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A Merged 1,2 and 1,3 Asymmetric Induction Model Describing Lewis Acid-Mediated Diastereoselective Reactions of Chiral N-Sulfonyl Imines and Nucleophilic Alkenes

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A Merged 1,2 and 1,3 Asymmetric Induction Model Describing Lewis Acid-Mediated Diastereoselective Reactions of Chiral *N*-Sulfonyl Imines and Nucleophilic Alkenes

By

ANNA LO

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

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in the

OFFICE OF GRADUATE STUDIES

of the

UNIVERSITY OF CALIFORNIA

DAVIS

Approved:

_____

Jared T. Shaw, Chair

_____

Dean J. Tantillo

_____

Neil E. Schore

Committee in Charge

2022

DEDICATION

to Mom and Dad
献给我的父母

you are my everything
没有你，那有我

The world to me was a secret, which I desired to discover.

THE MODERN PROMETHEUS

ACKNOWLEDGEMENTS

It seems there are never enough words to describe the immense gratitude I feel for the following individuals I was fortunate enough to cross paths with throughout my education. Below, I will attempt to immortalize every kind interaction, good influence, and helping hand I received while in Davis.

To Jared T. Shaw – Thank you for your support as my research advisor and your decision to ultimately take me into your group. While in your group, I watched you endure the pressures of the chair's office, an unprecedented pandemic, and funding insecurity. I can truly say that even in the toughest of times, you always did your best to support me in my endeavors. I am eternally grateful to you for providing the space and mentorship for me at UC Davis to grow into a synthetic chemist.

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To Neil E. Schore – Thank you for the lovely conversations about your family, trips, and love of music. Speaking with you, I am always reminded that there is more in life to enjoy than just my research accomplishments. You've taught me so many lessons during my time here at Davis, lessons I will not be quick to forget. Thank you for your warmth and unending optimism.

To Keith A. Woerpel – Keith, if you had not granted me an undergraduate position in your lab, I would not be where I am today. Thank you for nurturing my passion for synthetic organic chemistry. Thank you for lending your ear and intellect to all of my questions. Thank you for all the coffee runs. You have been and always will be the scientist I model myself after.

To the Shaw group, life has brought us together from all corners of the world and we will now be forever bonded through our shared experiences. Every experiment contained in this dissertation has been directly or indirectly made possible by the distribution of labor among all of my lab mates. And really, I would not trade the group for any other. Below, I'd like to highlight those I've worked more closely with over the years.

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DAG – You taught me to never wait on a chemical shipment if it can be synthesized in lab and the true meaning of leadership. DAG, you are the most relentless chemist I know,

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Outside of lab, I have been fortunate enough to cultivate friendships I hope to nurture for a lifetime. Thank you first and foremost to Elizabeth "Liz" Lotsof who became my roommate in 2019. Thank you for the late-night chats, the spontaneous dinners, and for teaching me how to be an adult. Most importantly, thank you for taking care of me when I broke my ankle. I could not have asked for a better roommate and friend in this adventure we call life, and I'm excited to see what's next for us. Thank you to Erika Ripley,

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A Merged 1,2 and 1,3 Asymmetric Induction Model Describing Lewis Acid-Mediated Diastereoselective Reactions of Chiral N-Sulfonyl Imines and Nucleophilic Alkenes

ABSTRACT OF DISSERTATION

The exploitation of resident stereogenic centers to construct new stereogenic centers is a powerful strategy employed in the synthesis of complex organic molecules. Although the influence of both α- and β-stereogenic centers on the diastereoselective addition of nucleophiles to aldehydes has been thoroughly studied, analogous studies of α- and β-substituted imines are sparse. This dissertation describes the comprehensive study of how inherent asymmetry impacts diastereoselective nucleophilic additions to α- and β-chiral *N*-sulfonyl imines. Chapter one discusses the development of stereodivergent Lewis acid-mediated nucleophilic additions to α-chiral *N*-sulfonyl imines. From this study, two sets of optimized and generalizable conditions were developed, allowing access to either *syn* or *anti* diastereomeric outcomes in >95:5 diastereomeric ratios. Chapter two discusses the diastereoselective Lewis acid-mediated nucleophilic additions to β-chiral *N*-sulfonyl imines. These reactions typically proceed through a six-membered chelate and result in *anti*-products. Experimental and computational evidence lead to the construction of a generalizable stereoelectronic model that predicts for the magnitude of selectivity observed based on conformational preferences of the substrate-Lewis acid chelate. These two chapters together constitute a complete study of how 1,2 and 1,3 asymmetric induction affect diastereoselective nucleophilic additions to chiral *N*-sulfonyl imines.

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Chapter 1:

Diastereoselective Nucleophilic Additions to α-Chiral *N*-Sulfonyl Aldimines

1.1 Introduction

Nucleophilic additions to α-chiral aldimines are stereoselective through 1,2-asymmetric induction. While asymmetric induction effects on nucleophilic additions to α-chiral aldehydes are well understood, the origins of diastereoselectivity in nucleophilic additions to α-chiral aldimines have been relatively underexplored. Establishing stereoelectronic models predictive of the diastereoselectivity of nucleophilic additions to sp^2 carbon electrophiles can lead to more efficient synthetic planning of stereochemically-complex synthetic targets. In the case of nucleophilic additions to α-chiral aldimines, establishing a predictive model would allow for the stereo-controlled formation of carbon–carbon bonds bearing nitrogen substituents. Our group endeavored to conduct a systematic investigation of how α-chiral substituents impact the stereoselectivity of Lewis acid-mediated nucleophilic additions. The results of this investigation led to the establishment of acyclic stereocontrol in α-chiral *N*-tosyl aldimines for a variety of nucleophilic additions.[1]

1.1.1 Overview of 1,2 Asymmetric Induction in Nucleophilic Additions to α-Chiral Aldehydes

Over the years, several stereoelectronic models have been proposed to generally rationalize the stereochemical outcomes of nucleophilic additions to α-chiral carbonyl

groups (Figure 1). The development of these models has supported the synthesis of various stereochemically complex targets.[2-6] Any new stereoelectronic model describing nucleophilic additions to α-chiral imines would benefit from a clear understanding of the models that describe nucleophilic additions to the analogous aldehydes. Herein, I will provide a condensed overview of the prevailing stereoelectronic models for 1,2-asymmetric induction as applied to α-chiral aldehydes. Some of these models will be referenced in the discussion of the experimental results procured for this chapter. For a more in-depth review of 1,2-asymmetric induction in aldehydes and imines, see the dissertation of my colleague, Dr. Lucas C. Moore (2019).

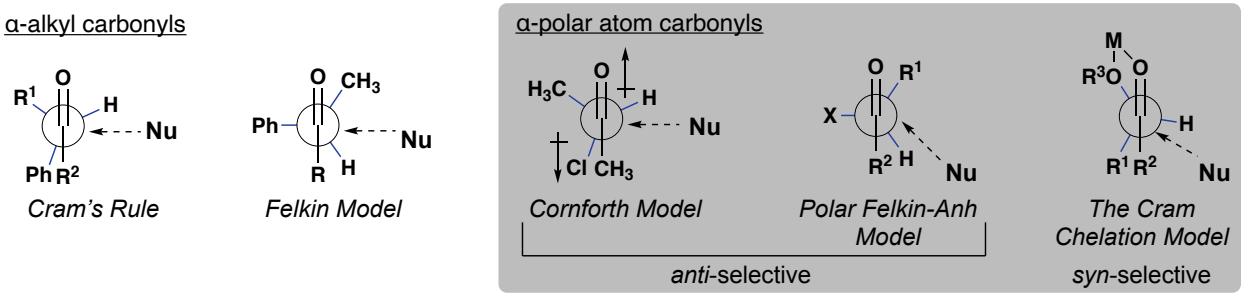


Figure 1. Common stereoelectronic models describing 1,2-asymmetric induction.

1,2-asymmetric induction in nucleophilic additions to α-chiral carbonyls result in two possible stereochemical outcomes (Figure 2). The *stereochemical preference* (eyrthreo/threo, syn/anti, Felkin/anti-Felkin) is typically the result of inherent geometric preferences of the substrate and substrate interactions with reagents or solvents in the reaction. The *magnitude* of the stereochemical outcome is typically the result of how rigid those geometric preferences are. For consistency, *syn* and *anti* will be the terms used to

describe the two diastereomers resulting from nucleophilic additions to α-chiral electrophiles in this chapter.

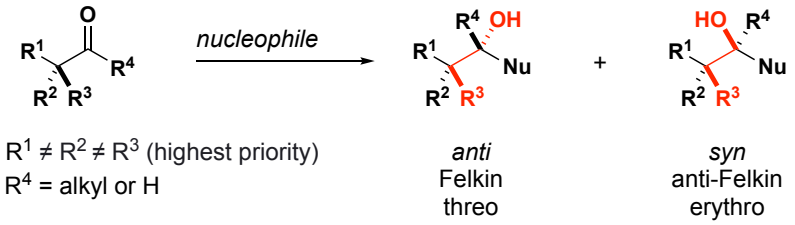


Figure 2. Possible stereochemical outcomes of nucleophilic additions to α-chiral carbonyls.

1.1.1.1 Cram's Rule and The Felkin Model

Cram's rule was one of the earliest attempts at rationalizing the diastereoselectivity of nucleophilic additions to alpha chiral carbonyl compounds. Published in 1952, Cram's rule[7] states:

> "*In non-catalytic reactions of the type shown, that diastereomer will predominate, which would be formed by the approach of the entering group from the* ***least hindered side*** *when the rotational conformation of the C–C bond is such that the double bond is flanked by the two least bulky groups attached to the adjacent asymmetric center*."

The accompanying reaction scheme shown in the original manuscript depicts a general α-chiral carbonyl compound with either carbon or hydrogen substituents proceeding to nucleophilic addition product (Figure 3). The rotational conformation of the C–C bond can be depicted using Newman projection **1**. The C=O bond is flanked by the two least bulky substituents at the alpha chiral center and nucleophilic addition is predicted to occur

preferentially at the least sterically hindered side of the carbonyl (whichever side that may be), to furnish product. Cram argued that the most significant steric interaction that would inform the stereoselectivity of nucleophilic addition was between that of the C=O (bound to Lewis acid) and the adjacent α-substituents.

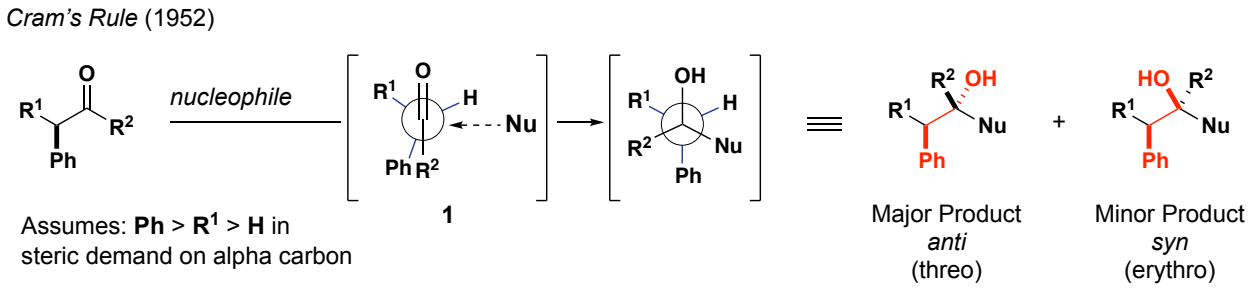


Figure 3. Cram's rule describing nucleophilic additions to α-chiral carbonyls.

While Cram's rule correlated with the observed diastereoselectivities of several nucleophilic addition reactions to α-chiral carbonyl compounds, it became apparent that there were several flaws in the rule: (1) Cram's rule predicted an eclipsed conformational preference of the carbonyl electrophile rather than a presumably less torsionally strained staggered conformation and (2) Cram's rule assumed a 90° angle of the approach of the nucleophile to the carbonyl C=O bond. Later reports would address the shortcomings of Cram's rule and provided stereoelectronic models that more closely aligned with experimental observations.

Felkin published an update to Cram's rule in 1968, which addressed some of the shortcomings of Cram's original rule, dubbed the Felkin model (Figure 4).[8] The Felkin model argues that the electrophilic carbonyl compound would most favorably adopt a fully staggered conformation rather than an eclipsed conformation. In this staggered transition-

state structure, the nucleophile would still most likely approach from the least hindered side of the carbonyl and results in the same diastereochemical outcome that Cram's rule predicts. Felkin's conclusions were supported by experimentally determined diastereomeric ratios of reductions of various ketones. Cram's rule would predict a decrease in diastereoselectivity as the R group of the ketone increased in steric bulk (due to destabilization of the eclipsed conformer **1**). In contrast, Felkin's experimental observations show an increase in diastereoselectivity with R group steric bulk that would be more consistent with a staggered conformation of electrophile resembling **2**. Therefore, Felkin concluded that the more impactful steric interaction to minimize would center around the carbonyl R substituent, rather than that of the carbonyl. The major diastereomer predicted by the Felkin model is often referred to as the Felkin product. The minor diastereomer is comparatively referred to as the anti-Felkin product.

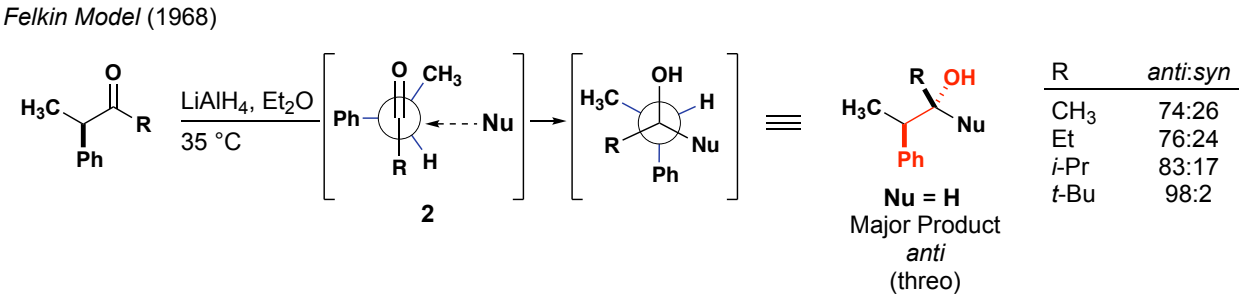


Figure 4. The Felkin model describing nucleophilic additions to α-chiral carbonyls.

Both Cram and Felkin's initial assumptions on a 90° angle of approach by the nucleophile to carbonyl were questioned after observations made by Bürgi and Dunitz in 1974 revealed that the favored approach of a nucleophile to a carbonyl bond was most likely closer to 107° (Figure 5).[9] This trajectory of nucleophilic approach is commonly

referred to as the Bürgi-Dunitz angle. While all of the stereoelectronic models describing nucleophilic additions to carbonyls published previous to the reports made by Bürgi and Dunitz did not consider the Bürgi-Dunitz angle, these models have since been modified later on to include a 107° angle of nucleophilic approach.

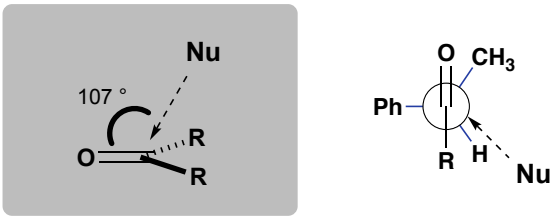


Figure 5. The Bürgi-Dunitz angle.

Considering Felkin's experimental observations, Cram's rule is unlikely to generally predict the anticipated diastereoselectivity of nucleophilic addition reactions to carbonyls. However, Cram's approach to the design of their model and the consideration of what steric interactions would be the most significant in informing the stereochemical outcome laid the groundwork for future stereoelectronic models. The fully-staggered conformation of the electrophile resembling **2** as described by Felkin is ultimately a closer-to-reality representation of these nucleophilic addition reactions.

1.1.1.2 The Cornforth Model and The Polar Felkin-Anh Model

Cornforth reported the first stereochemical investigation of nucleophilic additions to α-chloro carbonyl compounds in 1959.[10] Cram's rule was informed mainly by nucleophilic additions to α-alkyl substituted carbonyls, while Cornforth's investigations had to consider the polar effects of an α-chloro substituent in addition to steric effects.

The presence of a polar group at the alpha position of a carbonyl was proposed to result in a nucleophilic addition transition state structure that resembles **3** (Figure 6). In **3**, the α-chloro substituent is anti-periplanar to the carbonyl group and overall polarization of the carbonyl is minimized. Cornforth argued that the presence of the anti-periplanar α-chloro substituent would support the polarization of the C=O bond during nucleophilic addition. The nucleophile's approach in this conformation would be guided by steric effects of the remaining two α-substituents. This would result in major diastereomer **4** for the depicted example. Since Cornforth published their initial report prior to Bürgi and Dunitz's crystallography experiments, the original Cornforth model does not incorporate a Bürgi-Dunitz angle of approach.

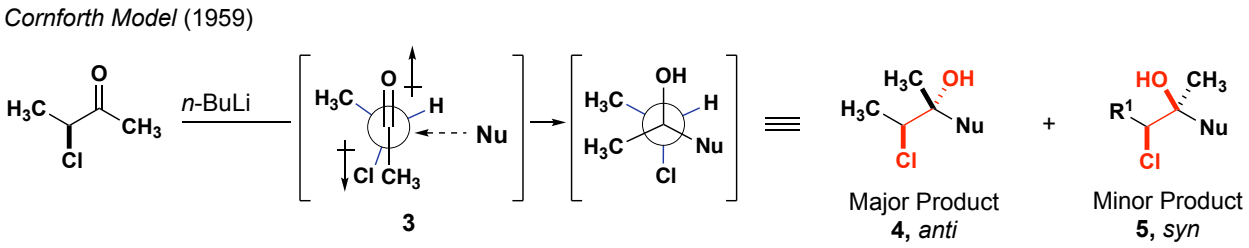


Figure 6. The Cornforth model describing nucleophilic additions to α-chiral carbonyls.

Felkin included a clause for polar α-substituents in their original report of the Felkin model that differed from the Cornforth model, though both models result in the same stereochemical outcome. Rather than an anti-periplanar conformation of the α-chloro position to the carbonyl, the polar Felkin model proposed a 90° orientation of the α-chloro substituent to the carbonyl, though this proposal did not include specific selectivities to support it (Figure 7). Anh and Eisenstein would later, in 1977, make several key additions

to the polar Felkin model to rationalize this conformational preference and generalize this model for both ketones and aldehydes.

Anh and Eisenstein proposed orbital interactions played a major role in nucleophilic addition reactions to α-chiral carbonyls.[11] A 90° orientation of the α-polar group in the transition state structure allows for optimal orbital overlap between the HOMO (developing σ C–Nu bond) and LUMO (σ* C–X) which they were able to confirm using theoretical studies. Furthermore, they were also able to incorporate the Bürgi-Dunitz angle into their model which revealed that there would ultimately be a build-up of steric hinderance between the incoming nucleophile and staggered alpha substituents. Therefore, two conformations of α-chiral carbonyl can be considered (**7**, **8**). Conformation **7** is ultimately more reactive to nucleophilic attack as it minimizes steric interactions between the incoming nucleophile and smaller R substituent. These additions to Felkin's original report would culminate in the polar Felkin-Anh model, which in parallel to the Cornforth model, describes nucleophilic additions to carbonyls with polar α-substituents.

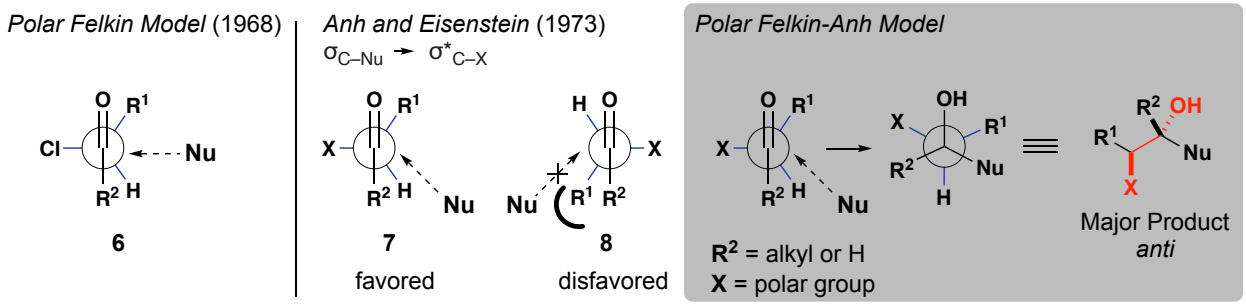


Figure 7. The polar Felkin and polar Felkin-Anh model describing nucleophilic additions to α-chiral carbonyls.

As both the Cornforth model and polar-Felkin-Anh model predicted for the same stereochemical outcome for nucleophilic additions to carbonyls with polar alpha substituents, it was a considerable challenge to distinguish between the two models from diastereoselectivity alone. Hoffmann,[12] and Evans[13 14] independently conducted impactful studies to examine the difference between the two models experimentally. They came to the conclusion that reactions run with nucleophiles bearing differentially substituted sp^2 carbon centers (such as crotylsilanes) adhered more closely to the Cornforth model rather than the polar Felkin-Anh model. Prior to these studies, the scientific community seemed to have placed a larger preference for utilizing the polar Felkin-Anh model over the Cornforth model. But due to these efforts, it has become clear that the Cornforth model is still an applicable model in certain cases and should not be ruled out when predicting stereoselectivity of nucleophilic additions to α-chiral carbonyls.

1.1.1.3 The Cram Chelation Model

The Cram chelation model describes a preorganization of the carbonyl electrophile with a chelateable Lewis acid, forming a metallocycle or chelate resembling **9** (Figure 8). [7 15] As the chelate locks the electrophile into a rigid conformation, the major product results from nucleophilic attack to the least sterically hindered side of the chelate ring. The magnitude of selectivity is typically high relative to that of selectivities predicted by conformationally free models such as the Cornforth and polar Felkin-Anh models. The Cram chelation model is applicable only in cases where the electrophile contains at least two Lewis basic sites (one of them being the carbonyl). It has been demonstrated that

electrophiles with Lewis basic substituents with sufficiently bulky and electron-withdrawing substituents (such as silyl-protected alcohols) are less prone to chelation with a Lewis acid.[16] In the absence of chelation, one expects little selectivity or selectivity for the other diastereomer (as predicted by the Cornforth or polar Felkin-Anh models).

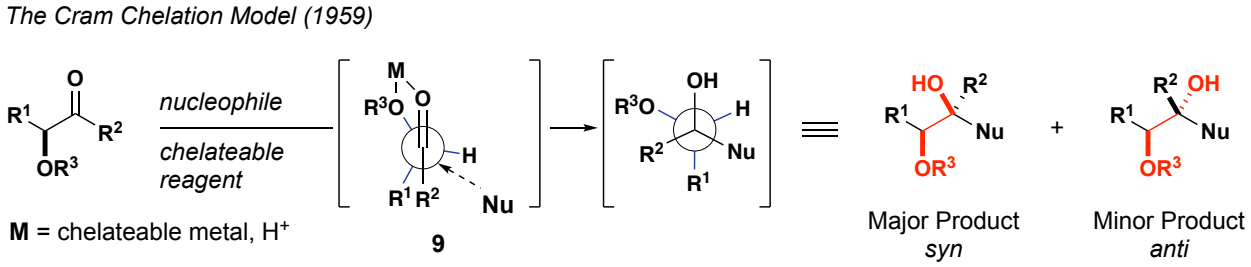


Figure 8. The Cram chelation model describing nucleophilic additions to α-chiral carbonyls.

Over the years, researchers have largely used the stereochemical outcomes of their experiments to guide whether or not chelation would be present under reaction conditions. In other words, the presence of an anti-Felkin or *syn* product is strongly associated with the presence of a chelateable reagent. Many instances of *syn* selectivity have been reported without an obvious chelateable reagent. A subset of these examples can be attributed to potential proton-chelation instead. As proton-activation of a carbonyl can occur catalytically, it is often times difficult to completely shut down chelation even when chelateable metals and Lewis acids are not used. For example, BF_3•OEt_2 and TMSOTf are common “non-chelateable” Lewis acids used in nucleophilic addition reactions to carbonyl compounds due to the presumed presence of only a single coordination site . However, both reagents are prone to hydrolysis, the byproducts of which can instead act as Brønsted acids. A small presence of Brønsted acid may have pronounced effects on the diastereoselectivity observed and therefore caution should

always be exercised when assessing the propensity for proton-chelation to impact reaction design and planning.

1.1.1.4 Models, A Summary

To a synthetic organic chemist, stereoelectronic models are the bedrock of our *understanding* of stereoselectivity and our ability to successfully *predict* stereochemical outcomes. Models by definition are imperfect, and as this part of the chapter has established, a model once proposed is a model that will one day fail and change. As my undergraduate research advisor would say, “models work until they don’t”. However, this should not discourage efforts in constructing models and revising and revisiting old ones. To establish a model is to learn how to break down reactions to smaller and smaller qualifiable interactions. The act of doing so allows the development of the requisite experiments to test the reaction’s sensitivity to those interactions. Furthermore, it sharpens the chemist’s instincts and enables one to scrutinize every reaction through the consideration of those interactions. Then, one can think further on how to exploit the qualified interactions to achieve one’s synthetic means. A common theme in my thesis research is how to navigate along this exact sequence of events. Through continuous iterations of establishing new models and revising old ones, we get closer to chemical truth.

1.1.2 Overview of 1,2-Asymmetric Induction in Nucleophilic Additions to α-Chiral Imines

Nucleophilic additions to α-chiral imines are precedented. Reports have been published describing stereoselective nucleophilic additions to α-chiral *N*-alkyl, -aryl, -silyl and -carbamoyl aldehyde derived imines. The electronic nature of the *N*-substituent dictates the overall electrophilicity of the imine itself, therefore informing the scope of nucleophiles employed in the reaction. Imines with electron-donating *N*-substituents such as alkyl and aryl groups react best with anionic nucleophiles such as Grignard and alkyl-lithium reagents. Imines bearing electron-withdrawing groups as the *N*-substituent can react with soft nucleophiles in the presence of Lewis acids or Brønsted acids. The identity and stereochemistry of the α-carbon and its substituents, as expected, dictate the preference and magnitude of selectivity. Common obstacles to methodologies exploring nucleophilic additions to α-chiral imines involve imine reactivity, epimerization of the alpha carbon due to competing enamine formation, and even the isolation or synthesis of the imine substrate itself. To get around the latter issue, imines can often be formed *in situ* (through condensation of aldehyde and amine) and nucleophilic addition can occur under multi-component reaction conditions. In this section, an overview of the scope of nucleophilic additions to α-chiral imines will be discussed that are relevant to the project. This section will be organized by *N*-substituent, then *syn* and *anti*-selective reactions (and their rationalizations) will be discussed.

1.1.2.1 Additions to α-Chiral *N*-Alkyl and *N*-Aryl Imines

The vast majority of nucleophilic additions to *N*-alkyl and *N*-aryl imines result in the *syn* product regardless of nucleophile employed (Figure 9).[17-41] The types of nucleophiles

used in additions to *N*-alkyl and *N*-aryl imines are typically organometallic reagents. Due to the high nucleophilicities of these reagents, many reactions can occur in the absence of an additional Lewis acid mediator. The Lewis basic α-substituent is usually an alkoxy group, but can also be a protected amine group or silyloxy group. Generally, the highest *syn*-selectivities are observed with alkoxy α-substituents. Even in the absence of an external Lewis acid, many organometallic nucleophiles (such as alkyl-titanium reagents) may serve as mediators *and* chelateable reagents in their own right, resulting in the observed chelate-derived *syn*-selectivities. Reactions with alkyl-tin reagents, Grignard reagents and TMSCN can be sensitive to external Lewis acids used in the reaction. Overall, there are a variety of ways to optimize addition reactions to *N*-alkyl and *N*-aryl imines to achieve high *syn*-selectivity.

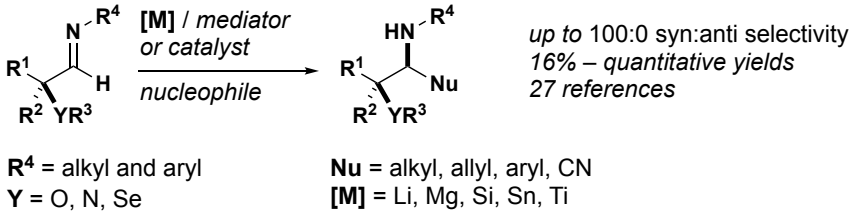


Figure 9. Nucleophilic additions to *N*-alkyl and -aryl α-chiral imines.

Anti-selectivity in nucleophilic additions to *N*-alkyl and *N*-aryl imines is rare but can be observed in substrates bearing multiple Lewis-basic substituents (such as α- and β-alkoxy imines resembling **10** and **11**) (Figure 10).[18-22] Grignard addition to *N*-benzyl imine **10** results in predominantly *anti*-product. However, this *anti*-selectivity is not always reliable as the same Grignard addition to imine **11** results in predominantly *syn*-product. Reports of *anti*-selective nucleophilic additions to *N*-alkyl and *N*-aryl imines are not

accompanied by any rationalization of the observed selectivities. Therefore, it is difficult to propose one without more experimental evidence. One can reasonably conclude that the presence of other β-Lewis basic groups may interfere with the formation and presence of the five membered ring chelate (formed by Lewis acid association to the α-Lewis basic site) one would expect from the canonical Cram-chelation model, resulting in aberrant selectivity.

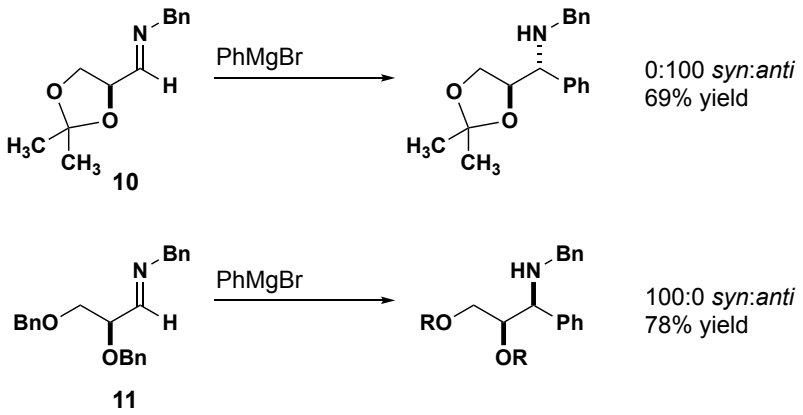


Figure 10. Divergent stereoselectivity in *N*-alkyl α,β-alkoxy imines.

While there are many reported nucleophilic additions to *N*-alkyl and *N*-aryl imines, there are major drawbacks to their utility in organic synthesis. One major drawback of using *N*-alkyl and *N*-aryl imines in reactions of this type is their lack of versatility (i.e. it is difficult to remove an alkyl or aryl group from a nitrogen). Another drawback is that full acyclic stereocontrol has not been achieved in the case of *N*-alkyl and *N*-aryl imines as *anti*-selective examples are rare and limited to certain substrates. Nevertheless, the nucleophilic scope of nucleophilic additions to *N*-alkyl and *N*-aryl imines is impressive, especially when compared to other *N*-substituted imines.

1.1.2.2 Additions to α-Chiral *N*-Silyl Imines

Similar to *N*-alkyl and *N*-aryl imines, *N*-silyl imines are reported to undergo nucleophilic substitution in the presence of organometallic reagents. Of the examples reported, only *O*-alkyl,[23, 24, 42] *O*-silyl [43 42 44] and *N*-alkyl [45] α-substituents were explored. Lewis acid activation is not always necessary. Reports of nucleophilic additions to *N*-silyl imines show that selectivity is variable (Figure 11). Ultimately, the highest levels of *syn* selectivity were observed with Grignard reagents or alkyl-lithium reagents. Reactions performed with Lewis acids did not show differing selectivities compared with reactions run without Lewis acids, demonstrating that a Lewis acid is not always necessary in nucleophilic reactions of this type. The Cram-chelation model was invoked to rationalize the *syn* selectivity observed in these cases. Conversely, allyl-Grignard additions to *N*-silyl imines led consistently to predominantly *anti*-products, even in the presence of chelateable Lewis acids (such as $ZnBr_2$). This *anti*-selectivity was never clearly rationalized by the reports studying these reactions, but was found to be consistent regardless of minor changes to substrate, temperature and solvents used.

Cainelli (1991, 1995)

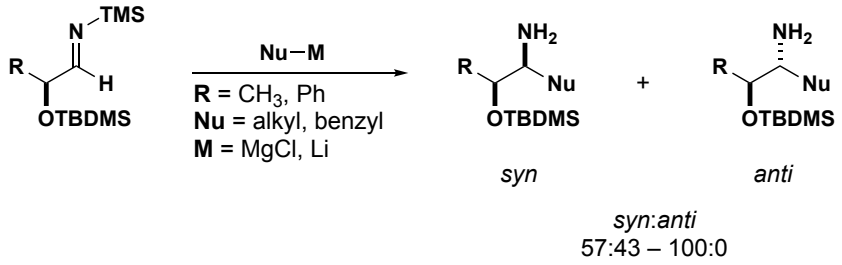


Figure 11. Nucleophilic additions to *N*-Si α-chiral imines.

While the number of studies showcasing *N*-silyl imines are few, there are some major benefits of incorporating *N*-silyl imines to a synthesis. One of the benefits of using *N*-silyl imines is that facile removal of the *N*-silyl group can occur during the work up of the addition reaction, leading to free amine products in one step after nucleophilic addition occurs. Based on the limited reports using alkyl and allyl-based nucleophiles, some degree of acyclic stereocontrol with *N*-silyl imines is possible.

1.1.2.3 Additions to α-Chiral *N*-Carbamoyl Imines

There are seven reported examples of stereoselective nucleophilic additions to α-chiral *N*-carbamoyl imines (Figure 12).[44, 46 47-51] The electron-withdrawing nature of the carbamate group on the imine render them reactive to nucleophilic additions by softer nucleophiles such as allylsilanes (in the presence of a Lewis acid). Anionic nucleophiles such as allyl-zinc reagents and enolates can add to *N*-carbamoyl imines in the absence of an external Lewis acid. The bulk of reactions with *N*-carbamoyl imines lean *syn*-selective. *Anti*-selective reactions have been reported in specific cases. Like *N*-silyl imines, *N*-carbamoyl imines are usually generated *in situ* prior to nucleophilic addition or generated through multi-component reaction conditions (involving the mixture of aldehyde precursor, amine and nucleophile in one pot). The synthetic utility of the addition products themselves is quite high as carbamoyl groups can be easily removed under mild conditions.

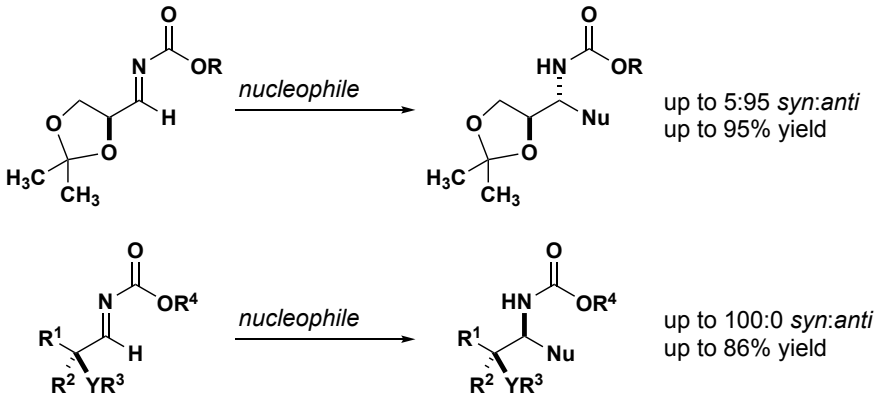


Figure 12. Nucleophilic additions to *N*-carbamoyl α-chiral imines.

1.1.2.4 Additions to α-Chiral *N*-Sulfonyl Imines

Nucleophilic additions to *N*-sulfonyl imines are precedented and there are a handful of reports that assess the diastereoselectivity of these reactions.[34, 45, 52-54 55, 56] Reetz and Walsh reported that nucleophilic additions to α-*N*-benzyl substituted imines were generally *anti*-selective for a variety of nucleophiles employed (Figure 13A). This set *N*-sulfonyl imines apart from the other chiral imines that were discussed in this section, and made them attractive substrates to study due to their unusual reactivity. Recent reports by Marek have also shown that *syn*-selectivity is possible through the utility of allyl-zinc reagents with α-chloro imines and unexpectedly, in the base-mediated anhydride Mannich reaction (AMR) published by our group with α-alkoxy and α-*N*-H-Cbz *N*-tosyl imines (Figure 13B). In the latter example, the absence of an obvious chelate-able reagent made it difficult to rationalize the high *syn*-selectivities observed. Nonetheless, *syn*-selectivity in α-chiral *N*-tosyl imines seemed more elusive than *anti*-selectivity as a whole. The selectivity-trends surrounding α-chiral *N*-sulfonyl imines are

the most difficult to rationalize given the stereoelectronic models proposed for α-chiral aldehydes. Therefore, they provide an interesting model-system to explore and perhaps the investigation of *N*-sulfonyl imines could lead to new stereoelectronic models.

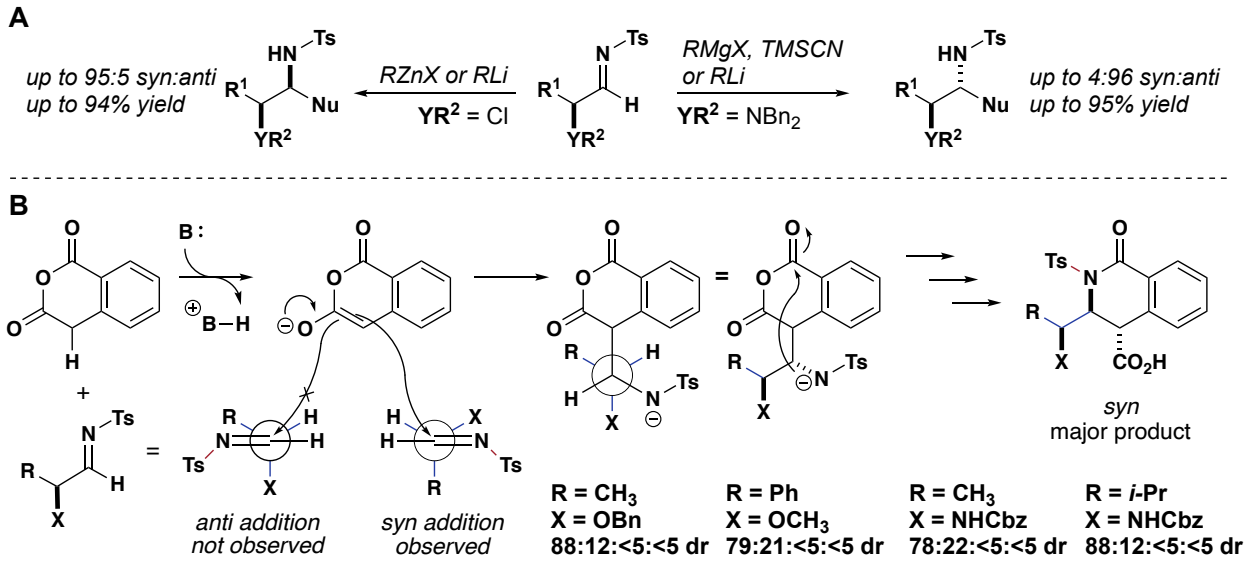


Figure 13. A) Nucleophilic additions to *N*-sulfonyl α-chiral imines. B) Unexpected *syn*-selectivity in base-mediated AMR.

1.2 Acyclic Stereocontrol in Nucleophilic Additions to α-Chiral *N*-Sulfonyl Aldimines

The Shaw group's interest in establishing acyclic stereocontrol in nucleophilic additions to α-chiral *N*-sulfonyl imines was sparked by the unexpected selectivity observed in the base-mediated AMR of *N*-sulfonyl imine and homophthalic anhydride. In the absence of an obvious chelateable reagent, high *syn*-selectivity was observed. Faced with this unexplained selectivity preference as well as the lack of overall studies focused

on acyclic stereocontrol in α-chiral *N*-sulfonyl imines, we set out to develop conditions that would allow predictive access to both *syn* and *anti*-addition products. Establishment of acyclic stereocontrol in this case will allow for more streamlined synthetic planning of stereochemically complex nitrogen-containing targets.

1.2.1 Substrate Synthesis

To probe the atypical selectivity exhibited in previous work, imines **18** and **19** were selected as model systems for optimization studies due to their synthetic accessibility and complementary structures (Figure 14). The α-chiral aldehydes **16a** and **16b** were synthesized from (-) ethyl-L-lactate and (+)-L-mandelic acid and then converted to *N*-tosyl imines via amidosulfones **17a** and **17b**. Methyl- and phenyl-substitution at the alpha position allowed for direct comparison of selectivity trends as steric bulk increased vicinal to the reactive center.

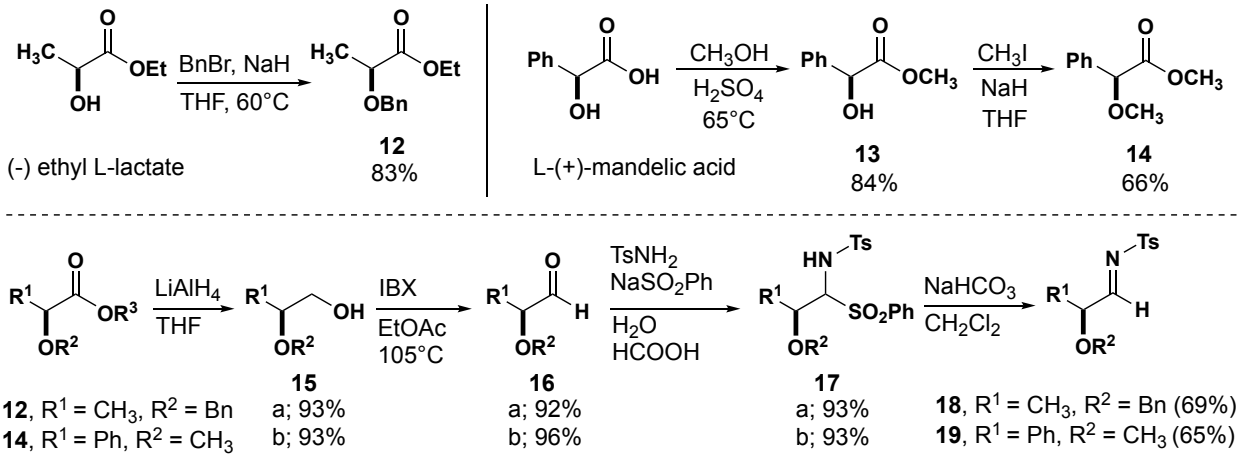


Figure 14. Representative routes for substrate synthesis.

While there are other methods of synthesizing imines from aldehydes, we chose the above method involving the isolation of an amidosulfone precursor because amidosulfones could be stored as chalky solids for long periods of time without significant decomposition. Additionally, the conversion of amidosulfone to imine is relatively facile. Procedurally, amidosulfone can be dissolved in dichloromethane and shaken with saturated aqueous sodium bicarbonate for one minute. Once the layers are separated and the organic layer is concentrated *in vacuo*, imine can be procured and used the same day with no need for further purification. α-Chiral aldimines themselves are difficult to store for long periods of time as they are prone to hydrolysis or enamine formation. Therefore, experiments using aldimines were carried out the typically the same day they were produced.

Optimized reaction conditions were later applied to other α-chiral imine substrates that were accessed in a similar fashion to imines **18** and **19** (Figure 15). All imines were derived from their analogous aldehyde precursors through an amidosulfone intermediate. The aldehydes themselves were typically synthesized from commercially available alpha chiral carboxylic acid derivatives using literature precedented procedures. Of the imines that were successfully synthesized, four were used in the published study. Several imines that were mechanistically interesting or synthetically valuable such as imines **23–25** could not be isolated using our synthetic route. The amidosulfone precursors to imines **23**–**25** could not be accessed through our protocol.

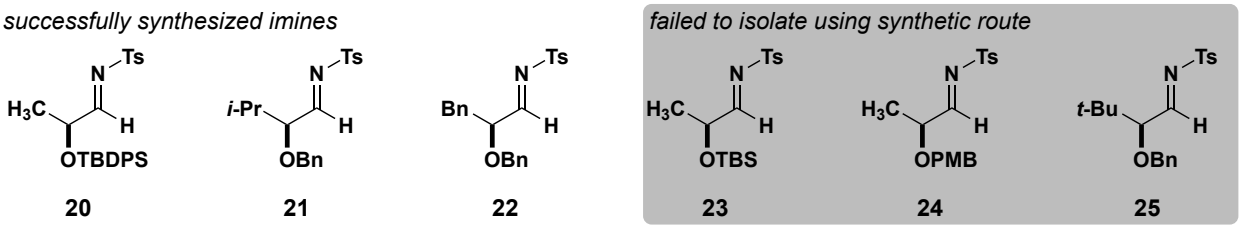
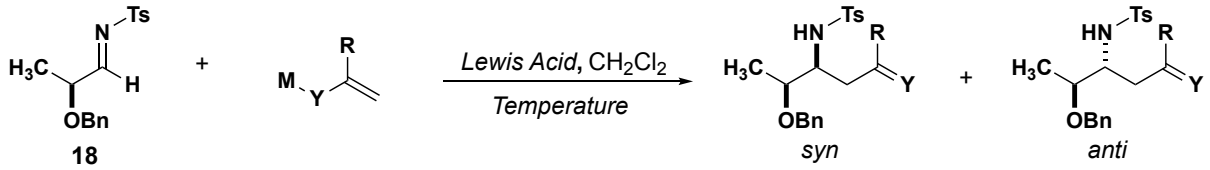


Figure 15. Imines synthesized (and attempted to be synthesized) from synthetic route.

1.2.2 Optimization of *Syn* selective Reaction Conditions

Optimization of *syn*-selective reaction conditions was achieve through an extensive Lewis acid screen with model imine **18** (Table 1). In the screen, several Lewis acids were used in nucleophilic addition reactions involving imine **18** and either allyltrimethylsilane or the silyl enol ether of acetophenone. These nucleophilic alkenes were selected as they led to homoallylic amines or ketone products which could serve as functional handles for subsequent reactions. Furthermore, these two nucleophiles represented different nucleophilicities according to Mayr, ensuring that the optimized reaction conditions will be general for a variety of nucleophiles, strong or weak.

Table 1. Lewis acid screen on imine **18**.



Entry[a]	R	Y	M	Lewis Acid	Temperature[b]	*syn*:*anti*[c]	NMR yield[d] (%)	
1	H	CH_2	TMS	$ZnBr_2$	–78	94:6	90	*syn-selective*
2	H	CH_2	TMS	$ZnBr_2$	23	96:4	82	
3	H	CH_2	TMS	$FeCl_3$	0	80:20	48	
4	H	CH_2	TMS	$ZnCl_2$	0	80:20	85	
5	H	CH_2	TMS	$AlCl_3$	0	80:20	—	
6	H	CH_2	TMS	$AlCl_3$	–78	77:23	93*	
7	H	CH_2	TMS	BF_3•OEt_2	–78	67:33	88*	
8	H	CH_2	TMS	$Sc(OTf)_3$	0	62:38	91	
9	H	CH_2	TMS	BF_3•OEt_2	0	56:44	—	
10	H	CH_2	TMS	$La(OTf)_3$	–78	48:52	67	
11	H	CH_2	TMS	$In(OTf)_3$	23	41:59	56	
12	H	CH_2	TMS	$Cu(OTf)_2$	0	36:64	86	
13	H	CH_2	TMS	$Mg(OTf)_2$	23	31:69	71	
14	H	CH_2	TMS	$MgBr_2$	23	—	—	
15	H	CH_2	TMS	$Zn(OTf)_2$	23	—	—	
16	Ph	O	TMS	$ZnBr_2$	–78	100:0	—	
17	Ph	O	TMS	$AlCl_3$	–78	100:0	—	
18	Ph	O	TMS	BF_3•OEt_2	–78	75:25	53	
19	Ph	O	TMS	$TiCl_4$	–78 to 23	—	—	
20	H	CH_2	$SnBu_3$	TMSOTf	–78 to 23	85:15	n.d.	
21	H	CH_2	$SnBu_3$	TMSOTf	–78 to 23	—	n.d.	
22	H	CH_2	$SnBu_3$	TfOH (10 mol%)	–78 to 23	85:15	n.d.	

[a] Reactions run with 1.1 equiv. of Lewis acid and 1.5 equiv. of nucleophile.
[b] Reactions monitored by TLC and warmed to drive to completion within a uniform time-frame.
[c] Determined by integration of unpurified ^1H NMR.
[d] Determined using 1,3,5 trimethylbenzene as an internal standard.

Most of the Lewis acids screened for these reactions resulted in predominantly the *syn* diastereomer of product. Reactions with $ZnBr_2$ were notable in their ability to consistently lead to *syn*-products in high selectivities and clean conversion (Table 1, entries 1, 2 and 16). Reactions run with BF_3•OEt_2, a non-chelateable Lewis acid, surprisingly also gave modest amounts of *syn* selectivity (entries 7, 9 and 18). Reactions run with $MgBr_2$, $Zn(OTf)_2$ and $TiCl_4$ would fail to give product and typically resulted in uninterpretable NMRs of the crude reaction mixture (entries 14, 15 and 19). From these

results, we concluded that $ZnBr_2$ would be the optimal Lewis acid used in *syn*-selective nucleophilic addition reactions moving forward. Temperatures of these reactions would be kept as low as possible to favor higher conversions without compromising selectivity.

1.2.3 Optimization of *Anti* selective Reaction Conditions

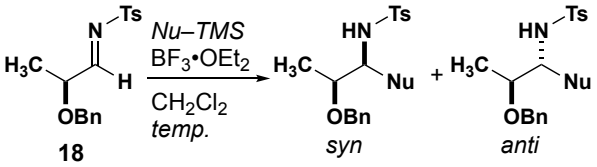
Compared to optimization of *syn*-selective reaction conditions, optimization of highly *anti*-selective reaction conditions proved more difficult to achieve. Known non-chelateable Lewis acids are fewer in number than chelateable Lewis acids. Our Lewis acid screen already demonstrated that reactions run with commonly used non-chelateable Lewis acid $BF_3{\bullet}OEt_2$ gave preferably *syn*-selectivity (or was otherwise unselective). Reactions run with TMSOTf, another commonly used non-chelateable Lewis acid also gave high *syn*-selectivity (Table 1, entry 20). This selectivity was later investigated through proton-scavenger experiments with 2,6 ditert-butylpyridine which resulted in no reaction (Table 1, entry 21). This experiment suggested that reactions with TMSOTf were Brønsted acid mediated through trace TfOH which may result from hydrolysis of TMSOTf. In the presence of a Brønsted acid, α-chiral imines such as **18** can chelate with a proton. The resulting selectivity would be chelate-derived, or *syn*, as in the case with the products of other reactions run with chelateable Lewis acids. The ability of a proton to chelate is not unprecedented and as Brønsted acid mediated reactions can occur catalytically, i.e. even a small amount of Brønsted acid could interfere with the selectivity of a reaction that is meant to be Lewis acid mediated. All of these factors made the optimization of *anti*-selective reaction conditions a complex endeavor.[51]

1.2.3.1 Temperature Effects of BF3•OEt2 Mediated Reactions

Our initial Lewis Acid screen revealed sensitivity of BF3•OEt2 mediated reactions to temperature (Table 1, entry 7 and 9). More reactions were run with imines **18** and **19** with allyltrimethylsilane, methallyltrimethylsilane and silyl enol ether of acetophenone to further explore temperature effects (Table 2A and 2B). The selectivities collected from these experiments show an upward trend in *anti*-selectivity with higher temperatures. While one expects subtle variances in selectivity due to temperature changes, the large swings in selectivity, and sometimes complete inversion of selectivity observed from –78 to room temperature suggest that there may be major changes in mechanism between reactions run at lower temperatures and reactions run at higher temperatures.

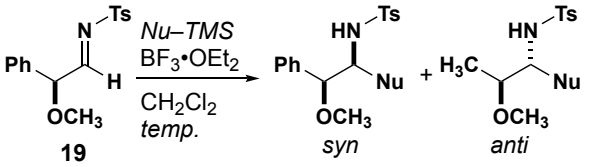
Table 2. Temperature effects on nucleophilic reactions with BF_3•OEt_2 on imines **18** and **19**.

A

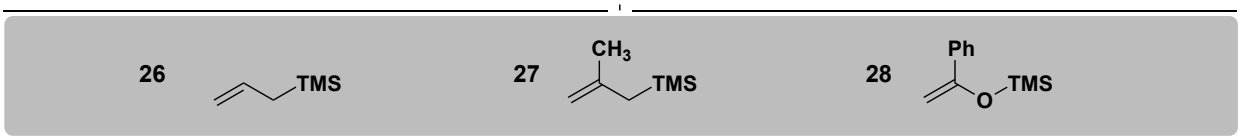


Entry	Nu	temp. (°C)	*syn*:*anti*
1	**26**	–78	67:33
2	**26**	23	56:44
3	**27**	–78	63:37
4	**27**	23	19:81
5	**28**	–78	55:45
6	**28**	23	20:80

B



Entry	Nu	temp. (°C)	*syn*:*anti*
1	**26**	–78	69:31
2	**26**	23	53:47
3	**27**	–78	40:60
4	**27**	23	21:79
5	**28**	–78	52:48
6	**28**	23	32:68

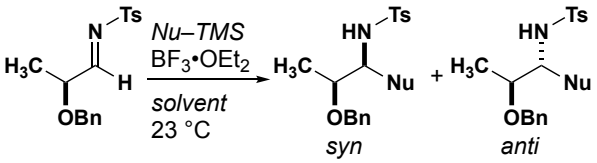


1.2.3.2 Solvent Effects of BF_3•OEt_2-Mediated Reactions

Next, we considered solvent effects by running nucleophilic addition reactions with BF_3•OEt_2 with a variety of solvents (Table 3A and 3B). Chloroform, toluene, acetonitrile, diethyl ether and *n*-hexane were chosen due to their range of properties such as polarity and Lewis basicity. Solvent screens revealed that reactions run in toluene and chloroform gave higher *anti*-selectivity than reactions run in other solvents. While chloroform and toluene have little in common as far as chemical properties, this selectivity was consistent across two imines and two nucleophiles. Reactions run in acetonitrile conversely gave better *syn*-selectivity than other solvents.

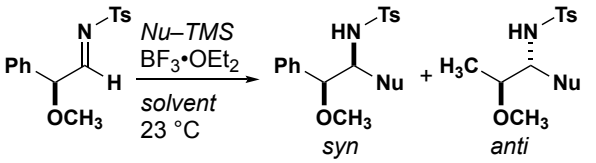
Table 3. Solvent effects (and their dielectric constants, epsilon or ε) on nucleophilic reactions with BF_3•OEt_2 on imines **18** and **19**.

A



Entry	Nu	solvent	*syn*:*anti*
1	**26**	$CHCl_3$	39:61
2	**26**	$PhCH_3$	38:62
3	**26**	CH_3CN	68:32
4	**26**	Et_2O	65:35
5	**26**	*n*-hexane	64:36
6	**27**	$CHCl_3$	29:71
7	**27**	$PhCH_3$	47:53
8	**27**	CH_3CN	53:47
9	**27**	Et_2O	65:35
10	**27**	*n*-hexane	—

B



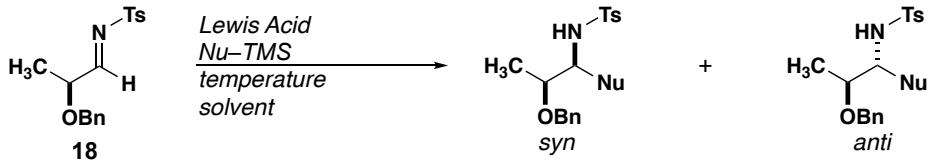
Entry	Nu	solvent	*syn*:*anti*
1	**26**	$CHCl_3$	38:62
2	**26**	$PhCH_3$	48:52
3	**26**	CH_3CN	91:9
4	**26**	Et_2O	—
5	**26**	*n*-hexane	—
6	**27**	$CHCl_3$	14:86
7	**27**	$PhCH_3$	17:83
8	**27**	CH_3CN	87:13
9	**27**	Et_2O	—
10	**27**	*n*-hexane	—

1.2.3.3 Highly *Anti*-selective reactions run with $Cu(OTf)_2$ and BF_3•OEt_2

We continued with our efforts to reach synthetically useful amounts of *anti*-selectivity in nucleophilic addition reactions of α-chiral *N*-sulfonyl imines by exploring reactions run with $Cu(OTf)_2$ (Table 4). $Cu(OTf)_2$ previously gave encouraging levels of *anti*-selectivity in our Lewis acid screens. Reactions with $Cu(OTf)_2$, toluene at room temperature gave 80:20 selectivity for the *anti*-product (Table 1, entry 2). Unfortunately, these conditions were not generalizable to other nucleophiles such as methallyltrimethylsilane **27** and silyl enol ether of acetophenone **28** (Table 4, entry 3, 4, 5).

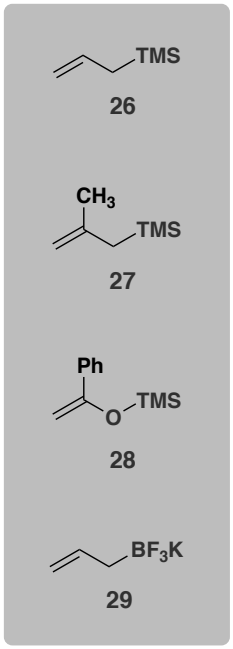
Through temperature and solvent screens, we felt that we had reached the limit of selectivity that BF_3•OEt_2 could provide. By further manipulating temperature effects, we arrived at the highest *anti*-selective diastereomeric ratio yet for the project (Table 4, entry 6). While reactions run at –20 degrees in chloroform with BF_3•OEt_2 worked well with nucleophiles **27** and **28**, diastereomeric ratios for allylations still proved lacking. A major breakthrough in the project was finally reached when we switched allylating reagents from allyltrimethylsilane **27** to a potassium allyltrifluoroborate salt **29** (Table 4, entry 9). This gave us superior *anti*-selectivity for allylation reactions in particular. Subsequent addition reactions were run with 18-crown-6 to maximize solubility of the allylating reagent and thus, yield. With this breakthrough, we were finally able to settle on BF_3•OEt_2 reactions run in chloroform at –20 °C as the optimal conditions for *anti*-selective nucleophilic addition reactions to *N*-tosyl imines.

Table 4. Optimization of *anti*-selectivity on imines **18**.



entry	Lewis acid	nucleophile	solvent	temp (°C)	*syn*:*anti*[a]
1	$Cu(OTf)_2$	**26**	$PhCH_3$	–20	32:63
2	$Cu(OTf)_2$	**26**	$PhCH_3$	23	20:80
3	$Cu(OTf)_2$	**27**	$PhCH_3$	23	60:40
4	$Cu(OTf)_2$	**28**	$PhCH_3$	23	71:29
5	$Cu(OTf)_2$	**28**	CH_2Cl_2	23	88:12
6	BF_3•OEt_2	**28**	$CHCl_3$	–20	< 05:95
7	BF_3•OEt_2	**27**	$CHCl_3$	–20	10:90
8	BF_3•OEt_2	**26**	$CHCl_3$	–20	30:70
9	BF_3•OEt_2	**29**	$CHCl_3$	–20	11:89

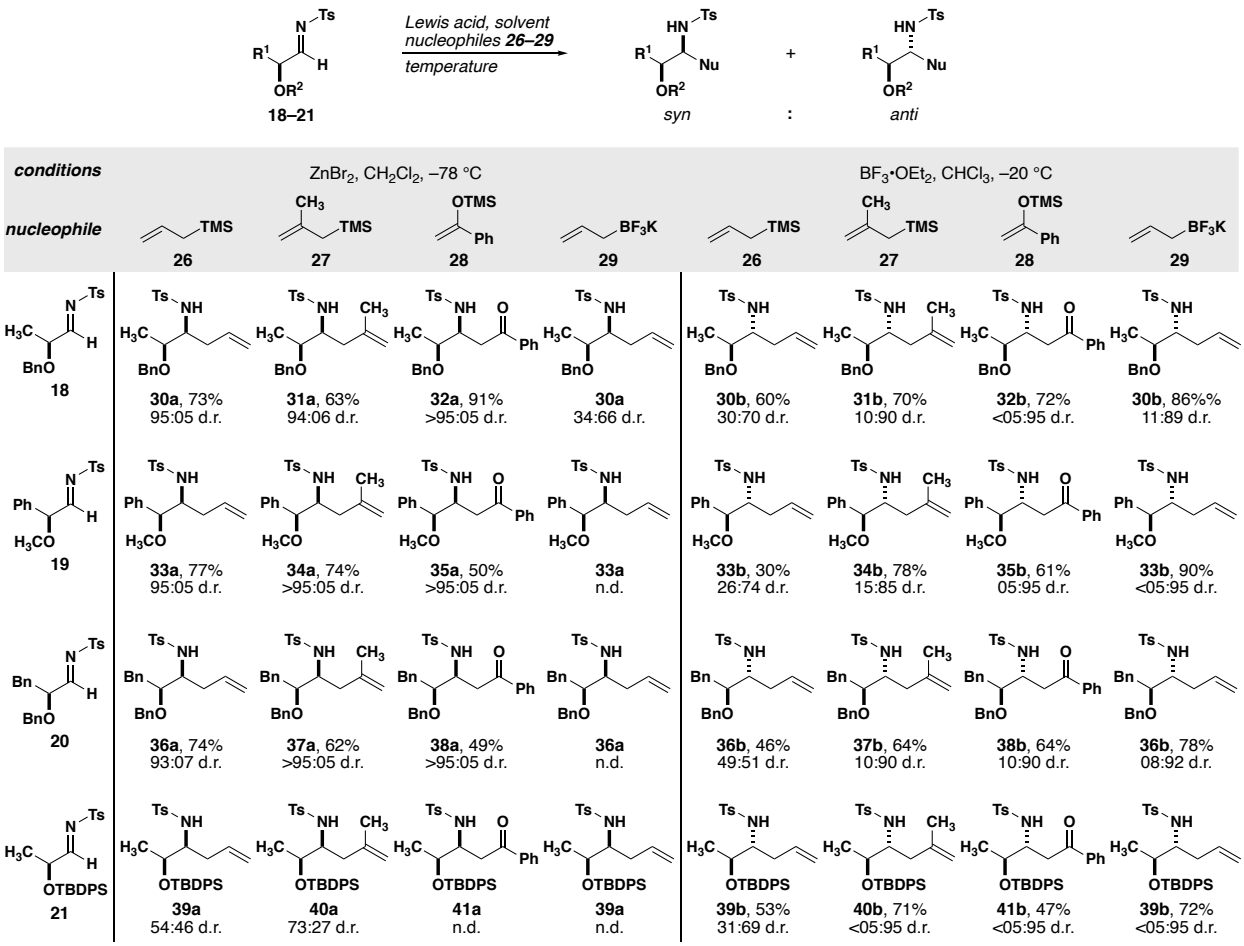
[a] *syn*:*anti* ratios determined by integration of ^1H NMR spectra of unpurified reaction mixtures



1.2.4 Substrate Scope

Through extensive reaction optimization, two sets of generalizable conditions were developed for stereoselective nucleophilic additions to α-chiral *N*-sulfonyl imines (Table 5). Imines **18–21** all led to addition products using the optimized reaction conditions. Reactions with $ZnBr_2$ in dichloromethane run at –78 °C led to *syn*-selectivities of up to >95:05 diastereomeric ratios for a variety of imines and nucleophiles. Conversely, reactions run with BF_3•OEt_2 in chloroform at –20 °C led to comparably high levels of *anti*-selectivity. *Anti*-selectivity of allylation reactions can be improved by switching to potassium allyltrifluoroborate as the allylating reagent.

Table 5. Acyclic stereocontrol in α-chiral *N*-tosyl imines.



Imines **18** and **21** show how alpha substituents can be manipulated in order to achieve specific stereochemical outcomes. α-Alkoxy imines like imine **18** can easily lead to high levels of *syn*-selectivity using the conditions reported. On the other hand, $ZnBr_2$ reactions run with α-silyloxy imine **21** result in poor *syn* selectivity. This was expected, as silyloxy substituents are poor Lewis bases and less likely to chelate. α-Silyloxy substituted imine **21** performs better in *anti*-selective reactions, however, and lead to significantly higher levels of *anti*-selectivity under reported conditions when nucleophile **29** is used. The optimal substrates for *syn*-selective nucleophilic additions are α-alkoxy substrates and the optimal substrates for *anti*-selective nucleophilic additions are α-silyloxy

substrates. Notably, benzyloxy and silyloxy α-substituents in addition products can later be removed using established chemistry, making their specific presences inconsequential in the context of a synthetic route.

1.2.5 Discussion of Reaction Mechanism

Throughout this project, the Shaw group worked tightly with the Houk group (University of California, Los Angeles) to elucidate the mechanistic origins of observed selectivities. Any experimental observation of interest and hypothesis developed to rationalize selectivities were computationally explored using DFT methods by Dr. Jason Fell, a former graduate student in the Houk group. Together, we sought to use experimental and computational methods to establish a predictive stereoelectronic model (akin to the Cram chelation model or polar-Felkin Anh model) that would describe nucleophilic additions to α-chiral imines.

Syn-selective reactions run with $ZnBr_2$ and Bronsted acid, were computationally explored. Fell determined the binding affinity of $ZnBr_2$ to imine **18** using DFT methods and the B3LYP[57, 58] functional. Geometry optimizations were performed with the 6-31(d) basis set. The LANL2DZ[59] pseudopotentials were utilized for heavier elements such as Zn and Br. These computational parameters have been previously reported to adequately describe similar systems.[60 61] Fell found chelate structures of truncated-imine **18** with a favorable energy of binding for both $ZnBr_2$ and proton (Figure 16). The presence of these chelates are most likely responsible for the *syn*-selectivites observed with reactions run with $ZnBr_2$ and TMSOTf. Furthermore, comparisons of binding energies of **43** and **44**

show that proton chelation is more energetically likely in the case of *N*-Ts imines compared to aldehydes. Nucleophilic addition likely proceeds through the Cram-chelation model to produce *syn*-addition products on such chelates.

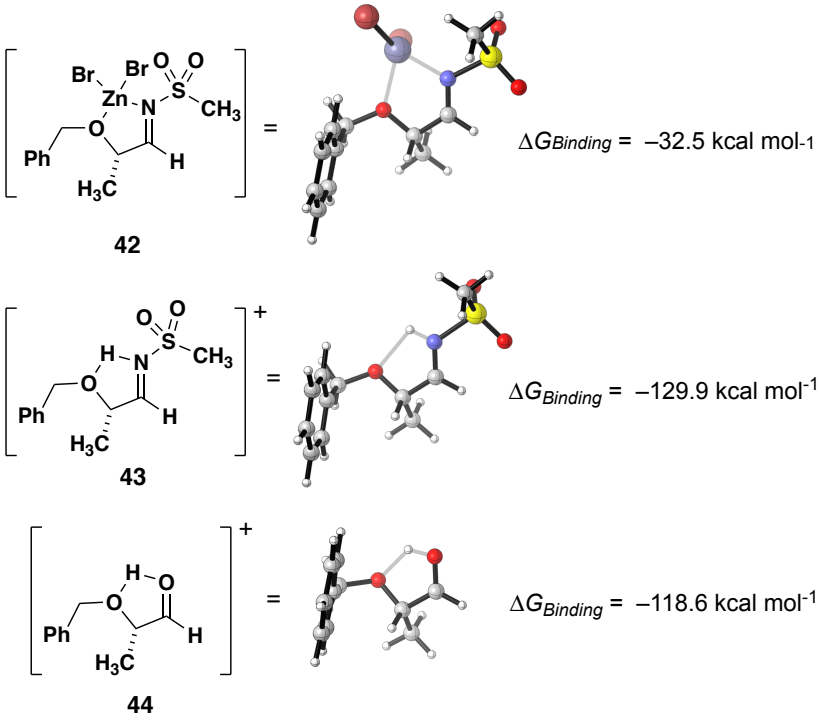


Figure 16. Binding affinities for $ZnBr_2$ and H^+ on truncated imine and aldehyde.

Anti-selective reactions run with BF_3•OEt_2 were also computationally examined by Fell. Compared to *syn*-selectivity, which is typically and reliably achieved through the presence of a chelate, *anti*-selectivity was less straight-forward to explain. Literature precedent and the variable selectivities we observed with BF_3•OEt_2 in our studies suggested to us that there were a variety of reactive intermediates that could be in play. Fell's computational results confirmed these suspicions as he found three reactive intermediates that were all energetically accessible from one another (less than 3 kcal/mol) at various temperatures (Figure 17). Reactive intermediate **45** is the most traditional of the three, arising from coordination of BF_3 to the nitrogen of the imine. The

conformational preferences of this intermediate in the transition-state structure of nucleophilic addition would ultimately determine the selectivity preference of the products. Reactive intermediate **47** is characterized by a second molecule of BF_3 potentially bound to the alpha alkoxy substituent of the imine. Reetz had proposed a reactive intermediate similar to **47** in their investigations of nucleophilic additions to beta alkoxy imines. Finally, the last and most unexpected intermediate was that of **46**, a BF_2 chelate that could potentially result from the disproportionation of **45** and a second molecule of BF_3 to furnish BF_4^- and **46**. The possibility of reactive intermediate **46** is enlightening as it is likely an intermediate that would lead to *syn*-products through the Cram-chelation model.

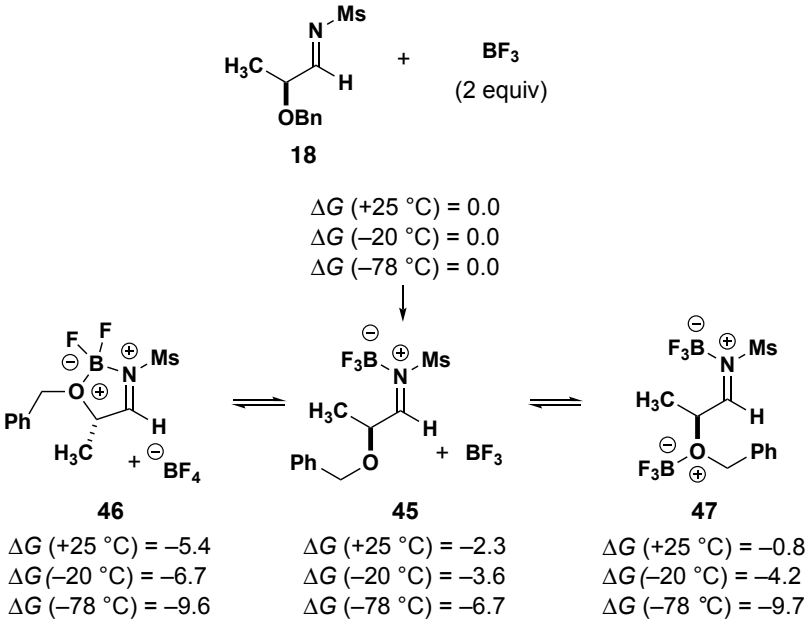
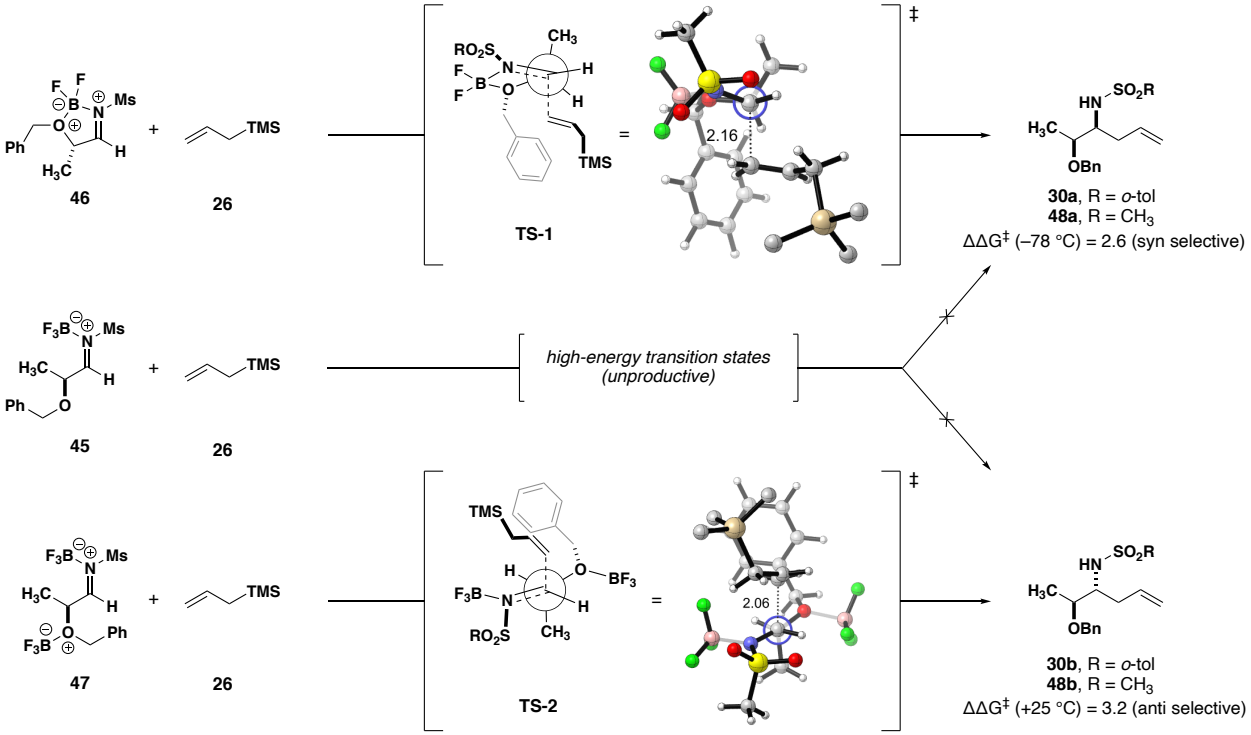


Figure 17. Possible reactive intermediates in BF_3 mediated nucleophilic addition reactions to *N*-Ts imines.

As all three reactive intermediates were relatively close to one another in energy, we would need to calculate transition state structures if we want to determine the reactive intermediate that most likely led to the products we observed. Dr. Fell was able to find

productive transition state structures for only intermediates **46** and **47**. Surprisingly, reactive intermediate **45** led to high-energy transition states that were deemed energetically unproductive relative to that of the other possible transition states (Figure 18).

A comparison of the lowest energy transition states leading from intermediates **46** and **47** provided an experimentally consistent rationalization of our observed selectivites. From intermediate **46**, TS-**1**, which leads to the *syn*-product, was favored over *anti*-addition transition states. From intermediate **45**, TS-**2**, which leads to the *anti*-product, prevailed over any *syn*-selective transition states. TS-**2** depicts a conformer in which the two strongest dipoles of the molecule are directed antiperiplanar to one another, resembling the conformation depicted in the Cornforth-Evans model. With intermediates **46** and **47** relatively close in energy, Curtin-Hammett principles would dictate that the major diastereomer of product would arise from the lower energy transition-state structure. At lower temperatures, TS-**1** was the favored transition state structure compared to TS-**2** and rationalizes the *syn*-selectivity observed at lower temperatures for imine **18** and BF_3•OEt_2. At higher temperatures, TS-**2**, is calculated to be lower in energy, rationalizing the high *anti*-selectivity observed when we increased the temperature of reactions run with BF_3•OEt_2.



entry	TS	ΔG‡ (–78 °C)	ΔG‡ (–20 °C)	ΔG‡ (+25 °C)
1	**TS-1**	18.7	19.7	23.5
2	**TS-2**	21.3	20.3	20.3

Figure 18. Calculated TS's for reactive intermediates **45–47**.

The collaboration between the Shaw and Houk groups allowed for the first proposal of a BF_2 chelate formed by BF_3•OEt_2 and imine. While the calculations performed only pertain to alpha chiral *N*-sulfonyl imines, the possibility of a BF_2 chelate should be considered in other systems as well. There are two previous reports of unexplained *syn*-selectivity in nucleophilic additions to imines using BF_3•OEt_2.[33] It is possible that there will be future instances of unexpected *syn*-selectivity that can also be rationalized by a BF_2 chelate. Moving forward, we have at least presented evidence that BF_3•OEt_2 should not be considered as *only* a non-chelateable Lewis acid. There are aspects of BF_3•OEt_2 reactivity that have yet to be uncovered.

1.2.6 Determination of Relative and Absolute Stereochemistry in Addition Products

Determination of relative stereochemistry of products was completed through X-ray crystallography and NMR correlations (Figure 19). One of the early goals of this project was to establish the identity of diastereomers to determine whether or not a reaction was *syn* or *anti*-selective. Fortunately for this project, many of the nucleophilic addition products were crystalline. Due to the high diastereoselectivity of the reactions, separated diastereomers of addition products were fully characterized. Solids were recrystallized in 20 mL scintillation vials typically using ethyl acetate and hexanes as solvents. Occasionally, diethyl ether and dichloromethane recrystallizations at cold temperatures were also performed to produce adequate crystals for recrystallizations. Relative stereochemistry of the addition adducts that were not crystalline were determined through NMR correlation or chemical derivatization.

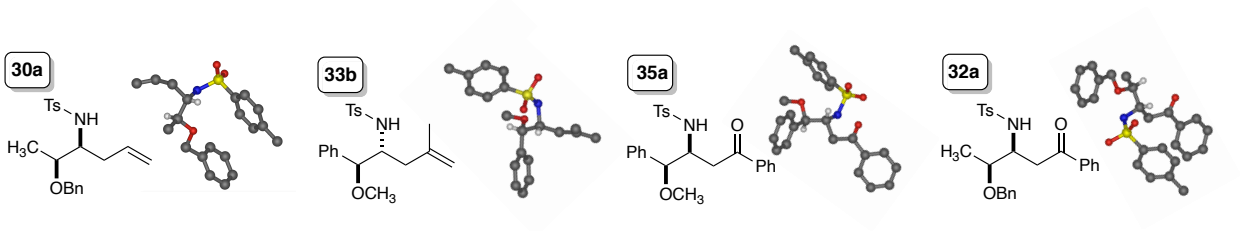


Figure 19. Nucleophilic addition products characterized by X-ray crystallography.

Determination of absolute stereochemistry was also completed for imine addition product **30a** using chiral-HPLC (Figure 20). We were curious whether or not our synthetic route to access imine and subsequent imine addition conditions would affect the enantio-integrity of the alpha stereogenic center. Our original synthetic route which utilized sodium

hydride and benzyl bromide to brominate the alpha hydroxy substituent resulted in erosion of stereochemistry at the alpha carbon. Reaction conditions for benzylation were revised. The new conditions using silver (II) oxide and benzyl bromide showed that no erosion of the alpha chiral center occurred. Furthermore, the subsequent steps of the synthetic route as well as the nucleophilic addition conditions themselves did not seem to affect the alpha stereogenic center. We concluded that, using our synthetic route and addition conditions, whatever enantiopurity of starting material used to make imine would be preserved using this method.

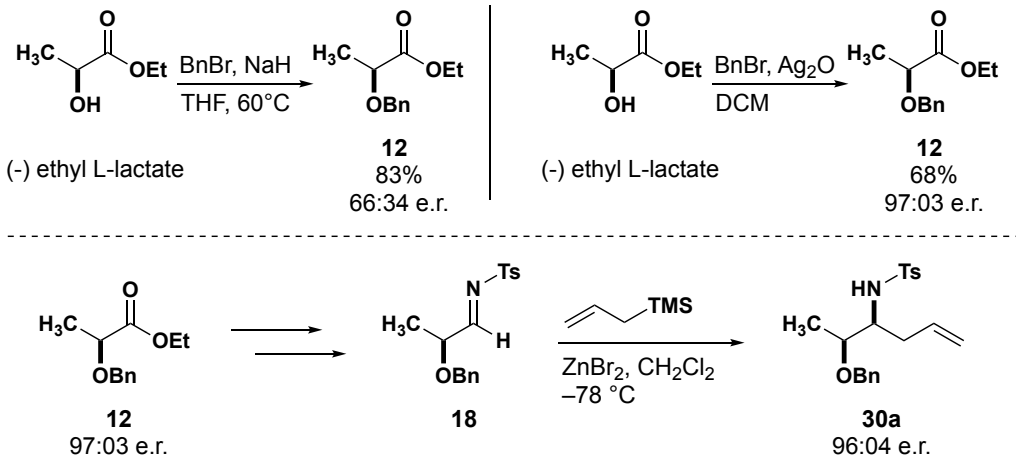


Figure 20. Determination of absolute stereochemistry using enantiomeric ratios measured by chiral HPLC.

1.2.7 Discovery of Silyl-Annulation Side Products

Nucleophilic allylations using allyltrimethylsilane and $ZnBr_2$ resulted in small amounts of silyl-annulation products **49** and **50** (Figure 21). These silyl annulation products were typically isolated in under 5% yield and were determined to not impact significantly the yield of the target homoallylic amine. Similar silyl-annulation products

have been reported in the past for allylations, typically at low temperatures, with carbonyl electrophiles and even *N*-boc imines. At the time of our publication, there were no pre-existing reports of an *N*-Ts silyl-annulation product. There were a couple of attempts to optimize for the silyl-annulation product by switching to bulkier silyl-nucleophiles, which demonstrated a greater propensity to form annulation products in analogous systems. These efforts ultimately did not result in significantly more annulation product in our system.

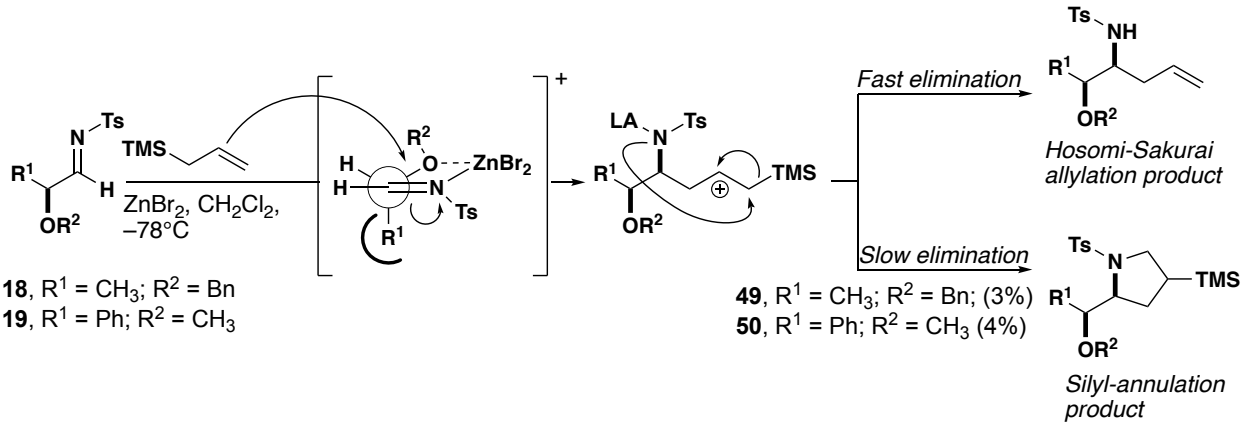


Figure 22. Silyl-annulation product formation from imines **18** and **19**.

1.3 Conclusion

In conclusion, acyclic imine stereocontrol was achieved in nucleophilic additions to alpha alkoxy *N*-Ts imines through the application of either $ZnBr_2$ or BF_3•OEt_2 as a Lewis acid mediator. Experimental and computational evidence were used in tandem to construct a stereoelectronic model to explain the diastereoselectivity of addition reactions.

Syn-products resulted from preorganization of imine substrate into a chelate by $ZnBr_2$. *Anti*-products likely result from a Cornforth-Evans like conformation of Lewis acid-substrate complex in the transition state. Experimental and computational evidence gathered also suggest that BF_3•OEt_2 is not as reliable of a non-chelateable Lewis acid as originally assumed and the possibility of the formation of a BF_2 chelate should not be ignored. In the absence of a BF_2 chelate, our results also demonstrate that *N*-Ts imines are sensitive to proton-chelation. A proton-chelate is currently the most likely explanation for the unexplained selectivity observed in the AMR.

1.4 Experimental

Unless otherwise specified, all commercially available reagents were used as received. All reactions using dried solvents were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring. Dry solvent was dispensed from a solvent purification system that passes solvent through two columns of dry neutral alumna. ^1H and ^{13}C NMR spectra were acquired at ambient temperature using Varian–600 (600 and 151 MHz, respectively), or Bruker–400 (400 and 100 MHz, respectively) spectrometers, as indicated. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane or referenced to residual solvent (^1H NMR: $CDCl_3$ δ 7.26. ^{13}C NMR: $CDCl_3$ δ 77.16) on the δ scale, multiplicity (appar = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, m = multiplet), coupling constants (Hz), and integration. High-resolution mass spectra (HRMS) were acquired on

a Thermo Electron LTQ-Orbitrap XL Hybrid mass spectrometer on positive ESI mode. Melting points were obtained on an EZ-melting apparatus and were uncorrected. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system silica gel (Fisher, 40-63 μm) packed in glass columns.

General Procedure A: Syn-selective additions to imines

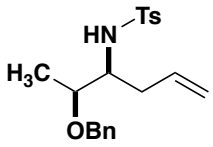
A solution of imine (1.0 equiv) in dry CH_2Cl_2 (0.1 M) was added to solid $ZnBr_2$ (1.1 equiv) and cooled to -78 °C. Nucleophile (1.1 or 1.5 equiv) was then added. The mixture was stirred at -78 °C overnight (16–20 h). The mixture was diluted with EtOAc and allowed to warm to ambient temperature. The resulting mixture was passed through a pad of silica (EtOAc rinse) and concentrated *in vacuo*.

General Procedure B: Anti-selective additions to imines

To a solution of imine (1.0 equiv) in dry $CHCl_3$ (0.1 M) cooled to -20 °C, nucleophile (1.1 or 1.5 equiv), then BF_3•OEt_2 (1.1 equiv) were added. The mixture was stirred at -20 °C overnight (16–20 h). A solution of CH_3OH, CH_2Cl_2, and Et_3N (1:1:1 v/v, pre-cooled to -20 °C) was added, then the resulting mixture was diluted with EtOAc and allowed to warm to ambient temperature. The solution was passed through a pad of silica (EtOAc rinse) and concentrated *in vacuo*.

General Procedure C: Anti-selective additions with allylBF$_3$K and 18-crown-6

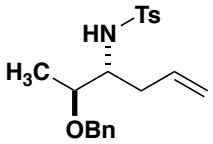
A solution of imine (1.0 equiv) in dry $CHCl_3$ (0.1 M) was added to a mixture of allylBF$_3$K (1.5 equiv) and 18-crown-6 (1.5 equiv) and cooled to -20 °C. BF_3•OEt_2 was added dropwise. The mixture was stirred at -20 °C overnight (16–20 h). A solution of CH_3OH, CH_2Cl_2, and Et_3N (1:1:1 v/v, pre-cooled to -20 °C) was added, then the resulting mixture was diluted with EtOAc and allowed to warm to ambient temperature. The solution was passed through a pad of silica (EtOAc rinse) and concentrated *in vacuo*.



***N*-((2*S*,3*S*)-2-(benzyloxy)hex-5-en-3-yl)-4-methylbenzenesulfonamide (30a)**

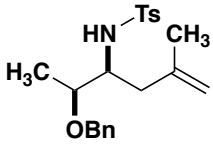
Using general procedure A, imine **18** (169 mg, 0.532 mmol), $ZnBr_2$ (132 mg, 0.585 mmol), and allylTMS (127 μL, 0.798 mmol) were combined in CH_2Cl_2 (5.3 mL) to afford **30a** (140 mg, 73%) as a 95:05 mixture of diastereomers. The major isomer was isolated by flash column chromatography (05:95 to 30:70 EtOAc:hexanes) as a colorless crystalline solid (melting point: 78.3 – 81.6°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.1 Hz, 2H), 7.38 – 7.26 (m, 7H), 5.56 – 5.41 (m, 1H), 4.96 – 4.84 (m, 2H), 4.71 (d, J = 8.3 Hz, 1H), 4.56 (d, J = 11.6 Hz, 1H), 4.33 (d, J = 11.6 Hz, 1H), 3.62 (qd, J = 6.2, 2.5 Hz, 1H), 3.28 – 3.17 (m, 1H), 2.41 (s, 3H), 2.40 – 2.30 (m, 1H), 2.16 – 2.06 (m, 1H), 1.07 (d, J = 6.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 143.1, 138.2, 138.1, 134.2, 129.5, 128.4, 127.8, 127.7,

127.0, 118.0, 73.9, 70.8, 57.6, 36.7, 21.5, 15.9; AMM (ESI-TOF) *m*/*z* calculated for $C_{20}H_{26}NO_3S^+$ $[M + H]^+$ 360.1628, found 360.1630.



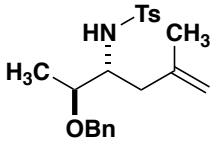
***N*-((2*S*,3*R*)-2-(benzyloxy)hex-5-en-3-yl)-4-methylbenzenesulfonamide (30b)**

Using general procedure C, imine **18** (82.9 mg, 0.261 mmol), BF_3•OEt_2 (36 μL, 0.287 mmol), allylBF_3K (58 mg, 0.392 mmol), and 18-crown-6 (104 mg, 0.392 mmol) were combined in $CHCl_3$ (2.6 mL) to afford **30b** (81.2 mg, 86%) as a 11:89 mixture of diastereomers. The major isomer was isolated by flash column chromatography (15:85 CH_2Cl_2:hexanes, R_f = 0.18) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.66 (m, 2H), 7.32 (q, J = 7.1, 6.3 Hz, 2H), 7.24 (s, 3H), 7.22 (s, 2H), 5.54 (dq, J = 16.2, 7.6 Hz, 1H), 4.97 (s, 1H), 4.94 (d, J = 5.2 Hz, 1H), 4.76 (d, J = 8.3 Hz, 1H), 4.48 (d, J = 11.6 Hz, 1H), 4.24 (d, J = 11.6 Hz, 1H), 3.50 (dd, J = 8.3, 3.7 Hz, 1H), 3.29 (tt, J = 8.5, 4.9 Hz, 1H), 2.40 (s, 3H), 2.33 (q, J = 7.2 Hz, 1H), 2.13 (dt, J = 13.8, 6.3 Hz, 1H), 1.14 (d, J = 6.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.2, 138.2, 138.0, 134.0, 129.5, 128.4, 127.6, 127.5, 127.2, 118.2, 75.8, 70.9, 57.1, 33.9, 21.5, 15.8; AMM (ESI-TOF) *m*/*z* calculated for $C_{20}H_{26}NO_3S^+$ $[M + H]^+$ 360.1628, found 360.1627.



***N*-((2*S*,3*S*)-2-(benzyloxy)-5-methylhex-5-en-3-yl)-4-methylbenzenesulfonamide (31a)**

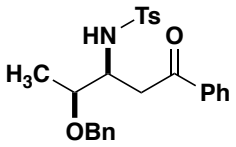
Using general procedure A, imine **18** (150 mg, 0.473 mmol), $ZnBr_2$ (117 mg, 0.520 mmol), and methallylTMS (91 μL, 0.520 mmol) were combined in CH_2Cl_2 (4.7 mL) to afford **31a** (111 mg, 63%) as a 94:06 mixture of diastereomers. The major isomer was isolated by flash column chromatography (0:100 to 50:50 EtOAc:hexanes) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.67 (m, 2H), 7.38 – 7.31 (m, 3H), 7.29 – 7.21 (m, 4H), 4.71 (d, *J* = 7.9 Hz, 1H), 4.67 (t, *J* = 1.8 Hz, 1H), 4.57 (d, *J* = 11.5 Hz, 1H), 4.54 (s, 1H), 4.34 (d, *J* = 11.5 Hz, 1H), 3.69 (qd, *J* = 6.3, 2.3 Hz, 1H), 3.32 (tdd, *J* = 8.2, 6.7, 2.3 Hz, 1H), 2.41 (s, 3H), 2.34 (dd, *J* = 13.6, 8.1 Hz, 1H), 1.96 (dd, *J* = 13.6, 6.6 Hz, 1H), 1.45 (s, 3H), 1.10 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ = 143.2, 141.8, 138.4, 138.2, 129.6, 128.5, 127.9, 127.8, 127.2, 114.2, 73.8, 71.0, 55.6, 40.1, 21.8, 21.6, 15.7; AMM (ESI-TOF) *m*/*z* calculated for $C_{21}H_{28}NO_3S^+$ $[M + H]^+$ 374.1784, found 374.1784.



***N*-((2*S*,3*R*)-2-(benzyloxy)-5-methylhex-5-en-3-yl)-4-methylbenzenesulfonamide (31b)**

Using general procedure B, imine **18** (164 mg, 0.517 mmol), BF_3•OEt_2 (70 μL, 0.568 mmol), and methallylTMS (136 μL, 0.775 mmol) were combined in $CHCl_3$ (5.0 mL) to

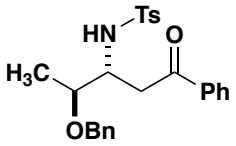
afford **31b** (136 mg, 70%) as a 90:10 mixture of diastereomers. The major isomer was isolated by flash column chromatography (0:100 to 30:70 EtOAc:hexanes) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, 2H), 7.32 (ddd, J = 13.3, 7.7, 5.9 Hz, 3H), 7.25 – 7.21 (m, 4H), 4.71 (s, 1H), 4.66 (s, 1H), 4.60 (d, J = 7.0 Hz, 1H), 4.46 (d, J = 11.6 Hz, 1H), 4.27 (d, J = 11.7 Hz, 1H), 3.67 (qd, J = 6.4, 3.0 Hz, 1H), 3.37 (dtd, J = 9.0, 5.6, 3.0 Hz, 1H), 2.41 (s, 3H), 2.30 – 2.14 (m, 2H), 1.46 (s, 3H), 1.12 (d, J = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.2, 141.6, 138.5, 137.9, 129.5, 128.3, 127.7, 127.6, 127.4, 114.3, 75.9, 71.2, 55.6, 37.8, 21.8, 21.6, 15.8; AMM (ESI-TOF) *m*/*z* calculated for $C_{21}H_{28}NO_3S^+$ $[M + H]^+$ 374.1784, found 374.1784.



***N*-((3*S*,4*S*)-4-(benzyloxy)-1-oxo-1-phenylpentan-3-yl)-4-methylbenzenesulfonamide (32a)**

Using general procedure A, imine **18** (169 mg, 0.532 mmol), $ZnBr_2$ (132 mg, 0.585 mmol), and 1-phenyl-1-trimethylsiloxyethylene (164 μL, 0.798 mmol) were combined in CH_2Cl_2 (5.0 mL) to afford **32a** (213 mg, 91%) as a >95:05 mixture of diastereomers. The major isomer was isolated by flash column chromatography (0:100 to 30:70 EtOAc:hexanes) as a colorless crystalline solid (melting point: 107.3 – 110.1°C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 – 7.69 (m, 4H), 7.54 (t, J = 7.4 Hz, 1H), 7.42 – 7.36 (m, 2H), 7.24 – 7.12 (m, 7H), 5.19 (q, J = 5.9, 4.9 Hz, 1H), 4.53 (d, J = 11.6 Hz, 1H), 4.23 (d, J = 11.6 Hz, 1H), 3.83 (tt,

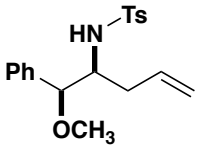
J = 7.9, 3.0 Hz, 1H), 3.67 (dtd, J = 8.2, 6.3, 3.4 Hz, 1H), 3.38 – 3.27 (m, 1H), 3.02 (dd, J = 17.1, 4.1 Hz, 1H), 2.35 (s, 3H), 1.04 (d, J = 6.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.4, 143.4, 138.0, 137.7, 136.5, 133.5, 129.7, 128.7, 128.5, 128.2, 128.0, 127.9, 127.3, 74.6, 71.0, 54.6, 41.2, 21.7, 16.1; AMM (ESI-TOF) *m*/*z* calculated for $C_{25}H_{28}NO_4S^+$ [M + H]$^+$ 438.1734, found 438.1728.



***N*-((3*R*,4*S*)-4-(benzyloxy)-1-oxo-1-phenylpentan-3-yl)-4-methylbenzenesulfonamide (32b)**

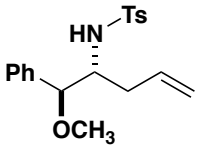
Using general procedure B, imine **18** (132 mg, 0.416 mmol), BF_3•OEt_2 (57 μL, 0.458 mmol), and 1-phenyl-1-trimethylsiloxyethylene (120 mg, 0.624 mmol) were combined in $CHCl_3$ (4.0 mL) to afford **32b** (262 mg, 72%) as a >95:05 mixture of diastereomers. The major isomer was isolated by flash column chromatography (0:100 to 30:70 EtOAc:hexanes) as a colorless oil. ^{1}H NMR (599 MHz, $CDCl_3$) δ 7.81 – 7.74 (m, 2H), 7.71 – 7.64 (m, 2H), 7.57 – 7.51 (m, 1H), 7.40 (t, *J* = 7.8 Hz, 2H), 7.27 – 7.20 (m, 3H), 7.17 (d, *J* = 7.9 Hz, 2H), 7.11 (dd, *J* = 6.9, 2.7 Hz, 2H), 5.54 (d, *J* = 8.5 Hz, 1H), 4.46 (d, *J* = 11.4 Hz, 1H), 4.16 (d, *J* = 11.4 Hz, 1H), 3.82 – 3.74 (m, 1H), 3.71 (p, *J* = 6.2 Hz, 1H), 3.43 (dd, *J* = 17.4, 4.4 Hz, 1H), 2.85 (dd, *J* = 17.4, 5.7 Hz, 1H), 2.34 (s, 3H), 1.17 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 199.0, 143.4, 137.9, 137.6, 136.6, 133.5, 129.7, 128.6,

128.4, 128.2, 127.82, 127.77, 127.2, 75.6, 71.0, 54.7, 37.9, 21.6, 16.3; AMM (ESI-TOF) *m*/*z* calculated for $C_{25}H_{28}NO_4S^+$ [M + H]$^+$ 438.1734, found 438.1736.



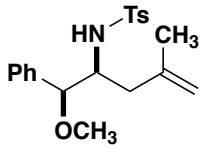
***N*-((1*S*,2*S*)-1-methoxy-1-phenylpent-4-en-2-yl)-4-methylbenzenesulfonamide (33a)**

Using general procedure A, imine **19** (241 mg, 0.793 mmol), $ZnBr_2$ (196 mg, 0.872 mmol), and allylTMS (189 μL, 1.19 mmol) were combined in CH_2Cl_2 (8.0 mL) to afford **33a** (212 mg, 77%) as a >95:05 mixture of diastereomers. The major isomer was isolated by flash column chromatography (10:90 EtOAc:hexanes) as a colorless oil. ^{1}H NMR (599 MHz, $CDCl_3$) δ 7.58 – 7.49 (m, 2H), 7.30 – 7.20 (m, 3H), 7.19 – 7.06 (m, 4H), 5.61 (ddt, *J* = 17.1, 10.1, 7.2 Hz, 1H), 5.04 – 4.95 (m, 2H), 4.71 (d, *J* = 7.2 Hz, 1H), 4.24 (d, *J* = 4.4 Hz, 1H), 3.40 (p, *J* = 6.3 Hz, 1H), 3.19 (s, 3H), 2.50 (dt, *J* = 14.1, 7.0 Hz, 1H), 2.39 (s, 3H), 2.08 – 1.97 (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 142.8, 137.6, 137.4, 133.9, 129.3, 128.3, 127.8, 127.2, 127.0, 118.4, 82.6, 58.2, 57.1, 36.1, 21.5; AMM (ESI-TOF) *m*/*z* calculated for $C_{19}H_{24}NO_3S^+$ [M + H]$^+$ 346.1471, found 346.1478.



***N*-((1*S*,2*R*)-1-methoxy-1-phenylpent-4-en-2-yl)-4-methylbenzenesulfonamide (33b)**

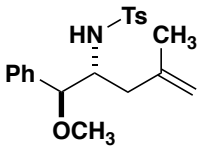
Using general procedure C, imine **19** (124 mg, 0.410 mmol), BF_3•OEt_2 (56 μL, 0.451 mmol), allylBF_3K (91 mg, 0.616 mmol), and 18-crown-6 (163 mg, 0.616 mmol) were combined in $CHCl_3$ (4.0 mL) to afford **33b** (128 mg, 90%) as a >95:05 mixture of diastereomers. The major isomer was isolated by flash column chromatography (10:90 to 20:80 EtOAc:hexanes) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.8 Hz, 2H), 7.33 – 7.25 (m, 5H), 7.16 (d, J = 7.4 Hz, 2H), 5.45 (ddd, J = 17.4, 14.9, 7.4 Hz, 1H), 4.91 (s, 1H), 4.88 (d, J = 7.0 Hz, 1H), 4.82 (d, J = 8.9 Hz, 1H), 4.21 (d, J = 3.7 Hz, 1H), 3.42 (tq, J = 7.8, 3.8 Hz, 1H), 3.18 (d, J = 1.4 Hz, 3H), 2.42 (s, 3H), 2.16 (dt, J = 15.8, 8.2 Hz, 1H), 2.00 (td, J = 13.8, 12.4, 5.5 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.3, 138.2, 138.0, 134.4, 129.6, 128.6, 127.9, 127.3, 126.8, 118.1, 84.8, 58.4, 57.8, 32.8, 21.6; AMM (ESI-TOF) *m*/*z* calculated for $C_{19}H_{24}NO_3S^+$ $[M + H]^+$ 346.1471, found 346.1472.



***N*-((1*S*,2*S*)-1-methoxy-4-methyl-1-phenylpent-4-en-2-yl)-4-methylbenzenesulfonamide (34a)**

Using general procedure A, imine **19** (202 mg, 666 mmol), $ZnBr_2$ (165 mg, 732 mmol), and methallylTMS (176 μL, 999 mmol) were combined in CH_2Cl_2 (6.6 mL) to afford **34a** (178 mg, 74%) as a 95:05 mixture of diastereomers. The major isomer was isolated by flash column chromatography (10:90 EtOAc:hexanes) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.49 (d, J = 8.0 Hz, 2H), 7.23 (dd, J = 5.3, 1.7 Hz, 3H), 7.17 – 7.08 (m,

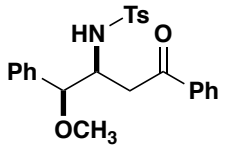
4H), 4.75 (t, J = 1.8 Hz, 1H), 4.67 – 4.64 (m, 1H), 4.55 (d, J = 7.6 Hz, 1H), 4.37 (d, J = 3.2 Hz, 1H), 3.48 (qd, J = 7.5, 3.2 Hz, 1H), 3.23 (s, 3H), 2.48 (dd, J = 13.6, 7.6 Hz, 1H), 2.38 (s, 3H), 2.01 (dd, J = 13.6, 7.2 Hz, 1H), 1.54 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 142.9, 142.0, 137.9, 137.6, 129.4, 128.3, 127.7, 127.2, 127.0, 114.5, 82.1, 57.5, 56.6, 40.6, 21.9, 21.6; AMM (ESI-TOF) *m*/*z* calculated for $C_{20}H_{26}NO_3S^+$ [M + H]$^+$ 360.1628, found 360.1629.



***N*-((1*S*,2*R*)-1-methoxy-4-methyl-1-phenylpent-4-en-2-yl)-4-methylbenzenesulfonamide (34b)**

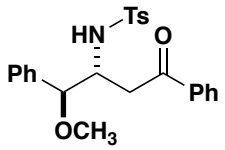
Using general procedure B, imine **19** (159 mg, 0.524 mmol), BF_3•OEt_2 (71 μL, 0.577 mmol), and methallylTMS (138 μL, 0.786 mmol) were combined in $CHCl_3$ (5.0 mL) to afford **34b** (147 mg, 78%) as a 85:15 mixture of diastereomers. The major isomer was isolated by flash column chromatography (10:90 EtOAc:hexanes) as a colorless crystalline solid (melting point: 86.3 – 89.8°C). ^{1}H NMR (599 MHz, $CDCl_3$) δ 7.79 (d, J = 8.0 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 7.4 Hz, 1H), 7.19 (d, J = 7.5 Hz, 2H), 4.72 (d, J = 8.0 Hz, 1H), 4.66 (s, 1H), 4.63 (s, 1H), 4.35 (d, J = 2.9 Hz, 1H), 3.51 (ddt, J = 11.2, 7.4, 3.4 Hz, 1H), 3.19 (s, 3H), 2.41 (s, 3H), 2.12 (dd, J = 14.3, 10.8 Hz, 1H), 1.90 (dd, J = 14.4, 3.7 Hz, 1H), 1.26 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4, 141.6, 138.3, 138.1, 129.6, 128.6, 127.8, 127.4, 126.6, 114.3, 84.5, 57.9,

57.0, 36.2, 21.6, 21.4; AMM (ESI-TOF) *m*/*z* calculated for $C_{20}H_{26}NO_3S^+$ [M + H]$^+$ 360.1628, found 360.1629.



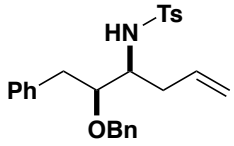
***N*-((1*S*,2*S*)-1-methoxy-4-oxo-1,4-diphenylbutan-2-yl)-4-methylbenzenesulfonamide (35a)**

Using general procedure A, imine **19** (170 mg, 559 mmol), $ZnBr_2$ (189 mg, 838 mmol), and 1-phenyl-1-trimethylsiloxyethylene (126 μL, 615 mmol) were combined in CH_2Cl_2 (5.6 mL) to afford **35a** (118 mg, 50%) as a 95:05 mixture of diastereomers. The major isomer was isolated by flash column chromatography (0:100 to 30:70 EtOAc:hexanes) as a colorless crystalline solid (melting point: 132.9 – 135.4°C). ^{1}H NMR (599 MHz, $CDCl_3$) δ 7.86 (d, J = 7.2 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.7 Hz, 3H), 7.37 (d, J = 8.2 Hz, 2H), 7.18 – 7.13 (m, 4H), 6.99 (d, J = 7.9 Hz, 2H), 5.15 (d, J = 8.0 Hz, 1H), 4.44 (d, J = 3.7 Hz, 1H), 3.92 (tt, J = 7.9, 3.9 Hz, 1H), 3.51 (dd, J = 17.2, 8.1 Hz, 1H), 3.20 (dd, J = 17.2, 4.0 Hz, 1H), 3.17 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.7, 142.8, 137.9, 136.8, 136.6, 133.6, 129.4, 128.7, 128.5, 128.2, 127.8, 127.0, 126.8, 82.9, 57.6, 55.8, 41.3, 21.6; AMM (ESI-TOF) *m*/*z* calculated for $C_{24}H_{26}NO_4S^+$ [M + H]$^+$ 424.1577, found 424.1572.



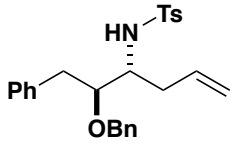
***N*-((1*S*,2*R*)-1-methoxy-4-oxo-1,4-diphenylbutan-2-yl)-4-methylbenzenesulfonamide (35b)**

Using Using general procedure B, imine **19** (124 mg, 0.410 mmol), BF_3•OEt_2 (56 μL, 0.451 mmol), and 1-phenyl-1-trimethylsiloxyethylene (92 μL, 0.451 mmol) were combined in $CHCl_3$ (4.0 mL) to afford **35b** (105 mg, 61%) as a 95:05 mixture of diastereomers. The major isomer was isolated by flash column chromatography (0:100 to 30:70 EtOAc:hexanes) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 – 7.65 (m, 2H), 7.53 (td, *J* = 8.2, 4.0 Hz, 3H), 7.41 – 7.34 (m, 2H), 7.27 (s, 3H), 7.22 – 7.15 (m, 2H), 7.10 (d, *J* = 7.9 Hz, 2H), 5.44 (d, *J* = 9.1 Hz, 1H), 4.44 (d, *J* = 5.5 Hz, 1H), 3.97 (dq, *J* = 10.6, 5.6 Hz, 1H), 3.33 (ddd, *J* = 16.8, 6.3, 1.3 Hz, 1H), 3.16 (d, *J* = 1.4 Hz, 3H), 3.02 – 2.90 (m, 1H), 2.34 (s, 3H); ^{13}C NMR (151 MHz, CD_3CN) δ 197.5, 143.3, 138.3, 138.2, 136.8, 133.0, 129.5, 128.46, 128.43, 127.90, 127.87, 127.0, 126.7, 84.6, 56.7, 55.9, 38.2, 20.5; AMM (ESI-TOF) *m*/*z* calculated for $C_{24}H_{26}NO_4S^+$ $[M + H]^+$ 424.1577, found 424.1576.



***N*-((2*S*,3*S*)-2-(benzyloxy)-1-phenylhex-5-en-3-yl)-4-methylbenzenesulfonamide (36a)**

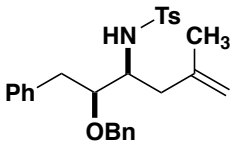
Using general procedure A, imine **22** (143 mg, 0.363 mmol), $ZnBr_2$ (90 mg, 0.400 mmol), and allylTMS (87 μL, 0.545 mmol) were combined in CH_2Cl_2 (3.6 mL) to afford **36a** (117 mg, 74%) as a 93:07 mixture of diastereomers. The major isomer was isolated by flash column chromatography (10:90 to 30:70 EtOAc:hexanes) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.9 Hz, 2H), 7.38 – 7.16 (m, 10H), 7.05 (d, *J* = 7.4 Hz, 2H), 5.36 (td, *J* = 16.8, 7.2 Hz, 1H), 4.92 – 4.85 (m, 2H), 4.80 (d, *J* = 17.1 Hz, 1H), 4.38 (d, *J* = 11.2 Hz, 1H), 4.30 (d, *J* = 11.2 Hz, 1H), 3.69 – 3.59 (m, 1H), 3.37 – 3.27 (m, 1H), 2.80 (dd, *J* = 13.7, 6.6 Hz, 1H), 2.72 (dd, *J* = 13.7, 6.7 Hz, 1H), 2.41 (s, 3H), 2.34 – 2.23 (m, 1H), 2.13 – 2.03 (m, 1H). ^{13}C NMR (100 MHz, CD_3CN) δ = 143.4, 139.0, 138.9, 138.5, 134.6, 129.6, 129.4, 128.2, 128.2, 127.9, 127.5, 126.9, 126.1, 117.0, 80.8, 72.0, 55.3, 36.1, 35.0, 20.5. AMM (ESI-TOF) *m*/*z* calculated for $C_{26}H_{30}NO_3S^+$ $[M + H]^+$ 436.1941, found 436.1946.



***N*-((2*S*,3*R*)-2-(benzyloxy)-1-phenylhex-5-en-3-yl)-4-methylbenzenesulfonamide (36b)**

Using general procedure C, imine **22** (91 mg, 0.231 mmol), BF_3•OEt_2 (32 μL, 0.254 mmol), allylBF_3K (51.3 mg, 0.347 mmol), and 18-crown-6 (91.7 mg, 0.347 mmol) were combined in $CHCl_3$ (2.3 mL) to afford **36b** (79 mg, 78%) as a 92:8 mixture of diastereomers. The major isomer was isolated by flash column chromatography (0:100 to 20:80

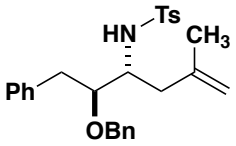
EtOAc:hexanes, R_f = 0.35 in 20:80 EtOAc:hexanes) as a colorless oil. ^{1}H NMR (600 MHz, cd_3cn) δ 7.49 (d, *J* = 8.0 Hz, 2H), 7.34 – 7.24 (m, 8H), 7.21 – 7.16 (m, 2H), 7.12 – 7.07 (m, 2H), 5.65 – 5.53 (m, 1H), 5.04 (dd, *J* = 17.1, 1.7 Hz, 1H), 4.93 (dd, *J* = 10.1, 2.0 Hz, 1H), 4.31 (d, *J* = 11.6 Hz, 1H), 4.25 (d, *J* = 11.5 Hz, 1H), 3.47 (td, *J* = 7.1, 2.8 Hz, 1H), 3.31 – 3.24 (m, 1H), 2.82 (dd, *J* = 13.8, 7.4 Hz, 1H), 2.68 (dd, *J* = 13.8, 6.8 Hz, 1H), 2.41 (s, 3H), 2.39 – 2.33 (m, 1H), 2.28 – 2.16 (m, 1H). ^{13}C NMR (150 MHz, CD_3CN) δ = 143.3, 143.2, 138.6, 138.4, 135.0, 129.6, 129.3, 128.4, 128.2, 127.7, 127.5, 126.8, 126.3, 116.8, 81.7, 71.7, 55.2, 36.5, 33.4, 20.6. AMM (ESI-TOF) *m*/*z* calculated for $C_{26}H_{30}NO_3S^+$ [M + H]$^+$ 436.1941, found 436.1941.



***N*-((2*S*,3*S*)-2-(benzyloxy)-5-methyl-1-phenylhex-5-en-3-yl)-4-methylbenzenesulfonamide (37a)**

Using general procedure A, imine **22** (143 mg, 0.363 mmol), $ZnBr_2$ (90 mg, 0.400 mmol), and methallylTMS (96 μL, 0.545 mmol) were combined in CH_2Cl_2 (3.6 mL) to afford **37a** (101 mg, 62%) as a >95:05 mixture of diastereomers. The major isomer was isolated by flash column chromatography (10:90 to 30:70 EtOAc:hexanes) as a colorless crystalline solid (melting point: 101.0-105.4°C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 7.8 Hz, 2H), 7.44 – 7.15 (m, 10H), 7.04 (d, *J* = 7.5 Hz, 2H), 4.82 (d, *J* = 8.1 Hz, 1H), 4.60 (s, 1H), 4.45 (d, *J* = 11.3 Hz, 1H), 4.41 (s, 1H), 4.32 (d, *J* = 11.3 Hz, 1H), 3.73 – 3.63 (m, 1H),

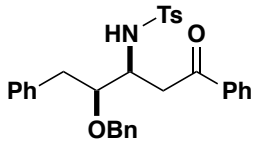
3.45 – 3.34 (m, 1H), 2.79 (qd, *J* = 13.4, 6.7 Hz, 2H), 2.42 (s, 3H), 2.28 (dd, *J* = 13.7, 8.9 Hz, 1H), 1.94 (dd, *J* = 13.8, 6.0 Hz, 1H), 1.21 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ = 143.4, 141.8, 138.4, 138.3, 138.1, 129.7, 129.6, 128.5, 128.5, 128.2, 128.0, 127.3, 126.4, 114.0, 79.7, 72.7, 52.7, 40.5, 36.6, 21.6, 21.3. AMM (ESI-TOF) *m*/*z* calculated for $C_{27}H_{32}NO_3S^+$ $[M + H]^+$ 450.2097, found 450.2093.



***N*-((2*S*,3*R*)-2-(benzyloxy)-5-methyl-1-phenylhex-5-en-3-yl)-4-methylbenzenesulfonamide (37b)**

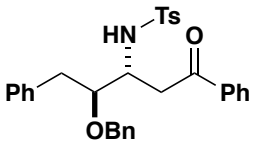
Using general procedure B, imine **22** (187 mg, 0.475 mmol), BF_3•OEt_2 (117 μL, 0.950 mmol), and methallylTMS (125 μL, 0.712 mmol) were combined in $CHCl_3$ (5.0 mL) to afford **37b** (137 mg, 64%) as a 90:10 mixture of diastereomers. The major isomer was isolated by flash column chromatography (0:100 to 20:80 EtOAc:hexanes, R_f = 0.38 in 20:80 EtOAc:hexanes) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.8 Hz, 2H), 7.36 – 7.26 (m, 6H), 7.21 (d, *J* = 7.4 Hz, 2H), 7.17 – 7.09 (m, 4H), 4.69 (d, *J* = 25.3 Hz, 2H), 4.45 (s, 2H), 4.43 (d, *J* = 5.4 Hz, 1H), 4.02 – 3.91 (m, 1H), 3.19 – 3.09 (m, 1H), 2.91 (dd, *J* = 13.8, 6.9 Hz, 1H), 2.61 (dd, *J* = 13.8, 8.0 Hz, 1H), 2.39 (s, 3H), 2.32 – 2.19 (m, 2H), 1.19 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 143.1, 141.4, 138.3, 137.7, 136.6, 129.4, 129.3, 128.6, 128.3, 127.8, 127.7, 127.3, 126.5, 114.6, 81.3, 73.0, 52.8,

37.5, 36.9, 21.5, 21.0. AMM (ESI-TOF) *m*/*z* calculated for $C_{27}H_{32}NO_3S^+$ [M + H]$^+$ 450.2097, found 450.2093.



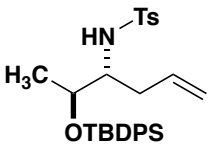
***N*-((3*S*,4*S*)-4-(benzyloxy)-1-oxo-1,5-diphenylpentan-3-yl)-4-methylbenzenesulfonamide (38a)**

Using general procedure A, imine **22** (143 mg, 0.363 mmol), $ZnBr_2$ (90 mg, 0.400 mmol), and 1-phenyl-1-trimethylsiloxyethylene (112 μL, 0.545 mmol) were combined in CH_2Cl_2 (3.6 mL) to afford **38a** (93 mg, 49%) as a 95:05 mixture of diastereomers. The major isomer was isolated by flash column chromatography (0:100 to 30:70 EtOAc:hexanes) as a white crystalline solid (melting point: 137.5 – 139.8°C). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (dd, *J* = 15.7, 7.8 Hz, 4H), 7.53 (t, *J* = 7.4 Hz, 1H), 7.38 (t, *J* = 7.6 Hz, 2H), 7.31 – 7.10 (m, 8H), 7.05 (dd, *J* = 14.4, 7.3 Hz, 4H), 5.18 (d, *J* = 8.8 Hz, 1H), 4.27 (d, *J* = 11.3 Hz, 1H), 4.06 (d, *J* = 11.4 Hz, 1H), 3.91 – 3.82 (m, 1H), 3.82 – 3.73 (m, 1H), 3.20 (dd, *J* = 17.0, 8.7 Hz, 1H), 3.07 (dd, *J* = 17.0, 4.4 Hz, 1H), 2.70 (qd, *J* = 13.8, 6.6 Hz, 2H), 2.36 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 198.2, 143.5, 138.0, 137.7, 137.6, 136.2, 133.5, 129.8, 129.5, 128.6, 128.5, 128.5, 128.3, 128.2, 128.0, 127.3, 126.5, 80.5, 73.3, 52.6, 41.3, 37.8, 21.7. AMM (ESI-TOF) *m*/*z* calculated for $C_{31}H_{32}NO_4S^+$ [M + H]$^+$ 514.2047, found 514.2042.



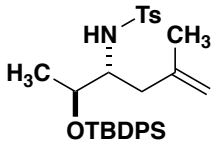
***N*-((3*R*,4*S*)-4-(benzyloxy)-1-oxo-1,5-diphenylpentan-3-yl)-4-methylbenzenesulfonamide (38b)**

Using Using general procedure B, imine **22** (187 mg, 0.475 mmol), BF_3•OEt_2 (117 μL, 0.950 mmol), and 1-phenyl-1-trimethylsiloxyethylene (107 μL, 0.523 mmol) were combined in $CHCl_3$ (5.0 mL) to afford **38b** (156 mg, 64%) as a 90:10 mixture of diastereomers. The major isomer was isolated by flash column chromatography (100:0 to 25:75 EtOAc:hexanes, R_f = 0.31 in 25:75 EtOAc:hexanes) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (dd, *J* = 8.0, 1.4 Hz, 2H), 7.57 (d, *J* = 8.2 Hz, 2H), 7.53 (td, *J* = 7.3, 1.4 Hz, 1H), 7.37 (t, *J* = 7.8 Hz, 2H), 7.28 (t, *J* = 7.4 Hz, 2H), 7.24 – 7.17 (m, 6H), 7.10 (d, *J* = 7.9 Hz, 2H), 6.97 (dd, *J* = 6.5, 2.9 Hz, 2H), 5.52 (d, *J* = 8.1 Hz, 1H), 4.17 (d, *J* = 11.1 Hz, 1H), 4.07 (d, *J* = 11.2 Hz, 1H), 3.95 – 3.90 (m, 1H), 3.82 – 3.76 (m, 1H), 3.36 (dd, *J* = 17.2, 5.5 Hz, 1H), 2.99 – 2.88 (m, 2H), 2.76 (dd, *J* = 14.1, 7.9 Hz, 1H), 2.31 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ = 198.9, 143.3, 138.0, 137.6, 137.1, 136.3, 133.4, 129.6, 129.5, 128.5, 128.5, 128.3, 128.1, 127.9, 127.7, 127.1, 126.4, 81.2, 73.1, 53.3, 37.9, 37.5, 21.5. AMM (ESI-TOF) *m*/*z* calculated for $C_{31}H_{32}NO_4S^+$ $[M + H]^+$ 514.2047, found 514.2039.



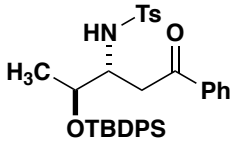
***N*-((2*S*,3*R*)-2-((*tert*-butyldiphenylsilyl)oxy)hex-5-en-3-yl)-4-methylbenzenesulfonamide (39b)**

Using general procedure C, imine **20** (89.3 mg, 0.201 mmol), BF_3•OEt_2 (27 μL, 0.221 mmol), allylBF_3K (44.6 mg, 0.302 mmol), and 18-crown-6 (79.7 mg, 0.302 mmol) were combined in $CHCl_3$ (2.0 mL) to afford **39b** (70.6 mg, 72%) as a >95:5 mixture of diastereomers. The major isomer was isolated by flash column chromatography (15:85 EtOAc:hexanes, R_f = 0.26) as a colorless oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 – 7.61 (m, 2H), 7.60 – 7.56 (m, 2H), 7.56 – 7.52 (m, 2H), 7.44 (dtd, *J* = 16.6, 7.2, 1.4 Hz, 2H), 7.36 (dt, *J* = 15.2, 7.5 Hz, 4H), 7.21 (d, *J* = 8.2 Hz, 2H), 5.55 – 5.40 (m, 1H), 4.94 (s, 1H), 4.92 (d, *J* = 5.4 Hz, 1H), 4.64 (d, *J* = 7.4 Hz, 1H), 3.81 (qd, *J* = 6.4, 3.6 Hz, 1H), 3.12 (tdd, *J* = 7.2, 5.7, 3.7 Hz, 1H), 2.48 – 2.42 (m, 1H), 2.41 (s, 3H), 2.16 – 2.10 (m, 1H), 1.02 (s, 9H), 0.94 (d, *J* = 6.3 Hz, 3H). ^{13}C NMR (150 MHz, cdcl$_3$) δ = 143.1, 137.8, 135.8, 135.8, 134.0, 133.7, 133.1, 129.9, 129.7, 129.5, 127.7, 127.5, 127.1, 118.1, 71.0, 58.7, 33.8, 27.0, 21.5, 19.5, 19.3. AMM (ESI-TOF) *m*/*z* calculated for $C_{31}H_{32}NO_4S^+$ [M + H]$^+$ 508.2336, found 508.2332.



***N*-((2*S*,3*R*)-2-((*tert*-butyldiphenylsilyl)oxy)-5-methylhex-5-en-3-yl)-4-methylbenzenesulfonamide (40b)**

Using general procedure B, imine **20** (207 mg, 0.445 mmol), BF_3•OEt_2 (100 μL, 0.889 mmol), and methallylTMS (117 μL, 0.667 mmol) were combined in $CHCl_3$ (4.5 mL) to afford **40b** (165 mg, 71%) as a >95:5 mixture of diastereomers. The major isomer was isolated by flash column chromatography (15:85 EtOAc:hexanes, R_f = 0.48 in 20:80 EtOAc:hexanes) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.9 Hz, 2H), 7.56 (d, *J* = 7.3 Hz, 2H), 7.51 (d, *J* = 7.4 Hz, 2H), 7.43 (q, *J* = 6.6, 5.7 Hz, 2H), 7.36 (dt, *J* = 13.6, 6.0 Hz, 4H), 7.17 (d, *J* = 8.0 Hz, 2H), 4.70 – 4.53 (m, 3H), 3.96 (dt, *J* = 8.4, 5.7 Hz, 1H), 3.17 (q, *J* = 7.9 Hz, 1H), 2.39 (s, 4H), 2.17 (dd, *J* = 14.3, 6.5 Hz, 1H), 1.31 (s, 3H), 1.02 (s, 9H), 0.95 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 143.1, 141.5, 137.5, 135.9, 133.8, 133.4, 129.9, 129.7, 129.5, 127.7, 127.6, 127.3, 114.0, 70.7, 57.1, 37.9, 27.0, 21.5, 19.3, 18.8. AMM (ESI-TOF) *m*/*z* calculated for $C_{31}H_{32}NO_4S^+$ $[M + H]^+$ 522.2493, found 522.2482.



***N*-((3*R*,4*S*)-4-((*tert*-butyldiphenylsilyl)oxy)-1-oxo-1-phenylpentan-3-yl)-4-methylbenzenesulfonamide (41b)**

Using general procedure B, imine **20** (304 mg, 0.647 mmol), BF_3•OEt_2 (159 μL, 1.29 mmol), and 1-phenyl-1-trimethylsiloxyethylene (146 μL, 0.712 mmol) were combined in $CHCl_3$ (6.5 mL) to afford **41b** (177 mg, 47%) as a >95:5 mixture of diastereomers. The major isomer was isolated by flash column chromatography (0:100 to 20:80

EtOAc:hexanes, R_f = 0.33 in 20:80 EtOAc:hexanes) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 7.8 Hz, 2H), 7.63 – 7.60 (m, 2H), 7.53 (d, J = 7.1 Hz, 5H), 7.40 (q, J = 7.7 Hz, 5H), 7.31 (t, J = 7.5 Hz, 5H), 7.14 (d, J = 7.9 Hz, 2H), 5.36 (d, J = 7.7 Hz, 1H), 4.05 (t, J = 6.1 Hz, 1H), 3.72 (t, J = 6.3 Hz, 1H), 3.49 (dd, J = 17.6, 4.8 Hz, 1H), 2.98 (dd, J = 17.5, 5.8 Hz, 1H), 2.33 (s, 3H), 0.96 (apparent s, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ = 198.4, 143.3, 137.5, 136.6, 135.9, 135.8, 133.7, 133.4, 133.0, 130.0, 129.8, 129.7, 128.6, 128.1, 127.8, 127.6, 127.2, 71.1, 56.3, 38.1, 27.1, 21.6, 20.1, 19.3. AMM (ESI-TOF) *m/z* calculated for $C_{34}H_{40}NO_4SSi^+$ $[M + 1]^+$ 586.2442, found 586.2432.

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Chapter 2:

Diastereoselective Nucleophilic Additions to β-Alkoxy *N*-Sulfonyl Aldimines

2.1 Introduction

Lewis acid-mediated allylations of β-alkoxy aldimines are stereoselective and result in *anti*-1,3 amino alcohol precursors through 1,3-asymmetric induction.[1] While there have been reports of nucleophilic addition reactions to β-alkoxy aldehydes resulting in high *anti*-selectivity, the origin of this selectivity is usually superficially discussed. Our group's investigations of nucleophilic additions to α-chiral *N*-tosyl imines revealed unexpected differences in reactivity between aldimines and their analogous aldehydes (Chapter 1). Based on these differences in reactivity, we sought to further explore how asymmetric induction affects diastereoselectivity in nucleophilic additions to β-alkoxy *N*-tosyl aldimines. To conduct this investigation, synthetic routes were devised to access a wide variety of β-alkoxy aldehydes and *N*-tosyl imines. Two methods of Lewis-acid mediated allylations were developed to access *anti*-1,3 amino ethers in synthetically practical yields and diastereoselectivities (Figure 1).[1] *Anti*-1,3 amino alcohols are commonly found structural motifs in biologically active synthetic targets.[2, 3] Then, using computational methods, the resulting stereoselectivity trends were used to construct a generalizable stereoelectronic rationale and model for the stereoselectivities observed. This model allows for the consideration of relative ground-state energies of six-membered ring chelates as a predictor for the magnitude of diastereoselectivities observed.

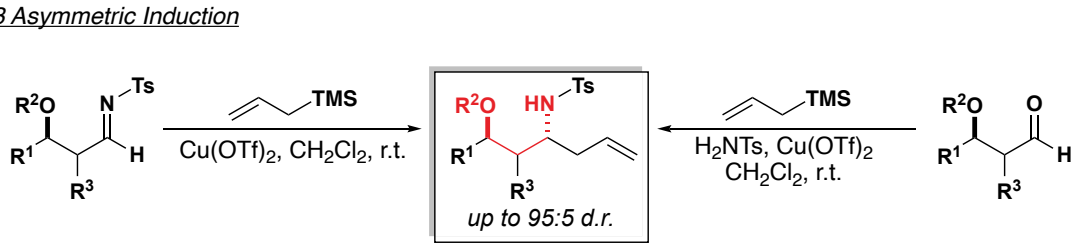


Figure 1. Nucleophilic additions to β-alkoxy imines result in *anti*-1,3 amino alcohol precursors.

2.1.1 Overview of 1,3-Asymmetric Induction in Nucleophilic Additions to β-Alkoxy Aldehydes

Nucleophilic additions to β-alkoxy aldehydes have been previously reported and are often highly diastereoselective for the *anti*-diastereomer of product. Models describing the observed diastereoselectivity can either be cyclic or acyclic in nature depending on the reagents employed (Figure 2). When chelateable reagents are used, *anti*-diastereoselectivity may be rationalized through a six-membered ring chelate reminiscent of the chelate depicted in the Cram chelation model. When Lewis acids or reagents with only one coordination site available are used, a handful of acyclic stereoelectronic models have been proposed to rationalize the ensuing *anti*-selectivity. There are isolated cases of *syn*-selective nucleophilic additions to β-alkoxy aldehydes, though they are vastly fewer in number relative to that of *anti*-selective nucleophilic additions. In this section, an overview of extant stereoelectronic models describing diastereoselective nucleophilic additions to β-alkoxy aldehydes will be presented to provide context for our investigations of β-alkoxy aldimines.

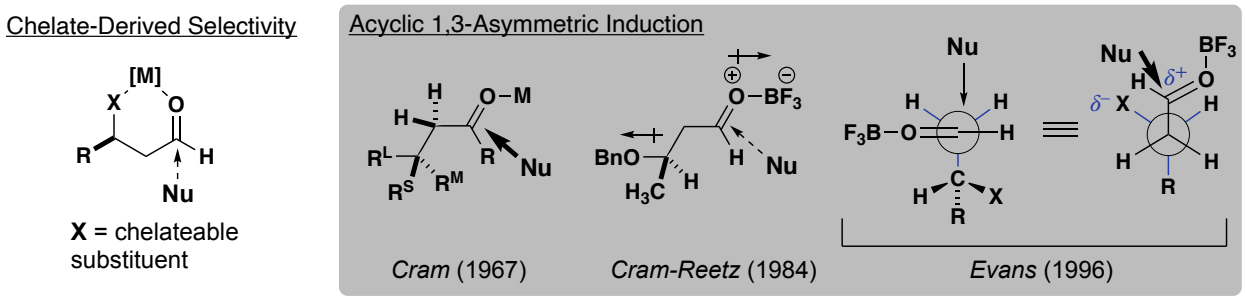


Figure 2. Extant stereoelectronic models describing nucleophilic additions to β-chiral aldehydes.

Like in nucleophilic additions to α-chiral carbonyls, nucleophilic additions to β-alkoxy aldehydes can result in two possible stereochemical outcomes (Figure 3). A clear understanding of the inherent geometric preferences of β-alkoxy aldehydes and analogous electrophiles is integral to predicting the stereochemical preference (*syn* or *anti*) of the reaction. The magnitude of the stereochemical outcome, whatever that may be, is related to how rigid those geometrical preferences are. It is important to note that while the inherent asymmetry of β-chiral carbonyls is one carbon further away from that of α-chiral carbonyls, the selectivity is usually very high and more than synthetically practical (e.g. >95:5 d.r.). The competitive influence of 1,3-asymmetric induction in β-alkoxy carbonyls suggests that the strength of asymmetric induction is not always a function of the proximity of a stereogenic center to the reaction center of the molecule.

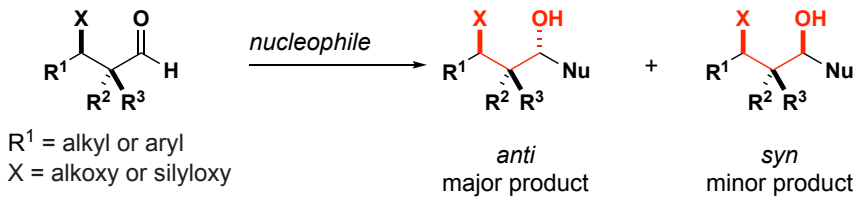


Figure 3. Possible stereochemical outcomes of nucleophilic additions to β-alkoxy aldehydes.

2.1.1.1 The Chelation Model

Nucleophilic additions to β-alkoxy carbonyls may lead to *anti*-products in high diastereoselectivities through the use of chelateable reagents. In the presence of a chelateable reagent, a six-membered ring chelate may form from coordination of the substrate to chelateable reagent (**1**, Figure 4). Nucleophiles would preferentially attack the six-membered ring chelate from the least sterically hindered side of the ring, leading to *anti*-product. It is notable that, compared to the five-membered ring chelate described in the Cram chelation model, the six-membered ring chelate formed from β-alkoxy carbonyl and chelate-able reagent is theoretically more conformationally flexible. Yet, the diastereoselectivities resulting from β-alkoxy carbonyls is nevertheless high. This implies that the six-membered ring chelate should have a high degree of preference for one major conformer, though the identity of this conformer is usually not speculated upon in accompanying reports of diastereoselectivities.

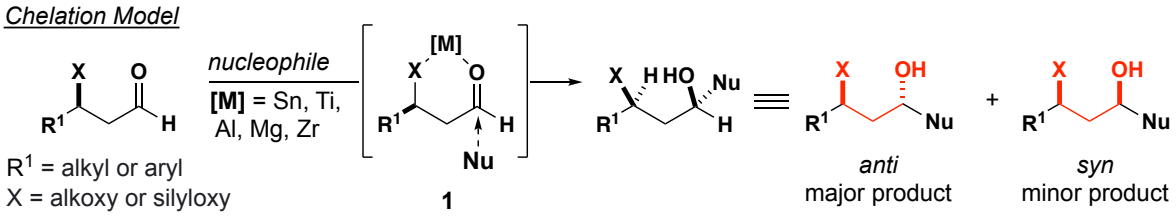


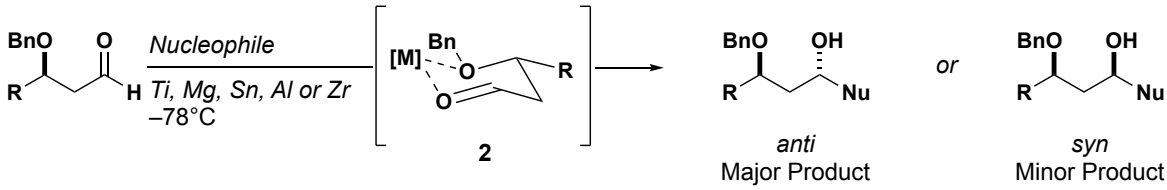
Figure 4. Chelation-derived diastereoselectivity in nucleophilic additions to β-alkoxy aldehydes.

Reetz reported high *anti*-selectivities for several titanium (IV) chloride mediated additions to β-benzyloxy aldehydes and was the first to invoke a six-membered ring chelate as the origin of their observed selectivities.[4] Prior to Reetz's report, stereocontrol in nucleophilic additions to β-alkoxy carbonyls proved elusive as Grignard reagents,

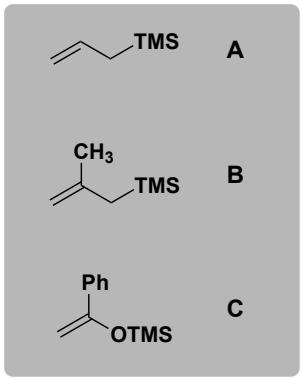
organolithium reagents and cuprate reagents all failed to give useful stereoselectivity. This was in stark contrast to their performance in nucleophilic additions to α-chiral carbonyls in which they were able to chelate effectively.

Reetz demonstrated that titanium-mediated nucleophilic additions of substituted and unsubstituted allylsilanes and enol ethers resulted in *anti*-products with greater than 90:10 diastereoselectivities in most cases (Table 1). Selectivities were rationalized through the presumed presence of a titanium chelate which Reetz depicted initially as chair-like conformer **2**, which bears an equatorial β-alkyl substituent. Selectivities did not increase dramatically with β-substituent bulk, although there is a subtle upward trend in diastereoselectivity with nucleophilicity of reagents used (e.g. entry 12 and entry 13). Subsequently, Reetz also examined the effects of other Lewis acids (e.g. Mg-, Sn-, Al- and Zr-based reagents) on diastereoselectivity.[5] Reetz's results showed that the effects of 1,3-asymmetric induction in β-alkoxy aldehydes were sensitive to the chelateable reagent involved. Specifically, the identity of the metal in the Lewis acid would have pronounced effects on the magnitude of chelate-derived stereoselectivity.

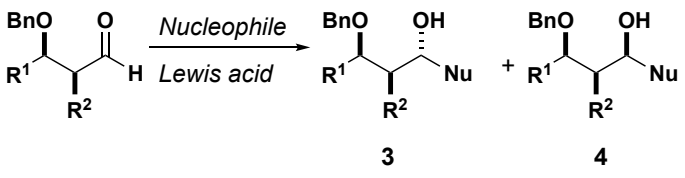
Table 1. Lewis Acid-Mediated Nucleophilic Additions to β-Alkoxy Aldehydes.



Entry	Conditions (L.A. and/or Nucleophile)	R	*anti*:*syn*
1	CH_3TiCl_3	CH_3	90:10
2	$TiCl_4$ / $CH_3Ti(O\text{-}i\text{-}Pr)_3$	CH_3	70:30
3	$TiCl_4$ / **A**	CH_3	95:5
4	$TiCl_4$ / **B**	CH_3	95:5
5	$TiCl_4$ / **C**	CH_3	92:8
6	$TiCl_4$ / $Zn(n\text{-}Bu)_2$	CH_3	90:10
7	allylMgCl	CH_3	40:60
8	$Zr(allyl)_4$	CH_3	81:19
9	$SnCl_4$ / **A**	CH_3	95:5
10	$AlCl_3$ / **A**	CH_3	89:11
11	CH_3TiCl_4	*n*-Bu	91:9
12	$TiCl_4$ / **A**	*n*-Bu	95:5
13	$TiCl_4$ / **B**	*n*-Bu	99:1



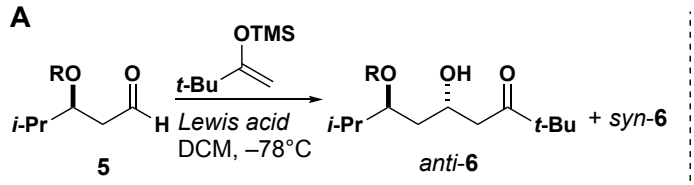
Subsequent to Reetz's report, Heathcock and Keck also published accounts of chelate-derived selectivity in nucleophilic additions to β-alkoxy aldehydes with allylsilanes[6, 7] and allyltributylstannane.[8] Heathcock determined that $SnCl_4$ was also an effective Lewis acid mediator and resulted in moderate to high levels of *anti*-selectivity in nucleophilic additions to β-alkoxy aldehydes (Figure 5). Keck provided spectroscopic evidence to further support the existence of a chelate in $TiCl_4$, $MgBr_2$ and $SnCl_4$ mediated reactions.[9] These congruent observations all support the invocation of chelate-derived selectivity in Lewis acid mediated allylations of β-alkoxy aldehydes.



Entry	L.A. / Nu	R^1	R^2	Yield (%)	**3**:**4**
1	$SnCl_4$ / **A**	H	CH_3	92	92:8
2	$SnCl_4$ / **B**	H	CH_3	83	91:9
3	$SnCl_4$ / **A**	CH_3	H	97	90:10
4	$SnCl_4$ / **B**	CH_3	H	86	88:12

Figure 5. $SnCl_4$-mediated nucleophilic additions to β-alkoxy aldehydes.

More recently, Evans reported on the chelating ability of methylaluminum chloride reagents in Mukaiyama aldol additions to α- and β-chiral aldehydes. Compared to other Lewis acids screened for this reaction, Me_2AlCl and $MeAlCl_2$ provided the highest levels of *anti*-selectivity (Figure 6A). Evans speculated for the first time on the conformation of the six-membered chelate formed from β-alkoxy aldehyde and methyl-aluminum chloride Lewis acids. Specifically, Evans theorized that the six-membered ring chelate **7** may resemble either boat-like conformer **8** or half-chair-like conformer **9** (Figure 6B). Computational studies revealed that the boat-like conformer **8** was lower in energy than conformer **9**. Nucleophilic addition to the sterically less hindered side of **8** would result in the observed major diastereomer. However, due to the specialized reactivity of methyl-aluminum chloride reagents compared with traditional Lewis acids, there is no guarantee that other Lewis acid mediated reactions would lead to the same boat-like chelates methylaluminum chloride reagents do.



Entry	Lewis acid	R	Yield (%)	*anti*:*syn*
1	$BF_3{\bullet}OEt_2$	Bn	75	87:13
2	$SnCl_4$	Bn	83	47:53
3	$TiCl_4$	Bn	87	89:11
4	Me_2AlCl	Bn	73	81:19
5	$MeAlCl_2$	Bn	88	79:21
6	$BF_3{\bullet}OEt_2$	TBS	84	88:12
7	$SnCl_4$	TBS	86	79:21
8	$TiCl_4$	TBS	64	81:19
9	Me_2AlCl	TBS	62	88:12
10	$MeAlCl_2$	TBS	92	94:6

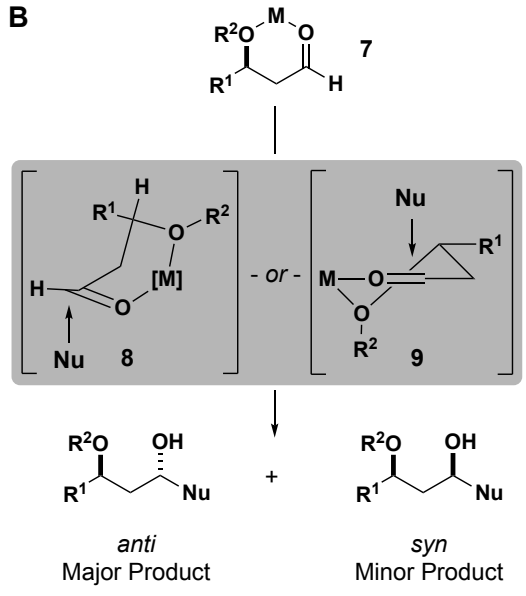


Figure 6. A) Tabulated diastereoselectivities of Mukaiyama aldol additions to aldehyde **5**. B) Conformational models describing nucleophilic additions to six-membered ring chelates.

2.1.1.2 The Cram-Reetz Model

Cram proposed the first open-chain acyclic model describing *anti*-selective nucleophilic additions to β-chiral ketones in 1968 (Figure 7).[10] Alkyl-lithium and alkyl-Grignard nucleophilic additions were carried out in the presence and absence of titanium- and aluminum-based Lewis acids. Cram's ketone substrates contained β-alkyl groups of differing sizes [i.e. R_S (small) vs R_M (medium) vs R_L (large)]. The stereoselectivities that resulted from these nucleophilic additions were all quite mild ranging from completely unselective to up to 76:24 selectivity for product **11**. Based off of their observed selectivities, a model was proposed. This model was built upon the minimization of torsional strain in the ketone substrate and resembles the fully-staggered conformation **10**. In conformation **10**, nucleophilic addition would occur preferentially at the least sterically demanding face of the ketone resulting in major diastereomer **11**.

Reetz modified Cram's acyclic model in their own investigations of nucleophilic additions to β-chiral aldehydes bearing β-alkoxy groups.[5] Reetz found that in addition to $TiCl_4$, $SnCl_4$, $AlCl_3$ and BF_3•OEt_2 mediated nucleophilic addition reactions all possessed moderately high *anti*-selectivity. BF_3•OEt_2, unlike the other Lewis acids used, is unique in that it is monodentate. Chelation was determined by Reetz to be unlikely in reactions run with BF_3•OEt_2 and an acyclic model resembling **13** was proposed to rationalize the observed major diastereomer. In **13**, the BF_3 coordinated aldehyde would possess a strong dipole moment that is minimized by an anti-periplanar-like orientation of the β-alkoxy C–O bond. In this conformation, nucleophilic addition would still be guided by steric effects resulting in the *anti*-diastereomer. The minimization of dipoles in **13** resembles

conformational arguments proposed by Cornforth for nucleophilic additions to α-chiral aldehydes bearing α-polar substituents.

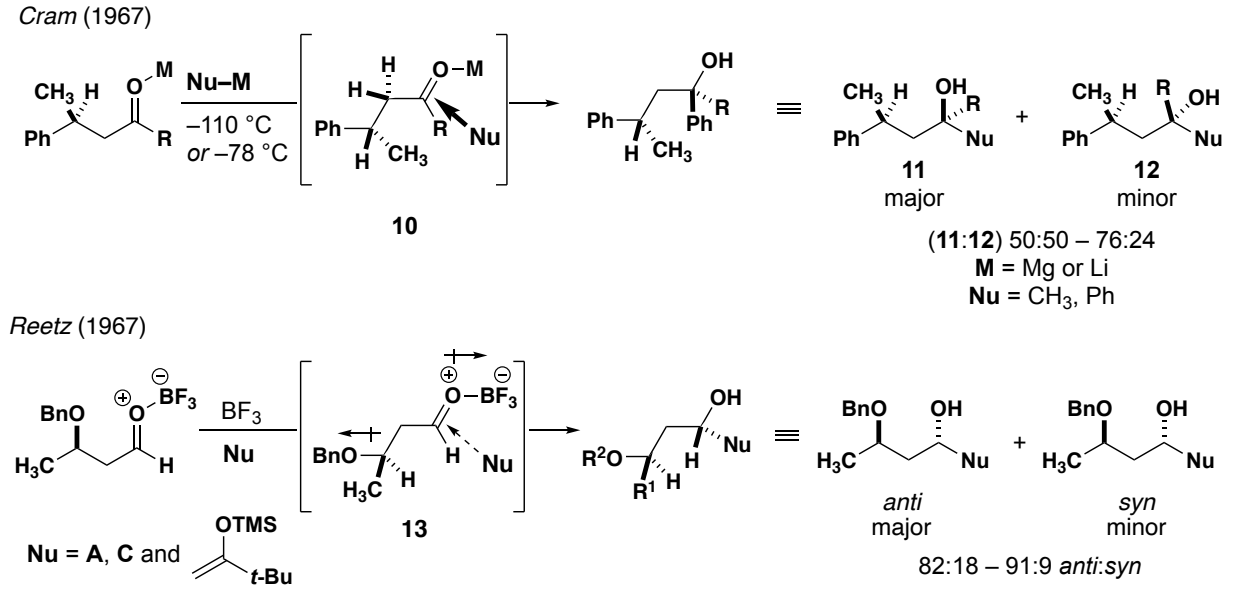


Figure 7. Separate acyclic models described by Cram and Reetz describing nucleophilic additions to β-chiral carbonyls.

2.1.1.3 The Evans Model

Evans reported a comprehensive investigation of 1,3-asymmetric induction effects in aldol reactions of metal enolates and enolsilanes to β-chiral aldehydes in 1994 (Figure 8).[11] In this investigation, Evans was able to assess the impacts of enolate identity and β-substituents on the stereoselectivity of nucleophilic additions. Through the investigations of 3-methyl-2-butanone derived enolate additions, Evans noted that *anti*-selectivity was particularly pronounced in Lewis acid mediated silyl enol ether addition reactions compared to reactions conducted with other metal enolates. Evans also observed diastereoselectivity was highest with a β-alkoxy substituent and that

diastereoselectivities were generally lower for nucleophilic additions for other O-substituents such as OAc and OTBS.

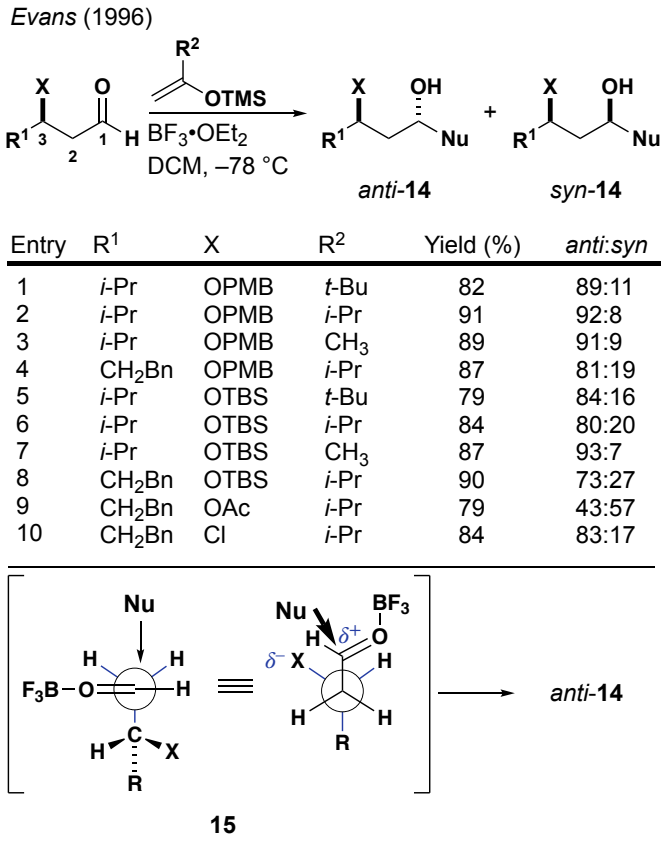


Figure 8. The acyclic Evans model describing nucleophilic additions to β-chiral carbonyls.

Evans proposed a slightly revised version of the Cram-Reetz model which resembles structure **15**. Nucleophilic addition to the least sterically hindered side of **15** results in the major diastereomer observed. According to Evans, the Cram-Reetz model suffered from a staggered-conformation of the C1 and C2 carbons which was shown to be less favorable than a Felkin-like staggered arrangement. In the Evans model, the β-carbon is rotated perpendicular to the aldehyde C=O bond. This allows for a fully "staggered" conformation which the Cram-Reetz model lacks. Evans proposed that in addition to alleviation of torsional strain, the most stable conformer **15** also possesses

favorable electrostatic interactions between the β-oxygen substituent and the activated carbonyl. Evans would later publish computational evidence to support the validity of **15** as a low-energy, and therefore relevant, conformation of substrate.[12]

2.1.1.4 The Issue of *Syn*-Selectivity

Syn-selective nucleophilic additions to β-chiral aldehydes are few and far between. So far, the investigations and models discussed in this chapter have largely been dominated by *anti*-selective nucleophilic addition reactions. Due to the sparsity of *syn*-selective nucleophilic additions in the literature for β-chiral aldehydes, one can only assume that *syn*-selectivity remains elusive through 1,3-asymmetric induction alone. In fact, many routes that target *syn*-diols will generate the *anti*-products first and perform a Mitsunobu reaction to achieve the *syn*-product rather than optimizing reaction conditions to produce adequate amounts of *syn*-product directly. There is a simple reason for why acyclic stereocontrol (e.g. the development of conditions to access all possible stereoisomers through one reaction) is harder to achieve in the case of β-chiral aldehydes relative to alpha chiral aldehydes. Whereas one could leverage chelating or non-chelating conditions to access either *syn* or *anti* stereochemical outcomes of nucleophilic additions to α-chiral aldehydes, both the chelate and non-chelate models describing nucleophilic additions to β-chiral aldehydes lead to the same diastereomer of product. Therefore, it is unlikely that any method to develop a *syn*-selective nucleophilic addition reaction to β-chiral aldehydes and other analogous electrophiles would involve a simple change in a mediating reagent.

2.1.2 Overview of 1,3-Asymmetric Induction in Nucleophilic Additions to β-Alkoxy Imines

Compared to nucleophilic additions to β-alkoxy aldehydes, nucleophilic additions to β-alkoxy imines are far fewer in number. A literature search revealed only two reports published prior to the initiation of this project within our group (Figure 9). One report investigated additions to isopropyl-substituted imine[13] and the other investigated additions to phenyl-substituted imine.[14] The former report noted *anti*-selectivity in allylations using a variety of allylating reagents. *Syn*-selectivity was achieved through the employment of a chiral auxiliary substituent on the imine nitrogen and reactions with 9-BBN. While this *syn*-selectivity is indeed synthetically practical, the resulting *N*-alkyl amine product would be unsuitable for subsequent deprotection and derivatization. The latter report demonstrated that reactions employing diethylzinc and $ZnCl_2$ resulted in the alkylation of imine **16** to produce **17** in 75% yield and >97:3 selectivity for the *anti*-product. Both reports proposed chelation resulted in the major diastereomer observed.

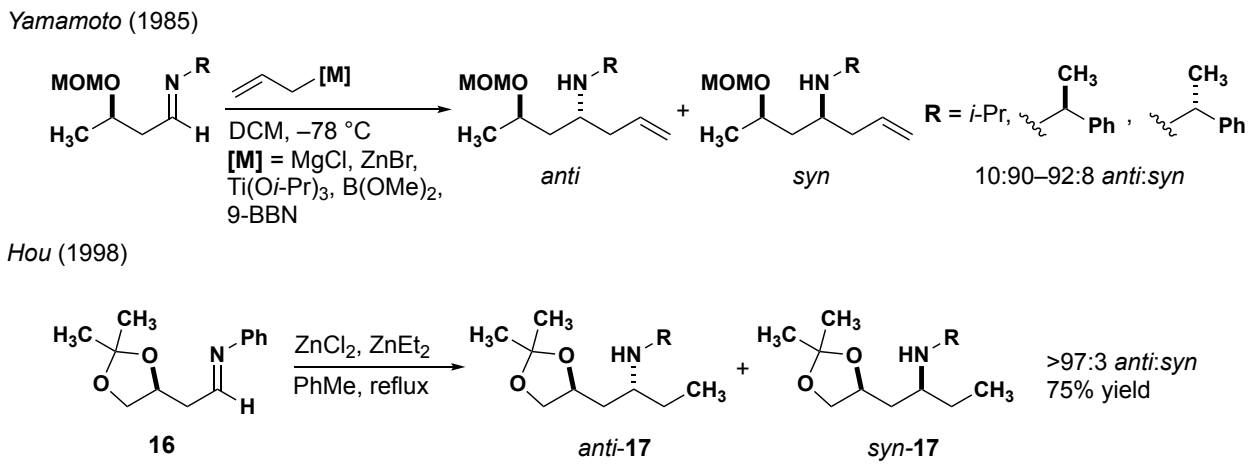


Figure 9. Known nucleophilic additions to β-alkoxy imines.

2.2 The Role of 1,3-Asymmetric Induction in Diastereoselective Nucleophilic Additions to Beta Alkoxy *N*-Tosyl Imines

My previous studies of diastereoselective nucleophilic additions to α-chiral *N*-Ts imines led to the further exploration of nucleophilic additions to β-chiral *N*-Ts imines. The initial goals of this investigation were to conduct a comprehensive investigation of β-alkoxy imines, the kind that was absent so far in literature, as well as pursue the possibility of acyclic stereocontrol for nucleophilic additions to *N*-Ts imines by leveraging our understanding of nucleophilic additions to α-chiral imines. The completion of these goals would allow for access to 1,3 amino alcohol precursors which are a common motif in biologically active targets. Furthermore, as was in the case of our previous study, a better understanding of imine substrate asymmetric induction effects will allow for more efficient synthetic planning in synthetic efforts to target nitrogen-containing natural products or drug candidates.

2.2.1 Substrate Synthesis

Several β-alkoxy aldehydes and aldimines were synthesized for this study (Figure 10). Before embarking on the synthesis of β-alkoxy imines, we initially assumed that the conditions developed for α-alkoxy imines could be applied directly to the synthesis of beta alkoxy imines with minimal changes. Throughout the development and execution of synthetic routes to access β-alkoxy imines, it became apparent that β-alkoxy imine synthesis required different approaches from that of α-chiral imines. Synthesis of β-alkoxy aldehydes and consequently, the imines themselves, are complicated by a variety of

factors. β-alkoxy groups of an ester, aldehyde or imine, are primed for elimination under basic and acidic conditions. These substrates may also undergo retro-Claisen, retro-aldol and retro-Mannich reactions respectively. The variety of side-products possible from each synthetic step of a route often complicated analysis of crude reaction mixtures. An account of how these obstacles were overcome for substrates employed in this study is presented in this part of the chapter. Failed substrates are also discussed.

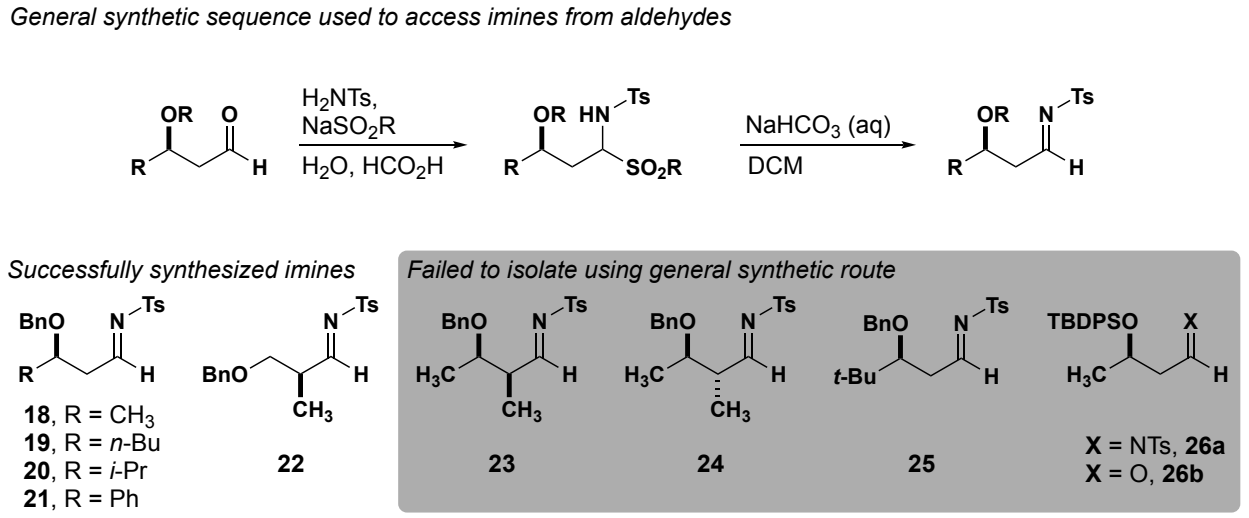


Figure 10. Successful and failed imine substrates derived from their analogous aldehydes using general synthetic route.

2.2.1.1 Synthesis of Imine 18

For this investigation, a model substrate **18** was chosen based off of ease of synthetic access and comparability to previous studies published with β-alkoxy aldehydes. **18** can be accessed from its analogous aldehyde using methods developed for α-alkoxy imine synthesis described in Chapter 1. There were many published synthetic routes to access **18** from a number of commercially available starting material. Furthermore, its analogous aldehyde was a commonly used substrate in the previous

reports investigating nucleophilic additions to β-alkoxy aldehydes discussed earlier in the chapter and so nucleophilic additions to imine **18** would be highly informative. This substrate would help to build foundational knowledge of the new terrain through a one-variable change (NTs instead of O) from what is known in the literature.

While there are several ways of accessing **18** from literature precedent, synthetic routes were explored until the most practical route emerged. Attempts to utilize a route analogous to the synthetic route described for α-chiral aldehydes were met with significant challenges from the very beginning. Benzylation of commercially available β-hydroxy ester **27** using sodium hydride produced a mixture of **28**, **29**, and **30**. It was concluded that under basic alkylating conditions, β-hydroxy esters are prone to elimination by deprotonation of α-hydrogens to produce α,β-unsaturated side products and benzyl alcohol resulting in **28**. The presence of benzyl ester **30** suggests that elimination in this case has downstream effects that complicate alkylation of β-hydroxy esters under basic conditions. While **29** and **30** could proceed in the synthetic route to access aldehyde, using previously employed $LiAlH_4$ reduction and IBX oxidation, a significant amount of benzyl alcohol (from the reduction) and subsequently benzaldehyde upon oxidation rendered this route impractical as extensive purification would be required.

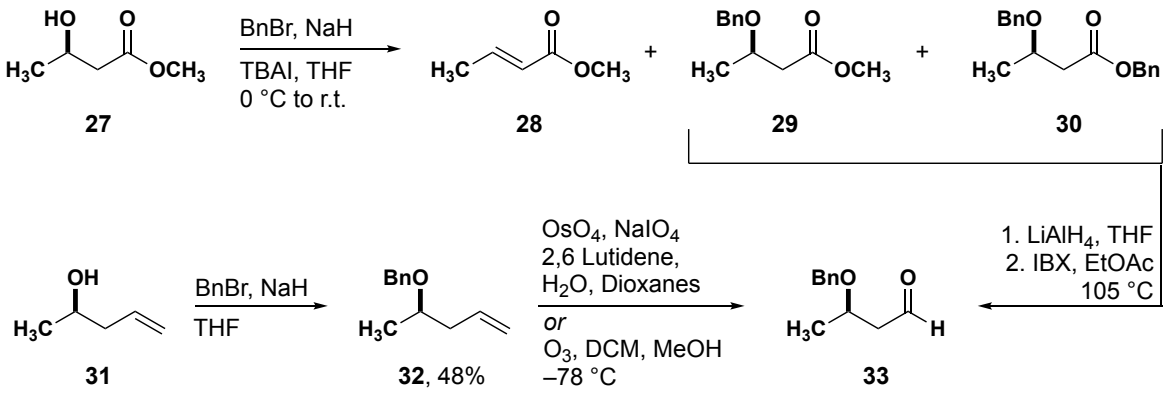


Figure 11. Attempts to access aldehyde **33** from starting materials **27** and **31**.

Our initial route was abandoned in favor of a new route which started with homoallylic alcohol **31**. Upon benzylation and Lemieux-Johnson oxidation, aldehyde precursor **33** was obtained. While the yield was modest, there was enough material to attempt amidosulfone formation and subsequent imine isolation, which were both successful (though poor yielding partially due to the small scale of the reactions). Although the Lemieux-Johnson oxidation is a reliable reaction and near quantitative in yield, it involves the use of OsO4 which is highly toxic. Milder ozonolysis condition were used in place of the Lemieux-Johnson oxidation and although aldehyde was produced, purification of the aldehyde was required as incomplete conversion was observed and PPh_3 used during the quenching of the reaction created unnecessary waste in the form of triphenylphosphine oxide.

The last and final route to access aldehyde **33** (and subsequently imine **18**) was determined to be the most practical. Starting from commercially available diol **34**, benzylidene acetal formation and regioselective ring opening[15] with DIBAL gave access to monobenzylated alcohol **36**. Alcohol **36** was oxidized to aldehyde **34** using IBX.

Notably, lower temperatures and shorter reaction times should be used in IBX oxidations of alcohols resembling **36** as over-oxidation to carboxylic acid was observed when the original temperature of 105 °C was applied. Amidosulfone formation was successful for this substrate in up to 70% yield.

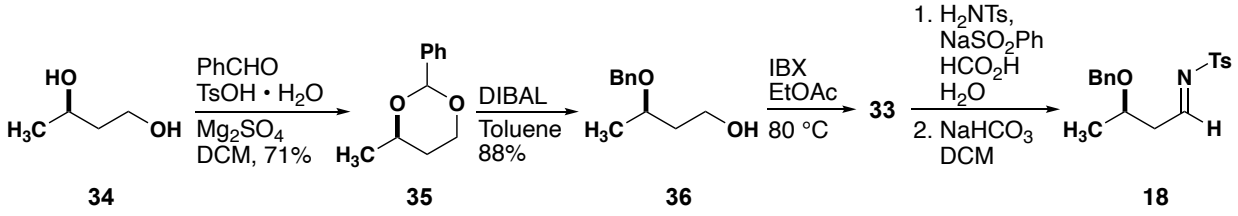


Figure 12. Final route to access imine **18**.

2.2.1.2 Synthesis of Imine 22

At the onset of the project, another model imine substrate **22** was selected as an additional point of comparison with imine **18**. Imine **22** bears α-chirality through a methyl substituent at the alpha position. However, it still retains an alkoxy group beta to the imine which should allow for the formation of a six-membered ring chelate. Compared with imine **18**, imine **22** should reveal the importance of the alkyl substituent's placement around the six-membered ring chelate under favorable chelating conditions. Due to the presence of an α-chiral carbon, it should also reveal whether or not 1,2 asymmetric induction plays a role in the stereoselective outcome of nucleophilic additions to α-chiral β-alkoxy imines. Furthermore, imine **22** is derived from aldehyde **39**, another commonly used β-alkoxy substrate from previous literature.

The development of a route to access imine **22** was comparatively more straight-forward than that of imine **18**. Starting from symmetrical diol **37**, mono-benzylation can

be achieved using silver (I) oxide and benzyl bromide in DCM.[16] This reaction is solvent sensitive as significant di-alkylation was observed when THF was used as the solvent. Oxidation of alcohol **38** to aldehyde **39** proceeded clearly with no need for purification. Unfortunately, amidosulfone formation using standard conditions failed to yield product (e.g. precipitation did not occur which complicated the isolation of any solid amidosulfone). Several amidosulfone formation conditions were screened until it became clear that carrying out the reaction in a higher ratio of formic acid to water yielded isolable solids. Furthermore, while our experience in working with α-chiral amidosulfones suggested that this reaction benefits more from scale (e.g. larger scale saw greater yields of product), for aldehyde **39**, reactions conducted at a larger scale would fail to produce solids. By dividing the starting material into smaller components and carrying out a set of smaller scale reactions, it ensured that amidosulfone would always form and be isolated. Our initial, failed, reaction was conducted at 3 mmol. All subsequent amidosulfone formation reactions were conducted at 2 mmol or lower scale. Finally, with amidosulfone in hand, access to imine **22** was granted using our previously developed conditions (saturated aqueous $NaHCO_3$ and DCM).

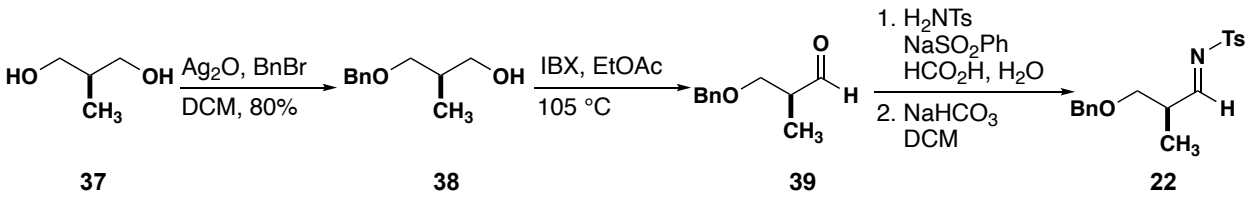


Figure 13. Synthesis of imine **22**.

2.2.1.3 Failed Syntheses of Imines 23 and 24

As we continued our investigations of β-alkoxy imines, α- and β-chiral imines **23** and **24** arose as mechanistically interesting substrates we could potentially target. Nucleophilic additions to imines **23** and **24** could provide a great deal of insight into the conformational preferences of a six-membered ring chelate, should it form. The two alkyl substituents placed at the α- and β-carbons of the imine were hypothesized to either have compounding or competing effects on the resulting stereoselectivity. Unfortunately, the very feature that made them mechanistically interesting to target also made them synthetically challenging to procure.

We first attempted to synthesize imine **23**. Starting from commercially available β-hydroxy ester **27**, α-methylation was performed using LDA, HMPA and methyl iodide yielding one major diastereomer **40** and small, yet detectable amounts of the minor diastereomer by ^{1}H NMR. The crude reaction mixture was taken into a benzylation using basic conditions and significant retro-aldol was observed by analysis of the crude material. Benzylation using silver (I) oxide yielded relatively cleaner conversion to **41** though extensive flash chromatography was still required and the isolated yield was generally low. **41** isolated from this reaction was reduced with lithium aluminum hydride in THF which yielded alcohol **42** in 19% yield (over 3 steps). Oxidation with IBX at 80 °C procured aldehyde **43** but as a 47:53 mixture of diastereomers. Presumably, the oxidation conditions epimerized whatever aldehyde was being formed in the reaction. Aldehyde **43** isolated from the above route as a mixture of diastereomers was sent into an amidosulfone formation reaction to assess the ability of either diastereomer to produce amidosulfone. This reaction was ultimately unsuccessful in producing isolable solids,

though it was unclear at the time whether or not the diastereomerically pure aldehydes would be more successful.

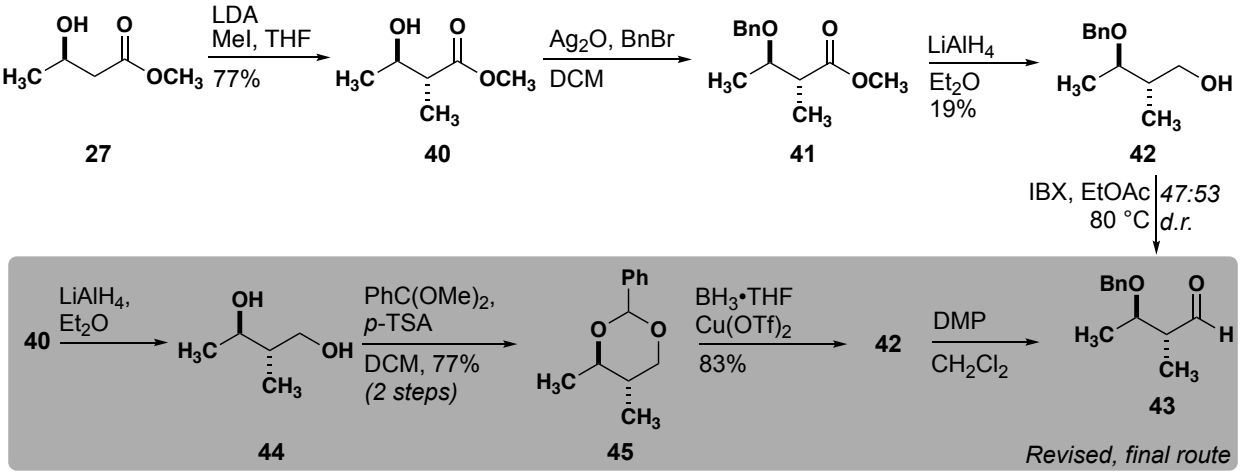


Figure 14. Synthesis of aldehyde **43**.

The above route was modified slightly to avoid epimerization at the oxidation step and improve yields, which allowed for the accomplishment of the final route. As methylation using LDA and THF procured mainly single diastereomer of product (>95:5 dr), the rest of the route was designed to avoid epimerization of the α-stereogenic center and improve the yield of benzylation. $LiAlH_4$ reduction of ester **40** proceeds cleanly to diol **44**. However, acetal formation with benzaldehyde and *p*-TsOH yielded no product. Instead, benzylidene acetal formation was accomplished using the dimethyl acetal of benzaldehyde and *p*-TsOH in good yields. DIBAL ring opening of **45** was unsuccessful and instead BH_3•THF conditions were found in the literature to perform similar regioselective ring openings with catalytic $Cu(OTf)_2$. Benzylated alcohol **42** was procured in good yields after flash column chromatography. Finally, DMP was found to be an effective oxidant and can used at lower temperatures. Switching oxidation conditions

seemed to avoid epimerization and aldehyde **43** was obtained as a single diastereomer. Unfortunately, our attempts to form amidosulfone with aldehyde **43** were all unsuccessful and later, we determined it to be unnecessary for the project.

The diastereoselective synthesis of aldehyde **52** was accomplished through the use of Evans auxiliary chemistry. Benzyl Evans auxiliary **46** can be acylated using literature reported conditions to procure **47**. Using **47**, an Evans aldol reaction was carried out using acetaldehyde, $TiCl_4$, NMP and TMEDA at cryogenic temperatures to procure **48** with high diastereoselectivity (>95:5). The Evans aldol reaction took a significant amount of time to optimize as it is highly sensitive to temperature, reaction times and reagent purity. Deviation from the temperatures and reaction times employed in the reaction may result in much poorer yields and diastereoselectivities for the reaction. Similarly, all reagents should be freshly purchased and or distilled prior to execution of the reaction. Once **48** was procured, the auxiliary was cleaved with $LiBH_4$, leading to diol **49**. Formation of the benzylidene acetal and ring opening with BH_3•THF and $Cu(OTf)_2$ provided alcohol **51** in reasonable yields. Unfortunately, alcohol **51** often co-eluted with benzyl alcohol during column chromatography (a remnant from the benzylidene acetal formation step). MnO_2 was often used to selectively oxidize the benzyl alcohol impurity present after ring-opening to enable easy purification of alcohol **51**. Finally, a DMP oxidation was used to avoid epimerization and unnecessary flash column chromatography. Like with aldehyde **43**, aldehyde **52** failed to provide amidosulfone products using the standard conditions within the lab.

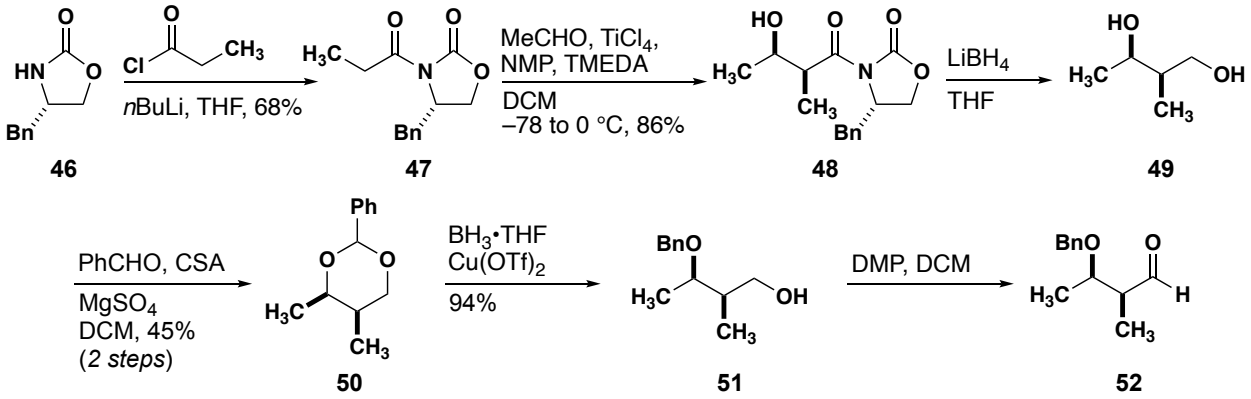


Figure 15. Synthesis of aldehyde **52**.

2.2.1.4 Syntheses of Other β-Benzyloxy Substrates

Several β-benzyloxy aldehydes (Figure 16) were synthesized with varying β-alkyl substituents to assess the steric impact of the β-alkyl group on diastereoselectivity. β-*n*-Bu-, -*i*-Pr-, -*t*-Bu- and -phenyl-substituted aldehydes were synthesized using the same synthetic sequence from their respective commercially available β-keto esters. While the basic $LiAlH_4$ conditions employed in the reduction of β-keto esters was low yielding, diols **54a**–**d** were all isolated in sufficient quantities to continue in the route. Diols resembling **54** are incredibly difficult to purify due to streaking during flash column chromatography. Instead, most diols were sent directly into benzylidene acetal formation and subsequent regioselective ring-opening. Purification of **55** and **56** provided sufficiently pure alcohol for DMP oxidation. Once obtained, aldehydes **57a**, **57b** and **57c** led to the formation of amidosulfone and consequently, imine. The *t*-Bu substituted **57d** failed to produce amidosulfone.

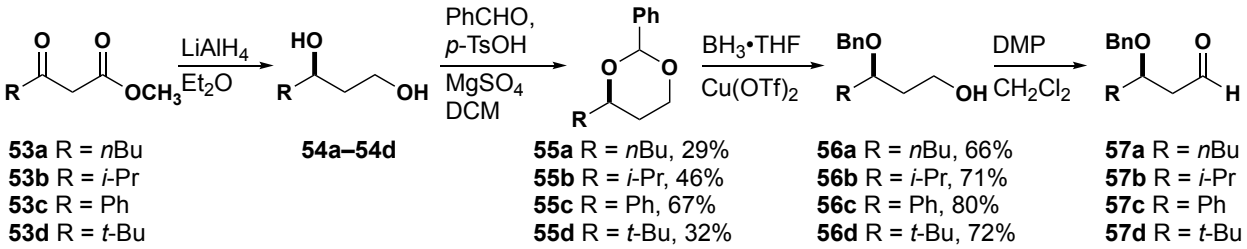


Figure 16. Synthesis of aldehydes **57a**–**57d**.

2.2.1.5 Synthesis of β-Silyloxy Aldehyde 26

A β-silyloxy substrate **26** was synthesized in order to assess the effects of chelation on diastereoselectivity (Figure 17). As bulky silyl groups such as TBDPS are known to disfavor chelation, the diastereoselectivity of reactions employing **26** should represent selectivity in the absence of a six-membered ring chelate. Known silyloxy aldehyde **26** was prepared according to literature procedure but like many of the other substrates, failed to produce amidosulfone using the general synthetic route described *vide supra*.

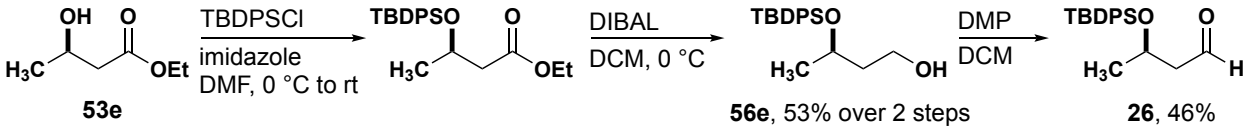


Figure 17. Synthesis of aldehyde **26**.

2.2.2 Lewis Acid-Mediated Nucleophilic Additions to β-Alkoxy Imines

Our investigation of 1,3-asymmetric induction in Lewis acid mediated nucleophilic additions to β-alkoxy imines began with imines **18** and **23** using different nucleophiles and Lewis acids. Several allylating reagents and silyl enol ethers were employed in our studies to varying degrees of success. We hypothesized that should a six-membered ring

chelate form with these imine substrates and addition was successful, *anti*-products would predominate in the case of β-chiral substrates resembling **18** (Figure 18), though the magnitude of the stereoselectivity was still unknown. Nevertheless, the results of these studies would inform the mechanism by which the stereoselectivity would result, and provide insight as to what are the optimal conditions for achieving high diastereoselectivity in such reactions.

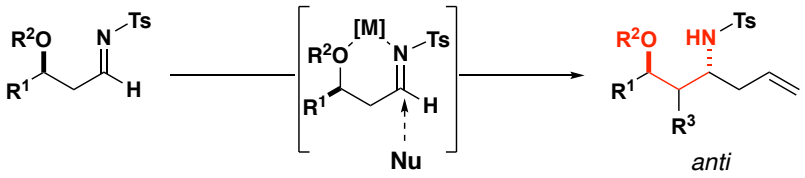


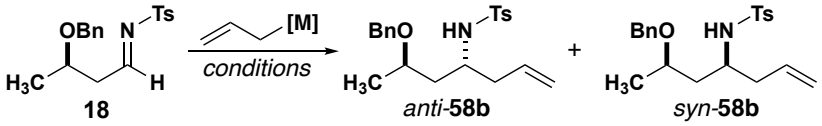
Figure 18. Nucleophilic attack on a six-membered ring chelate formed from β-chiral imines.

2.2.2.1 Lewis Acid-Mediated Nucleophilic Additions to Imine 18

Lewis acid mediated nucleophilic additions to imine **18** were mostly *anti*-selective as expected (Table 2). Several Lewis acids that were successful in addition reactions to α-chiral imines were employed in our initial Lewis acid screen. $AlCl_3$, $SnCl_4$ and $Cu(OTf)_2$ stood out as Lewis acids that provided the highest yields and diastereomeric ratios of product for the reaction. Notably, reactions conducted with BF_3•OEt_2 and TfOH were both *anti*-selective though modest-yielding. In the case of TfOH, proton-chelation is most likely responsible for the observed *anti*-selectivity. Overall, the selectivities of these reactions are less sensitive to temperature and solvent effects (compared to reactions of α-chiral imines). Furthermore, allylations using potassium allyltrifluoroborate were poor yielding and less selective. Regardless of the conditions employed, *anti*-selectivity for allylations conducted with imine **18** capped out at around 80:20. One reaction with silyl enol ether of

acetophenone was attempted with $SnCl_4$ and while the selectivity was marginally higher (87:13), the yield was quite poor.

Table 2. Nucleophilic Additions to Imine **18**.



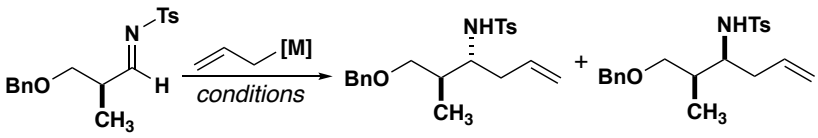
Entry	[M]	Lewis acid	Solvent	Temp (°C)	*anti*:*syn*[a]	yield[b]
1	TMS	$ZnBr_2$	CH_2Cl_2	–78 to 23	73:27	90%
2	TMS	ZnI_2	CH_2Cl_2	–78 to 23	78:22	32%
3	TMS	$AlCl_3$	CH_2Cl_2	–78 to 23	81:19	96%
4	TMS	$SnCl_4$	CH_2Cl_2	–78 to 23	80:20	92%
5	TMS	$TiCl_4$	CH_2Cl_2	–78 to 23	78:22	41%
6	TMS	TfOH	CH_2Cl_2	–78 to 23	82:18	57%
7	TMS	BF_3•OEt_2	CH_2Cl_2	–78 to 23	81:19	49%
8	TMS	BF_3•OEt_2	$CHCl_3$	–20	81:19	26%
9	TMS	$Cu(OTf)_2$	CH_2Cl_2	–78 to 23	79:21	72%
10	BF_3K	BF_3•OEt_2	$CHCl_3$	–20	68:32	13%
11	Bpin	BF_3•OEt_2	CH_2Cl_2	–78 to 23	n.d.	n.d.
12	$SnBu_3$	$AlCl_3$	CH_2Cl_2	–78 to 23	76:24	60%
13[c]	TMS	$Cu(OTf)_2$	CH_2Cl_2	–78 to 23	n.d.	n.d.

[a]*anti:syn* ratios determined by integration of ^{1}H NMR spectra of unpurified reaction mixtures. [b]Yields obtained by integration of ^{1}H NMR spectra with 1,3,5-trimethylbenzene as the internal standard. [c]Reaction run with 2.0 equiv. of 2,6-di-tertbutylpyridine.

2.2.2.2 Lewis acid-Mediated Nucleophilic Additions to Imine 22

Imine **22** was selected for nucleophilic additions to provide more insight on the conformational preferences on a six-membered ring chelate (Table 3). As imine **22** bears steric bulk closer to the electrophilic center of the molecule, selectivity should be higher if only steric crowding dictated the resulting selectivity. However, diastereoselectivities of reactions conducted with imine **22** were generally lower than that of reactions with imine **18**. Furthermore, reactions conducted with TfOH, $Cu(OTf)_2$ and BF_3•OEt_2 were all non-selective. Similarly, an addition reaction using methallyltrimethylsilane was unselective with $AlCl_3$.

Table 3. Nucleophilic Additions to Imine **22**



22 *anti*-**59** *syn*-**59**

Entry	[M]	Lewis-acid	Solvent	Temp (°C)	*anti*:*syn*[a]	yield[b]
1	TMS	$ZnBr_2$	CH_2Cl_2	–78 to 23	68:32	80%
2	TMS	ZnI_2	CH_2Cl_2	–78 to 23	29:71	6%
3	TMS	$AlCl_3$	CH_2Cl_2	–78 to 23	82:18	93%
4	TMS	$SnCl_4$	CH_2Cl_2	–78 to 23	71:29	32%
5	TMS	$TiCl_4$	CH_2Cl_2	–78 to 23	75:25	73%
6	TMS	TfOH	CH_2Cl_2	–78 to 23	50:50	95%
7	TMS	$FeCl_3$	CH_2Cl_2	–78 to 23	56:44	52%
8	TMS	$Cu(OTf)_2$	CH_2Cl_2	–20	60:40	88%
9	TMS	$BF_3{\bullet}OEt_2$	$CHCl_3$	–20	50:50	92%
10	BF_3K	$BF_3{\bullet}OEt_2$	$CHCl_3$	–20	52:48	53%

[a]*anti*:*syn* diastereomeric ratios determined by integration of ^{1}H NMR spectra of unpurified reaction mixtures. [b]Yields obtained by integration of ^{1}H NMR spectra with 1,3,5-trimethylbenzene as the internal standard.

2.2.2.3 Discussion of a Model that Rationalizes Observed Selectivities

Consideration of previously proposed models and observed experimental results allowed for the development of a working model describing Lewis acid mediated nucleophilic additions to β-alkoxy *N*-Ts imines. As mentioned above, the comparison of selectivities resulting from imine **18** and **22** suggest that a simple facial preference of a nucleophile to the least sterically hindered side of the chelate is an inadequate explanation for the observed selectivity. That is to say, for an otherwise flat six-membered ring chelate, one should see higher selectivity the closer the alkyl substituent (such as in the case with imine **22**). This should also be true if the six-membered ring chelate embodies a boat-like conformation. Instead, the diastereoselectivities observed in reactions using imine **22** are generally lower than that of reactions using with imine **18**.

A model that best captures the observed selectivities of this project is a model that depicts the six-membered ring chelate as a half-chair (Figure 19). In this model, two half-chair conformers are available to each chelate. For imine **18**, these half-chair conformers are **60a** and **60b**. **60a** is arguably lower in energy due to bearing a pseudo-equatorial alkyl substituent rather than an axial one. From these two half-chair conformers, four paths of nucleophilic approach can be considered. Two of the four would lead to higher-energy twist-boat products and therefore go through higher-energy transition-state structures. Of the remaining two, only one trajectory avoids steric interactions with the alkyl substituent. This trajectory of attack happens to most favorably occur with the lower-energy conformer **60a** and leads to *anti*-product for imine **18**.

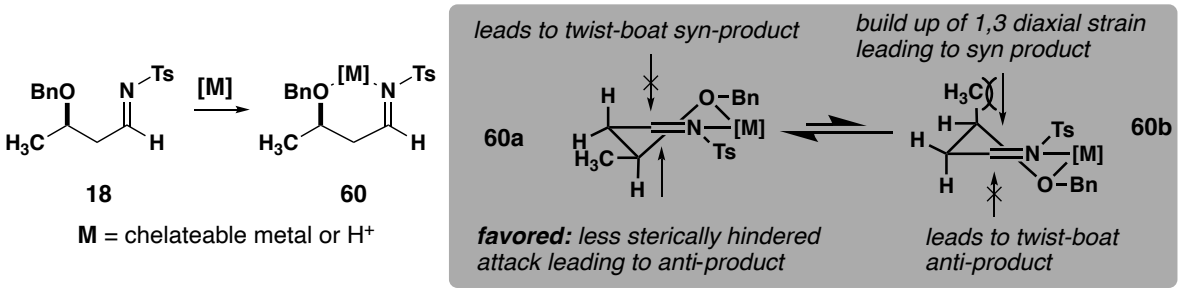


Figure 19. Nucleophilic attack on half-chair chelates formed from imine **18**.

When applied to imine **22**, the half-chair model reveals a potential explanation for the generally lower selectivities observed (Figure 20). A six-membered ring chelate **61** may be formed from imine **22**. This chelate will also possess two half-chair conformers with relative energies dictated by the orientation of its substituents, **61a** and **61b**. In this case, **61a** would be the presumed lower-energy conformer. Evaluation of the four modes of nucleophilic attack render two modes unfavorable due to the formation of twist-boat products. Of the remaining two, the least sterically hindered mode of attack would occur

on the *higher energy* conformer of chelate in order to lead to *anti*-product. Whereas in imine **18**, steric effects and conformational preference of chelate are reenforcing, for imine **22**, they are contradictory.

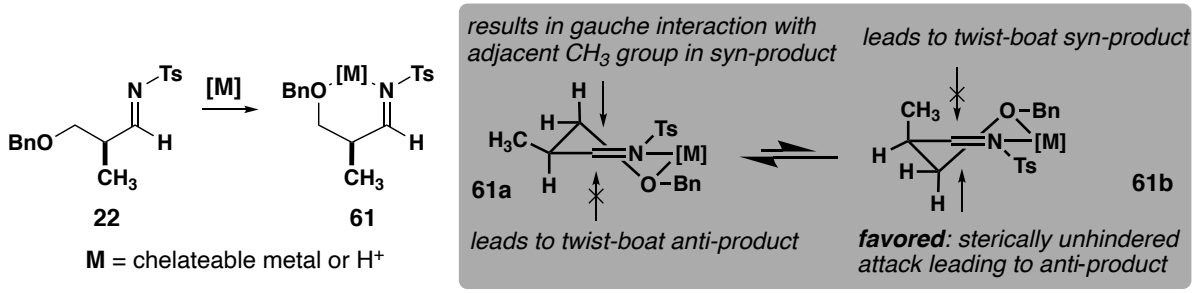


Figure 20. Nucleophilic attack on half-chair chelates formed from imine **22**.

The consideration of six-membered ring electrophiles as half-chair conformers has been discussed before in the cases of six-membered ring iminium ions[17] [18] and oxocarbenium ions.[19] The arguments proposed in our investigation aligns with those proposed in additions to iminium ions and oxocarbenium ions as nucleophilic trajectories are weighed against the formation of twist-boat products (similar to arguments proposed in the Fürst-Plattner rule[20]). As mentioned previously, Evans considered a half-chair conformer in their studies of dimethylaluminum chloride-mediated nucleophilic additions to β-alkoxy aldehydes. In Evans' investigations, their computational results showed that a half-chair-like conformer was less likely than a boat-like conformer and therefore they neglected to provide a half-chair conformational argument for their observed selectivities. As our own experimental observations seem to agree with a half-chair-like conformation of chelate, we attempted to further explore this hypothesis by investigating other imine substrates.

2.2.2.4 Discussion of BF_3•OEt_2-Mediated Reactions

BF_3•OEt_2-mediated nucleophilic additions to β-chiral *N*-Ts imines provided an additional outlook to evaluate the acyclic models previously proposed to rationalize *anti*-selectivity in the presence of mono-dentate BF_3•OEt_2. The *anti*-selectivity observed with BF_3•OEt_2 cannot be easily explained by the Cram-Reetz model. A fundamental difference between an aldehyde and an *N*-Ts imine is the mode of coordination between the Lewis acid and the Lewis base. Coordination of a Lewis acid to an aldehyde occurs *trans* to the aldehyde substituent along the C=O double bond. This is the fundamental assumption that the Cram-Reetz model and Evans model is based on. In *N*-Ts imines, Lewis acids must bond *cis* to the imine carbon substituent. This changes the direction of the major dipole moment of the molecule. In order to achieve the minimization of dipoles proposed by Reetz in the Cram-Reetz model, the C–O bond of the β-alkoxy substituent would have to rotate 180 °C from its orientation depicted in **13**. The nucleophile would preferentially attack the least sterically-hindered face of the electrophile and result in the *syn*-product instead of the *anti*-product observed through a conformation resembling **63** (Figure 21). Our previous work described in Chapter 1 lends credence to the possibility of a BF_2 chelate **64** which could be an alternative explanation for the *anti*-selectivity observed.

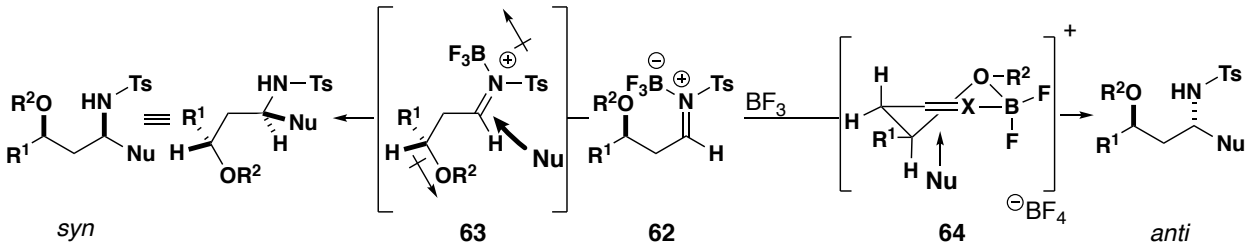


Figure 21. BF_3•OEt_2 mediated nucleophilic additions to β-alkoxy imines.

2.2.3 Multi-Component Reactions (MCRs) of β-Alkoxy Aldehydes

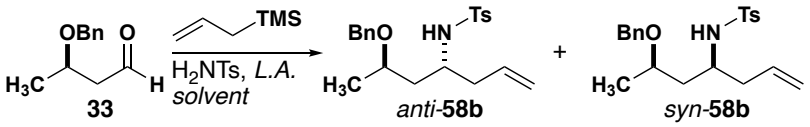
A major obstacle in our investigation so far has been the formation of amidosulfone products and thus imine from the aldehyde substrates we were able to painstakingly synthesize. To overcome this obstacle, we considered the employment of multi-component allylation conditions[21, 22] developed for aryl aldehydes and *N*-Cbz amine to β-alkoxy aldehydes that were synthesized but could not be converted to imine. We did not consider using these conditions in our studies of α-chiral imines as a MCR involving aldehyde, amine and allylating agent would most likely involve an iminium ion in its reaction mechanism. In our investigations of α-chiral imines, iminium ions would result in high *syn* (or chelate-derived) selectivity through proton-chelation and that would inevitably interfere with acyclic stereocontrol. In this investigation, the presence of a possible proton-chelate would not interfere as reactions conducted with chelate-control and the absence of chelateable conditions are both predicted to lead to the same diastereomer of product. By using MCR conditions to access allylated products, we can avoid issues with imine access due to the requisite amidosulfone formation step, thereby directly converting aldehydes to imine addition products.

2.2.3.1 Development of MCR Conditions

Using MCR conditions, homoallylic amines can be generated from the combination of tosyl amine, aldehyde and allylating agent in one pot through *N*-Ts imine formed *in situ.* To identify the optimal conditions for yield and selectivity, a Lewis acid screen was conducted (Table 4). Temperature and solvent effects were also assessed. $Cu(OTf)_2$ was

identified as the ideal Lewis acid for this transformation as it gave no discernable side products resulting from direct addition of the aldehyde. However, application of proton scavenger 2,6-di-tert-butylpyridine in tandem with a $Cu(OTf)_2$ mediated MCR resulted in no product (entry 12). This led us to conclude that reactions conducted with $Cu(OTf)_2$ were likely Brønsted acid mediated through residual TfOH. Notably, MCRs carried out directly with TfOH did not proceed as cleanly as reactions carried out with $Cu(OTf)_2$. In this case, $Cu(OTf)_2$ appears to be a convenient source of catalytic TfOH, which somewhat benefits the reaction as opposed to using stoichiometric amounts of TfOH directly.

Table 4. Lewis Acid-Mediated Allylations of Aldehyde **33** Using MCR Conditions.



Entry	Lewis acid	Solvent	Temp (°C)	*anti*:*syn*[a]	% addition to **33**[a]
1	$BF_3{\cdot}OEt_2$	MeCN	0	60:40	5
2	$BF_3{\cdot}OEt_2$	CH_2Cl_2	–20	79:21	35
3	$AlCl_3$	CH_2Cl_2	–20	68:32	19
4	$SnCl_4$	CH_2Cl_2	–20	68:32	11
5	$TiCl_4$	CH_2Cl_2	–20	70:30	24
6	$Cu(OTf)_2$	CH_2Cl_2	–20	82:18	—
7	$Cu(OTf)_2$	MeCN	–20	60:40	—
8	$Cu(OTf)_2$	PhMe	–20	80:20	—
9	$Cu(OTf)_2$	CH_2Cl_2	–20	80:20	—
10	$Cu(OTf)_2$	CH_2Cl_2	0	82:18	—
11	$Cu(OTf)_2$	CH_2Cl_2	rt	80:20	—
12[b]	$Cu(OTf)_2$	CH_2Cl_2	rt	n.d.	n.d.
13	TfOH	CH_2Cl_2	–20	75:25	4

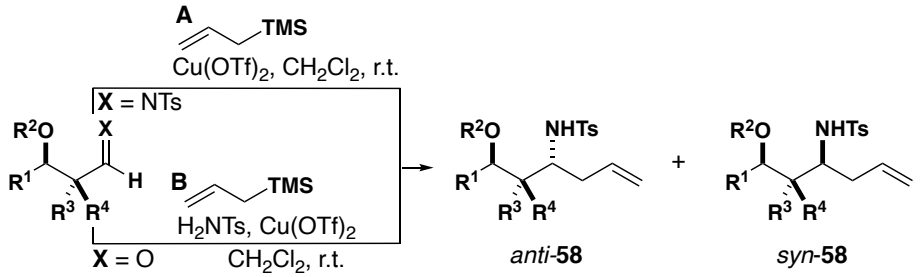
[a]Determined by intergration of ^1H NMR spectra of unpurified reaction mixtures. [b]Reaction run with 2.0 equiv. of 2,6-di-tert-butylpyridine.

2.2.3.2 MCR Substrate Scope

The optimized MCR conditions developed were applied to all of the aldehyde substrates previously synthesized and resulted in successful conversion to each addition product. Substrates that could undergo direct addition (by imine isolation) and MCR led

to similar diastereoselectivities regardless of method employed. The presence of a silyloxy β-substituent as opposed to an alkoxy β-substituent has a pronounced effect on stereoselectivity most likely due to its added steric bulk disfavoring chelation. Unfortunately, reactions using aldehydes **23** and **24** were both non-selective, contrary to our initial hypothesis. Nevertheless, a subtle trend is apparent showing diastereoselectivity increases with β-alkyl substituent size (entries 2–6). These selectivities would now serve as points of correlation for computational studies.

Table 4. MCR scope.



Entry	Electrophile	R^1	R^2	R^3	R^4	Product	Conditions **A** *anti*:*syn*[a] (yield%)	Conditions **B** *syn*:*anti*[a] (yield%)
1	**26b**	CH_3	TBDPS	H	H	**58a**	—	54:46 (70)
2	**18/34**	CH_3	Bn	H	H	**58b**	79:21 (72)	78:22 (44)
3	**19/57a**	*n*-Bu	Bn	H	H	**58c**	83:17 (74)	78:22 (55)
4	**20/57b**	*i*-Pr	Bn	H	H	**58d**	89:11 (45)	81:19 (37)
5	**57d**	*t*-Bu	Bn	H	H	**58e**	—	89:11 (44)
6	**21/57c**	Ph	Bn	H	H	**58f**	95:5	92:8 (76)
7	**43**	CH_3	Bn	CH_3	H	**58g**	—	49:51 (60)
8	**52**	CH_3	Bn	H	CH_3	**58h**	—	67:33 (47[b])

[a]*anti:syn* ratios determined by intergration of ^{1}H NMR spectra of unpurified reaction mixtures. [b]Yield obtained by intergration of ^{1}H NMR spectra with 1,3,5-trimethylbenzene as the internal standard.

2.2.4 Computational Exploration of Proposed Stereochemical Model

Diastereoselectivities gained from the MCRs we ran on several substrates provided an opportunity for us to explore the conformational preferences of six-membered ring chelate computationally. Proton-chelation through Brønsted acid mediation was

assumed for these reactions and therefore the identity of the chelate would be assumed to resemble **60** (where [M] is a chelateable proton). Our hypothesis describes two half-chairs possible for each substrate and as mentioned previously, each half-chair is assumed to lead to one diastereomer of product through Fürst-Plattner-like attack of the nucleophile. My approach to evaluating the validity of the half-chair model in describing nucleophilic additions to β-alkoxy imines was to compare the observed selectivities with the energy differences in half-chair conformers.

2.2.4.1 Description of Methods

Dr. Jason Fell and the Houk group's work in our studies of α-chiral imines informed the methods I chose to computationally evaluate the possibility of a proton chelate and examine relative energies of half-chairs **66–67**. Binding energies, geometries and free energies were calculated for all species using Gaussian16[23] and the B3LYP[24] density functional with a 6-31G(d,p) basis set. *N*-Ts imines were truncated to *N*-SO_2CH_3 imines to reduce computational cost and time. These methods were previously applied in our studies of α-chiral imines and computational fidelity was preserved.

2.2.4.2 Results

Binding of proton and truncated imine **18** to form chelate **65** was determined to be energetically favorable (Figure 22). Optimization of chelate **65** (regardless of input geometry) resulted in a half-chair-like geometry, consistent with our hypothesis. So, proton-chelate **65** may exist as either half-chair-like conformer **66b** or **67b**. Assuming that

facial trajectory of nucleophilic attack is best described by Fürst-Plattner-like approach which avoids the formation of twist-boat products, the magnitude of diastereoselectivity observed is best represented by the overall energy difference between conformers **66b** and **67b**.

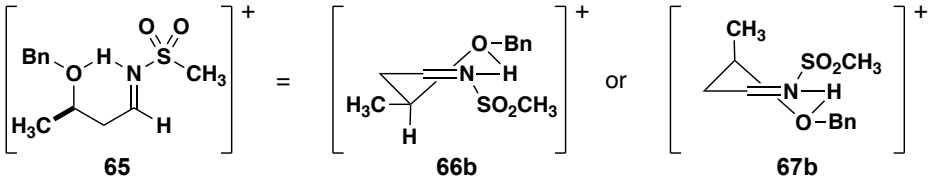
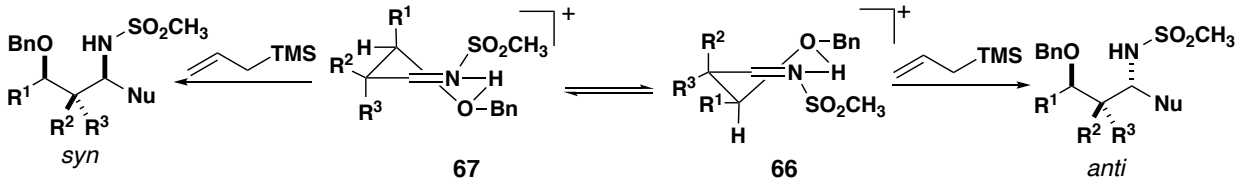


Figure 22. Calculated $\Delta G_{binding} = \Delta G(22) - (\Delta G(12)+\Delta G(H^+))$ for proton-chelate.

The relative energy differences between each of the two half-chairs possible of every substrate was calculated using the methods described above (Figure 23). These differences in free energies were then plotted with the diastereomeric ratios of products observed. A correlation is apparent between the difference in calculated free energies and observed selectivity with *tert*-butyl substrate (entry 4) as the sole, significant outlier. The *tert*-butyl substituted chelate was unique in that the lower energy conformer **67** bears a pseudo-axial *tert*-butyl group. On this conformer, nucleophilic addition would occur on the same side of the *tert*-butyl substituent in order to avoid twist-boat product formation. This build-up of 1,3 diaxial strain causes conformer **67** to theoretically be less reactive. So while **67** is energetically competitive to conformer **66**, the product ratios observed is more closely described by Curtin-Hammett principles wherein the product ratios are better correlated to transition-state energies as opposed to ground-state energies of the starting materials.



Entry	R^1	R^2	R^3	% of *anti*	Computed ΔG^a of **I:II**	% Major Conformer
1	CH_3	H	H	80	1.36	91
2	*n*-Bu	H	H	78	1.00	85
3	*i*-Pr	H	H	81	0.80	80
4	*t*-Bu	H	H	89	0.54	71
5	Ph	H	H	92	2.23	98
6	CH_3	H	CH_3	50	0.01	51
7	CH_3	CH_3	H	67	0.73	77

[a] Free energies calculated using Gaussian16 and the B3LYP density functional with the 6-31G(d,p) basis set

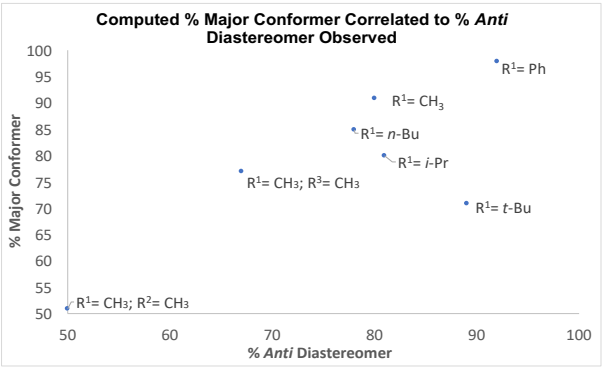


Figure 23. Computed free energies of **66** and **67** compared with observed selectivities.

2.3 Conclusion

To conclude, we have developed two allylation methods that result in *anti*-1,3 amino alcohols either from β-alkoxy imine or aldehyde starting materials. Experimental and computational results show that $Cu(OTf)_2$ mediated allylations of β-alkoxy imines are preceded by formation of a proton-chelate that can adopt two half-chair-like conformations. The observed diastereoselectivity of addition to the chelate is influenced by stereoelectronic interactions between half-chair chelates and nucleophile, as well as the conformational preferences of the chelate itself. Although the results from the typically monovalent Lewis acid BF_3 seem anomalous, they are consistent with the formation of a chelate structure through disproportionation to $L_2BF_2^+/BF_4^-$, as was reported previously. The stereoelectronic considerations described herein resemble that of the Stevens model, previously proposed to rationalize stereochemical outcomes of addition to tetrahydropyridinium ions. Together, we have constructed a generalizable

stereoelectronic model describing nucleophilic additions to β-alkoxy imines, which will inform retrosynthetic planning of stereochemically complex nitrogen-containing targets.

2.4 Materials and Experimental Procedures

2.4.1 Materials and Instrumentation

Unless otherwise specified, all commercially available reagents were used as received. All reactions using dried solvents were carried out under an atmosphere of argon in oven-dried glassware with magnetic stirring. Dry solvent was dispensed from a solvent purification system that passes solvent through two columns of dry neutral alumna. ^{1}H and ^{13}C NMR spectra were acquired at ambient temperature using Varian–600 (600 and 151 MHz, respectively), or Bruker–400 (400 and 100 MHz, respectively) spectrometers, as indicated. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane or referenced to residual solvent (^{1}H NMR: $CDCl_3$ δ 7.26. ^{13}C NMR: $CDCl_3$ δ 77.16) on the δ scale, multiplicity (appar = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, m = multiplet), coupling constants (Hz), and integration. High-resolution mass spectra (HRMS) were acquired on a Thermo Electron LTQ-Orbitrap XL Hybrid mass spectrometer on positive ESI mode. Melting points were obtained on an EZ-melting apparatus and were uncorrected. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system silica gel (Fisher, 40-63 μm) packed in glass columns.

2.4.2 Experimental Procedures

2.4.2.1 Allylation Products

General Procedure A: $Cu(OTf)_2$ mediated allyl additions to imines

Aldehyde (1.0 equiv), *p*-toluenesulfonamide (1.0 equiv) and sodium benzenesulfinate salt (1.15 equiv) were combined in a 1:1 mixture of H_2O and formic acid (0.66 M in solution). After stirring at room temperature for 72 hours, the resulting white precipitate is filtered and solids washed with hexanes and dried *in vacuo*. Amidosulfone is isolated as a mixture of inseparable diastereomers and a white, chalky solid, used without further purification.

Amidosulfone was dissolved in CH_2Cl_2 (0.1 mL/mg of amidosulfone) in a separatory funnel and shaken with aqueous saturated $NaHCO_3$ (0.2 mL/mg) for one minute. The layers are separated and the organics dried with Na_2SO_4, filtered and concentrated *in vacuo* to afford imine as a colorless oil. Imine is used without further purification. Representative spectra of imines **18, 19 and 22** are reported.

A solution of imine (1.0 equiv) and allylTMS (1.1 equiv) in dry CH_2Cl_2 (0.1 M) was cooled to –20 °C and then added to a flame-dried vial with pre-weighted solid $Cu(OTf)_2$ (1.1 equiv). The mixture was stirred at –20 °C overnight (16–20 h). The mixture was warmed to room temperature, then diluted with CH_2Cl_2 and washed with H_2O. The layers were

separated, and the aqueous layer was extracted three times with CH_2Cl_2. Combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*.

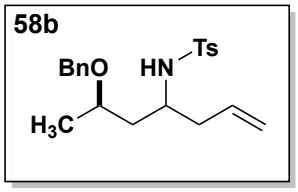
General Procedure B: $Cu(OTf)_2$ mediated multicomponent allylations

A solution of aldehyde (1.0 equiv) and allylTMS (1.1 equiv) in dry CH_2Cl_2 (0.1 M) at room temperature was added to added to a flame-dried vial with pre-weighted solid $Cu(OTf)_2$ (1.1 equiv) and H_2NTs (1.0 equiv). The mixture was stirred at room temperature overnight (16–20 h). The mixture was diluted with CH_2Cl_2 and washed with H_2O. The layers were separated, and the aqueous layer was extracted three times with CH_2Cl_2. Combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*.

** Inseparable mixtures of allylation product diastereomers were resolved upon hydrogenation using **General Procedure C** and major diastereomer fully characterized.

General Procedure C: Hydrogenation of Allylation Products

A solution of allylation product (1.0 equiv) in MeOH (0.25 M) was added to a vial containing 10% Pd/C (500 mg/mmol starting material) sparged with an Ar atmosphere. The mixture was then sparged with H_2 and stirred overnight under an H_2 atmosphere. After the mixture was stirred at room temperature overnight, the vial was evacuated and backfilled with Ar. The resulting mixture was filtered over celite, washed with MeOH, and concentrated *in vacuo*.



***N*-((6*R*)-6-(benzyloxy)hept-1-en-4-yl)-4-methylbenzenesulfonamide (58b)**

Using general procedure **A**, aldehyde **33** (1.50 g, 8.41 mmol) is combined with *p*-toluenesulfonamide (1.44 g, 8.41 mmol) and $NaSO_2Ph$ (1.52 g, 9.25 mmol) in H_2O (13 mL) and formic acid (13 mL) to afford amidosulfone (1.98 g, 50%) as a white, chalky solid. Amidosulfone **10a** (500 mg) was dissolved in CH_2Cl_2 (50 mL) and shaken with saturated aqueous $NaHCO_3$ (25 mL) in a separatory funnel to procure imine **18**, used without further purification. Imine **18** (343 mg, 1.03 mmol), $Cu(OTf)_2$ (410 mg, 1.13 mmol), and allylTMS (179 μL, 1.13 mmol) were combined in CH_2Cl_2 (10 mL) to afford **58b** (280 mg, 72%) as a 82:18 mixture of diastereomers. Diastereomers were purified as a mixture using flash column chromatography (15:85 to 20:80 EtOAc:hexanes) and isolated as a colorless oil.

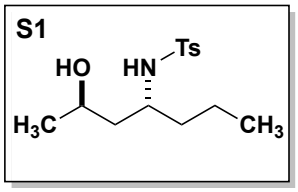
Using general procedure **B**, known aldehyde **33** (256 mg, 1.496 mmol), $Cu(OTf)_2$ (595 mg, 1.64 mmol), H_2NTs (256 mg, 1.496 mmol) and allylTMS (238 μL, 1.496 mmol) were combined in CH_2Cl_2 (15 mL) to afford **58b** (246 mg, 44%) as a 78:22 mixture of diastereomers. Diastereomers were purified as a mixture using flash column chromatography (15:85 to 20:80 EtOAc:hexanes) and isolated as a colorless oil.

Major: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.71 (dd, J = 8.3, 1.8 Hz, 2H), 7.43 – 7.21 (m, 7H), 5.66 – 5.52 (m, 1H), 5.26 (d, J = 7.9 Hz, 1H), 4.96 (dd, J = 54.9, 13.3 Hz, 2H), 4.54 (d, J

= 11.3 Hz, 1H), 4.32 (d, J = 11.1 Hz, 1H), 3.74 (ddd, J = 9.2, 6.1, 2.8 Hz, 1H), 3.57 – 3.49 (m, 1H), 2.40 (s, 3H), 2.20 (dt, J = 12.5, 5.7 Hz, 1H), 2.04 (dt, J = 14.6, 7.7 Hz, 1H), 1.58 – 1.43 (m, 2H), 1.08 (d, J = 6.2, 1.7 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 143.1, 138.9, 133.6, 129.2, 128.5, 127.9, 127.1, 117.9, 71.8, 70.5, 64.1, 50.7, 40.8, 39.8, 20.8, 19.3, 15.3.;

Minor: ^{1}H NMR (600 MHz, $CDCl_3$) δ 3.43 – 3.36 (m, 1H), 2.42 (s, 3H), 1.14 (dd, J = 6.2, 1.6 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (151 MHz, $CDCl_3$) δ 143.2, 138.3, 133.3, 127.7, 127.2, 119.5, 73.0, 70.0, 51.8, 41.0, 39.3, 21.5, 19.5.

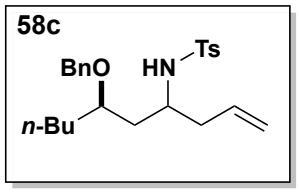
AMM (ESI-TOF) *m/z* calculated for $C_{21}H_{28}NO_3S^+$ $[M + H]^+$ 374.1790, found 374.1784



***N*-((2R,4R)-2-hydroxyheptan-4-yl)-4-methylbenzenesulfonamide (S1)**

Using general procedure **C**, allylation product **58b** (412 mg, 1.10 mmol) and 10% Pd/C (396 mg) were combined in MeOH (4.4 mL) to afford **S1** as a mixture of diastereomers. The major diastereomer *anti*-**S1** was isolated and purified using flash column chromatography (30:70 to 60:40 Et_2O:hexanes) and isolated as a white solid (178 mg, 54%): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.75 (d, J = 7.9 Hz, 2H), 7.28 (d, J = 7.9 Hz, 2H), 3.70 (q, J = 6.2 Hz, 1H), 3.28 (p, J = 6.5 Hz, 1H), 2.41 (s, 3H), 1.50 (t, J = 6.5 Hz, 2H), 1.37 (ddp, J = 26.7, 13.7, 6.4 Hz, 2H), 0.74 (t, J = 7.3 Hz, 3H). $^{13}C\{^{1}H\}$ NMR (151 MHz,

$CDCl_3$) δ 143.4, 138.0, 129.6, 127.0, 63.8, 51.2, 43.8, 37.9, 23.4, 21.5, 18.7, 13.7.; AMM (ESI-TOF) *m/z* calculated for $C_{15}H_{23}NO_3S^+$ $[M + H]^+$ 286.1477, found 286.1471.



***N*-((6*R*)-6-(benzyloxy)dec-1-en-4-yl)-4-methylbenzenesulfonamide (58c)**

Using general procedure **A**, aldehyde **57a** (112 mg, 0.508 mmol) is combined with *p*-toluenesulfonamide (87 mg, 0.508 mmol) and $NaSO_2Ph$ (100 mg, 0.559 mmol) in H_2O (0.77 mL) and formic acid (0.77 mL) to afford amidosulfone (199 mg, 74%) as a white, chalky solid. Amidosulfone was dissolved in CH_2Cl_2 (40 mL) and shaken with saturated aqueous $NaHCO_3$ (20 mL) in a separatory funnel to procure imine **19**, used without further purification. Imine **19** (125 mg, 0.334 mmol), $Cu(OTf)_2$ (38 mg, 0.334 mmol), and allylTMS (38 mg, 0.334 mmol) were combined in CH_2Cl_2 (3.3 mL) to afford **58c** (102 mg, 74%) as a 83:17 mixture of diastereomers. Diastereomers were purified as a mixture using flash column chromatography (5:95 to 20:80 EtOAc:hexanes) and isolated as a colorless oil.

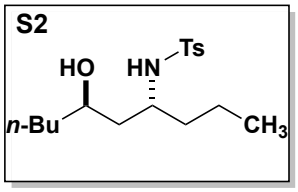
Using general procedure **B**, aldehyde **57a** (134 mg, 0.610 mmol), $Cu(OTf)_2$ (221 mg, 0.610 mmol), H_2NTs (104 mg, 0.610 mmol) and allylTMS (70 mg, 0.610 mmol) were combined in CH_2Cl_2 (2.4 mL) to afford **58c** (138 mg, 55%) as a 78:22 mixture of

diastereomers. Diastereomers were purified as a mixture using flash column chromatography (5:95 to 20:80 EtOAc:hexanes) and isolated as a colorless oil.

Major: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.65 (m, 2H), 7.42 – 7.21 (m, 7H), 5.67 – 5.47 (m, 1H), 5.30 (d, *J* = 6.3 Hz, 1H), 5.06 – 4.88 (m, 3H), 4.55 – 4.44 (m, 1H), 4.39 – 4.29 (m, 1H), 3.62 – 3.42 (m, 2H), 2.40 (s, 3H), 2.29 – 2.01 (m, 2H), 1.73 – 1.36 (m, 3H), 1.37 – 1.07 (m, 4H), 0.92 – 0.82 (m, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 143.1, 138.4, 138.1, 133.6, 129.5, 128.5, 127.9, 127.7, 127.2, 118.6, 76.2, 70.9, 50.8, 39.5, 37.7, 32.6, 27.0, 22.8, 21.5, 14.0;

Minor: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.44 – 3.33 (m, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 143.2, 137.9, 133.3, 128.4, 127.8, 127.6, 118.9, 70.1, 51.7, 39.3, 38.3, 33.0, 26.8.

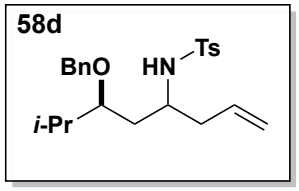
AMM (ESI-TOF) *m*/*z* calculated for $C_{24}H_{34}NO_3S^+$ $[M + H]^+$ 416.2254, found 416.2249



***N*-((6R)-6-hydroxydecan-4-yl)-4-methylbenzenesulfonamide (S2)**

Using general procedure **C**, allylation product **58c** (116 mg, 0.280 mmol) and 10% Pd/C (224 mg) were combined in MeOH (1.1 mL) to afford **S2** as a 70:20 mixture of

diastereomers. *Anti*-**S2** was isolated and purified using flash column chromatography (10:90 to 30:70 EtOAc:hexanes) and isolated as a colorless oil (55 mg, 60%). Relative stereochemistry of major diastereomer was assigned based on NMR correlation to **S1**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 5.16 – 5.04 (m, 1H), 3.86 (s, 1H), 3.51 – 3.38 (m, 1H), 2.71 (s, 1H), 2.43 (s, 3H), 1.50 – 1.20 (m, 10H), 1.09 (qt, *J* = 14.2, 6.4 Hz, 2H), 0.93 – 0.80 (m, 3H), 0.76 – 0.67 (m, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 143.3, 138.1, 129.6, 127.1, 67.7, 51.2, 41.9, 37.9, 37.1, 27.9, 22.7, 21.5, 18.8, 14.1, 13.8; AMM (ESI-TOF) *m*/*z* calculated for $C_{17}H_{30}NO_3S^+$ [M + H]$^+$ 328.1941, found 328.1939.



***N*-((6*S*)-6-(benzyloxy)-7-methyloct-1-en-4-yl)-4-methylbenzenesulfonamide (58d)**

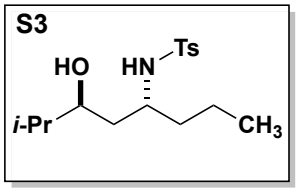
Using modified general procedure **A**, aldehyde **57b** (140 mg, 0.678 mmol) is combined with *p*-toluenesulfonamide (116 mg, 0.678 mmol) and $NaSO_2Tol$ (113 mg, 0.746 mmol) in H_2O (1.03 mL) and formic acid (1.03 mL) to afford amidosulfone (199 mg, 74%) as a white, chalky solid. Amidosulfone was dissolved in CH_2Cl_2 (40 mL) and shaken with saturated aqueous $NaHCO_3$ (20 mL) in a separatory funnel to procure imine **20** (195 mg, 56%) used without further purification. Imine **20** (111 mg, 0.309 mmol), $Cu(OTf)_2$ (112 mg, 0.309 mmol), and allylTMS (35 mg, 0.309 mmol) were combined in CH_2Cl_2 (3 mL) to afford **58d** (56 mg, 4%) as a 89:11 mixture of diastereomers. Diastereomers were purified

as a mixture using flash column chromatography (5:95 to 20:80 EtOAc:hexanes) and isolated as a colorless oil.

Using general procedure **B**, aldehyde **57b** (78 mg, 0.379 mmol), $Cu(OTf)_2$ (137 mg, 0.379 mmol), H_2NTs (65 mg, 0.379 mmol) and allylTMS (43 mg, 0.379 mmol) were combined in CH_2Cl_2 (1.5 mL) to afford **58d** (56 mg, 37%) as a 81:19 mixture of diastereomers. Diastereomers were purified as a mixture using flash column chromatography (5:95 to 20:80 EtOAc:hexanes) and isolated as a colorless oil.

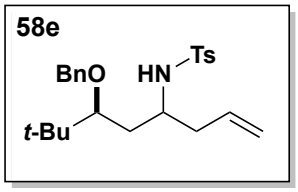
Major: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.2 Hz, 2H), 7.41 – 7.13 (m, 7H), 5.66 – 5.49 (m, 1H), 5.21 (d, *J* = 8.0 Hz, 1H), 5.05 – 4.87 (m, 2H), 4.56 – 4.47 (m, 1H), 4.41 – 4.29 (m, 1H), 3.57 – 3.46 (m, 1H), 3.46 – 3.35 (m, 1H), 2.40 (s, 3H), 2.25 – 2.10 (m, 1H), 2.09 – 1.83 (m, 2H), 1.50 – 1.35 (m, 2H), 0.86 – 0.73 (m, 6H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 143.1, 138.6, 138.2, 133.5, 129.5, 128.4, 127.9, 127.2, 118.6, 80.7, 71.3, 51.0, 39.5, 33.1, 29.2, 21.5, 18.6, 16.2;
Minor: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.19 (q, *J* = 5.4 Hz, 1H), 1.53 (t, *J* = 6.5 Hz, 2H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 143.2, 138.5, 137.9, 133.3, 128.4, 127.7, 127.6, 127.6, 127.2, 118.8, 81.4, 70.5, 52.0, 39.1, 33.7, 29.7, 18.1, 16.5.

AMM (ESI-TOF) *m*/*z* calculated for $C_{23}H_{32}NO_3S^+$ $[M + H]^+$ 402.2097, found 402.2106



***N*-((4R,6S)-6-hydroxy-7-methyloctan-4-yl)-4-methylbenzenesulfonamide (S3)**

Using general procedure **C**, allylation product **58d** (56 mg, 0.139 mmol) and 10% Pd/C (111 mg) were combined in MeOH (0.56 mL) to afford **S3** as a 80:20 mixture of diastereomers. *Anti*-**S3** was purified using flash column chromatography (10:90 to 30:70 EtOAc:hexanes) and isolated as a pale yellow oil (9 mg, 5%). Relative stereochemistry of major diastereomer was assigned based on NMR correlation to **S1**. ^{1}H NMR (600 MHz, cdcl$_3$) δ 7.77 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.87 (d, *J* = 9.7 Hz, 1H), 3.69 – 3.57 (m, 1H), 3.50 – 3.40 (m, 1H), 2.43 (s, 3H), 1.61 – 1.51 (m, 1H), 1.43 (ddd, *J* = 14.1, 10.8, 3.2 Hz, 1H), 1.36 – 1.22 (m, 4H), 1.20 – 1.00 (m, 2H), 0.86 (dd, *J* = 10.5, 6.8 Hz, 6H), 0.73 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 143.3, 138.1, 129.6, 127.1, 72.3, 51.3, 38.3, 37.9, 33.7, 21.5, 18.8, 18.6, 17.7, 13.8; AMM (ESI-TOF) *m*/*z* calculated for $C_{16}H_{28}NO_3S^+$ $[M + H]^+$ 314.1784, found 314.1788



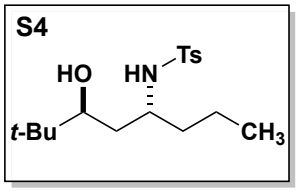
***N*-((6*S*)-6-(benzyloxy)-7,7-dimethyloct-1-en-4-yl)-4-methylbenzenesulfonamide (58e)**

Using general procedure **B**, aldehyde **57d** (80 mg, 0.362 mmol), $Cu(OTf)_2$ (132 mg, 0.362 mmol), H_2NTs (62 mg, 0.362 mmol) and allylTMS (41 mg, 0.362 mmol) were combined in CH_2Cl_2 (1.45 mL) to afford **58e** (66 mg, 44%) as a 89:11 mixture of diastereomers. Diastereomers were purified as a mixture using flash column chromatography (5:95 to 20:80 EtOAc:hexanes) and isolated as a colorless oil.

Major: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.64 (m, 2H), 7.39 – 7.24 (m, 7H), 5.63 – 5.46 (m, 1H), 5.09 – 4.92 (m, 1H), 4.85 (d, *J* = 17.1 Hz, 1H), 4.72 – 4.47 (m, 3H), 3.61 – 3.50 (m, 1H), 3.25 (dd, *J* = 8.0, 3.4 Hz, 1H), 2.41 (s, 3H), 2.21 – 2.04 (m, 1H), 2.02 – 1.90 (m, 1H), 1.56 – 1.44 (m, 2H), 0.90 (s, 9H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 143.4, 139.4, 138.4, 132.9, 129.7, 128.3, 127.2, 127.2, 119.2, 84.7, 74.8, 51.4, 39.8, 36.7, 36.1, 26.4, 26.2, 21.5.

Minor: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.0 Hz, 1H), 3.45 – 3.34 (m, 1H), 3.00 (dd, *J* = 8.0, 3.3 Hz, 1H), 1.65 (ddd, *J* = 14.5, 7.5, 3.4 Hz, 1H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 143.2, 138.9, 137.9, 129.6, 127.4, 127.3, 119.3, 73.8, 51.9, 38.6, 36.3, 29.7.

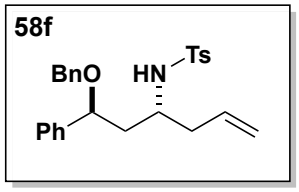
AMM (ESI-TOF) *m/z* calculated for $C_{24}H_{34}NO_3S^+$ $[M + H]^+$ 416.2254, found 416.2244



***N*-((4R,6S)-6-hydroxy-7,7-dimethyloctan-4-yl)-4-methylbenzenesulfonamide (S4)**

Using general procedure **C**, allylation product **58e** (35 mg, 0.084 mmol) and 10% Pd/C (67 mg) were combined in MeOH (0.3 mL) to afford **S4** as a 90:10 mixture of diastereomers. Major diastereomer *anti*-**S4** was purified using flash column chromatography (10:90 to 30:70 EtOAc:hexanes) and isolated as an amorphous solid (7 mg, 25%). Relative stereochemistry of major diastereomer was assigned based on NMR correlation to **S1.**

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.9 Hz, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 4.82 (d, *J* = 9.3 Hz, 1H), 3.49 – 3.43 (m, 2H), 2.43 (s, 3H), 2.33 (d, *J* = 4.9 Hz, 1H), 1.39 – 1.25 (m, 5H), 1.20 – 1.04 (m, 2H), 0.83 (s, 10H), 0.75 (t, *J* = 7.3 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 143.3, 138.2, 129.6, 127.1, 75.2, 51.5, 37.9, 35.4, 34.5, 25.6, 21.5, 18.9, 13.8; AMM (ESI-TOF) *m*/*z* calculated for $C_{17}H_{30}NO_3S^+$ [M + H]$^+$ 328.1941, found 328.1945



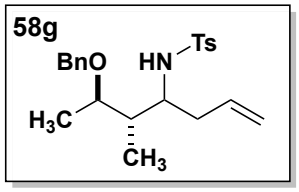
***N*-((1S,3R)-1-(benzyloxy)-1-phenylhex-5-en-3-yl)-4-methylbenzenesulfonamide (58f)**

Using modified general procedure **A**, aldehyde **57c** (206 mg, 0.859 mmol) is combined with *p*-toluenesulfonamide (147 mg, 0.859 mmol) and $NaSO_2Tol$ (168 mg, 0.945 mmol) in H_2O (1.30 mL) and formic acid (1.30 mL) to afford amidosulfone (390 mg, 83%) as a white, chalky solid. Amidosulfone was dissolved in CH_2Cl_2 (75 mL) and shaken with saturated aqueous $NaHCO_3$ (37 mL) in a separatory funnel to procure imine **21** (182 mg,

65%) used without further purification. Imine **21** (173 mg, 0.439 mmol), $Cu(OTf)_2$ (159 mg, 0.439 mmol), and allylTMS (50 mg, 0.439 mmol) were combined in CH_2Cl_2 (4.4 mL) to afford **58f** as a >95:5 mixture of diastereomers. The crude material was purified using flash column chromatography (5:95 to 20:80 EtOAc:hexanes) and isolated as a colorless oil (108 mg, 57%).

Using general procedure **B**, a solution of aldehyde **57c** (168 mg, 0.7 mmol) and allylTMS (88 mg, 0.77 mmol) in dry CH_2Cl_2 (7 mL) at room temperature was added to a flame-dried vial with pre-weighted solid $Cu(OTf)_2$ (243 mg, 0.77 mmol) and H_2NTs (120 mg, 0.7 mmol). The mixture was stirred at room temperature overnight (16h) to afford **58f** as a mixture of diastereomers (92:8 dr). The crude material was purified by flash chromatography (30:70 diethyl ether: hexanes) and isolated as single diastereomer *anti*-**58f** (205 mg, 76%) as a white solid.

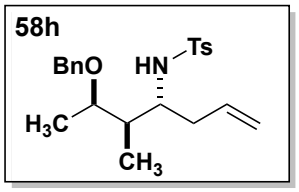
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.76 – 7.69 (m, 2H), 7.42 – 7.25 (m, 9H), 7.24 – 7.16 (m, 2H), 5.55 (dddd, *J* = 16.5, 10.2, 8.3, 6.1 Hz, 1H), 5.19 (d, *J* = 8.6 Hz, 1H), 5.05 – 4.97 (m, 1H), 4.91 (dq, *J* = 17.0, 1.6 Hz, 1H), 4.55 (dd, *J* = 10.3, 2.8 Hz, 1H), 4.34 (d, *J* = 11.1 Hz, 1H), 4.19 (d, *J* = 11.0 Hz, 1H), 3.62 (qd, *J* = 8.2, 4.2 Hz, 1H), 2.41 (s, 3H), 2.25 – 2.14 (m, 1H), 2.04 (dt, *J* = 14.5, 7.7 Hz, 1H), 1.77 (ddd, *J* = 14.9, 10.3, 3.2 Hz, 1H), 1.62 – 1.51 (m, 1H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 143.2, 141.8, 138.3, 138.0, 133.4, 129.6, 128.6, 128.5, 128.2, 127.8, 127.8, 127.2, 126.4, 118.8, 78.1, 77.3, 77.2, 77.0, 76.7, 70.6, 50.8, 42.4, 39.2, 21.5. AMM *m/z* calcd $C_{26}H_{29}NO_3S^+$ $(M + Na)^+$ 458.1760, found 458.1757



***N*-((5S,6R)-6-(benzyloxy)-5-methylhept-1-en-4-yl)-4-methylbenzenesulfonamide (58g)**

Using procedure **B**, a solution of aldehyde **43** (168 mg, 0.7 mmol) and allylTMS (109 mg, 0.95 mmol) in dry CH_2Cl_2 (8.6 mL 0.1 M) at room temperature was added to a flame-dried vial with pre-weighted solid $Cu(OTf)_2$ (313 mg, 0.86 mmol) and H_2NTs (148 mg, 0.86 mmol). The mixture was stirred at room temperature overnight (16 h). The mixture was diluted with CH_2Cl_2 and washed with H_2O. The layers were separated, and the aqueous layer was extracted three times with CH_2Cl_2. Combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford **58g** as a 51:49 mixture of diastereomers. The crude mixture was purified by flash chromatography (30:70 diethyl ether:hexanes) to afford a colorless oil (200 mg, 60%). ^{1}H NMR (400 MHz, Chloroform-d) δ 7.69 (dd, J = 8.1, 4.4 Hz, 3H), 7.43 – 7.23 (m, 13H), 5.56 (ddt, J = 17.1, 10.7, 7.1 Hz, 1H), 5.35 (d, J = 7.9 Hz, 1H), 5.31 – 5.22 (m, 1H), 5.00 – 4.87 (m, 3H), 4.61 (dd, J = 11.5, 7.7 Hz, 2H), 4.46 (t, J = 3.8 Hz, 1H), 4.40 – 4.29 (m, 2H), 3.57 – 3.37 (m, 3H), 2.44 (s, 2H), 2.43 (s, 3H), 2.25 – 2.03 (m, 3H), 2.02 – 1.89 (m, 1H), 1.63 (td, J = 7.5, 2.4 Hz, 1H), 1.16 (d, J = 6.1 Hz, 2H), 1.06 (d, J = 6.1 Hz, 3H), 0.86 (dd, J = 7.1, 4.6 Hz, 5H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 143.2, 143.0, 138.8, 138.3, 138.3, 137.5, 134.8, 133.9, 129.5, 129.4, 128.5, 128.4, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 118.8, 117.3, 77.2, 76.1,

70.6, 70.0, 55.4, 54.3, 41.7, 41.6, 36.4, 35.1, 21.5, 21.5, 16.8, 16.2, 12.7, 11.5. AMM m/z calcd $C_{22}H_{29}NO_3S$(M + H)+ 388.1941, found 388.1938.

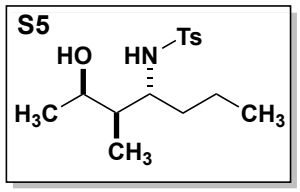


***N*-((5*R*,6*R*)-6-(benzyloxy)-5-methylhept-1-en-4-yl)-4-methylbenzenesulfonamide (58h)**

Using procedure **B**, a solution of aldehyde **52** (50 mg, 0.260 mmol) and allylTMS (0.041 mL, 0.260 mmol) in dry CH_2Cl_2 (2.6 mL, 0.1 M) at room temperature was added to a flame-dried vial with pre-weighted solid $Cu(OTf)_2$ (94 mg, 0.260 mmol) and H_2NTs (44 mg, 0.260 mmol). The mixture was stirred at room temperature overnight (16 h). The mixture was diluted with CH_2Cl_2 and washed with H_2O. The layers were separated, and the aqueous layer was extracted three times with CH_2Cl_2. Combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford **58h** as a 67:33 mixture of diastereomers. The crude mixture was purified by flash chromatography and the major diastereomer, *anti*-**58h** was isolated as a colorless oil (7 mg, 7%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.1 Hz, 2H), 7.46 – 7.22 (m, 8H), 5.88 (d, J = 6.7 Hz, 1H), 5.63 (ddt, J = 17.1, 10.1, 7.3 Hz, 1H), 5.05 – 4.90 (m, 2H), 4.61 (d, J = 11.4 Hz, 1H), 4.39 (d, J = 11.4 Hz, 1H), 3.86 (qd, J = 6.3, 2.4 Hz, 1H), 3.33 (ddd, J = 12.6, 7.2, 5.5 Hz, 1H), 2.43 (s, 3H), 2.36 – 2.26 (m, 1H), 2.18 (dt, J = 14.7, 7.8 Hz, 1H), 1.69 (ddt, J = 10.7, 7.2, 3.6 Hz, 1H), 1.11 (d, J = 6.3 Hz, 3H), 0.79 (d, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)

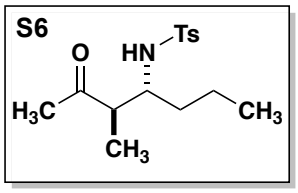
δ 143.0, 138.7, 138.3, 134.2, 129.6, 128.8, 128.2, 128.0, 127.2, 118.1, 74.3, 70.5, 57.1, 39.3, 37.9, 21.7, 16.5, 11.5. AMM *m/z* calcd $C_{26}H_{29}NO_3S^+$ $(M + Na)^+$ 388.1946, found 388.1941.

The major product's *anti* configuration was determined through derivatization which is described below:



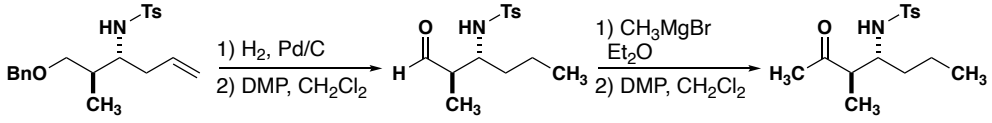
***N*-((2R,3R)-2-hydroxy-3-methylheptan-4-yl)-4-methylbenzenesulfonamide (S5)**

Using general procedure **C**, the major product of **58h** (82 mg, 0.210 mmol) and 10% Pd/C (100 mg) were combined in MeOH (1 mL) to afford **S5** as a single diastereomer. **S5** was purified using flash column chromatography (30:70 to 60:40 Et_2O:hexanes) and isolated as an amorphous solid (50 mg, 83%): ^1H NMR (600 MHz, $CDCl_3$) δ 7.78 – 7.71 (m, 2H), 7.29 (d, J = 7.9 Hz, 2H), 5.30 (d, J = 8.4 Hz, 1H), 4.21 (qd, J = 6.5, 2.4 Hz, 1H), 3.23 (dq, J = 8.4, 6.3 Hz, 1H), 2.42 (s, 3H), 1.50 – 1.33 (m, 3H), 1.20 – 1.11 (m, 4H), 1.09 – 0.97 (m, 1H), 0.76 (t, J = 7.1 Hz, 6H). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$) δ 143.3, 138.7, 129.7, 127.2, 66.7, 57.5, 41.2, 35.6, 21.7, 21.6, 18.6, 14.2, 10.1.; AMM (ESI-TOF) *m/z* calculated for $C_{16}H_{25}NO_3S^+$ $[M + H]^+$ 300.1633, found 300.1636.



4-methyl-*N*-((3R,4S)-3-methyl-2-oxoheptan-4-yl)benzenesulfonamide (S6)

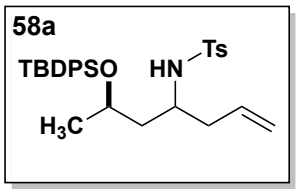
S5 (21 mg, 0.0728 mmol, 1.0 equiv), derived from the major product of **58h**, was combined with DMP (37 mg, 0.0874 mmol, 1.2 equiv) in CH_2Cl_2 (0.7 mL, 0.1 M) in a flame dried 20 mL vial and stirred overnight (16 h) at room temperature to afford **S6**. The crude material was purified using flash chromatography (10:90 to 20:80 EtOAc:Hexanes) to afford **S6** as a colorless oil (14 mg, 69%): ^{1}H NMR (600 MHz, $CDCl_3$) δ δ 7.75 (d, J = 7.8 Hz, 2H), 7.28 (d, J = 7.9 Hz, 2H), 5.25 (d, J = 9.0 Hz, 1H), 3.41 (td, J = 6.8, 3.2 Hz, 1H), 2.78 (dq, J = 10.0, 6.4 Hz, 1H), 2.42 (s, 3H), 2.11 (s, 3H), 1.35 – 1.22 (m, 4H), 1.16 (dq, J = 14.5, 7.1 Hz, 1H), 1.06 (d, J = 7.4 Hz, 4H), 0.74 (t, J = 7.4 Hz, 3H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 212.2, 143.3, 138.9, 129.7, 127.1, 56.1, 49.2, 35.7, 29.9, 21.7, 19.5, 13.9, 13.7.; AMM (ESI-TOF) m/z calculated for C16H25NO3NaS+ [M + Na]+ 321.1374, found 321.1337.



anti-**17** **S6**

S6's relative configuration, and thus the identity of the major diastereomer of **58h** was determined through transformations of *anti*-**59** (with known relative configuration), to **S6**

through a procedure described below. The ^{1}H spectrum of the ketone derived from *anti*-**17** matched **S6**: ^{1}H NMR (600 MHz, $CDCl_3$) δ δ 7.75 (d, J = 7.8 Hz, 2H), 7.28 (d, J = 7.9 Hz, 2H), 5.25 (d, J = 9.0 Hz, 1H), 3.41 (td, J = 6.8, 3.2 Hz, 1H), 2.78 (dq, J = 10.0, 6.4 Hz, 1H), 2.42 (s, 3H), 2.11 (s, 3H), 1.35 – 1.22 (m, 4H), 1.16 (dq, J = 14.5, 7.1 Hz, 1H), 1.06 (d, J = 7.4 Hz, 4H), 0.74 (t, J = 7.4 Hz, 3H).



***N*-((6*R*)-6-((*tert*-butyldiphenylsilyl)oxy)hept-1-en-4-yl)-4-methylbenzenesulfonamide (14h)**

Using general procedure **B**, known aldehyde **26b** (71 mg, 0.218 mmol), $Cu(OTf)_2$ (86 mg, 0.239 mmol), H_2NTs (40 mg, 0.239 mmol) and allylTMS (38 μL, 0.239 mmol) were combined in CH_2Cl_2 (2.1 mL) to afford **58a** as a 54:46 mixture of diastereomers. Diastereomers were purified and isolated as a mixture (79 mg, 70%) using flash column chromatography (20:80 EtOAc:hexanes) as a colorless oil.

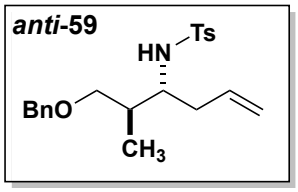
Mixture: ^{1}H NMR (400 MHz, CDCl3) δ 7.85 – 7.59 (m, 6H), 7.53 – 7.36 (m, 6H), 7.32 (d, J = 8.0 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 5.59 (dd, J = 6.1, 2.9 Hz, 1H), 5.57 – 5.39 (m, 1H), 5.08 – 4.86 (m, 2H), 2.32 – 1.95 (m, 2H), 1.66 – 1.36 (m, 2H). ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 143.1, 138.2, 138.1, 134.2, 129.5, 128.4, 127.8, 127.7, 127.0, 118.0, 73.9,

70.8, 57.6, 36.7, 21.5, 15.9; AMM (ESI-TOF) *m/z* calculated for $C_{30}H_3NO_3SSi^+$ $[M + H]^+$ 522.2498, found 522.2497

Major: ^1H NMR (400 MHz, $CDCl_3$) δ 3.66 (h, J = 6.1 Hz, 1H), 3.29 (dtt, J = 11.5, 8.1, 4.0 Hz, 1H), 2.42 (s, 3H), 1.04 (s, 9H), 0.91 (d, J = 6.0 Hz, 3H).

Minor: ^1H δ 3.98 (td, *J* = 6.2, 4.5 Hz, 1H), 3.44 (td, *J* = 7.7, 4.6 Hz, 1H), 2.46 (s, 3H), 1.09 (s, *J* = 1.6 Hz, 9H), 0.83 (d, *J* = 6.3 Hz, 3H).

Upon hydrogenation using General Procedure **C**, **58a** was converted to fully characterized **S1** in 19% yield.



_N_-((2_R_,3_R_)-1-(benzyloxy)-2-methylhex-5-en-3-yl)-4-methylbenzenesulfonamide (_anti_-17)

Using general procedure **A**, aldehyde **39** (112 mg, 0.508 mmol) is combined with *p*-toluenesulfonamide (87 mg, 0.508 mmol) and $NaSO_2Ph$ (100 mg, 0.559 mmol) in H_2O (0.77 mL) and formic acid (0.77 mL) to afford amidosulfone (199 mg, 74%) as a white, chalky solid. Amidosulfone was dissolved in CH_2Cl_2 (40 mL) and shaken with saturated aqueous $NaHCO_3$ (20 mL) in a separatory funnel to procure imine **22**, used without further purification. Imine **22** (137 mg, 0.416 mmol), $BF_3{\bullet}OEt_2$ (0.077 mL, 0.624 mmol), and allylBF_3K (92 mg, 0.624 mmol), 18-crown-6 (165 mg, 0.624 mmol) were combined in

CH_2Cl_2 (4.1 mL) at –20 °C for 24 h to afford **59** as a 52:48 mixture of diastereomers. Diastereomers were purified as a mixture using flash column chromatography (30:70 to 40:60 Et_2O:hexanes) in 53% yield (143 mg). *Anti*-**59** was separated and characterized as a white solid.

Anti-**17**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.1 Hz, 2H), 7.38 – 7.26 (m, 7H), 5.56 – 5.41 (m, 1H), 4.96 – 4.84 (m, 2H), 4.71 (d, J = 8.3 Hz, 1H), 4.56 (d, J = 11.6 Hz, 1H), 4.33 (d, J = 11.6 Hz, 1H), 3.62 (qd, J = 6.2, 2.5 Hz, 1H), 3.28 – 3.17 (m, 1H), 2.41 (s, 3H), 2.40 – 2.30 (m, 1H), 2.16 – 2.06 (m, 1H), 1.07 (d, J = 6.2 Hz, 3H); ^{13}C{^{1}H} NMR (151 MHz, $CDCl_3$) δ 142.4, 138.7, 137.1, 133.9, 129.4, 128.4, 127.7, 127.6, 127.1, 118.2, 73.2, 72.1, 56.5, 38.4, 36.1, 19.9, 14.9. Minor: AMM (ESI-TOF) *m*/*z* calculated for $NaC_{21}H_{27}NO_3S^+$ $[M + Na]^+$ 374.1790, found 374.1784.

2.2.4.2 Aldehyde Synthesis

General Procedure D: Reduction of Beta-Keto Ester and Benzylidene Acetal Formation

Beta-keto ester (1.0 equiv) was added dropwise to a flame-dried round bottom flask containing a suspension of $LiAlH_4$ (3.0 equiv) in dry Et_2O (0.3 M). The mixture was then allowed to stir at room temperature overnight (12-20 h). Then the mixture was cooled to 0 °C and quenched using the Fieser workup: H_2O (1 mL/g of $LiAlH_4$) was slowly added; the reaction was allowed to stir for 15 min at 0 °C. 10% NaOH (1 mL/g of $LiAlH_4$) was slowly added; the reaction was allowed to stir for another 15 min at 0 °C. Finally, H_2O (3 mL/g of $LiAlH_4$) was added; the reaction was allowed to stir for 30 min at room temperature. After Na_2SO_4 was added, the mixture was filtered over celite, washed with Et_2O, and concentrated *in vacuo* to afford a colorless oil. The resulting crude oil was used without further purification.

The crude diol (1.0 equiv) was dissolved in CH_2Cl_2 (1.0 M) in a round bottom flask. To the solution was added benzaldehyde (1.2 equiv), p-TsOH (0.1 equiv), and $MgSO_4$ (2.0 equiv). The mixture was then allowed to stir at room temperature overnight (16-22 h). The mixture was then filtered over celite and washed with CH_2Cl_2. The resulting filtrate was washed with $NaHCO_3$, H_2O, and brine. The organic layer was then dried with Na_2SO_4, filtered, and concentrated *in vacuo*, affording a pale yellow oil.

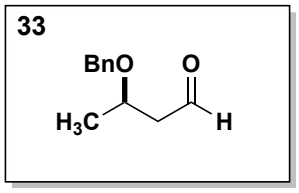
General Procedure E: $Cu(OTf)_2$ Acetal Opening

Acetal (1.0 equiv) and BH_3•THF (1.0 M, 5.0 equiv) were added to a flame-dried round bottom flask. The resulting mixture was stirred at room temperature for 10 minutes before adding $Cu(OTf)_2$ (0.1 equiv). The mixture was allowed to stir at room temperature until

complete consumption of starting material occurred (1-3 h), as indicated by TLC. The mixture was then cooled to 0 °C. NEt_3 (1.0 equiv) was slowly added, followed by MeOH (44.5 equiv). The resulting mixture was concentrated *in vacuo*, affording a colorless oil.

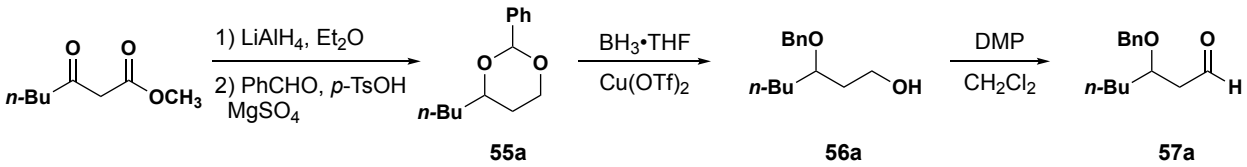
General Procedure F: Dess-Martin Oxidation of Benzylated Alcohol

Dess Martin periodinane (1.2 equiv) was added to a solution of benzylated alcohol (1.0 equiv) in CH_2Cl_2 (0.1 M). The resulting mixture was allowed to stir at room temperature for 1 h. The reaction was quenched with sat. Na_2SO_3 and Et_2O, then allowed to stir for an additional 10 minutes or until all of the solid dissolved. The organic layer was washed with sat. Na_2SO_3, then sat. $NaHCO_3$, then H_2O, and brine. The organic layer was then dried with Na_2SO_4 , filtered, and concentrated *in vacuo*, affording a colorless oil.



(*R*)-3-(benzyloxy)butanal (33)

Known aldehyde **33** was prepared according to previously reported procedure.[25] Spectral data matches previously reported data.[26] ^{1}H NMR (599 MHz, Chloroform-*d*) δ 9.78 (t, *J* = 2.1 Hz, 1H), 7.38 – 7.27 (m, 5H), 4.59 (d, *J* = 11.6 Hz, 1H), 4.47 (d, *J* = 11.6 Hz, 1H), 4.07 (p, *J* = 6.3 Hz, 1H), 2.69 (ddt, *J* = 16.4, 7.5, 2.0 Hz, 1H), 2.51 (dt, *J* = 16.4, 3.2 Hz, 1H), 1.29 (dd, *J* = 6.2, 1.5 Hz, 3H).



(4*R*)-4-butyl-2-phenyl-1,3-dioxane (55a)

Using general procedure **D**, commercially available ethyl 3-oxoheptanoate (1.5 mL, 9.54 mmol) and LAH (1.086 g, 28.62 mmol) were combined in Et_2O (31.8 mL). The resulting crude oil (1.121 g, 8.48 mmol), benzaldehyde (1.04 mL, 10.18 mmol), p-TsOH•H_2O (161 mg, 0.848 mmol), and $MgSO_4$ (2.042 g, 16.96 mmol) were combined in CH_2Cl_2 (8.5 mL) to afford **55a**. **55a** was purified using flash column chromatography (1:99 to 20:80 EtOAc:hexanes) and isolated as a pale yellow oil (607 mg, 29% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 – 7.46 (m, 2H), 7.40 – 7.27 (m, 3H), 5.50 (s, 1H), 4.26 (dd, *J* = 11.3, 5.0 Hz, 1H), 3.95 (td, *J* = 11.9, 2.6 Hz, 1H), 3.87 – 3.76 (m, 1H), 1.88 – 1.62 (m, 2H), 1.60 – 1.28 (m, 6H), 0.91 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (151 MHz, Acetone-*d*) δ 201.3, 139.1, 128.1, 127.4, 127.2, 81.7, 73.1, 45.6, 35.4, 25.5; AMM (ESI-TOF) *m*/*z* calculated for $C_{14}H_{21}O_2^+$ $[M + H]^+$ 221.1536, found 221.1539

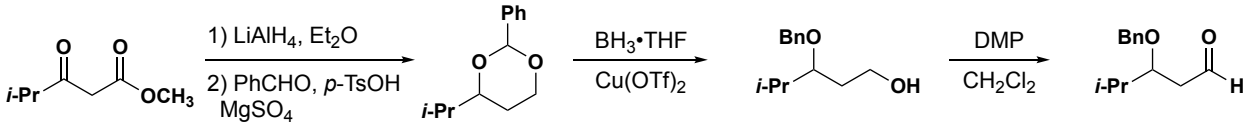
3-(benzyloxy)heptan-1-ol (56a)

Using general procedure **E**, benzylidene acetal **55a** (599 mg, 2.71 mmol), BH_3•THF (15.1 mL, 13.59 mmol), and $Cu(OTf)_2$ (98 mg, 0.271 mmol), were combined to afford **56a**. **56a** was purified using flash column chromatography (5:95 to 50:50 EtOAc:hexanes) and isolated as a colorless oil (396 mg, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 5H), 4.59 (d, *J* = 11.4 Hz, 1H), 4.48 (d, *J* = 11.4 Hz, 1H), 3.84 – 3.58 (m, 3H), 2.52 (s, 1H), 1.88 – 1.43 (m, 3H), 1.42 – 1.23 (m, 5H), 0.93 – 0.89 (m, 3H); ^{13}C NMR (151 MHz,

$CDCl_3$) δ 138.5, 128.5, 127.9, 127.7, 78.6, 70.9, 60.8, 35.9, 33.1, 27.3, 22.9, 14.1; AMM (ESI-TOF) *m/z* calculated for $C_{14}H_{23}O_2^+$ $[M + H]^+$ 223.1693, found 223.1697

3-(benzyloxy)heptanal (57a)

Using general procedure **F,** alcohol **56a** (364 mg, 1.64 mmol) was combined with DMP (834 mg, 1.97 mmol) in CH_2Cl_2 (16.4 mL) to produce aldehyde **57a** (274 mg, 76%). Compound **8b** was used without further purification in subsequent reactions. ^{1}H NMR of known compound **8b** matched with previously reported data.[27] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.80 (t, *J* = 2.3 Hz, 1H), 7.31 (qd, *J* = 8.6, 7.6, 4.1 Hz, 5H), 4.57 (d, *J* = 11.4 Hz, 1H), 4.52 (d, *J* = 11.5 Hz, 1H), 4.01 – 3.89 (m, 1H), 2.68 (ddd, *J* = 16.3, 7.2, 2.6 Hz, 1H), 2.56 (ddd, *J* = 16.3, 4.8, 1.9 Hz, 1H), 1.77 – 1.63 (m, 1H), 1.63 – 1.49 (m, 1H), 1.35 (dtd, *J* = 14.7, 10.2, 8.1, 5.6 Hz, 4H), 0.94 – 0.86 (m, 3H).



4-isopropyl-2-phenyl-1,3-dioxane (55b)

Using general procedure **D**, commercially available methyl isobutyrylacetate (1.0 mL, 7.03 mmol) and LAH (800 mg, 21.08 mmol) were combined in Et_2O (23.4 mL). The resulting crude oil (629 g, 5.32 mmol), PhCHO (0.65 mL, 6.38 mmol), p-TsOH•H_2O (101 mg, 0.572 mmol), and $MgSO_4$ (1.28 g, 10.6 mmol) were combined in CH_2Cl_2 (5.32 mL) to afford **55b** as an 80:20 mixture of inseparable diastereomers. **55b** was purified using flash column chromatography (0:100 to 20:80 EtOAc:hexanes) and isolated as a colorless oil

(673 mg, 46% over 2 steps). ^{1}H NMR of known compound **55b** matched with previously reported data.[27] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 – 7.85 (m, 1H), 7.58 – 7.46 (m, 2H), 7.39 – 7.28 (m, 2H), 5.50 (s, 1H), 4.29 (ddd, *J* = 11.4, 5.0, 1.5 Hz, 1H), 3.94 (ddd, *J* = 12.4, 11.3, 2.6 Hz, 1H), 3.52 (ddd, *J* = 11.3, 6.8, 2.4 Hz, 1H), 1.93 – 1.68 (m, 2H), 1.53 (dtd, *J* = 13.2, 2.5, 1.5 Hz, 1H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H).

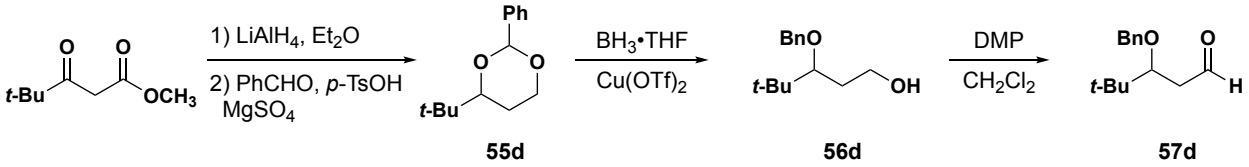
3-(benzyloxy)-4-methylpentan-1-ol (56b)

Using general procedure **E**, benzylidene acetal **55b** (673 mg, 3.26 mmol), BH_3•THF (18.1 mL, 18.1 mmol), and $Cu(OTf)_2$ (118 mg, 0.326 mmol), were combined to afford **56b**. **56b** was purified using flash column chromatography (5:95 to 30:70 EtOAc:hexanes) and isolated as a colorless oil (480 mg, 71%). ^{1}H NMR of known compound **56b** matched with previously reported data.[28] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.32 (m, 6H), 4.62 (d, *J* = 11.2 Hz, 1H), 4.48 (d, *J* = 11.3 Hz, 1H), 3.84 – 3.69 (m, 2H), 3.45 (dt, *J* = 11.6, 5.4 Hz, 1H), 2.33 (s, 1H), 2.06 (pd, *J* = 6.9, 5.1 Hz, 1H), 1.73 (q, *J* = 6.1 Hz, 2H), 0.94 (d, *J* = 2.7 Hz, 3H), 0.93 (d, *J* = 2.7 Hz, 3H).

3-(benzyloxy)-4-methylpentanal (57b)

Using general procedure **F**, benzylated alcohol **56b** (108 mg, 0.521 mmol) and DMP (265 mg, 0.626 mmol) were combined in CH_2Cl_2 (5.2 mL) to afford **57b** (78 mg, 73%)**. 57b** was used without further purification. ^{1}H NMR of known compound **57b** matched with

previously reported data.[28] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (dd, *J* = 2.7, 1.8 Hz, 1H), 7.41 – 7.29 (m, 5H), 4.60 (d, *J* = 11.4 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 3.82 (ddd, *J* = 8.5, 5.1, 3.8 Hz, 1H), 2.67 (ddd, *J* = 16.4, 8.2, 2.7 Hz, 1H), 2.52 (ddd, *J* = 16.4, 3.9, 1.8 Hz, 1H), 2.06 (dtd, *J* = 13.8, 6.9, 5.1 Hz, 1H), 0.98 (d, *J* = 2.1 Hz, 3H), 0.96 (d, *J* = 2.1 Hz, 3H).



55d **56d** **57d**

4-(*tert*-butyl)-2-phenyl-1,3-dioxane (55d)

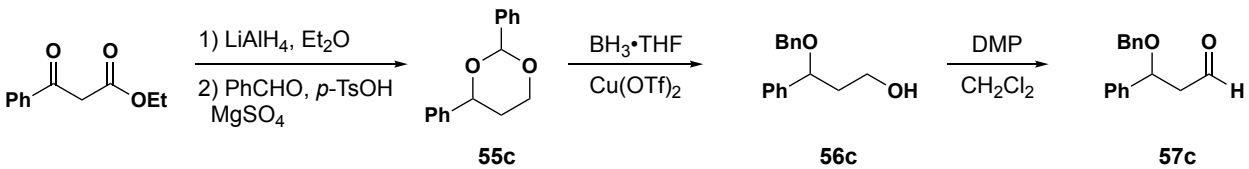
Using general procedure **D**, methyl 3-hydroxy-4,4-dimethylpentanoate (1.0 mL, 6.26 mmol) and LAH (712 mg, 18.77 mmol) were combined in Et_2O (20.9 mL). The resulting crude oil (629 mg, 4.76 mmol), PhCHO (0.58 mL, 5.71 mmol), p-TsOH•H_2O (91 mg, 0.476 mmol), and $MgSO_4$ (1.146 g, 9.52 mmol) were combined in CH_2Cl_2 (4.8 mL) to afford **55d**. **55d** was purified using flash column chromatography (1:99 to 10:90 EtOAc:hexanes) and isolated as a colorless oil (446 mg, 32% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 – 7.46 (m, 2H), 7.41 – 7.27 (m, 3H), 5.50 (s, 1H), 4.30 (dd, *J* = 11.3, 5.1 Hz, 1H), 3.94 (td, *J* = 11.8, 2.6 Hz, 1H), 3.46 (dd, *J* = 11.5, 2.2 Hz, 1H), 1.93 – 1.78 (m, 1H), 1.51 – 1.41 (m, 1H), 0.97 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 139.3, 128.5, 128.1, 126.0, 101.0, 84.8, 67.3, 34.1, 25.7, 25.6; AMM (ESI-TOF) *m/z* calculated for $C_{14}H_{21}O_2^+$ $[M + H]^+$ 221.1536, found 221.1540

3-(benzyloxy)-4,4-dimethylpentan-1-ol (56d)

Using general procedure **E**, benzylidene acetal **55d** (297 mg, 1.35 mmol), BH_3•THF (7.49 mL, 6.74 mmol), and $Cu(OTf)_2$ (49 mg, 0.135 mmol), were combined to afford **56d**. **56d** was purified using flash column chromatography (5:95 to 50:50 EtOAc:hexanes) and isolated as a colorless oil (217 mg, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.22 (m, 5H), 4.70 – 4.58 (m, 2H), 3.83 – 3.67 (m, 2H), 3.26 (dd, *J* = 9.8, 3.0 Hz, 1H), 1.93 (s, 1H), 1.87 – 1.63 (m, 2H), 0.96 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 138.8, 128.4, 127.6, 127.5, 85.9, 75.1, 61.0, 36.1, 33.6, 26.4; AMM (ESI-TOF) *m*/*z* calculated for $C_{14}H_{23}O_2^+$ $[M + H]^+$ 223.1693, found 223.1694

3-(benzyloxy)-4,4-dimethylpentanal (57d)

Using general procedure **F**, benzylated alcohol **56d** (172 mg, 0.773 mmol) and DMP (393 mg, 0.927 mmol) were combined in CH_2Cl_2 (7.7 mL) to afford **57d. 57d** was purified using flash column chromatography (5:95 to 20:80 EtOAc:hexanes) and isolated as a colorless oil (153 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.86 (t, *J* = 2.0 Hz, 1H), 7.38 – 7.22 (m, 5H), 4.61 (d, *J* = 11.3 Hz, 1H), 4.54 (d, *J* = 11.3 Hz, 1H), 3.66 (dd, *J* = 6.8, 4.5 Hz, 1H), 2.74 – 2.58 (m, 2H), 0.96 (s, 9H); ^{13}C NMR (151 MHz, Acetone) δ 139.8, 128.2, 127.8, 126.2, 100.8, 76.8, 66.6, 35.7, 31.4, 27.1, 22.4, 13.4; AMM (ESI-TOF) *m*/*z* calculated for $C_{14}H_{21}O_2^+$ $[M + H]^+$ 221.1536, found 221.1540



2,4-diphenyl-1,3-dioxane (55c)

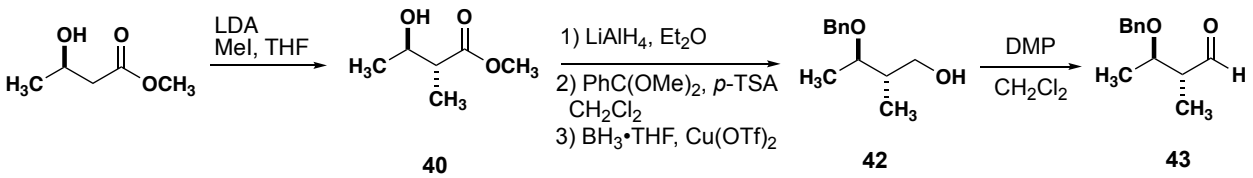
Using modified general procedure **D**, ethyl benzoylacetate (2.0 g, 10.4 mmol) and LAH (1.18 g, 31.0 mmol) were combined in Et_2O (34 mL). The resulting crude oil (1.58 g, 10.4 mmol), benzaldehyde dimethyl acetal (1.74 g, 11.4 mmol), *p*-toluenesulfonic acid (177 mg, 1.04 mmol) were combined in CH_2Cl_2 (34 mL) to afford **55c**. **55c** was purified using flash column chromatography (5:95 Et_2O:hexanes) and isolated as a colorless oil (1.67 g, 67% over 2 steps). ^{1}H NMR[29] is consistent with literature: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.57 (m, 2H), 7.48 – 7.44 (m, 2H), 7.43 – 7.35 (m, 6H), 5.75 (s, 1H), 4.95 (dd, *J* = 11.4, 2.6 Hz, 1H), 4.40 (ddd, *J* = 11.5, 4.9, 1.4 Hz, 1H), 4.21 – 4.16 (m, 1H), 2.21 – 2.09 (m, 1H), 1.83 (dtd, *J* = 13.4, 2.5, 1.4 Hz, 1H).

3-(benzyloxy)-3-phenylpropan-1-ol (56c)

Using general procedure **E**, benzylidene acetal **55c** (500 mg, 2.08 mmol), BH_3•THF (10.0 mL, 10.0 mmol), and $Cu(OTf)_2$ (38 mg, 0.100 mmol), were combined to afford **56c**. **56c** was purified using flash column chromatography (30:70 EtOAc:hexanes) and isolated as a colorless oil (325 mg, 80%). ^{1}H NMR[30] is consistent with literature: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.25 (m, 10H, Ar), 4.58 (dd, *J* = 4.0, 9.1 Hz, 1H), 4.48 (d, *J* = 11.6 Hz, 1H), 4.27 (d, *J* = 11.6Hz, 1H), 3.78–3.74 (m, 2H), 2.09 – 2.06 (m, 1H), 1.91 – 1.87 (m, 1H)

3-(benzyloxy)-3-phenylpropanal (57c)

Using general procedure **F**, alcohol **56c** (170 mg, 0.700 mmol) and DMP (328 mg, 0.770 mmol) were combined in CH_2Cl_2 (7.0 mL) to afford **57c. 57c** was used in subsequent reactions with no further purification. ^{1}H NMR[31] is consistent with literature: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (dd, *J* = 2.6, 1.6 Hz, 1H), 7.44 – 7.30 (m, 12H), 4.50 (d, *J* = 11.6 Hz, 1H), 4.33 (d, *J* = 11.6 Hz, 1H), 3.00 (ddd, *J* = 16.4, 9.2, 2.6 Hz, 1H), 2.68 (ddd, *J* = 16.5, 4.2, 1.7 Hz, 1H).



Methyl (2*R*,3*R*)-3-hydroxy-2-methylbutanoate (40)

Using previously reported procedure:[8] To a stirred solution of *N*,*N*-diisopropylamine (3.5 mL, 25.4 mmol, 3.0 equiv.) in dry THF (10 mL) was added *n*-BuLi (2.5 M in hexanes, 9.8 mL, 24.5 mmol, 2.9 equiv.) at –78 °C. After 30 min at –78 °C, (R)-methyl-3-hydroxybutyrate (1 mL, 8.6 mmol 1.0 equiv.) was added dropwise. The resulting mixture was stirred for 30 min at –78 °C, after which time methyl iodide (3.13 mL, 50.82 mmol, 6.0 equiv.) was added. The reaction was stirred at –78 °C for further 1.5 h after which time it was allowed to reach room temperature and aqueous 1M HCl (10 mL) was added. The product was extracted with CH_2Cl_2 (3 × 10 mL) and the organic layer was washed with brine (15 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude oil was purified by column chromatography on silica gel, eluting with 4:1 to 1:1

(cyclohexane/EtOAc) to furnish the desired compound as a pale yellow oil (888 mg, 77%). ^{1}H NMR[32] is consistent with literature. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 – 3.86 (m, 1H), 3.74 (s, 3H), 2.64 (d, *J* = 5.3 Hz, 1H), 2.49 (p, *J* = 7.2 Hz, 1H), 1.24 (d, *J* = 6.3 Hz, 3H), 1.21 (d, *J* = 7.2 Hz, 3H).

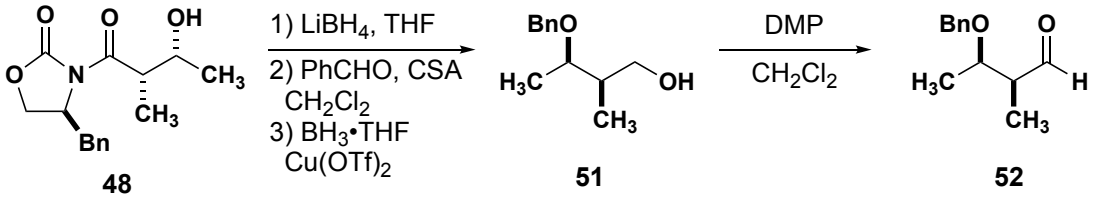
(2*S*,3*R*)-3-(benzyloxy)-2-methylbutan-1-ol (42)

Using modified general procedure **D**, ester **40** (888 mg, 67.0 mmol) and LAH (225 mg, 67.0 mmol) were combined in Et_2O (16 mL). Upon workup, the resulting crude oil (700 mg, 67.0 mmol), benzaldehyde dimethyl acetal (1.12 g, 7.00 mmol), *p*-toluenesulfonic acid (116 mg, 6.70 mmol). The crude reaction mixture was purified using flash column chromatography (5:95 Et_2O:hexanes) and the resulting benzylidene acetal was isolated as an inseparable mixture of diastereomers and colorless oil (1.00 g, 77% over 2 steps).

Using general procedure **E**, benzylidene acetal (820 mg, 4.27 mmol), BH_3•THF (21.0 mL, 21.0 mmol), and $Cu(OTf)_2$ (77 mg, 0.200 mmol), were combined to afford **42**. **42** was purified using flash column chromatography (30:70 Et_2O:hexanes) and isolated as a colorless oil (779 mg, 83%). ^{1}H NMR[33] is consistent with literature: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.30 (m, 5H), 4.68 (d, *J* = 11.5 Hz, 1H), 4.44 (d, *J* = 11.6 Hz, 1H), 3.70 – 3.56 (m, 2H), 3.51 (dq, *J* = 7.4, 6.2 Hz, 1H), 2.90 (s, 1H), 1.81 (hd, *J* = 7.0, 3.7 Hz, 1H), 1.28 (d, *J* = 6.1 Hz, 3H), 0.93 (d, *J* = 7.0 Hz, 3H).

(2*R*,3*R*)-3-(benzyloxy)-2-methylbutanal (43)

Using general procedure **F**, alcohol **42** (168 mg, 0.860 mmol) and DMP (404 mg, 0.950 mmol) were combined in CH_2Cl_2 (8.6 mL) to afford **43. 43** was used in subsequent reactions with no further purification. ^{1}H NMR[34] is consistent with literature: ^{1}H NMR (400 MHz, $CDCl_3$) 9.74 (d, J = 2.3 Hz, 1H), 7.37–7.27 (m, 5H), 4.63 (d, J = 11.7 Hz, 1H), 4.45 (d, J = 11.7 Hz, 1H), 3.81 (p, J = 6.3 Hz, 1H), 2.57 (pd, J = 7.1, 2.5 Hz, 1H), 1.25 (d, J = 6.2 Hz, 3H), 1.09 (d, J = 7.2 Hz, 3H).



(*S*)-4-benzyl-3-((2*S*,3*R*)-3-hydroxy-2-methylbutanoyl)oxazolidin-2-one (48)

Known compound **48** was prepared according to previously reported procedure.[35] ^{1}H NMR is consistent with literature. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.30 (m, 3H), 7.26 – 7.18 (m, 2H), 4.74 (ddt, *J* = 9.4, 7.4, 3.3 Hz, 1H), 3.77 (qd, *J* = 7.0, 2.9 Hz, 1H), 3.28 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.95 – 2.76 (m, 2H), 1.29 (d, *J* = 5.6 Hz, 3H), 1.24 (d, *J* = 6.4 Hz, 3H).

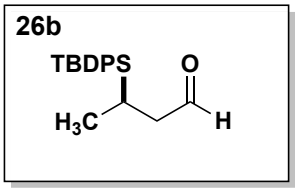
(2*R*,3*R*)-3-(benzyloxy)-2-methylbutan-1-ol (51)

48 (1.17 g, 4.20 mmol) was dissolved in THF (42 mL) and MeOH (0.5 mL). Lithium borohydride (2.0M in THF, 6.30 mL) was added dropwise. The reaction was stirred overnight at room temperature and quenched with sat. sodium tartrate (30 mL). The

mixture was stirred for 2 hours at room temperature and then extracted with diethyl ether (3 x 30 mL). Combined organics were dried over sodium sulfate, filtered and concentrated *in vacuo* to produce a crude colorless oil. The crude material was used without further purification and combined with benzaldehyde (0.857 mL, 8.10 mmol), camphorsulfonic acid (293 mg, 1.26 mmol) and magnesium sulfate (1.52 g, 12.6 mmol) in DCM (42 mL). The reaction was stirred overnight at room temperature and then the solids filtered off. The filtrate was washed with sat. sodium bicarbonate and sat. sodium sulfite. The organic layer was dried over sodium sulfate, filtered and concentrated in vacuo to produce a colorless oil. The crude material was used without further purification and combined with BH_3•THF (1.0 M in THF, 27.35 mL) in DCM (10 mL) and stirred at room temperature for 10 minutes. Then, copper triflate (198 mg, 0.547 mmol) was added and the reaction stirred for 2 hours. After 2 hours the reaction was cooled to 0 °C and 1 equiv. of triethylamine and MeOH (5 mL) was added dropwise. The mixture was stirred for 30 minutes and concentrated *in vacuo* to produce a colorless oil. The crude oil was purified using flash chromatography (10 to 20% EtOAc in Hexanes) to produce known compound **51** (120 mg, 63% over three steps). ^{1}H NMR[34] is consistent with literature: ^{1}H NMR (599 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 5H), 4.61 (d, *J* = 11.8 Hz, 1H), 4.45 (d, *J* = 11.8 Hz, 1H), 3.70 (ddt, *J* = 10.9, 7.3, 4.0 Hz, 2H), 3.55 (dt, *J* = 10.9, 5.3 Hz, 1H), 2.65 – 2.57 (m, 1H), 2.00 (tt, *J* = 7.5, 4.1 Hz, 1H), 1.20 (dd, *J* = 6.4, 1.8 Hz, 3H), 0.87 (dd, *J* = 7.2, 1.8 Hz, 3H).

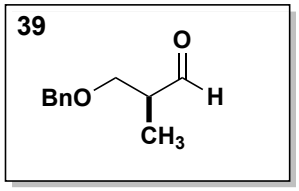
(2*S*,3*R*)-3-(benzyloxy)-2-methylbutanal (52)

Using general procedure **F**, alcohol **51** (120 mg, 0.618 mmol) and DMP (314 mg, 0.742 mmol) were combined in CH2Cl2 (6 mL) to afford **52**. **52** was used in subsequent reactions with no further purification. 1H NMR[34] is consistent with literature: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (d, *J* = 1.2 Hz, 1H), 7.40 – 7.27 (m, 5H), 4.61 (d, *J* = 11.8 Hz, 1H), 4.46 (d, *J* = 11.8 Hz, 1H), 3.96 (qd, *J* = 6.3, 4.3 Hz, 1H), 2.52 (qdd, *J* = 7.0, 4.4, 1.2 Hz, 1H), 1.26 (d, *J* = 6.4 Hz, 3H), 1.14 (d, *J* = 7.0 Hz, 3H).



(*R*)-3-((*tert*-butyldimethylsilyl)oxy)butanal (26b)

Known aldehyde **26b** was prepared according to previously reported procedure. ^{1}H NMR is consistent with literature.[26] ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.83 (t, *J* = 2.3 Hz, 1H), 7.34 (qd, *J* = 8.6, 7.6, 4.1 Hz, 5H), 4.63 – 4.49 (m, 2H), 4.07 – 3.90 (m, 1H), 2.70 (ddd, *J* = 16.3, 7.2, 2.6 Hz, 1H), 2.59 (ddd, *J* = 16.3, 4.8, 1.9 Hz, 1H), 1.83 – 1.66 (m, 1H), 1.66 – 1.52 (m, 1H), 1.37 (qd, *J* = 10.5, 9.6, 6.4 Hz, 4H), 0.97 – 0.89 (m, 3H).



(*S*)-3-(benzyloxy)-2-methylpropanal (39)

Known aldehyde **9** was prepared according to previously reported procedure. ^{1}H NMR is consistent with literature.[36] ^{1}H NMR (599 MHz, Chloroform-*d*) δ 9.72 (d, *J* = 1.7 Hz, 1H), 7.32 (dq, *J* = 15.8, 7.7 Hz, 5H), 4.52 (s, 3H), 3.71 – 3.60 (m, 3H), 2.66 (tdd, *J* = 7.1, 5.3, 1.7 Hz, 1H), 1.13 (d, *J* = 7.2 Hz, 3H).

2.5 Computational Methods and Results

All calculations were performed with Gaussian16.[23] Gas-phase ground state geometries were optimized in vacuo using the meta-hybrid density functional B3LYP[24, 37] and the 6-31G(d,p) basis set. Vibrational frequencies were computed to determine if the optimized structures are minima on the potential energy surface corresponding to ground state geometry. We have atomically truncated the *p*-tolSO_2 of the *N*-tosyl group to H_3CSO_2 for computational fidelity. We have performed a systematic conformational analysis of the initial imine reactants and the chelated intermediates and herein we report the lowest energy conformers for each species.

Cartesian Coordinates and Energies

All of the cartesian coordinates and sum of electronic and thermal free energies (Hartrees) correspond to B3LYP/6-31G(d,p)-optimized geometries.

H^+

Sum of electronic and thermal Free Energies = –0.0100000 Hartrees

```
H          0.00000        0.00000        0.00000
```

Imine (18)

Sum of electronic and thermal Free Energies = –1145.838400 Hartrees

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.479624	2.059365	0.862294
2	1	0	-1.770219	2.561600	-0.065555
3	1	0	-1.083127	2.808989	1.555233
4	1	0	-2.376732	1.624350	1.307927
5	6	0	-0.425408	0.987434	0.581570
6	1	0	-0.158198	0.490729	1.529535
7	6	0	0.844222	1.599208	-0.035617
8	1	0	1.214631	2.428373	0.572747
9	1	0	0.570376	1.998126	-1.022713
10	6	0	1.935275	0.592819	-0.233907
11	1	0	1.661495	-0.352940	-0.713659
12	7	0	3.130270	0.840972	0.150979
13	16	0	4.283456	-0.397174	-0.226744
14	8	0	3.621048	-1.669985	-0.551918
15	8	0	5.245049	0.191177	-1.162670
16	6	0	5.067312	-0.552701	1.384502
17	1	0	5.892560	-1.255996	1.261311
18	1	0	5.436485	0.427462	1.685337
19	1	0	4.339413	-0.938323	2.098946
20	8	0	-0.862092	-0.005691	-0.348468
21	6	0	-1.742550	-1.006947	0.155076
22	1	0	-1.513405	-1.907173	-0.428534
23	1	0	-1.506771	-1.234851	1.205082
24	6	0	-3.216377	-0.675845	0.011284
25	6	0	-3.690902	-0.047456	-1.147216
26	6	0	-4.129450	-1.042170	1.005674
27	6	0	-5.051650	0.210292	-1.304775
28	1	0	-2.982667	0.245945	-1.915959
29	6	0	-5.494003	-0.790737	0.846782
30	1	0	-3.772364	-1.527306	1.911382
31	6	0	-5.958021	-0.162653	-0.308943
32	1	0	-5.407034	0.700975	-2.206454
33	1	0	-6.191030	-1.079224	1.628314
34	1	0	-7.018163	0.037677	-0.433101

Conformer (66b)

Sum of electronic and thermal Free Energies = –1146.195110 Hartrees

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.086112	4.123447	0.061313

2	1	0	-0.469383	4.398854	1.048272
3	1	0	-0.529162	4.788329	-0.686209
4	1	0	0.993092	4.291702	0.047660
5	6	0	-0.414548	2.668884	-0.255606
6	1	0	0.019349	2.393438	-1.229982
7	6	0	-1.939885	2.439473	-0.312451
8	1	0	-2.389881	3.036312	-1.112091
9	1	0	-2.403634	2.794750	0.622667
10	6	0	-2.381531	1.022432	-0.476795
11	1	0	-3.344361	0.785318	-0.935887
12	7	0	-1.667944	0.031129	-0.075036
13	16	0	-2.127937	-1.708841	-0.442475
14	8	0	-3.477833	-1.586891	-0.966253
15	8	0	-1.001214	-2.202907	-1.210419
16	6	0	-2.114913	-2.388325	1.215934
17	1	0	-2.368960	-3.445404	1.101071
18	1	0	-1.107090	-2.280915	1.622684
19	1	0	-2.869168	-1.876421	1.814314
20	8	0	0.077232	1.756144	0.742238
21	6	0	1.522671	1.591592	0.823783
22	1	0	1.946309	2.440156	1.368795
23	1	0	1.937284	1.581521	-0.192479
24	1	0	-0.746905	0.295336	0.358504
25	6	0	1.778637	0.290285	1.534403
26	6	0	1.933014	0.255604	2.925878
27	6	0	1.798635	-0.912810	0.812281
28	6	0	2.104044	-0.960778	3.587220
29	1	0	1.925341	1.183346	3.491454
30	6	0	1.965115	-2.131741	1.473869
31	1	0	1.710166	-0.898853	-0.271821
32	6	0	2.116819	-2.155333	2.863203
33	1	0	2.234405	-0.976451	4.664621
34	1	0	2.002814	-3.054797	0.903421
35	1	0	2.262853	-3.100165	3.377551

Conformer (67b)

Sum of electronic and thermal Free Energies = –1146.192942 Hartrees

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.747240	-0.717118	1.479819
2	1	0	-1.786725	-0.590128	1.989873
3	1	0	-3.145601	-1.703597	1.734875
4	1	0	-3.441396	0.026919	1.876709
5	6	0	-2.602002	-0.573309	-0.035951
6	1	0	-3.577454	-0.737180	-0.512906
7	6	0	-1.619113	-1.602346	-0.636952
8	1	0	-1.740109	-1.647028	-1.732630
9	1	0	-1.837669	-2.612696	-0.276622
10	6	0	-0.164799	-1.333349	-0.443491
11	1	0	0.558049	-2.150546	-0.508004
12	7	0	0.316971	-0.153680	-0.261187
13	16	0	2.132880	0.153178	-0.312116
14	8	0	2.685789	-1.189352	-0.369439
15	8	0	2.281007	1.143859	-1.358534
16	6	0	2.376680	0.890021	1.304623

17	1	0	3.439284	1.142058	1.354388
18	1	0	1.771401	1.795406	1.370282
19	1	0	2.120728	0.157396	2.070462
20	8	0	-2.103075	0.715950	-0.420780
21	6	0	-3.051781	1.819507	-0.420349
22	1	0	-3.523057	1.896847	0.565130
23	1	0	-3.826760	1.594652	-1.163346
24	1	0	-0.382989	0.626969	-0.266653
25	6	0	-2.300179	3.075785	-0.757009
26	6	0	-1.889369	3.949733	0.258013
27	6	0	-1.972031	3.368655	-2.087967
28	6	0	-1.165465	5.101628	-0.052093
29	1	0	-2.154452	3.738560	1.291301
30	6	0	-1.245287	4.516916	-2.398218
31	1	0	-2.296083	2.701362	-2.882395
32	6	0	-0.841561	5.384282	-1.380223
33	1	0	-0.865195	5.782143	0.738650
34	1	0	-1.002306	4.740844	-3.432062
35	1	0	-0.284634	6.283701	-1.623557

Conformer (66c)

Sum of electronic and thermal Free Energies = –1264.065741 Hartrees

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-1.502565	-0.871673	-0.205988
2	1	0	-1.364742	-1.078591	-1.279385
3	6	0	-0.984817	-2.089010	0.591193
4	1	0	-1.541903	-2.991317	0.320298
5	1	0	-1.166135	-1.936605	1.667180
6	6	0	0.472835	-2.375158	0.460681
7	1	0	0.859708	-3.389639	0.583098
8	7	0	1.333332	-1.449416	0.219575
9	16	0	3.095245	-1.827709	-0.119983
10	8	0	3.204784	-3.232469	0.235734
11	8	0	3.303944	-1.312643	-1.459846
12	6	0	3.878613	-0.769818	1.096362
13	1	0	4.953647	-0.917536	0.964026
14	1	0	3.606603	0.264853	0.877072
15	1	0	3.568781	-1.086008	2.092860
16	8	0	-0.640253	0.223389	0.160057
17	6	0	-0.742315	1.430526	-0.648226
18	1	0	-1.624208	1.995595	-0.332318
19	1	0	-0.864830	1.144786	-1.700838
20	1	0	0.924891	-0.488231	0.095235
21	6	0	0.525233	2.213191	-0.435813
22	6	0	0.609790	3.171954	0.581545
23	6	0	1.659081	1.940643	-1.216301
24	6	0	1.807136	3.847727	0.817570
25	1	0	-0.265649	3.393899	1.185730
26	6	0	2.859876	2.613454	-0.978057
27	1	0	1.600464	1.219872	-2.028823
28	6	0	2.933890	3.567212	0.040957
29	1	0	1.859506	4.597077	1.601021
30	1	0	3.724617	2.411813	-1.602913

31	1	0	3.861573	4.102888	0.217184
32	6	0	-2.987274	-0.588915	0.055545
33	1	0	-3.299520	0.209954	-0.627717
34	1	0	-3.556546	-1.474813	-0.255458
35	6	0	-3.346777	-0.201839	1.496317
36	1	0	-2.714620	0.634936	1.819127
37	1	0	-3.127657	-1.033284	2.181271
38	6	0	-4.826159	0.179879	1.650894
39	1	0	-5.053029	1.017374	0.978113
40	1	0	-5.452545	-0.657197	1.316144
41	6	0	-5.198059	0.558511	3.086818
42	1	0	-4.611096	1.414205	3.438162
43	1	0	-6.254924	0.829173	3.160338
44	1	0	-5.020600	-0.273346	3.777249

Conformer (67c)

Sum of electronic and thermal Free Energies = –1264.064138 Hartrees

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.713367	3.250709	1.196126
2	1	0	-1.266645	2.477200	1.746944
3	1	0	0.255215	3.345804	1.699957
4	6	0	-0.447125	2.767193	-0.237559
5	1	0	0.014076	3.580725	-0.813962
6	6	0	-1.726975	2.340050	-0.989704
7	1	0	-1.521217	2.254796	-2.070227
8	1	0	-2.511223	3.097570	-0.901777
9	6	0	-2.305698	1.015031	-0.624896
10	1	0	-3.359054	0.801937	-0.823501
11	7	0	-1.609169	0.051774	-0.130325
12	16	0	-2.309171	-1.639939	0.044818
13	8	0	-3.711486	-1.447374	-0.284421
14	8	0	-1.397479	-2.468135	-0.717975
15	6	0	-2.083432	-1.896498	1.805337
16	1	0	-2.446735	-2.908373	2.003136
17	1	0	-1.019048	-1.826766	2.034632
18	1	0	-2.678324	-1.162598	2.349597
19	8	0	0.420686	1.621401	-0.268048
20	6	0	1.850578	1.869759	-0.175810
21	1	0	2.061955	2.462046	0.720852
22	1	0	2.147988	2.450872	-1.057417
23	1	0	-0.586634	0.250704	-0.006576
24	6	0	2.549652	0.541138	-0.120762
25	6	0	2.952056	0.001199	1.107713
26	6	0	2.774668	-0.188442	-1.296303
27	6	0	3.574357	-1.246499	1.160812
28	1	0	2.794682	0.567288	2.022677
29	6	0	3.392568	-1.436899	-1.243934
30	1	0	2.475301	0.228035	-2.254656
31	6	0	3.793041	-1.966674	-0.014963
32	1	0	3.897401	-1.650531	2.115246
33	1	0	3.570617	-1.991626	-2.159697
34	1	0	4.283557	-2.934256	0.024323
35	6	0	-1.450145	4.595877	1.288772
36	1	0	-2.447871	4.521300	0.833974
37	1	0	-0.904385	5.349402	0.704711

38	6	0	-1.605014	5.090758	2.734019
39	1	0	-0.610631	5.182141	3.189933
40	1	0	-2.141397	4.332641	3.320409
41	6	0	-2.340084	6.430276	2.830320
42	1	0	-3.351550	6.361404	2.415186
43	1	0	-2.430606	6.754344	3.870700
44	1	0	-1.808197	7.215857	2.283194

Conformer (66d)

Sum of electronic and thermal Free Energies = –1224.770847 Hartrees

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-2.204013	-0.405502	-0.346073
2	1	0	-2.125455	-0.525617	-1.438007
3	6	0	-1.842728	-1.751667	0.332921
4	1	0	-2.483521	-2.556524	-0.033584
5	1	0	-2.052525	-1.676246	1.413573
6	6	0	-0.430832	-2.216910	0.239290
7	1	0	-0.199531	-3.284676	0.264449
8	7	0	0.572863	-1.416904	0.160682
9	16	0	2.280977	-2.052099	-0.105711
10	8	0	2.139949	-3.472633	0.167368
11	8	0	2.661653	-1.514458	-1.397414
12	6	0	3.132992	-1.201207	1.221187
13	1	0	4.176034	-1.520664	1.149533
14	1	0	3.052360	-0.125370	1.050806
15	1	0	2.702430	-1.513705	2.173023
16	8	0	-1.201554	0.535630	0.087223
17	6	0	-0.819120	1.601504	-0.833292
18	1	0	-1.535374	2.421215	-0.749915
19	1	0	-0.846257	1.222314	-1.862274
20	1	0	0.337018	-0.400950	0.125549
21	6	0	0.570464	2.045514	-0.455023
22	6	0	0.783945	2.724163	0.755729
23	6	0	1.665738	1.760558	-1.281479
24	6	0	2.069398	3.109439	1.131094
25	1	0	-0.061035	2.954962	1.398404
26	6	0	2.955019	2.152530	-0.908452
27	1	0	1.514331	1.244346	-2.225640
28	6	0	3.157457	2.825513	0.298002
29	1	0	2.223357	3.644013	2.063248
30	1	0	3.792852	1.941630	-1.565479
31	1	0	4.155911	3.143479	0.582399
32	6	0	-3.653149	-0.002846	0.021005
33	6	0	-4.666057	-1.003652	-0.567239
34	1	0	-5.683082	-0.685468	-0.324874
35	1	0	-4.589587	-1.048370	-1.659826
36	1	0	-4.552394	-2.019073	-0.176440
37	6	0	-4.009381	1.423392	-0.423298
38	1	0	-3.420164	2.174849	0.106042
39	1	0	-3.872488	1.560887	-1.501942
40	1	0	-5.061148	1.623305	-0.201457
41	1	0	-3.723015	-0.036161	1.117552

Conformer (67d)

Sum of electronic and thermal Free Energies = –1224.772123 Hartrees

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.690540	-0.487441	-1.301660
2	1	0	2.067760	-1.223802	-2.023204
3	6	0	1.339356	0.801684	-2.092859
4	1	0	0.740842	0.543414	-2.983158
5	1	0	2.230229	1.296940	-2.486329
6	6	0	0.506941	1.802711	-1.367531
7	1	0	0.535501	2.859970	-1.642778
8	7	0	-0.320914	1.469467	-0.438474
9	16	0	-1.529617	2.673832	0.241948
10	8	0	-1.113426	3.929452	-0.359961
11	8	0	-2.810659	2.040068	-0.000230
12	6	0	-1.103638	2.611127	1.982454
13	1	0	-1.806496	3.283892	2.480892
14	1	0	-1.241613	1.589469	2.339538
15	1	0	-0.079872	2.964328	2.108831
16	8	0	0.490663	-0.994683	-0.688067
17	6	0	-0.271485	-1.968869	-1.462815
18	1	0	0.359104	-2.853705	-1.600907
19	1	0	-0.504943	-1.549783	-2.450686
20	1	0	-0.359515	0.440609	-0.223234
21	6	0	-1.525287	-2.288375	-0.701399
22	6	0	-1.528370	-3.306733	0.260932
23	6	0	-2.692271	-1.540971	-0.911972
24	6	0	-2.680226	-3.574185	0.999239
25	1	0	-0.630110	-3.896136	0.424570
26	6	0	-3.844312	-1.804969	-0.170623
27	1	0	-2.709635	-0.761258	-1.670119
28	6	0	-3.838129	-2.822562	0.785015
29	1	0	-2.677637	-4.371855	1.735319
30	1	0	-4.745349	-1.226323	-0.347089
31	1	0	-4.736683	-3.036475	1.355282
32	6	0	2.756564	-0.291088	-0.202679
33	1	0	2.356158	0.430247	0.525963
34	6	0	3.007748	-1.617906	0.529960
35	1	0	3.722457	-1.470200	1.343956
36	1	0	2.086624	-2.024134	0.951911
37	1	0	3.434275	-2.364058	-0.150483
38	6	0	4.070966	0.270336	-0.770509
39	1	0	4.466548	-0.372560	-1.565016
40	1	0	3.972783	1.284232	-1.170856
41	1	0	4.826434	0.313223	0.018155

Conformer (66e)

Sum of electronic and thermal Free Energies = –1264.059615 Hartrees

Center	Atomic	Atomic	Coordinates (Angstroms)

Number	Number	Type	X	Y	Z
1	6	0	-1.660198	-0.718083	-0.320890
2	1	0	-1.455318	-0.910610	-1.386093
3	6	0	-1.125858	-1.920049	0.496760
4	1	0	-1.596234	-2.851550	0.174685
5	1	0	-1.402023	-1.802560	1.557566
6	6	0	0.345532	-2.145322	0.498190
7	1	0	0.743717	-3.149679	0.662380
8	7	0	1.212443	-1.208974	0.338147
9	16	0	3.007325	-1.582467	0.189982
10	8	0	3.080474	-2.975807	0.597682
11	8	0	3.357843	-1.110983	-1.135499
12	6	0	3.653336	-0.488540	1.453650
13	1	0	4.737157	-0.630017	1.435200
14	1	0	3.399342	0.539930	1.187566
15	1	0	3.245293	-0.788545	2.419301
16	8	0	-0.857744	0.401083	0.107668
17	6	0	-0.708501	1.548381	-0.777934
18	1	0	-1.496571	2.271009	-0.553160
19	1	0	-0.816633	1.226116	-1.819631
20	1	0	0.823294	-0.254569	0.179007
21	6	0	0.653908	2.144150	-0.529280
22	6	0	0.899419	2.861652	0.652502
23	6	0	1.697734	1.961423	-1.446914
24	6	0	2.164688	3.388335	0.908769
25	1	0	0.092993	3.017164	1.364007
26	6	0	2.965213	2.492433	-1.193297
27	1	0	1.518976	1.417168	-2.370500
28	6	0	3.199358	3.205907	-0.015916
29	1	0	2.340565	3.956221	1.817171
30	1	0	3.761192	2.356390	-1.918269
31	1	0	4.178827	3.634260	0.174155
32	6	0	-3.202302	-0.525547	-0.147154
33	6	0	-3.538254	-0.052113	1.278892
34	1	0	-3.012490	0.873748	1.526695
35	1	0	-4.612302	0.135380	1.364986
36	1	0	-3.286778	-0.799551	2.040009
37	6	0	-3.919108	-1.863406	-0.445034
38	1	0	-4.999189	-1.698294	-0.478707
39	1	0	-3.624948	-2.277165	-1.416854
40	1	0	-3.741631	-2.622077	0.323178
41	6	0	-3.722974	0.511333	-1.167609
42	1	0	-3.383564	1.525414	-0.949492
43	1	0	-3.426491	0.258713	-2.191666
44	1	0	-4.816032	0.531062	-1.140728

Conformer (67e)

Sum of electronic and thermal Free Energies = –1264.060475 Hartrees

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.682440	-0.451969	-1.240089
2	1	0	1.989996	-1.138521	-2.037697
3	6	0	1.376496	0.913544	-1.920610

4	1	0	0.866011	0.734832	-2.882758
5	1	0	2.291944	1.447869	-2.184892
6	6	0	0.462442	1.851889	-1.211987
7	1	0	0.517292	2.925907	-1.406361
8	7	0	-0.473804	1.458026	-0.419802
9	16	0	-1.751951	2.614390	0.199364
10	8	0	-1.270916	3.908938	-0.254117
11	8	0	-2.997437	2.013007	-0.235653
12	6	0	-1.533042	2.419542	1.968138
13	1	0	-2.280669	3.069388	2.430353
14	1	0	-1.724251	1.377852	2.230159
15	1	0	-0.526390	2.740466	2.237369
16	8	0	0.469553	-0.949137	-0.641760
17	6	0	-0.216786	-2.019055	-1.359511
18	1	0	0.437220	-2.897099	-1.366564
19	1	0	-0.391508	-1.703517	-2.396360
20	1	0	-0.514219	0.421284	-0.260871
21	6	0	-1.510830	-2.292895	-0.648435
22	6	0	-1.569003	-3.243584	0.379019
23	6	0	-2.663550	-1.562856	-0.971961
24	6	0	-2.760269	-3.462394	1.069847
25	1	0	-0.682662	-3.819994	0.630371
26	6	0	-3.854437	-1.776283	-0.276971
27	1	0	-2.638896	-0.838769	-1.783267
28	6	0	-3.902665	-2.727482	0.743971
29	1	0	-2.799770	-4.209392	1.856340
30	1	0	-4.742939	-1.211765	-0.540966
31	1	0	-4.831415	-2.903689	1.277612
32	6	0	2.830319	-0.427314	-0.189491
33	6	0	2.526086	0.536688	0.971534
34	1	0	3.335343	0.502738	1.706303
35	1	0	2.451968	1.580271	0.638346
36	1	0	1.600754	0.263011	1.488259
37	6	0	2.988592	-1.859362	0.363351
38	1	0	3.229097	-2.569755	-0.435310
39	1	0	3.806687	-1.892566	1.088267
40	1	0	2.077940	-2.196795	0.863658
41	6	0	4.148096	-0.013525	-0.878063
42	1	0	4.980738	-0.129519	-0.178770
43	1	0	4.364203	-0.641085	-1.749541
44	1	0	4.151577	1.032902	-1.201059

Conformer (66f)

Sum of electronic and thermal Free Energies = –1337.889244 Hartrees

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.788101	-0.019213	-0.941667
2	1	0	1.324752	-0.293462	-1.901832
3	6	0	1.880543	1.524957	-0.866181
4	1	0	2.479602	1.909997	-1.696958
5	1	0	2.421295	1.815761	0.048363
6	6	0	0.576868	2.252520	-0.833806
7	1	0	0.491983	3.274243	-1.211647
8	7	0	-0.489353	1.716983	-0.352280
9	16	0	-2.128680	2.525103	-0.476473

10	8	0	-1.804843	3.862878	-0.942553
11	8	0	-2.921291	1.573021	-1.231226
12	6	0	-2.606340	2.518834	1.251113
13	1	0	-3.601894	2.969263	1.281957
14	1	0	-2.646718	1.482084	1.592046
15	1	0	-1.895684	3.121482	1.817465
16	8	0	0.901517	-0.399220	0.128400
17	6	0	0.480342	-1.795550	0.143306
18	1	0	1.316353	-2.408097	0.491078
19	1	0	0.225345	-2.097375	-0.880444
20	1	0	-0.367867	0.728122	-0.009278
21	6	0	-0.711425	-1.882571	1.056405
22	6	0	-0.551594	-2.184734	2.414208
23	6	0	-1.994838	-1.597831	0.564918
24	6	0	-1.654223	-2.201879	3.268916
25	1	0	0.437659	-2.413448	2.801097
26	6	0	-3.098791	-1.609841	1.420426
27	1	0	-2.138443	-1.391860	-0.493670
28	6	0	-2.927588	-1.911112	2.774529
29	1	0	-1.521346	-2.448180	4.317620
30	1	0	-4.090793	-1.412412	1.025384
31	1	0	-3.786393	-1.936203	3.438141
32	6	0	3.155774	-0.660109	-0.849049
33	6	0	3.749138	-1.214225	-1.988297
34	6	0	3.847495	-0.680550	0.370394
35	6	0	5.025705	-1.773926	-1.914720
36	1	0	3.215003	-1.211455	-2.935394
37	6	0	5.118333	-1.247382	0.444032
38	1	0	3.382893	-0.271120	1.263508
39	6	0	5.710372	-1.790806	-0.699465
40	1	0	5.479568	-2.201278	-2.803010
41	1	0	5.647084	-1.266898	1.391743
42	1	0	6.701089	-2.230014	-0.640455

Conformer (67f)

Sum of electronic and thermal Free Energies = –1337.885697 Hartrees

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.388055	2.807642	-0.149665
2	1	0	0.085222	3.644449	-0.681314
3	6	0	-1.730960	2.528912	-0.879983
4	1	0	-1.568695	2.536046	-1.970998
5	1	0	-2.449980	3.325830	-0.672855
6	6	0	-2.379901	1.212995	-0.612339
7	1	0	-3.463726	1.101705	-0.695166
8	7	0	-1.711407	0.147014	-0.341315
9	16	0	-2.512122	-1.504407	-0.271849
10	8	0	-3.927125	-1.185878	-0.358268
11	8	0	-1.788464	-2.279095	-1.259587
12	6	0	-2.049779	-1.999527	1.388760
13	1	0	-2.453812	-3.006762	1.519498
14	1	0	-0.960376	-2.017888	1.454849
15	1	0	-2.501381	-1.308622	2.101251
16	8	0	0.398152	1.626327	-0.320880
17	6	0	1.823530	1.736831	-0.036346

18	1	0	1.957059	2.284062	0.901605
19	1	0	2.285101	2.306876	-0.851064
20	1	0	-0.672580	0.264338	-0.294621
21	6	0	2.371366	0.340671	0.057620
22	6	0	2.505341	-0.284712	1.305416
23	6	0	2.704896	-0.370170	-1.103223
24	6	0	2.967100	-1.599006	1.390967
25	1	0	2.270897	0.268369	2.211773
26	6	0	3.164097	-1.684376	-1.018712
27	1	0	2.614817	0.110644	-2.073804
28	6	0	3.294611	-2.299980	0.228166
29	1	0	3.087322	-2.069070	2.362299
30	1	0	3.428505	-2.224181	-1.922433
31	1	0	3.662549	-3.319151	0.293947
32	6	0	-0.596708	3.207348	1.304622
33	6	0	-0.855296	4.550081	1.607960
34	6	0	-0.579408	2.265832	2.341212
35	6	0	-1.109755	4.943406	2.921565
36	1	0	-0.851231	5.295756	0.816080
37	6	0	-0.824538	2.661184	3.657212
38	1	0	-0.340641	1.228794	2.125492
39	6	0	-1.096568	3.998508	3.949027
40	1	0	-1.305755	5.987527	3.143317
41	1	0	-0.794801	1.926842	4.456407
42	1	0	-1.285101	4.304898	4.972845

Conformer (66g)

Sum of electronic and thermal Free Energies = –1185.485546 Hartrees

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	0.834859	-2.619966	-0.233778
2	6	0	2.113871	-1.902667	-0.746867
3	1	0	2.110613	-1.969117	-1.850318
4	6	0	2.144771	-0.420647	-0.504581
5	1	0	3.107392	0.097223	-0.476833
6	7	0	1.097195	0.312469	-0.371623
7	16	0	1.203292	2.147304	-0.336270
8	8	0	2.634306	2.391013	-0.255793
9	8	0	0.370280	2.559610	-1.448334
10	6	0	0.392247	2.478356	1.227488
11	1	0	0.350359	3.567597	1.309560
12	1	0	-0.615992	2.058933	1.196039
13	1	0	0.996526	2.057396	2.031571
14	8	0	-0.283967	-1.828490	-0.672800
15	6	0	-1.579605	-2.144568	-0.086668
16	1	0	-1.431983	-2.612549	0.893572
17	1	0	-2.085855	-2.860185	-0.742146
18	1	0	0.184705	-0.199243	-0.459186
19	6	0	-2.353456	-0.858733	0.045879
20	6	0	-2.587746	-0.292808	1.306745
21	6	0	-2.811467	-0.190320	-1.099979
22	6	0	-3.275190	0.918675	1.422022

23	1	0	-2.255753	-0.812576	2.202249
24	6	0	-3.485712	1.024949	-0.986162
25	1	0	-2.644816	-0.626797	-2.081025
26	6	0	-3.719941	1.580287	0.274742
27	1	0	-3.477786	1.334229	2.404609
28	1	0	-3.839137	1.532196	-1.878051
29	1	0	-4.260562	2.517487	0.362850
30	6	0	3.417872	-2.543565	-0.229809
31	1	0	3.510159	-3.568750	-0.588620
32	1	0	4.292202	-1.993146	-0.587855
33	1	0	3.446887	-2.559410	0.863802
34	1	0	0.858371	-2.614297	0.868464
35	6	0	0.731692	-4.056425	-0.737877
36	1	0	-0.195673	-4.515399	-0.387151
37	1	0	0.735212	-4.083194	-1.831681
38	1	0	1.554008	-4.670940	-0.364674

Conformer (67g)

Sum of electronic and thermal Free Energies = –1185.485567 Hartrees

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.606414	-1.897221	-0.768419
2	6	0	2.606877	-1.159443	0.159349
3	1	0	3.624769	-1.347696	-0.202414
4	6	0	2.436502	0.328607	0.189449
5	1	0	3.277854	0.972756	0.456770
6	7	0	1.309402	0.911318	-0.029328
7	16	0	1.142710	2.733033	-0.093198
8	8	0	2.438760	3.203271	0.365923
9	8	0	0.610759	2.978189	-1.419794
10	6	0	-0.127269	2.968367	1.151110
11	1	0	-0.342855	4.040003	1.152792
12	1	0	-1.013205	2.403243	0.854209
13	1	0	0.263242	2.654095	2.119385
14	8	0	0.307528	-1.410278	-0.385398
15	6	0	-0.868870	-2.126482	-0.846030
16	1	0	-0.840519	-3.142460	-0.435606
17	1	0	-0.857623	-2.187004	-1.939424
18	1	0	0.518340	0.271099	-0.290627
19	6	0	-2.062987	-1.354954	-0.354538
20	6	0	-2.723405	-1.726666	0.822025
21	6	0	-2.486986	-0.210355	-1.046533
22	6	0	-3.793697	-0.969436	1.300430
23	1	0	-2.406245	-2.615960	1.360188
24	6	0	-3.551586	0.552726	-0.564488
25	1	0	-1.998802	0.071040	-1.977131
26	6	0	-4.205705	0.172372	0.610879
27	1	0	-4.308458	-1.273376	2.206400
28	1	0	-3.886431	1.425303	-1.117202
29	1	0	-5.044056	0.755842	0.978609
30	6	0	2.528740	-1.649222	1.634718
31	1	0	2.824714	-2.700435	1.666949
32	1	0	3.203428	-1.092486	2.290613
33	1	0	1.506922	-1.556455	2.007821
34	6	0	1.905358	-1.692653	-2.253944

35	1	0	1.853744	-0.637472	-2.540791
36	1	0	2.906064	-2.065419	-2.492047
37	1	0	1.199556	-2.246390	-2.876949
38	1	0	1.667954	-2.967646	-0.527795

Conformer (66h)

Sum of electronic and thermal Free Energies = –1185.485234 Hartrees

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	1.903821	-3.541364	-0.573576
2	1	0	1.769962	-3.931263	0.438238
3	1	0	2.926256	-3.753139	-0.901458
4	1	0	1.231078	-4.084227	-1.241524
5	6	0	1.622927	-2.043351	-0.632392
6	1	0	1.644332	-1.716833	-1.684914
7	6	0	2.668542	-1.200562	0.144154
8	1	0	3.642719	-1.338599	-0.340696
9	6	0	2.387221	0.270042	0.106361
10	1	0	3.202027	0.992665	0.195426
11	7	0	1.195127	0.746501	0.017078
12	16	0	0.875078	2.541122	-0.171611
13	8	0	2.176796	3.136882	0.078886
14	8	0	0.172020	2.631823	-1.437255
15	6	0	-0.250445	2.803069	1.198659
16	1	0	-0.515568	3.862951	1.161520
17	1	0	-1.135536	2.183538	1.039185
18	1	0	0.265589	2.570382	2.130576
19	8	0	0.340777	-1.694675	-0.075823
20	6	0	-0.834982	-2.183332	-0.783534
21	1	0	-0.997238	-3.232534	-0.519850
22	1	0	-0.654302	-2.114671	-1.864029
23	1	0	0.434565	0.025927	-0.067608
24	6	0	-1.993713	-1.318792	-0.366442
25	6	0	-2.783014	-1.667206	0.736687
26	6	0	-2.253712	-0.117218	-1.042948
27	6	0	-3.815141	-0.829288	1.159410
28	1	0	-2.592788	-2.599565	1.261303
29	6	0	-3.284293	0.724645	-0.618045
30	1	0	-1.668308	0.151943	-1.919374
31	6	0	-4.064816	0.368428	0.485296
32	1	0	-4.428633	-1.113459	2.008491
33	1	0	-3.492649	1.640338	-1.163034
34	1	0	-4.876474	1.013466	0.807335
35	6	0	2.823933	-1.590033	1.643084
36	1	0	3.240744	-2.596113	1.711048
37	1	0	3.508344	-0.915411	2.164944
38	1	0	1.854044	-1.571313	2.143906

Conformer (67h)

Sum of electronic and thermal Free Energies = –1185.484067 Hartrees

Center Number	Atomic Number	Atomic Type	Coordinates (Angstroms) X	Y	Z
1	6	0	-0.731122	3.138963	1.381392
2	1	0	-1.252918	2.334277	1.909757
3	1	0	-1.338421	4.045160	1.445627
4	1	0	0.202135	3.339240	1.912561
5	6	0	-0.445357	2.767655	-0.074385
6	1	0	0.024611	3.620668	-0.582250
7	6	0	-1.712671	2.402744	-0.896215
8	1	0	-1.372423	2.256600	-1.937655
9	6	0	-2.299933	1.062168	-0.569810
10	1	0	-3.355568	0.867416	-0.778319
11	7	0	-1.619116	0.073316	-0.104087
12	16	0	-2.339279	-1.615878	0.000287
13	8	0	-3.736531	-1.395729	-0.333451
14	8	0	-1.429599	-2.424755	-0.785527
15	6	0	-2.133736	-1.944172	1.751481
16	1	0	-2.509693	-2.958990	1.905733
17	1	0	-1.071023	-1.895568	1.993532
18	1	0	-2.726290	-1.226057	2.318845
19	8	0	0.424519	1.629001	-0.175486
20	6	0	1.847960	1.864784	0.011177
21	1	0	2.014674	2.362430	0.972413
22	1	0	2.184377	2.532415	-0.791595
23	1	0	-0.595215	0.251691	0.032029
24	6	0	2.549000	0.536928	-0.034517
25	6	0	2.920679	-0.110326	1.150938
26	6	0	2.808522	-0.083617	-1.264364
27	6	0	3.546623	-1.356743	1.108769
28	1	0	2.737436	0.371339	2.108501
29	6	0	3.429553	-1.330693	-1.307338
30	1	0	2.532875	0.416552	-2.189182
31	6	0	3.799276	-1.968085	-0.120422
32	1	0	3.845752	-1.844232	2.031476
33	1	0	3.634082	-1.800892	-2.263957
34	1	0	4.292145	-2.934634	-0.154925
35	6	0	-2.795031	3.497235	-0.901545
36	1	0	-2.355733	4.450966	-1.202958
37	1	0	-3.587875	3.258123	-1.615319
38	1	0	-3.248829	3.629185	0.083521

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