ₃	-
3	TFA ^b	r.t.	C ₆ D ₆	-
4	TFA ^b	80 °C	CDCl ₃	-
5	TFA ^b	80 °C	C ₆ D ₆	-
6	TrOH ^b	80 °C	CDCl ₃	-
7	MgCl ₂	r.t.	THF	-
8	MgCl ₂	r.t.	DME	-
9	MgCl ₂	80 °C	THF	-
10	Cu(OTf) ₂	r.t.	CDCl ₃	-
11	Cu(OTf) ₂	r.t	DMSO-d ₆	-
12	Cu(OTf) ₂	80 °C	DMSO-d ₆	-

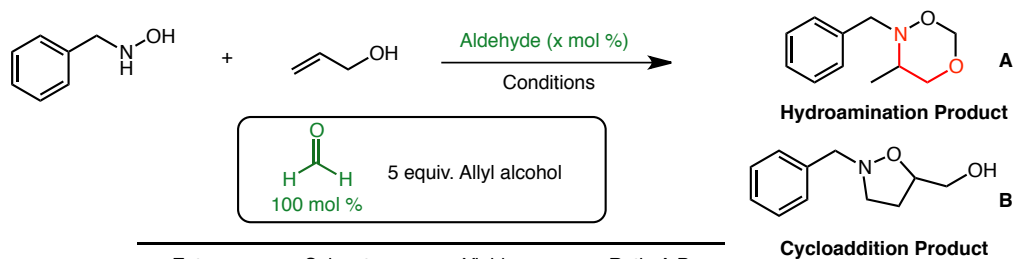
^a Conditions: (1 equiv.) Hydroxylamine, (1 equiv.) allylic alcohol, (1 equiv.) additive for 24 hours.

^b (0.5 equiv.) additive

At this time the focus shifted to formaldehyde and scanning several solvents to discover any reactivity. Utilizing stoichiometric amounts of formaldehyde and 5 equivalents of allylic alcohol a solvent scan was performed (Table 5.6). Encouragingly the reaction in chloroform showed a 18% NMR yield, which was the first time any product had been observed (**A**). Over the course of the solvent scan a side product was observed and thought to be from the [3+2] cycloaddition of the formaldehyde derived nitron and the alkene component of the allylic alcohol (**B**). When the temperature was increased this side product became the dominant species. The formaldehyde-derived nitron is very reactive and with a less nucleophilic reagent the species is long-lived and

participates in the side reaction resulting in the formation of product **B**.¹⁴⁵

Table 5.6 Solvent effects on formaldehyde's ability to catalyze the hydroamination of allylic alcohol and *N*-benzylhydroxylamine^a



Entry	Solvent	Yield	Ratio A:B
1	<i>t</i> -BuOH	0	-
2	DMSO	0	-
3	CHCl ₃	13	5:1
4	MeCN	8	5:1
5	EtOAc	2	-
6	acetone	8	-
7	DMF	2	-
8	dioxane	8	-
9	TFT	15	5:1

^a Conditions: (1 equiv.) Hydroxylamine, (1 equiv.) allylic alcohol, for 24 hours.
MeCN (acetonitrile), DMF (Dimethylformamide), TFT (Trifluorotoluene)

In order to overcome the difficult preassociation between the allylic alcohol and nitron as well as avoid the cycloaddition side product a new strategy needed to be employed. A collaboration was initiated with Dr. Kerr at the University of Western Ontario, utilizing our methodology and Dr. Kerr's high-pressure reactors. Hyperbaric conditions have been shown to accelerate difficult intermolecular reactions and could help promote preassociation in our system.¹⁴⁶ At 150,000 psi 4 reactions were run under

¹⁴⁵ Mr. Colin Hesp performed this solvent scan.

¹⁴⁶ *In Organic Synthesis at High Pressures*; Matsumoto, K., Acheson, R. M., Eds.; Wiley: Toronto, 1991;

varying conditions all at room temperature (Figure 5.3).¹⁴⁷ Formaldehyde **3.4** and α -benzyloxyacetaldehyde **2.1** were both separately tested at 40 % catalyst in *t*-BuOH. Unfortunately the reaction of aldehyde **3.4** provided evidence of only the cycloaddition product **B** in the NMR. Catalyst **2.1** showed significant decomposition of starting materials as observed via NMR (Entry 3 and 4). The reaction was also performed without catalyst in both *t*-BuOH and under neat conditions to completely eliminate any side reactions. In *t*-BuOH only starting material and traces of side products were observed. Gratifyingly a 40 % NMR yield of the desired product **A** was seen under neat conditions with 12 equivalents of allylic alcohol (Entry 1). As no tethering catalyst was present in this solution, the reaction was obviously undergoing a different mechanistic pathway. There has been precedence for hydrogen bonding directed Cope-type hydroamination between hydroxylamines and allylic amines.⁸⁶ Therefore, under high-pressure conditions, the rate of hydrogen-bond catalyzed hydroamination could be accelerated and result in improved reactivity (Figure 5.4). Due to a short visit to the University of Western Ontario this project needs more optimization and is still ongoing.

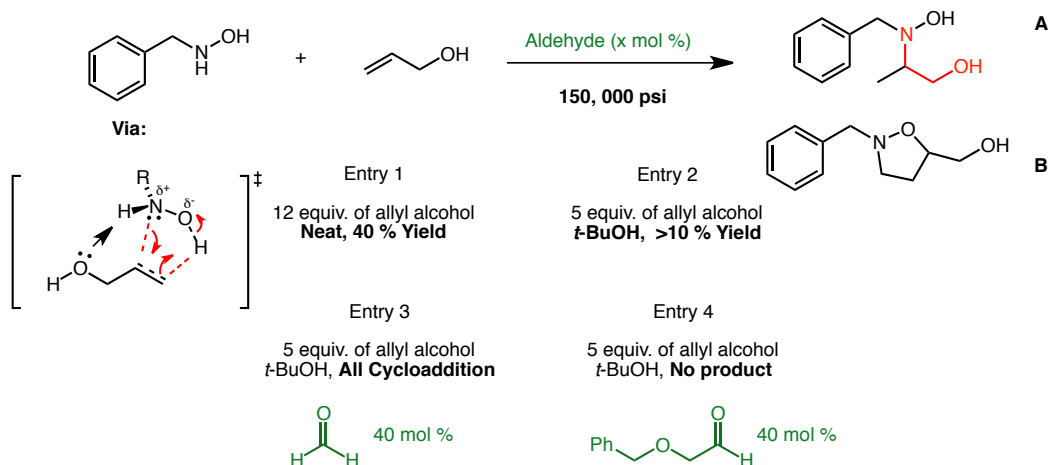


Figure 5.4 Experiments under high pressure with allylic alcohols and benzylhydroxylamine

5.4 Summary and Outlook

A reagent and substrate controlled diastereoselective Cope-type hydroamination has been presented. This methodology is the first catalytic example of a diastereoselective hydroamination that displays good to excellent selectivity and reactivity. The substrate scope is extremely diverse for a hydroamination reaction with internal alkenes and highly sterically hindered substrates reacting very well (42-92%). The resulting diamine compounds were derivatized to show utility in total synthesis and/or pharmaceutical industry. A double hydroamination cascade reaction was completed with mild conditions and reasonable reaction time. This method provides access to highly substituted and selective *N*-oxides.

Allylic alcohols were tested and optimized as a reagent in the organocatalytic tethering strategy. After several rounds of optimization both aldehydes **2.1** and **3.4** showed limited reactivity in their ability to catalyze the hydroamination of allyl alcohol

and *N*-benzylhydroxylamine. A [3+2] cycloaddition side reaction was observed to be favoured under high temperatures, and decreased the overall yield of the product. This method was tested under extreme high pressures (150,000 psi) with the help of a collaboration with the University of Western Ontario. This resulted in a very promising lead under neat conditions (40% NMR yield). The high pressure is most likely promoting hydrogen bonding between the two substrates, which is directing the reactivity. Several challenges still remain on this project such as limited reactivity and very difficult isolation.

In the future more effort should be placed on expanding the substrate scope of the reagent controlled Cope-type hydroamination and further derivatization to prove the diamines have significant roles in the literature.

Allylic alcohols remain a challenge for the aldehyde catalyzed Cope-type hydroamination. In the future, an optimization study should be run on the high-pressure experiments to try elevated temperatures and different substrates. The main problem with this methodology is trying to improve reactivity and selectivity over competing side reactions. The high-pressure experiments have a significant chance at forcing hydrogen-bonding reactivity and allowing this reaction to flourish.

Appendix I

Claims to Original Research

- 1) Development and optimization of Cope-type hydroamination of allylic amines and hydroxylamines, including expansion of substrate scope, and purification strategy for primary amines and the final diamine products.
- 2) Mechanistic investigations of this organocatalytic tethering strategy, including equilibrium studies with selected aldehydes.
- 3) Development and optimization of formaldehyde catalyzed version of this reaction, which resulted in a significant expansion of the substrate scope.
- 4) Development of high yielding, enantioselective intermolecular Cope-type hydroamination of allylic amines and hydroxylamines.
- 5) Discovery of a lead result in the aldehyde catalyzed asymmetric conjugate addition of benzylamine, and trans- β -nitrostyrene.
- 6) Expansion and optimization of the scope of a reagent controlled diastereoselective Cope-type hydroamination of allylic amines and *N*-benzylhydroxylamines.
- 7) Early development in the high-pressure reaction of allylic alcohols and *N*-benzylhydroxylamine.

Publications from This Work

- 1) *A Catalytic Tethering Strategy: Simple Aldehydes Catalyze Intermolecular Alkene Hydroaminations*, MacDonald, Melissa J.; Schipper, Derek J.; Ng, Peter; Moran, Joseph; Beauchemin, André M. *J. Am. Chem. Soc.* **2011**, *133*, 20100-20103.
- 2) *Catalysis through Temporary Intramolecularity: Mechanistic Investigations On Aldehyde-Catalyzed Cope-type hydroamination Led to the Discovery of a More Efficient Tethering Catalyst*, Guimond, Nicolas; MacDonald, Melissa J.; Lemieux, Valerie;

Beauchemin, André M. *J. Am. Chem. Soc.* **2012**, *134*, 16571– 16577.

3) *Highly Enantioselective Intermolecular Hydroaminations of Allylic Amines Using Chiral Aldehydes as Tethering Catalysts*, MacDonald, Melissa J.; Hesp, Colin R.; Schipper, Derek J.; Pesant, Marc; Beauchemin, André M. *Chem. Eur. J.* **2013**, *19*, 2597 – 2601.

4) *2-(Phenylmethoxy)Acetaldehyde*, MacDonald, Melissa J.; Beauchemin, André M. *Encyclopedia of Reagents for Organic Synthesis*. **2013**, John Wiley & Sons, Ltd. Article RN01652.

5) *Formaldehyde as Tethering Organocatalyst: Highly Diastereoselective Substrate and Reagent-Controlled Hydroaminations of Allylic Amines*, Hesp, Colin R., MacDonald, Melissa J.; Zhao, Shubin; Pesant, Marc; Beauchemin, André M. Submitted to *J. Am. Chem. Soc.* Manuscript ID: ja-2013-07145h, rejected on Aug 26, 2013. Revisions in progress.

Presentations from This Work

Oral presentation

1) Melissa J. MacDonald, Peter Ng, Derek Schipper, Joseph Moran and André Beauchemin. *Organocatalytic Tether Formation: A Strategy Enabling Room Temperature Hydroamination*. 21st Quebec & Ontario Mini-Symposium on Biological and Organic Chemistry, November 13th, 2010.

2) Melissa J. MacDonald, Colin R. Hesp, Marc Pesant and André Beauchemin. *Organocatalytic Tether Formation: A Strategy Enabling Directed Intermolecular Amination Reactions*. 245th ACS National Meeting and Exposition, April 10th 2013.

Poster presentation

1) Melissa J. MacDonald, Peter Ng and André Beauchemin, Peter Ng. *Organocatalytic Tether Formation: A Strategy Enabling Directed Intermolecular Amination Reactions*. 93rd Canadian Chemistry Conference & Exhibition, May 31, 2010.

- 2) Melissa J. MacDonald, Peter Ng, Derek Schipper, Joseph Moran and André Beauchemin. *Organocatalytic Tether Formation: A Strategy Enabling Directed Intermolecular Amination Reactions*. AstraZeneca Chemistry Symposium, October 1, 2010. Won 2nd place poster prize
- 3) Melissa J. MacDonald, Peter Ng, Derek Schipper, Joseph Moran and André Beauchemin. *Organocatalytic Tether Formation: A Strategy Enabling Directed Intermolecular Amination Reactions*. Ottawa and Carleton Chemistry Institute, May 27th, 2011.
- 4) Melissa J. MacDonald, Peter Ng, Derek Schipper, Joseph Moran and André Beauchemin. *Organocatalytic Tether Formation: A Strategy Enabling Directed Enantioselective Intermolecular Amination Reactions*. 94th Canadian Chemistry Conference & Exhibition, June 7, 2011. Won 2nd place poster prize
- 5) Melissa J. MacDonald, Colin R. Hesp and André Beauchemin. *Organocatalytic Tether Formation: A Strategy Enabling Enantioselective Intermolecular Amination Reactions*. 41st Spring Symposium in Organic Synthesis, June 7, 2012.
- 6) Melissa J. MacDonald, Colin R. Hesp, Marc Pesant and André Beauchemin. *Organocatalytic Tether Formation: A Strategy Enabling Enantioselective Intermolecular Amination Reactions*. 23rd Quebec-Ontario Mini-Symposium on Bioorganic and Organic Chemistry (QOMSBQC), November 9, 2012. Won poster prize.
- 7) Melissa J. MacDonald, Colin R. Hesp, Marc Pesant and André Beauchemin. *Organocatalytic Tether Formation: Asymmetric Hydroaminations*. US and Spain Workshop on Chemical Synthesis and Catalysis. April 12, 2013.
- 8) Melissa J. MacDonald, Colin R. Hesp, Marc Pesant and André Beauchemin. *“Organocatalytic Tether Formation: A Strategy Enabling Directed Intermolecular Amination Reactions”* 96th Canadian Chemistry Conference & Exhibition. May 29th, 2013.

Appendix II

Experimental Section

General Information. All reactions were performed in flame-dried round bottom flasks under an argon atmosphere unless otherwise noted. Purification of reaction products was carried out by flash column chromatography using 40-63 μm silica gel. Analytical thin layer chromatography (TLC) was performed on aluminum sheets pre-coated with silica gel 60 F₂₅₄, cut to size. Visualization was accomplished with UV light followed by dipping in a potassium permanganate solution and heating.

Infrared (IR) spectra were obtained as neat thin films on a sodium chloride disk and were recorded on a Bruker EQUINOX 55 Fourier transform infrared spectrometer (FTIR). ¹H NMR spectra were recorded on Bruker AVANCE 300 or 400 MHz spectrometers at ambient temperature unless otherwise noted, and are reported in ppm using solvent as the internal standard (CDCl₃ at 7.26 ppm or C₆D₆ at 7.15 ppm). Data are reported as: multiplicity (ap = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration and coupling constant(s) in Hz. ¹³C NMR spectra were recorded at 75 or 100 MHz. Chemical shifts are reported in ppm from tetramethylsilane, with the residual solvent resonance employed as the internal standard (CDCl₃ at 77.0 ppm or C₆D₆ at 128.02 ppm). High-resolution mass spectroscopy (HRMS) was performed on a Kratos Concept IHH mass spectrometer with an electron beam of 70 eV. High Performance Liquid Chromatography (HPLC) was performed on an Agilent 1200 series.

Materials. Unless otherwise noted, all deuterated solvents and reagents were used without further purification. Solvents were either distilled according to standard techniques or degassed prior to use.

NMR Yields. NMR yields were determined using 1,4-dimethoxybenzene as an internal standard. These results are subject to the uncertainty of NMR integrations and the error

resulting from the measurement of 1,4-dimethoxybenzene. As a general rule, this data normally ranges anywhere from 5-10% and only reactivity trends are drawn as conclusions.

PROCEDURES AND CHARACTERIZATION FOR CHAPTER 2

General comments

N-Alkyl/arylhydroxylamines were prepared by reductive amination of the corresponding oximes according to the method of House and Lee.¹⁴⁸ *N*-Benzylhydroxylamine,¹⁴⁹ *N*-cyclohexylhydroxylamine,¹⁴⁹ *N*-sec-butylhydroxylamine,¹⁴⁹ *p*-methoxybenzylhydroxylamine¹⁵⁰ and *o*-hydroxybenzylhydroxylamine¹⁵¹ were prepared according to literature procedures. Aldehyde **2.2** was purchased from Sigma Aldrich.

General procedure A for identifying a temporary tether to perform catalyzed hydroaminations of allylic amines with *N*-alkylhydroxylamines. A 2-mL screwed cap vial was charged with a stir bar, selected aldehyde (x equiv.), hydroxylamine (1 equiv.) and allylamine (1.5 equiv.). The reaction was stirred at room temperature for 24 hours. 1,4-dimethoxybenzene was added (0.25 equiv.) as an internal standard, which was used to calculate an NMR yield.

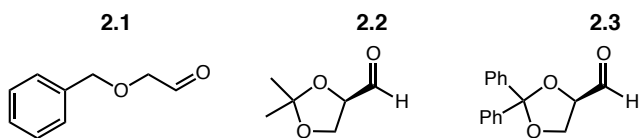
General procedure B for tethered hydroaminations of allylic amines with *N*-alkylhydroxylamines. A 10-mL round bottom flask was charged with a stir bar, hydroxylamine (1 equiv.), degassed solvent (1.0 M), aldehyde **2.1/2.2/2.3** (0.2 equiv.) and amine (1.5 equiv.). The reaction was stirred at room temperature, and monitored by TLC or ¹H NMR. The crude reaction mixture was concentrated under reduced pressure and purified by column chromatography to give the corresponding *N,N*-dialkylhydroxylamine products.

¹⁴⁸ House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863-869.

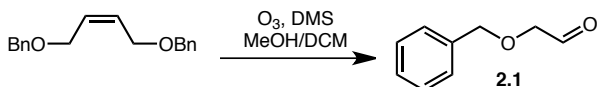
¹⁴⁹ Pfeiffer, J. Y.; Beauchemin, A. M. *J. Org. Chem.* **2009**, *74*, 8381-8383.

¹⁵⁰ Gordon, I. M.; Maskill, H. *J. Chem. Soc., Perkin Trans. 2.* **2002**, 2059-2062.

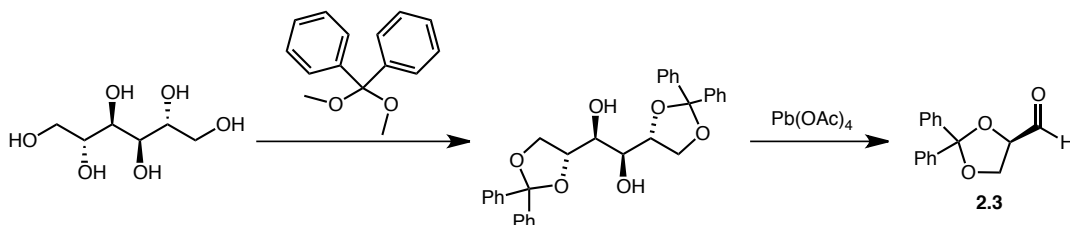
¹⁵¹ Shiino, M.; Watanabe, Y.; Umezawa, K. *Bioorg. Chem.* **2003**, *31*, 129-135.



Synthesis of aldehydes used for Cope-type hydroamination:



2-(Benzyloxy)acetaldehyde (Catalyst 2.1). This catalyst was prepared from 1,4-bis(benzyloxy)but-2-en¹⁵² according to a modified procedure of Hiersemann.¹⁵³ Through a solution of alkene (2.0 g, 7.5 mmol) in CH₂Cl₂/MeOH (14 mL/5.0 mL) at -78°C was bubbled a stream of ozone until the colourless solution became blue. Nitrogen was bubbled to remove excess ozone, and then dimethyl sulfide (2.3 g, 2.8 mL, 38 mmol) was added at -78°C . The reaction was allowed to warm to room temperature and stirred overnight. The solution was concentrated under reduced pressure then purified by column chromatography (20 % EtOAc/hexanes) to afford the product as a colourless liquid (1.6 g, 72 %). Spectral datum was consistent with literature.¹⁵³



(R)-2,2-Diphenyl-1,3-dioxolane-4-carbaldehyde (Catalyst 2.3). Aldehyde 2.3 was prepared from D-mannitol according to a modified procedure of Banerjee *et al.*¹⁵⁴ A solution of the sugar (2.0 g, 10.1 mmol), benzophenone dimethyl acetal (5.01 g, 21.9 mmol) and SnCl₂ (0.025 g, 0.13 mmol) in freshly distilled dimethoxyethane (50 mL) was

¹⁵² Nishizono, N.; Akama, Y.; Agata, M.; Sugo, M.; Yamaguchi, Y.; Oda, K. *Tetrahedron* **2011**, 67, 358-363.

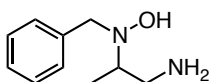
¹⁵³ Pollex, A.; Millet, A.; Müller, J.; Hiersemann, M.; Abraham, L. *J. Org. Chem.* **2005**, 70, 5579-5591.

¹⁵⁴ Banerjee, A.; Schepmann, D.; Kohler, J.; Wurthwein, E.; Wunsch, B. *Bioorg. Med. Chem.* **2010**, 18, 7855-7867.

heated at reflux for 16 hours. Solvent was evaporated and the product was purified by column chromatography (30% EtOAc/Petroleum Ether). The protected diol (0.307 g, 0.603 mmol) was dissolved in CH₂Cl₂ and cooled down to 0 °C. Then Pb(OAc)₄ (0.401 g, 1.58 mmol) was added. The mixture was stirred at 0 °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 datum was consistent with literature.¹⁵⁴

Diamine compounds

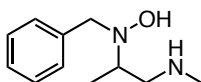
2-(Benzyl(hydroxy)amino)propan-1-amine (**2a**) - (Table 2.5, entry 1)



Diamine **2a** was synthesized according to the general procedure (CHCl₃, 24 h) using (0.334 g, 2.71 mmol) *N*-benzylhydroxylamine. A small amount was isolated for characterization as follows: The crude reaction mixture was concentrated under reduced pressure, and then re-dissolved in CHCl₃ (2 mL). A solution of 4:1 THF/10 % HCl (4 mL) was added, and the resulting biphasic mixture was stirred for 1 h at room temperature. The phases were separated and the aqueous phase was made basic with a saturated aqueous Na₂CO₃ solution. The aqueous solution was extracted three times with CH₂Cl₂, and the combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated under reduced pressure, giving the product as a white solid from the reaction with aldehyde **2.1** (83 %). TLC *R*_f 0.11 (15 % MeOH/CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 7.39-7.29 (m, 5H), 4.00 (d, *J* = 13.1 Hz, 1H), 3.74 (d, *J* = 13.1 Hz, 1H), 2.86-2.24 (m, 3H), 1.12 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 138.5 (C), 129.2 (CH), 128.3 (CH), 127.2 (CH), 62.4 (CH), 60.8 (CH₂), 45.4 (CH₂), 11.2 (CH₃); IR (film): 2931, 2872, 1569, 1491, 1455, 1371, 1027, 927, 735, 698 cm⁻¹; HRMS (EI): Exact

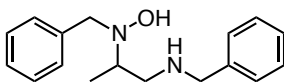
mass calcd for $C_{10}H_{16}N_2O$ $[M]^+$: 180.1263. Not found. Exact mass calcd for $C_9H_{12}NO$ $[M-H_2NCH_2]^+$: 150.0919. Found: 150.0870.¹⁵⁵

2-(Benzyl(hydroxy)amino)-*N*-methylpropan-1-amine (2b) - (Table 2.5, entry 2 and Table 2.6, entry 1)



Diamine **2b** was synthesized according to the general procedure (C_6H_6 , 24 h) using 1.5 mmol of *N*-benzylhydroxylamine. 0.204 g of product was isolated from the reaction with aldehyde **2.1** (72 %) and isolated 0.265 g from the reaction with aldehyde **2.2** (91 %) as a pale yellow oil after column chromatography (1 % Et_3N /10 % $MeOH/CH_2Cl_2$). TLC R_f 0.19 (15 % $MeOH/CH_2Cl_2$); 1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.26 (m, 5H), 3.97 (d, $J = 13.2$ Hz, 1H), 3.72 (d, $J = 13.2$ Hz, 1H), 3.08-2.97 (m, 1H), 2.78 (dd, $J = 12.2, 8.5$ Hz, 1H), 2.56 (dd, $J = 12.2, 4.0$ Hz, 1H), 2.35 (s, 3H), 1.12 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6 (C), 129.3 (CH), 128.2 (CH), 127.1 (CH), 60.4 (CH_2), 59.0 (CH), 55.1 (CH_2), 35.6 (CH_3), 11.5 (CH_3); IR (film): 3397, 2926, 2854, 1641, 1447, 1371 cm^{-1} ; HRMS (EI): Exact mass calcd for $C_{11}H_{18}N_2O$ $[M]^+$: 194.1419. Found: 194.1403.

***N*-Benzyl-2-(benzyl(hydroxy)amino)propan-1-amine (2c) - (Table 2.5, entry 2 and Table 2.6, entries 3 and 4)**



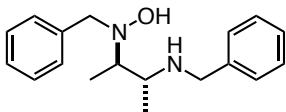
Diamine **2c** was synthesized according to the general procedure (C_6H_6 , 24 h). 0.290 g of product was isolated from the reaction with aldehyde **2.1** (75 %) and 0.377 g was isolated from the reaction with aldehyde **2.2** (93 %) and 0.356 (91%) was isolated from the reaction with aldehyde **2.3** all using 1.5 mmol of *N*-benzylhydroxylamine. In all cases the compound was isolated as a yellow oil after column chromatography (1 % Et_3N /10 %

¹⁵⁵ While most compounds failed to provide a HRMS peak for the molecule ion (except **2b**, **2e**, **2g**, **2h** and **2i**), a common fragment was observed for all hydroamination products. Presence of this ion is consistent

with C-C bond cleavage in the diamine region:

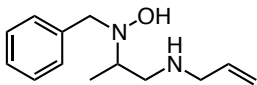
MeOH/CH₂Cl₂). TLC *R*_f 0.25 (1 % MeOH/CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 7.37-7.24 (m, 10H), 3.93 (d, *J* = 13.2 Hz, 1H), 3.73 (d, *J* = 13.1 Hz, 1H), 3.72 (d, *J* = 13.3 Hz, 1H), 3.67 (d, *J* = 13.2 Hz, 1H), 3.08-3.02 (m, 1H), 2.80 (dd, *J* = 12.2, 8.5 Hz, 1H), 2.64 (dd, *J* = 12.2, 4.0 Hz, 1H), 1.11 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 139.5 (C), 138.51 (C), 129.4 (CH), 128.3 (CH), 128.2 (CH), 128.1 (CH), 127.0 (CH), 127.0 (CH), 60.1 (CH₂), 58.9 (CH), 53.0 (CH₂), 51.8 (CH₂), 11.3 (CH₃); IR (film): 3063, 3032, 2926, 2850, 1497, 1451, 1364, 1155, 1026, 733, 698 cm⁻¹; HRMS (EI): Exact mass calcd for C₁₇H₂₂N₂O [M]⁺: 270.1732. Not found. Exact mass calcd for C₉H₁₂NO [M-BnNHCH₂]⁺: 150.0919. Found 150.0929.¹⁵⁵

(2*R*,3*R*)-*N*-Benzyl-3-(benzyl(hydroxy)amino)butan-2-amine (2d) - (Table 2.5, entry 4)



Diamine **2d** was synthesized according to the general procedure (C₆H₆, 60 °C 48 h). 0.257g of product was isolated using 1.5 mmol of *N*-benzylhydroxylamine from the reaction with aldehyde **2.1** (61 %) as a yellow oil after column chromatography (1 % Et₃N/10 % MeOH/CH₂Cl₂), and characterized as one diastereomer (20:1). TLC *R*_f 0.45 (1 % MeOH/CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 7.30-7.23 (m, 10H), 3.83-3.55 (m, 4H), 2.73-2.67 (m, 2H), 1.087 (d, *J* = 6.0 Hz, 3H). Spectral datum was consistent with the literature.⁸⁶

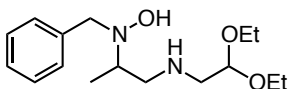
***N*-(2-(Benzyl(hydroxy)amino)propyl)prop-2-en-1-amine (2e) - (Table 2.5, entry 5 and Table 2.6, entry 2)**



Diamine **2e** was synthesized according to the general procedure (C₆H₆, 24 h). The product was isolated as 0.151 g using 1.0 mmol of *N*-benzylhydroxylamine from the reaction with aldehyde **2.1** (69 %) and isolated as 0.267 g using 1.5 mmol of *N*-benzylhydroxylamine from the reaction with aldehyde **2.2** (81 %). In all cases the

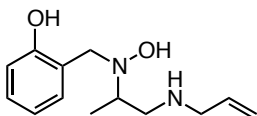
compound was isolated as a yellow oil after column chromatography (1 % Et₃N 5 % MeOH/CH₂Cl₂). TLC *R_f* 0.10 (5 % MeOH/CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 7.36-7.24 (m, 5H), 5.74 (ddt, *J* = 16.4, 10.2, 6.2 Hz, 1H), 5.06 (dt, *J* = 17.1, 1.5 Hz, 2H), 3.92 (d, *J* = 13.0 Hz, 1H), 3.69 (d, *J* = 13.0 Hz, 1H), 3.02 (d, *J* = 5.8 Hz, 1H), 2.98-2.95 (m, 1H), 2.69 (dd, *J* = 12.4, 9.2 Hz, 1H), 2.43 (dd, *J* = 12.4, 4.1 Hz, 1H), 1.06 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 138.5 (C), 136.1 (CH), 129.4 (CH), 128.1 (CH), 127.0 (CH), 116.4 (CH₂), 60.3 (CH₂), 59.0 (CH), 51.8 (CH₂), 51.5 (CH₂), 11.1 (CH₃); IR (film): 3032, 2972, 2930, 2842, 1641, 1496, 1451, 1371, 1059, 1026, 991, 919, 735, 698 cm⁻¹; HRMS (EI): Exact mass calcd for C₁₃H₂₀N₂O [M]⁺: 220.1576. Found: 220.1592.

2-(Benzyl(hydroxy)amino)-*N*-(2,2-diethoxyethyl)propan-1-amine (2f) - (Table 2.5, entry 6)



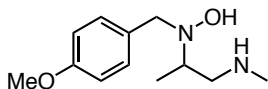
Diamine **2f** was synthesized according to the general procedure (C₆H₆, 96 h). 0.216 g of product was isolated using 1.5 mmol of *N*-benzylhydroxylamine from the reaction with aldehyde **2.1** (56 %) as a yellow oil after column chromatography (10 % MeOH/CH₂Cl₂). Alternatively, it was synthesized in 29 h at 60 °C by the general procedure, and isolated in 56 % yield (0.24 g). TLC *R_f* 0.29 (10 % MeOH/CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 7.39-7.38 (m, 5H), 4.58 (t, *J* = 5.6 Hz, 1H), 3.97 (d, *J* = 13.2 Hz, 1H), 3.72 (d, *J* = 13.2 Hz, 1H), 3.67 (tt, *J* = 8.9, 4.7 Hz, 2H), 3.51 (dq, *J* = 14.2, 7.1, 0.9 Hz, 2H), 3.07-2.96 (m, 1H), 2.86-2.67 (m, 4H), 1.20 (t, *J* = 7.0 Hz, 3H), 1.18 (t, *J* = 7.0 Hz, 3H), 1.11 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 138.5 (C), 129.2 (CH), 128.2 (CH), 127.1 (CH), 101.7 (CH), 62.7 (CH₂), 62.1 (CH₂), 60.4 (CH₂), 59.7 (CH), 53.3 (CH₂), 51.6 (CH₂), 15.3 (CH₃), 11.7 (CH₃); IR (film): 3029, 2975, 2877, 1493, 1451, 1371, 1341, 1121, 1064, 735, 698 cm⁻¹; HRMS (EI): Exact mass calcd for C₁₆H₂₈N₂O₃ [M]⁺: 296.2100. Not found. Exact mass calcd C₉H₁₂NO [M-(OEt)₂CHCH₂NHCH₂]⁺: 150.0919. Found: 150.0924.¹⁵⁵

2-(((1-(Allylamino)propan-2-yl)(hydroxy)amino)methyl)phenol (2g) - (Table 2.5, entry 7)



Diamine **2g** was synthesized according to the general procedure (CHCl_3 , 46 h). 0.143 g of product was isolated using 1.0 mmol of *N*-benzylhydroxylamine from the reaction with aldehyde **2.1** (61 %) as a yellow oil after column chromatography (10 % $\text{MeOH}/\text{CH}_2\text{Cl}_2$). TLC R_f 0.36 (15 % $\text{MeOH}/\text{CH}_2\text{Cl}_2$); ^1H NMR (300 MHz, CDCl_3) δ 7.18 (dt, $J = 8.1, 1.7$ Hz, 1H), 7.04 (dd, $J = 7.5, 1.3$ Hz, 1H), 6.87 (dd, $J = 8.1, 1.0$ Hz, 1H), 6.80 (dt, $J = 7.5, 1.1$ Hz, 1H), 5.89 (ddt, $J = 16.7, 10.4, 6.3$ Hz, 1H), 5.24-5.16 (m, 2H), 4.16 (d, $J = 13.7$ Hz, 1H), 3.93 (d, $J = 13.9$ Hz, 1H), 3.29 (dq, $J = 13.9, 6.1$ Hz, 1H), 3.11 (td, $J = 13.2, 6.5$ Hz, 1H), 2.86 (dq, $J = 12.9, 6.4$ Hz, 1H), 1.15 (d, $J = 6.5$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 156.9 (C), 134.4 (CH), 129.7 (CH), 129.0 (CH), 122.2 (CH), 119.4 (CH), 117.9 (CH_2), 116.5 (CH), 58.1 (CH), 57.9 (CH_2), 51.8 (CH_2), 51.3 (CH_2), 11.5 (CH_3); IR (film): 3078, 2835, 1892, 1493, 1455, 1254, 1155, 1037, 995, 923, 756 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_{13}\text{H}_{20}\text{N}_2\text{O}_2$ $[\text{M}]^+$: 236.1525. Found: 236.1522.

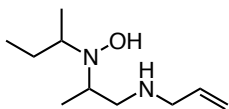
***N*-(4-Methoxybenzyl)-*N*-hydroxy-1-(methyamino)propan-2-amine (2h) - (Table 2.5, entry 8)**



Diamine **2h** was synthesized according to the general procedure (C_6H_6 , 24 h). 0.062 g was isolated using 0.5 mmol of *N*-benzylhydroxylamine from the reaction with aldehyde **2.1** (51 %) as a yellow oil after column chromatography (1 % $\text{Et}_3\text{N}/10$ % $\text{MeOH}/\text{CH}_2\text{Cl}_2$). TLC R_f 0.10 (10 % $\text{MeOH}/\text{CH}_2\text{Cl}_2$); ^1H NMR (300 MHz, CDCl_3) δ 7.24 (d, $J = 8.7$ Hz, 2H), 6.82 (d, $J = 8.7$ Hz, 2H), 3.85 (d, $J = 13.0$ Hz, 1H), 3.75 (s, 3H), 3.61 (d, $J = 13.0$ Hz, 1H), 2.93-2.99 (m, 1H), 2.70-2.81 (m, 1H), 2.41-2.56 (m, 1H), 2.23 (s, 3H), 1.04 (s, $J = 6.5$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.7 (C), 130.6 (CH), 130.5 (CH), 113.6

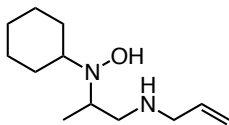
(C), 59.8 (CH₂) 58.4 (CH), 55.3 (CH₃), 54.8 (CH₂), 35.4 (CH₃); IR (film): 3302, 2934, 2887, 2835, 1612, 1510, 1462, 1301, 1173, 1020, 787 cm⁻¹; HRMS (EI): Exact mass calcd for C₁₂H₂₀N₂O₂ [M]⁺: 224.1524. Found: 224.1462.

***N*-(1-(Allylamino)propan-2-yl)-*N*-hydroxybutan-2-amine (2i) - (Table 2.5, entry 9)**



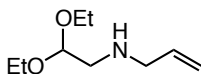
Diamine **2i** was synthesized according to the general procedure (CHCl₃, 24 h). 0.0571 g of product was isolated using 0.5 mmol of *N*-benzylhydroxylamine from the reaction with aldehyde **2.1** (61 %) as a white solid after column chromatography (1 % Et₃N/ 10 % MeOH/CH₂Cl₂), and characterized as an inseparable mixture of diastereomers (1:1). TLC *R*_f 0.38 (10 % MeOH/CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 5.88 [ddt, *J* = 16.4, 10.5, 6.0 Hz, 1H (mix)], 5.15 [d, *J* = 17.3 Hz, 1H (mix)], 5.08 [d, *J* = 10.2 Hz, 1H (mix)], 3.29-3.19 [m, 2H (mix)], 3.14-3.04 [m, 1H (mix)], 2.83-2.71 [m, 2H (mix)], 2.61-2.53 [m, 1H (mix)], 1.82-1.69 [m, 1H (minor)], 1.66-1.53 [m, 1H (major)], 1.11 [d, *J* = 6.3 Hz, 3H (first diastereomer)], 1.02 [d, *J* = 6.4 Hz, 3H (second diastereomer)], 0.97 [d, *J* = 6.3 Hz, 3H (first diastereomer)], 0.95 [d, *J* = 6.2 Hz, 3H (second diastereomer)], 0.88 [t, *J* = 7.4 Hz, 3H (first diastereomer)], 0.87 [t, *J* = 7.5 Hz, 3H (second diastereomer)]; ¹³C NMR (75 MHz, CDCl₃) δ 136.4 (CH, major), 136.3 (CH, minor), 116.2 (CH₂, minor), 116.1 (CH₂, major), 59.0 (CH, major), 58.8 (CH, minor), 55.4 (CH, mix), 53.2 (CH₂, minor), 52.6 (CH₂, major), 52.1 (CH₂, major), 52.0 (CH₂, minor), 27.2 (CH₂, major), 24.9 (CH₂, minor), 16.7 (CH₃, major), 13.8 (CH₃, minor), 12.1 (CH₃, minor), 11.7 (CH₃, minor), 10.3 (CH₃, major), 10.1 (CH₃, major); IR (film): 3298, 3082, 2972, 2941, 2880, 1645, 1457, 1371, 1170, 991, 919 cm⁻¹; HRMS (EI): Exact mass calcd for C₁₀H₂₂N₂O [M]⁺: 186.1732. Found: 186.1720.

***N*-(2-(Cyclohexyl(hydroxy)amino)propyl)prop-2-en-1-amine (2j) - (Table 2.5, entry 10)**



Diamine **2j** was synthesized according to the general procedure (CHCl_3 , 29 h). 0.0581 g of product was isolated using 0.5 mmol of *N*-benzylhydroxylamine from the reaction with aldehyde **2.1** (57 %) as a yellow oil after column chromatography (1 % Et_3N /5 % $\text{MeOH}/\text{CH}_2\text{Cl}_2$). TLC R_f 0.11 (5 % $\text{MeOH}/\text{CH}_2\text{Cl}_2$); ^1H NMR (300 MHz, CDCl_3) δ 5.90 (ddt, $J = 16.6, 10.5, 6.1$ Hz, 1H), 5.16 (dd, $J = 19.8, 13.7$ Hz, 2H), 4.74 (br s, 2H), 3.33-3.12 (m, 3H), 2.85 (dd, $J = 12.0, 8.5$ Hz, 1H), 2.64 (br s, 1H) 2.57 (dd, $J = 12.1, 4.3$ Hz, 1H), 2.06 (m, 1H), 1.75 (m, 3H), 1.59 (d, $J = 10.4$ Hz, 1H) 1.32-1.10 (m, 5H), 0.98 (d, $J = 6.4$ Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 135.4 (CH), 117.1 (CH_2), 61.1 (CH), 53.9 (CH), 51.9 (CH_2), 51.6 (CH_2), 31.1 (CH_2), 28.5 (CH_2), 25.9 (CH_2), 24.9 (CH_2), 24.8 (CH_2), 10.7 (CH_3); IR (film): 3291, 3082, 2930, 2854, 1641, 1451, 1371, 1261, 1162, 995, 919 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_{12}\text{H}_{24}\text{N}_2\text{O}$ $[\text{M}]^+$: 212.1889. Found: 212.1887.

***N*-(2,2-Diethoxyethyl)prop-2-en-1-amine**



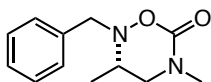
This allylamine was synthesized according to a modified procedure of Stach *et al.*¹⁵⁶ A mixture of bromoacetaldehyde diethyl acetal (2.00 g, 1.50 mL, 0.102 mmol) in allylamine (11.4 g, 15.0 mL, 0.200 mol) was heated at 100 °C for 3 h. Then, a solution of NaOH (1.0 g) in distilled water (10.0 mL) was added, and the mixture was stirred for 30 min. The mixture was then extracted with Et_2O , and the organic phase was separated, dried over MgSO_4 , filtered and concentrated under reduced pressure. After column chromatography (3:1 Et_2O /Petroleum ether), the product was obtained as a dark red liquid in 71 % yield (1.26 g). R_f 0.36 (3:1 Et_2O /pentane); ^1H NMR (300 MHz, CDCl_3) δ 5.87

¹⁵⁶ Stach, L. J., Hotz, R. D. & Richter, S. B. Dioxolane substituted amides. U.S. Patent 4,113.464, September 12, 1978.

(ddt, $J = 16.3, 10.2, 6.0$ Hz, 1H), 5.11 (ddd, $J = 13.7, 11.2, 1.3$ Hz, 2H), 4.58 (t, $J = 5.6$ Hz, 1H), 3.68 (qd, $J = 9.4, 7.1$ Hz, 2H), 3.52 (qd, $J = 9.4, 7.1$ Hz, 2H), 3.24 (d, $J = 6.0$ Hz, 2H), 2.71 (d, $J = 5.6$ Hz, 2H), 1.22 (br s, 1H), 1.19 (t, $J = 7.1$ Hz, 6H); ^{13}C NMR (75 MHz, CDCl_3) δ 136.6 (CH), 116.0 (CH_2), 102.2 (CH), 62.4 (CH_2), 52.3 (CH_2), 51.5 (CH_2), 15.3 (CH_3); IR (film): 2979, 2918, 1371, 1121, 1060 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_9\text{H}_{19}\text{NO}_2$ $[\text{M}]^+$: 173.1416. Not found. Exact mass calcd for $\text{C}_7\text{H}_{14}\text{NO}$ $[\text{M}-\text{OEt}]^+$: 128.1075. Found: 128.1078.

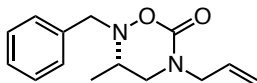
Procedures for determining the enantiomeric excess of substrates 2b, 2c and 2e

(S)-2-Benzyl-3,5-dimethyl-1,2,5-oxadiazinan-6-one (2b.1)-(Table 2.6, entry 1)



N-Benzyl-*N*-hydroxy-1-(methyl-amino)propan-2-amine (0.142 g) was dissolved in CH_2Cl_2 (2 mL). 1,1'-Carbonyldiimidazole (0.17 g, 1.5 equiv.) was then added to the solution. After stirring at room temperature for 3 hours under argon atmosphere the solvent was then removed *in vacuo* and the residue purified by flash chromatography over silica gel. The title compound was obtained as a white solid in 75 % yield (0.127 g) and 72/28 enantiomeric ratio. R_f 0.6 (95:5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$). ^1H 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, $J = 6.2$ 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} ; $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_2$ $[\text{M}]^+$: 220.1128. Found: 220.11978. Chiral HPLC: ChiralPak OJ-H, *i*PrOH/hexane = 10/90, 1.0 mL/min, 210 nm, $t_{\text{major}} = 28.3$ min, $t_{\text{minor}} = 31.7$ min.

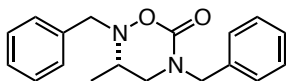
(S)-5-Allyl-2-benzyl-3-methyl-1,2,5-oxadiazinan-6-one (2e.1)-(Table 2.6, entry 2)



N-(2-(Benzyl(hydroxy)-amino)propyl)-prop-2-en-1-amine (0.270 g) was dissolved in CH_2Cl_2 (2 mL). 1,1'-Carbonyldiimidazole (0.293 g, 1.5 equiv.) was then added to the

solution. After stirring at room temperature for 3 hours under argon atmosphere the solvent was then removed *in vacuo* and the residue purified by flash chromatography over silica gel. The title compound was obtained as a white solid in 70 % yield (0.206 g) and 89/11 enantiomeric ratio. R_f 0.32 (1:1 EtOAc/Petroleum Ether). ^1H NMR (400 MHz, CDCl_3) δ 7.39-7.24 (m, 5H), 5.81 (ddt, $J = 15.8, 10.9, 6.1$ Hz, 1H), 5.19 (dt, $J = 16.2, 1.2$ Hz, 2H), 4.28 (d, $J = 14.0$ Hz, 1H), 4.30-3.88 (m, 3H), 3.27-3.02 (m, 3H), 1.19 (d, $J = 6.3$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 154.1, 135.3, 132.3, 132.1, 129.3, 128.4, 127.7, 118.3, 58.9, 51.5, 50.6. IR (film): 2986, 2973, 1703, 1485, 1447, 1292 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_2$ $[\text{M}]^+$: 246.1368. Found: 246.1712 Chiral HPLC: ChiralPak AD-H, *i*PrOH/hexane = 5/95, 1.0 mL/min, 210 nm, $t_{\text{major}} = 36.8$ min, $t_{\text{minor}} = 32.5$ min.

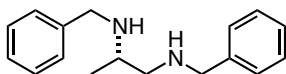
(S)-2,5-Dibenzyl-3-methyl-1,2,5-oxadiazinan-6-one (2c.1)-(Table 2.6, entries 3 and 4)



N-Benzyl-2-(benzyl(hydroxy)-amino)propan-1-amine (0.088 g) was dissolved in CH_2Cl_2 (2 mL). 1,1'-Carbonyldiimidazole (0.053 g, 1.5 equiv.) was then added to the solution. After stirring at room temperature for 2 hours under argon atmosphere the solvent was then removed *in vacuo* and the residue purified by flash chromatography over silica gel. The title compound was obtained as a white solid in 93 % yield (0.090 g) and 88/12 enantiomeric ratio with catalyst **2.2** and 91% yield (0.3147 g) and 94/6 12 enantiomeric ratio for catalyst **2.3**. TLC R_f 0.28 (30 % EtOAc/Petroleum Ether). ^1H NMR (400 MHz, CDCl_3) δ 7.37-7.42 (2H, m), 7.24-7.36 (8H, m), 4.59 (1H, d, $J = 14.8\text{Hz}$), 4.48 (1H, d, $J = 15.2\text{Hz}$), 4.29 (1H, d, $J = 14.0\text{Hz}$), 3.91 (1H, d, $J = 14.0\text{Hz}$), 3.14-3.25 (2H, m), 2.95-3.05 (1H, m), 1.14 (3H, d, $J = 6.2\text{Hz}$). ^{13}C NMR (100 MHz, CDCl_3) 154.6, 136.2, 135.3, 129.3, 128.7, 128.4, 128.2, 127.8, 127.7, 58.9, 54.2, 51.6, 51.3, 14.0; IR (film): 3034, 2920, 1700, 1487, 1238, 707 cm^{-1} ; HRMS (EI) calculated for $\text{C}_{18}\text{H}_{20}\text{N}_2\text{O}_2$ $[\text{M}]^+$: 296.1525. Found: 296.1527. Chiral HPLC: ChiralPak AD-H, *i*PrOH/hexane = 5/95, 1.0 mL/min, 210 nm, $t_{\text{major}} = 41.0$ min, $t_{\text{minor}} = 43.5$ min.

Assignment of absolute configuration of *N*-dibenzyl-1,2-diaminopropane

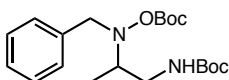
(*S*)-*N*-Dibenzyl-1,2-diaminopropane (**2c.2**)



Prepared by the method of Goti and coworkers.¹⁵⁷ *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 NH₄Cl (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/CH₂Cl₂). The mixture was cooled to ambient temperature and filtered through a pad of Celite. The Celite was washed with methanol. The washings were combined with the filtrate and concentrated under reduced pressure. A saturated Na₂CO₃ solution (15 mL) was added, and the product is extracted with ethyl acetate (3 ×15 mL). The organic phase was dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The product was purified by silica gel chromatography (5 % MeOH/CH₂Cl₂) afford the titled amine (0.15 g, 45 %). The ¹H NMR spectrum was found to be consistent with the literature.¹⁵⁸

The optical rotation was determined using a Perkin Elmer Model 141 polarimeter: [α]_D = +39.3° (c = 0.8, EtOH). Literature data for (*R*)-*N*-dibenzyl-1,2-diaminopropane is [α]_D = −37.3°, ¹⁵⁹ thus allowing assignement of the absolute configuration of **2c** as *S*.

tert-butyl(2-(benzyl((*tert* butoxycarbonyl)oxy)amino)propyl)carbamate (**2.6**)



¹⁵⁷ Cicchi, S.; Bonanni, M.; Cardona, F.; Revuelta, J.; Goti, A. *Org. Lett.* **2003**, 5, 1773-1776.

¹⁵⁸ Ralambomanana, D. A.; Razafimahefa-Ramilison, D.; Rakotohova, A.; Maugein, J.; Pelinski, L. *Bioorgan. Med. Chem.* **2008**, 16, 9546-9553.

¹⁵⁹ Kurganov, A. A.; Davankov, V. A.; Zhuchkova, Y. A.; Ponomaryova, T. M. *Inorg. Chimi. Acta.* **1980**, 39, 237-241.

N-Benzyl-1-(benzylamino)-*N*-hydroxypropan-2-amine (0.26g, 1.4 mmol) was dissolved in CH₂Cl₂ (1.3 mL) and (Boc)₂O (1.1g, 2.6 equiv, dissolved in 1.5 mL of CH₂Cl₂) was added drop wise. The solution was stirred for 24 hours then, diluted in ether and extracted with sodium bicarbonate and brine. The product was purified by flash chromatography (5 % ether/toluene) to give a white solid (0.27g, 73%). ¹H NMR (300MHz, CDCl₃) δ ppm 7.39-7.27 (m, 5H), 5.77 (br, 1H), 4.16 (d, *J* = 13.3 Hz, 1H), 3.83 (d, *J* = 13.3 Hz, 1H), 3.37 (br, 1H), 3.03-2.80 (br, 2H), 1.42 (s, 9H), 1.29 (s, 9H), 1.13 (d, *J* = 6.5 Hz, 3H); ¹³C NMR (400 MHz, CDCl₃) δ ppm 155.9 (C), 153.8 (C), 136.1 (C), 129.4 (CH), 128.3, (CH), 127.6 (CH), 83.1 (CH₂), 78.9 (CH), 60.9 (CH₂), 59.9 (C), 43.3 (C), 28.5 (CH₃), 27.5 (CH₃); IR (film) 3421, 2974.6, 1758.4, 1715.0, 1501.8, 1368.2, 1248.8, 1152.1. HRMS (EI): Exact mass calculated for C₂₀H₃₂N₂O₅ [M]⁺ = 380.4785. C₁₂H₁₄N₂O₄ [M]⁺ = 250. 2506 Found: 251.1024.

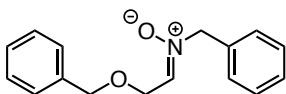
PROCEDURES AND CHARACTERIZATION FOR CHAPTER 3

General Comments

The benzene used for aldehyde screening was degassed and stored over 4-Å molecular sieves. Due to the instability of the α -benzyloxyacetaldehyde, a 1 M solution in benzene was prepared according to a modified procedure from the literature and used for all the experiments performed in benzene.¹⁵³

Molecules for mechanistic experiments

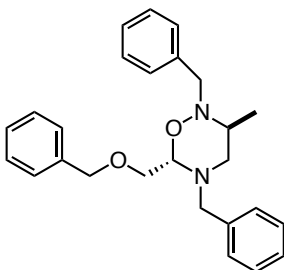
C-Benzyloxymethane-*N*-benzylnitron (3.1)



N-Benzylhydroxylamine (0.271 g, 2.19 mmol, 1.1 equiv.) was added to a mixture of 2-benzyloxyacetaldehyde (0.300 g, 1.99 mmol, 1.0 equiv.) in CHCl_3 (5 mL). After stirring for 3 hours TLC showed complete conversion. The solvent was evaporated under reduced pressure and the purification was made by flash column chromatography using 10 % *i*-PrOH in toluene as eluent. The product obtained is an off-white solid (0.510 g, 99%). Spectral datum was consistent with literature.¹⁶⁰

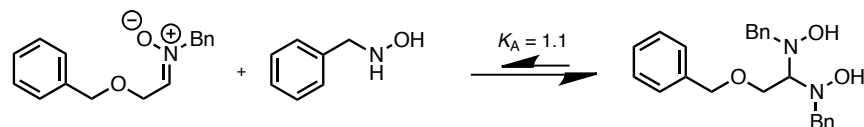
¹⁶⁰ (a) Guimond N.; MacDonald, M. J.; Lemieux, V.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2012**, *134*, 16571-16577. (b) Guimond, N. "Part A: Rhodium-Catalyzed Synthesis of Heterocycles Part B: Mechanistic Studies on Tethering Organocatalysis Applied to Cope-Type Alkene Hydroamination," PhD Thesis, University of Ottawa, ON, 2013.

Oxadiazinane (3.2)

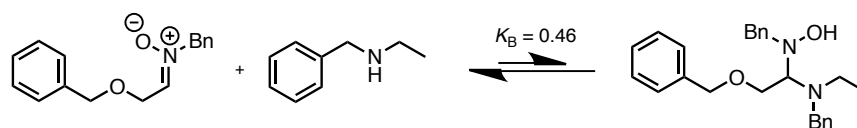


N-Allylbenzylamine (0.157 mL, 1.0 mmol, 1.0 equiv.) was added to a mixture of *C*-benzyloxymethane-*N*-benzyl nitron (0.255 g, 1.0 mmol, 1 equiv.) in CHCl₃. The mixture was heated at 50 °C in an oil bath under argon for 48 h. Volatiles were then evaporated under reduced pressure and the resulting mixture was purified by flash column chromatography using 8% EtOAc in Petroleum ether as eluent. The product was obtained as a clear oil (0.184 g, 46%). Spectral datum was consistent with literature.¹⁶⁰

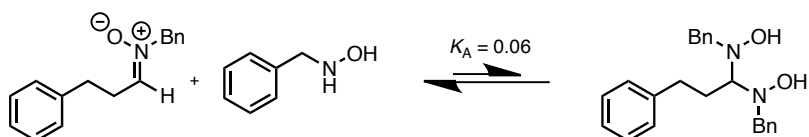
Equilibrium experiments



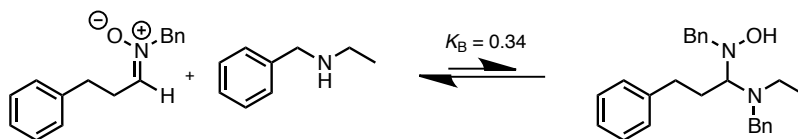
A solution of *C*-benzyloxymethane-*N*-benzyl nitron (**3.1**, 0.025g, 0.1 mmol) and *N*-benzylhydroxylamine (0.0616 g, 0.500 mmol) in 0.50 mL of C₆D₆ was loaded in a ¹H NMR tube. The reaction was monitored by ¹H NMR. After 18 hours, equilibrium was reached. A ratio of 48:52 gave a *K_A* of 1.19. Another NMR tube was filled with *C*-benzyloxymethane-*N*-benzyl nitron (**3.1**, 0.025 g, 0.10 mmol), *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) and 0.50 mL of C₆D₆. The reaction was monitored by ¹H NMR. After 18 hours, equilibrium was reached. A ratio of 37:63, gave a *K_A* of 1.00. The average *K_A* for the two runs was 1.1 ± 0.1.



A solution of *C*-benzyloxymethane-*N*-benzyl nitron (3.1, 0.025 g, 0.10 mmol) and *N*-benzylethylamine (0.0743 mL, 0.500 mmol) in 0.50 mL of C₆D₆ was loaded in a ¹H NMR tube. The reaction was monitored by ¹H NMR. After 18 hours, equilibrium was reached. A ratio of 68:32 gave a *K_B* of 0.57. Another NMR tube was filled with *C*-benzyloxymethane-*N*-benzyl nitron (3.1, 0.025 g, 0.10 mmol), *N*-benzylethylamine (0.149 mL, 1.00 mmol) and 0.45 mL of C₆D₆. The reaction was monitored by ¹H NMR. After 18 hours, equilibrium was reached. A ratio of 65:35, gave a *K_B* of 0.36. The average *K_B* for the two runs was 0.5 ± 0.1.



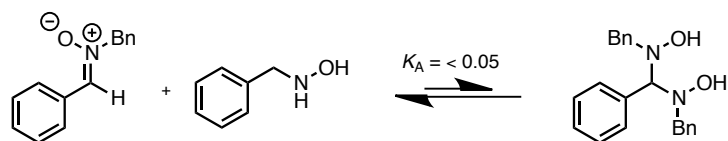
A solution of *N*-(3-phenylpropylidene)benzenemethanamine *N*-oxide¹⁶¹ (0.023 g, 0.10 mmol) and *N*-benzylhydroxylamine (0.0616 g, 0.500 mmol) in 0.50 mL of C₆D₆ was loaded in a ¹H NMR tube. The reaction was monitored by ¹H NMR. After 18 hours, equilibrium was reached. A ratio of 93:7 gave a *K_A* of 0.08. Another NMR tube was filled *N*-(3-phenylpropylidene)benzenemethanamine *N*-oxide (0.023 g, 0.10 mmol), *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) and 0.50 mL of C₆D₆. The reaction was monitored by ¹H NMR. After 18 hours, equilibrium was reached. A ratio of 93:7, gave a *K_A* of 0.04. The average *K_A* for the two runs was 0.06 ± 0.01.



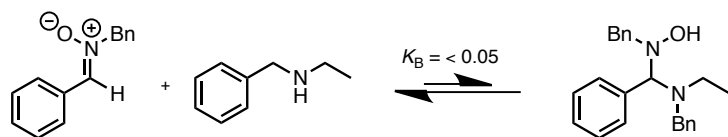
A solution of *N*-(3-phenylpropylidene)benzenemethanamine *N*-oxide¹⁶¹ (0.023 g, 0.10 mmol) and *N*-benzylethylamine (0.0743 mL, 0.500 mmol) in 0.43 mL of C₆D₆ was loaded in a ¹H NMR tube. The reaction was monitored by ¹H NMR. After 18 hours, equilibrium was reached. A ratio of 75:25 gave a *K_B* of 0.34. Another NMR tube was

¹⁶¹ Prepared according to a literature procedure: Naito, T.; Shirakawa, M.; Ikai, M.; Ninomiya, I.; Kiguchi, T. *Recl. Trav. Chim. Pays-Bas* **1996**, *115*, 13-19.

filled with *N*-(3-phenylpropylidene)benzenemethanamine *N*-oxide (0.023 g, 0.10 mmol), *N*-benzylethylamine (0.149 mL, 1.00 mmol) and 0.35 mL of C₆D₆. The reaction was monitored by ¹H NMR. After 18 hours, equilibrium was reached. A ratio of 61:39, gave a *K_B* of 0.34. The average *K_B* for the two runs was 0.34 ± 0.01.



A solution of (*E*)-*N*-benzylidene-1-phenylmethanamine oxide¹⁶² (0.021 g, 0.10 mmol) and *N*-benzylhydroxylamine (0.0616 g, 0.500 mmol) in 0.50 mL of C₆D₆ was loaded in a ¹H NMR tube. The reaction was monitored by ¹H NMR. After 18 hours, equilibrium was reached. A ratio of > 95:5 gave a *K_A* of < 0.05. Another NMR tube was filled with (*E*)-*N*-benzylidene-1-phenylmethanamine oxide (0.021 g, 0.10 mmol), *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) and 0.50 mL of C₆D₆. The reaction was monitored by ¹H NMR. After 18 hours, equilibrium was reached. A ratio of > 95:5, gave a *K_A* of < 0.05. The average *K_A* for the two runs is lower than 0.05 ± 0.01.



A solution of (*E*)-*N*-benzylidene-1-phenylmethanamine oxide¹⁶² (0.021 g, 0.10 mmol) and *N*-benzylethylamine (0.0743 mL, 0.500 mmol) in 0.43 mL of C₆D₆ was loaded in a ¹H NMR tube. The reaction was monitored by ¹H NMR. After 18 hours, equilibrium was reached a ratio of > 95:5 gave a *K_B* of < 0.05. Another NMR tube was filled with (*E*)-*N*-benzylidene-1-phenylmethanamine oxide (0.021 g, 0.10 mmol), *N*-benzylethylamine (0.149 mL, 1.00 mmol) and 0.35 mL of C₆D₆. The reaction was monitored by ¹H NMR. After 18 hours, equilibrium was reached. A ratio of > 95:5 gave a *K_B* of < 0.05. The

¹⁶² Prepared according to a literature procedure: Aschwanden, P.; Kvaerno, L.; Geisser, R. W.; Kleinbeck, F.; Carreira, E. M. *Org. Lett.* **2005**, 7, 5741-5742.

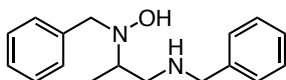
average K_B for the two runs is lower than 0.05 ± 0.01 .

Paraformaldehyde-catalyzed Cope-type hydroamination of allylic amines with *N*-Alkylhydroxylamines

General procedure 3.1

A 5-mL unsealed tube was charged with a stir bar, amine (1.50 equiv.) paraformaldehyde (0.05-0.10 equiv.), hydroxylamine (1.00 equiv.) and *t*-BuOH (1.0 M). The tube was sealed and the reaction was stirred at 30 °C, and monitored by TLC or ^1H NMR. The crude reaction mixture was concentrated under reduced pressure and purified by column chromatography to give the corresponding *N,N*-dialkylhydroxylamine products.

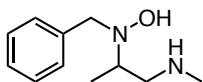
N-Benzyl-2-(benzyl(hydroxy)amino)propan-1-amine. (3a)



The compound was prepared following the general procedure 3.1 using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) and paraformaldehyde (0.05 equiv.). 0.230 g of product was isolated as a white solid (85%) after column chromatography (1 % Et_3N /1 % $\text{MeOH}/\text{CH}_2\text{Cl}_2$). ^1H NMR (300 MHz, CDCl_3) δ 7.37-7.24 (m, 10H), 3.93 (d, J = 13.2 Hz, 1H), 3.73 (d, J = 13.1 Hz, 1H), 3.72 (d, J = 13.3 Hz, 1H), 3.67 (d, J = 13.2 Hz, 1H), 3.08-3.02 (m, 1H), 2.80 (dd, J = 12.2, 8.5 Hz, 1H), 2.64 (dd, J = 12.2, 4.0 Hz, 1H), 1.11 (d, J = 6.5 Hz, 3H). Spectral datum was consistent with literature.¹⁶³

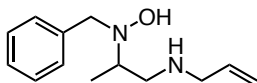
¹⁶³ See Chapter 2. Supporting Information: MacDonald, M. J “ Organocatalytic tethering strategy: Applications in the Cope-type hydroamination of alkenes” PhD Thesis, University of Ottawa, ON, 2014.

2-(Benzyl(hydroxy)amino)-*N*-methylpropan-1-amine. (3b)



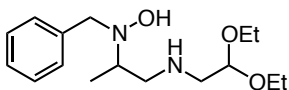
The compound was prepared following the general procedure 3.1 using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) and paraformaldehyde (0.05 equiv.). 0.191 g of product was isolated as a pale yellow oil (98%) after column chromatography (1 % Et₃N/ 10 % MeOH/CH₂Cl₂). ¹H NMR (300 MHz, CDCl₃) δ 7.39-7.26 (m, 5H), 3.97 (d, *J* = 13.2 Hz, 1H), 3.72 (d, *J* = 13.2 Hz, 1H), 3.08-2.97 (m, 1H), 2.78 (dd, *J* = 12.2, 8.5 Hz, 1H), 2.56 (dd, *J* = 12.2, 4.0 Hz, 1H), 2.35 (s, 3H), 1.12 (d, *J* = 6.5 Hz, 3H). Spectral datum was consistent with literature.¹⁶³

***N*-(2-(Benzyl(hydroxy)amino)propyl)prop-2-en-1-amine. (3c)**



The compound was prepared following the general procedure 3.1 using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) and paraformaldehyde (0.05 equiv.). 0.203 g of product was isolated as a pale yellow oil (92%) after column chromatography (1 % Et₃N/ 5 % MeOH/CH₂Cl₂). ¹H NMR (300 MHz, CDCl₃) δ 7.36- 7.24 (m, 5H), 5.74 (ddt, *J* = 16.4, 10.2, 6.2 Hz, 1H), 5.06 (dt, *J* = 17.1, 1.5 Hz, 2H), 3.92 (d, *J* = 13.0 Hz, 1H), 3.69 (d, *J* = 13.0 Hz, 1H), 3.02 (d, *J* = 5.8 Hz, 1H), 2.98-2.95 (m, 1H), 2.69 (dd, *J* = 12.4, 9.2 Hz, 1H), 2.43 (dd, *J* = 12.4, 4.1 Hz, 1H), 1.06 (d, *J* = 6.5 Hz, 3H). Spectral datum was consistent with literature.¹⁶³

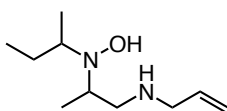
2-(Benzyl(hydroxy)amino)-*N*-(2,2-diethoxyethyl)propan-1-amine. (3d)



The compound was prepared following the general procedure 3.1 using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) and paraformaldehyde (0.10 equiv.). 0.196 g

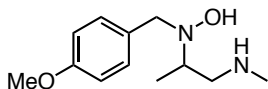
of product was isolated as a pale yellow oil (66%) after column chromatography (1 % Et₃N/ 5 % MeOH/CH₂Cl₂). ¹H NMR (300 MHz, CDCl₃) δ 7.39-7.38 (m, 5H), 4.58 (t, *J* = 5.6 Hz, 1H), 3.97 (d, *J* = 13.2 Hz, 1H), 3.72 (d, *J* = 13.2 Hz, 1H), 3.67 (tt, *J* = 8.9, 4.7 Hz, 2H), 3.51 (dq, *J* = 14.2, 7.1, 0.9 Hz, 2H), 3.07-2.96 (m, 1H), 2.86-2.67 (m, 4H), 1.20 (t, *J* = 7.0 Hz, 3H), 1.18 (t, *J* = 7.0 Hz, 3H), 1.11 (d, *J* = 6.5 Hz, 3H). Spectral datum was consistent with literature.¹⁶³

***N*-(2-(*sec*-Butyl(hydroxy)amino)propyl)prop-2-en-1-amine. (3e)**



The compound was prepared following the general procedure 3.1 using *N*-(*sec*-butyl)hydroxylamine (0.089 g, 1.0 mmol) and paraformaldehyde (0.10 equiv.). 0.138 g of product was isolated as a pale yellow oil and mixture of 1:1 diastereomers (72%) after column chromatography (1 % Et₃N/ 10 % MeOH/CH₂Cl₂). ¹H NMR (300 MHz, CDCl₃) δ 5.88 [ddt, *J* = 16.4, 10.5, 6.0 Hz, 1H (mix)], 5.15 [d, *J* = 17.3 Hz, 1H (mix)], 5.08 [d, *J* = 10.2 Hz, 1H (mix)], 3.29-3.19 [m, 2H (mix)], 3.14-3.04 [m, 1H (mix)], 2.83-2.71 [m, 2H (mix)], 2.61-2.53 [m, 1H (mix)], 1.82-1.69 [m, 1H (minor)], 1.66-1.53 [m, 1H (major)], 1.11 [d, *J* = 6.3 Hz, 3H (first diastereomer)], 1.02 [d, *J* = 6.4 Hz, 3H (second diastereomer)], 0.97 [d, *J* = 6.3 Hz, 3H (first diastereomer)], 0.95 [d, *J* = 6.2 Hz, 3H (second diastereomer)], 0.88 [t, *J* = 7.4 Hz, 3H (first diastereomer)], 0.87 [t, *J* = 7.5 Hz, 3H (second diastereomer)]. Spectral datum was consistent with literature.¹⁶³

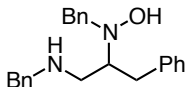
2-(Hydroxy(4-methoxybenzyl)amino)-*N*-methylpropan-1-amine. (3f)



The compound was prepared following the general procedure 3.1 using *N*-(4-methoxybenzyl)hydroxylamine (0.153 g, 1.00 mmol) and paraformaldehyde (0.10 equiv.). 0.122 g of product was isolated as a pale yellow oil (80%) after column

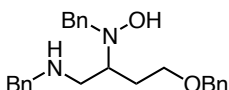
chromatography (1 % Et₃N/ 10 % MeOH/CH₂Cl₂). ¹H NMR (300 MHz, CDCl₃) δ 7.24 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 3.85 (d, *J* = 13.0 Hz, 1H), 3.75 (s, 3H), 3.61 (d, *J* = 13.0 Hz, 1H), 2.93 (m, 1H), 2.70 (m, 1H), 2.406 (m, 1H), 2.23 (s, 3H), 1.04 (s, *J* = 6.5 Hz, 3H). Spectral datum was consistent with literature.¹⁶³

***N*-Benzyl-2-(benzyl(hydroxy)amino)-3-phenylpropan-1-amine. (3g)**



The compound was prepared following the general procedure using *N*-benzylhydroxylamine (0.153 g, 1.00 mmol) and paraformaldehyde (0.10 equiv.) at 50°C. 0.277 g of product was isolated as a white solid (80%) after column chromatography (1 % NH₄OH/ 1 % MeOH/CH₂Cl₂). ¹H NMR (300 MHz, CDCl₃): δ 7.55 (d, *J* = 6.9 Hz, 2H), 7.51-7.30 (m, 4H), 7.25-7.07 (m, 6H), 6.97-6.87 (m, 2H), 4.35 (d, *J* = 12.4 Hz, 1H), 4.08 (d, *J* = 13.4 Hz, 1H), 3.80 (d, *J* = 13.2 Hz, 1H), 3.46-3.29 (m, 2H), 3.12-2.94 (m, 2H), 2.63 (m, 1H), 2.40 (m, 1H). Spectral datum was consistent with literature.⁸⁶

***N*-Benzyl-2-(benzyl(hydroxy)amino)-4-(benzyloxy)butan-1-amine. (3h and 3i)**



The compound was prepared following the general procedure using *N*-benzylhydroxylamine (0.153 g, 1.00 mmol) and paraformaldehyde (0.10 equiv.) at 50 °C on two different substrates. Using (*Z*)-*N*-benzyl-4-(benzyloxy)but-2-en-1-amine (0.401 g, 1.50 mmol), 0.381 g of the desired product was isolated as a white solid (97%). Using (*E*)-*N*-benzyl-4-(benzyloxy)but-2-en-1-amine (0.401 g, 1.50 mmol), 0.324 g was isolated as a white solid (83%) after column chromatography (1 % NH₄OH/ 1 % MeOH/CH₂Cl₂). ¹H NMR (300 MHz, CDCl₃): δ 7.35-7.19 (m, 15H), 4.50-4.43 (m, 2H), 3.88-3.80 (m, 2H), 3.59-3.48 (m, 4H), 3.04 (dd, *J* = 7.8, 3.8 Hz, 1H), 2.73 (dd, *J* = 26.2, 6.1 Hz, 2H), 2.12 (m, 1H), 1.69 (m, 1H). Spectral datum was consistent with literature.⁸⁶

PROCEDURES AND CHARACTERIZATION FOR CHAPTER 4

General Comments

High Performance Liquid Chromatography (HPLC) was performed on an Agilent 1200 series instrument. Unless otherwise noted, all deuterated solvents and reagents were used without further purification. Solvents were either distilled according to standard techniques or degassed prior to use.

Allylamines

N-Allylglycine ethyl ester,¹⁶⁴ *N*-allyl- β -alanine methyl ester,¹⁶⁵ *N*-(2,2-diethoxyethyl)prop-2-en-1-amine¹⁶⁶ and *N*-benzylallylamine¹⁶⁷ were prepared according to literature procedures.

Aldehydes

(4*S*)-3-(2,2-Dimethylpropanoyl)-2,2-dimethyl-1,3-oxazolidine-4-carbaldehyde was ordered from TCI America and (4*R*)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde was purchased from Sigma Aldrich. (2*R*,5*R*,6*R*)-5,6-Dimethoxy-5,6-dimethyl-1,4-dioxane-2-carbaldehyde,¹⁶⁸ (2*S*)-2-(benzyloxy)propane,¹⁶⁹ (4*R*)-2,2-diphenyl-1,3-dioxolane-4-carbaldehyde¹⁵⁴ and 2,3:4,5-di-*O*-isopropylidene-aldehydo- β -D-arabino-hexosulo-2,6-pyranose¹⁷⁰ were prepared according to literature procedures. A racemic sample of [(4*S*)-2,2-diphenyl-1,3-dioxolan-4-yl]methanol¹⁷¹ was prepared as reported in the literature.

¹⁶⁴ Reichwein, J. F.; Liskamp, R. M. J. *Eur. J. Org. Chem.* **2000**, 12, 2335-2344.

¹⁶⁵ Brass, S.; Gerber, H. D.; Doerr, S.; Diederich, W. E. *Tetrahedron* **2006**, 62, 1777-1786.

¹⁶⁶ MacDonald, M. J.; Schipper, D. J.; Ng, P. J.; Moran, J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2011**, 133, 20100-20103.

¹⁶⁷ Mukherjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, 129, 11336-11337.

¹⁶⁸ Michel, P.; Ley, S. V. *Angew. Chem., Int. Ed.* **2010**, 49, 8984-8987.

¹⁶⁹ Enders, D.; von Berg, S.; Jandeleit, B. *Org. Synth.* **2002**, 41, 3895-3898.

¹⁷⁰ Cubero, I. I.; Lopez-Espinosa, M T. Plaza. *Carbohydrate Res.* **1990**, 250, 293-304.

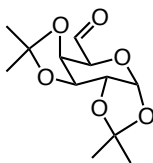
¹⁷¹ Sax, M.; Ebert, K.; Schepmann, D.; Wibbeling, B.; Wunsch, B. *Bioorg. Med. Chem.* **2006**, 14, 5955-5962.

Racemic hydroamination products

Authentic racemic samples for entries **4.1-4.20** were prepared according to two different procedures: 1) a related racemic reaction with α -benzyloxyacetaldehyde¹⁶⁶ or 2) upon heating a mixture of hydroxylamine and allylamine under solvent-free conditions at 80°C.⁸⁶ Derivatization of the racemic hydroamination product for determination of enantiomeric ratio was performed as described below.

Preparation of aldehydes

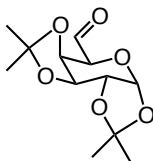
(3a*R*,5*S*,5a*R*,8a*R*,8b*R*)-2,2,7,7-Tetramethyltetrahydro-3a*H*-bis[1,3]dioxolo[4,5-*b*:4',5'-*d*]pyran-5-carbaldehyde (**4g**)



To a 50 mL round bottom flask equipped with a magnetic stirrer was added 1,2:3,4-di-*O*-isopropylidene-beta-D-fructopyranose (1.01 g, 3.84 mmol), CH₂Cl₂ (25 mL). The mixture is then cooled to 0°C in an ice bath followed by DMSO (2.10 mL, 14.3 mmol), Et₃N (2.56 mL, 17.9 mmol), and SO₃•pyridine (2.27 g, 14.3 mmol). The mixture was stirred at 0°C for 2 hours before quenching with NaHCO₃. The organics were extracted 3 times with CH₂Cl₂ (40 mL), washed with water, brine, and dried over Na₂SO₄ 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%). TLC *R*_f 0.17 (30% EtOAc/ Hexane). Spectral datum was consistent with literature.¹⁷² ¹H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (100 MHz, CDCl₃) δ 200.3, 110.0, 109.0, 96.2, 73.2, 71.7, 70.5, 70.4, 26.0, 25.8, 24.8, 24.2.

¹⁷² Serra, F.; Olszewski, T. K.; Grison, C.; Coutrot, P.; Esteve-Quelquejeu, M.; Herson, P. *Eur. J. Org. Chem.* **2011**, 10, 1841-1847.

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



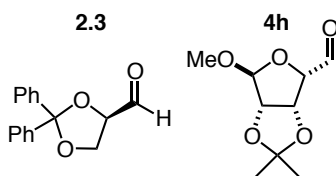
Prepared according to Barton *et al.* from D-mannose¹⁷³. The aldehyde was purified by flash column chromatography on silica gel using Hexane/EtOAc (40:60). TLC R_f 0.23 (30% EtOAc/ Hexane). ^1H NMR (400 MHz, CDCl_3) δ 9.66 (d, J = 1.2 Hz, 1H), 5.10-5.04 (m, 2H), 4.61 (d, J = 5.6 Hz, 1H), 4.38 (d, J = 4.0 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} .

Procedure for screening chiral aldehydes as potential catalysts (Table 4.1)

A 5 mL round bottom flask was charged with a stir bar, aldehyde (**2.2**, **2.3**, **4c-4h**) (0.20 mmol), C_6H_6 or C_6F_6 (1 mL) *N*-benzylhydroxylamine (1 mmol) and *N*-benzylallylamine (1.5 mmol). The reaction was stirred at room temperature for 24 hours. 1,4-Dimethoxybenzene 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* isomer (See Chapter 2 supporting information for determination of absolute configuration).

General procedures for tethered hydroaminations of allylic amines with *N*-alkylhydroxylamines (Table 4.3)

¹⁷³ Barton, D. H. R.; Gero, S. D.; Quiclet-Sire, B.; Samadi, M. *Tetrahedron: Asymmetry* **1994**, 5, 2123-2136.



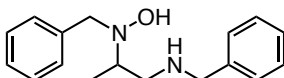
General procedure 4.1

A 5-mL round bottom flask was charged with a stir bar, hydroxylamine (1 equiv.), C₆F₆ (1.0 M to hydroxylamine), amine (1.5 equiv) and **2.3** (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.

General procedure 4.2

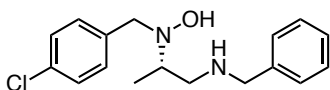
A 5-mL round bottom flask was charged with a stir bar, **4h** (0.2 equiv.), C₆H₆ (1M to hydroxylamine), hydroxylamine (1 equiv.), and amine (1.5 equiv.). The reaction was stirred at room temperature for 72 hours. The crude reaction mixture was concentrated under reduced pressure and purified by column chromatography to give the corresponding *N,N*-dialkylhydroxylamine products.

*N*¹,*N*²-Dibenzyl-*N*²-hydroxypropane-1,2-diamine (**4.1**) - (Table 4.3, Entry 1 (*S*) & (*R*))



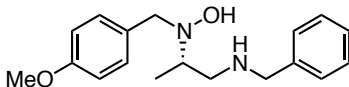
Following general procedure 4.1 using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) the indicated compound was purified by flash column chromatography on silica gel using (1 % Et₃N/10 % MeOH/CH₂Cl₂) to give a pale yellow oil (0.270 g, 91%). Following general procedure 4.2 using *N*-benzylhydroxylamine (0.0615 g, 0.500 mmol) gave (0.107 g, 79%). Spectral datum was consistent with literature.¹⁶³

(S)-N¹-Benzyl-N²-(4-chlorobenzyl)-N²-hydroxypropane-1,2-diamine (4.2) - (Table 4.3)



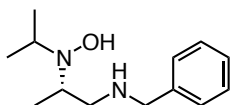
Following general procedure 4.1 using *N*-4-chlorobenzylhydroxylamine (0.157 g, 1.27 mmol) the indicated compound was purified by flash column chromatography on silica gel (gradient 1% MeOH/CH₂Cl₂ to 1 % Et₃N/5 % MeOH/CH₂Cl₂). The title compound was obtained as a pale yellow oil (0.314 g, 81%). TLC *R*_f 0.25 (1 % MeOH/CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 7.36-7.22 (m, 9H), 3.87 (d, *J* = 16.0 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* = 4.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₇H₂₁N₂OCl [M]⁺: 304.1342. Found: 304.1347.

(S)-N¹-Benzyl-N²-hydroxy-N²-(4-methoxybenzyl)propane-1,2-diamine (4.3) - (Table 4.3)



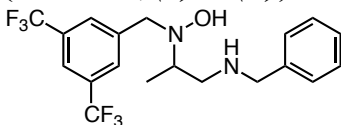
Following general procedure 4.1 using *N*-4-methoxybenzylhydroxylamine (0.153 g, 1.00 mmol). The indicated compound was purified by flash column chromatography on silica gel (gradient 1% MeOH/CH₂Cl₂ to 1 % Et₃N/5 % MeOH/CH₂Cl₂). The title compound was obtained as a pale yellow oil (0.300 g, 86%). TLC *R*_f 0.18 (10% MeOH/CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₈H₂₄N₂O₂ [M]⁺: 300.1838. Found: 300.1835.

(S)-N¹-Benzyl-N²-hydroxy-N²-(propan-2-yl)propane-1,2-diamine (4.4) - (Table 4.3)



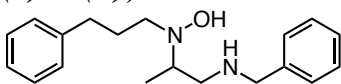
Following general procedure 4.1 using *N*-isopropylhydroxylamine (0.0445 g, 0.316 mmol) the indicated compound was purified by flash column chromatography on silica gel (gradient 1% MeOH/CH₂Cl₂ to 1 % Et₃N/5 % MeOH/CH₂Cl₂). The title compound was obtained as a pale yellow oil (0.0480 g, 60%). TLC *R*_f 0.22 (5 % MeOH/CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) 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* = 4.1 Hz, 3H), 0.97 (t, *J* = 4.1 Hz, 6.0 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) 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 C₁₄H₂₂N₂O [M⁺] 222.1732. Found: 222.1731.

***N*-Benzyl-2-((3,5-bis(trifluoromethyl)benzyl)(hydroxy)amino)propan-1-amine (4.5) - (Table 4.3, (S) & (R))**



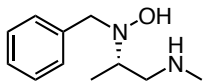
Following general procedure 4.1 using 1-[3,5-bis(trifluoromethyl)phenyl]-*N*-hydroxymethanamine (0.259 g, 1.00 mmol) the indicated compound was purified by flash column chromatography on silica gel using (1 % Et₃N/10 % MeOH/CH₂Cl₂) to give a pale yellow oil (0.406 g, 82%). Following general procedure 4.2 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/CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 7.85-7.74 (4H, m), 7.36-7.25 (m, 4H), 4.12 (s, 1H), 3.98 (d, *J* = 14.0, 1H), 3.82-3.68 (m, 3H), 2.88-2.72 (m, 2H), 1.12 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₉H₂₀F₆N₂O [M]⁺: 406.1480. Found: 406.1528.

***N*¹-Benzyl-*N*²-hydroxy-*N*²-(3-phenylpropyl)propane-1,2-diamine (4.6) - (Table 4.3, (*S*) & (*R*))**



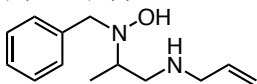
Following general procedure 4.1 using *N*-(3-phenylpropyl)hydroxylamine (0.151 g, 1.00 mmol) the indicated compound was purified by flash column chromatography on silica gel using (1 % Et₃N/10 % MeOH/CH₂Cl₂) to give a pale yellow oil (0.188 g, 63%). Following General Procedure 4.2 using *N*-(3-phenylpropyl)hydroxylamine (0.0755 g, 0.500 mmol) gave (0.0564 g, 60%). TLC *R*_f 0.15 (10 % MeOH/CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 7.35-7.10 (m, 10H), 3.76 (q, *J* = 11.5 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); ¹³C NMR (100 MHz, CDCl₃) δ 142.3, 128.5, 128.4, 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 C₁₉H₂₆N₂O [M]⁺: 298.2045. Found: 298.2010.

***(S)*-*N*²-Benzyl-*N*²-hydroxy-*N*¹-methylpropane-1,2-diamine (4.7) - (Table 4.3)**



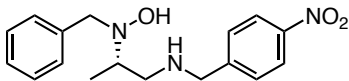
Following general procedure 4.1 using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) the indicated compound was purified by flash column chromatography on silica gel using (1 % Et₃N/10 % MeOH/CH₂Cl₂) to give a pale yellow oil (0.194 g, 91%). Spectral data was consistent with literature.¹⁶³

***N*²-Benzyl-*N*²-hydroxy-*N*¹-(prop-2-en-1-yl)propane-1,2-diamine (4.8) - (Table 4.3, (*S*) & (*R*))**



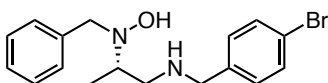
Following general procedure 4.1 using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) the indicated compound was purified by flash column chromatography on silica gel (1 % Et₃N/10 % MeOH/CH₂Cl₂) to give a pale yellow oil (0.187 g, 85%). Following General Procedure 4.2 using *N*-benzylhydroxylamine (0.123 g, 0.999 mmol) gave (0.167 g, 76%). Spectral data was consistent with literature.¹⁶³

(S)-N²-Benzyl-N²-hydroxy-N¹-(4-nitrobenzyl)propane-1,2-diamine (4.9) - (Table 4.3)



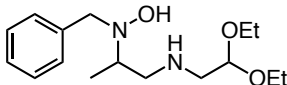
Following general procedure 4.1 using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) the indicated compound was purified by flash column chromatography on silica gel (gradient 1% MeOH/CH₂Cl₂ to 1 % Et₃N/5 % MeOH/CH₂Cl₂). The title compound was obtained as a pale yellow oil (0.315 g, 83%). TLC *R*_f 0.19 (1 % MeOH/CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) 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* = 12.0 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* = 8.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₇H₂₁N₃O₃ [M]⁺: 315.1583 Found: 315.1555.

(S)-N²-Benzyl-N¹-(4-bromobenzyl)-N²-hydroxypropane-1,2-diamine (4.10) - (Table 4.3)



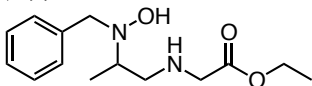
Following general procedure 4.1 using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) the indicated compound was purified by flash column chromatography on silica gel (gradient 1% MeOH/CH₂Cl₂ to 1 % Et₃N/5 % MeOH/CH₂Cl₂). The title compound was obtained as a pale yellow oil (0.282 g, 81%). TLC *R*_f 0.15 (5 % MeOH/CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 7.39 (d, *J* = 6.0 Hz, 2H), 7.34-7.20 (m, 5H), 7.07 (d, *J* = 6.0 Hz, 2H), 3.90 (d, *J* = 15.0 Hz, 1H), 3.70 (d, *J* = 15.0 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) ¹³C NMR (100 MHz, CDCl₃) 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 C₁₇H₂₁N₂OBr [M]⁺: 348.0837. Not found. Exact mass calcd for C₉H₁₂NO [M-BnNHCH₂]⁺: 150.0919. Found 150.0929.

***N*²-Benzyl-*N*¹-(2,2-diethoxyethyl)-*N*²-hydroxypropane-1,2-diamine (4.11) - (Table 4.3, (*S*) & (*R*))**



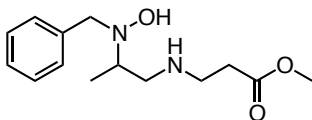
Following general procedure 4.1 using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) the indicated compound was purified by flash column chromatography on silica gel using (1 % Et₃N/10 % MeOH/CH₂Cl₂) to give a pale yellow oil (0.183 g, 62%). Following General Procedure 4.2 using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) gave (0.150 g, 51%). Spectral data was consistent with literature.¹⁶³

Ethyl ({2-[benzyl(hydroxy)amino]propyl}amino)acetate (4.12) - (Table 4.3, (*S*) & (*R*))



Following general procedure 4.1 using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) the indicated compound was purified by flash column chromatography on silica gel using (1 % Et₃N/10 % MeOH/CH₂Cl₂) to give a pale yellow oil (0.199 g, 75%). Following general procedure 4.2 using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) gave (0.188 g, 71%). TLC *R*_f 0.25 (1 % MeOH/CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 7.42-7.14 (m, 5H), 4.13 (q, *J* = 7.1 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); ¹³C NMR (400 MHz, CDCl₃) 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 C₁₄H₂₂N₂O₃ [M]⁺: 266.1630. Found: 266.1561.

Methyl 3-({2-[benzyl(hydroxy)amino]propyl}amino)propanoate (4.13) - (Table 4.3, (S) & (R))



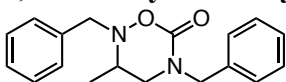
Following general procedure 4.1 using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) compound 4.13 was purified by flash column chromatography on silica gel using (1 % Et₃N/10 % MeOH/CH₂Cl₂) to give a pale yellow oil (0.194 g, 73%). Following General Procedure 4.2 using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol) gave (0.175 g, 66%). TLC *R*_f 0.25 (1 % MeOH/CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) 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 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₄H₂₂N₂O₃ [M]⁺: 266.1630. Found: 266.1561.

General procedure for determining the enantiomeric excess of substrates 4.1-4.13 (Table 4.3)

General procedure 4.3

The hydroamination product (**4.1-4.13**) (1 equiv.) was dissolved in CH₂Cl₂ (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).

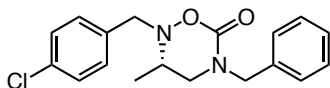
2,5-Dibenzyl-3-methyl-1,2,5-oxadiazinan-6-one (4.2.1).



Following General Procedure 4.3 using **4.1** (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%). The enantiomeric ratio of 98.5/1.5 was obtained using **Catalyst 2.3** and 94/6 was obtained using **Catalyst 4h**. TLC *R*_f 0.28 (30 % EtOAc/Petroleum Ether). Spectral datum was consistent with literature.¹⁶³

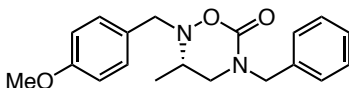
Chiral HPLC: ChiralPak AD-H, *i*-PrOH/hexane = 5/95, 1.0 mL/min, 210 nm; Catalyst **2.3** t_{major} = 43.3 min, t_{minor} = 45.8 min, Catalyst **4h** t_{major} = 43.6 min, t_{minor} = 40.9 min.

(S)-5-Benzyl-2-(4-chlorobenzyl)-3-methyl-1,2,5-oxadiazinan-6-one (4.2.2).

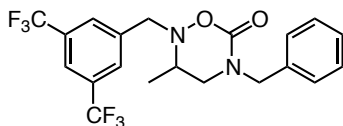


Following general procedure 4.3 using **4.2** (0.0752 g, 0.247 mmol) the indicated compound was purified by flash column chromatography on silica gel using (50% EtOAc/Hexane) to give a white solid (0.0621 g, 76%) and 97/3 enantiomeric ratio using **Catalyst 2.3**. TLC R_f 0.6 (95:5 CH₂Cl₂/MeOH). ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.22 (m, 10H), 3.87 (d, J = 13.0 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); ¹³C NMR (100 MHz, CDCl₃) 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; C₁₈H₁₉N₂O₂Cl [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.

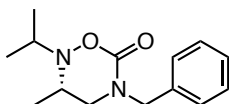
(S)-5-Benzyl-2-(4-methoxybenzyl)-3-methyl-1,2,5-oxadiazinan-6-one (4.2.3).



Following general procedure 4.3 using **4.3** (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%) in 96/4 enantiomeric ratio using **Catalyst 2.3**. TLC R_f 0.6 (95:5 CH₂Cl₂/MeOH). ¹H NMR (400 MHz, CDCl₃) δ 7.39 (m, 7H), 6.88 (d, J = 8.8 Hz, 2H), 4.73-4.37 (m, 2H), 4.26 (d, J = 14.0 Hz, 1H), 3.88 (d, J = 14.0 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). ¹³C NMR (75 MHz, CDCl₃) 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; C₁₉H₂₂N₂O₃ [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

5-Benzyl-2-(3,5-bis(trifluoromethyl)benzyl)-3-methyl-1,2,5-oxadiazinan-6-one (4.2.5)

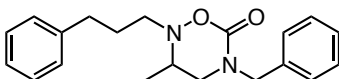
Following general procedure 4.3 using **4.5** (0.0521 g, 0.128 mmol) the indicated compound was purified by flash column chromatography on silica gel using (50% EtOAc/Hexane) to give a white solid (0.0376 g, 68%). An enantiomeric ratio of 91/9 was obtained using **Catalyst 2.3** and 96/4 using **Catalyst 4h**. TLC R_f 0.6 (95:5 CH₂Cl₂/MeOH). ¹H NMR (400 MHz, CDCl₃) δ 7.91-7.74 (m, 3H), 7.38-7.25 (m, 5H), 4.62 (d, J = 11.0 Hz, 1H), 4.45 (d, J = 11.0 Hz, 1H), 4.29 (d, J = 11.0 Hz, 1H), 3.92 (d, J = 11.0 Hz, 1H), 3.35-3.13 (m, 2H), 3.13-3.02 (m, 1H), 1.19 (d, J = 4.5 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) 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. C₂₀H₁₈N₂O₂F₆ [M]⁺: 432.1272 Found: 432.1300. Chiral HPLC: ChiralPak AD-H, *i*-PrOH/hexane = 5/95, 1.0 mL/min, 210 nm; Catalyst **2.3** t_{major} = 28.1 min, t_{minor} = 37.5 min; Catalyst **4h** t_{major} = 38.5 min, t_{minor} = 31.0 min.

(S)-5-Benzyl-2-isopropyl-3-methyl-1,2,5-oxadiazinan-6-one (4.2.4)

Following General Procedure 4.3 using **4.4** (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 2.3**. TLC R_f 0.6 (95:5 CH₂Cl₂/MeOH). ¹H NMR (300 MHz, CDCl₃) δ 7.36-7.24 (m, 5H), 4.62 (d, J = 14.8 Hz, 1H), 4.42 (d, J = 16.0 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). ¹³C NMR (75 MHz, CDCl₃) 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;

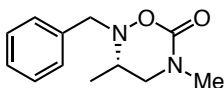
C₁₄H₂₀N₂O₂ [M]⁺: 248.1525. Found: 248.1521. Chiral HPLC: ChiralPak OD-H, *i*-PrOH/hexane = 5/95, 1.0 mL/min, 210 nm, *t*_{major} = 17.9 min, *t*_{minor} = 14.4 min.

5-Benzyl-3-methyl-2-(3-phenylpropyl)-1,2,5-oxadiazinan-6-one (4.2.6).



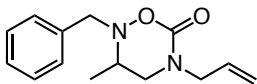
Following General Procedure 4.3 using **4.6** (0.0394 g, 0.132 mmol) the indicated compound was purified by flash column chromatography on silica gel using (50% EtOAc/Hexane) to give a white solid (0.0158 g, 37%). An enantiomeric ratio of 85.5/14.5 was obtained using **Catalyst 2.3** and 88.5/11.5 was obtained using **Catalyst 4h**. TLC *R*_f 0.6 (95:5 CH₂Cl₂/MeOH). ¹H NMR (300 MHz, CDCl₃) δ 7.33-7.26 (m, 10H), 4.65-4.43 (m, 2H), 3.14-2.94 (m, 4H), 2.77-2.60 (m, 3H), 2.15-1.96 (m, 2H), 1.01 (d, *J* = 6.1 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) 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; C₂₀H₂₄N₂O₂ [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 (4.2.7).



Following general procedures 4.3 using **4.7** (0.142 g, 0.276 mmol) the indicated compound was purified by flash column chromatography on silica gel using (50% EtOAc/Hexane) to give a yellow oil (0.0463 g, 76%) and 80/20 enantiomeric ratio using **Catalyst 2.3**. Spectral datum was consistent with literature.¹⁶³ 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.

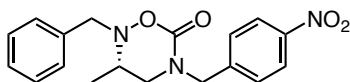
5-Allyl-2-benzyl-3-methyl-1,2,5-oxadiazinan-6-one (4.2.8).



Following General Procedure 4.3 using **4.8** (0.270 g, 1.23 mmol) the indicated compound was purified by flash column chromatography on silica gel using (50% EtOAc/Hexane)

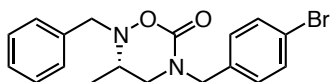
to give a yellow oil (0.226 g, 70%). Enantiomeric ratio of 81/19 was obtained using **Catalyst 2.3** and enantiomeric ratio of 94/6 using **Catalyst 4h**. TLC R_f 0.32 (1:1 EtOAc/Petroleum Ether). Spectral datum was consistent with literature.¹⁶³ Chiral HPLC: ChiralPak AD-H, *i*-PrOH/hexane = 5/95, 1.0 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 (4.2.9).



Following General Procedure 4.3 using **4.9** (0.0845 g, 0.268 mmol) the indicated compound was purified by flash column chromatography on silica gel using (50% EtOAc/Hexane) to give an off white solid (0.0856 g, 64%) and 97.5/2.5 enantiomeric ratio using **Catalyst 2.3**. TLC R_f 0.6 (95:5 CH₂Cl₂/MeOH). ¹H NMR (400 MHz, CDCl₃) δ 8.23 (d, J = 12.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.44-7.29 (m, 5H), 4.72-4.56 (m, 2H), 4.34 (d, J = 12.0 Hz, 1H), 3.95 (d, J = 12.0 Hz, 1H), 3.33-3.18 (m, 1H), 3.13-3.01 (m, 1H), 1.20 (d, J = 8.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) 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; C₁₈H₁₉N₃O₄ [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.

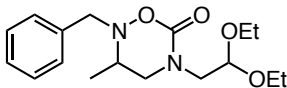
(S)-2-Benzyl-5-(4-bromobenzyl)-3-methyl-1,2,5-oxadiazinan-6-one (4.2.10).



Following General Procedure 4.3 using **4.10** (0.0328 g, 0.0939 mmol) the indicated compound was purified by flash column chromatography on silica gel using (50% EtOAc/Hexane) to give a white solid (0.0243 g, 69%) and 96/4 enantiomeric ratio using **Catalyst 2.3**. TLC R_f 0.6 (95:5 CH₂Cl₂/MeOH). ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.28 (m, 9H), 4.67-4.43 (m, 2H), 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 = 6.2 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) 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;

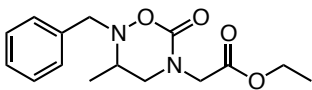
$C_{18}H_{19}N_2O_2Br$ $[M]^+$: 374.0630. Found: 374.0626. Chiral HPLC: ChiralPak OD-H, *i*-PrOH/hexane = 7/93, 1.0 mL/min, 210 nm, t_{major} = 69.6 min, t_{minor} = 58.4 min.

2-Benzyl-5-(2,2-diethoxyethyl)-3-methyl-1,2,5-oxadiazinan-6-one (4.2.11).



Following General Procedure 4.3 using **4.11** (0.0148 g, 0.0501mmol) the indicated compound was purified by flash column chromatography on silica gel using (50% EtOAc/Hexane) to give a yellow oil (7.73 mg, 49%). This compound resulted in an enantiomeric ratio of 80/20 using **Catalyst 2.3** and 94/6 using **Catalyst 4h**. TLC R_f 0.4 (50:50 Hexane/EtOAc). 1H 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 = 14.0 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); ^{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; $C_{12}H_{16}N_2O_2$ $[M]^+$: 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.

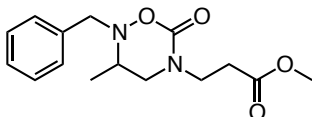
Ethyl 2-(2-benzyl-3-methyl-6-oxo-1,2,5-oxadiazinan-5-yl)acetate (4.2.12).



Following General Procedure 4.3 using **4.12** (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%). This compound resulted in an enantiomeric ratio of 86/14 using **Catalyst 2.3** and 95.5/4.5 using **Catalyst 4h**. TLC R_f 0.6 (95:5 CH_2Cl_2 /MeOH). 1H 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, 61.4, 58.9, 52.9, 49.1, 30.9, 25.3, 14.1; IR (film): 2912, 2856, 1647, 1274; $C_{12}H_{16}N_2O_2$ $[M]^+$: 292.1423 Found: 292.1427 Chiral HPLC: ChiralPak AD-H, *i*-

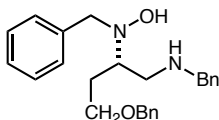
PrOH/hexane = 5/95, 1.0 mL/min, 210 nm, Catalyst **2.3** t_{major} = 35.4 min, t_{minor} = 30.0 min. Catalyst **4h** t_{major} = 41.8 min, t_{minor} = 38.9 min.

Methyl 3-(2-benzyl-3-methyl-6-oxo-1,2,5-oxadiazinan-5-yl)propanoate (4.2.13).



Following General Procedure 4.3 using **4.13** (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%). This compound resulted in an enantiomeric ratio of 91/9 using **Catalyst 2.3** and 95/5 using **Catalyst 4h**. TLC R_f 0.6 (95:5 CH₂Cl₂/MeOH). ¹H NMR (400 MHz, CDCl₃) 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), 3.21-3.19 (m, 2H), 3.10 (br, 1H), 2.62-2.59 (m, 2H), 1.20 (d, J = 6.2 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 172.4, 154.4, 135.3, 129.3, 128.4, 127.7, 60.9, 58.9, 53.2, 51.9, 44.6, 32.2, 31.0; IR (film): 3119, 2925, 2857, 1690, 1322, 1067, 784 cm⁻¹; C₁₅H₂₀N₂O₄ [M]⁺: 292.1423. Found: 220.11978. Chiral HPLC: ChiralPak OJ-H, *i*-PrOH/hexane = 10/90, 1.0 mL/min, 210 nm, Catalyst **2.3** t_{major} = 297.2 min, t_{minor} = 245.9 min, Catalyst **4h** t_{major} = 249.0 min, t_{minor} = 379.5 min.

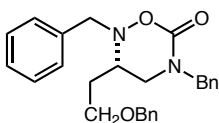
(S)-N-Benzyl-2-(benzyl(hydroxy)amino)-4-(benzyloxy)butan-1-amine (4.14).



This compound was prepared following general procedure 4.1 using *N*-benzylhydroxylamine (0.123 g, 1.00 mmol); however, the solvent was *t*-BuOH and the temperature was 60°C, the indicated compound was purified by flash column chromatography on silica gel using (1 % NH₄OH/1 % MeOH/CH₂Cl₂) to give a pale yellow oil (0.121 g, 31%). ¹H NMR (300 MHz, CDCl₃): δ 7.35-7.19 (m, 15H), 4.50-4.43 (m, 2H), 3.88-3.80 (m, 2H), 3.59-3.48 (m, 4H), 3.04 (dd, J = 7.8, 3.8 Hz, 1H), 2.73 (dd, J

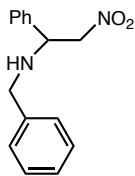
= 12.2, 3.1 Hz, 2H), 2.12 (m, 1H), 1.69 (m, 1H). Spectral datum was consistent with literature.⁸⁶

(S)-2,5-Dibenzyl-3-(2-(benzyloxy)ethyl)-1,2,5-oxadiazinan-6-one (4.2.14).



Following general procedure 4.3, (*S*)-*N*-benzyl-2-(benzyl(hydroxy)amino)-4-(benzyloxy)butan-1-amine (0.0506g, 0.130 mmol) the indicated compound was purified by flash column chromatography on silica gel using (50% EtOAc/Hexane) to give a yellow oil (0.0537 g, 31%). Enantiomeric ratio of 98/2 was obtained using **Catalyst 2.3**. ¹H NMR (400 MHz, CDCl₃) δ 7.35-7.14 (m, 15H), 4.61 (d, *J* = 14.9 Hz, 1H), 4.46-4.18 (m, 4H), 4.02 (d, *J* = 13.6 Hz, 1H), 3.27-3.50 (m, 4H), 3.03 (dd, *J* = 10.9, 4.4, Hz, 1H), 2.06-2.14 (m, 1H), 1.62-1.69 (m, 1H). ¹³C NMR (75 MHz, CDCl₃) δ 154.4, 137.9, 136.2, 135.3, 129.2, 128.8, 128.5, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6, 73.1, 66.3, 58.9, 54.9, 51.9, 47.8; Exact mass calcd C₂₆H₂₈N₂O₃ [M]⁺: 416.2100. Not found. Exact mass calcd for C₁₇H₂₀NO [M-121.0891, OH]⁺: 254.1545. Found: 254.1554.¹⁵⁵ Chiral HPLC ChiralPak AD-H, *i*-PrOH/hexane = 5/95, 1.0 mL/min, 210 nm, Catalyst **2.3** *t*_{major} = 7.5 min, *t*_{minor} = 8.2 min.

***N*-Benzyl-2-nitro-1-phenylethanamine (4.15).**

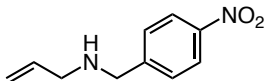


This compound was synthesized by dissolving **Catalyst 2.3** (0.0508 g, 0.2 mmol) in 1 mL of benzene. This was followed by the addition of benzylamine (0.109 mL, 1 mmol) and trans-β-nitrostyrene (0.149 g, 1 mmol). After 24 hours the solution was reduced under concentrated pressure and purified by flash column chromatography on silica gel using (19% EtOAc/Hexane) to give a yellow oil (0.195 g, 76%) and 76/24 enantiomeric

ratio using **Catalyst 2.3**. ^1H NMR (400 MHz, CDCl_3) δ 7.46-7.22 (m, 10H), 4.59 (dd, $J = 12.3, 9.3$, Hz, 1H), 4.51 (d, $J = 4.4$ Hz, 1H), 4.43 (td, $J = 10.0, 4.4$ Hz, 1H), 3.72 (d, $J = 13.2$ Hz, 1H), 3.57 (d, $J = 13.2$ Hz, 1H). Spectral data was consistent with literature.¹⁷⁴ Chiral HPLC: ChiralPak OD-H, *i*-PrOH/hexane = 1/99, 1.0 mL/min, 210 nm, Catalyst **2.3** $t_{\text{major}} = 26.1$ min, $t_{\text{minor}} = 29.6$ min.

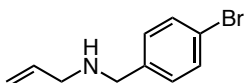
Miscellaneous Materials

N-(4-Nitrobenzyl)prop-2-en-1-amine



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 2 M 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 colourless oil (2.05 g, 61%). ^1H 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, $J = 6.2$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 154.4, 154.1, 135.3, 129.3, 128.4, 127.7, 58.9, 54.3 Spectral datum was consistent with literature.¹⁷⁵

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



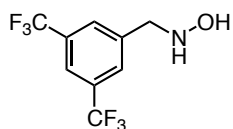
Allylamine (2.00 g, 35 mmol) was added to a 100 mL round-bottom flask equipped with a magnetic stir bar and dissolved in CH_2Cl_2 (25 mL). 4-Bromobenzylbromide (4.37 g,

¹⁷⁴ Uraguchi D.; Nakashima, D.; Ooi, T. *J. Am. Chem. Soc.* **2009**, *131*, 7242–7243.

¹⁷⁵ Harvey, D. F.; Sigano, D. M. *J. Org. Chem.* **1996**, *61*, 2268-2272.

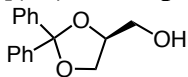
17.5 mmol) dissolved in CH₂Cl₂ (25 mL) was added dropwise over 3 hours. The reaction was allowed to stir for an additional 2 hours before concentrating the mixture under reduced pressure. Diethyl ether (50 mL) and 2 M NaOH (50 mL) were added to the residue. The aqueous layer was extracted twice more with diethyl ether (50 mL). The collected organics were then washed with water, brine, and dried over Na₂SO₄. After column chromatography (Et₂O) the title compound was obtained as a colourless oil (2.57 g, 67%). ¹H NMR (400 MHz, CDCl₃) 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* = 6.2 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 154.4, 154.1, 135.3, 129.3, 128.4, 127.7, 58.9, 54.3. Spectral datum was consistent with literature.¹⁷⁶

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



Prepared by reductive amination of the corresponding oxime according to the method of House and Lee.¹⁴⁸ ¹H NMR (400 MHz, CDCl₃) 7.87-7.90 (m, 3H), 4.93 (br, 1H), 4.17 (s, 2H). δ ¹³C NMR (75 MHz, CDCl₃) 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; C₁₅H₂₀N₂O₄ [M]⁺: 259.0432 Found: 259.0432.

[(4*S*)-2,2-Diphenyl-1,3-dioxolan-4-yl]methanol



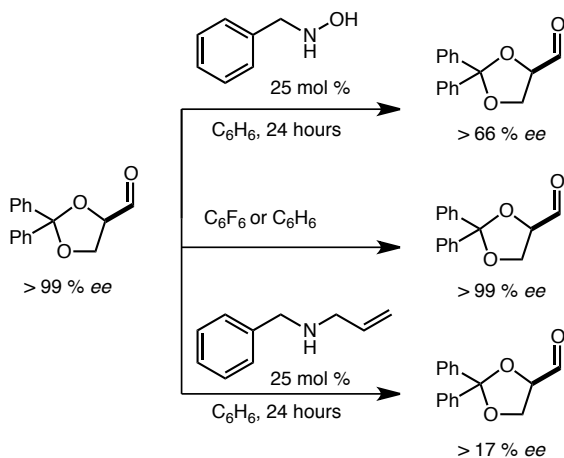
A dry 10 mL round-bottom flask was charged with a magnetic stir bar, catalyst **2.3** (0.0513 g, 0.202 mmol, 1 equiv.), and Et₂O (10 mL). The mixture was cooled to 0°C in an ice bath before adding LiAlH₄ (1.5 equiv.). The mixture was stirred for 30 minutes before quenching with sodium potassium tartrate and allowed to stir for an additional 30 minutes. The reaction mixture was then diluted with water and the organic phase separated and extracted twice with Et₂O the title compound was obtained as a yellow oil (0.0143 g, 71%). ¹H NMR (400 MHz, CDCl₃) δ 7.36-7.28 (m, 5H), 4.27 (d, *J* = 14.0 Hz,

¹⁷⁶ Tehrani, K. A.; Van, T. N.; Karikomi, M.; Rottiers, M.; Kimpe, N. D. *Tetrahedron* **2002**, 58, 7145-7152.

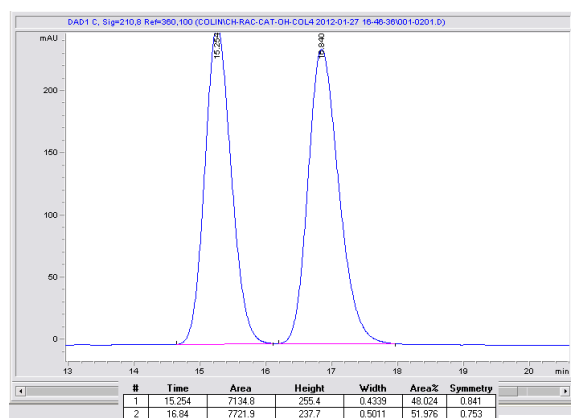
1H), 3.89 (d, $J = 14.0$ Hz, 1H), 3.26-3.10 (m, 3H), 1.20 (d, $J = 6.2$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ 154.4, 135.3, 129.3, 128.4, 127.7, 58.9, 54.3. Spectral datum was consistent with literature.¹⁴ Chiral HPLC: ChiralPak OD-H, *i*-PrOH/hexane = 2/98, 1.0 mL/min, 210 nm, Catalyst **2.3** $t_{\text{major}} = 16.8$ min, $t_{\text{minor}} = 15.3$ min.

Epimerization of Catalyst **2.3**

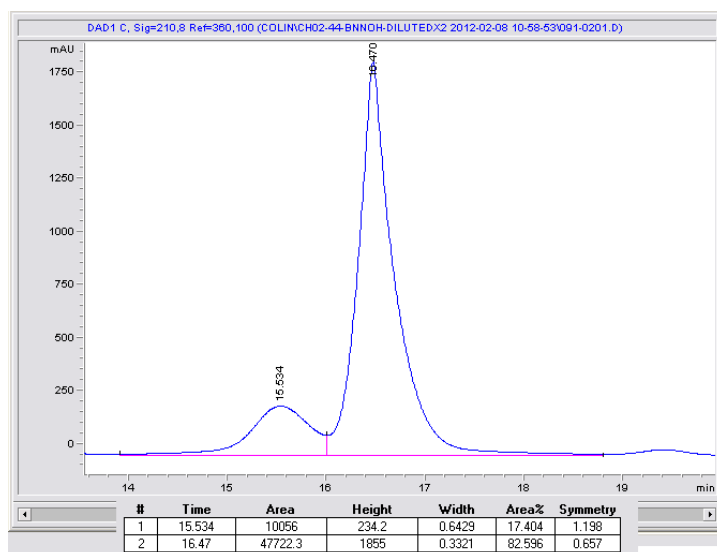
To probe catalyst **2.3**'s tendency to epimerize under the reaction conditions, catalyst **2.3** (0.064 g, 0.25 mmol, 1 equiv.) was stirred either with (0.0077 g, 0.063 mmol, 0.25 equiv) of *N*-benzylhydroxylamine or *N*-benzylallylamine (9.8 μL , 0.063 mmol, 0.25 equiv) in benzene (1M) for 24 hours. The reaction mixture was 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 enantiopurity determined by chiral HPLC. Chiral HPLC: ChiralPak OD-H, *i*-PrOH/hexane = 2/98, 1.0 mL/min, 210 nm, Catalyst **2.3** $t_{\text{major}} = 16.8$ min, $t_{\text{minor}} = 15.3$ min.



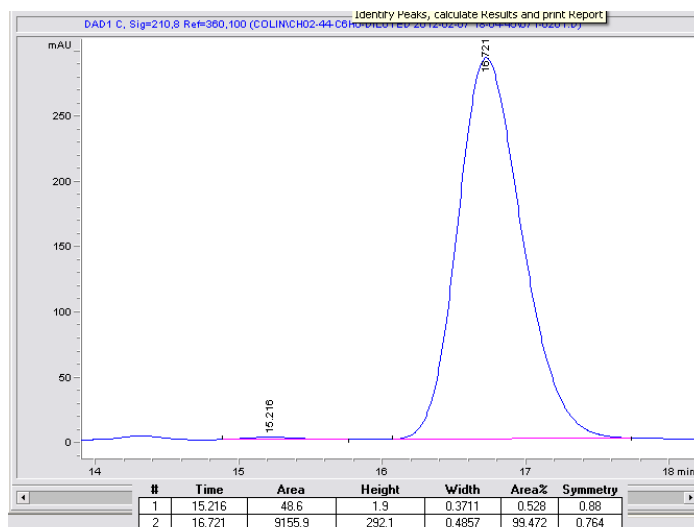
Racemic



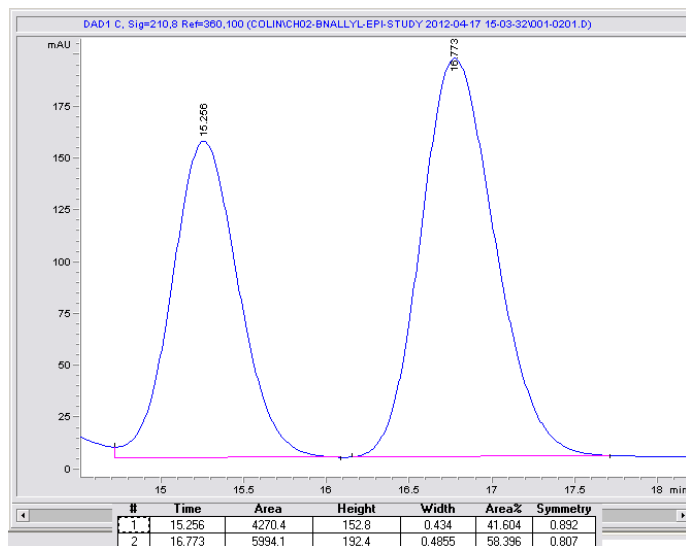
24 hours *N*-Benzylhydroxylamine

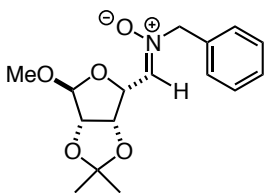


24 hours Benzene



24 hours *N*-Benzylallylamine





(Z)-N-(5-Deoxy-2,3-O-isopropylidene-1-O-methyl-D-xyo-1,4-furanose-5-ylidene)benzylamine *N*-oxide (Nitrone S1)

Aldehyde **4h** (0.161g, 0.797 mmol) was transferred to a 10 mL round bottom flask containing a magnetic stir bar and then the flask was purged with argon. The aldehyde was dissolved in 5 mL of CH₂Cl₂. *N*-Benzylhydroxylamine (0.0981 g, 0.0798 mmol) was then added to the flask and mixture was allowed to stir for 9 hours. MgSO₄ was then added and the mixture stirred for an additional 30 minutes before filtering the mixture and removing solvents to yield pure Nitrone S1 (0.210 g, 86%). Spectral datum matched those published in the literature.¹⁸⁰

PROCEDURES AND CHARACTERIZATION FOR CHAPTER 5

Formaldehyde Stock Solution

The formaldehyde stock solutions used in this study were prepared using a 37 wt. % of formaldehyde in H₂O, which contains 10-15% methanol as stabilizer (purchased from Aldrich). Formaldehyde (commercial solution described above; 0.74 mL, 10 mmol) was added to a 20 mL graduated cylinder, which was then filled with *t*-BuOH (19.3 mL). This 0.5 M solution was sealed under argon and transferred into a vial that was kept in the freezer. This solution has a long shelf life (2 months).

Hydroxylamines

N-(1-Phenylethyl)hydroxylamine¹⁷⁷ and *N*-benzylhydroxylamine¹⁴⁹ were prepared according to literature procedures.

Allylic amines

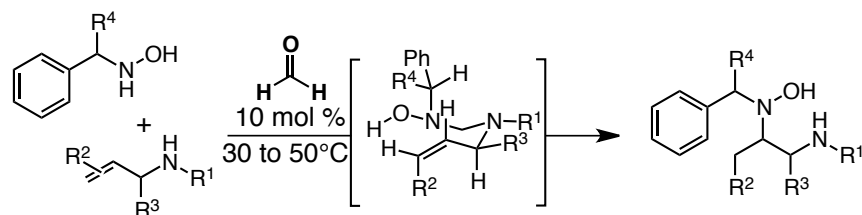
N-Allyl-β-alanine methyl ester¹⁶⁵, 3-(allylamino)-*N,N*-dimethylpropanamide¹⁷⁸, (*Z*)-*N*-benzyl-4-(benzyloxy)but-2-en-1-amine¹⁷⁵, *N*-(4-methoxybenzyl)prop-2-en-1-amine¹⁸² and *N*-benzyl-allylamine¹⁷⁹ were prepared according to literature procedures.

¹⁷⁷ Kurtzweil, M. L.; Loo, D.; Beak, P. *J. Am. Chem. Soc.* **1993**, *115*, 421-427.

¹⁷⁸ Leitner, A.; Shekhar, S.; Pouy, M. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15506-15514.

¹⁷⁹ Hirano, K.; Biju, A. T.; Piel I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 14190-14190.

**General procedures for tethered hydroaminations of allylic amines with
N-alkylhydroxylamines (Table 5.2 and Table 5.3)**



General procedure 5.1

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.

General procedure 5.2

A 0.1 M solution of formalin in *t*-BuOH was prepared using commercially available formalin. An oven dried microwave vial (2-5 mL) containing a magnetic stir bar was allowed to cool to room temperature before adding hydroxylamine (1 equiv), followed by allylic amine (1-1.5 equiv). Formaldehyde (0.1 equiv) via the 0.1 M stock solution was then added such that the concentration of hydroxylamine reached 1 M. The vial was then capped, purged with argon, and placed in an oil bath at the specified temperature and time. After completion the mixture was allowed to cool to room temperature before removing the solvent under reduced pressure. The crude was then purified by flash column chromatography to give the corresponding *N,N*-dialkylhydroxylamine products.

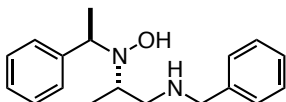
General Procedures for the synthesis of *N*-benzyl and *N*-methyl allylic amines (5.3)

Allylic amines were prepared using the method of Dondoni, Merino and co-workers.¹⁸⁰ 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 NaHCO₃ (2.2 equiv.). Dichloromethane (0.2 M to hydroxylamine) was then added followed by dropwise addition of the appropriate aldehyde (1 equiv) and then MgSO₄ (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 nitron was dissolved in THF (0.1 M) and cooled to 0 °C. A Grignard reagent (1.5 equiv.) is added dropwise to the nitron and the mixture is allowed to stir for 2 hours at 0°C before quenching with a saturated solution of NH₄Cl followed by dilution with Et₂O and H₂O. The organic layer was separated and the aqueous portion was extracted twice with Et₂O. The combined organic fractions were washed with brine, dried over MgSO₄, filtered through a short silica gel plug, washed with Et₂O 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 Et₂O and filtering over Celite. The solvents were removed in vacuo and the mixture neutralized with saturated aqueous NaHCO₃ followed by extracting the organic layer three times with CH₂Cl₂. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The crude amine was then purified by column chromatography over silica gel.

¹⁸⁰ 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.; Tejero, T. *Synthesis* **1994**, 1450-1456. (c) Dondoni, A.; Merchan, F. L.; Merino, P.; Tejero, T. *Chem. Commun.* **1994**, 1731-1733.

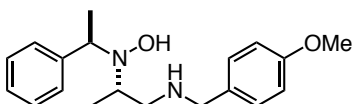
Formaldehyde catalyzed intermolecular Cope-type hydroamination products:

(±)-(S*)-N-Benzyl-2-(hydroxy((R*)-1-phenylethyl)amino)propan-1-amine (5a).



Following general procedure 5.1 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 % NH₄OH/2 % MeOH/CH₂Cl₂) to give a white solid (0.235 g, 83%). TLC *R_f* 0.35 (1 % MeOH/CH₂Cl₂); Diagnostic peaks for *d.r.* ¹H NMR (300 MHz, CDCl₃) δ 1.46 (d, *J* = 6.4, 3H), 1.11 (d, *J* = 6.6, 3H) (6:1 *d.r.*) **Major Diastereomer:** ¹H NMR (300 MHz, CDCl₃) 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) ¹³C NMR (75 MHz, CDCl₃) 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 (CH₂), 52.6 (CH₂), 22.2 (CH₃), 9.8 (CH₃); IR (film): 3324, 3070, 3024, 2933, 1595, 1500, 1454, 1321, 1154, 1086, 976 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₈H₂₄N₂O [M]⁺: 284.1889. Found: 284.1877.

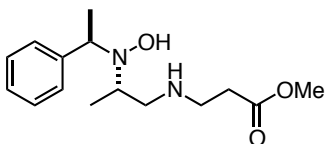
(±)-(S*)-2-(Hydroxy((R*)-1-phenylethyl)amino)-N-(4-methoxybenzyl)propan-1-amine (5b).



Following general procedure 5.1 using *N*-(1-phenylethyl)hydroxylamine (0.137 g, 1.00 mmol) the indicated compound was purified by flash column chromatography on silica gel (1 % NH₄OH/1 % MeOH/CH₂Cl₂). The title compound was obtained as a pale yellow oil (0.148 g, 47%). TLC *R_f* 0.25 (1 % MeOH/CH₂Cl₂); Diagnostic peaks for *d.r.* ¹H NMR (300 MHz, CDCl₃) δ 1.42 (d, *J* = 6.4, 3H), 1.10 (d, *J* = 6.6 Hz, 3H) (6:1 *d.r.*) **Major Diastereomer:** ¹H NMR (300 MHz, CDCl₃) 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

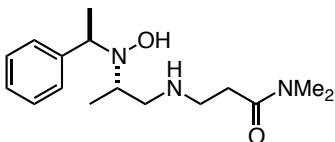
(m, 2H), 2.39 (m, 1H), 1.42 (d, $J = 6.4$ Hz, 3H), 0.93 (d, $J = 6.0$ Hz, 3H) ^{13}C NMR (75 MHz, CDCl_3) δ 158.7 (C), 143.6 (C), 131.7 (C), 129.5 (CH), 128.6 (CH), 127.7 (CH), 127.3 (CH), 113.8 (CH), 63.4 (CH), 55.3 (CH), 54.6 (CH_3), 52.4 (CH_2), 52.3 (CH_3), 22.3, 9.8 (CH_3); IR (film): 3324, 3070, 3024, 2933, 1595, 1500, 1454, 1321, 1154, 1086, 976 cm^{-1} . HRMS (EI): Exact mass calcd for $\text{C}_{19}\text{H}_{26}\text{N}_2\text{O}_2$ $[\text{M}]^+$: 314.1994. Found: 314.2402.

($\pm$)-Methyl 3-(((S^*)-2-(hydroxy((R^*)-1-phenylethyl)amino)propyl)amino)propanoate (5c).



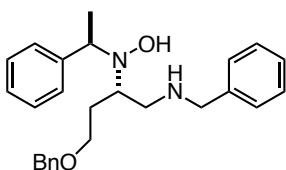
Following general procedure 5.1 using *N*-(1-phenylethyl)hydroxylamine (0.137 g, 1.00 mmol) the indicated compound was purified by flash column chromatography on silica gel (1 % NH_4OH /4 % $\text{MeOH}/\text{CH}_2\text{Cl}_2$). The title compound was obtained as a pale yellow oil (0.140 g, 50%). TLC R_f 0.18 (4% $\text{MeOH}/\text{CH}_2\text{Cl}_2$); Diagnostic peaks for *d.r.* ^1H 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:** ^1H 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} . Exact mass calcd for $\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}_3$ $[\text{M}]^+$: 280.1787. Found: 280.1795.

(±)-3-(((*S)-2-(Hydroxy(*R**)-1-phenylethyl)amino)propyl)amino)-*N,N*-dimethylpropanamide (5d).**



Following general procedure 5.1 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 % NH₄OH/5 % MeOH/CH₂Cl₂) to give a pale yellow oil as a mixture of diastereoisomers (0.249 g, 85%, 6:1 d.r.). ¹H NMR (300 MHz, CDCl₃) 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) ¹³C NMR (75 MHz, CDCl₃) 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 C₁₆H₃₇N₃O₂ [M]⁺: 293.2103. Found: 293.2146.

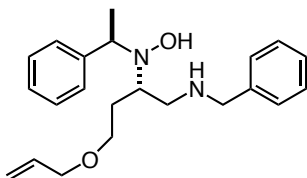
(*S*)-*N*-Benzyl-4-(benzyloxy)-2-(hydroxy(*R*)-1-phenylethyl)amino)butan-1-amine (5e).



Following general procedure 5.1 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 % NH₄OH/1 % MeOH/CH₂Cl₂) to give a pale yellow oil (0.169 g, 42%, 20:1 d.r.) TLC *R*_f 0.19 (1% MeOH/CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) 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). ¹³C NMR (75 MHz, CDCl₃) δ 144.2 (C), 139.5

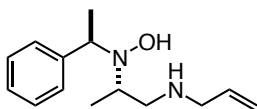
(C), 138.5 (C), 128.6 (CH), 128.4 (CH), 128.4 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 127.2 (CH), 127.1 (CH), 126.0 (CH), 72.9 (CH), 68.0 (CH₂), 63.5 (CH₂), 56.5 (CH), 52.5 (CH₂), 49.0 (CH₂), 26.1 (CH₂), 20.5 (CH₃). IR (film): 3309, 3298, 3032, 2857, 1683, 1477, 1371, 1080, 1033 cm⁻¹. HRMS (EI): Exact mass calcd for C₂₆H₃₂N₂O₂ [M]⁺: 404.2464. Found: 404.2394.

(±)-(S*)-4-(Allyloxy)-N-benzyl-2-(hydroxy((R*)-1-phenylethyl)amino)butan-1-amine (5f).



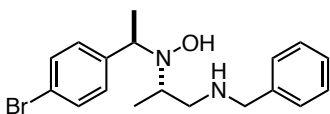
Following general procedure 5.1 using *N*-(1-phenylethyl)hydroxylamine (0.137 g, 1.00 mmol) the indicated compound was purified by flash column chromatography on silica gel using (1 % NH₄OH/1 % MeOH/CH₂Cl₂) to give a pale yellow oil (0.202 g, 57%, 20:1 d.r.) TLC *R*_f 0.16 (1% MeOH/CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) 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) ¹³C NMR (75 MHz, CDCl₃) 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 (CH₂), 71.8 (CH), 67.9 (CH₂), 63.5 (CH₂), 56.5 (CH), 52.7 (CH₂), 48.9 (CH₂), 26.1 (CH₂), 22.0 (CH₃). IR (film): 3305, 3032, 2937, 2861, 1648, 1443, 1090, 915 cm⁻¹. HRMS (EI): Exact mass calcd for C₂₂H₃₀N₂O₂ [M]⁺: 354.2307. Found: 354.2344.

***N*-((*S*)-2-(Hydroxy((*R*)-1-phenylethyl)amino)propyl)prop-2-en-1-amine (5g).**



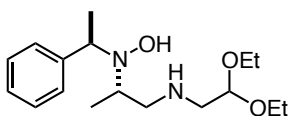
Following general procedure 5.1 using *N*-(1-phenylethyl)hydroxylamine (0.068 g, 0.50 mmol) the indicated compound was purified by flash column chromatography on silica gel using (1 % NH₄OH/5 % MeOH/CH₂Cl₂) to give a pale yellow oil (0.057 g, 49%, 4:1 d.r. Diagnostic peaks for *d.r.* ¹H NMR (300 MHz, CDCl₃) δ 1.45 (d, *J* = 6.9 Hz, 3H), 1.31 (d, *J* = 6.6 Hz, 3H). (4:1 d.r.) **Major Diastereomer:** TLC *R*_f 0.19 (5% MeOH/CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 7.31-7.24 (m, 5H), 5.81 (dd, *J* = 17.1 Hz, 10.3 Hz, 1H), 5.09 (m, 2H), 3.93 (q, *J* = 6.4 Hz, 1H), 3.10-2.95 (m, 2H), 2.83-2.73 (m, 2H), 2.30 (dd, *J* = 12.2 Hz, 3.1 Hz, 1H) 1.5 (d, *J* = 6.4 Hz, 3H), 0.92 (d, *J* = 6.2 Hz, 3H). ¹³C NMR (75 MHz, CDCl₃) δ 143.8 (C), 136.3 (CH), 128.6 (CH), 127.5 (CH), 127.3 (CH), 116.4 (CH₂), 63.5 (CH), 54.1 (CH), 51.9 (CH₂), 51.4 (CH₂), 35.0 (CH₂), 22.6 (CH₃), 9.4 (CH₃). Exact mass calcd for C₁₄H₂₂N₂O₂ [M]⁺: 234.1732. Found: 234.1735.

***(S)*-*N*-Benzyl-2-(((*R*)-1-(4-bromophenyl)ethyl)(hydroxy)amino)propan-1-amine (5h).**



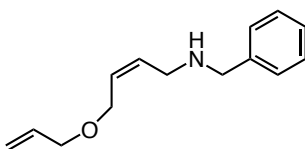
Following general procedure 5.1 using *N*-(1-phenylethyl)hydroxylamine (0.068 g, 0.5000 mmol) the crude sample was obtained as a mixture of diastereoisomers (3:1 d.r.). Diagnostic peaks for *d.r.* ¹H NMR (300 MHz, CDCl₃) δ 1.49 (d, *J* = 6.9 Hz, 3H), 1.37 (d, *J* = 6.4 Hz, 3H). (3:1 d.r.).

(S)-N-(2,2-Diethoxyethyl)-2-(hydroxy((R)-1-phenylethyl)amino)propan-1-amine (5i).



Following general procedure 5.1 using *N*-(1-phenylethyl)hydroxylamine (0.068 g, 0.500 mmol) the crude sample was as a mixture of diastereoisomers (3:1 d.r.). Diagnostic peaks for *d.r.* ^1H NMR (300 MHz, CDCl_3) δ 1.48 (d, $J = 6.9$ Hz, 3H), 1.43 (d, $J = 6.4$ Hz, 3H). (3:1 d.r.).

(Z)-4-(Allyloxy)-N-benzylbut-2-en-1-amine

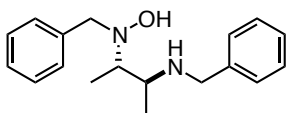


NaH (1.60 g, 66.7, 1 equiv) was added slowly to a mixture of (*Z*)-but-2-ene-1,4-diol (16.4 mL, 200 mmol, 3 equiv) in THF (40 mL) at 0 °C. The reaction was stirred at room temperature for 1 hour and then allyl bromide (5.77 mL, 66.7, 1 equiv) was added slowly. The mixture was stirred at reflux for 1 h followed by 1 M HCl to quench the reaction carefully. The reaction was extracted with CH_2Cl_2 , dried with MgSO_4 , filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel using (20 % EtOAc/pentane then 50% EtOAc/pentane) to give a clear liquid (65%, 3.16 g).¹⁸¹ (*Z*)-4-(Allyloxy)but-2-en-1-ol (1.00 g, 7.81 mmol, 1 equiv.) was then dissolved in CH_2Cl_2 (22 mL) and NEt_3 (1.21 mL, 8.74 mmol, 1.12 equiv.) at 0 °C. MsCl (1.81 mL, 3 equiv.) was added and the reaction was stirred for 3 hours at room temperature. The mixture was extracted with 10% HCl/ CH_2Cl_2 /brine. The organic solvent was dried with MgSO_4 and concentrated under reduced pressure. The crude mixture was then dissolved in ether (10 mL) and benzylamine (4.27 mL, 39.0 mmol, 5 equiv) was added slowly. The reaction was stirred at room temperature for 17 hours and quenched with 1M NaOH. The crude mixture was extracted with CH_2Cl_2 /brine

¹⁸¹ Hirano, K.; Akkattu, T. B.; Piel, I.; Glorius, F. *J. Am. Chem. Soc.* **2009**, *131*, 14190-14191.

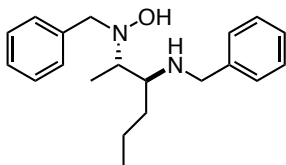
and concentrated under reduced pressure. The compound was purified by flash column chromatography on silica gel using (100 % ether) to give a pale yellow oil (41%, 0.69 g). ^1H NMR (300 MHz, CDCl_3) 7.31-7.23 (m, 5H), 5.93-5.82 (m, 1H), 5.75-5.63 (m, 2H), 5.28-5.14 (m, 2H), 4.00-3.97 (m, 2H), 3.94 (dt, $J = 5.7$ Hz, 1.4 Hz, 2H), 3.77 (s, 2H), 3.29 (m, 2H), 1.60 (br, 1H) ^{13}C NMR (75 MHz, CDCl_3) δ 140.0 (C), 134.7 (CH), 131.4 (CH), 128.5 (CH), 128.4 (CH), 128.2 (CH), 127.1 (CH), 117.2 (CH_2), 71.3 (CH_2), 65.7 (CH_2), 53.3 (CH_2), 45.7 (CH_2). IR (film): 2937, 2789, 2420, 1424, 915 cm^{-1} . Exact mass calcd for $\text{C}_{14}\text{H}_{19}\text{NO}$ $[\text{M}]^+$: 217.1467. Found: 217.1501.

($\pm$)-(2*S,3*S**)-*N*-Benzyl-*N*-[3-(benzylamino)butan-2-yl]hydroxylamine (5j).**



The general procedure 5.2 was followed using *N*-benzylhydroxylamine (0.0617 g, 0.501 mmol), and allylic amine (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.⁸⁶

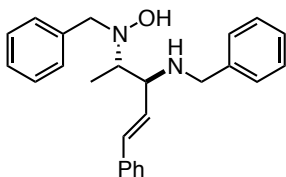
($\pm$)-(2*S,3*S**)-*N*-Benzyl-*N*-[3-(benzylamino)hexan-2-yl]hydroxylamine (5k).**



The general procedure 5.2 was followed using *N*-benzylhydroxylamine (0.0618 g, 0.501 mmol), and allylic amine (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). ^1H 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);

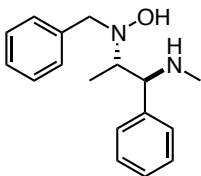
^{13}C NMR (100 MHz, CDCl_3) δ 140.3, 138.5, 129.1, 128.4, 128.3, 128.2, 127.0, 61.7, 60.0, 59.7, 51.6, 33.3, 18.4, 14.5, 9.7; IR (film): 3069, 3030, 2964, 2926, 2867, 1494, 1447, 1370, 1211, 1022, 968, 906, 728, 693 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}$ $[\text{M}]^+$: 312.2202 Found 312.2208.

($\pm$)-(2*S,3*S**)-*N*-Benzyl-*N*-[(4*E*)-3-(benzylamino)-5-phenylpent-4-en-2-yl]hydroxylamine (5l) .**



The general procedure 5.2 was followed using *N*-benzylhydroxylamine (0.0617 g, 0.501 mmol), and allylic amine (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). ^1H 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 $\text{C}_{25}\text{H}_{28}\text{NO}$ $[\text{M}]^+$: 372.2202 Found 372.2205.

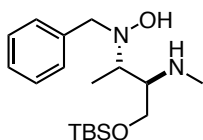
($\pm$)-(2*S,3*S**)-*N*-Benzyl-*N*-[1-(methylamino)-1-phenylpropan-2-yl]hydroxylamine (5m).**



The general procedure 5.2 was followed using *N*-benzylhydroxylamine (0.0617 g, 0.501 mmol), and allylic amine (0.0751 g, 0.510 mmol) and 0.5 mL of catalyst stock solution.

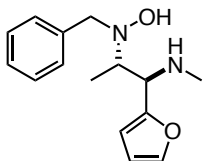
The reaction was stirred at 30 °C in an oil bath for 24 hours. The title compound was purified by column chromatography (5% MeOH/CH₂Cl₂) to yield a white solid (0.108 g, 80%, 95:5 dr). ¹H NMR (400 MHz, CDCl₃) δ 7.44-7.17 (m, 10H), 3.87 (d, *J* = 13.2 Hz, 1H), 3.68 (d, *J* = 13.2 Hz, 1H), 3.36-3.20 (m, 2H), 1.74 (s, 3H), 0.88 (d, *J* = 6.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₇H₂₂N₂O [M]⁺: 270.1732 Found 270.1737.

(±)-(2*S,3*R**)-*N*-Benzyl-*N*-{4-[(*tert*-butyldimethylsilyl)oxy]-3-(methylamino)butan-2-yl}hydroxylamine (5n).**



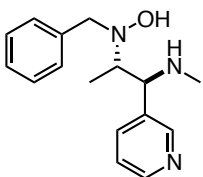
The general procedure 5.2 was followed using *N*-benzylhydroxylamine (0.0618 g, 0.501 mmol), and allylic amine (0.0754 g, 0.55 mmol) and 0.5 mL of catalyst stock solution. The reaction was stirred at 30 °C in an oil bath for 24 hours. The title compound was purified by column chromatography (5% MeOH/CH₂Cl₂) to yield a white solid (0.118 g, 70%, 95:5 dr). ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₈H₃₄N₂O₂ [M]⁺: 338.2390 Not found. Found fragments C₉H₂₂NOSi 188.1471 and C₉H₁₂NO 150.0919.

(±)-(2*S,3*R**)-*N*-Benzyl-*N*-[1-(furan-2-yl)-1-(methylamino)propan-2-yl]hydroxylamine (5o).**



The general procedure 5.2 was followed using *N*-benzylhydroxylamine (0.0618 g, 0.501 mmol), and allylic amine (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/CH₂Cl₂) to yield an off-white solid (0.112 g, 86%, 95:5 dr). ¹H NMR (400 MHz, CDCl₃) δ 7.42-7.25 (m, 6H), 6.33-6.29 (m, 2H), 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₅H₂₀N₂O₂ [M]⁺: 260.1525 Found fragments: C₆H₈NO 110.0608 and C₉H₁₂NO 150.0919.

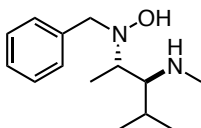
(±)-(2*S,3*S**)-*N*-Benzyl-*N*-[1-(methylamino)-1-(pyridin-3-yl)propan-2-yl]hydroxylamine (5p).**



The general procedure 5.2 was followed using *N*-benzylhydroxylamine (0.0618 g, 0.501 mmol), and allylic amine (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 CH₂Cl₂) to yield a white solid (0.110 g, 81%, 95:5 dr). ¹H NMR (400 MHz, CDCl₃) 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,

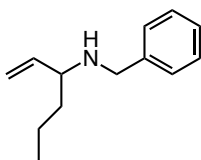
3H), 0.869 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 150.5, 149.1, 138.6, 136.3, 135.7, 129.5, 128.4, 127.4, 123.8, 66.2, 65.8, 33.5, 8.7; IR (film): 1640, 1593, 1580, 1453, 1426, 1379, 1022, 906, 822, 735, 719, 692 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_{16}\text{H}_{21}\text{N}_3\text{O}$ $[\text{M}]^+$: 271.1685 Found 271.1688.

($\pm$)-(2*S,3*S**)-*N*-Benzyl-*N*-[4-methyl-3-(methylamino)pentan-2-yl]hydroxylamine
(5q)**



The general procedure 5.2 was followed using *N*-benzylhydroxylamine (0.0618 g, 0.501 mmol), and allylic amine (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). ^1H 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 $\text{C}_{14}\text{H}_{24}\text{N}_2\text{O}$ $[\text{M}]^+$: 236.1889. Found fragments $\text{C}_9\text{H}_{12}\text{NO}$ 150.0920 and $\text{C}_5\text{H}_{12}\text{N}$ 86.0972.

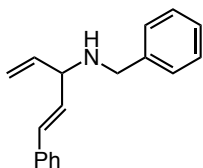
($\pm$)-*N*-Benzylhex-1-en-3-amine



Synthesized following the general procedure 5.3 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

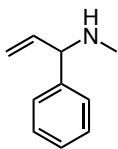
(40% from aldehyde). Spectral datum was consistent with literature.¹⁸² ¹H NMR (400 MHz, CDCl₃) δ 7.32-7.22 (m, 5H), 5.62 (ddd, *J* = 16.8, 10.4, 7.6, 1H), 5.14 (dd, *J* = 10.4, 1.6 Hz, 1H), 5.10 (dd, *J* = 16.8, 1.6 Hz, 1H), 3.83 (d, *J* = 13.2 Hz, 1H), 3.64 (d, *J* = 13.2 Hz, 1H), 3.03 (dt, *J* = 7.6, 6.0 Hz, 1H), 1.52-1.25 (m, 5H), 0.89 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) 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



This amine was synthesized following general procedure 5.3 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 CH₂Cl₂) to give 0.961 g of the desired amine (55 % from aldehyde). Spectral datum was consistent with literature.¹⁸³ ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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



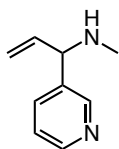
This amine was synthesized following general procedure 5.3 using benzaldehyde (0.956 g, 9.01 mmol), vinyl magnesium bromide (13.5 mL of a 1 M solution in THF, 13.5

¹⁸² Leitner, A.; Shekhar, S.; Pouy, M. J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15506-15514.

¹⁸³ Zheng, W.; Sun, N.; Hou, X. *Org. Lett.* **2005**, *7*, 5151-5154.

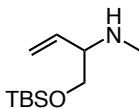
mmol) and zinc dust (2.94 g, 45.1 mmol). The title compound was purified by column chromatography over silica gel (5% MeOH/CH₂Cl₂) to give 0.663 g of the desired amine (50 % from aldehyde). Spectral datum was consistent with literature.¹⁷⁸ ¹H NMR (400 MHz, CDCl₃) δ 7.30-7.15 (m, 5H), 5.96-5.77 (m, 1H), 4.03-3.97 (m, 2H), 4.01 (m, 1H) 2.32 (s, 3H), 1.48 (bs, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 142.4, 140.5, 128.3, 127.6, 127.0, 114.9, 67.8, 34.1.

(±)-Methyl[1-(pyridin-3-yl)prop-2-en-1-yl]amine



This amine was synthesized following general procedure 5.3 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/CH₂Cl₂) to give 1.53 g of the desired amine (69% from aldehyde). Spectral datum was consistent with literature.¹⁷⁸ ¹H NMR (400 MHz, CDCl₃) δ 8.53 (d, *J* = 2.2 Hz, 1H), 8.48 (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); ¹³C NMR (100 MHz, CDCl₃) δ 149.1, 148.6, 139.6, 137.8, 134.9, 123.6, 116.2, 65.5, 34.2.

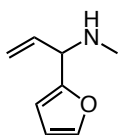
(±)-1-((*tert*-Butyldimethylsilyl)oxy)-*N*-methylbut-3-en-2-amine



This amine was synthesized following general procedure 5.3 using a TBS-protected aldehyde¹⁵⁷ (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/CH₂Cl₂) to give 0.948 g of the desired amine (40 % from aldehyde). ¹H NMR (400 MHz, CDCl₃) 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* =

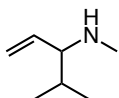
9.9 and 4.2 Hz, 1H), 3.06 (td, $J = 8.0$ and 4.2 Hz, 1H), 2.39 (s, 3H), 0.901 (s, 9H), 0.066 (s, 6H); ^{13}C NMR (100 MHz, CDCl_3) δ 137.3, 117.9, 66.0, 65.3, 33.9, 25.9, 18.3, 5.4; IR (film): 2956, 2926, 2860, 1511, 1475, 1254, 997, 937, 832, 778 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_{11}\text{H}_{25}\text{NOSi}$ $[\text{M}]^+$: 215.1705. Found fragments: $\text{C}_9\text{H}_{22}\text{NOSi}$: 188.1419 and C_2H_3 : 27.0245.

($\pm$)-[1-(Furan-2-yl)prop-2-en-1-yl](methyl)amine



This amine was synthesized following general procedure 5.3 using 2-furaldehyde (1.81 mL, 21.9 mmol), vinyl magnesium bromide (33.0 mL of a 1 M 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). ^1H 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 $\text{C}_8\text{H}_{11}\text{NO}$ $[\text{M}]^+$: 137.0841 Found 137.0827.

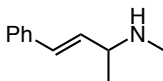
($\pm$)-Methyl(4-methylpent-1-en-3-yl)amine



This amine was synthesized following general procedure 5.3 using isobutyraldehyde (0.790 g, 30.0 mmol), vinyl magnesium bromide (45.0 mL of a 1 M 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). ^1H 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),

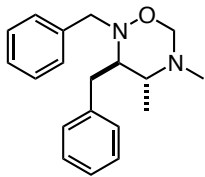
0.88 (d, $J = 6.8$ Hz, 3H), 0.83 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 138.7, 116.9, 69.9, 34.4, 32.1, 19.4, 18.1; IR (film): 2965, 2923, 2867, 1711, 1637, 1466, 1380, 1365, 989, 912 cm^{-1} ; HRMS (EI): Exact mass calcd for $\text{C}_7\text{H}_{15}\text{N}$ $[\text{M}]^+$: 113.1205 Found: 113.1204.

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



This amine was synthesized following general procedure 5.3 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% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to give 1.38 g of the desired amine (27% from aldehyde). ^1H 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 $\text{C}_{11}\text{H}_{15}\text{N}$ $[\text{M}]^+$: 161.1205. Found: 161.1203.

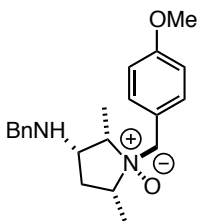
2,3-Dibenzyl-4,5-dimethyl-1,2,5-oxadiazinane (5r).



To a microwave vial was added a magnetic stir bar, *N*-benzylhydroxylamine (0.0618 g, 0.501 mmol), (*E*)-*N*-methyl-4-phenylbut-3-en-2-amine (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). ^1H 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 $\text{C}_{19}\text{H}_{24}\text{N}_2\text{O}$ $[\text{M}]^+$: 296.1889 found 296.1891.

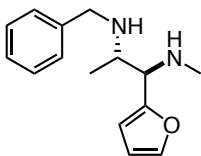
($\pm$)-(1*R,2*S**,3*S**,5*R**)-3-(Benzylamino)-1-(4-methoxybenzyl)-2,5-dimethylpyrrolidine 1-oxide (5s).**



This compound was synthesized according to a procedure by Beauchemin et al⁸⁶ (60 °C, 36 hours) using 1.00 mmol of *N*-(4-methoxybenzyl)hydroxylamine (0.153 g) and 1.10 mmol of *N*-benzylbut-3-en-2-amine (0.187 g). The product was obtained as a single diastereomer as judged by ^1H NMR analysis and isolated as 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 datum was consistent with literature.⁸⁶ 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).

Derivatization:

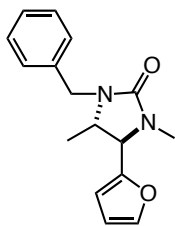
(±)-(1*R**,2*S**)-*N*²-Benzyl-1-(furan-2-yl)-*N*¹-methylpropane-1,2-diamine (5.1).



This diamine was prepared by a modified method of Shuto and coworkers,¹⁸⁴ 0.031g of (±) *N*-benzyl-*N*-[1-(furan-2-yl)-1-(methylamino)propan-2-yl]hydroxylamine was dissolved in 3 mL of 5:1 CH₂Cl₂/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 CH₂Cl₂. The crude mixture was purified by flash column chromatography on silica gel using (1 % NH₄OH/4 % MeOH/CH₂Cl₂) to give a pale yellow oil (0.014 g, 37%). ¹H NMR (300 MHz, CDCl₃) 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) ¹³C NMR (75 MHz, CDCl₃) 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 (CH₂), 34.2 (CH₃), 17.1 (CH₃). IR (film): 2933, 2865, 1645, 1454, 1082 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₅H₂₀N₂O [M]⁺: 244.1576. Not found. Exact mass calcd for C₆H₉NO [M-C₉H₁₃N]⁺: 111.0684. Found 111.0683.

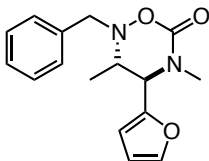
¹⁸⁴ Kazuta, Y.; Abe, H.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2004**, *69*, 9143-9150.

(±)-(4*S,5*R**)-3-Benzyl-1,4-dimethyl-5-(furan-2-yl)imidazolidin-2-one (5.2).**



*N*²-Benzyl-1-(furan-2-yl)-*N*¹-methylpropane-1,2-diamine (7.7 mg, 1 equiv.) was dissolved in CH₂Cl₂ (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 product was purified by flash column chromatography on silica gel using (1 % NH₄OH/2 % MeOH/CH₂Cl₂) to give a pale yellow oil (3.4 mg, 41%). ¹H NMR (300 MHz, CDCl₃) 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) ¹³C NMR (100 MHz, CDCl₃) 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 (CH₂), 45.9 (CH), 29.8 (CH₃), 17.6 (CH₃). IR (film): 2975, 2929, 1705, 1443, 1226, 1093, 1006 cm⁻¹. HRMS (EI): Exact mass calcd for C₁₆H₁₈N₂O₂ [M]⁺: 270.1368. Found: 270.1377.

(±)-(3*S,4*R**)-2-Benzyl-4-(furan-2-yl)-3,5-dimethyl-1,2,5-oxadiazinan-6-one (5.3).**



To a 5-mL round bottom flask was added a magnetic stir bar, (±)-*N*-benzyl-*N*-[1-(furan-2-yl)-1-(methylamino)propan-2-yl]hydroxylamine (0.026 g, 0.10 mmol) and CH₂Cl₂ (2 mL). CDI (0.0243 g, 0.15 mmol) was 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). ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR

(100 MHz, CDCl₃) 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 (CH₂), 33.7 (CH₃), 13.7 (CH₃); IR: 2930, 1704, 1497, 1453, 1433, 1401, 1353, 1311, 1261, 1240, 736, 697, 594 cm⁻¹; HRMS (EI): Exact mass calcd for C₁₆H₁₈N₂O₃ [M]⁺: 286.3310 found 286.3310.

X-ray crystallographic proof of structure - Summary

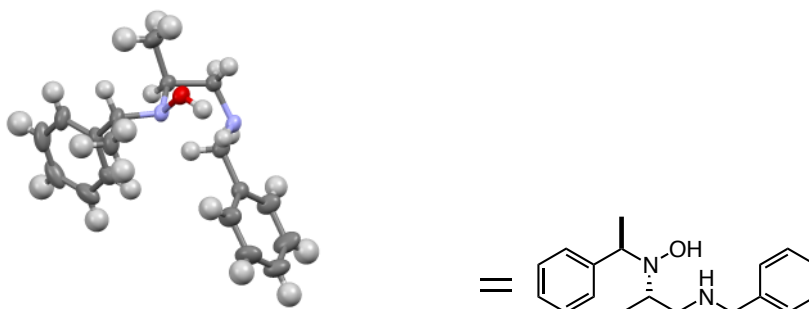


Table S1. Crystal data and structure refinement for (±)-(S*)-N-Benzyl-2-(hydroxy((R*)-1-phenylethyl)amino)propan-1-amine (Table 5.2, Entry 5a)

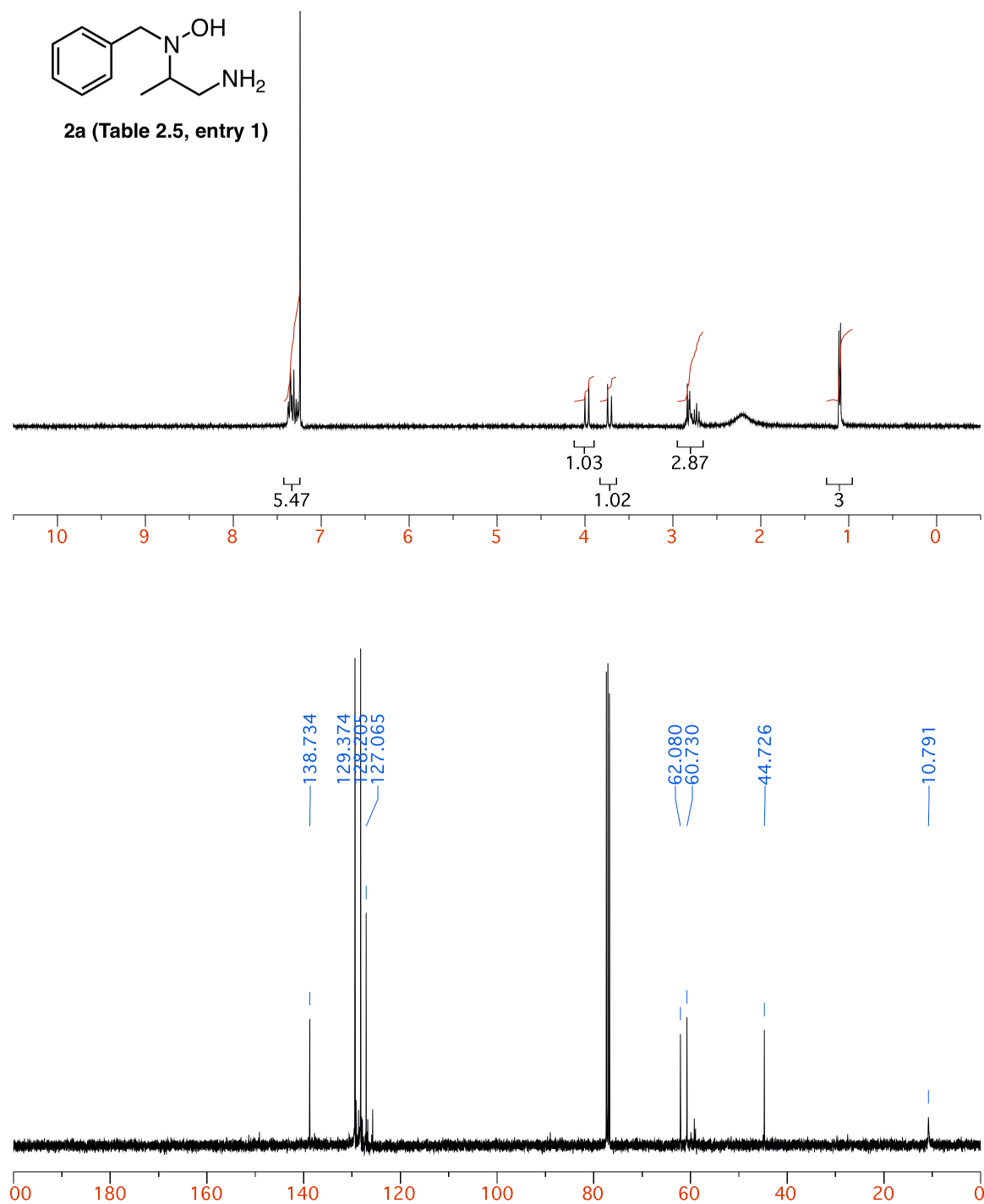
Empirical formula	C ₃₆ H ₄₈ N ₄ O ₂
Formula weight	568.78
Temperature	200(2) K
Temperature	0.71073 Å
Crystal system, space group	Monoclinic, P2(1)/c
Unit cell dimensions	a = 21.3158(6) Å alpha = 90 deg. b = 9.1395(3) Å beta = 107.403(2) deg. c = 17.5654(5) Å gamma = 90 deg.
Volume	3265.37(17) Å ³
Z, Calculated density	4, 1.157 Mg/m ³
Absorption coefficient	0.072 mm ⁻¹
F(000)	1232

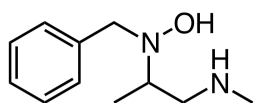
Crystal size	0.18 x 0.18 x 0.12 mm
Theta range for data collection	2.00 to 28.32 deg.
Limiting indices	-28<=h<=28, -12<=k<=12, -23<=l<=23
Reflections collected / unique	44511 / 8078 [R(int) = 0.0253]
Completeness to theta	= 28.32 99.2 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9914 and 0.9872
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	8078 / 0 / 381
Goodness-of-fit on F ²	1.022
Final R indices [I>2sigma(I)]	R1 = 0.0434, wR2 = 0.1117
R indices (all data)	R1 = 0.0653, wR2 = 0.1273
Largest diff. peak and hole	0.240 and -0.197 e.A ⁻³

NOTE: Full details are available from CCDC. Data for CCDC 939263 can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

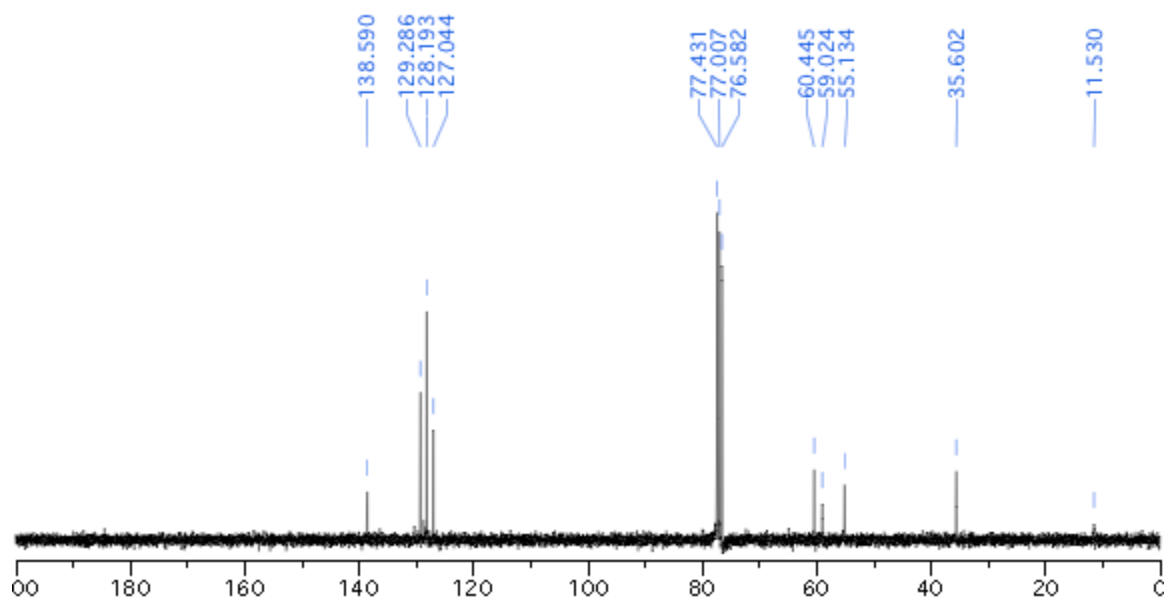
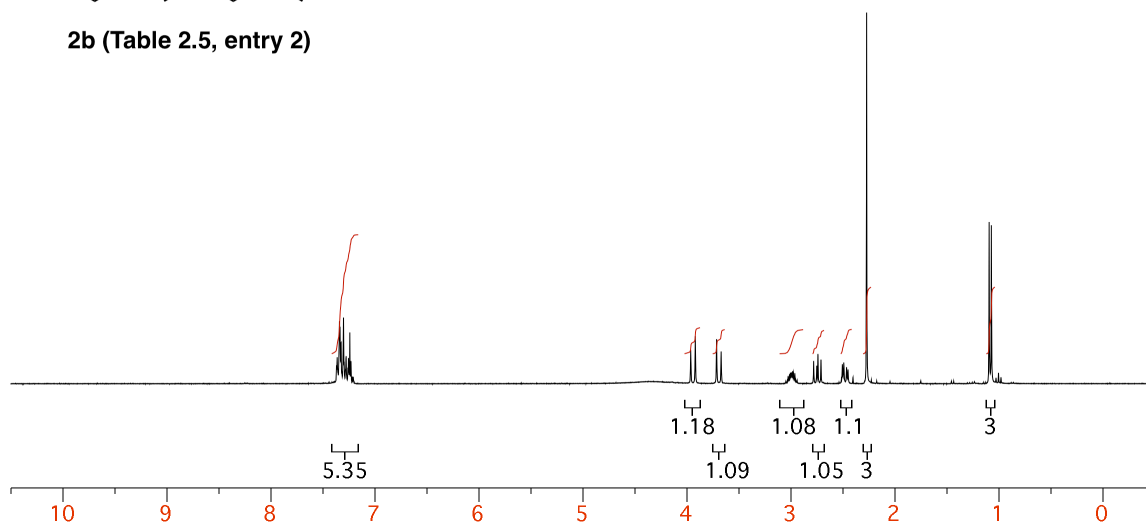
Appendix III

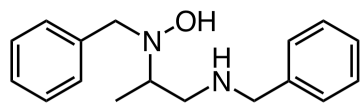
NMR/HPLC data for Chapter 2



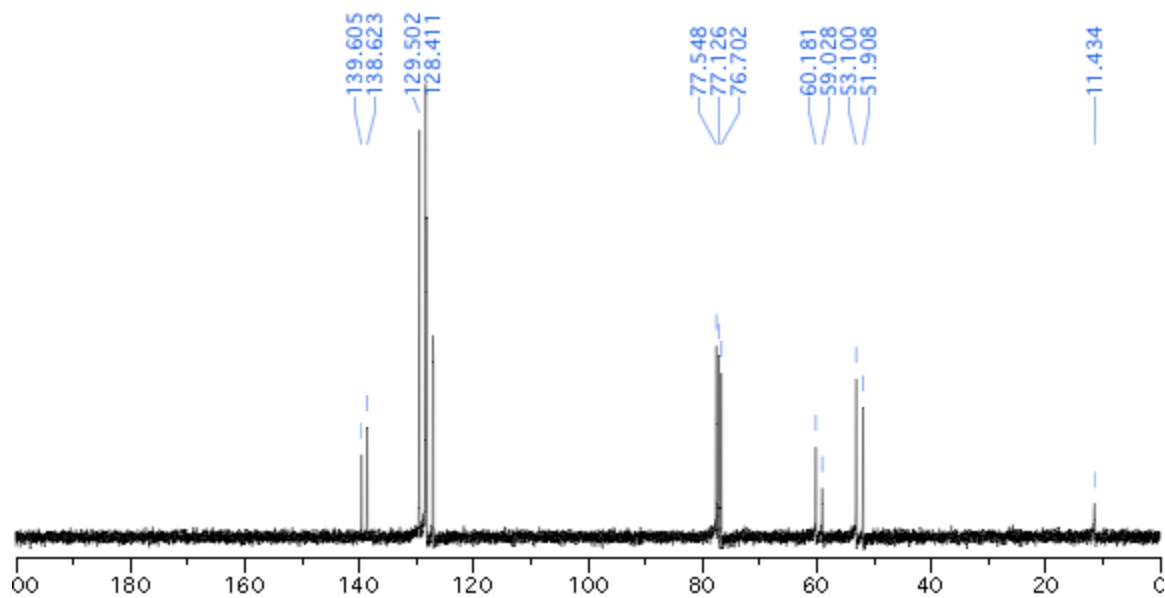
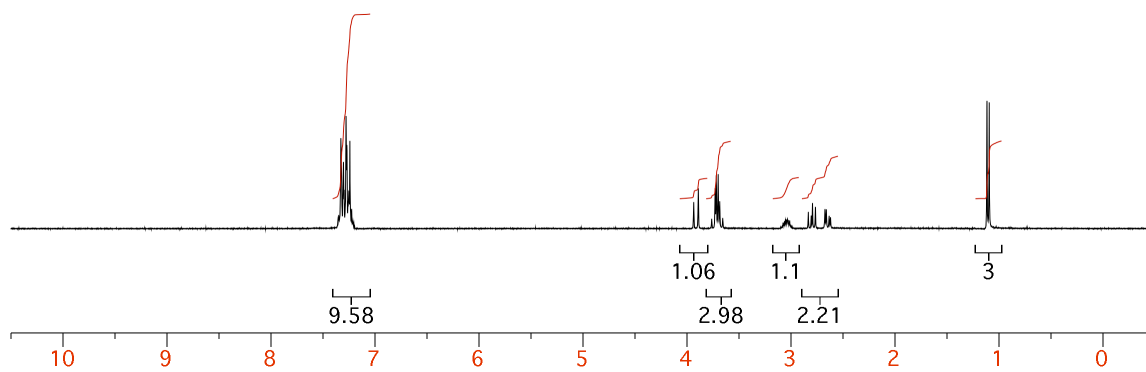


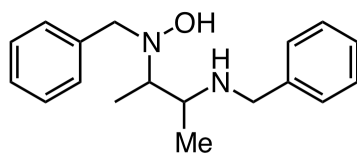
2b (Table 2.5, entry 2)



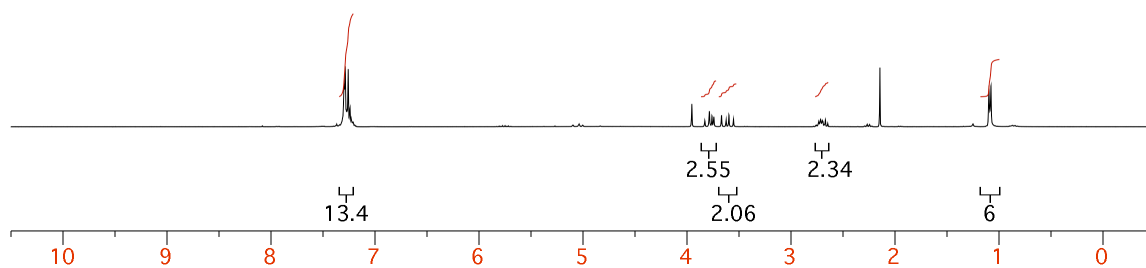


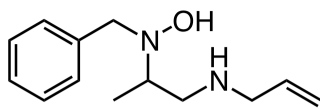
2c (Table 2.5, entry 3)



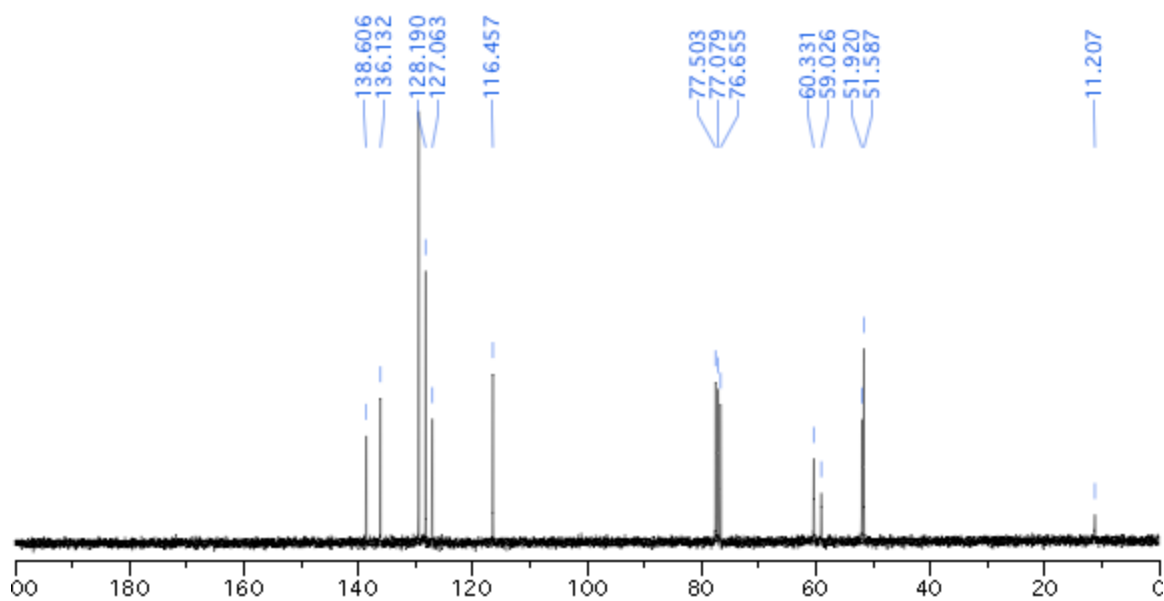
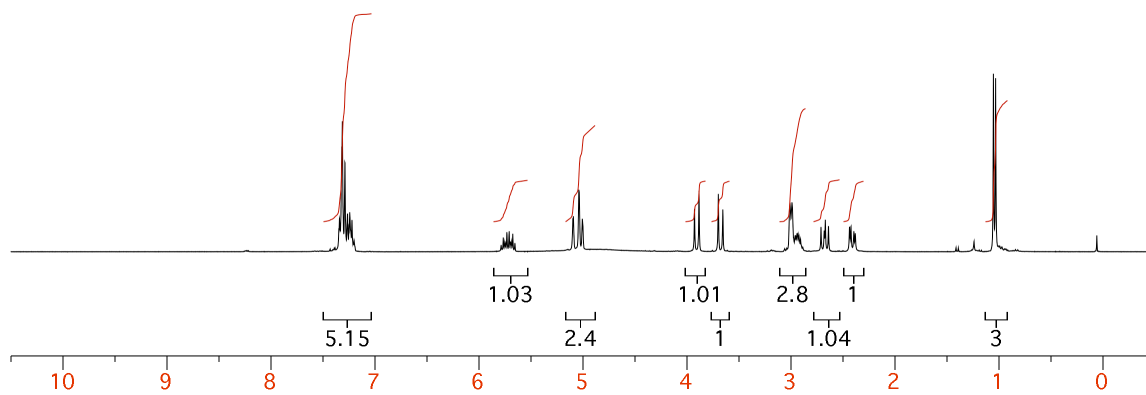


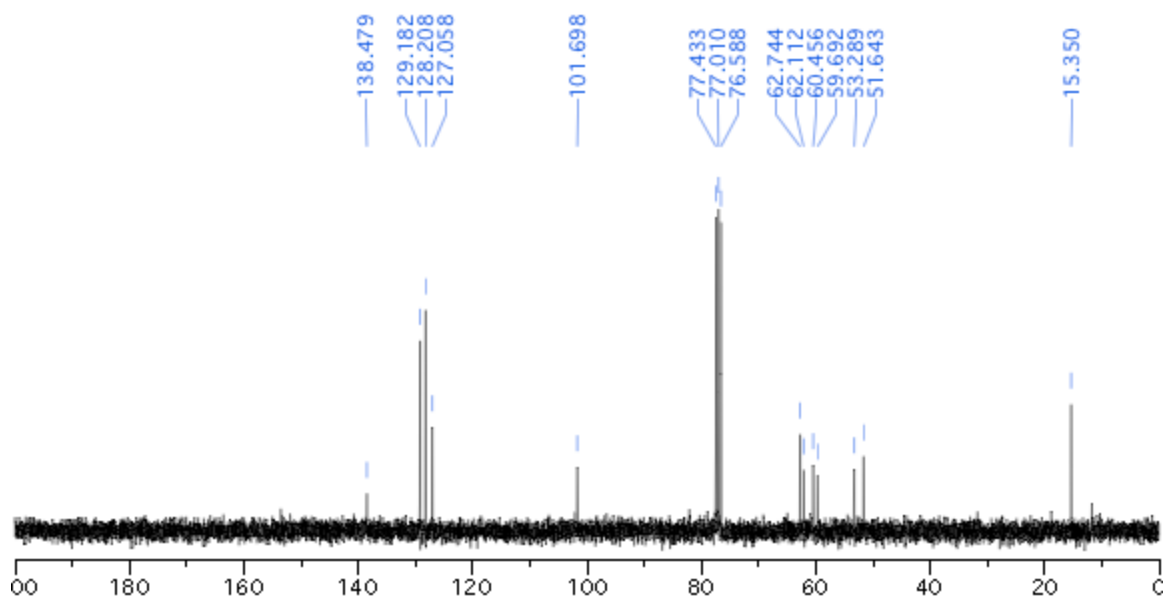
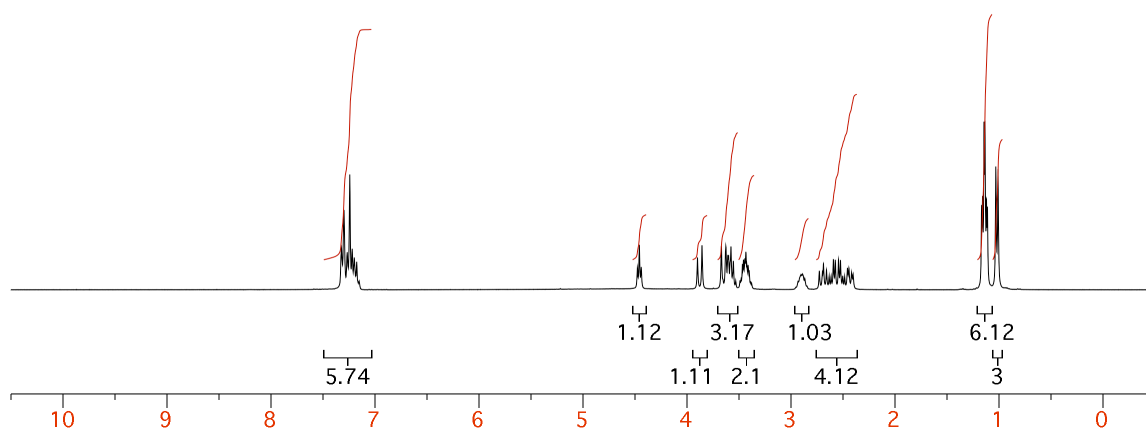
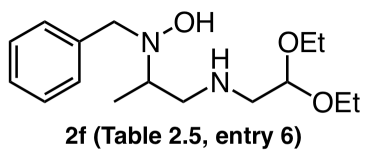
2d (Table 2.5, entry 4)

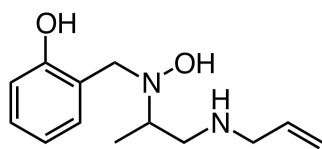




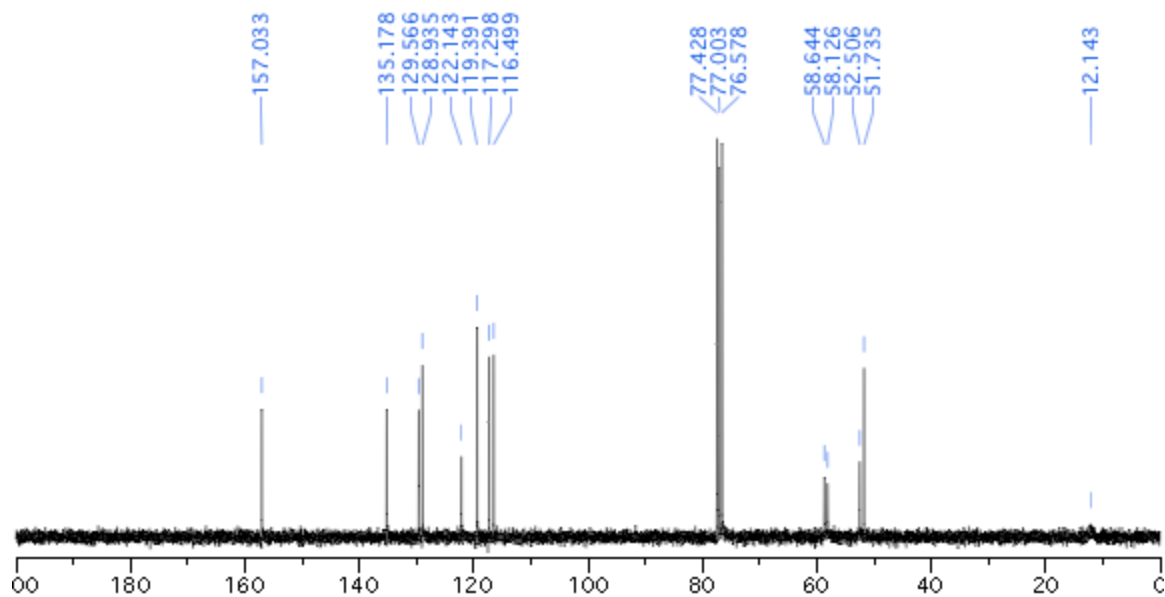
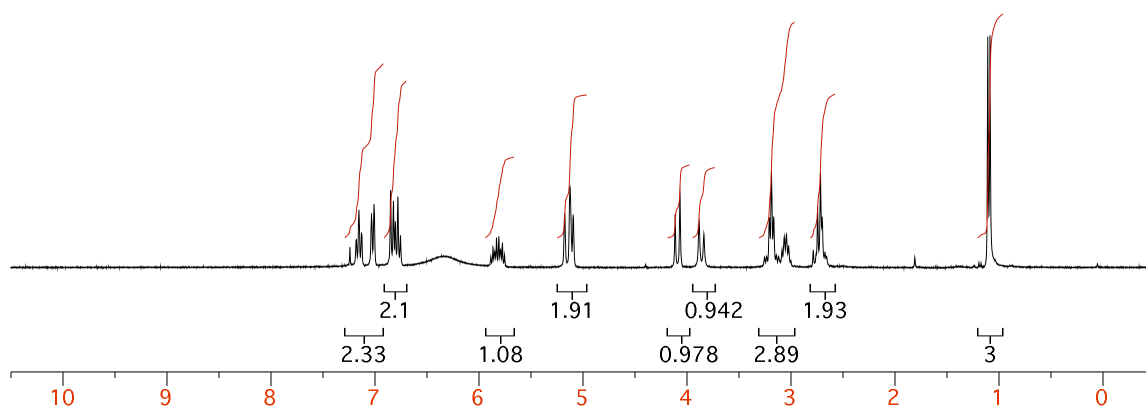
2e (Table 2.5, entry 5)

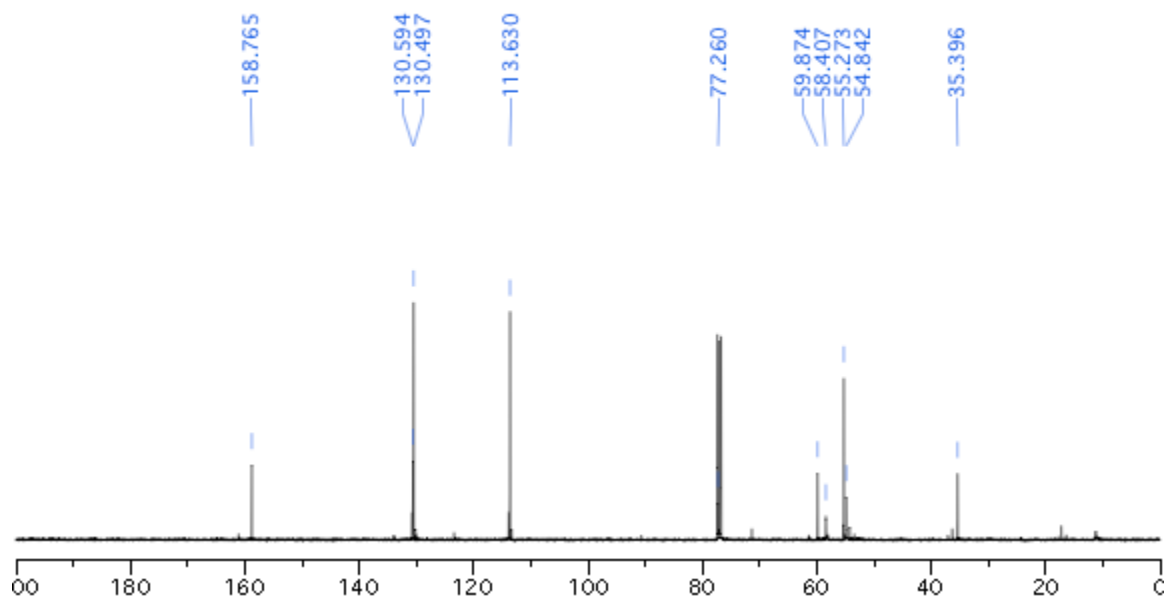
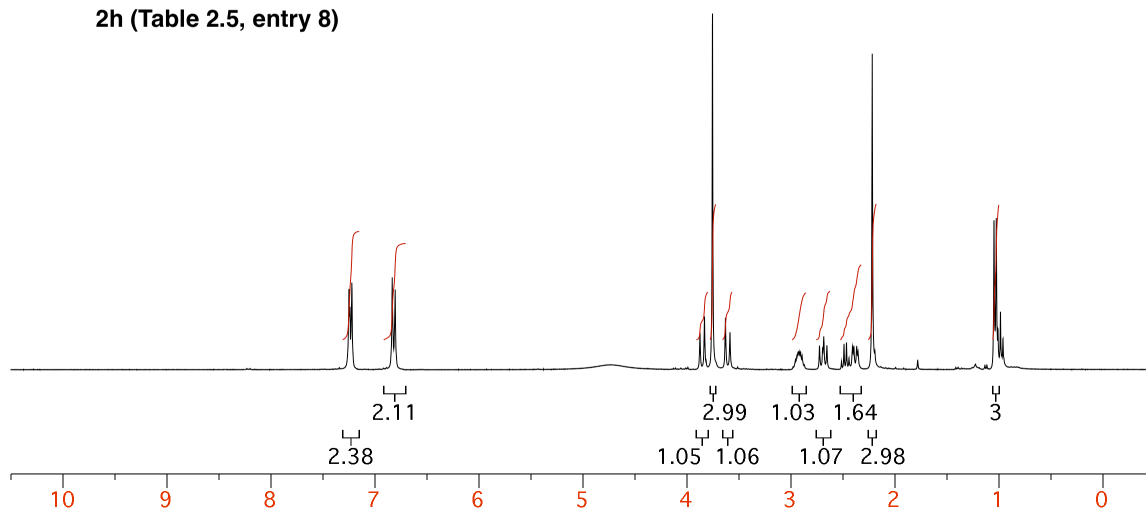
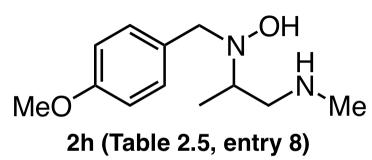


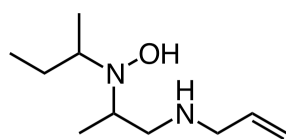




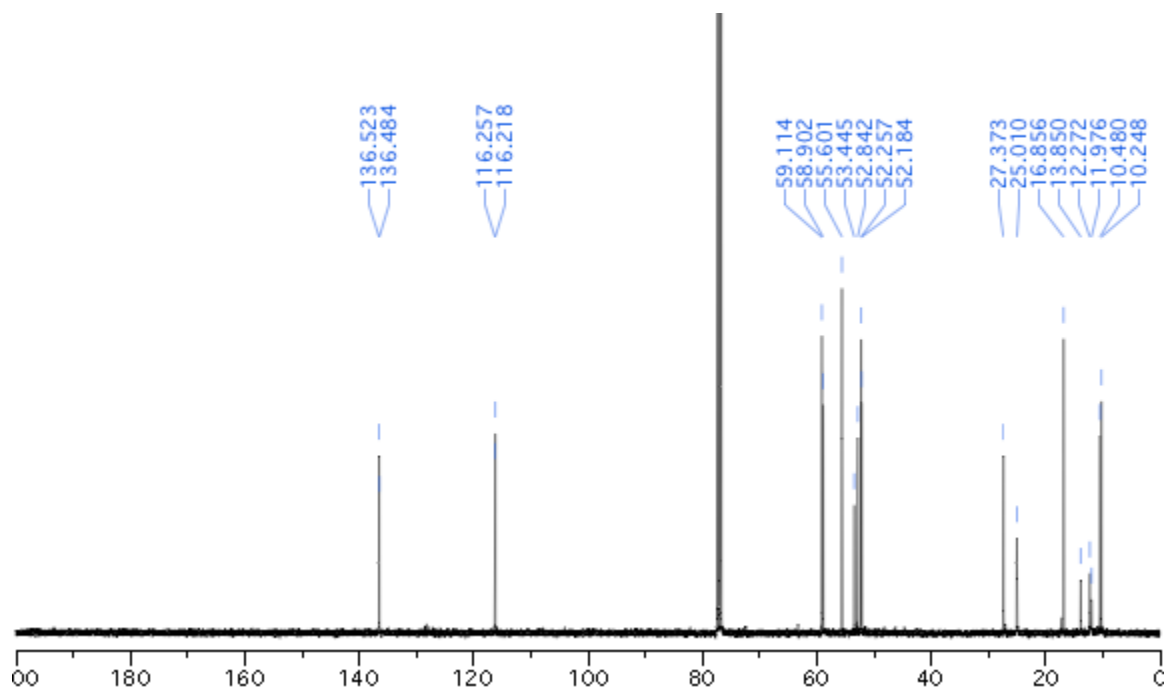
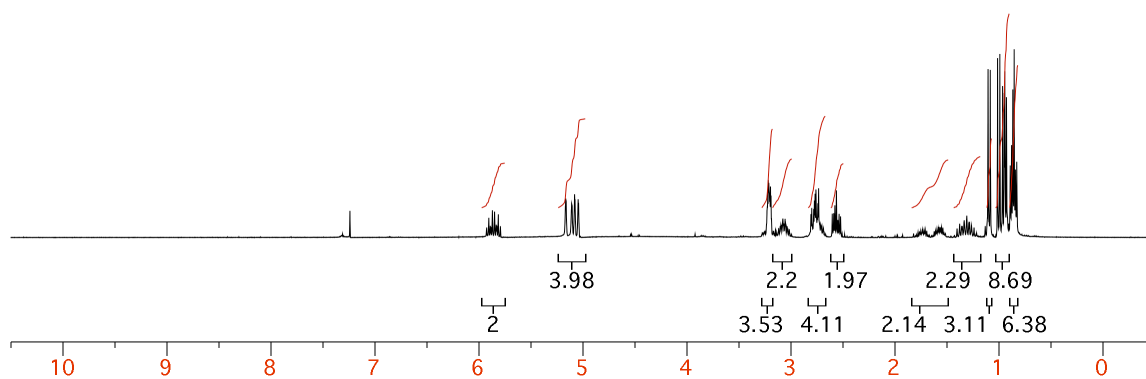
2g (Table 2.5, entry 7)

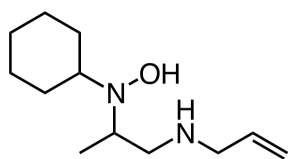




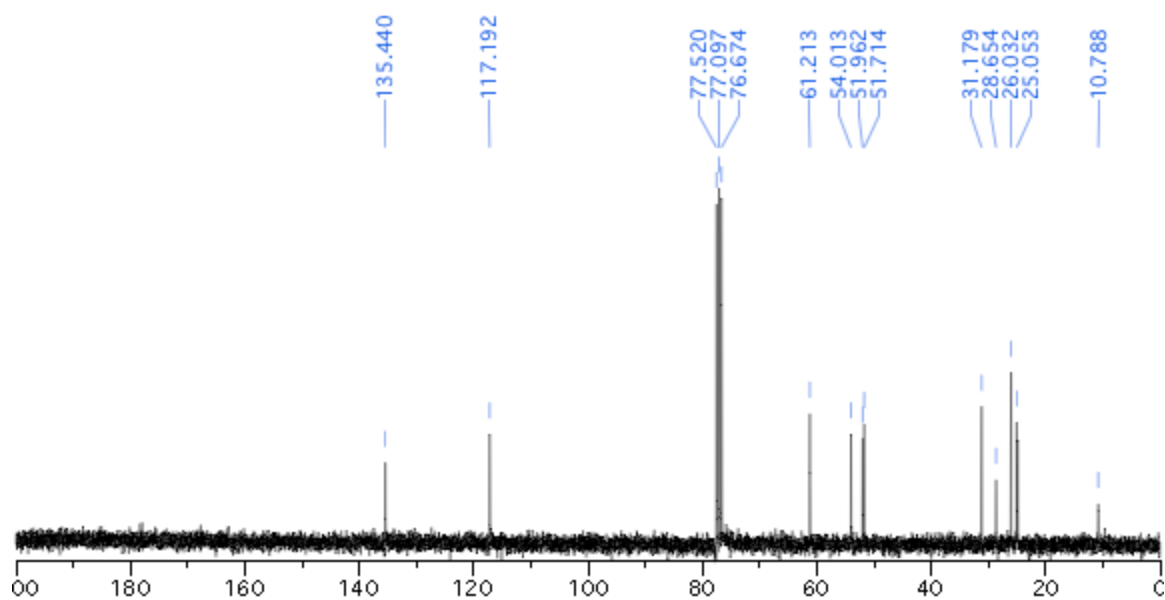
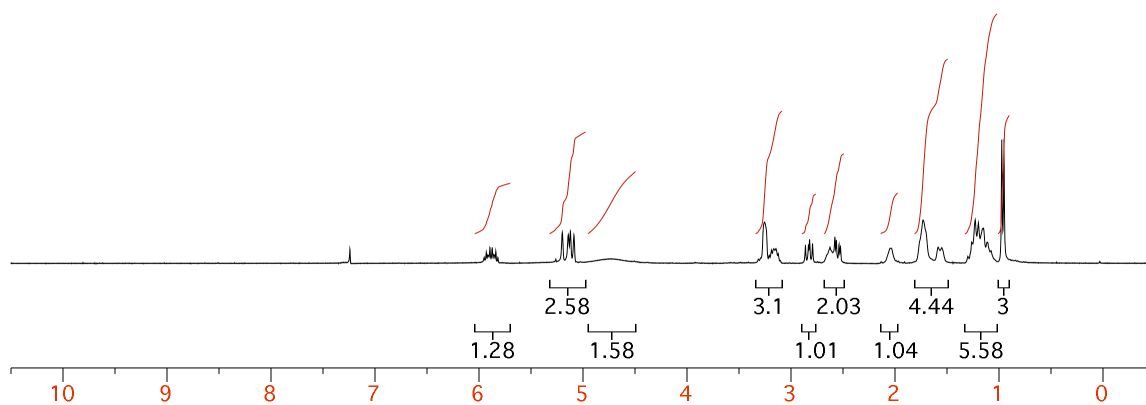


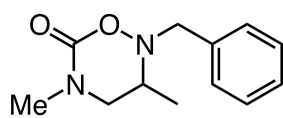
2i (Table 2.5, entry 9)



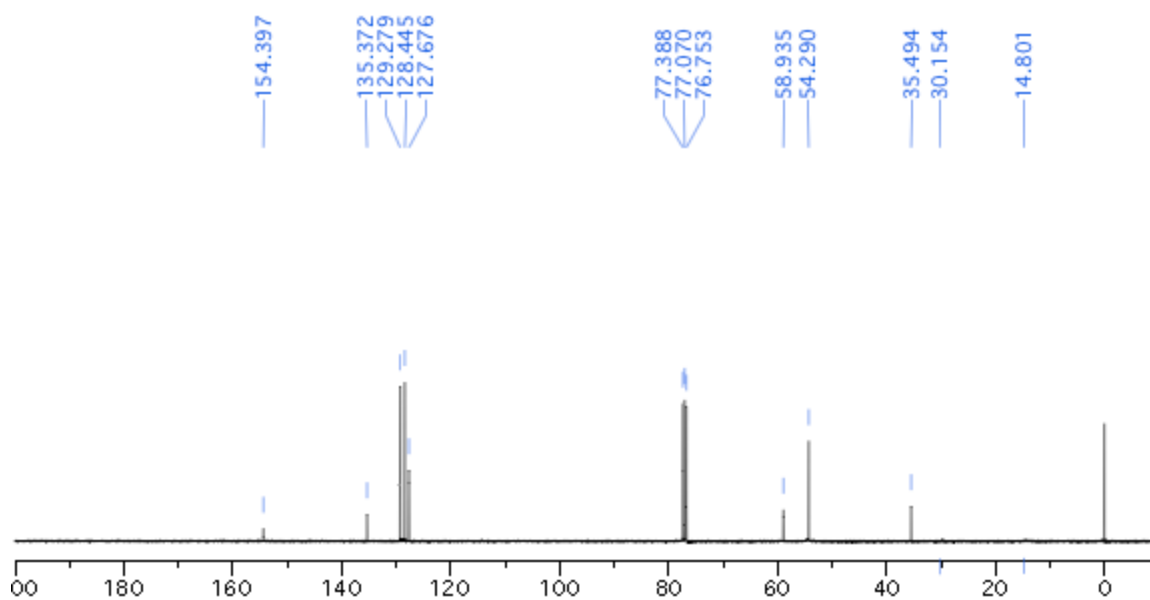
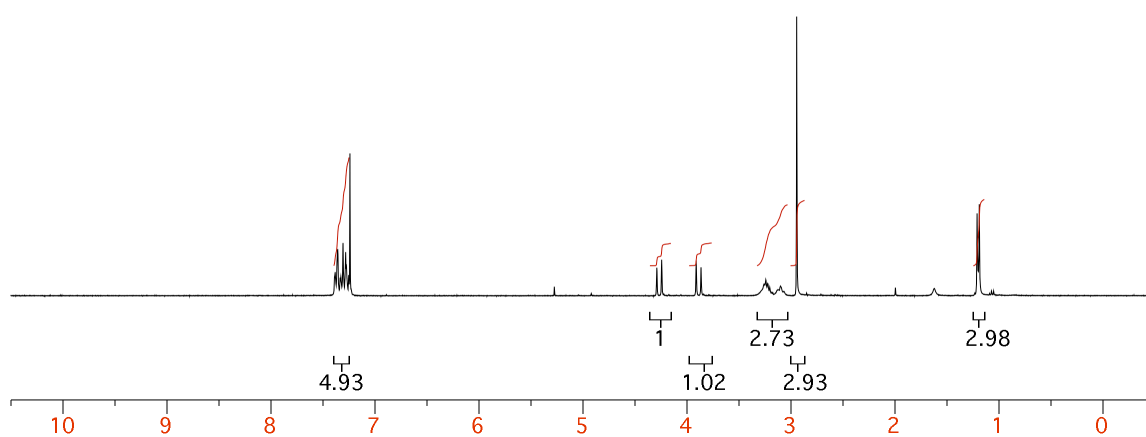


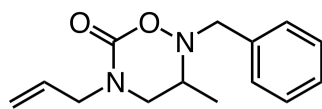
2j (Table 2.5, entry 10)



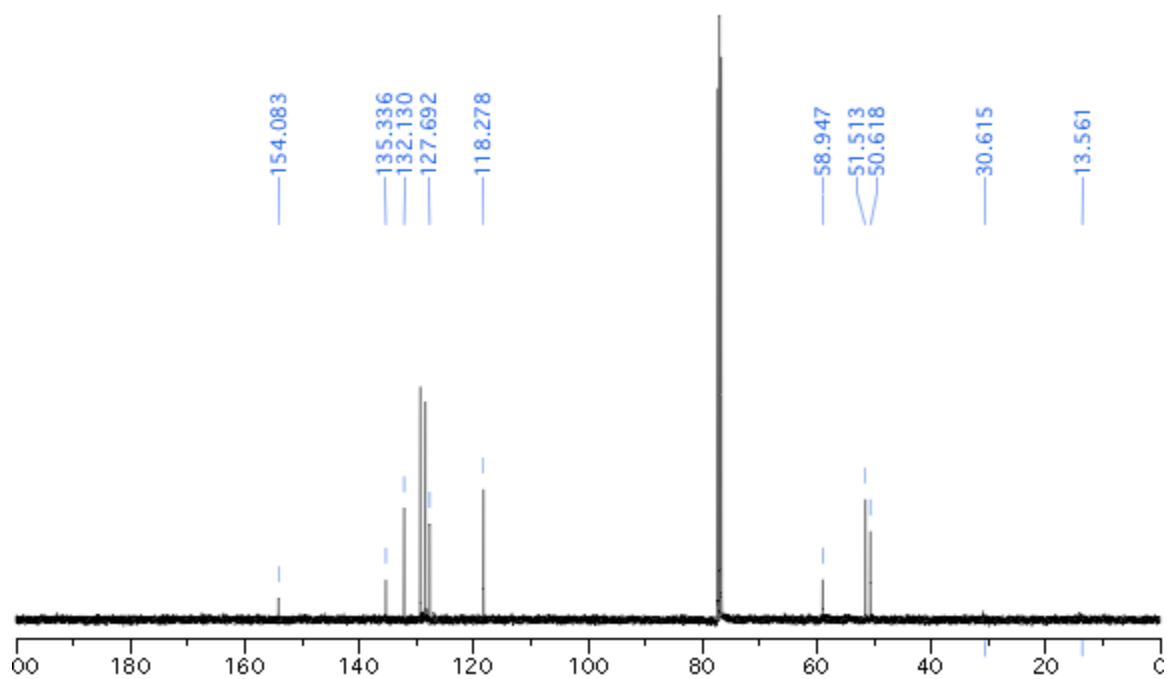
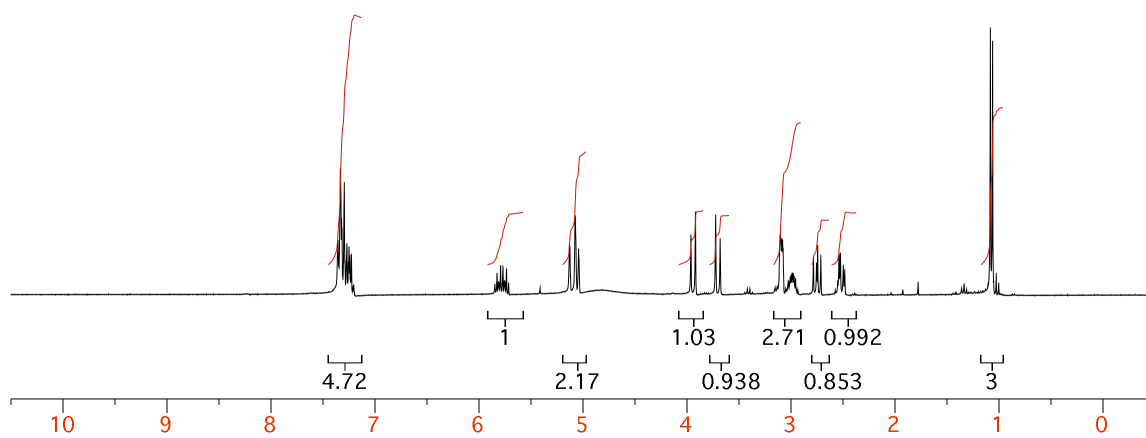


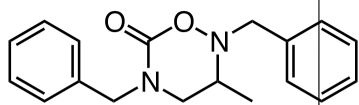
2.1a (Table 2.6, entry 1)



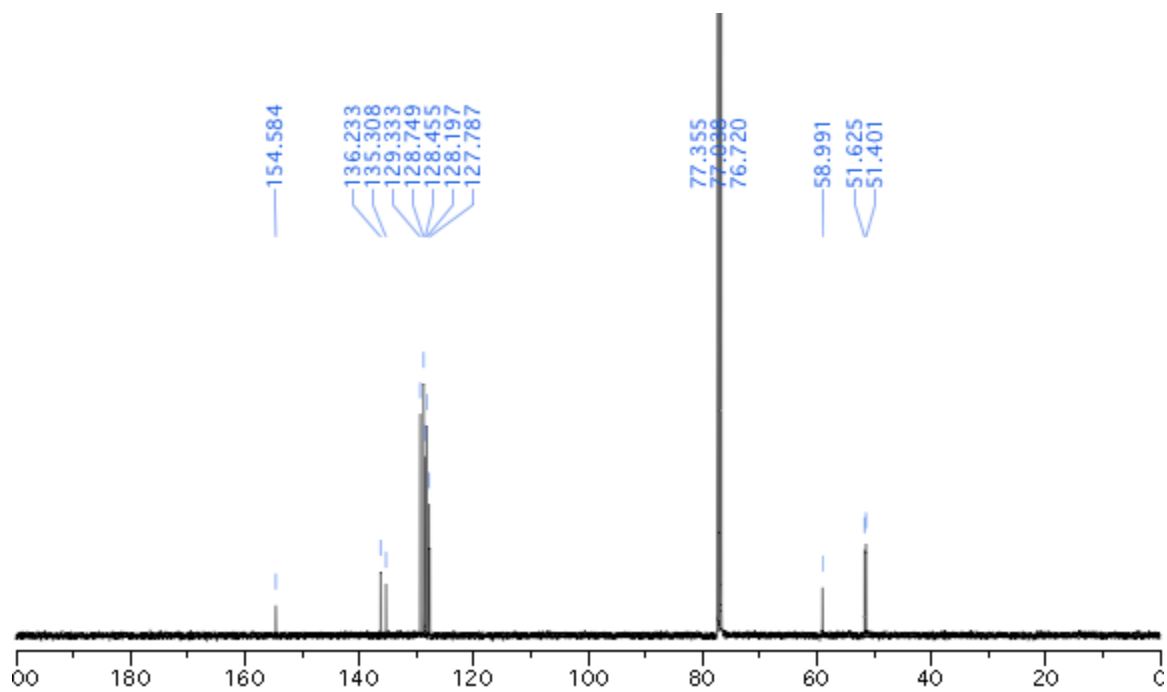
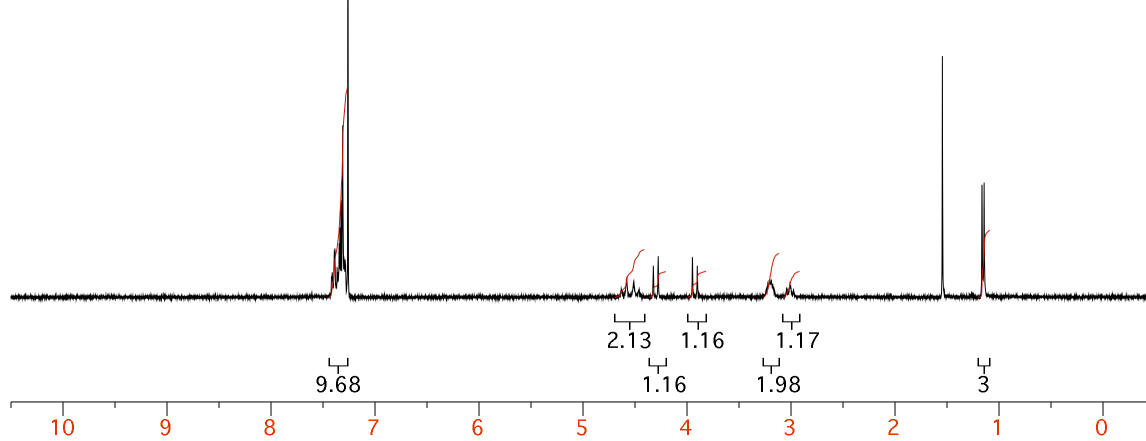


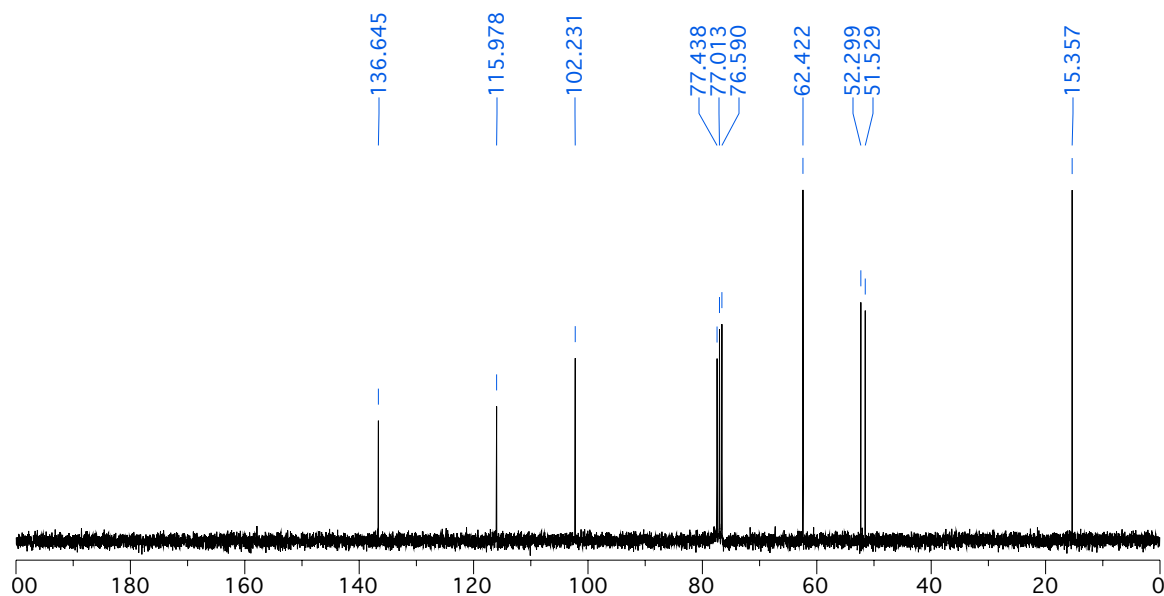
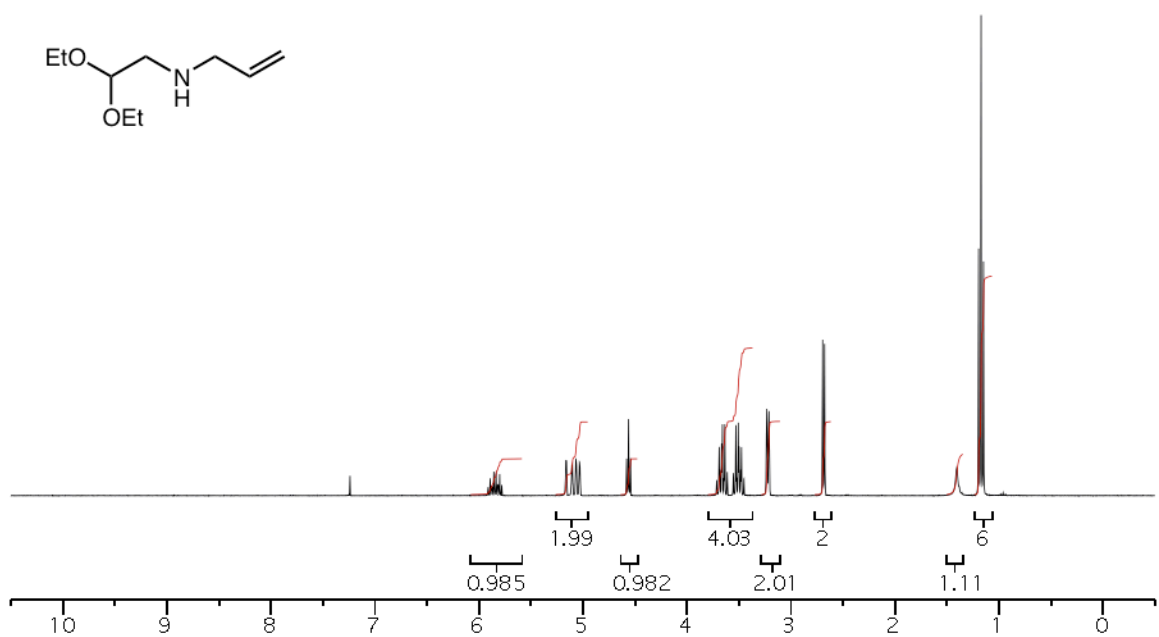
2.1b (Table 2.6, entry 2)

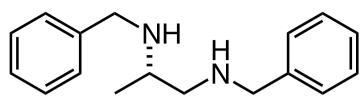




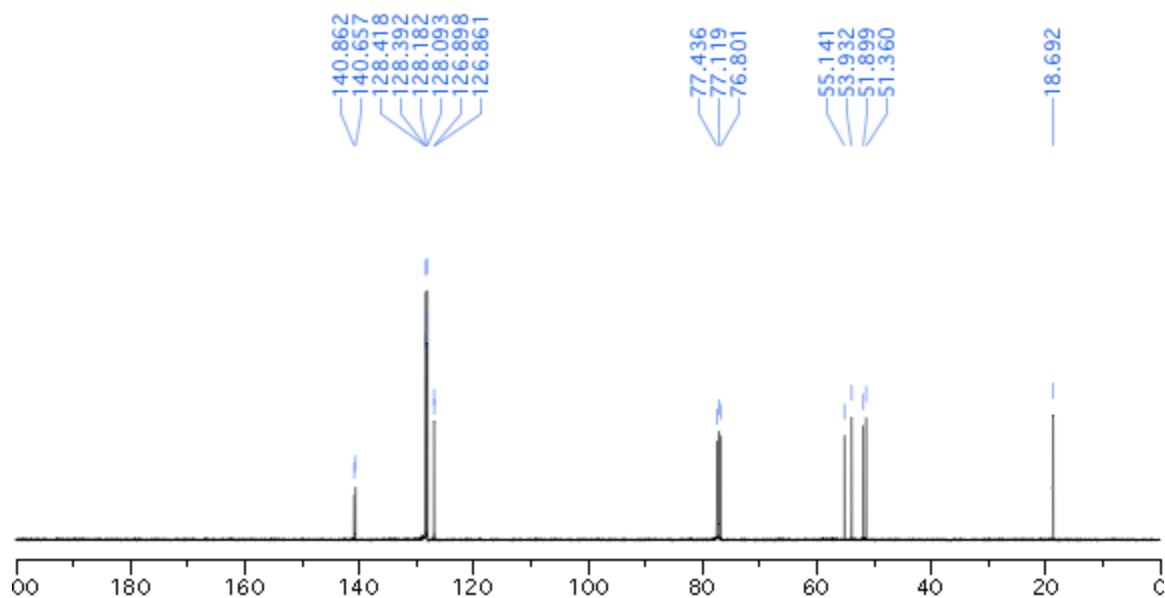
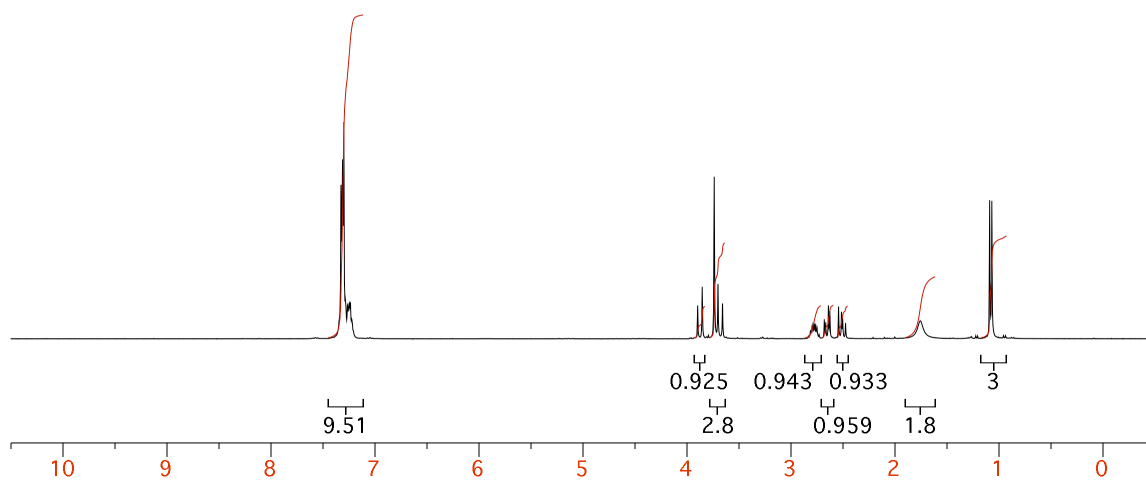
2.1c (Table 2.6, entries 3 and 4)

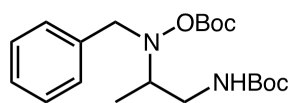




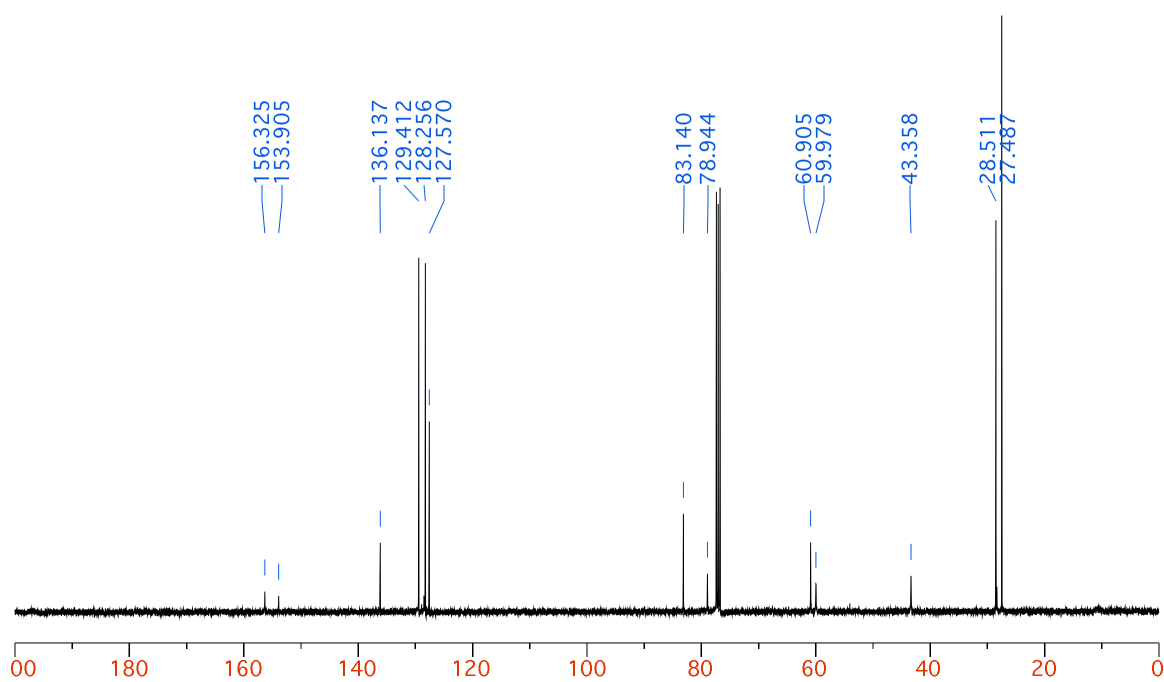
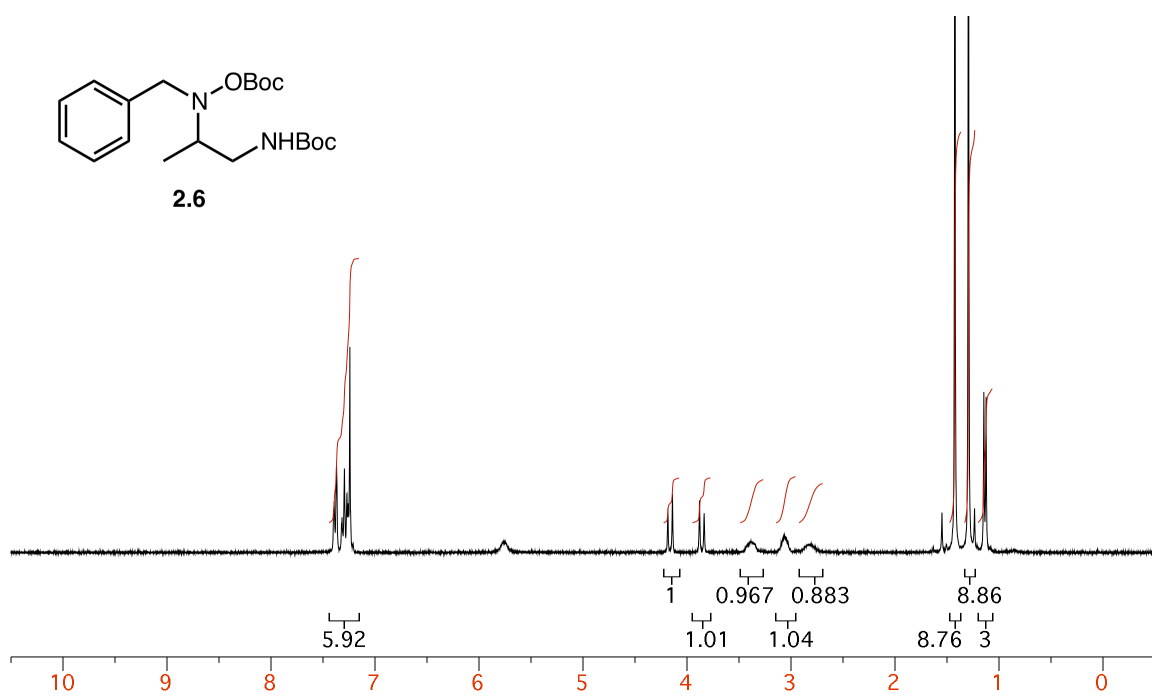


2.1d

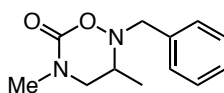




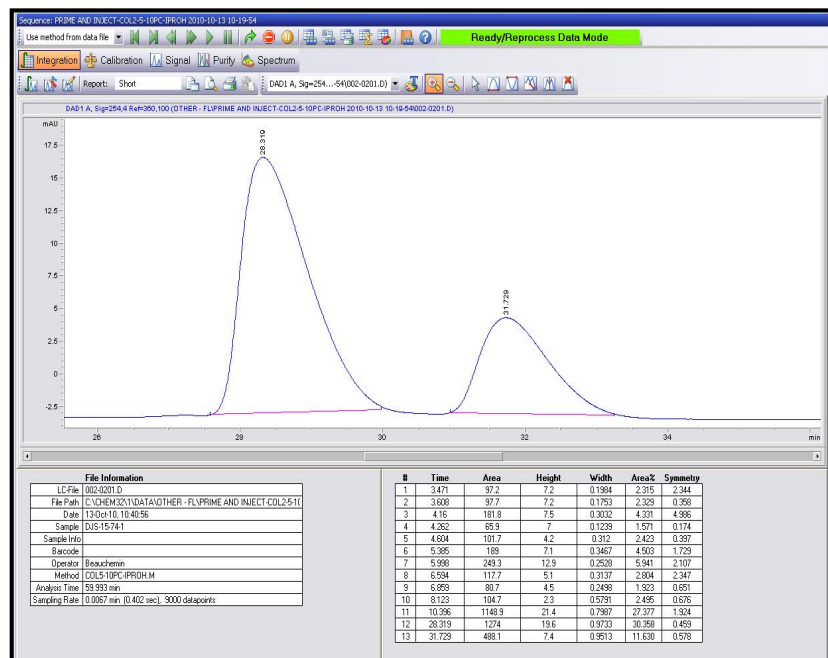
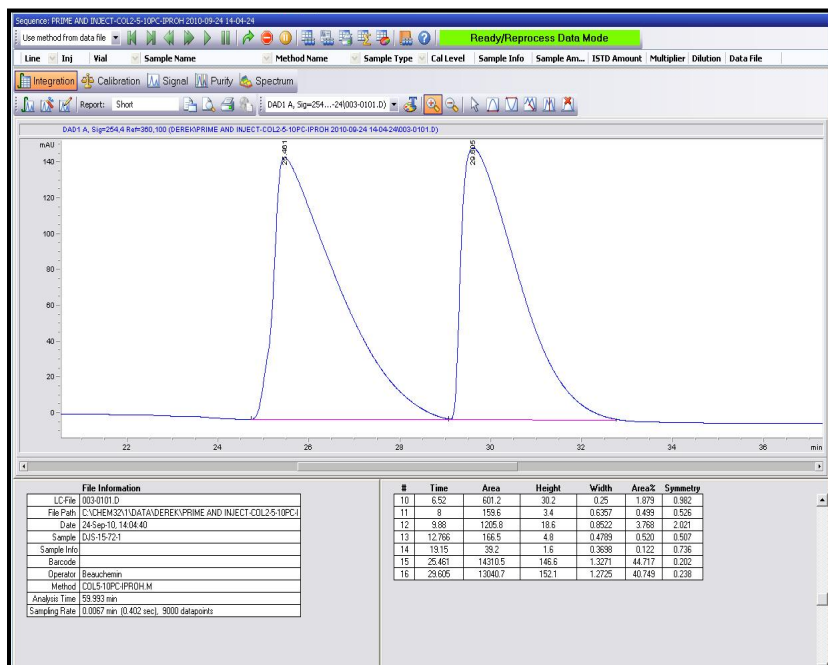
2.6

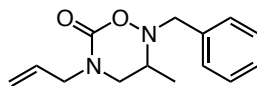


HPLC Spectra of 2.1a-c

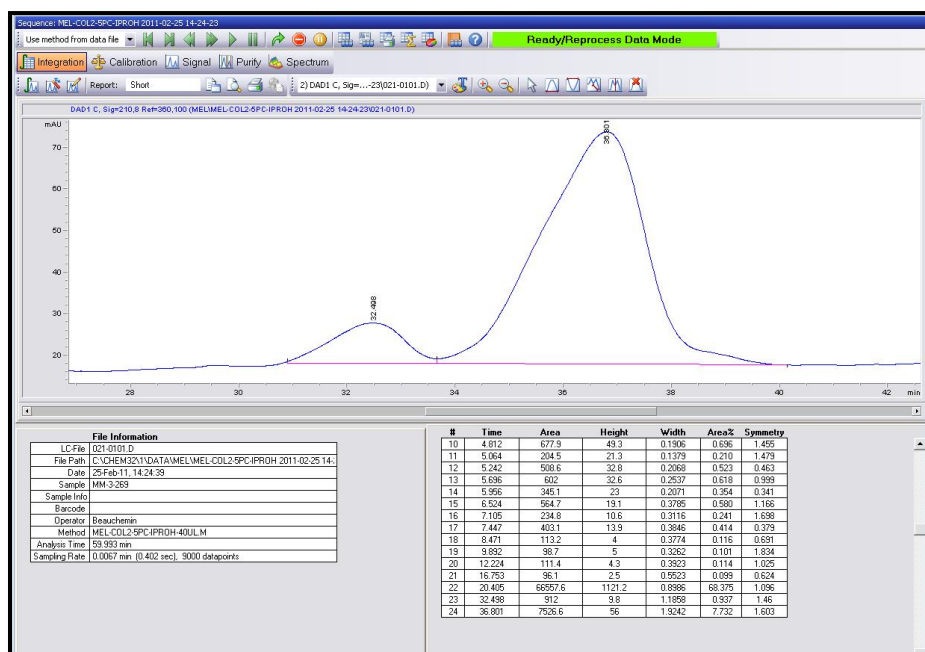
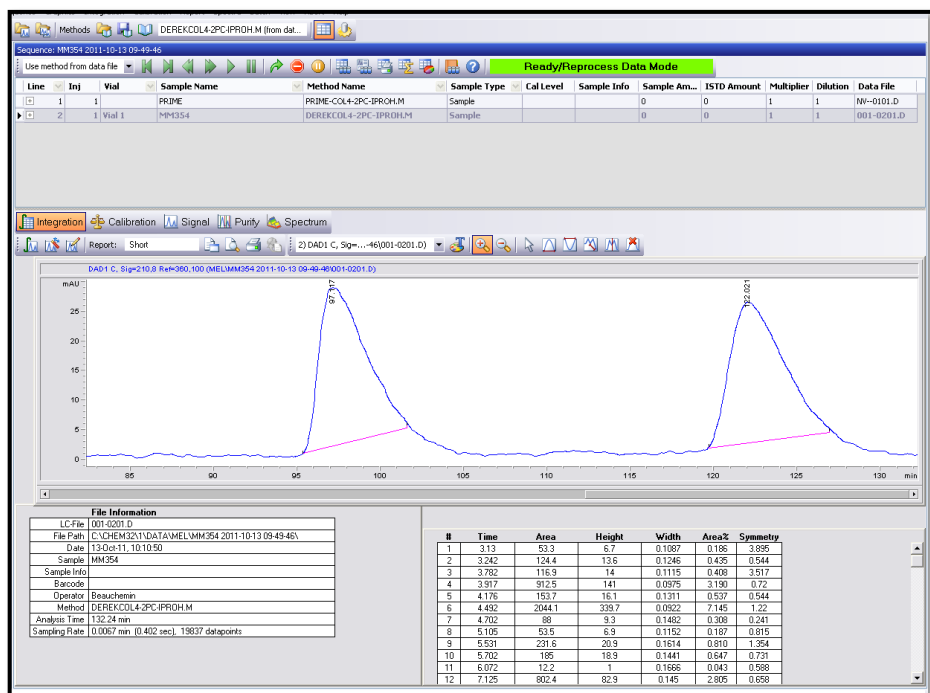


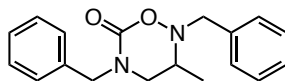
2.1a (Table 2.6, entry 1)



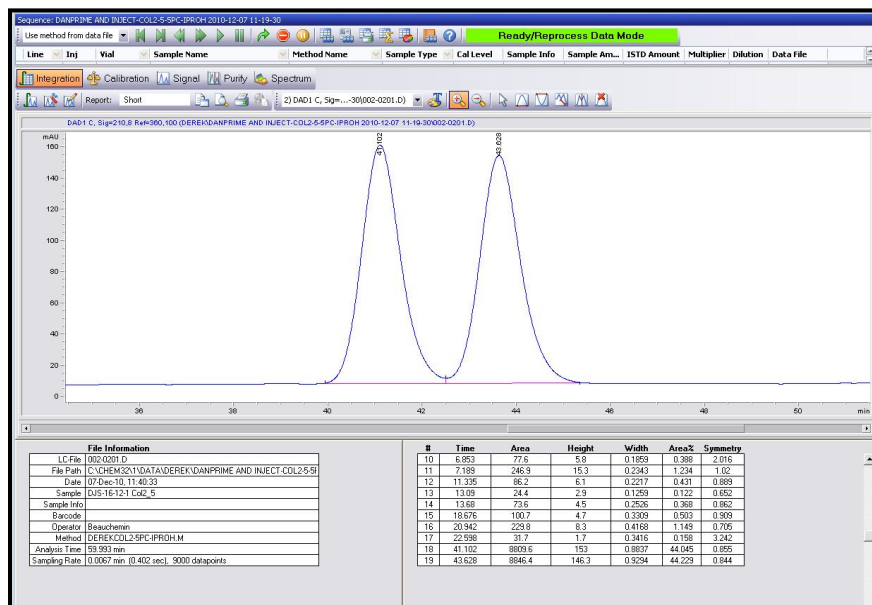


2.1b (Table 2.6, entry 2)

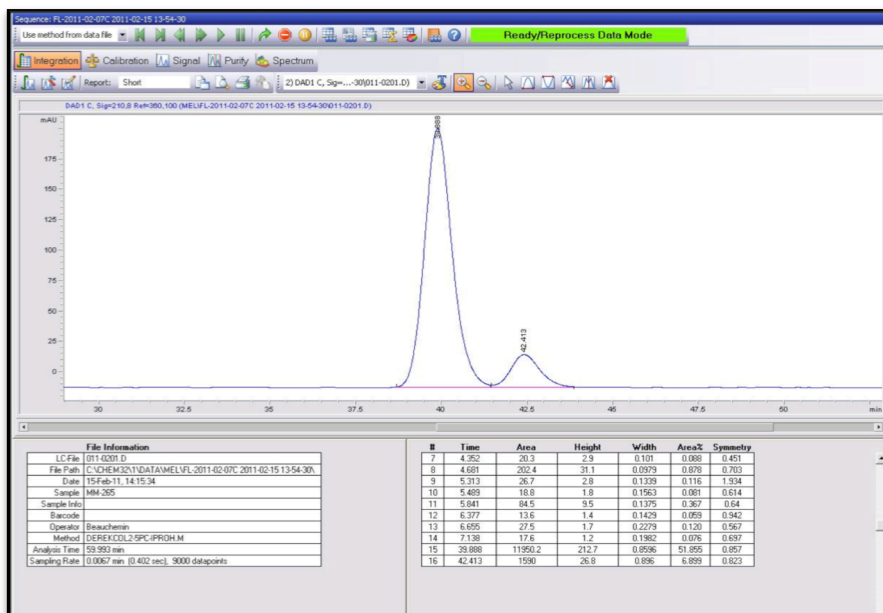




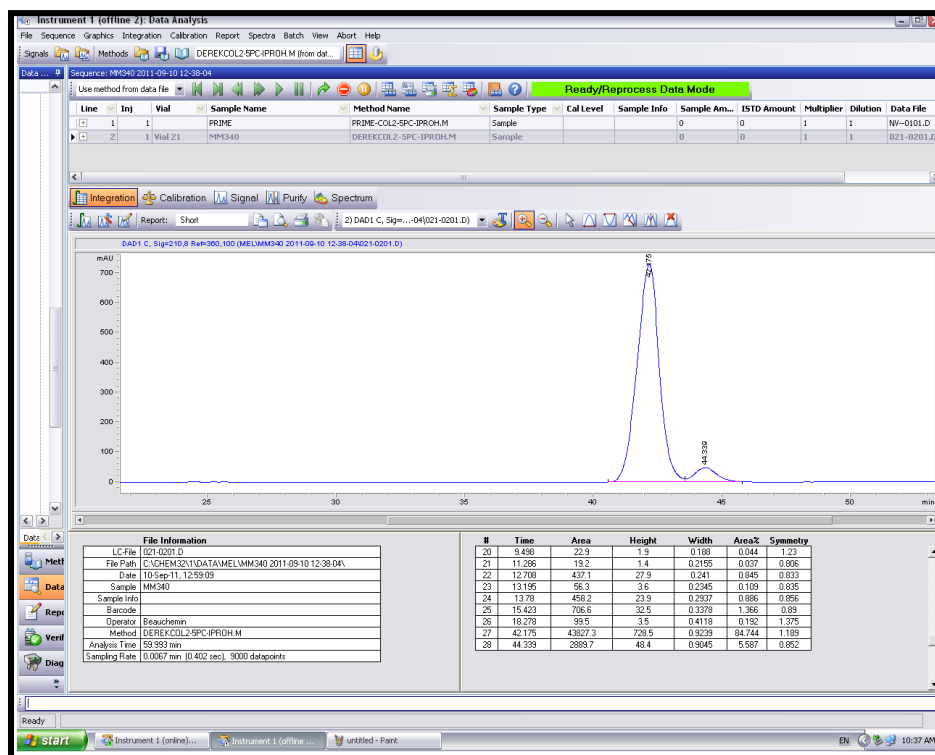
2.1c (Table 2.6, entries 3 and 4)



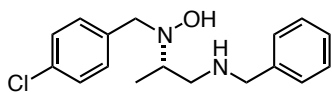
Using catalyst 2.3:



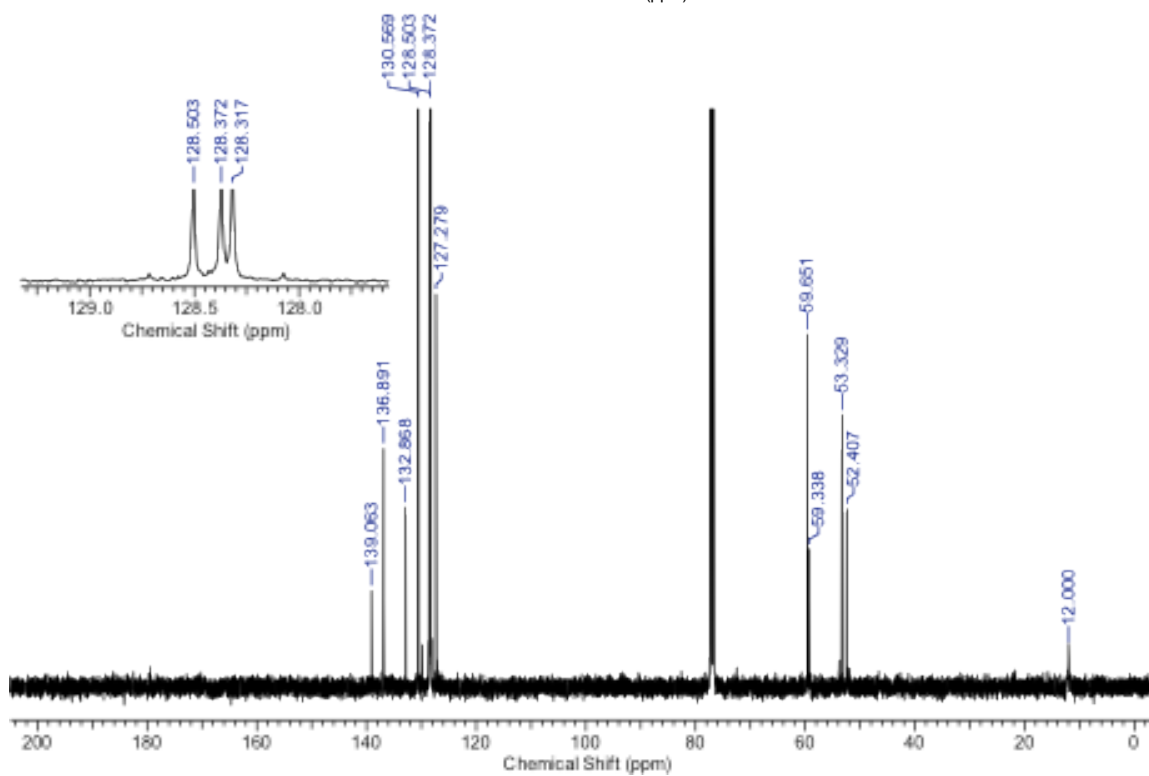
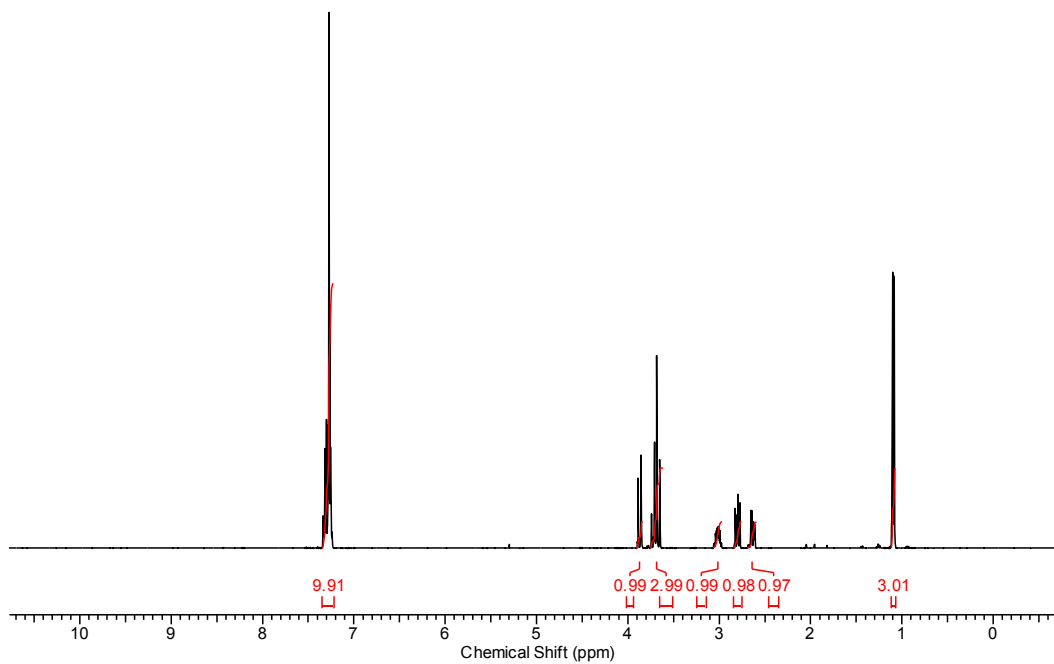
Using catalyst 2.3:



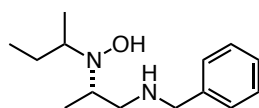
Chapter 4 Supporting Information



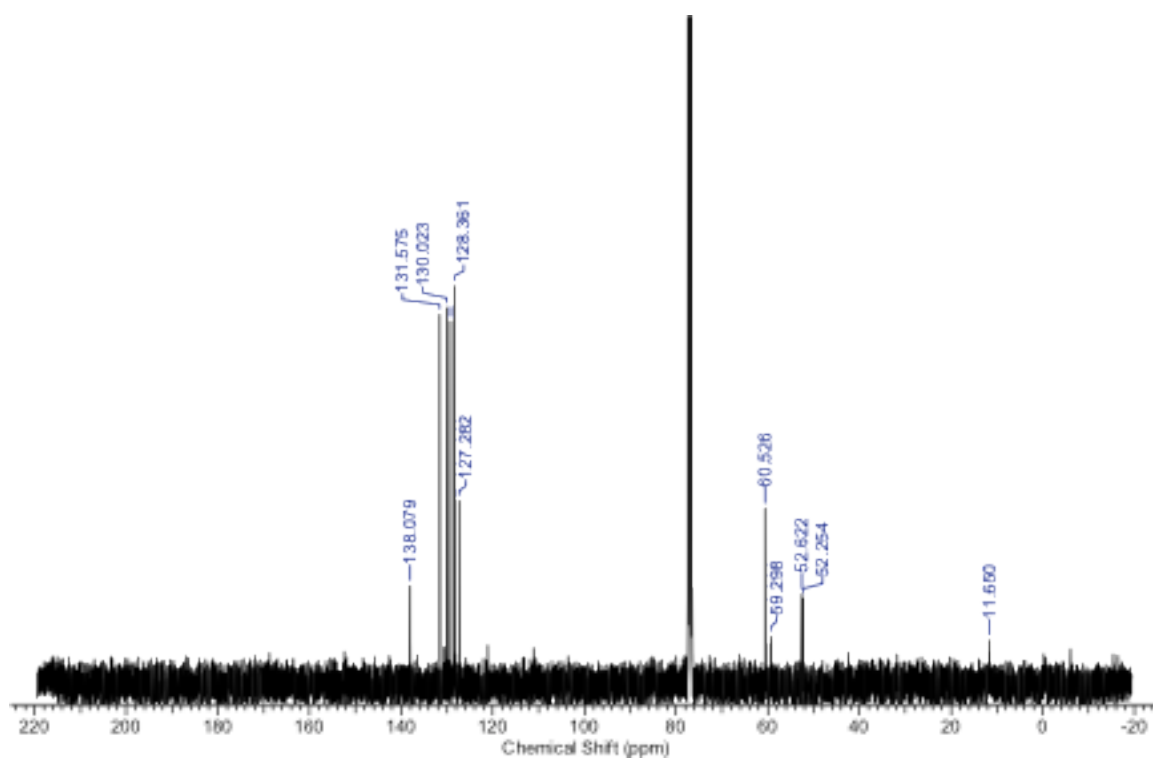
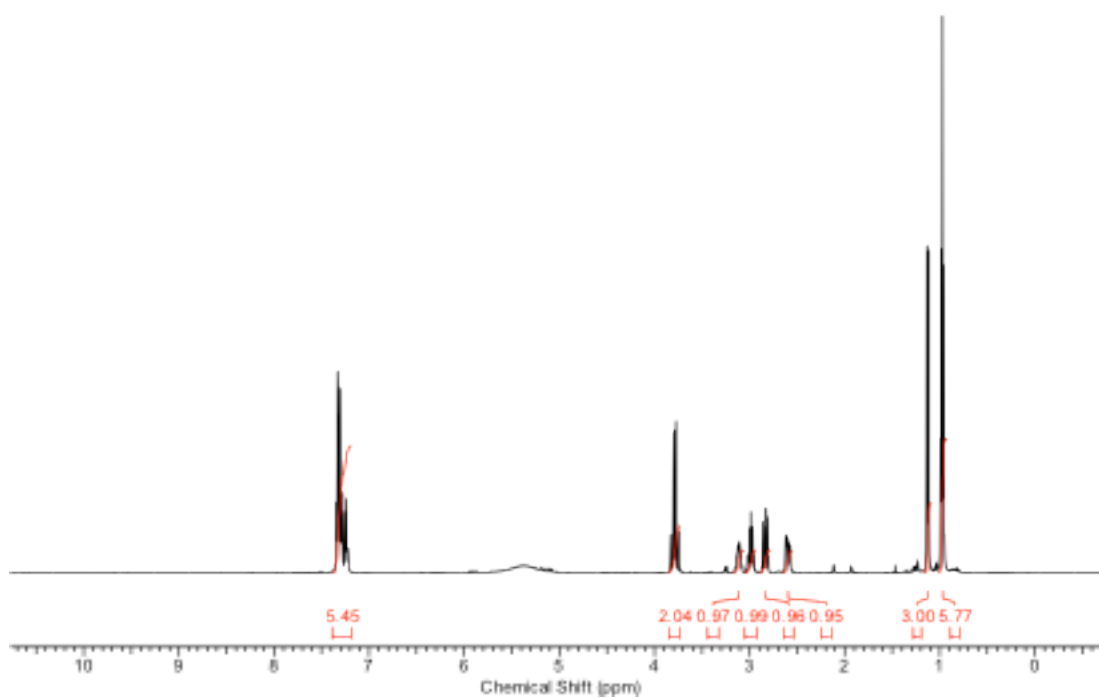
4.2, Table 4.3

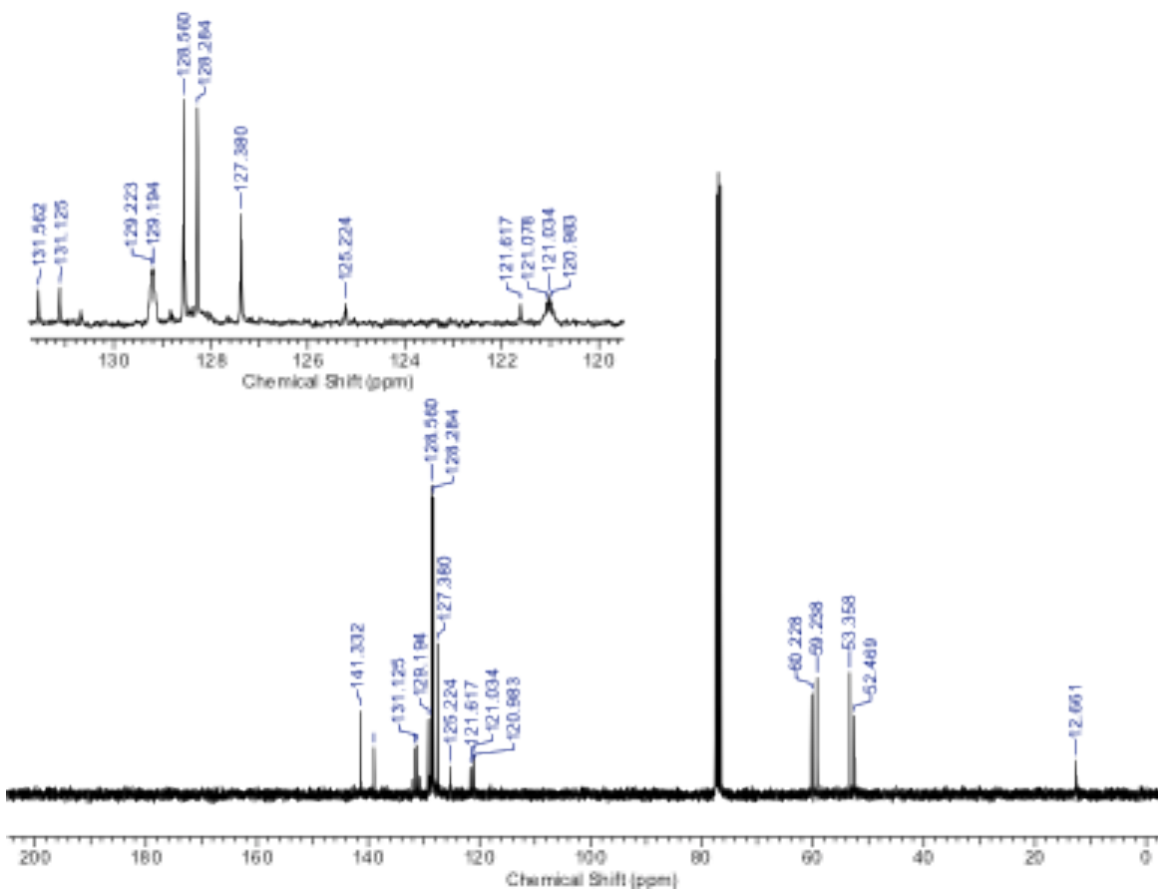
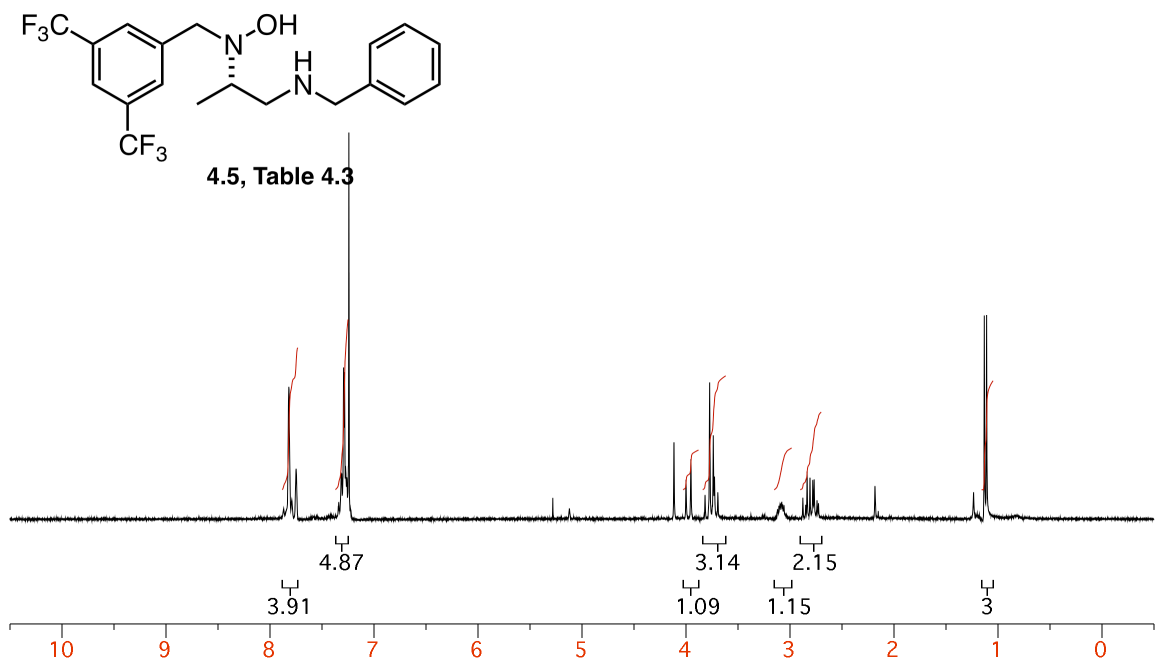


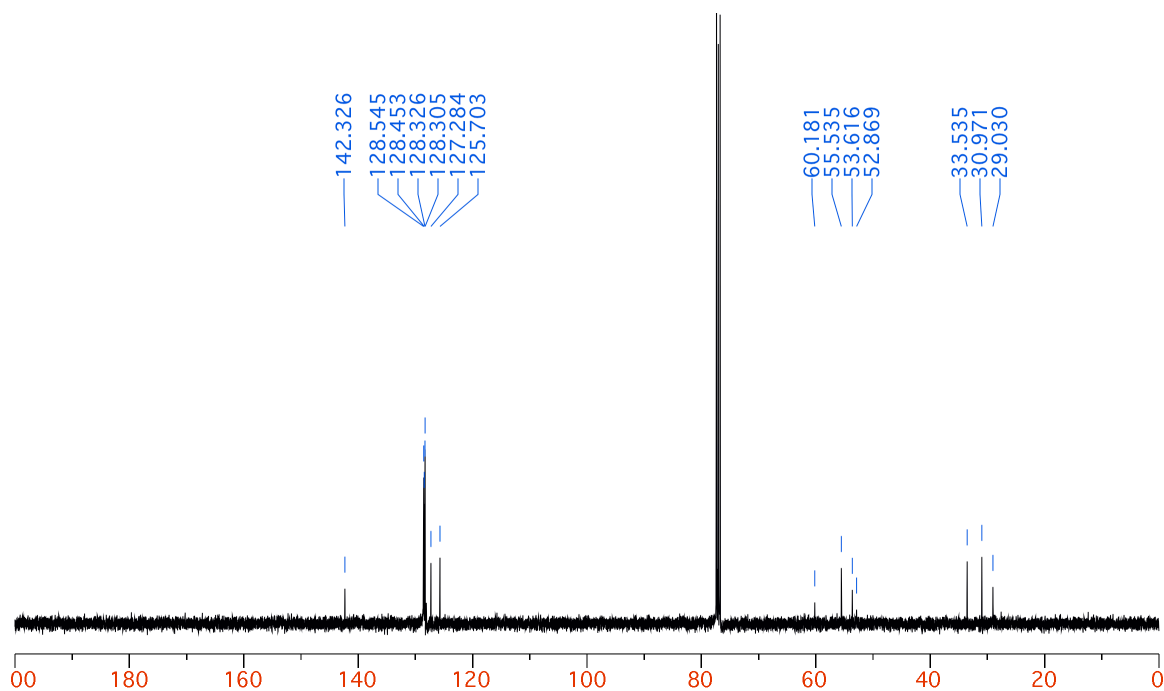
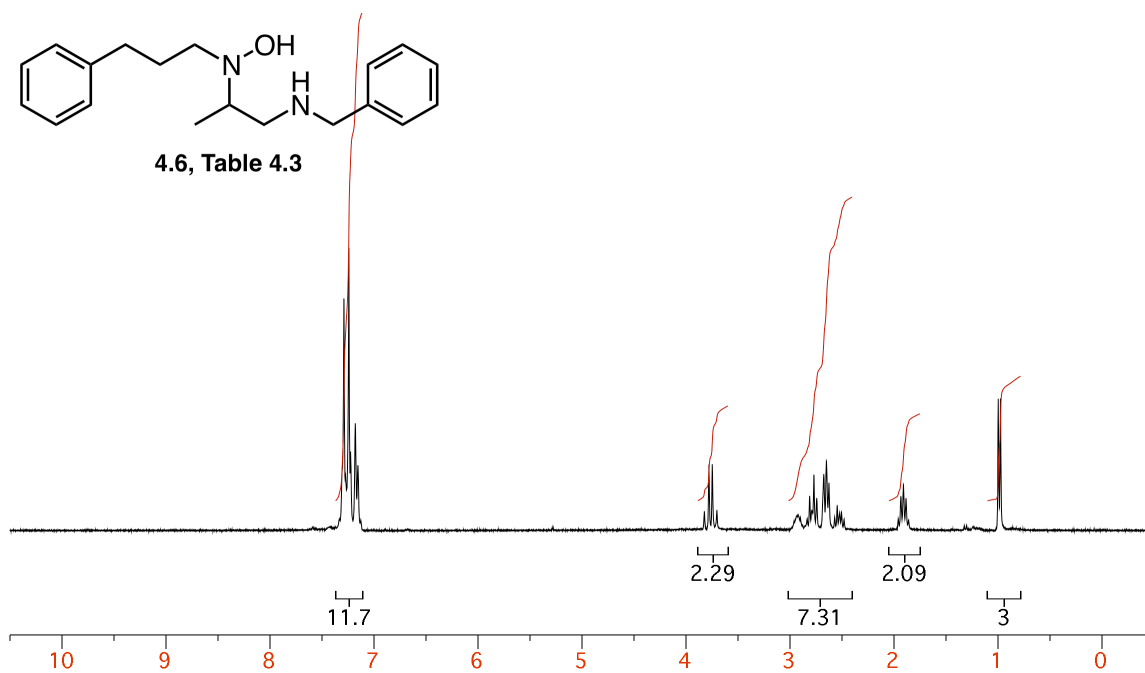


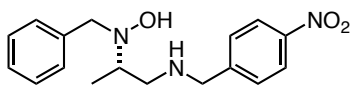


4.4, Table 4.3

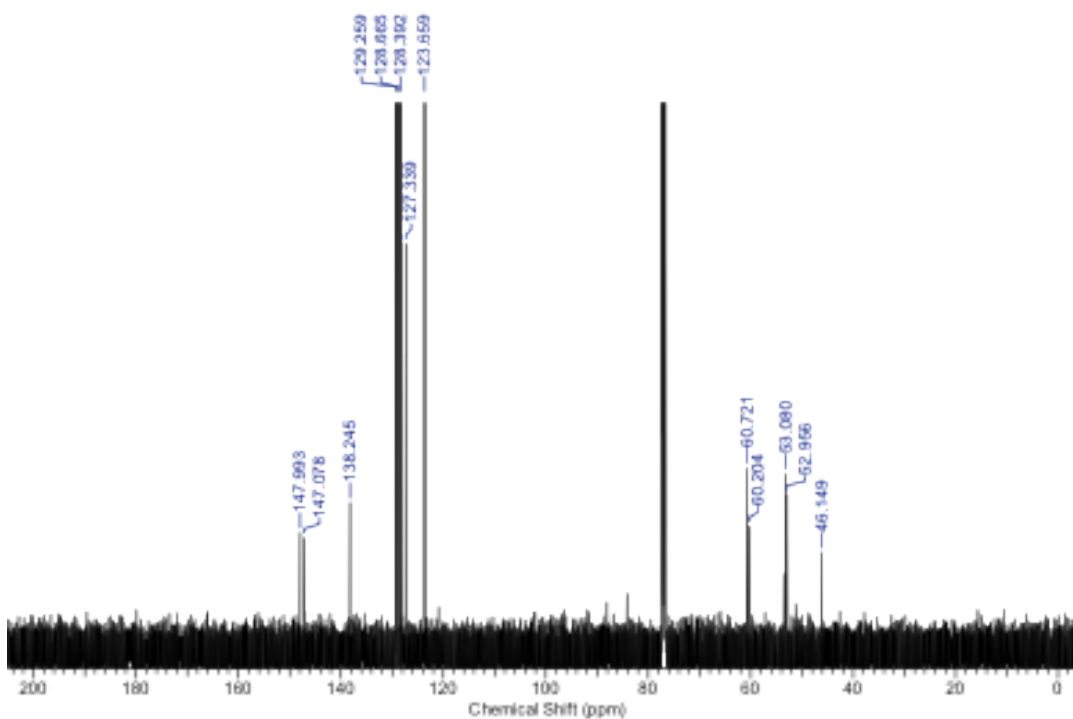
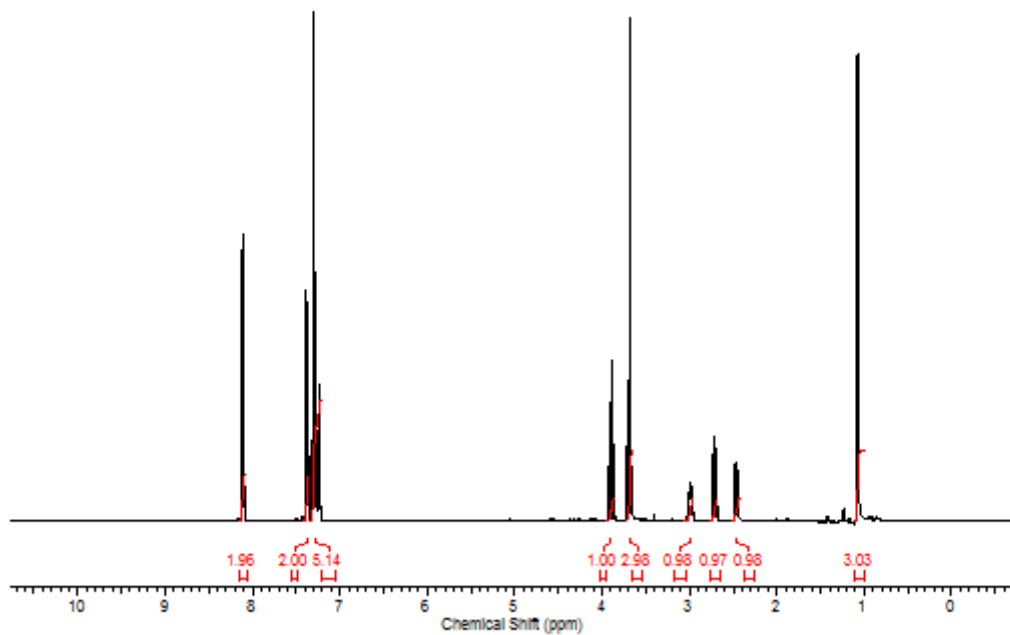


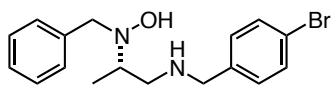




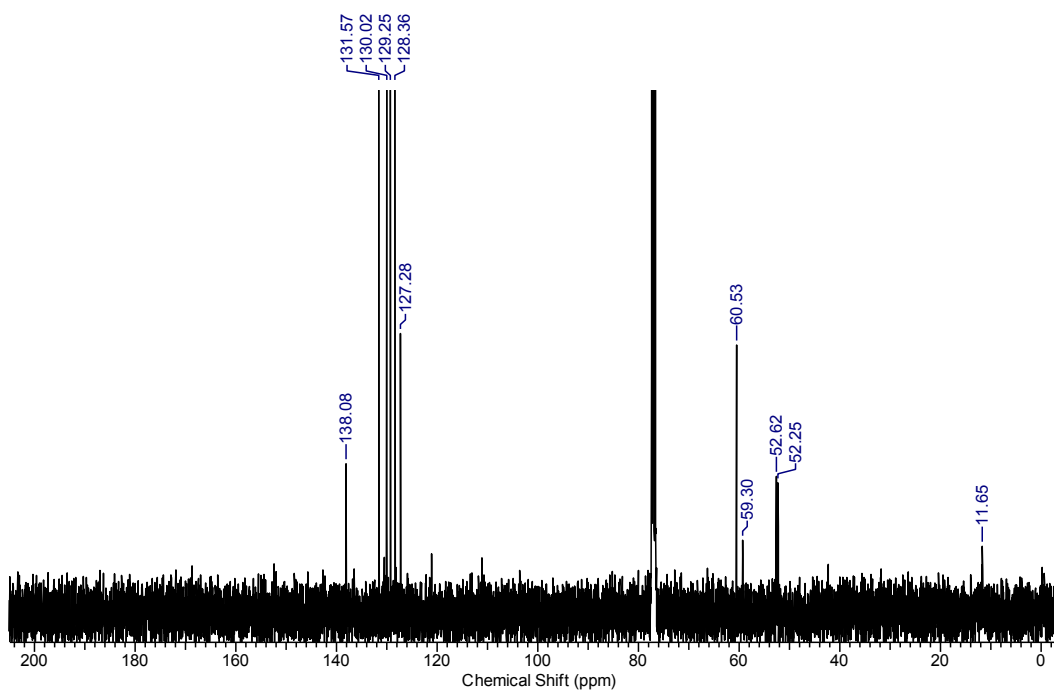
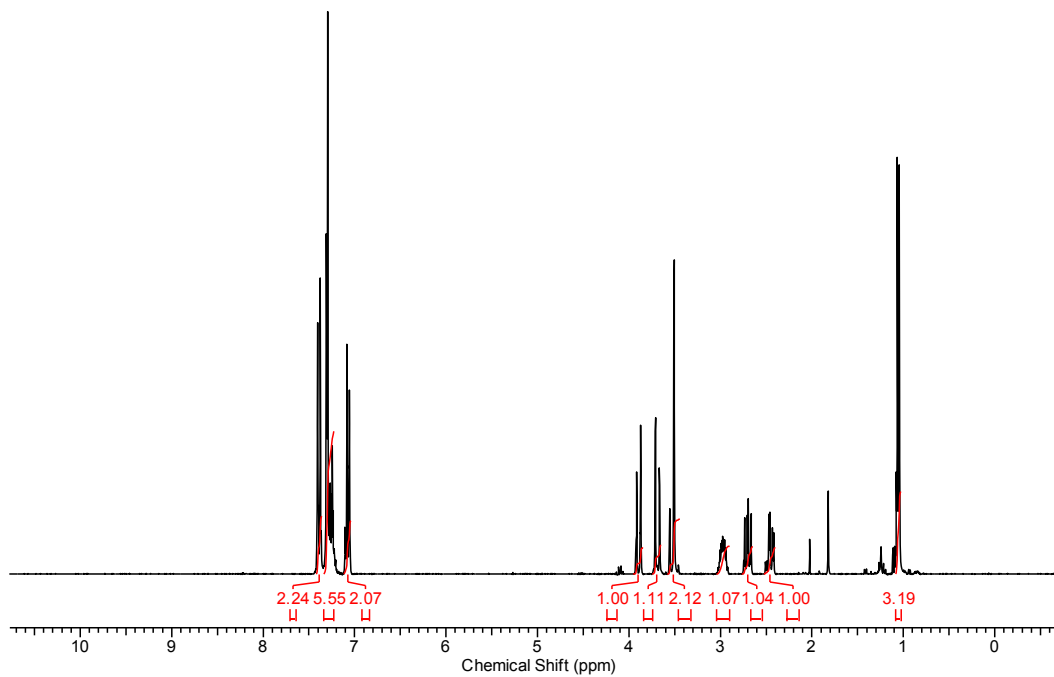


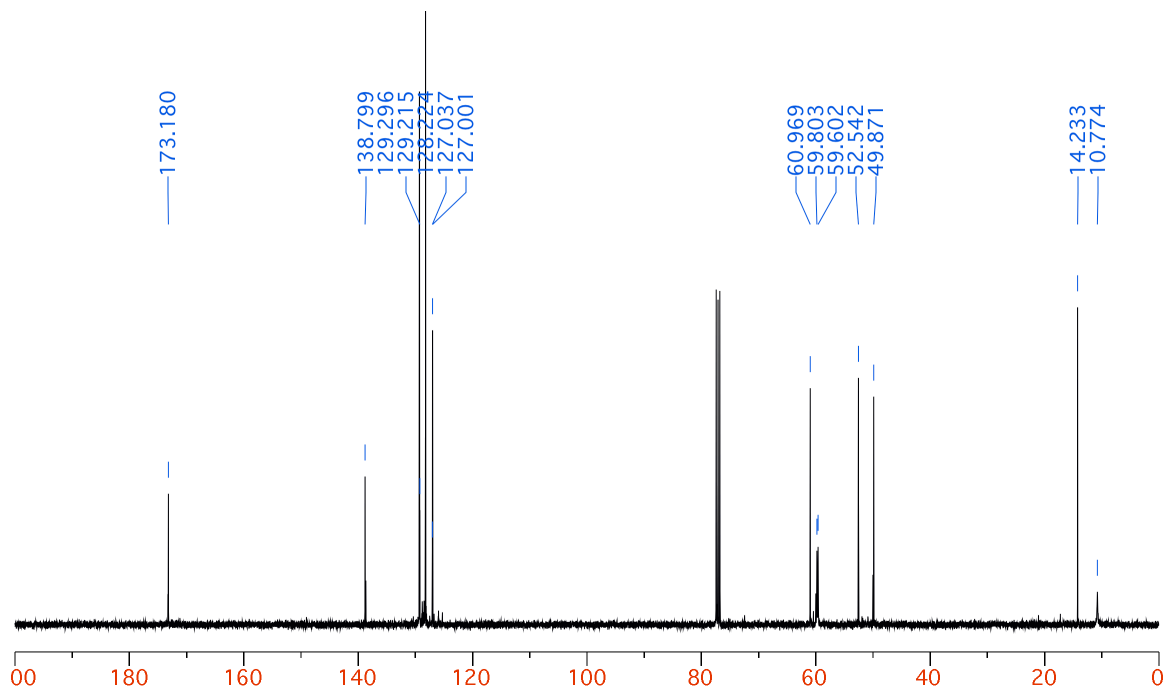
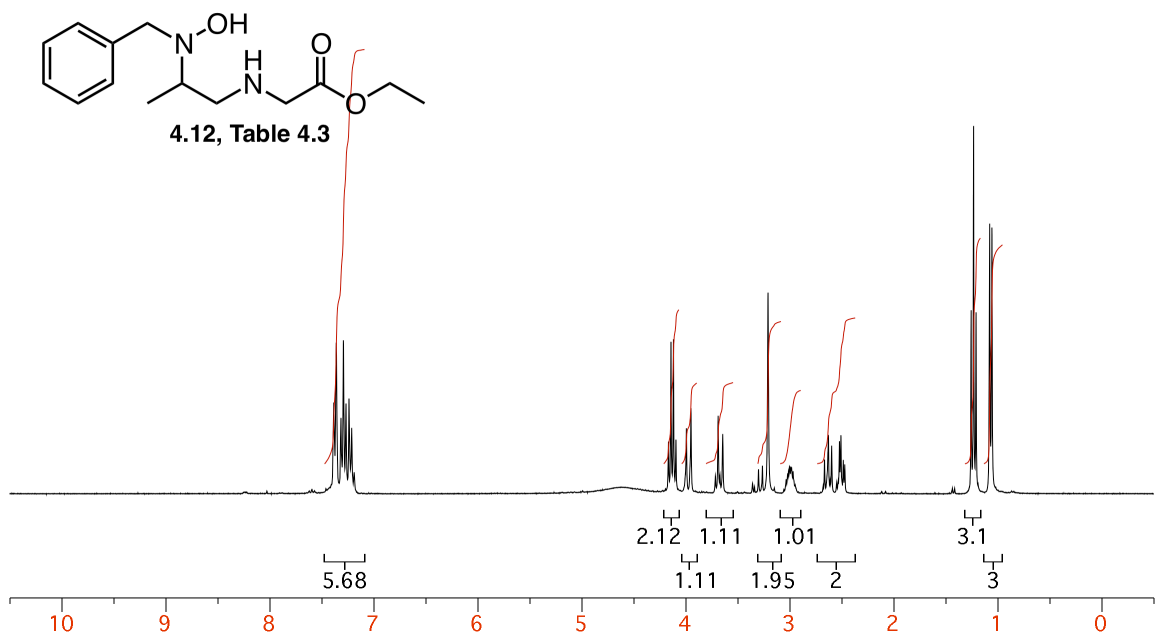
4.9, Table 4.3

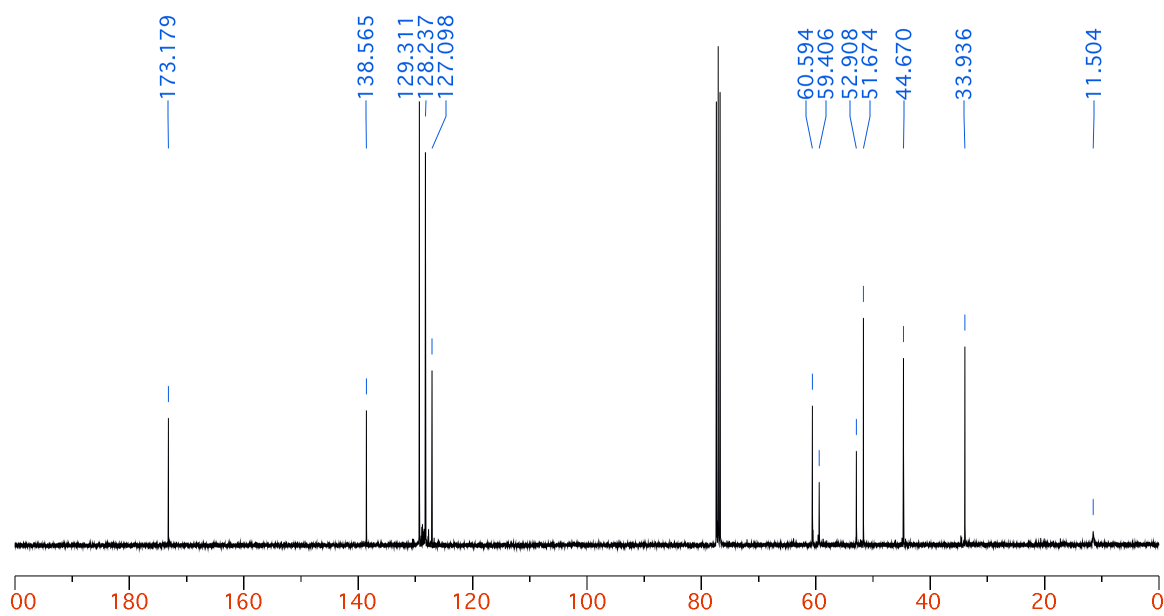
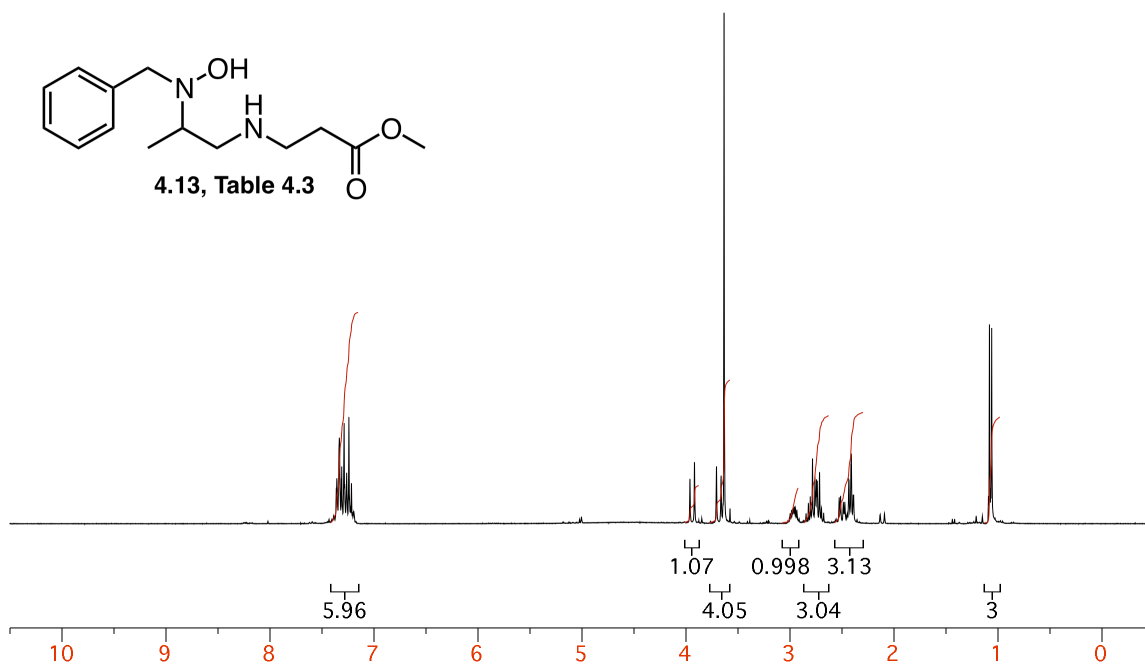




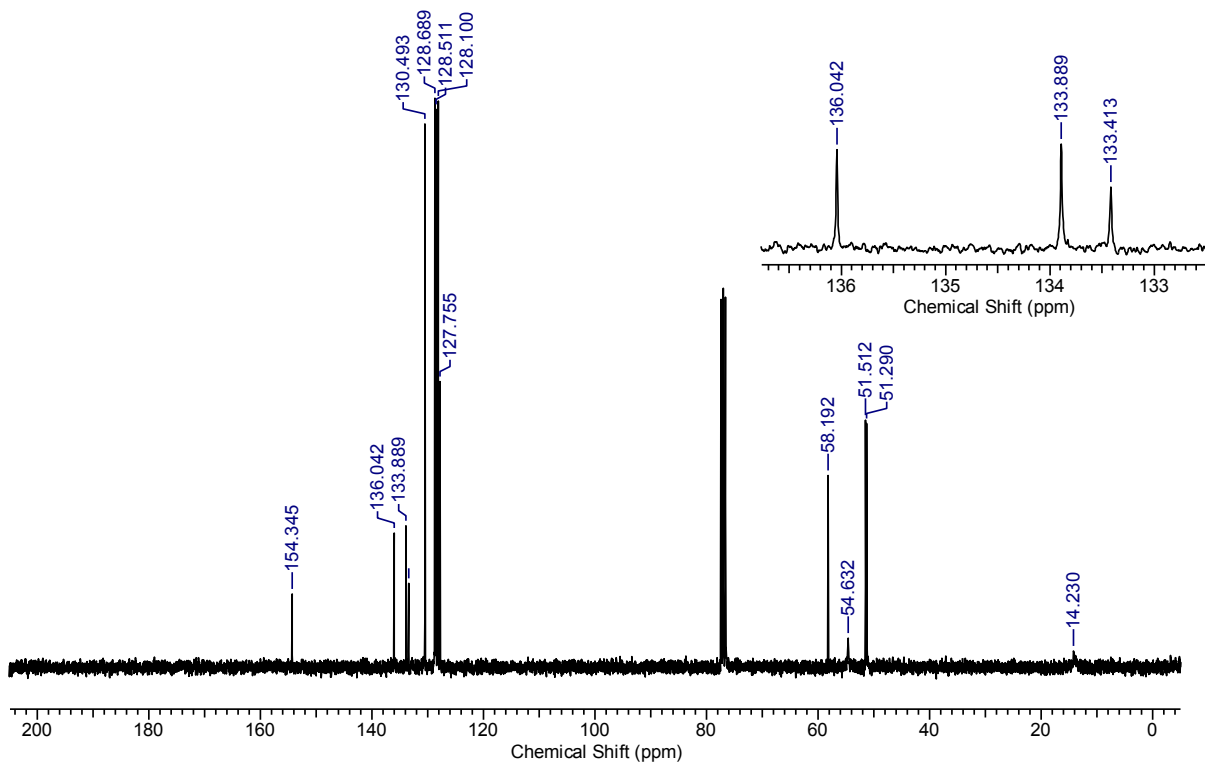
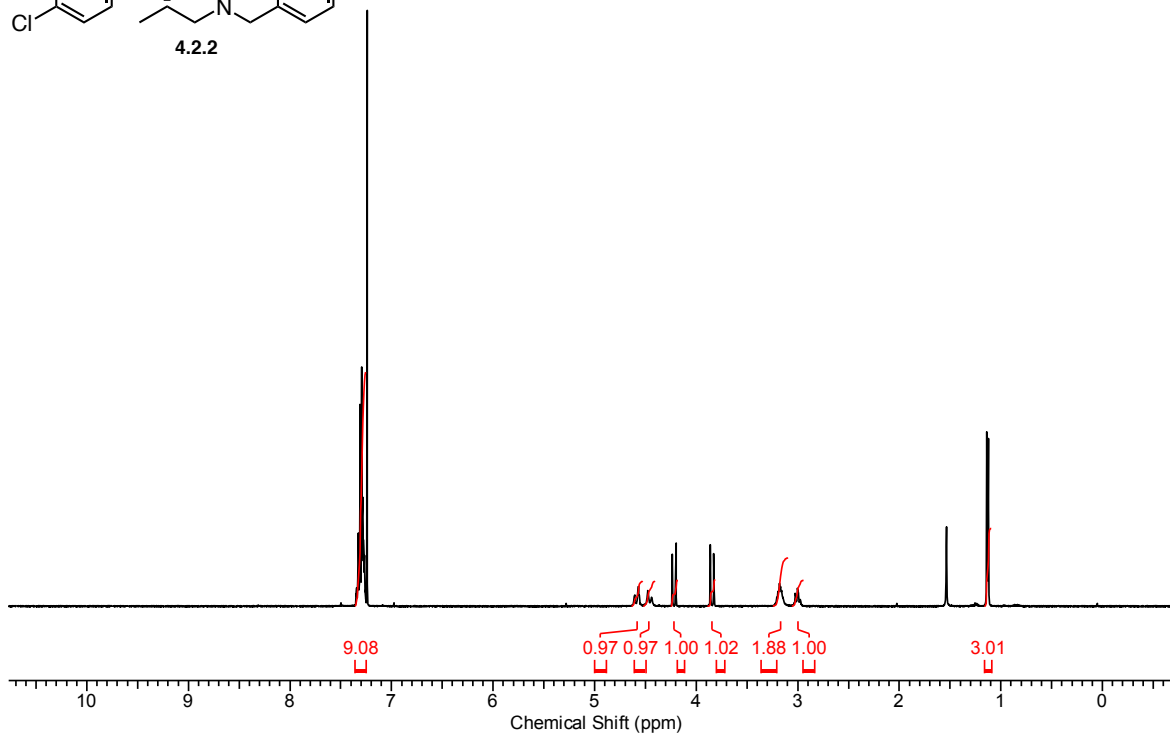
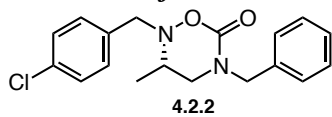
4.10, Table 4.3





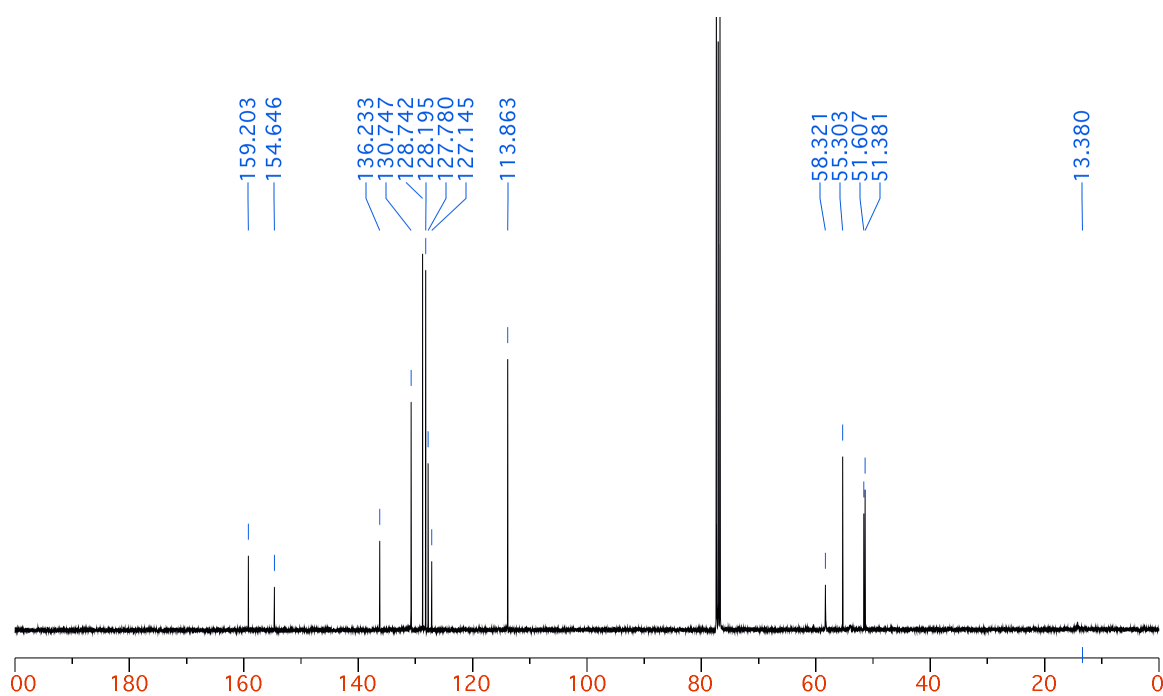


Derivative of 4.2

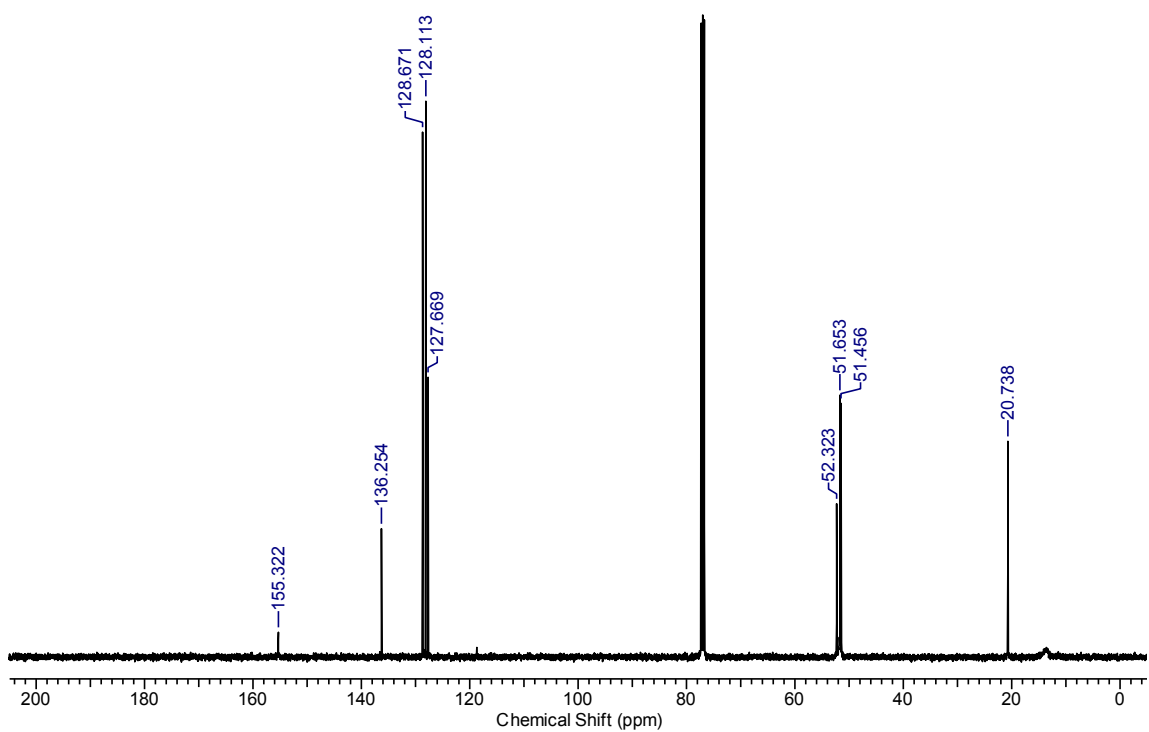
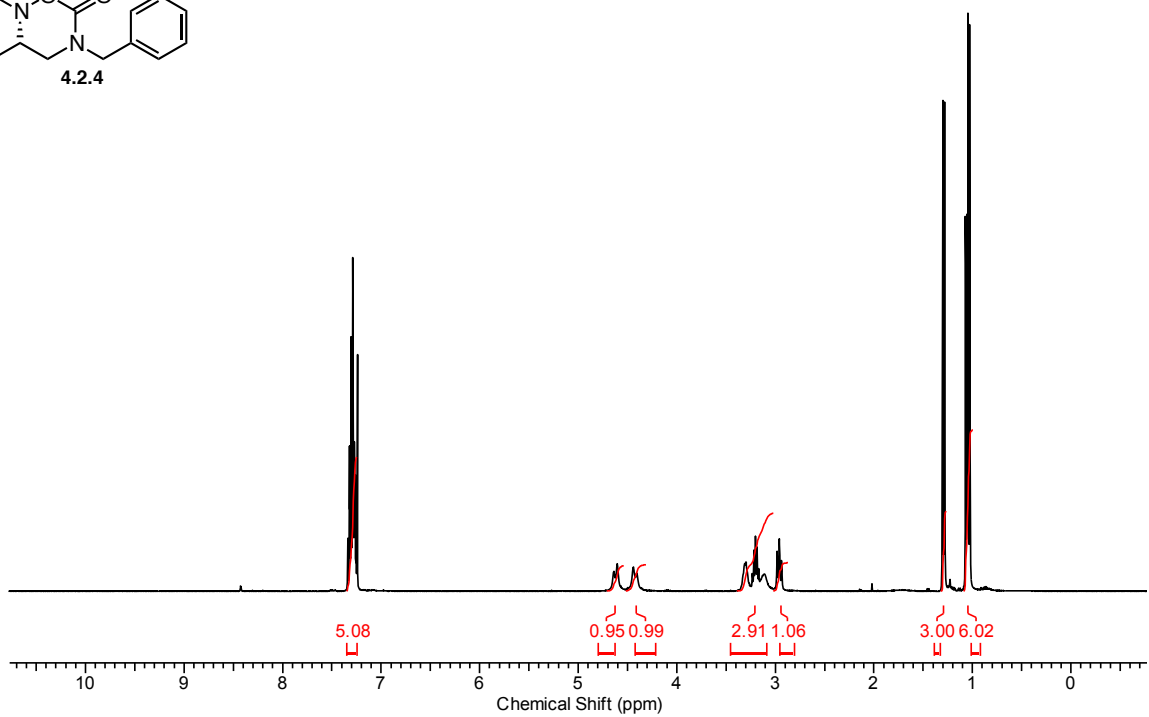
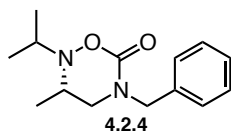


COc1ccc(cc1)CN2[C@H](C)CN(Cc3ccccc3)C(=O)O2

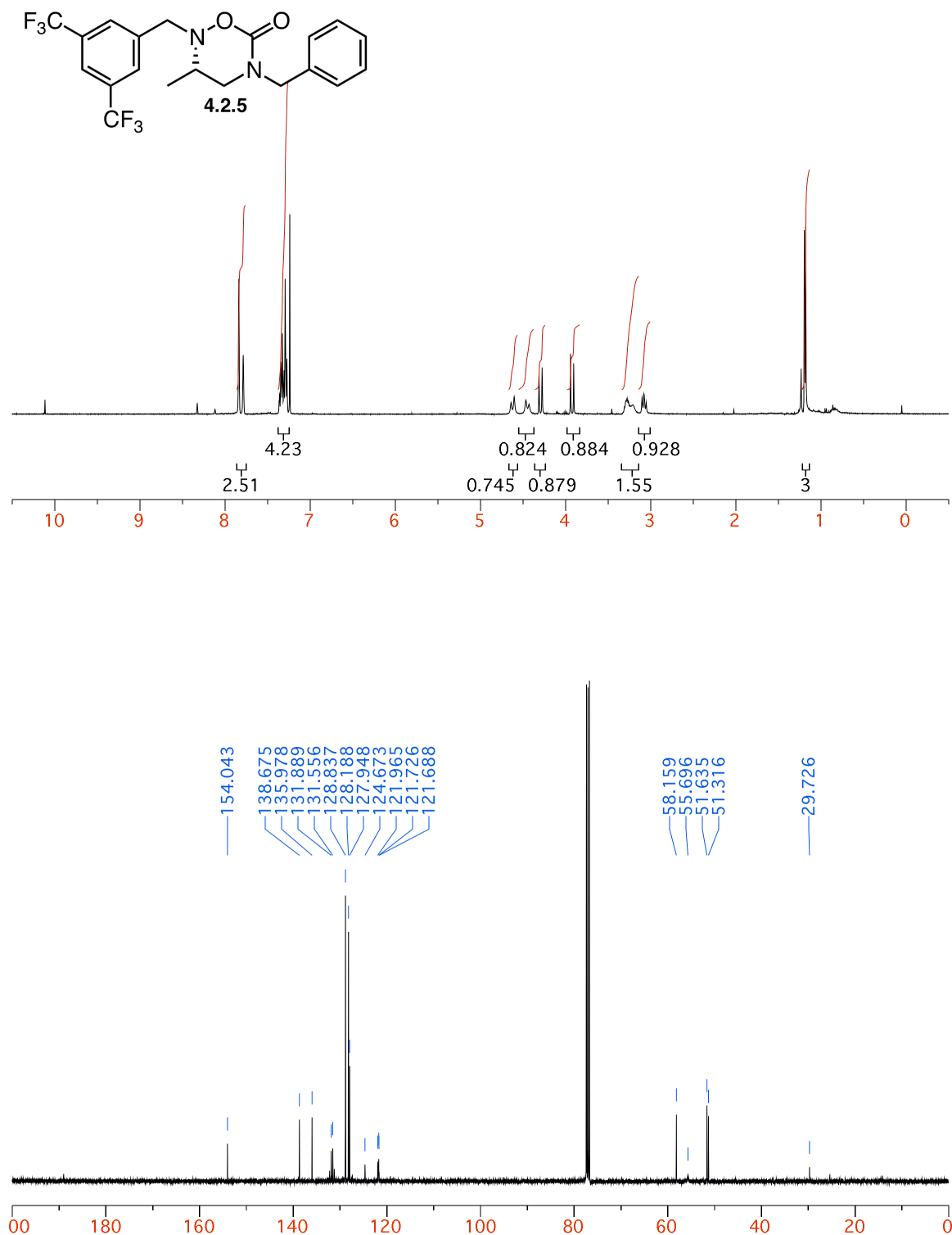
Chemical Shift (ppm)	Integration
7.21	7.21
7.00	1.96
6.96	1.96
3.83	3.35
3.35	1.02
1.84	1.84
0.00	3



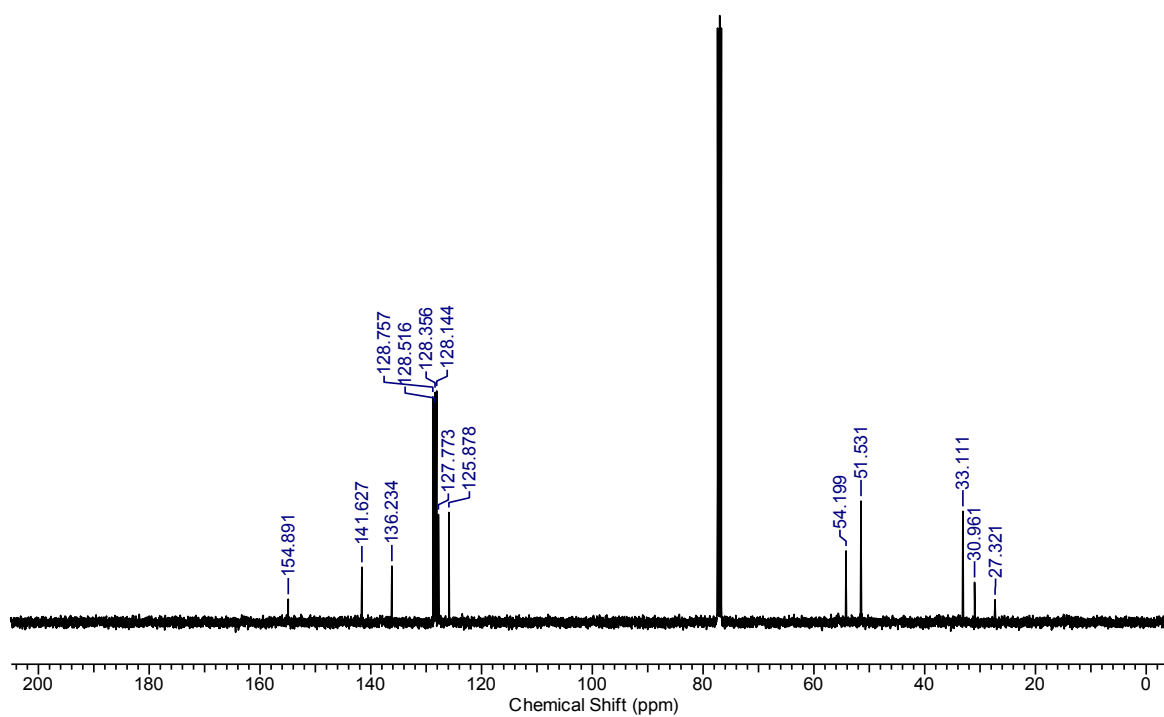
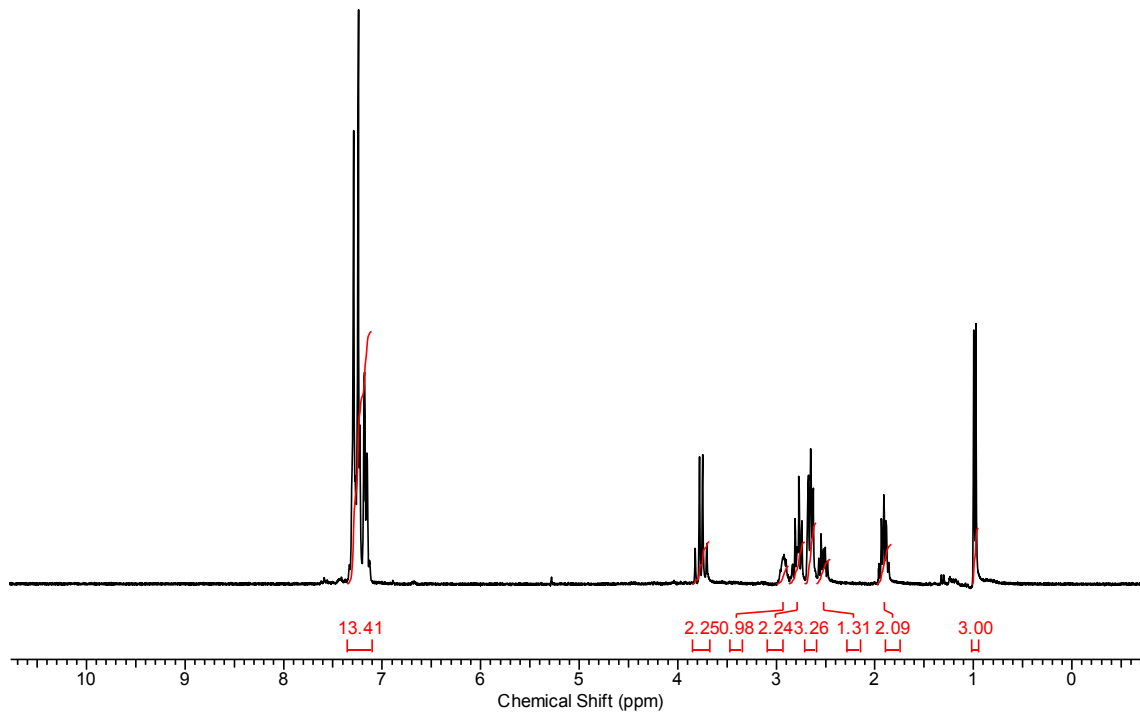
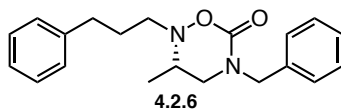
Derivative of 4.4



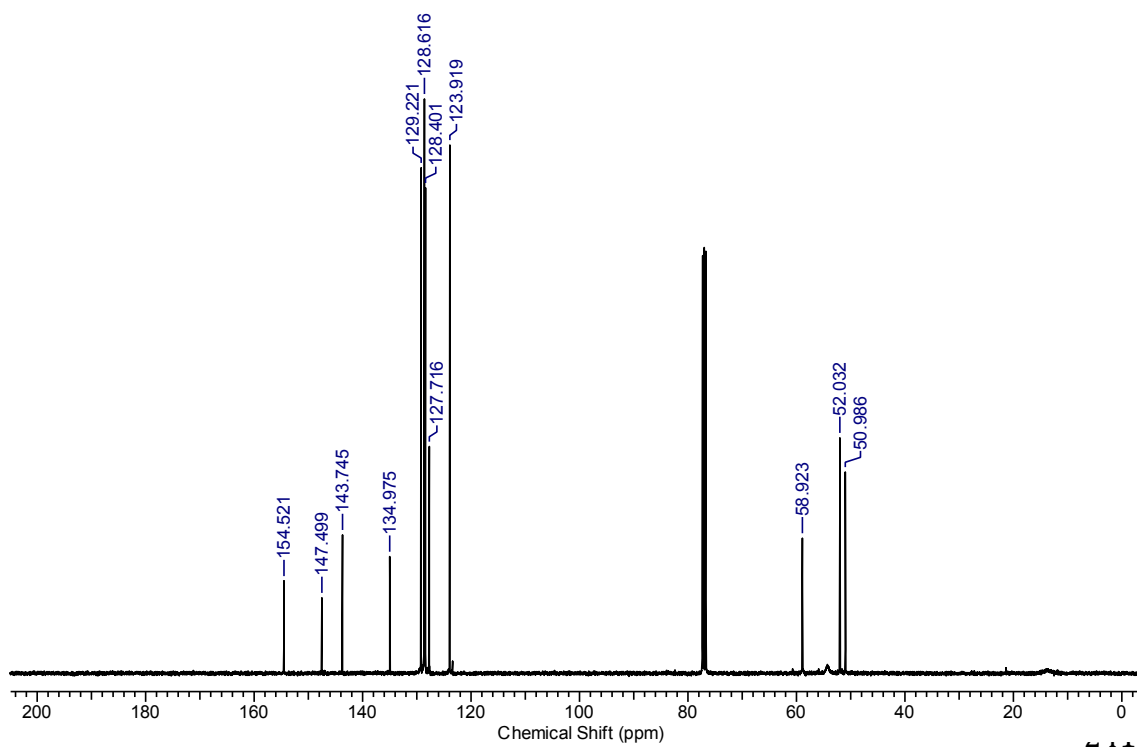
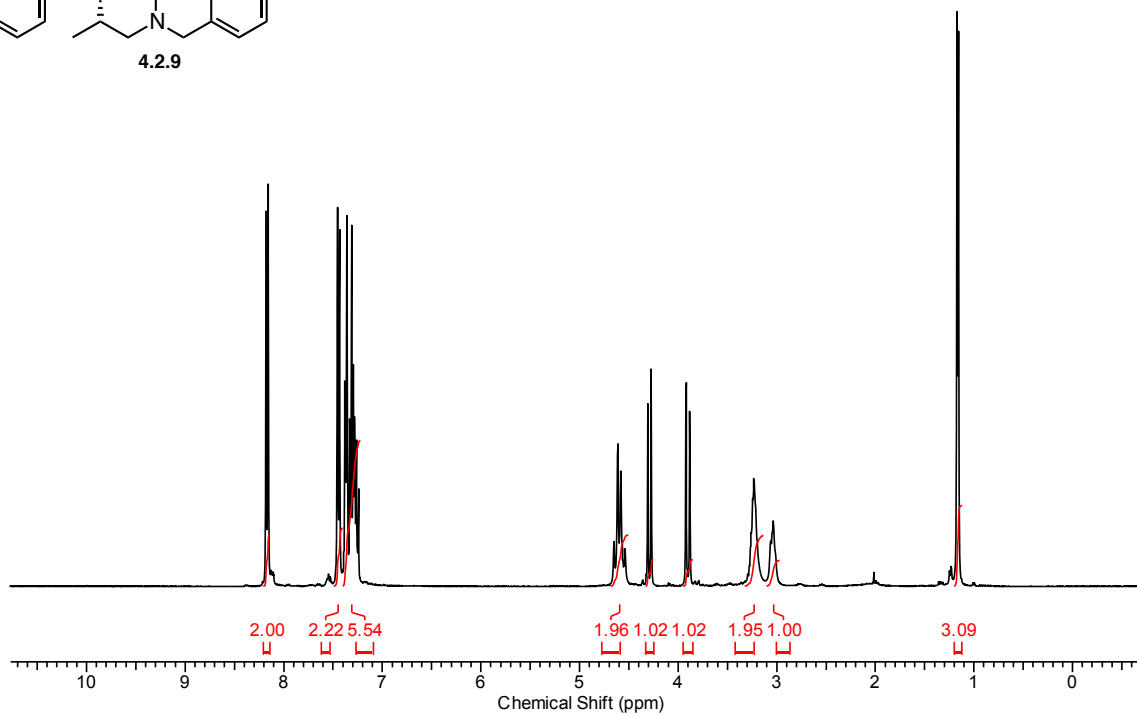
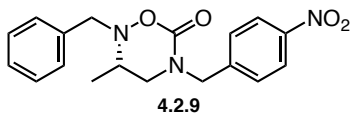
Derivative of 4.5



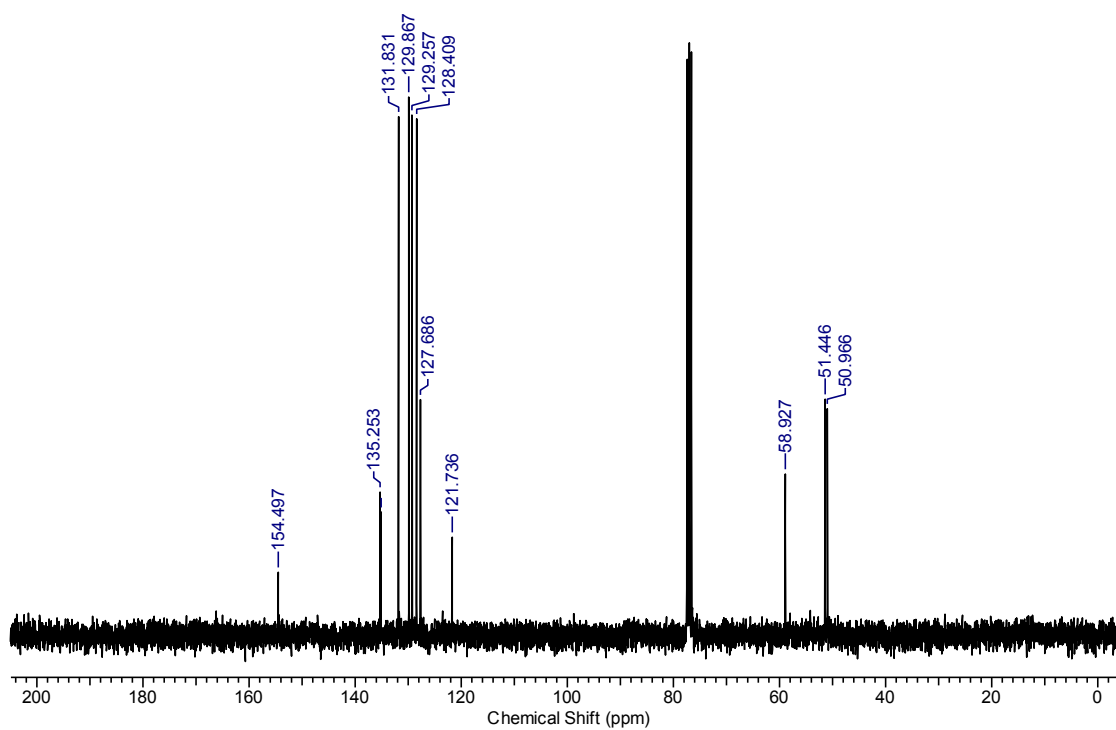
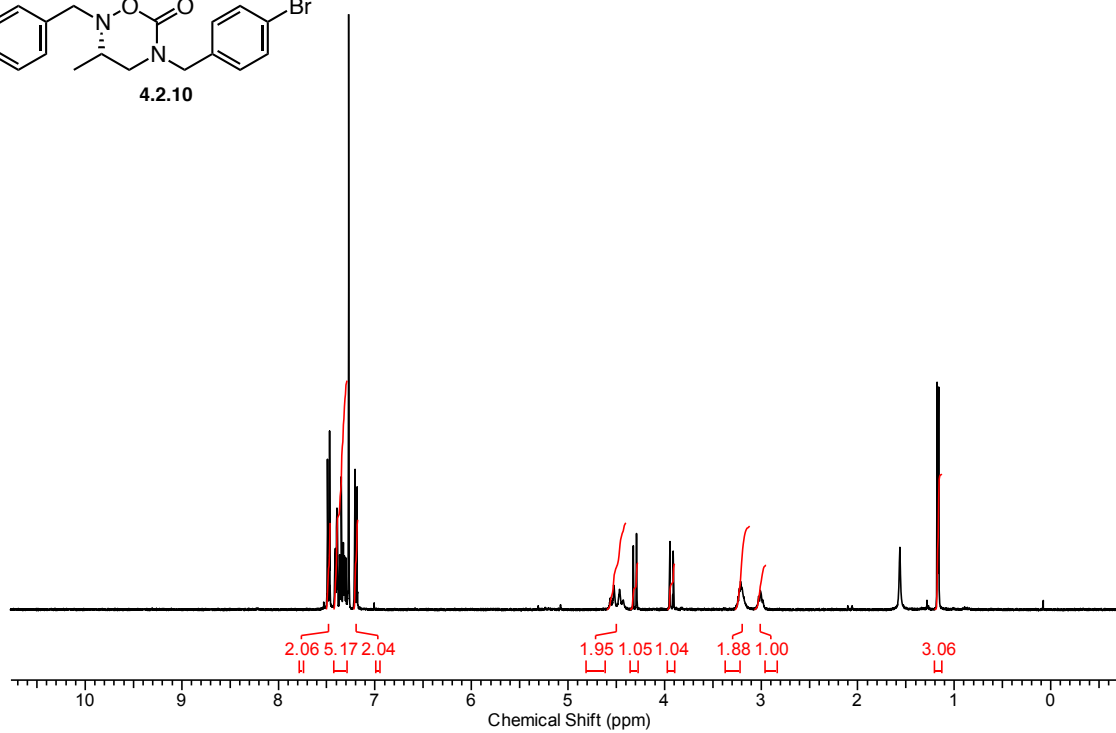
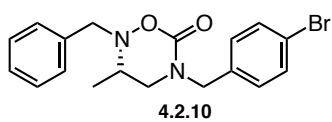
Derivative of 4.6



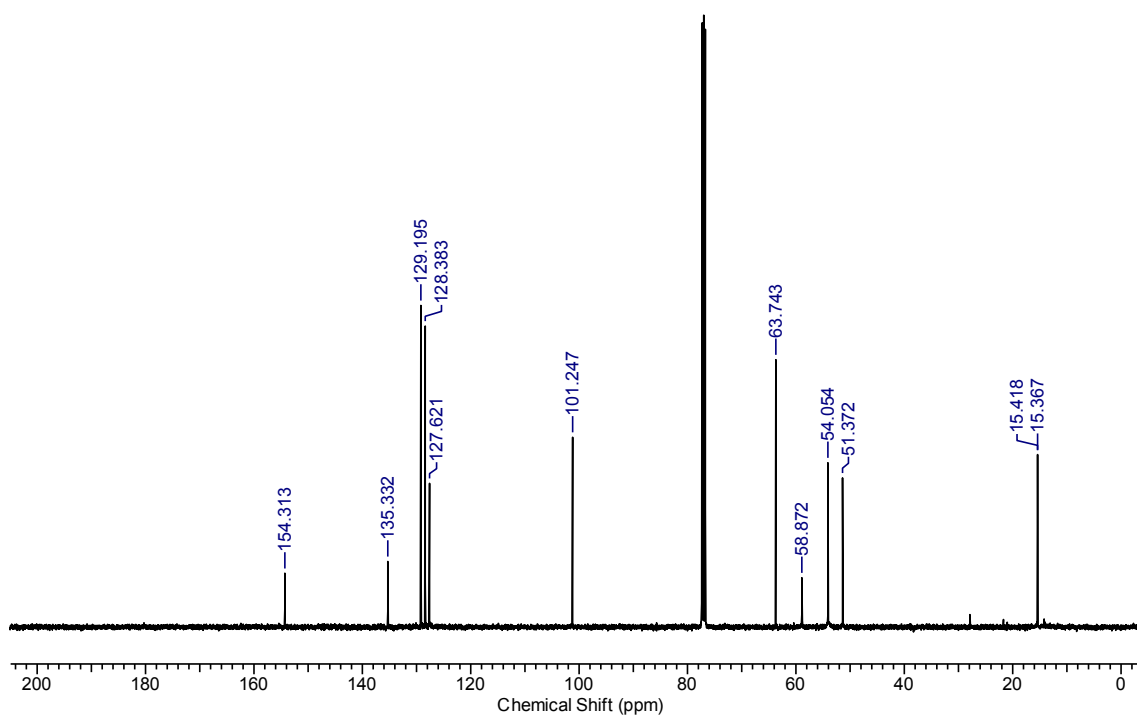
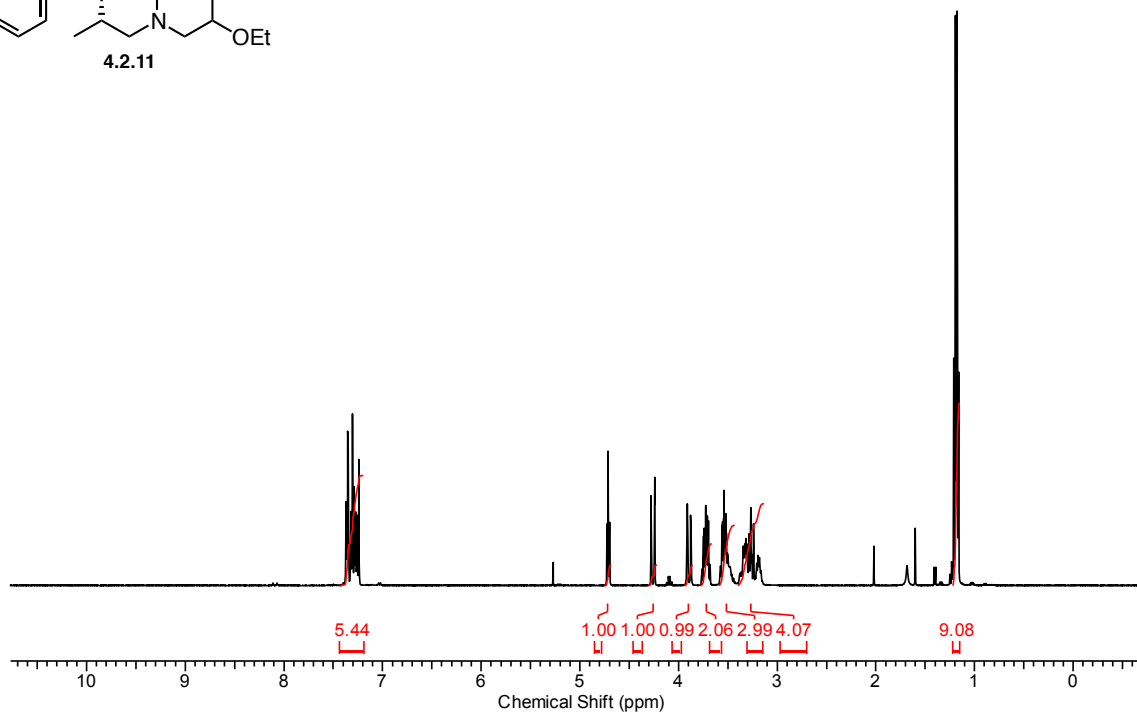
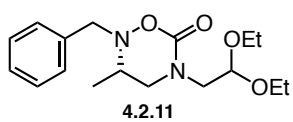
Derivative of 4.9



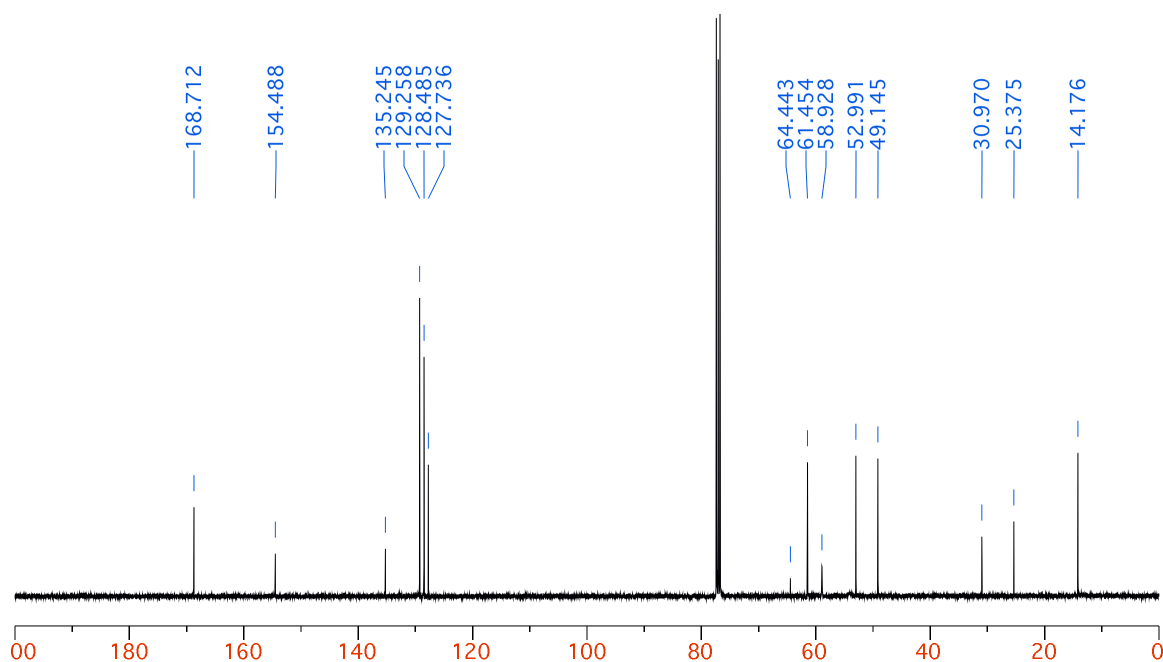
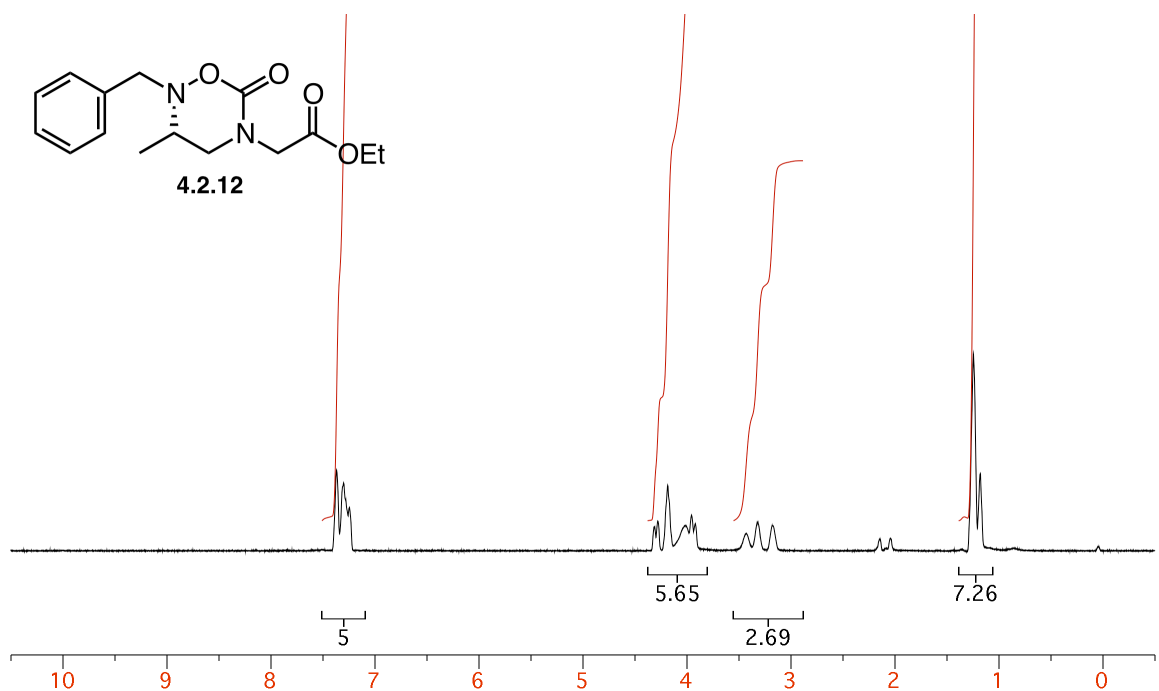
Derivative of 4.10



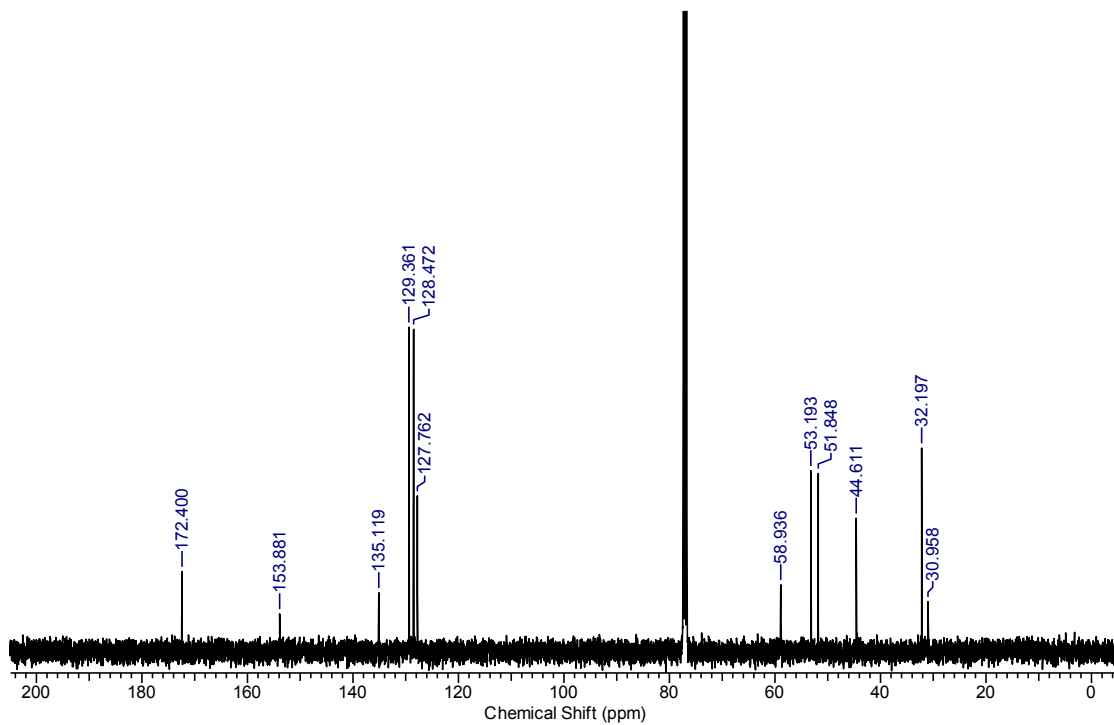
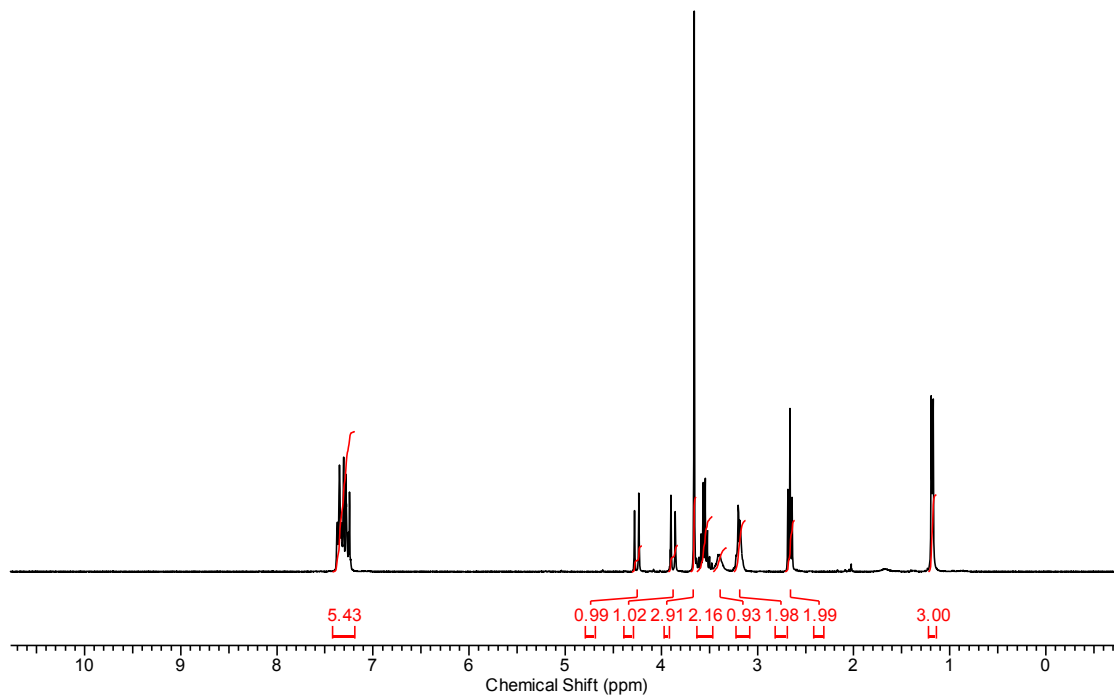
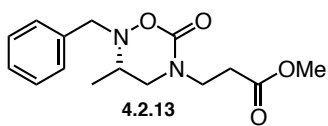
Derivative of 4.11



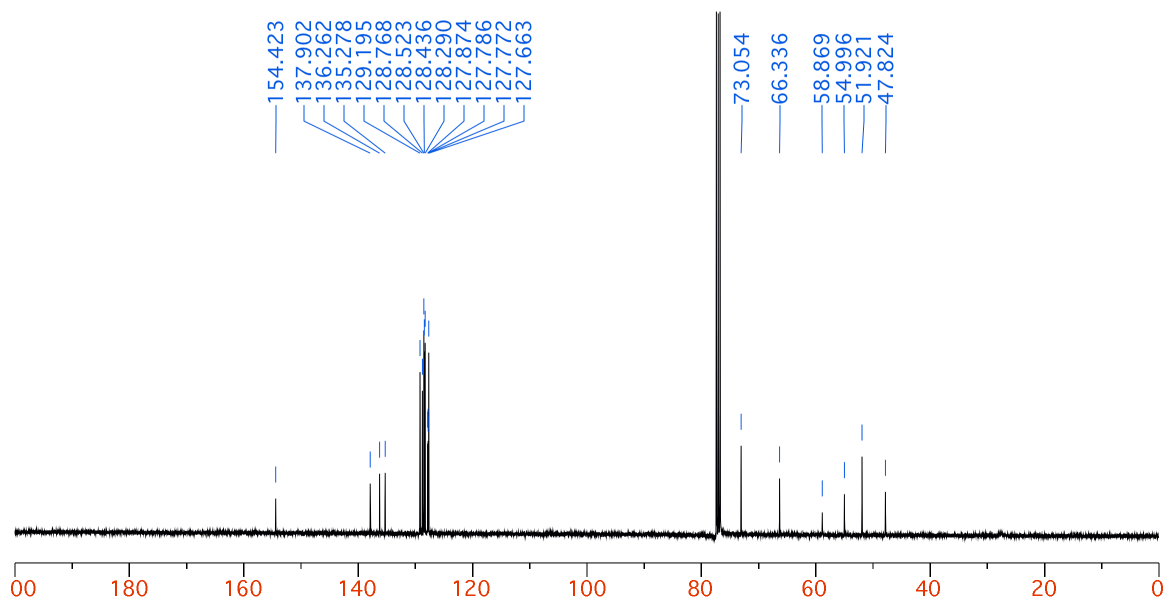
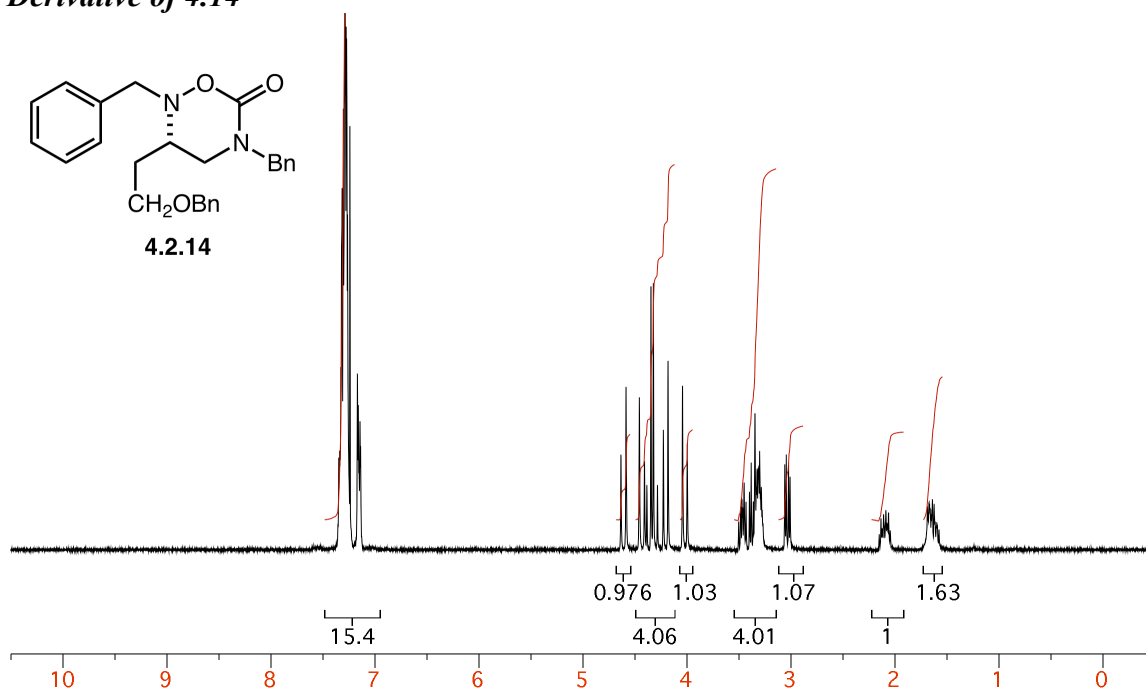
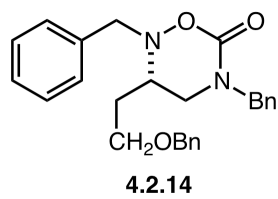
Derivative of 4.12

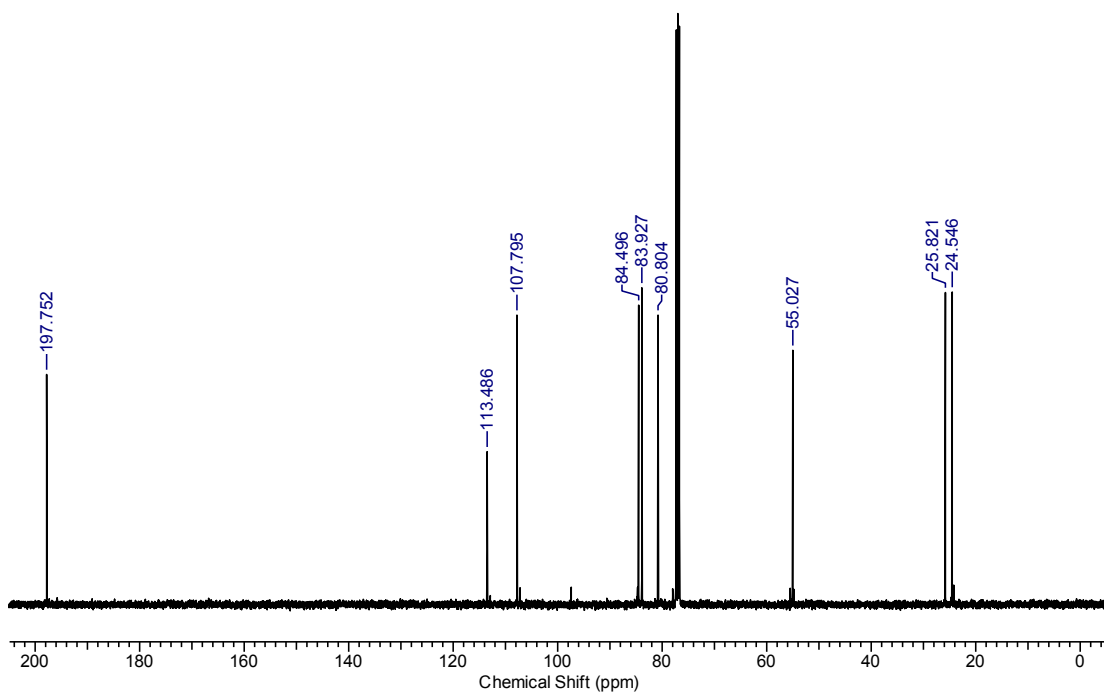
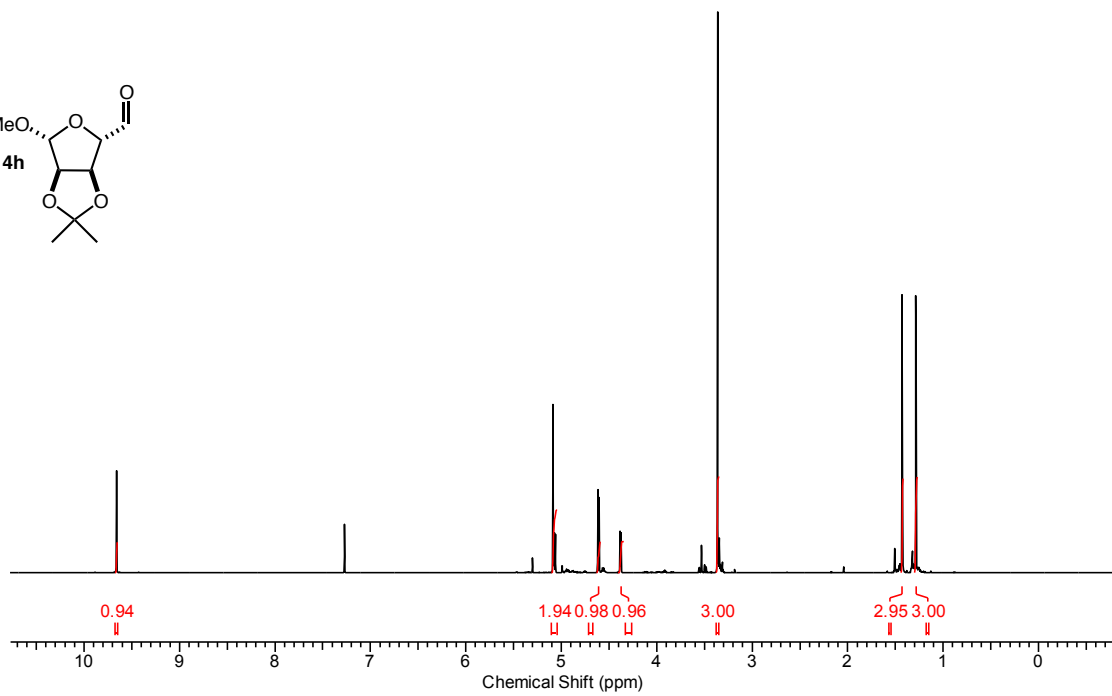
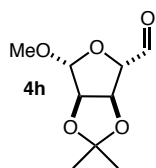


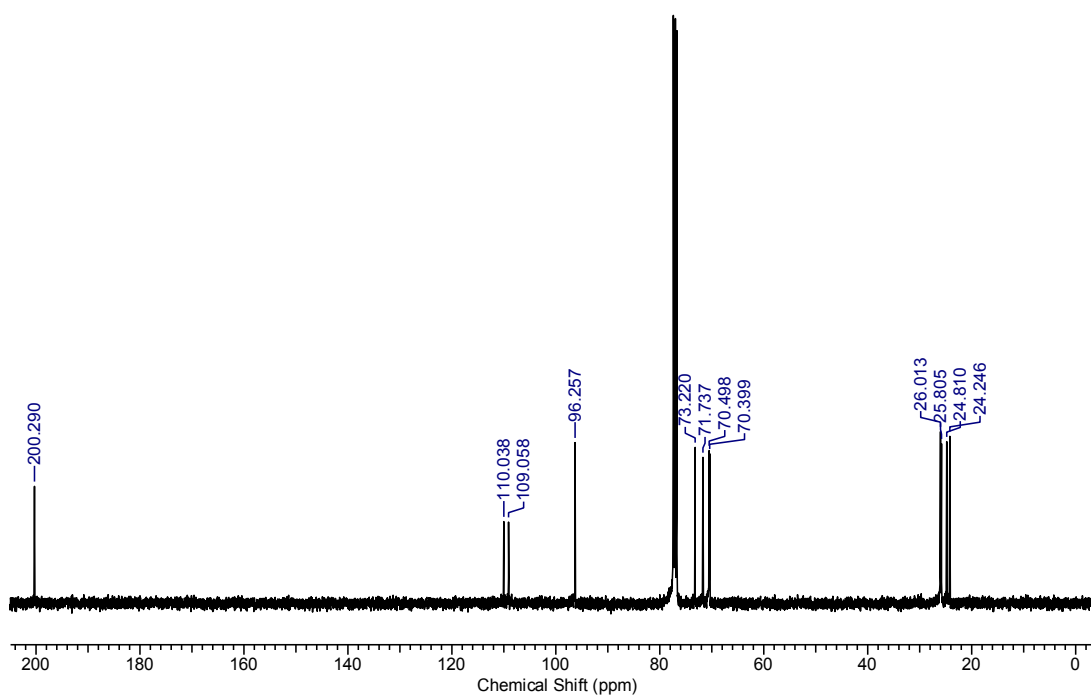
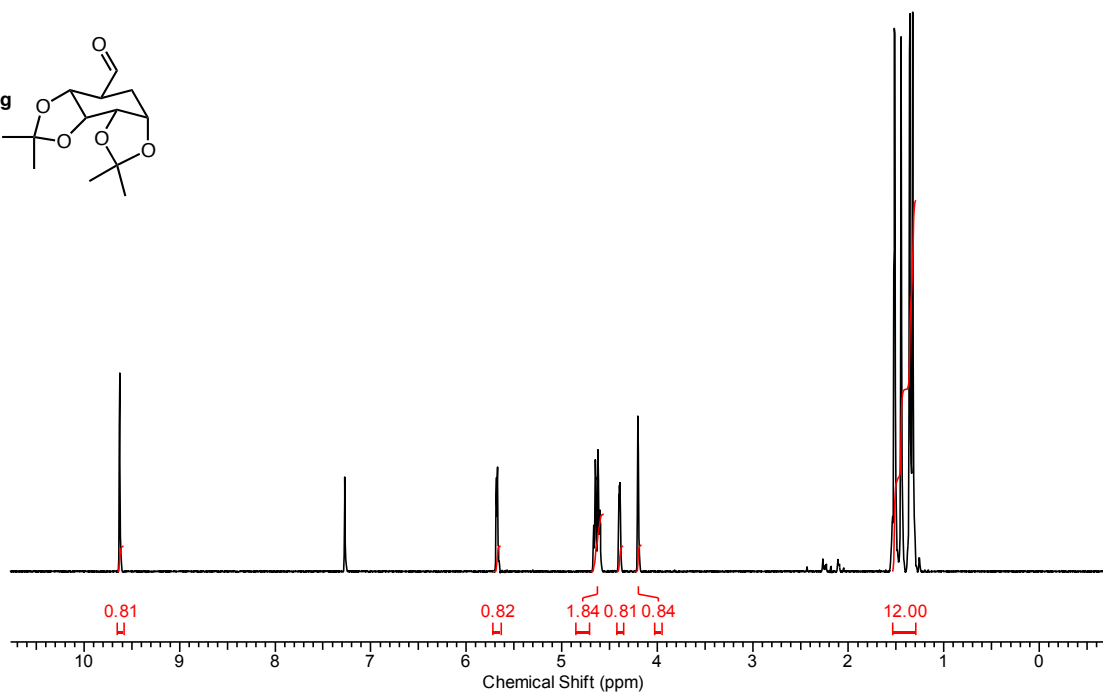
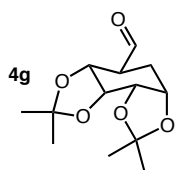
Derivative of 4.13

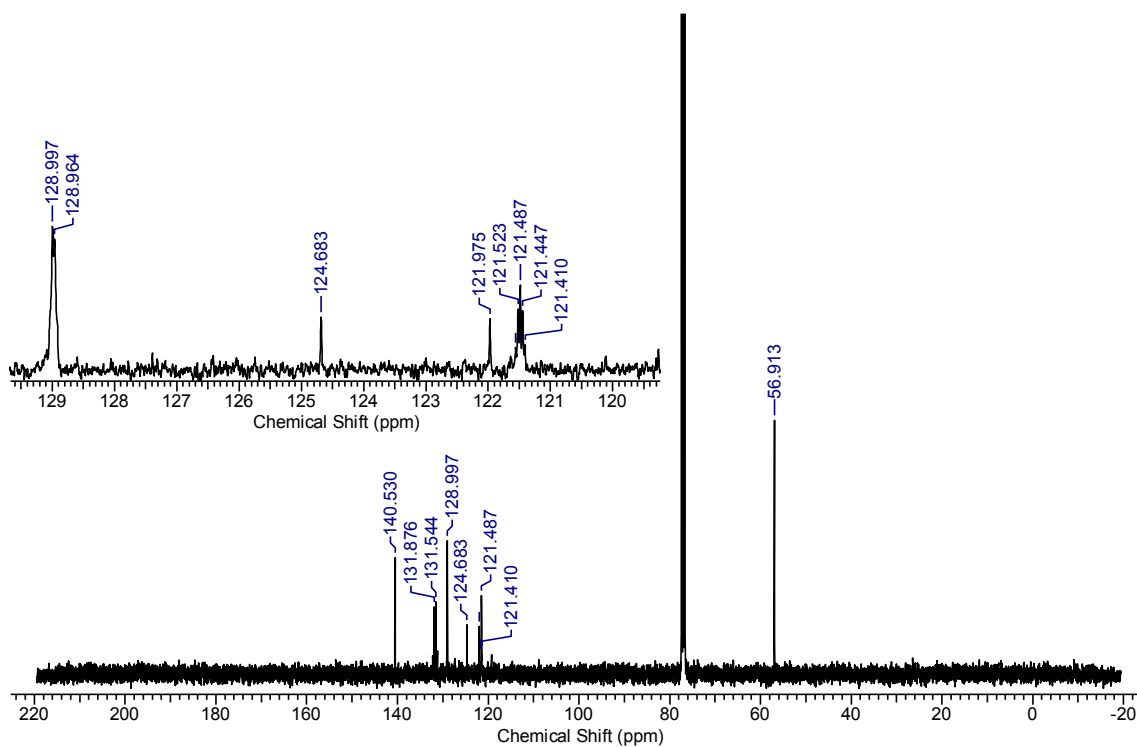
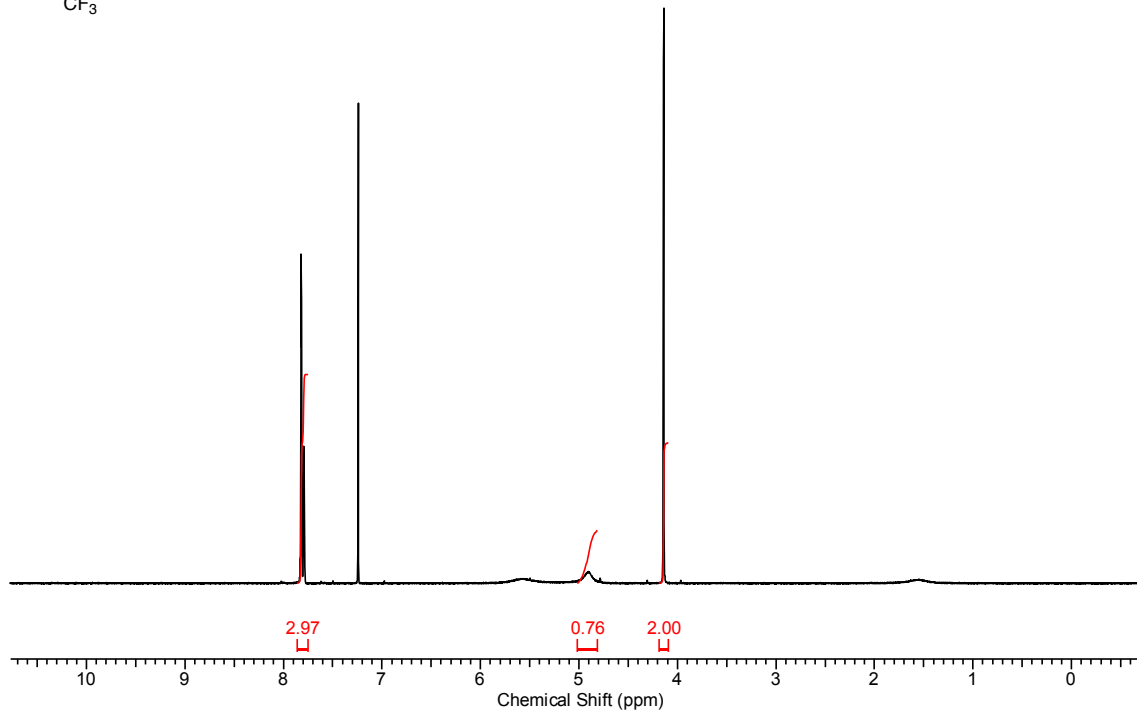
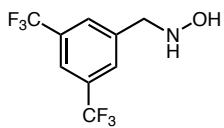


Derivative of 4.14

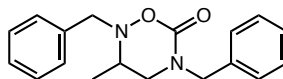




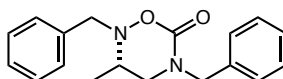
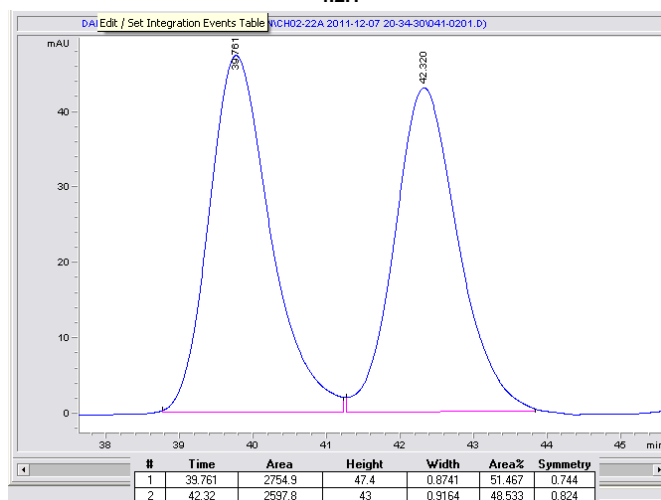




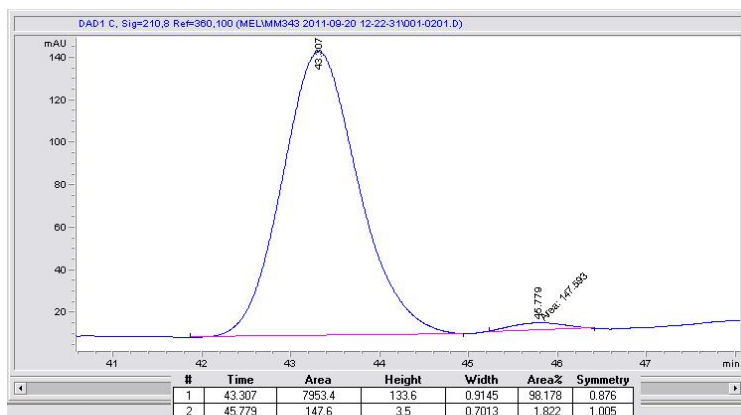
Copies of HPLC Spectra of 4.1-4.13

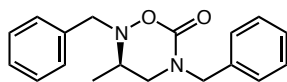


4.2.1

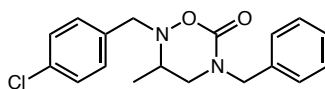
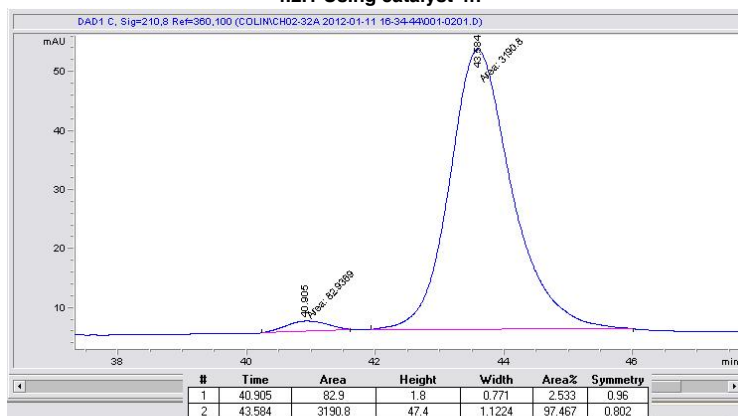


4.2.1 Using catalyst 2.3

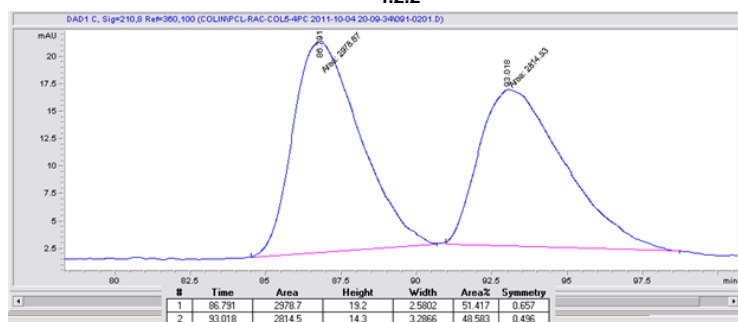


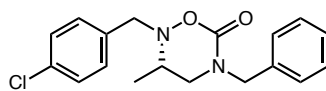


4.2.1 Using catalyst 4h

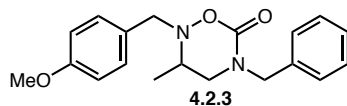
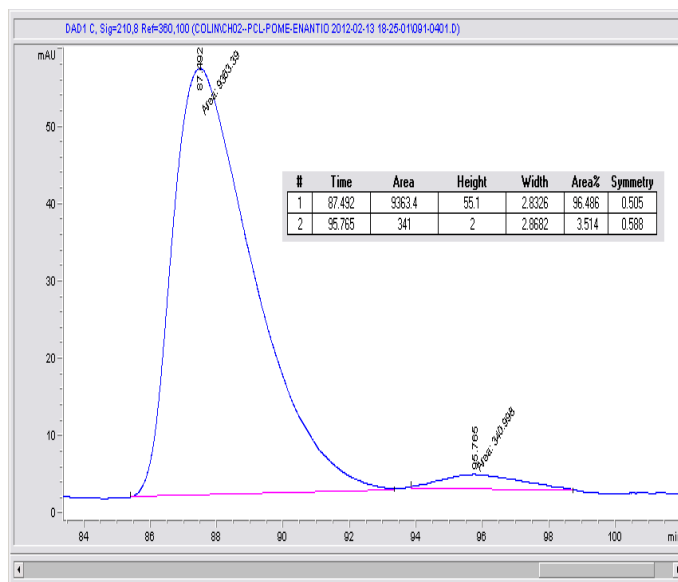


4.2.2

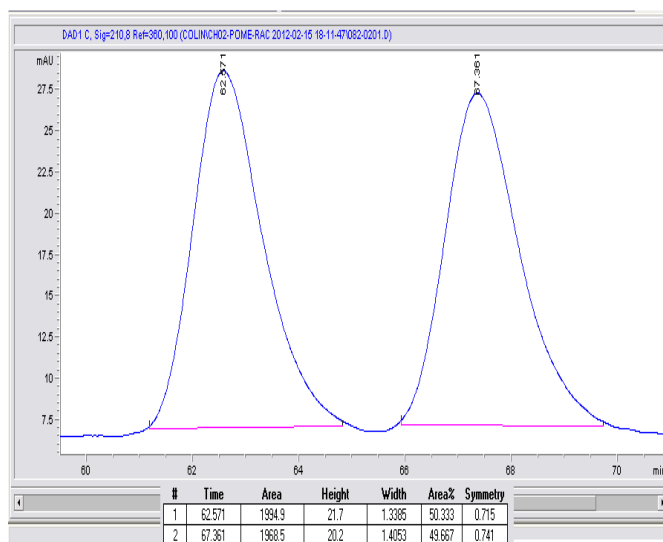


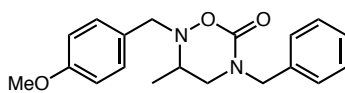


4.2.2 Using catalyst 2.3

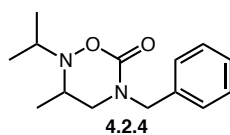
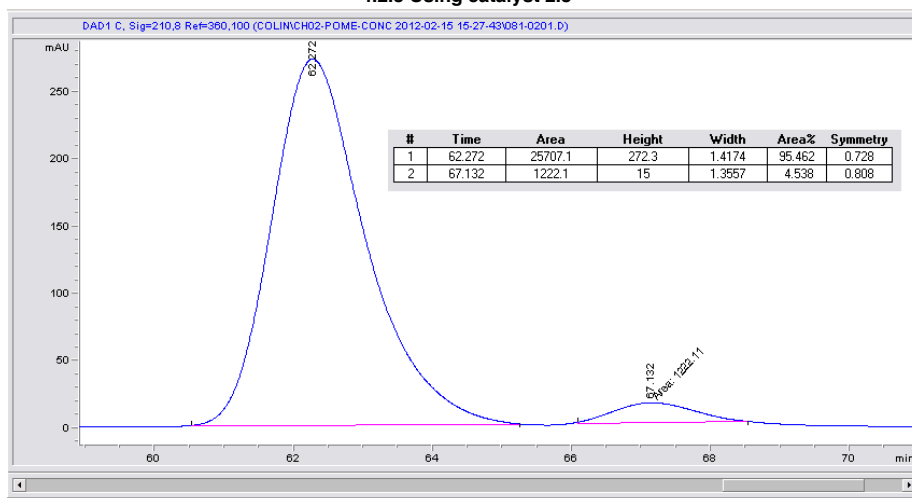


4.2.3

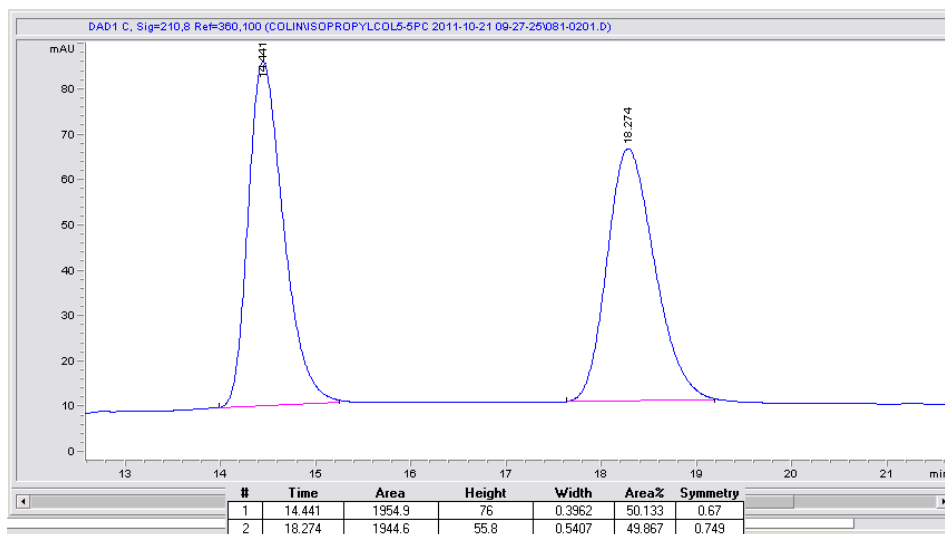


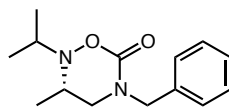


4.2.3 Using catalyst 2.3

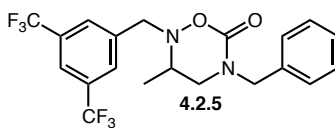
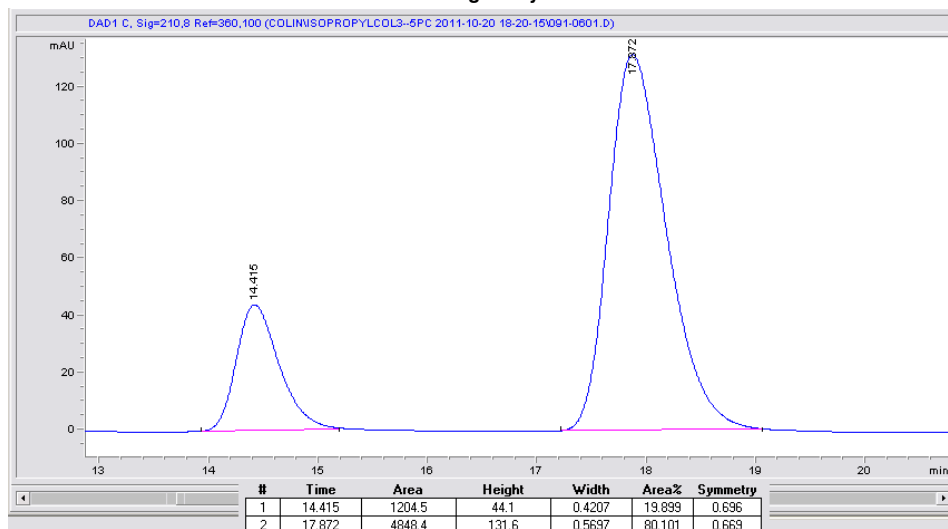


4.2.4

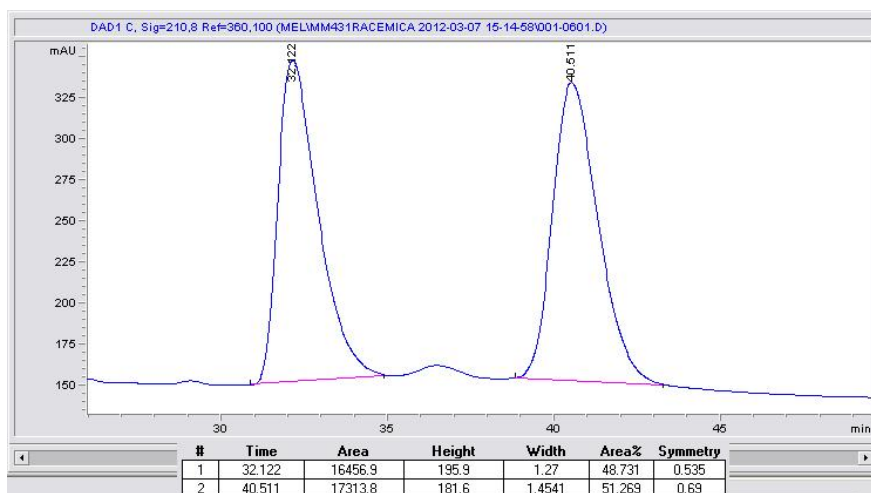


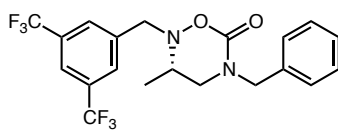


4.2.4 Using catalyst 2.3

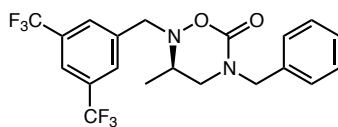
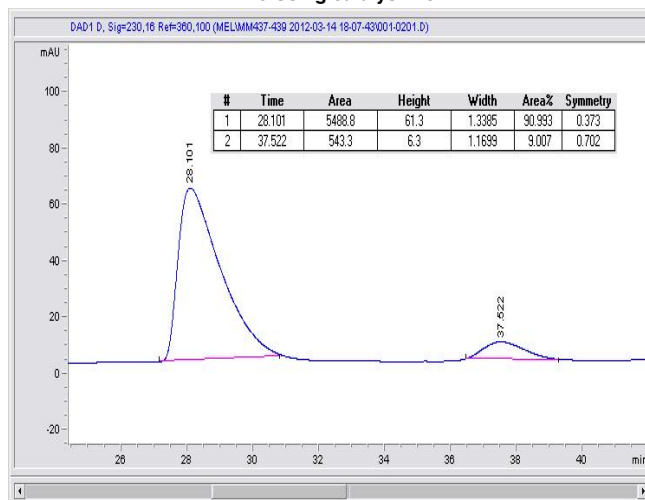


4.2.5

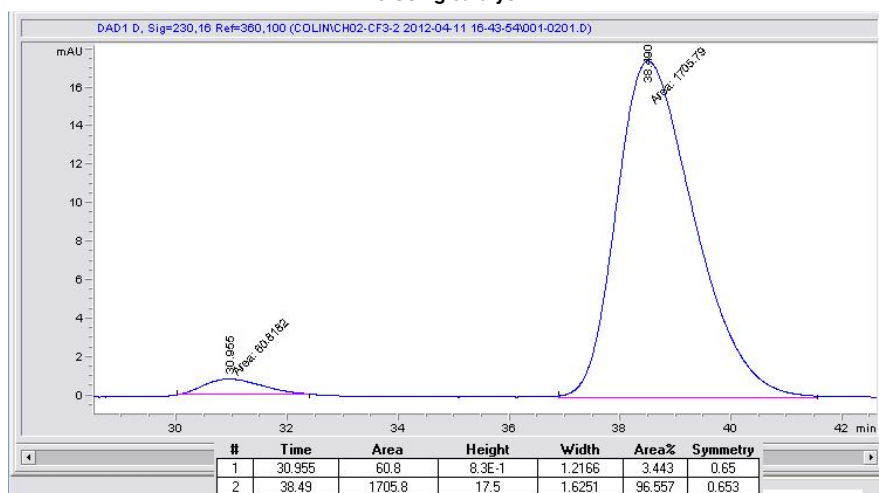


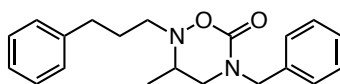


4.2.5 Using catalyst 2.3

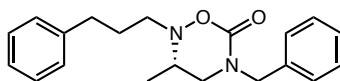
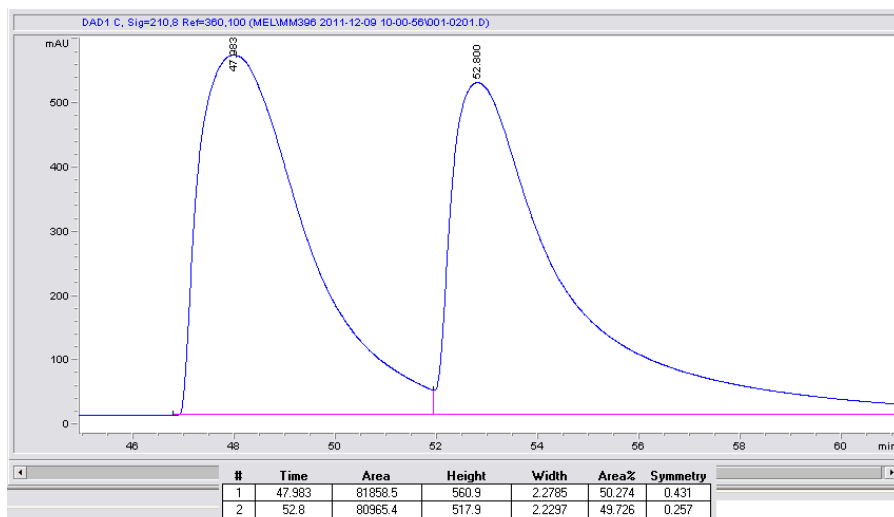


4.2.5 Using catalyst 4h

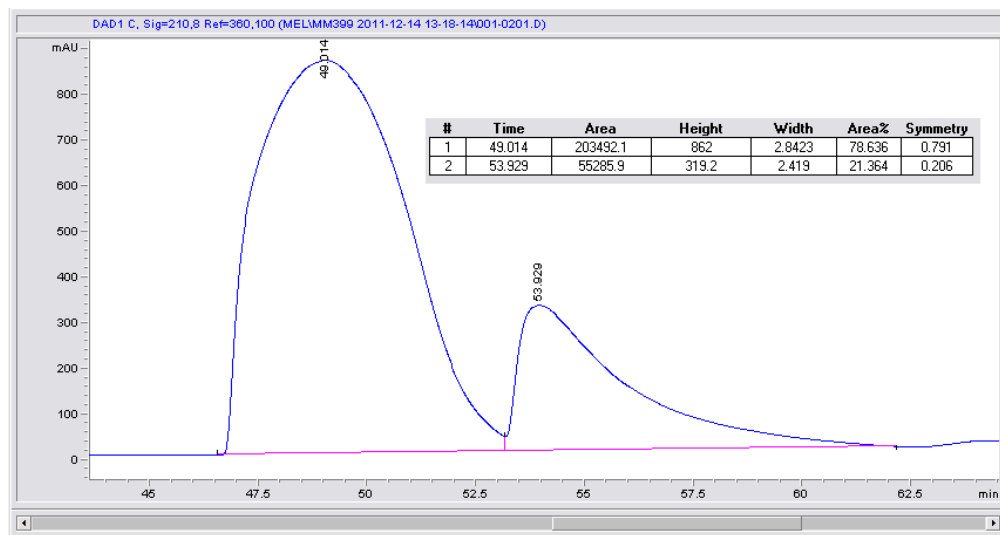


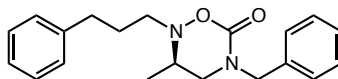


4.2.6

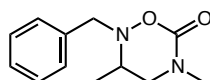
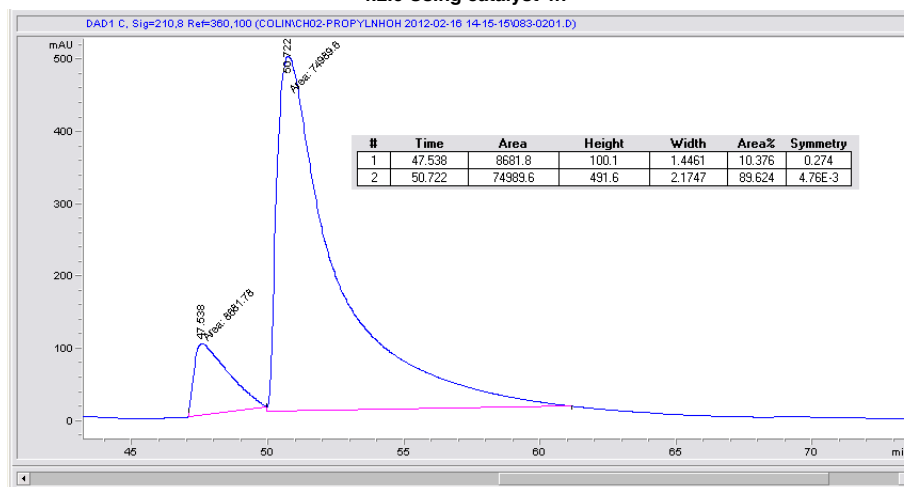


4.2.6 Using catalyst 2.3

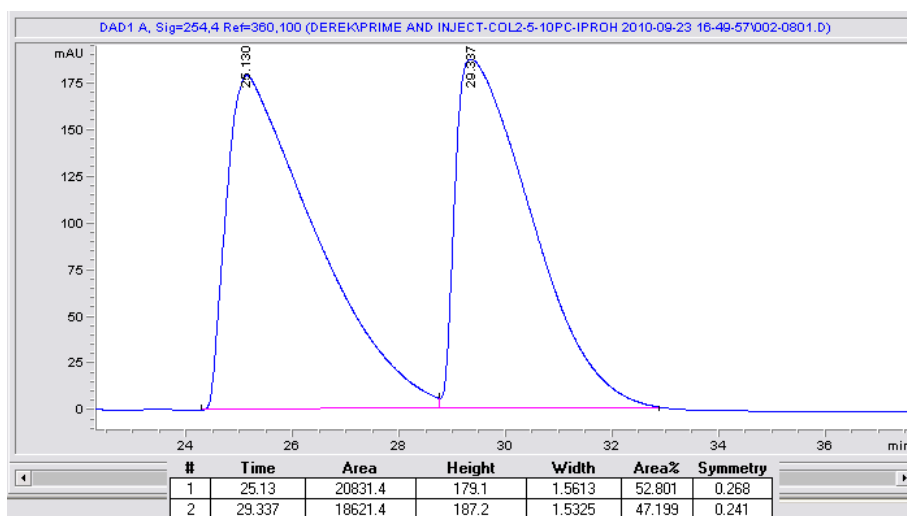


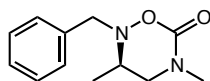


4.2.6 Using catalyst 4h

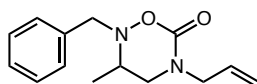
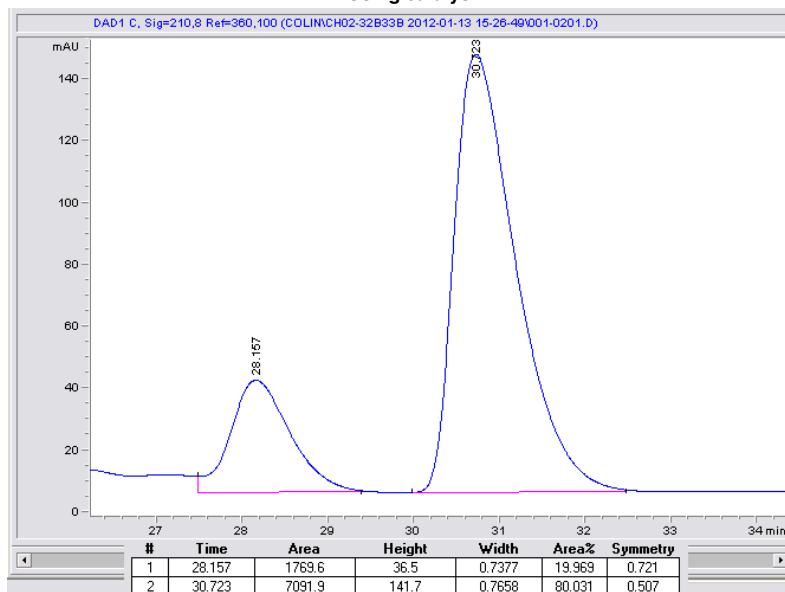


4.2.7

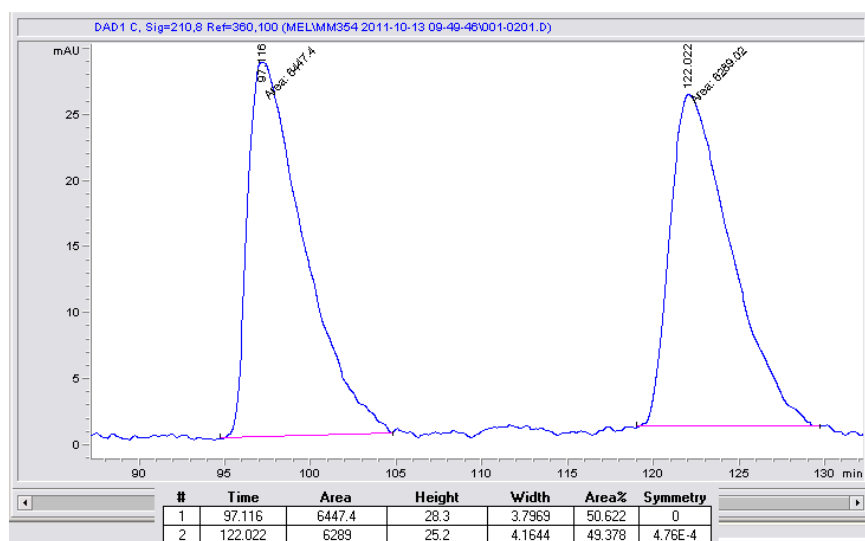


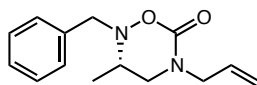


4.2.7 Using catalyst 4h

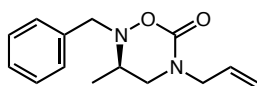
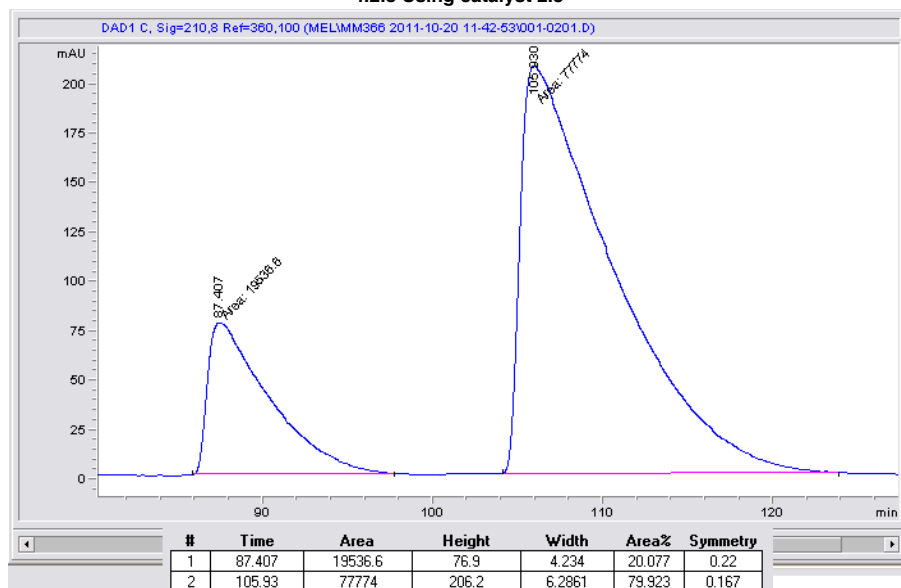


4.2.8

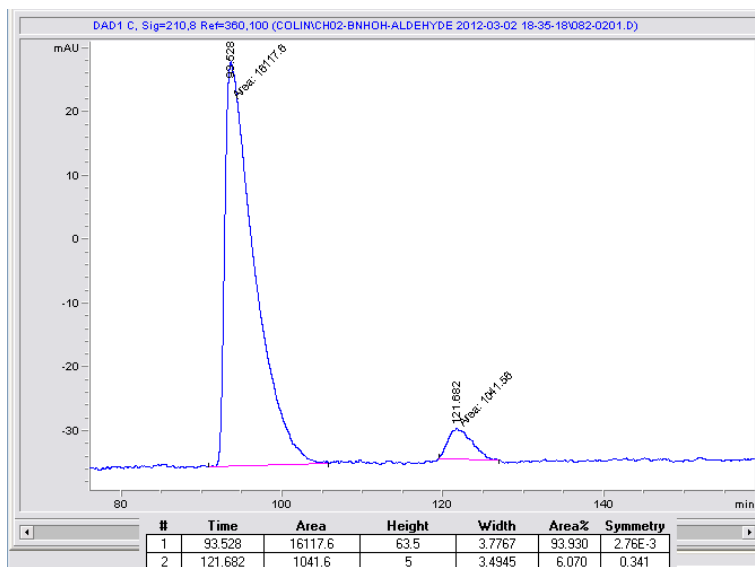


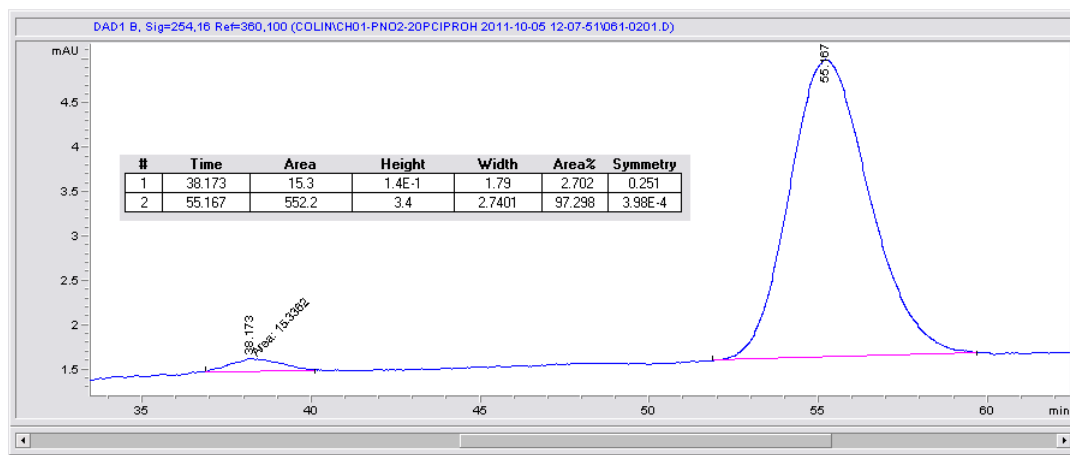
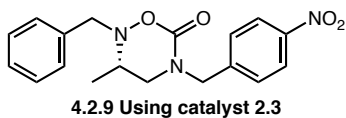
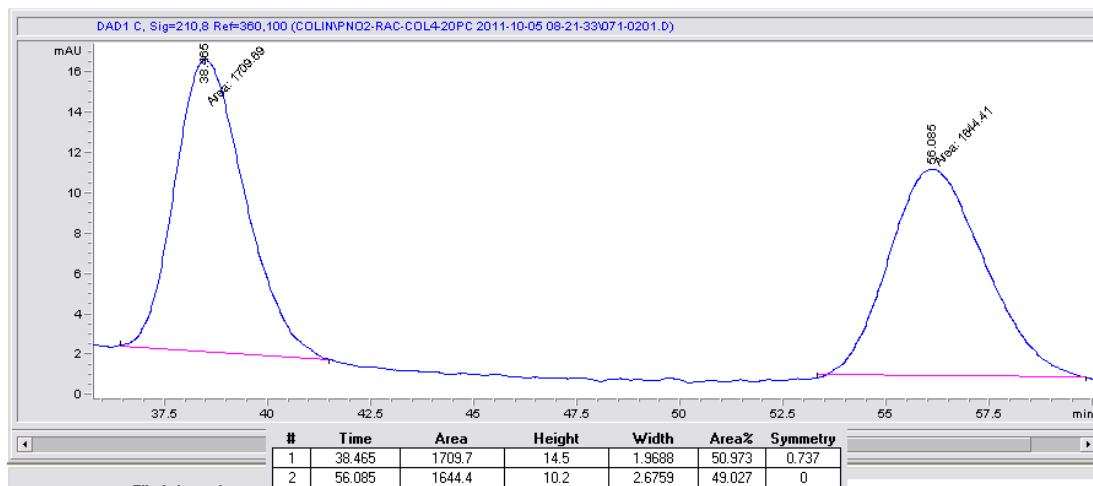
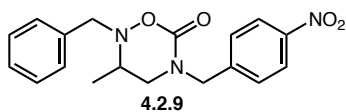


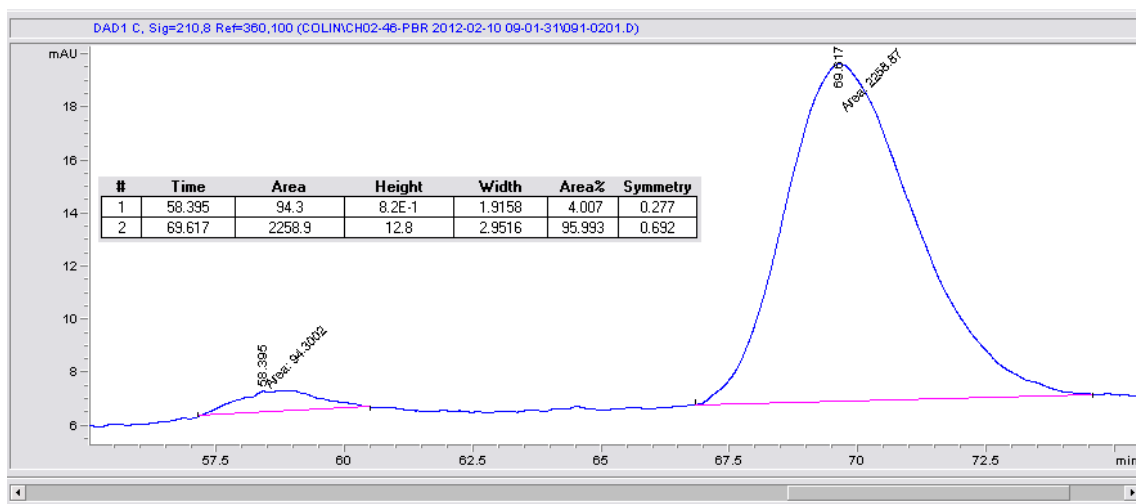
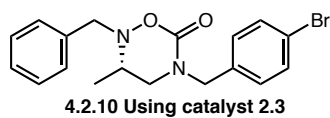
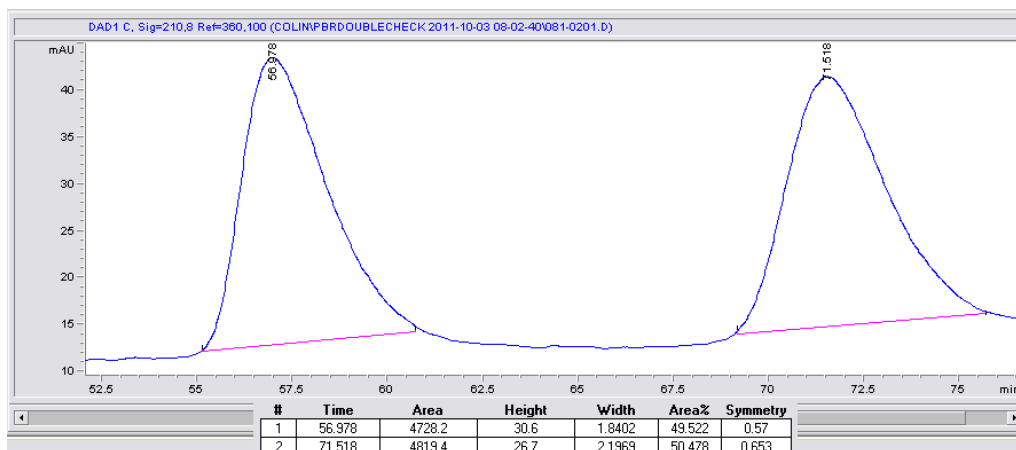
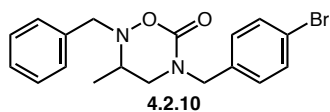
4.2.8 Using catalyst 2.3

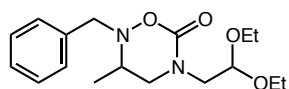


4.2.8 Using catalyst 4h

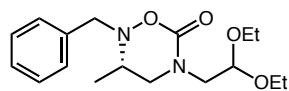
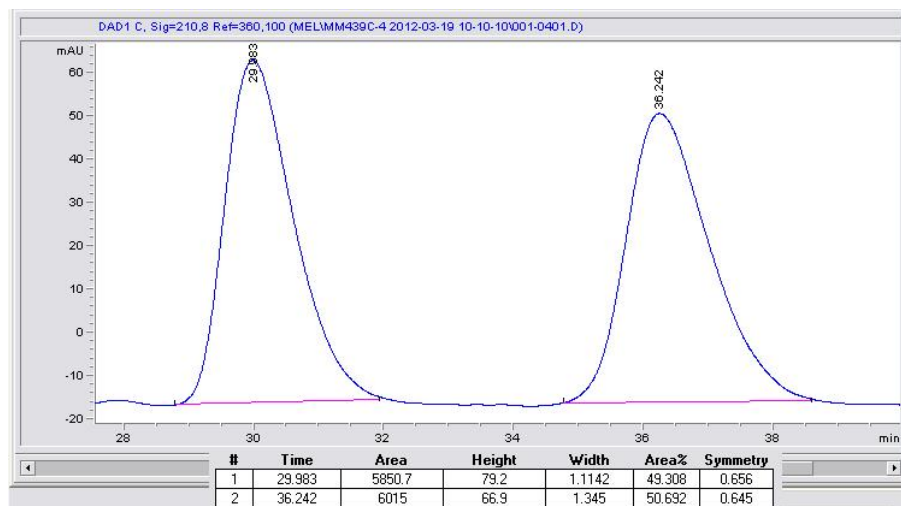




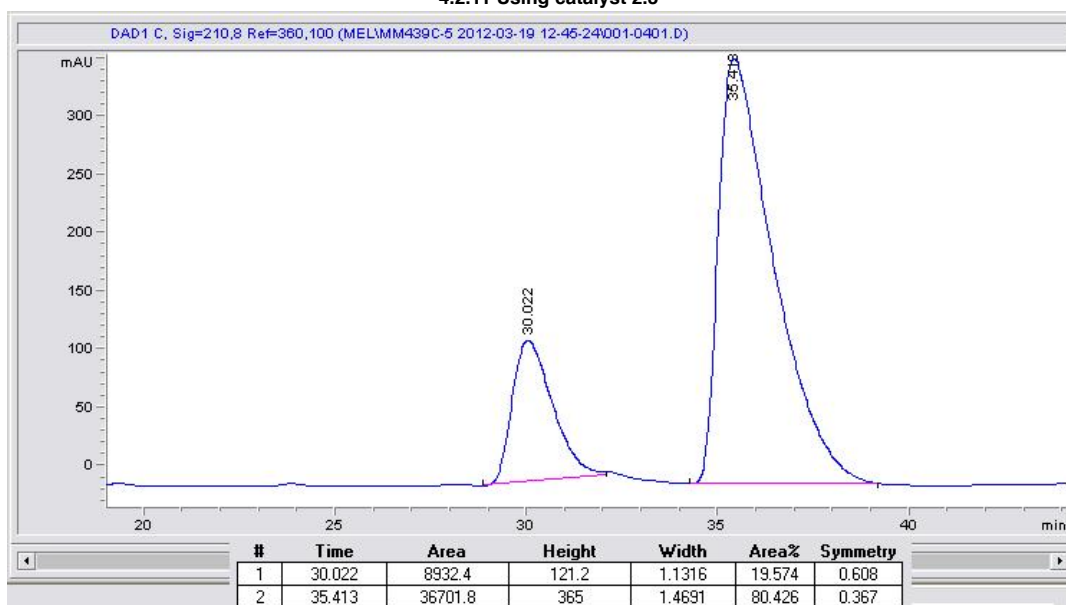


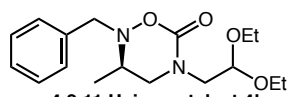


4.2.11

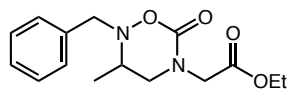
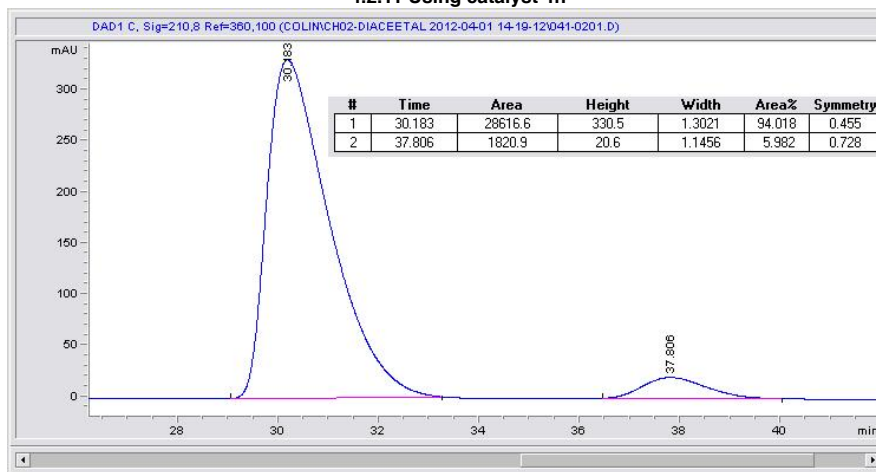


4.2.11 Using catalyst 2.3

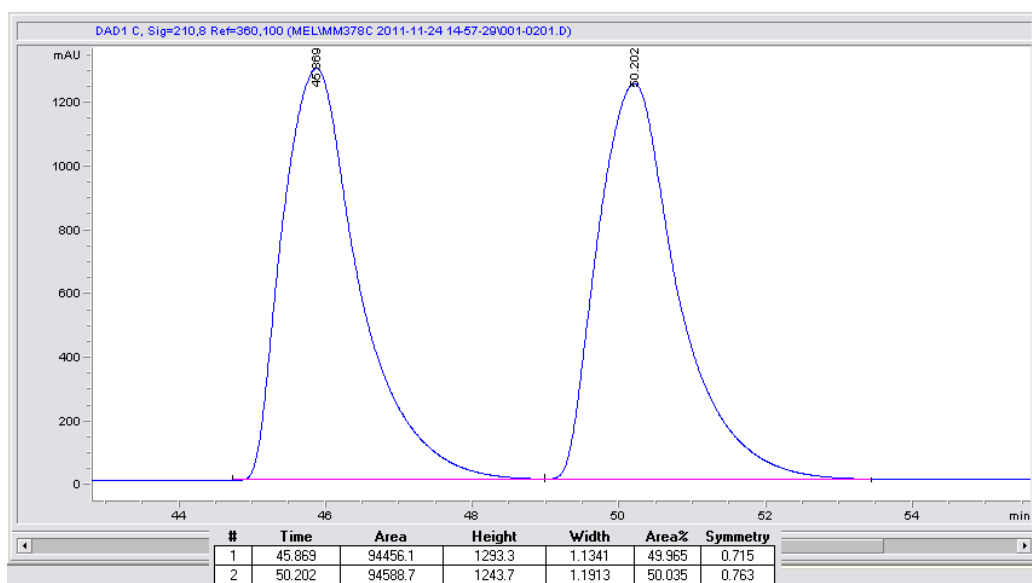


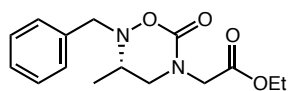


4.2.11 Using catalyst 4h

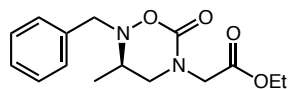
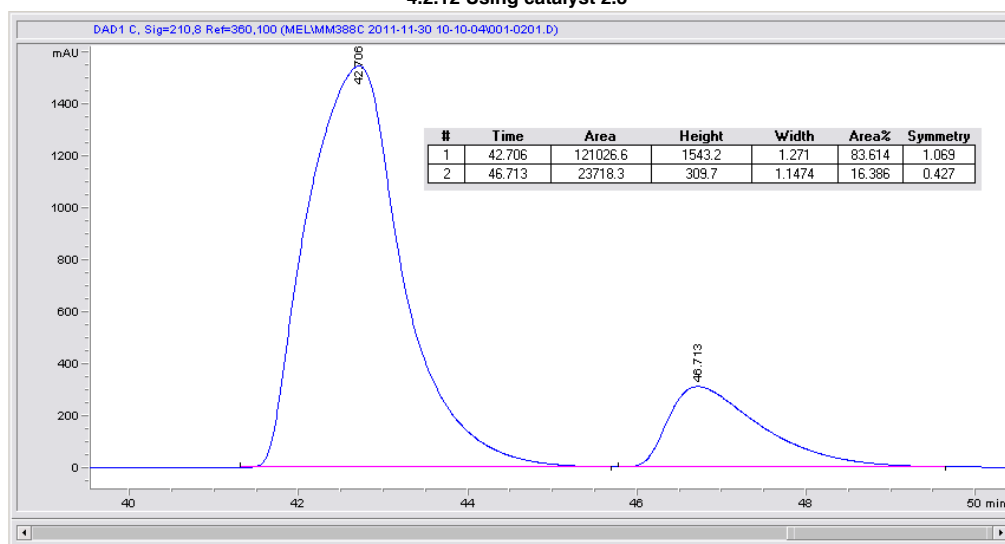


4.2.12

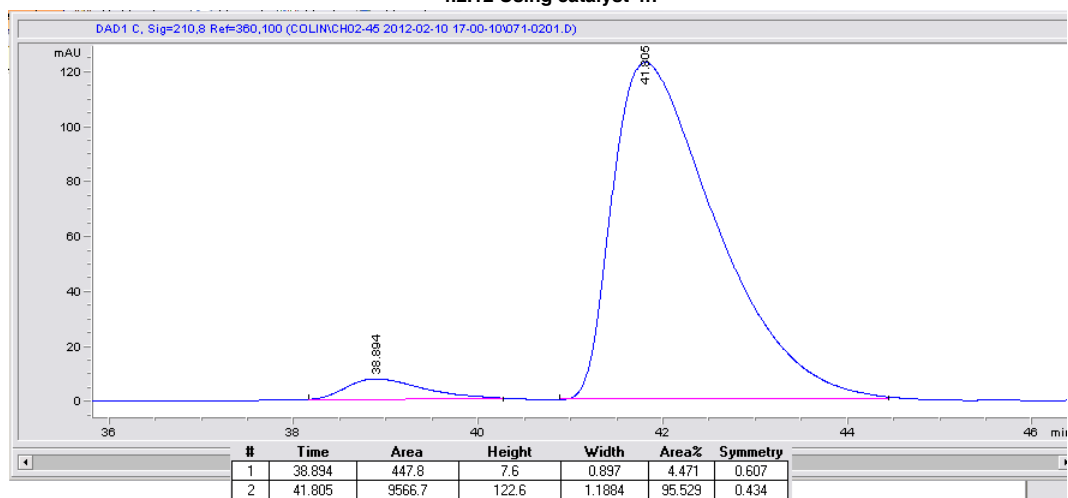


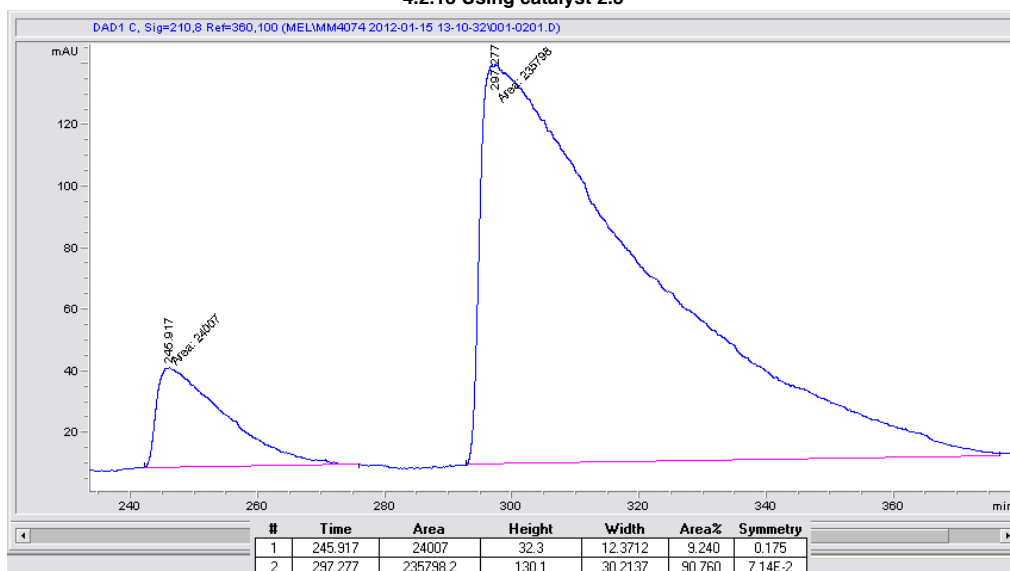
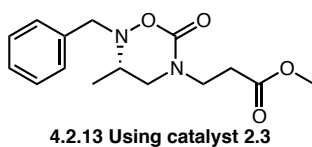
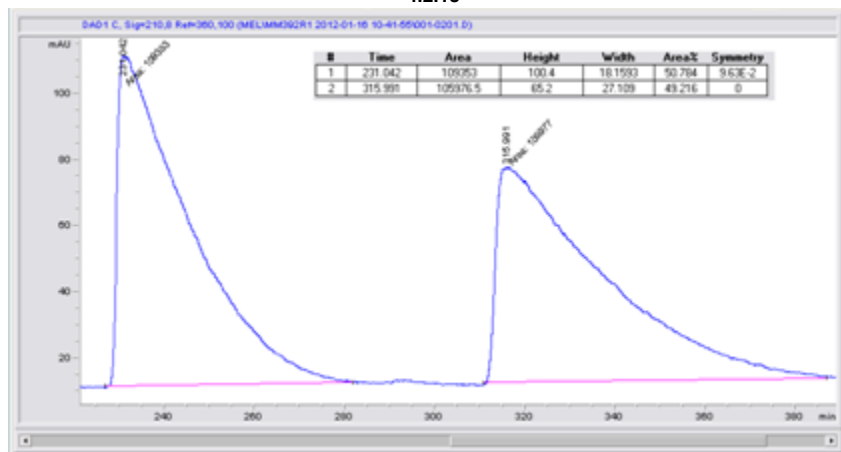
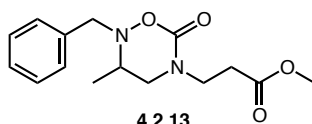


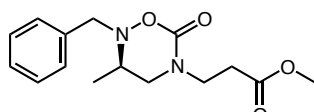
4.2.12 Using catalyst 2.3



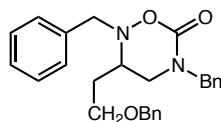
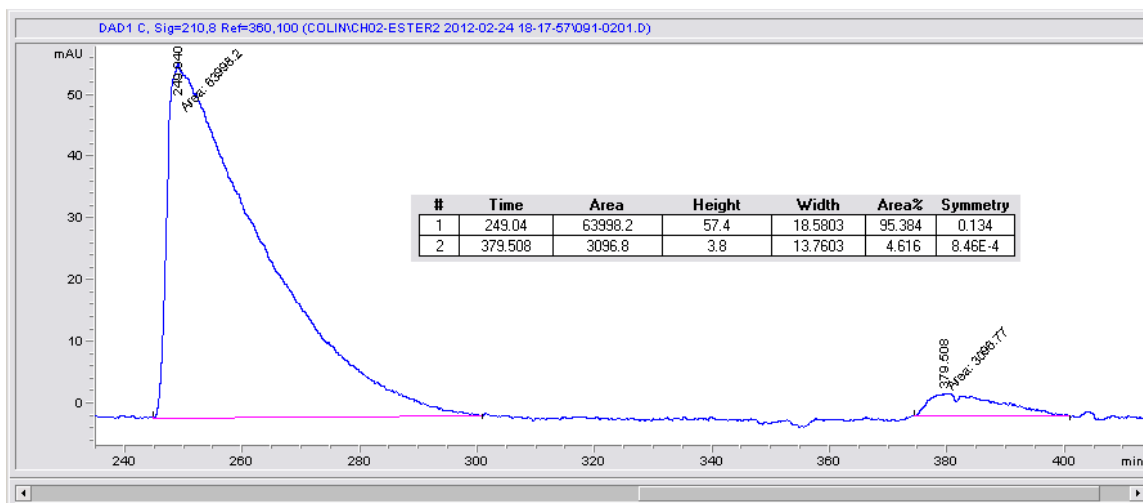
4.2.12 Using catalyst 4h



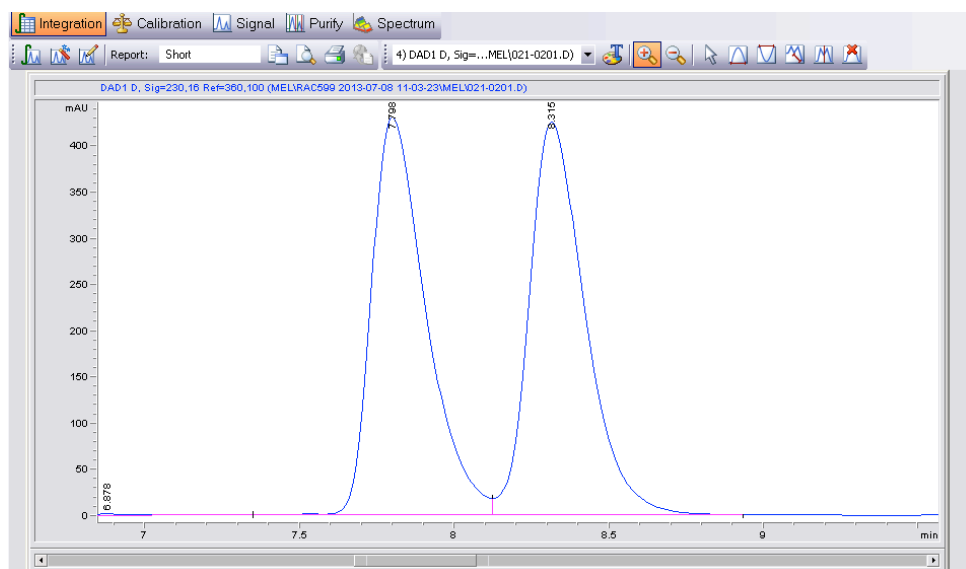


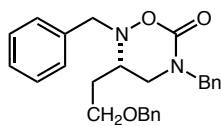


4.2.13 Using catalyst 4h

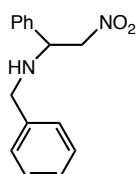
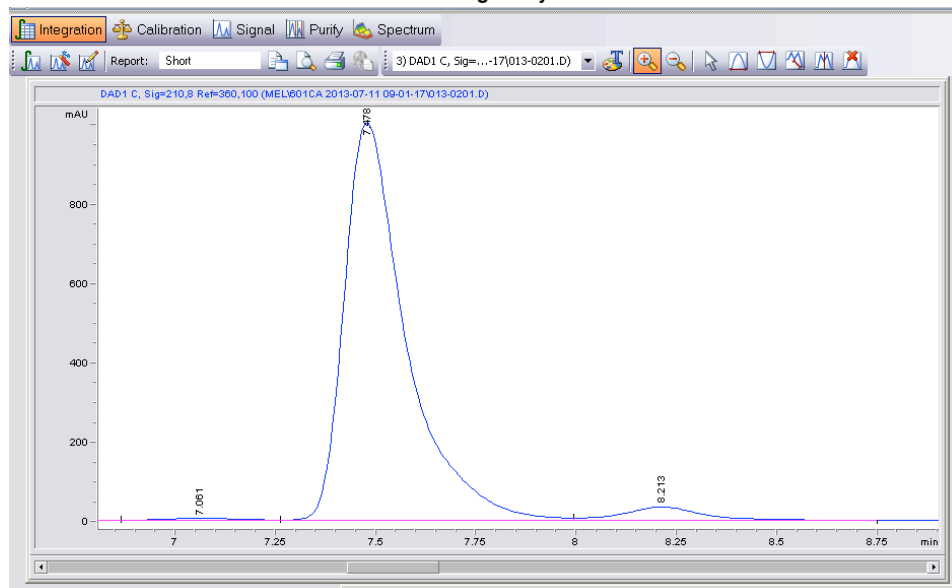


4.2.14

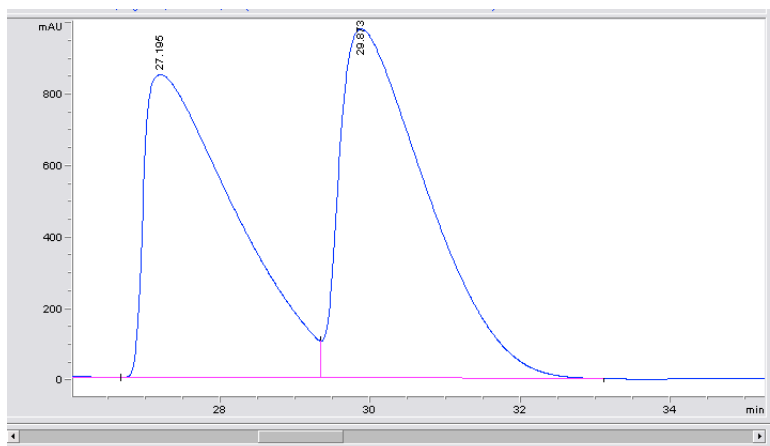


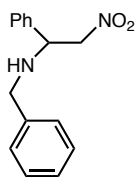


4.2.14 Using catalyst 2.3

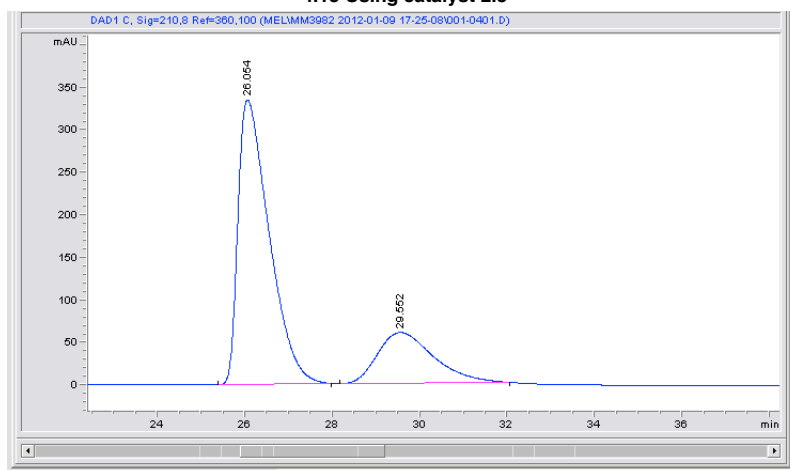


4.15

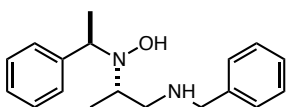




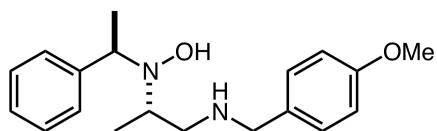
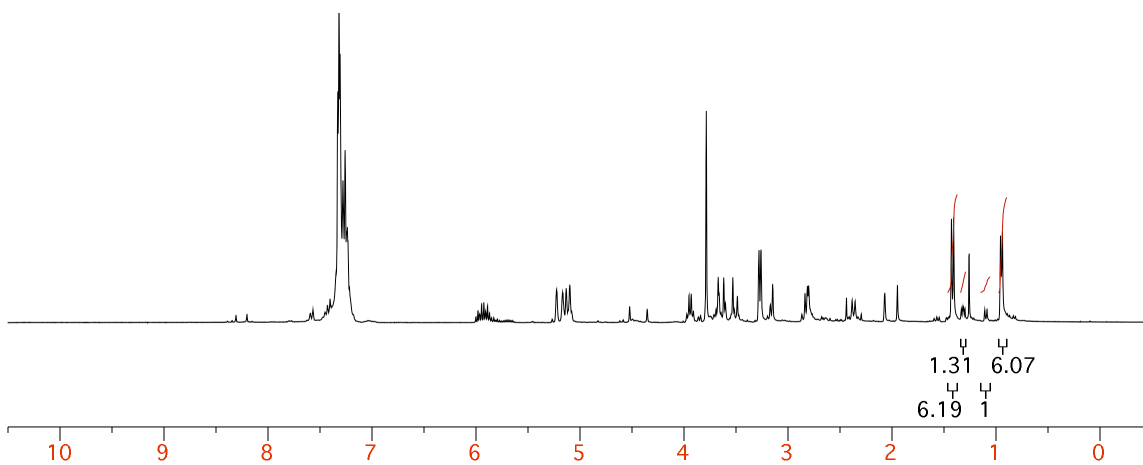
4.15 Using catalyst 2.3



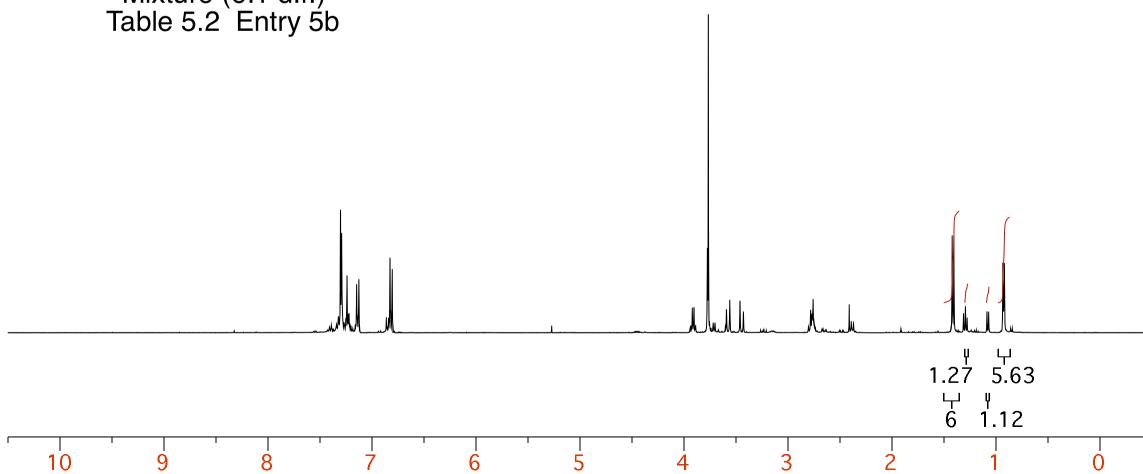
Chapter 5 Supporting Information

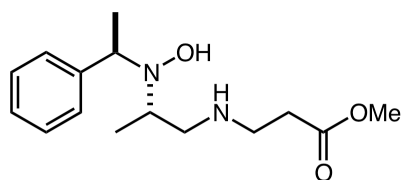


Crude (6:1 d.r.)
Table 5.2, Entry 5a



Mixture (6:1 d.r.)
Table 5.2 Entry 5b





Mixture (6:1 d.r.)
Table 5.2, Entry 5c

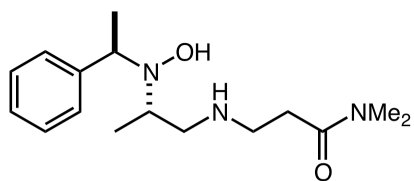
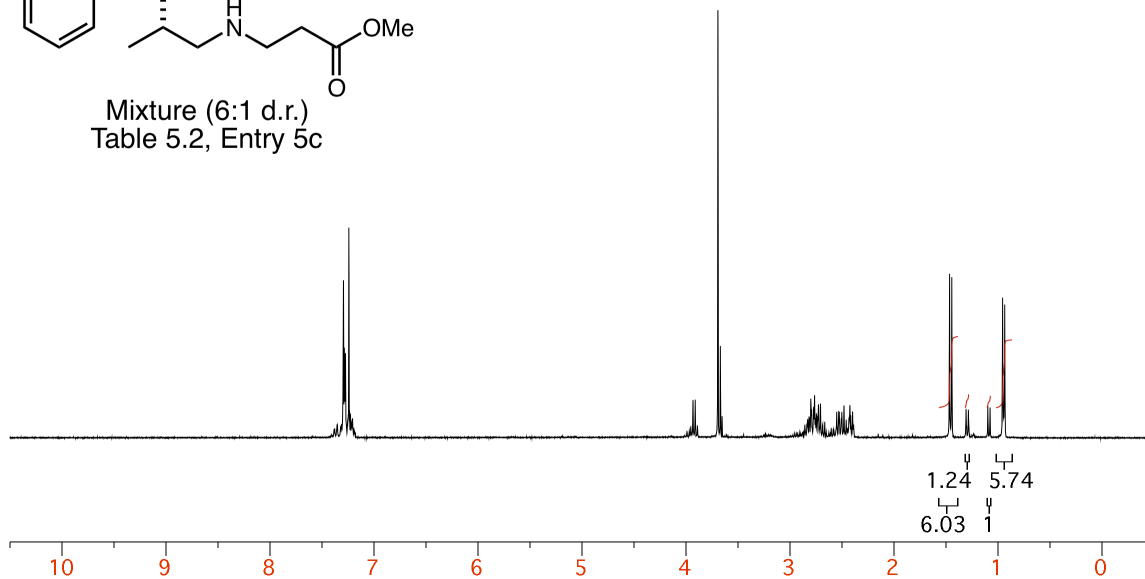
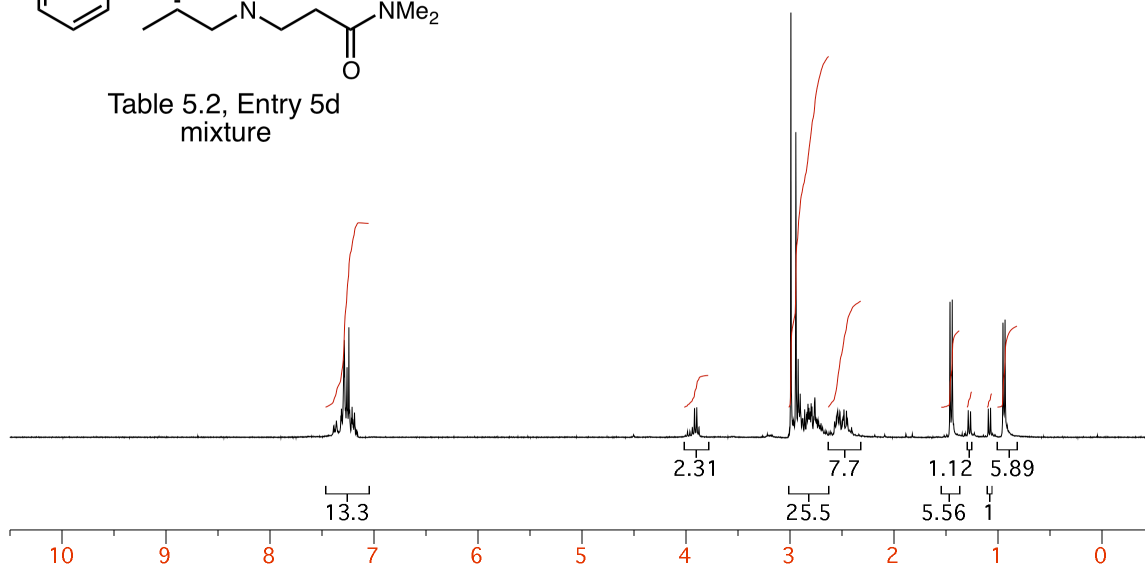
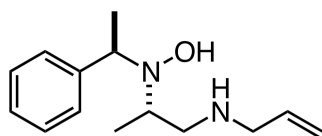
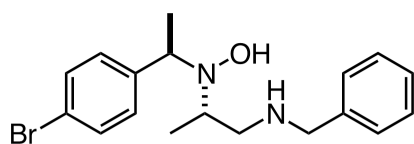
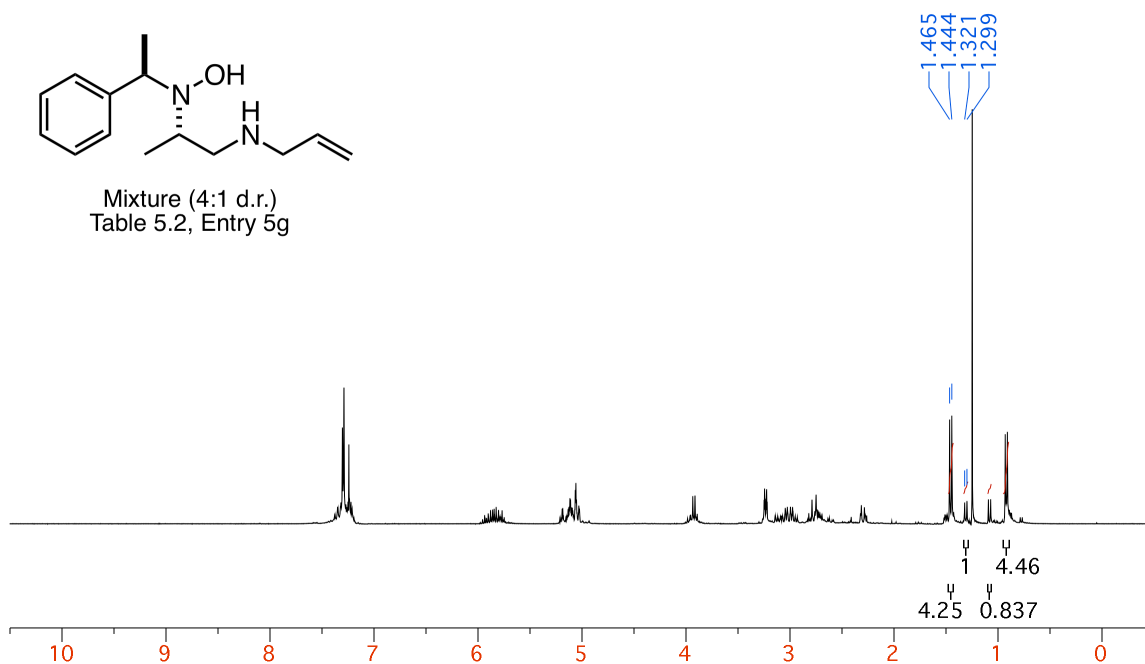


Table 5.2, Entry 5d
mixture

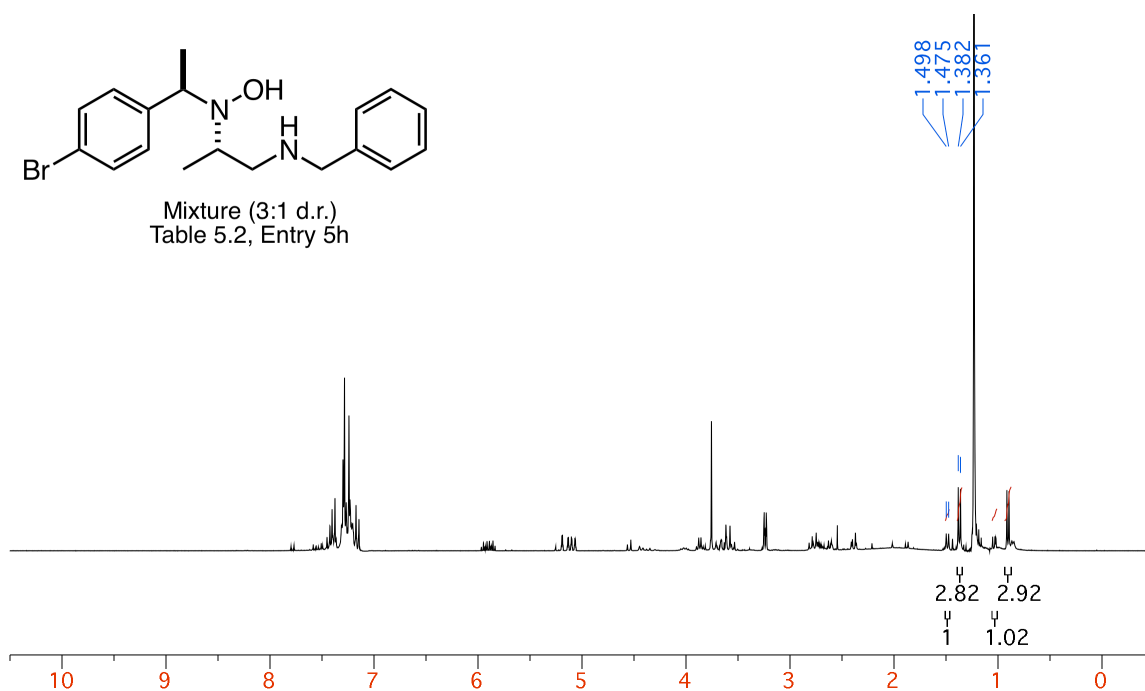


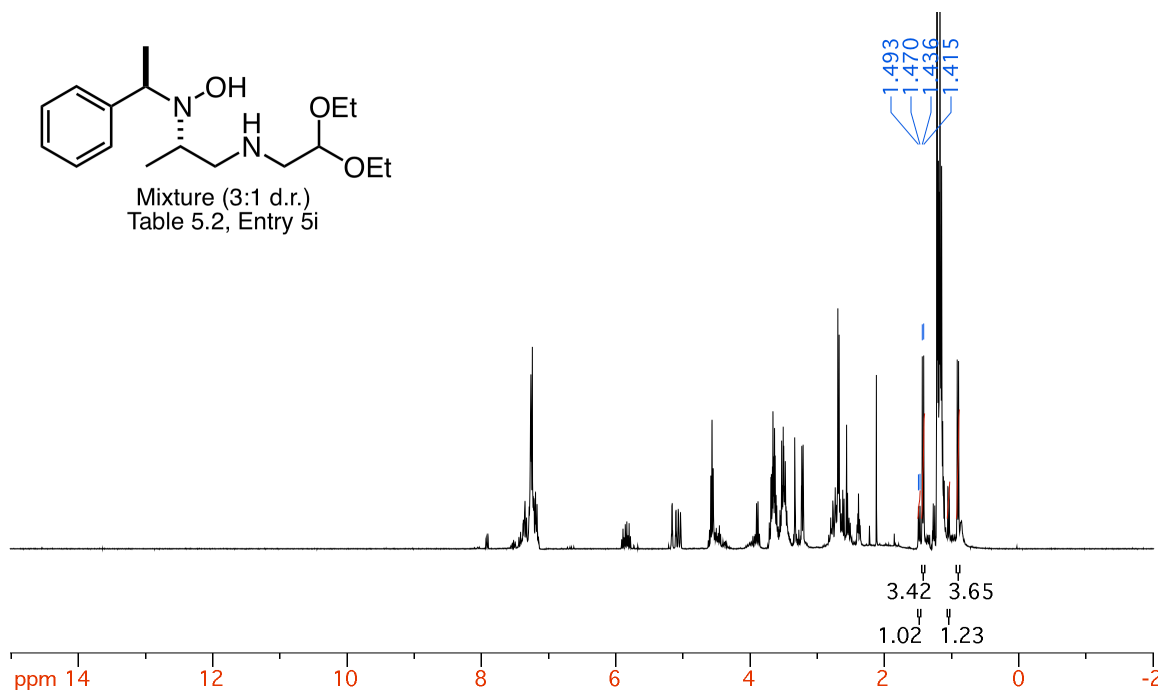


Mixture (4:1 d.r.)
Table 5.2, Entry 5g

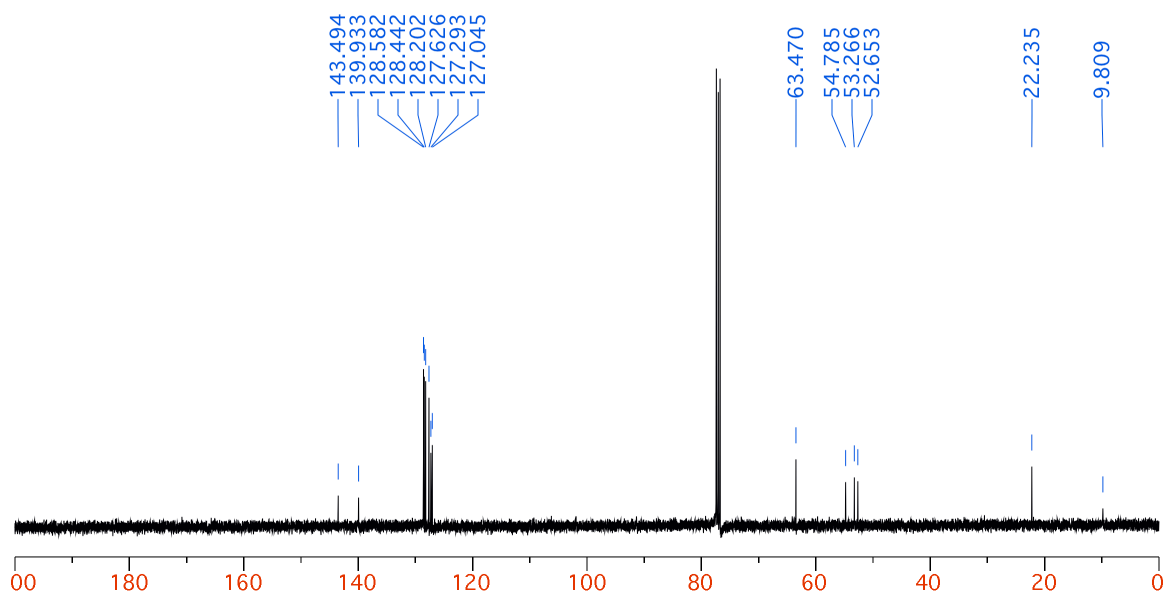
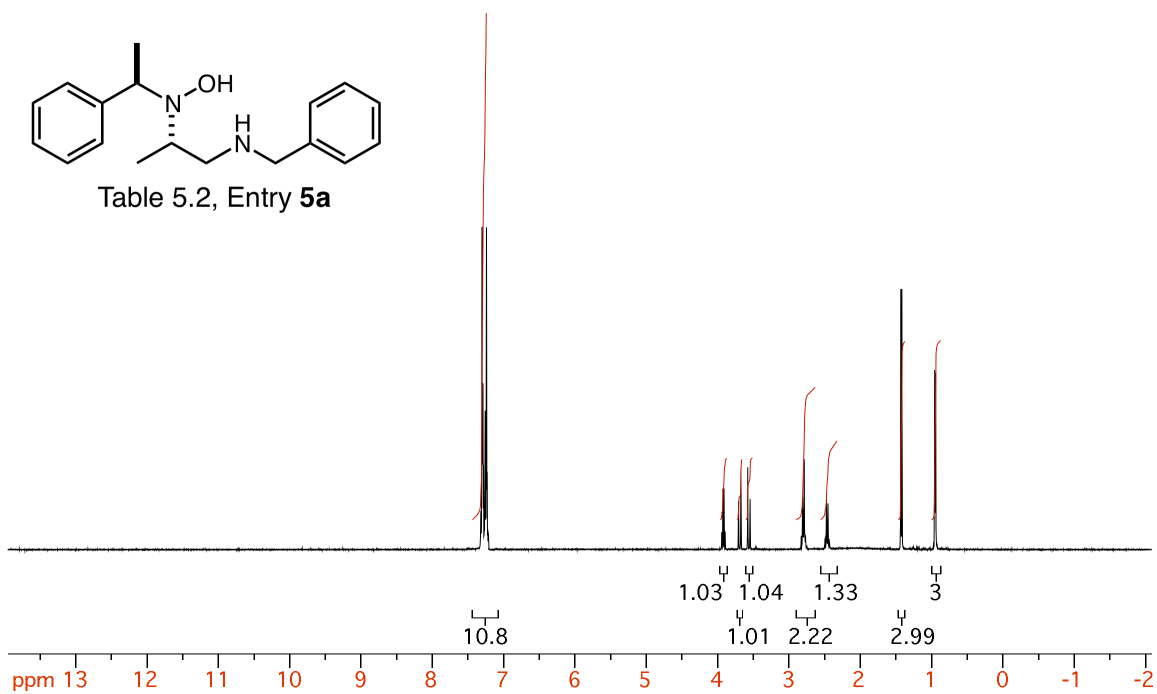


Mixture (3:1 d.r.)
Table 5.2, Entry 5h





NMR Spectra for Major Diastereomer



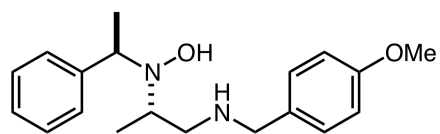
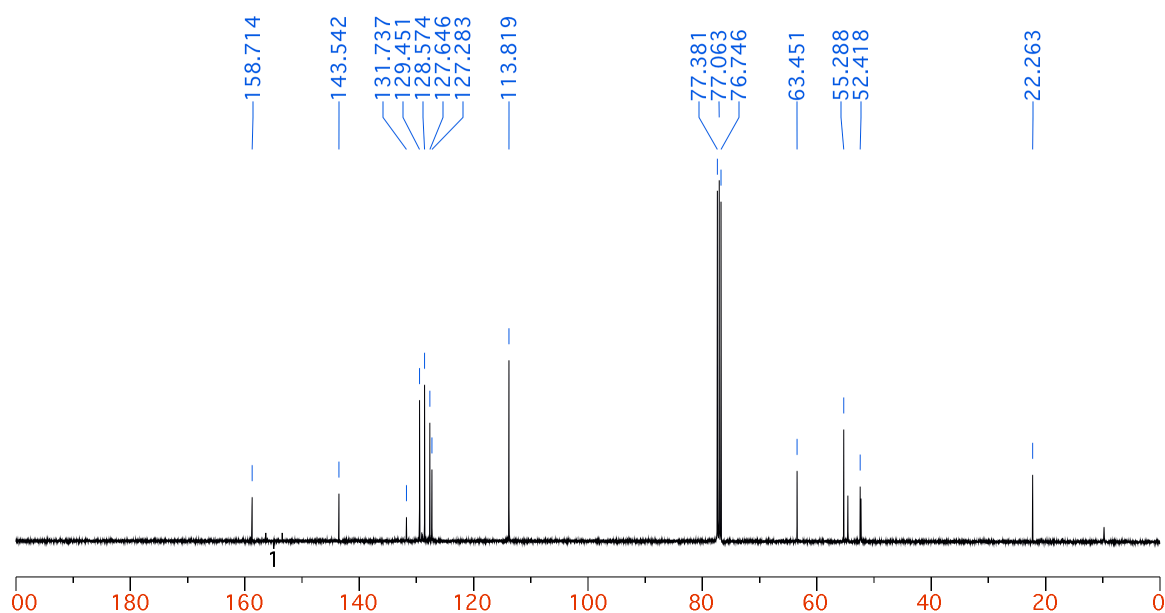
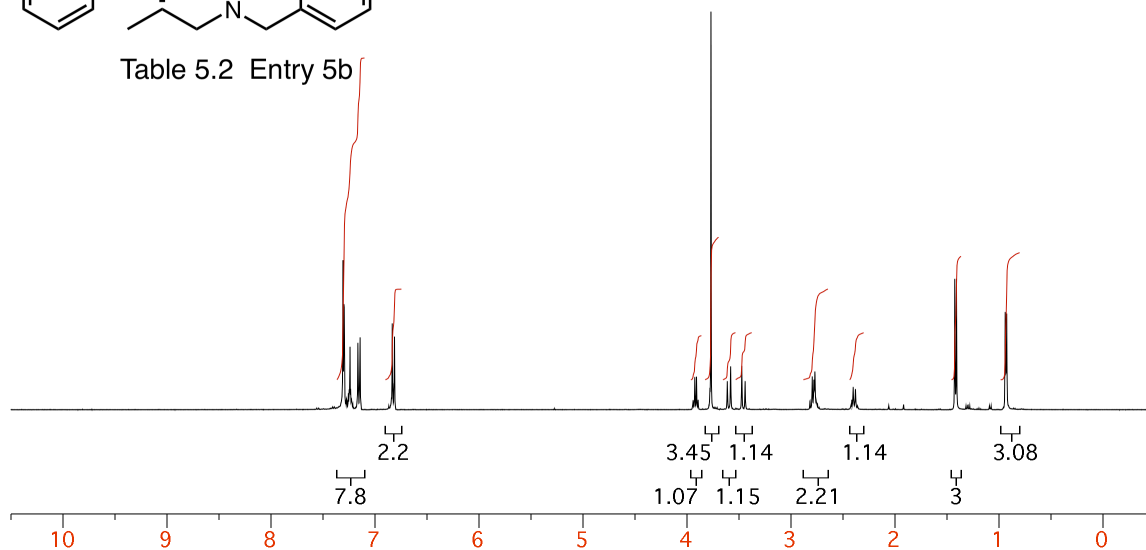


Table 5.2 Entry 5b



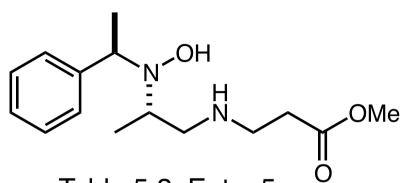
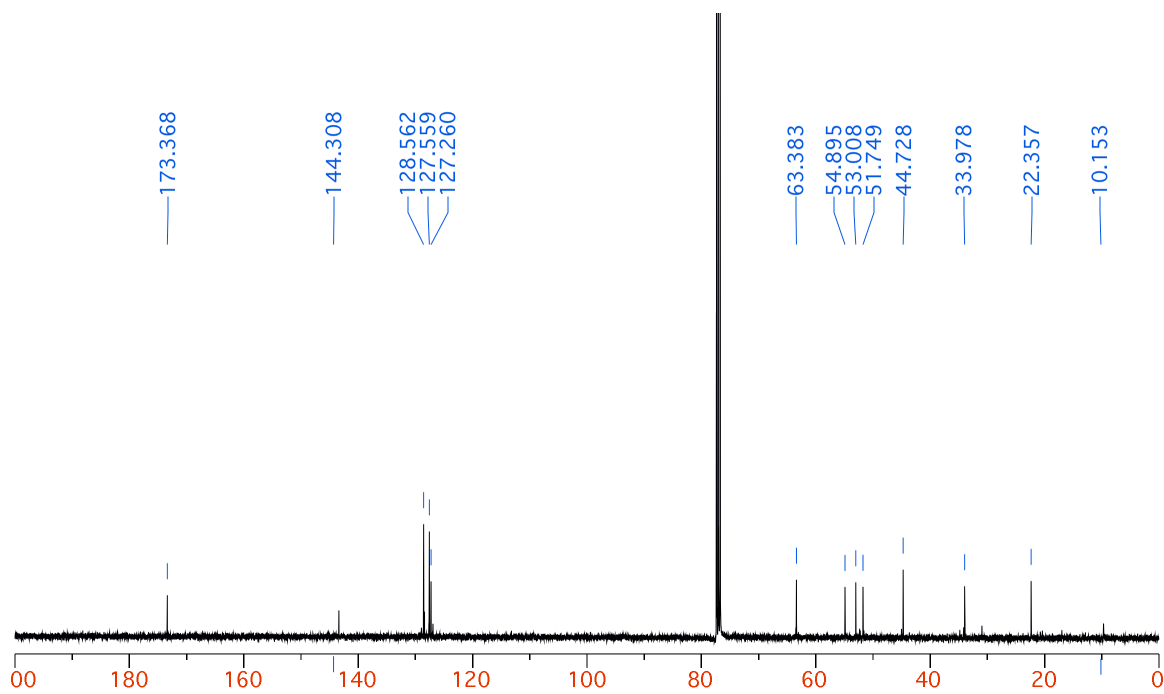
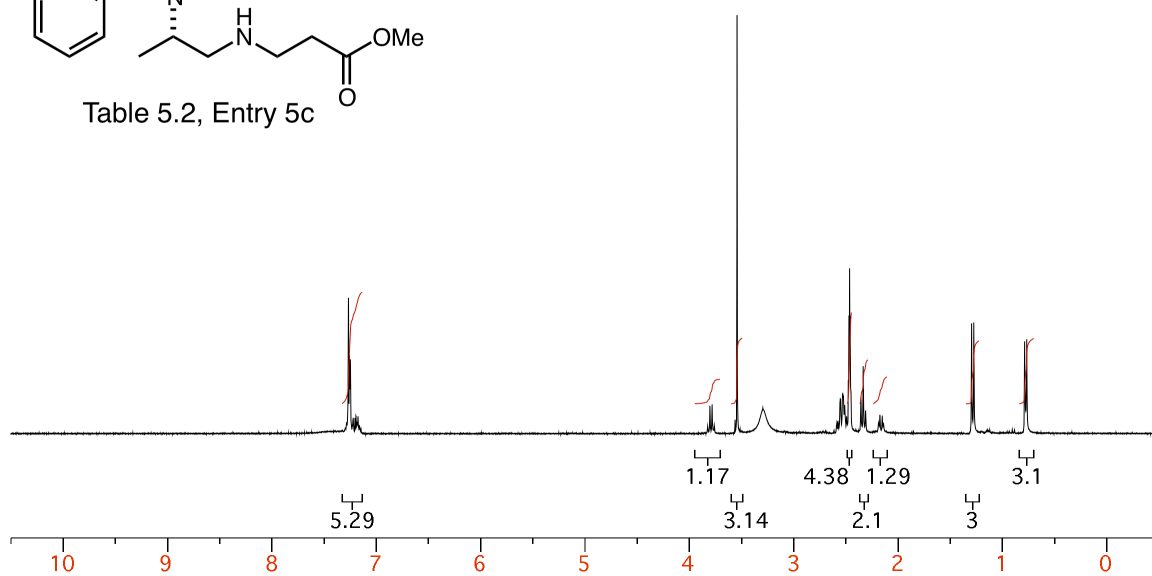


Table 5.2, Entry 5c



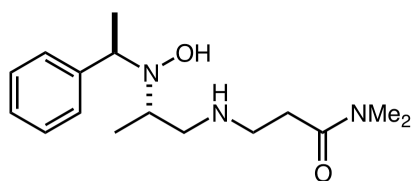
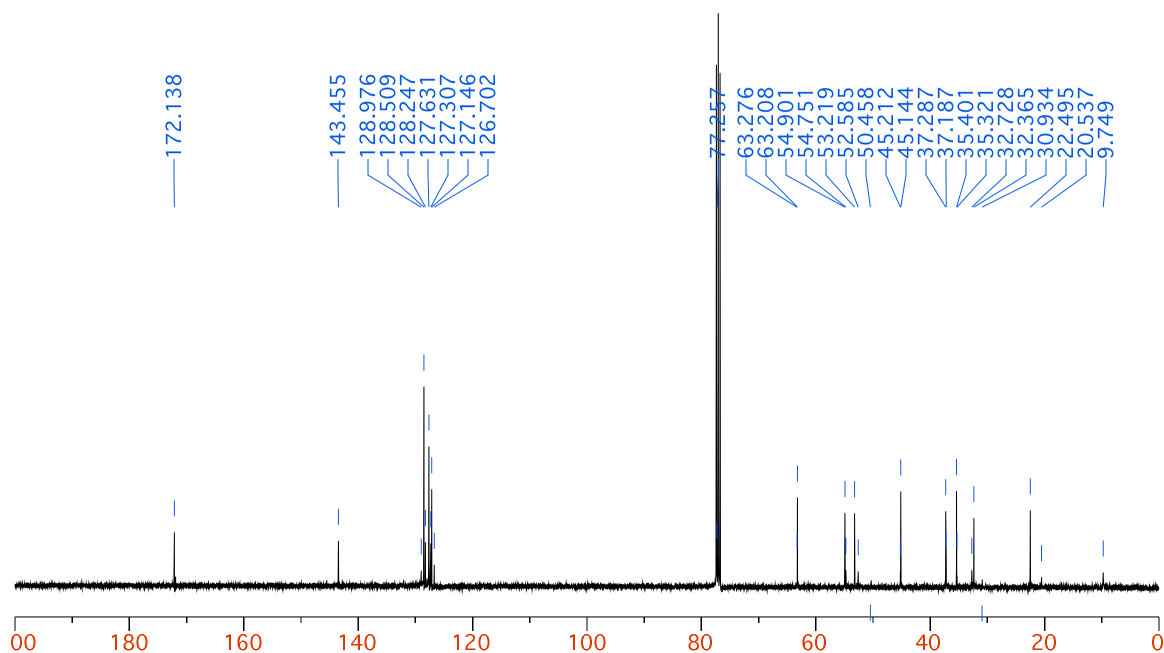
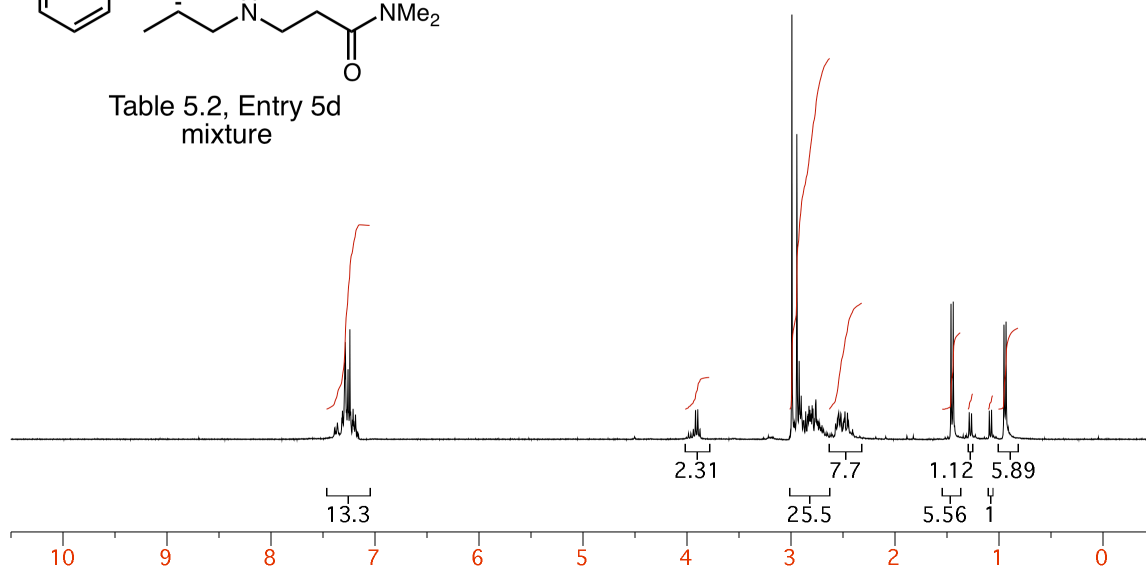
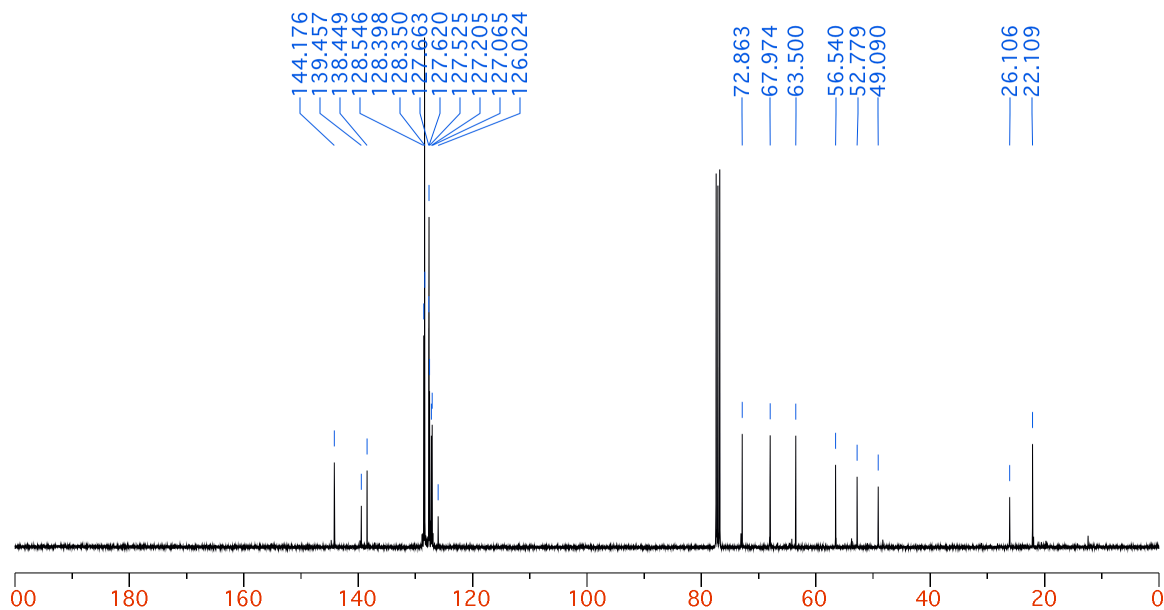
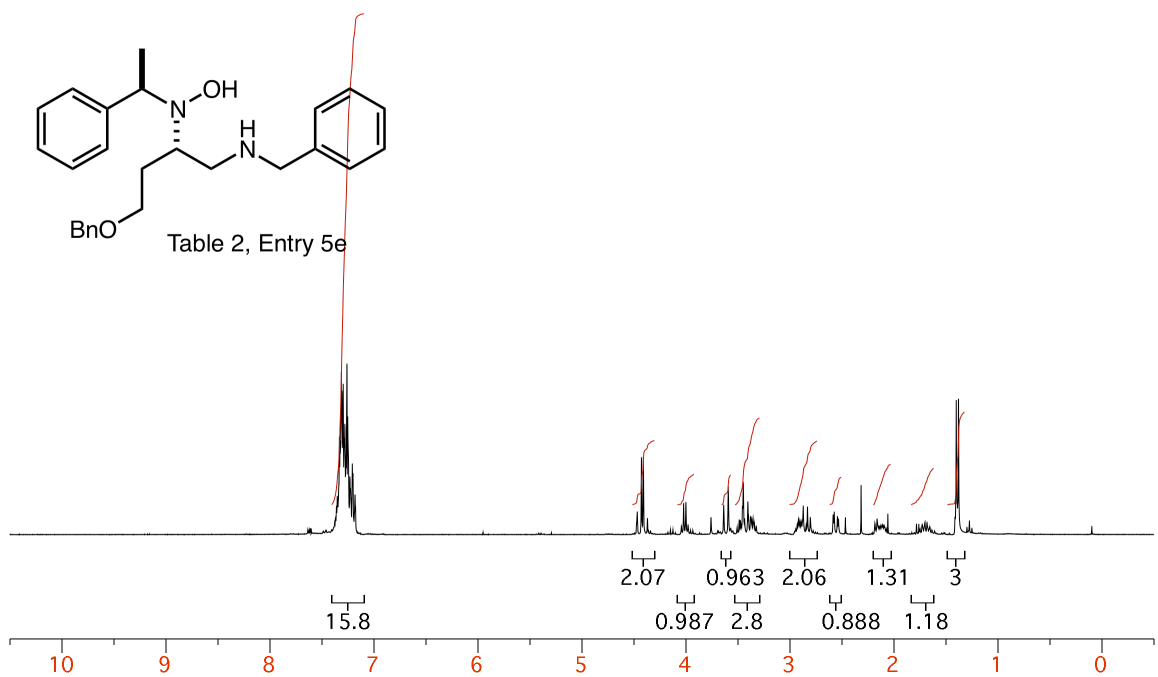
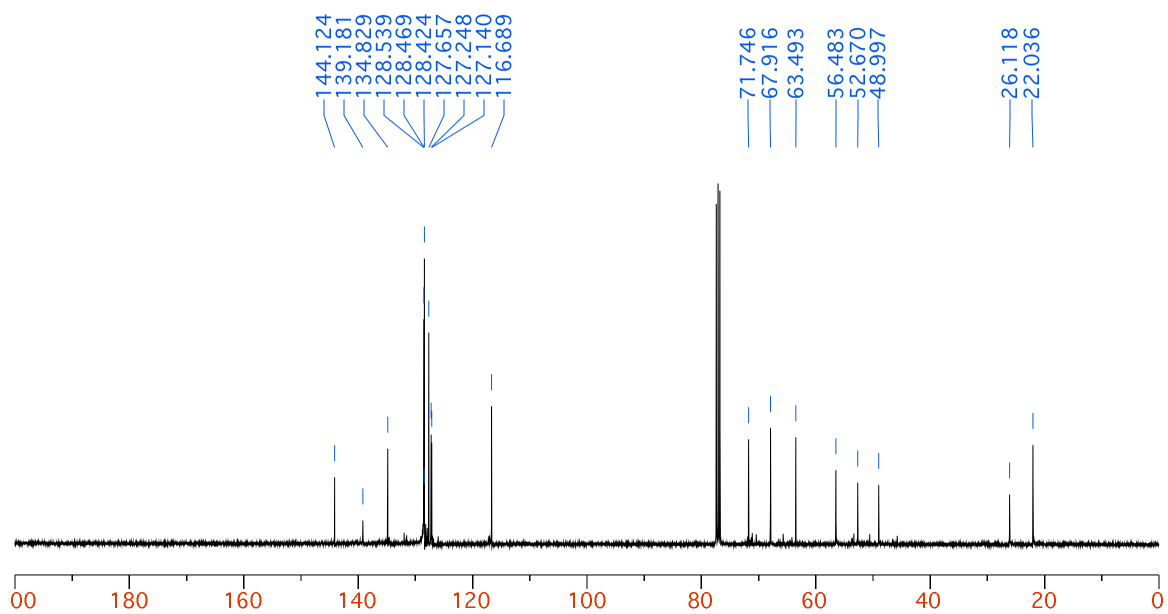
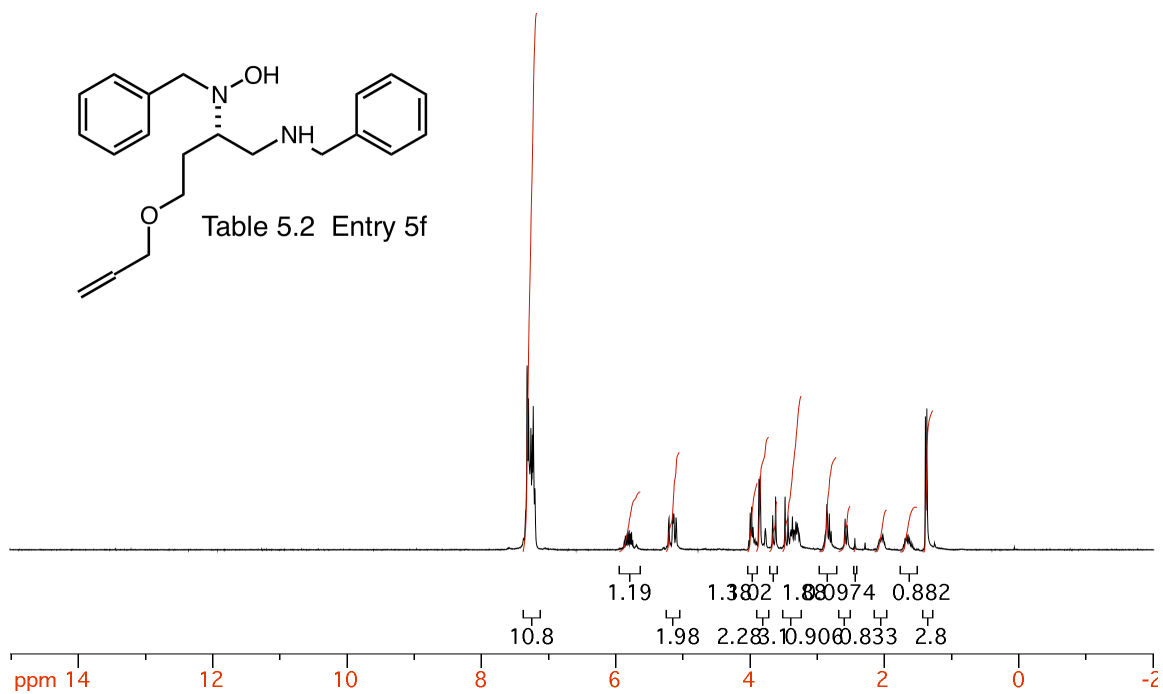


Table 5.2, Entry 5d
mixture







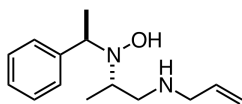
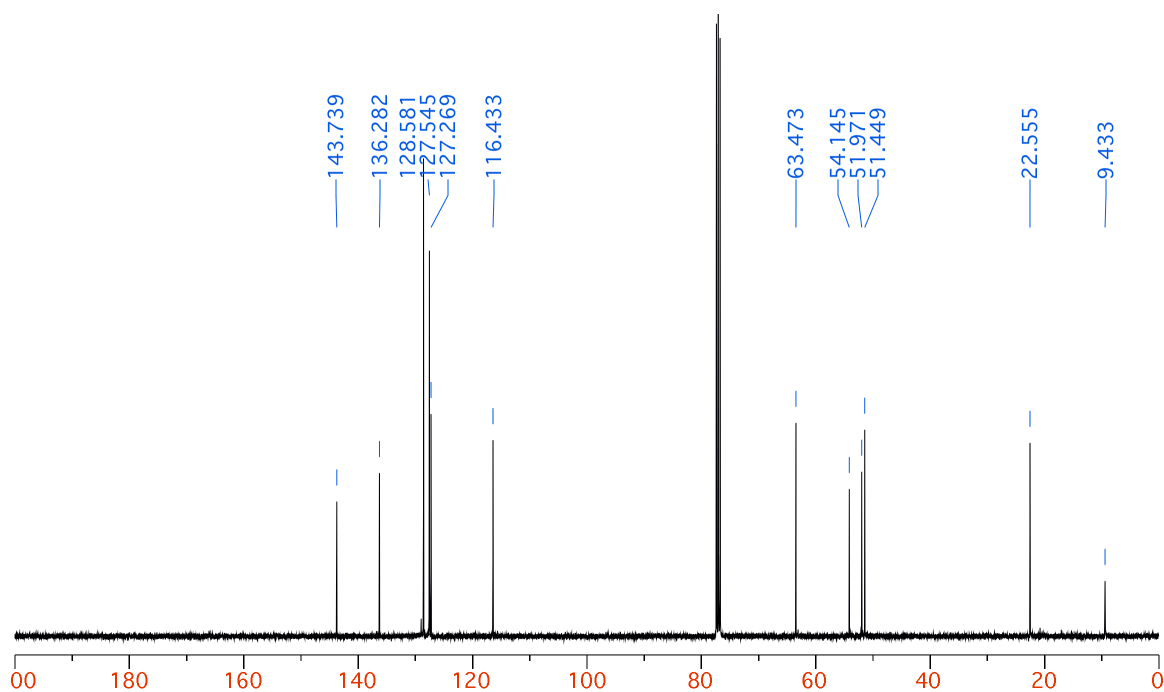
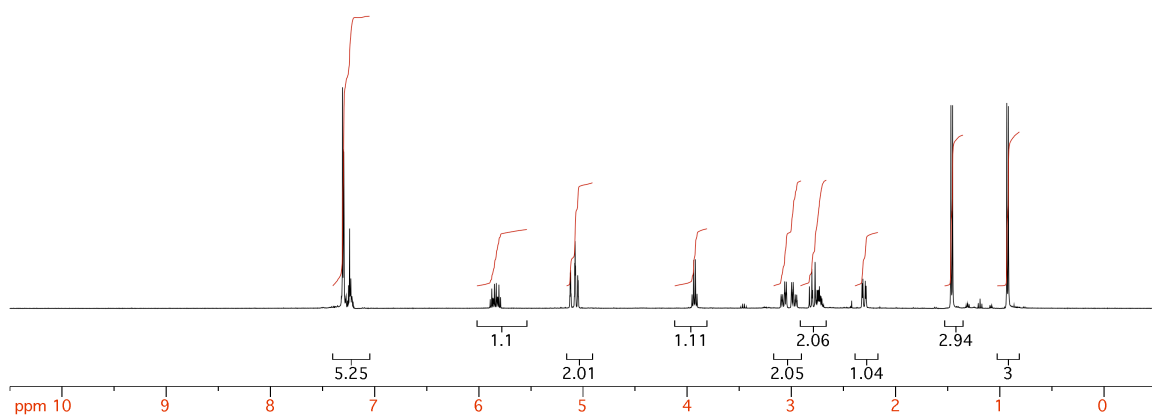
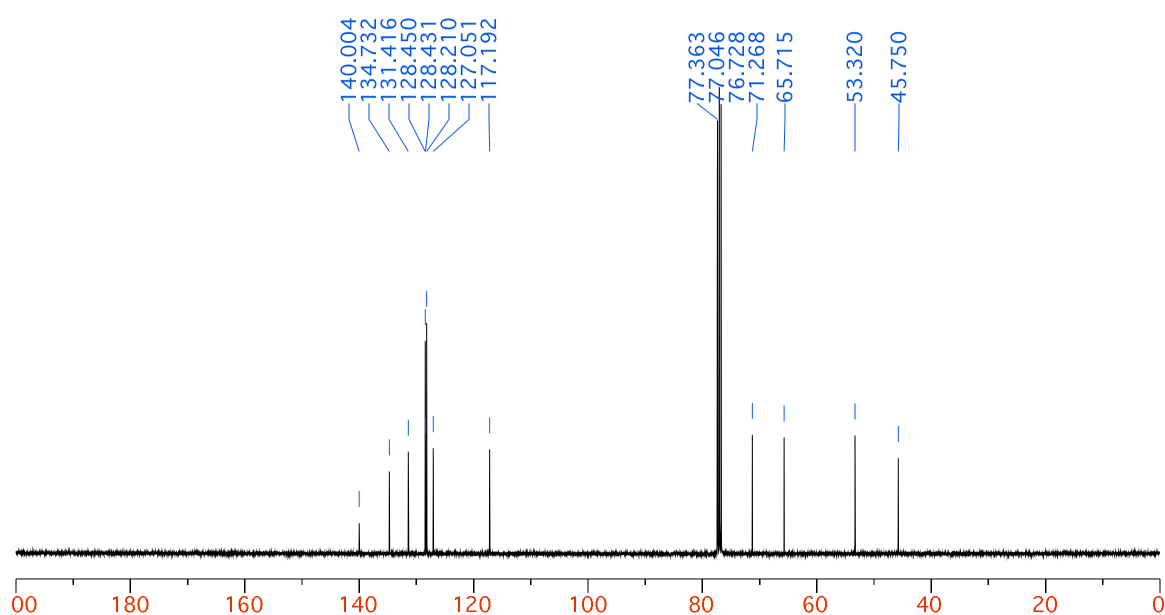
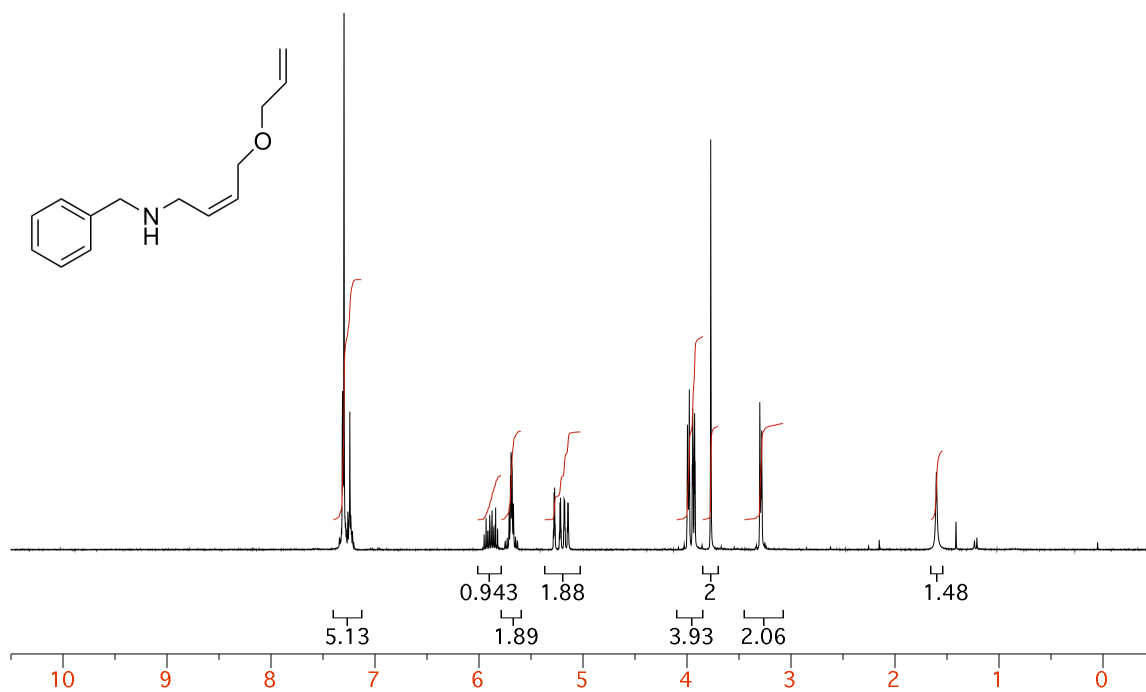
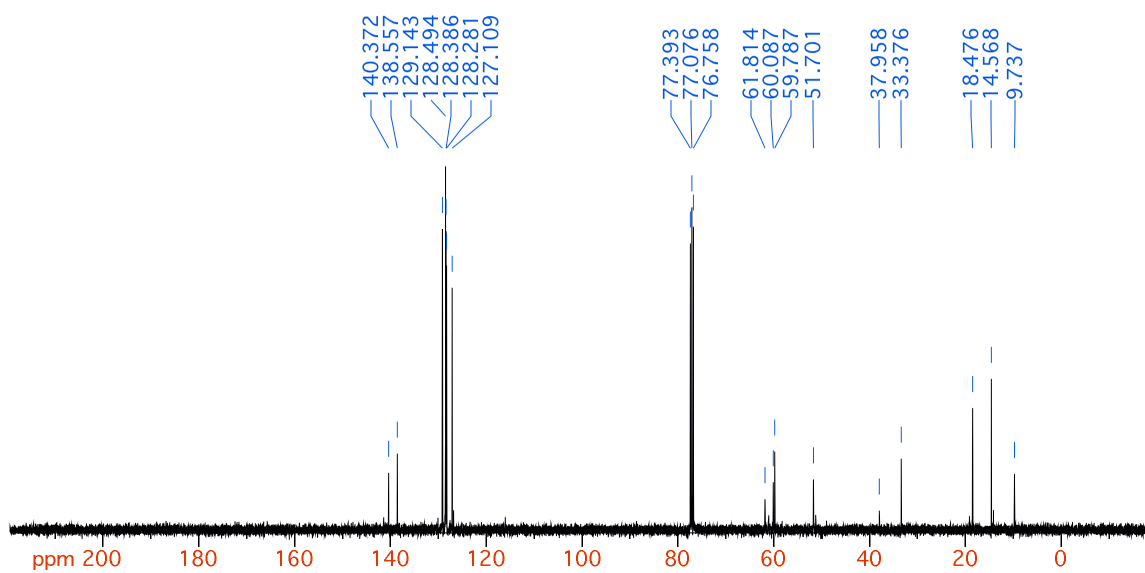
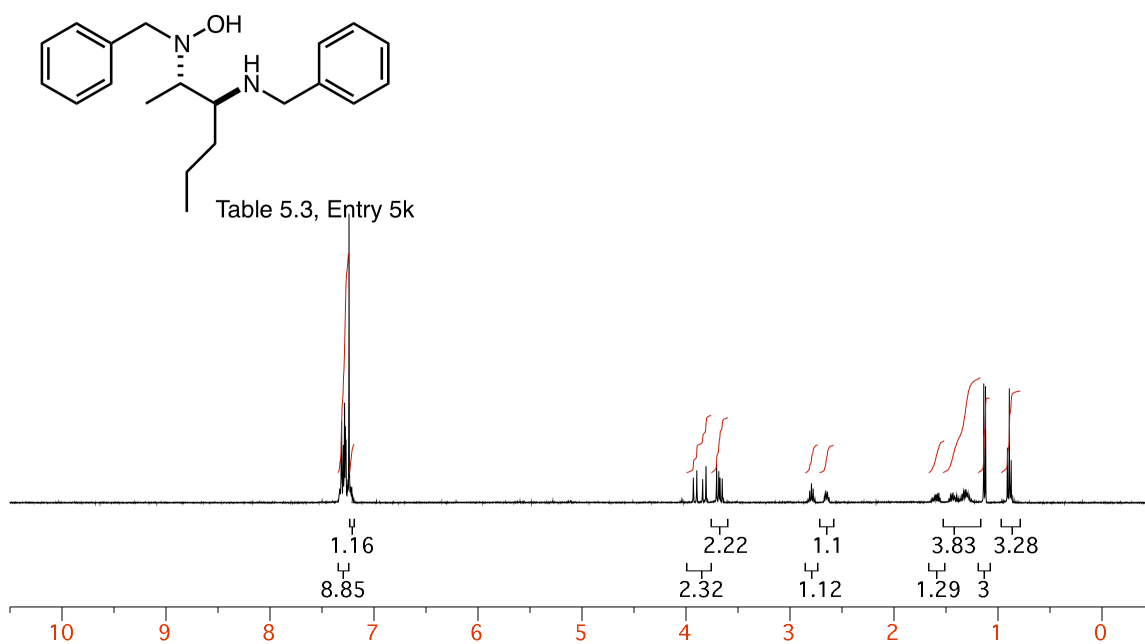
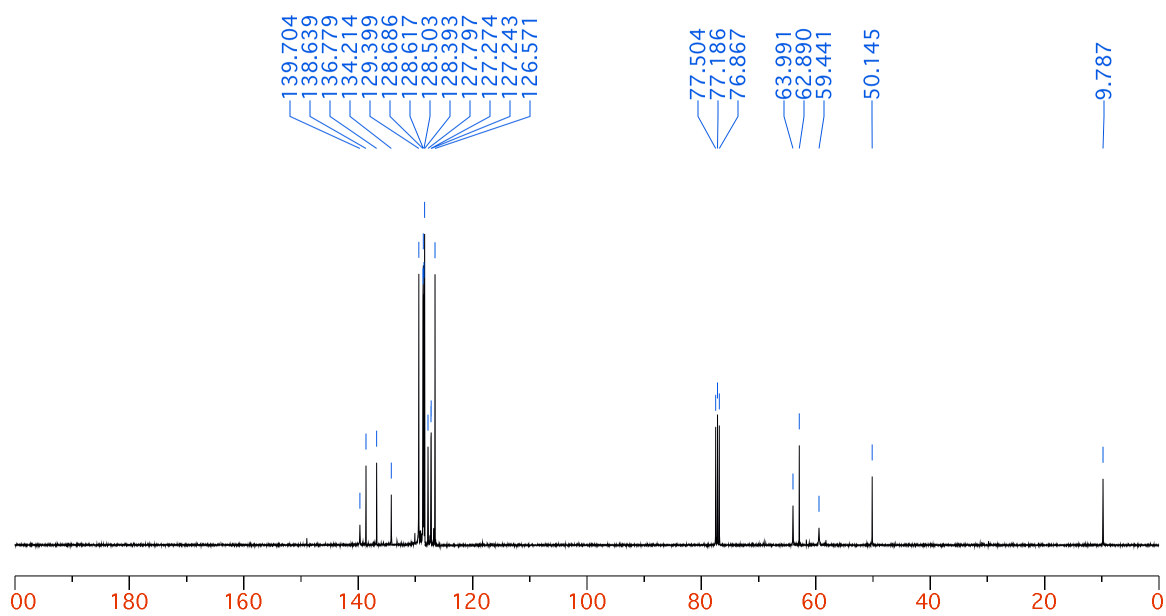
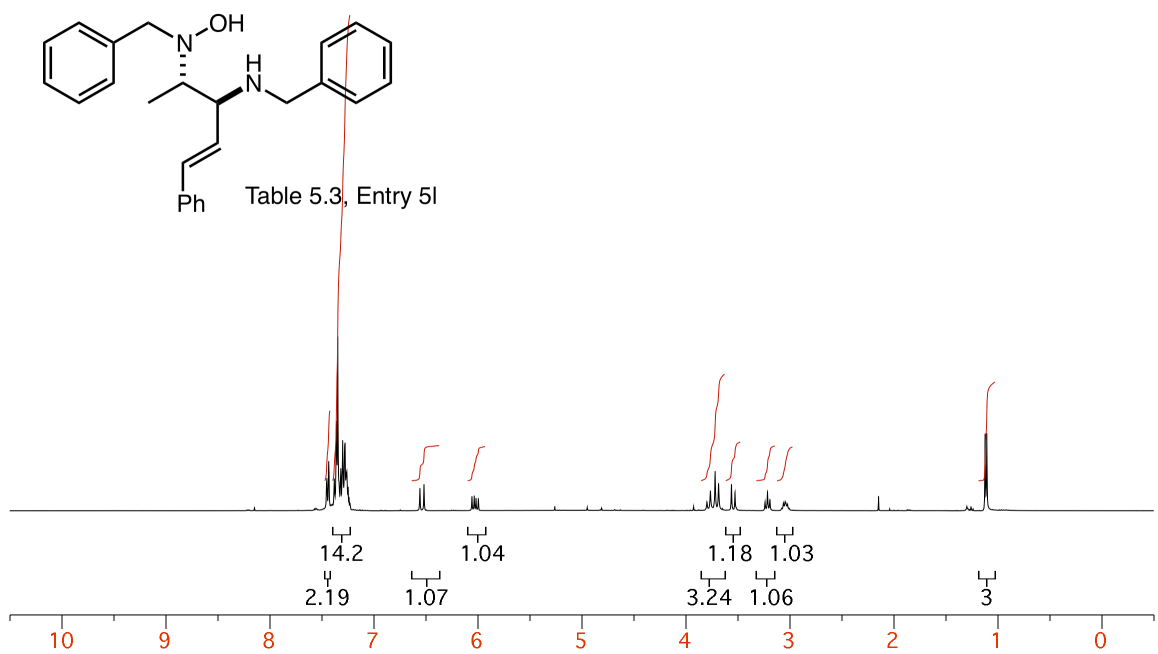


Table 5.2, Entry 5g









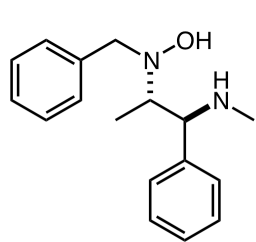
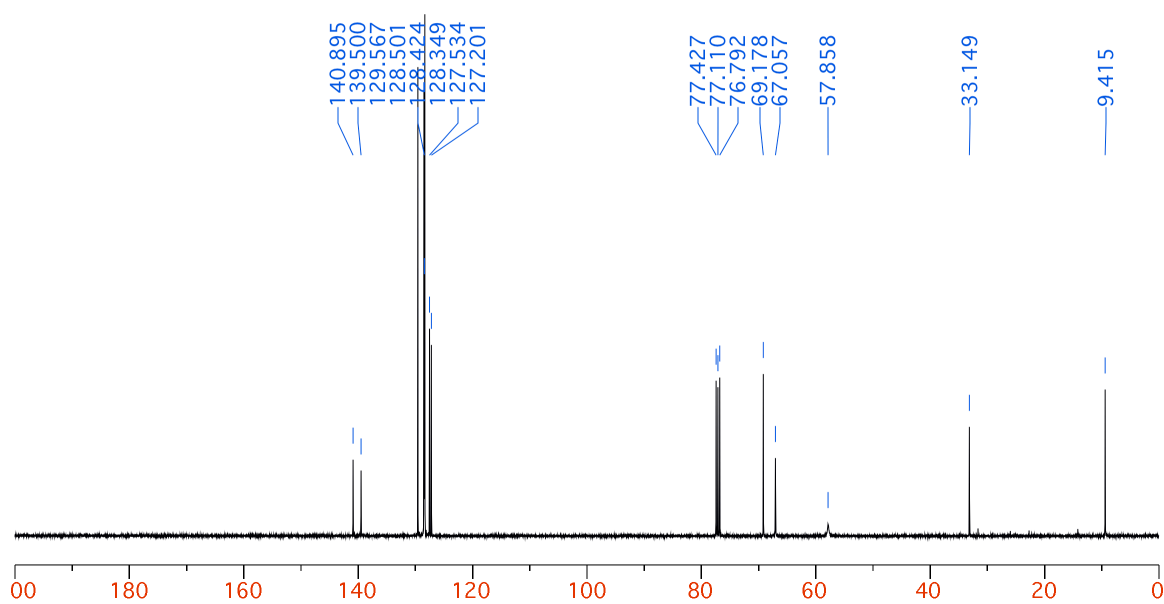
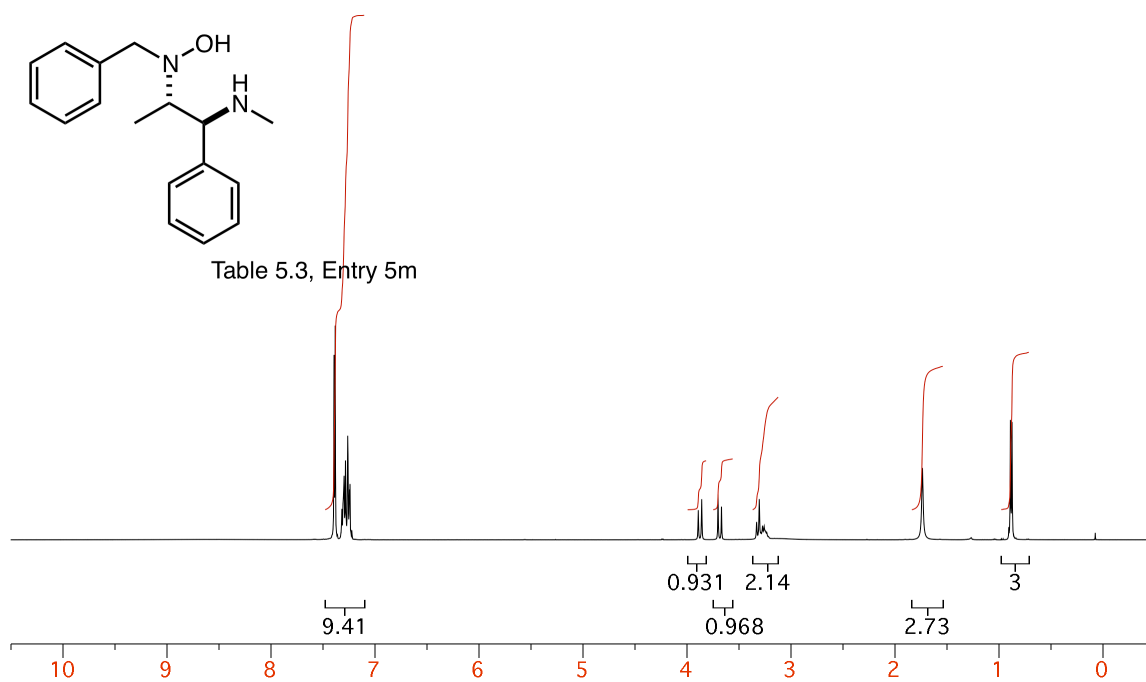


Table 5.3, Entry 5m



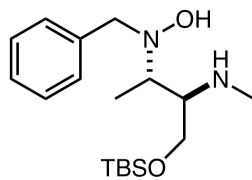
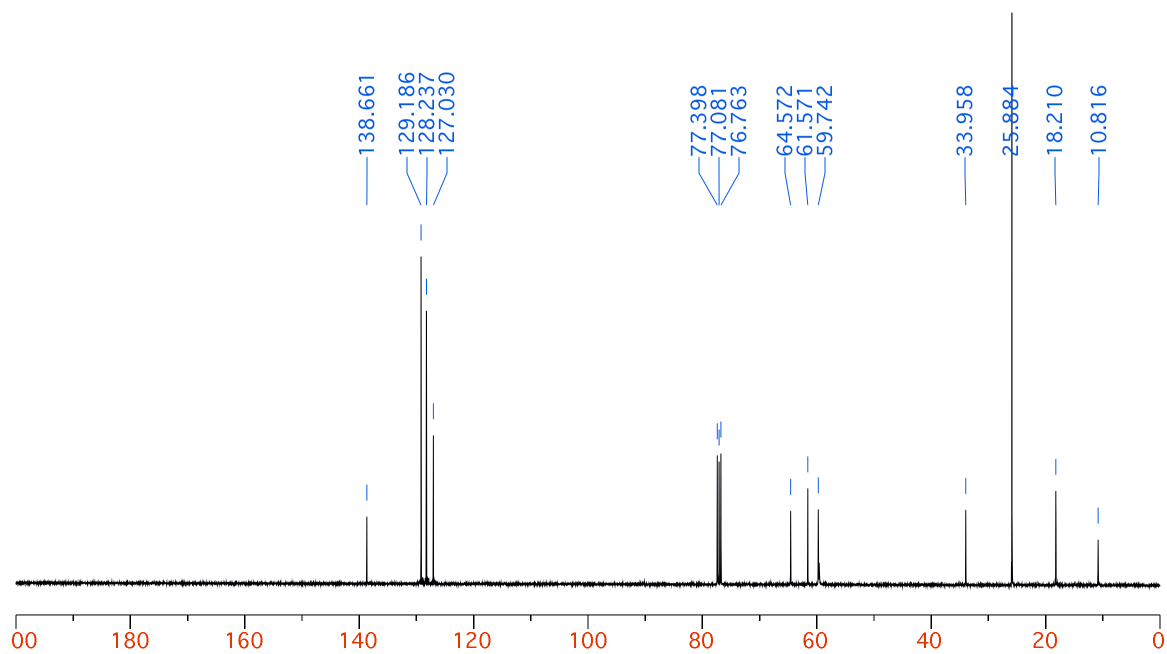
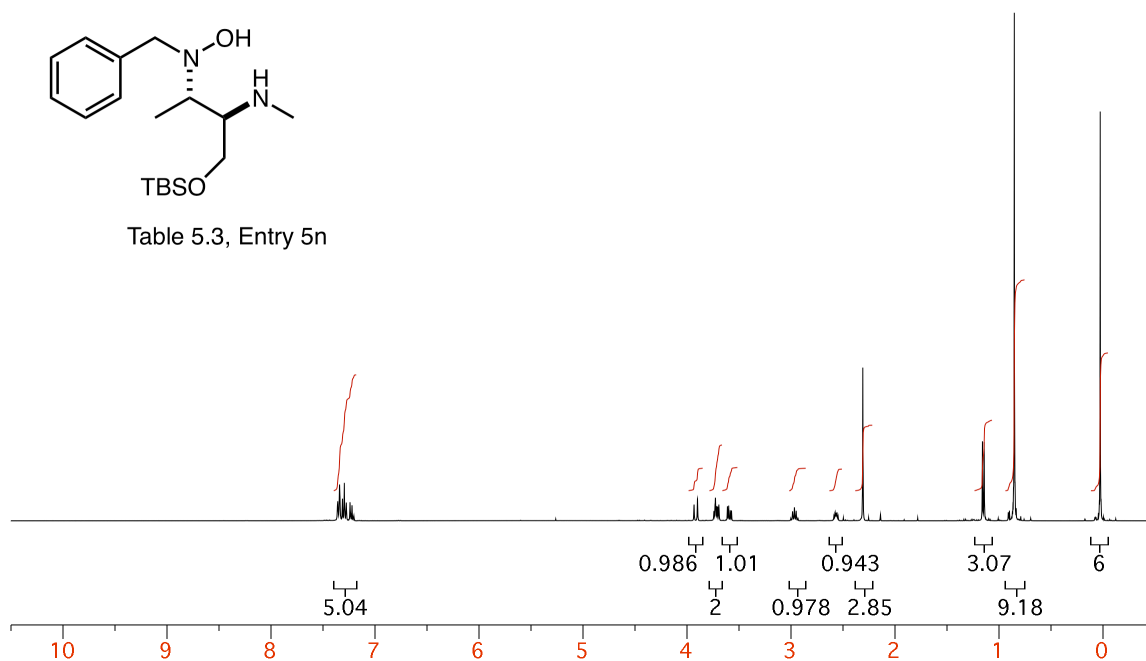
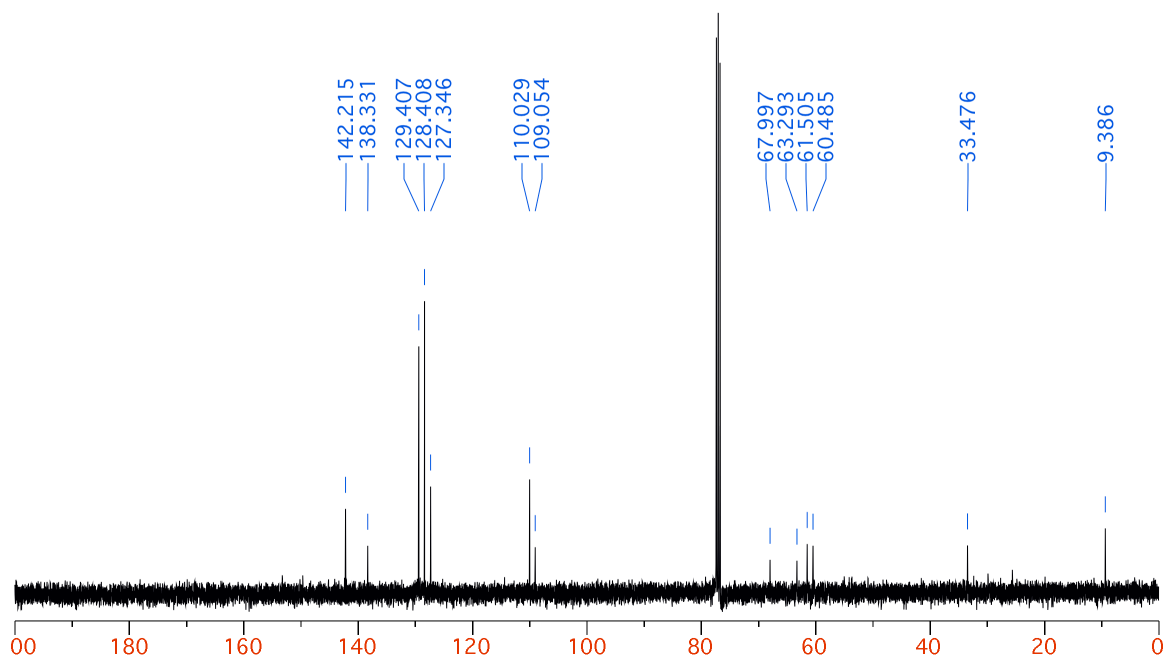
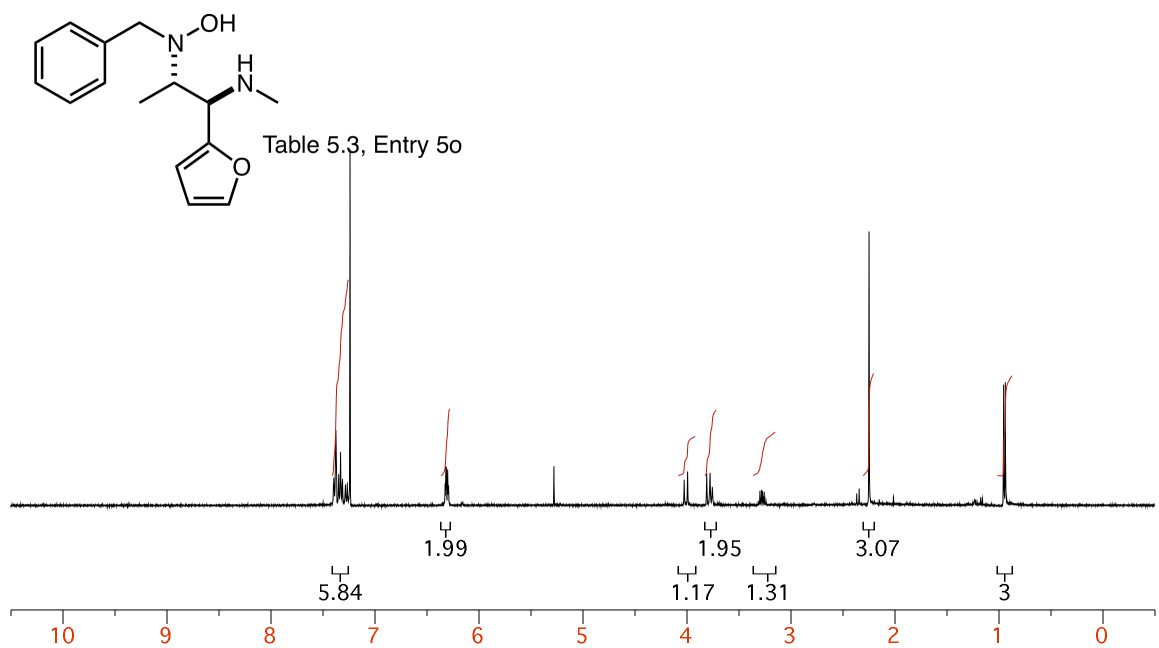
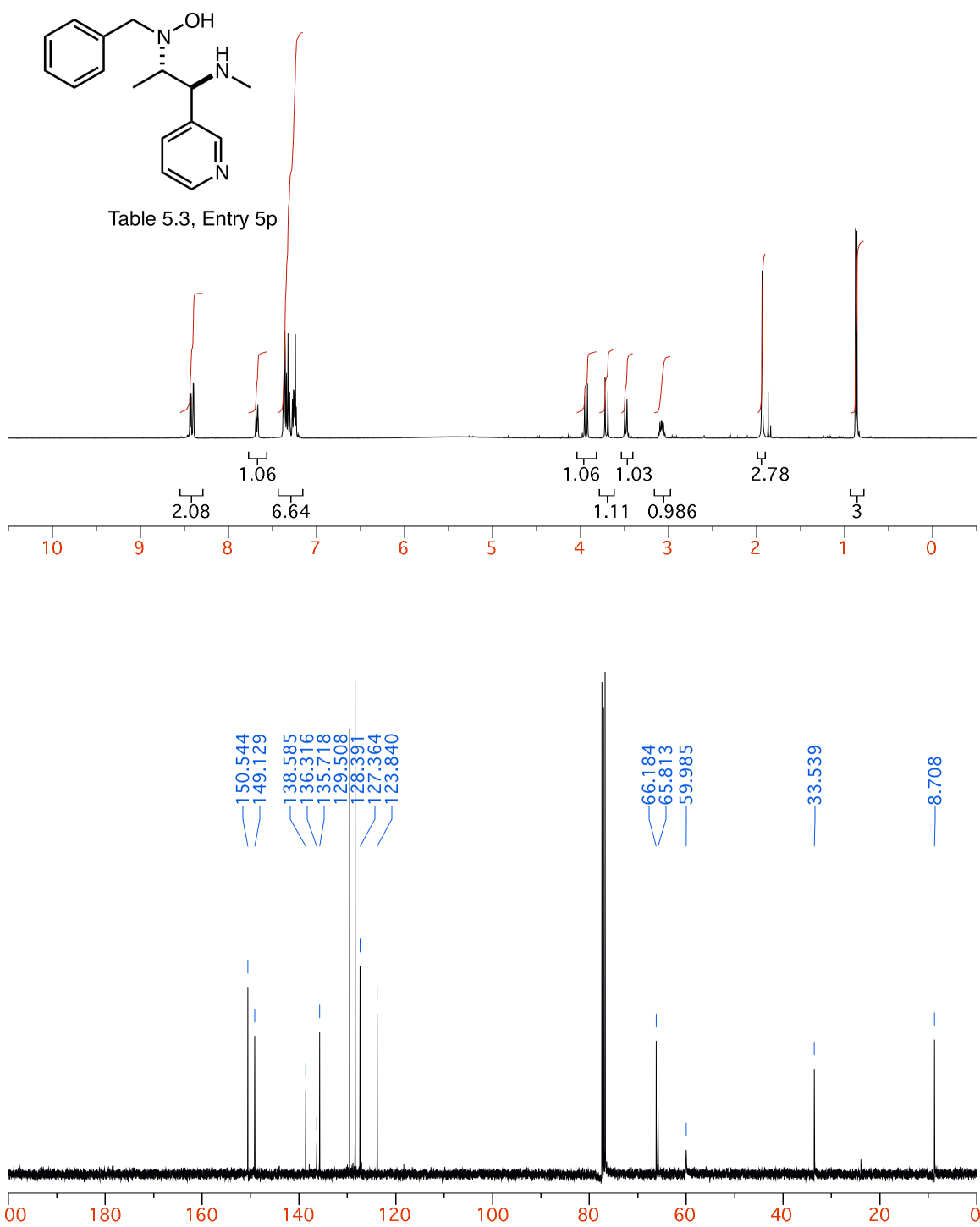


Table 5.3, Entry 5n







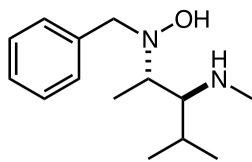
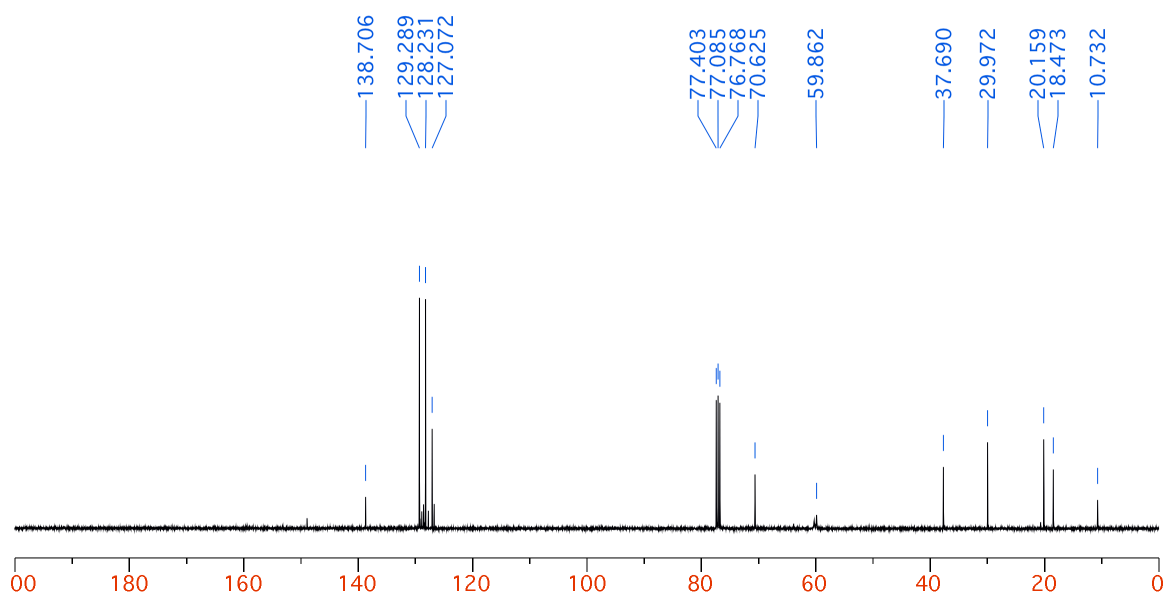
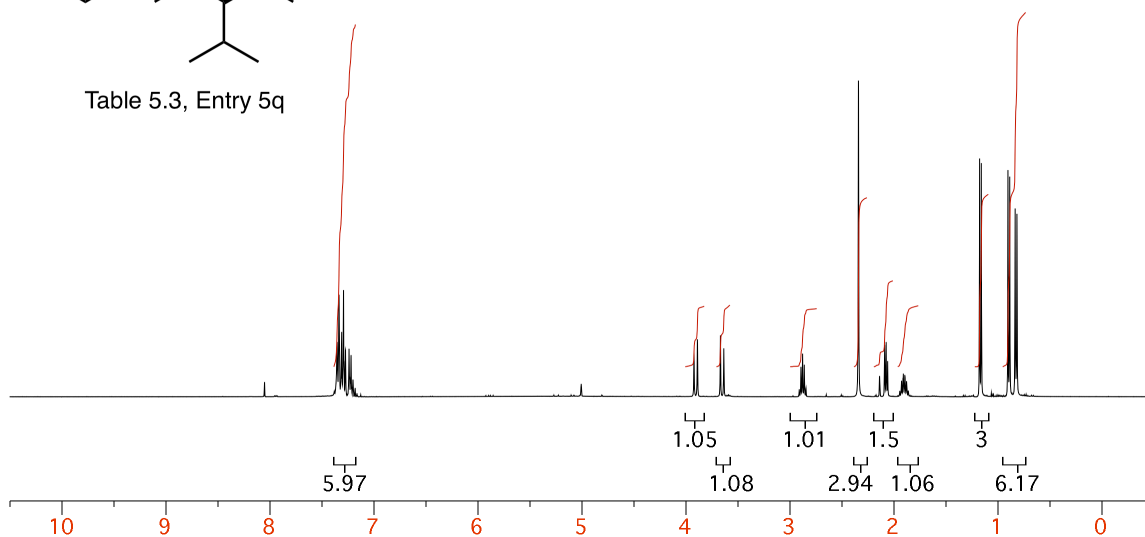
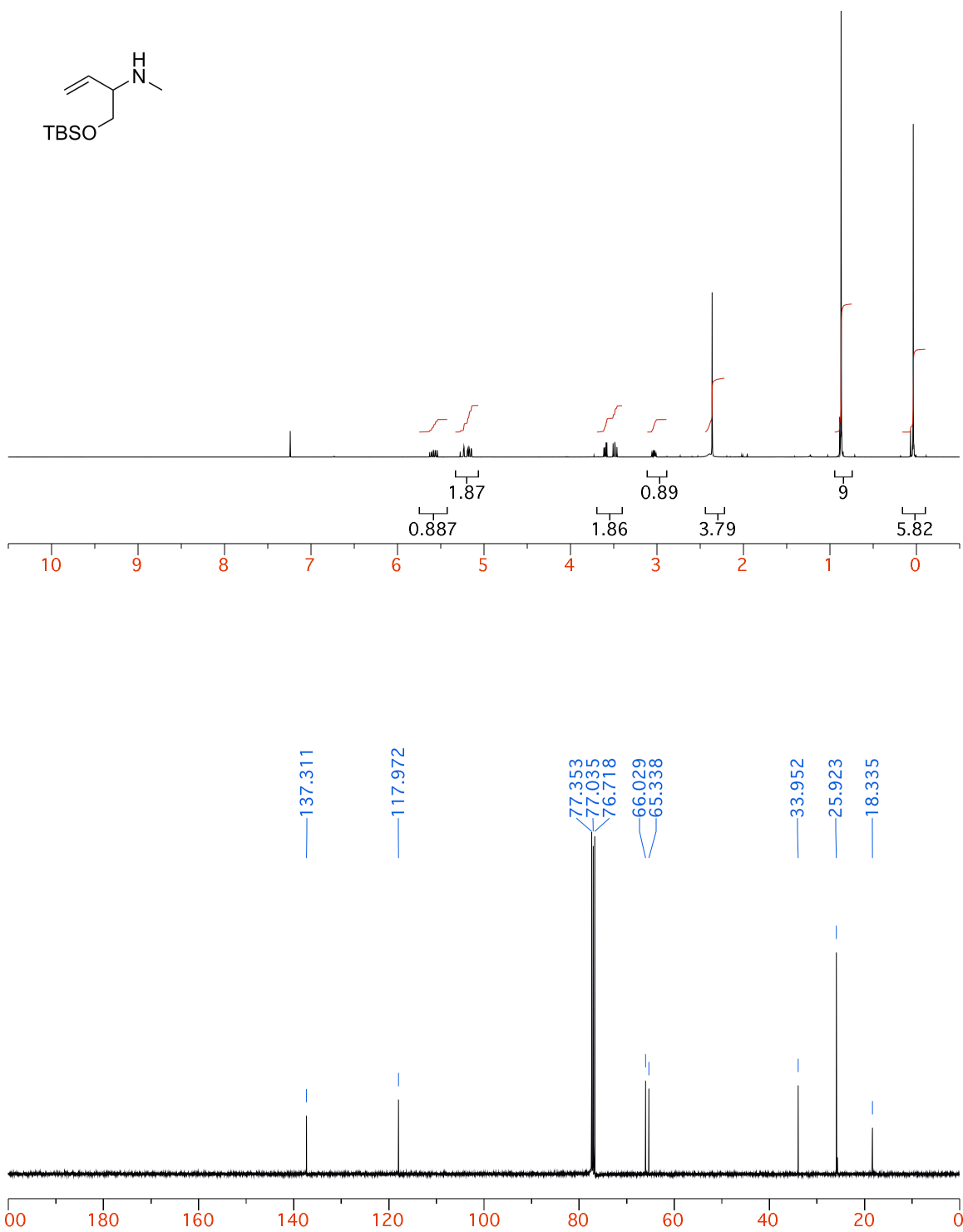
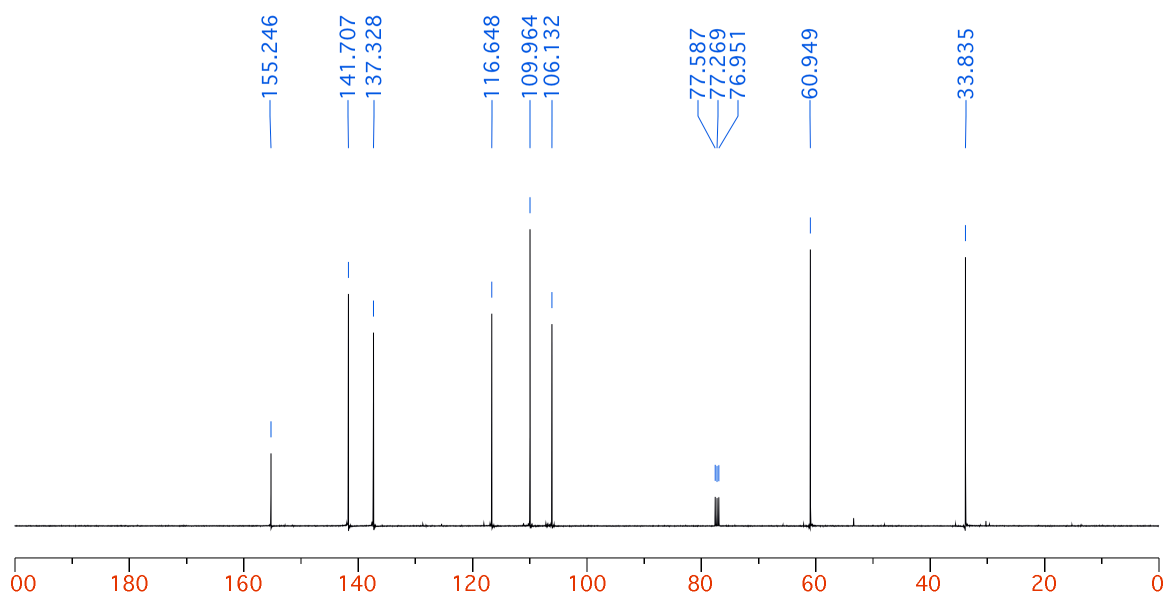
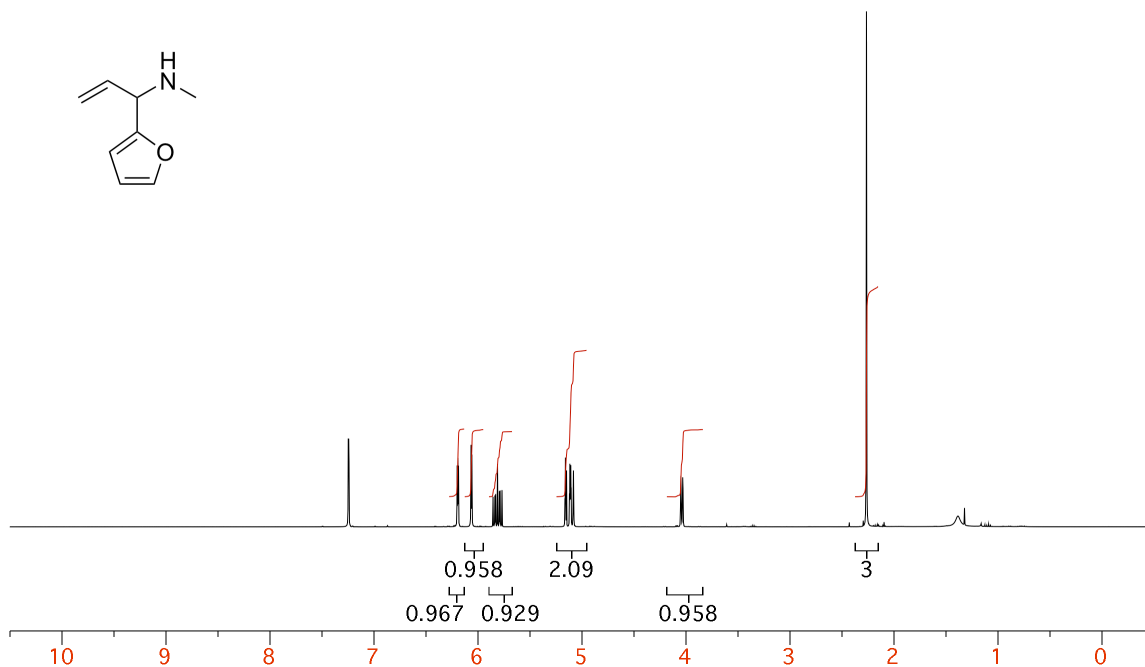
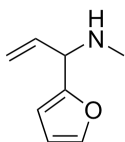
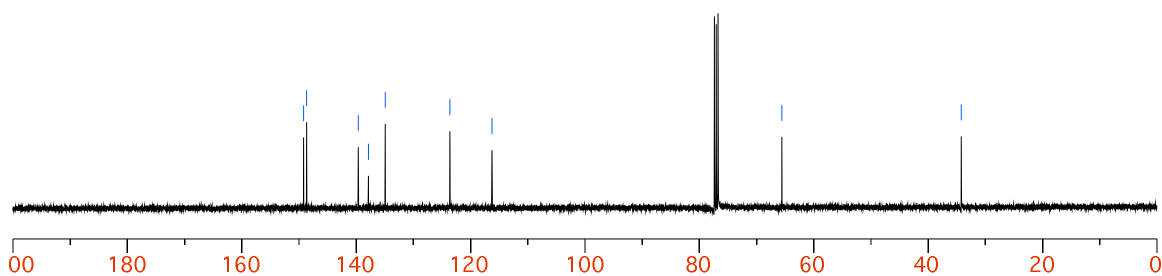
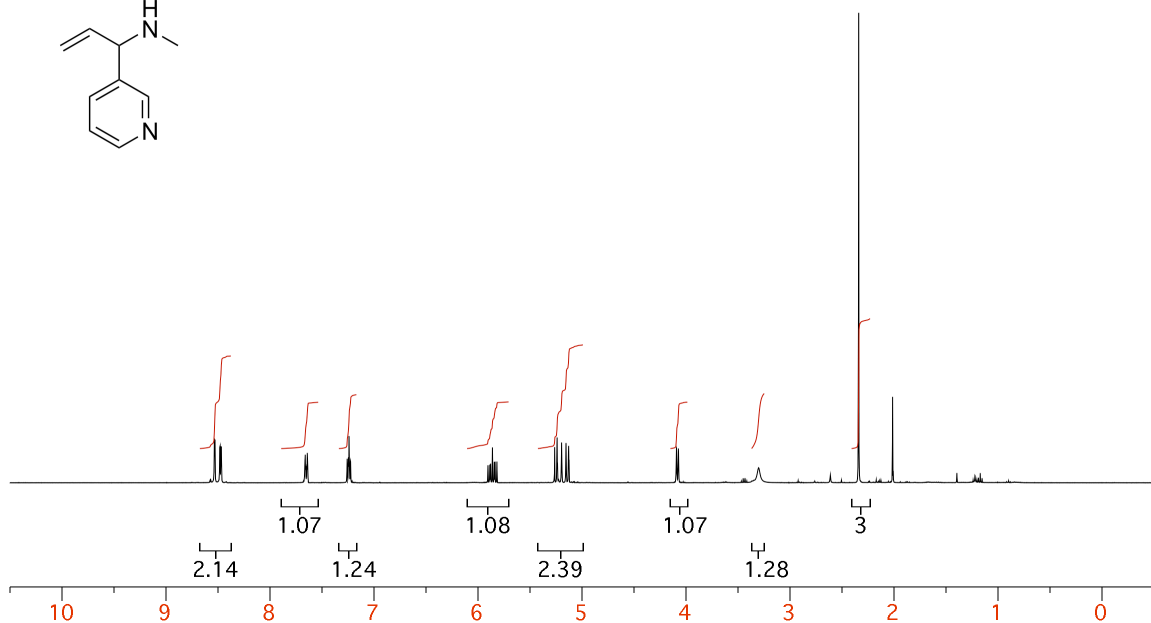
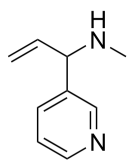


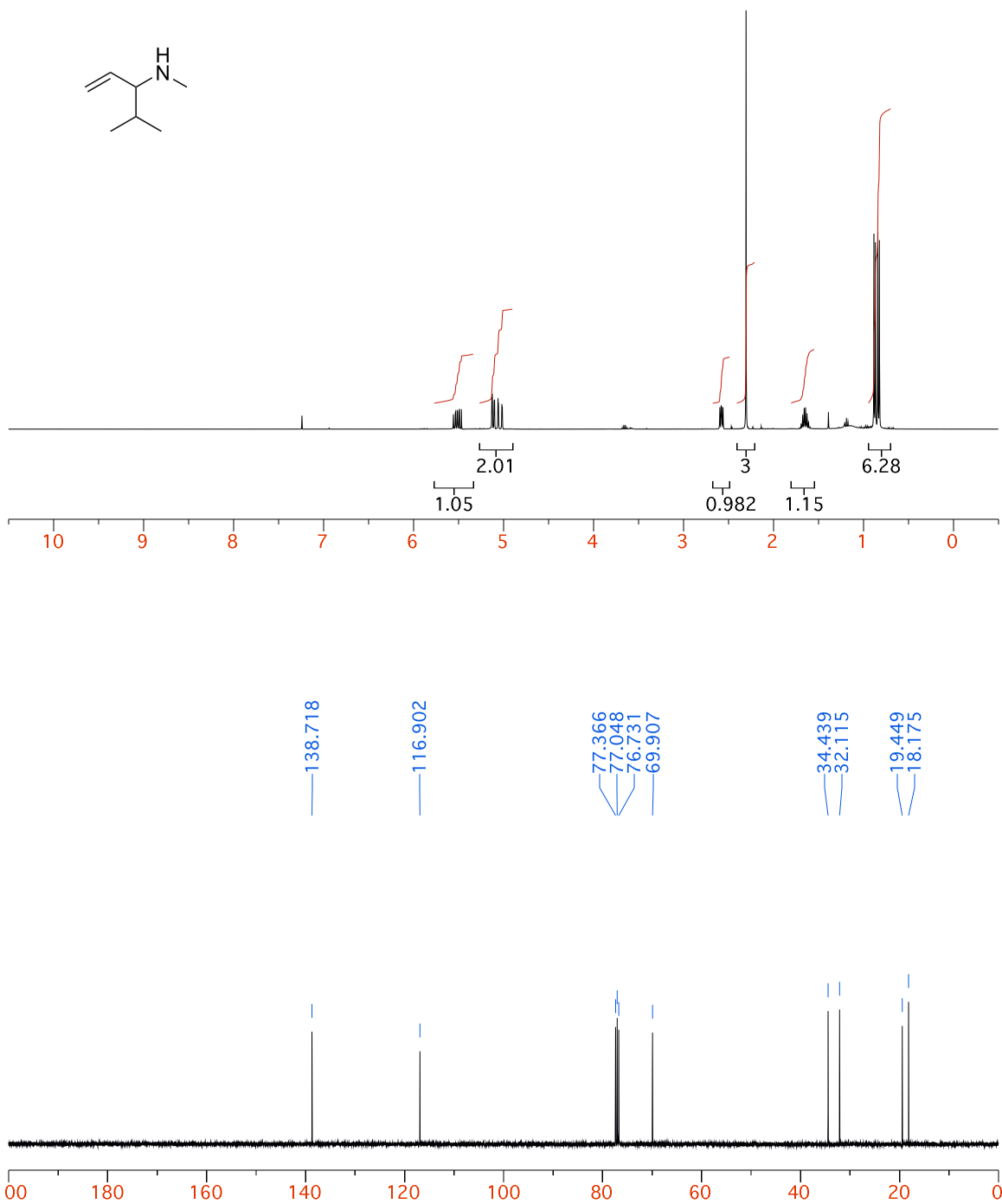
Table 5.3, Entry 5q

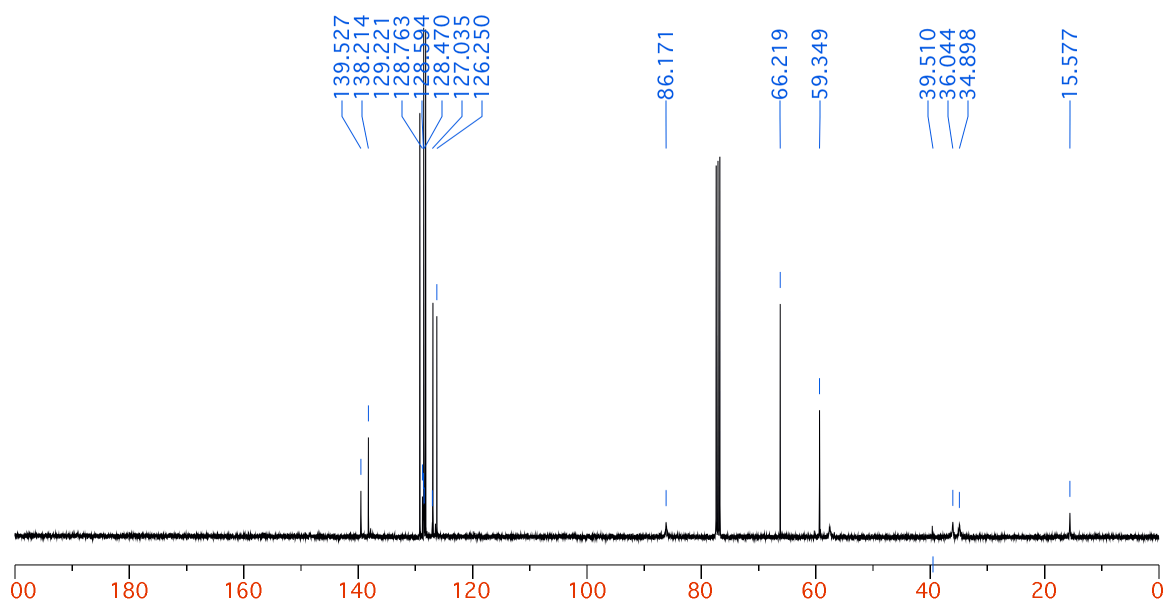
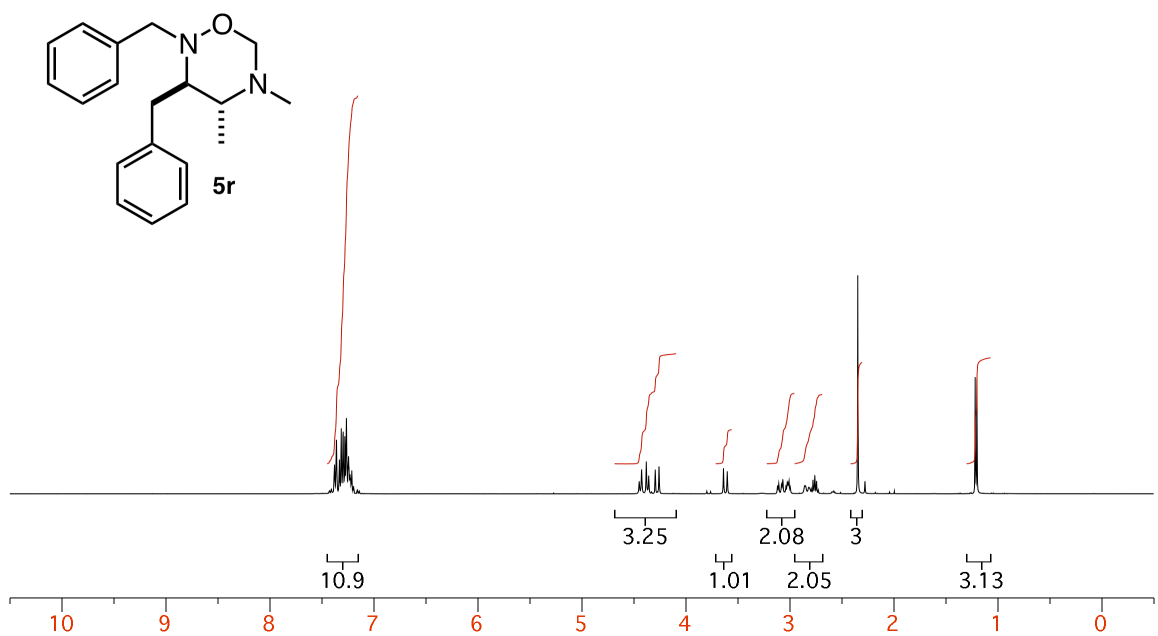


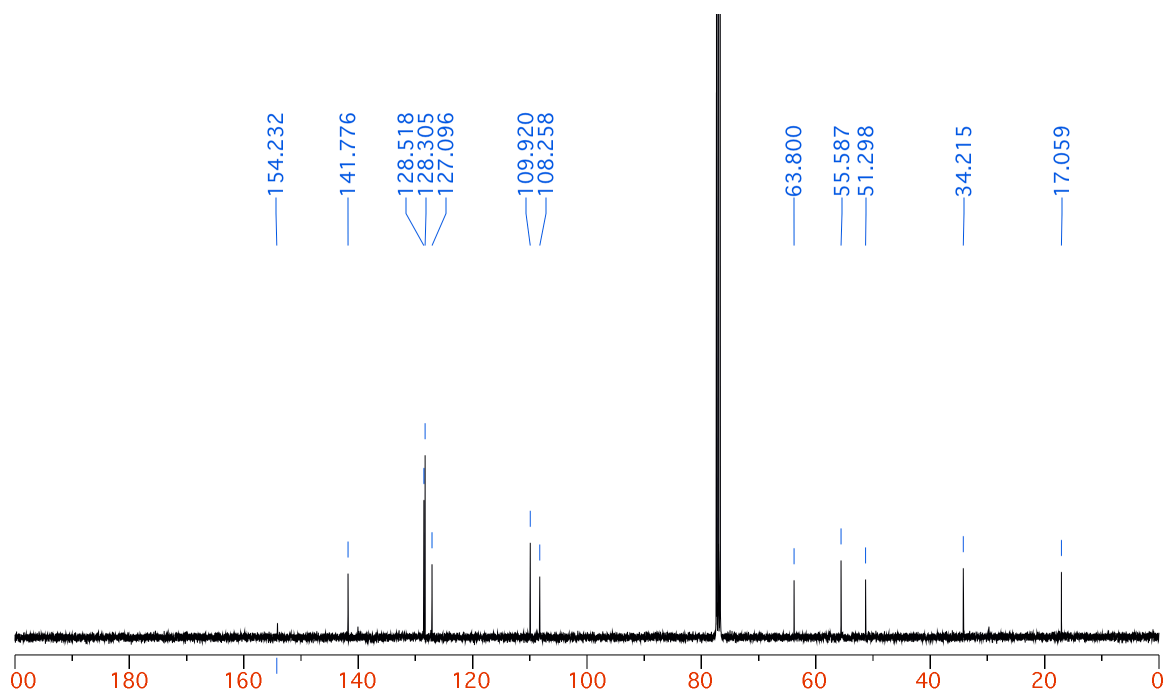
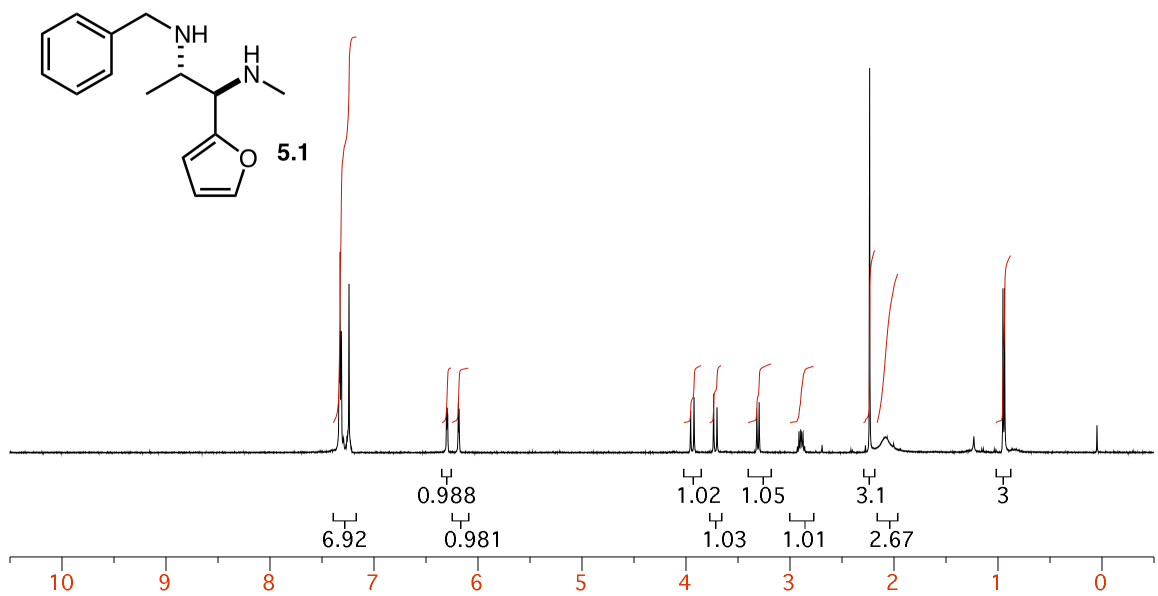


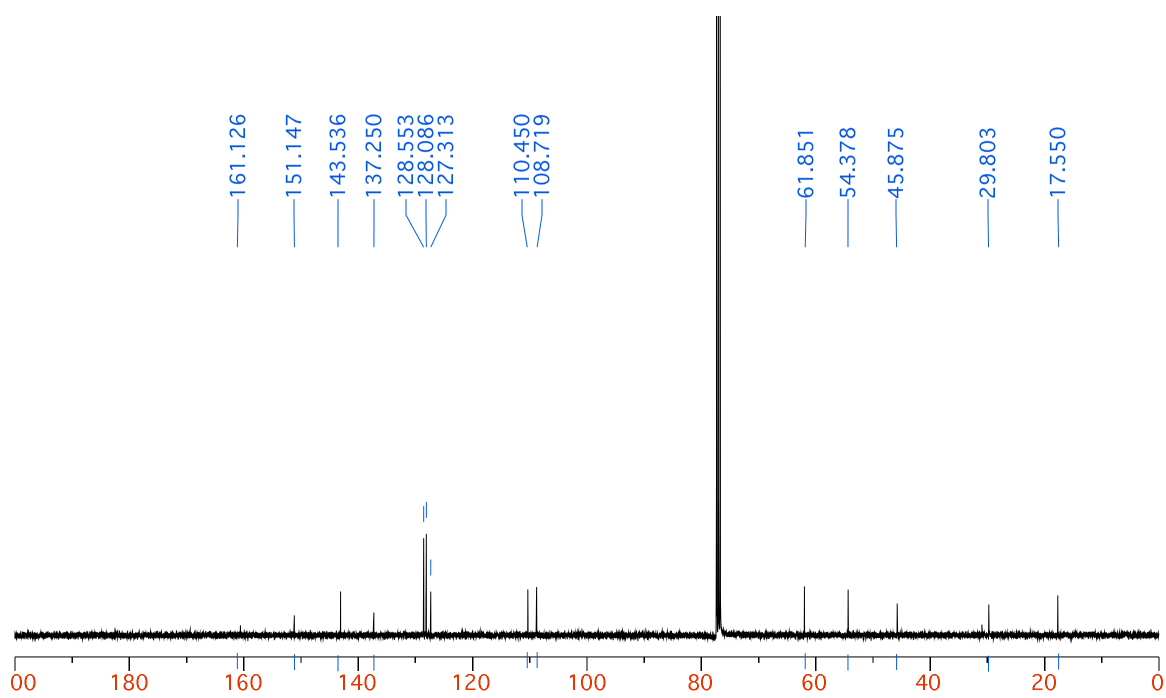
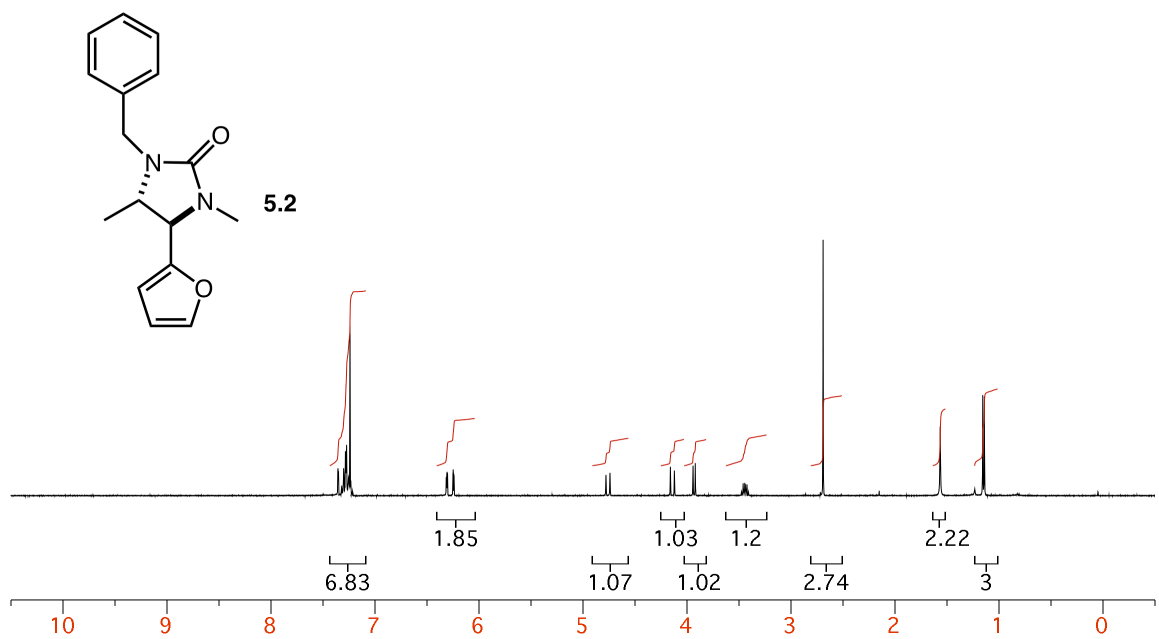


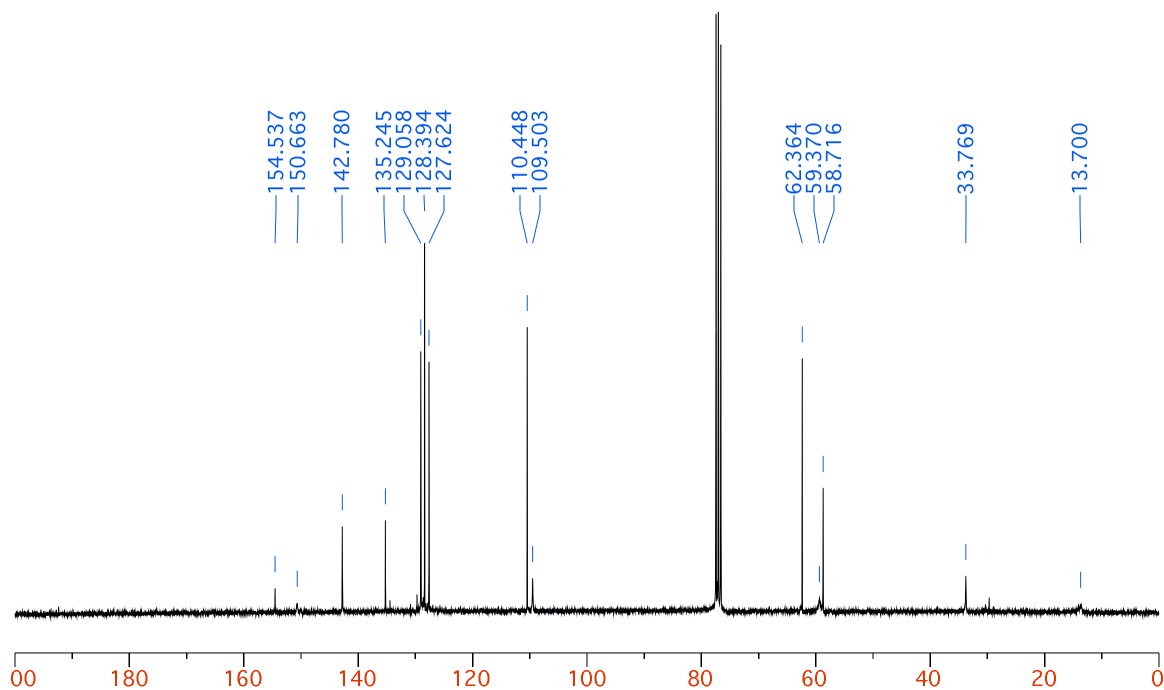
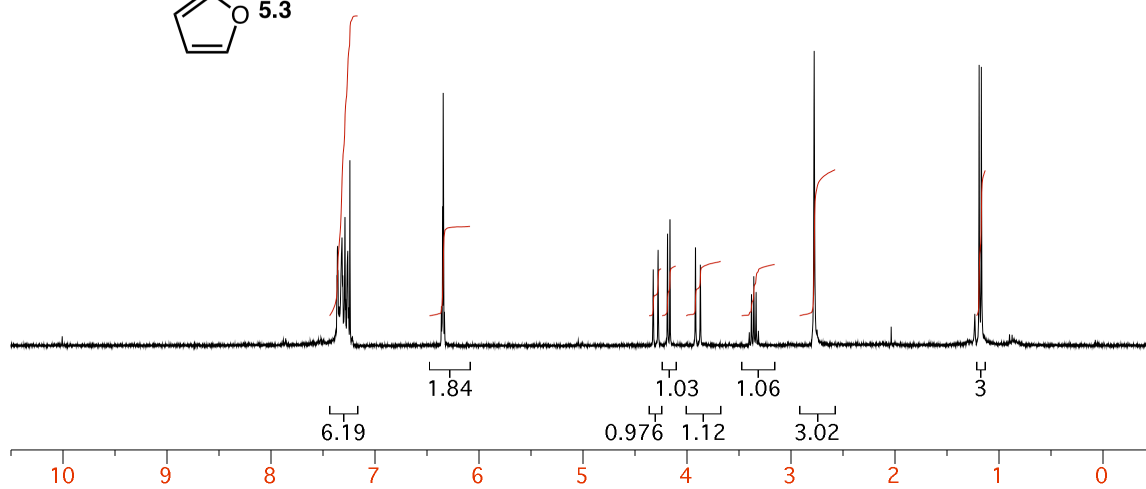












Appendix IV

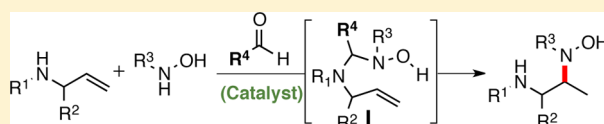
Catalysis through Temporary Intramolecularity: Mechanistic Investigations on Aldehyde-Catalyzed Cope-type Hydroamination Lead to the Discovery of a More Efficient Tethering Catalyst

Nicolas Guimond, Melissa J. MacDonald, Valérie Lemieux, and André M. Beauchemin*

Centre for Catalysis Research and Innovation, Department of Chemistry, University of Ottawa, 10 Marie-Curie, Ottawa, Ontario K1N 6N5, Canada

S Supporting Information

ABSTRACT: Mechanistic investigations on the aldehyde-catalyzed intermolecular hydroamination of allylic amines using *N*-alkylhydroxylamines are presented. Under the reaction conditions, the presence of a specific aldehyde catalyst allows formation of a mixed aminal intermediate, which permits intramolecular Cope-type hydroamination. The reaction was determined to be first-order in both the aldehyde catalyst (α -benzyloxyacetaldehyde) and the allylic amine. However, the reaction displays an inverse order behavior in benzylhydroxylamine, which reveals a significant off-cycle pathway and highlights the importance of an aldehyde catalyst that promotes a reversible aminal formation. Kinetic isotope effect experiments suggest that hydroamination is the rate-limiting step of this catalytic cycle. Overall, these results enabled the elaboration of a more accurate catalytic cycle and led to the development of a more efficient catalytic system for alkene hydroamination. The use of 5–10 mol % of paraformaldehyde proved more effective than the use of 20 mol % of α -benzyloxyacetaldehyde, leading to high yields of intermolecular hydroamination products within 24 h at 30 °C.



Key mechanistic data: • First order in aldehyde
• Two catalyst inhibition pathways were identified
• Hydroamination is the proposed rate determining step
• Destabilized aldehydes favor preassociation to form I

INTRODUCTION

Catalysis of intermolecular reactions is necessary to perform a variety of chemical transformations with high efficiency and control. Bifunctional catalysts and enzymes are particularly effective, as they execute this by combining the ability to perform substrate activation while favoring substrate preassociation. In many respects, the synthetic catalysts developed so far attempt to emulate the remarkable efficiency of enzymes in catalyzing intermolecular reactions (with rate accelerations as high as 10^{17}).¹ To achieve such high activity and control, enzymes preorganize reagents and consequently induce a “temporary intramolecularity” that minimizes the entropic penalty associated with intermolecular reactions. It is generally accepted that rate accelerations of 10^4 – 10^8 for 1 M reactants can be obtained for room temperature reactions involving such temporary intramolecularity.² From this perspective, it is not surprising that synthetic chemists have developed multiple transformations building on preassociation^{3,4} and that several families of bifunctional catalysts have emerged.⁵ In contrast, the catalysis of chemical transformations *only* through temporary intramolecularity or by building high effective concentrations of reagents has received less attention from the synthetic community.⁶ Indeed, simple catalysts operating only through this pathway are rare, perform relatively simple synthetic transformations, and highly efficient examples of enantioselective catalysis have not been reported.

A limited number of examples of catalysis induced only through temporary intramolecularity have been reported using carbonyl catalysts.^{6,7} This type of catalysis was developed

mainly for hydrolysis reactions, and the original work of Commeyras et al. on the hydrolysis of α -aminoamides using formaldehyde is an illustrative example (Figure 1).⁸ In this reaction, the amine moiety of an α -aminoamide reacts with formaldehyde to transiently generate a hemiaminal. The alcohol portion of this hemiaminal then undergoes an intramolecular addition onto the amide moiety. Hydrolysis of the resulting intermediate regenerates the formaldehyde catalyst and yields the corresponding amino acid. Several related reactions building on temporary intramolecularity were developed: CO₂ and aldehyde promoted ester hydrolysis,^{9,10} ketone mediated α -thioamide hydrolysis,¹¹ and ketone and aldehyde catalyzed nitrile hydration.¹² However, common to all these hydrolysis reactions is the use of stoichiometric amounts of a carbonyl catalyst, even though turnover should occur according to the proposed mechanism. This highlights the underdevelopment and opportunities associated with tethering catalysis: simple systems achieving high catalytic efficiency (catalyst turnover number and rates) remain to be established. In addition, highly stereoselective variants and the application of this strategy to complex reactions have barely been studied.¹³

Building on these reports and, most importantly, on the work of Knight et al. on the synthesis of cyclic 1,2-diamine motifs from nitrones and allylamines (Figure 1),¹⁴ we recently disclosed that simple aldehydes catalyze intermolecular Cope-type hydroaminations^{15,16} *solely* via temporary intramolecularity.

Received: April 5, 2012

Published: September 12, 2012



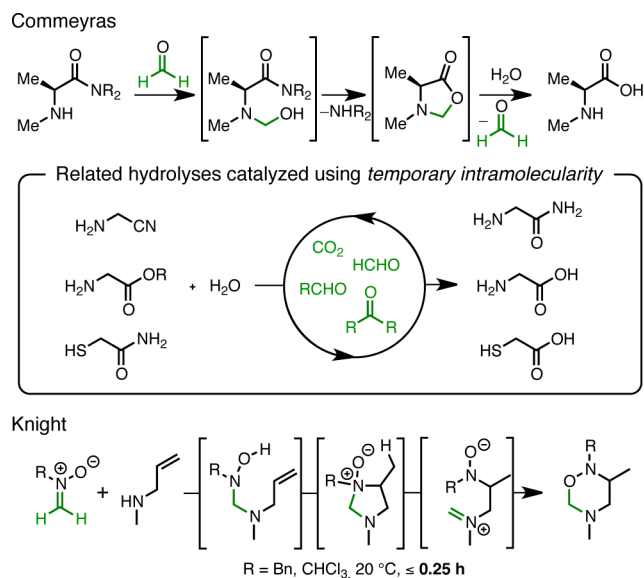


Figure 1. Selected reports of Commeyras and Knight using formaldehyde.

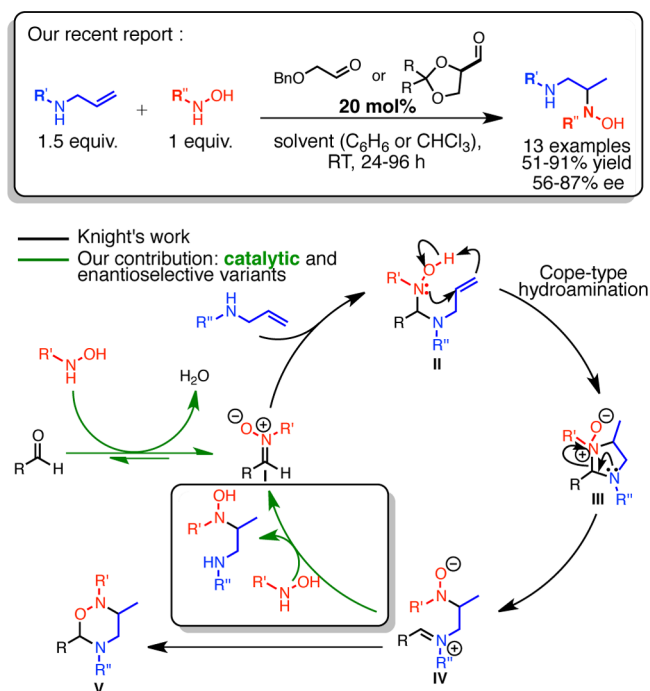


Figure 2. Intermolecular Cope-type hydroamination using aldehydes as tethering catalysts.

ity. As illustrated in Figure 2, the reaction proceeds via the key in situ formation of a mixed aminal (II), which allows for a facile intramolecular hydroamination event.¹⁷ As opposed to more traditional tethering strategies,¹⁸ this catalytic method does not require additional synthetic steps for the installation and cleavage of the tether. It also allows room temperature reactivity with a minimal excess of one of the reaction components. Additionally, it enables the formation of enantioenriched molecules through efficient transfer of stereochemical information using a chiral aldehyde catalyst.¹⁹ Given the lack of precedence for such complex catalytic tethering systems (Figure 2) and our desire to achieve higher efficiency and enantioselectivity, we initiated mechanistic studies to probe

the catalytic cycle of this transformation. Herein we present a complete picture of this catalytic cycle, including information on the rate-determining step and catalyst inhibition pathways. We also report a system that builds on this information to perform hydroamination reactions with higher catalytic efficiency than previously reported by using only 5 mol % of paraformaldehyde as precatalyst.

RESULTS AND DISCUSSION

Our interest in the development of catalytic tethering reactivity stems from ongoing efforts directed toward intermolecular Cope-type hydroamination reactions of alkenes,²⁰ which typically require forcing conditions and catalysis to occur. Currently, these reactions show limited applicability: biased alkenes are generally required and highly enantioselective variants are rare. As previously observed,^{20b} strained alkenes and vinylarenes (e.g., norbornene and styrene) require heating at elevated temperatures (90 and 140 °C, respectively), and little to no reactivity is detected with unbiased alkenes. Consequently, our efforts were naturally drawn to systems where preassociation or temporary intramolecularity could help to obtain increased reactivity. Indeed, room temperature Cope-type hydroamination is typically efficient in five-membered ring systems.¹⁵ The challenge thus resided in the identification of a practical catalytic tethering method.

Our inspiration toward tethering catalysis was drawn from a key precedent from Knight et al. involving the reaction of various nitrones with allyl amines.¹⁴ In this system, 1,2-nucleophilic addition of allylic amines triggers a one-pot sequence featuring Cope-type hydroamination, aminal opening, and ring closure (Figures 1 and 2). The products of this sequence were 1,2,5-oxadiazinanes or cyclic derivatives of vicinal diamines. From this well-developed work, we hypothesized that it would be possible, using a substoichiometric amount of an appropriate aldehyde, to achieve catalyst turnover via a transimination step as shown in Figure 2. Encouragingly, extensive screening of carbonyl compounds revealed that α -oxygenated aldehydes were competent catalysts for this transformation (see Table 1 for representative data). Our working hypothesis is that inductively destabilized aldehydes favor thermodynamically the formation of aminals, which likely is an important feature for catalysts operating via temporary intramolecularity.

Table 1. Selected Examples of Aldehydes Tested for Catalytic Activity^a

		Catalyst 20 mol% C ₆ D ₆ RT, 24 h		4a	
1a	2a				
3a 2%	3b ^b 5%	3c 11%	3d ^c 11%	3e 4%	
3f 50%	3g 1%	3h 33%	3i 71%		

^aConditions: 1a (1.5 equiv), 2a (1 equiv), catalyst (20 mol %), C₆D₆, rt, 24 h. ^bUsed as a 40% solution in water. ^cUsed as the hydrate.

Although the prototypical catalytic cycle was based on literature precedents from the work of Knight et al.,¹⁴ the catalyst resting state and potential inhibition pathways were still unknown at this point. Further experiments were thus conducted to identify the rate-determining and kinetically significant steps of this process. To do so, the reaction of *N*-allylbenzylamine **1b** (1.5 equiv) with *N*-benzylhydroxylamine **2a** using α -benzyloxyacetaldehyde **3i** (20 mol %) as catalyst was investigated. The typical reaction conditions employed (1 M in benzene, room temperature) are the result of a thorough optimization previously described.^{17a}

At the outset, the order of every component implicated in the reaction was evaluated (Figure 3). It was first determined from the log plots of initial rate versus the initial catalyst

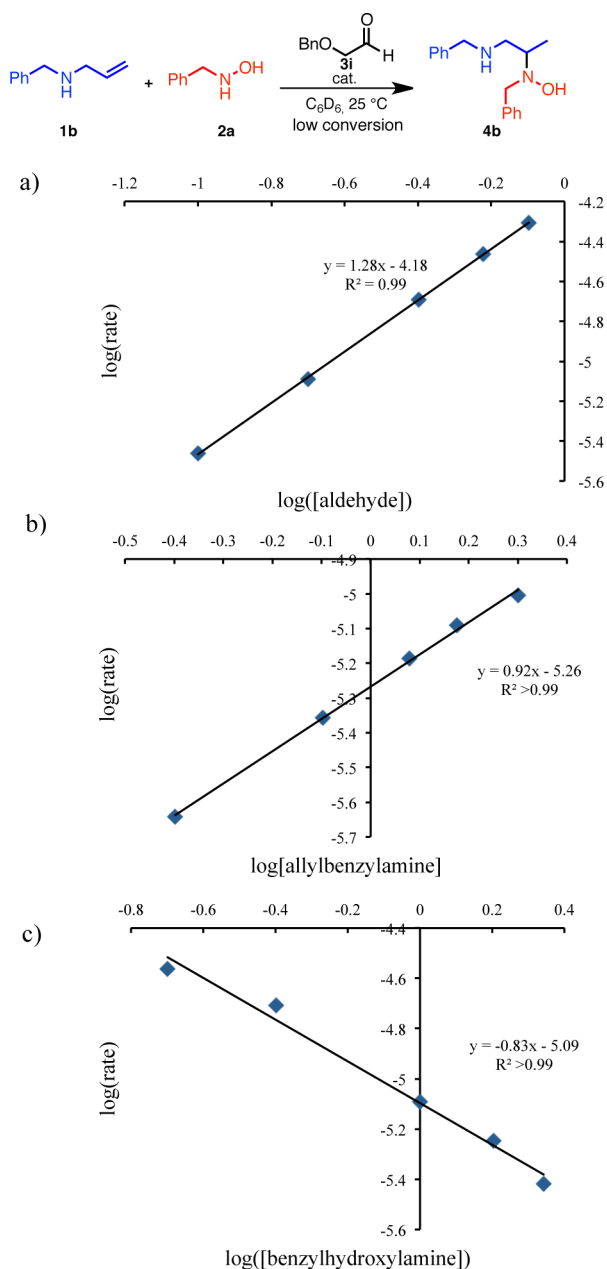


Figure 3. Initial rate dependence on the concentration of the reaction components showing (a) first-order dependence in organocatalyst (**3i**), (b) first-order dependence in allylbenzylamine (**1b**), and (c) inverse-order dependence in benzylhydroxylamine (**2a**).

concentration that the reaction is approximately first-order in aldehyde (Figure 3a). This is well in agreement with a catalytic cycle where only one molecule of aldehyde is involved prior to or at the rate-determining step. Then, plotting the log of the initial rate of the reaction versus the log of the initial allylbenzylamine concentration also revealed a first order-behavior (Figure 3b). This is again consistent with a single molecule of allylamine being involved before or at the rate-limiting step. Next, the order of *N*-benzylhydroxylamine was probed. Interestingly, a slope of -0.83 , indicative of an inverse order, was found for this reaction component (Figure 3c). To gain further insight into the reaction mechanism and explain this result, the title reaction was conducted in a ^1H NMR probe using C_6D_6 as solvent (Figure 4). From this experiment, it was

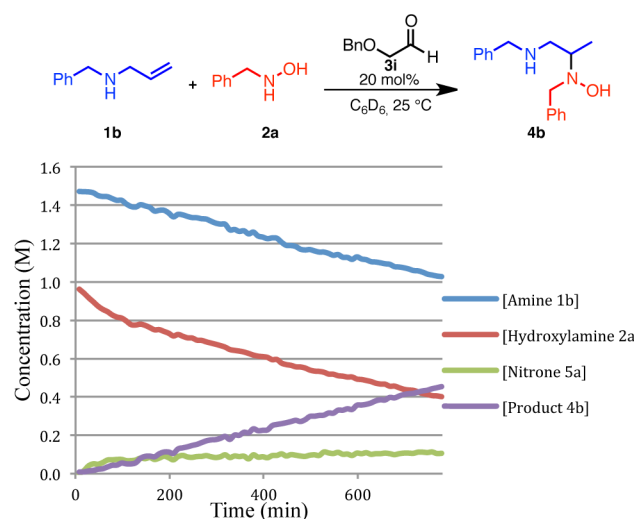


Figure 4. Representative reaction profile over 13 h for a 1 M reaction. Conditions: **1b** (0.75 mmol, 1.5 equiv), **2a** (0.5 mmol, 1 equiv), and **3i** (0.1 mmol, 20 mol %) in C_6D_6 (1 M).

determined that nitron formation occurs rapidly upon addition of the reagents. The concentration of this intermediate can easily be monitored as the reaction proceeds. It proved to be quite steady while still displaying a very slight increase over time.²¹ Of note, the product was formed at a constant rate for the 13 h period monitored (the ^1H NMR yield of product formation was 45% after 13 h). This suggests that there is little to no product inhibition under the reaction conditions. This can also be well-rationalized by the fact that the hydroxylamine becomes *N,N*-disubstituted as the alkene undergoes hydroamination. Thus, the product cannot interfere with nitron formation.

Taken together, these results are consistent with initial formation of nitron **5a** (observed by ^1H NMR) followed by the competitive addition of either *N*-benzylhydroxylamine or *N*-allylbenzylamine (Figure 5). The addition of *N*-benzylhydroxylamine affords an unreactive aminal (**6a**).²² This off-cycle pathway is (fortunately) reversible. On the other hand, the addition of *N*-allylbenzylamine leads to the formation of a key mixed aminal (**7a**) that can undergo the critical Cope-type hydroamination step. Of note, the addition of water to the reaction did not slow down the catalytic process. This rules out the competitive addition of water on the nitron (or other intermediates) as a potential catalyst deactivation pathway(s).

To get a better picture of the association processes displayed in Figure 5, the equilibrium constants K_A and K_B were

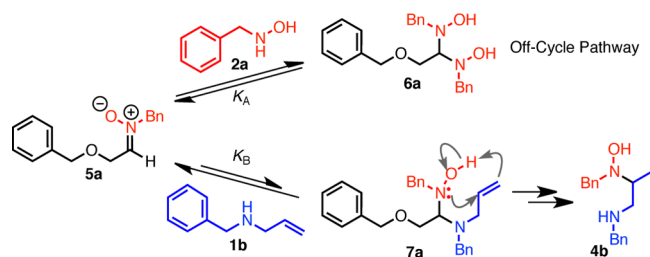
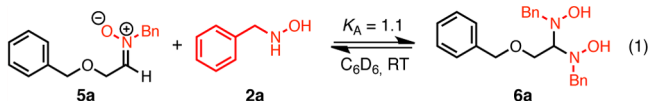
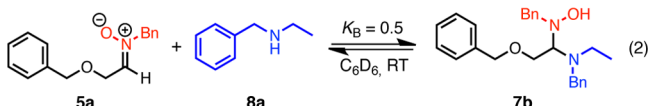


Figure 5. Competing 1,2-addition of **2a** and **1b** on **5a**, which explains the inverse order behavior in **2a**.

measured independently. The value obtained for the reaction of nitron **5a** with benzylhydroxylamine **2a** forming the symmetrical adduct **6a** is 1.1 (eq 1). This constant suggests that the

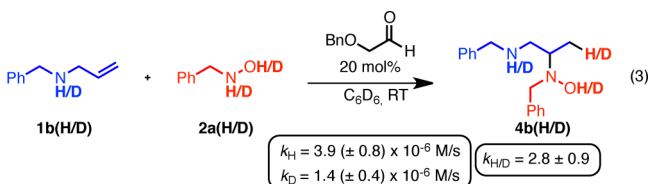


equilibrium is slightly shifted toward the symmetrical adduct **6a** under the initial reaction conditions. It also accounts for a concentration of nitron a little under 0.1 M during the first hours of the reaction. Experiments to probe the value of the equilibrium constant K_B were also conducted. Since we needed to prevent the Cope-type hydroamination, *N*-benzylethylamine **8a** was used in place of **1b**. A value of 0.5 was obtained for this constant (eq 2). Overall, these values are consistent with the



symmetrical adduct **6a** being the resting state of the catalyst at low conversion and the mixed aminal being a thermodynamically disfavored species.²³

Deuterium kinetic isotope effect (DKIE) experiments were also conducted to probe the nature of the rate-determining step. All exchangeable protons of both starting materials were replaced by deuterium and the initial rate of the reaction was measured. As shown in eq 3, a primary DKIE of 2.8 ± 0.9 was



obtained for this reaction. If we assume the proton transfer steps to have a low energy barrier, this result suggests that hydroamination is the rate-determining step of this catalytic process.

Toward the turnover-enabling step of the originally proposed catalytic cycle (Figure 2), two competing reactions can occur. The first one, which is desired, is a transimination providing the nitron catalyst **I** and the hydroamination product (Figures 2 and 7). The second possibility is to generate adduct **V**, which results from a 6-endo-trig addition of the negatively charged oxygen onto the iminium ion in **IV** (Figures 2 and 7, off-cycle straight arrow). The latter gives a 6-membered heterocycle (**V**) that has been extensively described by Knight et al.¹⁴ If the

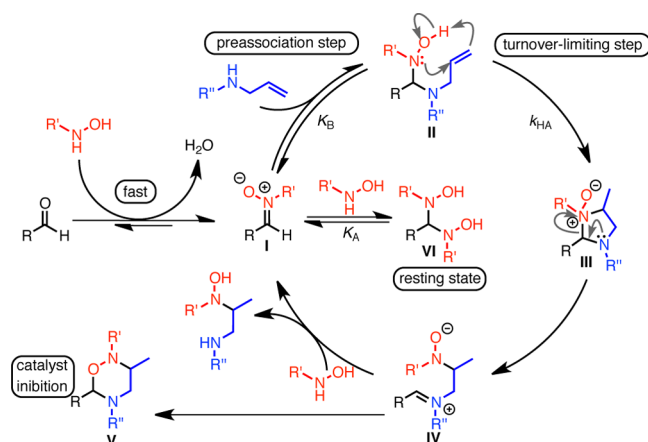
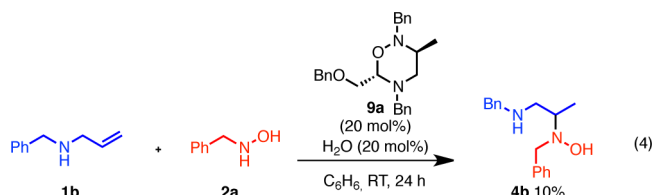


Figure 7. Proposed catalytic cycle.

formation of this cyclized product is irreversible, this might represent an important source of catalyst inhibition. To test this, the cyclic compound **9a** was synthesized according to Knight's procedure and utilized as a precatalyst for our hydroamination reaction (eq 4). Interestingly, only a 10% yield of **4b** was obtained. This observation suggests that this pathway (**IV** → **V**) is hardly reversible and leads to catalyst inhibition.

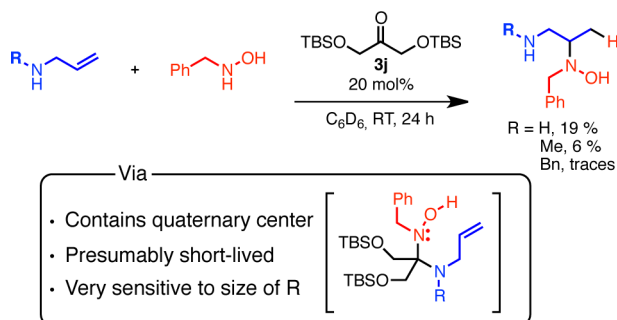


Taking into account the results obtained herein, a more accurate catalytic cycle can now be drawn (Figure 7). The first step is a rapid reaction of the aldehyde precatalyst with benzylhydroxylamine to afford the nitron catalyst (**I**). From this point, either another molecule of benzylhydroxylamine or the allylamine can effect a 1,2-addition. The reaction of the later yields a mixed aminal (**II**) that can then undergo the proposed rate-determining hydroamination.²⁴ It is believed that the reason why only a limited number of aldehydes with very specific electronic properties are competent catalysts can be explained as follows. If the aldehyde is not inductively destabilized enough (i.e., most aliphatic aldehydes) or is stabilized (i.e., aromatic or conjugated aldehydes), the nitron is stable, and consequently, the tetrahedral intermediate is only present in a low concentration. Since the rate of the hydroamination step (rate-determining step) of the reaction is function of the concentration of the mixed aminal **II**, stable nitrones that disfavor the formation of aminals would be poor catalysts. On the other hand, if the aldehyde is too destabilized, it is believed that the aminal could be too stable and thus not easily returned to the nitron. Since the formation of symmetrical aminal **VI** can compete with the mixed aminal **II**, a situation where the symmetrical aminal is formed and hardly returns to the nitron could be very detrimental to the reaction. It is thus important to have a nitron catalyst that favors preassociation while also allowing reversibility between the nitron and the aminal species. In other words, an ideal catalyst would allow for a high and renewable concentration of mixed aminal **II** via the destabilization of nitron **I**.²⁵

Having a better understanding of the operative catalytic cycle, we decided to reinvestigate the catalyst design in order to increase the rate of the reaction and hopefully broaden its scope. It was initially thought that promoting hydroamination, the proposed rate-limiting step, would lead to increased reactivity. To do so, the possibility of using a ketone catalyst was explored. The rationale was to benefit from a Thorpe-Ingold effect that would favor the difficult cyclization: this is well-known for intramolecular hydroaminations¹⁶ and for Cope-type hydroaminations in particular.¹⁵

However, intensive screening of electron-deficient ketones revealed that only poor reactivity could be achieved. The best results obtained were with the inductively destabilized ketone **3j**. In contrast to the results obtained with aldehyde **3i**, the ketone precatalysts seemed to be considerably more sensitive to steric factors. Hydroamination of a primary allylamine with benzylhydroxylamine using ketone **3j** provided a ¹H NMR yield of 21% over 24 h. The use of methylallylamine (6%) and benzylallylamine (trace) gave much lower yields (Scheme 1).

Scheme 1. Importance of Steric Factors with a Ketone Precatalyst^a



^aConditions: allylamine (1.5 equiv), **2a** (1 equiv), **3j** (20 mol %), C₆D₆, rt, 24 h.

This data suggests that the added steric hindrance present in the mixed aminal (increasing with R = H < Me < Bn) leads to an unfavorable preassociation equilibrium (**I** ⇌ **II**) and that this negative effect is more important than the probable acceleration of the Cope-type hydroamination step (**II** ⇌ **III**). As such, this observation is related to the concept of tether strain recently discussed by Krenske et al. in related systems.²⁶ In addition, the increased stability of ketonitrone relative to aldonitrone should also result in a disfavored preassociation equilibrium.

Taking these results into account, we aimed at improving the reaction rate by using a more destabilized nitron, to provide a more favorable preassociation equilibrium for the mixed aminal intermediate. Initial attempts with paraformaldehyde in C₆H₆ and CHCl₃ (i.e., original reaction conditions) resulted in low conversion. However, polar solvents proved superior, and the use of either *t*-BuOH or DMSO led to high yields of the desired hydroamination products, with slightly better results using *t*-BuOH (see the Supporting Information for optimization data). In order to compare the performance of α -benzyloxyacetaldehyde (**3i**) and formaldehyde (**3k**), the reaction rates of both catalytic systems were determined in DMSO-*d*₆. Interestingly, the rate at low conversion is lower with paraformaldehyde than with aldehyde **3i**, but it becomes ca. 3 times faster after an induction period (Figure 8). This is presumably due to the slow depolymerization of the paraformaldehyde precatalyst employed in this reaction.

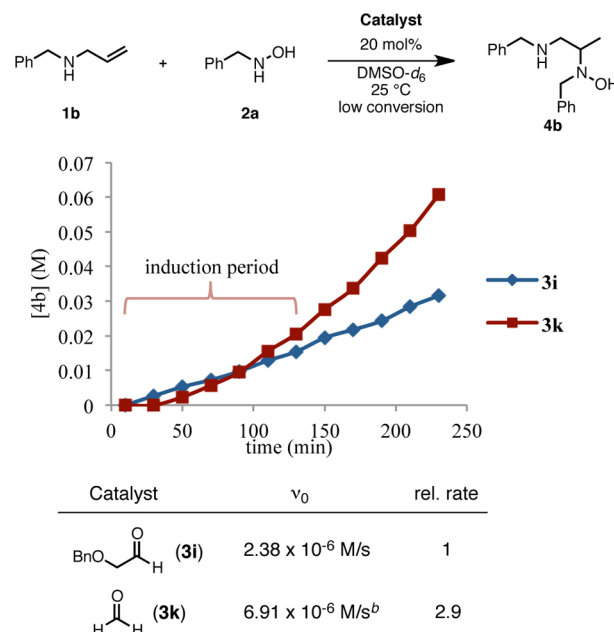
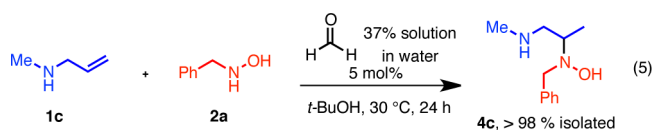


Figure 8. Initial rate comparison in DMSO-*d*₆ using **1b** (1.5 equiv), **2a** (1 equiv), catalyst **3i** or **3k** (20 mol %), and DMSO-*d*₆ (1 M), at 25 °C. ^b Value obtained after induction period.

Encouraged by this result, we next sought to determine if this improved reactivity would translate into improved catalytic activity. Gratifyingly, it was found that the catalyst loading in “formaldehyde” could be reduced to 5 mol % while still displaying increased yields compared to reactions using 20 mol % of α -benzyloxyacetaldehyde (**3j**). As shown in Table 2, isolated yields for alkene hydroamination using diverse secondary allylamines are significantly higher. *N*-Methyl, *N*-allyl, and *N*-benzyl allylamines provided quantitative, 92%, and 85% yields, respectively (entries 1–3). Using several other starting materials also gave yield increases compared to the first-generation conditions, albeit using 10 mol % of catalyst (entries 4–6). These results not only make for a more efficient alkene hydroamination method, but also for a more practical approach to vicinal diamines given that paraformaldehyde is inexpensive and readily available.

Building on these results under anhydrous (but initially heterogeneous) conditions, we explored the use of a concentrated aqueous solution of formaldehyde (formalin, in which formaldehyde is present as a hydrate). Gratifyingly, a similar result was observed using this convenient precatalyst (eq 5).



This result again highlights that high catalytic efficiency is achievable with tethering catalysis. The early development of an efficient tethering organocatalytic system operating at 5 mol % despite the presence of two different catalyst inhibition pathways suggests that this concept will be applicable to other reactions. Efforts along this path and the development of a highly enantioselective variant of this tethered hydroamination reactivity are ongoing and will be reported in due course.

Table 2. Comparative Reaction Scope for the Formaldehyde-Catalyzed Cope-type Hydroamination^a

Entry	Product	Conditions using 3i	Yield using 3i	Yield using 3k
1		C ₆ H ₆ , RT, 24 h	75%	85%
2		C ₆ H ₆ , RT, 24 h	72%	>98%
3		C ₆ H ₆ , RT, 24 h	69%	92%
4		CHCl ₃ , 60 °C, 96 h	56%	66% ^b
5		CHCl ₃ , RT, 24 h	61%	74% ^b
6		CHCl ₃ , RT, 24 h	51%	80% ^b

^aConditions: **3i** catalyzed (red), allylamine (1.5 equiv), hydroxylamine (1 equiv), **3i** (20 mol %), C₆H₆ or CHCl₃ (1 M), 24–96 h; **3k** catalyzed (blue), allylamine (2 equiv), hydroxylamine (1 equiv), **3k** (5 mol %), *t*-BuOH (1 M), 30 °C, 24 h. ^bUsing 10 mol % **3k**.

CONCLUSION

In conclusion, the reaction mechanism of the recently developed aldehyde-catalyzed intermolecular Cope-type hydroaminations was investigated. Key observations that should help the development of tethering catalysis through temporary intramolecularity were made. As expected, the reaction was determined to be approximately first-order in both the aldehyde catalyst (α -benzyloxyacetaldehyde) and the allylic amine. However, the reaction displays an inverse order behavior in benzylhydroxylamine, which reveals a significant off-cycle pathway, leading to an unproductive symmetrical tether. This highlights the importance of an aldehyde precatalyst that ensures reversible aminal formation. Kinetic isotope effect experiments ($k_H/k_D = 2.8 \pm 0.9$) suggest that hydroamination is the rate-limiting step of this catalytic cycle. Overall, the complete mechanistic picture reveals that aldehyde **3i** is a particularly effective precatalyst since its reduced stability and higher kinetic reactivity inherently lead to a more efficient preassociation to access the productive mixed aminal tether. Given that the formation of symmetrical tethers is also possible, reversibility is required for efficient catalysis to occur. Finally, the results obtained enabled the elaboration of a more accurate catalytic cycle and the development of a more efficient catalytic system for alkene hydroamination. Indeed, the use of 5–10 mol % of paraformaldehyde, a destabilized aldehyde known to hydrate or polymerize readily, proved more effective than the

use of 20 mol % of α -benzyloxyacetaldehyde, leading to high yields of intermolecular hydroamination products within 24 h at 30 °C in *t*-BuOH.

ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures and characterization. This material is available free of charge via the Internet at <http://pubs.acs.org>.

AUTHOR INFORMATION

Corresponding Author

andre.beauchemin@uottawa.ca

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was initiated through support of an Enantioselective Synthesis Grant [sponsored by the Canadian Society for Chemistry, AstraZeneca Canada, Boehringer Ingelheim (Canada) Ltd. and Merck Frosst Canada] and the NSERC collaborative R & D program. Support from the University of Ottawa, the Canadian Foundation for Innovation, the Ontario Ministry of Research and Innovation (Ontario Research Fund and Early Researcher Award to A.M.B.), NSERC (Discovery Grant and Discovery Accelerator Supplement to A.M.B.) and AstraZeneca are also gratefully acknowledged. Acknowledgment is also made to the donors of The American Chemical Society Petroleum Research Fund for support of related research efforts. N.G. thanks NSERC for a CGS D scholarship. M.J.M. thanks Boehringer Ingelheim (Canada) Ltd for a collaborative graduate scholarship. We also thank Marc Pesant for stimulating discussions. We also thank Prof. Derek Pratt (University of Ottawa) and the reviewers for insightful comments and suggestions.

REFERENCES

- (1) Radzicka, A.; Wolfenden, R. *Science* **1995**, 267, 90.
- (2) Jencks, W. P. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1975**, 43, 219.
- (3) (a) For a review on substrate-directable chemical reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, 93, 1307–1370. (b) For a recent review on removable or catalytic directing groups, see: Rousseau, G.; Breit, B. *Angew. Chem., Int. Ed.* **2011**, 50, 2450–2494.
- (4) For selected examples in which the catalytic systems operate via preassociation and substrate activation, see: (a) Sammakia, T.; Hurley, T. B. *J. Am. Chem. Soc.* **1996**, 118, 8967. (b) Sammakia, T.; Hurley, T. B. *J. Org. Chem.* **1999**, 64, 5652. (c) Sammakia, T.; Hurley, T. B. *J. Org. Chem.* **2000**, 65, 974. (k) Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem., Int. Ed.* **2003**, 42, 112. (d) Lightburn, T. E.; Dombrowski, M. T.; Tan, K. L. *J. Am. Chem. Soc.* **2008**, 130, 9210. (e) Grünanger, C. U.; Breit, B. *Angew. Chem., Int. Ed.* **2008**, 47, 7346. (f) Fuchs, D.; Rousseau, G.; Diab, L.; Gellrich, U.; Breit, B. *Angew. Chem., Int. Ed.* **2012**, 51, 2178. (l) Worthy, A. D.; Joe, C. L.; Lightburn, T. E.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, 132, 14757. (g) Sun, X.; Worthy, A. D.; Tan, K. L. *Angew. Chem., Int. Ed.* **2011**, 50, 8167. (h) Murphy, S. K.; Coulter, M. M.; Dong, V. *Chem. Sci.* **2012**, 3, 355. (i) Worthy, A. D.; Sun, X.; Tan, K. L. *J. Am. Chem. Soc.* **2012**, 134, 7321. For a review, see: (j) Tan, K. L.; Sun, X.; Worthy, A. D. *Synlett* **2012**, 23, 321.
- (5) For an entry in the literature on bifunctional catalysis, see: (a) Rowlands, G. J. *Tetrahedron* **2001**, 57, 1865. (b) Ma, J. A.; Cahard, D. *Angew. Chem., Int. Ed.* **2004**, 43, 4566. (c) Bhadury, P. S.; Song, B. A.; Yang, S.; Hu, D. Y.; Xue, W. *Curr. Org. Synth.* **2009**, 6, 380. (d) Connon, S. J. *Chem. Commun.* **2008**, 2499.

(6) (a) For excellent reviews, see: Tan, K. L. *ACS Catal.* **2011**, *1*, 877. (b) Pascal, R. *Eur. J. Org. Chem.* **2003**, 1813.

(7) For an example of hydrogen bonding templated intramolecularity, see: Kelly, T. R.; Bridger, G. J.; Zhao, C. J. *Am. Chem. Soc.* **1990**, *112*, 8024.

(8) Pascal, R.; Laspéras, M.; Taillades, J.; Commeyras, A. *New J. Chem.* **1987**, *11*, 235.

(9) (a) Wieland, V. T.; Lambert, R.; Lang, H. U.; Schramm, G. *Justus Liebigs Ann. Chem.* **1956**, 597, 181. (b) Wieland, V. T.; Jaenicke, F. *Justus Liebigs Ann. Chem.* **1956**, 599, 125.

(10) (a) Capon, B.; Capon, R. J. *Chem. Soc., Chem. Commun.* **1965**, 20, 502. (b) Hay, R. W.; Main, L. *Aust. J. Chem.* **1968**, *21*, 155.

(11) Ghosh, M.; Conroy, J. L.; Seto, C. T. *Angew. Chem., Int. Ed.* **1999**, *38*, 514.

(12) (a) Pascal, R.; Taillades, J.; Commeyras, A. *Tetrahedron* **1978**, *34*, 2275. (b) Pascal, R.; Taillades, J.; Commeyras, A. *Bull. Soc. Chim. Fr.* **1978**, 177. (c) Pascal, R.; Taillades, J.; Commeyras, A. *Tetrahedron* **1980**, *36*, 2999. (d) Sola, R.; Brugidou, J.; Taillades, J.; Commeyras, A. *Tetrahedron Lett.* **1983**, *24*, 1501. (e) Sola, R.; Brugidou, J.; Taillades, J.; Commeyras, A. *New J. Chem.* **1984**, *8*, 459. (f) Sola, R.; Taillades, J.; Brugidou, J.; Commeyras, A. *New J. Chem.* **1989**, *13*, 881. (g) Taillades, J.; Beuzelin, I.; Gabrel, L.; Tabacik, V.; Bied, C.; Commeyras, A. *Origins Life Evol. Biospheres* **1996**, *28*, 61. For discussion and representative experimental procedures, see: (h) Pascal, R.; Marnier, M. L.; Rousset, A.; Commeyras, A.; Taillades, J.; Mion, L. *Process for the Chemical Catalytic Hydrolysis of an α -Aminonitrile or of One of the Salts Thereof*. U.S. Patent 4,243,814, Jan 6, 1981. For kinetic resolution using chiral ketones, see: (i) Tadros, Z.; Lagriffoul, P. H.; Mion, L.; Taillades, J.; Commeyras, A. *J. Chem. Soc., Chem. Commun.* **1991**, 1373. (j) Taillades, J.; Garrel, L.; Lagriffoul, P.-H.; Commeyras, A. *Bull. Soc. Chim. Fr.* **1992**, 129, 191. (k) Lagriffoul, P.-H.; Tadros, Z.; Taillades, J.; Commeyras, A. *J. Chem. Soc. Perkin Trans. 2* **1992**, 1279. (l) Taillades, J.; Garrel, L.; Guillen, F.; Collet, H.; Commeyras, A. *Bull. Soc. Chim. Fr.* **1995**, 132, 119. (m) Taillades, J.; Garrel, L.; Guillen, F.; Collet, H.; Commeyras, A. *React. Polym.* **1995**, *24*, 261.

(13) Laspéras, M.; Pascal, R.; Taillades, J.; Commeyras, A. *New J. Chem.* **1986**, *10*, 111.

(14) (a) Gravestock, M. B.; Knight, D. W.; Thornton, S. R. *J. Chem. Soc., Chem. Commun.* **1993**, 169. (b) Coogan, M. P.; Gravestock, M. B.; Knight, D. W.; Thornton, S. R. *Tetrahedron Lett.* **1997**, *38*, 8549. (c) Gravestock, M. B.; Knight, D. W.; Malik, K. M. A.; Thornton, S. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3292.

(15) Such reactions are also often called reverse Cope cyclization or reverse Cope eliminations in the literature. For an excellent review, see: Cooper, N. J.; Knight, D. W. *Tetrahedron* **2004**, *60*, 243.

(16) For selected reviews on hydroamination, see: (a) Müller, T. E.; Hultsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795. (b) Aillaud, I.; Collin, J.; Hannedouche, J.; Schulz, E. *Dalton Trans.* **2007**, 5105. (c) Hultsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367. (d) Nobis, M.; Driessen-Hölscher, B. *Angew. Chem., Int. Ed.* **2001**, *40*, 3983. (e) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675.

(17) (a) MacDonald, M. J.; Schipper, D. J.; Ng, P.; Moran, J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 20100. For discussion of this work, see: (b) List, B.; Čorić, I. *Synfacts* **2012**, *8*, 210. (c) Tan, K. L. *Nat. Chem.* **2012**, *4*, 253.

(18) For reviews on the (stepwise) use of temporary tethers to achieve increased reactivity and control, see: (a) Diederich, F. S.; Stang, P. J. *Templated Organic Synthesis*; Wiley-VCH: Chichester, 2000. (b) Gauthier, D. R., Jr.; Zandi, K. S.; Shea, K. J. *Tetrahedron* **1998**, *54*, 2289. (c) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253. (d) Fensterbank, L.; Malacria, M.; Sieburt, S. *Synthesis* **1997**, 813.

(19) For a review relating to transfer of chirality, see: Seebach, D.; Sting, A. R.; Hoffman, M. *Angew. Chem., Int. Ed.* **1996**, *35*, 2708.

(20) (a) Beauchemin, A. M.; Moran, J.; Lebrun, M.-E.; Séguin, C.; Dimitrijevic, E.; Zhang, L.; Gorelsky, S. I. *Angew. Chem., Int. Ed.* **2008**, *47*, 1410. (b) 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. (c) Bourgeois, J.; Dion, I.; Cebrowski, P. H.; Loiseau, F.

Bédard, A. C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 874. (d) Roveda, J.-G.; Clavette, C.; Hunt, A. D.; Whipp, C. J.; Gorelsky, S. I.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 8740. (e) Loiseau, F.; Clavette, C.; Raymond, M.; Roveda, J.-G.; Burrell, A.; Beauchemin, A. M. *Chem. Commun.* **2011**, 562.

(21) The aldehyde **3i** was not seen in the reaction mixture, even at low conversion.

(22) For related hydroxylamine behavior, see: Turega, S. M.; Lorenz, C.; Sadownik, J. W.; Philp, D. *Chem. Commun.* **2008**, 4076.

(23) Equilibrium constants for the reaction of **2a** and **8a** with nitrones made from aldehyde **3f** and **3g** were also measured. Significantly lower equilibrium values were obtained. See Supporting Information for more details.

(24) The kinetic equation for the proposed catalytic cycle can be expressed as follows:

$$\text{rate} = \frac{k_{\text{HA}}K_{\text{B}}[\mathbf{1}][\mathbf{3}]}{1 + K_{\text{B}}[\mathbf{1}] + K_{\text{A}}[\mathbf{2}]}$$

See the Supporting Information for more details.

(25) In contrast, a higher concentration of tetrahedral intermediate obtained by stabilization of the aminal instead of destabilization of the nitron could lead to a reduction of the hydroamination rate (k_{HA}).

(26) Krenske, E. H.; Davison, E. C.; Forbes, I. T.; Warner, J. A.; Smith, A. L.; Holmes, A. B.; Houk, K. N. *J. Am. Chem. Soc.* **2012**, *134*, 2434.