New Pd and Cu-Based Catalysts for Carbon-Heteroatom Bond Formation

By

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B.Sc. Biochemistry
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Submitted to the Department of Chemistry in Partial Fulfillment of the Requirement for the Degree of

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at the
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New Pd and Cu-Based Catalysts for Carbon-Heteroatom Bond Formation

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ABSTRACT

The research presented in this dissertation is aimed at the development of novel methodologies for carbon-heteroatom cross-coupling reactions catalyzed by late-transition metals. Both palladium and copper are central to the field of transition metal-catalysis and are integral to the catalyst systems developed as part of our continual advancement in cross-coupling reactions. The first part of this thesis focuses on the use of palladium catalysts to form carbon-sulfur bonds directed towards aryl sulfonamide synthesis. The second part of the thesis describes the recent development in the copper(I) hydride mediated formation of carbon-nitrogen bonds via hydroamination of olefins.

Part I.
Chapter 1. Palladium-Catalyzed Chlorosulfonylation of Arylboronic Acids

Using a biaryl phosphine ligand platform, the first palladium-catalyzed cross-coupling reaction of phenyl chlorosulfate with arylboronic acids was achieved. In this context, the arylsulfonyl chloride products serve as useful precursors to a variety of sulfonyl functional groups, such as aryl sulfonylamides, aryl sulfoxides, and arenesulfonyl esters. In particular, this method allows for the preparation of a number of arylsulfonyl chlorides that are not accessible via electrophilic aromatic substitution pathways and under mild reaction conditions. Additionally, this methodology points to an unprecedented selectivity for the phenylchlorosulfate electrophiles used in the cross-coupling reactions.

Part II.
Chapter 2. Enantio- and Regioselective Copper-Catalyzed Hydroamination of Styrenes and the Extension of the Methodology towards Anti-Markovnikov Hydroamination of Terminal Aliphatic Alkenes

The development of a copper-mediated strategy towards the hydroamination of styrene derivatives is reported. In this system, the reaction proceeds regioselectively and enantioselectively to generate α-branched amines. The system can transform a wide variety of substituted styrenes, including trans-, cis-, and β-disubstituted styrenes. In addition, our
extension to copper-catalyzed hydroamination reactions of unactivated aliphatic olefins is reported. Using terminal aliphatic alkenes, the copper-catalyzed hydroamination reactions proceed with anti-Markovnikov regioselectivity. Preliminary results point to the application of this methodology towards β-chiral amine synthesis via the hydroamination of 1,1-disubstituted alkenes.

Chapter 3. α-Aminosilane Synthesis via Copper-Catalyzed Hydroamination of Vinylsilanes

The copper-catalyzed hydroamination of vinylsilanes is described. This regioselective reaction generates α-chiral aminosilanes in high yields and enantioselectivities. The method is compatible with differentially substituted vinylsilanes and allows access to many valuable chiral organosilicon compounds.

Chapter 4. Synthesis of γ-Chiral Amines via Copper-Catalyzed Hydroamination of 3,3-Disubstituted Allylic Alcohols and 3,3-Disubstituted Allylic Benzoates

An investigation into the copper-catalyzed hydroamination of allylic alcohols and allylic benzoates is reported. The reaction proceeds via a β-alkoxy elimination, setting a stereogenic center at the 3-postion to generate γ-chiral amine products. The reaction is more efficient using allylic benzoates. This method is completely regioselective and is applicable to aliphatic allylic benzoates as well as aromatic allylic benzoates. Additionally, we demonstrated that this strategy is applicable towards an allylic epoxide substrate to generate δ-chiral amine.

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ACKNOWLEDGEMENT

Graduate school is the part of my life that allows me to grow not just professionally but personally. Coming into graduate school, I was excited to learn new chemistries and expose myself to areas of research I knew nothing about. My advisor, Prof. Stephen L. Buchwald, had provided me with such an opportunity, and had convinced me to go for something that is far outside my comfort zone, in order for me to have acquired the most from the graduate experience. With that I will forever be grateful to him for continuously believing in my ability, and for constantly pushing me to work as hard and to learn as much. I also would like to thank my thesis committee members, Prof. Tim Jamison and Prof. Tim Swager, for the extra guidance and support, and for helping me throughout my oral exam to my thesis defense.

Being is Steve’s lab has many advantages, which contribute to the speed of doing research. This includes not only the available resources in terms equipment we have access to, but also the human resources. I have been very fortunate in being trained by, working with, and alongside extremely talented graduate students and post-docs. I would like to first acknowledge Dr. Robb DeBergh and Dr. Shaolin Zhu, who I have had the opportunity to work with on the same projects, and whom I consider to be great mentors. They both are incredible chemists, and I am very proud to have been a part of their teams in contributing to the development of groundbreaking research.

To go back to the beginning, I have to thank Brett Fors for training me on all the basic skills needed to be an accomplished experimentalist. Brett Fors, Sophie Rousseaux, and Luca Salvi were the first people who welcomed me into the lab, and were always there whenever a first year like me needed guidance. They gave me the best introduction to graduate school and to the Buchwald lab anyone could have asked for, and I cherish the friendship that I have developed with them throughout the years.

I also had the opportunity to work alongside Nate Jui, Alex Spokoyny, Andrew DeAngelis, Andrew Parsons, Tom Maimone, Ye Zhu, Tim Noel, and Kashif Khan, all of whom are not just great friends, but amazing mentors. I feel very fortunate to have had the opportunity to learn from them. You all have taught me a great deal and also helped me to be as accomplished as I am in my graduate career. I am very thankful for your eagerness to help me develop professionally, and for your time in being great friends to me.
Apart from the incredible post-docs we have in the lab, I am very thankful for all the talented graduate students that I have worked alongside. Special thanks to Phill Milner, Mingjuan Su, Nathan Park, and Nick Bruno, who were always there for me for chemistry and non-chemistry related problems; Todd Senecal and Georgiy Teverovskiy for their eagerness to help younger graduate students; Yang Yang who I have learned a great deal from and really enjoyed talking chemistry with; and Spencer Shinabery, for all the time he sacrificed to make sure our lab is a very safe and organized working environment. Also special thank to Katrin Niederman, Katya Vinogradova, and Christine Nguyen for showing me that graduate school is not just about doing research, but also about creating balance. To Rong Zhu, Paula Ruiz-Castillo, James Colombe, Yuxuan Ye, and Pedro Arrechea, my graduate school experience would not have been complete without you guys.

I would also like to acknowledge the recent post-docs whom despite the short amount of time working together, have still taught me a great deal. Aaron Sather, Daniel Cohen, Yiming Wang, Dawen Nui, Mike Pirnot, Jeff Bandar, Sandra King, John Nguyen, Esben Olsen, Kurt Amburst and Shiliang Shi. I really enjoyed working with all of you, and am very thankful for the knowledge and wisdom that you have shared with me.

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PREFACE

Parts of this thesis have been adapted from the following published articles co-written by the author.


This thesis is the result of collaborative effort of the author and other colleagues at MIT. The specific contributions of the author are detailed below.

The work disclosed in Chapter 1 resulted from collaboration between Dr. J. Robb DeBergh and the author. Dr. DeBergh performed the initial experiments for this project. The author contributed in the areas of ligand design and synthesis, and reaction optimization. Dr. DeBergh and the author collaborated on the examination of the scope of chlorosulfonylation as well as the one-pot arylsulfonamide synthesis. The author conducted the application of the reaction towards arenesulfonate ester synthesis and diarylsulfone synthesis.

The work disclosed in Chapter 2 resulted from collaboration between Dr. Shaolin Zhu and the author. Dr. Zhu is credited with discovering the initial reaction and the optimization. Dr. Zhu and the author collaborated on the exploration of the scope of this method.

The work disclosed in Chapter 3 resulted from collaboration between Dr. Shaolin Zhu and the author. Dr. Zhu and the author collaborated on the investigation of the initial hydroamination conditions towards vinylsilanes. The author is responsible for all optimization and synthetic work presented in this chapter. Dr. Zhu assisted the author in the mechanistic studies as presented in Scheme 4.

The work disclosed in Chapter 4 was a collaborative effort between Dr. Shaolin Zhu and the author. Dr. Zhu discovered the initial reaction. Dr. Zhu and the author collaborated on reaction optimization (Table 1 and 2), as well as exploration of the substrate scope. The author carried out the experiments in Scheme 7. Dr. Zhu carried out the experiments in Schemes 9, 12, and 13. Both the author and Dr. Zhu collaborated on the experiments and the substrate synthesis for Schemes 3, 4, 8, and 10–11.
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INTRODUCTION

Transition metal-catalyzed transformations play a pivotal role in synthetic organic chemistry as chemists seek to improve the yield, selectivity, scalability, and safety of known reactions, as well as to develop fundamentally new chemical transformations. Recent advances in homogenous catalysis have positively impacted the fields of natural product synthesis, medicinal chemistry, and material science. Although many late-transition metal-catalyzed methodologies have been developed, there is still room for advancement of other desirable, efficient, and selective transformations. The design and implementation of new cross-coupling methodologies can provide alternate methods that overcome current limitations.

Over the past decades, much advancement has been made in the fields of palladium and copper catalysis. Both of these transition metals have been used in numerous carbon-carbon bond-forming reactions as well as more recently in carbon-heteroatom bond-forming reactions. Fundamental to the activities of these late transition metals are their distinct modes of catalysis. For generic palladium-catalyzed cross-coupling reactions, the catalytic cycle begins with a Pd(0) species, which then undergoes oxidative addition with an electrophile to afford a Pd(II) species, followed by transmetalation with a nucleophile, and reductive elimination to yield the cross-coupled product and regenerate the Pd(0) species (Scheme 1). The copper catalytic cycle begins with a Cu(I) species, which undergoes transmetalation with a nucleophile, followed by oxidative addition with an electrophile to a Cu(III) species, and reductive elimination to deliver the cross-coupled product and regenerate the Cu(I) species (Scheme 2).

\[ \text{Scheme 1. Fundamental steps of Pd(0)/Pd(II) catalytic cycle.} \]
Despite the apparent simplicity of their catalytic cycles, there are many elements that must align to overcome the formation of undesired byproducts and achieve successful bond formation. These issues are present at every step including the initial active catalyst generation. Often some palladium and copper precursors require a change in oxidation state; the palladium cycle may require the generation of active Pd(0) species from Pd(II) precursors and copper cycle may require the generation of active Cu(I) species from Cu(II) precursors. Additionally, these metals needed to bind to the right supporting ligands in order to enable catalysis of the desired transformations.

There have been many developments in active catalyst generations for palladium-catalyzed cross-coupling reactions. These range from the simple pre-stirring of a Pd(0) source with a phosphine ligand to the in situ reduction of Pd(II) to active L₁Pd(0) species using excess amounts of ligand or water activation. These methods have drawbacks in that the Pd(0) source often has ligands that can interfere with the reaction, such as in the case of Pd₂(dba)₃ to Pd(0). Additionally, reduction of Pd(II) is not always an efficient process and can consume precious ligand. Recently, our laboratory has developed Pd-precatalysts to overcome the problems associated with catalyst pre-activation (Figure 1). These Pd-precatalysts (categorized as 1st to 3rd generation precatalysts) are pre-monoligated Pd(II) species that are readily converted to L₁Pd(0) under ambient conditions with weak base.
As the experience of reagent’s reactivity and compatibility for cross-coupling reactions increase, understanding around these factors help us fine-tune these systems to limit the formation of by-products (e.g. from homocoupling and reduction) and improve the reaction efficiency (e.g. milder conditions and lower catalyst loadings). Although there are many factors which are key to the success of both palladium and copper catalyzed reactions, advances in transition metal-catalyzed cross-coupling reactions can be credited largely to the development of new supporting ligands. The supporting ligand can play a significant role on each step of the catalytic cycle in addition to contributing to the overall stability of the catalyst.

Phosphine ligands play a crucial role in the success of both Pd-catalyzed and Cu-catalyzed bond forming reactions. In this context, our laboratory has invested tremendous efforts to develop biaryl phosphine ligands that can be tailored to a variety of Pd-catalyzed cross-coupling reactions. These ligands play a significant role in catalyst activity as well as stability. First, the presence of the bottom aryl ring (Figure 2) provides a secondary interaction to Pd via the “ipso” interaction, which enables the formation of reactive monoligated L₁Pd(0) complexes, thereby promoting oxidative addition of electrophiles. Second, biaryl phosphine ligands can help facilitate transmetalation. Furthermore, the ability of the bottom aryl ring to provide a secondary interaction with Pd and the choice of the substituent on the phosphine can further assist reductive elimination. As will be demonstrated in the following chapters, the structure of supporting ligands is crucial to the success of transition metal-catalyzed transformations.
Figure 2. Structural Element of Biarylphosphine Ligands and Their Contribution to the Elementary Steps in the Catalytic Cycle

The amount of knowledge regarding palladium and copper catalytic cycles has enabled significant contributions to the applications of these catalysts. The results reported herein focus on the development of palladium and copper catalysts to carry out novel carbon-heteroatom bond-forming reactions through functionalization of arenes and alkenes. The body of work presented in this thesis will fall into two distinct parts. The first is the development of palladium-catalyzed cross-coupling reactions between arylchlorosulfate electrophiles with organometallic reagents to generate arylsulfonyl chlorides and the applications thereof. The second part details a copper-catalyzed formal hydroamination reaction which utilizes a copper(I) hydride species to effect C–N bond formation and the application of this methodology towards the synthesis of various classes of chiral amines.
References


Part I.

Chapter 1.
Palladium-Catalyzed Chlorosulfonylation of Arylboronic Acids

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Synthesis of Aryl Sulfonamides via Palladium-Catalyzed Chlorosulfonylation of Arylboronic Acids

J. Robb DeBergh, Nootaree Niljianskul, and Stephen L. Buchwald

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1.1 Introduction

Sulfonyl subunits (-SO₂-) are important due to their presence in many molecular building blocks and biologically active compounds. For instance, aryl sulfonamides are contained in several important pharmaceuticals currently on the market. Diaryl sulfone structural units can be found in biologically active molecules as well as polymer materials (Figure 1). Thus, a general method to install these sulfonyl groups would serve as a powerful tool to many industries.

Figure 1. Important Molecules Containing the Sulfonyl Subunit

Aryl sulfonamides in medicinal chemistry can be traced back to the 1930's, with the discovery and development of the first commercially available antibiotics, sulfanilamide (Figure 2). Today, the presence of sulfonamides in medicinal agents is widespread; close to ten percent of the top 100 pharmaceuticals prescribed in 2011 either bear a sulfonamide subunit or are co-administered with a sulfonamide-containing drug. In general, aryl sulfonamides can be prepared by the straightforward reaction of a sulfonyl chloride with an amine. However, the difficulties associated with sulfonamide synthesis stem not from the amination reaction, but from the preparation of sulfonyl chlorides.

Figure 2. Structure of Prontosil, the Prodrug to the First Sulfonamide Antibiotics
The following two processes represent the state of the art methods in arylsulfonyl chloride synthesis: (1) electrophilic aromatic substitution (EAS) with chlorosulfonic acid\textsuperscript{5} (Scheme 1, Eq. 1) and (2) oxidative chlorination of organosulfur compounds (Eq. 2).\textsuperscript{6-10} Both approaches suffer from significant limitations. In particular, the acidic conditions required for the EAS processes (and most oxidative chlorination methods) impose severe restrictions on substrate scope. Furthermore, desired substitution patterns may be inaccessible via EAS as the regioselectivity is dictated by the intrinsic properties of the parent arene. Traditionally, oxidative chlorination involves the use of hazardous reagents (e.g., aqueous chlorine)\textsuperscript{7} or strong chlorinating agents (e.g., SOCl\textsubscript{2} and SO\textsubscript{2}Cl\textsubscript{2}).\textsuperscript{8} Although milder conditions have been reported,\textsuperscript{10} oxidative chlorination of thiophenol derivatives ultimately require prior formation of a carbon–sulfur bond.

**Scheme 1. Preparation of Arylsulfonyl Chlorides**

1) *Electrophilic Aromatic Substitution:*

\[
\begin{align*}
&\text{Me} \quad \text{HOSO}_2\text{Cl} \\
&\quad \text{0-5 °C} \\
&\quad \text{Me}_6 \quad \text{Me}_6
\end{align*}
\]

(Eq. 1)

2) *Oxidative Chlorination:*

*[oxidant: Cl\textsubscript{2} / H\textsubscript{2}O, NaOCl / HCl, H\textsubscript{2}O\textsubscript{2} / SOCl\textsubscript{2}, NCS / HCl] (Eq. 2)*

\[R = \text{H, Ac, SR', etc.}\]

In principle, a transition metal catalyst could obviate the need for such reagents and permit the convergent synthesis of aryl sulfonamide analogs (as well as diaryl sulfones), allowing variation of both sulfonyl (–SO\textsubscript{2}–) substituents. Unfortunately, the success of Pd-catalyzed arylsulfonamide synthesis is limited to a single aminosulfonylation process, initially reported by Willis in 2010, to prepare *N*-amino-sulfonamides from aryl iodides and hydrazines (Scheme 2).\textsuperscript{11} While this example represents an important achievement in sulfonylation chemistry, amine nucleophiles remain incompatible with these types of couplings.\textsuperscript{11,12}

**Scheme 2. Synthesis of *N*-amino-sulfonamides via Pd-catalysis**

\[
\begin{align*}
&(\text{DABCO}) \cdot (\text{SO}_2)_2 \\
&\text{or} \quad \text{K}_2\text{S}_2\text{O}_5 \\
&\text{or} \quad \text{Pt}_8\text{u} \cdot \text{HBF}_4 (20-30 \text{ mol\%}) \\
&\quad \text{Ar–I} \\
&\quad \text{H}_2\text{N}–\text{N}–\text{R}' \quad \text{R}’ \quad \text{Ar}–\text{S}–\text{N}–\text{R}' \quad \text{R}’
\end{align*}
\]

Additive

1,4-dioxane

70-100 °C, 12-16 h
On the other hand, diaryl sulfones are traditionally synthesized by the oxidation of the corresponding sulfide or by the Friedel-Crafts reaction of arenes with arenesulfonyl halides. The sulfide precursors to sulfones are typically prepared via an Ullmann coupling of thiophenol derivatives with aryl halides. Current strategies to synthesize aryl sulfones through transition metal-catalysis are less common and often employ aryl sulfinate nucleophiles (Scheme 3). These methods are either limited by the availability of aromatic sulfinates and thio-arenes, or require multiple synthetic operations to access the desired sulfone.

**Scheme 3. Synthesis of Diarylsulfones via Pd-catalysis**

![Scheme 3](image)

To address these limitations in arylsulfonylamine and diarylsulfone synthesis, we devised an alternative strategy (Figure 3). This strategy involves oxidative addition of LPd(0) to an electrophile of the type X–SO₂–X' (A), where X and X' represent leaving groups of different reactivity, to generate an oxidative addition complex B. Subsequent coupling with an organometallic nucleophile would afford electrophilic species C, which in turn, would serve as useful precursors to a variety of sulfonyl functional groups, such as aryl sulfonamides (D), aryl sulfones (E), and arenesulfonate esters (F).

**Figure 3. Palladium-Catalyzed Sulfonylation of Activated Arenes**

![Figure 3](image)

We envisioned that when using a readily prepared aryl chlorosulfate (1) as our electrophile (Figure 4), Pd(0) would insert into the SO₂–Cl bond (pathway (i)), and the cross-coupling with a weak nucleophile such as an arylboronic acid would then generate the arenesulfonate ester (2). The resultant intermediate could subsequently react with a carbon- or heteroatom-based nucleophile to afford the desired sulfonyl products (D-F, see Figure 3). An
alternative pathway (ii) involving Pd(0) insertion into the SO₂–OAr bond of 1 to generate the arenesulfonyl chloride (3) after coupling with the boronic acid is also possible. The catalytic cycle corresponding to pathway (i) is illustrated in Figure 5.

**Figure 4. Palladium-Catalyzed Sulfonylation of Activated Arenes**

Other similar electrophiles, such as sulfonyl chlorides (RSO₂Cl, R = aryl, alkenyl, benzyl, 2-methallyl) have been employed as the electrophilic reagents in metal-catalyzed desulfitative cross-coupling reactions to construct carbon–carbon bonds.¹⁵ The insertion of Pd(0) into the S–Cl bond of arenesulfonyl chlorides is generally followed by the loss of SO₂ from the resulting Cl-Pd-SO₂R complexes to generate the Cl-Pd-R species (Scheme 4).¹⁶ However, this desulfonylation process can be suppressed by carrying out reactions at low temperatures (≤ 25 °C), as has been previously used to generate sulfones.¹⁷ In addition, electron-rich phosphine ligands have been shown to improve the stability of Cl-Pd-SO₂R complexes.¹⁸ Thus, we
expected to overcome the undesired pathway through ligand design and reaction optimization. Based on the known stability of phosphine-ligated Pd-SO₂ complexes, we hypothesized that electron-rich biarylphosphines would serve as ideal ligands to help stabilize Pd-SO₂ complexes.¹⁸

Scheme 4. Palladium-Catalyzed Desulfitative Cross-coupling
1.2 Results and Discussion

We began our study by examining the reaction of phenyl chlorosulfate (1a) and coupling partner arylboronic acid using Pd(OAc)$_2$ as the palladium source in conjunction with an electron-rich ligand and an inorganic base. We chose phenyl chlorosulfate (1a) because of its simplicity, ease of preparation, and it is an easy to handle liquid. We selected arylboronic acids as coupling partners because of their compatibility with other functional groups as well as ready availability and ease of handling.

**Table 1. Preliminary Investigation of Reaction Conditions$^a$**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Base</th>
<th>2a (%)$^b$</th>
<th>3a (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>t-BuBrettPhos</td>
<td>K$_3$PO$_4$</td>
<td>31</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>t-BuBrettPhos</td>
<td>K$_2$CO$_3$</td>
<td>15</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>t-BuBrettPhos</td>
<td>Na$_2$CO$_3$</td>
<td>4</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>t-BuBrettPhos</td>
<td>none</td>
<td>0</td>
<td>59</td>
</tr>
<tr>
<td>5</td>
<td>DavePhos</td>
<td>none</td>
<td>0</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>none$^c$</td>
<td>none</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$Performed on a 0.5 mmol scale with respect to 1a. $^b$GC yields. $^c$Performed without palladium catalyst for 24 h.
Results from a preliminary survey of bases are outlined in Table 1, utilizing 4-methoxyphenylboronic acid in combination with a catalyst derived from Pd(OAc)$_2$ and tert-ButylBrettPhos or DavePhos. Unexpectedly, we observed mixtures of 2a and the corresponding sulfonyl chloride (3a) when excess base was used (Table 1, entries 1–3). However, we discovered that 3a could be formed exclusively in the absence of base (entries 4 and 5). Without the use of base, we proposed that we could inhibit the hydrolysis of our electrophiles. Further, control experiments showed that neither product is formed in the absence of palladium or phosphine ligand (entry 6). 20

In light of these results, we tested the system on other arylboronic acids, with the attempt to generate arylsulfonyl chlorides. However, these newly identified conditions proved ineffective for ortho-substituted arylboronic acids. For example, subjecting 2-methoxyphenylboronic acid to these conditions resulted in near complete recovery of phenyl chlorosulfate (1a) (Scheme 5). Additionally, upon the examination of the $^{31}$P NMR signals at the end of the reaction, we observed multiple peaks, which corresponded to oxidized phosphine. This leads us to speculate that the ligand may be oxidized under the reaction conditions with the phenylchlorosulfate electrophile acting as a strong oxidizing reagent.

Scheme 5. Reactions with Ortho-Substituted Arylboronic Acids

We proposed that we could minimize the oxidation of the ligand by employing a preligated Pd complex. Additionally, we hypothesized that phosphine ligand with more electron-deficient substituents at the phosphine would be slower to oxidize. To this end we investigated the pre-ligated Pd complexes in conjunction with 2-methoxyphenylboronic.

Figure 6 shows the ligands examined when pre-ligated palladium complexes were used. The use of palladacyclic precatalysts (P1–P7) allowed for these experiments to be conducted at lower temperatures presumably due to the milder conditions needed for the generation of LPd(0) complex. In this case, a catalytic amount of base (5 mol% Na$_2$CO$_3$) was needed for precatalyst activation. Solvent investigations showed the reaction to be optimal using anhydrous acetone.
As shown in the coupling of 1a with 2-methoxyphenylboronic acid (Figure 6), precatalysts based on diphenyl- (L3 and L5) and di-tert-butylbiaryl phosphine ligands (L2 and L7) proved to be the most effective. In particular, the PhCPhos precatalyst (P5) afforded 3b in the highest yield (82%), albeit with only a slight improvement over that derived from tert-BuDavePhos, L2 (80%). 26 In contrast, the use of XPhos (L6), 27 previously reported to be an excellent ligand for Suzuki–Miyaura reactions, provided little product.

**Figure 6. Ligand Effects**
We verified that aryl sulfonate esters (2) are not converted to the corresponding sulfonyl chlorides (3) under the reaction conditions (Scheme 6). However, we noted that the ester 2a is generated when crude reaction mixtures of 3a were treated with excess K$_3$PO$_4$ or K$_2$CO$_3$ (following complete consumption of 1a in the absence of base, Scheme 7). This supports that the arylsulfonyl chloride is the cross-coupling product.

**Scheme 6. Control Experiment: To confirm that sulfonate esters are not converted to sulfonyl chlorides**

\[
\begin{align*}
\text{PhO} & \quad \text{SO}_2\text{Cl} & \quad \text{PhO} & \quad \text{Cl} \\
1a & \quad (1.0 \text{ equiv}) & \quad (1.0 \text{ equiv}) & \quad (1.5 \text{ equiv})
\end{align*}
\]

Acetone (0.5 M) 50 °C, 12 h

\[
\begin{align*}
\text{Me} & \quad \text{Ph} & \quad \text{Me} & \quad \text{Me} \\
(1.0 \text{ equiv}) & \quad (1.0 \text{ equiv}) & \quad (1.5 \text{ equiv})
\end{align*}
\]

P$_5$ (2 mol%) Na$_2$CO$_3$ (5 mol%)

90% yield

100% recovered

(Eq. 1)

**Scheme 7. Control Experiment: To confirm that Sulfonate Esters are generated in situ from Sulfonyl Chlorides**

\[
\begin{align*}
\text{PhO} & \quad \text{SO}_2\text{Cl} & \quad \text{PhO} & \quad \text{Cl} \\
1a & \quad (1.0 \text{ equiv}) & \quad (1.5 \text{ equiv})
\end{align*}
\]

Acetone (0.5 M) rt, 2h

K$_3$PO$_4$ or K$_2$CO$_3$ (3 equiv)

50 °C, 12 h

\[
\begin{align*}
\text{Me} & \quad \text{Ph} & \quad \text{Me} & \quad \text{Me} \\
(1.0 \text{ equiv}) & \quad (1.0 \text{ equiv}) & \quad (1.5 \text{ equiv})
\end{align*}
\]

P$_5$ (2 mol%) Na$_2$CO$_3$ (5 mol%)

85% yield

The above results suggested a catalytic cycle in which Pd(0) inserted into the SO$_2$–OPh bond of phenyl chlorosulfate (1a, Figure 7). The phenoxy substituent of the resulting Pd-sulfinate complex (6) would be expected to facilitate transmetalation without the aid of a base; subsequent reductive elimination from intermediate 8 would yield sulfonyl chloride 3 and regenerate the active Pd(0) catalyst. Base likely promotes the generation of phenoxide, which in turn would react with the sulfonyl chloride to provide sulfonate ester 2. To the best of our knowledge, such a reactivity pattern with a Pd(0)/Pd(II) system has never been reported.
However, Buncel and co-workers have previously observed the displacement of aryloxide from aryl chlorosulfate derivatives (1) in the context of direct nucleophilic additions (Scheme 8). They rationalized the preferred displacement as attributed by relief in the internal steric strain, and that the partial rupture of the S–O bond in the bipyramidal transition state is accompanied by a gain in vibrational and rotational degrees of freedom which combined to yield a more positive change in the transition state entropy. This precedent demonstrates the lability of the SO$_2$–OPh bond, as we have observed for the transfer of –SO$_2$Cl in the analogous Pd-catalyzed process.

**Scheme 8. S–O Bond Scission for Reaction with Piperidine**

Regarding the oxidative addition step, we surmised that the sp$^3$ oxygen atom of 1a might direct the insertion of Pd(0) into the proximal PhO–SO$_2$ bond. However, results from a competition experiment between 1b and the bulkier 1c (Scheme 9, Eq. 1) revealed that 1c is slightly more reactive than 1b (ratio of recovered 1b/1c = 1.7:1). Moreover, this trend in reactivity is not specific to Pd-catalysis. For example, reacting a 1:1 mixture of 1b and 1c with piperidine (Scheme 9, Eq. 2) resulted in a comparable ratio of recovered 1b/1c (1.6:1) along...
with formation of the sulfamoyl chloride (9) derived from piperidine. This is consistent with Buncel’s rationale in which elongation of the S–O bond relieves considerable strain in the bipyramidal transition state, which according to the authors, such relieve of strain would not accompany partial rupture of the S–Cl bond. In this regard, increasing the size of the aryloxy substituent of 2 may intensify this stereoelectronic effect and further weakens the S–O bond.

Scheme 9. Competition Experiment of Aryl Chlorosulfate Electrophiles

\[
\begin{array}{c}
\text{OSO}_2\text{Cl} \\
\text{Me} \\
\text{(1.0 equiv)} \\
\text{38% conv.}
\end{array}
\quad
\begin{array}{c}
\text{OSO}_2\text{Cl} \\
\text{Pr} \\
\text{(1.0 equiv)} \\
\text{60% conv.}
\end{array}
\quad
\begin{array}{c}
\text{4-MeOPh-B(OH)_2} \\
\text{(1.0 equiv)} \\
P5 (2 mol%) \\
\text{Na}_2\text{CO}_3 (5 mol%) \\
\text{Acetone-}D_6 (0.5 M) \\
\text{40 °C, 8 h}
\end{array}
\quad
\begin{array}{c}
\text{OSO}_2\text{Cl} \\
\text{Pr} \\
\text{(1.0 equiv)} \\
\text{87%}
\end{array}
\quad
\begin{array}{c}
\text{OH} \\
\text{R}^1 \\
\text{R}^2 \\
\text{(Eq. 1)}
\end{array}
\quad
\begin{array}{c}
\text{Me Acetone-}D_6 (0.5 M) \\
\text{1b 1c} \\
\text{40 °C, 8 h} \\
\text{3a} \\
\text{R}^1 = \text{Me, } R^2 = \text{H; 36%} \\
\text{R}^1 = \text{H, } R^2 = \text{Pr; 61%}
\end{array}

\begin{array}{c}
\text{OSO}_2\text{Cl} \\
\text{Pr} \\
\text{(1.0 equiv)} \\
\text{22% conv.}
\end{array}
\quad
\begin{array}{c}
\text{OSO}_2\text{Cl} \\
\text{Pr} \\
\text{(1.0 equiv)} \\
\text{51% conv.}
\end{array}
\quad
\begin{array}{c}
piperidine \\
\text{(1.0 equiv)} \\
\text{CD}_2\text{Cl}_2 \\
\text{-78 °C, 18 h}
\end{array}
\quad
\begin{array}{c}
\text{N} \\
\text{Cl} \\
\text{9; 62%}
\end{array}
\quad
\begin{array}{c}
\text{NH} + \text{HX} \\
\text{(Eq. 2)}
\end{array}
\quad
\begin{array}{c}
\text{~37%}
\end{array}

We note that while others have demonstrated that arylsulfonyl chlorides are efficient cross-coupling partners for various Pd-catalyzed processes, these intermediates are essentially unreactive under our mild chlorosulfonylation conditions. For instance, palladium typically catalyzes the desulfonylation of arylsulfonyl chlorides; and these substrates (3) are often used as aryl halide equivalents for carbon–carbon bond-forming processes. In contrast, we found that using our palladium precatalyst in conjunction with biarylbiphenyl CPhos ligand, the other undesired pathways were suppressed, allowing us to obtain the arylsulfonyl chloride products.

With the improved protocol, utilizing 2 mol % P5 and 5 mol % of Na$_2$CO$_3$ in acetone, we next prepared a number of arylsulfonyl chlorides (Scheme 12). In general, electron-rich, electron-neutral, and electron-deficient arylboronic acid reagents were all compatible substrates. Couplings with electron-rich substrates can be conducted at 50 °C, while reactions with electron-deficient substrates are typically slower and require higher temperatures. The cross-
coupling reaction is tolerant of iodo-, bromo-, and chloro-substituted phenylboronic acids as well as those bearing ester and acetyl groups (Table 2). Furthermore, substitution patterns that cannot be accessed by an EAS processes can now be achieved (3h–3j). We noted that while most of the sulfonyl chlorides are stable to chromatography, electron-deficient compounds, such as 3h and 3j, were found to decompose to varying degrees upon attempted purification, resulting in lower isolated yields in these cases.\textsuperscript{30}

\textbf{Table 2. Palladium-Catalyzed Chlorosulfonylation of Arylboronic Acids}\textsuperscript{a}

\textbf{Table 2. Palladium-Catalyzed Chlorosulfonylation of Arylboronic Acids}\textsuperscript{a}

\begin{center}
\begin{tabular}{lcc}
 & 3c & 3d \\
Ar-B(OH)\textsubscript{2} (1.5 equiv) & F\textsubscript{3}CO & I \\
Temperature & 60 °C, 88% & 55 °C, 77% \\
& 60 °C, 71% & 55 °C, 83% \\

& 3g & 3h \\
Temperature & 50 °C, 75% & 70 °C, 54% \\

& 3i & 3j \\
Temperature & 55 °C, 80% & 60 °C, 69% \\

\end{tabular}
\end{center}

\textsuperscript{a}Yields represent isolated yields (average of two runs): 1a (1 mmol), ArB(OH)\textsubscript{2} (1.5 mmol), Na\textsubscript{2}CO\textsubscript{3} (5 mol %), P5 (2 mol %), degassed, anhydrous acetone (2 mL), 50-70 °C, 12 h.

To demonstrate the synthetic utility of this method we attempted to prepare a range of arenesulfonyl compounds by reacting the sulfonyl chloride intermediates with a variety of nucleophiles. Nitrogen-based nucleophiles were first examined in efforts to synthesize aryl sulfonamides in a one-pot process. We found that various sulfonamides can be generated in good yields from primary (4k–4o) and secondary amines (4a–4j) (Table 3). Even weakly nucleophilic aniline derivatives can be incorporated into the sulfonamide moiety with the use of pyridine to facilitate the amination step (4n, 4o). The chlorosulfonylation reaction also tolerates chlorosubstituted arylboronic acids (4j) as well as substrates containing TBS-ethers (4d), esters (4n), and acetyl functional groups (4e). Heteroaryl substrates, such as 3-thiophene (4m) and 2-
dibenzo[4,4]furan boronic acid were also suitable coupling partners (4m, 4k). Additionally, for electron-deficient sulfonyl chlorides such as 3h and 3j, instability to chromatography is obviated by this one-pot process.

Since diaryl sulfones are also important motifs useful in medicinal chemistry and material science, we next explored the applications of our Pd-catalyzed chlorosulfonylation product towards their syntheses. The organozinc reagents were tested as nucleophiles for the synthesis of sulfones. Our first attempt used the readily prepared benzo[b]thiophen-2-ylzinc chloride (10), which was added directly to the crude reaction mixture (Scheme 10). However, this one-pot...
protocol was unsuccessful as the major product of the reaction was the phenyl arenesulfonate ester 2b. It appears that the phenol generated from the initial oxidative insertion reacted with the arylzinc reagent to form phenoxide, which further reacted with the arylsulfonyl chloride to generate sulfonate ester 2b. We noted that using pure arenesulfonyl chlorides 3, the reaction with arylzinc chloride 10 proceeded cleanly to generate the corresponding sulfones (11, Scheme 11). Product 2b was not reactive towards substitution by organozinc, -magnesium, and -lithium reagents at ambient condition, however, it does react with phenyl lithium upon refluxing in toluene (Scheme 12).

**Scheme 10. Attempted One-Pot Synthesis of Unsymmetrical Diaryl Sulfones via Arylsulfonyl Chlorides**

**Scheme 11. Synthesis of Arylsulfones from Purified Arylsulfonyl Chlorides**

**Scheme 12. Reaction of Aryl Sulfonate Ester with Aryl Lithium Reagent**

As harsh conditions were required for conversion of phenyl arenesulfonate esters to diaryl sulfones, we felt that they were not optimal intermediates for this process. Thus, we sought to transform the arylsulfonyl chloride products into an arene sulfonate that would be more reactive and could be done in a one-pot sequence. By exploiting the higher acidity of the perfluorophenol when compared to the phenol, we proposed conversion of the arylsulfonyl chloride to its corresponding perfluorophenyl arenesulfonate. Indeed, treating the crude reaction mixture with perfluorophenol and diisopropylethylamine, we were able to generate the
corresponding perfluorophenyl arenesulfonate (6b, Scheme 13).

**Scheme 13. Synthesis of Arenesulfonate Esters from Sulfonyl Chlorides**

\[
\text{Precatalyst 1 (2 mol%), Na}_2\text{CO}_3 (5 mol%) \rightarrow \text{PhSO}_2\text{Cl} \rightarrow \text{PhSO}_2\text{Cl} \text{O} + \text{PhCl} \text{O}
\]

(a) Diisopropylethylamine (2 mmol, 2 equiv), 0 °C to rt, 2 h. (b) Pentafluorophenol (2 mmol, 2 equiv), diisopropylethylamine (1.5 mmol, 1.5 equiv), 0 °C to rt, 2 h. Isolated yields.

With the more electron-withdrawing perfluorophenyl ester (6b), nucleophilic substitution using phenyl lithium proceeded at room temperature to generate the diaryl sulfone (Scheme 14). Additionally, these perfluorophenyl arenesulfonates are desirable products themselves as they are significantly more stable than the corresponding chlorides.\(^{43}\) We have demonstrated the one-pot synthesis of a range of perfluorophenyl arenesulfonate derivatives (Table 4). In particular, we have synthesized analogues of arylsulfonyl chlorides that are unstable (6d), as well as other perfluoroarene sulfonates with an aryl halide moiety (6b, 6e).

**Scheme 14. Synthesis of Arylsulfone from Perfluorophenyl Arenesulfonate**
Table 4. One-pot Preparation of Perfluorophenyl Arenesulfonates via Arylsulfonyl Chlorides\textsuperscript{a}

<table>
<thead>
<tr>
<th>Step</th>
<th>Reaction</th>
<th>Conditions</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>( \text{PhSO}_2\text{Cl} ) + Ar-B(OH)(_2)</td>
<td>Pd(_{5}) (2 mol %), Na(_2)CO(_3) (5 mol %), Acetone (0.5 M), 50-70 °C, 12 h</td>
<td>Ar-SO(_2)Cl</td>
</tr>
<tr>
<td>3</td>
<td>Ar-SO(_2)Cl</td>
<td>Pentafluorophenol (2 equiv), DIPEA (1.5 equiv)</td>
<td>0 °C to rt, 2 h</td>
</tr>
<tr>
<td>6b</td>
<td>50 °C, 84%</td>
<td>6c</td>
<td>50 °C, 74%</td>
</tr>
<tr>
<td>6d</td>
<td>70 °C, 56%</td>
<td>6e</td>
<td>55 °C, 77%</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: Precatalyst 1 (2 mol %), 1a (1.0 mmol, 1.0 equiv), ArB(OH)\(_2\) (1.5 mmol, 1.5 equiv), Na\(_2\)CO\(_3\) (0.05 mmol), Acetone (2 mL); isolated yields.

1.3 Conclusions

In conclusion, the first Pd(0)/Pd(II)-catalyzed chlorosulfonylation reaction of arylboronic acids has been developed. We have demonstrated that phenyl chlorosulfate (1a) represents an excellent \([\text{SO}_2\text{Cl}]^+\) synthon in the context of Pd-catalyzed Suzuki-Miyaura cross-coupling. The chlorosulfonylation reaction exhibits considerable functional group tolerance and the transformation is inherently regioselective; the substitution patterns of many of the products shown (such as 3h–3j) cannot be accessed by EAS processes. Several additional features of this chemistry are also noteworthy. First, Pd(0) reacts with phenyl chlorosulfate (1a) in preference to aryl iodide groups bearing electron-withdrawing sulfonyl groups \textit{para} to the iodo-substituents (e.g. 3e and 4i). Second, while others have demonstrated that arylsulfonyl chlorides are efficient cross-coupling partners for various Pd-catalyzed processes\textsuperscript{33–35}, these intermediates are essentially unreactive under the chlorosulfonylation conditions. As such, this reaction represents a useful alternative to known methods of installing SO\(_2\)-Cl functional groups. Furthermore, the sulfonyl chlorides can be derivatized and isolated as the corresponding sulfonamides, sulfones, and sulfonate esters. Investigations aimed at broadening the scope of this transformation are currently in progress.
1.4 Experimental

I. General Information

*General Reagent Information*

Unless otherwise stated, all reactions were set-up on the bench top and carried out under an argon atmosphere. Anhydrous acetone was purchased from Acros Organics. All other solvents were purified and dried by passage through successive alumina and Q5 reactant-packed columns on a solvent purification system. Sulfuryl chloride, phenol, pyridine, and N,N-diisopropylethylamine were purchased from Aldrich Chemical Co. and used as received. Anhydrous Na$_2$CO$_3$ was received from VWR. The arylboronic acid substrates were purchased from Frontier Scientific, Combi-Blocks, and Aldrich and used as received without further purification. Ligand PhDavePhos (L3) was purchased from Strem, and tert-BuDavePhos (L2) was obtained from Aldrich. CPhos (L4) and precatalysts of P1, P2, P6, and P7 were synthesized according to literature procedures. Compounds were purified by flash chromatography using Silicycle SiliaFlashP60 (230-400 mesh) silica gel.

*General Analytical Information*

All compounds (starting materials and products) were characterized by $^1$H NMR, $^{13}$C NMR, $^{31}$P NMR (when applicable), $^{19}$F NMR (when applicable), IR spectroscopy, melting point (when applicable), and elemental analysis or mass spectrometry. The $^1$H, $^{13}$C, $^{31}$P, and $^{19}$F NMR spectra can be found in Section 1.6. $^1$H, $^{13}$C, $^{31}$P, and $^{19}$F NMR spectra were recorded on Varian 300 MHz, Varian 500 MHz or Bruker 400 MHz spectrometers. The spectra were calibrated according to residual solvent peaks (CDCl$_3$: 7.26 ppm for $^1$H NMR and 77.0 ppm for $^{13}$C NMR; CD$_2$Cl$_2$: 5.32 ppm for $^1$H NMR and 53.84 ppm for $^{13}$C NMR), an external reference (H$_3$PO$_4$: 0 ppm for $^{31}$P), or an internal reference (CF$_3$Ph: -63.7 ppm for $^{19}$F). The $^{13}$C, and $^{31}$P NMR spectra were obtained with $^1$H decoupling, and the $^{19}$F NMR spectra were obtained without $^1$H decoupling. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m= multiplet, br = broad, app = apparent. IR spectra were obtained on a Thermo Scientific iD5 ATR Nicolet iS5 FT-IR spectrometer. Elemental analyses were carried out by Atlantic Microlab, Inc., Norcross, GA. ESI-MS spectra were recorded on a Bruker Daltonics APEXIV 4.7 Tesla Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR-MS). Melting points (m.p.) were obtained on a Mel-Temp capillary
melting point apparatus. Gas chromatographic (GC) analyses were performed on an Agilent 7890A instrument (FID detector) using a J&W DB-1 column (10m, 0.1 mm I.D.). Reactions were monitored by GC and thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) or Fluka aluminum oxide/TLC-cards using UV light as a visualizing agent.
II. Experimental Procedures and Characterization Data

A) Synthesis of PhCPPhos (L5):

\[
\begin{align*}
\text{S1} & \quad \text{i. } n\text{-BuLi, THF, } -78 \, ^\circ\text{C} \\
\text{L5: PhCPPhos} & \quad \text{ii. } \text{Ph}_2\text{P-Cl, } -78 \, ^\circ\text{C to rt}
\end{align*}
\]

\textbf{2'-(Diphenylphosphino)-6-methoxy-N,N-dimethylbiphenyl-2-amine (L5):} The starting material, 2'-bromo-6-methoxy-N,N-dimethylbiphenyl-2-amine (S1), was synthesized according to a procedure reported by Han and Buchwald.\(^{38}\) An oven-dried 250 mL round-bottom flask, which was equipped with a magnetic stir bar and fitted with a Teflon septum, was charged with S1 (4.58 g, 14.35 mmol, 1.0 equiv). The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times). THF (58.0 mL) was added via syringe and the solution was cooled to -78 °C. n-Butyllithium (2.5 M solution in hexanes, 6.06 mL, 15.1 mmol, 1.05 equiv) was added dropwise via syringe over 15 min and the resulting mixture was stirred at -78 °C for 45 min. Chlorodicyclohexylphosphine (2.85 mL, 15.1 mmol, 1.05 equiv) was then added dropwise via syringe over 15 min. The reaction mixture was stirred at -78 °C for 2 h and then allowed to slowly warm to room temperature overnight (~12 h). The reaction was quenched by addition of methanol (~1.0 mL), filtered through a pad of SiO\(_2\) topped with a layer of Celite, and eluted with ethyl acetate (300 mL). The filtrate was concentrated \textit{in vacuo} to afford a yellow solid. Recrystallization from dichloromethane and methanol provided the title compound as a white solid (5.13 g, 84% yield); \textit{mp} = 134-136 °C.

\textbf{\textsuperscript{1}H NMR} (300 MHz, CDCl\(_3\)) \(\delta\) 7.56 – 7.38 (m, 3H), 7.35 (d, \(J = 8.1\) Hz, 1H), 7.32 – 7.21 (m, 11H), 6.88 (d, \(J = 8.0\) Hz, 2H), 2.22 (s, 12H). \textbf{\textsuperscript{13}C NMR} (75 MHz, CDCl\(_3\)) \(\delta\) 153.0, 145.8, 145.3, 140.3, 140.1, 136.5, 136.4, 136.3, 136.2, 133.1, 132.9, 132.4, 132.3, 129.9, 129.8, 128.9, 128.6, 127.9, 127.8, 127.4, 126.3, 113.3, 43.4 (Observed complexity due to C—P splitting). \textbf{\textsuperscript{31}P NMR} (121 MHz, CDCl\(_3\)) \(\delta\) -13.8. \textbf{IR} (neat, cm\(^{-1}\)): 2934, 2824, 2778, 1573, 1462, 1432, 1293, 1163, 1088, 1043, 1005, 935, 808, 768, 742, 694, 570. \textbf{Anal.} Calculated for C\(_{16}\)H\(_{15}\)BrN\(_2\): C, 79.22; H, 6.89. Found C, 79.34; H, 6.94.
B) Synthesis of Pd-Precatalysts P3–P5:

PhDavePhos (L3) Palladacyclic Precatalyst, P3: An oven-dried flask equipped with a magnetic stir bar was charged with µ-mesylate dimer S2 (370 mg, 0.5 mmol, 0.50 equiv) and PhDavePhos (389 mg, 1.0 mmol, 1.0 equiv). The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times), and anhydrous THF (4 mL) was then added via syringe. After the mixture was allowed to stir for 30 min at room temperature, the stir bar was removed and ~90% of solvent was removed under vacuum at room temperature. The residue was then triturated with pentane, and the resulting yellow crystals were isolated via filtration and further dried under vacuum. Precatalyst P3 was obtained as an inseparable mixture of two phosphorous-containing compounds (0.71g total, 94% yield).

\(^1\text{H NMR}\ (300 \text{ MHz}, \text{CD}_2\text{Cl}_2) \delta 8.00 (ddt, J = 11.7, 6.1, 1.7 \text{ Hz}, 2H), 7.86 – 7.49 (m, 4H), 7.50 – 6.76 (m, 18H), 6.63 (td, J = 7.4, 6.7, 1.3 \text{ Hz}, 1H), 6.18 – 5.93 (m, 1H), 3.49 (d, J = 11.1 \text{ Hz}, 1H), 3.07 (s, 1H), 2.57 (s, 6H), 2.39 (s, 3H). \(^{13}\text{C NMR}\ (75 \text{ MHz}, \text{CD}_2\text{Cl}_2) \delta 154.2, 148.3, 147.9, 147.6, 139.6, 137.5, 137.3, 137.3, 136.6, 136.5, 135.1, 134.9, 134.3, 133.4, 133.4, 133.1, 132.4, 132.2, 131.6, 130.9, 130.8, 130.6, 130.0, 129.9, 129.09, 128.4, 128.3, 128.1, 128.0, 127.9, 127.5, 127.3, 127.2, 126.4, 125.6, 121.3, 120.7, 117.3, 43.7, 39.5, 34.3. (Observed complexity due to C—P splitting). \(^{31}\text{P NMR}\ (121 \text{ MHz}, \text{CD}_2\text{Cl}_2) \delta 40.5, 35.5. \text{IR} \ (\text{neat, cm}^{-1}): 3050, 1575, 1493, 1434, 1421, 1191, 1157, 1096, 1035, 1020, 1001, 946, 737, 693, 616, 569, 557.
CPhos (L4) Palladacyclic Precatalyst, P4: An oven-dried flask equipped with a magnetic stir bar was charged with µ-mesylate dimer S2 (1.85 g, 5.0 mmol, 0.50 equiv) and CPhos (2.19 mg, 1.0 mmol, 1.0 equiv). The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times), and anhydrous THF (20 mL) was then added via syringe. After the mixture was allowed to stir for 2 h min at room temperature, the stir bar was removed from the vessel and the reaction mixture was transferred to a scintillation vial. The majority of solvent was removed under vacuum at room temperature until ~10% of the initial volume remained. The residue was then triturated with pentane. The resulting yellow solid was isolated via filtration and further dried under vacuum to afford 4.03 g of P4 (98% yield). This compound is light sensitive, and so it was stored in a scintillation vial wrapped with aluminum foil.

\(^1\)H NMR (300 MHz, CD$_2$Cl$_2$) δ 7.81 (t, J = 8.1 Hz, 1H), 7.67 (t, J = 7.7, 1H), 7.56 – 7.29 (m, 4H), 7.29 – 6.94 (m, 9H), 5.44 (d, J = 9.7 Hz, 1H), 2.78 – 2.58 (m, 1H), 2.57-2.19 (m, 2H), 2.51 (s, 6H), 2.39 (s, 3H), 2.30 (s, 6H), 2.10 – 1.59 (m, 6H), 1.58 – 1.16 (m, 9H), 1.07-0.79 (m, 4H), 0.45 – 0.11 (m, 1H). \(^{13}\)C NMR (126 MHz, CD$_2$Cl$_2$) δ 159.4, 154.9, 146.2, 146.1, 142.7, 140.4, 139.3, 137.4, 137.3, 135.0, 134.6, 134.2, 133.8, 132.1, 128.3, 127.7, 127.0, 126.9, 125.6, 120.9, 113.2, 113.0, 111.7, 68.1, 44.9, 43.8, 39.6, 37.38, 37.2, 37.0, 36.9, 31.1, 30.3, 30.2, 29.9, 29.6, 28.4, 27.6, 27.2, 26.3, 26.3, 26.0, 26.0 (Observed complexity due to C—P splitting). \(^{31}\)P NMR (121 MHz, CD$_2$Cl$_2$) δ 40.8. IR (neat, cm$^{-1}$): 2928, 2852, 1569, 1491, 1421, 1211, 1191, 1164, 1131, 1034, 1018, 1002, 780, 758, 737, 555.
**PhCPhos (L5) Palladacyclic Precatalyst, P5:** An oven-dried flask equipped with a magnetic stir bar was charged with µ-mesylate dimer S2 (591 mg, 0.80 mmol, 0.50 equiv) and PhCPhos (678 mg, 1.6 mmol, 1.0 equiv). The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times), and anhydrous THF (6.5 mL) was then added via syringe. After the mixture was allowed to stir for 1 h at room temperature, the stir bar was removed from the vessel and the reaction mixture was transferred to a scintillation vial. The majority of solvent was removed under vacuum at room temperature until ~10% of the initial volume remained. The residue was then triturated with pentane. The resulting yellow solid was isolated via filtration and further dried under vacuum to afford 1.27 g of P5 (quantitative yield).

**1H NMR** (300 MHz, CD2Cl2) δ 7.86 (t, J = 8.1 Hz, 1H), 7.65 – 7.48 (m, 4H), 7.47 – 7.03 (m, 16H), 7.00 (t, J = 7.3 Hz, 1H), 6.89 (dd, J = 8.1, 0.9 Hz, 1H), 6.67 (dddd, J = 8.0, 7.2, 1.7, 0.9 Hz, 1H), 6.37 (ddd, J = 7.6, 6.3, 1.1 Hz, 1H), 6.03 (dd, J = 10.7, 4.9 Hz, 1H), 2.73-2.61 (m, 1H), 2.69 (s, 6H), 2.31 (s, 3H), 1.88 (s, 6H). **13C NMR** (75 MHz, CD2Cl2) δ 156.9, 155.2, 146.0, 145.7, 145.1, 140.1, 138.8, 137.9, 137.8, 136.7, 136.0, 135.8, 135.2, 134.7, 134.3, 134.2, 134.0, 132.8, 132.4, 132.2, 131.5, 131.3, 130.2, 129.5, 128.9, 128.8, 128.7, 128.5, 128.4, 128.2, 128.1, 127.9, 127.6, 127.0, 126.7, 125.7, 121.2, 113.8, 113.2, 112.1, 44.7, 43.2, 39.5 (Observed complexity due to C—P splitting). **31P NMR** (121 MHz, CD2Cl2) δ 40.2. **IR** (neat, cm⁻¹): 3286, 2942, 1571, 1492, 1434, 1424, 1226, 1175, 1160, 1091, 1035, 1019, 1001, 793, 771, 748, 697, 614, 572.
C) Preparation of Aryl Chlorosulfates (1a–1c):

Representative Procedure:

Phenyl chlorosulfate (1a): An oven-dried 500 mL round-bottom flask equipped with a large stir bar was charged with phenol (9.5 g, 100 mmol, 1.0 equiv). The vessel was evacuated and backfilled with nitrogen (this process was repeated a total of 3 times). Anhydrous Et₂O (125 mL) and pyridine (8.09 mL, 100 mmol, 1.0 equiv) were then added via syringe and the solution was cooled to -78 °C. A separate oven-dried 200 mL round-bottom flask was evacuated and backfilled with nitrogen (this process was repeated a total of 3 times). Anhydrous Et₂O (125 mL) was added to the 200 mL flask via syringe, and the flask was placed in a separate dry ice/acetone bath and allowed to cool to -78 °C. Neat sulfuryl chloride (8.36 mL, 100 mmol, 1.0 equiv) was then added via syringe to the 200 mL flask at -78 °C (the addition of neat SO₂Cl₂ to anhydrous Et₂O is exothermic and will cause the Et₂O to evaporate if not performed at lower temperatures). The cooled solution of SO₂Cl₂ in Et₂O was transferred slowly (over 20 min) via canula to the vigorously stirred solution of phenol and pyridine at -78 °C. (Note: Stirring becomes difficult as the pyridinium salt is formed, and so periodic swirling of the reaction flask by hand may be required. We observed no problems with stirring when an IKA RCT Basic stir plate was used, however). After stirring for 2 h at -78 °C, no additional dry ice was added to the cooling bath and the reaction mixture was allowed to slowly warm to room temperature overnight. The crude reaction mixture was filtered through a pad of celite, and the reaction flask was washed with additional Et₂O (100-200 mL). The filtrate was then concentrated and the resulting residue was purified immediately via SiO₂ flash chromatography (0-3% EtOAc in hexanes) to afford 2a as a colorless oil (16.19 g, 84 % yield).

¹H NMR (400 MHz, CDCl₃) δ 7.53-7.37 (m, 5H). ¹³C NMR (100 MHz, CDCl₃) δ 150.0, 130.2, 128.8, 121.6. IR (neat, cm⁻¹): 1586, 1485, 1410, 1197, 1172, 1131, 1023, 913, 875, 774, 657, 685, 611, 584. EI-MS (m/z): 192 [M]+.
4-Methylphenyl chlorosulfate (1b): Following the representative procedure for the preparation of 2a, the title compound was prepared using p-cresol (5.34 g, 50 mmol, 1.0 equiv), pyridine (4.1 mL, 50 mmol, 1.0 equiv), and sulfuryl chloride (4.18 mL, 50 mmol, 1.0 equiv). The crude product was purified by flash column chromatography (0-1% EtOAc in hexanes) to afford 2b as a clear, colorless oil (9.5 g, 92% yield).

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.28 (s, 4H), 2.40 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 148.0, 139.0, 130.7, 121.4, 21.0. IR (neat, cm$^{-1}$): 1500, 1411, 1199, 1175, 1132, 1018, 880, 823, 802, 720, 692, 639, 591, 576. EI-MS (m/z): 206 [M]$^+$. 

2,6-Diisopropylphenyl chlorosulfate (1c): Following the representative procedure for the preparation of 2a, the title compound was prepared using 2,6-diisopropylphenol (9.55 mL, 50 mmol, 1.0 equiv), pyridine (4.1 mL, 50 mmol, 1.0 equiv), and sulfuryl chloride (4.18 mL, 50 mmol, 1.0 equiv). The crude product was purified by flash column chromatography (0-1% EtOAc in hexanes) to afford 2c as a clear, colorless oil (10.1 g, 73% yield).

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.33 (dd, $J$ = 8.2, 7.1 Hz, 1H), 7.24 (d, $J$ = 7.6 Hz, 2H), 3.43 (m, 2H), 1.27 (d, $J$ = 6.8 Hz, 12H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 147.0, 141.8, 128.9, 125.2, 27.76, 23.6. IR (neat, cm$^{-1}$): 1406, 1387, 1192, 1129, 1071, 1045, 889, 864, 799, 767, 744, 618, 571. EI-MS (m/z): 276 [M]$^+$. 

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D) Preparation of Arylsulfonyl Chlorides (3c–j)

Generation Procedure A:

An oven-dried test tube equipped with a magnetic stir bar was charged with P5 (0.02 mmol, 2 mol%), Na$_2$CO$_3$ (5.3 mg, 0.05 mmol, 5 mol%), and the aryloboronic acid (1.5 mmol, 1.5 equiv) and the tube was sealed with a Teflon screw-cap septum. The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times), and anhydrous acetone (2.0 mL) was then added via syringe. After the mixture was allowed to stir for ~3 min at room temperature, neat phenyl chlorosulfate (133 µL, 1.0 mmol, 1.0 equiv) was added. The vessel was then placed in a preheated oil bath and the reaction mixture was allowed to stir at the desired temperature for 12 h. After the reaction mixture was allowed to cool to room temperature, it was diluted with EtOAc and filtered through a pad of silica gel topped with a layer of celite, which was washed with additional EtOAc. The filtrate was concentrated and the resulting residue was purified by flash chromatography (using a Biotage Isolera Four system with a SNAP 25 g cartridge) to afford the desired sulfonyl chloride.

Naphthalene-1-sulfonyl chloride (3c): Following General Procedure A, the title compound was prepared using 1-naphthalenecarboxylic acid (258 mg, 1.5 mmol). The reaction was judged as complete by TLC and GC after 12 h at 60 °C. The crude product was purified by flash column chromatography (Biotage, 25g SNAP column, 0-5% EtOAc in hexanes) to afford 3c as a white solid (200 mg, 88% yield); mp = 60-62 °C (lit. 64-67 °C).

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.79 (d, J = 8.6 Hz, 1H), 8.37 (dd, J = 7.5, 1.3 Hz, 1H), 8.22 (d, J = 8.3 Hz, 1H), 8.01 (d, J = 8.3, 1H), 7.81 (ddd, J = 8.6, 6.9, 1.4 Hz, 1H), 7.70 (ddd, J = 8.1, 6.9, 1.2 Hz, 1H), 7.60 (dd, J = 7.9 Hz, J = 7.9 Hz, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 139.3, 137.0, 134.3, 129.4, 129.3, 129.2, 127.6, 127.2, 123.9, 123.8. IR (neat, cm$^{-1}$): 1592, 1504, 1365.
1346, 1169, 1136, 966, 830, 800, 760, 736, 673, 619, 572, 559. **HRMS-ESI (m/z) [M + NH₄]⁺** Calcd. for C₁₀H₇ClO₂S, 244.0194; found, 244.0196.

4-(Trifluoromethoxy)benzenesulfonyl chloride (3d): Following **General Procedure A**, the title compound was prepared using 4-trifluoromethoxyphenylboronic acid (309 mg, 1.5 mmol). The reaction was judged as complete by TLC and GC after 12 h at 60 °C. The crude product was purified by flash column chromatography (Biotage, 25g SNAP column, 0-3% EtOAc in hexanes) to afford 3d as a colorless oil (173 mg, 66% yield).

**¹H NMR (300 MHz, CDCl₃)** δ 8.18 - 8.05 (m, 2H), 7.44 (d, J = 7.8 Hz, 2H). **¹³C NMR (75 MHz, CDCl₃)** δ 154.1 (q, J = 1.9), 142.2, 129.7, 120.4 (q, J = 260.8), 121.3. **¹⁹F NMR (282 MHz, CDCl₃)** δ -57.8. **IR (neat, cm⁻¹):** 1589, 1493, 1381, 1254, 1207, 1156, 1082, 1015, 840, 808, 688, 667, 583, 559. **HRMS-ESI (m/z) [M + NH₄]⁺** Calcd. for C₁₂H₈ClF₃O₃S, 277.9860; found, 277.9868.

4-Iodobenzenesulfonyl chloride (3e): Following **General Procedure A**, the title compound was prepared using 4-iodophenylboronic acid (372 mg, 1.5 mmol). (Note: Stirring was difficult during the first 1-2 h of this reaction, and so an IKA RCT Basic stir plate was used to facilitate stirring). The reaction was judged as complete by TLC and GC after 12 h at 55 °C. The crude product was purified by flash column chromatography (Biotage, 25g SNAP column, 0-7% EtOAc in hexanes) to afford 3e as a white solid (183 mg, 64%); mp = 83-86 °C (lit. 39 80-82 °C).

**¹H NMR (300 MHz, CDCl₃)** δ 8.00 (d, J = 8.8 Hz, 2H), 7.74 (d, J = 8.8 Hz, 2H). **¹³C NMR (75 MHz, CDCl₃)** δ 144.0, 139.3, 128.3, 104.0. **IR (neat, cm⁻¹):** 1560, 1369, 1176, 1157, 1076, 1051, 1005, 834, 813, 729, 694, 581, 551. **HRMS-ESI (m/z) [M + NH₄]⁺** Calcd. for C₆H₄ClIO₂S, 319.9004; found, 319.9020.
4-Fluorobenzenesulfonyl chloride (3f): Following General Procedure A, the title compound was prepared using 4-fluorophenylboronic acid (210 mg, 1.5 mmol). The reaction was judged as complete by TLC and GC after 12 h at 70 °C. The crude product was purified by flash column chromatography (Biotage, 25g SNAP column, 0-4% EtOAc in hexanes) to afford 3f as a yellow solid (165 mg, 85% yield); mp = 33-36 °C (lit.29 29-31 °C; lit.30 34 °C).

\[ \text{1H NMR (300 MHz, CDCl}_3\text{) } \delta 8.13 - 8.02 \text{ (m, 2H), 7.38 - 7.21 \text{ (m, 2H). 13C NMR (75 MHz, CDCl}_3\text{) } \delta 166.6 \text{ (d, } J = 259.8 \text{ Hz), 140.5 \text{ (d, } J = 3.2 \text{ Hz), 130.4 \text{ (d, } J = 10.1 \text{ Hz), 117.4 \text{ (d, } J = 23.2 \text{ Hz). 19F NMR (282 MHz, CDCl}_3\text{) } \delta -99.6. IR (neat, cm}^{-1} \text{: 1587, 1491, 1409, 1377, 1294, 1242, 1178, 1156, 1081, 838, 816, 706, 658, 561. HRMS-ESI (m/z) [M + NH}_4^+ \text{] Calcd. for C}_6\text{H}_4\text{ClFO}_2\text{S, 211.9943; found, 211.9946.} \]

2-Methylbenzenesulfonyl chloride (3g): Following General Procedure A, the title compound was prepared using 2-methylphenylboronic acid (204 mg, 1.5 mmol). The reaction was judged as complete by TLC and GC after 12 h at 50 °C. The crude product was purified by flash column chromatography (Biotage, 25g SNAP column, chromatography (Biotage, 25g SNAP column, 0-6% EtOAc in hexanes) to afford 3g as a colorless oil (143 mg, 75% yield). Note: The chemical shifts in the \textsuperscript{1H NMR spectrum of 3g were consistent with those in the \textsuperscript{1H NMR spectrum of an authentic sample obtained from Sigma-Aldrich.}

\[ \text{1H NMR (300 MHz, CDCl}_3\text{) } \delta 8.07 \text{ (dd, } J = 8.4, 1.4 \text{ Hz, 1H), 7.76 - 7.52 \text{ (m, 1H), 7.48 - 7.31 \text{ (m, 2H), 2.79 \text{ (s, 3H). 13C NMR (75 MHz, CDCl}_3\text{) } \delta 143.2, 138.3, 135.5, 133.6, 129.0, 127.0, 20.5. IR (neat, cm}^{-1} \text{: 1471, 1365, 1280, 1173, 1131, 1057, 1036, 806, 757, 700, 686, 577, 558. HRMS-ESI (m/z) [M + NH}_4^+ \text{] Calcd. for C}_7\text{H}_7\text{ClO}_2\text{S, 208.0194; found, 208.0198.} \]

4-Trifluoromethylbenzenesulfonyl chloride (3h): Following General Procedure A, the title compound was prepared using 4-trifluorophenylboronic acid (285 mg, 1.5 mmol) and Na\textsubscript{2}CO\textsubscript{3} (10.6 mg, 0.1 mmol, 10 mol%). The reaction was judged as complete by TLC and
GC after 12 h at 70 °C. The crude product was purified by flash column chromatography (Biotage, 25 g SNAP column, 0-4% EtOAc in hexanes) to afford 4h as a off-white solid (131 mg, 54% yield); mp = 30-32 °C (lit.41 oil). Note: Compound 4h undergoes significant decomposition upon purification with SiO₂ gel. The chemical shifts in the ¹H NMR spectrum of 4h were consistent with those obtained from an authentic sample from Sigma-Aldrich.

¹H NMR (300 MHz, CDCl₃) δ 8.20 (d, J = 8.2 Hz, 2H), 7.92 (d, J = 8.3 Hz, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 147.1 (app d, J = 1.4 Hz), 136.7 (q, J = 33.6 Hz), 127.6, 127.0 (q, J = 3.7 Hz), 122.7 (q, J = 273.4 Hz). ¹⁹F NMR (282 MHz, CDCl₃) δ -63.5. IR (neat, cm⁻¹): 1407, 1382, 1319, 1174, 1135, 1109, 1061, 842, 711, 600, 578, 557. EI-MS (m/z) : 244 [M⁺].

2-Bromobenzenesulfonyl chloride (3i): Following General Procedure A, the title compound was prepared using 2-bromophenylboronic acid (301 mg, 1.5 mmol). The reaction was judged as complete by TLC and GC after 12 h at 55 °C. The crude product was purified by flash column chromatography (Biotage, 25 g SNAP column, 3-10% EtOAc in hexanes) to afford 3i as a yellow solid (202 mg, 79% yield); mp = 50-52 °C (lit.39 49-52 °C; lit.4² 45-48 °C).

¹H NMR (300 MHz, CDCl₃) δ 8.23 – 8.12 (m, 1H), 7.91 – 7.79 (m, 1H), 7.64 – 7.49 (m, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 143.2, 136.7, 136.2, 131.0, 128.3, 120.9. IR (neat, cm⁻¹): 1567, 1445, 1429, 1369, 1252, 1179, 1098, 1021, 759, 735, 694, 646, 573, 551. HRMS-ESI (m/z) [M + H⁺] Calcd. for C₆H₄BrClO₂S, 254.8877; found, 254.8890.

4-(Methoxycarbonyl)benzenesulfonyl chloride (3j): Following General Procedure A, the title compound was prepared using 4-methoxycarbonylphenylboronic acid (270 mg, 1.5 mmol). The reaction was judged as complete by TLC and GC after 12 h at 60 °C. The crude product was purified by flash column chromatography (Biotage, 25 g SNAP column, 2-7% EtOAc in hexanes) to afford 3j as a slightly pink solid (152 mg, 65% yield); mp = 73-76 °C.
\[ ^1H \text{NMR} \text{ (300 MHz, CDCl}_3 \text{)} \delta 8.28 (d, J = 8.9 \text{ Hz, 2H}), 8.12 (d, J = 8.9 \text{ Hz, 2H}), 3.99 (s, 3H). \]

\[ ^{13}C \text{NMR} \text{ (75 MHz, CDCl}_3 \text{)} \delta 165.1, 147.6, 136.3, 131.1, 127.3, 53.2. \text{ IR (neat, cm}^{-1}) : 1725, 1435, 1400, 1377, 1280, 1188, 1168, 1106, 1011, 966, 866, 832, 758, 733, 684, 582, 560. \]

\text{HRMS-ESI (m/z)} [M + \text{NH}_4]^+ \text{ Calcd. for } C_8H_7ClO_4S, 252.0092; \text{ found, 252.0101.}
E) Preparation of Aryl Sulfonamides (4a–4o)

\[
\begin{align*}
\text{PhSO}_2\text{Cl}_1 + \text{Ar-B(OH)}_2 \xrightarrow{\text{P5 (2 mol %)}} \left[ \begin{array}{c} \text{SO}_3 \text{Cl} \end{array} \right] \left[ \begin{array}{c} \text{Ar-N} \end{array} \right] \\
\text{Acetone (0.5 M), 50-70 °C, 12 h} \quad \rightarrow \quad \left[ \begin{array}{c} \text{RR'NH} \end{array} \right] \\
\end{align*}
\]

Generation Procedure B: Preparation of Sulfonamides Derived from Secondary Amines.

Following General Procedure A, a mixture of P5 (15.9 mg, 0.02 mmol, 2 mol%), Na₂CO₃ (5.3 mg, 0.05 mmol, 5 mol%), arylboronic acid (1.5 mmol, 1.5 equiv), and phenyl chlorosulfate (133 µL, 1.0 mmol, 1.0 equiv) in anhydrous acetone (2.0 mL) was stirred at the desired temperature for 12 h. After the reaction mixture was allowed to cool to room temperature, it was placed under a positive atmosphere of argon and anhydrous THF (1.0 mL) was added via syringe (additional THF was not added to reactions in which a commercially available 2.0 M solution of Me₂NH in THF was used). The reaction mixture was cooled to 0 °C and the desired secondary amine (2.2 mmol, 2.2 equiv) was then added to the vigorously stirred solution of crude sulfonyl chloride. After stirring for 5 min at 0 °C, the reaction vessel was removed from the ice bath, allowed to warm to room temperature, and stirred for 1.5 h. The reaction mixture was then diluted with EtOAc and filtered through a pad of silica gel topped with a layer of celite, which was washed with additional EtOAc. The filtrate was concentrated and the resulting residue was purified by flash chromatography (using a Biotage Isolera Four system with a SNAP 25 g cartridge) to afford the desired sulfonamide.

Generation Procedure C: Preparation of Sulfonamides Derived from Primary Amines.

Following General Procedure A, a mixture of P5 (15.9 mg, 0.02 mmol, 2 mol%), Na₂CO₃ (5.3 mg, 0.05 mmol, 5 mol%), arylboronic acid (1.5 mmol, 1.5 equiv), and phenyl chlorosulfate (133 µL, 1.0 mmol, 1.0 equiv) in anhydrous acetone (2.0 mL) was stirred at the desired temperature for 12 h. After the mixture was allowed to cool to room temperature, the reaction mixture was placed under a positive atmosphere of argon and anhydrous THF (1.0 mL) was added via syringe. The reaction was cooled to 0 °C and the desired primary amine (3.0 mmol, 3.0 equiv or 2.2 mmol, 2.0 equiv) was then added to the vigorously stirred solution of crude sulfonyl chloride. After stirring for 5 min at 0 °C, the reaction vessel was removed from the ice bath,
allowed to warm to room temperature, and stirred for 1.5 h at this temperature. The reaction mixture was then diluted with EtOAc and filtered through a pad of silica gel topped with a layer of celite, which was washed with additional EtOAc. The filtrate was concentrated and the resulting residue was purified by flash chromatography (using a Biotage Isolera Four system with a SNAP 25 g cartridge) to afford the desired sulfonamide.

**Generation Procedure D: Preparation of Sulfonamides Derived from Anilines.**

Following General Procedure A, a mixture of PS (15.9 mg, 0.02 mmol, 2 mol%), Na₂CO₃ (5.3 mg, 0.05 mmol, 5 mol%), arylboronic acid (1.5 mmol, 1.5 equiv), and phenyl chlorosulfate (133 µL, 1.0 mmol, 1.0 equiv) in anhydrous acetone (2.0 mL) was stirred at the desired temperature for 12 h. The reaction mixture was allowed to cool to room temperature, placed under a positive atmosphere of argon, and then cooled to 0 °C. The desired aniline (1.2 mmol, 1.2 equiv.) and pyridine (0.245 mL, 3.0 mmol, 3.0 equiv) were then added successively to the vigorously stirred solution of the crude sulfonyl chloride at 0 °C. After stirring for 30 min at 0 °C, the reaction vessel was removed from the ice bath, allowed to warm to room temperature, and stirred for 5 h at this temperature. The reaction mixture was then diluted with EtOAc and filtered through a pad of silica gel topped with a layer of celite, which was washed with additional EtOAc. The filtrate was concentrated and the resulting residue was purified by flash chromatography (using a Biotage Isolera Four system with a SNAP 25 g cartridge) to afford the desired sulfonamide.

![4-Methoxybenzenesulfonylmorpholide (4a):](image)

4-Methoxybenzenesulfonylmorpholide (4a): Following General Procedure B, the title compound was prepared using 4-methoxyphenylboronic acid (228 mg, 1.5 mmol) and PS. The chlorosulfonylation reaction reaction was carried out at 50 °C for 12 h. Morpholine (192 µL, 2.2 mmol) was used as the secondary amine to form the desired sulfonamide. The crude product was purified by flash column chromatography (Biotage, 25g SNAP column, 5-50% EtOAc in hexanes) to afford 4a as a white solid (246 mg, 96% yield); mp = 110-111 °C.

**¹H NMR (300 MHz, CDCl₃)** δ 7.72-7.61 (m, 2H), 7.04-6.99 (m, 2H), 3.88 (s, 3H), 3.76-3.72
(m, 4H), 2.99-2.96 (m, 4H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 163.0, 129.8, 126.3, 114.1, 65.8, 55.5, 45.8. IR (neat, cm\(^{-1}\)): 3103, 2928, 2847, 1598, 1578, 1499, 1439. Anal. Calcd. for C\(_{11}\)H\(_{15}\)NO\(_4\)S: C, 51.35; H, 5.88; N, 5.44. Found C, 51.38; H, 5.96.

**2-Methoxybenzenesulfonylmorpholide (4b):** Following General Procedure B, the title compound was prepared using 2-methoxyphenylboronic acid (228 mg, 1.5 mmol) and PS. The chlorosulfonylation reaction was carried out at 50 °C for 12 h. Morpholine (192 \(\mu\)L, 2.2 mmol) was used as the secondary amine to form the desired sulfonamide. The crude product was purified by flash column chromatography (Biotage, 25g SNAP column, 5-45% EtOAc in hexanes) to afford 4b as a white solid (216 mg, 84% yield); mp = 86.0-86.5 °C.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.83 (dd, \(J = 8.0, 1.8\) Hz, 1H), 7.49 (ddd, \(J = 8.3, 7.4, 1.8\) Hz, 1H), 7.07 - 6.88 (m, 2H), 3.88 (s, 3H), 3.74 - 3.56 (m, 4H), 3.22 - 3.08 (m, 4H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 157.0, 134.8, 131.8, 125.7, 120.4, 112.4, 66.7, 56.0, 46.0. IR (neat, cm\(^{-1}\)): 2968, 2921, 2863, 1592, 1579, 1480, 1465, 1447, 1433, 1342, 1331, 1325, 1279, 1262, 1155, 1141, 1114, 1078, 1062, 1044, 1016, 944, 924, 858, 768, 758, 735, 614, 588, 573, 567, 565. Anal. Calcd. for C\(_{11}\)H\(_{15}\)NO\(_4\)S: C, 51.35; H, 5.88; N, 5.44. Found C, 51.54; H, 5.80.

**3-Fluorobenzenesulfonylmorpholide (4c):** Following General Procedure B, the title compound was prepared using 3-fluorophenylboronic acid (210 mg, 1.5 mmol) and PS. The chlorosulfonylation reaction was carried out at 70 °C for 12 h. Morpholine (192 \(\mu\)L, 2.2 mmol) was used as the secondary amine to form the desired sulfonamide. The crude product was purified by flash column chromatography (Biotage, 25g SNAP column, 5-30% EtOAc in hexanes) to afford 4c as a white solid (161 mg, 66% yield); mp = 112.2-113.2 °C.

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.59-7.51 (m, 2H), 7.49-7.44 (m, 1H), 7.39-7.30 (m, 1H), 3.77-3.73 (m, 4H), 3.04-3.00 (m, 4H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 162.4 (d, \(J = 252.0\) Hz), 137.2
(d, J = 6.5 Hz), 130.9 (d, J = 7.8 Hz), 123.5 (d, J = 3.4 Hz), 120.2 (d, J = 21.2 Hz), 115.0 (d, J = 24.2 Hz), 65.9, 45.9. \(^1\)\(^9\)F NMR (376.5 MHz, CDCl\(_3\)) \(\delta\) -109.4 (s, 1F). \(\text{IR (neat, cm}^{-1}\)): 2917, 2863, 1589, 1475, 1392, 1346, 1329, 1294, 1272, 1261, 1220, 1155, 1112, 1088. \text{Anal. Calculated for C}_{10}H_{10}FNO_3S: C, 48.97; H, 4.93. Found C, 48.98; H, 4.82.

1-Methylpiperazine-4-(4-(\text{tert-butyldimethylsilyloxy})benzenesulfonamide (5d): Following a modification of \textit{General Procedure B}, the title compound was prepared using \text{4-(\text{tert-butyldimethylsilyloxy})phenyl boronic acid (378 mg, 1.5 mmol)} and \text{P5}. The cross-coupling reaction was carried out at 50 °C for 12 h. Following complete chlorosulfonylation, the reaction was cooled to 0 °C, and \text{DIPEA (0.348 mL, 2 mmol, 2.0 equiv)} and 1-Methylpiperazine (0.135 mL, 1.2 mmol, 1.0 equiv) were added successively. After 5 min, the reaction vessel was removed from the ice bath and stirred for 1.5 h at rt. The mixture was then diluted with \text{EtOAc} and filtered through a plug of SiO\(_2\), using 30% MeOH in EtOAc as the eluent. The product was purified by flash column chromatography (Biotage, 25g SNAP column, 50-100% EtOAc in hexanes, followed by 15% MeOH in EtOAc) to afford 4d as a yellow solid (296 mg, 80% yield); mp = 70-73 °C. \text{Note: Compound 4d was characterized immediately following purification because it undergoes rapid desilylation to form the corresponding free phenol.}

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.63 (d, J = 9.0 Hz, 2H), 6.92 (d, J = 8.9 Hz, 2H), 3.02 (br s, 4H), 2.55 – 2.40 (m, 4H), 2.27 (s, 3H), 0.98 (s, 9H), 0.23 (s, 6H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 159.7, 129.8, 127.4, 120.1, 53.9, 45.8, 45.6, 25.4, 18.1, -4.50. \text{IR (neat, cm}^{-1}\)): 2934, 2856, 2794, 2765, 1590, 1490, 1472, 1405, 1384, 1371, 1342, 1329, 1285, 1252, 1167, 1152, 1144, 1098, 1065, 890, 854, 825, 783, 758, 666, 631, 610, 581, 575, 563, 557. \text{Anal. Calcd. for C}_{17}H_{30}N_{2}O_{5}SSi: C, 55.10; H, 8.16. Found C, 55.07; H, 8.09.

\textbf{Pyrrolidine-4-Acetylbenzenesulfonamide (4e):} Following \textit{General Procedure B}, the title compound was prepared using \text{4-acetylphenylboronic acid (246 mg, 1.5 mmol)} and \text{P5}. The chlorosulfonylation reaction reaction was carried out at 60 °C for 12 h. Pyrrolidine (181 µL, 2.2 mmol) was used as the secondary amine to form the desired...
sulfonamide. The crude product was purified by flash column chromatography (Biotage, 25g SNAP column, 10-50% EtOAc in hexanes) to afford 4e as a white solid (187 mg, 74% yield); mp = 143.5-144.5 °C.

\[ ^1\text{H NMR} \quad (300 \text{ MHz, CDCl}_3 \quad \delta \ 8.09 \ (d, \ J = 8.8 \text{ Hz, } 2 \text{H}), \ 7.93 \ (d, \ J = 8.8 \text{ Hz, } 2 \text{H}), \ 3.53 - 3.03 \ (m, \ 4 \text{H}), \ 2.66 \ (s, \ 3 \text{H}), \ 1.84 - 1.72 \ (m, \ 4 \text{H}). \]

\[ ^{13}\text{C NMR} \quad (101 \text{ MHz, CDCl}_3 \quad \delta \ 196.8, \ 140.7, \ 139.8, \ 128.7, \ 127.5, \ 47.8, \ 26.7, \ 25.1. \]

IR (neat, cm\(^{-1}\)): 3096, 2968, 2873, 1692, 1595, 1396, 1292, 1006, 774, 1066, 958, 852, 774, 748, 725, 634.

**Anal.** Calcd. for C\(_{12}\)H\(_8\)N\(_2\)O\(_3\)S: C, 56.90; H, 5.97. Found C, 56.86; H, 5.81.

\[ N, N\text{-dimethyl-4-(trifluoromethyl)benzenesulfonamide} \quad (4f): \]

Following *General Procedure B*, the title compound was prepared using 4-trifluorophenylboronic acid (285 mg, 1.5 mmol) and P\(_5\). The chlorosulfonylation reaction was carried out at 70 °C for 12 h. Dimethylamine (0.5 M in THF, 1.1 mL, 2.2 mmol) was used as the secondary amine to form the desired sulfonamide. The crude product was purified by flash column chromatography (Biotage, 25g SNAP column, 3-15% EtOAc in hexanes) to afford 4f as a yellow solid (165 mg, 65% yield); mp = 80.5-81.5 °C.

\[ ^1\text{H NMR} \quad (300 \text{ MHz, CDCl}_3 \quad \delta \ 7.92 \ (d, \ J = 8.2 \text{ Hz, } 2 \text{H}), \ 7.82 \ (d, \ J = 8.2 \text{ Hz, } 2 \text{H}), \ 2.75 \ (s, \ 6 \text{H}). \]

\[ ^{13}\text{C NMR} \quad (101 \text{ MHz, CDCl}_3 \quad \delta \ 139.4, \ 134.3 \ (q, \ J = 33.0 \text{ Hz}), \ 128.1, \ 126.2 \ (q, \ J = 3.7 \text{ Hz}), \ 123.3 \ (q, \ J = 272.9 \text{ Hz}), \ 37.8. \]

\[ ^{19}\text{F NMR} \quad (376.5 \text{ MHz, CDCl}_3 \quad \delta \ -63.2. \]

IR (neat, cm\(^{-1}\)): 1458, 1407, 1337, 1325, 1314, 1296, 1148, 1110, 1092, 1015, 947, 840, 788, 742, 692, 596, 582, 574, 566. **Anal.** Calcd. for C\(_9\)H\(_{10}\)F\(_3\)NO\(_2\)S: C, 42.69; H, 3.98. Found C, 42.87; H, 3.94.

\[ N, N\text{-dimethyl-3-(trifluoromethoxy)benzenesulfonamide} \quad (4g): \]

Following *General Procedure B*, the title compound was prepared using 3-trifluoromethoxyphenylboronic acid (309 mg, 1.5 mmol) and P\(_5\). The chlorosulfonylation reaction was carried out at 65 °C for 12 h. Dimethylamine (0.5 M in THF, 1.1 mL, 2.2 mmol) was used as the secondary amine to form the desired sulfonamide. The crude product was purified by flash column chromatography (Biotage, 25g SNAP column, 2-15% EtOAc in hexanes) to afford 4g as a white solid (207 mg, 77% yield); mp = 46.0-48.0 °C.
$^1$H NMR (300 MHz, CDCl$_3$) δ 7.71 (dd, $J = 7.8$, 1.7 Hz, 1H), 7.65 - 7.57 (m, 2H), 7.50 - 7.42 (m, 1H), 2.73 (s, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 149.2 (q, $J = 2.0$ Hz), 137.5, 130.7, 125.3, 125.0 (q, $J = 1.0$ Hz), 120.21 (q, $J = 258.8$ Hz), 120.16 (q, $J = 1.1$ Hz), 37.8. $^{19}$F NMR (376.5 MHz, CDCl$_3$) δ -58.1 (s, 3F). IR (neat, cm$^{-1}$): 1473, 1458, 1437, 1337, 1307, 1280, 1256, 1221, 1204, 1179, 1143, 1094, 1082, 1050, 1000, 950, 919, 682. **Anal.** Calcd. for C$_9$H$_{10}$F$_3$NO$_3$S: C, 40.15; H, 3.74. Found C, 40.26; H, 3.66.

**N,N-dimethyl-4-dibenzofuransulfonamide (4h):** Following General Procedure B, the title compound was prepared using dibenzofuran-4-boronic acid (318 mg, 1.5 mmol) and P5. The chlorosulfonylation reaction was carried out at 60 °C for 12 h and P1 as the catalyst. (Note: Stirring was difficult during the first 1-2 h of the chlorosulfonylation reaction, and so an IKA RCT Basic stir plate was used to facilitate stirring). Dimethylamine (0.5 M in THF, 1.1 mL, 2.2 mmol) was used as the secondary amine to form the desired sulfonamide. The crude product was purified by flash column chromatography (Biotage, 25g SNAP column, 3-18% EtOAc in hexanes) to afford 4h as a white solid (195 g, 71% yield); mp = 146.5-147.5 °C.

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.17 (dd, $J = 7.7$, 1.3 Hz, 1H), 8.00 (ddd, $J = 7.7$, 1.4, 0.7 Hz, 1H), 7.91 (dd, $J = 7.8$, 1.3 Hz, 1H), 7.72 - 7.63 (m, 1H), 7.59 - 7.38 (m, 3H), 2.90 (s, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 156.3, 151.6, 128.3, 128.0, 126.5, 125.3, 123.7, 122.8, 122.7, 121.1, 120.9, 112.2, 37.8. IR (neat, cm$^{-1}$): 1469, 1441, 1418, 1354, 1339, 1188, 1161, 1154, 1111, 1059, 960, 637, 582, 577. **Anal.** Calcd. for C$_{14}$H$_{13}$NO$_3$S: C, 61.07; H, 4.76. Found C, 60.81; H, 4.79.

**N,N-dimethyl-4-iodobenzenesulfonamide (4i):** Following General Procedure B, the title compound was prepared using 4-iodophenylboronic acid (372 mg, 1.5 mmol) and P5. The chlorosulfonylation reaction was carried out at 55 °C for 12 h. (Note: Stirring was difficult during the first 1-2 h of the chlorosulfonylation reaction, and so an IKA RCT Basic stir plate was used to facilitate stirring). Dimethylamine (0.5 M in THF, 1.1 mL, 2.2 mmol) was used as the secondary amine to form the desired sulfonamide. The crude product
was purified by flash column chromatography (Biotage, 25g SNAP column, 3-10% EtOAc in hexanes) to afford 4i as a white solid (233 g, 75% yield); mp = 134-135 °C.

\textbf{1H NMR} (300 MHz, CDCl$_3$) $\delta$ 7.90 (d, $J = 8.7$ Hz, 2H), 7.49 (d, $J = 8.6$ Hz, 2H), 2.71 (s, 6H).

\textbf{13C NMR} (101 MHz, CDCl$_3$) $\delta$ 138.3, 135.3, 129.1, 100.2, 37.9. IR (neat, cm$^{-1}$): 3079, 1567, 1466, 1450, 1387, 1341, 1328, 1271, 1257, 1180, 1163, 1088. Anal. Calcd. for C$_9$H$_{10}$N$_2$O$_2$: C, 30.88; H, 3.24. Found C, 31.15; H, 3.08. HRMS-ESI ($m/z$) [M + H]$^+$ Calcd. for C$_9$H$_{10}$N$_2$O$_2$, 311.9550; found, 311.9548.

\textbf{N,N-dimethyl-2-chlorobenzenesulfonamide (4j):} Following \textit{General Procedure B}, the title compound was prepared using 2-chlorophenylboronic acid (235 mg, 1.5 mmol) and P5. The chlorosulfonylation reaction was carried out at 60 °C for 12 h. Dimethylamine (0.5 M in THF, 1.1 mL, 2.2 mmol) was used as the secondary amine to form the desired sulfonamide. The crude product was purified by flash column chromatography (3-15% EtOAc in hexanes) to afford 4j as a white solid (145 g, 66% yield); mp = 40.0-41.8 °C.

\textbf{1H NMR} (400 MHz, CDCl$_3$) $\delta$ 8.05 (dd, $J = 7.9$, 1.6 Hz, 1H), 7.55 - 7.45 (m, 2H), 7.39 (ddd, $J = 7.9$, 7.1, 1.6 Hz, 1H), 2.88 (s, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 135.9, 133.5, 132.1, 132.0, 126.9, 37.3. (Note: only 6 carbon signals for 4j resolve in the $^{13}$C spectrum). IR (neat, cm$^{-1}$): 3090, 2872, 1569, 1450, 1346, 1256, 1160, 1106, 1041, 954, 754, 713, 690, 654, 578. Anal. Calcd. for C$_{9}$H$_{10}$ClNO$_2$: C, 43.74; H, 4.54. Found C, 43.99; H, 4.68.

\textbf{N-[2-(3,4-dimethoxyphenyl)ethyl]-1,3-benzodioxole-5-sulfonamide (4k):} Following \textit{General Procedure C}, the title compound was prepared using 3,4-methylenedioxyphenylboronic acid (249 mg, 1.5 mmol) and P5. The chlorosulfonylation reaction was carried out at 50 °C for 12 h. 3,4-Dimethoxyphenethylamine (373 µL, 2.2 mmol) was used as the primary amine to form the desired sulfonamide. The crude product was purified by flash column chromatography (Biotage, 25g SNAP column, 20% EtOAc in hexanes) to afford 4k as a white solid (274 mg, 75% yield); mp = 118-120 °C.
$^1$H NMR (400 MHz, CDCl$_3$) δ 7.36 (dd, $J = 8.2$, 1.9 Hz, 1H), 7.15 (d, $J = 1.9$ Hz, 1H), 6.84 (d, $J = 8.2$ Hz, 1H), 6.77 (d, $J = 8.1$ Hz, 1H), 6.63 (dd, $J = 8.1$, 2.0 Hz, 1H), 6.57 (d, $J = 2.0$ Hz, 1H), 6.07 (s, 2H), 4.55 - 4.25 (m, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 3.19 (app q, $J = 6.6$ Hz, 2H), 2.71 (t, $J = 6.8$ Hz, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 151.1, 148.9, 148.1, 147.7, 132.9, 130.1, 122.6, 120.6, 111.6, 111.1, 107.9, 107.1, 102.2, 55.8, 55.7, 44.3, 35.2. IR (neat, cm$^{-1}$): 3231, 2931, 1594, 1512, 1501, 1483, 1471, 1356, 1328, 1255, 1231, 1174, 1147, 1137, 1111, 1069, 1022, 936, 909, 858, 846, 830, 764, 727, 709, 667, 634, 618, 602, 573, 561, 558, 551. Anal. Calcd. for C$_{17}$H$_{19}$N$_{10}$O$_6$S: C, 55.88; H, 5.24. Found C, 55.59; H, 5.31.

*N-*cyclopropyl*naphthalene-2-*sulfonamide* (41): Following *General Procedure C*, the title compound was prepared using 2-*naphthalene*boronic acid (258 mg, 1.5 mmol) and P5. The chlorosulfonylation reaction was carried out at 50 °C for 12 h. Cyclopropylamine (208 µL, 3.0 mmol) was used as the primary amine to form the desired sulfonamide. The crude product was purified by flash column chromatography (Biotage, 25g SNAP column, 5-30% EtOAc in hexanes) to afford 41 as a white solid (200 g, 81% yield); mp = 99.5-101.0 °C.

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.50 (s, 1H), 8.08 - 7.76 (m, 4H), 7.75 - 7.52 (m, 2H), 5.04 (br s, 1H), 2.31-2.23 (m, 1H), 0.66-0.53 (m, 4H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 136.4, 134.7, 132.0, 129.3, 129.1, 128.7, 128.7, 127.8, 127.4, 122.4, 24.2, 5.99. IR (neat, cm$^{-1}$): 3279, 1591, 1455, 1406, 1366, 1306, 1226, 1160, 967, 884, 751, 694, 640, 567. Anal. Calcd. for C$_{13}$H$_{13}$N$_{10}$O$_2$: C, 63.13; H, 5.30. Found C, 63.05; H, 5.33.

*N-*cyclohexylthiophene-3-*sulfonamide* (4m): Following of the *General Procedure C*, the title compound was prepared using 3-*thiophene*boronic acid (192 mg, 1.5 mmol) and P4 (16.1 mg, 0.02 mmol, 2 mol%). The chlorosulfonylation reaction was carried out at 55 °C for 12 h. Cyclohexylamine (343 µL, 3.0 mmol) was used as the primary amine to form the desired sulfonamide. The crude product was purified by flash column chromatography...
(Biotage, 25g SNAP column, 5-25% EtOAc in hexanes) to afford 4m as a white solid (171 mg, 70% yield); mp = 94.0-95.0 °C.

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.96 (dd, $J = 3.1, 1.3$ Hz, 1H), 7.41 (dd, $J = 5.1, 3.1$ Hz, 1H), 7.35 (dd, $J = 5.1, 1.3$ Hz, 1H), 4.49 (d, $J = 7.8$ Hz, 1H), 3.33 – 3.02 (m, 1H), 1.90 – 1.39 (m, 5H), 1.37 – 1.03 (m, 5H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 141.5, 129.9, 127.9, 125.5, 52.8, 33.8, 25.1, 24.6. IR (neat, cm$^{-1}$): 3264, 3106, 2932, 2854, 1448, 1312, 1297, 1209, 927, 998, 891, 881, 815, 800, 729, 698, 641, 629, 597. Anal. Calcd. for C$_{10}$H$_{15}$NO$_2$S$_2$: C, 48.95; H, 6.16. Found C, 49.08; H, 6.20.

Methyl 3-(N-(4-fluorophenyl)sulfamoyl)benzoate (4n):
Following General Procedure D, the title compound was prepared using 3-methoxycarbonylphenylboronic acid (270 mg, 1.5 mmol) and P5. The chlorosulfonylation reaction was carried out at 60 °C for 12 h. 4-Fluoroaniline (114 μL, 1.2 mmol) was used as the aniline to form the desired sulfonamide. The crude product was purified by flash column chromatography (Biotage, 25g SNAP column, 5-25% EtOAc in hexanes) to afford 4n as an off-white solid (247 mg, 80% yield); mp = 104.8-105.8 °C.

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.53 – 8.38 (m, 1H), 8.20 (ddd, $J = 7.8, 1.7, 1.2$ Hz, 1H), 7.89 (ddd, $J = 7.9, 1.9, 1.2$ Hz, 1H), 7.58 – 7.46 (m, 1H), 7.31 (s, 1H), 7.11 – 7.02 (m, 2H), 6.97 – 6.87 (m, 2H), 3.91 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 165.5, 160.7 (d, $J = 246$ Hz), 139.3, 133.8, 131.9 (d, $J = 2.96$), 131.3, 131.2, 129.3, 128.3, 124.7 (d, $J = 9.0$ Hz), 116.2 (d, $J = 22.8$ Hz), 52.7. $^{19}$F NMR (282 MHz, CDCl$_3$) δ -115.8. IR (neat, cm$^{-1}$): 3239, 1728, 1505, 1437, 1336, 1309, 1292, 1259, 1232, 1204, 1191, 1170, 1156, 1124, 1098, 1085, 1076, 1014, 965, 856, 831, 814, 751, 678, 639, 589, 575. Anal. Calcd. for C$_{14}$H$_{15}$FNOS: C, 54.36; H, 3.91. Found C, 54.49; H, 3.91.

3-Bromo-N-phenylbenzenesulfonamide (4o):
Following General Procedure D, the title compound was prepared using 3-bromophenylboronic acid (301 mg, 1.5 mmol) and P5. The cross-coupling reaction was carried out at 55 °C for 12 h. Aniline (109 μL,
1.2 mmol) was used as the aniline to form the desired sulfonamide. The crude product was purified by flash column chromatography (Biotage, 25g SNAP column, 5-25% EtOAc in hexanes) to afford 4o as a yellow solid (259 g; 83% yield); mp = 104.5-105.5 °C.

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.92 (s, 1H), 7.66 (d, $J = 8$ Hz, 2H), 7.33-7.24 (m, 3H), 7.19-7.13 (m, 1H), 7.09-7.05 (m, 2H), 6.68 (br s, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 140.6, 136.0, 135.8, 130.5, 130.0, 129.4, 125.7, 125.7, 122.9, 121.8. IR (neat, cm$^{-1}$): 3259, 1600, 1571, 1481, 1463, 1339, 1298, 1154, 1096, 1086, 920, 902, 785, 767, 752, 619, 580, 573, 558. Anal. Calcd. for C$_{12}$H$_{10}$BrNO$_2$S: C, 46.17; H, 3.23. Found C, 46.32; H, 3.22.
F) Preparation of Perfluorophenyl Arenesulfonates (6b-6e)

Generation Procedure D: Preparation of Perfluorophenyl Arenesulfonates

Following *General Procedure A*, a mixture of *P1* (15.9 mg, 0.02 mmol, 2 mol%), Na$_2$CO$_3$ (5.3 mg, 0.05 mmol, 5 mol%), arylboronic acid (1.5 mmol, 1.5 equiv), and phenyl chlorosulfate (133 µL, 1.0 mmol, 1.0 equiv) in anhydrous acetone (2.0 mL) was stirred at the desired temperature for 12 h. After the reaction mixture was allowed to cool to room temperature, it was placed under a positive atmosphere of argon and anhydrous THF (1.0 mL) was added via syringe (additional THF was not added to reactions in which a commercially available 2.0 M solution of Me$_2$NH in THF was used). The reaction mixture was cooled to 0 °C. Pentafluorophenol (214 µL, 2.0 mmol, 2.0 equiv) was then added via a syringe, followed by the addition of anhydrous diisopropylethylamine (261 µL, 1.5 mmol, 1.5 equiv) via a syringe. The reaction was then removed from the cooling bath and stirred at rt for 2 h, after which the crude product was concentrated and loaded directly onto Biotage SNAP 25 g cartridge and purified by flash column chromatography (using a Biotage Isolera Four system with a SNAP 25 g cartridge) to afford the desired pentafluorophenyl arenesulfonates.

**Perfluorophenyl 2-chlorobenzenesulfonate (6b):** Following *General Procedure D*, the title compound was prepared using 2-chlorophenylboronic acid (235 mg, 1.5 mmol) as the arylboronic acid. The cross-coupling reaction was carried out at 55 °C for 12 h, after which the crude reaction mixture was carried forward to the desired perfluorophenyl arenesulfonate. The crude product was purified by flash column chromatography (Biotage, 25g SNAP column, EtOAc/hexane gradient: 0% EtOAc for 5 CV, 0-10% for 10 CV, 10% for 10 CV) to afford the product as an off-white solid (302 mg, 84% yield); mp 92.0-92.7 °C.
$^1$H NMR (400 MHz, CDCl$_3$) δ 8.01-7.98 (dd, $J$ = 8.4, 1.2 Hz, 1H), 7.71-7.66 (m, 2H), 7.50-7.45 (m, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 143.5 (m, 1C), 141.7 (m, 1C), 140.8 (m, 1C), 139.3-139.0 (m, 2C), 136.6 (m, 1C), 136.0 (s, 1C), 133.9 (s, 1C), 133.4 (s, 1C), 132.5 (s, 1C), 131.7 (s, 1C), 127.2 (s, 1C). $^{19}$F NMR (376.5 MHz, CDCl$_3$) δ -150.7 (m, 2F), -155.1 (t, 1F), -161.1 (m, 2F). IR (neat, cm$^{-1}$): 1514, 1457, 1437, 1389, 1376, 1195, 1022, 989, 966, 770, 761, 718, 668, 605, 578, 564, 553. Anal. Calculated for C$_{12}$H$_4$ClF$_5$O$_3$S: C, 40.18; H, 1.12; Cl, 9.88; F, 26.48; O, 13.38; S, 8.94. Found C, 40.40; H, 1.08.

Perfluorophenyl 2-methoxybenzenesulfonate (6c): Following General Procedure D, the title compound was prepared using 2-methoxyphenylboronic acid (228 mg, 1.5 mmol) as the arylboronic acid. The cross-coupling reaction was carried out at 50 °C for 12 h, after which the crude reaction mixture was carried forward to the desired perfluorophenyl arenesulfonate. The crude product was purified by flash column chromatography (Biotage, 25g SNAP column, EtOAc/hexane gradient: 0% EtOAc for 5 CV, 0-10% for 10 CV, 10% for 10 CV) to afford the product as a brown solid (262 mg, 74% yield); mp 123-126 °C.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.88-7.86 (dd, $J$ = 7.9, 1.7 Hz, 1H), 7.72-7.67 (ddd, $J$ = 8.3, 7.9, 1.7 Hz, 1H), 7.14-7.11 (dd, $J$ = 8.3, 1.0 Hz, 1H), 7.10-7.08 (td, $J$ = 7.9, 1.0 Hz, 1H), 3.99 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 158.3 (s, 1C), 143.6 (m, 1C), 141.0 (m, 1C), 140.9 (m, 1C), 138.9 (m, 1C), 137.3 (s, 1c), 136.6 (m, 1C), 131.5 (s, 1c), 124.6 (m, 1C), 122.8 (s, 1C), 120.3 (S, 1C), 112.7 (s, 1C), 56.3 (s, 1C). $^{19}$F NMR (376.5 MHz, CDCl$_3$) δ -150.72 (m, 2F), -156.2 (t, 1F), -161.8 (m, 2F). IR (neat, cm$^{-1}$): 1594, 1578, 517, 1482, 1469, 1434, 1380, 1287, 1255, 1188, 1166, 1149, 1135, 1068, 990, 809, 786, 763, 746, 723, 696, 601, 588, 567. Anal. Calculated for C$_{13}$H$_7$F$_6$O$_5$S$_2$: C, 44.08; H, 1.99; F, 26.82; O, 18.07; S, 9.05. Found C, 44.12; H, 2.15.

Perfluorophenyl 4-(trifluoromethyl)benzenesulfonate (6d) Following General Procedure D, the title compound was prepared using 4-trifluorophenylboronic acid (285 mg, 1.5
mmol) as the arylboronic acid. The cross-coupling reaction was carried out at 70 °C for 12 h, after which the crude reaction mixture was carried forward to the desired perfluorophenyl arenesulfonate. The crude product was purified by flash column chromatography (Biotage, 25g SNAP column, EtOAc/hexane gradient: 0% EtOAc for 5 CV, 0-10% for 10 CV, 10% for 10 CV) to afford the product as a white solid (220 mg, 56% yield); mp 70-72 °C.

\[ ^1H\text{ NMR (400 MHz, CDCl}_3\] \( \delta \) 8.16-8.13 (d, \( J = 8.3 \text{ Hz, 2H} \)), 7.92-7.90 (d, \( J = 8.3 \text{ Hz, 2H} \)). \[ ^{13}C\text{ NMR (101 MHz, CDCl}_3\] \( \delta \) \( 143.5 \text{ (m, 2C), 141.8 \text{ (m, 1C), 140.9 \text{ (m, 2C), 139.2 \text{ (m, 1C), 138.5 \text{ (s, 1C), 137.3-136.3 \text{ (q, \( J = 33.6 \text{ Hz, 1C) ), 129.1 \text{ (s, 2C), 126.8-126.7 \text{ (q, \( J = 3.7 \text{ Hz, 2C) }, 126.0-118.7 \text{ (q, \( J = 273 \text{ Hz, 1C) 。} ^{19}F\text{ NMR (376.5 MHz, CDCl}_3\] \( \delta \) -63.5 (s, 3F), -150.7 (m, 2F), -154.6 (t, 1F), -160.6 (m, 2F). IR (neat, cm\(^{-1}\))): 1514, 1397, 1380, 1198, 1188, 1169, 1148, 1110, 1027, 1016, 990, 849, 790, 756, 722, 710, 615, 598. \text{Anal. Calculated for } C_{13}H_4F_8O_3S: C, 39.81; H, 1.03; F, 38.75; O, 12.24; S, 8.18. Found C, 40.14, H, 1.00.

**Perfluorophenyl 3-bromobenzenesulfonate (6e):** Following General Procedure D, the title compound was prepared using 3-bromophenylboronic acid (301 mg, 1.5 mmol) as the arylboronic acid. The cross-coupling reaction was carried out at 55 °C for 12 h, after which the crude reaction mixture was carried forward to the desired perfluorophenyl arenesulfonate. The crude product was purified by flash column chromatography (Biotage, 25g SNAP column, EtOAc/hexane gradient: 0% EtOAc for 5 CV, 0-2% for 5 CV, 2% for 2 CV then 5% for 10 CV) to afford the product as yellow oil (308.4 mg, 77% yield).

\[ ^1H\text{ NMR (300 MHz, CDCl}_3\] \( \delta \) 8.13-8.12 (t, \( J = 1.8 \text{ Hz 2H) ), 7.93-7.88 (m, 2H), 7.54-7.49 (t, \( J = 8.0 \text{ Hz, 1H) 。} ^{13}C\text{ NMR (101 MHz, CDCl}_3\] \( \delta \) \( 143.5 \text{ (m, 1C), 141.7 \text{ (m, 1C), 140.8 \text{ (m, 1C), 139.3-139.0 \text{ (m, 2C), 138.3 \text{ (s, 1C), 136.6 \text{ (m, 1C), 136.5 \text{ (s, 1C), 131.2 \text{ (s, 1C), 131.0 \text{ (s, 1C), 127.0 \text{ (s, 1C), 123.4 \text{ (s, 1C).} ^{19}F\text{ NMR (376.5 MHz, CDCl}_3\] \( \delta \) -150.7 (m, 2F), -155.1 (t, 1F), -160.9 (m, 2F). IR (neat, cm\(^{-1}\))): 1514, 1466, 1394, 1194, 1021, 989, 782, 743, 715, 673, 656, 604, 591, 581, 570. \text{Anal. Calculated for } C_{12}H_4BrF_5O_3S: C, 35.75; H, 1.00; Br, 19.82; F, 23.56; O, 11.91; S, 7.95. Found C, 36.03, H, 0.95.
G) Control Experiments: To confirm that sulfonate esters are not converted to sulfonyl chlorides:

Two separate oven-dried test tubes, each equipped with a magnetic stir bar, were charged with P5 (7.94 mg, 0.01 mmol, 2 mol%), Na₂CO₃ (2.65 mg, 0.025 mmol, 5 mol%), either phenylboronic acid (for Eq. S1, 93 mg, 0.75 mmol, 1.5 equiv) or 4-methylphenylboronic acid (for Eq. S2, 104 mg, 0.75 mmol, 1.5 equiv), and either phenyl tosylate (for Eq. S1, 124 mg, 0.5 mmol, 1.0 equiv) or phenyl benzenesulfonate (for Eq. S2, 117 mg, 0.5 mmol, 1.0 equiv). The tubes were sealed with a Teflon screw-cap septum. The vessels were evacuated and backfilled with argon (this process was repeated a total of 3 times), and anhydrous acetone (1.0 mL) was then added via syringe. After the mixtures were allowed to stir for ~3 min at room temperature, neat phenyl chlorosulfate (66 µL, 0.5 mmol, 1.0 equiv) was added. The vessels were then placed in a preheated oil bath at 50 °C and the reaction mixtures were allowed to stir for 12 h. After the reaction mixtures were allowed to cool to room temperature, an internal standard was added (tetradecane) and the mixtures were diluted with EtOAc and filtered through a short plug of silica gel. The crude reaction mixtures were analyzed by GC and the results are shown in Equations S1 and S2. In each case, 100% of the phenyl sulfonate ester was recovered while the sulfonyl chloride derived from the arylboronic acid was formed in near quantitative yield, thus demonstrating that the sulfonate esters are not converted to the corresponding sulfonyl chlorides under these conditions.
H) Competition Experiments Between 1b and 1c:

An oven-dried test tube equipped with a magnetic stir bar was charged with P5 (0.01 mmol, 2 mol%), Na$_2$CO$_3$ (2.65 mg, 0.025 mmol, 5 mol%), and the 4-methoxyphenylboronic acid (76 mg, 0.5 mmol, 1.0 equiv), and the tube was sealed with a Teflon screw-cap septum. The vessel was evacuated and backfilled with argon (this process was repeated a total of 3 times), and deuterated acetone-$_6$ (1.0 mL) was then added via syringe. After the mixture was allowed to stir for ~3 min at room temperature, neat 1b (75.4 µL, 0.5 mmol, 1.0 equiv) and 1c (116 µL, 0.5 mmol, 1.0 equiv) were added sequentially. The vessel was then placed in a preheated oil bath at 40 °C and the reaction mixture was allowed to stir for 8 h. After the reaction mixture was allowed to cool to room temperature, an internal standard (1,3,5-trimethoxybenzene, 28.03 mg) was added. A small aliquot (~0.2 mL) of the crude reaction mixture was filtered through a short plug of SiO$_2$ (~1.5 cm in a pipette with a cotton filter), which was further washed with CD$_3$Cl (~0.6 mL). The resulting yellow solution was then analyzed by $^1$H NMR. Because both 1b and 1c are converted to the same sulfonyl chloride product (3a, 87% NMR yield), the amounts of recovered 1b (40%) and 1c (62%) were quantified along with the corresponding phenol byproducts. The NMR data show that 1c undergoes higher conversion to 3a, which suggests that the more sterically hindered substrate (1c) is slightly more reactive than 1b (Figure 8).
Figure 8. $^1$H NMR Analysis of Crude Reaction Mixture of Equation 3.

Note: The integrals of the benzylic protons of 1c and 2,6-diisopropylphenol were used to calculate the NMR yields of these compounds, but these signals overlap to a small degree in the $^1$H NMR spectrum above. The benzylic protons signals completely resolve from one another if the crude reaction mixture is first filtered through a short plug of SiO$_2$, concentrated and then dissolved in CD$_3$Cl. However, 1b is volatile, and a significant amount of this compound is removed upon concentrating the sample; therefore, this workup procedure was not used to prepare the NMR sample used to analyze the substrate and product distributions of Eq. S3. To show an example of a spectrum in which the signals of 1c and 2,6-diisopropylphenol are completely differentiated from one another, we included the $^1$H NMR spectrum of the crude reaction mixture of Eq. S3 below (Figure 9). In order to promote full conversion of the arylboronic acid to 1a, the reaction depicted in Eq. S3 was conducted at 50 °C for 10 h, but under otherwise identical conditions to those depicted in Eq. 3.
Figure 9. $^1$H NMR Analysis of Crude Reaction Mixture of Equation S3 (Crude Reaction Mixture Filtered through SiO$_2$, Concentrated, and Dissolved in CDCl$_3$)
Additionally, the control experiment (Eq. S4) was performed to show that 1c is not converted to 1b during the competition experiments (Eq. 3 and Eq. S3). First, substrate 1b was subjected to the chlorosulfonylation conditions in the absence of 1c. Following complete conversion of 1b to the sulfonyl chloride (3a), substrate 1c was then added and the reaction mixture was allowed to stir at 50 °C for 10 h. Analysis by 'H NMR showed 91% recovery of 1c, 0% recovery of 1b, and >90% NMR yield of 3a.
I) Competition Experiment with Piperidine:

An oven-dried test tube equipped with a magnetic stir bar was sealed with a Teflon screw-cap septum. The vessel was evacuated and backfilled with N₂ (this process was repeated a total of 3 times), and neat 1b (75.4 µL, 0.5 mmol, 1.0 equiv), neat 1c (116 µL, 0.5 mmol, 1.0 equiv), and CD₂Cl₂ (2.0 mL) were added under a N₂ atmosphere. The vessel was allowed to cool to -78 °C in a dry ice/acetone bath, and a solution of piperidine (50 µL, 0.5 mmol, 1.0 equiv) in CD₂Cl₂ (0.5 mL) was added slowly via syringe (over 2 min) along the inner wall of the vessel. The reaction mixture was stirred for 18 h at -78 °C. Immediately after the reaction mixture was allowed to warm to room temperature, an internal standard (1,3,5-trimethoxybenzene, 28.03 mg) was added, and a small aliquot (~0.2 mL) of the crude reaction mixture was diluted with CD₂Cl₂ (~0.6 mL) and analyzed by ¹H NMR. **Note:** The signals of the sulfamoyl chloride (8) and the piperidinium salt overlap in the ¹H NMR spectrum. Therefore, a separate aliquot (~0.2 mL) of the crude reaction mixture was filtered through a short plug of SiO₂ (~1.5 cm in a pipette with a cotton filter) to remove the piperidinium salt. The filter was further washed with CD₂Cl₂ (~0.6 mL) and the combined filtrate was analyzed by ¹H NMR (see expanded region on Figure 10). Because both 1b and 1c are converted to the same sulfamoyl chloride product (9), the amounts of recovered 1b and 1c were quantified. The NMR data show that a larger amount of the sterically hindered substrate (1c) is consumed than 1b. In addition, 1b and 1c react with piperidine to form the corresponding sulfamoyl chloride (9), demonstrating that S-O bond cleavage is also favored in the absence of a palladium catalyst.
Figure 10. $^1$H NMR Analysis of Crude Reaction Mixture of Eq. 4 (Expanded signal C taken from Spectrum Recorded After Piperidinium Salt Removed via SiO$_2$ Filtration)
1.5 References and Notes


19) Phenyl chlorosulfate is prepared by reacting phenol $\text{SO}_2\text{Cl}_2$ and pyridine at $-78^\circ\text{C}$. Compound 2a is stable in neat form for at least one year when stored at 4 °C.

20) No reaction was observed when solutions of 4-methoxyphenylboronic acid (1.5 equiv) and la (1.0 equiv) in toluene or 1,4-dioxane were stirred at 110 °C for 24 h.

21) See the experimental section for details.

22) An alternative mechanism might involve reversible oxidative addition to la, with transmetalation occurring at the –OPh group of 8 in preference to the –Cl group of the related Pd–Cl species. Oxidative addition is typically considered an irreversible process, although examples of reductive elimination of aryl halides have been reported. See: (a) Roy, A. H.;


26) The diarylphosphine moiety is essential for most substrates because more electron-rich dialkylphosphine ligands were oxidized under the reaction conditions (as indicated by the $^{31}$P NMR spectra of the crude reaction mixtures).


28) Both Pd(0) and phosphine ligands can potentially react with 3; thus, to limit product decomposition and promote complete conversion of 1a, we chose to increase the reaction temperatures accordingly rather than adjust the respective catalyst loadings.

29) Electron-poor arylboronic acids typically undergo transmetalation at a slower rate than electron-neutral and electron-rich arylboronic acids.

30) The volatility of 3d–3i may also contribute to lower yields.

31) The stoichiometry of the amine can be reduced to 1.2 equiv if DIPEA is used as a sacrificial base. See conditions for product 4d (Table 3).

32) Currently, boronic acids derived from nitrogen heterocycles do not couple in useful yields. This inefficiency is due to deboronation of the starting material and/or the instability of the corresponding sulfonyl chlorides. See: Caldwell, W. T.; Kornfeld, E. C. *J. Am. Chem. Soc.* **1950**, *72*, 4890.

33) The order of reactivity of electrophiles for Suzuki–Miyaura cross-coupling is ArI > ArSO$_2$Cl > ArBr ≫ ArCl (see ref 16a).
34) Aryl sulfonyl chlorides have been used as precursors to diaryl sulfones. See: Bandgar, B. P.; Bettigeri, S. V.; Phopase, J. Org. Lett. 2004, 6, 2105.


36) We observe homocoupling (< 15% biaryl) of certain electron-deficient and ortho-substituted arylboronic acids (e.g. corresponding to 5f and 5j). This side reaction may occur at the expense of 2a via an oxidative addition/desulfonylation pathway.

37) A control experiment in which 2c is introduced after complete conversion of 2b verified that 2c is not converted to 2b. See Supporting Information for details.


39) Melting point listed on Sigma-Aldrich website


43) ¹H NMR of perfluorophenyl arenesulfonates stored under ambient conditions after 3 years showed no decomposition of the materials.
1.5 $^1\text{H}$, $^{13}\text{C}$, $^{19}\text{F}$, and $^{31}\text{P}$ NMR Spectra
L5: PhCPhos
L5: PhCPhos
L5: PhCPhos
PhDavePhos = 

\[
\text{PhDavePhos} = \begin{array}{c}
\text{NH}_2 \\
\text{Pd-PhDavePhos} \\
\text{OMs} \\
\text{P3}
\end{array}
\]
CPhos = Me₂N₉
\[
\text{Pd-CPhos} \quad \text{OMs}
\]

\[
\text{P4}
\]
NH₂
Pd-CPhos
OMs
P4

CPhos =

PCy₂
Me₂N
NMe₂
NH$_2$ Pd-PhCPhos OM$_2$

PhCPhos =

Me$_2$N NMe$_2$
$\text{3e}$

\[ \text{S-O-Cl} \]

$\delta$ (ppm)
4b

MeO
SO
O

1H NMR spectrum of 4b.
4c

[Chemical structure]

[Graphical representation of the chemical structure]
The image contains a chemical structure labeled as 6b, along with a chemical shift spectrum. The spectrum shows peaks at various frequencies, with annotations indicating specific chemical shifts and multiplicities. The spectrum spans from 8.10 to 7.15 ppm.
6e

![Chemical Structure](image)

![NMR Spectrogram](image)
Part II.

Chapter 2.
Enantio- and Regioselective Copper-Catalyzed Hydroamination of Styrenes and the Extension of the Methodology towards Anti-Markovnikov Hydroamination of Terminal Aliphatic Alkenes

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Enantio- and Regioselective CuH-Catalyzed Hydroamination of Alkenes

Shaolin Zhu, Nootaree Niljianskul, and Stephen L. Buchwald

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2.1 Introduction

Chiral amines are an important class of compounds ubiquitous in the pharmaceutical industry and natural products (Figure 1). Because chiral amines are valuable synthons and synthetic targets, many approaches towards their synthesis have been developed. Some examples include nucleophilic addition to imines, radical addition to imino compounds, chiral Bronsted acid-catalyzed transformation, asymmetric reduction, and asymmetric reductive amination.

Figure 1. Pharmaceutical Drugs Containing Chiral Amine Motifs

Hydroamination, the formation of a C-N bond by the formal addition of an amine to an olefin, is one of the most direct methods to access amine derivatives. Additionally, this method has the potential to gain access to amine products from readily available feedstocks such as alkenes and alkynes. Indeed, over the past six decades, many hydroamination reactions have been developed.

Despite the significant progress that has been made in the field of late transition metal-catalyzed hydroamination, several challenges still exist. For example, the intermolecular system requires activated alkenes such as vinyl arenes or acrylic acid derivatives. For the asymmetric variants, the state of art systems are the palladium-catalyzed approaches as reported
by Hartwig, Hii, and Lin (Scheme 1). Although this represents a significant advancement in the field of late transition metal-catalyzed hydroamination reactions, the systems are limited to the addition of aryl amines to simple β-unsubstituted styrene derivatives and achieve only moderate levels of enantiomeric excess (Scheme 1).

Scheme 1. Enantioselective Hydroamination Reactions Catalyzed by Late Transition Metals

```latex
\begin{align*}
\text{R}^1\text{C} = \text{CH} + \text{Ph-NH}_2 &\xrightarrow{\text{Pd-Ligand}^*} \text{R^1CH} = \text{NPh} \\
\text{Markovnikov addition products} &\quad 70-93\% \text{ yield, } 59-84\% \text{ ee}
\end{align*}
```

Furthermore, the hydroamination of unactivated alkenes using metal catalysis is still quite limited. Currently, there is no precedent for late-transition metal catalyzed anti-Markovnikov intermolecular hydroamination of unactivated olefins. However, Lalic has recently reported a strategy to achieve intermolecular anti-Markovnikov hydroamination products from aliphatic alkenes by intermediate hydroboration of the olefin, followed by a copper-catalyzed amination (Scheme 2).

Scheme 2. Anti-Markovnikov Hydroamination of Aliphatic Alkenes

\begin{align*}
\text{Alkyl} &\xrightarrow{9\text{-BBN-H, then}} \text{Alkyl} \quad \middle| \quad \text{R}_1\text{R}_2\text{N-OBz} \\
\text{cat. CuCl, LiO} &\xrightarrow{\text{Bu}} \text{H} \quad \text{BBN} \\
\text{Alkyl} &\xrightarrow{\text{H}} \text{Alkyl} \quad \text{N} \quad \text{R}^1 \\
\text{Alkyl} &\text{R}^2
\end{align*}

Thus, there remains a need to develop asymmetric hydroamination reaction conditions.
that tolerate a wide variety of substitution patterns on both the alkene and the amine components, which possess high regio- and enantioselectivity. We are, therefore, interested in pursuing a mild and general approach to synthesize a broad range of chiral amines. Challenges that we specifically wanted to address included incompatibilities with alkyl amine substrates and $\beta$-substituted substrates.

Over the last decade our group has explored and developed successful asymmetric reduction methods, one of which is the asymmetric copper hydride-mediated (CuH) transformation shown in Scheme 3. This asymmetric reduction strategy exploits a copper hydride species, formed in situ, to promote a conjugate reduction of $\alpha,\beta$-unsaturated compounds (Scheme 4). It was proposed that this reaction occurs via CuH addition to the olefin, a "hydrocupration process," which generates a copper-enolate species. Transmetalation of the cuprate with a silane reagent affords a silyl enol ether while regenerating the CuH species.

**Scheme 3. Previously Reported CuH-Catalyzed Asymmetric Reduction**

**Scheme 4. Proposed Catalytic Cycle for CuH-Catalyzed Asymmetric Reduction**
As shown in Scheme 5, we envisioned an approach for asymmetric intermolecular hydroamination that would include a hydrocupration process to generate an alkyl-copper complex (II). An electrophilic amine synthon (3) could then intercept this alkyl-copper complex via an oxidative addition to provide Cu(III) intermediate (III). Reductive elimination and transmetalation would follow to regenerate CuH (I) while providing chiral amine product 3.

**Scheme 5. Our Strategy Towards CuH-Catalyzed Asymmetric Hydroamination**

Two classes of electrophilic alkylamine reagents, N,N-disubstituted-N-chloroamines (A) and N,N-disubstituted-O-benzoylhydroxylamines (B), were attractive to us due to the versatility of substitution on the amines (Figure 2). O-benzoylhydroxylamine electrophiles (B) were previously observed to undergo purported oxidative addition with copper, where as N-chloroamines (A) have only been shown to undergo oxidative addition with nickel. Additionally, it is known that more basic Cu-carboxylate species, generated from the use of the benzyloxyamines (B), undergo facile transmetalation with silane reagents, whereas copper(I) chloride species, generated from a chloroamine reagent (B), would require transformation to a more basic species before transmetalation with a silane could occur.
We envisioned applying these strategies towards activated olefins such as styrenes. It was postulated that the intermolecular hydroamination of styrenes would proceed regioselectively to afford Markovnikov products as there is an electronic advantage for the copper to form a benzylic-Cu intermediate (Scheme 6). We note that Marder has previously reported calculations on the regiochemistry of insertion reactions of styrenes in an analogous borylcupration process, which supports the formation of a benzylic-Cu intermediate\textsuperscript{13}

**Scheme 6. Proposed Regioselectivity for CuH-Catalyzed Hydroamination of Styrene Derivatives**

For terminal aliphatic alkenes, we proposed that the reaction would proceed to give the anti-Markovnikov regioselectivity. This is because the hydride migration from the copper catalyst should proceed to form the less sterically crowded terminal copper intermediate (Scheme 7) since there is no electronic advantage. Thus, we expected the steric property of the substrate to control the regioselectivity of hydrocupration.

**Scheme 7. Proposed Regioselectivity for Copper-Catalyzed Hydroamination of Terminal Aliphatic Alkene**
2.2 Results and Discussion

We began our investigation by attempting the hydroamination of styrene (1a) using readily available Cu(OAc)$_2$ (Table 1). As previously discussed, O-benzoylhydroxylamine electrophiles were previously shown to be efficient for copper-catalysis.$^6$ We chose to employ electrophilic amine reagent 2a for our initial screening. We investigated common hydride reagents using BINAP (L1), a ligand previously shown to be effective toward our Cu-catalyzed asymmetric reduction chemistry (entry 1-3).$^{5a-c}$

**Table 1. Reaction Optimization**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu(OAc)$_2$</th>
<th>Hydride Reagent</th>
<th>L</th>
<th>Yield 4a$^a$</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 mol%</td>
<td>HBpin</td>
<td>L1</td>
<td>2%</td>
<td>nd$^b$</td>
</tr>
<tr>
<td>2</td>
<td>10 mol%</td>
<td>PMHS</td>
<td>L1</td>
<td>40%</td>
<td>-74%</td>
</tr>
<tr>
<td>3</td>
<td>10 mol%</td>
<td>DEMS</td>
<td>L1</td>
<td>64%</td>
<td>-73%</td>
</tr>
<tr>
<td>4</td>
<td>10 mol%</td>
<td>DEMS</td>
<td>L2</td>
<td>83%</td>
<td>-65%</td>
</tr>
<tr>
<td>5</td>
<td>10 mol%</td>
<td>DEMS</td>
<td>L3</td>
<td>99%</td>
<td>-95%</td>
</tr>
<tr>
<td>6</td>
<td>10 mol%</td>
<td>DEMS</td>
<td>L4</td>
<td>99%</td>
<td>79%</td>
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<tr>
<td>7</td>
<td>10 mol%</td>
<td>DEMS</td>
<td>L5</td>
<td>99%</td>
<td>97%</td>
</tr>
<tr>
<td>8$^c$</td>
<td>2 mol%</td>
<td>DEMS</td>
<td>L5</td>
<td>97%</td>
<td>97%</td>
</tr>
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$^a$GC yields with dodecane as the internal standard. $^b$Not determined. $^c$Reaction was carried out at 40 °C.
This study of hydride reagents showed silyl hydrides to be proficient for CuH generation, while borohydrides yielded only trace amounts of product (entry 1–3). We found that using polymethylhydosiloxane (PMHS), the hydride reagent shown to be superior for our copper-catalyzed asymmetric conjugate reduction chemistry, in combination with O-benzoyl-N,N-dibenzylhydroxylamine (2a), we were able to generate the desired Markovnikov addition product in good level of enantioselectivity, albeit in moderate yield after 36 hours (entry 2). We proposed that a more reactive hydride reagent could enhance the rate of transmetalation to regenerate the copper hydride species and consequently leads to an increase in reaction rate as well as allows for a decrease in catalyst and hydride reagent loading. Indeed, diethoxymethylsilane (DEMS) proved to be more reactive than its polymeric counterpart (PMHS) (entry 3). We were discouraged from examining more reactive hydride reagents such as trialkoxysilanes due to their tendency to disproportionate to the pyrophoric silane gas SiH₄.¹⁷

Next, we studied the effect of the ligands on the reaction efficiency as well as the enantioselectivities. When BINAP (L₁) was used as the supporting ligand, the reaction generated the desired product in 64% yield (entry 3). The yield was increased to 83% when p-Tol-BINAP (L₂) was employed. We found that near quantitative yields were achieved using BIPHEP-type ligand L₃ and SEGPHOS-type ligands L₄ and L₅. The enantiomeric excess of the product increased as the steric bulk of the supporting ligand was increased to the bulkier 3,5-t-Bu-MeOBIPHEP (L₃) (entry 5). The enantiomeric excess was also improved by switching from SEGPHOS (L₄) to a bulkier DTBM-SEPHOS ligand (L₅, entry 6 versus 7). Although the level of enantiomeric excess was similar for 3,5-t-Bu-MeOBIPHEP (L₃, entry 5) when compared to DTBM-SEGPHOS (L₅, entry 7), we pursued L₅ due to its lower cost. We believe that the larger ligand cone angle as a result of the ortho substituents on the phosphine provide a more restrictive chiral pocket, which was necessary for high levels of enantioselectivity.

Further optimization revealed that the reaction proceeded with low catalyst loading (2 mol%) at 40 °C (entry 8) without diminishing the yield or enantioselectivity. Regioselectivity was excellent as the reaction exclusively generated α-branched amines, consistent with our proposal that the hydride migration from the copper catalyst to the alkene would generate the more stable benzylic Cu species.¹²,¹³

With the optimized protocol in hand, we then explored the substrate scope with respect to the styrene component (Table 2). The hydroamination reaction tolerates a variety of electron
withdrawing substituents on styrene, including fluorides (3b), chlorides (3c), and trifluoromethyl groups (3d) as well as electron-donating groups (3f). The reaction also tolerates ortho-substituents (3e and 3e) and vinyl naphthalene (3g), albeit at a slightly diminished level of enantioselectivity.

As previously mentioned, a persisting challenge for late transition-metal catalyzed hydroamination is incompatibility with $\beta$-substitution.\textsuperscript{2j-l} Thus, we pursued the hydroamination of $\beta$-substituted styrenes. We found that the reaction works efficiently with both trans- and cis-$\beta$-substituted styrenes (3h–3o). However, trans-$\beta$-substituted styrenes afforded the desired products at higher levels of enantioselectivity than their cis counterparts. Additionally, we found that our system is compatible with hindered $\beta$-disubstituted styrenes with the desired product generated in high yield and ee (3p–3q). Notably, the hydroamination of $\beta$-disubstituted styrene 1q gave the product 3q as a single diastereomer.

We believed that under our Cu-catalyzed hydroamination strategy, $\beta$-substituents are tolerated as the reaction proceeds via a benzylic-Cu intermediate (Scheme 6). For the palladium-catalyzed approach as reported by Hartwig, Hii, and Lin (Scheme 1), a Wacker-type mechanism is proposed.\textsuperscript{2j-l} With this mechanism, an intermediate where palladium is bounded at the $\beta$-position is generated (Scheme 8). With the reaction going through $\beta$-Pd-bound intermediate i, it is expected that $\beta$-substituents could significantly impede the reaction of these substrates.
Table 2. Scope of Different Styrene Derivatives $^a$

![Chemical Structures](image)

<table>
<thead>
<tr>
<th>Substrate Scope: Styrenes</th>
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<tbody>
<tr>
<td><img src="image" alt="Chemical Structures" /></td>
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<td>3a</td>
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<th>Substrate Scope: $\beta$-Substituted Styrene</th>
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<th>Substrate Scope: $\beta$-Disubstituted Styrene</th>
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$^a$Isolated yields (average of two runs). 2 (1 mmol), O-benzoyl-$N,N$-dibenzylhydroxylamine (1.2 mmol), Cu(OAc)$_2$ (2 mol%), (R)-DTBM-SEGPHOS (2.2 mol%), diethoxymethylsilane (2 mmol), THF (0.5 M), 40 $^\circ$C, up to 36 h. $^b$Cu(OAc)$_2$ (4 mol%), (R)-DTBM-SEGPHOS (4.4 mol%). $^c$THF (1 M).
Scheme 8. Proposed Intermediate for Palladium-Catalyzed Approach

We next explored the use of other electrophilic amine reagents. It was observed that these conditions are amenable to several alkyl- and dialkyl-N-OBz amines (Table 3). N-(OBz)azepane (3t) and other heterocyclic-N-OBz (3s) amines also furnished the respective hydroamination products in high yields and enantiomeric selectivities.

**Table 3. Scope of Amine Electrophiles with Styrene**

<table>
<thead>
<tr>
<th>R'</th>
<th>R''</th>
<th>2 (1.2 equiv)</th>
<th>2 mol% Cu(OAc)$_2$</th>
<th>2.2 mol% (R)-DTBM-SEGPHOS</th>
<th>2.0 equiv Si(OEt)$_2$Me-H</th>
<th>THF (1 M), 40 °C, 36 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bn</td>
<td>NMe</td>
<td>3r$^b$</td>
<td>87% yield, 94% ee</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>3s</td>
<td>87% yield, 98% ee</td>
<td></td>
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</tr>
<tr>
<td>3t</td>
<td>Me</td>
<td>86% yield, &gt;99% ee</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3u</td>
<td>n-Bu</td>
<td>90% yield, 90% ee</td>
<td></td>
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</tr>
</tbody>
</table>

$^a$Isolated yields (average of two runs). 2 (1 mmol), O-benzoylhydroxylamine (1.2 mmol), Cu(OAc)$_2$ (2 mol %), (R)-DTBM-SEGPHOS (2.2 mol %), diethoxymethylsilane (2 mmol), THF (1 M), 40 °C, up to 36 h. $^b$THF (0.5 M).

As a demonstration of the robustness and practicality of this method, the hydroamination reaction was carried out at a 10-mmol scale (Scheme 9). We ran the reaction using ((E)-(3-
methoxyprop-1-en-1-yl)benzene) (1k) because β-substituted styrenes are known to be difficult substrates in asymmetric hydroamination reactions. We were able to lower the catalyst loading to 1 mol% with no decrease in yield or enantioselectivity of the desired product dibenzylamine 3k.

**Scheme 9. Large-scale Hydroamination Reaction of β-substituted Styrene**

![Scheme 9]

Since the hydroamination of unactivated alkenes remained a challenge, we next investigated the developed protocol with aliphatic alkenes. This began with the use of mono-substituted terminal aliphatic alkenes. These transformations were carried out under the conditions initially developed for the copper-catalyzed hydroamination of styrenes. Using readily available Cu(OAc)₂ and O-benzoylhydroxylamine 2a, we found that terminal aliphatic alkenes effectively underwent hydroamination reaction to afford alkyl amines (5) (Table 4).

As Table 4 illustrates, the reactions proceed to generate the anti-Markovnikov addition products exclusively. This protocol tolerated alkenes containing primary alkyl bromides (5e), epoxides (5g), sulfonamides (5d), amides (5e), pyridines (5f), and tert-butyldimethylsilyl ethers (5i). Additionally, we found that the reaction is compatible with geminally disubstituted aliphatic alkenes (5h and 5i). The compatibility of this methodology with 1,1-disubstituted alkenes was of paramount significance as this implied that this method could potentially be applied towards the synthesis of β-chiral amines.16
Table 4. Hydroamination of Terminal Aliphatic Alkenes 

<table>
<thead>
<tr>
<th>Alkyl</th>
<th>$\text{Bn} \cdot \text{N} \cdot \text{Bn}$</th>
<th>$\text{Bn} \cdot \text{N} \cdot \text{Bn}$</th>
<th>$\text{Bn} \cdot \text{N} \cdot \text{Bn}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{R}$</td>
<td></td>
<td>2 mol% Cu(OAc)$_2$</td>
<td>2 mol% Cu(OAc)$_2$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.2 mol% (±)-DTBM-SEGPHOS</td>
<td>2.2 mol% (±)-DTBM-SEGPHOS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.0 equiv Si(OME)$_3$Me-H</td>
<td>2.0 equiv Si(OME)$_3$Me-H</td>
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<tr>
<td></td>
<td></td>
<td>THF (0.5 M), 40 °C, 36 h</td>
<td>THF (0.5 M), 40 °C, 36 h</td>
</tr>
</tbody>
</table>

**We next explored the use of other amine electrophiles and found this reaction to tolerate several alkyl- and dialkyl-$\text{N} \cdot \text{OBz}$ amines (Table 5). Cyclic $\text{O}$-benzoylhydroxyamine (5k), as well as sterically hindered diisopropyl $\text{O}$-benzoylhydroxyamine (5l), and tetramethylpiperidine $\text{O}$-benzoylhydroxyamine (5m) furnished their respective anti-Markovnikov hydroamination products in high yield.**
Table 5. Scope of Amine Electrophiles with 4-Phenyl-1-butene

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>5j</td>
<td>92%</td>
</tr>
<tr>
<td>5k</td>
<td>99%</td>
</tr>
<tr>
<td>5l</td>
<td>97%</td>
</tr>
<tr>
<td>5m</td>
<td>80%</td>
</tr>
</tbody>
</table>

*Isolated yields (average of two runs). 2 (1 mmol), O-benzoylethoxylamine (1.2 mmol), Cu(OAc)$_2$ (2 mol %), (±)-DTBM-SEGPHOS (2.2 mol %), DEMS (2 mmol), THF (1 M), 40 °C, up to 36 h. "THF (0.5 M)."

Counter to the styrenes, our hypothesis for the observed anti-Markovnikov selectivity is that the hydride migration from the copper catalyst proceeds to form the less sterically crowded terminal copper intermediate as there is no electronic advantage to form the secondary alkyl-Cu intermediate (Scheme 6). Oxidative addition of the O-benzoylethoxylamine (2) and subsequent reductive elimination of this terminal organocuprate would generate the unbranched tertiary amine (5).

Scheme 6. Anti-Markovnikov Hydroamination of Aliphatic Alkenes
2.3 Conclusion

In summary, a copper-catalyzed hydroamination strategy applicable towards activated and unactivated olefins has been developed. We have reported a mild method for synthesizing chiral tertiary amines by employing an asymmetric copper-catalyzed hydroamination of styrenes. Substitution occurs in a regioselective manner to generate a C–N bond at the α-position of styrene derivatives. This method has been shown to be compatible with various substituents on the aryl ring as well as styrenes with β-substitution. Additionally, we have reported the first anti-Markovnikov hydroamination of unactivated olefins via a copper-catalyzed hydroamination strategy. This method tolerates a wide range of functional groups on the alkene and was compatible with heterocyclic as well as sterically hindered electrophilic amine reagents. Investigations into expanding the scope of this transformation towards the synthesis of β-chiral amines has been carried out in our lab. The optimization and development of this transformations towards additional classes of alkenes will be described in the following chapters.
2.4 Experimental

I. General Information

**General Reagent Information**

Unless otherwise stated, all reactions were set-up on the bench top and carried out under an argon atmosphere. All solvents were purified and dried by passage through successive alumina and Q5 reactant-packed columns on a solvent purification system. Diethoxymethylsilane was purchased from TCI America and stored under nitrogen at 4 °C in a Schlenk flask (diethoxymethylsilane is moisture sensitive, and proper Schlenk technique was used for handling this reagent. O-benzoyl-N,N-dialkylhydroxylamines were synthesized according to a published procedure. Styrene reagents, amines, benzoyl peroxide, and copper(I)acetate were purchased from Frontier Scientific, Combi-Blocks, GFS chemicals, Ark Pharm, Alfa Aesar, Sigma-Aldrich, or Strem Chemicals, and were used as received. DTBM-SEGPHOS (L5) was purchased from Takasago. Ligands L1 – L4 were purchased from Strem Chemicals. Compounds were purified using Silicycle SiliaFlashP60 (230-400 mesh) silica gel on a Biotage SP4 instrument.

**General Analytical Information**

All compounds (starting materials and products) were characterized by $^1$H NMR, $^{13}$C NMR, $^{19}$F NMR (when applicable), IR spectroscopy, melting point (when applicable), and elemental analysis or mass spectrometry. The $^1$H, $^{13}$C, and $^{19}$F NMR spectra can be found in Section III of the supporting information. $^1$H, $^{13}$C, $^{31}$P, and $^{19}$F NMR spectra were recorded on Varian 300 MHz, Varian 500 MHz or Bruker 400 MHz spectrometers. The spectra were calibrated according to residual solvent peaks (CDCl$_3$: 7.26 ppm for $^1$H NMR and 77.0 ppm for $^{13}$C NMR; CD$_2$Cl$_2$: 5.32 ppm for $^1$H NMR and 53.84 ppm for $^{13}$C NMR), or an internal reference (CF$_3$Ph: -63.7 ppm for $^{19}$F). The $^{13}$C, and $^{31}$P NMR spectra were obtained with $^1$H decoupling, and the $^{19}$F NMR spectra were obtained without $^1$H decoupling. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m= multiplet, br = broad, app = apparent. IR spectra were obtained on a Thermo Scientific iD5 ATR Nicolet iS5 FT-IR spectrometer. Elemental analyses were carried out by Atlantic Microlab, Inc., Norcross, GA. ESI-MS spectra were recorded on a Bruker Daltonics APEXIV 4.7 Tesla Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR-MS). Melting points (m.p.) were obtained on a Mel-Temp capillary melting point apparatus. Gas
chromatographic (GC) analyses were performed on an Agilent 7890A instrument (FID detector) using a J&W DB-1 column (10m, 0.1 mm I.D.). Reactions were monitored by GC and thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) or Fluka aluminum oxide/TLC-cards using UV light, I₂, or by treatment with a solution of phosphomolybdic acid in ethanol followed by heating to assist in visualization. High pressure liquid chromatography (HPLC) was performed on Hewlett-Packard 1100 Series chromatographs using a chiral column (25 cm) and guard column (5 cm) as noted for each compound. Optical rotations were measured on a Jasco P-1010 polarimeter with [α]₀ values reported in degrees; concentration (c) in g/100 mL. For N-(1-phenylethyl)amine (3r, u), the enantiomeric excesses were determined by ¹H NMR analysis using our previously published procedure.¹²
II. Experimental Procedures and Characterization Data

A) Cu-Catalyzed Hydroamination of Alkenes

**General Procedure for Cu-Catalyzed Hydroamination of Styrenes.**

Cu(OAc)$_2$ (3.6 mg, 2 mol%) and (R)-DTBM-SEGPHOS (25.9 mg, 2.2 mol%) were added to a screw-cap test tube. The tube was then sealed evacuated and backfilled with Argon. The process was repeated for a total of three times. Anhydrous THF (2.0 mL, 0.5 M) was added. The mixture was stirred for 15 min, then diethoxymethylsilane (270 mg, 320 µL, 2.0 equiv.) was added dropwise and the stirring was continued for another 10 min at rt before being added by a syringe to another screw-cap test tube containing styrene (104 mg, 1.0 mmol, 1.0 equiv.) and $O$-benzoyl-$N,N$-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv.). The reaction tube was stirred at 40°C for 36 h. Dodecane (100 µL) was added as the internal standard for GC analysis. The reaction mixture was diluted with EtOAc, quenched with saturated aqueous Na$_2$CO$_3$ solution, extracted with EtOAC, dried over Na$_2$SO$_4$, filtered through a pad of silica, concentrated, and purified by column chromatography on silica gel.

(S)-$N,N$-dibenzyl-1-phenylethan-1-amine (Table 2, entry 3a). Prepared following the general procedure using 2 mol% Cu(OAc)$_2$, 2.2% (R)-DTBM-SEGPHOS, styrene (104 mg, 1.0 mmol, 1.0 equiv.), $O$-benzoyl-$N,N$-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40°C. The reaction mixture was purified by flash chromatography on silica gel using 0-5% EtOAc in hexane to provide the title compound as a liquid in 95% and 86% yield.

IR (thin film) 3028, 2820, 1493, 1452, 1123, 1027, 742, 695 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.46 - 7.18 (m, 15H), 3.94 (q, $J$ = 6.9 Hz, 1H), 3.63 (d, $J$ = 14.0 Hz, 2H), 3.48 (d, $J$ = 13.6 Hz, 2H).
Hz, 2H), 1.46 (d, J = 6.9 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ: 142.86, 140.56, 128.77, 128.31, 128.15, 128.08, 126.85, 126.83, 56.30, 53.71, 13.91. HRMS (DART-TOF) calculated for C$_{22}$H$_{23}$N $[M+H]^+$ m/z 302.1903, found 302.1901. Anal. Calcd. for C$_{22}$H$_{23}$N: C, 87.66; H, 7.69. Found: C, 87.64; H, 7.79. [$\alpha$]$_D^{25}$ = -97.1 (c = 1.29, CHCl$_3$); HPLC analysis (OD-H, 3% IPA/hexane, 0.8 mL/min, 220 nm) indicated 97% ee: t$_R$ (major) = 4.8 minutes, t$_R$ (minor) = 5.4 minutes.

(S)-N$_2$N-dibenzy1-1-(4-fluorophenyl)ethan-1-amine (Table 2, entry 3b). Prepared following the general procedure using 2 mol% Cu(OAc)$_2$, 2.2% (R)-DTBM-SEGPHOS, 4-fluorostyrene (122.1 mg, 1.0 mmol, 1.0 equiv.), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 0-5% EtOAc in hexane to provide the title compound as a liquid in 86% and 85% yield. IR (thin film) 1602, 1506, 1453, 1221, 807, 740, 697 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.44 – 7.37 (m, 6H), 7.36 – 7.30 (m, 4H), 7.28 – 7.21 (m, 2H), 7.05 (t, J = 8.7 Hz, 2H), 3.93 (q, J = 6.9 Hz, 1H), 3.60 (d, J = 13.8 Hz, 2H), 3.49 (d, J = 13.8 Hz, 2H), 1.45 (d, J = 6.9 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ: 161.84 (d, J = 244.6 Hz), 140.37, 138.72 (d, J = 3.0 Hz), 129.54 (d, J = 7.8 Hz), 128.75, 128.36, 126.95, 114.80 (d, J = 20.9 Hz), 55.53, 53.60, 13.49; $^{19}$F NMR (376 MHz, CDCl$_3$) δ: -116.43; HRMS (ESI-TOF) calculated for C$_{22}$H$_{22}$FN $[M+H]^+$ m/z 320.1809, found 320.1807. Anal. Calcd. for C$_{26}$H$_{25}$FN: C, 82.72; H, 6.94. Found: C, 82.54; H, 6.82. [$\alpha$]$_D^{25}$ = -79.6 (c = 1.10, CHCl$_3$); HPLC analysis (OD-H, 5% IPA/hexane, 0.8 mL/min, 220 nm) indicated 97% ee: t$_R$ (major) = 4.8 minutes, t$_R$ (minor) = 5.5 minutes.

(S)-N$_2$N-dibenzy1-1-(2-chlorophenyl)ethan-1-amine (Table 2, entry 3c). Prepared following the general procedure using 2 mol% Cu(OAc)$_2$, 2.2% (R)-DTBM-SEGPHOS, 2-chlorostyrene (138.6 mg, 1.0 mmol, 1.0 equiv.), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 0-5% EtOAc in hexane to provide the title compound as a white solid in 79 % and 92%
yield. m.p. 67-68°C. IR (thin film, CHCl₃) 3025, 2802, 1493, 1453, 1367, 1035, 746, 696 cm⁻¹; 
¹H NMR (400 MHz, CDCl₃) δ: 7.78 (dd, J = 7.8, 1.7 Hz, 1H), 7.48 – 7.41 (m, 5H), 7.41 – 7.33 (m, 5H), 7.33 – 7.27 (m, 2H), 7.27 – 7.21 (m, 1H), 4.51 (q, J = 6.8 Hz, 1H), 3.84 (d, J = 14.1 Hz, 2H), 3.69 (d, J = 14.2 Hz, 2H), 1.45 (d, J = 6.8 Hz, 3H); 
¹³C NMR (101 MHz, CDCl₃) δ: 142.12, 140.30, 134.17, 129.84, 128.85, 128.14, 127.95, 126.77, 126.76, 56.79, 54.96, 18.15; 
[α]D²⁵ = +53.0 (c = 1.13, CHCl₃); HPLC analysis (OD-H, 3% IPA/hexane, 0.8 mL/min, 220 nm) indicated 92% ee: t_R (major) = 5.2 minutes, t_R (minor) = 5.8 minutes.

(3d)-N,N-dibenzyl-1-(4-(trifluoromethyl)phenyl)ethan-1-amine (Table 2, entry 3d). Prepared following the general procedure using 4 mol% Cu(OAc)₂, 4.4% (R)-DTBM-SEGPHOS, 4-(trifluoromethyl)styrene (172.2 mg, 1.0 mmol, 1.0 equiv), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 0-5% EtOAc in hexane to provide the title compound as a liquid in 92% and 84% yield. IR (thin film) 3028, 2973, 2804, 1323, 1162, 1120, 1069, 1016, 737, 696 1453, 1367, 1035, 843, 746, 696 cm⁻¹; 
¹H NMR (400 MHz, CDCl₃) δ: 7.72 – 7.64 (m, 2H), 7.64 – 7.58 (m, 2H), 7.50 – 7.43 (m, 4H), 7.42 – 7.35 (m, 4H), 7.35 – 7.29 (m, 2H), 4.05 (q, J = 6.8 Hz, 1H), 3.68 (d, J = 13.8 Hz, 2H), 3.58 (d, J = 13.8 Hz, 2H), 1.53 (d, J = 6.9 Hz, 3H); 
¹³C NMR (101 MHz, CDCl₃) δ: 147.45 (q, J = 1.3 Hz), 140.08, 129.07 (q, J = 32.2 Hz), 128.76, 128.45, 128.33, 127.09, 125.05 (q, J = 3.8 Hz), 124.52 (q, J = 272.7 Hz), 56.02, 53.76, 13.16; 
¹⁹F NMR (376 MHz, CDCl₃) δ: -62.11; HRMS (ESI-TOF) calculated for C₂₃H₂₂F₃N [M+H]+ m/z 370.1777, found 370.1775. Anal. Calcd. for C₂₃H₂₂F₃N: C, 74.78; H, 6.00. Found: C, 74.81; H, 6.14. [α]D²⁵ = -93.8 (c = 1.12, CHCl₃); HPLC analysis (OD-H, 3% IPA/hexane, 0.8 mL/min, 220 nm) indicated 95% ee: t_R (major) = 4.8 minutes, t_R (minor) = 6.5 minutes.
(S)-N,N-dibenzyl-1-(o-tolyl)ethan-1-amine (Table 2, entry 3e). Prepared following the general procedure using 2 mol% Cu(OAc)$_2$, 2.2% (R)-DTBM-SEGPHOS, 2-methylstyrene (118.2 mg, 1.0 mmol, 1.0 equiv.), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 0-5% EtOAc in hexane to provide the title compound as a white solid in 85% and 74% yield. m.p.: 83.5-84.0 °C. IR (thin film, CHCl$_3$) 3026, 2970, 2801, 1739, 1494, 1453, 1377, 741, 677 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.54 (d, $J = 7.5$ Hz, 1H), 7.33 – 7.29 (m, 8H), 7.28 – 7.18 (m, 3H), 7.18 – 7.15 (m, 2H), 4.14 (q, $J = 6.8$ Hz, 1H), 3.68 (d, $J = 13.6$ Hz, 2H), 3.63 (d, $J = 13.7$ Hz, 2H), 2.19 (s, 3H), 1.44 (d, $J = 6.8$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$: 142.22, 140.38, 137.27, 130.69, 129.15, 128.11, 127.19, 126.79, 126.68, 125.60, 54.95, 54.50, 19.55, 14.44; HRMS (ESI-TOF) calculated for C$_{23}$H$_{25}$N $[M+H]^+$ m/z 316.2060, found 316.2057. Anal. Calcd. for C$_{23}$H$_{25}$N: C, 87.57; H, 7.99. Found: C, 87.68; H, 7.96. $[^{[\alpha]}]_D^{25} = +34.8$ (c = 0.92, CHCl$_3$); HPLC analysis (OJ, 3% IPA/hexane, 0.8 mL/min, 220 nm) indicated 92% ee: $t_R$ (major) = 6.2 minutes, $t_R$ (minor) = 8.7 minutes.

(S)-N,N-dibenzyl-1-(4-methoxyphenyl)ethan-1-amine (Table 2, entry 3f). Prepared following the general procedure using 2 mol% Cu(OAc)$_2$, 2.2% (R)-DTBM-SEGPHOS, 4-vinylanisole (134.2 mg, 1.0 mmol, 1.0 equiv.), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 5-10% EtOAc in hexane to provide the title compound as a liquid in 89% and 88% yield. IR (thin film) 3025, 2960, 2833, 1510, 1244, 1176, 1028, 832, 739, 697 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.47 – 7.39 (m, 4H), 7.39 – 7.30 (m, 6H), 7.28 – 7.20 (m, 2H), 6.93 (d, $J = 8.7$ Hz, 2H), 3.92 (q, $J = 6.9$ Hz, 1H), 3.85 (s, 3H), 3.63 (d, $J = 13.8$ Hz, 2H), 3.49 (d, $J = 13.9$ Hz, 2H), 1.45 (d, $J = 6.9$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$: 158.46, 140.64, 134.84, 129.14, 128.74, 128.28, 126.81, 113.39, 55.55, 55.28, 53.58, 13.96; HRMS (DART-TOF) calculated for C$_{23}$H$_{25}$NO $[M+H]^+$ m/z 332.2009, found 332.2006. Anal. Calcd. for C$_{23}$H$_{25}$NO: C, 83.34; H, 7.60. Found: C, 83.28; H, 7.60. $[^{[\alpha]}]_D^{25} = -117.3$ (c = 0.93, CHCl$_3$); HPLC analysis (OJ, 10% IPA/hexane, 0.8 mL/min, 220 nm) indicated 99% ee: $t_R$ (major) = 6.3 minutes, $t_R$ (minor) = 8.7 minutes.
(S)-N,N-dibenzyl-1-(naphthalen-2-yl)ethanamine (Table 3, entry 3g).

Prepared following the general procedure using 2 mol% Cu(OAc)$_2$, 2.2% (R)-DTBM-SEGPHOS, 2-vinyl naphthalene (154 mg, 1.0 mmol, 1.0 equiv.), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 0-5% EtOAc in hexane to provide the title compound as a colorless crystal in 83% and 89% yield. m. p. 123~124 °C. IR (thin film) 3057, 3024, 2968, 1500, 1453, 1379, 1224, 857, 819, 582, 579, 560, 557 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.90 (dd, $J = 7.6, 3.3$ Hz, 3H), 7.85 - 7.80 (m, 1H), 7.72 (dd, $J = 8.5, 1.7$ Hz, 1H), 7.56 - 7.50 (m, 2H), 7.48 (m, 4H), 7.38 (m, 4H), 7.32 - 7.26 (m, 2H), 4.16 (q, $J = 6.8$ Hz, 1H), 3.70 (d, $J = 13.6$ Hz, 2H), 3.63 (d, $J = 13.6$ Hz, 2H), 1.61 (d, $J = 6.8$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ: 140.83, 140.52, 133.28, 132.71, 128.86, 128.34, 128.02, 127.67, 127.31, 126.91, 126.10, 125.94, 125.64, 56.35, 53.76, 13.24. HRMS (DART-TOF) calculated for C$_{26}$H$_{25}$N [M+H$^+$] m/z 352.2060, found 352.2059. Anal. Calcd. for C$_{26}$H$_{25}$N: C, 87.57; H, 7.99. Found: C, 87.45; H, 8.16. [α]$_D^{25}$ = -149.63 (c = 1.00, CHCl$_3$); HPLC analysis (OJ, 10% IPA/hexane, 0.8 mL/min, 220 nm) indicated 97% ee: $t_R$ (major) = 10.9 minutes, $t_R$ (minor) = 36.2 minutes.

(S)-N,N-dibenzyl-1-phenylpropan-1-amine (Table 2, entry 3h & 3l).

Prepared following the general procedure using 2 mol% Cu(OAc)$_2$, 2.2% (R)-DTBM-SEGPHOS, trans-β-methyl styrene or cis-β-methyl styrene (118.2 mg, 1.0 mmol, 1.0 equiv.), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 0-5% EtOAc in hexane to provide the title compound as a liquid. 97% and 98% yields from trans-β-methyl styrene; 89% and 87% from cis-β-methyl styrene. IR (thin film) 3025, 2960, 2930, 2800, 1493, 1452, 1027, 739, 695 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.47 - 7.39 (m, 6H), 7.35 (t, $J = 7.5$ Hz, 5H), 7.30 - 7.23 (m, 4H), 3.87 (d, $J = 13.8$ Hz, 2H), 3.64 (t, $J = 7.5$ Hz, 1H), 3.20 (d, $J = 13.9$ Hz, 2H), 2.12 (dt, $J = 13.7$, 7.3 Hz, 1H), 1.96 - 1.75 (m, 1H), 0.97 (t, $J = 7.3$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ:
140.56, 139.08, 129.07, 128.80, 127.95, 126.98, 126.75, 63.83, 53.74, 24.31, 11.81; HRMS (DART-TOF) calculated for C_{23}H_{25}N [M+H]^+ m/z 316.2060, found 316.2053. Anal. Calcd. for C_{23}H_{25}N: C, 87.57; H, 7.99. Found: C, 87.45; H, 8.16. \([\alpha]_D^{25} = -112.9 \text{ (c = 1.19, CHCl}_3\); HPLC analysis (OD-H, 5% IPA/hexane, 0.8 mL/min, 220 nm) indicated >99% ee (from trans-), 96% ee (from cis-): \(t_R\) (major) = 4.8 minutes, \(t_R\) (minor) = 5.6 minutes.

\(1,2\)-diphenylethan-1-amine (Table 2, entry 3i & 3m). Prepared following the general procedure using 2 mol\% Cu(OAc)\(_2\), 2.2\% \((R)\)-DTBM-SEGPHOS, trans-stilbene or cis-stilbene (180.2 mg, 1.0 mmol, 1.0 equiv.), \(O\)-benzoyl-\(N\)-\(N\)-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 0-5% EtOAc in hexane to provide the title compound as a white solid. 95% and 94% yields from trans-stilbene; 93% and 93% from cis-stilbene. m. p. 73.5-74.0 °C. IR (thin film, CHCl\(_3\)) 3025, 1493, 1452, 1028, 740, 695 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.43 (t, \(J = 7.7\) Hz, 2H), 7.38 – 7.21 (m, 16H), 7.14 (d, \(J = 7.7\) Hz, 2H), 4.11 (t, \(J = 7.7\) Hz, 1H), 3.94 (d, \(J = 13.9\) Hz, 2H), 3.44 (dd, \(J = 14.0\), 8.4 Hz, 1H), 3.25 (d, \(J = 14.0\) Hz, 2H), 3.13 (dd, \(J = 14.0\), 6.9 Hz, 1H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\): 140.10, 139.96, 138.57, 129.69, 129.17, 128.76, 128.28, 128.13, 128.07, 127.26, 126.83, 126.04, 63.32, 53.69, 37.75; HRMS (DART-TOF) calculated for C\(_{28}\)H\(_{27}\)N [M+H]^+ m/z 378.2216, found 378.2203. Anal. Calcd. for C\(_{28}\)H\(_{27}\)N: C, 89.08; H, 7.21. Found: C, 89.13; H, 7.29. \([\alpha]_D^{25} = -55.7 \text{ (c = 0.97, CHCl}_3\); HPLC analysis (OD-H, 5% IPA/hexane, 0.8 mL/min, 220 nm) indicated >99% ee (from trans-), 88% ee (from cis): \(t_R\) (major) = 5.2 minutes, \(t_R\) (minor) = 6.5 minutes.

(S)-N,N-dibenzyl-1-(4-methoxyphenyl)propan-1-amine (Table 2, entry 3j). Prepared following the general procedure using 2 mol\% Cu(OAc)\(_2\), 2.2\% \((R)\)-DTBM-SEGPHOS, trans-anethole (148.2 mg, 1.0 mmol, 1.0 equiv.), \(O\)-benzoyl-\(N\)-\(N\)-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 0-5% EtOAc in hexane to provide the title compound as a
colorless liquid in 91% and 92% yield. IR (thin film) 2932, 2832, 1510, 1453, 1247, 1178, 1037, 826, 741, 697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.56 – 7.46 (m, 4H), 7.45 – 7.35 (m, 4H), 7.35 – 7.27 (m, 2H), 7.27 – 7.20 (m, 2H), 7.04 – 6.95 (m, 2H), 3.91 (d, J = 13.9 Hz, 2H), 3.91 (s, 3H), 3.66 (t, J = 7.5 Hz, 1H), 3.25 (d, J = 13.9 Hz, 2H), 2.16 (dt, J = 13.7, 7.3 Hz, 1H), 1.95 – 1.78 (m, 1H), 1.02 (t, J = 7.3 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ: 158.60, 140.70, 131.22, 130.09, 128.84, 128.29, 126.78, 113.34, 63.17, 55.29, 53.75, 24.55, 11.91; HRMS (DART-TOF) calculated for C₂₄H₂₇NO [M+H⁺] m/z 346.2165, found 346.2171. Anal. Calcd. for C₂₄H₂₇NO: C, 83.44; H, 7.88. Found: C, 83.58; H, 7.82. [α]D²⁵ = −137.0 (c = 1.95, CHCl₃); HPLC analysis (OJ, 10% EtOH/hexane, 0.8 mL/min, 220 nm) indicated >99% ee: tR (major) = 8.3 minutes, tR (minor) = 23.6 minutes.

(S)-N,N-dibenzyl-3-methoxy-1-phenylpropan-1-amine (Table 2, entry 3k). Prepared following the general procedure using 2 mol% Cu(OAc)₂, 2.2% (R)-DTBM-SEGPHOS, (E)-(3-methoxyprop-1-en-1-yl)benzene (148.2 mg, 1.0 mmol, 1.0 equiv.), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40 ºC. The reaction mixture was purified by flash chromatography on silica gel using 0-5% EtOAc in hexane to provide the title compound as a colorless liquid in 94% and 95% yield. IR (thin film) 2932, 2832, 1493, 1452, 1113, 739, 696 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.50 – 7.42 (m, 6H), 7.42 – 7.35 (m, 3H), 7.34 – 7.26 (m, 4H), 4.00 – 3.85 (m, 3H), 3.56 – 3.47 (m, 2H), 3.33 (d, J = 0.9 Hz, 3H), 3.23 (d, J = 13.8 Hz, 2H), 2.45 (ddd, J = 13.9, 7.6, 6.4 Hz, 1H), 2.21 – 1.96 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ: 140.32, 138.49, 129.05, 128.85, 128.33, 128.10, 127.26, 126.90, 70.58, 58.94, 58.59, 53.82, 31.61; HRMS (DART-TOF) calculated for C₂₄H₂₇NO [M+H⁺] m/z 346.2165, found 346.2162. Anal. Calcd. for C₂₄H₂₇NO: C, 83.44; H, 7.88. Found: C, 83.17; H, 8.02. [α]D²⁵ = −89.9 (c = 0.91, CHCl₃); HPLC analysis (OD-H, 3% IPA/hexane, 0.8 mL/min, 220 nm) indicated 98% ee (for 1 mmol scale), 99% ee (for 10 mmol scale): tR (major) = 6.0 minutes, tR (minor) = 6.7 minutes.

(S)-N,N-dibenzyl-2,3-dihydro-1H-inden-1-amine (Table 2, entry 3n). Prepared following the general procedure using 2 mol% Cu(OAc)₂, 2.2% (R)-
DTBM-SEGPHOS, s indene (116.2 mg, 1.0 mmol, 1.0 equiv), O-benzoyl-N,N-
dibenzyldihydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), THF 2 mL for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 0-5% EtOAc in hexane to provide the title compound as a white solid in 95% and 73% yield. m. p. 89-90 °C. IR (thin film) 3024, 2934, 2798, 1493, 1452, 1117, 1027, 742, 696 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.71–7.59 (m, 1H), 7.56 (m, 4H), 7.40 (m, 4H), 7.33–7.19 (m, 2H), 4.57 (t, J = 7.8 Hz, 1H), 3.67 (d, J = 13.6 Hz, 2H), 3.50 (d, J = 13.6 Hz, 2H), 3.03 (t, J = 16.1, 6.4 Hz, 1H), 2.86 (dt, J = 16.3, 8.5 Hz, 1H), 2.21 (tdd, J = 8.3, 6.4, 1.7 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ: 144.51, 143.69, 140.47, 128.66, 128.33, 127.39, 126.88, 126.48, 124.72, 124.62, 64.65, 54.31, 30.61, 23.46; HRMS (DART-TOF) calculated for C₂₃H₂₃N [M+H⁺] m/z 314.1903, found 314.1902. Anal. Calcd. for C₂₃H₂₃N: C, 88.13; H, 7.40. Found: C, 87.84; H, 7.31. 

(S)-N,N-dibenzyl-1,2,3,4-tetrahydropyren-1-amine (Table 2, entry 3o).

Prepared following the general procedure using 2 mol% Cu(OAc)₂, 2.2% (R)-
DTBM-SEGPHOS, 1,2-dihydronaphthalene (130.2 mg, 1.0 mmol, 1.0 equiv),
O-benzoyl-N,N-dibenzyldihydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), THF (2
mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 0-5% EtOAc in hexane to provide the title compound as a colorless liquid in 92% and 82% yield. IR (thin film) 2928, 1493, 1452, 1366, 1121, 1027, 973, 740, 696 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 8.07 (dt, J = 7.8, 1.2 Hz, 1H), 7.53 (d, J = 7.3 Hz, 4H), 7.38 (dd, J = 8.2, 6.9 Hz, 4H), 7.32–7.22 (m, 3H), 7.17 (tt, J = 7.3, 1.1 Hz, 1H), 7.09 (d, J = 7.9 Hz, 1H), 4.00 (dd, J = 10.2, 5.7 Hz, 1H), 3.87 (d, J = 13.6 Hz, 2H), 3.54 (d, J = 13.6 Hz, 2H), 2.91–2.66 (m, 2H), 2.32–2.14 (m, 1H), 2.06 (dt, J = 13.7, 5.6, 3.1 Hz, 1H), 1.85 (tdd, J = 12.5, 10.1, 2.8 Hz, 1H), 1.76–1.58 (m, 1H); ¹³C NMR (101 MHz, CDCl₃) δ: 140.51, 139.20, 138.84, 128.76, 128.69, 128.34, 128.10, 126.88, 126.22, 126.02, 56.45, 53.77, 30.27, 22.37, 20.67; HRMS (DART-TOF) calculated for C₂₄H₂₅N [M+H⁺] m/z 328.2060, found 328.2068. Anal. Calcd. for C₂₄H₂₅N: C, 88.03; H, 7.70. Found: C, 87.77; H, 7.74. [α]D° = -77.0 (c = 1.09, CHCl₃); HPLC analysis (OJ, 3% IPA/hexane, 0.8 mL/min, 220 nm) indicated 86% ee: tR (major) = 5.8 minutes, tR (minor) = 7.6 minutes.
(S)-N,N-dibenzyl-2-methyl-1-phenylpropan-1-amine (Table 2, entry 3p). Prepared following the general procedure using 2 mol% Cu(OAc)$_2$, 2.2% (R)-DTBM-SEGPHOS, 2-methyl-1-phenylpropene (132.2 mg, 1.0 mmol, 1.0 equiv), O-benzoyl-N,N-dibenzyldihydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 0-5% EtOAc in hexane to provide the title compound as a colorless liquid in 77% and 76% yield. IR (thin film) 3025, 2955, 1493, 1452, 1092, 1069, 1121, 1028, 761, 696 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.47 (d, $J = 7.6$ Hz, 4H), 7.42 (t, $J = 7.3$ Hz, 2H), 7.35 (t, $J = 7.5$ Hz, 5H), 7.29 – 7.22 (m, 2H), 7.15 (d, $J = 6.9$ Hz, 2H), 3.93 (d, $J = 13.8$ Hz, 2H), 3.22 (d, $J = 10.9$ Hz, 1H), 3.00 (d, $J = 13.9$ Hz, 2H), 2.54 – 2.35 (m, 1H), 1.31 (d, $J = 6.5$ Hz, 3H), 0.63 (d, $J = 6.5$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$: 140.45, 137.03, 129.68, 128.89, 128.37, 127.91, 126.97, 126.82, 69.37, 53.68, 28.68, 21.29, 20.92; HRMS (DART-TOF) calculated for C$_{24}$H$_{21}$N [M+H$^+$] m/z 330.2216, found 330.2216. Anal. Calcd. for C$_{24}$H$_{25}$N: C, 87.49; H, 8.26. Found: C, 87.29; H, 8.43. $[\alpha]_D$ $^{25}$ $= -114.5$ (c = 1.14, CHCl$_3$); HPLC analysis (OD-H, 5% IPA/hexane, 0.8 mL/min, 220 nm) indicated >99% ee, single isomer: $t_R$ (major) = 4.7 minutes, $t_R$ (minor) = 6.1 minutes.

(1S,2R)-N,N-dibenzyl-3-((tert-butyldimethylsilyl)oxy)-2-methyl-1-phenylpropan-1-amine (Table 2, entry 3q). Prepared following the general procedure using 2 mol% Cu(OAc)$_2$, 2.2% (R)-DTBM-SEGPHOS, (E)-tert-butyldimethyl((2-methyl-3-phenylallyl)oxy)silane (262.5 mg, 1.0 mmol, 1.0 equiv), O-benzoyl-N,N-dibenzyldihydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 0-5% EtOAc in hexane to provide the title compound as a colorless solid in 84% and 82% yield. m. p. 93–94 °C. IR (thin film) 2955, 2927, 2855, 1494, 1453, 1257, 1084, 834, 763, 698 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.45 – 7.37 (m, 6H), 7.37 – 7.30 (m, 5H), 7.29 – 7.21 (m, 2H), 7.20 – 7.13 (m, 2H), 4.49 (dd, $J = 9.8$, 3.9 Hz, 1H), 3.93 (d, $J = 13.9$ Hz, 2H), 3.54 – 3.33 (m, 2H), 3.01 (d, $J = 13.9$ Hz, 2H), 2.60 – 2.44 (m, 1H), 0.97 (s, 9H), 0.66 (d, $J = 6.5$ Hz, 3H), 0.12 (d, $J = 5.2$ Hz, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$: 140.05, 135.91, 129.73, 128.72, 128.29, 127.87, 127.04, 126.80, 66.74, 65.63, 53.70, 36.07, 26.14, 18.55, 15.68, -5.13, -5.17.
HRMS (DART-TOF) calculated for C_{30}H_{41}NOSi [M+H]^+ m/z 460.3030, found 460.3026. Anal. Calcd. for C_{30}H_{41}NOSi: C, 78.38; H, 8.99. Found: C, 78.54; H, 9.01. [α]_D^{25} = -73.5 (c = 0.86, CHCl_3); HPLC analysis (OD-H, 3% IPA/hexane, 0.8 mL/min, 220 nm) indicated >99% ee, single isomer: t_R (major) = 4.3 minutes, t_R (minor) = 4.9 minutes.

(S)-N-benzyl-N-methyl-1-phenylethanamine (Table 3, entry 3r). Prepared following the general procedure using 2 mol% Cu(OAc)\textsubscript{2}, 2.2% (R)-DTBM-SEGPHOS, styrene (104 mg, 1.0 mmol, 1.0 equiv), O-benzoyl-N-benzyl-N-methylhydroxylamine (290 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 0-5% EtOAc in hexane to provide the title compound as a colorless liquid crystal in 90% and 84% yield. IR (thin film) 2971, 2784, 1494, 1451, 1028, 761, 735, 698 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ: 7.44 (m, 2H) 7.42 – 7.22 (m, 8H), 3.69 – 3.64 (q, J = 6.7 Hz, 1H), 3.63 – 3.59 (d, J = 13.3 Hz, 1H), 3.35 – 3.32 (d, J = 13.3 Hz, 1H), 2.16 (s, 3H), 1.46 – 1.44 (d, J = 6.7 Hz, 3H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ: 128.89, 128.31, 128.3, 127.8, 126.9, 126.9, 63.4, 59.0, 38.5, 18.5; HRMS (DART-TOF) calculated for C\textsubscript{16}H\textsubscript{19}N [M+H]^+ m/z 226.1590, found 226.1582. Anal. Calcd. for C\textsubscript{16}H\textsubscript{19}N: C, 82.70; H, 11.28. Found: C, 82.64; H, 11.28. [α]_D^{25} = -15.3 (c = 1.02, CHCl\textsubscript{3}); \textsuperscript{1}H NMR analysis of the amine and (R) and (S)-O-acetylmandelic acid indicated 94% ee.

(S)-4-(1-phenylethyl)morpholine (Table 3, entry 3s). Prepared following the general procedure using 2 mol% Cu(OAc)\textsubscript{2}, 2.2% (R)-DTBM-SEGPHOS, styrene (104 mg, 1.0 mmol, 1.0 equiv), morpholino benzoate (207.23 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 0-5% EtOAc in hexane to provide the title compound as a liquid in 88% and 85% yield. IR (thin film) 2957, 2851, 2803, 1450, 1116, 946, 865, 759, 700 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ: 7.39 – 7.31 (m, 4H), 7.29 – 7.23 (m, 1H), 3.72 (dd, J = 5.3, 4.1 Hz, 4H), 3.33 (q, J = 6.7 Hz, 1H), 2.62 – 2.45 (m, 2H), 2.45 – 2.30 (m, 2H), 1.38 (d, J = 6.7 Hz, 3H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ: 144.05, 128.33, 127.61, 127.00, 67.22, 65.40, 51.37, 19.96; HRMS (DART-TOF) calculated for C\textsubscript{12}H\textsubscript{17}NO [M+H]^+ m/z 192.1383, found 192.1381. Anal. Calcd. for C\textsubscript{12}H\textsubscript{17}NO: C, 75.35; H, 8.96. Found:
C, 75.09; H, 8.81. [α]D24 = -36.5 (c = 0.98, CHCl3); [α]D25 = -41.0 (c = 1.10, EtOH); Literature [α]D25 = -41.6 (c = 1.10, EtOH). \( \text{ee} > 98\% \). GC condition: Varian CP7502 column (25 m × 0.25 mm × 0.25 μm, chiralsil-DEX CB), H2 2.7 mL/min, programmed from 100 °C to 125 °C at 0.5 °C/min; \( t_R \) (minor) = 28.41 min, and \( t_R \) (major) = 29.24 min.

(5)-1-(1-phenylethyl)azepane (Table 3, entry 3t). Prepared following the general procedure using 2 mol% Cu(OAc)2, 2.2% (R)-DTBM-SEGPHOS, styrene (104 mg, 1.0 mmol, 1.0 equiv), azepan-1-yl benzoate (219 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 20–50% EtOAc in hexane to provide the title compound as a liquid in 86% yield for both runs. IR (thin film) 2922, 1492, 1451, 1128, 909, 762, 697 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl3) \( \delta \): 7.43–7.37 (m, 2H), 7.37–7.30 (m, 2H), 7.28–7.21 (m, 1H), 3.80 (q, \( J = 6.7 \) Hz, 1H), 2.66 (s, 4H), 1.62 (s, 8H), 1.39 (d, \( J = 6.7 \) Hz, 3H); \(^{13}\)C NMR (126 MHz, CDCl3) \( \delta \): 144.94, 127.95, 127.60, 126.46, 63.21, 52.06, 28.96, 27.07, 18.26; HRMS (DART-TOF) calculated for C14H21N [M+H]⁺ m/z 204.1747, found 204.1745. Anal. Calcd. for C14H21N: C, 82.70; H, 10.41. Found: C, 82.58; H, 10.47. [α]D25 = +6.5 (c = 1.10, CHCl3); ee > 99%. GC condition: Varian CP7502 column (25 m × 0.25 mm × 0.25 \( \mu \)m, chiralsil-DEX CB), H2 2.7 mL/min, programmed from 100 °C to 125 °C at 0.5 °C/min; \( t_R \) = 35.2 min (minor) and \( t_R \) = 35.8 min (major).

(5)-N-butyl-N-(1-phenylethyl)butan-1-amine (Table 3, entry 3u). Prepared following the general procedure using 2 mol% Cu(OAc)2, 2.2% (R)-DTBM-SEGPHOS, styrene (104 mg, 1.0 mmol, 1.0 equiv), 0-benzoyl-N,N-dibutylhydroxylamine (249 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40 °C. The reaction mixture was quenched with Na2CO₃ solution, and the crude product extracted with ethyl acetate (x3) (NB: This step is necessary to remove N-OBz compounds). The reaction was then purified by an acid-base treatment, where the amine was first protonated with dilute HCl solution and the aqueous layer washed with ethyl acetate (x1), then treated with 1 M NaOH to deprotonate the amine. The aqueous layer was then extracted with EtOAc (x3), and the organic combined and concentrated to give the pure product as a yellow liquid in 90% yields (for both runs). IR (thin film) 2955, 2929, 2871, 1452, 1367, 1081, 776, 759, 697, 553
cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.42 (m, 2H), 7.39 - 7.31 (m, 2H), 7.30 - 7.22 (m, 1H), 3.90 (q, $J = 6.8$ Hz, 1H), 2.58 - 2.47 (m, 2H), 2.42 (m, 2H), 1.54 - 1.41 (m, 4H), 1.38 (m, 3H), 1.36 - 1.18 (m, 4H), 0.92 (t, $J = 7.3$ Hz, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$: 145.00, 127.89, 127.76, 126.39, 58.96, 49.65, 30.0, 20.62, 16.49, 14.14; HRMS (DART-TOF) calculated for C$_{24}$H$_{21}$N [M+H]$^+$ m/z 334.2216, found 334.2209. Anal. Calcd. for C$_{16}$H$_{21}$N: C, 83.76; H, 11.10. Found: C, 83.63; H, 11.28. $[\alpha]_D^{25} = +2.9$ (c = 0.57, CHCl$_3$); $^1$H NMR analysis of the amine and ($R$) and (S)-O-acetylmandelic acid indicated 90% ee.
B) Cu-Catalyzed Hydroamination of Alkenes

General Procedure for Cu-Catalyzed Hydroamination of Aliphatic Alkenes.

Cu(OAc)$_2$ (3.6 mg, 2 mol%) and (+)-DTBM-SEGPHOS (25.9 mg, 2.2 mol%) were added to a screw-cap test tube. The tube was then sealed evacuated and backfilled with Argon. The process was repeated for a total of three times. Anhydrous THF (2.0 mL, 0.5 M) was added. The mixture was stirred for 15 min, then diethoxymethylsilane (270 mg, 320 µL, 2.0 equiv) was added dropwise and the stirring was continued for another 10 min at rt before being added by a syringe to another screw-cap test tube containing styrene (104 mg, 1.0 mmol, 1.0 equiv) and O-benzoyl-N, N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv). The reaction tube was stirred at 40°C for 36 h. Dodecane (100 µL) was added as the internal standard for GC analysis. The reaction mixture was diluted with EtOAc, quenched with saturated aqueous Na$_2$CO$_3$ solution, extracted with EtOAc, dried over Na$_2$SO$_4$, filtered through a pad of silica, concentrated, and purified by column chromatography on silica gel.

$N,N$-dibenzyl-4-phenylbutan-1-amine (Table 4, entry 5a). Prepared following the general procedure using 2 mol% Cu(OAc)$_2$, 2.2% (+)-DTBM-SEGPHOS, but-3-en-1-ylbenzene (132.2 mg, 1.0 mmol, 1.0 equiv), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 0-5% Ether in hexane to provide the title compound as a colorless liquid in 90% and 87% yield. IR (thin film) 2933, 2792, 1494, 1451, 1125, 1027, 732 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.51 – 7.09 (m, 15H), 3.61 (s, 4H), 2.58 (t, $J$ = 7.4 Hz, 2H), 2.51 (t, $J$ = 6.8 Hz, 2H), 1.74 – 1.58 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ: 142.74, 140.10, 128.91, 128.52, 128.34, 128.27, 126.87, 125.71, 58.47, 53.20, 35.73, 29.00, 26.65; HRMS
(DART-TOF) calculated for C_{24}H_{27}N [M+H]^+ m/z 330.2216, found 330.2215. Anal. Calcd. for C_{24}H_{27}N: C, 87.49; H, 8.26. Found: C, 87.48; H, 8.27.

\[ \text{Bn} \]
\[ \text{I} \]
\[ \text{N,N-dibenzyldodecan-1-amine (Table 4, entry 5b). Prepared following the general procedure using 2 mol\% Cu(OAc)\_2, 2.2\% (±)-DTBM-SEGPHOS, dodec-1-ene (168.3 mg, 1.0 mmol, 1.0 equiv), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 0-5% EtOAc in hexane to provide the title compound as a colorless liquid in 94% and 95% yield. IR (thin film) 2922, 2852, 1494, 1452, 1028, 734, 696 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta: 7.60 - 7.09\) (m, 10H), 3.58 (s, 4H), 2.43 (t, \(J = 7.2\) Hz, 2H), 1.67 – 1.42 (m, 2H), 1.41 – 1.09 (m, 18H), 0.92 (t, \(J = 6.8\) Hz, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta: 140.11, 128.79, 128.13, 126.71, 58.29, 53.43, 31.97, 29.71, 29.68\) (3C), 29.54, 29.40, 27.29, 27.00, 22.74, 14.17; HRMS (Dart-TOF) calculated for C\(_{24}\)H\(_{39}\)N [M+H]^+ m/z 366.3155, found 366.3147. Anal. Calcd. for C\(_{26}\)H\(_{39}\)N: C, 85.42; H, 10.75. Found: C, 85.40; H, 10.78.

\[ \text{Bn} \]
\[ \text{Br} \]
\[ \text{N,N-dibenzyl-10-bromodecan-1-amine (Table 4, entry 5c). Prepared following the general procedure using 2 mol\% Cu(OAc)\_2, 2.2\% (±)-DTBM-SEGPHOS, 10-bromo-1-decene (219.2 mg, 1.0 mmol, 1.0 equiv), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 5-10% Ethyl acetate in hexane to provide the title compound as a colorless liquid in 89% and 90% yield. IR (thin film) 2925, 2853, 1494, 1452, 742, 696 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta: 7.44 - 7.38\) (m, 4H), 7.34 (t, \(J = 7.4\) Hz, 4H), 7.28 (s, 2H), 3.58 (s, 4H), 3.44 (t, \(J = 6.8\) Hz, 2H), 2.43 (t, \(J = 7.2\) Hz, 2H), 1.84 – 1.90 (m, 2H), 1.59 – 1.48 (m, 2H), 1.48 – 1.37 (m, 2H), 1.37 – 1.17 (m, 10H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta: 140.10, 128.81, 128.18, 126.76, 58.38, 53.42, 34.06, 32.91, 29.58, 29.50, 29.48, 28.83, 28.25, 27.28, 27.06; HRMS (DART-TOF) calculated for C\(_{24}\)H\(_{34}\)NBr [M+H]^+ m/z 416.1947, found 416.1943. Anal. Calcd. for C\(_{24}\)H\(_{34}\)NBr: C, 69.22; H, 8.23. Found: C, 69.51; H, 8.13.

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**N-benzyl-N-(5-(dibenzylamino)pentyl)-4-methylbenzenesulfonamide**  
(Table 4, entry 5d). Prepared following the general procedure using 2 mol% Cu(OAc)$_2$, 2.2% (±)-DTBM-SEGPHOS, N-benzyl-4-methyl-N-(pent-4-en-1-yl)benzenesulfonamide (329.5 mg, 1.0 mmol, 1.0 equiv), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 10-15% EtOAc in hexane (contain 0.5% TEA) to provide the title compound as a colorless liquid in 95% and 95% yield. IR (thin film) 2932, 1494, 1338, 1155, 1090, 734 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.73 (m, 2H), 7.46 - 7.14 (m, 17H), 4.29 (s, 2H), 3.50 (s, 4H), 3.16 - 2.95 (t, $J$ = 7.6 Hz, 2H), 2.45 (s, 3H), 2.29 (t, $J$ = 7.2 Hz, 2H), 1.42 - 1.19 (m, 4H), 1.17 - 0.96 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ: 143.13, 139.93, 137.17, 136.66, 129.69, 128.74, 128.52, 128.25, 128.17, 127.70, 127.19, 126.78, 58.27, 53.18, 51.92, 48.11, 27.87, 26.53, 24.31, 21.55; HRMS (DART-TOF) calculated for C$_{33}$H$_{39}$N$_2$O$_2$S $[M+H]^+$ m/z 527.2727, found 527.2738.

**6-(dibenzylamino)-1-(indolin-1-yl)hexan-1-one** (Table 4, entry 5e). Prepared following the general procedure using 2 mol% Cu(OAc)$_2$, 2.2% (±)-DTBM-SEGPHOS, 1-(indolin-1-yl)hex-5-en-1-one (215.3 mg, 1.0 mmol, 1.0 equiv), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 15-20% EtOAc in hexane (contain 0.5% TEA) to provide the title compound as a colorless liquid in 85% and 91% yield. IR (thin film) 2932, 1658, 1598, 1481, 1404, 1262, 747, 697 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ: 8.29 (d, $J$ = 8.1 Hz, 1H), 7.41 (d, $J$ = 7.3 Hz, 4H), 7.34 (t, $J$ = 7.5 Hz, 4H), 7.30 - 7.17 (m, 4H), 7.09 - 6.99 (m, 1H), 4.01 (t, $J$ = 8.5 Hz, 1.78 H) & 4.17 (m, 0.22 H) due to rotamer, 3.61 (s, 4H), 3.20 (t, $J$ = 8.5 Hz, 1.78 H) & 3.07 (m, 0.22H) due to rotamer, 2.49 (t, $J$ = 7.2 Hz, 2H), 2.38 (t, $J$ = 7.5 Hz, 1.78H) & 2.65 (m, 0.22H) due to rotamer, 1.79 - 1.66 (m, 2H), 1.66 - 1.53 (m, 2H), 1.47 - 1.35 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ: 171.40, 143.20, 140.02, 131.09, 128.87, 128.23, 127.60, 126.84, 124.55, 123.51, 117.06, 58.44, 53.43, 48.03, 35.97, 28.10, 27.12, 27.04, 24.55; HRMS (DART-TOF) calculated for C$_{28}$H$_{32}$N$_2$O $[M+H]^+$ m/z 413.2587, found 413.2595. Anal. Calcd. for C$_{28}$H$_{32}$N$_2$O: C, 81.28; H, 7.83. Found: C, 81.28; H, 7.83.

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**N,N-dibenzyl-4-((6-methylpyridin-3-yl)oxy)butan-1-amine** (Table 4, entry 5f). Prepared following the general procedure using 2 mol% Cu(OAc)$_2$, 2.2% (±)-DTBM-SEGPHOS, 5-(but-3- en-1-yloxy)-2-methylpyridine (163.2 mg, 1.0 mmol, 1.0 equiv), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 20-50% EtOAc in hexane (contain 0.5% TEA) to provide the title compound as a colorless liquid in 92% yield for both runs. IR (thin film) 2942, 2793, 1494, 1262, 825 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ: 8.15 (dd, $J=2.6$, 1.0 Hz, 1H), 7.42 – 7.35 (m, 4H), 7.35 – 7.29 (m, 4H), 7.28 – 7.22 (m, 2H), 7.08 – 6.99 (m, 2H), 3.85 (t, $J=6.3$ Hz, 2H), 3.59 (s, 4H), 2.51 (s, 3H), 2.50 (t, $J=6.9$ Hz, 2H), 1.86 – 1.76 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ: 153.20, 150.10, 139.85, 136.79, 128.86, 128.45, 128.22, 126.88, 123.24, 121.96, 67.99, 58.43, 52.56, 26.73, 23.42, 23.36; HRMS (DART-TOF) calculated for C$_{24}$H$_{29}$N$_2$O [M+H]$^+$ m/z 361.2274, found 361.2270. Anal. Calcd. for C$_{24}$H$_{29}$N$_2$O: C, 79.96; H, 7.83. Found: C, 79.83; H, 7.75.

**N,N-dibenzyl-6-(oxiran-2-yl)hexan-1-amine** (Table 4, entry 5g). Prepared following the general procedure using 2 mol% Cu(OAc)$_2$, 2.2% (±)-DTBM-SEGPHOS, 1,2-epoxy-7-octene (126.2 mg, 1.0 mmol, 1.0 equiv), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 5-10% EtOAc in hexane (contain 0.5% TEA) to provide the title compound as a colorless liquid in 90% and 91% yield. IR (thin film) 2942, 2855, 2790, 1494, 1128, 1028, 743, 697 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.40 (d, $J=6.7$ Hz, 4H), 7.34 (t, $J=7.4$ Hz, 4H), 7.26 (t, $J=7.2$ Hz, 2H), 3.58 (s, 4H), 2.96 – 2.87 (m, 1H), 2.77 (dd, $J=5.0$, 4.0 Hz, 1H), 2.48 (dd, $J=5.0$, 2.7 Hz, 1H), 2.44 (t, $J=7.2$ Hz, 2H), 1.62 – 1.37 (m, 6H), 1.37 – 1.22 (m, 4H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ: 140.03, 128.77, 128.14, 126.74, 58.36, 53.25, 52.31, 47.07, 32.47, 29.24, 27.12, 26.91, 25.96; HRMS (DART-TOF) calculated for C$_{22}$H$_{28}$N$_2$O [M+H]$^+$ m/z 324.2322, found 324.2314.
N,N-dibenzyl-2-methyl-3-phenylpropan-1-amine (Table 4, entry 5h). Prepared following the general procedure using 2 mol% Cu(OAc)$_2$, 2.2% (±)-DTBM-SEGPHOS, (2-methylallyl)benzene (132.2 mg, 1.0 mmol, 1.0 equiv), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), THF (1 mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 5-10% EtOAc in hexane to provide the title compound as a colorless liquid in 87% and 90% yields. IR (thin film) 3025, 2795, 1494, 1452, 1066, 1028, 735, 697 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.46 – 7.40 (m, 4H), 7.36 (t, $J = 7.4$ Hz, 4H), 7.28 (s, 4H), 7.22 (d, $J = 7.3$ Hz, 1H), 7.15 – 7.08 (m, 2H), 3.62 (d, $J = 13.6$ Hz, 2H), 3.58 (d, $J = 13.6$ Hz, 2H), 2.97 (dd, $J = 13.1$, 4.6 Hz, 1H), 2.38 (dd, $J = 12.5$, 7.3 Hz, 1H), 2.29 (dd, $J = 12.4$, 6.9 Hz, 1H), 2.15 (dd, $J = 13.1$, 9.1 Hz, 1H), 2.11 – 1.99 (m, 1H), 0.86 (d, $J = 6.4$ Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$: 141.64, 139.96, 129.26, 129.04, 128.28, 128.22, 126.91, 125.70, 60.72, 59.08, 41.50, 33.68, 18.09; HRMS (DART-TOF) calculated for C$_{24}$H$_{21}$N $[\text{M+H}]^+$ m/z 330.2216, found 330.2203. Anal. Calcd. for C$_{24}$H$_{21}$N: C, 87.49; H, 8.26 Found: C, 87.59; H, 8.24.

N,N-dibenzyl-3-(((tert-butyldimethylsilyl)oxy)-2-methylpropan-1-amine (Table 4, entry 5i). Prepared following the general procedure using 2 mol% Cu(OAc)$_2$, 2.2% (±)-DTBM-SEGPHOS, tert-butyldimethyl((2-methylallyl)oxy)silane (132.2 mg, 1.0 mmol, 1.0 equiv), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), THF (1 mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 5-10% EtOAc in hexane to provide the title compound as a colorless liquid in 88% an 87% yield. IR (thin film) 2927, 1452, 1086, 834, 773, 743, 696 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.39 – 7.27 (m, 8H), 7.25 – 7.19 (m, 2H), 3.63 – 3.54 (m, 3H), 3.47 (d, $J = 13.6$ Hz, 2H), 3.28 (dd, $J = 9.8$, 6.7 Hz, 1H), 2.37 (dd, $J = 12.6$, 6.7 Hz, 1H), 2.18 (dd, $J = 12.5$, 7.6 Hz, 1H), 1.99 – 1.85 (m, 1H), 0.87 (m, 3H), 0.87 (s, 9H), 0.01 (s, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$: 140.01, 128.99, 128.23, 126.86, 67.12, 58.99, 57.51, 34.43, 26.12, 18.49, 15.80, -5.19; HRMS (DART-TOF) calculated for C$_{24}$H$_{31}$NOSi $[\text{M+H}]^+$ m/z 384.2717, found 384.2718.
**N-benzyl-N-methyl-4-phenylbutan-1-amine** (Table 5, entry 5j). Prepared following the general procedure using 2 mol% Cu(OAc)$_2$, 2.2% (±)-DTBM-SEGPHOS, but-3-en-ylbenzene (132.2 mg, 1.0 mmol, 1.0 equiv), O-benzoyl-N-benzyl-N-methylhydroxylamine (290 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 20-50% EtOAc in hexane (contain 0.5% TEA) to provide the title compound as a colorless liquid in 91% and 92% yield. IR (thin film) 2937, 2785, 1495, 1452, 1027, 736, 697 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.37 – 7.25 (m, 7H), 7.24 – 7.17 (m, 3H), 3.51 (s, 2H), 2.64 (t, $J = 7.6$ Hz, 2H), 2.42 (t, $J = 7.6$ Hz, 2H), 2.21 (s, 3H), 1.74 – 1.64 (m, 2H), 1.64 – 1.54 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ: 142.67, 139.32, 129.14, 128.50, 128.34, 128.27, 126.97, 125.73, 62.50, 57.35, 42.34, 35.90, 29.30, 27.10; HRMS (DART-TOF) calculated for C$_{10}$H$_{23}$N [M+H]$^+$ m/z 254.1903, found 254.1897. Anal. Calcd. for C$_{10}$H$_{23}$N: C, 85.32; H, 9.15 Found: C, 85.06; H, 9.14.

**1-(4-phenylbutyl)piperidine** (Table 5, entry 5k). Prepared following the general procedure using 4 mol% Cu(OAc)$_2$, 4.4% (±)-DTBM-SEGPHOS, but-3-en-ylbenzene (132.2 mg, 1.0 mmol, 1.0 equiv), piperidin-1-yl benzoate (246.3 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 10-20% EtOAc in hexane (contain 1% TEA) to provide the title compound as a colorless liquid in 99% yield for both runs. IR (thin film) 2931, 1738, 1453, 1350, 1122, 1039, 745 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.35 – 7.25 (m, 2H), 7.25 – 7.15 (m, 3H), 2.65 (t, $J = 7.5$ Hz, 2H), 2.40 – 2.33 (m, 4H), 2.33 (t, $J = 7.5$ Hz, 2H), 1.73 – 1.51 (m, 8H), 1.51 – 1.39 (m, 2H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ: 142.52, 128.39, 128.23, 125.63, 59.44, 54.68, 35.91, 29.63, 26.67, 26.02, 24.53; HRMS (DART-TOF) calculated for C$_{13}$H$_{25}$N [M+H]$^+$ m/z 218.1903, found 218.1895. Anal. Calcd. for C$_{13}$H$_{25}$N: C, 82.89; H, 10.67 Found: C, 82.76; H, 10.69.
**N,N-diisopropyl-4-phenylbutan-1-amine** (Table 5, entry 5i). Prepared following the general procedure using 4 mol% Cu(OAc)$_2$, 4.4% ($\pm$)-DTBM-SEGPHOS, but-3-en-1-ylbenzene (132.2 mg, 1.0 mmol, 1.0 equiv.), O-benzoyl-N,N-diisopropylhydroxylamine (246.3 mg, 1.2 mmol, 1.2 equiv), THF (1 mL) for 36 h at 40 °C. The reaction mixture was purified by flash chromatography on silica gel using 20-50% EtOAc in hexane (containing 1% TEA) to provide the title compound as a colorless liquid in 97% yield for both runs. IR (thin film) 2961, 2933, 1453, 1384, 1360, 1206, 1158, 742, 698 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.33 – 7.26 (m, 2H), 7.24 – 7.16 (m, 3H), 3.13 – 2.89 (m, 2H), 2.64 (t, $J$ = 7.6 Hz, 2H), 2.43 (t, $J$ = 7.6 Hz, 2H), 1.69 – 1.57 (m, 2H), 1.55 – 1.40 (m, 2H), 1.02 (d, $J$ = 6.6 Hz, 12H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$: 142.91, 128.40, 128.23, 125.57, 48.40, 45.10, 35.99, 31.13, 29.33, 20.71; HRMS (DART-TOF) calculated for C$_{16}$H$_{21}$N [M+H]$^+$ m/z 234.2216, found 234.2213. Anal. Calc'd. for C$_{16}$H$_{21}$N: C, 82.34; H, 11.66. Found: C, 82.086; H, 11.66.

**2,2,6,6-Tetramethyl-1-(4-phenylbutyl)piperidine** (Table 5, entry 5m). Prepared following the general procedure using 4 mol% Cu(OAc)$_2$, 4.4% ($\pm$)-DTBM-SEGPHOS, but-3-en-1-ylbenzene (132.2 mg, 1.0 mmol, 1.0 equiv), 2,2,6,6-tetramethylpiperidin-1-yl benzoate (314 mg, 1.2 mmol, 1.2 equiv), THF (2 mL) for 36 h at 40 °C. The reaction mixture was quenched with Na$_2$CO$_3$ solution, and the crude product extracted with EtOAc (x3) (NB: This step is necessary to remove N-OBz compounds). The reaction was then purified by an acid-base treatment, where the amine was first protonated with dilute HCl solution and the aqueous layer washed with EtOAc (x1), then treated with 1 M NaOH to deprotonate the amine. The aqueous layer was then extracted with EtOAc (x3), and the organic combined and concentrated to give the pure product as a yellow liquid in 83% and 76% yields. IR (thin film) 2963, 2925, 2868, 1453, 1377, 1359, 1350, 1261, 1175, 1129, 1108, 1025, 746, 697 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.38 – 7.26 (m, 2H), 7.24 – 7.18 (m, 3H), 2.65 (t, $J$ = 7.5 Hz, 2H), 2.47 – 2.35 (m, 2H), 1.60 – 1.50 (m, 6H), 1.47 – 1.39 (m, 4H), 1.05 (s, 12H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$: 143.05, 128.44, 128.33, 125.67, 54.58, 45.12, 41.28, 36.12, 35.87, 29.55, 27.63, 17.92; HRMS (DART-TOF) calculated for C$_{19}$H$_{31}$N [M+H]$^+$ m/z 274.2529, found 274.2519.
C. Substrate Preparation

Synthesis of substrates 1q:

\[
\text{OTBS} \quad (E)-\text{tert-butylimethyl}(2\text{-methyl-3-phenylallyl})\text{oxy)silane} \quad \text{(Table 2, 1q)}
\]

To a 50 mL round-bottom flask containing trans-2-Methyl-3-phenyl-2-propen-1-ol (2.964 g, 20 mmol, 1.00 equiv), imidazole (26 mmol, 1.3 equiv) was added DMF (20 mL). Then TBSCI (3.62 g, 24 mmol, 1.2 equiv) was added in one portion. The mixture was allowed to stir overnight. It was then diluted with ethyl acetate and washed with water, extracted 2 times with ethyl acetate and the combined organic layers were washed with brine and dried over Na₂SO₄. The mixture was purified by flash chromatography on silica gel using 0-5% EtOAc in hexane to provide the title compound in 90% yield as a colorless oil. IR (thin film) 2957, 2928, 2855, 1257, 1110, 1076, 835, 776 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 7.40 – 7.29 (m, 4H), 7.23 (t, J = 7.1 Hz, 1H), 6.56 (s, 1H), 4.26 – 4.14 (m, 2H), 1.86 (d, J = 1.3 Hz, 3H), 0.98 (s, 9H), 0.15 (s, 6H); ¹³C NMR (101 MHz, CDCl₃) δ: 138.17, 137.62, 129.03, 128.19, 126.25, 123.83, 68.64, 26.12, 18.61, 15.15, -5.09; HRMS (DART-TOF) calculated for C₁₆H₂₆OSi [M+H]+ m/z 263.1826, found 263.1889.
2.5 References and Notes


6). (a) O-benzoyl protected secondary hydroxylamine electrophiles were previously demonstrated as effective electrophiles in copper-catalysis (ref. 6b-d). (b) Berman, A. M.; Johnson, J. S. 


11). The catalytic pathway we described here is different from the one reported in the hydroamination of aliphatic alkene using 9-BBN-H (see ref. 4). We proposed the intermediacy of Cu-H as a species that transfers the hydride onto the alkene.


2.6 $^1$H, $^{13}$C, and $^{19}$F NMR Spectra
\( \text{MeO} \)  

\( \text{Me} \)  

\( 3j \)
Racemic 3r with (R)-Acetylmandelic Acid
Sample 3r with (S)-Acetylmandelic Acid
Racemic 3u with (R)-Acetylmandelic Acid
Sample of 3u with (R)-Acetylmandelic Acid
The image shows a 1D NMR spectrum with peaks labeled at different chemical shifts. The spectrum appears to be of a compound labeled as 5c, which has a molecular structure involving bromine (Br) and benzyl (Bn) groups. The spectrum includes peaks at various ppm values.
2.7 Chiral HPLC and Chiral GC Spectra
(S)-N,N-dibenzyl-1-phenylethan-1-amine (Table 2, entry 3a): HPLC analysis (OD-H, 3% IPA/hexane, 0.8 mL/min, 220 nm) indicated 97% ee: \( t_R \) (major) = 4.8 minutes, \( t_R \) (minor) = 5.4 minutes.

\[
\text{Rac-3a}
\]

\[
\begin{array}{cccccc}
\text{Peak} & \text{RetTime} & \text{Type} & \text{Width} & \text{Area} & \text{Height} \\
& \text{[min]} & & \text{[min]} & \text{[mAU s]} & \text{[mAU]} \\
1 & 4.791 & VV & 0.2825 & 3560.30688 & 174.18317 & 48.9500 \\
2 & 5.403 & VB & 0.3406 & 3713.04492 & 178.58705 & 51.0500 \\
\end{array}
\]

Totals : 7273.35181 352.77022

(S)-3a from styrene (1a): 97% ee

\[
\begin{array}{cccccc}
\text{Peak} & \text{RetTime} & \text{Type} & \text{Width} & \text{Area} & \text{Height} \\
& \text{[min]} & & \text{[min]} & \text{[mAU s]} & \text{[mAU]} \\
1 & 4.733 & VV & 0.2684 & 4479.54980 & 237.15596 & 98.8905 \\
2 & 5.388 & VB & 0.2378 & 50.25723 & 2.61964 & 1.1095 \\
\end{array}
\]

Totals : 4529.80703 239.77560

266
(S)-N,N-dibenzyl-1-(4-fluorophenyl)ethan-1-amine (Table 2, entry 3b): HPLC analysis (OD-H, 5% IPA/hexane, 0.8 mL/min, 220 nm) indicated 97% ee: $t_R$ (major) = 4.8 minutes, $t_R$ (minor) = 5.5 minutes.

Rac-3b

(S)-3b from 1-Fluoro-4-vinylbenzene (1b): 97% ee
(S)-N,N-dibenzyl-1-(2-chlorophenyl)ethan-1-amine (Table 2, entry 3c): HPLC analysis (OD-H, 3% IPA/hexane, 0.8 mL/min, 220 nm) indicated 92% ee: t<sub>R</sub> (major) = 5.2 minutes, t<sub>R</sub> (minor) = 5.8 minutes.

Rac-3c

(S)-3c from 1-Chloro-2-vinylbenzene (1c): 92% ee
(S)-N,N-dibenzyl-1-(4-(trifluoromethyl)phenyl)ethan-1-amine (Table 2, entry 3d): HPLC analysis (OD-H, 3% IPA/hexane, 0.8 mL/min, 220 nm) indicated 95% ee: $t_R$ (major) = 4.8 minutes, $t_R$ (minor) = 6.5 minutes.

**Rac-3d**

![HPLC chromatogram](image)

<table>
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<th>Area</th>
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<tr>
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<td></td>
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<td>[min] [mA* s] [mA] %</td>
<td></td>
</tr>
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<td>6.462</td>
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<tr>
<td>Totals</td>
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<td>0.2209</td>
<td>1535.72363</td>
<td>108.66138</td>
</tr>
</tbody>
</table>

(S)-3d from 1-(trifluoromethyl)-4-vinylbenzene (1d): 95% ee

![HPLC chromatogram](image)

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<th>Area</th>
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</thead>
<tbody>
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<td></td>
<td></td>
<td>[min] [mA* s] [mA] %</td>
<td></td>
</tr>
<tr>
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<td>4.818</td>
<td>0.2209</td>
<td>1535.72363</td>
<td>108.66138</td>
</tr>
<tr>
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<td>6.451</td>
<td>0.2230</td>
<td>38.67113</td>
<td>2.36222</td>
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<tr>
<td>Totals</td>
<td></td>
<td>1574.39477</td>
<td>111.02360</td>
<td></td>
</tr>
</tbody>
</table>
(S)-N,N-dibenzyl-1-(o-tolyl)ethan-1-amine (Table 2, entry 3e): HPLC analysis (OJ, 3% IPA/hexane, 0.8 mL/min, 220 nm) indicated 92% ee: $t_R$ (major) = 6.2 minutes, $t_R$ (minor) = 8.7 minutes.

Rac-3e

| Peak RetTime Type Width Area Height Area |
|---|---|---|---|---|
| # | [min] | [min] | [mAU*s] | [mAU] |
| 1 | 6.204 | 0.4134 | 35.83410 | 50.2459 |
| 2 | 8.689 | 0.6719 | 18.23969 | 49.7541 |

Totals: 1891.30627 54.07379

(S)-3e from 1-Meth 1-2-vinylbenzene (1e): 92% ee

| Peak RetTime Type Width Area Height Area |
|---|---|---|---|---|
| # | [min] | [min] | [mAU*s] | [mAU] |
| 1 | 6.220 | 0.4081 | 41.01268 | 93.8658 |
| 2 | 8.739 | 1.0644 | 70.32650 | 6.1342 |

Totals: 1146.47005 42.11388

270
(S)-N,N-dibenzyl-1-(4-methoxyphenyl)ethan-1-amine (Table 2, entry 3f): HPLC analysis (OJ, 10% IPA/hexane, 0.8 mL/min, 220 nm) indicated 99% ee: $t_R\text{ (major)} = 9.0$ minutes, $t_R\text{ (minor)} = 17.9$ minutes.

**Rac-3f**

![HPLC Analysis Graph for Rac-3f](image)

<table>
<thead>
<tr>
<th>Peak</th>
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<th>Type</th>
<th>Width (min)</th>
<th>Area (mAU*s)</th>
<th>Height (mAU)</th>
<th>Area (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>8.963</td>
<td>BB</td>
<td>0.6829</td>
<td>1.2494e4</td>
<td>272.52264</td>
<td>100.000</td>
</tr>
<tr>
<td>2</td>
<td>17.905</td>
<td>BB</td>
<td>1.8692</td>
<td>8854.01953</td>
<td>195.07523</td>
<td>51.3217</td>
</tr>
</tbody>
</table>

Totals:

- $1.2494e4$ mAU
- 272.52264 mAU

**(S)-3f from 1-Methoxy-4-vinylbenzene (1f): >99% ee**

![HPLC Analysis Graph for (S)-3f](image)

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<tr>
<th>Peak</th>
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<th>Type</th>
<th>Width (min)</th>
<th>Area (mAU*s)</th>
<th>Height (mAU)</th>
<th>Area (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>8.764</td>
<td>VB</td>
<td>0.6829</td>
<td>1.2494e4</td>
<td>1.2494e4</td>
<td>100.000</td>
</tr>
</tbody>
</table>

Totals:

- $1.2494e4$ mAU
- 272.52264 mAU
(S)-\(N,N\)-dibenzyl-1-(naphthalen-2-yl)ethanamine (Table 3, entry 3g): HPLC analysis (OJ, 10% IPA/hexane, 0.8 mL/min, 220 nm) indicated 97% ee: \(t_R\) (major) = 10.9 minutes, \(t_R\) (minor) = 36.2 minutes.

\[
\text{Rac-3g}
\]

\[
\text{(S)-3g from 1-Fluoro-4-vinylbenzene (1g): 97% ee}
\]
(S)-N,N-dibenzyl-1-phenylpropan-1-amine (Table 2, entry 3h & 3l): HPLC analysis (OD-H, 5% IPA/hexane, 0.8 mL/min, 220 nm) indicated >99% ee (from trans-), 96% ee (from cis-): $t_R$ (major) = 4.8 minutes, $t_R$ (minor) = 5.6 minutes.

Rac-3h, l

(S)-3h from trans- $\beta$-methylstyrene (E)-1h: >99% ee
(S)-31 from cis-β -methylstyrene ((Z)-11): 96% ee

![HPLC graph]

<table>
<thead>
<tr>
<th>Peak</th>
<th>Ret Time [min]</th>
<th>Type</th>
<th>Width [min]</th>
<th>Area [mAU*s]</th>
<th>Height [mAU]</th>
<th>Area [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.683</td>
<td>VV</td>
<td>0.2669</td>
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<tr>
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<td>78.41167</td>
<td>3.54871</td>
<td>1.8917</td>
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</table>

**Totals:** 4145.10455 252.06528
(S)-N,N-dibenzyl-1,2-diphenylethan-1-amine (Table 2, entry 3i & 3m): HPLC analysis (OD-H, 5% IPA/hexane, 0.8 mL/min, 220 nm) indicated >99% ee (from trans-), 88% ee (from cis): t_R (major) = 5.2 minutes, t_R (minor) = 6.5 minutes.

Rac-3i, m

(S)-3i from trans-stilbene ((E)-1i): >99% ee
(S)-3 from cis-stilbene ((Z)-1m): 88% ee

<table>
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<tr>
<th>Peak RetTime</th>
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<th>Area %</th>
</tr>
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<td>0.2352</td>
<td>6644.63623</td>
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<td>2</td>
<td>BB</td>
<td>0.2555</td>
<td>454.40648</td>
<td>27.69054</td>
<td>6.2255</td>
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</table>

Totals: 7299.04071 478.37481
(S)-N,N-dibenzyl-1-(4-methoxyphenyl)ethan-1-amine (Table 2, entry 3j): HPLC analysis (OJ, 10% EtOH/hexane, 0.8 mL/min, 220 nm) indicated >99% ee: \( t_R \) (major) = 8.3 minutes, \( t_R \) (minor) = 23.6 minutes.

**Rac-3j**

![Rac-3j chart](image)

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<tr>
<th>Peak</th>
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<td>1</td>
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<td>89.23178</td>
<td>49.9411</td>
</tr>
</tbody>
</table>

**Totals**: 2.32556e4 574.98404

(S)-3j from (E)-1-methoxy-4-(prop-1-en-1-yl)benzene (1j): >99% ee

![S-3j chart](image)

<table>
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<tr>
<th>Peak</th>
<th>RetTime [min]</th>
<th>Type</th>
<th>Width [min]</th>
<th>Area Height [mAU]</th>
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<tbody>
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<td>100.0000</td>
</tr>
</tbody>
</table>

**Totals**: 1517.36401 50.87385

277
(S)-N,N-dibenzyl-3-methoxy-1-phenylpropan-1-amine (Table 2, entry 3k): HPLC analysis (OD-H, 3% IPA/hexane, 0.8 mL/min, 220 nm) indicated 98% ee: $t_R$ (major) = 6.0 minutes, $t_R$ (minor) = 6.7 minutes.

**Rac-3k**

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<tr>
<td>1 6.051 VV 0.2538 1.41525e4 851.76758 50.4456</td>
<td></td>
</tr>
<tr>
<td>2 7.049 VB 0.2805 1.39025e4 770.35675 49.5544</td>
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</tr>
</tbody>
</table>

Totals: 2.80549e4 1622.12433

(S)-3k from (E)-(3-methoxyprop-1-en-1-yl)benzene (1k): 1 mmol scale: 98% ee

<table>
<thead>
<tr>
<th>Peak Ret Time Type Width Area Height Area</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 6.000 MF 0.2921 2.81014e4 1603.61926 99.1340</td>
<td></td>
</tr>
<tr>
<td>2 6.966 FM 0.3587 245.47841 11.40637 0.8660</td>
<td></td>
</tr>
</tbody>
</table>

Totals: 2.83469e4 1615.02564

278
10 mmol scale: 99% ee

<table>
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<tr>
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<td>0.2091</td>
<td>17.57214</td>
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<td>0.4466</td>
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</table>

Totals: 3934.49377 269.95948
**(S)**-N,N-dibenzyl-2,3-dihydro-1H-inden-1-amine (Table 2, entry 3n): HPLC analysis (OJ, 5% IPA/hexane, 0.8 mL/min, 220 nm) indicated 95% ee: t<sub>R</sub> (major) = 5.9 minutes, t<sub>R</sub> (minor) = 7.6 minutes.

**Rac-3n**

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<td>[min]</td>
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<td>[mAU]</td>
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<td>7.579</td>
<td>VB</td>
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**Totals:** 2.76120e4 804.07405

**(S)-3n** from 1H-indene (1n): 95% ee

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<td>7.641</td>
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**Totals:** 3316.73227 135.34968
(S)-N,N-dibenzyl-1,2,3,4-tetrahydronaphthalen-1-amine (Table 2, entry 30): HPLC analysis (OJ, 3% IPA/hexane, 0.8 mL/min, 220 nm) indicated 86% ee: $t_R$ (major) = 5.8 minutes, $t_R$ (minor) = 7.7 minutes.

Rac-30

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<tr>
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<tr>
<td>Totals</td>
<td></td>
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6946.22754 173.67303

(S)-30 from (E)-(3-methoxyprop-1-en-1-yl)benzene (1o): 86% ee

<table>
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<tr>
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</table>

858.05611 29.80495
(S)-N,N-dibenzyl-2-methyl-1-phenylpropan-1-amine (Table 2, entry 3p): HPLC analysis (OD-H, 5% IPA/hexane, 0.8 mL/min, 220 nm) indicated >99% ee, single isomer: $t_R$ (major) = 4.7 minutes, $t_R$ (minor) = 6.1 minutes.

**Rac-3p**

![Graph showing HPLC analysis of Rac-3p](image)

<table>
<thead>
<tr>
<th>Peak</th>
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<th>Type</th>
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<th>Area [mAU*s]</th>
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<td>FM</td>
<td>0.2809</td>
<td>2792.93506</td>
<td>165.68793</td>
<td>48.4369</td>
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</table>

**Totals:**

5766.13037 359.11876

---

(S)-3p from (2-methylprop-1-en-1-yl)benzene (1p): >99% ee

![Graph showing HPLC analysis of (S)-3p](image)

<table>
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<tr>
<th>Peak</th>
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<th>Type</th>
<th>Width</th>
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<tr>
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</table>

**Totals:**

5107.73134 391.66062

282
(1S,2R)-N,N-dibenzyl-3-((tert-butyldimethylsilyl)oxy)-2-methyl-1-phenylpropan-1-amine (Table 2, entry 3q): HPLC analysis (OD-H, 3% IPA/hexane, 0.8 mL/min, 220 nm) indicated >99% ee, single isomer: t_R (major) = 4.3 minutes, t_R (minor) = 4.9 minutes.

Rac-3q

(S)-3q from (E)-tert-butyldimethyl((2-methyl-3-phenylallyl)oxy)silane (1q): >99% ee
(S)-4-(1-phenylethyl)morpholine (Table 3, entry 3s): GC condition: Varian CP7502 column (25 m×0.25 mm×0.25 µm, chiralsil-DEX CB), H2 2.7 mL/min, programmed from 100 °C to 125 °C at 0.5 °C/min; $t_R$ (minor) = 28.41 min, and $t_R$ (major) = 29.24 min.

Rac-3s

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<td>[min]</td>
<td>[pA's] [pA]</td>
</tr>
<tr>
<td>1 28.414 MMB</td>
<td>0.2280</td>
<td>180.10864 13.16769 49.93779</td>
</tr>
<tr>
<td>2 29.245 MMB</td>
<td>0.2727</td>
<td>180.55737 11.03511 50.06221</td>
</tr>
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</table>

(S)-3s from styrene (1a): 98% ee

<table>
<thead>
<tr>
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<th>Area Height Area</th>
</tr>
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<tbody>
<tr>
<td># [min]</td>
<td>[min]</td>
<td>[pA's] [pA]</td>
</tr>
<tr>
<td>1 28.616 MMB</td>
<td>0.1567</td>
<td>5.60086 5.95790e-1 1.15522</td>
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<tr>
<td>2 29.025 MMB</td>
<td>0.3406</td>
<td>479.23149 23.44999 99.94470</td>
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</table>
(S)-N,N-dibenzyl-3-methoxy-1-phenylpropan-1-amine (Table 2, entry 3t): HPLC analysis (OD-H, 3% IPA/hexane, 0.8 mL/min, 220 nm) indicated >99% ee: tR (major) = 6.0 minutes, tR (minor) = 6.7 minutes.

Rac-3t

(S)-3t from styrene (1a): >99% ee
Chapter 3.
\(\alpha\)-Aminosilanes Synthesis via Copper-Catalyzed Hydroamination of Vinylsilanes

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Enantioselective Synthesis of \(\alpha\)-Aminosilanes by Copper-Catalyzed Hydroamination of Vinylsilanes

Nootaree Niljianskul, Shaolin Zhu, and Stephen L. Buchwald

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3.1 Introduction

Organosilicon compounds have recently gained prominence within the field of medicinal chemistry. Silicon is often used as an isostere for carbon due to its similar valency and tetrahedral bonding pattern.\(^1\) In addition, because of its larger covalent radius, electronegative/lipophilic nature, and low intrinsic toxicity, silicon is complementary to carbon and is valuable in medicinal chemistry.\(^2\) Among the many subclasses of organosilicon compounds, chiral \(\alpha\)-aminosilanes in particular have demonstrated significant bioactivities.\(^3\) Several potent inhibitors of proteolytic enzymes possess the \(\alpha\)-aminosilane motif, and \(\alpha\)-aminosilanes have been incorporated into peptide isosteres (Figure 1).\(^2\) Thus, the development of robust methods for the construction of chiral \(\alpha\)-aminosilanes is an important area of research.

**Figure 1. Examples of Silicon-Containing Peptidomimetics and Amino Acids**

- **Silanediol protease inhibitors:**
  - angiotensin-converting enzyme (ACE) inhibitor
  - serine protease human neutrophil elastase (HNE) inhibitor

- **Chiral diarylsilylamino acid analogues:**
  - valine mimic
  - methionine mimic
  - leucine mimic
  - lysine mimic

Although there has been progress in the synthesis of racemic \(\alpha\)-aminosilanes,\(^5\) enantioselective approaches remain limited. Previous methods include asymmetric deprotonation followed by reverse aza-Brook rearrangement (Scheme 1, eq. 1).\(^7\) Other approaches have utilized Davis' or Ellman's chiral auxiliary-protected aldimines in conjunction
with silyllithium reagents (eq. 2). Recently, Oestreich reported an elegant process catalyzed by a chiral N-heterocyclic carbene-Cu complex using Suginome’s Ph(Me)₂SiBpin reagent (eq. 3). However, these methods have limitations with respect to the scope of the amine, and, with the exception of Oesterich’s report, require the use of a stoichiometric chiral auxiliary or reagent.

Scheme 1. Previous Approaches Towards the Synthesis of Chiral \( \alpha \)-Aminosilanes

**Reverse aza-Brook Rearrangement Approach: Voyer, Sieburth**

\[
\begin{align*}
\text{SiR}_3^3 + s-\text{BuLi(-)-sparteine} & \quad [1,2] \text{ silicon shift} \\
\text{Boc}^+ \text{N} & \quad \text{R} \\
\end{align*}
\]

(Eq. 1)

**Chiral Auxiliary Approach: Scheidt, Skrydstrup, Sieburth**

\[
\begin{align*}
\text{O} & \quad \text{S}^\text{N} \quad \text{R}^\text{I} \quad \text{Li}-\text{SiR}^3_3 \\
\text{R} & \quad \text{H} \\
\text{THF, } & \quad \text{MeOH} \\
\text{5\% AcOH/MeOH} & \quad [1,2] \text{ silicon shift} \\
\text{Boc}^+ \text{N} & \quad \text{R} \\
\end{align*}
\]

(Eq. 2)

**Cu-catalyzed Approach: Oestreich**

\[
\begin{align*}
\text{SO}_2\text{Tol} & \quad \text{Bpin-SiR}^3_3 \\
\text{R} & \quad \text{H} \\
5 \text{ mol\% NHC-CuCl} & \quad 1.5 \text{ equiv. NaOMe} \\
\text{HN} & \quad \text{SiR}^3_3 \\
\end{align*}
\]

(Eq. 3)

Recently, we developed the copper-catalyzed asymmetric Markovnikov hydroamination of styrenes. We felt that this methodology applied to vinylsilanes substrates would allow for the generation of a broad range of chiral \( \alpha \)-aminosilanes (Scheme 2). As vinylsilanes are readily prepared and bench stable, they are attractive as starting materials for the synthesis of \( \alpha \)-aminosilanes. We proposed that the intermolecular hydroamination of vinylsilanes would proceed regioselectively to give chiral \( \alpha \)-aminosilanes (III) via the \( \alpha \)-silyl alkylcopper intermediate II (Scheme 2) based on literature precedent. Subsequent reaction with \( O \)-benzoyl hydroxylamine electrophile 2 would provide the desired \( \alpha \)-aminosilane (III).
Scheme 2. Our Strategy Towards the Synthesis of Chiral α-Aminosilanes and the Regioselectivity Rationale

\[
\text{Rational:}
\]

\[
\begin{align*}
\text{(I)} & \quad \text{L}^* \text{Cu-H} \\
& \quad \text{(II)} \\
& \quad \text{(III)} \\
\end{align*}
\]

3.2 Results and Discussion

We began our investigation by examining the hydroamination of \((E)\)-triethylsilylvinsilane \(1a\) using conditions previously developed for the hydroamination of styrene (Table 1).\(^9\) The reaction regioselectively furnished \(α\)-aminosilane \(3a\) in quantitative yield with >99% ee after 8 h (entry 1). Switching the solvent to cyclohexane, diethyl ether, or toluene (entries 2–4) had no effect, but no conversion was seen in dichloromethane (entry 5). We also examined other chiral ligands that were previously shown to be effective in reactions mediated by a copper(I)hydride complex (entries 6–8).\(^1^7\) However, the use of \((R)\)-DTBM-SEGPHOS was found to give the highest reactivity and selectivity.
\textbf{Table 1. Reaction Optimization}\textsuperscript{a}

\begin{tabular}{llccc}
\hline
Entry & Solvent & L & Yield 3a [%]\textsuperscript{b} & ee [%]\textsuperscript{c} \\
\hline
1 & THF & L1 & >99 & >99 \\
2 & cyclohexane & L1 & >99 & >99 \\
3 & Et\textsubscript{2}O & L1 & >99 & >99 \\
4 & toluene & L1 & >99 & >99 \\
5 & CH\textsubscript{2}Cl\textsubscript{2} & L1 & 0\textsuperscript{e,f,g,l} & - \\
6 & THF & L2 & 37\textsuperscript{f} & 95 \\
7 & THF & L3 & 92\textsuperscript{d,l} & 98 \\
8\textsuperscript{c} & THF & L4 & 0\textsuperscript{e,f,h,l} & - \\
\hline
\end{tabular}

\textsuperscript{a} Reaction conditions: 1a (0.5 mmol), 2a (0.6 mmol), Cu(OAc)\textsubscript{2} (0.02 mmol), Ligand (0.022 mmol), solvent (1 mL). \textsuperscript{b}Isolated yields. \textsuperscript{c}Determined by chiral HPLC analysis. \textsuperscript{d}16 h. \textsuperscript{e}Yield determined by GC (dodecane as an internal standard). \textsuperscript{f}36 h. \textsuperscript{g}77\% of 1a remained. \textsuperscript{h}96\% of 1a remained.

\begin{align*}
\text{Ar} &= 3,5\text{-t-Bu-4-MeOC}_6\text{H}_2 \\
(R)\text{-DTBM-SEGPHOS (L1)} & (S,S)-\text{Ph-BPE (L2)} \\
& (S)\text{-3,5-t-Bu-MeO-BIPHEP (L3)} \\
& (R,S)\text{-Josiphos (L4)}
\end{align*}
We next investigated the influence of the nature of the silyl group and olefin geometry on reactivity and enantioselectivity (Table 2). The reaction was compatible with vinylsilanes containing triethylsilyl (3a), trimethylsilyl (3b), dimethylphenylsilyl (3c), and methyldiphenylsilyl groups (3d). In all cases, the reactions proceeded regioselectively to give α-aminosilane products. Interestingly, we found: 1) both (E) and (Z)-isomers provided the same enantiomeric product, and 2) (E) substrates invariably reacted faster and with a higher level of enantioselectivity than the corresponding (Z) substrates.

**Table 2. Influence of the Silyl Group and Olefin Geometry on Yield and Enantioselectivity**

\[
\begin{align*}
1a - 1d & \quad 2.0 \text{ mol\% Cu(OAc)}_2 \\
 & + \quad 2.2 \text{ mol\% (R)-DTBM-SEGPHOS}
\end{align*}
\]

\[
2 \text{a (1.2 equiv)} \quad 2 \text{equiv Me(EtO)}_2 \text{Si-H} \quad \text{THF (1.0 M), 40 °C, 36 h} \quad 3a - 3d
\]

- **(Z)-Vinylsilanes**
  - 3a: 80% yield, 93% ee
  - 3b: 99% yield, 92% ee
  - 3c: 80% yield, 93% ee
  - 3d: 84% yield, 84% ee

- **(E)-Vinylsilanes**
  - 3a: 99% yield, >99% ee
  - 3b: 90% yield, 99% ee
  - 3c: 92% yield, 99% ee
  - 3d: 86% yield, 99% ee

*Reaction conditions: 1a - 1d (1 mmol), 2a (1.2 mmol), Cu(OAc)$_2$ (0.02 mmol), (R)-DTBM-SEGPHOS (0.022 mmol), THF (1 mL), 40 °C, 36 h. Yields are isolated yields (average of two runs). $^b$Cu(OAc)$_2$ (0.04 mmol), (R)-DTBM-SEGPHOS (0.044 mmol). $^c$8 h. $^d$Cu(OAc)$_2$ (0.04 mmol), (R)-DTBM-SEGPHOS (0.044 mmol), THF (0.5 mL, 2 M).

Thus, we chose to examine the scope of the hydroamination of E-vinylsilanes. This method accommodates a broad range of functional groups (Table 3). Vinylsilanes containing a nitrile...
(5a), an alkyl chloride (5b), an ester (5c), a sulfonamide (5d), a t-butyldimethylsilyl ether (5e), and an allylic ether moiety (5f) were readily handled. Minor competitive elimination of alkoxide was observed with ether 5f.\(^9\) Additionally, we applied our method to the synthesis of \(\alpha\)-amino acid mimics by hydroamination of 2\(^{\circ}\) benzylamine 5i, \(\beta\)-disubstituted vinylsilane 5j, and \(\beta\)-isopropyl-substituted vinylsilane 5k, to provide mimics of lysine, valine, and leucine, respectively.

**Table 3. Hydroamination of (E)-Vinylsilanes**\(^a\)

<table>
<thead>
<tr>
<th>Vinyl Triethylsilanes</th>
<th>Vinyl Dimethylphenylsilanes</th>
<th>Vinyl Diphenylmethylsilanes</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a(^b)</td>
<td>5e</td>
<td>5j(^c)</td>
</tr>
<tr>
<td>73% yield, 99% ee</td>
<td>96% yield, 96% ee</td>
<td>99% yield, 99% ee</td>
</tr>
<tr>
<td>5b</td>
<td>5f(^c)</td>
<td></td>
</tr>
<tr>
<td>96% yield, &gt;99% ee</td>
<td>90% yield, 99% ee</td>
<td></td>
</tr>
<tr>
<td>5c</td>
<td>5g</td>
<td>5k(^c)</td>
</tr>
<tr>
<td>80% yield, 99% ee</td>
<td>99% yield, 98% ee</td>
<td>99% yield, 94% ee</td>
</tr>
<tr>
<td>5d(^c)</td>
<td>5h(^c)</td>
<td></td>
</tr>
<tr>
<td>98% yield, 99% ee</td>
<td>90% yield, 92% ee</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: 4a – 4k (1 mmol), 2a (1.2 mmol), Cu(OAc)\(_2\) (0.02 mmol), (R)-DTBMSEGPHOS (0.022 mmol), THF (1 mL), 40 °C, 36 h. Yields are isolated yields (average of two runs). \(^b\)16h reaction time. \(^c\)Cu(OAc)\(_2\) (0.04 mmol), (R)-DTBM-SEGPHOS (0.044 mmol), THF (1 mL, 1 M). \(^d\)From (Z)-4g.
The compatibility of this reaction with a variety of O-benzoyl hydroxylamine electrophiles was then examined (Table 4). Acyclic dialkyl (6a), cyclic dialkyl (6b), and alkylbenzylamine-based electrophiles (6c) were all suitable partners, delivering the hydroaminated products with high yields and enantioselectivities. In addition, a heterocycle-containing electrophile was also tolerated (6d). Hydroamination to install a bis(p-methoxybenzyl)amino group was also successful (6e).

**Table 4. Scope of O-Benzoyl Hydroxylamine Electrophiles**

<table>
<thead>
<tr>
<th>Electrophile</th>
<th>Yield</th>
<th>Enantiomeric Excess</th>
</tr>
</thead>
<tbody>
<tr>
<td>6a</td>
<td>78%</td>
<td>&gt;99% ee</td>
</tr>
<tr>
<td>6b</td>
<td>99%</td>
<td>&gt;99% ee</td>
</tr>
<tr>
<td>6c</td>
<td>94%</td>
<td>98% ee</td>
</tr>
<tr>
<td>6d</td>
<td>87%</td>
<td>&gt;99% ee</td>
</tr>
<tr>
<td>6e</td>
<td>99%</td>
<td>&gt;99% ee</td>
</tr>
</tbody>
</table>

Reaction conditions: 1a (1 mmol), 2a (1.2 mmol), Cu(OAc)₂ (0.02 mmol), (R)-DTBM-SEGPHOS (0.022 mmol), THF (1 mL), 40 °C, 36 h. Yields are isolated yields (average of two runs).

As previously mentioned (Table 2), both (E) and (Z) substrates provide product that is the same enantiomer. However, (E) substrates react faster and afford a higher level of enantioselectivity than the corresponding (Z) substrates. We thus wondered whether, in the case of (Z)-alkenes, most of the hydroamination product was formed by isomerization of the slower
reacting (Z)-isomer, followed by transformation of the nascent (E)-isomer. We investigated this possibility through the use of a deuterated silane reagent. In this case, L*Cu-D would form and the olefin would insert into it via a syn-addition process (Scheme 3). For the more reactive (E)-substrate, subsequent reaction with the O-benzoyl hydroxylamine would generate the (R,R) product. For the (Z)-substrate, if no isomerization occurs, the reaction should generate the (R,S) product. However, if the (Z)-substrate undergoes Cu-catalyzed isomerization to the (E)-alkene prior to hydroamination, the major product would contain approximately 2 deuteria.

_Scheme 3. Possible Reaction Pathways_

Deuterium-labelling experiments (Scheme 4) revealed that the hydroamination of (E)-4g was completely diastereoselective with ca. 99% deuterium incorporation to give the mono-deuterated (R,R)-isomer 5g' (eq. 1). For the (Z)-4g, the reaction was also diastereoselective to give the mono-deuterated (R,S)-isomer 5g' with ca. 96% deuterium incorporation (eq. 2). The stereochemical result and the presence of the mono-deuterated product from the (Z)-substrate indicates that most of the product does not formed via isomerization of the substrate to the (E)-isomer.
Lastly, to demonstrate the scalability of this transformation, we carried out the hydroamination of 1a with O-benzoyl-\(N,N\)-dibenzylhydroxylamine (2a) on a 10 mmol scale (Scheme 5). Full conversion of the vinylsilane was achieved with a catalyst loading of only 0.5 mol%. The yield and the enantioselectivity was the same as for the 1 mmol scale reaction (Table 1).

### Scheme 4. Large-Scale Hydroamination Reaction of (E)-Triethylsilylvinylsilane

\[
\begin{align*}
\text{Et}_3\text{Si} & + \text{Bn}_2\text{N} \cdot \text{OBz} \\
\text{1a} & \quad \text{2a} \\
(10 \text{ mmol}) & \quad (1.2 \text{ equiv}) \\
& \quad 99\% \text{ yield, } 99\% \text{ ee}
\end{align*}
\]

### 3.3 Conclusion

In summary, we have developed an enantioselective Cu-catalyzed hydroamination of vinylsilanes. The reaction proceeds in a regioselective manner to provide enantioenriched \(\alpha\)-amino silanes in high yield with outstanding levels of enantioselectivity. The method is applicable to a variety of substrates, and provides rapid access to a family of valuable chiral organosilicon building blocks and bioactive molecules.
3.4 Experimental
I. General Information

**General Reagent Information**

Unless otherwise stated, all reactions were set up on the bench top and carried out under an argon atmosphere. Anhydrous cyclohexane was purchased from Sigma-Aldrich in Sure-Seal bottles and used as received. All other solvents were purified and dried by passage through successive alumina and Q5 reactant-packed columns on a solvent purification system. Diethoxymethylsilane was purchased from TCI America and stored under nitrogen at 4 °C in a Schlenk flask (diethoxymethylsilane is moisture sensitive, and proper Schlenk technique was used for handling this reagent). Diphenyl(silane-d₂) was purchased from Sigma-Aldrich and was stored and used in the nitrogen-filled glovebox. Other silane reagents, alkynes, benzoyl peroxide, amines, platinum dichloride, copper(II)acetate, and bases (MeLi and Na₂CO₃) were purchased from Frontier Scientific, Combi-Blocks, GFS chemicals, Ark Pharm, Alfa Aesar, Sigma-Aldrich, or Strem Chemicals, and were used as received. DTBM-SEGPHOS (L1) was purchased from Takasago. Ligands L2 - L4 were purchased from Strem Chemicals. Compounds were purified using Silicycle SiliaFlashP60 (230-400 mesh) silica gel on a Biotage SP4 instrument.

**General Analytical Information**

All compounds (starting materials and products) were characterized by ¹H NMR, ¹³C NMR, IR spectroscopy, melting point (where applicable), and elemental analysis or high-resolution mass spectrometry. ¹H and ¹³C NMR spectra were recorded on Varian 300 MHz or Bruker 400 MHz spectrometers. The spectra were calibrated according to residual solvent peaks (CDCl₃: δ 7.26 ppm for ¹H NMR and δ 77.0 ppm for ¹³C NMR). The ¹³C NMR spectra were obtained with ¹H decoupling. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, sept = septet, and m= multiplet. IR spectra were obtained on a Thermo Scientific iD5 ATR Nicolet iS5 FT-IR spectrometer. Elemental analyses were carried out by Atlantic Microlab, Inc., Norcross, GA. ESI-MS spectra were recorded on a Bruker Daltonics APEXIV 4.7 Tesla Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR-MS). Melting points (m.p.) were obtained on a Mel-Temp capillary melting point apparatus. Gas chromatographic (GC) analyses were performed.
on an Agilent 7890A instrument (FID detector) using a J&W DB-1 column (10m, 0.1 mm I.D.). Reactions were monitored by GC analysis and thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) or Fluka aluminum oxide/TLC-cards using UV light as a visualizing agent. High pressure liquid chromatography (HPLC) was performed on Hewlett-Packard 1100 Series using a chiral column (25 cm) and guard column (5 cm) as noted for each compound. Optical rotations were measured on a Jasco P-1010 polarimeter with $[\alpha]_D$ values reported in degrees; concentration (c) is in g/100 mL. The yields reported for the CuH-catalyzed hydroamination of vinylsilanes are of isolated compounds and are the average of at least two experiments.
II. Experimental Procedures and Characterization Data

A) Cu-Catalyzed Hydroamination of Vinylsilanes

**General Procedure for Cu-Catalyzed Hydroamination of Vinylsilanes:**

1. To an oven-dried test tube equipped with a magnetic stir bar was added Cu(OAc)$_2$ (2.0–4.0 mol%) and (R)-DTBM-SEGPHOS (2.2–4.4 mol%). The tube was sealed with a teflon-lined screw cap and evacuated and backfilled with argon (this process was repeated a total of 3 times).

2. Anhydrous THF (1.0–2.0 mL) was added, and the mixture was stirred for 10 min, at which time diethoxymethylsilane (320 µL, 2.0 mmol, 2.0 equiv) was added and the stirring was continued for another 15 min at rt. Into a separate oven-dried test tube was added vinylsilane (1.0 mmol, 1.0 equiv) and O-benzoyl hydroxylamine (1.2 mmol, 2 equiv). The tube was sealed with a teflon-line screw cap and evacuated and backfilled with argon (this process was repeated a total of 3 times). The catalyst solution was then transferred via syringe to the reaction tube containing the substrates, and the reaction mixture was stirred at 40 °C for up to 36 h.

3. Dodecane (100 µL) was added as the internal standard for GC analysis. The reaction mixture was quenched with saturated aqueous Na$_2$CO$_3$ solution, extracted with EtOAc, dried over Na$_2$SO$_4$, filtered through a pad of silica, concentrated, and purified by column chromatography on silica gel.

**Example: (R)-N,N-dibenzyl-5-phenyl-1-(triethylysilyl)pentan-1-amine** (Table 2, entry 3a): From (Z)-triethyl(5-phenylpent-1-en-1-yl)silane ((Z)-1a) (261 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)$_2$ (7.3 mg, 0.04 mmol, 4 mol%), (R)-DTBM-SEGPHOS (52 mg, 0.044 mmol, 4.4 mol%), and O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol). The reaction mixture was stirred in THF (1 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0–5% EtOAc in hexanes) to afford 3a as a clear colorless oil (run 1: 375 mg (82%); run 2: 358 mg (78%));
average yield: 80%). HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm) indicated 93% ee: t_R (minor) = 6.4 min, t_R (major) = 6.9 min.

From (E)-triethyl(5-phenylpent-1-en-1-yl) silane ((E)-1a) (261 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)_2 (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), and O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol). The reaction mixture was stirred in THF (1 mL) at 40 °C for 8 h. The crude product was purified by flash column chromatography (0–5% EtOAc in hexanes) to afford 3a as a clear colorless oil (run 1: 456 mg (99%); 452 mg (99%); average yield: 99%). HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm) indicated >99% ee: t_R (minor) = 6.4 min, t_R (major) = 6.9 min. [α]_D^24 = -0.1 (c = 1.0, CHCl_3).

From Scheme 3, 10 mmol scale: From (E)-triethyl(5-phenylpent-1-en-1-yl)silane ((E)-1a) (2.60 g, 10.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)_2 (9.1 mg, 0.005 mmol, 0.5 mol%), (R)-DTBM-SEGPHOS (65 mg, 0.0055 mmol, 0.55 mol%), and O-benzoyl-N,N-dibenzylhydroxylamine (3.81 g, 12.0 mmol). The reaction mixture was stirred in THF (10 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0–5% EtOAc in hexanes) to afford 3a as a clear colorless oil (4.57 g, 99% yield). HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm) indicated >99% ee: t_R (minor) = 6.4 min, t_R (major) = 6.9 min.

^{1}H\ NMR (400 MHz, CDCl_3) δ 7.35 – 7.27 (m, 10H), 7.23 – 7.16 (m, 5H), 3.62 (s, 4H), 2.60 – 2.57 (t, J = 7.2 Hz, 2H), 2.33 – 2.30 (t, J = 5.2 Hz, 1H), 1.84 – 1.77 (m, 1H), 1.56 – 1.23 (m, 5H) 0.91 – 0.87 (t, J = 8.0 Hz, 9H), 0.91 – 0.87 (t, J = 8.0 Hz, 9H), 0.71 – 0.54 (m, 6H). ^{13}C\ NMR (101 MHz, CDCl_3) δ 142.7, 140.7, 129.0, 128.4, 128.2, 128.3, 126.6, 125.6, 56.6, 47.3, 35.9, 31.7, 28.9, 26.1, 7.8, 3.9. IR (neat, cm^{-1}): 3025, 2933, 2873, 1739, 1494, 1453, 136. Anal. Calcd. for C_{31}H_{43}NSi: C, 81.34; H, 9.47 Found: C, 81.10; H, 9.71.

(R)-N,N-dibenzyl-5-phenyl-1-(trimethylsilyl)pentan-1-amine

(Table 2, entry 3b): From (Z)-trimethyl(5-phenylpent-1-en-1-
yl)silane ((Z)-1b) (218 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)$_2$ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), and O-benzoyl-N,N-dibenzyldihydroxylamine (381 mg, 1.2 mmol). The reaction mixture was stirred in THF (1 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0–3% EtOAc in hexanes) to afford 3b as a clear colorless oil (run 1: 411 mg (99%); run 2: 411 mg (99%); average yield: 99%). HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm) indicated 92% ee: $t_R$ (minor) = 5.4 min, $t_R$ (major) = 6.5 min.

From (E)-trimethyl(5-phenylpent-1-en-1-yl)silane ((E)-1b) (207 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)$_2$ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), and O-benzoyl-N,N-dibenzyldihydroxylamine (381 mg, 1.2 mmol). The reaction mixture was stirred in THF (1 mL) at 40 °C for 8 h. The crude product was purified by flash column chromatography (0–3% EtOAc in hexanes) to afford 3b as a clear colorless oil (run 1: 369 mg (89%); run 2: 373 mg (90%); average run: 90%). HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm) indicated 99% ee: $t_R$ (minor) = 5.4 min, $t_R$ (major) = 6.5 min. [$\alpha$]$_D^{24}$ = $-4.2$ (c = 1.0, CHCl$_3$).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.49 – 7.47 (dd, $J = 6.8$, 10.2 Hz, 4H), 7.44 – 7.92 (m, 2H), 7.67 – 7.40 (m, 6H), 7.36 – 7.28 (m, 5H), 3.79 (s, 1H), 2.73 – 2.70 (t, $J = 8.0$ Hz, 2H), 2.32 – 2.28 (t, $J = 6.0$ Hz, 1H), 1.94 – 1.90 (m, 2H), 1.67 – 1.42 (m, 5H), 0.22 (s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 142.7, 140.8, 128.8, 128.4, 128.2, 128.1, 126.6, 125.6, 56.4, 49.7, 35.9, 31.6, 28.6, 26.0, -0.4. IR (neat, cm$^{-1}$): 3084, 3062, 3025, 2928, 2854, 1737, 1602, 1494, 1453, 1361, 1260, 1247, 832, 743, 696. Anal. Calcd. for C$_{28}$H$_{37}$NSi: C, 80.90; H, 8.97 Found: C, 80.80; H, 9.06.

$^{(R)}$N,N-dibenzyldi-(dimethyl(phenyl)silyl)-5-phenylpentan-1-amine (Table 2, entry 3c): From (Z)-dimethyl(phenyl)(5-phenylpent-1-en-1-yl)silane ((Z)-1c) (280 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)$_2$ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), and O-benzoyl-
N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol). The reaction mixture was stirred in THF (1 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0-5% EtOAc in hexanes) to afford 3c as a clear colorless oil (run 1: 354 mg (78%); run 2: 380 mg (82%); average yield: 80%). HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm) indicated 93% ee: tR (minor) = 8.0 min, tR (major) = 9.0 min.

From (E)-dimethyl(phenyl)(5-phenylpent-1-en-1-yl)silane ((E)-le) (280 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)2 (3.6 mg, 0.02 mmol, 2 mol%), (R)-OTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), and O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol). The reaction mixture was stirred in THF (1 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0-5% EtOAc in hexanes) to afford 3c as a clear colorless oil (run 1: 422 mg (88%); 453 mg (95%); average yield 92%). HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm) indicated 99% ee: tR (minor) = 8.0 min, tR (major) = 9.0 min. [α]24D = -13.0 (c = 1.0, CHCl3).

1H NMR (400 MHz, CDCl3) δ 7.5 - 7.42 (m, 2H), 7.33 - 7.19 (m, 16H), 7.11 - 7.09 (dd, J = 7.6, 1.6 Hz, 2H), 3.60 (s, 4H), 2.49 - 2.45 (t, J = 8.4 Hz, 2H), 2.43 - 2.40 (t, J = 5.2 Hz, 1H), 1.78 - 1.76 (m, 1H), 1.46 - 1.36 (m, 4H), 1.19 - 1.17 (m, 1H), 0.38 (d, J = 2.8 Hz, 6H). 13C NMR (101 MHz, CDCl3) δ 142.7, 140.6, 134.0, 128.9, 128.8, 128.4, 128.2, 128.0, 127.7, 126.7, 125.5, 56.3, 49.5, 35.8, 31.4, 28.4, 26.0, -1.6, -2.7. IR (neat, cm⁻¹): 3062, 3024, 2928, 2854, 1739, 1602, 1494, 1453, 1427, 1365, 1246, 1229, 1217, 1108, 830, 806, 732, 695. Anal. Calcd. for C33H39NSi: C, 82.96; H, 8.23 Found: C, 82.77; H, 8.19.

(R)-N,N-dibenzyl-1-(methylenebiphenylsilyl)-5-phenylpentan-1-amine (Table 2, entry 3d): From (Z)-methylbiphenyl(5-phenylpent-1-en-1-yl)silane ((Z)-1d) (342 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)2 (7.3 mg, 0.04 mmol, 4 mol%), (R)-DTBM-SEGPHOS (52 mg, 0.044 mmol, 4.4 mol%), and O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol). The reaction mixture was stirred in THF (0.5 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0-5%
EtOAc in hexanes) to afford 3d as a clear colorless oil (run 1: 448 mg (83%); 453 mg (84%); average yield: 84%). HPLC analysis (OT-(+), 1% IPA/hexanes, 0.8 mL/min, 220 nm) indicated 84% ee: \( t_R \) (minor) = 8 min, \( t_R \) (major) = 10 min.

From \((E)\)-methyldiphenyl-(5-phenylpent-1-en-1-yl)silane ((E)-ld) (342 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)\(_2\) (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), and O-benzoyl-\(N,N\)-dibenzylhydroxylamine (381 mg, 1.2 mmol). The reaction mixture was stirred in THF (1 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0–5% EtOAc in hexanes) to afford 3d as a clear colorless oil (run 1: 456 mg (84%); run 2: 472 mg (87%); average yield: 86%). HPLC analysis (OT-(+), 1% IPA/hexanes, 0.8 mL/min, 220 nm) indicated 99% ee: \( t_R \) (minor) = 8 min, \( t_R \) (major) = 10 min. \[ \alpha \] \( \text{D} \) = +6.5 (c = 2.0, CHCl\(_3\)).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.55 – 7.53 (dt, \( J = 6.0, 1.6 \) Hz, 2H), 7.50 – 7.48 (dt, \( J = 6.4, 1.6 \) Hz, 2H), 7.42 – 7.23 (m, 19H), 7.15 – 7.12 (dd, \( J = 8.0, 0.8 \) Hz, 2H), 3.65 (s, 4H), 3.02 – 2.98 (t, \( J = 7.2 \) Hz, 1H), 2.53 – 2.47 (td, \( J = 7.4, 2.8 \) Hz, 2H), 1.96 – 1.91 (m, 1H), 1.61 – 1.59 (m, 1H), 1.50 – 1.40 (m, 3H), 1.28 – 1.21 (m, 1H), 0.78 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 142.6, 140.4, 137.7, 136.8, 134.9, 134.8, 129.1, 129.0, 128.4, 128.1, 128.0, 127.8, 127.7, 126.7, 125.5, 56.3, 48.2, 35.7, 31.3, 28.4, 26.2, -3.2. IR (neat, cm\(^{-1}\)): 3024, 2927, 2854, 1739, 1494, 1453, 1427, 1365, 1229, 1217, 1104, 1027, 785, 734, 695. Anal. Caled. for C\(_{15}\)H\(_{16}\)N\(_2\): C, 84.55; H, 7.66 Found: C, 84.78; H, 7.43.

\((R)\)-6-(dibenzamido)-6-(triethylsilyl)hexanenitrile (Table 3, entry 5a): From \((E)\)-6-(triethylsilyl)hex-5-enenitrile (209 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)\(_2\) (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (25.9 mg, 0.022 mmol, 2.2 mol%), and O-benzoyl-\(N,N\)-dibenzylhydroxylamine (381 mg, 1.2 mmol). The reaction mixture was stirred in THF (1 mL) at 40 °C for 16 h. The crude product was purified by flash column chromatography (5% EtOAc in hexanes) to afford 5a as a clear colorless oil (run 1: 312 mg (77%); run 2: 282 mg (69%); average yield: 73%). HPLC analysis
(OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm) indicated 99% ee: $t_R$ (minor) = 16.0 min, $t_R$ (major) = 18.3 min. $[\alpha]_D^{24} = -28.8$ (c = 2.0, CHCl$_3$).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.35 - 7.28 (m, 8H), 7.25 - 7.20 (m, 2H), 3.69 - 3.58 (d, $J = 13.2, 14.8$ Hz, 4H), 2.33 - 2.30 (dd, $J = 4.8, 4.0$ Hz, 1H), 2.22 - 2.18 (t, $J = 6.8$ Hz, 2H), 1.78 - 1.76 (m, 1H), 1.55 - 1.28 (m, 5H), 0.96 - 0.92 (t, $J = 8.0$ Hz, 9H), 0.91 - 0.87 (t, $J = 8.0$ Hz, 9H), 0.77 - 0.61 (m, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 140.5, 129.0, 128.1, 126.8, 119.7, 56.7, 46.6, 27.7, 26.3, 25.2, 17.1, 7.8, 4.1. IR (neat, cm$^{-1}$): 2949, 2873, 1493, 1453, 1418, 1360, 1239, 1109, 1004, 722, 697. Anal. Calcd. for C$_{26}$H$_{35}$N$_2$Si: C, 76.79; H, 9.42 Found: C, 77.18; H, 9.06.

(R)-$N$$_2$N-dibenzyl-5-chloro-1-(triethylsilyl)pentan-1-amine (Table 3, entry 5b): From (E)-(5-chloropent-1-en-1-yl)triethylsilane (209 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)$_2$ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), and O-benzoyl-$N$$_2$N-dibenzylhydroxylamine (381 mg, 1.2 mmol). The reaction mixture was stirred in THF (1 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0–5% EtOAc in hexanes) to afford 5b as a clear colorless oil (run 1: 391 mg (94%); run 2: 410 mg (98%); average yield 96%). SFC analysis$^{21}$ (Chiralpak IC(4.6x150 mm, 3µm), isocratic 3% EtOH) indicated >99% ee: $t_R$ (minor) = 1.15 minute, $t_R$ (major) = 1.28 min. $[\alpha]_D^{24} = -18.5$ (c = 1.0, CHCl$_3$).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.43 - 7.42 (dd, $J = 6.4, 1.6$ Hz, 4H), 7.39 - 7.35 (tt, $J = 7.2, 1.6$ Hz, 4H), 3.71 (s, 4H), 3.54 - 3.51 (t, $J = 5.6$ Hz, 2H), 2.41 - 2.38 (dd, $J = 8.0, 5.6$ Hz, 1H), 1.90 - 1.82 (m, 1H), 1.72 - 1.56 (m, 3H), 1.49 - 1.37 (m, 2H), 1.01 - 0.97 (t, $J = 8.0$ Hz, 9H), 0.84 - 0.65 (m, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 140.6, 129.0, 128.1, 126.7, 56.6, 47.0, 45.0, 32.6, 26.2, 25.8, 7.8, 4.0. IR (neat, cm$^{-1}$): 2952, 2873, 1494, 1453, 1359, 1104, 1027, 1003, 725, 653. Anal. Calcd. for C$_{25}$H$_{38}$CIN$_2$: C, 72.16; H, 9.20 Found: C, 72.13; H, 9.21.

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(R)-N,N-dibenzyl-5-chloro-1-(triethylsilyl)pentan-1-amine (Table 3, entry 5c): From (E)-methyl 6-(triethylsilyl)hex-5-enoate (242 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)$_2$ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), and O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol). The reaction mixture was stirred in THF (1 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0–5% EtOAc in hexanes) to afford 5c as a clear colorless oil (run 1: 343 mg (78%); run 2: 360 mg (82%); average yield: 80%). HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm) indicated 99% ee: $t_R$ (minor) = 7.4 min, $t_R$ (major) = 7.9 min. $[\alpha]_D^{24} = -9.3$ (c = 2.0, CHCl$_3$).

$1^H$ NMR (400 MHz, CDCl$_3$) $\delta$ 7.36 – 7.34 (m, 8H), 7.24 – 7.20 (tt, $J$ = 7.2, 1.6 Hz, 2H), 3.69 (s, 3H), 3.63 (s, 4H), 2.33 – 2.26 (m, 3H), 1.81 – 1.76 (m, 1H), 1.60 – 1.21 (m, 5H), 0.93 – 0.89 (t, $J$ = 8.0 Hz, 9H), 0.74 – 0.57 (m, 6H). $^{13}C$ NMR (101 MHz, CDCl$_3$) $\delta$ 174.2, 140.6, 129.0, 128.0, 126.7, 56.6, 51.4, 47.2, 34.1, 28.7, 26.0, 25.2, 7.8, 3.9. IR (neat, cm$^{-1}$): 2950, 2874, 1739, 1494, 1453, 1360, 1168, 1075, 966, 827, 726, 697. HRMS (DART-TOF) calculated for C$_{21}$H$_{41}$N$_2$O$_2$Si [M+H]$^+$ m/z 440.2979, found 440.2992.

(R)-N-benzyl-N-(4-(dibenzylamino)-4-(triethylsilyl)butyl)-4-methylbenzenesulfonamide (Table 3, entry 5d): From (E)-N-benzyl-4-methyl-N-(4-(triethylsilyl)but-3-en-1-yl)benzene sulfonamide ((E)-1h) (430 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)$_2$ (7.3 mg, 0.04 mmol, 4 mol%), (R)-DTBM-SEGPHOS (52 mg, 0.044 mmol, 4.4 mol%), and O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol). The reaction mixture was stirred in THF (1 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0–5% EtOAc in hexanes) to afford 5d as a clear colorless oil (run 1: 606 mg (97%); run 2: 624 mg (99%); average yield: 98%). HPLC analysis (OD-H, 5% IPA/pentane, 0.8 mL/min, 220 nm) indicated 99% ee: $t_R$ (minor) = 15.7 min, $t_R$ (major) = 18.0 min. $[\alpha]_D^{24} = -7.2$ (c = 1.0, CHCl$_3$).
\textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.76 - 7.72 (dt, \(J = 10.8, 3.2\) Hz, 2H), 7.40 - 7.18 (m, 16H), 4.30 (s, 2H), 3.57 - 3.40 (dd, \(J = 30.4, 18.0\) Hz, 2H), 3.11 - 2.96 (m, 2H), 2.43 (s, 3H), 2.14 - 2.10 (t, \(J = 8.0\) Hz, 1H), 1.55 - 1.39 (m, 2H), 0.85 - 0.80 (t, \(J = 10.4\) Hz, 9H), 0.63 - 0.43 (m, 6H).

\textbf{\textsuperscript{13}C NMR} (101 MHz, CDCl\textsubscript{3}) \(\delta\) 143.1, 140.4, 137.2, 136.6, 129.7, 128.9, 128.5, 128.2, 128.0, 127.7, 127.1, 126.7, 56.4, 51.9, 48.6, 47.3, 28.0, 23.4, 21.5, 7.7, 3.7. IR (neat, cm\textsuperscript{-1}): 3026, 2949, 2873, 1599, 1494, 1453, 1340, 1158, 1092, 1027, 1010, 814, 726, 696, 656. Anal. Calcd. for C\textsubscript{38}H\textsubscript{50}N\textsubscript{2}O\textsubscript{2}Si: C, 72.80; H, 8.04 Found: C, 72.77; H, 7.90.

\textbf{(R)-N,N-dibenzyl-4-((tert-butylidimethylsilyl)oxy)-1-(dimethyl(phenyl)silyl)butan-1-amine} (Table 3, entry 5e): From (E)-\textit{tert}-\textsuperscript{Si(Me\textsubscript{2})\textsubscript{2}Ph}butyl(4-(dimethyl(phenyl)silyl)but-3-en-1-yl)oxy)dimethylsilane (321 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)\textsubscript{2} (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 2.2 mol%), and O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol). The reaction mixture was stirred in THF (1 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0-5% EtOAc in hexanes) to afford 5e as a clear colorless oil (run 1: 503 mg (97%); run 2: 487 mg (94%); average yield: 96%). HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm) indicated 96% ee: \(t_r\) (minor) = 5.0 min, \(t_r\) (major) = 5.5 min. \([\alpha]_D^{24}\) = -24.5 (c = 1.0, CHCl\textsubscript{3}).

\textbf{\textsuperscript{1}H NMR} (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.35 - 7.27 (m, 2H), 7.42 - 7.32 (m, 11H), 7.30 - 7.25 (m, 2H), 3.69 (s, 4H), 3.57 - 3.47 (m, 2H), 2.52 - 2.47 (td, \(J = 7.0, 2.0\) Hz, 1H), 1.92 - 1.84 (m, 1H), 1.69 - 1.56 (m, 2H), 1.47 - 1.37 (m, 1H), 0.97 (s, 9H), 0.48 (s, 6H), 0.09 (s, 6H). \textbf{\textsuperscript{13}C NMR} (101 MHz, CDCl\textsubscript{3}) \(\delta\) 140.5, 139.3, 134.0, 128.9, 128.8, 128.0, 127.7, 126.7, 63.0, 56.3, 49.4, 32.3, 26.0, 22.3, 18.3, -1.6, -2.5, -5.6. IR (neat, cm\textsuperscript{-1}): 2927, 2855, 1494, 1453, 1248, 1096, 1027, 807, 227, 732, 696. Anal. Calcd. for C\textsubscript{32}H\textsubscript{41}NOSi: C, 74.21; H, 9.15 Found: C, 73.94; H, 9.25.
(R)-N,N-dibenzyl-1-(dimethyl(phenyl)silyl)-3-methoxypropan-1-amine (Table 3, entry 5f): From (E)-(3-methoxyprop-1-en-1-yl)dimethyl(phenyl)silane (206 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)$_2$ (7.3 mg, 0.04 mmol, 4 mol%), (R)-DTBM-SEGPHOS (52 mg, 0.044 mmol, 4.4 mol%), and O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol). The reaction mixture was stirred in THF (0.5 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (5–10% EtOAc in hexanes) to afford 5f as a clear colorless oil (run 1: 366 mg (91%); run 2: 354 mg (88%); average yield: 90%). HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm) indicated 99% ee: $t_R$ (minor) = 6.2 min, $t_R$ (major) = 7.5 min. $[\alpha]_D^{24} = -40.4$ (c = 1.0, CHCl$_3$).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.51 – 7.48 (m, 2H), 7.39 – 7.22 (m, 13H), 3.63 (s, 4H), 3.43 – 3.80 (m, 1H), 3.20 (s, 3H), 3.20 – 3.15 (m, 1H), 2.58 – 2.54 (dd, $J = 8.4, 5.6$ Hz, 1H), 2.11 – 2.02 (m, 5H) 1.77 – 1.68 (m, 1H), 0.43 – 0.42 (d, $J = 3.6$ Hz, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 140.4, 138.9, 134.0, 128.9, 128.9, 128.0, 127.7, 126.7, 72.2, 58.3, 56.4, 46.6, 26.6, -1.9, -2.8. IR (neat, cm$^{-1}$): 2923, 1494, 1453, 1248, 1109, 807, 732, 696. HRMS (DART-TOF) calculated for C$_{26}$H$_{33}$NOSi [M+H]$^+$ m/z 404.2404, found 404.2419.

(R)-N,N-dibenzyl-1-(dimethyl(phenyl)silyl)-3-phenylpropan-1-amine (Table 3, entry 5g): From (E)-dimethyl(phenyl)(3-phenylprop-1-en-1-yl)silane (252 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)$_2$ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), and O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol). The reaction mixture was stirred in THF (1 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0–5% EtOAc in hexanes) to afford 5g as a clear colorless oil (run 1: 444 mg (99%); run 2: 443 mg (99%); average yield: 99%). HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm) indicated 98% ee: $t_R$ (minor) = 6.1 min, $t_R$ (major) = 8.9 min. $[\alpha]_D^{24} = +7.4$ (c = 1.0, CHCl$_3$).
From \((Z)\)-dimethyl(phenyl)(3-phenylprop-1-en-1-yl)silane (252 mg, 1.0 mmol), the title compound was prepared following the general procedure using \(\text{Cu(OAc)}_2\) (3.6 mg, 0.02 mmol, 2 mol%), \((R)\)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), and \(O\)-benzoyl-\(N,N\)-dibenzylhydroxylamine (381 mg, 1.2 mmol). The reaction mixture was stirred in THF (1 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0–5% EtOAc in hexanes) to afford \(5g\) as a clear colorless oil (run 1: 443 mg (98%); run 2: 436 mg (97%); average yield: 98%). HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm) indicated 89% ee: \(t_R\) (minor) = 6.7 min, \(t_R\) (major) = 9.7 min. \([\alpha]_D^{24} = +5.4\) (c = 1.0, CHCl₃).

\(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 7.58 – 7.55 (m, 2H), 7.44 – 7.37 (m, 11H), 7.36 – 7.30 (m, 4H), 7.28 – 7.23 (m, 1H), 7.08 – 7.06 (dd, \(J = 8.0, 1.6\) Hz, 2H), 3.75 (s, 4H), 2.80 – 2.72 (m, 1H), 2.63 – 2.60 (dd, \(J = 6.4, 1.2\) Hz, 1H), 2.45 – 2.37 (m, 1H), 2.20 – 2.11 (m, 1H), 1.90 – 1.80 (m, 1H), 0.53 – 0.52 (d, \(J = 2.4\) Hz, 6H). \(^{13}\)C NMR (101 MHz, CDCl₃) \(\delta\) 142.9, 140.5, 139.2, 134.0, 129.0, 128.9, 128.3, 128.3, 128.1, 127.8, 127.7, 126.7, 125.6, 56.4, 49.6, 35.3, 28.9, -1.6, -2.7. IR (neat, cm⁻¹): 3024, 1601, 1494, 1453, 1427, 1247, 1108, 1067, 1027, 806, 731, 694. HRMS (DART-TOF) calculated for \(\text{C}_{31}\text{H}_{35}\text{NSi}^+\text{M+H}^+\) m/z 450.2612, found 450.2631.

\((R)\)-\(N,N\)-dibenzyl-1-(dimethyl(phenyl)silyl)-2-(1-methoxycyclohexyl)ethanamine (Table 3, entry 5h): From \((E)\)-(2-(1-methoxycyclohexyl)vinyl)dimethyl(phenyl)silane (274 mg, 1.0 mmol.), the title compound was prepared following the general procedure using \(\text{Cu(OAc)}_2\) (7.2 mg, 0.04 mmol, 4 mol%), \((R)\)-DTBM-SEGPHOS (52 mg, 4.4 mol%), and \(O\)-benzoyl-\(N,N\)-dibenzylhydroxylamine (381 mg, 1.2 mmol). The reaction mixture was stirred in THF (0.5 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0–20% EtOAc in hexanes) to afford 5h as white solid (run 1: 415 mg (88%); run 2: 401 mg (85%); average yield: 86%); m.p. = 110–112 °C. HPLC analysis (OD-H, 90:5:0.1 Hexanes: IPA: Diethylamine, 0.8 mL/min, 220 nm) indicated 92% ee: \(t_R\) (minor) = 7.4 min, \(t_R\) (major) = 7.9 min. \([\alpha]_D^{24} = -35.2\) (c = 1.0, CHCl₃).
\[ \text{H NMR} \ (400 \text{ MHz, CDCl}_3) \delta \ 7.60 - 7.55 \ (m, \ 2H), \ 7.39 - 7.32 \ (m, \ 11H), \ 7.30 - 7.44 \ (m, \ 2H), \\
3.81 - 3.60 \ (dd, \ J = 72.6, \ 13.2 \ Hz, \ 4H), \ 2.98 \ (s, \ 3H), \ 2.75 - 2.72 \ (dd, \ J = 7.8, \ 3.2 \ Hz, \ 1H), \ 1.99 \\
- 1.93 \ (dd, \ J = 14.8, \ 7.62 \ Hz, \ 1H), \ 1.59 - 1.36 \ (m, \ 5H), \ 1.32 - 1.25 \ (m, \ 3H) \ 1.20 - 1.13 \ (td, \ J = \\
12.2, \ 3.6 \ Hz, \ 1H), \ 0.98 - 0.83 \ (m, \ 2H), \ 0.53 - 0.51 \ (d, \ J = 9.2 \ Hz, \ 6H). \ ]

\[ \text{C NMR} \ (101 \text{ MHz, CDCl}_3) \delta \ 140.3, \ 139.7, \ 134.1, \ 129.3, \ 128.7, \ 128.0, \ 127.7, \ 126.7, \ 76.0, \ 56.7, \ 47.6, \ 45.8, \ 34.3, \\
33.5, \ 32.5, \ 25.3, \ 22.0, \ 21.9, -0.4, -2.2. \ ]

IR (neat, cm\(^{-1}\)): 2945, 2856, 1491, 1453, 1244, 1070, 806, 796, 745, 732, 697. HRMS (DART-TOF) calculated for \( \text{C}_{31}\text{H}_{41}\text{NOSi} \ [\text{M}+\text{H}]^+ \) m/z \( 472.3030 \), found 472.3024.

\chem{(R)—N^1,N^1,N^2\text{-tribenzyl-1-}(\text{methylidiphenylsilyl)pentane-1,5-}}
\text{diamine} \ (\text{Table 3, entry 5i}) \text{: From (E)-N-benzyl-5-}
\text{(methylidiphenylsilyl)pent-4-en-1-amine} \ (372 \text{ mg, 1.0 mmol), the}
\text{title compound was prepared following the general procedure using}
\text{Cu(OAc)}_2 \ (7.2 \text{ mg, 4 mol%), (R)-DTBM-SEGPHOS} \ (52 \text{ mg, 4.4 mol%), and O-benzoyl-N,N-}
\text{dibenzylhydroxylamine} \ (381 \text{ mg, 1.2 mmol). The reaction mixture was stirred in THF} \ (0.5 \text{ mL})
at 40 ^\circ \text{C for 36 h. The crude product was purified by flash column chromatography (0–20%}
\text{EtOAc in hexanes) to afford 5i as a yellow oil (run 1: 542 mg (95%); run 2: 507 mg (89%)};
\text{average yield: 92%). HPLC analysis (OD-H, 90:5:0.1 Hexanes: IPA: Diethylamine, 0.8}
\text{mL/min, 220 nm) indicated 93% ee: } t_R \text{ (major) = 12.3 min, } t_R \text{ (minor) = 13.5 min. } [\alpha]_D^{24} \text{ = } +0.2
\text{(c = 1.0, CHCl}_3).
(R)-N,N-dibenzyl-2-methyl-1-(methyldiphenylsilyl)propan-1-amine

(Table 3, entry 5j): From methyl(2-methylprop-1-en-1-yl)diphenylsilane (274 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)$_2$ (7.2 mg, 0.04 mmol, 4 mol%), (R)-DTBM-SEGPHOS (52 mg, 0.044 mmol, 4.4 mol%), and O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol). The reaction mixture was stirred in THF (0.5 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0-3% EtOAc in hexanes) to afford 5j as a clear colorless oil (run 1: 322 mg (72%); run 2: 339 mg (75%); average yield: 74%). HPLC analysis (OT(+), 1% IPA/Hexanes, 0.8 mL/min, 220 nm) indicated 99% ee: t$_R$ (minor) = 6.7 min, t$_R$ (major) = 9.3 min. [α]$_D$$^{24}$ = -27.2 (c = 1.0, CHCl$_3$).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.61 - 7.57 (m, 4H), 7.42 - 7.26 (m, 16H), 3.86 - 3.75 (dd, $J$= 17.6, 13.6 Hz, 4H), 0.84 - 0.82 (d, $J$ = 6.4 Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 140.4, 138.8, 138.1, 135.2, 134.7, 129.3, 128.9, 128.8, 128.0, 127.76, 127.7, 126.7, 56.9, 55.1, 29.2, 23.4, 23.1, -1.8. IR (neat, cm$^{-1}$): 3024, 29545, 1601, 1493, 1453, 1427, 1254, 1103, 1068, 786, 728, 696, 2856, 1491, 1453, 1244, 1070, 806, 796, 745, 732, 697. HRMS (DART-TOF) calculated for C$_{31}$H$_{37}$NSi [M+H]$^+$ m/z 450.2612, found 450.2592.

(R)-N,N-dibenzyl-3-methyl-1-(methyldiphenylsilyl)butan-1-amine

(Table 3, entry 5k): From (E)-methyl(3-methylbut-1-en-1-yl)diphenylsilane (266 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)$_2$ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), and O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol). The reaction mixture was stirred in THF (1 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0-3% EtOAc in hexanes) to afford 5k as colorless crystals (run 1: 462 mg (99%); run 2: 462 mg (99%); average yield: 99%); m.p. = 82-85 °C. HPLC analysis (OD-H, 97% Hexanes/ 3% of '97 Hexanes: 3 EtOH: 0.2 TFA: 0.1 DEA', 0.8 mL/min, 220 nm) indicated 94% ee: t$_R$ (minor) = 5.4 min, t$_R$ (major) = 5.9 min. [α]$_D$$^{24}$ = -22.9 (c = 1.0, CHCl$_3$).
\textbf{H NMR} (400 MHz, CDCl$_3$) ð 7.60 – 7.57 (dt, $J = 5.6$, 1.6 Hz, 2H), 7.55 – 7.52 (dt, $J = 6.0$, 1.6 Hz, 2H), 7.44 – 7.26 (m, 16H), 3.71 – 3.62 (dd, $J = 13.6$, 6.4 Hz, 4H), 3.14 – 3.10 (dd, $J = 6.0$, 1.6 Hz, 1H), 1.82 – 1.66 (m, 2H), 1.40 – 1.34 (m, 1H), 0.84 (s, 3H), 0.81 – 0.80 (d, $J = 6.8$ Hz, 3H) 0.59 – 0.58 (d, $J = 6.4$ Hz, 3H).

\textbf{13C NMR} (101 MHz, CDCl$_3$) ð 140.6, 137.9, 136.8, 134.9, 134.9, 129.1, 129.0, 129.0, 128.0, 127.8, 127.7, 126.7, 56.2, 45.9, 36.2, 25.3, 23.0, 22.1, -3.0.

\textbf{IR} (neat, cm$^{-1}$): 3025, 2952, 1601, 1494, 1427, 1104, 1027, 784, 734, 724, 696. Anal. Calcd. for C$_{32}$H$_{31}$NSi: C, 82.88; H, 8.04 Found: C, 82.60; H, 8.11.

\textbf{HRMS} (DART-TOF) calculated for C$_{32}$H$_{31}$NSi [M+H]$^+$ m/z 390.3551, found 390.3534.

\textbf{(R)-N,N-dibutyl-5-phenyl-1-((triethylsilyl)pentan-1-amine} (Table 4, entry 6a): From (E)-triethyl(5-phenylpent-1-en-1-yl)silane ((E)-1a) (260 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)$_2$ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 2.2 mol%), and O-benzoyl-N,N-dibutylhydroxylamine (299 mg, 1.2 mmol). The reaction mixture was stirred in THF (1 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0-5% EtOAc in hexanes) to afford 6a as a clear colorless oil (run 1: 305 mg (78%); run 2: 303 mg (78%); average yield: 78%). HPLC analysis (3 connected OD-H columns, 97% Hexanes/3% of '92 Hexanes: 8 EtOH: 0.2 TFA: 0.1 DEA', 0.55 mL/min, 220 nm) indicated >99% ee: $t_R$ (major) = 51 min, $t_R$ (minor) = 54 min. $[\alpha]_D^{24} = -4.0$ (c = 1.0, CHCl$_3$).

\textbf{H NMR} (400 MHz, CDCl$_3$) ð 7.30 – 7.26 (m, 2H), 7.19 – 7.15 (m, 3H), 2.63 – 2.60 (t, $J = 7.6$ Hz, 2H), 2.46 – 2.35 (m, 4H), 2.25 – 2.22 (t, $J = 5.2$ Hz, 1H), 1.66 – 1.53 (m, 3H), 1.51– 1.46 (m, 1H), 1.39 – 1.23 (m, 10H), 0.98 – 0.94 (t, $J = 8.0$ Hz, 9H), 0.92 – 0.88 (t, $J = 7.2$ Hz, 6H), 0.66 – 0.53 (m, 6H). \textbf{13C NMR} (101 MHz, CDCl$_3$) ð 128.48, 128.2, 125.5, 53.5, 36.0, 32.1, 31.9, 29.2, 27.1, 20.6, 14.2, 7.9, 4.0. \textbf{IR} (neat, cm$^{-1}$): 2953, 2928, 2872, 1496, 1453, 1076, 1010, 721, 697. HRMS (DART-TOF) calculated for C$_{25}$H$_{47}$NSi [M+H]$^+$ m/z 390.3551, found 390.3534.
(R)-4-(5-phenyl-1-(triethylsilyl)pentyl)morpholine (Table 4, entry 6b): From (E)-triethyl(5-phenylpent-1-en-1-yl)silane ((E)-1a) (260 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)$_2$ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), and morpholino benzoate (249 mg, 1.2 mmol). The reaction mixture was stirred in THF (1 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0–5% EtOAc in hexanes) to afford 6b as a clear colorless oil (run 1: 347 mg (99%); run 2: 345 mg (99%); average yield: 99%). HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm) indicated >99% ee: t$_R$ (minor) = 8.0 min, t$_R$ (major) = 10.4 min. [$\alpha$]$_{D}^{24}$ = -7.4 (c = 2.0, CHCl$_3$).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.31 – 7.26 (m, 2H), 7.20 – 7.16 (m, 3H), 3.64 – 3.62 (t, $J$ = 4.4 Hz, 4H), 2.68 – 2.53 (m, 4H), 2.59 – 2.53 (m, 2H), 2.10 – 2.07, (m, $J$ = 8.8, 4.8 Hz, 1H), 1.74 – 1.57 (m, 2H), 1.55 – 1.45 (m, 1H), 1.42 – 1.32 (m, 2H), 0.99 – 0.95 (t, $J$ = 8.0 Hz, 9H), 0.64 – 0.56 (m, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 142.7, 128.4, 128.2, 125.6, 67.8, 55.0, 52.2, 35.9, 31.7, 29.7, 26.4, 7.8, 3.9. IR (neat, cm$^{-1}$): 2950, 2873, 2850, 1496, 1453, 1415, 1117, 1001, 878, 715, 697. HRMS (DART-TOF) calculated for C$_{21}$H$_{31}$NOSi [M+H]$^+$ m/z 348.2717, found 348.2727.

(R)-N-benzyl-N-methyl-5-phenyl-1-(triethylsilyl)pentan-1-amine (Table 4, entry 6c): From (E)-triethyl(5-phenylpent-1-en-1-yl)silane ((E)-1a) (260 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)$_2$ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), and O-benzoyl-N-benzyl-N-methylhydroxylamine (290 mg, 1.2 mmol). The reaction mixture was stirred in THF (1 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0–5% EtOAc in hexanes) to afford 6c as a clear colorless oil in (run 1: 359 mg (94%); run 2: 359 mg (94%); average yield: 94%). [$\alpha$]$_{D}^{24}$ = -12.5 (c = 2.0, CHCl$_3$).

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\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.33 - 7.28 \) (m, 6H), \(7.26 - 7.18 \) (m, 4H), \(3.69 - 3.68 \) (d, \(J = 4.0 \) Hz, 2H), \(2.68 - 2.64 \) (t, \(J = 8.0 \) Hz, 2H), \(2.33 - 2.30 \) (dd, \(J = 8.4, 5.2 \) Hz, 1H), \(2.23 \) (s, 3H), \(1.86 - 1.76 \) (m, 1H), \(1.68 - 1.63 \) (m, 2H), \(1.57 - 1.54 \) (m, 1H), \(1.47 - 1.37 \) (m, 2H), \(1.01 - 0.99 \) (t, \(J = 7.6 \) Hz, 9H), \(0.73 - 0.58 \) (m, 6H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 142.8, 141.0, 128.5, 128.4, 128.2, 128.0, 126.5, 125.6, 61.6, 53.7, 40.1, 36.0, 31.9, 29.5, 26.4, 7.9, 4.0.\) IR (neat, cm\(^{-1}\)):

3026, 2932, 2873, 2784, 1739, 1494, 1453, 1365, 1229, 1217, 1119, 1006, 725, 696. Anal. Calcd. for C\(_{25}\)H\(_{39}\)NSi: C, 78.67; H, 10.30. Found: C, 78.54; H, 10.27.

This product was transformed into \((R)-N\)-methyl-\(N\)-(5-phenyl-1-(triethylsilyl)pentyl)acetamide for chiral HPLC analysis using the following procedure. 6c (76 mg, 0.2 mmol), Pd(OH)\(_2\) on carbon (20 wt%, 76 mg), and acetic anhydride (1 mL) were added to a round bottom flask equipped with a stir bar. The flask was evacuated and backfilled with hydrogen (this process was repeated a total of 3 times) and stirred at rt overnight (~12 h) under a H\(_2\) atmosphere (1 atm). The reaction mixture was filtered through a pad of Celite, then quenched with saturated aqueous Na\(_2\)CO\(_3\) solution, extracted with EtOAc, dried over Na\(_2\)SO\(_4\), and the solvent was removed under reduced pressure. The crude product was purified by preparative TLC (50% EtOAc in hexanes) to afford the title compound as a yellow oil (run 1: 50 mg (75%); run 2: 60 mg (90%); average yield: 82%). HPLC analysis (OD-H, 1% IPA/hexanes, 0.8 mL/min, 220 nm) indicated 98% ee: \(t_R\) (minor) = 13 min, \(t_R\) (major) = 15 min.

\((R)-2-(4-(5-phenyl-1-(triethylsilyl)pentyl)piperazin-1-yl)pyrimidine\) (Table 4, entry 6d): From \((E)-triethyl(5-phenylpent-1-en-1-yl)silane\) \((E)-1a\) (260 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)\(_2\) (3.6 mg, 0.02 mmol, 2 mol%), \((R)-DTBM-SEGPHOS\) (26 mg, 0.022 mmol, 2.2 mol%), and \(4-(pyrimidin-2-yl)piperazin-1-yl\) benzoate \((2b)\) (341 mg, 1.2 mmol). The reaction mixture was stirred in THF (1 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0–10% EtOAc in hexanes) to afford \(6d\) as a clear colorless oil (run 1: 360 mg (85%); run 2: 375 mg (88%);
average yield: 87%). HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm) indicated >99% ee: $t_R$ (minor) = 10.6 min, $t_R$ (major) = 11.5 min. $[\alpha]_D^{24} = -1.5$ (c = 1.0, CHCl$_3$).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.30 - 8.29 (d, $J = 4.8$ Hz, 2H), 7.29 - 7.24 (m, 2H), 7.18 - 7.14 (m, 3H), 6.46 - 6.43 (t, $J = 4.4$ Hz, 1H), 3.75 - 3.73 (t, $J = 4.8$ Hz, 4H), 2.73 - 2.66 (m, 2H), 2.64 - 2.56 (m, 4H), 2.20 - 2.17 (dd, $J = 8.8$, 4.8 Hz, 1H), 1.74 - 1.68 (m, 1H), 1.66 - 1.57 (m, 1H), 1.51 - 1.44 (m, 1H), 1.42 - 1.31 (m, 2H), 0.99 - 0.95 (t, $J = 8.0$ Hz, 9H), 0.64 - 0.58 (m, 6H).

$^1^3$C NMR (101 MHz, CDCl$_3$) $\delta$ 161.7, 157.6, 142.7, 128.3, 128.3, 125.6, 109.4, 54.9, 51.7, 44.6, 35.9, 31.7, 29.8, 26.5, 7.8, 3.9. IR (neat, cm$^{-1}$): 3024, 2932, 2872, 1738, 1584, 1545, 1495, 1445, 1355, 1259, 1217. Anal. Calcd. for C$_{25}$H$_{40}$N$_4$Si: C, 70.70; H, 9.47. Found: C, 70.40; H, 9.53.

(R)-N,N-bis(4-methoxybenzyl)-5-phenyl-1-(triethylsilyl)pentan-1-amine (Table 4, entry 6e): From (E)-triethyl(5-phenylpent-1-en-1-yl)silane ((E)-1a) (260 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)$_2$ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), and O-benzoyl-N-benzyl-N-methylhydroxylamine (2c) (290 mg, 1.2 mmol). The reaction mixture was stirred in THF (1 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0-5% EtOAc in hexanes) to afford 6e as a clear colorless oil (run 1: 517 mg (99%); run 2: 515 mg (99%); average yield: 99%). HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm) indicated >99% ee: $t_R$ (minor) = 9.8 min, $t_R$ (major) = 11.8 min. $[\alpha]_D^{24} = -6.7$ (c = 1.0, CHCl$_3$).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.33 - 7.28 (tt, $J = 8.0$, 0.8 Hz, 2H), 7.25 - 7.17 (m, 7H), 6.86 - 6.82 (td, $J = 8.8$, 2.8 Hz, 5H), 3.80 (s, 6H), 3.54 (s, 4H), 2.61 - 2.57 (t, $J = 8.4$ Hz, 2H), 2.33 - 2.30 (dd, $J = 5.6$, 2.0 Hz, 2H), 1.82 - 1.74 (m, 1H), 1.56 - 1.22 (m, 5H), 0.93 - 0.87 (t, $J = 8.0$ Hz, 9H), 0.71 - 0.55 (m, 6H).

$^{1^3}$C NMR (101 MHz, CDCl$_3$) $\delta$ 158.4, 142.8, 132.9, 130.0, 128.4, 128.2, 125.5, 113.4, 55.7, 55.2, 46.9, 35.9, 31.6, 28.8, 26.2, 7.8, 4.0. IR (neat, cm$^{-1}$): 2933, 2873, 1611, 1585, 1509, 1453, 1440, 1300, 1246, 1169, 1099, 1036, 1011, 822, 723, 698. HRMS (DART-TOF) calculated for C$_{33}$H$_{47}$NO$_2$Si [M+H]$^+$ m/z 518.3449, found 518.3436.
B) Determination of Absolute Configuration

The absolute configuration was determined by comparison of the optical rotation of compound 51' with that of a known compound. The absolute configurations of all the other aminosilanes were tentatively assigned by analogy.

[α]D24 = −37.4° (c = 1.0, CHCl3, >99% ee)

[α]D20 = −34.7° (c = 0.12, CHCl3, 89% ee)

Compound 51' was synthesized according to the following procedure:

(R)-N,N-dibenzyl-3-methyl-1-(dimethyl(phenyl)silyl)butan-1-amine (51): From (E)-dimethyl(3-methylbut-1-en-1-yl)(phenyl)silane (204 mg, 1.0 mmol), the title compound was prepared following the general procedure for CuH-catalyzed hydroamination of vinylsilanes (see section A) using Cu(OAc)2 (7.2 mg, 0.04 mmol, 4 mol%), (R)-DTBM-SEGPHOS (52 mg, 0.044 mmol, 4.4 mol%), and O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol). The reaction was stirred in THF (0.5 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0–3% EtOAc in hexanes) to afford 51 as a clear colorless oil (381 mg, 95% yield).

1H NMR (300 MHz, CDCl3) δ 7.48 – 7.41 (m, 2H), 7.36 – 7.16 (m, 2H), 7.44 – 7.26 (m, 13H), 3.59 – 3.58 (d, J = 3.3 Hz, 4H), 2.52 – 2.48 (t, J = 6.3 Hz, 1H), 1.66 – 1.54 (m, 2H), 1.25 – 1.12
(m, 1H), 0.73 – 0.71 (d, J = 6.3 Hz, 3H), 0.50 – 0.48 (d, J = 6.3 Hz, 3H), 0.40 – 0.38 (d, J = 4.8 Hz, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 140.7, 139.4, 134.0, 128.9, 128.7, 128.0, 127.7, 126.6, 56.3, 47.1, 35.8, 25.5, 23.0, 22.2, -1.44, -2.62. IR (neat, cm$^{-1}$): 3025, 2952, 1601, 1494, 1453, 1427, 1366, 1247, 1108, 1067, 1027, 965, 830, 808, 768, 731. HRMS (DART-TOF) calculated for C$_{21}$H$_{35}$NSi [M+H]$^+$ m/z 402.2612, found 402.2628.

This product 5I was transformed into \((R)-N-(1-(dimethyl(phenyl)silyl)-3-methylbutyl)-4-methylbenzenesulfonamide (5I')\) for measurement of optical rotation using the following procedure: A round bottom flask, equipped with a stir bar was charged with 5I (161 mg, 0.4 mmol), Pd(OH)$_2$ on carbon (20 wt%, 50 mg), and MeOH (4 mL). The flask was evacuated and backfilled with hydrogen (this process was repeated a total of 3 times) and stirred at rt overnight (~12 h) under a H$_2$ atmosphere (1 atm). The reaction mixture was filtered thorough were added to a round bottom flask equipped with a stir bar. The flask was then capped with a 3-neck joint, with the 2nd neck attached to a H$_2$ balloon, and the 3rd neck attached to a vacuum pump. The reaction flask was then evacuated and backfilled with H$_2$ (g) (this process was repeated a total of 3 times). The reaction was stirred at rt overnight (~12 h) under H$_2$ atmosphere (1 atm). The reaction mixture was filtered through a pad of Celite and the solvent was removed under reduced pressure. TsCl (114 mg, 0.6 mmol), DMAP (5 mg, 0.4 mmol), and CH$_2$Cl$_2$ (4 mL) were then added to the flask containing the crude primary amine. The reaction mixture was cooled to 0 °C and DIPEA (2.0 equiv) was added. The reaction mixture was stirred at rt for 4 h. The crude product was purified by by flash column chromatography (7–11% EtOAc in hexanes) to provide 5I' as a yellow oil (135 mg, 90% yield).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.70 – 7.67 (dd, J = 6.6, 1.2 Hz, 2H), 7.45 – 7.42 (dt, J = 8.6, 2.0 Hz, 2H), 7.41 – 7.30 (m, 1H), 7.25 – 7.23 (d, J = 6.6, 1.2 Hz, 2H), 4.20 (s, 1H), 3.07 – 3.01 (q, J = 7.2 Hz, 1H), 2.41 (s, 3H), 1.43 – 1.34 (sept, J = 6.8, 1H), 1.21 – 1.18 (t, J = 7.2 Hz, 2H), 0.70 – 0.65 (dd, J = 6.4, 4.4 Hz, 6H), 0.28 – 0.25 (d, J = 11.6 Hz, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 142.8, 138.5, 135.4, 134.0, 129.5, 129.3, 128.0, 127.0, 41.9, 41.9, 24.9, 22.9, 21.7, 21.4, -4.4, -5.3. IR (neat, cm$^{-1}$): 3200, 2955, 1597, 1427, 1323, 1248, 1155, 1094, 998, 836, 812, 775, 732, 700, 659. HRMS (DART-TOF) calculated for C$_{20}$H$_{29}$NO$_2$SSi [M+NH$_4$]$^+$ m/z 393.2027, found 393.2049.
C) Deuterium-labelling Experiments:

i. Reaction set-up

Compound 5g’ was synthesized according to the following procedure:

\[
\text{Ph(Me)\textsubscript{2}Si} + \text{Bn} \xrightarrow{\text{Cu(OAc\textsubscript{2})}_{2.0-10.0 \text{mol\%}}, \text{(R)-DTBM-SEGPHOS}_{2.2-11.0 \text{mol\%}}, \text{THF (1 M), 40 °C, 36 h}} \text{Ph, Bn, D, N. Ph, Bn, \text{Si(Me)\textsubscript{2}Ph}}
\]

In a nitrogen-filled glovebox, Cu(OAc\textsubscript{2}) (2.0–10.0 mol%), (R)-DTBM-SEGPHOS (2.2–11.0 mol%), and THF (0.2 mL) were added to an oven-dried test tube equipped with a magnetic stir bar. The mixture was stirred for 10 min, at which time diphenyl(silane-d\textsubscript{2}) (97 atom % D, 74 µL, 0.4 mmol, 2.0 equiv) was added and the stirring was continued for another 15 min at rt. Into a separate oven-dried test tube was added vinylsilane (0.2 mmol, 1.0 equiv) and 0-benzoyl-N,N-dibenzyldihydroxylamine (76 mg, 0.24 mmol, 2 equiv). The catalyst solution was then transferred via syringe to the reaction tube containing the substrates, and the reaction tube was capped, removed from the glovebox, and placed in a pre-heated oil bath at 40 °C for up to 36 h. Dodecane (20 µL) was added as the internal standard for GC analysis. The reaction mixture was quenched with saturated aqueous Na\textsubscript{2}CO\textsubscript{3} solution, extracted with EtOAc, dried over Na\textsubscript{2}SO\textsubscript{4}, filtered through a pad of silica, concentrated, and purified by column chromatography on silica gel.

NB: Diphenyl(silane-d\textsubscript{2}) is less reactive than diethoxymethylsilane, and was used only for the deuterium-labeling study.

From (E)-dimethyl(phenyl)(3-phenylprop-1-en-1-yl)silane ((E)-4g): (R,R)-N,N-dibenzyldimethyl(phenyl)silyl)-3-phenylpropan-1-amine (5g’ (R,R), Scheme 4, eq. 1): The title compound was prepared following the above procedure using Cu(OAc\textsubscript{2}) (0.7 mg, 0.004 mmol, 2 mol%), (R)-DTBM-SEGPHOS (5 mg, 0.0044 mmol, 2.2 mol%). The reaction mixture was stirred in THF (0.2 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0–5% EtOAc in hexanes) to afford 5g’ (R,R) as a clear colorless oil (yield: 44...
mg (49%). HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm) indicated 98% ee: \( t_R \) (minor) = 6.1 min, \( t_R \) (major) = 8.9 min.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.58 – 7.55 (m, 2H), 7.44 – 7.24 (m, 16H), 7.09 – 7.06 (m, 2H), 3.75 (s, 4H), 2.79 – 2.73 (dt, \( J = 11.8, 2.0 \) Hz, 1H), 2.62 – 2.60 (dd, \( J = 8.0, 2.0 \) Hz, 1H), 2.44 – 2.39 (dd, \( J = 13.8, 3.6 \) Hz, 1H), 1.86 – 1.80 (m, 1H), 0.54 – 0.52 (d, \( J = 2.0 \) Hz, 6H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 142.9, 140.5, 139.2, 134.0, 129.0, 128.9, 128.3, 128.3, 128.1, 127.8, 126.7, 125.6, 56.4, 49.5, 35.2, 28.7 – 28.3 (t, \( J = 18.7 \) Hz, 1C), -1.6, -2.7. HRMS (DART-TOF) calculated for C\(_{31}\)H\(_{34}\)DNSi [M+H]\(^+\) m/z 451.2674, found 451.2664.

From (Z)-dimethyl(phenyl)(3-phenylprop-1-en-1-yl)silane ((E)-4g): (R,S)-N,N-dibenzyl-1-(dimethyl(phenyl)silyl)-3-phenylpropan-1-amine (5g' (R,R), Scheme 4, eq. 2): The title compound was prepared following the above procedure using Cu(OAc)\(_2\) (3.6 mg, 0.02 mmol, 10 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 11 mol%). The reaction mixture was stirred in THF (0.2 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0–5% EtOAc in hexanes) to afford 5g' (R,S) as a clear colorless oil (yield: 45 mg (51%)). HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm) indicated 88% ee: \( t_R \) (minor) = 6.1 min, \( t_R \) (major) = 8.9 min.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.58 – 7.55 (m, 2H), 7.45 – 7.26 (m, 16H), 7.09 – 7.06 (dd, \( J = 8.0, 1.6 \) Hz, 2H), 3.75 (s, 4H), 2.79 – 2.73 (m, 1H), 2.62 – 2.60 (dt, \( J = 7.6, 2.4 \) Hz, 1H), 2.45 – 2.37 (m, 1H), 2.17 – 2.11 (m, 1H), 0.53 – 0.52 (d, \( J = 2.4 \) Hz, 6H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 142.8, 140.5, 139.2, 134.0, 129.0, 128.9, 128.3, 128.3, 128.1, 127.8, 126.7, 125.6, 56.4, 49.5, 35.2, 28.6 – 28.3 (t, \( J = 18.7 \) Hz, 1C), -1.5, -2.7. HRMS (DART-TOF) calculated for C\(_{31}\)H\(_{34}\)DNSi [M+H]\(^+\) m/z 451.2674, found 451.2663.
ii. Determination of deuterium incorporation by NMR spectroscopy and mass spectrometry

Incorporation of deuterium was analyzed by $^1$H NMR (Figure 1) and $^2$H NMR (Figure 2). The relevant region is enlarged and aligned for comparison. For $^1$H NMR, the diastereotopic protons $H_A$ ($\delta$ 1.88 – 1.78 ppm) and $H_B$ ($\delta$ 2.17 – 2.10 ppm) have distinct chemical shifts. The disappearance of the corresponding signal indicates deuterium incorporation, and percent deuterium incorporation was derived from the integration value of this signal.

Note: We have tentatively assigned the relative configuration of $\beta$-diastereotopic protons $H_A$ and $H_B$ by the absence of $^1$H NMR signal in the deuterated product, based on syn-addition of Cu-D to the alkene.

Figure 1. $^1$H NMR Spectroscopy (Bruker 400 MHz)
$^1$H and $^2$H NMR spectroscopy reveals that (E)-4g gives the exclusive mono-deuterated product, and the result was confirmed by GC/MS. For (Z)-4g, $^1$H NMR shows that there is a high level of deuterium incorporation (ca. 96%) at H_A and a small amount of deuterium incorporation at H_B (ca. 5%), which this was also confirmed by $^2$H NMR (Figure 2). Additionally, GC/MS shows that there is di-deuterio (H_A, H_B = D) incorporation (ca. 1%) into the product from (Z)-4g. 

From the $^1$H NMR, $^2$H NMR, and GC-MS data, we can conclude that ca. 99% of the product from the reaction of (Z)-4g did not form via isomerization of the substrate to the (E)-isomer. Additionally, we can conclude that the hydroamination of (E)-4g is completely diastereoselective (dr>99:1). The hydroamination of (Z)-4g is also diastereoselective with dr = 95:4, and 1% dideuterated product.
D) Synthesis of (Z)-Vinylsilanes:

Representative Procedure:

\[
\text{Ph} \quad \text{Ph} \quad \text{i. n-ButLi, THF, -78 °C to rt} \quad \text{Ph}_2\text{(Me)Si} \quad \text{Ph} \quad \text{ii. Cl-Si(Me)Ph}_2, -78 °C \quad \text{DIBAL-H} \quad \text{Et}_2\text{O, 0 °C to rt} \quad \text{Sil}(\text{Me})\text{Ph}_2 \quad \text{(Z)-1d}
\]

(Z)-methyldiphenyl(5-phenylpent-1-en-1-yl)silane ((Z)-1d): An oven-dried round bottom flask equipped with a stir bar and sealed with a rubber septum was evacuated and backfilled with nitrogen (this process was repeated a total of 3 times). The flask was charged with 5-phenyl-1-pentyne (1.57 mL, 10 mmol) and anhydrous THF (30 mL, 0.33 M). The solution was cooled to -78 °C for 10 min before dropwise addition of n-Butyllithium (2.5 M in hexanes, 4.2 mL, 10.5 mmol, 1.05 equiv) via syringe. The reaction mixture was stirred at rt for 30 min. The flask was again cooled to -78 °C for 10 min and chloromethyldiphenylsilane (2.31 mL, 11 mmol) was added. The reaction mixture was allowed to warm to rt and stirred overnight (~12 h). The crude reaction mixture was quenched with saturated aqueous \(\text{NH}_4\text{Cl}\) solution, extracted with EtOAc, and the combined organic layers were dried over \(\text{Na}_2\text{SO}_4\) and concentrated in vacuo. Purification by flash chromatography (0-5% EtOAc in hexanes) afforded methyldiphenyl(5-phenylpent-1-en-1-yl)silane in quantitative yield. The purified compound was transferred to an oven-dried round bottom flask equipped with a stir bar, and the vessel was evacuated and backfilled with nitrogen (this process was repeated a total of 3 times). Anhydrous Et\(_2\)O (10 mL, 1 M) was added, and the solution was cooled to 0 °C for 10 min. DIBAL-H (1 M in hexanes, 16 mL, 16 mmol) was then added slowly to the reaction mixture, which was allowed to stir at rt overnight. The reaction mixture was then cooled to 0 °C, and quenched with saturated \(\text{NH}_4\text{Cl}\) solution. The biphasic mixture was filtered through Celite, extracted with EtOAc, dried over \(\text{Na}_2\text{SO}_4\), concentrated, and purified by flash chromatography (0-5% EtOAc in hexane). (Z)-1d was obtained as a clear colorless oil (2.31 g, 68 % yield).

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 7.57 – 7.55 (dd, \(J = 7.6, 2.8\) Hz, 4H), 7.41 – 7.34 (m, 6H), 7.26 – 7.22 (td, \(J = 8.0, 0.8\) Hz, 2H) 7.18 – 7.14 (tt, \(J = 7.2, 1.6\) Hz, 1H), 7.06 – 7.03 (dd, \(J = 7.2, 1.6\) Hz, 2H), 6.64 – 6.57 (dt, \(J = 13.6, 7.6\) Hz, 1H), 5.88 – 5.84 (d, \(J = 13.6\) Hz, 1H), 2.39 – 2.35 (t, \(J = 8\) Hz, 2H), 2.05 – 2.01 (dt, \(J = 7.6, 5.6\) Hz, 2H), 1.57 – 1.51 (tt, \(J = 8, 5.6\) Hz, 2H), 0.63 (s, 3H). \(^{13}\text{C NMR}\) (101 MHz, CDCl\(_3\)) \(\delta\) 151.9, 142.3, 137.6, 134.6, 129.1, 128.3, 128.2, 127.8, 127.0.
125.6, 125.2, 35.5, 33.7, 31.1, -2.0. **IR** (neat, cm⁻¹): 3066, 3033, 2924, 2855, 1601, 1495, 1486, 1453, 1427, 1250, 1110, 789, 726. HRMS (DART-TOF) calculated for C₂₄H₂₆Si [M+NH₄⁺]⁺ m/z 360.2142, found 360.2151.

(Z)-trimethyl(5-phenylpent-1-en-1-yl)silane (Z)-1b, (Z)-triethyl(5-phenylpent-1-en-1-yl)silane (Z)-1a, (Z)-dimethyl(phenyl)(5-phenylpent-1-en-1-yl)silane (Z)-1c, (Z)-trimethyl(styryl)silane (7a), and (Z)-triisopropyl(styryl)silane (7b) are known compounds and were synthesized according to the above procedure.
E) Synthesis of (E)-Vinylsilanes:

(E)-Vinylsilanes ((E)-1a to (E)-1d, and 4a to 4k)) were synthesized according to the literature procedure unless otherwise noted. All of the (E)-vinylsilanes used are known compounds except for the those listed below.

(E)-Methyldiphenyl(5-phenylpent-1-en-1-yl)silane ((E)-1d):
Following the reported procedure for hydrosilylation of alkynes, the title compound was prepared from 5-phenyl-1-pentyne (1.57 mL, 10 mmol, 1.0 equiv) and methyldiphenylsilane (3.0 mL, 15 mmol, 1.5 equiv). The crude product was purified by flash column chromatography (5% CH₂Cl₂ in hexanes) to afford (E)-1d as a clear, colorless oil (3.1 g, 90% yield).

**1 H NMR** (400 MHz, CDCl₃) δ 7.73 - 7.70 (m, 4H), 7.54 - 7.51 (m, 6H), 7.46 - 7.42 (m, 2H), 7.36 - 7.31 (m, 3H), 7.06 - 7.03 (dd, J = 7.2, 1.6 Hz, 2H), 6.41 - 6.33 (dt, J = 18.4, 6.4 Hz, 1H), 6.21 - 6.15 (d, J = 18.4 Hz, 1H), 2.83 - 2.79 (t, J = 7.6 Hz, 2H), 2.46 - 2.39 (td, J = 7.2, 6.4 Hz, 2H), 1.98 - 1.91 (tt, J = 7.6, 7.2 Hz, 2H), 0.80 (s, 3H). **13 C NMR** (101 MHz, CDCl₃) δ 150.8, 142.1, 127.1, 51.4, 51.4, 36.2, 33.3, 23.9, 7.3, 3.4. **IR** (neat, cm⁻¹): 3066, 3023, 2930, 1614, 1427, 1111, 788, 731. HRMS (DART-TOF) calculated for C₄₄H₃₂Si [M+NH₄]⁺ m/z 360.2142, found 360.2151.

(E)-Methyl 6-(triethylsilyl)hex-5-enoate (4c):
Following the reported procedure for hydrosilylation of alkynes, the title compound was prepared from methyl 5-hexynoate (1.3 mL, 10 mmol, 1.0 equiv) and triethylsilane (2.4 mL, 15 mmol, 1.5 equiv). The crude product was purified by flash column chromatography (2–5% acetone in hexanes) to afford 4c as a clear, colorless oil (2.2 g, 91% yield).

**1 H NMR** (400 MHz, CDCl₃) δ 6.01 – 5.93 (dt, J = 18.8, 7.6 Hz, 1H), 5.58 – 5.53 (d, J = 18.8 Hz, 1H), 3.64 (s, 3H), 2.30 – 2.27 (t, J = 7.6 Hz, 2H), 2.17 – 2.11 (td, J = 7.6, 6.8 Hz, 2H), 1.76 – 1.68 (tt, J = 7.6, 6.8 Hz, 2H), 0.92 – 0.88 (t, J = 8.0 Hz, 9H), 0.55 – 0.49 (q, J = 8.0 Hz, 6H). **13 C NMR** (101 MHz, CDCl₃) δ 174.0, 146.9, 127.1, 51.4, 51.4, 36.2, 33.3, 23.9, 7.3, 3.4. **IR**
(E)-N-benzyl-4-methyl-N-(4-(triethylsilyl)but-3-en-1-yl)benzene sulfonamide (4d): Following the reported procedure for hydrosilylation of alkynes\(^{24}\), the title compound was prepared from N-benzyl-N-(but-3-yn-1-yl)-4-methylbenzenesulfonamide (3.1 g mL\(^{-1}\), 10 mmol, 1.0 equiv) and triethylsilane (2.4 mL, 15 mmol, 1.5 equiv). The crude product was purified by flash column chromatography (5% EtOAc in hexanes) to afford 4d as a clear, colorless oil (4.2 g, 97% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\) \(\delta 7.75-7.73 \text{ (dt, } J = 8.4, 2.0 \text{ Hz, } 2H) \), 7.34 – 7.25 (m, 7H), 5.81 – 5.73 (dt, \(J = 18.8, 6.4 \text{ Hz, } 1H\) ), 5.46 – 5.40 (dt, \(J = 18.8, 1.2 \text{ Hz, } 1H\) ), 4.34 (s, 2H), 3.20 – 3.16 (t, \(J = 7.6 \text{ Hz, } 2H\) ), 2.18 – 2.12 (dt, \(J = 7.6, 6.4 \text{ Hz, } 2H\) ), 0.90 – 0.86 (t, \(J = 8.0 \text{ Hz, } 9H\) ), 0.52 – 0.46 (q, \(J = 8.0 \text{ Hz, } 6H\) ). \(^{13}\)C NMR (101 MHz, CDCl\(_3\) \(\delta 143.7, 143.2, 137.3, 136.5, 129.7, 129.2, 128.5, 128.2, 127.7, 127.1, 51.9, 47.3, 35.7, 21.5, 7.3, 3.3. IR (neat, cm\(^{-1}\)): 2950, 2873, 1616, 1455, 1340, 1156, 1095, 993, 814, 784, 762, 771, 654, 600. HRMS (DART-TOF) calculated for C\(_{24}\)H\(_{35}\)N\(_2\)O\(_2\)S\(_2\)Si [M+H\(^+\)] m/z 430.2231, found 430.2232.

(E)-tert-butyl((4-(dimethyl(phenyl)silyl)but-3-en-1-yl)oxy) dimethylsilane (4e): Following the reported procedure for hydrosilylation of alkynes\(^{24}\), the title compound was prepared from (but-3-yn-1-yloxyl)(tert-butyl)dimethylsilane (1.84 g, 10 mmol, 1.0 equiv) and dimethylphenylsilane (2.3 mL, 15 mmol, 1.5 equiv). The crude product was purified by flash column chromatography (0–10% EtOAc in hexanes) to afford 4e as a clear, colorless oil (2.8 g, 87% yield).

\(^1\)H NMR (400 MHz, CDCl\(_3\) \(\delta 7.569-7.53 \text{ (m, } 2H\) ), 7.38 – 7.37 (m, 3H), 6.19 – 6.10 (dt, \(J = 18.4, 6.4 \text{ Hz, } 1H\) ), 5.88 – 5.84 (d, \(J = 18.4 \text{ Hz, } 1H\) ), 3.73 – 3.70 (t, \(J = 6.8 \text{ Hz, } 2H\) ), 2.43 – 2.38 (dt, \(J = 6.8, 6.4 \text{ Hz, } 2H\) ), 0.918 (s, 9H), 0.35 (s, 6H), 0.07 (s, 6H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\) \(\delta 145.7, 139.1, 133.8, 129.8, 128.8, 127.7, 62.5, 40.3, 36.4, 25.9, 18.4, -2.5, -5.3. IR (neat, cm\(^{-1}\)
(E)-N-benzyl-5-(methyldiphenylsilyl)pent-4-en-1-amine (4i): Following the reported procedure for hydrosilylation of alkynes\textsuperscript{24}, the title compound was from prepared \textit{N}-benzylpent-4-yn-1-amine (1.87 g, 10 mmol, 1.0 equiv) and methyldiphenylsilane (3.0 mL, 15 mmol, 1.5 equiv). The crude product was purified by flash column chromatography (0–20% EtOAc in 1:99 triethylamine:hexanes mixture) to afford 4i as a clear, colorless oil (3.4 g, 92% yield).

\textbf{H NMR} (400 MHz, CDCl\textsubscript{3}) \(\delta 7.60 - 7.57\) (m, 4H), \(7.44 - 7.28\) (m, 11H), \(6.27 - 6.20\) (dt, \(J = 18.4, 6.0\) Hz, 1H), \(6.07 - 6.02\) (d, \(J = 18.4\) Hz, 1H), \(3.84\) (s, 2H), \(2.73 - 2.70\) (t, \(J = 7.2\) Hz, 2H), \(2.34 - 2.29\) (dt, \(J = 7.6, 6.0\) Hz, 2H), \(1.76 - 1.69\) (tt, \(J = 7.2, 7.6\) Hz, 2H), \(0.68\) (s, 3H).

\textbf{C NMR} (101 MHz, CDCl\textsubscript{3}) \(\delta 150.7, 140.48, 136.9, 134.7, 129.1, 128.3, 128.0, 127.7, 126.8, 125.7, 53.9, 49.0, 48.8, 34.5, 28.8, -3.7.

\textbf{IR} (neat, cm\textsuperscript{-1}): 3066, 2929, 1739, 1614, 1427, 1351, 1111, 986, 820, 773, 728, 697. HRMS (DART-TOF) calculated for \(C_{18}H_{32}O_{S}Si\) [M+H\textsuperscript{+}] m/z 321.2064, found 321.2080.

Methyl(2-methylprop-1-en-1-yl)diphenylsilane (4j): An oven-dried flask equipped with a stir bar was evacuated and backfilled with nitrogen (this process was repeated a total of 3 times). Chloromethyldiphenylsilane (2.1 mL, 10 mmol, 1 equiv) and anhydrous THF (10 mL) were added via syringe, and the solution was cooled to 0 °C. 2-Methyl-1-propenylmagnesium bromide (1.84 g, 10 mmol, 1.0 equiv) was added dropwise, and the reaction was removed from the ice bath and stirred at rt for 6 h. The crude reaction mixture was quenched with saturated aqueous NH\textsubscript{4}Cl solution, extracted with EtOAc, and the combined organic layers were dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated. Purification by column chromatography (0–5% EtOAc in hexanes) afforded 4j as a clear, colorless oil (1.7 g, 68% yield).

\textbf{H NMR} (400 MHz, CDCl\textsubscript{3}) \(\delta 7.65 - 7.61\) (m, 4H), \(7.44 - 7.40\) (m, 6H), \(5.63\) (s, 1H), \(2.02\) (s, 3H), \(1.75\) (s, 3H), \(0.72\) (s, 3H). \textbf{C NMR} (101 MHz, CDCl\textsubscript{3}) \(\delta 155.5, 138.0, 134.6, 128.9, 128.0, 127.7, 126.8, 125.7, 53.9, 49.0, 48.8, 34.5, 28.8, -3.7. IR (neat, cm\textsuperscript{-1}): 3066, 2929, 1739, 1614, 1427, 1111, 986, 820, 773, 728, 697. HRMS (DART-TOF) calculated for \(C_{29}H_{29}NSi\) [M+H\textsuperscript{+}] m/z 372.2142, found 372.2141.
(E)-Methyl(3-methylbut-1-en-1-yl)diphenylsilane (4k): Following the reported procedure for hydrosilylation of alkynes\textsuperscript{24}, the title compound was prepared from 3-methylbut-1-yn\textsuperscript{e} (1.02 g, 10 mmol, 1.0 equiv) and diphenylmethylsilane (3.0 mL, 15 mmol, 1.5 equiv). The crude product was purified by distillation to afford 4k as a clear, colorless oil (2.2 g, 82% yield).

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.62 – 7.59 (dd, \(J = 5.2, 1.2\) Hz, 4H), 7.45 – 7.39 (m, 6H), 6.28 – 6.21 (dt, \(J = 18.8, 6.8\) Hz, 1H), 6.00 – 5.95 (d, \(J = 18.8\) Hz, 1H), 2.50 – 2.40 (tt, \(J = 8.0, 6.8\) Hz, 1H), 1.11 – 1.09 (d, \(J = 8.0\) Hz, 6H), 0.68 (s, 3H). \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) \(\delta\) 158.0, 137.2, 134.8, 129.1, 127.7, 121.2, 34.5, 21.7, -3.6. IR (neat, cm\textsuperscript{-1}): 2957, 1738, 1613, 1427, 1380, 1249, 1108, 998, 815, 794, 732, 700, 696. HRMS (DART-TOF) calculated for C\textsubscript{16}H\textsubscript{22}Si [M+H]\textsuperscript{+} m/z 267.1564, found 267.1582.
F) Synthesis of O-Benzoyl Hydroxylamines:

O-Benzoyl hydroxylamines were synthesized according to the literature procedure\textsuperscript{25} unless otherwise noted. All of the O-benzoyl hydroxylamines used are known compounds except for those listed below.

4-(pyrimidin-2-yl)piperazin-1-yl benzoate (2d): Following the reported procedure,\textsuperscript{25} the title compound was prepared from 2-(piperazin-1-yl)pyrimidine (8.21 g, 50 mmol, 1.0 equiv), benzoyl peroxide (24.2 g, 100 mmol, 2 equiv), and dipotassium hydrogen phosphate (17.4 g, 100 mmol, 2 equiv). The crude product was purified by flash column chromatography (25–33% EtOAc in hexanes) to afford 2d as a white solid (12.8 g, 90% yield); m.p. = 83.0–83.7 °C.

\[ \text{C NMR} (101 \text{ MHz, CDCl}_3) \delta 164.8, 161.6, 157.9, 133.3, 129.6, 129.3, 128.6, 110.5, 56.0, 42.3. \text{ IR (neat, cm}^{-1}) : 2852, 1723, 1612, 1585, 1509, 1302, 1239, 1169, 1089, 1025, 987, 816, 807, 700. \text{ HRMS (DART-TOF) calculated for C}_{15}H_{16}N_4O_2: [M+H]^+ m/z 318.1159, found 318.1152. \]

O-benzoyl-N,N-bis(4-methoxybenzyl)hydroxylamine (2e): Following the reported procedure,\textsuperscript{25} the title compound was prepared from bis(4-methoxybenzyl)amine (5.0 g, 19.4 mmol, 1.05 equiv), benzoyl peroxide (4.5 g, 18.5 mmol, 1.0 equiv), and dipotassium hydrogen phosphate (4.8 g, 27.8 mmol, 1.5 equiv). The crude product was purified by flash recrystallization (EtOAc in hexanes) to afford 2e as a white solid (5.2 g, 71% yield); m.p. = 93.7–96.6 °C.

\[ \text{H NMR} (400 \text{ MHz, CDCl}_3) \delta 7.86 – 7.86 (d, J = 8.2, 1.2 Hz, 4H), 7.53 – 7.48 (td, J = 7.2, 1.6 Hz, 1H), 7.39 – 7.33 (m, 6H), 6.85 – 6.82 (m, 4H), 4.12 (s, 4H), 3.77 (s, 6H). \text{ C NMR} (101 \text{ MHz, CDCl}_3) \delta 164.9, 159.1, 132.8, 130.7, 129.4, 129.3, 128.3, 128.0, 113.7, 77.4, 77.1, 76.7, 61.3, 55.2. \text{ IR (neat, cm}^{-1}) : 1723, 1612, 1585, 1509, 1302, 1239, 1169, 1089, 1068, 1025, 987, 816, 807, 700. \text{ HRMS (DART-TOF) calculated for C}_{23}H_{23}NO_4 [M+H]^+ m/z 378.1700, found 378.1708. \]
3.5 References and Notes


6). For an examples of a transition metal-catalyzed approach, see: Vyas, D. J.; Frohlich, R.; Oestreich, M. Org. Lett. 2011, 13, 2094.


11) For vinylsilanes, the partial positive charge is more pronounced at the \( \beta \)-position (to the silicon) due to the \( \beta \)-silicon effect (see ref. 12 and 13). The partial negative charge that develops at the \( \alpha \)-position is stabilized by the silyl group (see ref. 14 and 15). Furthermore, intermediate II (Scheme 2) is thermodynamically stabilized by hyperconjugation of the \( s \) orbital of the Cu-alkyl bond with a \( s^* \) orbital on the silicon-carbon bond (see ref 16).


18). The hydroamination reaction is slow for vinylsilanes with large silyl groups such as TIPS and TBDPS. After 36 h, no conversion was observed for (Z)-triisopropyl(5-phenylpent-1-en-1-yl)silane and only 16% conversion was observed for (Z)-tert-butyldiphenyl(5-phenylpent-1-en-1-yl)silane.


20). Experimental section II, part C for a detailed analysis.

21). We thank Dr. Erik L. Regalado (Merck, Rahway, NJ) for assistance with this chiral separation.

22). Due to overlap of the two peaks, we were unable to reliably determine the relative percentage of deuterium incorporation for $D_A$ and $D_B$ from (Z)-4g. Using the NMR deconvolution function, we approximate the ratio of $D_B$ and $D_A$ to be 7.6:92.4. (We thank Dr. Jeffrey H. Simpson (MIT, DCIF facility, jsimpson@mit.edu) for assistance with $^2$H NMR spectroscopy, and for carrying out deconvolution of the overlapping peaks to obtain the relative ratio of $D_A$ and $D_B$.)

23). GC/MS calculation was performed by assuming the (M-1)$^+$ peak derived from the di-deuterated product have negligible contribution.


[Image of an NMR spectrum with peaks labeled in ppm.]

(Z)-1d

Si(Me)Ph2
Ph\textsubscript{2}(Me)Si-\text{Ph} \quad (E)-1d
\( \text{Ph}_2\text{(Me)}\text{Si} - \text{Ph} \)

\((E)-1d\)
$^1$H NMR (CDCl$_3$)
3c

![NMR Spectrum](image-url)
Ph(Pe)₂Si OTBS

4e
$\text{Bn} \quad \text{Bn}$

$\text{Si(Me)}_2\text{Ph}$

$\text{OTBS}$

$5e$
$5i$
\[ \text{HN} \]  
\[ \text{Me} \]  
\[ \text{Me} \]  
\[ \text{Si(Me)Ph}_2 \]  
\[ \text{5j} \]
\[ 5k \]

\[ \text{Bn} \quad \text{N} \quad \text{Bn} \]

\[ \text{i-Pr} \]

\[ \text{Si(Me)Ph}_2 \]
3.7 Chiral HPLC Spectra
(R)-N,N-dibenzyl-5-phenyl-1-(triethylsilyl)pentan-1-amine (Table 2, entry 3a): HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm): \( t_R \) (minor) = 6.4 min, \( t_R \) (major) = 7.0 min.

3a

\[ (R)-3a \]

Rac-3a

\[ \text{Table 2, entry 3a): HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm): } t_R \text{ (minor)} = 6.4 \text{ min, } t_R \text{ (major)} = 7.0 \text{ min.} \]

\[ \text{(R)-3a from (Z)-triethyl(5-phenylpent-1-en-1-yl)silane ((Z)-1a): 93% } ee \]

Signal 1: DAD1 A, Sig=230.4 Ref=360.100

\[ \text{Table 2, entry 3a): HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm): } t_R \text{ (minor)} = 6.4 \text{ min, } t_R \text{ (major)} = 7.0 \text{ min.} \]
(R)-3a from (E)-triethyl(5-phenylpent-1-en-1-yl)silane ((E)-1a): >99% ee
(R)-N,N-dibenzyl-5-phenyl-1-(trimethylsilyl)pentan-1-amine (Table 2, entry 3b): HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm): $t_R$ (minor) = 5.4 min, $t_R$ (major) = 6.5 min.

Rac-3b

(R)-3b from (Z)-trimethyl(5-phenylpent-1-en-1-yl)silane ((Z)-1b): 92% ee

### Table 1

<table>
<thead>
<tr>
<th>Peak RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
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<td>1</td>
<td>0.2044</td>
<td>1.12807e4</td>
<td>875.23779</td>
<td>49.8289</td>
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<td>6.396 VB</td>
<td>2</td>
<td>0.1883</td>
<td>1.13582e4</td>
<td>930.91498</td>
<td>50.1711</td>
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</table>

Totals: 2.26389e4 1806.15277

### Table 2

<table>
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<td>1383.07605</td>
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<td>0.2319</td>
<td>3.30151e4</td>
<td>2267.42139</td>
<td>95.9792</td>
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Totals: 3.43982e4 2385.80713
(R)-3b from (E)-trimethyl(5-phenylpent-1-en-1-yl)silane ((E)-1b): 99% ee

<table>
<thead>
<tr>
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<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>16.37866</td>
<td>0.3585</td>
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<tr>
<td>2</td>
<td>6.497</td>
<td>MM T</td>
<td>0.367</td>
<td>5.61438e4</td>
<td>2545.17285</td>
<td>99.6415</td>
</tr>
</tbody>
</table>

Totals: 5.63458e4 2561.55151
(R)-N,N-dibenzyl-1-(dimethyl(phenyl)silyl)-5-phenylpentan-1-amine (Table 2, entry 3c): HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm): t_R (minor) = 8.0 min, t_R (major) = 9.0 min.

3c

**Rac-3c**

![HPLC trace of Rac-3c](image)

<table>
<thead>
<tr>
<th>Peak</th>
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<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.083</td>
<td>BB</td>
<td>0.2528</td>
<td>120.53931</td>
<td>49.2802</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>9.364</td>
<td>BB</td>
<td>0.3256</td>
<td>2071.25000</td>
<td>98.37413</td>
<td>50.7198</td>
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</tbody>
</table>

Totals: 4083.71216 218.91344

(R)-3c from (Z)-dimethyl(phenyl)(5-phenylpent-1-en-1-yl)silane ((Z)-1c): 93% ee

![HPLC trace of (R)-3c](image)

<table>
<thead>
<tr>
<th>Peak</th>
<th>RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8.220</td>
<td>BB</td>
<td>0.2483</td>
<td>156.70294</td>
<td>9.43168</td>
<td>3.2779</td>
</tr>
<tr>
<td>2</td>
<td>9.502</td>
<td>BB</td>
<td>0.4204</td>
<td>4685.85156</td>
<td>183.07094</td>
<td>96.7221</td>
</tr>
</tbody>
</table>

Totals: 4841.55450 192.50262
(R)-3c from (E)-dimethyl(phenyl)(S-phenylpent-1-en-1-yl)silane ((E)-1c): 99% ee

![Graph](image)

<table>
<thead>
<tr>
<th>Peak</th>
<th>RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area</th>
<th>%</th>
</tr>
</thead>
<tbody>
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<td>8.013</td>
<td>MM</td>
<td>0.3359</td>
<td>20.7659</td>
<td>1.0304</td>
<td>0.3949</td>
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<tr>
<td>2</td>
<td>9.053</td>
<td>BB</td>
<td>0.3269</td>
<td>5237.6823</td>
<td>245.5871</td>
<td>99.6051</td>
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</tr>
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</table>

Totals: 5258.44795 246.61758
(R)-N,N-dibenzyl-1-(methyldiphenylsilyl)-5-phenylpentan-1-amine (Table 2, entry 3d): HPLC analysis (OT(+), 1% IPA/hexanes, 0.8 mL/min, 220 nm): $t_R$ (minor) = 8 min, $t_R$ (major) = 10 min.

3d

Rac-3d

(R)-3d from (Z)-methyldiphenyl(5-phenylpent-1-en-1-yl)silane ((Z)-ld): 84% ee

405
(R)-3d from (E)-methyldiphenyl(5-phenylpent-1-en-1-yl)silane ((E)-1d): 99% ee

<table>
<thead>
<tr>
<th>Peak</th>
<th>Ret Time</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>8.227</td>
<td>MM</td>
<td>0.5136</td>
<td>57.2118</td>
<td>1.63225</td>
<td>0.5166</td>
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<tr>
<td>2</td>
<td>10.297</td>
<td>BB</td>
<td>1.0349</td>
<td>1.10185e4</td>
<td>116.97504</td>
<td>99.4834</td>
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</table>

Totals: 1.10757e4 118.60729
(R)-6-(dibenzylamino)-6-(triethylsilyl)hexanenitrile (Table 3, entry 5a): HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm): $t_R$ (minor) = 16.0 min, $t_R$ (major) = 18.3 min.

Rac-5a

(R)-5a from (E)-6-(triethylsilyl)hex-5-enenitrile: 99% ee

### Table 1

<table>
<thead>
<tr>
<th>Peak Ret Time</th>
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<tbody>
<tr>
<td>1</td>
<td>BB</td>
<td>0.4587</td>
<td>871.26416</td>
<td>28.49911</td>
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<td>2</td>
<td>BB</td>
<td>0.5159</td>
<td>825.78236</td>
<td>19.27070</td>
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Totals: 1697.05652 47.76981

### Table 2

<table>
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<tbody>
<tr>
<td>1</td>
<td>MM</td>
<td>0.6182</td>
<td>21.87559</td>
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<td>2</td>
<td>BB</td>
<td>0.6406</td>
<td>2975.90381</td>
<td>66.18115</td>
<td>99.2703</td>
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Totals: 2997.77939 66.77093
(R)-N,N-dibenzyl-5-chloro-1-(triethylsilyl)pentan-1-amine (Table 3, entry 5b): SFC analysis\textsuperscript{21} (Chiralpak IC(4.6x150 mm, 3µm), isocratic 3% EtOH): t\textsubscript{R} (minor) = 1.15 minute, t\textsubscript{R} (major) = 1.28 min.

\textbf{5b}

\textit{Rac-5b}

\textit{(R)-5b from (E)-(5-chloropent-1-en-1-yl)triethylsilane: >99% ee}
**(R)**-**N**,N-dibenzyl-5-chloro-1-(triethylsilyl)pentan-1-amine (Table 3, entry 5c): HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm): tR (minor) = 7.4 min, tR (major) = 7.9 min.

**Rac-5c**

<table>
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<tr>
<td>1</td>
<td>7.327 BV</td>
<td>0.2307 2729.22632</td>
<td>122.22719</td>
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<td>2</td>
<td>7.939 VB</td>
<td>0.2681 2627.57666</td>
<td>148.75972</td>
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</tbody>
</table>

Totals: 5356.00290 330.98691

**(R)**-5c from (E)-**methyl 6-(triethylsilyl)hex-5-enoate**: 99% ee

<table>
<thead>
<tr>
<th>Peak RetTime Type</th>
<th>Width</th>
<th>Area Height</th>
<th>Area %</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>7.413 MM T</td>
<td>0.3181 8.02908</td>
<td>4.70222e-1</td>
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<tr>
<td>2</td>
<td>7.941 BB</td>
<td>0.2458 1403.23486</td>
<td>88.12594</td>
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</table>

Totals: 1412.06394 88.59716
**(R)-N-benzyl-N-(4-(dibenzylamino)-4-(triethylsilyl)butyl)-4-methylbenzenesulfonamide** (Table 3, entry 5d): HPLC analysis (OD-H, 5% IPA/pentane, 0.8 mL/min, 220 nm): 

- **t<sub>R</sub> (minor) = 15.7 min, t<sub>R</sub> (major) = 18.0 min.**

**Rac-5d**

![HPLC analysis of Rac-5d](image)

<table>
<thead>
<tr>
<th>Peak RetTime</th>
<th>Width</th>
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<th>Height</th>
<th>Area</th>
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</thead>
<tbody>
<tr>
<td>15.688 min</td>
<td></td>
<td></td>
<td>8.8 MB</td>
<td></td>
</tr>
<tr>
<td>17.981 min</td>
<td></td>
<td></td>
<td>17.0 MB</td>
<td></td>
</tr>
</tbody>
</table>

Totals: 1.4333*10<sup>4</sup> 33.4 2686

**(R)-5d from (E)-N-benzyl-4-methyl-N-(4-(triethylsilyl)but-3-en-1-yl)benzene sulfonamide ((E)-1h): 99% ee**

![HPLC analysis of (E)-5d](image)

<table>
<thead>
<tr>
<th>Peak RetTime</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.514 min</td>
<td>0.9460</td>
<td>60.7 MB</td>
<td>1.721 MB</td>
<td>99.4504</td>
</tr>
<tr>
<td>17.646 min</td>
<td>0.7027</td>
<td>1.804 MB</td>
<td>390.91562</td>
<td>99.4504</td>
</tr>
</tbody>
</table>

Totals: 1.8149*10<sup>4</sup> 395.68741
(R)-N,N-dibenzyl-4-((tert-butyl(dimethyl)silyl)oxy)-1-(dimethyl(phenyl)silyl)butan-1-amine (Table 3, entry 5e): HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm): t\(_R\) (minor) = 5.0 min, t\(_R\) (major) = 5.5 min.

\[ \text{Rac-5e} \]

\[
\begin{array}{cccc}
\text{Peak RetTime} & \text{Type} & \text{Width} & \text{Area} \\
1 & 5.044 & M T & 0.1885 \\
2 & 5.481 & M R & 0.2172 \\
\end{array}
\]

\[ \text{Totals:} \quad 1.3011 \times 10^4 \quad 1139.92004 \]

(R)-5e from (E)-tert-butyl((4-(dimethyl(phenyl)silyl)but-3-en-1-yl)oxy)dimethylsilane: 96\% ee

\[
\begin{array}{cccc}
\text{Peak RetTime} & \text{Type} & \text{Width} & \text{Area} \\
1 & 5.204 & M T & 0.1010 \\
2 & 5.471 & M R & 0.1101 \\
\end{array}
\]

\[ \text{Totals:} \quad 7865.32556 \quad 665.13412 \]
(R)-N,N-dibenzyl-1-(dimethyl(phenyl)silyl)-3-methoxypropan-1-amine (Table 3, entry 5f; HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm): t_R (minor) = 6.2 min, t_R (major) = 7.5 min.

5f

Rac-5f

(R)-5f from (E)-(3-methoxyprop-1-en-1-yl)dimethyl(phenyl)silane: 99% ee
(R)-N,N-dibenzyl-1-(dimethyl(phenyl)silyl)-3-phenylpropan-1-amine (Table 3, entry 5g): HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm): $t_R$ (minor) = 6.1 min, $t_R$ (major) = 8.9 min.

### 5g

**Rac-5g**

![HPLC chromatogram for Rac-5g](image)

<table>
<thead>
<tr>
<th>Peak</th>
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<td>0.1627</td>
<td>1927.91431</td>
<td>191.35358</td>
<td>50.0432</td>
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<td>2</td>
<td>8.859</td>
<td>BB</td>
<td>0.2509</td>
<td>1924.89480</td>
<td>111.84303</td>
<td>49.9568</td>
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</table>

Totals: 3852.50378 302.19340

(R)-5g from (E)-dimethyl(phenyl)(3-phenylprop-1-en-1-yl)silane: 98% ee

![HPLC chromatogram for (R)-5g from (E)-dimethyl(phenyl)(3-phenylprop-1-en-1-yl)silane](image)

<table>
<thead>
<tr>
<th>Peak</th>
<th>RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.207</td>
<td>BV</td>
<td>0.2723</td>
<td>333.47437</td>
<td>17.34593</td>
<td>1.0407</td>
</tr>
<tr>
<td>2</td>
<td>8.579</td>
<td>BB</td>
<td>0.2558</td>
<td>3.17093e4</td>
<td>1949.43457</td>
<td>98.9593</td>
</tr>
</tbody>
</table>

Totals: 3.20427e4 1966.78050
(R)-5g from (Z)-dimethyl(phenyl)(3-phenylprop-1-en-1-yl)silane: 89% ee

Peak RetTime Type Width Area Height Area
# [min] [min] [mAUs] [mAUs] %
-----|-----------|--------|----------|--------|-----|
1 6.667 BB 0.1740 261.61649 23.12520 5.5435
2 9.722 BB 0.2608 4457.73047 264.22803 94.4565

Totals: 4719.34695 287.35323

(R)-5g' from (E)-dimethyl(phenyl)(3-phenylprop-1-en-1-yl)silane with d-Ph₂SiD₂: 98% ee

Peak RetTime Type Width Area Height Area
# [min] [min] [mAUs] [mAUs] %
-----|-----------|--------|----------|--------|-----|
1 6.173 BV 0.1671 26.84967 2.19017 1.0612
2 8.743 VV 0.2399 2689.64868 174.41940 98.9388

Totals: 2718.49835 176.61758
(R)-5g' from (Z)-dimethyl(phenyl)(3-phenylprop-1-en-1-yl)silane with \(d\)-Ph\(_2\)Si\(_2\): 88% ee

![Chromatogram](image)

<table>
<thead>
<tr>
<th>Peak RetTime Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.224</td>
<td>VB</td>
<td>0.1743</td>
<td>306.18033</td>
</tr>
<tr>
<td>2</td>
<td>8.715</td>
<td>VB</td>
<td>0.2365</td>
<td>4877.93945</td>
</tr>
</tbody>
</table>

Totals: 5184.11978 346.26379
(R)-N,N-dibenzyl-1-(dimethyl(phenyl)silyl)-2-(1-methoxycyclohexyl)ethanamine (Table 3, entry 5h): HPLC analysis (OD-H, 90:5:0.1 Hexanes: IPA: Diethylamine, 0.8 mL/min, 220 nm): \( t_R \) (minor) = 7.4 min, \( t_R \) (major) = 7.9 min.

5h

\[ \text{Rac-5h} \]

\[
\begin{array}{|c|c|c|c|c|}
\hline
\text{Peak RetTime Type} & \text{Width} & \text{Area} & \text{Height} & \text{Area} \\
\text{#} & \text{[min]} & \text{[min]} & \text{[mAU*s]} & \text{[mAU]} & \% \\
\hline
1 & 6.577 & 0.1123 & 759.85693 & 95.04185 & 50.4694 \\
2 & 6.836 & 0.1320 & 745.72137 & 85.33576 & 49.5306 \\
\hline
\end{array}
\]

Totals: \( 1505.57831 \) \( 189.37761 \)

(R)-5h from \((E)-(2-(1-methoxycyclohexyl)vinyl)dimethyl(phenyl)silane: 92\% ee\)

\[
\begin{array}{|c|c|c|c|c|}
\hline
\text{Peak RetTime Type} & \text{Width} & \text{Area} & \text{Height} & \text{Area} \\
\text{#} & \text{[min]} & \text{[min]} & \text{[mAU*s]} & \text{[mAU]} & \% \\
\hline
1 & 6.617 & 0.1326 & 547.07605 & 78.61522 & 3.7938 \\
2 & 6.852 & 0.1350 & 1.38733e4 & 1712.52979 & 96.2062 \\
\hline
\end{array}
\]

Totals: \( 1.44203e4 \) \( 1791.14500 \)
(R)-N\(^1\),N\(^3\),N\(^5\)-tribenzyl-1-(methyldiphenylsilyl)pentane-1,5-diamine
(Table 3, entry 5i): HPLC analysis (OD-H, 90:5:0.1 Hexanes: IPA:
Diethylamine, 0.8 mL/min, 220 nm): t\(_R\) (major) = 12.3 min, t\(_R\) (minor) = 13.5 min.

\textit{Rac-5i}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{hplc_1.png}
\end{figure}

Peak RetTime Type Width Area Height Area
\hline
1 & 12.384 & VV & 0.3080 & 8475.35059 & 424.74690 & 46.5247
2 & 13.201 & VB & 0.3711 & 9741.52637 & 393.12570 & 53.4753
\hline
\textbf{Totals}: & & & & 1.82169e+04 & 817.87560 &
\end{figure}

(R)-5i from (E)-N-benzyl-5-(methyldiphenylsilyl)pent-4-en-1-amine: 93% ee

\begin{figure}
\centering
\includegraphics[width=\textwidth]{hplc_2.png}
\end{figure}

Peak RetTime Type Width Area Height Area
\hline
1 & 12.326 & VV & 0.3209 & 2.62779e+04 & 1272.02495 & 96.3053
2 & 13.442 & VB & 0.6708 & 1008.12732 & 18.98435 & 3.6947
\hline
\textbf{Totals}: & & & & 2.72806e+04 & 1291.70830 &
\end{figure}
(R)-N,N-dibenzyl-2-methyl-1-(methyldiphenylsilyl)propan-1-amine (Table 3, entry 5j): HPLC analysis (OT(+), 1% IPA/Hexanes, 0.8 mL/min, 220 nm): \( t_R \) (minor) = 6.7 min, \( t_R \) (major) = 9.3 min.

\[ \text{Signal 3: DAD1 C, Sig=210,8 Ref=360,100} \]

\[
\begin{array}{cccccc}
\# & \text{RetTime} \ [\text{min}] & \text{Type} & \text{Width} \ [\text{min}] & \text{Area} \ [\text{mAU*}\text{sec}] & \text{Height} \ [\text{mAU}] & \% \\
1 & 6.672 & \text{VV} & 0.6154 & 7.63435\times10^4 & 1790.56201 & 48.3340 \\
2 & 8.862 & \text{MM} & 0.3304 & 1.29153\times10^4 & 93.53019 & 99.4194 \\
\text{Totals} & & & 1.57950\times10^5 & 2360.59430 & & \\
\end{array}
\]

(R)-5j from methyl(2-methylprop-1-en-1-yl)diphenylsilane: 99% ee

\[
\begin{array}{cccccc}
\# & \text{RetTime} \ [\text{min}] & \text{Type} & \text{Width} \ [\text{min}] & \text{Area} \ [\text{mAU*}\text{sec}] & \text{Height} \ [\text{mAU}] & \% \\
1 & 6.700 & \text{BB} & 0.3616 & 75.41872 & 2.56045 & 0.5806 \\
2 & 8.862 & \text{MM} & 0.3014 & 1.29153\times10^4 & 93.53019 & 99.4194 \\
\text{Totals} & & & 1.29907\times10^4 & 96.09064 & & \\
\end{array}
\]

418
(R)-N,N-dibenzyl-3-methyl-1-(methyldiphenylsilyl)butan-1-amine
(Table 3, entry 5k): HPLC analysis (OD-H, 97% Hexanes/3% of '97
Hexanes: 3 EtOH: 0.2 TFA: 0.1 DEA, 0.8 mL/min, 220 nm): \( t_R \) (minor) = 5.4
min, \( t_R \) (major) = 5.9 min.

Rac-5k

Peak RetTime Type Width Area Height Area
# [min] [min] [mAU*s] [mAU] %

\begin{array}{|c|c|c|c|c|}
\hline
\# & RetTime & Type & Width & Area \\
\hline
1 & 5.323 & VV & 0.1486 & 4096.5376 \\
2 & 5.938 & VB & 0.4180 & 3956.6186 \\
\hline
\hline
\text{Totals} & & & 0.1486 & 557.63245 \\
\end{array}

(R)-5k from (Z)-methyl(3-methylbut-1-en-1-yl)diphenylsilane: 94% ee

(R)-5k

Peak RetTime Type Width Area Height Area
# [min] [min] [mAU*s] [mAU] %

\begin{array}{|c|c|c|c|c|}
\hline
\# & RetTime & Type & Width & Area \\
\hline
1 & 5.405 & VV & 0.1634 & 566.84027 \\
2 & 5.874 & VB & 0.3861 & 1.94566e4 \\
\hline
\hline
\text{Totals} & & & 2.0035e4 & 783.95698 \\
\end{array}
(R)-N-(1-(dimethyl(phenyl)silyl)-3-methylbutyl)-4-methylbenzenesulfonamide (5'I): HPLC analysis (OD-H, 1% IPA/Hexanes, 0.8 mL/min, 220 nm): $t_R$ (minor) = 26.6 min, $t_R$ (major) = 28.5 min.

5'I

Rac-5'I

(R)-5'I from (R)-N-(1-(dimethyl(phenyl)silyl)-3-methylbutyl)-4-methylbenzenesulfonamide: >99% ee
(R)-N,N-dibutyl-5-phenyl-1-(triethysilyl)pentan-1-amine (Table 4, entry 6a): From (E)-triethyl(5-phenylpent-1-en-1-yl)silane ((E)-1a) (3 connected OD-H columns, 97% Hexanes/ 3% of '92 Hexanes: 8 EtOH: 0.2 TFA: 0.1 DEA', 0.55 mL/min, 220 nm): \( t_R \) (major) = 51 min, \( t_R \) (minor) = 54 min.

\[ \text{Peak Ret Time Type Width Area Height Area} \]
\[ \begin{array}{cccccc}
\# & \text{[min]} & \text{[min]} & \text{[mAU*s]} & \text{[mAU]} & \% \\
1 & 51.021 & MF T & 1.5758 & 245.52043 & 2.59674 & 49.7294 \\
2 & 53.848 & FM T & 1.7471 & 248.19196 & 2.36761 & 50.2706 \\
\end{array} \]

Totals: 493.71239 4.96434

(R)-6a from (E)-triethyl(5-phenylpent-1-en-1-yl)silane ((E)-1a): >99% ee

\[ \text{Peak Ret Time Type Width Area Height Area} \]
\[ \begin{array}{cccccc}
\# & \text{[min]} & \text{[min]} & \text{[mAU*s]} & \text{[mAU]} & \% \\
1 & 50.603 & MM T & 1.4914 & 128.15466 & 1.43212 & 100.0000 \\
\end{array} \]

Totals: 128.15466 1.43212

421
(R)-4-(5-phenyl-1-(triethylsilyl)pentyl)morpholine (Table 4, entry 6b): HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm): 
$t_R$ (minor) = 8.0 min, $t_R$ (major) = 10.4 min.

Rac-6b

(R)-6b from (E)-triethyl(5-phenylpent-1-en-1-yl)silane ((E)-1a); >99% ee
(R)-N-benzyl-N-methyl-5-phenyl-1-(triethylsilyl)pentan-1-amine (Table 4, entry 6c): This product was derivatized into (R)-N-methyl-N-(5-phenyl-1-(triethylsilyl)pentyl)acetamide for chiral HPLC analysis. HPLC analysis (OD-H, 1% IPA/hexanes, 0.8 mL/min, 220 nm): \( t_R \) (minor) = 13 min, \( t_R \) (major) = 15 min.

Rac-6c

<table>
<thead>
<tr>
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<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
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Totals: 3250.48975 122.91273

(R)-6c from (E)-triethyl(5-phenylpent-1-en-1-yl)silane ((E)-1a): 98% ee

<table>
<thead>
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<th>Width</th>
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<tr>
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<td>5342.72559</td>
<td>177.48306</td>
<td>99.0954</td>
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</tr>
</tbody>
</table>

Totals: 5391.49593 178.95421
(R)-2-(4-(5-phenyl-1-(triethylsilyl)pentyl)piperazin-1-yl)pyrimidine (Table 4, entry 6d): HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm): t_R (minor) = 10.6 min, t_R (major) = 11.5 min.

Rac-6d

![HPLC chromatogram](image)

<table>
<thead>
<tr>
<th>Peak</th>
<th>Ret Time (min)</th>
<th>Width (min)</th>
<th>Area (mAU*s)</th>
<th>Height (mAU)</th>
<th>Area (%)</th>
</tr>
</thead>
<tbody>
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<td>2</td>
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<td>4886.66846</td>
<td>253.81593</td>
<td>49.3258</td>
</tr>
</tbody>
</table>

Totals: 9906.92725 547.13637

(R)-6d Starting from (E)-triethyl(5-phenylpent-1-en-1-yl)silane ((E)-1a): >99% ee

![HPLC chromatogram](image)

<table>
<thead>
<tr>
<th>Peak</th>
<th>Ret Time (min)</th>
<th>Width (min)</th>
<th>Area (mAU*s)</th>
<th>Height (mAU)</th>
<th>Area (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>0.2395</td>
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<td>2</td>
<td>11.824</td>
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<td>622.88629</td>
<td>99.8230</td>
</tr>
</tbody>
</table>

Totals: 1.26341e4 624.03297

424
(R)-N,N-bis(4-methoxybenzyl)-5-phenyl-1-(triethylsilyl)pentan-1-amine (Table 4, entry 6e): HPLC analysis (OD-H, 1% IPA/pentane, 0.8 mL/min, 220 nm): \( t_R \) (minor) = 9.8 min, \( t_R \) (major) = 11.8 min.

### Rac-6e

![Graph of Rac-6e](image)

<table>
<thead>
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<th>Peak</th>
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<th>Width</th>
<th>Area Height</th>
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</tr>
</thead>
<tbody>
<tr>
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<td>11.763</td>
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<td>370.71255</td>
<td>51.4436</td>
</tr>
</tbody>
</table>

**Totals:** 1.70385e4 813.40921

### (R)-6e from (E)-triethyl(5-phenylpent-1-en-1-yl)silane ((E)-1a)

![Graph of (R)-6e](image)

<table>
<thead>
<tr>
<th>Peak</th>
<th>Ret Time</th>
<th>Width</th>
<th>Area Height</th>
<th>Area Width</th>
<th>Area %</th>
</tr>
</thead>
<tbody>
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<td>959.88342</td>
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</table>

**Totals:** 2.43803e4 961.29092
Chapter 4.
Synthesis of γ-Chiral Amines via Copper-Catalyzed Hydroamination of 3,3-Disubstituted Allylic Alcohols and 3,3-Disubstituted Allylic Benzoates
4.1 Introduction

Recently, our laboratory has reported copper-catalyzed hydroamination methodologies to access an array of chiral amines (Figure 1).\(^1\)\(^2\) Our hydroamination strategy relies on the use of a silane, a chiral phosphine ligand (L*), and a Cu(II) salt to generate a ligated copper hydride species (L*CuH) and the use of O-benzoylhydroxylamine as an electrophilic amine source. With this method, \(\alpha\)-chiral amines can be accessed from the Markovnikov hydroamination of styrenes and vinylsilanes (Figure 1, A),\(^1\) and \(\beta\)-chiral amines can be accessed by the anti-Markovnikov hydroamination of 1,1-disubstituted aliphatic alkenes (Figure 1, B).\(^2\)

**Figure 1. Our Strategies Towards Chiral 1,2-Aminoalcohol Synthesis**

We envisioned that the extension of this methodology towards the hydroamination of 3-substituted allylic ethers (Figure 1, C) would allow for the generation of chiral amino alcohols, which are important structural subunits.\(^3\) We postulated that coordination of the alkoxy group would direct copper to the 2-position (Eq. 1),\(^4\) and subsequent reaction with electrophilic amine source would generate chiral protected 1,2-amino alcohols.

\[
\text{R} = \text{R}^1\text{R}^2\text{OR}' + \text{R}^1\text{N}^2\text{R}^2\text{OBz} \xrightarrow{\text{L}^*\text{CuH}} \text{R}^1\text{N}^2\text{R}^2\text{OR}' \quad (\text{Eq. 1})
\]
Unexpectedly, we observed that the reaction of 3-methylallyl benzyl ether generated the corresponding achiral linear amine (N,N-dibenzylbutan-1-amine) with no formation of the desired 1,2-amino alcohol product (Eq. 2). Based on this result, we proposed that following hydrocupration of I to produce II, β-alkoxy elimination occurred to generate the terminal olefin III, which then underwent anti-Markovnikov hydroamination to generate the observed terminal amine (Scheme 1).

Concomitantly, we were also exploring the application of our Cu-catalyzed hydroamination methodology to tri-substituted alkenes for the synthesis of α,β-chiral amines. This is because β-disubstituted chiral amines with two contiguous stereocenters are important structural motifs found in natural products and pharmaceuticals, but methods to access this class of compounds predominantly rely on the use of chiral auxiliaries or sequential transformations. However, using 2-methylbut-2-ene as a representative trisubstituted alkene gave no product formation under the standard reaction conditions (Eq. 3).
We reasoned that the copper hydride insertion is unfavorable for trialkyl-substituted olefins. Thus, we proposed integrating the use of a leaving group, as in the case of the 3-monosubstituted allylic ether $I$, to help drive the unfavorable insertion step with trisubstituted olefin substrates (Figure 2). In this way, we could convert allylic alcohols into $\gamma$-chiral amines. This is of interest as $\gamma$-chiral amines are prevalent structural subunits in both natural products and pharmaceuticals (Figure 3). Conventional strategies to access $\gamma$-chiral amines from allylic alcohols are multistep and, thus, less efficient. A method that could access these chiral compounds via simultaneous installation of the chiral center and the amine would be of considerable importance.

**Figure 2. Rationale For New Proposed Substrate Class**

**Proposed Substrate Class:**

**3,3-Disubstituted Allylic Ether**

\[
\begin{align*}
\text{R}^1 \text{CH} = \text{CH} \text{OR}^2 + \text{R}^1 \text{N} \text{R}^2 & \rightarrow \text{L}^* \text{CuH} \\
\text{R}^1 \text{CH} = \text{CH} \text{OR}^2 + \text{R}^1 \text{N} \text{R}^2 & \rightarrow \text{L}^* \text{CuH} \\
\text{R}^1 \text{CH} = \text{CH} \text{OR}^2 + \text{R}^1 \text{N} \text{R}^2 & \rightarrow \text{L}^* \text{CuH} \\
\gamma\text{-chiral amines}
\end{align*}
\]
The overall catalytic cycle is shown in Scheme 2. Following the hydrocupration of 3,3-disubstituted allylic ethers (I) to generate the β-alkoxy copper species II, irreversible β-alkoxy elimination (ii) would furnish the chiral terminal alkene III and ligated copper alkoxide IV.\(^5^6\) The ligated copper alkoxide can undergo transmetalation (iii) with diethoxymethylsilane to regenerate \(\text{L}^+\text{CuH}\) (I). Then, terminal olefin III could undergo anti-Markovnikov hydrocupration (iv) followed by amine transfer (v) from \(O\)-benzoylhydroxylamine 2 to generate the \(\gamma\)-chiral amine 3. Subsequent transmetalation (vi) would then reform I.
Scheme 2. Proposed Mechanism for Copper-Catalyzed Hydroamination of 3,3-Disubstituted Allylic Ethers

\[
\begin{align*}
R'\text{=\text{-}}\text{OR} + R^1 R^2 \text{N} & \xrightarrow{\text{Cu(OAc)}_2, \text{L}^*} R'\text{=\text{-}}R^1 R^2 \text{N} \\
\text{Me(EtO)}_2 \text{SiH} & \xrightarrow{\text{Me(EtO)}_2 \text{SiH}} L'\text{CuH} \\
\text{Cu(OAc)}_2 & \xrightarrow{\text{L}^*, \text{Me(EtO)}_2 \text{SiH}} R'\text{=\text{-}}\text{OR} \\
\text{L}'\text{CuH} & \xrightarrow{\text{Me(EtO)}_2 \text{SiH}} L'\text{Cu}-\text{OBz} \\
R^1 R^2 \text{N} & \xrightarrow{\text{CuL}^*} R'\text{=\text{-}}\text{OR} \\
\text{CuL}^* & \xrightarrow{\text{R'}=\text{OR}} \text{L}'\text{Cu(OR)} \\
\text{R'}=\text{OR} & \xrightarrow{\text{Me(EtO)}_2 \text{SiH}} \text{L}'\text{CuH} \\
\end{align*}
\]
4.2 Results and Discussion

To assess the feasibility of the outlined allylic hydroamination (Scheme 2), we explored the reaction of geranyl benzyl ether using our previously reported conditions (Eq. 3). The hydroamination of this 3,3-disubstituted allylic ether was successful in affording the γ-chiral amine (+)3a in high yield and enantioselectivity. Since it is well known that alcohols undergo dehydrogenative silylation in situ using a variety of metal catalysts, we explored the hydroamination of geraniol using an additional equivalent of the silane reagent. Indeed reactions with geraniol first generated intermediate VII, which then proceeded to give γ-chiral amine (+)3a in good yield and enantioselectivity (Eq. 4).

We next applied the developed reaction conditions to a variety of allylic alcohols (Scheme 3) and showed that the stereochemical outcome of the reaction was dependent on the alkene geometry (E/Z), as geraniol generated the (S)-isomer of the chiral amine ((+)3a) and nerol generated the (R)-isomer of the product ((-)3a). For aliphatic substrates, we demonstrated that the hydroamination of simple 3,3-disubstituted allylic alcohols proceeded with excellent yields and enantioselectivities (3b and 3c).
Scheme 3. Copper-Catalyzed Hydroamination of 3,3-Disubstituted Allylic Alcohols

\[
\begin{align*}
R^2 &\quad + \quad \text{Me~NBn}_2 \quad \text{Me Me} \\
\text{OBz} &\quad \text{Bn N} &\quad \text{Bn} \\
\text{1} &\quad \text{2a} \quad \text{(1.2 equiv)}
\end{align*}
\]

\[2.0 \text{ mol\% Cu(OAc)}_2, 2.2 \text{ mol\% (R)-DTBM-SEGPHOS, 4.5 equiv (EtO)}_2\text{MeSiH, THF (1.0 M), 40 °C, 36 h} \]

\[3\]

\[\begin{align*}
\text{Me} &\quad \text{Me} \\
\text{R}^2 &\quad \text{R}^1 \\
(+)\text{3a} &\quad \text{75\% yield, 97\% ee} \\
\text{Me} &\quad \text{Me} \\
\text{Me} &\quad \text{OH} \\
\text{Geraniol}
\end{align*}\]

\[\begin{align*}
\text{Me} &\quad \text{Me} \\
\text{Me} &\quad \text{Me} \\
(-)\text{3a} &\quad \text{71\% yield, 87\% ee} \\
\text{Me} &\quad \text{Me} \\
\text{Me} &\quad \text{OH} \\
\text{Nerol}
\end{align*}\]

\[\begin{align*}
\text{Cl} &\quad \text{Me} \\
\text{Me} &\quad \text{Me} \\
\text{3b} &\quad \text{92\% yield, 96\% ee} \\
\text{Me} &\quad \text{Me} \\
\text{Ph} &\quad \text{Me} \\
\text{3c} &\quad \text{82\% yield, 98\% ee}
\end{align*}\]

\[\text{"Reaction conditions: 1 (1 mmol), 2a (1.2 mmol), Cu(OAc)}_2 (0.02 \text{ mmol), (R)-DTBM-SEGPHOS (0.022 mmol), diethoxymethylsilane (4.5 equiv), THF (1 mL), 40 °C, 36 h. Yields are isolated yields (average of two runs). Enantioselectivities were determined by chiral HPLC analysis."

Attempts to expand the scope of this method to other allylic alcohols showed that the reactions sometimes proceeded with low efficiency. For example, the hydroamination of 1d generated the \(\gamma\)-chiral amine 3d in only 18\% yield (Eq. 6); the remainder was the silylated starting material.

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We proposed that increasing the leaving group ability of the $-OR$ moiety should improve the overall reactivity of the trisubstituted olefin, presumably by increasing the rate of “$\beta$-alkoxide” elimination from II (Scheme 2). An additional benefit is that the quantity of silane reagent that was necessary would be reduced.

We examined a broad range of $-OR$ groups. Reaction of methyl and silyl ethers showed no increase in the yield of the desired product (entries 2–4, Table 1) when compared to geraniol (entry 1). Substrates containing more stabilized alkoxy groups, such as the 3,3-disubstituted allylic acetate (entry 5) and the 3,3-disubstituted allylic methyl carbonate (entry 6), also gave similar yields to the reaction employing geraniol (entry 1). The use of a 3,3-disubstituted allylic phosphate gave a slightly improved yield of 80%.

We were also interested in exploring the reaction of 3,3-disubstituted allylic benzoates since $\beta$-alkoxy elimination (ii) would generate $L^*$Cu-OBz species (IV, Scheme 2). This is the same intermediate generated following the reaction with the $O$-hydroxylamine benzoates (Scheme 4), and can be effectively converted into I.\(^1\)\(^2\) We found that the reaction of geranyl benzoate generated the desired allylic hydroamination product in higher yield than that of geranyl phosphate (entry 8, Table 1). Incorporating an electron-withdrawing benzoate to increase the leaving group ability was found instead to significantly reduce the yield (entry 9). In contrast, using electron-donating substituents, such as 4-(dimethylamino)benzoate (entry 10), produced near quantitative yield of the $\gamma$-chiral amine (+)3a. We speculated that the faster reaction with the electron-rich benzoate is due to the faster transmetalation of the intermediate Cu-OBz with diethoxymethylsilane. We are currently examining how the structure of the benzoate affects the transmetalation step.
**Table 1. Exploration of Allylic Leaving Group on Reactivity**

<table>
<thead>
<tr>
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<th>-OR</th>
<th>Yield (%)</th>
<th>ee (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>OH</td>
<td>70</td>
<td>97</td>
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<tr>
<td>2</td>
<td>OMe</td>
<td>57</td>
<td>96</td>
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<td>OAc</td>
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<td>96</td>
</tr>
<tr>
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<td>OCO(OMe)</td>
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<td>98</td>
</tr>
<tr>
<td>7</td>
<td>OPO(OEt)</td>
<td>80</td>
<td>97</td>
</tr>
<tr>
<td>8</td>
<td>OBz</td>
<td>88</td>
<td>97</td>
</tr>
<tr>
<td>9</td>
<td>p-CO₂MeC₆H₄CO₂</td>
<td>27</td>
<td>97</td>
</tr>
<tr>
<td>10</td>
<td>p-NMe₂C₆H₄CO₂</td>
<td>92</td>
<td>97</td>
</tr>
</tbody>
</table>

*a Reaction conditions: 1 (0.2 mmol), 2a (0.24 mmol), Cu(OAc)₂ (0.004 mmol), (R)-DTBM-SEGPHOS (0.0044 mmol), diethoxymethylsilane (3.5 equiv), THF (0.2 mL), 40 °C, 36 h. b Yields were determined by GC using dodecane or tetradecane as an internal standard. c Enantioselectivities were determined by chiral HPLC analysis. d 4.5 equiv of diethoxymethylsilane was used.

Lastly, we explored the effect of the chiral ligand on this reaction (Table 2). Ligands other than DTBM-SEGPHOS L₁, particularly those previously shown to be effective in copper-catalyzed reactions involving ligated copper hydride species, were also investigated for impact on enantioselectivity as well as reactivity. ¹¹ We used geranyl 4-(dimethylamino)benzoate ((E)-la) for this ligand study and found that (R)-DTBM-SEGPHOS (L₁) was superior to all the other chiral ligands in terms of both yield and enantioselectivity (entries 1–5, Table 2). When (S)-DTBM-MeO-BIPHEP (L₂) was used as the supporting ligand, the reaction generated the
desired product in 74% yield and -95% ee (entry 2). Only modest yield and enantioselectivity were observed with L3 (entry 2). Using L5 afforded the desired product (+)-3a with a high level of enantioselectivity (98% ee), but in a modest 52% yield (entry 5). The desired product was not detected when using L4 or the achiral ligand XantPhos (L6) (entries 4 and 6).

**Table 2. Examination of Bidentate Phosphine Ligands**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
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<td>1&lt;sup&gt;d&lt;/sup&gt;</td>
<td>L1</td>
<td>92</td>
<td>97</td>
</tr>
<tr>
<td>2&lt;sup&gt;d&lt;/sup&gt;</td>
<td>L2</td>
<td>74</td>
<td>-95</td>
</tr>
<tr>
<td>3</td>
<td>L3</td>
<td>12</td>
<td>-70</td>
</tr>
<tr>
<td>4</td>
<td>L4</td>
<td>0</td>
<td>nd&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>L5</td>
<td>52</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>L6</td>
<td>0</td>
<td>nd</td>
</tr>
</tbody>
</table>

<sup>d</sup>Reaction conditions: (E)-1a (0.2 mmol), 2a (0.22 mmol), Cu(OAc)<sub>2</sub> (0.020 mmol), (R)-DTBM-SEGPHOS (0.022 mmol), diethoxymethylsilane (3.5 equiv), THF (0.2 mL), 40 °C, 36 h. <sup>e</sup>Yields were determined by GC using dodecane as an internal standard. <sup>c</sup>Enantioselectivities were determined by chiral HPLC analysis. <sup>d</sup>Cu(OAc)<sub>2</sub> (0.004 mmol), (R)-DTBM-SEGPHOS (0.0044 mmol), see Table 1 entry 10. <sup>e</sup>Not determined.

With the optimized protocol in hand, we next investigated the application of this reaction to various 3,3-dialkyl substituted allyl 4-(dimethylamino)benzoates (Scheme 4). As with allylic alcohols (Scheme 3), the stereochemical outcome of the reaction is dependent on the alkene geometry (3a). Various 3,3-disubstituted allylic 4-(dimethylamino)benzoates
containing an alkyl chloride (3b), an aryl group (3c), a sulfonamide (3d), an acetal group (3g), a benzyl ether (3h), and a tert-butylidemethylsilyl ether (3j) were also compatible with the protocol (Scheme 4). The hydroamination reaction also accommodates sterically encumbered groups at the 3-position including a cyclohexyl group (3e) and a tert-butyl group (3f). Free alcohols (3i), and free N-H groups (3l) were also tolerated; the free hydroxyl-containing substrates were converted to diethoxymethylsilyl ethers that can be easily cleaved during work-up using tetraethylammonium fluoride (TBAF). When aldehyde-containing substrates were employed, reduction to the alcohol was observed to produce amino alcohol product (3m).

**Scheme 4. Hydroamination of 3,3-Dialkyl Substituted Allyl 4-(dimethylamino)benzoates**

\[
\begin{align*}
\text{R}^2 &= \text{CH}_2\text{CH}_2\text{Cl}, \quad 85\% \text{ yield, } 96\% \text{ ee} \\
\text{R} &= \text{Bn}, \quad 86\% \text{ yield, } 98\% \text{ ee} \\
\text{R} &= \text{NTsBn}, \quad 88\% \text{ yield, } 97\% \text{ ee} \\
\text{R} &= \text{Cy}, \quad 85\% \text{ yield, } >99\% \text{ ee} \\
\text{R} &= \text{t-Bu}, \quad 66\% \text{ yield, } >99\% \text{ ee} \\
\text{R} &= \text{OBn}, \quad 69\% \text{ yield, } 99\% \text{ ee} \\
\text{R} &= \text{OH}, \quad 69\% \text{ yield, } 98\% \text{ ee} \\
\text{R} &= \text{OTBS}, \quad 92\% \text{ yield, } 97\% \text{ ee} \\
\text{R} &= p-\text{NMe}_2\text{C}_6\text{H}_4\text{CO}_2, \quad 92\% \text{ yield, } 94\% \text{ ee} \\
\text{R} &= \text{NHTr}, \quad 78\% \text{ yield, } 99\% \text{ ee} \\
\end{align*}
\]

\(^{a}\)Reaction conditions: 1 (1 mmol), 2a (1.2 mmol), Cu(OAc)\(_2\) (0.02 mmol), (R)-DTBM-SEGPHOS (0.022 mmol), diethoxymethylsilane (3.5 equiv), THF (1 mL), 40 °C, 36 h. Yields are isolated yields (average of two runs). Enantioselectivities were determined by chiral HPLC analysis. \(^b\)4.5 equiv of diethoxymethylsilane was used. \(^c\)Yield after work-up with TBAF. \(^d\)See Eq. 7.
Notably, hydroamination of 1,4-bisallylic 4-(dimethylamino)benzoate 1k afforded γ-chiral amine 3k (Scheme 4 and Eq. 7). Our hypothesis for this observed selectivity is that the olefin insertion proceeds to form the less sterically hindered copper intermediate VIII.

![Chemical structure](image1)

The dependence on olefin geometry for the stereochemical outcome of hydride addition in these reactions is noteworthy. As we have previously mentioned, E- and Z-trisubstituted alkenes provide different enantiomers of the product (3a, Schemes 3 and 4). Further, we found that use of the E isomer leads to formation of γ-chiral amine 3a with a higher level of enantioselectivity than seen for the Z-isomer. The same trend was also observed with styrenes and vinylsilanes (Chapters 2 and 3).\textsuperscript{1a,2} However, for disubstituted styrenes and vinylsilanes, reaction of both Z- and E-olefins gave the same absolute configuration of the product (Figure 4),\textsuperscript{1a,2} suggesting that the facial selectivity of copper hydride addition is independent of olefin geometry.

**Figure 4. Stereoconvergence of (E)- and (Z)-Styrene and Vinylsilane Substrates**

![Styrenes and Vinylsilanes](image2)
In addition to the catalyst controlled facial selectivity, we have shown through deuterium labeling experiments that subjecting Z- and E-vinylsilanes to our reaction conditions yields diastereomeric products (Chapter 3). This supports syn-addition of the L*CuD species to the alkene (Scheme 5, Eq. 8 and 9).

**Scheme 5. Deuterium-labeling Experiments**

\[
\begin{align*}
\text{(E)-Vinylsilane} & \quad 55\% \text{ conv.} \\
\text{(Z)-Vinylsilane} & \quad 53\% \text{ conv.}
\end{align*}
\]

For the allylic alcohol and benzoate substrates, the regioselectivity of L*CuH addition to the olefin is mainly determined by steric effects. It is more favorable for copper to bind to the least substituted end of the olefin. The stereochemical outcome is a result of the syn addition of L*CuH as depicted in Scheme 6. For geraniol or (E)-1a, the product results from Si,Re addition, while for nerol or (Z)-1a, the product results from Si,Si addition. Thus, we obtain the same stereochemistry where the copper adds to the olefin, and opposite stereochemistry where the hydride adds.

**Scheme 6. The Effect of Olefin Geometry on Stereochemical Outcome**

\[
\begin{align*}
\text{Reaction of E Substrate:} & \\
\text{Geraniol or (E)-1a} & \quad \text{L*CuH} \\
\text{Reaction of Z Substrate:} & \\
\text{Nerol or (Z)-1a} & \quad \text{L*CuH}
\end{align*}
\]
We rationalized the observed facial selectivities using quadrant diagrams and calculation performed by Mr. Yang Yang in another context (Figure 5).12 The southeast quadrant is the most sterically hindered and therefore controls the facial selectivity. Thus, the most favored olefin orientation would be to put hydrogen, the smallest group, in the southeast quadrant and the bulky alkoxy group in the southwest quadrant. For the $E$-substrate (Figure 5a), the smaller methyl group is situated in the northwest quadrant (second least favorable position), and the larger R group in the northeast quadrant. For the $Z$-substrate (Figure 5c), the larger R group resides in the northwest quadrant (second least favorable position) and the smaller methyl group in the northeast quadrant.

To access the minor enantiomer, the $E$-substrate would have to approach $L^*$CuH in the most energetically unfavorable orientation (Figure 5b), where both the large alkoxy group and the R group are placed in the least favorable southeast and northwest quadrants, respectively. As for the $Z$-substrate (Figure 5d), the minor enantiomer would result from placing the large alkoxy group in the least favorable southeast quadrant, while placing the R group in a more favorable northeast site. Since products generated from the $E$-olefin represented the lowest and the highest energy conformations, whereas products generated from the $Z$-olefin represented the two intermediate energy conformations, $E$-olefins generated products with higher ee than $Z$-olefins.
Figure 5. Rationalization for Facial Selectivity (SEGPHOS Backbone is Omitted for Clarity)\textsuperscript{12}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{rationalization_diagram}
\caption{Rationalization for Facial Selectivity}
\end{figure}

\textbf{E-Olefin with [(R)-DTBM-SEGPHOS]CuH:}

\begin{enumerate}
\item[(a)] Favored Si, Re addition to give (S)-product
\item[(b)] Disfavored Re, Si addition to give (R)-product
\end{enumerate}

\textbf{Z-Olefin with [(R)-DTBM-SEGPHOS]CuH:}

\begin{enumerate}
\item[(c)] Favored Si, Si addition to give (R)-product
\item[(d)] Disfavored Re, Re addition to give (S)-product
\end{enumerate}
We next investigated the hydroamination of 3-aryl-substituted allylic benzoates, as the aryl- and allyl benzoate functional groups have opposing electronic influence on the regioselectivity of L*CuH addition (Scheme 7). While we have shown above that aliphatic allylic alcohols exhibit anti-Markovnikov selectivity, there is an electronic preference to form a benzylic-Cu intermediate, which could compromise the general regioselectivity displayed in Scheme 4. We found, however, that the regiochemical course with aryl substituted allylic benzoates was the same as with dialkyl-substituted allylic benzoates, and γ-chiral amines were furnished in high yields and enantioselectivities in all cases (Scheme 7, 3n – 3s).

**Scheme 7. Allylic Hydroamination of 3,3-Alkyl,Aryl Substituted Allyl 4-(dimethylamino)benzoates**

\[ R^2 \text{CH}_2\text{CH(OH)CH}_2\text{NMe}_2 + \text{Bn}_2\text{N} \text{OB}_2 \rightarrow \text{R}^2 \text{CH}_2\text{CH(NBn}_2 \text{)} \text{CH}_2\text{R}^1 \]

**3n:** 74% yield, >99% ee  
**3o:** 85% yield, 98% ee  
**3p:** 62% yield, 99% ee  
**3q:** 77% yield, 98% ee  
**3r:** 91% yield, 99% ee  
**3s:** 70% yield, 99% ee

*Reaction conditions: 1 (1 mmol), 2a (1.2 mmol), Cu(OAc)\(_2\) (0.02 mmol), (R)-DTBM-SEGPHOS (0.022 mmol), diethoxymethylsilane (3.5 equiv), THF (1 mL), 40 °C, 36 h. Yields are isolated yields (average of two runs). Enantioselectivities were determined by chiral HPLC analysis.*
Similar to aromatic allylic benzoates, silyl allylic benzoates also have an opposing electronic influence on the regioselectivity of the $L^*$CuH addition as there is preference for copper to form an $\alpha$-silyl-Cu intermediate.\textsuperscript{10} Despite that, the hydroamination of the silyl allylic benzoate 1t proceeded with the same regiochemical outcome as the aliphatic (Scheme 4) and aromatic (Scheme 7) allylic benzoate substrates to provide the $\gamma$-chiral silyl amine 3t (Scheme 8).

**Scheme 8. Hydroamination of Silyl Substituted Allyl 4-(dimethylamino)benzoates**

\[
\text{Me}_2\text{PhSi}-\text{O} + \text{Bn}_2\text{N}_2\text{OBz} \xrightarrow{2 \text{ mol}\% \text{Cu(OAc)}_2, 2.2 \text{ mol}\% (R)-DTBM-SEGPHOS, 3.5 \text{ equiv (EtO)}_2\text{MeSiH, THF (1.0 M), 40 °C, 36 h}} \text{Me}_2\text{PhSi}-\text{N}\text{Bn}_2
\]

3t: 92% yield, 98% ee

In addition to a variety of 3,3-disubstituted allylic benzoates, this protocol is applicable to 1,3-substituted allylic benzoates (Scheme 9). Thus, trans-1-phenylbut-2-en-1-yl benzoate 1u underwent allylic hydroamination to generate $\alpha$-branched chiral amine product 3u.

**Scheme 9. Hydroamination of 1,3 Substituted Allyl 4-(dimethylamino)benzoates**

\[
\text{Me}_2\text{PhN}-\text{O} + \text{Bn}_2\text{N}_2\text{OBz} \xrightarrow{2 \text{ mol}\% \text{Cu(OAc)}_2, 2.2 \text{ mol}\% (R)-DTBM-SEGPHOS, 3.5 \text{ equiv (EtO)}_2\text{MeSiH, THF (1.0 M), 40 °C, 36 h}} \text{Bn}_2\text{N}\text{Ph-Me}
\]

3u: 71% yield, 98% ee

The application of this methodology was further extended to the synthesis of an amine with a more distal chiral center via an allylic hydroamination cascade. We envisioned that hydroamination of allylic epoxide IX would ultimately generate the corresponding $\delta$-chiral amine (Scheme 10). Hydrocupration of the allylic epoxide IX would generate copper intermediate X, which could then eliminate the internal epoxide C–O bond to yield allylic alcohol XI. This allylic alcohol is expected to undergo Cu-catalyzed dehydrogenative silylation, followed by hydrocupration and irreversible $\beta$-alkoxy elimination of intermediate
XII, furnishing the δ-chiral alkene XIII. Thus, anti-Markovnikov hydroamination of this olefin would provide the δ-chiral amine.

**Scheme 10. Proposed Cascade Hydroamination of Allylic Epoxides**

Indeed, use of the racemic allylic epoxide 1v yielded the desired δ-chiral amine 3v, in moderate yield (Scheme 11).

**Scheme 11. Cascade Hydroamination of an Allylic Epoxide**

Many O-benzoylhydroxylamine electrophiles can be utilized with our method (Scheme 12). Of note, enantiomerically enriched hydroxylamine esters can be employed to generate diastereomeric products with a $dr$ of >50:1 (4a and 4a') with complete catalyst control of the diastereomer being formed. Other O-benzoyl hydroxylamine electrophiles are suitable partners including the smaller alkylbenzylamine electrophiles (4b) and cyclic amine electrophiles, including the bulkier tetramethylpiperidine electrophiles, allowing for the generation of heterocyclic γ-chiral amines (4c - 4f).
Scheme 12. Scope of O-Benzoylhydroxylamine Electrophiles

\[
\begin{align*}
\text{R'} & \quad \text{O} \quad \text{NMe}_2 \\
\text{R}'' & \quad \text{O} \quad \text{Bz} \\
\text{R}_1 \quad \text{R}_2 & \quad \text{N} \quad \text{Me} \\
& \quad \text{with L1} \\
\text{4a} & \quad 91\% \text{ yield, } >50:1 \text{ dr} \\
\end{align*}
\]

\[
\begin{align*}
\text{with ent-L1} \\
\text{4a'} & \quad 90\% \text{ yield, } >50:1 \text{ dr} \\
\text{4b} & \quad 92\% \text{ yield, } >99\% \text{ ee} \\
\end{align*}
\]

\[
\begin{align*}
\text{Et} & \quad \text{Bn} \\
\text{Me} & \quad \text{Me} \\
\text{Ph} & \quad \text{Me} \\
\text{NMe}_2 & \quad \text{p-NMe}_2 \text{C}_6 \text{H}_4 \text{CO}_2 \\
\text{4c} & \quad 89\% \text{ yield, } 96\% \text{ ee} \\
\text{4d} & \quad 91\% \text{ yield, } 96\% \text{ ee} \\
\text{4e} & \quad 87\% \text{ yield, } 98\% \text{ ee} \\
\text{4f} & \quad 78\% \text{ yield, } 97\% \text{ ee} \\
\end{align*}
\]

\(\text{Reaction conditions: 1 (1 mmol), 2a (1.2 mmol), Cu(OAc)_2 (0.02 mmol), (R)-DTBM-SEGPHOS (0.022 mmol), THF (1 mL), 40 °C, 36 h. Yields are isolated yields (average of two runs). diethoxymethylsilane (3.5 equiv), THF (1 mL), 40 °C, 36 h. Yields are isolated yields (average of two runs). Enantioselectivities were determined by chiral HPLC analysis.}\)
Lastly, to demonstrate the scalability of the developed procedure, we performed the reaction on a 10-mmol scale. As depicted in Scheme 13, in this case the allylic hydroamination can be carried out with a reduced catalyst loading of 0.5 mol % Cu(OAc)$_2$. The use of inexpensive triphenylphosphine as an additive helps to stabilize the active catalyst species at this low catalyst loading.$^{13}$

**Scheme 13. Large Scale Cu-Catalyzed Allylic Hydroamination**

![Scheme 13](image)

**4.3 Conclusion**

In summary, we have developed a new enantioselective Cu-catalyzed allylic hydroamination strategy to access γ-chiral amines from 3,3-disubstituted allylic alcohols and N,N-dimethylbenzoates in one step. The reactions proceed with good yields and excellent enantioselectivities and allow for the generation of a broad scope of γ-chiral amines. In addition, we have demonstrated that the methodology is applicable towards an internal allylic benzoate substrate to generate an α-chiral amine. Hydroamination of an allylic epoxide is also illustrated to further remove the chiral center from the amine moiety and generate a δ-chiral amine. Since this method promotes an unprecedented installation of the amine and the generation of a distal chiral center in a single synthetic manipulation, we anticipate it will find considerable use in natural product and pharmaceutical synthesis.
4.4 Experimental

I. General Information

**General Reagent Information**

Unless otherwise stated, all reactions were set up on the bench top and carried out under an argon atmosphere. Anhydrous cyclohexane was purchased from Sigma-Aldrich in Sure-Seal® bottles and used as received. All other solvents were purified and dried by passage through successive alumina and Q5 reactant-packed columns on a solvent purification system. Diethoxymethylsilane was purchased from TCI America and stored under nitrogen at 4 °C in a Schlenk flask (diethoxymethylsilane is moisture sensitive, and proper Schlenk technique was used for handling this reagent). Other commercial reagents were purchased from Aldrich Chemical, Alfa Aesar, TCI, Strem, Acros, Oakwood, Frontier Scientific, or Combi-Block and were used as received. DTBM-SEGPHOS (L1) was purchased from Takasago. Ligands L2 – L4 were purchased from Strem Chemicals. Flash chromatography was either performed using glass columns with SiliaFlash® P60 (SiliCycle, 230-400 mesh), or on pre-packed Biotage® SNAP columns using a Biotage Isolera Automated Flash Chromatography System.

**General Analytical Information**

All compounds (starting materials and products) were characterized by ¹H NMR, ¹³C NMR, IR spectroscopy, melting point (where applicable), and elemental analysis or high-resolution mass spectrometry. ¹H NMR spectra were recorded on Bruker 400 MHz or Bruker 600 MHz spectrometer and are referenced relative to residual CDCl₃ proton signals at δ 7.26 ppm. ¹⁹F NMR spectra were recorded on a Bruker 400 MHz spectrometer and are referenced to CFCI₃ (δ 0.0 ppm). Data for ¹H and ¹⁹F NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, ap = apparent), integration, and coupling constant (Hz). ¹³C NMR spectra were recorded on a Bruker 400 MHz or Bruker 600 MHz spectrometer and are referenced to CDCl₃ at δ 77.16 ppm. The ¹³C NMR spectra were obtained with ¹H decoupling. Data for ¹³C NMR are reported in terms of chemical shift and multiplicity where appropriate. IR spectra were obtained on a Thermo Scientific Nicolet iS5 spectrometer (iD5 ATR, diamond) and are reported in terms of frequency of
absorption (cm⁻¹). GC analyses were performed on an Agilent 6890 gas chromatograph with an FID detector using a J & W DB-1 column (10 m, 0.1 mm I.D.). Elemental analyses were performed by Atlantic Microlabs Inc., Norcross, GA. High Resolution Mass spectra were obtained from a Bruker Daltonics APEX IV 4.7 Tesla Fourier transform ion cyclotron resonance mass spectrometer (FT-ICR-MS). Melting points (m.p.) were obtained on a Mel-Temp capillary melting point apparatus. High-pressure liquid chromatography (HPLC) was performed on Agilent 1200 Series chromatographs using chiral columns (25 cm) as noted for each compound. Optical rotations were measured on a Jasco P-1010 polarimeter with [α]D values reported in degrees; concentration (c) is in g/100 mL. Reactions were monitored by GC analysis and thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) or Fluka aluminum oxide/TLC-cards using UV light as a visualizing agent. The yields reported are the average of at least two experiments, unless otherwise indicated.
II. Experimental Procedures and Characterization Data

A) Cu-Catalyzed Hydroamination of 3,3-Disubstituted Allylic Alcohols and 3,3-Disubstituted Allylic Benzoates

General Procedure:

\[
\begin{align*}
R^1 & \quad R^2 \\
\text{OR} & \quad \text{OBz}
\end{align*}
\]

To an oven-dried 4 mL screw-cap vial equipped with a magnetic stir bar was charged with Cu(OAc)_2 (2.0-5.0 mol%) and (R)-DTBM-SEGPHOS (2.2-5.5 mol%). The tube was sealed with a teflon-lined screw cap, evacuated, and backfilled with argon (this process was repeated a total of 3 times). Anhydrous THF (1.0 mL) was added, and the mixture was stirred for 10 min, at which time diethoxymethylsilane (3.5-4.5 equiv) was added and the stirring was continued for another 5 min at rt. Into a separate oven-dried medium-sized screw-cap test tube was added the 3,3-disubstituted allylic alcohol (or 3,3-disubstituted allylic benzoate) (1.0 mmol, 1.0 equiv) and O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 2 equiv). The tube was sealed with a teflon-line screw cap and evacuated and backfilled with argon (this process was repeated a total of 3 times). The catalyst solution was then transferred via syringe to the reaction tube containing the substrates, and the reaction mixture was stirred at 40 °C for up to 36 h. Dodecane (100 µL) was added as an internal standard for GC analysis or trimethoxybenzene (56 mg, 0.33 mmol, 0.33 equiv) was added as the internal standard for ¹H NMR analysis. After cooling to rt, the reaction mixture was quenched with saturated aqueous Na₂CO₃ solution, extracted with EtOAc, dried over Na₂SO₄, filtered through a pad of silica, concentrated, and purified by column chromatography on silica gel or by acid-base extraction as indicated for each substrate. The enantiomeric excess (% ee) was determined by HPLC analysis using chiral stationary phases.

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} \\
\text{NBn}_2 & \quad \text{NBn}_2
\end{align*}
\]

(S)-N,N-dibenzyl-3,7-dimethyloct-6-en-1-amine (Scheme 3 and 4, entry (+)3a): From geraniol (154 mg, 1.0 mmol), the title
compound was prepared following the general procedure using Cu(OAc)₂ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), O-benzoyl-\(N,N\)-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (720 \(\mu\)L, 4.5 mmol, 4.5 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 40 °C. The crude material was purified by flash column chromatography (5–9% EtOAc in hexanes) to provide the title compound as a colorless liquid in 75% yield (251 mg).

From (E)-3,7-dimethylocta-2,6-dien-1-yl 4-(dimethylamino)benzoate ((E)-la) (301 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)₂ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), O-benzoyl-\(N,N\)-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (560 \(\mu\)L, 3.5 mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 40 °C. The crude material was purified by flash column chromatography (5–9% EtOAc in hexanes) to provide the title compound as a colorless liquid in 94% yield (315 mg).

IR (neat, cm⁻¹) 2916, 2793, 1494, 1452, 1375, 1028; \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\): 7.52 – 7.40 (m, 4H), 7.40 – 7.33 (m, 4H), 7.33 – 7.23 (m, 2H), 5.13 (t, \(J = 7.5\) Hz, 1H), 3.65 (d, \(J = 13.7\) Hz, 2H), 3.57 (d, \(J = 13.7\) Hz, 2H), 2.50 (t, \(J = 7.3\) Hz, 2H), 2.11 – 1.91 (m, 2H), 1.74 (s, 3H), 1.65 (s, 3H), 1.63 – 1.48 (m, 2H), 1.43 – 1.26 (m, 2H), 1.22 – 1.09 (m, 1H), 0.83 (d, \(J = 6.3\) Hz, 3H); \(^{13}\)C NMR (100.6 MHz, CDCl₃) \(\delta\): 140.18, 131.09, 128.93, 128.24, 126.83, 125.09, 58.44, 51.44, 37.25, 34.17, 30.52, 25.87, 25.62, 19.76, 17.79. Anal. Calcd. for C₂₄H₃₃N: C, 85.91; H, 9.91. Found: C, 85.71; H, 10.04. \([\alpha]D^{24}_2 = +0.27\) (\(c = 1.00\), CHCl₃); HPLC analysis (OJ-H, 50% (hexanes:EtOH:TFA:Diethylamine = 95:5:0.2:0.1)/hexanes, 0.8 mL/min, 220 nm) indicated 97% ee: \(t_R\) (major) = 12.0 min, \(t_R\) (minor) = 14.9 min for both reactions using geraniol or (E)-la.

(R)-\(N,N\)-dibenzyl-3,7-dimethyloct-6-en-1-amine (Scheme 3 and 4, entry (−)3a): From nerol (154 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)₂ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2
mol%), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv),
diethoxymethylsilane (720 µL, 4.5 mmol, 4.5 equiv), and THF (1.0 mL). The reaction mixture
was stirred for 36 h at 40 °C. The crude material was purified by flash column chromatography
(5–9% EtOAc in hexanes) to provide the title compound as a colorless liquid in 71% yield (238 mg).

From (Z)-3,7-dimethylocta-2,6-dien-1-yl 4-(dimethylamino)benzoate ((Z)-1a) (301 mg, 1.0
mmol), the title compound was prepared following the general procedure using Cu(OAc)$_2$ (3.6
mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), O-benzoyl-
N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (560 µL, 3.5
mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 40 °C. The
crude material was purified by flash column chromatography (5–9% EtOAc in hexanes) to
provide the title compound as a colorless liquid in 63% yield (212 mg).

IR (neat, cm$^{-1}$) 2914, 2791, 1494, 1452, 1375, 1028; $^1$H NMR (600 MHz, CDCl$_3$) δ: 7.44 – 7.38
(m, 4H), 7.37 – 7.31 (m, 4H), 7.30 – 7.23 (m, 2H), 5.11 (t, $J = 7.1$ Hz, 1H), 3.63 (d, $J = 13.6$ Hz,
2H), 3.55 (d, $J = 13.6$ Hz, 2H), 2.48 (t, $J = 7.3$ Hz, 2H), 2.01 (dq, $J = 14.6$, 6.9 Hz, 1H), 1.93
dt, $J = 14.3$, 7.5 Hz, 1H), 1.72 (s, 3H), 1.63 (s, 3H), 1.61 – 1.57 (m, 1H), 1.53 (dq, $J = 12.8$, 6.7
Hz, 1H), 1.36 (dt, $J = 13.1$, 7.1 Hz, 1H), 1.33 – 1.23 (m, 1H), 1.18 – 1.07 (m, 1H), 0.81 (d, $J =
6.6$ Hz, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$) δ: 140.18, 131.12, 128.92, 128.23, 126.82, 125.08,
58.42, 51.43, 37.26, 34.16, 30.51, 25.88, 25.62, 19.76, 17.80. HRMS (DART-TOF) calcd. for
C$_{24}$H$_{33}$N $[M+H]^+$ m/z 336.2586, found 336.2656. $[\alpha]_D^{24} = -0.55$ (c = 1.00, CHCl$_3$); HPLC
analysis (OJ-H, 50% (hexanes:EtOH:TFA:Diethylamine = 95:5:0.2:0.1)/hexanes, 0.8 mL/min,
220 nm) indicated 87% ee: $t_R$ (minor) = 10.0 min, $t_R$ (major) = 12.0 min for both reactions using
nerol or (Z)-1a.

(S)-N,N-dibenzyl-7-chloro-3-methylheptan-1-amine (Scheme 3
and 4, entry 3b). From (E)-7-chloro-3-methylhept-2-en-1-ol
(163 mg, 1.0 mmol), the title compound was prepared following
the general procedure using Cu(OAc)$_2$ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS
(26 mg, 0.022 mmol, 2.2 mol%), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (720 µL, 4.5 mmol, 4.5 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 40 °C. The crude material was purified by flash column chromatography (0–7% EtOAc in hexanes) to provide the title compound as a colorless liquid in 82% yield (317 mg).

From (E)-7-chloro-3-methylhept-2-en-1-yl 4-(dimethylamino)benzoate (1b) (310 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)$_2$ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (560 µL, 3.5 mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 40 °C. The crude material was purified by flash column chromatography (0–7% EtOAc in hexanes) to provide the title compound as a colorless liquid in 85% yield (292 mg).

IR (neat, cm$^{-1}$) 2924, 1494, 1452, 746, 698, 668; $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.45 – 7.39 (m, 4H), 7.39 – 7.32 (m, 4H), 7.31 – 7.25 (m, 2H), 3.62 (d, $J$ = 13.6 Hz, 2H), 3.57 (d, $J$ = 14.4 Hz, 2H), 3.53 (t, $J$ = 6.8 Hz, 2H), 2.55 – 2.37 (m, 2H), 1.81 – 1.66 (m, 2H), 1.62 – 1.48 (m, 2H), 1.48 – 1.29 (m, 3H), 1.29 – 1.17 (m, 1H), 1.15 – 1.01 (m, 1H), 0.81 (d, $J$ = 6.4 Hz, 3H);

$^{13}$C NMR (100.6 MHz, CDCl$_3$) δ: 140.14, 128.93, 128.24, 126.86, 58.52, 51.26, 45.27, 36.17, 34.16, 33.03, 30.68, 24.37, 19.81; HRMS (DART-TOF) calcd. for C$_{22}$H$_{30}$ClN [M+H]$^+$ m/z 344.2140, found 344.2127 Anal. Calcd. for C$_{22}$H$_{30}$ClN: C, 76.83; H, 8.20. Found: C, 76.76; H, 8.92. $[\alpha]_D^{24}$ = −3.1 (c = 1.15, CHCl$_3$); HPLC analysis (2 connected AD-H columns, 95:5:0.2:0.1 Hexanes:IPA:TFA:Diethylamine, 0.8 mL/min, 220 nm), 0.8 mL/min, 220 nm) indicated 96% ee: $t_R$ (major) = 80.0 min, $t_R$ (minor) = 83.8 min for both reactions using (E)-7-chloro-3-methylhept-2-en-1-ol or 1b.

![Ph](S)-N,N-dibenzyl-3-methyl-6-phenylhexan-1-amine (Scheme 3 and 4, entry 3c). From (E)-3-methyl-6-phenylhex-2-en-1-ol (190 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)$_2$ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26
mg, 0.022 mmol, 2.2 mol%), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (720 µL, 4.5 mmol, 4.5 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 40 °C. The crude material was purified by flash column chromatography (0–5% EtOAc in hexanes) to provide the title compound as a colorless liquid in 82% yield (305 mg).

From (E)-3-methyl-6-phenylhex-2-en-1-yl 4-(dimethylamino)benzoate (1c) (337 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)₂ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (560 µL, 3.5 mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 40 °C. The crude material was purified by flash column chromatography (0–9% EtOAc in hexanes) to provide the title compound as a colorless liquid in 86% yield (320 mg).

IR (neat, cm⁻¹) 2926, 2854, 2791, 1494, 1452, 1364, 1125, 744, 697; ¹H NMR (400 MHz, CDCl₃) δ: 7.52 – 7.44 (m, 4H), 7.44 – 7.30 (m, 8H), 7.30 – 7.23 (m, 3H), 3.68 (d, J = 13.6 Hz, 2H), 3.62 (d, J = 13.7 Hz, 2H), 2.70 – 2.58 (m, 2H), 2.58 – 2.47 (m, 2H), 1.60 (d, J = 19.0 Hz, 4H), 1.50 – 1.29 (m, 2H), 1.27 – 1.12 (m, 1H), 0.87 (d, J = 6.5 Hz, 3H); ¹³C NMR (100.6 MHz, CDCl₃) δ: 142.96, 140.11, 128.89, 128.45, 128.31, 128.20, 126.81, 125.66, 58.43, 51.30, 36.75, 36.37, 34.14, 30.74, 29.03, 19.81. Anal. Calcd. for C₂₇H₃₃N: C, 87.28; H, 8.95. Found: C, 87.06; H, 9.01. [α]D₂⁴ = −3.4 (c = 1.50, CHCl₃); HPLC analysis (OD-H, 3% IPA/hexanes, 0.8 mL/min, 220 nm) indicated 98% ee: tₚ (minor) = 5.4 min, tₚ (major) = 6.4 min for both reactions using 1c or (E)-3-methyl-6-phenylhex-2-en-1-ol.

(R)-N-benzyl-N-(5-(dibenzylamino)-3-methylpentyl)-4-methylbenzenesulfonamide (Scheme 4, entry 3d). From (E)-5-((N-benzyl-4-methylphenyl)sulfonamido)-3-methylpent-2-en-1-yl 4-(dimethylamino)benzoate (1d) (507 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)₂ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), 1.0 equiv), O-benzoyl-N,N-
dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (560 µL, 3.5 mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 40 °C. The crude material was purified by flash column chromatography (15–25% EtOAc in hexanes) to provide the title compound as a colorless liquid in 88% yield (476 mg). IR (neat, cm⁻¹) 3028, 2923, 1453, 1338, 1216, 1158, 1090, 1028, 815, 750, 598; ¹H NMR (400 MHz, CDCl₃) δ: 7.80 – 7.68 (m, 2H), 7.40 – 7.20 (m, 17H), 4.28 (s, 2H), 3.55 (d, J = 13.7 Hz, 2H), 3.46 (d, J = 13.7 Hz, 2H), 3.08 (t, J = 7.8 Hz, 2H), 2.46 (s, 3H), 2.31 (t, J = 7.2 Hz, 2H), 1.41 – 1.24 (m, 3H), 1.23 – 1.05 (m, 2H), 1.06 (d, J = 6.3 Hz, 3H); ¹³C NMR (100.6 MHz, CDCl₃) δ: 143.12, 139.87, 137.14, 136.61, 129.69, 128.75, 128.51, 128.32, 128.15, 127.71, 127.18, 126.78, 58.28, 58.28, 51.84, 51.05, 46.17, 34.94, 33.82, 28.56, 21.52, 19.25. HRMS (DART-TOF) calcd. for C₃₄H₄₀N₂O₂S [M+H]+ m/z 541.2883, found 541.2897. [α]D²⁴ = -1.8 (c = 1.00, CHCl₃); HPLC analysis (OD-H, 5% IPA/hexanes, 0.8 mL/min, 220 nm) indicated 97% ee: tₗₗ (minor) = 18.2 min, tₗₜ (major) = 20.1 min.

\[
\text{(R)-N,N-dibenzyl-3-cyclohexylbutan-1-amine (Scheme 4, entry 3e). From (E)-3-cyclohexylbut-2-en-1-yl 4-(dimethylamino)benzoate (1e)}
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(301 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)₂ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (560 µL, 3.5 mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 40 °C. The crude material was purified by flash column chromatography (0–8% EtOAc in hexanes) to provide the title compound as a colorless liquid in 85% yield (285 mg). IR (neat, cm⁻¹) 2920, 2850, 2790, 1494, 1449, 1365, 1124, 1074, 1028, 743, 730, 697; ¹H NMR (400 MHz, CDCl₃) δ: 7.51 – 7.43 (m, 4H), 7.43 – 7.36 (m, 4H), 7.35 – 7.29 (m, 2H), 3.69 (d, J = 13.6 Hz, 2H), 3.60 (d, J = 13.6 Hz, 2H), 2.59 – 2.43 (m, 2H), 1.87 – 1.76 (m, 2H), 1.76 – 1.67 (m, 2H), 1.67 – 1.57 (m, 2H), 1.52 – 1.34 (m, 2H), 1.32 – 1.14 (m, 4H), 1.14 – 0.96 (m, 2H), 0.80 (d, J = 6.7 Hz, 3H); ¹³C NMR (100.6 MHz, CDCl₃) δ: 140.19, 128.93, 128.22, 126.81, 58.44, 51.67, 42.64, 35.85, 31.22, 30.79, 28.68, 27.05, 27.02, 26.93, 16.27. Anal. Calcd. for C₂₄H₃₃N: C, 85.91; H, 9.91. Found: C, 85.61; H, 9.96. [α]D²⁴ = +5.30 (c = 1.50, CHCl₃); HPLC
analysis (AD-H, hexanes:EtOH:TFA:Diethylamine = 95:5:0.2:0.1, 1.0 mL/min, 220 nm) indicated >99% ee: t_R (major) = 9.9 min, t_R (minor) = 11.3 min.

\[ \text{(R)-N,N-dibenzyl-3,4,4-trimethylpentan-1-amine} \]

(Scheme 4, entry 3f). From \((E)-3,4,4\text{-trimethylpent-2-en-1-yl 4-(dimethylamino)benzoate} \) (1f) (275 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)_2 (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (560 µL, 3.5 mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 40 °C. The crude material was purified by flash column chromatography (0–8% EtOAc in hexanes) to provide the title compound as a colorless liquid in 66% yield (182 mg). IR (neat, cm\(^{-1}\)) 2960, 1494, 1453, 1364, 1216, 795, 697; \(^1\)H NMR (400 MHz, CDCl_3) \(\delta: 7.48 - 7.41 \) (m, 4H), 7.41 - 7.34 (m, 4H), 7.33 - 7.26 (m, 2H), 3.75 (d, \(J = 13.7 \) Hz, 2H), 3.51 (d, \(J = 13.7 \) Hz, 2H), 2.57 - 2.42 (m, 2H), 1.94 - 1.81 (m, 1H), 1.30 - 1.20 (m, 1H), 1.15 - 1.05 (m, 1H), 0.90 (s, 9H), 0.73 (d, \(J = 6.7 \) Hz, 3H); \(^{13}\)C NMR (100.6 MHz, CDCl_3) \(\delta: 140.14, 128.95, 128.24, 126.84, 58.42, 52.74, 40.76, 33.14, 28.97, 27.46, 14.43. \) HRMS (DART-TOF) calcd. for C_{22}H_{31}N \([M+H]^+ m/z\) 310.2529, found 310.2515. \([\alpha]_{D}^{24} = +5.30 \) (c = 1.50, CHCl_3); HPLC analysis (AD-H, hexanes:EtOH:TFA:Diethylamine = 95:5:0.2:0.1, 1.0 mL/min, 220 nm) indicated >99% ee: t_R (major) = 7.9 min, t_R (minor) = 8.9 min.

\[ \text{(R)-N,N-dibenzyl-3-(2-methyl-1,3-dioxolan-2-yl)butan-1-amine} \]

(Scheme 4, entry 3g). From \((E)-3-(2\text{-methyl-1,3-dioxolan-2-yl)but-2-en-1-yl 4-(dimethylamino)benzoate} \) (1g) (305 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)_2 (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (560 µL, 3.5 mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 40 °C. The crude material was purified by flash column chromatography (5–15% EtOAc in hexanes)
to provide the title compound as a colorless liquid in 67% yield (227 mg). IR (neat, cm\(^{-1}\)) 2937, 2876, 2794, 1494, 1453, 1379, 1219, 1149, 1062, 868, 746, 1098; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) : 7.44 (s, 4H), 7.41 – 7.33 (m, 4H), 7.32 – 7.25 (m, 2H), 4.03 – 3.85 (m, 4H), 3.77 (d, \(J = 13.6\) Hz, 2H), 3.49 (d, \(J = 13.6\) Hz, 2H), 2.66 – 2.44 (m, 2H), 2.10 – 1.96 (m, 1H), 1.91 – 1.80 (m, 1H), 1.29 (s, 3H), 1.34 – 1.20 (m, 1H), 0.85 (d, \(J = 6.8\) Hz, 3H). \(^1\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) : 140.03, 128.90, 128.17, 126.78, 112.46, 64.59, 58.23, 51.49, 38.87, 28.93, 20.28, 14.58; HRMS (DART-TOF) calcd. for C\(_{22}\)H\(_{29}\)NO\(_2\) [M+H]\(^+\) m/z 340.2271, found 340.2249. \([\alpha]\)\(_D\)\(^{24}\) = +16.8 (c = 1.00, CHCl\(_3\)); HPLC analysis (OD-H, hexanes:EtOH:TFA:Diethylamine = 95:5:0.2:0.1, 1.0 mL/min, 220 nm) indicated >99% ee: \(t_R\) (minor) = 18.5 min, \(t_R\) (major) = 21.5 min.

\(\text{(S)}\)\(_N\)\(_N\)-dibenzy1-7-(benzyloxy)-3-methylheptan-1-amine

(Scheme 4, entry 3h). From \((E)\)-7-(benzyloxy)-3-methylhept-2-en-1-yl 4-(dimethylamino)benzoate (1h) (382 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)\(_2\) (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), O-benzoyl-\(N\)\(_N\)-dibenzy1hydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (560 \(\mu\)L, 3.5 mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 40 °C. The crude material was purified by flash column chromatography (0–7% EtOAc in hexanes) to provide the title compound as a colorless liquid in 69% yield (288 mg). IR (neat, cm\(^{-1}\)) 2930, 2855, 2791, 1494, 1452, 1363, 1219, 1101, 1028, 772, 731, 696; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) : 7.44 – 7.30 (m, 13H), 7.29 – 7.23 (m, 2H), 4.55 (s, 2H), 3.62 (d, \(J = 13.7\) Hz, 1H), 3.56 (d, \(J = 13.7\) Hz, 1H), 3.48 (t, \(J = 6.6\) Hz, 2H), 2.47 (t, \(J = 7.6\) Hz, 2H), 1.69 – 1.45 (m, 4H), 1.45 – 1.30 (m, 3H), 1.30 – 1.19 (m, 1H), 1.16 – 1.03 (m, 1H), 0.80 (d, \(J = 6.5\) Hz, 3H); \(^1\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) : 140.17, 138.86, 128.92, 128.47, 128.23, 127.74, 127.59, 126.83, 72.98, 70.61, 58.45, 51.37, 36.95, 34.20, 30.89, 30.19, 23.70, 19.83; Anal. Calcd. for C\(_{29}\)H\(_{31}\)NO: C, 83.81; H, 8.97. Found: C, 83.57; H, 9.08. \([\alpha]\)\(_D\)\(^{24}\) = –1.0 (c = 2.00, CHCl\(_3\)); HPLC analysis (OD-H, 5% IPA/hexanes, 1.0 mL/min, 220 nm) indicated >99% ee: \(t_R\) (major) = 15.0 min, \(t_R\) (minor) = 31.9 min.
(S)-7-(dibenzylamino)-5-methylheptan-1-ol (Scheme 4, entry 3i). From (E)-7-hydroxy-3-methylhept-2-en-1-yl 4-(dimethylamino)benzoate (1i) (291 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)$_2$ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (720 µL, 4.5 mmol, 4.5 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 40 °C and quenched by adding 5 mL TBAF (1 M in THF) and stirring for an extra 1 h. The crude material was purified by flash column chromatography (15–30% EtOAc in hexanes) to provide the title compound as a colorless liquid in 69% yield (225 mg). IR (neat, cm$^{-1}$) 2928, 2859, 2792, 1494, 1452, 1365, 1068, 1028, 745, 697; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.46 – 7.40 (m, 4H), 7.40 – 7.33 (m, 4H), 7.31 – 7.25 (m, 2H), 3.63 (d, $J$ = 13.5 Hz, 2H), 3.63 (t, $J$ = 6.6 Hz, 2H), 3.57 (d, $J$ = 13.6 Hz, 2H), 2.49 (t, $J$ = 7.3 Hz, 2H), 1.68 – 1.48 (m, 5H), 1.43 – 1.21 (m, 4H), 1.17 – 1.05 (m, 1H), 0.82 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$: 140.08, 128.90, 128.20, 126.81, 130.40, 58.43, 51.30, 36.81, 34.11, 33.15, 30.81, 23.18, 19.81; HRMS (DART-TOF) calcd. for C$_{22}$H$_{31}$NO [M+H]$^+$ m/z 326.2478, found 326.2457. [$\alpha$]$_D^{24}$ = –1.3 (c = 1.00, CHCl$_3$). HPLC analysis (OD-H, 5% IPA in hexanes, 0.8 mL/min, 220 nm) indicated 98% ee: $t_R$ (minor) = 9.3 min, $t_R$ (major) = 10.6 min.

(R)-N,N-dibenzyl-4-((tert-butyldimethylsilyl)oxy)-3-methylbutan-1-amine (Scheme 4, entry 3j). From (E)-4-((tert-butyldimethylsilyl)oxy)-3-methylbutan-2-en-1-yl 4-(dimethylamino)benzoate (1j) (364 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)$_2$ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (560 µL, 3.5 mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 40 °C. The crude material was purified by flash column chromatography (0–8% EtOAc in hexanes) to provide the title compound as a colorless liquid in 92% yield (365 mg). IR (neat, cm$^{-1}$) 2953, 2927, 2855, 2792, 1494, 1452, 1361, 1250, 1088, 1006, 773, 696; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.42 – 7.37 (m, 4H), 7.36 – 7.30 (m, 4H), 457
7.28 – 7.22 (m, 2H), 3.63 (d, J = 13.6 Hz, 2H), 3.53 (d, J = 13.6 Hz, 2H), 3.44 – 3.28 (m, 2H), 2.48 (t, J = 7.2 Hz, 2H), 1.80 – 1.62 (m, 2H), 1.34 – 1.19 (m, 1H), 0.91 (s, 9H), 0.78 (d, J = 6.6 Hz, 3H), 0.04 (s, 3H), 0.03 (s, 3H); 13C NMR (100.6 MHz, CDCl3) δ: 140.12, 128.98, 128.24, 126.85, 68.30, 58.37, 51.26, 33.89, 30.38, 26.11, 18.48, 16.86, -5.22; Anal. Calcd. for C25H39NOSi: C, 75.51; H, 9.89. Found: C, 75.23; H, 10.00. [α]D24 = +2.1 (c = 1.50, CHCl3).

HPLC analysis (AD-H, hexanes:EtOH:TFA:Diethylamine = 95:5:0.2:0.1, 1.0 mL/min, 220 nm) indicated 97% ee: τR (major) = 5.4 min, τR (minor) = 5.7 min.

(R)-N,N-dibenzyl-4-(((tert-butyldimethylsilyl)oxy)-3-methylbutan-1-amine (Scheme 4, entry 3k). From (E)-4-(((tert-butyldimethylsilyl)oxy)-3-methylbut-2-en-1-yl 4-(dimethylamino)benzoate (1k) (364 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)2 (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (560 µL, 3.5 mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 40 °C. The crude material was purified by flash column chromatography (0–8% EtOAc in hexanes) to provide the title compound as a colorless liquid in 92% yield (365 mg). IR (neat, cm⁻¹) 2930, 2802, 1700, 1608, 1525, 1452, 1366, 1275, 1182, 1105, 770, 698; 1H NMR (400 MHz, CDCl3) δ: 8.02 – 7.89 (m, 2H), 7.49 – 7.40 (m, 4H), 7.40 – 7.31 (m, 4H), 7.31 – 7.23 (m, 2H), 6.71 – 6.63 (m, 2H), 4.17 – 4.01 (m, 2H), 3.68 (d, J = 13.6 Hz, 2H), 3.56 (d, J = 13.6 Hz, 2H), 3.07 (s, 6H), 2.63 – 2.49 (m, 2H), 2.14 – 1.98 (m, 1H), 1.89 – 1.77 (m, 1H), 1.52 – 1.37 (m, 1H), 0.93 (d, J = 6.7 Hz, 3H); 13C NMR (100.6 MHz, CDCl3) δ: 167.07, 153.31, 139.89, 131.27, 128.92, 128.24, 126.87, 117.41, 110.78, 69.01, 58.40, 50.94, 40.13, 30.91, 30.85, 17.02; Anal. Calcd. for C28H34N2O2: C, 78.10; H, 7.96. Found: C, 77.80; H, 8.03. [α]D24 = –10.1 (c = 2.00, CHCl3). HPLC analysis (IA, 10% EtOH in hexanes, 0.8 mL/min, 220 nm) indicated 94% ee: τR (minor) = 8.9 min, τR (major) = 9.6 min.

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(R)-N\textsubscript{2}N\textsuperscript{4}-dibenzyl-2-methyl-N\textsuperscript{1}-tritylbutane-1,4-diamine (Scheme 4, entry 3l). From (E)-3-methyl-4-(tritylamino)but-2-en-1-yl 4-(dimethylamino)benzoate (1I) (491 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)\textsubscript{2} (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (560 µL, 3.5 mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 40 °C. The crude material was purified by flash column chromatography (0–8% EtOAc in hexanes) to provide the title compound as a colorless liquid in 78% yield (408 mg). IR (neat, cm\textsuperscript{-1}) 3026, 2924, 1493, 1449, 1219, 772, 698; \textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}) δ: 7.51 – 7.46 (m, 6H), 7.42 – 7.36 (m, 4H), 7.35 – 7.28 (m, 10H), 7.27 – 7.23 (m, 2H), 7.23 – 7.19 (m, 3H), 3.64 (d, J = 13.7 Hz, 2H), 3.52 (d, J = 13.7 Hz, 2H), 2.53 – 2.33 (m, 2H), 2.08 – 1.97 (m, 1H), 1.95 – 1.88 (m, 1H), 1.78 – 1.64 (m, 2H), 1.51 – 1.42 (m, 1H), 1.37 – 1.29 (m, 1H), 0.86 (d, J = 6.5 Hz, 3H); \textsuperscript{13}C NMR (151 MHz, CDCl\textsubscript{3}) δ: 146.44, 140.01, 128.89, 128.78, 128.25, 127.83, 126.86, 126.21, 70.82, 58.39, 51.28, 49.71, 32.38, 32.09, 18.47; HRMS (DART-TOF) calcd. for C\textsubscript{38}H\textsubscript{40}N\textsubscript{2} [M+H]\textsuperscript{+} m/z 525.3264, found 525.3264 [\text{[a]}\textsubscript{D}\textsuperscript{24} = -11.1 (c = 1.00, CHCl\textsubscript{3}). HPLC analysis (IA, hexanes:EtOH:TFA:Diethylamine = 95:5:0:2:0.1, 0.8 mL/min, 220 nm) indicated >99% ee: \text{t}_R (major) = 9.4 min, \text{t}_R (minor) = 12.2 min.

(R)-4-(dibenzylamino)-2-methylbutan-1-ol (Scheme 4, entry 3m). From (E)-3-methyl-4-oxobut-2-en-1-yl 4-(dimethylamino)benzoate (1m) (247 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)\textsubscript{2} (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (720 µL, 4.5 mmol, 4.5 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 40 °C and after cooling to rt, was quenched by adding 5 mL TBAF (1 M in THF) and stirred for an additional 1h. The crude material was purified by flash column chromatography (15–30% EtOAc in hexanes) to provide the title compound as a colorless liquid in 70% yield (199 mg). IR (neat, cm\textsuperscript{-1}) 2921, 2798, 1494, 1452, 1366, 1028, 746, 698; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ: 7.52 – 7.33 (m, 8H), 7.33 – 7.23 (m, 2H), 4.87 (s, 1H),
3.72 (d, J = 13.3 Hz, 2H), 3.51 (d, J = 13.3 Hz, 2H), 3.46 (dd, J = 11.1, 4.3 Hz, 2H), 3.33 (dd, J = 11.0, 7.1 Hz, 1H), 2.64 – 2.44 (m, 2H), 1.78 – 1.50 (m, 3H), 0.83 (d, J = 6.7 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ: 138.06, 129.52, 128.40, 127.28, 68.24, 58.37, 52.06, 35.59, 32.44, 17.67; HRMS (DART-TOF) calcd. for C$_{19}$H$_{25}$NO $[M+H]^+$ m/z 284.2009, found 284.1994. Anal. Calcd. for C$_{19}$H$_{25}$NO: C, 80.52; H, 8.89. Found: C, 80.22; H, 8.91. $[\alpha]_D^{24} = + 17.0$ (c = 1.00, CHCl$_3$). HPLC analysis (AD, 5% IPA in hexanes, 0.8 mL/min, 220 nm) indicated 92% ee: $t_R$ (minor) = 11.7 min, $t_R$ (major) = 12.6 min.

(R)-$N,N$-dibenzyl-3-phenylbutan-1-amine (Scheme 7, entry 3n). From (E)-3-phenylbut-2-en-1-yl 4-(dimethylamino)benzoate (1n) (295 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)$_2$ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), O-benzoyl-$N,N$-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (560 µL, 3.5 mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 40 °C. The crude material was purified by flash column chromatography (0–8% EtOAc in hexanes) to provide the title compound as a colorless liquid in 74% yield (244 mg). IR (neat, cm$^{-1}$) 3026, 2925, 2795, 1493, 1451, 1367, 1265, 1125, 1074, 1028, 968, 968, 908, 732, 697; $^1$H NMR (600 MHz, CDCl$_3$) δ: 7.44 – 7.33 (m, 8H), 7.33 – 7.24 (m, 4H), 7.24 – 7.18 (m, 1H), 7.18 – 7.11 (m, 2H), 3.67 – 3.50 (m, 4H), 2.87 – 2.76 (m, 1H), 2.54 – 2.45 (m, 1H), 2.45 – 2.34 (m, 1H), 1.97 – 1.86 (m, 1H), 1.86 – 1.73 (m, 1H), 1.20 (m, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 147.77, 139.98, 128.96, 128.40, 128.25, 127.03, 126.85, 125.88, 58.39, 51.64, 37.65, 35.72, 22.33; HRMS (DART-TOF) calcd. for C$_{24}$H$_{27}$N $[M+H]^+$ m/z 330.2216, found 330.2214. $[\alpha]_D^{24} = - 39.0$ (c = 1.00, CHCl$_3$). HPLC analysis (AD-H, hexanes:EtoH:TFA:Diethylamine = 95:5:0.2:0.1, 0.8 mL/min, 220 nm) indicated >99% ee: $t_R$ (major) = 17.1 min, $t_R$ (minor) = 18.3 min.
(R)-N,N-dibenzyl-3-(4-methoxyphenyl)butan-1-amine (Scheme 7, entry 3o). From (E)-3-(4-methoxyphenyl)but-2-en-1-yl 4-(dimethylamino)benzoate (1o) (325 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)₂ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol), diethoxymethylsilane (560 µL, 3.5 mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture was stirred in THF (1 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0–4% EtOAc in hexanes) to provide the title compound as a clear colorless oil in 85% yield (306 mg). IR (neat, cm⁻¹): 3027, 2926, 2794, 1618, 1494, 1452, 1420, 1323, 1162, 1118, 1068, 1028, 1016, 839, 744, 732, 696, 607; ¹H NMR (400 MHz, CDCl₃) δ 7.34 – 7.28 (m, 4H), 7.25 – 7.20 (m, 2H), 7.00 – 6.98 (dt, J = 8.4, 2.0 Hz, 2H), 6.79 – 6.75 (dt, J = 8.4, 2.0 Hz, 2H), 3.78 (s, 3H), 3.56 – 3.48 (dd, J = 18.0, 13.6 Hz, 4H), 2.74 – 2.65 (m, 1H), 2.44 – 2.29 (m, 2H), 1.83 – 1.68 (m, 2H), 1.12 – 1.10 (d, J = 6.8 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 157.6, 139.9, 139.7, 128.8, 128.1, 127.7, 126.7, 113.6, 58.3, 55.2, 51.5, 36.7, 35.8, 22.4; HRMS (DART-TOF) calculated for C₂₅H₂₉NO [M+H]⁺ m/z 360.2322, found 348.2322. [α]D²³.⁸ = −47.28 (c = 1.00, CHCl₃). HPLC analysis (OJ-H, 1% IPA/Hexanes, 0.8 mL/min, 220 nm) indicated 98% ee: tᵣ (minor) = 18.1 min, tᵣ (major) = 25.4 min.

(R)-N,N-dibenzyl-3-(4-(trifluoromethyl)phenyl)butan-1-amine (Scheme 7, entry 3p). From (E)-3-(4-(trifluoromethyl)phenyl)but-2-en-1-yl 4-(dimethylamino)benzoate (1p) (363 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)₂ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol), diethoxymethylsilane (560 µL, 3.5 mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture was stirred in THF (1 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0–4% EtOAc in hexanes) to provide the title compound as a clear colorless oil in 62% yield (246 mg). IR (neat, cm⁻¹): 3027, 2926, 2794, 1618, 1494, 1452, 1323, 1162, 1118, 1068, 1028, 1016, 839, 744, 732, 696; ¹H NMR (400 MHz, CDCl₃) δ 7.47 –
7.45 (d, J = 8.0 Hz, 2H), 7.37 – 7.22 (m, 10H), 7.15 – 7.12 (d, J = 8.0 Hz, 2H), 3.61–3.54 (dd, J = 25.4, 13.2 Hz, 4H), 2.88 – 2.79 (m, 1H), 2.42 – 2.28 (m, 2H), 1.84 – 1.77 (m, 2H), 1.16 – 1.14 (d, J = 6.8 Hz, 3H); 13C NMR (101 MHz, CDCl3) δ 151.5, 139.7, 128.8, 128.1, 127.2, 126.8, 125.2 (q, J = 3.9 Hz), 58.4, 51.1, 37.4, 35.4, 22.1; 19F NMR (376 MHz, CDCl3) δ -62.7. Anal. Calcd. for C25H26F3N: C, 75.54; H, 6.59 Found: C, 75.65; H, 6.67. [α]D23 = -47.33 (c = 1.82, CHCl3). HPLC analysis (OJ-H, 1% IPA/Hexanes, 0.8 mL/min, 220 nm) indicated 99% ee: tR (minor) = 19.0 min, tR (major) = 26.0 min.

(R)-N,N-dibenzyl-3-(3-fluorophenyl) butan-1-amine (Scheme 7, entry 3q): From (E)-3-(3-fluorophenyl)but-2-en-1-yl 4-(dimethylamino)benzoate (1q) (313 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)2 (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol), diethoxymethylsilane (560 µL, 3.5 mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture was stirred in THF (1 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0–5% EtOAc in hexanes) to afford provide the title compound as a clear colorless oil in 77% yield (268 mg). IR (neat, cm⁻¹): 3027, 2926, 2795, 1614, 1589, 1493, 1451, 1365, 1243, 1151, 1128, 1069, 1028, 967, 782, 732, 695; 1H NMR (400 MHz, CDCl3) δ 7.36 – 7.30 (m, 8H), 7.27 – 7.23 (m, 2H), 7.20 – 7.14 (m, 1H), 6.87 – 6.82 (m, 2H), 6.81 – 6.78 (dt, J = 10.4, 2.0 Hz, 1H), 3.58–3.50 (dd, J = 16.8, 13.6 Hz, 4H), 2.81 – 2.73 (m, 1H), 2.45 – 2.32 (m, 2H), 1.86 – 1.72 (m, 2H), 1.14 – 1.12 (d, J = 6.8 Hz, 3H); 13C NMR (101 MHz, CDCl3) δ 162.9 (d, J = 245.7 Hz), 150.3 (d, J = 6.8 Hz), 139.7, 129.6 (d, J = 6.8 Hz), 128.8, 128.1, 126.8, 122.6 (d, J = 10.4 Hz), 113.6 (d, J = 20.9 Hz), 112.5 (d, J = 21.2 Hz), 58.4, 51.3, 37.3, 35.5, 22.1; 19F NMR (376 MHz, CDCl3) δ -114.2. HRMS (DART-TOF) calculated for C25H26F3N [M+H]+ m/z 348.2122, found 348.2109. HPLC analysis (OJ-H, 3% IPA/Hexanes, 1 mL/min, 220 nm) indicated 98% ee: tR (minor) = 7.3 min, tR (major) = 10.3 min. [α]D23 = -48.27 (c = 1.08, CHCl3).
**(R)-N,N-dibenzyl-3-(3-chlorophenyl)butan-1-amine** (Scheme 7, entry 3r). From **(E)-3-(3-chlorophenyl)but-2-en-1-yl 4-(dimethylamino)benzoate** (1r) (325 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)₂ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), and O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol), diethoxymethylsilane (560 µL, 3.5 mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture was stirred in THF (1 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0–4% EtOAc in hexanes) to provide the title compound as a clear colorless oil in 91% yield (331 mg).

**IR (neat, cm⁻¹):** 3060, 3026, 2924, 2794, 1595, 1571, 1493, 1452, 1429, 1365, 1076, 1027, 782, 744, 695; ¹H NMR (400 MHz, CDCl₃) δ 7.35 - 7.22 (m, 1OH), 7.14 - 7.07 (m, 3H), 6.94 - 6.91 (m, 1H), 3.57 - 3.50 (dd, J = 16.4, 13.6 Hz, 4H), 2.78 - 2.63 (m, 1H), 2.41 - 2.34 (m, 2H), 1.85 - 1.69 (m, 2H), 1.12 - 1.11 (d, J = 6.8 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 149.7, 139.7, 134.0, 129.5, 128.8, 128.1, 127.0, 126.8, 125.9, 125.29, 58.4, 51.3, 37.4, 35.4, 22.1. HRMS (DART-TOF) calculated for C₂₄H₂₆ClN [M+H⁺] m/z 364.1827, found 364.1830. [α]₀²³.₈ = –53.43 (c = 1.41, CHCl₃). HPLC analysis (OJ-H, 3% IPA/Hexanes, 0.8 mL/min, 220 nm) indicated 99% ee: tᵣ (minor) = 7.5 min, tᵣ (major) = 9.2 min.

**(R)-N,N-dibenzyl-3-(thiophen-3-yl)butan-1-amine** (Scheme 7, entry 3s): From **(E)-3-(thiophen-3-yl)but-2-en-1-yl 4-(dimethylamino)benzoate** (1s) (301 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)₂ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol), diethoxymethylsilane (560 µL, 3.5 mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture was stirred in THF (1 mL) at 40 °C for 36 h. The crude product was purified by flash column chromatography (0–4% EtOAc in hexanes) to provide the title compound as a clear colorless oil (run 1: 230 mg (68%); run 2: 245 mg (73%); average yield: 70%). IR (neat, cm⁻¹): 3061, 3025, 2924, 2792, 1600, 1493, 1451, 1365, 1235, 1124, 1027, 743, 731, 694; ¹H NMR (400 MHz, CDCl₃) δ 7.39 – 7.32 (m, 8H), 7.28 – 7.24 (tt, J = 5.2, 1.2 Hz, 1H), 6.89 – 6.87 (dd, J = 5.2, 3.6 Hz, 1H), 463
6.66-6.66 (dd, J = 3.6, 1.2 Hz, 1H), 3.61-3.54 (dd, J = 7.2, 3.6 Hz, 4H), 3.18-3.10 (m, 1H),
2.52 - 2.46 (m, 2H), 1.97 - 1.74 (m, 2H), 1.23 - 1.21 (d, J = 7.2 Hz, 3H); 
13C NMR (101 MHz, CDCl3) δ 128.9, 128.1 126.8, 126.34 122.5, 122.3, 58.3, 51.2, 36.6, 33.0, 23.0. Anal. Calcd. for 
C22H25NS: C, 78.76; H, 7.51. Found: C, 78.37; H, 7.46. [α]D23.8 = -41.25 (c = 1.09, CHCl3).
HPLC analysis (IA, 97:5:0.2:0.1 Hexanes:EtOH:TFA:Diethylamine, 1.0 mL/min, 220 nm) indicated 99% ee: tR (minor) = 12.8 min, tR (major) = 13.6 min.

(R)-N,N-dibenzyl-3-(dimethyl(phenyl)silyl)butan-1-amine (Scheme 8, entry 3t). From (E)-3-phenylbut-2-en-1-yl 4-(dimethylamino)benzoate (1t) (354 mg, 1.0 mmol), the title compound was prepared following the general procedure using 
Cu(OAc)2 (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), O-benzoyl-N,N-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (560 µL, 3.5 mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 40 °C. The crude material was purified by flash column chromatography (0-8% EtOAc in hexanes) to provide the title compound as a colorless liquid in 92% yield (358 mg). IR (neat, cm⁻¹) 2952, 1494, 1453, 1427, 1248, 1111, 832, 813, 734, 698; 
1H NMR (400 MHz, CDCl3) δ: 7.53 - 7.46 (m, 2H), 7.44 - 7.31 (m, 11H), 7.30 - 7.23 (m, 2H), 3.64 (d, J = 13.6 Hz, 2H), 3.44 (d, J = 13.6 Hz, 2H), 2.47 (t, J = 7.5 Hz, 2H), 1.88 - 1.71 (m, 1H), 1.31 - 1.19 (m, 1H), 1.06 - 0.90 (m, 1H), 0.83 (d, J = 7.3 Hz, 3H), 0.25 (d, J = 0.9 Hz, 6H); 
13C NMR (101 MHz, CDCl3) δ: 140.10, 138.73, 134.04, 128.95, 128.86, 128.23, 127.75, 126.83, 58.42, 52.44, 28.99, 16.72, 14.15, -4.59, -4.95; HRMS (DART-TOF) calcd. for C26H33NSi [M+H]+ m/z 388.2455, found 388.2434. [α]D24 = +6.4 (c = 1.00, CHCl3). HPLC analysis (OJ-H, 5% EtOH in hexanes, 0.8 mL/min, 220 nm) indicated 98% ee: tR (major) = 9.8 min, tR (minor) = 14.4 min.

(S)-N,N-dibenzyl-1-phenylbutan-1-amine (Scheme 9, entry 3u). From (E)-1-phenylbut-2-en-1-yl 4-(dimethylamino)benzoate (1u) (295 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)2 (9.1
mg, 0.05 mmol, 5.0 mol%) and \((R)\)-DTBM-SEGPHOS (65 mg, 0.055 mmol, 5.5 mol%), \(O\)-benzoyl-\(N,N\)-dibenzylhydroxylamine (476 mg, 1.2 mmol, 1.5 equiv), diethoxymethylsilane (560 µL, 3.5 mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 40 °C. The crude material was purified by flash column chromatography (0-8% EtOAc in hexanes) to provide the title compound as a colorless liquid in 71% yield (244 mg). IR (neat, cm\(^{-1}\)) 3025, 2931, 2801, 1493, 1452, 772, 744; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta:\) 7.80 – 7.29 (m, 15H), 3.97 (d, \(J = 13.8\) Hz, 2H), 3.85 (t, \(J = 7.5\) Hz, 1H), 3.30 (d, \(J = 13.9\) Hz, 2H), 2.04 – 1.80 (m, 1H), 1.71 – 1.52 (m, 1H), 1.52 – 1.31 (m, 1H), 1.00 (t, \(J = 7.3\) Hz, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta:\) 140.60, 139.26, 129.11, 128.87, 128.30, 128.00, 127.02, 126.82, 61.70, 53.76, 33.73, 20.29, 14.35; HRMS (DART-TOF) calcd. for C\(_{24}\)H\(_{21}\)N \([M+H]^+\) \(m/z\) 330.2216, found 330.2209. [\(\alpha\)]\(_D\)\(^{24}\) = –98.5 (c = 2.00, CHCl\(_3\)). HPLC analysis (OD-H, 2% IPA in hexanes, 0.8 mL/min, 220 nm) indicated 98% ee: \(t_R\) (major) = 4.9 min, \(t_R\) (minor) = 5.6 min.

\[(S)\,-N,N\,-dibenzyl-4,8\,-dimethylnon-7\,-en-1\,-amine\] \((\text{Scheme 11, entry 3v}).\) From \((E)-2\,-(2,6\,-dimethylhepta-1,5\,-dien-1\,-yl)\,oxirane\) \((1v)\) (166 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)\(_2\) (3.6 mg, 0.02 mmol, 2.0 mol%) and \((R)\)-DTBM-SEGPHOS (23 mg, 0.022 mmol, 2.2 mol%), \(O\)-benzoyl-\(N,N\)-dibenzylhydroxylamine (381 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (640 µL, 4.0 mmol, 4.0 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 40 °C. The crude material was purified by flash column chromatography (0-8% EtOAc in hexanes) to provide the title compound as a colorless liquid in 55% yield (192 mg). IR (neat, cm\(^{-1}\)) 2925, 2792, 1494, 1452, 1375, 1125, 1068, 1028, 978, 739, 696; \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta:\) 7.43 (m, 4H), 7.36 (m, 4H), 7.28 (m, 2H), 5.14 (t, \(J = 7.0\) Hz, 1H), 3.61 (m, 4H), 2.45 (t, \(J = 7.2\) Hz, 2H), 2.00 (m, 1H), 1.94 (m, 1H), 1.74 (s, 3H), 1.65 (s, 3H), 1.63 – 1.56 (m, 1H), 1.52 (m, 1H), 1.44 – 1.28 (m, 3H), 1.21 – 1.09 (m, 2H), 0.89 (d, \(J = 6.4\) Hz, 3H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta:\) 140.20, 131.11, 128.87, 128.24, 126.81, 125.17, 58.43, 53.94, 37.25, 34.60, 32.44, 25.89, 25.72, 24.52, 19.70, 17.79; Anal. Calcd. for C\(_{25}\)H\(_{35}\)N: C, 85.90; H, 10.09. Found: C, 85.74; H, 10.21. [\(\alpha\)]\(_D\)\(^{24}\) = +2.9 (c = 1.0, CHCl\(_3\)). HPLC analysis (AD-H and OJ-H column in sequence, 50% (hexanes:EtOH:TFA:Diethylamine = 95:5:0:2:0:1) in hexanes, 0.8 mL/min, 210
nm) indicated 93% ee: $t_R$ (major) = 25.1 min, $t_R$ (minor) = 26.4 min.

(S)-N-benzyl-3-methyl-N-((R)-1-phenylethyl)pentan-1-amine
(Scheme 12, entry 4a). From (E)-3-methylpent-2-en-1-yl 4-(dimethylamino)benzoate (1w) (247 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)$_2$ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), (R)-O-benzoyl-N-benzyl-N-(1-phenylethyl)hydroxylamine (398 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (560 µL, 3.5 mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 40 °C. The crude material was purified by flash column chromatography (0-5% EtOAc in hexanes) to provide the title compound as a colorless liquid in 91% yield (269 mg). IR (neat, cm$^{-1}$) 2960, 2926, 2873, 1493, 1452, 748, 697; $^1$H NMR (600 MHz, CD$_2$Cl$_2$) δ: 7.48 – 7.42 (m, 2H), 7.42 – 7.38 (m, 2H), 7.38 – 7.34 (m, 2H), 7.34 – 7.30 (m, 2H), 7.28– 7.21 (m, 2H), 3.94 (q, $J$ = 6.8 Hz, 1H), 3.61 (d, $J$ = 14.1 Hz, 1H), 3.52 (d, $J$ = 14.1 Hz, 1H), 2.54 (ddd, $J$ = 14.4, 9.0, 5.6 Hz, 1H), 2.39 (ddd, $J$ = 13.1, 9.4, 5.5 Hz, 1H), 1.55 – 1.47 (m, 1H), 1.41 (d, $J$ = 6.8 Hz, 3H), 1.39 – 1.27 (m, 2H), 1.27 – 1.18 (m, 1H), 1.06 (dq, $J$ = 13.7, 7.4 Hz, 1H), 0.82 (t, $J$ = 7.4 Hz, 3H), 0.78 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (151 MHz, CD$_2$Cl$_2$) δ: 144.70, 141.84, 129.12, 128.60, 128.49, 128.43, 127.10, 127.08, 58.49, 54.92, 47.73, 34.64, 32.99, 29.95, 19.82, 15.83, 11.79; Anal. Calcd. for C$_{21}$H$_{29}$N: C, 85.37; H, 9.89. Found: C, 85.07; H, 9.94. [α]$_D^{24}$ = +34.7 (c = 1.00, CHCl$_3$). $^1$H NMR analysis of the crude reaction mixture indicated >50:1 dr.

(R)-N-benzyl-3-methyl-N-((R)-1-phenylethyl)pentan-1-amine
(Scheme 12, entry 4a'). From (E)-3-methylpent-2-en-1-yl 4-(dimethylamino)benzoate (1w) (247 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)$_2$ (3.6 mg, 0.02 mmol, 2 mol%), (S)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), (R)-O-benzoyl-N-benzyl-N-(1-phenylethyl)hydroxylamine (398 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (560 µL, 3.5 mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture
was stirred for 36 h at 40 °C. The crude material was purified by flash column chromatography (0-5% EtOAc in hexanes) to provide the title compound as a colorless liquid in 90% yield (266 mg). IR (neat, cm\(^{-1}\)) 2960, 2924, 1493, 1452, 1372, 1219, 772, 697; \(^{1}\)H NMR (600 MHz, CD\(_2\)Cl\(_2\)) δ: 7.50 – 7.44 (m, 2H), 7.42 – 7.37 (m, 2H), 7.37 – 7.34 (m, 2H), 7.34 – 7.30 (m, 2H), 7.29 – 7.21 (m, 2H), 3.95 (q, \(J = 6.8\) Hz, 1H), 3.57 (d, \(J = 14.4\) Hz, 1H), 3.55 (d, \(J = 14.4\) Hz, 1H), 2.58 (ddd, \(J = 13.8, 9.2, 5.0\) Hz, 1H), 2.37 (ddd, \(J = 13.0, 9.1, 6.3\) Hz, 1H), 1.59 – 1.50 (m, 1H), 1.41 (d, \(J = 6.8\) Hz, 3H), 1.35 (dt, \(J = 12.6, 6.2\) Hz, 1H), 1.32 – 1.22 (m, 2H), 1.11 (dq, \(J = 13.5, 7.4\) Hz, 1H), 0.84 (t, \(J = 7.4\) Hz, 3H), 0.73 (d, \(J = 6.6\) Hz, 3H); \(^{13}\)C NMR (151 MHz, CD\(_2\)Cl\(_2\)) δ: 144.84, 141.75, 129.04, 128.48, 128.36, 128.35, 126.96, 58.11, 54.71, 47.54, 34.39, 32.87, 30.14, 19.44, 15.00, 11.64; Anal. Calcd. for C\(_{21}\)H\(_{28}\)N: C, 85.37; H, 9.89. Found: C, 85.07; H, 10.06. [\(\alpha\)]\(_D\)\(^{24}\) = +16.4 (c = 2.00, CHCl\(_3\)). \(^{1}\)H NMR analysis of the crude reaction mixture indicated <1:50 dr.

(R)-4-(benzyl(methyl)amino)-2-methylbutyl 4-(dimethylamino)benzoate (Scheme 12, entry 4b). From ((E)-2-methylbut-2-ene-1,4-diyl bis(4-(dimethylamino)benzoate) (1k) (396 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)\(_2\) (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), O-benzoyl-N-benzyl-N-methylhydroxylamine (290 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (560 µL, 3.5 mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 40 °C. The crude material was purified by flash column chromatography (0-40% EtOAc in hexanes, containing 1% NEt\(_3\)) to provide the title compound as a colorless liquid in 92% yield (325 mg). IR (neat, cm\(^{-1}\)) 2939, 2791, 1699, 1607, 1525, 1452, 1366, 1274, 1182, 1104, 971, 770, 698; \(^{1}\)H NMR (400 MHz, CDCl\(_3\)) δ: 7.97 (d, \(J = 8.8\) Hz, 2H), 7.46 – 7.17 (m, 3H), 6.66 (d, \(J = 8.7\) Hz, 2H), 4.29 – 4.02 (m, 2H), 3.56 (d, \(J = 13.2\) Hz, 1H), 3.50(d, \(J = 12.8\) Hz, 1H), 3.03 (s, 6H), 2.51 (t, \(J = 7.4\) Hz, 2H), 2.24 (s, 3H), 2.08 (dq, \(J = 13.0, 6.5\) Hz, 1H), 1.80 (dq, \(J = 13.3, 7.4\) Hz, 1H), 1.49 (dq, \(J = 14.2, 7.4\) Hz, 1H), 1.05 (d, \(J = 6.7\) Hz, 3H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) δ: 166.91, 153.17, 139.12, 131.14, 128.95, 128.12, 126.83, 117.19, 110.64, 68.86, 62.32, 55.01, 42.10, 39.94, 31.10, 31.03, 17.11; Anal. Calcd. for
C₂₂H₃₀N₂O₂: C, 74.54; H, 8.53. Found: C, 74.36; H, 8.56. [α]D²⁴ = -6.0 (c = 2.00, CHCl₃).

HPLC analysis (IA, 10% EtOH in (hexanes:EtOH:TFA:Diethylamine = 95:5:0.2:0.1), 0.8 mL/min, 230 nm) indicated 98% ee: tᵣ (minor) = 16.6 min, tᵣ (major) = 18.5 min.

(R)-2-methyl-4-(2,2,6,6-tetramethylpiperidin-1-yl)butyl 4-(dimethylamino)benzoate (Scheme 12, entry 4c). From ((E)-2-methylbut-2-ene-1,4-diyl bis(4-(dimethylamino)benzoate) (1k) (396 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)₂ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), 2,2,6,6-tetramethylpiperidin-1-yl benzoate (314 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (560 µL, 3.5 mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 40 °C. The crude material was purified by flash column chromatography (0-100% EtOAc in DCM, containing 1% NEt₃) to provide the title compound as a colorless liquid in 89% yield (335 mg). IR (neat, cm⁻¹) 2928, 1703, 1608, 1565, 1366, 1275, 1183, 1105, 770; ¹H NMR (400 MHz, CDCl₃) δ: 7.93 (d, J = 9.0 Hz, 2H), 6.65 (d, J = 8.7 Hz, 2H), 4.16 (dd, J = 10.7, 6.0 Hz, 1H), 4.07 (dd, J = 10.7, 6.7 Hz, 1H), 3.04 (s, 6H), 2.60 – 2.39 (m, 2H), 1.88 (dq, J = 13.1, 6.6 Hz, 1H), 1.71 – 1.59 (m, 1H), 1.59 – 1.49 (m, 2H), 1.48 – 1.34 (m, 5H), 1.04 (d, J = 6.7 Hz, 3H), 1.04 (s, 12H); ¹³C NMR (101 MHz, CDCl₃) δ: 167.12, 153.30, 131.27, 117.43, 110.74, 54.64, 42.97, 41.24, 40.13, 39.74, 32.00, 27.60, 17.85, 17.54; Anal. Calcd. for C₂₃H₃₅N₂O₂: C, 73.75; H, 10.23. Found: C, 73.77; H, 10.22. [α]D²⁴ = +0.41 (c = 2.00, CHCl₃). HPLC analysis (AD-H, 10% EtOH in (hexanes:EtOH:TFA:Diethylamine = 95:5:0.2:0.1), 0.8 mL/min, 280 nm) indicated 96% ee: tᵣ (minor) = 13.9 min, tᵣ (major) = 20.6 min.

(R)-4-(4-(4-(dimethylamino)benzoyloxy)-3-methylbutyl)piperazine-1-carboxylate (Scheme 12, entry 4d). From ((E)-2-methylbut-2-ene-1,4-diyl bis(4-(dimethylamino)benzoate) (1k) (396
mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)$_2$ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), tert-butyl 4-(benzoyloxy)piperazine-1-carboxylate (368 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (560 µL, 3.5 mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 50 °C. The crude material was purified by flash column chromatography (0-100% EtOAc in hexanes, containing 1% NEt$_3$) to provide the title compound as a colorless liquid in 91% yield (382 mg). IR (neat, cm$^{-1}$) 2929, 1692, 1606, 1364, 1273, 1180, 1102, 769; $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.92 (d, $J = 9.0$ Hz, 2H), 6.67 (d, $J = 9.0$ Hz, 2H), 4.23 – 4.06 (m, 2H), 3.44 (t, $J = 5.1$ Hz, 4H), 2.51 – 2.32 (m, 6H), 2.08 – 1.91 (m, 1H), 1.80 – 1.68 (m, 1H), 1.56 – 1.36 (m, 1H), 1.48 (s, 9H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ: 166.98, 154.75, 153.30, 131.21, 117.17, 79.53, 68.81, 56.38, 53.10, 43.95, 40.07, 31.36, 30.59, 28.47, 17.22; HRMS (DART-TOF) calcd. for C$_{23}$H$_{37}$N$_3$O$_4$ [M+H]$^+$ m/z 420.2857, found 420.2853. [α]$_D^{24}$ = +1.7 (c = 1.0, CHCl$_3$). HPLC analysis (AD-H, 10% EtOH in hexanes:EtOH:TFA:Diethylamine = 95:5:0:2:0.1), 1.0 mL/min, 280 nm) indicated 96% ee: $t_R$ (minor) = 24.8 min, $t_R$ (major) = 36.3 min.

(R)-2-methyl-4-(4-(pyrimidin-2-yl)piperazin-1-yl)butyl 4-(dimethylamino)benzoate (Scheme 12, entry 4e). From ((E)-2-methylbut-2-ene-1,4-diyli bis(4-(dimethylamino)benzoate) (1k) (396 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)$_2$ (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), 4-(pyrimidin-2-yl)piperazin-1-yl benzoate (341 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (560 µL, 3.5 mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 40 °C. The crude material was purified by flash column chromatography (0-100% EtOAc in DCM, containing 1% NEt$_3$) to provide the title compound as a colorless liquid in 89% yield (345 mg). IR (neat, cm$^{-1}$) 2937, 2810, 1698, 1607, 1584, 1445, 1358, 1274, 1181, 1103, 982, 769; $^1$H NMR (400 MHz, CDCl$_3$) δ: 8.30 (d, $J = 4.7$ Hz, 2H), 7.91 (d, $J = 9.0$ Hz, 2H), 6.64 (d, $J = 9.2$ Hz, 2H), 6.47 (t, $J = 4.7$ Hz, 1H), 4.27 – 4.04 (m, 2H), 3.97 – 3.71 (m,
4H), 3.03 (s, 6H), 2.63 - 2.36 (m, 6H), 2.01 (dq, J = 13.2, 6.5 Hz, 1H), 1.77 (dq, J = 14.6, 6.3 Hz, 1H), 1.49 (dq, J = 14.0, 7.8 Hz, 1H), 1.05 (d, J = 6.7 Hz, 3H); 13C NMR (101 MHz, CDCl3) δ: 167.04, 161.70, 157.74, 153.33, 131.26, 117.22, 110.76, 109.86, 68.86, 56.50, 53.18, 43.66, 40.12, 31.48, 30.60, 17.26; Anal. Calcd. for C22H31N5O2: C, 66.47; H, 7.86. Found: C, 66.29; H, 7.89. 

\[ [\alpha]_{D}^{24} = -3.7 \ (c = 1.50, \text{CHCl}_3). \]

HPLC analysis (IA, 10% EtOH in hexanes:EtOH:TFA:DEA = 95:5:0.2:0.1), 0.8 mL/min, 230 nm) indicated 98% ee: \( t_R \) (minor) = 40.9 min, \( t_R \) (major) = 46.6 min.

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(R)-4-(4-(benzo[c][1,2,5]thiadiazol-5-yl)piperazin-1-yl)-2-methylbutyl 4-(dimethylamino)benzoate (Scheme 12, entry 4f). From ((E)-2-methylbut-2-en-1,4-diyl bis(4-(dimethylamino)benzoate) (1k) (396 mg, 1.0 mmol), the title compound was prepared following the general procedure using Cu(OAc)2 (3.6 mg, 0.02 mmol, 2 mol%), (R)-DTBM-SEGPHOS (26 mg, 0.022 mmol, 2.2 mol%), 4-(benzo[c][1,2,5]thiadiazol-5-yl)piperazin-1-yl benzoate (407 mg, 1.2 mmol, 1.2 equiv), diethoxymethylsilane (560 µL, 3.5 mmol, 3.5 equiv), and THF (1.0 mL). The reaction mixture was stirred for 36 h at 40 °C. The crude material was purified by flash column chromatography (0-100% EtOAc in DCM, containing 1% NEt3) to provide the title compound as a deep green solid in 78% yield (351 mg).

m. p. 103-105 °C. IR (neat, cm⁻¹) 2920, 1698, 1608, 1525, 1447, 1367, 1276, 1183, 1106, 770, 753; 1H NMR (400 MHz, CDCl3) δ: 7.92 (d, J = 8.7 Hz, 2H), 7.78 (d, J = 9.6 Hz, 1H), 7.43 (d, J = 9.7 Hz, 1H), 7.08 (s, 1H), 6.65 (d, J = 8.9 Hz, 2H), 4.26 - 4.04 (m, 2H), 3.45 - 3.22 (m, 4H), 3.03 (s, 6H), 2.79 - 2.57 (m, 4H), 2.50 (t, J = 7.0 Hz, 2H), 2.13 - 1.93 (m, 1H), 1.77 (dq, J = 13.7, 6.5 Hz, 1H), 1.48 (dq, J = 14.1, 7.6 Hz, 1H), 1.06 (d, J = 6.7 Hz, 3H); 13C NMR (101 MHz, CDCl3) δ: 166.98, 156.57, 153.28, 152.24, 150.76, 131.21, 124.77, 120.96, 117.12, 110.69, 101.16, 68.78, 56.23, 52.93, 48.96, 40.05, 31.36, 30.59, 17.24; HRMS (DART-TOF) calcd. for C22H31N5O2S [M+H]⁺ m/z 454.2271, found 454.2266. \([\alpha]_{D}^{24} = +4.5 \ (c = 1.0, \text{CHCl}_3).\)

HPLC analysis (AD-H, 30% IPA in hexanes, 0.8 mL/min, 254 nm) indicated 97% ee: \( t_R \) (minor) = 18.4 min, \( t_R \) (major) = 20.7 min.
B) Synthesis of the Substrates for Table 1

Substrates in Table 1 are known compounds synthesized according to literature procedures, except for the substrates used in entries 9 and 10.

Preparation of substrate for Table 1, entry 9:

\[(E)-3,7\text{-dimethyl} \text{octa-2,6-dien-1-yl methyl terephthalate} \text{ (Table 1, entry 9, 1a(9))} \]

To a solution of geraniol (5.30 mL, 30.0 mmol), mono-methyl terephthalate (5.96 g, 33.0 mmol, 1.1 equiv), EDCI (5.59 g, 36.0 mmol, 1.20 equiv) and DMAP (366 mg, 3.00 mmol, 0.10 equiv) in dichloroethane (150 mL, 0.2 M) was added DIPEA (12.3 mL, 75.0 mmol, 2.5 equiv). The reaction mixture was stirred in an oil bath at 50 °C overnight (12 h). The crude reaction mixture was purified by flash column chromatography (8-10% EtOAc in hexanes) to provide the title compound in 89% yield (8.45 g) as a colorless liquid. IR (neat, cm\(^{-1}\)) 2914, 1717, 1436, 1264, 1248, 1100, 1019, 928, 728; \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\): 8.16 – 7.96 (m, 4H), 5.47 (t, \(J = 7.6\) Hz, 1H), 5.20 – 5.03 (m, 1H), 4.86 (d, \(J = 6.9\) Hz, 2H), 3.95 (s, 3H), 2.21 – 1.94 (m, 4H), 1.77 (s, 3H), 1.67 (s, 3H), 1.60 (s, 3H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\): 166.41, 165.90, 142.91, 134.41, 133.86, 131.97, 129.66, 129.59, 123.77, 118.17, 62.39, 52.51, 39.65, 26.37, 25.78, 17.81, 16.68; Anal. Calcd. for C\(_{19}\)H\(_{34}\)O\(_4\): C, 72.13; H, 7.65. Found: C, 72.00; H, 7.63.
C) Synthesis of γ-Disubstituted Allylic 4-(Dimethylamino)benzoate

3,3-Disubstituted allylic benzoates were synthesized from the corresponding allylic alcohol following general procedures A or B (see below). All the 3,3-disubstituted allylic alcohols are known compounds synthesized according to literature procedures with slight modification\textsuperscript{15,16} The modification from literature procedures is outlined in Scheme 14 for the synthesis of 3,3-dialkyl-substituted allylic alcohols and in Scheme 15 for the synthesis of 3,3-alkyl,aryl-substituted allylic alcohols.

**Scheme 14. Synthesis of 3,3-Alkyl,alkyl-substituted Allylic Alcohols**

\[ \text{R} - \equiv + \text{AlMe}_3 \quad \text{(1.5 equiv)} \quad \xrightarrow{1\text{.} \ Zr\text{Cp}_2\text{Cl}_2 \quad (1.0 \text{ equiv})} \quad \text{DIBAL-H \quad (2.2 equiv) \quad 1.0 \text{ M in hexanes}} \]

1. \text{ZrCp}_2\text{Cl}_2 \quad (1.0 \text{ equiv})
   - 10 mol\% \text{H}_2\text{O}
   - (0.22 M) \text{CH}_2\text{Cl}_2: \text{ClCH}_2\text{CH}_2\text{Cl} \quad (8:1 \text{ V/V})
   - -23 \degree \text{C} \text{ to rt, 18 h}

2. \text{ClCO}_2\text{Et} \quad (3.0 \text{ equiv})
   - 0 \degree \text{C} \text{ to rt, 1.5 h}
   - (ref. 15)

\[ \text{R} \quad \text{OH} \quad \text{CH}_2\text{Cl}_2 \quad (1.0 \text{ M}) \quad \text{-78 \degree \text{C} \text{ to rt, 8-12 h Me}} \]

**Scheme 15. Synthesis of 3,3-Alkyl,aryl-substituted Allylic Alcohols**

\[ \text{CO}_2\text{Me} + \text{ArB(OH)}_2 \quad (2.0 \text{ equiv}) \quad \xrightarrow{1\text{.} \ 6 \text{ mol\% Pd(OAc)}_2 \quad 18 \text{ mol\% SPhos}} \quad \text{DIBAL-H \quad (2.2 equiv) \quad 1.0 \text{ M in hexanes}} \]

6 mo\% Pd(OAc)_2
18 mo\% SPhos
C_8H_8CO_3 \quad (2.1 equiv)

\[ \text{H}_2\text{O} \quad (10 \text{ equiv}) \quad \text{Tol \quad (0.5 M \quad \text{rt, 18 h)}} \quad (ref. 16) \]

\[ \text{Ar} \quad \text{OH} \quad \text{CH}_2\text{Cl}_2 \quad (1.0 \text{ M}) \quad \text{-78 \degree \text{C} \text{ to rt, 8-12 h Me}} \]
**General Procedure A:**

\[ R-\text{CH} = \text{CH} - \text{OH} + \text{HO-C-CH} = \text{CH} \text{-Ar} \xrightarrow{\text{EDCI (1.2 equiv)}} R-\text{CH} = \text{CH-O-C-CH} = \text{CH-} \text{Ar} \]

To a solution of allylic alcohol (1.0 equiv), 4-(dimethylamino)benzoic acid (1.1 equiv), EDCI (1.2 equiv), and DMAP (0.1 equiv) in dichloroethane (0.2 M) was added DIPEA (2.5 equiv). Then the reaction mixture was stirred in an oil bath at 50 °C overnight (8–12 h). The reaction mixture was allowed to cool to rt, diluted with DCM, and quenched with Na₂CO₃ (aq). The aqueous phase was extracted with DCM (2x). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography to provide the corresponding γ-disubstituted allylic 4-(dimethylamino)benzoate.

**General Procedure B:**

\[ R-\text{CH} = \text{CH} - \text{OH} + \text{HO-C-CH} = \text{CH} \text{-Ar} \xrightarrow{\text{DCC (1.2 equiv)}} R-\text{CH} = \text{CH-O-C-CH} = \text{CH-} \text{Ar} \]

To a round bottom flask containing the allylic alcohol (1.0 equiv), 4-(dimethylamino)benzoic acid (1.2 equiv), DCC (1.2 equiv), and DMAP (1.0 equiv) was added dichloroethane (0.2 M). The reaction mixture was stirred in an oil bath at 50 °C overnight (8–12 h). The reaction mixture was allowed to cool to rt, diluted with DCM, and quenched with Na₂CO₃ (aq). The aqueous phase was extracted with DCM (2x). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography to provide the corresponding γ-disubstituted allylic 4-(dimethylamino)benzoate.
(E)-1a Prepared following general procedure A using geraniol (2.64 mL, 15 mmol). The crude reaction mixture was purified by flash column chromatography (8-10% EtOAc in hexanes) to provide the title compound in 87% yield (3.92 g) as a white solid. m.p. 44–45 °C. IR (neat, cm⁻¹) 2913, 1699, 1606, 1524, 1444, 1270, 1180, 1097, 946, 828, 769, 698; ¹H NMR (400 MHz, CDCl₃) δ: 7.94 (d, J = 9.1 Hz, 2H), 6.66 (d, J = 9.1 Hz, 2H), 5.49 (td, J = 7.0, 1.2 Hz, 1H), 5.26 – 5.04 (m, 1H), 4.82 (d, J = 7.0 Hz, 2H), 3.05 (s, 6H), 2.25 – 2.02 (m, 4H), 1.78 (s, 3H), 1.71 (s, 3H), 1.63 (s, 3H); ¹³C NMR (100.6 MHz, CDCl₃) δ: 167.14, 153.34, 141.55, 131.84, 131.37, 123.98, 119.19, 117.46, 110.77, 61.27, 40.15, 39.69, 26.48, 25.80, 17.81, 16.66, 0.11; HRMS (DART-TOF) calcd. for C₁₉H₂₁N₂O₂ [M+H]+ m/z 302.2115, found 302.2121. Anal. Calcd. for C₁₉H₂₁N₂O₂: C, 75.71; H, 9.03. Found: C, 75.42; H, 9.13.

(Z)-1a Prepared following general procedure A using nerol (3.52 mL, 20 mmol). The crude reaction mixture was purified by flash column chromatography (8-10% EtOAc in hexanes) to provide the title compound in 86% yield (5.19 g) as a white solid. m.p. 49–50 °C. IR (neat, cm⁻¹) 2913, 1698, 1606, 1524, 1444, 1365, 1270, 1180, 1098, 946, 828, 768, 698; ¹H NMR (400 MHz, CDCl₃) δ: 7.94 (d, J = 9.0 Hz, 2H), 6.63 (d, J = 9.1, 2.4 Hz, 2H), 5.51 (t, J = 7.0 Hz, 1H), 5.24 – 5.06 (m, 1H), 4.79 (d, J = 7.8 Hz, 2H), 3.02 (dd, J = 3.1, 1.2 Hz, 6H), 2.25 – 2.17 (m, 2H), 2.14 (q, J = 7.6, 7.1 Hz, 2H), 1.81 (s, 3H), 1.70 (s, 3H), 1.63 (s, 3H); ¹³C NMR (100.6 MHz, CDCl₃) δ: 167.02, 153.23, 141.81, 132.05, 131.27, 123.75, 120.01, 117.30, 110.65, 60.87, 40.02, 32.28, 26.76, 25.73, 23.57, 17.71; HRMS (DART-TOF) calcd. for C₁₉H₂₇NO₂ [M+H]+ m/z 302.2115, found 302.2124. Anal. Calcd. for C₁₉H₂₇NO₂: C, 75.71; H, 9.03. Found: C, 75.42; H, 9.13.
**Scheme 4, 1b** Prepared following general procedure A from corresponding allylic alcohol (600 mg, 3.7 mmol). The crude reaction mixture was purified by flash column chromatography (8-10% EtOAc in hexanes) to provide the title compound in 86% yield (982 mg) as a white solid. m.p. 40–41 °C. IR (neat, cm⁻¹) 2940, 1695, 1605, 1525, 1366, 1272, 1181, 1097, 946, 830, 751; H NMR (400 MHz, CDCl₃) δ: 7.93 (d, J = 9.1 Hz, 2H), 6.67 (d, J = 9.1 Hz, 2H), 5.49 (t, J = 7.6 Hz, 1H), 4.81 (d, J = 6.9 Hz, 2H), 3.57 (t, J = 6.6 Hz, 2H), 3.06 (s, 6H), 2.11 (t, J = 7.5 Hz, 2H), 1.85 – 1.74 (m, 2H), 1.78 (s, 3H), 1.67 – 1.59 (m, 2H); C NMR (100.6 MHz, CDCl₃) δ: 167.12, 153.36, 140.96, 131.37, 119.71, 117.33, 110.77, 61.16, 45.07, 40.16, 38.77, 32.18, 24.84, 16.46; HRMS (DART-TOF) calcd. for C₁₁H₂₄ClN₂O₂ [M+H]⁺ m/z 310.1568, found 310.1562. Anal. Calcd. for C₁₁H₂₄ClN₂O₂: C, 65.90; H, 7.81. Found: C, 65.78; H, 7.46.

**Scheme 4, 1c** Prepared following general procedure A from corresponding allylic alcohol (800 mg, 8.4 mmol). The crude reaction mixture was purified by flash column chromatography (8-10% EtOAc in hexanes) to provide the title compound in 82% yield (2.32 g) as a white solid. m.p. 47–48 °C. IR (neat, cm⁻¹) 2936, 1695, 1607, 1525, 1366, 1273, 1182, 1099, 750; H NMR (400 MHz, CDCl₃) δ: 8.03 – 7.82 (m, 2H), 7.33 – 7.19 (m, 2H), 7.19 – 7.04 (m, 3H), 6.69 – 6.45 (m, 2H), 5.57 – 5.35 (m, 1H), 4.79 (d, J = 6.9 Hz, 2H), 2.95 (s, 6H), 2.63 – 2.50 (m, 2H), 2.07 (t, J = 7.7 Hz, 2H), 1.81 – 1.64 (m, 2H), 1.73 (s, 3H); C NMR (100.6 MHz, CDCl₃) δ: 166.97, 153.20, 142.32, 141.18, 131.23, 128.42, 128.25, 125.68, 119.39, 117.24, 110.64, 61.08, 39.95, 39.01, 35.40, 29.29, 16.44; HRMS (DART-TOF) calcd. for C₂₁H₂₂ClN₂O₂ [M+H]⁺ m/z 338.2115, found 338.2121. Anal.
Calcd. for C_{22}H_{21}N_{2}O_{2}: C, 78.30; H, 8.06. Found: C, 78.16; H, 8.06.

\[ \text{Ts} \quad \text{N} \quad \text{NMe}_2 \quad (E)-5-((N\text{-benzyl-4-methylphenyl})\text{sulfonamido})-3\text{-methylpent-2-en-1-yl} \quad 4-(\text{dimethylamino})\text{benzoate} \]

(Scheme 4, 1d) Prepared following general procedure A from corresponding allylic alcohol (2.16 g, 6.0 mmol). The crude reaction mixture was purified by flash column chromatography (20-30\% EtOAc in hexanes) to provide the title compound in 86\% yield (2.62 g) as a white solid. m.p. 101–102 °C. IR (neat, cm\(^{-1}\)) 2921, 1695, 1605, 1365, 1336, 1273, 1181, 1156, 1098, 946, 770; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta: 7.91\ (d, J = 9.1\ Hz, 2H), 7.77\ (d, J = 8.3\ Hz, 2H), 7.41 – 7.24\ (m, 7H), 6.65\ (d, J = 9.1\ Hz, 2H), 5.26\ (t, J = 7.4\ Hz, 1H), 4.69\ (d, J = 6.8\ Hz, 2H), 4.37\ (s, 2H), 3.27 – 3.16\ (m, 2H), 3.04\ (s, 6H), 2.45\ (s, 3H), 2.17 – 2.00\ (m, 2H), 1.58\ (s, 3H); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta: 166.89, 153.30, 143.31, 137.74, 137.14, 136.33, 131.26, 129.77, 128.61, 128.41, 127.86, 127.19, 121.50, 117.03, 110.67, 60.77, 52.10, 46.45, 40.05, 38.25, 21.54, 16.33; HRMS (DART-TOF) calcd. for C\(_{29}\)H\(_{34}\)N\(_{2}\)O\(_{4}\)S \([\text{M}+\text{H}]^+\) m/z 507.2312, found 507.2330. Anal. Calcd. for C\(_{29}\)H\(_{34}\)N\(_{2}\)O\(_{4}\)S: C, 68.75; H, 6.76. Found: C, 68.49; H, 6.82.

\[ \text{Cy} \quad \text{Me} \quad \text{NMe}_2 \quad (E)-3\text{-cyclohexylbut-2-en-1-yl} \quad \text{4-(dimethylamino)benzoate} \]

(Scheme 4, 1e) Prepared following general procedure A from corresponding allylic alcohol (1.90 g, 12.3 mmol). The crude reaction mixture was purified by flash column chromatography (8-10\% EtOAc in hexanes) to provide the title compound in 77\% yield (2.85 g) as a white solid. m.p. 63 °C. IR (neat, cm\(^{-1}\)) 2922, 2850, 1699, 1605, 1524, 1445, 1362, 1270, 1180, 1097, 946, 828, 768, 698; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta: 8.03 – 7.85\ (m, 2H), 6.75 – 6.53\ (m, 2H), 5.47\ (tt, J = 6.7, 1.1\ Hz, 1H), 4.82\ (d, J = 6.8\ Hz, 2H), 3.01\ (s, 6H), 1.91\ (t, J = 11.3\ Hz, 1H), 1.84 – 1.64\ (m, 8H), 1.40 – 1.11\ (m, 5H); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta: 166.96, 153.17, 146.25, 131.21, 117.30, 117.25, 110.60, 61.28, 47.17, 39.95, 31.66, 26.63, 26.33, 14.89; HRMS (DART-TOF) calcd. for C\(_{19}\)H\(_{21}\)NO\(_{2}\) \([\text{M}+\text{H}]^+\) m/z 302.2115, found
Anal. Calcd. for $C_{19}H_{27}NO_2$: C, 75.71; H, 9.03. Found: C, 75.63; H, 9.03.

\((E)-3,4,4\text{-trimethylpent-2-en-1-yl}\) 4-(dimethylamino)benzoate (Scheme 4, 1f) Prepared following general procedure A from corresponding allylic alcohol (770 mg, 6.0 mmol). The crude reaction mixture was purified by flash column chromatography (8–10% EtOAc in hexanes) to provide the title compound in 73% yield (1.20 g) as a white solid. m.p. 45–46 °C. IR (neat, cm$^{-1}$) 2963, 1700, 1607, 1526, 1362, 1273, 1181, 1102, 947, 770; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.95 (d, $J$ = 8.8 Hz, 2H), 6.65 (d, $J$ = 7.4 Hz, 2H), 5.65 – 5.35 (m, 1H), 4.85 (d, $J$ = 6.5 Hz, 2H), 3.02 (s, 6H), 1.76 (s, 3H), 1.10 (s, 9H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$: 167.03, 153.23, 148.48, 131.27, 117.31, 116.26, 110.66, 61.84, 40.01, 36.31, 28.85, 13.14; HRMS (DART-TOF) calcd. for $C_{19}H_{27}NO_2$ [M+H]$^+$ $m/z$ 276.1958, found 276.1966.

\((E)-3\text{-}(2\text{-methyl-1,3-dioxolan-2-yl})\text{but-2-en-1-yl}\) 4-(dimethylamino)benzoate (Scheme 4, 1g) Prepared following general procedure A from corresponding allylic alcohol (3.16 g, 20 mmol). The crude reaction mixture was purified by flash column chromatography (10-20% EtOAc in hexanes) to provide the title compound in 82% yield (5.01 g) as a white solid. m.p. 92–93 °C. IR (neat, cm$^{-1}$) 1696, 1605, 1525, 1367, 1271, 1181, 1108, 1039, 944, 771; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.93 (d, $J$ = 9.0 Hz, 2H), 6.66 (d, $J$ = 9.1 Hz, 2H), 6.00 – 5.85 (m, 1H), 4.85 (d, $J$ = 6.5 Hz, 2H), 4.01 – 3.94 (m, 2H), 3.89 – 3.80 (m, 2H), 3.05 (s, 6H), 1.78 (s, 3H), 1.50 (s, 3H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$: 166.96, 153.41, 139.47, 131.40, 120.47, 117.15, 110.78, 109.46, 64.44, 61.11, 40.16, 23.91, 12.68; HRMS (DART-TOF) calcd. for $C_{17}H_{23}NO_4$ [M+H]$^+$ $m/z$ 306.1700, found 306.1707. Anal. Calcd. for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59. Found: C, 66.92;
The crude reaction mixture was purified by flash column chromatography (8–10% EtOAc in hexanes) to provide the title compound in 84% yield (2.89 g) as a white solid. m.p. 36 °C. IR (neat, cm⁻¹) 2930, 1696, 1607, 1525, 1366, 1275, 1218, 1183, 1102, 947, 770; ¹H NMR (600 MHz, CDCl₃) δ: 7.95 (d, J = 9.0 Hz, 2H), 7.37 (d, J = 4.4 Hz, 4H), 7.31 (q, J = 4.5 Hz, 1H), 6.73–6.60 (m, 2H), 5.49 (s, 1H), 4.82 (d, J = 6.8 Hz, 2H), 4.53 (s, 2H), 3.51 (t, J = 6.4 Hz, 2H), 3.06 (s, 6H), 2.10 (t, J = 7.4 Hz, 2H), 1.77 (s, 3H), 1.71–1.62 (m, 2H), 1.62–1.49 (m, 2H); ¹³C NMR (151 MHz, CDCl₃) δ: 167.17, 153.34, 141.57, 138.77, 131.39, 128.47, 127.75, 127.60, 119.30, 117.41, 110.78, 72.99, 70.34, 61.28, 40.19, 39.43, 29.46, 24.31, 16.54; HRMS (DART-TOF) calcd. for C₂₄H₃₁N₀₃ [M+H]⁺ m/z 382.2377, found 382.2374. Anal. Calcd. for C₂₄H₃₁N₀₃: C, 75.56; H, 8.19. Found: C, 75.49; H, 8.21.

Prepared following general procedure A from corresponding allylic alcohol (3.00 g, 7.84 mmol). The reaction was worked up with TBAF (12 mL, 1 M in THF, 1.5 equiv, remove the TBDPS group). The crude reaction mixture was purified by flash column chromatography (20–30% EtOAc in hexanes) to provide the title compound in 91% yield (1.70 g) as a colorless oil. IR (neat, cm⁻¹) 2932, 1697, 1603, 1525, 1444, 1366, 1270, 1180, 1097, 946, 828, 769, 698; ¹H NMR (600 MHz, CDCl₃) δ: 7.93 (d, J = 8.9 Hz, 2H), 6.66 (d, J = 8.9 Hz, 2H), 5.49 (t, J = 6.9 Hz, 1H), 4.80 (d, J = 6.9 Hz, 2H), 3.67 (t, J = 6.1 Hz, 2H), 3.05 (s, 6H), 2.10 (t, J = 7.2 Hz, 2H), 1.77 (s, 3H), 1.67–1.44 (m, 5H); ¹³C NMR (151 MHz, CDCl₃) δ: 167.20, 153.34, 141.45, 131.37, 119.34, 117.31, 110.76, 62.91, 61.27, 40.17, 39.32, 32.41, 23.81, 16.52; HRMS (DART-TOF) calcd. for C₁₇H₂₅N₀₃ [M+H]⁺ m/z 292.1907, found 292.1914.
(E)-4-((tert-butyldimethylsilyl)oxy)-3-methylbut-2-en-1-yl 4-(dimethylamino)benzoate (Scheme 4, 1j)

Prepared following general procedure A from corresponding allylic alcohol (9.95 g, 46.0 mmol). The crude reaction mixture was purified by flash column chromatography (8–10% EtOAc in hexanes) to provide the title compound in 89% yield (14.9 g) as a white solid. m.p. 118–119 °C. IR (neat, cm⁻¹) 2927, 2855, 1700, 1606, 1525, 1363, 1271, 1180, 1097, 1066, 947, 830, 769; ¹H NMR (400 MHz, CDCl₃) δ: 7.94 (d, J = 9.1 Hz, 2H), 6.66 (d, J = 9.0 Hz, 2H), 5.85 – 5.70 (m, 1H), 4.86 (d, J = 6.9 Hz, 2H), 4.09 (s, 2H), 3.05 (s, 6H), 1.75 (s, 3H), 0.95 (s, 9H); ¹³C NMR (100.6 MHz, CDCl₃) δ: 167.09, 153.36, 140.17, 131.39, 118.51, 117.36, 110.78, 67.82, 60.85, 40.17, 26.07, 18.54, 13.82, -5.18; HRMS (DART-TOF) calcd. for C₂₀H₃₃N₀₃Si [M+H]+ m/z 364.2302, found 364.2305. Anal. Calcd. for C₂₀H₃₃N₀₃Si: C, 66.07; H, 9.15. Found: C, 66.06; H, 9.13.

(E)-2-methylbut-2-ene-1,4-diyl bis(4-(dimethylamino)benzoate) (Scheme 4, 1k)

Prepared following general procedure A from corresponding allylic alcohol (2.49 g, 10.0 mmol). The crude reaction mixture was purified by flash column chromatography (8–10% EtOAc in hexanes) to provide the title compound in 83% yield (3.29 g) as a white solid. m.p. 133–134 °C. IR (neat, cm⁻¹) 2885, 1692, 1605, 1523, 1364, 1269, 1179, 1095, 946, 825, 767; ¹H NMR (400 MHz, CDCl₃) δ: 8.04 – 7.88 (m, 4H), 6.82 – 6.58 (m, 4H), 5.85 (t, J = 7.2 Hz, 1H), 4.89 (d, J = 6.7 Hz, 2H), 4.75 (s, 2H), 3.06 (d, J = 2.1 Hz, 12H), 1.88 (s, 3H); ¹³C NMR (100.6 MHz, CDCl₃) δ: 167.04, 166.75, 153.51, 153.44, 136.15, 131.51, 131.47, 122.10, 117.13, 116.97, 110.85, 110.81, 68.54, 60.68, 40.20, 14.47; HRMS (DART-TOF) calcd. for C₂₃H₂₇N₂O₄ [M+H]+ m/z 397.2122, found 397.2116. Anal. Calcd. for C₂₃H₂₇N₂O₄: C, 69.68; H, 7.12. Found: C, 69.38; H, 6.95.
Prepared following general procedure A from corresponding allylic alcohol (3.43 g, 10.0 mmol). The crude reaction mixture was purified by flash column chromatography (8–10% EtOAc in hexanes) to provide the title compound in 84% yield (4.12 g) as a white solid. m.p. 58–59 °C. IR (neat, cm\(^{-1}\)) 1495, 1607, 1525, 1366, 1275, 1215, 1183, 1103, 947, 744; \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\): 7.98 (d, \(J = 9.0\) Hz, 2H), 7.63 – 7.51 (m, 6H), 7.40 – 7.30 (m, 6H), 7.27 – 7.19 (m, 3H), 6.74 – 6.63 (m, 2H), 5.91 (t, \(J = 6.3\) Hz, 1H), 4.91 (d, \(J = 7.2\) Hz, 2H), 3.07 (s, 6H), 2.74 (s, 2H), 1.85 (s, 3H), 1.69 (s, 1H); \(^1\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\): 167.15, 153.37, 146.17, 140.49, 131.41, 128.70, 127.95, 126.37, 119.14, 117.28, 110.78, 70.79, 61.11, 50.95, 40.18, 16.10; HRMS (DART-TOF) calcd. for C\(_{33}\)H\(_{34}\)N\(_2\)O\(_2\) [M+H\(^{+}\)]\(^{m/z}\) 491.2693, found 491.2697. Anal. Calcd. for C\(_{33}\)H\(_{34}\)N\(_2\)O\(_2\): C, 80.78; H, 6.99. Found: C, 80.56; H, 7.12.

(E)-3-methyl-4-oxobut-2-en-1-yl 4-(dimethylamino)benzoate (Scheme 4, 1m) To a solution of 1j (6.29 g, 17.3 mmol) in THF was added TBAF (15 mL, 1.5 equiv, 1.0 M in THF). After 4 h at rt, the crude reaction mixture was purified by flash column chromatography (10–30% EtOAc in hexanes) to provide (E)-4-hydroxy-3-methylbut-2-en-1-yl 4-(dimethylamino)benzoate in 83% yield (3.60 g) as a white solid. This allylic alcohol (3.60 g, 14.4 mmol) was then dissolved in CH\(_2\)Cl\(_2\) (72 mL), and Dess-Martin periodinane (7.33 g, 17.3 mmol, 1.2 equiv) was added at rt. The resulting solution was stirred for 2 h at rt. The reaction mixture was diluted with ether and quenched with a saturated solution of Na\(_2\)SO\(_3\) and NaHCO\(_3\) (40 mL each). The reaction mixture was passed through a pad of celite. The combined organic phases were dried over anhydrous MgSO\(_4\), concentrated, and purified by silica gel column chromatography to afford aldehyde 1m (1.20 g, 34%) as a white solid. m.p. 132–133 °C. IR (neat, cm\(^{-1}\)) 1695, 1616, 1426, 1374, 1275, 1190, 1114, 1078, 769; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 9.50 (s, 1H), 7.95 (d, \(J = 9.1\) Hz, 2H), 6.68 (d, \(J = 9.0\) Hz, 2H), 6.67 – 6.63 (m, 1H), 5.12 (dd, \(J = 5.8, 1.1\) Hz, 1H), 3.08 (s, 6H), 1.87 (s, 3H); \(^1\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\): 194.41,
HRMS (DART-TOF) calcd. for C\textsubscript{14}H\textsubscript{17}N\textsubscript{03} [M+H]\textsuperscript{+} m/z 248.1281, found 248.1283. Anal. Calcd. for C\textsubscript{14}H\textsubscript{17}N\textsubscript{03}: C, 68.00; H, 6.93. Found: C, 67.87; H, 6.98.

\(\text{(E)-3-phenylbut-2-en-1-yl 4-(dimethylamino)benzoate}\) (Scheme 7, 1\textsubscript{n}) Prepared following general procedure A from corresponding allylic alcohol (2.96 g, 20 mmol). The crude reaction mixture was purified by flash column chromatography (8–10% EtOAc in hexanes) to provide the title compound in 62% yield (3.69 g) as a white solid. m.p. 80–81 °C. IR (neat, cm\textsuperscript{-1}) 2920, 1697, 1605, 1525, 1367, 1272, 1180, 1097, 946, 757, 697; \(^1\text{H NMR}\) (600 MHz, CDCl\textsubscript{3}) \(\delta\): 7.99 (d, \(J=9.0\) Hz, 2H), 7.57 – 7.44 (m, 2H), 7.44 – 7.35 (m, 2H), 7.35 – 7.24 (m, 1H), 6.68 (d, \(J=9.0\) Hz, 2H), 6.08 (t, \(J=6.3\) Hz, 1H), 5.03 (d, \(J=6.7\) Hz, 2H), 3.07 (s, 6H), 2.21 (s, 3H); \(^{13}\text{C NMR}\) (151 MHz, CDCl\textsubscript{3}) \(\delta\): 167.07, 153.39, 142.81, 139.59, 131.42, 128.35, 127.47, 125.95, 122.35, 117.11, 110.76, 61.60, 40.14, 16.37; HRMS (DART-TOF) calcd. for C\textsubscript{19}H\textsubscript{21}N\textsubscript{02} [M+H]\textsuperscript{+} m/z 296.1645, found 296.1631. Anal. Calcd. for C\textsubscript{19}H\textsubscript{21}N\textsubscript{02}: C, 77.26; H, 7.71. Found: C, 77.40; H, 7.11.

\(\text{(E)-3-(4-methoxyphenyl)but-2-en-1-yl 4-(dimethylamino)benzoate}\) (Scheme 7, 1\textsubscript{o}) Prepared following general procedure B from corresponding allylic alcohol (1.0 g, 5.7 mmol). The crude reaction mixture was purified by flash column chromatography (10–20% EtOAc in hexanes) followed by recrystallization from hexanes/EtOAc to provide the title compound in 76% yield (1.40 g) as a white solid. m.p. 91.6–92.5 °C. IR (neat, cm\textsuperscript{-1}) 2913, 1703, 1602, 1510, 1460, 1429, 1366, 1181, 1093, 1019, 829, 767; \(^1\text{H NMR}\) (400 MHz, CDCl\textsubscript{3}) \(\delta\): 7.96 – 7.92 (dt, \(J=8.8, 2.8\) Hz, 2H), 7.40 – 7.37 (dt, \(J=8.8, 3.2\) Hz, 2H), 6.88 – 6.85 (dt, \(J=12.0, 3.2\) Hz, 2H), 6.68 – 6.64 (dt, \(J=8.8, 3.2\) Hz, 2H), 6.00 – 5.95 (tq, \(J=6.8, 1.2\) Hz, 1H), 4.98 – 4.96 (d, \(J=13.2\) Hz, 2H), 3.82 (s, 3H), 3.04 (m, 6H), 2.15 (s, 3H); \(^{13}\text{C NMR}\) (151 MHz, CDCl\textsubscript{3}) \(\delta\): 167.04, 159.11, 153.31, 139.05, 135.16, 131.36, 126.97, 120.56, 117.14, 113.63, 110.73, 61.60, 55.31, 40.08, 16.26;
HRMS (DART-TOF) calcd. for C_{20}H_{23}N_{03} [M+H]^+ m/z 326.1751, found 326.1760. Anal. Calcd. for C_{20}H_{23}N_{03}: C, 73.82; H, 7.12. Found: C, 73.73; H, 7.12.

\[(E)-3-(4-(trifluoromethyl)phenyl)but-2-en-1-yl 4-(dimethylamino)benzoate\] (Scheme 7, 1p) Prepared following general procedure B from corresponding allylic alcohol (1.7 g, 7.8 mmol). The crude reaction mixture was purified by flash column chromatography (10% EtOAc in hexanes) followed by recrystallization from hexanes/EtOAc to provide the title compound in 53% yield (1.50 g) as a white solid. m.p. 102.7–103.6 °C. IR (neat, cm\(^{-1}\)) 1697, 1600, 1521, 1361, 1272, 1186, 1155, 1103, 1057, 828, 769; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\): 7.96 – 7.92 (dt, \(J = 9.2, 2.8 \) Hz, 2H), 7.59 – 7.57 (dt, \(J = 8.0, 0.8 \) Hz, 2H), 7.53 – 7.51 (dt, \(J = 8.0, 0.8 \) Hz, 2H), 6.69 – 6.65 (dt, \(J = 9.2, 2.8 \) Hz, 2H), 6.10 – 6.07 (tq, \(J = 5.8, 1.2 \) Hz, 1H), 3.05 (s, 6H), 2.18 – 2.18 (d, \(J = 1.2 \) Hz, 3H); \(^13\)C NMR (151 MHz, CDCl\(_3\)) \(\delta\): 170.00, 153.43, 146.35, 138.30, 131.49, 129.32 (q, \(J = 29.0 \) Hz), 126.3, 125.35, 124.6, 117.07 (q, \(J = 6.4 \) Hz), 110.90, 61.42, 40.25, 16.37; \(^19\)F NMR (376 MHz, CDCl\(_3\)) \(\delta\) -62.5. HRMS (DART-TOF) calcd. for C_{20}H_{20}F_{3}N_{02} [M+H]^+ m/z 364.1519, found 364.1515. Anal. Calcd. for C_{20}H_{20}F_{3}N_{02}: C, 66.11; H, 5.55. Found: C, 66.35; H, 5.50.

\[(E)-3-(3-fluorophenyl)but-2-en-1-yl 4-(dimethylamino)benzoate\] (Scheme 7, 1q) Prepared following general procedure B from corresponding allylic alcohol (768 mg, 4.6 mmol). The crude reaction mixture was purified by flash column chromatography (0–20% EtOAc in hexanes) followed by recrystallization from hexanes/EtOAc to provide the title compound in 91% yield (1.32 g) as a white solid. m.p. 90.0–91.0 °C. IR (neat, cm\(^{-1}\)) 2920, 1697, 1611, 1578, 1486, 1430, 1373, 1280, 1185, 1120, 1094, 947, 874, 767; \(^1\)H NMR (600 MHz, CDCl\(_3\)) \(\delta\): 7.98 – 7.96 (dt, \(J = 5.2, 1.6 \) Hz, 2H), 7.33 – 7.28 (m, 1H), 7.25 – 7.23 (m, 2H), 7.17 – 7.14 (m, 1H), 7.01 – 6.97 (m, 1H), 6.69 – 6.81 (d, \(J = 7.2 \) Hz, 2H), 6.10 – 6.08 (tq, \(J = 5.4, 1.8 \) Hz, 1H), 5.02 – 5.01 (d, \(J =
6.6 Hz, 2H), 3.07 (s, 6H), 2.18 (s, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$: 167.02, 163.76 – 162.14 (d, $J = 245$ Hz), 153.41, 145.14 (d, $J = 7.4$ Hz), 138.37 (d, $J = 2.3$ Hz), 131.47, 129.80 (d, $J = 8.5$ Hz), 123.47, 121.61 (d, $J = 2.9$ Hz), 117.11, 114.30 (d, $J = 21$ Hz), 113.01 (d, $J = 21$ Hz), 110.87, 61.45, 40.22, 16.33; $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$: -113.6.

HRMS (DART-TOF) calcd. for C$_{19}$H$_{20}$FNO$_2$ [M+H]$^+$ m/z 314.1551, found 314.1552. Anal. Calcd. for C$_{19}$H$_{20}$FNO$_2$: C, 72.82; H, 6.43. Found: C, 72.99; H, 6.41.

(E)-3-(3-chlorophenyl)but-2-en-1-yl 4-(dimethylamino)benzoate (Scheme 7, 1r) Prepared following general procedure B from corresponding allylic alcohol (3.6 mg, 19.6 mmol). The crude reaction mixture was purified by flash column chromatography (10–20% EtOAc in hexanes) followed by recrystallization from hexanes/EtOAc to provide the title compound in 42% yield (2.73 g) as a white solid. m.p. 56.9–57.4 °C. IR (neat, cm$^{-1}$) 1689, 1594, 1526, 1427, 1369, 1268, 1178, 1103, 898, 829, 768; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.95 – 7.93 (dt, $J = 4.8$, 2.0 Hz, 2H), 7.42 – 7.41 (m, 1H), 7.32 – 7.22 (m, 3H), 6.67 – 6.64 (dq, $J = 9.2$, 2.8 Hz, 2H), 6.06 – 6.02 (m, 1H), 4.99 – 4.97 (d, $J = 6.8$ Hz, 2H), 3.04 (s, 6H), 2.15 (s, 3H); $^{13}$C NMR (151 MHz, CDCl$_3$) $\delta$: 166.94, 153.36, 144.60, 138.19, 134.25, 131.40, 129.55, 127.40, 126.12, 124.08, 123.60, 116.95, 110.77, 61.36, 40.12, 16.26. HRMS (DART-TOF) calcd. for C$_{19}$H$_{20}$ClNO$_2$ [M+H]$^+$ m/z 330.1255, found 330.1253. Anal. Calcd. for C$_{19}$H$_{20}$ClNO$_2$: C, 69.19; H, 6.11. Found: C, 69.15; H, 6.09.

(E)-3-(thiophen-3-yl)but-2-en-1-yl 4-(dimethylamino)benzoate (Scheme 7, 1s) Prepared following general procedure B from corresponding allylic alcohol (616 mg, 4 mmol). The crude reaction mixture was purified by flash column chromatography (10–20% EtOAc in hexanes) followed by recrystallization from hexanes/EtOAc to provide the title compound in 83% yield (1.0 g) as a white solid. m.p. 88.4–89.2 °C. IR (neat, cm$^{-1}$) 2925, 1688, 1600, 1530, 1426, 1369, 1274, 1180, 1114, 972, 829, 768, 722, 698; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 7.95 – 7.91 (dt, $J = 8.8$,
2.0 Hz, 2H), 7.09 – 7.07 (dd, \( J = 3.6, 1.2 \) Hz, 1H), 6.99 – 6.97 (dd, \( J = 5.2, 3.6 \) Hz, 1H), 6.66 – 6.63 (dq, \( J = 9.2, 2.8 \) Hz, 2H), 6.19 – 6.14 (tq, \( J = 6.0, 1.2 \) Hz, 1H), 4.97 – 4.95 (d, \( J = 8.0 \) Hz, 2H), 3.04 (s, 6H), 2.19 (s, 3H); \(^{13}\)C NMR (151 MHz, CDCl\(_3\)) \( \delta \): 167.02, 153.39, 146.66, 133.67, 131.48, 127.45, 124.35, 123.66, 120.57, 117.18, 110.87, 61.12, 40.24, 16.31. HRMS (DART-TOF) calcd. for C\(_{11}\)H\(_{19}\)N\(_2\)O\(_2\)S \([M+H]^+ m/z\) 302.1209, found 302.1222. Anal. Calcd. for C\(_{11}\)H\(_{19}\)N\(_2\)O\(_2\)S: C, 67.74; H, 6.35. Found: C, 67.89; H, 6.44.

\((E)-3\text{-}(\text{dimethyl(phenyl)silyl})\text{but-2-en-1-yl}) 4\text{-}(\text{dimethylamino})\text{benzoate} \) (Scheme 8, 1t) Prepared following general procedure A from corresponding allylic alcohol\(^{17}\) (1.45 g, 7.0 mmol). The crude reaction mixture was purified by flash column chromatography (10–15% EtOAc in hexanes) to provide the title compound in 82% yield (2.03 g) as a white solid. m.p. 61–62 °C. IR (neat, cm\(^{-1}\)) 2955, 1699, 1607, 1525, 1365, 1271, 1181, 1104, 947, 30, 815, 699; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 8.04 (d, \( J = 9.0 \) Hz, 2H), 7.61 (dd, \( J = 6.3, 3.1 \) Hz, 2H), 7.50 – 7.35 (m, 3H), 6.71 (d, \( J = 9.1 \) Hz, 2H), 6.14 (ddt, \( J = 7.4, 5.6, 1.5 \) Hz, 1H), 5.02 (d, \( J = 5.8 \) Hz, 2H), 3.07 (s, 6H), 1.87 (s, 3H), 0.47 (s, 6H); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \( \delta \): 166.86, 153.28, 139.04, 137.72, 135.26, 133.98, 131.33, 129.05, 127.81, 117.04, 110.68, 61.32, 39.99, 15.31, -3.59; HRMS (DART-TOF) calcd. for C\(_{21}\)H\(_{21}\)N\(_2\)Si \([M+H]^+ m/z\) 354.1884, found 354.1877. Anal. Calcd. for C\(_{21}\)H\(_{21}\)N\(_2\)Si: C, 71.35; H, 7.70. Found: C, 71.07; H, 7.70.

\((E)-3\text{-}(\text{dimethyl(phenyl)silyl})\text{but-2-en-1-yl}) 4\text{-}(\text{dimethylamino})\text{benzoate} \) (Scheme 8, 1t) Prepared following general procedure A from corresponding allylic alcohol\(^{17}\) (1.45 g, 7.0 mmol). The crude reaction mixture was purified by flash column chromatography (10–15% EtOAc in hexanes) to provide the title compound in 82% yield (2.03 g) as a white solid. m.p. 61–62 °C. IR (neat, cm\(^{-1}\)) 2955, 1699, 1607, 1525, 1365, 1271, 1181, 1104, 947, 30, 815, 699; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 8.04 (d, \( J = 9.0 \) Hz, 2H), 7.61 (dd, \( J = 6.3, 3.1 \) Hz, 2H), 7.50 – 7.35 (m, 3H), 6.71 (d, \( J = 9.1 \) Hz, 2H), 6.14 (ddt, \( J = 7.4, 5.6, 1.5 \) Hz, 1H), 5.02 (d, \( J = 5.8 \) Hz, 2H), 3.07 (s, 6H), 1.87 (s, 3H), 0.47 (s, 6H); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \( \delta \): 166.86, 153.28, 139.04, 137.72, 135.26, 133.98, 131.33, 129.05, 127.81, 117.04, 110.68, 61.32, 39.99, 15.31, -3.59; HRMS (DART-TOF) calcd. for C\(_{21}\)H\(_{21}\)N\(_2\)Si \([M+H]^+ m/z\) 354.1884, found 354.1877. Anal. Calcd. for C\(_{21}\)H\(_{21}\)N\(_2\)Si: C, 71.35; H, 7.70. Found: C, 71.07; H, 7.70.

\((E)-1\text{-phenylbut-2-en-1-yl}) 4\text{-}(\text{dimethylamino})\text{benzoate} \) (Scheme 9, 1u) Prepared following general procedure A from corresponding allylic alcohol (2.22 g, 15.0 mmol). The crude reaction mixture was purified by flash column chromatography (8–10% EtOAc in hexanes) to provide the title compound in 83% yield (3.68 g) as a white solid. m.p. 85 °C. IR (neat, cm\(^{-1}\)) 2900, 1695, 1605, 1525, 1446, 1367, 1317, 1267, 1178, 1095, 963, 828, 768, 697; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \): 8.00 (d, \( J = 9.0 \) Hz, 2H), 7.49 – 7.41 (m, 2H), 7.41 – 7.34 (m, 2H), 7.34 – 7.27 (m, 1H), 6.68 (d, \( J = 8.9 \) Hz, 2H), 6.47 (d, \( J = 6.2 \) Hz, 1H), 6.18 (d, \( J = 6.2 \) Hz, 1H), 4.71 – 4.64 (m, 2H), 3.52 – 3.26 (m, 1H), 3.06 (dd, \( J = 2.8, 1.2 \) Hz, 1H), 2.23 (s, 3H), 1.99 – 1.91 (m, 2H), 1.69 – 1.55 (m, 4H), 1.47 – 1.33 (m, 2H), 0.86 (t, \( J = 6.8 \) Hz, 3H), 0.82 (d, \( J = 6.8 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \): 166.86, 153.28, 139.04, 137.72, 135.26, 133.98, 131.33, 129.05, 127.81, 117.04, 110.68, 61.32, 39.99, 15.31, -3.59; HRMS (DART-TOF) calcd. for C\(_{21}\)H\(_{21}\)N\(_2\)Si \([M+H]^+ m/z\) 354.1884, found 354.1877. Anal. Calcd. for C\(_{21}\)H\(_{21}\)N\(_2\)Si: C, 71.35; H, 7.70. Found: C, 71.07; H, 7.70.
5.95 - 5.70 (m, 2H), 3.06 (s, 6H), 1.76 (d, J = 6.0 Hz, 3H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ: 166.09, 153.49, 140.61, 131.55, 130.29, 129.16, 128.55, 127.77, 126.90, 117.38, 110.83, 75.91, 40.21, 17.95; HRMS (DART-TOF) calcd. for C$_{19}$H$_{21}$NO$_2$ [M+H]$^+$ m/z 296.1645, found 296.1638. Anal. Calcd. for C$_{19}$H$_{21}$NO$_2$: C, 77.26; H, 7.17. Found: C, 77.19; H, 7.13.

![image](1v)

(E)-2-(2,6-dimethylhepta-1,5-dien-1-yl)oxirane (Scheme 11, 1v) Prepared following the literature procedure.$^{18}$ The compound was characterized to ensure the (E)-olefin geometry is unchanged during the oxidation. IR (neat, cm$^{-1}$) 2968, 2913, 2855, 1445, 1377, 1251, 1106, 938, 872, 835, 772; $^1$H NMR (600 MHz, CDCl$_3$) δ: 5.08 (t, J = 6.8 Hz, 1H), 4.82 (d, J = 8.8 Hz, 1H), 3.57 (dd, J = 8.7, 2.9 Hz, 1H), 3.03 – 2.93 (m, 1H), 2.65 (d, J = 5.2, 2.7 Hz, 1H), 2.16 – 2.07 (m, 2H), 2.07 – 1.99 (m, 2H), 1.82 (s, 3H), 1.68 (s, 3H), 1.60 (s, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ: 144.08, 132.02, 123.81, 122.07, 49.13, 49.08, 39.78, 26.36, 25.80, 17.82, 16.86.

![image](1w)

(E)-3-methylpent-2-en-1-yl 4-(dimethylamino)benzoate (Scheme 12, 1w) Prepared following general procedure A from corresponding allylic alcohol (1.45 g, 7.0 mmol). The crude reaction mixture was purified by flash column chromatography (10–15% EtOAc in hexanes) to provide the title compound in 82% yield (2.03 g) as a white solid. m.p. 32–33 °C. IR (neat, cm$^{-1}$) 2964, 1697, 1604, 1524, 1365, 1269, 1179, 1095, 946, 828, 769; $^1$H NMR (400 MHz, CDCl$_3$) δ: 7.94 (d, J = 9.0 Hz, 2H), 6.66 (d, J = 8.8 Hz, 2H), 5.60 – 5.40 (m, 1H), 4.82 (d, J = 7.0 Hz, 2H), 3.05 (s, 6H), 2.09 (q, J = 7.5 Hz, 2H), 1.78 (s, 3H), 1.06 (t, J = 7.4 Hz, 3H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ: 167.17, 153.33, 143.36, 131.35, 117.89, 117.49, 110.73, 61.35, 40.22, 32.36, 16.61, 12.37; HRMS (DART-TOF) calcd. for C$_{15}$H$_{21}$NO$_2$ [M+H]$^+$ m/z 248.1645, found 248.1641. Anal. Calcd. for C$_{15}$H$_{21}$NO$_2$: C, 72.84; H, 8.56. Found: C, 72.57; H, 8.58.

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D) Preparation of O-Benzoyl Hydroxylamines

O-Benzoyl hydroxylamines were synthesized according to the literature procedure. All of the O-benzoyl hydroxylamines used are known compounds except for 2g.

4-(benzo[c][1,2,5]thiadiazol-5-yl)piperazin-1-yl benzoate (Scheme 8, 2g). To a solution of benzoyl peroxide (5.33 g, 22 mmol, 1.1 equiv) and K₂HPO₄ (6.96 g, 40 mmol, 2.0 equiv) in DMF (50 mL) was added 5-(piperazin-1-yl)benzo[c][1,2,5]thiadiazole (4.41 g, 20 mmol, 1.0 equiv). The reaction mixture was stirred at rt overnight and then diluted with EtOAc and H₂O. The aqueous layer was extracted with EtOAc (2x), and the combined organic layers were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The crude material was purified by flash column chromatography (10–100% EtOAc in hexanes) to provide the title compound as a white solid in 73% yield (4.97 g), m.p. 128–129 °C. IR (neat, cm⁻¹) 2825, 1733, 1609, 1450, 1242, 1083, 1022, 748, 706; ¹H NMR (600 MHz, CDCl₃) δ: 8.02 (d, J = 7.2 Hz, 2H), 7.82 (d, J = 9.6 Hz, 1H), 7.60 – 7.55 (m, 1H), 7.48 – 7.42 (m, 3H), 7.15 (s, 1H), 3.85 – 3.56 (m, 4H), 3.45 – 3.14 (m, 4H); ¹³C NMR (151 MHz, CDCl₃) δ: 164.67, 156.42, 151.46, 150.94, 133.38, 129.54, 129.07, 128.58, 124.73, 121.40, 102.03, 55.58, 47.55. HRMS (DART-TOF) calcd. for C₁₀H₁₁N₄S [M–OBz]⁺ m/z 219.0699, found 219.0686. Anal. Calcd. for C₁₁H₁₆N₄O₂S: C, 59.98; H, 4.74, Found: C, 60.25; H, 4.78.
4.5 References and Notes


10). We observed quantitative conversion of geraniol to the silyl ether in the presence of the copper catalyst and the silane. Additionally, silyl ether could be observed by GC/GC-MS in the aliquot of the crude reaction mixture prior to reaction completion.


12). The structure of the (R)-DTBM-SEGPHOS used in the quadrant model was based from geometry optimization of interaction between [(R)-DTBM-SEGPHOS]CuH with \( \beta \)-methylstyrene using B3LYP//SDD-6-31G(d) level. (Unpublished data by Yang Yang).


4.6 $^1$H, $^{13}$C, and $^{19}$F NMR Spectra
CH$_2$=CH-CHO

3b
\[
\begin{align*}
\text{BnO} & \quad \text{Me} \\
\text{N}\text{Bn}_2
\end{align*}
\]

3h
The image contains a chemical structure labeled as 3I, with a set of peaks and ppm values. There are also notes indicating various chemical shifts and degradation products.
HO\textsubscript{Me} N\textsubscript{Bn\textsubscript{2}}

3m
MeO-\[\begin{array}{c}
\text{Me} \\
\text{NBr}_2
\end{array}\]

3o
$3q$
$^{3}C$ NMR Spectra of 3r

-149.699
-134.986
-129.284
-126.986
-122.589
-120.023
-113.785
-108.924
-102.189

$^{1}H$ NMR Spectra of 3r

-7.767 CDCl3
-7.682 CDCl3

-177.317 CDCl3
-177.000 CDCl3

-56.859
-51.177
-37.350
-35.385
-22.085
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76.81 CDCl3

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N
N
Me
Me

4f

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)
Characterization of Substrates:

[Chemical Structure Image]

1a(9)
586
$^{19}F$ NMR spectrum of compound $1p$.
$^{1}H$ NMR spectra of 1q.
Chemical structure and NMR spectrum of compound 1r.
4.7 Chiral HPLC Spectra
(S)-N,N-dibenzyl-3,7-dimethyloct-6-en-1-amine (Scheme 3 and 4, entry (+)3a). HPLC analysis (OJ-H, 50% (hexanes:EtOH:TFA:Diethylamine = 95:5:0.2:0.1)/hexanes, 0.8 mL/min, 220 nm) indicated 97% ee: \( t_R \) (major) = 12.0 min, \( t_R \) (minor) = 14.9 min.

Rac-3a

(+)3a: 97% ee (average of 2 runs)
(R)-N,N-dibenzyl-3,7-dimethyloct-6-en-1-amine (Scheme 3 and 4, entry 3a). HPLC analysis (OJ-H, 50% (hexanes:EtOH:TFA:Diethylamine = 95:5:0.2:0.1)/hexanes, 0.8 mL/min, 220 nm) indicated 87% ee: $t_R$ (major) = 10.0 min, $t_R$ (minor) = 12.0 min.

Rac-3a

(-)3a: 87% ee (average of 2 runs)
(S)-N,N-dibenzyl-7-chloro-3-methylheptan-1-amine (Scheme 3 and 4, entry 3b). HPLC analysis (2 connected AD-H columns, 95:5:0.2:0.1 Hexanes: IPA: TFA: Diethylamine, 0.8 mL/min, 220 nm), 0.8 mL/min, 220 nm) indicated 96% ee: $t_R$ (major) = 80.0 min, $t_R$ (minor) = 83.8 min.

**Rac-3b**

![HPLC chromatogram for Rac-3b](image)

<table>
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<th>Peak RetTime</th>
<th>Type</th>
<th>Width</th>
<th>Area</th>
<th>Height</th>
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</table>

(S)-3b: 96% ee (average of 2 runs)

![HPLC chromatogram for (S)-3b](image)

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<td>MM T</td>
<td>1.2717</td>
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(S)-N,N-dibenzyl-3-methyl-6-phenylhexan-1-amine (Scheme 3 and 4, entry 3c). HPLC analysis (OD-H, 3% IPA/hexanes, 0.8 mL/min, 220 nm) indicated 98% ee: $t_R$ (minor) = 5.4 min, $t_R$ (major) = 6.4 min.

**Rac-3c**

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(S)-3c: 98% ee (average of 2 runs)

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(R)-N-benzyl-N-(5-(dibenzylamino)-3-methylpenty)-4-methylbenzenesulfonamide (Scheme 4, entry 3d). HPLC analysis (OD-H, 5% IPA/hexanes, 0.8 mL/min, 220 nm) indicated 97% ee: \( t_R \) (minor) = 18.2 min, \( t_R \) (major) = 20.1 min.

**Rac-3d**

![HPLC Chromatogram for Rac-3d](image1)

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<td>193.024</td>
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(R)-3d: 97% ee (average of 2 runs)

![HPLC Chromatogram for (R)-3d](image2)

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<td>0.555</td>
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<td>98.5784</td>
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</table>
(R)-N,N-dibenzyl-3-cyclohexylbutan-1-amine (Scheme 4, entry 3e). HPLC analysis (AD-H, hexanes:EtOH:TFA:Diethylamine = 95:5:0.2:0.1, 1.0 mL/min, 220 nm) indicated >99% ee: \( t_R \) (major) = 9.9 min, \( t_R \) (minor) = 11.3 min.

\[
\begin{array}{c|c|c|c|c|c}
\text{Peak} & \text{Ret Time} & \text{Width} & \text{Height} & \text{Area} & \% \\
\hline
1 & 9.920 & 0.2544 & 114.28241 & 6.65403 & 51.3536 \\
2 & 11.311 & 0.2619 & 108.25762 & 5.05387 & 48.6464 \\
\end{array}
\]

(R)-3e: >99% ee (average of 2 runs)

\[
\begin{array}{c|c|c|c|c|c|c}
\text{Peak} & \text{Ret Time} & \text{Width} & \text{Height} & \text{Area} & \% \\
\hline
1 & 9.535 & 0.3052 & 7062.52441 & 385.62714 & 100.0000 \\
\end{array}
\]
(R)-\textit{N,N}-dibenzyl-3,4,4-trimethylpentan-1-amine (Scheme 4, entry 3f). HPLC analysis (AD-H, hexanes:EtOH:TFA:Diethylamine = 95:5:0.2:0.1, 1.0 mL/min, 220 nm) indicated >99% ee: \( t_R \) (major) = 7.9 min, \( t_R \) (minor) = 8.9 min.

\textit{Rac-3f}

\begin{center}
\begin{tabular}{cccccc}
\hline
Peak RetTime & Type & Width & Area & Height & Area \\
\text{#} & \text{[min]} & \text{[min]} & \text{[mAU*s]} & \text{[mAU]} & \%
\hline
1 & 7.894 FM & 0.2067 & 3441.03320 & 277.43228 & 49.0493 \\
2 & 8.875 PM & 0.2470 & 3574.43018 & 241.19066 & 50.5507 \\
\hline
\end{tabular}
\end{center}

(R)-3f: >99% ee (average of 2 runs)

\begin{center}
\begin{tabular}{cccccc}
\hline
Peak RetTime & Type & Width & Area & Height & Area \\
\text{#} & \text{[min]} & \text{[min]} & \text{[mAU*s]} & \text{[mAU]} & \%
\hline
1 & 7.906 FM & 0.2046 & 3137.57959 & 255.63755 & 100.0000 \\
\hline
\end{tabular}
\end{center}
(R)-N,N-dibenzyl-3-(2-methyl-1,3-dioxolan-2-yl)butan-1-amine (Scheme 4, entry 3g). HPLC analysis (OD-H, hexanes:EtOH:TFA:Diethylamine = 95:5:0.2:0.1, 1.0 mL/min, 220 nm) indicated >99% ee: \( t_R \) (minor) = 18.5 min, \( t_R \) (major) = 21.5 min.

\( \text{Rac-3g} \)

\begin{verbatim}
Peak RetTime Type Width Area Height Area
#  [min] [min] [mAU*s] [mAU] %
----- | ------ | ------- | ---------- | ------- |------|
1 18.443 MF 0.6353 2230.67554 58.51597 47.1070
2 21.539 FM 0.7292 2504.66699 57.24741 52.6930
\end{verbatim}

(R)-3g: >99% ee (average of 2 runs)

\begin{verbatim}
Peak RetTime Type Width Area Height Area
#  [min] [min] [mAU*s] [mAU] %
----- | ------ | ------- | ---------- | ------- |------|
1 21.510 MF 0.7386 4785.82813 108.08333 100.0000
\end{verbatim}
(S)-N,N-dibenzyl-7-(benzyloxy)-3-methylheptan-1-amine (Scheme 4, entry 3h). HPLC analysis (OJ-H, 5% IPA/hexanes, 1.0 mL/min, 220 nm) indicated >99% ee: $t_R$ (major) = 15.0 min, $t_R$ (minor) = 31.9 min.

Rac-3h

(R)-3h: >99% ee (average of 2 runs)
(S)-7-(dibenzylamino)-5-methylheptan-1-ol (Scheme 4, entry 3i).
HPLC analysis (OD-H, 5% IPA in hexanes, 0.8 mL/min, 220 nm) indicated 98% ee: $t_R$ (minor) = 9.3 min, $t_R$ (major) = 10.6 min.

Rac-3i

(S)-3i: 98% ee (average of 2 runs)
**TBSO~NBn2**

(R)-N,N-dibenzyl-4-((tert-butyldimethylsilyl)oxy)-3-methylbutan-1-amine (Scheme 4, entry 3j). HPLC analysis (AD-H, hexanes:EtOH:TFA:DEA = 95:5:0.2:0.1, 1.0 mL/min, 220 nm) indicated 97% ee: $t_R$ (major) = 5.4 min, $t_R$ (minor) = 5.7 min.

**Rac-3j**

![HPLC graph for Rac-3j](image)

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</table>

(R)-3j: 97% ee (average of 2 runs)

![HPLC graph for (R)-3j](image)

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<td>0.1471</td>
<td>55.06427</td>
<td>6.23912</td>
<td>1.8276</td>
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</table>
(R)-N,N-dibenzyl-4-((tert-butyldimethylsilyl)oxy)-3-methylbutan-1-amine (Scheme 4, entry 3k). HPLC analysis (IA, 10% EtOH in hexanes, 0.8 mL/min, 220 nm) indicated 94% ee: $t_R$ (minor) = 8.9 min, $t_R$ (major) = 9.6 min.

**Rac-3k**

![HPLC chromatogram](image1)

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<td>[min]</td>
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</table>

**3k**: 94% ee (average of 2 runs)

![HPLC chromatogram](image2)

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<td>VV</td>
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<td>9310.84082</td>
<td>632.84418</td>
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</table>
(R)-N\textsuperscript{4},N\textsuperscript{4}-dibenzyl-2-methyl-N\textsuperscript{1}-tritylbutane-1,4-diamine (Scheme 4, entry 3l). HPLC analysis (IA, hexanes:EtOH:TFA:Diethylamine = 95:5:0.2:0.1, 0.8 mL/min, 220 nm) indicated >99% ee: $t_R$ (major) = 9.4 min, $t_R$ (minor) = 12.2 min.

**Rac-3l**

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<td>196.48405</td>
<td>2.17870</td>
<td>45.6213</td>
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</table>

(R)-3l: >99% ee (average of 2 runs)
(R)-4-(dibenzylamino)-2-methylbutan-1-ol (Scheme 4, entry 3m). HPLC analysis (AD, 5% IPA in hexanes, 0.8 mL/min, 220 nm) indicated 92% ee: $t_R$ (minor) = 11.7 min, $t_R$ (major) = 12.6 min.

**Rac-3m**

![HPLC chromatogram of Rac-3m](image)

| Peak RetTime Type Width Area Height Area |
|---------------------------------------|------------|----------------|----------------|----------------|----------------|
| # [min] [min] [mAUs] [mAUs] [%]       |            |                |                |                |                |
| 1 11.906 BV 0.3140 2955.79785 147.39079 48.9426 |            |                |                |                |                |
| 2 12.810 VV 0.3294 3083.51831 143.11217 51.0574 |            |                |                |                |                |

(R)-3m: 92% ee (average of 2 runs)

![HPLC chromatogram of (R)-3m](image)

| Peak RetTime Type Width Area Height Area |
|---------------------------------------|------------|----------------|----------------|----------------|----------------|
| # [min] [min] [mAUs] [mAUs] [%]       |            |                |                |                |                |
| 1 11.743 VB 0.2382 244.31319 12.27296 3.7715 |            |                |                |                |                |
| 2 12.650 BV 0.3240 6233.52783 250.93024 96.2285 |            |                |                |                |                |
(R)-N,N-dibenzyl-3-phenylbutan-1-amine (Scheme 7, entry 3n). HPLC analysis (AD-H, hexanes:EtOH:TFA:Diethyamine = 95:5:0.2:0.1, 0.8 mL/min, 220 nm) indicated >99% ee: $t_R$ (major) = 17.1 min, $t_R$ (minor) = 18.3 min.

Rac-3n

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</table>

(R)-3n: 98% ee (average of 2 runs)
(R)-N,N-dibenzyl-3-(4-methoxyphenyl)butan-1-amine (Scheme 7, entry 3o): HPLC analysis (OJ-H, 1% IPA/Hexanes, 0.8 mL/min, 220 nm) indicated 98% ee: $t_R$ (minor) = 18.1 min, $t_R$ (major) = 25.4 min.

Rac-3o

(R)-3o: 98% ee (average of 2 runs)
(R)-N,N-dibenzyl-3-(4-(trifluoromethyl)phenyl)butan-1-amine
(Scheme 7, entry 3p): HPLC analysis (OJ-H, 1% IPA/Hexanes, 0.8 mL/min, 220 nm) indicated 99% ee: t_R(minor) = 19.0 min, t_R(major) = 26.0 min.

\[ \text{Rac-3p} \]

\[ \begin{array}{cccccc}
\text{Peak} & \text{RetTime} & \text{Type} & \text{Width} & \text{Area} & \text{Height} & \text{Area} \\
1 & 19.010 & \text{MM} & 2.0508 & 620.97321 & 5.07567 & 49.7242 \\
2 & 26.004 & \text{MM} & 4.2521 & 627.86237 & 2.46100 & 50.2758 \\
\end{array} \]

(R3p): 99% ee (average of 2 runs)

\[ \begin{array}{cccccc}
\text{Peak} & \text{RetTime} & \text{Type} & \text{Width} & \text{Area} & \text{Height} & \text{Area} \\
1 & 19.327 & \text{MM} & 1.3004 & 18.12873 & 2.32353e-1 & 0.7543 \\
2 & 25.881 & \text{MM} & 4.3159 & 2385.29395 & 9.21125 & 99.2457 \\
\end{array} \]
(R)-N,N-dibenzyl-3-(3-fluorophenyl)butan-1-amine (Scheme 7, entry 3q): HPLC analysis (OJ-H, 3% IPA/Hexanes, 1 mL/min, 220 nm) indicated 98% ee: $t_R$ (minor) = 7.3 min, $t_R$ (major) = 10.3 min.

Rac-3q

(R)-3q: 98% ee (average of 2 runs)
(R)-N,N-dibenzyl-3-(3-chlorophenyl)butan-1-amine (Scheme 7, entry 3r): HPLC analysis (OJ-H, 3% IPA/Hexanes, 0.8 mL/min, 220 nm) indicated 99% ee: t_R (minor) = 7.5 min, t_R (major) = 9.2 min.

Rac-3r

(R)-3r: 95% ee (average of 2 runs)
\[(R)-N,N-dibenzyl-3-(thiophen-3-yl)butan-1-amine\] (Scheme 7, entry 3s):
HPLC analysis (IA, 97:5:0.2:0.1 Hexanes/EtOH/TFA/Diethylamine, 1.0 mL/min, 220 nm) indicated 99% ee: \(t_R\) (minor) = 12.8 min, \(t_R\) (major) = 13.6 min.

\[3s\]

\[\text{Rac-3s}\]

\[\text{(R)-3s: 99\% ee (average of 2 runs)}\]
(R)-N,N-dibenzyl-3-(dimethyl(phenyl)silyl)butan-1-amine (Scheme 8, entry 3t). HPLC analysis (OJ-H, 5% EtOH in hexanes, 0.8 mL/min, 220 nm) indicated 98% ee: $t_R$ (major) = 9.8 min, $t_R$ (minor) = 14.4 min.

3t

Rac-3t

(R)-3t: 98% ee (average of 2 runs)
(S)-N,N-dibenzyl-1-phenylbutan-1-amine (Scheme 9, entry 3u). HPLC analysis (OD-H, 2% IPA in hexanes, 0.8 mL/min, 220 nm) indicated 98\% ee: $t_R$ (major) = 4.9 min, $t_R$ (minor) = 5.6 min.

3u

Rac-3u

$(S)$-3u: 99\% ee (average of 2 runs)
(S)-N,N-dibenzyl-4,8-dimethylnon-7-en-1-amine (Scheme 11, entry 3v). HPLC analysis (AD-H and OJ-H in sequence, 50% (hexanes:EtOH:TFA:Diethylamine = 95:5:0.2:0.1) in hexanes, 0.8 mL/min, 210 nm) indicated 93% ee: \( t_R \) (major) = 25.1 min, \( t_R \) (minor) = 26.4 min.

**Rac-3v**

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<th>[min]</th>
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</table>

(S)-3v: 93% ee (average of 2 runs)

<table>
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<th>#</th>
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<th>[min]</th>
<th>[mAU's]</th>
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</table>

630
(R)-4-(benzyl(methyl)amino)-2-methylbutyl 4-(dimethylamino)benzoate (Scheme 12, entry 4b). HPLC analysis (IA, 10% EtOH in hexanes:EtOH:TFA:Diethyamine = 95:5:0.2:0.1, 0.8 mL/min, 230 nm) indicated 98% ee: $t_R$ (minor) = 16.6 min, $t_R$ (major) = 18.5 min.

Rac-4b

(R)-4b: 98% ee (average of 2 runs)
(R)-2-methyl-4-(2,2,6,6-tetramethylpiperidin-1-yl)butyl 4-(dimethylamino)benzoate (Scheme 12, entry 4c). HPLC analysis (AD-H, 10% EtOH in (hexanes:EtOH:TFA:Diethylamine = 95:5:0.2:0.1), 0.8 mL/min, 280 nm) indicated 96% ee: $t_R$(minor) = 13.9 min, $t_R$ (major) = 20.6 min.

Rac-4c

(R)-4c: 96% ee (average of 2 runs)
(R)-4-((4-(dimethylamino)benzoyl)oxy)-3-methylbutyl)piperazine-1-carboxylate (Scheme 12, entry 4d). HPLC analysis (AD-H, 10% EtOH in (hexanes:EtOH:TFA:Diethylamine = 95:5:0.2:0.1), 1.0 mL/min, 280 nm) indicated 96% ee: $t_R$ (minor) = 24.8 min, $t_R$ (major) = 36.3 min.

**Rac-4d**

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(R)-4d: 96% ee (average of 2 runs)

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(R)-2-methyl-4-(4-(pyrimidin-2-yl)piperazin-1-yl)butyl 4-(dimethylamino)benzoate (Scheme 12, entry 4e). HPLC analysis (IA, 10% EtOH in (hexanes:EtOH:TFA:Diethylamine = 95:5:0.2:0.1), 0.8 mL/min, 230 nm) indicated 98% ee: $t_R$ (minor) = 40.9 min, $t_R$ (major) = 46.6 min.

**Rac-4e**

![HPLC chromatogram](image)

| Peak Ret Time Type Width Area Height Area % |
|------------------------------------------|------------------------------------------|
| 1 40.917 MF 1.2072 4785.63665 66.12748 48.3011 |
| 2 46.589 FM 1.3661 5126.56299 62.54295 51.6389 |

(R)-4e: 98% ee (average of 2 runs)

![HPLC chromatogram](image)

| Peak Ret Time Type Width Area Height Area % |
|------------------------------------------|------------------------------------------|
| 1 41.479 FM 0.9204 29.18092 5.10507e-1 1.2239 |
| 2 46.559 FM 1.3976 2275.24658 27.13250 98.7761 |
(R)-4-(4-(benzo[c][1,2,5]thiadiazol-5-yl)piperazin-1-yl)-2-methylbutyl 4-(dimethylamino)benzoate (Scheme 12, entry 4f). HPLC analysis (AD-H, 30% IPA in hexanes, 0.8 mL/min, 254 nm) indicated 97% ee: $t_R$ (minor) = 18.4 min, $t_R$ (major) = 20.7 min.

Rac-4f

(R)-4f: 97% ee (average of 2 runs)