Directed Organocatalytic Intermolecular Cope-type Hydroamination of Alkenes

by

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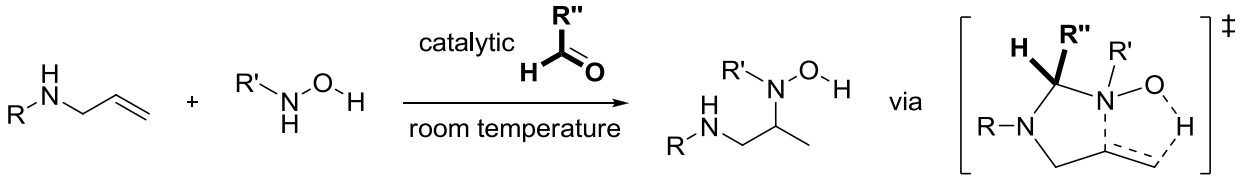
Abstract

Intermolecular reactions are inherently more difficult than intramolecular reactions, and several transformations can only occur as cyclizations, often to form 5-membered rings. The use of directing or tethering groups allowing preassociation with a reagent or catalyst is a common strategy to overcome such low reactivity, which can lead to increases in the rate, regioselectivity and stereoselectivity of intermolecular reactions. Typically, such preassociation involves hydrogen bonds, coordination to a metal ion/catalyst or stepwise installation of a temporary tether. As part of ongoing investigations on metal-free hydroaminations, it was speculated that a simple organic molecule could allow the formation of a temporary tether and enable directed intermolecular Cope-type hydroaminations to proceed at room temperature. Recently, it was found that alkylhydroxylamines add to allylic amines regioselectively in the presence of an aldehyde catalyst. This thesis presents the background material, design elements, optimization and scope of this reactivity.



Acknowledgements

I applied for graduate school with much uncertainty. I didn't know if I could handle it, if I would enjoy it, or if I would even be accepted. Then when I met with Professor André Beauchemin and mentioned that I had spent more than a year completely removed from chemistry altogether, I thought I didn't have a chance. To my surprise however, he offered me a position in his lab, and I'm glad I accepted it. André was just what I could have hoped for in a supervisor. He always gave the right amount of leeway, he was strict when he needed to be, and most importantly, he let us have fun. Also a great motivator, I typically left his office after meetings feeling like I could accomplish anything, whether it was from words of encouragement when things didn't work out or a solid handshake when things did. André's enthusiasm and optimism were infectious, and whatever the future has waiting for me, I hope I can approach it with the same zeal that André did with his research. I always felt that he took a chance on me, a relatively inexperienced and slightly immature 24-year-old, when he extended the offer so I wanted to make him proud, and I hope I was successful.

Working in the lab would not have been as enjoyable if it wasn't for the people who worked with me. They all made a significant impact on me, but none more so than the one who joined the group at the same time that I did: Ashley Hunt ("Bright Eyes"). I knew that we were meant to be good friends since the Halloween when she was a bathtub and I was a toilet. We experienced all the ups and downs of lab life and grad school together and shared countless memories that'll stay with me forever. She'll always be my "baby sister" and I hope we'll continue to be there for each other through each phase of our lives. When I arrived in 2008,

the first member of the Beauchemin group that I met was Francis Loiseau. Over the last two years, he was not only a co-worker, but also a teacher, advisor, boss, drinking partner, and even role model (even though he's only six months older). Most importantly, he was always a friend. I learned much from our frequent long conversations, and I'm looking forward to the next one, either over beers at a pub or late at night after hours of partying. I was also welcomed by Isabelle Dion (two years in the large, luxurious lab of 432), Toni Rizk (former hoodmate, I found his secret bathroom), Jennifer Pfeiffer (fashion consultant and #1 massage client), Dr. Joseph Moran (guitar partner and another role model), Hao Peng (looks good in a suit) and Jean-Grégoire Roveda (former noisy roommate/landlord).

In 2009, it was my turn to welcome new faces. Joining the group were Melissa MacDonald (blonde and fabulous research partner), "Big Boy" Matt Whitmore (I'll win the link war, but he'll always win the beard-offs) and Christian Clavette (labmate/tentmate/couchmate/bedmate), while Nicolas Guimond (with his fingerfeet) and Tom "T-Word" Markiewicz (killer Simpsons allusions, killer moustache) joined us later. I also had the pleasure of meeting a number of undergrads who came through our group: Eric Bilodeau, Lei Zhang, J.P. Wan, Catherine Seguin, "Chinatown" Nicholas Wong, Mark Dornan, Alishya Burrell, Michaël "The Boy" Raymond, Amy Toderian, Sandrine Taing and Patrick Moon, the almost undergrad. We had many great times together, and I thank them all for being a part of them.

I'd also like to acknowledge some of the people around the department. Anna Balcerzak was one of the few outside of the Beauchemin lab with whom I regularly spoke, and we shared quite a few laughs and misadventures while TAing together and when I invaded her fumehood

(I know she had fun, even though she won't admit it). Roger Tam taught me to run my first ozonolysis, so my project may not have worked without him. Though I didn't venture much from my own lab, there were moments that I'll remember involving members of other groups, namely the Ben group (the hazy night at CSC), the Barriault group (Beauchemin vs. Barriault softball) and the Fagnou group (their incredible stories). I also thank professors Bill Ogilvie, Louis Barriault and the late Keith Fagnou for passing on their knowledge to me. To those inside and outside of the department that I didn't mention: we may not have spoken much, but my experience would not have been the same without you.

Finally, thanks go out to Dad, Mom, Jon, Andrew and Grandma for supporting me from afar. Knowing I had a home to which I could return made it so much easier to venture out on my own.

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List of Abbreviations

Å	angstrom (10^{-10} metres)
Ac	acetyl
acac	acetylacetonyl
AIBN	2,2'-azo bisisobutyronitrile
anti	against, opposite
aq	aqueous
Ar	aryl
BINAP	2,2'-*bis*(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
Bu	butyl
cat.	catalytic
Cbz	benzyloxycarbonyl
°C	degree Celsius
cis	on the same side
cod	1,5-cyclooctadiene
coe	cyclooctene
conc.	concentrated
Cp (Cp')	cyclopentadienyl (pentamethylcyclopentadienyl)

Cy	cyclohexyl
δ	chemical shift in parts per million
d	deuterium (in NMR solvents)
DAB	dimethyl-2,2'-azobisisobutyrate
DMA	*N*,*N*-dimethylacetamide
DMAP	*N*,*N*-4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
E	*Ger*., entgegen
ee	enantiomeric excess
EI	electron impact
equiv	equivalent
Et	ethyl
FT	Fourier transform
g	gram
h	hour
h	Planck's constant (6.626×10^{-34} J s)
*h*ν	light; electromagnetic radiation
HMDS	1,1,1,3,3,3-hexamethyldisilazane
HRMS	high-resolution mass spectrometry
Hz	Hertz
i	iso

IR	infrared
J	coupling constant
L	litre; ligand
Ln	lanthanide
µL	microlitre
m	meta
M	molar; metal
Me	methyl
mg	milligram
min	minute
mL	millilitre
mmol	millimole
MS	molecular sieves
n	normal
nbd	norbornadiene
Nu	nucleophile
NMR	nuclear magnetic resonance
p	para
PCC	pyridinium chlorochromate
Ph	phenyl
Piv	pivaloyl
ppm	parts per million

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

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Chapter 1. Tethered and Directed Reactions

1.1 Introduction

In organic chemistry, it is widely known that intramolecular reactions proceed at higher rates than intermolecular reactions. This is in large part due to the negative entropy change associated with intermolecular reactions, resulting in an increase in the activation energy. In contrast, the entropy change for intramolecular reactions is nearly zero (Figure 1.1). Additionally, intramolecular reactions tend to occur with higher degrees of regio- and stereoselectivity.

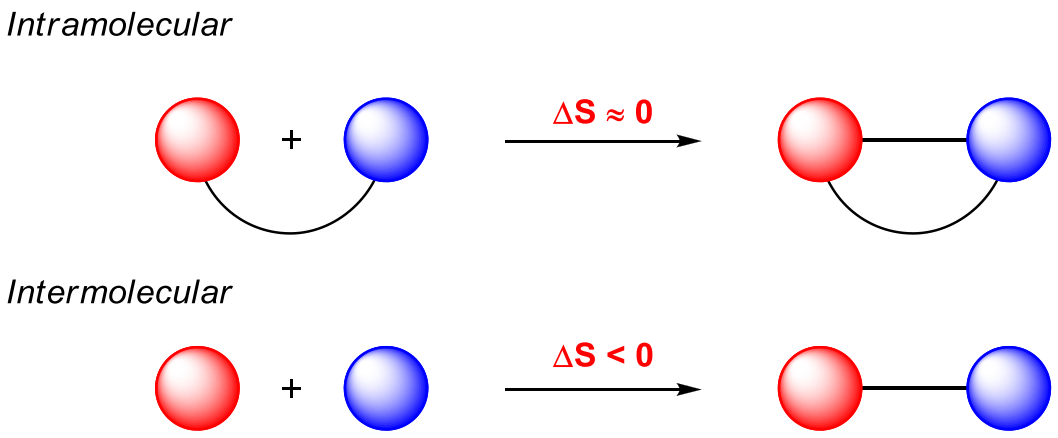


Figure 1.1: Intramolecular vs. intermolecular reactions

1.2 Tethered reactions

A popular strategy for overcoming this negative entropy change in intermolecular reactions is to temporarily join the reacting partners through a covalently-bonded tether (Figure 1.2).[1] In this fashion, the intermolecular reaction becomes an intramolecular reaction, typically enhancing the rate of reaction by virtually eliminating the Δ*S* term of the activation energy. This has been utilized to facilitate difficult intermolecular reactions, and allow them to

(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. (c) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253. (d) Fensterbank, L.; Malacria, M.; Sieburth, S. M. *Synthesis* **1997**, 813.

occur with improved control. The tethers can then be removed at a convenient stage of a synthetic sequence, or be further functionalized, displaying their versatility as synthetic tools. However, a major drawback is that the incorporation and removal of these tethers is typically stepwise and stoichiometric, requiring additional steps and examples with catalytic tethers are very rare.[2]

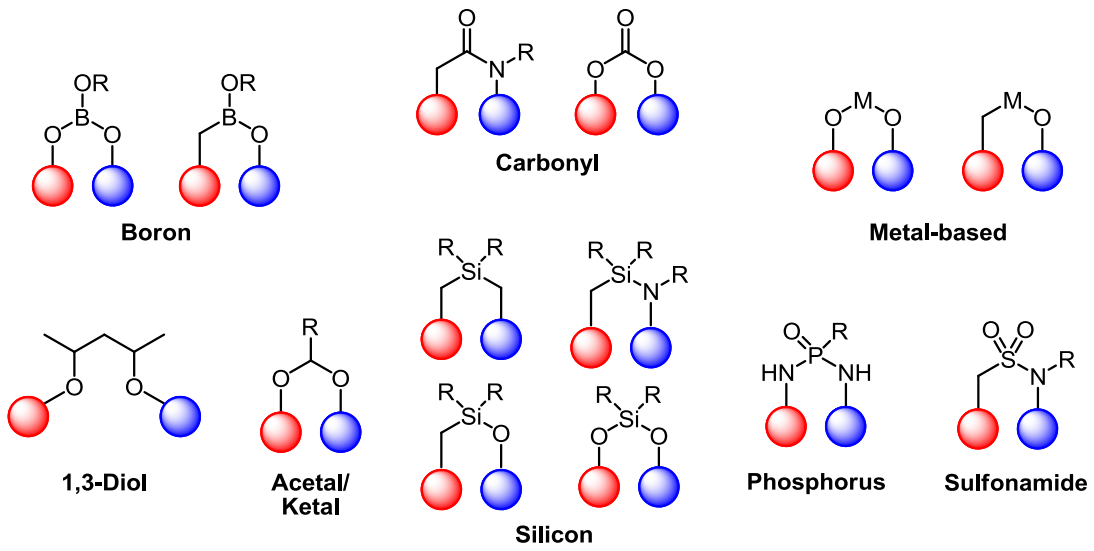
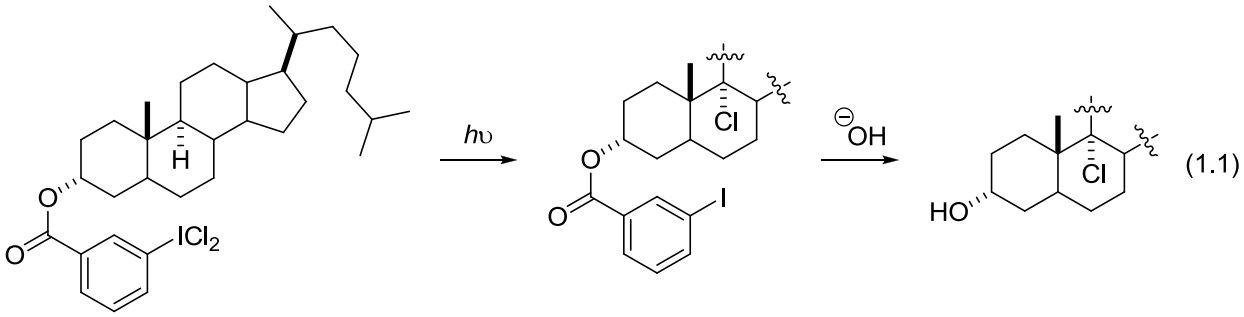


Figure 1.2: Examples of tethers found in literature

One of the earliest examples was reported by Breslow in 1980, who achieved a selective chlorination of steroids using phenyliodine dichlorides, which were tethered through a simple ester linkage (equation 1.1).[3] Various types of tethers have since been reported, and have been applied to a variety of reactions. Thus, it is a strategy that is widely applicable in organic synthesis.[1]

(2) Some enzymes catalyze reactions through "temporary 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. See section 1.3.1

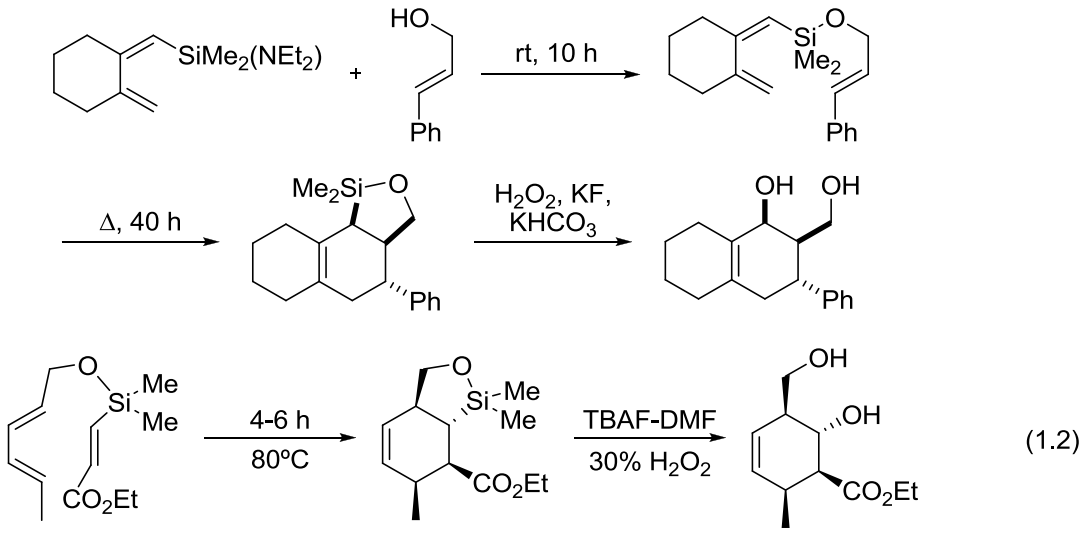
(3) (a) Breslow, R.; Corcoran, R.; Dale, J. A.; Liu, S.; Kalicky, P. *J. Am. Chem. Soc.* **1974**, *96*, 1973. (b) Breslow, R.; Corcoran R. J.; Snider, B. B.; Doll, R. J.; Khanna, P. L.; Kaleya, R. *J. Am. Chem. Soc.* **1977**, *99*, 905.



1.2.1 The Diels-Alder reaction

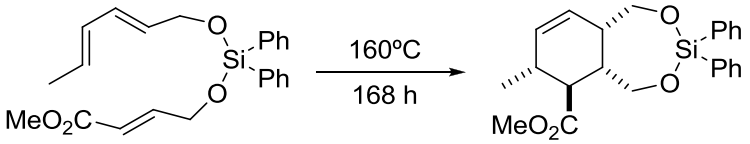
The Diels-Alder reaction is of paramount importance in organic synthesis, and tethers have often been used to carry out this reaction with high levels of control. One of the earliest examples was reported by Tamao and co-workers in 1989 using a silicon tether to generate the cycloaddition adduct as a single isomer (Scheme 1.1).[4] Soon after, the groups of Sieburth and Stork (equation 1.2) further explored this reactivity with vinylsilanes.[5]

Scheme 1.1: Tamao's silicon-tethered Diels-Alder reaction



(4) Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* **1989**, *111*, 6478.
(5) (a) Stork, G.; Chan, T. Y.; Breault, G. A. *J. Am. Chem. Soc.* **1992**, *114*, 7578. (b) Sieburth, S. M.; Fensterbank, L. *J. Org. Chem.* **1992**, *57*, 5279.

In 1990, Craig and co-workers investigated the use of silyl acetals. They also performed tethered Diels-Alder reactions with high stereocontrol, generating the expected adduct as a single stereoisomer (equation 1.3).[6] Conversely, a related intermolecular analogue afforded a mixture of four isomeric products. However, synthesis of the silyl acetal substrate was problematic, as undesired symmetric side products were often observed (equation 1.4).



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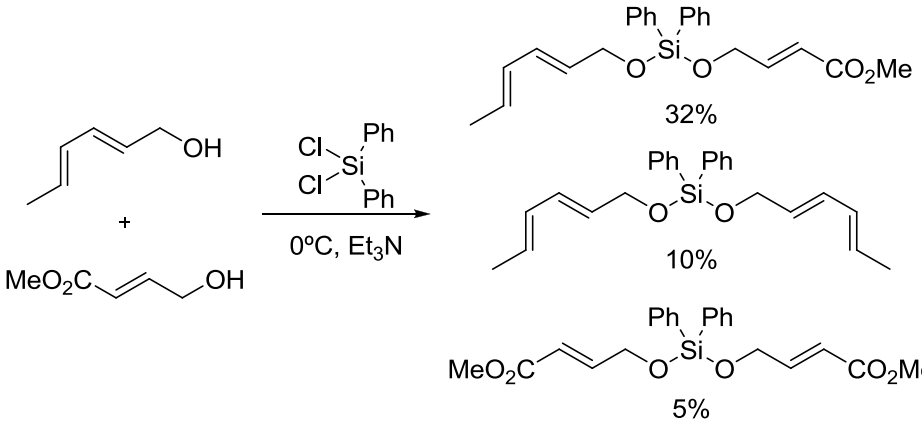
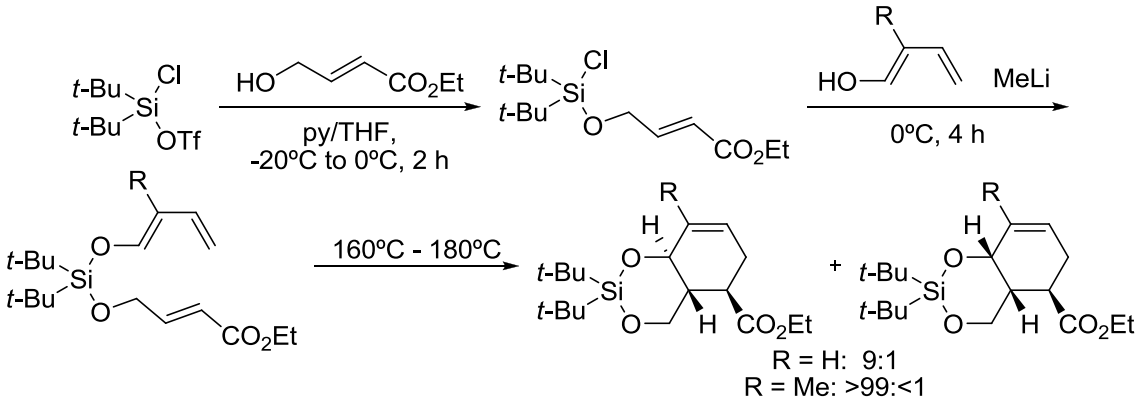


(1.4)

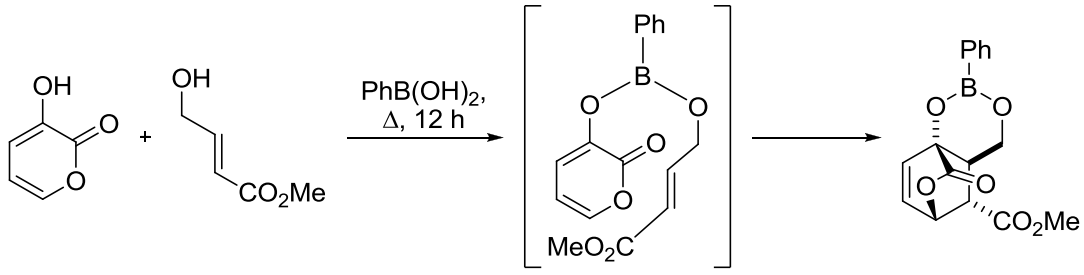
Fortin and co-workers addressed this issue by exploiting the difference in reactivity between chlorides and triflates.[7] This allowed for the smooth preparation of the desired Diels-Alder substrates, which when heated, generated the cycloaddition products with excellent selectivity (Scheme 1.2).

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

Scheme 1.2: Silicon-tethered Diels-Alder by Fortin and co-workers

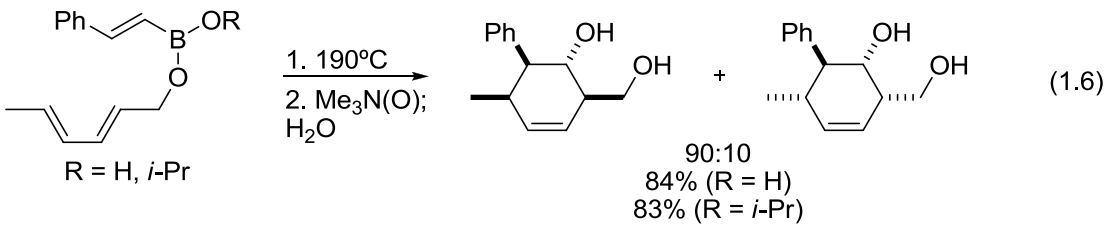


In 1991, Narasaka reported a highly regio- and stereoselective tethered Diels-Alder using phenylboronic acid to form a boronate ester linkage *in situ* (equation 1.5).[8] The borate ester was then easily cleaved by treatment with 2,2-dimethyl-1,3-propanediol to afford the corresponding diol. Furthermore, no reaction was observed in the absence of the boronic acid, indicating that this process only occurs in intramolecular cases. In 1999, Batey and co-workers developed similar boron-tethered Diels-Alder reactions in which, rather than simple cleavage, the tether could undergo further functionalization (equation 1.6).[9] In this example, oxidation of the intermediate boracycle with TMANO produced the corresponding diols.



(1.5)

(8) Narasaka, K.; Shimada, S.; Osoda, K.; Iwasawa, N. *Synthesis* **1991**, 1171.
(9) Batey, R. A.; Thadani, A. N.; Lough, A. J. *J. Am. Chem. Soc.* **1999**, *121*, 450.



(1.6)

Diels-Alder reactions have also been performed with tethers based on metals, such as zinc, aluminum and magnesium,[10] with moderate to excellent selectivity (equation 1.7). In some cases, the presence of the metal tether even facilitated the cycloaddition, as shown in Table 1.1.[5a,10a] While the reaction involving the magnesium-tethered triene produced the cyclohexenyl alcohol upon heating at 80°C for only 1 h (entry 1), cycloadditions of the silicon-tethered substrate and the analogous allylic ether required longer reaction times at higher temperatures (entries 2 and 3).

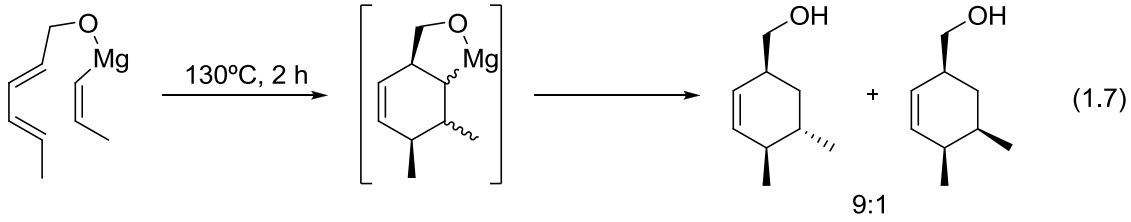


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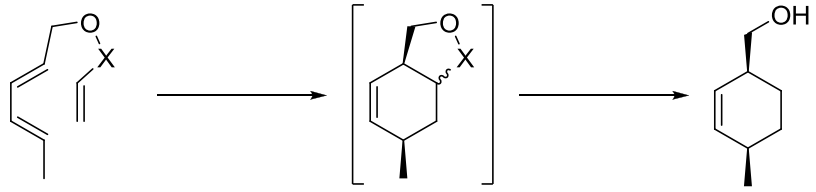
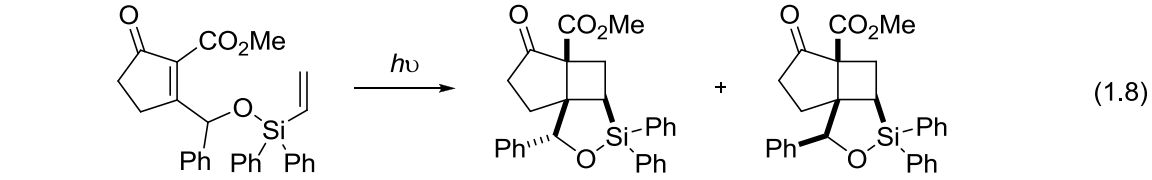
Table 1.1: Comparison of tethers in intramolecular Diels-Alder reactions



	X	time (h)	temperature (ºC)	yield (%)
1	Mg	1	80	70
2	$SiMe_2$	3	160	70
3	CH_2	10	160	no yield given

(10) (a) Stork, G.; Chan, T. Y. *J. Am. Chem. Soc.* **1995**, *117*, 6595. (b) Bertozzi, F.; Olsson, R.; Frejd, T. *Org. Lett.* **2000**, *2*, 1283. (c) Ward, D. E.; Abaee, M. S. *Org. Lett.* **2000**, *2*, 3937.

Tethering strategies have been applied to other cycloadditions as well. Silicon linkages have been used for [2+2] photocycloadditions (equations 1.8 and 1.9),[11] as well as with a variety of other tethers.[12] Examples of tethered cycloadditions found in the literature also include [5+2] cycloadditions,[13] [3+2] dipolar additions[14] and *meta* photocycloadditions.[15]



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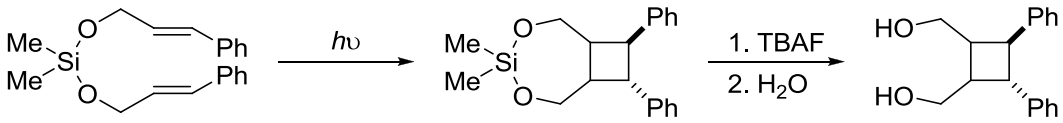


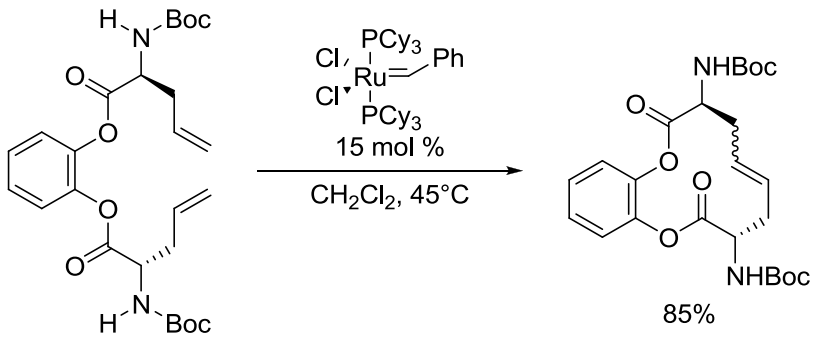
(1.9)

1.2.2 Olefin and enyne metathesis

The tethering strategy has also been employed to both facilitate and control ruthenium-catalyzed metathesis of olefins. In 1998, Grubbs and co-workers reported that while attempts at the metathesis of Boc-protected (*S*)-*C*-allylglycine methyl ester were unsuccessful, the reaction proceeded smoothly in good yields after coupling with catechol (equation 1.10).[16] Soon after, reports of highly *Z*-selective olefin metatheses using silicon tethers were

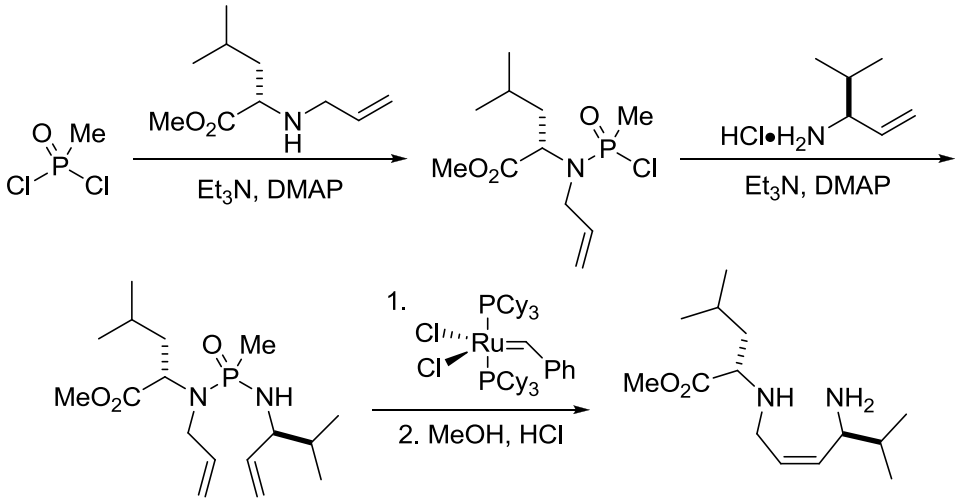
(11) (a) Crimmins, M. T.; Guise, L. E. *Tetrahedron Lett.* **1994**, *35*, 1657. (b) Fleming, S. A.; Ward, S. C. *Tetrahedron Lett.* **1992**, *33*, 1013. (c) Ward, S. C.; Fleming, S. A. *J. Org. Chem.* **1994**, *59*, 6476.
(12) Gülten, S.; Sharpe, A.; Baker, J. R.; Booker-Milburn, K. I. *Tetrahedron* **2007**, *63*, 3659.
(13) Rumbo, A.; Castedo, L.; Mourino, A.; Mascarenas, J. L. *J. Org. Chem.* **1993**, *58*, 5585.
(14) (a) Garner, P. P.; Cox, P. B.; Klippenstein, S. J.; Youngs, W. J.; McConville, D. B. *J. Org. Chem.* **1994**, *59*, 6510. (b) Righi, P.; Marotta, E.; Landuzzi, A.; Rosini, G. *J. Am. Chem. Soc.* **1996**, *118*, 9446. (c) Denmark, S. E.; Hurd, A. R.; Sacha, H. J. *J. Org. Chem.* **1997**, *62*, 1668.
(15) (a) Penkett, C. S.; Byrne, P. W.; Teobald, B. J.; Rola, B.; Ozanne, A.; Hitchcock, P. B. *Tetrahedron* **2004**, *60*, 2771. (b) Sugimura, T.; Yamasaki, A.; Okuyama, T. *Tetrahedron: Asymmetry* **2005**, *16*, 675.
(16) O'Leary, D. J.; Miller, S. J.; Grubbs, R. H. *Tetrahedron Lett.* **1998**, *39*, 1689.

published,[17] and Hanson developed a phosphorus-tethered ring-closing metathesis as a route to functionalized 1,4-diamines (Scheme 1.3).[18]



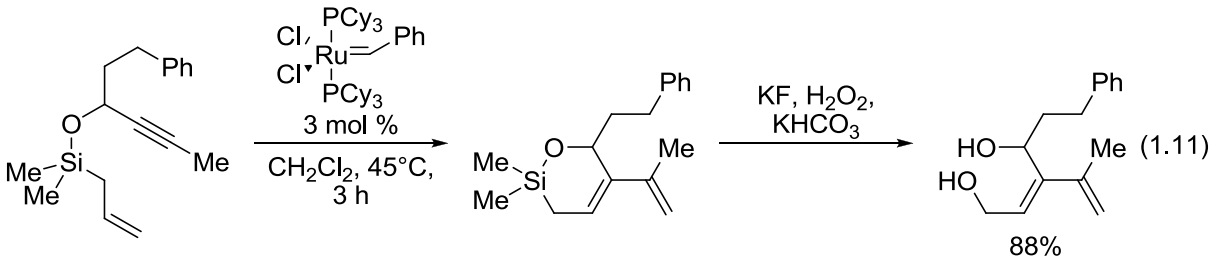
(1.10)

Scheme 1.3: Phosphorus-tethered ring-closing metathesis



Alkene-alkyne metathesis[19] has also benefited from the use of temporary tethers. A silicon-tethered enyne metathesis was accomplished by Yao in 2001 with complete regiocontrol to afford the desired dienes in good yields (equation 1.11).[19a]

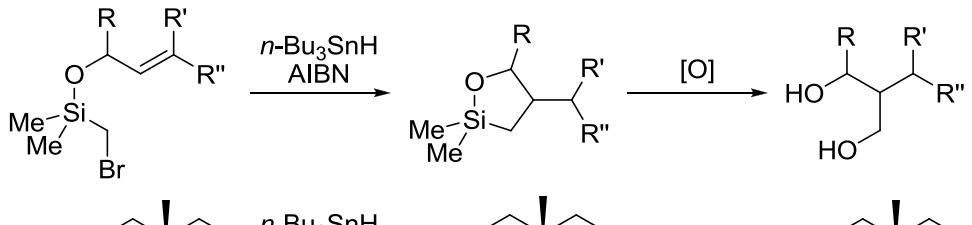
(17) (a) Evans, P. A.; Murthy, V. S. *J. Org. Chem.* **1998**, *63*, 6768. (b) Hoye, T. R.; Promo, M. A. *Tetrahedron Lett.* **1999**, *40*, 1429. (c) Gierasch, T. M.; Chytil, M.; Didiuk, M. T.; Park, J. Y.; Urban, J. J.; Nolan, S. P.; Verdine, G. L. *Org. Lett.* **2000**, *2*, 3999. (d) Lobbel, M.; Köll, P. *Tetrahedron: Asymmetry* **2000**, *11*, 393. (e) Evans, P. A.; Cui, J.; Buffone, G. P. *Angew. Chem. Int. Ed.* **2003**, *42*, 1734.
(18) Sprott, K. T.; McReynolds, M. D.; Hanson, P. R. *Org. Lett.* **2001**, *3*, 3939.
(19) (a) Yao, Q. *Org. Lett.* **2001**, *3*, 2069. (b) Grimm, J. B.; Otte, R. D.; Lee, D. *J. Organomet. Chem.* **2005**, *690*, 5508.



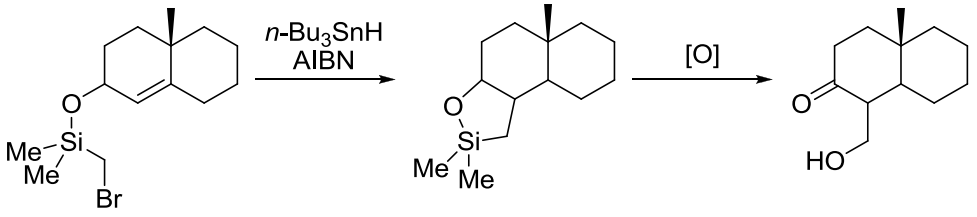
(1.11)

1.2.3 Radical reactions

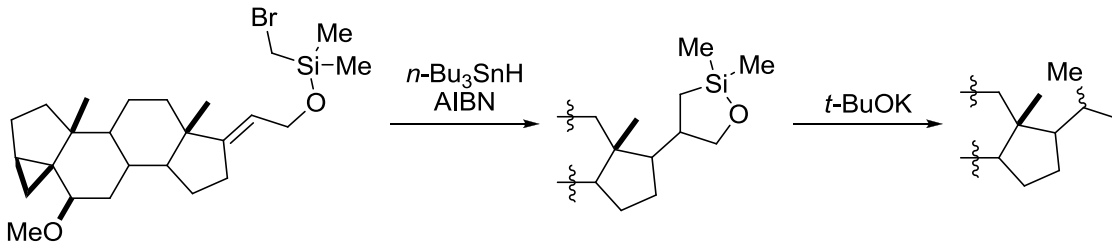
Tethered radical cyclizations involving silicon were reported in the 1980s by Nishiyama and Stork (equations 1.12 and 1.13),[20] and this was followed years later by Wicha,[21] who followed the radical cyclization with a protodesilylation instead of oxidation to the diol (equation 1.14). A boron variant was then reported from the Batey group more than ten years later (equation 1.15).[22]



(1.12)

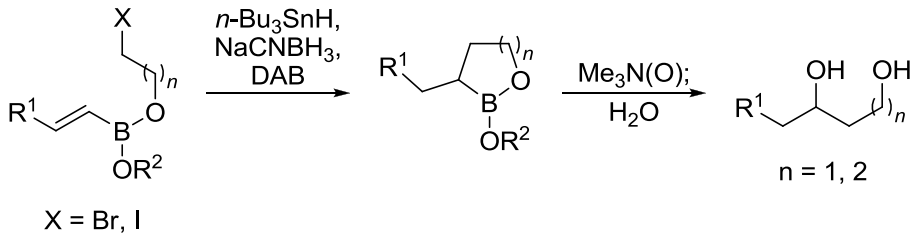


(1.13)



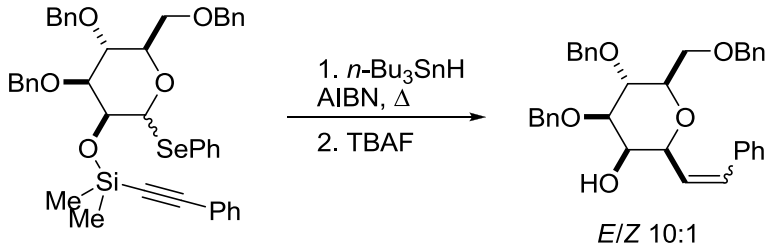
(1.14)

(20) (a) Nishiyama, H.; Kitajima, T.; Matsumoto, M.; Itoh, K. *J. Org. Chem.* **1984**, *49*, 2298. (b) Stork, G.; Kahn, M. *J. Am. Chem. Soc.* **1985**, *107*, 500.
(21) (a) Kurek-Tyrlik, A.; Wicha, J.; Snatzke, G. *Tetrahedron Lett.* **1988**, *29*, 4001. (b) Kurek-Tyrlik, A.; Wicha, J.; Zarecki, A.; Snatzke, G. *J. Org. Chem.* **1990**, *31*, 4445.
(22) Batey, R. A.; Smil, D. V. *Angew. Chem. Int. Ed.* **1999**, *38*, 1798.

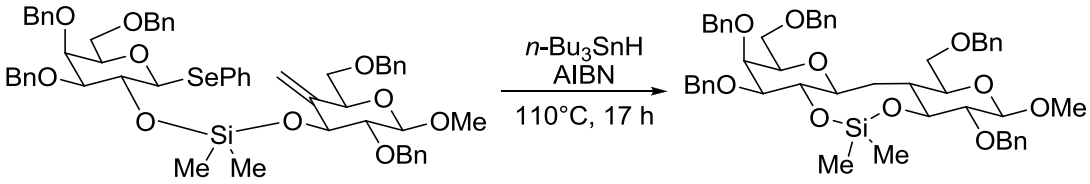


(1.15)

The approach of tethered radical-mediated reactions was also applied to the stereospecific synthesis of *C*-glycosides (equation 1.16),[23] and the construction of *C*-disaccharides has been performed in a similar manner (equation 1.17).[24a]



(1.16)



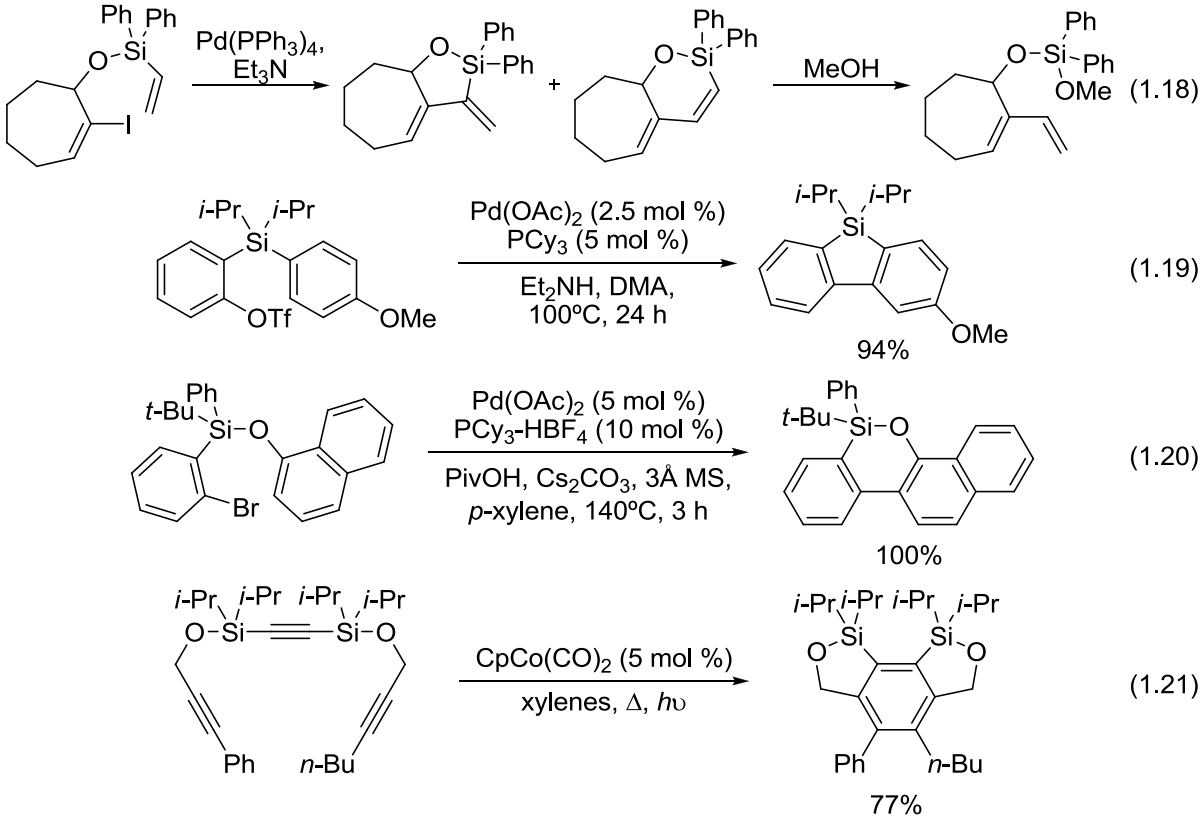
(1.17)

1.2.4 Metal-catalyzed reactions

The tethering strategy has also been used in combination with metal-catalyzed intermolecular reactions. Young developed a silicon-tethered Heck reaction (equation 1.18) in 2001 to access a key intermediate in the total synthesis of the natural product curcusone A,[25] and palladium-catalyzed couplings of silicon-tethered aryl triflates and halides[26] were reported

(23) Stork, G.; Suh, H. S.; Kim, G. *J. Am. Chem. Soc.* **1991**, *113*, 7054.
(24) (a) Rubinstenn, G.; Mallet, J.-M.; Sinaÿ, P. *Tetrahedron Lett.* **1998**, *39*, 3697. See also: (b) Rubinstenn, G.; Esnault, J.; Mallet, J.-M.; Sinaÿ, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1327.
(25) Mayasundari, A.; Young, D. G. J. *Tetrahedron Lett.* **2001**, *42*, 203.
(26) (a) Shimizu, M.; Mochida, K.; Hiyama, T. *Angew. Chem. Int. Ed.* **2008**, *47* , 9760. (b) Huang, C.; Gevorgyan, V. *J. Am. Chem. Soc.* **2009**, *131*, 10844. (c) Mochida, K.; Shimizu, M.; Hiyama, T. *J. Am. Chem. Soc.* **2009**, *131*, 8350.

more recently (equations 1.19 and 1.20). Another example of a metal-catalyzed reaction involving tethered substrates was demonstrated by Malacria and co-workers.[27] His group achieved a copper-catalyzed chemo- and regioselective cyclotrimerization of alkynes to access functionalized aryl rings using up to two silicon tethers (equation 1.21), which were cleaved to give the corresponding diols.



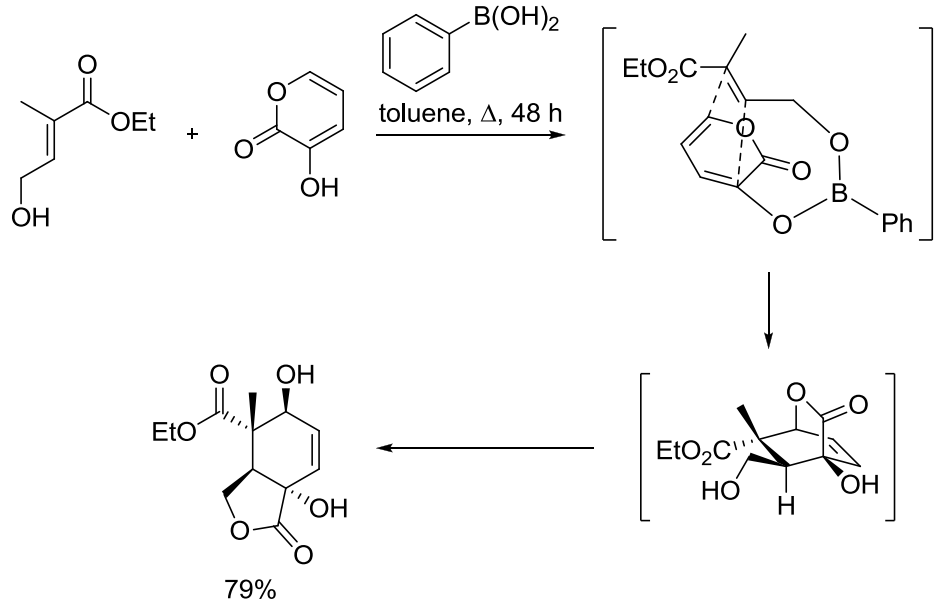
1.2.5 Tethers in total synthesis

Tethered reactions have also been used in the total syntheses of complex molecules, further displaying the versatility and applicability of this strategy. After struggling with the regioselectivity of an intermolecular Diels-Alder reaction towards the total synthesis of taxol,

(27) Chouraqui, G.; Petit, M.; Aubert, C.; Malacria, M. *Org. Lett.* **2004**, *6*, 1519.

Nicolaou turned to a boron tether using phenylboronic acid.[28] After removal of the boronic ester linkage with 2.2-dimethyl-1,3-propanediol, the desired synthetic intermediate was obtained in 79% yield (Scheme 1.4).

Scheme 1.4: Synthesis of key intermediate of taxol via boron-tethered Diels-Alder reaction

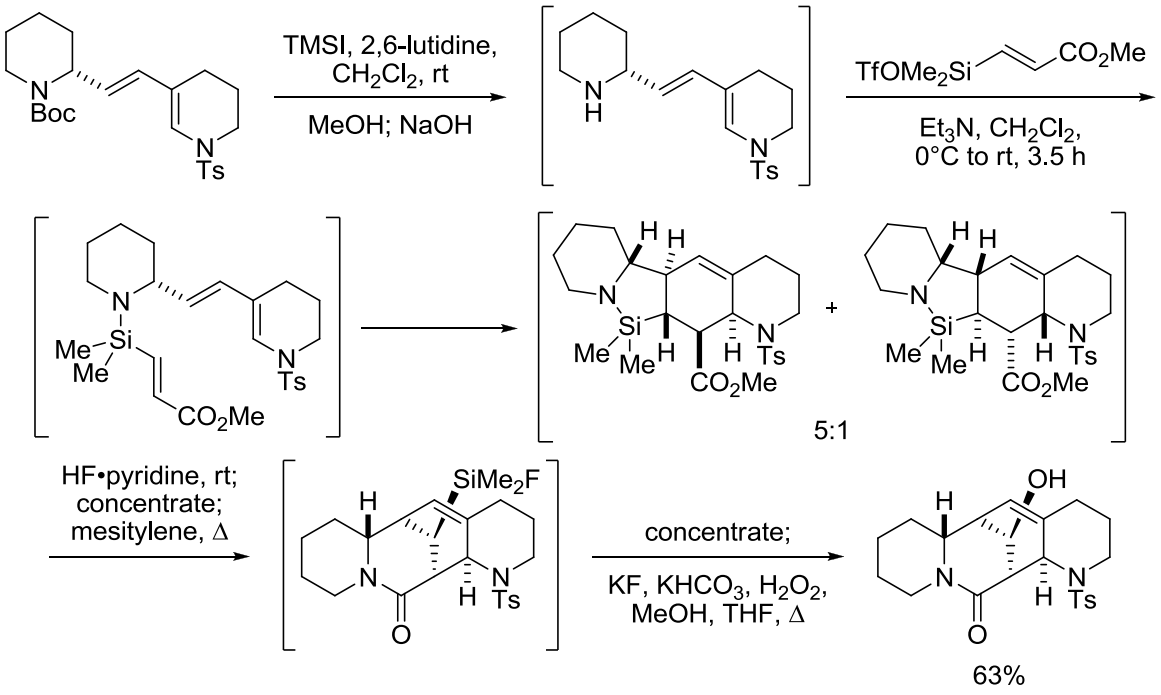


The Overman group also utilized a tethering strategy after struggling with an intermolecular Diels-Alder reaction in their total synthesis of (+)-aloperine.[29] Upon formation of the silicon-tethered triene, the desired cycloadduct was obtained directly in a 5:1 ratio (Scheme 1.5). The moisture-sensitive cycloadduct was then converted to the more stable tetracyclic alcohol through a number of steps in a 63% yield from the Boc-protected diene.

(28) 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.
(29) Brosius, A. D.; Overman, L. E.; Schwink, L. *J. Am. Chem. Soc.* **1999**, *121*, 700.

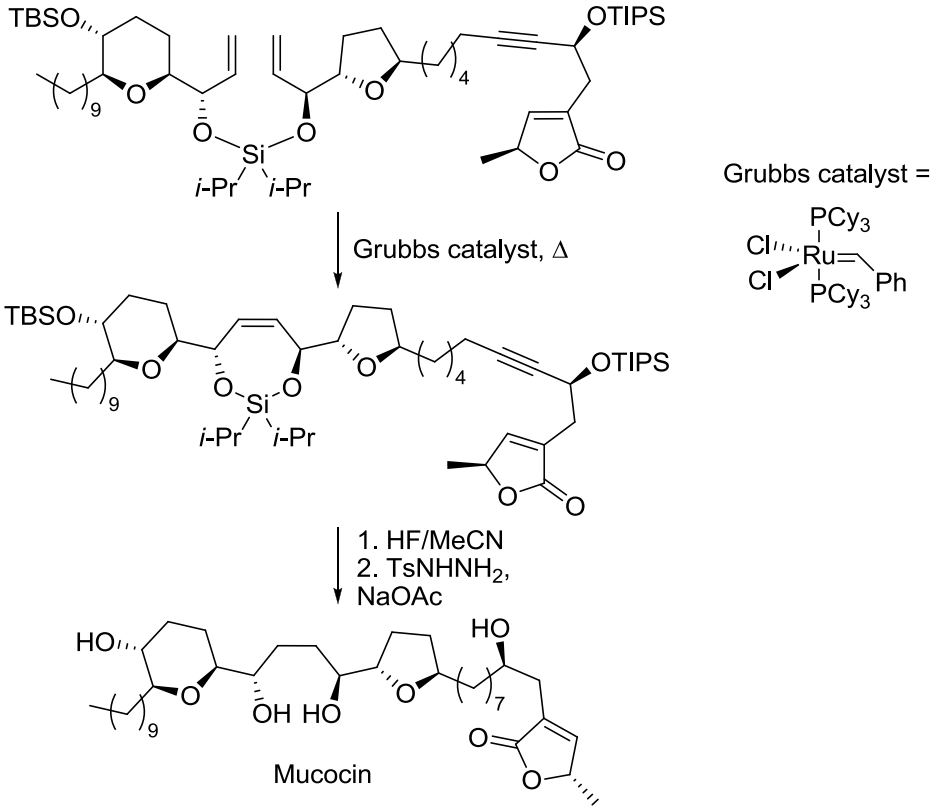
In 2003, Evans and co-workers employed a silicon-tethered olefin metathesis in the total synthesis of the antitumor agent (−)-mucocin.[30] This strategy allowed them to access the required *Z*-alkene product, which was obtained in 83% yield (Scheme 1.6).

Scheme 1.5: Silicon-tethered Diels-Alder reaction towards the total synthesis of (+)-aloperine



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

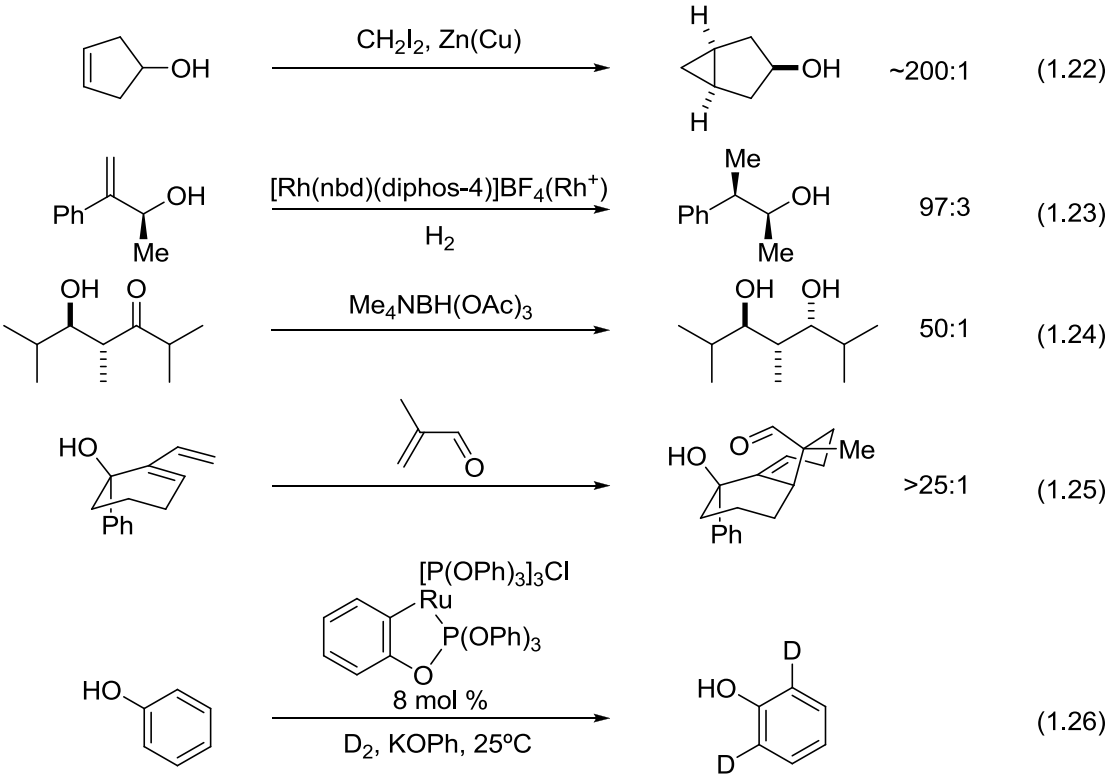
Scheme 1.6: Total synthesis of (−)-mucocin via silicon-tethered ring-closing metathesis



Many other organic transformations have been carried out using tethering groups, thus it is clear that tethering is a widely applicable strategy. They allow these transformations to proceed with excellent control and selectivity and can greatly facilitate difficult intermolecular reactions by alleviating the negative entropy change associated with these processes, making it a versatile and powerful tool for organic chemists. However, the use of tethering strategies typically results in a lengthening of synthetic schemes due to the stoichiometric and stepwise incorporation and removal of tethers.

1.3 Directed reactions

In intermolecular reactions, selectivity is typically governed through nonbonding interactions or by stereoelectronic effects which dictate the path of attack of the incoming reagent. However, preassociation of the reacting species through hydrogen bonding, covalent bonding or Lewis acid-base interactions can result in chemical transformations with very high selectivities, often opposite to those predicted by steric effects.[31]



Directing groups have been employed for stereocontrol in a variety of organic transformations, including cyclopropanation,[32] hydrogenation,[33] reduction,[34] cycloaddition,[35]

(31) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.
(32) (a) Winstein, S.; Sonnenberg, J. *J. Am. Chem. Soc.* **1961**, *83*, 3235. See also: (b) Simmons, H. E.; Smith, R. D. *J. Am. Chem. Soc.* **1959**, *81*, 4256.
(33) (a) Brown, J. M.; Naik, R. G. *J. Chem. Soc., Chem. Commun.* **1982**, 348. See also: (b) Brown, J. M.; Cutting, I. *J. Chem. Soc., Chem. Commun.* **1985**, 578. (c) Thompson, H. W.; McPherson, E. *J. Am. Chem. Soc.* **1974**, *96*, 6232.

and orthometalation[36] (equations 1.22-1.26). These examples typically feature oxygen-containing functional groups in the vicinity of the reaction centre and exhibit excellent regio- and stereoselectivities.

1.3.1 Directed epoxidation

Directed epoxidation is one transformation that demonstrates the power of this strategy. In 1957, Henbest and Wilson reported that treatment of cyclohex-2-en-1-ol with perbenzoic acid resulted predominantly in the formation of *syn* epoxy alcohol (equation 1.27), with a diastereomeric ratio of 10:1.[37] In contrast, the oxidation of the acetyl derivative provided the product in the *anti* configuration in a 4:1 ratio, and was found to proceed at a much slower rate (equation 1.28). Thus, Henbest postulated that the hydroxyl group, through hydrogen bonding with the peracid, had a definite role in both facilitating the reaction and determining the stereochemical outcome (Figure 1.3). Directed epoxidations are not limited to cyclic allylic alcohols, however, as cyclic homoallylic alcohols and various acyclic alkenyl alcohols have also been oxidized with high degrees of stereocontrol.

---

(34) (a) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939. For selected examples, see also: (b) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273. (c) Turnbull, M. D.; Hatter, G.; Ledgerwood, D. E. *Tetrahedron Lett.* **1984**, *25*, 5449. (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. (f) Adams, J.; Poupart, M.-A.; Grenier, L. *Tetrahedron Lett.* **1989**, *30*, 1753.
(35) (a) Barriault, L.; Thomas, J. D. O.; Clément, R. *J. Org. Chem.* **2003**, *68*, 2317. For other examples of directed cycloadditions, see: (b) Krafft, M. E.; *J. Am. Chem. Soc.* **1988**, *110*, 968. (c) Krafft, M. E.; Juliano, C. A.; Scott, I. L.; Wright, C.; McEachin, M. D. *J. Am. Chem. Soc.* **1991**, *113*, 1693. (d) Curran, D. P.; Choi, S. M.; Gothe, S. A.; Lin, F. T. *J. Org. Chem.* **1990**, *55*, 3710.
(36) (a) Lewis, L. N. *Inorg. Chem.* **1985**, *24*, 4433. See also: (b) Parshall, G. W.; Knoth, W. H.; Schunn, R. A. *J. Am. Chem. Soc.* **1969**, *91*, 4990. (c) Lewis, L. N.; Smith, J. F. *J. Am. Chem. Soc.* **1986**, *108*, 2728. For selected reviews on orthometalations, see: (d) Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1. (e) Ritleng, V.; Sirlin, C.; Pfeffer, M. *Chem. Rev.* **2002**, *102*, 1731.
(37) Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1957**, 1958.

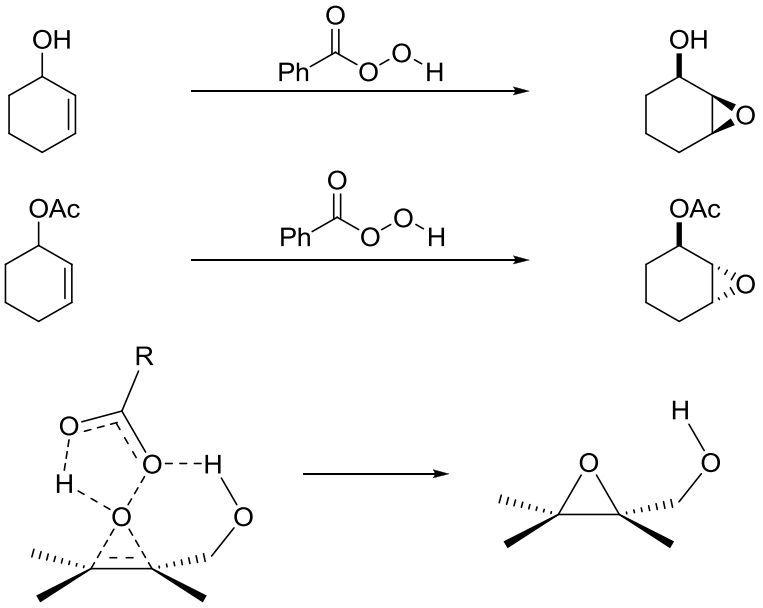
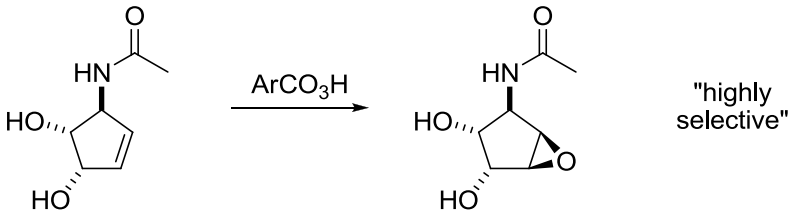


Figure 1.3: Proposed mechanism of directed peracid epoxidation

Alcohols are not the only functional groups capable of directing epoxidations. Highly selective epoxidations directed by amides,[38] ureas[39] and urethanes[40] have been reported for both cyclic and acyclic olefins, while silyl ethers,[41] carbamates[40] and nitro groups[42] have acted as proton *acceptors*, forming hydrogen bonds with the peracid proton (equations 1.29-1.33).



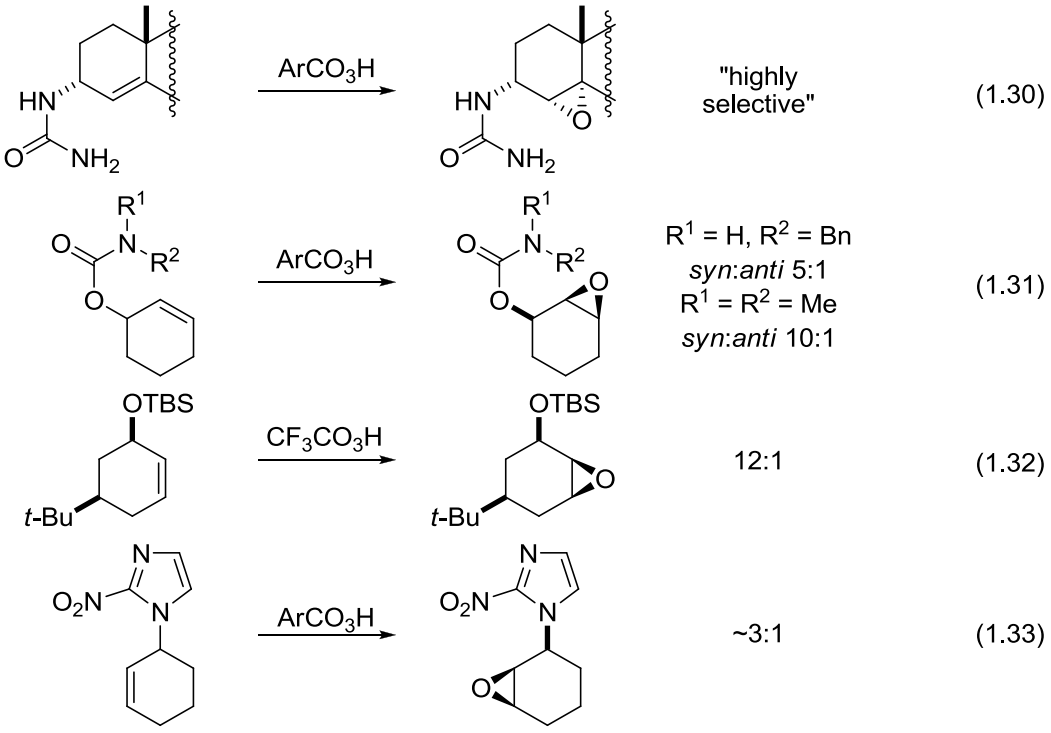
(38) (a) Mohamadi, F.; Spees, M. M. *Tetrahedron Lett*. **1989**, *30*, 1913. (b) Hasegawa, A.; Sable, H. Z. *J. Org. Chem*. **1966**, *31*, 4154. (c) Goodman, L.; Winstein, s.; Boschan, R. *J. Am. Chem. Soc.* **1958**, *80*, 4312. (d) Lukacs, G.; Fukushima, D. K. *J. Org. Chem.* **1969**, *34*, 2707.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

(39) Fukushima, D. K.; Smulowitz, M.; Liang, J. S.; Lukacs, G. *J. Org. Chem.* **1969**, *34*, 2702. Also, ref 38e.

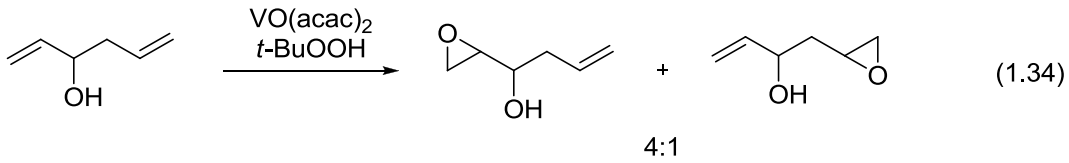
(40) (a) Rotella, D. P. *Tetrahedron Lett.* **1989**, *30*, 1913. (b) Kogen, H.; Nishi, T. *J. Chem. Soc., Chem. Commun.* **1987**, 311. See also ref 38e.

(41) McKittrick, B. A.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 4895.

(42) Threadgill, M. D.; Webb, P. *J. Chem. Soc., Chem Commun.* **1991**, 269.



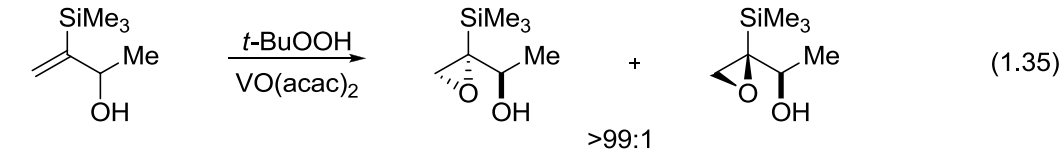
Directed metal-catalyzed epoxidations have been reported as well, commonly with vanadium and molybdenum catalysts. In 1970, Sheng and Zajacek demonstrated that these metals catalyzed the regioselective epoxidation of 1,5-hexadien-3-ol with *tert*-butyl hydroperoxide, but did not determine the diastereoselectivity (equation 1.34).[43]



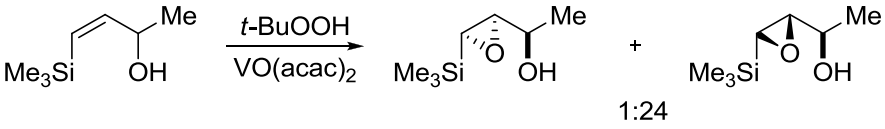
Three years later, Sharpless observed that vanadium and molybdenum catalyzed the epoxidations of allylic and homoallylic alcohols with exceedingly high stereoselectivity. Oxidations of both cyclohex-2-en-1-ol and cyclohex-3-en-1-ol provided the epoxy alcohols in excellent *syn*:*anti* ratios of 98:2 with *t*-BuOOH and catalytic $Mo(CO)_6$ or $VO(acac)_2$.[44] Cyclic

(43) Sheng, M. N.; Zajacek, J. G. *J. Org.Chem.* **1970**, *35*, 1839.
(44) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

allylic alcohols of smaller and larger ring sizes were epoxidized with tremendously high *syn*:*anti* ratios compared to those provided by epoxidation with peracids,[45] and homoallylic and bishomoallylic alcohols are also known to effectively direct this reaction.[46]



(1.35)



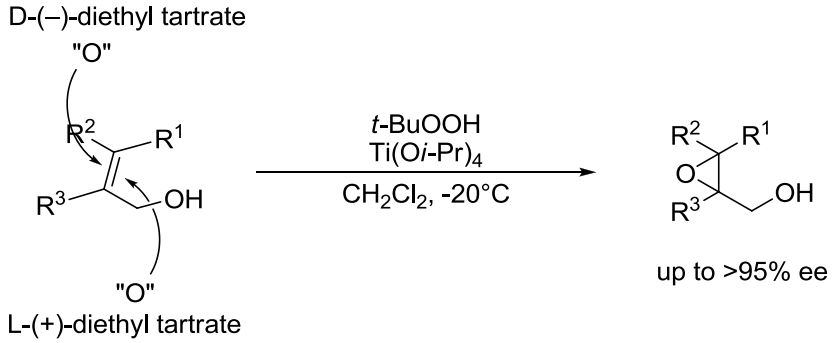
(1.36)

Metal-catalyzed epoxidations of acyclic olefinic alcohols are highly selective as well. In allylic systems, the minimization of A(1,2) and A(1,3) strain typically dictates this selectivity. Systems containing high A(1,2) strain favour the formation of the *anti* isomer (equation 1.35), while the *syn* isomer is favoured for systems with A(1,3) strain (equation 1.36).[47] Acyclic homoallylic and even bis- and trishomoallylic alcohols are also known to undergo metal-catalyzed epoxidations with high diastereoselection.[48]

However, the landmark discovery in directed epoxidations was reported by Sharpless in 1980.[49] Using both stoichiometric and catalytic amounts of Ti(O*i*-Pr)$_4$ and L-(+)-diethyl tartrate with *t*-BuOOH, he achieved the first practical asymmetric epoxidation of various allylic alcohols

(45) (a) Itoh, T.; Kaneda, K.; Teranishi, S. *J. Chem. Soc., Chem. Commun.* **1976**, 421. (b) Dehnel, R. B.; Whitham, G. H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 953.
(46) (a) Pearson, A. J.; Ong, C. W. *Tetrahedron Lett.* **1980**, *21*, 4641. (b) Corey, E. J.; De, B. *J. Am. Chem. Soc.* **1984**, *106*, 2735. (c) Stork, G.; Nakahara, Y.; Nakahara, Y.; Greenlee, W. J. *J. Am. Chem. Soc.* **1978**, *100*, 7775. (d) Irvine, R. W.; Russell, R. A.; Warrener, R. N. *Tetrahedron Lett.* **1985**, *26*, 6117.
(47) Narula, A. S. *Tetrahedron Lett.* **1982**, *23*, 5485.
(48) For selected examples, see: (a) Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 7690. (b) Hanamoto, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 6191. (c) Mohr, P.; Tamm, C. *Tetrahedron Lett.* **1987**, *28*, 391. (d) Fukuyama, T.; Vranesic, B.; Negri, D. P.; Kishi, Y. *Tetrahedron Lett.* **1978**, *19*, 2741. (e) Hanessian, S.; Cooke, N. G.; DeHoff, B.; Sakito, Y. *J. Am. Chem. Soc.* **1990**, *112*, 5276.
(49) Katsuki, T.; Sharpless, K. B. *J. Am. Cem. Soc.* **1980**, *102*, 5974.

with enantiomeric excess (ee) of up to >95% (equation 1.37). A particularly noteworthy observation was that the peroxide reacted almost exclusively with one face of the olefin for a given tartrate enantiomer, and that the opposite face was attacked when using the opposite enantiomer. One could argue that a titanium atom plays a tethering role in the proposed transition state, bonding with both the allylic alcohol and the peroxide. For this work, he was awarded the Nobel Prize in chemistry which he shared in 2002 with Knowles and Noyori.



(1.37)

1.3.2 Recent advances in directed reactions

Researchers in the Tan group have developed a new strategy employing a catalytic "scaffolding" ligand,[50] which simultaneously binds alcoholic substrates and a metal catalyst in a reversible manner (Figure 1.4). This strategy was applied towards the hydroformylation of various homoallylic alcohols with good to excellent regioselectivity and high diastereomeric ratios (equation 1.38). The scope of this reaction has since been extended to allylic sulphonamides for the preparation of β-amino aldehydes.[50b]

(50) (a) Lightburn, T. E.; Dombrowski, M. T.; Tan, K. L. *J. Am. Chem. Soc.* **2008**, *130*, 9210. (b) Worthy, A. D.; Gagnon, M. M.; Dombrowski, M. T.; Tan, K. L. *Org. Lett.* **2009**, *11*, 2764. (c) Sun, X.; Frimpong, K.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 11841.

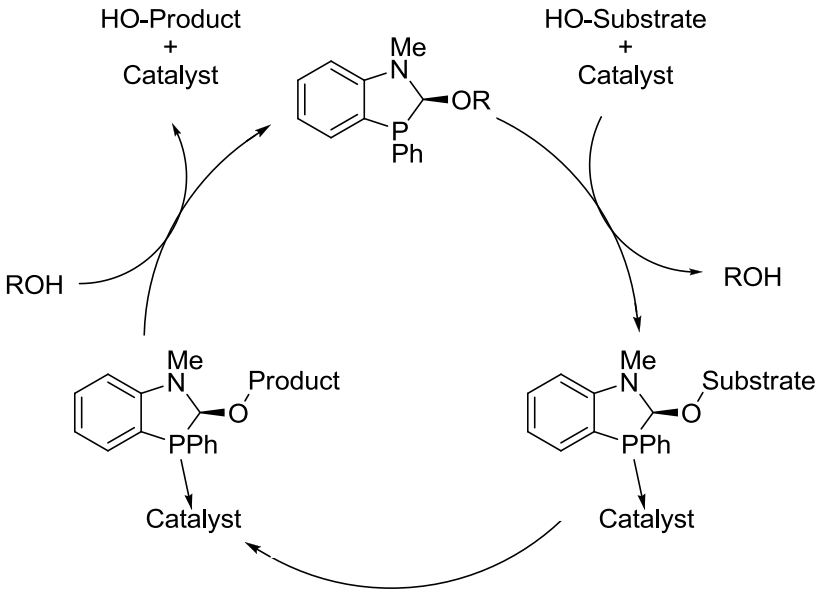
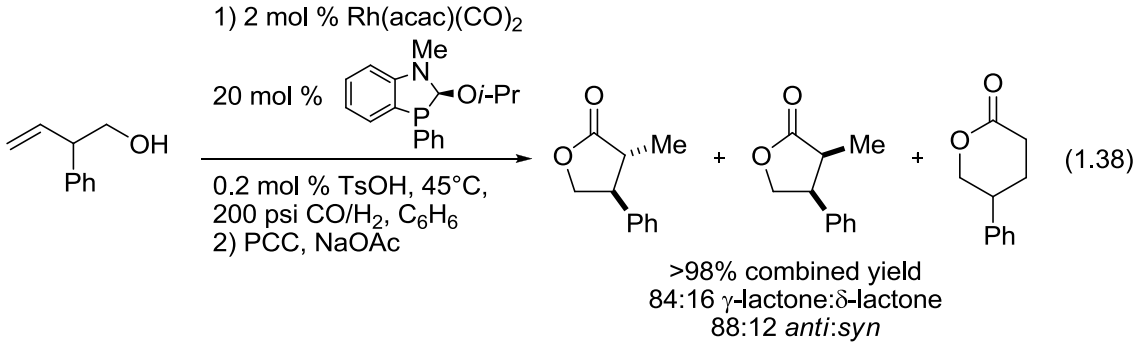


Figure 1.4: Catalytic cycle of scaffold-directed hydroformylation



Another new and similar strategy in directed reactions developed by Breit involves supramolecular catalysts that bind to a metal centre and the substrate through multiple hydrogen bonds (Figure 1.5).[51] The biologically-inspired system exhibited excellent catalytic activity (TOF = 250 h^{-1}), and was applied to the hydroformylation of unsaturated carboxylic acids in high yields and with high regioselectivity (equation 1.39).[51a] Lower reactivity and

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

regioselectivity were observed for γ,δ-unsaturated carboxylic acids compared with β,γ-unsaturated acids, and were further decreased for β,γ-unsaturated esters.

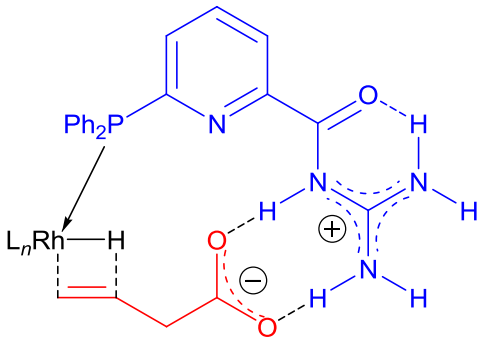
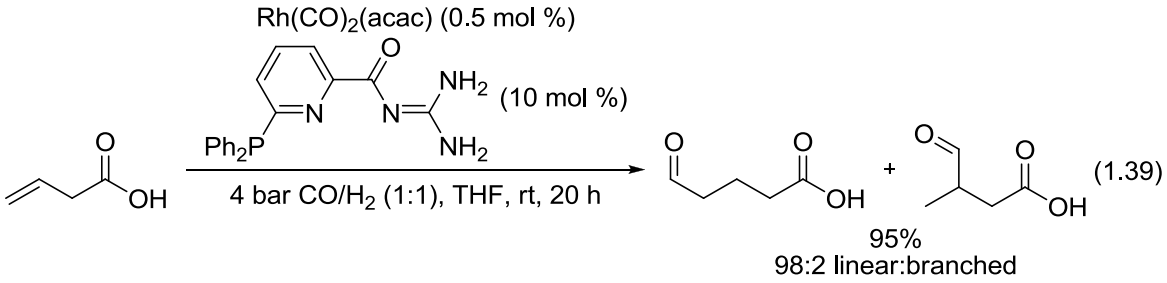


Figure 1.5: Breit's design for supramolecular catalyst



This strategy was also applied to the decarboxylative hydroformylation of α,β-unsaturated carboxylic acids.[51b] The proposed mechanism is comprised of three main steps (Figure 1.6): First, the substrate coordinates to the rhodium centre via the olefin and to the supramolecular ligand through hydrogen bonding with the guanidine moiety. Hydroformylation occurs selectively at the α-position, forming the α-formyl acid intermediate, which decarboxylates to provide the aldehyde product.

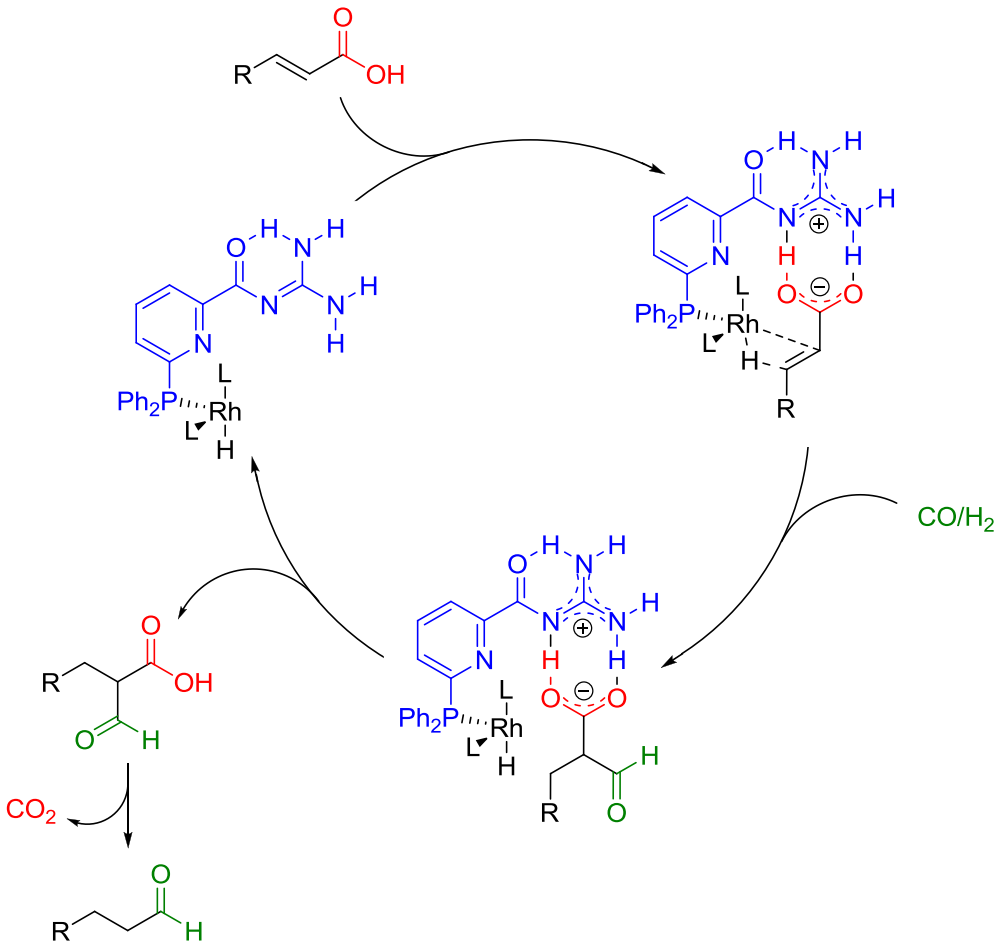


Figure 1.6: Proposed catalytic cycle of decarboxylative hydroformylation via supramolecular catalysis

Indeed, directing groups provide high levels of regio- and stereocontrol in organic transformations. Many examples of directed reactions have been reported in the literature, giving organic chemists an alternative approach to performing highly selective intermolecular reactions.

1.4 Conclusion and future potential

It is clear that tethers and directing groups can enhance the rate and control of a variety of intermolecular reactions. This is achieved through the preassociation of the substrate with the reagent, such that the reaction temporarily becomes intramolecular. Examples of catalytic

tethers are very rare, but the groups of Tan and Breit have developed ligands that act as catalytic directing groups, simultaneously binding the substrate and a metal centre. Due to the versatility of tethering strategies and the lack of non-stoichiometric variants, we became interested in developing a catalytic approach involving a small organic molecule as the tether (Figure 1.7). In this way, we hoped to address the negative entropy problems and low selectivity of difficult intermolecular reactions, without the stepwise and stoichiometric tether incorporation and cleavage.

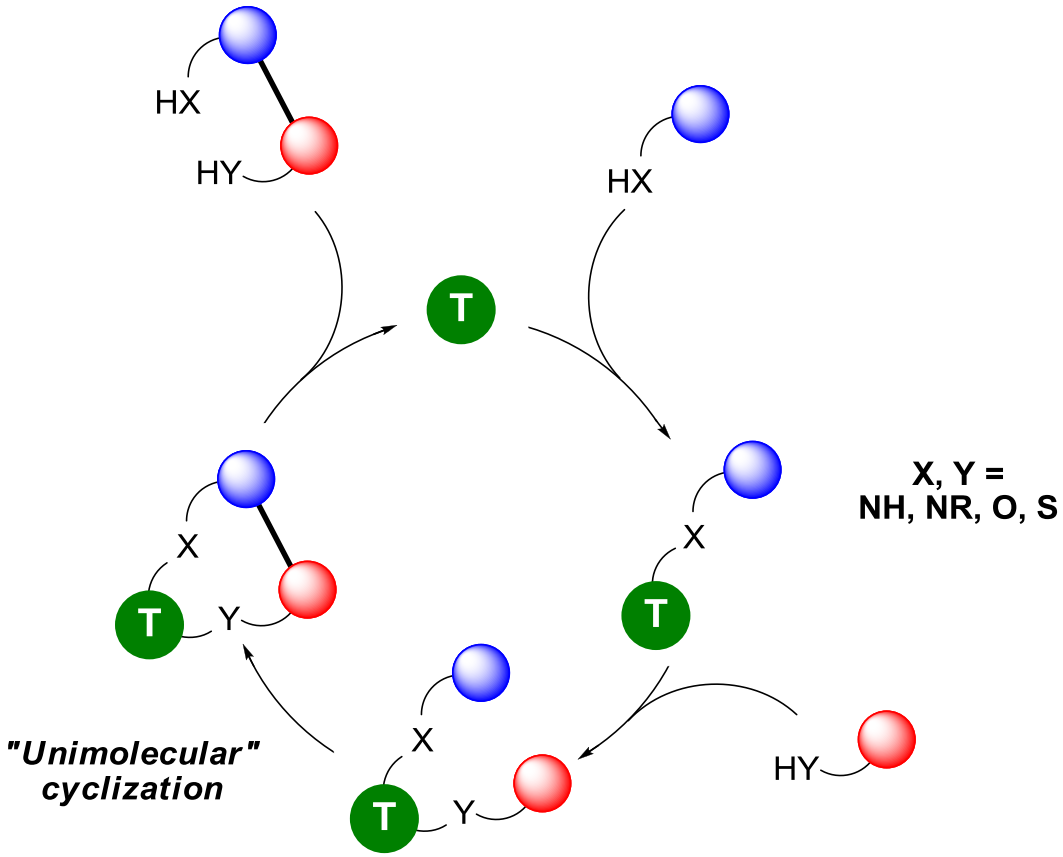


Figure 1.7: Cycle for proposed catalytic tether

Chapter 2. Intermolecular Hydroamination of Alkenes

2.1 Introduction

Nitrogen-containing molecules are ubiquitous both in nature and in laboratory environments. More than 90% of drugs include a nitrogen atom, and 15% of reactions in the pharmaceutical industry involve the formation of a carbon-nitrogen bond.[52] Thus, it is clear that the construction of nitrogen-containing molecules is of great importance. With the low cost and wide availability of olefins, hydroamination, the addition of an N-H bond across an unsaturated carbon-carbon bond, is one of the simplest and most attractive routes to these desired compounds (Figure 2.1). Hydroamination has become the subject of intense study in recent years, however no general solution currently exists.[53] Especially in the intermolecular case of alkenes, the challenge arises due to the negative entropy change of this reaction. Thus, increasing temperature is generally not a solution for overcoming the high activation energy. Many reports of intermolecular hydroaminations with varying degrees of success have been given in the literature, and examples will be touched upon in this chapter.

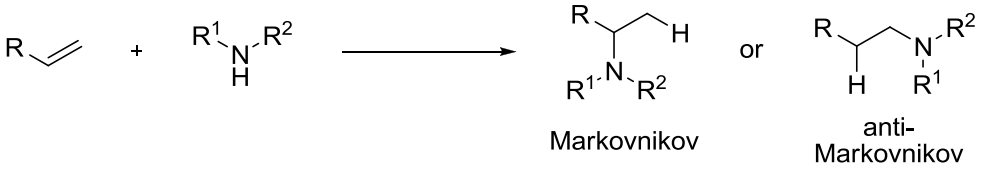


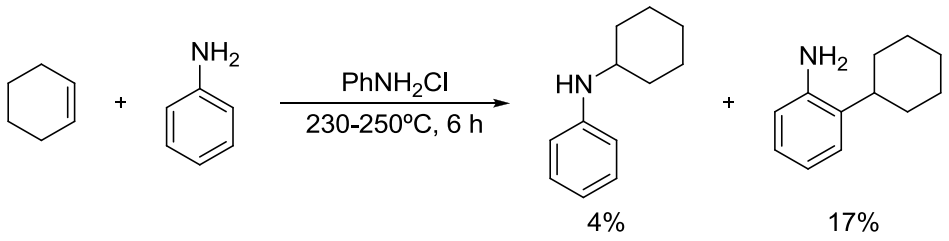
Figure 2.1: Intermolecular hydroamination of alkenes

(52) (a) Dugger, R. W.; Ragan, J. A.; Brown Ripin, D. H. *Org. Proc. Res. Dev.* **2005**, *9*, 253. (b) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* **2006**, *4*, 2337.
(53) For a recent comprehensive review, see: Müller, T.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795.

2.2 Acid-catalyzed hydroamination

Acid catalysis is a simple and direct method for the hydroamination of alkenes. Similar to the Ritter reaction,[54] a carbocation generated through alkene protonation combines with an amine to provide the hydroamination adduct and regenerate the acidic proton. However, since amines are inherently basic, acid-base reactions occur, causing the deactivation of the amine and insufficient alkene protonation. Thus, acid-catalyzed hydroaminations in literature typically feature weakly basic nitrogen-containing compounds, such as sulphonamides, amides or anilines.

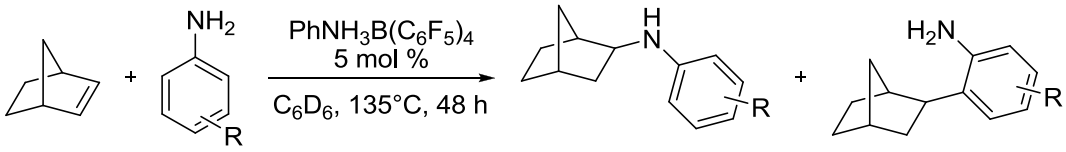
The first intermolecular hydroamination of alkenes under acidic conditions was reported by Hickinbottom in 1932,[55] requiring very high temperatures and with poor yields. Cyclohexene was heated in the presence of aniline and anilinium chloride, providing the hydroamination product in only 4% yield (equation 2.1). Additions to 1,4-dihydronaphthalene, styrene and butadiene were also reported, again at high temperatures and in low yields.[55b,c]



(2.1)

(54) (a) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045. For a review of the Ritter reaction, see: (b) Krimen, L. I.; Cota, D. J. *Org. React.* **1969**, *17*, 213.
(55) (a) Hickinbottom, W. J. *J. Chem. Soc.* **1932**, 2646. (b) Hickinbottom, W. J. *J. Chem. Soc.* **1934**, 319. (c) Hickinbottom, W. J. *J. Chem. Soc.* **1934**, 1981.

More than 70 years later in 2005, Bergman reported the hydroamination and hydroarylation of norbornene using aniline derivatives with catalytic $PhNH_3B(C_6F_5)_4$.[56] Electron-poor aniline derivatives favoured the hydroamination product, while the hydroarylation was preferred when the aniline possessed electron-donating substituents (equation 2.2). Under these conditions, Markovnikov hydroamination and hydroarylation of styrene derivatives was also reported with similar results. Notably, the hydroamination was favoured at lower temperatures and with shorter reaction times, while the opposite favoured Ar-H addition. Reactions with cyclic alkenes and dienes provided mainly the hydroarylation products, however electron-poor anilines gave exclusively the hydroamination product. Doye has reported addition of anilines to similar substrates catalyzed by aqueous HI, however again, hydroarylation was a competitive side reaction.[57]

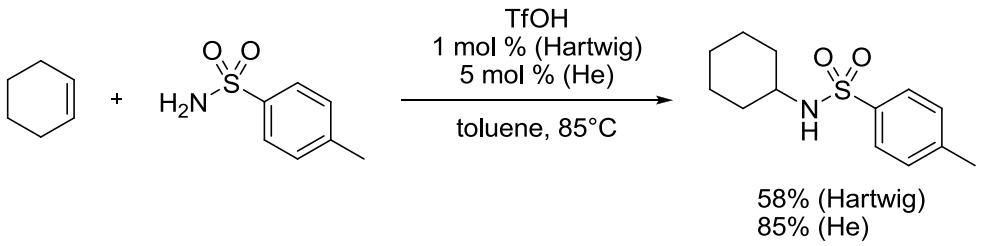


(2.2)

In 2006, Hartwig and He nearly simultaneously reported triflic acid catalyzed hydroaminations of various alkenes in moderate to excellent yields.[58] As little as 1 mol % of triflic acid was sufficient to catalyze the addition of less basic amines, such as amides, sulphonamides and carbamates, to strained alkenes, vinylarenes, and cyclic and acyclic alkenes

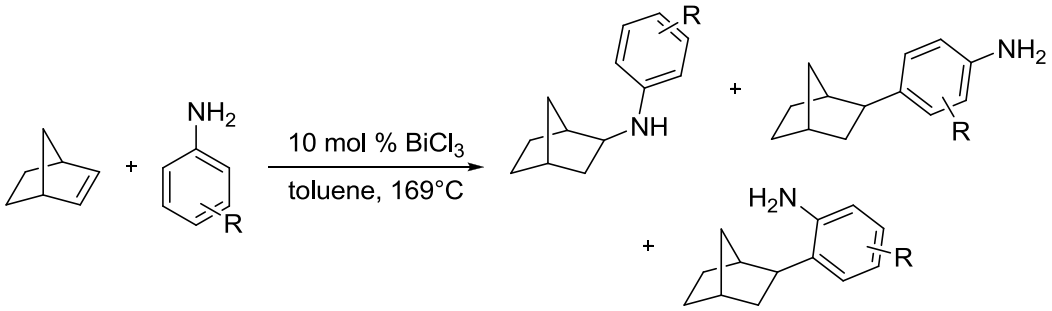
(56) Anderson, L. L.; Arnold, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 14542.
(57) Marcseková, K.; Doye, S. *Synthesis* **2007**, 145.
(58) (a) Li, Z.; Zhang, J.; Brouwer, C.; Yang, C.-G.; Reich, N. W.; He, C. *Org. Lett.* **2006**, *8*, 4175. (b) Rosenfeld, D. C.; Shekhar, S.; Takemiya, A.; Utsunomiya, M.; Hartwig. J. F. *Org. Lett.* **2006**, *8*, 4179.

and dienes (equation 2.3). Kaneda experienced comparable success utilizing a proton-exchanged montmorillonite as a heterogeneous Brønsted acid catalyst.[59]



(2.3)

Lewis acids have catalyzed intermolecular hydroaminations through the generation of Brønsted acids by reacting with the nitrogen nucleophile. $AlCl_3$, $FeCl_3$, $BiCl_3$ and $SnCl_4$ have catalyzed the additions of anilines in good yields[60] with hydroarylation once again as a competitive side reaction (equation 2.4). However, the formation of these side products can be reduced or eliminated with electron-withdrawing groups on the aniline.



(2.4)

Tilley and Bell have reported that Pt(II) complexes catalyze the hydroaminations of alkenes with weakly nucleophilic amines, such as sulphonamides and electron-poor anilines (equation 2.5),[61] and mechanistic studies showed that these complexes operated through a

(59) Motokura, K.; Nakagiri, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Jitsukawa, K.; Kaneda, K. *Org. Lett.* **2006**, *8*, 4617.
(60) (a) Wei, H.; Qian, G.; Xia, Y.; Li, K.; Li, Y.; Li, W. *Eur. J. Org. Chem.* **2007**, 4471. (b) Michaux, J.; Terrasson, V.; Marque, S.; Wehbe, J.; Prim, D.; Campagne, J.-M. *Eur. J. Org. Chem.* **2007**, 2601.
(61) (a) Karshtedt, D.; Bell, A. T.; Tilley, T. D. *J. Am. Chem. Soc.* **2005**, *127*, 12640. (b) McBee, J. L.; Bell, A. T.; Tilley, T. D. *J. Am. Chem. Soc.* **2008**, *130*, 16562.

similar metal-generated acid catalysis (Figure 2.2).[61b] Other Lewis acids reported to catalyze hydroaminations include $TiCl_4$,[62] $InBr_3$,[63] and $Bi(OTf)_3$,[64] however, alternate mechanisms were suggested for these reactions. Hydroaminations catalyzed by Au(I)[65] complexes appear to operate in this fashion, however such a mechanism was not proposed by the authors.

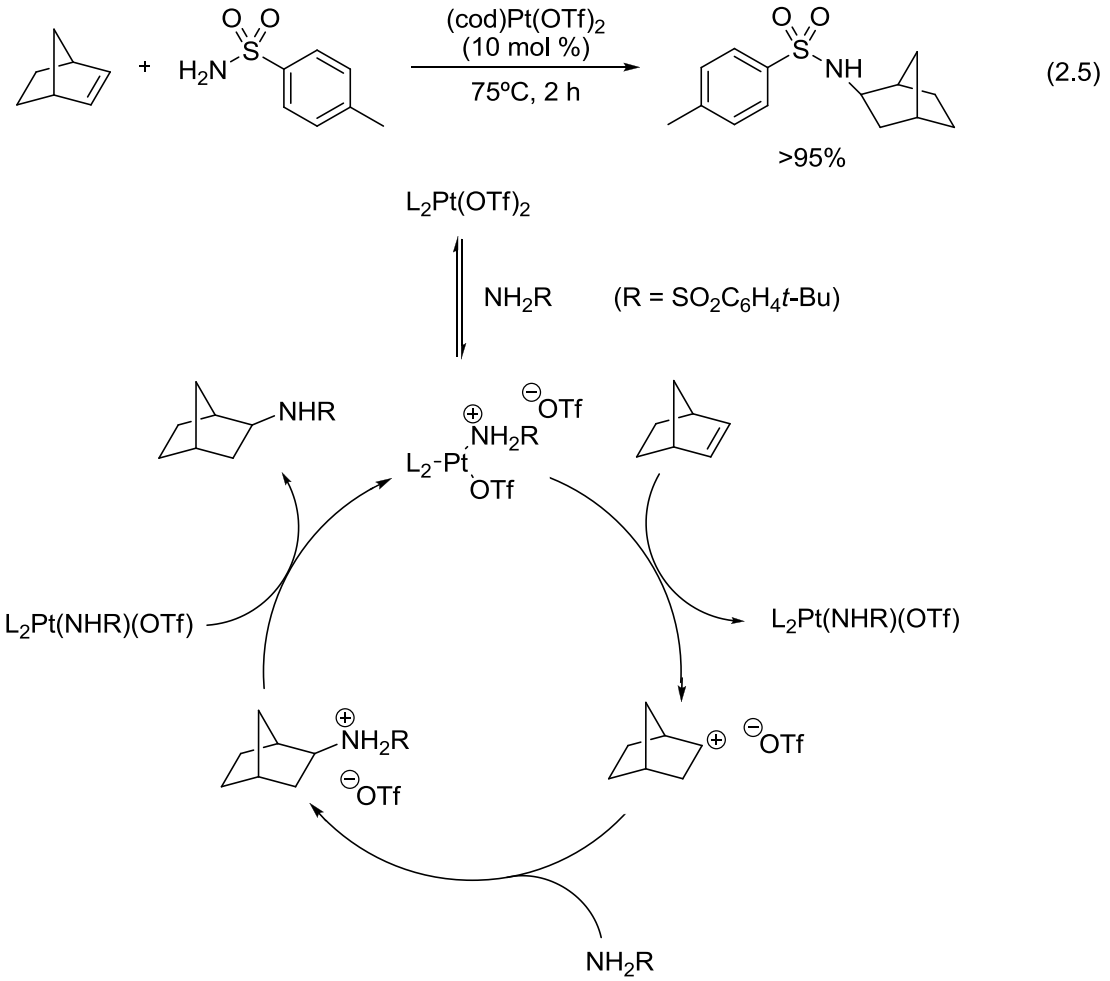
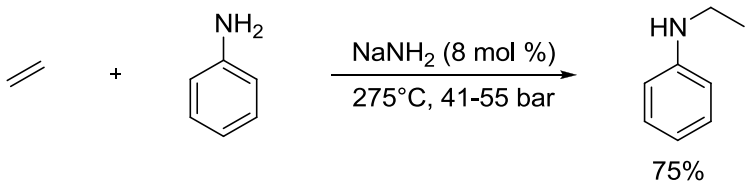


Figure 2.2: Catalytic cycle of Pt-catalyzed hydroamination of norbornene

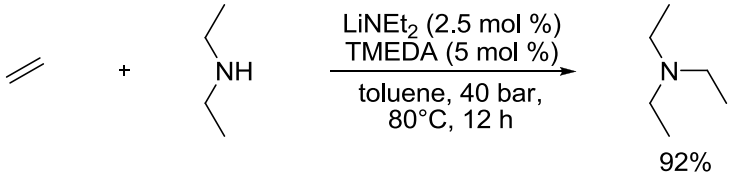
(62) (a) Ackermann, L.; Kaspar, L. T.; Gschrei, C. J. *Org. Lett.* **2004**, *6*, 2515. (b) Kaspar, L. T.; Fingerhut, B.; Ackermann, L. *Angew. Chem. Int. Ed.* **2005**, *44*, 5972.
(63) Huang, J.-M.; Wong, C.-M.; Xu, F.-X.; Loh, T.-P. *Tetrahedron Lett.* **2007**, *48*, 3375.
(64) Qin, H.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 1611.
(65) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798.

2.3 Base-catalyzed hydroamination

Deprotonation greatly increases the nucleophilicity of amines, allowing the use of more basic nitrogen compounds.[66] However, this is incompatible with substrates that feature electrophiles or functional groups more acidic than amines, and bishydroaminations are frequently observed. Typically, strong bases are used, and high pressures and temperatures are often required.[67] Early examples were described by Whitman and co-workers, featuring alkali metal catalysis for the amination of olefins, and similar work was reported by Kolka several years later (equation 2.6). Many years later, the groups of Beller and Hultzsch found that chelating ligands such as TMEDA and (−)-sparteine enhanced reactivity (equations 2.7 and 2.8).[68]

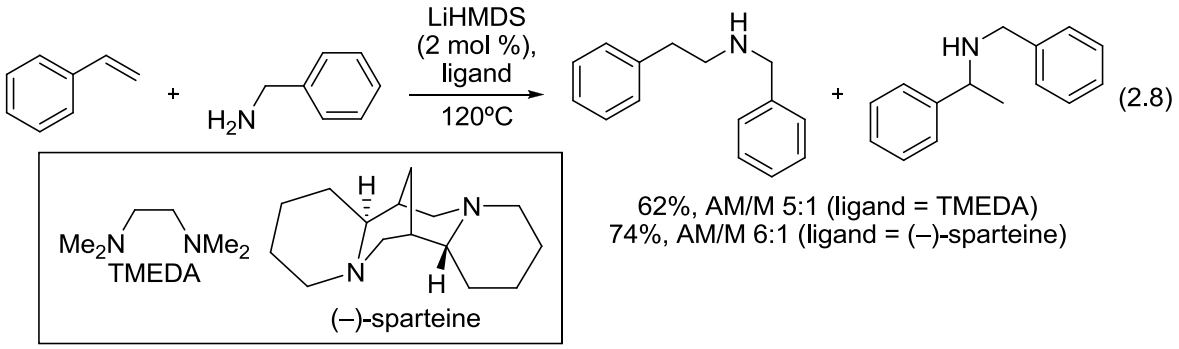


(2.6)



(2.7)

(66) For a review on base-catalyzed hydroamination, see: Seayad, J.; Tillack, A.; Hartung, C. G.; Beller, M. *Adv. Synth. Catal.* **2002**, *344*, 795.
(67) (a) Howk, B. W.; Little, E. L.; Scott, S. L.; Whitman, G. M. *J. Am. Chem. Soc.* **1954**, *76*, 1899. (b) Closson, R. D.; Napolitano, J. P.; Ecke, G. G.; Kolka, A. J. *J. Org. Chem.* **1957**, *22*, 646.
(68) (a) Khedkar, V.; Tillack, A.; Benisch, C.; Melder, J.-P.; Beller, M. *J. Mol. Cat. A: Chem.* **2005**, *241*, 175. (b) Horrillo-Martinez, P.; Hultzsch, K. C.; Gil, A.; Branchadell, V. *Eur. J. Org. Chem.* **2007**, 3311.



(2.8)

Though not explicitly base-catalyzed, lanthanide complexes effectively catalyze intermolecular hydroaminations through similar amine activation.[69] In these systems, coordination of the amine facilitates the addition of the Ln-N bond across olefins in an anti-Markovnikov fashion (Figure 2.3). In vinylarenes, this regioselectivity is attributed to the interaction between the arene π-system and the electrophilic lanthanide centre. While these reactions with vinylarenes are quite efficient, substrates without arene rings are sluggish and display low turnover frequencies.[70]

(69) For a review on lanthanide-catalyzed hydroamination, see: Hong, S.; Marks, T. J. *Acc. Chem. Res.* **2004**, *37*, 673.
(70) (a) Li, Y.; Marks, T. J. *Organometallics* **1996**, *15*, 3770. (b) Ryu, J.-S.; Li, G. Y.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 12584.

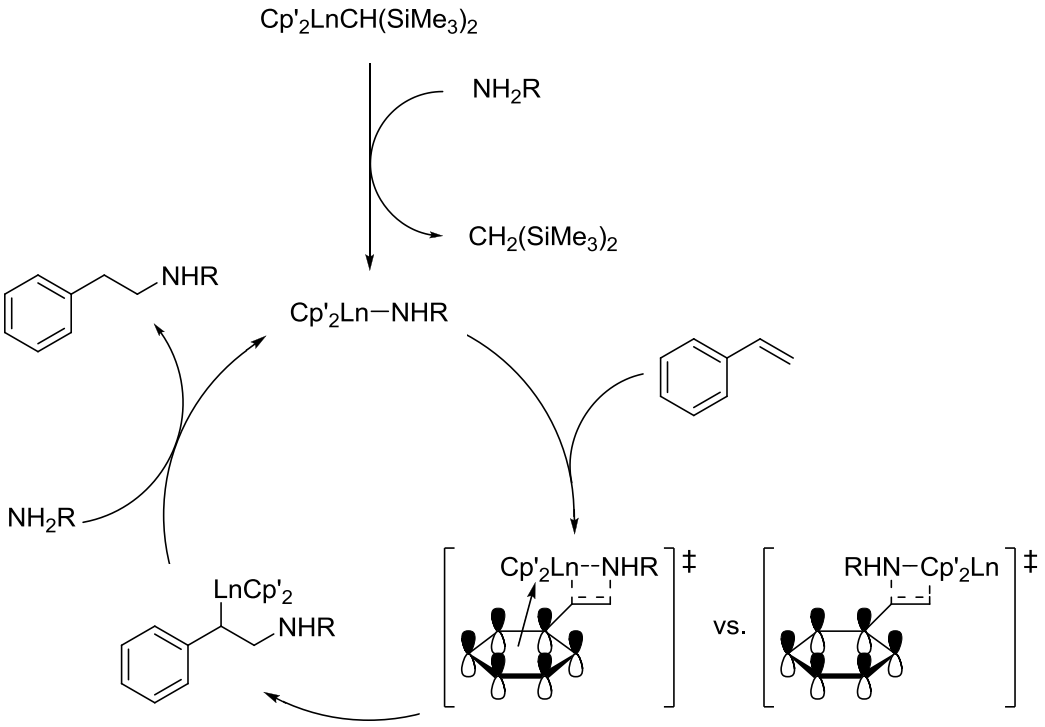


Figure 2.3: Proposed catalytic cycle of organolanthanide-catalyzed hydroamination of vinylarenes

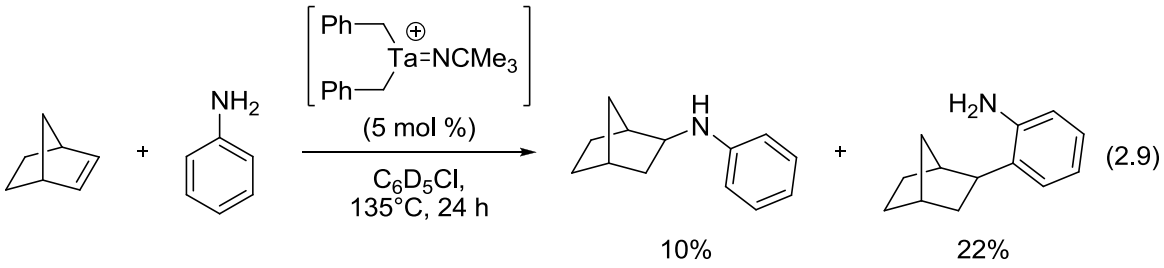
2.4 Transition metal-catalyzed hydroamination

Transition metal-catalyzed hydroaminations are widespread in the literature.[71] Metal catalysis offers the potential for asymmetric additions to alkenes and tolerates labile functional groups, however they are often expensive and toxic, and tend to be air and moisture sensitive.

(71) For reviews, see: (a) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675. (b) Hultzsch, K. C. *Adv. Synth. Catal.* **2005**, *347*, 367. (c) Reference 53.

2.4.1 Group 5 metals

In 2004, Bergman reported the hydroamination of norbornene with aniline using tantalum imido complexes.[72] Unoptimized conditions of this reaction afforded only a 32% yield of the hydroamination and hydroarylation adducts in a 1:2 ratio, with significant amounts of higher molecular weight byproducts (equation 2.9).



(2.9)

2.4.2 Group 8 metals

The group of Hartwig reported anti-Markovnikov additions of amines to vinylarenes with a ruthenium catalyst in the presence of chelating diphosphine ligand DPPPent (1,5-bis-diphenylphosphinopentane) and triflic acid co-catalyst in moderate to excellent yields (equation 2.10).[73] This was proposed to react through nucleophilic attack on the terminal position of the alkene of a ruthenium-(π-arene) complex. Arene exchange between the hydroamination adduct and a new substrate closes the catalytic cycle (Figure 2.4).[74]

(72) Anderson, L. L.; Arnold, J.; Bergman, R. G. *Org. Lett.* **2004**, *6*, 2519.
(73) Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2004**, *126*, 2702.
(74) Takaya, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 5756.

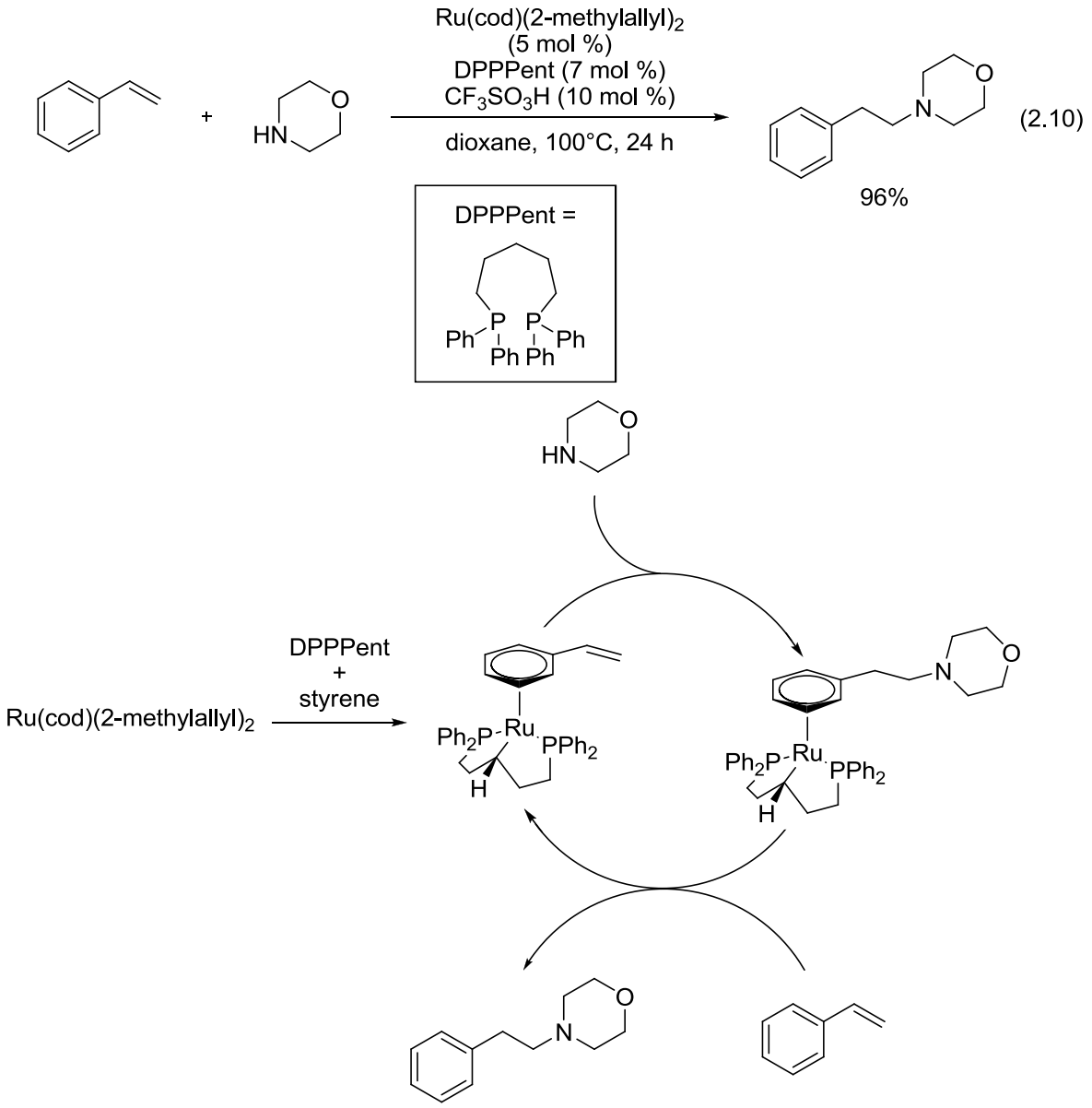


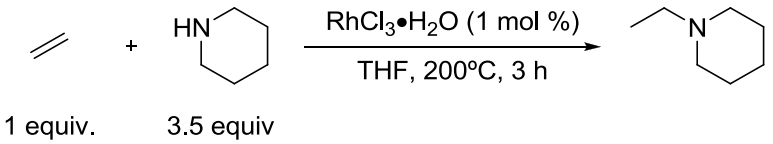
Figure 2.4: Catalytic cycle of ruthenium-catalyzed vinylarene hydroamination

2.4.3 Group 9 metals

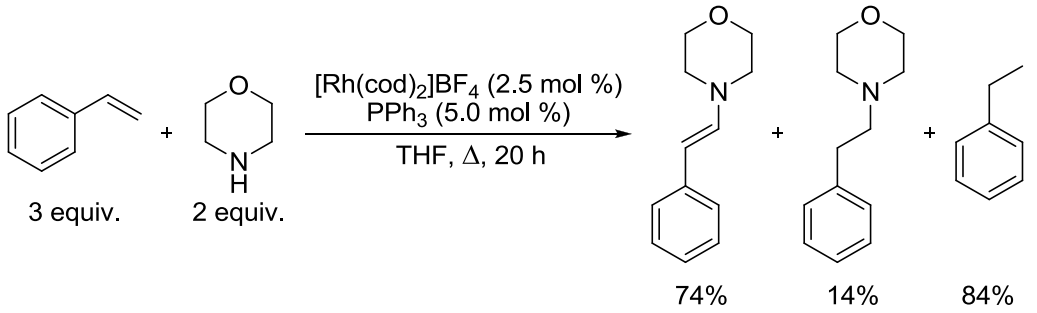
The first transition-metal catalyzed hydroaminations were reported in 1971 by chemists at Du Pont, who used rhodium[75] and iridium salts in the addition of secondary aliphatic amines

(75) For Rh-catalyzed hydroaminations, see: (a) Coulson, D. R. *Tetrahedron Lett.* **1971**, *5*, 429. (b) Diamond, S. E.; Szalkiewicz, A.; Mares, F. *J. Am. Chem. Soc.* **1979**, *101*, 490. (c) Brunet, J.-J.; Neibecker, D.; Philippot, K. *J. Chem.*

to ethylene (equation 2.11).[75a] The scope of this reaction was very limited however, as primary amines and ammonia were unreactive, as were more substituted olefins. Additions of aniline to ethylene and norbornene were also reported.[75b] Also, anti-Markovnikov addition of amines to vinylarenes have been reported as a minor side product to the major oxidative amination products (equation 2.12),[75f] and this was the case in all examples with the exceptions of 2- and 4-vinylpyridine.[75e]



(2.11)



(2.12)

However, in 2003, Hartwig reported a rhodium-catalyzed anti-Markovnikov hydroamination with high amine:enamine ratios for a wider scope of vinyarenes.[75g] He found high conversions of amine products using the DPEphos ligand (equation 2.13), while similar phosphine ligands like Xantphos, DBFphos and BIPHEphos displayed little to no reactivity towards the hydroamination adducts. Electron-rich vinylarenes were more selective than electron-poor vinylarenes under the same conditions, however higher selectivities were

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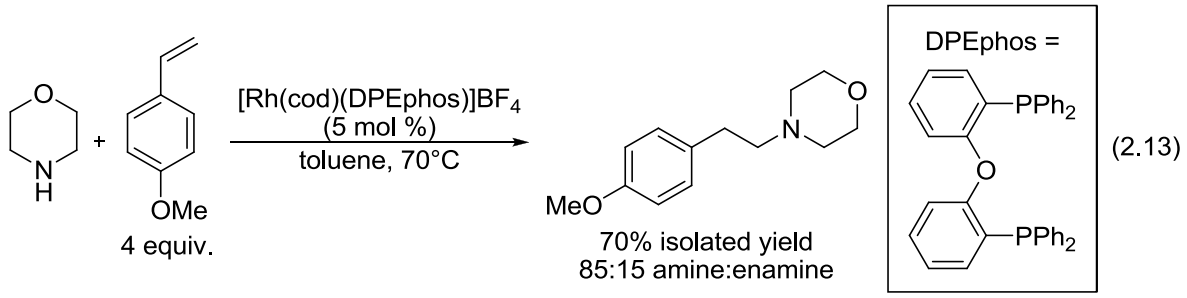
Soc., Chem. Commun. **1992**, 1215. (d) Brunet, J.-J.; Commenges, G.; Neibecker, D.; Philippot, K. *J. Organomet. Chem.*. **1994**, *469*, 221. (e) Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Müller, T. E. *Eur. J. Inorg. Chem.* **1999**, 1121. (f) Beller, M.; Trauthwein, H.; Eichberger, M.; Breindl, C.; Herwig, J.; Müller, T. E.; Thiel, O. R. *Chem. Eur. J.* **1999**, *5*, 1306. (g) Utsunomiya, M.; Kuwano, R.; Kawatsura, M.; Hartwig, J. F. *J. Am .Chem. Soc.* **2003**, *125*, 5608.

observed at lower substrate concentrations. This dependence on concentration can be explained in Figure 2.5.



In the metallacycle, formed either through attack by the amine on the coordinated olefin or insertion of the olefin after N-H activation, reductive elimination is favoured due to the inaccessibility of the β-hydrogen to the metal. High concentrations favour the coordination of a second vinylarene, which opens the metallacycle and allows either reductive elimination or β-hydride elimination. Furthermore, insertion of the second vinylarene produces a dialkyl complex that only undergoes β-hydride elimination. This coordination of a second vinylarene also explains the tendency towards forming enamines for electron-poor substrates.

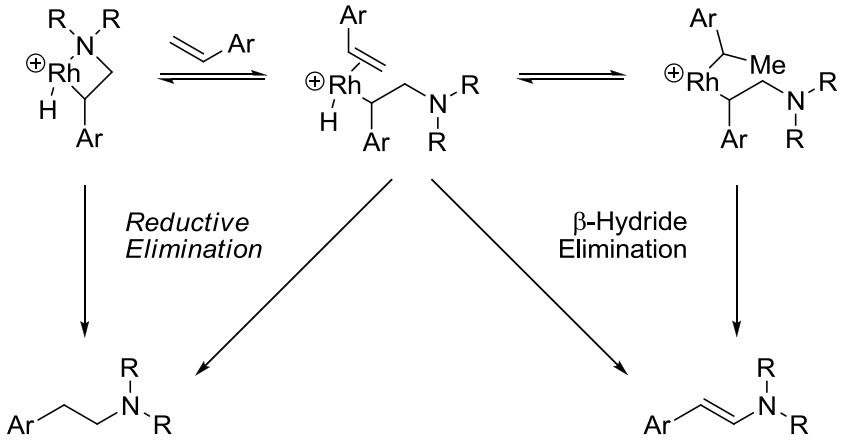
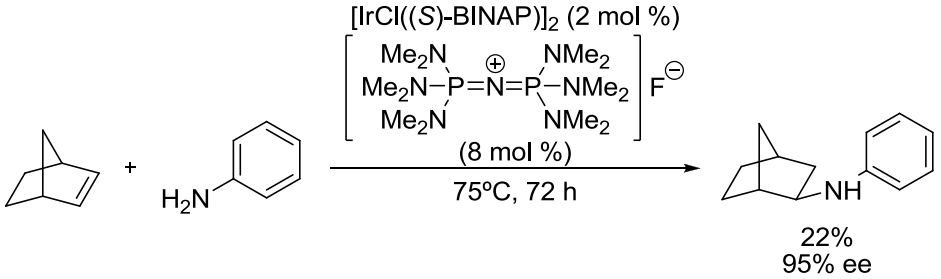


Figure 2.5: Dependence on vinylarene concentration of Ru-catalyzed hydroamination

Milstein reported iridium-catalyzed hydroamination of norbornene in 1988, which occurred through N-H oxidative addition, followed by the formation of an azometallacycle then

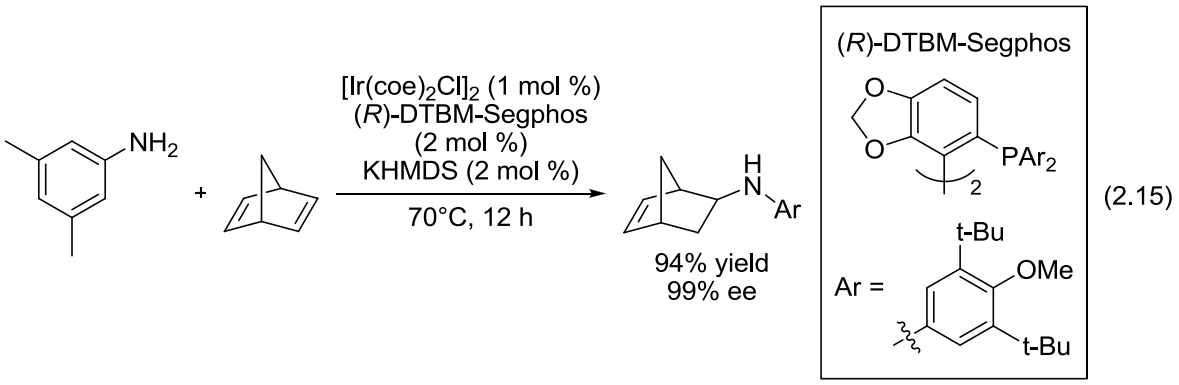
C-H reductive elimination.[76] Nearly ten years later, Togni described the first enantioselective intermolecular hydroamination,[77] which was catalyzed by an iridium-diphosphine complex, achieving selectivities of up to 95% ee and in moderate yields (equation 2.14).[78] The key feature of this report was the beneficial effect of fluoride ion on selectivity, however its precise role was not revealed.



(2.14)

The origin of this beneficial effect was uncovered by Hartwig and co-workers more than a decade later. It was found that fluoride acted as a base, deprotonating the arylamine and generating small amounts of the corresponding amide. Thus, substitution with an organic base dramatically increased turnover numbers and enantioselectivity in the presence of a chiral ligand (equation 2.15).[79]

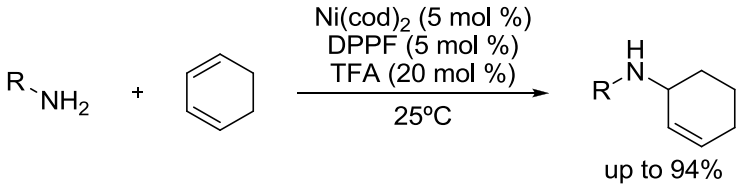
(76) Casalnuovo, A. L.; Calabrese, J. C.; Milstein, D. *J. Am. Chem. Soc.* **1988**, *110*, 6738.
(77) Asymmetric intermolecular hydroaminations are rare in literature. For reviews on asymmetric hydroaminations, see: Hultzsch, K. C. *Org. Biomol. Chem.* **2005**, *3*, 1819, and ref 63b
(78) Dorta, R.; Egli, P.; Zürcher, F.; Togni, A. *J. Am. Chem.. Soc.* **1997**, *119*, 10857.
(79) Zhou, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 12220.



(2.15)

2.4.4 Group 10 metals

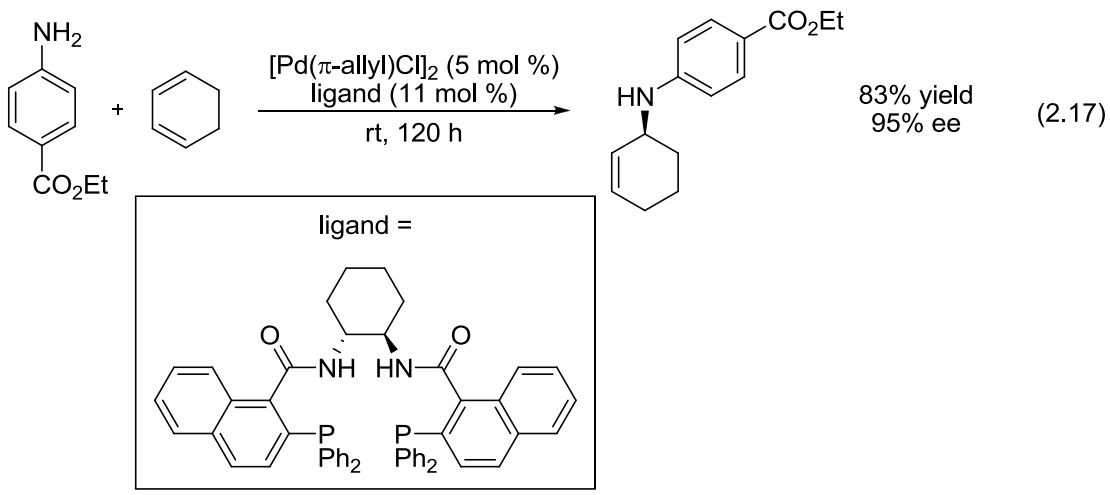
Nickel-catalyzed hydroaminations of 1,3-dienes were reported by Hartwig in 2002. Utilizing $Ni(cod)_2$ with a DPPF (1,1'-bis(diphenylphosphino)ferrocene) ligand and an acid co-catalyst, aliphatic amines were added to cyclic and acyclic 1,3-dienes in high yields (equation 2.16).[80]



(2.16)

Reports from the Hartwig group of palladium-catalyzed hydroaminations have been published over the past several years for additions of anilines and alkylamines to vinylarenes and 1,3-dienes, in some cases showing the potential for high enantioselecitivity (equation 2.17).[81]

(80) Pawlas, J.; Nakao, Y.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 3669.
(81) (a) Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 9546. (b) Löber, O.; Kawatsura, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 4366. (c) Nettekoven, U.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *124*, 1166. (d) Utsunomiya, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 14286. (e) Johns, A. M.; Utsunomiya, M.; Incarvito, C. D.; Hartwig. J. F. *J. Am. Chem. Soc.* **2006**, *128*, 1828. See also: (f) Hu, A.; Ogasawara, M.; Sakamoto, T.; Okada, A.; Nakajima, K.; Takahashi, T.; Lin, W. *Adv. Synth. Catal.* **2006**, *348*, 2051. (g) Li, K.; Horton, P. N.; Hursthouse, M. B.; Hii, K. K. M. *J. Organomet. Chem.* **2003**, *665*, 250.



Mechanistically, for 1,3-dienes, initial addition of the arylamine releases the π-allyl ligand along with one equivalent of acid, generating the active catalytic species (Figure 2.6). The formation of an η^3-allyl complex with the diene is then followed by the turnover-limiting nucleophilic attack of the arylamine. From here, the product is released either through replacement by another diene to the η^3-allyl complex, or by deprotonation of the ammonium salt formed during the reaction. A similar mechanism was proposed for the hydroamination of vinylarenes through η^3-benzyl complexes.[81e]

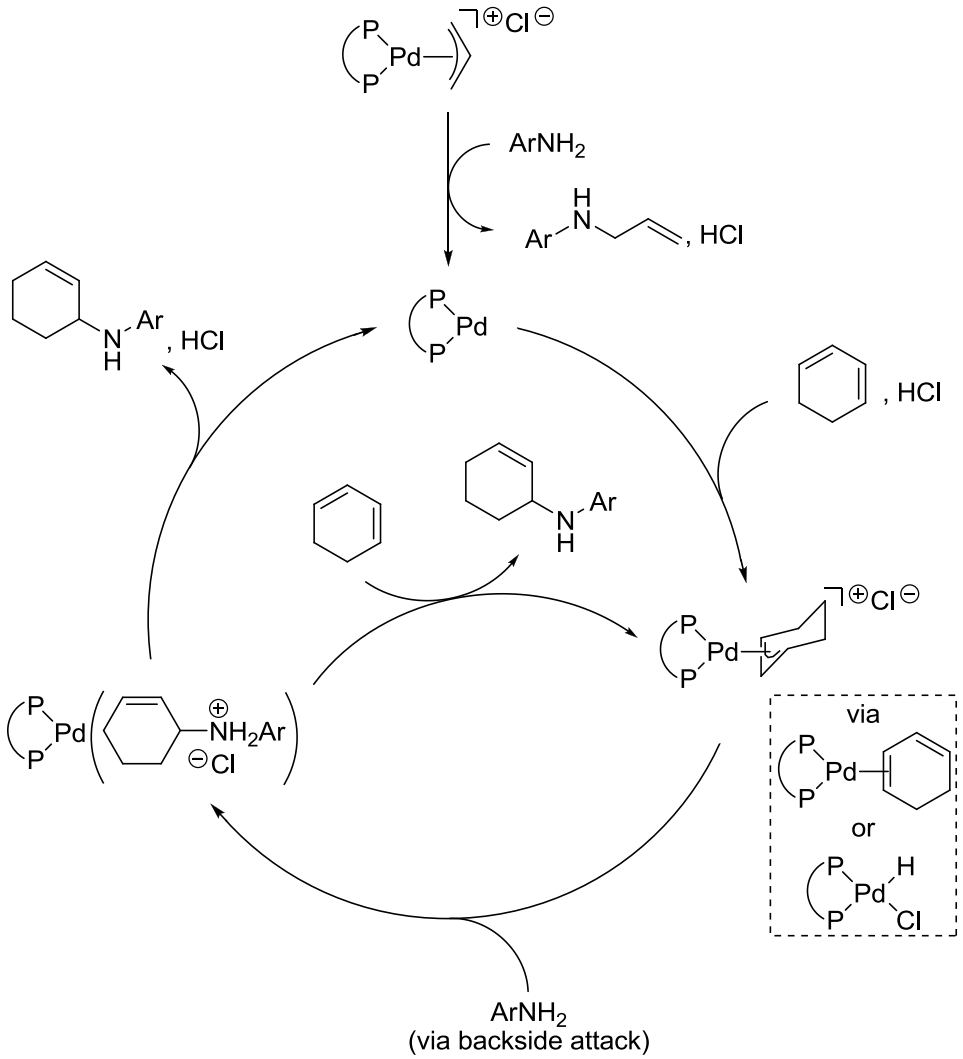
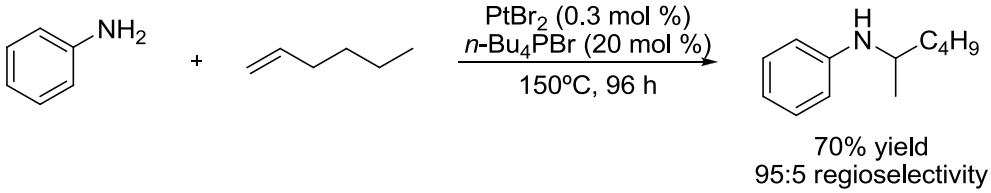


Figure 2.6: Catalytic cycle for Pd-catalyzed hydroamination of 1,3-dienes

While platinum has been shown to catalyze intermolecular hydroaminations through Brønsted acid generation,[61] alternate mechanisms have been described for different systems. Brunet has reported the addition of anilines and dialkylamines to ethylene catalyzed by $PtBr_2$ in ionic liquids.[82] Additions to substituted olefins were highly selective for the Markovnikov

(82) (a) Brunet, J.-J.; Cadena, M.; Chu, N. C.; Diallo, O.; Jacob, K.; Mothes, E. *Organometallics,* **2004**, *23*, 1264. (b) Brunet, J.-J.; Chu, N. C.; Diallo, O. *Organometallics,* **2005**, *24*, 3104. (c) Rodriguez-Zubiri, M.; Anguille, S.; Brunet, J.-J. *J. Mol. Cat. A: Chem.* **2007**, *271*, 145.

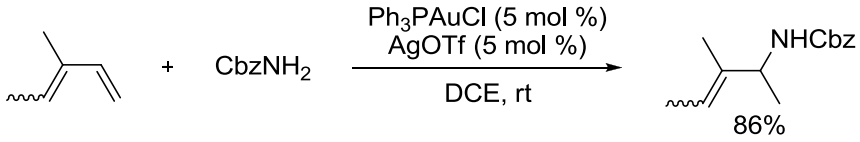
regioisomer (equation 2.18), and no competitive hydroarylation side products were observed except in reactions with norbornene. Similarly, Widenhoefer reported high yielding platinum-catalyzed hydroaminations of ethylene and propylene with amides and carbamates.[83]



(2.18)

2.4.5 Group 11 metals

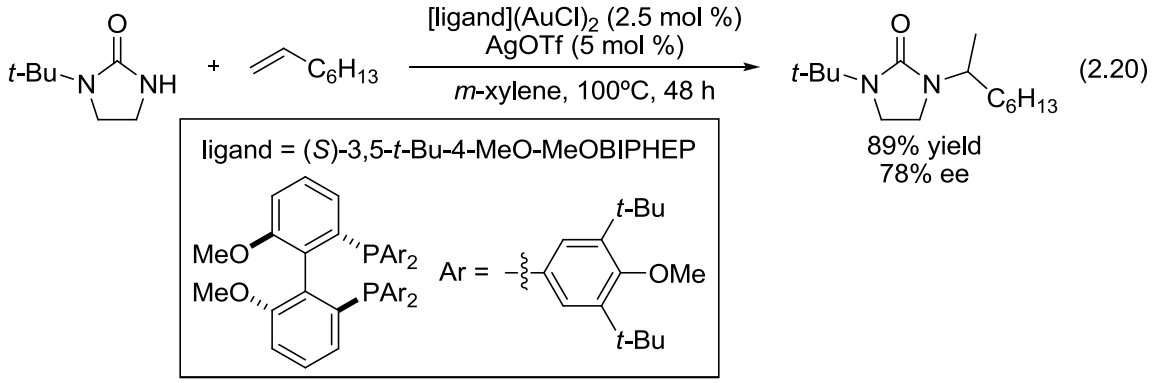
Intermolecular hydroamination of 1,3-dienes by gold catalysis was reported by He in 2006, showing high selectivity for 1,2-addition (equation 2.19).[84] Unlike other gold-catalyzed hydroaminations reported by the He group which appear to operate through Lewis acid catalysis, this was proposed to occur through a nucleophilic attack on a gold-diene complex.



(2.19)

Recently, Widenhoefer reported intermolecular hydroamination of unactivated alkenes with a Au/Ag catalyst system with a variety of cyclic carbamates and ureas (equation 2.20). This was found not only to be highly regioselective, but also showed enantioselectivities of up to 78% ee.[85]

(83) (a) Wang, X.; Widenhoefer, R. A. *Organometallics,* **2004**, *23*, 1649. (b) Qian, H.; Widenhoefer, R. A. *Org. Lett.* **2005**, *7*, 2635.
(84) Brouwer, C.; He, C. *Angew. Chem. Int. Ed.* **2006**, *45*, 1744.
(85) Zhang, Z.; Lee, S. D.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 5372.



(2.20)

2.5 Cope-type hydroamination

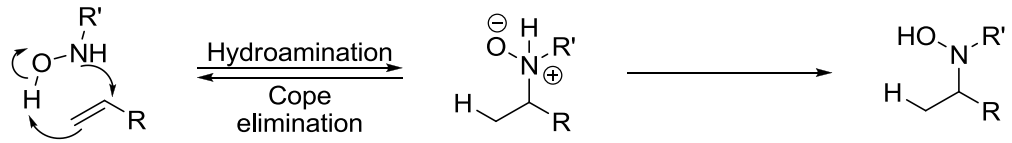
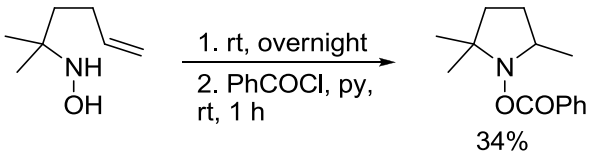


Figure 2.7: Cope elimination and hydroamination

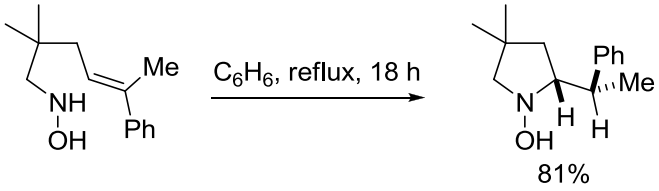
The Cope-type hydroamination proceeds through the reverse of the Cope elimination (Figure 2.7).[86] In cyclic systems, this is known as the "reverse Cope cyclization",[87] and was first reported by House in 1976, who found that an unsaturated hydroxylamine smoothly cyclized to a pyrrolidine derivative upon standing at room temperature (equation 2.21) through a proposed free radical mechanism.[88] However, Black and Doyle reported that the addition of radical inhibitors had no effect on the rate of these cyclizations,[89] and studies by Ciganek and co-workers on the scope and limitations revealed a concerted mechanism.[90] In 1994, Oppolzer provided evidence to support the idea of a concerted mechanism, when he showed that the cyclizations afforded products in a single epimer (equations 2.22 and 2.23), thus it was

(86) For reviews, see: (a) DePuy, C. H.; King, R. W. *Chem. Rev.* **1960**, *60*, 431. (b) Cope, A. C.; Trumbull, E. R. *Org. React.* **1960**, *11*, 317.
(87) For a review, see: Cooper, N. J.; Knight, D. W. *Tetrahedron* **2004**, *60*, 243.
(88) (a) House, H. O.; Manning, D. T.; Melillo, D. G.; Lee, L. F.; Haynes, O. R.; Wilkes, B. E. *J. Org. Chem.* **1976**, *41*, 855. (b) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863.
(89) Black, D. St. C.; Doyle, J. E. *Aust. J. Chem.* **1978**, *31*, 2317.
(90) Ciganek, E. *J. Org. Chem.* **1990**, *55*, 3007.

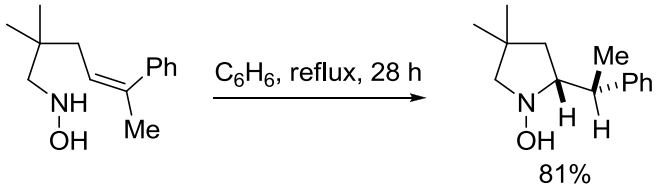
concluded that the suprafacial C-N and N-H bond formations must occur through a planar, five-membered transition state.[91]



(2.21)



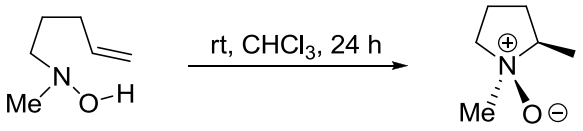
(2.22)



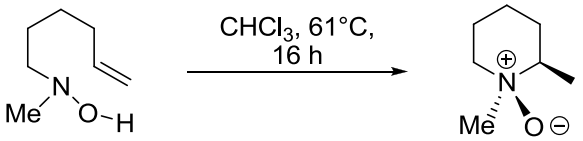
(2.23)

Other studies have shown that *N*-methyl substitution accelerates the rate of cyclization, however larger substituents hinder the reaction. Rates of cyclizations also benefit from a large Thorpe-Ingold effect, however they are reduced by substitution at the distal position of the alkene.[92] Ring size of the cyclization products also plays a significant role. Five-membered rings form smoothly at room temperature, while formation of six-membered rings is more sluggish and requires heating (equations 2.24 and 2.25).[92] Cyclization to three- and four-membered rings does not occur, and seven-membered rings cannot be accessed under these conditions as well.

(91) Oppolzer, W.; Spivey, A. C.; Bochet, C. G. *J. Am. Chem. Soc.* **1994**, *116*, 3139.
(92) Ciganek, E.; Read, J. M. Jr.; Calabrese, J. C. *J. Org. Chem.* **1995**, *60*, 5795.

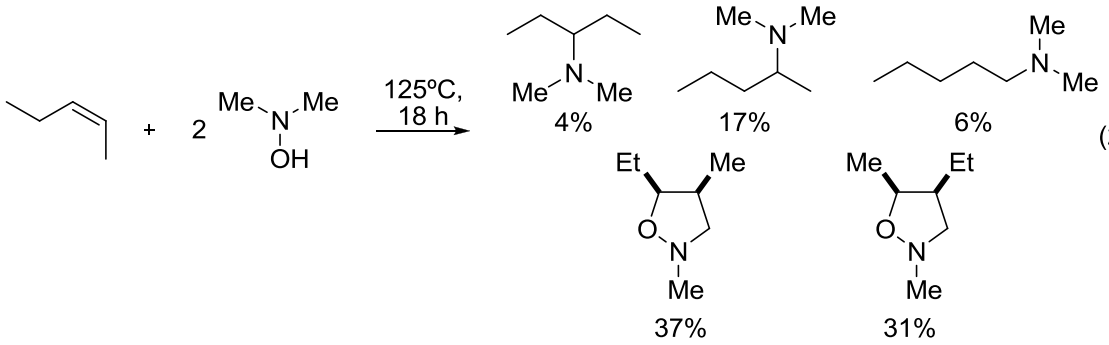


(2.24)



(2.25)

In contrast, intermolecular variants of this reactivity are rare in literature. Niu and Zhao reported the 1,4-addition of *N*-alkylhydroxylamines to α,β-unsaturated esters to form isoxazolidinones in good yields,[93] but relied on activated olefins. In 1973, Laughlin reported intermolecular hydroamination between unactivated alkenes and *N*,*N*-dimethylhydroxylamine.[94] In a reaction with *cis*-2-pentene, hydroamination adducts were observed as minor side products (equation 2.26), suggesting that hydroamination through the reverse of Cope elimination was possible. The exact reaction pathway could not be ascertained, but plausible mechanisms have been suggested.[87]

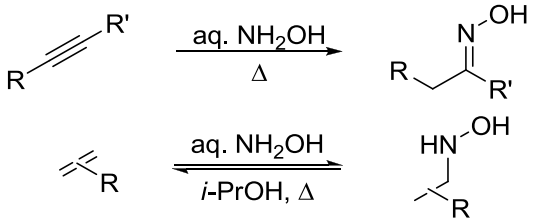


(2.26)

In the past few years, research in our group has been directed at intermolecular Cope-type hydroamination. It was found that aqueous hydroxylamine added to both alkynes and

(93) Niu, D.; Zhao, K. *J. Am. Chem. Soc.* **1999**, *121*, 2456.
(94) Laughlin, R. G. *J. Am. Chem. Soc.* **1973**, *95*, 3295.

alkenes when heated in a protic solvent, providing synthetically useful oximes and alkylhydroxylamines, respectively (equations 2.27 and 2.28).[95] The key step in this process was the bimolecular, solvent-assisted proton transfer of the *N*-oxide formed via Cope-type hydroamination (Figure 2.8).



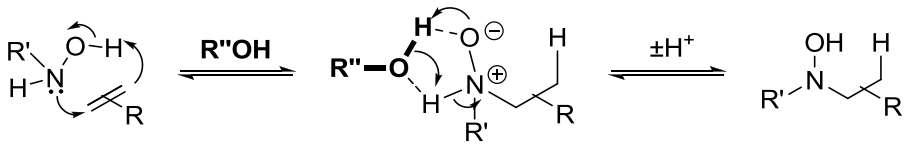
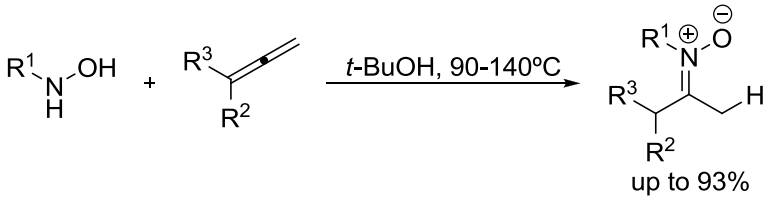


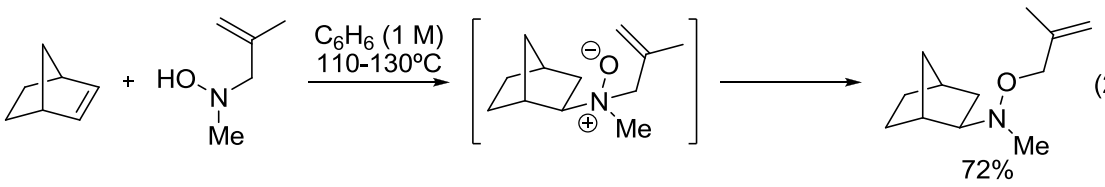
Figure 2.8: Mechanism of Cope-type alkene hydroamination and bimolecular proton transfer

The observation of bis-hydroamination led to the exploration of *N*-alkylhydroxylamines, resulting in the formation of nitrones and *N*,*N*-dialkylhydroxylamines from alkynes and alkenes, respectively.[95] In addition, the scope of this reactivity has been extended to allenes, providing oximes from aqueous hydroxylamine and nitrones from *N*-alkylhydroxylamines (equation 2.29).[96]



(95) (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.
(96) Moran, J.; Pfeiffer, J. Y.; Gorelsky, S. I.; Beauchemin, A. M. *Org. Lett.* **2009**, *11*, 1895.

Due to the near thermoneutral nature of this transformation, tandem processes were explored in which the hydroamination is followed by a second irreversible reaction. To this end, *N*-methallylhydroxylamine was used to effect a tandem Cope-type hydroamination/Meisenheimer[97] rearrangement, providing more stable hydroamination products and removing the possibility of Cope elimination (equation 2.30).[98] In addition to intermolecular reactions, this strategy was successfully applied towards difficult cyclizations in the total syntheses of coniine and norreticuline. Cope-type hydroamination has also been achieved with other bifunctional reagents such as hydrazines[99] and hydrazides,[100] and aromatic nitrogen heterocycles have been prepared through intramolecular hydroamination of alkynes with oximes.[101]



(2.30)

2.6 Conclusion

Significant progress towards intermolecular hydroamination of alkenes has been made with a variety of approaches. Acid- and base-catalysis are cheap and simple, but are limited by a narrow substrate scope and low functional group compatibility. Lanthanide-catalyzed hydroaminations exhibit *anti*-Markovnikov selectivity for vinylarenes, but also have a narrow

(97) See: Cope, A. C.; Towle, P. H. *J. Am. Chem. Soc.* **1949**, *71*, 3423 and references cited therein.
(98) Bourgeois, J.; Dion, I.; Cebrowski, P. H.; Loiseau, F.; Bédard, A.-C.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 874.
(99) Cebrowski, P. H.; Roveda, J.-G.; Moran, J.; Gorelsky, S. I.; Beauchemin, A. M. *Chem. Commun.* **2008**, 492.
(100) Roveda, J.-G.; Clavette, C.; Hunt, A. D.; Gorelsky, S. I.; Whipp, C. J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2009**, *131*, 8740.
(101) Rizk, T.; Bilodeau, E. J.-F.; Beauchemin, A. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 8325.

substrate scope and are typically air and moisture sensitive. Transition metal catalysts are less sensitive with higher functional group compatibility and have achieved asymmetric hydroaminations with modest to excellent degrees of enantioselectivity, while the Cope-type hydroamination is a practical and quite general approach developed in our labs. Despite the success of these and other methods, the intermolecular hydroamination of alkenes remains a challenging transformation, due to the negative entropy term of the activation energy. This is especially true for alkenes that are not electronically biased, and stereoselective variants remain underdeveloped. Also, directed hydroaminations have not been reported in the literature. However, temporarily joining the amine and an alkene fragment possessing a directing group would allow this process to occur intramolecularly, virtually eliminating the entropic cost, and may enhance the efficiency of this desirable reaction.

Chapter 3. Tethered Cope-type hydroamination

3.1 Introduction

The metal-free intermolecular hydroamination using hydroxylamines developed by our group represents a general approach to carbon-nitrogen bond formation. However, hydroxylamines are prone to decomposition at the elevated temperatures required for these transformations. Additionally, these reactions are conducted at high concentrations, which may result in side reactions such as hydroxylamine dimerization. Furthermore, regiochemistry is difficult to control. Faced with these issues, it was postulated that the use of a temporary "tether" would allow the Cope-type hydroamination to occur, not only under milder conditions, but also with a higher degree of regiocontrol, and possibly diastereocontrol (Figure 3.1).

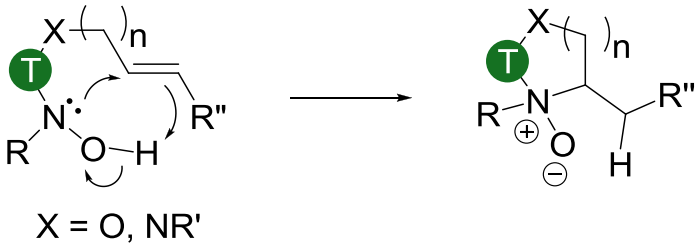
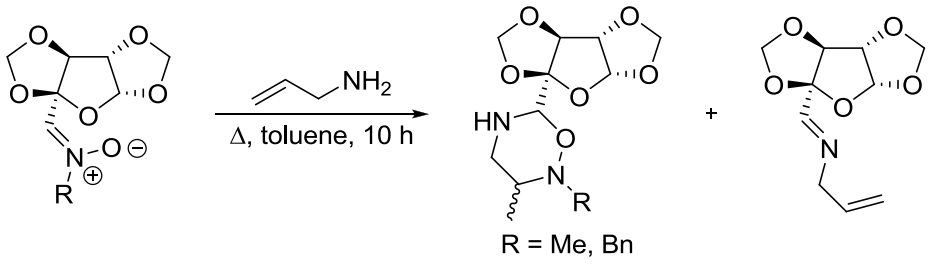


Figure 3.1: Proposed Cope-type hydroamination via a temporary tether

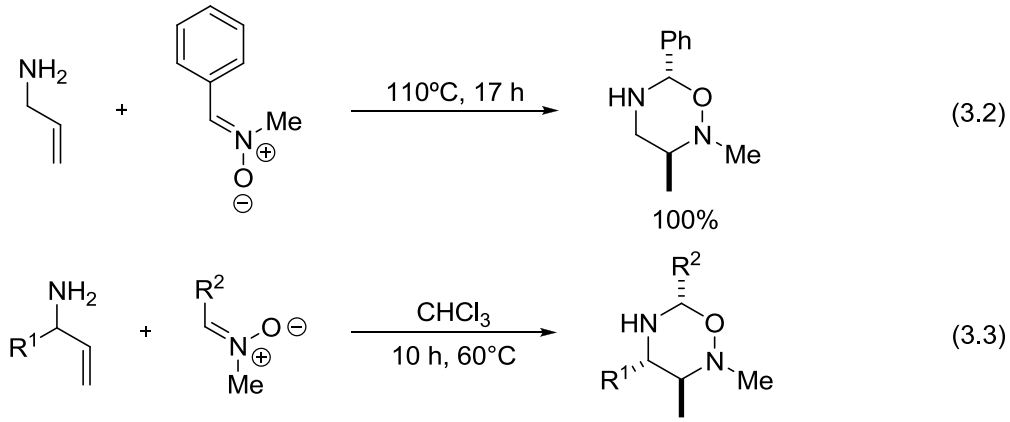
3.1.1 Precedence for Directed Cope-type Hydroamination



(3.1)

While attempting a [1,3]-dipolar cycloaddition between allylamine and a nitrone derived from hexulofuranosonic acid, Knight and co-workers isolated isomeric oxadiazinanes and trace

amounts of imine instead of the expected cycloaddition adduct (equation 3.1).[102] The same result was observed in the reaction between allylamine and a benzaldehyde-derived nitrone (equation 3.2). This was thought to arise through a four-step sequence involving a reverse Cope cyclization (Figure 3.2). Addition of allylamine to the nitrone generates an aminal species that undergoes reverse Cope cyclization to provide an imidazolidine-*N*-oxide. A ring opening follows, and then *6-endo*-trig ring closure on the resulting iminium affords the observed oxadiazinane with exclusively the *trans* geometry. Furthermore, reactions with α-substituted allylamines showed that this transformation is also fully diastereoselective (equation 3.3).[103]



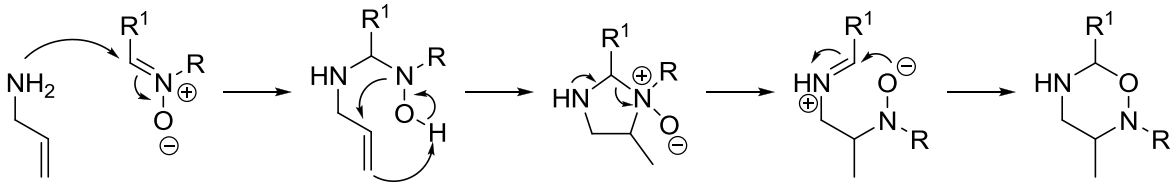
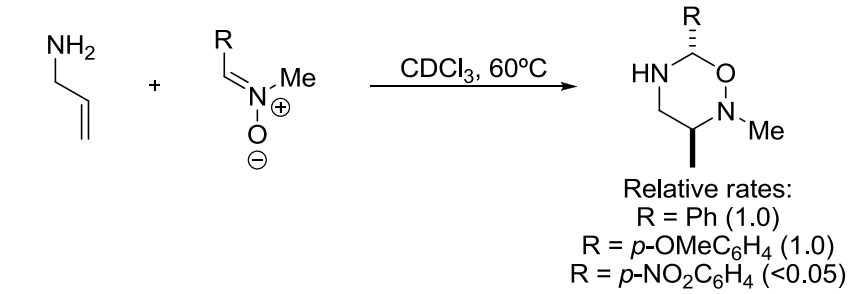


Figure 3.2: Mechanism of reverse Cope cyclization/rearrangement sequence

Further examination of this reactivity found that, congruent with other reverse Cope cyclizations, distal alkene substitution greatly hindered the reaction, as crotyl- and

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

cinnamylamine required longer reactions times and produced lower yields.[102a] The same was observed for *N*-substitution of the allylamine with aryl and large alkyl groups.[103] On the other hand, substitution at the allylic position and on the internal carbon of the alkene had no appreciable effect. Substitution on the benzaldehyde nitrone with electron-donating and electron-withdrawing groups typically either impeded the reaction or had no appreciable effect (equation 3.4), but when replaced with a *C*-cyclopropylnitrone, reaction with *N*-methylallylamine produced the expected oxadiazinane in excellent yield at room temperature (equation 3.5).[102b,103] The nitrone derived from *n*-heptanal yielded similar results. More impressively, when *N*-methylallylamine was reacted with a formaldehyde-derived nitrone, formation of the oxadiazinane was complete at room temperature in only fifteen minutes (equation 3.6).[103]



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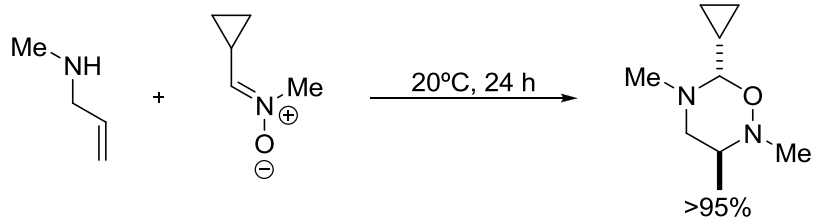
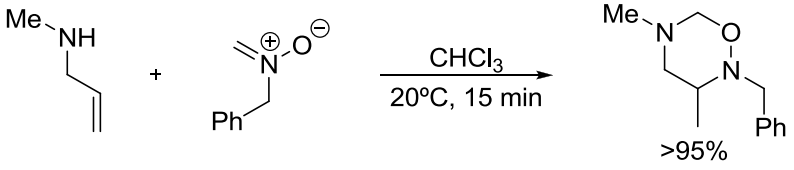
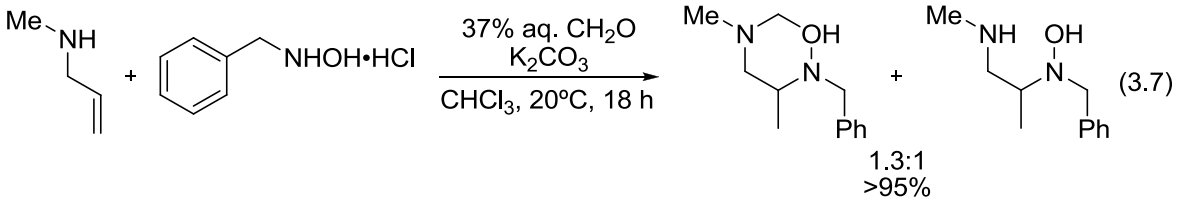


(3.5)



(3.6)

Due to the instability of the formaldehyde-derived nitrone, the Knight group attempted to replicate these results through *in situ* generation of the nitrone. They found that a stirred mixture of equimolar amounts of *N*-methylallylamine, *N*-benzylhydroxylamine hydrochloride, potassium carbonate and 37% aqueous formaldehyde gave the desired oxadiazinane and an aminohydroxylamine in a 1.3:1 ratio in a combined yield of >95% (equation 3.7).[103] The side product was proposed to arise through the hydrolysis of the iminium intermediate, releasing the aldehyde.



(3.7)

Inspired by these results, it was wondered whether the nitrone could turn over and make this reactivity catalytic. Since it is known that reverse Cope cyclizations smoothly form five-membered rings at room temperature, this would represent a directed, intermolecular hydroamination by means of an organocatalytic tether strategy. The use of this tether would also virtually eliminate the negative entropy change of reaction, greatly reducing the activation energy and thereby facilitating the hydroamination. As shown in Figure 3.3, addition of an allylamine to an *in situ*-generated nitrone forms an aminal. Following hydroamination, ring opening to the iminium intermediate leads not to the closure of a six-membered ring, but rather to nucleophilic addition of a new hydroxylamine, releasing the diamine product and regenerating the catalytic nitrone species. It is suggested that this can be accomplished by employing an electron-poor aldehyde, and that the use of a *chiral* aldehyde brings about the potential for enantioselective reactivity.

The research of the Knight group has revealed potential obstacles. Formation of the oxadiazinanes, if irreversible, can shut down catalytic activity or lead to catalyst inhibition. In the case of primary amines, amine exchange at the nitrone by either the allylamine or the hydroamination product causes catalyst inhibition through imine formation. Furthermore, the limitations of the reverse Cope cyclization may narrow the scope of the reaction, for example, distal alkene substitution and hydroxylamines with bulky alkyl groups.

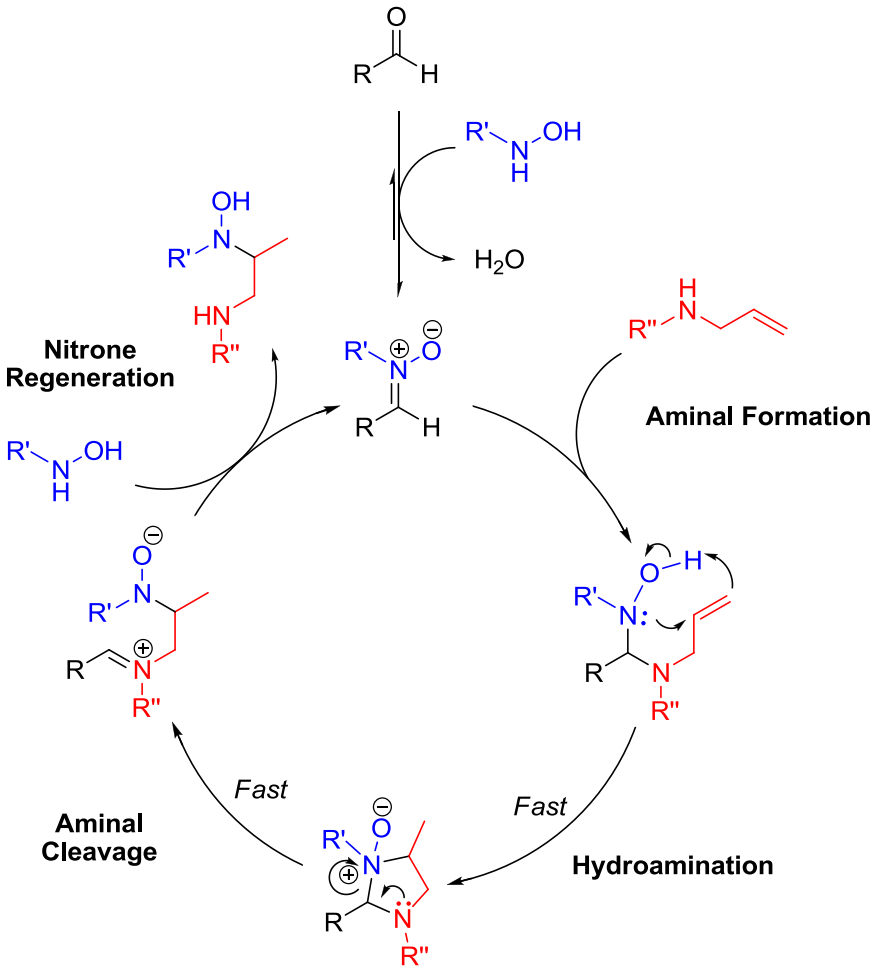


Figure 3.3: Catalytic cycle of proposed "tethered" intermolecular hydroamination

3.2 Results and Discussion

3.2.1 Initial Results

Preliminary investigations were carried out by Dr. Joseph Moran, who studied the hydroamination of allylamine with hydroxylamines and the effect of catalytic amounts of nitrones generated *in situ* from an aldehyde (Figure 3.4). Given that nitrones derived from benzaldehyde led to the formation of a 1:1:1 cyclic hemiaminal, it was surmised that electron-withdrawing groups would facilitate the nitrone regeneration by disfavouring the cyclic product. Of these aldehydes, only glyoxamide **1** displayed the desired reactivity and was best when paired with *N*-benzylhydroxylamine. The formation of the vicinal diamine product **2a** was shown by ^{1}H NMR through a newly formed doublet (J = 6 Hz, 3H) at 1.12 ppm, which was assigned to the methyl group of the product. Efforts to isolate this tremendously polar product by column chromatography were unsuccessful.

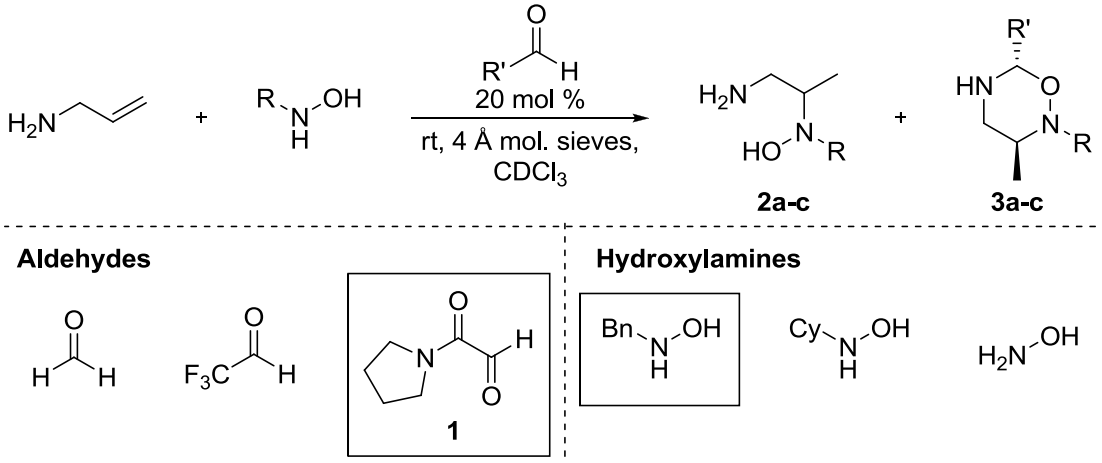
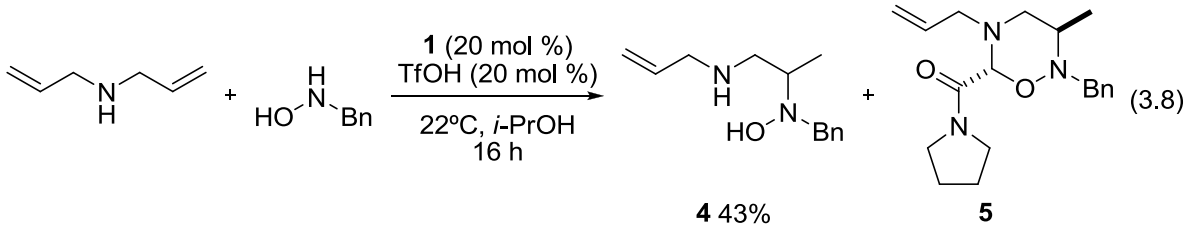


Figure 3.4: Preliminary screen of aldehyde catalysts and hydroxylamines

In order to address this difficulty and simultaneously explore the allylamine scope, a reaction was performed with diallylamine and triflic acid as an acid co-catalyst to speed up

proton transfers (equation 3.8). Under these conditions, a 43% conversion was obtained, indicating that catalytic turnover had been achieved. Product isolation by column chromatography once again proved difficult, however a small amount was obtained for ^{1}H NMR and MS data, which confirmed the structure of **4**.



(3.8)

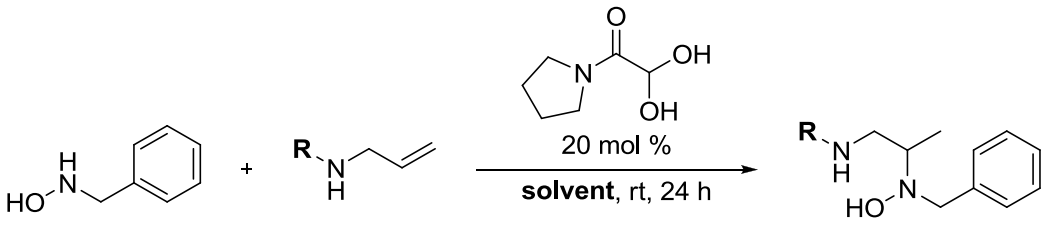
It was observed that glyoxamide **1** decomposed simply upon standing in the freezer, as well as under the reaction conditions. Thus, a more robust catalyst was needed to fully investigate this reaction. Also, the problem of product isolation was still to be addressed. At this point, this project was picked up and continued with the foundation built by Dr. Moran.

Secondary amines, *N*-methylallylamine[104] and *N*-benzylallylamine,[105] were prepared and subjected to the reaction conditions to attempt isolation and further examine the scope of the reaction (Table 3.1). Evidence of hydroamination was observed after 2 h, and after 24 h, the corresponding hydroamination products with *N*-benzylhydroxylamine were obtained in approximately 33% and 14% yields, respectively (entries 1 and 2). The reaction was tested in CD_3OD in an attempt to accelerate the Cope-type hydroamination by facilitating the proton transfer. However, ^{1}H NMR data indicated that the use of this polar protic solvent only inhibited the reaction (entry 3). The effect of water was also investigated, and similar results

(104) Morrison, A. L.; Rinderknecht, H. *J. Chem. Soc.* **1950**, 1478.
(105) Harvey, D. F.; Sigano, D. M. *J. Org. Chem.* **1996**, *61*, 2268.

were observed. Despite numerous repeated experiments, hydroamination products were not isolated successfully.

Table 3.1: Tethered Cope-type hydroamination of secondary amines[a]



Entry	R	Solvent	Additive	Conversion (%)[b]
1	Me	$CDCl_3$ (1.0 M)	4Å MS	33
2	Bn	$CDCl_3$ (1.0 M)	4Å MS	14
3	Me	CD_3OD (1.0 M)	4Å MS	9
4	Me	$CDCl_3$ (1.0 M)	10 eq. H_2O	----------
5	Me	$CDCl_3$ (0.5 M)		18 (8 h)

[a] Conditions: 1 equiv. hydroxylamine, 1 equiv. amine.
[b] Estimated based on relative integration of remaining hydroxylamine to product.

3.2.2 Catalyst Screen

Due to the sensitivity and difficulty in purification of glyoxamide **1**, a search was carried out for a less sensitive aldehyde that also exhibited the same catalytic potential. Allylamine and *N*-benzylhydroxylamine were dissolved in $CDCl_3$ in an NMR tube along with a stoichiometric amount of various carbonyl compounds (Figure 3.5). In most cases, a mixture of condensation adducts of the carbonyl compound with the allylamine and the hydroxylamine was observed, with very little to no evidence of hydroamination. For aldehydes that were commercially available as acetals (trifluoroacetaldehyde, which is available as the ethyl hemiacetal) or in polymeric form (ethyl glyoxylate), very little to no condensation was observed by ^{1}H NMR with either the hydroxylamine or the amine. Attempts at *in situ* nitrone formation with

benzaldehyde dimethyl acetal and dimethoxymethane using the hydrochloride salt *N*-methylhydroxylamine also proved to be ineffective. However, when 2-benzyloxyacetaldehyde (**6**) was used, the diagnostic doublet at 1.0 ppm was found. This reaction was immediately repeated using a catalytic amount (20 mol %) of the aldehyde, achieving a 63% yield after 24 h, which implied that catalytic turnover had been achieved. In an effort to increase the yield, the reaction was repeated at 80°C. However, the ^{1}H NMR spectrum of the crude reaction mixture was not particularly clean and could not be analyzed.

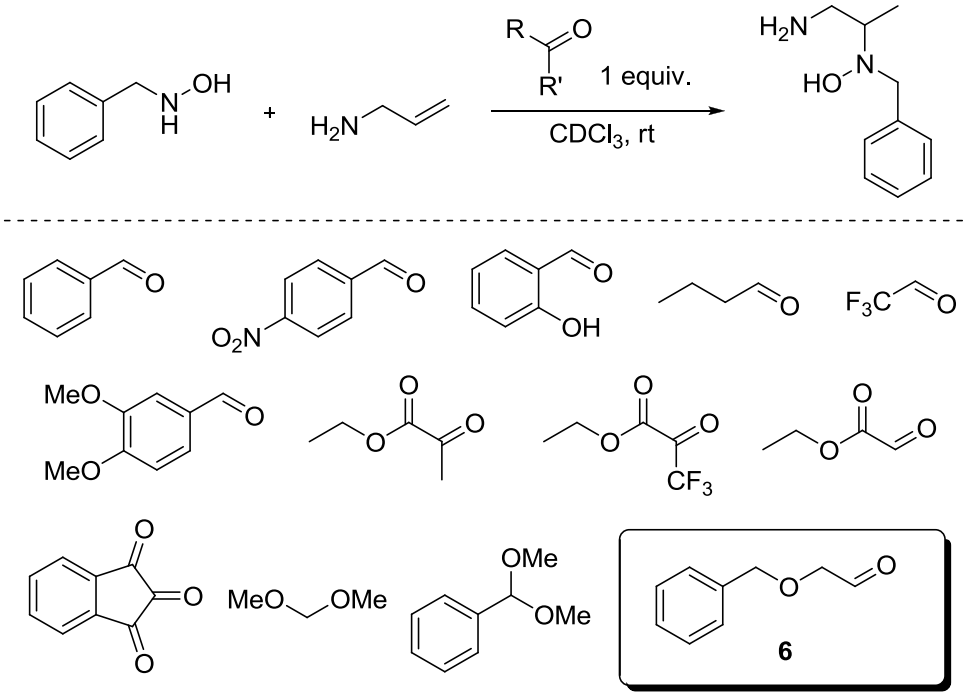


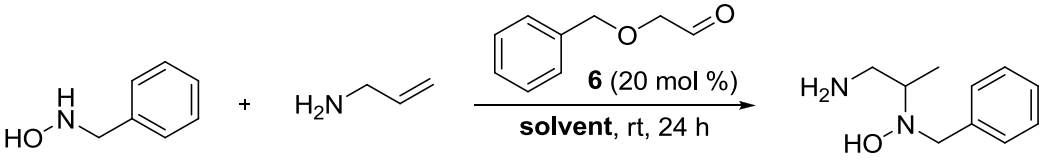
Figure 3.5: Secondary screen for aldehyde catalysts

3.2.3 Optimization

3.2.3.1 Solvent Scan

Following this exciting result, optimization of the reaction conditions was performed, beginning with a solvent scan (Table 3.2). Again, polar protic solvents were found to inhibit the reaction (entries 3 & 7), along with solvents containing a carbonyl moiety (entry 5). Moderate yields were obtained in both polar and non-polar aprotic solvents, with $CDCl_3$ and C_6D_6 providing the best results. Subsequent optimization was carried out in these solvents. The reaction was performed at various concentrations as well, and 1.0 M with respect to the amine was found to be the optimal conditions.

Table 3.2: Solvent optimization for 2-benzyloxyacetaldehyde[a]



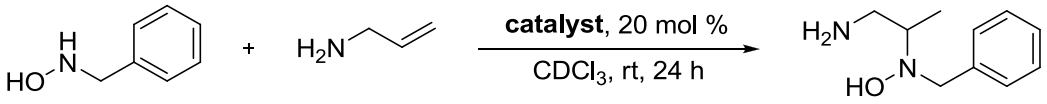
Entry	Solvent	NMR yield (%)[b]
1	$CDCl_3$	63
2	C_6D_6	68
3	CD_3OD	6
4	DMSO-d_6	47
5	Acetone-d_6	2
6	CD_3CN	59
7	D_2O	5
8	$CDCl_3$ (0.5 M)	40
9	$CDCl_3$ (2 M)	50
10	$CDCl_3$ (3 M)	56
11	C_6D_6 (0.5 M)	49
12	C_6D_6 (2 M)	53

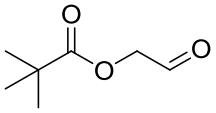
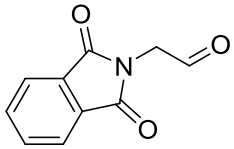
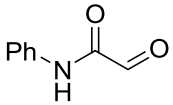
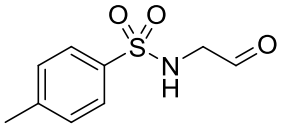
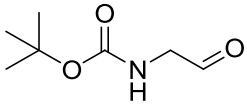
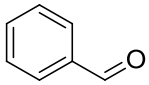
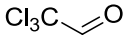
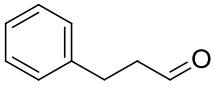
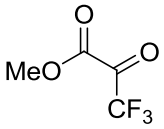
[a] Conditions: 1 equiv. hydroxylamine, 1 equiv. allylamine, 0.2 equiv. aldehyde, solvent (1 M).
[b] Determined using 1,4-dimethoxybenzene as internal standard.

3.2.3.2 Catalyst Structure

After identifying the optimal solvents, efforts were made to increase the yield of the reaction, beginning with an examination of the catalyst structure. Given the success of **6**, other aldehydes featuring an α-heteroatom were explored. While 2-pivaloyloxyacetaldehyde provided similar results (Table 3.3, entry 1), aldehydes containing an α-nitrogen substituent were much less fruitful. With 2-(1,3-dioxoisoindolin-2-yl)acetaldehyde, only 11% and 13% NMR yields were obtained in $CDCl_3$ and C_6D_6, respectively (entry 2). This may be attributed to the lower electronegativity of the nitrogen atom compared to that of oxygen. Aldehydes containing secondary α-nitrogen atoms were examined in hopes that intramolecular hydrogen bonding would activate the nitrone towards nucleophilic attack. However, these compounds faced similar sensitivity and stability issues as did glyoxamide **1**, and were prone to hydration or polymerization, resulting in low yields. On a positive note, the reaction involving catalytic amounts of *tert*-butyl-2-oxoethylcarbamate (entry 5) generated the hydroamination product in 55% yield. This indicated that turnover had occurred, albeit very slowly, and that these compounds should be the subject of further examination. A re-investigation of aldehydes with other electron-poor structures was less fruitful, as only hydrocinnamaldehyde showed any potential for the desired reactivity (entry 8). Despite multiple attempts, neither the hydroamination adducts nor the 1:1:1 cyclic hemiaminals reported by Knight could be isolated by column chromatography.

Table 3.3: Investigation of α-heteroatom aldehydes[a]



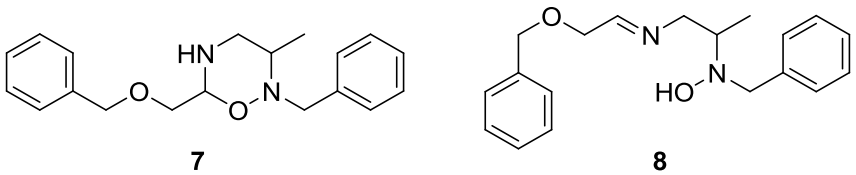
Entry	Catalyst	NMR yield (%)[b]
1		57 55 (C_6D_6)
2		11 13 (C_6D_6)
3		5[c] (DMSO-d_6)
4		9 12 (C_6D_6)
5		55 (~7 days)
6		1
7		0
8		19
9		0

[a] Conditions: 1 equiv. hydroxylamine, 1 equiv. allylamine, 0.2 equiv. aldehyde, $CDCl_3$ (1 M).
[b] Determined using 1,4-dimethoxybenzene as internal standard.
[c] Estimated based on relative integration of remaining allylamine to product.

3.2.3.3 Catalyst loading

The effect of catalyst loading was also examined. As expected, lower catalyst loadings resulted in reduced product formation in both $CDCl_3$ and C_6D_6 (Table 3.4, entries 1-4). Yields were also reduced at higher catalyst loadings, which may be attributed to catalyst poisoning by

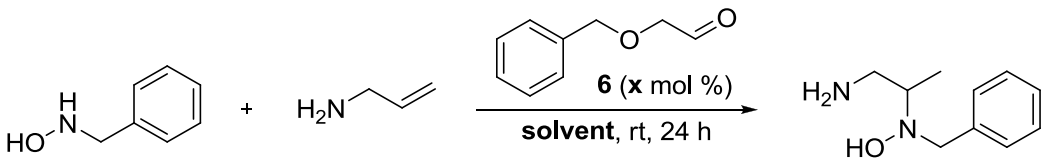
the condensation of the aldehyde with the hydroamination product. This explains the presence of other sets of doublets, which have been tentatively assigned to the cyclic 1:1:1 hemiaminal adduct **7** and the imine **8**, resulting from the aldehyde and hydroamination adduct (Figure 3.6). Attempts to isolate these side products were unsuccessful. Alternatively, side reactions such as the Cannizzaro reaction or trimerization/oligomerization of the aldehyde could be more favourable at higher concentrations.



7 **8**

Figure 3.6: Possible side products resulting in catalyst inhibition

Table 3.4: Optimization of catalyst loadings[a]



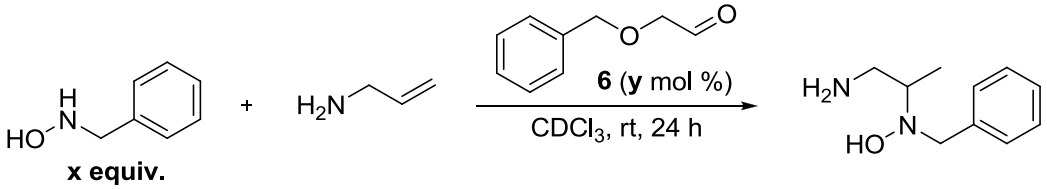
Entry	Solvent	Catalyst loading (mol %)	NMR yield (%)[b]
1	$CDCl_3$	5	15
2	C_6D_6	5	26
3	$CDCl_3$	10	25
4	C_6D_6	10	47
5	$CDCl_3$	25	58
6	$CDCl_3$	30	45
7	$CDCl_3$	35	41
8	$CDCl_3$	40	33

[a] Conditions: 1 equiv. hydroxylamine, 1 equiv. allylamine, 0.05-0.4 equiv. aldehyde, solvent (1 M).
[b] Determined using 1,4-dimethoxybenzene as internal standard.

3.2.3.4 Catalyst loading and equivalence of hydroxylamine

Due to the supposed catalyst poisoning at higher loadings, it was hypothesized that a slight excess of the hydroxylamine would favour the formation of the nitrone over the imine and the cyclic adduct, leading to greater catalyst turnover. Indeed, increased yields were observed, though only slightly and with seemingly lower turnover (Table 3.5, entries 1-4). Yields were further increased under higher concentrations (entries 5-7). Despite these efforts, a significant increase in yield was not achieved. However, using an excess of allylamine gave the highest yield that had been obtained to this point (entry 8). The hydroamination product could not be isolated, but a subsequent optimization was carried out.

Table 3.5: Optimization of catalyst loading and equivalents of hydroxylamine[a]

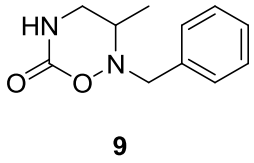


Entry	Equivalents	Catalyst loading (mol %)	NMR yield (%)[b]
1	1.2	20	44
2	1.25	25	53
3	1.3	30	51
4	1.35	35	57
5	1.25	20	61 (2 M $CDCl_3$)
6	1.3	25	70 (2 M $CDCl_3$)
7	1.35	30	72 (2 M $CDCl_3$)
8	1 (1.5 equiv. of amine)	20	83

[a] Conditions: 1.2-1.35 equiv. hydroxylamine, 1 equiv. allylamine, 0.2-0.35 equiv. aldehyde, $CDCl_3$ (1 M).
[b] Determined using 1,4-dimethoxybenzene as internal standard.

3.2.3.5 Derivatization

Efforts towards derivatization of the highly polar primary amine product were made in order to circumvent isolation by column chromatography. Treatment of the crude reaction with carbonyldiimidazole[106] (CDI) led to a complex mixture as observed by ^{1}H NMR, and the desired oxadiazinone **9** was not recovered following column chromatography. Reaction with benzyl chloroformate[107] gave a mixture of mono- and bisprotected products **10** and **11**, along with unreacted material. None of these were successfully isolated by column chromatography. Under tosylation conditions, the monotosylated product **12** was obtained and a small amount was recovered and characterized (see Experimental Information).



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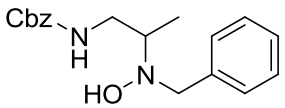

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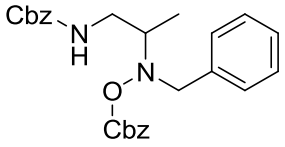

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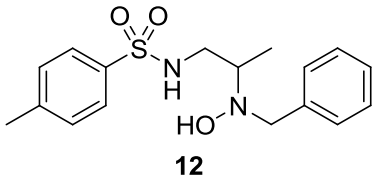

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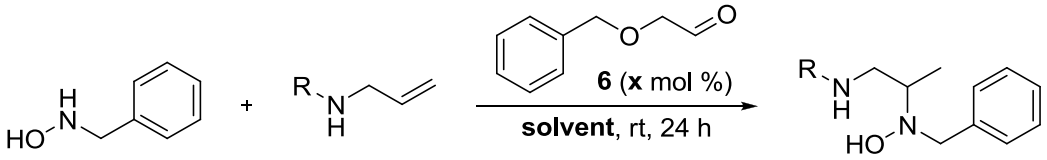
3.2.4 Secondary Optimization and Substrate Scope

Following the discovery of the beneficial effect of excess allylamine, experiments were performed once more to seek out the optimal conditions (Table 3.6). It was found that $CHCl_3$ and C_6H_6 remained the optimal solvents, with C_6H_6 being the superior solvent for secondary

(106) Geffken, D.; von Zydowitz, H.; Ploetz, A. *Z. Naturforsch.* **2005**, *60*, 967.
(107) Hamada, Y.; Shibata, M.; Sugiura, T.; Kato, S.; Shiori, T. *J. Org. Chem.* **1987**, *52*, 1252.

amines (entries 16 and 17). The optimal catalyst loading remained at 20 mol %, though high conversions were obtained at a 10% catalyst loading with extended reaction times. No reaction was observed in the absence of **6**.

Table 3.6: Secondary optimization of solvent and catalyst loading[a]



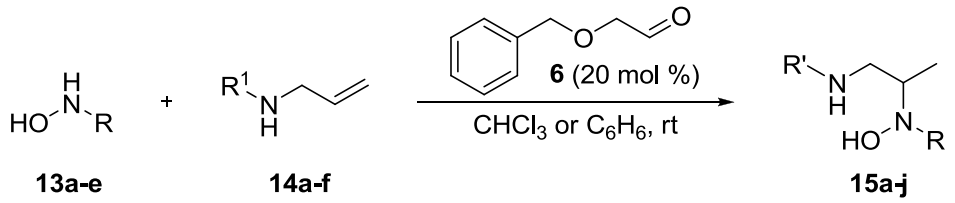
Entry	R	Solvent	Catalyst loading (mol %)	NMR yield (%)[a]
1	H	$CDCl_3$	20	83
2	H	CD_3CN	20	75
3	H	DMSO-d_6	20	59
4	H	C_6D_6	20	84
5	H	CD_3OD	20	10
6	H	$(CD_3)_2CO$	20	5
7	H	$CDCl_3$	10	59
8	H	$CDCl_3$	10	89 (72 h)
9	H	$CDCl_3$	15	77
10	H	$CDCl_3$	20	86
11	H	$CDCl_3$	25	81
12	H	$CDCl_3$	30	76
13	H	$CDCl_3$	0	0
14	H	$CDCl_3$ (0.5 M)	20	76
15	H	$CDCl_3$ (2 M)	20	77
16	$-CH_2CH=CH_2$	$CHCl_3$	20	49
17	$-CH_2CH=CH_2$	C_6H_6	20	74
18	$-CH_2CH=CH_2$	$CDCl_3$	0	0

[a] Conditions: 1 equiv. hydroxylamine, 1.5 equiv. allylamine, 0.2 equiv. aldehyde, solvent (1 M).
[b] Determined using 1,4-dimethoxybenzene as internal standard.

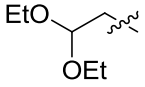
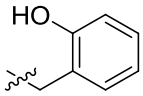
Under these new conditions, an investigation of the substrate scope was carried out (Table 3.7). Secondary allylamines were tolerated, though longer reaction times were typically required for bulkier alkyl groups. However, this could be circumvented by performing the

reaction at a slightly elevated temperature (entry 5). To explore the hydroxylamine scope, a secondary amine was desired to facilitate product isolation. Despite generating the highest yields, *N*-methylallylamine was not selected, due to its high cost and difficult preparation. Thus, the less expensive diallylamine was used. Although higher yields were obtained for secondary amines with C_6H_6 as the solvent, $CHCl_3$ was used instead due to solubility issues. It was found that a variety of *N*-alkylhydroxylamines was also tolerated, however at reduced yields compared to *N*-benzylhydroxylamine. *N*-Alkylhydroxylamine hydrochloride salts can also be used directly in the presence of an equimolar amount of triethylamine (entry 8). *N*-Salicylhydroxylamine was investigated to explore the possibility of nitrone activation by intramolecular hydrogen bonding (entry 10). However, this appeared only to have a detrimental effect to the reactivity. The small differences in R_f between the hydroamination products and allylic amine starting materials led to difficult isolation by column chromatography, in some cases requiring multiple columns or repeated experiments. This difficulty accounts for the large discrepancies between NMR yields and isolated yields. It was also found that the hydroamination products decomposed over time, and thus isolation should be carried out immediately. In all cases, bishydroamination products of diallylamine were not isolated.

Table 3.7: Preliminary substrate scope[a]



13a-e **14a-f** **15a-j**

Entry	R		R^1		Product	Solvent	Time (h)	Yield (%)[b]
1	Bn	**13a**	H	**14a**	**15a**	$CHCl_3$	24	83
2	Bn		Me	**14b**	**15b**	C_6H_6	22	82 (72)
3	Bn		Bn	**14c**	**15c**	C_6H_6	28	60 (45)
4	Bn		$-CH_2CH=CH_2$	**14d**	**15d**	C_6H_6	27	66 (29)
5	Bn			**14e**	**15e**	C_6H_6 C_6H_6	96 27[c]	55 (39) 67 (56)
6	Bn		Ph	**14f**	**15f**	C_6H_6 C_6H_6	29	0 6[c]
7	Cy	**13b**	$-CH_2CH=CH_2$		**15g**	$CHCl_3$	29	40 (25)
8	Me	**13c**	$-CH_2CH=CH_2$		**15h**	$CHCl_3$	29	56 (32)
9	*s*-Bu	**13d**	$-CH_2CH=CH_2$		**15i**	$CHCl_3$	24	51 (29)
10		**13e**	$-CH_2CH=CH_2$		**15j**	$CHCl_3$	46	(61)

[a] Conditions: 1 equiv. alkylhydroxylamine, 1.5 equiv. allylamine, 0.2 equiv. aldehyde, 1.0 M
[b] NMR yield (isolated yield given in parentheses)
[c] Ran at 60°C

Less nucleophilic amines, such as *N*-tosylallylamine and allylaniline, did not undergo hydroamination at room temperature, and heating led only to a low conversion to the hydroamination product (entry 6), which was not isolated successfully. Attempts at the hydroamination of allyl alcohol were unsuccessful under these conditions, also most likely due to its lower nucleophilicity, and no reaction was observed upon addition of catalytic amounts of a weak base (diisopropylethylamine). Surprisingly, no reaction was observed as well for *N*-ethyl-2-methylallylamine at room temperature.

3.2.5 Towards asymmetric intermolecular Cope-type hydroamination

Looking to build upon the success of the tethered Cope-type hydroamination, we postulated that controlling the nucleophilic addition of the allylic amine to the nitrone would allow for a stereoselective hydroamination to occur. Asymmetric additions to α-heteroatom carbonyl compounds are well-known and have shown exceedingly high selectivities based on the polar Felkin-Anh or Evans-Cornforth models (Figure 3.7).[108]

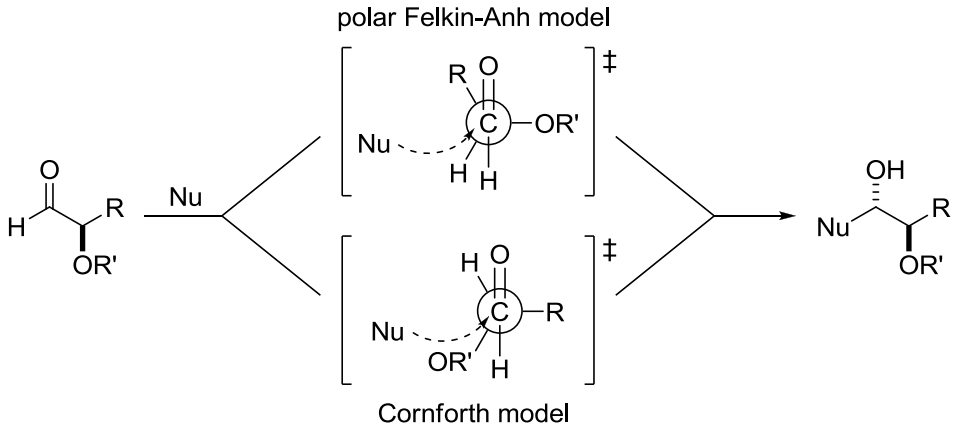
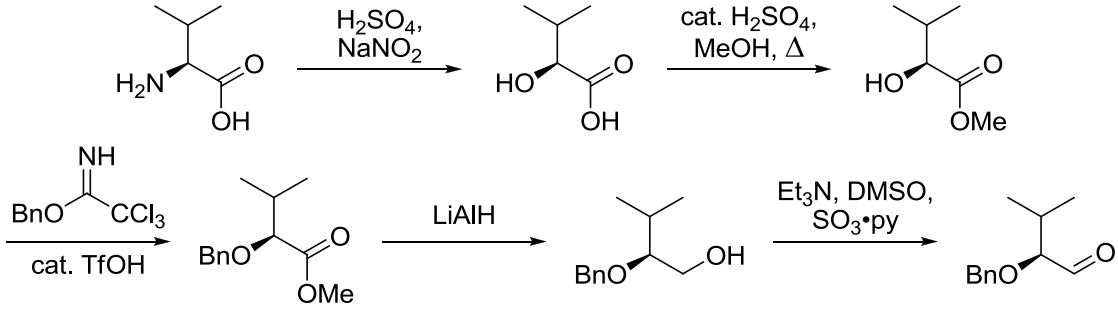


Figure 3.7: Nucleophilic additions on α-alkoxy aldehydes

Based on this model, and with the success of 2-(benzyloxy)acetaldehyde, (*S*)-2-(benzyloxy)-3-methylbutanal was targeted as the chiral catalyst for preliminary studies on asymmetric hydroaminations (Scheme 3.1). However, this synthesis was not completed and will be taken up by other researchers in our labs.

(108) For studies on asymmetric enolate additions on α-heteroatom aldehydes, see (a) Evans, D. A.; Siska, S. J.; Cee, V. J. *Angew. Chem. Int. Ed.* **2003**, *42*, 1761. (b) Evans, D. A.; Cee, V. J.; Siska, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 9433. For a review on asymmetric induction in nucleophilic additions, see: (c) Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191.

Scheme 3.1: Synthesis of chiral aldehyde catalyst for asymmetric hydroamination



3.3 Conclusion and Outlook

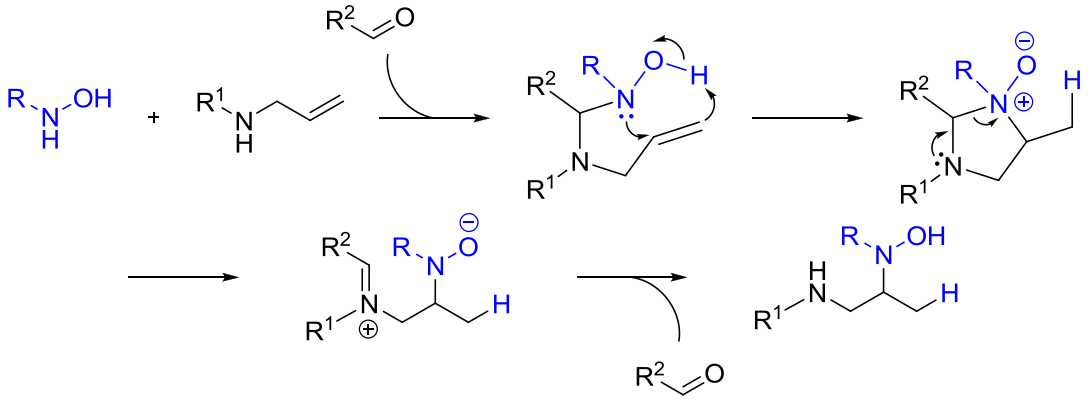
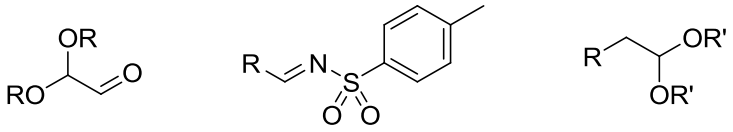


Figure 3.8: Tethered intermolecular Cope-type hydroamination

In summary, an organocatalytic tethering strategy has been developed and applied to the intermolecular Cope-type hydroamination of allylic amines at room temperature (Figure 3.8). The transformation was completely regioselective, reacting only at the internal position of the double bond, and can operate efficiently at catalyst loadings as low as 10%. Both primary and secondary amines were tolerated, and a variety of hydroxylamines, including hydrochloride salts, could be used as well. However substitution at various positions of the allyl chain will help to expand the full scope of this reaction. Further alteration of catalyst structure may lead to increases in reactivity and turnover frequency (Figure 3.9). For example, an α,α-

bisalkoxyaldehyde **16** may increase reactivity by providing a more electron-poor environment, imine derivatives such as sulphonamide **17** may cause the initial nitrone formation to be irreversible by eliminating the extrusion of water, or acetals **18** under acidic conditions to favour nitrone formation entropically. More significantly, stereoselective variants of this reaction may be possible with chiral aldehydes. Progress towards an enantiopure chiral catalyst has been made, and this work will be continued in our labs. This novel approach to catalysis may also be applied to other difficult intermolecular reactions, and research in this area is also underway.



16 **17** **18**

Figure 3.9: Potential alternative precatalysts for tethered hydroamination

3.4 Experimental Information

General Information. All reactions were performed in flame-dried or oven-dried round-bottom flasks under an argon atmosphere unless otherwise noted. Purification of reaction products was carried out by flash column chromatography using Silicycle silica gel (40-63 µm). Analytical thin layer chromatography (TLC) was performed on aluminum sheets pre-coated with silica gel 60 F_{254} (E. Merck), 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 unless otherwise noted on a sodium chloride disk and were recorded on a Bomem Michelson 100 Fourier transform infrared spectrometer (FTIR). ^{1}H NMR spectra were recorded on a Bruker Avance300 (300 MHz) or Avance400 (400 MHz) spectrometer at ambient temperature and are reported in ppm using the solvent as the internal standard ($CDCl_3$ at 7.26 ppm or DMSO-d_6 at 2.50 ppm). Data are reported as: multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration and coupling constant(s) in Hz. ^{13}C NMR spectra were recorded on a Bruker Avance300 (75 MHz) or Avance400 (100 MHz) spectrometer. Chemical shifts are reported in ppm from tetramethylsilane, with the residual solvent resonance as the internal standard ($CDCl_3$ at 77.0 ppm or DMSO-d_6 at 39.43 ppm). High resolution mass spectrometry (HRMS) was performed on a Kratos Concept-11A mass spectrometer with an electron beam of 70eV at the Ottawa-Carleton Mass Spectrometry Centre.

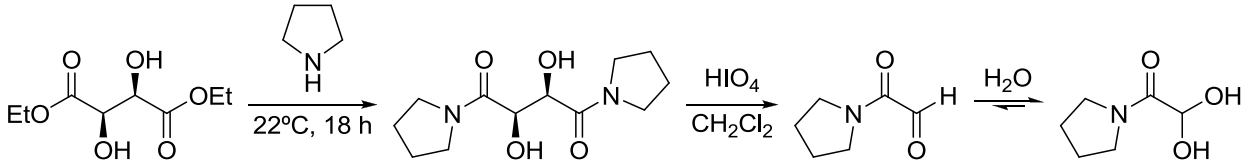
Materials. Unless otherwise noted, all commercial materials were purchased and used without further purification. *N*-Alkylhydroxylamines (**13abde**) were synthesized by reduction of the corresponding oxime according to the procedure of House.[88]

3.4.1 Reactions of Allylic Amines with N-*Alkylhydroxylamines with an Aldehyde Tether.*

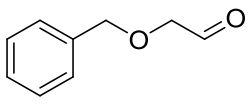
3.4.1.1 Catalyst screens (Figure 3.5 and Table 3.3).

A glass vial was charged with *N*-benzylhydroxylamine (62 mg, 0.50 mmol), $CDCl_3$ (0.5 mL), aldehyde (0.2 or 1.0 equiv.) and allylamine (29 mg, 38 μL, 0.50 mmol). For experiments involving 0.2 equivalents of aldehyde, 1,4-dimethoxybenzene (17.3 mg, 0.125 mmol) was added as an internal standard. The reaction solution was transferred to an NMR tube and capped, and

allowed to sit at room temperature for 24 h. The ^{1}H NMR spectra of these reactions were recorded, and the yield was calculated based on the relative integration of the resonance corresponding to one third of the product's methyl groups (3H) at 1.12 ppm compared to the integration of the resonance corresponding to a 1,4-dimethoxybenzene proton (1H) at 6.83 ppm.

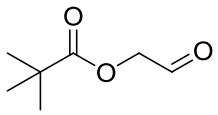


Synthesis of glyoxamide 1. Prepared in two steps from diethyl tartrate by the procedure of Suzuki and a modified procedure of Gauuan.[109] A mixture of diethyl tartrate (5.06 g, 4.20 mL, 24.5 mmol) and pyrrolidine (6.0 mL, 72 mmol) was stirred at room temperature for 18 h then concentrated in vacuo. The residue was purified by column chromatography (10% MeOH/CH_2Cl_2) to give (*R,R*)-(+)-*N,N*:*N'N'*-(+)-bistetramethylenetartramide as a pale yellow solid (3.8 g, 62%). To a solution of the diol (3.0 g, 12 mmol) in CH_2Cl_2 (75 mL) was added $HIO_4 \cdot 2H_2O$ (3.33 g, 14.6 mmol) under argon at 0°C. The reaction was stirred for 24 h at room temperature, then filtered through a cotton plug and concentrated at reduced pressure to provide the crude product (1.4 g, 47%), which was purified by column chromatography (10% MeOH/CH_2Cl_2). Spectral data was consistent with literature.[110]

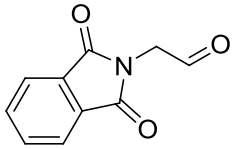


(109) (a) Suzuki, M.; Kimura, Y.; Terashima, S. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3559. (b) Trova, M. P.; Gauuan, P. J. F.; Pechulis, A. D.; Bubb, S. M.; Bocckino, S. B.; Crapo, J. D.; Day, B. J. *Bioorg. Med. Chem.* **2003**, *11*, 2695.
(110) Stetter, H.; Skobel, H. *Chem. Ber.* **1987**, *120*, 643.

2-(Benzyloxy)acetaldehyde (6). Prepared from 1,4-bis(benzyloxy)but-2-ene[111] according to a modified procedure of Hiersemann.[112] Through a solution of alkene (2.0 g, 7.5 mmol) in CH_2Cl_2/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 methyl sulphide (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 data was consistent with literature.

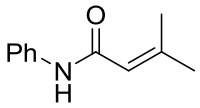


2-Oxoethyl pivalate. Prepared in two steps according to the procedure of Percy.[113] After column chromatography (100% CH_2Cl_2), the desired aldehyde was obtained as a colourless oil (0.86 g, 72%). Spectral data was consistent with literature.[114]

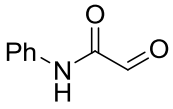


2-(1,3-Dioxoisoindolin-2-yl)acetaldehyde. Prepared according to the procedure of Barbas III.[115] After recrystallization from CH_2Cl_2/hexanes, the product was obtained as a white solid (0.25 g, 25%). Spectral data was consistent with literature.[116]

(111) Dunn, T. B. PhD. Thesis, Harvard University, June 2005.
(112) Pollex, A.; Millet, A.; Müller, J.; Hiersemann, M.; Abraham, L. *J. Org. Chem.* **2005**, *70*, 5579.
(113) Audouard, C.; Fawcett, J.; Griffiths, G. A.; Percy, J. M.; Pintat, S.; Smith, C. A. *Org. Biomol. Chem.*. **2004**, *2*, 528.
(114) McGrath, D. V.; Grubbs, R. H. *Organometallics* **1994**, *13*, 224.



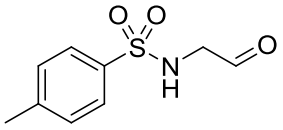
3-Methyl-*N*-phenylbut-2-enamide. To a solution of freshly distilled aniline (3.42 g, 3.35 mL, 36.7 mmol) and pyridine (5.26 g, 5.38 mL, 66.5 mmol) in Et_2O (111 mL) was added 3,3-dimethylacryloyl chloride (4.3 g, 4.0 mL, 36 mmol) dropwise at 0°C (ice bath). The ice bath was removed and the mixture was allowed to stir at room temperature. After 2 h, the reaction was diluted in Et_2O, washed with 10% aq. HCl (3x), sat. aq. $NaHCO_3$ solution and brine. The organic phase was dried over $MgSO_4$, filtered and concentrated, providing 6.1 g (96%) of the product as a pale yellow solid, and was used without further purification. Spectral data was consistent with literature.[117]



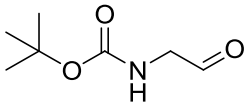
2-Oxo-*N*-phenylacetamide. Through a solution of 3-methyl-*N*-phenylbut-2-enamide (1.0 g, 5.7 mmol) in CH_2Cl_2/MeOH (1:1, 20 mL) was bubbled a stream of ozone at -78°C until the yellow solution became dark green (~40 min). Nitrogen was bubbled to remove excess ozone, then methyl sulphide (1.77 g, 2.11 mL, 28.5 mmol) was added and the reaction was allowed to warm to room temperature and stirred overnight. The reaction solution was concentrated then diluted in Et_2O and transferred to a 500-mL separatory funnel. The solution was washed four

(115) Thayumanavan, R.; Tanaka, F.; Barbas, C. F., III. *Org. Lett.* **2004**, *6*, 3541.
(116) Wang, X.; Bhatia, P. A.; Daanen, J. F.; Latsaw, S. P.; Rohde, J.; Kolasa, T.; Hakeem, A. A.; Matulenko, M. A.; Nakane, M.; Uchic, M. E.; Miller, L. N.; Chang, R.; Moreland, R. B.; Brioni, J. D.; Stewart, A. O. *Bioorg. Med. Chem.* **2005**, *13*, 4667.
(117) Evans, D. A.; Aye, Y.; Wu, J. *Org. Lett.* **2006**, *8*, 2071.

times with H_2O, and azeotroped twice with a mixture of Et_2O (10 mL) and H_2O (1.5 mL). The product was isolated and used as the hydrate. Spectral data was consistent with literature.[117]



4-Methyl-*N*-(2-oxoethyl)benzenesulphonamide. Prepared from *N*-tosylallylamine[118] according to the procedure of Aggarwal.[119] The moisture-sensitive product was obtained as a sticky white solid (0.36 g, 71%) that polymerized slowly, and was used as a mixture in experimental trials.



***tert*-Butyl 2-oxoethylcarbamate.** Prepared from *tert*-butyl allylcarbamate according to the procedure of Whitesides.[120] Product was obtained as a colourless oil (0.15 g, 15%) after column chromatography (40% EtOAc/hexanes). Spectral data was consistent with literature.[120]

*3.4.1.2 Optimization of tethered hydroamination of allylamine with N-benzylhydroxylamine and aldehyde **6** (Table 3.6).*

NOTE: 2-(Benzyloxy)acetaldehyde decomposes slowly over time upon sitting in the freezer and should be distilled occasionally before use (bp 70-75°C, 0.2 Torr).

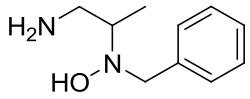
Solvent scan (entries 1-6). A glass vial was charged with *N*-benzylhydroxylamine (0.12 g, 1.0 mmol), solvent (1.0 mL), aldehyde **6** (0.030 g, 28 µL, 0.20 mmol) and allylamine (86 mg, 0.11

(118) Amrein, S.; Timmermann, A.; Studer, A. *Org. Lett.* **2001**, *3*, 2357.
(119) Unthank, M. G.; Hussain, N.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2006**, *45*, 7066.
(120) Bischofberger, N.; Waldmann, H.; Saito, T.; Simon, E. S.; Lees, W.; Bednarksi, M. D.; Whitesides, G. M. *J. Org. Chem.* **1988**, *53*, 3457.

mL, 1.5 mmol). Then, 1,4-dimethoxybenzene (34.5 mg, 0.250 mmol) was added and the resulting reaction solution was transferred to an NMR tube, capped, and allowed to sit at room temperature for 24 h. The ^{1}H NMR spectra of these reactions were recorded and the yield was calculated based on the relative integration of the resonance corresponding to one third of the product's methyl groups (3H) at 1.12 ppm compared to the integration of the resonance corresponding to a 1,4-dimethoxybenzene proton (1H) at 6.83 ppm.

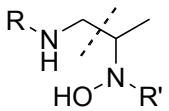
Concentration and catalyst loading (entries 7-14). A glass vial was charged with *N*-benzylhydroxylamine (0.12 g, 1.0 mmol), solvent (0.5-2.0 mL), aldehyde **6** (0.0-0.3 equiv.) and allylamine (86 mg, 0.11 mL, 1.5 mmol). Then, 1,4-dimethoxybenzene (35 mg, 0.25 mmol) was added, and the resulting reaction solution was transferred to an NMR tube, capped, and allowed to sit at room temperature for 24 h. The ^{1}H NMR spectra of these reactions were recorded, and the yield was calculated based on the relative integration of the resonance corresponding to one third of the product's methyl groups (3H) at 1.12 ppm compared to the integration of the resonance corresponding to a 1,4-dimethoxybenzene proton (1H) at 6.83 ppm.

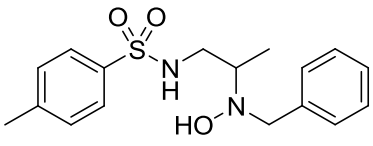
General Procedure for tethered hydroaminations of allylic amines with N-*alkylhydroxylamines* (Table 3.7). A 10-mL round bottom flask was charged with a stir bar, hydroxylamine (1 equiv.), solvent (1.0 M), aldehyde **6** (0.2 equiv.) and amine (1.5 equiv.). The reaction was stirred at room temperature, and monitored by TLC or ^{1}H NMR. The crude reaction mixture was concentrated at reduced pressure and purified by flash chromatography to give the corresponding *N*,*N*-dialkylhydroxylamine products.



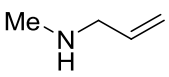
2-(Benzyl(hydroxy)amino)propan-1-amine (15a, Table 3.7, entry 1). Synthesized according to the general procedure ($CHCl_3$, 24 h) using 0.33 g, 2.7 mmol of *N*-benzylhydroxylamine. A small amount was isolated for characterization as follows: The crude reaction mixture was concentrated under reduced pressure, then re-dissolved in $CHCl_3$ (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 Na_2CO_3 solution. The aqueous solution was extracted three times with CH_2Cl_2, and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure, giving the product as a white solid. TLC R_f 0.11 (15% MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.29 (m, 5H), 4.00 (d, *J* = 13.1 Hz, 1H), 3.74 (d, *J* = 13.2 Hz, 1H), 2.86-2.24 (m, 3H), 1.12 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5 (C), 129.2 (CH), 128.3 (CH), 127.2 (CH), 62.4 (CH), 60.8 (CH_2), 45.4 (CH_2), 11.2 (CH_3); 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 $C_9H_{12}NO$ $[M\text{-}H_2NCH_2]^+$: 150.0919. Found: 150.0870.[121]

(121) While most compounds failed to provide a HRMS peak for the molecular ion (except compounds **15b**, **15d**, **15g**, **15i** and **15j**), a common fragment could be observed for all hydroamination products. This ion would be formed upon C-C bond cleavage in the diamine region.

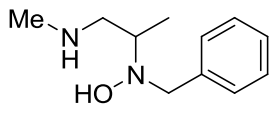




***N*-(2-(Benzyl(hydroxy)amino)propyl)-4-methylbenzenesulfonamide (12).** Alternatively, the above product was subjected to tosylation conditions[118] and characterized as the sulphonamide as follows: The crude reaction mixture was concentrated under reduced pressure then dissolved in CH_2Cl_2 (0.1 mL). Triethylamine (22 mg, 31 µL, 0.22 mmol) was added and the reaction was cooled to 0°C. A solution of *p*-toluenesulfonic acid chloride (42 mg, 0.22 mmol) in CH_2Cl_2 (0.3 mL) was added dropwise, then the reaction was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was washed with a saturated aqueous NH_4Cl solution, brine, then dried over $MgSO_4$ and concentrated under reduced pressure. After column chromatography (2:1 Et_2O:pentane), a small amount (~5 mg) of the desired sulphonamide was obtained and characterized. TLC R_f 0.30 (1:1 Et_2O/pentane); ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.2 Hz, 2H), 7.38-7.28 (m, 7H), 5.23 (br s, 1H), 4.46 (br s, 1H), 3.92 (d, *J* = 13.1 Hz, 1H), 3.63 (d, *J* = 13.1 Hz, 1H), 3.11-2.88 (m, 3H), 2.43 (s, 3H), 1.10 (d, *J* = 6.3 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 143.2 (C), 137.4 (C), 136.9 (C), 129.6 (CH), 129.3 (CH), 128.4 (CH), 127.4 (CH), 127.0 (CH), 60.6 (CH_2), 59.5 (CH), 45.8 (CH_2), 21.4 (CH_3), 10.7 (CH_3); IR (film): 3500, 3291, 2987, 2344, 1314, 1159, 1094, 813 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{17}H_{22}N_2O_3S$ $[M]^+$: 334.1351. Not found. Exact mass calcd for $C_9H_{12}NO$ $[M\text{-}TsNHCH_2]^+$: 150.0919. Found: 150.0911.[121]

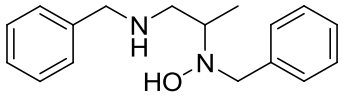


***N*-Methylprop-2-en-1-amine (14b).** Synthesized according to a modified procedure of Morrison and Rinderknecht.[104] Allylamine (5.7 g, 7.5 mL, 0.10 mol) was added dropwise to benzaldehyde (11.2 g, 10.7 mL, 0.105 mol) at room temperature with stirring. After stirring overnight, the mixture was diluted in Et_2O and extracted to remove water. The organic extract was concentrated under reduced pressure, then azeotroped in C_6H_6 (2 x 100 mL) to remove the remaining traces of water. The crude Schiff base was transferred to a 75-mL sealed tube and methyl iodide (18 g, 8.1 mL, 0.13 mol) was added with stirring. The tube was sealed and the reaction was stirred at 80°C for 16 h. At this time, the reaction was stopped and allowed to cool to room temperature, whereupon an orange solid appeared in the reaction vessel. The orange solid was washed with C_6H_6, collected on a Büchner funnel with a sintered glass frit and allowed to dry. The solid was then transferred to a round-bottom flask, dissolved in distilled water (8 mL) and stirred overnight. The biphasic mixture was separated and the aqueous layer was extracted with Et_2O until no UV-active TLC spot was observed. The aqueous layer was concentrated under reduced pressure and then made basic with a 50% (w/w) aqueous NaOH solution. After approximately 5 mL were added, a second layer appeared. The upper layer was collected and distilled (bp 62-65°C, 760 torr), affording 4.4 g (62%) of the desired product as a clear, colourless liquid. Spectral data was consistent with data from commercial sources.

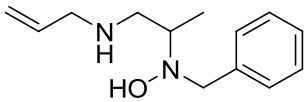


2-(Benzyl(hydroxy)amino)-*N*-methylpropan-1-amine (15b, Table 3.7, entry 2). Synthesized according to the general procedure (C_6H_6, 22 h). Isolated 0.20 g (72%) as a pale yellow oil after column chromatography (1% Et_3N/10% MeOH/CH_2Cl_2). TLC R_f 0.19 (15% MeOH/CH_2Cl_2); ^1H

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.

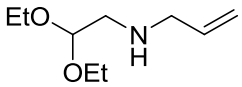


***N*-Benzyl-2-(benzyl(hydroxy)amino)propan-1-amine (15c, Table 3.7, entry 3)**. Synthesized according to the general procedure (C_6H_6, 28 h). Isolated 0.20 g (45%) as a yellow oil after column chromatography (10% MeOH/CH_2Cl_2). TLC R_f 0.25 (10% MeOH/CH_2Cl_2); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.24 (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); ^{13}C NMR (75 MHz, $CDCl_3$) 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 (CH_2), 58.9 (CH), 53.0 (CH_2), 51.8 (CH_2), 11.3 (CH_3); IR (film): 3063, 3032, 2926, 2850, 1497, 1451, 1364, 1155, 1026, 733, 698 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{17}H_{22}N_2O$ $[M]^+$: 270.1732. Not found. Exact mass calcd for $C_9H_{12}NO$ $[M\text{-}BnNHCH_2]^+$: 150.0919. Found: 150.0929.[121]



***N*-(2-(Benzyl(hydroxy)amino)propyl)prop-2-en-1-amine (15d, Table 3.7, entry 4)**. Synthesized according to the general procedure (C_6H_6, 27 h). Isolated 0.10 g (29%) as a yellow oil after column chromatography (10% MeOH/CH_2Cl_2). TLC R_f 0.42 (15% MeOH/CH_2Cl_2); ^1H NMR (300

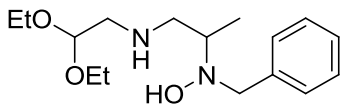
MHz, $CDCl_3$) δ 7.36-7.24 (m, 5H), 5.74 (tdd, *J* = 16.4, 10.2, 6.2 Hz, 1H), 5.06 (dt, *J* = 17.1, 1.5 Hz, 2H), 3.92 (d, *J* = 13.0 Hz, 1H), 3.69 (d, *J* = 13.0 Hz, 1H), 3.02 (d, *J* = 5.8 Hz, 1H), 2.98-2.95 (m, 1H), 2.69 (dd, *J* = 12.4, 9.2 Hz, 1H), 2.43 (dd, *J* = 12.4, 4.1 Hz, 1H), 1.06 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5 (C), 136.1 (CH), 129.4 (CH), 128.1 (CH), 127.0 (CH), 116.4 (CH_2), 60.3 (CH_2), 59.0 (CH), 51.8 (CH_2), 51.5 (CH_2), 11.1 (CH_3); IR (film): 3032, 2972, 2930, 2842, 1641, 1496, 1451, 1371, 1059, 1026, 991, 919, 735, 698 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{13}H_{20}N_2O$ $[M]^+$: 220.1576. Found: 220.1592.



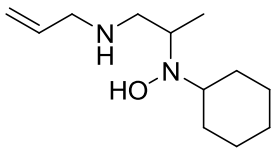
***N*-(2,2-Diethoxyethyl)prop-2-en-1-amine (14e).** Synthesized according to a modified procedure of Stach, et. al.[122] A mixture of bromoacetaldehyde diethyl acetal (2.00 g, 1.50 mL, 0.102 mol) in allylamine (11.4 g, 15.0 mL, 0.200 mol) was heated at 100°C for 3 h. Then, a solution of NaOH (1.0 g) 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/pet. ether), the product was obtained as a dark red liquid in 71% yield (1.26 g). TLC R_f 0.36 (3:1 Et_2O/pentane); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (tdd, *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

(122) Stach, L. J.; Hotz, R. D.; Richter, S. B. Dioxolane substituted amides. U.S. Patent 4,113.464, September 12, 1978,

$C_9H_{19}NO_2$ $[M]^+$: 173.1416. Not found. Exact mass calcd for $C_7H_{14}NO$ $[M\text{-}OEt]^+$: 128.1075. Found: 128.1078.

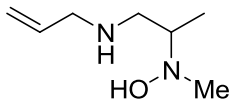


2-(Benzyl(hydroxy)amino)-N-(2,2-diethoxyethyl)propan-1-amine (15e, Table 3.7, entry 5). Synthesized according to the general procedure (C_6H_6, 96 h). Isolated 0.26 g (39%) as a yellow oil after column chromatography (10% MeOH/CH_2Cl_2). Alternatively, it was synthesized in 29 h at 60°C by the general procedure, and isolated in 56% yield (0.24 g). TLC R_f 0.29 (10% MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) 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 (dqd, *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); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5 (C), 129.2 (CH), 128.2 (CH), 127.1 (CH), 101.7 (CH), 62.7 (CH_2), 62.1 (CH_2), 60.4 (CH_2), 59.7 (CH), 53.3 (CH_2), 51.6 (CH_2), 15.3 (CH_3), 11.7 (CH_3); IR (film): 3029, 2975, 2877, 1493, 1451, 1371, 1341, 1121, 1064, 735, 698 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{16}H_{28}N_2O_3$ $[M]^+$: 296.2100. Not found. Exact mass calcd for $C_9H_{12}NO$ $[M\text{-}(OEt)_2CHCH_2NHCH_2]^+$: 150.0919. Found: 150.0924.[121]

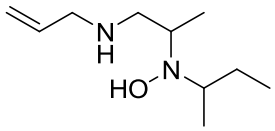


***N*-(2-(Cyclohexyl(hydroxy)amino)propyl)prop-2-en-1-amine (15g, Table 3.7, entry 7).** Synthesized according to the general procedure ($CHCl_3$, 29 h). Isolated 58.1 mg (25%) as a yellow oil after column chromatography (10% MeOH/CH_2Cl_2). TLC R_f 0.11 (10% MeOH/CH_2Cl_2);

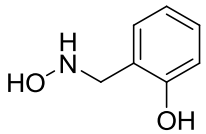
^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (tdd, *J* = 16.6, 10.5, 6.1 Hz, 1H), 5.16 (dd, *J* = 19.8, 13.7 Hz, 1H), 4.74 (br s, 2H), 3.33-3.12 (m, 3H), 2.85 (dd, *J* = 12.0, 8.5 Hz, 1H), 2.64 (br s, 1H) 2.57 (dd, *J* = 12.1, 4.3 Hz, 1H), 2.06 (m, 1H), 1.75 (m, 3H), 1.59 (d, *J* = 10.4 Hz, 1H) 1.32-1.10 (m, 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 $C_{12}H_{24}N_2O$ $[M]^+$: 212.1889. Found: 212.1887.



***N*-(2-(Hydroxy(methyl)amino)propyl)prop-2-en-1-amine (15h, Table 3.7, entry 8).** Synthesized according to the general procedure, but with 1 equiv. of Et_3N ($CHCl_3$, 29 h). Isolated 73.8 mg (32%) as a white solid after column chromatography (1% Et_3N/10% MeOH/CH_2Cl_2). TLC R_f 0.31 (15% MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (br s, 2H), 6.13 (tdd, *J* = 17.2, 10.3, 7.0 Hz, 1H), 5.49 (dd, *J* = 17.2, 1.1 Hz, 1H), 5.46 (dd, *J* = 10.2, 0.8 Hz, 1H), 3.65 (d, *J* = 6.8 Hz, 1H), 3.22-3.13 (m, 1H), 3.00 (dd, *J* = 12.2, 10.4 Hz, 1H), 2.86 (dd, *J* = 12.4, 4.4 Hz, 1H), 2.65 (s, 3H), 1.07 (d, *J* = 6.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 128.2 (CH), 123.7 (CH_2), 57.6 (CH), 49.6 (CH_2), 49.0 (CH_2), 44.2 (CH_3), 8.8 (CH_3); IR (film): 3329, 2991, 2956, 2812, 2763, 2724, 2413, 1588, 1440, 1041, 991, 942, 874, 832, 744 cm^{-1}; HRMS (EI): Exact mass calcd for $C_7H_{16}N_2O$ $[M]^+$: 144.1263. Not found. Exact mass calcd for $C_7H_{15}N_2$ $[M\text{-}OH]^+$: 127.1240. Found: 127.1240.

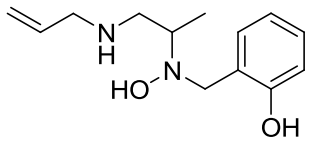


***N*-(2-(Hydroxy(methyl)amino)propyl)prop-2-en-1-amine (15i, Table 3.7, entry 9).** Synthesized according to the general procedure ($CHCl_3$, 24 h). Isolated 58.0 mg (29%) as a white solid after column chromatography (10% MeOH/CH_2Cl_2), and characterized as an inseparable mixture of diastereomers. TLC R_f 0.38 (15% MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 [tdd, *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)]; ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.4 (CH, major), 136.3 (CH, minor), 116.2 (CH_2, minor), 116.1 (CH_2, major), 59.0 (CH, major), 58.8 (CH, minor), 55.4 (CH, mix), 53.2 (CH_2, minor), 52.6 (CH_2, major), 52.1 (CH_2, major), 52.0 (CH_2, minor), 27.2 (CH_2, major), 24.9 (CH_2, minor), 16.7 (CH_3, major), 13.8 (CH_3, minor), 12.1 (CH_3, minor), 11.7 (CH_3, minor), 10.3 (CH_3, major), 10.1 (CH_3, major); IR (film): 3298, 3082, 2972, 2941, 2880, 1645, 1457, 1371, 1170, 991, 919 cm^{-1}; HRMS (EI): Exact mass calcd for $C_{10}H_{22}N_2O$ $[M]^+$: 186.1732. Found: 186.1720.



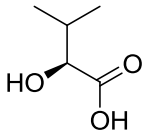
2-((Hydroxyamino)methyl)phenol (13e). Synthesized from the reduction of the corresponding oxime according to the procedure of House.[88] Isolated 0.22 g (8.0%) as a white solid after column chromatography (2:1 EtOAc/hexanes). TLC R_f 0.44 (1:1 EtOAc/hexanes); ^{1}H NMR (300

MHz, DMSO-d_6) δ 7.16 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.06 (dt, *J* = 8.0, 1.7 Hz, 1H), 6.76-6.70 (m, 2H), 3.90 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.0 (C), 129.8 (CH), 127.8 (CH), 124.0 (C), 118.6 (CH), 115.0 CH), 53.7 (CH_2); IR (Nujol): 3188, 2721, 2660, 1702, 1592, 1459, 1375, 1273, 1238, 1121, 1056, 1018, 969, 889, 855, 748, 722, 627 cm^{-1}; HRMS (EI): Exact mass calcd for $C_7H_9NO_2$ $[M]^+$: 139.0633. Found: 139.0615.

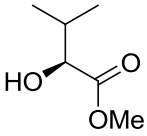


2-(((1-(Allylamino)propan-2-yl)(hydroxy)amino)methyl)phenol (15j, Table 3.7, entry 10). Synthesized according to the general procedure ($CHCl_3$, 46 h). Isolated 98.1 mg (61%) as a yellow oil after column chromatography (10% MeOH/CH_2Cl_2). TLC R_f 0.36 (15% MeOH/CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$) 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 (tdd, *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 $C_{13}H_{20}N_2O_2$ $[M]^+$: 236.1525. Found: 236.1522.

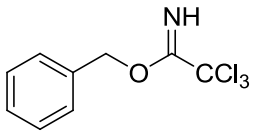
3.4.2 Towards the synthesis of chiral catalyst, (S)-2-(benzyloxy)-3-methylbutanal (Scheme 3.1).



(*S*)-2-Hydroxy-3-methylbutanoic acid. Synthesized from L-valine according to the procedure of Joullié.[123] The target alcohol was obtained as a white solid (9.0 g, 56%) and used without further purification. Spectral data consistent with literature.



(*S*)-Methyl 2-hydroxy-3-methylbutanoate. Synthesized according to a modified procedure of Joullié.[123] A solution of (*S*)-2-hydroxy-3-methylbutanoic acid (2.0 g, 17 mmol) in MeOH (20 mL) was refluxed with a catalytic amount of conc. H_2SO_4 (0.4 mL) for 24 h. The reaction was concentrated then diluted with Et_2O, and washed with saturated aqueous $NaHCO_3$ (20 mL) and saturated aqueous NaCl (20 mL) solutions. The organic phase was dried (Na_2SO_4), filtered and concentrated. The crude oil was distilled *in vacuo* (bp 27°C, 0.2 Torr) to afford the ester as a colourless oil (1.26 g, 56%). Spectral data consistent with literature.

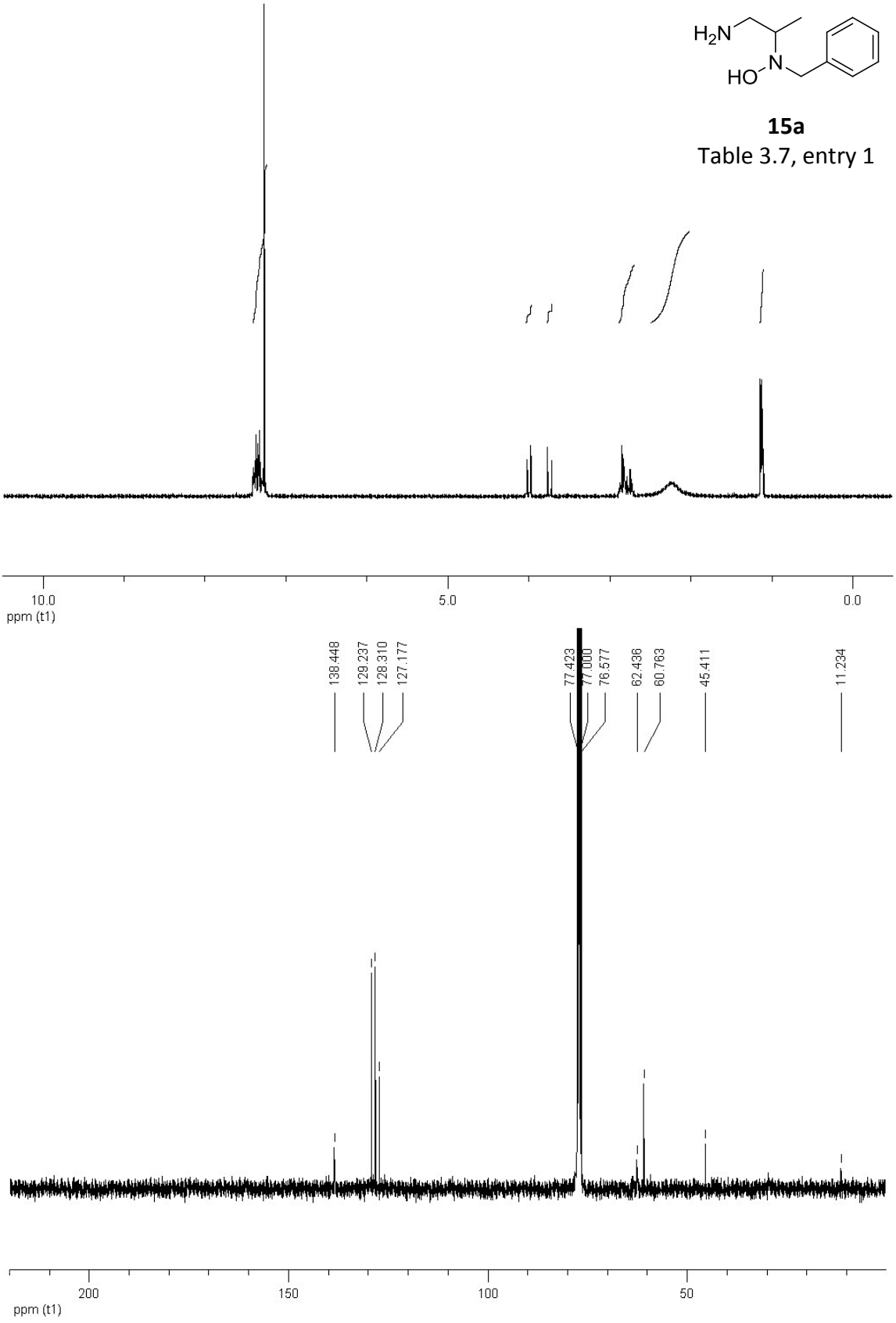


(123) Li, W.-R.; Ewing, W. R.; Harris, B. D.; Joullié, M. M. *J. Am. Chem. Soc.* **1990**, *112*, 7659.

Benzyl 2,2,2-trichloroacetimidate. Synthesized according to the procedure of Paquette.[124] After distillation (bp 107°C, 0.2 Torr), product was obtained as a colourless oil (6.5 g, 52%). Spectral data was consistent with data from commercial sources.

(124) Paquette, L. A.; Guevel, R.; Sakamoto, S.; Kim, I. H.; Crawford, J. *J. Org. Chem.* **2003**, *68*, 6096.

Appendix I. Supporting Information for Chapter 3



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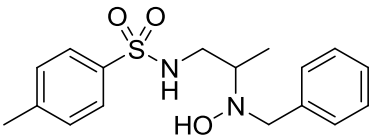
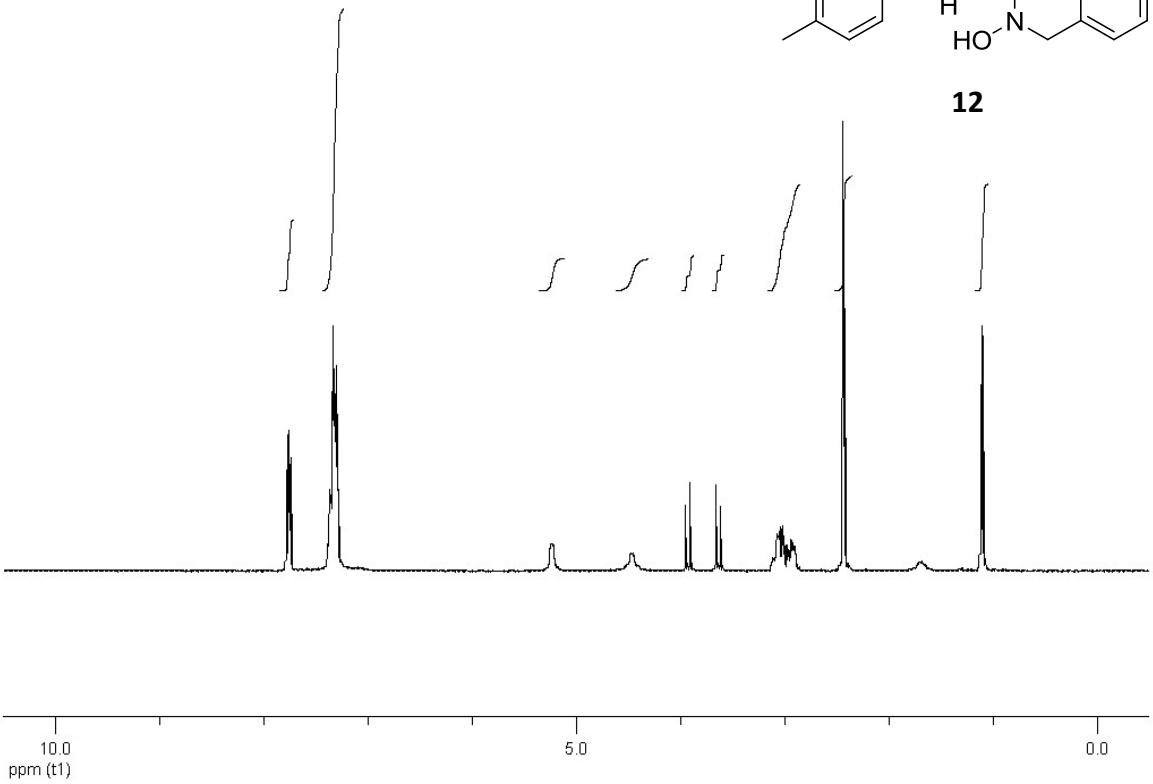


12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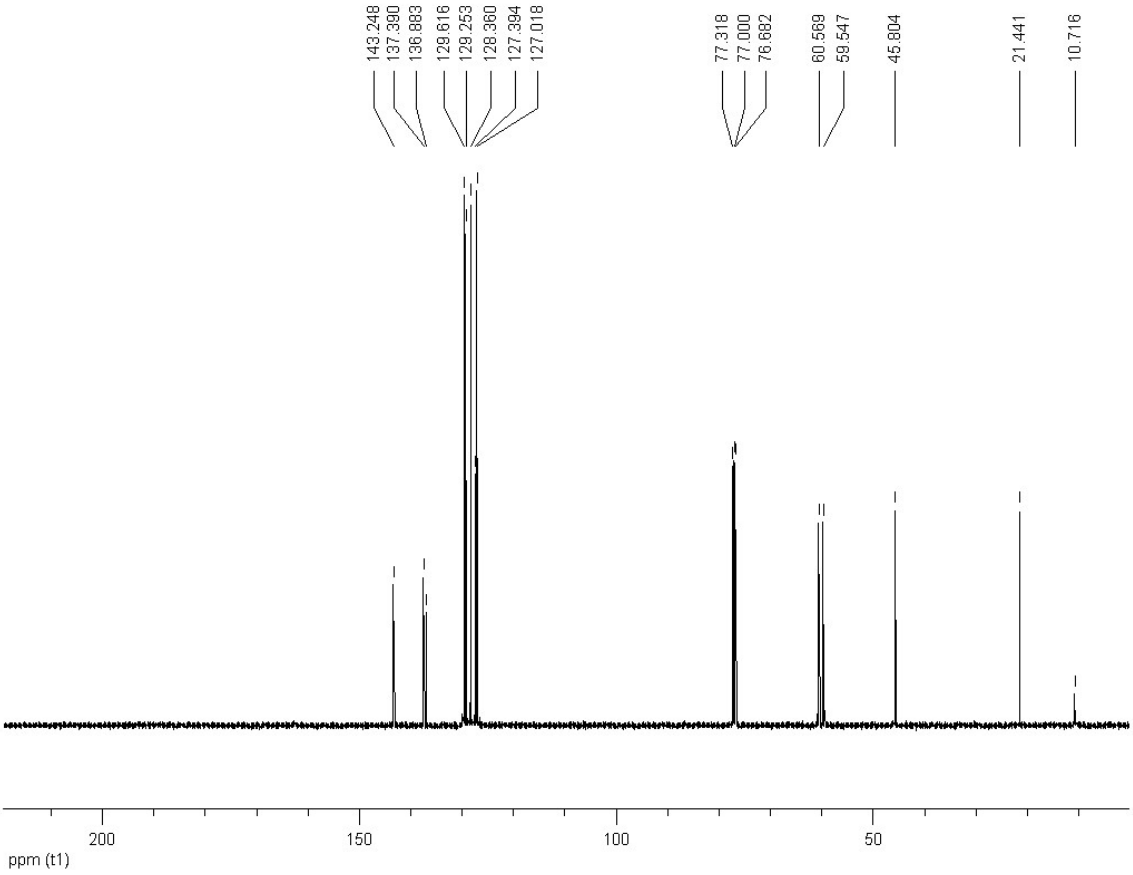
5.0
0.0
ppm (t1)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137.390
136.883
129.616
129.253
128.360
127.394
127.018
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76.682
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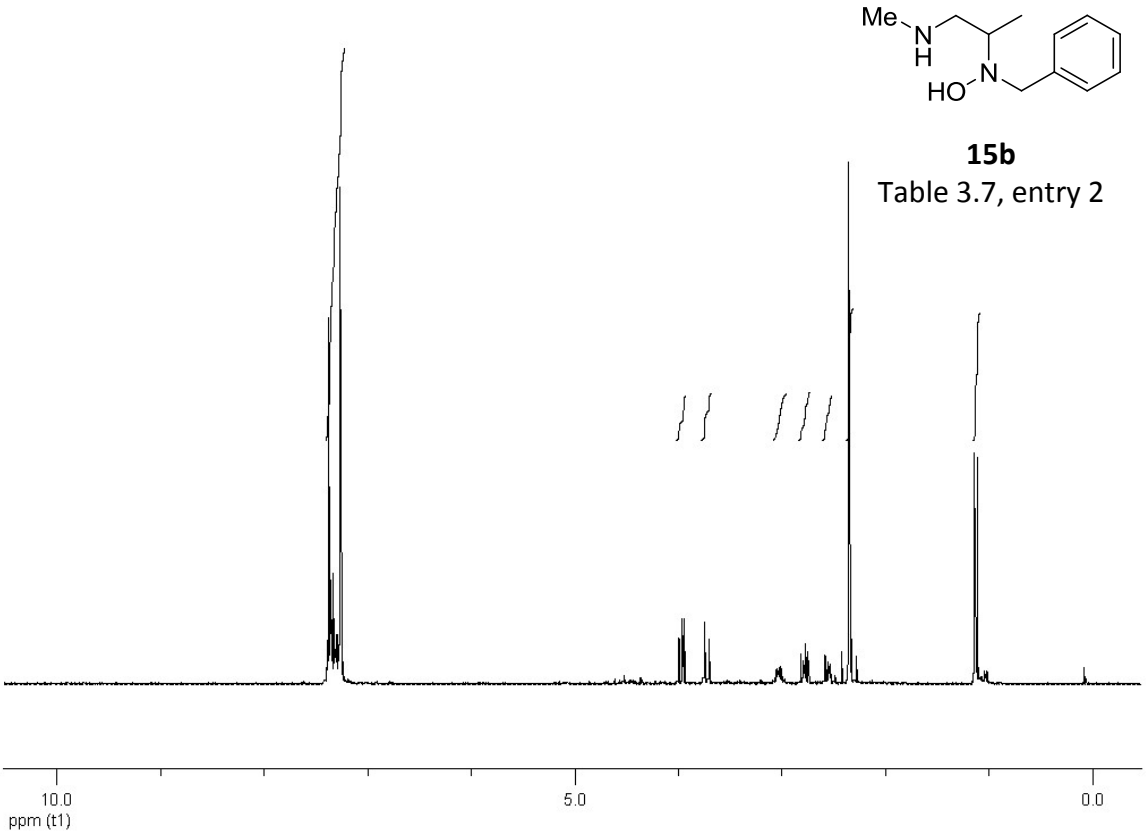
21.441
10.716
200
150
100
50
ppm (t1)



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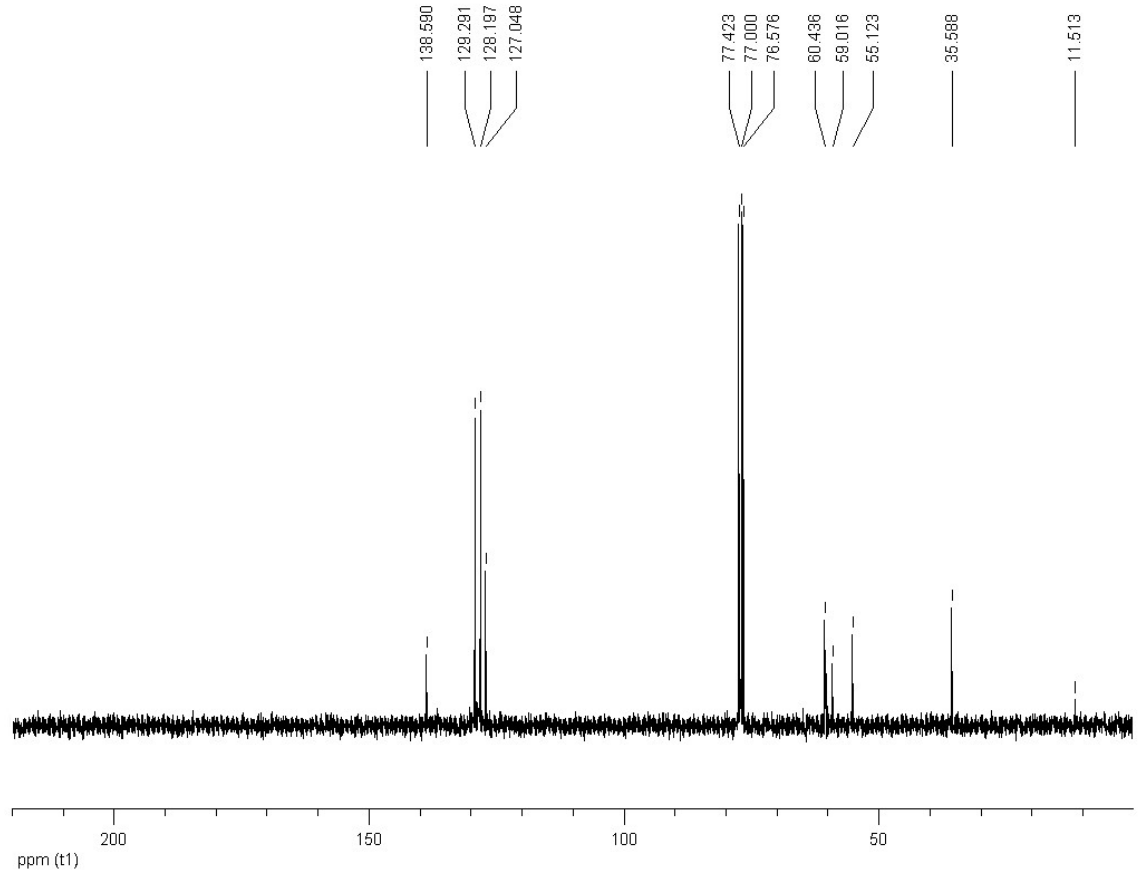

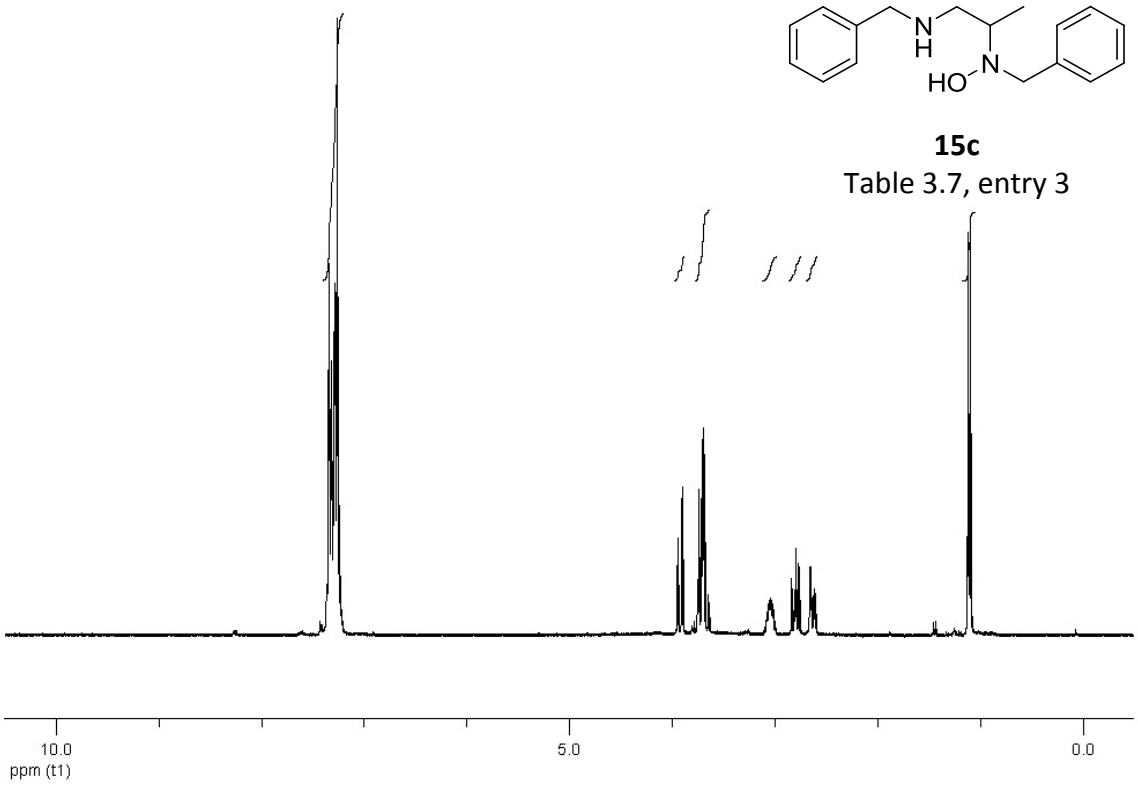

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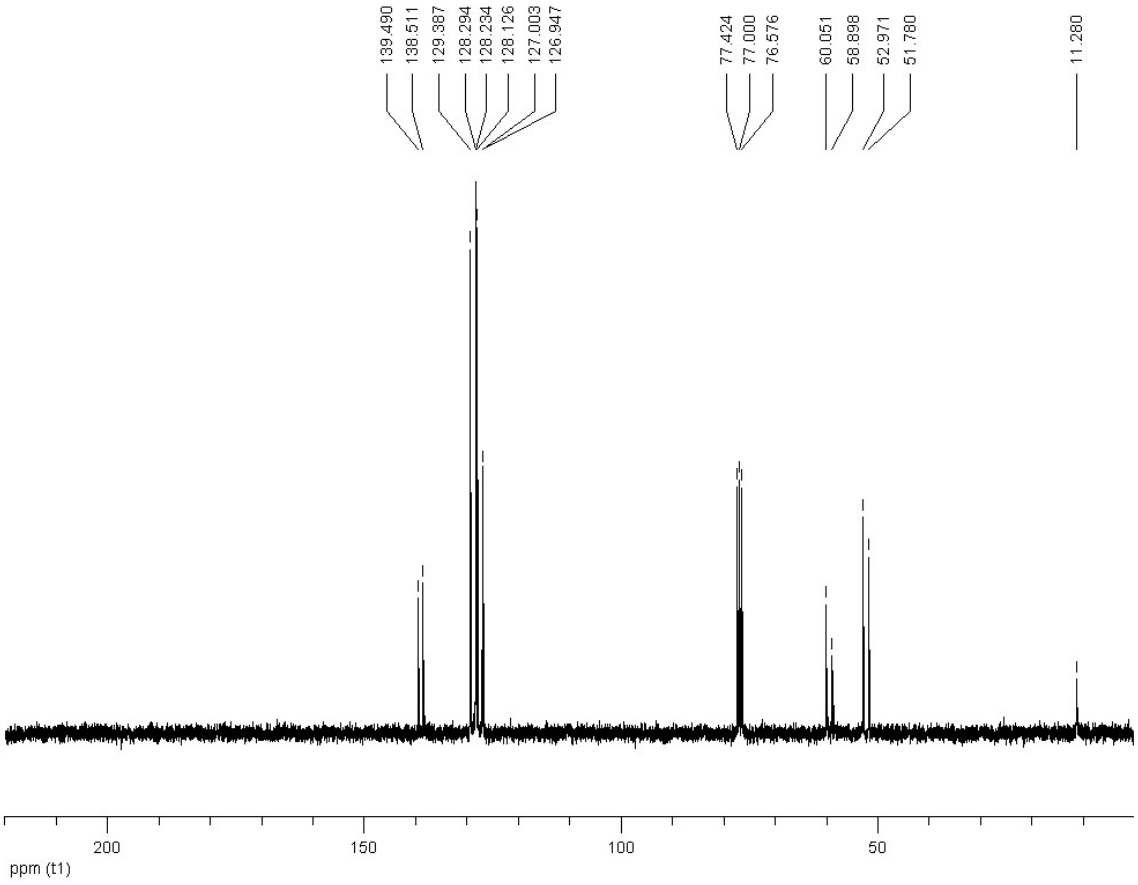

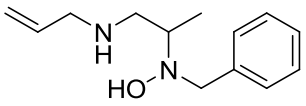

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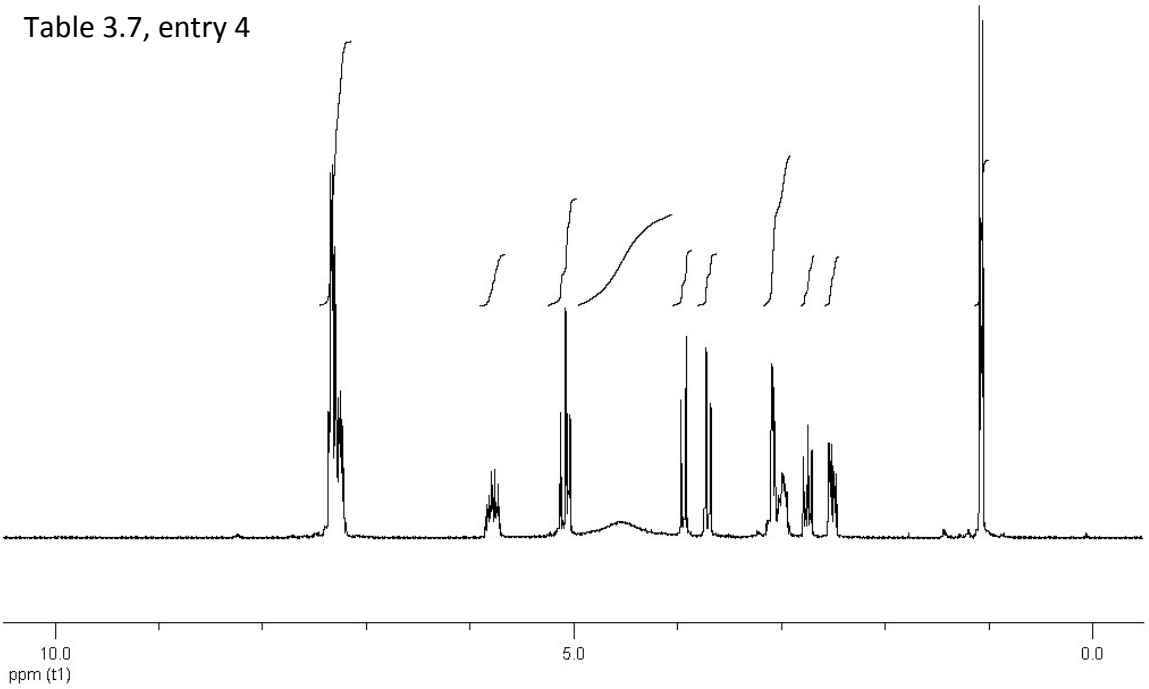

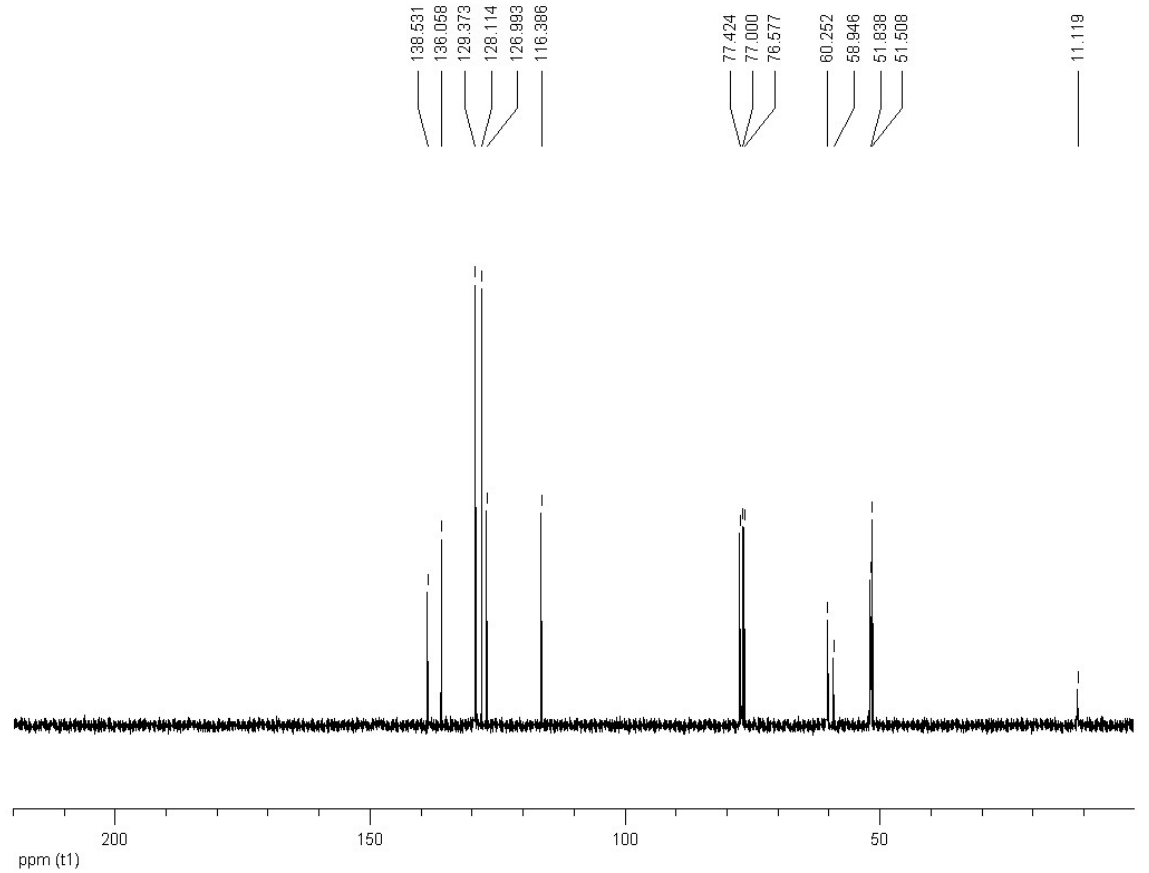

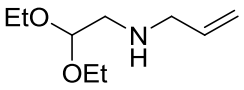

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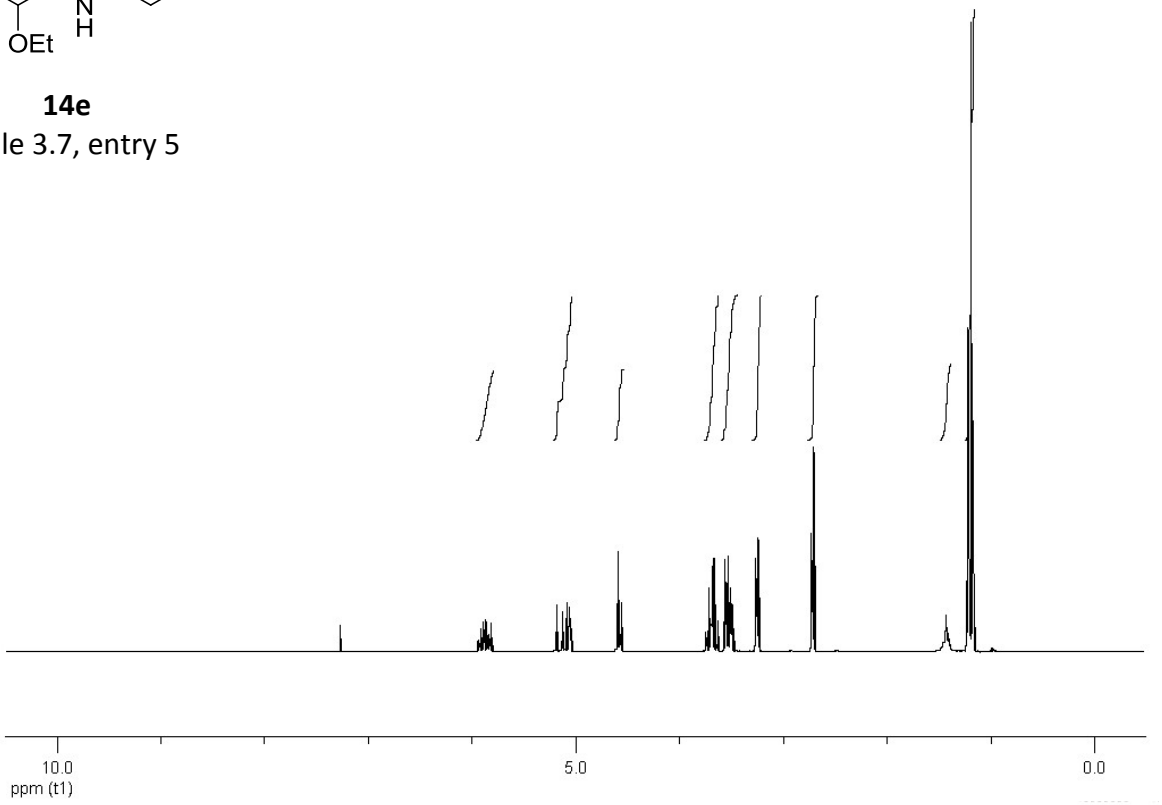

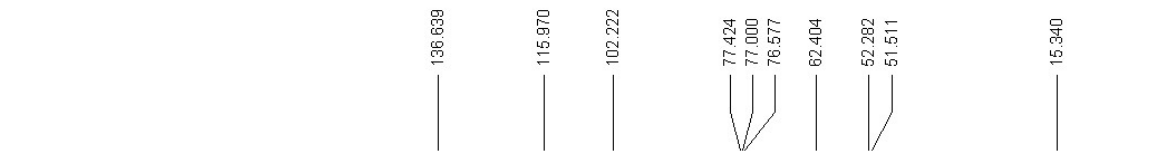

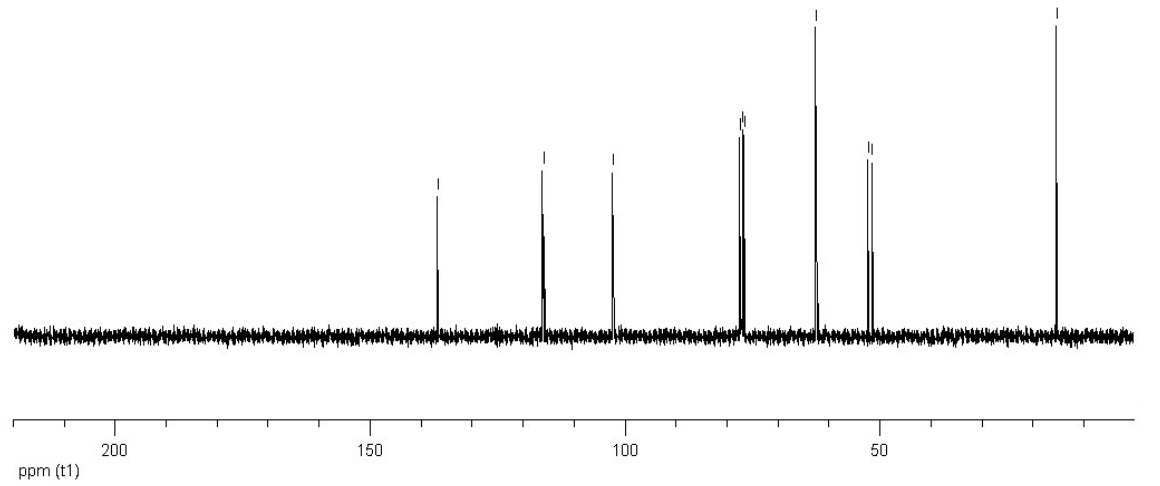

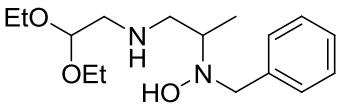

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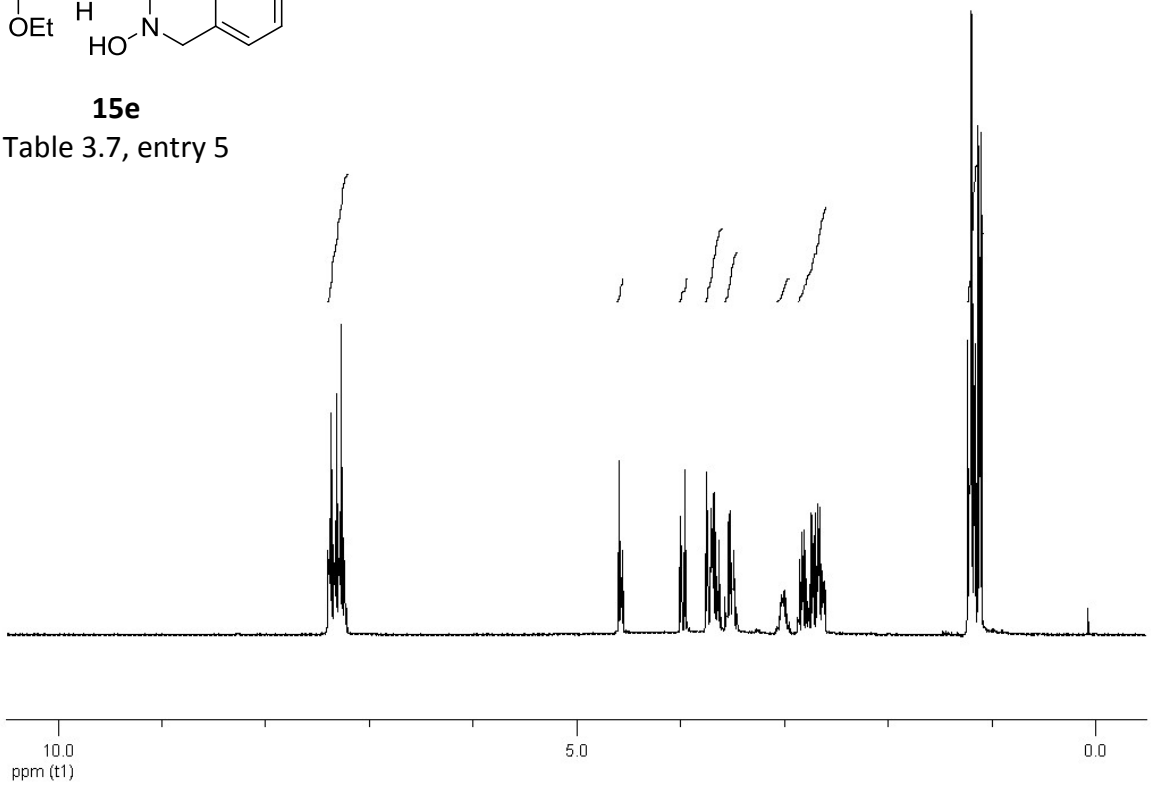

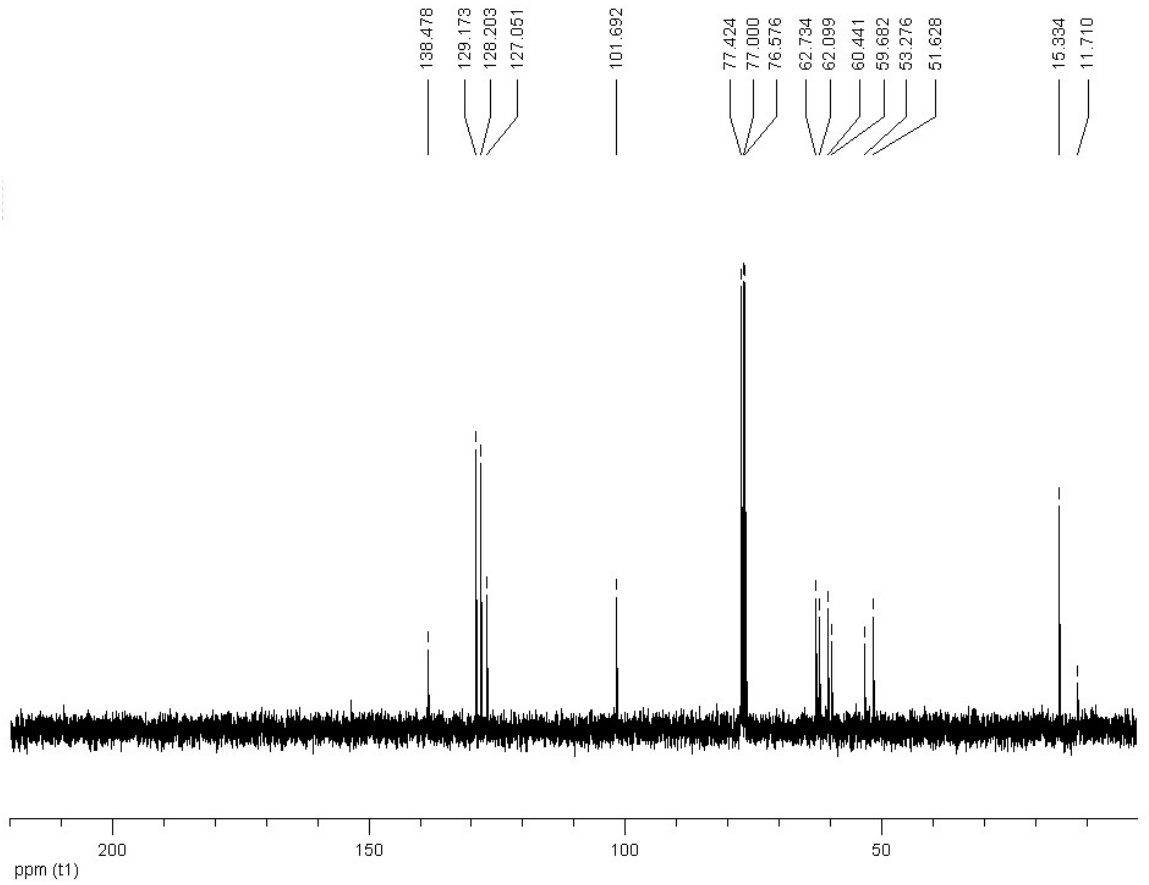

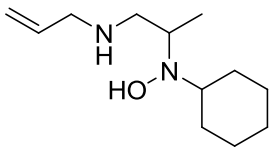

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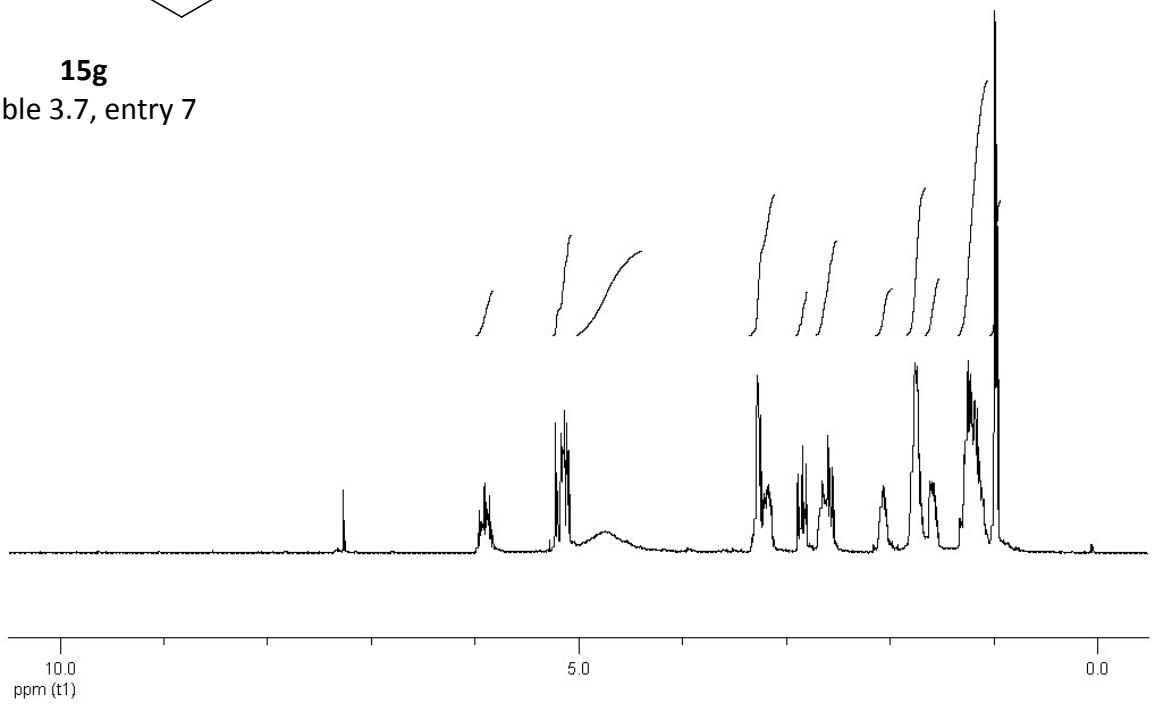

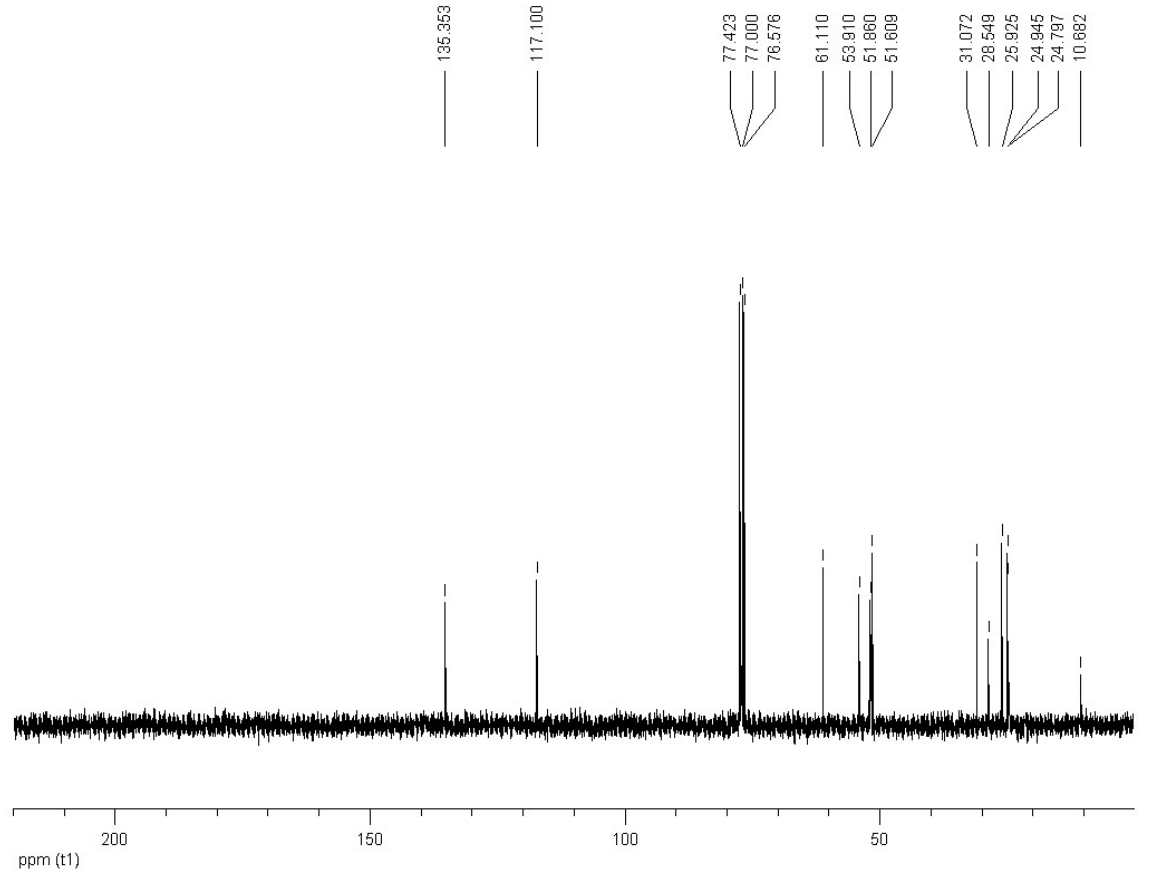

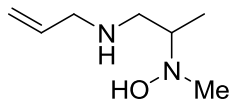

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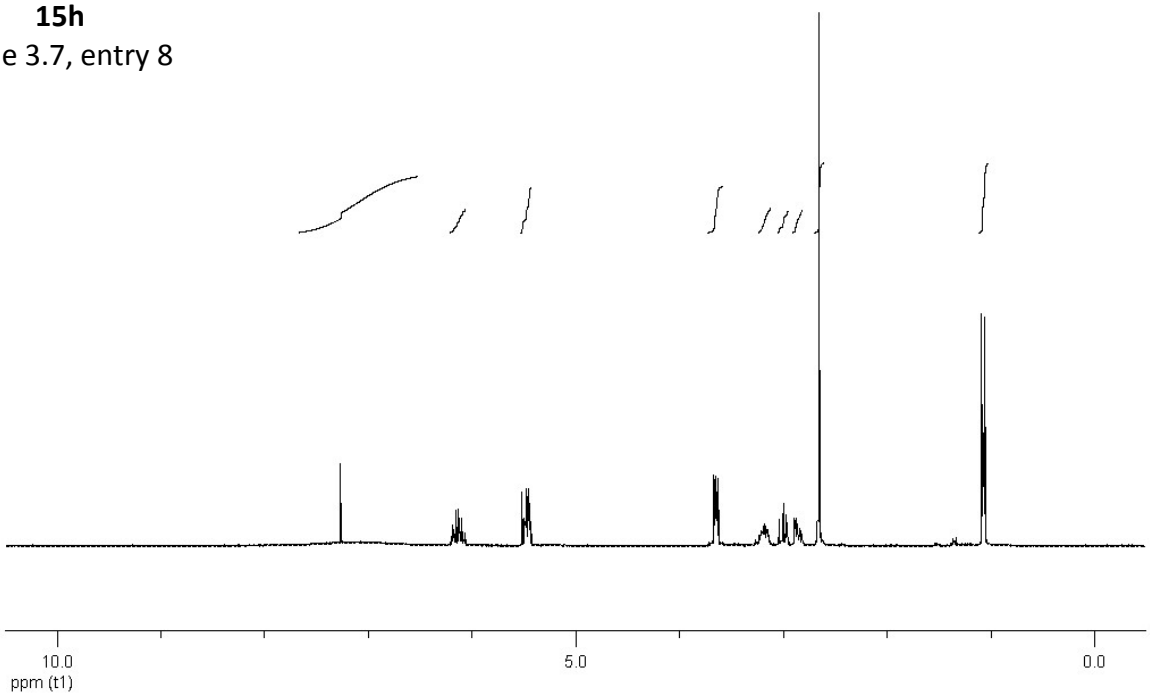

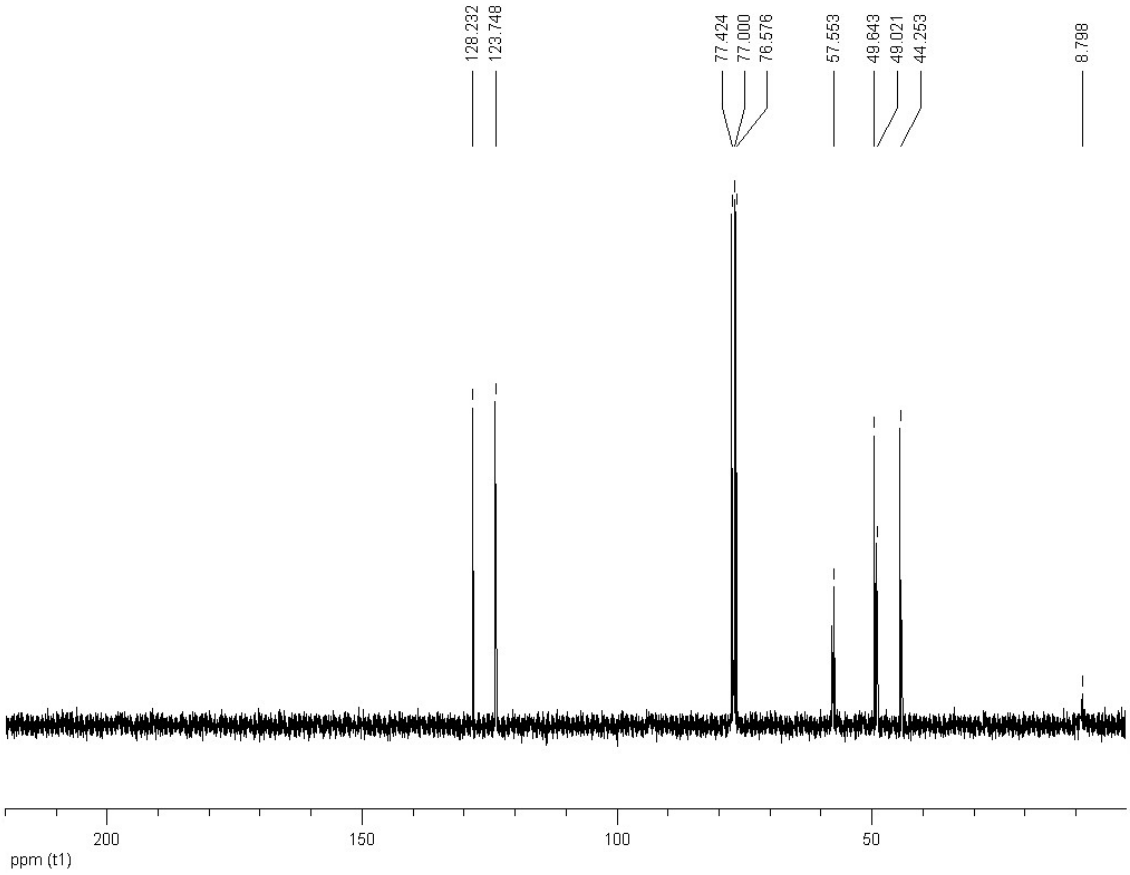

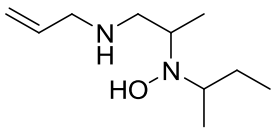

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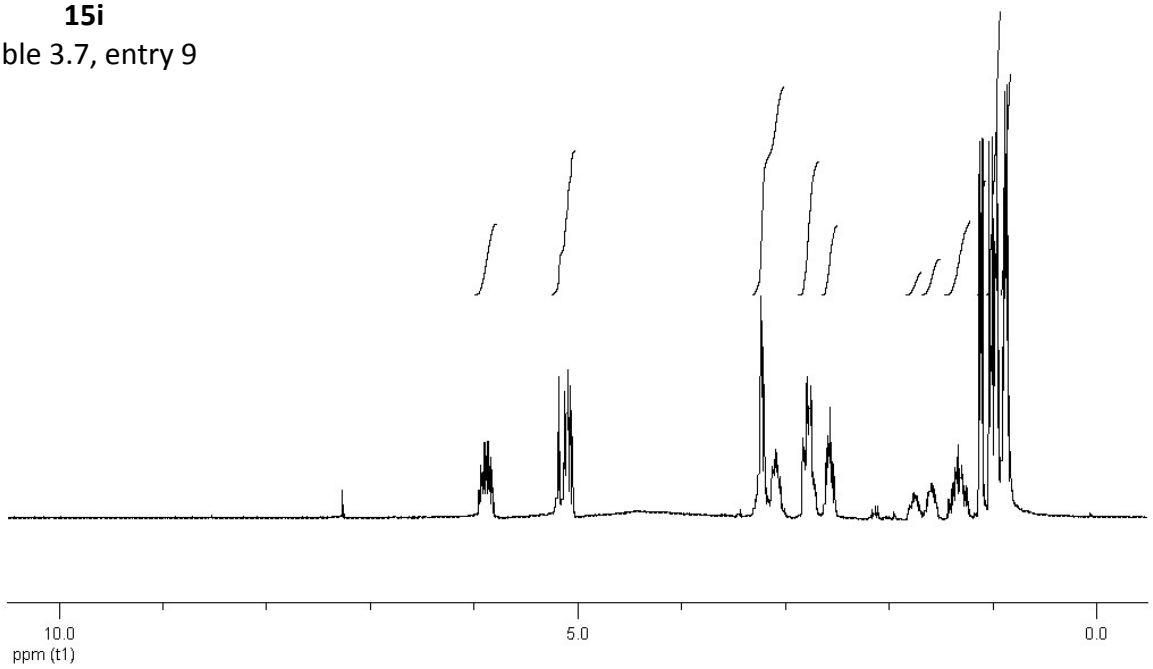

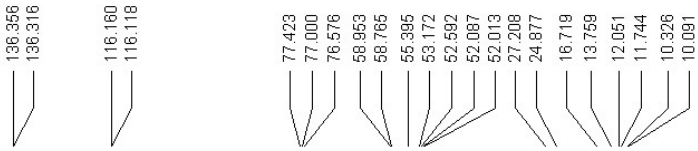

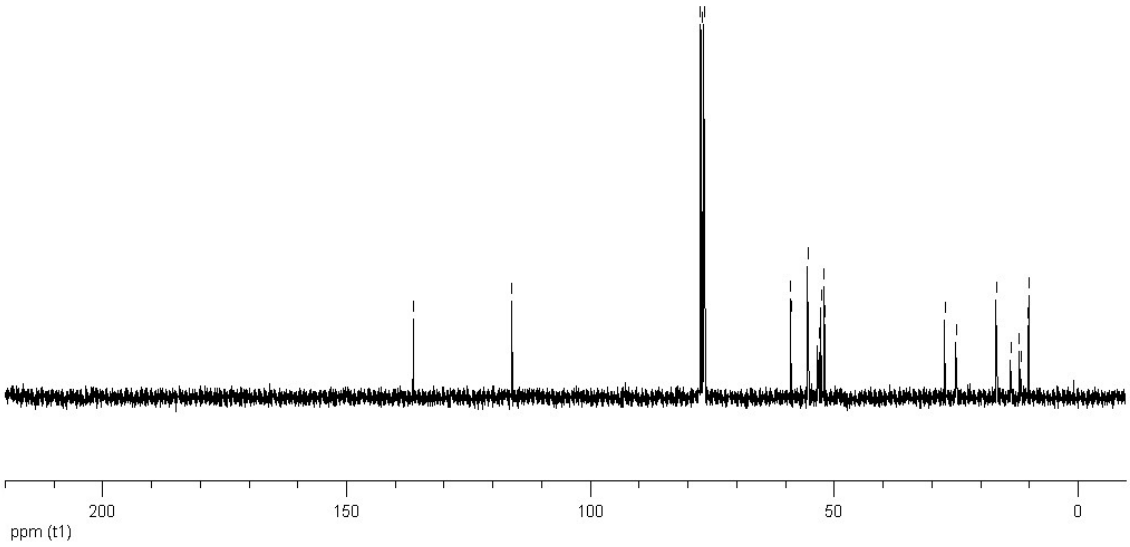

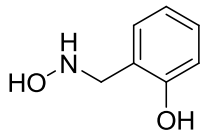

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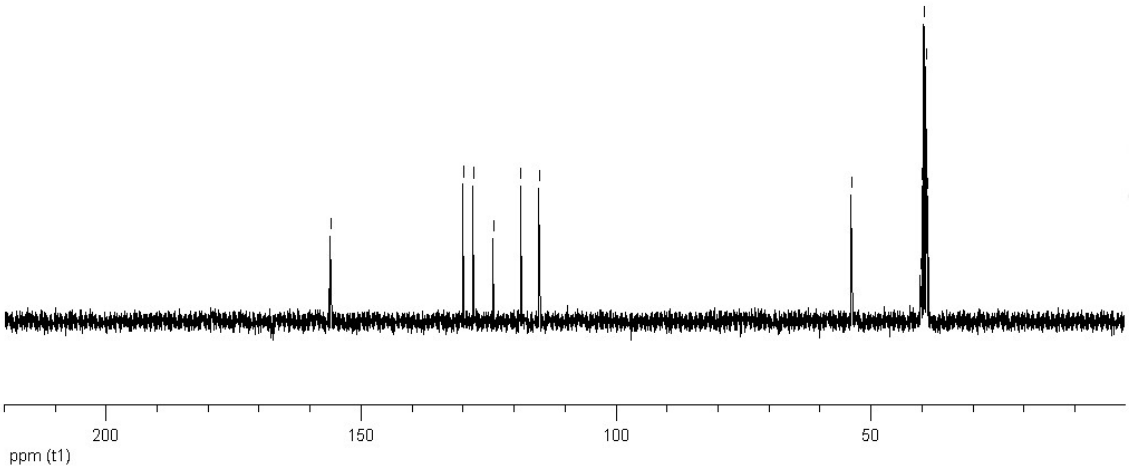

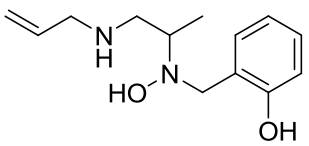

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