



I. Engaging Cationic Intermediates in Asymmetric Catalysis: Enantioselective Reactions of Carbenium Ions and N,N-Dialkyliminium Ions

II. Enantioselective Catalysis of the Cope-Type Hydroamination by H-Bond Donors

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**I. Engaging Cationic Intermediates in Asymmetric Catalysis: Enantioselective Reactions
of Carbenium Ions and *N,N*-Dialkyliminium Ions**

II. Enantioselective Catalysis of the Cope-Type Hydroamination by H-Bond Donors

A dissertation presented

by

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to

The Department of Chemistry and Chemical Biology

in partial fulfillment of the requirements

for the degree of

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Chemistry

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I. Engaging Cationic Intermediates in Asymmetric Catalysis: Enantioselective Reactions of Carbenium Ions and *N,N*-Dialkyliminium Ions

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Abstract

The research described here explores the ability of dual H-bond donor catalysts to induce asymmetry in a variety of synthetically useful transformations that proceed via diverse reactive intermediates. In Chapters 1–3, we investigate ureas and thioureas as anion-binding catalysts for asymmetric reactions that proceed via cationic intermediates with little precedent as electrophiles in asymmetric catalysis. Chapter 4 details our application of H-bond donor catalysis to the Cope-type hydroamination.

Chapter 1 describes the development of an asymmetric aldehyde alkylation catalyzed by a bifunctional primary aminothiurea. A variety of 2-aryl propionaldehydes are alkylated with benzhydryl bromides in moderate to good yields and good enantioselectivities. Catalyst structure-activity relationship studies of the alkylation pointed towards electrophile activation by the dual H-bond donor moiety. Experiments aimed at gaining a better understanding of the electrophile activation mode and characterizing the activated electrophilic intermediate in the alkylation reaction are described in Chapter 2.

The development of an enantioselective cyanide addition to *N,N*-dialkyliminium intermediates is the subject of Chapter 3. A variety of strategies for accessing *N,N*-dialkyliminium ions are established, and chiral thioureas are shown to promote the addition of cyanide to such intermediates with moderate enantioselectivities.

Chapter 4 details our discovery that thioureas bearing polarizable and conformationally constrained aromatic groups catalyze highly enantioselective Cope-type hydroaminations. This powerful transformation provides a variety of chiral pyrrolidine products under mild reaction conditions.

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I am very pleased to have had the good fortune of working with Eric Jacobsen for almost six years. During this time, Eric has provided invaluable encouragement and advice, but has also given me the necessary scientific freedom which has allowed me to grow and develop as a scientist. Thanks for everything, Eric, I feel very privileged to be among the students you have advised over the years.

I thank Tobias Ritter, Emily Balskus, and Theodore Betley for serving on my graduate advising committee. Their advice and guidance during my committee meetings have been very useful, and they have helped me to communicate my ideas with more clarity and purpose.

I appreciate all that Nicole Minotti does to keep the lab running smoothly. Despite the stresses of working with a bunch of crazy chemists, Nicole manages to keep a friendly and kind demeanor and is always incredibly helpful.

I first crossed paths with Gary Molander in my first semester of organic chemistry at the University of Pennsylvania. Gary was an excellent and inspiring teacher, and he was gracious enough to allow me carry out research in his laboratory. I learned a great deal about chemistry and how research is done while in the Molander group, and I have little doubt that my experiences there positioned me well for a successful graduate career. I am also grateful to Magnus Besev and Dan Petrillo, who were extremely helpful to me during my undergraduate years.

Naomi Rajapaksa, Sean Kedrowski, David Ford, and Charles Yeung all read and corrected parts of this thesis. They caught many errors, and their suggestions certainly improved the

clarity of discussion presented here. I appreciate their efforts – any remaining errors are my own.

During my time in the Jacobsen group I have had the privilege of working with many talented scientists. My early days in the group were spent in the M202C along with Rebecca Loy, K.C. O'Brien and Abigail Doyle, who all treated me very well despite my inability to control the stench of the aldehydes I was working with at the time. In addition to being friendly and helpful, Abigail was a great role model with respect to how to think about science carefully and how to work efficiently. Rebecca's friendly disposition made the bay a pleasant place to work, and her love for margaritas (even blue ones) won't be forgotten.

While the Jacobsen labs were being renovated I spent quite a bit of time with Stephan Zuend, Christopher Uyeda, and Rebekka Klausen in our temporary lab space. It was inspiring to work with such a talented and hard-working group of people, and I benefited from the example that they set and from the conversations that we shared. Stephan and Chris were great friends both at work and away from the lab, and I am grateful to both of them for the good times that we shared. I was also fortunate enough to collaborate with Chris on the Cope-type hydroamination research described in Chapter 4 of this thesis – his input in how to present that work as well as his help editing the final manuscript were very useful.

I have shared my entire time in the Jacobsen group with Naomi Rajapaksa, and during this time she has been an amazing friend and coworker. Despite our disagreements about certain aspects of lab etiquette, I have thoroughly enjoyed sharing a bay with Naomi since moving into the renovated labs. Naomi's kind but frank way of approaching problems, her intelligence, and her excellent work ethic will certainly serve her well in the future.

David Ford, Jim Birrell, and Song Lin make up an incredibly talented class of graduate students one year my junior. These guys, along with Andreas Rötheli, have been a huge part of my graduate school experience and I am sure we will all remain close friends in the years ahead. Dave's passion and intensity are inspiring. He takes on everything – whether it is an experiment, an outdoor activity, or a pint of ice cream – full speed ahead. Among these guys, Jim's mind is unmatched, or at least it is with respect to finding ways to save money. Jim has been a great friend and office-mate and I have thoroughly enjoyed our discussions of ion-pairing, sports, and fantasy football over the years. Song is an incredibly talented chemist and comedian, and I will thoroughly miss his cutting barbs. Andreas Rötheli is more than a just beautiful man; he is an exceptionally talented researcher and teacher, and a really kind person. We have shared many great nights out in Cambridge and Boston, and I look forward to many more over the next few years.

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Although my graduate studies have taken me far from home, my family has always supported me fully in my endeavors, and for this I am thankful. I love you all and thank you so much for your love and encouragement over the years.

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to my wife Lisa

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List of Abbreviations

$[\alpha]_D^{25}$	Specific rotation at 25 °C and 589 nm
Ac	Acetyl
AcBr	Acetyl bromide
AcCN	Acetyl cyanide
AcOH	Acetic Acid
Al ₂ O ₃	Aluminum oxide
aq.	Aqueous
Bn	Benzyl
BnBr	Benzyl bromide
BnNHMe	<i>N</i> -benzylmethylamine
Boc	<i>tert</i> -butoxycarbonyl
(Boc) ₂	Di- <i>tert</i> -butyl dicarbonate
(BzO) ₂	Benzoyl peroxide
BzOH	Benzoic acid
° C	Degree Celsius
CAN	Ceric ammonium nitrate
CF ₃ COOH	Trifluoroacetic acid
C ₆ H ₆	Benzene
CH ₂ Cl ₂	Dichloromethane
CHCl ₃	Chloroform
conv.	Conversion
CuBr	Copper bromide

Cu(OTf) ₂	Copper Triflate
Cy	Cyclohexyl
d	Days
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM	Dichloromethane
DIBAL-H	Diisobutylaluminum hydride
DIPEA	Diisopropylethylamine
DME	Dimethoxyethane
d.r.	Diastereomeric ratio
ee	Enantiomeric excess
<i>ent</i>	Enantiomeric
equiv.	Equivalent
Et	Ethyl
EtI	Ethyl iodide
Et ₃ B	Triethylborane
Et ₃ N	Triethylamine
Et ₂ NH	Diethylamine
Et ₂ O	Ethyl ether
Et ₂ Zn	Diethylzinc
g	Gram
h	Hours
HBr	Hydrogen bromide
HCl	Hydrogen chloride

HCN	Hydrogen cyanide
H ₂ O	Water
HONH ₃ Cl	Hydroxylamine hydrochloride
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectroscopy
IPA	Isopropanol
<i>i</i> Pr	Isopropyl
<i>i</i> Pr ₂ NH	Isopropylamine
kcal	Kilocalorie
K ₂ CO ₃	Potassium carbonate
KF	Potassium fluoride
KIE	Kinetic isotope effect
KO <i>t</i> Bu	Potassium <i>tert</i> -butoxide
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
LiCl	Lithium chloride
LRMS	Low resolution mass spectroscopy
M	Molar
Me	Methyl
MeCN	Acetonitrile
MHz	Megahertz
MeI	Methyl iodide
mL	Milliliter

(MeO) ₃ CCH ₃	Trimethylorthoacetate
MeOH	Methanol
mmol	Millimol
MnO ₂	Manganese Oxide
MTBE	Methyl <i>tert</i> -butyl ether
MS	Mass spectroscopy
NaOAc	Sodium acetate
NaBH ₄	Sodium borohydride
NaCNBH ₃	Sodium cyanoborohydride
NaHCO ₃	Sodium bicarbonate
NaOH	Sodium hydroxide
NaOtBu	Sodium <i>tert</i> -butoxide
<i>n</i> -BuLi	<i>n</i> -Butyllithium
NMR	Nuclear magnetic resonance
OMe	Methoxy
Pd(OAc) ₂	Palladium acetate
Ph	Phenyl
PMB	<i>para</i> -methoxybenzyl
POCl ₃	Phosphorus oxychloride
PPh ₃	Triphenylphosphine
<i>rac</i>	Racemic
r.t.	Room temperature
TBS	<i>tert</i> -butyldimethylsilyl

TFA	Trifluoroacetic acid
TMS	Trimethylsilyl
TMSCN	Trimethylsilyl cyanide
THF	Tetrahydrofuran

Chapter 1

Enantioselective Primary Aminothioureacatalyzed Aldehyde α -Alkylation¹

1.1. Introduction

The direct α -alkylation of simple aldehydes is a synthetically useful carbon-carbon bond-forming reaction that allows access to chiral α -branched aldehydes, which have broad utility as synthetic intermediates towards biologically active compounds. Despite the utility of this class of transformation, few catalytic, asymmetric variants have been developed. The lack of reported asymmetric aldehyde α -alkylations is not due to a lack of interest in the transformation, but instead is a product of the challenges associated with catalyzing the transformation.² Herein, we review strategies for asymmetric aldehyde α -alkylation, including recent advances in catalytic

¹ Portions of this chapter have been published: Brown, A. R.; Kuo, W.-H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 9286.

² Commonly cited challenges for catalysis include the propensity of aldehydes to undergo side reactions, such as self-Aldol reactions or Canizzaro or Tishchenko disproportionation reactions. Additionally, catalyst deactivation by alkylation can be a challenge.

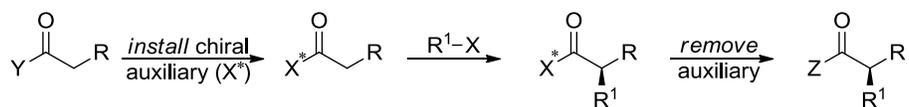
asymmetric methods.³ Our strategy and results for effecting the transformation are also presented and discussed.

1.2 Strategies for Asymmetric α -Alkylation of Aldehydes

1.2.1 Chiral Auxiliary Strategies

Chiral auxiliary technology is a robust and commonly utilized strategy for the construction of chiral α -substituted aldehydes. Implementation of this strategy requires the use of a stoichiometric amount of a chiral auxiliary, as well as additional synthetic steps for the installation and removal of the auxiliary (Scheme 1.1). An ideal chiral auxiliary is easy to install, promotes a highly selective enolization process, provides high selectivity in the desired bond forming reaction, and can be easily removed (and ideally recycled) without racemization of the desired product.⁴ A number of auxiliaries have been developed that meet these requirements, and the synthetic utility of chiral auxiliary approaches to carbonyl α -alkylation is therefore high.

Scheme 1.1. Chiral Auxiliary Strategy for Asymmetric Carbonyl Alkylation



Seminal work demonstrating the use of chiral auxiliaries for carbonyl alkylation was reported by Meyers and coworkers in 1976⁵ and Enders and coworkers in 1977.⁶ Meyers and coworkers

³ For a comprehensive review of strategies for asymmetric carbonyl α -alkylation see: Doyle, A. G.; Ph.D. dissertation, Harvard University, **2008**, and references therein.

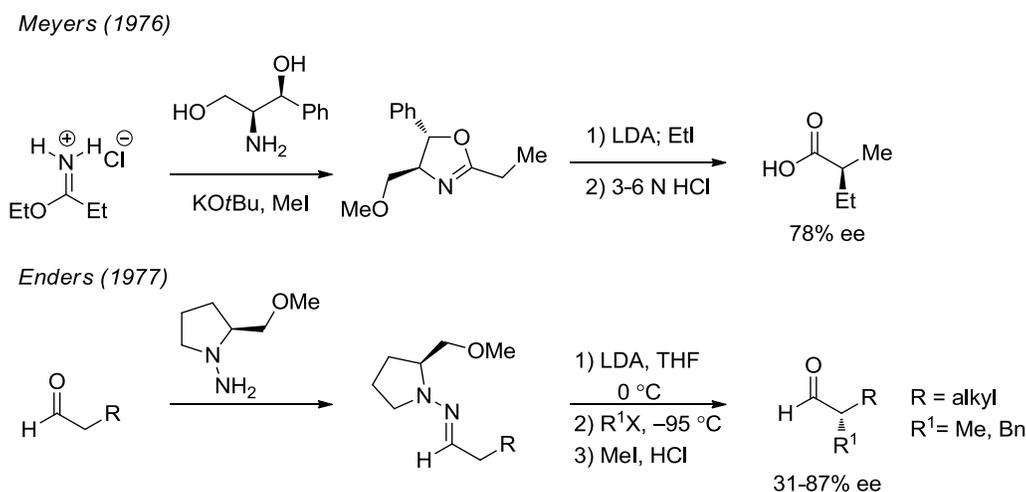
⁴ Evans, D. A. in *Asymmetric Synthesis – The Essentials* 2007 Wiley-VCH Weinheim, Germany. Editors Mathias Christmann and Stefan Bräse

⁵ Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567.

⁶ Enders, D.; Eichenauer, H. *Tetrahedron Lett.* **1977**, *18*, 1977.

showed that chiral 2-oxazolines could be alkylated with high degrees of selectivity, and then unmasked to yield the corresponding enantioenriched carboxylic acids (Scheme 1.2). Enders and coworkers reported the use of (*S*)-1-amino-2-methyl-oxyethyl-pyrroline (SAMP) as a chiral auxiliary for the methylation and benzylation of a variety of aliphatic aldehydes. The method involves conversion of aldehydes into their corresponding chiral hydrazones, deprotonation with LDA, and alkylation. The alkylated hydrazones are converted to aldehydes via hydrolysis or ozonolysis (Scheme 1.2).

Scheme 1.2. Early Chiral Auxiliary Approaches to Asymmetric Carbonyl Alkylation



Since these early examples, a variety of chiral auxiliaries have been developed that provide high degrees of selectivity for a diverse range of asymmetric transformations. Some of the most robust and highly selective auxiliary methods for carbonyl α -alkylation are those that make use of the oxazolidinone auxiliaries developed by Evans⁷ and the pseudoephedrine auxiliaries developed by Myers.⁸ These predictable and highly selective methods utilize readily available

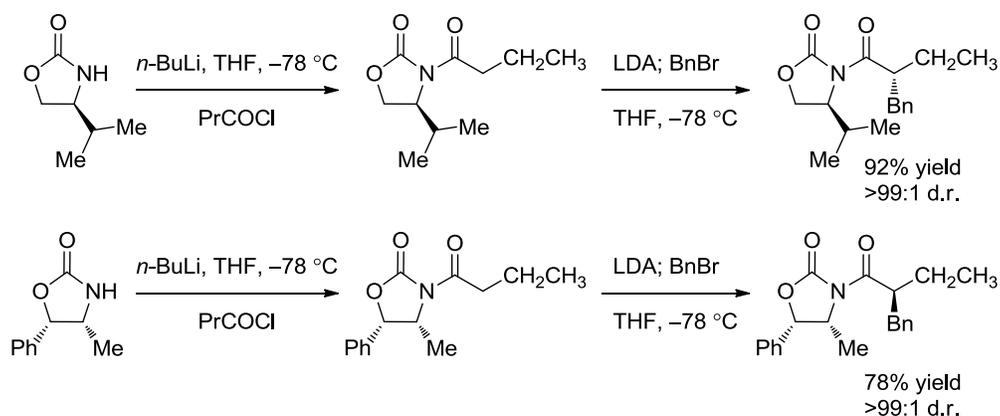
⁷ Evans, D. A.; Ennis, M. D.; Mathre, D. J. *J. Am. Chem. Soc.* **1982**, *104*, 1737.

⁸ Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496.

auxiliaries and represent the state-of-the-art in chiral auxiliary approaches to asymmetric alkylation.

First introduced for asymmetric alkylations in 1982 (Scheme 1.3), oxazolidinone auxiliaries are straightforward to install and can be removed easily after alkylation to yield ester, amide or acid products. Since their introduction, many variations of the oxazolidinone auxiliary have been developed.⁹ A number of these auxiliaries are commercially available, and they have been extensively used in complex molecule synthesis.¹⁰

Scheme 1.3. Two Enantiocomplimentary Oxazolidinone Auxiliaries Introduced by Evans



Twelve years after the introduction of the oxazolidinone auxiliaries by Evans, another exceedingly practical auxiliary was introduced by Myers. Pseudoephedrine is a commodity chemical, and it was inexpensive and readily available in bulk quantities at the time that these methods were developed.¹¹ *N*-acyl pseudoephedrine derivatives can be alkylated with high

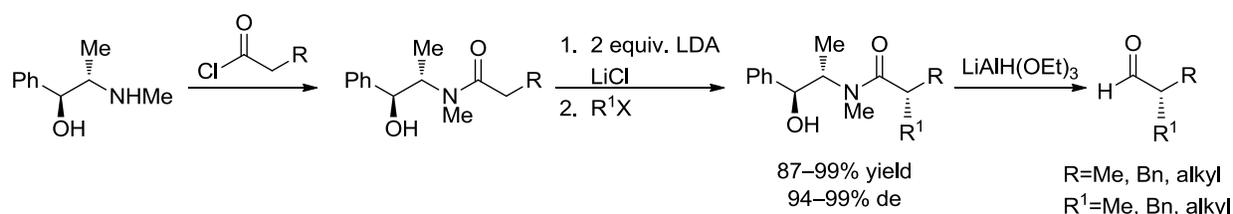
⁹ See Evans, D. A.; Shaw, J. T. *l'actualité chimique*, **2003**, 35 and references therein.

¹⁰ For example, see: Evans, D. A.; Dow, R. L.; Shih, T. L.; Takacs, J. M.; Zahler, R. *J. Am. Chem. Soc.* **1990**, *112*, 5290.

¹¹ Because pseudoephedrine can be easily converted into methamphetamine and other illegal drugs, its distribution is illegal in many countries and highly regulated in others. Pseudoephedrine has recently been developed as

selectivity for a variety of substrates and with many alkylating agents (Scheme 1.4). The alkylation products can then be converted to a range of functional groups, including a direct procedure to access aldehyde products. More recently, it has been shown that α -substituted *N*-acyl pseudoephedrine derivatives can be alkylated with high levels of selectivity, allowing access to enantioenriched α -quaternary carbonyl derivatives.¹²

Scheme 1.4. Alkylation of Pseudoephedrine-Derived Chiral Auxiliary



Chiral auxiliary approaches to asymmetric aldehyde α -alkylation are well-developed and often utilized due to their consistently high selectivity and broad substrate scope. Despite these advantages, one cannot discount the lack of chemical efficiency of these processes due to the requirements for incorporation of stoichiometric amounts of chiral auxiliary, and due to the multiple synthetic steps required for installation and removal of the auxiliary. Direct catalytic, asymmetric processes would address these problems, and they have therefore been the subject of significant chemical research.

1.2.2 Catalytic Asymmetric Aldehyde α -Alkylation

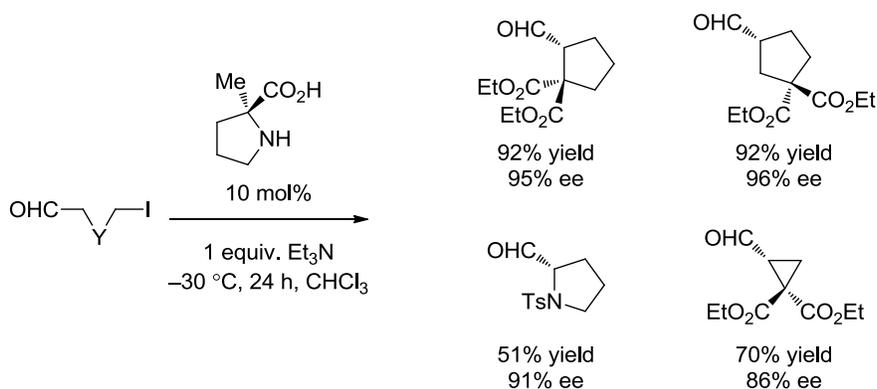
Despite the synthetic utility of catalytic, asymmetric aldehyde α -alkylation, the first example of this type of transformation was not reported until 2004, when List and coworkers reported an

alternative auxiliary to pseudoephedrine: Morales, M. R.; Mellem, K. T.; Myers, A. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 4568.

¹² Kummer, D. A.; Chain, W. J.; Morales, M. R.; Quiroga, O.; Myers, A. G. *J. Am. Chem. Soc.* **2008**, *130*, 13231.

intramolecular aldehyde α -alkylation catalyzed by α -methyl proline.¹³ The transformation proceeds with good yields and enantioselectivities to generate cyclopentane, cyclopropane, and pyrrolidine products, provided that the starting materials are activated for cyclization by the presence of geminal diester groups (Scheme 1.5). The conditions for the intramolecular alkylation were tested for the intermolecular alkylation reactions of cyclohexanone and propionaldehyde with benzyl bromide. These intermolecular alkylations were not successful, however, as catalyst benzylation was observed as the major byproduct.

Scheme 1.5. List's Intramolecular Aldehyde α -Alkylation

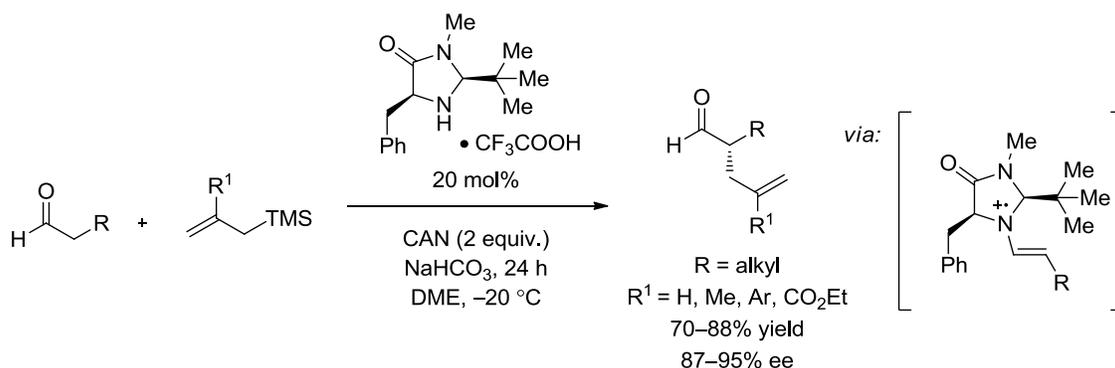


Following the initial report of catalytic asymmetric intramolecular aldehyde α -alkylation by List and coworkers, a number of research groups devoted significant effort to the development of intermolecular variants of the transformation. In fact, some of the newest and most innovative strategies for asymmetric catalysis were applied toward the transformation: MacMillan's organocatalysis using SOMO activation, List's Asymmetric Counterion Directed Catalysis (ACDC), and anion-abstraction catalysis by our group (this work).

¹³ (a) Vignola, N.; List, B. *J. Am. Chem. Soc.* **2004**, *126*, 450. For a mechanistic study of the transformation see: (b) Fu, A.; List, B.; Thiel, W. *J. Org. Chem.* **2006**, *71*, 320.

In 2007, MacMillan and coworkers introduced the concept of SOMO catalysis with its application toward asymmetric aldehyde α -allylation (Scheme 1.6).¹⁴ This unique mode of catalytic activation involves a single electron oxidation of an enamine to generate a radical cation intermediate, which can be trapped by π -rich nucleophiles. In the context of the aldehyde α -allylation, excellent yields and enantioselectivities were observed for the transformation. Since this initial report, this novel activation mode has been applied to a variety of impactful catalytic, asymmetric transformations.¹⁵

Scheme 1.6. MacMillan's SOMO Activation for Aldehyde α -Allylation



A year later, MacMillan and coworkers reported an extension of their SOMO activation strategy to the alkylation of aldehydes by merging photoredox catalysis and organocatalysis.¹⁶ Enamine catalysis is also central in this system, in which a catalyst derived enamine reacts with an electron deficient radical. The radical is generated from the corresponding alkyl halide following reduction by $\text{Ru}(\text{bpy})_3^+$. This strategy provided enantioenriched α -substituted

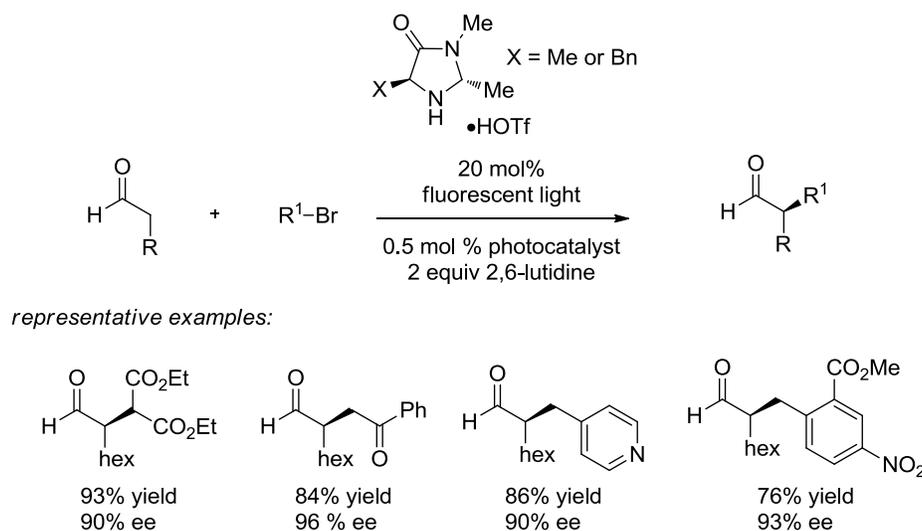
¹⁴ Beeson, T. D.; Mastracchio, A.; Hong, J.-B.; Ashton, K.; MacMillan, D. W. C. *Science* **2007**, *316*, 582.

¹⁵ For example, see: (a) Jang, H.; Hong, J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2007**, *129*, 7004. (b) Kim, H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *130*, 398. (c) Rendler, S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 5027. (d) Jui, N. T.; Garber, J. A. O.; Finelli, F. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2012**, *134*, 11400.

¹⁶ Nicewicz, D. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2008**, *322*, 77.

aldehydes in good yields and excellent enantioselectivities, but it is limited to electron deficient alkyl halides such as α -bromo ketones or bromomalonates. The strategy was expanded further by using *fac*-Ir(ppy)₃ as the photoredox catalyst, which enabled the electrophile scope to be expanded to highly electron deficient benzyl bromides (Scheme 1.7).¹⁷

Scheme 1.7. Aldehyde α -Alkylation via Photoredox Organocatalysis



Shortly following MacMillan's initial report of aldehyde α -allylation by SOMO activation, List and coworkers reported that their recently developed concept of asymmetric counteranion directed catalysis (ACDC)¹⁸ could be applied to the asymmetric α -allylation of aldehydes.¹⁹ Using *N*-benzhydryl allyl amine as the allylating agent, α -branched aldehydes are allylated under palladium and phosphoric acid co-catalysis. A variety of electronically diverse 2-aryl propionaldehydes underwent allylation under these conditions to yield highly enantioenriched α -

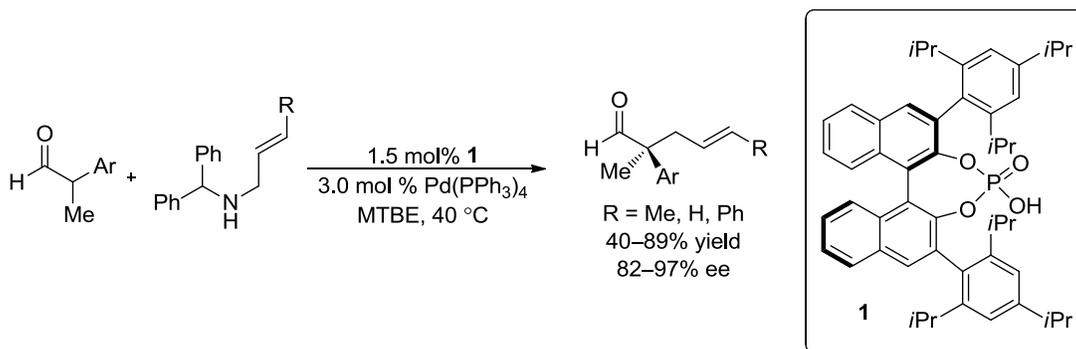
¹⁷ Shih, H.-W.; Vander Wal, M. N.; Grange, R. L.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 13600

¹⁸ Mayer, S.; List, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4193.

¹⁹ (a) Mukherjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 11336. For preliminary results on for this strategy, see the supporting information of: (b) Ibrahem, I.; Córdova, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1952.

quaternary aldehydes (Scheme 1.8). More recent extensions of this transformation have allowed for the use of simple allylic alcohols as the allylating agent.²⁰

Scheme 1.8. Application of List's ACDC Strategy to Aldehyde α -Allylation

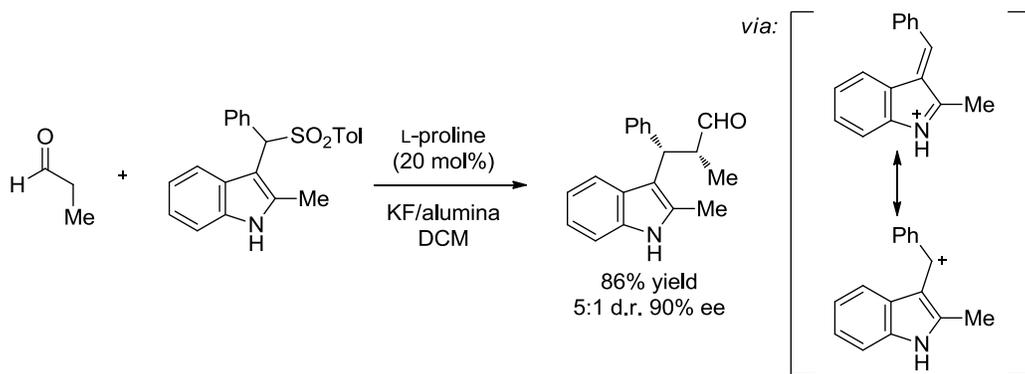


Advances in aldehyde α -alkylation have also been realized by engaging electrophiles with significant cationic character in the transformation. This approach was first reported in 2008 by Melchiorre and coworkers in the context of a proline catalyzed formal α -alkylation employing arylsulfonyl indoles as electrophiles (Scheme 1.9).²¹ In the presence of potassium fluoride supported on basic alumina, 3-(1-arylsulfonylalkyl)indoles provide vinylogous imine intermediates following elimination of the sulfonyl group. The vinylogous imine is then protonated to yield a vinylogous iminium intermediate, which could also be described as a stabilized carbenium ion, depending on the resonance character of the intermediate. For this system, the alkylation proceeds with good yields, moderate diastereoselectivity, and good enantioselectivity.

²⁰ Jiang, G.; List, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 9471.

²¹ Shaikh, R. R.; Mazzanti, A.; Petrini, M.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8707.

Scheme 1.9. Melchiorre's Alkylation of Cationic Electrophiles

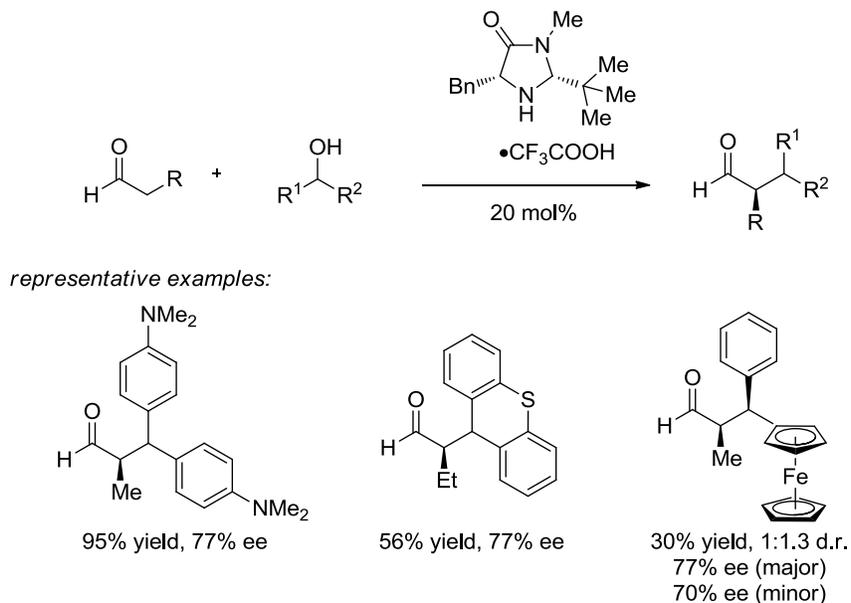


More recently, Cozzi and coworkers were successful in achieving aldehyde α -alkylation with highly stabilized diarylmethine carbocations generated from the corresponding alcohols (Scheme 1.10).²² Yields for the transformation are moderate to good, and the observed enantioselectivities are moderate. It is notable that only very highly stabilized diarylmethine cations participate in the transformation.²³

²² Cozzi, P. G.; Benfatti, F.; Zoli, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 1313.

²³ For an extension of the method where the cationic intermediates are generated by alternate methods see: (a) Benfatti, F.; Capdevila, M. G.; Zoli, L.; Benedetto, E.; Cozzi, P. G. *Chem. Commun.* **2009**, 5919. (b) Benfatti, F.; Benedetto, E.; Cozzi, P. G. *Chem. Asian J.* **2010**, *5*, 2047. (c) Xiao, J. *Org. Lett.* **2012**, *14*, 1716.

Scheme 1.10. Cozzi's Aldehyde α -Alkylation with Highly Stabilized Diarylmethine Cations



Although general catalytic asymmetric methods for aldehyde α -alkylation have yet to be discovered, significant steps toward realizing this transformation have been made. Efforts to develop the transformation have impacted the field of asymmetric catalysis, as many catalysis strategies developed for aldehyde α -alkylation have proven useful for a variety of other synthetic methods.

1.3. Results and Discussion

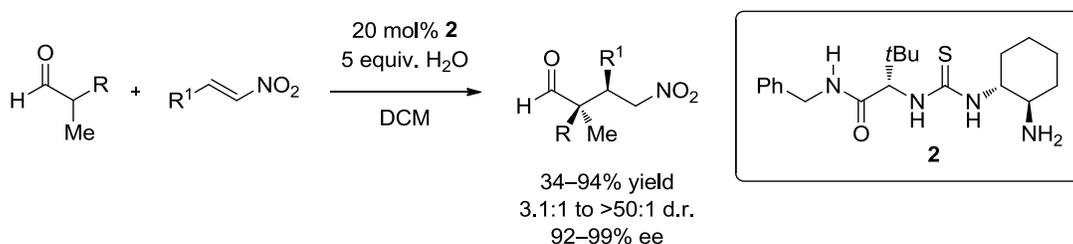
1.3.1. Primary Aminothioureas as Bifunctional Catalysts

Primary aminothioureas are bifunctional catalysts that have the ability to activate nucleophiles via enamine catalysis and electrophiles via H-bonding, and they have been successful in catalyzing highly enantioselective aldehyde α -functionalization reactions (Scheme 1.11).²⁴ We

²⁴ (a) Tsogoeva, S. B.; Wei, S. *Chem. Commun.* **2006**, 1451. (b) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 7170. (c) Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366. For primary aminothiourea catalyzed oxidopyrylium-based [5 + 2] Cycloadditions see: (d) Burns, N. Z.; Witten, M. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 14578. For a primary aminothiourea catalyzed formal aza-Diels-Alder

sought to utilize this catalyst class to achieve asymmetric intermolecular aldehyde α -alkylation. We expected that a bifunctional catalyst capable of synergistic nucleophilic and electrophilic activation would not require an alkylating agent with high intrinsic reactivity. Therefore, some of the challenges associated with catalytic aldehyde α -alkylation, such as catalyst deactivation via alkylation, could be overcome.

Scheme 1.11. Primary Aminothiurea Catalyzed Aldehyde α -Functionalization



1.3.2. Preliminary Experiments

with Wen-Hsin Kuo

We evaluated the alkylation of 2-phenyl propionaldehyde with a variety of electrophiles in the presence of primary aminourea **3** as well as *N*-acyl cyclohexyldiamine **4**. Interestingly, alkylation was observed using both allyl iodide and benzhydryl bromide (Table 1.1).²⁵ The fact that amine **4**, which lacks the dual H-bond donor motif, successfully catalyzed the alkylation with allyl iodide to the same extent as urea **3** indicated that electrophile activation is likely not necessary for this electrophile. The lack of dual activation observed for the allyl substrate, in addition to the fact that asymmetric allylation of this class of aldehyde had been established^{19a} influenced our decision to explore the alkylation reaction with benzhydryl electrophiles.

see: (e) Lalonde, M. P.; McGowan, M. A.; Rajapaksa, N. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2013**, *135*, 1891.
(f) Rajapaksa, N. S.; McGowan, M. A.; Rienzo, M.; Jacobsen, E. N. *Org. Lett.* **2013**, *15*, 706.

²⁵ Experiments in Table 1.1 were carried out and analyzed by Wen-Hsin Kuo.

Table 1.1. Preliminary Aldehyde α -Alkylation Results

entry	catalyst	alkylating agent	yield	ee
1	3	allyl iodide	18	n.d.
2	4	allyl iodide	22	n.d.
3	3	benzhydryl bromide	12	68
4	4	benzhydryl bromide	0	n.a.

Although catalyst **3** was successful in catalyzing the alkylation transformation, a significant amount of α -oxygenation byproduct was also observed under the catalytic conditions. This required the development of a freeze-pump-thaw procedure for the reaction setup.²⁶ Limited oxidation byproducts were observed under this procedure, which enabled further reaction optimization.

1.3.3. Catalyst Optimization

A variety of diverse primary amine containing thiourea and urea catalysts were evaluated for the α -alkylation of 2-phenyl propionaldehyde with benzhydryl bromide. Although more than thirty urea and thiourea catalysts were evaluated for the transformation, the results can be summarized by discussion of a few representative catalysts (Scheme 1.12).

Tertiary amino Takemoto's catalyst **6** doesn't promote the reaction at all, supporting our hypothesis of catalysis via a catalyst-derived enamine (Scheme 1.12, compare catalysts **5** and **6**).

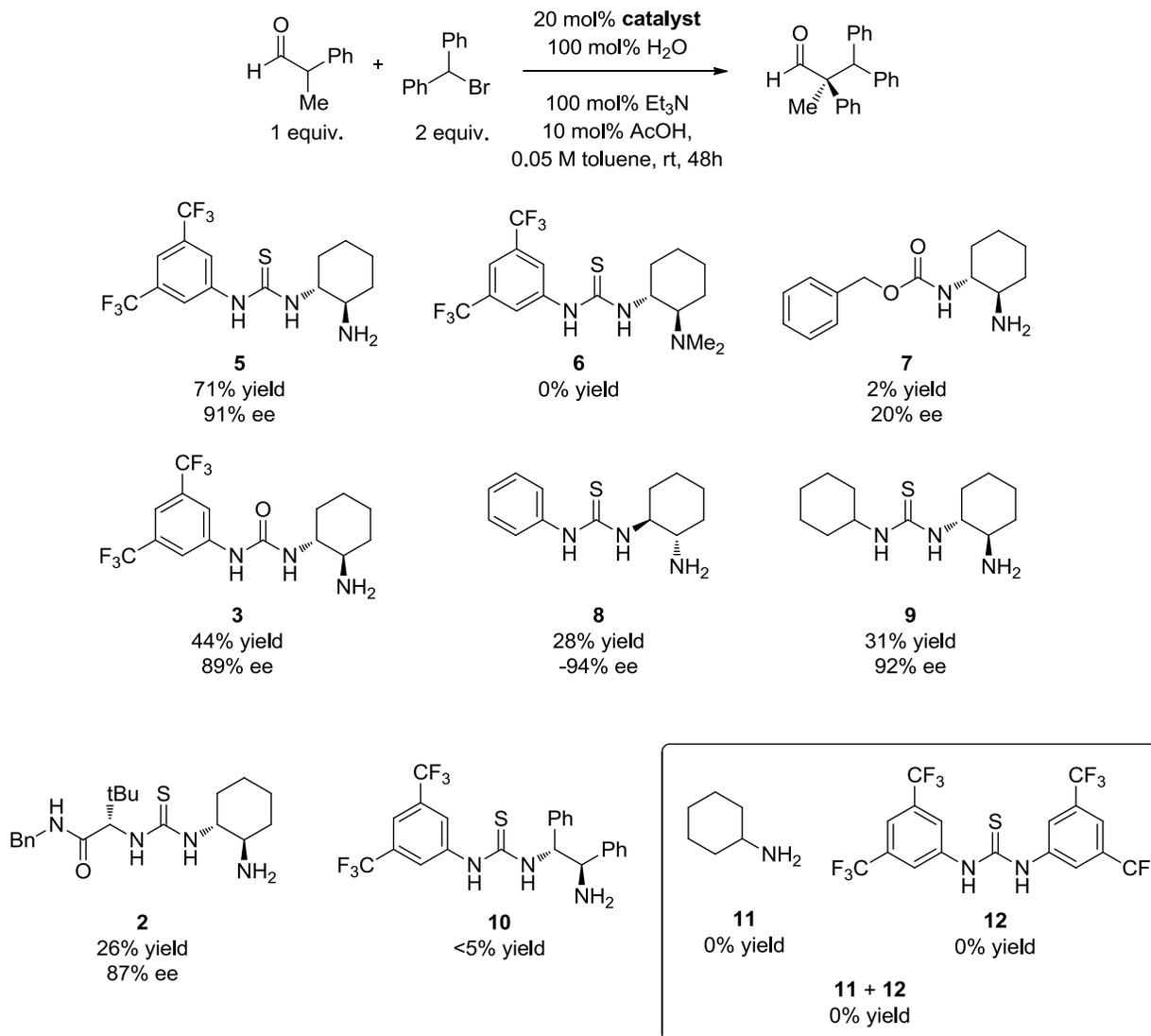
²⁶ See experimental section for further details.

Catalyst **7**, which contains a primary amine and a carbamate capable of donating a single H-bond, only provides a trace amount of the desired product under the reaction conditions, indicating that activation of the electrophile by the dual H-bond donor is necessary. Together these results indicate that *both* a dual H-bond donor and a primary amine are necessary for catalysis of the alkylation reaction. Further, the primary amine activation of the nucleophile and electrophilic activation by the dual H-bond donor are cooperative, as a combination of the two as separate catalysts does not promote the reaction (Scheme 1.12, catalysts **11** + **12**).

As is the case for many dual H-bond donor catalyzed reactions, thioureas typically outperform the analogous urea slightly with respect to both reaction rate and enantioselectivity (Scheme 1.12, compare catalysts **3** and **5**). This indicates that the catalytic activity of the thiourea moiety is likely due to its H-bonding properties, not due to nucleophilic catalysis with the thiocarbonyl. Variation of the diamine portion of the catalyst indicated that cyclohexyldiamine-containing catalysts were uniquely effective in catalyzing the transformation (Scheme 1.12, compare catalysts **5** and **10**).

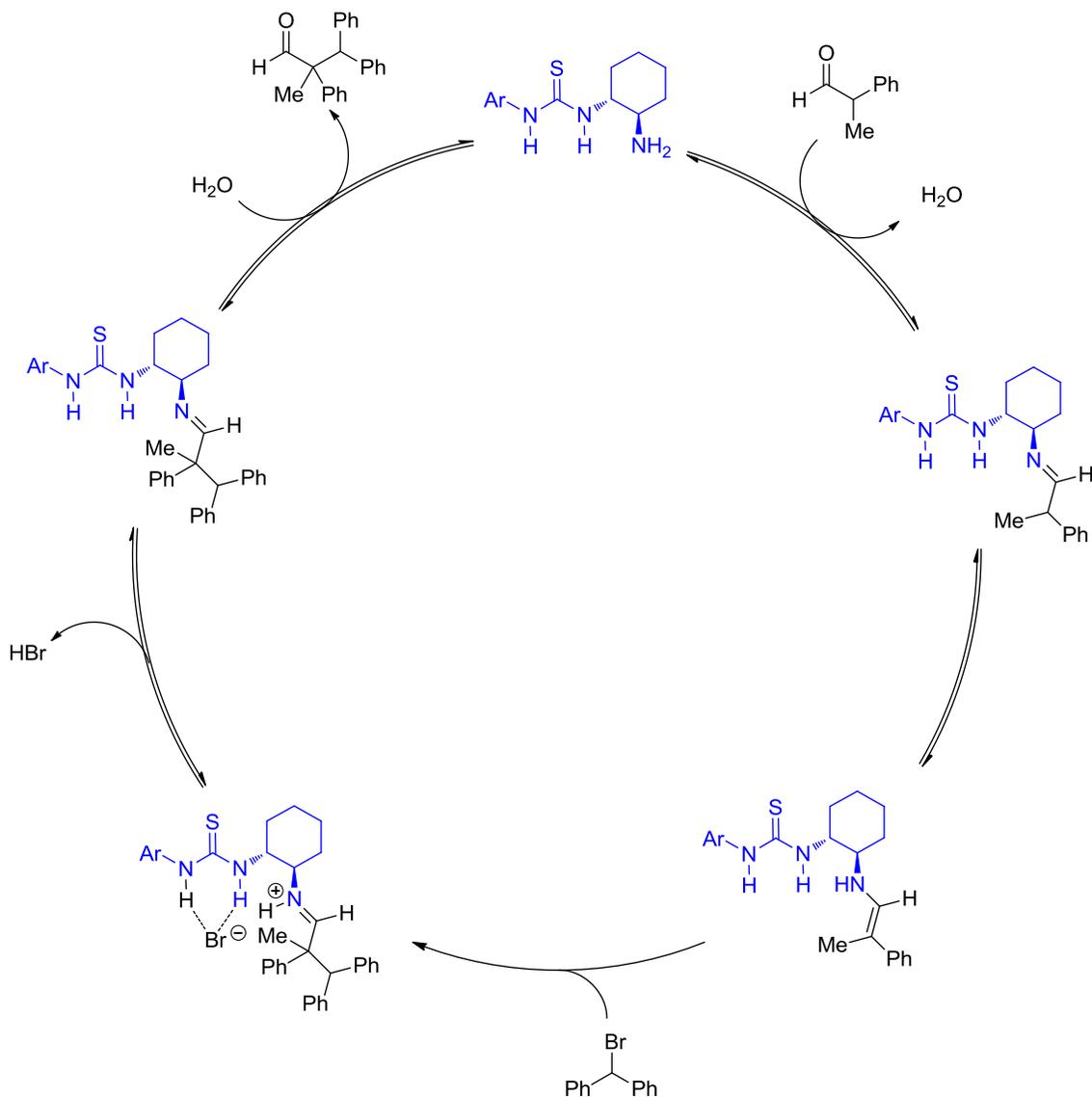
Changes to the left side of the catalyst (as depicted in Scheme 1.12) had minimal impact on the enantioselectivity of the transformation, but significantly affected the reaction rate (Scheme 1.12, compare catalyst **5**, **8**, and **9**). In general, catalysts with more electron rich left hand portions were less effective catalysts with respect to reaction rate. It is notable that simple catalysts such as **5** that only contain one stereochemical element are highly enantioselective catalysts, while catalysts with additional stereochemical elements offer no advantage (Scheme 1.12, compare catalysts **2** and **5**).

Scheme 1.12. Selected Catalyst Optimization Data



Yields determined by ^1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard

Scheme 1.13. Proposed Catalytic Cycle



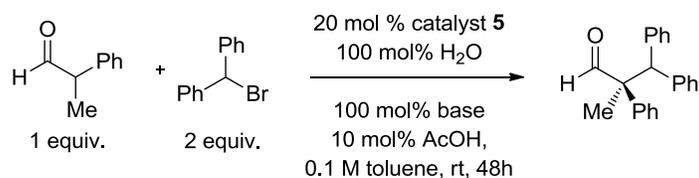
Our catalyst optimization studies pointed toward a mechanism involving nucleophilic activation via a catalyst-derived enamine. A proposed catalytic cycle is presented in Scheme 1.13. Analysis of the catalytic cycle reveals imine formation, imine hydrolysis, and proton transfer steps, along with production of a stoichiometric amount of hydrogen bromide. A basic additive capable of neutralizing the hydrogen bromide seemed necessary to prevent catalyst deactivation by protonation. In addition, it seemed likely that additives capable of shuttling

protons could facilitate some of the imine formation, imine hydrolysis, and proton transfer steps.²⁷ Based on these hypotheses, an empirical evaluation of reaction additives was carried out.

1.3.4. Optimization of Reaction Conditions

Due to the fact that a stoichiometric quantity of hydrogen bromide was being generated over the course of the alkylation reaction, a basic additive was required. A variety of amine bases were examined (Table 1.2), with triethylamine proving optimal. The enantioselectivity of the reaction was relatively insensitive to the identity of the amine base, with the exception of DBU, which may promote alkylation via alternate mechanisms due to its high basicity. The reaction was lower-yielding in the presence of pyridine bases, likely because these additives were less basic than the primary amine catalyst, and some catalyst deactivation by protonation occurred.

Table 1.2. Optimization of Basic Additive



entry	base	yield (%) ^a	ee (%)
1	Et ₃ N	54	90
2	DIPEA	57	85
3	DBU	12	44
4	pyridine	8	88
5	2,6-lutidine	15	89
6	Me ₂ NEt	54	89
7	Et ₂ NH	29	87

^a Yields determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard

²⁷ Water and weak acid have been shown to be beneficial in previously reported primary aminothiourea-catalyzed reactions (See ref. 24b-c)

Solvent optimization was carried out, and it was observed that the enantioselectivity of the alkylation reaction was relatively insensitive to the identity of the solvent (Table 1.3). The alkylation proceeded with good enantioselectivity in a variety of solvents, with the only exception being acetonitrile.

Table 1.3. Solvent Optimization

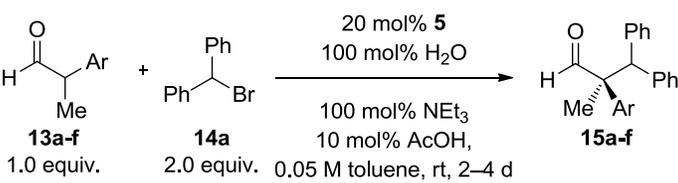
	<table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th style="border-top: 1px solid black; border-bottom: 1px solid black;">entry</th> <th style="border-top: 1px solid black; border-bottom: 1px solid black;">solvent</th> <th style="border-top: 1px solid black; border-bottom: 1px solid black;">ee (%)</th> </tr> </thead> <tbody> <tr><td>1</td><td>toluene</td><td>90</td></tr> <tr><td>2</td><td>TBME</td><td>88</td></tr> <tr><td>3</td><td>Et₂O</td><td>88</td></tr> <tr><td>4</td><td>hexanes</td><td>79</td></tr> <tr><td>5</td><td>THF</td><td>87</td></tr> <tr><td>6</td><td>DCM</td><td>83</td></tr> <tr><td>7</td><td>trifluorotoluene</td><td>83</td></tr> <tr><td style="border-bottom: 1px solid black;">8</td><td style="border-bottom: 1px solid black;">acetonitrile</td><td style="border-bottom: 1px solid black;">44</td></tr> </tbody> </table>	entry	solvent	ee (%)	1	toluene	90	2	TBME	88	3	Et ₂ O	88	4	hexanes	79	5	THF	87	6	DCM	83	7	trifluorotoluene	83	8	acetonitrile	44
entry	solvent	ee (%)																										
1	toluene	90																										
2	TBME	88																										
3	Et ₂ O	88																										
4	hexanes	79																										
5	THF	87																										
6	DCM	83																										
7	trifluorotoluene	83																										
8	acetonitrile	44																										

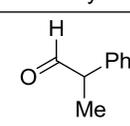
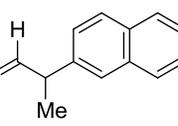
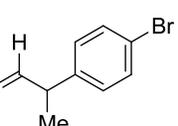
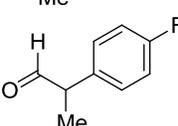
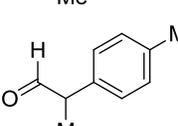
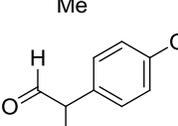
As noted previously, the catalytic cycle for primary amine catalyzed transformations requires imine formation, imine hydrolysis, and proton transfer steps. In our previous work on primary aminothiurea catalyzed transformations we had observed beneficial effects on reaction rate when water or weak acids were added to the reaction mixture.^{24b-c} For the aldehyde alkylation reaction, the identity and amount of the carboxylic acid present affected the rate of the reaction, and had little to no effect on the enantioselectivity of the transformation. The amount of water present in the reaction mixture also did not affect the enantioselectivity of the reaction, and the optimal amount was determined empirically. These results are consistent with the hypothesis that the water and acetic acid additives are not involved in the enantioselectivity-determining alkylation step, and they instead influence the imine formation, imine hydrolysis and proton transfer steps.

1.3.5. Aldehyde Scope and Limitations

The α -alkylation of a variety of α -branched aldehydes was investigated under the optimized reaction conditions. Electronically varied 2-aryl proprionaldehydes reacted with benzhydryl bromide in moderate to good yields and good to excellent enantioselectivity (Table 1.4).

Table 1.4. Reaction Scope With Respect to Aldehyde



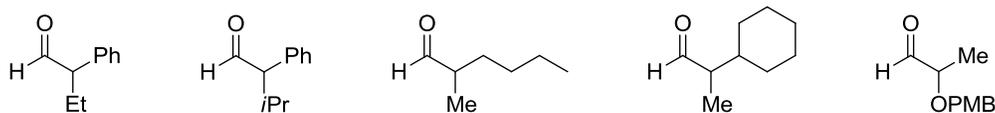
entry	aldehyde	yield (%) ^a	ee (%)
1		70	91
2		68	92
3		56	94
4		57	92
5		59	85
6		52	85

^a Yield of isolated alcohol following reduction with NaBH₄

The scope of the alkylation was strictly limited to 2-aryl proprionaldehydes. Any variation from aldehydes bearing α -methyl and α -aryl groups was not tolerated, as no alkylation product

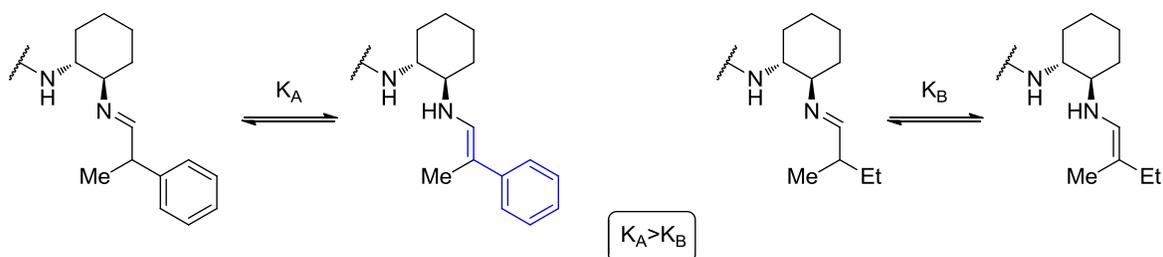
was observed for these substrates. Aldehydes that failed to yield any alkylation product under the optimized conditions are shown below (Scheme 1.14).

Scheme 1.14. Unsuccessful Aldehydes for Alkylation



We hypothesize that the strict requirement for α -aryl aldehydes is due to the imine-enamine equilibrium of the aldehyde-catalyst derivative. Conjugation between the enamine tautomer and the α -aryl group is likely stabilizing, which increases the amount of enamine tautomer present (Scheme 1.15). Such an interaction is not possible with aldehydes lacking α -aryl groups.

Scheme 1.15. Hypothesis for Requirement of Aldehyde α -Aryl Substituent



1.3.6. Electrophile Scope and Limitations

The electrophile scope of the aldehyde α -alkylation reaction was studied. First, we examined the effect of the electrophile leaving group (Table 1.5). In alkylation reactions that employed electrophiles bearing acetate or trifluoroacetate leaving groups, no alkylation products were observed. Benzhydryl chloride provided very modest quantities of highly enantioenriched alkylation product, and benzhydryl bromide proved to be optimal, giving good yields and high enantioselectivities for the alkylation. The similar enantioselectivities that are observed for the

bromide and chloride electrophile are striking, and are atypical for reactions that proceed via an anion binding mechanism.²⁸

Table 1.5. Leaving Group Optimization

entry	x	yield (%) ^a	ee
1	OAc	0	–
2	OCOCF ₃	0	–
3	Cl	7	91
4	Br	71	92

^a Yields determined by ¹H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard

A variety of electronically varied benzhydryl bromides were examined under the optimal alkylation conditions (Table 1.6). While moderate variation of the electronic properties of the benzhydryl electrophiles was tolerated, benzhydryl electrophiles with strongly electron donating groups provided racemic products, while benzhydryl electrophiles with strongly electron withdrawing groups failed to react.

²⁸ See Chapter 2 of this thesis for discussion of the anion binding mechanism and its implications in the aldehyde α -alkylation.

Table 1.6. Reaction Scope With Respect to Electrophile

entry	R	yield (%) ^a	ee (%)
1		44	<5
2		60	90
3		61	91
4		61	91
5		0	n.d.

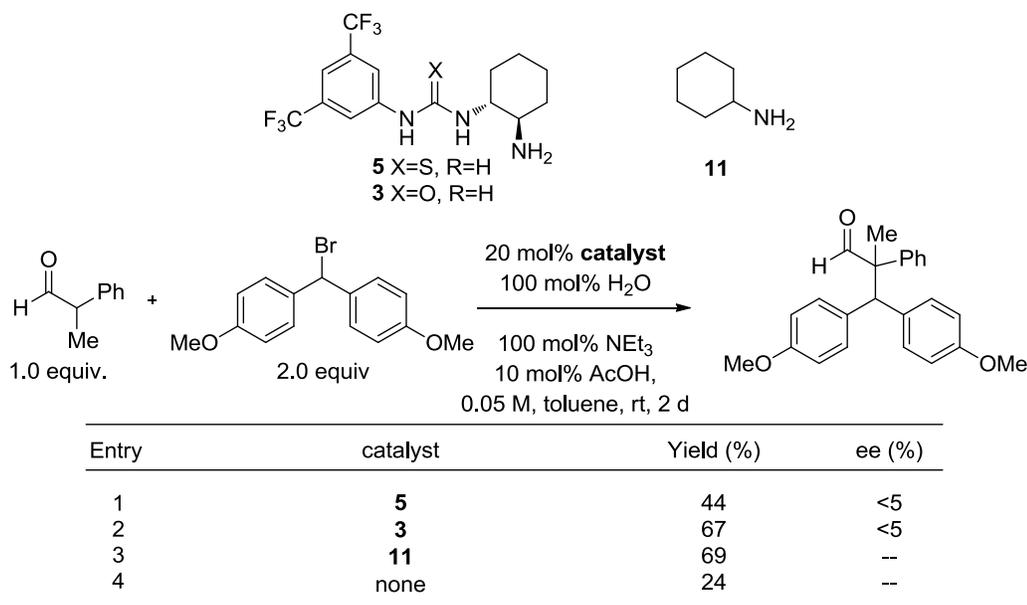
^a Yield of isolated alcohol following reduction with NaBH₄ (entries 1 and 4).
Yield of isolated aldehyde (entries 2–3).

Alkylation using 4,4'-(bromomethylene)bis(methoxybenzene), which gives rise to a highly stabilized carbocation, proceeded with very low enantioselectivity using optimal catalyst **5** (Table 1.6, entry 1). We hypothesized that activation by the thiourea was not necessary for this electrophile, and alkylation was therefore proceeding via an unselective pathway. This hypothesis was confirmed (Table 1.7, entries 2–3), as primary amine catalyst **11** lacking the dual hydrogen bond donor functionality provided similar yields to primary aminourea catalyst **3**.²⁹ Interestingly, a primary amine catalyst was not necessary to observe product formation (Table

²⁹ The yields using thiourea catalyst **4** are reduced because of catalyst decomposition pathways via alkylation of the thiocarbonyl.

1.7, entry 4), suggesting that an enol alkylation pathway may be also be operative for this electrophile.

Table 1.7. Explanation for Racemic Reaction with Electrophiles Bearing Highly Electron Donating Groups



1.4. Conclusions

Our goal at the outset of this project was to develop a highly enantioselective aldehyde alkylation reaction through the use of bifunctional primary aminothiourea catalysts. We discovered that primary aminothioureas were capable of promoting the desired alkylation reaction with high levels of enantioselectivity, but the scope of the reaction was somewhat limited with respect to both the aldehyde component and the alkylating agent. Further studies were carried out in order to gain a better understanding of the electrophile activation mode at work in the aminothiourea catalyzed aldehyde α -alkylation reaction. These studies are presented in Chapter 2 of this thesis.

1.5. Experimental Procedures

1.5.1. General Information

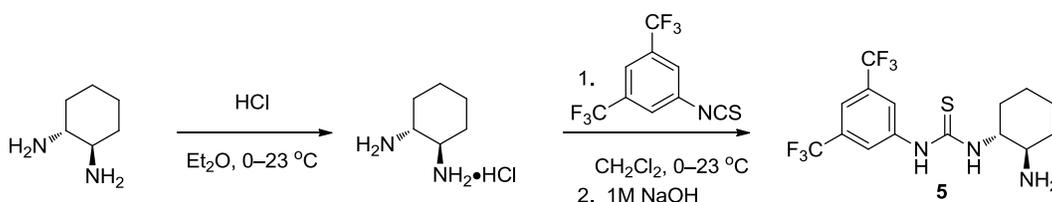
General Procedure. Unless otherwise noted, all reactions were performed in flame-dried round-bottom flasks sealed with a rubber septum under a nitrogen atmosphere. Air and moisture sensitive liquids were transferred using stainless steel cannulae or syringes. Flash chromatography was performed using silica gel ZEOprep60 ECO 40-63 micron from America International Chemical, Inc.

Materials. Commercial reagents were purchased from VWR, Acros, and Sigma-Aldrich and used as received with the following exceptions: 2-phenyl propionaldehyde was purified by distillation before use. Bromodiphenylmethane was purified by recrystallization from hexanes before use. Toluene, dichloromethane, and *t*-butyl methyl ether were dried by passing through columns of activated alumina. Acetonitrile was dried by passing through a column of activated molecular sieves. Triethylamine was distilled from CaH₂ at 760 torr.

Instrumentation. Proton nuclear magnetic resonance (¹H NMR) spectra and carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded on a Varian Inova-500 (500 MHz) NMR spectrometer. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to the NMR solvent residual peak (CHCl₃: δ7.27). Chemical shifts for carbons are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the NMR solvent (CDCl₃: δ77.0). Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet), and coupling constants in Hertz (Hz). The mass spectroscopic data were obtained at the Harvard University mass spectrometry facility.

Infrared (IR) spectra were obtained using a Bruker Tensor 27 FTIR spectrophotometer. Data are represented as follows: frequency of absorption (cm^{-1}), intensity of absorption (s = strong, m = medium, w = weak). Optical rotation data were obtained using a 1 mL cell with a 0.5 dm path length on a Jasco P-2000 polarimeter. Chiral HPLC analysis was performed using a Shimadzu VP series instrument.

1.5.2. Catalyst Preparation and Characterization Data



Preparation of catalyst **5**. A flame dried 100 mL round-bottom flask was charged with (*R,R*)-1,2-*trans*-diaminocyclohexane³⁰ (1.01 g, 9.6 mmol) and diethyl ether (30 mL) under nitrogen. The mixture was cooled to 0 °C, and 1M HCl in diethyl ether (9.6 mL) was added dropwise. The reaction was stirred for 1h while warming to room temperature. The white solid precipitate was filtered and washed with diethyl ether to give the mono-HCl diamine salt (1.38g, 9.18 mmol), which was dissolved in CH₂Cl₂ (30 mL) and cooled to 0 °C. 3,5-bis-trifluoromethyl isothiocyanate (990 mg, 3.65 mmol) was dissolved in CH₂Cl₂ (6 mL), and added to the mono-HCl diamine salt over 1 h. The reaction was stirred overnight while warming to room temperature. 1M NaOH (20 mL) was then added to the reaction mixture, and the mixture was extracted with CH₂Cl₂ (3x 25 mL). The combined organic phases were dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash

³⁰ Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem.* **1994**, *59*, 1939–1942.

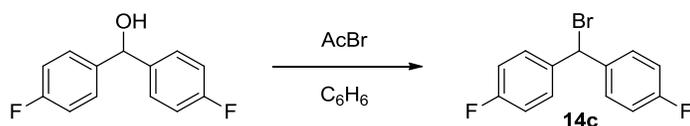
chromatography, eluting with 10% MeOH in CH₂Cl₂ to give **5** as a white solid (954 mg, 68% yield). The spectral data obtained were in accordance with those described in the literature.³¹

Catalysts **2-3** and **6-7** were prepared using previously reported methods.³² Catalysts **8-10** were prepared in an analogous fashion to catalyst **5**.

1.5.3. Substrate Preparation and Characterization Data

Preparation of Aldehydes: 2-Phenyl-propionaldehyde was purchased from Sigma-Aldrich, and was purified by distillation before use. All other aldehydes are known compounds, and were prepared using previously reported methods.³³

Preparation of Benzhydryl Electrophiles: Bromodiphenylmethane was purchased from Sigma-Aldrich, and recrystallized from hexanes before use.



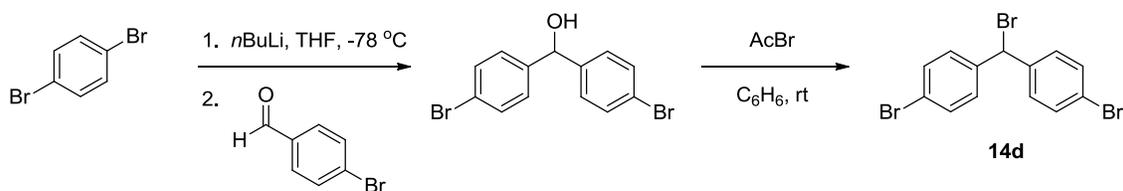
4,4'-difluorobenzhydryl bromide (14c). A flame-dried 25 mL round-bottom flask was charged with 4,4'-difluorobenzhydrol (1.026g, 4.6 mmol) and benzene (9 mL) under nitrogen. Acetyl bromide (1.0 mL, 13.4 mmol) was added, and the reaction was stirred at room temperature for 6 h. The reaction mixture was concentrated to give 4,4'-difluorobenzhydryl bromide as a clear oil

³¹ Procuranti, B.; Connon, S. J. *Chem. Comm.* **2007**, 1421.

³² For catalyst **2** see Lalonde, M. P.; Chen, Y.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6366. For catalyst **3** see Tan, K.; Jacobsen, E. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 1315. For catalyst **6** see Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 12672. For catalyst **7** see Wu, C.; Kobayashi, H.; Sun, B.; Yoo, T. M.; Paik, C. H.; Gansow, O. A.; Carrasquillo, J. A.; Pastan, I.; Brechbiel, M. W. *Bioorg. and Med. Chem.* **1997**, *5*, 1925.

³³ Hoffman, S.; Nicoletti, M.; List, B. *J. Am. Chem. Soc.* **2006**, *128*, 13074.

(1.02g, 78% yield). The spectral data obtained were in accordance with those described in the literature.³⁴



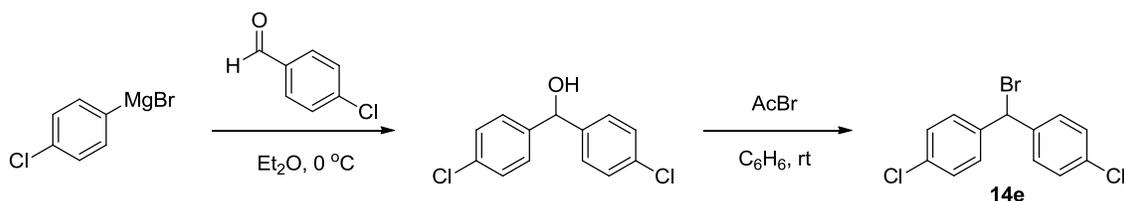
4,4'-dibromobenzhydryl bromide (14d). A flame-dried 100 mL round-bottom flask was charged with 1,4-dibromobenzene (2.35g, 10 mmol) and THF (25 mL) under nitrogen. The reaction was cooled to -78 °C, and *n*BuLi (2.5 M in hexanes, 4 mL, 10 mmol) was added dropwise and the reaction was stirred for 20 minutes. *p*-bromobenzaldehyde (1.85g, 10 mmol), as a solution in THF (25 mL) was added. The reaction was stirred for 20 minutes, after which H₂O (~50 mL) was added. The mixture was extracted with CH₂Cl₂ (3x 25 mL), the combined organic phases were dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography to give 4,4'-dibromobenzhydryl alcohol as a white solid (2.71g, 79% yield). The spectral data obtained were in accordance with those described in the literature.³⁵

A flame-dried 25 mL round-bottom flask was charged with 4,4'-dibromobenzhydryl alcohol (1.03g, 3 mmol) and benzene (9 mL) under nitrogen. Acetyl bromide (1.0 mL, 13.4 mmol) was added, and the reaction was stirred at room temperature for 6 h. The reaction mixture was concentrated to give an orange solid, which was recrystallized from hexanes to give 4,4'-dibromobenzhydryl bromide as a white solid (820mg, 68% yield). ¹H NMR (500MHz, CDCl₃) δ = 7.49 (d, *J* = 8.7

³⁴ Ohkawa, S.; Masaki, S.; Terashita, Z. Tricyclic compounds, their production and use. U.S. Patent 6,248,766, June 19, 2001.

³⁵ Tour, J. M.; Rawlett, A. M.; Kozaki, M.; Yao, Y.; Jagessar, R. C.; Dirk, S. M.; Price, D. W.; Reed, M. A.; Zhou, C.; Chen, J.; Wang, W.; Campbell, I. *Chemistry: A European Journal* **2001**, 7, 5118.

Hz, 16 H), 7.31 (d, $J = 8.7$ Hz, 10 H), 6.18 (s, 5 H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125MHz, CDCl_3) $\delta = 139.6$, 131.8, 130.0, 122.4, 53.2; FTIR (neat, cm^{-1}): 1484 (m), 1398 (m), 1070 (m), 1008 (m), 852 (w), 810 (m), 786 (s).



4,4'-dichlorobenzhydryl bromide (14e). A flame-dried 250 mL round-bottom flask was charged with *p*-chlorobenzaldehyde (1.41g, 10 mmol) and diethyl ether (50 mL) under nitrogen. The mixture was cooled to $0\text{ }^\circ\text{C}$, and *p*-chlorophenyl magnesium bromide (1 M in diethyl ether, 12 mL, 12 mmol) was added dropwise. The reaction was stirred at $0\text{ }^\circ\text{C}$ for 1 h. H_2O (~50 mL) was added, and the mixture was extracted with CH_2Cl_2 (3x 25 mL). The combined organic phases were dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography to give 4,4'-dichlorobenzhydryl alcohol as a white solid (2.32g, 92% yield). The spectral data were in accordance with those described in the literature.³⁶

A flame-dried 25 mL round-bottom flask was charged with 4,4'-dichlorobenzhydryl alcohol (759mg, 3 mmol) and benzene (9 mL) under nitrogen. Acetyl bromide (1.0 mL, 13.4 mmol) was added, and the reaction was stirred at room temperature for 6 h. The reaction mixture was concentrated to give an orange solid, which was recrystallized from hexanes to give 4,4'-dichlorobenzhydryl bromide as a white solid (422mg, 45% yield). The spectral data obtained were in accordance with those described in the literature.³⁷

³⁶ Kharul, R. K.; Goswami, A.; Gite, A.; Godha, A. K.; Jain, M.; Patel, P. R. *Synth. Comm.* **2008**, *38*, 1703.

³⁷ Baker, R. K.; Hale, J. J.; Miao, S.; Rupprecht, K. M. Heterocycle-substituted 3-alkyl azetidines derivatives. U.S. Patent Application 20070123505, May 31, 2007.

1.5.4. General Procedure for the Asymmetric Alkylation Reaction.

Preparation of Reaction Mixture Stock Solution. In a flame dried 10 mL Schlenk flask under nitrogen, benzhydryl bromide (0.750 mmol) was added, and the flask was sealed with a rubber septum. The flask was evacuated and backfilled with nitrogen (x4). Aldehyde (0.375 mmol), AcOH (2.1 μ L, 0.0375 mmol), Et₃N (52 μ L, 0.375 mmol), and toluene (7.5 mL) were added to the flask, and the rubber septum was replaced with a glass stopper under positive nitrogen flow. The mixture was degassed (3 freeze-pump-thaw cycles), and the glass stopper was replaced with a rubber septum.

Addition of Stock Solution to Catalyst. In a flame dried 10 mL Schlenk flask under nitrogen, thiourea catalyst **5** (22.4 mg, 0.058 mmol) was added, and the flask was sealed with a rubber septum. The flask was evacuated and backfilled with nitrogen (x4). In a GC vial, nitrogen was bubbled through deionized H₂O (~1 mL) for 10 minutes. A gas-tight microsyringe was used to transfer H₂O (5.2 μ L, 0.29 mmol) from the GC vial to the Schlenk flask. The reaction mixture stock solution (6 mL, 0.29 mmol aldehyde, 0.58 mmol bromide) was added to the Schlenk flask, with care taken to wash the water from the side of the flask. The rubber septum was replaced with a glass stopper under positive nitrogen flow, the Schlenk flask was sealed, and the reaction was stirred at room temperature.

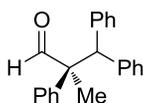
Work-up A: Isolation of aldehyde product. 3 mL of 1N aqueous HCl was added to the reaction mixture, and the mixture was stirred for 15 minutes. The mixture was extracted with CH₂Cl₂ (3x 15 mL), the combined organics were dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography to give the aldehyde product.

Work up B: Reduction and isolation of the alcohol product. 3 mL of 1N aqueous HCl was added to the reaction mixture, and the mixture was stirred for 15 minutes. The mixture was extracted with CH₂Cl₂ (3x 15 mL), the combined organics were dried over sodium sulfate, and concentrated under reduced pressure. To the residue was added MeOH (~10 mL) and CH₂Cl₂ (~5 mL), and the mixture was cooled to 0 °C. NaBH₄ (113 mg, 3.0 mmol) was added, and the reaction was stirred at 0 °C for 15 minutes. The reaction was then allowed to warm to room temperature and stirred for 30 minutes. H₂O (~10 mL) was added, and the mixture was stirred for 30 minutes. The mixture was extracted with CH₂Cl₂ (3x 15 mL), the combined organics were dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography to give the alcohol product.

Preparation of racemic products. Racemic products were prepared following the general procedure described above using racemic thiourea catalyst **5**.

1.5.5. Product Characterization

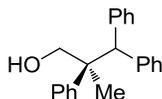
(S)-2-methyl-2,3,3-triphenylpropanal (**15a**):



According to the general procedure, 2-phenyl propionaldehyde (0.29 mmol) was reacted with bromodiphenylmethane (0.58 mmol). After 72h, workup A provided the product aldehyde **15a** (61.1 mg, 70% yield) as a clear oil. $[\alpha]_D^{21} = -51.4^\circ$ (c = 0.147, CH₂Cl₂); ¹H NMR (500MHz, CDCl₃) δ = 9.77 (s, 1 H), 7.35 - 7.02 (m, 15 H), 5.07 (s, 1 H), 1.60 (s, 3 H); ¹³C{¹H}NMR (125 MHz, CDCl₃) δ = 201.9, 140.9, 140.5, 139.0, 130.3, 130.2, 128.6, 128.3, 128.2, 127.8, 127.2, 126.6, 126.3, 57.9, 56.9, 18.4; HRMS [M+Na]⁺ calculated for C₂₂H₂₀O: 323.14064, found:

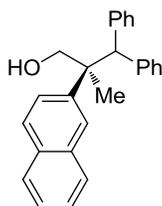
323.13941; FTIR (neat, cm^{-1}): 3082 (w), 3060 (m), 2923 (w), 1722 (s), 1684 (m), 1599 (m), 1495 (s), 1449 (s), 1032 (m), 700 (s).

(S)-2-methyl-2,3,3-triphenylpropan-1-ol (**15a-red**):



The aldehyde was reduced with NaBH_4 and the alcohol was determined to be 91% ee by chiral HPLC analysis (OD-H, 2% IPA in hexanes, 1.0 mL/min, 220 nm, $t_r(\text{major})= 23.7$ min, $t_r(\text{minor})= 21.1$ min); $[\alpha]_D^{22} = -67.6^\circ$ ($c = 0.100$, CH_2Cl_2); $^1\text{H NMR}$ (500MHz, CDCl_3) $\delta = 7.31 - 7.05$ (m, 15 H), 4.55 (s, 1 H), 3.83 (dd, $J = 5.4, 11.0$ Hz, 1 H), 3.60 (dd, $J = 7.8, 11.0$ Hz, 1 H), 1.53 (s, 3 H), 1.28 (dd, $J = 5.4, 7.8$ Hz, 1 H); $^{13}\text{C NMR}$ (126MHz, CDCl_3) $\delta = 143.1, 141.7, 141.5, 130.6, 130.3, 128.1, 128.0, 127.9, 127.6, 126.4, 126.4, 126.0, 70.9, 58.5, 47.1, 20.7$; HRMS $[\text{M}+\text{Na}]^+$ calculated for $\text{C}_{22}\text{H}_{22}\text{O}$: 325.15629, found: 325.15888; FTIR (neat, cm^{-1}): 3283 (m), 3025 (w), 2891 (w), 1598 (w), 1495 (m), 1448 (m), 1046 (s).

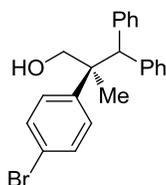
(S)-2-methyl-2-(naphthalen-2-yl)-3,3-diphenylpropan-1-ol (**15b-red**):



According to the general procedure, 2-(naphthalen-2-yl)propanal (0.29 mmol) was reacted with bromodiphenylmethane (0.58 mmol). After 48h, workup B provide the product alcohol **15b-red** (69.0 mg, 68% yield) as a white solid. The material was determined to be 92% ee by chiral HPLC analysis (OD-H, 2% IPA in hexanes, 1.0 mL/min, 230 nm, $t_r(\text{major})= 31.6$ min,

$t_r(\text{minor}) = 39.5 \text{ min}$); $[\alpha]_D^{22} = -76.1^\circ$ ($c = 0.110$, CH_2Cl_2); $^1\text{H NMR}$ (500MHz, CDCl_3) $\delta = 7.87 - 7.81$ (m, 1 H), 7.79 - 7.73 (m, 2 H), 7.62 (d, $J = 1.5 \text{ Hz}$, 1 H), 7.52 - 7.47 (m, 2 H), 7.36 (dd, $J = 2.0, 8.8 \text{ Hz}$, 1 H), 7.30 - 7.21 (m, 5 H), 7.17 - 7.09 (m, 5 H), 4.67 (s, 1 H), 3.93 (d, $J = 10.7 \text{ Hz}$, 1 H), 3.70 (dd, $J = 4.4, 10.7 \text{ Hz}$, 1 H), 1.65 (s, 3 H), 1.37 (br. s., 1 H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125MHz, CDCl_3) $\delta = 141.7, 141.4, 140.6, 133.0, 132.0, 130.6, 130.3, 128.1, 127.9, 127.7, 127.4, 127.3, 127.3, 126.4, 126.2, 126.0, 125.9, 125.8, 70.9, 58.4, 47.3, 21.0$; HRMS $[\text{M}+\text{Na}]^+$ calculated for $\text{C}_{26}\text{H}_{24}\text{O}$: 375.17194, found: 375.16959; FTIR (neat, cm^{-1}): 3558 (s), 3023 (w), 2919 (w), 1493 (m), 1449 (m), 1043 (s).

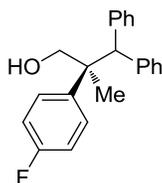
(S)-2-(4-bromophenyl)-2-methyl-3,3-diphenylpropan-1-ol (**15c-red**):



According to the general procedure, 2-(4-bromophenyl)propanal (0.29 mmol) was reacted with bromodiphenylmethane (0.58 mmol). After 96h, workup B provided the product alcohol **15c-red** (61.5 mg, 56% yield) as a clear oil. The material was determined to be 94% ee by chiral HPLC analysis (OD-H, 2% IPA in hexanes, 1.0 mL/min, 230 nm, $t_r(\text{major}) = 20.5 \text{ min}$, $t_r(\text{minor}) = 25.5 \text{ min}$); $[\alpha]_D^{21} = -38.5^\circ$ ($c = 0.253$, CH_2Cl_2); $^1\text{H NMR}$ (500MHz, CDCl_3) $\delta = 7.40$ (d, $J = 8.3 \text{ Hz}$, 2 H), 7.32 - 7.20 (m, 5 H), 7.20 - 7.13 (m, 3 H), 7.10 (d, $J = 6.8 \text{ Hz}$, 2 H), 7.04 (d, $J = 8.3 \text{ Hz}$, 2 H), 4.52 (s, 1 H), 3.77 (d, $J = 11.2 \text{ Hz}$, 1 H), 3.60 (d, $J = 11.2 \text{ Hz}$, 1 H), 1.49 (s, 3 H), 1.39 (br. s., 1 H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126MHz, CDCl_3) $\delta = 142.4, 141.4, 141.1, 130.9, 130.5, 130.2, 130.0, 128.0, 127.8, 126.5, 126.2, 120.5, 70.5, 58.1, 46.9, 20.8$; HRMS $[\text{M}+\text{Na}]^+$ calculated for

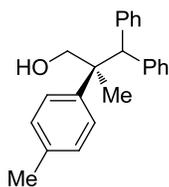
C₂₂H₂₁BrO: 403.06680, found: 403.06677; FTIR (neat, cm⁻¹): 3394 (m), 3026 (w), 2973 (w), 1492 (s), 1449 (m), 1396 (m), 1086 (m), 1031 (s), 1007 (s).

(S)-2-(4-fluorophenyl)-2-methyl-3,3-diphenylpropan-1-ol (**15d-red**):



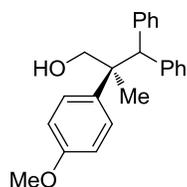
According to the general procedure, 2-(4-fluorophenyl)propanal (0.29 mmol) was reacted with bromodiphenylmethane (0.58 mmol). After 96h, workup B provided the product alcohol **15d-red** (53.2 mg, 57% yield) as a clear oil. The material was determined to be 92% ee by chiral HPLC analysis (OD-H, 2% IPA in hexanes, 1.0 mL/min, 230 nm, $t_r(\text{major})= 22.1$ min, $t_r(\text{minor})= 26.5$ min); $[\alpha]_D^{21} -36.1^\circ$ (c= 0.260, CH₂Cl₂); ¹H NMR (500MHz, CDCl₃) $\delta = 7.32 - 7.21$ (m, 5 H), 7.20 - 7.08 (m, 7 H), 7.02 - 6.94 (m, 2 H), 4.51 (s, 1 H), 3.80 (d, $J = 11.0$ Hz, 1 H), 3.63 (d, $J = 11.2$ Hz, 1 H), 1.52 (s, 3 H), 1.41 (br. s., 1 H); ¹³C{¹H} (125MHz, CDCl₃) $\delta = 162.7, 160.7, 141.7, 139.1, 130.6, 130.1, 130.0, 128.2, 128.0, 126.8, 126.4, 114.9, 71.0, 58.9, 47.0, 21.3$; HRMS [M+Na]⁺ calculated for C₂₂H₂₁FO: 343.14686, found: 343.14706; FTIR (neat, cm⁻¹): 3406 (m), 3027 (w), 2925 (w), 1600 (m), 1510 (s), 1495 (m), 1450 (m), 1232 (s), 1167 (s), 1032 (s).

(S)-2-methyl-3,3-diphenyl-2-(p-tolyl)propan-1-ol (**15e-red**):



According to the general procedure, 2-*p*-tolylpropanal (0.29 mmol) was reacted with bromodiphenylmethane (0.58 mmol). After 48h, workup B provide the product alcohol **15e-red** (53.8 mg, 59% yield) as a clear oil. The material was determined to be 85% ee by chiral HPLC analysis (OD-H, 2% IPA in hexanes, 1.0 mL/min, 235 nm, $t_r(\text{major})=13.4$ min, $t_r(\text{minor})=15.2$ min); $[\alpha]_D^{23} = -53.9^\circ$ (c= 0.136, CH₂Cl₂); ¹H NMR (500MHz , CDCl₃) $\delta = 7.32 - 7.18$ (m, 5 H), 7.17 - 7.02 (m, 9 H), 4.52 (s, 1 H), 3.78 (d, $J = 11.2$ Hz, 1 H), 3.57 (d, $J = 10.3$ Hz, 1 H), 2.34 (s, 3 H), 1.50 (s, 3 H), 1.33 (br. s., 1 H); ¹³C{¹H} NMR (125MHz ,CDCl₃) $\delta = 141.8, 141.6, 139.8, 135.9, 130.6, 130.3, 128.7, 128.1, 127.8, 127.6, 126.3, 125.9, 70.9, 58.4, 46.7, 20.9, 20.8$; HRMS [M+Na]⁺ calculated for C₂₃H₂₄O: 339.17194, found: 323.16937; FTIR (neat, cm⁻¹): 3412 (m), 3026 (w), 2921 (w), 1514 (m), 1494 (m), 1449 (m), 1032 (s).

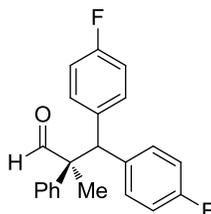
(S)-2-(4-methoxyphenyl)-2-methyl-3,3-diphenylpropan-1-ol (**15f-red**):



According to the general procedure, 2-(4-methoxyphenyl)propanal (0.29 mmol) was reacted with bromodiphenylmethane (0.58 mmol). After 72h, workup B provide the product alcohol **15f-red** (49.0 mg, 52% yield) as a clear oil. The material was determined to be 85% ee by chiral HPLC analysis (ss-welk, 2% IPA in hexanes, 1.0 mL/min, 240 nm, $t_r(\text{major})=18.0$ min, $t_r(\text{minor})=38.2$

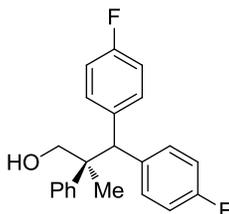
min); $[\alpha]_D^{23} = -38.7^\circ$ (c= 0.066, CH₂Cl₂); ¹H NMR (500MHz , CDCl₃) $\delta = 7.29 - 7.18$ (m, 5 H), 7.17 - 7.03 (m, 7 H), 6.85 - 6.77 (m, 2 H), 4.47 (s, 1 H), 3.81 (s, 3 H), 3.77 (d, $J = 11.2$ Hz, 1 H), 3.58 (d, $J = 11.2$ Hz, 1 H), 1.48 (s, 3 H), 1.37 (br. s., 1 H); ¹³C{¹H} NMR (125MHz , CDCl₃) $\delta = 158.0, 141.8, 141.5, 134.7, 130.5, 130.3, 129.3, 127.9, 127.6, 126.4, 126.0, 113.2, 70.8, 58.7, 55.1, 46.5, 21.2$; HRMS [M+Na]⁺ calculated for C₂₃H₂₄O₂: 355.16685, found: 355.15314; FTIR (neat, cm⁻¹): 3431 (m), 3026 (w), 2933 (w), 1609 (m), 1513 (s), 1450 (m), 1295 (m), 1250 (s), 1187 (m), 1031 (s).

(S)-3,3-bis(4-fluorophenyl)-2-methyl-2-phenylpropanal (16c):



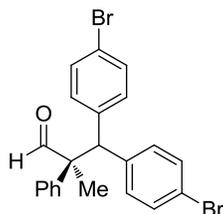
According to the general procedure, 2-phenyl propionaldehyde (0.145 mmol) was reacted with 4,4'-difluorobenzhydryl bromide (0.29 mmol). After 72h, workup A provided the product aldehyde **16c** (29.2 mg, 60% yield) as a clear oil. $[\alpha]_D^{23} = -28.4^\circ$ (c= 0.142, CH₂Cl₂); ¹H NMR (500MHz , CDCl₃) $\delta = 9.65$ (s, 1 H), 7.34 - 7.24 (m, 3 H), 7.15 (dd, $J = 5.4, 8.8$ Hz, 2 H), 7.10 (d, $J = 6.8$ Hz, 2 H), 7.00 - 6.91 (m, 4 H), 6.81 (t, $J = 8.5$ Hz, 2 H), 5.03 (s, 1 H), 1.55 (s, 3 H); ¹³C{¹H} NMR (125MHz , CDCl₃) $\delta = 201.5, 162.4, 160.5, 138.3, 136.6, 136.2, 131.7, 131.6, 128.7, 128.4, 127.6, 115.1, 114.7, 58.1, 55.1, 18.4$; FTIR (neat, cm⁻¹): 3061 (w), 1724 (m), 1603 (m), 1508 (s), 1226 (s), 1160 (m), 831 (m).

(S)-3,3-bis(4-fluorophenyl)-2-methyl-2-phenylpropan-1-ol (16c-red):



The aldehyde was reduced with NaBH₄ and the alcohol was determined to be 90% ee by chiral HPLC analysis (OD-H, 2% IPA in hexanes, 1.0 mL/min, 220 nm, t_r(major)= 28.7 min, t_r(minor)= 23.1 min); [α]_D²³ = -44.7° (c = 0.065, CH₂Cl₂); ¹H NMR (500MHz, CDCl₃) δ = 7.33 - 7.22 (m, 3 H), 7.18 - 7.11 (m, 4 H), 7.02 (dd, J = 5.3, 8.9 Hz, 2 H), 6.95 (t, J = 8.6 Hz, 2 H), 6.83 (t, J = 8.7 Hz, 2 H), 4.58 (s, 1 H), 3.75 (dd, J = 5.5, 11.0 Hz, 1 H), 3.57 (dd, J = 7.6, 11.0 Hz, 1 H), 1.48 (s, 3 H), 1.35 (dd, J = 5.5, 7.6 Hz, 1 H); ¹³C{¹H} NMR (125MHz, CDCl₃) δ = 162.6, 160.6, 142.9, 137.6, 137.4, 132.1, 131.9, 128.3, 128.3, 126.9, 115.0, 114.8, 70.8, 56.5, 47.2, 20.8; HRMS [M+Na]⁺ calculated for C₂₂H₂₀F₂O: 361.13744, found: 361.13863; FTIR (neat, cm⁻¹): 3418 (m), 3060 (w), 2975 (m), 1602 (m), 1507 (s), 1226 (s), 1160 (m), 1039 (m), 831 (s).

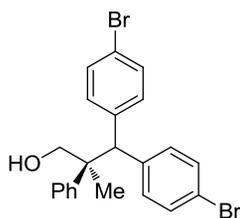
(S)-3,3-bis(4-bromophenyl)-2-methyl-2-phenylpropanal (16d):



According to the general procedure, 2-phenyl propionaldehyde (0.145 mmol) was reacted with 4,4'-dibromobenzhydryl bromide (0.29 mmol). After 72h, workup A provided the product aldehyde **16d** (40.5 mg, 61% yield) as a clear oil. [α]_D²² = -13.8 (c= 0.370, CH₂Cl₂); ¹H NMR (500MHz, CDCl₃) δ = 9.62 (s, 1 H), 7.39 (d, J = 8.3 Hz, 2 H), 7.35 - 7.22 (m, 5 H), 7.12 (dd, J =

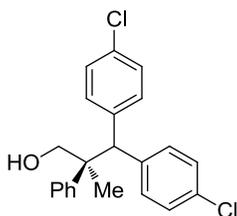
1.2, 8.1 Hz, 2 H), 7.07 (d, $J = 8.3$ Hz, 2 H), 6.89 (d, $J = 8.8$ Hz, 2 H), 5.00 (s, 1 H), 1.57 (s, 3 H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125MHz, CDCl_3) $\delta = 201.4, 139.9, 139.4, 138.2, 132.2, 132.1, 131.6, 131.3, 128.9, 128.8, 128.0, 121.2, 120.8, 58.0, 55.6, 18.6$; FTIR (neat, cm^{-1}): 3057 (w), 2814 (w), 2713 (w), 1722 (m), 1487 (s), 1074 (m), 1009 (s), 814 (m), 700 (m).

(S)-3,3-bis(4-bromophenyl)-2-methyl-2-phenylpropan-1-ol (16d-red):



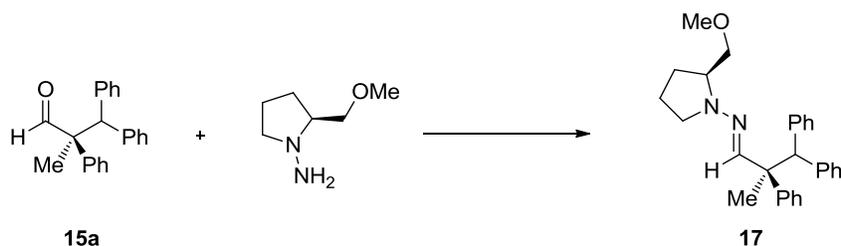
The aldehyde was reduced with NaBH_4 and the alcohol was determined to be 91% ee by chiral HPLC analysis (OD-H, 2% IPA in hexanes, 1.0 mL/min, 240 nm, $t_r(\text{major}) = 34.6$ min, $t_r(\text{minor}) = 26.9$ min); $[\alpha]_D^{20} = -40.7^\circ$ ($c = 0.052$, CH_2Cl_2); ^1H NMR (500MHz, CDCl_3) $\delta = 7.39$ (d, $J = 8.5$ Hz, 2 H), 7.33 - 7.23 (m, 5 H), 7.15 (dd, $J = 1.3, 8.4$ Hz, 2 H), 7.05 (d, $J = 8.5$ Hz, 2 H), 6.92 (d, $J = 8.5$ Hz, 2 H), 4.57 (s, 1 H), 3.71 (dd, $J = 5.6, 11.1$ Hz, 1 H), 3.55 (dd, $J = 7.3, 11.1$ Hz, 1 H), 1.46 (s, 3 H), 1.39 (dd, $J = 5.6, 7.3$ Hz, 1 H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125MHz, CDCl_3) $\delta = 142.4, 140.3, 140.1, 132.2, 131.9, 131.1, 130.9, 128.2, 127.9, 126.8, 120.7, 120.2, 70.4, 56.3, 46.7, 20.5$; FTIR (neat, cm^{-1}): 3417 (m), 3056 (w), 2975 (w), 2882 (w), 1487 (s), 1402 (m), 1074 (m), 1038 (m), 1009 (s), 817 (s), 736 (s), 702 (s).

(S)-3,3-bis(4-chlorophenyl)-2-methyl-2-phenylpropan-1-ol (16e-red):



According to the general procedure, 2-phenyl propionaldehyde (0.145 mmol) was reacted with 4,4'-dichlorobenzhydryl bromide (0.29 mmol). After 72h, workup B provided the product alcohol **16e-red** (33.0 mg, 61% yield) as a clear oil. The material was determined to be 91% ee by chiral HPLC analysis (OD-H, 2% IPA in hexanes, 1.0 mL/min, 240 nm, $t_r(\text{major})= 32.9$ min, $t_r(\text{minor})= 24.4$ min); $[\alpha]_D^{22} = -56.6$ ($c= 0.065$, CH_2Cl_2); ^1H NMR (500MHz , CDCl_3) $\delta = 7.35 - 7.20$ (m, 5 H), 7.17 - 7.13 (m, 2 H), 7.10 (dd, $J = 2.7, 8.5$ Hz, 4 H), 6.98 (d, $J = 8.8$ Hz, 2 H), 4.59 (s, 1 H), 3.71 (dd, $J = 3.9, 11.2$ Hz, 1 H), 3.54 (dd, $J = 5.9, 10.7$ Hz, 1 H), 1.46 (s, 3 H), 1.38 (br. s., 1 H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125MHz , CDCl_3) $\delta = 142.7, 140.1, 139.9, 132.7, 132.3, 132.0, 131.8, 128.4, 128.4, 128.2, 128.1, 127.0, 70.7, 56.5, 47.1, 20.7$; HRMS $[\text{M}+\text{Na}]^+$ calculated for $\text{C}_{22}\text{H}_{20}\text{Cl}_2\text{O}$: 393.07834, found: 393.07825; FTIR (neat, cm^{-1}): 3407 (m), 3056 (w), 2927 (w), 1490 (s), 1406 (w), 1265 (w), 1091 (s), 1028 (m), 1013 (s), 820 (m), 738 (m), 701 (s).

1.5.6. Absolute Structure Determination



A flame-dried 5mL round-bottom flask was charged with aldehyde **15a** (134 mg, 0.45 mmol) and (S)-(-)-1-amino-2-methoxymethylpyrrolidine (60 μ L, 0.45 mmol). After stirring at room temperature for 4 days, the reaction mixture was purified by flash chromatography to give the product as a clear oil (103 mg, 55% yield). By ¹H NMR analysis, the diastereomeric ratio was >20:1. $[\alpha]_D^{21} = -95.5^\circ$ (c = 0.088, CH₂Cl₂); ¹H NMR (500MHz, CDCl₃) $\delta = 7.27 - 7.00$ (m, 16 H), 4.66 (s, 1 H), 3.59 (dd, *J* = 3.2, 9.0 Hz, 1 H), 3.50 - 3.43 (m, 2 H), 3.41 (s, 3 H), 3.35 (m, 1 H), 2.83 (q, *J* = 7.8 Hz, 1 H), 1.98 (s, 4 H), 1.54 (s, 3 H) ¹³C{¹H}NMR (125MHz, CDCl₃) ¹³C NMR (126MHz, CDCl₃) $\delta = 147.3, 142.4, 142.0, 141.9, 139.5, 130.8, 130.6, 127.9, 127.9, 127.7, 126.3, 126.2, 126.1, 75.0, 63.4, 62.5, 59.5, 49.9, 48.9, 26.8, 25.4, 22.2$; LRMS [M+H]⁺ calculated for C₂₈H₃₂N₂O: 413.3, found: 413.2; FTIR (neat, cm⁻¹): 2867 (m), 1596 (m), 1493 (m), 1446 (m), 1342 (w), 1193 (m), 1119 (m), 1032 (w), 973 (w), 901 (w), 760 (m), 746 (m), 697 (s).

The oil was dissolved in diethyl ether, and crystallized by evaporation at room temperature. The structure of the crystal was determined by X-ray crystallography.

X-Ray Structure of 17

Data Collected and refined by Doug Ho

Report generated by Richard Staples

Experimental Section:

A colorless Prism crystal with dimensions 0.40 x 0.30 x 0.175 mm was mounted on a Nylon loop using very small amount of paratone oil.

Data were collected using a Bruker CCD (charge coupled device) based diffractometer equipped with an Oxford Cryostream low-temperature apparatus operating at 173 K. Data were measured using omega and phi scans of 0.5° per frame for 30 s. The total number of images was based on results from the program COSMO³⁸ where redundancy was expected to be 4.0 and completeness of 100% out to 0.83 Å. Cell parameters were retrieved using APEX II software³⁹ and refined using SAINT on all observed reflections. Data reduction was performed using the SAINT software⁴⁰ which corrects for Lp. Scaling and absorption corrections were applied using SADABS⁴¹ multi-scan technique, supplied by George Sheldrick. The structures are solved by the direct method using the SHELXS-97 program and refined by least squares method on F², SHELXL- 97, which are incorporated in SHELXTL-PC V 6.10.⁴²

The structure was solved in the space group P2₁2₁2₁ (# 19). All non-hydrogen atoms are refined anisotropically. Hydrogens were calculated by geometrical methods and refined as a riding model. The Flack⁴³ parameter is used to determine chirality of the crystal studied, the value

³⁸ COSMO V1.58, *Software for the CCD Detector Systems for Determining Data Collection Parameters*. Bruker Analytical X-ray Systems, Madison, WI (2008).

³⁹ APEX2 V2008.5-0 *Software for the CCD Detector System*; Bruker Analytical X-ray Systems, Madison, WI (2008).

⁴⁰ SAINT V 7.34 *Software for the Integration of CCD Detector System* Bruker Analytical X-ray Systems, Madison, WI (2008).

⁴¹ SADABS V2.008/2 Program for absorption corrections using Bruker-AXS CCD based on the method of Robert Blessing; Blessing, R.H. *Acta Cryst.* A51, 1995, 33-38.

⁴² Sheldrick, G.M. "A short history of SHELX". *Acta Cryst.* A64, 2008, 112-122.

⁴³ Flack, H. D. *Acta Cryst.* A39, 1983, 876-881.

should be near zero, a value of one is the other enantiomer and a value of 0.5 is racemic. The Flack parameter was refined to 0.4(14), confirming that we are unable with the x-ray data to confirm the stereochemistry, although the relative stereo chemistry is known. The crystal used for the diffraction study showed no decomposition during data collection. All drawings are done at 50% ellipsoids.

Acknowledgement. The CCD based x-ray diffractometer at Michigan State University were upgraded and/or replaced by departmental funds.

^a Obtained with graphite monochromated Mo K α ($\lambda = 0.71073 \text{ \AA}$) radiation.

^b $R_1 = \sum || F_o | - | F_c | | / \sum | F_o |$. ^c $wR_2 = \{ \sum [w(F_o^2 - F_c^2)^2] / \{ \sum [w(F_o^2)^2] \} \}^{1/2}$.

The following are 50% thermal ellipsoidal drawings of the molecule in the asymmetric cell with various amount of labeling.

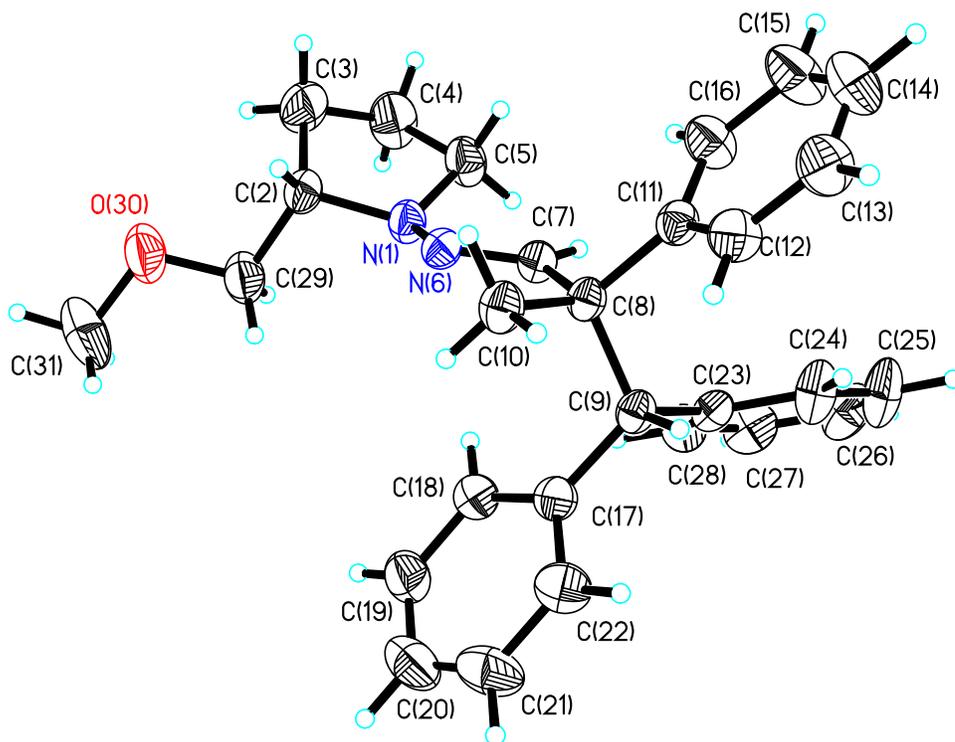


Figure 1.1. X-Ray structure of **17**

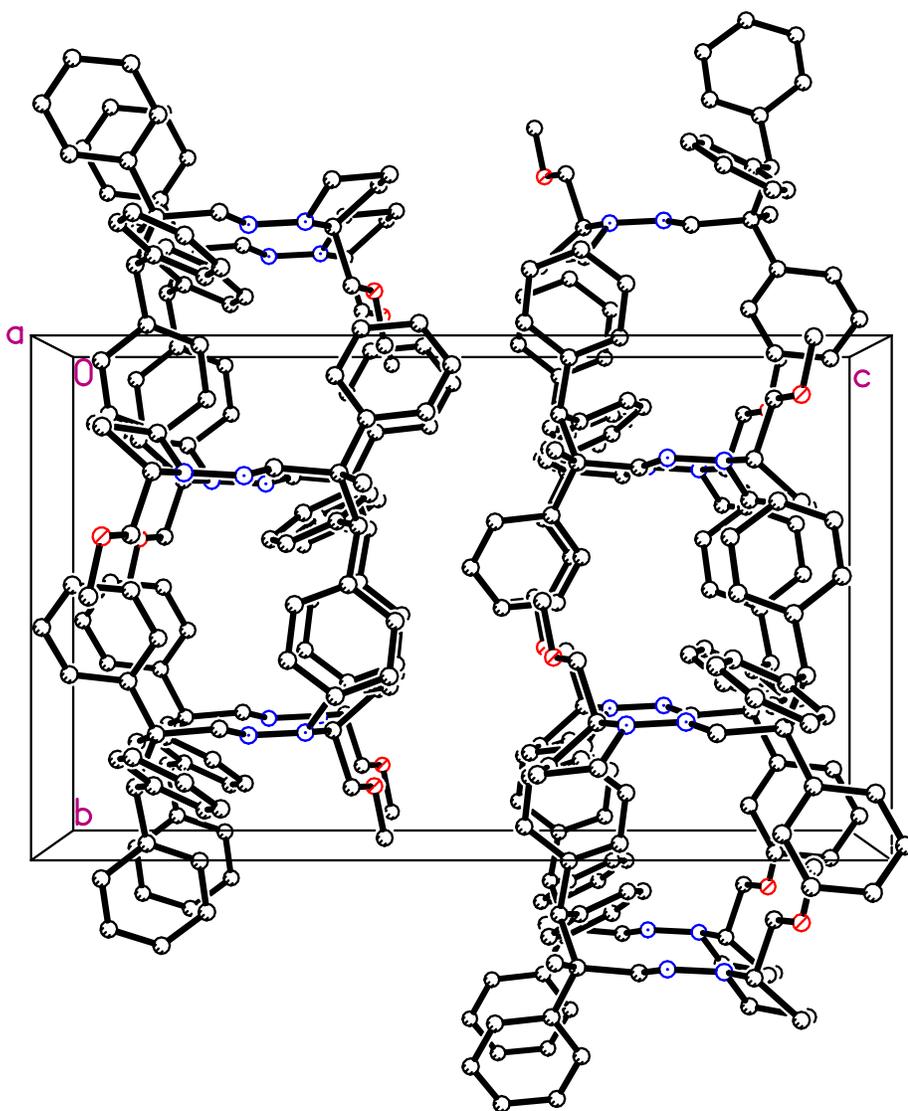


Figure 1.2. Packing of **17** along the a-axis

Crystal data and structure refinement for enj093.

Identification code	enj093
Empirical formula	C ₂₈ H ₃₂ N ₂ O
Formula weight	412.56
Temperature	193(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	P 21 21 21
Unit cell dimensions	a = 9.7107(4) Å α = 90°. b = 12.3459(5) Å β = 90°. c = 20.2414(8) Å γ = 90°.
Volume	2426.69(17) Å ³
Z	4
Density (calculated)	1.129 Mg/m ³
Absorption coefficient	0.068 mm ⁻¹
F(000)	888
Crystal size	0.40 x 0.30 x 0.17 mm ³
Theta range for data collection	1.93 to 27.50°.
Index ranges	-12 ≤ h ≤ 12, -16 ≤ k ≤ 16, -26 ≤ l ≤ 26
Reflections collected	31743
Independent reflections	5580 [R(int) = 0.0195]
Completeness to theta = 25.00°	100.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9892 and 0.9682
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	5580 / 0 / 281
Goodness-of-fit on F ²	1.056
Final R indices [I > 2σ(I)]	R1 = 0.0393, wR2 = 0.1023
R indices (all data)	R1 = 0.0426, wR2 = 0.1054
Absolute structure parameter	0.4(14)
Largest diff. peak and hole	0.358 and -0.151 e.Å ⁻³

Chapter 2

Thiourea Promoted Anion Abstraction

Enables Aldehyde α -Alkylation via an S_N1

Pathway¹

2.1. Introduction

Trivalent carbocations, or carbenium ions, are highly reactive electrophilic intermediates that undergo chemical transformations with a diverse set of nucleophilic partners. Although these intermediates have been thoroughly studied and their reactivity is well understood,² very few examples of their participation in catalytic asymmetric reactions are known. The scarcity of catalytic asymmetric methods that proceed via carbenium intermediates can be attributed to the

¹ Portions of this chapter have been published: Brown, A. R.; Kuo, W.-H.; Jacobsen, E. N. “ *J. Am. Chem. Soc.* **2010**, *132*, 9286.

² (a) Olah, G. A.; Schleyer, P. v. R. (eds.) *Carbonium Ions*, Wiley: New York, 1968. (b) Olah, G. A. *Carbocations and Electrophilic Reactions*, Wiley: New York, 1973.

high reactivity of such intermediates, which makes their use as discriminating electrophiles in asymmetric reactions very challenging. Here, we highlight some examples in which carbenium ions are intermediates in catalytic asymmetric processes. We then present our research towards characterizing the cationic intermediates that are generated via H-bond donor mediated anion abstraction in the context of the catalytic asymmetric aldehyde α -alkylation discussed in Chapter 1 of this thesis.

2.2. Carbenium Ion Intermediates in Selective Asymmetric Catalytic Transformations

Two strategies have emerged to access carbenium intermediates in catalytic asymmetric reactions: (1) activation of an electrophilic functional group for intramolecular reaction with an electron rich olefin or (2) activation of an oxygen-containing leaving group by a Lewis or Bronsted acid. Examples of these strategies are highlighted here.

2.2.1. Metal-Catalyzed Cycloisomerization Reactions via Carbenium Intermediates

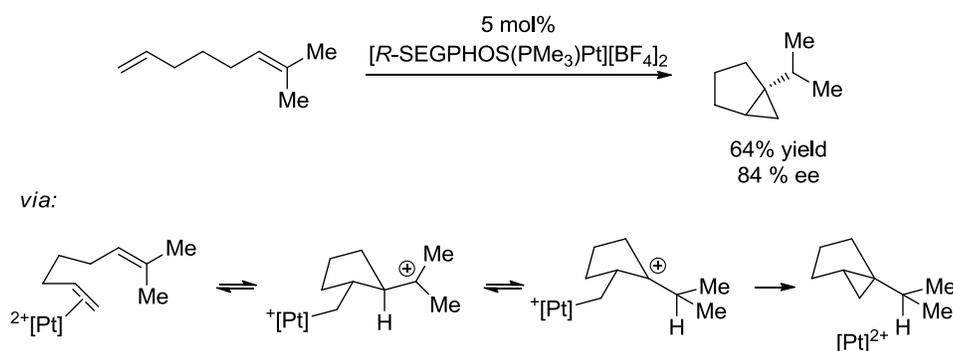
Cationic metal species are capable of activating unsaturated functional groups, such as an olefin or an allene. The activated electrophilic species then reacts in an intramolecular sense with an electron rich olefin, giving rise to a carbenium intermediate, which is capable of undergoing further transformations.

An example of this type of reactivity was reported by Gagné and coworkers in 2006 in the context of a diene cycloisomerization.³ In this platinum-catalyzed transformation, the cationic metal complex activates a terminal olefin for intramolecular reaction with an electron rich olefin, giving rise to a tertiary carbocation intermediate. A hydride shift provides access to another tertiary carbocation intermediate, which undergoes a cyclopropanation reaction to provide the

³ Feducia, J. A.; Campbell, A. N.; Doherty, M. Q.; Gagné, M. R. *J. Am. Chem. Soc.* **2006**, *128*, 13290.

bicyclopropane product (Scheme 2.1). Mechanistic studies have revealed that alkene activation and initial reaction with the electron rich alkene is rapid and reversible on the time scale of product formation, but it isn't clear whether hydride transfer or cyclopropanation is rate-determining.⁴ In either case, the enantiodetermining step involves the reaction of a carbenium intermediate.

Scheme 2.1. Platinum-Catalyzed Diene Cycloisomerization

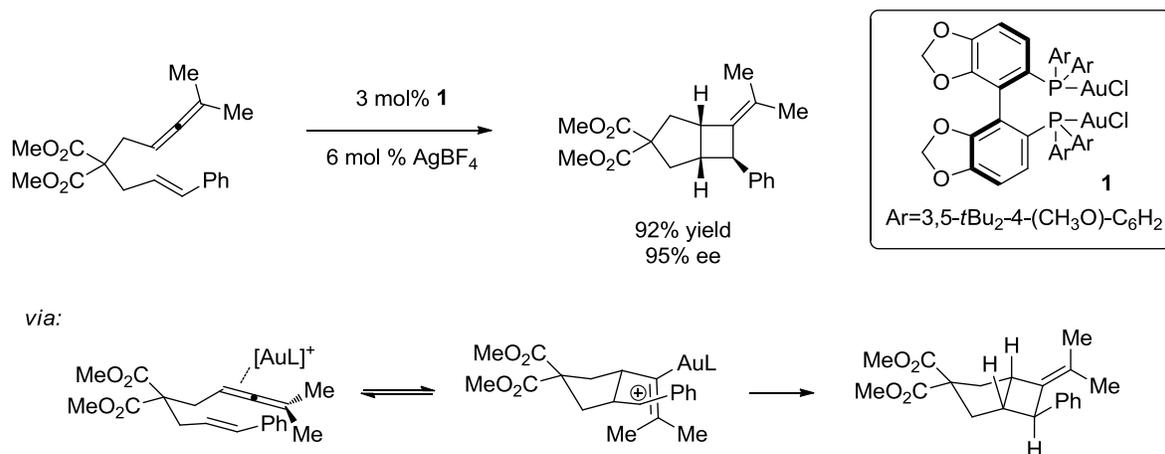


A year later, Toste and coworkers reported a gold(I)-catalyzed formal [2+2]-cycloaddition that proceeds via the intermediacy of a benzylic carbenium intermediate.⁵ In this case, the cationic gold species activates an allene for nucleophilic attack by a pendant styrene, which provides a benzylic cation. This species reacts intramolecularly with a vinyl-gold species to yield highly enantioenriched bicyclo[3.1.0]hexane structures (Scheme 2.2). Mechanistically, this transformation is similar to the platinum-catalyzed reaction discussed previously. The initial cyclization is reversible, and the enantiodetermining step is the reaction of the carbenium intermediate to form the cyclobutane ring.

⁴ Kerber, W. D.; Gagné, M. R. *Org. Lett.* **2005**, 7, 3379.

⁵ Luzung, M. R.; Mauleón, P.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, 129, 12402.

Scheme 2.2. Gold-Catalyzed Formal [2+2]-Cycloaddition



2.2.2. Leaving Group Activation to Access Carbenium Intermediates

An alternative and likely more general approach to access carbenium ions is the activation of a leaving group for ionization. Recently, some promising examples of this activation strategy have emerged through the use of chiral catalysts. After the ionization event, the catalysts are associated with the resultant cationic intermediate, and can influence the addition of nucleophiles to these intermediates.

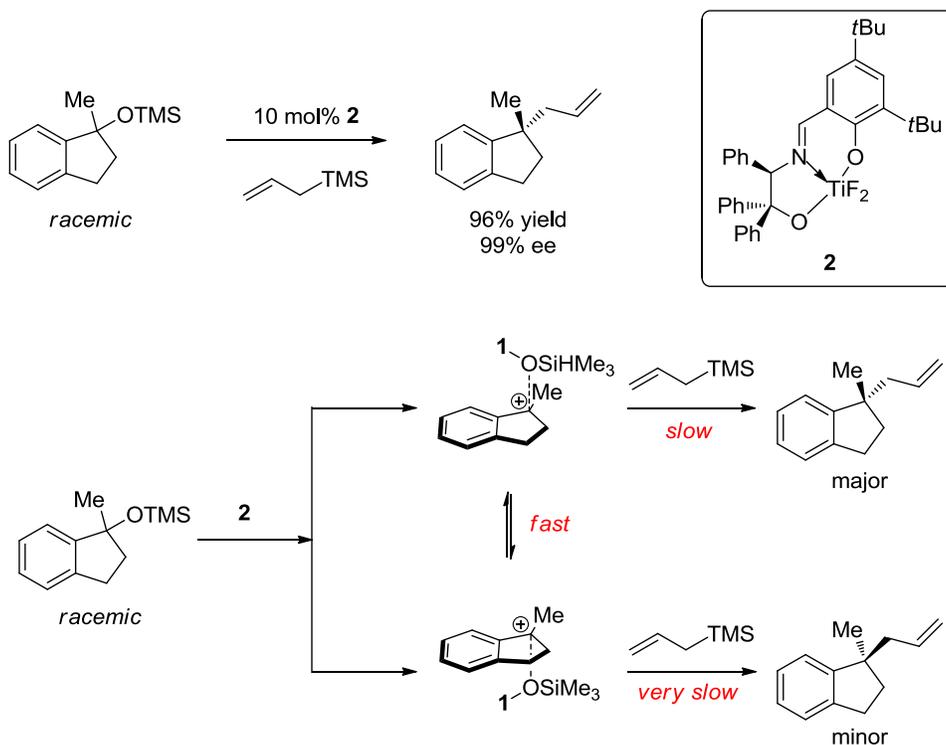
In 2004, Braun and coworkers reported that racemic silyl ethers undergo allylation with high enantioselectivity and nearly quantitative yield in the presence of titanium(IV) catalysts.⁶ This rather impressive transformation provides chiral products containing a quaternary stereogenic center. The fact that a racemic starting material is converted to a single enantiomer of product in high yield is indicative that a dynamic kinetic process is taking place.⁷ In this case, it is proposed that the catalyst promotes the formation of two diastereomeric ion pairs from the two enantiomers of starting materials, and that equilibration between the two ion pairs is fast. One of

⁶ Braun, M.; Kotter, W. *Angew. Chem., Int. Ed.* **2004**, *43*, 514.

⁷ Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. *Chem. Soc. Rev.* **2001**, *30*, 321.

the diastereomeric ion pairs reacts faster with allylsilane than the other, which allows for the preferential formation of one enantiomer of product (Scheme 2.3). Despite the apparent promise of this approach as a general solution for accessing carbenium intermediates and controlling highly selective nucleophilic additions to them, no further studies have been published in the ten years subsequent to the initial report.

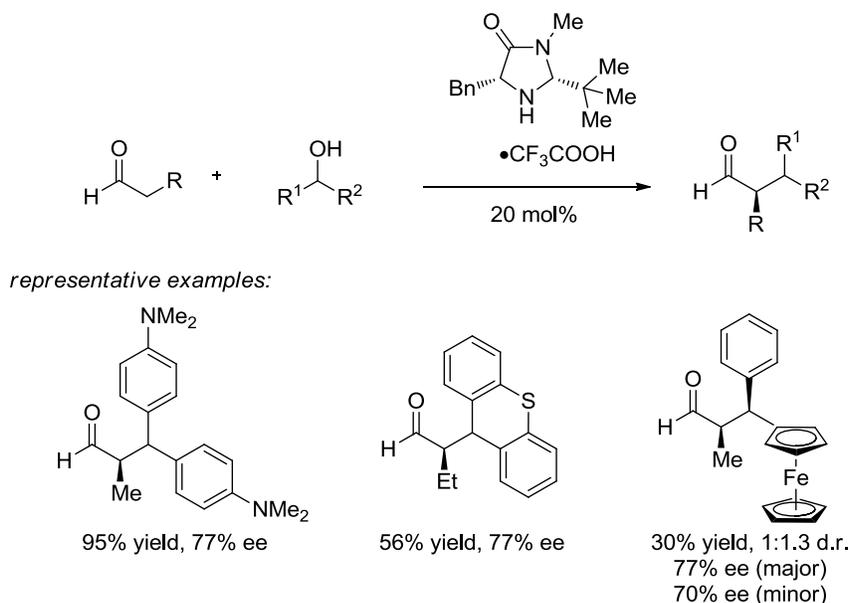
Scheme 2.3. Dynamic Kinetic Resolution *via* Carbenium Intermediate Enables Asymmetric Allylation



More recently, Cozzi and coworkers were successful in accessing benzhydryl carbenium intermediates via protonation of the corresponding benzhydrol starting materials in the context of

an asymmetric aldehyde α -alkylation (Scheme 2.4).⁸ The carbenium intermediates that are generated undergo alkylation with a catalyst-derived enamine to provide products in moderate to good yields and moderate enantioselectivity.⁹

Scheme 2.4. Cozzi's Aldehyde α -Alkylation with Highly Stabilized Diarylmethine Cations



In 2011, and subsequent to our research that is described in this chapter, Rueping reported that chiral Bronsted acids can activate alcohols as leaving groups via protonation to access allylic cationic intermediates. In this report, *N*-triflylphosphoramidate catalyst **3** promotes the highly enantioselective cyclization of racemic allylic alcohols to provide chiral chromene products (Scheme 2.5).¹⁰ Mechanistic studies of the reaction point towards the intermediacy of two diastereomeric ion pairs which are in rapid equilibration. One of the diastereomeric ion pairs

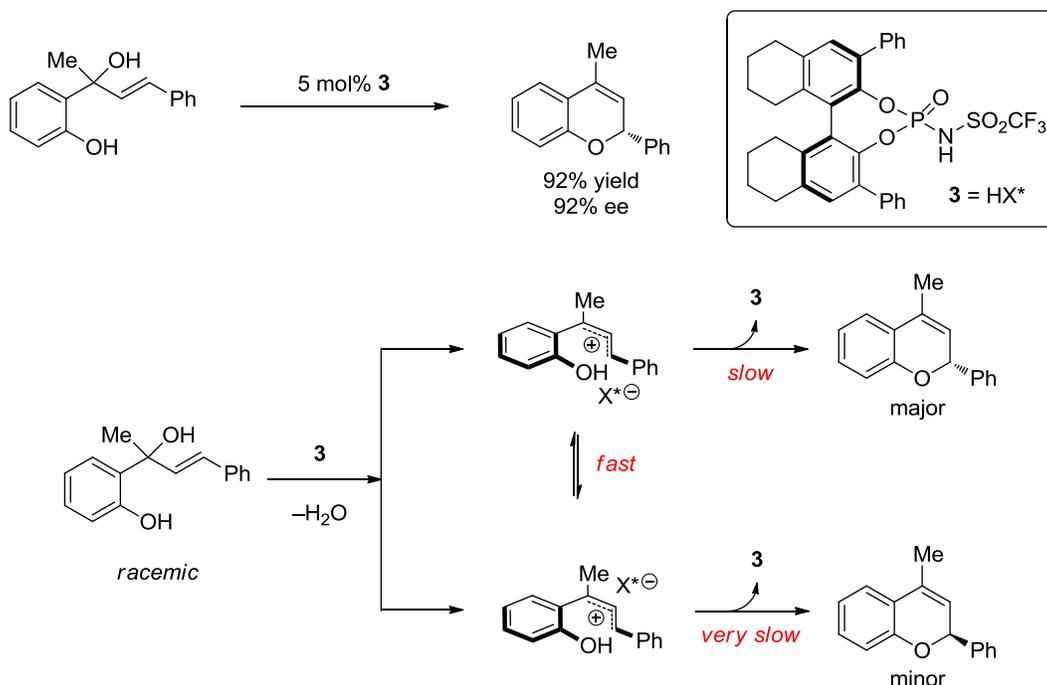
⁸ Cozzi, P. G.; Benfatti, F.; Zoli, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 1313.

⁹ For an extension of the method where the cationic intermediates are generated by alternate methods see: (a) Benfatti, F.; Capdevila, M. G.; Zoli, L.; Benedetto, E.; Cozzi, P. G. *Chem. Commun.* **2009**, 5919. (b) Benfatti, F.; Benedetto, E.; Cozzi, P. G. *Chem. Asian J.* **2010**, *5*, 2047. (c) Xiao, J. *Org. Lett.* **2012**, *14*, 1716.

¹⁰ Rueping, M.; Uria, U.; Lin, M.-Y.; Atodiresei, I. *J. Am. Chem. Soc.* **2011**, *133*, 3732.

reacts more rapidly with the pendant alcohol than the other, giving rise to enantioenriched products. This report provides important proof of concept that chiral ion strategies are viable for controlling asymmetric reactions of carbenium intermediates.

Scheme 2.5. Chiral Bronsted Acid Promoted Allylic Substitution



2.3. Anion Abstraction by Dual H-Bond Donor Catalysts Provides Access to Cationic Intermediates

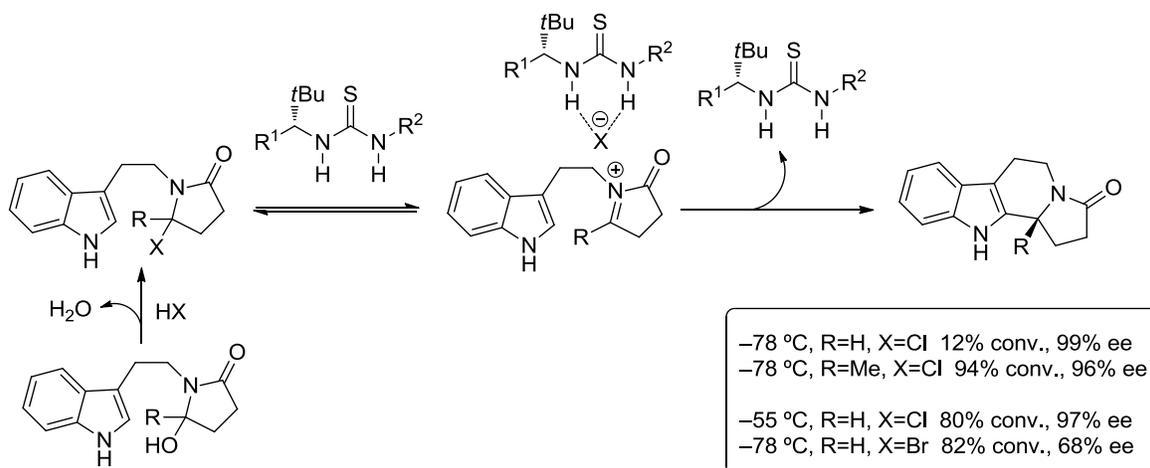
The field of H-bond donor catalysis has rapidly developed in recent years, and this maturation has led to the discovery of numerous substrate activation strategies.¹¹ Anion abstraction is an example of such a strategy, which provides access to highly reactive cationic intermediates. This class of transformation is characterized by H-bond donor assisted abstraction of an anion from a

¹¹ (a) Doyle, A. G.; Jacobsen, E. N. *Chem. Rev.* **2007**, *107*, 5713. (b) Brak, K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2013**, *52*, 534.

neutral organic precursor to generate a more reactive cationic intermediate. In principle, this strategy could be applied to access carbenium intermediates.

Pioneering work in catalysis by anion abstraction was carried out by our group in the context of the asymmetric *N*-acyl Pictet–Spengler reaction. In this transformation an *in situ* generated chlorolactam starting material underwent asymmetric cyclization in the presence of a chiral thiourea catalyst. Based on substrate substituent effects, counterion effects, and DFT computational analysis, a mechanism consisting of catalysis via anion abstraction was proposed (Scheme 2.6).¹²

Scheme 2.6. Seminal Work in Anion Abstraction Catalysis



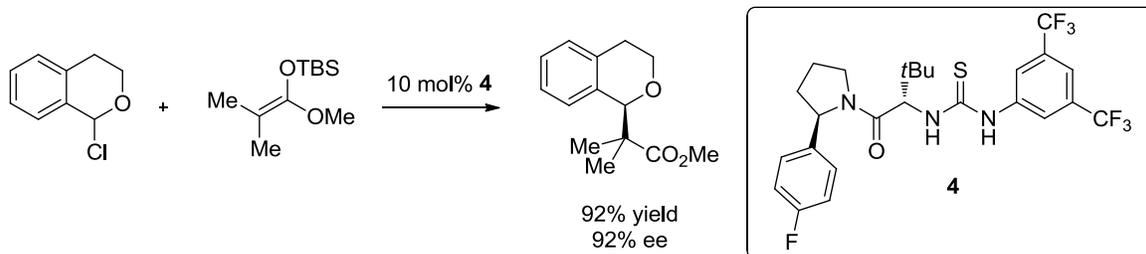
Since this initial report, this mode of catalysis has also been used to engage oxocarbenium ions in asymmetric catalysis via a similar strategy. Our group demonstrated that racemic α -chloroethers undergo enantioselective alkylation with silyl ketene acetals in high yields and enantioselectivities (Scheme 2.7).¹³ The ability to control the asymmetric addition to

¹² Raheem, I. T.; Thiara, P. S.; Peterson, E. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2007**, *129*, 13404.

¹³ Reisman, S. E., Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198.

oxocarbenium ions has wide reaching implications in its application to a variety of synthetic methods, such as diastereoselective *O*-glycosidation reactions or enantioselective Prins reactions.¹⁴

Scheme 2.7. Thiourea-Catalyzed Alkylation of α -Chloroethers



2.4. Results and Discussion

Although thiourea-promoted electrophile activation by anion abstraction had been applied to substrates giving rise to heteroatom-stabilized cationic intermediates, we were interested in applying the strategy to nonheteroatom-stabilized carbenium ions. Studies with benzhydryl derivatives have helped to establish many of the conceptual foundations of carbocation reactivity,¹⁵ and these compounds have been especially useful for characterizing the nature and stereochemical properties of ion pairs.¹⁶ Benzhydryl halides therefore represented an ideal class of electrophiles with which test our proposal, and to use to gain insight into the properties of putative catalyst-bound cationic intermediates. The α -alkylation of aldehydes was chosen as a model reaction because of the high value of chiral aldehydes bearing α -quaternary stereocenters

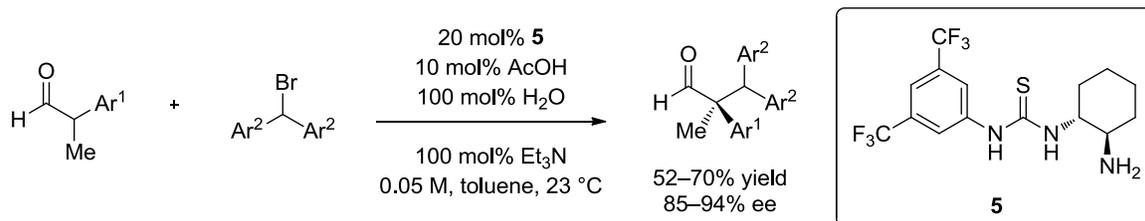
¹⁴ Doyle, A. G.; Ph.D. dissertation, Harvard University, **2008**.

¹⁵ (a) Deno, N. C.; Jaruzelski, J. J.; Schriesheim, A. *J. Am. Chem. Soc.* **1955**, *77*, 3044. (b) Deno, N. C.; Schriesheim, A. *J. Am. Chem. Soc.* **1955**, *77*, 3051. (c) Mayr, H.; Bug, T.; Gotta, M. F.; Hering, N.; Irrgang, B.; Janker, B.; Kempf, B.; Loos, R.; Ofial, A. R.; Remennikov, G.; Schimmel, H. *J. Am. Chem. Soc.* **2001**, *123*, 9500.

¹⁶ (a) Winstein, S.; Gall, J. S.; Hojo, M.; Smith, S. *J. Am. Chem. Soc.* **1960**, *82*, 1010. (b) Winstein, S.; Gall, J. S. *Tetrahedron Lett.* **1960**, *1*, 31. (c) Winstein, S.; Ledwith, A.; Hojo, M. *Tetrahedron Lett.* **1961**, *2*, 341. (d) Goering, H. L.; Briody, R. G.; Levy, J. F. *J. Am. Chem. Soc.* **1963**, *85*, 3059.

as synthetic intermediates, and the inherent challenges associated with asymmetric catalysis of this type of transformation.¹⁷

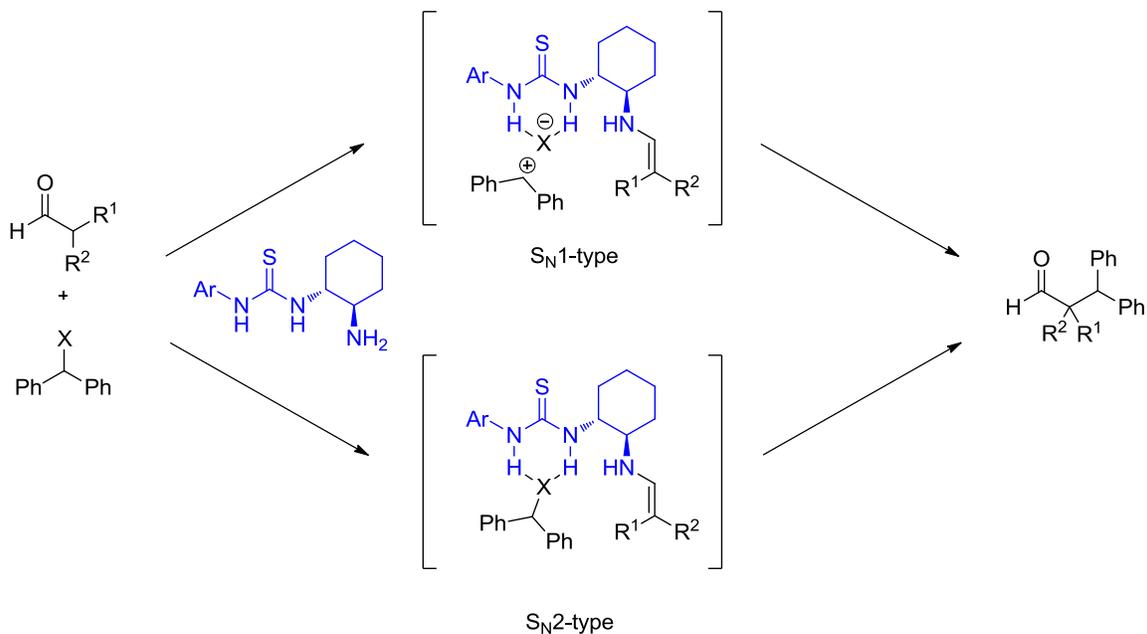
Scheme 2.8. Enantioselective Primary Aminothiourea-Catalyzed Aldehyde α -Alkylation



As discussed in Chapter 1 of this thesis, we discovered that primary aminothiourea **5** promoted the α -alkylation of a variety of electronically diverse 2-arylpropionaldehydes with benzhydryl bromides in moderate to good yields and good enantioselectivities (Scheme 2.8). Catalyst structure-activity studies indicated that activation of the nucleophile as a catalyst-derived enamine was necessary, as was activation of the electrophile by a dual H-bond donor. The essential role of the catalyst thiourea moiety in promoting these enantioselective alkylation reactions may be ascribed to electrophile activation by H-bonding to the leaving group in either of two limiting mechanisms: 1) general acid catalysis to induce a concerted, S_N2-like substitution, or 2) formation of an ion-pair intermediate and promotion of an S_N1-like pathway (Scheme 2.9).

¹⁷ See Chapter 1 for background on enantioselective aldehyde α -alkylation, and a detailed account of the discovery of the primary aminothiourea-catalyzed aldehyde α -alkylation

Scheme 2.9. Limiting Electrophile Activation Modes



In an effort to distinguish between these possibilities, the effects of isotopic and electronic substitution of the electrophile on the reaction were analyzed. Competition experiments between different classes of electrophiles were also carried out, as were experiments to characterize the stereochemical course of the alkylation. These experiments and their analysis are presented in the following sections.

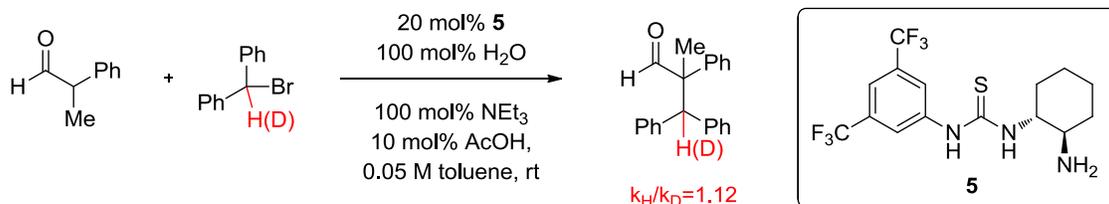
2.4.1. Kinetic Isotope Effect Experiments

The relative reaction rates of benzhydryl bromide and its deuterated analogue were examined via an intermolecular competition experiment. A normal secondary kinetic isotope effect (k_H/k_D) of 1.12 was observed upon deuterium-substitution of the benzhydryl proton (Scheme 2.10A), indicating a change in hybridization of the electrophilic carbon from sp^3 to sp^2 in the

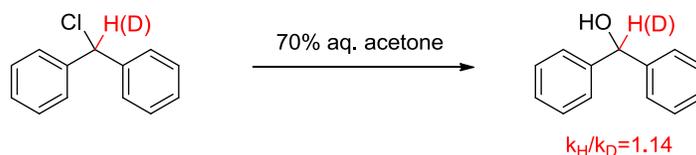
transition state. This kinetic isotope effect is consistent with what has been observed for the solvolysis of benzhydryl chlorides (Scheme 2.10B),¹⁸ which are prototypical S_N1 reactions.

Scheme 2.10. Kinetic Isotope Experiments

A. Observed KIE for Asymmetric Aldehyde α -Alkylation



B. Reported KIE for Benzhydryl Chloride Solvolysis (Ref. 18)

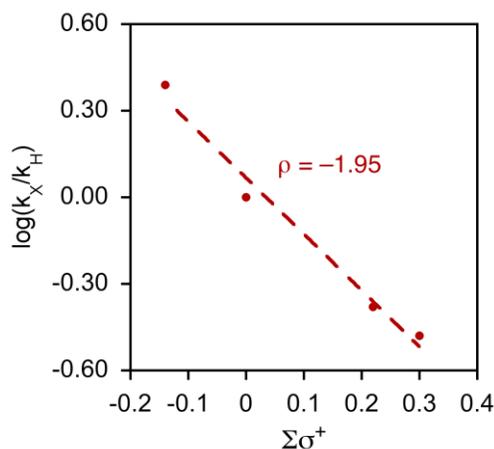
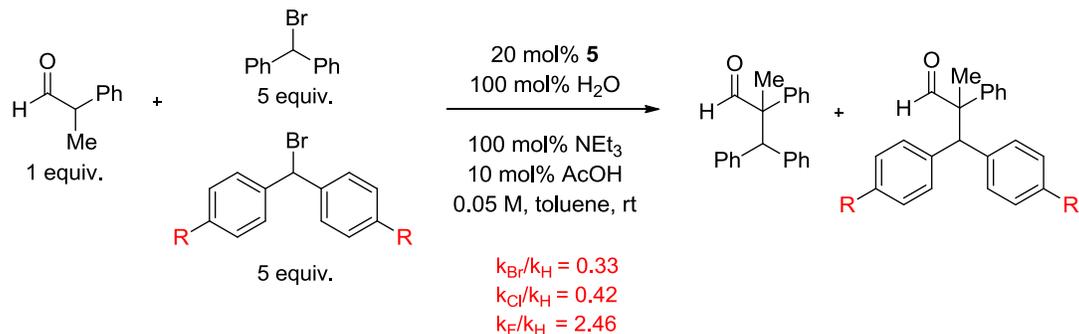


2.4.2. The Electronic Properties of the Electrophile Affect Relative Rates

Intermolecular competition experiments between electronically varied benzhydryl bromides were carried out to determine the relative reaction rates of these species in the aldehyde α -alkylation reaction. Correlating the observed relative rates to the corresponding Hammett substituent constants revealed a strong dependence on the electronic properties of the electrophile, with benzhydryl derivatives bearing electron-donating substituents reacting more rapidly (Scheme 2.11).

¹⁸ Streitwieser, A.; Klein, H. S. *J. Am. Chem. Soc.* **1964**, *86*, 5170.

Scheme 2.11. Hammett Analysis of Aldehyde α -Alkylation



Mayr and coworkers have recently studied both $S_{\text{N}}1$ and $S_{\text{N}}2$ reactions of benzhydryl bromides.¹⁹ The rates of $S_{\text{N}}1$ reactions of benzhydryl bromides (solvolysis in DMSO) depend strongly on the electronic properties of the electrophile ($\rho = -2.9$),²⁰ while the rates of $S_{\text{N}}2$ reactions of benzhydryl bromides with amines are only marginally affected and display poor Hammett correlations. The results of our experiments are therefore much more consistent with reactions proceeding via $S_{\text{N}}1$ mechanisms.

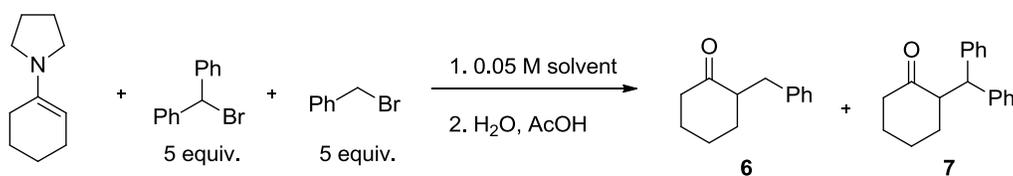
¹⁹ Phan, T. B.; Nolte, C.; Kobayashi, S.; Ofial, A. R.; Mayr, H. *J. Am. Chem. Soc.* **2009**, *131*, 11392.

²⁰ The benzhydryl bromides used in Mayr's Hammett analysis of the solvolysis reactions only had substituents on one of the aryl groups of the electrophile. In our experiments, the electrophiles were symmetrically substituted on both aryl groups of the benzhydryl electrophiles. Since both aromatic rings of the benzhydryl electrophile are likely not simultaneously in conjugation with the benzhydryl position, the ρ value observed for our experiments is likely smaller in magnitude than it would have been if benzhydryl electrophiles with only one substituted aryl group. For a discussion of nonadditive substituent effects for benzhydryl substrates see: Uddin, K.; Fujio, M.; Kim, H.-J.; Rappoport, Z.; Tsuno, Y. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 1371.

2.4.3. Competition Experiments Between S_N1- and S_N2-Type Electrophiles

Additional evidence for a catalyst-induced S_N1 pathway was provided through the evaluation of benzyl bromide as a potential electrophile in the alkylation reaction. Compared to benzhydryl bromide, benzyl bromide is less sterically encumbered and is also less effective in stabilizing positive charge buildup. Therefore, it is reasonable to conclude that benzyl bromide is a superior electrophile for S_N2 pathways while benzhydryl bromide is more suited for S_N1 pathways. In competition experiments, alkylation of 1-cyclohexenylpyrrolidine was found to proceed exclusively with benzyl bromide in the presence of equimolar amounts benzhydryl bromide. This selectivity is attributable to the relative reactivity of these electrophiles in S_N2 pathways typical of enamine nucleophiles (Table 2.1).

Table 2.1. Alkylation of 1-cyclohexenylpyrrolidine



entry	solvent	time	temp	yield 6	yield 7
1	MeCN	2h	r.t.	51	0
2	toluene	2h	r.t.	0	0
3	toluene	2h	60 °C	20	0
4	toluene	8h	60 °C	39	0

In contrast, under the catalytic conditions, no alkylation of 2-phenylpropionaldehyde was obtained with benzyl bromide (Table 2.2, entry 2). This absence of reactivity could not be ascribed to catalyst deactivation, as experiments with mixtures of benzyl bromide and benzhydryl bromide demonstrated that the catalyst maintained activity (Table 2.2, entry 3).

Taken together, the results from these experiments indicate that enamines inherently react selectively via S_N2 pathways, but under the catalytic conditions an S_N1 pathway is favored.

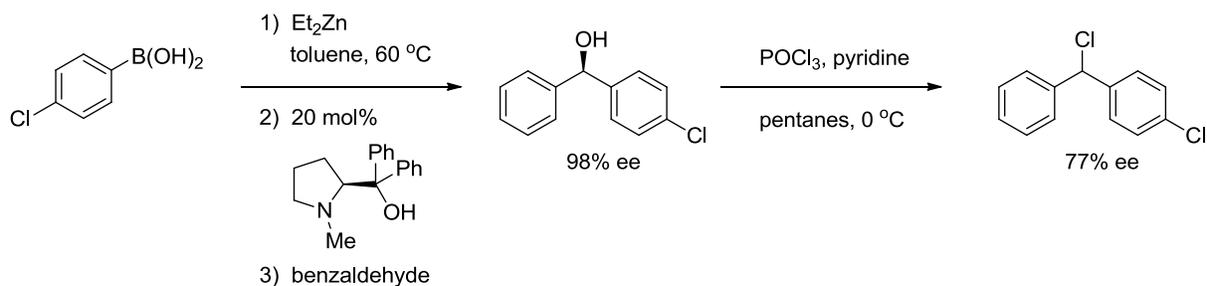
Table 2.2. Electrophile Competition Experiments Under Catalytic Conditions

entry	equiv 8	equiv 9	yield 10	ee (%) 10	yield 11
1	2	0	71	91	-
2	0	2	-	n.a.	0
3	2	2	49	90	0

2.4.4. Stereochemical Outcome of the Aldehyde α -Alkylation

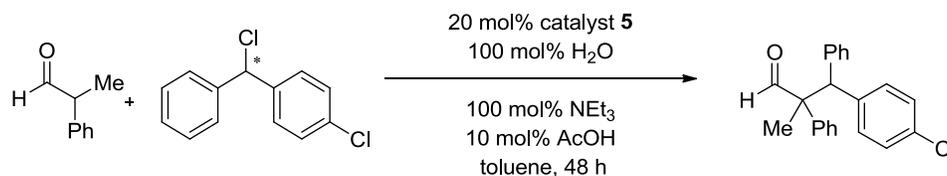
We were interested in characterizing the stereochemical course of the thiourea-catalyzed aldehyde α -alkylation in order to better understand the cationic intermediate that is generated, and also to evaluate the possibility of diastereoselective alkylation with chiral electrophiles. We synthesized an enantioenriched benzhydryl chloride electrophile from the corresponding enantioenriched alcohol (Scheme 2.12), and carried out alkylation studies with this electrophile.

Scheme 2.12. Synthesis of Enantioenriched Benzhydryl Chloride



The diastereoselectivity of the alkylation of 2-phenyl propionaldehyde with *p*-chlorobenzhydryl chloride was highly dependent on the enantiomeric purity of the chloride starting material (Table 2.3). A very cursory analysis of the results indicates that the alkylation proceeds with a high degree of stereospecificity. Further analysis of the data that corrects for the inherent diastereoselectivity that is observed for racemic chloride and allows the quantification of the stereospecificity of the reaction (Table 2.4).

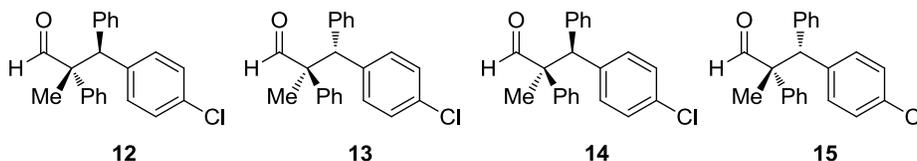
Table 2.3. Experiments with Enantioenriched Chloride



entry	catalyst	e.r. chloride SM	d.r. product	e.r. product
1	5	1 : 1	1 : 1.3	10.1 : 1 (major) 10.7 : 1 (minor)
2	1	1 : 7.7	1 : 6.1	55 : 1 (major) 1.5 : 1 (minor)
3	<i>ent</i> - 5	1 : 7.7	3.4 : 1	57 : 1 (major) 1.3 : 1 (minor)

Table 2.4. Product Distribution for Experiments Outlined in Table 2.3, and Determination of Chirality Transfer

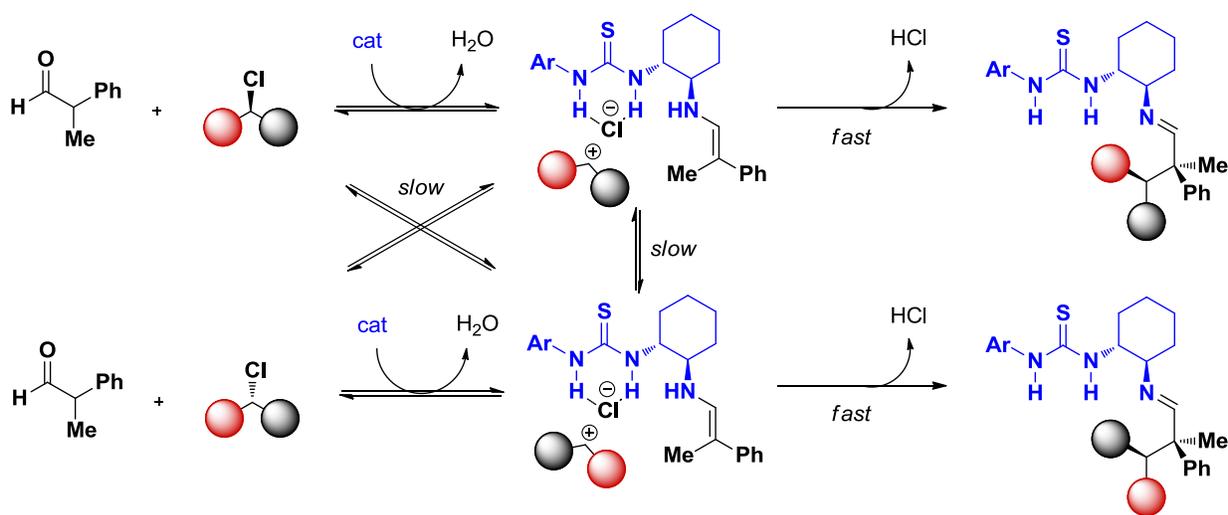
	12	13	14	15	(13+15)/(12+14)	correct for intrinsic selectivity	chirality transfer
Table 2.3, entry 1	1.37	13.9	10.7	1	1.23		
Table 2.4, entry 2	1	55.1	5.55	3.65	8.97	8.97/1.23=7.29	7.29/7.7=0.95
Table 2.5, entry 3	9.69	7.25	1	56.6	5.97	(5.97)(1.23)=7.34	7.34/7.7=0.95



The absolute configuration beta to the carbonyl has not been determined, but the relationships between the stereoisomers are correct.

The high stereospecificity (95%) observed for the alkylation indicates that addition of the catalyst-associated enamine to the ion-pair intermediate is rapid relative to ion-pair reorganization (Scheme 2.13). This is in line with the known reactivity of benzhydryl cations and enamines as analyzed by Mayr,²¹ which would predict that these partners should undergo reaction at the diffusion limit.

Scheme 2.13. Implications of High Observed Stereospecificity



2.5. Conclusions

This work demonstrates that thiourea derivatives effectively induce alkylation through carbenium ions via anion abstraction. An important extension of this strategy would be to the activation of chiral electrophiles and the subsequent control of nucleophilic addition to prochiral carbenium ions. Our results characterizing the stereochemical course of the aldehyde α -alkylation indicate that this would be difficult for reactions where the nucleophilic reaction partner is tethered to the activated electrophile. We anticipate that this challenge may be overcome in the context of intermolecular transformations, or by using electrophiles that give

²¹ For quantitative data describing the reactivity the reactivity of these reacting partners see ref. 15c and: Kempf, B.; Hampel, N.; Ofial, A. R.; Mayr, H. *Chem. –Eur. J.* **2003**, 9, 2209.

rise to more stabilized carbenium intermediates. Further, catalysts capable of stabilizing the high-energy carbenium intermediate that is generated following anion abstraction may hold promise for these systems. Stabilizing such intermediates would increase their lifetime, making equilibration between diastereomeric ion pairs prior to nucleophilic addition more likely.

2.6. Experimental Procedures

2.6.1. General Information

General Procedure. Unless otherwise noted, all reactions were performed in flame-dried round-bottom flasks sealed with a rubber septum under a nitrogen atmosphere. Air and moisture sensitive liquids were transferred using stainless steel cannulae or syringes. Flash chromatography was performed using silica gel ZEOprep60 ECO 40-63 micron from America International Chemical, Inc.

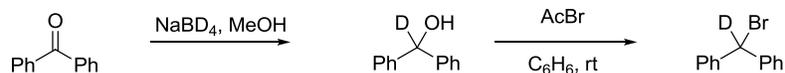
Materials. Commercial reagents were purchased from VWR, Acros, and Sigma-Aldrich and used as received with the following exceptions: 2-phenyl propionaldehyde was purified by distillation before use. Bromodiphenylmethane was purified by recrystallization from hexanes before use. Toluene, dichloromethane, and *t*-butyl methyl ether were dried by passing through columns of activated alumina. Acetonitrile was dried by passing through a column of activated molecular sieves. Triethylamine was distilled from CaH₂ at 760 torr.

Instrumentation. Proton nuclear magnetic resonance (¹H NMR) spectra and carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded on a Varian Inova-500 (500 MHz) NMR spectrometer. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to the NMR solvent residual peak (CHCl₃: δ7.27). Chemical shifts for carbons are reported in parts per million downfield from tetramethylsilane

and are referenced to the carbon resonances of the NMR solvent (CDCl₃: δ 77.0). Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet), and coupling constants in Hertz (Hz). The mass spectroscopic data were obtained at the Harvard University mass spectrometry facility. Infrared (IR) spectra were obtained using a Bruker Tensor 27 FTIR spectrophotometer. Data are represented as follows: frequency of absorption (cm⁻¹), intensity of absorption (s = strong, m = medium, w = weak). Optical rotation data were obtained using a 1 mL cell with a 0.5 dm path length on a Jasco P-2000 polarimeter. Chiral HPLC analysis was performed using a Shimadzu VP series instrument.

2.6.2. Kinetic Isotope Effect Experimental Procedure and Data

Preparation of α -Deuterio-diphenylmethylbromide.



A 50 mL round-bottom flask was charged with benzophenone (729 mg, 4 mmol) and MeOH (20 mL). The solution was cooled to 0 °C, and NaBD₄ (167 mg, 4 mmol) was added, and the reaction was stirred at 0 °C for 15 minutes. The reaction was then allowed to warm to room temperature and stirred for 30 minutes. H₂O (~10 mL) was added, and the mixture was stirred for 30 minutes. The mixture was extracted with CH₂Cl₂ (3x 15 mL), the combined organics were dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography to give the alcohol product (704 mg, 95% yield). The spectral data obtained were in accordance with those described in the literature.²²

²² Pucheault, M.; Darses, S.; Genet, J. –P. *J. Am. Chem. Soc.* **2004**, *126*, 15356.

A flame-dried 25 mL round-bottom flask was charged with 1-deuteriodiphenylmethanol (741 mg, 4 mmol) and benzene (9 mL) under nitrogen. Acetyl bromide (1.0 mL, 13.4 mmol) was added, and the reaction was stirred at room temperature for 6 h. The reaction mixture was concentrated to give an orange solid, which was recrystallized from hexanes to give α -Deuterio-diphenylmethylbromide as a white solid (431 mg, 43% yield). ^1H NMR (500MHz, CDCl_3) δ = 7.52 - 7.47 (m, 2 H), 7.40 - 7.34 (m, 2 H), 7.33 - 7.28 (m, 1 H); $^{13}\text{C}\{^1\text{H}\}$ NMR (126MHz, CDCl_3) δ = 141.2, 128.8, 128.7, 128.3, 55.3; FTIR (neat, cm^{-1}): 3059 (w), 3025 (w), 1492 (m), 1448 (m), 1246 (w), 1178 (w), 1082 (w), 1029 (w), 885 (m), 788 (s), 745 (s).

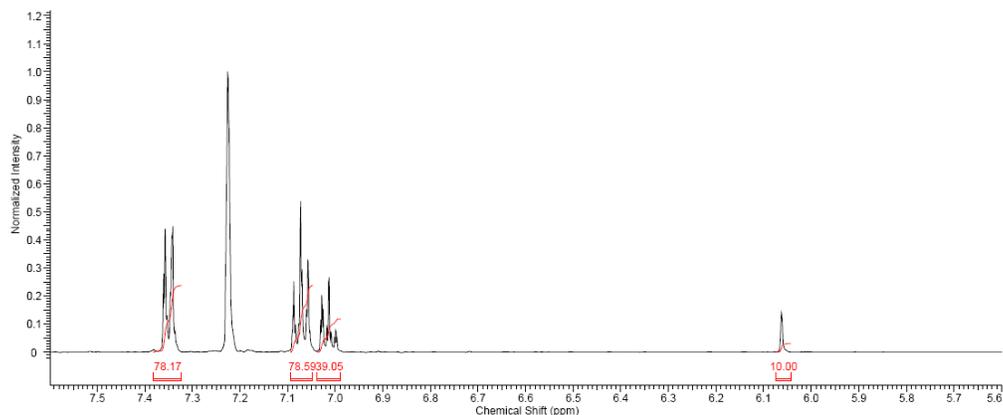
Preparation of a Stock Solution of Bromodiphenylmethane and α -Deuterio-diphenylmethylbromide. In a flame dried 10 mL Schlenk flask under nitrogen, bromodiphenylmethane (185.3 mg, 0.750 mmol) and α -deuterio-diphenylmethylbromide (186.1 mg, 0.750 mmol) were added, and the flask was sealed with a rubber septum. The flask was evacuated and backfilled with nitrogen (x4). Toluene (1.5 mL) was added to the flask, and the rubber septum was replaced with a glass stopper under positive nitrogen flow. The mixture degassed (3 freeze-pump-thaw cycles), and the glass stopper was replaced with a rubber septum. Analysis of the solution by ^1H NMR provided R_0 .

Preparation of a Stock Solution of 2-phenyl-propionaldehyde, AcOH, and Et_3N . In a flame dried 10 mL Schlenk flask under nitrogen, 2-phenyl-propionaldehyde (53.3 μL , 0.4 mmol), AcOH (2.3 μL , 0.04 mmol), Et_3N (55.5 μL , 0.4 mmol), and toluene (4 mL) were added to the flask, and the rubber septum was replaced with a glass stopper under positive nitrogen flow. The mixture degassed (3 freeze-pump-thaw cycles), and the glass stopper was replaced with a rubber septum.

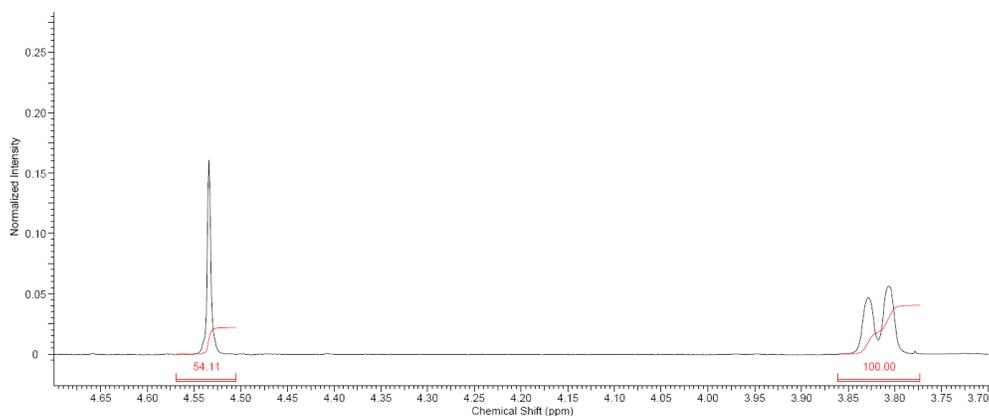
Addition of Stock Solutions to Catalyst. In a flame dried 10 mL Schlenk flask under nitrogen, thiourea catalyst **5** (7.7 mg, 0.02 mmol) was added, and the flask was sealed with a rubber septum. The flask was evacuated and backfilled with nitrogen (x4). In a GC vial, nitrogen was bubbled through deionized H₂O (~1 mL) for 10 minutes. A gas-tight microsyringe was used to transfer H₂O (1.8 μL, 0.1 mmol) from the GC vial to the Schlenk flask. The aldehyde stock solution (1 mL, 0.1 mmol aldehyde) and the bromide stock solution (1 mL, 0.5 mmol bromodiphenylmethane, 0.5 mmol α-deuterio-diphenylmethylbromide) were added to the Schlenk flask, with care taken to wash the water from the side of the flask. The rubber septum was replaced with a glass stopper under positive nitrogen flow, the Schlenk flask was sealed, and the reaction was stirred at room temperature.

Work up. After 45h, 3 mL of 1N aqueous HCl was added to the reaction mixture, and the mixture was stirred for 15 minutes. The mixture was extracted with CH₂Cl₂ (3x 15 mL), the combined organics were dried over sodium sulfate, and concentrated under reduced pressure. 1,3,5-trimethoxybenzene (5.6 mg, 0.033 mmol) was added as an internal standard, and the yield of the aldehyde product was determined by ¹H NMR analysis of the reaction mixture. To the crude aldehyde was added MeOH (~10 mL) and CH₂Cl₂ (~5 mL), and the mixture was cooled to 0 °C. NaBH₄ (113 mg, 3.0 mmol) was added, and the reaction was stirred at 0 °C for 15 minutes. The reaction was then allowed to warm to room temperature and stirred for 30 minutes. H₂O (~10 mL) was added, and the mixture was stirred for 30 minutes. The mixture was extracted with CH₂Cl₂ (3x 15 mL), the combined organics were dried over sodium sulfate, and concentrated under reduced pressure. The residue was purified by flash chromatography to give the alcohol product. Analysis of the product by ¹H NMR provided R_p.

Partial ^1H NMR spectrum of benzhydryl bromide starting material stock solution for expt. 1



Partial ^1H NMR spectrum of purified alcohol product for expt. 1



Data Analysis²³

Expt.	R_o	R_p	KIE ^a
1	0.953	0.848	1.12
2	0.944	0.852	1.11

^aKIE = $k_H/k_D = \ln(1-F) / \ln((1-F) R_p/R_o)$ where

F = conversion of deuterated starting material.

At low conversion (limit where F approaches 0), KIE = $k_H/k_D = R_o/R_p$

This simplification is valid because a large excess of deuterated starting material is used.

²³ Melander, L.; Saunders, W. H. *Reaction Rates of Isotopic Molecules*, Robert E. Kreiger Publishing Company, Malabar, 1987.

2.6.3. Linear Free-Energy Correlation Experimental Procedure and Data

Representative Experimental Procedure for the Determination of k_X/k_H : Determination of k_{Br}/k_H

Preparation of a Stock Solution of 2-phenyl-propionaldehyde, AcOH, and Et₃N. In a flame dried 10 mL Schlenk flask under nitrogen, 2-phenyl-propionaldehyde (50 μ L, 0.375 mmol), AcOH (2.1 μ L, 0.0375 mmol), Et₃N (52 μ L, 0.375 mmol), and toluene (7.5 mL) were added to the flask, and the rubber septum was replaced with a glass stopper under positive nitrogen flow. The mixture degassed (3 freeze-pump-thaw cycles), and the glass stopper was replaced with a rubber septum.

Addition of Stock Solutions to Catalyst and Electrophiles. In a flame dried 10 mL Schlenk flask under nitrogen, thiourea catalyst **5** (5.8 mg, 0.015 mmol), bromodiphenylmethane (92.7 mg, 0.375 mmol), 4,4'-(bromomethylene)bis(bromobenzene) (151.8 mg, 0.375 mmol) were added, and the flask was sealed with a rubber septum. The flask was evacuated and backfilled with nitrogen (x4). In a GC vial, nitrogen was bubbled through deionized H₂O (~1 mL) for 10 minutes. A gas-tight microsyringe was used to transfer H₂O (1.4 μ L, 0.075 mmol) from the GC vial to the Schlenk flask. The aldehyde stock solution (1.5 mL, 0.075 mmol aldehyde) was added to the Schlenk flask, with care taken to wash the water from the side of the flask. A small aliquot was taken and analyzed by ¹H NMR, providing [Br]₀/[H]₀=1.02. The rubber septum was replaced with a glass stopper under positive nitrogen flow, the Schlenk flask was sealed, and the reaction was stirred at room temperature.

Work up. After 24h, 3 mL of 1N aqueous HCl was added to the reaction mixture, and the mixture was stirred for 15 minutes. The mixture was extracted with CH₂Cl₂ (3x 15 mL), the

combined organics were dried over sodium sulfate, and concentrated under reduced pressure. 1,3,5-trimethoxybenzene (4.2 mg, 0.025 mmol) was added as an internal standard and ^1H NMR analysis of the concentrate provided $[\text{Br}]_{\text{F}}/[\text{H}]_{\text{F}}=0.33$.

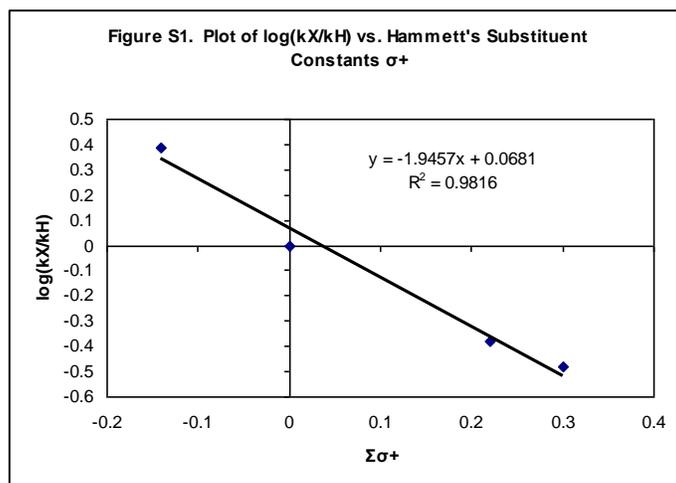
$$k_{\text{Br}}/k_{\text{H}} = ([\text{Br}]_0/[\text{H}]_0) / ([\text{Br}]_{\text{F}}/[\text{H}]_{\text{F}}) = 0.32$$

Using the general procedure described above, the following relative rates were determined:

$$k_{\text{Cl}}/k_{\text{H}} = 0.42$$

$$k_{\text{F}}/k_{\text{H}} = 2.51$$

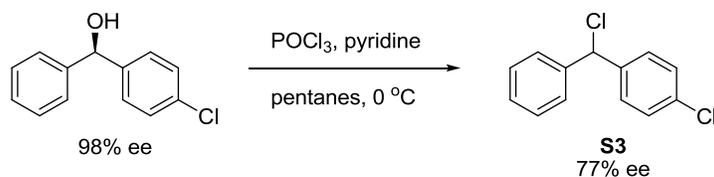
Linear Free Energy Relationship Analysis. Hammett plots of $\log k_{\text{rel}}$ vs. Hammett's substituent constants (σ^+) are shown below (Figure S1).²⁴



²⁴ Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.

2.6.4. Enantioenriched Chloride Experimental Procedure and Data

Preparation of Enantioenriched *p*-chlorobenzhydryl chloride.



A flame-dried 50 mL round-bottom flask was charged with (*R*)-(4-chlorophenyl)(phenyl)methanol²⁵ (219 mg, 1 mmol, 98% ee). Pentanes (14 mL) and pyridine (240 μ L, 3 mmol) were added, and the mixture was cooled to 0 °C. Phosphorus oxychloride (150 μ L, 1.6 mmol) was added, and the reaction was stirred at 0 °C for 5h. Saturated sodium bicarbonate (~10 mL) was added, and the organics were extracted with CH₂Cl₂ (3x 15 mL). The combined organics were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by flash chromatography (10:1 hexanes/EtOAc, R_f =0.6, which is necessary to avoid decomposition) to give the chloride product (100 mg, 42% yield). The spectral data obtained were in accordance with those described in the literature.²⁶ The chloride was determined to be 77% ee by chiral HPLC analysis (OD-H, 0.03% IPA in hexanes, 1.0 mL/min, 254 nm, t_r(major)= 17.9 min, t_r(minor)= 17.0 min). $[\alpha]_D^{22} = 10.4^\circ$ (c = 0.111, CH₂Cl₂); The absolute configuration of the chloride product was not determined.

Preparation of Reaction Mixture Stock Solution. In a flame dried 10 mL Schlenk flask under nitrogen, 1-chloro-4-(chloro(phenyl)methyl)benzene (32 mg, 0.135 mmol) was added, and the flask was sealed with a rubber septum. The flask was evacuated and backfilled with nitrogen

²⁵ Braga, A. L.; Ludtke, D. S.; Schneider, P.H.; Vargas, F.; Schneider, A.; Wessjohan, L. A.; Paixao, M. W. *Tetrahedron Lett.* **2005**, *46*, 7827.

²⁶ Denegri, B.; Streiter, A.; Juric, S.; Ofial, A. R.; Kronja, O.; Mayr, H. *Chemistry--A European Journal*, **2006**, *12*, 1648.

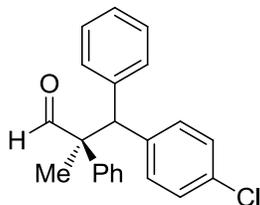
(x4). 2-phenylpropionaldehyde (90 μL , 0.675 mmol), AcOH (4 μL , 0.0675 mmol), Et_3N (94 μL , 0.675 mmol), and toluene (750 μL) were added to the flask, and the rubber septum was replaced with a glass stopper under positive nitrogen flow. The mixture degassed (3 freeze-pump-thaw cycles), and the glass stopper was replaced with a rubber septum.

Addition of Stock Solution to Catalyst. In a flame dried 10 mL Schlenk flask under nitrogen, thiourea catalyst **5** (21.4 mg, 0.056 mmol) was added, and the flask was sealed with a rubber septum. The flask was evacuated and backfilled with nitrogen (x4). In a GC vial, nitrogen was bubbled through deionized H_2O (~1 mL) for 10 minutes. A gas-tight microsyringe was used to transfer H_2O (5 μL , 0.28 mmol) from the GC vial to the Schlenk flask. The reaction mixture stock solution (400 μL , 0.28 mmol aldehyde, 0.056 mmol chloride) was added to the Schlenk flask, with care taken to wash the water from the side of the flask. The rubber septum was replaced with a glass stopper under positive nitrogen flow, the Schlenk flask was sealed, and the reaction was stirred at room temperature.

Work Up. After 48h, 3 mL of 1N aqueous HCl was added to the reaction mixture, and the mixture was stirred for 15 minutes. The mixture was extracted with CH_2Cl_2 (3x 15 mL), the combined organics were dried over sodium sulfate, and concentrated under reduced pressure. 1,3,5-trimethoxybenzene (3.1 mg, 0.019 mmol) was added as an internal standard, and the yield and diastereomeric ratio were determined by ^1H analysis of the crude concentrate. The aldehyde was reduced with NaBH_4 and the enantiomeric excess of the resulting alcohol was determined using HPLC analysis.

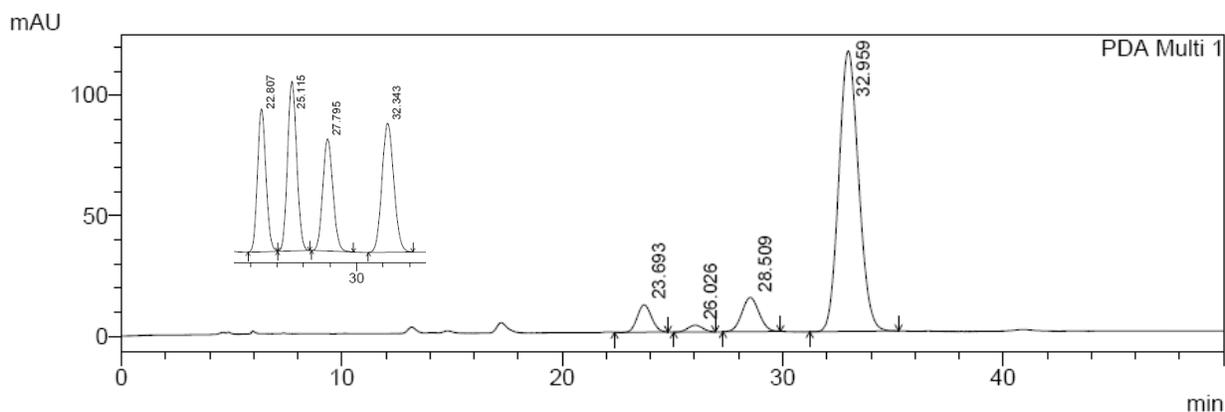
Product Characterization.

(2S)-3-(4-chlorophenyl)-2-methyl-2,3-diphenylpropanal:



The product was isolated as an inseparable mixture of diastereomers (6.1:1). (major) ^1H NMR (500MHz, CDCl_3) δ = 9.70 (s, 1 H), 7.54 - 6.87 (m, 14 H), 5.06 (s, 1 H), 1.58 (s, 3 H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125MHz, CDCl_3) δ = 201.4, 140.6, 139.2, 138.5, 132.2, 131.7, 130.1, 128.7, 128.4, 128.3, 127.9, 127.5, 126.8, 57.9, 56.0, 18.3; (minor) ^1H NMR (500MHz, CDCl_3) δ = 9.71 (s, 1 H), 7.42 - 6.94 (m, 14 H), 5.03 (s, 1 H), 1.59 (s, 3 H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125MHz, CDCl_3) δ = 201.7, 140.1, 139.5, 138.5, 132.5, 131.6, 130.2, 128.6, 128.4, 128.3, 128.0, 127.4, 126.5, 57.9, 56.2, 18.6; HRMS $[\text{M}+\text{Na}]^+$ calculated for $\text{C}_{22}\text{H}_{19}\text{ClO}$: 357.10166, found: 357.10156; FTIR (neat, cm^{-1}): 3060 (w), 3029 (w), 2814 (w), 1723 (s), 1492 (s), 1093 (m), 1015 (m), 909 (m), 733 (s), 700 (s).

The aldehyde was reduced with NaBH_4 and the major diastereomer of the alcohol was determined to be 96% ee by chiral HPLC analysis (OD-H, 2% IPA in hexanes, 1.0 mL/min, 225 nm, $t_r(\text{major})$ = 33.0 min, $t_r(\text{minor})$ = 26.0 min). The minor diastereomer was determined to be 21% ee by chiral HPLC analysis OD-H, 2% IPA in hexanes, 1.0 mL/min, 225 nm, $t_r(\text{major})$ = 28.5 min, $t_r(\text{minor})$ = 23.7 min).



1 PDA Multi 1/225nm 4nm

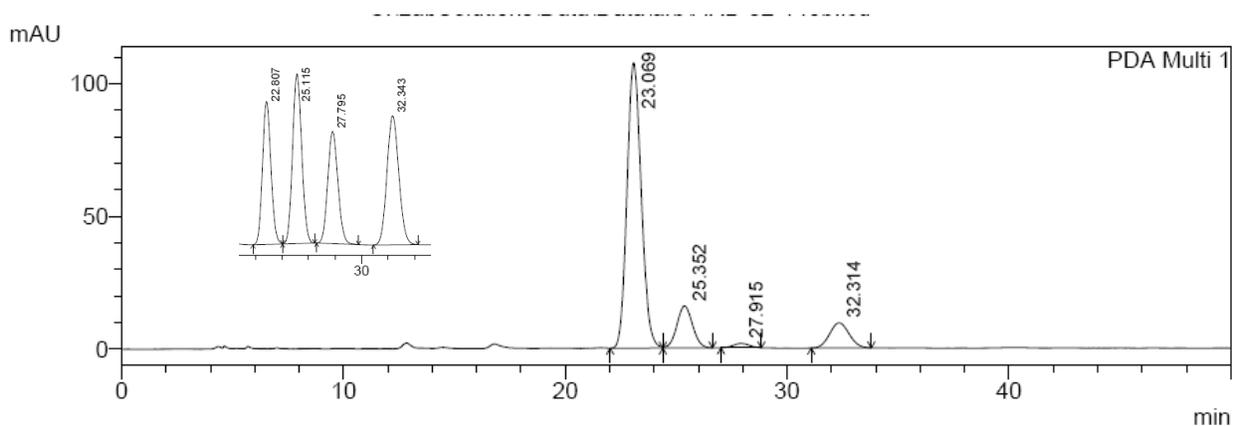
PeakTable

PDA Ch1 225nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	23.693	504449	11370	5.815	7.849
2	26.026	131915	2849	1.521	1.967
3	28.509	768661	14171	8.861	9.783
4	32.959	7269936	116461	83.804	80.401
Total		8674961	144851	100.000	100.000

The reaction of the enantioenriched chloride was also carried out using catalyst *ent-5*. The product was isolated as an inseparable mixture of diastereomers (3.4:1). (major) ^1H NMR (500MHz, CDCl_3) δ = 9.71 (s, 1 H), 7.42 - 6.94 (m, 14 H), 5.03 (s, 1 H), 1.59 (s, 3 H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125MHz, CDCl_3) (minor) ^1H NMR (500MHz, CDCl_3) δ = 9.70 (s, 1 H), 7.54 - 6.87 (m, 14 H), 5.06 (s, 1 H), 1.58 (s, 3 H); $^{13}\text{C}\{^1\text{H}\}$ NMR (125MHz, CDCl_3) δ = 201.4, 140.6, 139.2, 138.5, 132.2, 131.7, 130.1, 128.7, 128.4, 128.3, 127.9, 127.5, 126.8, 57.9, 56.0, 18.3; δ = 201.7, 140.1, 139.5, 138.5, 132.5, 131.6, 130.2, 128.6, 128.4, 128.3, 128.0, 127.4, 126.5, 57.9, 56.2, 18.6; HRMS $[\text{M}+\text{Na}]^+$ calculated for $\text{C}_{22}\text{H}_{19}\text{ClO}$: 357.10166, found: 357.10156; FTIR (neat, cm^{-1}): 3060 (w), 3029 (w), 2814 (w), 1723 (s), 1492 (s), 1093 (m), 1015 (m), 909 (m), 733 (s), 700 (s).

The aldehyde was reduced with NaBH₄ and the major diastereomer of the alcohol was determined to be 96% ee by chiral HPLC analysis (OD-H, 2% IPA in hexanes, 1.0 mL/min, 225 nm, t_r(major)= 23.1 min, t_r(minor)= 27.9 min). The minor diastereomer was determined to be 14% ee by chiral HPLC analysis OD-H, 2% IPA in hexanes, 1.0 mL/min, 225 nm, t_r(major)= 25.4 min, t_r(minor)= 32.3 min).



1 PDA Multi 1/225nm 4nm

PeakTable

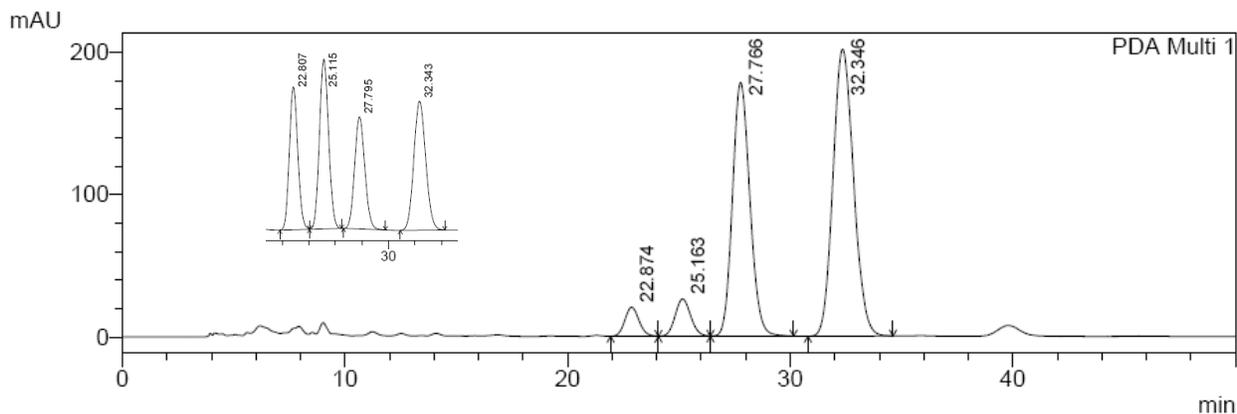
PDA Ch1 225nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	23.069	4823019	107593	76.930	79.905
2	25.352	778483	15859	12.417	11.778
3	27.915	85403	1687	1.362	1.253
4	32.314	582495	9512	9.291	7.064
Total		6269401	134652	100.000	100.000

The reaction was also carried out using racemic chloride and catalyst **5**. The product was isolated as an inseparable mixture of diastereomers (1.3:1). (major) ¹H NMR (500MHz, CDCl₃) δ = 9.70 (s, 1 H), 7.54 - 6.87 (m, 14 H), 5.06 (s, 1 H), 1.58 (s, 3 H); ¹³C{¹H}NMR (125MHz, CDCl₃) δ = 201.4, 140.6, 139.2, 138.5, 132.2, 131.7, 130.1, 128.7, 128.4, 128.3, 127.9, 127.5, 126.8, 57.9, 56.0, 18.3; (minor) ¹H NMR (500MHz, CDCl₃) δ = 9.71 (s, 1 H), 7.42 - 6.94 (m, 14 H), 5.03 (s, 1 H), 1.59 (s, 3 H); ¹³C{¹H}NMR (125MHz, CDCl₃) δ = 201.7, 140.1, 139.5, 138.5,

132.5, 131.6, 130.2, 128.6, 128.4, 128.3, 128.0, 127.4, 126.5, 57.9, 56.2, 18.6; HRMS $[M+Na]^+$ calculated for $C_{22}H_{19}ClO$: 357.10166, found: 357.10156; FTIR (neat, cm^{-1}): 3060 (w), 3029 (w), 2814 (w), 1723 (s), 1492 (s), 1093 (m), 1015 (m), 909 (m), 733 (s), 700 (s).

The aldehyde was reduced with $NaBH_4$ and the major diastereomer of the alcohol was determined to be 82% ee by chiral HPLC analysis (OD-H, 2% IPA in hexanes, 1.0 mL/min, 225 nm, $t_r(\text{major})=32.4$ min, $t_r(\text{minor})=25.2$ min). The minor diastereomer was determined to be 83% ee by chiral HPLC analysis OD-H, 2% IPA in hexanes, 1.0 mL/min, 225 nm, $t_r(\text{major})=27.8$ min, $t_r(\text{minor})=22.9$ min).



1 PDA Multi 1/225nm 4nm

PeakTable

PDA Ch1 225nm 4nm

Peak#	Ret. Time	Area	Height	Area %	Height %
1	22.874	905322	20398	3.646	4.784
2	25.163	1275823	26183	5.138	6.141
3	27.766	9713769	178166	39.120	41.789
4	32.346	12935655	201599	52.096	47.285
Total		24830569	426347	100.000	100.000

Chapter 3

Enantioselective Thiourea-Catalyzed Addition of Cyanide to *N,N*-Dialkyliminium Ions

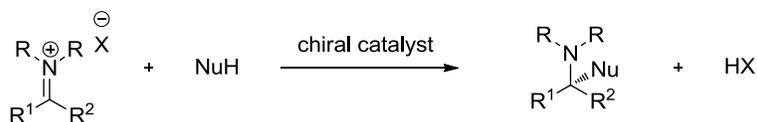
3.1. Introduction

Although chiral tertiary amines are known to be important structural motifs in biologically active compounds (Figure 3.1),¹ efficient synthetic methods for their direct asymmetric synthesis have not been well-developed. Catalytic asymmetric methods for chiral amine synthesis typically yield protected primary amine products, which must undergo deprotection and

¹ For example, see: (a) Mašič, L. P. *Curr. Drug. Metab.* **2011**, *12*, 35. (b) Cole, D. C.; Lennox, W. J.; Lombardi, S.; Ellingboe, J. W.; Bernotas, R. C.; Tawa, G. J.; Masandarani, H.; Smith, D. L.; Zhang, G.; Coupet, J.; Schechter, L. *E. J. Med. Chem.* **2005**, *48*, 353. (c) Krise, J. P.; Zygmunt, J.; Georg, G. I.; Stella, V. J. *J. Med. Chem.* **1999**, *42*, 3094.

alkylation to access the desired tertiary amine product.² A straightforward approach to address this problem would be the direct asymmetric 1,2-addition of nucleophiles to *N,N*-dialkyliminium

Scheme 3.1. Asymmetric Additions to *N,N*-Dialkyliminium Ions Provides Chiral Tertiary Amines Directly



ions (Scheme 3.1). Despite the apparent simplicity of this approach, methods utilizing such a strategy are not well-established. In this chapter, we will highlight the asymmetric 1,2-additions to *N,N*-dialkyliminium intermediates that are present in the literature, and we will discuss our research toward the development of an enantioselective thiourea-catalyzed addition of cyanide to *N,N*-dialkyliminium ions.

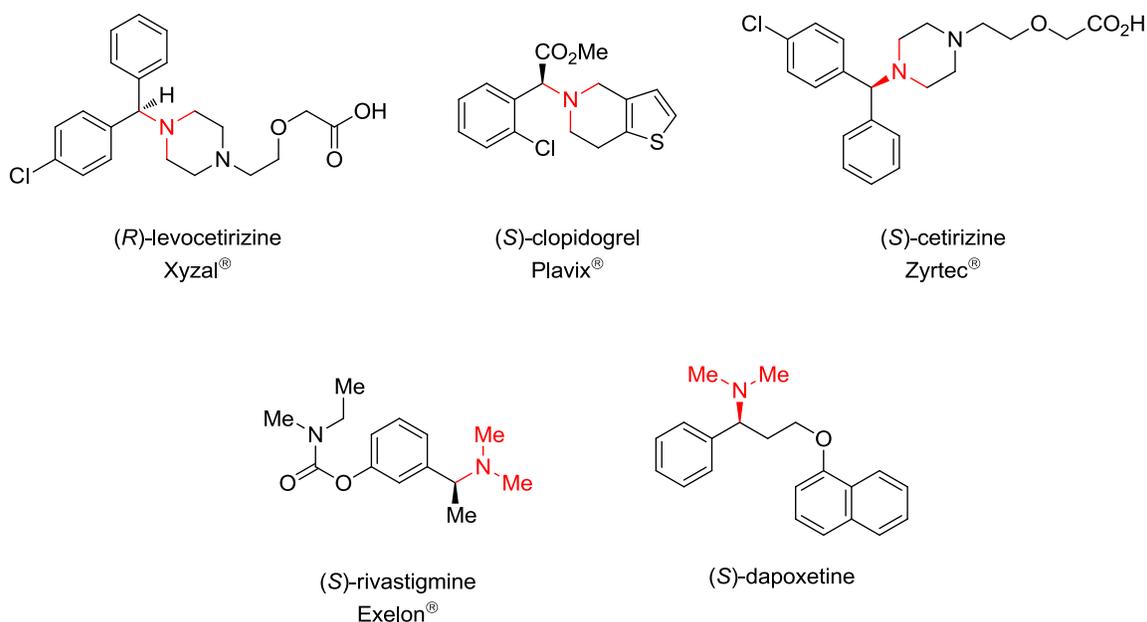


Figure 3.1. Selected Biologically Active Tertiary Amines

² For example, see: Kang, S.; Lee, H.-K. *J. Org. Chem.* **2010**, *75*, 237.

3.2. Enantioselective 1,2-Additions to *N,N*-dialkyliminium Ions

Although general methods for the enantioselective 1,2-addition of nucleophiles to *N,N*-dialkyliminium ions do not exist, a few isolated examples have been reported. The earliest examples of this class of transformation involved the addition of chiral copper alkyne species to dialkyliminium intermediates. Since the chiral element in these reactions is associated with the nucleophile, this is not a general strategy for the addition of a variety of other nucleophiles to *N,N*-dialkyliminium intermediates. More recently, asymmetric transformations have been developed that control nucleophilic additions to *N,N*-dialkyliminium intermediates by establishing an asymmetric environment around the electrophilic reaction partner. Such strategies are promising as a general solutions to control additions to *N,N*-dialkyliminium ions.

3.2.1. Propargyl Amine Synthesis via Asymmetric Copper-Catalyzed Alkyne Additions

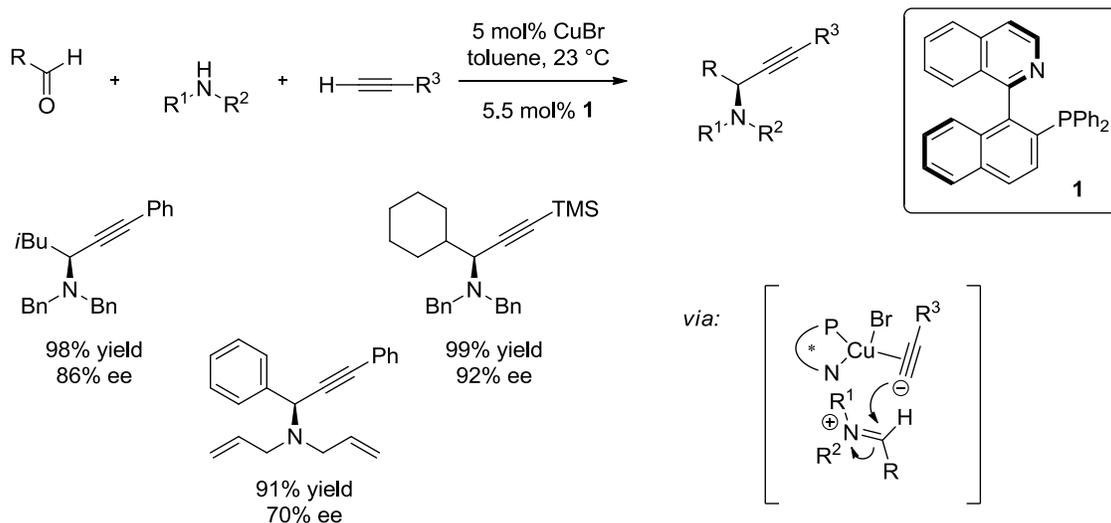
Tertiary propargyl amines are important synthetic intermediates³ that can be accessed via the addition of alkynyl nucleophiles to *N,N*-dialkyliminium intermediates. In 2002, Knochel and coworkers reported the copper-catalyzed asymmetric addition of alkynes to *N,N*-dialkyliminium intermediates generated *in situ* from enamines.⁴ The following year, the same group reported a similar transformation that presumably proceeds via a similar mechanism, but in this case the dialkyliminium intermediate was generated *in situ* from the corresponding aldehyde and amine.⁵ These transformations proceed with good yields and moderate to good enantioselectivities (Scheme 3.2).

³ Zhdanov, V. P.; Kasemo, B. *Surf. Sci. Rep.* **2000**, *39*, 25, and references therein.

⁴ Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535.

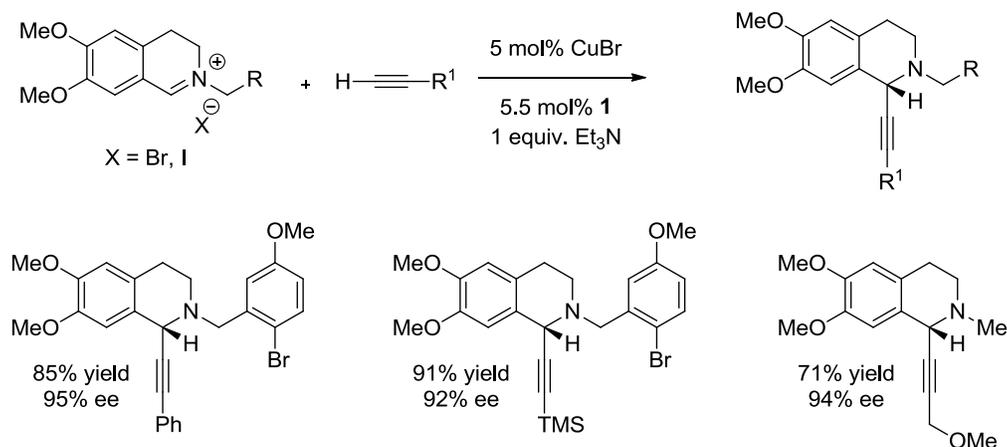
⁵ Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763.

Scheme 3.2. Copper-Catalyzed Propargyl Amine Synthesis



The technology developed by Knochel and coworkers was utilized a few years later by Schreiber and coworkers in the context of a diversity-oriented synthesis (DOS) of isoquinoline-derived alkaloids. These studies showed that Knochel's copper mediated alkylation was also applicable for additions to discrete dialkyliminium species, as a variety of terminal alkynes were added to alkyloisoquinolinium salts with high levels of enantioselectivity (Scheme 3.3).⁶

Scheme 3.3. Addition of Terminal Alkynes to Alkyloisoquinolinium Salts

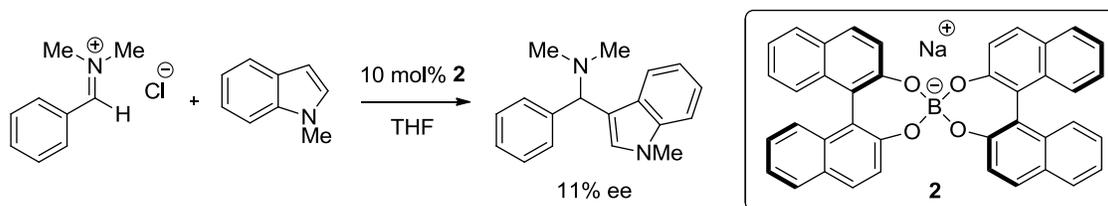


⁶ Taylor, A. M.; Schreiber, S. L. *Org. Lett.* **2006**, *8*, 143.

3.2.2. Chiral Anion Approaches to Asymmetric Additions to *N,N*-Dialkyliminium Ions

A few chiral anion approaches have been developed to control the stereochemical outcome of 1,2-addition to *N,N*-dialkyliminium ions. The first of these was reported in 2003 by Nelson and coworkers. In this study, chiral borate anions were shown to induce very moderate amounts of asymmetry to the addition of indole to *N,N*-dialkyliminium chloride intermediates (Scheme 3.3).⁷ The results are quite modest, but the principle of using a chiral anion approach to promote an enantioselective reaction with the corresponding cation was quite novel at the time. Today, this type of asymmetric induction represents a field of study that is rather well-developed.⁸

Scheme 3.3. Asymmetric Induction by Chiral Borate Anions



More recently, a chiral phosphate anion approach has been used for asymmetric Pictet-Spengler reactions of *N,N*-dialkyliminium ions.⁹ Although this class of phosphoric acid catalysts have been used for a multitude of reactions involving various cationic intermediates,¹⁰ this is the

⁷ Carter, C.; Fletcher, S.; Nelson, A. *Tetrahedron: Asymmetry* **2003**, *14*, 1995.

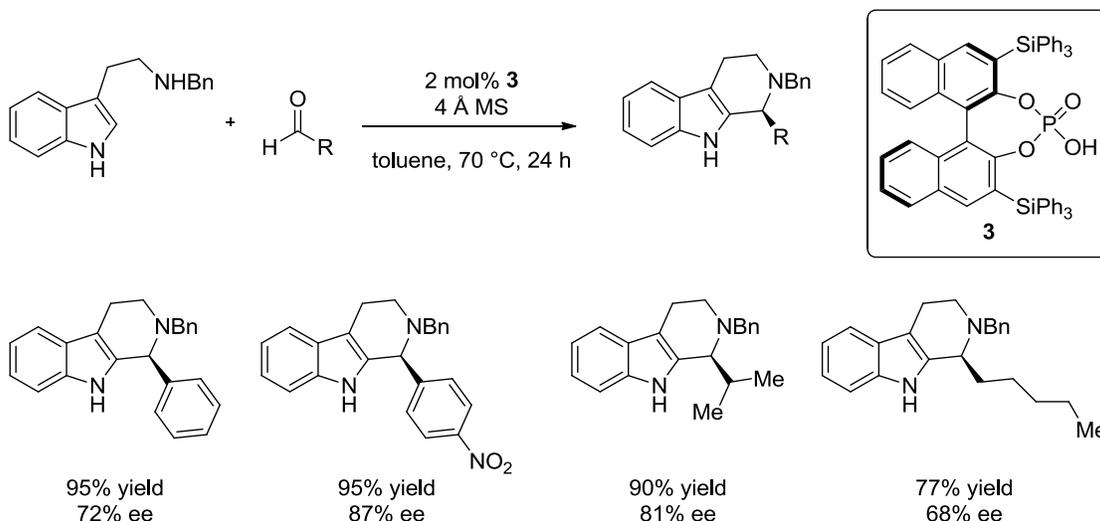
⁸ (a) Phipps, R. J.; Hamilton, G. L.; Toste, F. D. *Nature Chem.* **2012**, *4*, 603 (b) Brak, K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2013**, *52*, 534.

⁹ (a) Sewgobind, N. V.; Wanner, M. J.; Ingemann, S.; de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2008**, *73*, 6405. For an application to the synthesis of (-)-arboricine see: (b) Wanner, M. J.; Boots, R. N. A.; Eradus, B.; Gelder, de Gelder, R.; van Maarseveen, J. H.; Hiemstra, H. *Org. Lett.* **2009**, *11*, 2579.

¹⁰ (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) Mahlau, M.; List, B. *Angew. Chem., Int. Ed.* **2013**, *52*, 518.

only example involving *N,N*-dialkyliminium intermediates.¹¹ The reaction proceeds with moderate to good enantioselectivities for a variety of aromatic and aliphatic aldehyde substrates (Scheme 3.4).

Scheme 3.4. Phosphoric Acid-Catalyzed Pictet-Spengler Reaction



3.2.3. Enantioselective Three-Component Petasis Reaction

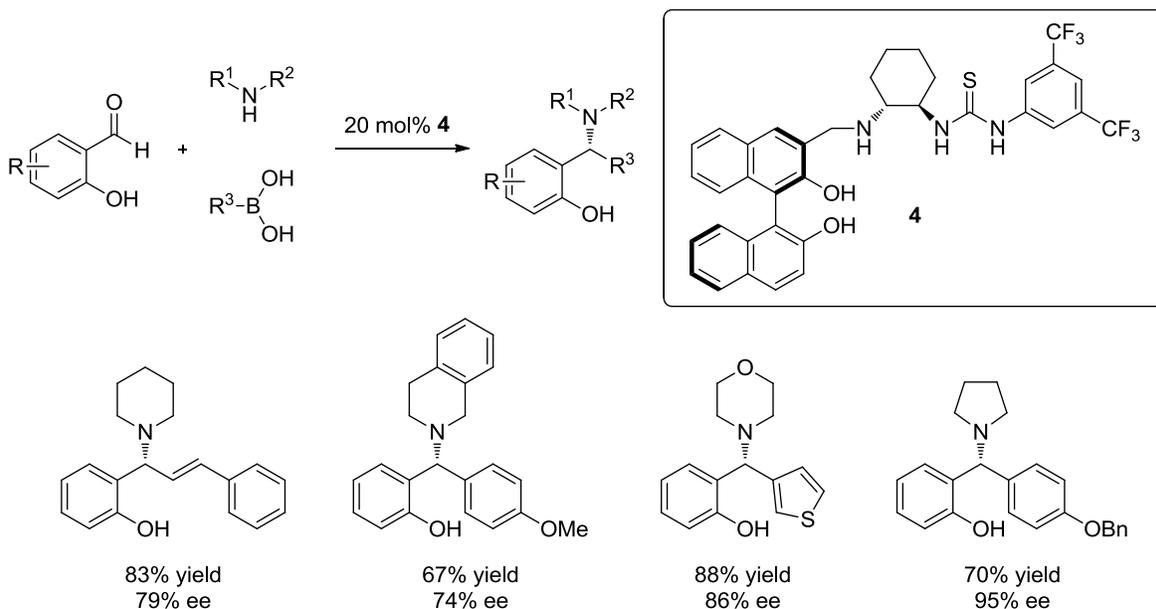
Subsequent to our work in this area, which will be discussed later in this chapter, Yuan and coworkers disclosed a highly enantioselective Petasis reaction that proceeds via the intermediacy of an *N,N*-dialkyliminium intermediate.¹² These transformations are catalyzed by thiourea-BINOL catalyst **4**, and proceed with moderate to good levels of enantioselectivity. The three component reaction is limited to salicylaldehydes as the aldehydic component, but a variety of amines and boronic acids are tolerated (Scheme 3.5). The authors propose the intermediacy of a BINOL-derived borate ester for the transformation, but the evidence to support this hypothesis is not particularly strong as catalysts that do not contain alcohol functionality promote the reaction

¹¹ A similar approach has been reported for 1,4-additions to *N,N*-dialkyliminium reactions: Mayer, S.; List, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 4193.

¹² Han, W.-Y.; Wu, Z.-J.; Zhang, X.-M.; Yuan, W.-C. *Org. Lett.* **2012**, *14*, 976

with moderate enantioselectivity. Despite the mechanistic ambiguity of the transformation, it is an impressive example of asymmetric 1,2-addition to *N,N*-dialkyliminium ions.

Scheme 3.5. Asymmetric Three-Component Petasis Reaction



3.3 Results and Discussion

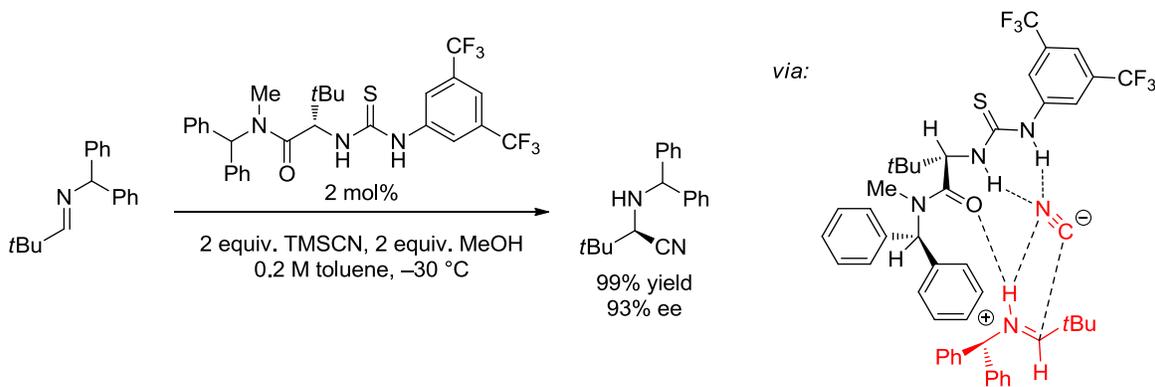
3.3.1. Rationale for the Choice of Cyanide as Nucleophilic Reaction Partner

Dual H-bond donor catalysts are known to promote asymmetric bond-forming reactions that proceed via cationic intermediates and were explored as catalysts for the asymmetric addition of cyanide to *N,N*-dialkyliminium ions. The choice of cyanide as the preliminary nucleophile in our study was a strategic one. Our group had previously established that chiral thioureas can interact with cyanide, and facilitate its highly selective addition to prochiral cationic protoiminium intermediates.¹³ During these studies, a key H-bonding interaction was identified between the

¹³ Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. *Nature* **2009**, *461*, 968.

amide of the catalyst and the N-H of the protoiminium ion.¹⁴ This H-bonding interaction positions the prochiral protoiminium ion in an orientation that allows for highly selective nucleophilic addition (Scheme 3.6).¹⁵

Scheme 3.6. Key H-Bonding Interaction in Asymmetric Strecker Reaction



The structure of *N,N*-dialkyliminium ions precludes such a hydrogen bonding interaction between the substrate and the chiral catalyst, making selective additions to these electrophiles challenging (Figure 3.2). However, the discovery of catalysts that promote highly enantioselective additions to *N,N*-dialkyliminium ions would provide an opportunity to study non-covalent interactions that were either not present or not important for anchoring protoiminium ions. Ultimately, an understanding of these non-covalent interactions could be applied to the design of chiral catalysts that interact with other cationic species lacking heteroatom-H bonds, such as oxocarbenium ions or carbenium ions.

¹⁴ Zuend, S. J.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2009**, *131*, 15358.

¹⁵ For another example of a key H-bonding interaction between a dual H-bond donor catalyst and a protoiminium ion see: Xu, H.; Zuend, S. J.; Woll, M. P.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, *327*, 986

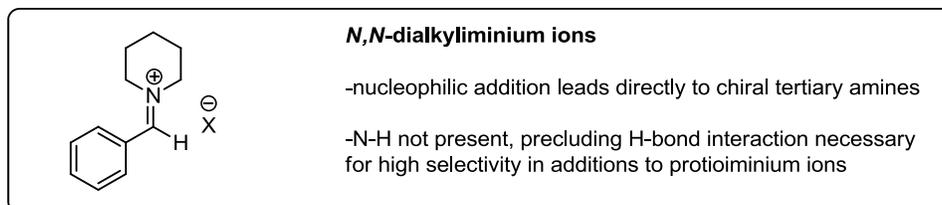
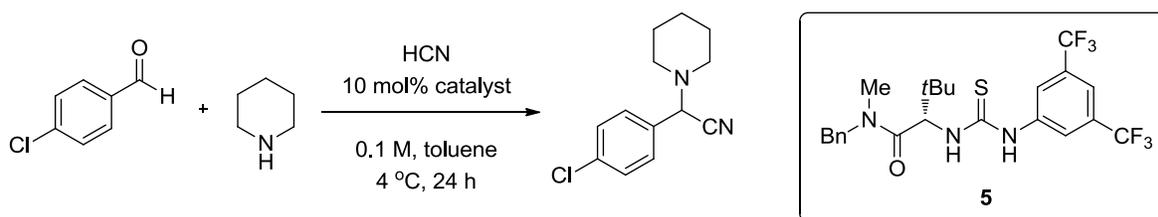


Figure 3.2. Key Secondary Interaction for Asymmetric Addition to Protoiminium Ions is Not Possible for *N,N*-Dialkyliminium Substrates

3.3.2. Preliminary Experiments

We examined the reaction of an amine, aldehyde and hydrogen cyanide in the presence of thiourea **5**. Although an increase over the background rate was observed in the presence of catalyst **5**, the cyanation reaction was quite slow and proceeded with very low levels of enantioselectivity (Table 3.1).

Table 3.1. Preliminary Results for Asymmetric Strecker Reaction



entry	catalyst	yield (%)	ee (%)
1	--	6	–
2	5	23	1
3	<i>ent</i> - 5	23	–1

3.3.3. Symmetrical Aminals as Precursors to *N,N*-Dialkyliminium Ions

We considered the mechanism of the transformation in an effort to understand the slow observed rate. The aldehyde and amine component of the reaction likely react to form

hemiaminal intermediate **7**, which must be protonated by hydrogen cyanide before expulsion of water to generate dialkyliminium intermediate **8** (Scheme 3.7A). We hypothesized that symmetrical aminal **9** would be more basic than hemiaminal **7**, and therefore protonation would be more facile (Scheme 3.7B). Consistent with our hypothesis, we observed that aminal **9a** reacted with hydrogen cyanide at cryogenic temperatures in the presence of thiourea catalysts, giving product with measurable levels of enantioenrichment (Table 3.2).

Scheme 3.7. Rational for Higher Rate with Symmetrical Aminal Substrate

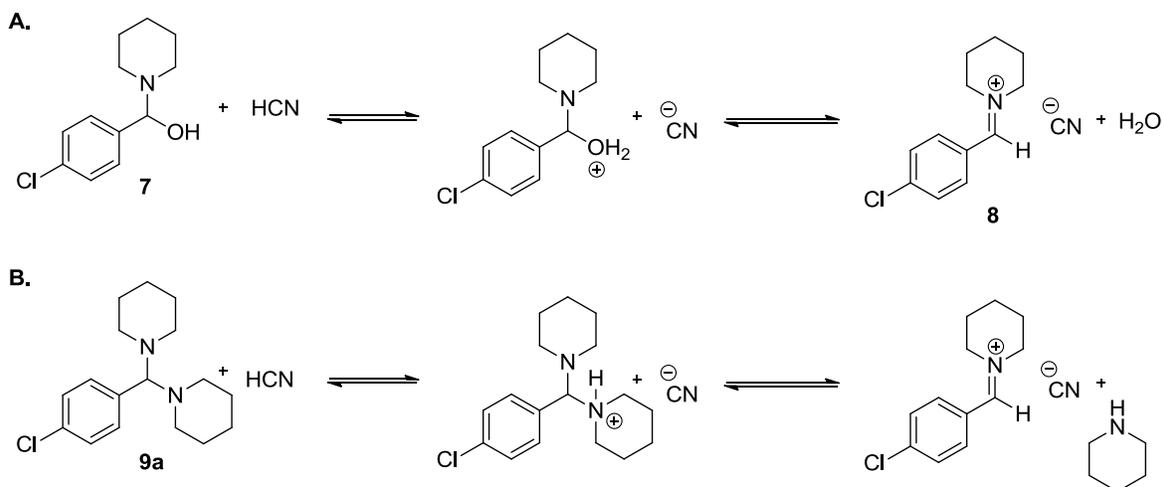
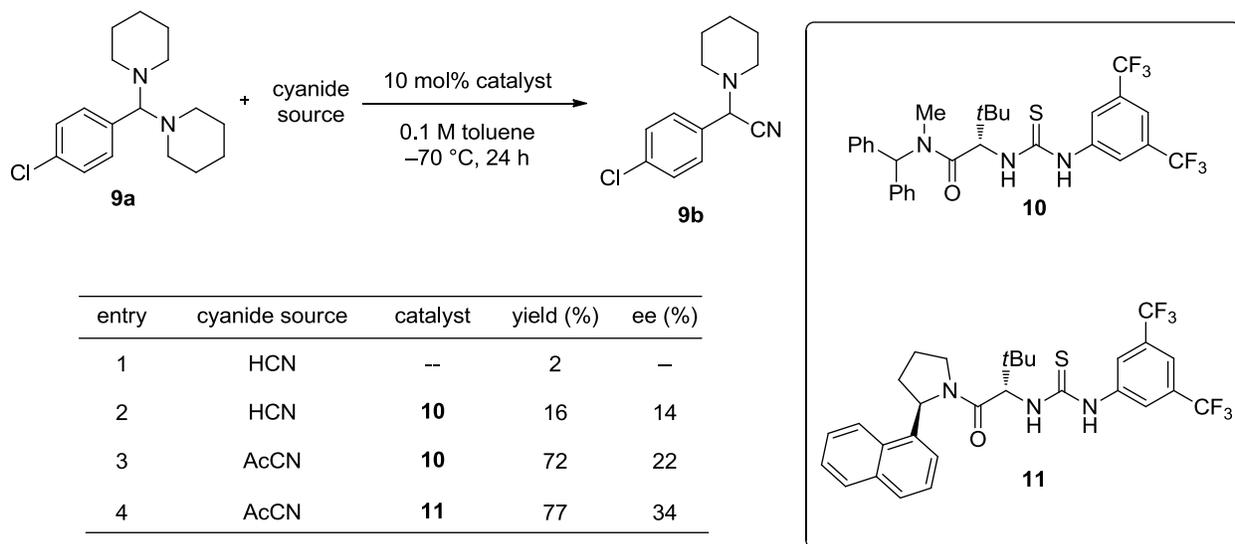
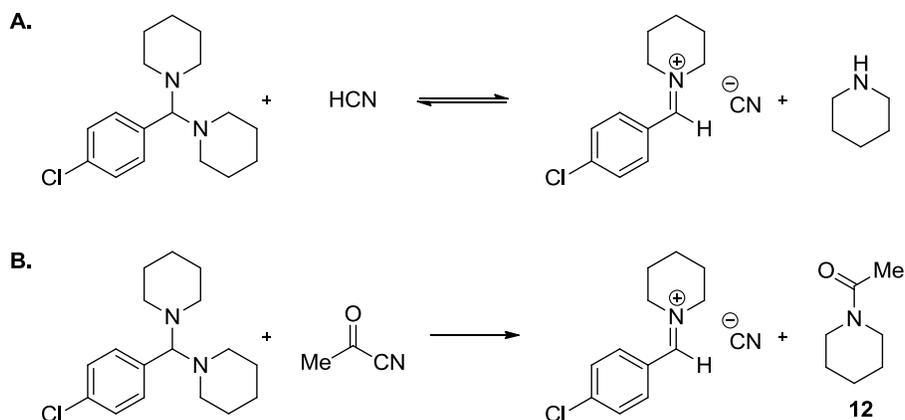


Table 3.2. Reaction of Symmetrical Aminal **9**

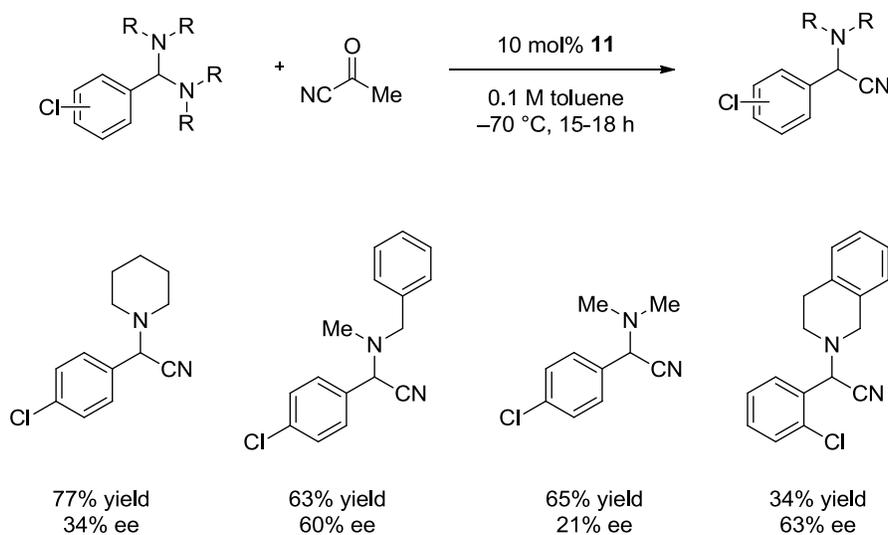
Alternate cyanide sources were also examined for the transformation. Symmetrical aminals are known to react with acetyl chloride to provide dialkyliminium chloride intermediates.⁷ We hypothesized that acetyl cyanide would react in a similar manner with aminals to generate the desired dialkyliminium cyanide intermediates for the asymmetric cyanation. Acetyl cyanide was used as the cyanide source in the presence of thiourea catalyst **10** and **11**, and the desired product was observed in improved yield and enantioselectivity compared to the analogous reactions using hydrogen cyanide (Table 3.2). We attribute the increased reaction rate for the reactions with acetyl cyanide to the formation of amide **12**, which makes the dialkyliminium formation from the parent aminal an irreversible process (Scheme 3.8B). When hydrogen cyanide is used, the dialkyliminium formation is reversible (Scheme 3.8A). Additionally, under the hydrogen cyanide conditions, free amine is generated as a stoichiometric byproduct, which is more basic than the aminal starting material and could therefore inhibit the reaction by reacting with hydrogen cyanide.

Scheme 3.8. Reversibility of Dialkyliminium Formation in the Presence of Hydrogen Cyanide and Acetyl Cyanide.



Experiments were conducted to determine the sensitivity of the reaction to changes in substrate structure (Scheme 3.9). We found that substrates bearing *N*-benzyl groups reacted with much higher enantioselectivity than substrates lacking such functionality. This was also the case for substrates where the *N*-benzyl group was part of a cyclic tetrahydroisoquinoline system.

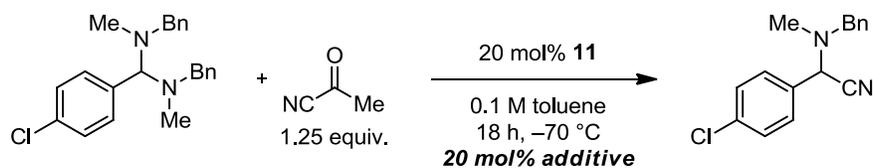
Scheme 3.9. Preliminary Substrate Scope Under Suboptimal Reaction Conditions



3.3.4. Discovery of Weak Acid Co-Catalyst

During the reaction optimization process, we noticed that reactions set up under identical conditions were not yielding identical results. Notably, the results obtained from reactions that were carried out in January of 2011 were different than those obtained from reaction carried out in August of the previous year. In order to understand these differences, we tested the effect of a series of additives on the cyanation reaction. Interestingly, the presence of basic additives inhibited the reaction, while acidic additive provided an increase in rate and did not diminish the observed enantioselectivity.

Table 3.3. Investigation of Irreproducibility via Addition of Additives



entry ^a	additive	yield	ee
1	none	85	70
2	none	37–50 ^b	79–80 ^b
3	H ₂ O	52	71
4	Et ₃ N	4	n.d.
5	<i>i</i> Pr ₂ NH	2	n.d.
6	BnNHMe	34	66
7	BzOH	92	80

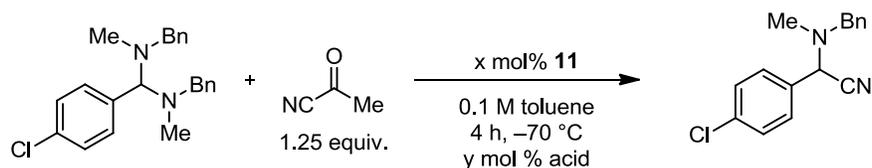
^a Entry 1 carried out Aug 2010, entries 2–7 carried out Jan 2011

^b Range of 5 reactions

We optimized the reaction conditions with respect to the ratio of catalyst to acid and found that equal amounts of thiourea **11** and acid were optimal (Table 3.4). Additionally, we observed the effect of a variety of acidic additives on the reaction. Interestingly, a variety of structurally diverse carboxylic acids of similar acidity gave comparable results for the cyanation. Highly

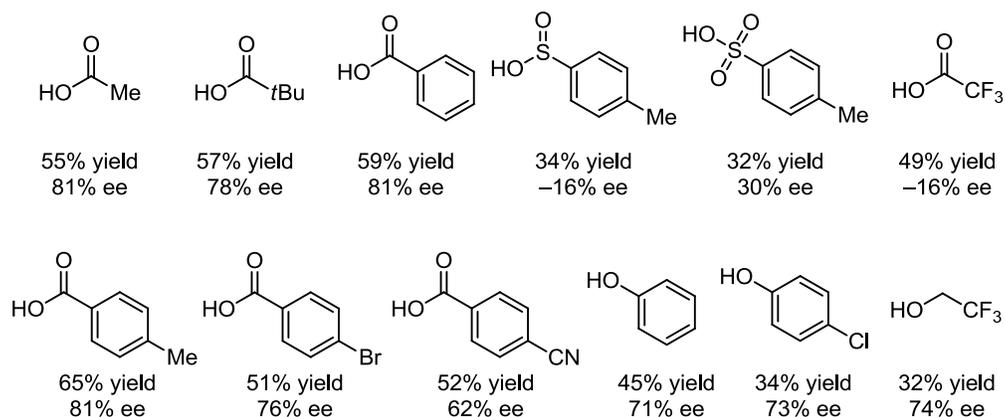
acidic additives such as trifluoroacetic acid caused significant decreases in the enantioselectivity of the reactions, while less acidic additives such as phenol were also less effective.

Table 3.4. Evaluation of Optimal Acid Co-Catalyst Conditions



entry	acid	x	y	yield	ee
1	AcOH	0	20	16	–
2	AcOH	5	5	15	75
3	AcOH	10	10	30	77
4	AcOH	20	20	55	81
5	AcOH	20	10	58	79
6	AcOH	10	20	76	73
7	–	20	0	34	68

Acid Screen: 20 mol% **11** and 20 mol% acid

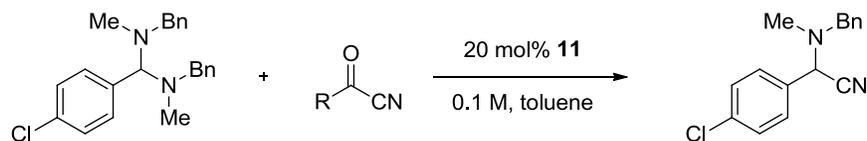


3.3.5. Optimization of Cyanide Source

Other commercially available acyl cyanide reagents were also evaluated as alternatives to acetyl cyanide for the cyanation reaction (Table 3.5). At $-70\text{ }^{\circ}\text{C}$, benzoyl cyanide and Mander's reagent only provided small amounts of the desired product (Table 3.5, entries 2–3). However,

at $-50\text{ }^{\circ}\text{C}$ all three acyl cyanide reagents provided increased yields. Acetyl cyanide was optimal with respect to the observed enantioselectivity for the transformation.

Table 3.5. Acyl Cyanide Optimization.



entry	temp ($^{\circ}\text{C}$)	time (h)	R	yield	ee
1	-70	4	Me	55	81
2	-70	4	Ph	7	n.d.
3	-70	4	OMe	13	n.d.
4	-50	13	Me	96	66
5	-50	13	Ph	96	59
6	-50	13	OMe	18	43

3.3.6. Catalyst Optimization

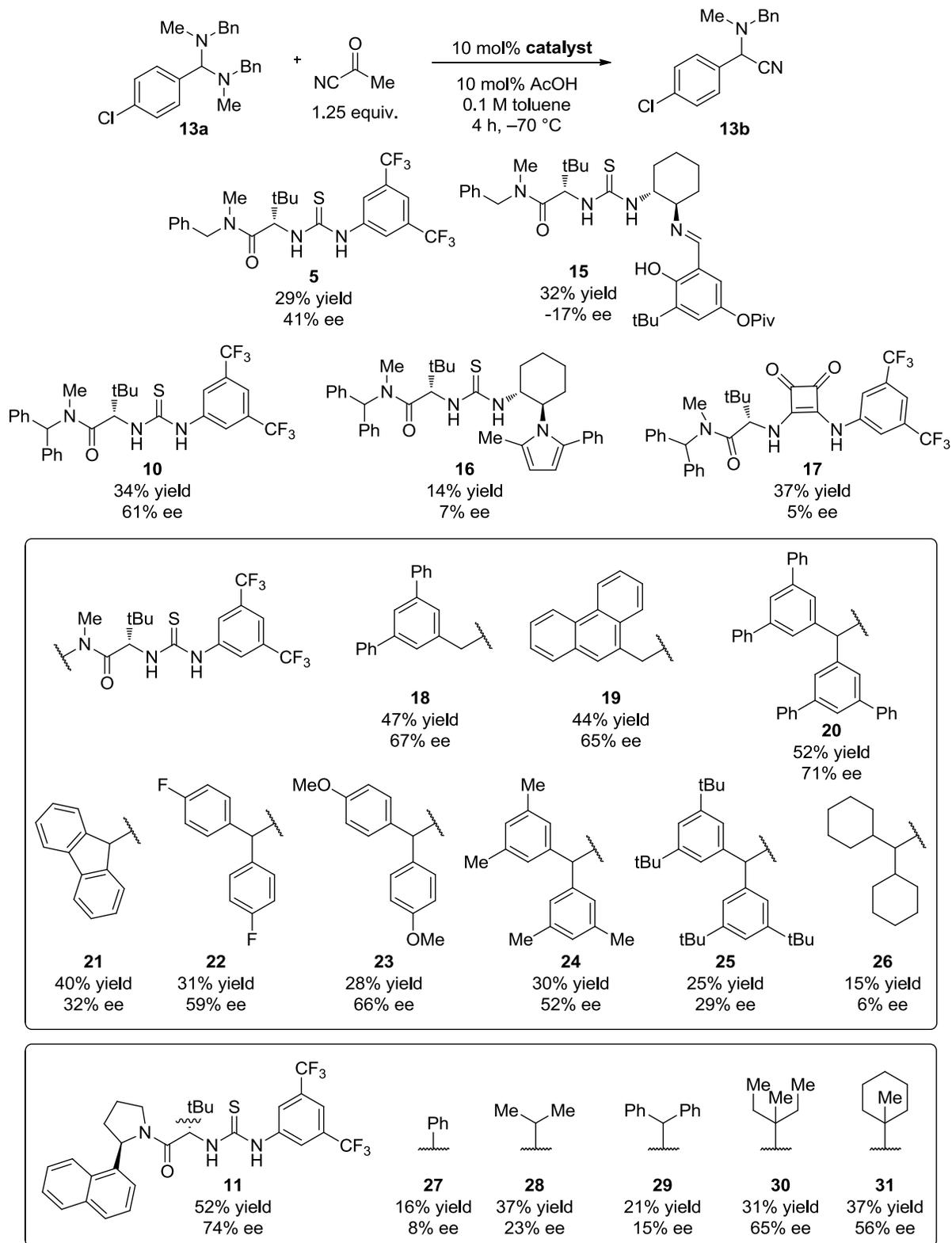
With optimal conditions identified, we evaluated the performance of a variety of dual H-bond donor catalysts for the cyanation of aminal **13a**. The catalysts of this class that have been developed in the Jacobsen group are modular in nature, with one side of the dual H-bond donor bearing an amino acid derived amide functionality and the other side bearing a range of functional groups, such as *N*-aryl groups, cyclohexylamino pyrroles, or salicaldehyde derived imines. We first varied the non-amino acid derived side of the catalyst and found that thioureas bearing *N*-aryl groups were optimal (Scheme 3.10, compare catalysts **5**, **15–17**). We then evaluated the effect of the amide portion of the catalyst and found that *N*-benzylmethyl and -benzhydrylmethyl amides were good catalysts for the transformation (Scheme 3.10, catalyst **5** and **10**). Increasing the size of the benzyl or benzhydryl group was beneficial with respect to the

enantioselectivity of the transformation (Scheme 3.10, catalyst **18–25**), but even catalysts with very large benzhydryl groups did not promote the reaction with high enantioselectivity. Catalysts bearing 1-naphthyl pyrrolidine moieties proved to be optimal for the transformation, with catalyst **11** providing the product in 74% ee.¹⁶

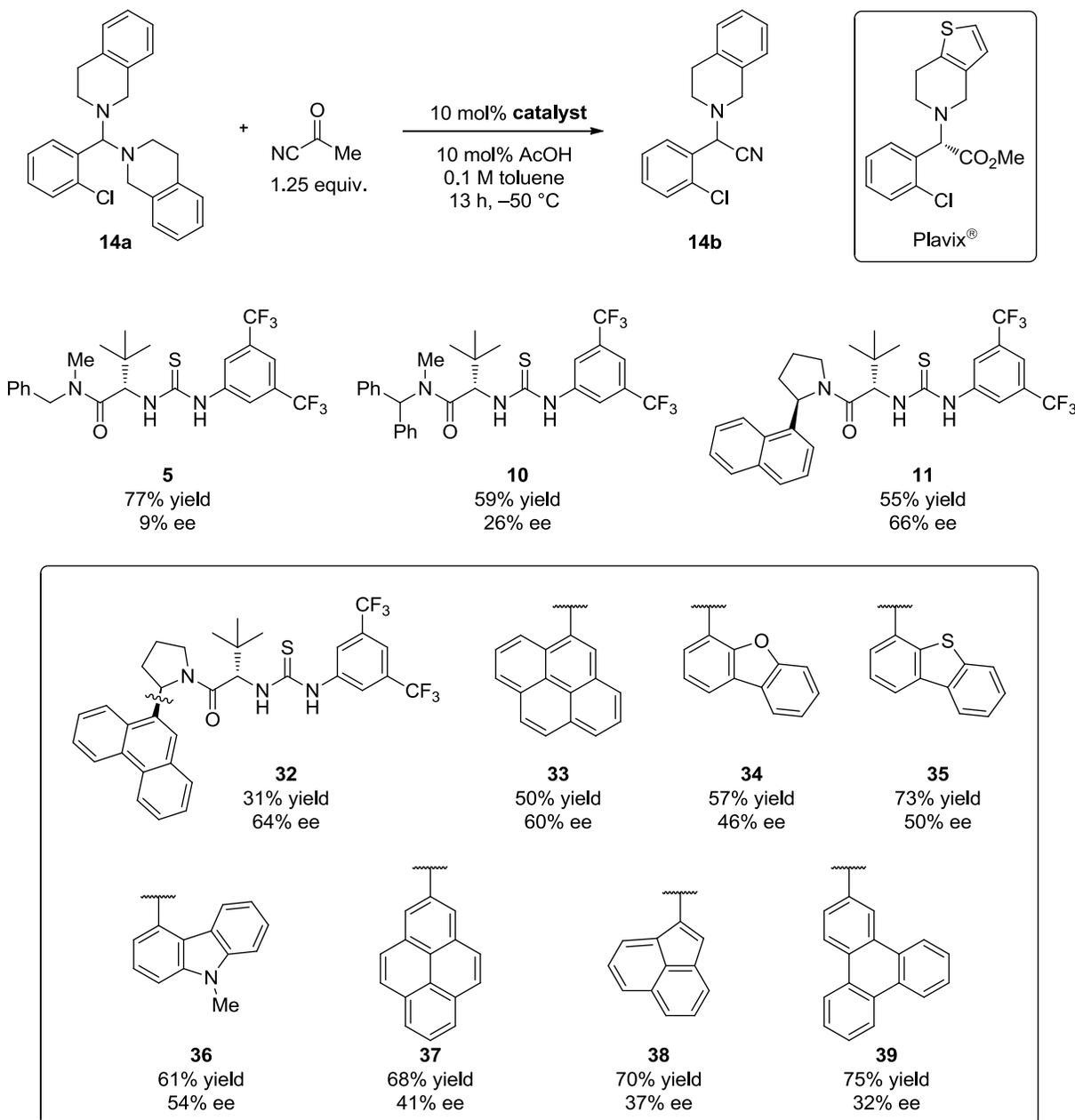
We carried out catalyst optimization for tetrahydroquinoline derived substrate **14a** as well in order to investigate whether catalyst trends that were observed for the *N*-benzylmethanamine derived substrate **13a** were general to a range of substrates. We were also particularly interested in the tetrahydroisoquinoline derived substrate due to its structural similarity to the blockbuster drug Plavix[®]. Catalysts bearing *N*-benzylmethyl and –benzhydrylmethyl amides catalyzed the reaction of aminal **14a** with low enantioselectivity (Scheme 3.11, catalysts **5** and **10**), while aryl pyrrolidine containing catalysts proved to be optimal for this substrate. A variety of catalysts bearing varied aryl groups were examined in the cyanation reaction and the 1-naphthyl pyrrolidine catalyst was found to be optimal (Scheme 3.11, catalysts **11** and **32–39**).

¹⁶ Catalysts with varied aryl pyrrolidine moieties were investigated for the cyanation of aminal **13a** under conditions without acid additives, and the 1-naphthyl aryl group was found to be optimal under those conditions.

Scheme 3.10. Catalyst Optimization



Scheme 3.11. Catalyst Optimization

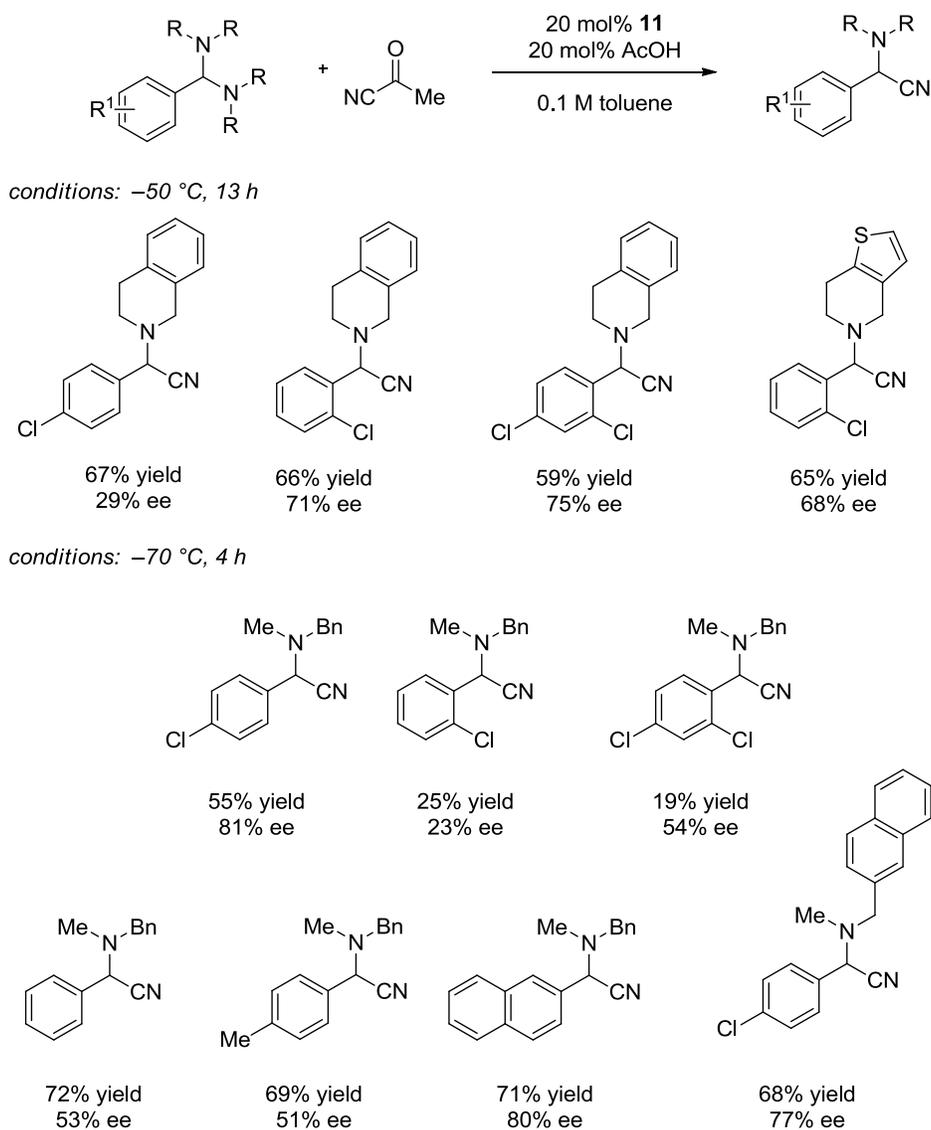


3.3.7. Evaluation of Substrate Scope and Limitations

We evaluated the substrate scope of the transformation (Scheme 3.12). A variety of tetrahydroisoquinoline and *N*-benzylmethylamine derived aminals undergo the cyanation reaction with moderate to good enantioselectivity. For tetrahydroisoquinoline derived aminals,

ortho-substitution on the benzaldehyde derived portion of the substrate is required for good enantioselectivity. In contrast, for *N*-benzylmethylamine derived amins, *ortho*-substitution on the benzaldehyde derived portion of the substrate leads to reduced enantioselectivity. The pronounced effect of substitution on the benzaldehyde portion of the substrate is difficult to understand, as changes in enantioselectivity cannot be easily attributed to steric or electronic variation.

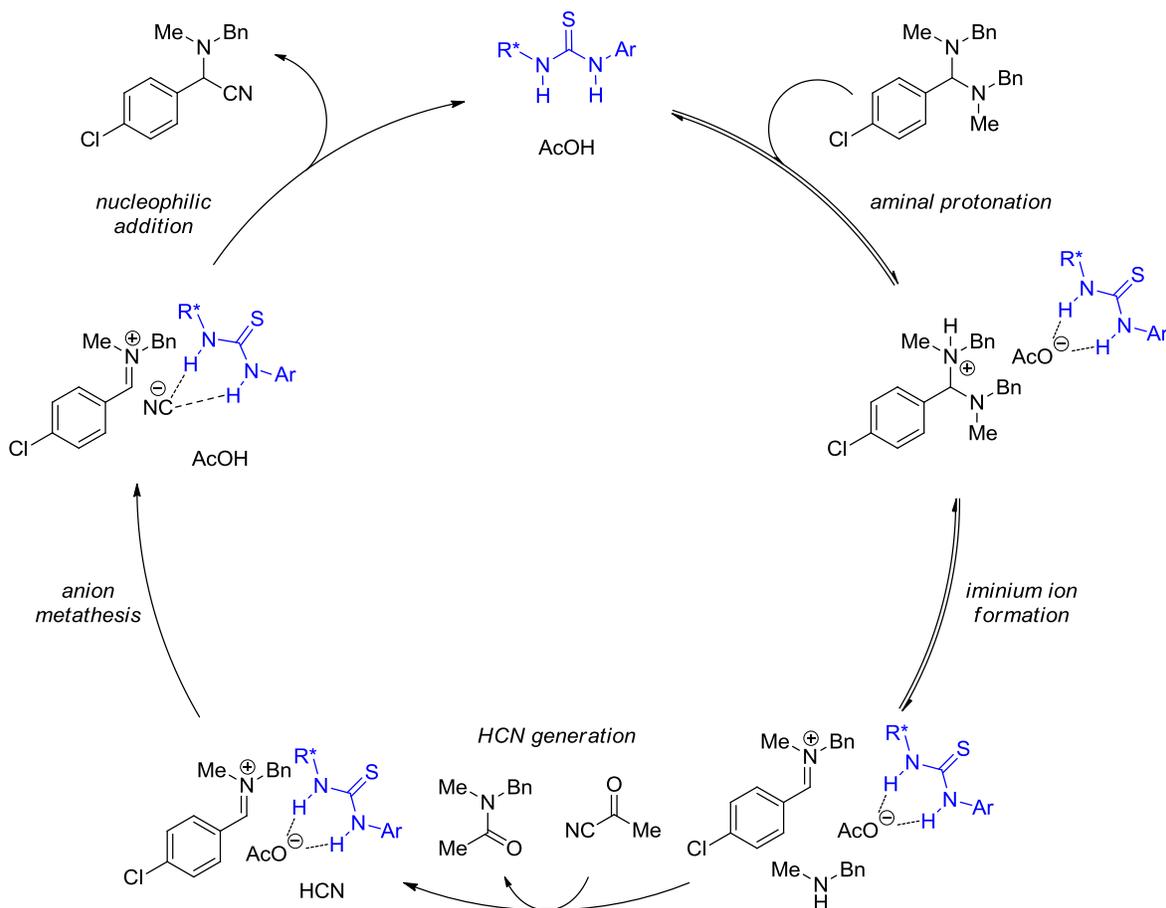
Scheme 3.12. Investigation of Substrate Scope and Limitations



3.3.8. Proposed Catalytic Cycle for Cyanation of Symmetrical Amino Substrates

A proposed catalytic cycle for the cyanation reaction is presented below (Scheme 3.13). We propose that the presence of acetic acid facilitates the breakdown of the amino starting material to the dialkyliminium acetate and *N*-benzylmethylamine. The generated 2° amine is much more nucleophilic than the amino, and can react with acetyl cyanide to generate hydrogen cyanide. Since reactions with a number of structurally diverse acids proceed with similar levels of enantioselectivity it seems unlikely that the acetate is intimately involved in the enantiodetermining step. We therefore propose the depicted anion metathesis prior to cyanide addition to the dialkyliminium intermediate.

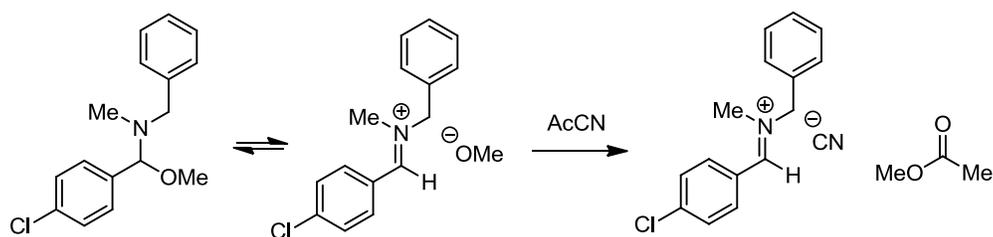
Scheme 3.13. Proposed Catalytic Cycle for Asymmetric Cyanation



3.3.9. Aminal Ethers as Precursors to *N,N*-Dialkyliminium Ions

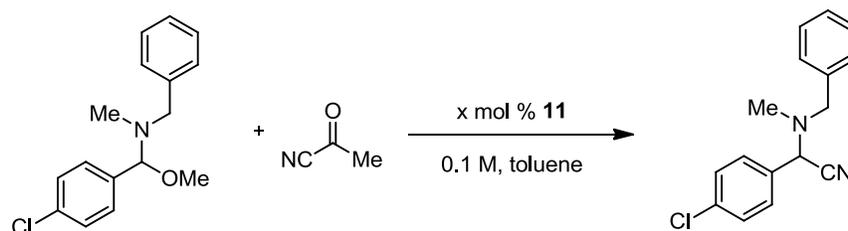
We also examined alternative routes for accessing dialkyliminium intermediates starting from aminal ether intermediates (Scheme 3.14). We anticipated that a thiourea catalyst could facilitate the ionization of the aminal ether via anion abstraction to generate a *N,N*-dialkyliminium methoxide intermediate. The methoxide could then react with acetyl cyanide to generate the cyanide anion which could add to the dialkyliminium intermediate.

Scheme 3.14. Access to *N,N*-Dialkyliminium Intermediates from Aminal Ether Substrates



Consistent with our hypothesis, the aminal ether did undergo the reaction to provide the desired cyanide addition product in good enantioselectivity in the presence of thiourea **11**. However, the reaction was very slow, and increasing the reaction temperature led to a significant decrease in enantioselectivity (Table 3.6). Perhaps the most cumbersome characteristic of this approach was the purification of the aminal ether starting materials, which limited our interest in this strategy for accessing *N,N*-dialkyliminium intermediates.¹⁷

¹⁷ Approaches for generating aminal ethers *in situ* were also examined, but were not successful.

Table 3.6. Enantioselective Cyanation from Aminal Ether Starting Materials

entry	temp (°C)	mol % 11	time (h)	yield	ee
1	-70	0	18	4	–
2	-70	20	18	12	87
3	-70	0	60	6	–
4	-70	20	60	31	86
5	-50	0	15	9	–
6	-50	20	15	35	75
7	-30	0	15	32	–
8	-30	20	15	67	66

We also evaluated this strategy using tethered aminal ether substrates. Due to the intramolecular nature of the alkoxide abstraction, higher temperatures were required for reactions of this substrate class. Although very little background reaction was observed, only low to moderate enantioselectivities were observed for a variety of substrates in the presence of number of aryl pyrrolidine containing catalysts (Scheme 3.15).

future development of new classes of H-bond donor catalysts may enable highly enantioselective additions to *N,N*-dialkyliminium ion intermediates using the strategies for accessing such intermediates developed here.

3.5. Experimental Section

3.5.1. General Information

General Procedure. Unless otherwise noted, all reactions were performed in flame-dried round-bottom flasks sealed with a rubber septum under a nitrogen atmosphere. Air and moisture sensitive liquids were transferred using stainless steel cannulae or syringes. Flash chromatography was performed using silica gel ZEOprep60 ECO 40-63 micron from American International Chemical, Inc.

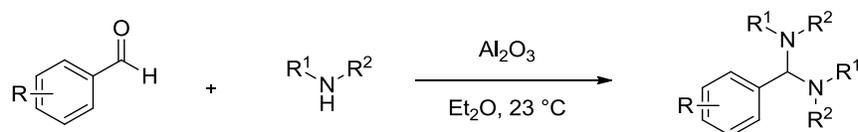
Materials. Commercial reagents were purchased from VWR, Acros, and Sigma-Aldrich and used as received with the following exceptions: dichloromethane and tetrahydrofuran were dried by passing through columns of activated alumina. Acetonitrile was dried by passing through a column of activated molecular sieves. Triethylamine and *N,N*-diisopropylethylamine were distilled from CaH₂ at 760 torr.

Instrumentation. Proton nuclear magnetic resonance (¹H NMR) spectra and carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded on a Varian Inova-500 (500 MHz) NMR spectrometer. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to the NMR solvent residual peak (CHCl₃: δ7.27). Chemical shifts for carbons are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the NMR solvent (CDCl₃: δ77.0). Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q

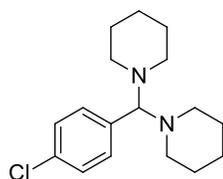
= quartet, p = pentet, m = multiplet), and coupling constants in Hertz (Hz). Mass spectroscopic (MS) data were obtained using an Agilent 6120 Single Quadrupole LC/MS instrument equipped with an ESI-APCI multimode source. Infrared (IR) spectra were obtained using a Bruker Tensor 27 FTIR spectrophotometer. Data are represented as follows: frequency of absorption (cm⁻¹), intensity of absorption (s = strong, m = medium, w = weak). Optical rotation data were obtained using a 1 mL cell with a 0.5 dm path length on a Jasco P-2000 polarimeter. Chiral HPLC analysis was performed using Agilent 1200 series instruments.

3.5.2. Preparation of Symmetrical Amino and Amino Ether Substrates

General Synthetic Scheme for Synthesis of Symmetrical Aminals



1,1'-((4-chlorophenyl)methylene)dipiperidine (7):

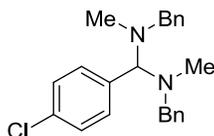


To a suspension of 4-chlorobenzaldehyde (2.8 g, 20 mmol) and chromatographic alumina (7g) in diethyl ether (15 mL) was added piperidine (5 mL, 50 mmol). The mixture was stirred overnight at room temperature. The resultant suspension was filtered through celite and concentrated *in vacuo* to yield the desired amino as a white solid in quantitative yield.¹⁸ If necessary, the amino can be purified by recrystallization from hexanes. ¹H NMR (500MHz, CDCl₃) δ = 7.29 (d, J =

¹⁸ Excess piperidine was removed *in vacuo*.

8.3 Hz, 2 H), 7.14 (d, $J = 8.3$ Hz, 2 H), 3.55 (s, 1 H), 2.29 (m, 8 H), 1.57 - 1.46 (m, 8 H), 1.41 - 1.31 (m, 4 H).

N,N'-dibenzyl-1-(4-chlorophenyl)-*N,N'*-dimethylmethanediimine:

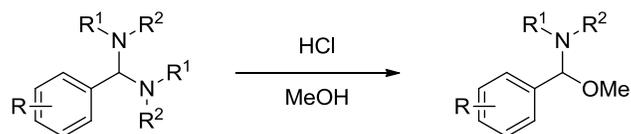


To a suspension of 4-chlorobenzaldehyde (700 mg, 5 mmol) and chromatographic alumina (1.7g) in diethyl ether (3.5 mL) was added *N*-benzylmethylamine (1.3 mL, 10 mmol). The mixture was stirred overnight at room temperature. The resultant suspension was filtered through celite and concentrated *in vacuo* to yield the desired aminal as a white solid in quantitative yield.¹⁹ If necessary, the aminal can be purified by recrystallization from hexanes. Often, the reaction would not proceed to full conversion. In those cases, it was useful to dissolve the crude aminal and remaining starting material in toluene and store over activated molecular sieves. ¹H NMR (500MHz, CDCl₃) $\delta = 7.50 - 7.2$ (m, 14 H), 3.98 (s, 1 H), 3.71 (d, 2 H), 3.61 (d, 2 H), 2.13 (s, 6 H).

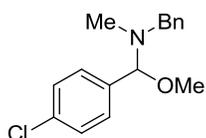
All other symmetrical aminals were synthesized via analogous procedures.

¹⁹ Excess piperidine was removed *in vacuo*.

General Synthetic Scheme for Synthesis of Amino Ether Substrates

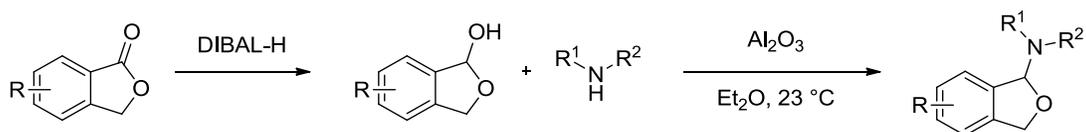


N-benzyl-1-(4-chlorophenyl)-1-methoxy-N-methylmethanamine:



Symmetrical aminal (2.26 g, 6.2 mmol) was dissolved in *n*-hexane containing methanol (0.5 mL, 12.4 mmol) and cooled to 0 °C. A 4 M solution of HCl in dioxane (1.55 mL, 6.2 mmol) was slowly added and the mixture was stirred at ambient temperature for 2 h. The precipitated amine hydrochloride was filtered off and washed with an additional portion of hexane. The clear solution was evaporated and the residual liquid was purified by distillation to yield to desired amino ether product.

All other amino ethers were synthesized via analogous methods.

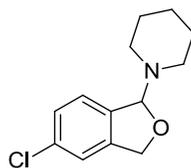


5-Substituted Phthalides were synthesized via previously reported methods.²⁰

Reduction of Phthalides with DIBAL-H was carried out according to previously reported methods.²¹ The resultant hemiacetals must be carried on to the amino ether formation immediately after purification to avoid decomposition.

²⁰ Faigl, F.; Thurner, A.; Molnár, B.; Simig, G.; Volk, B. *Org. Process Res. Dev.* **2010**, *14*, 617.

1-(5-chloro-1,3-dihydroisobenzofuran-1-yl)piperidine:



To a suspension of the hemiacetal (3 mmol) and chromatographic alumina (900 mg) in diethyl ether (2.0 mL) was added piperidine (0.446 mL, 4.5 mmol). The mixture was stirred overnight at room temperature. The resultant suspension was filtered through celite and concentrated *in vacuo* to yield the desired aminal as a white solid in quantitative yield. $^1\text{H NMR}$ (500MHz, CDCl_3) δ = 7.29 - 7.22 (m, 2 H), 7.19 (s, 1 H), 5.92 (s, 1 H), 4.99 (s, 2 H), 2.67 - 2.50 (m, 4 H), 1.58 - 1.40 (m, 6 H)

All other tethered aminal ether substrates were synthesized via analogous procedures. For substrates bearing amines that cannot be removed *in vacuo* a 1:1 ratio of amine and hemiacetal must be used.

3.6.3. Procedure for Thiourea-Catalyzed Cyanation Reaction

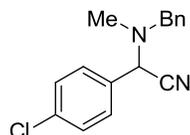
General Procedure for Symmetrical Aminal Substrates

Symmetrical aminal (0.1 mmol) and catalyst (0.02 mmol) are dissolved in toluene (1 mL) in a 1 dram vial equipped with a small football-shaped stirbar. Acetic acid (0.02 mmol) is added, and the mixture is cooled to $-78\text{ }^\circ\text{C}$. With stirring, acetyl cyanide (0.125 mmol) is added. The mixtures are stirred at $-70\text{ }^\circ\text{C}$ for 4 h. The reaction is quenched at $-78\text{ }^\circ\text{C}$ by the addition of 2M hydrogen chloride (0.5 mL) and sodium borohydride (50 mg). The mixture is stirred at $-78\text{ }^\circ\text{C}$ for 30 minutes, then 20% aqueous potassium carbonate is added, and the mixture is warmed to

²¹ Mikami, K.; Ohmura, H. *Org. Lett.* **2002**, *4*, 3355.

room temperature. The mixtures are extracted with dichloromethane, dried over sodium sulfate and concentrated. 1,3,5-trimethoxybenzene (0.1 mmol) is added, and the yield is determined by ^1H NMR analysis.

2-(benzyl(methyl)amino)-2-(4-chlorophenyl)acetonitrile:

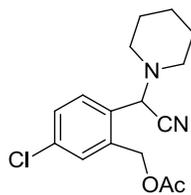


Following the general procedure 2-(benzyl(methyl)amino)-2-(4-chlorophenyl)acetonitrile was formed in 55% yield and 81% ee. ^1H NMR (500MHz, CDCl_3) δ = 7.52 - 7.47 (m, 2 H), 7.42 - 7.35 (m, 6 H), 7.34 - 7.29 (m, 1 H), 4.85 (s, 1 H), 3.83 (d, J = 12.8 Hz, 1 H), 3.57 (d, J = 13.3 Hz, 1 H), 2.32 - 2.24 (m, 3 H). ^{13}C NMR (126MHz, CDCl_3) δ = 137.2, 134.7, 132.4, 129.0, 128.9, 128.8, 128.7, 127.8, 114.8, 59.5, 59.3, 38.3. Enantiomers were resolved on Chiralcel AS-H column using 2% IPA in hexanes.

General Procedure for Amino Ether Substrates

Amino ether (0.1 mmol) and catalyst (0.02 mmol) are dissolved in toluene (1 mL) in a 1 dram vial equipped with a small football-shaped stirbar. Acetic acid (0.02 mmol) is added, and the mixture is cooled to -78 °C. With stirring, acetyl cyanide (0.125 mmol) is added. The mixtures are stirred at -70 °C. The reaction is quenched at -78 °C by the addition of 2M hydrogen chloride (0.5 mL) and sodium borohydride (50 mg). The mixture is stirred at -78 °C for 30 minutes, then 20% aqueous potassium carbonate is added, and the mixture is warmed to room temperature. The mixtures are extracted with dichloromethane, dried over sodium sulfate and concentrated. 1,3,5-trimethoxybenzene (0.1 mmol) is added, and the yield is determined by ^1H NMR analysis.

5-chloro-2-(cyano(piperidin-1-yl)methyl)benzyl acetate:



Key resonances from crude reaction mixture used for analysis. ^1H NMR (500MHz, Benzene) δ
= 5.07 (d, J = 13.2 Hz, 1 H), 4.89 (d, J = 13.7 Hz, 1 H), 4.55 (s, 1 H), 1.58 (s, 3 H).

Enantiomers were resolved on Chiralcel AS-H column using 5% IPA in hexanes.

Chapter 4

Enantioselective Thiourea-Catalyzed Intramolecular Cope-Type Hydroamination¹

4.1. Introduction

Enantioselective intramolecular olefin hydroamination² affords a direct and atom-economical synthetic approach to chiral nitrogen heterocycles with useful properties as biologically active compounds,³ small-molecule catalysts,⁴ and ligands.⁵ Significant advances in metal-catalyzed

¹ Portions of this chapter have been published: Brown, A. R.; Uyeda, C.; Brotherton, C. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2013**, *135*, 6747.

² For recent reviews on hydroamination see: (a) Chemler, S. R. *Org. Biomol. Chem.* **2009**, *7*, 3009. (b) Müller, T. E.; Hultsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. *Chem. Rev.* **2008**, *108*, 3795.

³ (a) Hensler, M. E.; Bernstein, G.; Nizet, V.; Nefzi, A. *Biorg. Med. Chem. Lett.* **2006**, *16*, 5073. (b) Li, X.; Li, J. *Mini-Rev. Med. Chem.* **2010**, *10*, 794. (c) Lexa, K. W. *Proteins* **2011**, *79*, 2282. (d) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748. (e) Cole, D. C.; Lennox, W. J.; Lombardi, S.; Ellingboe, J. W.; Bernotas, R. C.; Tawa, G. J.; Masandarani, H.; Smith, D. L.; Zhang, G.; Coupet, J.; Schechter, L. E. *J. Med. Chem.* **2005**, *48*, 353.

⁴ (a) Zhang, S.; Wang, W. *Privileged Chiral Ligands and Catalysts*; Zhou, Q.-L., Ed.; Wiley-VCH: Weinheim, Germany, 2011; pp 409–439. (b) Watson, A. J. B.; MacMillan, D. W. C. Enantioselective Organocatalysis Involving Iminium, Enamine SOMO and Photoredox Activation. In *Catalytic Asymmetric Synthesis*, 3rd ed.; Ojima, I.; Ed.; Wiley & Sons: Hoboken, NJ, 2010; pp 39–57.

asymmetric intramolecular hydroaminations have relied mostly on highly air- and moisture-sensitive lanthanide,⁶ group 4 metal (Zr, Ti),⁷ or highly electropositive main group metal (Mg, Li) complexes.⁸ Late transition metal-catalyzed hydroamination⁹ and carboamination¹⁰ reactions have been identified that hold promise for broader functional group tolerance and concomitant substrate generality.¹¹ Herein, strategies for accessing enantioenriched nitrogen heterocycles via enantioselective intramolecular hydroamination and carboamination are reviewed, and our research towards a thiourea catalyzed intramolecular Cope-type hydroamination is presented.

⁵ For a review of chiral amine ligands, see: Caputo, C. A.; Jones, N. D. *Dalton Trans.* **2007**, 4627.

⁶ (a) Giardello, M. A.; Conticello, V. P.; Brard, L.; Gagne, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1994**, *116*, 10241. (b) Hong, S.; Tian, S.; Metz, M. V.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 14768. (c) Kim, J. Y.; Livinghouse, T. *Org. Lett.* **2005**, *7*, 1737. (d) Collin, J.; Daran, J.; Jacquet, O.; Schulz, E.; Trifonov, A. *Chem. Eur. J.* **2005**, *11*, 3455. (e) Riegert, D.; Collin, J.; Meddour, A.; Schulz, E.; Trifonov, A. *J. Org. Chem.* **2006**, *71*, 2514 (f) Gribkov, D. V.; Hultsch, K. C.; Hampel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3748. (g) Chapurina, Y.; Ibrahim, H.; Guillot, R.; Kolodziej, E.; Collin, J.; Trifonov, A.; Schulz, E.; Hannedouche, J. **2011**, *76*, 10163.

⁷ (a) Knight, P. D.; Munslow, I.; O'Shaughnessy, P. N.; Scott, P. *Chem. Comm.* **2004**, 894. (b) Watson, D. A.; Chiu, M.; Bergman, R. G. *Organometallics* **2006**, *25*, 4731. (c) Wood, M. C.; Leitch, D. C.; Yeung, C. S.; Kozak, J. A.; Schafer, L. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 354. (d) Gott, A. L.; Clarke, A. J.; Clarkson, G. J.; Scott, P. *Organometallics*, **2007**, *26*, 1729. (e) Zi, G.; Liu, X.; Xiang, L.; Song, H. *Organometallics*, **2009**, *28*, 1127. (f) Manna, K.; Xu, S.; Sadow, A. D. *Angew. Chem., Int. Ed.* **2011**, *50*, 1865.

⁸ (a) Martinez, P. H.; Hultsch, K. C.; Hampel, F. *Chem. Comm.* **2006**, 2221. (b) Ogata, T.; Ujihara, A.; Tsuchida, S.; Shimizu, T.; Kaneshige, A.; Tomioka, K. *Tetrahedron Lett.* **2007**, *48*, 6648. (c) Zhang, X.; Emge, T. J.; Hultsch, K. C. *Angew. Chem., Int. Ed.* **2012**, *51*, 394.

⁹ (a) Shen, X.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 564. (b) Turnpenny, B. W.; Hyman, K. L.; Chemler, S. R. *Organometallics* **2012**, *31*, 7819.

¹⁰ (a) Yip, K.-T.; Yang, M.; Law, K.-L.; Zhu, N.-Y.; Yang, D. *J. Am. Chem. Soc.* **2006**, *128*, 3130. (b) Zeng, W.; Chemler, S. R. *J. Am. Chem. Soc.* **2007**, *129*, 12948. (c) Zeng, W.; Chemler, S. R. *J. Org. Chem.* **2008**, *73*, 6045. (d) Duy, M. N.; Wolfe, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 12157. (e) Liwosz, T. W.; Chemler, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 2020. (f) Hopkins, B. A.; Wolfe, J. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 9886.

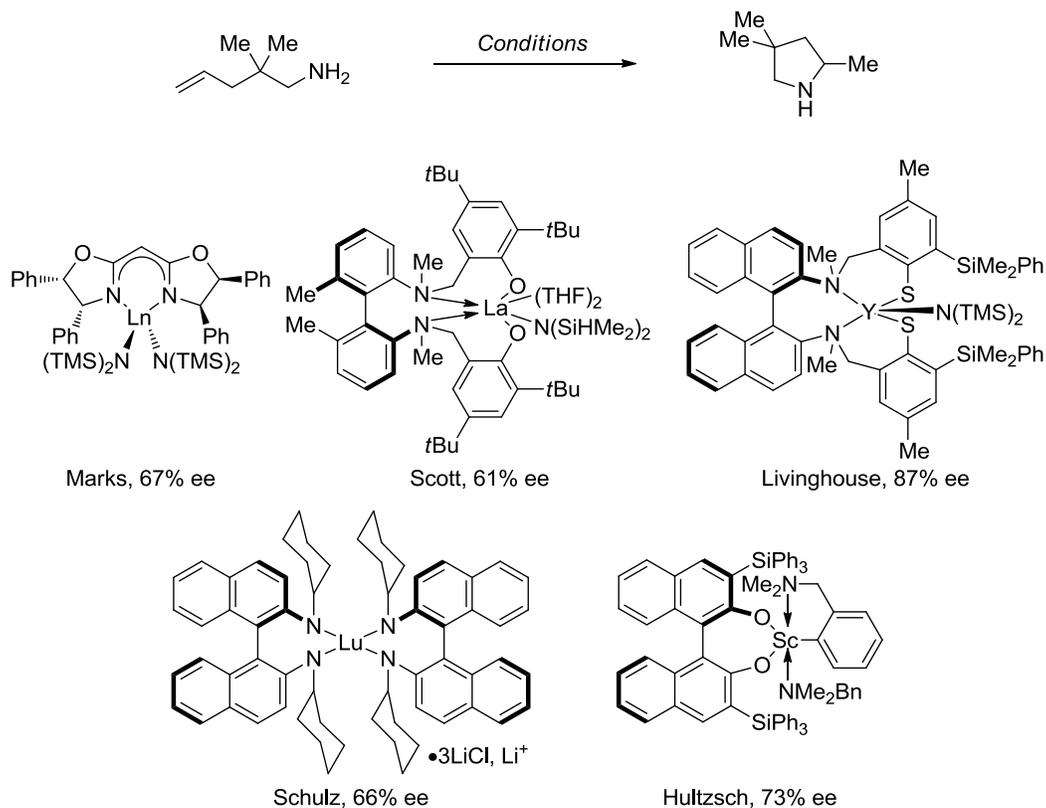
¹¹ Asymmetric hydroaminations of allenes and dienes have also been identified that proceed under mild reaction conditions: (a) Hamilton, G. L.; Kang, E. J.; Mba, M.; Toste, F. D. *Science* **2007**, *317*, 496. (b) LaLonde, R. L.; Sherry, B. D.; Kang, E. J.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 2453. (c) Zhang, Z.; Bender, C. F.; Widenhofer, R. A. *Org. Lett.* **2007**, *9*, 2887. (d) Zhang, Z.; Bender, C. F.; Widenhofer, R. A. *J. Am. Chem. Soc.* **2007**, *129*, 14148. (e) Kanno, O.; Kuriyama, W.; Wang, Z. J.; Toste, F. D. *Angew. Chem., Int. Ed.* **2011**, *42*, 9919. (f) Shapiro, N. D.; Rauniyar, V.; Hamilton, G. L.; Wu, J.; Toste, F. D. *Nature*. **2011**, *470*, 245.

4.2. Strategies for Asymmetric Intramolecular Hydroamination

4.2.1. Rare-Earth Metal-Catalyzed Hydroaminations

Seminal work in asymmetric intramolecular olefin hydroamination was carried out by Marks and coworkers. In 1994, a hydroamination catalyzed by a cyclopentadienyl containing C_1 -symmetric chiral organolanthanide was reported that proceeded with moderate enantioselectivity.^{6a} These systems provided the first examples of catalytic asymmetric olefin hydroamination, but the chiral catalyst complexes were not configurationally stable in the presence of protic amines, which complicated their analysis and limited their utility. Almost a decade later, the same group reported that configurationally stable chiral bis(oxazoline) lanthanide complexes are also capable of catalyzing asymmetric hydroaminations.^{6b} Mechanistic study of the system revealed rate and enantiodetermining Ln–N alkene insertion. Since these initial reports by Marks, a number of other groups have reported rare-earth metal-catalyzed asymmetric intramolecular hydroaminations, some of which proceed with high enantioselectivity (Scheme 4.1).^{6c–g}

Scheme 4.1. Chiral Lanthanide Ligand Complexes for Hydroamination



4.2.2. Group 4 Metal-Catalyzed Hydroaminations

Over the past ten years, a number of group 4 metal-catalyzed asymmetric intramolecular hydroaminations have been developed, most of which are catalyzed by zirconium or titanium complexes. The first example of this class of transformation was reported by Scott and coworkers in 2004 (Figure 4.1).^{7a} In this pioneering work, secondary amines were found to cyclize with moderate enantioselectivity in the presence of a cationic zirconium catalyst. This system was not compatible with primary amines, however, presumably due to catalyst deactivation via the formation of a zirconium imido species. Shortly after the report by Scott, the groups of Bergman and Schafer independently reported zirconium catalyzed intramolecular hydroaminations with primary amine substrates (Figure 4.1).^{7b-c} Higher enantioselectivities

were reported by Schafer, but only terminal olefin substrates with β -quaternary carbons were included. Bergman reported the results for a wider range of substrates, but the enantioselectivities observed were only moderate. More recently, Sadow and coworkers have developed a chiral oxazolinylborate zirconium complex that that promotes the highly enantioselective hydroamination of a number primary aminoalkenes (Figure 4.1).^{7f} Similar to Schafer's report, only terminal olefin substrates with geminal disubstitution at the 2-position reacted. Although the mechanistic properties of a number of these zirconium mediated transformations have been investigated, a consistent mechanistic picture has not yet emerged.

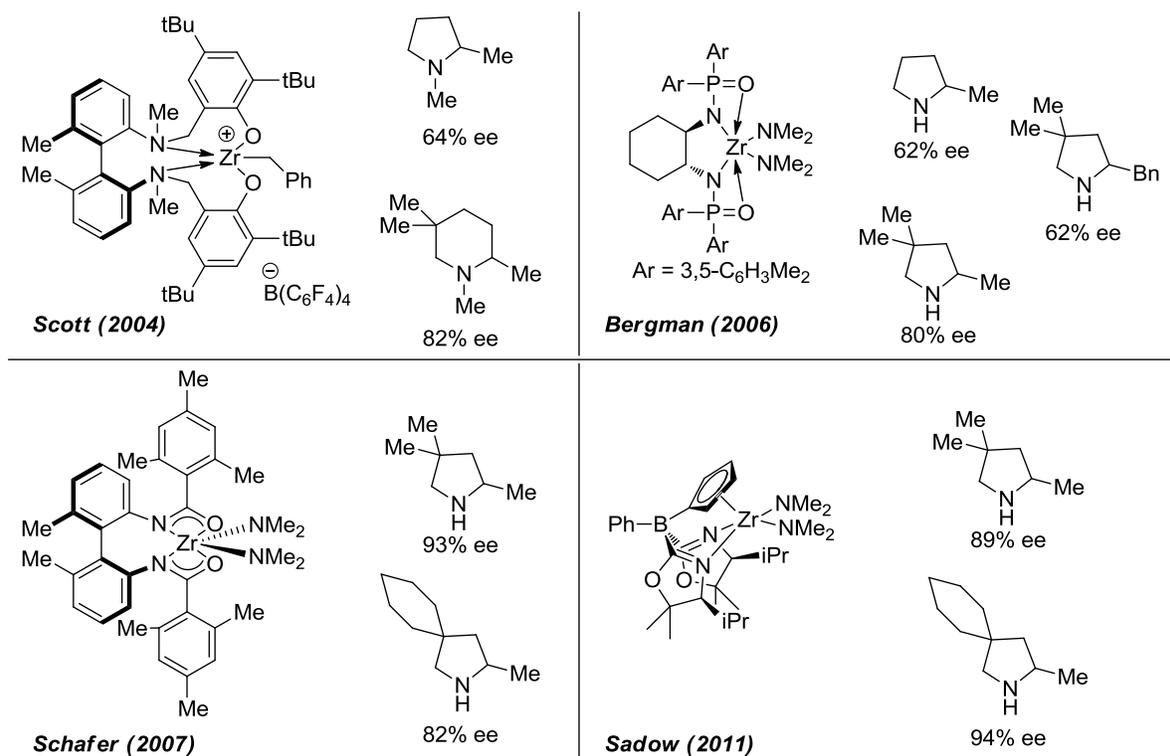


Figure 4.1. Selected Zirconium-Catalyzed Asymmetric Hydroaminations

4.2.3. Main Group Metal-Catalyzed Hydroaminations

Recently, main group metal-catalyzed hydroaminations have appeared in the literature. In 2006, the Hultsch group reported a lithium-based hydroamination using diamidobinaphthyl ligands that provided hydroamination products with moderate enantioenrichment.^{8a-b} In a subsequent report, the same group showed that phenoxyamine magnesium catalysts are impressive catalysts for intramolecular hydroamination.^{8c} These catalysts promote the transformation of a number aminoalkenes with moderate to excellent enantioselectivity (Figure 4.2).

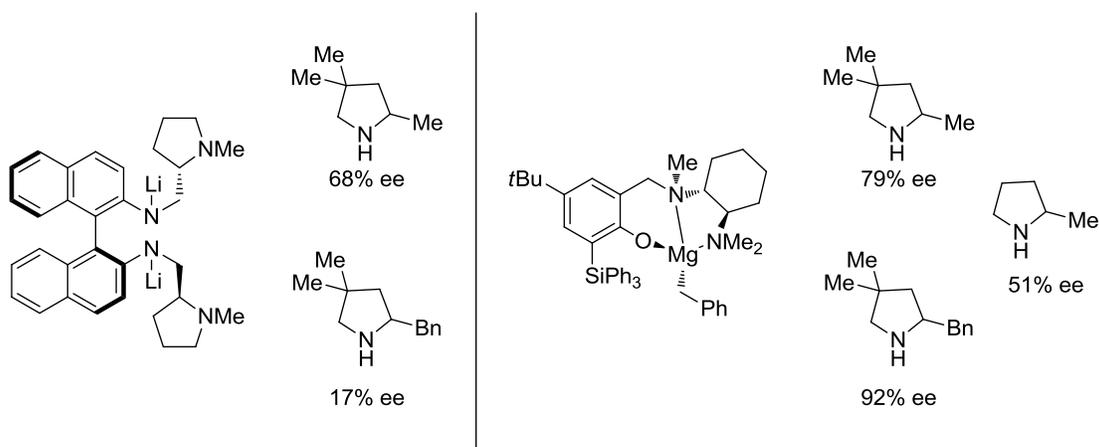


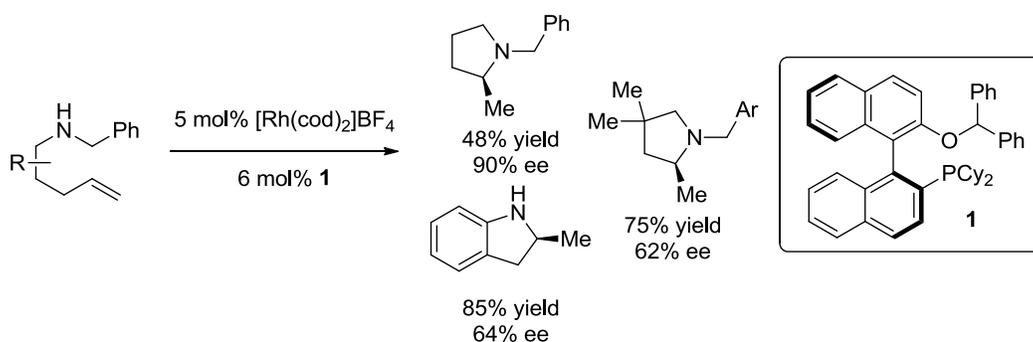
Figure 4.2. Hultsch's Main Group Metal-Catalyzed Hydroaminations

4.2.4. Late Transition Metal-Catalyzed Hydroaminations

The metal-catalyzed asymmetric intramolecular hydroaminations discussed thus far have relied mostly on highly air- and moisture-sensitive lanthanide, group 4 metal (Zr, Ti), or highly electropositive main group metal (Mg, Li) complexes. Late transition metal catalyzed hydroaminations would provide functional group tolerant alternatives to the previously discussed systems. However, until very recently this class of metals had not been shown to catalyze

intramolecular asymmetric hydroaminations. In 2011, Buchwald and coworkers reported a rhodium-catalyzed method for the hydroamination of *N*-benzyl aminoalkenes.^{9a} Buchwald's method provides a variety of α -methyl pyrrolidine products with moderate to good enantiomeric excess, but is limited to terminal olefin substrates (Scheme 4.2). More recently, Chemler and coworkers demonstrated that intramolecular hydroaminations of sulfonamides can be catalyzed by chiral copper complexes to yield electronically varied indoline products.^{9b} These pioneering studies indicate that late-metal catalyzed hydroaminations may soon be synthetically relevant strategies for the construction of chiral nitrogen heterocycles.

Scheme 4.2. Buchwald's Rhodium-Catalyzed Hydroamination



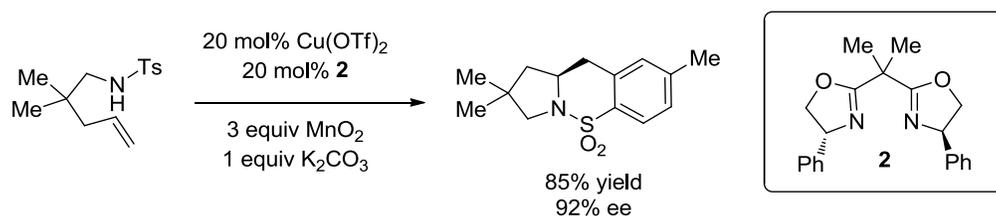
4.3. Late Transition Metal-Catalyzed Carboamination

Asymmetric intramolecular carboamination is a synthetic route to chiral nitrogen heterocycles that is complementary to hydroamination. These transformations forge new carbon-nitrogen and carbon-carbon bonds in the addition reaction of amines to olefins. Known asymmetric reactions of this type are catalyzed by late transition metals, and therefore proceed under synthetically convenient conditions and have broad functional group compatibility.

Chemler and coworkers reported an early example of an asymmetric carboamination reaction in 2007, which was promoted by a copper bis(oxazoline) complex (Scheme 4.3).^{10b} The

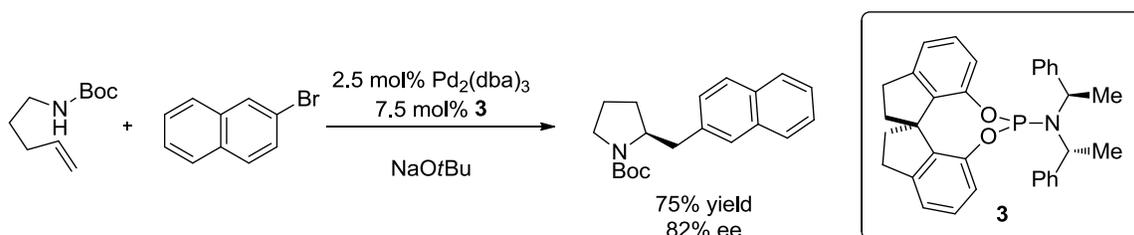
reaction provides chiral polycyclic sultams, which can be reduced to the corresponding pyrrolidine. A range of sulfonamide starting materials undergo the carboamination reaction with good to excellent enantioselectivities, and the utility of the method has been demonstrated in an application to the total synthesis of (+)-tylophorine.^{10c}

Scheme 4.3. Chemler's Copper-Catalyzed Carboamination



More recently, Wolfe and coworkers have reported a palladium catalyzed asymmetric carboamination reaction in which aryl bromides are used as the carbon source for the carbon-carbon bond being formed in the transformation.^{10d} This modular approach to 2-benzyl pyrrolidines proceeds with good yields and enantioselectivities for a range of substrates (Scheme 4.4).

Scheme 4.4. Wolfe's Palladium-Catalyzed Carboamination



Late metal catalyzed hydroaminations and carboaminations have begun to address the need for functional group tolerant asymmetric additions of amines to olefins. Despite the elegance and utility of these systems, they are limited in their substrate scope and the level of

enantioselectivity that is observed. Further research towards asymmetric olefin aminofunctionalization is therefore warranted.

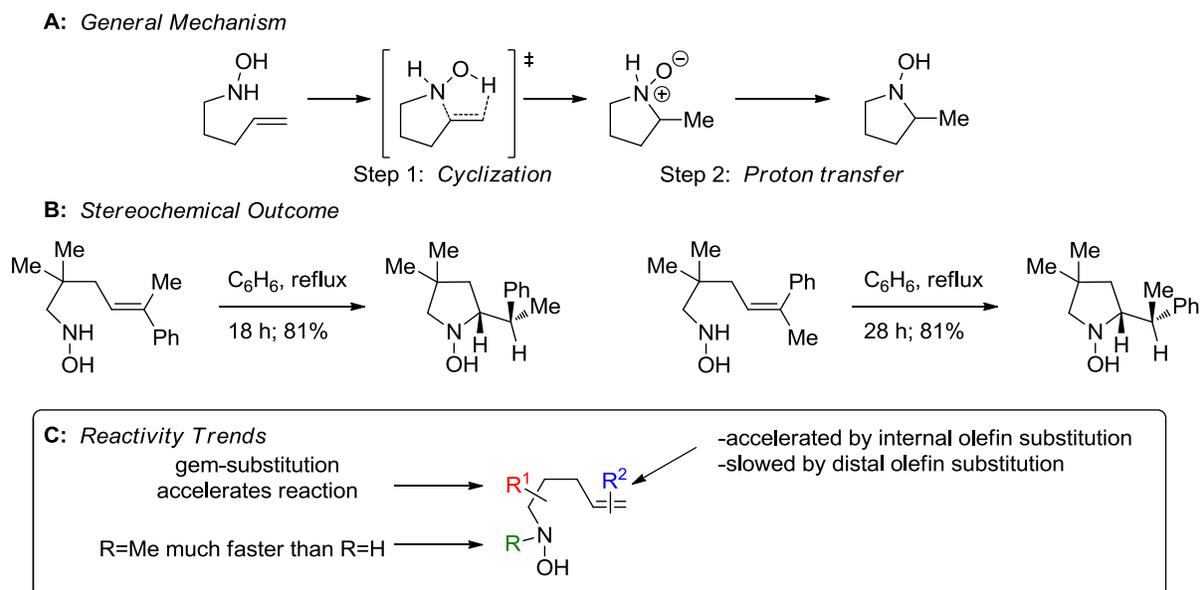
4.4. The Reverse Cope Elimination

The reverse Cope elimination reaction (Scheme 4.5) represents a mechanistically distinct alternative to metal-catalyzed processes for alkene hydroamination. In this type of transformation, a hydroxylamine undergoes reaction with an olefin in a pericyclic pathway involving concerted C–H and C–N bond formation (Scheme 4.5A). The transformation was first discovered serendipitously, and was first reported by House and coworkers in 1976.¹² After some dispute about the mechanism of the transformation, strong evidence for a concerted mechanism was provided by Oppolzer and coworkers in 1994. In an elegant set of experiments, Oppolzer showed that one olefin isomer of starting material is converted to one diastereomer of product, while the opposite olefin isomer is converted to the opposite diastereomer of product (Scheme 4.5B).¹³ Therefore, the cyclization involves suprafacial formation of C–N and C–H bonds via a planar five-membered transition state. The mechanism of the reverse Cope elimination is, as its name implies, the microscopic reverse of the Cope elimination. The forward reaction is therefore termed a Cope-type hydroamination.

¹² For a review on the transformation see: (a) Copper, N. J.; Knight, D. W. *Tetrahedron* **2004**, *60*, 243. See also: (b) House, H. O.; Manning, D. T.; Melillo, D. G.; Lee, L. F.; Haynes, O. R.; Wilkes, B. E. *J. Org. Chem.* **1976**, *41*, 855. (c) House, H. O.; Lee, L. F. *J. Org. Chem.* **1976**, *41*, 863. (d) Black, D. St. C.; Doyle, J. E. *Aust. J. Chem.* **1978**, *31*, 2317. (e) Oppolzer, W.; Siles, S.; Snowden, R. L.; Bakker, B. H.; Petrzilka, M. *Tetrahedron Lett.* **1979**, *20*, 4391.

¹³ Oppolzer, W.; Spivey, A. C.; Bochet, C. G. *J. Am. Chem. Soc.* **1994**, *116*, 3139.

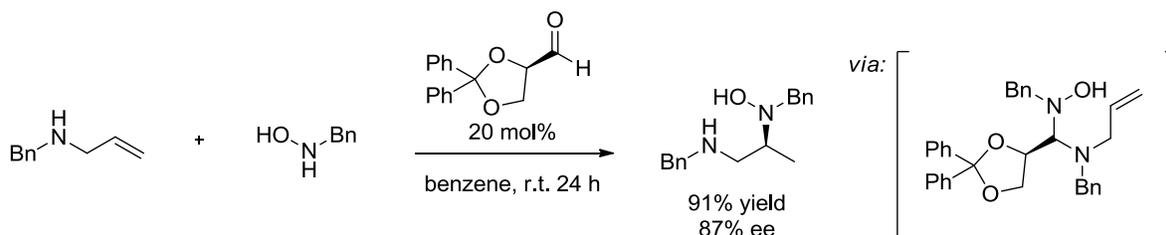
Scheme 4.5. The Reverse Cope Elimination



Recently, Beauchemin and coworkers have applied the reverse Cope elimination to asymmetric catalytic intermolecular hydroamination via an elegant tethering strategy.¹⁴ By using such a strategy, intermolecular reactions are temporarily rendered intramolecular, allowing for faster reaction rates due to the high relative concentration of reactants in the tethered system. Beauchemin's catalytic tethering agent is an aldehyde, and the reactants are therefore tethered via the intermediacy of an amination. When a chiral aldehyde is used as a catalyst, good enantioselectivities are observed for the intermolecular hydroamination (Scheme 4.6).

¹⁴ (a) MacDonald, M. J.; Schipper, D. J.; Ng, P. J.; Moran, J.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2011**, *133*, 20100. (b) Guimond, N.; MacDonald, M. J.; Lemieux, V.; Beauchemin, A. M. *J. Am. Chem. Soc.* **2012**, *134*, 16571.

Scheme 4.6. Intermolecular Cope-Type Hydroamination via Temporary Intramolecularity



4.5. Results and Discussion

Protic solvents have been shown to accelerate the Cope-type hydroamination,¹⁵ and computational studies have identified specific stabilizing H-bonding interactions in the polar cyclization transition structure to account for this effect.¹⁶ We considered whether ureas and thioureas, which have demonstrated utility as enantioselective dual hydrogen-bond donor catalysts, could facilitate the Cope-type hydroamination in a similar manner.¹⁷ In order to evaluate this hypothesis, we analyzed the effect of a simple thiourea on the reaction coordinate for the Cope reaction using DFT methods (Figure 4.3).¹⁸ This analysis predicts that the thiourea lowers the activation barrier for the cyclization by 3.1 kcal/mol, thereby supporting the hypothesis that this family of H-bond donors could serve as viable catalysts for the hydroamination reaction.

¹⁵ (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.

¹⁶ Acevedo, O.; Jorgensen, W. L. *J. Am. Chem. Soc.* **2006**, *128*, 6141.

¹⁷ For acceleration of the Claisen rearrangement by a similar strategy see: (a) Curran, D. P.; Kuo, L. H. *Tetrahedron Lett.* **1995**, *36*, 6647. (b) Kirsten, M.; Rehbein, J.; Hiersemann, M.; Strassner, T. *J. Org. Chem.* **2007**, *72*, 4001.

¹⁸ DFT calculations were carried out by Dr. Christopher Uyeda.

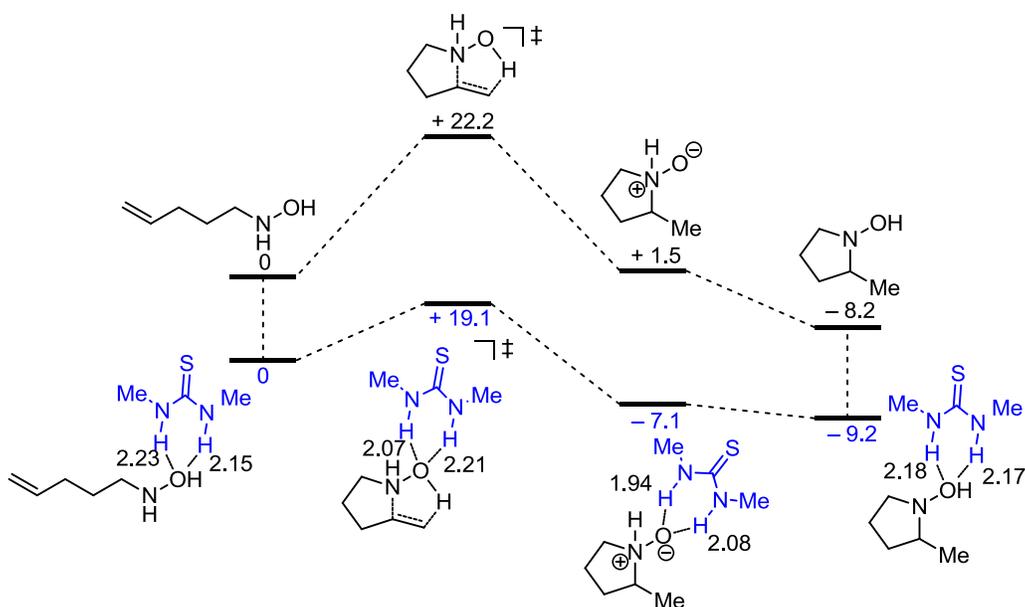


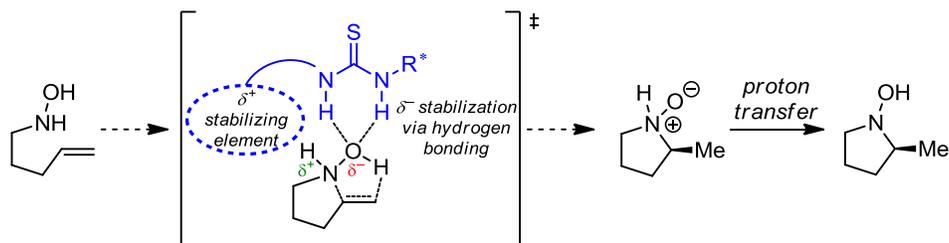
Figure 4.3. Calculated electronic energies for the optimized structures of the substrate, transition state, N-oxide intermediate, and product for both an uncatalyzed (black, top) and a N,N'-dimethylthiourea-catalyzed (blue, bottom) Cope hydroamination reaction (B3LYP/6-311+G(d, p) level of DFT). Relative energies are in kcal/mol and key hydrogen bonding distances are shown in Angstroms.

The principle we applied to the design of chiral catalysts for the Cope hydroamination is outlined in Scheme 4.7. In prior work on enantioselective catalytic Claisen rearrangements,¹⁹ the combined effect of hydrogen-bonding and secondary stabilization in the dipolar transition structure was shown to underlie the observed rate acceleration and asymmetric induction.²⁰ We reasoned that the polar character of the Cope-type hydroamination transition structure might render it susceptible to analogous cooperative, attractive, non-covalent interactions with the appropriate polyfunctional catalyst framework.

¹⁹ (a) Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 9228. (b) Uyeda, C.; Rötheli, A. R.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 9753.

²⁰ Uyeda, C.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 5062.

Scheme 4.7. Design Strategy for Enantioselective Cope-Type Hydroamination Catalyst

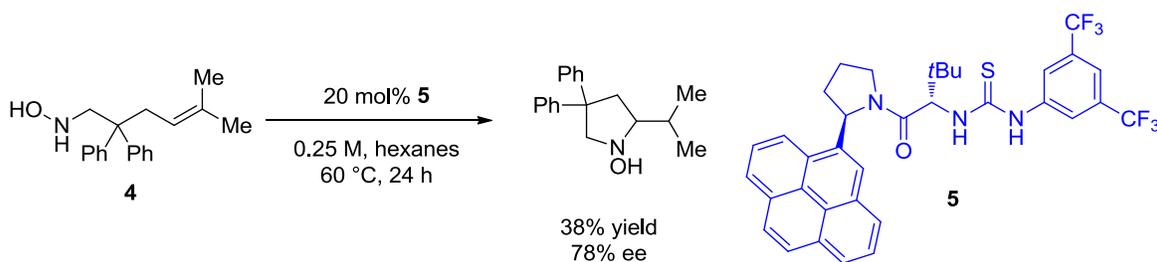


4.5.1. Preliminary Experiments

with Carolyn Brotherton

We carried preliminary experiments to explore the validity of our hypothesis that dual H-bond donors are capable of catalyzing the Cope-type hydroamination. After some preliminary catalyst screening and reaction optimization, we found that hydroxylamine **4** cyclized in the presence of thiourea **5** to give moderately enantioenriched product. Although we observed high conversion for the transformation, the yield was quite low, likely due to product decomposition or side reactions at the elevated temperatures required for the cyclization.

Scheme 4.8. Discovery of Asymmetric Catalysis for the Cope-Type Hydroamination



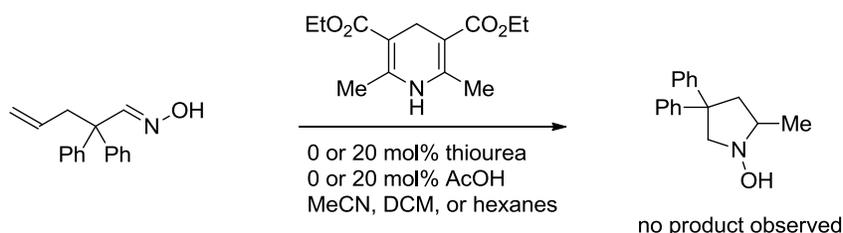
4.5.2. *In situ* Hydroxylamine Generation

We synthesized a variety of hydroxylamine products that we anticipated would cyclize at lower temperatures than hydroxylamine **4**. Although we were successful in synthesizing such substrates, it was difficult to isolate the hydroxylamine starting material and subject it to the

desired catalytic reaction conditions without background thermal cyclization occurring. We realized that a system that allowed *in situ* generation of the hydroxylamine starting material would be necessary.

Our synthetic route toward the hydroxylamine starting material involved a final step oxime reduction to generate the desired hydroxylamine using sodium cyanoborohydride in glacial acetic acid. Since these conditions were not compatible for enantioselective catalysis with thioureas, we sought to identify reduction conditions that would be compatible. We examined Hantzsch's ester as an *in situ* reducing agent under a variety of conditions, but the desired cyclization product was never observed (Scheme 4.9).

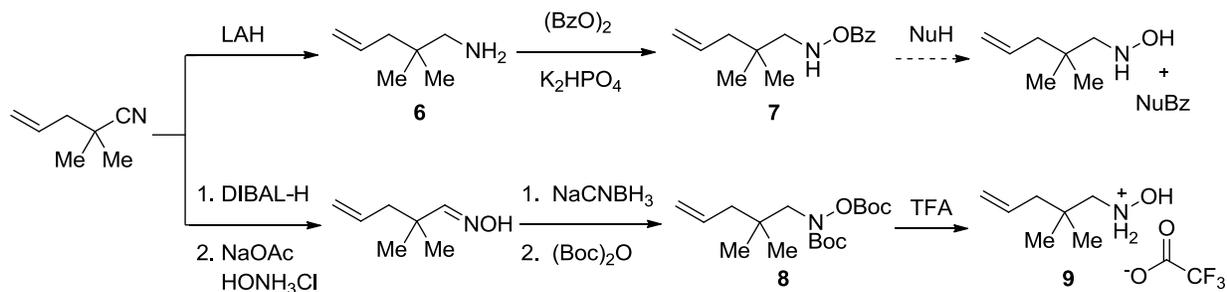
Scheme 4.9. Attempted *in situ* Oxime Reduction



Two other options for *in situ* hydroxylamine formation were also considered (Scheme 4.10), both of which were compatible with our synthetic strategy for accessing the hydroxylamine starting materials. The first involved oxidation of the parent amine **6** using benzoyl peroxide to reveal an *O*-benzoylated hydroxylamine **7**. Treatment with a strong nucleophile would reveal the desired hydroxylamine *in situ*. A number of nucleophiles were examined, but none were successful in cleaving the benzoyl group. The second strategy involved the intermediacy of a bis-Boc protected hydroxylamine **8**, which could be deprotected under acidic conditions to give the salt of the hydroxylamine **9**. The salt could be converted to the desired hydroxylamine starting material under basic conditions. Preliminary NMR experiments confirmed this strategy

as no cyclization of the trifluoroacetate salt was observed in CDCl_3 at room temperature, but upon addition of triethylamine rapid cyclization was observed.

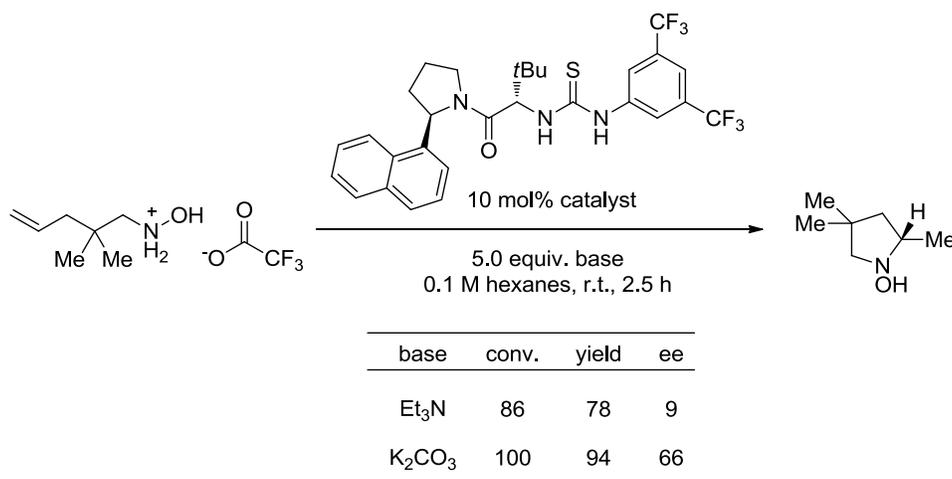
Scheme 4.10. Strategies for *in situ* Hydroxylamine Generation



The *in situ* strategy was examined in the context of the catalytic reaction conditions (Table 4.1). The addition of amine bases and inorganic bases revealed the hydroxylamine and led to efficient product formation. The use of triethylamine as the base for the deprotonation led to much lower enantioselectivity for the hydroamination than when solid inorganic potassium carbonate was used. Alkyl ammonium salts are known to bind to thioureas via anion binding,²¹ and we therefore attribute the low enantioselectivities with triethylamine to counterproductive interactions between the catalyst and the triethyl ammonium trifluoroacetate salt. Potassium trifluoroacetate likely has very low solubility in hexanes and therefore does not have a negative effect on the reaction.

²¹ Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198.

Table 4.1. *In situ* Hydroxylamine Generation Under Catalytic Conditions



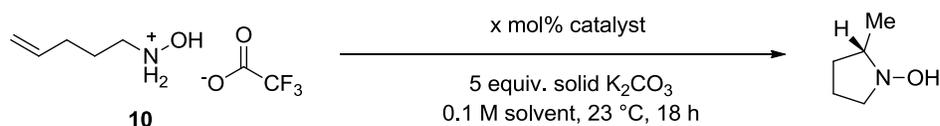
The *in situ* hydroxylamine generation was tested for a number of other substrates, and it proved to be rather general. The method is limited to substrates that are stable to the Boc deprotection conditions. Substrates containing electron rich olefins, such as trisubstituted olefins, decomposed under the Boc deprotection conditions. Terminal olefin substrates were well tolerated, as were (*E*)-styrenyl olefin substrates that did not have electron donating substituents on the aryl ring.

4.5.3. Reaction Optimization

Preliminary solvent and catalyst optimization was carried out on unfunctionalized hydroxylamine **10** (Table 4.2). We found that highly nonpolar solvents were optimal, with hexanes being the superior solvent. Although cyclohexane and pentane were not tested as solvents for the cyclization of hydroxylamine **10**, we found that these solvents performed similarly to hexanes for the hydroamination of various other substrates. Our initial catalyst screening revealed that catalysts with pyrrole motifs were superior to their 3,5-bis(trifluoromethyl)phenyl analogues (Table 4.2, compare catalyst **11a** and **12a**), and that aryl

pyrrolidine catalysts performed well for the transformation (Table 4.2, compare catalyst **11a** and **11c**). Combining these two elements led to the discovery of an improved catalyst **12c**.

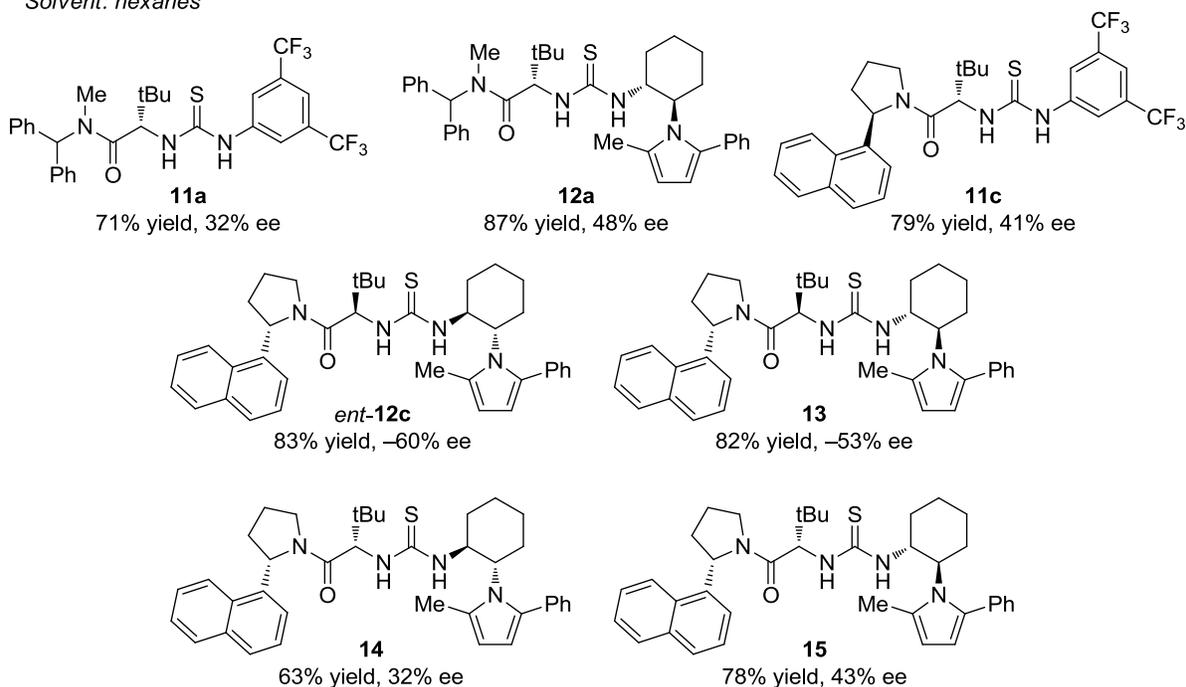
Table 4.2. Preliminary Reaction Optimization for Unfunctionalized Hydroxylamine Salt **10**



entry ^a	catalyst	mol% catalyst	solvent	yield (%) ^b	ee (%) ^c
1	—	0	hexanes	25	—
2	11c	10	hexanes	79	41
3	11c	10	toluene	84	29
4	11c	10	TBME	42	4
5	11c	10	THF	41	0

^a Reactions were quenched by the addition of *p*-NO₂ benzoyl chloride. ^b Yields of the *O*-benzoylated products were determined by ¹H NMR analysis using mesitylene as an internal standard. ^c Determined by HPLC analysis using commercial chiral columns.

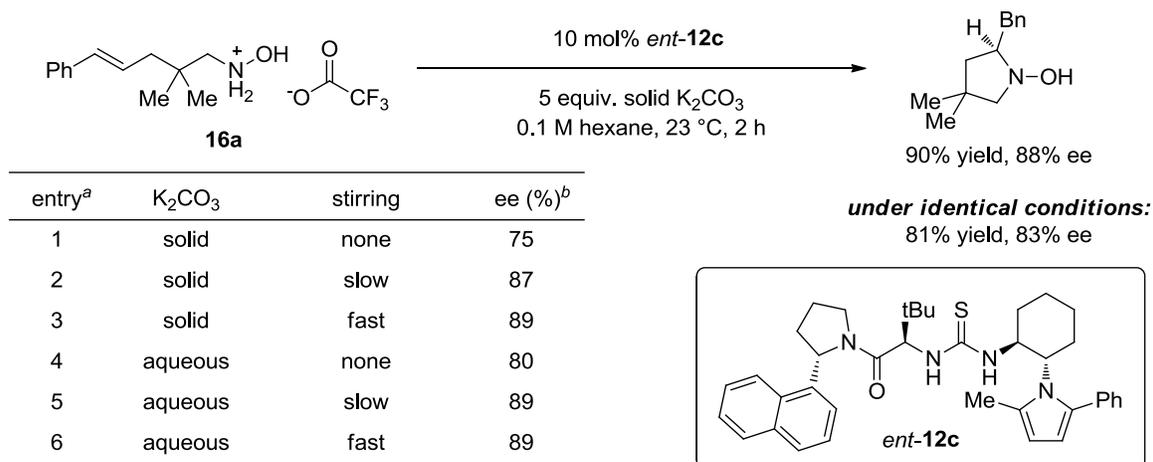
Solvent: hexanes



The fact that catalyst **12c** was capable of inducing moderate levels of enantioselectivity for highly unfunctionalized substrate **10** was encouraging. We investigated the hydroamination in

the context of a number of different substrates with varied olefin substitution patterns. The first group of substrates we tested were hydroxylamines with (*E*)-styrenyl olefins.

Table 4.3. Stirring Rate Affects Enantioselectivity for Hydroamination



^a Reactions were quenched by the addition of *p*-NO₂ benzoyl chloride. ^b Determined by HPLC analysis using commercial chiral columns.

(*E*)-Styrenyl olefin substrate **16a** cyclized with high enantioselectivity in the presence of catalyst *ent-12c*. However, we repeated the reaction and observed substantially lower enantioselectivity for that reaction. Due to the heterogeneous nature of the reaction, we tested the effect of stirring on the reaction enantioselectivity, and we found it to be highly dependent on stirring rate (Table 4.3). Reaction mixtures that were not stirred produced product with significantly less enantioenrichment. We also examined the 20% aqueous potassium carbonate as a base, and found that the enantioselectivity of reactions under these conditions were less sensitive to stirring rate.²² Moving forward, reactions were set up with aqueous potassium carbonate as the base and were stirred vigorously.

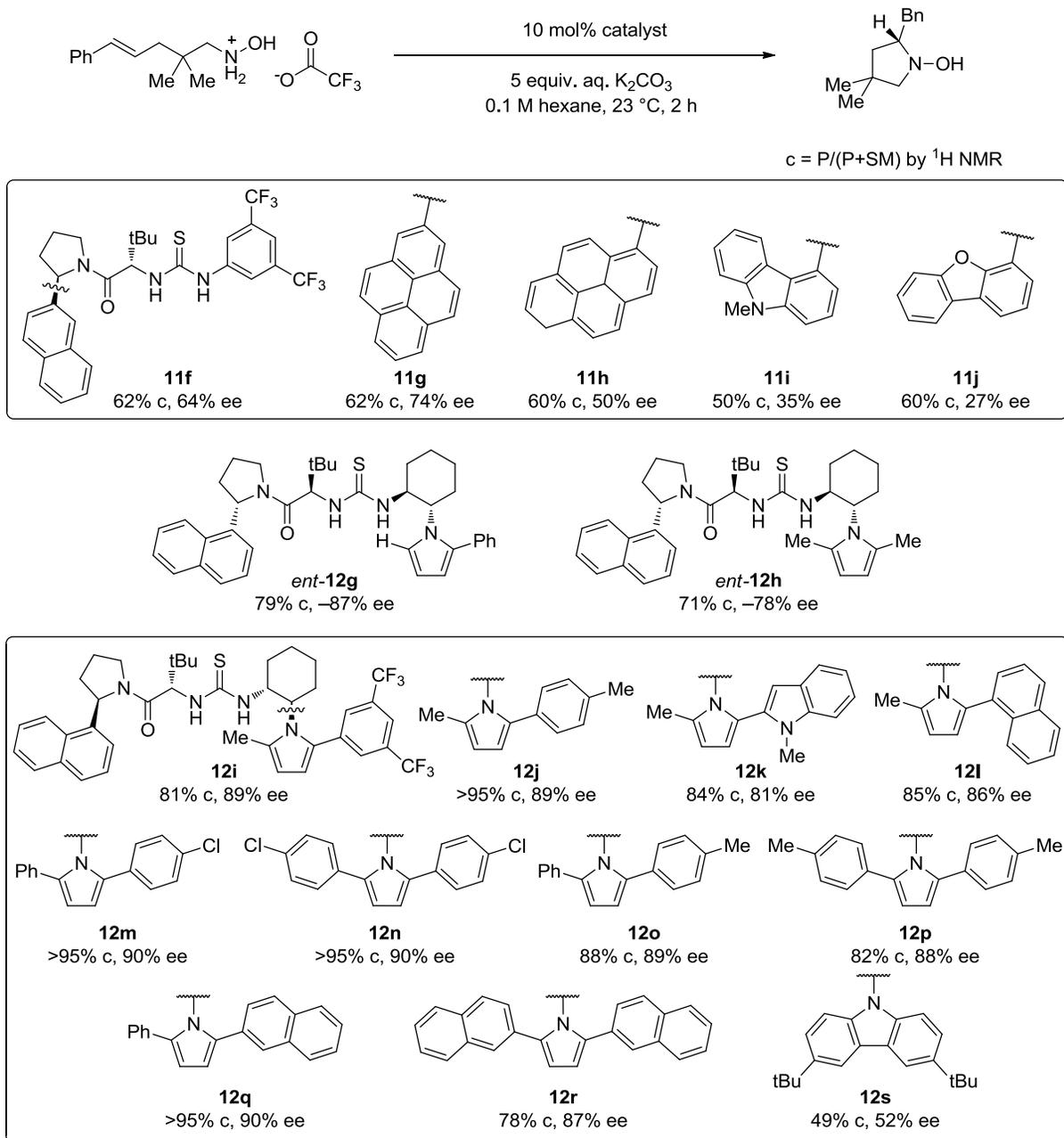
²² Unsubstituted substrate **10** was not compatible with the aqueous basic conditions, presumably due to solubility in the aqueous phase.

The cyclization of hydroxylamine **16a** was evaluated in the presence of a variety of thiourea catalysts bearing polarizable and conformationally constrained aromatic components (Table 4.4). While catalysts **11a–b** (Table 4.4, entries 2–3) provided modest acceleration over the background uncatalyzed reaction, catalysts containing electron rich π -systems, such as extended arenes or aryl-pyrroles, led to more significant rate enhancements. For catalysts **11b–11e** (Table 1, entries 3–6), an increase in yield and enantioselectivity was observed as the expanse of the α -aryl group of the pyrrolidine was increased. Comparable correlations between arene expanse and rate and enantioselectivity have been observed previously for this class of catalysts (**11c–11e**) in the context of polyene cyclizations and episulfonium ion ring-openings.²³ In these systems, stabilizing cation- π interactions between the catalyst arene and the cationic transition state were identified.

Catalysts bearing aryl-pyrrole components capable of similar interactions were also found to be effective and highly enantioselective catalysts for the model transformation (Table 4.4, compare entries 2 and 7). For catalysts containing both a pyrrole and an α -aryl pyrrolidine moiety, the level of enantioinduction was relatively insensitive to the size of the aryl group on the pyrrolidine portion of the catalyst (Table 4.4, entries 8–11). These results suggest that catalyst-transition state interactions with the aryl-pyrrole are stronger than those with the aryl pyrrolidine for this class of catalysts. After extensive optimization of these structural motifs (Scheme 4.11), thiourea **12f** was identified as the optimal catalyst for the hydroamination.

²³ (a) Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030. (b) Lin, S.; Jacobsen, E. N. *Nat. Chem.* **2012**, *4*, 817.

Scheme 4.11. Further Catalyst Optimization



Reactions were quenched by the addition of *p*-NO₂ benzoyl chloride.

4.5.4. Evaluation of Substrate Scope

With the optimal catalyst identified, the substrate scope of the hydroamination reaction was evaluated. Several 4-alkenyl-1-hydroxylamines bearing electronically diverse (*E*)-styryl groups

underwent cyclization in the presence of thiourea **12f** in good yields and moderate to excellent enantioselectivities (Table 4.5, entries 1-10). Substrates bearing electron-rich arenes reacted at much lower rates than those with electron-deficient arenes. *Ortho*, *meta*, and *para* substitution on the arene were all well tolerated (Table 4.5, entries 3, 6 and 7), as were halogen- and oxygen-containing functionalities (Table 4.5, entries 3 and 5). Substrates with geminal disubstitution at the 2-position reacted more rapidly and with higher enantioselectivity than substrates lacking such groups (Table 4.5, entries 1, 8, and 9), presumably as a result of a favorable Thorpe–Ingold effect in the cyclization reaction. Terminal olefin substrate **16j** also underwent cyclization to the desired pyrrolidine product, albeit with slightly lower enantioselectivity than the corresponding styrenyl analogues (Table 4.5, entries 11-12). The catalytic efficiency of the system is also notable, as the catalyst loading could be decreased from 10 to 2 mol% with only slight diminution of enantioselectivity (Table 4.5, entry 2).

Table 4.5. Scope of Cope-Type Hydroamination


entry	R	R ¹	product	time (h)	temp (°C)	yield ^b	ee ^c
1	C ₆ H ₅	Me	18a	12	3	83	94
2 ^d	C ₆ H ₅	Me	18a	72	3	79	92
3	<i>p</i> -ClC ₆ H ₄	Me	18b	5	3	87	95
4	<i>p</i> -(Me)C ₆ H ₄	Me	18c	36	3	84	87
5	<i>p</i> -(OMe)C ₆ H ₄	Me	18d	96	3	96	91
6	<i>o</i> -ClC ₆ H ₄	Me	18e	5	3	91	92
7	<i>m</i> -ClC ₆ H ₄	Me	18f	5	3	87	94
8	C ₆ H ₅	-CH ₂ (CH ₂) ₃ CH ₂ -	18g	5	3	82	96
9	C ₆ H ₅	H	18h	72	30	68	81
10	<i>p</i> -ClC ₆ H ₄	H	18i	36	30	93	83
11	H	Me	18j	2	3	86	78
12 ^e	H	Me	18j	2	3	91	85

^a Reactions were performed on a 0.18-0.25 mmol scale, and were quenched by the addition of *p*-NO₂ benzoyl chloride. For entries 1-3, 6-8, and 11-12 the hydroxylamine was generated *in situ* from the corresponding trifluoroacetate salt by addition of aqueous potassium carbonate.

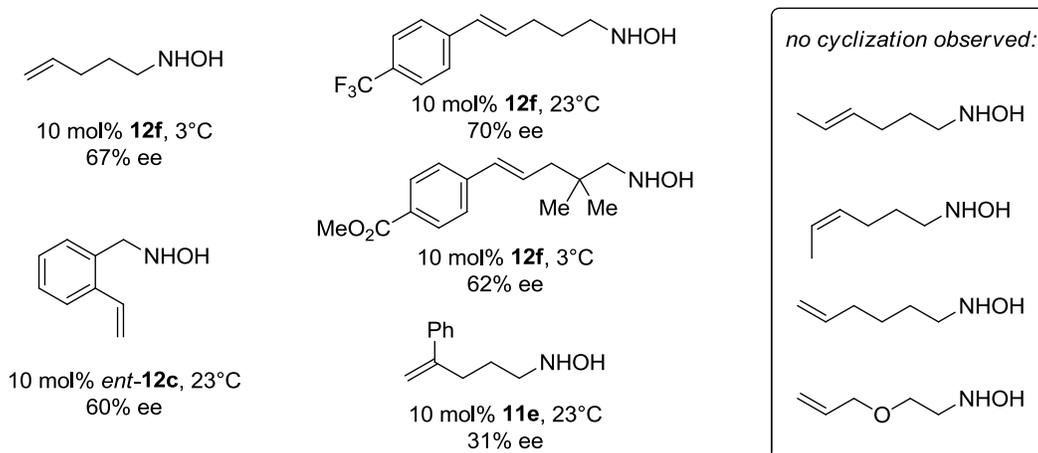
^b Isolated yield of *O*-benzoylated products after purification on silica gel. ^c Determined by HPLC analysis of *O*-benzoylated products using commercial chiral columns. ^d 2 mol% of **12f** was used.

^e 10 mol% of **11e** was used as the catalyst.

A number of other substrates were also examined. Some failed to cyclize, and others cyclized with moderate enantioselectivity (Figure 4.4). Substrates leading to piperidine products failed to cyclize, as did substrates with olefins containing dialkyl substitution. The enantioselective cyclization of the trisubstituted olefin is particularly notable, as asymmetric hydroaminations of this class of olefin are quite rare.²⁴

Figure 4.4. Selected Suboptimal Substrates

²⁴Chapurina, Y.; Ibrahim, H.; Guillot, R.; Kolodziej, E.; Collin, J.; Trifonov, A.; Schulz, E.; Hannedouche, J. *J. Org. Chem.* **2011**, *76*, 10163



4.6. Conclusions

In conclusion, we have developed a highly enantioselective thiourea-catalyzed Cope-type hydroamination that provides access to a variety of pyrrolidine products under mild reaction conditions. A striking correlation between the electronics of the olefin and the rate of the Cope-type hydroamination reaction was observed. An understanding of this observation would likely shed light on the character of the cyclization transition state. Further, thiourea catalysts capable of stabilizing the dipolar transition structure in the pericyclic reaction via multiple non-covalent interactions were found to be most effective for catalysis and enantioinduction. Elucidation of the specific catalyst-substrate interactions at play could be applied to future catalyst-design strategies.

4.7. Experimental Section

4.7.1. General Information

General Procedure. Unless otherwise noted, all reactions were performed in flame-dried round-bottom flasks sealed with a rubber septum under a nitrogen atmosphere. Air and moisture sensitive liquids were transferred using stainless steel cannulae or syringes. Flash chromatography was performed using silica gel ZEOprep60 ECO 40-63 micron from American International Chemical, Inc.

Materials. Commercial reagents were purchased from VWR, Acros, and Sigma-Aldrich and used as received with the following exceptions: dichloromethane and tetrahydrofuran were dried by passing through columns of activated alumina. Acetonitrile was dried by passing through a column of activated molecular sieves. Triethylamine and *N,N*-diisopropylethylamine were distilled from CaH_2 at 760 torr.

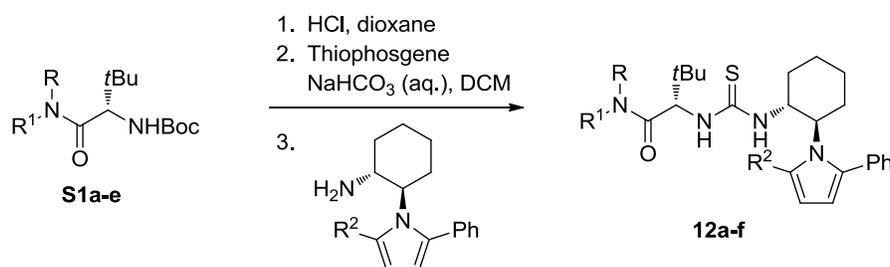
Instrumentation. Proton nuclear magnetic resonance (^1H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian Inova-500 (500 MHz) NMR spectrometer. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to the NMR solvent residual peak (CHCl_3 : $\delta 7.27$). Chemical shifts for carbons are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the NMR solvent (CDCl_3 : $\delta 77.0$). Data are represented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet), and coupling constants in Hertz (Hz). Mass spectroscopic (MS) data were obtained using an Agilent 6120 Single Quadrupole LC/MS instrument equipped with an ESI-APCI multimode source. Infrared (IR) spectra were obtained using a Bruker Tensor

27 FTIR spectrophotometer. Data are represented as follows: frequency of absorption (cm⁻¹), intensity of absorption (s = strong, m = medium, w = weak). Optical rotation data were obtained using a 1 mL cell with a 0.5 dm path length on a Jasco P-2000 polarimeter. Chiral HPLC analysis was performed using Agilent 1200 series instruments.

4.7.2. Catalyst Preparation and Characterization Data

Catalysts **11a-e** were synthesized via previously reported methods. The spectral data matched those reported in the literature.²⁵

General synthetic route for the preparation of catalysts **12a-f**.

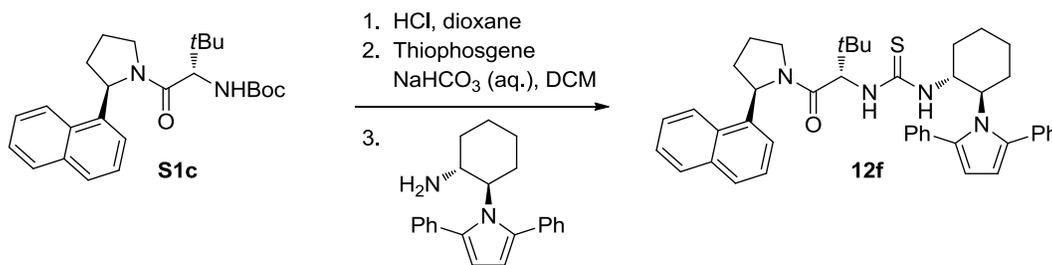


Intermediates **S1a-e** were synthesized via previously reported methods. The spectral data matched those reported in the literature.²⁵ 2-pyrrolylcyclohexylamines were synthesized via previously reported methods. The spectral data matched those reported in the literature.²⁶

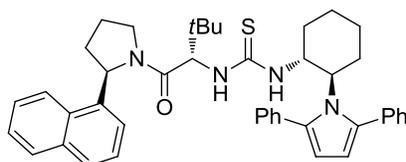
²⁵ For catalyst **3a** see: (a) Zuend, S. J.; Coughlin, M. P.; Lalonde, M. P.; Jacobsen, E. N. *Nature* **2009**, *461*, 968. For catalyst **3b** see: (b) Reisman, S. E.; Doyle, A. G.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 7198. For catalyst **3c-e** see: (c) Knowles, R. R.; Lin, S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2010**, *132*, 5030.

²⁶ (a) Taylor, M. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 10558 (b) Jones, C. R.; Pantos, G. D.; Morrison, A. J.; Smith, M. D. *Angew. Chem., Int. Ed.* **2009**, *48*, 7391.

Synthesis of optimal catalyst **12f**.



1-((S)-3,3-dimethyl-1-((R)-2-(naphthalen-1-yl)pyrrolidin-1-yl)-1-oxobutan-2-yl)-3-((1R,2R)-2-(2,5-diphenyl-1H-pyrrol-1-yl)cyclohexyl)thiourea (**12f**):



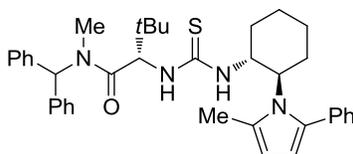
To Boc-protected amine **S1c** (640 mg, 1.56 mmol) was added excess hydrogen chloride (7.8 mL, 4M in dioxane) and the mixture was stirred for 1 h at 23 °C. The mixture was concentrated to yield the crude hydrochloride salt. Dichloromethane (12 mL) and saturated aqueous sodium bicarbonate (12 mL) were added to the crude salt, and the mixture was cooled to 0 °C. Thiophosgene (0.130 mL, 1.7 mmol) was added to the organic (lower) phase of the mixture by syringe, and the mixture was stirred at 0 °C for 30 minutes. Dichloromethane (20 mL) was added, and organic portion was separated. The aqueous was extracted with dichloromethane (2 x 20 mL) and the combined organic extracts were dried over sodium sulfate and concentrated *in vacuo*. The crude isothiocyanate was dissolved in dichloromethane (5 mL) and the pyrrolylcyclohexylamine (642 mg, 2.03 mmol) was added as a solution in dichloromethane (5 mL). The mixture was stirred at 23 °C for 14 h, then concentrated *in vacuo*, and purified by flash chromatography on silica gel to yield the desired product **5** (755 mg, 72% yield). $[\alpha]_D^{23} = -$

10.2° (c=1.0, CHCl₃). The compound exists as a 2.5:1 mixture of amide rotamers in CDCl₃. ¹H NMR (500MHz, CDCl₃) major rotamer resonances δ = 7.98 (d, *J* = 8.2 Hz, 1 H), 7.80 (d, *J* = 8.2 Hz, 1 H), 7.65 - 7.34 (m, 13 H), 7.24 - 7.19 (m, 1 H), 7.02 (d, *J* = 6.9 Hz, 1 H), 6.19 (br. s., 2 H), 5.88 (d, *J* = 7.8 Hz, 1 H), 5.70 (d, *J* = 9.6 Hz, 1 H), 5.53 (d, *J* = 9.6 Hz, 1 H), 5.34 (br. s., 1 H), 4.62 - 4.49 (m, 1 H), 4.04 - 3.94 (m, 1 H), 3.89 - 3.72 (m, 1 H), 3.58 - 3.41 (m, 1 H), 2.49 - 2.31 (m, 1 H), 2.27 - 2.10 (m, 1 H), 2.03 - 1.23 (m, 10 H), 1.13 (s, 9 H); selected minor rotamer resonances: δ = 8.29 (d, *J* = 8.2 Hz, 1 H), 7.89 (d, *J* = 8.2 Hz, 1 H), 7.78 (d, *J* = 8.2 Hz, 1 H), 6.30 (br. s, 1 H), 5.64 (d, *J* = 9.6 Hz, 1 H), 5.12 (br. s, 1 H), 5.02 (d, *J* = 10.1 Hz, 1 H), 4.16 - 4.05 (m, 1 H), 0.72 (s, 9 H); ¹³C NMR (126MHz, CDCl₃) major and minor rotamer resonances δ = 181.6, 181.4, 181.4, 172.0, 169.8, 138.4, 136.7, 134.0, 133.8, 131.4, 130.0, 128.7, 128.6, 127.8, 127.0, 126.3, 125.8, 125.7, 125.2, 124.5, 124.0, 123.9, 123.2, 121.6, 112.7, 109.8, 62.8, 62.0, 61.0, 60.7, 59.1, 58.1, 57.3, 56.3, 48.5, 47.3, 35.6, 34.9, 34.6, 34.0, 33.8, 33.5, 33.2, 32.9, 32.8, 29.0, 26.7, 26.6, 25.9, 25.7, 25.3, 24.1, 23.9, 23.4, 22.6, 21.4, 20.7 (the carbon resonances for the 2,5-aryl groups of the pyrrole are broadened and difficult to assign); FTIR: 3372 (w), 3256 (w), 3069 (w), 2953 (m), 2868 (m), 1638 (s), 1610 (s), 1506 (s), 1443 (s), 1308 (m); LRMS [M+Na]⁺ calculated for C₄₃H₄₈N₄NaOS: 691.34, found: 691.2

Characterization data for all novel catalysts in Table 4.4.

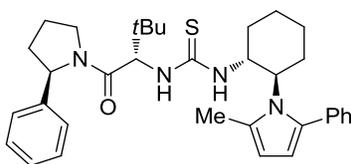
These catalysts were synthesized by an analogous procedure to catalyst **12f**.

(S)-N-benzhydryl-N,3,3-trimethyl-2-(3-((1R,2R)-2-(2-methyl-5-phenyl-1H-pyrrol-1-yl)cyclohexyl)thioureido)butanamide (12a):



$[\alpha]_D^{23} = -16.0^\circ$ (c=1.0, CHCl_3); $^1\text{H NMR}$ (500MHz, CDCl_3) $\delta = 7.55 - 7.04$ (m, 15 H), 6.09 - 5.98 (m, 2 H), 5.85 (br. s., 1 H), 5.49 (d, $J = 9.2$ Hz, 1 H), 5.23 (br. s., 1 H), 4.47 (br. s, 1 H), 4.16 - 3.93 (m, 2 H), 3.04 (s, 3 H), 2.49 (br. s., 3 H), 1.89 (m, 2 H), 1.81 - 1.65 (m, 2 H), 1.52 - 1.19 (m, 4 H), 0.97 (s, 9 H); $^{13}\text{C NMR}$ (126MHz, CDCl_3) $\delta = 182.1, 172.7, 139.2, 138.1, 136.0, 134.2, 129.8, 129.4, 128.7, 128.5, 128.4, 128.1, 127.6, 127.1, 127.0, 110.2, 108.7, 60.9, 60.4, 59.8, 56.1, 36.1, 33.7, 33.2, 32.3, 26.6, 25.7, 24.6, 15.3$; FTIR: 3358 (m), 3292 (m), 3062 (m), 3030 (m), 2939 (s), 2861 (m), 1631 (s), 1522 (s), 1446 (m), 1408 (m), 1366 (m); LRMS $[\text{M}+\text{Na}]^+$ calculated for $\text{C}_{38}\text{H}_{46}\text{N}_4\text{NaOS}$: 629.33, found: 629.3

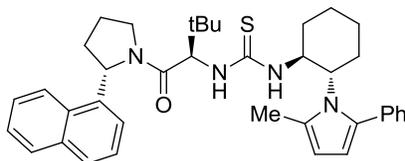
1-((S)-3,3-dimethyl-1-oxo-1-((R)-2-phenylpyrrolidin-1-yl)butan-2-yl)-3-((1R,2R)-2-(2-methyl-5-phenyl-1H-pyrrol-1-yl)cyclohexyl)thiourea (12b):



$[\alpha]_D^{24} = 19.8^\circ$ (c=1.0, CHCl_3); The compound exists as a 1.25:1 mixture of amide rotamers in CDCl_3 . $^1\text{H NMR}$ (500MHz, CDCl_3) major rotamer resonances $\delta = 7.49 - 7.05$ (m, 10 H), 5.94 - 5.80 (m, 3 H), 5.40 (d, $J = 9.2$ Hz, 1 H), 5.22 (br. s., 1 H), 5.14 (d, $J = 7.8$ Hz, 1 H), 4.70 - 4.51 (m, 1 H), 4.37 (t, $J = 8.0$ Hz, 1 H), 3.84 - 3.62 (m, 2 H), 2.47 (br. s., 3 H), 2.37 - 1.58 (m, 12 H),

1.08 - 0.99 (m, 9 H); ^{13}C NMR (126MHz, CDCl_3) major and minor rotamer resonances $\delta =$ 181.8, 171.8, 169.9, 144.2, 142.4, 136.0, 134.3, 134.1, 129.6, 129.5, 129.1, 128.8, 128.6, 128.4, 128.3, 127.2, 127.0, 126.9, 126.7, 126.4, 125.3, 110.3, 109.9, 108.8, 108.6, 62.3, 61.2, 60.8, 60.1, 59.7, 56.1, 55.9, 48.4, 47.0, 35.7, 35.4, 35.3, 34.2, 33.7, 32.3, 32.1, 29.7, 29.0, 26.5, 26.4, 25.7, 25.6, 24.6, 24.5, 23.1, 21.9, 15.6, 15.4; FTIR: 3385 (m), 3066 (w), 2948 (m), 2870 (m), 1635 (s), 1518 (s), 1436 (s); LRMS $[\text{M}+\text{Na}]^+$ calculated for $\text{C}_{34}\text{H}_{44}\text{N}_4\text{NaOS}$: 579.31, found: 579.2

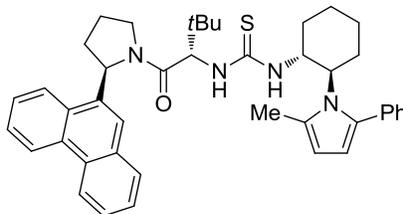
1-((R)-3,3-dimethyl-1-((S)-2-(naphthalen-1-yl)pyrrolidin-1-yl)-1-oxobutan-2-yl)-3-((1S,2S)-2-(2-methyl-5-phenyl-1H-pyrrol-1-yl)cyclohexyl)thiourea (*ent*-**12c**):



$[\alpha]_D^{24} = -15.2^\circ$ (c=1.0, CHCl_3); The compound exists as a 2.5:1 mixture of amide rotamers in CDCl_3 . ^1H NMR (500MHz, CDCl_3) major rotamer resonances $\delta =$ 8.00 (d, $J = 8.2$ Hz, 1 H), 7.85 (d, $J = 8.7$ Hz, 1 H), 7.63 - 7.28 (m, 8 H), 7.08 (d, $J = 6.9$ Hz, 1 H), 6.02 (br. s., 1 H), 5.96 - 5.89 (m, 2 H), 5.49 (d, $J = 9.2$ Hz, 1 H), 5.30 (br. s., 1 H), 4.56 (br. s., 1 H), 4.35 - 4.19 (m, 1 H), 4.00 (br. s., 1 H), 3.87 - 3.77 (m, 1 H), 3.76 - 3.65 (m, 1 H), 2.50 (br. s., 3 H), 2.42 - 1.79 (m, 10 H), 1.01 (s, 9 H); ^{13}C NMR (126MHz, CDCl_3) major and minor rotamer resonances $\delta =$ 181.8, 171.9, 170.0, 138.3, 136.7, 136.0, 134.1, 133.8, 133.1, 130.1, 130.0, 129.6, 129.5, 128.9, 128.8, 128.6, 128.5, 128.5, 128.0, 127.8, 127.1, 126.2, 125.8, 125.7, 125.3, 125.3, 124.5, 124.1, 123.8, 123.3, 121.7, 110.4, 109.9, 108.7, 108.7, 62.5, 61.5, 60.4, 60.1, 59.7, 59.0, 58.2, 56.2, 56.0, 48.5, 47.1, 37.0, 35.7, 35.3, 33.9, 33.7, 33.7, 32.8, 32.4, 32.2, 26.7, 26.5, 25.7, 25.6, 24.7, 24.5, 23.3, 21.5; FTIR: 3340 (m), 3275 (m), 3055 (w), 2934 (m), 2866 (m), 1640 (m), 1607 (s), 1512 (s),

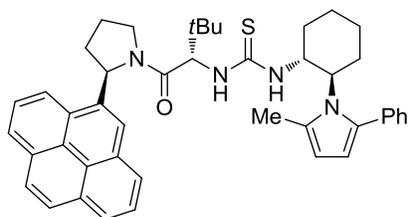
1445 (s), 1363 (m), 1311 (s); LRMS $[M+Na]^+$ calculated for $C_{38}H_{46}N_4NaOS$: 629.33, found: 629.2

1-((*S*)-3,3-dimethyl-1-oxo-1-((*R*)-2-(phenanthren-9-yl)pyrrolidin-1-yl)butan-2-yl)-3-((1*R*,2*R*)-2-(2-methyl-5-phenyl-1*H*-pyrrol-1-yl)cyclohexyl)thiourea (**12d**):



$[\alpha]_D^{25} = 59.1^\circ$ ($c=0.45$, $CHCl_3$); The compound exists as a 1.6:1 mixture of amide rotamers in $CDCl_3$. 1H NMR (500MHz, $CDCl_3$) major rotamer resonances $\delta = 8.72$ (d, $J = 7.8$ Hz, 1 H), 8.61 (d, $J = 8.7$ Hz, 1 H), 8.04 (d, $J = 8.2$ Hz, 1 H), 7.90 (d, $J = 7.3$ Hz, 1 H), 7.73 - 7.29 (m, 10 H), 6.14 - 5.88 (m, 3 H), 5.82 (br. s., 1 H), 5.56 (br. s., 1 H), 5.47 (d, $J = 9.6$ Hz, 1 H), 4.73 (d, $J = 10.5$ Hz, 1 H), 3.94 (br. s., 1 H), 3.90 - 3.80 (m, 1 H), 3.72 (d, $J = 16.9$ Hz, 1 H), 2.34 (s, 3 H), 2.21 - 1.61 (m, 12 H), 1.10 (s, 9 H); ^{13}C NMR (126MHz, $CDCl_3$) major and minor resonances $\delta = 182.0, 182.0, 172.1, 170.2, 136.2, 136.1, 134.2, 131.5, 131.3, 131.0, 130.8, 130.7, 130.3, 130.0, 129.8, 129.6, 129.2, 129.2, 129.0, 128.9, 128.5, 128.4, 127.3, 127.1, 126.7, 126.7, 126.5, 126.4, 126.1, 126.0, 125.0, 124.5, 123.9, 123.3, 123.0, 122.9, 122.4, 122.2, 122.1, 110.4, 109.8, 108.6, 66.7, 63.2, 61.5, 60.1, 59.7, 59.3, 58.4, 56.2, 55.8, 48.4, 47.1, 35.5, 35.2, 33.7, 33.5, 32.2, 26.8, 26.6, 26.5, 25.7, 25.4, 24.7, 24.3, 23.3, 21.6, 15.6, 15.4$; FTIR: 3395 (m), 3155 (w), 3074 (m), 2947 (m), 2871 (m), 1638 (s), 1525 (s), 1435 (m); LRMS $[M+Na]^+$ calculated for $C_{42}H_{48}N_4NaOS$: 679.34, found: 679.3

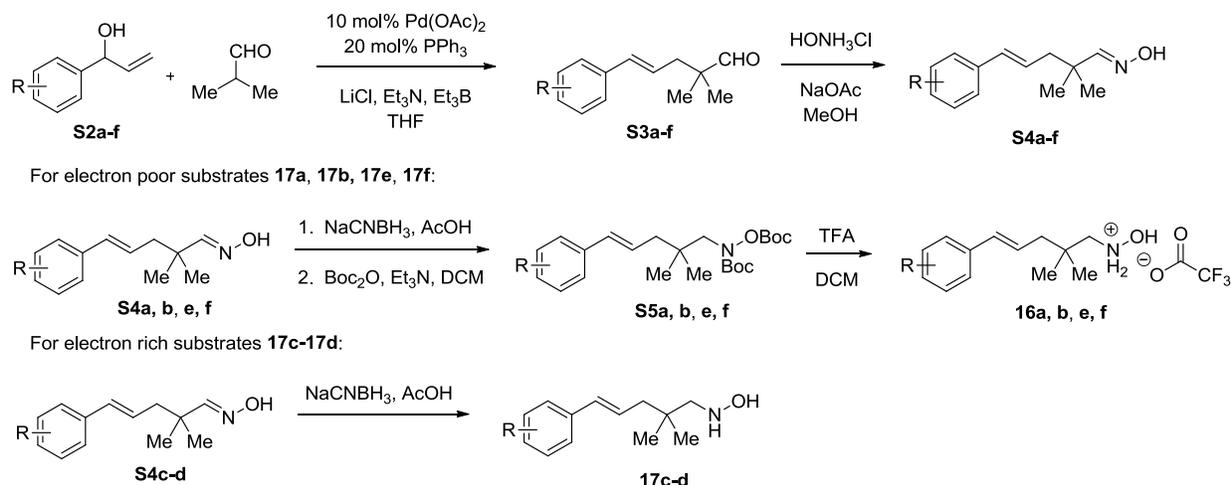
1-((S)-3,3-dimethyl-1-oxo-1-((R)-2-(pyren-4-yl)pyrrolidin-1-yl)butan-2-yl)-3-((1R,2R)-2-(2-methyl-5-phenyl-1H-pyrrol-1-yl)cyclohexyl)thiourea (12e):



$[\alpha]_D^{25} = 90.0^\circ$ (c=0.30, CHCl₃); The compound exists as a 1.4:1 mixture of amide rotamers in CDCl₃. ¹H NMR (500MHz, CDCl₃) major rotamer resonances $\delta = 8.31$ (d, $J = 7.8$ Hz, 1 H), 8.25 - 7.97 (m, 5 H), 7.95 - 7.86 (m, 2 H), 7.84 (s, 1 H), 7.66 - 7.34 (m, 5 H), 6.14 (d, $J = 8.2$ Hz, 1 H), 6.01 (d, $J = 3.2$ Hz, 1 H), 5.94 (d, $J = 2.7$ Hz, 1 H), 5.55 (d, $J = 9.2$ Hz, 2 H), 4.82 (t, $J = 8.5$ Hz, 1 H), 4.06 - 3.81 (m, 3 H), 2.39 (s, 3 H), 2.23 - 1.49 (m, 12 H), 1.16 - 1.10 (m, 9 H); ¹³C NMR (126MHz, CDCl₃) major and minor resonances $\delta = 182.1, 182.0, 172.1, 170.2, 137.2, 136.2, 135.3, 134.4, 131.6, 131.4, 130.9, 130.4, 129.9, 129.8, 129.0, 128.9, 128.6, 128.4, 127.6, 127.4, 127.2, 127.0, 126.0, 125.8, 125.8, 125.7, 125.5, 125.3, 125.3, 125.2, 124.9, 124.8, 124.6, 124.1, 123.9, 123.0, 122.3, 120.8, 110.6, 109.9, 108.8, 63.2, 61.5, 60.1, 59.7, 59.4, 58.5, 56.2, 55.8, 48.5, 47.0, 36.0, 35.7, 35.3, 34.6, 34.5, 33.7, 33.5, 32.3, 29.7, 29.0, 26.9, 26.6, 26.2, 25.7, 25.4, 25.2, 24.7, 24.3, 23.5, 21.8, 20.7, 18.7, 15.5$; FTIR: 3396 (m), 3280 (w), 3054 (m), 2962 (m), 2870 (w), 1638 (s), 1610 (s), 1520 (s), 1445 (s), 1311 (m); LRMS [M+Na]⁺ calculated for C₄₄H₄₈N₄NaOS: 703.34, found: 703.2

4.7.3. Substrate Preparation and Characterization Data

General synthetic route for the preparation of substrates 17a-f.



General Procedure:

Branched allylic alcohols **S2a-f** were synthesized via previously reported methods. The spectral data matched those reported in the literature.²⁷

Tsuji-Trost Alkylation:²⁸ To a solution of palladium acetate (112 mg, 0.5 mmol), triphenylphosphine (262 mg, 1.0 mmol) and lithium chloride (211 mg, 5.0 mmol) in dry tetrahydrofuran (5 mL) were successively added isobutyraldehyde (500 μ L, 5.5 mmol), branched allylic alcohol **S2a-f** (5.0 mmol), triethylamine (836 μ L, 6.0 mmol), and triethylborane (12 mmol, 1.0 M solution in hexanes) via syringe at ambient temperatures under nitrogen. The mixture was stirred at ambient temperature for 48 h. The mixture was filtered through a Celite pad and washed with ethyl acetate. The filtrate was washed with saturated aqueous sodium

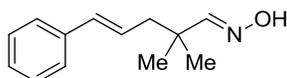
²⁷ (a) Bouziane, A.; Helou, M.; Carboni, B.; Carreaux, F.; Demerseman, B.; Bruneau, C.; Renaud, J. *Chem. Eur. J.* **2008**, *14*, 5630-5637. (b) Logan, A. W. J.; Parker, J. S.; Hallside, M. S.; Burton, J. W. *Org. Lett.* **2012**, *14*, 2940. (c) Lafrance, M.; Roggen, M.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 3470.

²⁸ Kimura, M.; Horino, Y.; Mukai, R.; Tanaka, S.; Tamaru, Y. *J. Am. Chem. Soc.* **2001**, *123*, 10401.

bicarbonate, and the organic phase was dried over magnesium sulfate, concentrated in vacuo and carried forward to the following reaction without further purification.

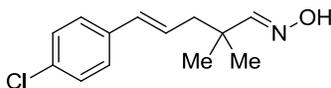
Oxime formation: To aldehyde **S3a-f** (5.0 mmol) in a solution of methanol (50 mL) was added hydroxylamine hydrochloride (870 mg, 12.5 mmol) and sodium acetate (1.025 g, 12.5 mmol). A reflux condenser was fitted to the flask, and the mixture heated at reflux for 14 h. Upon cooling to ambient temperature, water (~50 mL) was added to the reaction mixture, and the mixture was extracted with dichloromethane (3 x 25 mL). The organic phase was dried over sodium sulfate, concentrated *in vacuo*, and purified by flash chromatography on silica gel to give the desired oxime **S4a-f**.

(1E,4E)-2,2-dimethyl-5-phenylpent-4-enal oxime (S4a):



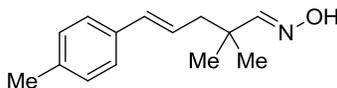
Following the general procedure (850 mg, 84% yield over 2 steps) of the desired product was isolated as a clear oil. ^1H NMR (500MHz, CDCl_3) δ = 8.12 (s, 1 H), 7.43 (s, 1 H), 7.37 (d, J = 7.8 Hz, 2 H), 7.32 (t, J = 7.6 Hz, 2 H), 7.24 (t, J = 7.3 Hz, 1 H), 6.44 (d, J = 15.6 Hz, 1 H), 6.20 (td, J = 7.3, 15.6 Hz, 1 H), 2.34 (d, J = 7.3 Hz, 2 H), 1.17 (s, 6 H); ^{13}C NMR (126MHz, CDCl_3) δ = 158.6, 137.4, 133.2, 128.5, 127.1, 126.1, 125.6, 44.4, 37.2, 25.2; FTIR: 3319 (br), 3027 (w), 2965 (m), 2925 (w), 1598 (w), 1496 (m), 1449 (s), 967 (s), 942 (s); LRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{13}\text{H}_{18}\text{NO}$: 238.09, found: 238.1

(1E,4E)-5-(4-chlorophenyl)-2,2-dimethylpent-4-enal oxime (S4b):



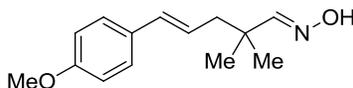
Following the general procedure (1.01 g, 85% yield over 2 steps) of the desired product was isolated as a white solid. ^1H NMR (500MHz, CDCl_3) δ = 8.03 (s, 1 H), 7.40 (s, 1 H), 7.28 (s, 4 H), 6.37 (d, J = 16.0 Hz, 1 H), 6.16 (td, J = 7.3, 16.0 Hz, 3 H), 2.33 (dd, J = 1.4, 7.3 Hz, 2 H), 1.15 (s, 6 H); ^{13}C NMR (126MHz, CDCl_3) δ = 158.4, 135.8, 132.7, 132.0, 128.6, 127.3, 126.5, 44.3, 37.2, 25.2; FTIR: 3325 (br), 3028 (w), 2967 (s), 2926 (m), 1652 (w), 1594 (w), 1491 (s), 1095 (s); LRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{13}\text{H}_{17}\text{ClNO}$: 204.13, found: 204.1

(1E,4E)-2,2-dimethyl-5-p-tolylpent-4-enal oxime (S4c):



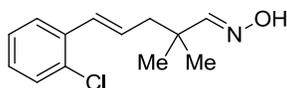
Following the general procedure (870 mg, 80% yield over 2 steps) of the desired product was isolated as a white solid. ^1H NMR (500MHz, CDCl_3) δ = 8.60 - 7.97 (br. s, 1 H), 7.42 (s, 1 H), 7.27 (d, J = 7.8 Hz, 2 H), 7.13 (d, J = 8.3 Hz, 2 H), 6.40 (d, J = 15.6 Hz, 1 H), 6.15 (td, J = 7.6, 15.5 Hz, 1 H), 2.35 (s, 3 H), 2.33 (dd, J = 1.2, 7.6 Hz, 2 H), 1.16 (s, 6 H); ^{13}C NMR (126MHz, CDCl_3) δ = 158.6, 136.9, 134.6, 133.0, 129.2, 126.0, 124.5, 44.4, 37.2, 25.1, 21.1; FTIR: 3284 (m), 2966 (s), 2923 (m), 2869 (m), 1510 (m), 1453 (m), 1427 (m), 1309 (m); LRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{14}\text{H}_{20}\text{NO}$: 218.15, found: 218.1

(1E,4E)-5-(4-methoxyphenyl)-2,2-dimethylpent-4-enal oxime (S4d):



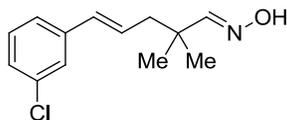
Following the general procedure (865 mg, 74% yield over 2 steps) of the desired product was isolated as a white solid. ^1H NMR (500MHz, CDCl_3) δ = 8.19 (s, 1 H), 7.42 (s, 1 H), 7.30 (d, J = 8.7 Hz, 2 H), 6.86 (d, J = 8.7 Hz, 2 H), 6.37 (d, J = 15.6 Hz, 1 H), 6.05 (td, J = 7.3, 15.6 Hz, 1 H), 3.82 (s, 3 H), 2.31 (d, J = 7.8 Hz, 2 H), 1.15 (s, 6 H); ^{13}C NMR (126MHz, CDCl_3) δ = 158.9, 158.6, 132.5, 130.2, 127.2, 123.4, 113.9, 55.3, 44.4, 37.2, 25.1; FTIR: 3318 (br), 2964 (m), 2836 (w), 1607 (m), 1510 (s), 1463 (m), 1299 (m), 1246 (s); LRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{14}\text{H}_{20}\text{NO}_2$: 234.14, found: 234.1

(1E,4E)-5-(2-chlorophenyl)-2,2-dimethylpent-4-enal oxime (S4e):



Following the general procedure (825 mg, 69% yield over 2 steps) of the desired product was isolated as a white solid. ^1H NMR (500MHz, CDCl_3) δ = 7.98 (s, 1 H), 7.50 (dd, J = 1.8, 7.8 Hz, 1 H), 7.43 (s, 1 H), 7.35 (dd, J = 1.4, 7.8 Hz, 1 H), 7.19 (dtd, J = 1.4, 7.3, 23.8 Hz, 2 H), 6.80 (d, J = 16.0 Hz, 1 H), 6.17 (td, J = 7.3, 15.1 Hz, 1 H), 2.39 (dd, J = 0.9, 7.8 Hz, 2 H), 1.17 (s, 6 H); ^{13}C NMR (126MHz, CDCl_3) δ = 158.5, 135.6, 132.6, 129.6, 129.5, 128.8, 128.2, 126.9, 126.7, 44.4, 37.1, 25.2; FTIR: 3314 (br), 2966 (m), 2927 (w), 1649 (w), 1470 (s), 1440 (s), 1384 (m); LRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{13}\text{H}_{18}\text{NO}$: 238.09, found: 238.1

(1E,4E)-5-(3-chlorophenyl)-2,2-dimethylpent-4-enal oxime (S4f):



Following the general procedure (980 mg, 82% yield over 2 steps) of the desired product was isolated as a white solid. ^1H NMR (500MHz, CDCl_3) δ = 7.76 (s, 1 H), 7.41 (s, 1 H), 7.35 (s, 1 H), 7.26 - 7.17 (m, 3 H), 6.36 (d, J = 15.6 Hz, 1 H), 6.21 (td, J = 7.8, 15.6 Hz, 1 H), 2.34 (d, J = 7.8 Hz, 2 H), 1.16 (s, 6 H); ^{13}C NMR (126MHz, CDCl_3) δ = 158.5, 139.2, 134.4, 131.9, 129.7, 127.5, 127.1, 126.0, 124.4, 44.2, 37.1, 25.3; FTIR: 3319 (br), 2966 (s), 2927 (m), 1651 (w), 1594 (s), 1568 (s), 1474 (s), 1426 (s); LRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{13}\text{H}_{18}\text{NO}$: 238.09, found: 238.1

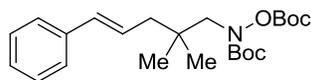
Oxime reduction: A solution of oxime **S4a**, **b**, **e**, or **f** (1.5 mmol) in acetic acid (2.5 mL) was cooled to 15 °C, and sodium cyanoborohydride (188 mg, 3.0 mmol) was added in one portion. After stirring at 15 °C for 5 mins, the mixture was warmed to 23 °C and stirred for 1 h. The reaction was quenched by the addition of 20% aq. potassium carbonate (20 mL) and extracted with diethyl ether. The organics were washed with 20% aq. potassium carbonate (20 mL) dried over magnesium sulfate, concentrated *in vacuo* and carried forward to the following reaction without further purification.

To prevent excessive thermal cyclization, the hydroxylamine must be subjected to the Boc protection conditions immediately following workup.

Boc protection: To crude hydroxylamine **17a**, **b**, **e**, or **f** (1.5 mmol) in a solution of dichloromethane (10 mL) was added di-*tert*-butyl dicarbonate (1.3 g, 6.0 mmol) and triethylamine (1.7 mL, 12.0 mmol). The mixture was stirred at 23 °C for 14 h. Water (20 mL) was added, and the organics were extracted with dichloromethane (2 x 25 mL), washed with 1M

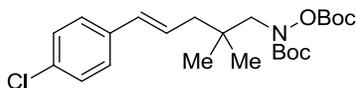
HCl (25 mL), dried over sodium sulfate, concentrated *in vacuo* and purified by flash chromatography on silica gel to give the desired Boc-protected hydroxylamine **S5a, b, e, or f**.

(E)-tert-butyl (tert-butoxycarbonyl)oxy(2,2-dimethyl-5-phenylpent-4-en-1-yl)carbamate (S5a):



Following the general procedure on a 3.5 mmol scale (1.18 g, 83% yield over 2 steps) of the desired product was isolated as a clear oil. $^1\text{H NMR}$ (500MHz, CDCl_3) δ = 7.36 (d, J = 7.3 Hz, 2 H), 7.30 (t, J = 7.6 Hz, 2 H), 7.20 (t, J = 7.3 Hz, 1 H), 6.41 (d, J = 16.0 Hz, 1 H), 6.25 (td, J = 7.3, 16.0 Hz, 1 H), 3.69 (br. s, 1 H), 3.30 (br. s, 1 H), 2.21 (d, J = 7.3 Hz, 2 H), 1.53 (s, 9 H), 1.48 (s, 9 H), 0.99 (s, 6 H); $^{13}\text{C NMR}$ (126MHz, CDCl_3) δ = 155.3, 152.2, 137.7, 132.7, 128.4, 126.9, 126.7, 126.0, 84.8, 82.1, 60.3, 43.5, 35.8, 28.1, 27.6, 25.3; FTIR: 2979 (m), 2933 (w), 1781 (s), 1719 (s), 1369 (s), 1249 (s); LRMS $[\text{M}+\text{Na}]^+$ calculated for $\text{C}_{23}\text{H}_{35}\text{NNaO}_5$: 428.24, found: 428.1

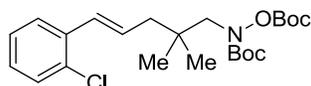
(E)-tert-butyl (tert-butoxycarbonyl)oxy(5-(4-chlorophenyl)-2,2-dimethylpent-4-en-1-yl)carbamate (S5b):



Following the general procedure on a 1.0 mmol scale (220 mg, 50% yield over 2 steps) of the desired product was isolated as a clear oil. $^1\text{H NMR}$ (500MHz, CDCl_3) δ = 7.29 - 7.22 (m, 4 H), 6.35 (d, J = 15.6 Hz, 1 H), 6.22 (td, J = 7.6, 15.5 Hz, 1 H), 3.65 (br. s, 1 H), 3.25 (br. s, 1 H), 2.19 (d, J = 7.3 Hz, 2 H), 1.51 (s, 9 H), 1.47 (s, 9 H), 0.97 (s, 6 H); $^{13}\text{C NMR}$ (126MHz, CDCl_3) δ = 155.3, 152.2, 136.2, 132.4, 131.5, 128.6, 127.6, 127.2, 84.8, 82.2, 60.3, 43.5, 35.8, 28.1,

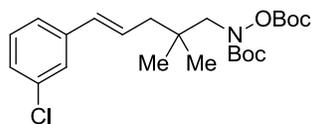
27.6, 25.3; FTIR: 2978 (m), 2932 (w), 1782 (s), 1718 (s), 1491 (w), 1370 (s), 1248 (s); LRMS [M+Na]⁺ calculated for C₂₃H₃₅ClNNaO₅: 462.20, found: 462.1

(E)-tert-butyl (tert-butoxycarbonyl)oxy(5-(2-chlorophenyl)-2,2-dimethylpent-4-en-1-yl)carbamate (S5e):



Following the general procedure on a 1.0 mmol scale (257 mg, 58% yield over 2 steps) of the desired product was isolated as a clear oil. ¹H NMR (500MHz, CDCl₃) δ = 7.51 (d, *J* = 7.8 Hz, 1 H), 7.33 (d, *J* = 7.8 Hz, 1 H), 7.20 (t, *J* = 6.8 Hz, 1 H), 7.14 (t, *J* = 7.3 Hz, 1 H), 6.77 (d, *J* = 15.6 Hz, 1 H), 6.23 (td, *J* = 7.6, 15.5 Hz, 1 H), 3.67 (br. s, 1 H), 3.27 (br. s, 1 H), 2.25 (d, *J* = 7.8 Hz, 2 H), 1.52 (s, 9 H), 1.49 (s, 9 H), 1.00 (s, 6 H); ¹³C NMR (126MHz, CDCl₃) δ = 155.3, 152.2, 135.9, 132.5, 129.9, 129.5, 129.0, 127.9, 126.8, 126.7, 84.8, 82.2, 60.4, 43.6, 35.8, 28.1, 27.6, 25.3; FTIR: 2980 (m), 2932 (m), 1782 (s), 1719 (s), 1471 (m), 1370 (s), 1254 (s); LRMS [M+Na]⁺ calculated for C₂₃H₃₅ClNNaO₅: 462.20, found: 462.1

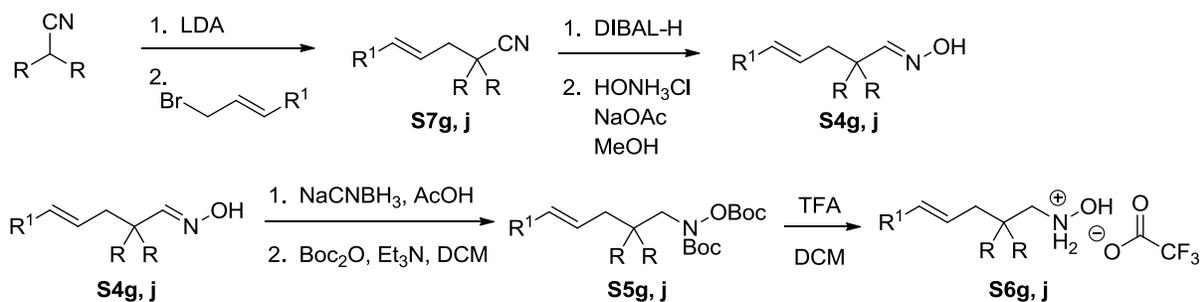
(E)-tert-butyl (tert-butoxycarbonyl)oxy(5-(3-chlorophenyl)-2,2-dimethylpent-4-en-1-yl)carbamate (S5f):



Following the general procedure (361 mg, 55% yield over 2 steps) of the desired product was isolated as a clear oil. ¹H NMR (500MHz, CDCl₃) δ = 7.34 (s, 1 H), 7.25 - 7.19 (m, 2 H), 7.19 - 7.14 (m, 1 H), 6.35 (d, *J* = 15.6 Hz, 1 H), 6.26 (td, *J* = 7.3, 15.6 Hz, 1 H), 3.65 (br. s, 1 H), 3.26 (br. s, 1 H), 2.21 (d, *J* = 6.4 Hz, 2 H), 1.52 (s, 9 H), 1.49 (s, 9 H), 0.98 (s, 6 H); ¹³C NMR

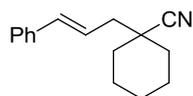
(126MHz, CDCl₃) δ = 155.3, 152.2, 139.6, 134.4, 131.4, 129.6, 128.5, 126.8, 125.9, 124.3, 84.9, 82.2, 60.3, 43.4, 35.8, 28.1, 27.6, 25.3; FTIR: 2979 (m), 2933 (w), 1780 (s), 1717 (s), 1594 (m), 1568 (w), 1475 (m), 1426 (m), 1369 (s); LRMS [M+Na]⁺ calculated for C₂₃H₃₅CINNaO₅: 462.20, found: 462.1

General synthetic route for the preparation of substrates 1g and 1j.



Nitrile alkylation: To a flame-dried 100 mL round-bottom flask was added diisopropyl amine (1.4 mL, 10 mmol) and tetrahydrofuran (20 mL) under nitrogen. The mixture was cooled to -78 °C, and *n*BuLi (4.2 mL of a 2.5 M solution in hexanes, 10.5 mmol) was added dropwise. The mixture was warmed to 0 °C and stirred for 10 minutes, then cooled to -78 °C. The nitrile (10 mmol) was then added dropwise as a solution in tetrahydrofuran (5 mL), and the mixture was warmed to 0 °C and stirred for 5 minutes. The bromide (12 mmol) was then added as a solution in tetrahydrofuran (5 mL), and the mixture was warmed to 23 °C and stirred for 14 h. The reaction was quenched by the addition of water (25 mL) and extracted with diethyl ether (3 x 25 mL). The organics were washed with water (25 mL) and brine (25 mL), dried over magnesium sulfate, and concentrated *in vacuo*. **S7g** was purified by flash chromatography on silica gel. **S7j** (2,2-dimethylpent-4-enenitrile) was carried on to the following reaction without further purification.

1-cinnamylcyclohexanecarbonitrile (S7g):



Following the general procedure, the alkylation was performed on a 10 mmol scale, and the desired product was isolated as a clear oil (1.82 g, 81% yield). The spectral data matched those reported in the literature.²⁹

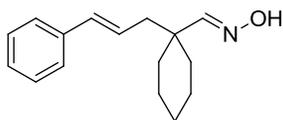
Nitrile reduction: In a flame-dried 100 mL round-bottom flask a solution of nitrile (8.1 mmol) in tetrahydrofuran (20 mL) was cooled to -78 °C. A solution of diisobutylaluminum hydride (12.2 mL of a 1.0 M solution in hexanes, 12.2 mmol) was added dropwise. The mixture was stirred at -78 °C for 15 minutes, and warmed to 23 °C and stirred for 2 h. The mixture was cooled to 0 °C and 1 M aq. HCl was added (20 mL). Diethyl ether was added, and the mixture was stirred for 1 h at 23 °C. The phases were separated, and the aqueous phase was extracted with diethyl ether (2 x 25). The combined organics were dried over magnesium sulfate, and concentrated *in vacuo* to yield the aldehyde product, which was carried on to the following reaction without further purification.

Oxime formation: To the crude aldehyde (8.1 mmol) in a solution of methanol (65 mL) was added hydroxylamine hydrochloride (1.4 g, 20.25 mmol) and sodium acetate (1.7 g, 20.25 mmol). A reflux condenser was fitted to the flask, and the mixture heated at reflux for 14 h. Upon cooling to ambient temperature, water (~80 mL) was added to the reaction mixture, and the mixture was extracted with dichloromethane (3 x 35 mL). The organic phase was dried over

²⁹ Fleming, F. F.; Zhang, Z.; Liu, W.; Knochel, P. *J. Org. Chem.* **2005**, *70*, 2200.

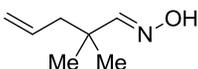
sodium sulfate, concentrated *in vacuo*, and purified by flash chromatography on silica gel to give the desired oxime.

(E)-1-cinnamylcyclohexanecarbaldehyde oxime (S4g):



Following the general procedure (1.81 g, 92% over 2 steps) of the desired product was isolated as a clear oil. ^1H NMR (500MHz, CDCl_3) δ = 7.97 (s, 1 H), 7.37 - 7.34 (m, 2 H), 7.33 (s, 1 H), 7.32 - 7.28 (m, 2 H), 7.24 - 7.19 (m, 1 H), 6.41 (d, J = 15.6 Hz, 1 H), 6.18 (td, J = 7.3, 15.1 Hz, 1 H), 2.35 (d, J = 7.3 Hz, 2 H), 1.83 - 1.69 (m, 2 H), 1.62 - 1.25 (m, 8 H); ^{13}C NMR (126MHz, CDCl_3) δ = 157.8, 137.5, 132.9, 128.4, 127.1, 126.1, 125.5, 43.5, 40.6, 34.2, 26.0, 22.1; FTIR: 3320 (m), 3026 (m), 2926 (s), 2852 (m), 1649 (w), 1598 (w), 1495 (m), 1448 (s), 1305 (m); LRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{16}\text{H}_{22}\text{NO}$: 244.16, found 244.2

(E)-2,2-dimethylpent-4-enal oxime (S4j):



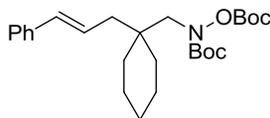
Following the general procedure the desired product was isolated as a clear oil. ^1H NMR (500MHz, CDCl_3) δ = 8.77 (br. s, 1 H), 7.35 (s, 1 H), 5.76 (m, 1H), 5.14 - 4.97 (m, 2 H), 2.16 (d, J = 7.3 Hz, 2 H), 1.09 (s, 6 H); ^{13}C NMR (126MHz, CDCl_3) δ = 158.4, 133.8, 118.1, 45.2, 36.6, 25.0; FTIR: 3327 (br), 3078 (m), 2968 (s), 2910 (m), 1641 (m), 1462 (m), 1436 (m), 1384 (m), 1366 (m); LRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_7\text{H}_{14}\text{NO}$: 128.10, found 128.1

Oxime reduction: A solution of oxime **S4g**, or **j** (1.5 mmol) in acetic acid (2.5 mL) was cooled to 15 °C, and sodium cyanoborohydride (188 mg, 3.0 mmol) was added in one portion. After stirring at 15 °C for 5 mins, the mixture was warmed to 23 °C and stirred for 1 h. The reaction was quenched by the addition of 20% aq. potassium carbonate (20 mL) and extracted with diethyl ether. The organics were washed 20% aq. potassium carbonate (20 mL), dried over magnesium sulfate, concentrated *in vacuo* and carried forward to the following reaction without further purification.

To prevent excessive thermal cyclization, the hydroxylamine must be subjected to the Boc protection conditions immediately following workup.

Boc protection: To crude hydroxylamine **17g** or **j** (1.5 mmol) in a solution of dichloromethane (10 mL) was added di-*tert*-butyl dicarbonate (1.3 g, 6.0 mmol) and triethylamine (1.7 mL, 12.0 mmol). The mixture was stirred at 23 °C for 14 h. Water (20 mL) was added, and the organics were extracted with dichloromethane (2 x 25 mL), washed with 1M HCl (25 mL), dried over sodium sulfate, concentrated *in vacuo* and purified by flash chromatography on silica gel to give the desired Boc-protected hydroxylamine **S5g** or **j**.

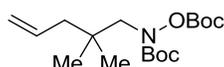
(*E*)-*tert*-butyl (*tert*-butoxycarbonyl)oxy((1-cinnamylcyclohexyl)methyl)carbamate (**S5g**):



Following the general procedure (417 mg, 62% yield over 2 steps) of the desired product was isolated as a clear oil. ¹H NMR (500MHz, CDCl₃) δ = 7.35 (d, *J* = 7.3 Hz, 2 H), 7.29 (t, *J* = 7.6 Hz, 2 H), 7.19 (t, *J* = 6.8 Hz, 1 H), 6.43 (d, *J* = 15.6 Hz, 1 H), 6.26 (td, *J* = 7.6, 15.5 Hz, 1 H), 3.84 - 3.70 (m, 1 H), 3.38 - 3.25 (m, 1 H), 2.30 (d, *J* = 7.3 Hz, 2 H), 1.50 (s, 9 H), 1.48 (s, 9 H),

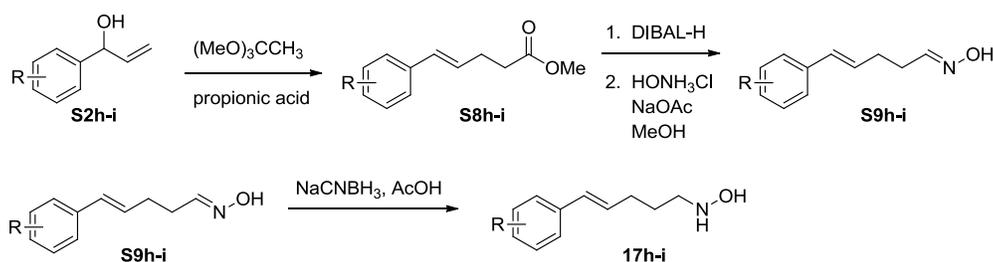
1.47 - 1.32 (m, 10 H); ^{13}C NMR (126MHz, CDCl_3) δ = 155.5, 152.3, 137.9, 132.6, 128.4, 126.8, 126.6, 126.0, 84.8, 82.2, 57.3, 39.3, 37.9, 34.1, 33.6, 33.3, 28.1, 27.6, 26.1, 21.5; FTIR: 2980 (m), 2928 (m), 2855 (w), 1778 (s), 1715 (s), 1599 (w), 1455 (m), 1392 (m), 1369 (s), 1236 (s); LRMS $[\text{M}+\text{Na}]^+$ calculated for $\text{C}_{26}\text{H}_{39}\text{NNaO}_5$: 468.27, found 468.2

tert-butyl (*tert*-butoxycarbonyl)oxy(2,2-dimethylpent-4-en-1-yl)carbamate (**S5j**):



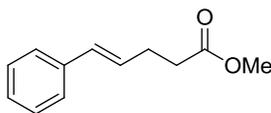
Following the general procedure on a 4.7 mmol scale (562 mg, 36% yield over 2 steps) of the desired product was isolated as a clear oil. ^1H NMR (500MHz, CDCl_3) δ = 5.81 (s, 1 H), 5.09 - 4.95 (m, 2 H), 3.60 (br. s, 1 H), 3.22 (br. s, 1 H), 1.54 (s, 9 H), 1.47 (s, 9 H), 0.93 - 0.90 (m, 6 H); ^{13}C NMR (126MHz, CDCl_3) δ = 155.2, 152.2, 134.8, 117.4, 84.7, 82.1, 60.2, 44.5, 35.0, 28.1, 27.6, 25.1; FTIR: 3078 (m), 2982 (m), 1781 (s), 1715 (s), 1370 (s), 1248 (s); LRMS $[\text{M}+\text{Na}]^+$ calculated for $\text{C}_{17}\text{H}_{31}\text{NNaO}_5$: 352.21, found 352.1

General synthetic route for the preparation of substrates 17h-i.



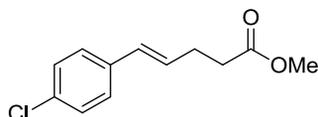
Branched allylic alcohols **S2h-i** were synthesized via previously reported methods. The spectral data matched those reported in the literature.²⁷

(E)-methyl 5-phenylpent-4-enoate (S8h):



Prepared by previously reported methods. The spectral data matched those reported in the literature.³⁰

(E)-methyl 5-(4-chlorophenyl)pent-4-enoate (S8i):



To 1-(4-chlorophenyl)prop-2-en-1-ol (169 mg, 1.0 mmol) in a microwave vial was added trimethyl orthoacetate (0.673 mL, 5.0 mmol) and propionic acid (2 drops, catalytic). The vial was sealed, and heated at 140 °C for 14 h. The mixture was cooled, and purified by flash chromatography on silica gel to give the desired ester product (128 mg, 57% yield) as a white solid. ¹H NMR (500MHz, CDCl₃) δ = 7.26 (s, 4 H), 6.39 (d, *J* = 15.6 Hz, 1 H), 6.19 (td, *J* = 6.7, 15.9 Hz, 1 H), 3.70 (s, 3 H), 2.58 - 2.46 (m, 4 H); ¹³C NMR (126MHz, CDCl₃) δ = 173.3, 135.8, 132.7, 129.8, 129.1, 128.6, 127.3, 51.6, 33.7, 28.2; FTIR: 3031 (w), 2951 (m), 1739 (s), 1492 (s), 1437 (m), 1169 (m)

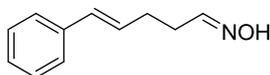
Ester reduction: To a solution of ester (2.5 mmol) in dichloromethane (10 mL) at -78 °C was added diisobutylaluminum hydride (2.75 mL of a 1.0 M solution in hexanes, 2.75 mmol) dropwise. The mixture was stirred for 1 h at -78 °C. A saturated solution of Rochelle's salt (15 mL) was added, and the mixture was warmed to 23 °C and stirred until a separation of phases

³⁰ Blunt, A. J.; Bailey, C. D.; Cons, B. D.; Edwards, S. J.; Elsworth, J. D.; Pheko, T.; Willis, C. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 3901.

was observed. The organics were extracted with dichloromethane (2 x 25 mL), dried over sodium sulfate, concentrated *in vacuo* and carried forward to the following reaction without further purification.

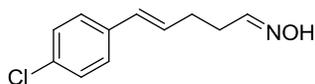
Oxime formation: To the crude aldehyde (2.5 mmol) in a solution of methanol (20 mL) was added hydroxylamine hydrochloride (434 mg, 6.25 mmol) and sodium acetate (513 mg, 6.25 mmol). A reflux condenser was fitted to the flask, and the mixture heated at reflux for 14 h. Upon cooling to ambient temperature, water (~30 mL) was added to the reaction mixture, and the mixture was extracted with dichloromethane (3 x 15 mL). The organic phase was dried over sodium sulfate, concentrated *in vacuo*, and purified by flash chromatography on silica gel to give the desired oxime.

(4E)-5-phenylpent-4-enal oxime (S9h):



Following the general procedure on a 2.9 mmol scale, the desired product (400 mg, 79% yield over two steps) was isolated as a white solid as a 3.5:1 mixture of oxime isomers. The following NMR data is for the major isomer. ^1H NMR (500MHz, CDCl_3) δ = 8.75 (br. s., 1 H), 7.39 - 7.34 (m, 2 H), 7.33 - 7.29 (m, 2 H), 7.25 - 7.19 (m, 1 H), 6.80 (t, J = 5.3 Hz, 1 H), 6.46 (d, J = 16.0 Hz, 1 H), 6.22 (td, J = 6.7, 15.9 Hz, 1 H), 2.59 (dt, J = 5.5, 7.3 Hz, 2 H), 2.48 - 2.37 (m, 2 H); ^{13}C NMR (126MHz, CDCl_3) δ = 151.8, 137.3, 130.9, 128.7, 128.5, 127.1, 126.0, 29.3, 24.5; FTIR: 3189 (s), 3083 (s), 3027 (s), 2869 (s), 1666 (m), 1596 (w), 1577 (w), 1490 (s), 1320 (m), 1233 (m); LRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{11}\text{H}_{14}\text{NO}$: 176.10, found 176.2

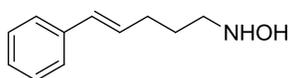
(4E)-5-(4-chlorophenyl)pent-4-enal oxime (S9i):



Following the general procedure on a 4.9 mmol scale, the desired product (800 mg, 78% yield over two steps) was isolated as a white solid. ^1H NMR (500MHz, CDCl_3) δ = 7.94 - 7.76 (m, 1 H), 7.31 - 7.23 (m, 4 H), 6.79 (t, J = 5.5 Hz, 1 H), 6.42 (d, J = 15.6 Hz, 1 H), 6.20 (td, J = 6.8, 15.7 Hz, 1 H), 2.59 (dt, J = 5.5, 7.3 Hz, 2 H), 2.44 (q, J = 7.3 Hz, 2 H); ^{13}C NMR (126MHz, CDCl_3) δ = 152.1, 136.1, 133.0, 130.0, 129.7, 128.9, 127.5, 29.5, 24.6; FTIR: 3188 (m), 3087 (m), 3037 (m), 2874 (m), 1896 (w), 1723 (m), 1666 (m), 1594 (m), 1490 (s), 1445 (m), 1406 (m), 1352 (m); LRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{11}\text{H}_{13}\text{ClNO}$: 210.06, found 210.1

Oxime reduction: A solution of oxime **S9h**, or **i** (1.5 mmol) in acetic acid (2.5 mL) was cooled to 15 °C, and sodium cyanoborohydride (188 mg, 3.0 mmol) was added in one portion. After stirring at 15 °C for 5 mins, the mixture was warmed to 23 °C and stirred for 1 h. The reaction was quenched by the addition of 20% aq. potassium carbonate (20 mL) and extracted with diethyl ether. The organics were washed with 20% aq. potassium carbonate (20 mL) dried over magnesium sulfate, concentrated *in vacuo*, and purified by flash chromatography on silica gel to give the desired hydroxylamine product.

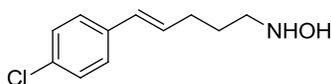
(E)-N-(5-phenylpent-4-en-1-yl)hydroxylamine (17h):



Following the general procedure on a 2.3 mmol scale, the desired product was isolated as a white solid (195 mg, 48% yield). ^1H NMR (500MHz, CDCl_3) δ = 7.37 - 7.33 (m, 2 H), 7.33 - 7.28 (m,

2 H), 7.23 - 7.19 (m, 1 H), 6.42 (d, $J = 15.6$ Hz, 1 H), 6.22 (td, $J = 7.1, 15.6$ Hz, 1 H), 3.01 (t, $J = 7.1$ Hz, 2 H), 2.29 (q, $J = 6.9$ Hz, 2 H), 1.76 (quin, $J = 7.3$ Hz, 2 H); ^{13}C NMR (126MHz, CDCl_3) $\delta = 137.6, 130.4, 129.9, 128.5, 126.9, 125.9, 53.3, 30.5, 26.6$; FTIR: 3265 (m), 3246 (m), 3122 (m), 3024 (m), 2944 (m), 2836 (m), 1513 (w), 1492 (m), 1451 (s), 1436 (m), 1374 (m), 1146 (m); LRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{11}\text{H}_{16}\text{NO}$: 178.12, found 178.2

(E)-N-(5-(4-chlorophenyl)pent-4-en-1-yl)hydroxylamine (17i):

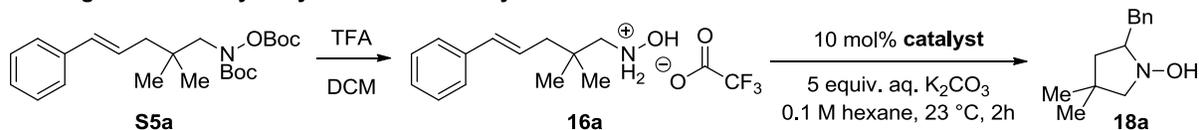


Following the general procedure on a 3.8 mmol scale, the desired product was isolated as a white solid (270 mg, 34% yield). ^1H NMR (500MHz, CDCl_3) $\delta = 7.26$ (s, 4 H), 6.36 (d, $J = 16.0$ Hz, 1 H), 6.19 (td, $J = 6.9, 16.0$ Hz, 1 H), 3.00 (t, $J = 7.1$ Hz, 2 H), 2.28 (q, $J = 7.3$ Hz, 2 H), 1.74 (quin, $J = 7.3$ Hz, 2 H); ^{13}C NMR (126MHz, CDCl_3) $\delta = 136.1, 132.5, 130.7, 129.2, 128.6, 127.1, 53.3, 30.5, 26.6$; FTIR: 3278 (m), 3149 (m), 2929 (s), 2828 (s), 1592 (w), 1544 (m), 1491 (s), 1432 (m), 1406 (m), 1371 (m); LRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{11}\text{H}_{15}\text{ClNO}$: 212.08, found 212.1

4.7.4. General Procedure for the Thiourea-Catalyzed Cope-Type Hydroamination

Due to rapid thermal cyclization of hydroxylamine substrates, in many cases the hydroxylamine starting materials were generated *in situ* from the corresponding trifluoroacetate salts by the addition of aqueous potassium carbonate. This was necessary for hydroxylamines **17a-b**, **17e-g** and **17j** (see methods A and B below).

***In situ* generation of hydroxylamine under catalytic conditions**



For hydroxylamines **17c-d**, it was not necessary to generate the hydroxylamine *in situ*, but they were not stable to purification by flash chromatography on silica gel. For these substrates, the hydroxylamine was generated from reduction of the parent oxime, and carried into the catalytic hydroamination without further purification (see method C below).

Hydroxylamines **17h-i** were stable to purification by flash chromatography. These substrates were generated from the reduction of the parent oxime, purified by flash chromatography on silica gel, and then subjected to the catalytic reaction conditions (see method D below).

Method A (catalyst screening):

Deprotection: To a solution of Boc-protected hydroxylamine **S5a** (101 mg, 0.25 mmol) in dichloromethane (2.4 mL) was added trifluoroacetic acid (0.6 mL). The mixture was stirred for 1 h at 23 °C, then concentrated *in vacuo* to yield salt **16a**. The salt was left under reduced pressure (~0.5 torr) for 1 h, and then dissolved in dichloromethane (2.25 mL). 0.5 mL of solution was added to each of four one-dram vials, and the contents of the vials were concentrated. To one vial, mesitylene was added as an internal standard, and the amount of salt in that vial was determined by ¹H NMR (0.046-0.049 mmol), which provided the yield for the deprotection (85-90%) and the amount of salt in the remaining three vials for the catalyst screening reactions.

Hydroamination: To a one dram vial containing trifluoroacetate salt **16a** (0.046 mmol) was added hexanes (0.46 mL) and catalyst (0.0046 mmol). 20% aq. potassium carbonate (0.153 mL,

0.23 mmol) was added, and the mixture was stirred *vigorously* for 2 h. The mixture was extracted with dichloromethane (3 x 3 mL). *p*-Nitrobenzoyl chloride (34 mg, 0.18 mmol) and triethylamine (0.05 mL, 0.36 mmol) were added to the combined organics, and the mixture was stirred for 2 h. 20% aq. potassium carbonate (5 mL) was added, and the organics were extracted with dichloromethane (3 x 5 mL), dried over sodium sulfate, and concentrated *in vacuo*. Mesitylene was added as an internal standard, and the yield was determined by ¹H NMR. The *O*-benzoylated product was purified by flash chromatography on silica gel and the enantiomeric excess was determined by HPLC analysis.

Method B (synthetic scale for substrates 17a-b, 17e-g and 17j):

Deprotection: To a solution of Boc-protected hydroxylamine **S5a** (0.3 mmol) in dichloromethane (2.4 mL) was added trifluoroacetic acid (0.6 mL). The mixture was stirred for 1 h at 23 °C, then concentrated *in vacuo* to yield salt **16a**. The salt was left under reduced pressure (~0.5 torr) for 1 h, and then dissolved in dichloromethane (1.25 mL). 0.1 mL of the solution was added to a one-dram vial, and 1.0 mL of the solution was added to a 10 mL round bottom flask. The contents of the vial and flask were concentrated. To the vial, mesitylene was added as an internal standard, and the amount of salt in that vial was determined by ¹H NMR (0.025 mmol), which allowed for the determination of the amount of salt in the round bottom flask (0.25 mmol).

Hydroamination: To round bottom flask containing trifluoroacetate salt **16a** (0.25 mmol) was added hexanes (2.5 mL) and catalyst **12f** (16.7 mg, 0.025 mmol). The mixture was cooled to 0 °C and 20% aq. potassium carbonate (0.864 mL, 1.25 mmol) was added. The mixture was stirred *vigorously* for 12 h at 3 °C. The mixture was extracted with dichloromethane (3 x 10 mL). *p*-Nitrobenzoyl chloride (185 mg, 1.0 mmol) and triethylamine (0.279 mL, 2.0 mmol) were added

to the combined organics, and the mixture was stirred for 2 h. 20% aq. potassium carbonate (10 mL) was added, and the organics were extracted with dichloromethane (3 x 10 mL), dried over sodium sulfate, concentrated *in vacuo* and purified by flash chromatography on silica gel.

Method C (synthetic scale for substrates 1c-d):

Oxime reduction: A solution of oxime **S4c** (0.6 mmol) in acetic acid (1.2 mL) was cooled to 15 °C, and sodium cyanoborohydride (75 mg, 1.2 mmol) was added in one portion. After stirring at 15 °C for 5 mins, the mixture was warmed to 23 °C and stirred for 1 h. The reaction was quenched by the addition of ~10 mL aq. potassium carbonate (200 mg/mL) and extracted with diethyl ether. The organics were washed with ~10 mL aq. potassium carbonate (200 mg/mL) dried over magnesium sulfate and concentrated *in vacuo* to yield the desired hydroxylamine. The crude hydroxylamine was dissolved in diethyl ether (1.2 mL). 0.5 mL of solution was added to each of two 10 mL round bottom flasks, and the contents of the flasks were concentrated. Mesitylene was added to one of the flasks as an internal standard, and the amount of hydroxylamine (0.19 mmol) in that flask was determined by ¹H NMR, which allowed for the determination of the amount of hydroxylamine (0.19 mmol) present in the other round bottom flask, which was *immediately* carried forward to the catalytic hydroamination.

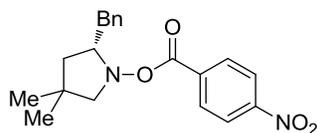
Hydroamination: To round bottom flask dram vial containing hydroxylamine **17c** (0.19 mmol) was added hexanes (1.9 mL) and catalyst **12f** (12.7 mg, 0.019 mmol). The mixture was stirred *vigorously* for 36 h at 3 °C. To the mixture was added dichloromethane (10 mL), *p*-nitrobenzoyl chloride (141 mg, 0.76 mmol) and triethylamine (0.212 mL, 1.52 mmol), and the mixture was stirred for 2 h. 20% aq. potassium carbonate (10 mL) was added, and the organics were extracted with dichloromethane (3 x 10 mL), dried over sodium sulfate, concentrated *in vacuo* and purified by flash chromatography on silica gel.

Method D (synthetic scale for substrates 17h-i):

Hydroamination: To round bottom flask dram vial containing hydroxylamine **17h** (0.20 mmol) was added hexanes (2.0 mL) and catalyst **12f** (13.4 mg, 0.02 mmol). The mixture was stirred *vigorously* for 36 h at 3 °C. To the mixture was added dichloromethane (10 mL), *p*-nitrobenzoyl chloride (141 mg, 0.76 mmol) and triethylamine (0.212 mL, 1.52 mmol), and the mixture was stirred for 2 h. 20% aq. potassium carbonate (10 mL) was added, and the organics were extracted with dichloromethane (3 x 10 mL), dried over sodium sulfate, concentrated *in vacuo* and purified by flash chromatography on silica gel.

4.7.5. Product Characterization

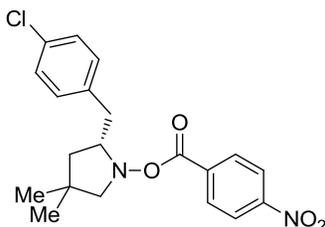
(S)-2-benzyl-4,4-dimethylpyrrolidin-1-yl 4-nitrobenzoate (**18a-Bz**):



According to the general procedure (method B), hydroxylamine **17a** (0.25 mmol) was reacted for 12 h to give the desired *O*-benzoylated hydroxylamine **18a-Bz** (74.0 mg, 83% yield) as a clear oil. The material was determined to be 94% ee by chiral HPLC analysis (AS-H, 5% IPA in hexanes, 1.0 mL/min, 254 nm, $t_r(\text{major})=7.2$ min, $t_r(\text{minor})=10.2$ min) $[\alpha]_D^{25}=19.7^\circ$ ($c=0.95$, CHCl_3); $^1\text{H NMR}$ (500MHz, CDCl_3) $\delta = 8.21$ (d, $J = 8.8$ Hz, 2 H), 7.91 (d, $J = 8.3$ Hz, 2 H), 7.24 - 7.16 (m, 4 H), 7.14 - 7.03 (m, 1 H), 3.66 (qd, $J = 6.9, 10.5$ Hz, 1 H), 3.57 (d, $J = 10.3$ Hz, 1 H), 3.04 (dd, $J = 6.3, 13.7$ Hz, 1 H), 2.85 (dd, $J = 7.1, 13.4$ Hz, 1 H), 2.79 (d, $J = 10.3$ Hz, 1 H), 1.82 (dd, $J = 7.3, 13.2$ Hz, 1 H), 1.63 - 1.53 (m, 1 H), 1.22 (s, 3 H), 1.15 (s, 3 H); $^{13}\text{C NMR}$ (126MHz, CDCl_3) $\delta = 163.3, 150.3, 139.1, 134.6, 130.4, 129.0, 128.3, 126.1, 123.3, 70.1, 69.1, 43.2, 40.1,$

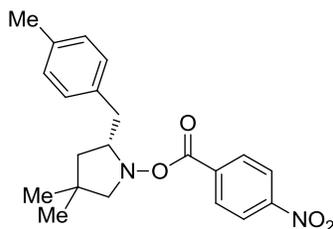
34.9, 30.4, 29.9; FTIR (neat, cm^{-1}): 3110 (w), 3059 (w), 3028 (m), 2868 (m), 1742 (s), 1606 (m), 1526 (s), 1347 (s), 1259 (s); LRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{20}\text{H}_{22}\text{N}_2\text{O}_4$: 355.16, found: 355.2

(S)-2-(4-chlorobenzyl)-4,4-dimethylpyrrolidin-1-yl 4-nitrobenzoate (**18b-Bz**):



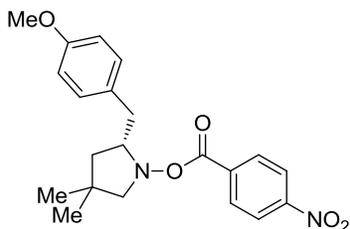
According to the general procedure (method B), hydroxylamine **17b** (0.20 mmol) was reacted for 5 h to give the desired *O*-benzoylated hydroxylamine **18b-Bz** (67.5 mg, 87% yield) as a clear oil. The material was determined to be 95% ee by chiral HPLC analysis (AS-H, 5% IPA in hexanes, 1.0 mL/min, 254 nm, $t_r(\text{major})=9.6$ min, $t_r(\text{minor})=17.6$ min) $[\alpha]_D^{25}=25.1^\circ$ ($c=0.46$, CHCl_3); ^1H NMR (500MHz, CDCl_3) $\delta = 8.21$ (d, $J = 8.8$ Hz, 2 H), 7.88 (d, $J = 8.3$ Hz, 2 H), 7.15 - 7.08 (m, 4 H), 3.61 (qd, $J = 6.9, 10.6$ Hz, 1 H), 3.53 (d, $J = 10.3$ Hz, 1 H), 2.93 (dd, $J = 6.8, 13.7$ Hz, 1 H), 2.83 (dd, $J = 6.3, 13.7$ Hz, 1 H), 2.77 (d, $J = 10.3$ Hz, 1 H), 1.80 (dd, $J = 7.6, 12.9$ Hz, 1 H), 1.53 (m, 1 H), 1.19 (s, 3 H), 1.16 - 1.12 (m, 3 H); ^{13}C NMR (126MHz, CDCl_3) $\delta = 163.2, 150.4, 137.6, 134.3, 131.9, 130.3, 130.2, 128.4, 123.3, 70.0, 68.8, 43.1, 39.4, 34.8, 30.3, 29.9$; FTIR (neat, cm^{-1}): 3111 (w), 2959 (m), 2929 (m), 2868 (m), 1742 (s), 1607 (m), 1526 (s), 1492 (m), 1259 (s); LRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{20}\text{H}_{22}\text{ClN}_2\text{O}_4$: 389.12, found: 389.1

(S)-4,4-dimethyl-2-(4-methylbenzyl)pyrrolidin-1-yl 4-nitrobenzoate (**18c-Bz**):



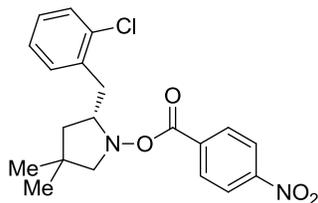
According to the general procedure (method C), hydroxylamine **17c** (0.19 mmol) was reacted for 36 h to give the desired *O*-benzoylated hydroxylamine **18c-Bz** (59.1 mg, 84% yield) as a clear oil. The material was determined to be 87% ee by chiral HPLC analysis (AS-H, 5% IPA in hexanes, 1.0 mL/min, 230 nm, $t_r(\text{major})=6.4$ min, $t_r(\text{minor})=8.2$ min) $[\alpha]_D^{24}=23.3^\circ$ ($c=0.84$, CHCl_3); $^1\text{H NMR}$ (500MHz, CDCl_3) $\delta = 8.21$ (d, $J = 9.2$ Hz, 2 H), 7.91 (d, $J = 8.7$ Hz, 2 H), 7.09 (d, $J = 8.2$ Hz, 2 H), 6.99 (d, $J = 7.8$ Hz, 2 H), 3.63 (qd, $J = 7.0, 10.5$ Hz, 1 H), 3.56 (d, $J = 10.5$ Hz, 1 H), 2.99 (dd, $J = 6.4, 13.7$ Hz, 1 H), 2.87 - 2.74 (m, 2 H), 2.20 (s, 3 H), 1.82 (dd, $J = 7.3, 12.8$ Hz, 1 H), 1.64 - 1.51 (m, 1 H), 1.25 (s, 3 H), 1.15 (s, 3 H); $^{13}\text{C NMR}$ (126MHz, CDCl_3) $\delta = 163.3, 150.3, 136.0, 135.5, 134.6, 130.4, 129.0, 128.8, 123.2, 70.1, 69.2, 43.2, 39.6, 34.8, 30.4, 29.9, 20.8$; FTIR (neat, cm^{-1}): 3111 (w), 2957 (m), 2867 (m), 1742 (s), 1607 (m), 1526 (s), 1451 (m), 1347 (s), 1258 (s); LRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_4$: 369.17, found: 369.1

(S)-2-(4-methoxybenzyl)-4,4-dimethylpyrrolidin-1-yl 4-nitrobenzoate (18d-Bz):



According to the general procedure (method C), hydroxylamine **17d** (0.18 mmol) was reacted for 96 h to give the desired *O*-benzoylated hydroxylamine **18d-Bz** (63.5 mg, 96% yield) as a clear oil. The material was determined to be 91% ee by chiral HPLC analysis (AS-H, 5% IPA in hexanes, 1.0 mL/min, 254 nm, $t_r(\text{major})=9.7$ min, $t_r(\text{minor})=14.1$ min) $[\alpha]_D^{25} = -26.5^\circ$ ($c=0.92$, CHCl_3); $^1\text{H NMR}$ (500MHz, CDCl_3) $\delta = 8.21$ (d, $J = 8.7$ Hz, 2 H), 7.93 (d, $J = 8.7$ Hz, 2 H), 7.11 (d, $J = 8.7$ Hz, 2 H), 6.71 (d, $J = 8.7$ Hz, 2 H), 3.66 (s, 3 H), 3.61 (qd, $J = 6.9, 10.5$ Hz, 1 H), 3.55 (d, $J = 10.1$ Hz, 1 H), 2.96 (dd, $J = 6.4, 13.7$ Hz, 1 H), 2.83 - 2.74 (m, 2 H), 1.81 (dd, $J = 7.3, 12.8$ Hz, 1 H), 1.61 - 1.51 (m, 1 H), 1.21 (s, 3 H), 1.14 (s, 3 H); $^{13}\text{C NMR}$ (126MHz, CDCl_3) $\delta = 163.3, 157.9, 150.3, 134.6, 131.1, 130.3, 129.8, 123.2, 113.7, 70.1, 69.2, 55.0, 43.1, 39.1, 34.8, 30.4, 29.9$; FTIR (neat, cm^{-1}): 3112 (w), 2958 (m), 2868 (m), 1742 (s), 1610 (m), 1527 (s), 1513 (s), 1348 (m), 1249 (s); LRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_5$: 385.17, found: 385.1

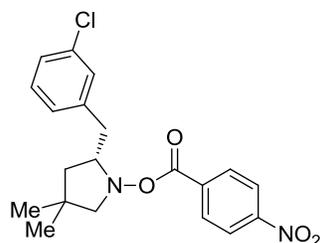
(S)-2-(2-chlorobenzyl)-4,4-dimethylpyrrolidin-1-yl 4-nitrobenzoate (18e-Bz):



According to the general procedure (method B), hydroxylamine **17e** (0.18 mmol) was reacted for 5 h to give the desired *O*-benzoylated hydroxylamine **18e-Bz** (64.0 mg, 91% yield) as a clear oil.

The material was determined to be 92% ee by chiral HPLC analysis (AS-H, 5% IPA in hexanes, 1.0 mL/min, 254 nm, $t_r(\text{major})=6.8$ min, $t_r(\text{minor})=8.0$ min) $[\alpha]_D^{25}=3.2^\circ$ ($c=0.67$, CHCl_3); ^1H NMR (500MHz, CDCl_3) $\delta = 8.21$ (d, $J = 8.7$ Hz, 2 H), 7.93 (d, $J = 8.7$ Hz, 2 H), 7.32 - 7.20 (m, 2 H), 7.02 (dquin, $J = 1.6, 7.0$ Hz, 2 H), 3.80 (qd, $J = 6.9, 10.4$ Hz, 1 H), 3.59 (d, $J = 10.1$ Hz, 1 H), 3.17 (dd, $J = 6.6, 13.5$ Hz, 1 H), 2.98 (dd, $J = 6.6, 13.5$ Hz, 1 H), 2.76 (d, $J = 10.1$ Hz, 1 H), 1.83 (dd, $J = 7.3, 12.8$ Hz, 1 H), 1.59 (m, 1 H), 1.27 - 1.20 (m, 1 H), 1.15 (s, 1 H); ^{13}C NMR (126MHz, CDCl_3) $\delta = 163.2, 150.3, 136.8, 134.5, 133.8, 131.5, 130.3, 129.4, 127.7, 126.7, 123.3, 70.0, 66.7, 43.0, 38.0, 34.8, 30.4, 29.9$; FTIR (neat, cm^{-1}): 3111 (w), 2959 (m), 2868 (m), 1743 (s), 1607 (m), 1527 (s), 1474 (m), 1444 (m), 1348 (s), 1259 (s); LRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{20}\text{H}_{22}\text{ClN}_2\text{O}_4$: 389.12, found: 389.1

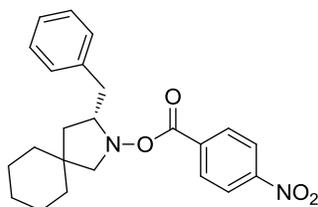
(S)-2-(3-chlorobenzyl)-4,4-dimethylpyrrolidin-1-yl 4-nitrobenzoate (**2f-Bz**):



According to the general procedure (method B), hydroxylamine **17f** (0.22 mmol) was reacted for 5 h to give the desired *O*-benzoylated hydroxylamine **18f-Bz** (74.3 mg, 87% yield) as a clear oil. The material was determined to be 94% ee by chiral HPLC analysis (AS-H, 5% IPA in hexanes, 1.0 mL/min, 254 nm, $t_r(\text{major})=8.8$ min, $t_r(\text{minor})=12.8$ min) $[\alpha]_D^{25}=14.4^\circ$ ($c=0.65$, CHCl_3); ^1H NMR (500MHz, CDCl_3) $\delta = 8.22$ (d, $J = 8.2$ Hz, 2 H), 7.92 (d, $J = 8.7$ Hz, 2 H), 7.20 (s, 1 H), 7.13 - 7.06 (m, 2 H), 7.03 - 6.98 (m, 1 H), 3.65 (qd, $J = 7.1, 10.4$ Hz, 1 H), 3.55 (d, $J = 10.1$ Hz, 1 H), 2.97 (dd, $J = 6.6, 13.5$ Hz, 1 H), 2.84 (dd, $J = 6.4, 13.7$ Hz, 1 H), 2.79 (d, $J = 10.1$ Hz, 1 H),

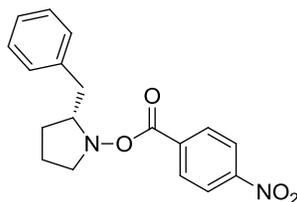
1.83 (dd, $J = 7.8, 12.8$ Hz, 1 H), 1.60 - 1.50 (m, 1 H), 1.21 (s, 3 H), 1.16 (s, 3 H); ^{13}C NMR (126MHz, CDCl_3) $\delta = 163.2, 150.4, 141.2, 134.4, 134.1, 130.3, 129.6, 129.0, 127.2, 126.3, 123.3, 70.2, 68.7, 43.1, 39.8, 34.9, 30.3, 29.9$; FTIR (neat, cm^{-1}): 2958 (m), 2868 (m), 1745 (s) 1600 (m), 1528 (s), 1477 (w), 1349 (m), 1261 (s); LRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{20}\text{H}_{22}\text{ClN}_2\text{O}_4$: 389.12, found: 389.1

(S)-3-benzyl-2-azaspiro[4.5]decan-2-yl 4-nitrobenzoate (**18g-Bz**):



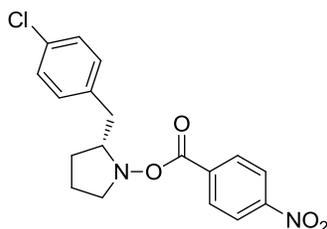
According to the general procedure (method B), hydroxylamine **17g** (0.20 mmol) was reacted for 5 h to give the desired *O*-benzoylated hydroxylamine **18g-Bz** (64.8 mg, 82% yield) as a clear oil. The material was determined to be 96% ee by chiral HPLC analysis (AS-H, 5% IPA in hexanes, 1.0 mL/min, 254 nm, $t_r(\text{major}) = 7.7$ min, $t_r(\text{minor}) = 10.6$ min) $[\alpha]_D^{25} = 25.9^\circ$ ($c = 0.61$, CHCl_3); ^1H NMR (500MHz, CDCl_3) $\delta = 8.21$ (d, $J = 8.8$ Hz, 2 H), 7.90 (d, $J = 8.3$ Hz, 2 H), 7.21 (d, $J = 4.4$ Hz, 4 H), 7.13 - 7.06 (m, 1 H), 3.67 (d, $J = 10.3$ Hz, 1 H), 3.60 (qd, $J = 6.8, 10.7$ Hz, 1 H), 3.03 (dd, $J = 6.3, 13.7$ Hz, 1 H), 2.85 (dd, $J = 6.8, 13.7$ Hz, 1 H), 2.74 (d, $J = 9.8$ Hz, 1 H), 1.86 (dd, $J = 7.1, 12.9$ Hz, 1 H), 1.64 - 1.31 (m, 10 H); ^{13}C NMR (126MHz, CDCl_3) $\delta = 163.3, 150.3, 139.2, 134.6, 130.4, 128.9, 128.4, 126.1, 123.3, 68.3, 40.9, 40.0, 39.1, 38.9, 25.6, 23.4, 23.3$; FTIR (neat, cm^{-1}): 3110 (w), 2926 (s), 2853 (m), 1743 (s), 1606 (m), 1527 (s), 1452 (m), 1319 (m), 1261 (s); LRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{23}\text{H}_{26}\text{N}_2\text{O}_4$: 395.19, found: 395.1

(R)-2-benzylpyrrolidin-1-yl 4-nitrobenzoate (**18h-Bz**):



According to the general procedure (method D), hydroxylamine **17g** (0.20 mmol) was reacted for 72 h at 30 °C to give the desired *O*-benzoylated hydroxylamine **18f-Bz** (44.6 mg, 68% yield) as a clear oil. The material was determined to be 81% ee by chiral HPLC analysis (AS-H, 10% IPA in hexanes, 1.0 mL/min, 254 nm, $t_r(\text{major}) = 8.8$ min, $t_r(\text{minor}) = 10.0$ min) $[\alpha]_D^{25} = 8.7^\circ$ (c=0.98, CHCl₃); ¹H NMR (500MHz, CDCl₃) $\delta = 8.22$ (d, $J = 8.7$ Hz, 2 H), 7.94 (d, $J = 8.2$ Hz, 2 H), 7.24 - 7.16 (m, 4 H), 7.12 - 7.04 (m, 1 H), 3.77 - 3.65 (m, 1 H), 3.53 (qd, $J = 7.1, 9.4$ Hz, 1 H), 3.14 - 2.96 (m, 2 H), 2.83 (dd, $J = 7.3, 13.7$ Hz, 1 H), 2.14 - 1.86 (m, 3 H), 1.78 - 1.61 (m, 1 H); ¹³C NMR (126MHz, CDCl₃) $\delta = 163.5, 150.4, 139.1, 134.6, 130.4, 128.9, 128.4, 126.1, 123.3, 69.1, 56.6, 39.8, 27.0, 20.0$; FTIR (neat, cm⁻¹): 3110 (w), 3028 (w), 2977 (m), 2869 (m), 1741 (s), 1606 (m), 1526 (s), 1496 (m), 1347 (s), 1259 (s); LRMS [M+H]⁺ calculated for C₁₈H₁₈N₂O₄: 327.13, found: 327.1

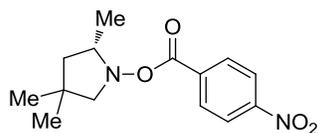
(R)-2-(4-chlorobenzyl)pyrrolidin-1-yl 4-nitrobenzoate (**18h-Bz**):



According to the general procedure (method D), hydroxylamine **17h** (0.20 mmol) was reacted for 72 h at 30 °C to give the desired *O*-benzoylated hydroxylamine **18h-Bz** (67.1 mg, 93% yield)

as a clear oil. The material was determined to be 83% ee by chiral HPLC analysis (AS-H, 10% IPA in hexanes, 1.0 mL/min, 254 nm, $t_r(\text{major})=9.7$ min, $t_r(\text{minor})=12.2$ min) $[\alpha]_D^{25}=17.0^\circ$ ($c=1.45$, CHCl_3); $^1\text{H NMR}$ (500MHz, CDCl_3) $\delta = 8.22$ (d, $J = 9.2$ Hz, 2 H), 7.91 (d, $J = 8.7$ Hz, 2 H), 7.16 - 7.07 (m, 4 H), 3.68 (ddd, $J = 4.1, 7.1, 10.8$ Hz, 1 H), 3.48 (qd, $J = 7.2, 9.2$ Hz, 1 H), 3.09 - 2.90 (m, 2 H), 2.83 (dd, $J = 6.4, 13.7$ Hz, 1 H), 2.11 - 1.87 (m, 3 H), 1.73 - 1.57 (m, 1 H); $^{13}\text{C NMR}$ (126MHz, CDCl_3) $\delta = 163.4, 150.4, 137.5, 134.3, 132.0, 130.3, 128.4, 123.3, 68.8, 56.5, 39.2, 26.9, 19.9$; FTIR (neat, cm^{-1}): 3019 (m), 2955 (m), 2864 (w), 1742 (s), 1607 (m), 1529 (s), 1492 (m), 1348 (m), 1261 (s), 1216 (s); LRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{18}\text{H}_{18}\text{ClN}_2\text{O}_4$: 361.09, found: 361.0

(S)-2,4,4-trimethylpyrrolidin-1-yl 4-nitrobenzoate (**2i-Bz**):



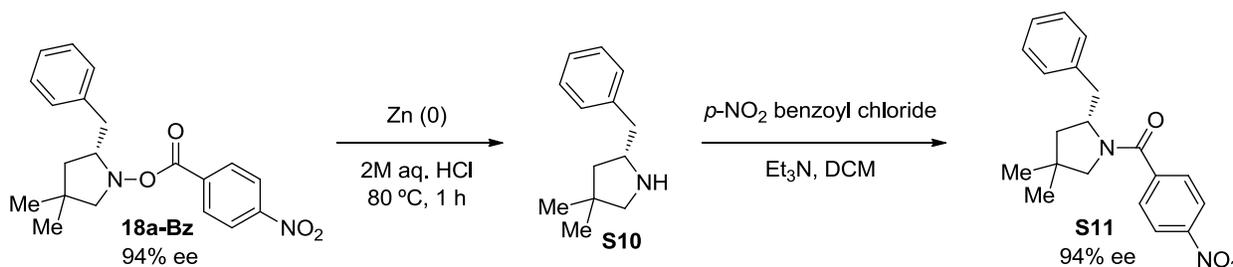
According to the general procedure (method B) with the exception that **11e** was used as the catalysy, hydroxylamine **17i** (0.24 mmol) was reacted for 2 h at 3 °C to give the desired *O*-benzoylated hydroxylamine **18i-Bz** (60.9 mg, 91% yield) as a clear oil. The material was determined to be 85% ee by chiral HPLC analysis (AD-H, 5% IPA in hexanes, 1.0 mL/min, 254 nm, $t_r(\text{major})=11.0$ min, $t_r(\text{minor})=10.4$ min) $[\alpha]_D^{25}=38.2^\circ$ ($c=0.82$, CHCl_3); $^1\text{H NMR}$ (500MHz, CDCl_3) $\delta = 8.27$ (d, $J = 8.7$ Hz, 2 H), 8.16 (d, $J = 8.7$ Hz, 2 H), 3.58 - 3.38 (m, 2 H), 2.83 (d, $J = 10.1$ Hz, 1 H), 1.84 (dd, $J = 7.3, 12.8$ Hz, 1 H), 1.49 (m, 1 H), 1.24 (d, $J = 6.0$ Hz, 3 H), 1.21 (s, 3 H), 1.16 (s, 3 H); $^{13}\text{C NMR}$ (126MHz, CDCl_3) $\delta = 163.4, 150.4, 134.8, 130.4, 123.5, 70.1, 63.7, 45.1, 35.3, 30.6, 30.1, 17.8$; FTIR (neat, cm^{-1}): 3112 (w), 2960 (m), 2868 (m), 1742 (s), 1607

(m), 1526 (s), 1347 (s), 1258 (s); LRMS $[M+H]^+$ calculated for $C_{14}H_{18}N_2O_4$: 279.13, found: 279.1

4.7.6. Reduction of *O*-Benzoylated Products

Hydroxylamines can be reduced to the corresponding amine under a variety of conditions.³¹

Reduction of *O*-benzoylated hydroxylamine product **2a-Bz**:



To **18a-Bz** (24 mg, 0.068 mmol) was added water (2.5 mL) and zinc powder (44.5 mg, 0.68 mmol). The mixture was stirred, and concentrated HCl (0.5 mL) was added slowly. A reflux condenser was fitted to the flask, and the mixture was heated at 80 °C for 1 h. The mixture was cooled to 0 °C, and 4M sodium hydroxide was added (3 mL). The aqueous phase was extracted with dichloromethane (3 x 15 mL). The organics were dried over sodium sulfate, and concentrated *in vacuo* to give amine **S10** (75% yield by ¹H NMR analysis using mesitylene as internal standard). The spectral data for **S10** matched those reported in the literature.³²

S10 was benzoylated in order to facilitate analysis by HPLC.

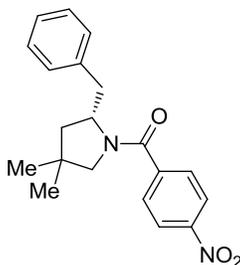
To a solution of amine **S10** (0.051 mmol) in dichloromethane (2 mL) was added *p*-NO₂ benzoyl chloride (28 mg, 0.15 mmol) and triethylamine (0.042 mL, 0.3 mmol). The reaction was stirred

³¹ See Cicci, S.; Bonanni, M.; Cardona, F.; Revuelta, J.; Goti, A. *Org. Lett.* **2003**, *5*, 1773 and references therein.

³² Zhang, X.; Emge, T. J.; Hultsch, K. C. *Angew. Chem., Int. Ed.* **2012**, *51*, 394.

for 14 h, then quenched by the addition of 20% aq. potassium carbonate (2 mL). The organics were extracted with dichloromethane, concentrated *in vacuo* and purified by chromatography on silica gel to give the product as a white solid.

(2-benzyl-4,4-dimethylpyrrolidin-1-yl)(4-nitrophenyl)methanone (S11):



$[\alpha]_D^{23} = 132.6^\circ$ (c=0.46, CHCl_3); $^1\text{H NMR}$ (500MHz, CDCl_3) $\delta = 8.29$ (d, $J = 8.7$ Hz, 2 H), 7.68 (d, $J = 8.7$ Hz, 2 H), 7.38 - 7.32 (m, 2 H), 7.30 - 7.25 (m, 3 H), 4.65 - 4.52 (m, 1 H), 3.30 (dd, $J = 3.2, 12.8$ Hz, 1 H), 3.00 (dd, $J = 8.5, 13.0$ Hz, 1 H), 2.95 (s, 2 H), 1.79 (dd, $J = 7.6, 12.6$ Hz, 1 H), 1.65 (dd, $J = 10.1, 12.4$ Hz, 1 H), 0.98 (s, 3 H), 0.89 (s, 3 H); $^{13}\text{C NMR}$ (126MHz, CDCl_3) $\delta = 167.9, 148.6, 142.9, 137.8, 129.8, 128.5, 128.3, 126.5, 123.7, 63.0, 58.1, 43.8, 38.7, 38.2, 25.5, 25.5$; FTIR: 3106 (w), 3028 (w), 2958 (m), 2869 (m), 1631 (s), 1522 (s), 1494 (m), 1422 (s), 1349 (s), 1292 (m), 1210 (m); LRMS $[\text{M}+\text{H}]^+$ calculated for $\text{C}_{20}\text{H}_{23}\text{N}_2\text{O}_3$: 339.16, found: 339.2

For enantioenriched **18a-Bz** (94% ee) no erosion of enantioenrichment was observed during the sequence.

4.7.7. Absolute Stereochemistry Determination

Absolute stereochemistry was determined by derivatization of the pyrrolidine **S10** to corresponding Mosher amide and comparison of the ^{19}F spectroscopic data to the previously assigned configuration for that compound.^{32,33}

Procedure for Mosher amide formation and ^{19}F NMR Analysis:

(*R*)-Mosher acid was converted to the corresponding (*S*)-Mosher acid chloride according to the literature procedure.³⁴

Amine **S10** (0.04 mmol) was diluted with CDCl_3 (1.0 mL). DIPEA (0.017 mL, 0.1 mmol) and (*S*)-Mosher acid chloride (0.6 mmol) were added to the mixture with stirring. After 5 minutes, the reaction mixture was analyzed by ^{19}F NMR analysis at 50 °C.

Mosher adduct: ^{19}F NMR (CDCl_3 , 50 °C) δ -70.0 (major), -71.0 (minor). Referenced to the (*S*)-Mosher acid chloride resonance at -70.5

4.7.8. Calculations³⁵

Calculations were executed at Harvard University on the Odyssey research computing cluster using the Gaussian 03³⁶ program with the B3LYP³⁷ method. The 6-311+G(d,p) basis sets of

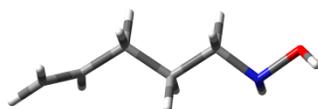
³³ Gribkov, D. V.; Hultsch, K. C.; Hampel, F. *J. Am. Chem. Soc.* **2006**, *128*, 3748.

³⁴ Smith, P. M.; Thomas, E. J. *J. Chem. Soc. Perkin Trans. 1* **1998**, 3541.

³⁵ Calculations carried out by Dr. Christopher Uyeda.

³⁶ Gaussian 03, Revision E.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, Jr., J. A.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.;

Pople and co-workers was used.³⁸ All stationary points are fully optimized and verified by frequency calculations using the rigid-rotor/harmonic-oscillator assumption. Transition structures were characterized by the existence of a single imaginary frequency corresponding to the process of interest and local minima were characterized by the absence of any imaginary frequencies. Energies are reported in units of hartrees.



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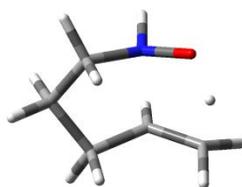
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Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; and Pople, J. A.; Gaussian, Inc., Wallingford CT, 2004.

³⁷ B3LYP = Becke-3-Lee-Yang-Parr density functional theory. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

³⁸ (a) Ditchfield, R.; Hehre, W. J.; Pople, J. A. *J. Chem. Phys.* **1971**, *54*, 724. (b) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257. (c) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta.* **1973**, *28*, 213.

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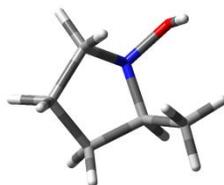
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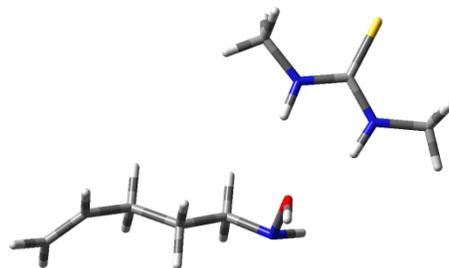
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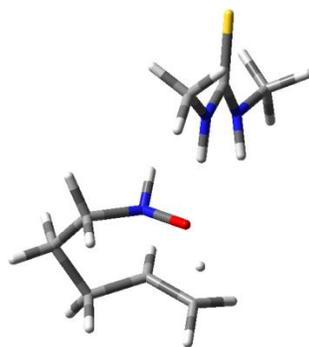
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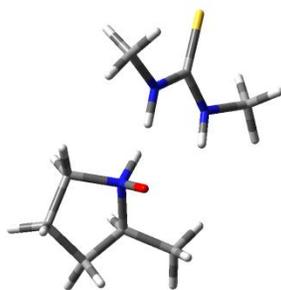
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C	-2.36350500	0.09183600	0.07099900
H	-0.94508000	-0.87669500	1.16484300
N	-1.51873200	1.17490900	0.03885500
C	-1.93914500	2.48011500	-0.45092800
H	-0.77374500	1.16488600	0.72742500
H	-1.08380200	3.15591300	-0.38702600
H	-2.26297200	2.40865300	-1.48923300
H	-2.76953300	2.89219900	0.13176000
S	-3.84493900	0.06396400	-0.72686200
C	1.96672000	-1.43874000	-0.65018300
H	1.25323400	-1.96173400	-1.29344800
H	2.15000300	-2.05512900	0.23181800
C	4.06469600	-0.14715700	-0.45866700
H	4.92796100	0.26179200	-0.99511300
H	4.45517100	-0.69846800	0.40317000
C	3.27429300	-1.10120400	-1.37105800
H	3.05464700	-0.60988300	-2.32577000
H	3.84304000	-2.00614900	-1.60133800



Charge: 0

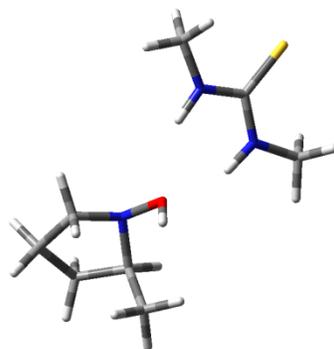
Multiplicity: 1

E = -954.10632561

Imaginary Frequencies: 0

C	2.61417900	2.06656800	0.46394700
H	1.82467400	2.73393000	0.10755200
H	3.56263900	2.60503400	0.39353400
C	2.69284400	0.79993600	-0.36483100
H	2.75890300	1.04453200	-1.43171800
N	1.43162400	-0.05195500	-0.23724900
H	0.65443600	0.39208600	-0.75645600
O	1.04914800	-0.23432800	1.06955700
H	-2.56812800	-2.73618600	-0.37422500
C	-2.35428300	-2.37495400	0.63594700
H	-1.71329000	-3.09384600	1.14947300
H	-3.30604600	-2.30032200	1.16768400
N	-1.66556700	-1.09839000	0.61342400
C	-2.19365300	0.03169500	0.08996400
H	-0.71040500	-1.03458200	0.97938500
N	-1.35087600	1.12167200	0.18141700
C	-1.82967800	2.47937800	-0.04330100
H	-0.60313000	1.00899900	0.86749300
H	-0.98699300	3.16149200	0.08935300
H	-2.21873700	2.58225100	-1.05610500
H	-2.62910500	2.75721900	0.65171200
S	-3.71228000	0.10376900	-0.63343200
C	1.83125000	-1.34406700	-0.89720000
H	1.80229400	-1.18686900	-1.97969900
H	1.10039700	-2.09914400	-0.62031600
C	3.79833100	-0.19631800	0.01311800
H	4.72840900	0.05478200	-0.49972300
H	3.98284900	-0.14966400	1.08670300
C	3.25719300	-1.59685500	-0.38528900

H	3.86228400	-2.07242800	-1.15875400
H	3.23917200	-2.25947000	0.47881300
H	2.41972200	1.81491500	1.50647300



Charge: 0

Multiplicity: 1

E = -954.10969404

Imaginary Frequencies: 0

C	-3.37492300	-1.45489300	1.11119300
H	-2.57508200	-1.80420500	1.77082400
H	-4.01879500	-2.31490000	0.91178400
C	-2.82669500	-0.91313000	-0.21754500
H	-2.27785400	-1.70953200	-0.72598400
N	-1.91999000	0.25404100	-0.10377100
O	-0.89904500	0.09145300	0.87448600
H	3.03787500	2.68475500	-0.71409600
C	2.62451800	2.44451000	0.26910800
H	1.86960700	3.18796200	0.53235900
H	3.44043200	2.48943100	0.99440400
N	1.98777500	1.14024400	0.27371100
C	2.63791600	-0.02122600	-0.00405900
H	0.99297900	1.09336200	0.45189600
N	1.84811700	-1.12754600	0.03075100

C	2.32366900	-2.47013200	-0.24823700
H	0.86648600	-1.00002800	0.23919000
H	1.47876700	-3.15400600	-0.14585200
H	2.72828400	-2.54830800	-1.26073700
H	3.11101400	-2.76587200	0.44947600
S	4.28612300	-0.08531300	-0.35653000
C	-2.75403400	1.43091200	0.16449300
H	-2.19646600	2.33968100	-0.06583500
H	-3.05070500	1.47801100	1.22655400
C	-3.91808800	-0.31215900	-1.12157900
H	-3.63646400	-0.42855400	-2.16896500
H	-4.87600600	-0.81497600	-0.97931900
C	-3.97558200	1.19981700	-0.74530400
H	-3.92272200	1.82165200	-1.63931000
H	-4.89974200	1.45709700	-0.22565300
H	-3.97489600	-0.71572200	1.65044300
H	-1.31431600	0.04817000	1.75417300