LEWIS BASE CATALYZED ENANTIOSELECTIVE SULFENOAMINATION OF ALKENES

BY

HYUNG MIN CHI

DISSERTATION

Submitted in partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Chemistry
in the Graduate College of the
University of Illinois at Urbana-Champaign, 2016

Urbana, Illinois

Doctoral Committee:

Professor Scott E. Denmark, Chair
Professor Martin D. Burke
Professor Wilfred A. van der Donk
Professor Thomas B. Rauchfuss

Abstract

The concept of Lewis base activation of Lewis acid has been successfully applied to the enantioselective sulfenoamination of olefins. The unreactive, achiral Lewis acidic sulfenylating agent, *N*-arylthiophthalimide, is activated by the coordination of a chiral Lewis base, binaphthyl-derived selenophosphoramide, in presence of a Brønsted acid as a co-catalyst. The Lewis base-acid adduct exhibits a strong sulfenylating ability towards various olefins with formation of enantioenriched thiiranium ion intermediates. These configurationally stable thiiranium ions are stereospecifically captured by amines and anilines to afford nitrogen-containing heterocycles, such as piperidines, azepanes, and tetrahydroquinolines.

In the course of developing an enantioselective carbosulfenylation of alkenes, a seemingly contradicting phenomenon of a catalyst inhibiting a stoichiometric reaction was observed. In the absence of catalyst, the background reaction rates were comparable to or greater than the catalyzed process, despite the observation of highly enantioenriched product when a chiral, nonracemic catalyst was employed. Detailed kinetic and spectroscopic studies revealed that the conversion of the Lewis base pre-catalyst to the catalytically active species was responsible for the observed comparable reactivity. Specifically, the equimolar formation of the byproducts of the catalyst activation, sulfonate ion and phthalimide, buffered the Brønsted acid, resulting in inhibition of the uncatalyzed racemic pathway. Therefore, the operating background reaction under catalytic conditions cannot be represented by simply omitting the catalyst.

To my beloved wife Jongmi,

My children Luke and Matthew,

And my Parents

Acknowledgements

I know *a man* who about sixty years ago traveled across the ocean to learn chemistry. Thirty years later, *another man* came across the ocean to study chemistry. It is not clear to me if it was their will or their destiny to come from far places to study chemistry. However, what I do know is that their will and destiny have become my own, and compelled me to live a life of a chemist. Before I give thanks to anyone else, I would want to give my deepest regards to both my Grandfather Ungup Chi, and my Father Dae Yoon Chi, *the man* who brought me to the World of Chemistry.

I have never had the opportunity to write such a volume of work. I sincerely admit that this work could have not been possible without the endless support and encouragement from family, friends, and group members. I would like to thank all of the current and past group members of the Denmark Group for their guidance and friendship. I especially want to thank Prof. Nate Werner and Dr. Larry Wolf for hosting me to the Denmark group when I was searching for labs. Special gratitude is expressed to Dr. David Kornfilt, who had been an amazing forerunner for me throughout the course of my Ph.D. I want to give special thanks to my former bay buddy Dr. Brian Casey, not only for the friendship and mentorship, but also for his exhaustive devotion struggling with my writings. I also want to thank Dr. Alex Jaunet, Dr. Sergio Rossi, Dr. Matt Webster, Dr. Eduard Hartmann, Dr. Stanley Eey, Dr. Pavel Ryabchuk, Dr. Dietrich Böse, and Dr. Scott Barraza who have been spectacular mentors to me and been great friends to me and my family. While most of aforementioned post-docs were in the same subgroup, I want to express my thanks to the entire Lewis base members for providing food for thought every Thursday.

Looking back at the recent years I spent in the Denmark group, I have to admit that every day was full of new learnings, realizations, and surprises. For that, I must acknowledge my advisor Prof. Scott E. Denmark, whom I give immeasurable thanks for his professional and generous guidance, endless understanding of my mistakes and faults, and continuous encouragement on my struggles. He is *the man* who taught me to breathe, think, and live like any chemist should do in the World of Chemistry.

This last word of gratitude and acknowledgement I have saved for my beloved wife Jongmi, all of this would have been impossible without your devotion, support, and sacrifice. With you, all these years have been made the best years of my life. Thank you.

September 2016. Urbana-Champaign.

Hyung Min Chi

Table of Contents

CHAPTER 1: Introduction

1.1 General Considerations

1.1.1 Lewis Definition of Acids and Bases

Acids and bases are one of the most fundamental concepts in chemistry that is required for understanding the reactivities of molecules. The first modern definition of acids and bases was formulated by Svante Arrhenius in 1896.[1] His definition, *an acids and bases are substances that dissociate hydrogen ions or hydroxide ions in aqueous solutions*, clearly showed its limitation for it being only applicable to aqueous solutions. In 1923, Johannes Brønsted and Martin Lowry devised an improved definition of acids and bases, focusing on the *ability to donate and accept the hydrogen ions*. While this definition removed the restriction of aqueous solutions, it still required a hydrogen atom to be present in the molecule to qualify as a Brønsted acid. Interestingly, in the same year of 1923, Gilbert N. Lewis stated, *"…we may say that* ***a basic substance is one which has a lone pair of electrons which may be used to complete the stable group of another atom and that an acid substance is one which can employ a lone pair from another molecule*** *in completing the stable group of one of its own atoms. In other words, the basic substance furnishes a pair of electrons for a chemical bond; the acid substance accepts such a pair."*[2]

The true impact of Lewis's definition is that each molecule's affinity towards electrons is the only factor considered for categorizing and explaining acidic and basic substances. That is, in simple words, a Lewis base is an electron-pair donor, and a Lewis acid is an electron-pair acceptor. This pioneering, revolutionary concept for acid and base has become the basis for understanding chemical reactivity in modern organic chemistry[3]

The interaction of a Lewis base with a Lewis acid is manifested by the octet rule. This rule describes that an atom is in a thermodynamically most stable "noble state" when its valence shell is fully occupied with electrons. As supported by many examples,[4] Lewis bases interact with acids to form more stable adduct, which the process is driven by fulfilling the noble state of both donor and acceptor. However, formation of a thermodynamically stable Lewis base-acid adduct does not necessarily mean reduction in reactivity.[5]

1.1.2 Jensen's Orbital Analysis of Lewis Base-Lewis Acid Adducts

Lewis acids and bases can influence reactions in various ways, such as by activating the substrates, or by modulating its electrochemical properties. To better understand the fundamental details of how reactions are influenced by Lewis acids and bases, Jensen classified the types of Lewis base-acid bonding interactions (Table 1).[3]

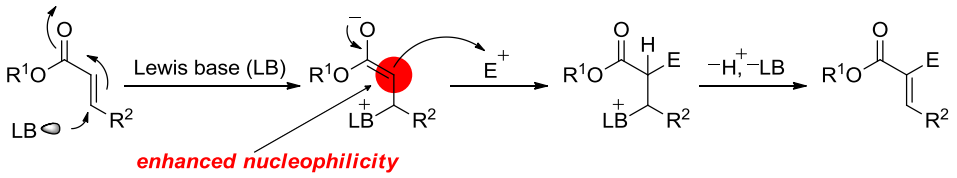
Table 1. Jensen's Orbital Analysis of Lewis Base-Lewis Acid Adducts.

Donor \ Acceptor	n*	σ*	π*
n	n-n*	n-σ*	n-π*
σ	σ-n*	σ-σ*	σ-π*
π	π-n*	π-σ*	π-π*

Overall 9 types of Lewis base-acid bonding interactions were proposed based on the available combination of three kinds of each of donor and acceptor orbitals. Among the possible donor-acceptor orbital interactions, only three orbital combinations are classified as important interactions that can increase chemical reactivity. Those three are interactions of non-bonding orbital (n) with: (1) anti-bonding π orbitals (n-π*) (2) anti-bonding σ orbitals (n-σ*), and (3) vacant non-bonding orbitals (n-n*).

Among the three orbital interactions mentioned above, the combination of the nonbonding electron pair of a Lewis base with an anti-bonding π orbital (n-π*) is the most common interaction that results with increased reactivity.[6] The Morita-Baylis-Hillman reaction is a good representative example of this type of activation (Scheme 1).[7] Conjugate addition of a phosphine (Lewis base, n) to α,β-unsaturated enone (Lewis acid, π*) generates zwitterionic enolate, which undergoes nucleophilic attack to the second carbonyl unit. Effectively, the enolate intermediate is activated by addition of a Lewis base, possessing an increased nucleophilic character at the α-carbon.

Scheme 1



The n-σ* and n-n* activation modes are the other two orbital interactions that can positively influence the reactivities. While these types of orbital interactions more exotic and exhibit a simultaneous increase in both nucleophilic and electrophilic character of the adduct, it requires the acceptor (Lewis acid) to be capable of forming a hypervalent species. This intriguing reactivity enhancement of the hypervalent adducts are best explained by Gutmann's analysis on Lewis base-acid interactions.[5]

1.1.3 Gutmann's Analysis

When a Lewis base (donor) interacts with a Lewis acid (acceptor), the electron density is transferred from the donor to the acid moiety. As a result, the overall electron density of the acid is increased and a stronger nucleophilicity is expected. However, enhancement of electrophilicity

of the adduct is simultaneously observed in some reactions. In 1978, Gutmann proposed an explanation for this counter-intuitive phenomenon, by identifying the uneven distribution of the electron density during the formation of the Lewis base-acid adduct (Figure 1).[5c]

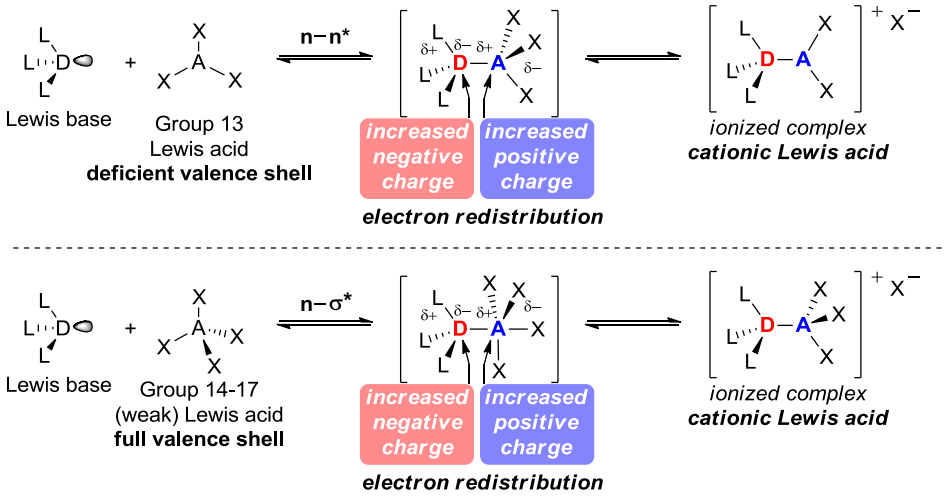
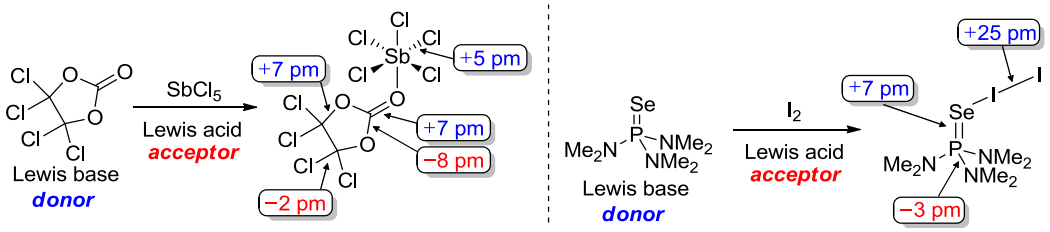


Figure 1. Structural redistribution of the donor-acceptor pair.

Gutmann formulated four rules from the empirical analyses of X-ray structures:[5c] (1) The smaller the intramolecular distance between the donor atom (D) and the acceptor atom (A), the greater the induced lengthening of the peripheral bonds (A–X), (2) the longer the bond between D and A, the greater the degree of polarization of electron density across the intramolecular bond, (3) as the coordination number of an atom increases, so do the lengths of all the bonds originating from that coordination center, and (4) the bonds adjacent to D and A will either contract or elongate to compensate for the changes in electron density at D and A. Described as the "spill-over" effect, the electron density is redistributed to the more electronegative substituent atoms. Consequently, the Lewis acidic central atom becomes more electrophilic compared to the parent Lewis acid, while the peripheral atoms are rendered more nucleophilic.

Upon treatment of a Lewis acid with a Lewis base, elongation of the bond between the central atom A and peripheral atom X is observed in the X-ray structure (Scheme 2). For example, the Lewis base-acid complex resulting from tetrachloroethylene carbonate with antimony pentachloride shows elongated Sb–Cl bond.[5c] Similarly, binding of Lewis base selenophosphoramide to Lewis acid iodine forms a complex with a significant lengthening of the I–I bond by 25 pm.[8]

Scheme 2



1.1.4 Hypervalent Bonding Analysis

The Lewis base-acid adducts form by n-σ* type interactions exhibit unusual properties that cannot be classified with conventional bonding structures. The newly formed bond between the donor (D) and the acceptor (A) is structurally identified as three-center four-electron (3c-4e) bondings, which are are highly electron-rich hypervalent bonds.[6,9] The characteristic feature of these 3c-4e bonds is that the both terminal atoms D, X are electron-rich, and the center atom A is electron-deprived. This can be better explained by analysis of a molecular orbital diagram of the hypervalent bond, obtained from combination of the three atomic orbitals D, A, and X (Figure 2). Whereas the bonding orbital (Ψ^1) equally shares electrons for all three atoms, the non-bonding orbital (Ψ^2) contains a node at the center atom A with increased electron density at terminal atoms. This means that the electron density is polarized toward the terminal atoms D and X. The energy gap between the Ψ^1 and Ψ^2 orbitals increases as the strength of donor increase.

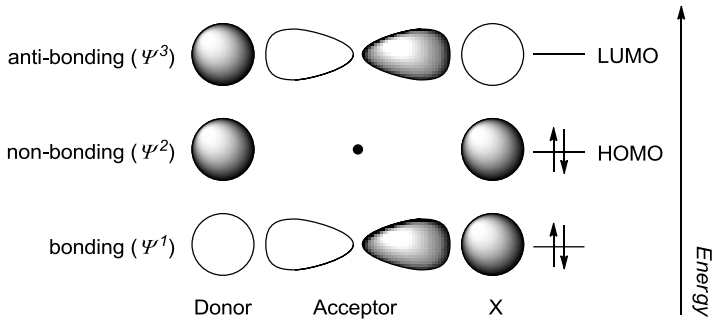
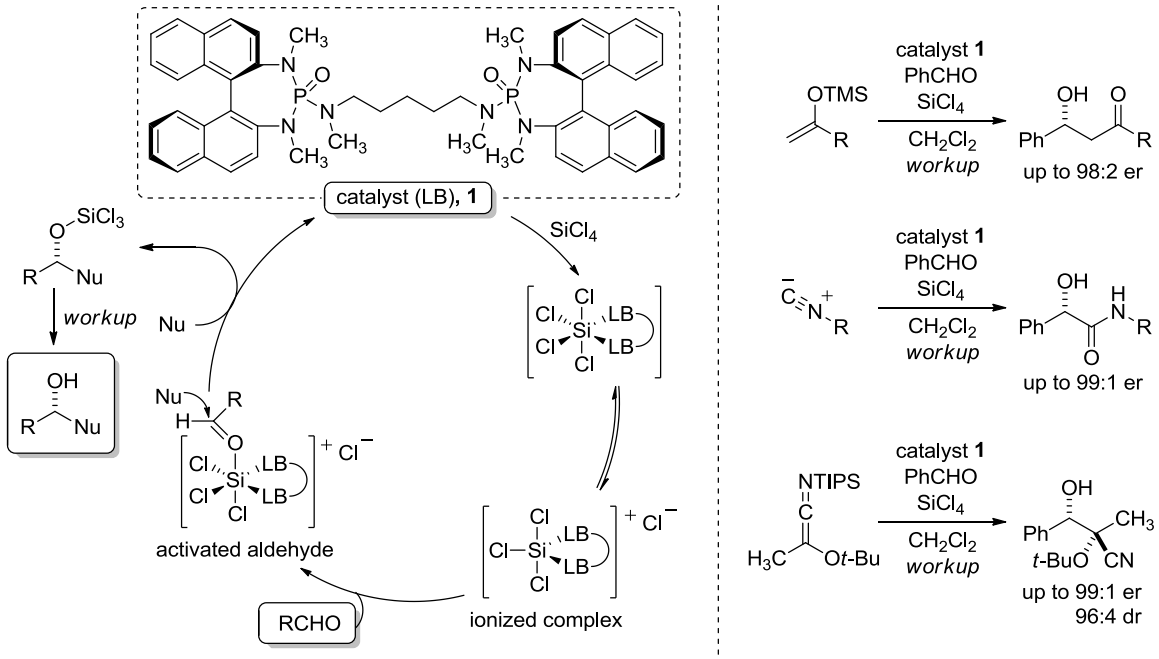


Figure 2. MO diagram of 3-center-4-electron hybrid bonding.

1.2 Lewis Base Catalysis

These laboratories have been focusing on reaction development employing n-σ* type Lewis base activation of a variety of Lewis acids including silicon(IV),[10] selenium(II),[11] and sulfur(II) reagents.[12]

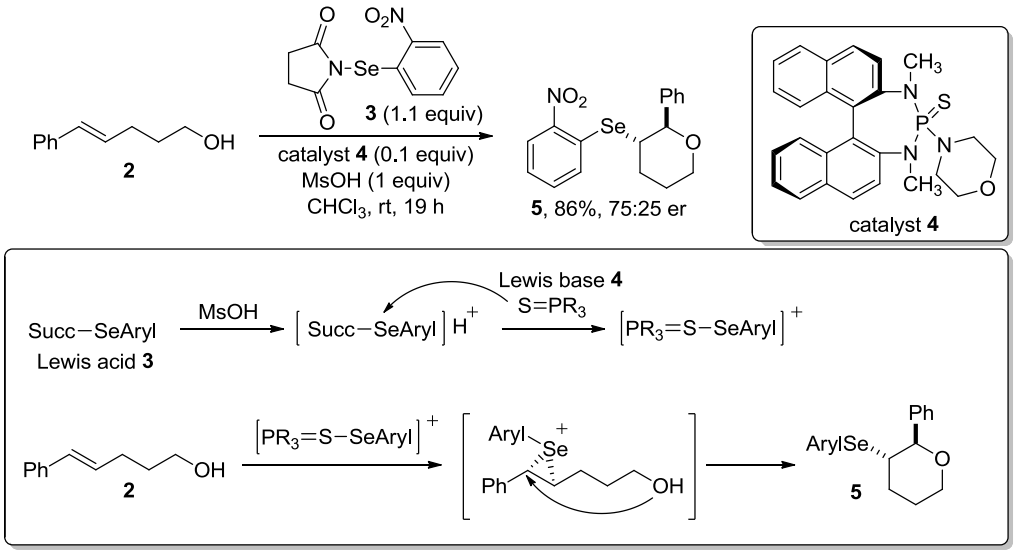
Scheme 3



In the Lewis base-catalyzed aldol reactions, Group 14 Lewis acid $SiCl_4$ is activated by chelation of bisphosphoramide **1** (Scheme 3). This generates highly activated chiral $[SiCl_4LB_2]$

complex,[10a] which binds to the carbonyl and enhances the electrophilic character towards incoming nucleophiles. An extensive scope of nucleophiles have been employed for the enantioselective, catalytic aldol reactions, such as silyl enol ethers, isocyanides, silyl ketene imines and many more.[10b]

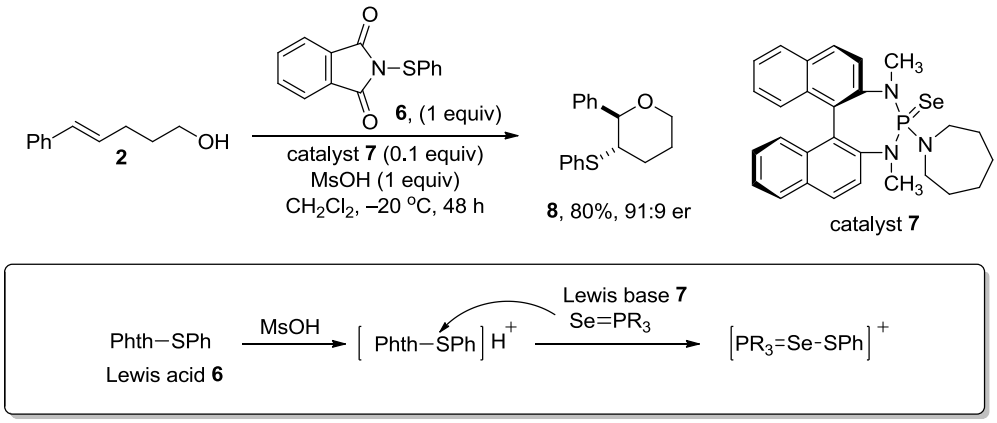
Scheme 4



More recently, selenofunctionalization reactions were developed by applying n-σ* type activation to Group 16 elements (Scheme 4).[11] Interaction of protonated arylselenyl succinimide **3** (Lewis acid) with chiral thiophosphoramide **4** (Lewis base) generates highly activated adduct, which is the *in situ* formed key chiral sulfenylating agent. Effectively, the arylselenium group is transferred from succinimide to thiophosphoramide **4** to generate the activated chiral selenylating species. This aryl selenium group is then subsequently delivered to the alkene **2** to form an enantioenriched seleniranium ion intermediate. This seleniranium ion is captured by pendant hydroxyl group to yield 3-selenotetrahydropyrans **5**. Configurational stability of the seleniranium ion was increased by installing an electron withdrawing nitro group on the *S*-aryl moiety, which resulted in enhanced enantiomeric composition of the cyclized product.

The n-σ* activation to Group 16 elements have been expanded to electrophilic sulfurs reagents for enantioselective oxysulfenylation of olefins (Scheme 5).[12] In a similar manner to selenofunctionalizations, the catalytically active complex $[R_3P{=}Se\text{-}SPh]^+$ was generated by interaction of selenophosphoramide **7** (Lewis base) with protonated *N*-phenylthiophthalimide **6** (Lewis acid). Various unactivated disubstituted olefins successfully afforded 3-sulfenylated tetrahydropyrans in high yields and enantioselectivities.

Scheme 5



1.3 Dissertation Objectives

In past years, the concept of Lewis base activation of acids has been successfully applied to the aforementioned reactions with good to excellent selectivities. While sulfenofunctionalization reactions have some more opportunity for improvement in enantioselectivity, it has not yet been explored with nitrogen-based nucleophiles for access of azaheterocycles. The objectives for this study is (1) to design Lewis base catalyzed, enantioselective sulfenoamination reactions with various nitrogen-based nucleophiles, (2) to engineer the Lewis base catalyst for selectivity enhancement, and (3) to explore mechanistic details of the sulfenofunctionalization reactions.

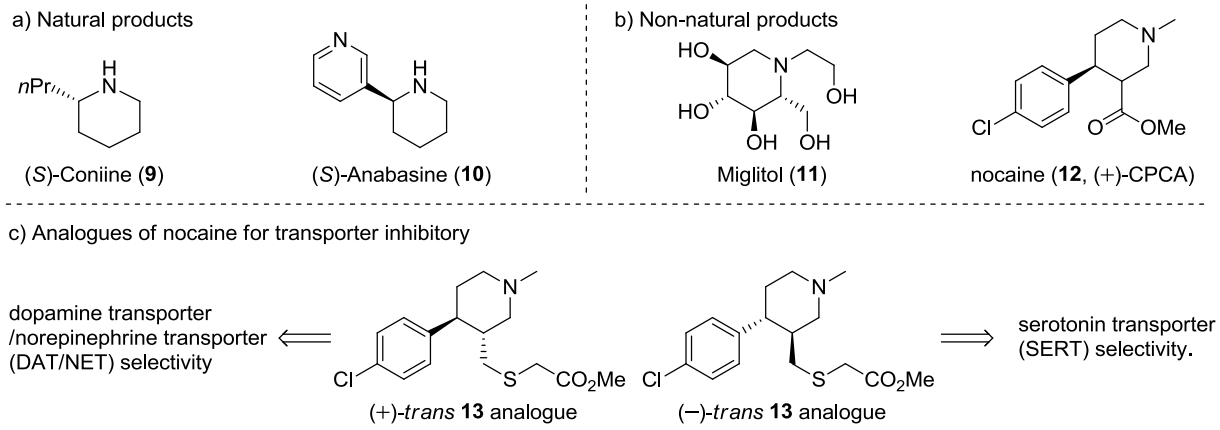
CHAPTER 2: Lewis Base Catalyzed, Enantioselective, Intramolecular Sulfenoamination of Olefins[13]

2.1 Introduction

2.1.1 Piperidines

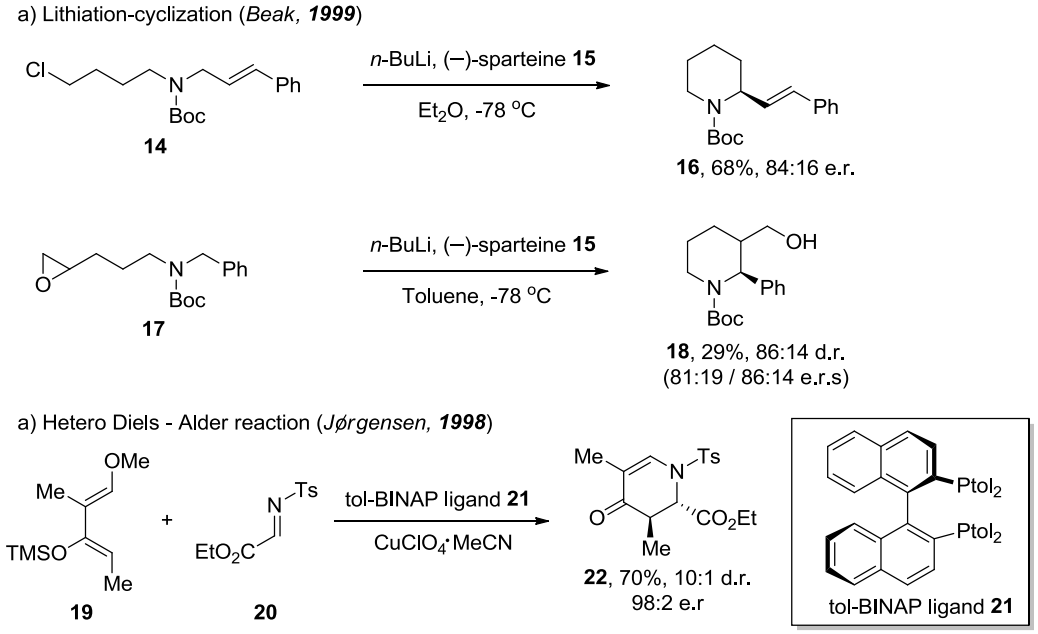
Piperidines are one of the most common subunits found in biologically important natural products and pharmaceutical compounds.[14,15] For example, both (*S*)-coniine (**9**),[15a] a poisonous alkaloid that disrupts human nerve systems found in hemlock, and (*S*)-anabasine (**10**),[15b] an insecticide found in tree tobacco plant, are simple natural products which contain a piperidine moiety (Scheme 6a). Miglitol (**11**),[15c] an FDA approved drug for type II diabetes, and nocaine (**12**),[15d] a stimulant drug developed to as a treatment for cocaine addiction, are non-natural compounds that have piperidine subunits (Scheme 6b). Interestingly, while investigating nocaine analogues **13**, the enantiomers of one set of analogues were shown to possess entirely different inhibitory potencies against targets (Scheme 6c).[15d] While the (+)-*trans* analogue was shown to selectively inhibit against the dopamine/norepinephrine transporter, the (–)-*trans* analogue inhibited serotonin transporter. These interesting regulation abilities has implications on the treatment of psychological conditions such as depression, or Parkinson's disease.[16]

Scheme 6



Due to the prevalence of stereodefined piperidine moieties in biologically and pharmaceutically active compounds, numerous strategies have been developed to generate piperidines chemo-, regio-, and stereoselectively for various types of substitutions.[14] For instance, enantioselective lithiation-cyclization of Boc-protected chlorobutylcinnamylamine **14** gave enantioenriched piperidines **16** by employing (–)-sparteine **15** as a chiral ligand (Scheme 7a).[17] In another example, an asymmetric Diels-Alder reaction of imines **20** with dienes **19** was developed to generate enantioenriched piperidinones **22**, which are common precursors to functionalized piperidines (Scheme 7b).[18] The development of general, efficient methods to produce enantiomerically enriched piperidine compounds would be significantly important to the pharmaceutical industry. In this Chapter, the development of a catalytic enantioselective sulfenoamination reaction as an effective route to synthesize 2,3-functionalized piperidines is described.

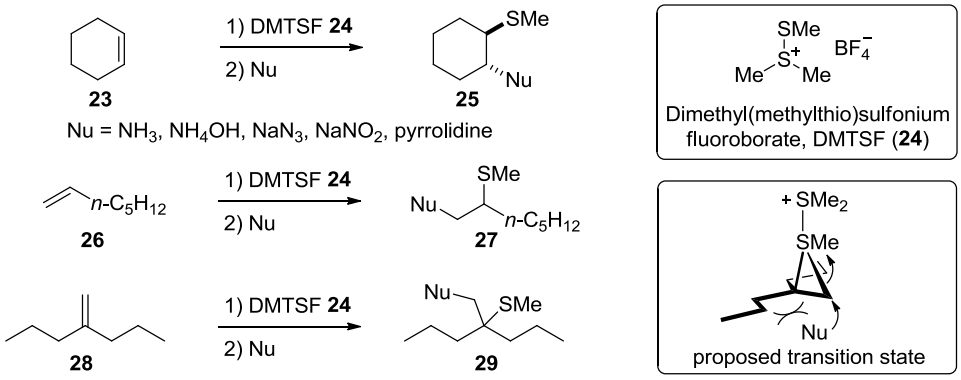
Scheme 7



2.1.2 Sulfenoamination of Olefins

Sulfenofunctionalization of alkenes with electrophilic sulfur reagents has been known since 1960s in the context of thiiranium ion chemistry.[19] Among them, sulfenoamination reaction, which involves incorporation of nitrogen and sulfur atoms into olefins in a stereodefined manner, provides access to the stereoselective synthesis of sulfenofunctionalized *N*-containing compounds.[20] In 1982, Trost and coworkers reported the first sulfenoamination of olefins with dimethyl(methylthio)sulfonium fluoroborate (DMTSF, **24**) and either ammonia, amine, azide, or nitrite as a nucleophile (Scheme 8).[21] Although the mechanism was not elucidated, the reactions were thought to proceed via olefin adducts of DMTSF because *anti*-Markovnikov products were obtained.[22]

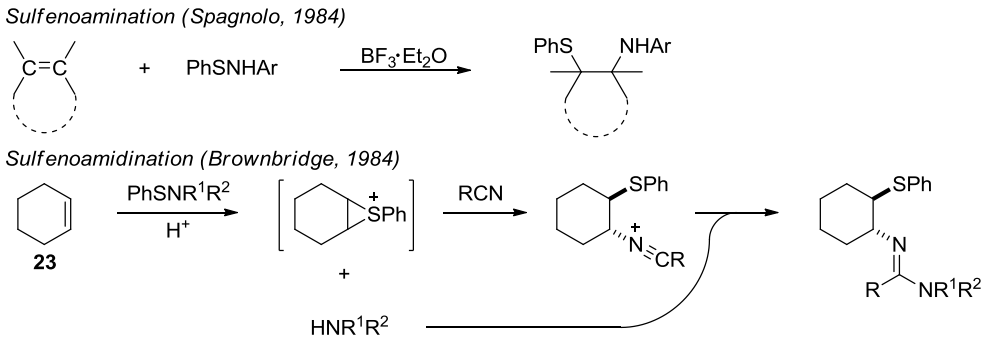
Scheme 8



In 1984, Spagnolo and coworkers illustrated the *anti* addition of sulfenanilides PhSNHAr to olefins in presence of BF_3·etherate (Scheme 9).[23] For these reactions, exclusive formation of the *anti* adduct suggested a thiiranium ion as a probable intermediate. In the same year, Brownbridge reported a sulfenoamidination reaction as an interesting extension of this method.[24] The author proposed that the reaction proceeds via the formation of a thiiranium ion due to the exclusive formation of *trans* products. The thiiranium ion is captured by the nitrogen atom of the

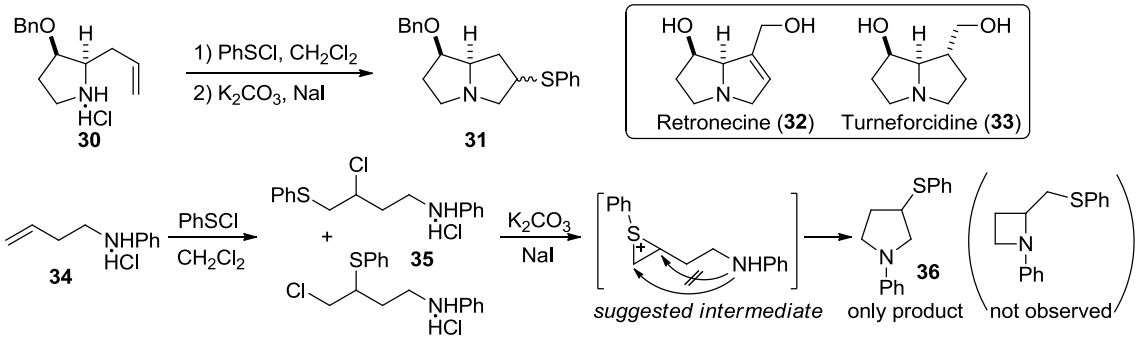
nitrile nucleophile and the corresponding nitrilium ion is subsequently captured with liberated amine generating the sulfenoamidine product.

Scheme 9



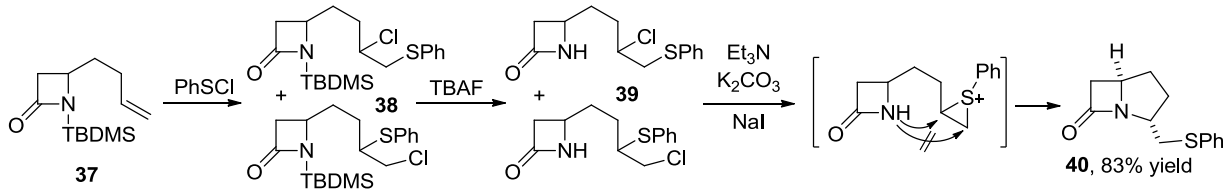
An intramolecular electrophilic sulfenoamination of β-alkenylamines by a 5-*endo*-trig closure constructing the pyrrolizidine ring was described by Kametani and coworkers (Scheme 10).[25] This sulfenoamination process was applied in a synthesis of pyrrolizidine-based natural products retronecine (**32**) and turneforcidine (**33**). The authors considered two possibilities (5-*endo*-trig and 4-*exo*-trig) for the ring closure (*vide infra*). Treatment of the terminal olefin **34** with benzenethiochloride (PhSCl) and an aniline nucleophile afforded two chlorosulfenylated intermediates **35**, and subsequent treatment of the mixture with K_2CO_3 and NaI afforded the pyrrolidine ring **36** as a single product. The reaction was proposed to proceed via a thiiranium ion based on the observation that both chlorosulfenylated intermediates lead to a single product.

Scheme 10



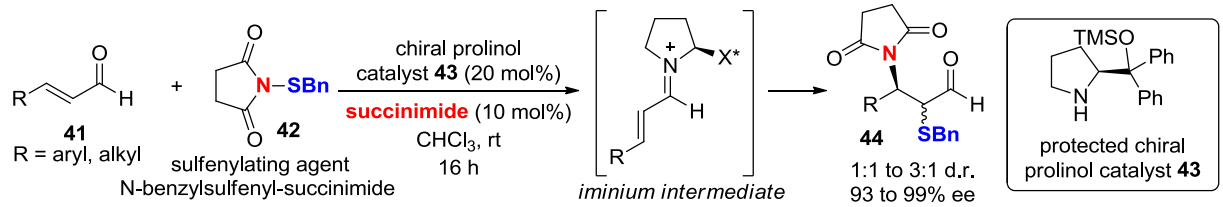
Another interesting example of intramolecular sulfenoamination is an application in the synthesis of β-lactam antibiotics (Scheme 11).[26] The reaction proceeds analogously to the above example, giving a mixture of two isomers **39** prior to intramolecular cyclization. Interestingly, the observed product **40** arose from a 5-*exo* cyclization instead of a 6-*endo*, indicating the formation of 5-membered rings is favored over 4- and 6-membed rings for terminal olefins.

Scheme 11



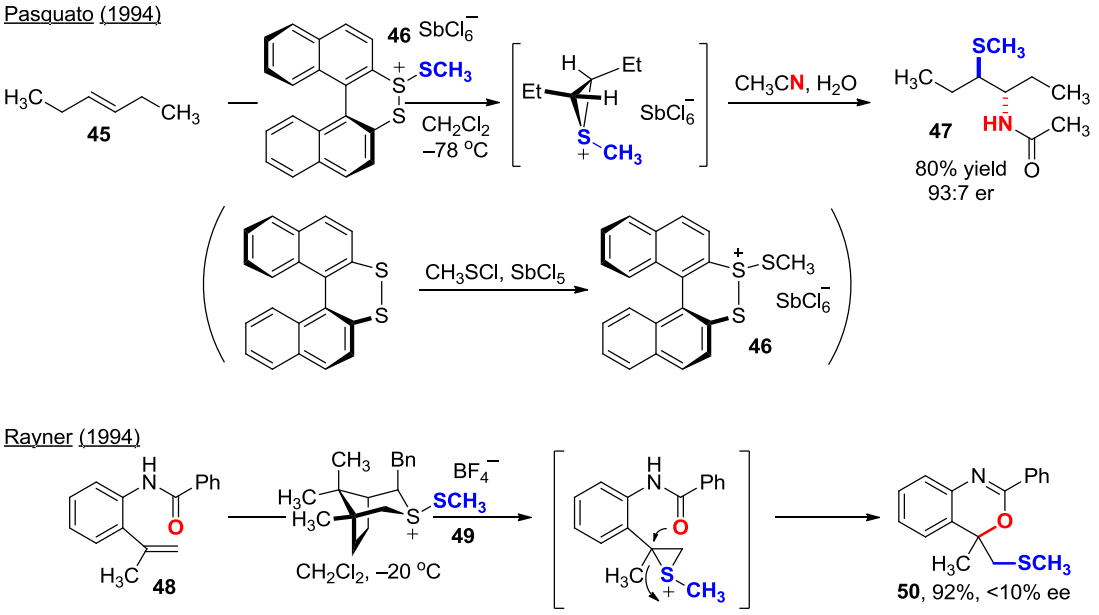
Catalytic, asymmetric variants of sulfenoamination have been developed by Cordova and coworkers (Scheme 12).[27] The reaction affords Michael-type adducts by employing a stoichiometric amount of the electrophilic sulfenylating reagent **42** with a catalytic amount of chiral prolinol-based organocatalyst **43**. α,β-Unsaturated aldehydes **41** reacts with prolinols **43** to generate iminium ion intermediate which is followed by vinylogous addition of succinimide at the β-position. Resulting enamine attacks electrophilic sulfur source **42** and releases succinimide to re-enter the catalytic cycle. The substitute pattern on the olefin is fairly broad with various aryl and alkyl substitutents proceeding with excellent enantioselectivity. However, reaction scope is limited to enals because of the enantiotopic facial discrimination of the olefin is believed to be achieved by formation of the iminium intermediate.

Scheme 12



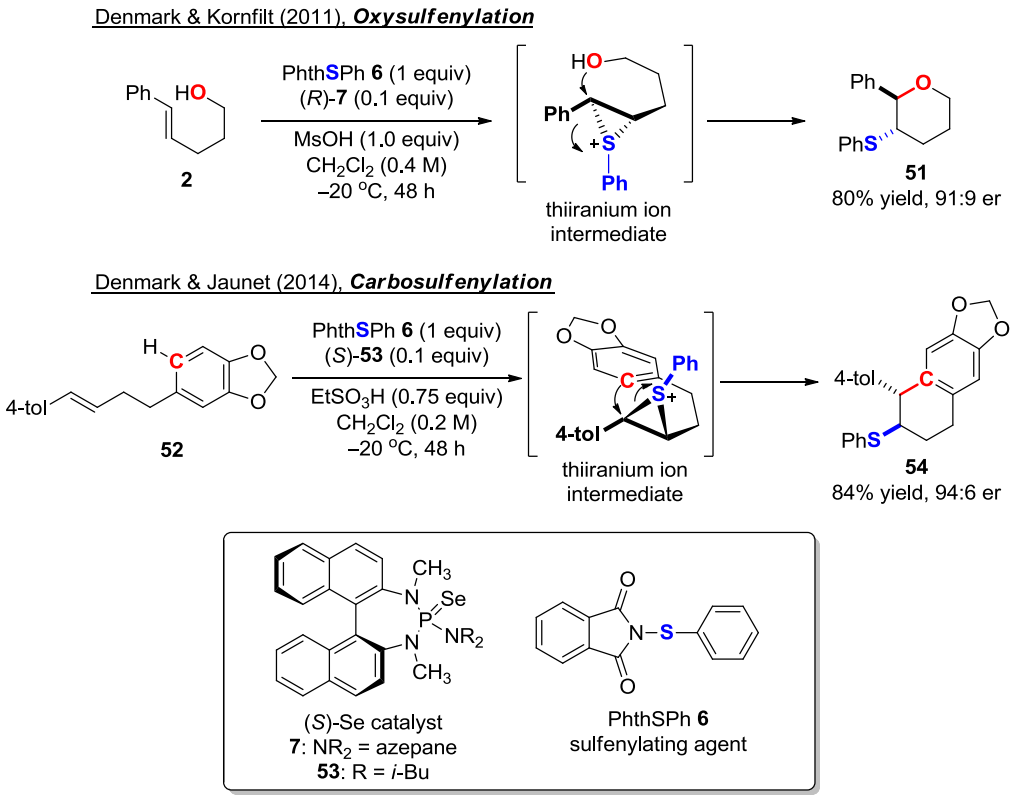
Given the amount of research performed in this field, the asymmetric sulfenoamination of unactivated olefins still remains underdeveloped. To date, only two examples of enantioselective sulfenylation reactions of unactivated olefins have been reported (Scheme 13).[28,29] In 1994, Pasquato and coworkers disclosed an enantioselective sulfenoamination of *trans*-3-hexene **45** by employing a binaphthyl-derived sulfenylating agent **46** as a stoichiometric reagent.[28] Subsequently, intermolecular capture of the thiiranium ions by acetonitrile in presence of water in a Ritter-type fashion afforded highly enantioenriched thioacetamides **47**. Generation of the thiiranium ions at lower temperatures (–78 °C) led to formation of the products with higher enantiomeric purities, which is consistent with temperature dependence on the configurational stability. Rayner reported the intramolecular capture of thiiranium ions generated from a chiral methylthiosulfonium salt **49** to afford benzoxazines **50**.[29] While the reaction proceeded cleanly with high yield, it only gave marginal stereoselection at –20 °C.

Scheme 13



Foregoing studies from these laboratories have described the first examples of the catalytic, enantioselective sulfenofunctionalization of unactivated olefins with oxygen-,[12] and carbon-based[30] nucleophiles (scheme 14). These reactions employ chiral Lewis base catalysts and proceed with high selectivities and to provide access to tetrahydropyrans, and tetralins, respectively. While terminal alkenes and *trans*-disubstituted alkenes showed high reactivities and enantioselectivities, trisubstituted alkenes and electron deficient alkenes and were found to react sluggishly. Unlike the work of Pasquato, which required stoichiometric amount of the sulfenylating agent, this reaction system was capable of generating a reactive chiral sulfenylating species *in situ* using a catalytic amount of BINAM-based chiral Lewis bases (**7** and **53**). Successful nucleophilic capture of the thiiranium ions with a pendant alcohol or aryl carbon afforded sulfenofunctionalized products with high enantioselectivities.

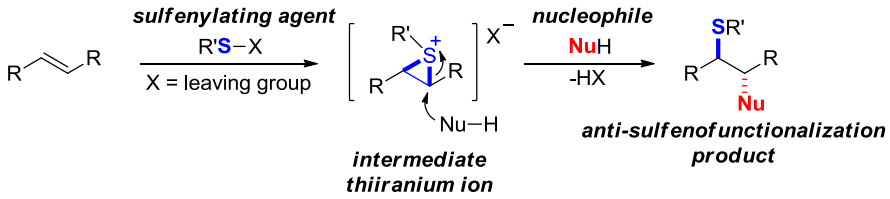
Scheme 14



2.1.3 The Intermediacy of Thiiranium Ions

Thiiranium ions (also called episulfonium ions) are analogous to epoxides and aziridinium ions in their ability to undergo ring opening with a variety of nucleophiles to install stereogenic centers (Scheme 15).[31] Thiiranium ions are typically generated from reaction of alkenes with electrophilic sulfur reagents, such as sulfenyl halides, thiosulfonium salts, and disulfides.[19,32] Despite the high reactivity of thiiranium ions, they are configurationally stable at low temperature and undergo stereospecific S_N2 ring opening by nucleophiles, thus leading to anti-sulfenofunctionalized products.[33]

Scheme 15



The electrophilic addition reaction of an olefin to a sulfur-based electrophile reagent is believed to proceed through formation of a thiiranium intermediate.[34] Subsequent nucleophilic attack at one of the carbon atoms of this intermediate leads to the desired sulfenofunctionalization. For this system to function both catalytically and enantioselectively, three criteria must be met: (1) the two enantiotopic faces of the olefin generate an enantioenriched chiral thiiranium ion, (2) the thiiranium ion must be configurationally stable, and (3) the capture of the thiiranium ion must occur selectively at the carbon atom.

For the first criterion, the formation of the activated chiral sulfenylating complex is critical (Figure 3).[33] Because the thiiranium ions are generated by electrophilic addition of the alkenes to the sulfur electrophile, the sulfenylating complex must exist in a chiral environment.

The resulting chiral sulfenylating complex can potentially interact favorably with one of the two enantiotopic faces of the alkene.

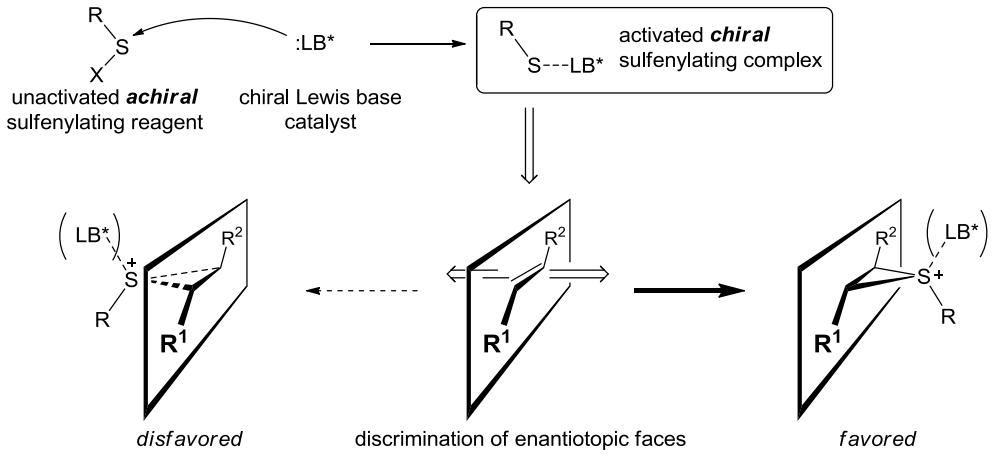


Figure 3. Formation of the activated chiral sulfenylating complex.

Secondly, racemization of the thiiranium ion intermediate needs to be avoided because racemization after the enantioselective formation of the thiiranium ion would lead to a loss of configuration homogeneity. The thiiranium ion can racemize via two pathways (Figure 4): (1) nucleophilic attack at the sulfur atom,[35] or (2) olefin-to-olefin transfer.[36]

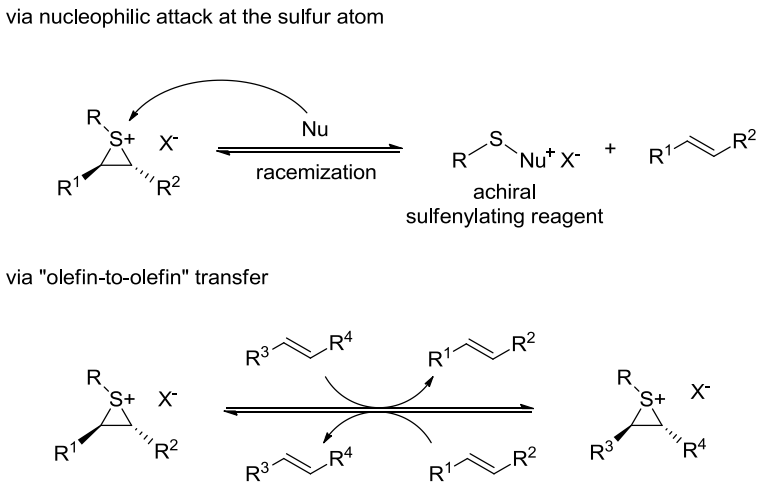
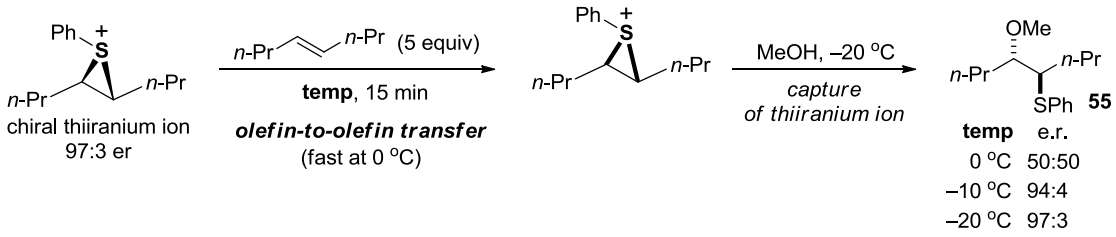


Figure 4. Potential racemization pathways of thiiranium ions.

Nucleophilic attack at the sulfur atom will produce an achiral sulfenylating reagent, which would lead to racemization of thiiranium ions upon delivery to olefins. Alternatively,

olefinic substrates present under catalytic condition could potentially lead to racemization via direct "olefin-to-olefin" transfer of the thiiranium moiety. Studies have shown that while the seleniranium ions are configurationally instable at –20 °C, *S*-phenyl thiiranium ions are stable and therefore preserve the configurational identity by the catalyst (Scheme 16).[33,36]

Scheme 16



Lastly, the nucleophile must open up the thiiranium ion by attacking the carbon atom (Figure 5). Attack at the sulfur atom not only promotes racemization as mentioned above, but also represents an unproductive pathway. To produce the desired sulfenofunctionalization product, nucleophilic attack at the carbon atom of the thiiranium ion is essential. Indeed, it was demonstrated experimentally that nucleophilic attack occurs preferentially at the carbon atom compared to the sulfur atom on the thiiranium moiety with stronger nucleophiles.[35]

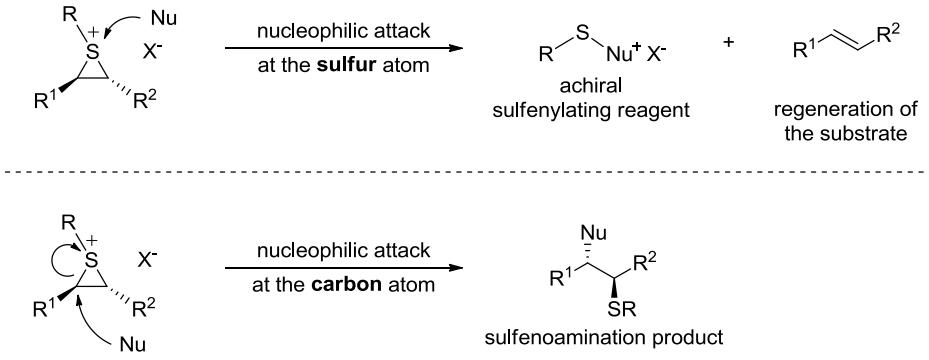
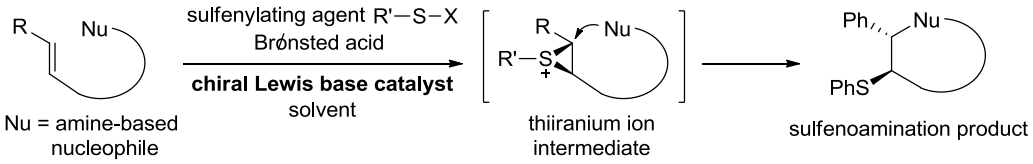


Figure 5. Two possible ways of capturing the thiiranium ion.

2.1.4 Project Design

Investigation of mechanistic details on the intermediate thiiranium ions proved their configurational stability at low temperatures.[33,36] Moreover, successful sulfenofunctionalization of alkenes with oxygen-[12] and carbon-based nucleophiles[30] encouraged to expand the scope of functionalization with nitrogen-based nucleophiles. The overall goal of this research project is to develop a catalytic method for the asymmetric sulfenoamination of olefins using an achiral sulfenylating reagent in presence of a chiral Lewis base catalyst (Scheme 17).

Scheme 17



Several key insights from the previous study on the oxysulfenylation[12] were important in the initial design of this reaction system (see Scheme 15 in Section 2.1.2). The weak achiral sulfur electrophile was activated with a chiral Lewis base to generate the reactive chiral sulfenylating species *in situ*. This kinetically activated sulfenylating complex was able to distinguish the two enantiotopic faces of the olefin to stereoselectively form a chiral thiiranium ion, which was found to be configurationally stable at low temperature [33,36] Nucleophilic capture of this thiiranium ion at a carbon atom with a pendant alcoholic nucleophile afforded enantioenriched sulfenofunctionalized products.

In addition to the oxysulfenylation reaction, very recent work in these laboratories has led to a catalytic enantioselective carbosulfenylation reaction employing an electron rich aromatic moiety as the nucleophile (see Scheme 14 in Section 2.1.2).[30] In terms of catalyst design, it is interesting to note that diisobutylamine substituted-BINAM catalyst (*S*)-**53** was found to give better enantioselectivity than the catalyst (*S*)-**7** which used in oxysulfenylation reactions. This

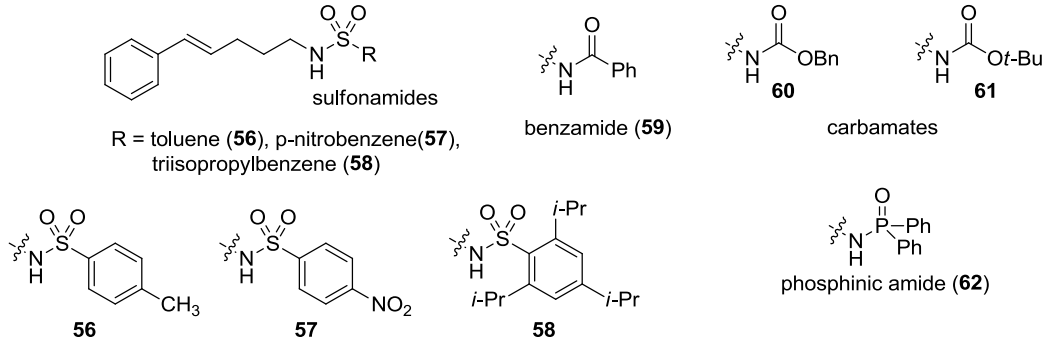
finding implied that steric bulk around the amino group of the catalyst may play an important role in the selective formation of cyclized products. On the basis of these previous findings, efforts have been made to develop a catalytic enantioselective aminosulfenylation of olefins via cyclization with a pendant amine.

2.2 Results

2.2.1 Selecting a Suitable Nucleophile for Sulfenoamination

In the initial stage of the project, it was important to select an appropriate nitrogen-based nucleophile with good reactivity. In the previous sulfenofunctionalization studies, a Brønsted acid co-activator was required for these types of reactions.[12,30] As a result, the present reaction required a nucleophile that remained active in acidic media. That is, the nitrogen must be sufficiently nucleophilic to form the C-N bond, but also sufficiently non-basic to avoid protonation. Therefore, several protected amines were selected as candidates for nucleophiles: sulfonamides, benzamides, carbamates, and phosphinic amides (Chart 1).[37]

Chart 1

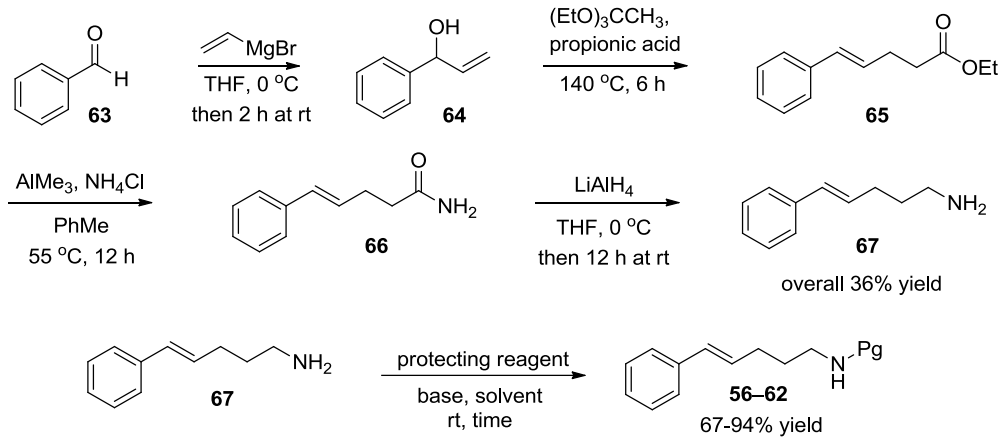


2.2.1.1 Synthesis of Protected Amines Substrates

The model substrates **56-62** were designed to have a pendant amine so that it can undergo intramolecular cyclization, which can have an entropic advantage for reactivity and site-

selectivity on thiiranium ion capture. The model candidate substrates were prepared from the precursor amine **67**, which was prepared by modification of the methods developed for the formation for the corresponding alcohol by Breit and coworkers (Scheme 18).[38]

Scheme 18



Addition of vinylmagnesium bromide to benzaldehyde **63** afforded a secondary allylic alcohol **64**, which was then combined with excess triethylorthoacetate in the presence of a catalytic amount of acid to afford the corresponding ester **65** via the Johnson-Claisen rearrangement.[38,39] The ester was transformed into the precursor amine **67** in two steps, by treatment with trimethylaluminum and ammonium chloride to afford amide **66**,[40] followed by reduction with lithium aluminum hydride.[41] Amine **67** was then converted to the targeted substrates **56-62** with respective protecting groups following literature procedures.[42] All of seven amine-protected substrates were prepared in good yields.

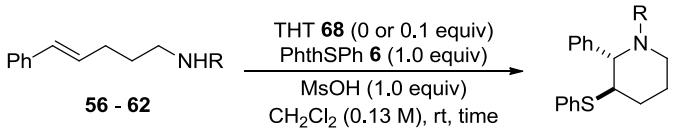
2.2.1.2 Reactivity Investigation of Protected Amines

To examine the reactivities of the various protected amine substrates, the initial reaction condition was adopted from the preceding sulfenofunctionalization reactions. Although many Lewis basic catalysts exist, tetrahydrothiophene (THT, **68**), which has been used in previous

studies, was chosen for its robust Lewis base reactivity.[12,30,33] THT (**68**) is a suitable catalyst that is active under the acidic reaction conditions, exhibiting both strong Lewis basicity and weak Brønsted basicity.[43] For the electrophile, *N*-(phenylthio)phthalimide (PhthSPh, **6**) was employed for its stability and commercial availability.[44]

To evaluate the reactivity of the nucleophiles, each of the substrates was initially subjected to the reaction conditions developed for the oxysulfenylation reaction both with and without THT (**68**) (Table 2).[12] Preliminary evaluation of the protected amine substrates **56**-**62** with sulfenylating agent **6** (1 equiv) in presence of an achiral Lewis base catalyst **68** (0.1 equiv) and a Brønsted acid (MsOH, 1.0 equiv) at room temperature showed that sulfonamide substrates **56**-**58** rapidly formed piperidines in good yields (entries 1, 3, and 5). The structure of the product determined to be piperidines (See Section 2.2.2.2 for details).

Table 2. Survey of the Nucleophiles.



entry	substrate (R)	THT (equiv)	time[a]	yield, %[d]
1	**56** (Ts)	0.1	5 min[b]	93
2	**56** (Ts)	0	48 h[c]	4
3	**57** (Ns)	0.1	5 min[b]	95
4	**57** (Ns)	0	48 h[c]	11
5	**58** (Tris)	0.1	5 min[b]	84
6	**58** (Tris)	0	48 h[c]	2
7	**59** (Bz)	0.1	48 h[b]	86
8	**60** (Cbz)	0.1	48 h[b]	81
9	**61** (Boc)	0.1	-[e]	-[e]
10	**62** (DPP)	0.1	-[e]	-[e]

[a] Conversion monitored by TLC. [b] The time full conversion observed. [c] The time reaction was quenched. [d] Isolated yields. [e] Decomposed under the reaction condition.

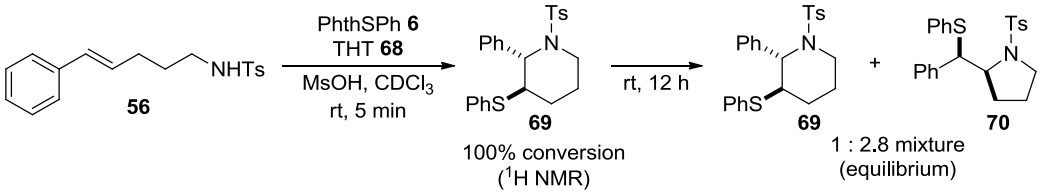
For sulfonamide substrates **56**-**58**, the high rate of reaction was visibly apparent with immediate precipitation of phthalimide observed upon addition of MsOH. Although both tosylamide **56** and nosylamide **57** displayed excellent reactivity in the presence of THT (**68**), tosylamide **56** possessed a slower lower background rate when the Lewis base was omitted (entries 2 and 4). In contrast to the sulfonamides, cyclization of benzamide **59** (entry 7) and benzyl carbamate **60** (entry 8) were found to be slow under the reaction conditions such that 48 h was required to reach high conversions. Unsurprisingly, the *t*-butylcarbamate substrate **61** (entry 9) and the diphenylphosphinic amide **62** (entry 10) decomposed under the strongly acidic conditions. Only trace conversion was observed in the absence of the Lewis base at room temperature, indicating that cyclization via simple acid-catalysis was negligible. On the basis of these results, 4-toluenesulfonylamides were chosen as the nucleophiles for exploration of substrate scope.

2.2.2 Isomerization of Sulfenoamination Product Under Acidic Conditions

2.2.2.1 Control Experiments

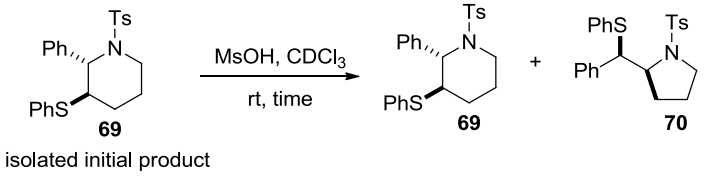
Interestingly, whereas the sulfonamide substrates gave full conversion to a single product within a short period of time, a side-product was observed when the reaction was allowed to run for an extended period of time (Scheme 19). This conversion of "*initially*" formed product **69** to "*converted*" constitutional isomer **70**, demanded attention because this indicated that the product could be unstable under the reaction conditions. Specifically, treatment of tosylamide **56** with THT and MsOH (1.0 equiv) afforded piperidine **69** quantitatively within 5 min at room temperature. However, piperidine **69** isomerized into a 1:2.8 mixture of **69** and pyrrolidine **70** by allowing the mixture to stir for 12 h.

Scheme 19



To further understand the proposed isomerization, initial product **69** and converted product **70** were isolated and individually treated with 1.0 equiv of MsOH in $CDCl_3$ (Scheme 20). Independent treatment of either **69** or **70** resulted in the establishment of an equilibrium reaching a thermodynamic mixture of 1:2.8 (*initial*:*converted*) was observed by ^{1}H NMR at room temperature over 12 h. The isomerization of **69** to **70** is driven by alleviation of the steric interactions between the *N*-tosyl group and the 2-phenyl group in piperidine **69**.[45]

Scheme 20



Time	**69** : **70**
10 min	major : trace
0.5 h	5 : 1
1 h	2 : 1
3 h	1 : 1
12 h	1 : 2.8
2 d	1 : 2.8

2.2.2.2 Structural Determination of the Cyclized Product

Compounds **69** and **70** were speculated to be the 6- and 5- membered cyclized products, respectively, with neither being reported in the chemical literature. Chemical shift comparisons between tosyl and nosyl products, **69** and **71**, provided some information regarding product identity (Figure 6). Because nosyl is a stronger electron withdrawing group than tosyl, the protons that are α-to the nitrogen atom should be more deshielded than the protons at the β-positions. In the case of 6-membered rings **69** and **71** the H^1 proton should be more deshielded than H^2, and in case of 5-membered rings **70** and **72**, the H^2 proton should be affected more than

H^1. Unfortunately, this logic was not applicable to the spectral data comparison for determination of the structure, because one set of chemical shifts shifted 0.02 ppm upfield while the other set shifted 0.02 ppm downfield.

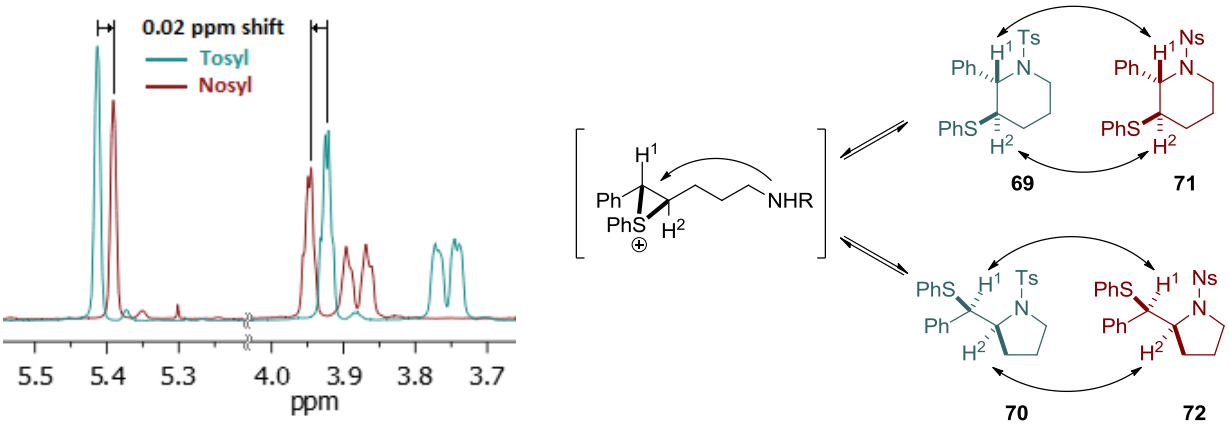
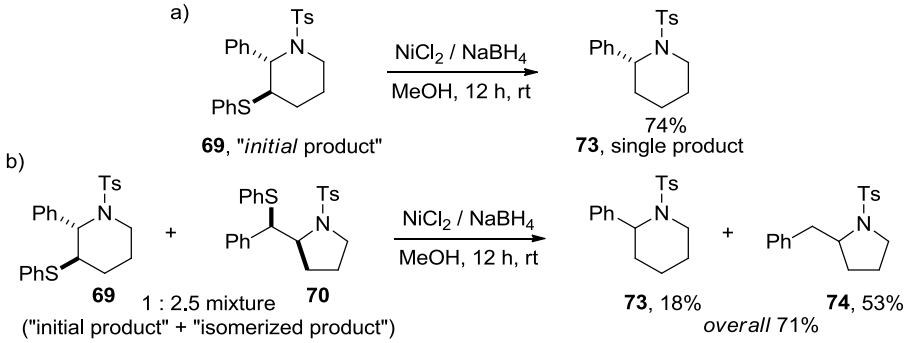


Figure 6. Comparison of ^{1}H NMR spectra for between "initial" products **69** / **71** (or **70** / **72**).

The next attempt to determine the structure of these products was to remove the phenylthio group from the cyclized compounds by treatment with nickel boride[46] to generate known compound **73** (Scheme 21).[47] Desulfurization of C-S bond from the initially observed compound **69** afforded a desulfurized product, which after comparison with the literature (^{1}H and ^{13}C NMR spectroscopic data) was found to be *N*-tosylpiperidine **73.**[47] To rule out the possibility of isomerization during the sulfide reduction, a 1:2.8 mixture (initially cyclized **69** : isomerized **70**) of the products was subjected to the nickel boride reaction. This experiment afforded a mixture with a conserved ratio of the 2-substituted piperidine **73** and 2-substituted pyrrolidine **74,** where **74** is also a known compound reported in literature.[47, 48] These experiments unambiguously determined the initially formed product to be the 2,3-substituted *N*-tosylpiperidine **69**, and isomerized product to be 2-substituted *N*-tosylpyrrolidine **70**.

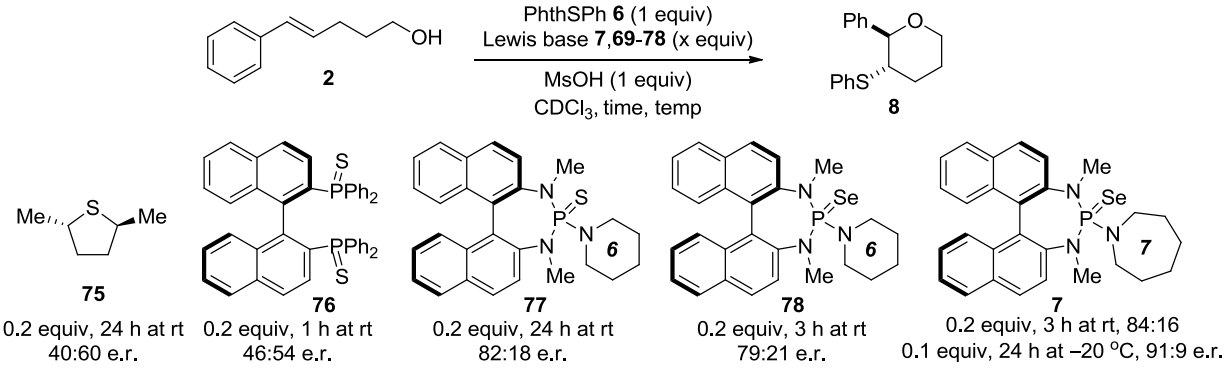
Scheme 21



2.2.3 Optimization of Reaction Conditions

Previous research in these laboratories explored a broad range of known achiral Lewis base catalysts oxysulfenylation reactions.[12] In these studies, THT **68**, dimethylpropylene urea (DMPU), triphenylphosphine (Ph_3P), tricyclohexylphosphine (Cy_3P), hexamethylphosphoramide (HMPA), hexamethylthiophosphoramide (HMPA=S), and hexamethylselenophosphoramide (HMPA=Se) were examined with Brønsted acids (methanesulfonic acid (MsOH), trifluoroacidic acid (TFA)).

Chart 2

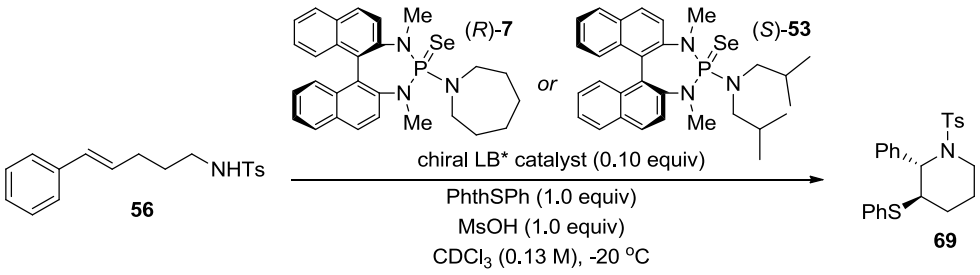


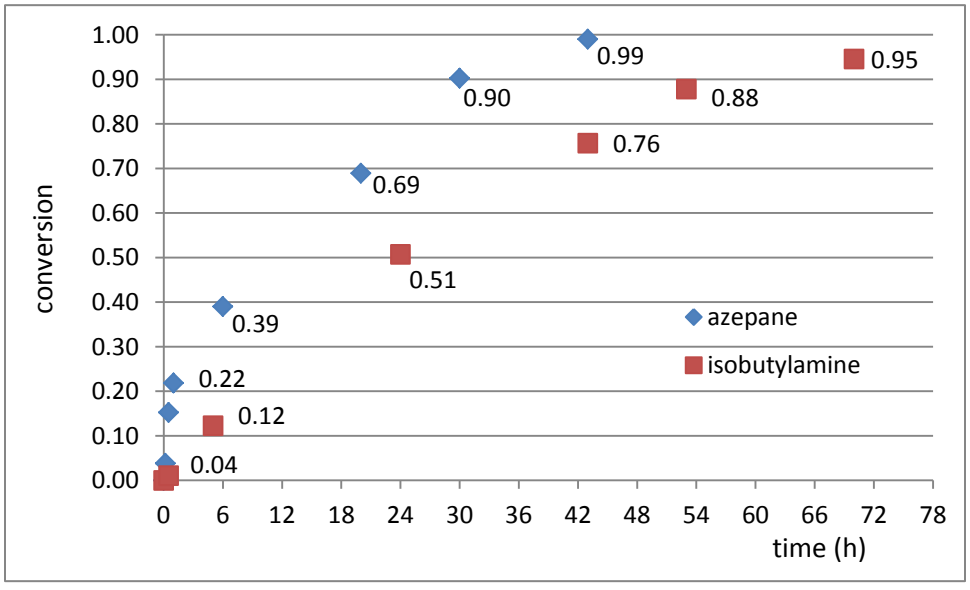
Among the Lewis base catalysts surveyed, THT **68**, phosphines Ph_3P, Cy_3P and HMPA=Se were shown to give the best conversion. However, in the oxysulfenylation of alcohol **2**, chiral analogues of THT, e.g. sulfide **75** and phosphine **76** gave poor enantiomeric ratios of

product **8** (Chart 2). On the other hand, improved enantioselectivity was observed with the BINAM-based chiral selenophosphoramide derivatives **77**, **78**, and **7**.

On the basis of these studies, to initially probe the impact of catalyst structure on reaction rate, the cyclization of tosylamide **56** to *N*-tosylpiperidine was monitored by ^{1}H NMR spectroscopy (Chart 3). For these studies, catalyst (*R*)-**7** and (*S*)-**53**, which were shown to be successful in the previous oxysulfenylation[12] and carbosulfenylation[30] reactions, were selected. ^{1}H NMR spectroscopy showed that with catalyst (*R*)-**7**, the reaction reached full conversion after 43 hours at –20 ^{o}C, while with catalyst (*S*)-**53**, the reaction reached >95% conversion after 72 hours at –20 ^{o}C. On the basis of these results, the reactions for the catalyst screen (*vide infra*) were allowed to run for 72 hours at –20 ^{o}C.

Chart 3

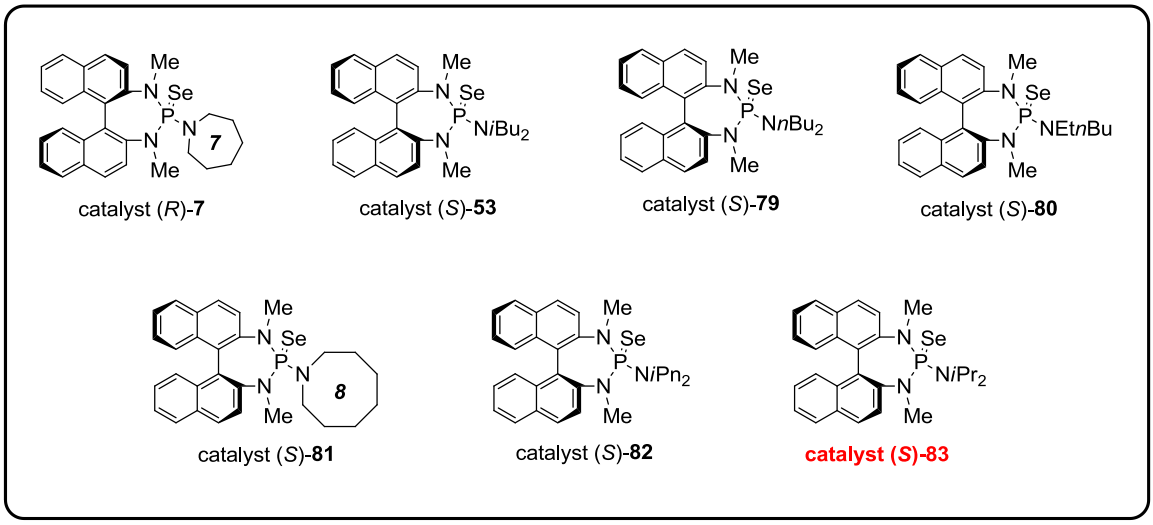




2.2.3.1 Investigation of Chiral Lewis Bases

After confirming the reactivity of selenophosphoramide catalyst (*R*)-**7** and (*S*)-**53** in sulfenoamination reaction at –20 °C, a number of BINAM-based selenophosphoramides **79**-**83**[30] with different amine substituents were investigated (Chart 4). Initial evaluations were performed with substrate **56** (63 μmol), PhthSPh **6** (1.0 equiv), catalysts **79**-**83** (0.1 equiv), and MsOH (1.0 equiv) in CH_2Cl_2 for 72 h at –20 °C. After aqueous work up, cyclized product **69** was isolated to compare yields and enantiomeric ratios.

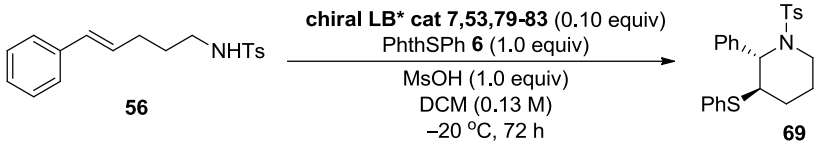
Chart 4



The azapane substituted catalyst (*R*)-**7** was examined first because it gave the best result in the analogous oxylsulfenylation reaction.[12] For the reaction at –20 °C, catalyst (*R*)-**7** generated the product with 89:11 e.r. (Table 3, entry 1). Interestingly, diisobutylamine substituted catalyst (*S*)-**53**, which was the most effective catalyst in the carbosulfenylation reaction,[30] showed slower conversion than (*R*)-**7**, but with no improvement in enantioselectivity 89:11 e.r. (entry 2). As expected, the Lewis base catalyst derived from the opposite enantiomers of BINAM gave the opposite sense of enantioselectivity. Di-*n*-butylamine-substituted catalyst (*S*)-**79** and *n*-

butylethylamine substituted catalyst (*S*)-**80** gave lower yield and selectivity than (*R*)-**7** (entries 3, and 4). Azocane substituted catalyst (*S*)-**81** and diisopentylamine substituted catalyst (*S*)-**82** afforded the product in slightly lower yield but improved the enantioselectivity to 91:9 and 93:7 e.r., respectively (entries 5, and 6). The best enantioselectivity, 95:5 e.r., was achieved with diisopropylamine substituted catalyst (*S*)-**83** (entry 7).

Table 3. Survey of Chiral Lewis Bases.



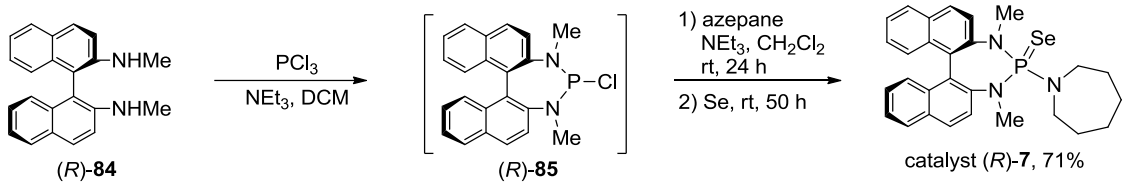
entry	catalyst, R_2	yield, %[a]	e.r.[b]
1	(*R*)-**7**, $(CH_2)_6$	90	11.5 : 88.5
2	(*S*)-**53**, $(i\text{-Bu})_2$	88	89.4 : 10.6
3	(*S*)-**79**, $(n\text{-Bu})_2$	29	85.8 : 14.2
4	(*S*)-**80**, *n*-Bu, Et	79	88.1 : 11.9
5	(*S*)-**81**, $(CH_2)_7$	67	91.4 : 8.6
6	(*S*)-**82**, $(i\text{-amyl})_2$	82	92.8 : 7.2
7	(*S*)-**83**, $(i\text{-Pr})_2$	75	94.6 : 5.4

[a] Isolated yields. [b] The enantiomeric ratio was determined by CSP-SFC analysis.

2.2.3.2 Synthesis of Chiral Lewis Base (*S*)-83

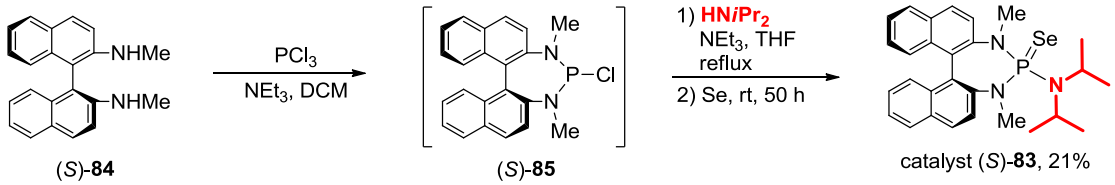
Chiral Lewis base (*S*)-**83** was initially prepared from the precursor *N*,*N'*-dimethyl-BINAM **84**[49] by applying an established procedure for synthesis of other selenophosphoramide catalysts **79**-**83**.[50] The typical procedure for synthesis of Lewis base catalysts **7**, **53**, and **79**-**83** was to treat precursor **84** with PCl_3, and Et_3N in CH_2Cl_2 which affords the phosphorus(III) intermediate **85**. This intermediate **85** was then subsequently treated with corresponding secondary amines, followed by oxidation with selenium to afford selenophosphoramides **7**, **53**, and **79**-**83** (Scheme 22).[12,50]

Scheme 22



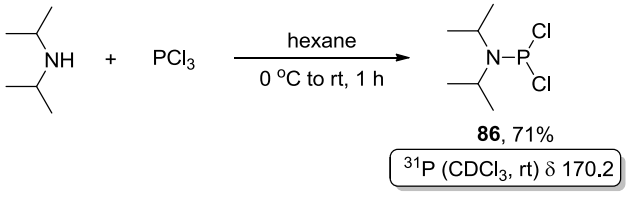
Unfortunately, applying the established protocol for Lewis base catalysts to did not furnish **83**, the most selective catalyst, in synthetically useful yields (21% yield) (Scheme 23). Moreover, many side-products made purification challenging. As a result, development of an improved route to (*S*)-**83** was required. The main difference between catalysts **7**-**82** and catalyst **83** is that selenophosphoramide catalysts **7**-**82** contain an amine with two primary alkyl substituents, whereas the diisopropylamine substituted catalyst **83** has an amine with two secondary alkyl groups.[51] Therefore, the steric congestion originating from diisopropylamine is impeding the nucleophilic addition to phosphorus (III) intermediate **85** in the final step.

Scheme 23



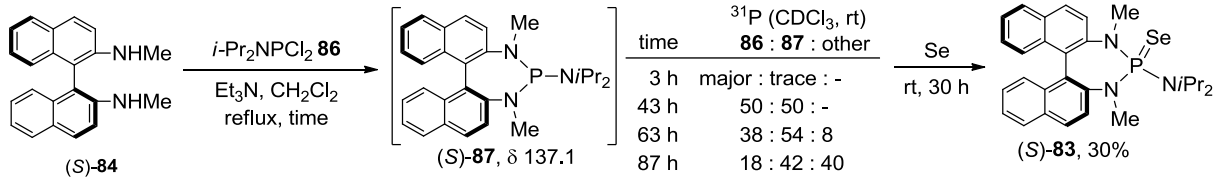
To overcome this problem, the P-N bond between the phosphorus and diisopropylamine was formed before the reacting with BINAM **84**. Following the procedure reported by Nurminen, *N*,*N*-diisopropylphosphoramidodichloridite reagent **86** was prepared (Scheme 24).[52]

Scheme 24



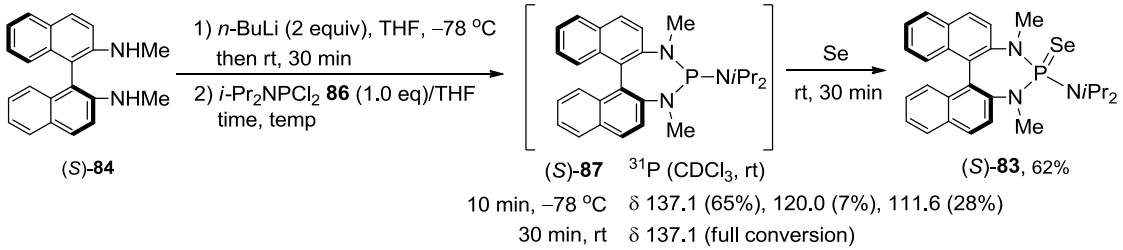
The reaction intermediates were monitored by ^{31}P NMR spectroscopy for optimization (Scheme 25). The ^{31}P NMR chemical shifts for dichlorophosphoramidite **86**, and intermediate (*S*)-**87** show up at 170 ppm and 137 ppm, respectively. In the initial attempt, the reaction employing triethylamine reached only 50% conversion after refluxing for 43 h. With extended reaction time for high conversion, a decomposition of the intermediate **87** into other unidentified phosphorus species was observed. After the treatment with elemental selenium powder, the target product **83** was obtained with its characteristic broad ^{31}P NMR singlet around 80 ppm.[51]

Scheme 25

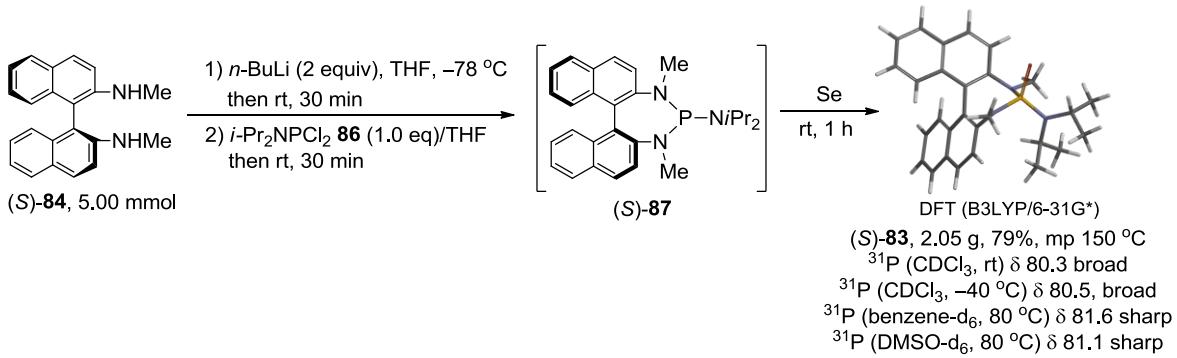


In contrast, when *n*-BuLi was employed as a base for deprotonation, a fast conversion to the intermediate (*S*)-**87** was observed reaching 65% within 10 min at –78 °C (Scheme 26). By elevating the temperature after addition of phosphoramidite **86** to room temperature, full conversion to the intermediate (*S*)-**87** was achieved within 30 min. Oxidization of the resulting intermediate (*S*)-**87** with selenium gave clean conversion to the target selenophosphoramide (*S*)-**83** with within 30 min. Repeating the reaction in larger scale afforded desired Lewis base catalyst (*S*)-**83** in 79% yield after chromatography and recrystallization.

Scheme 26



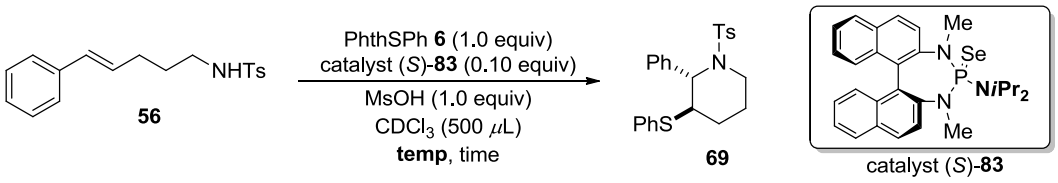
Scheme 26 (cont.)



2.2.3.3 Optimization of Temperature

With the parent substrate and optimum catalyst (*S*)-**83** in hand, the impact of temperature on reactivity and selectivity was investigated. Experiments at a five different temperatures ranging from –20 °C to 20 °C were performed (Table 4). Experiments were set up with substrate **56** (63 μmol), PhthSPh **6** (1.0 equiv), catalyst (*S*)-**83** (0.1 equiv), MsOH (1.0 equiv) in $CDCl_3$ at five temperatures (–20, –10, 0, 5, and 20 °C) and was monitored by ^{1}H NMR to check completion. The reactions were quenched upon completion, however, 72 h was set as maximum time frame to be a practical method. After aqueous work up, cyclized product **69** was isolated to compare yields and enantiomeric ratios.

Table 4. Investigation of Effects on Temperature.



entry	temp (°C)	time (h)	yield, %[b]	e.r.[c]
1	20	72[a]	73	94.6 : 5.4
2	10	72[a]	85	93.9 : 6.1
3	0	48	95	93.6 : 6.4
4	5	48	95	93.0 : 7.0
5	20	6	96	91.5 : 8.5

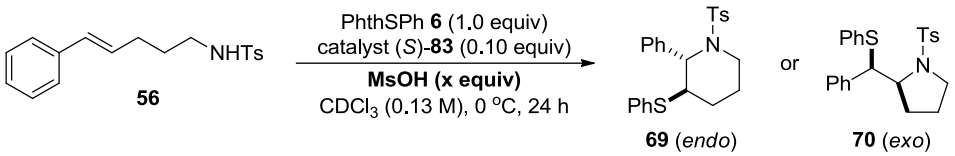
[a] The reaction was incomplete. [b] Isolated yield. [c] The enantiomeric ratio was determined by CSP-SFC analysis.

Increasing the temperature from –20 °C to 0 °C (entries 1, 2, and 3), gave increased reaction rate with full conversion at 0 °C after 48 h. Importantly, enantioselectivity was maintained. In fact, reactions performed at room temperature proceeded to completion with only a small decrease in enantioselectivity (entry 5). Taking into account reaction time and enantioselectivity, 48 h at 0 °C was considered to be optimal.

2.2.3.4 Examination of Acid Concentration

Another important component of this reaction system is the Brønsted acid. Methanesulfonic acid (MsOH), which is a strong Brønsted acid (pK_a = 1.6 in DMSO),[43c] has showen superior reactivity over trifluoroacetic acid (TFA) in oxysulfenylation reactions.[12] Given the similarity between the two reaction systems, MsOH was initially examined, and gave satisfying results. However, since MsOH-induced product isomerization, additional optimization was required to find the optimal acid loading for the sulfenoamination reaction (Table 5).

Table 5. Survey of Acid Loadings.



entry	MsOH (equiv)	conv, %[a,b]	*endo*:*exo*[b]	e.r.[c]
1	1.00	100	85.7:14.3	91.6 : 8.4
2	0.75	100	98.9:1.1	92.9 : 7.1
3	0.50	100	99.2:0.8	93.5 : 6.5
4	0.25	98	99.4:0.6	93.6 : 6.4
5	0.10	69	99.5:0.5	93.9 : 6.1

[a] The conversion was monitored by ^{1}H NMR spectroscopy (6 h, 12 h, and 24 h). [b] Determined by ^{1}H NMR spectroscopy of the crude mixture. [c] The enantiomeric ratio was determined by CSP-SFC analysis.

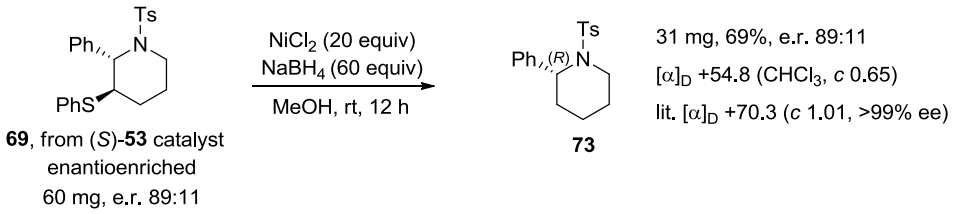
With 1.0 equiv of MsOH at 0 °C, isomerization of **69** to **70** was observed. Interestingly, using less than 1.0 equiv of MsOH greatly reduced the amount of product isomerization.

Whereas reactions with loadings of 0.5 and 0.75 equivs of MsOH afforded comparable results (entries 2 and 3), 0.5 equivs led to slightly higher enantioselectivity. The reaction with 0.25 equiv of MsOH displayed slightly slower reaction rate, reaching full conversion at 24 h (entry 4). Although the reaction with 0.10 equivalents gave high e.r., the reaction rate was unacceptably slow (entry 5).

2.2.3.5 Determination of Absolute Configuration of 69

The absolute configuration of the product **69** was determined via desulfurization,[46] using the method outlined in Section 2.2.2.2. Desulfurization from the enantioenriched cyclized product **69** gave 2-phenyl-*N*-tosylpiperidine **73** with optical rotation $[\alpha]_D$ = +54.8 ($CHCl_3$, *c* 0.65) (Scheme 27). Comparison of this data to known optical rotation data reported in the literature for (*R*)-2-phenyl-*N*-tosylpiperidine ($[\alpha]_D$ = +70.3 ($CHCl_3$, *c* 1.01, >99% e.e.))[47] gave 89:11 e.r. which is in agreement with the e.r. of the initial cyclized product **69**.

Scheme 27

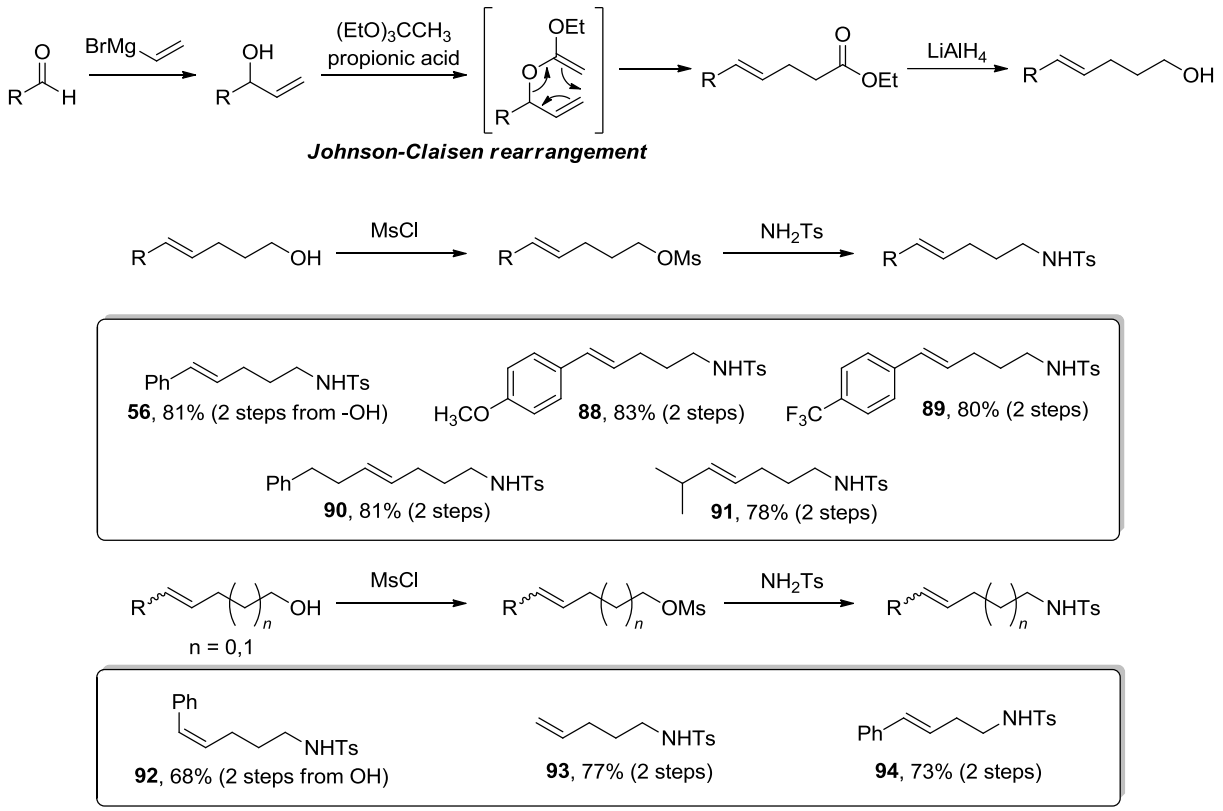


2.2.4 Synthesis of Substrates

Having the optimum reaction conditions established, in terms of yield, rate, and enantioselectivity, the scope of olefins was investigated. The majority of the *trans* olefin substrates were synthesized from the corresponding esters and alcohols, which were prepared via a Johnson-Claisen rearrangement[38,39] of the allylic alcohols (Scheme 28). The most important reason for selecting this route was because [3,3] rearrangement afforded exclusively *trans* olefins (see Chapter 5: Experimental Section for detailed reaction conditions). Substrates **56**, and **88**-**91**

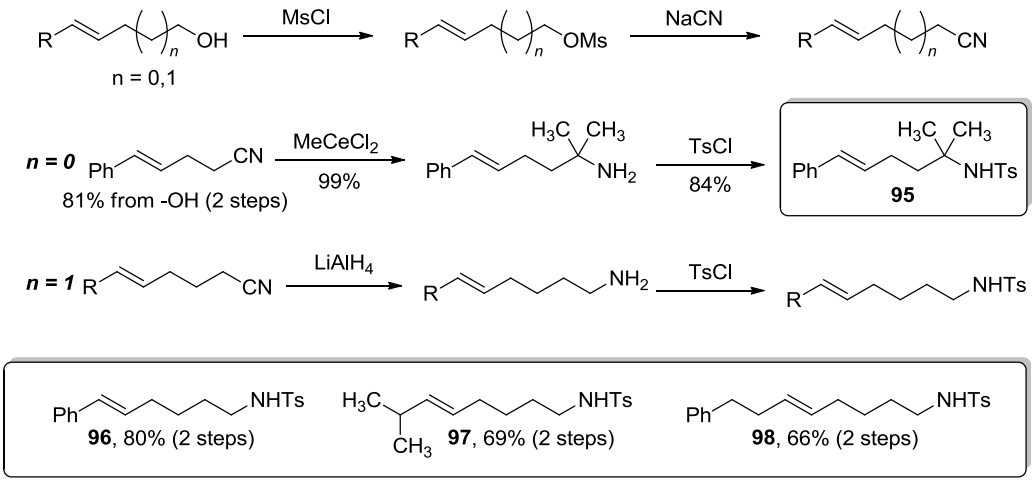
was synthesized by mesylation of the corresponding alcohols, followed by nucleophilic addition of tosylamide.[42c] Substrates **92**-**94** were prepared in a similar route, converting the corresponding alcohol to the tosylamide through two step sequence.

Scheme 28



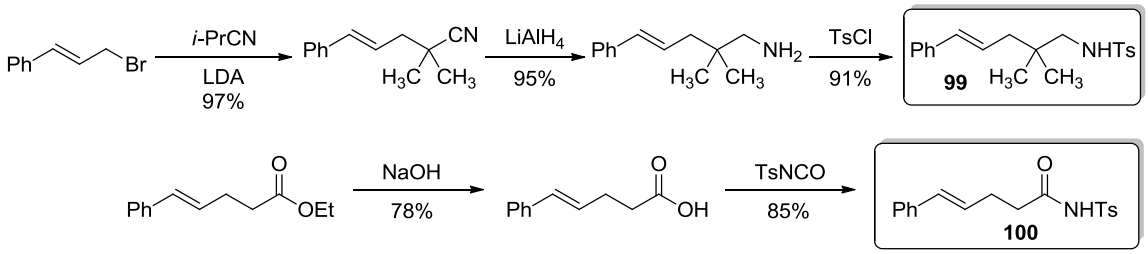
Various nitriles were synthesized to access α,α-dimethyl substrate **95** and longer-tethered substrates **96**-**97** (Scheme 29). Mesylates were treated with sodium cyanides to afford the nitrile intermediates. Addition of methyl organocerium reagent to 4-phenyl-3-butenyl nitrile gave α,α-dimethylamine in quantitative yield.[53] Protection of the free amine with tosyl chloride afforded α,α-dimethyl substrate **95** in 84% yield. Substrates having extended tethers were prepared by a four-step sequence from the one-carbon shorter alcohols. The alcohols were mesylated, then treated with cyanides, and the resulting nitriles were reduced to primary amines by $LiAlH_4$ reduction, which were followed by subsequent tosyl protection of the amine groups.

Scheme 29



β,β-Dimethyl substrate **99** was synthesized by following a reported procedure (Scheme 30).[42b] Addition of isopropyl nitrile to cinnamyl bromide generated β,β-disubstituted nitrile, and subsequent $LiAlH_4$ reduction and tosyl protection afforded **99**. Lastly, carboxamide **100** was prepared in one-step from 5-phenyl-4-pentenoic acid by treating with tosyl isocyanate.[54]

Scheme 30



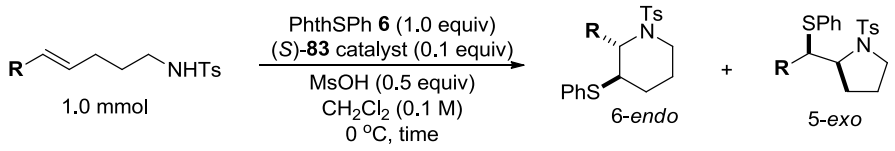
2.2.5 Survey of Substrate Scope

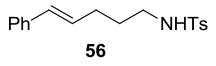
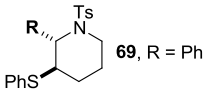
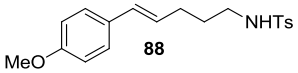
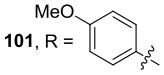
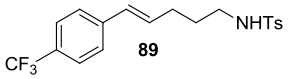
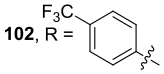
Above 14 substrates were evaluated in terms of reactivity and stereoselectivity. Reactions were monitored by TLC every 12 h, and quenched with saturated $NaHCO_3$ aqueous solution at 0 ^{o}C when full conversion was observed. The *endo*:*exo* ratio was determined by ^{1}H NMR spectroscopy of crude product after aqueous work up, prior to purification.

2.2.5.1 Influence of Electron Density of the Alkene

Olefins with varying electron density were tested to examine the influence of the electronic properties of the alkene on reaction rate and stereoselectivity. Substrate **88** with a 4-anisyl-substituted double bond possessing greater electron density than **56**, showed comparable reactivity with a slight drop in enantioselectivity (Table 6, entry 1). In contrast, substrate **89**, bearing a strongly electron withdrawing 4-trifluoro-methylphenyl substituent, afforded only a 39% yield after 48 h (54% conv., entry 3). Interestingly, the observed e.r. (91.9:8.1) for **102** was comparable to that for **101**. It is important to note that substrates **56**, **88**, and **89** (entries 1, 2, and 3) afforded piperidines, as established by ^{1}H NMR spectroscopy.

Table 6. Investigation of the Effects of Olefin Electron Density.



entry	substrate	product	time	yield, %[a]	*endo*:*exo*[b]	e.r.[c]
1	 **56**	 **69**, R = Ph	24 h	93	>99 : 1	93.6 : 6.4
2	 **88**	 **101**, R =	24 h	91	46 : 1	91.8 : 8.2
3	 **89**	 **102**, R =	48 h	39[d]	27 : 1	91.9 : 8.1

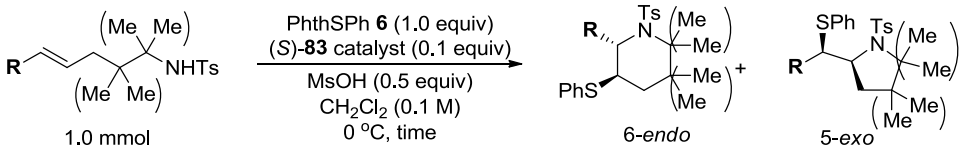
[a] Isolated yields of analytically pure material. [b] Constitutional selectivity determined by ^{1}H NMR spectroscopy of the crude mixture. [c] The enantiomeric ratio of the major constitutional isomer was determined by CSP-SFC analysis, and the absolute configurations of the products were assigned by analogy to **69**. [d] Incomplete conversion on quenching at 48 h.

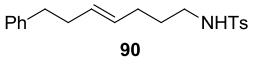
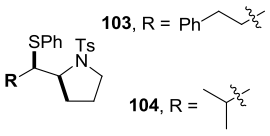
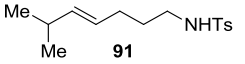
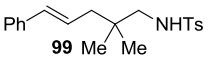
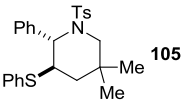
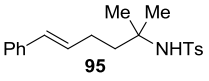
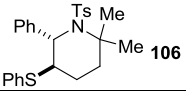
2.2.5.2 Influence of Steric Factors

Substrate **90** bearing a non-conjugated, dialkylsubstituted olefin afforded a mixture of *endo* and *exo* products in 1:3 ratio in 91% yield with excellent e.r.s (Table 7, entry 1). The reduced *endo* to *exo* ratio is likely due to the less-biased electron density of the alkene. In

contrast, isopropyl-substituted olefin **91** showed a highly improved *exo* selectivity (with high yield and e.r. preserved), thus implicating an important role for the steric bulk around the alkene environment (entry 2). To examine the proximal effect of steric bulk on the reaction outcome, substrate bearing geminal dimethyl groups on the tether were tested. Interestingly, reaction of alkene **99**, a substate containing a dimethyl moiety at 2-position of the tether, afforded high yield with retention of excellent enantioselectivity (entry 3). However, when the dimethyl moiety was further moved to 1-position, slightly diminished enantioselectivity was observed (entry 4).

Table 7. Investigation of the Effects of Steric Parameters.



entry	substrate	product	time	yield, %[a]	*endo*:*exo*[b]	e.r.[c]
1	 **90**	 **103**, R = Ph; **104**, R =	24 h	91	1 : 3	95.9 : 4.1(*exo*) 95.8 : 4.2(*endo*)
2	 **91**		48 h	89	1 : 15	96.8 : 3.2
3	 **99**	 **105**	24 h	91	80 : 1	96.3 : 3.7
4	 **95**	 **106**	24 h	93	20 : 1	91.8 : 8.2

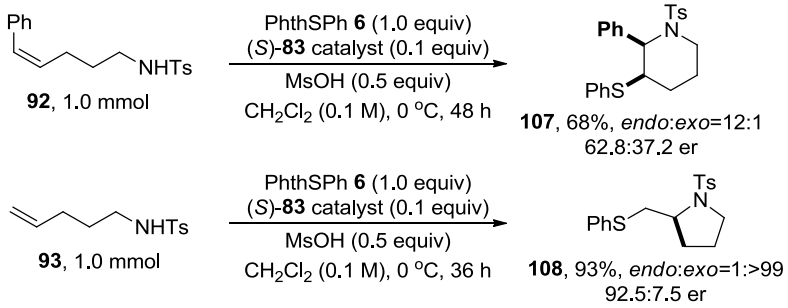
[a] Isolated yields of analytically pure material. [b] Constitutional selectivity determined by ^{1}H NMR spectroscopy of the crude mixture. [c] The enantiomeric ratio of the major constitutional isomer was determined by CSP-SFC analysis, and the absolute configurations of the products were assigned by analogy to **69**. [d] Incomplete conversion on quenching at 48 h.

2.2.5.3 Influence of Olefin Geometry

Other olefins with different substitution patterns were also investigated (Scheme 31). Contrary to its *trans* counterpart **56**, *cis* olefin **92** reacted very slowly (75% conv. in 48 h) with moderate *endo*:*exo* ratio and poor enantioselectivity (62.8:37.2). Remarkably, the reaction of terminal olefin **93** gave good yield and high enantioselectivity of 92.5:7.5 with exclusive *exo*

cyclization. This result was very promising considering the fact that distinguishing the two enantiotopic faces of terminal olefins is known to be difficult.[55]

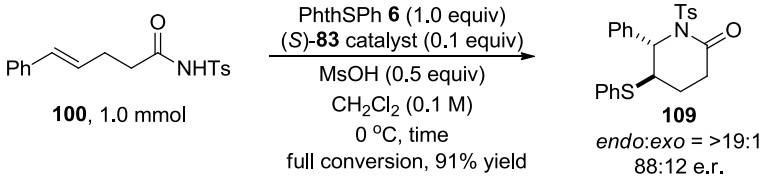
Scheme 31



2.2.5.4 Influence of Internal Carbonyl Group

To extend the scope of accessible product scaffolds, carboxamide **100** was tested (Scheme 32). Cyclization of carboxamide substrate **100** afforded δ-lactam **109** in high yield with high constitutional selectivity, but with diminished enantiomeric ratio of 88:12. Presumably, protonation of the carbonyl group attenuates the nucleophilicity of the nitrogen and prevents rapid capture of the intermediate thiiranium ion, thus allowing racemization.

Scheme 32

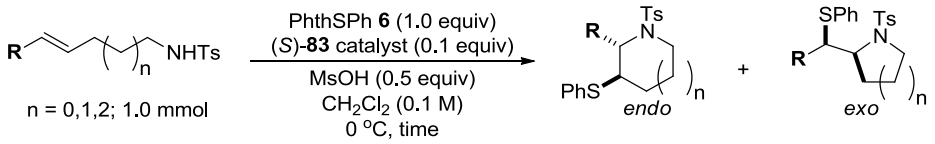


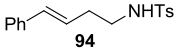
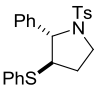
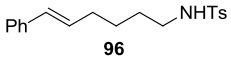
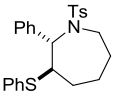
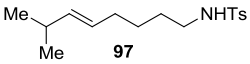
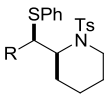
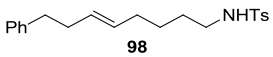
2.2.5.5 Influence of Carbon Tether Length

Since piperidine scaffold was the predominant product in most cases of 3-carbon tethered substrates, the following question arose: What would be the major product for substrates with shorter or longer chains? To address this question, substrates with different tether lengths were prepared and examined (Table 8). Using the same reaction protocol, two carbon-tethered

substrate **94** cyclized to pyrrolidine **110** in 86% yield and 91.3:8.7 e.r. with complete *endo* selectivity (entry 1). Interestingly, four carbon-tethered substrate **96** showed the impact of conjugation on biasing the two olefinic carbons by affording exclusively azepane **110** (entry 2). The structure and the absolute configuration of **110** were established by X-ray crystallography.[56] In contrast, the non-conjugated substrates **97** and **98** afforded only piperidine products **112** and **113** via *exo* cyclization, indicating the preference to form the 6-membered rings for dialkyl-substituted olefins. Additionally, reactions with both **97** and **98** gave the products in good yields and excellent enantioselectivities.

Table 8. Survey on Length of the Tether.



entry	substrate	product	time	yield, %[a]	*endo*:*exo*[b]	e.r.[c]
1	 **94**	 **110**	36 h	86	>99 : 1	91.3 : 8.7
2	 **96**	 **111**	36 h	84	>99 : 1	92.7 : 7.3
3	 **97**	 **112** R = 	48 h	87	1 : >99	95.4 : 4.6
4	 **98**	**113** R =	48 h	91	1 : >99	97.4 : 2.6

[a] Isolated yields of analytically pure material. [b] Constitutional selectivity determined by ^{1}H NMR spectroscopy of the crude mixture. [c] The enantiomeric ratio of the major constitutional isomer was determined by CSP-SFC analysis, and the absolute configurations of the products were assigned by analogy to **69**. [d] Incomplete conversion on quenching at 48 h.

2.3 Discussion

2.3.1 Selection of Nucleophile

The survey of nucleophiles revealed that sulfonamides performed well as nucleophiles for the sulfenoamination reaction. However, benzamide- and benzylcarbamate-protected nucleophiles were much less reactive. The basicity of benzenesulfonamine (pK_a = 16.1 in DMSO) is lower when compared to benzamide (pK_a = 23.3 in DMSO) or benzylcarbamate (pK_a = 24.2 in DMSO).[43c] In this reaction system, nucleophiles with higher pK_a values will be more readily protonated resulting in lower reactivity.

2.3.2 Reaction Condition Optimization

During the initial planning of this project, the stability of the product **69** in acidic media was considered. While the achiral Lewis base (THT) demonstrated excellent catalytic activity under acidic conditions, chiral catalyst had slower reaction rates and as a result product isomerization was a potential complication. Surprisingly, no isomerization was observed during the examination of chiral Lewis base catalysts. These results were perplexing until the purity of MsOH was investigated (see Section 2.3.5). Repeating the reaction with the purified MsOH gave a mixture of isomerized products. This problem will be discussed in more detail in Section 2.3.5.

Investigation of the Lewis bases showed that the diisopropylamine substituted catalyst **83** was the best catalyst for the sulfenoamination reaction of parent olefin **56**; 95% isolated yield of **69** was obtained giving 93:7 e.r. at 0 ^{o}C after 48 h. Based on the results from catalyst screen, the steric bulk around the monodentate amine is considered to be playing a major role in the catalyst's ability to discriminate between the two enantiotopic faces. This hypothesis will be more closely investigated and discussed with other substrates in the following Section 2.3.3.

While the impact of temperature on enantioselectivity was small, the range from 94:6 at –20 ^{o}C to 92:8 at room temperature is significantly smaller than the temperature dependence of oxysulfenylation reactions (84:16 at 23 ^{o}C to 91:9 at –20 ^{o}C). This observation indicates a shorter life time of thiiranium ion; a species known to be unstable at elevated temperatures.[28,36] That is, after the formation of the thiiranium ion, its capture with a pendant tosylamine nucleophile is apparently faster than an alcoholic nucleophile.

2.3.3 Sufenoamination

On the basis of these experimental results, *trans* substituted olefins were determined to be competent substrates for this system affording products in good yields with high *endo*:*exo* ratio and enantioselectivities. The consistently high enantiomeric composition of the product throughout most of the substrate scope indicates that the described reactions proceed through a common intermediate. Thiiranium ions are the common intermediates for these electrophilic sulfenylation reactions, and formations of these ions are typically known as the enantiodetermining step (discussed in Section 2.3.4.3).

However, some exceptions with diminished enantiomeric ratio were observed. The *cis* olefin substrate **92** showed a significant drop in enantioselectivity. This observation is in agreement with the oxysulfenylation reactions[12] and carbosulfenylation reactions.[30] It suggests that the interaction between the *trans* olefin and activated catalytic complex is quite different from the *cis* olefin. This hypothesis is illustrated in Figure 7. As the olefin approaches the electrophilic sulfur atom (Figure 7a) the steric bulk of the binding pocket-like surroundings around the sulfur atom leads to specific orientation of the olefin substrate. While the *trans* conformation has only one favored binding orientation possible, the *cis* conformation has two (Figure 7b). In addition, the survey of substrates with different degrees of steric hindrance

(Section 2.2.5.2) supports the importance of steric congestion near the olefin, and suggests a pivotal role in aiding the catalyst to differentiate the two enantiotopic faces. This hypothesis is further supported by the results from the chiral Lewis base survey (Section 2.2.3.1). That is, diisopropylamine-substituted BINAM selenophosphoramide (*S*)-**83**, which is the most sterically encumbered catalyst of the screening pool, showed the best enantioselectivity.

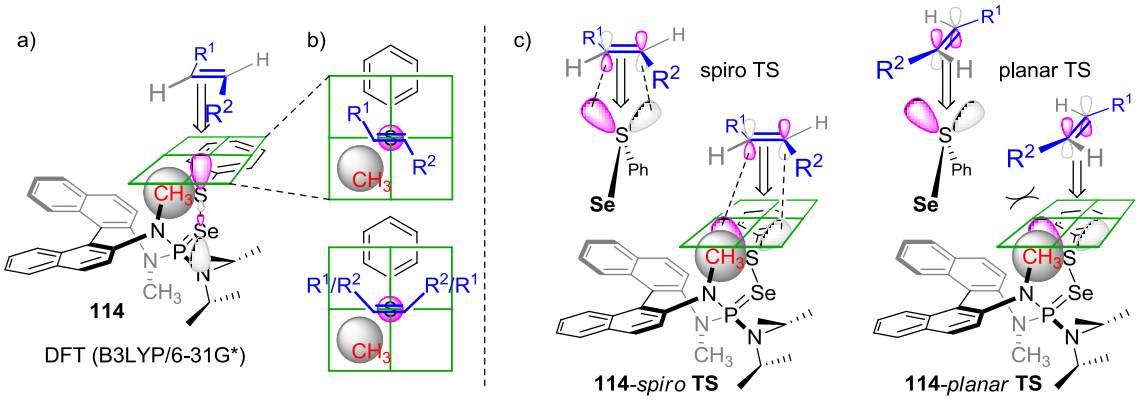


Figure 7. Suggested interaction between the olefin and the catalytically active complex.

To further rationalize the observed relationship between the steric hindrance and the enantiotopic facial selectivity of the olefin, the interaction between nucleophilic π-orbital of olefin and the electron deficient σ*-orbital of S-Se can be considered (Figure 7a). To maximize the interaction between olefin and the active complex, the orbital overlap between the π-orbital of olefin and σ*-orbital of S-Se should be maximized. That is, the olefin must be on the trajectory of the σ*-orbital of S-Se.[57] Due to the bulky isopropyl substituent and binaphthyl backbone, the orientation of the sulfenium is locked in transition state **114** (B3LYP/6-31G*) as illustrated in Figure 6a. Considering four quadrants around the σ*-orbital trajectory of S-Se, *N*-methyl group occupies one quadrant (Figure 7b).

Previous researches on the impact of catalyst structure show that these methyl substituents were critical experimentally. Replacement of methyl with either smaller (H) or

larger groups (Et, Bn) afforded lower stereoselectivity.[58] Additionally, by analogy to oxirane formation,[59] stabilizing interaction of a sulfur lone pair with π*-orbital of the olefin makes the spiro transition state favored over the planar transition state (Figure 7c).[30b]

2.3.4 Mechanistic Details

2.3.4.1 Proposed Catalytic Cycle

Based on the experimental observations for this reaction and known mechanistic studies for electrophilic addition reactions of olefins, the catalytic cycle for sulfenoamination is proposed in Figure 8.[12,60]

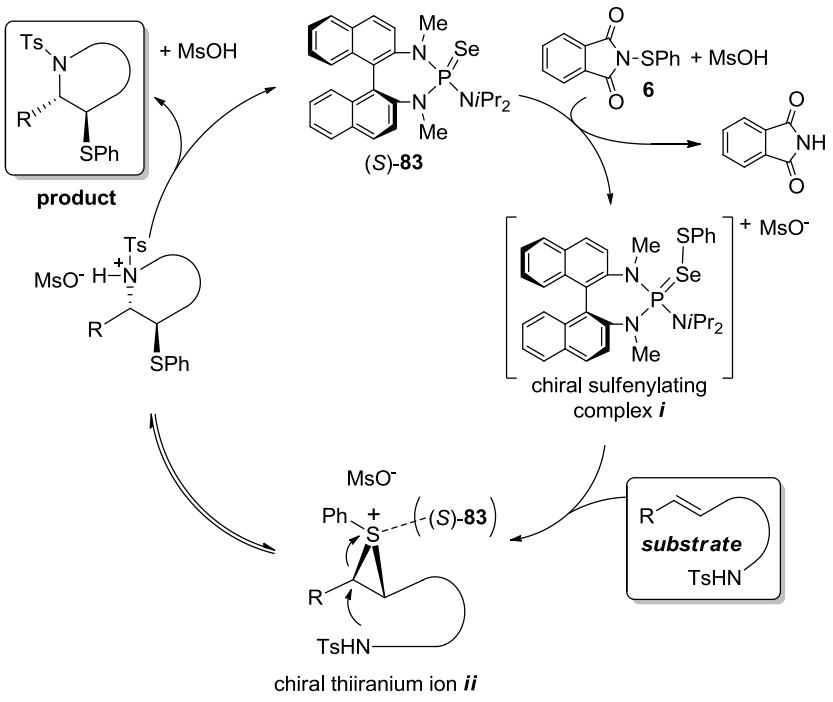


Figure 8. Proposed catalytic cycle for the asymmetric sulfenoamination.

The proposed catalytic cycle begins with the activation of the unactivated sulfenylating agent (PhthSPh, **6**) by a Brønsted acid (MsOH). Upon reaction with the chiral Lewis base catalyst **83**, the active catalytic complex ***i*** is formed which is thought to be the resting state in the catalytic cycle based on the fact that ^{31}P NMR signal for the complex ***i*** shifts from 82.2 ppm to

59.8 ppm immediately under the reaction conditions. This upfield shift is can be rationalized by the electron density of the phosphorus atom being removed with the formation of the Se-S bond. Transfer of the sulfenium ion from the activated complex ***i*** to the olefin substrate furnishes the enantioenriched chiral thiiranium ion intermediate ***ii***. Lastly, subsequent capture of the thiiranium ion ***ii*** with the pendant tosylamine affords the enantioenriched product.

2.3.4.2 Rate-Determining Step

In the course of evaluating substrate scope, trifluoromethylphenyl substituted substrate **89** showed a significant reduction in reactivity (Section 2.2.5.1). This observation indicates that a change on the electron density of the olefin impacts the rate-determining step. Formation of the activated catalytic complex ***i***, which is believed to be the resting state, occurs significantly faster compared to the overall reaction time. Moreover, isomerization of the cyclized products which was observed for several substrates implies the possibility of reversible capture of the thiiranium ion. Taken together, these data suggest the formation of the thiiranium ion to be the rate-determining step.

Comparison of the rate between two analogous systems, such as oxysulfenylation[12] and sulfenoamination, may provide additional evidence for the determination of the rate-determining step. The reaction of olefins with different pendant nucleophiles, ROH and RNHTs should give the same rate if formation of the thiiranium ion is rate-limiting. However, a full rate study to determine the reaction orders of the components is required to obtain a complete mechanistic profile for this reaction system.

2.3.4.3 Enantiodetermining Step

For hyper-reactive thiiranium ions, there is no analytical method currently available to monitor their configurational stability directly and accurately.[33] As a result, it is difficult to

directly monitor the enantiopurity of the thiiranium ions being formed during the reaction. However, in theory, two possibilities may be considered as the enantiodetermining step: (1) formation of the thiiranium ion, or (2) the capture of the thiiranium ion. In the first case, chiral complex ***i*** distinguishes two enantiotopic faces of the olefin and produces enantio-enriched thiiranium ion ***ii***, which is captured by the nitrogen nucleophile to produce the cyclized product. In the second case, both enantiomers of the thiiranium ions are formed, while thiiranium ions are still bound to chiral Lewis base catalyst. Then, the nucleophile selectively captures one diastereomer of the two thiiranium-Lewis base complexes ***ii***-LB* to produce enantioenriched product. Mechanistically, for this catalytic cycle to make to full turnover, the second route requires formation of ***ii***-LB* to be reversible.

Experiments evaluating the effects of tether lengths (Section 2.2.5.5) provides useful information for identifying the enantiodetermining step. By comparing the substrates **56**/**94**/**96**, and **91**/**97**, which gave results with identical enantiomeric ratios regardless of the tether length, it is fair to suggest that the formation of the thiiranium ion rather than nucleophilic capture is the enantiodetermining step.

The dependence of the enantioselectivity on reaction temperature (Section 2.2.3.3) may provide additional valuable information. The observation of cyclization at higher temperatures resulting in reduced enantioselectivity is in agreement with the instability of thiiranium ions at elevated temperatures. However, while these data support the proposed mechanistic hypothesis, more studies are required to conclude that formation of the thiiranium is the enantiodetermining step. One simple experiment that could be done is the treatment of the isolated racemic product with MsOH and enantioenriched Lewis base catalyst to form a mixture of constitutional isomers. As seen in Section 2.2.2, the piperidine product isomerizes into pyrrolidine in presence of a

Brønsted acid with no diastereomers being observed. This stereocontrol indicates that the isomerization undergoes through a thiiranium ion intermediate, which should be racemic. Therefore, examination of the enantiomeric ratio of these isomerized compounds will provide information on whether capture of thiiranium ion is the enantiodetermining step. If the capture of the thiiranium ion is indeed the enantiodetermining step, chiral Lewis base catalyst may re-coordinate to the *in situ* generated thiiranium ion and induce some enantioenrichment of the constitutional isomers. However, if the both isomers remain as racemic, it would be hard to argue that the capture of the thiiranium ion is the enantiodetermining step. Therefore, this experiment can provide an additional piece of information to determine the enantiodetermining step.

2.3.5 Impact of MsOH Purity on Reactions

During the development of the current project, cyclization results from the earlier stage of the project were found to be irreproducible. Both faster conversion rate and faster isomerization from piperidine to pyrrolidine was observed for latter stage experiments. This disturbing result difference was consistently obtained after repetitive runs with the same protocol.

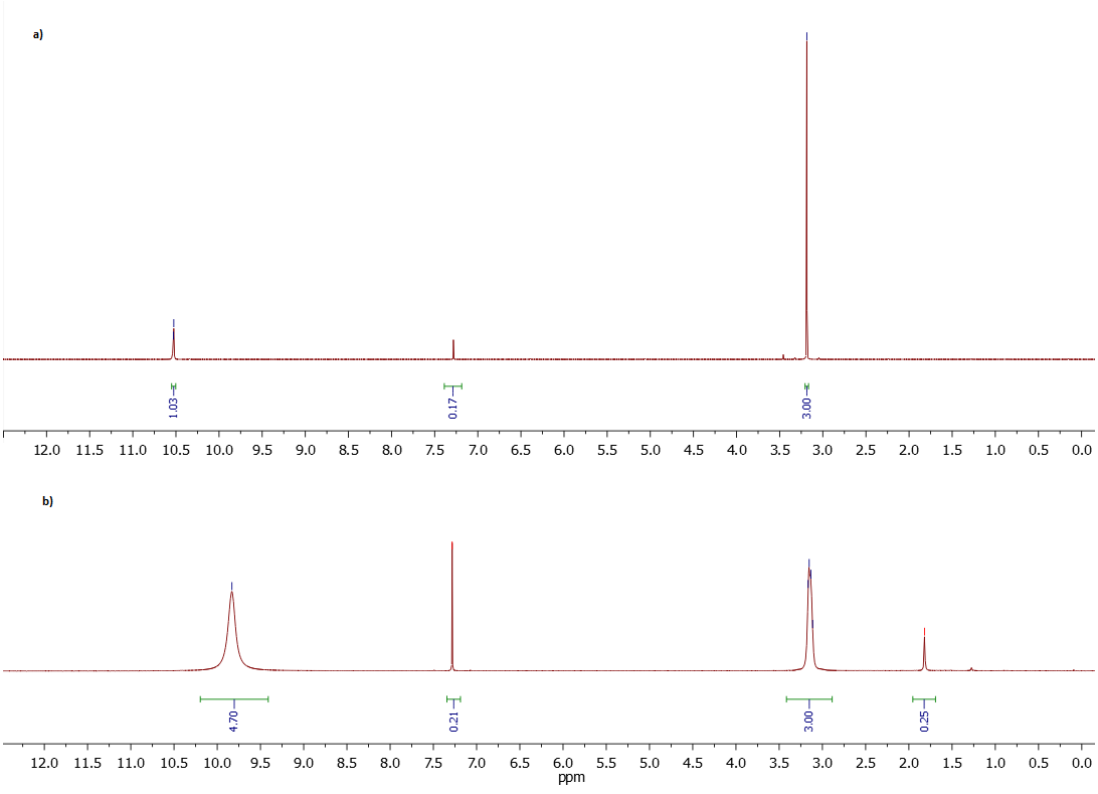
Control experiments were performed to determine the discrepancy. Two sulfenoamination reactions were setup with olefin substrate **56**, PhthSPh **6**, catalyst (*S*)-**83**, and solvent, all taken from the same batch. Only MsOH was drawn from a different source, because the old bottle was running low. Eventually it was determined that the new MsOH was the caveat for the increased conversion rate and isomerization observed. Strictly speaking, the impure *"wet"* MsOH decelerated reaction rate and suppressed the isomerization.

^{1}H NMR spectroscopic studies showed that the bottle of MsOH used in the reactions reported in the results section of this paper (Chart 5b) contained a significant amount of water.

This finding indicates that a lower loading of acid or a buffering effect of water (or both) could be responsible for the slower conversion rate and inhibition of isomerization.

Chart 5

^{1}H NMR spectra of (500 MHz, 0.1 M in $CDCl_3$): (a) distilled MsOH, (b) the *"wet"* MsOH



Serendipitously, critical insights were gained from this unintended incident. Whereas the conversion rate and isomerization rate were affected by the purity of acid, the enantioselectivity was maintained across MsOH sources. That is, both catalyst activation and stability of the cyclized products are dependent on the amount of acid or water, while the facial selectivity during the formation of the thiiranium ion is not affected with the water content in the reaction.

2.4 Future Directions

2.4.1 Impact of the Acid in Sulfenofunctionalization Reactions

As the amount of acid loaded, or pH of the reaction mixture, was found to be critical, the first goal for this project is to reestablish a general reaction protocol using a reliable source of MsOH which can be consistently used by this, and any other laboratory (See Chapter 3 for more details). Also, more thorough investigation is needed on amount of acid required for the formation of the catalytically active species ***i***. Titration of the sulfenylating agent and the Lewis base catalyst with the purified MsOH may provide further mechanistic insight for sulfenofunctionalization reactions (See Chapter 3 for more details).

2.4.2 Olefins with Higher Order Substitution

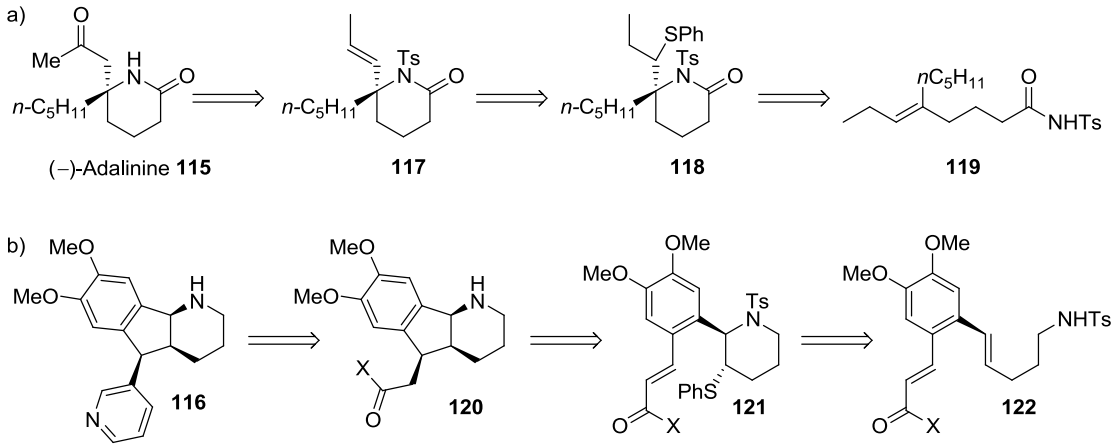
For this sulfenoamination to be a general method for olefin functionalization, it is necessary to expand the scope to include higher order substituted olefin substrates. A variety of trisubstituted and tetrasubstituted olefins are to be examined. While these are more electron rich, it may decelerate the reaction rate due to the highly congested nature of the olefin. A simple way to get around this potential pitfall is to run at elevated temperatures. In this sulfenoamination studies, it was shown that the reactions run at higher temperatures could result in a minimal decrease in the enantiomeric ratio. Adjustment of the temperature may provide an opportunity to balance between a reasonable reaction time and acceptable enantioselectivity. Alternatively, employment of a novel electrophile with better activity may improve reaction rates. For example, nitro group, as seen in selenolactonization reactions, improved the enantiomeric composition of the lactones by effectively suppressing the racemization of the seleniranium ions. Also, isolation of the electrophile-catalyst complex ***i*** may provide a better understanding of the transition state and thus facilitate the design of a suitable catalyst for higher-order substituted olefins.

2.4.3 Application to a Synthesis of Natural Products

There are a number of natural products and bioactive molecules that contain piperidine or azaheterocycle moieties (Chart 6).[15] For example, (–)-adalinine (**115**) is one of the alkaloids found in defensive fluid emitted by ladybird beetles.[61] It is a chiral molecule consisting of a δ-lactam skeleton bearing two alkyl substituents on the 6-carbon. Using the developed method for sulfenoamination, cyclization of a trisubstituted olefin **119** with a four carbon tether may generate the 6,6-disubstituted-δ-lactam backbone **118** (Scheme 33a). Another interesting application would be the synthesis of bioactive molecule **116** which is a potential antidepressant.[62] Asymmetric sulfenoamination can be applied in synthesis of this compound via **121** as an intermediate followed by a radical-induced cyclization[63] to afford the tricyclic core **120** (Scheme 33b).

Chart 6

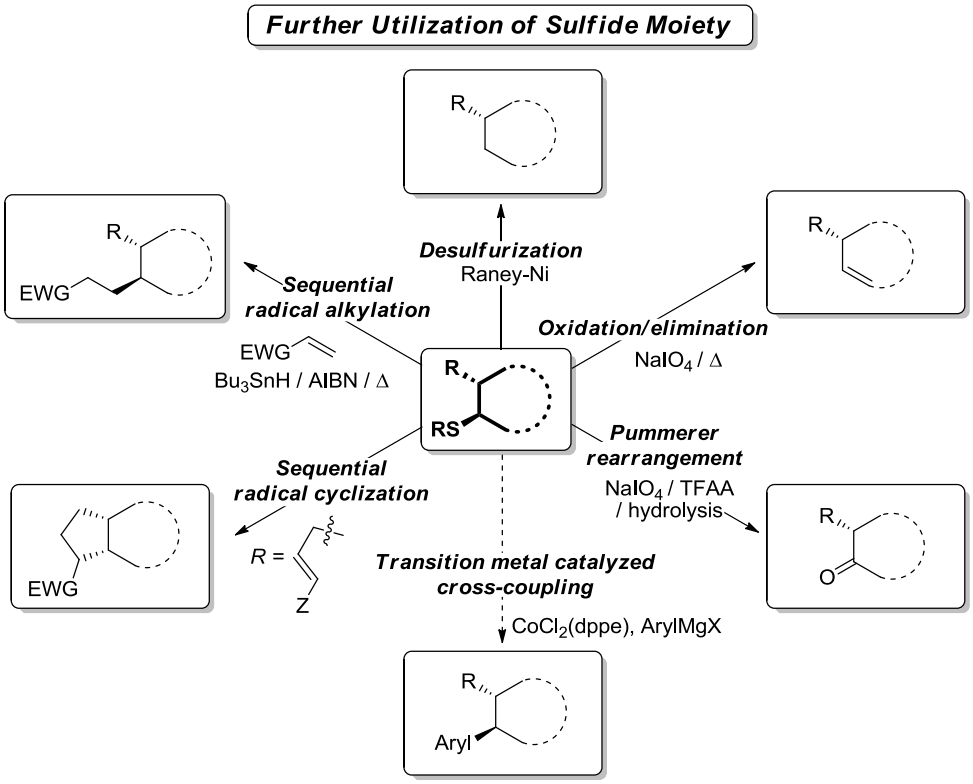
Scheme 33



2.4.4 Utility Demonstration of the Sulfenylated Products

Due to the versatile nature of sulfur, subsequent reaction of the sulfenoaminated product can be envisioned. Besides the simple cleavage of the sulfide,[64] oxidation and elimination of the sulfenoaminated products can be performed to give cyclic olefins[65] or Pummerer rearrangement can be carried out to give a cyclic ketone (Scheme 34).[66]

Scheme 34



Also, as shown in the retrosynthesis example of potent antidepressant **116** (Section 2.4.3), sequential radical induced cyclization[63] could be performed to afford complex polycyclic scaffolds. However, in all cases mentioned thus far, the stereochemical information of the C-S bond is lost. One potentially promising transformation of the sulfide moiety would to exploit it as a precursor for transition metal-catalyzed, cross-coupling reactions. While organonickel compounds have been shown to promote fast elimination of sulfides containing β-heteroatomic

substrates,[67] cobalt(II) salts are able to cross-couple halides with β-heteroatomic groups.[68] Based on these previous studies, it would be interesting to investigate reactions in which the C-S bond serves as a cross-coupling precursor.

2.5 Conclusions

The first catalytic enantioselective sulfenoamination of olefins has been demonstrated using a novel BINAM-derived diisopropylamino selenophosphoramide (*S*)-**83** as the chiral Lewis base. The fundamental principle behind this reaction relies on the Lewis base activation of a Lewis acid. A survey of various nucleophiles revealed that tosylamides are excellent nucleophiles under the acidic reaction conditions. High yields and high enantioselectivities were obtained for a number of *trans* olefins. Interestingly, it was serendipitously found that the purity of methanesulfonic acid have influence on the isomerization rate of cyclized product and reactivity but not on enantioselectivity. Further investigations of the impact of acid on sulfenofunctionalization reaction conditions, as well as the application of this methodology to the synthesis of a natural product are underway.

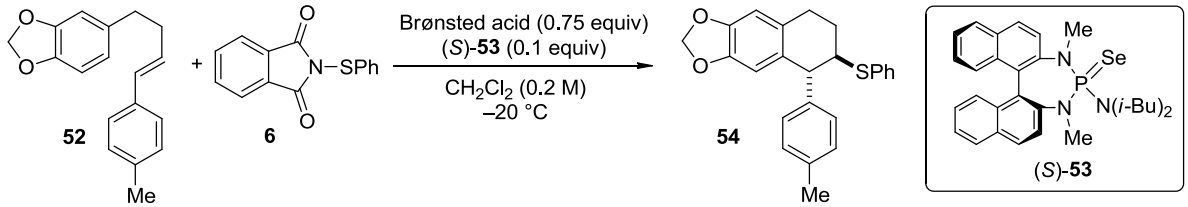
CHAPTER 3: Mechanistic Aspects of Catalytic, Enantioselective, Intramolecular Carbosulfenylation of Olefins: A Remarkable Case of Negative Catalysis[69]

3.1 Introduction

3.1.1 Brønsted Acid−Lewis Base Co-Catalytic Carbosulfenylation of Alkenes

Recently published studies from these laboratories detail the optimization and development of a catalytic, enantioselective carbosulfenylation of alkenes using electron-rich arenes as the nucleophilic partner (Scheme 35).[30] In the course of optimization of this process, it was discovered that the enantioselectivity was not reliably reproduced from orienting experiments (0.2 mmol) to descriptive scale (1.0 mmol). Consideration of the experimental variables that could be responsible led to detailed reevaluation of the role of the Brønsted acid co-catalyst, methanesulfonic acid (MsOH). Foregoing studies in these laboratories on the related heterofunctionalization of alkenes revealed the need for a Brønsted acid co-catalyst to enable Lewis base activation of both Group 16 and Group 17 electrophiles.[11,12,34c] However, in none of these previous studies was the Brønsted acid dependence found to be problematic and, in general, a full equivalent with respect to the substrate could be employed without affecting reproducibility. For the carbosulfenylation, empirical optimization outlined in the preceding studies[30] led to the use of 0.75 equivs of ethanesulfonic acid ($EtSO_3H$) for all preparative experiments. Satisfactory rates and reproducible enantioselectivities were found.

Scheme 35



Despite the successful deployment of these conditions for the method, it was nonetheless of significant interest to elucidate the basis for the heightened sensitivity of this particular sulfenofunctionalization toward the Brønsted acid. In addition, as part of our general program in Lewis base activation of Lewis acids, we were interested in a more fundamental understanding of the role of all reaction components and the mechanistic underpinnings of this type of catalysis.

3.1.2 Objectives of This Study

The goal of this study was to provide a detailed understanding of the mechanism of catalysis of carbosulfenylation using the combination of chiral Lewis base (*S*)-**53** and Brønsted acids MsOH and $EtSO_3H$ with **6** and substrate **52** (Scheme 35). To gain insight into this process, a number of different spectroscopic and kinetic studies were carried out to provide answers to the following questions: (1) What are the rates of the catalyzed and uncatalyzed reactions promoted by varying amounts of MsOH and $EtSO_3H$? (2) What is the protonation state of the sulfenylating agent under catalytic conditions with MsOH and $EtSO_3H$? (3) What is the resting state of (*S*)-**53** under catalytic conditions? (4) What is the structure of the catalytically active species? (5) What is the protonation state of the catalyst in the absence of sulfenylating agent **6**? The answers to these questions are provided below and together provide a refined picture of the mechanism of catalysis and a striking illustration of how seemingly contradictory results can be understood in the light of thorough mechanistic analysis.

3.2 Results

3.2.1 Rates of Catalyzed and Uncatalyzed Reactions

To establish the rates of the Lewis base catalyzed cyclization and the uncatalyzed cyclization in the presence of both Brønsted acids, MsOH and $EtSO_3H$, NMR kinetic analysis

with an internal standard was performed at −20 °C for the reaction of alkene 3 to produce 4. Reactions were carried out at 0.2 M concentrations.[70]

3.2.1.1 Observations on the Purity of Alkylsulfonic Acids

As part of the optimization experiments designed to elucidate the origin of the variable enantioselectivity, the purity (i.e., hydration level) of the sulfonic acids was investigated. The hydration level of the highly hygroscopic alkylsulfonic acids could be specified by integration of the OH signal in the ^{1}H NMR spectra in $CDCl_3$. It was found that the hydration level significantly influenced the rate and enantioselectivity of the cyclization such that high hydration levels (e.g., 20 mol % water) led to slower, but more selective reactions. Accordingly, to vouchsafe the quality of the sulfonic acid for reproducibility, both MsOH and $EtSO_3H$ were rigorously dried by established procedures (see Chapter 5: Experimental for details), and the hydration levels were checked by ^{1}H NMR integration on a regular basis. All of the experiments described below were performed with MsOH and $EtSO_3H$ of specified purity.

3.2.1.2 Reaction Rates at 0.2 M

The time course for the catalyzed reaction with MsOH at the preparative reaction concentration (Figure 9a) reveals clean and high-yielding conversion of **52** to **54**, reaching completion in 12 h.[71] Surprisingly, the uncatalyzed reaction is significantly faster than the catalyzed process and follows apparent zeroth-order kinetic behavior (Figure 9b). Curiously, the formation of **54** was accompanied by formation of **123**, the product of proton-initiated cyclization (ca. 15%). Thus, the competitive production of racemic **54** at a rate comparable to that of the catalyzed process clearly reveals the problems associated with irreproducible enantioselectivity in the presence of MsOH.

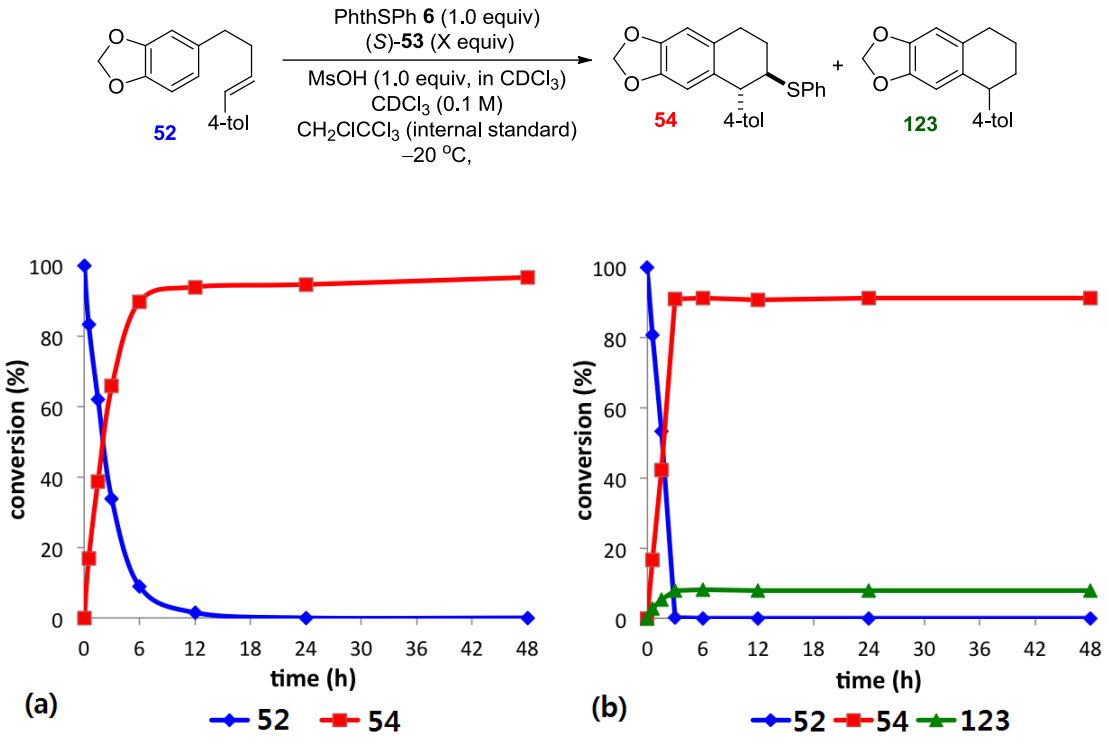


Figure 9. Reactions with MsOH (1.0 equiv). (a) Rate profile for catalyzed cyclization with 0.1 equiv of (*S*)-**53**. (b) Rate profile for uncatalyzed cyclization.

The time courses for the corresponding reactions in the presence of $EtSO_3H$ are similar to those in the presence of MsOH. The catalyzed cyclizations at various loadings of $EtSO_3H$ (Figure 10a) display normal first-order kinetic behavior, but in this case, the initial rates of the reaction at all loadings of $EtSO_3H$ are similar. Interestingly, the enantiomeric composition of **54** eroded only slightly at higher loadings of $EtSO_3H$.[72]

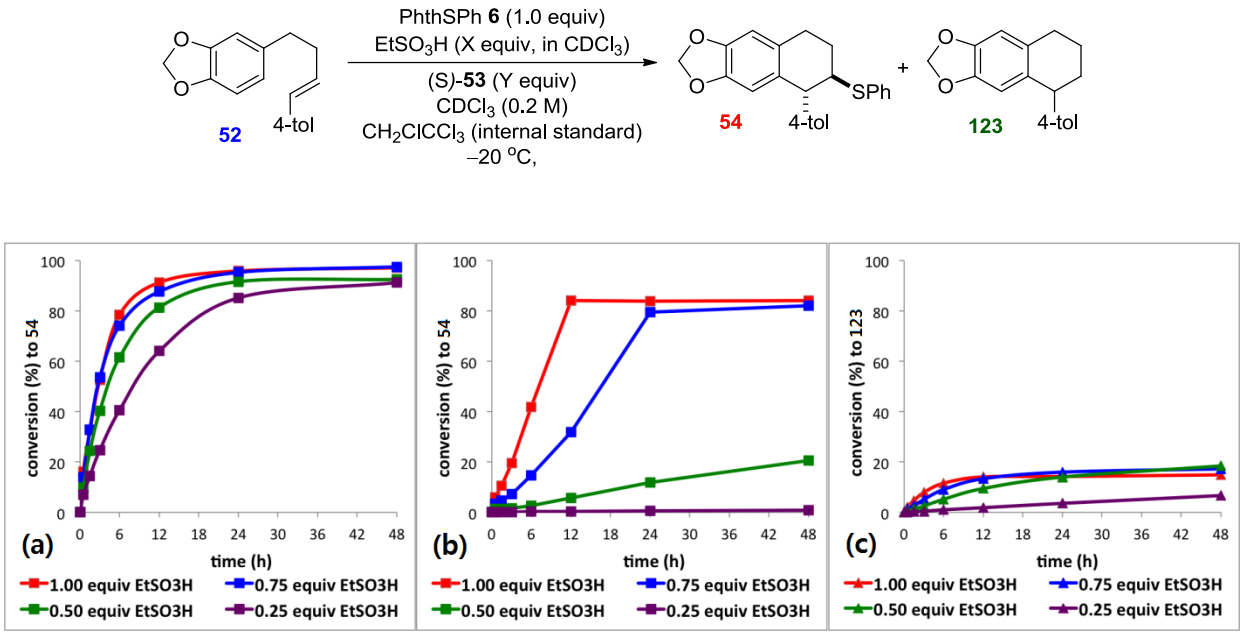


Figure 10. Reactions with $EtSO_3H$ (X equiv). (a) Rate profile for catalyzed cyclization with 0.1 equiv of (*S*)-**53**. (b) Rate profile for formation of **54** in the uncatalyzed cyclization. (c) Rate profile for formation of **123** in the uncatalyzed cyclization.

The uncatalyzed reactions of **52** in the presence of varying amounts of $EtSO_3H$ (Figure 10b,c) mimic the results obtained with MsOH. Interestingly, with 1.00 equiv of $EtSO_3H$, the rate of formation of **54** was comparable to that in the presence of (*S*)-**53** and again displayed zeroth-order kinetic behavior. Here again, **123**, the product of proton-initiated cyclization, was formed in minor amounts.

Four critical insights were gained from the low-temperature NMR kinetic studies: (1) Both MsOH and $EtSO_3H$ are competent Brønsted acids for both the catalyzed and the uncatalyzed carbosulfenylations. (2) Proton-initiated cyclization to form **123** was observed in the absence of catalyst (*S*)-**53** but not in its presence. (3) Overall first-order kinetic behavior was observed under catalysis by (*S*)-**53**. (4) Overall zeroth-order kinetic behavior was observed for the formation of **54** in the absence of (*S*)-**53**.[70]

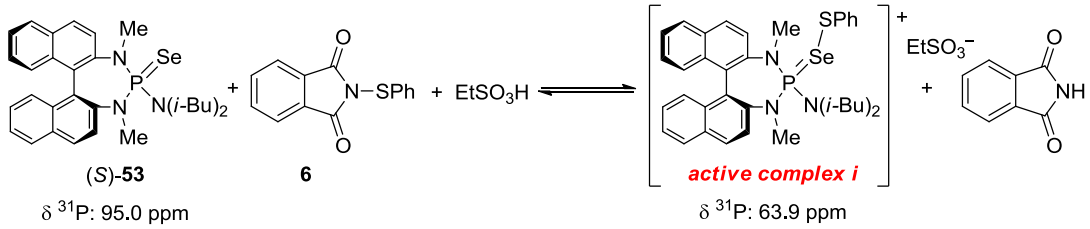
In addition to these important insights, the kinetic analysis also raises interesting questions: (1) How is it possible to obtain enantiomerically enriched **54** if the background, uncatalyzed, racemic reaction is comparable to ($EtSO_3H$) or faster than (MsOH) the reaction catalyzed by chiral Lewis base (*S*)-**53**? (2) How can the formation of **123** in the background reaction be reconciled with its absence in the catalyzed reactions? Answers to these questions require a better understanding of what actually constitutes the background reaction and will be addressed in the following sections.

3.2.2 Catalyst Resting State and Titration Studies

3.2.2.1 Identifying and Quantifying the Catalytically Active Species

Foregoing studies with (*S*)-**53** established that the catalytically active sulfenylating agent is formed by sulfenyl group transfer from **6** to the selenophosphoramide mediated by a Brønsted acid. In view of the unusual dependence of the rate of catalyzed carbosulfenylation on acid loading (Figure 10a), it was of interest to establish the magnitude of the pre-equilibrium formation of that species. Thus, low-temperature NMR experiments were undertaken under catalytic conditions without substrate (**6**/(*S*)-**53**, 10.0:1.0) with varying amounts of $EtSO_3H$ at −20 °C (8.3 μM in (*S*)-**53**). At this temperature, the exchange between (*S*)-**53** and catalytically active species ***i*** was too fast to allow accurate integration, so the experiments were repeated at −50 °C (Table 9).[73] Under these conditions, both species could be detected simultaneously, and this revealed that the catalyst becomes saturated as complex ***i*** somewhere between 2.5 and 5.0 equiv of $EtSO_3H$ (with respect to (*S*)-**53**).

Table 9. Determination of Equilibrium for Formation of Complex *i* at 8.3 μM in (*S*)-53.



reagents (equiv)			^{31}P NMR (δ, ppm)	
i-Bu cat. **53**	PhthSPh **6**	$EtSO_3H$	at –20 °C	at –50 °C
1.0	10.0	0.0	95.0	–
1.0	10.0	1.0	94.9 (br)	95.2 (br)
1.0	10.0	2.5	94.3 (br), 64.7 (br)	95.4 (br), 63.9 (br) (ratio=1.00:0.91)
1.0	10.0	5.0	63.7 (br)	64.0
1.0	10.0	7.5	63.7	64.0
1.0	10.0	10.0	63.6	63.9

Repeating the titration experiments at −57 °C and at higher concentration (25 μM in (*S*)-**53**) allowed a more accurate determination of the saturation point (Table 10).[73] Thus, approximately 4.0 equiv of $EtSO_3H$ was needed to convert ca. 98% of (*S*)-**53** into complex ***i***, whereas with 2.5 equiv of $EtSO_3H$ only 65% of (*S*)-**53** was converted.

Table 10. Determination of Equilibrium for Formation of Complex *i* at 25 μM in (*S*)-53.

reagents (equiv)			ratio of ^{31}P NMR signals at 95 ppm and 64 ppm (–57 °C)
i-Bu cat. **53**	PhthSPh **6**	$EtSO_3H$	
1.0	10.0	1.0	3.12:1.00
1.0	10.0	2.5	1.00:1.86
1.0	10.0	3.0	1.00:4.07
1.0	10.0	3.5	1.00:24.88
1.0	10.0	4.0	1.00:54.49

3.2.2.2 Calculation of Equilibrium Constants (K_{eq})

Equilibrium constants were calculated for the two preceding experiments both at the 2.5 equiv data points. Calculations were carried out assuming that the catalytically active species ***i*** exists either as a solvent-separated ion pair (Figure 11) or as an intimate ion pair (Figure 12).

Solving the equations at two concentrations for the tight ion pair afforded the same equilibrium constant, whereas solving for the solvent-separated ion pair did not. Thus, it can be safely (and logically) concluded that complex ***i*** is a tight ion pair in dichloromethane under the reaction conditions.

Method 1: Solvent-separated ion pair

Catalyst (5 μmol) : PhthSPh : $EtSO_3H$ = 1.0 : 10.0 : 2.5 (600 μL $CDCl_3$, -50 °C) ^{31}P NMR 95 ppm : 64 ppm ratio: 1.00 : 0.91

Catalyst	Phth−SPh	$EtSO_3H$	$\rightleftharpoons$	[catalyst−SPh]$^+$	[$EtSO_3$]$^-$	PhthH
8.3 μM	83.3 μM	20.8 M		0 μM	0 μM	0 μM
8.3 - X μM	83.3 - X	20.8 - X μM		X μM	X μM	X μM

(8.3 - X) : X = 1.00 : 0.91

X = 3.97

$$K_{eq} = \frac{X^3}{(8.3 - X)(83.3 - X)(20.8 - X)} = 1.08 \times 10^{-2}$$

Catalyst (15 μmol) : PhthSPh : $EtSO_3H$ = 1.0 : 10.0 : 2.5 (600 μL $CDCl_3$, -57 °C) ^{31}P NMR 95 ppm : 64 ppm ratio: 1.00 : 1.86

Catalyst	Phth−SPh	$EtSO_3H$	$\rightleftharpoons$	[catalyst−SPh]$^+$	[$EtSO_3$]$^-$	PhthH
25 μM	250 μM	62.5 μM		0 μM	0 μM	0 μM
25 - X μM	250 - X μM	62.5 - X μM		X μM	X μM	X μM

(25 - X) : X = 1.00 : 1.86

X = 16.3

$$K_{eq} = \frac{X^3}{(25 - X)(250 - X)(62.5 - X)} = 4.55 \times 10^{-2}$$

Figure 11. Calculation of K_{eq} for complex ***i*** assuming solvent-separated ion pair structure.

Method 2: Intimate ion pair

Catalyst (5 μmol) : PhthSPh : $EtSO_3H$ = 1.0 : 10.0 : 2.5 (600 μL $CDCl_3$, -50 °C) ^{31}P NMR 95 ppm : 64 ppm ratio 1.00 : 0.91

Catalyst	Phth−SPh	$EtSO_3H$	$\rightleftharpoons$	[catalyst−SPh]$^+$ [$EtSO_3$]$^-$	PhthH
8.3 μM	83.3 μM	20.8 μM		0 μM	0 μM
8.3 - X μM	83.3 - X	20.8 - X μM		X μM	X μM

(8.3 - X) : X = 1.00 : 0.91

X = 3.97

$$K_{eq} = \frac{X^2}{(8.3 - X)(83.3 - X)(20.8 - X)} = 2.73 \times 10^{-3}$$

Catalyst (15 μmol) : PhthSPh : $EtSO_3H$ = 1.0 : 10.0 : 2.5 (600 μL $CDCl_3$, -57 °C) ^{31}P NMR 95 ppm : 64 ppm ratio 1.00 : 1.86

Catalyst	Phth−SPh	$EtSO_3H$	$\rightleftharpoons$	[catalyst−SPh]$^+$ [$EtSO_3$]$^-$	PhthH
25 μM	250 μM	62.5 μM		0 μM	0 μM
25 - X μM	250 - X μM	62.5 - X μM		X μM	X μM

(25 - X) : X = 1.00 : 1.86

X = 16.3

$$K_{eq} = \frac{X^2}{(25 - X)(250 - X)(62.5 - X)} = 2.80 \times 10^{-3}$$

Figure 12. Calculation of K_{eq} for complex ***i*** assuming intimate ion pair structure.

3.2.2.3 Protonation State of Phenylsulfenophthalimide (6) and the Catalyst ((*S*)-53)

To gain insight into the curious behavior of noncatalyzed cyclizations, the protonation states of (*S*)-**53** and **6** were determined by VT-NMR experiments. The exchange rate between **6** and **6**·$H^+RSO_3^-$ was sufficiently rapid at −20 °C (125 MHz ^{13}C) to allow observation of a sharp singlet for the carbonyl groups that shifted from 167.8 ppm (no RSO_3H) to 168.9 ppm (10.0−15.0 equiv of RSO_3H, Figure 13a).

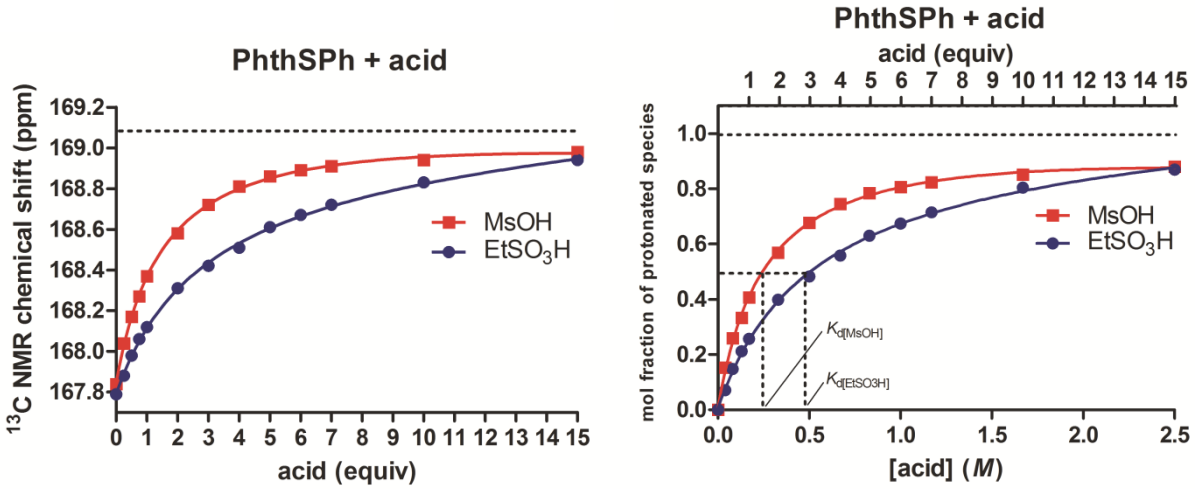


Figure 13. Titration curves for protonation of PhthSPh **6** with MsOH and $EtSO_3H$.

These data were fitted to a curve with nonlinear regression (single-site total binding model). Extrapolation of the curve for MsOH gave 169.2 ppm as the chemical shift of **6**·$H^+RSO_3^-$, whereas doing the same for $EtSO_3H$ gave 169.0 ppm. These extrapolated values lead to a single, apparent K_{eq} = 3.63 M^{-1} for MsOH and K_{eq} = 2.05 M^{-1} for $EtSO_3H$ (K_d = 0.276 ± 0.018 M for MsOH and K_d = 0.488 ± 0.049 M for $EtSO_3H$). As expected, the K_{eq} value for MsOH is larger than that for $EtSO_3H$, because the ability of MsOH to protonate **6** is greater than that of $EtSO_3H$. By using the average of the extrapolated chemical shifts of **6**·$H^+RSO_3^-$, the mole fraction of **6**·$H^+RSO_3^-$ present at various loadings of acid could be calculated (Figure 13b); at

1.00 equiv of acid, **6**·$H^+RSO_3^-$ is present at 41 mol % with MsOH and 26 mol % with $EtSO_3H$. These numbers represent a significant amount of an active, achiral sulfenylating agent that is responsible for the background reaction. However, given the high enantioselectivities observed, the actual amount of **6**·$H^+RSO_3^-$ must be significantly less, the reason for which is addressed below.

The protonation of catalyst (*S*)-**53** was examined briefly. Addition of 1.0 equiv of $EtSO_3H$ to a 0.1 mM solution of (*S*)-**53** in $CHCl_3$ had no effect on the ^{31}P NMR chemical shift, indicating a negligible degree of protonation.

3.2.3 Effect of the Presence of Sulfonate Anion on the Rate of the Uncatalyzed Reaction

The realization that (1) formation of catalytically active species ***i*** is quantitative under the catalytic reaction conditions, (2) sulfenylating agent **6** is partially protonated under these conditions, and (3) both of these species carry sulfonate counterions led to the recognition that the action of the remaining Brønsted acid could be attenuated by the buffering effect of the sulfonate. Thus, a modified version of the background reaction was formulated in which the amounts of complex ***i*** and protonated **6** formed under catalytic conditions were mimicked by adding varying amounts of tetrabutylammonium mesylate ($Bu_4N^+OMs^-$) (Figure 14).

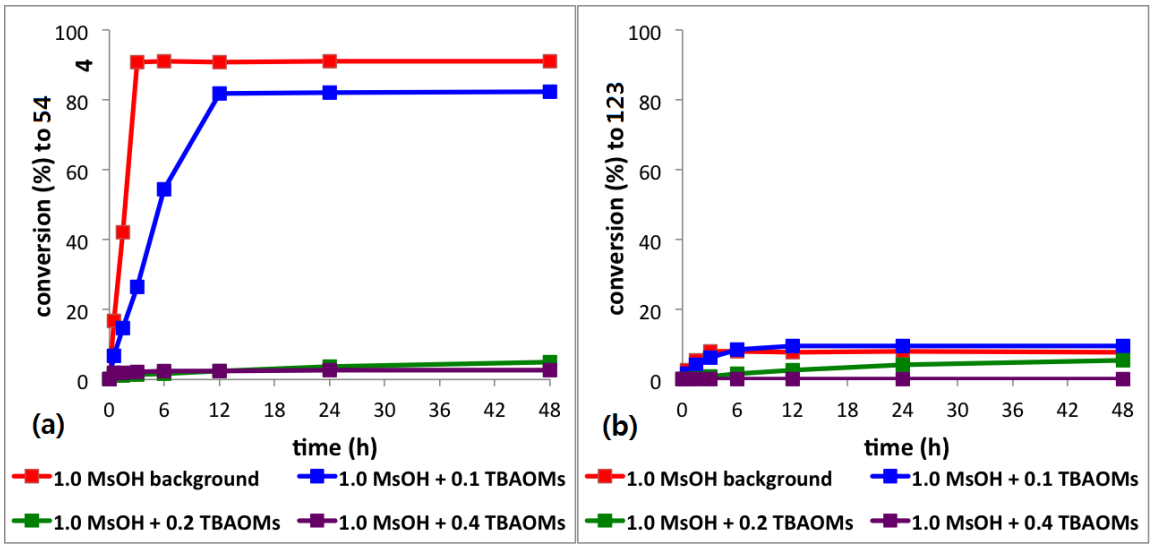


Figure 14. Reactions with MsOH (1.0 equiv) and $Bu_4N^+OMs^-$. (a) Rate profile for formation of **54** in the uncatalyzed cyclization. (b) Rate profile for formation of **123** in the uncatalyzed cyclization.

The results were striking: whereas 0.1 equiv of $Bu_4N^+OMs^-$ slows the formation of **54** (but not **123**), 0.2 equiv of $Bu_4N^+OMs^-$ was able to almost completely shut down the formation of **54** and **123** in the presence of 1.0 equiv of MsOH. This observation implies that the actual background reaction operating under catalytic conditions is not accurately represented by simply omitting the catalyst. Moreover, reconsideration of the components present under catalytic conditions reveals that the actual amount of MsOH available is only 0.9 equiv and that 0.1 equiv of phthalimide is also present, both as a consequence of the formation of complex ***i***. Figure 15a shows the rate profile for the uncatalyzed reaction with 0.9 equiv of MsOH and 0.1 equiv of $Bu_4N^+OMs^-$; Figure 15b shows the rate for the same uncatalyzed reaction but with also 0.1 equiv of phthalimide. Here again, suppression of the formation of **54** is striking, illustrating that both methanesulfonate and phthalimide are serving as buffers to attenuate the acidity of MsOH in the medium. Figure 15c shows the superposition of all of these experiments.

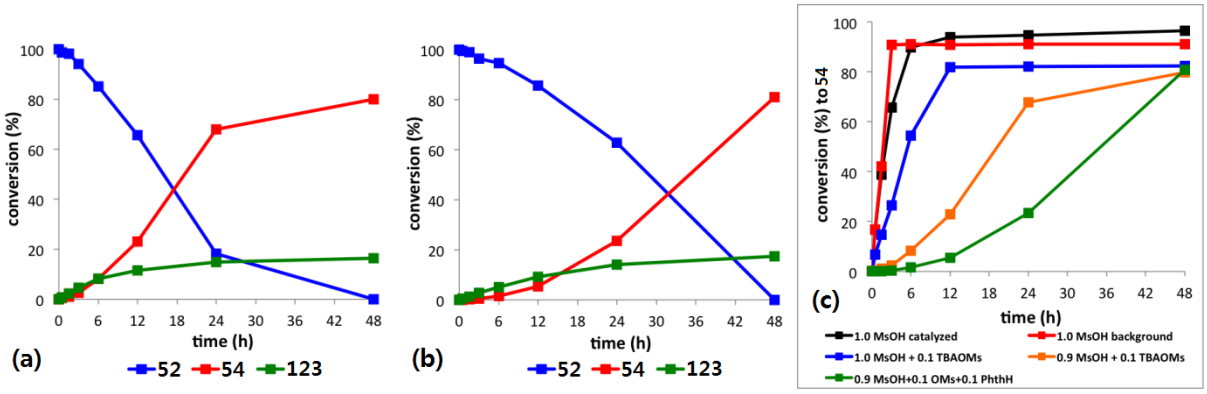


Figure 15. (a) Rate profile for the uncatalyzed reaction with 0.9 equiv of MsOH and 0.1 equiv of $Bu_4N^+OMs^-$. (b) Rate profile for the uncatalyzed reaction with 0.9 equiv of MsOH, 0.1 equiv of $Bu_4N^+OMs^-$, and 0.1 equiv of phthalimide. (c) Superposition of all reactions with MsOH; only formation of **54** is depicted.

It is now easy to see how a catalyzed reaction (black line) can be slower than the corresponding uncatalyzed reaction (red line) and still give rise to high enantioselectivities. One must consider the circumstances under which the uncatalyzed reaction is proceeding under the conditions of the catalyzed process. Simply removing the catalyst is not sufficient to accurately mimic those conditions.

The true background formation of **54** under "catalytic conditions" was significantly slower than assumed on the basis of the results shown in Figure 15c. In the time required for complete consumption of substrate **52** under catalytic conditions, only 8.6% of **54** is produced in the background reaction. Obviously, this amount would be considerably less in the catalyzed reaction because the concentration of **52** would be decreasing faster (and the amount of phthalimide would be increasing faster) as a result of the productive enantioselective pathway. However, the formation of byproduct **123**, which is not observed in any of the catalytic reactions,

suggests that this experiment is still not perfectly mimicking the actual catalytic reaction conditions.

3.3 Discussion

3.3.1 Role of the Brønsted Acid

The irreproducibility of the catalytic carbosulfenylations upon scale-up for descriptive purposes revealed a dramatic sensitivity to the Brønsted acid that was not seen in the preceding studies on oxysulfenylation reactions.[12] Systematic reinvestigation of the effects of Brønsted acid loading on the rate and selectivity of the reactions, the formation of the catalytically active sulfenylating agent, and the protonation equilibria for **6** was highly informative and revealed a dramatic sensitivity of the reaction behavior to the stoichiometry of the acid and also overall concentration.

3.3.1.1 Comparison of Methane- and Ethanesulfonic Acids

The Brønsted acidity of sulfonic acids has been the subject of intense study for many years.[74] Alkylsulfonic acids are classified as "moderately strong acids", with pK_a's between +2 and −2, and as such are amenable to a variety of acidity determinations. In water, methanesulfonic acid has pK_a = −1.92, whereas that of ethanesulfonic acid is −1.68. Similarly small differences have been found in DMSO and acetonitrile. The slightly weaker acidity of $EtSO_3H$ has been manifested in all of the experiments described above: both catalyzed and uncatalyzed cyclizations of **52** proceed more slowly with $EtSO_3H$ than with MsOH.[75] The preparative advantage of $EtSO_3H$ that was used for all descriptive cyclizations arises from the slightly larger difference in the catalyzed and uncatalyzed reactions at lower loadings and also the lower melting point that allowed cold delivery of the acid.

3.3.1.2 Effect of Brønsted Acid on the Rate and Enantioselectivity of the Carbosulfenylation

The use of MsOH (1.0 equiv) in the catalytic carbosulfenylation led to a rapid consumption of the alkene, leveling off at 98.5% conversion at 12 h to afford **54** with a 75:25 er (Figure 9a). In the absence of catalyst (*S*)-**53**, the reaction profile showed zeroth-order decay, leveling off at >99% conversion at 3 h.[76] Under these conditions, the product composition was ca. 91% **54** and 8% **123**.

The use of $EtSO_3H$ in varying stoichiometries led to very similar reaction profiles albeit at overall lower rates compared to MsOH. The carbosulfenylation of **52** proceeded with normal first-order kinetics to afford **54** with highly reproducible and higher enantioselectivities (ca. 92.5:7.5 er) (Figure 10a). With 1.0 equiv of $EtSO_3H$ the rates of the catalyzed and uncatalyzed reactions are comparable, leveling off at 98.6% conversion of **52** at 24 h with (*S*)-**53** and 99.3% conversion at 12 h without (*S*)-**53**. Here again, the uncatalyzed reaction is competitive at 1.00 and 0.75 equiv of $EtSO_3H$ (Figure 10b).[77] The reason for the difference between MsOH and $EtSO_3H$ will be discussed below in the section on protonation equilibria with **6**.

3.3.1.3 Effect of Brønsted Acid on the Resting State of the Catalyst

The unusual similarity of the rate profiles for the catalyzed carbosulfenylation in the presence of various amounts of $EtSO_3H$ (Figure 10a) stimulated an investigation into the effect of the Brønsted acid on the conversion of catalyst (*S*)-**53** into the catalytically active sulfenylating agent ***i***. Low-temperature ^{31}P NMR titration experiments revealed that catalyst (*S*)-**53** becomes saturated as ***i*** with ca. 4.0 equiv of $EtSO_3H$ and 10.0 equiv of **6** with respect to (*S*)-**53** (i.e., 0.40 equiv with respect to **6** and substrate **52** under catalytic conditions). Thus, the similarity of rates for 1.00, 0.75, and 0.50 equiv of $EtSO_3H$ and the lower rate for 0.25 equiv can

be readily understood from the amount of active sulfenylating agent ***i*** present. Above 0.4 equiv of $EtSO_3H$, the catalyst is saturated, and thus the rate has reached a maximum.

An additional insight into the nature of the active sulfenylating agent was secured by taking advantage of the fact that the equilibrium formation of ***i*** was measured at two different concentrations (Figures 11 and 12). The K_{eq} was calculated at both concentrations (using data from 2.5 equiv of $EtSO_3H$) assuming that ***i*** was either a solvent-separated ion pair (Figure 11, Method 1) or an intimate ion pair (Figure 12, Method 2). Interestingly, the solution for the two concentrations using Method 1 produced two different K_{eq}'s, whereas the solution using Method 2 gave nearly identical K_{eq}'s. From these data, we assume that the catalytically active species is an intimate ion pair in dichloromethane.

3.3.1.4 Protonation Equilibria for *N*-Phenylsulfenylphthalimide (6)

Sulfenylating agent **6** was shown to be significantly protonated under standard reaction conditions (0.2 M, 1.00 equiv of RSO_3H). The high rate of the uncatalyzed reaction (in the absence of (*S*)-**53**) can be ascribed to the reactivity and concentration of $\mathbf{6}\cdot H^+RSO_3^-$. The greater *difference* in the rates of the catalyzed and uncatalyzed reactions for $EtSO_3H$ compared to MsOH can be understood from the differing consequences of their acidities. The rates of the catalyzed reactions are very similar because these reactions are governed by the concentration of the active sulfenylating agent ***i***, which reaches its (saturated) maximum in the presence of both acids at 1.00 equiv loading. However, the weaker proton-donating strength of $EtSO_3H$ compared to MsOH, as illustrated in the measured K_{eq}'s of protonation of **6**, has a greater rate-attenuating effect on the uncatalyzed reaction, thus leading to a larger "split" in the catalyzed/uncatalyzed rates, which leads to a better-behaved system for enantioselectivity.

The dramatic drop in the rate of the uncatalyzed reaction upon the addition of *n*-$Bu_4N^+OMs^-$ and phthalimide together with the attendant decrease in the amount of MsOH implies that the concentration of **6**·$H^+RSO_3^-$ must be substantially lower under the condition of the catalytic reaction for reasons described below.

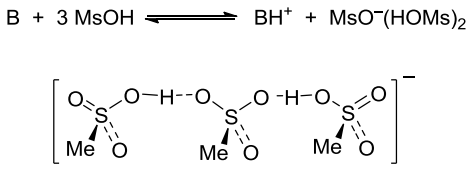
3.3.2 Role of Sulfonate Ions in the Uncatalyzed Cyclization: The Structure of Ion Pairs

The counterintuitive observation that the cyclization of **52** in the absence of catalyst ("racemic background reaction") proceeded with a rate comparable to that of the catalyzed cyclization of **52** (which afforded high enantioselectivity) demanded a reevaluation of the actual racemic background reaction that may intervene under catalytic conditions. As shown in Figures 14 and 15, sulfonate ions and phthalimide (necessary consequences of the formation of the catalytically active species ***i***) were effective inhibitors of the racemic background reaction. The results shown in Figure 15c were most informative. With as little as 0.1 equiv of *n*-$Bu_4N^+OMs^-$, 0.1 equiv of phthalimide, and 0.9 equiv of MsOH (the actual stoichiometries with respect to **52** at the beginning of the catalyzed reaction), the cyclization is extremely slow, reaching less than 10% conversion in the same time that the catalytic reaction would be complete. *Thus, the apparent contradiction seen in Figures 9 and 10 is, in reality, a consequence of the incorrect assumption that the racemic background reaction is accurately represented by simply leaving out the catalyst*.

A possible explanation for the inhibition of the racemic background reaction under catalytic conditions may be found in the buffering effect of the sulfonate ion. The strong buffering effect of sulfonate ions on the acidity of sulfonic acids has in fact been studied in nonaqueous media, but not in chlorinated solvents. The self-association of acids with their conjugate bases, known as the "homoconjugation reaction", has been studied for sulfonic acids

in dipolar aprotic solvents.[78] In the conductometric titration of MsOH in benzonitrile (with Et_3N), a large maximum is observed at one-third of the equivalence point. Such maxima are characteristic of the formation of triple ions[79] according to the formula shown in Scheme 36. The maximum at one-third equivalence for MsOH is much larger than that for $PhSO_3H$ or TsOH because of its weaker acidity and corresponding greater basicity of MsO^-, thus leading to a higher concentration of the triple ion. In the cyclization reactions, the base (B) is *N*-phenylthiophthalimide (**6**). With 1.00 equiv of $EtSO_3H$, **6** is ca. 25% protonated, leading to a significant concentration of the triple ion which sequesters two additional molecules of $EtSO_3H$.

Scheme 36



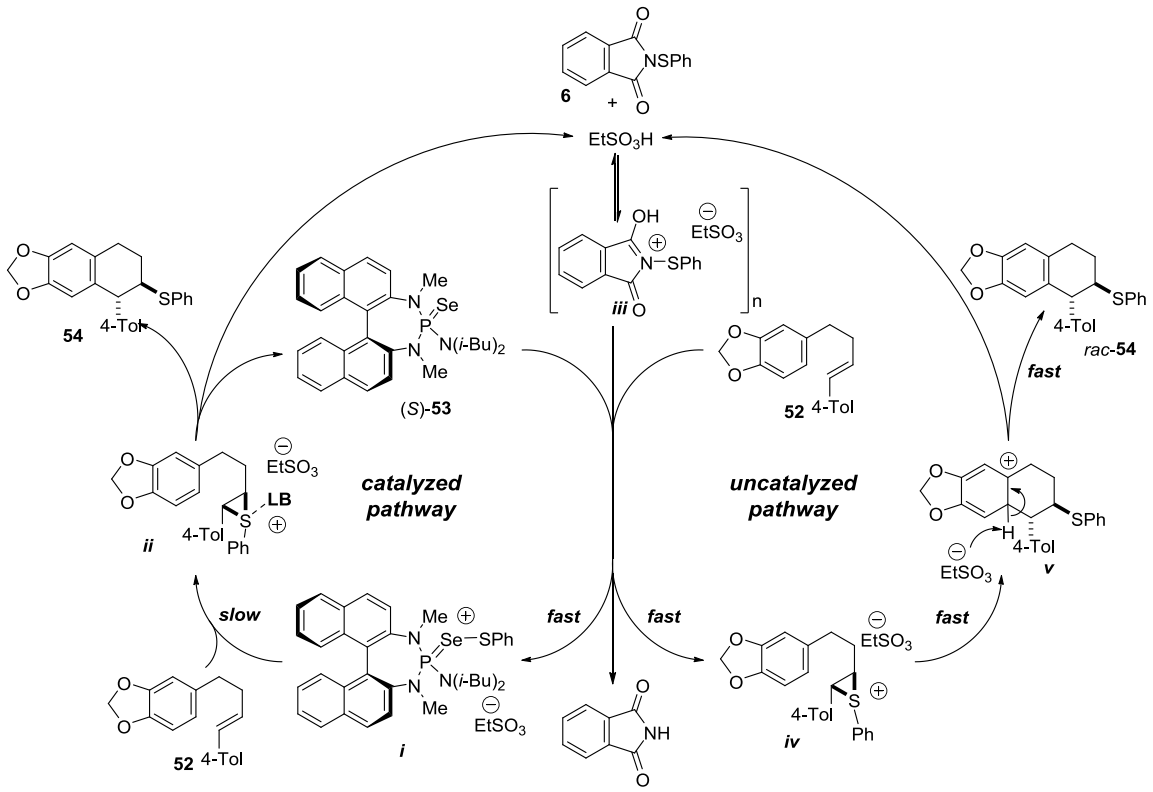
An important issue that could well impact the understanding of this phenomenon is the actual structure of the ion pairs involved in the various stages of the reaction. Although the structure of the catalytically active species ***i*** could be established as an intimate ion pair in $CHCl_3$, the structures of **6**·$H^+RSO_3^-$ and protonated phthalimide could not be established. Clearly, the buffering power (i.e., homoconjugation strength) will depend on the structure of the ion such that the more solvent-separated the ions, the greater their ability to bind to their conjugate acids.[80]

3.3.3 Mechanistic Rationale and Catalytic Cycles

The formation of (racemic) **54** at a rate greater than that of the catalyzed reaction provided a compelling explanation for the variability of the enantioselectivities in preparative reactions, but also presented a conundrum: how can a catalytic reaction outcompete a faster stoichiometric reaction and produce enantiomerically enriched products?

The answer to this question has been found in a deeper understanding of the stoichiometry for generation of the catalytically active sulfenylating agent ***i*** and in the buffering effect of sulfonate ions and phthalimide formed under catalytic conditions. These phenomena result in the simultaneous operation of two catalytic cycles illustrated in Scheme 37.

Scheme 37



Initiation of both cycles begins with the pre-equilibrium protonation of **6** to form species ***iii***. Under catalytic conditions (i.e., with 0.1 equiv of (*S*)-**53**) the catalyst is saturated as the kinetically active sulfenylating agent ***i*** with as little as 0.4 equiv of $EtSO_3H$ (with respect to **6**). Once ***i*** is stoichiometrically generated, the catalytic cycle has no further need for $EtSO_3H$ (as was seen in the similarity of rates in Figure 10a). Any additional acid would be deleterious in promoting the uncatalyzed pathway, but the presence of MsO^- from both ***i*** and ***iii*** (**6**·$H^+RSO_3^-$) serves to neutralize the excess acid and inhibit the racemic background reaction. First-order

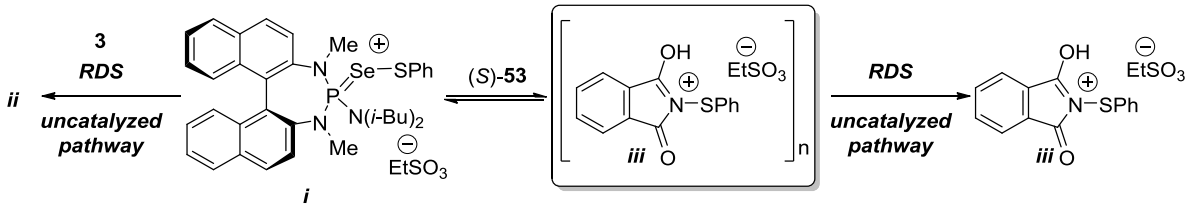
kinetic behavior requires that the formation of episulfonium ion ***ii*** be the rate-determining step which is followed by rapid cyclization and rearomatization.

The striking behavior of this catalytic system bears some resemblance to the inhibition of the asymmetric catalytic pathway in the Povarov reaction elegantly analyzed by Jacobsen.[81] In that study a similar observation was made regarding the suppression of a Brønsted acid catalyzed racemic background reaction that they ascribed to "negative catalysis".[82] The high association constant of the chiral urea for the protonated imine resulted in the removal of the Brønsted acid from the reaction. In our system, this behavior is reflected in the formation of species ***i***. However, Jacobsen et al. employed only half as much Brønsted acid as catalyst loading, whereas in our system the Brønsted acid is deployed in stoichiometric quantities with respect to substrate. Thus, consuming 0.1 equiv of $EtSO_3H$ in the formation of ***i*** is insufficient to explain the inhibition of the background reaction. Instead, we have identified the crucial role of the conjugate base $EtSO_3^-$ in sequestering the excess Brønsted acid through the homoconjugation reaction, which forms triple ions, as well as the buffering effect of the phthalimide generated from **6**.

Although not directly relevant to the focus of this study, the curious zeroth-order dependence for the formation of **54** in the absence of (*S*)-**53** warrants comment (Figures 9b and 9b). This unusual behavior implies that the rate of cyclization depends only on the Brønsted acid, whose concentration does not change over the course of the reaction (Scheme 37). This unique dependence would obtain if the cyclization becomes rate determining in the absence of the Lewis base catalyst. In this scenario, the resting state is the species ***iv***, whose concentration is set by the amount of Brønsted acid employed. Since this step is an intramolecular reaction, it will exhibit zeroth-order kinetic dependence on **6** and substrate **52**. The subsequent rearomatization step from ***v*** should be very fast. This hypothesis posits that intermediate ***iv*** should be observable under the

reaction conditions. However, NMR analysis of the uncatalyzed reactions revealed a consistently high mass balance (>98%) consisting of only **6**, **52**, and **54**.

Scheme 38



An alternative explanation for zeroth-order behavior would be a rate-determining step outside of the catalytic cycle. If the protonated sulfenylating agent ***iii*** existed in an aggregated state (perhaps intermolecularly hydrogen bonded) which had to dissociate to form a catalytically competent agent, and all downstream reactions were faster than dissociation, overall zeroth-order behavior would be observed (Scheme 38). The amount of reactive monomer would be dependent on the amount of ***iii***, which is dependent only on the amount of Brønsted acid. In the presence of (*S*)-**53**, either the monomer is rapidly intercepted to form ***i*** or the catalyst is capable of reacting with the aggregate in a rapid pre-equilibrium which (as was established above) is acid dependent.[83]

3.4 Conclusion

Detailed kinetic and spectroscopic analysis of the enantioselective Lewis base/Brønsted acid co-catalyzed carbosulfenylation reaction has revealed a number of interesting features that explain previously observed, contradictory behavior. The unusual observation that the rate of the catalyzed reaction is similar to that of the uncatalyzed process, yet still affords high enantioselectivity, is now understood. The actual background reaction operating under catalytic conditions is not accurately mimicked by simply leaving out the catalyst. In the presence of the Lewis base catalyst, the active sulfenylating agent **6** is formed quantitatively. Two byproducts of this step conspire to inhibit the Brønsted acid catalyzed pathway, namely, equimolar amounts of a sulfonate and phthalimide. The sulfonate forms triple ions with the remaining sulfonic acid, thus sequestering twice its molar concentration, and the phthalimide serves as a buffer to neutralize additional amounts of the acid. The consequences of these observations on other Brønsted acid catalyzed reactions are currently under investigation.

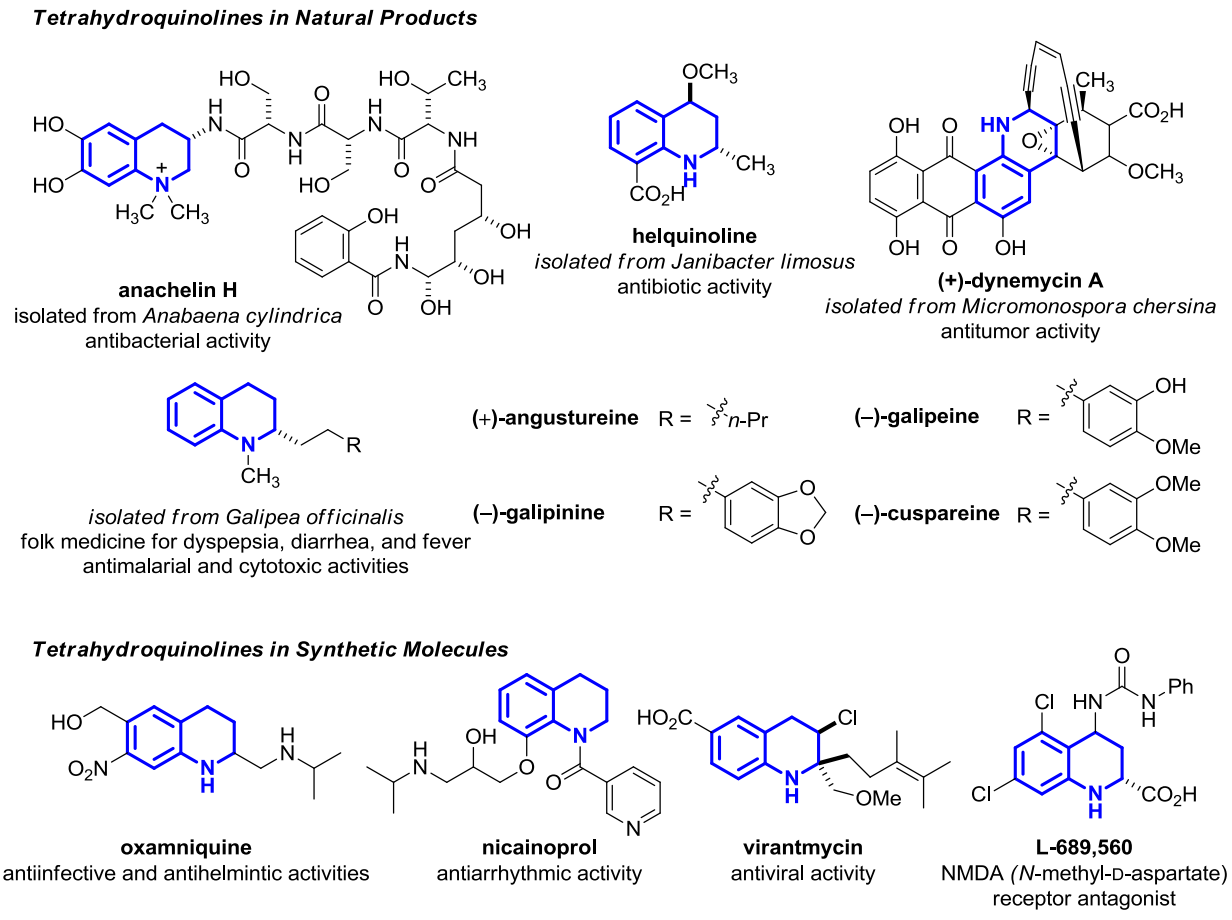
CHAPTER 4: Catalytic, Enantioselective, Intramolecular Sulfenoamination of Alkenes with Anilines[84]

4.1 Introduction

4.1.1 Tetrahydroquinolines

As an important member of the class of nitrogen-containing biologically-relevant motifs, the tetrahydroquinoline ring system is common to a wide range of natural and synthetic compounds that exhibit biological activities (Chart 7).[85] These compounds display, *inter alia* antitumor, antiarrhytmic, antibiotic, antidepressant, cardiovascular, antithrombotic, antiallergenic, antiheumatic, immunosuppressant, and antifertility activity.[85]

Chart 7



4.1.1.1 Synthesis of Tetrahydroquinolines

Due to their diverse applications in pharmaceutical and medicinal chemistry, the development of novel strategies for the synthesis of tetrahydroquinolines has been an active area of research. Traditional approaches to the synthesis of the tetrahydroquinoline core can be classified into three categories: (1) construction of the tetrahydropyridine fragment, (2) construction of the aryl ring, and (3) reduction/hydrogenation of quinolines (Figure 16). Among these, the first strategy is the most common and involves the formation of C-C or C-N bonds with creation of stereogenic sp^3 carbon centers. A few reports employ the second strategy of which the intramolecular Diels-Alder reaction of a furan followed by thermal aromatization is a representative example.[86] On the other hand, the third strategy (partial hydrogenation of quinolines) is often more direct and can be accomplished enantioselectively. Indeed, many enantioselective hydrogenation methods have been developed for the synthesis of *syn*-2,3-substituted tetrahydroquinolines.[87] Of course, the preparation of the starting quinolines then becomes the challenge.[85b]

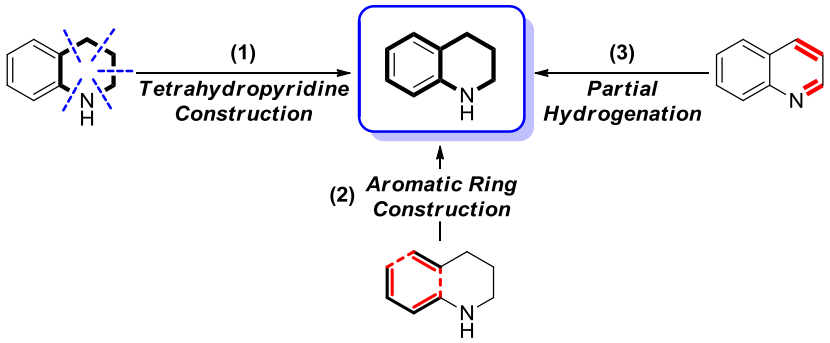


Figure 16. Three strategies for the synthesis of tetrahydroquinolines.

4.1.1.2 Enantioselective Syntheses of Tetrahydroquinolines

Numerous strategies for the synthesis of the tetrahydropyridine fragment have been developed that target different bond disconnections and stereocontrol elements. The

enantioselective syntheses of the tetrahydropyridine ring can be further divided into two subcategories by the number of bonds formed in the key step. The first category is a cyclization that forms one bond, and the second is an annulation that forms two or more bonds. Most enantioselective methods leverage facile cyclization whereas only a few enantioselective variants of annulation processes have been reported.

Enantioselective, intramolecular, one-bond construction of tetrahydroquinolines can be categorized into four types based on the bond that is formed: (1) N-C_2, (2) C_2-C_3, (3) C_3-C_4, and (4) C_4-C_{4a} (Figure 17). Disconnection strategy of N-C_{8a} is also well described and represented by transition metal catalyzed amination reactions,[88] but they inherently cannot be enantioselective.

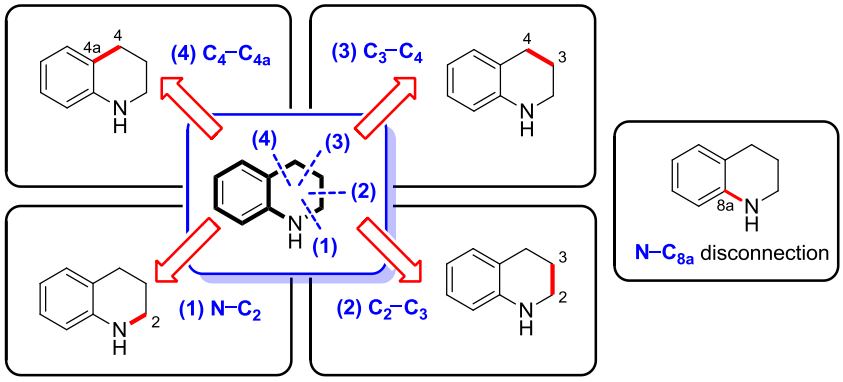
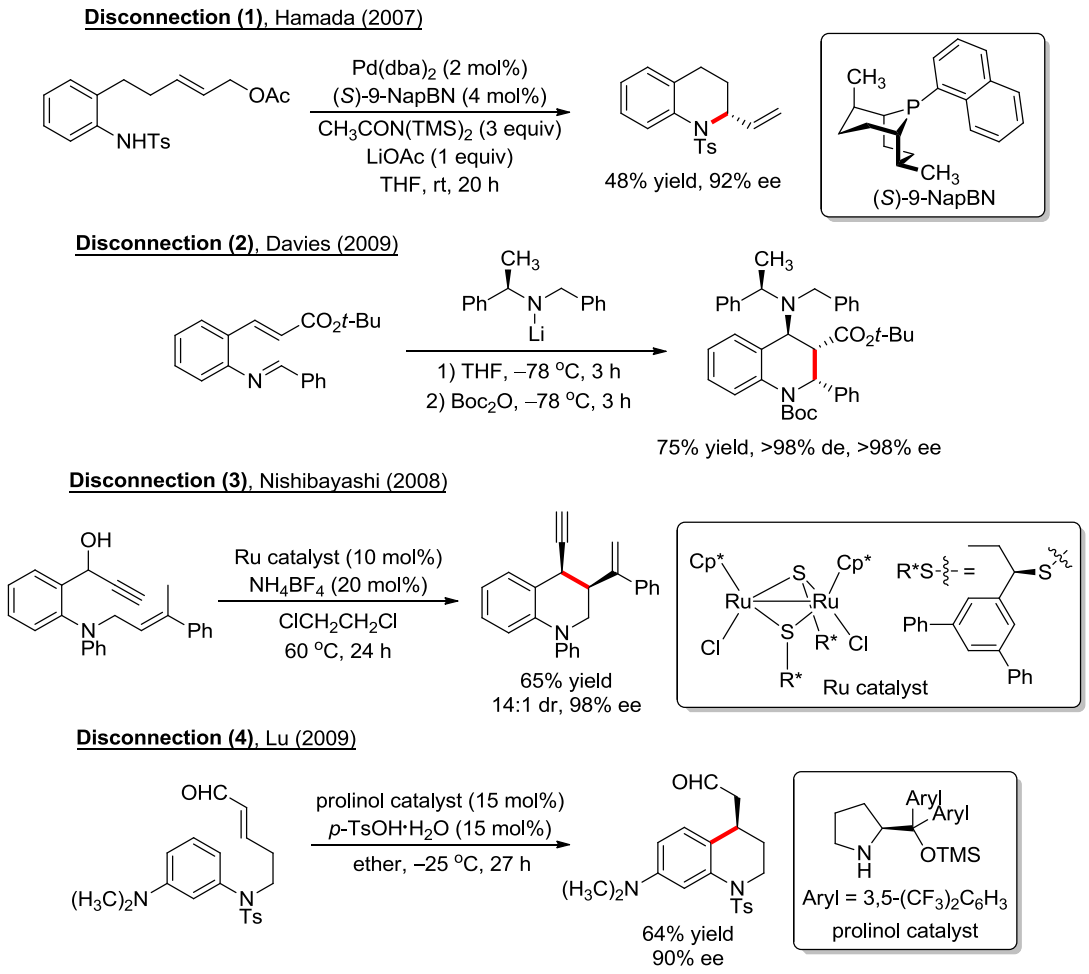


Figure 17. Different connectivity-based approaches to tetrahydroquinoline ring construction.

For disconnection (1), Hamada and coworkers reported an enantioselective amination of an allylic acetate catalyzed by $Pd(dba)_2$ in the presence of a chiral phosphabicyclononane ligand (Scheme 39).[89] The reaction is speculated to proceed through an intermediate chiral, π-allyl palladium complex. For disconnection (2), Davies and coworkers reported the addition of chiral lithium amides to α,β-unsaturated esters to furnish 2,3,4-functionalized tetrahydroquinoline derivatives.[90] The lithium amide initiates a tandem conjugate addition/cyclization reaction connecting C_2-C_3 bond with excellent diastereo- and enantioselectivity. For disconnection (3),

Nishibayashi and coworkers reported a ruthenium-catalyzed enantioselective synthesis of 3,4-functionalized tetrahydroquinolines with excellent enantioselectivity.[91] In this process a propargylic alcohol undergoes an intramolecular ene reaction with a pendant allyl amine under catalysis by a thiolate-bridged diruthenium complex. Finally, for disconnection (4), Lu and coworkers reported an enantioselective Friedel-Crafts alkylation using a prolinol silyl ether catalyst.[92]

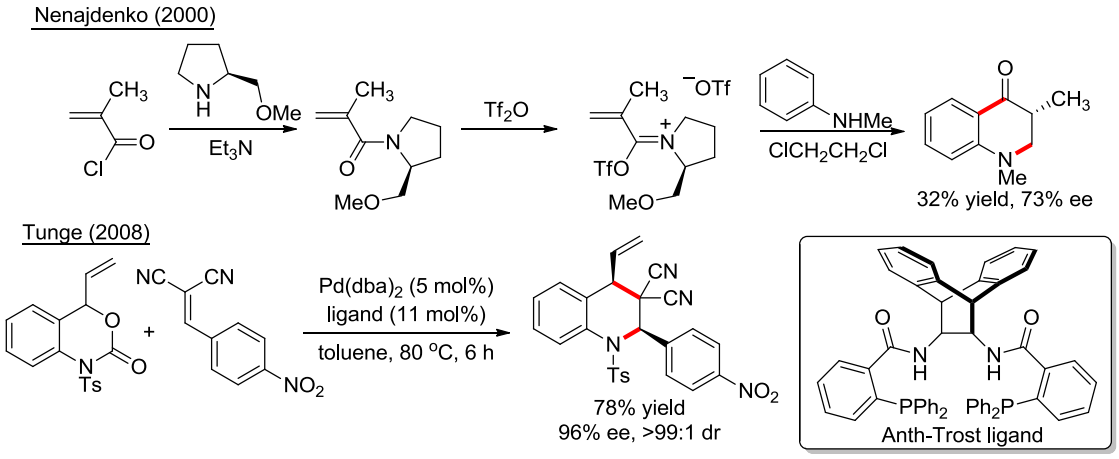
Scheme 39



Enantioselective, intermolecular tetrahydroquinoline syntheses involving multi-bond construction have also been developed (Scheme 40). Nenajdenko and coworkers reported synthesis of tetrahydroquinolines via a two-bond formation approach using a (*S*)-methoxymethyl

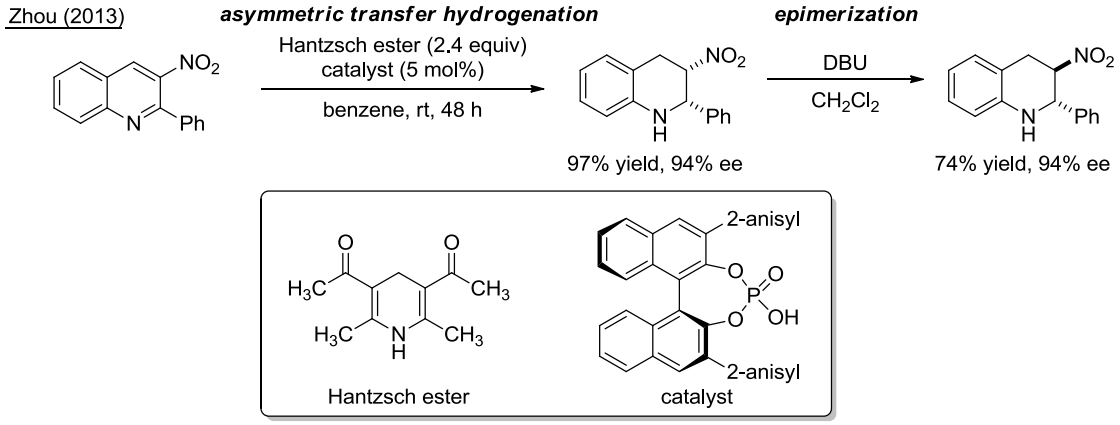
pyrrolidine chiral auxiliary.[93] Tunge and coworkers reported the Pd-catalyzed synthesis of tetrahydroquinoline from benzoxazinanones and benzylidene malononitriles in the presence of chiral bidentate phosphine ligands.[94]

Scheme 40



Unfortunately, application of these methods to the construction of enantioenriched *anti*-2,3-difunctionalized tetrahydroquinolines is not trival, with most existing methods requiring multiple steps. In 2013, Zhou and coworkers reported a two-step sequence of asymmetric transfer hydrogenation followed by epimerization to afford *anti*-2,3-difunctionalized tetrahydroquinoline with high enantioselectivity (Scheme 41).[95]

Scheme 41

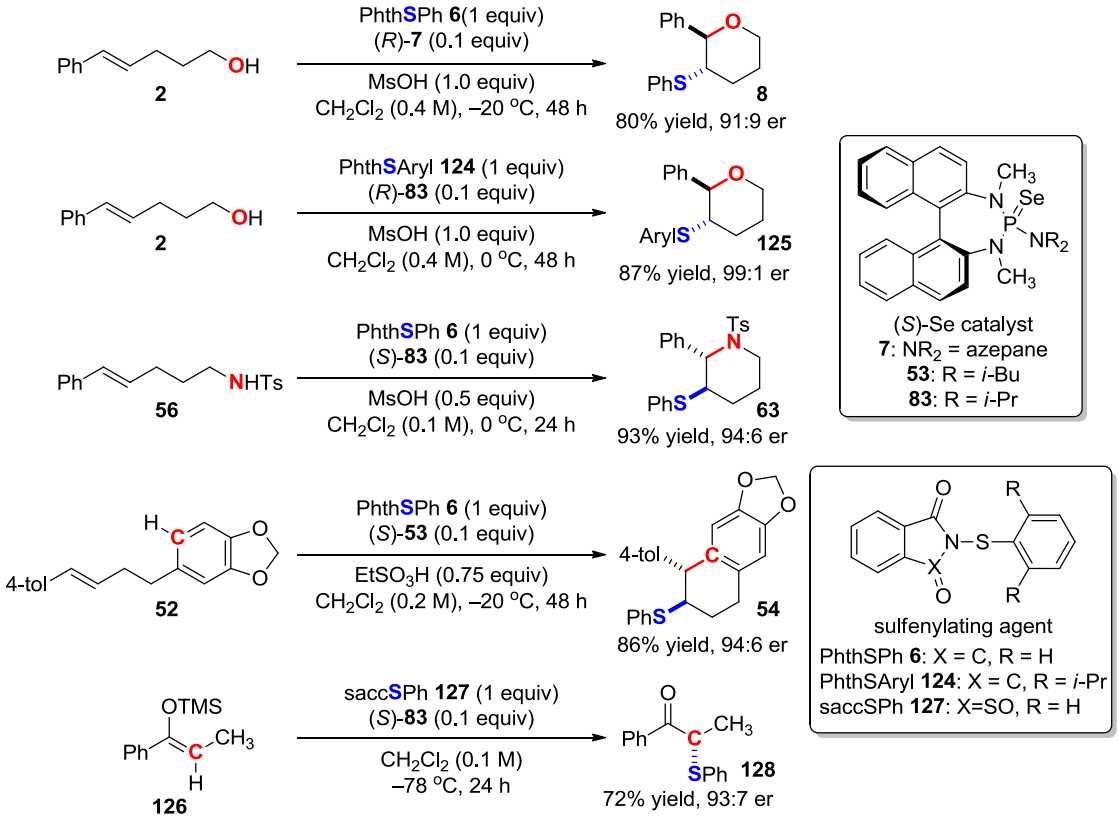


4.1.2 Sulfenofunctionalization Reactions

4.1.2.1 Enantioselective Sulfenofunctionalization

As mentioned earlier in Section 2.1.2, only two enantioselective sulfenofunctionalization reactions have been reported until recent development of Lewis base catalyzed variants (Schemes 13 and 14).[28,29] Foregoing studies from these laboratories have described catalytic, enantioselective sulfenofunctionalizations of isolated alkenes with oxygen-,[12,96] carbon-,[30,69] and nitrogen-based[13,96] nucleophiles (Scheme 42). These reactions employ chiral Lewis bases **7**, **53**, and **83** and proceed with high selectivities and to provide access to tetrahydropyrans, tetralins, and piperidines, respectively.

Scheme 42



Enantioselective α-sulfenylation of silyl enol ethers has also been developed using a saccharin-derived sulfenylating agent **126**[97] More recently, a sterically encumbered sulfenylating

agent (2,6-diisopropylphenyl)thiophthalimide (PhthSAryl, **124**) has been introduced to provide improved enantioselectivities for these sulfenylation reactions.[96] To recapitulate, in all of these reports on sulfenofunctionalization, selenophosphoramide catalysts showed superior selectivity on *trans*-disubstituted alkenes compared to *cis*-disubstituted or trisubstituted alkenes.

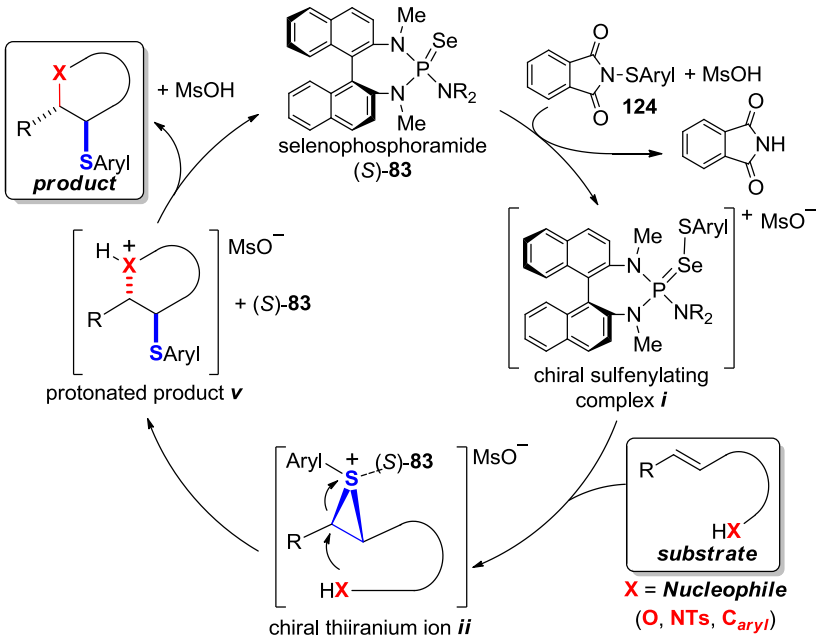


Figure 18. Catalytic cycle for enantioselective sulfenofunctionalization reaction.

4.1.2.2 Catalytic Cycle of Sulfenofunctionalization

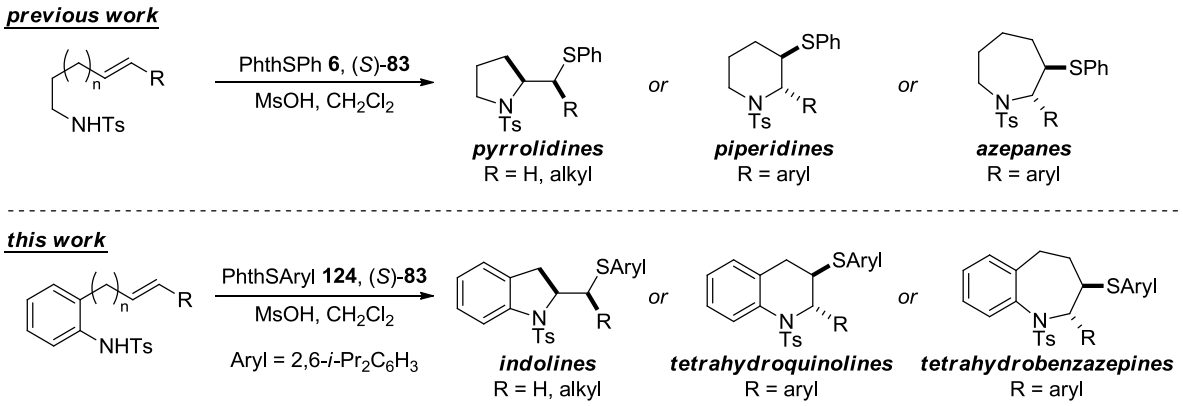
The mechanistic details of this process have been thoroughly investigated by kinetic, spectroscopic, crystallographic, and computational analysis.[69,96] The catalytic cycle begins with the protonation of the Lewis acid **124** by a Brønsted acid (MsOH) (Figure 18). This step is followed by transfer of the arylsulfenium group to the chiral Lewis base catalyst to form the catalytically active complex ***i***. This sulfenylated complex ***i*** is the resting state of the catalyst and has been characterized by NMR spectroscopy and X-ray crystallographic analysis.[96] The complex ***i*** then transfers the sulfenium ion to the carbon-carbon double bond to generate the enantioenriched thiiranium ion intermediate ***ii***. Lastly, capture of the thiiranium ion with a

tethered nucleophile forms the protonated species ***v*** with release of the catalyst; subsequent proton transfer affords the enantioenriched, sulfenofunctionalized product.

4.1.3 Project Design

Among the series of above mentioned sulfenofunctionalization reactions, the enantioselective sulfenoamination of alkenes have demonstrated the synthesis of *anti*-2,3-disubstituted *piperidines* and *azepanes* with high enantioselectivity (See Chapter 2 for more details, Scheme 43).[13] Therefore, it was logical that *anti*-2,3-disubstituted tetrahydroquinolines could be analogously accessed by substituting aniline nucleophiles in place of the established amines. Anilines are unique functional groups in both their steric and electronic properties when compared to the aliphatic amines. While the conformational restriction from the planar geometry of aniline influences the cyclization, variable substitution pattern allows evaluation of the electronic properties of the nucleophiles. Their utilization would expand the scope of the reaction for the construction of other chiral nitrogen-containing heterocycles as well, such as indolines and tetrahydrobenzazepines.

Scheme 43



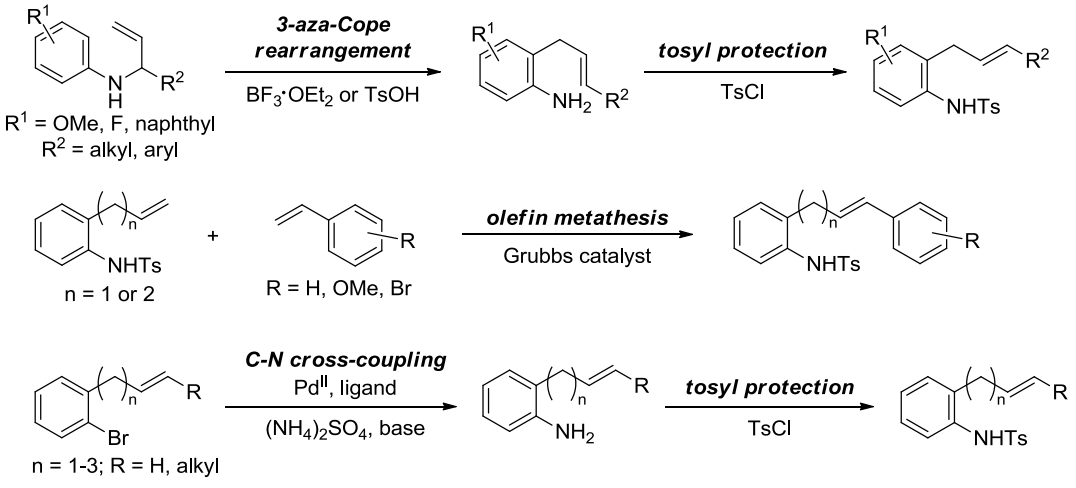
4.2 Results

Previously, the influence of the electronic and steric properties of the *alkenes* on the rate, site-selectivity, and enantioselectivity of the enantioselective sulfenoamination reaction were investigated.[13] The electron property of the amine was varied by installing different protecting groups on the amine. Also, the tether length between the alkene and amine was varied to examine the accessibility of medium-sized rings. In a similar manner, the following goals were set for this study to investigate the effect of: (1) the electronic properties of the aniline nucleophile, (2) the steric and electronic properties of the olefin, and (3) the tether length for the sulfenoamination reaction of olefins with anilines.

4.2.1 Substrate Preparation

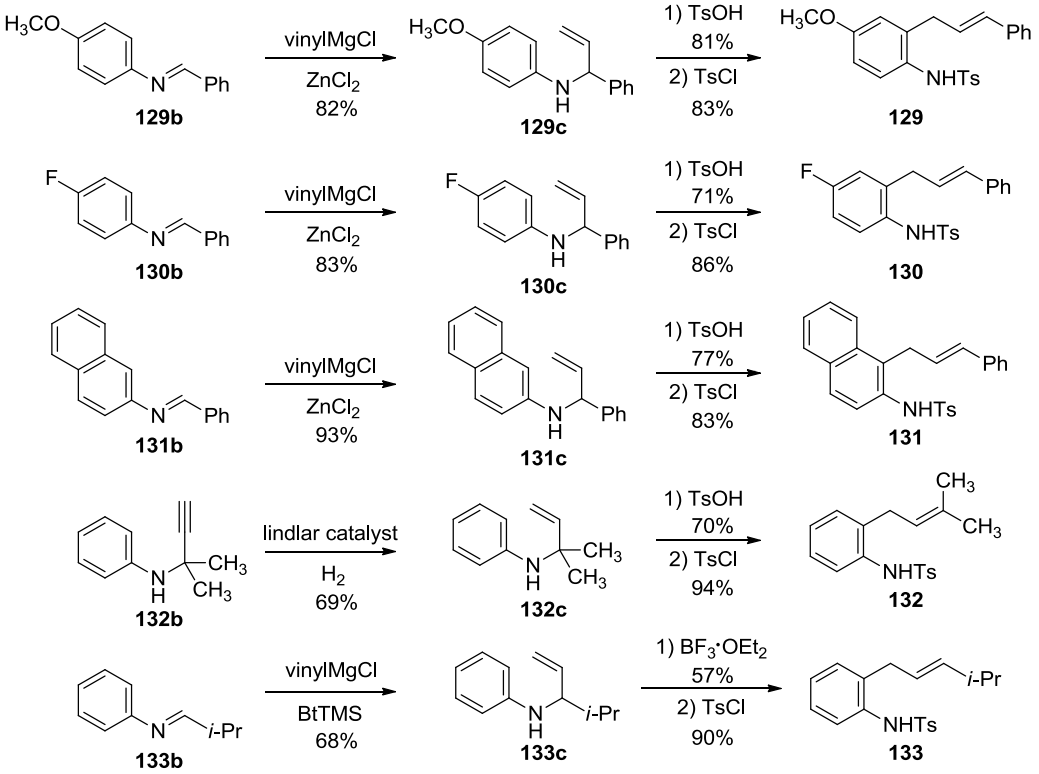
To evaluate all of these structural parameters required efficient access to range of aniline-containing substrates. These substrates were prepared by three main routes: (1) 3-aza-Cope rearrangement of *N*-allylic anilines, (2) metathesis of terminal olefins, and (3) Pd-catalyzed C-N coupling (Scheme 44).

Scheme 44



2-Cinnamylaniline substrates were synthesized via 3-aza-Cope rearrangement of α-substituted allylic anilines, which was especially attractive route due to its inherent high stereospecificity (Scheme 45).[98] Imines were prepared by condensation of the appropriate anilines and aldehydes, and subsequent addition of vinylmagnesium chloride in the presence of zinc chloride afforded α-substituted allylic anilines.[99] This 3-step sequence was very effective for synthesis of substrates **129**-**131**. However, a modified Grignard addition method,[100] developed by Katritzky, was required for the synthesis of substrate **133** due to the acidic α-proton on the imine.

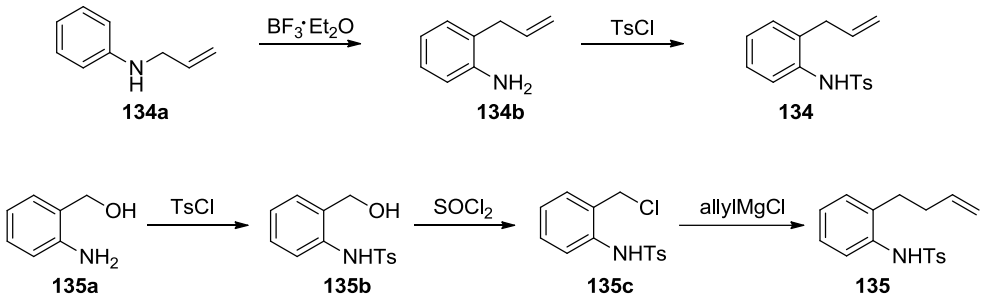
Scheme 45



N-Tosyl-2-allylaniline **134** and *N*-tosyl-2-homoallylaniline **135** was prepared following a reported procedure (Scheme 46).[101,102] *N*-Allylaniline was heated in the presence of boron trifluoride diethyl etherate to promote 3-aza-Cope rearrangement. Resulting 2-allylaniline was

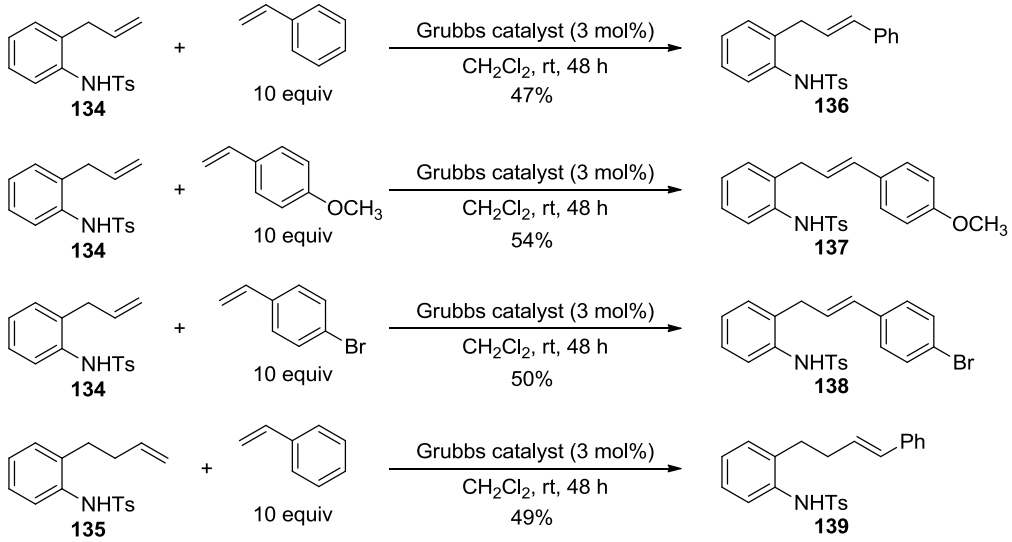
subsequently protected with a tosyl group to furnish *N*-tosyl-2-allylaniline **135**. *N*-Tosyl-2-homoallylaniline was synthesized from 2-aminobenzyl alcohol in a 3-step sequence. Tosyl protection of the aniline followed by chlorination furnished benzyl chloride. Addition of allyl Grignard reagent to the benzyl chloride afforded desired substrate **135**.

Scheme 46



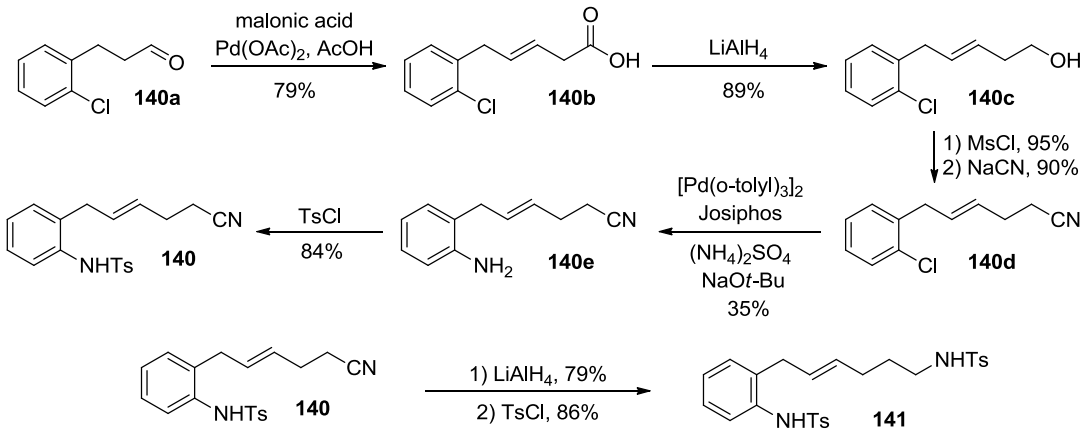
2-Cinnamylaniline derivatives with substituents on the styrene ring **136-139** were prepared by cross-metathesis of olefins with Grubbs catalyst (Scheme 47).[103] Grubbs 1st generation indenylidene catalyst showed strong cross-metathesis of 2-allylaniline **134** and 2-homoallylaniline **135** with various styrenes. While metathesis with styrenes afforded the *trans*-olefin exclusively, 1-pentene gave approximately a mixture of *trans*- and *cis*-disubstituted olefins.

Scheme 47



Olefin metathesis with linear aliphatic alkenes resulted in poor geometrical selectivity, forcing the development of a different route (Scheme 48). Knoevenagel-Doebner condensation of malonic acid to 2-chlorophenylpropanal **140a** cleanly afforded non-conjugated carboxylic acid **140b**.[104] Reduction of the acid to the alcohol **140c**, followed by mesylation and S_N2 displacement with cyanide furnished the nitrile intermediate **140d** for the aryl amination.[13] The resulting 2-aryl chloride **140d** was coupled with ammonium sulfate to form aniline **140e** via Pd-catalyzed C-N coupling method developed by Hartwig and co-workers.[105] Unfortunately, the desired product was generated in low yield with a significant amount of olefin-migrated side products. However, tosylation of the aniline afforded nitrile substrate **140**. Nitrile group was reduced with $LiAlH_4$ to the free amine,[13] and subsequential tosyl protection of the amine furnished bistosylamide **141**.

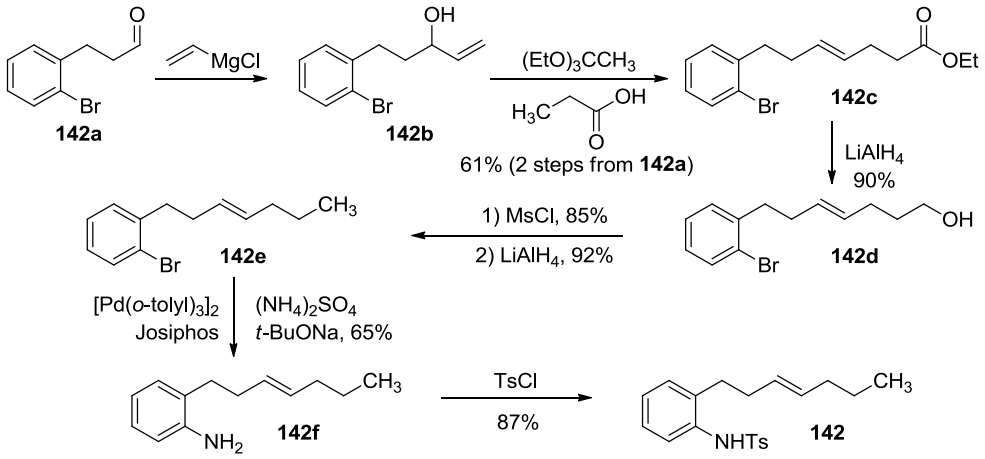
Scheme 48



As with single methylene tether substrate preparation, synthesis of the dialkyl olefin substrate was shown to be less *trans* selective via cross-metathesis. To achieve selective synthesis of the *trans* dialkyl substituted olefin, a Johnson-Claisen rearrangement was again employed as the key stereogenerating step for the construction of the main scaffold of **142** (Scheme 49). Addition of vinyl Grignard reagent to aldehyde **142a** afforded allylic alcohol **142b**,

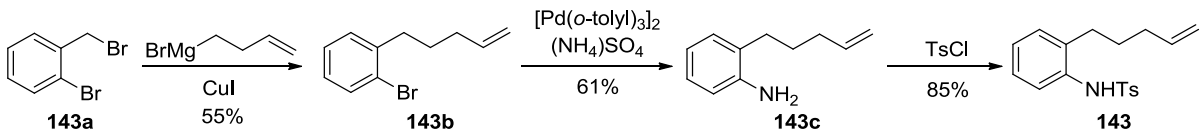
which was subsequently treated with triethylorthoacetate in the presence of catalytic acid and heat to promote [3,3] sigmatropic rearrangement.[106] Reduction of the resulting ester **142c** to alcohol **142d**,[106] followed by a two-step sequence of mesylation-hydride reduction afforded the aryl bromide **142e**.[107] The aryl bromide **142e** was then subjected to the Hartwig's C-N coupling method.[105] Gratifyingly, in contrast to the one methylene tethered system, no olefin migration was observed. Tosyl protection of the primary aniline furnished the target substrate **142**.

Scheme 49



2-Pentenylanilines were prepared from 2-bromobenzyl bromide, by addition of butenyl Grignard with catalytic assistance of copper (I) iodide to afford 2-pentenylaryl bromide (Scheme 50).[108] Hartwig's C-N coupling methodology was then employed to install the amine moiety,[105] and the resulting primary aniline was protected with a tosyl group to furnish the target olefin substrate **143**.

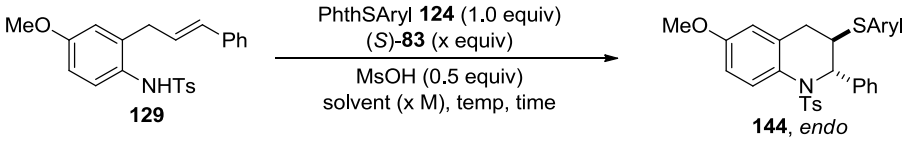
Scheme 50



4.2.2 Optimization of the Sulfenoamination Reaction

To investigate the properties of aniline substrates, reaction conditions were adapted from the previously reported enantioselective sulfenoamination reaction: PhthSAryl **124** was employed as the sulfenylating agent, MsOH as the Brønsted acid, and selenophosphoramide (*S*)-**83** as the Lewis base catalyst,[13] at room temperature at 0.1 M in substrate.[96]

Table 11. Optimization of the Sulfenoamination Reaction.



entry	catalyst loading (equiv)	solvent (concentration, M)	conditions temp (°C), time (h)	conversion/yield[b], %	er[c]
1	0.1	$CDCl_3$ (0.1)	20, 6	52/–	–
2	0.1	$CDCl_3$ (0.1)	20, 12	77/–	–
3	0.1	$CDCl_3$ (0.1)	20, 24	94/–	–
4	0.1	$CDCl_3$ (0.1)	20, 48	100/82	90:10
5	0	$CDCl_3$ (0.1)	20, 48	no conversion	–
6	0.1	CH_2Cl_2 (0.1)	0 °C, 48	80[a]/64	94:6
7	0.1	CH_2Cl_2 (0.4)	0 °C, 48	100[a]/80	93:7

[a] Conversion and constitutional selectivity determined by ^{1}H NMR spectroscopy of the crude mixture. [b] Yields of isolated purified compounds, low yields due to difficulty in separation from the residual starting materials in case of incomplete conversion. [c] The enantiomeric ratio of the major constitutional isomer was determined by CSP-HPLC analysis.

2-Cinnamyl-*N*-tosylanisidine (**129**) was selected as the test substrate for reaction optimization. Initially, the reaction was carried out in NMR tubes to monitor the rate profile at room temperature over 2 days (Table 11, entries 1, 2, 3, and 4). The reaction reached full conversion after 48 hours under the above conditions to afford tetrahydroquinoline **144**, favoring 6-*endo* cyclization exclusively. However, the enantiomeric composition of the product was much lower than expected, 90:10 er. To ensure that no competing racemic pathway was operative, the reaction was carried out in absence of the selenophosphoramide catalyst (entry 5). No product

was formed suggesting that the attenuated selectivity arose from other factors. Therefore, the reaction was performed at a lower temperature (0 ^{o}C) to enhance the configurational stability of the thiiranium ion intermediate, which resulted in an improved enantiomeric ratio of 94:6 er (entry 6). However, the conversion over the monitored time dropped to 80%, comparable to the 12 h time point at room temperature reaction. To improve the conversion, the overall concentration was increased to 0.4 M (entry 7). Gratifyingly, the reaction showed full conversion to tetrahydroquinoline **144** with excellent *endo* selectivity and negligible enantiomeric erosion.

4.2.3 Survey of Substrate Scope

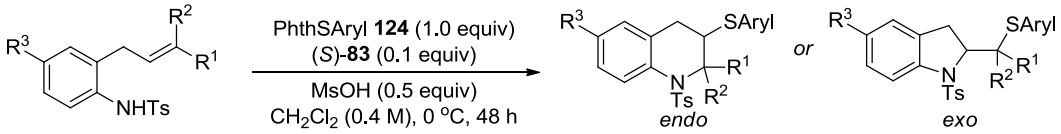
4.2.3.1 Sulfenoamination of Olefins with One-Methylene Tether

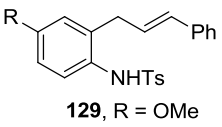
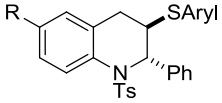
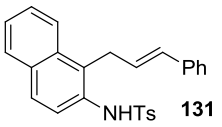
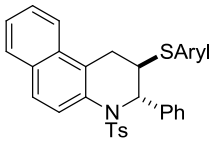
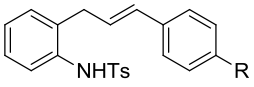
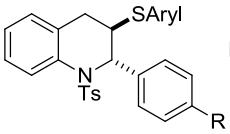
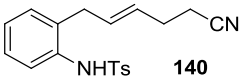
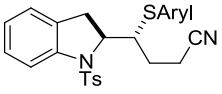
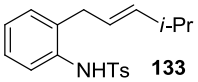
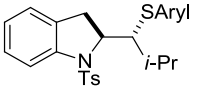
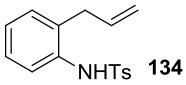
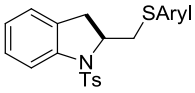
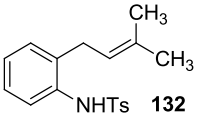
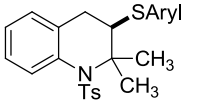
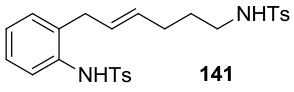
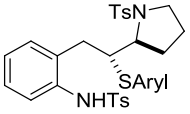
Both indoline and tetrahydroquinoline scaffolds were accessible with single-methylene tethered substrates, depending on the mode of cyclization (5-*exo* vs 6-*endo*). To evaluate the influence of electronic properties of the aniline nucleophile on reaction outcome, a series of substrates with varying substitutions on the nucleophile was prepared. The model substrate, electron-rich anisidine **129** afforded 2,3-difunctionalized tetrahydroquinoline **144** with high site- and enantioselectivity (Table 12, entry 1). Electron-neutral anilines **136** and **130** both cyclized into tetrahydroquinolines **145** and **146** with comparable enantioselectivity to **144** (entries 2, 3). However, the cyclization of *para*-fluoro aniline **130** was much slower in contrast to anilines **129** and **136**, requiring 6 days to reach full conversion (compared to 2 days). Cyclization of naphthyl substrate **131** cleanly furnished tetrahydrobenzo[*f*]quinoline **131** with high enantioenrichment (entry 4). In all single-methylene tethered styrenyl cases, excellent site-selectivity was observed for 6-*endo* cyclization.

The influences of the electronic properties of the olefin were also investigated. Styrenes with electron-donating substituents **137** and **138** afforded tetrahydroquinolines via *endo*

cyclization with high yields and enantioselectivities (entries 5, 6). The reaction times required for full conversion were comparable to the model substrate **129**. Electron-deficient styrenes are known to exhibit poor reactivity and therefore not examined.[12,13,30]

Table 12. Scope of the Sulfenoamination of Substrates with One-Methylene Tether.



entry	substrate	major product	yield, %[a]	*endo* : *exo*[b]	er[c]
1	 **129**, R = OMe **136**, R = H **130**, R = F	 **144** R = OMe	87	>20 : 1	94 : 6
2		**145** R = H	92	>20 : 1	95 : 5
3		**146** R = F	86[d]	>20 : 1	96 : 4
4	 **131**	 **147**	93	>20 : 1	98 : 2
5	 **137**, R = OMe **138**, R = Br	 **148** R = OMe	93	>20 : 1	96 : 4
6		**149** R = Br	88	>20 : 1	97 : 3
7	 **140**	 **150**	86	1 : 4	86 : 14
8	 **133**	 **151**	85	1 : 12	98 : 2
9	 **134**	 **152**	90	>20 : 1	98 : 2
10	 **132**	 **153**	89	>20 : 1	88 : 12
11	 **141**	 **154**	70	1 : 4	95 : 5

[a] Isolated yields of analytically pure material. [b] Constitutional selectivity determined by ^{1}H NMR spectroscopy of the crude mixture. [c] The enantiomeric ratio of the major constitutional isomer was determined by CSP-HPLC analysis, and the absolute configurations of the products were assigned by comparison of their CD spectra with **144**. [d] Reaction time of 6 d.

Next, dialkyl-substituted olefins were tested to explore the steric influences of the olefin on the reaction outcome. Cyclization of the nitrile-appended aliphatic olefin **140** afforded a 4:1 mixture of *exo* and *endo* cyclized products, with diminished enantiomeric ratio of 86:14 (entry 7). However, olefin **133**, having a sterically demanding isopropyl group, cyclized with improved constitutional selectivity favoring 5-*exo* cyclization (*exo*:*endo* = 12:1) and excellent enantioselectivity (98:2 er) (entry 8).

Olefins with different numbers of substitutions were also examined. In the previous sulfenofunctionalization studies, cyclizations of terminal olefins resulted in high enantioselectivities whereas cyclizations of trisubstituted olefins did not.[12,13,30] Terminal olefin containing substrate **134** transformed cleanly into 2-substituted indoline **152** via 5-*exo* cyclization with excellent enantioselectivity (entry 9). In contrast, trisubstituted olefin substrate **132** afforded 2,2-dimethyl substituted tetrahydroquinoline **153** via 6-*endo* cyclization with a reduced enantiomeric ratio (88:12 er) (entry 10).

Lastly, a substrate was devised to compare the relative reactivity of the two different types of nucleophiles, amines and anilines, toward the capture of the thiiranium ion. Substrate **141**, containing competing aniline and amine nucleophiles afforded pyrrolidine **154** as the major product (entry 11). This result clearly shows the superior thiiranium ion capturing ability of the aliphatic amines.

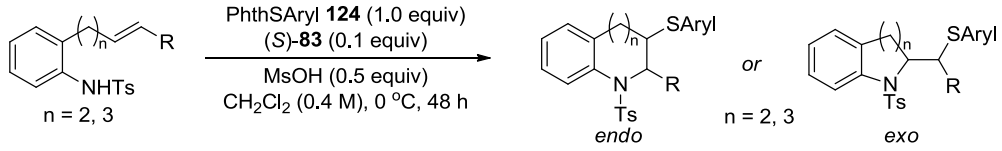
4.2.3.2 Sulfenoamination of Olefins with Longer Tethers

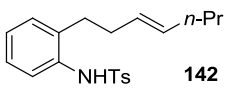
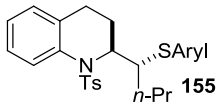
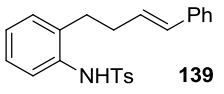
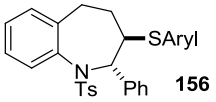
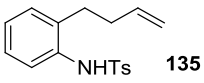
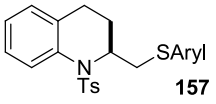
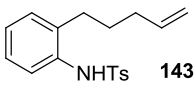
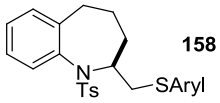
Substrates with longer tethers were explored to gauge the potential to access larger *N*-containing heterocycles such as tetrahydrobenzazepines. In Table 12, tetrahydroquinolines with 2-aryl substituents were accessible from 2-cinnamyl anilines with excellent site-selectivity, while those with aliphatic substituents at the 2-position were generated with reduced site-selectivity.

To address this problem, substrates bearing longer tethers were examined. Specifically, dialkyl substituted olefin **142** cleanly afforded 2-alkyltetrahydroquinoline **155** by 6-*exo* cyclization with excellent enantioselectivity (98:2 er) (Table 13, entry 1). On the other hand, electronically biased styrenyl olefin substrate **139** furnished 2-phenyltetrahydrobenzazepine **156** via 7-*endo* cyclization with high site- and enantioselectivity (entry 2).

Terminal olefins with longer tethers were also examined. Cyclization of 2-homoallyl aniline **135** furnished 2-alkyltetrahydroquinoline **157** also via 6-*exo* closure with excellent constitutional and enantioselectivity (entry 3). Lastly, aniline **143** bearing an *ortho*-4-pentenyl chain cyclized to form 2-alkyltetrahydrobenzazepine **158** via the 7-*exo* mode with high enantioselectivity (entry 4).

Table 13. Scope of the Sulfenoamination of Substrates with Longer Tethers.



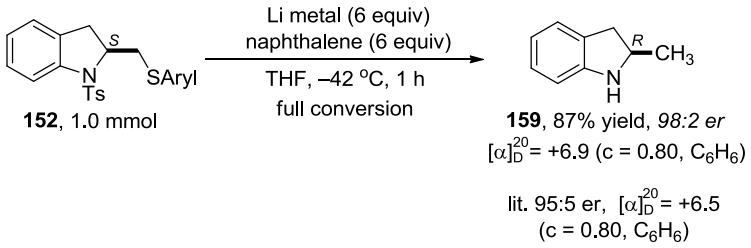
entry	substrate	product	yield, %[a]	*endo* : *exo*[b]	er[c]
1			93	1 : >20	98 : 2
2			91	>20 : 1	95 : 5
3			93	1 : >20	98 : 2
4			89	1 : >20	93 : 7

[a] Isolated yields of analytically pure material. [b] Constitutional selectivity determined by ^{1}H NMR spectroscopy of the crude mixture. [c] The enantiomeric ratio of the major constitutional isomer was determined by CSP-HPLC analysis, and the absolute configurations of the products were assigned by comparison of their CD spectra with **144**.

4.2.4 Desulfurization of the Sulfenoamination Products

In contrast to phenyl sulfides, which are easily cleaved with nickel boride under mild conditions,[109] 2,6-diisopropylphenyl sulfides required more forcing desulfurization conditions. The 2,6-diisopropyl sulfide moiety was cleanly reduced by lithium naphthalenide, along with the concomitant reductive cleavage of the tosyl protecting group (Scheme 51).[110] The absolute configuration of the reduced product, 2-methylindoline (**159**), was compared to literature values and assigned the (*R*)-configuration.[111]

Scheme 51



4.3 Discussion

The primary objective for this project was to expand the scope of the enantioselective, catalytic sulfenoamination of olefins to tethered aniline nucleophiles to synthesize enantioenriched benzannulated nitrogen-containing heterocycles, *e.g.* indolines, tetrahydroquinolines, and tetrahydrobenzazepines. The influence of nucleophile, alkene environment, and tether length on the rate, enantioselectivity and site-selectivity are discussed.

4.3.1 Optimization of the Sulfenoamination Reaction

4.3.1.1 Overall Concentration

During the optimization surveys, the overall concentration was the only factor altered from the typical reaction condition, which was increased four-fold to 0.4 M from 0.1 M. The main concern with this alteration was that higher concentration could result in racemization via

"olefin-to-olefin" transfer of the sulfenium group.[33] However, in contrast to the effects of elevated temperature, increased concentration showed enhanced conversion with no significant enantiomeric erosion, indicating that olefin-to-olefin transfer is disfavored at 0 ^{o}C.

4.3.1.2 Catalyst and Brønsted Acid

An extensive catalyst survey was unnecessary, having been performed in the preceding studies. The third generation, diisopropylamine substituted selenophosphoramide catalyst (*S*)-**83** provided the best selectivity for all O-,[112] N-,[13] and C-nucleophile[97] sulfenofunctionalization reactions. The improved performance of the PhthSAryl **124** relative to other sulfenylating agents (*e.g.* PhthSPh **6**) attributed to its enhanced steric environment that leads to the distortion of the catalyst for better differentiation of the two enantiotopic faces of the olefin, ultimately resulting in excellent enantioselectivies.[96]

The Brønsted acid loading was adopted unchanged from the previous sulfenoamination reaction conditions. According to the titration studies, the catalytically active species ***i*** reached saturation above 4.0 equivs of Brønsted acid with respect to the catalyst (Figure 18).[69] In this sulfenoamination study, 0.5 equivs of MsOH were sufficient for full activation of the catalytically active species ***i*** (^{31}P NMR at 60 ppm), and showed anticipated reactivity for the cyclization. Therefore, the acid loading required no further optimization.

4.3.2 Structural Effects on Rate and Selectivity

4.3.2.1 Influence of the Nucleophile

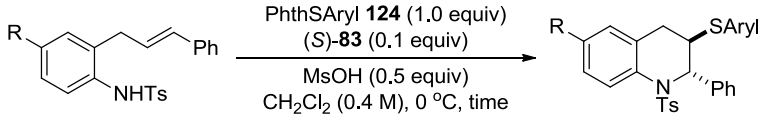
Many factors can influence the rate, enantioselectivity, and site-selectivity of the sulfenoamination reaction, such as electronic and steric properties of the olefin and the nucleophile, or the length of the tether connecting them. Because these factors were also

explored in the preceding cyclization studies with aliphatic tosylamides, the results from this work will be compared to those previous results.

4.3.2.1.1 Reaction Rate

Anilines with electron donating (**129**) and withdrawing (**130**) substituents on the *para*-position were both examined (Scheme 52). Whereas no noticeable enhancement on rate was observed with more electron rich nucleophile relative to the electron neutral substrate **136**, the reaction slowed significantly with electron poor nucleophile **130** which required 6 days to reach full completion.

Scheme 52



R	time (d)	yield (%)	er
OMe (**129**)	2	93	94:6
H (**136**)	2	92	95:5
F (**130**)	6	88	96:4

This observation may be explained by a change in the turnover limiting step (TOLS) (Figure 19).

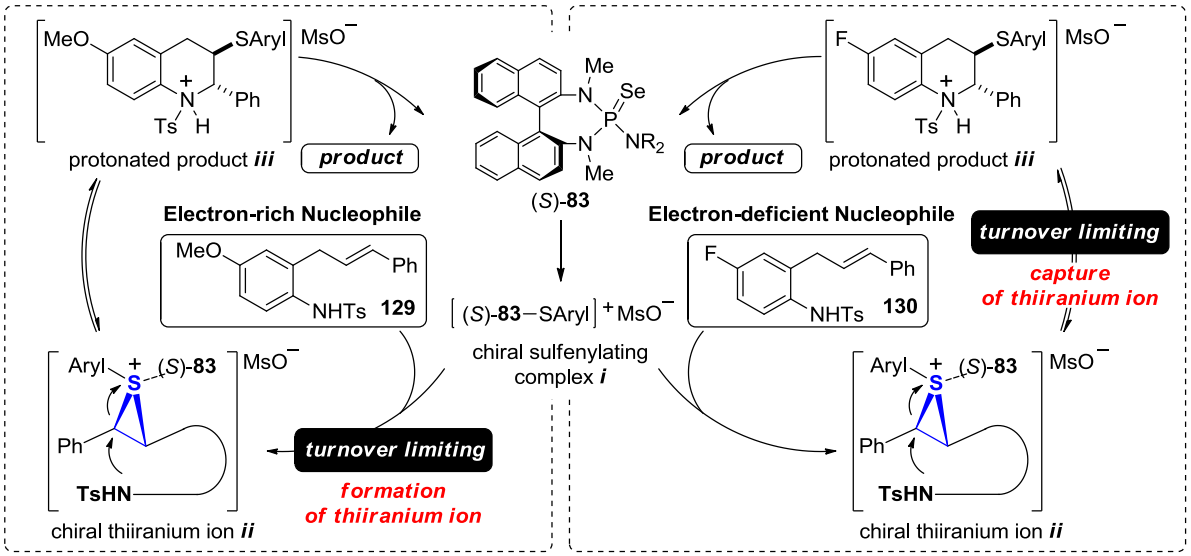


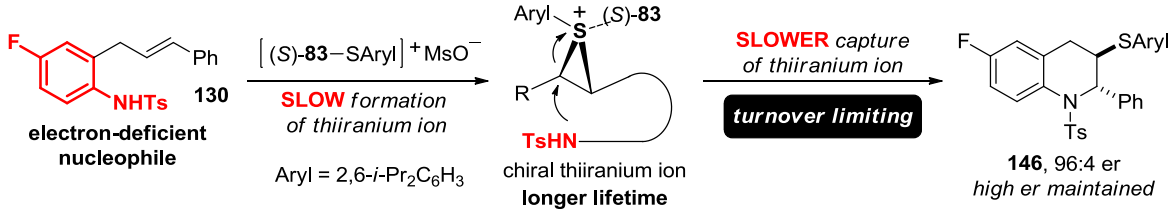
Figure 19. Unified mechanistic scheme for different TOLS.

For sulfenofunctionalization reactions involving thiiranium ion intermediates, the formation of the thiiranium ion is typically considered to be turnover limiting.[96] Therefore, electron-rich anilines do not enhance the reaction rate, because the formation of the thiiranium ion is not affected by the electronic character of the aniline ring. However, with a 4-fluoro substituent, which is π-donating but σ-withdrawing,[113] the rate was substantially retarded. This outcome can be interpreted as an inductive effect of the 4-fluoro group, resulting in decreased nucleophilicity of the nitrogen atom and thus disfavored capture of the thiiranium ion. Since the thiiranium ion formation should not be affected by the electron withdrawing character of the aniline ring, the observed rate deceleration can be interpreted as a change of TOLS for **130**, from thiiranium formation to nucleophilic capture.

4.3.2.1.2 Enantioselectivity

The enantiomeric compositions of the sulfenoamination products were consistently high and exhibited the same absolute configuration across a range of nucleophiles possessing varying electronic properties. This behavior is consistent with the formation of the thiiranium ion being the enantiodetermining step. However, the shift in the turnover limiting step implies an extended lifespan of the thiiranium ion species. As stated earlier in Section 2.1.3, *S*-phenyl thiiranium ions are known to be configurationally unstable at 0 °C toward "olefin-to-olefin" sulfenium group transfer.[33] Therefore, decreased enantioselectivity would be expected for slow cyclizations implying a slow capture of the thiiranium ion.

Scheme 53



However, for the cyclization of 4-fluoro aniline substrate **130**, high enantioselectivity was observed despite the slow capture of the thiiranium ion (Scheme 53). This result implied that the *S*-2,6-diisopropylphenyl thiiranium ion preserved its enantioenrichment at 0 ^{o}C. Therefore, it may be safely argued that the configurational stability of the *S*-2,6-diisopropylphenyl thiiranium ion is much greater than that of *S*-phenyl thiiranium ion at 0 ^{o}C.

4.3.2.1.3 Site-Selectivity

The site-selectivity of the cyclization reaction is heavily dominated by the electronic properties of the alkenes. (*E*)-2-Cinnamylaniline derivatives **129**, **136**, **130**, and **131** afforded 6-*endo* cyclized products exclusively, regardless of the electronic properties of the nucleophile. Therefore, the variation on electron density of the nucleophile had no observable influence on the site-selectivity of sulfenoamination reaction.

4.3.2.2 Influence of Alkene Substitution

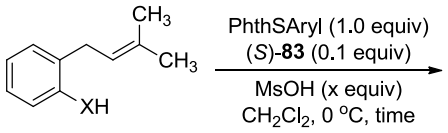
In the previous sulfenofunctionalization studies, the alkene environment had a profound influence on both rate and selectivity.[12,13,30] The reaction rate is heavily dependent on the electron density of the olefin because the formation of the thiiranium ion is generally the TOLS, while the enantioselectivity is mainly governed by the geometrical and steric environment of the olefin. These properties dictate the affinity of the olefin for the catalytically active species ***i***. On the basis of the assumption that the formation of the thiiranium ions is typically the TOLS, the overarching reactivity trend on the alkene for the sulfenofunctionalizations was established. Therefore, it seemed unnecessary to explore the individual rate of the each reaction; the reactions were set up for 48 h to reach completion by default based on the results from the initial reactivity optimization.

4.3.2.2.1 Enantioselectivity

During the examination of substrate scope, the enantiomeric ratios of the cyclized products were mostly unaffected by the alkene environment, with the exception of nitrile substrates **140**[114]and trisubstituted olefin **132**. Various aryl- and alkyl-substituted *trans*-alkenes were sulfenoaminated with high (95:5 er) to excellent (98:2 er) enantioselectivities. The consistency of enantiomeric composition observed for the cyclized products implies that the sulfenoamination proceeds through a common, enantioenriched thiiranium ion intermediate. This is strong evidence for the current understanding of the thiiranium ion formation being the enantiodetermining step.

In the case of the trisubstituted olefin **132**, several hypotheses may account for the diminished enantioselectivity. The first possibility is the lower inherent facial-selectivity of the catalyst toward this class of olefin, and the second is the existence of a competitive racemic pathway. However, in contrast to the case of **132**, high enantioselectivity has recently been obtained for oxysulfenylation of 2-prenylphenol employing (*S*)-**83**, PhthSAryl **124** and 0.25 equivs of MsOH (Scheme 54),[112] which strongly suggests that the first possibility is not likely.

Scheme 54



X	MsOH (equiv)	time (h)	yield (%)	er
O	0.25	24	93	95:5
NTs (**132**)	0.5	48	92	88:12

The disparity between these two similar trisubstituted substrates may be explained by pH-dependent reactivity differences. During the optimization of oxysulfenylation reaction, comparable rates and enantioselectivities were observed employing 0.25, 0.50, and 0.75 equivs of MsOH, hence 0.25 equivs of MsOH was chosen as the optimal condition.[112] However, the

optimization process of the sulfenoamination reaction with anisidine **124** showed that 0.5 equivs of MsOH was adequate without observing a background reaction.

From a titration study, as mentioned earlier, it was found that 4.0 equivs of Brønsted acid with respect to the catalyst was required to fully generate the catalytically active species ***i***.[69] This implies that employing 5.0 equivs of Brønsted acid with respect to the catalyst (the amount of acid loading found to be operative from optimizations) leaves an extra 1.0 equiv of the acid as a free state. This excess free acid can increase the population of protonated, achiral sulfenylating species **124**·H^+.

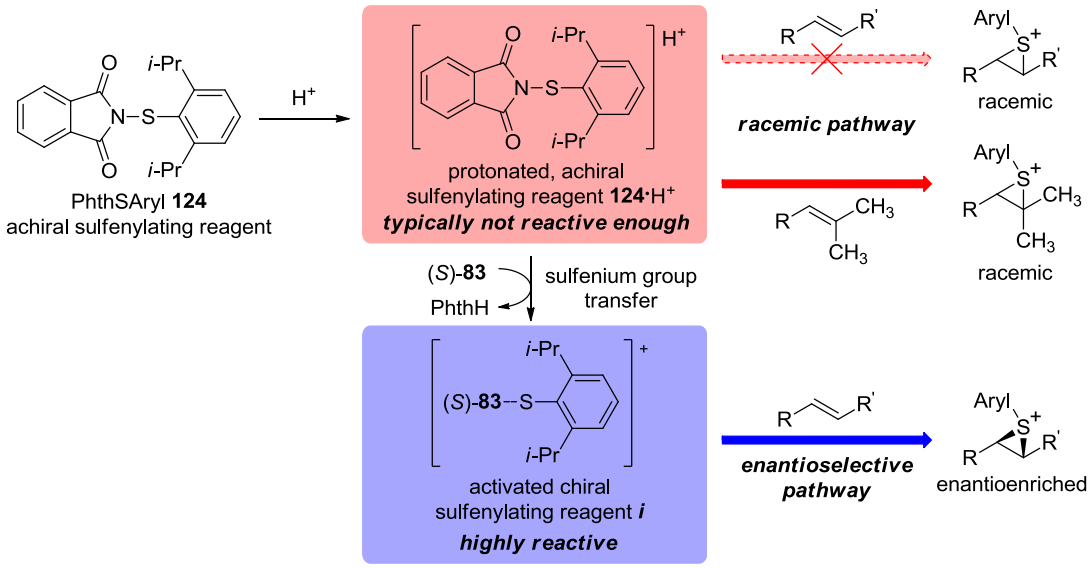


Figure 20. Two pathways for generation of the thiiranium ion intermediates.

In the initial step of the catalytic cycle, PhthSAryl **124** is protonated under the acidic conditions (Figure 20). Typically these protonated sulfenylating species are not reactive enough to effect direct thiiranium ion formation with unactivated disubstituted olefins, evidenced by no conversion in absence of the Lewis base catalyst (Table 11, entry 5). However, trisubstituted alkenes are more electron-rich than disubstituted alkenes, and the subsequent transfer of the sulfenium group to the alkene could generate a racemic thiiranium ion intermediate. Therefore,

under stronger acidic conditions, a small quantity of racemic thiiranium ion may be generated from trisubstituted alkenes that may attenuate the observed enantioselectivity.

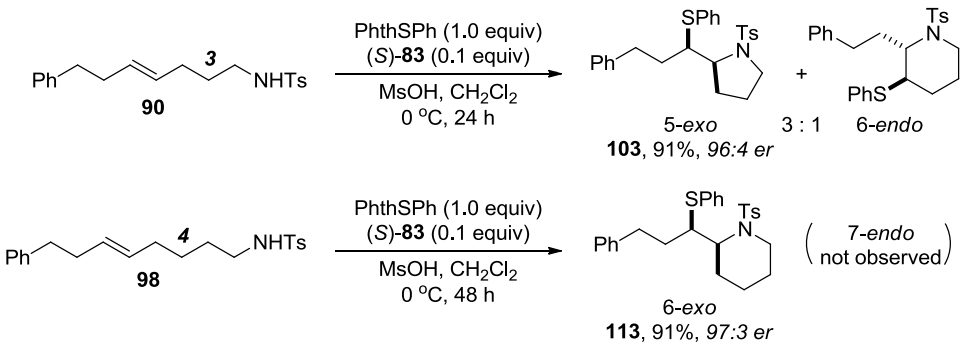
4.3.2.2.2 Site-Selectivity

Among the factors governing the site-selectivity of the nucleophilic attack, the electron density distribution in the alkene appears to be the most important. For example, styrenyl substrates **136** and **139** cyclized into tetrahydroquinoline **145** and tetrahydrobenzazepine **156**, respectively, with complete *endo* selectivity. In contrast, aliphatic alkenes cyclized with *exo* selectivity. Steric factors seem to be less important than electronic factors, yet the influence of the olefin steric environment on site-selectivity is evident in highly-hindered substrates. Isopropyl substituted olefin **133** afforded an enhanced *exo*/*endo* ratio compared to other alkyl-substituted olefins, possibly due to the increased steric repulsion between the olefin substituent and the incoming nucleophile. 2-Prenylaniline **132** cyclized to 2,2-dimethyltetrahydroquinoline **153** via a 6-*endo* pathway demonstrating that the site-selectivity is governed by the electronic, not steric factors (Markovnikov rule).

4.3.2.3 Influence of the Tether Length

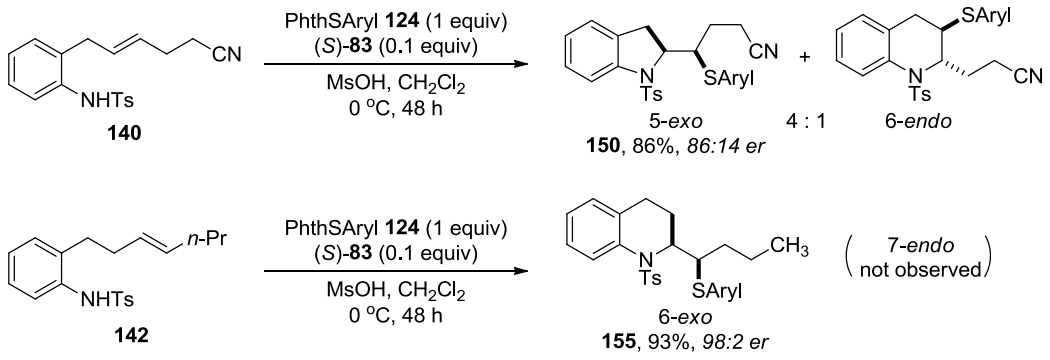
From previous studies on sulfenoamination reactions, influence of the tether length was found to be an important factor in controlling the site-selectivity (See Chapter 2 for details, Scheme 55).[13] As is now commonly observed, the enantioselectivities are not affected by the tether length if the alkene substitution pattern is the same.

Scheme 55



These trends were also observed in the sulfenoamination with aniline substrates. In the case of electronically and sterically unbiased, aliphatic olefins **140** and **142**, indoline **150** (5-*exo* vs 6-*endo*) and tetrahydroquinoline **155** (6-*exo* vs 7-*endo*) are generated, respectively (Scheme 56). Whereas **150** was generated in a 4:1 mixture of constitutional isomers favoring the *exo* approach, **155** was formed with exclusive *exo* selectivity. However, in terms of enantioselectivity comparison, substrate **140** was unfortunate choice of selection. Enantioselectivity for cyclization of **140** was much lower, presumably due to the interference of the nitrile moiety.[115]

Scheme 56

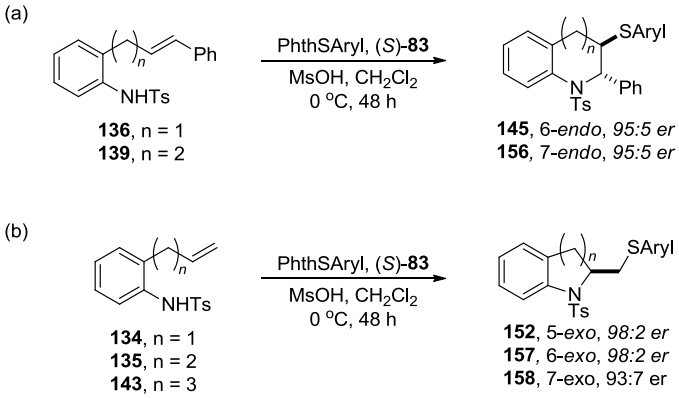


This difference in site-selectivity is likely attributed to higher activation entropy required for the formation of larger size rings. The site-selectivity for a cyclization of an electronically

non-biased alkene should be dependent on the size of the rings that are formed. The rates for the cyclization of *N*-tosylazacycloalkanes are known in the order of 5 > 6 > 7-membered rings.[116] Therefore, the cyclization of **140** should favor the formation of an indoline over a tetrahydroquinoline via 5-*exo* closure. The cyclization of substrate **142** also shows good agreement with the reported rate (6-membered ring formation is 200 fold faster than 7-membered ring formation) affording only tetrahydroquinoline **155** via 6-*exo* closure.

Electronically biased alkene substrates with different tethers were also investigated. Both cinnamyl substrates **136** and **139** afforded tetrahydroquinoline **145** and tetrahydrobenzazepine **156** respectively, with a kinetic preference of *endo* cyclization (Scheme 57a). Similar to the trend observed in the previous studies, the enantioselectivities were comparable for both heterocyclic products. The alkenes in substrates **134**, **135**, and **143** bearing different length tethers are electronically biased in the opposite direction (Scheme 57b). All three terminal olefins cyclized via *exo* closure into indolines, tetrahydroquinolines, and tetrahydrobenzazepines with excellent site-selectivity. Both of the cinnamyl and terminal alkene substrates demonstrated that the site-selectivity is governed by the Markovnikov rule.

Scheme 57



4.4 Conclusion

In conclusion, the catalytic, enantioselective sulfenoamination of olefins with aniline nucleophiles has been developed, using a chiral selenophosphoramide Lewis base catalyst. This method allows rapid access to highly enantioenriched *N*-heterocycles, including biologically-relevant indolines, tetrahydroquinolines, and tetrahydrobenzazepines with excellent site-selectivity. Systematic investigation of the nucleophile component and tether enabled to identify their influence on rate, enantioselectivity, and site-selectivity. Whereas rates on cyclizations of electron-neutral and -rich anilines were comparable, those of electron-deficient anilines were greatly decelerated, suggesting a change in the TOLS. Enantioselectivity was unaffected with modifications in nucleophile component or tether length. Excellent site-selectivity for styrenyl alkenes were observed, favoring nucleophilic capture at the benzylic carbon. Site-selectivity for cyclization of electronically non-biased alkenes was low for one-methylene tethers but high for longer tethers. The configurational stability of the thiiranium ions was increased by employing (2,6-diisopropylphenyl)thiophthalimide, leading to enhanced enantioselectivities. Utilization of the arylsulfenyl moiety of the product is currently under investigation. Also development of new catalyst designs suitable for the enantioselective sulfenofunctionalization of *cis*- and higher-order substituted alkenes are underway.

CHAPTER 5: Experimental Procedures

5.1 General Experimental

All reactions were performed in oven dried (140 ℃) and/or flame dried glassware under an atmosphere of dry argon, unless noted. Internal temperatures of low temperature reactions were measured using Teflon coated thermocouples unless otherwise noted. A ThermoNesLab CC-100 or a ThermoNesLab IBC-4A cryocool with an attached cryotrol was used for reactions at subambient temperatures.

Boiling points for Kugelrohr distillations correspond to corrected air bath temperatures (ABT). Melting points (mp) were determined on a Thomas-Hoover capillary melting point apparatus in sealed tubes under vacuum and are corrected. Analytical thin-layer chromatography was performed on Merck silica gel plates with QF-254 indicator. R_f values reported were measured using a 10 × 2 cm TLC plate in a developing chamber containing the solvent system described. Visualization was accomplished with UV (254 nm), and/or potassium permanganate ($KMnO_4$), or ceric ammonium molybdate (CAM). Column chromatography was performed using Merck silica 60 (40-63 μm particle size) gel purchased from Aldrich.

Analytical chiral stationary phase supercritical fluid chromatography (CSP-SFC) was performed on an Agilent 1100 HPLC equipped with an Aurora Systems A-5 supercritical CO2 adapter for supercritical fluid chromatography and a UV detector (220 nm or 254 nm) using Daicel Chiralcel OD, OJ, OB or Chiralpak AD, and AS columns as well as a Regis Whelk-O1 column. Normal Phase HPLC was performed on an Agilent 1100 HPLC equipped with AD-H, OJ-H, IB-3, Naphtholeucine and *R*,*R*-Beta-Gem columns. Reverse-Phase HPLC was performed on an Agilent 1100 HPLC using a Chiralpak AD-RH or Chiralcel OJ-RH column. Optical rotations were measured using a Jasco DIP-360 digital polarimeter in Fischer spectranalyzed

grade $CHCl_3$ containing approximately 0.75% EtOH as a preservative and are reported as follows: concentration (c = g/dL), and solvent.

^{1}H and ^{13}C NMR spectra were recorded on Varian Unity (400 MHz, ^{1}H; 101 MHz, ^{13}C) or Inova (500 MHz, ^{1}H; 126 MHz, ^{13}C) spectrometers. ^{31}P NMR and ^{19}F spectra were recorded on Inova (202 MHz) and Inova (470 MHz) spectrometers respectively.^{1}H NMR Spectra and ^{13}C NMR spectra were acquired in $CDCl_3$ referenced to residual $CHCl_3$ at 7.26 and 77.00 ppm respectively. Assignments were obtained by reference to COSY, HSQC and HMBC correlations. Chemical shifts are reported in ppm, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), sext (sextet), sept (septet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hertz, and integration is provided and assignments are indicated.

Mass spectroscopy (MS) was performed by the University of Illinois Mass Spectrometry Center. ESI mass spectra were performed on a Waters or Micromass Q-Tof Ultima instrument. EI mass spectra were performed on a 70-VSE instrument. Data are reported in the form of (m/z) versus intensity. Infrared spectra (IR) were recorded on a Mattson Galaxy 5020 spectrophotometer in KBr pellets or NaCl cells (film) or Perkin-Elmer FT-IR system. Peaks are reported in cm^{-1} with indicated relative intensities: s (strong, 67-100%); m (medium, 34-66%); w (weak, 0-33%). Elemental analyses were performed by the University of Illinois Microanalytical Service Laboratory and Robertson Microlit Laboratories, Inc.

5.2 Commercial Chemicals

Reaction solvents tetrahydrofuran (Fisher, HPLC grade), diethyl ether (Fisher, BHT stabilized ACS grade), and CH_2Cl_2 (Fisher, unstabilized HPLC grade) were dried by passage through two columns of neutral alumina in a solvent dispensing system. Reaction solvents hexane (Fisher, OPTIMA grade) was dried by percolation through a column packed with neutral alumina and a column packed with Q5 reactant, a supported copper catalyst for scavenging oxygen, in a solvent dispensing system. Reaction solvent *N*,*N*-dimethylformamide (Fisher, HPLC grade) was dried by percolation through a column packed with molecular sieves in a solvent dispensing system. Solvents for chromatography, filtration and recrystallization were CH_2Cl_2 (Aldrich, ACS grade), ethyl acetate (Fisher, ACS grade), diethyl ether (Fisher, ACS grade), hexane (Fisher, Optima) and toluene (Aldrich, Optima) were used as received. Isopropylamine (Aldrich), triethylamine (Alfa-Aesar) and pyridine (Fisher) were freshly distilled from CaH_2. Methanol (Fisher, ACS grade) was distilled from magnesium. "Brine" refers to a saturated aqueous solution of sodium chloride.

5.3 Literature Preparations

Literature Preparations for Chapter 2:

Electrophile *N*-(phenylthio)-phthalimide **6**[44] was prepared according to a literature procedure.

Chiral selenophosphoramide catalysts (*R*)-**7**,[12] (*S*)-**53**,[30] (*S*)-**79**,[30] (*S*)-**80**,[30] (*S*)-**81**,[30] (*S*)-**82**[30] were prepared as described.

Substrates and intermediates (*E*)-5-phenyl-4-penten-1-ol **2**,[12] (*E*)-*N*-(5-phenyl-4-penten-1-yl)-4-toluenesulfonamide **56**,[42c] (*E*)-ethyl 5-phenyl-4-pentenoate **65**,[117] (*Z*)-*N*-(5-phenyl-4-

penten-1-yl)-4-toluenesulfonamide **92**,[42c] *N*-(4-penten-1-yl)-4-toluenesulfonamide **93**,[118] (*E*)-*N*-(4-phenyl-3-buten-1-yl)-4-toluenesulfonamide **94**,[42a] (*E*)-*N*-(2,2-dimethyl-5-phenyl-4-penten-1-yl)-4-toluenesulfonamide **99**,[42b] (*E*)-5-(4-methoxyphenyl)-4-penten-1-ol **160**, [119] (*E*)-5-(4-trifluoromethylphenyl)-4-penten-1-ol **161**,[120] (*E*)-7-phenyl-4-hepten-1-ol **162**,[38] (*E*)-6-methyl-4-hepten-1-ol **163**,[121] (*E*)-5-phenyl-4-pentenenitrile **167**,[42b] (*E*)-5-phenyl-4-pentenoic acid **168**[122] were prepared according to a literature procedure.

Literature Preparations for Chapter 3:

Substrate alkene **52**[30], *N*-(phenylthio)-phthalimide **6**[44], and chiral selenophosphoramide catalyst (S)-**53**[30] was prepared according to literature procedures.

Literature Preparations for Chapter 4:

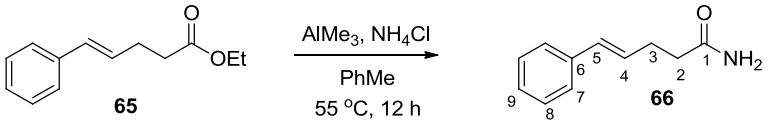
Intermediates and substrates **129b**,[123a] **130b**,[123b] **131b**,[123c] **132**,[124] **133b**,[123d] **134**,[101] **135**,[102] **140c**,[125] (*E*)-7-(2-bromophenyl)-4-hepten-1-ol **142d**,[126] 1-bromo-2-(4-pentenyl)benzene **143b**[127] were prepared according to a literature procedure.

Caution! *Sodium cyanide is extremely toxic and great care should be taken when handling these reagents. All reactions should be performed in a well-ventilated fume-hood and the appropriate protective clothing should be worn at all times.*

5.4 Experimental Procedures for Chapter 2

Preparation of Amines with Varying Protecting Groups (Chart1 and Scheme 18)

Preparation of (*E*)-5-Phenylpent-4-enamide (66)[128] (Scheme 18) [HMC1030]



An oven-dried 250 mL Schlenk flask was equipped with a stir bar, septum and a positive argon inlet. Solid ammonium chloride (16.1 g, 302 mmol, 2.80 equiv) was loaded into the flask which was purged with argon. Anhydrous toluene was added via syringe to afford a suspension of ammonium chloride/toluene. The suspension was cooled in an ice-bath for five minutes. To the suspension was added a solution of trimethylaluminum (151 mL, 302 mmol, 2.0 M in toluene, 2.80 equiv) dropwise via addition funnel over 1 h with observation of gas evolution. The mixture was allowed to stir at 0 ^{o}C for 1 h at it became homogeneous. Then the mixture was allowed to warm to room temperature and was stirred for an additional 30 min. The aluminum reagent mixture was then transferred via cannula over 1 h to a solution of the ester **65**[117] (22.0 g, 108 mmol) in toluene (150 mL) in an oven-dried, argon purged 1000-mL, 3-necked round-bottomed-flask. After addition, the mixture was heated at 55 ^{o}C under argon for 14 h. After completion, the reaction was quenched with slow addition of 1 M HCl (150 mL) at 0 ^{o}C. The mixture was diluted with water (250 mL) and ethyl acetate (250 mL) and phases were separated. The aqueous layer was extracted with ethyl acetate (300 mL x3) and the combined organic extracts were washed with brine (300 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* (30 ^{o}C, 10 mmHg) to afford a white solid. Recrystallization of the solid with hot ethyl acetate (77 ^{o}C, 40 mL) afforded 11.1 g (76%) of **66** as white crystals. The spectroscopic data matched those reported in the literature.[128]

Data for **66**:

mp: 132-133 ^{o}C (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.40 – 7.18 (m, 5 H), 6.46 (d, *J* = 16.0 Hz, 1 H,), 6.23 (dt, *J* = 16.0, and 7.0 Hz, 1

H), 5.61 (brs, 1 H), 5.50 (brs, 1 H), 2.60 – 2.53 (m, 2 H), 2.42 – 2.37 (m, 2 H).

^{13}C NMR: (126 MHz, $CDCl_3$)

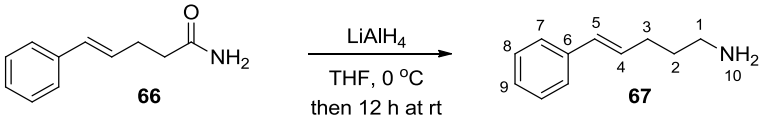
δ 174.5, 137.2, 131.2, 128.5, 127.3, 126.1, 125.9, 35.4, 28.7.

MS: (ESI)

117 (51), 159 (25), 176 (M+H, 100), 177 (14), 198 (10)

HRMS: calcd for $C_{11}H_{14}NO$: 176.1075, found: 176.1079

Preparation of (*E*)-5-Phenylpent-4-enylamine (67) [HMC1033]



An oven-dried, 500-mL Schlenk flask was equipped with a stir bar, was charged with a solution of amide **66** (10.0 g, 57.1 mmol) in anhydrous tetrahydrofuran (190 mL) at 0 °C. To the solution was added lithium aluminum hydride (3.25 g, 85.6 mmol, 1.50 equiv) in portions with caution. Then the mixture allowed to warm to room temperature and was 12 h. The standard Fieser and Fieser work up was used,[129] adding 3.24 mL of water, 3.24 mL of 15% NaOH solution, and 9.75 mL of water in sequence under 0 °C. Then the mixture was allowed to warm to room temperature and stir for 15 min. To the mixture was added 5 g of $MgSO_4$ and the resulting solids were filtered through a pad of Celite (5 g, 35 mm). The resulting solution was concentrated under concentrated *in vacuo* (30 °C, 10 mmHg) and purified by passing through a short pad of silica (SiO_2, 5 g, 20 mm Ø, dichloromethane/methanol = 9:1, then dichloromethane/methanol = 9:1 with 1% triethylamine) to afford 7.3 g (79%) of the primary amine **67**. The spectroscopic data matched those reported in the literature.[122]

Data for **67**:

^{1}H NMR: (500 MHz, $CDCl_3$)

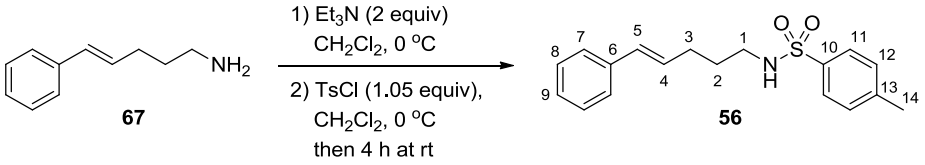
δ 7.36 – 7.16 (m, 5 H), 6.40 (d, *J* = 15.5 Hz, 1 H), 6.22 (d, *J* = 16.0 Hz, 1 H), 2.77 (t, *J* = 7.0 Hz, 2 H), 2.27 (q, *J* = 7.5 Hz, 2 H), 1.87 (brs, 2 H), 1.64 (p, *J* = 7.5 Hz, 2 H).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 137.7, 130.2, 130.2, 128.4, 126.9, 125.9, 41.6, 33.1, 30.3.

Protection of Precursor Amine (Scheme 18)

Preparation of (*E*)-*N*-(4-Toluenesulfonyl)-5-phenylpent-4-enylamine (56)[42a,b] (Scheme 18) [HMC1072]



To an oven-dried, 25-mL Schlenk flask equipped with a magnetic stir bar, purged with positive pressure of argon, were added a solution of parent amine **67** (500 mg, 3.10 mmol) in dichloromethane (4 mL) and a solution of triethylamine (864 μL, 6.20 mmol, 2.00 equiv) in dichloromethane (3 mL). After equilibration at 0 ^{o}C (internal temperature), to the mixture was added a solution of tosyl chloride (621 mg, 3.26 mmol, 1.05 equiv) in dichloromethane (3 mL) portion wise. The resulting reaction mixture was allowed to warm to room temperature and was stirred for 4 h. The resulting mixture was diluted with 20 mL of dichloromethane and washed with 20 mL of 1 M HCl, 1 M NaOH, water and brine, respectively. The resulting organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* (30 ^{o}C, 10 mmHg) to afford the crude yellow liquid. Purification via silica gel flash column chromatography (SiO_2, 15 g, 20 mm Ø, hexanes/EtOAc, 9:1 to 4:1) afforded 792 mg (81%) of **56**, as a white solid. The spectroscopic data matched those reported in the literature.[42c]

Data for **56**:

mp: 59-60 ^{o}C (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.76 (d, *J* = 8.5 Hz, 2 H), 7.35 – 7.16 (m, 7 H), 6.34 (dt, *J* = 16.0, and 1.5 Hz, 1 H), 6.09 (dt, *J* = 16.0, and 7.0 Hz, 1 H), 4.46 (t, *J* = 6.5 Hz, 1 H), 3.01 (q, *J* = 7.0, and 6.5 Hz, 2 H), 2.42 (s, 3 H), 2.25 – 2.19 (m, 2 H), 1.66 (p, *J* = 7.0 Hz, 2 H)

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 143.3, 137.4, 136.9, 130.9, 129.7, 128.9, 128.4, 127.1, 127.0, 125.9, 42.5, 29.8, 29.1, 21.4.

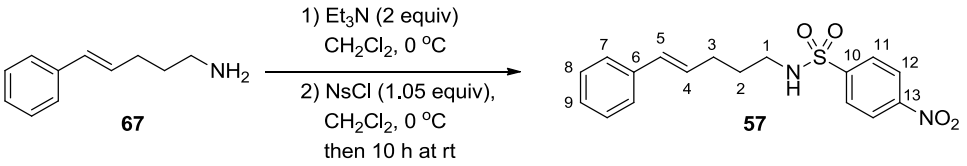
MS: (ESI)

316 (M+H, 100), 317 (22), 333 (10), 338 (18)

HRMS: calcd for $C_{18}H_{22}NO_2S$: 316.1371, found: 316.1365

TLC: R_f 0.32 (hexanes/EtOAc, 7:3) [UV/$KMnO_4$]

Preparation of (*E*)-*N*-(4-Nitrobenzenesulfonyl)-5-phenylpent-4-enylamine (57) (Scheme 18) [HMC1038]



To an oven-dried, 25-mL round-bottomed-flask equipped with a magnetic stir bar, purged with positive pressure of argon, were added a solution of parent amine **67** (250 mg, 1.55 mmol) in dichloromethane (3 mL) and triethylamine (432 μL, 3.10 mmol, 2.00 equiv). After equilibration at 0 ^oC (internal temperature), to the mixture was added a solution of *p*-nitrobenzenesulfonyl chloride (361 mg, 1.63 mmol, 1.05 equiv) in dichloromethane (2 mL). The resulting reaction mixture was allowed to warm to room temperature and was stirred for 10 h. The resulting mixture was diluted with 10 mL of dichloromethane and washed with 10 mL of 1 M HCl, 1 M NaOH, water and brine, respectively. The resulting organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* (30 ^oC, 10 mmHg) to afford the crude yellow liquid. Purification via silica gel flash column chromatography (SiO_2, 15 g, 20 mm Ø, hexanes/EtOAc, 9:1 to 4:1) afforded 445 mg (83%) of **57**, as a white solid. The spectroscopic data matched those reported in the literature.[42d]

Data for **57**:

mp: 97-98 ^oC (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.33 (d, *J* = 9.0 Hz, 2 H), 8.05 (d, *J* = 9.0 Hz, 2 H), 7.32 – 7.20(m, 5 H), 6.34 (d, *J* = 16.0 Hz, 1 H), 6.08 (dt, *J* = 16.0, 7.0 Hz, 1 H), 4.81 (t, *J* = 6.0 Hz, 1 H), 3.08 (q, *J* = 7.0 Hz, 2 H), 2.24 (q, *J* = 7.0 Hz, 2 H), 1.71 (p, *J* = 7.0 Hz, 2 H).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 150.0, 145.9, 137.1, 131.3, 128.6, 128.3, 128.2, 127.3, 125.9, 124.4, 42.7, 29.7, 29.2.

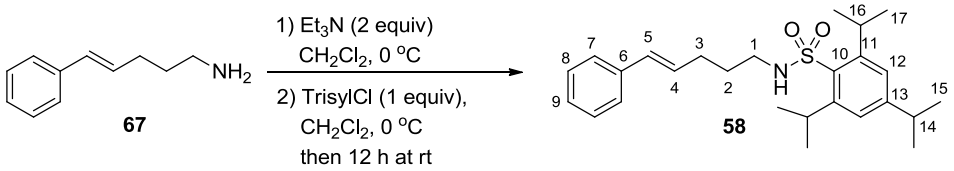
MS: (ESI)

145 (24), 255 (14), 317 (18), 347 (M+H, 100), 348 (20), 364 (58), 369 (41), 385 (15), 421 (26)

HRMS: calcd for $C_{17}H_{19}N_2O_4S$: 347.1066, found: 347.1063

TLC: R_f 0.27 (hexanes/EtOAc, 7:3) [UV/$KMnO_4$]

Preparation of (*E*)-*N*-(2,4,6-Triisopropylbenzenesulfonyl)-5-phenylpent-4-enylamine (58) (Scheme 18) [HMC1055]



To an oven-dried, 25-mL Schlenk flask equipped with a magnetic stir bar, purged with positive pressure of argon, were added a solution of parent amine **67** (250 mg, 1.55 mmol) in dichloromethane (2 mL) and a solution of triethylamine (432 μL, 3.10 mmol, 2.00 equiv) in dichloromethane (1.5 mL). After equilibration at 0 ^{o}C (internal temperature), to the mixture was added a solution of trisyl chloride (470 mg, 1.55 mmol, 1.00 equiv) in dichloromethane (1.5 mL) portion wise. The resulting reaction mixture was allowed to warm to room temperature and was stirred for 12 h. The resulting mixture was diluted with 10 mL of dichloromethane and washed with 15 mL of 1 M HCl, 1 M NaOH, water and brine, respectively. The resulting organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* (30 ^{o}C, 10 mmHg) to afford the crude yellow liquid. Purification via silica gel flash column chromatography (SiO_2, 15 g, 20 mm Ø, hexanes/EtOAc, 4:1) afforded 504 mg (76%) of **58**, as a white solid.

Data for **58**:

mp: 85-86 ^{o}C (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.31 – 7.18 (m, 7 H), 6.35 (d, *J* = 16.0 Hz, 1 H), 6.12 (dt, *J* = 16.0, 7.0 Hz, 1H), 4.47 (t, *J* = 6.0 Hz, 1 H), 4.24 – 4.34 (m, 2 H), 3.05 (app. q, *J* = 7.5, 7.0 Hz, 2H), 2.96 – 2.88 (m, 1 H), 2.24 (app. q, *J* = 7.5, 7.0 Hz, 2 H), 1.70 (p, *J* = 7.0 Hz, 2 H), 1.28 (t, *J* = 6.0 Hz, 18 H).

^{13}C NMR: (126 Hz, $CDCl_3$)

δ 152.6, 150.2, 137.3, 132.3, 130.9, 128.9, 128.4, 127.0, 125.9, 123.8, 42.3, 34.1, 30.0, 29.6, 29.4, 24.8, 23.5.

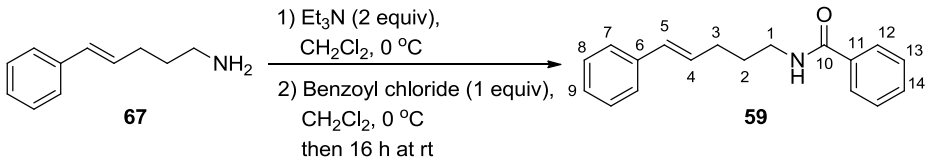
MS: (ESI)

428 (M+H, 100), 429 (35), 430 (17), 445 (13), 450 (11)

HRMS: calcd for $C_{26}H_{38}NO_2S$: 428.2623, found: 428.2615

TLC: R_f 0.54 (hexanes/EtOAc, 7:3) [UV/$KMnO_4$]

Preparation of (*E*)-*N*-Benzoyl-5-phenylpent-4-enylamine (59) (Scheme 18)[42e] [HMC1040]



To an oven-dried, 25-mL Schlenk flask equipped with a magnetic stir bar, purged with positive pressure of argon, were added a solution of parent amine **67** (250 mg, 1.55 mmol) in dichloromethane (2 mL) and a solution of triethylamine (432 μL, 3.10 mmol, 2.00 equiv) in dichloromethane (1.5 mL). After equilibration at 0 °C (internal temperature), to the mixture was added a solution of benzoyl chloride (180 μL, 1.55 mmol, 1.00 equiv) in dichloromethane (1.5 mL) portion wise. The resulting reaction mixture was allowed to warm to room temperature and was stirred for 16 h. The resulting mixture was diluted with 15 mL of dichloromethane and washed with 20 mL of water, 1 M HCl, and sat. $NaHCO_3$ aq. solution, respectively. The resulting organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* (30 °C, 10 mmHg) to afford the crude orange oil. Purification via silica gel flash column chromatography (SiO_2, 15 g, 20 mm Ø, hexanes/EtOAc, 4:1) afforded 304 mg (74%) of **59**, as a white solid. The melting point data matched the literature value.[128]

Data for **59**:

mp: 62-63 °C (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.74 (d, *J* = 8.0 Hz, 2 H), 7.50 – 7.19 (m, 8 H), 6.44 (d, *J* = 16.0 Hz, 1 H), 6.32 (brs, 1 H), 6.25 (dt, *J* = 16.0, and 7.0 Hz, 1 H), 3.53 (td, *J* = 7.0, and 7.0 Hz, 2 H),

2.33 (td, *J* = 7.0, and 7.0 Hz, 2 H), 1.82 (p, *J* = 7.0 Hz, 2 H).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 167.4, 137.4, 134.7, 131.3, 130.7, 129.7, 128.5, 128.5, 127.0, 126.8, 126.0, 39.8, 30.7, 29.3.

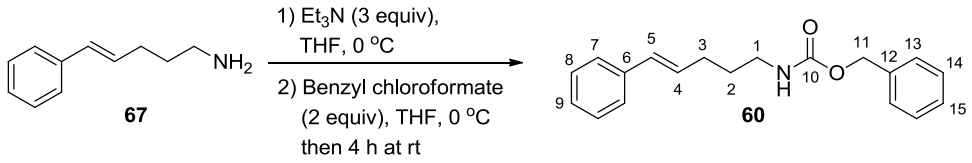
MS: (ESI)

105 (40), 122 (25), 145 (20), 266 (M+H, 100), 267 (23), 282 (15), 288 (22)

HRMS: calcd for $C_{18}H_{20}NO$: 266.1545, found: 266.1540

TLC: R_f 0.20 (hexanes/EtOAc, 7:3) [UV/$KMnO_4$]

Preparation of Benzyl ((*E*)-5-phenylpent-4-enyl)carbamate (60) (Scheme 18)[42f] [HMC1039]



To an oven-dried, 25-mL Schlenk flask equipped with a magnetic stir bar, purged with positive pressure of argon, were added a solution of parent amine **67** (250 mg, 1.55 mmol) in THF (2 mL) and a solution of triethylamine (648 μL, 4.65 mmol, 3.00 equiv) in THF (1.5 mL). After equilibration at 0 °C (internal temperature), to the mixture was added a solution of benzyl chloroformate (529 mg, 3.10 mmol, 2.00 equiv) in THF (1.5 mL) portion wise. The resulting reaction mixture was allowed to warm to room temperature and was stirred for 4 h. The resulting mixture was diluted with 10 mL of dichloromethane and was added 10 mL of 1 M HCl. The resulting biphasic mixture was extracted with dichloromethane (10 mL x 5) and was washed with 30 mL of sat. $NaHCO_3$ aq. solution, brine, respectively. The resulting organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* (30 °C, 10 mmHg) to afford a crude yellow liquid. Purification via silica gel flash column chromatography (SiO_2, 15 g, 20 mm Ø, hexanes/EtOAc, 9:1) afforded 348 mg (76%) of **60**, as a white solid.

Data for **60**:

mp: 50-51 °C (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.40 – 7.16 (m, 10 H), 6.40 (d, *J* = 16.0 Hz, 1 H), 6.19 (dt, *J* = 16.0, and 7.0 Hz, 1

H), 5.10 (s, 2 H), 4.78 (brs, 1 H), 3.26 (q, *J* = 7.0, and 7.0 Hz, 2 H), 2.26 (q, *J* = 7.0, and 7.0 Hz, 2 H), 1.70 (p, *J* = 7.0 Hz, 2 H).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 156.4, 137.5, 136.6, 130.6, 129.5, 128.5, 128.5, 128.1, 127.0, 126.0, 66.6, 40.6, 30.2, 29.6.

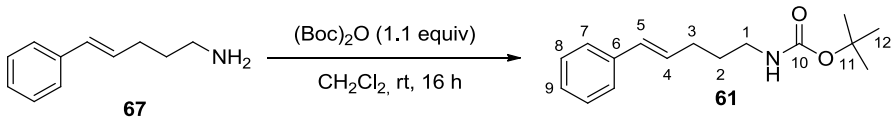
MS: (ESI)

91 (19), 218 (17), 235 (26), 252 (100), 253 (26), 296 (M+H, 65), 297 (14), 313 (26), 318 (34)

HRMS: calcd for $C_{19}H_{22}NO_2$: 296.1651, found: 296.1651

TLC: R_f 0.38 (hexanes/EtOAc, 7:3) [UV/$KMnO_4$]

Preparation of *tert*-Butyl ((*E*)-5-phenylpent-4-enyl)carbamate (61) (Scheme 18)[42g] [HMC1046]



To an oven-dried, 25-mL Schlenk flask equipped with a magnetic stir bar, purged with positive pressure of argon, were added a solution of parent amine **67** (250 mg, 1.55 mmol) in dichloromethane (3 mL) and a solution of di-*tert*-butyl carbonate (372 mg, 1.71 mmol, 1.10 equiv) in dichloromethane (2 mL) portion wise and the resulting reaction mixture was stirred for 16 h at room temperature. The resulting mixture was diluted with 10 mL of dichloromethane and 10 mL of water. The biphasic mixture was extracted with dichloromethane (10 mL x 3), and the combined organic layer was washed with sat. $NaHCO_3$ aq. solution. The resulting organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo* (30 ^{o}C, 10 mmHg) to afford the crude yellow solid. Purification via silica gel flash column chromatography (SiO_2, 15 g, 20 mm Ø, hexanes/EtOAc, 9:1) afforded 380 mg (94%) of **61**, as a white solid. The spectroscopic data matched those reported in the literature.[42 h]

Data for **61**:

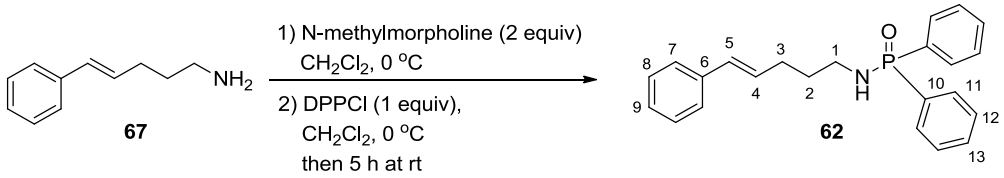
^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.40 – 7.18 (m, 5 H), 6.41 (d, *J* = 16.0 Hz, 1 H), 6.21 (dt, *J* = 16.0, and 7.0 Hz, 1 H), 4.58 (brs, 1 H), 3.23 – 3.15 (m, 2 H), 2.26 (app. q, 7.0 Hz, 2 H), 1.68 (p, *J* = 7.0 Hz, 2 H), 1.46 (s, 9 H).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 155.9, 137.5, 130.5, 129.7, 128.4, 126.9, 125.9, 79.1, 40.2, 30.3, 29.7, 28.4.

Preparation of *P,P*-Diphenyl-*N*-((*E*)-5-phenylpent-4-enyl)phosphinic amide (62) (Scheme 18)[42i] [HMC1041]



To an oven-dried, 25-mL Schlenk flask equipped with a magnetic stir bar, purged with positive pressure of argon, were added a solution of parent amine **67** (250 mg, 1.55 mmol) in dichloromethane (2 mL) and a solution of *N*-methylmorpholine (341 μL, 3.10 mmol, 2.00 equiv) in dichloromethane (1.5 mL). After equilibration at 0 ^{o}C (internal temperature), to the mixture was added a solution of diphenylphosphinic chloride (296 μL, 1.55 mmol, 1.00 equiv) in dichloromethane (1.5 mL) portion wise. The resulting reaction mixture was allowed to warm to room temperature and was stirred for 5 h. The resulting mixture was diluted with 15 mL of dichloromethane and was added 5 mL of 1 M HCl. The resulting biphasic mixture was extracted with dichloromethane (15 mL x 3). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* (30 ^{o}C, 10 mmHg) to afford the crude yellow oil. The product was purified via silica gel flash column chromatography (SiO_2, 15 g, 20 mm Ø , hexanes/EtOAc, 30:1) affording 375 mg (67%) of **62**, as a white solid.

Data for **62**:

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 7.90 – 7.81 (m, 4 H), 7.50 – 7.12 (m, 11 H), 6.34 (d, *J* = 16.0 Hz, 1 H), 6.12 (dt, *J* = 16.0, and 6.8 Hz, 1 H), 3.05 – 2.93 (m, 2 H), 2.87 (brs, 1 H), 2.23 (dt, *J* = 6.8, and 6.8 Hz, 2 H), 1.73 (p, *J* = 6.8 Hz, 2 H).

^{13}C NMR: (101 MHz, $CDCl_3$)

δ 132.2, 132.1, 131.8, 131.7, 130.7, 129.7, 128.6, 128.5, 127.0, 126.0, 40.5, 31.8, 30.2.

^{31}P NMR: (202 MHz, $CDCl_3$)

δ 24.36.

MS: (ESI)

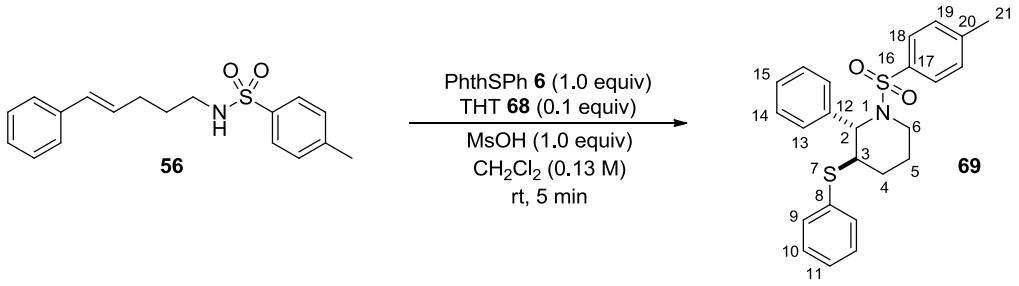
362 (M+H, 100), 363 (27), 364 (23), 378 (44), 379 (11)

HRMS: calcd for $C_{23}H_{25}NOP$: 362.1674, found: 362.1672

General Procedure I: Survey of Amine Protecting Groups (Table 2)

An oven-dried, 4-mL vial equipped with a magnetic stir bar was charged with the protected amine substrate (**56-62**, 0.063 mmol), *N*-(phenylthio)phthalimide **6** (PhthSPh, 16.2 mg, 0.063 mmol, 1.0 equiv), tetrahydrothiophene **68** (THT, none or 0.10 equiv), and CH_2Cl_2 (500 μL, 0.13 M) and capped with a septum cap. After stirring the mixture until a homogeneous solution was obtained, methanesulfonic acid (MsOH, none or 1.0 equiv) was added at room temperature. The reaction was monitored by TLC at 5 min, 1 h, 3 h, 12 h, 24 h, and 48 h time points until no amine substrate was detected. Upon completion, the reaction mixture was quenched by addition of 1 mL of sat. $NaHCO_3$ aq solution and the biphasic mixture was extracted with CH_2Cl_2 (1 mL x 3). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* (30 ^{o}C, 10 mmHg) to afford the crude product. The product was purified via silica gel flash column chromatography. In case of incomplete reaction after 48 h, the reaction mixture was quenched following above method, and the crude product was analyzed by ^{1}H NMR spectroscopy to assess conversion.

Table 2 Entry 1 [HMC1035]



Following General Procedure I, an oven-dried vial was charged with **56** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), THT **68** (0.6 μL, 6.3 μmol, 0.10 equiv), and CH_2Cl_2 (500 μL). To the mixture MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added and the reaction was monitored by TLC. TLC analysis showed immediate full conversion to **69** at 5 min. The reaction was quenched at 5 min and the crude product was purified via silica gel flash column chromatography (SiO_2, 5 g, 10 mm Ø, hexanes/EtOAc, 19:1) affording 25 mg (93%) of *rac*-**69** as white solid.

Data for *rac*-**69**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.82 (dd, *J* = 6.5, and 2.0 Hz, 2 H, HC(18)), 7.51 – 7.46 (m, 2 H, HC(13)), 7.37 – 7.18 (m, 10 H, HC(aryl)), 5.41 (s, 1 H, HC(2)), 3.92 (d, *J* = 2.5 Hz, 1 H, HC(3)), 3.76 (dd, *J* = 13.5, and 2.5 Hz, 1 H, HC(6)), 3.23 (td, *J* = 13.0, and 3.0 Hz, 1 H, HC(6)), 2.43 (s, 3 H, HC(21)), 1.92 – 1.73 (m, 3 H, HC(4,5)), 1.44 – 1.37 (m, 1 H, HC(5)).

^{13}C NMR: (126 MHz, $CDCl_3$)

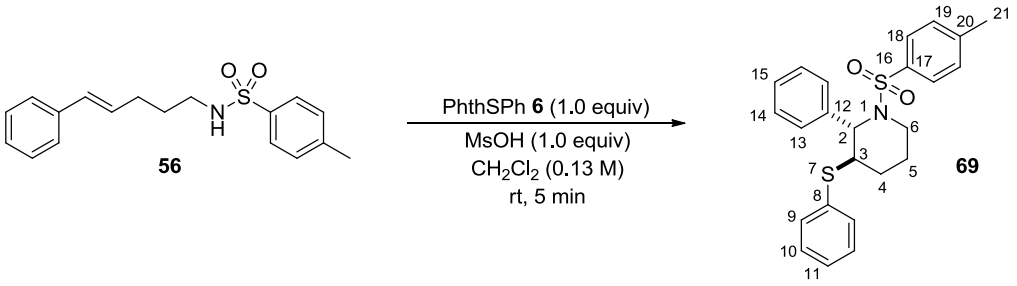
δ 143.0 (C(20)), 138.8 (C(7)), 137.7 (C(17)), 135.1 (C(12)), 132.3 (C(13)), 129.2 (C(19)), 129.2 (C(14)), 128.7 (C(9)), 127.7 (C(18)), 127.5 (C(15)), 127.1 (C(10)), 126.8 (C(8)), 60.0 (C(2)), 49.7 (C(3)), 41.8 (C(6)), 24.1 (C(4)), 21.5 (C(21)), 19.9 (C(5)).

MS: (ESI) 314 (100), 315 (23), 424 (M+H, 49), 425 (14), 441 (11), 446 (18), 462 (12)

HRMS: calcd for $C_{24}H_{26}NO_2S_2$: 424.1405, found: 424.1406

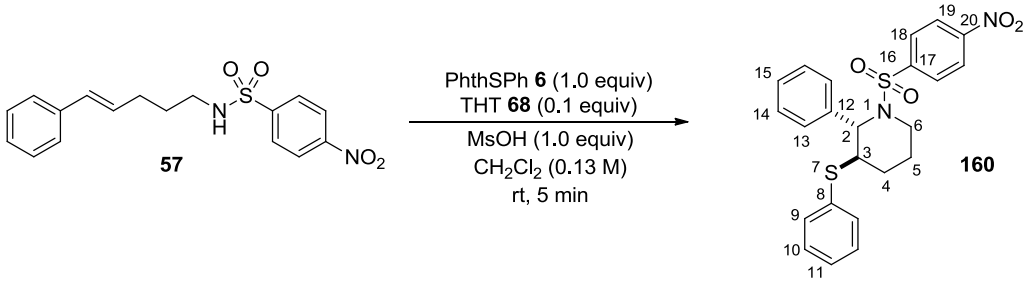
TLC: R_f 0.48 (hexanes/EtOAc, 7:3) [UV/$KMnO_4$]

Table 2 Entry 2 (Background reaction) [HMC1054]



Following General Procedure I, an oven-dried vial was charged with **56** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), and CH_2Cl_2 (500 μL). To the mixture MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added and the reaction was monitored by TLC. The reaction was incomplete at 48 h. The reaction was quenched and worked up. The conversion to **69** (4%) was determined by analysis of ^{1}H NMR spectroscopy of the crude product. Conversion to product was measured by the appearance of the diagnostic ^{1}H NMR resonance for the product **69** at 5.41 ppm with respect to the substrate peaks at 6.34 ppm and 6.09 ppm.

Table 2 Entry 3 [HMC1042]



Following General Procedure I, an oven-dried vial was charged with **57** (22 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), THT **68** (0.6 μL, 6.3 μmol, 0.10 equiv), and CH_2Cl_2 (500 μL). To the mixture MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added and the reaction was monitored by TLC. TLC analysis showed immediate full conversion to **42** at 5 min. The reaction was quenched at 5 min and the crude product was purified via silica gel flash column chromatography (SiO_2, 5 g, 10 mm Ø, hexanes/EtOAc, 19:1) affording 25 mg (95%) of *rac*-**160** as white solid.

Data for *rac*-**160**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.29 (dt, *J* = 9.0, and 2.0 Hz, 2 H), 8.05 (dt, *J* = 9.0, and 2.0 Hz, 2 H), 7.44 – 7.19 (m, 10 H), 5.39 (s, 1H), 3.95, (d, *J* = 2.0 Hz, 1 H), 3.88 (dd, *J* = 13.5, and 2.5 Hz, 1 H), 3.30 (td, *J* = 12.0, and 3.0 Hz, 1 H), 1.90 – 1.75 (m, 3 H), 1.54 – 1.45 (m, 1 H).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 149.8, 146.3, 138.0, 134.5, 131.8, 129.4, 128.9, 128.7, 127.6, 127.6, 126.7, 123.9, 60.6, 49.1, 42.3, 23.8, 19.9.

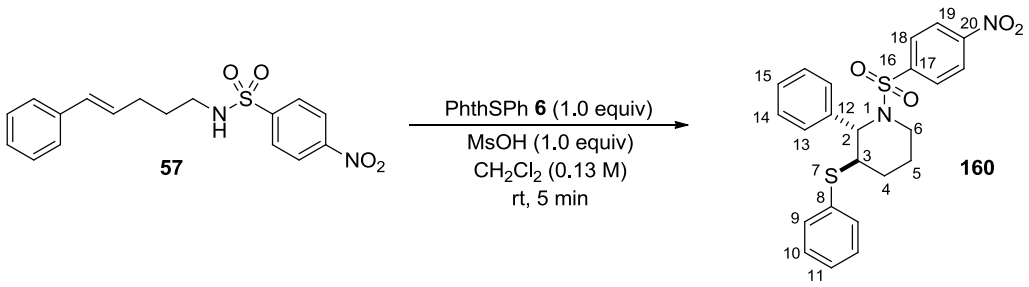
MS: (ESI)

345 (100), 346 (21), 455 (M+H, 54), 456 (15), 471 (33), 472 (83), 473 (26), 474 (14), 477 (11), 482 (12), 493 (12)

HRMS: calcd for $C_{23}H_{23}N_2O_4S_2$: 455.1099, found: 455.1102

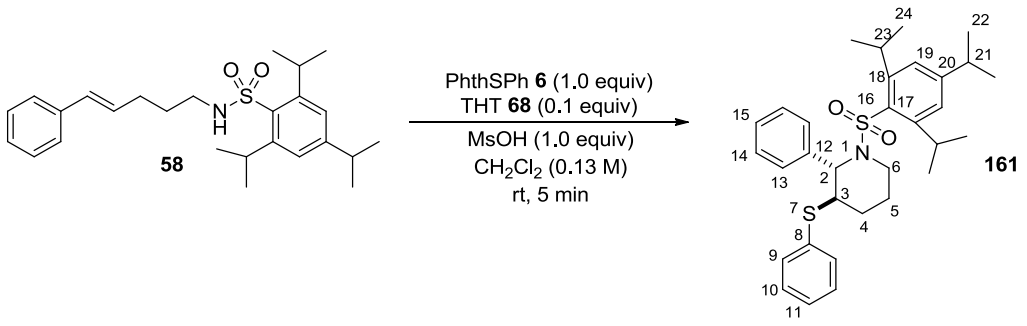
TLC: R_f 0.45 (hexanes/EtOAc, 7:3) [UV/$KMnO_4$]

Table 2 Entry 4 (Background reaction) [HMC1053]



Following General Procedure I, an oven-dried vial was charged with **57** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), and CH_2Cl_2 (500 μL). To the mixture MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added and the reaction was monitored by TLC. The reaction was incomplete at 48 h. The reaction was quenched and worked up. The conversion to **160** (11%) was determined by analysis of ^{1}H NMR spectroscopy of the crude product. Conversion to product was measured by the appearance of the diagnostic ^{1}H NMR resonance for the product **160** at 5.39 ppm with respect to the substrate peaks at 6.34 ppm and 6.08 ppm.

Table 2 Entry 5 [HMC1056]



Following General Procedure I, an oven-dried vial was charged with **58** (27 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), THT **68** (0.6 μL, 6.3 μmol, 0.10 equiv), and CH_2Cl_2 (500 μL). To the mixture MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added and the reaction was monitored by TLC. TLC analysis showed immediate full conversion to **161** at 5 min. The reaction was quenched at 5 min and the crude product was purified via silica gel flash column chromatography (SiO_2, 5 g, 10 mm Ø, hexanes/EtOAc, 19:1) affording 29 mg (84%) of *rac*-**161** as white solid.

Data for *rac*-**161**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.35 – 7.09 (m, 12 H), 5.03 (s, 1 H), 4.00 – 3.85 (m, 3 H), 3.68 (d, *J* = 3.5 Hz, 1 H), 3.60 (td, *J* = 12.0, and 3.0 Hz, 1H), 2.92 (sept, *J* = 7.0 Hz, 1 H), 2.10 – 1.82 (m, 3 H), 1.70 – 1.58 (m, 1 H), 1.28 (d, *J* = 6.0 Hz, 6 H), 1.23 (d, *J* = 6.0 Hz, 6 H), 1.19 (d, *J* = 6.0 Hz, 6 H).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 152.6, 151.4, 140.1, 132.7, 129.0, 128.2, 127.6, 127.4, 127.2, 126.4, 123.8, 123.0, 60.6, 51.3, 42.2, 34.2, 29.8, 25.5, 25.2, 24.9, 23.6, 23.5, 21.2.

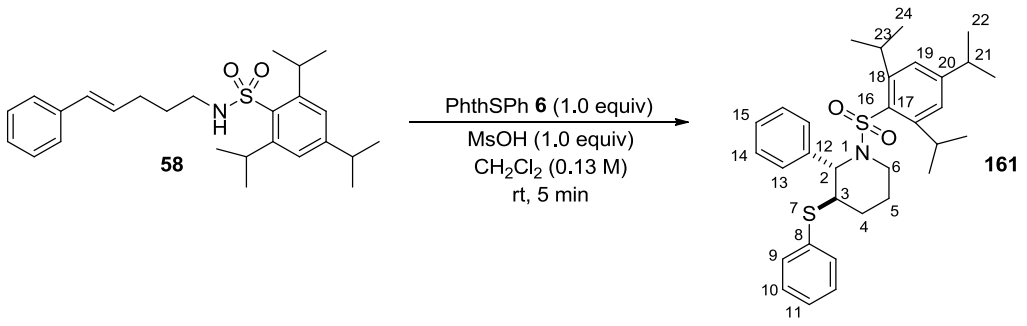
MS: (ESI)

384 (22), 426 (11), 536 (M+H, 100), 537 (40), 538 (18), 558 (12)

HRMS: calcd for $C_{32}H_{42}NO_2S_2$: 536.2657, found: 536.2656

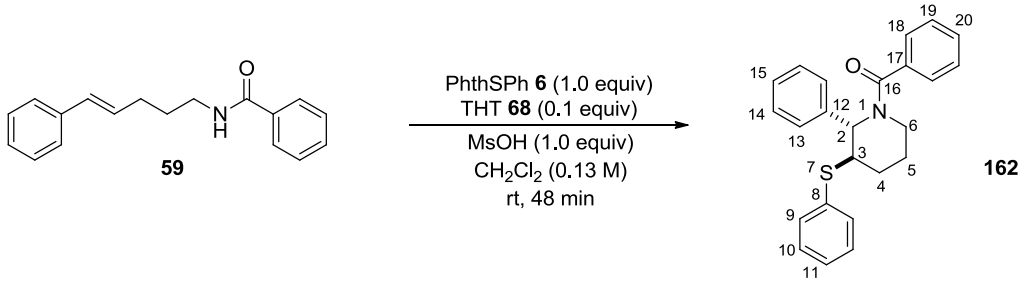
TLC: R_f 0.63 (hexanes/EtOAc, 7:3) [UV/$KMnO_4$]

Table 2 Entry 6 (Background reaction with no catalyst) [HMC1057]



Following General Procedure I, an oven-dried vial was charged with **7** (27 mg, 0.063 mmol), PhthSPh **2** (16.2 mg, 0.063 mmol, 1.0 equiv), and CH_2Cl_2 (500 μL). To the mixture MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added and the reaction was monitored by TLC. The reaction was incomplete at 48 h. The reaction was quenched and worked up. The conversion to **161** (2%) was determined by analysis of ^{1}H NMR spectroscopy of the crude product. Conversion to product was measured by the appearance of the diagnostic ^{1}H NMR resonance for the product **161** at 5.03 ppm with respect to the substrate peaks at 6.35 ppm and 6.12 ppm.

Table 2 Entry 7 [HMC1023]



Following General Procedure I, an oven-dried vial was charged with **59** (17 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), THT **68** (0.6 μL, 6.3 μmol, 0.10 equiv), and CH_2Cl_2 (500 μL). To the mixture MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added and the reaction was monitored by TLC. TLC analysis showed full conversion to **162** at 48 h. The reaction was quenched and the crude product was purified via silica gel flash column chromatography (SiO_2, 5 g, 10 mm Ø , hexanes/EtOAc, 9:1) affording 20 mg (86%) of *rac*-**162** as white solid.

Data for *rac*-**162**:

^{1}H NMR: (500 MHz, $CDCl_3$, –40 °C)

Major rotamer: δ 7.70 – 7.09 (m, 15 H), 5.11 (s, 1 H), 4.80 (d, *J* = 16.5 Hz, 1 H), 4.10 (s, 1 H), 2.92 (td, *J* = 16.5, and 3.5 Hz, 1 H), 2.15 – 1.96 (m, 1 H), 1.92 – 1.78 (m, 2 H), 1.50 (d, *J* = 16.5 Hz, 1 H).

Minor rotamer: δ 7.70 – 7.09 (m, 15 H), 6.05 (s, 1 H), 4.24, (s, 1 H), 3.65 (d, *J* = 17.5 Hz, 1 H), 3.00 (t, *J* = 15.0 Hz, 1 H), 2.15 – 1.96 (m, 1 H), 1.92 – 1.78 (m, 2 H), 1.36 (d, *J* = 8.5 Hz, 1 H).

^{13}C NMR: (126 MHz, $CDCl_3$, –40 °C)

δ 172.8, 172.1, 137.6, 137.4, 136.1, 135.4, 134.6, 134.0, 133.6, 130.9, 129.6, 129.5, 129.1, 129.0, 128.8, 128.5, 128.2, 127.9, 127.3, 127.0, 126.7, 126.4, 126.1, 61.1, 54.5, 49.0, 48.3, 43.6, 38.3, 24.8, 24.7, 21.0, 20.0.

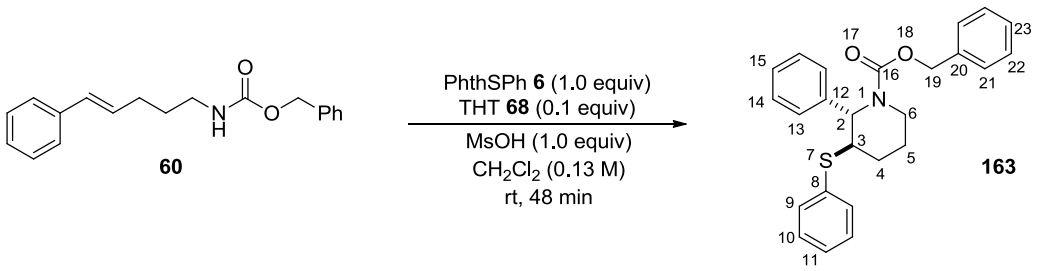
MS: (ESI)

264 (100), 265 (21), 374 (M+H, 80), 375 (22), 396 (18)

HRMS: calcd for $C_{24}H_{24}NOS$: 374.1579, found: 374.1582

TLC: R_f 0.36 (hexanes/EtOAc, 7:3) [UV/$KMnO_4$]

Table 2 Entry 8 [HMC1025]



Following General Procedure I, an oven-dried vial was charged with **60** (19 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), THT **68** (0.6 μL, 6.3 μmol, 0.10 equiv), and CH_2Cl_2 (500 μL). To the mixture MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added and the reaction was monitored by TLC. TLC analysis showed full conversion to **163** at 48 h. The reaction was quenched and the crude product was purified via silica gel flash column chromatography (SiO_2, 5 g, 10 mm Ø , hexanes/EtOAc, 9:1) affording 21 mg (81%) of *rac*-**163** as white solid.

Data for *rac*-**163**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.52 – 7.14 (m, 15 H), 5.59 (s, 1 H), 5.24 (d, *J* = 12.0 Hz, 1 H), 5.18 (d, *J* = 12.0 Hz, 1 H), 4.27 (d, *J* = 12.0 Hz, 1 H), 4.08 (d, 1 H), 4.92 (td, *J* = 13.0, and 3.0 Hz, 1 H), 2.10 – 1.98 (m, 1 H), 1.96 – 1.83 (m, 2 H), 1.44 (d, *J* = 13.0 Hz, 1 H).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 156.6, 138.8, 136.8, 135.1, 132.5, 129.1, 128.8, 128.4, 127.8, 127.7, 127.4, 127.0, 126.3, 67.4, 57.4, 48.3, 40.2, 24.5, 20.3.

MS: (ESI)

160 (11), 204 (61), 250 (29), 294 (67), 295 (14), 404 (M+H, 100), 405 (30), 421 (45), 426 (36), 442 (20)

HRMS: calcd for $C_{25}H_{26}NO_2S$: 404.1684, found: 404.1689

TLC: R_f 0.53 (hexanes/EtOAc, 7:3) [UV/$KMnO_4$]

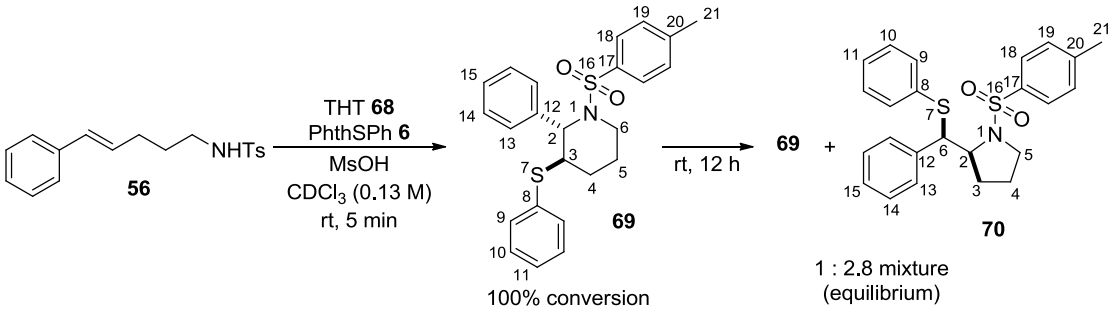
Table 2 Entry 9 [HMC1047]

Following General Procedure I, an oven-dried vial was charged with **61** (17 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), THT **68** (0.6 μL, 6.3 μmol, 0.10 equiv), and CH_2Cl_2 (500 μL). To the mixture MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added and the reaction was monitored by TLC. TLC analysis indicated partial consumption of the substrate. However, after quenching the reaction at 48 h, analysis of the crude mixture by ^{1}H NMR spectroscopy gave a complex mixture.

Table 2 Entry 10 [HMC1050]

Following General Procedure I, an oven-dried vial was charged with **62** (23 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), THT **68** (0.6 μL, 6.3 μmol, 0.10 equiv), and CH_2Cl_2 (500 μL). To the mixture MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added and the reaction was monitored by TLC. TLC analysis indicated partial consumption of the substrate. However, after quenching the reaction at 48 h, analysis of the crude mixture by ^{1}H NMR spectroscopy gave a complex mixture.

Isomerization Study (Scheme 19) [HMC1032]



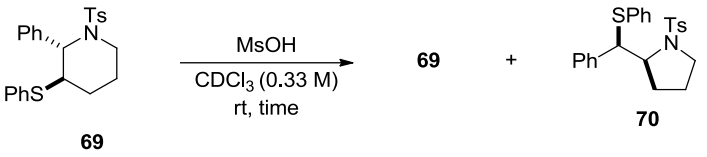
An oven-dried, 5-mm NMR tube was charged with **56** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), THT **68** (0.6 μL, 6.3 μmol, 0.10 equiv), and $CDCl_3$ (500 μL, 0.13 M) and capped with a rubber septum cap. After shaking the mixture well making a homogeneous solution, MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added via syringe at room temperature. Conversion to product was measured by the appearance of the diagnostic ^{1}H NMR resonance for the "*initial*" product (proposed to be **69**) at 5.41 ppm and the "*converted*" product (proposed to be **70**) at 4.07 ppm with respect to the substrate peaks at 6.34 ppm and 6.09 ppm. Generally, no other products were observed in the ^{1}H NMR spectra. Formation of phthalimide byproduct was visually confirmed by the precipitation out of the solution. Full conversion was observed after 5 min by ^{1}H NMR spectroscopy giving **69** as only product. However, after 12 h, a 1:2.8 mixture of two products ("*initial*":"*converted*") was observed.

Data for **69**+**70**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.82 (d, *J* = 8.0 Hz, **69**), 7.68 (d, *J* = 8.0 Hz, **70**) 7.60 – 7.44 (m, **69**+**70**), 7.41 – 7.10 (m, **69**+**70**), 5.41 (s, **69**), 5.05 (d, *J* = 3.5 Hz, **70**), 4.10 – 4.05 (m, **70**), 3.92 (s, **69**), 3.76 (d, *J* = 14.5 Hz, **69**), 3.49 – 3.39 (m, **70**), 3.23 (td, *J* = 12.0, 3.0 Hz, **69**), 2.43 (s, **69**), 2.38 (s, **70**), 2.15 – 2.03 (m, **70**), 1.95 – 1.73 (m, **69**+**70**), 1.70 – 1.55 (m, **70**), 1.44 – 1.30 (m, **69**+**70**).

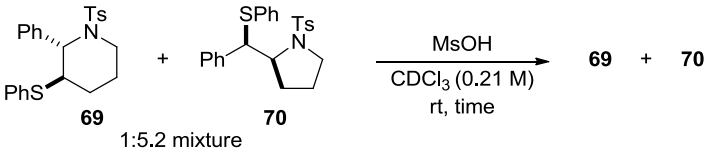
Isomerization on Under Acidic Media (Scheme 20) [HMC6084]



Time	ratio **69**:**70**
5 m	1 : 1.28
10 m	1 : 2.15
15 m	1 : 2.69
20 m	1 : 2.79
12 h	1 : 2.80

An oven-dried, 5-mm NMR tube was charged with **69** (140 mg, 0.33 mmol), and $CDCl_3$ (1.0 mL, 0.33 M) and capped with a rubber septum cap. After shaking the mixture well making a homogeneous solution, MsOH (21.4 μL, 0.33 mmol, 1.0 equiv) was added via syringe at room temperature. Conversion between two compounds was measured by the appearance of the diagnostic ^{1}H NMR resonance for the "*initial*" product (proposed to be **69**) at 5.41 ppm and the "*converted*" product (proposed to be **70**) at 4.07 ppm. No other products were observed in the ^{1}H NMR spectra. ^{1}H NMR spectra were recorded at 5 min, 10 min, 15 min, 20 min, and 12 h. Converted product **70** was already observed at 5 min, until it reached the equilibrium after 20 min. At the equilibrium, 1:2.8 mixture of two products ("*initial*":"*converted*") was observed.

Reverse Direction Isomerization on Under Acidic Media [HMC6086]



Time	ratio **69**:**70**
immediate	1 : 4.54
5 min	1 : 3.61
10 m	1 : 3.27
2 h	1 : 2.92
12 h	1 : 2.83

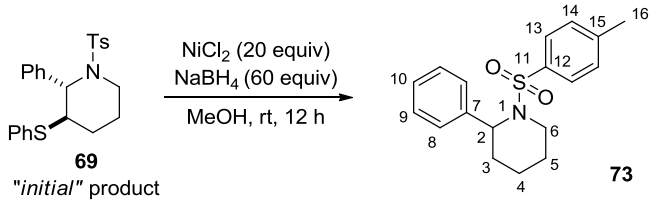
From the above isomerization experiment, a pyrrolidine-enriched (**69**:**69**, 1:5.2) fraction was isolated by chromatotron (SiO_2, 4 mm plate, hexanes/EtOAc, 9:1 to 6:1). An oven-dried, 5-mm NMR tube was charged with the mixture of **69**+**70** (53.5 mg, 0.13 mmol), and $CDCl_3$ (0.6 mL, 0.21 M) and capped with a rubber septum cap. After shaking the mixture well making a homogeneous solution, MsOH (8.2 μL, 0.13 mmol, 1.0 equiv) was added via syringe at room temperature. Conversion between two compounds was measured by the diagnostic ^{1}H NMR resonance for the "*initial*" product (proposed to be **69**) at 5.41 ppm and the "*converted*" product (proposed to be **70**) at 4.07 ppm. No other products were observed in the ^{1}H NMR spectra. ^{1}H

NMR spectra were recorded at 0 min (immediately after MsOH addition), 5 min, 10 min, 2 h, and 12 h. Conversion of pyrrolidine **70** to piperidine **69** was already observed at 0 min, until it reached the equilibrium after 12 h. At the equilibrium, 1:2.8 mixture of two products ("*initial*":"*converted*") was observed.

General Procedure II:[46] Determination of the Product Structure by Desulfurization

An oven-dried, round-bottomed-flask equipped with a magnetic stir bar was charged with a solution of the sulfenyl compound (1 equiv) in methanol (0.005 M). To the solution was then added $NiCl_2 \cdot 6H_2O$ (20 equiv), which turned into a green solution upon stirring. The suspension was cooled to 0 ^oC (internal temperature) and $NaBH_4$ (60 equiv) was added slowly portion wise, in order to minimize the gas evolution. The black suspension was then allowed to warm to room temperature and thoroughly stirred for indicated time. After this time, water (3 mL) was added slowly at 0 ^oC and the black resulting mixture was passed through a short pad of Celite (5 g, 35 mm) to remove the nickel salts. The resulting solution was concentrated *in vacuo* (40 ^oC, 10 mmHg). To the resulting crude oil was added water (30 mL) and extracted with Et_2O (30 mL x 3). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* (23 ^oC, 10 mmHg). The crude product was purified via silica gel flash column chromatography afforded the desulfurized products.

Desulfurization of 69 to 2-Phenyl-*N*-(4-toluenesulfonyl)piperidine (73) (Scheme 21) [HMC1044]



69
"*initial*" product

73

Following General Procedure II, an oven-dried, 50-mL round-bottomed-flask was charged with a solution of the "*initial*" product **69** (36 mg, 0.086 mmol) in methanol (17 mL, 0.005 M). To the solution was then added $NiCl_2 \cdot 6H_2O$ (407 mg, 1.71 mmol, 20 equiv). The suspension was cooled to 0 ^oC and $NaBH_4$ (194 mg, 5.14 mmol, 60 equiv) was added portion

wise. After 12 h of stirring at room temperature, the reaction was quenched and worked up. The crude product was purified via silica gel flash column chromatography (SiO_2, 5 g, 10 mm Ø, hexanes/EtOAc, 9:1) affording 20 mg (74%) of **73** as white solid. The spectroscopic data matched those reported in the literature.[47]

Data for **73**:

mp: 138-139 °C (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

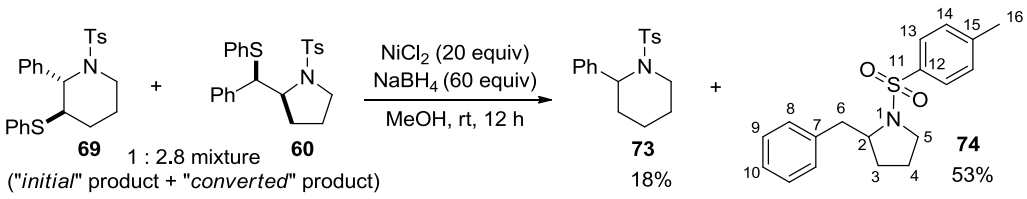
δ 7.76 (d, *J* = 8.5 Hz, 2 H), 7.40 – 7.23 (m, 7 H), 5.27 (d, *J* = 4.5 Hz, 1 H), 3.84 (d, *J* = 14.0 Hz, 1 H), 3.01 (td, *J* = 13.5, and 3.0 Hz, 1 H), 2.44 (s, 3 H), 2.21 (d, *J* = 13.0 Hz, 1 H), 1.71 – 1.62 (m, 1 H), 1.54 – 1.47 (m, 1 H), 1.44 – 1.35 (m, 2 H), 1.34 – 1.24 (m, 1 H).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 142.9, 138.9, 138.7, 129.6, 128.6, 127.00, 126.96, 126.8, 55.2, 41.8, 27.3, 24.3, 21.5, 18.9.

MS: (EI) 315 (M+), 238 (100), 207 (19), 161 (18), 160 (81), 159 (52), 91 (65).

Desulfurization of 69 and 70 mixture to 73 and 2-Benzyl-*N*-(4-toluenesulfonyl)pyrrolidine (74) (Scheme 21) [HMC1045]



Following General Procedure II, an oven-dried, 500-mL round-bottomed-flask was charged with a solution of the mixture of "*initial*" product **69** and "*converted*" product **70** (230 mg, 0.543 mmol) in methanol (109 mL, 0.005 M). To the solution was then added $NiCl_2 \cdot 6H_2O$ (2.58 g, 10.9 mmol, 20 equiv). The suspension was cooled to 0 ^oC and $NaBH_4$ (1.23 g, 32.6 mmol, 60 equiv) was added portion wise. After 12 h of stirring at room temperature, the reaction was quenched and worked up. The crude product was purified via silica gel flash column chromatography (SiO_2, 5 g, 10 mm Ø, hexanes/EtOAc, 19:1) affording 30 mg (18%) of **73** as a white solid and 91 mg (53%) of **74** as white solid (overall 71% yield). The spectroscopic data

matched those reported in the literature.[47,48]

Data for **74**:

^{1}H NMR: (500 MHz, $CDCl_3$)

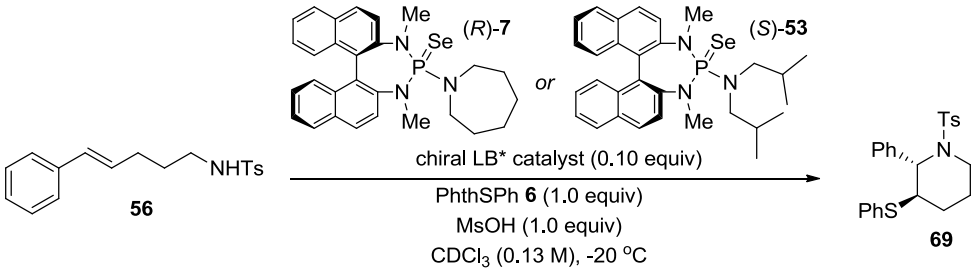
δ 7.77 (d, *J* = 8.0 Hz, 2 H), 7.36 – 7. 20 (m, 7 H), 3.88 – 3.80 (m, 1 H), 3.44 – 3.38 (m, 1 H), 3.26 (dd, *J* = 13.0, and 3.5 Hz, 1 H), 3.18 – 3.11 (m, 1 H), 2.77 (dd, *J* = 13.0, and 10.0 Hz, 1 H), 2.43 (s, 3H), 1.71 – 1.60 (m, 2 H), 1.51 – 1.39 (m, 2 H).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 143.3, 138.5, 134.7, 129.6, 129.6, 128.4, 127.5, 126.4, 61.6, 49.2, 42.7, 29.9, 23.8, 21.5.

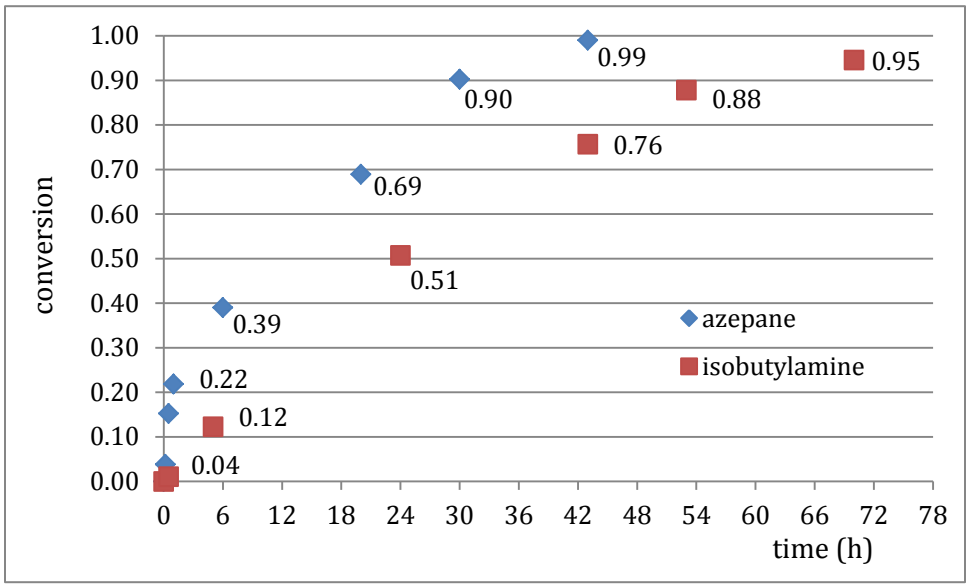
Optimization of Reaction Conditions

Conversion study with (*R*)-17, (*S*)-18 catalysts at –20 ^{o}C (Chart 3) [HMC1064, HMC1066]



An oven-dried, 5-mm NMR tube was charged with **56** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), chiral Lewis base catalyst ((*R*)-**7**, 3.3 mg or (*S*)-**53**, 3.5 mg, 6.3 μmol, 0.10 equiv), and $CDCl_3$ (500 μL, 0.13 M) and capped with a rubber septum cap. After shaking the mixture well making a homogeneous solution, the tube was cooled to –20 ^{o}C in a cryocool unit. After reaching equilibrium, MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added via syringe. Conversion to product was measured by the appearance of the diagnostic ^{1}H NMR resonance for the piperidine **69** at 5.41 ppm and the pyrrolidine **70** at 4.07 ppm with respect to the substrate peaks at 6.34 ppm and 6.09 ppm. Interestingly, no pyrrolidine products were observed by the ^{1}H NMR spectra for neither (*R*)-**7** nor (*S*)-**53** catalysts. Formation of phthalimide byproduct was visually confirmed by the precipitation out of the solution. Monitoring by ^{1}H NMR spectroscopy was done by freezing the NMR tube in a dewar flask with dry-ice/acetone bath (–78 ^{o}C) while transferring to a pre-cooled (–20 ^{o}C) NMR instrument.

Chart 3 (reproduced)

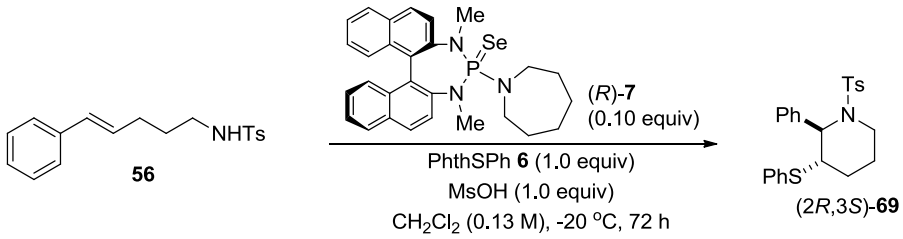


General Procedure III: Survey of Chiral Lewis Base Catalysts

An oven-dried, 4-mL vial equipped with a magnetic stir bar was charged with **56** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), chiral Lewis base catalyst (**7, 53, 79-83**, 6.3 μmol, 0.10 equiv), and solvent (CH_2Cl_2 or $CDCl_3$, 500 μL, 0.13 M) and capped with a septum cap. After stirring the mixture well making a homogeneous solution, the vial was cooled to –20 ^{o}C in a Cryocool unit. After reaching equilibrium, MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added via syringe. After indicated time, the reaction mixture was quenched by rapid addition of 1 mL of sat. $NaHCO_3$ aq solution upon stirring and the biphasic mixture was extracted with CH_2Cl_2 (1 mL x 3). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* (30 ^{o}C, 10 mmHg) to afford the crude product. The product was purified via silica gel flash column chromatography (SiO_2, 5 g, 10 mm Ø, hexanes/EtOAc, 9:1) prior to SFC analysis.

Survey of Chiral Lewis Base Catalysts (Table 3)

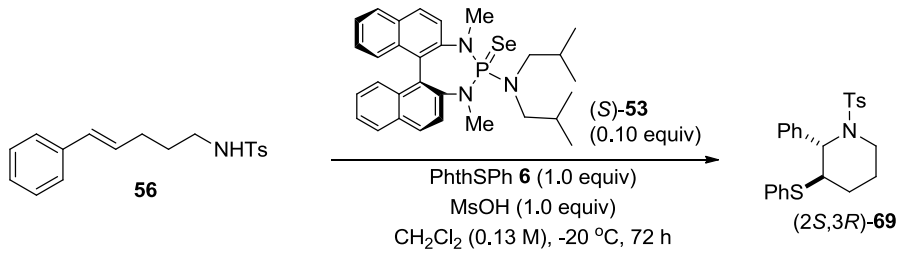
Table 3 Entry 1 [HMC1064]



Following General Procedure III, an oven-dried NMR tube was charged with **56** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), chiral Lewis base catalyst (*R*)-**7** (3.3 mg, 6.3 μmol, 0.10 equiv), and CH_2Cl_2 (500 μL, 0.13 M) and capped. The vial was cooled to –20 ^oC and MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added via syringe. After 72 h, the reaction was quenched, and purified by flash chromatography afforded 24 mg (90%) of pure **69.**

SFC: (2*S*,3*R*)-**69,** t_R 14.8 min (11.5%); (2*R*,3*S*)-**69,** t_R 16.5 min (88.5%) (Chiralcel OJ, Gradient 3% MeOH in CO_2 to 8% MeOH in CO_2 over 30 min, 2.5 mL/min, 220 nm, 40 ^oC)

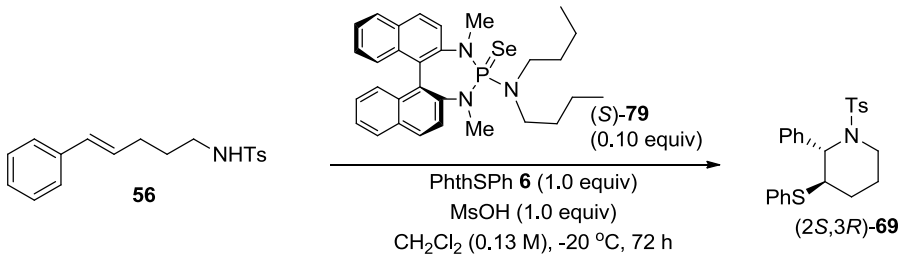
Table 3 Entry 2 [HMC1066]



Following General Procedure III, an oven-dried NMR tube was charged with **56** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**53** (3.3 mg, 6.3 μmol, 0.10 equiv), and CH_2Cl_2 (500 μL, 0.13 M) and capped. The vial was cooled to –20 ^oC and MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added via syringe. After 72 h, the reaction was quenched, and purified by flash chromatography afforded 24 mg (88%) of pure **69.**

SFC: (2*S*,3*R*)-**69,** t_R 14.8 min (89.4%); (2*R*,3*S*)-**69,** t_R 16.5 min (10.6%) (Chiralcel OJ, Gradient 3% MeOH in CO_2 to 8% MeOH in CO_2 over 30 min, 2.5 mL/min, 220 nm, 40 ^oC)

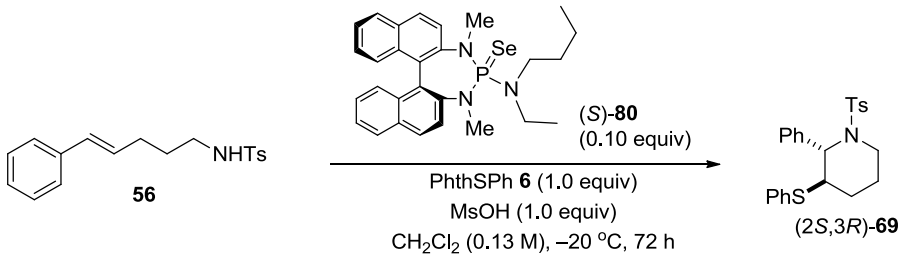
Table 3 Entry 3 [HMC1068]



Following General Procedure III, an oven-dried NMR tube was charged with **56** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**79** (3.5 mg, 6.3 μmol, 0.10 equiv), and CH_2Cl_2 (500 μL, 0.13 M) and capped. The vial was cooled to –20 ^oC and MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added via syringe. After 72 h, the reaction was quenched, and purified by flash chromatography afforded 8 mg (29%) of pure **69.**

SFC: (2*S*,3*R*)-**69,** t_R 14.8 min (85.8%); (2*R*,3*S*)-**69,** t_R 16.5 min (14.2%) (Chiralcel OJ, Gradient 3% MeOH in CO_2 to 8% MeOH in CO_2 over 30 min, 2.5 mL/min, 220 nm, 40 ^oC)

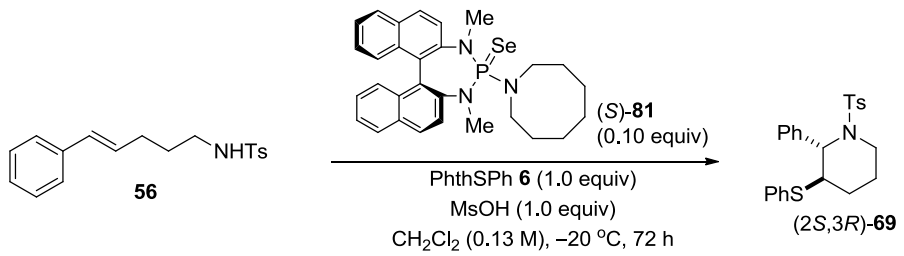
Table 3 Entry 4 [HMC1071]



Following General Procedure III, an oven-dried NMR tube was charged with **56** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**80** (3.4 mg, 6.3 μmol, 0.10 equiv), and CH_2Cl_2 (500 μL, 0.13 M) and capped. The vial was cooled to –20 ^oC and MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added via syringe. After 72 h, the reaction was quenched, and purified by flash chromatography afforded 21 mg (79%) of pure **69.**

SFC: (2*S*,3*R*)-**69,** t_R 14.8 min (88.1%); (2*R*,3*S*)-**69,** t_R 16.5 min (11.9%) (Chiralcel OJ, Gradient 3% MeOH in CO_2 to 8% MeOH in CO_2 over 30 min, 2.5 mL/min, 220 nm, 40 ^oC)

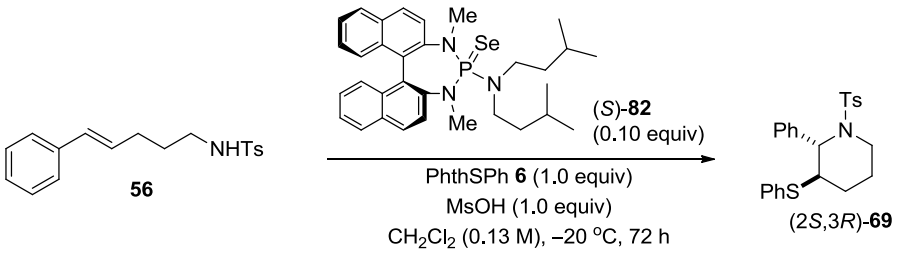
Table 3 Entry 5 [HMC1069]



Following General Procedure III, an oven-dried NMR tube was charged with **56** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**81** (3.4 mg, 6.3 μmol, 0.10 equiv), and CH_2Cl_2 (500 μL, 0.13 M) and capped. The vial was cooled to –20 ^oC and MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added via syringe. After 72 h, the reaction was quenched, and purified by flash chromatography afforded 18 mg (67%) of pure **69.**

SFC: (2*S*,3*R*)-**69,** t_R 14.8 min (91.4%); (2*R*,3*S*)-**69,** t_R 16.5 min (8.6%) (Chiralcel OJ, Gradient 3% MeOH in CO_2 to 8% MeOH in CO_2 over 30 min, 2.5 mL/min, 220 nm, 40 ^oC)

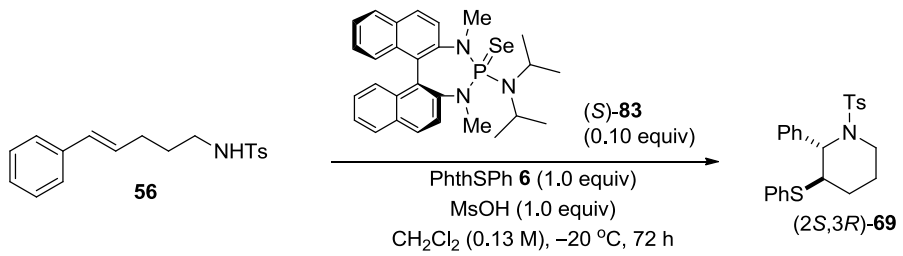
Table 3 Entry 6 [HMC1070]



Following General Procedure III, an oven-dried NMR tube was charged with **56** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**82** (3.7 mg, 6.3 μmol, 0.10 equiv), and CH_2Cl_2 (500 μL, 0.13 M) and capped. The vial was cooled to –20 ^oC and MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added via syringe. After 72 h, the reaction was quenched, and purified by flash chromatography afforded 22 mg (82%) of pure **69.**

SFC: (2*S*,3*R*)-**69,** t_R 14.8 min (92.8%); (2*R*,3*S*)-**69,** t_R 16.5 min (7.2%) (Chiralcel OJ, Gradient 3% MeOH in CO_2 to 8% MeOH in CO_2 over 30 min, 2.5 mL/min, 220 nm, 40 ^oC)

Table 3 Entry 7 [HMC1067]

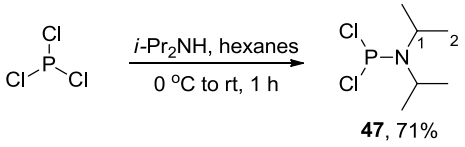


Following General Procedure III, an oven-dried NMR tube was charged with **56** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**83** (3.3 mg, 6.3 μmol, 0.10 equiv), and CH_2Cl_2 (500 μL, 0.13 M) and capped. The vial was cooled to –20 ^oC and MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added via syringe. After 72 h, the reaction was quenched, and purified by flash chromatography afforded 20 mg (75%) of pure **69.**

SFC: (2*S*,3*R*)-**69,** t_R 14.8 min (94.6%); (2*R*,3*S*)-**69,** t_R 16.5 min (5.4%) (Chiralcel OJ, Gradient 3% MeOH in CO_2 to 8% MeOH in CO_2 over 30 min, 2.5 mL/min, 220 nm, 40 ^oC)

Synthesis of P-N Reagent (Scheme 24)

Preparation of *N*,*N*-Diisopropylphosphoramidodichloridite (86)[52] [HMC3023]



A flame-dried, 100-mL two-necked, round-bottomed-flask equipped with a magnetic stir bar, a septum, and a argon inlet was added a solution of PCl_3 (2 mL, 22.9 mmol, 1 equiv) in hexanes (53 mL) via syringe under argon. The solution was cooled to 0 ^oC (internal temperature) and was added diisopropylamine (6 mL, 42.9 mmol, 1.87 equiv) dropwise, whereupon the solution turned immediately into a white suspension. After stirring for 1 h at room temperature, a Schlenk filter was connected and the white suspension was filtered to a flame-dried, 250-mL round-bottomed-flask under high vacuum (0.1 mmHg). Rinsing the original flask with hexanes (30 mL x 3) gave a turbid suspension, and excess hexane was evaporated *in vacuo* (23 ^oC, 10 mmHg). Distillation of the resulting residue was through short-path distillation (115-116 ^oC at 30

mmHg) afforded 3.27 g (71%) of compound **86** as clear liquid which solidified in freezer. The spectroscopic data matched those reported in the literature.[52]

Data for **86**:

mp: 26-27 °C (upon standing)

bp: 115-116 °C, 30 mmHg

^{1}H NMR: (500 MHz, $CDCl_3$)

3.93 (brm, 2 H, HC(1)), 1.29 (d, 12 H, *J* = 7.0 Hz, HC(2)).

^{13}C NMR: (126 MHz, $CDCl_3$)

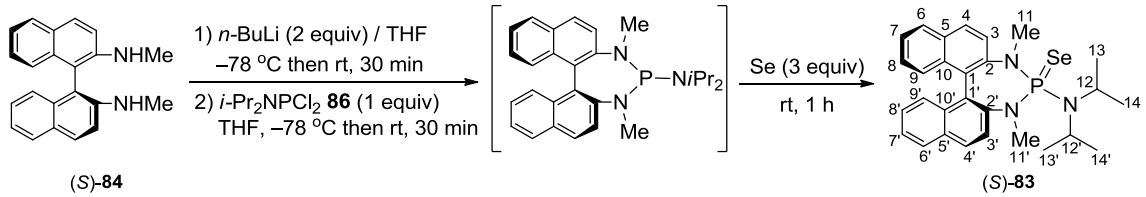
48.1 (d, C(1)), 23.4 (br, C(2)).

^{31}P NMR: (202 MHz, $CDCl_3$)

170.2 (br).

Synthesis of Chiral Lewis Base (*S*)-83 (Scheme 26)

Preparation of (*S*)-4-(Diisopropylamino)-3,5-dimethyl-4,5-dihydro-3*H*-dinaphtho[2,1-*d*:1',2'-f][1,3,2]diazaphosphepine-4-selenide ((*S*)-83) [HMC3024]



(*S*)-**84** (*S*)-**83**

To a flame-dried, 100-mL Schlenk flask equipped with a magnetic stir bar was added (*S*)-dimethyl BINAM (*S*)-**84**[49] (1.56 g, 5.00 mmol) under argon and capped with a septum. To the flask was added anhydrous THF (33.3 mL, 0.15 M) via syringe under argon. After stirring for 30 min at -74 °C (internal temperature) in a dry-ice/*i*-PrOH bath, to the homogeneous solution was added a solution of *n*-BuLi in hexanes (2.29 M, 4.37 mL, 10.0 mmol, 2.0 equiv) dropwise over 10 min whereupon the solution turned to yellow-orange. The dry-ice/*i*-PrOH bath was removed after the addition and the solution was stirred for 30 min at room temperature as the color turned yellowish black. Then the flask was immersed back into the dry-ice/*i*-PrOH bath and was allowed to equilibrate for another 30 min. To the mixture was added a freshly prepared solution

of **86**[52] in THF (910 μL in 8.3 mL of THF, 5.00 mmol, 1.0 equiv) dropwise over 10 min, whereupon the color of the solution turned to burgundy-red immediately. After warming to room temperature by removing the dry-ice/*i*-PrOH bath the solution turned to bright red then bright orange after stirring for 30 min. To the bright orange solution was added powdered selenium (1.18 g, 15.0 mmol, 3.0 equiv) at room temperature under gentle argon flow whereupon the color turned brown-black immediately. The mixture was stirred for an hour at an ambient temperature and the resulting heterogeneous mixture was filtered through a pad of Celite (10 g, 35 mm), which was rinsed with EtOAc (50 mL). The bright orange filtrate was concentrated in vacuo (40 ^{o}C, 10 mmHg) to afford an orange solid. Purification by Combiflash® column chromatography (SiO_2, 24 g Luknova column, hexanes/EtOAc, 100:0 to 20:1) afforded an off-white solid (2.24 g). Recrystallization of this solid with *n*-pentane (1.0 L, 36 ^{o}C) afforded 2.06 g (79%) of (*S*)-**83** as an off-white, crystalline solid.

Data for (*S*)-**83**:

mp: 148-150 ℃ (sealed tube)

^{1}H NMR: (500 MHz, DMSO-d_6, 80 ^{o}C, heating for sharpening diisopropyl region)
δ 8.05 (t, *J* = 10.0 Hz, 2 H, HC(4) and HC(4')), 7.99 (d, *J* = 8.0 Hz, 1 H, HC(6)), 7.95 (d, *J* = 8.0 Hz, 1 H, HC(6')), 7.81 (d, *J* = 9.0 Hz, 1 H, HC(3)), 7.66 (d, *J* = 9.0 Hz, 1 H, HC(6')), 7.43 (t, *J* = 7.5 Hz, 1 H, HC(7)), 7.39 (t, *J* = 7.5 Hz, 1 H, HC(7')), 7.23 (t, *J* = 7.5 Hz, 1 H, HC(8)), 7.14 (t, *J* = 7.5 Hz, 1 H, HC(8')), 7.06 (d, *J* = 8.5 Hz, 1 H, HC(9)), 6.83 (d, *J* = 8.5 Hz, 1 H, HC(9')), 3.64 – 3.50 (m, 2 H, HC(12) and HC(12')), 3.24 (d, *J* = 12.5 Hz, 3 H, H_3C(11)), 3.03 (d, *J* = 14.0 Hz, 3 H, H_3C(11')), 1.39 (d, *J* = 6.5 Hz, 6 H, H_3C(13) and H_3C(13')), 1.28 (d, *J* = 6.0 Hz, 6 H, H_3C(14) and H_3C(14'))

^{13}C NMR: (126 MHz, DMSO-d_6, 80 ^{o}C, heating for sharpening diisopropyl region)
δ 142.7 (d, *J* = 5.9 Hz, C(2)), 141.8 (C(2')), 131.6 (C(10)), 131.3 (C(10')), 130.6 (d, *J* = 2.0 Hz, C(5')), 130.0 (C(5)), 128.2 (C(4')), 128.1 (C(4)), 127.61 (C(6')), 127.57 (C(C6)), 126.9 (C(9)), 126.8 (d, *J* = 3.8 Hz, C(1')), 126.21 (C(1)), 126.16 (C(9')), 125.8 (C(8)), 125.4 (C(8')), 124.6 (C(7)), 124.4 (C(7')), 122.7 (C(3')), 122.6 (C(3)), 47.4 (C(12) and C(12')), 36.8 (d, *J* = 11.8 Hz, C(11)), 36.0 (d, *J* = 5.9 Hz, C(11')), 23.9 (C(13,13')), 21.9 (C(14,14'))

^{31}P NMR: (202 MHz, DMSO-d_6, 80 ^{o}C)

81.07 (t, J = 414.7 Hz, Se satellite)

IR: (KBr)

3059 (w), 2961 (m), 1618 (w), 1590 (w), 1503 (m), 1465 (m), 1365 (m), 1330 (m), 1271 (m), 1257 (m), 1174 (s), 1143 (m), 1084 (m), 980 (s), 928 (s), 848 (w), 810 (s), 751 (s)

MS: (EI)

55 (26), 57 (34), 67 (10), 68 (11), 69 (82), 70 (13), 71 (20), 81 (43), 83 (17), 84 (42), 85 (14), 86 (28), 86 (10), 95 (16), 97 (13), 100 (22), 109 (10), 136 (11), 137 (15), 281 (14), 341 (100), 342 (25), 521 (M+)

HRMS: calcd for $C_{28}H_{32}N_3PSe$: 521.1499, found: 521.1502

TLC: R_f 0.41 (hexanes/EtOAc, 9:1) [CAM]

Opt Rot: $[\alpha]_D^{24}$ 438.9 (c = 1.01, $CHCl_3$) [non-linear ORD]

SFC: (*R*)-**83**, $t_{R,}$ 7.9 min (0.2%); (*S*)-**83**, t_R 9.3 min (99.8%) (Chiralcel OJ, Gradient 3% MeOH in CO_2 to 8% MeOH in CO_2, 2.5 mL/min, 220 nm.)

Analysis: $C_{28}H_{32}N_3PSe$ (520.51)

Calcd:	C, 64.61;	H, 6.20%	N, 8.07%
Found:	C, 64.36;	H, 6.22%	N, 7.77%

General Procedure IV: Optimization of Reaction Temperature

An oven-dried, 5-mm NMR tube was charged with **5** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**83** (3.3 mg, 6.3 μmol, 0.10 equiv), and $CDCl_3$ (500 μL, 0.13 M) and capped with a rubber septum cap. After shaking the mixture well making a homogeneous solution, the NMR tube was set to an indicated temperature (external temperature) in a Cryocool unit or a cold room. After reaching equilibrium, MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added via syringe. Conversion to product was measured by the appearance of the diagnostic ^{1}H NMR resonance for the piperidine **69** at 5.41 ppm and the pyrrolidine **70** at 4.07 ppm with respect to the substrate peaks at 6.34 ppm and 6.09 ppm. Generally, no other products were observed in the ^{1}H NMR spectra. Formation of phthalimide byproduct was visually confirmed by the precipitation out of the solution. Monitoring by ^{1}H

NMR spectroscopy was done at 30 min, 3 h, 6 h, 12 h, 24 h, 48 h, and 72 h, by freezing the NMR tube in a Dewar flask with dry-ice/acetone bath (–78 ^{o}C) while transferring to a pre-cooled (–20 ^{o}C) NMR instrument. Reactions were run until complete consumption of **5** was observed by ^{1}H NMR spectroscopy or at 72 h. The reaction mixture was quenched by rapidly pouring into 1 mL of sat. $NaHCO_3$ aq solution and the biphasic mixture was extracted with CH_2Cl_2 (1 mL x 3). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* (30 ^{o}C, 10 mmHg) to afford the crude product. The product was purified via silica gel flash column chromatography (SiO_2, 5 g, 10 mm Ø , hexanes/EtOAc, 9:1) prior to SFC analysis.

Temperature Survey (Table 4)

Table 4 Entry 1 (–20 ^{o}C) [HMC1067]

Following General Procedure IV, an oven-dried, 5-mm NMR tube was charged with **56** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**83** (3.3 mg, 6.3 μmol, 0.10 equiv), and $CDCl_3$ (500 μL, 0.13 M) and capped. The NMR tube was cooled to –20 ^{o}C in a Cryocool unit and MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added via syringe. The reaction was incomplete at 72 h, whereupon the reaction mixture was quenched. Purification of the crude product via silica gel flash column chromatography (SiO_2, 5 g, 10 mm Ø , hexanes/EtOAc, 9:1) afforded 20 mg (73%) of **69**.

SFC: (2*S*,3*R*)-**69,** t_R 14.8 min (94.6%); (2*R*,3*S*)-**69,** t_R 16.5 min (5.4%) (Chiralcel OJ, Gradient 3% MeOH in CO_2 to 8% MeOH in CO_2 over 30 min, 2.5 mL/min, 220 nm, 40 ^{o}C)

Table 4 Entry 2 (–10 ^{o}C) [HMC1081]

Following General Procedure IV, an oven-dried, 5-mm NMR tube was charged with **56** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**83** (3.3 mg, 6.3 μmol, 0.10 equiv), and $CDCl_3$ (500 μL, 0.13 M) and capped. The NMR tube was cooled to –10 ^{o}C in a Cryocool unit and MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added via syringe. The reaction was incomplete at 72 h, whereupon the reaction mixture was quenched.

Purification of the crude product via silica gel flash column chromatography (SiO_2, 5 g, 10 mm Ø , hexanes/EtOAc, 9:1) afforded 23 mg (85%) of **69**.

SFC: (2*S*,3*R*)-**69,** t_R 14.8 min (93.9%); (2*R*,3*S*)-**69,** t_R 16.5 min (6.1%) (Chiralcel OJ, Gradient 3% MeOH in CO_2 to 8% MeOH in CO_2 over 30 min, 2.5 mL/min, 220 nm, 40 ^oC)

Table 4 Entry 3 (0 ^{o}C) [HMC1098]

Following General Procedure IV, an oven-dried, 5-mm NMR tube was charged with **56** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**83** (3.3 mg, 6.3 μmol, 0.10 equiv), and $CDCl_3$ (500 μL, 0.13 M) and capped. The NMR tube was cooled to 0 ^oC in a Cryocool unit and MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added via syringe. The reaction was complete at 48 h, whereupon the reaction mixture was quenched. Purification of the crude product via silica gel flash column chromatography (SiO_2, 5 g, 10 mm Ø , hexanes/EtOAc, 9:1) afforded 25 mg (95%) of **69**.

SFC: (2*S*,3*R*)-**69,** t_R 14.8 min (93.6%); (2*R*,3*S*)-**69,** t_R 16.5 min (6.4%) (Chiralcel OJ, Gradient 3% MeOH in CO_2 to 8% MeOH in CO_2 over 30 min, 2.5 mL/min, 220 nm, 40 ^oC)

Table 4 Entry 4 (5 ^{o}C) [HMC1091]

Following General Procedure IV, an oven-dried, 5-mm NMR tube was charged with **56** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**83** (3.3 mg, 6.3 μmol, 0.10 equiv), and $CDCl_3$ (500 μL, 0.13 M) and capped. The NMR tube was cooled to 5 ^oC in a cold room and MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added via syringe. The reaction was complete at 48 h, whereupon the reaction mixture was quenched. Purification of the crude product via silica gel flash column chromatography (SiO_2, 5 g, 10 mm Ø , hexanes/EtOAc, 9:1) afforded 26 mg (95%) of **69**.

SFC: (2*S*,3*R*)-**69,** t_R 14.8 min (93.0%); (2*R*,3*S*)-**69,** t_R 16.5 min (7.0%) (Chiralcel OJ, Gradient 3% MeOH in CO_2 to 8% MeOH in CO_2 over 30 min, 2.5 mL/min, 220 nm, 40 ^oC)

Table 4 Entry 5 (20 °C) [HMC1096]

Following General Procedure IV, an oven-dried, 5-mm NMR tube was charged with **56** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**83** (3.3 mg, 6.3 μmol, 0.10 equiv), and $CDCl_3$ (500 μL, 0.13 M) and capped. The NMR tube was allowed run at 20 °C (room temperature) in a water bath and MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added via syringe. The reaction was complete at 6 h, but the reaction mixture was quenched at 24 h. Purification of the crude product via silica gel flash column chromatography (SiO_2, 5 g, 10 mm Ø, hexanes/EtOAc, 9:1) afforded 26 mg (96%) of **69**.

SFC: (2*S*,3*R*)-**69,** t_R 14.8 min (91.5%); (2*R*,3*S*)-**69,** t_R 16.5 min (8.5%) (Chiralcel OJ, Gradient 3% MeOH in CO_2 to 8% MeOH in CO_2 over 30 min, 2.5 mL/min, 220 nm, 40 °C)

General Procedure V: Survey of Acid Loadings

An oven-dried, 5-mm NMR tube was charged with **56** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**83** (3.3 mg, 6.3 μmol, 0.10 equiv), and $CDCl_3$ (500 μL, 0.13 M) and capped with a rubber septum cap. After shaking the mixture well making a homogeneous solution, the NMR tube was set to 0 °C in a Cryocool unit. After reaching equilibrium, indicated amount of MsOH was added via syringe. Conversion to product was measured by the appearance of the diagnostic ^{1}H NMR resonance for the piperidine **69** at 5.41 ppm and the pyrrolidine **70** at 4.07 ppm with respect to the substrate peaks at 6.34 ppm and 6.09 ppm. Generally, no other products were observed in the ^{1}H NMR spectra. Formation of phthalimide byproduct was visually confirmed by the precipitation out of the solution. Monitoring by ^{1}H NMR spectroscopy was done at 6 h, 12 h, 24 h, and 72 h, by freezing the NMR tube in a Dewar flask with dry-ice/acetone bath (–78 °C) while transferring to a pre-cooled (–20 °C) NMR instrument. After 48 h, the reaction mixture was quenched by rapidly pouring into 1 mL of sat. $NaHCO_3$ aq solution and the biphasic mixture was extracted with CH_2Cl_2 (1 mL x 3). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* (30 °C, 10 mmHg) to afford the crude product. The ratio of **69** to **70** was determined by analysis with ^{1}H NMR spectroscopy of the reaction mixture and the crude product. The product was purified via silica gel flash column chromatography (SiO_2, 5 g, 10 mm Ø, hexanes/EtOAc, 9:1) prior to SFC analysis.

Acid Loading Study (Table 5)

Table 5 Entry 1 [HMC4069]

Following General Procedure V, an oven-dried, 5-mm NMR tube was charged with **56** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**83** (3.3 mg, 6.3 μmol, 0.10 equiv), and $CDCl_3$ (500 μL, 0.13 M) and capped. The NMR tube was cooled to 0 ^oC in a Cryocool unit and MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) was added via syringe. The ratio of **69** to **70** of the reaction mixture were 97.5:2.5 (76.1% conversion, 6 h), 94.4:5.6 (93.4% conversion, 12 h), 86.4:13.6 (full conversion at 24 h), and of the crude product was 85.7:14.3. Purification of the crude product via silica gel flash column chromatography (SiO_2, 5 g, 10 mm Ø , hexanes/EtOAc, 9:1) gave 22 mg (82%) of **69**.

SFC: (2*S*,3*R*)-**69,** t_R 14.8 min (91.6%); (2*R*,3*S*)-**70,** t_R 16.5 min (8.4%) (Chiralcel OJ, Gradient 3% MeOH in CO_2 to 8% MeOH in CO_2 over 30 min, 2.5 mL/min, 220 nm, 40 ^oC)

Table 5 Entry 2 [HMC4068]

Following General Procedure V, an oven-dried, 5-mm NMR tube was charged with **56** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**83** (3.3 mg, 6.3 μmol, 0.10 equiv), and $CDCl_3$ (500 μL, 0.13 M) and capped. The NMR tube was cooled to 0 ^oC in a Cryocool unit and MsOH (3.1 μL, 0.048 mmol, 0.75 equiv) was added via syringe. The ratio of **69** to **70** of the reaction mixture were 99.2:0.8 (76.9% conversion, 6 h), 99.3:0.7 (93.5% conversion, 12 h), 99.0:1.0 (full conversion at 24 h), and of the crude product was 98.9:1.1. Purification of the crude product via silica gel flash column chromatography (SiO_2, 5 g, 10 mm Ø , hexanes/EtOAc, 9:1) afforded 23 mg (84%) of **69**.

SFC: (2*S*,3*R*)-**69,** t_R 14.8 min (92.9%); (2*R*,3*S*)-**70,** t_R 16.5 min (7.1%) (Chiralcel OJ, Gradient 3% MeOH in CO_2 to 8% MeOH in CO_2 over 30 min, 2.5 mL/min, 220 nm, 40 ^oC)

Table 5 Entry 3 [HMC4067]

Following General Procedure V, an oven-dried, 5-mm NMR tube was charged with **56** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**83** (3.3 mg, 6.3 μmol, 0.10 equiv), and $CDCl_3$ (500 μL, 0.13 M) and capped. The NMR tube was cooled to 0 ^oC in a Cryocool unit and MsOH (2.1 μL, 0.032 mmol, 0.50 equiv) was added via syringe. The ratio of **69** to **70** of the reaction mixture were 99.3:0.7 (73.8% conversion, 6 h), 99.3:0.7 (92.9% conversion, 12 h), 99.2:0.8 (full conversion at 24 h), and of the crude product was 99.2:0.8. Purification of the crude product via silica gel flash column chromatography (SiO_2, 5 g, 10 mm Ø , hexanes/EtOAc, 9:1) afforded 26 mg (96%) of **69**.

SFC: (2*S*,3*R*)-**69,** t_R 14.8 min (93.5%); (2*R*,3*S*)-**70,** t_R 16.5 min (6.5%) (Chiralcel OJ, Gradient 3% MeOH in CO_2 to 8% MeOH in CO_2 over 30 min, 2.5 mL/min, 220 nm, 40 ^oC)

Table 5 Entry 4 [HMC4066]

Following General Procedure V, an oven-dried, 5-mm NMR tube was charged with **56** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**83** (3.3 mg, 6.3 μmol, 0.10 equiv), and $CDCl_3$ (500 μL, 0.13 M) and capped. The NMR tube was cooled to 0 ^oC in a Cryocool unit and MsOH (1.0 μL, 0.016 mmol, 0.25 equiv) was added via syringe. The ratio of **69** to **70** of the reaction mixture were 99.4:0.6 (62.0% conversion, 6 h), 99.4:0.6 (85.0% conversion, 12 h), 99.4:0.6 (97.9% conversion at 24 h), and of the crude product was 99.4:0.6. Purification of the crude product via silica gel flash column chromatography (SiO_2, 5 g, 10 mm Ø , hexanes/EtOAc, 9:1) gave 23 mg (87%) of **69**.

SFC: (2*S*,3*R*)-**69,** t_R 14.8 min (93.6%); (2*R*,3*S*)-**69,** t_R 16.5 min (6.4%) (Chiralcel OJ, Gradient 3% MeOH in CO_2 to 8% MeOH in CO_2 over 30 min, 2.5 mL/min, 220 nm, 40 ^oC)

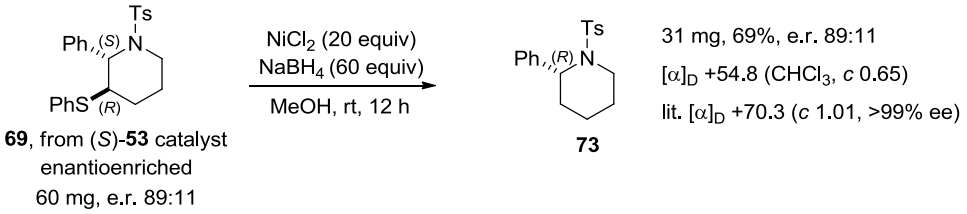
Table 5 Entry 5 [HMC4065]

Following General Procedure V, an oven-dried, 5-mm NMR tube was charged with **56** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**83** (3.3 mg, 6.3 μmol, 0.10 equiv), and $CDCl_3$ (500 μL, 0.13 M) and capped. The NMR tube was cooled to 0 ^oC in a Cryocool unit and MsOH (0.4 μL, 0.0063 mmol, 0.10 equiv) was added via syringe. Since the reaction was incomplete at 24 h, the reaction mixture was quenched at 72 h. The ratio of **69** to **69** of the reaction mixture were (no data points at 6 h, and 12 h due to overlapping) 99.5:0.5 (68.7% conversion, 24 h), 99.3:0.7 (87.2% conversion, 72 h), and of the crude product was 99.3:0.7. Purification of the crude product via silica gel flash column chromatography (SiO_2, 5 g, 10 mm Ø , hexanes/EtOAc, 9:1) gave 21 mg (79%) of **69**.

SFC: (2*S*,3*R*)-**69,** t_R 14.8 min (93.9%); (2*R*,3*S*)-**69,** t_R 16.5 min (6.1%) (Chiralcel OJ, Gradient 3% MeOH in CO_2 to 8% MeOH in CO_2 over 30 min, 2.5 mL/min, 220 nm, 40 ^oC)

Determination of the Absolute Configuration (Scheme 27)

Preparation of (*R*)-2-Phenyl-*N*-(4-toluenesulfonyl)piperidine ((*R*)-48) [HMC1087]



69, from (*S*)-**53** catalyst
enantioenriched
60 mg, e.r. 89:11

73

Following General Procedure II, an oven-dried, 50-mL round-bottomed-flask was charged with a solution of the "*initial*" product **69** (60 mg, 0.14 mmol) in methanol (28 mL, 0.005 M). To the solution was then added $NiCl_2 \cdot 6H_2O$ (673 mg, 2.83 mmol, 20 equiv). The suspension was cooled to 0 ^oC and $NaBH_4$ (322 mg, 8.50 mmol, 60 equiv) was added portion wise. After 12 h of stirring at room temperature, the reaction was quenched and worked up. The crude product was purified via silica gel flash column chromatography (SiO_2, 5 g, 10 mm Ø , hexanes/EtOAc, 9:1) affording 31 mg (69%) of (*R*)-**73** as white solid. The spectroscopic data matched those reported in the literature.[47]

Data for (*R*)-**73**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.76 (d, *J* = 8.5 Hz, 2 H), 7.40 – 7.23 (m, 7 H), 5.27 (d, *J* = 4.5 Hz, 1 H), 3.84 (d, *J* = 14.0 Hz, 1 H), 3.01 (td, *J* = 13.5, and 3.0 Hz, 1 H), 2.44 (s, 3 H), 2.21 (d, *J* = 13.0 Hz, 1 H), 1.71 – 1.62 (m, 1 H), 1.54 – 1.47 (m, 1 H), 1.44 – 1.35 (m, 2 H), 1.34 – 1.24 (m, 2 H).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 142.9, 138.9, 138.7, 129.6, 128.5, 127.00, 126.96, 126.7, 55.2, 41.8, 27.2, 24.3, 21.5, 18.9.

MS: (EI)

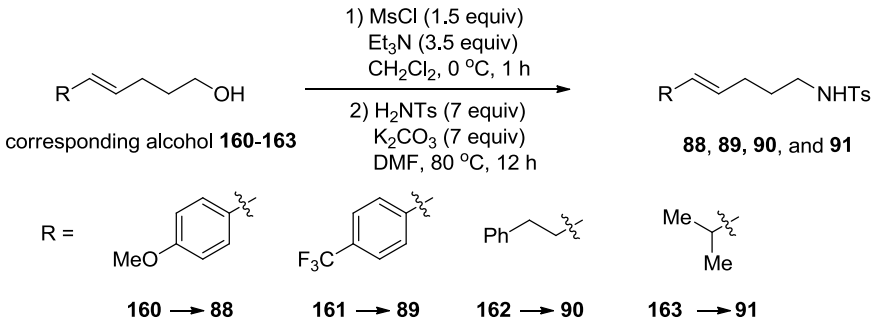
315 (M+), 238 (100), 207 (19), 161 (18), 160 (81), 159 (52), 91 (65).

Opt Rot. : $[\alpha]_D^{24}$ +54.8 (c = 0.65, $CHCl_3$, 89:11 er.)

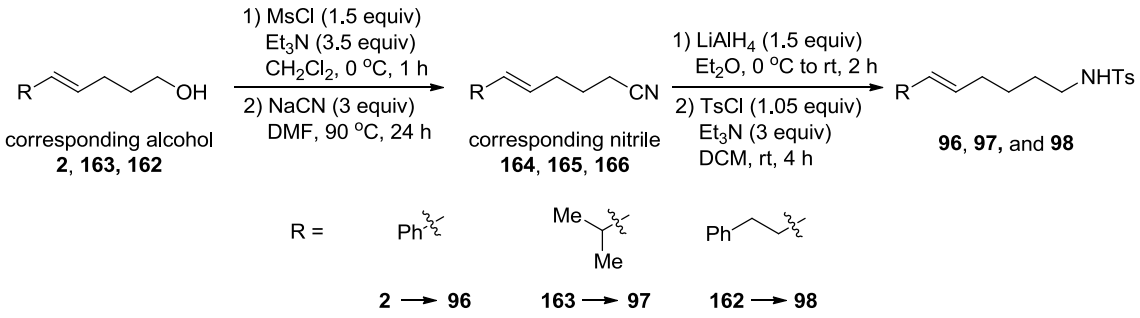
Substrate Preparation (Scheme 28 – 30)

Compounds **56**,[42c] **92**,[42c] **93**,[118] **94**,[42a] and **99**[42b] were prepared according to literature procedures.

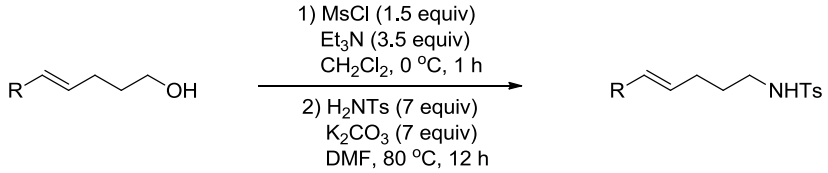
Compounds **88**, **89**, **90**, and **91** were prepared by following an established procedure for sequential mesylation and tosylamine substitution[42] of the corresponding precursor alcohols **160**,[119] **161**,[120] **162**,[38] and **163**,[121] respectively (See General Procedure VI). The corresponding alcohols were prepared according to literature procedures.



Compounds **96**, **97**, and **98** were prepared by sequential mesylation,[42] nitrile substitution,[130] reduction,[42] and tosylation[42] of the corresponding precursor alcohols **2**,[120] **163**,[121] and **162**,[38] respectively (See General Procedure VII). The corresponding alcohols were prepared according to literature procedures.



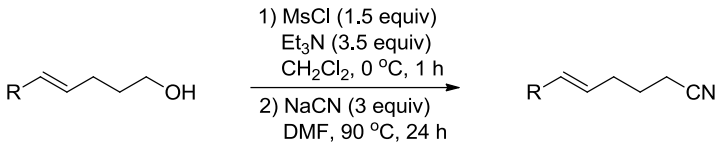
General Procedure VI: Substrate Preparation I



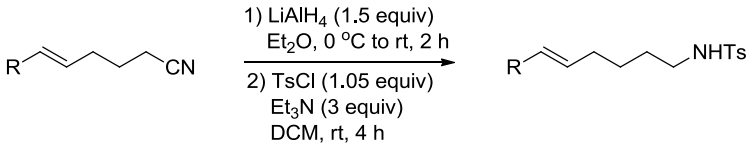
An oven-dried, 50-mL Schlenk flask equipped with a magnetic stir bar, a septum, and a argon inlet were charged with a solution of alcohol (2.0 mmol, 1 equiv) in CH_2Cl_2 (20 mL), and Et_3N (0.98 mL, 7.0 mmol, 3.5 equiv) dropwise via syringe. The solution was cooled to 0 ^oC (internal temperature), and to the flask was added methanesulfonyl chloride (232 μL, 3.0 mmol, 1.5 equiv) via syringe. After stirring for 1 h at 0 ^oC, the reaction solution was quenched by slowly addition of water (20 mL) over 5 min. The resulting biphasic mixture was extracted with CH_2Cl_2 (20 mL x 3). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* (40 ^oC, 10 mmHg) to afford the crude mesylate. The crude mesylate was directly dissolved in DMF (20 mL) and transferred to an oven-dried, 50-mL round-bottomed-flask. To the flask were added K_2CO_3 (1.93 g, 14.0 mmol, 7 equiv) and *p*-toluenesulfonamide (2.40 g, 14.0 mmol, 7 equiv) and equipped with a reflux condenser. The suspension was heated to 80 ^oC (internal temperature) and stirred for 12 h. Upon reaction completion monitored by TLC, the suspension was cooled to 0 ^oC (internal temperature) and quenched by adding 2 M HCl (20 mL) dropwise. The resulting mixture was extracted with Et_2O (20 mL x 5). The combined

organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* (80 ^oC, 10 mmHg) to afford the crude product. The crude product was purified via silica gel flash column chromatography (SiO_2, 15 g, 20 mm Ø , toluene/EtOAc, 9:1 to 4:1).

General Procedure VII: Substrate Preparation II

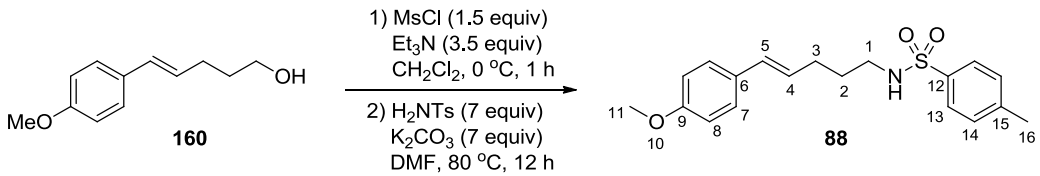


An oven-dried, 250-mL Schlenk flask equipped with a magnetic stir bar, a septum, and a argon inlet were charged with a solution of alcohol (10.0 mmol, 1 equiv) in CH_2Cl_2 (100 mL), and Et_3N (4.88 mL, 35.0 mmol, 3.5 equiv) dropwise via syringe. The solution was cooled to 0 ^oC (internal temperature), to the flask was added methanesulfonyl chloride (1.16 mL, 15.0 mmol, 1.5 equiv) via syringe. After stirring for 1 h at 0 ^oC, the reaction solution was quenched by slowly adding water (100 mL) over 10 min. The resulting biphasic mixture was extracted with CH_2Cl_2 (100 mL x 3). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* (40 ^oC, 10 mmHg) to afford the crude product. Purification via silica gel flash column chromatography (SiO_2, 30 g, 30 mm Ø , hexanes/EtOAc, 9:1) afforded mesylate as a colorless oil. Then to an oven-dried, 250-mL round-bottomed-flask were added a solution of the resulted mesylate (1 equiv) in DMF (100 mL) and NaCN (3 equiv) as a solid in one portion. The flask was equipped with a reflux condenser and heated to 90 ^oC (internal temperature) and stirred for 24 h. Upon reaction completion monitored by TLC, the suspension was cooled to 0 ^oC (internal temperature) and quenched by adding water pre-cooled to 0 ^oC (50 mL) dropwise. The resulting mixture was extracted with Et_2O (100 mL x 5). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* (80 ^oC, 10 mmHg) to afford the crude nitrile. Purification via silica gel flash column chromatography (SiO_2, 30 g, 30 mm Ø , hexanes/EtOAc, 19:1) afforded nitrile.



An oven-dried, 100-mL Schlenk flask equipped with a magnetic stir bar was charged with $LiAlH_4$ (285 mg, 7.5 mmol, 1.5 equiv) and capped with a septum under argon. The flask was immersed in an ice-bath and was added Et_2O (10 mL). To the resulting suspension was added a solution of nitrile (5.0 mmol, 1 equiv) in Et_2O (7 mL) via syringe over 10 min at 0 ^oC (internal temperature). After addition was complete, the suspension was warmed to room temperature and stirred for 2 h. Upon reaction completion monitored by TLC, the suspension was cooled to 0 ^oC (internal temperature) and quenched by slow addition of 1 M NaOH (5 mL) dropwise. The resulting slurry was filtered through a pad of Celite (5 g, 35 mm) and concentrated *in vacuo* (23 ^oC, 10 mmHg). The resulting amine was then acidified by addition of 2 M HCl in Et_2O (2.5 mL, 5 mmol, 1 equiv) to afford the corresponding amine·HCl salt, which was thoroughly dried *in vacuo* (23 ^oC, 0.1 mmHg). Then an oven-dried, 50-mL Schlenk flask equipped with a magnetic stir bar were charged with amine·HCl salt (5.0 mmol, 1 equiv), CH_2Cl_2 (10 mL), and Et_3N (2.09 mL, 15.0 mmol, 3 equiv) and capped with a septum under argon. The solution was cooled to 0 ^oC (internal temperature) and was added a solution of *p*-toluenesulfonyl chloride (1.00 g, 5.25 mmol, 1.05 equiv) in CH_2Cl_2 (7 mL) via syringe. The solution was warmed to room temperature and was stirred for 4 h. Upon reaction completion monitored by TLC, the mixture was cooled to 0 ^oC (internal temperature) and quenched by adding 1 M HCl (15 mL) dropwise. The resulting biphasic mixture was extracted with CH_2Cl_2 (20 mL x 3). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* (23 ^oC, 10 mmHg) to afford the crude product. Purification via silica gel flash column chromatography (SiO_2, 15 g, 20 mm Ø , hexanes/EtOAc, 9:1 to 4:1) afforded the homologated tosylamine.

Preparation of (*E*)-*N*-(4-Toluenesulfonyl)-5-(4-methoxyphenyl)pent-4-enylamine (88) [HMC2023, HMC2024]



Following General Procedure VI, an oven-dried, 50-mL Schlenk flask equipped with a magnetic stir bar, a septum, and a argon inlet were charged with a solution of alcohol **160**[119] (443 mg, 2.3 mmol, 1 equiv) in CH_2Cl_2 (23 mL), and Et_3N (1.12 mL, 8.07 mmol, 3.5 equiv). After cooled to 0 ^oC, to the flask was added methanesulfonyl chloride (268 μL, 3.46 mmol, 1.5 equiv) via syringe. After stirring for 1 h at 0 ^oC, the reaction solution was quenched. After the work-up, the crude mesylate (604 mg, 2.23 mmol) was dissolved in DMF (22 mL) and transferred to an oven-dried, 50-mL round-bottomed-flask. To the flask were added K_2CO_3 (2.16 g, 15.6 mmol, 7 equiv) and *p*-toluenesulfonamide (2.68 g, 15.6 mmol, 7 equiv) and equipped with a reflux condenser. The suspension was heated to 80 ^oC (internal temperature) and stirred for 12 h. Upon reaction completion, the suspension was cooled to 0 ^oC and quenched. Purification via silica gel flash column chromatography (SiO_2, 15 g, 20 mm Ø, toluene/EtOAc, 9:1 to 4:1) afforded 664 mg (86% over two steps from **160**) of **88** as a white solid.

Data for **88**:

mp: 99-100 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.76 (d, *J* = 8.0 Hz, 2 H, HC(13)), 7.31 (d, *J* = 8.5 Hz, 2 H, HC(14)), 7.24 (d, *J* = 8.5 Hz, 2 H, (HC(7)), 6.85 (d, *J* = 8.5 Hz, 2 H, HC(8)), 6.29 (d, *J* = 16.0 Hz, 1 H, HC(5)), 5.95 (dt, *J* = 15.5, and 7.0 Hz, 1 H, HC(4)), 4.47 (br, 1 H, HN), 3.82 (s, 3 H, HC(11)), 3.01 (q, *J* = 7.0 Hz, 2 H, HC(1)), 2.44 (s, 3 H, HC(16)), 2.20 (q, *J* = 7.0 Hz, 2 H, HC(3)), 1.66 (p, *J* = 7.0 Hz, 2 H, HC(2)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 158.8 (C(9)), 143.4 (C(12)), 136.9 (C(15)), 130.3 (C(5)), 130.1 (C(6)), 129.7 (C(14)), 127.1 (C(7/13)), 126.6 (C(4)), 113.9 (C(8)), 55.3 (C(11)), 42.6 (C(1)), 29.8

(C(3)), 29.3 (C(2)), 21.5 (C(16)).

IR: (Neat)

3247 (w), 1605 (w), 1511 (m), 1436 (w), 1323 (m), 1305 (m), 1288 (w), 1247 (s), 1166 (s), 1155 (s), 1095 (m), 1070 (m), 1059 (m), 1024 (m), 969 (s), 910 (m), 872 (w), 834 (m), 815 (s), 797 (m), 762 (w).

MS: (ESI)

175 (35), 346 (M+H, 100), 347 (25), 362 (12), 363 (25), 368 (17)

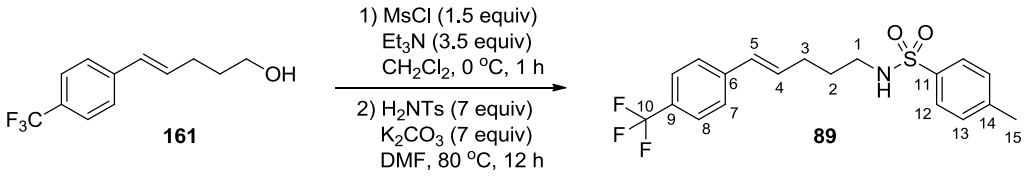
HRMS: (ESI) calcd for $C_{19}H_{24}NO_3S$ ($M+H^+$): 346.1477, found: 346.1461

TLC: R_f 0.39 (hexanes/EtOAc, 3:2) [UV/$KMnO_4$]

Analysis: $C_{19}H_{23}NO_3S$ (345.46)

Calcd:	C, 66.06;	H, 6.71%	N, 4.05%
Found:	C, 65.74;	H, 6.68%	N, 4.03%

Preparation of (*E*)-*N*-(4-Toluenesulfonyl)-5-(4-trifluoromethylphenyl)pent-4-enylamine (89) [HMC2031, HMC2032]



Following General Procedure VI, an oven-dried, 50-mL Schlenk flask equipped with a magnetic stir bar, a septum, and a argon inlet were charged with a solution of alcohol **161**[120] (460 mg, 2.0 mmol, 1 equiv) in CH_2Cl_2 (20 mL), and Et_3N (0.98 mL, 7.0 mmol, 3.5 equiv). After cooled to 0 °C, to the flask was added methanesulfonyl chloride (232 μL, 3.0 mmol, 1.5 equiv) via syringe. After stirring for 1 h at 0 °C, the reaction solution was quenched. After the work-up, the crude mesylate was dissolved in DMF (20 mL) and transferred to an oven-dried, 50-mL round-bottomed-flask. To the flask were added K_2CO_3 (1.93 g, 14.0 mmol, 7 equiv) and *p*-toluenesulfonamide (2.40 g, 14.0 mmol, 7 equiv) and equipped with a reflux condenser. The suspension was heated to 80 °C (internal temperature) and stirred for 12 h. Upon reaction completion, the suspension was cooled to 0 °C and quenched. Purification via silica gel flash

column chromatography (SiO_2, 15 g, 20 mm Ø , toluene/EtOAc, 9:1 to 4:1) afforded 659 mg (86% over two steps from **161**) of **89** as a white solid.

Data for **89**:

mp: 116-117 °C

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.76 (d, *J* = 8.0 Hz, 2 H, HC(12)), 7.54 (d, *J* = 8.5 Hz, 2 H, HC(8)), 7.39 (d, *J* = 8.0 Hz, 2 H, HC(7)), 7.30 (d, *J* = 8.5 Hz, 2 H, HC(13)), 6.38 (d, *J* = 16.0 Hz, 1 H, HC(5)), 6.21 (dt, *J* = 16.0, and 7.0 Hz, 1 H, HC(4)), 4.48 (t, *J* = 6.0 Hz, 1 H, HN), 3.01 (q, *J* = 7.0 Hz, 2 H, HC(1)), 2.42 (s, 3 H, HC(15)), 2.26 (q, *J* = 7.0 Hz, 2 H, HC(3)), 1.69 (p, *J* = 7.0 Hz, 2 H, HC(2)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 143.4 (C(11)), 140.8 (C(6)), 136.9 (C(14)), 131.8 (C(4)), 129.8 (C(5)), 129.7 (C(13)), 128.9 (q, *J* = 32 Hz, C(9)), 127.1 (C(12)), 126.1 (C(7)), 125.4 (q, *J* = 3.8 Hz, C(8)), 124.2 (q, *J* = 272 Hz, C(10)), 42.5 (C(1)), 29.8 (C(3)), 29.0 (C(2)), 21.5 (C(15)).

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -62.90

IR: (Neat)

3237 (w), 1613 (w), 1416 (w), 1319 (s), 1305 (m), 1288 (m), 1156 (s), 1114 (s), 1100 (s), 1068 (s), 1035 (m), 1016 (m), 971 (m), 910 (m), 871 (m), 851 (m), 833 (m), 815 (s), 801 (m).

MS: (ESI)

364 (28), 384 (M+H, 100), 385 (26), 401 (50), 406 (19)

HRMS: (ESI) calcd for $C_{19}H_{21}F_3NO_2S$ ($M+H^+$): 384.1245, found: 384.1236

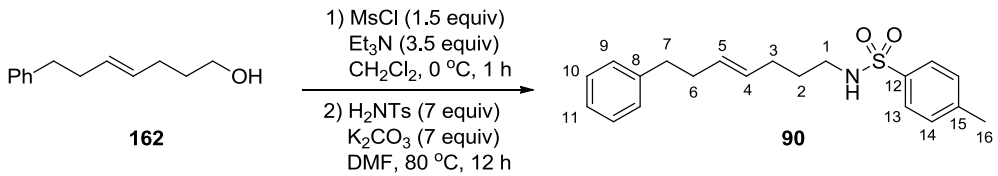
TLC: R_f 0.43 (hexanes/EtOAc, 3:2) [UV/$KMnO_4$]

Analysis: $C_{19}H_{20}F_3NO_2S$ (383.43)

Calcd: C, 59.52; H, 5.26% N, 3.65%

Found: C, 59.80; H, 5.32% N, 3.54%

Preparation of (*E*)-*N*-(4-Toluenesulfonyl)-7-phenylhept-4-enylamine (90) [HMC3028, HMC3029]



Following General Procedure VI, an oven-dried, 50-mL Schlenk flask equipped with a magnetic stir bar, a septum, and a argon inlet were charged with a solution of alcohol **162**[38] (381 mg, 2.0 mmol, 1 equiv) in CH_2Cl_2 (20 mL), and Et_3N (0.98 mL, 7.0 mmol, 3.5 equiv). After cooled to 0 ^oC, to the flask was added methanesulfonyl chloride (232 μL, 3.0 mmol, 1.5 equiv) via syringe. After stirring for 1 h at 0 ^oC, the reaction solution was quenched. After the work-up, the crude mesylate was dissolved in DMF (20 mL) and transferred to an oven-dried, 50-mL round-bottomed-flask. To the flask were added K_2CO_3 (1.93 g, 14.0 mmol, 7 equiv) and *p*-toluenesulfonamide (2.40 g, 14.0 mmol, 7 equiv) and equipped with a reflux condenser. The suspension was heated to 80 ^oC (internal temperature) and stirred for 12 h. Upon reaction completion, the suspension was cooled to 0 ^oC and quenched. Purification via silica gel flash column chromatography (SiO_2, 15 g, 20 mm Ø , toluene/EtOAc, 9:1 to 4:1) afforded 577 mg (84% over two steps from **162**) of **90** as a colorless oil.

Data for **90**:

bp: 165 ℃ at 3 x 10^{-5} mm Hg

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.75 (d, *J* = 8.0 Hz, 2 H, HC(13)), 7.32 (d, *J* = 8.0 Hz, 2 H, HC(14)), 7.27 (t, *J* = 7.5 Hz, 3 H, HC(10)), 7.19 (d, *J* = 7.0 Hz, 1 H, HC(11)), 7.16 (d, *J* = 7.0 Hz, 2 H, HC(9)), 5.41 (dt, *J* = 15.0, and 7.0 Hz, 1 H, HC(5)), 5.31 (dt, *J* = 15.0, and 7.0 Hz, 1 H, HC(4)), 4.34 (brs, 1 H, HN), 2.91 (t, *J* = 7.0 Hz, 2 H, HC(1)), 2.64 (t, *J* = 7.5 Hz, 2 H, HC(7)), 2.43 (s, 3 H, HC(16)), 2.28 (q, *J* = 7.5 Hz, 2 H, HC(6)), 1.97 (q, *J* = 7.0 Hz, 2 H, HC(3)), 1.51 (p, *J* = 7.0 Hz, 2 H, HC(2)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 143.3 (C(12)), 141.9 (C(8)), 137.0 (C(15)), 130.8 (C(5)), 129.7 (C(14)), 129.2

(C(4)), 128.4 (C(9)), 128.2 (C(10)), 127.1 (C(13)), 125.7 (C(11)), 42.6 (C(1)), 35.9 (C(7)), 34.3 (C(6)), 29.4 (C(3)), 29.2 (C(2)), 21.5 (C(16)).

IR: 3289 (m), 2926 (m), 1496 (m), 1455 (s), 1430 (m), 1416 (m), 1337 (s), 1158 (m), 1093 (m), 970 (m), 815 (m).

MS: (ESI)

173 (45), 344 (M+H, 100), 345 (24), 361 (16), 366 (25), 382 (12)

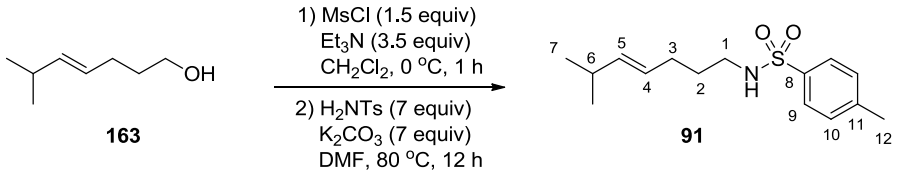
HRMS: (ESI) calcd for $C_{20}H_{26}NO_2S$ ($M+H^+$): 344.1684, found: 344.1676

TLC: R_f 0.50 (hexanes/EtOAc, 3:2) [UV/$KMnO_4$]

Analysis: $C_{20}H_{25}NO_2S$ (343.48)

Calcd:	C, 69.93;	H, 7.34%	N, 4.08%
Found:	C, 69.90;	H, 7.42%	N, 4.25%

Preparation of (*E*)-*N*-(4-Toluenesulfonyl)-6-methylhept-4-enylamine (91) [HMC2058, HMC2059]



Following General Procedure VI, an oven-dried, 100-mL Schlenk flask equipped with a magnetic stir bar, a septum, and a argon inlet were charged with a solution of alcohol **163**[121] (600 mg, 4.68 mmol, 1 equiv) in CH_2Cl_2 (47 mL), and Et_3N (2.28 mL, 16.4 mmol, 3.5 equiv). After cooled to 0 °C, to the flask was added methanesulfonyl chloride (543 μL, 7.02 mmol, 1.5 equiv) via syringe. After stirring for 1 h at 0 °C, the reaction solution was quenched. After the work-up, the crude mesylate was dissolved in DMF (49 mL) and transferred to an oven-dried, 100-mL round-bottomed-flask. To the flask were added K_2CO_3 (4.34 g, 31.4 mmol, 7 equiv) and *p*-toluenesulfonamide (5.38 g, 31.4 mmol, 7 equiv) and equipped with a reflux condenser. The suspension was heated to 80 °C (internal temperature) and stirred for 12 h. Upon reaction completion, the suspension was cooled to 0 °C and quenched. Purification via silica gel flash column chromatography (SiO_2, 120 g, 35 mm Ø , toluene/EtOAc, 9:1 to 4:1) afforded 1.02 g (81% over two steps from **163**) of **91** as a colorless oil.

Data for **91**:

bp: decomposed at 150 °C, 2.5 x 10^{-5} mm Hg

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.76 (d, *J* = 8.0 Hz, 2 H, HC(9)), 7.31 (d, *J* = 8.0 Hz, 2 H, HC(10)), 5.32 (dd, *J* = 15.5, and 6.5 Hz, 1 H, HC(5)), 5.23 (dt, *J* = 15.5, and 6.5 Hz, 1 H, HC(4)), 4.74 (t, *J* = 6.0 Hz, 1 H, HN), 2.92 (q, *J* = 6.5 Hz, 2 H, HC(1)), 2.43 (s, 3 H, HC(12)), 2.18 (hept, *J* = 7.0 Hz, 1 H, HC(6)), 1.95 (q, *J* = 7.0 Hz, 2 H, HC(3)), 1.52 (p, *J* = 7.0 Hz, 2 H, HC(2)), 0.92 (d, *J* = 7.0 Hz, 6 H, HC(7)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 143.2 (C(8)), 138.9 (C(5)), 137.0 (C(11)), 129.6 (C(10)), 127.1 (C(9)), 125.3 (C(4)), 42.6 (C(1)), 30.9 (C(6)), 29.4 (C(3)), 29.2 (C(2)), 22.5 (C(7)), 21.5 (C(12)).

IR: 3289 (m), 3024 (w), 2958 (m), 2869 (m), 1456 (m), 1324 (s), 1216 (w), 1159 (s), 1094 (s), 971 (m), 814 (m), 757 (s).

MS: (ESI)

184 (21), 224 (38), 238 (16), 280 (71), 282 (M+H, 100), 283 (22), 296 (14), 299 (13), 304 (10), 331 (51), 336 (20)

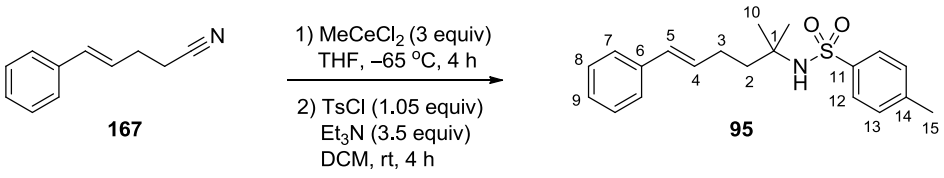
HRMS: (ESI) calcd for $C_{15}H_{24}NO_2S$ ($M+H^+$): 282.1528, found: 282.1520

TLC: R_f 0.53 (hexanes/EtOAc, 3:2) [UV/$KMnO_4$]

Analysis: $C_{15}H_{23}NO_2S$ (281.41)

Calcd:	C, 64.02;	H, 8.24%	N, 4.98%
Found:	C, 63.91;	H, 8.09%	N, 4.94%

Preparation of (*E*)-*N*-(4-Toluenesulfonyl)-1,1-dimethyl-5-phenylpent-4-enylamine (95) [HMC4080, HMC5023]



Following a reported procedure for addition of organocerium reagents to nitriles,[53] an flame-dried, three-necked, 50-mL Schlenk flask equipped with a magnetic stir bar, two glass stopper, and a argon inlet was charged with finely ground $CeCl_3 \cdot 7H_2O$ (4.02 g, 10.8 mmol, 3 equiv). $CeCl_3 \cdot 7H_2O$ was dried by following a reported process.[131] After purging with argon, the flask was cooled to 0 ^oC (external temperature) and was added anhydrous THF (21 mL). The white suspension was warmed to room temperature and stirred for 2 h. The suspension was cooled to -72 ^oC (internal temperature) in a dry-ice/*i*-PrOH bath and was added a solution of MeLi (1.61 M in Et_2O, 6.68 mL, 10.8 mmol, 3 equiv), whereupon the suspension turned yellow. After stirring for 30 min at -72 ^oC, the flask was transferred to a cold bath (-65 ^oC), controlled with a Cryocool unit. To the flask was added a solution of nitrile **167**[42b] (565 mg, 3.6 mmol, 1 equiv, pre-cooled to -65 ^oC) in THF (6 mL) via cannula at -65 ^oC (internal temperature). After 4 h, the reaction was complete, and the reaction solution was quenched by adding concentrated NH_4OH solution (6.5 mL) dropwise at -65 ^oC. The resulting mixture was warmed to room temperature and was filtered through a pad of Celite (5 g, 35 mm), rinsed thoroughly with CH_2Cl_2 (50 mL). The filtrate was dried over $NaSO_4$, filtered, and concentrated *in vacuo* (50 ^oC, 10 mmHg) to afford crude oil. The crude oil was dissolved in toluene (20 mL) and was added a solution of H_3PO_4 (3%, 20 mL) and was stirred for 15 min. The organic layer was separated from the aqueous layer, and was added concentrated NH_4OH solution (20 mL). The biphasic mixture was extracted with CH_2Cl_2 (20 mL x 5), dried over $NaSO_4$, filtered, and concentrated *in vacuo* (70 ^oC, 10 mmHg) to afford crude amine. Then an oven-dried, 50-mL Schlenk flask equipped with a magnetic stir bar were charged with the amine (680 mg, 3.59 mmol, 1 equiv), CH_2Cl_2 (12 mL), and Et_3N (1.75 mL, 12.6 mmol, 3.5 equiv) and capped with a septum under argon. The solution was cooled to 0 ^oC (internal temperature) and was added a solution of *p*-toluenesulfonyl chloride (754 mg, 3.95 mmol, 1.1 equiv) in CH_2Cl_2 (2 mL) via syringe. The solution was warmed to room temperature and was stirred for 24 h. Upon reaction completion monitored by TLC, the solution was cooled to 0 ^oC (internal temperature) and quenched by adding 1 M HCl (10 mL) dropwise. The resulting biphasic mixture was extracted with CH_2Cl_2 (10 mL x 3). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* (23 ^oC, 10 mmHg) to afford the crude product. Purification via silica gel flash column chromatography (SiO_2, 15 g, 20 mm Ø, hexanes/EtOAc, 9:1 to 4:1) afforded 1.04 g (84%) the tosylamine **95** as white solid.

Data for **95**:

mp: 111-112 ℃

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.80 (d, *J* = 8.5 Hz, 2 H, HC(12)), 7.32 – 7.27 (m, 6 H, HC(7,8,13)), 7.24 – 7.18 (m, 1 H, HC(9)), 6.32 (d, *J* = 16.0 Hz, 1 H, HC(5)), 6.08 (dt, *J* = 16.0, and 7.0 Hz, 1 H, HC(4)), 4.64 (brs, 1 H, HN), 2.42 (s, 3 H, HC(15)), 2.23 – 2.17 (m, 2 H, HC(3)), 1.70 – 1.65 (m, 2 H, HC(2)), 1.23 (s, 6 H, HC(10)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 142.9 (C(11)), 140.5 (C(14)), 137.6 (C(6)), 137.2 (C(5)), 129.8 (C(4)), 129.5 (C(13)), 128.5 (C(8)), 127.0 (C(12)), 126.9 (C(9)), 125.9 (C(7)), 57.0 (C(1)), 42.2 (C(2)), 27.8 (C(10)), 27.6 (C(3)), 21.5 (C(15)).

IR: (Neat)

3296 (w), 2920 (w), 1426 (w), 1321 (m), 1220 (w), 1149 (s), 1089 (m), 1019 (w), 991 (m), 966 (m), 867 (w), 847 (w), 819 (m), 742 (m).

MS: (ESI)

117 (14), 173 (82), 174 (16), 344 (M+H, 100), 345 (25), 361 (100), 362 (27), 366 (18)

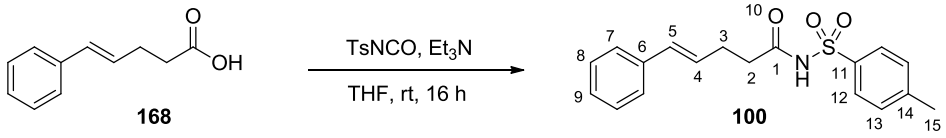
HRMS: (ESI) calcd for $C_{20}H_{26}NO_2S$ ($M+H^+$): 344.1684, found: 344.1683

TLC: R_f 0.51 (hexanes/EtOAc, 3:2) [UV/$KMnO_4$]

Analysis: $C_{20}H_{25}NO_2S$ (343.48)

Calcd:	C, 69.93;	H, 7.34%	N, 4.08%
Found:	C, 69.98;	H, 7.40%	N, 4.28%

Preparation of (*E*)-*N*-(4-Toluenesulfonyl)-5-phenylpent-4-enamide (100)[54] [HMC2082]



An oven-dried, 25-mL Schlenk flask equipped with a magnetic stir bar, a septum, and a argon inlet were charged with a solution of carboxylic acid **168**[132] (352 mg, 2.0 mmol, 1 equiv) in THF (7 mL), and Et_3N (558 μL, 4.0 mmol, 2 equiv). After stirring 5 min at room temperature,

to the flask was added *p*-toluenesulfonyl isocyanate (321 μL, 2.1 mmol, 1.05 equiv) dropwise via syringe with observation of gas evolution. After stirring for 16 h at room temperature, the reaction was complete monitored by TLC. The reaction mixture was cooled to 0 ^{o}C (internal temperature) and was added 2 M HCl (7 mL) to quench the reaction. Resulting biphasic mixture was extracted with Et_2O (7 mL x 3). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo* (50 ^{o}C, 10 mmHg) to afford the crude product. Purification via silica gel flash column chromatography (SiO_2, 15 g, 20 mm Ø , toluene/EtOAc, 3:1) afforded 593 mg (90%) of **100** as white solid.

Data for **100**:

mp: 113-114 ℃

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 8.42 (brs, 1 H, HN), 7.93 (d, *J* = 8.0 Hz, 2 H, HC(12)), 7.33 – 7.20 (m, 7 H, HC(7,8,9,13)), 6.33 (d, *J* = 16.0 Hz, 1 H, HC(5)), 6.07 (dt, *J* = 16.0, and 6.5 Hz, 1 H, HC(4)), 2.51 – 2.42 (m, 4 H, HC(2,3)), 2.42 (s, 3 H, HC(15)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 170.3 (C(1)), 145.1 (C(11)), 137.0 (C(6)), 135.4 (C(14)), 131.5 (C(5)), 129.6 (C(13)), 128.4 (C(8)), 128.2 (C(12)), 127.3 (C(4)), 127.2 (C(9)), 126.1 (C(7)), 35.9 (C(2)), 27.6 (C(3)), 21.6 (C(15)).

IR: (Neat)

3290 (w), 1719 (s), 1594 (w), 1433 (m), 1415 (m), 1373 (w), 1335 (m), 1187 (w), 1169 (s), 1118 (m), 1082 (s), 1042 (w), 1019 (w), 959 (m), 859 (s), 848 (m), 815 (s), 774 (w).

MS: (ESI)

158 (22), 330 (M+H, 100), 331 (24), 347 (20), 352 (21)

HRMS: (ESI) calcd for $C_{18}H_{20}NO_3S$ ($M+H^+$): 330.1164, found: 330.1166

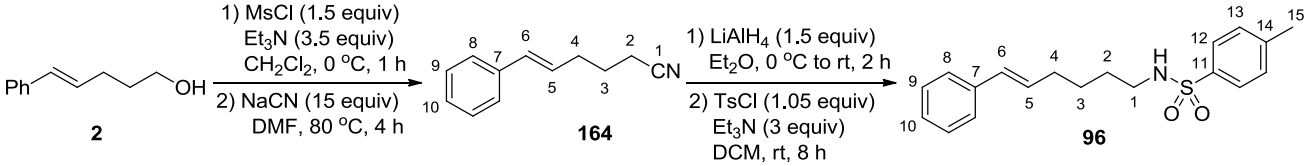
TLC: R_f 0.27 (hexanes/EtOAc, 3:2) [UV/$KMnO_4$]

Analysis: $C_{18}H_{19}NO_3S$ (329.41)

Calcd: C, 65.63; H, 5.81% N, 4.25%

Found: C, 65.33; H, 5.84% N, 4.30%

Preparation of (*E*)-*N*-(4-Toluenesulfonyl)-6-phenylpent-5-enylamine (96) [HMC5060, HMC5061, HMC5062, HMC5063]



Following General Procedure VII, an oven-dried, 250-mL Schlenk flask equipped with a magnetic stir bar, a septum, and a argon inlet were charged with a solution of alcohol **2**[120] (2.43 g, 15.0 mmol, 1 equiv) in CH_2Cl_2 (150 mL), and Et_3N (7.32 mL, 52.5 mmol, 3.5 equiv). The solution was cooled to 0 °C, to the flask was added methanesulfonyl chloride (1.74 mL, 22.5 mmol, 1.5 equiv). After stirring for 1 h at 0 °C, the reaction was quenched. Purification via silica gel flash column chromatography (SiO_2, 30 g, 30 mm Ø, hexanes/EtOAc, 9:1) afforded 3.16 g (88%) of mesylate as a colorless oil. Then to an oven-dried, 250-mL round-bottomed-flask were added a solution of the resulted mesylate (3.16 g, 13.1 mmol, 1 equiv) in DMF (44 mL) and NaCN (9.67 g, 197 mmol, 15 equiv) as a solid in one portion. The flask was equipped with a reflux condenser and heated to 80 °C and stirred for 4 h. Upon reaction completion the reaction was quenched. Purification via silica gel flash column chromatography (SiO_2, 30 g, 30 mm Ø, hexanes/EtOAc, 19:1) afforded 1.92 g (86%) of nitrile **164** as a colorless oil. The ^{1}H NMR spectroscopic data matched those reported in the literature.[133]

Data for **164**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.42 – 7.25 (m, 5 H), 6.49 (d, *J* = 16.0 Hz, 1 H), 6.15 (dt, *J* = 16.0, and 7.0 Hz, 1 H), 2.45 – 2.37 (m, 4 H), 1.86 (qt, *J* = 7.0 Hz, 2 H).

An oven-dried, 100-mL Schlenk flask equipped with a magnetic stir bar was charged with $LiAlH_4$ (569 mg, 15.0 mmol, 1.5 equiv) and capped with a septum under argon. The flask was immersed in an ice-bath and was added Et_2O (26 mL). To the resulting suspension was added a solution of nitrile **164**[133] (1.71 g, 10.0 mmol, 1 equiv) in Et_2O (7 mL). The suspension was warmed to room temperature and stirred for 2 h. The reaction was quenched upon completion, and acidified to afford the corresponding amine·HCl salt. Then an oven-dried, 50-

mL Schlenk flask equipped with a magnetic stir bar was charged with amine·HCl salt (1.47 g, approx. 8.39 mmol, 1 equiv), CH_2Cl_2 (21 mL), and Et_3N (3.51 mL, 25.2 mmol, 3 equiv). To the solution was added a solution of *p*-toluenesulfonyl chloride (1.68 g, 8.81 mmol, 1.05 equiv) in CH_2Cl_2 (7 mL) at 0 ^oC. The solution was warmed to room temperature and was stirred for 8 h. The reaction was quenched upon completion. Purification via silica gel flash column chromatography (SiO_2, 30 g, 30 mm Ø, hexanes/EtOAc, 9:1 to 4:1) afforded 2.63 g (80% over two steps from **164**) of the homologated tosylamine **96** as white solid. The ^1H NMR spectroscopic data matched those reported in the literature.[42a]

Data for **96**:

mp: 61-62 ℃

^1H NMR: (500 MHz, $CDCl_3$)

δ 7.76 (d, *J* = 8.5 Hz, 2 H, HC(12)), 7.34 – 7.28 (m, 6 H, HC(8,9,13)), 7.23 – 7.19 (m, 1 H, HC(10)), 6.34 (d, *J* = 16.0 Hz, 1 H, HC(6)), 6.13 (dt, *J* = 16.0, and 7.0 Hz, 1 H, HC(5)), 4.61 (brt, *J* = 5.5 Hz, 1 H, HN), 2.97 (q, *J* = 6.5 Hz, 2 H, HC(1)), 2.42 (s, 3 H, HC(15)), 2.17 (q, *J* = 7.0 Hz, 2 H, HC(4)), 1.56 – 1.42 (m, 4 H, HC(2,3)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 143.3 (C(11)), 137.5 (C(7)), 136.9 (C(14)), 130.3 (C(5)), 129.9 (C(4)), 129.6 (C(13)), 128.4 (C(9)), 127.0 (C(12)), 126.9 (C(10)), 125.9 (C(8)), 43.0 (C(1)), 32.3 (C(4)), 29.0 (C(2)), 26.1 (C(3)), 21.5 (C(15)).

IR: (Neat)

3255 (w), 2944 (w), 1495 (w), 1421 (w), 1321 (s), 1290 (w), 1159 (s), 1094 (m), 1067 (w), 968 (m), 911 (w), 872 (w), 820 (m), 741 (m).

MS: (ESI)

330 (M+H, 100), 331 (23), 347 (12), 352 (17)

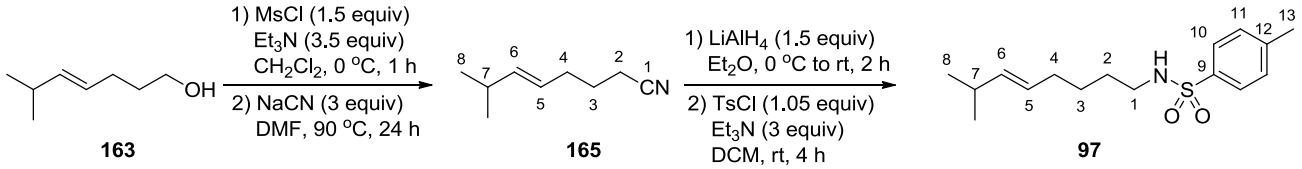
HRMS: (ESI) calcd for $C_{19}H_{24}NO_2S$ ($M+H^+$): 330.1528, found: 330.1525

TLC: R_f 0.48 (hexanes/EtOAc, 3:2) [UV/$KMnO_4$]

Analysis: $C_{19}H_{23}NO_2S$ (329.46)

Calcd:	C, 69.27;	H, 7.04%	N, 4.25%
Found:	C, 69.38;	H, 7.16%	N, 4.48%

Preparation of (*E*)-*N*-(4-Toluenesulfonyl)-6-phenylpent-5-enylamine (97) [HMC4021, HMC4022, HMC4023, HMC4024]



Following General Procedure VII, an oven-dried, 250-mL Schlenk flask equipped with a magnetic stir bar, a septum, and a argon inlet were charged with a solution of alcohol **163**[25] (1.28 g, 10.0 mmol, 1 equiv) in CH_2Cl_2 (100 mL), and Et_3N (4.88 mL, 35.0 mmol, 3.5 equiv). The solution was cooled to 0 °C, to the flask was added methanesulfonyl chloride (1.16 mL, 15.0 mmol, 1.5 equiv). After stirring for 1 h at 0 °C, the reaction was quenched. Purification via silica gel flash column chromatography (SiO_2, 30 g, 30 mm Ø, hexanes/EtOAc, 9:1) afforded 1.90 g (92%) of mesylate as a colorless oil. Then to an oven-dried, 250-mL round-bottomed-flask were added a solution of the resulted mesylate (1.90 g, 9.20 mmol, 1 equiv) in DMF (100 mL) and NaCN (1.35 g, 27.6 mmol, 3 equiv) as a solid in one portion. The flask was equipped with a reflux condenser and heated to 90 °C and stirred for 24 h. Upon reaction completion the reaction was quenched. Purification via silica gel flash column chromatography (SiO_2, 30 g, 30 mm Ø, hexanes/EtOAc, 19:1) afforded 1.09 g (86%) of nitrile **165** as a colorless oil. The ^{1}H NMR spectroscopic data matched those reported in the literature.[121]

Data for **165**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 5.49 (ddt, *J* = 15.5, 6.5, and 1.5 Hz, 1 H, HC(6)), 5.28 (dtd, *J* = 15.5, 6.5, and 1.5 Hz, 1 H, HC(5)), 2.33 (t, *J* = 7.0 Hz, 2 H, HC(1)), 2.30 – 2.22 (m, 1 H, HC(7)), 2.15 (q, *J* = 7.0 Hz, 2 H, HC(4)), 1.73 (p, *J* = 7.0 Hz, 2 H, HC(3)), 0.98 (d, *J* = 6.5 Hz, 6 H, HC(8)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 140.2 (C(6)), 124.1 (C(5)), 119.3 (C(1)), 31.2 (C(4)), 31.0 (C(7)), 25.1 (C(3)), 22.5 (C(8)), 16.2 (C(2)).

An oven-dried, 100-mL Schlenk flask equipped with a magnetic stir bar was charged with $LiAlH_4$ (285 mg, 7.5 mmol, 1.5 equiv) and capped with a septum under argon. The flask was immersed in an ice-bath and was added Et_2O (10 mL). To the resulting suspension was added a solution of nitrile **165**[121] (686 mg, 5.0 mmol, 1 equiv) in Et_2O (7 mL). The suspension was warmed to room temperature and stirred for 2 h. The reaction was quenched upon completion, and acidified to afford the corresponding amine·HCl salt. Then an oven-dried, 50-mL Schlenk flask equipped with a magnetic stir bar was charged with amine·HCl salt (5.0 mmol, 1 equiv), CH_2Cl_2 (10 mL), and Et_3N (2.09 mL, 15.0 mmol, 3 equiv). To the solution was added a solution of *p*-toluenesulfonyl chloride (1.00 g, 5.25 mmol, 1.05 equiv) in CH_2Cl_2 (7 mL) at 0 ^oC. The solution was warmed to room temperature and was stirred for 4 h. The reaction was quenched upon completion. Purification via silica gel flash column chromatography (SiO_2, 30 g, 30 mm Ø, hexanes/EtOAc, 9:1 to 4:1) afforded 1.02 g (69% over two steps from **165**) of the homologated tosylamine **97** as a colorless oil.

Data for **97**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.76 (d, *J* = 8.5 Hz, 2 H, HC(10)), 7.29 (d, *J* = 8.0 Hz, 2 H, HC(11)), 5.31 (dd, *J* = 15.5, and 6.5 Hz, 1 H, HC(6)), 5.23 (dt, *J* = 15.5, and 6.5 Hz, 1 H, HC(5)), 5.02 (t, *J* = 6.0 Hz, 1 H, HN), 2.90 (q, *J* = 7.0 Hz, 2 H, HC(1)), 2.41 (s, 3 H, HC(13)), 2.18 (hept, *J* = 6.5 Hz, 1 H, HC(7)), 1.89 (q, *J* = 7.0 Hz, 2 H, HC(4)), 1.44 (dt, *J* = 15.0, and 7.0 Hz, 2 H, HC(2)), 1.30 (p, *J* = 7.44 Hz, 2 H, HC(3)), 0.92 (d, *J* = 7.0 Hz, 6 H, HC(8)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 143.1 (C(9)), 138.1 (C(6)), 136.9 (C(12)), 129.5 (C(11)), 127.0 (C(10)), 126.2 (C(5)), 43.0 (C(1)), 31.8 (C(4)), 30.8 (C(7)), 28.8 (C(2)), 26.4 (C(3)), 22.5 (C(8)), 21.4 (C(13)).

IR: 3283 (m), 2933 (m), 2868 (w), 1598 (w), 1456 (m), 1325 (s), 1158 (s), 1093 (m), 971 (w), 937 (w), 815 (m).

MS: (ESI)

252 (31), 294 (100), 296 (M+H, 49), 310 (32), 350 (17)

HRMS: (ESI) calcd for $C_{16}H_{26}NO_2S$ ($M+H^+$): 296.1677, found: 296.1684

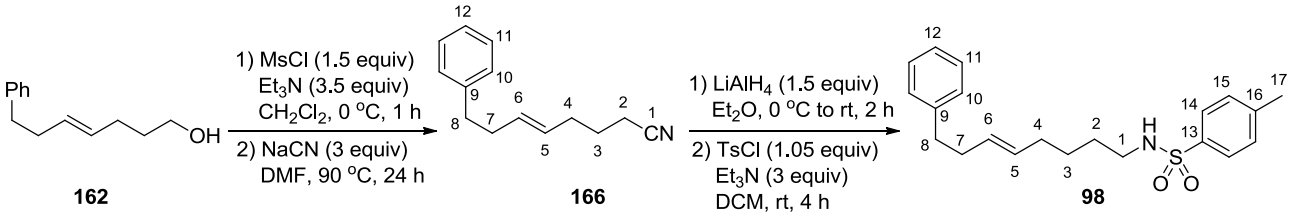
TLC: R_f 0.56 (hexanes/EtOAc, 3:2) [UV/$KMnO_4$]

Analysis: $C_{16}H_{25}NO_2S$ (295.44)

Calcd: C, 65.05; H, 8.53% N, 4.74%

Found: C, 64.98; H, 8.34% N, 4.65%

Preparation of (*E*)-*N*-(4-Toluenesulfonyl)-8-phenylpent-5-enylamine (98) [HMC4031, HMC4033, HMC4037, HMC4039]



Following General Procedure VII, an oven-dried, 250-mL Schlenk flask equipped with a magnetic stir bar, a septum, and a argon inlet were charged with a solution of alcohol **162**[38] (1.90 g, 10.0 mmol, 1 equiv) in CH_2Cl_2 (100 mL), and Et_3N (4.88 mL, 35.0 mmol, 3.5 equiv). The solution was cooled to 0 °C, to the flask was added methanesulfonyl chloride (1.16 mL, 15.0 mmol, 1.5 equiv). After stirring for 1 h at 0 °C, the reaction was quenched. Purification via silica gel flash column chromatography (SiO_2, 30 g, 30 mm Ø, hexanes/EtOAc, 9:1) afforded 2.47 g (92%) of mesylate as a colorless oil. Then to an oven-dried, 250-mL round-bottomed-flask were added a solution of the resulted mesylate (2.47 g, 9.23 mmol, 1 equiv) in DMF (100 mL) and NaCN (1.35 g, 27.6 mmol, 3 equiv) as a solid in one portion. The flask was equipped with a reflux condenser and heated to 90 °C and stirred for 24 h. Upon reaction completion the reaction was quenched. Purification via silica gel flash column chromatography (SiO_2, 30 g, 30 mm Ø, hexanes/EtOAc, 19:1) afforded 1.65 g (90%) of nitrile **166** as a colorless oil.

Data for **166**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.29 (t, *J* = 7.5 Hz, 2 H, HC(11)), 7.21 – 7.15 (m, 3 H, HC(12,10)), 5.52 (dt, *J* = 15.0, and 7.0 Hz, 1 H, HC(6)), 5.30 (dt, *J* = 15.0, and 7.0 Hz, 1 H, HC(5)), 2.69 (t, *J* = 7.5 Hz, 2 H, HC(8)), 2.34 (q, *J* = 7.5 Hz, 2 H, HC(7)), 2.20 (t, *J* = 7.5 Hz, 2 H,

HC(2)), 2.13 (q, *J* = 7.0 Hz, 2 H, HC(4)), 1.67 (p, *J* = 7.0 Hz, 2 H, HC(3)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 141.7 (C(9)), 132.0 (C(6)), 128.5 (C(10)), 128.2 (HC(11)), 128.2 (HC(5)), 125.8 (C(12)), 119.7 (C(1)), 35.7 (C(8)), 34.2 (C(7)), 31.1 (C(4)), 24.9 (C(3)), 16.1 (C(2)).

IR: 3026 (m), 2933 (s), 2851 (m), 2245 (m), 1496 (s), 1454 (s), 1079 (w), 1030 (w), 970 (s), 747 (s).

MS: (ESI)

200 (M+H, 100), 201 (18), 219 (33), 224 (32), 227 (46), 231 (34), 232 (20)

HRMS: (ESI) calcd for $C_{14}H_{18}N$ ($M+H^+$): 200.1439, found: 200.1436

TLC: R_f 0.61 (hexanes/EtOAc, 3:2) [UV/$KMnO_4$]

Analysis: $C_{14}H_{17}N$ (199.29)

Calcd:	C, 84.37;	H, 8.60%	N, 7.03%
Found:	C, 84.58;	H, 8.58%	N, 7.11%

An oven-dried, 100-mL Schlenk flask equipped with a magnetic stir bar was charged with $LiAlH_4$ (285 mg, 7.5 mmol, 1.5 equiv) and capped with a septum under argon. The flask was immersed in an ice-bath and was added Et_2O (10 mL). To the resulting suspension was added a solution of nitrile **166** (996 mg, 5.0 mmol, 1 equiv) in Et_2O (7 mL). The suspension was warmed to room temperature and stirred for 2 h. The reaction was quenched upon completion, and acidified to afford the corresponding amine·HCl salt. Then an oven-dried, 50-mL Schlenk flask equipped with a magnetic stir bar was charged with amine·HCl salt (5.0 mmol, 1 equiv), CH_2Cl_2 (10 mL), and Et_3N (2.09 mL, 15.0 mmol, 3 equiv). To the solution was added a solution of *p*-toluenesulfonyl chloride (1.00 g, 5.25 mmol, 1.05 equiv) in CH_2Cl_2 (7 mL) at 0 ^oC. The solution was warmed to room temperature and was stirred for 4 h. The reaction was quenched upon completion. Purification via silica gel flash column chromatography (SiO_2, 15 g, 20 mm Ø, hexanes/EtOAc, 9:1 to 4:1) afforded 1.22 g (66% over two steps from **166**) of the homologated tosylamine **98** as a white solid.

Data for **98**:

mp: 68-69 ℃

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.75 (d, *J* = 8.5 Hz, 2 H, HC(14)), 7.31 (d, *J* = 8.0 Hz, 2 H, HC(15)), 7.27 (t, *J* = 7.5 Hz, 2 H, HC(11)), 7.20 – 7.14 (m, 3 H, HC(12,10)), 5.43 – 5.35 (m, 1 H, HC(6)), 5.35 – 5.27 (m, 1 H, HC(5)), 4.47 (brs, 1 H, HN), 2.90 (q, *J* = 6.5 Hz, 2 H, HC(1)), 2.65 (t, *J* = 8.0 Hz, 2 H, HC(8)), 2.43 (s, 3 H, HC(17)), 2.28 (q, *J* = 7.0 H, 2 H, HC(7)), 1.91 (q, *J* = 7.0 Hz, 2 H, HC(4)), 1.43 – 1.35 (m, 2 H, HC(2)), 1.33 – 1.24 (m, 2 H, HC(3)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 143.3 (C(13)), 142.0 (C(9)), 136.9 (C(16)), 130.1 (C(6)), 130.0 (C(5)), 129.6 (C(15)), 128.4 (C(10)), 128.2 (11)), 127.1 (C(14)), 125.7 (C(12)), 43.0 (C(1)), 35.9 (C(8)), 34.3 (C(7)), 31.8 (C(4)), 28.8 (C(2)), 26.2 (C(3)), 21.5 (C(17)).

IR: 3244 (m), 2924 (w), 2857 (w), 1596 (w), 1449 (2), 1424 (w), 1322 (s), 1307 (m), 1163 (s), 1153 (s), 1093 (m), 1074 (m), 1027 (w), 973 (m), 906 (w), 813 (m), 750 (m).

MS: (ESI)

358 (M+H, 100), 359 (28), 375 (22), 380 (22), 396 (10)

HRMS: (ESI) calcd for $C_{21}H_{28}NO_2S$ ($M+H^+$): 358.1841, found: 358.1829

TLC: R_f 0.53 (hexanes/EtOAc, 3:2) [UV/$KMnO_4$]

Analysis: $C_{21}H_{27}NO_2S$ (357.51)

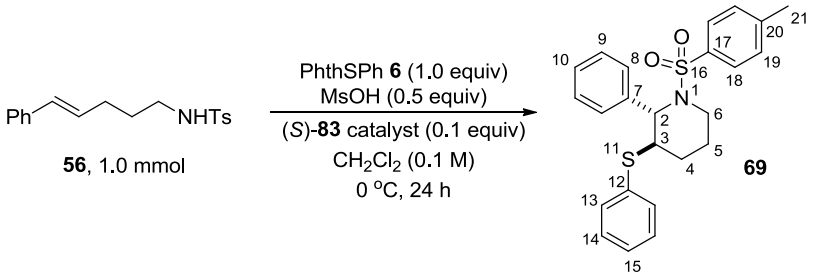
Calcd:	C, 70.55;	H, 7.61%	N, 3.92%
Found:	C, 70.55;	H, 7.57%	N, 3.98%

General Procedure VIII: Cyclization

An oven-dried, 25-mL Schlenk flask equipped with a stir bar was charged with substrate (1.0 mmol, 1.0 equiv), PhthSPh **6** (255 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.10 equiv), and CH_2Cl_2 (10.0 mL, 0.10 M) and capped with a rubber septum. The flask was placed into a isopropyl alcohol bath, and the bath was cooled to 0 ^oC via a Cryocool unit. The temperature of the mixture was monitored via a thermocouple digital temperature probe. After the temperature stabilized, MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) was added and the mixture was allowed to stir for the indicated time. The reaction was quenched while cold by addition of pre-cooled sat. $NaHCO_3$ aq. solution upon vigorous stirring. The resulting mixture was extracted with CH_2Cl_2 (10 mL x 3). The combined organic extracts were dried over Na_2SO_4, filtered through glass wool and then concentrated *in vacuo* (23 ^oC, 10 mm Hg) to afford the crude product. The product was purified via silica gel flash column chromatography prior to SFC analysis.

Sulfenoamination Reactions with (*S*)-83 (Table 6 – 8 and Scheme 31 – 32)

Preparation of (2*S*,3*R*)-*N*-(4-Toluenesulfonyl)-2-phenyl-3-(phenylthio)piperidine (69) (Table 6 Entry 1) [HMC5087]



Following General Procedure VIII, a 25-mL Schlenk flask was charged with **56** (315 mg, 1.0 mmol, 1.0 equiv), PhthSPh **6** (255 mg, 0.2 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (10.0 mL, 0.1 M). After cooled to 0 ^oC, the mixture was added MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) and was allowed to stir for 24 h. The reaction was worked up following the general procedure. The product **69** was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 393 mg (93%) of a **69** as a white solid.

Data for **69**:

mp: 51-53 ^{o}C (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.80 (d, *J* = 8.0 Hz, 2 H, HC(18)), 7.47 (d, *J* = 8.5 Hz, 2 H, HC(13)), 7.31 (t, *J* = 8.0 Hz, 2 H, HC(14)), 7.29 – 7.16 (m, 8 H, HC(aryl)), 5.41 (s, 1 H, HC(2)), 3.91 (d, *J* = 2.0 Hz, 1H, HC(3)), 3.75 (dd, *J* = 13.0, and 3.0 Hz, 1 H, HC(6)), 3.21 (td, *J* = 12.0, and 3.0 Hz, 1 H, HC(6)), 2.39 (s, 3 H, HC(21)), 1.91 – 1.70 (m, 3 H, HC(4,5)), 1.38 (dt, *J* = 13.5, and 3.0 Hz, 1 H, HC(5)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 142.9 (C(20)), 138.8 (C(7)), 137.7 (C(17)), 135.0 (C(12)), 132.2 (C(13)), 129.2 (C(19)), 129.1 (C(14)), 128.6 (C(9)), 127.6 (C(18)), 127.4 (C(15)), 127.0 (C(10)), 126.8 (C(8)), 60.0 (C(2)), 49.7 (C(3)), 41.7 (C(6)), 24.1 (C(4)), 21.5 (C(21)), 19.9 (C(5)).

IR: 3025 (w), 2947 (w), 2869 (w), 1598 (w), 1495 (w), 1479 (w), 1438 (m), 1377 (w), 1337 (s), 1304 (m), 1287 (m), 1214 (m), 1182 (w), 1157 (s), 1107 (m), 1090 (s), 1068 (w), 1049 (m), 1003 (w), 942 (s), 915 (w), 882 (w), 859 (w), 827 (w), 814 (w), 760 (s)

MS: (ESI)

314 (98), 315 (27), 316 (10), 424 (M+H, 100), 425 (27), 426 (13), 441 (19), 446 (21), 462 (12)

HRMS: calcd for $C_{24}H_{26}NO_2S_2$: 424.1405, found: 424.1408

TLC: R_f 0.54 (hexanes/EtOAc, 3:2) [UV/$KMnO_4$]

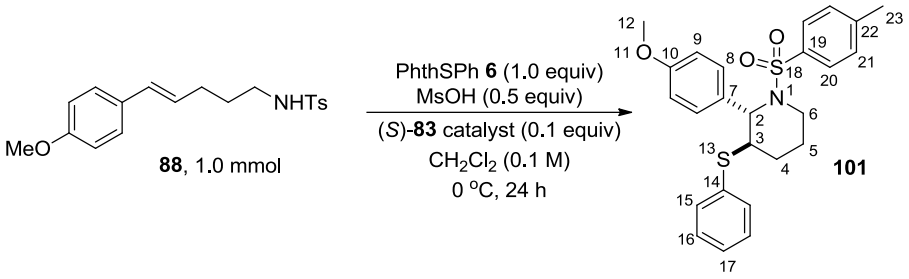
Opt Rot: $[\alpha]_D^{24}$ 73.0 (c = 1.00, $CHCl_3$)

SFC: (2*S*,3*R*)-**69**, t_R 13.6 min (93.6%); (2*R*,3*S*)-**69,** t_R 15.2 min (6.4%) (Chiralcel OJ, Gradient 3% MeOH in CO_2 to 8% MeOH in CO_2 over 30 min, 2.5 mL/min, 220 nm, 40 ^{o}C)

Analysis: $C_{24}H_{25}NO_2S_2$ (423.59)

Calcd:	C, 68.05;	H, 5.95%	N, 3.31%
Found:	C, 67.93;	H, 6.11%	N, 3.02%

Preparation of (2*S*,3*R*)-*N*-(4-Toluenesulfonyl)-2-(4-methoxyphenyl)-3-(phenylthio)piperidine (101) (Table 6 Entry 2) [HMC5088]



Following General Procedure VIII, a 25-mL Schlenk flask was charged with **88** (345 mg, 1.0 mmol, 1.0 equiv), PhthSPh **6** (255 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.10 equiv), and CH_2Cl_2 (10.0 mL, 0.1 M). After cooled to 0 ^oC, the mixture was added MsOH (32.5 μL, 0.5 mmol, 0.5 equiv) and was allowed to stir for 24 h. The reaction was worked up following the general procedure. The product **101** was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 414 mg (91%) of **101** as a white solid.

Data for **101**:

mp: 53-54 ^oC (sealed tube)

^1H NMR: (500 MHz, $CDCl_3$)

δ 7.84 (d, *J* = 8.5 Hz, 2 H, HC(20)), 7.48 (d, *J* = 7.5 Hz, 2 H, HC(15)), 7.36 (t, *J* = 7.5 Hz, 2 H, HC(16)), 7.32 – 7.26 (m, 3 H, HC(17,21)), 7.18 (d, *J* = 9.0 Hz, 2 H, HC(8)), 6.84 (d, *J* = 9.0 Hz, 2 H, HC(9)), 5.38 (s, 1 H, HC(2)), 3.90 (brd, *J* = 2.5 Hz, 1 H, HC(3)), 3.80 (s, 3 H, HC(12)), 3.75 (d, *J* = 13.5 Hz, 1 H, HC(6)), 3.27 – 3.19 (m, 1 H, HC(6)), 2.45 (s, 3 H, HC(23)), 1.93 – 1.78 (m, 3 H, HC(4,5)), 1.47 – 1.40 (m, 1 H, HC(5)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 158.6 (C(10)), 142.9 (C(19)), 137.8 (C(22)), 135.2 (C(14)), 132.2 (C(15)), 130.8 (C(7)), 129.2 (C(21)), 129.2 (C(16)), 128.1 (C(8)), 127.1 (C(20)), 127.4 (C(17)), 114.0 (C(9)), 59.7 (C(2)), 55.3 (C(12)), 49.6 (C(3)), 41.7 (C(6)), 24.1 (C(4)), 21.5 (C(23)), 20.1 (C(5)).

IR: 3026 (w), 2948 (w), 2869 (w), 1610 (w), 1582 (w), 1512 (m), 1459 (w), 1438 (w), 1374 (w), 1336 (m), 1304 (m), 1285 (w), 1252 (m), 1212 (w), 1181 (m), 1157 (s),

1107 (w), 1089 (m), 1069 (w), 1048 (w), 1034 (w), 1003 (w), 944 (m), 929 (m), 886 (w), 863 (w), 839 (w), 814 (w), 751 (m)

MS: (ESI)

344 (M+H, 100), 345 (24), 346 (14), 454 (15), 476 (22)

HRMS: calcd for $C_{25}H_{28}NO_3S_2$: 454.1511, found: 454.1513

TLC: R_f 0.53 (hexanes/EtOAc, 3:2) [UV/$KMnO_4$]

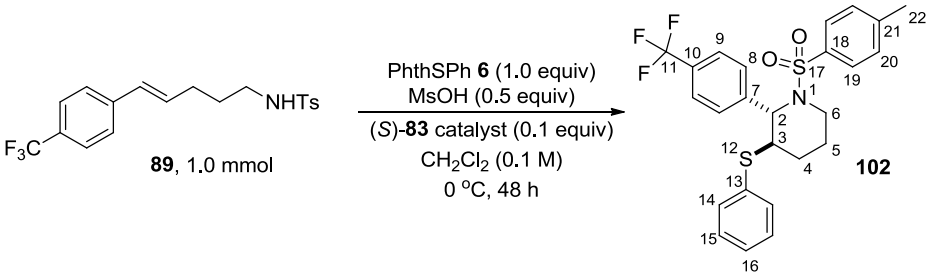
Opt Rot: $[\alpha]_D^{24}$ 41.3 (c = 1.00, $CHCl_3$)

SFC: (2*S*,3*R*)-**101**, t_R 18.0 min (91.8%); (2*R*,3*S*)-**101,** t_R 22.0 min (8.2%) (Chiralpak AD, 10% MeOH in CO_2, 2.0 mL/min, 220 nm, 40 °C)

Analysis: $C_{25}H_{27}NO_3S_2$ (453.62)

Calcd:	C, 66.19;	H, 6.00%	N, 3.09%
Found:	C, 66.26;	H, 5.82%	N, 2.99%

Preparation of (2*S*,3*R*)-*N*-(4-Toluenesulfonyl)-2-(4-trifluoromethylphenyl)-3-(phenylthio)piperidine (102) (Table 6 Entry 3) [HMC5089]



Following General Procedure VIII, a 25-mL Schlenk flask was charged with **89** (383 mg, 1.0 mmol, 1.0 equiv), PhthSPh **6** (255 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.10 equiv), and CH_2Cl_2 (10.0 mL, 0.1 M). After cooled to 0 °C, the mixture was added MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) and was allowed to stir for 48 h. The reaction was worked up following the general procedure. The product **102** was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 191 mg (39%) of **102** as a white solid.

Data for **102**:

mp: 107-108 °C (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.82 (d, *J* = 8.5 Hz, 2 H, HC(19)), 7.54 (d, *J* = 8.5 Hz, 2 H, HC(9)), 7.49 (d, *J* = 7.0 Hz, 2 H, HC(14)), 7.39 – 7.30 (m, 5 H, HC(8,15,16)), 7.28 (d, *J* = 8.0 Hz, 2 H, HC(20)), 5.40 (s, 1 H, HC(2)), 3.88 (q, *J* = 3.5 Hz, 1 H, HC(3)), 3.79 (m, 1 H, HC(6)), 3.25 (ddd, *J* = 13.5, 12.5, and 3.5 Hz, 1 H, HC(6)), 2.44 (s, 3 H, HC(22)), 1.95 – 1.81 (m, 2 H, HC(4,5)), 1.79 – 1.70 (m, 1 H, HC(4)), 1.51 – 1.43 (m, 1 H, HC(5)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 143.3 (C(21)), 143.2 (C(7)), 137.4 (C(18)), 134.6 (C(13)), 132.6 (C(14)), 129.4 (q, *J* = 32 Hz, C(10)), 129.3 (C(20)), 129.3 (C(15)), 127.8 (C(16)), 127.6 (C(19)), 127.3 (C(8)), 125.6 (q, *J* = 3.8 Hz, C(9)), 123.9 (q, *J* = 272 Hz, C(11)), 60.0 (C(2)), 50.0 (C(3)), 42.0 (C(6)), 24.3 (C(4)), 21.5 (C(21)), 19.9 (C(5)).

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -63.05.

IR: 3025 (w), 2948 (m), 2872 (w), 1918 (w), 1619 (m), 1598 (w), 1984 (w), 1493 (w), 1479 (w), 1438 (m), 1411 (m), 1336 (s), 1286 (m), 1212 (m), 1132 (s), 1090 (m), 1069 (s), 1050 (m), 1015 (m), 938 (s), 889 (w), 863 (w), 845 (m), 814 (m), 747 (s)

MS: (ESI)

382 (50), 383 (12), 492 (M+H, 100), 493 (31), 494 (15), 514 (15)

HRMS: calcd for $C_{25}H_{25}NO_2S_2F_3$: 492.1279, found: 492.1276

TLC: R_f 0.60 (hexanes/EtOAc, 3:2) [UV/$KMnO_4$]

Opt Rot: $[\alpha]_D^{24}$ 46.5 (c = 1.00, $CHCl_3$)

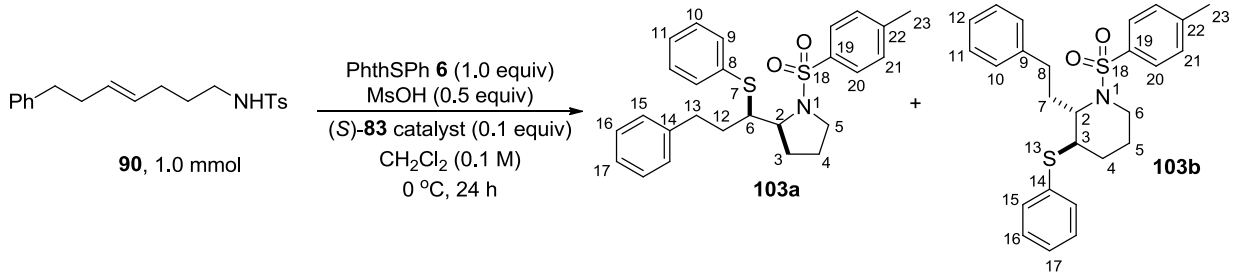
SFC: (2*R*,3*S*)-**102**, t_R 16.9 min (8.1%); (2*S*,3*R*)-**102,** t_R 17.9 min (91.9%) (Chiralcel OD, Gradient 3% MeOH in CO_2 to 5% MeOH in CO_2 over 30 min, 2.0 mL/min, 220 nm, 40 ^oC)

Analysis: $C_{25}H_{24}F_3NO_2S_2$ (491.59)

Calcd: C, 61.08; H, 4.92 % N, 2.85%

Found: C, 61.13; H, 4.70% N, 2.58%

Preparation of (2*S*,6*R*)-*N*-(4-Toluenesulfonyl)-2-(3-phenyl-1-(phenylthio)propyl)pyrrolidine (103a) and (2*S*,3*R*)-*N*-(4-Toluenesulfonyl)-2-phenethyl-3-(phenylthio)piperidine (103b) (Table 7 Entry 1) [HMC6012]



Following General Procedure VIII, a 25-mL Schlenk flask was charged with **90** (343 mg, 1.0 mmol, 1.0 equiv), PhthSPh **6** (255 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.10 equiv), and CH_2Cl_2 (10.0 mL, 0.1 M). After cooled to 0 ^oC, the mixture was added MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) and was allowed to stir for 24 h. The reaction was worked up following the general procedure. The product **103** was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø, hexanes/EtOAc, 19:1) to afford 411 mg (91%) of a 3.3:1 mixture of **103a**:**103b** as a white solid.

Data for **103a+103b**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.84 (d, *J* = 7.5 Hz, 2 H, HC(20')), 7.65 (d, *J* = 7.5 Hz, 2 H, HC(20)), 7.50 (d, *J* = 8.0 Hz, 2 H, HC(9)), 7.38 (d, *J* = 8.0 Hz, 2 H, HC(aryl')), 7.35 – 7.17 (m, 10 H+8 H('), HC(aryl, aryl')), 7.10 (d, *J* = 8.0 Hz, 2 H, HC(aryl')), 4.29 (t, *J* = 7.0 Hz, 1 H, HC(2')), 3.93 (dt, *J* = 9.0, and 5.0 Hz, 1 H, HC(2)), 3.70 (dt, *J* = 9.0, and 4.5 Hz, 1 H, HC(6)), 3.63 (d, *J* = 11.0 Hz, 1 H, HC(6')), 3.42 – 3.31 (m, 2 H+1 H('), HC(5,3')), 3.10 – 2.97 (m, 1 H+1 H('), HC(13,6')), 2.75 (ddd, *J* = 13.5, 10.0, and 6.0 Hz, 1 H, HC(13)), 2.63 (t, *J* = 8.0 Hz, 2 H, HC(8')), 2.45 (s, 3 H, HC(23')), 2.43 (s, 3 H, HC(23)), 2.07 (ddt, *J* = 14.0, 10.0, and 5.5 Hz, 1 H, HC(12)), 2.00 – 1.79 (m, 3 H+5 H('), HC(3,4,12,4',5',7')), 1.68 (dt, *J* = 13.5, and 7.0 Hz, 1 H, (3)), 1.44 (d, *J* = 13.5 Hz, 1 H, HC(5')), 1.38 – 1.27 (m, 1 H, HC(4)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 143.3 (C(19)), 142.9 (C(19')), 141.6 (C(14)), 141.1 (C(9')), 135.8 (C(8)), 135.1

(C(22)), 132.2 (C(aryl')), 131.5 (C(9)), 129.6 (C(21)), 129.4(C(21')), 129.1 (C(aryl')), 128.9 (C(10)), 128.5 (C(aryl)), 128.4 (C(aryl')), 128.4 (C(aryl)), 128.3 (C(aryl')), 127.7 (C(20')), 127.5 (C(20)), 127.2 (C(aryl')), 126.6 (C(11)), 126.0 (C(aryl')), 125.9 (C(aryl)), 63.8 (C(2)), 57.0 (C(2')), 55.3 (C(6)), 49.7 (C(5)), 47.6 (C(3')), 40.3 (C(6')), 35.9 (C(12)), 33.7 (C(13)), 32.9 (C(8')), 32.6 (C(4')), 28.0 (C(3)), 24.8 (C(4)), 23.9 (C(7')), 21.5 (C(23,23')), 20.1 (C(5')).

IR: 3025 (m), 2946 (w), 1598 (w), 1495 (w), 1479 (w), 1452 (w), 1438 (w), 1343 (m), 1302 (w), 1216 (m), 1157 (s), 1091 (m), 1019 (w), 989 (w), 927 (w), 815 (w), 755 (s)

MS: (ESI)

342 (24), 452 (M+H, 100), 453 (18), 474 (19)

HRMS: calcd for $C_{26}H_{30}NO_2S_2$: 452.1718, found: 452.1716

TLC: R_f 0.58 (hexanes/EtOAc, 3:2) [UV/$KMnO_4$]

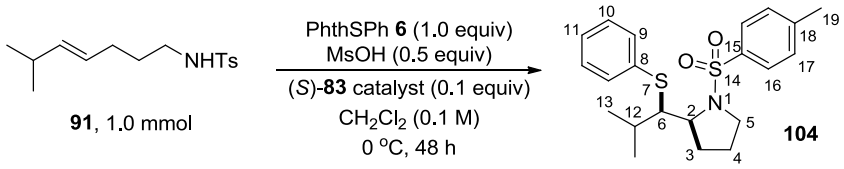
Opt Rot: $[\alpha]_D^{24}$ -46.9 (c = 1.00, $CHCl_3$)

SFC: (2*S*,6*R*)-**103a**, t_R 23.5 min (95.9% (73.6%)); (2*S*,3*R*)-**103b**, t_R 24.9 min (95.8% (22.3%); (2*R*,6*S*)-**103a**, t_R 27.8 min (4.1% (3.1%)); (2*R*,6*S*)-**103b**, t_R 29.7 min (4.2% (1.0%)) (Welk, 5% MeOH in CO_2, 2.0 mL/min, 220 nm, 40 ^oC);

Analysis: $C_{26}H_{29}NO_2S_2$ (451.64)

Calcd:	C, 69.14;	H, 6.47 %	N, 3.10%
Found:	C, 68.65;	H, 6.44%	N, 3.43%

Preparation of (2*S*,6*R*)-*N*-(4-Toluenesulfonyl)-2-(2-methyl-1-(phenylthio)propyl)pyrrolidine (104) (Table 7 Entry 2) [HMC5097]



Following General Procedure VIII, a 25-mL Schlenk flask was charged with **91** (281 mg, 1.0 mmol, 1.0 equiv), PhthSPh **6** (255 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.10 equiv), and CH_2Cl_2 (10.0 mL, 0.1 M). After cooled to 0 ^oC, the mixture was added MsOH (32.5 μL, 0.5 mmol, 0.5 equiv) and was allowed to stir for 48 h. The reaction was worked up

following the general procedure. The product **104** was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 346 mg (89%) of **104** as a white solid.

Data for **104**:

mp: 140-141 ^oC (sealed tube)

^1H NMR: (500 MHz, $CDCl_3$)

δ 7.66 (d, *J* = 8.0 Hz, 2 H, HC(16)), 7.53 (dd, *J* = 8.5, and 1.0 Hz, 2 H, HC(9)), 7.32 – 7.25 (m, 4 H, HC(10,17)), 7.19 (t, *J* = 7.5 Hz, 1 H, HC(11)), 4.01 (ddd, *J* = 8.5, 5.5, and 4.0 Hz, 1 H, HC(2)), 3.60 (dd, *J* = 6.5, and 4.0 Hz, 1 H, HC(6)), 3.36 (ddd, *J* = 8.0, 5.5, and 2.5 Hz, 2 H, HC(5)), 2.42 (s, 3 H, HC(19)), 2.01 (sept, 1 H, HC(12)), 1.89 (dtd, *J* = 13.0, 7.5, and 5.5 Hz, 1 H, HC(3)), 1.79 (dtt, *J* = 12.0, 5.5, and 5.5 Hz, 1 H, HC(4)), 1.67 (dtd, *J* = 13.0, 8.0, and 5.5 Hz, 1 H, HC(3)), 1.24 (dtt, *J* = 12.0, 8.0, and 8.0 Hz, 1 H, HC(4)), 1.12 (d, *J* = 6.5 Hz, 3 H, HC(13)), 1.10 (d, *J* = 6.5 Hz, 3 H, HC(13)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 143.3 (C(15)), 137.4 (C(8)), 134.9 (C(18)), 130.8 (C(9)), 129.7 (C(17)), 128.8 (C(10)), 127.5 (C(16)), 126.2 (C(11)), 63.3 (C(6)), 62.2 (C(2)), 49.6 (C(5)), 32.1 (C(12)), 28.6 (C(3)), 24.9 (C(4)), 21.5 (C(19)), 21.0 (C(13)), 20.4 (C(13)).

IR: (neat)

2960 (w), 1583 (w), 1482 (w), 1332 (s), 1309 (w), 1201 (w), 1155 (s), 1111 (w), 1088 (m), 1027 (m), 993 (m), 867 (w), 826 (s), 743 (s)

MS: (ESI)

184 (13), 219 (16), 224 (16), 280 (100), 281 (17), 390 (M+H, 71), 391 (21), 392 (10), 412 (95), 413 (24), 414 (12), 428 (60), 429(17), 430 (10)

HRMS: calcd for $C_{21}H_{28}NO_2S_2$: 390.1561, found: 390.1574

TLC: R_f 0.60 (hexanes/EtOAc, 3:2) [UV/$KMnO_4$]

Opt Rot: $[\alpha]_D^{24}$ -20.8 (c = 1.00, $CHCl_3$)

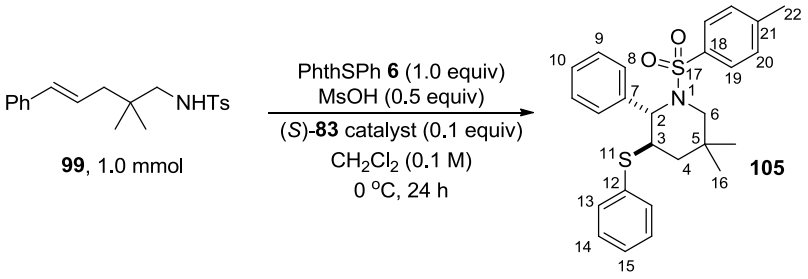
SFC: (2*S*,6*R*)-**104**, t_R 7.9 min (96.8%); (2*R*,6*S*)-**104,** t_R 10.3 min (3.2%) (Chiralpak AD, 10% MeOH in CO_2, 2.0 mL/min, 220 nm, 40 ^oC)

Analysis: $C_{21}H_{27}NO_2S_2$ (389.57)

Calcd: C, 64.74; H, 6.99 % N, 3.60%

Found: C, 64.57; H, 6.95% N, 3.86%

Preparation of (2*S*,3*R*)-*N*-(4-Toluenesulfonyl)-5,5-dimethyl-2-phenyl-3-(phenylthio)piperidine (23) (Table 7 Entry 3) [HMC5090]



Following General Procedure VIII, a 25-mL Schlenk flask was charged with **99** (343 mg, 1.0 mmol, 1.0 equiv), PhthSPh **6** (255 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.10 equiv), and CH_2Cl_2 (10.0 mL, 0.1 M). After cooled to 0 °C, the mixture was added MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) and was allowed to stir for 24 h. The reaction was worked up following the general procedure. The product **105** was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 410 mg (91%) of **105** as a white solid.

Data for **105**:

mp: 100-101 °C (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.50 (d, *J* = 8.0 Hz, 2 H, HC(19)), 7.37 (dd, *J* = 8.0, and 1.5 Hz, 2 H, HC(13)), 7.32 – 7.25 (m, 3 H, HC(14,15)), 7.22 – 7.12 (m, 7 H, HC(8,9,10,20)), 4.94 (d, *J* = 6.0 Hz, 1 H, HC(2)), 3.67 (ddd, *J* = 7.5, 6.0, and 4.5 Hz, 1 H, HC(3)), 3.30 (d, *J* = 13.5 Hz, 1 H, HC(6)), 3.20 (d, *J* = 13.5 Hz, 1 H, HC(6)), 2.39 (s, 3 H, HC(22)), 1.85 (dd, *J* = 14.0, and 4.5 Hz, 1 H, HC(4)), 1.67 (dd, *J* = 14.0, 7.5 Hz, 1 H, HC(4)), 1.03 (s, 3 H, HC(16)), 0.96 (s, 3 H, HC(16)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 142.6 (C(21)), 138.5 (C(7)), 137.4 (C(18)), 134.8 (C(12)), 132.6 (C(13)), 129.0 (C(20)), 128.9 (C(14)), 128.1 (C(9)), 127.7 (C(8)), 127.5 (C(15)), 127.4 (C(10)), 127.3 (C(19)), 62.6 (C(2)), 53.3 (C(6)), 49.7 (C(3)), 40.9 (C(4)), 31.5 (C(5)), 27.7 (C(16)), 27.6 (C(16)), 21.4 (C(22)).

IR: (neat)

2957 (w), 2868 (w), 1581 (w), 1494 (w), 1476 (w), 1454 (m), 1441 (w), 1393 (w),

1337 (m), 1313 (s), 1287 (m), 1183 (w), 1148 (s), 1092 (m), 1037 (m), 1026 (m), 1000 (m), 956 (w), 905 (m), 844 (m), 809 (m), 776 (s), 741 (s)

MS: (ESI)

342 (100), 343 (24), 452 (M+H, 38), 453 (12), 469 (12), 474 (33), 490 (15)

HRMS: calcd for $C_{26}H_{30}NO_2S_2$: 452.1718, found: 452.1717

TLC: R_f 0.58 (hexanes/EtOAc, 3:2) [UV/$KMnO_4$]

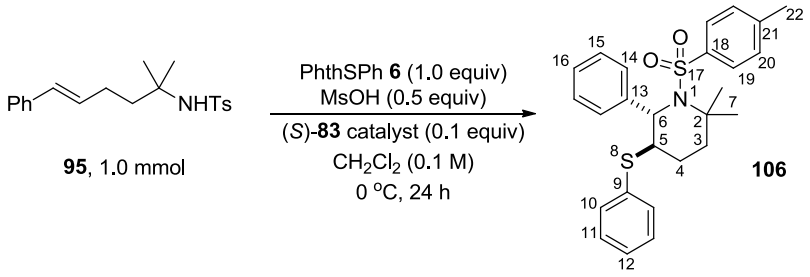
Opt Rot: $[\alpha]_D^{24}$ 43.4 (c = 1.00, $CHCl_3$)

SFC: (2*R*,3*S*)-**105**, t_R 37.0 min (3.7%); (2*S*,3*R*)-**105,** t_R 38.6 min (96.3%) (Chiralcel OD, Gradient 1% MeOH in CO_2 to 5% MeOH in CO_2 over 60 min, 2.0 mL/min, 220 nm, 40 °C)

Analysis: $C_{26}H_{29}NO_2S_2$ (451.64)

Calcd:	C, 69.14;	H, 6.47%	N, 3.10%
Found:	C, 68.79;	H, 6.08%	N, 2.80%

Preparation of (5*R*,6*S*)-*N*-(4-Toluenesulfonyl)-2,2-dimethyl-6-phenyl-5-(phenylthio)piperidine (106) (Table 7 Entry 4) [HMC5092]



Following General Procedure VIII, a 25-mL Schlenk flask was charged with **95** (343 mg, 1.0 mmol, 1.0 equiv), PhthSPh **6** (255 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.10 equiv), and CH_2Cl_2 (10.0 mL, 0.1 M). After cooled to 0 °C, the mixture was added MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) and was allowed to stir for 24 h. The reaction was worked up following the general procedure. The product **106** was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 421 mg (93%) of **106** as a white solid.

Data for **106**:

mp: 137-138 °C (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.87 (d, *J* = 8.5 Hz, 2 H, HC(19)), 7.53 (d, *J* = 7.5 Hz, 2 H, HC(14)), 7.32 (t, *J* = 7.5 Hz, 2 H, HC(15)), 7.23 (t, *J* = 7.5 Hz, 1 H, HC(16)), 7.13 – 7.03 (m, 5 H, HC(11,12,20)), 6.97 (d, *J* = 7.0 Hz, 2 H, HC(10)), 4.82 (d, *J* = 3.0 Hz, 1 H, HC(6)), 4.38 (ddd, *J* = 9.5, 3.0, and 1.5 Hz, 1 H, HC(5)), 2.36 (td, *J* = 12.5, and 7.5 Hz, 1 H, HC(3)), 2.29 (s, 3 H, HC(22)), 2.00 (dd, *J* = 13.5, and 8.0 Hz, 1 H, HC(4)), 1.86 – 1.77 (m, 1 H, HC(4)), 1.77 (s, 3 H, HC(7)), 1.714 (dd, *J* = 12.5, and 6.5 Hz, 1 H, HC(3)), 1.49 (s, 3 H, HC(7)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 142.7 (C(18)), 139.8 (C(13)), 139.3 (C(21)), 135.6 (C(9)), 129.2 (C(20)), 128.9 (C(10)), 128.5 (C(15)), 128.4 (C(11)), 128.3 (C(14)), 127.3 (C(19)), 127.2 (C(16)), 125.5 (C(12)), 67.9 (C(2)), 66.6 (C(5)), 56.7 (C(6)), 41.5 (C(3)), 28.8 (C(7)), 27.1 (C(7)), 23.9 (C(4)), 21.3 (C(22)).

IR: 2993 (w), 2963 (m), 1595 (w), 1579 (w), 1491 (m), 1475 (m), 1446 (m), 1393 (w), 1351 (w), 1328 (s), 1309 (m), 1286 (w), 1253 (w), 1234 (m), 1205 (m), 1182 (w), 1153 (s), 1117 (m), 1084 (s), 1014 (s), 980 (s), 941 (w), 905 (w) 862 (w), 846 (w), 814 (m), 761 (s)

MS: (ESI)

181 (41), 281 (57), 282 (14), 342 (95), 343 (24), 452 (M+H, 100), 453 (30), 474 (44), 475 (14), 490 (18)

HRMS: calcd for $C_{26}H_{30}NO_2S_2$: 452.1718, found: 452.1715

TLC: R_f 0.64 (hexanes/EtOAc, 3:2) [UV/$KMnO_4$]

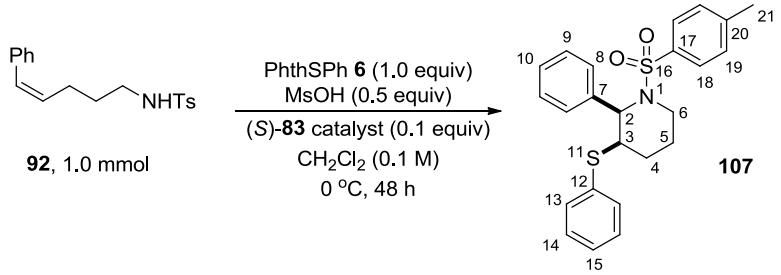
Opt Rot: $[\alpha]_D^{24}$ -38.1 (c = 1.00, $CHCl_3$)

SFC: (5*R*,6*S*)-**106**, t_R 18.4 min (91.8%); (5*S*,6*R*)-**106**, t_R 20.3 min (8.2%) (Chiralcel OD, Gradient 3% MeOH in CO_2 to 5% MeOH in CO_2 over 30 min, 2.0 mL/min, 220 nm, 40 ^{o}C)

Analysis: $C_{26}H_{29}NO_2S_2$ (451.64)

Calcd:	C, 69.14;	H, 6.47%	N, 3.10%
Found:	C, 69.06;	H, 6.38%	N, 2.89%

Preparation of (2*R*,3*R*)-*N*-(4-Toluenesulfonyl)-2-phenyl-3-(phenylthio)piperidine (107) (Scheme 31 Entry 1) [HMC6013]



Following General Procedure VIII, a 25-mL Schlenk flask was charged with **92** (315 mg, 1.0 mmol, 1.0 equiv), PhthSPh **6** (255 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.10 equiv), and CH_2Cl_2 (10.0 mL, 0.1 M). After cooled to 0 °C, the mixture was added MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) and was allowed to stir for 48 h. The reaction was worked up following the general procedure. The product **107** was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 288 mg (68%) of **107** as a white solid.

Data for **107**:

mp: 54-55 °C (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.42 – 7.37 (m, 4 H, HC(8,18)), 7.34 – 7.22 (m, 8 H, HC(aryl)), 7.09 (d, *J* = 8.5 Hz, 2 H, HC(19)), 5.36 (d, *J* = 5.5 Hz, 1 H, HC(2)), 3.85 (dd, *J* = 13.5, and 4.0 Hz, 1 H, HC(6)), 3.50 (dt, *J* = 13.0, and 5.0 Hz, 1 H, HC(3)), 3.06 (td, *J* = 13.5, and 3.0 Hz, 1 H, HC(6)), 2.37 (s, 3 H, HC(21)), 2.10 (qd, *J* = 13.0, and 4.0 Hz, 1 H, HC(4)), 2.00 (dd, *J* = 13.5, and 3.5 Hz, 1 H, HC(4)), 1.83 (brd, *J* = 13.5 Hz, 1 H, HC(5)), 1.70 (qt, *J* = 13.5, and 5.0 Hz, 1 H, HC(5)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 142.8 (C(17)), 137.0 (C(20)), 136.6 (C(7)), 134.4 (C(12)), 131.9 (C(13/14)), 129.7 (C(8)), 129.3 (C(19)), 129.0 (C(14/13)), 128.0 (C(9)), 127.8 (C(15)), 127.3 (C(10)), 127.0 (C(18)), 59.2 (C(2)), 48.7 (C(3)), 40.8 (C(6)), 26.3 (C(4)), 25.5 (C(5)), 21.4 (C(21)).

IR: 3058 (w), 3027 (m), 2949 (w), 2869 (w), 1598 (w), 1583 (w), 1495 (w), 1479 (w), 1454 (w), 1438 (m), 1334 (s), 1304 (w), 1286 (w), 1216 (s), 1175 (m), 1159 (s),

1133 (m), 1095 (s), 1037 (w), 1022 (w), 1000 (m), 946 (s), 887 (w), 872 (w), 814 (m), 748 (s)

MS: (ESI)

314 (100), 315 (22), 424 (M+H, 53), 425 (14), 446 (16)

HRMS: calcd for $C_{24}H_{26}NO_2S_2$: 424.1405, found: 424.1398

TLC: R_f 0.53 (hexanes/EtOAc, 3:2) [UV/$KMnO_4$]

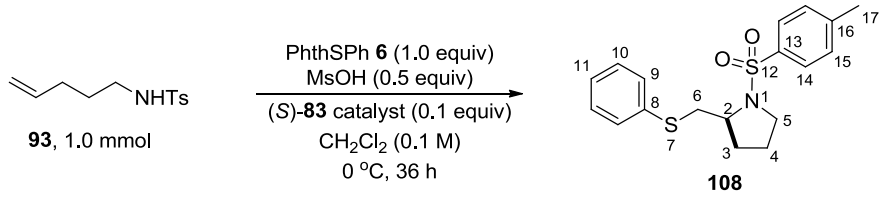
Opt Rot: $[\alpha]_D^{24}$ -14.9 (c = 1.00, $CHCl_3$)

SFC: (2*R*,3*R*)-**107**, t_R 10.9 min (62.8%); (2*S*,3*S*)-**107**, t_R 12.4 min (37.2%) (Chiralcel OD, 10% MeOH in CO_2, 2.0 mL/min, 220 nm, 40 ^oC)

Analysis: $C_{24}H_{25}NO_2S_2$ (423.59)

Calcd:	C, 68.05;	H, 5.95%	N, 3.31%
Found:	C, 67.80;	H, 5.89%	N, 3.27%

Preparation of (2*S*)-*N*-(4-Toluenesulfonyl)-2-((phenylthio)methyl)pyrrolidine (108) (Scheme 31 Entry 2) [HMC6014]



Following General Procedure VIII, a 25-mL Schlenk flask was charged with **93** (239 mg, 1.0 mmol, 1.0 equiv), PhthSPh **6** (255 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.10 equiv), and CH_2Cl_2 (10.0 mL, 0.1 M). After cooled to 0 ^oC, the mixture was added MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) and was allowed to stir for 36 h. The reaction was worked up following the general procedure. The product **108** was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 323 mg (93%) of **108** as a white solid.

Data for **108**:

mp: 85-86 ^oC (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.58 (d, *J* = 8.0 Hz, 2 H, HC(14)), 7.49 (d, *J* =7.5 Hz, 2 H, HC(9)), 7.37 (t, *J* = 7.5 Hz, 2 H, HC(10)), 7.28 – 7.21 (m, 3 H, HC(11,15)), 3.71 (ddd, *J* = 13.5, and 3.0 Hz,

1 H, HC(6)), 3.65 (ddt, *J* = 11.0, 7.0, and 3.0 Hz, 1 H, HC(2)), 3.51 (ddd, *J* = 10.5, 6.5, and 4.5 Hz, 1 H, HC(5)), 3.12 (ddd, *J* = 10.0, 8.0, and 6.5 Hz, 1 H, HC(5)), 2.79 (dd, *J* = 13.5, and 11.0 Hz, 1 H, HC(6)), 2.42 (s, 3 H, HC(17)), 1.94 – 1.86 (m, 1 H, HC(3)), 1.86 – 1.77 (m, 1 H, HC(4)), 1.70 – 1.60 (m, 1 H, HC(3)), 1.58 – 1.50 (m, 1 H, HC(4)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 143.4 (C(13)), 135.3 (C(8)), 133.7 (C(16)), 129.6 (C(15)), 129.0 (C(10)), 128.9 (C(9)), 127.4 (C(14)), 126.0 (C(11)), 58.8 (C(2)), 49.7 (C(5)), 38.3 (C(6)), 30.2 (C(3)), 23.7 (C(4)), 21.5 (C(17)).

IR: 2975 (w), 2869 (w), 1597 (w), 1481 (m), 1439 (m), 1345 (s), 1197 (m), 1159 (s), 1092 (m), 1062 (w), 1027 (m), 986 (w), 910 (s), 815 (m), 734 (s)

MS: (ESI)

238 (31), 348 (M+H, 100), 349 (24), 350 (14), 370 (20), 386 (11)

HRMS: calcd for $C_{18}H_{22}NO_2S_2$: 348.1092, found: 348.1086

TLC: R_f 0.51 (hexanes/EtOAc, 3:2) [UV/$KMnO_4$]

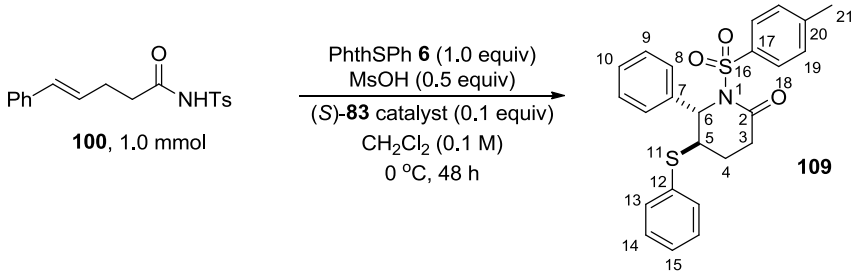
Opt Rot: $[\alpha]_D^{24}$ -228.7 (c = 1.00, $CHCl_3$)

SFC: (2*S*)-**108**, t_R 13.8 min (92.5%); (2*R*)-**108**, t_R 15.0 min (7.5%) (Chiralcel OD, 5% MeOH in CO_2, 2.0 mL/min, 220 nm, 40 °C)

Analysis: $C_{24}H_{25}NO_2S_2$ (347.49)

Calcd:	C, 62.21;	H, 6.09%	N, 4.03%
Found:	C, 62.06;	H, 5.69%	N, 3.96%

Preparation of (5*R*,6*S*)-*N*-(4-Toluenesulfonyl)-6-phenyl-5-(phenylthio)piperidin-2-one (109) (Scheme 32) [HMC6011]



Following General Procedure VIII, a 25-mL Schlenk flask was charged with **100** (329 mg,

1.0 mmol, 1.0 equiv), PhthSPh **6** (255 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.10 equiv), and CH_2Cl_2 (10.0 mL, 0.1 M). After cooled to 0 ^oC, the mixture was added MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) and was allowed to stir for 48 h. The reaction was worked up following the general procedure. The product **109** was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 372 mg (85%) of **109** as a white solid.

Data for **109**:

mp: 73-74 ^oC (sealed tube)

^1H NMR: (500 MHz, $CDCl_3$)

δ 7.77 (d, *J* = 8.5 Hz, 2 H, HC(18)), 7.55 (d, *J* = 7.0 Hz, 2 H, HC(13)), 7.44 – 7.28 (m, 6 H, HC(14,15,9,10)), 7.25 (d, *J* = 8.0 Hz, 2 H, HC(19)), 7.12 (d, *J* = 7.5 Hz, 2 H, HC(8)), 5.75 (s, 1 H, HC(6)), 3.76 (q, *J* = 3.0 Hz, 1 H, HC(5)), 2.75 (ddd, *J* = 19.5, 12.0, and 8.0 Hz, 1 H, HC(3)), 2.52 (dd, *J* = 19.5, and 6.5 Hz, 1 H, HC(3)), 2.43 (s, 3 H, HC(21)), 2.07 – 1.98 (m, 1 H, HC(4)), 1.79 – 1.70 (m, 1 H, HC(4)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 169.4 (C(2)), 144.7 (C(17)), 139.8 (C(7)), 135.7 (C(20)), 133.0 (C(13)), 132.7 (C(12)), 129.5 (C(14,18)), 128.9 (C(9,19)), 128.4 (C(15)), 128.1 (C(10)), 126.0 (C(8)), 63.8 (C(6)), 49.7 (C(5)), 29.6 (C(3)), 21.7 (C(21)), 20.2 (C(4)).

IR: 3028 (w), 2941 (w), 1731 (m), 1694 (s), 1597 (w), 1495 (w), 1480 (w), 1454 (m), 1359 (s), 1295 (m), 1263 (m), 1218 (m), 1169 (s), 1130 (m), 1088 (m), 1024 (w), 963 (m), 822 (m), 751 (s)

MS: (ESI)

328 (100), 329 (25), 438 (M+H, 91), 439 (27), 440 (14), 460 (32), 476 (14)

HRMS: calcd for $C_{24}H_{24}NO_3S_2$: 438.1198, found: 438.1189

TLC: R_f 0.44 (hexanes/EtOAc, 3:2) [UV/$KMnO_4$]

Opt Rot: $[\alpha]_D^{24}$ 30.0 (c = 1.00, $CHCl_3$)

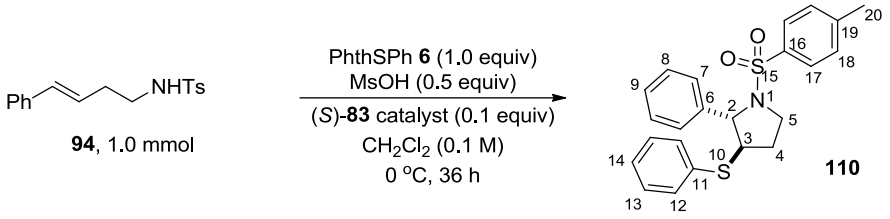
SFC: (5*R*,6*S*)-**109**, t_R 13.8 min (83.7%); (5*S*,6*R*)-**109**, t_R 15.7 min (16.3%) (Chiralcel OJ, Gradient 3% MeOH in CO_2 to 8% MeOH in CO_2 over 30 min, 2.5 mL/min, 220 nm, 40 ^oC)

Analysis: $C_{24}H_{23}NO_3S_2$ (437.57)

Calcd: C, 65.88; H, 5.30% N, 3.20%

Found: C, 66.03; H, 5.00% N, 3.12%

Preparation of (2*S*,3*R*)-*N*-(4-Toluenesulfonyl)-2-phenyl-3-(phenylthio)pyrrolidine (110) (Table 8 Entry 1) [HMC5093]



Following General Procedure VIII, a 25-mL Schlenk flask was charged with **94** (301 mg, 1.0 mmol, 1.0 equiv), PhthSPh **6** (255 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.10 equiv), and CH_2Cl_2 (10.0 mL, 0.1 M). After cooled to 0 ^oC, the mixture was added MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) and was allowed to stir for 36 h. The reaction was worked up following the general procedure. The product **110** was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 352 mg (86%) of **110** as a white solid.

Data for **110**:

mp: 72-73 ^oC (sealed tube)

^1H NMR: (500 MHz, $CDCl_3$)

δ 7.74 (d, *J* = 8.0 Hz, 2 H, HC(17)), 7.36 (d, *J* = 8.5 Hz, 2 H, HC(18)), 7.34 – 7.16 (m, 10 H, HC(aryl)), 4.67 (s, 1 H, HC(2)), 3.82 (ddd, *J* = 9.0, 8.0, 2.5 Hz, 1 H, HC(5)), 3.68 – 3.59 (m, 2 H, HC(5(left),3(right))), 2.50 (s, 3 H, HC(20)), 2.38 – 2.28 (m, 1 H, HC(4)), 1.86 – 1.78 (m, 1 H, HC(4)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 143.4 (C(16)), 141.6 (C(6)), 134.6 (C(19)), 133.6 (C(11)), 132.2 (C(13)), 129.5 (C(18)), 129.0 (C(12)), 128.4 (C(8)), 127.8 (C(17)), 127.6 (C(14)), 127.4 (C(9)), 126.0 (C(7)), 68.7 (C(2)), 55.5 (C(3)), 47.8 (C(5)), 29.2 (C(4)), 21.6 (C(20)).

IR: 3026 (w), 2947 (w), 2882 (w), 1598 (w), 1494 (w), 1479 (w), 1439 (w), 1347 (s), 1305 (w), 1216 (m), 1182 (m), 1160 (s), 1096 (s), 1055 (w), 1022 (w), 1009 (m), 814 (m), 752 (s)

MS: (EI)

91 (12), 118 (100), 135 (18), 151 (25), 155 (12), 253 (10), 254 (44), 299 (88), 300 (18), 409 (M+, 81), 410 (18)

HRMS: calcd for $C_{23}H_{23}NO_2S_2$: 409.1170, found: 409.1162

TLC: R_f 0.54 (hexanes/EtOAc, 3:2) [UV/$KMnO_4$]

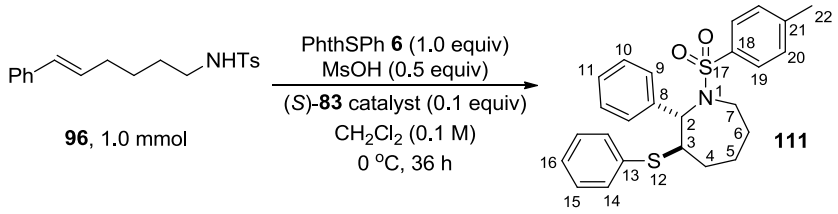
Opt Rot: $[\alpha]_D^{24}$ 103.4 (c = 1.00, $CHCl_3$)

SFC: (2*R*,3*S*)-**110**, t_R 12.9 min (8.7%); (2*S*,3*R*)-**110**, t_R 15.3 min (91.3%) (Chiralpak AD, 10% MeOH in CO_2, 2.0 mL/min, 220 nm, 40 °C)

Analysis: $C_{23}H_{23}NO_2S_2$ (409.56)

Calcd:	C, 67.45;	H, 5.66%	N, 3.42%
Found:	C, 67.73;	H, 5.49%	N, 3.65%

Preparation of (2*S*,3*R*)-*N*-(4-Toluenesulfonyl)-2-phenyl-3-(phenylthio)azepane (111) (Table 8 Entry 2) [HMC5095]



Following General Procedure VIII, a 25-mL Schlenk flask was charged with **96** (329 mg, 1.0 mmol, 1.0 equiv), PhthSPh **6** (255 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.10 equiv), and CH_2Cl_2 (10.0 mL, 0.1 M). After cooled to 0 °C, the mixture was added MsOH (32.5 μL, 0.5 mmol, 0.5 equiv) and was allowed to stir for 36 h. The reaction was worked up following the general procedure. The product **111** was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 368 mg (84%) of **111** as a white solid.

Data for **111**:

mp: 129-130 °C (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.33 – 7.18 (m, 12 H, HC(aryl)), 7.50 (d, *J* = 8.0 Hz, 2 H, HC(20)), 5.04 (d, *J* = 10.5 Hz, 1 H, HC(2)), 3.69 (d, *J* = 15.5 Hz, 1 H, HC(7)), 3.48 (t, *J* = 9.5 Hz, 1 H, HC(3)), 2.45 (ddd, *J* = 15.0, 11.5, and 1.5 Hz, 1 H, HC(7)), 2.33 (s, 3 H, HC(22)), 2.27 (dd, J = 15.0, and 6.0 Hz, 1 H, HC(4)), 2.03 – 1.89 (m, 2 H, HC(4,5)), 1.88 – 1.77 (m, 1 H, HC(6)), 1.74 – 1.66 (m, 1 H, HC(6)), 1.48 – 1.35 (m, 1 H, HC(5)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 142.5 (C(21)), 140.2 (C(8)), 137.6 (C(18)), 134.4 (C(13)), 132.2 (C(14)), 129.0

(C(20)), 128.9 (C(10)), 128.3 (C(15)), 127.7 (C(11)), 127.6 (C(9)), 127.2 (C(16)), 127.2 (C(19)), 64.3 (C(2)), 54.2 (C(3)), 45.7 (C(7)), 34.4 (C(4)), 29.4 (C(6)), 28.6 (C(5)), 21.4 (C(22)).

IR: (neat)

2922 (w), 2854 (w), 1598 (w), 1494 (w), 1476 (w), 1460 (w), 1437 (w), 1378 (w), 1332 (s), 1306 (w), 1252 (w), 1184 (w), 1157 (s), 1138 (m), 1101 (m), 1088 (m), 1067 (w), 1027 (m), 982 (w), 933 (s), 850 (m), 811 (m), 781 (s)

MS: (ESI)

328 (100), 329 (25), 438 (M+H, 38), 439 (10), 455 (20), 460 (37), 461 (11), 476 (18)

HRMS: calcd for $C_{25}H_{28}NO_2S_2$: 438.1561, found: 438.1563

TLC: R_f 0.58 (hexanes/EtOAc, 3:2) [UV/$KMnO_4$]

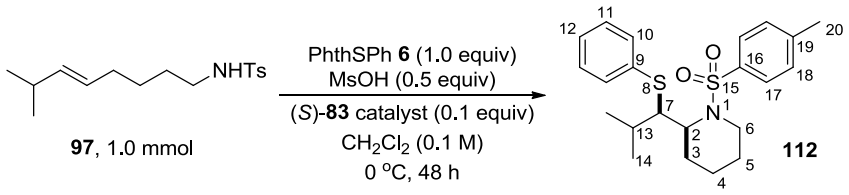
Opt Rot: $[\alpha]_D^{24}$ 45.5 (c = 1.00, $CHCl_3$)

SFC: (2*S*,3*R*)-**111**, t_R 6.0 min (92.7%); (2*R*,3*S*)-**111**, t_R 10.4 min (7.3%) (Chiralcel OB, 15% MeOH in CO_2, 2.0 mL/min, 220 nm, 40 ^oC)

Analysis: $C_{25}H_{27}NO_2S_2$ (437.62)

Calcd:	C, 68.61;	H, 6.22%	N, 3.20%
Found:	C, 68.60;	H, 5.97%	N, 3.28%

Preparation of (2*S*,7*R*)-*N*-(4-Toluenesulfonyl)-2-(2-methyl-1-(phenylthio)propyl)piperidine (112) (Table 8 Entry 3) [HMC6015]



Following General Procedure VIII, a 25-mL Schlenk flask was charged with **97** (295 mg, 1.0 mmol, 1.0 equiv), PhthSPh **6** (255 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.10 equiv), and CH_2Cl_2 (10.0 mL, 0.1 M). After cooled to 0 ^oC, the mixture was added MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) and was allowed to stir for 48 h. The reaction was worked up following the general procedure. The product **112** was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 351 mg (87%) of **112** as a white solid.

Data for **112**:

mp: 36-37 ^{o}C (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.75 (d, *J* = 8.0 Hz, 2 H, HC(17)), 7.44 (d, *J* = 7.5 Hz, 2 H, HC(10)), 7.29 (d, *J* = 8.0 Hz, 2 H, HC(18)), 7.25 (t, *J* = 8.0 Hz, 2 H, HC(11)), 7.18 (t, *J* = 7.5 Hz, 1 H, HC(12)), 4.19 (dd, *J* = 11.0, and 5.0 Hz, 1 H, HC(2)), 3.75 (dd, *J* = 15.0, and 3.5 Hz, 1 H, HC(6)), 3.33 (dd, *J* = 11.0, and 2.0 Hz, 1 H, HC(7)), 2.86 (ddd, *J* = 15.0, 13.5, and 3.0 Hz, 1 H, HC(6)), 2.42 (s, 3 H, HC(20)), 2.35 (heptd, *J* = 6.5, and 2.5 Hz, 1 H, HC(13)), 2.17 (d, *J* = 14.0 Hz, 1 H, HC(3)), 1.31 – 1.21 (m, 1 H, HC(3)), 1.25 (d, *J* = 7.0 Hz, 3 H, HC(14)), 1.16 (d, *J* = 13.5 Hz, 1 H, HC(5)), 1.07 – 1.01 (m, 1 H, HC(4)), 1.03 (d, *J* = 6.5 Hz, 3 H, HC(14)), 1.01 – 0.92 (m, 1 H, HC(5)), 0.79 (qt, J = 13.0, and 4.0 Hz, 1 H, HC(4)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 143.0 (C(19)), 138.7 (C(16)), 137.4 (C(9)), 131.4 (C(10)), 129.6 (C(18)), 128.9 (C(11)), 127.1 (C(17)), 126.6 (C(12)), 57.7 (C(7)), 56.3 (C(2)), 41.0 (C(6)), 27.3 (C(13)), 24.6 (C(3)), 22.6 (C(5)), 22.4 (C(14)), 21.4 (C(20)), 18.2 (C(4)), 16.2 (C(14)).

IR: 3024 (w), 2957 (m), 2870 (w), 1598 (w), 1581 (w), 1478 (w), 1464 (w), 1446 (w), 1353 (m), 1336 (s), 1304 (w), 1290 (w), 1216 (w), 1191 (m), 1157 (s), 1116 (w), 1091 (s), 1067 (w), 1042 (w), 1025 (w), 1001 (w), 930 (s), 880 (w), 840 (w), 815 (m), 755 (s)

MS: (ESI)

123 (22), 233 (43), 238 (19), 294 (80), 295 (18), 348 (34), 404 (M+H, 100), 405 (28), 406 (14), 426 (32), 442 (14)

HRMS: calcd for $C_{22}H_{30}NO_2S_2$: 404.1718, found: 404.1719

TLC: R_f 0.63 (hexanes/EtOAc, 3:2) [UV/$KMnO_4$]

Opt Rot: $[\alpha]_D^{24}$ 21.6 (c = 1.00, $CHCl_3$)

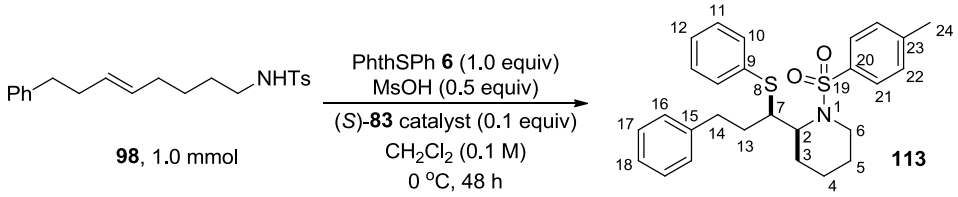
SFC: (2*S*,7*R*)-**112**, t_R 7.4 min (95.4%); (2*R*,7*S*)-**112**, t_R 9.1 min (4.6%) (Chiralpak AD, 10% MeOH in CO_2, 2.0 mL/min, 220 nm, 40 ^{o}C)

Analysis: $C_{22}H_{29}NO_2S_2$ (402.60)

Calcd: C, 65.47; H, 7.24% N, 3.47%

Found: C, 65.20; H, 7.04% N, 3.62%

Preparation of (2*S*,7*R*)-*N*-(4-Toluenesulfonyl)-2-(3-phenyl-1-(phenylthio)propyl)piperidine (113) (Table 8 Entry 4) [HMC5096]



Following General Procedure VIII, a 25-mL Schlenk flask was charged with **98** (358 mg, 1.0 mmol, 1.0 equiv), PhthSPh **6** (255 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.10 equiv), and CH_2Cl_2 (10.0 mL, 0.1 M). After cooled to 0 °C, the mixture was added MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) and was allowed to stir for 48 h. The reaction was worked up following the general procedure. The product **113** was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø, hexanes/EtOAc, 19:1 to 9:1) to afford 423 mg (91%) of **113** as a sticky white solid.

Data for **113**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.68 (d, *J* = 8.0 Hz, 2 H, HC(21)), 7.44 (d, *J* = 7.0 Hz, 2 H, HC(10)), 7.35 – 7.28 (m, 5 H, HC(11,12,17)), 7.26 – 7.18 (m, 5 H, HC(16,18,22)), 4.03 (dd, *J* = 10.5, and 4.0 Hz, 1 H, HC(2)), 3.80 (d, *J* = 14.5 Hz, 1 H, HC(6)), 3.25 (td, *J* = 10.5, and 3.0 Hz, 1 H, HC(7)), 3.14 (ddd, *J* = 13.5, 9.0, and 4.0 Hz, 1 H, HC(14)), 2.88 (dt, *J* = 14.0, and 8.5 Hz, 1 H, HC(14)), 2.67 (td, *J* = 15.0, and 2.5 Hz, 1 H, HC(6)), 2.42 (s, 3 H, HC(24)), 2.28 (d, *J* = 13.0 Hz, 1 H, HC(3)), 2.17 (dtd, *J* = 14.5, 8.5, and 3.0 Hz, 1 H, HC(13)), 1.73 (dtt, *J* = 14.0, 9.5, and 4.5 Hz, 1 H, HC(13)), 1.33 – 1.22 (m, 3 H, HC(3,4,5)), 1.18 – 1.02 (m, 2 H, HC(4,5)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 142.8 (C(20)), 141.6 (C(15)), 138.6 (C(23)), 134.2 (C(9)), 132.8 (C(10)), 129.5 (C(22)), 128.9 (C(11)), 128.6 (C(16)), 128.2 (C(17)), 127.4 (C(12)), 126.9 (C(21)), 125.7 (C(18)).

IR: 3025 (w), 2941 (m), 2856 (w), 1599 (w), 1494 (w), 1453 (m), 1336 (s), 1302 (m), 1216 (m), 1182 (w), 1154 (s), 1120 (m), 1091 (m), 1012 (w), 983 (w), 928 (s), 815 (m), 752 (s)

MS: (ESI)

185 (12), 356 (41), 357 (23), 358 (11), 466 (M+H, 100), 467 (55), 468 (26), 483 (45), 484 (17), 488 (12)

HRMS: calcd for $C_{27}H_{32}NO_2S_2$: 466.1874, found: 466.1871

TLC: R_f 0.60 (hexanes/EtOAc, 3:2) [UV/$KMnO_4$]

Opt Rot: $[\alpha]_D^{24}$ -17.6 (c = 1.00, $CHCl_3$)

SFC: (2*S*,7*R*)-**113**, t_R 11.6 min (97.4%); (2*R*,7*S*)-**113,** t_R 17.1 min (2.6%) (Chiralcel OJ, Gradient 3% MeOH in CO_2 to 8% MeOH in CO_2 over 30 min, 2.5 mL/min, 220 nm, 40 ^oC)

Analysis: $C_{27}H_{31}NO_2S_2$ (465.67)

Calcd:	C, 69.64;	H, 6.71%	N, 3.01%
Found:	C, 69.68;	H, 6.78%	N, 2.88%

NMR Study on the Catalytically Active Complex *i*[12,69] (Section 2.3.4.1) [HMC4063]

To an oven-dried, 5-mm NMR tube was charged with (*S*)-**83** (10 mg, 0.02 mmol), PhthSPh **6** (51 mg, 0.2 mmol, 10 equiv), and $CDCl_3$ (500 μL). The resulting solution was monitored with ^{31}P NMR spectroscopy.

Data for [(*S*)-**83**+PhthSPh(**6**)]:

^{31}P NMR: (202 MHz, $CDCl_3$)

δ 81.19 (br).

To an oven-dried, 5-mm NMR tube was charged with (*S*)-**83** (10 mg, 0.02 mmol), PhthSPh **6** (51 mg, 0.2 mmol, 10 equiv), $CDCl_3$ (500 μL) and MsOH (13 μL, 0.2 mmol, 10 equiv). The resulting solution of catalytically active complex ***i*** was monitored immediately with ^{31}P NMR spectroscopy.

Data for [(*S*)-**83**+PhthSPh(**6**)+MsOH] (***i***):

^{31}P NMR: (202 MHz, $CDCl_3$)

δ 59.77 (sharp).

Impact of the Purity of MsOH on Reaction (Section 2.3.5)

The following experiments were performed to investigate the impact of the purity of MsOH:

Experiment 1: Using bottle A of MsOH (non-distilled "*old & wet*" MsOH) [HMC4062]

Following General Procedure IV, an oven-dried, 5-mm NMR tube was charged with **56** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**83** (3.3 mg, 6.3 μmol, 0.10 equiv), and $CDCl_3$ (500 μL, 0.13 M). To the NMR tube was added MsOH (4.1 μL, 0.063 mmol, 1.0 equiv) at 0 ^{o}C. Conversion to product was measured by the appearance of the diagnostic ^{1}H NMR resonance for the piperidine **69** at 5.41 ppm and the pyrrolidine **70** at 4.07 ppm with respect to the substrate peaks at 6.34 ppm and 6.09 ppm. Interestingly, pyrrolidine 13 was not observed throughout the reaction. Conversion monitored by ^{1}H NMR spectroscopy was 20% (6 h), 44% (12 h), 63% (24 h), and 80% (48 h), whereupon only **69** was observed. Purification via silica gel flash column chromatography (SiO_2, 5 g, 10 mm Ø, hexanes/EtOAc, 9:1) afforded 21 mg (77%) of **69**.

SFC: (2*S*,3*R*)-**69**, t_R 14.8 min (92.0%); (2*R*,3*S*)-**69**, t_R 16.5 min (8.0%) (Chiralcel OJ, Gradient 3% MeOH in CO_2 to 8% MeOH in CO_2 over 30 min, 2.5 mL/min, 220 nm, 40 ^{o}C)

Experiment 2: Using bottle B of MsOH (distilled MsOH[69]) [HMC4069]

Following General Procedure IV, an oven-dried, 5-mm NMR tube was charged with **56** (20 mg, 0.063 mmol), PhthSPh **6** (16.2 mg, 0.063 mmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**83** (3.3 mg, 6.3 μmol, 0.10 equiv), and $CDCl_3$ (500 μL, 0.13 M). To the NMR tube was added distilled MsOH[34] (4.1 μL, 0.063 mmol, 1.0 equiv) at 0 ^{o}C. Conversion to product was measured by the appearance of the diagnostic ^{1}H NMR resonance for the piperidine **69** and the pyrrolidine **70** with respect to the substrate peaks. The ratio of **69** to **70** of the reaction mixture were 97:3 (76% conversion, 6 h), 94:6 (93% conversion, 12 h), 86:14 (full conversion at 24 h), and of the crude product was 86:14. Purification via silica gel flash column chromatography (SiO_2, 5 g, 10 mm Ø, hexanes/EtOAc, 9:1) afforded 22 mg (82%) of **69**.

SFC: (2*S*,3*R*)-**69,** t_R 14.8 min (91.6%); (2*R*,3*S*)-**69,** t_R 16.5 min (8.4%) (Chiralcel OJ, Gradient 3% MeOH in CO_2 to 8% MeOH in CO_2 over 30 min, 2.5 mL/min, 220 nm, 40 ^{o}C)

X-Ray Crystal Structure of 111

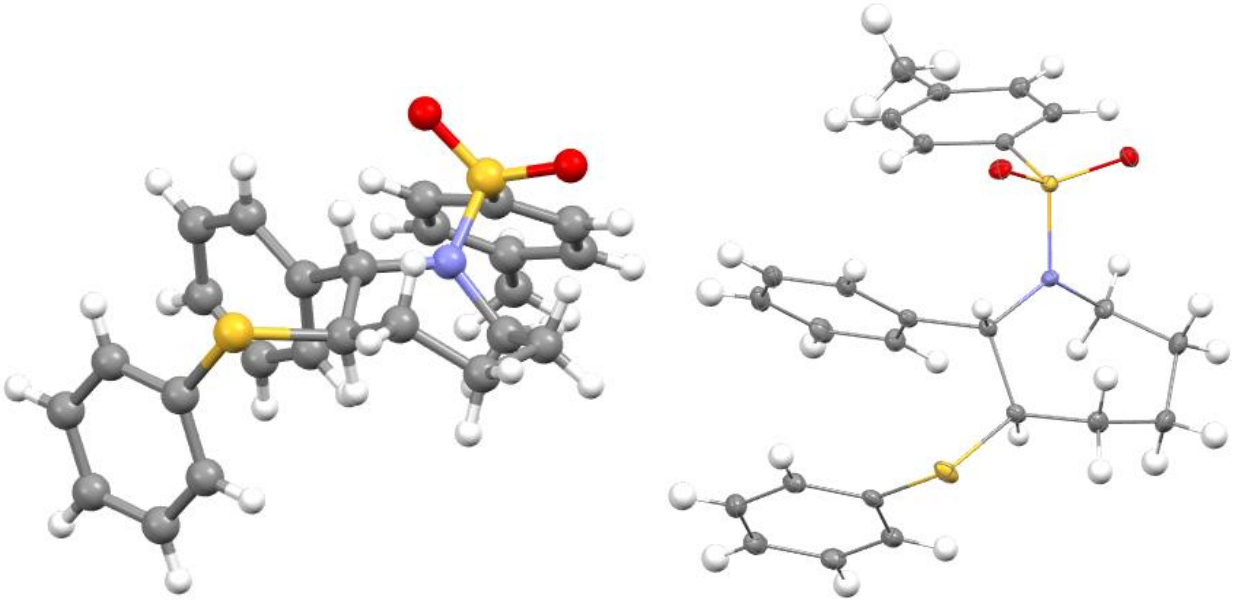


Figure 21. ORTEP images of X-ray crystal structure of **111**.

Recrystallization of **111** in THF/pentane resulted a white crystal. The crystallographic coordinates of **111** have been deposited with the Cambridge Crystallographic Data Centre (CCDC); deposition no. 981943. These data can be obtained free of charge via from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; via www.ccdc.cam.ac.uk/conts/retrieving.html or deposit@ccdc.cam.ac.uk).

Table A. Crystal data and structure refinement for cd24gsa.

Identification code	cd24gsa	
Empirical formula	C25 H27 N O2 S2	
Formula weight	437.59	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 6.0841(5) Å	α= 90°.
	b = 15.6924(12) Å	β= 90°.
	c = 22.5997(18) Å	γ = 90°.
Volume	2157.7(3) Å ^{3}	

Table A. (cont.)

Z	4
Density (calculated)	1.347 Mg/m^3
Absorption coefficient	0.269 mm^{-1}
F(000)	928
Crystal size	0.565 x 0.183 x 0.124 mm^3
Theta range for data collection	2.596 to 29.186°.
Index ranges	-8<=h<=8, -21<=k<=21, -28<=l<=30
Reflections collected	40407
Independent reflections	5825 [R(int) = 0.0374]
Completeness to theta = 25.242°	99.9 %
Absorption correction	Integration
Max. and min. transmission	0.97430 and 0.91819
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5825 / 0 / 272
Goodness-of-fit on F^2	1.059
Final R indices [I>2sigma(I)]	R1 = 0.0253, wR2 = 0.0625
R indices (all data)	R1 = 0.0272, wR2 = 0.0634
Absolute structure parameter	-0.034(15)
Extinction coefficient	n/a
Largest diff. peak and hole	0.289 and -0.255 e.$Å^{-3}$

Table B. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for cd24gsa. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
S(1)	428(1)	9470(1)	167(1)	10(1)
S(2)	3564(1)	7888(1)	2124(1)	16(1)
O(1)	-624(2)	9070(1)	-331(1)	14(1)
O(2)	2754(2)	9628(1)	152(1)	14(1)
N(1)	-11(2)	8878(1)	747(1)	10(1)
C(1)	1659(3)	8834(1)	1227(1)	11(1)
C(2)	1270(3)	8028(1)	1602(1)	12(1)
C(3)	1080(3)	7211(1)	1225(1)	16(1)

Table B. (cont.)

C(4)	-1296(3)	6990(1)	1058(1)	18(1)
C(5)	-2419(3)	7608(1)	635(1)	16(1)
C(6)	-2259(3)	8542(1)	820(1)	12(1)
C(7)	-971(3)	10444(1)	285(1)	11(1)
C(8)	-3025(3)	10553(1)	31(1)	13(1)
C(9)	-4263(3)	11272(1)	169(1)	14(1)
C(10)	-3470(3)	11882(1)	565(1)	14(1)
C(11)	-1359(3)	11775(1)	797(1)	15(1)
C(12)	-103(3)	11064(1)	662(1)	14(1)
C(13)	-4864(3)	12633(1)	744(1)	19(1)
C(14)	1813(3)	9650(1)	1591(1)	11(1)
C(15)	3741(3)	10128(1)	1576(1)	14(1)
C(16)	3928(3)	10880(1)	1905(1)	18(1)
C(17)	2177(3)	11155(1)	2246(1)	20(1)
C(18)	239(3)	10688(1)	2261(1)	18(1)
C(19)	56(3)	9936(1)	1935(1)	14(1)
C(20)	2828(3)	8545(1)	2737(1)	14(1)
C(21)	4336(3)	9147(1)	2942(1)	17(1)
C(22)	3832(3)	9644(1)	3434(1)	20(1)
C(23)	1816(3)	9553(1)	3714(1)	20(1)
C(24)	312(3)	8957(1)	3510(1)	18(1)
C(25)	822(3)	8446(1)	3024(1)	16(1)

Table C. Bond lengths [Å] and angles [°] for cd24gsa.

S(1)-O(2)	1.4370(12)
S(1)-O(1)	1.4379(12)
S(1)-N(1)	1.6294(13)
S(1)-C(7)	1.7702(16)
S(2)-C(20)	1.7827(17)
S(2)-C(2)	1.8407(17)
N(1)-C(6)	1.475(2)
N(1)-C(1)	1.486(2)
C(1)-C(14)	1.524(2)

Table C. (cont.)

C(1)-C(2)	1.542(2)
C(1)-H(1A)	1.0000
C(2)-C(3)	1.545(2)
C(2)-H(2A)	1.0000
C(3)-C(4)	1.534(3)
C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-C(5)	1.524(2)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-C(6)	1.528(2)
C(5)-H(5A)	0.9900
C(5)-H(5B)	0.9900
C(6)-H(6A)	0.9900
C(6)-H(6B)	0.9900
C(7)-C(8)	1.386(2)
C(7)-C(12)	1.397(2)
C(8)-C(9)	1.393(2)
C(8)-H(8A)	0.9500
C(9)-C(10)	1.395(2)
C(9)-H(9A)	0.9500
C(10)-C(11)	1.397(2)
C(10)-C(13)	1.508(2)
C(11)-C(12)	1.386(2)
C(11)-H(11A)	0.9500
C(12)-H(12A)	0.9500
C(13)-H(13A)	0.9800
C(13)-H(13B)	0.9800
C(13)-H(13C)	0.9800
C(14)-C(15)	1.393(2)
C(14)-C(19)	1.396(2)
C(15)-C(16)	1.398(2)
C(15)-H(15A)	0.9500
C(16)-C(17)	1.384(3)
C(16)-H(16A)	0.9500

Table C. (cont.)

C(17)-C(18)	1.388(3)
C(17)-H(17A)	0.9500
C(18)-C(19)	1.396(2)
C(18)-H(18A)	0.9500
C(19)-H(19A)	0.9500
C(20)-C(25)	1.392(2)
C(20)-C(21)	1.396(2)
C(21)-C(22)	1.392(2)
C(21)-H(21A)	0.9500
C(22)-C(23)	1.388(3)
C(22)-H(22A)	0.9500
C(23)-C(24)	1.388(3)
C(23)-H(23A)	0.9500
C(24)-C(25)	1.394(2)
C(24)-H(24A)	0.9500
C(25)-H(25A)	0.9500

O(2)-S(1)-O(1)	119.74(8)
O(2)-S(1)-N(1)	106.13(7)
O(1)-S(1)-N(1)	107.96(7)
O(2)-S(1)-C(7)	109.13(7)
O(1)-S(1)-C(7)	106.30(7)
N(1)-S(1)-C(7)	106.97(7)
C(20)-S(2)-C(2)	103.75(8)
C(6)-N(1)-C(1)	122.46(12)
C(6)-N(1)-S(1)	116.39(11)
C(1)-N(1)-S(1)	120.07(10)
N(1)-C(1)-C(14)	113.43(12)
N(1)-C(1)-C(2)	109.53(13)
C(14)-C(1)-C(2)	113.58(13)
N(1)-C(1)-H(1A)	106.6
C(14)-C(1)-H(1A)	106.6
C(2)-C(1)-H(1A)	106.6
C(1)-C(2)-C(3)	112.84(13)
C(1)-C(2)-S(2)	109.55(11)

Table C. (cont.)

C(3)-C(2)-S(2)	108.18(11)
C(1)-C(2)-H(2A)	108.7
C(3)-C(2)-H(2A)	108.7
S(2)-C(2)-H(2A)	108.7
C(4)-C(3)-C(2)	113.19(14)
C(4)-C(3)-H(3A)	108.9
C(2)-C(3)-H(3A)	108.9
C(4)-C(3)-H(3B)	108.9
C(2)-C(3)-H(3B)	108.9
H(3A)-C(3)-H(3B)	107.8
C(5)-C(4)-C(3)	115.67(14)
C(5)-C(4)-H(4A)	108.4
C(3)-C(4)-H(4A)	108.4
C(5)-C(4)-H(4B)	108.4
C(3)-C(4)-H(4B)	108.4
H(4A)-C(4)-H(4B)	107.4
C(4)-C(5)-C(6)	114.22(14)
C(4)-C(5)-H(5A)	108.7
C(6)-C(5)-H(5A)	108.7
C(4)-C(5)-H(5B)	108.7
C(6)-C(5)-H(5B)	108.7
H(5A)-C(5)-H(5B)	107.6
N(1)-C(6)-C(5)	111.81(14)
N(1)-C(6)-H(6A)	109.3
C(5)-C(6)-H(6A)	109.3
N(1)-C(6)-H(6B)	109.3
C(5)-C(6)-H(6B)	109.3
H(6A)-C(6)-H(6B)	107.9
C(8)-C(7)-C(12)	120.51(15)
C(8)-C(7)-S(1)	118.50(12)
C(12)-C(7)-S(1)	120.82(12)
C(7)-C(8)-C(9)	119.61(15)
C(7)-C(8)-H(8A)	120.2
C(9)-C(8)-H(8A)	120.2
C(8)-C(9)-C(10)	120.85(15)

Table C. (cont.)

C(8)-C(9)-H(9A)	119.6
C(10)-C(9)-H(9A)	119.6
C(9)-C(10)-C(11)	118.47(15)
C(9)-C(10)-C(13)	120.92(16)
C(11)-C(10)-C(13)	120.61(15)
C(12)-C(11)-C(10)	121.33(15)
C(12)-C(11)-H(11A)	119.3
C(10)-C(11)-H(11A)	119.3
C(11)-C(12)-C(7)	119.12(16)
C(11)-C(12)-H(12A)	120.4
C(7)-C(12)-H(12A)	120.4
C(10)-C(13)-H(13A)	109.5
C(10)-C(13)-H(13B)	109.5
H(13A)-C(13)-H(13B)	109.5
C(10)-C(13)-H(13C)	109.5
H(13A)-C(13)-H(13C)	109.5
H(13B)-C(13)-H(13C)	109.5
C(15)-C(14)-C(19)	119.00(15)
C(15)-C(14)-C(1)	119.42(14)
C(19)-C(14)-C(1)	121.58(15)
C(14)-C(15)-C(16)	120.70(16)
C(14)-C(15)-H(15A)	119.6
C(16)-C(15)-H(15A)	119.6
C(17)-C(16)-C(15)	119.72(17)
C(17)-C(16)-H(16A)	120.1
C(15)-C(16)-H(16A)	120.1
C(16)-C(17)-C(18)	120.22(16)
C(16)-C(17)-H(17A)	119.9
C(18)-C(17)-H(17A)	119.9
C(17)-C(18)-C(19)	120.05(17)
C(17)-C(18)-H(18A)	120.0
C(19)-C(18)-H(18A)	120.0
C(14)-C(19)-C(18)	120.31(16)
C(14)-C(19)-H(19A)	119.8
C(18)-C(19)-H(19A)	119.8

Table C. (cont.)

C(25)-C(20)-C(21)	119.80(15)
C(25)-C(20)-S(2)	121.23(13)
C(21)-C(20)-S(2)	118.93(13)
C(22)-C(21)-C(20)	119.95(17)
C(22)-C(21)-H(21A)	120.0
C(20)-C(21)-H(21A)	120.0
C(23)-C(22)-C(21)	120.16(17)
C(23)-C(22)-H(22A)	119.9
C(21)-C(22)-H(22A)	119.9
C(24)-C(23)-C(22)	119.95(16)
C(24)-C(23)-H(23A)	120.0
C(22)-C(23)-H(23A)	120.0
C(23)-C(24)-C(25)	120.22(17)
C(23)-C(24)-H(24A)	119.9
C(25)-C(24)-H(24A)	119.9
C(20)-C(25)-C(24)	119.90(16)
C(20)-C(25)-H(25A)	120.1
C(24)-C(25)-H(25A)	120.1

Symmetry transformations used to generate equivalent atoms:

Table D. Anisotropic displacement parameters ($Å^2 x 10^3$) for cd24gsa. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S(1)	11(1)	9(1)	9(1)	0(1)	1(1)	0(1)
S(2)	18(1)	17(1)	12(1)	-1(1)	-2(1)	7(1)
O(1)	17(1)	13(1)	10(1)	-2(1)	-1(1)	1(1)
O(2)	11(1)	15(1)	15(1)	2(1)	3(1)	-1(1)
N(1)	10(1)	10(1)	10(1)	2(1)	0(1)	-2(1)
C(1)	10(1)	12(1)	10(1)	0(1)	-1(1)	1(1)
C(2)	14(1)	11(1)	10(1)	0(1)	-1(1)	2(1)
C(3)	24(1)	10(1)	14(1)	-2(1)	-2(1)	2(1)
C(4)	26(1)	12(1)	17(1)	0(1)	-2(1)	-5(1)

Table D. (cont.)

C(5)	17(1)	14(1)	17(1)	0(1)	-2(1)	-6(1)
C(6)	10(1)	13(1)	13(1)	1(1)	1(1)	-2(1)
C(7)	14(1)	9(1)	10(1)	1(1)	1(1)	0(1)
C(8)	14(1)	12(1)	13(1)	1(1)	-1(1)	-2(1)
C(9)	12(1)	13(1)	16(1)	2(1)	-2(1)	-1(1)
C(10)	17(1)	11(1)	14(1)	3(1)	2(1)	1(1)
C(11)	21(1)	12(1)	14(1)	-1(1)	-5(1)	0(1)
C(12)	15(1)	13(1)	14(1)	1(1)	-4(1)	0(1)
C(13)	22(1)	14(1)	21(1)	-3(1)	-1(1)	5(1)
C(14)	14(1)	11(1)	10(1)	1(1)	-2(1)	2(1)
C(15)	14(1)	14(1)	13(1)	0(1)	-3(1)	0(1)
C(16)	21(1)	14(1)	18(1)	1(1)	-7(1)	-3(1)
C(17)	31(1)	13(1)	16(1)	-4(1)	-7(1)	2(1)
C(18)	24(1)	17(1)	14(1)	-4(1)	0(1)	6(1)
C(19)	16(1)	14(1)	14(1)	-1(1)	0(1)	0(1)
C(20)	19(1)	14(1)	9(1)	1(1)	-2(1)	3(1)
C(21)	18(1)	20(1)	13(1)	3(1)	-1(1)	-2(1)
C(22)	27(1)	17(1)	16(1)	0(1)	-4(1)	-5(1)
C(23)	31(1)	16(1)	13(1)	-2(1)	1(1)	1(1)
C(24)	22(1)	20(1)	13(1)	2(1)	2(1)	1(1)
C(25)	20(1)	15(1)	12(1)	2(1)	-2(1)	-2(1)

Table E. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å ^{2}x 10 ^{3}) for cd24gsa.

	x	y	z	U(eq)
H(1A)	3116	8760	1029	13
H(2A)	-120	8102	1833	14
H(3A)	1949	7285	858	19
H(3B)	1723	6728	1447	19
H(4A)	-1310	6416	876	22
H(4B)	-2177	6960	1426	22

Table E. (cont.)

H(5A)	-3991	7451	603	19
H(5B)	-1754	7543	237	19
H(6A)	-3286	8885	577	15
H(6B)	-2708	8599	1239	15
H(8A)	-3586	10139	-236	15
H(9A)	-5664	11349	-8	17
H(11A)	-773	12199	1053	18
H(12A)	1329	11000	823	17
H(13A)	-6391	12533	625	29
H(13B)	-4313	13149	550	29
H(13C)	-4795	12705	1175	29
H(15A)	4941	9942	1340	17
H(16A)	5252	11201	1894	21
H(17A)	2301	11665	2470	24
H(18A)	-962	10880	2494	22
H(19A)	-1271	9617	1947	17
H(21A)	5706	9217	2746	20
H(22A)	4870	10045	3578	24
H(23A)	1466	9899	4046	24
H(24A)	-1070	8898	3701	22
H(25A)	-198	8030	2890	19

Table F. Torsion angles [°] for cd24gsa.

O(2)-S(1)-N(1)-C(6)	-172.93(11)
O(1)-S(1)-N(1)-C(6)	-43.39(13)
C(7)-S(1)-N(1)-C(6)	70.65(12)
O(2)-S(1)-N(1)-C(1)	18.65(13)
O(1)-S(1)-N(1)-C(1)	148.19(11)
C(7)-S(1)-N(1)-C(1)	-97.77(12)
C(6)-N(1)-C(1)-C(14)	-96.20(16)
S(1)-N(1)-C(1)-C(14)	71.50(16)
C(6)-N(1)-C(1)-C(2)	31.85(19)
S(1)-N(1)-C(1)-C(2)	-160.45(11)

Table F. (cont.)

N(1)-C(1)-C(2)-C(3)	51.09(18)
C(14)-C(1)-C(2)-C(3)	179.05(14)
N(1)-C(1)-C(2)-S(2)	171.67(10)
C(14)-C(1)-C(2)-S(2)	-60.37(16)
C(20)-S(2)-C(2)-C(1)	84.47(12)
C(20)-S(2)-C(2)-C(3)	-152.15(11)
C(1)-C(2)-C(3)-C(4)	-92.82(17)
S(2)-C(2)-C(3)-C(4)	145.81(12)
C(2)-C(3)-C(4)-C(5)	67.42(19)
C(3)-C(4)-C(5)-C(6)	-50.6(2)
C(1)-N(1)-C(6)-C(5)	-89.95(17)
S(1)-N(1)-C(6)-C(5)	101.93(13)
C(4)-C(5)-C(6)-N(1)	71.27(18)
O(2)-S(1)-C(7)-C(8)	147.58(12)
O(1)-S(1)-C(7)-C(8)	17.16(14)
N(1)-S(1)-C(7)-C(8)	-98.00(13)
O(2)-S(1)-C(7)-C(12)	-37.18(15)
O(1)-S(1)-C(7)-C(12)	-167.61(13)
N(1)-S(1)-C(7)-C(12)	77.23(14)
C(12)-C(7)-C(8)-C(9)	-2.3(2)
S(1)-C(7)-C(8)-C(9)	172.98(12)
C(7)-C(8)-C(9)-C(10)	-0.6(2)
C(8)-C(9)-C(10)-C(11)	3.1(2)
C(8)-C(9)-C(10)-C(13)	-176.18(15)
C(9)-C(10)-C(11)-C(12)	-2.9(2)
C(13)-C(10)-C(11)-C(12)	176.42(16)
C(10)-C(11)-C(12)-C(7)	0.1(2)
C(8)-C(7)-C(12)-C(11)	2.5(2)
S(1)-C(7)-C(12)-C(11)	-172.63(13)
N(1)-C(1)-C(14)-C(15)	-114.96(16)
C(2)-C(1)-C(14)-C(15)	119.12(16)
N(1)-C(1)-C(14)-C(19)	64.1(2)
C(2)-C(1)-C(14)-C(19)	-61.8(2)
C(19)-C(14)-C(15)-C(16)	0.7(2)
C(1)-C(14)-C(15)-C(16)	179.81(15)

Table F. (cont.)

C(14)-C(15)-C(16)-C(17)	-0.4(2)
C(15)-C(16)-C(17)-C(18)	-0.1(3)
C(16)-C(17)-C(18)-C(19)	0.4(3)
C(15)-C(14)-C(19)-C(18)	-0.4(2)
C(1)-C(14)-C(19)-C(18)	-179.54(15)
C(17)-C(18)-C(19)-C(14)	-0.1(3)
C(2)-S(2)-C(20)-C(25)	55.09(15)
C(2)-S(2)-C(20)-C(21)	-127.34(13)
C(25)-C(20)-C(21)-C(22)	0.1(2)
S(2)-C(20)-C(21)-C(22)	-177.48(13)
C(20)-C(21)-C(22)-C(23)	-1.2(3)
C(21)-C(22)-C(23)-C(24)	1.0(3)
C(22)-C(23)-C(24)-C(25)	0.3(3)
C(21)-C(20)-C(25)-C(24)	1.1(2)
S(2)-C(20)-C(25)-C(24)	178.66(13)
C(23)-C(24)-C(25)-C(20)	-1.3(3)

Symmetry transformations used to generate equivalent atoms:

5.5 Experimental Procedures for Chapter 3

Purification and Specification of Sulfonic Acids

Specification of the Methanesulfonic Acid [HMC4064]

Following the established procedure,[134a] an oven-dried 100-mL round-bottomed-flask was charged with methanesulfonic acid (MsOH, 50 mL, 770 mmol, 1 equiv) and P_2O_5 (2.00 g, 14.0 mmol, 0.018 equiv). The mixture was stirred for 30 min at 100 ^oC (external temperature). Then the mixture was cooled to room temperature and purified via short path distillation (120 ^oC at 0.075 mmHg) gave 68.5 g (93% recovery) of MsOH as a pale yellow liquid.

Data for MsOH:

^1H NMR: (500 MHz, 0.1 M in $CDCl_3$)

δ 10.52 (s, 1 H, HO), 3.19 (s, 3 H, H_3C)

Integration ratio: 1.02 (HO): 3.00 (H_3C)

Specification of the Ethanesulfonic Acid [HMC5014]

Wet $EtSO_3H$ can be dried to the specification provided by the azeotropic removal of water with benzene.[134b] An oven-dried 100-mL round-bottomed-flask was charged with $EtSO_3H$ (8.2 mL, 100 mmol) and anhydrous benzene (60 mL). Simple distillation (80 ^oC, 1 atm) of this solution gave turbid liquid. This process was repeated until ^1H NMR spectrum of the pink residue showed no significant change in integration of the OH signal. This residue was then connected to high vacuum (0.010 mmHg) for 3 h to remove residual benzene. Purification of the acid by short path distillation (83-84 ^oC at 0.010 mmHg) gave 9.3 g (84% recovery) of $EtSO_3H$ as a pale yellow liquid. In our experience, the azeotropic water removal process was repeated as many as six times to ensure that the $EtSO_3H$ was dry.

Data for $EtSO_3H$:

^1H NMR: (500 MHz, 0.1 M in $CDCl_3$)

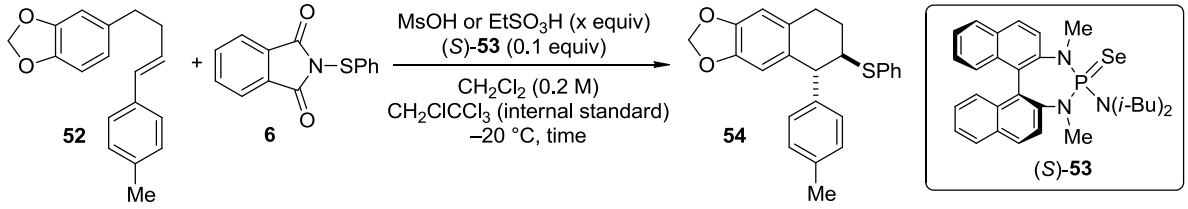
δ 10.61 (s, 1 H, HO), 3.25 (t, J = 7.0 Hz, 2 H, H_2C), 1.48 (t, J = 7.5 Hz, 3 H, H_3C)

Integration ratio: 1.15 (HO) : 2.00 (H_2C) : 3.02 (H_3C)

Experimental Procedures

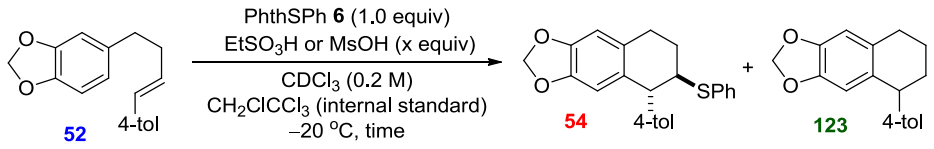
Optimization of Brønsted Acid (Figures 9 and 10)

General Procedure IX: Effect of Acid Loading on Catalyzed Reactions at 0.2 M Concentration



For experiments with a Lewis base catalyst, an oven-dried 5-mm NMR tube was charged with starting alkene **52** (32.0 mg, 120 μmol), *N*-phenylthiophthalimide **6** (30.7 mg, 120 μmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**53** (6.6 mg, 12.0 μmol, 0.1 equiv), 1,1,1,2-tetrachloroethane (CH_2ClCCl_3, 12.6 μL, 120 μmol, 1.0 equiv, internal standard) and $CDCl_3$ (600 μL) and capped with a septum cap. After shaking the mixture well making a homogeneous solution, the NMR tube was cooled to –20 ℃ in a cryocool unit. After reaching equilibrium, the indicated amount of $EtSO_3H$ or MsOH was added via syringe to the upper wall of the NMR tube. After 5 min of equilibrium in the cryocool unit, the tube was shaken to dissolve acid into the solution. The reaction progress was monitored by the appearance of the diagnostic ^{1}H NMR resonance for the sulfenylated product **54** at 4.09 ppm (doublet, 1 H), and disappearance of starting alkene **52** at 6.37 ppm (doublet, 1 H) with respect to the internal standard at 4.30 ppm (singlet, 2 H). ^{1}H NMR spectra were obtained at 0.5 h, 1.5 h, 3 h, 6 h, 12 h, 24 h, and 48 h, by freezing the NMR tube in a dewar flask with dry-ice/acetone bath (–78 ℃) while transferring to a pre-cooled (–20 ℃) NMR instrument. After 48 h, the reaction mixture was quenched by rapidly pouring into 1 mL of sat. $NaHCO_3$ aq solution and the biphasic mixture was extracted with CH_2Cl_2 (1 mL × 3). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo (30 ℃, 10 mmHg) to afford the crude product. The product was purified via Combiflash® column chromatography (SiO_2, 4 g, RediSep® column, hexanes/Et_2O, 100:0 to 96:4 (hexane/Et_2O=19:1 solution was substituted with neat Et_2O with gradient to 80% to make 96:4)) prior to SFC analysis.

General Procedure X: Effect of Acid Loading on Uncatalyzed Reactions at 0.2 M Concentration



For background experiments, an oven-dried 5-mm NMR tube was charged with starting alkene **52** (32.0 mg, 120 μmol), *N*-phenylthiophthalimide **6** (30.7 mg, 120 μmol, 1.0 equiv), 1,1,1,2-tetrachloroethane (CH_2ClCCl_3, 12.6 μL, 120 μmol, 1.0 equiv, internal standard) and $CDCl_3$ (600 μL) and capped with a septum cap. After shaking the mixture well making a homogeneous solution, the NMR tube was cooled to –20 ℃ in a cryocool unit. After reaching equilibrium, the indicated amount of $EtSO_3H$ or MsOH was added via syringe to the upper wall of the NMR tube. After 5 min of equilibrium in the cryocool unit, the tube was shaken to dissolve acid into the solution. The reaction progress was monitored by the appearance of the diagnostic ^{1}H NMR resonance for the sulfenylated product **54** at 4.09 ppm (doublet, 1 H), and proton-initiated cyclization product **123** at 4.00 ppm (triplet, 1 H), and disappearance of starting alkene **52** at 6.37 ppm (doublet, 1 H) with respect to the internal standard at 4.30 ppm (singlet, 2 H). ^{1}H NMR spectra were obtained at 0.5 h, 1.5 h, 3 h, 6 h, 12 h, 24 h, and 48 h, by freezing the NMR tube in a dewar flask with dry-ice/acetone bath (–78 ℃) while transferring to a pre-cooled (–20 ℃) NMR instrument.

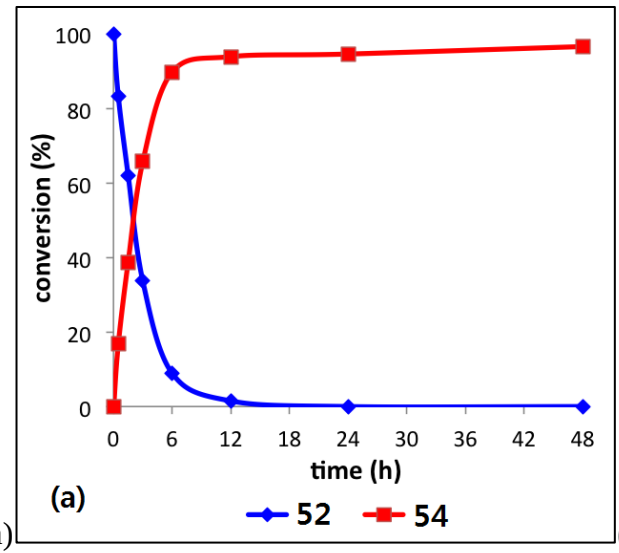
Acid Loading Study with MsOH

Figure 9a (1.00 equiv, catalyzed) [HMC5036]

Following General Procedure IX, an oven-dried, 5-mm NMR tube was charged with starting alkene **52** (32.0 mg, 120 μmol), *N*-phenylthiophthalimide **6** (30.7 mg, 120 μmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**53** (6.6 mg, 12.0 μmol, 0.1 equiv), 1,1,1,2-tetrachloroethane (12.6 μL, 120 μmol, 1.0 equiv) and $CDCl_3$ (600 μL) and capped. The NMR tube was cooled to −20 °C in a cryocool unit and MsOH (7.8 μL, 1.00 equiv) was added via syringe. The reaction progress was monitored by ^{1}H NMR spectroscopy. After 48 h, the reaction mixture was quenched. Purification of the crude product via Combiflash® column chromatography (SiO_2, 4 g, RediSep® column, hexanes/Et_2O, 100:0 to 96:4) gave 42 mg (93%) of **54**.

SFC: (5*S*,6*S*)-**54,** t_R 14.5 min (21%); (5*R*,6*R*)-**54,** t_R 16.4 min (79%) (Chiralpak AD, 5% MeOH in CO_2, 2.0 mL/min, 220 nm, 40 °C)

(a)



(b)

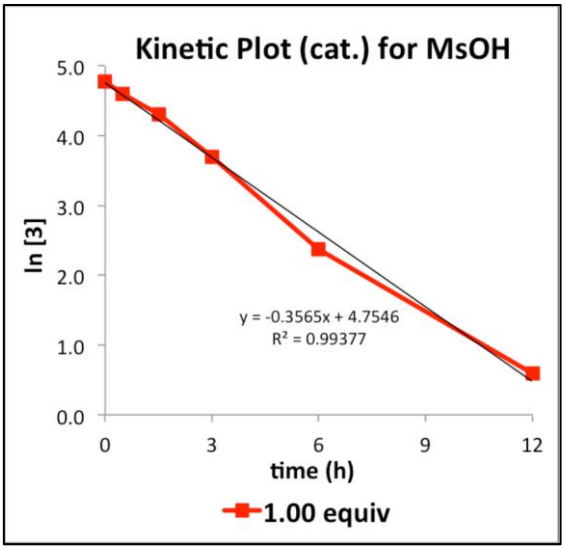


Figure 22. (a) Catalyzed reaction with 1.00 equiv MsOH. (b) First order kinetic plot.

Figure 9b (1.00 equiv, uncatalyzed) [HMC5031]

Following General Procedure X, an oven-dried, 5-mm NMR tube was charged with starting alkene **52** (32.0 mg, 120 μmol), *N*-phenylthiophthalimide **6** (30.7 mg, 120 μmol, 1.0 equiv), 1,1,1,2-tetrachloroethane (12.6 μL, 120 μmol, 1.0 equiv) and $CDCl_3$ (600 μL) and capped. The NMR tube was cooled to −20 °C in a cryocool unit and MsOH (7.8 μL, 1.00 equiv) was added via syringe. The reaction progress was monitored by ^{1}H NMR spectroscopy.

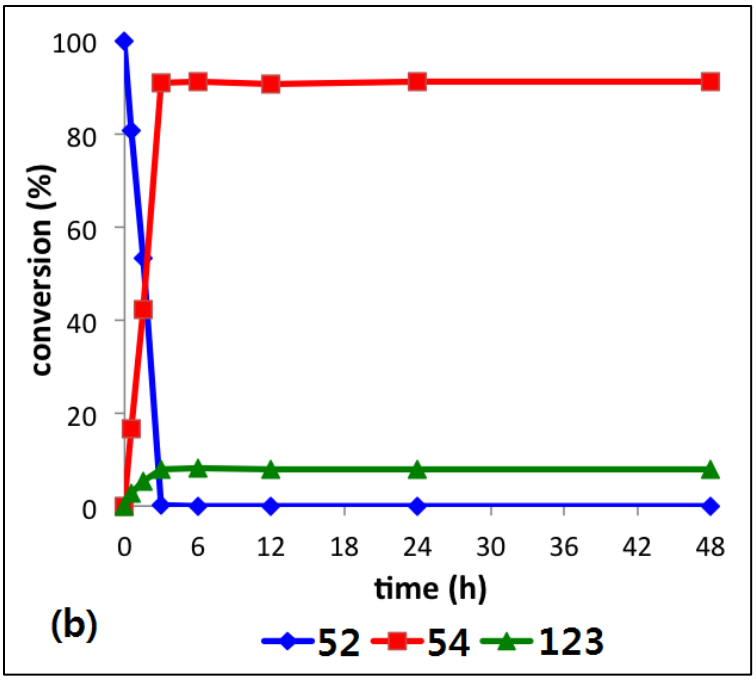


Figure 23. Uncatalyzed reaction with 1.00 equiv MsOH.

Acid Loadings Study with $EtSO_3H$

Figure 10a (1.00 equiv, catalyzed) [HMC5037]

Following General Procedure IX, an oven-dried, 5-mm NMR tube was charged with starting alkene **52** (32.0 mg, 120 μmol), *N*-phenylthiophthalimide **6** (30.7 mg, 120 μmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**53** (6.6 mg, 12.0 μmol, 0.1 equiv), 1,1,1,2-tetrachloroethane (12.6 μL, 120 μmol, 1.0 equiv) and $CDCl_3$ (600 μL) and capped. The NMR tube was cooled to –20 °C in a cryocool unit and $EtSO_3H$ (9.8 μL, 1.00 equiv) was added via syringe. The reaction progress was monitored by ^{1}H NMR spectroscopy. After 48 h, the reaction mixture was quenched. Purification of the crude product via Combiflash® column chromatography (SiO_2, 4 g, RediSep® column, hexanes/Et_2O, 100:0 to 96:4) gave 41 mg (92%) of **54**.

SFC: (5*S*,6*S*)-**54,** t_R 14.7 min (13%); (5*R*,6*R*)-**54,** t_R 16.5 min (87%) (Chiralpak AD, 5% MeOH in CO_2, 2.0 mL/min, 220 nm, 40 °C)

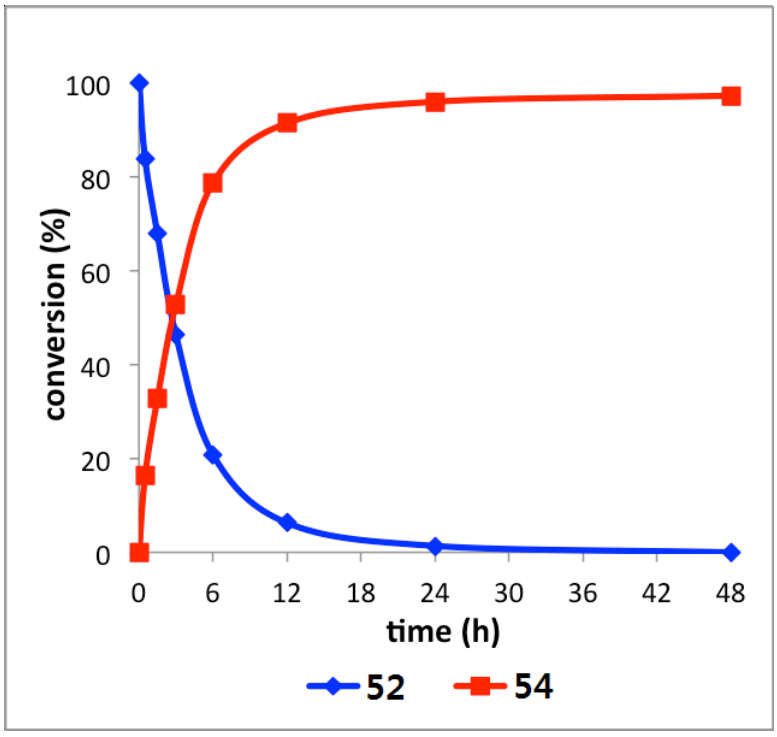


Figure 24. Catalyzed reaction with 1.00 equiv $EtSO_3H$.

Figure 10a (0.75 equiv, catalyzed) [HMC5038]

Following General Procedure IX, an oven-dried, 5-mm NMR tube was charged with starting alkene **52** (32.0 mg, 120 μmol), *N*-phenylthiophthalimide **6** (30.7 mg, 120 μmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**53** (6.6 mg, 12.0 μmol, 0.1 equiv), 1,1,1,2-tetrachloroethane (12.6 μL, 120 μmol, 1.0 equiv) and $CDCl_3$ (600 μL) and capped. The NMR tube was cooled to –20 °C in a cryocool unit and $EtSO_3H$ (7.3 μL, 0.75 equiv) was added via syringe. The reaction progress was monitored by ^1H NMR spectroscopy. After 48 h, the reaction mixture was quenched. Purification of the crude product via Combiflash® column chromatography (SiO_2, 4 g, RediSep® column, hexanes/Et_2O, 100:0 to 96:4) gave 41 mg (91%) of **54**.

SFC: (5*S*,6*S*)-**54,** t_R 14.8 min (10%); (5*R*,6*R*)-**54,** t_R 16.5 min (90%) (Chiralpak AD, 5% MeOH in CO_2, 2.0 mL/min, 220 nm, 40 °C)

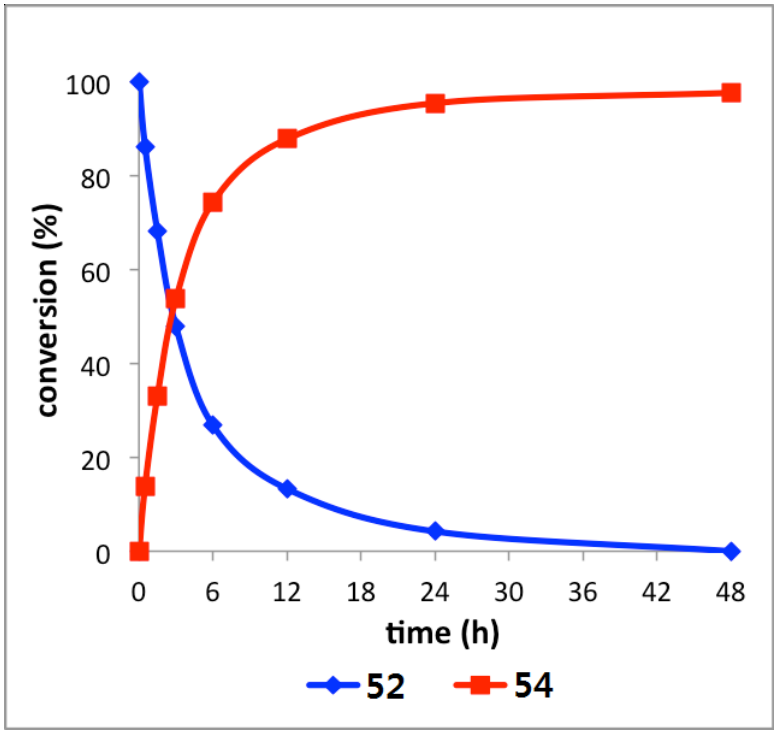


Figure 25. Catalyzed reaction with 0.75 equiv $EtSO_3H$.

Figure 10a (0.50 equiv catalyzed) [HMC5039]

Following General Procedure IX, an oven-dried, 5-mm NMR tube was charged with starting alkene **52** (32.0 mg, 120 μmol), *N*-phenylthiophthalimide **6** (30.7 mg, 120 μmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**53** (6.6 mg, 12.0 μmol, 0.1 equiv), 1,1,1,2-tetrachloroethane (12.6 μL, 120 μmol, 1.0 equiv) and $CDCl_3$ (600 μL) and capped. The NMR tube was cooled to –20 °C in a cryocool unit and $EtSO_3H$ (4.9 μL, 0.50 equiv) was added via syringe. The reaction progress was monitored by ^1H NMR spectroscopy. After 48 h, the reaction mixture was quenched. Purification of the crude product via Combiflash® column chromatography (SiO_2, 4 g, RediSep® column, hexanes/Et_2O, 100:0 to 96:4) gave 40 mg (89%) of **54**.

SFC: (5*S*,6*S*)-**54,** t_R 14.8 min (7%); (5*R*,6*R*)-**54,** t_R 16.5 min (93%) (Chiralpak AD, 5% MeOH in CO_2, 2.0 mL/min, 220 nm, 40 °C)

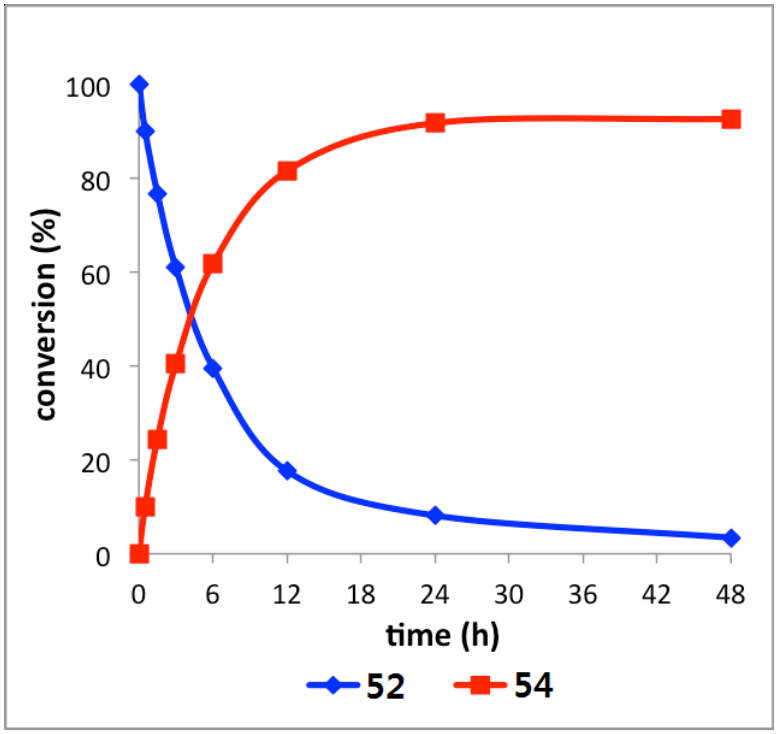


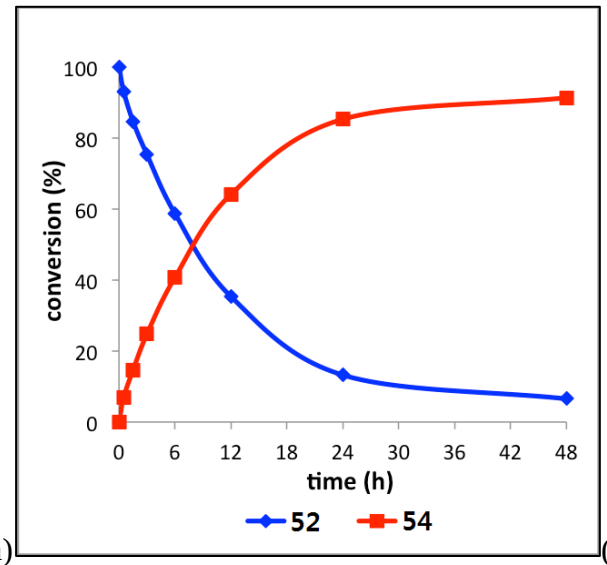
Figure 26. Catalyzed reaction with 0.50 equiv $EtSO_3H$.

Figure 10a (0.25 equiv, catalyzed) [HMC5040]

Following General Procedure IX, an oven-dried, 5-mm NMR tube was charged with starting alkene **52** (32.0 mg, 120 μmol), *N*-phenylthiophthalimide **6** (30.7 mg, 120 μmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**53** (6.6 mg, 12.0 μmol, 0.1 equiv), 1,1,1,2-tetrachloroethane (12.6 μL, 120 μmol, 1.0 equiv) and $CDCl_3$ (600 μL) and capped. The NMR tube was cooled to –20 °C in a cryocool unit and $EtSO_3H$ (2.4 μL, 0.25 equiv) was added via syringe. The reaction progress was monitored by ^1H NMR spectroscopy. After 48 h, the reaction mixture was quenched. Purification of the crude product via Combiflash® column chromatography (SiO_2, 4 g, RediSep® column, hexanes/Et_2O, 100:0 to 96:4) gave 39 mg (87%) of **54**.

SFC: (5*S*,6*S*)-**54,** t_R 14.8 min (7%); (5*R*,6*R*)-**54,** t_R 16.5 min (93%) (Chiralpak AD, 5% MeOH in CO_2, 2.0 mL/min, 220 nm, 40 °C)

(a)



(b)

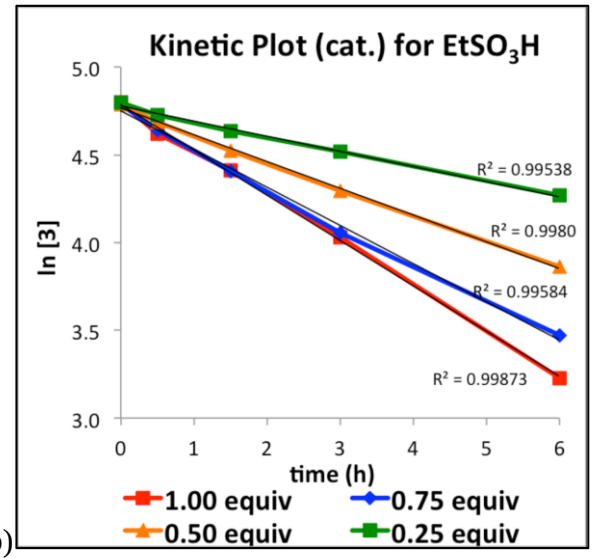


Figure 27. (a) Catalyzed reaction with 0.25 equiv $EtSO_3H$. (b) First order kinetic plot.

Figure 10b (1.00 equiv, uncatalyzed) [HMC5032]

Following General Procedure X, an oven-dried, 5-mm NMR tube was charged with starting alkene **52** (32.0 mg, 120 μmol), *N*-phenylthiophthalimide **6** (30.7 mg, 120 μmol, 1.0 equiv), 1,1,1,2-tetrachloroethane (12.6 μL, 120 μmol, 1.0 equiv) and $CDCl_3$ (600 μL) and capped. The NMR tube was cooled to –20 °C in a cryocool unit and $EtSO_3H$ (9.8 μL, 1.00 equiv) was added via syringe. The reaction progress was monitored by ^1H NMR spectroscopy.

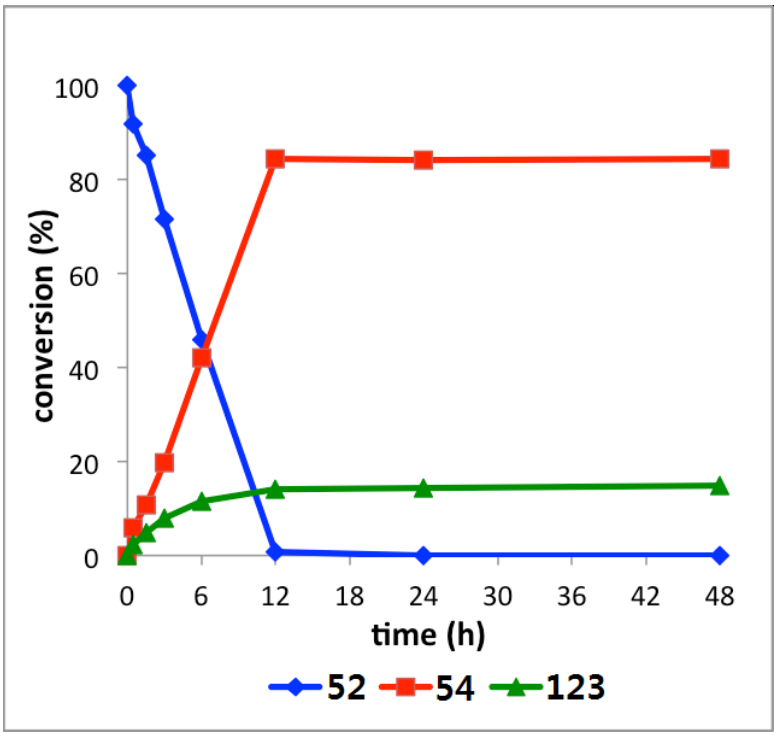


Figure 28. Uncatalyzed reaction with 1.00 equiv $EtSO_3H$.

Figure 10b (0.75 equiv, uncatalyzed) [HMC5033]

Following General Procedure X, an oven-dried, 5-mm NMR tube was charged with starting alkene **52** (32.0 mg, 120 μmol), *N*-phenylthiophthalimide **6** (30.7 mg, 120 μmol, 1.0 equiv), 1,1,1,2-tetrachloroethane (12.6 μL, 120 μmol, 1.0 equiv) and $CDCl_3$ (600 μL) and capped. The NMR tube was cooled to –20 °C in a cryocool unit and $EtSO_3H$ (7.3 μL, 0.75 equiv) was added via syringe. The reaction progress was monitored by ^1H NMR spectroscopy.

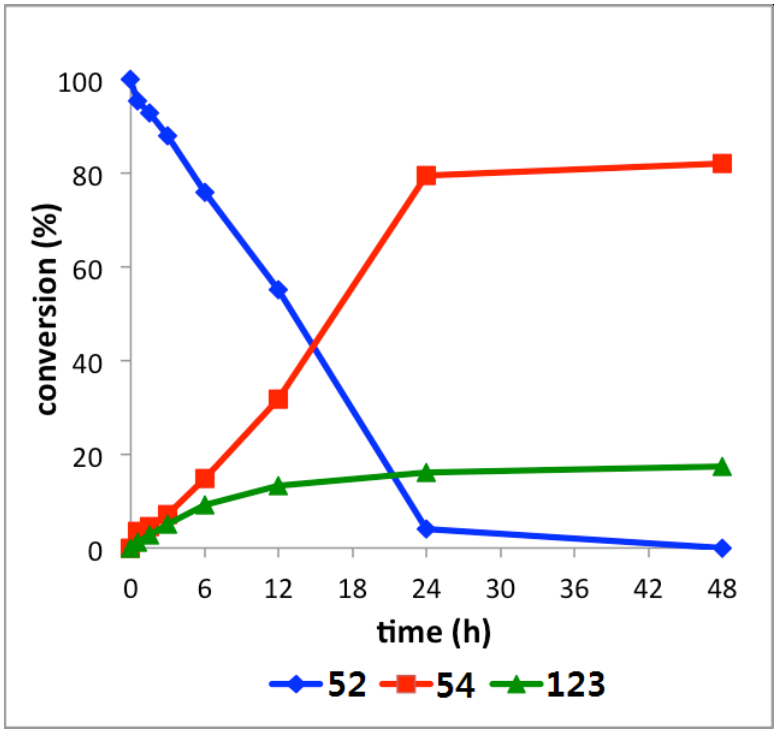


Figure 29. Uncatalyzed reaction with 0.75 equiv $EtSO_3H$.

Figure 10b (0.50 equiv, uncatalyzed) [HMC5034]

Following General Procedure X, an oven-dried, 5-mm NMR tube was charged with starting alkene **52** (32.0 mg, 120 μmol), *N*-phenylthiophthalimide **6** (30.7 mg, 120 μmol, 1.0 equiv), 1,1,1,2-tetrachloroethane (12.6 μL, 120 μmol, 1.0 equiv) and $CDCl_3$ (600 μL) and capped. The NMR tube was cooled to –20 °C in a cryocool unit and $EtSO_3H$ (4.9 μL, 0.50 equiv) was added via syringe. The reaction progress was monitored by ^1H NMR spectroscopy.

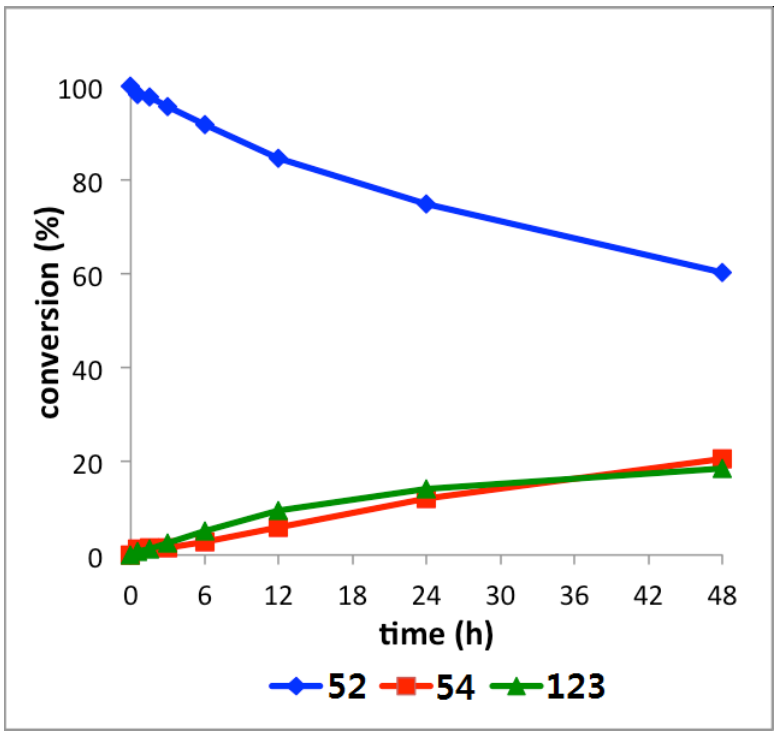


Figure 30. Uncatalyzed reaction with 0.50 equiv $EtSO_3H$.

Figure 10b (0.25 equiv, uncatalyzed) [HMC5035]

Following General Procedure X, an oven-dried, 5-mm NMR tube was charged with starting alkene **52** (32.0 mg, 120 μmol), *N*-phenylthiophthalimide **6** (30.7 mg, 120 μmol, 1.0 equiv), 1,1,1,2-tetrachloroethane (12.6 μL, 120 μmol, 1.0 equiv) and $CDCl_3$ (600 μL) and capped. The NMR tube was cooled to –20 °C in a cryocool unit and $EtSO_3H$ (2.4 μL, 0.25 equiv) was added via syringe. The reaction progress was monitored by ^1H NMR spectroscopy.

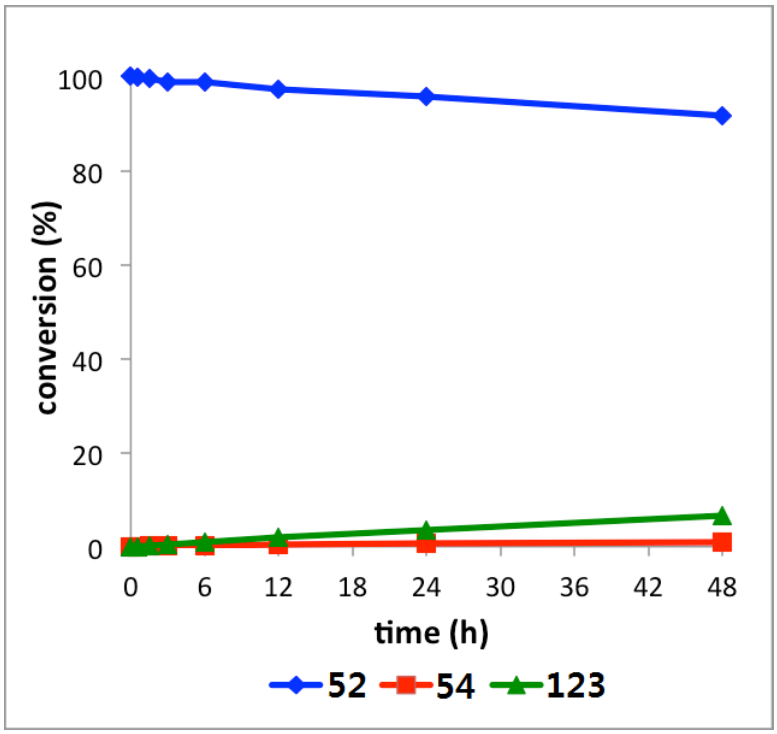
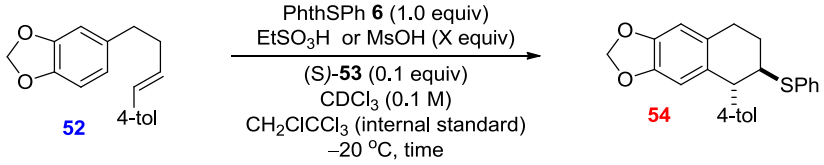


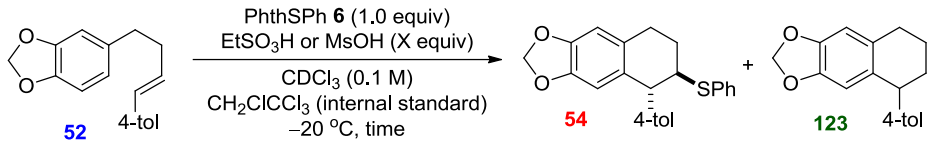
Figure 31. Uncatalyzed reaction with 0.25 equiv $EtSO_3H$.

General Procedure XI: Effect of Acid Loading on Catalyzed Reactions at 0.1 M Concentration



For experiments with a Lewis base catalyst, an oven-dried 5-mm NMR tube was charged with starting alkene **52** (13.3 mg, 50 μmol), *N*-phenylthiophthalimide **6** (12.8 mg, 50 μmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**53** (2.7 mg, 5.0 μmol, 0.1 equiv), 1,1,1,2-tetrachloroethane (CH_2ClCCl_3, 5.0 μL, 48 μmol, 0.95 equiv, internal standard) and $CDCl_3$ (500 μL) and capped with a septum cap. After shaking the mixture well making a homogeneous solution, the NMR tube was cooled to –20 ℃ in a cryocool unit. After reaching equilibrium, the indicated amount of $EtSO_3H$ or MsOH was added via syringe to the upper wall of the NMR tube. After 5 min of equilibrium in the cryocool unit, the tube was shaken to dissolve acid into the solution. The reaction progress was monitored by the appearance of the diagnostic ^{1}H NMR resonance for the sulfenylated product **54** at 4.09 ppm (doublet, 1 H), and disappearance of starting alkene **52** at 6.37 ppm (doublet, 1 H) with respect to the internal standard at 4.30 ppm (singlet, 2 H). ^{1}H NMR spectra were obtained at 1 h, 3 h, 6 h, 12 h, 24 h, and 48 h, by freezing the NMR tube in a dewar flask with dry-ice/acetone bath (–78 ℃) while transferring to a pre-cooled (–20 ℃) NMR instrument. After 48 h, the reaction mixture was quenched by rapidly pouring into 1 mL of sat. $NaHCO_3$ aq solution and the biphasic mixture was extracted with CH_2Cl_2 (1 mL × 3). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo (30 ℃, 10 mmHg) to afford the crude product. The product was purified via Combiflash® column chromatography (SiO_2, 4 g, RediSep® column, hexanes/Et_2O, 100:0 to 96:4 (hexane/Et_2O, 19:1 solution was substituted with neat Et_2O with gradient to 80% to make 96:4)) prior to SFC analysis.

General Procedure XII: Effect of Acid Loading on Uncatalyzed Reactions at 0.1 M Concentration



For background experiments, an oven-dried 5-mm NMR tube was charged with starting alkene **52** (13.3 mg, 50 μmol), *N*-phenylthiophthalimide **6** (12.8 mg, 50 μmol, 1.0 equiv), 1,1,1,2-tetrachloroethane (CH_2ClCCl_3, 5.0 μL, 48 μmol, 0.95 equiv, internal standard) and $CDCl_3$ (500 μL) and capped with a septum cap. After shaking the mixture well making a homogeneous solution, the NMR tube was cooled to –20 ℃ in a cryocool unit. After reaching equilibrium, the indicated amount of $EtSO_3H$ or MsOH was added via syringe to the upper wall of the NMR tube. After 5 min of equilibrium in the cryocool unit, the tube was shaken to dissolve acid into the solution. The reaction progress was monitored by the appearance of the diagnostic ^{1}H NMR resonance for the sulfenylated product **54** at 4.09 ppm (doublet, 1 H), and proton-initiated cyclization product **123** at 4.00 ppm (triplet, 1 H), and disappearance of starting alkene **52** at 6.37 ppm (doublet, 1 H) with respect to the internal standard at 4.30 ppm (singlet, 2 H). ^{1}H NMR spectra were obtained at 1 h, 3 h, 6 h, 12 h, 24 h, and 48 h, by freezing the NMR tube in a dewar flask with dry-ice/acetone bath (–78 ℃) while transferring to a pre-cooled (–20 ℃) NMR instrument.

Acid Loading Study with MsOH

(1.00 equiv, catalyzed) [HMC4097]

Following General Procedure XI, an oven-dried, 5-mm NMR tube was charged with starting alkene **52** (13.3 mg, 50 μmol), *N*-phenylthiophthalimide **6** (12.8 mg, 50 μmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**53** (2.7 mg, 5.0 μmol, 0.1 equiv), 1,1,1,2-tetrachloroethane (5.0 μL, 48 μmol, 0.95 equiv) and $CDCl_3$ (500 μL) and capped. The NMR tube was cooled to −20 °C in a cryocool unit and MsOH (3.2 μL, 1.00 equiv) was added via syringe. The reaction progress was monitored by ^{1}H NMR spectroscopy. After 48 h, the reaction mixture was quenched. Purification of the crude product via Combiflash® column chromatography (SiO_2, 4 g, RediSep® column, hexanes/Et_2O, 100:0 to 96:4) gave 17 mg (92%) of **54**.

SFC: (5*S*,6*S*)-**54** t_R 14.3 min (25%); (5*R*,6*R*)-**54,** t_R 16.2 min (75%) (Chiralpak AD, 5% MeOH in CO_2, 2.0 mL/min, 220 nm, 40 °C)

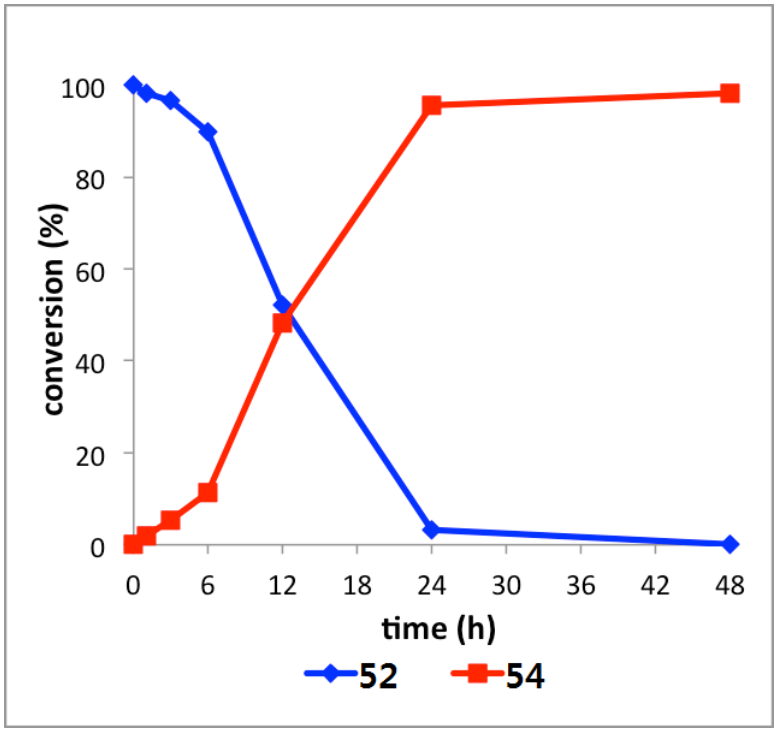


Figure 32. Catalyzed reaction with 1.00 equiv MsOH.

Acid Loading Study with MsOH

(1.00 equiv, uncatalyzed) [HMC4098]

Following General Procedure XII, an oven-dried, 5-mm NMR tube was charged with starting alkene **52** (13.3 mg, 50 μmol), *N*-phenylthiophthalimide **6** (12.8 mg, 50 μmol, 1.0 equiv), 1,1,1,2-tetrachloroethane (5.0 μL, 48 μmol, 0.95 equiv) and $CDCl_3$ (500 μL) and capped. The NMR tube was cooled to −20 °C in a cryocool unit and MsOH (3.2 μL, 1.00 equiv) was added via syringe. The reaction progress was monitored by ^{1}H NMR spectroscopy.

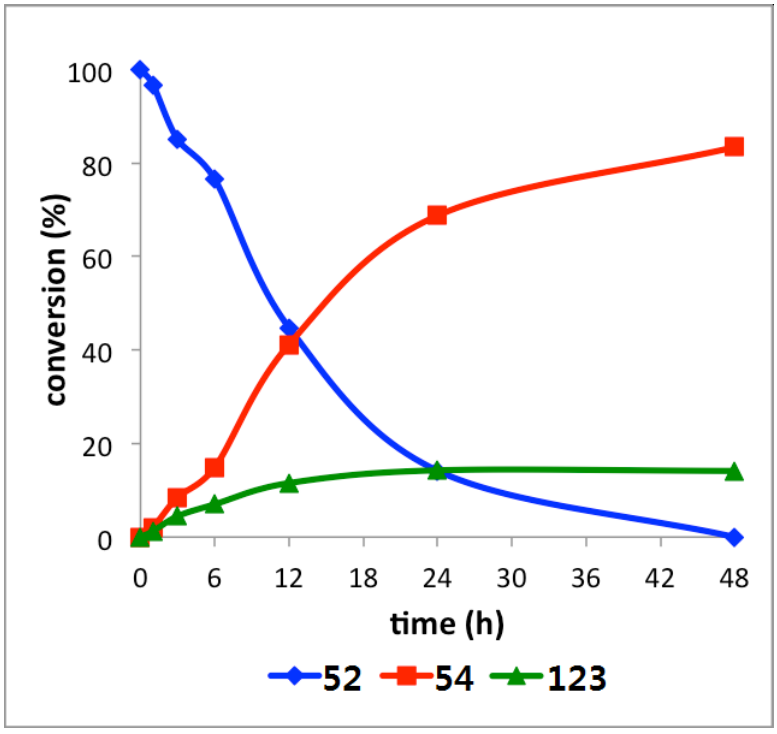


Figure 33. Uncatalyzed reaction with 1.00 equiv MsOH.

Acid Loadings Study with $EtSO_3H$

(1.00 equiv, catalyzed) [HMC4099]

Following General Procedure XI, an oven-dried, 5-mm NMR tube was charged with starting alkene **52** (13.3 mg, 50 μmol), *N*-phenylthiophthalimide **6** (12.8 mg, 50 μmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**53** (2.7 mg, 5.0 μmol, 0.1 equiv), 1,1,1,2-tetrachloroethane (5.0 μL, 48 μmol, 0.95 equiv) and $CDCl_3$ (500 μL) and capped. The NMR tube was cooled to −20 °C in a cryocool unit and $EtSO_3H$ (4.1 μL, 1.00 equiv) was added via syringe. The reaction progress was monitored by ^{1}H NMR spectroscopy. After 48 h, the reaction mixture was quenched. Purification of the crude product via Combiflash® column chromatography (SiO_2, 4 g, RediSep® column, hexanes/Et_2O, 100:0 to 96:4) gave 17 mg (89%) of **54**.

SFC: (5*S*,6*S*)-**54,** t_R 14.3 min (8%); (5*R*,6*R*)-**54,** t_R 16.2 min (92%) (Chiralpak AD, 5% MeOH in CO_2, 2.0 mL/min, 220 nm, 40 °C)

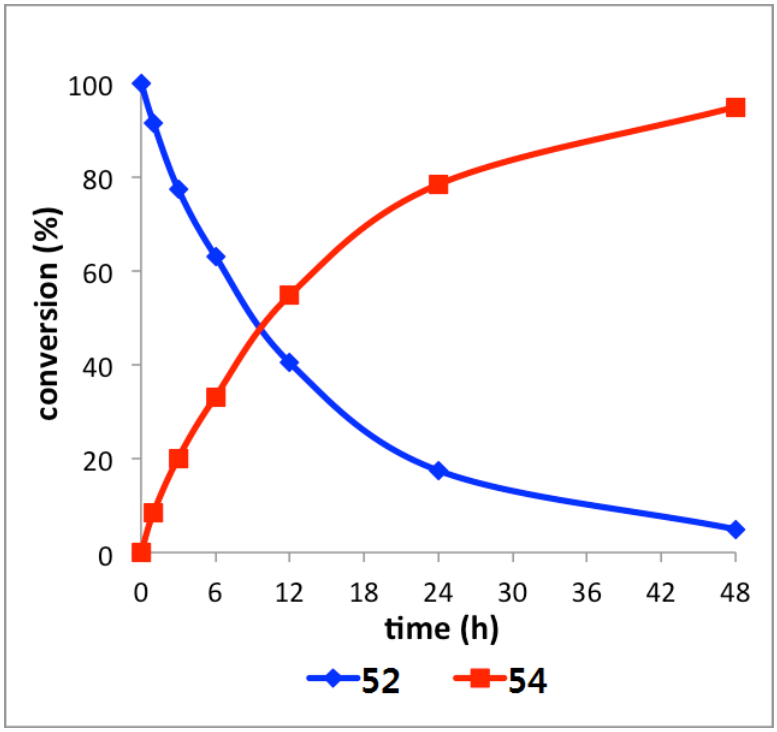


Figure 34. Uncatalyzed reaction with 1.00 equiv $EtSO_3H$.

Acid Loading Study with $EtSO_3H$

(0.75 equiv, catalyzed) [HMC5017]

Following General Procedure XI, an oven-dried, 5-mm NMR tube was charged with starting alkene **52** (13.3 mg, 50 μmol), *N*-phenylthiophthalimide **6** (12.8 mg, 50 μmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**53** (2.7 mg, 5.0 μmol, 0.1 equiv), 1,1,1,2-tetrachloroethane (5.0 μL, 48 μmol, 0.95 equiv) and $CDCl_3$ (500 μL) and capped. The NMR tube was cooled to −20 °C in a cryocool unit and $EtSO_3H$ (3.1 μL, 0.75 equiv) was added via syringe. The reaction progress was monitored by ^1H NMR spectroscopy. After 48 h, the reaction mixture was quenched. Purification of the crude product via Combiflash® column chromatography (SiO_2, 4 g, RediSep® column, hexanes/Et_2O, 100:0 to 96:4) gave 17 mg (91%) of **54**.

SFC: (5*S*,6*S*)-**54,** t_R 14.2 min (7%); (5*R*,6*R*)-**54,** t_R 16.1 min (93%) (Chiralpak AD, 5% MeOH in CO_2, 2.0 mL/min, 220 nm, 40 °C)

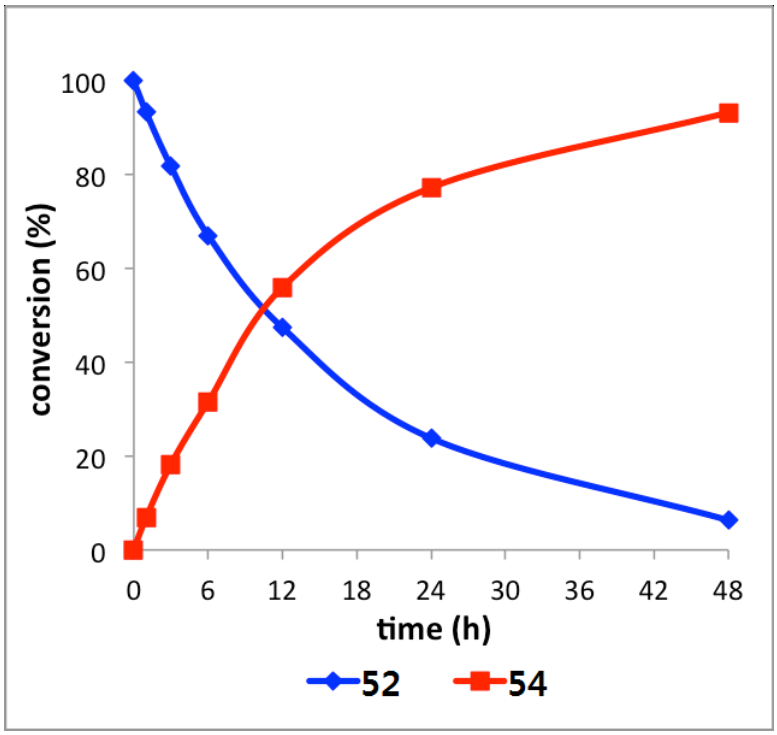


Figure 35. Uncatalyzed reaction with 0.75 equiv $EtSO_3H$.

Acid Loading Study with $EtSO_3H$

(0.50 equiv catalyzed) [HMC5019]

Following General Procedure XI, an oven-dried, 5-mm NMR tube was charged with starting alkene **52** (13.3 mg, 50 μmol), *N*-phenylthiophthalimide **6** (12.8 mg, 50 μmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**53** (2.7 mg, 5.0 μmol, 0.1 equiv), 1,1,1,2-tetrachloroethane (5.0 μL, 48 μmol, 0.95 equiv) and $CDCl_3$ (500 μL) and capped. The NMR tube was cooled to −20 °C in a cryocool unit and $EtSO_3H$ (2.0 μL, 0.50 equiv) was added via syringe. The reaction progress was monitored by ^1H NMR spectroscopy. After 48 h, the reaction mixture was quenched. Purification of the crude product via Combiflash® column chromatography (SiO_2, 4 g, RediSep® column, hexanes/Et_2O, 100:0 to 96:4) gave 16 mg (86%) of **54**.

SFC: (5*S*,6*S*)-**54,** t_R 14.3 min (7%); (5*R*,6*R*)-**54,** t_R 16.4 min (93%) (Chiralpak AD, 5% MeOH in CO_2, 2.0 mL/min, 220 nm, 40 °C)

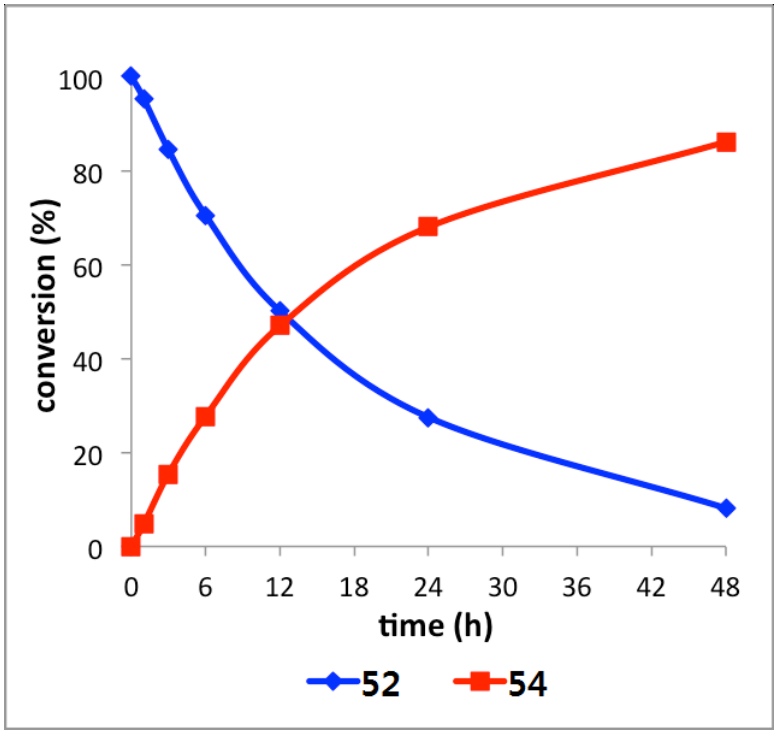


Figure 36. Uncatalyzed reaction with 0.50 equiv $EtSO_3H$.

Acid Loading Study with $EtSO_3H$

(0.25 equiv, catalyzed) [HMC5011]

Following General Procedure XI, an oven-dried, 5-mm NMR tube was charged with starting alkene **52** (13.3 mg, 50 μmol), *N*-phenylthiophthalimide **6** (12.8 mg, 50 μmol, 1.0 equiv), chiral Lewis base catalyst (*S*)-**53** (2.7 mg, 5.0 μmol, 0.1 equiv), 1,1,1,2-tetrachloroethane (5.0 μL, 48 μmol, 0.95 equiv) and $CDCl_3$ (500 μL) and capped. The NMR tube was cooled to −20 °C in a cryocool unit and $EtSO_3H$ (1.0 μL, 0.25 equiv) was added via syringe. The reaction progress was monitored by ^1H NMR spectroscopy. After 48 h, the reaction mixture was quenched. Purification of the crude product via Combiflash® column chromatography (SiO_2, 4 g, RediSep® column, hexanes/Et_2O, 100:0 to 96:4) gave 6 mg (31%) of **54**.

SFC: (5*S*,6*S*)-**54,** t_R 14.4 min (8%); (5*R*,6*R*)-**54,** t_R 16.5 min (92%) (Chiralpak AD, 5% MeOH in CO_2, 2.0 mL/min, 220 nm, 40 °C)

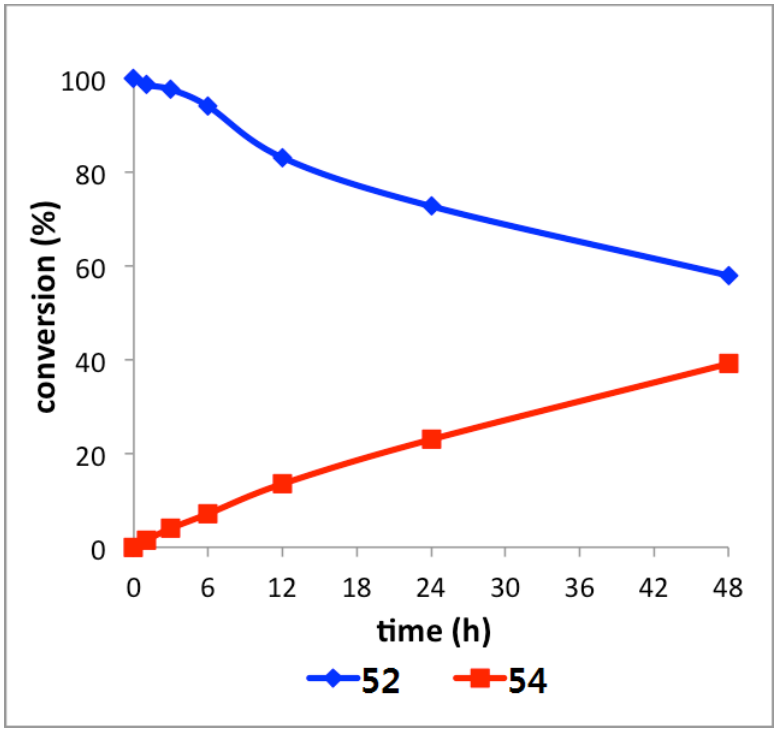


Figure 37. Uncatalyzed reaction with 0.25 equiv $EtSO_3H$.

Acid Loading Study with $EtSO_3H$

(1.00 equiv, uncatalyzed) [HMC4100]

Following General Procedure XII, an oven-dried, 5-mm NMR tube was charged with starting alkene **52** (13.3 mg, 50 μmol), *N*-phenylthiophthalimide **6** (12.8 mg, 50 μmol, 1.0 equiv), 1,1,1,2-tetrachloroethane (5.0 μL, 48 μmol, 0.95 equiv) and $CDCl_3$ (500 μL) and capped. The NMR tube was cooled to −20 °C in a cryocool unit and $EtSO_3H$ (4.1 μL, 1.00 equiv) was added via syringe. The reaction progress was monitored by ^{1}H NMR spectroscopy.

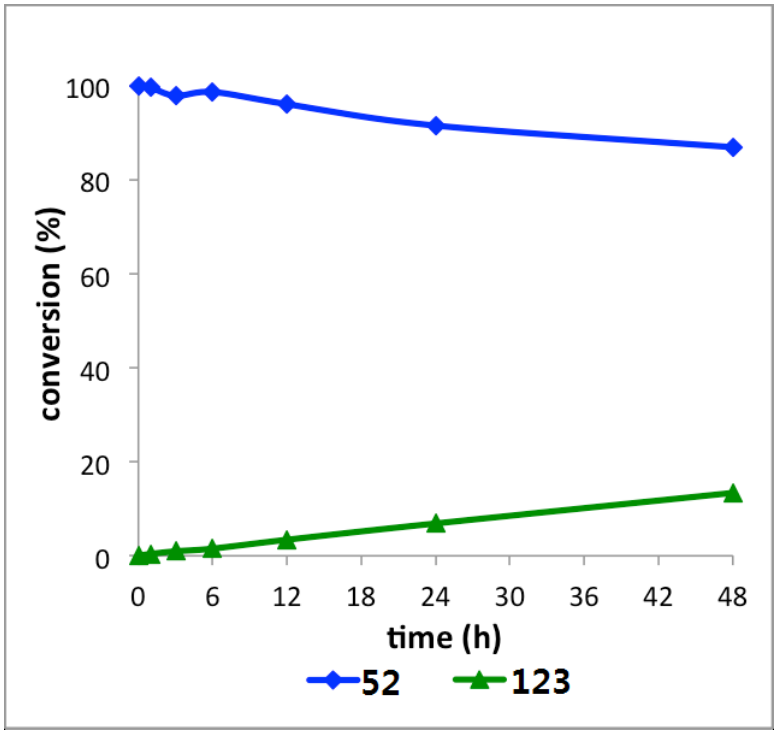


Figure 38. Uncatalyzed reaction with 1.00 equiv $EtSO_3H$.

Acid Loading Study with $EtSO_3H$

(0.75 equiv, uncatalyzed) [HMC5018]

Following General Procedure XII, an oven-dried, 5-mm NMR tube was charged with starting alkene **52** (13.3 mg, 50 μmol), *N*-phenylthiophthalimide **6** (12.8 mg, 50 μmol, 1.0 equiv), 1,1,1,2-tetrachloroethane (5.0 μL, 48 μmol, 0.95 equiv) and $CDCl_3$ (500 μL) and capped. The NMR tube was cooled to −20 °C in a cryocool unit and $EtSO_3H$ (3.1 μL, 0.75 equiv) was added via syringe. The reaction progress was monitored by ^{1}H NMR spectroscopy.

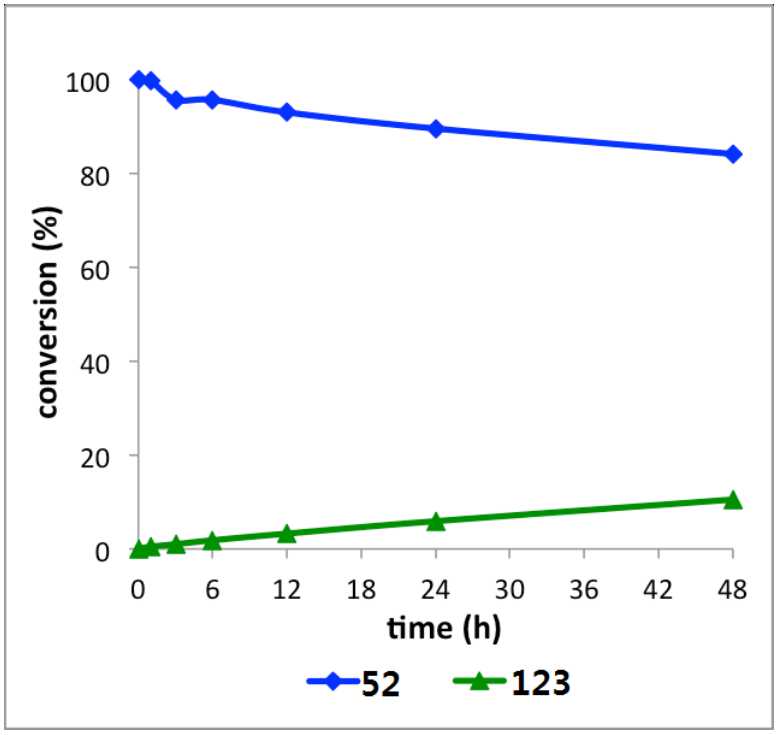


Figure 39. Uncatalyzed reaction with 0.75 equiv $EtSO_3H$.

Acid Loading Study with $EtSO_3H$

(0.50 equiv, uncatalyzed) [HMC5020]

Following General Procedure XII, an oven-dried, 5-mm NMR tube was charged with starting alkene **52** (13.3 mg, 50 μmol), *N*-phenylthiophthalimide **6** (12.8 mg, 50 μmol, 1.0 equiv), 1,1,1,2-tetrachloroethane (5.0 μL, 48 μmol, 0.95 equiv) and $CDCl_3$ (500 μL) and capped. The NMR tube was cooled to −20 °C in a cryocool unit and $EtSO_3H$ (2.0 μL, 0.50 equiv) was added via syringe. The reaction progress was monitored by ^{1}H NMR spectroscopy.

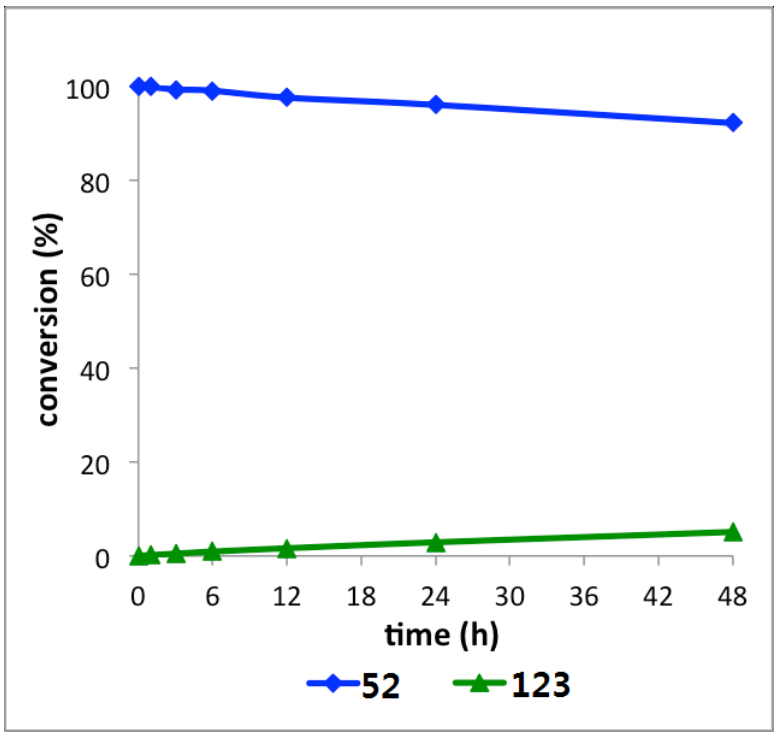


Figure 40. Uncatalyzed reaction with 0.50 equiv $EtSO_3H$.

Acid Loading Study with $EtSO_3H$

(0.25 equiv, uncatalyzed) [HMC5012]

Following General Procedure XII, an oven-dried, 5-mm NMR tube was charged with starting alkene **52** (13.3 mg, 50 μmol), *N*-phenylthiophthalimide **6** (12.8 mg, 50 μmol, 1.0 equiv), 1,1,1,2-tetrachloroethane (5.0 μL, 48 μmol, 0.95 equiv) and $CDCl_3$ (500 μL) and capped. The NMR tube was cooled to −20 °C in a cryocool unit and $EtSO_3H$ (1.0 μL, 0.25 equiv) was added via syringe. The reaction progress was monitored by ^{1}H NMR spectroscopy.

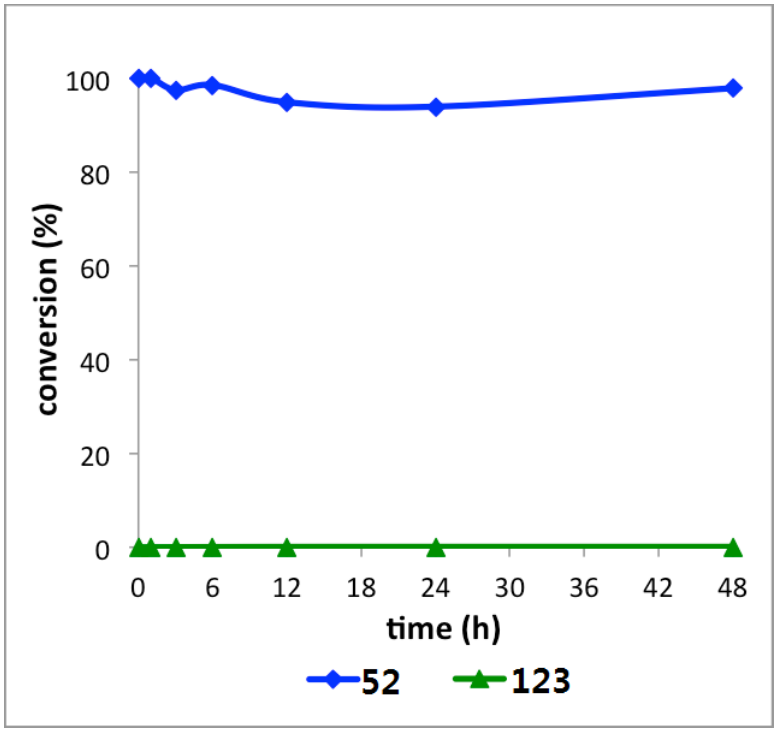
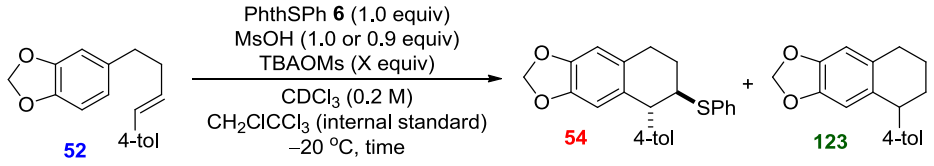


Figure 41. Uncatalyzed reaction with 0.25 equiv $EtSO_3H$.

Effect of TBAOMs as Additive

General Procedure XIII: Effect of Acid Loading on Uncatalyzed Reactions with Additional Sulfonate at 0.2 M Concentration



An oven-dried 5-mm NMR tube was charged with starting alkene **52** (32.0 mg, 120 μmol), *N*-phenylthiophthalimide **6** (30.7 mg, 120 μmol, 1.0 equiv), and brought into a glovebox. In the glovebox, to the NMR tube was added indicated amount of tetrabutylammonium methanesulfonate (TBAOMs, highly hygroscopic) and capped with a septum cap. The NMR tube was brought back out from the glovebox and 1,1,1,2-tetrachloroethane (CH_2ClCCl_3, 12.6 μL, 120 μmol, 1.0 equiv, internal standard) and $CDCl_3$ (600 μL) were added via syringe. After shaking the mixture well making a homogeneous solution, the NMR tube was cooled to –20 ℃ in a cryocool unit. After reaching equilibrium, the indicated amount of MsOH was added via syringe to the upper wall of the NMR tube. After 5 min of equilibrium in the cryocool unit, the tube was shaken to dissolve acid into the solution. The reaction progress was monitored by the appearance of the diagnostic ^{1}H NMR resonance for the sulfenylated product **54** at 4.09 ppm (doublet, 1 H), and proton-initicated cyclization product **123** at 4.00 ppm (triplet, 1 H), and disappearance of starting alkene **52** at 6.37 ppm (doublet, 1 H) with respect to the internal standard at 4.30 ppm (singlet, 2 H). ^{1}H NMR spectra were obtained at 0.5 h, 1.5 h, 3 h, 6 h, 12 h, 24 h, and 48 h, by freezing the NMR tube in a dewar flask with dry-ice/acetone bath (–78 ℃) while transferring to a pre-cooled (–20 ℃) NMR instrument.

Figure 14 (1.0 equiv MsOH + 0.1 equiv TBAOMs, uncatalyzed) [HMC5041]

Following General Procedure XIII, an oven-dried, 5-mm NMR tube was charged with starting alkene **52** (32.0 mg, 120 μmol), PhthSPh **6** (30.7 mg, 120 μmol, 1.0 equiv), TBAOMs (4.1 mg, 12 μmol, 0.1 equiv), 1,1,1,2-tetrachloroethane (12.6 μL, 120 μmol, 1.0 equiv) and $CDCl_3$ (600 μL). The NMR tube was cooled to –20 °C in a cryocool unit and MsOH (7.8 μL, 1.00 equiv) was added via syringe. The reaction progress was monitored by ^{1}H NMR spectroscopy.

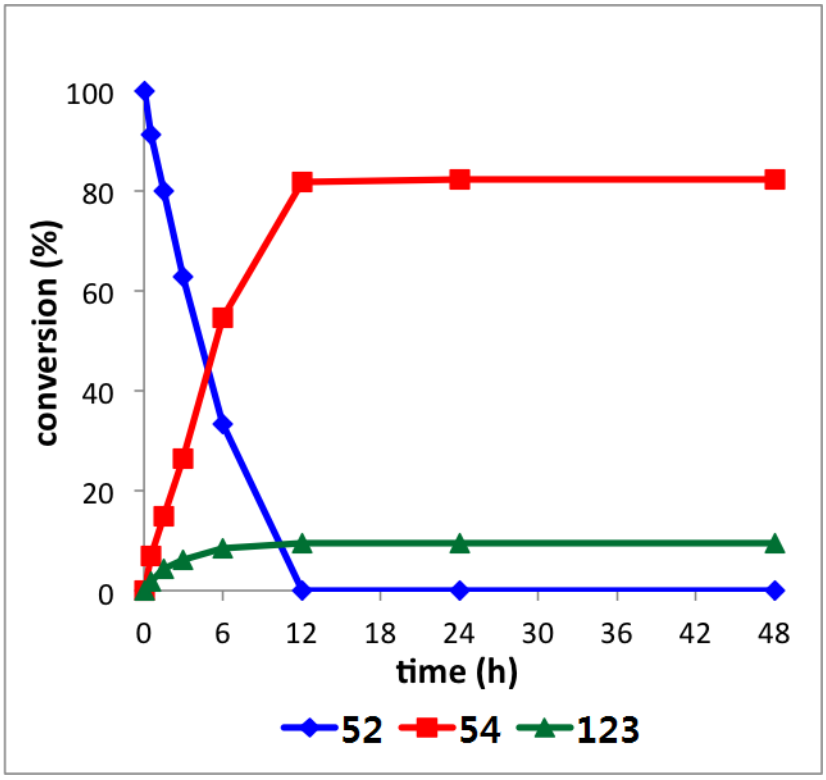


Figure 42. Uncatalyzed reaction with 1.00 equiv MsOH, 0.1 equiv TBAOMs.

Figure 14 (1.0 equiv MsOH + 0.2 equiv TBAOMs, uncatalyzed) [HMC5042]

Following General Procedure XIII, an oven-dried, 5-mm NMR tube was charged with starting alkene **52** (32.0 mg, 120 μmol), PhthSPh **6** (30.7 mg, 120 μmol, 1.0 equiv), TBAOMs (8.1 mg, 24 μmol, 0.2 equiv), 1,1,1,2-tetrachloroethane (12.6 μL, 120 μmol, 1.0 equiv) and $CDCl_3$ (600 μL). The NMR tube was cooled to −20 °C in a cryocool unit and MsOH (7.8 μL, 1.00 equiv) was added via syringe. The reaction progress was monitored by ^{1}H NMR spectroscopy.

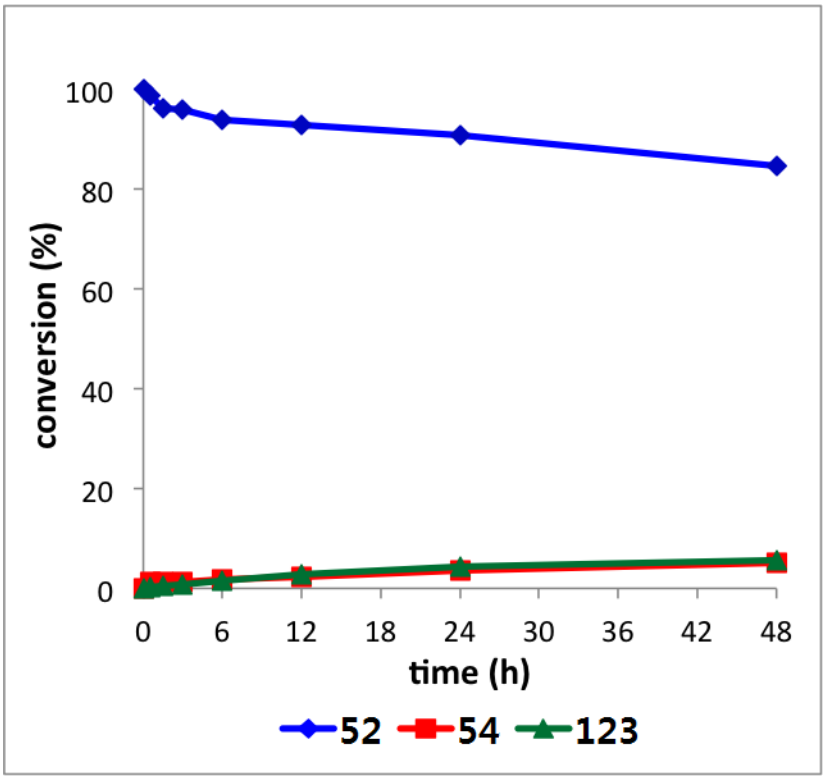


Figure 43. Uncatalyzed reaction with 1.00 equiv MsOH, 0.2 equiv TBAOMs.

Figure 14 (1.0 equiv MsOH + 0.4 equiv TBAOMs, uncatalyzed) [HMC5043]

Following General Procedure XIII, an oven-dried, 5-mm NMR tube was charged with starting alkene **52** (32.0 mg, 120 μmol), PhthSPh **6** (30.7 mg, 120 μmol, 1.0 equiv), TBAOMs (16.2 mg, 48 μmol, 0.1 equiv), 1,1,1,2-tetrachloroethane (12.6 μL, 120 μmol, 1.0 equiv) and $CDCl_3$ (600 μL). The NMR tube was cooled to −20 °C in a cryocool unit and MsOH (7.8 μL, 1.00 equiv) was added via syringe. The reaction progress was monitored by ^{1}H NMR spectroscopy.

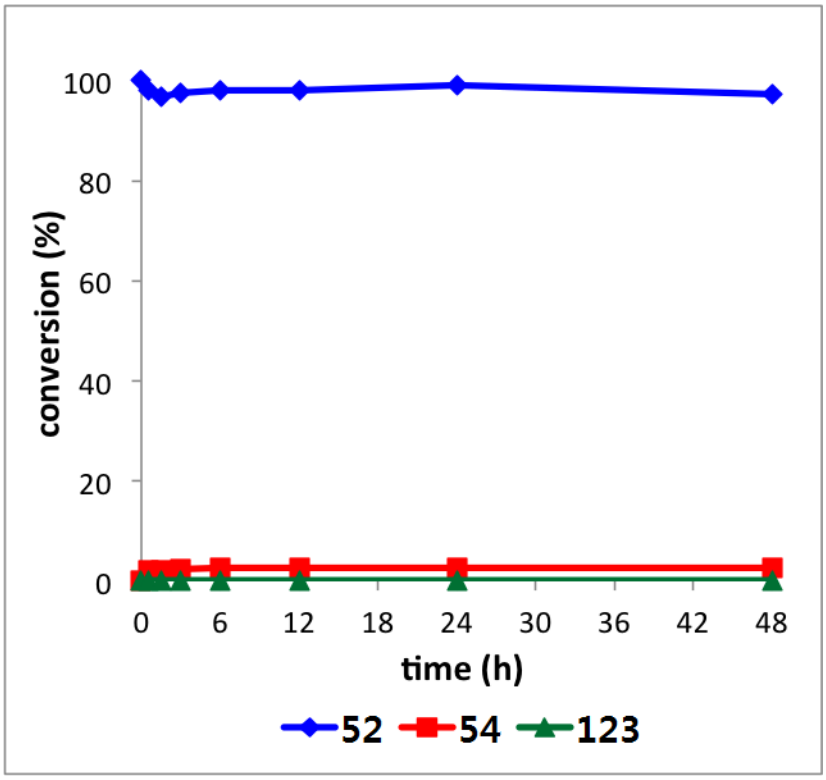


Figure 44. Uncatalyzed reaction with 1.00 equiv MsOH, 0.4 equiv TBAOMs.

Figure 15a and 15b (0.9 equiv MsOH + 0.1 equiv TBAOMs + 0 or 0.1 equiv PhthH) [HMC5057, HMC5058]

The experiments for Figure 15a and 15b were set up as '*twin batch*' to minimize error from weighing, following a slightly modified version of General Procedure XIII. An oven-dried, 4-mL vial was charged with starting alkene **52** (63.9 mg, 240 μmol), *N*-phenylthiophthalimide **6** (55.1 mg, 108 μmol, 0.9 equiv), and brought into a glovebox. In the glovebox, to the vial was added TBAOMs (8.1 mg, 24 μmol, 0.1 equiv) and capped with a cap with a silicon septum. The vial was brought back out from the glovebox and 1,1,1,2-tetrachloroethane (CH_2ClCCl_3, 25.2 μL, 240 μmol, 1.0 equiv, internal standard) and $CDCl_3$ (1.2 mL) were added via syringe. After shaking the mixture well making a homogeneous solution, the solution was equally distributed to two oven-dried, 5-mm NMR tubes capped with a septum via syringe. One NMR tube (experiment for Figure 15b) was pre-charged with PhthH (1.8 mg, 12 μmol, 0.1 equiv) before the distribution of the solution. Both NMR tubes with homogeneous solution were cooled to −20 °C in a cryocool unit and MsOH (7.0 μL, 0.90 equiv) was added via syringe. The reaction progress was monitored by ^{1}H NMR spectroscopy.

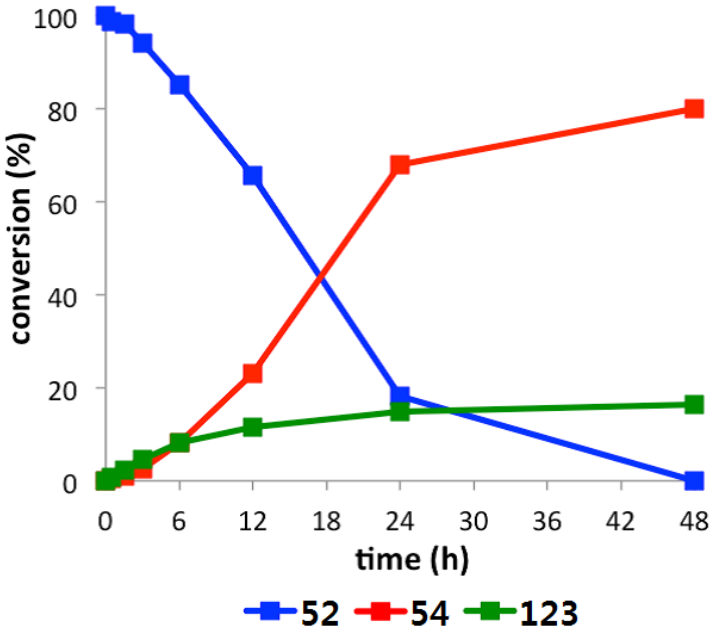


Figure 45. Uncatalyzed reaction with 0.9 equiv MsOH + 0.1 equiv TBAOMs.

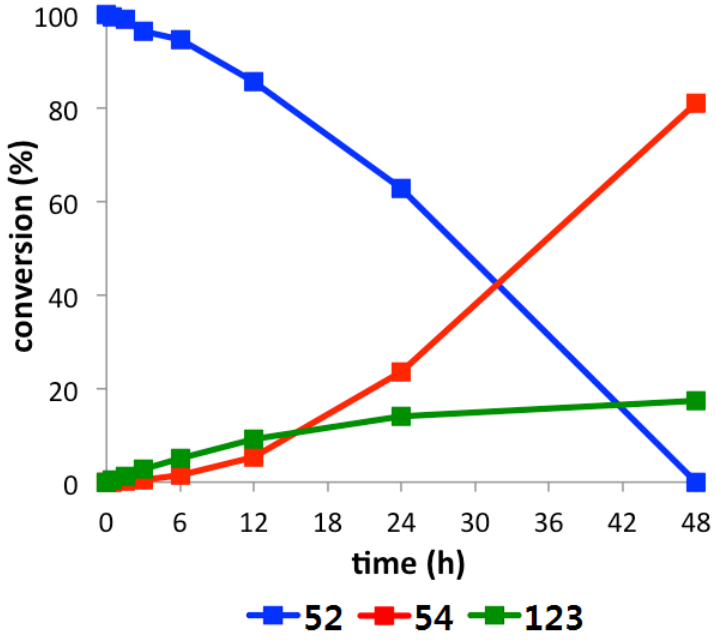


Figure 46. Uncatalyzed reaction with 0.9 equiv MsOH + 0.1 equiv TBAOMs + 0.1 equiv phthalimide.

Preparation of an Authentic Sample of Proton-Initiated Cyclization Product (123) [HMC4096]

An oven-dried 5-mm NMR tube were charged with starting alkene **52** (50 mg, 0.19 mmol), and $CDCl_3$ (940 μL) and capped with a septum cap. After shaking the mixture well making a homogeneous solution, $EtSO_3H$ (30.6 μL, 0.38 mmol, 2.0 equiv) was added to the solution via syringe at room temperature. The reaction was monitored by ^{1}H NMR spectroscopy, which was shown to be complete by 1 h. The reaction mixture was quenched by pouring into 5 mL of sat. aq. $NaHCO_3$ solution and the biphasic mixture was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo (30 ℃, 10 mmHg) to afford the crude product. The product was purified via Combiflash® column chromatography (SiO_2, 4 g, RediSep® column, hexanes/EtOAc, 100:0 to 95:5) affording 48 mg (95%) of **123** as a colorless oil.

Data for **123**:

^{1}H NMR: (500 MHz, $CDCl_3$)

7.09 (d, J = 8.0 Hz, 2 H, HC(13)), 6.98 (d, J = 8.0 Hz, 2 H, HC(12)), 6.59 (s, 1 H, HC(6)), 6.30 (s, 1 H, HC(9)), 5.86 – 5.82 (m, 2 H, OCH_2O)), 3.97 (t, J = 6.5 Hz, 1 H, HC(1)), 2.85 – 2.68 (m, 2 H, HC(4)), 2.32 (s, 3 H, HC(15)), 2.14 – 2.06 (m, 1 H, HC(2)), 1.88 – 1.76 (m, 2 H, HC(3,2)), 1.73 – 1.64 (m, 1 H, HC(3))

^{13}C NMR: (125 MHz, $CDCl_3$)

145.7 (C(7)), 145.6 (C(8)), 144.5 (C(14)), 135.4 (C(11)), 132.4 (C(10)), 130.6 (C(5)), 128.9 (C(13)), 128.6 (C(12)), 109.7 (C(9)), 108.3 (C(6)), 100.5 (OCH_2O), 45.2 (C(1)), 33.3 (C(2)), 29.9 (C(4)), 21.0 (C(3)), 20.9 (C(15))

MS: (EI^+, 70 eV)

267.1 (20.2), 266.1 (100.0), 251.1 (12.6), 251.0 (12.3), 238.1 (34.4), 238.1 (32.5), 223.0 (38.7), 175.1 (22.4), 174.0 (20.0), 165.0 (19.4), 117.0 (11.8), 115.0 (20.4),

109.1 (12.6), 105.0 (17.2), 97.1 (12.3), 95.1 (15.4), 91.1 (17.8), 91.0 (17.4), 89.0 (12.1), 83.1 (13.5), 83.1 (11.7), 81.1 (14.4), 77.0 (12.5), 69.1 (19.7), 67.1 (13.8), 57.1 (16.9), 55.1 (25.3)

HRMS: calcd for $C_{18}H_{18}O_2$: 266.1307, found: 266.1316

TLC: R_f 0.56 (hexanes/Et_2O, 96:4) [$KMnO_4$]

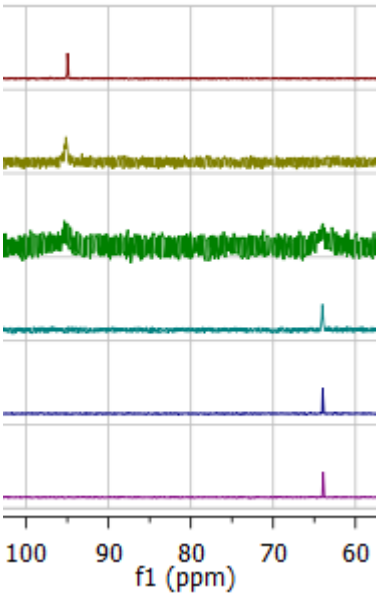
Catalyst Resting State and Titration Studies.

Experiment 1 (8.3 μM in (*S*)-53) [HMC5013]

An oven-dried 5-mm NMR tube was charged with isobutyl-substituted selenophosphoramide Lewis base catalyst (*S*)-**53** (2.7 mg, 5.0 μmol), *N*-phenylthiophthalimide **6** (PhthSPh, 12.8 mg, 50 μmol, 10.0 equiv) and $CDCl_3$ (600 μL) and the NMR tube was capped with a septum. After the NMR tube was shaken thoroughly, the resulting homogeneous solution was monitored by ^{31}P NMR spectroscopy at –20 °C. To this solution, neat amounts of $EtSO_3H$ were added to provide solutions with the equivalents shown in Table 1. ^{31}P NMR spectra at –20 and –50 °C were obtained for each solution.

Table 14. Catalyst Resting State at –20 and –50 °C.

^{31}P NMR at -50 °C

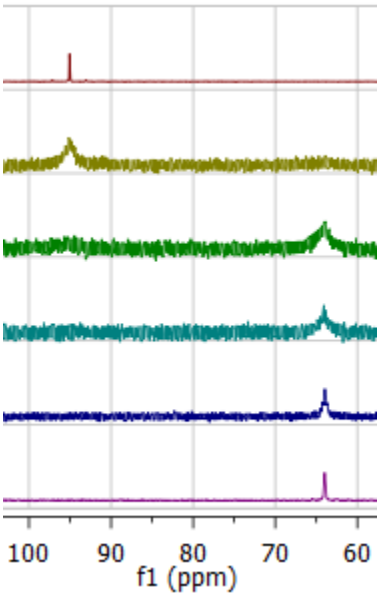


Reagents			^{31}P NMR δ ppm	
***i*-Bu cat (equiv)**	**PhthSPh (equiv)**	**$EtSO_3H$ (equiv)**	**at -20 °C**	**at -50 °C**
1.0	10.0	0.0	94.99	
1.0	10.0	1.0	94.94 (br)	95.18 (br)
1.0	10.0	2.5	94.28 (br) 64.26 (br)	95.35 (br), 63.93 (br) (ratio=1.00:0.91)
1.0	10.0	5.0	63.70 (br)	64.01
1.0	10.0	7.5	63.67	63.98
1.0	10.0	10.0	63.60	63.92

Experiment 2 (25 μM in (*S*)-1) [HMC5015]

An oven-dried 5-mm NMR tube was charged with isobutyl-substituted selenophosphoramide Lewis base catalyst (*S*)-**53** (8.2 mg, 15.0 μmol), *N*-phenyltihophthalimide **6** (38.4 mg, 150 μmol, 10.0 equiv) and $CDCl_3$ (600 μL) and the NMR tube was capped with a septum. After the NMR tube was shaken thoroughly, the resulting homogeneous solution was monitored by ^{31}P NMR spectroscopy at -50 ℃. To this solution, neat amounts of $EtSO_3H$ were added to provide solutions with the equivalents shown in Table 2. ^{31}P NMR spectra at -57 ℃ were obtained for each solution.

Table 15. Catalyst Resting State at –57 ˚C.

^{31}P NMR at -57 ℃	**Reagents**			**Ratio of ^{31}P NMR signals at 95 ppm and 64 ppm (-57 ℃)**
	***i*Bu cat (equiv)**	**PhthSPh (equiv)**	**$EtSO_3H$ (equiv)**	
	1.0	10.0	0.0	N/A (only 95 ppm signal was observed)
	1.0	10.0	1.0	3.12 : 1.00
	1.0	10.0	2.5	1.00 : 1.86
	1.0	10.0	3.0	1.00 : 4.07
	1.0	10.0	3.5	1.00 : 24.88
	1.0	10.0	4.0	1.00 : 54.49

Calculation of Equilibrium Constants (K_{eq}) [HMC5013, HMC5015]

Equilibrium constants were calculated for above two experiments both at 2.5 equivalent data points. The calculation indicated that the catalytically active species exist as tight ionic pair under the given reaction conditions.

Method 1: Separate ion pair

Catalyst (5 *m*mol) : PhthSPh : $EtSO_3H$ = 1.0 : 10.0 : 2.5 (600 *m*L $CDCl_3$, -50 ^oC) ^{31}P NMR 95 ppm : 64 ppm ratio: 1.00 : 0.91

Catalyst	Phth−SPh	$EtSO_3H$	$\rightleftharpoons$	$[catalyst-SPh]^+$	$[EtSO_3]^-$	PhthH
8.3 mM	83.3 mM	20.8 M		0 mM	0 mM	0 mM
8.3 - X mM	83.3 - X	20.8 - X mM		X mM	X mM	X mM

(8.3 - X) : X = 1.00 : 0.91

X = 3.97

$$K_{eq} = \frac{X^3}{(8.3 - X)(83.3 - X)(20.8 - X)} = 1.08 \times 10^{-2}$$

Catalyst (15 *m*mol) : PhthSPh : $EtSO_3H$ = 1.0 : 10.0 : 2.5 (600 *m*L $CDCl_3$, -57 ^oC) ^{31}P NMR 95 ppm : 64 ppm ratio: 1.00 : 1.86

Catalyst	Phth−SPh	$EtSO_3H$	$\rightleftharpoons$	$[catalyst-SPh]^+$	$[EtSO_3]^-$	PhthH
25 mM	250 mM	62.5 mM		0 mM	0 mM	0 mM
25 - X mM	250 - X mM	62.5 - X mM		X mM	X mM	X mM

(25 - X) : X = 1.00 : 1.86

X = 16.3

$$K_{eq} = \frac{X^3}{(25 - X)(250 - X)(62.5 - X)} = 4.55 \times 10^{-2}$$

Method 2: Tight ion pair

Catalyst (5 *m*mol) : PhthSPh : $EtSO_3H$ = 1.0 : 10.0 : 2.5 (600 *m*L $CDCl_3$, -50 ^oC) ^{31}P NMR 95 ppm : 64 ppm ratio 1.00 : 0.91

Catalyst	Phth−SPh	$EtSO_3H$	$\rightleftharpoons$	$[catalyst-SPh]^+ [EtSO_3]^-$	PhthH
8.3 mM	83.3 mM	20.8 mM		0 mM	0 mM
8.3 - X mM	83.3 - X	20.8 - X mM		X mM	X mM

(8.3 - X) : X = 1.00 : 0.91

X = 3.97

$$K_{eq} = \frac{X^2}{(8.3 - X)(83.3 - X)(20.8 - X)} = 2.73 \times 10^{-3}$$

Catalyst (15 *m*mol) : PhthSPh : $EtSO_3H$ = 1.0 : 10.0 : 2.5 (600 *m*L $CDCl_3$, -57 ^oC) ^{31}P NMR 95 ppm : 64 ppm ratio 1.00 : 1.86

Catalyst	Phth−SPh	$EtSO_3H$	$\rightleftharpoons$	$[catalyst-SPh]^+ [EtSO_3]^-$	PhthH
25 mM	250 mM	62.5 mM		0 mM	0 mM
25 - X mM	250 - X mM	62.5 - X mM		X mM	X mM

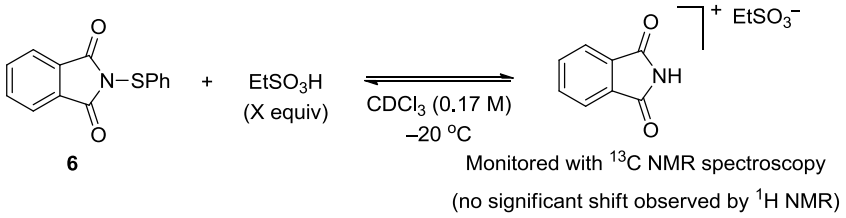
(25 - X) : X = 1.00 : 1.86

X = 16.3

$$K_{eq} = \frac{X^2}{(25 - X)(250 - X)(62.5 - X)} = 2.80 \times 10^{-3}$$

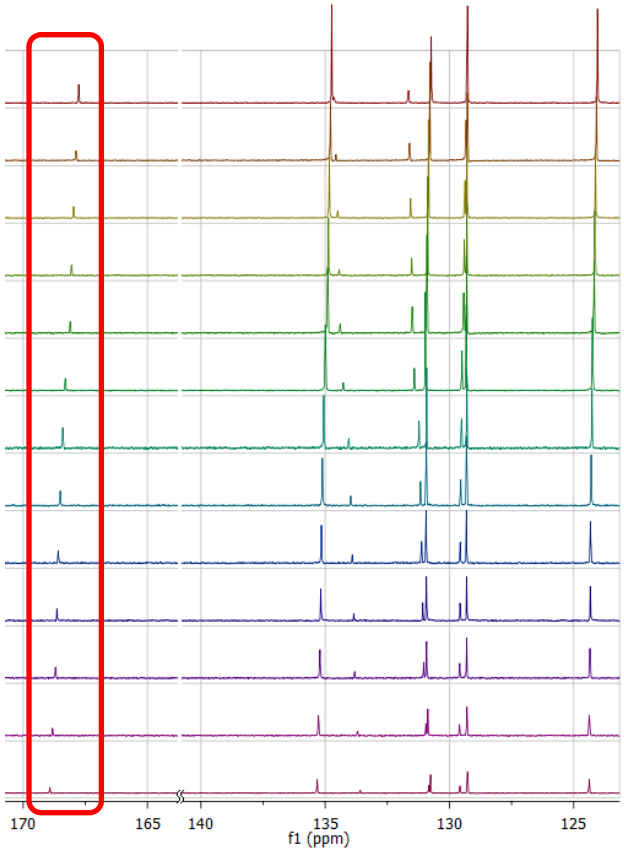
$\Longrightarrow$ **Same K_{eq}!**

Protonation Equilibrium for *N*-Phenylthiophthalimide 6 [HMC5016, HMC5024]

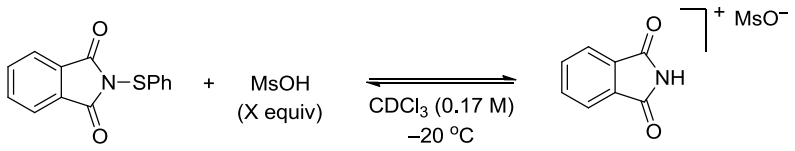


An oven-dried 5-mm NMR tube was charged with *N*-phenylthiophthalimide **6** (25.5 mg, 0.10 mmol) and $CDCl_3$ (600 μL) and the NMR tube was capped with a septum. After the NMR tube was shaken thoroughly, the resulting homogeneous solution was monitored by ^{13}C NMR spectroscopy at –20 ℃. To the solution was added $EtSO_3H$ (2.0 μL, 25 μmol, 0.25 equiv) and monitored the change of chemical shifts at –20 ℃. Addition of 0.25 equivalent of $EtSO_3H$ was repeated 3 more times for 0.50, 0.75, and 1.00 equivalents. To the solution was then added $EtSO_3H$ (8.2 μL, 0.10 mmol, 1.0 equiv) and monitored at –20 ℃. Addition of 1.0 equivalent of $EtSO_3H$ was repeated 5 more times for 3.0, 4.0, 5.0, 6.0, and 7.0 equivalents. To the solution was then added $EtSO_3H$ (24.5 μL, 0.30 mmol, 3.0 equiv) and monitored the result for 10.0 equiv at –20 ℃. Lastly, to the solution was then added $EtSO_3H$ (40.8 μL, 0.50 mmol, 5.0 equiv) and monitored the result for 15.0 equiv at –20 ℃.

Table 16. Protonation of 6 with $EtSO_3H$.
^{13}C NMR at −20 °C



Amount of $EtSO_3H$ (equiv)	^{13}C NMR δ of carbonyl carbon (ppm)
0.0	167.8
0.25	167.9
0.50	168.0
0.75	168.1
1.00	168.1
2.00	168.3
3.00	168.4
4.00	168.5
5.00	168.6
6.00	168.7
7.00	168.7
10.00	168.8
15.00	168.9



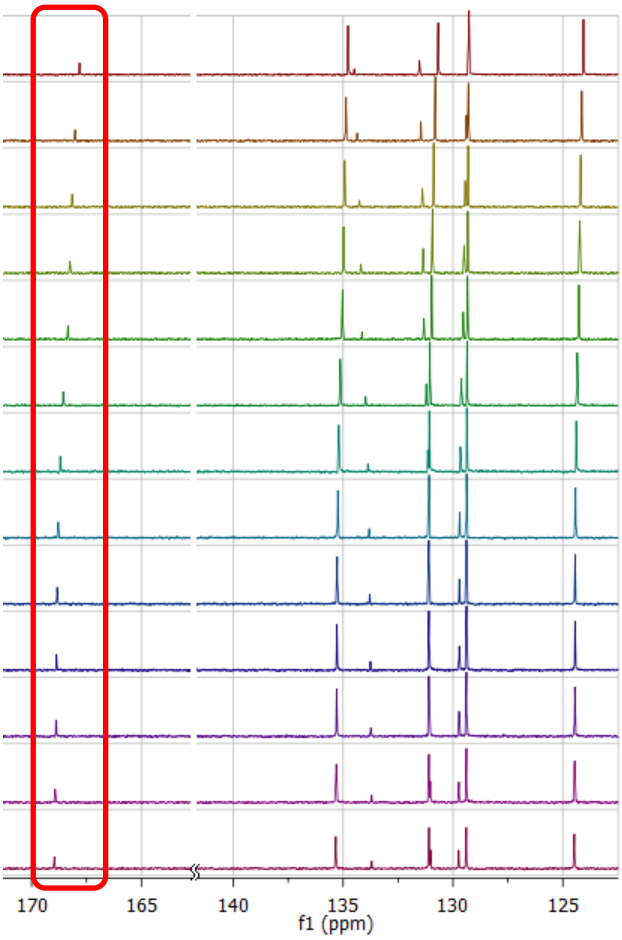
Monitored with ^{13}C NMR spectroscopy
(no significant shift observed by ^{1}H NMR)

An oven-dried 5-mm NMR tube was charged with *N*-phenylthiophthalimide **6** (25.5 mg, 0.10 mmol) and $CDCl_3$ (600 μL) and the NMR tube was capped with a septum. After the NMR tube was shaken thoroughly, the resulting homogeneous solution was monitored by ^{13}C NMR spectroscopy at –20 °C. To the solution was added MsOH (1.6 μL, 25 μmol, 0.25 equiv) and the change of chemical shifts at –20 °C was monitored. Addition of 0.25 equivalent of MsOH was

repeated 3 more times for 0.50, 0.75, and 1.00 equivalents. To the solution was then added MsOH (6.5 μL, 0.10 mmol, 1.0 equiv) and monitored at –20 ℃. Addition of 1.0 equiv of MsOH was repeated 1 more time for 3.0 equiv. To the solution was then added MsOH (13.0 μL, 0.20 mmol, 2.0 equiv) for 5.0 equiv at –20 ℃. Lastly, to the solution was then added MsOH (32.5 μL, 0.50 mmol, 5.0 equiv) for 10.0 equiv at –20 ℃.

Table 17. Protonation of 6 with $EtSO_3H$.

^{13}C NMR at –20 ℃



Amount of MsOH (equiv)	^{13}C NMR δ of carbonyl carbon (ppm
0.0	167.8
0.25	168.0
0.50	168.2
0.75	168.3
1.00	168.4
2.00	168.6
3.00	168.7
4.00	168.8
5.00	168.9
6.00	168.9
7.00	168.9
10.00	168.9
15.00	169.0

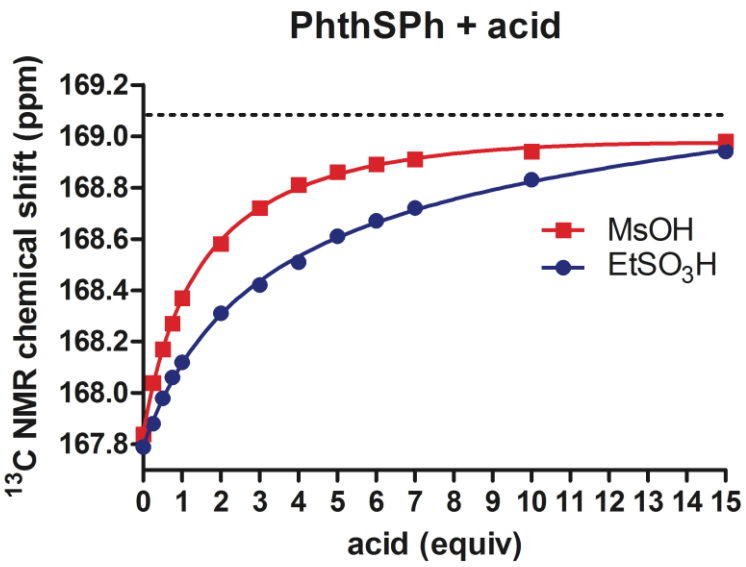


Figure 47. Protonation position of **6** by ^{13}C chemical shift.

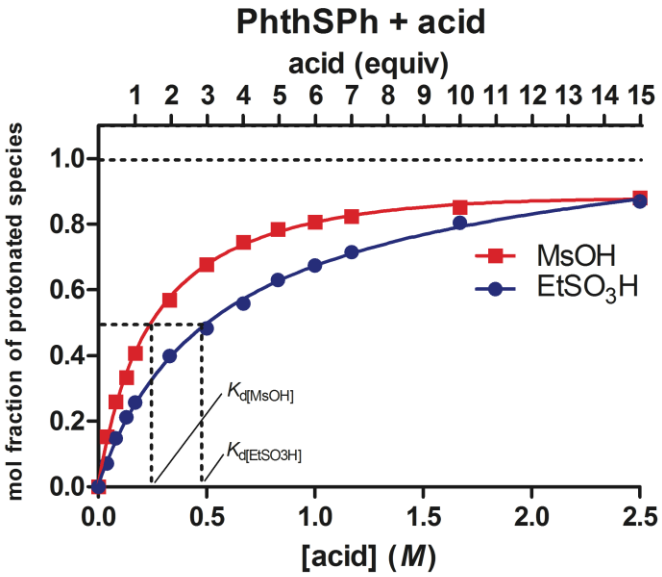
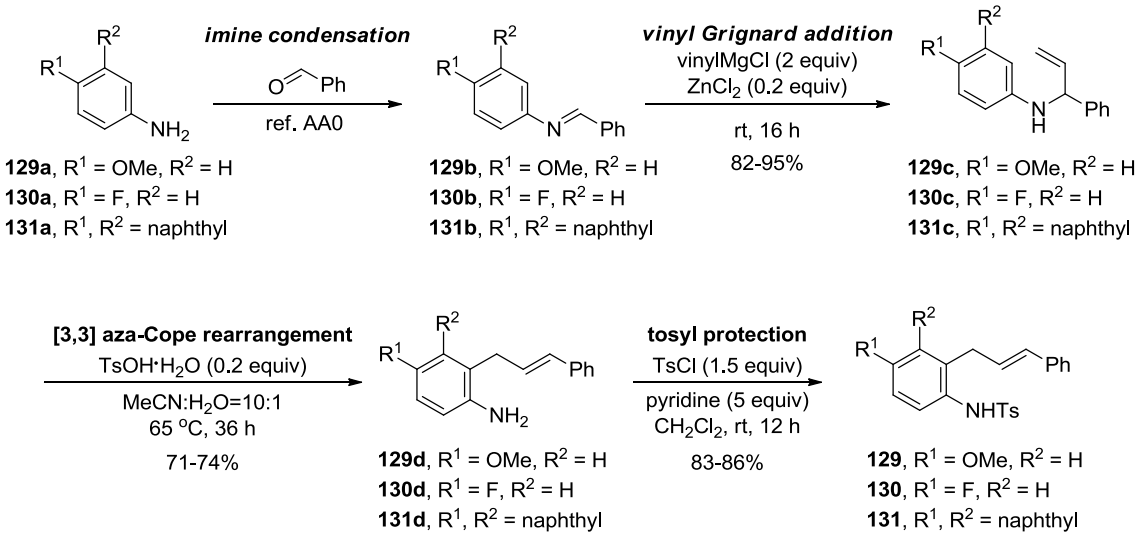


Figure 48. Protonation equilibrium calculation of **6** with MsOH and $EtSO_3H$.

5.6 Experimental Procedures for Chapter 4

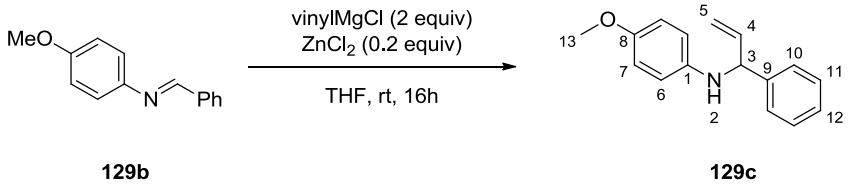
Substrate Preparations

General Scheme for Preparation of Substrate 129-133[123] (Scheme 45)



Compound **132** was prepared by following a reported procedure.[124]

Preparation of 4-Methoxy-N-(1-phenylallyl)-aniline (129c)[99] (Scheme 45) [ZY-DW7237]



To a flame-dried 100 mL Schlenk flask was added a solution of vinylmagnesium chloride in THF (18.8 mL, 1.6 M, 30 mmol, 2 equiv) and a solution of $ZnCl_2$ in THF (3 mL, 1.0 M, 3 mmol, 0.2 equiv). After stirring the solution for 20 min at rt, imine **129b**[123a] (3.17 g, 15 mmol) was added under positive argon pressure. The solution was stirred at room temperature for 16 h. The reaction was quenched with saturated NH_4Cl aqueous solution (30 mL) and extracted with EtOAc (30 x 3 mL). The organic layers were combined, washed with brine (30 mL) and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure (30 ^oC, 10 mmHg) to afford a dark brown oil. Purification via silica gel flash column chromatography (SiO_2, 18 cm x 5 cm; 1000 mL of 93:5:2, hexane/EtOAc/Et_3N, 500 mL of 95:5 hexane/EtOAc, 300 mL of 93:7

hexane/EtOAc, 300 mL of 90:10 hexane/EtOAc) afforded 2.93 g (82%) of **129c** as a brown liquid. The spectroscopic data matched those reported in the literature.[135]

Data for **129c**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.42 – 7.32 (m, 4 H, HC(10,11), 7.31 – 7.24 (m, 1 H, HC(12)), 6.78 – 6.72 (m, 2 H, HC(7)), 6.61 – 6.54 (m, 2 H, HC(6)), 6.04 (ddd, *J* = 17.2, 10.2, 6.0 Hz, 1 H, HC(4)), 5.32 – 5.19 (m, 2 H, HC(5)), 4.87 (d, *J* = 6.1 Hz, 1 H, HC(3)), 3.82 (s, 1 H, HN(2)), 3.73 (s, 3 H, HC(13)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 170.6 (C(8)), 152.4 (C(1)), 142.3 (C(9)), 141.7 (C(4)), 139.7 (C(4)), 128.9 (C(11)), 127.6 (C(12)), 127.4 (C(10)), 116.1 (C(6)), 115.1 (C(5)), 114.9 (C(7)), 61.0 (C(3)), 55.9 (C(13)).

FTIR: (neat)

3394 (w), 3027 (w), 2831 (w), 1617 (w), 1508 (s), 1463 (m), 1451 (m), 1442 (w), 1406 (w), 1308 (w), 1290 (w), 1240 (s), 1229 (s), 1178 (m), 1156 (w), 1139 (w), 1114 (w), 1094 (w), 1034 (m), 991 (w), 923 (m), 817 (s), 764 (m), 746 (m)

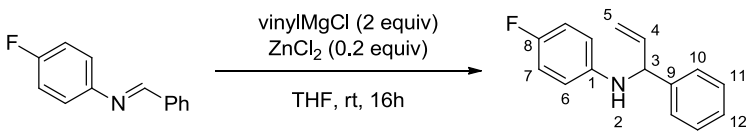
MS: (ESI)

117 (33), 217 (25), 240 ($[M+H]^+$, 75), 241 (13), 262 (22), 270 (21), 328 (100), 329 (29), 371 (96), 372 (31), 479 (23)

HRMS: calcd for $C_{16}H_{18}NO$ ($[M+H]^+$): 240.1388, found: 240.1393

TLC: R_f 0.44 (Hexanes/Ethylacetate, 4:1) [UV]

Preparation of 4-Fluoro-*N*-(1-phenylallyl)-aniline (130c)[99] (Scheme 45) [ZY-DW7236]



130b **130c**

To a flame-dried 50 mL Schlenk flask was added a solution of vinylmagnesium chloride in THF (18.8 mL, 1.6 M, 30 mmol, 2 equiv) and a solution of $ZnCl_2$ in THF (3 mL, 1.0 M, 3 mmol, 0.2 equiv). After stirring the solution for 20 min at rt, imine **130b**[123b] (2.99 g, 15 mmol)

was added under positive argon pressure. The solution was stirred at room temperature for 16 h. The reaction was quenched with saturated NH_4Cl aqueous solution (30 mL) and extracted with EtOAc (40 x 3 mL). The organic layers were combined, washed with brine (30 mL) and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure (30 ^oC, 10 mmHg) to afford 3.05 g of dark brown oil. Purification via silica gel flash column chromatography (SiO_2, 16 cm x 5 cm; 800 mL of 93:5:2, hexane/EtOAc/Et_3N, 200 mL of 90:10 hexane/EtOAc, 200 mL of 85:15 hexane/EtOAc, 200 mL of 80:20 hexane/EtOAc) afforded 2.84 g (83%) of **130c** as a brown liquid. The spectroscopic data matched those reported in the literature.[135]

Data for **130c**:

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.46 – 7.38 (m, 4 H, HC(10,11)), 7.34 (tt, *J* = 6.5, 1.5 Hz, 1 H, HC(12)), 6.93 – 6.87 (m, 2 H, HC(7)), 6.61 – 6.55 (m, 2 H, HC(6)), 6.09 (ddd, *J* = 16.5, 10.0, and 6.0 Hz, 1 H, HC(4)), 5.37 – 5.26 (m, 2 H, HC(5)), 4.93 (d, *J* = 6.0 Hz, 1 H, HC(3)), 3.99 (s, 1 H, HN(2)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 155.8 (d, *J* = 235.2 Hz, C1), 143.5 (C1), 141.7 (C9), 139.0 (C4), 128.7 (C10), 127.5 (C12), 127.0 (C11), 116.1 (C5), 115.5 (C7), 114.4 (C6), 61.5 (C3).

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -128.15 Hz

FTIR: (neat)

3413 (w), 3029 (w), 1612 (w), 1506 (s), 1452 (m), 1401 (w), 1312 (m), 1217 (s), 1156 (m), 1139 (w), 1108 (w), 1066 (w), 1028 (w), 991 (w), 817 (s), 779 (m), 748 (m)

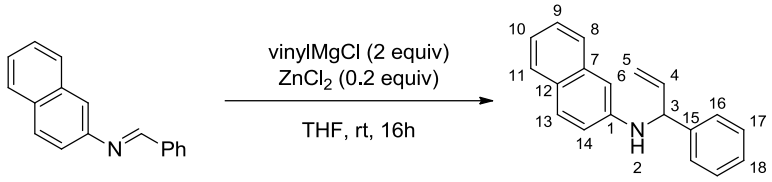
MS: (ESI)

117 (27), 145 (24), 183 (16), 200 (18), 228 ($[M+H]^+$, 12), 280 (15), 290 (100), 291 (32), 317 (24), 342 (15), 370 (21), 404 (19)

HRMS: calcd for $C_{15}H_{15}FN$ ($[M+H]^+$): 228.1189, found: 228.1197

TLC: R_f 0.54 (hexanes/EtOAc, 9:1) [UV]

Preparation of *N*-(1-Phenylallyl)-naphthalen-2-amine (131c)[99] (Scheme 45) [ZY-DW7242]



131b **131c**

To a flame-dried 50 mL Schlenk flask was added a solution of vinylmagnesium chloride in THF (18.8 mL, 1.6 M, 30 mmol, 2 equiv) and a solution of $ZnCl_2$ in THF (3 mL, 1.0 M, 3 mmol, 0.2 equiv). After stirring the solution for 20 min at rt, imine **131b**[123c] (3.47 g, 15 mmol) was added under positive argon pressure. The solution was stirred at room temperature for 16 h. The reaction was quenched with saturated NH_4Cl aqueous solution (30 mL) and extracted with EtOAc (40 x 3 mL). The organic layers were combined, washed with brine (30 mL) and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure (30 ^oC, 10 mmHg) to afford 3.05 g of dark brown oil. Purification via silica gel flash column chromatography (SiO_2, 16 cm x 5 cm; 800 mL of 93:5:2, hexane/EtOAc/Et_3N, 200 mL of 90:10 hexane/EtOAc, 200 mL of 85:15 hexane/EtOAc, 200 mL of 80:20 hexane/EtOAc) afforded 3.70 g (95%) of **131c** as a brown liquid. The spectroscopic data matched those reported in the literature.[136]

Data for **131c**:

^{1}H NMR: (400 MHz, $CDCl_3$)

δ 7.65 (d, *J* = 8.1 Hz, 1 H, HC(11)), 7.62 (d, *J* = 8.8 Hz, 1 H, HC(13)), 7.54 (dd, *J* = 8.3, 1.1 Hz, 1 H, HC(8)), 7.54 (d, *J* = 8.2 Hz, 1 H, HC(16)), 7.45 – 7.41 (m, 2 H, HC(17)), 7.37 (t, *J* = 7.6 Hz, 2 H, HC(9)), 7.34 – 7.27 (m, 2 H, HC(18)), 7.18 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1 H, HC(10)), 6.92 (dd, *J* = 8.8, 2.4 Hz, 1 H, HC(14)), 6.77 (d, *J* = 2.4 Hz, 1 H, HC(6)), 6.10 (ddd, *J* = 17.1, 10.2, 5.8 Hz, 1 H, HC(4)), 5.33 (dt, *J* = 17.1, 1.4 Hz, 1 H, HC(5)), 5.27 (dt, *J* = 10.2, 1.3 Hz, 1 H, HC(5)), 5.08 (t, *J* = 5.5 Hz, 1 H, (C(3)), 4.22 (d, *J* = 5.2 Hz, 1 H, HN(2)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 144.7 (C1), 141.6 (C15), 138.7 (C4), 134.9 (C7), 128.8 (C13,17), 127.6 (C11), 127.5 (C18), 127.5 (C12), 127.2 (C16), 126.2 (C9), 126.0 (C8), 122.1 (C10), 118.1 (C14), 116.2 (C5), 105.9 (C6), 60.8 (C3).

FTIR: (neat)

3409 (w), 3056 (w), 3026 (w), 2847 (w), 1627 (s), 1601 (m), 1519 (s), 1478 (m), 1451 (m), 1424 (w), 1396 (m), 1358 (m), 1301 (w), 1265 (w), 1223 (m), 1188 (m), 1157 (w), 1145 (w), 1125 (w), 1094 (w), 1066 (w), 1028 (w), 1018 (w), 990 (w), 967 (w), 954 (w), 924 (m), 909 (m), 865 (w), 827 (s), 806 (s), 743 (s)

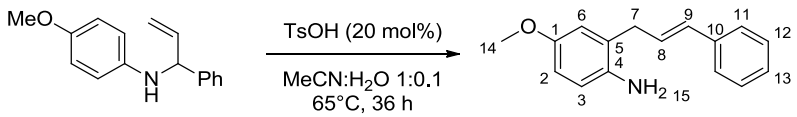
MS: (ESI)

117 (100), 156 (63), 234 (48), 260 ($[M+H]^+$, 60), 274 (31, 400 (20), 415 (19), 517 (34),

HRMS: calcd for $C_{19}H_{18}N$ ($[M+H]^+$): 260.1439, found: 260.1445

TLC: R_f 0.35 (hexanes/EtOAc, 4:1) [UV]

Preparation of (*E*)-2-Cinnamyl-4-methoxy-aniline (129d)[98] (Scheme 45) [ZY-DW7252]



129c **129d**

To a flame dried, 100-mL Schlenk flask equipped with a magnetic stir bar were added 4-methoxy-*N*-(1-phenylallyl)aniline (**129c**) (239 mg, 1 mmol), *p*-toluenesulfonic acid monohydrate (39 mg, 0.2 mmol, 0.2 equiv), and a mixed solution of acetonitrile (10 mL) and water (1 mL). The solution was heated to 65℃ in an oil bath while the reaction was monitored by NMR (the reaction stalled after 36 hours). Volatiles were removed under reduced pressure and the residue was extracted with diethyl ether (10 mL x 3). Combined organic layer was washed with 1 M NaOH (10 mL) and H_2O (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure (30 ^oC, 10 mmHg). The residue was purified by flash chromatography (SiO_2, 16 cm x 2 cm; 500 mL of 95:5:2, hexane/EtOAc/Et_3N, 200 mL of 90:10 hexane/EtOAc, 200 mL of 50:50 hexane/EtOAc), to afford 195 mg of brown liquid. Recrystallization of the brown liquid was done by dissolving in boiling ether (0.5 mL) followed by slow addition of pentane (3 mL). The solution was cooled to rt and then to -20 ℃ in a freezer. Filtration over a glass wool afforded 170 mg (71%) of **129d** as white needle-like crystals.

Data for **129d**:

mp: 63-64 °C (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.35 (d, *J* = 7.0 Hz, 2H, HC(11)), 7.31 – 7.27 (m, 2H, HC(12)), 7.24 – 7.17 (m, 1H, HC(13)), 6.72 (d, *J* = 2.8 Hz, 1H, HC(6)), 6.67 (dd, J = 8.4, 2.9 Hz, 1H, HC(2)), 6.65 (d, *J* = 8.5 Hz, 1H, HC(3)), 6.45 (dt, *J* = 16.0, 1.4 Hz, 1H, HC(9)), 6.33 (dt, *J* = 15.8, 6.2 Hz, 1H, HC(8)), 3.75 (s, 3H, HC(14)), 3.45 (d, *J* = 7.3 Hz, 4H, HC(7) and HN(15)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 153.2 (C(1)), 138.5 (C(4)), 137.4 (C(5)), 131.6 (C(9)), 128.8 (C(12)), 127.7 (C(8)), 127.5 (C(13)), 126.4 (C(11)), 126.2 (C(10)), 117.3 (C(3)), 116.3 (C(6)), 113.0 (C(2)), 56.0 (C(14)), 36.0 (C(7)).

FTIR: (neat)

3358 (w), 3024 (w), 2998 (w), 2936 (w), 2906 (w), 2831 (w), 1607 (w), 1500 (s), 1465 (m), 1448 (m), 1432 (m), 1323 (w), 1286 (w), 1242 (s), 1211 (w), 1189 (w), 1154 (m), 1075 (w), 1040 (m), 969 (m) 940 (w), 870 (w), 854 (w), 811 (m), 747 (m), 732 (m), 692 (s), 566 (m), 498 (w), 475 (m)

MS: (ESI)

136 ($[M\text{-Styrene}]^+$, 51), 239 (12), 240 ($[M+H]^+$, 100), 241 (17)

HRMS: calcd for $C_{16}H_{18}NO$ ($[M+H]^+$): 240.1383, found: 240.1391

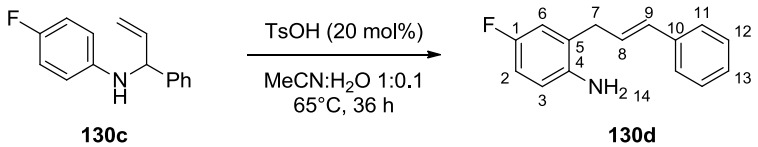
TLC: R_f 0.25 (hexanes/EtOAc, 4:1) [UV]

Analysis: $C_{16}H_{17}NO$ (239.31)

Calcd: C, 80.30; H, 7.16% N, 5.85%

Found: C, 80.25; H, 7.05% N, 5.93%

Preparation of (*E*)-4-Fluoro-*N*-(1-phenylallyl)-aniline (130d)[98] (Scheme 45) [ZY-DW7243]



130c 130d

To a flame dried, 500-mL Schlenk flask equipped with a magnetic stir bar were added 4-

fluoro-*N*-(1-phenylallyl)aniline (**130c**) (2.05 g, 9.0 mmol), *p*-toluenesulfonic acid monohydrate (352 mg, 1.8 mmol, 0.2 equiv), and a mixed solution of acetonitrile (90 mL) and water (10 mL). The solution was heated to 65°C in an oil bath while the reaction was monitored by NMR (the reaction stalled after 36 hours). Volatiles were removed under reduced pressure and the residue was extracted with diethyl ether (30 mL x 3). Combined organic layer was washed with 1 M NaOH (30 mL) and H_2O (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure (30 ^oC, 10 mmHg). The residue was purified by flash chromatography (SiO_2, 9.5 cm x 5 cm; 500 mL of 88:10:2, hexane/EtOAc/Triethylamine, 200 mL of 90:10 hexane/EtOAc, 200 mL of 80:20 hexane/EtOAc, 250 mL of 50:50 hexane/EtOAc), to afford 1.45 g (71%) of **130d** as a brown liquid. The spectroscopic data matched those reported in the literature.[136]

Data for **130d**:

mp: 63-64 ^oC (sealed tube)

^1H NMR: (400 MHz, $CDCl_3$)

δ 7.45 – 7.23 (m, 5 H, (C(11,12,13)), 6.88 (ddt, *J* = 19.9, 8.5, 2.7 Hz, 2 H, HC(2,6)), 6.65 (dd, *J* = 8.7, 4.9 Hz, 1 H, HC(3)), 6.50 (d, *J* = 15.9 Hz, 1 H, HC(9)), 6.35 (dtd, *J* = 15.8, 6.3, 1.8 Hz, 1 H, HC(8)), 3.59 (s, 2 H, HN(14)), 3.45 (d, *J* = 6.3 Hz, 2 H, HC(7)).

^{13}C NMR: (101 MHz, $CDCl_3$)

δ 156.7 (d, *J* = 235.9 Hz, C(1)), 141.1 (C(4)), 137.3 (C(10)), 132.0 (C(13)), 128.9 (C(12)), 127.8 (C(9 or 11)), 127.0 (C(9 or 11)), 126.5 (C(8)), 126.2 (d, *J* = 6.6 Hz, C(5)), 116.9 (d, *J* = 5.7 Hz, C(3)), 116.7 (d, *J* = 20.4 Hz, C(6)), 114.1 (d, *J* = 22.1 Hz, C(2)), 35.6 (C(7)).

FTIR: (neat)

3444 (w), 3367 (w), 3032 (w), 1624 (m), 1610 (w), 1596 (w), 1577 (w), 1494 (s), 1448 (w), 1436 (s), 1420 (m), 1352 (w), 1332 (w), 1277 (w), 1261 (m), 1197 (m), 1144 (m), 1081 (w), 1070 (w), 1055 (w), 1028 (w), 990 (m), 983 (m), 972 (w), 951 (s), 859 (s), 822 (m), 807 (s), 751 (s)

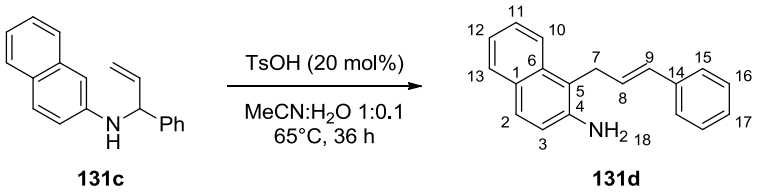
MS: (ESI)

124 (41), 228 ($[M+H]^+$, 100), 229 (29)

HRMS: calcd for $C_{15}H_{15}NF$ ($[M+H]^+$): 228.1189, found: 228.1192

TLC: R_f 0.26 (hexanes/EtOAc, 4:1) [UV]

Preparation of (*E*)-1-Cinnamyl-naphthalen-2-amine (131d)[98] (Scheme 45) [ZY-DW7249]



131c **131d**

To a flame dried, 50-mL Schlenk flask equipped with a magnetic stir bar were added *N*-(1-phenylallyl)naphthalen-2-amine (**131c**) (259 mg, 1.0 mmol), *p*-toluenesulfonic acid monohydrate (39 mg, 0.2 mmol, 0.2 equiv), and a mixed solution of acetonitrile (10 mL) and water (1 mL). The solution was heated to 65℃ in an oil bath for 6 h. The solution was cooled to rt at which point a solid started to form. To this suspension was added 2 M NaOH (10 mL) and ether (20 mL). The organic layer was separated, washed with brine (10 mL), dried over $MgSO_4$, and then concentrated under reduced pressure (30 ^oC, 10 mmHg). The residue was purified by flash chromatography (SiO_2, 16 cm x 2 cm; 300 mL of 95:5 hexane/EtOAc, 200 mL of 90:10 hexane/EtOAc, 250 mL of 50:50 hexane/EtOAc), to afford 210 mg of brown liquid. Recrystallization of the brown liquid was done by dissolving in boiling ether (0.5 mL) followed by slow addition of pentane (2 mL). The solution was cooled to rt and then to -20 ℃ in a freezer. Filtration over a glass wool afforded 192 mg (74%) of **131d** as white crystals.

Data for **131d**:

mp: 66-68 ^oC (sealed tube)

^1H NMR: (500 MHz, $CDCl_3$)

δ, 7.88 (d, *J* = 8.6 Hz, 1 H, HC(10)), 7.75 (dt, *J* = 8.1, 0.7 Hz, 1 H, HC(13)), 7.64 (d, *J* = 8.7 Hz, 1 H, HC(2)), 7.45 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1 H, HC(11)), 7.28 (tt, *J* = 5.4, 1.5 Hz, 3 H, HC(12,15)), 7.26 – 7.22 (m, 2 H, HC(16)), 7.17 (tt, *J* = 7.2, 2.2 Hz, 1 H, HC(17)), 6.99 (d, *J* = 8.7 Hz, 1 H, HC(3)), 6.44 – 6.34 (m, 2 H, HC(8,9)), 3.86 (d, *J* = 4.5 Hz, 4 H, HC(7) and HN(18)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 142.3 (C(4)), 137.4 (C(14)), 133.6 (C(6)), 130.7 (C(9)), 128.9 (C(13)), 128.8 (C(1)), 128.7 (C(16)), 128.3 (C(2)), 127.4 (C(17)), 127.3 (C(8)), 126.8 (C(11)), 126.3 (C(12)), 122.5 (C(10)), 122.4 (C(15)), 119.1 (C(3)), 114.7 (C(5)), 29.9 (C(7)).

FTIR:(neat)

3023 (w), 1622 (s), 1600 (m), 1496 (m), 1473 (m), 1446 (m), 1435 (m), 1393 (m), 1356 (w), 1282 (m), 1259 (m), 1222 (w), 1164 (w), 964 (s), 908 (m), 857 (w), 811 (s), 782 (m), 731 (s), 691 (s), 672 (m), 648 (m), 617 (m), 599 (m), 586 (m), 545 (m), 518 (m), 500 (m), 477 (m).

MS: (ESI)

156 ([M-Styrene]$^+$, 100), 157 (11), 260 ([M+H]$^+$), 261 (10)

HRMS: calcd for $C_{19}H_{18}N$ ([M+H]$^+$): 260.1434, found: 260.1441

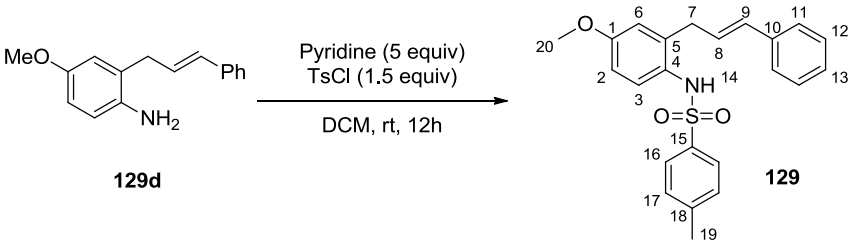
Analysis: $C_{19}H_{17}N$ (259.35)

Calcd: C, 87.99; H, 6.61% N, 5.40%

Found: C, 87.76; H, 6.44% N, 5.50%

TLC: R_f 0.40 (hexanes/EtOAc, 4:1) [UV]

Preparation of (*E*)-*N*-(2-Cinnamyl-4-methoxyphenyl)-4-methyl-benzenesulfonamide (129) (Scheme 45)[101] [ZY-DW7248]



129d **129**

To a flame-dried, 25-mL Schlenk flask equipped with a magnetic stir bar, purged with positive pressure of argon, were added aniline **129d** (1.17 g, 4.9 mmol) and CH_2Cl_2 (15 mL, 0.3 M). The solution was cooled to 0 ^oC and added pyridine (1.97 mL, 24.5 mmol, 5.0 equiv) and 4-toluenesulfonyl chloride (1.4 g, 7.35, mmol, 1.5 equiv). The reaction mixture was warmed to rt and stirred for 12 h. After 12 h, brine (30 mL) was added to the solution and extracted with CH_2Cl_2 (30 mL x 3). Organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo* (30 ^oC, 10 mmHg). The crude solid was purified via recrystallization by dissolving in boiling EtOAc (10 mL). The solution was cooled to rt and then to –20 ^oC in a freezer. Collected 1st crop by filtration and mother liquor was concentrated and recrystallized again in boiling EtOAc (5 mL). After cooling again at –20 ^oC and filtration, combined yield of 1.6 g (83%) of **129** was obtained as white solid.

Data for **129**:

mp: 114-115 °C (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.58 (d, J = 8.2 Hz, 2 H, HC(16)), 7.31 – 7.27 (m, 4 H, HC(11,12)), 7.24 – 7.20 (m, 3 H, HC(17,13)), 7.19 (d, *J* = 8.7 Hz, 1 H, HC(3)), 6.72 (dd, *J* = 8.7, 3.0 Hz, 1 H, HC(2)), 6.69 (d, *J* = 2.9 Hz, 1 H, HC(6)), 6.31 (s, 1 H, HN(14)), 6.26 (dt, *J* = 15.8, 1.7 Hz, 1 H, HC(9)), 6.06 (dt, *J* = 15.9, 6.5 Hz, 1 H, HC(8)), 3.77 (s, 3 H, HC(20)), 3.17 (dd, *J* = 6.5, 1.6 Hz, 2 H, HC(7)), 2.39 (s, 3 H, HC(19)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 158.68 (C(1)), 143.92 (C(18)), 137.02 (C(10)), 136.99 (C(5)), 132.03 (C(9)), 129.85 (C(17)), 128.79 (C(12)), 128.50 (C(3)), 127.73 (C(13)), 127.69 (C(10) or C(15)), 127.49 (C(16)), 127.41 (C(10) or C(15)), 127.30 (C(8)), 126.46 (C(11)), 116.04 (C(6)), 112.59 (C(2)), 55.63 (C(20)), 35.36 (C(7)), 21.82 (C(19).

FTIR: (neat)

3271 (w), 3027 (w), 2957 (w), 2837 (w), 1599 (m), 1581 (w), 1496 (s), 1464 (w), 1448 (w), 1433 (w), 1399 (m), 1327 (m), 1304 (m), 1290 (m), 1215 (m), 1185 (w), 1159 (s), 1092 (m), 1038 (m), 968 (m), 945 (w), 899 (m), 814 (m), 753 (m), 731 (m), 693 (m), 665 (m), 596 (w), 550 (m)

MS: (ESI)

239 ($[M-Ts]^+$, 100), 240 (18), 394 ($[M+H]^+$, 45), 395 (12), 411 (10)

HRMS: calcd for $C_{23}H_{24}NO_3S$ ($[M+H]^+$): 394.1471, found: 394.1479

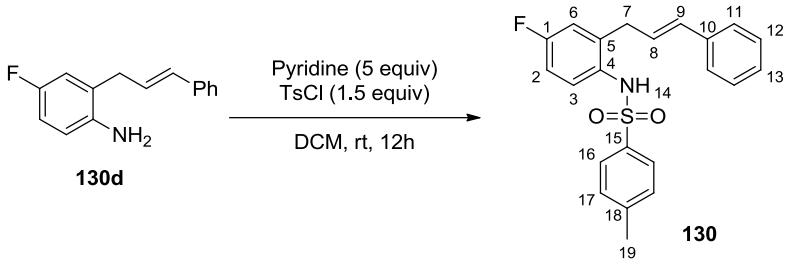
Analysis: $C_{23}H_{23}NO_3S$ (393.50)

Calcd: C, 70.20; H, 5.89% N, 3.56%

Found: C, 69.85; H, 5.81% N, 3.59%

TLC: R_f 0.30 (hexanes/EtOAc, 4:1) [UV]

Preparation of (*E*)-*N*-(2-Cinnamyl-4-fluorophenyl)-4-methyl-benzenesulfonamide (130) (Scheme 45)[101] [ZY-DW7245]



To a flame-dried, 50-mL Schlenk flask equipped with a magnetic stir bar, purged with positive pressure of argon, were added aniline **130d** (1.13 g, 5.0 mmol) and CH_2Cl_2 (15 mL, 0.3 M). The solution was cooled to 0 ^oC and added pyridine (2.0 mL, 25.0 mmol, 5.0 equiv) and 4-toluenesulfonyl chloride (1.43 g, 7.5, mmol, 1.5 equiv). The reaction mixture was warmed to rt and stirred for 12 h. After 12 h, brine (30 mL) was added to the solution and extracted with CH_2Cl_2 (30 mL x 3). Organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo* (30 ^oC, 10 mmHg). The crude solid was purified via flash chromatography (SiO_2, 8 cm x 5 cm; 500 mL of 90:10 hexane/EtOAc, 200 mL of 85:15 hexane/EtOAc, 200 mL of 80:20 hexane/EtOAc, 200 mL of 75:25 hexane/EtOAc, 200 mL of 50:50 hexane/EtOAc), to afford 1.88 g of brown liquid. Recrystallization of the brown liquid was done by dissolving in boiling EtOAc (10 mL). The solution was cooled to rt and then to -20 ^oC in a freezer. Collected 1st crop by filtration and mother liquor was concentrated and recrystallized again in boiling EtOAc (5 mL). After cooling again at -20 ^oC and filtration, combined yield of 1.63 g (86%) of **130** was obtained as a fluffy solid.

Data for **130**:

mp: 128-129 ^oC (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ, 7.57 (d, *J* = 8.3 Hz, 2 H, HC(16)), 7.31 – 7.26 (m, 6 H, HC(3,11,12,13)), 7.21 (d, *J* = 8.1 Hz, 2 H, HC(17)), 6.89 (ddd, *J* = 19.0, 8.6, 3.0 Hz, 2 H, HC(2 and 6)), 6.32 (s, 1 H, HN(14)), 6.27 (dt, *J* = 16.2, 0.9 Hz, 1 H, HC(9)), 6.04 (dt, *J* = 15.9, 6.5 Hz, 1 H, HC(8)), 3.18 (d, *J* = 6.01Hz, 2 H, HC(7)), 2.39 (s, 3 H, HC(19).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 162.3 (C(1)), 144.2 (C(18)), 136.7 (C(15)), 136.6 (C(4)), 132.7 (C(9)), 130.6 (C(5)

or C(10)), 130.5 (C(5) or C(10)), 129.9 (C(17)), 128.8 (C(6)), 128.0 (d, J = 6.0 Hz, C(3)), 127.9 (C(12)), 127.8 (C13)), 127.4 (C(16)), 126.5 (C11)), 126.4 (C(8)), 117.3 (d, J = 22.7 Hz, C(6)), 114.6 (d, J = 22.2 Hz, C(2)), 35.2 (C(7)), 21.8 (C(19)).

^{19}F NMR: (470 MHz, $CDCl_3$)

δ -115.22

FTIR: (neat)

3270 (w), 3028 (w), 2924 (w), 1614 (w), 1598 (w), 1494 (m), 1448 (w), 1435, (w), 1392 (w), 1328 (w), 1305 (w), 1273 (w), 1200 (w), 1184 (w), 1157 (s), 1120 (w), 1092 (w), 1019 (w), 963 (w), 904 (w), 814 (w), 754 (w), 730 (w), 706 (w), 692 (w), 664 (m), 595 (w), 548 (m), 527 (m), 493 (w)

MS: (ESI)

226 (21), 227 ($[M\text{-}Ts]^+$, 100), 228 (18), 382 ($[M+H]^+$, 72), 399 (36), 404 (17)

HRMS: calcd for $C_{22}H_{21}FNO_2S$ ($[M+H]^+$): 382.1271, found: 382.1273

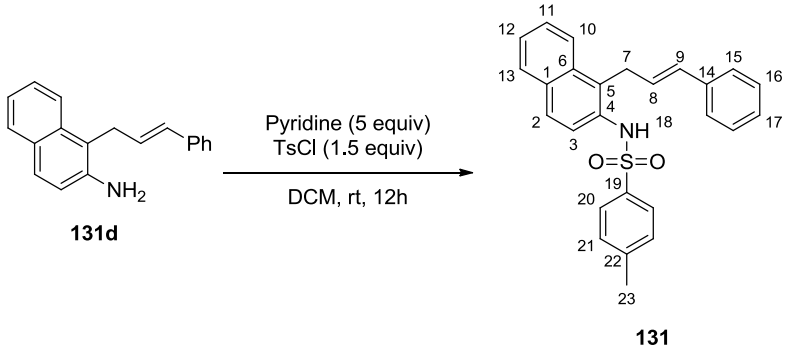
Analysis: $C_{22}H_{20}FNO_2S$ (381.46)

Calcd: C, 69.27; H, 5.28% N, 3.67%

Found: C, 69.36; H, 5.20% N, 3.70%

TLC: R_f 0.32 (hexanes/EtOAc, 4:1) [UV]

Preparation of (*E*)-*N*-(1-Cinnamyl-2-naphthyl)-4-methyl-benzenesulfonamide (131) (Scheme 45)[101] [ZY-DW7251]



131d **131**

To a flame-dried, 50-mL Schlenk flask equipped with a magnetic stir bar, purged with positive pressure of argon, were added aniline **131d** (1.43 g, 5.5 mmol) and CH_2Cl_2 (17 mL, 0.3 M). The solution was cooled to 0 ^oC and added pyridine (2.2 mL, 27.5 mmol, 5.0 equiv) and 4-

toluenesulfonyl chloride (1.57 g, 8.25, mmol, 1.5 equiv). The reaction mixture was warmed to rt and stirred for 12 h. After 12 h, brine (30 mL) was added to the solution and extracted with CH_2Cl_2 (30 mL x 3). Organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo* (30 ^oC, 10 mmHg) to afford dark brown oil. The crude product was dissolved in ether and yellow solid precipitated immediately. Recrystallization was done by dissolving the yellow solid in boiling EtOAc (10 mL), and then the solution was cooled to rt and subsequently to -20 ^oC in a freezer. Collected 1st crop by filtration and mother liquor was concentrated and recrystallized again in boiling EtOAc (5 mL). After cooling again at -20 ^oC and filtration, combined yield of 1.9 g (83%) of **131** was obtained as a yellow solid.

Data for **131**:

mp: 148-149 ^oC (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.92 (d, *J* = 8.5 Hz, 1 H, HC(10)), 7.84 (d, *J* = 8.1 Hz, 1 H, HC(2)), 7.75 (d, *J* = 8.8 Hz, 1 H, HC(13)), 7.66 (d, *J* = 8.8 Hz, 1 H, HC(12)), 7.61 (d, *J* = 8.1 Hz, 2 H, HC(20)), 7.53 – 7.42 (m, 2 H, HC(11,3)), 7.24 (dd, *J* = 7.2, 1.2 Hz, 2 H, HC(16)), 7.22 – 7.17 (m, 3 H, HC(15,17)), 7.13 (d, *J* = 7.9 Hz, 2 H, HC(21)), 6.64 (s, 1 H, HN(18)), 6.19 (dtd, *J* = 16.1, 5.1, 1.1 Hz, 1 H, (HC(8)), 6.13 (d, *J* = 16.1 Hz, 1 H, HC(9)), 3.65 (dd, *J* = 5.4, 1.3 Hz, 2 H, HC(7)), 2.31 (s, 3 H, HC(23)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 144.1 (C(22)), 136.9 (C(14)), 136.8 (C(19)), 132.7 (C(6)), 132.6(C(1)), 132.4 (C(5)), 131.6 (C(9)), 129.9 (C(21)), 129.8 (C(4)), 128.9 (C(2)), 128.7 (C(16)), 128.4 (C(13)), 127.7 (C(17)), 127.5 (C(5)), 127.4 (C(20)), 127.0 (C(11)), 126.8 (C(8)), 126.4 (C(15)), 125.8 (C(3)), 124.5 (C(10)), 123.6 (C(12)), 30.0 (C(7)), 21.8 (C(23)).

FTIR: (neat)

3283 (w), 1598 (m), 1512 (w), 1496 (w), 1468 (w), 1447 (w), 1407 (m), 1367 (m), 1320 (m), 1304 (m), 1234 (w), 1185 (w), 1159 (s), 1092 (m), 1067 (w), 1019 (w), 966 (m), 907 (m), 864 (w), 847 (w), 813 (m), 763 (m), 733 (s), 706 (m), 691 (m), 669 (s), 598 (m), 552 (s), 532 (m), 494 (w).

MS: (ESI)

258 (22), 259 ([M-Ts]$^+$, 100), 260 (18), 436 ([M+Na]$^+$, 25)

HRMS: calcd for $C_{26}H_{23}NO_2SNa$ ([M+Na]$^+$): 436.1342, found: 436.1347

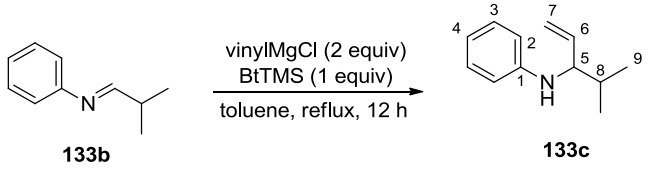
Analysis: $C_{26}H_{23}NO_2S$ (413.53)

Calcd: C, 75.52; H, 5.61% N, 3.39%

Found: C, 75.19; H, 5.63% N, 3.51%

TLC: R_f 0.38 (hexanes/EtOAc, 4:1) [UV]

Preparation of *N*-[1-(1-Methylethyl)-2-propen-1-yl]-benzenamine (133c)[100] (Scheme 45) [HMC11054]



133b **133c**

By adopting the described procedure,[100] to an oven-dried 100-mL round-bottomed flask equipped with a magnetic stir bar were added imine **133b**[123d] (736 mg, 5 mmol) and toluene (30 mL, 0.17 M). After installing a condenser, the flask was purged with argon and was added trimethylsilylbenzotriazole (957 mg, 5 mmol, 1 equiv) via syringe. After stirring for 30 min at rt, the reaction mixture was cooled to 0 ^oC in an ice bath and was added a solution of vinylmagnesium chloride in THF (6.25 mL, 1.6 M, 10 mmol, 2 equiv) via syringe. To the resulting yellow turbid mixture was added 10 mL of ether. The reaction mixture was refluxed under heat (bath temperature 90 ^oC) for 20 h. After cooling the reaction mixture to rt, it was quenched by pouring to ice water (30 mL) and extracted with ether (60 x 3 mL). The organic layers were combined and washed with 2 M NaOH aqueous solution (20 mL x 2) and water (30 mL x 2). Resulting organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure (30 ^oC, 10 mmHg). Purification via silica gel flash column chromatography (SiO_2, 40 g, 25 mm Ø, hexanes to hexanes/EtOAc, 19:1) afforded 595 mg (68%) of **133c**, as pale yellow oil. An analytically pure sample was obtained by Kugelrohr distillation (60 ^oC at 0.01 mmHg) affording 550 mg (63%) of **133c** as a colorless oil. The spectroscopic data matched those reported in the literature.[135]

Data for **133c**:

bp: 60 °C (at 0.01 mmHg)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.18 (t, *J* = 8.0 Hz, 2 H, HC(3), 6.69 (t, *J* = 7.5 Hz, 1 H, HC(4)), 6.63 (d, *J* = 8.5 Hz, 2 H, HC(2)), 5.76 (ddd, *J* = 17.0, 10.5, and 6.0 Hz, 1 H, HC(6)), 5.27 – 5.16 (m, 2 H, HC(7)), 3.75 – 3.63 (brs+m, 2 H, HN+HC(5)), 1.90 (dq, *J* = 13.5, 6.5 Hz, 1 H, HN(8)), 1.01 (dd, *J* = 15.0, 7.0 Hz, 6 H, HC(9)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 147.8 (C(1)), 137.9 (C(6)), 129.1 (C(3)), 117.0 (C(4)), 116.0 (C(7)), 113.3 (C(2)), 61.4 (C(5)), 32.4 (C(8)), 18.8 (C(9)), 18.5 (C(9)).

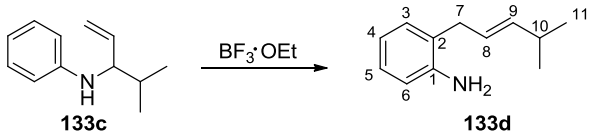
MS: (ESI)

94 (20), 97 (22), 98 (15), 106 (14), 114 (56), 118 (28), 138 (16), 140 (13), 142 (26), 148 (34), 150 (28), 176 (M+H, 78), 188 (50), 202 (43), 219 (100), 220 (17), 230 (16), 235 (69), 248 (16), 251 (19), 258 (25), 262 (14), 274 (40).

HRMS: calcd for $C_{12}H_{18}N$ ($[M+Na]^+$): 176.1439, found: 176.1440

TLC: R_f 0.58 (Hexanes/Ethyl acetate, 4:1) [UV]

Preparation of (*E*)-2-(4-Methyl-2-penten-1-yl)-benzenamine (133d) (Scheme 45)[98] [HMC11056]



133c **133d**

By adopting the described procedure,[101] to an oven-dried, 38-mL pressure tube with side arm in the neck equipped with a magnetic stir bar were added allylaniline **133c** (350 mg, 2.0 mmol) and xylenes (4 mL, 0.5 M). The tube was capped with a septum and purged with positive pressure of argon. The solution was cooled to –40 °C in MeCN/dri-ice bath under positive pressure of argon. To the tube was added BF_3•OEt_2 (48% solution, 0.3 mL, 2.4 mmol, 1.2 equiv). The reaction mixture was warmed to rt and replaced septum with pressure screw cap under positive stream of argon. Then it was heated to 180 °C and stirred for 17 h. After completion, the reaction mixture was cooled to 0 °C with continuous vigorous stirring and quenched with 2 M

NaOH (15 mL) at 0 ^{o}C. Resulting biphasic layer was extracted with ether (15 mL x 3). Organic layers were combined, filtered over celite, and concentrated *in vacuo* (30 ^{o}C, 10 mmHg). The crude solid was purified via flash chromatography (SiO_2, 30 g, 20 mm Ø, hexanes to hexanes/EtOAc, 6:1) afforded 199 mg (57%) of **133d**, as yellow oil. An analytically pure sample was obtained by Kugelrohr distillation (80 ^{o}C at 0.01 mmHg) affording 179 mg (51%) of **133d** as a colorless oil.

Data for **133d**:

bp: 80 ^{o}C (at 0.01 mmHg)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.14 – 7.07 (m, 2 H, HC(3,5)), 6.80 (tt, *J* = 7.5, 1.5 Hz, 1 H, HC(4)), 6.72 (dd, *J* = 7.5, 1.5 Hz, 1 H, HC(6)), 5.63 – 5.50 (m, 2 H, HC(8,9)), 3.75 (brs, 2 H, H_2N), 3.30 (d, *J* = 5.5 Hz, 2 H, HC(7)), 2.35 (heptd, *J* = 6.5, 2.0 Hz, 1 H, HC(10)), 1.04 (dd, *J* = 7.0, 2.0 Hz, 6 H, HC(11)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 144.9 (C1), 139.5 (C9), 129.9 (C5), 127.3 (C3), 125.1 (C2), 124.3 (C8), 118.7 (C4), 115.7 (C6), 35.4 (C7), 31.0, (C10) 22.5 (C11).

MS: (ESI)

106 (100), 114 (27), 176 ($[M+H]^+$, 13), 177 (13)

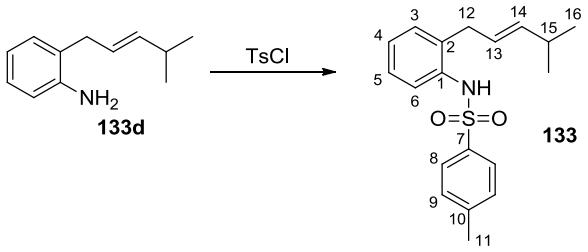
HRMS: calcd for $C_{12}H_{18}N$ ($[M+H]^+$): 176.1439, found: 176.1443

TLC: R_f 0.43 (hexanes/EtOAc, 4:1) [UV]

Analysis: $C_{12}H_{17}N$ (175.27)

Calcd:	C, 82.23;	H, 9.78%	N, 7.99%
Found:	C, 82.25;	H, 10.00%	N, 7.80%

Preparation of (*E*)-*N*-[2-(4-Methyl-2-penten-1-yl)-phenyl]-4-methyl-bezenesulfonamide (133) (Scheme 45)[101] [HMC10081]



To a oven-dried, 50-mL round-bottomed flask equipped with a magnetic stir bar were added aniline **133d** (876 mg, 5.0 mmol) and CH_2Cl_2 (10 mL, 0.5 M) under positive pressure of argon. The solution was cooled to 0 ^oC and added pyridine (1.21 mL, 15.0 mmol, 3.0 equiv) and 4-toluenesulfonyl chloride (1.05 g, 5.5, mmol, 1.1 equiv). The reaction mixture was warmed to rt and stirred for 24 h. To quench the reaction, water (20 mL) was added to the solution and extracted with CH_2Cl_2 (20 mL x 3). Organic layers were combined, dried over Na_2SO_4, filtered, and concentrated *in vacuo* (30 ^oC, 10 mmHg). The crude solid was purified via flash chromatography (SiO_2, 40 g, 25 mm Ø, hexanes to hexanes/EtOAc, 6:1) afforded 1.48 g (90%) of **133**, as yellow solid. An analytically pure sample was obtained by recrystallization in boiling pentane (50 mL). The solution was cooled to rt and then to -20 ^oC in a freezer. After collecting 1st crop by filtration, mother liquor was concentrated and recrystallized again in boiling pentane (10 mL). After cooling again at -20 ^oC and filtration, combined yield of 1.34 g (82%) of **133** was obtained as a white crystalline solid.

Data for **133**:

mp: 128-129 ^oC (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.60 (d, *J* = 8.0 Hz, 2 H, HC(8)), 7.43 (d, *J* = 8.0 Hz, 1 H, HC(6)), 7.22 (d, *J* = 8.0 Hz, 2 H, HC(9)), 7.19 (t, *J* = 7.5 Hz, 1 H, HC(5)), 7.09 (t, *J* = 7.5 Hz, 1 H, HC(4)), 7.04 (d, *J* = 7.5 Hz, 1 H, HC(3)), 6.69 (s, 1 H, HN), 5.44 (dd, *J* = 15.5, 6.5 Hz, 1 H, HC(14)), 5.31 (dt, *J* = 15.5, 6.0 Hz, 1 H, HC(13)), 2.93 (d, *J* = 6.0 Hz, 1 H, HC(12)), 2.39, (s, 3 H, HC(11)), 2.34 – 2.22 (m, 1 H, HC(15)), 0.99 (d, *J* = 7.0 Hz, 6 H, HC(16))

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 143.7 (C10), 140.7 (C14), 136.9 (C7), 135.3 (C1), 132.2 (C2), 130.3 (C3), 129.6 (C9), 127.6 (C5), 127.0 (C8), 125.9 (C4), 124.0 (C13), 123.9 (C6), 35.5 (C12), 31.0 (C15), 22.3 (C16), 21.5 (C11)

FTIR: (neat)

3286 (m), 2963 (w), 1489 (m), 1458 (w), 1391 (m), 1334 (s), 1307 (w), 1291 (w), 1275 (w), 1187 (w), 1166 (s), 1119 (w), 1090 (s), 1045 (w), 1021 (w), 969 (m), 901 (m), 834 (w), 810 (m), 762 (s).

MS: (ESI)

118 (52), 132 (22), 146 (13), 160 (39), 174 (17), 175 (100), 176 (14), 330 (M+H, 36), 352 (42)

HRMS: calcd for $C_{19}H_{24}NO_2S$ ($[M+H]^+$): 330.1528, found: 330.1526

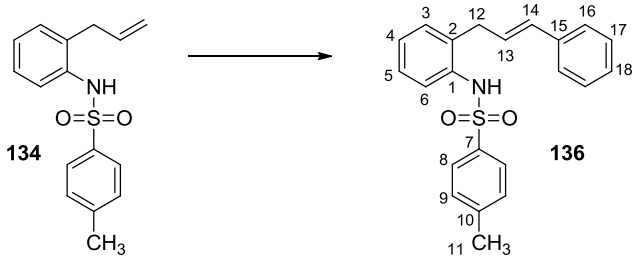
TLC: R_f 0.32 (hexanes/EtOAc, 4:1) [UV]

Analysis: $C_{19}H_{23}N$ (329.46)

Calcd:	C, 69.27;	H, 7.04%	N, 4.25%
Found:	C, 69.42;	H, 7.23%	N, 4.26%

Preparation of Substrate 131-134 via Olefin Metathesis (Scheme 47)

Preparation of (*E*)-4-Methyl-*N*-[2-(3-phenyl-2-propen-1-yl)phenyl]benzenesulfonamide (136) (Scheme 47) [HMC10070]



An oven-dried 50 mL Schlenk flask was equipped with a stir bar was introduced into a glove box. Grubbs 1st generation indenylidene catalyst (CAS #250220-36-1, 111 mg, 0.12 mmol, 0.03 equiv) was loaded into the flask, sealed with a septum and exited the glove box. The Schlenk flask was hooked up to a Schlenk manifold and was purged thoroughly with argon. To a

separate 50 mL round-bottomed flask was added sulfonamide **134** (1.15 g, 4.0 mmol, 1 equiv), styrene (4.60 mL, 40.0 mmol, 10 equiv), and CH_2Cl_2 (20 mL, 0.2 M, degassed with Ar), then sealed with a septum. The mixture turned into a solution while the mixture was degassed for additional 30 min with Ar (needle and a bubbler outlet attached). Premixed, degassed solution of two olefin substrates was transferred to the Schlenk flask via syringe. The top area of the Schlenk flask including the needle-punctured septum was thoroughly sealed with parafilm. The black mixture was allowed to stir for 48 h at rt. The the mixture was filtered through a plug of silica, then rinsed with CH_2Cl_2 (25 mL x 2), and EtOAc (25 mL x 2) to afford a dark solution. The filtrate was concentrated under reduced pressure (30 ^oC, 10 mmHg) to afford a black solid. Purification via silica gel flash column chromatography (SiO_2, 40 g, 25 mm Ø, hexanes to hexanes/EtOAc, 9:1) afforded 685 mg (47%) of **136**, as a white solid. Recrystallization of the solid with hot pentane (36 ^oC, 30 mL) afforded 630 mg (43%) of **136** as white crystals. The spectroscopic data matched those reported in the literature.[137]

Data for **136**:

mp: 159-160 ^oC (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.60 (d, *J* = 8.0 Hz, 2 H, HC(8)), 7.43 (d, *J* = 8.0 Hz, 1 H, HC(6)), 7.35 – 7.21 (m, 6 H, HC(aryl)), 7.21 – 7.13 (m, 4 H, HC(aryl)), 6.52 (brs, 1 H, HN), 6.29 (dt, *J* = 16.0, 1.5 Hz, 1 H, HC(14)), 6.11 (dt, *J* = 16.0, 6.5 Hz, 1 H, HC(13)), 3.25 (dd, *J* = 6.5, 1.5 Hz, 2 H, HC(12)), 2.39 (s, 3 H, HC(11)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 143.8 (C10), 136.6 (C7), 136.6 (C15), 134.9 (C1), 132.2 (C2), 131.9 (C14), 130.5 (C3), 129.6 (C9), 128.6 (C17), 127.8, 127.6, 127.2 (C8), 127.0 (C13), 126.2 (C16), 126.2, 124.2 (C6), 35.2 (C12), 21.5 (C11).

FTIR: (neat)

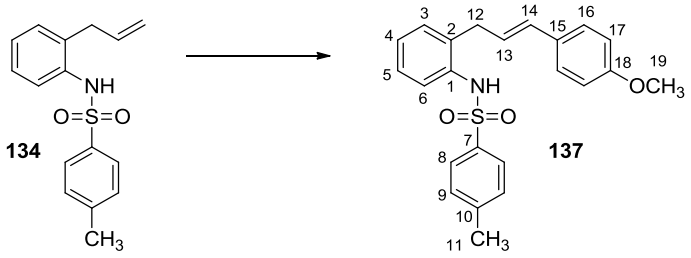
3281 (m), 1596 (w), 1584 (w), 1492 (m), 1448 (w), 1402 (m), 1333 (s), 1304 (w), 1291 (w), 1278 (w), 1184 (w), 1165(s), 1119 (w), 1090 (s), 1053 (w), 1040 (w), 1018 (w), 969 (m), 954 (w), 906 (s), 810 (m), 756 (m).

MS: (ESI)

208 (15), 209 (100), 210 (24), 364 (M+H, 28), 381 (44), 382 (13), 386 (17)

HRMS: calcd for $C_{22}H_{22}NO_2S$ ($[M+H]^+$): 364.1371, found: 364.1373

Preparation of (*E*)-4-Methyl-*N*-{2-[3-(4-anisyl)-2-propen-1-yl]-phenyl}-benzenesulfonamide (137) (Scheme 47) [HMC10063]



An oven-dried 25 mL Schlenk flask was equipped with a stir bar was introduced into a glove box. Grubbs 1st generation indenylidene catalyst (CAS #250220-36-1, 55 mg, 0.06 mmol, 0.03 equiv) was loaded into the flask, sealed with a septum and exited the glove box. The Schlenk flask was hooked up to a Schlenk manifold and was purged thoroughly with argon. To a separate 25 mL round-bottomed flask was added sulfonamide **134** (575 mg, 2.0 mmol, 1 equiv), 4-vinylanisole (2.66 mL, 20.0 mmol, 10 equiv), and CH_2Cl_2 (10 mL, 0.2 M, degassed with Ar), then sealed with a septum. The mixture turned into a solution while the mixture was degassed for additional 30 min with Ar (needle and a bubbler outlet attached). Premixed, degassed solution of two olefin substrates was transferred to the Schlenk flask via syringe. The top area of the Schlenk flask including the needle-punctured septum was thoroughly sealed with parafilm. The black mixture was allowed to stir for 48 h at rt. The the mixture was filtered through a plug of silica, then rinsed with CH_2Cl_2 (15 mL x 2), and EtOAc (15 mL x 2) to afford a dark solution. The filtrate was concentrated under reduced pressure (30 ^oC, 10 mmHg) to afford a black solid. Purification via silica gel flash column chromatography (SiO_2, 25 g, 20 mm Ø, hexanes to hexanes/EtOAc, 9:1) afforded 425 mg (54%) of **137**, as a white solid. Recrystallization of the solid with hot pentane (36 ^oC, 30 mL) afforded 396 mg (50%) of **137** as white crystals.

Data for **137**:

mp: 117-118 ^oC (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.58 (d, *J* = 8.5 Hz, 2 H, HC(8)), 7.42 (d, *J* = 8.0 Hz, 1 H, HC(6)), 7.25 – 7.13 (m, 7 H), 6.84 (d, *J* = 8.5 Hz, 2 H, HC(17)), 6.56 (brs, HN), 6.22 (d, *J* = 16.0 Hz, 1 H, HC(14)), 5.94 (dt, *J* = 16.0, 6.5 Hz, 1 H, HC(13)), 3.81 (s, 3 H, HC(19)), 3.19 (dd, J

= 6.5, 2.0 Hz, HC(12)), 2.37 (s, 3 H, HC(11)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 159.1 (C18), 143.7 (C10), 136.6 (C7), 134.9 (C1), 132.3 (C2), 131.3 (C14), 130.5 (C3), 129.6 (C9), 129.4, 127.6, 127.4 (C8), 127.1 (C16), 126.1, 124.7 (C13), 124.0 (C6), 113.9 (C17), 55.3 (C19), 35.1 (C12), 21.5 (C11).

FTIR: (neat)

3271 (m), 3005 (w), 2965 (w), 1739 (w), 1606 (m), 1578 (w), 1510 (m), 1488 (m), 1469 (w), 1456 (w), 1437 (w), 1406 (m), 1332 (m), 1308 (w), 1292 (m), 1275 (w), 1251 (s), 1177 (w), 1160 (s), 1121 (w), 1109 (w), 1089 (m), 1066 (w), 1032 (m), 1018 (w), 969 (m), 908 (m), 862 (w), 820 (m), 812 (m), 778 (w), 761 (m), 754 (m).

MS: (ESI)

238 (17), 239 (100), 240 (37), 297 (34), 394 (M+H, 52), 395 (16), 411 (79), 412 (25)

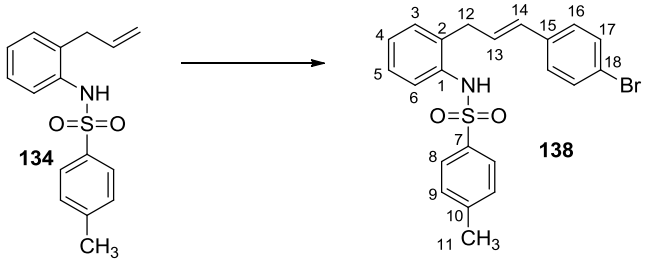
HRMS: calcd for $C_{23}H_{24}NO_3S$ ($[M+H]^+$): 394.1477, found: 394.1484

TLC: R_f 0.20 (hexanes/EtOAc, 4:1) [UV]

Analysis: $C_{23}H_{23}NO3S$ (393.50)

Calcd:	C, 70.20;	H, 5.89%	N, 3.56%
Found:	C, 70.05;	H, 5.81%	N, 3.55%

Preparation of (*E*)-4-Methyl-*N*-{2-[3-(4-bromophenyl)-2-propen-1-yl]-phenyl}-benzenesulfonamide (138) (Scheme 47) [HMC10064]



An oven-dried 25 mL Schlenk flask was equipped with a stir bar was introduced into a glove box. Grubbs 1st generation indenylidene catalyst (CAS #250220-36-1, 55 mg, 0.06 mmol, 0.03 equiv) was loaded into the flask, sealed with a septum and exited the glove box. The Schlenk flask was hooked up to a Schlenk manifold and was purged thoroughly with argon. To a separate 25 mL round-bottomed flask was added sulfonamide **134** (575 mg, 2.0 mmol, 1 equiv),

4-bromostyrene (2.62 mL, 20.0 mmol, 10 equiv), and CH_2Cl_2 (10 mL, 0.2 M, degassed with Ar), then sealed with a septum. The mixture turned into a solution while the mixture was degassed for additional 30 min with Ar (needle and a bubbler outlet attached). Premixed, degassed solution of two olefin substrates was transferred to the Schlenk flask via syringe. The top area of the Schlenk flask including the needle-punctured septum was thoroughly sealed with parafilm. The black mixture was allowed to stir for 48 h at rt. The the mixture was filtered through a plug of silica, then rinsed with CH_2Cl_2 (15 mL x 2), and EtOAc (15 mL x 2) to afford a dark solution. The filtrate was concentrated under reduced pressure (30 ^oC, 10 mmHg) to afford a black solid. Purification via silica gel flash column chromatography (SiO_2, 25 g, 20 mm Ø, hexanes to hexanes/EtOAc, 5:1) afforded 440 mg (50%) of **138**, as a white solid. Recrystallization of the solid with hot pentane (36 ^oC, 30 mL) afforded 404 mg (46%) of **138** as white crystals.

Data for **138**:

mp: 141-142 ^oC (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.62 (d, *J* = 8.5 Hz, 2 H, HC(8)), 7.45 (d, *J* = 8.5 Hz, 2 H, HC(17)), 7.41 (dd, *J* = 8.0, 1.0 Hz, 1 H, HC(6)), 7.25 (ddd, *J* = 8.5, 6.0, and 3.0 Hz, 1 H, HC(aryl)), 7.22 (dd, *J* = 8.0, 1.0 Hz, 2 H, HC(9)), 7.20 – 7.15 (m, 4 H, HC(aryl)), 6.5 (brs, 1H, HN), 6.23 (d, *J* = 16.0 Hz, 1 H, HC(14)), 6.15 (dt, *J* = 16.0, 6.0 Hz, 1 H, HC(13)), 3.29 (dd, *J* =6.0, 1.5 Hz, 2 H, HC(12)), 2.41 (s, 3 H, HC(11)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 144.1 (C10), 136.8 (C7), 135.8 (C15), 135.0 (C1), 132.5 (C2), 131.9 (C17), 130.9 (C14), 130.8 (C3), 129.9 (C9), 128.2 (C13), 128.1 (C5), 128.0 (C16), 127.4 (C8), 126.7 (C4), 124.6 (C6), 121.6 (C18), 35.3 (C12), 21.8 (C11).

MS: (ESI)

440 ($[M]^+$, 95), 441 (22), 442 (100), 443 (23), 456 (13)

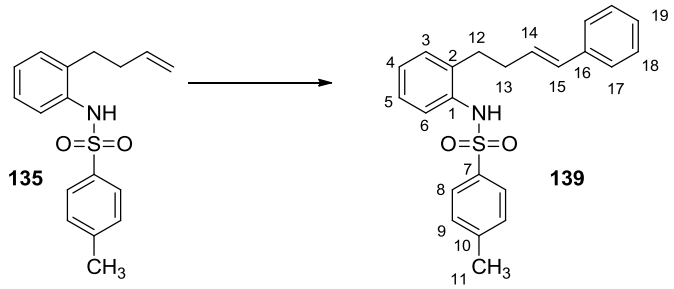
HRMS: calcd for $C_{22}H_{19}NO_2SBr$ ($[M]^+$): 440.0320, found: 440.0318

TLC: R_f 0.22 (hexanes/EtOAc, 4:1) [UV]

Analysis: $C_{22}H_{20}BrNO_2S$ (442.37)

Calcd:	C, 59.73;	H, 4.56%	N, 3.17%
Found:	C, 59.93;	H, 4.39%	N, 3.13%

Preparation of (*E*)-4-Methyl-*N*-[2-(4-phenyl-3-buten-1-yl)-phenyl]-benzenesulfonamide (139) (Scheme 47) [HMC10078]



An oven-dried 50 mL Schlenk flask was equipped with a stir bar was introduced into a glove box. Grubbs 1st generation indenylidene catalyst (CAS #250220-36-1, 110 mg, 0.12 mmol, 0.03 equiv) was loaded into the flask, sealed with a septum and exited the glove box. The Schlenk flask was hooked up to a Schlenk manifold and was purged thoroughly with argon. To a separate 25 mL round-bottomed flask was added sulfonamide **135** (1.21 g, 4.0 mmol, 1 equiv), styrene (4.60 mL, 40.0 mmol, 10 equiv), and CH_2Cl_2 (16 mL, 0.25 M, degassed with argon), then sealed with a septum. The mixture turned into a solution while the mixture was degassed for additional 30 min with argon (needle and a bubbler outlet attached). Premixed, degassed solution of two olefin substrates was transferred to the Schlenk flask via syringe. The top area of the Schlenk flask including the needle-punctured septum was thoroughly sealed with parafilm. The black mixture was allowed to stir for 48 h at rt. The the mixture was filtered through a plug of silica, then rinsed with CH_2Cl_2 (30 mL x 2), and EtOAc (30 mL x 2) to afford a dark solution. The filtrate was concentrated under reduced pressure (30 ^oC, 10 mmHg) to afford a black solid. Purification via silica gel flash column chromatography (SiO_2, 40 g, 25 mm Ø, hexanes to hexanes/EtOAc, 5:1) afforded 740 mg (49%) of **139**, as a grey solid. Recrystallization of the solid with boiling EtOAc/pentane (1:10 mixture, 20 mL) afforded 649 mg (43%) of **139** as white crystals.

Data for **139**:

mp: 110-111 ^oC (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.64 (d, *J* = 8.5 Hz, 2 H, HC(8)), 7.36 – 7.30 (m, 5 H, HC(17,18,aryl)), 7.28 –

7.22 (m, 3 H, HC(aryl,9)), 7.20 – 7.15 (m, 1 H, (HC(aryl)), 6.33 (d+brs, *J* = 16.0 Hz, 2 H, HC(15)+HN), 6.13 (dt, *J* = 16.0, 7.0 Hz, 1 H, HC(14)), 2.57 (dd, *J* = 9.0, 6.5 Hz, 2 H, HC(12)), 2.40 (s, 3 H, HC(11)), 2.33 (qd, *J* = 7.5, 7.0 Hz, 2 H, HC(13)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 143.8 (C10), 137.3 (C16), 136.7 (C7), 135.1 (C2), 134.0 (C1), 131.0 (C14), 129.9 (C3), 129.6 (C9), 128.9 (C15), 128.5 (C18), 127.2 (C8), 127.2, 127.1, 126.5, 126.0 (C17), 124.8 (C6), 33.2 (C13), 30.7 (C12), 21.5 (C11).

FTIR: (neat)

3222 (m), 1597 (w), 1493 (w), 1456 (w), 1448 (w), 1411 (w), 1324 (s), 1305 (w), 1294 (w), 1269 (w), 1185 (w), 1155 (s), 1120 (w), 1090 (s), 985 (w), 964 (m), 913 (m), 812 (m), 795 (w), 766 (s).

MS: (ESI)

194 (13), 222 (22), 223 (100), 224 (16), 378 (M+H, 49), 379 (13), 400 (32).

HRMS: calcd for $C_{23}H_{24}NO_2S$ ($[M+H]^+$): 378.1528, found: 378.1525

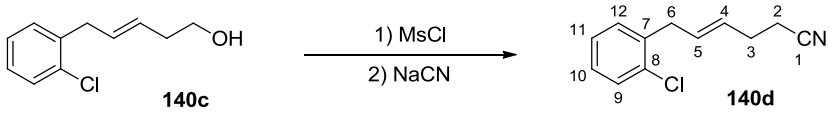
TLC: R_f 0.25 (hexanes/EtOAc, 4:1) [UV]

Analysis: $C_{23}H_{23}NO_2S$ (377.50)

Calcd:	C, 73.18;	H, 6.14%	N, 3.71%
Found:	C, 72.99;	H, 6.29%	N, 3.62%

Preparation of Substrates 140, 141 via C-N Cross-coupling (Scheme 48)

Preparation of (*E*)-6-(2-Chlorophenyl)-4-hexenenitrile (140d) (Scheme 48) [HMC11089, HMC11090]



To an oven-dried 200-mL round-bottomed flask was equipped with a magnetic stir bar were added homoallylic alcohol **140c**[125] (787 mg, 4.0 mmol), CH_2Cl_2 (40 mL, 0.1 M), and then the flask was connected to an argon inlet. The solution was cooled to 0 ^{o}C in ice bath, and were added Et_3N (1.95 mL, 14.0 mmol, 3.5 equiv), and methanesulfonic chloride (0.46 mL, 6.0 mmol, 1.5 equiv) via syringe. The reaction mixture was stirred for 1 h at 0 ^{o}C. The reaction was

quenched by adding water (20 mL) and the resulting biphasic solution was separated. The aqueous layer was further extracted with CH_2Cl_2 (30 mL x 2). Combined organic layer was dried over Na_2SO_4, and filtered over a glass wool. The filtrate was concentrated under reduced pressure (30 ^oC, 10 mmHg) to afford a brown oil. Purification via silica gel plug filtration (SiO_2, 10 g, 30 mm Ø, hexanes/EtOAc, 7:3) afforded 1.04 g (95%) of mesylate as a pale yellow oil. (The mesylate intermediate slowly turned into a dark oil upon standing.) To an oven-dried 100-mL round-bottomed flask with a magnetic stir bar were added mesylate (1.04 g, 3.79 mmol), DMF (30 mL, 0.125 M), and sodium cyanide (557 mg, 11.4 mmol, 3 equiv). A condenser was installed to the flask, and connected to an argon inlet. The flask was purged with argon and the solution was stirred for 12 h at 40 ^oC. After 12 h, the flask was cooled to room temperature and the reaction was quenched by pouring into an ice-water (30 mL). The aqueous layer was extracted with CH_2Cl_2 (30 mL x 3), and each layer was washed with brine (20 mL x 2). The organic layers were combined and dried over Na_2SO4, and evaporated under reduced pressure (25 ^oC, 10 mmHg). Residual DMF was additionally removed by passing through a silica plug (10 g), rinsed with 4:1 hexanes:EtOAc. Collected organic layer was concentrated, and was purified by silica gel flash chromatography (SiO_2, 40 g, 25 mm Ø, hexanes to hexanes/EtOAc, 4:1) afforded 701 mg (90%) of **140d**, as a colorless oil. An analytically pure sample was obtained by Kugelrohr distillation (80 ^oC at 0.1 mmHg) affording 670 mg (86%) of **140d** as a colorless oil.

Data for **140d**:

bp: 80 ^oC (at 0.1 mmHg)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.39 (dd, *J* = 8.0, 1.5 Hz, 1 H, HC(9)), 7.28 – 7.16 (m, 3 H, HC(aryl)), 5.79 (dtd, *J* = 15.0, 6.5, and 1.5 Hz, 1 H, HC(5)), 5.54 (dddt, *J* = 15.0, 6.5, 5.0, and 1.5 Hz, 1 H, HC(4)), 3.52 (dd, *J* = 6.5, 1.5 Hz, 2 H, HC(6)), 2.47 – 2.36 (m, 4 H, HC(2,3)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 137.6 (C7), 133.9 (C8), 130.6 (C5), 130.3 (C12), 129.4 (C9), 127.8 (C4), 127.6 (C11), 126.9 (C10), 119.2 (C1), 36.3 (C6), 28.3 (C3), 17.5 (C2).

MS: (EI)

89 (11), 115 (30), 116 (25), 125 (30), 128 (25), 129 (100), 130 (26), 151 (64), 153

(20), 164 (14), 170 (50), 205 (M, 45), 207 (14.6).

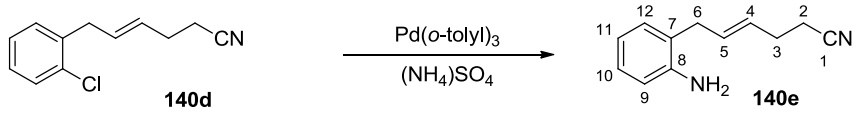
HRMS: calcd for $C_{15}H_{12}NCl$: 205.0658, found: 205.0662

TLC: R_f 0.53 (hexanes/EtOAc, 4:1) [UV]

Analysis: $C_{15}H_{12}NCl$ (205.68)

Calcd:	C, 70.07;	H, 5.88%	N, 6.81%
Found:	C, 69.99;	H, 5.81%	N, 6.76%

Preparation of (*E*)-6-(2-Aminophenyl)-4-hexenenitrile (140e) (Scheme 48) [HMC11093]



Following the procedure procedure developed by Hartwig,[105] to an oven-dried, 38-mL pressure tube equipped with a magnetic stir bar were added aryl bromide **140d** (737 mg, 3.6 mmol) and ammonium sulfate (710 mg, 5.4 mmol, 1.5 equiv) and then introduced into a glove box. In the glove box, a separate oven-dried 20-mL vial with a magnetic stir bar were added $Pd[P(o\text{-tolyl})_3]_2$[138] (12.8 mg, 0.018 mmol, 0.005 equiv), Josiphos (CAS#158923-11-6, 9.9 mg, 0.018 mmol, 0.005 equiv), and dioxane (1 mL) and stirred for 5 min. To the pressure tube were added NaO*t*-Bu (1.55 g, 16.1 mmol, 4.5 equiv), dioxane (18 mL, 0.2 M) and the Pd/Josiphos solution (1 mL). The pressure tube was tightly sealed with the screw cap and exited the glove box. The reaction mixture was heated to 100 ^oC and stirred for 12 h. After 12 h, the reaction mixture was cooled to rt and was diluted with EtOAc (10 mL). Resulting dark mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure (30 ^oC, 10 mmHg) to yield a brown oil. Purification via silica gel flash column chromatography (SiO_2, 40 g, 25 mm Ø, hexanes to hexanes/EtOAc, 9:1) afforded 274 mg (41%) of **140e**, as a pale yellow oil. An analytically pure sample was obtained by Kugelrohr distillation (90 ^oC at 0.01 mmHg) affording 236 mg (35%) of **140e** as a colorless oil.

Data for **140e**:

bp: 90 ^oC (at 0.01 mmHg)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.11 – 7.02 (m, 2 H, HC(10,12)), 6.77 (t, *J* = 7.5 Hz, 1 H, HC(11)), 6.69 (d, *J* = 7.5 Hz, 1 H, HC(9)), 5.71 (dtd, *J* = 15.0, 6.5, and 1.5 Hz, 1 H, HC(5)), 5.53 (ddd, *J* = 15.0, 6.5, and 4.5 Hz, 1 H, HC(4)), 3.63 (brs, 2 H, HN), 3.21 (dd, *J* = 6.5, 1.5 Hz, 2 H, HC(6)), 2.46 – 2.35 (m, 4 H, HC(2,3)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 139.5 (C7), 136.7 (C8), 130.4 (C5), 129.3 (C12), 128.1 (C4), 126.4 (C10), 119.1 (C11), 119.1 (C1), 115.1 (C9), 33.6 (C6), 28.4 (C3), 17.5 (C2).

MS: (ESI)

103 (17), 187 (M+H, 100), 209 (26).

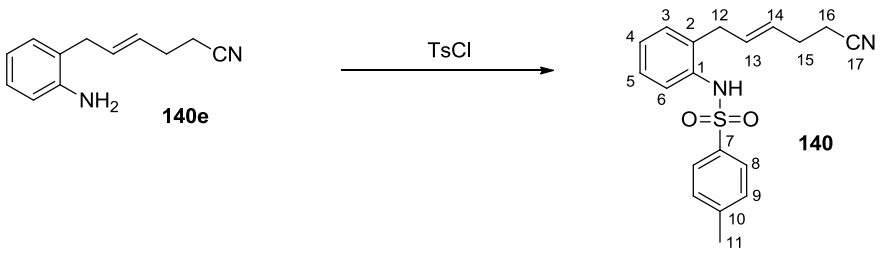
HRMS: calcd for $C_{12}H_{15}N_2$: 187.1235, found: 187.1232

TLC: R_f 0.41 (hexanes/EtOAc, 4:1) [UV]

Analysis: $C_{12}H_{14}N_2$ (186.12)

Calcd:	C, 77.38;	H, 7.58%	N, 15.04%
Found:	C, 77.24;	H, 7.41%	N, 14.92%

Preparation of (*E*)-*N*-[2-(5-Cyano-2-pentenyl)-phenyl]-4-methylbenzenesulfonamide[101] (140) (Scheme 48) [HMC11096]



To an oven-dried, 25-mL round-bottomed flask equipped with a magnetic stir bar were added aniline **140e** (236 mg, 1.27 mmol), CH_2Cl_2 (2.5 mL, 0.5 M), pyridine (133 μL, 1.65 mmol, 1.3 equiv), and 4-toluenesulfonyl chloride (266 mg, 1.39 mmol, 1.1 equiv) in order at rt. After stirring for 24 h, the reaction mixture was washed with 1 M HCl solution (3 mL) and brine (3 mL x 2). Resulting organic layer was dried over Na_2SO_4, filtered, and concentrated reduced pressure (30 ^{o}C, 10 mmHg) to yield an yellow oil. The crude product was purified via flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes to hexanes/EtOAc, 4:1) afforded 372 mg (86%) of **140**, as a yellow solid. An analytically pure sample was obtained by recrystallization of the

solid with boiling EtOAc/pentane (1:10 mixture, 15 mL), affording 341 mg (79%) of **140** as pale yellow crystals.

Data for **140**:

mp: 91-92 °C (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.65 (d, *J* = 8.0 Hz, 2 H, HC(8)) 7.39 (d, *J* = 7.5 Hz, 1 H, HC(3)), 7.22 (d, *J* = 7.5 Hz, 2 H, HC(9)) 7.19 – 7.09 (m, 3 H, HC(aryl), 6.47 (brs, 1 H, HN), 5.75 (dt, *J* = 15.0, 6.0 Hz, 1 H, HC(13)), 5.59 (ddd, *J* = 15.0, 6.0, and 4.5 Hz, 1 H, HC(14)), 3.23 (dd, *J* = 6.5, 1.5 Hz, 2 H, HC(12)), 2.42 (s, 3 H, HC(11)), 2.50 – 2.35 (m, 4 H, HC(15,16)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 143.6 (C10), 136.5 (C7), 135.9 (C2), 134.1 (C1), 131.6 (C14), 130.5 (C13), 129.8 (C6), 129.6 (C9), 127.1 (C4), 127.1 (C3), 127.0 (C8), 126.9 (C5), 119.0 (C17), 35.9 (C12), 28.4 (C15), 21.5 (C11), 17.4 (C16).

MS: (ESI)

105 (23), 118 (67), 130 (20), 184 (27), 185 (40), 186 (100), 272 (15), 340 (M+H, 52), 357 (10), 363 (11).

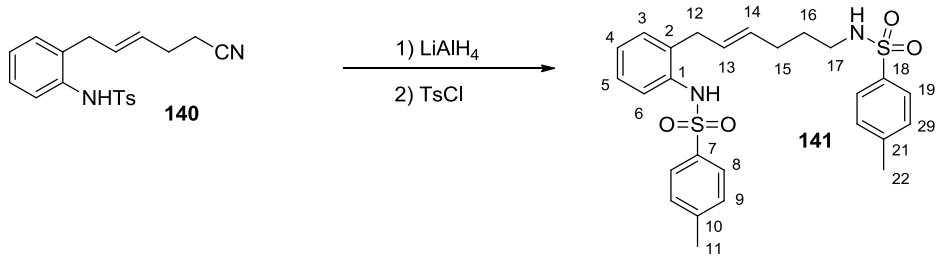
HRMS: calcd for $C_{19}H_{21}N_2O_2S$: 340.1245, found: 340.1248

TLC: R_f 0.35 (hexanes/EtOAc, 4:1) [UV]

Analysis: $C_{19}H_{20}N_2O_2S$ (340.44)

Calcd:	C, 67.03;	H, 5.92%	N, 8.23%
Found:	C, 67.17;	H, 6.10%	N, 8.31%

Preparation of (*E*)-*N*-{2-[6-(4-Methylbenzenesulfonamido)-2-hexenyl]phenyl}-4-methylbenzenesulfonamide (141) (Scheme 48) [HMC10056, HMC10057]



An oven-dried, 100-mL Schlenk flask equipped with a magnetic stir bar was charged with $LiAlH_4$ (223 mg, 5.87 mmol, 2.0 equiv) and capped with a septum under argon. The flask was immersed in an ice-bath and was added THF (10 mL). To the resulting suspension was added a solution of nitrile **140** (1.0 g, 2.94 mmol, 1 equiv) in THF (10 mL). The suspension was stirred for 2 h at 0 ^oC and gradually warmed to room temperature over 1 h. The reaction was cooled to 0 ^oC and slowly quenched with aqueous 1 M NaOH solution (0.4 mL) upon completion. The resulting emulsion was filtered through a short pad of Celite and rinsed with ether (15 mL x 3). Evaporation of the filtrate at reduced pressure (25 ^oC, 10 mmHg) gave 799 mg (79%) of amine. Then an oven-dried, 25-mL Schlenk flask equipped with a magnetic stir bar was charged with the crude amine (689 mg, approx. 2.0 mmol, 1 equiv), CH_2Cl_2 (4 mL), and pyridine (210 μL, 2.6 mmol, 1.3 equiv). To the solution was added *p*-toluenesulfonyl chloride (419 mg, 2.2 mmol, 1.1 equiv) portionwise at 0 ^oC under positive stream of argon. The solution was warmed to room temperature and was stirred for 4 h. The reaction mixture was washed with aqueous 1 M HCl (4 mL), then brine (4 mL x 2). Resulting organic layer was dried over Na_2SO_4 and evaporated under reduced pressure (25 ^oC, 10 mmHg). Purification via silica gel flash column chromatography (SiO_2, 40 g, 25 mm Ø, hexanes only to hexanes/EtOAc, 4:1) afforded 858 mg (59% over two steps from **140**) of the homologated tosylamine **141** as white solid. An analytically pure sample was obtained by recrystallization of the solid with boiling EtOAc/pentane (1:10 mixture, 30 mL), affording 756 mg (52%) of **141** as white crystals.

Data for **141**:

mp: 104-105 ^oC (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.74 (d, *J* = 8.0 Hz, 2 H, HC(19)), 7.65 (d, *J* = 8.0 Hz, 2 H, HC(8)) 7.39 (d, *J* = 7.5 Hz, 1 H, HC(3)), 7.33 (d, *J* = 8.0 Hz, 2 H, HC(20)), 7.22 (d, *J* = 7.5 Hz, 2 H, HC(9)) 7.19 – 7.09 (m, 3 H, HC(aryl), 6.47 (brs, 1 H, HN), 5.69 (dt, *J* = 15.0, 6.5 Hz, 1 H, HC(13)), 5.54 (dd, *J* = 15.0, 7.0 Hz, 1 H, HC(14)), 4.65 (brs, 1 H, HN), 3.24 (dd, *J* = 6.5, 1.5 Hz, 2 H, HC(12)), 2.92 (appq, *J* = 7.0 Hz, 2 H, HC(17)), 2.43 (s, 3 H, HC(22)), 2.41 (s, 3 H, HC(11)), 1.98 (appq, *J* = 7.0 Hz, 2 H, HC(15)), 1.52 (appp, *J* = 7.0 Hz, 2 H, HC(16)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 143.6 (C10), 143.3 (C21), 137.0 (C18), 136.5 (C7), 135.9 (C2), 134.1 (C1), 130.7 (C13), 129.9 (C14), 129.8 (C6), 129.7 (C20), 129.6 (C9), 127.1 (C4), 127.1 (C3), 127.1 (C19), 127.0 (C8), 126.9 (C5), 42.6 (C17), 35.8 (C12), 29.3 (C15), 29.2 (C16), 21.5 (C11), 21.5 (C22).

MS: (ESI)

118 (21), 273 (13), 344 (36), 499 (M+H, 100), 521 (53), 537 (24).

HRMS: (ESI) calcd for $C_{26}H_{31}N_2O_4S_2$: 499.1725, found: 499.1728

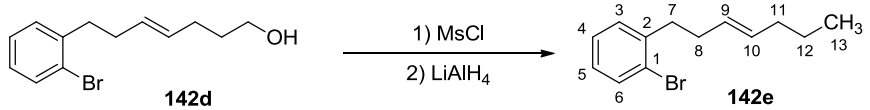
TLC: R_f 0.28 (hexanes/EtOAc, 4:1) [UV]

Analysis: $C_{26}H_{30}N_2O_4S_2$ (498.66)

Calcd:	C, 62.62;	H, 6.06%	N, 5.62%
Found:	C, 62.85;	H, 6.23%	N, 5.69%

Preparation of Substrates 142 via C-N Cross-coupling (Scheme 49)

Preparation of (*E*)-1-Bromo-2-(3-hepten-1-yl)-benzene (142e) (Scheme 49) [HMC10028, HMC10029]



To an oven-dried 250-mL round-bottomed flask was equipped with a magnetic stir bar were added bromoalcohol **142d**[126] (3.21 g, 11.9 mmol), CH_2Cl_2 (120 mL, 0.1 M), and then the flask was connected to an argon inlet. The solution was cooled to 0 ^oC in ice bath, and were added Et_3N (5.83 mL, 41.8 mmol, 3.5 equiv), and methanesulfonic chloride (1.38 mL, 17.9 mmol, 1.5 equiv) via syringe. The reaction mixture was stirred for 1 h at 0 ^oC. The reaction was

quenched by adding water (30 mL) and the resulting biphasic solution was separated. The aqueous layer was further extracted with CH_2Cl_2 (30 mL x 2). Combined organic layer was dried over Na_2SO_4, and filtered over a glass wool. The filtrate was concentrated under reduced pressure (30 ^oC, 10 mmHg) to afford a brown oil. Purification via silica gel plug filtration (SiO_2, 10 g, 30 mm Ø, hexanes/EtOAc, 7:3) afforded 3.52 g (85%) of mesylate as a pale yellow oil. (The mesylate intermediate slowly turned into a dark oil upon standing.) To an oven-dried 200-mL round-bottomed flask with a magnetic stir bar were added mesylate (2.5 g, 7.2 mmol), and THF (80 mL, 0.09 M). The flask was connected to an argon inlet and capped with a septum. The solution was cooled to 0 ^oC in an ice bath and was added a suspension of $LiAlH_4$ (273 mg, 7.2 mmol, 1 equiv in 10 mL of THF) via cannula dropwise. The resulting reaction mixture was stirred for 4 h at 0 ^oC. Fieser & Fieser workup method was used to quench the reaction, adding water (0.3 mL), 15% NaOH (0.3 mL), water (0.9 mL) in order, dropwise via syringe at 0 ^oC. The resulting white slurry was filtered through celite and rinsed with ether (20 mL x 2). The colorless filtrate was concentrated under reduced pressure (30 ^oC, 10 mmHg) to afford a colorless oil. Purification via silica gel flash chromatography (SiO_2, 120 g, 35 mm Ø, hexanes to hexanes/EtOAc, 19:1) afforded 1.68 g (92%) of **142e**, as a colorless oil. An analytically pure sample was obtained by Kugelrohr distillation (80 ^oC at 0.1 mmHg) affording 1.62 g (89%) of **142e** as a colorless oil.

Data for **142e**:

bp: 80 ^oC (at 0.1 mmHg)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.53 (d, *J* = 8.0 Hz, 1 H, HC(6)), 7.25 – 7.17 (m, 2 H, HC(3,4)), 7.07 – 7.02 (m, 1 H, HC(5)), 5.46 (q, *J* = 5.0 Hz, 2 H, HC(9,10)), 2.83 – 2.76 (m, 2 H, HC(7)), 2.35 – 2.27 (m, 2 H, HC(8)), 1.97 (q, *J* = 7.0, 6.5 Hz, 2 H, HC(11)), 1.36 (app. sext, *J* = 7.5 Hz, 2 H, HC(12)), 0.88 (t, *J* = 7.5 Hz, 3 H, HC(13)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 141.3 (C(1)), 132.7 (C(6)), 131.2 (C(10)), 130.4 (C(3)), 129.0 (C(9)), 127.4 (C(5)), 127.2 (C(4)), 124.4 (C(2)), 36.4 (C(7)), 34.7 (C(11)), 32.8 (C(8)), 22.6 (C(12)), 12.7 (C(13)).

MS: (EI)

55 (92), 67 (15), 82 (48), 83 (70), 89 (20), 90 (33), 91 (17), 117 (34), 169 (100), 171 (98), 173 (43), 182 (18), 184 (17), 252 (M, 20), 254 (20).

HRMS: calcd for $C_{13}H_{17}Br$: 252.0514, found: 252.0507

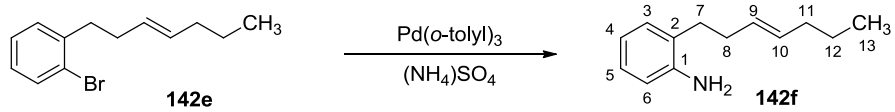
TLC: R_f 0.67 (hexanes/EtOAc, 4:1) [UV]

Analysis: $C_{13}H_{17}Br$ (253.18)

Calcd: C, 61.67; H, 6.77%

Found: C, 62.01; H, 6.69%

Preparation of (*E*)-2-(3-Hepten-1-yl)-benzenamine (142f) (Scheme 49) [HMC10030]



Following the procedure procedure developed by Hartwig,[105] to an oven-dried, 200-mL pressure tube equipped with a magnetic stir bar were added aryl bromide **142e** (1.52 g, 6.0 mmol) and ammonium sulfate (1.19 g, 9.0 mmol, 1.5 equiv) and then introduced into a glove box. In the glove box, a separate oven-dried 20-mL vial with a magnetic stir bar were added $Pd[P(o\text{-tolyl})_3]_2$ [138] (21.5 mg, 0.03 mmol, 0.005 equiv), Josiphos (CAS#158923-11-6, 16.6 mg, 0.03 mmol, 0.005 equiv), and dioxane (1 mL) and stirred for 5 min. To the pressure tube were added NaO*t*-Bu (2.60 g, 27.0 mmol, 4.5 equiv), dioxane (60 mL) and the Pd/Josiphos solution (1 mL). The pressure tube was tightly sealed with the screw cap and exited the glove box. The reaction mixture was heated to 100 ^oC and stirred for 12 h. After 12 h, the reaction mixture was cooled to rt and was diluted with EtOAc (30 mL). Resulting dark mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure (30 ^oC, 10 mmHg) to yield a brown oil. Purification via silica gel flash column chromatography (SiO_2, 120 g, 35 mm Ø, hexanes to hexanes/EtOAc, 9:1) afforded 738 mg (65%) of **142f**, as a pale yellow oil. An analytically pure sample was obtained by Kugelrohr distillation (110 ^oC at 0.1 mmHg) affording 701 mg (62%) of **142f** as a colorless oil.

Data for **142f**:

bp: 110 °C (at 0.1 mmHg)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.08 – 7.01 (m, 2 H, HC(3,5)), 6.74 (t, *J* = 7.5 Hz, 1 H, HC(4)), 6.68 (d, *J* = 8.0 Hz, 1 H, HC(6)), 5.50 (m, 2 H, HC(9,10)), 3.62 (brs, 2 H, NH_2), 2.55 (dd, *J* = 9.0, 6.5 Hz, 2 H, HC(7)), 2.32 (m, 2 H, HC(8)), 1.98 (m, 2 H, HC(11)), 1.38 (tq, *J* = 7.5, 7.5 Hz, 2 H, HC(12)), 0.89 (t, *J* = 7.5 Hz, 3 H, HC(13)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 144.1 (C(1)), 131.1 (C(10)), 129.4 (C(3)) 129.4 (C(9)), 126.9 (C(5)), 126.3 (C(2)), 118.7 (C(4)), 115.5 (C(6)), 34.7 (C(11)), 31.8 (C(8)), 31.5 (C(7)), 22.6 (C(12)), 13.7 (C(13)).

MS: (ESI)

106 (13), 190 (M+H, 100), 191 (32).

HRMS: calcd for $C_{13}H_{20}N$: 190.1596, found: 190.1595

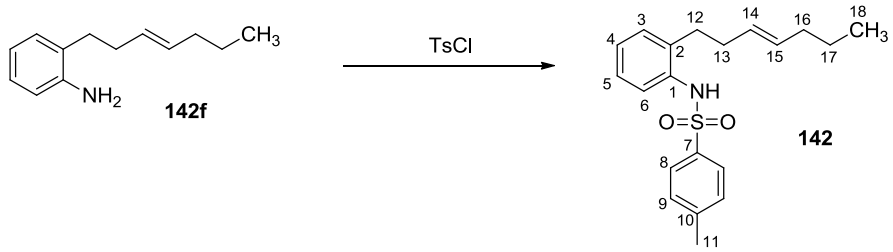
TLC: R_f 0.43 (hexanes/EtOAc, 4:1) [UV]

Analysis: $C_{13}H_{19}N$ (189.30)

Calcd: C, 82.48; H, 10.12% N, 7.40%

Found: C, 82.48; H, 9.95% N, 7.69%

Preparation of (*E*)-*N*-[2-(3-Hepten-1-yl)-phenyl]-4-methyl-bezenesulfonamide[101] (142) (Scheme 49) [HMC10031]



To an oven-dried, 25-mL round-bottomed flask equipped with a magnetic stir bar were added aniline **142f** (568 mg, 3.0 mmol), CH_2Cl_2 (6 mL, 0.5 M), pyridine (315 μL, 3.9 mmol, 1.3 equiv), and 4-toluenesulfonyl chloride (686 mg, 3.6 mmol, 1.2 equiv) in order at rt. After stirring for 12 h, the reaction mixture was washed with 1 M HCl solution (5 mL) and brine (5 mL x 2).

Resulting organic layer was dried over Na_2SO_4, filtered, and concentrated reduced pressure (30 ^oC, 10 mmHg) to yield an yellow oil. The crude product was purified via flash chromatography (SiO_2, 80 g, 30 mm Ø, hexanes to hexanes/EtOAc, 5:1) afforded 896 mg (87%) of **142**, as an yellow oil which crystallized upon standing. An analytically pure sample was obtained by recrystallization of the solid with boiling EtOAc/pentane (1:10 mixture, 20 mL), affording 841 mg (82%) of **142** as pale yellow crystals.

Data for **142**:

mp: 58-59 ^oC (sealed tube)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.64 (d, *J* = 8.5 Hz, 2 H, HC(8)) 7.38 (d, *J* = 7.5 Hz, 1 H, HC()), 7.25 (d, *J* = 7.5 Hz, 2 H, HC(9)) 7.20 – 7.10 (m, 3 H, HC(aryl), 6.51 (brs, 1 H, HN), 5.41 – 5.29 (m, 2 H, HC(14,15)), 2.42 (s, 3 H, HC(11)), 2.41 – 2.35 (m, 2 H, HC(12)), 2.10 (q, *J* = 7.0 Hz, 2 H, HC(13)), 1.97 (q, *J* = 6.5 Hz, 2 H, HC(16)), 1.38 (septd, *J* =7.5, 1.0 Hz, 2 H, HC(17)), 0.90 (td, *J* = 7.5, 1.0 Hz, 3 H, HC(18)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 143.7 (C10), 136.6 (C7), 135.1 (C2), 134.0 (C1), 132.1 (C15), 129.9 (C6), 129.6 (C9), 128.5 (C14), 127.1 (C8), 126.9 (C5), 126.2 (C4), 124.5 (C3), 34.6 (C16), 32.8 (C13), 30.9 (C12), 22.5 (C17), 21.5 (C11), 13.7 (C18).

MS: (ESI)

118 (25), 130 (19), 132 (76), 146 (17), 187 (29), 188 (37), 189 (100), 190 (13), 205 (13), 286 (13), 342 (13), 344 (M+H, 38), 360 (12), 366 (12).

HRMS: calcd for $C_{20}H_{26}NO_2S$ ($[M+H]^+$): 344.1684, found: 344.1680

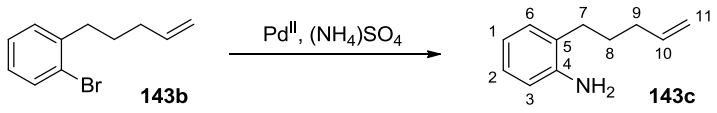
TLC: R_f 0.35 (hexanes/EtOAc, 4:1) [UV]

Analysis: $C_{20}H_{25}NO_2S$ (343.48)

Calcd:	C, 69.93;	H, 7.34%	N, 4.08%
Found:	C, 69.89;	H, 7.56%	N, 4.05%

Preparation of Substrate 138 via C-N Cross-coupling (Scheme 50)

Preparation of 2-(4-Penten-1-yl)-benzenamine (143c) (Scheme 50) [HMC10011]



Adopting the C-N amination procedure,[105] to an oven-dried, 250-mL pressure tube equipped with a magnetic stir bar were added aryl bromide **143b**[108] (2.45 g, 10.9 mmol) and ammonium sulfate (2.16 g, 16.3 mmol, 1.5 equiv) and then introduced into a glove box. In the glove box, a separate oven-dried 20-mL vial with a magnetic stir bar were added Pd[P(*o*-tolyl)$_3$]$_2$[138] (38.9 mg, 0.054 mmol, 0.005 equiv), Josiphos (CAS#158923-11-6, 30.2 mg, 0.054 mmol, 0.005 equiv), and dioxane (1 mL) and stirred for 5 min. To the pressure tube were added NaO*t*-Bu (4.71 g, 49.0 mmol, 4.5 equiv), dioxane (110 mL), and the Pd/Josiphos solution (1 mL). The pressure tube was tightly sealed with the screw cap and exited the glove box. The reaction mixture was heated to 100 ^{o}C and stirred for 12 h. After 12 h, the reaction mixture was cooled to rt and was diluted with EtOAc (50 mL). Resulting dark mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure (30 ^{o}C, 10 mmHg) to yield a brown oil. Purification via silica gel flash column chromatography (SiO_2, 120 g, 35 mm Ø, hexanes to hexanes/EtOAc, 6:1) afforded 1.07 g (61%) of **143c**, as a pale yellow oil. An analytically pure sample was obtained by Kugelrohr distillation (70 ^{o}C at 0.1 mmHg) affording 1.01 g (57%) of **143c** as a colorless oil.

Data for **143c**:

bp: 70 ^{o}C (at 0.1 mmHg)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.07 (td, *J* = 7.5, 1.5 Hz, 2 H, HC(3,5)), 6.76 (tt, *J* = 7.5, 1.5 Hz, 1 H, HC(4)), 6.70 (d, *J* = 8.0 Hz, 1 H, HC(6)), 5.89 (ddtd, *J* = 17.0, 10.0, 6.5, and 1.5 Hz, 1 H, HC(10)), 5.09 (dp, *J* = 17.0, 1.5 Hz, 1 H, HC(11)), 5.04 (dt, *J* = 10.0, 1.5 Hz, 1 H, HC(11)), 3.62 (brs, 2 H, H_2N), 2.53 (t, *J* = 8.0 Hz, 2 H, HC(7)), 2.18 (q, *J* = 6.5, 1.5 Hz, 2 H, HC(9)), 1.76 (qdd, *J* = 8.5, 7.0, and 1.5 Hz, 2 H, HC(8)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 143.9 (C1), 138.4 (C10), 129.5 (C3), 126.9 (C5), 126.5 (C2), 118.8 (C4), 115.6

(C6), 114.9 (C11), 33.5 (C9), 30.5 (C7), 27.8 (C8).

MS: (ESI)

106 (10), 162 (M+H, 100), 163 (15), 174 (10), 216 (25).

HRMS: calcd for $C_{11}H_{16}N$ ($[M+H]^+$): 162.1283, found: 162.1288

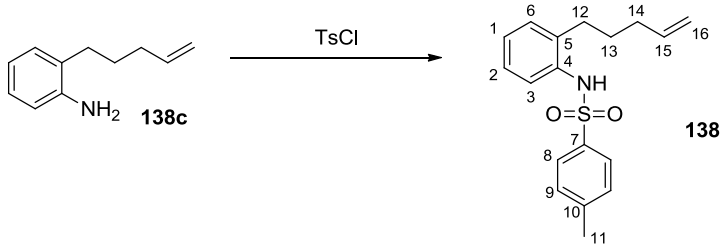
TLC: R_f 0.34 (hexanes/EtOAc, 4:1) [UV]

Analysis: $C_{11}H_{15}N$ (161.24)

Calcd: C, 81.94; H, 9.38% N, 8.69%

Found: C, 81.97; H, 9.13% N, 8.63%

Preparation of 4-Methyl-*N*-[2-(4-penten-1-yl)-phenyl]-bezenesulfonamide (143) (Scheme 50)[101] [HMC10012]



To an oven-dried, 25-mL round-bottomed flask equipped with a magnetic stir bar were added aniline **143c** (806 mg, 5.0 mmol), CH_2Cl_2 (10 mL, 0.5 M), pyridine (526 μL, 6.5 mmol, 1.3 equiv), and 4-toluenesulfonyl chloride (1.14 g, 6.0 mmol, 1.2 equiv) in order at rt. A condenser was installed on top of the flask and refluxed for 12 h. The reaction mixture was cooled to rt and washed with 1 M HCl solution (10 mL) and brine (5 mL x 3). Resulting organic layer was dried over Na_2SO_4, filtered, and concentrated reduced pressure (30 ^oC, 10 mmHg) to yield an yellow oil. The crude product was purified via flash chromatography (SiO_2, 120 g, 35 mm Ø, hexanes to hexanes/EtOAc, 5:1) afforded 1.34 g (85%) of **143**, as an white crystalline solid. An analytically pure sample was obtained by recrystallization of the solid with boiling pentane (50 mL), affording 1.23 g (78%) of **143** as white crystals.

Data for **143**:

mp: 70-71 ^oC (pentane)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.64 (d, *J* = 8.0 Hz, 2 H, HC(8)), 7.40 (d, *J* = 8.0 Hz, 1 H, HC(6)), 7.25 (d, *J* = 8.0 Hz, 2 H, HC(9)), 7.21 – 7.11 (m, 3 H, HC(3,4,5)), 6.36 (brs, 1 H, HN), 5.78 (ddt, *J* = 17.0, 10.5, and 6.5 Hz, 1 H, HC(15)), 5.09 – 5.01 (m, 2 H, HC(16)), 2.43 (s, 3 H, HC(11)), 2.34 (appt, *J* = 7.5 Hz, 2 H, HC(12)), 2.01 (appq, *J* = 7.0 Hz, 2 H, HC(14)), 1.49 (appp, *J* = 7.5 Hz, 2 H, HC(13)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 143.8 (C10), 138.0 (C15), 136.6 (C7), 135.2 (C1), 134.0 (C2), 129.7 (C3), 129.6 (C9), 127.2 (C8), 126.9 (C4), 126.2 (C5), 124.5 (C6), 115.4 (C16), 33.1 (C14), 29.8 (C12), 29.0 (C13), 21.5 (C11).

FTIR: (neat)

3280 (m), 1490 (m), 1392 (m), 1335 (s), 1305 (w), 1291 (w), 1274 (w), 1185 (w), 1160 (s), 1120 (m), 1092 (s), 1019 (w), 993 (w), 951 (w), 910 (s), 886 (w), 875 (w), 832 (w), 814 (m), 762 (m).

MS: (ESI)

160 (15), 161 (93), 162 (16), 316 (M+H, 100), 317 (20), 333 (34), 335 (38), 338 (95), 339 (22), 492 (72), 493 (47).

HRMS: calcd for $C_{18}H_{22}NO_2S$ ($[M+H]^+$): 316.1371, found: 316.1376

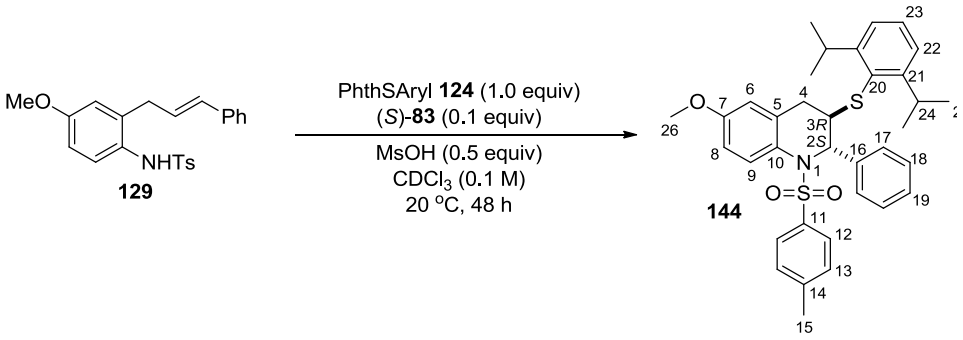
TLC: R_f 0.30 (hexanes/EtOAc, 4:1) [UV]

Analysis: $C_{18}H_{21}NO_2S$ (315.43)

Calcd:	C, 68.54;	H, 6.71%	N, 4.44%
Found:	C, 68.43;	H, 6.92%	N, 4.31%

Optimization of the Sulfenoamination Reaction (Table 11)

Table 11 Entry 1-4 [HMC9073]



An oven-dried, 5-mm NMR tube was charged with anisidine **129** (39.4 mg, 0.1 mmol), N-(2,6-diisopropyl)thiophthalimide **124** (33.9 mg, 0.1 mmol, 1 equiv), catalyst (*S*)-**83** (5.2 mg, 0.01 mmol, 0.1 equiv), and $CDCl_3$ (1 mL, 0.1 M). The tube was capped with a septum and shaken thoroughly. Subsequently, MsOH (3.2 mL, 0.05 mmol, 0.5 equiv) was added via syringe at 20 ^oC, and the resulting mixture was shaken again. The NMR tube was kept in a water bath (20 ^oC), and taken out for NMR spectroscopy at 6, 12, 24, and 48 h. Conversion to product was measure by the apprearance of the diagnostic ^1H NMR resonance for the product at 5.14 pp, with respect to the substrate peaks at 6.11, 6.31, and 3.80 ppm. No other products were observed in the ^1H NMR spectra. Formation of phthalimide byproduct was visually confirmed by the precipitation. After 48 h, the reaction mixture was quenched by addition of saturated $NaHCO_3$ aqueous solution (1 mL) and extracted with CH_2Cl_2 (1 mL x 3). Combined organic layer was dried over Na_2SO_4, filtered, and evaporated. Purification by flash column chromatography (SiO_2, 5 g, 20 mm Ø , hexanes/EtOAc = 19:1) gave 48 mg (82%) of **144** as white solid.

Data for **144**:

^1H NMR: (500 MHz, $CDCl_3$)

δ 7.62 (d, *J* = 8.5 Hz, 1 H, HC(8)), 7.54 (d, *J* = 8.0 Hz, 2 H, HC(12)) 7.39 – 7.27 (m, 8 H, HC(aryl)), 7.10 (d, *J* = 7.5 Hz, 2 H, HC(22)), 6.87 (dd, J = 9.0, 3.0 Hz, 1 H, HC(7)), 6.40 (d, *J* = 3.0 Hz, 1 H, HC(5)), 5.15 (d, *J* = 9.0 Hz, 1 H, HC(2)), 3.79 (s, 3 H, HC(26)), 3.35 (brs, 2 H, HC(24)), 2.83 (ddd, *J* = 12.5, 9, and 4.0 Hz, 1 H, HC(3)), 2.48 (s, 3 H, HC(15)), 2.18 (dd, *J* = 14.0, 4.0 Hz, 1 H, HC(4)), 1.52 (t, *J* = 13.0 Hz, 1 H, HC(4)), 1.06 (d, *J* = 7.0 Hz, 6 H, HC(25)), 0.98 (d, *J* = 7.0 Hz, 6 H, HC(25)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 158.0 (C6), 153.7 (C20), 143.5 (C11), 142.5 (C16), 136.3 (C14), 135.7 (C10), 129.5 (C19), 129.5 (C13), 129.2 (C9), 128.9 (C8), 128.8 (C21), 128.3 (C17), 127.5 (C23), 127.2 (C12), 127.0 (C18), 123.6 (C22), 112.9 (C7), 112.6 (C5), 64.6 (C2), 55.5 (C26), 55.4 (C3), 33.8 (C4), 31.2 (C24), 24.5 (C25), 23.8 (C25), 21.6 (C15).

HPLC: (2*R*,3*S*)-**144,** t_R 7.1 min (9.9%); (2*S*,3*R*)-**144,** t_R 8.2 min (90.1%) (Chiralpak AD, 220 nm, 90:10, hexanes:*i*-PrOH, 1 mL/min)

Table 11 Entry 5 (Background reaction) [HMC9057]

An oven-dried, 5-mm NMR tube was charged with anisidine **129** (19.7 mg, 0.05 mmol), *N*-(2,6-diisopropyl)thiophthalimide **124** (17.0 mg, 0.05 mmol, 1 equiv), and $CDCl_3$ (0.5 mL, 0.1 M). The tube was capped with a septum and shaken thoroughly. Subsequently, MsOH (1.6 mL, 0.025 mmol, 0.5 equiv) was added via syringe at 20 ^oC, and the resulting mixture was shaken again. The NMR tube was kept in a water bath (20 ^oC), and taken out for NMR spectroscopy at 6, 12, 24, and 48 h. No conversion to product was observed by ^1H NMR spectroscopy.

Table 11 Entry 6 [HMC9085]

An oven-dried, 4-mL vial with a magnetic stir bar was charged with anisidine **129** (39.4 mg, 0.1 mmol), N-(2,6-diisopropyl)thiophthalimide **124** (33.9 mg, 0.1 mmol, 1 equiv), catalyst (*S*)-**83** (5.2 mg, 0.01 mmol, 0.1 equiv), and CH_2Cl_2 (1 mL, 0.1 M). The vial was capped with a septum and stirred thoroughly for 10 min at 0 ^oC bath. Subsequently, MsOH (3.2 mL, 0.05 mmol, 0.5 equiv) was added via syringe at 0 ^oC (be aware of MsOH freezing), and the resulting mixture was stirred again for 48 h at 0 ^oC. The reaction mixture was quenched by adding saturated $NaHCO_3$ aqueous solution (1 mL) and extracted with CH_2Cl_2 (1 mL x 3). Combined organic layer was dried over Na_2SO_4, filtered, and evaporated. ^1H NMR spectroscopy of the crude product mixture showed 80% conversion after 48 h. Conversion to product was measure by the apprearance of the diagnostic ^1H NMR resonance for the product at 5.14 pp, with respect to the substrate peaks at 6.11, 6.31, and 3.80 ppm. Purification by flash column chromatography (SiO_2, 5 g, 20 mm Ø , hexanes/EtOAc = 19:1) gave 37 mg (64%) of **144** as white solid.

Data for **144**:

HPLC: (2*R*,3*S*)-**144,** t_R 7.2 min (6.1%); (2*S*,3*R*)-**144,** t_R 8.2 min (93.9%) (Chiralpak AD, 220 nm, 90:10, hexanes:*i*-PrOH, 1 mL/min)

Table 11 Entry 7 [HMC9093]

An oven-dried, 4-mL vial with a magnetic stir bar was charged with anisidine **129** (39.4 mg, 0.1 mmol), N-(2,6-diisopropyl)thiophthalimide **124** (33.9 mg, 0.1 mmol, 1 equiv), catalyst (*S*)-**83** (5.2 mg, 0.01 mmol, 0.1 equiv), and $CDCl_3$ (0.25 mL, 0.4 M). The vial was capped with a septum and stirred thoroughly for 10 min at 0 ^oC bath. Subsequently, MsOH (3.2 mL, 0.05 mmol, 0.5 equiv) was added via syringe at 0 ^oC (be aware of MsOH freezing), and the resulting mixture

was stirred again for 48 h at 0 ^{o}C. The reaction mixture was quenched by adding saturated $NaHCO_3$ aqueous solution (1 mL) and extracted with CH_2Cl_2 (1 mL x 3). Combined organic layer was dried over Na_2SO_4, filtered, and evaporated. ^{1}H NMR spectroscopy of the crude product mixture showed full conversion after 48 h. Conversion to product was measure by the apprearance of the diagnostic ^{1}H NMR resonance for the product at 5.14 pp, with respect to the substrate peaks at 6.11, 6.31, and 3.80 ppm. Purification by flash column chromatography (SiO_2, 5 g, 20 mm Ø , hexanes/EtOAc = 19:1) gave 47 mg (80%) of **144** as white solid.

Data for **144**:

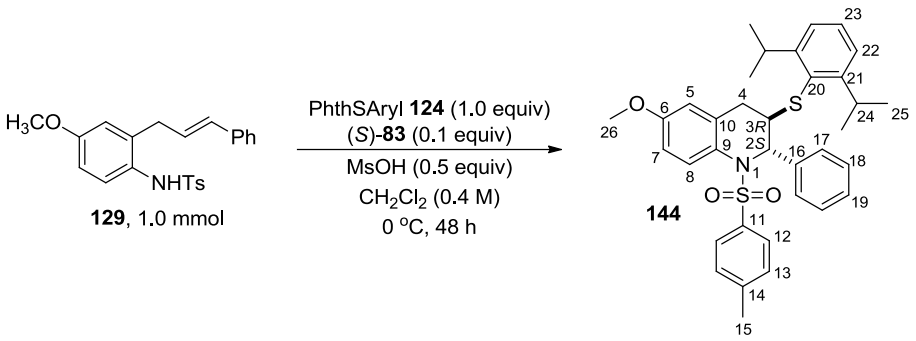
HPLC: (2*R*,3*S*)-**144,** t_R 7.1 min (6.6%); (2*S*,3*R*)-**144,** t_R 8.2 min (93.4%) (Chiralpak AD, 220 nm, 90:10, hexanes:*i*-PrOH, 1 mL/min)

Survey of Substrate Scope (Table 12)

General Procedure XIII: Sulfenoamination of Anilines

An oven-dried, 10-mL Schlenk flask equipped with a stir bar was charged with substrate (1.0 mmol, 1.0 equiv), PhthSAryl **124** (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.10 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M) then capped with a rubber septum followed by argon purge. The flask was placed in 0 ^{o}C isopropyl alcohol bath cooled via a Cryocool unit. The temperature of the mixture was monitored via a thermocouple digital temperature probe. After the temperature stabilized, MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) was added slowly via syringe (internal temperature was maintained below 4 ^{o}C while addition of MsOH, and MsOH was dropped carefully far from the top to prevent freezing in the syringe) and the mixture was allowed to stir for the indicated time. The reaction was quenched while cold by addition of pre-cooled sat. $NaHCO_3$ aq. solution (5 mL) upon vigorous stirring. The biphasic resulting mixture was extracted with CH_2Cl_2 (5 mL x 3). The combined organic extracts were dried over Na_2SO_4, filtered through glass wool and then concentrated *in vacuo* (23 ^{o}C, 10 mm Hg) to afford the crude solid product. The product was purified via silica gel flash column chromatography.

Preparation of (2*S*,3*R*)-3-[(2,6-Diisopropyl)phenylthio]-6-methoxy-2-phenyl-1-tosyl-1,2,3,4-tetrahydroquinoline (144) (Table 12 Entry 1) [HMC11030]



Following General Procedure XIII, a 10-mL Schlenk flask was charged with **129** (393.5 mg, 1.0 mmol, 1.0 equiv), PhthSAryl **124** (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) at 0 ^oC and the stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 510 mg (87%) of a **144** as a white solid.

Data for **144**:

mp: 157-158 ^oC (pentane)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.62 (d, *J* = 8.5 Hz, 1 H, HC(8)), 7.54 (d, *J* = 8.0 Hz, 2 H, HC(12)) 7.39 – 7.27 (m, 8 H, HC(aryl)), 7.10 (d, *J* = 7.5 Hz, 2 H, HC(22)), 6.87 (dd, J = 9.0, 3.0 Hz, 1 H, HC(7)), 6.40 (d, *J* = 3.0 Hz, 1 H, HC(5)), 5.15 (d, *J* = 9.0 Hz, 1 H, HC(2)), 3.79 (s, 3 H, HC(26)), 3.35 (brs, 2 H, HC(24)), 2.83 (ddd, *J* = 12.5, 9, and 4.0 Hz, 1 H, HC(3)), 2.48 (s, 3 H, HC(15)), 2.18 (dd, *J* = 14.0, 4.0 Hz, 1 H, HC(4)), 1.52 (t, *J* = 13.0 Hz, 1 H, HC(4)), 1.06 (d, *J* = 7.0 Hz, 6 H, HC(25)), 0.98 (d, *J* = 7.0 Hz, 6 H, HC(25)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 158.0 (C6), 153.7 (C20), 143.5 (C11), 142.5 (C16), 136.3 (C14), 135.7 (C10), 129.5 (C19), 129.5 (C13), 129.2 (C9), 128.9 (C8), 128.8 (C21), 128.3 (C17), 127.5 (C23), 127.2 (C12), 127.0 (C18), 123.6 (C22), 112.9 (C7), 112.6 (C5), 64.6 (C2), 55.5 (C26), 55.4 (C3), 33.8 (C4), 31.2 (C24), 24.5 (C25), 23.8 (C25), 21.6 (C15).

MS: (ESI)

148 (13), 236 (11), 431 (100), 432 (31), 586 (M+H, 11), 608 (22)

HRMS: calcd for $C_{35}H_{40}NO_3S_2$: 586.2450, found: 586.2440

TLC: R_f 0.34 (hexanes/EtOAc, 4:1) [UV]

IR: 2965 (w), 1495 (m), 1457 (w), 1354 (m), 1343 (w), 1222 (m), 1164 (s), 1089 (w), 1053 (m), 1032 (w), 960 (w), 868 (m), 811 (w), 802 (m), 750 (w)

Opt Rot: $[\alpha]_D^{24}$ -35.7 (c = 0.90, $CHCl_3$)

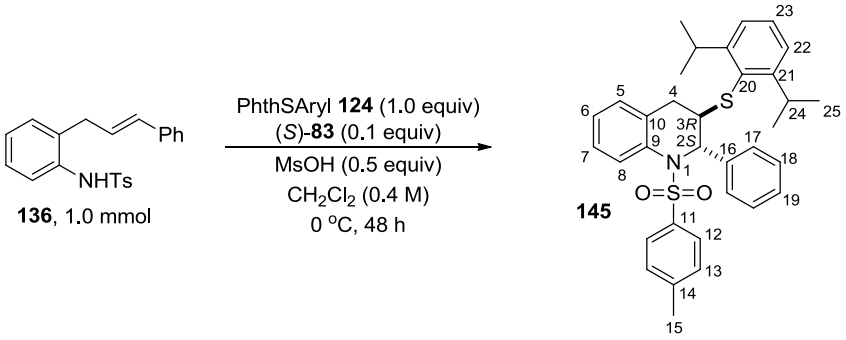
CD: (-), Cotton sign, 230-280 nm

HPLC: (2*R*,3*S*)-**144,** t_R 7.1 min (6.3%); (2*S*,3*R*)-**144,** t_R 8.2 min (93.7%) (Chiralpak AD, 220 nm, 90:10, hexanes:*i*-PrOH, 1 mL/min)

Analysis: $C_{35}H_{39}NO_3S_2$ (585.82)

Calcd:	C, 71.76;	H, 6.71%	N, 2.39%
Found:	C, 71.63;	H, 6.59%	N, 2.26%

Preparation of (2*S*,3*R*)-3-[(2,6-Diisopropyl)phenylthio]-2-phenyl-1-tosyl-1,2,3,4-tetrahydroquinoline (145) (Table 12 Entry 2) [HMC11029]



Following General Procedure XIII, a 10-mL Schlenk flask was charged with **136** (363.5 mg, 1.0 mmol, 1.0 equiv), PhthSAryl **124** (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) at 0 °C and the stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 510 mg (92%) of a **145** as a white solid.

Data for **145**:

mp: 172-173 °C (pentane)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.72 (d, *J* = 8.0 Hz, 1 H, HC(8)), 7.56 (d, *J* = 8.0 Hz, 2 H, HC(12)) 7.37 – 7.25 (m, 9 H, HC(aryl)), 7.14 (td, *J* = 7.5, 1.0 Hz, 1 H, HC(6)), 7.10 (d, *J* = 7.5 Hz, 2 H, HC(22)), 6.88 (d, *J* = 7.5 Hz, 1 H, HC(5)), 5.26 (d, *J* = 8.5 Hz, 1 H, HC(2)), 3.37 (brs, 2 H, HC(24)), 2.89 (ddd, *J* = 11.5, 8.5, and 4.0 Hz, 1 H, HC(3)), 2.46 (s, 3 H, HC(15)), 2.31 (dd, *J* = 14.0, 4.0 Hz, 1 H, HC(4)), 1.71 (dd, *J* = 14.0, 12.0 Hz, 1 H, HC(4)), 1.07 (d, *J* = 7.0 Hz, 6 H, HC(25)), 0.99 (d, *J* = 7.0 Hz, 6 H, HC(25)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 159.0 (C6), 153.7 (C20), 143.7 (C11), 142.2 (C16), 136.3 (C14), 135.8 (C10), 131.0 (C9), 129.6 (C19), 129.5 (C13), 129.0 (C8), 128.7 (C21), 128.3 (C17), 127.6 (C23), 127.2 (C12), 127.0 (C18), 123.7 (C22), 113.4 (C7), 113.4 (C5), 64.6 (C2), 55.3 (C3), 33.6 (C4), 31.2 (C24), 24.5 (C25), 23.8 (C25), 21.6 (C15).

MS: (ESI)

169 (17), 259 (22), 286 (28), 440 (95), 442 (100), 522 (41), 556 (M+H, 10), 636 (40)

HRMS: calcd for $C_{34}H_{38}NO_2S_2$: 556.2344, found: 556.2340

TLC: R_f 0.43 (hexanes/EtOAc, 4:1) [UV]

IR: 2965 (w), 1487 (w), 1461 (w), 1356 (m), 1169 (s), 1093 (w), 1054 (w), 1005 (w), 960 (m), 817 (m), 807 (m), 761 (w), 753 (w)

Opt Rot: $[\alpha]_D^{24}$ -43.0 (c = 0.90, $CHCl_3$)

CD: (-), Cotton sign, 230-280 nm

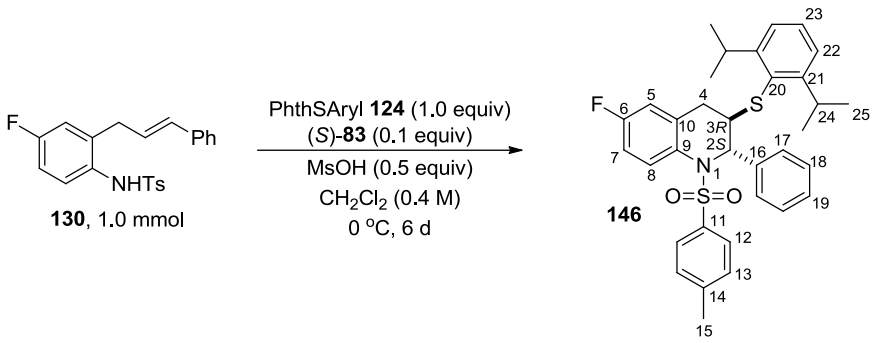
HPLC: (2*R*,3*S*)-**145,** t_R 8.5 min (5.2%); (2*S*,3*R*)-**145,** t_R 10.1 min (94.8%) (Chiralpak AD, 220 nm, 90:10, hexanes:*i*-PrOH, 1 mL/min)

Analysis: $C_{34}H_{37}NO_2S_2$ (555.79)

Calcd: C, 73.47; H, 6.71% N, 2.52%

Found: C, 73.23; H, 6.53% N, 2.30%

Preparation of (2*S*,3*R*)-3-[(2,6-Diisopropyl)phenylthio]-6-fluoro-2-phenyl-1-tosyl-1,2,3,4-tetrahydroquinoline (146) (Table 12 Entry 3) [HMC11031]



Following General Procedure XIII, a 10-mL Schlenk flask was charged with **130** (381.5 mg, 1.0 mmol, 1.0 equiv), PhthSAryl **124** (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) at 0 ^oC and the stirred for 6 d. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 493 mg (86%) of a **146** as a white solid.

Data for **146**:

mp: 198-199 ^oC (pentane)

^1H NMR: (500 MHz, $CDCl_3$)

δ 7.69 (ddd, *J* = 9.0, 5.0, and 2.0 Hz, 1 H, HC(8)), 7.56 (d, *J* = 8.0 Hz, 2 H, HC(12)) 7.38 – 7.28 (m, 8 H, HC(aryl)), 7.11 (d, *J* = 7.5 Hz, 2 H, HC(22)), 7.03 (td, *J* = 8.5, 3.0 Hz, 1 H, HC(7)), 6.62 (dd, *J* = 8.5, 3.0 Hz, 1 H, HC(5)), 5.21 (dd, *J* = 9.0, 2.5 Hz, 1 H, HC(2)), 3.35 (brs, 2 H, HC(24)), 2.90 – 2.83 (m, 1 H, HC(3)), 2.49 (s, 3 H, HC(15)), 2.28 – 2.21 (m, 1 H, HC(4)), 1.60 (d, *J* = 14.0, 12.0 Hz, 1 H, HC(4)), 1.07 (d, *J* = 6.5 Hz, 6 H, HC(25)), 0.99 (d, *J* = 7.0 Hz, 6 H, HC(25)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 160.7 (d, *J* = 248.3 Hz, C6), 153.6 (C20), 143.8 (C11), 142.1 (C16), 136.2 (C14), 136.0 (d, *J* = 7.4 Hz, C10), 132.4 (d, *J* = 2.8 Hz, C9), 129.7 (C19), 129.6 (C13), 129.0 (d, *J* = 8.3 Hz, C8), 128.6 (C21), 128.4 (C17), 127.7 (C23), 127.2 (C12), 126.9 (C18), 123.7 (C22), 114.6 (d, *J* = 22.6 Hz, C7), 114.2 (d, *J* = 22.8 Hz, C5), 64.5 (C2), 55.1 (C3), 33.4 (C4), 31.2 (C24), 24.5 (C25), 23.8 (C25), 21.6 (C15).

^{19}F NMR: δ -115.42 (app q, *J* = 7.2 Hz)

MS: (ESI)

181 (19), 224 (35), 380 (100), 381 (25), 574 (M+H, 42), 596 (M+Na, 36)

HRMS: calcd for $C_{34}H_{37}NO_2S_2F$: 574.2250, found: 574.2245

TLC: R_f 0.45 (hexanes/EtOAc, 4:1) [UV]

IR: 2965 (w), 1490 (m), 1356 (m), 1347 (m), 1184 (w), 1168 (s), 1141 (m), 1042 (m), 940 (w), 872 (m), 818 (w), 799 (m), 747 (m)

Opt Rot: $[\alpha]_D^{24}$ -17.9 (c = 0.90, $CHCl_3$)

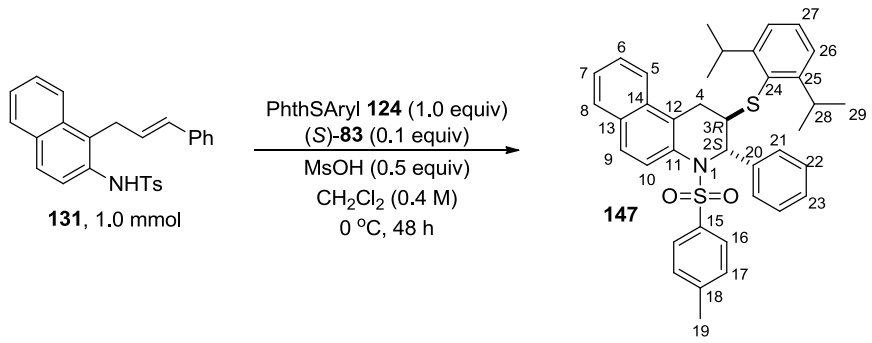
CD: (-), Cotton sign, 230-280 nm

HPLC: (2*R*,3*S*)-**146,** t_R 6.9 min (4.4%); (2*S*,3*R*)-**146,** t_R 8.5 min (95.6%) (Chiralpak AD, 220 nm, 90:10, hexanes:*i*-PrOH, 1 mL/min)

Analysis: $C_{34}H_{36}NO_2S_2F$ (573.78)

Calcd:	C, 71.17;	H, 6.32%	N, 2.44%
Found:	C, 71.17;	H, 6.30%	N, 2.36%

Preparation of (2*S*,3*R*)-3-[(2,6-Diisopropyl)phenylthio]-2-phenyl-1-tosyl-1,2,3,4-tetrahydrobenzo[*f*]quinoline (147) (Table 12 Entry 4) [HMC11034]



Following General Procedure XIII, a 10-mL Schlenk flask was charged with **131** (413.5 mg, 1.0 mmol, 1.0 equiv), PhthSAryl **124** (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) at 0 °C and the stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 563 mg (93%) of a **147** as a white solid.

Data for **147**:

mp: 214-215 °C (pentane)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.91 (d, *J* = 9.0 Hz, 1 H, HC(9)), 7.86 (d, *J* = 8.0 Hz, 1 H, HC(5)) 7.81 (d, *J* = 9.0 Hz, 1 H, HC(10)), 7.59 (d, *J* = 8.5 Hz, 2 H, HC(16)), 7.50 (d, *J* = 8.5 Hz, 1 H, HC(8)), 7.45 (t, *J* = 7.0 Hz, 1 H, HC(6)), 7.40 (t, *J* = 7.0 Hz, 1 H, HC(7)), 7.35 – 7.27 (m, 6 H, HC(aryl)), 7.22 (d, *J* = 8.0 Hz, 2 H, HC(17)), 7.11 (d, *J* = 7.5 Hz, 1 H, HC(26)), 5.41 (d, *J* = 7.5 Hz, 1 H, HC(2)), 3.44 (brs, 2 H, HC(28)), 3.05 – 2.96 (m, 2 H, HC(3,4)), 2.43 (s, 3 H, HC(19)), 1.84 (td, *J* = 12.0, 4.0 Hz, 1 H, HC(4)), 1.07 (d, *J* = 7.0 Hz, 6 H, HC(29)), 0.97 (d, *J* = 7.0 Hz, 6 H, HC(29)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 153.7 (C24), 143.7 (C15), 142.1 (C20), 136.5 (C18), 134.4 (C12), 131.7 (C14), 130.5 (C13), 129.7 (C23), 129.5 (C17), 128.9 (C25), 128.6 (C5), 128.4 (C21), 127.9 (C11), 127.6 (C10), 127.5 (C27), 127.3 (C16), 126.9 (C22), 126.3 (C7), 125.5 (C6), 125.1 (C9), 123.7 (C26), 122.4 (C8), 64.3 (C2), 55.2 (C3), 31.3 (C28), 27.6 (C4), 24.4 (C29), 23.9 (C29), 21.6 (C19).

MS: (ESI)

167 (34), 168 (59), 256 (48), 257 (25), 412 (58), 413 (17), 451 (100), 452 (34), 606 (M+H, 91), 607 (41), 628 (M+Na, 68), 629 (29).

HRMS: calcd for $C_{38}H_{40}NO_2S_2$: 606.2500, found: 606.2501

TLC: R_f 0.40 (hexanes/EtOAc, 4:1) [UV]

IR: 2965 (w), 1455 (w), 1358 (s), 1239 (w), 1170 (s), 1091 (w), 1048 (w), 1025 (w), 990 (m), 807 (m), 762 (w), 747 (m)

Opt Rot: $[\alpha]_D^{24}$ -92.5 (c = 0.90, $CHCl_3$)

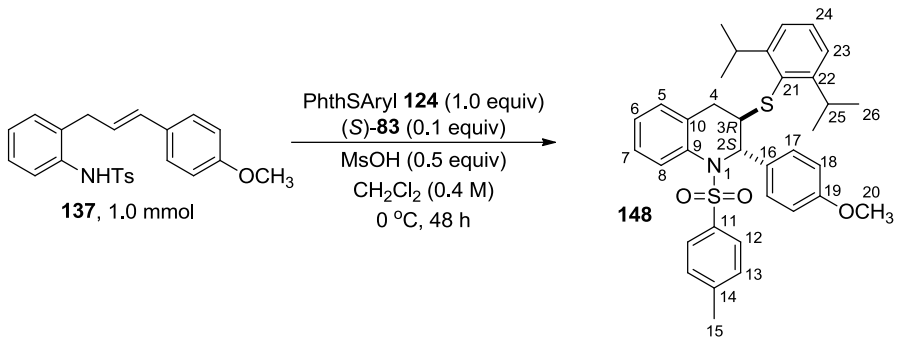
CD: (-), Cotton sign, 230-280 nm

HPLC: (2*R*,3*S*)-**147,** t_R 9.5 min (2.3%); (2*S*,3*R*)-**147,** t_R 13.3 min (97.7%) (Chiralpak AD, 220 nm, 90:10, hexanes:*i*-PrOH, 1 mL/min)

Analysis: $C_{38}H_{39}NO_2S_2$ (605.85)

Calcd:	C, 75.33;	H, 6.49%	N, 2.31%
Found:	C, 74.93;	H, 6.37%	N, 2.41%

Preparation of (2*S*,3*R*)-3-[(2,6-Diisopropyl)phenylthio]-2-(4-methoxy)phenyl-1-tosyl-1,2,3,4-tetrahydroquinoline (148) (Table 12 Entry 5) [HMC11032]



Following General Procedure XIII, a 10-mL Schlenk flask was charged with **137** (393.5 mg, 1.0 mmol, 1.0 equiv), PhthSAryl **124** (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) at 0 ^oC and the stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 546 mg (93%) of a **148** as a white solid.

Data for **148**:

mp: 161-162 ^oC (pentane)

^1H NMR: (500 MHz, $CDCl_3$)

δ 7.69 (d, *J* = 8.0 Hz, 1 H, HC(8)), 7.55 (d, *J* = 8.0 Hz, 2 H, HC(12)) 7.33 – 7.23 (m, 6 H, HC(aryl)), 7.15 – 7.08 (m, 3 H, HC(aryl)), 6.89 – 6.85 (m, 3 H, HC(aryl)), 5.22 (d, *J* = 8.5 Hz, 1 H, HC(2)), 3.84 (s, 3 H, HC(20)), 3.41 (brs, 2 H, HC(25)), 2.89 (ddd, *J* = 11.5, 8.5, and 4.0 Hz, 1 H, HC(3)), 2.45 (s, 3 H, HC(15)), 2.29 (dd, *J* = 14.0, 4.0 Hz, 1 H, HC(4)), 1.68 (dd, *J* = 14.0, 11.5 Hz, 1 H, HC(4)), 1.08 (d, *J* = 7.0 Hz, 6 H, HC(26)), 1.00 (d, *J* = 7.0 Hz, 6 H, HC(26)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 159.0 (C19), 153.6 (C21), 143.5 (C11), 136.5 (C14), 136.4 (C16), 134.6 (C10), 133.4 (C9), 129.5 (C7), 129.4 (C13), 128.9 (C22), 128.1 (C17), 127.7 (C24), 127.5 (C5), 127.2 (C12), 126.7 (C8), 126.1 (C6), 123.6 (C23), 113.7 (C18), 64.2 (C2), 55.3 (C3), 55.3 (C20), 33.2 (C4), 31.2 (C25), 24.5 (C26), 23.9 (C26), 21.6 (C15).

MS: (ESI)

114 (44), 121 (100), 142 (17), 150 (28), 236 (64), 392 (70), 608 (M+Na, 78), 609

(31), 624 (20).

HRMS: calcd for $C_{35}H_{39}NO_3S_2Na$: 608.2269, found: 608.2257

TLC: R_f 0.35 (hexanes/EtOAc, 4:1) [UV]

IR: 2965 (w), 1497 (m), 1455 (w), 1347 (m), 1341 (w), 1225 (w), 1163 (s), 1090 (w), 1053 (m), 1030 (w), 958 (w), 853 (m), 812 (w), 800 (m), 749 (w)

Opt Rot: $[\alpha]_D^{24}$ -27.6 (c = 0.90, $CHCl_3$)

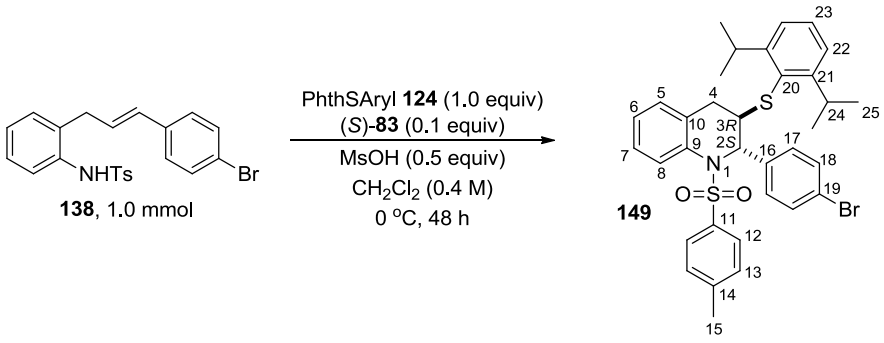
CD: (-), Cotton sign, 230-280 nm

HPLC: (2*R*,3*S*)-**148,** t_R 10.5 min (3.9%); (2*S*,3*R*)-**148,** t_R 14.6 min (96.1%) (Chiralpak AD, 220 nm, 90:10, hexanes:*i*-PrOH, 1 mL/min)

Analysis: $C_{35}H_{39}NO_3S_2$ (585.82)

Calcd:	C, 71.76;	H, 6.71%	N, 2.39%
Found:	C, 71.68;	H, 6.89%	N, 2.41%

Preparation of (2*S*,3*R*)-2-(4-Bromo)phenyl-3-[(2,6-diisopropyl)phenylthio]-1-tosyl-1,2,3,4-tetrahydroquinoline (149) (Table 12 Entry 6) [HMC11033]



Following General Procedure XIII, a 10-mL Schlenk flask was charged with **138** (442.4 mg, 1.0 mmol, 1.0 equiv), PhthSAryl **124** (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) at 0 °C and the stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 557 mg (88%) of a **149** as a white solid.

Data for **149**:

mp: 183-184 °C (pentane)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.72 (d, *J* = 8.0 Hz, 1 H, HC(8)), 7.53 (d, *J* = 8.5 Hz, 2 H, HC(12)), 7.47 (d, *J* = 8.5 Hz, 2 H, HC(18)), 7.35 – 7.22 (m, 6 H, HC(7,13,17,23)), 7.14 (td, *J* = 7.5, 1.0 Hz, 1 H, HC(6), 7.11 (d, *J* = 7.5 Hz, 2 H, HC(22)), 6.87 (d, *J* = 7.5 Hz, 1 H, HC(5)), 5.16 (d, *J* = 9.0 Hz, 1 H, HC(2)), 3.34 (brs, 2 H, HC(24)), 2.79 (ddd, *J* = 11.5, 9.0, and 4.0 Hz, 1 H, HC(3)), 2.46 (s, 3 H, HC(15)), 2.30 (dd, *J* = 14.0, 4.0 Hz, 1 H, HC(4)), 1.66 (dd, *J* = 14.0, 11.5 Hz, 1 H, HC(4)), 1.08 (d, *J* = 7.0 Hz, 6 H, HC(25)), 0.99 (d, *J* = 7.0 Hz, 6 H, HC(25)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 153.6 (C20), 143.8 (C11), 141.5 (C16), 136.2 (C14), 136.1 (C10), 133.4 (C9), 131.4 (C18), 129.7 (C7), 129.5 (C13), 128.7 (C17), 128.5 (C21), 127.9 (C23), 127.5 (C5), 127.2 (C12), 126.8 (C8), 126.4 (C6), 123.7 (C22), 121.5 (C19), 64.2 (C2), 55.2 (C3), 33.3 (C4), 31.2 (C21), 24.5 (C25), 23.9 (C25), 21.6 (C15).

MS: (ESI)

169 (14), 171 (16), 259 (22), 261 (21), 284 (27), 286 (28), 287 (10), 440 (96), 441 (24), 442 (100), 443 (24), 634 (M+H, 39), 635 (17), 636 (45), 637 (17), 656 (M+Na, 30), 657 (12), 658 (34), 659 (13).

HRMS: calcd for $C_{34}H_{37}NO_2S_2Br$: 634.1449, found: 634.1448

TLC: R_f 0.43 (hexanes/EtOAc, 4:1) [UV]

IR: 2963 (w), 1488 (w), 1350 (m), 1342 (m), 1180 (m), 1167 (s), 1139 (m), 1047 (m), 1041 (m), 960 (w), 940 (w), 867 (m), 815 (w), 799 (m), 746 (m)

Opt Rot: $[\alpha]_D^{24}$ -51.2 (c = 0.90, $CHCl_3$)

CD: (-), Cotton sign, 230-280 nm

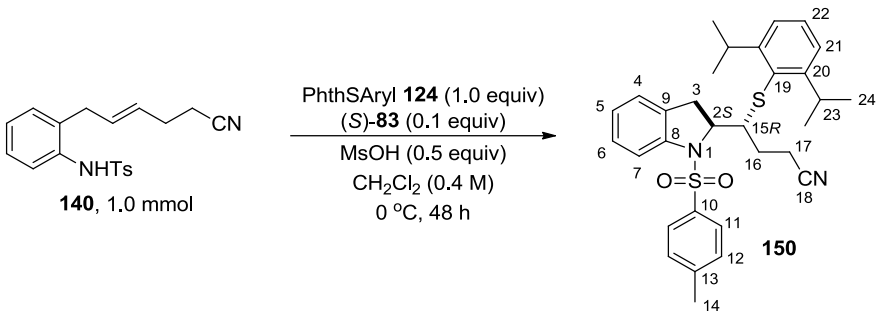
HPLC: (2*R*,3*S*)-**149,** t_R 6.5 min (3.3%); (2*S*,3*R*)-**149,** t_R 8.8 min (96.7%) (Chiralpak AD, 220 nm, 90:10, hexanes:*i*-PrOH, 1 mL/min)

Analysis: $C_{35}H_{39}NO_3S_2$ (634.69)

Calcd: C, 64.34; H, 5.72% N, 2.21%

Found: C, 64.53; H, 5.58% N, 2.17%

Preparation of (2*S*,15*R*)-2-{3-[1-(2,6-Diisopropyl)phenylthio]cyanopropyl}-1-tosylindoline (150) (Table 12 Entry 7) [HMC11050]



Following General Procedure XIII, a 10-mL Schlenk flask was charged with **140** (340.4 mg, 1.0 mmol, 1.0 equiv), PhthSAryl **124** (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) at 0 °C and the stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 457 mg (86%) of a **150** as a white solid.

Data for **150**:

mp: 144-145 °C (pentane)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.71 (d, *J* = 8.0 Hz, 1 H, HC(7)), 7.39 (t, *J* = 7.5 Hz, 1 H, HC(22)), 7.33 (d, *J* = 8.5 Hz, 2 H, HC(11)), 7.27 – 7.21 (m, 3 H, HC(6,21)), 7.18 – 7.05 (m, 4 H, HC(4,5,12)), 4.03 (dd, *J* = 11.0, 9.5 Hz, 1 H, HC(2)), 3.93 (sept, *J* = 7.0 Hz, 2 H, HC(23)), 3.39 (dd, *J* = 13.5, 3.0 Hz, 1 H, HC(15)), 2.95 (dd, *J* = 16.0, 3.0 Hz, 1 H, HC(3)), 2.94 (dd, *J* = 16.0, 9.0 Hz, 1 H, HC(3)), 2.47 – 2.33 (m, 4 H, HC(16,17)), 2.38 (s, 3 H, HC(14)), 1.30 (d, *J* = 7.0 Hz, 6 H, HC(24)), 1.22 (d, *J* = 7.0 Hz, 6 H, HC(24)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 153.2 (C19), 144.0 (C10), 141.5 (C8), 134.2 (C13), 130.7 (C9), 129.8 (C20), 129.2 (C12), 129.1 (C22), 127.6 (C6), 126.8 (C11), 125.0 (C4), 124.8 (C5), 123.8 (C21), 119.1 (C18), 117.4 (C7), 61.5 (C2), 43.1 (C15), 33.9 (C3), 31.5 (C23), 28.3 (C16), 24.3 (C24), 24.2 (C24), 21.4 (C14), 17.5 (C17).

MS: (ESI)

169 (14), 171 (16), 259 (22), 261 (21), 284 (27), 286 (28), 287 (10), 440 (96), 441 (24), 442 (100), 443 (24), 634 (M+H, 39), 635 (17), 636 (45), 637 (17), 656 (M+Na, 30), 657 (12), 658 (34), 659 (13).

HRMS: calcd for $C_{31}H_{37}N_2O_2S_2$: 533.2296, found: 533.2293

TLC: R_f 0.49 (hexanes/EtOAc, 4:1) [UV]

IR: 2965 (w), 2249 (s), 1456 (w), 1323 (m), 1159 (s), 1089 (w), 1054 (m), 1029 (m), 961 (m), 921 (w), 816 (w), 807 (m), 755 (w), 749 (w)

Opt Rot: $[\alpha]_D^{24}$ -21.4 (c = 0.90, $CHCl_3$)

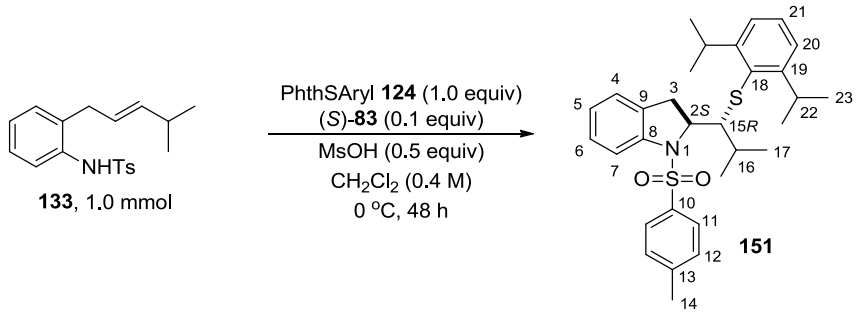
CD: (-), Cotton sign, 230-280 nm

HPLC: (2*R*,15*S*)-**150,** t_R 7.3 min (13.6%); (2*S*,15*R*)-**150,** t_R 9.1 min (86.4%) (Chiralpak AD, 220 nm, 90:10, hexanes:*i*-PrOH, 1 mL/min)

Analysis: $C_{31}H_{36}N_2O_2S_2$ (532.76)

Calcd:	C, 69.89;	H, 6.81%	N, 5.26%
Found:	C, 69.71;	H, 6.64%	N, 5.21%

Preparation of (2*S*,15*R*)-2-{2-[(2,6-Diisopropyl)phenylthio]isobutyl}-1-tosylindoline (151) (Table 12 Entry 8) [HMC11044]



Following General Procedure XIII, a 10-mL Schlenk flask was charged with **133** (329.5 mg, 1.0 mmol, 1.0 equiv), PhthSAryl **124** (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) at 0 °C and the stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 443 mg (85%) of a **151** as a white solid.

Data for **151**:

mp: 131-132 °C (pentane)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.65 (d, *J* = 7.5 Hz, 1 H, HC(7)), 7.44 (t, *J* = 8.0 Hz, 1 H, HC(21)), 7.31 (d, *J* = 8.5 Hz, 2 H, HC(11)), 7.29 – 7.05 (m, 7 H, HC(4,5,6,12,20)), 4.06 (ddt, *J* = 11.5, 9.5, and 2.0 Hz, 1 H, HC(2)), 3.95 (sept, *J* = 7.0 Hz, 2 H, HC(22)), 3.53 (m, 1 H, HC(15)), 2.99 (dd, *J* = 16.5, 3.5 Hz, 1 H, HC(3)), 2.91 (dd, *J* = 16.5, 9.0 Hz, 1 H, HC(3)), 2.36 (s, 3 H, HC(14)), 2.10 (sept, 1 H, HC(16)), 1.30 (d, *J* = 7.0 Hz, 6 H, HC(23)), 1.23 (d, *J* = 7.0 Hz, 6 H, HC(23)), 1.11 (d, *J* = 6.5 Hz, 3 H, HC(17)), 1.09 (d, *J* = 6.5 Hz, 3 H, HC(17)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 153.0 (C18), 144.1 (C10), 141.5 (C8), 134.2 (C13), 130.1 (C19), 129.9 (C9), 129.5 (C12), 129.4 (C21), 127.7 (C6), 126.5 (C11), 125.4 (C4), 124.7 (C5), 123.6 (C20), 117.0 (C7), 61.3 (C2), 60.0 (C15), 33.9 (C3), 32.1 (C16), 31.4 (C22), 24.4 (C23), 24.1 (C23), 21.5 (C14), 21.1 (C17), 20.5 (C17).

MS: (ESI)

169 (14), 171 (16), 259 (22), 261 (21), 284 (27), 286 (28), 287 (10), 440 (96), 441 (24), 442 (100), 443 (24), 634 (M+H, 39), 635 (17), 636 (45), 637 (17), 656 (M+Na, 30), 657 (12), 658 (34), 659 (13).

HRMS: calcd for $C_{31}H_{40}NO_2S_2$: 522.2500, found: 522.2504

TLC: R_f 0.47 (hexanes/EtOAc, 4:1) [UV]

IR: 2964 (w), 1486 (w), 1356 (m), 1160 (s), 1093 (w), 1076 (w), 1054 (m), 1029 (m), 1002 (w), 961 (m), 813 (m), 805 (m), 761 (w), 751 (m)

Opt Rot: $[\alpha]_D^{24}$ -31.2 (c = 0.90, $CHCl_3$)

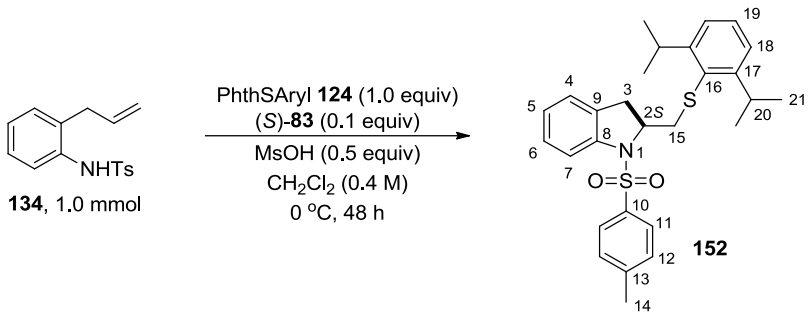
CD: (-), Cotton sign, 230-280 nm

HPLC: (2*R*,15*S*)-**151,** t_R 7.8 min (2.2%); (2*S*,15*R*)-**151,** t_R 10.4 min (97.8%) (Chiralpak AD, 220 nm, 90:10, hexanes:*i*-PrOH, 1 mL/min)

Analysis: $C_{31}H_{39}NO_2S_2$ (521.78)

Calcd:	C, 71.36;	H, 7.53%	N, 2.68%
Found:	C, 71.51;	H, 7.72%	N, 2.70%

Preparation of (2*S*)-2-{[(2,6-Diisopropyl)phenylthio]methyl}-1-tosylindoline (152) (Table 12 Entry 9) [HMC11077]



Following General Procedure XIII, a 10-mL Schlenk flask was charged with **134** (287.4 mg, 1.0 mmol, 1.0 equiv), PhthSAryl **124** (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) at 0 °C and the stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 432 mg (90%) of a **152** as a white solid.

Data for **152**:

mp: 127-128 °C (pentane)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.69 (d, *J* = 8.0 Hz, 1 H, HC(7)), 7.42 (t, *J* = 7.5 Hz, 1 H, HC(19)), 7.30 (d, *J* = 8.5 Hz, 2 H, HC(11)), 7.28 – 7.20 (m, 3 H, HC(6,18)), 7.16 – 7.04 (m, 4 H, HC(4,5,12)), 4.06 (ddt, *J* = 11.0, 9.5, and 2.5 Hz, 1 H, HC(2)), 3.95 (sept, *J* = 7.0 Hz, 2 H, HC(20)), 3.28 (dd, *J* = 13.0, 3.5 Hz, 1 H, HC(15)), 3.00 (dd, *J* = 16.5, 3.5 Hz, 1 H, HC(3)), 2.92 (dd, *J* = 16.5, 9.0 Hz, 1 H, HC(3)), 2.80 (dd, *J* = 12.5, 11.0 Hz, 1 H, HC(15)), 2.38 (s, 3 H, HC(14)), 1.31 (d, *J* = 7.0 Hz, 6 H, HC(21)), 1.24 (d, *J* = 7.0 Hz, 6 H, HC(21)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 153.4 (C16), 143.8 (C10), 141.4 (C8), 134.4 (C13), 130.9 (C9), 129.8 (C17), 129.5 (C12), 129.4 (C19), 127.8 (C6), 126.9 (C11), 125.2 (C4), 124.7 (C5), 123.8 (C18), 117.1 (C7), 61.1 (C2), 43.0 (C15), 33.8 (C3), 31.5 (C20), 24.4 (C21), 24.2 (C21), 21.5 (C14).

MS: (ESI)

272 (15), 318 (40), 325 (46), 326 (11), 480 (M+H, 100), 481 (31), 482 (14), 502 (M+Na, 55), 503 (18), 518 (12).

HRMS: calcd for $C_{28}H_{34}NO_2S_2$: 480.2031, found: 480.2027

TLC: R_f 0.46 (hexanes/EtOAc, 4:1) [UV]

IR: 2965 (w), 1480 (w), 1458 (w), 1358 (s), 1331 (w), 1169 (s), 1104 (m), 1091 (w), 1021 (m), 997 (w), 955 (m), 811 (m), 803 (s), 763 (m), 752 (s)

Opt Rot: $[\alpha]_D^{24}$ +34.6 (c = 0.90, $CHCl_3$)

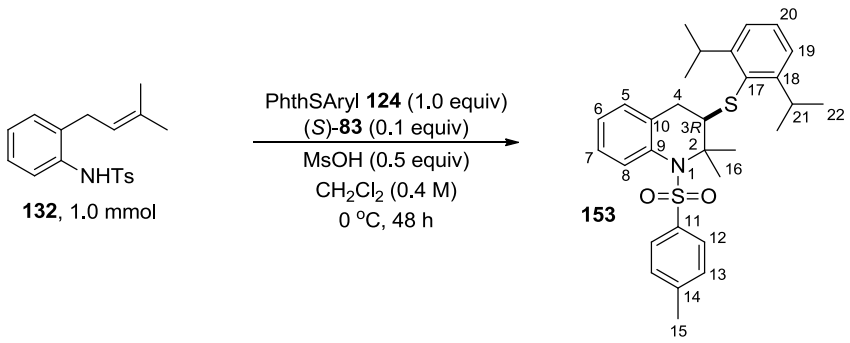
CD: (-), Cotton sign, 230-280 nm

HPLC: (2*R*,15*S*)-**152,** t_R 8.1 min (1.8%); (2*S*,15*R*)-**152,** t_R 9.6 min (98.2%) (Chiralpak AD, 220 nm, 90:10, hexanes:*i*-PrOH, 1 mL/min)

Analysis: $C_{28}H_{33}NO_2S_2$ (479.70)

Calcd:	C, 70.11;	H, 6.93%	N, 2.92%
Found:	C, 69.90;	H, 6.95%	N, 2.83%

Preparation of (3*R*)-3-[(2,6-Diisopropyl)phenylthio]-2,2-dimethyl-1-tosyl-1,2,3,4-tetrahydroquinoline (153) (Table 12 Entry 10) [HMC11043]



Following General Procedure XIII, a 10-mL Schlenk flask was charged with **132** (315.4 mg, 1.0 mmol, 1.0 equiv), PhthSAryl **124** (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) at 0 °C and the stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 451 mg (89%) of a **153** as a white solid.

Data for **153**:

mp: 167-168 ^{o}C (pentane)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.63 (d, *J* = 8.0 Hz, 1 H, HC(8)), 7.37 (d, *J* = 8.5 Hz, 2 H, HC(12)), 7.34 (t, *J* = 8.0 Hz, 1 H, HC(20)), 7.22 (t, *J* = 7.5 Hz, 1 H, HC(7)), 7.18 (d, *J* = 7.5 Hz, 2 H, HC(19)), 7.11 (d, *J* = 8.0 Hz, 2 H, HC(13)), 7.07 (t, *J* = 7.5 Hz, 1 H, HC(6)), 7.05 (d, *J* = 6.5 Hz, 1 H, HC(5)), 4.36 (dd, *J* = 9.0, 1.5 Hz, 1 H, HC(3)), 3.97 (sept, *J* = 7.0 Hz, 2 H, HC(21)), 3.20 (dd, *J* = 16.5, 1.5 Hz, 1 H, HC(4)), 2.63 (dd, *J* = 17.0, 9.0 Hz, 1 H, HC(4)), 2.35 (s, 3 H, HC(15)), 1.31 (brd, *J* = 47.0 Hz, 6 H, HC(22)), 1.31 (s, 3 H, HC(16)), 1.07 (brd, *J* = 32.5 Hz, 6 H, HC(22)), 0.90 (s, 3 H, HC(16)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 155.4 (C17, broadened due to slow rotation), 143.8 (C14), 142.8 (C9), 134.8 (C10), 134.7 (C11), 129.8 (C20), 129.3 (C13), 127.7 (C18), 127.5 (C7), 127.3 (C12), 125.8 (C6), 124.1 (C5), 123.5 (C19), 119.3 (C8), 70.2 (C3), 55.3 (C2), 32.0 (C21), 31.7 (C4), 26.5 (C16), 26.0 (C22), 23.7 (C16), 22.7 (C22), 22.3 (C22), 21.5 (C15).

MS: (ESI)

158 (16), 272 (11), 314 (100), 315 (20), 353 (11), 508 (M+H, 17), 530 (M+Na, 30), 531 (10).

HRMS: calcd for $C_{30}H_{38}NO_2S_2$: 508.2344, found: 508.2339

TLC: R_f 0.48 (hexanes/EtOAc, 4:1) [UV]

IR: 2964 (w), 1458 (w), 1356 (s), 1168 (s), 1131 (w), 1115 (w), 1090 (m), 998 (m), 956 (m), 812 (m), 804 (m), 767 (s), 757 (w), 747 (m)

Opt Rot: $[\alpha]_D^{24}$ -87.1 (c = 0.90, $CHCl_3$)

CD: (-), Cotton sign, 230-280 nm

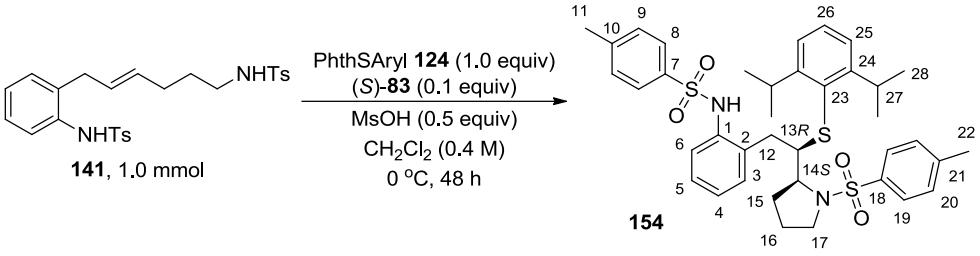
HPLC: (2*R*,3*S*)-**153,** t_R 7.5 min (11.8%); (2*S*,3*R*)-**153,** t_R 9.9 min (88.2%) (Chiralpak AD, 220 nm, 90:10, hexanes:*i*-PrOH, 1 mL/min)

Analysis: $C_{30}H_{37}NO_2S_2$ (507.75)

Calcd: C, 70.96; H, 7.34% N, 2.76%

Found: C, 70.87; H, 7.25% N, 2.71%

Preparation of (13*R*,14*S*)-*N*-(2-{2-[(2,6-Diisopropylphenyl)thio]-2-(1-tosylpyrrolidin-2-yl)ethyl}phenyl)-4-toluenesulfonamide (154) (Table 12 Entry 11) [HMC11053]



Following General Procedure XIII, a 10-mL Schlenk flask was charged with **141** (498.7 mg, 1.0 mmol, 1.0 equiv), PhthSAryl **124** (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) at 0 °C and the stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 451 mg (89%) of a **154** as a white solid.

Data for **154**:

mp: 184-185 °C (pentane)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.66 (d, *J* = 8.0 Hz, 2 H, HC(19)), 7.64 (d, *J* = 8.5 Hz, 2 H, HC(8)), 7.38 (d, *J* = 7.5 Hz, 1 H, HC(6)), 7.33 – 7.23 (m, 5 H, HC(9,20,26)), 7.20 – 7.09 (m, 5 H, HC(3,4,5,25)), 6.39 (brs, 1 H, HN), 4.08 (sept, *J* = 7.0 Hz, 2 H, HC(27)), 4.01 (ddd, *J* = 8.5, 5.5, and 4.0 Hz, 1 H, HC(14)), 3.41 – 3.30 (m, 3 H, HC(13,17)), 2.43 (s, 3 H, HC(22)), 2.42 (s, 3 H, HC(11)), 2.41 – 2.35 (m, 2 H, HC(12)), 1.89 (dtd, *J* = 13.0, 7.5, and 5.5 Hz, 1 H, HC(15)), 1.79 (dtt, *J* = 12.0, 5.5, and 5.5 Hz, 1 H, HC(16)), 1.67 (dtd, *J* = 13.0, 8.0, and 5.5 Hz, 1 H, HC(15)), 1.24 (m, 1 H, HC(16)), 1.25 (d, *J* = 7.0 Hz, 6 H, HC(28)), 1.24 (d, *J* = 7.0 Hz, 6 H, HC(28)).

^{13}C NMR: (126 MHz, $CDCl_3$)

153.9 (C23), 143.7 (C10), 143.3 (C(18)), 136.6 (C7), 135.1 (C2), 134.9 (C(21)), 134.0 (C1), 130.3 (C24), 129.9 (C6), 129.7 (C(20)), 129.6 (C9), 128.9 (C26), 127.5 (C(19)), 127.1 (C8), 126.9 (C5), 126.2 (C4), 124.5 (C3), 123.6 (C25), 62.2 (C(14)), 57.5 (C13), 49.6 (C(17)), 31.2 (C27), 30.9 (C12), 28.6 (C(15)), 24.9 (C(16)), 24.6 (C28), 24.2 (C28), 21.5 (C(22)), 21.5 (C11).

MS: (ESI)

342 (25), 691 (M+H, 100), 692 (18), 713 (19), 729 (11).

HRMS: calcd for $C_{38}H_{47}N_2O_4S_3$: 691.2698, found: 691.2694

TLC: R_f 0.32 (hexanes/EtOAc, 4:1) [UV]

IR: 3025 (m), 2946 (w), 1598 (w), 1475 (w), 1451 (w), 1343 (m), 1303 (w), 1216 (m), 1157 (s), 1091 (m), 1028 (m), 990 (w), 927 (w), 813 (w), 745 (m)

Opt Rot: $[\alpha]_D^{24}$ -45.9 (c = 0.90, $CHCl_3$)

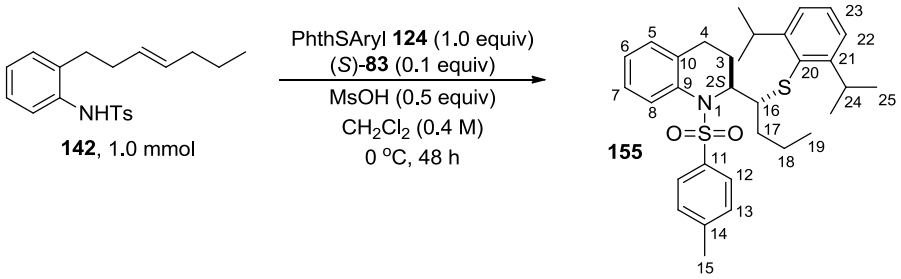
CD: (-), Cotton sign, 230-280 nm

HPLC: (13*S*,14*R*)-**154,** t_R 9.6 min (5.5%); (13*R*,14*S*)-**154,** t_R 12.0 min (94.5%) (Chiralpak AD, 220 nm, 90:10, hexanes:*i*-PrOH, 1 mL/min)

Analysis: $C_{38}H_{46}N_2O_4S_3$ (690.98)

Calcd:	C, 66.05;	H, 6.71%	N, 4.05%
Found:	C, 65.91;	H, 6.55%	N, 3.98%

Preparation of (2*S*,16*R*)-2-{1-[(2,6-Diisopropyl)phenylthio]butyl}-1-tosyl-1,2,3,4-tetrahydroquinoline (155) (Table 13 Entry 1) [HMC11035]



Following General Procedure XIII, a 10-mL Schlenk flask was charged with **142** (343.5 mg, 1.0 mmol, 1.0 equiv), PhthSAryl **124** (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) at 0 °C and the stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 499 mg (93%) of a **155** as a white solid.

Data for **155**:

mp: 158-159 °C (pentane)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.80 (d, *J* = 8.0 Hz, 1 H, HC(8)), 7.33 – 7.26 (m, 4 H, HC(7,12,23)), 7.19 – 7.13 (m, 5 H, HC(6,13,22)), 6.94 (d, *J* = 7.5 Hz, 1 H, HC(5)), 4.41 – 4.36 (m, 1 H, HC(2)), 4.08 (sept, *J* = 7.0 Hz, 2 H, HC(24)), 3.35 (dt, *J* = 9.5, 5.0 Hz, 1 H, HC(16)), 2.39 (s, 3 H, HC(15)), 2.19 (dt, *J* = 15.0, 4.5 Hz, 1 H, HC(4)), 2.01 – 1.93 (m, 1 H, HC(3)), 1.83 – 1.74 (m, 1 H, HC(3)), 1.67 – 1.51 (m, 2 H, HC(17)), 1.49 – 1.35 (m, 2 H, HC(17)), 1.35 – 1.27 (m, 1 H, HC(4)), 1.25 (d, *J* = 7.0 Hz, 6 H, HC(25)), 1.24 (d, *J* = 7.0 Hz, 6 H, HC(25)), 0.85 (t, *J* = 7.0 Hz, 3 H, HC(19)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 153.9 (C20), 143.3 (C14), 136.5 (C11), 135.7 (C9), 135.5 (C10), 130.3 (C21), 129.3 (C13), 128.9 (C23), 128.5 (C8), 127.1 (C5), 127.0 (C12), 126.9 (C7), 126.1 (C6), 123.6 (C22), 58.8 (C2), 57.5 (C16), 36.0 (C17), 31.2 (C24), 25.3 (C4), 25.2 (C3), 24.6 (C25), 24.2 (C25), 21.5 (C15), 20.1 (C18), 14.0 (C19).

MS: (ESI)

132 (22), 342 (17), 381 (54), 382 (15), 536 (M+H, 100), 537 (37), 538 (16), 558 (51), 559 (19).

HRMS: calcd for $C_{32}H_{42}NO_2S_2$: 536.2657, found: 536.2657

TLC: R_f 0.48 (hexanes/EtOAc, 4:1) [UV]

IR: 2966 (w), 1463 (w), 1350 (m), 1163 (s), 1092 (w), 1054 (w), 1025 (w), 966 (m), 817 (w), 805 (m), 759 (w), 748 (m)

Opt Rot: $[\alpha]_D^{24}$ +57.9 (c = 0.90, $CHCl_3$)

CD: (-), Cotton sign, 230-280 nm

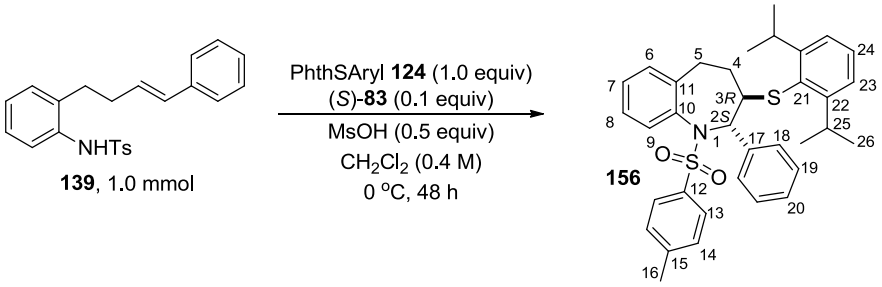
HPLC: (2*R*,3*S*)-**155,** t_R 6.1 min (1.7%); (2*S*,3*R*)-**155,** t_R 8.7 min (98.3%) (Chiralpak AD, 220 nm, 90:10, hexanes:*i*-PrOH, 1 mL/min)

Analysis: $C_{32}H_{41}NO_2S_2$ (535.80)

Calcd: C, 71.73; H, 7.71% N, 2.61%

Found: C, 71.61; H, 7.84% N, 2.47%

Preparation of (2*S*,3*R*)-3-[(2,6-Diisopropyl)phenylthio]-2-phenyl-1-tosyl-2,3,4,5-tetrahydrobenzazepine (156) (Table 13 Entry 2) [HMC11049]



Following General Procedure XIII, a 10-mL Schlenk flask was charged with **139** (377.5 mg, 1.0 mmol, 1.0 equiv), PhthSAryl **124** (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) at 0 ^oC and the stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 516 mg (91%) of a **156** as a white solid.

Data for **156**:

mp: 143-144 ^oC (pentane)

^1H NMR: (500 MHz, $CDCl_3$)

δ 7.36 (d, *J* = 7.5 Hz, 2 H, HC(13), 7.32 – 7.27 (m, 3 H, HC(19,20)), 7.25 – 7.18 (m, 2 H, HC(7,24)), 7.22 – 7.16 (m, 2 H, HC(18)), 7.12 – 7.00 (m, 6 H, HC(6,8,14,23), 6.73 (d, *J* = 7.0 Hz, 1 H, HC(9)), 5.43 (d, *J* = 10.5 Hz, HC(2)), 3.51 (brs, 2 H, HC(25)), 3.02 – 2.89 (m, 2 H, HC(3,5)), 2.43 – 2.36 (m, 1 H, HC(5)), 2.36 (s, 3 H, HC(16)), 2.09 – 1.98 (m, 1 H, HC(4)), 1.80 – 1.69 (brs, 1 H, HC(4)), 1.05 (brs, 6 H, HC(26)), 0.93 (d, *J* = 5.0 Hz, 6 H, HC(26)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 153.5 (C21), 143.0 (C15), 140.3 (C11), 140.2 (C17), 138.8 (C12), 135.0 (C10), 131.3 (C9), 129.7 (C6,22), 129.1 (C14), 129.0 (C24), 128.9 (C7), 128.1 (C19), 128.0 (C20), 127.7 (C18), 127.3 (C13), 126.8 (C8), 123.6 (C23), 65.4 (C2), 50.2 (C3), 31.2 (C25), 29.4 (C5), 28.4 (C4), 24.5 (C26), 23.7 (C26), 21.5 (C16).

MS: (ESI)

220 (15), 376 (100), 377 (26), 570 (M+H, 22), 571 (9), 592 (21).

HRMS: calcd for $C_{35}H_{40}NO_2S_2$: 570.2500, found: 570.2495

TLC: R_f 0.41 (hexanes/EtOAc, 4:1) [UV]

IR: 2965 (w), 1455 (w), 1345 (m), 1153 (s), 1117 (w), 1091 (m), 1054 (w), 1042 (w), 1026 (m), 980 (w), 960 (w), 815 (w), 800 (w), 749 (m)

Opt Rot: $[\alpha]_D^{24}$ +41.2 (c = 0.90, $CHCl_3$)

CD: (-), Cotton sign, 230-280 nm

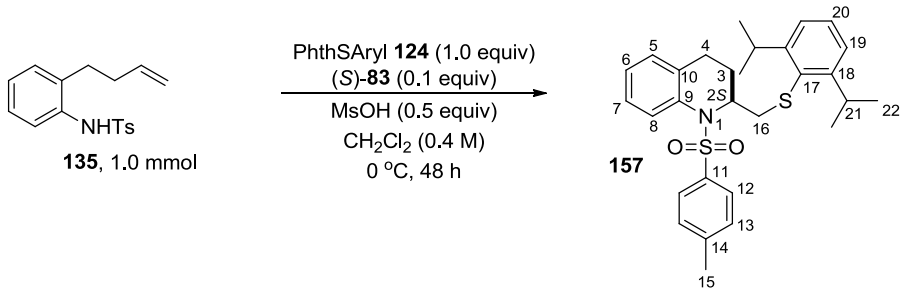
HPLC: (2*R*,3*S*)-**156,** t_R 8.1 min (5.3%); (2*S*,3*R*)-**156,** t_R 10.3 min (94.7%) (Chiralpak AD, 220 nm, 90:10, hexanes:*i*-PrOH, 1 mL/min)

Analysis: $C_{35}H_{39}NO_2S_2$ (569.82)

Calcd: C, 73.77; H, 6.90% N, 2.46%

Found: C, 73.79; H, 6.35% N, 2.58%

Preparation of (2*S*)-3-[(2,6-Diisopropyl)phenylthio]-2,2-dimethyl-1-tosyl-1,2,3,4-tetrahydroquinoline (157) (Table 13 Entry 3) [HMC11028]



Following General Procedure XIII, a 10-mL Schlenk flask was charged with **135** (301.4 mg, 1.0 mmol, 1.0 equiv), PhthSAryl **124** (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) at 0 °C and the stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 459 mg (93%) of a **157** as a white solid.

Data for **157**:

mp: 129-130 °C (pentane)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.71 (d, *J* = 8.0 Hz, 1 H, HC(8)), 7.31 (d, *J* = 8.5 Hz, 2 H, HC(12)), 7.30 (t, *J* = 8.0 Hz, 1 H, HC(20)), 7.23 (t, *J* = 7.5 Hz, 1 H, HC(7)), 7.16 (d, *J* = 7.5 Hz, 2 H,

HC(19)), 7.15 (d, *J* = 8.0 Hz, 2 H, HC(13)), 7.12 (t, *J* = 7.5 Hz, 1 H, HC(6)), 6.98 (d, *J* = 7.5 Hz, 1 H, HC(5)), 4.39 – 4.31 (m, 1 H, HC(2)), 3.88 (sept, *J* = 7.0, 2 H, HC(21)), 2.98 (dd, *J* = 12.0, 5.0 Hz, 1 H, HC(16)), 2.77 (dd, *J* = 12.0, 8.5 Hz, 1 H, HC(16)), 2.43 – 2.34 (m, 1 H, HC(4)), 2.38 (s, 3 H, HC(15)), 2.11 – 2.02 (m, 1 H, HC(3)), 1.83 – 1.75 (m, 1 H, HC(4)), 1.68 – 1.59 (m, 1 H, HC(3)), 1.22 (d, *J* = 7.0 Hz, 6 H, HC(22)), 1.20 (d, *J* = 7.0 Hz, 6 H, HC(22)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 153.1 (C18), 143.0 (C15), 142.5 (C11), 138.6 (C12), 135.4 (C10), 131.3 (C9), 131.1 (C19), 129.8 (C6), 129.4 (C14), 129.1 (C21), 128.4 (C8), 127.2 (C13), 126.6 (C7), 123.7 (C20), 56.4 (C2), 40.0 (C17), 33.7 (C5), 32.9 (C3), 31.4 (C22), 24.4 (C23), 24.3 (C23), 21.5 (C16), 20.8 (C4).

MS: (ESI)

132 (37), 339 (91), 340 (23), 494 (M+H, 100), 495 (34), 496 (15), 516 (72), 517 (24), 518 (11), 532 (13).

HRMS: calcd for $C_{29}H_{36}NO_2S_2$: 494.2187, found: 494.2183

TLC: R_f 0.44 (hexanes/EtOAc, 4:1) [UV]

IR: 2965 (w), 1347 (s), 1161 (s), 1089 (m), 1053 (m), 966 (m), 818 (m), 801 (m), 767 (m), 760 (m), 748 (m)

Opt Rot: $[\alpha]_D^{24}$ +71.2 (c = 0.90, $CHCl_3$)

CD: (-), Cotton sign, 230-280 nm

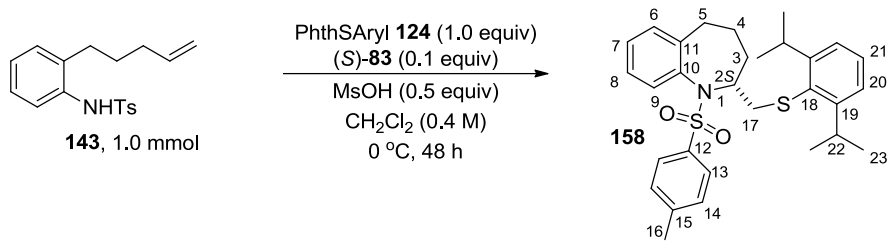
HPLC: (2*R*,3*S*)-**157,** t_R 5.4 min (2.0%); (2*S*,3*R*)-**157,** t_R 7.7 min (98.0%) (Chiralpak AD, 220 nm, 90:10, hexanes:*i*-PrOH, 1 mL/min)

Analysis: $C_{29}H_{35}NO_2S_2$ (493.72)

Calcd: C, 70.55; H, 7.15% N, 2.84%

Found: C, 70.55; H, 7.03% N, 3.05%

Preparation of (2*S*)-2-{[(2,6-Diisopropyl)phenylthio]methyl}-1-tosyl-2,3,4,5-tetrahydrobenzazepine (158) (Table 13 Entry 4) [HMC11036]



Following General Procedure XIII, a 10-mL Schlenk flask was charged with **143** (315.4 mg, 1.0 mmol, 1.0 equiv), PhthSAryl **124** (339.5 mg, 1.0 mmol, 1.0 equiv), (*S*)-**83** (52.1 mg, 0.1 mmol, 0.1 equiv), and CH_2Cl_2 (2.5 mL, 0.4 M). To the mixture was added MsOH (32.5 µL, 0.5 mmol, 0.5 equiv) at 0 °C and the stirred for 48 h. The reaction was worked up following the general procedure. The crude product was purified by flash chromatography (SiO_2, 25 g, 30 mm Ø , hexanes/EtOAc, 19:1 to 9:1) to afford 450 mg (89%) of a **158** as a white solid.

Data for **158**:

mp: 60-61 °C (pentane)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.55 (d, *J* = 8.0 Hz, 2 H, HC(13)), 7.29 (t, *J* = 7.5 Hz, 1 H, HC(21)), 7.22 (d, *J* = 8.0 Hz, 1 H, HC(9)), 7.21 (t, *J* = 8.0, 1 H, HC(8)), 7.20 (d, *J* = 8.0 Hz, 2 H, HC(14)), 7.14 (t, *J* = 8.0 Hz, 1 H, HC(7)), 7.11 (d, *J* = 7.5 Hz, 2 H, HC(20)), 7.10 (d, *J* = 8.0 Hz, 1 H, HC(6)), 4.63 (tt, *J* = 7.5, 4.0 Hz, 1 H, HC(2)), 3.69 (sept, *J* = 7.0 Hz, 2 H, HC(22)), 2.53 (dd, *J* = 12.5, 7.5 Hz, 1 H, HC(17)), 2.47 (t, *J* = 5.0 Hz, 2 H, HC(5)), 2.41 (s, 3 H, HC(16)), 2.28 (ddd, *J* = 12.0, 7.5, and 1.0 Hz, 1 H, HC(17)), 2.12 (ddt, *J* = 16.0, 12.5, and 4.0 Hz, 1 H, HC(3)), 1.91 (dd, *J* = 14.5, 4.5 Hz, 1 H, HC(3)), 1.71 (dt, *J* = 14.0, 4.5 Hz, 1 H, HC(4)), 1.35 (dtt, *J* = 14.0, 5.0, and 2.5 Hz, 1 H, HC(4)), 1.14 (d, *J* = 7.0 Hz, 6 H, HC(23)), 1.13 (d, *J* = 7.0 Hz, 6 H, HC(23)).

^{13}C NMR: (126 MHz, $CDCl_3$)

δ 153.1 (C18), 143.0 (C15), 142.5 (C11), 138.6 (C12), 135.4 (C10), 131.3 (C9), 131.1 (C19), 129.8 (C6), 129.4 (C14), 129.1 (C21), 128.4 (C8), 127.2 (C13), 126.6 (C7), 123.7 (C20), 56.4 (C2), 40.0 (C17), 33.7 (C5), 32.9 (C3), 31.4 (C22), 24.4 (C23), 24.3 (C23), 21.5 (C16), 20.8 (C4).

MS: (ESI)

314 (20), 353 (15), 508 (M+H, 100), 509 (34), 510 (15), 530 (44), 531 (15).

HRMS: calcd for $C_{30}H_{38}NO_2S_2$: 508.2344, found: 508.2345

TLC: R_f 0.45 (hexanes/EtOAc, 4:1) [UV]

IR: 2960 (w), 1455 (w), 1345 (m), 1158 (s), 1092 (m), 1053 (m), 1029 (m), 923 (w), 813 (w), 801 (m), 763 (m), 744 (m)

Opt Rot: $[\alpha]_D^{24}$ +27.4 (c = 0.90, $CHCl_3$)

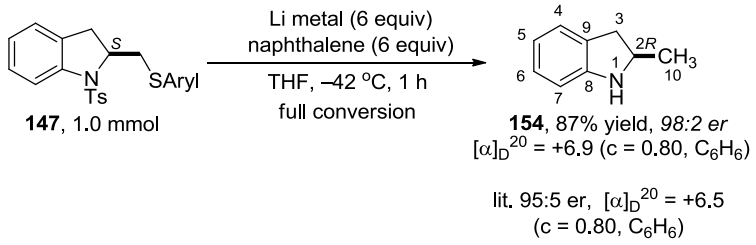
CD: (-), Cotton sign, 230-280 nm

HPLC: (2*R*)-**153,** t_R 8.7 min (6.9%); (2*S*)-**153,** t_R 10.8 min (93.1%) (Chiralpak AD, 220 nm, 90:10, hexanes:*i*-PrOH, 1 mL/min)

Analysis: $C_{30}H_{37}NO_2S_2$ (507.75)

Calcd:	C, 70.96;	H, 7.34%	N, 2.76%
Found:	C, 70.69;	H, 7.39%	N, 2.99%

Desulfurization of Sulfenoamination Products[110] [HMC11100]



In a glovebox, an oven-dried, 10-mL Schlenk flask equipped with a stir bar was lithium metal (42 mg, 6.0 mmol, 6 equiv, cut into parts smaller than 3 mm), and naphthalene (769 mg, 6.0 mmol, 6 equiv). The flask was capped with a septum, it was transferred to a Schlenk line after exiting the glove box. To the flask was added THF (2 mL) via syringe at –42 °C. The resulting mixture was stirred for 30 min at –42 °C with development of green color. To the lithium-naphthylide solution was added a solution of sulfenylated product in THF (1.0 mmol in 2 mL, 0.5 M) via syringe at –42 °C. The color of the reaction mixture gradually turned into yellow while stirring for 1 h at –42 °C. The reaction mixture was decanted into a suspension of hexanes, water, NH_4Cl (10 mL: 5 mL: 5 mL). Residual lithium in Schlenk flask was rinsed with TBME (5 mL x 2). The biphasic mixture was separated, and the organic layer was washed with 1 M KOH

solution (10 mL x 2), and brine (10 mL). Resulting organic layer was dried over Na_2SO_4 and evaporated under reduced pressure (25 ^oC, 10 mmHg) to yield a yellow odorous oil. Purification via silica gel flash column chromatography (SiO_2, 40 g, 25 mm Ø, hexanes to hexanes/EtOAc, 9:1) afforded 116 mg (87%) of **154**, as a colorless oil. The spectroscopic data matched those reported in the literature.[111]

Data for **154**:

bp: 110 ^oC (at 15 mmHg)

^{1}H NMR: (500 MHz, $CDCl_3$)

δ 7.07 (d, *J* = 7.0 Hz, 1 H), 7.01 (t, *J* = 7.5 Hz, 1 H), 6.69 (td, J = 7.5, 1.0 Hz, 1 H), 6.60 (d, J = 7.5 Hz, 1 H), 3.99 (ddq, *J* = 8.5, 8.0, and 6.0 Hz, 1 H, HC(2)), 3.14 (dd, *J* = 15.5, 8.5 Hz, 1 H, HC(3)), 2.64 (ddt, *J* = 15.5, 8.0, and 1.0 Hz, 1 H, HC(3)), 1.29 (d, *J* = 6.0 Hz, 3 H, HC(10)).

Opt Rot: $[\alpha]_D^{24}$ +6.9 (c = 0.80, C_6H_6)

References

(1) Arrhenius S. *London, Edinburgh Dublin Philos. Mag. J. Sci.* **1896**, *41*, 237–276.

(2) Lewis, G. N. *Valence and The Stucture of Atoms and Molecules*; Chemical Catalog: New York, 1923. However, this was not elaborated until 1938, which Lewis wrote "*To restrict the group of acids to those substances which contain hydrogen interferes as seriously with the systematic understanding of chemistry as would the restriction of the term oxidizing agent to substances containing oxygen.*" (a) Lewis, J. *Franklin Inst.* **1938**, *226*, 293-313; (b) Hall. N. F. *J. Chem. Educ.* **1940**, *17*, 124-128.

(3) (a) Jensen, W. B. In *The Lewis Acid-Base Concept*; Wiley-Interscience, New York, 1980; (b) Jensen, W. B. *Chem. Rev.* **1978**, *78*, 1.

(4) (a) Collum, D. B. *Acc. Chem. Res.* **1992**, *25*, 448-454; (b) Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 92-138; (c) Seebach, D.; Beck, A. K.; Studer, A. *Mod. Synth. Methods* **1995**, *7*, 1; (d) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868-2877; (e) Brunner, H.; Zettlmeyer, W. *Handbook of Enantioselective Catalysts*; Wiley-VCH: Weinheim, 1993; (f) Tang, W. J.; Zhang, X. M. *Chem. Rev.* **2003**, *103*, 3029-3069; (g) Stephan, D. W.; Erker, G. *Angew. Chem., Int. Ed.* **2010**, *49*, 46-76.

(5) (a) Gutmann, V. *Coord. Chem. Rev.* **1976**, *18*, 225-255; (b) Gutmann, V.; Schmid, R. *Coord. Chem. Rev.* **1974**, *12*, 263-293; (c) Gutmann, V. In *The Donor-Acceptor Approach to Molecular Interactions*; Plenum Press: New York, 1978.

(6) (a) Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 1560-1638; (b) Denmark, S. E.; Fujimori, S. *Catalytic, Enantioselective Aldol Reactions with Chiral Lewis Bases.* In *Modern Aldol Reactions*; Mahrwald, R., Ed. Wiley-VCH: Weinheim, 2004; Vol. 2, Chapt.7.

(7) (a) Wei, Y.; Shi, M. *Chem. Rev.* **2013**, *113*, 6659-6690; (b) Wei, Y.; Shi, M. *Acc. Chem. Res.* **2010**, *43*, 1005-1018.

(8) M. Godfrey, S.; L. Jackson, S.; A. McAuliffe, C.; G. Pritchard, R. *J. Chem. Soc., Dalton Trans.* **1997**, 4499-4502.

(9) (a) Musher, J. I. *Angew. Chem., Int. Ed.* **1969**, *8*, 54-68; (b) Curnow, O. J. *J. Chem. Educ.* **1998**, *75*, 910-915.

(10) (a) Denmark, S. E.; Wilson, T. W.; Burk, M. T.; Heemstra, Jr. J. R. *J. Am. Chem. Soc.* **2007**, *129*, 14864-14865; (b) Denmark, S. E.; Eklov, B. M.; Yao, P. J.; Eastgate, M. D. *J. Am. Chem. Soc.* **2009**, 131, 11770-11787; (c) Beutner, G. L.; Denmark, S. E. *Angew. Chem. Int. Ed.* **2013**, 52, 9086-9096.

(11) Denmark, S. E.; Kalyani, D.; Collins, W. R. *J. Am. Chem. Soc.* **2010**, *132*, 15752-15765.

(12) Denmark, S. E.; Kornfilt, D. J. P.; Vogler, T., *J. Am. Chem. Soc.* **2011**, *133*, 15308-15311.

(13) Denmark, S. E.; Chi, H. M. *J. Am. Chem. Soc.* **2014**, *136*, 8915–8918.

(14) For a leading references on piperidines, see: (a) Strunz, G. M.; Findlay, J. A. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: New York, 1985, Vol. 26, Chapter 3; (b) Rubiralta, M.; Giralt, E.; Diez, A. In *Studies in Organic Chemistry: Piperidine Structure, Preparation, Reactivity, and Synthetic Applications of Piperidine and its Derivatives*; Elesevier Science: Amsterdam, 1991, Vol. 43; (c) Royer, J. In *Asymmetric Synthesis of Nitrogen Heterocycles*; Wiley-VCH: Weinheim, 2009. (d) Bailey, P. D.; Milwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, 633-640. (e) Laschat, S.; Dickner, T. *Synthesis* **2000**, *13*, 1781-1813. (f) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435 - 446. (g) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetraheron* **2003**, *59*, 2953-2989. (f) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701–1729.

(15) (a) Enders, D.; Tiebes, J. *Liebig's Ann. Chem.* **1993**, 173-177; (b) Gersdorff, W. A. *J. Am. Chem. Soc.* **1933**, *55*, 2941-2945; (c) Dragutan, I.; Dragutan, V.; Demonceau, A. *RSC Adv.* **2012**, *2*, 719-736; (d) He, R.; Kurome, T.; Giberson, K. M.; Johnson, K. M.; Kozikowski, A. P. *J. Med. Chem.* **2005**, *48*, 7970-7979; (e) Rinehart, K. L.; Holt, T. G.; Fregeau, N. L.; Stroh, J. G.; Keifer, P. A.; Sun, F.; Li, L. H.; Martin, D. G. *J. Org. Chem.* **1990**, *55*, 4512–4515; (f) Nara, S.; Tanaka, R.; Eishima, J.; Hara, M.; Takahashi, Y.; Otaki, S.; Foglesong, R. J.; Hughes, P. F.; Turkington, S.; Kanda, Y. *J. Med. Chem.* **2003**, *46*, 2467-2473; (g) Pei, Z.; Li, X; von Geldern, T. W.; Longenecker, K.; Pireh, D.; Stewart, K. D.; Backes, B. J.; Lai, C.; Lubben, T. H.; Ballaron, S. J.; Beno, D. W. A.; Kempf-Grote, A. J.; Sham, H. L.; Trevillyan, J. M. *J. Med. Chem.* **2007**, *50*, 1983-1987.

(16) (a) Malison, R. T.; Price, L. H.; Berman, R.; van Dyck, C. H.; Pelton, G. H.; Captenter, L.; Sanacora, G.; Owens, M. J.; Nemeroff, C. B.; Rajeevan, N.; Baldwin, R. M.; Seibyl, J. P.; Innis, R. B.; Charney, D. S. *Biol. Psychiatry* **1998**, *44*, 1090-1098. (b) Kim, H. J.; Im, J.

H.; Yang, S. O.; Moon, D. H.; Ryu, J. S.; Bong, J. K.; Nam, K. P.; Cheon, J. H.; Lee, M. C.; Lee, H. K. *J. Nucl. Med.* **1997**, *38*, 1703-1711.

(17) Serino, C.; Stehle, N.; Park, Y. S.; Florio, S.; Beak, P. *J. Org. Chem.* **1999**, *64*, 1160-1165.

(18) (a) Yao, S.; Johannsen, M.; Hazell, R. G.; Jørgensen, K. K. *Angew. Chem., Int. Ed.* **1998**, *37*, 3121; (b) Boger, D. L.; Weinreb, S. M. In *Hetero Diels – Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987.

(19) (a) Schmid, G. H.; Garratt, D. G. In *The Chemistry of Double-Bonded Functional Groups, Part 2*; John Wiley & Sons: London, 1977; pp 725−912; (b) Schmid, G. H. Supplement A: In *The Chemistry of Double-Bonded Functional Groups, Part 1*; John Wiley & Sons: London, 1989; Vol. 2, pp 679−731; (c) Capozzi, G.; Modena, G.; Pasquato, L. In *The Chemistry of Sulphenic Acids and Their Derivatives*; Patai, S., Ed.; John Wiley & Sons Ltd.: West Sussex, UK, 1990; pp 403−516; (d) Rayner, C. M. In *Organosulfur Chemistry: Synthetic Aspects*, Page, P., Ed.; Academic Press: London, 1995; pp 89−131; (f) Capozzi, G.; Modena, G. In *Organic Sulfur Chemistry*: Theoretical and Experimental Advances, Bernardi, F., Csizmadia, I. G., Mangini, A., Eds.; Elsevier: Amsterdam, 1985; Vol. 19, pp 246−298.

(20) (a) Trost, B. M.; Semmelhack, M. F.; Fleming, I. In *Comprehensive Organic Synthesis: Selectivity, Strategy & Efficiency in Modern Organic Chemistry*; Pergamon Press: New York, 1991; Vol. 4; (b) Smith, M. B.; March, J. In *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*; Wiley-Interscience: New York, 2007.

(21) (a) Trost, B. M.; Shibata, T. *J. Am. Chem. Soc.* **1982**, *104*, 3225-3228; (b) Trost, B. M.; Shibata, T.; Martin, S. J. *J. Am. Chem. Soc.* **1982**, *104*, 3228-3230.

(22) (a) Helmkamp, C. K.; Olsen, B. A.; Pettitt, D. J. *J. Org. Chem.* **1965**, *30*, 676-677; (b) Helmkamp, G. K.; Olsen, B. A.; Koskinen, J. R. *J. Org. Chem.* **1965**, *30*, 1623-1626; (c) Capozzi, G.; DeLucchi, O.; Lucchni, V.; Modena, G. *Tetrahedron Lett.* **1975**, *16*, 2603-2604.

(23) Benati, L.; Montevecchi, P.C.; Spagnolo, P. *Tetrehedron Lett.* **1984**, *25*, 2039-2042.

(24) Brownbridge, P. *Tetrehedron Lett.* **1984**, *25*, 3759-3762.

(25) Ohsawa, T.; Ihara, M.; Fukumoto, K.; Kametani, T. *J. Org. Chem.* **1983**, *48*, 3644-3648.

(26) Ihara, M.; Haga, Y.; Yonekura, M.; Ohsawa, T.; Fukumoto, K.; Kametani, T. *J. Am. Chem. Soc.* **1983**, *105*, 7345-7352.

(27) Zhao, G.-L.; Rios, R.; Vesely, J.; Eriksson, L.; Córdova, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 8468–8472.

(28) Lucchini, V.; Modena, G.; Pasquato, L. *J. Chem. Soc., Chem. Commun.* **1994**, 1565-1566.

(29) Archer, N. J.; Rayner, C. M.; Bell, D.; Miller, D. *Synlett* **1994**, 617–619.

(30) (a) Denmark, S. E.; Jaunet, A. *J. Am. Chem. Soc.* **2013**, *135*, 6419–6422; (b) Denmark, S. E.; Jaunet, A. *J. Org. Chem.* **2014**, *79*, 140–171.

(31) (a) Padwa, A.; Murphree, S. S. *Arkivoc* **2006**, *3*, 6-33; (b) Aggarwal, V. K.; Badine, D. M.; Moorthie, V. A. In *Aziridines and Epoxides in Organic Synthesis*, Yudin, A. K., Ed.; WILEY-VCH Verlag GmbH & Co. KGaA: Weinheim, 2006.

(32) (a) Modena, G.; Pasquato, L.; Lucchini, V. *Phosphorus, Sulfur Silicon Relat. Elem.* **1994**, *95−96*, 265−282; (b) Drabowicz, J.; Lyzwa, P.; Mikolajczyk, M. In *The Chemistry of Sulphenic Acids and Their Derivatives*, Patai, S., Ed.; John Wiley & Sons Ltd.: West Sussex, UK, 1990; pp 187−292.

(33) Denmark, S. E.; Vogler, T. *Chem. Eur. J.* **2009**, *15*, 11737-11745.

(34) (a) Rayner, C. M. In *Organosulfur Chemistry: Synthetic Aspects*; Page, P., Ed.; Academic Press: London, 1995; (b) Smit, V. A.; Zefirov, N. S.; Bodrikov, I. V.; Krimer, M. Z. *Acc. Chem. Res.* **1979**, *12*, 282-288; (c) Denmark, S. E.; Collins, W. R. *Org. Lett.* **2007**, *9*, 3801-3804.

(35) Lucchini, V.; Modena, G.; Pasquato, L. *J. Am. Chem. Soc.* **1988**, *110*, 6900-6901.

(36) Denmark, S. E.; Collins, W. R.; Cullen, M. D. *J. Am. Chem. Soc.* **2009**, *131*, 3490-3492.

(37) Wuts, P. G. M.; Greene, T. W. In *Greene's Protective Groups in Organic Synthesis*; Wiley-Interscience: New York, 1991.

(38) Grünanger, C. U.; Breit, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 967–970.

(39) Hill, R. K.; Soman, R.; Sawada, S. *J. Org. Chem.* **1972**, *37*, 3737-3740.

(40) Procedure from these laboratory [MDC-XI-098].

(41) Magnus, P.; Gallagher, T.; Brown, P.; Huffman, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 2105-2114.

(42) (a) Schlummer, B.; Hartwig, J. F. *Org. Lett.* **2002**, *4*, 9, 1471 – 1474; (b) Lovick, H. M.; Michael, F. E. *J. Am. Chem. Soc.* **2010**, *132*, 1249 – 1251; (c) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2007**, *129*, 6328 – 6335; (d) Mancheno, D. E.; Thornton, A. R.; Stoll, A. H.; Kong, A.; Blakey, S. B. *Org. Lett.* **2010**, *12*, 4110 – 4113; (e) Reddy, D. N.; Prabhakaran, E. N. *J. Org. Chem.* **2011**, *76*, 680 – 683; (f) Bertrand, M. B.; Neukom, J. D.; Wolfe, J. P. *J. Org. Chem.* **2008**, *73*, 8851 – 8860; (g) Mattingly, P. G. *Synthesis* **1990**, *4*, 366 – 368; (h) Chandrasekhar, S.; Reddy, M. V.; Rajaiah, G. *Tetrahedron Lett.* **2000**, *41*, 10131 – 10134; (i) Ramage, R.; Hopton, D.; Parrott, M. J.; Kenner, G. W.; Moore, G. A. *J. Chem. Soc., Perkin Trans. 1* **1984**, *0*, 1357 - 1370.

(43) (a) Destro, R.; Lucchini, V.; Modena, G.; Pasquato, L. *J. Org. Chem.* **2000**, *65*, 3367-3370; (b) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533-3539; (c) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456-463.

(44) Klose, J.; Reese, C. B.; Song, Q. *Tetrahedron* **1997**, *53*, 14411-14416.

(45) Li, L.; Wang, H.; Huang, D.; Shi, Y. *Tetrahedron* **2012**, *68*, 9853-9859.

(46) Guanti, G.; Banfi, L.; Riva, R. *Tetrahedron: Asym.* **1994**, *5*, 1745-1762.

(47) (a) Evans, P.; McCabe, T.; Morgan, B. S.; Reau, S. *Org. Lett.* **2005**, *7*, 43-46; (b) Kondo, M.; Kochi, T.; Kakiuchi, F. *J. Am. Chem. Soc.* **2011**, *133*, 12394 - 12397.

(48) Zhang, g.; Cui, L.; Wang, Y.; Zhang, L. *J. Am. Chem. Soc.* **2010**, *132*, 1474-1475.

(49) The precursor **84** was synthesized from 2,2'-dinaphthyldiamine (BINAM) which was kindly provided from Dr. Rossi.

(50) Wilson, T. W., Post-doctoral report.

(51) While (*R*)-**7** gave a spectrum with all chemical shift being sharp, (*S*)-**83** gave broad shifts for isopropyl protons on ^{1}H and phosphorus on ^{31}P NMR spectra from slow rotation, most likely due to steric hindrance.

(52) Nurminen, E. J.; Mattinen, J. K.; Lönnberg, H. *J. Chem. Soc., Perkin Trans. 2* **1998**, *0*, 1621-1628.

(53) Ciganek, E. *J. Org. Chem.* **1992**, *57*, 4521-4527.

(54) Wu, L.; Qiu, S.; Liu, G. *Org. Lett.* **2009**, *11*, 2707-2710.

(55) Colladon, M.; Scarso, A.; Sgarbossa, P.; Michelin, R. A.; Strukul, G. *J. Am. Chem. Soc.* **2006**, *128*, 14006-14007.

(56) The crystallographic coordinates of **111** have been deposited with the CCDC; deposition no. 981943. These data can be obtained free of charge via from the Cambridge Crystallographic Data Centre, at www.ccdc.cam.ac.uk/conts/retrieving.html or deposit@ccdc.cam.ac.uk.

(57) (a) Modena, G.; Pasquato, L.; Lucchini, V. *Chem. Eur. J.* **2000**, *6*, 589-590; (b) Sølling, T. I.; Wild, S. B.; Radom, L. *Chem. Eur. J.* **2000**, *6*, 590-591.

(58) Vogler, T., Post-doctoral report.

(59) Houk, K. N.; Liu, J.; DeMello, N. C.; Condroski, K. R. *J. Am. Chem. Soc.* **1997**, 119, 10147-10152.

(60) Jones, M.; Fleming, S. A. In *Organic chemistry*; W.W. Norton: New York, 2009.

(61) (a) Yamazaki, N.; Ito, T.; Kibayashi, C. *Tetrahedron Lett.* **1999**, *40*, 739–742; (b) Honda, T.; Hisa, C. *Heterocycles* **2010**, *80*, 1381-1406.

(62) Kunstmann, R.; Lerch, U.; Gerhards, H.; Leven, M.; Schacht, U. *J. Med. Chem.* **1984**, *27*, 432-439.

(63) Choi, K.-W.; Ha, D.-C.; Hart, D. J.; Lee, C.-H.; Ramesh, S.; Wu, S. *J. Org. Chem.* **1989**, *54*, 279-290.

(64) (a) Alonso, D. A.; Najera, C. *Org. React.* **2008**, *72*, 367-637; (b) Pettit, G. R.; van Tamelen, E. E. *Org. React.* **1962**, *12*, 356-530.

(65) Kingsbury, C. A.; Cram, D. J. *J. Am. Chem. Soc.* **1960**, *82*, 1810-1819.

(66) DeLucchi, O.; Miotti, U.; Modena, G. *Org. React.* **1991**, *40*, 157-405.

(67) Shiu, L. L.; Yu, C. C.; Wong, K. T.; Chen, B. L.; Cheng, W. L.; Yuan, T. M.; Luh, T. Y. *Organometallics* **1993**, *12*, 1018-1020.

(68) Shinokubo, H.; Oshima, K. *Eur. J. Org. Chem.* **2004**, *10*, 2081-2091.

(69) Denmark, S. E.; Chi, H. M. *J. Am. Chem. Soc.* **2014**, *136*, 3655–3663.

(70) A parallel set of experiments run at 0.1 M concentration displayed dramatically different behavior than those run at 0.2 M. For example, with MsOH (1.0 equiv), the catalyzed reaction showed an induction period of ca. 6 h before the rapid onset of reaction, approximating an autocatalytic process. Moreover, with $EtSO_3H$, the uncatalyzed reaction afforded only **123**, the product of proton-initiated cyclization. These results, while intriguing and potentially informative, did not represent the preparative-scale reactions

and as such were not further investigated or analyzed. See Chapter 5: Experimental for details.

(71) The enantiomeric ratio (er) for **54** in this run using purified MsOH was only 75:25.

(72) Enantiomeric ratios: 1.00 equiv, 86.9:13.1; 0.75 equiv, 90.2:9.8; 0.50 equiv, 92.6:7.4; 0.25 equiv, 92.9:7.1.

(73) It is recognized that the equilibria measured at −50 and −57 °C may not be exactly the same as the equilibrium at the reaction temperature (−20 °C); however, the temperature difference is not large.

(74) For reviews, see: (a) King, J. F. In *The chemistry of sulphonic acids, esters and their derivatives*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: Chichester, 1991; Chapt. 6. (b) Furukawa, N.; Fujihara, H. In *The chemistry of sulphonic acids, esters and their derivatives*; Patai, S., Rappoport, Z., Eds.; John Wiley & Sons: Chichester, 1991; Chapt 7.

(75) Only at 0.1 M concentration were the differences more pronounced. $EtSO_3H$ did not promote the formation of **54** in the uncatalyzed reaction but afforded only **123** in a process that exhibited zeroth-order kinetic behavior. See Chapter 5: Experimental Section for details.

(76) The different overall reaction order makes comparison of the relative rates difficult. Under these conditions the times to 50% conversions are calculated to be 2.0 h for the catalyzed reaction and 1.67 h for the uncatalyzed reaction.

(77) The initial rates of the catalyzed reactions are actually greater than those of the uncatalyzed runs at comparable $EtSO_3H$ loadings, but the differences in overall reaction order make comparisons difficult. For example, the time to 50% conversion using 1.0 equiv of $EtSO_3H$ is calculated to be 2.4 h for the catalyzed reaction and 7.1 h for the uncatalyzed reaction.

(78) Hojo, M.; Chen, Z. *Anal. Sci.* **1999**, *15*, 303−306.

(79) Hojo, M.; Hasegawa, H.; Miyauchi, Y.; Moriyama, H.; Yoneda, H.; Arisawa, S. *Electrochim. Acta* **1994**, *39*, 629−638.

(80) Szwarc, M. In *Ions and Ion Pairs in Organic Reactions*; Szwarc, M., Ed.; Wiley-Interscience: New York, 1972; Vol. 1, Chapt. 1.

(81) (a) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, *327*, 986−990; (b) Knowles, R. R.; Jacobsen, E. N. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20678−20685.

(82) (a) Rétey, J. *Angew. Chem., lnt. Ed.* **1990**, *29*, 355−361; (b) Breslow, R. *Acc. Chem. Res.* **1991**, *24*, 317−324; (c) Abel, E. *Adv. Catal.* **1957**, *9*, 330−338.

(83) An intriguing consequence of this interpretation is that this system may be operating analogously to the negative catalysis observed by Jacobsen. If the amount of reactive monomer is small relative to the amount of catalyst, then the interception of this highly reactive species to form the less reactive, but chiral ***i*** could also explain these observations. Studies on the colligative properties of ***iii*** are underway.

(84) Denmark, S. E.; Chi, H. M. *Manuscript in preparation*.

(85) (a) Sridharan, V.; Suryavanshi, P. A.; Menéndez, J. C. *Chem. Rev.* **2011**, *111*, 7157–7259; (b) Katritzky, A.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15030–15070; (c) Nammalwar, B.; Bunce, R. A. *Molecules* **2014**, *19*, 204–232; (d) Muñoz, G. D.; Dudley, G. B. *Org. Prep. Proced. Int.* **2015**, *47*, 179–206.

(86) (a) Padwa, A.; Brodney, M. A.; Dimitroff, M.; Liu, B.; Wu, T. *J. Org. Chem.* **2001**, *66*, 3119; (b) Boonsombat, J.; Zhang, H.; Chughtai, M. J.; Hartung, J.; Padwa, A. *J. Org. Chem.* **2008**, *73*, 3539.

(87) (a) Rueping, M.; Antonchick, A. P.; Theissmann, T. *Angew. Chem., Int. Ed.* **2006**, *45*, 3683-3686; (b) Rueping, M.; Theissmann, T.; Raja, S.; Bats, J. W. *Adv. Synth. Catal.* **2008**, *350*, 1001-1006; (c) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. *Chem. Rev.* **2012**, *112*, 2557–2590.

(88) (a) Chen, B.-L.; Wang, B.; Lin, G.-Q. *J. Org. Chem.* **2010**, 75, 941-944; (b) Klapars, A.; Parris, S.; Anderson, K. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126*, 3529-3533.

(89) Hara, O.; Koshizawa, T.; Makino, K.; Konimune, I.; Namiki, A.; *Tetrahedron* **2007**, *63*, 6170–6181.

(90) Davies, S. G.; Mujtaba, N.; Roberts, P. M.; Smith, A. D.; Thomson, J. E. *Org. Lett.* **2009**, *11*, 1959–1962.

(91) Fukamizu, K.; Miyake, Y.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2008**, *130*, 10498–10499.

(92) Lu, H.-H.; Liu, H.; Wu, W.; Wang, X.-F.; Lu, L.-Q.; Xiao, W.-J. *Chem. Eur. J.* **2009**, *15*, 2742–2746.

(93) Baraznenok, I. L.; Nenajdenko, V. G.; Churakov, A. V.; Nesterenko, P. N.; Balenkova, E. S. *Synlett* **2000**, *4*, 514–516.

(94) Wang, C.; Tunge. J. A. *J. Am. Chem. Soc.* **2008**, *130*, 8118–8119.

(95) Cai, X.-F.; Chen, M.-W.; Ye, Z.-S.; Guo, R.-N.; Shi, L.; Li, Y.-Q.; Zhou, Y.-G. *Chem. Asian J.* **2013**, *8*, 1381–1385.

(96) Denmark, S. E.; Hartmann, E.; Kornfilt, D. J. P.; Wang, H. *Nat. Chem.* **2014**, *6*, 1056–1064.

(97) Denmark, S. E.; Rossi, S.; Webster, M. P.; Wang, H. *J. Am. Chem. Soc.* **2014**, *136*, 13016–13028.

(98) (a) Yip, K.-T.; Yang, M.; Law, K.-L.; Zhu, N.-Y.; Yang, D. *J. Am. Chem. Soc.* **2006**, *128*, 3130-3131; (b) Cooper, M. A.; Lucas, M. A.; Taylor, J. M.; Ward, A. D.; Williamson, N. M. *Synthesis* **2001**, *4*, 621-625.

(99) Hatano, M.; Suzuki, S.; Ishihara, K. *J. Am. Chem. Soc.* **2006**, *128*, 9998-9999.

(100) Katritzky, A. R.; Hong, Q.; Yang, Z. *J. Org. Chem.* **1994**, *59*, 7947-7948.

(101) Yamamoto, H.; Ho, E.; Namba, K.; Imagawa, H.; Nishizawa, M. *Chem. Eur. J.* **2010**, *16*, 11271 – 11274.

(102) Jiang, F.; Wu, Z.; Zhang, W. *Tetrahedron* **2011**, *67*, 1501-1505.

(103) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360-11370.

(104) Wang, J.; Chen, J.; Kee, C. W.; Tan, C.-H. *Angew. Chem. Int. Ed.* **2012**, *51*, 2382 –2386.

(105) Green, R. A.; Hartwig, J. F. *Org. Lett.* **2014**, *16*, 4388−4391.

(106) Nakhla, J. S.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 2893 – 2901.

(107) Racouchot, S.; Sylvestre, I.; Ollivier, J.; Kozyrkov, Y. Y.; Pukin, A.; Kulinkovich, O. G.; Salaün, J. *Eur. J. Org. Chem.* **2002**, 2160–2176.

(108) Watson, I. D. G.; Ritter, S.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 2056-2057.

(109) Back, T. G.; Yang, K. *J. C. S., Chem. Commun.* **1990**, 819–820.

(110) Göhl, M.; Seifert, K. *Eur. J. Org. Chem.* **2015**, 6249–6258.

(111) Xiao, Y.-C.; Wang, C.; Yao, Y.; Sun, J.; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2011**, *50*, 10661–10664.

(112) Denmark, S. E.; Kornfilt, D. J. P. *Manuscript in preparation*.

(113) Hansch, C; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165–195.

(114) While different catalyst (*R*)-**7** and (*S*)-**53** are used, trisubstituted alkenes have gave diminished er in earlier reports.[12,30]

(115) Possible explanations that may be account for the diminished enantioselectivity of **150** are: (a) the formation of an achiral sulfenylating species with the Lewis basic nitrile moiety, (b) pre-coordination of the nitrile to the catalytically active species ***i***, thus disrupting the interaction between the alkene and ***i***, and (c) the reversing of the thiiranium ion formation by attacking with nitrile moiety. The viability of thiophilic attack by nitriles has been reported.[28]

(116) Di Martino, A.; Galli, C.; Gargano, P.; Mandolini, L. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1345–1349.

(117) (a) Arnold, R. T.; Kulenovic, S. T. *J. Org. Chem.* **1980**, *45*, 891 – 894; (b) Logan, A. W. J.; Parker, J. S.; Hallside, M. S.; Burton, J. W. *Org. Lett.* **2012**, *14*, 2940 – 2943.

(118) Marcotullio, M. C.; Campagna, V.; Sternativo, S.; Costantino, F.; Curini, M. *Synthesis* **2006**, *16*, 2760 - 2766.

(119) Hamilton, D. S.; Nicewicz, D. A. *J. Am. Chem. Soc.* **2012**, *134*, 18577 – 18580.

(120) (a) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brocksom, T. J.; Li, T.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741 – 743; (b) Weyerstahl, H. A.; Weyerstahl, P. *Tetrahedron* **1984**, *40*, 2003 – 2009.

(121) Kaga, H.; Goto K.; Takahashi, T.; Hino, M.; Tokuhashi, T.; Orito, K. *Tetrahedron* **1996**, *52*, 8451 – 8470.

(122) Lewis, F. D.; Dasharatha R.; Schneider, S.; Ga, M. *J. Am. Chem. Soc.* **1991**, *113*, 3498 – 3506.

(123) (a) Grote, R. E.; Jarvo, E. R. *Org. Lett.* **2009**, *11*, 485 – 488; (b) Sadownik, J. W.; Philp, D. *Angew. Chem. Int. Ed.* **2008**, 47, 9965 – 9970; (c) Kozlov, N. G.; Basalaeva, L. I. *Russ. J. Gen. Chem.* **2001**, *71*, 250 – 256; (d) Narasaka, K.; Shibata, T. *Heterocycles* **1993**, *35*, 1039 – 1053.

(124) (a) Cooper, M. A.; Lucas, M. A.; Taylor, J. M.; Ward, A. D.; Williamson, N. M. *Synthesis* **2001**, *4*, 621–625; (b) Cooper, M. A.; Francis, C. L.; Holman, J. W.; Kasum, B.; Taverner, T.; Tiekink, E. R. T.; Ward, A. D. *Aust. J. Chem.* **2000**, *53*, 123-129.

(125) WO2015/088271, p155.

(126) Bruyère, D.; Bouyssi, D.; Balme, G. *Tetrahedron* **2004**, *60*, 4007 – 4017.

(127) Watson, I. D. G.; Ritter, S.; Toste, F. D. *J. Am. Chem. Soc.* **2009**, *131*, 2056-2057.

(128) (a) Group procedure [MDC-XI-098]; (b) Fujisawa, T.; Sugasawa, S. *Tetrahedron* **1959**, *7*, 185 - 188.

(129) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis* **1967**, 581 - 595.

(130) Horner, J. H.; Taxil, E.; Newcomb, M. *J. Am. Chem. Soc.* **2002**, *124*, 5402 – 5410.

(131) Takeda, N.; Imamoto, T. *Org. Synth.* **2004**, *Coll. Vol 10*, 200.

(132) Denmark, S. E.; Burk, M. *Proc. Nat. Acad. Sci. U.S.A.* **2010**, *107*, 20655 - 20660.

(133) Giese, b.; Thoma, G. *Helv. Chim. Act.* **1991**, *74*, 1143 - 1155.

(134) (a) Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals, 6th Ed.*; Elsevier: Oxford, 2009; p 159; (b) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. R. *Purification of Laboratory Chemicals, 2nd Ed.*; Pergamon Press: Oxford, 1980; p 551.

(135) Arnold, J. S.; Stone, R. F. Nguyen, H. M. *Org. Lett.* **2010**, *12*, 4580–4583.

(136) Shu, C.; Leither, A.; Hartwig, J. F. *Angew. Chem. Int. Ed.* **2004**, *43*, 4797-4800.

(137) Yin, Y.; Zhao, G. *J. Fluor. Chem.* **2007**, *128*, 40-45.

(138) Harding, B. A.; Melvin, P. R.; Dougherty Jr, W.; Kassel, S.; Goodson, F. E. *Organometallics* **2013**, *32*, 3570-3573.