**Title**
Transition Metal-Catalyzed Enantioselective Silylation of C–H bonds: Reaction Development and Mechanistic Studies



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# Transition Metal-Catalyzed Enantioselective Silylation of C–H bonds: Reaction Development and Mechanistic Studies

By

Taegyo Lee

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requirements for the degree of

Doctor of Philosophy

in

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University of California, Berkeley

Committee in charge:

Professor John F. Hartwig, Chair
Professor F. Dean Toste
Professor Alexis T. Bell

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## Abstract

Transition Metal-Catalyzed Enantioselective Silylation of C–H bonds:
Reaction Development and Mechanistic Studies

By Taegyo Lee

Doctor of Philosophy in Chemistry

University of California, Berkeley

Professor John F. Hartwig, Chair

The following dissertation discusses the development of catalytic enantioselective silylation of aryl, cyclopropyl and unactivated aliphatic C–H bonds. This work also includes in-depth studies that reveal the mechanism of the enantioselective silylation and the origin of enantioselectivity.

Chapter 1 reviews transition metal-catalyzed reactions that functionalize C–H bonds with an emphasis on enantioselective transformations. This review describes the representative strategies of C–H bond functionalization to obtain site-selectivity. Discussions on the development of enantioselective functionalizations of C–H bonds with representative examples follow.

Chapter 2 discusses the development of rhodium-catalyzed enantioselecitve silylation of aryl C–H bonds. Hydrosilyl ethers that are formed *in situ* by hydrosilylation of benzophenone or its derivatives undergo enantioselective C−H silylation in the presence of a rhodium catalyst. Enantioenriched benzoxasilole products from the silylation process undergo a range of transformations to form C−C, C−O, C−I, or C−Br bonds without erosion of enantiomeric excess.

Chapter 3 discusses experimental and theoretical studies on the mechanism of rhodium-catalyzed enantioselective silylation of aryl C−H bonds. The identity of the resting states of the catalyst, the kinetic data, and the results of DFT calculations provide detailed insights into the mechanism of intramolecular enantioselective silylation of aryl C−H bonds and the origin of enantioselectivity.

Chapter 4 discusses the development of rhodium-catalyzed enantioselecitve silylation of cyclopropyl C–H bonds. Hydrosilyl ethers, generated *in situ* by the dehydrogenative silylation of cyclopropylmethanols with diethylsilane, undergo enantioselective silylation of cyclopropyl C–H bonds in the presence of a rhodium catalyst. The resulting enantioenriched oxasilolanes are suitable substrates for the Tamao–Fleming oxidation to form cyclopropanols with conservation of the ee value from the C–H silylation.

Chapter 5 discusses the development of iridium-catalyzed silylation of unactivated $sp^3$ C–H bonds of amines. The introduction of silylmethyl group on a secondary amine allows a site-selective functionalization of β-C–H bonds of amines to form silapyrrolidines. Development of both non-enantioselective and enantioselective catalysts is described. The silapyrrolidne product serves as a precursor to 1,2-amino alcohols by the oxidation of the silapyrrolidines, leading to an overall site-selective, and even enantioselective, oxidation of amines at the β-C–H bonds.

## Table of Contents

## Acknowledgement

I still cannot believe that five years have already gone by since I moved to the US from South Korea and I am receiving a PhD from UC Berkeley. I have truly enjoyed my time as a graduate student and will always cherish my memories here at Berkeley where I have become a true scientist. Because I would not have been able to successfully accomplish this without support from the people around me, I would like to show my gratitude towards them here.

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Finally, I cannot express how fortunate I am to have my partner in my life, who always believed in me even when I was in doubt and supported me throughout my PhD. Although we have been apart for most of the last few years, our love has only grown stronger. We finally made it. I am excited for our future together.

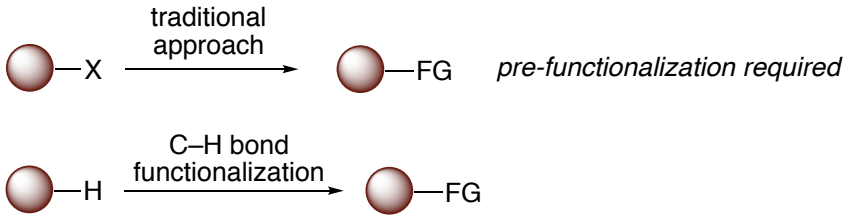
# CHAPTER 1

## Overview of Transition Metal-Catalyzed Enantioselective Functionalization of C–H Bonds

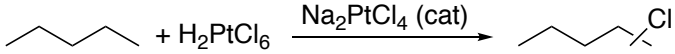
## 1.1 Transition metal-catalyzed functionalization of C–H bonds

Development of selective functionalization of C–H bonds has been considered a "holy grail" in organic synthesis and attracted significant attention from the community (Scheme 1.1).[1,2] This is due to its potential to dramatically streamline the synthetic routes. Methods that allow the selective functionalization of C–H bonds can eliminate the requirement of pre-existing functional groups, introduce new disconnections that were previously not accessible, and minimize waste formation. This chapter presents a brief history of transition metal-catalyzed functionalization of C–H bonds with strategies to obtain high site-selectivity, followed by discussions on the development of enantioselective transformations with representative examples.

**Scheme 1.1** Transition metal-catalyzed functionalization of C–H bonds

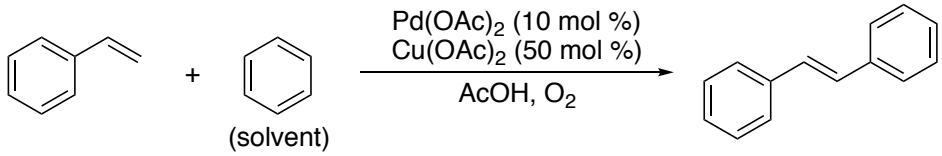



One of the earliest efforts on the metal-catalyzed functionalization of C–H bonds was reported by Shilov and coworkers on alkane oxidation (eq 1).[3] In the early 1970s, they reported that alkanes can undergo halogenation in the presence of a Pt(II) catalyst with a Pt(IV) reagent as a terminal oxidant. Although this transformation required a stoichiometric amount of precious metal as an oxidant, this report demonstrated the possibility that a transition metal catalyst can react with unactivated aliphatic C–H bonds to introduce useful functional groups.




(1)

At around the same time, Fujiwara reported an oxidative olefination of arenes catalyzed by palladium acetate with cupric acetate and molecular oxygen as terminal oxidants (eq 2).[4] This work provided foundations for recent development of functionalization of aryl C–H bonds.



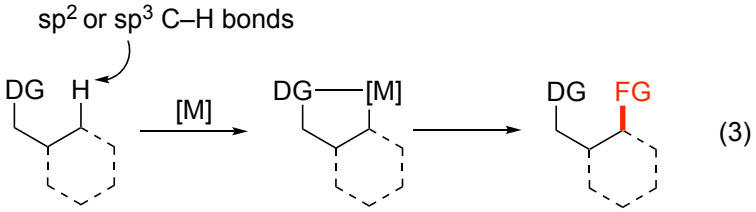

(2)

Another useful functional group that can be introduced from activation of C–H bonds is a double bond because olefins can undergo a wide range of transformations. In the 1980s, Crabtree and Felkin reported dehydrogenation of alkanes catalyzed by iridum and rhenium complexes to form olefins.[5-8] Despite the relatively low turnover numbers and the limited scope, these works showed that homogeneous catalysts could be applied

to the functionalization of petroleum-derived feedstock chemicals and inspired much research in this field.[9]

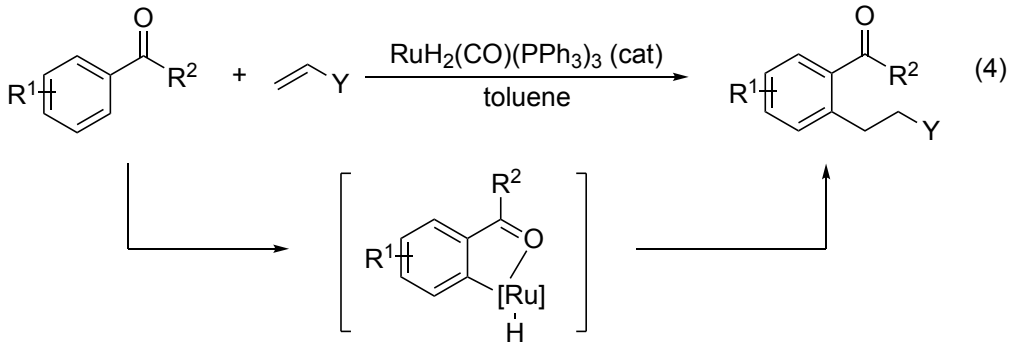
Based upon these historical achievements, a number of discoveries were made in recent years. Most of the efforts have been devoted to obtaining high site-selectivity.

One of the most common strategies to obtain high site-selectivity is the use of directing groups (eq 3). Directing groups are more capable of binding to the metal catalyst than C–H bonds are, thereby allowing more efficient interaction between the substrate and the metal catalyst, and these groups "direct" the metal to react with C–H bonds proximal to the directing group to render the process site-selective.




(3)

Murai and coworkers reported one of the first examples that demonstrated the power of a directing group in catalytic C–H bond functionalizations.[10] In this work, they showed that the carbonyl group in aryl ketones significantly increased the reactivity of the substrate and induced alkylation *ortho* to the carbonyl substituent.




(4)

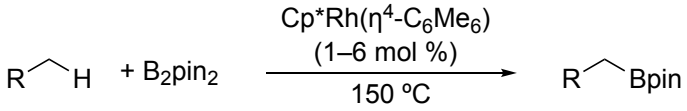
Since this seminal report, a number of directed functionalizations of both alkyl and aryl C–H bonds have been disclosed.[11,12] Notably, directing groups, such as nitrogen-containing heterocycles and nitrogen-based functional groups, have been widely studied because they can strongly coordinate to metal catalysts.[13] This strategy has led to the development of a wide range of transformations, such as acetoxlyation,[14,15] halogenation,[16,17] alkylation,[18,19] and arylation of $sp^2$ and $sp^3$ C–H bonds.[20] The presence of directing groups is not always desirable because they can be difficult to install or to remove or both. For these reasons, functional groups that are more commonly occurring in organic molecules have been investigated.[21] Functional groups such as carboxylates,[22] triflamides,[23] and alcohols[24,25] have been demonstrated as an effective directing group for metal-catalyzed C–H bond functionalization. Although most reports of arene functionalization focus on the reactions of *ortho* C–H bonds, directing groups have been designed that induce functionalization at the position *meta* to the directing group.[26,27]

The functionalizations of C–H bonds in the absence of a directing group have been reported.[28] In their seminal report from 2000, Hartwig and coworkers disclosed a

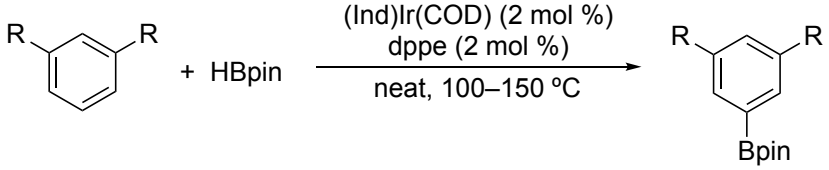
borylation of primary C–H bonds of unactivated alkanes catalyzed by rhodium complexes (Scheme 1.2a).[29] These reactions occur at a primary C–H bond over a secondary C–H bond in high site-selectivity because of the steric clash between the secondary alkyl group and the large boryl group during the reductive elimination that forms the carbon–boron bond in the product.[30]

**Scheme 1.2** Early reports of borylation of C–H bonds catalyzed by Rh and Ir catalysts

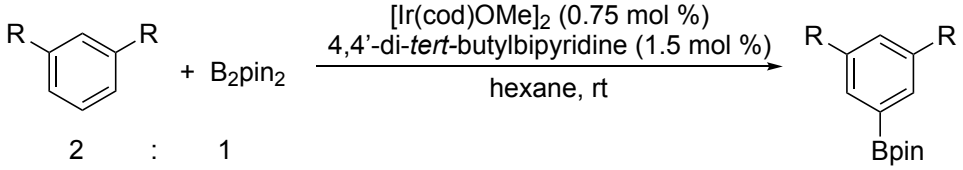
a) Borlyation of aliphatic C–H bonds




b) Borylation of aryl C–H bonds catalyzed by a Ir complex containing a bisphosphine

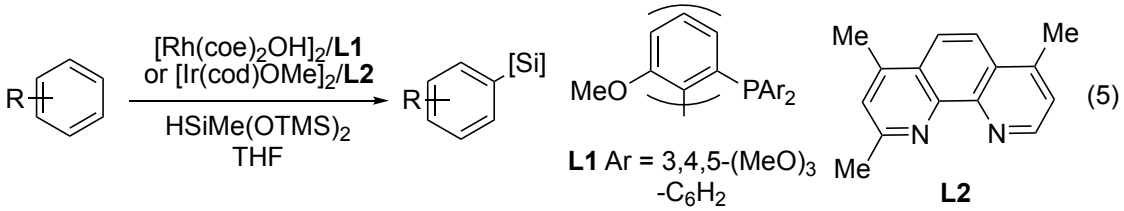



c) Borylation of aryl C–H bonds catalyzed by a Ir complex containing a bipyridine



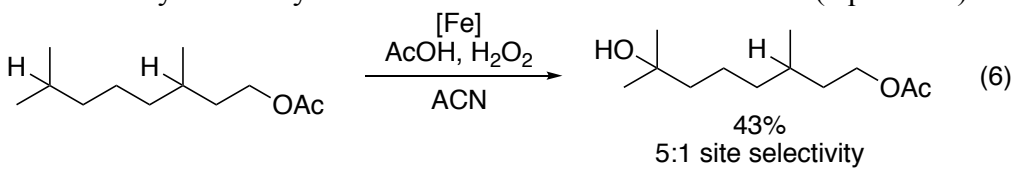

In 2002, Smith and the groups of Ishiyama, Miyaura, and Hartwig reported iridium-catalyzed borylations of aryl C–H bonds. The reaction disclosed by Smith was catalyzed by an iridium complex containing a bisphosphine ligand in neat arene at 100–150 °C (Scheme 1.2b).[31] On the other hand, the reaction disclosed by Ishiyama, Miyaura, and Hartwig was catalyzed by an iridium complex containing a bipyridine ligand at a temperature as low as room temperature (Scheme 1.3c).[32] These borylation processes occur at C–H bonds that are sterically accessible, and this selectivity is complementary to that of traditional arene functionalizations, such as electrophilic substitution.

In addition, Hartwig and coworkers disclosed the silylation of aryl C–H bonds catalyzed by a rhodium complex containing a bisphosphine ligand or an iridium

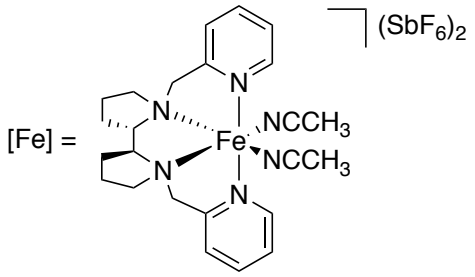


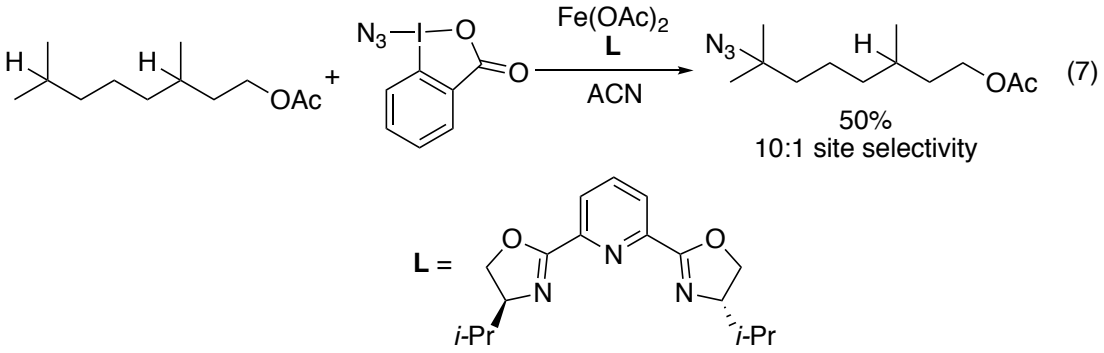

complex containing a phenanthroline ligand (eq 5).[33-35] Again, the selectivity of these reactions is determined by the steric properties of the arene substrates.

Electronic properties of the substrates can govern the site selectivity of C–H bond functionalization. For example, iron-catalyzed hydroxylation and azidation of C–H bonds occur at secondary or tertiary C–H bonds that are most electron-rich (eq 6 and 7).[36,37]



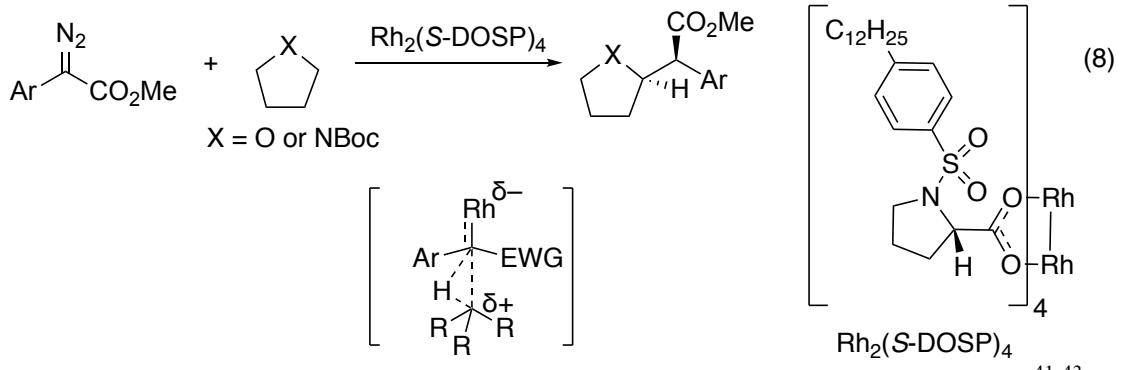

(6)




(7)

Insertion of carbenes and nitrenes also occurs with an electronically controlled site-selectivity.[38-40] For example, carbene insertion reactions of cyclic ethers or amines occur at C–H bonds α to oxygen or nitrogen (eq 8).[38,39] Positive charge accumulates at the reacting carbon in the transition state; therefore, the reaction occurs at the carbon where this positive charge can be stabilized most.

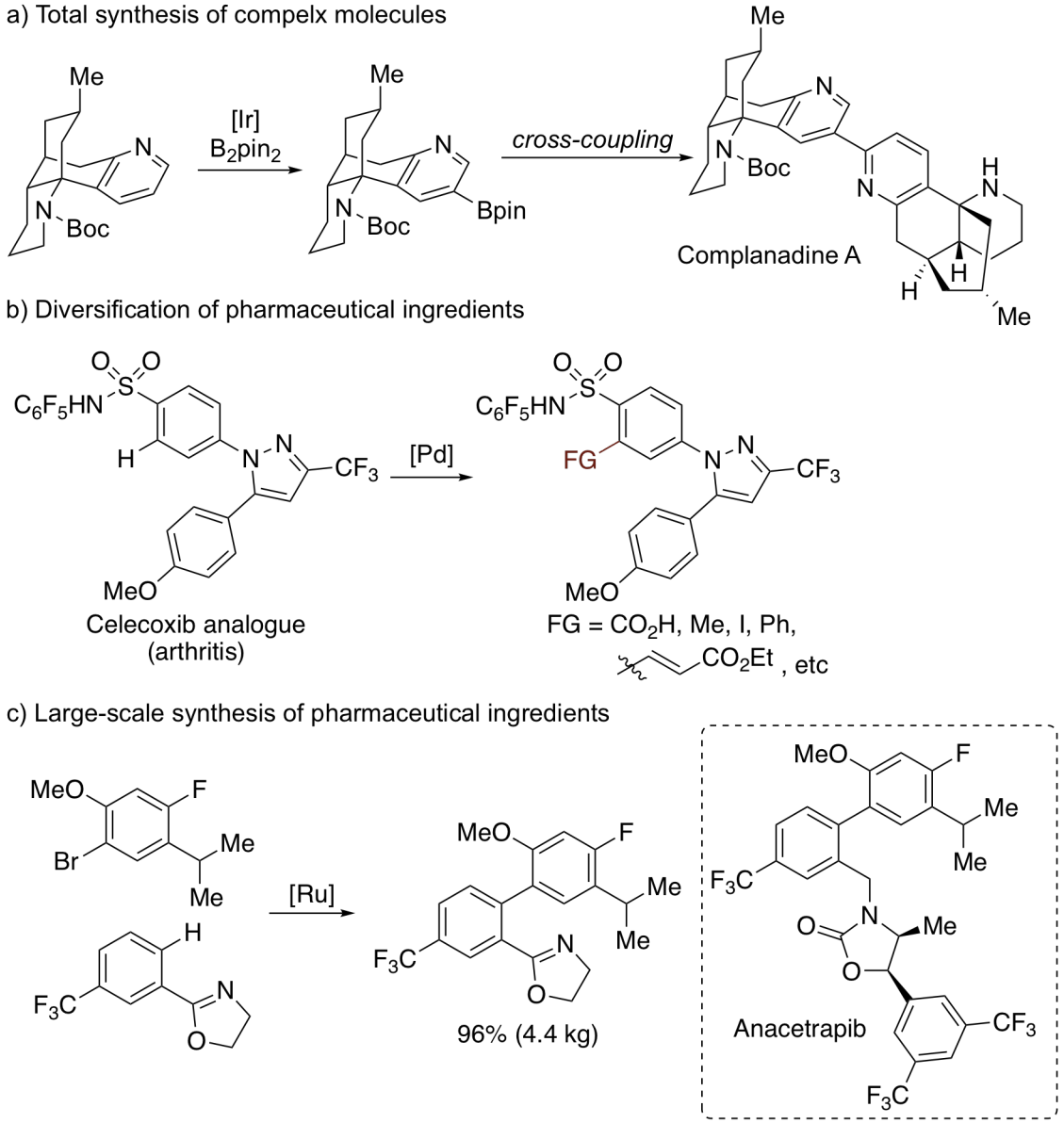



(8)

In addition, reactions of heteroarenes such as C–H borylation[41-43] and arylation[44,45] occur with high site selectivity determined by electronic properties of substrates.

The utility of C–H bond functionalizations have been demonstrated in the context of total synthesis or applications in pharmaceutical industry (Scheme 1.3). In the total synthesis of complanadine A reported by Sarpong and coworkers, iridium-catalyzed borylation of a C–H bond allowed a key bond disconnections between the two heteroarene cores with a regioselectivity suitable for the target molecule (Scheme 1.3a).[46] In addition, Yu group and Pfizer have prepared a variety of analogues ofcelecoxib through palladium-catalyzed, directed C–H bond functionalization and demonstrated the utility of the transformation in the context of medicinal chemistry (Scheme 1.3b).[47]

**Scheme 1.3** Applications of transition metal-catalyzed functionalization of C–H bonds



Lastly, Merck has applied ruthenium-catalyzed arylation directed by oxazoline towards a large-scale synthesis of biaryl core of anacetrapib (Scheme 1.3c).[48]

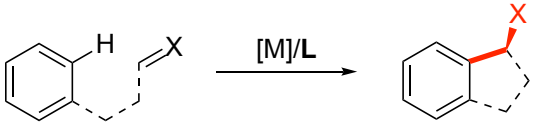
## 1.2 Transition metal-catalyzed enantioselective functionalization of C–H bonds

Catalytic enantioselective functionalization of C–H bonds presents a new frontier in the field of C–H bond functionalization. This process introduces a stereogenic center with a functional group at the same time and therefore substantially streamlines synthetic sequences. Research in this area has taken advantage of previous strategies from site-selective functionalization along with the innovative choice of chiral ligands.[49-54]

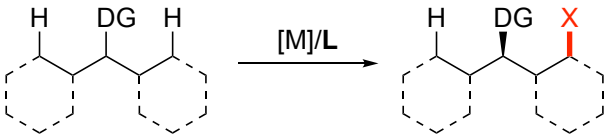
In general, three approaches have been employed to achieve this goal (Scheme 1.4). One approach is the combination of site-selective activation of a $sp^2$ C–H bond and asymmetric addition of the resulting organometallic species to a prochiral functional group (Scheme 1.4a). The second and third approaches involve enantioselective activation of a C–H bond in which the stereogenic center is formed directly during the C–H bond cleavage process. This process could be done in the form of desymmetrization in which the stereogenic center is not formed at the same carbon that reacts with the transition metal catalyst (Scheme 1.4b). Alternatively, the catalyst can be employed to differentiate two C–H bonds in one methylene group to set the stereogenic center on the same carbon where the functionalization occurs (Scheme 1.4c).

**Scheme 1.4** Strategies of enantioselective C–H activation

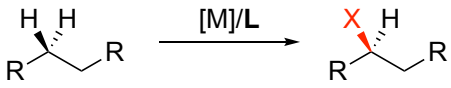
a) Site-selective C–H activation / enantioselective addition to a prochiral functional group




b) Desymmetrizing C–H bond functionalization




c) Differentiation of two C–H bonds in a methylene group

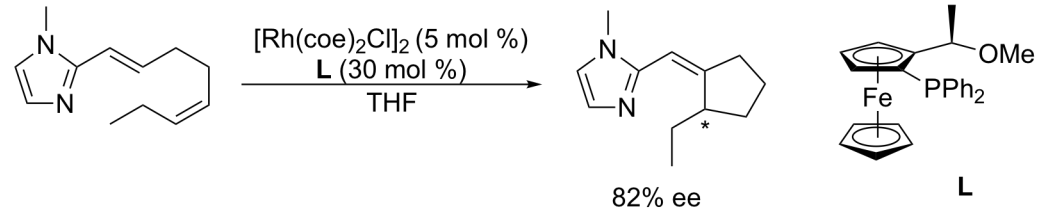



The first approach of asymmetric C–H functionalization takes an advantage of two known reactivities of site-selective C–H bond functionalization and asymmetric nucleophilic addition of organometallic species (Scheme 1.4a).[55] Representative examples in this class of the reactions are summarized in Scheme 1.5. Murai and

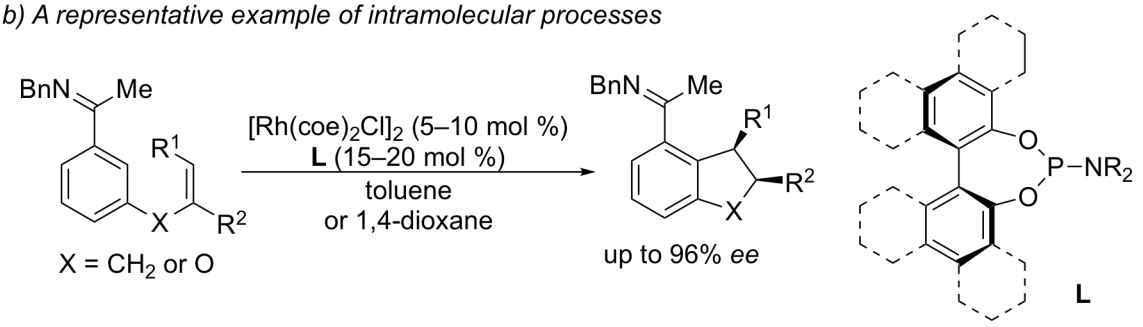
coworkers reported one of the first reactions in this class (Scheme 1.5a).[56] They showed that a rhodium complex containing a phosphine ligand can catalyze the activation of vinyl C–H bonds and subsequent intramolecular addition into a double bond in a moderate enantiomeric excess. Bergman and Ellman reported a highly enantioselective process catalyzed by Rh precursors and chiral phosphoramidite ligands in which regioselective functionalization of an aryl C–H bond occurs with the aid of an imine directing group and the resulting aryl rhodium species adds into the pending alkene (Scheme 1.5b).[57,58] Subsequently, Cramer and coworkers reported *inter*molecular reactions catalyzed by Rh complexes comtaining chiral Cp ligands (Scheme 1.5c).[59,60]

**Scheme 1.5** Representative examples of directed C–H bond functionalization followed by addition to prochiral functional groups

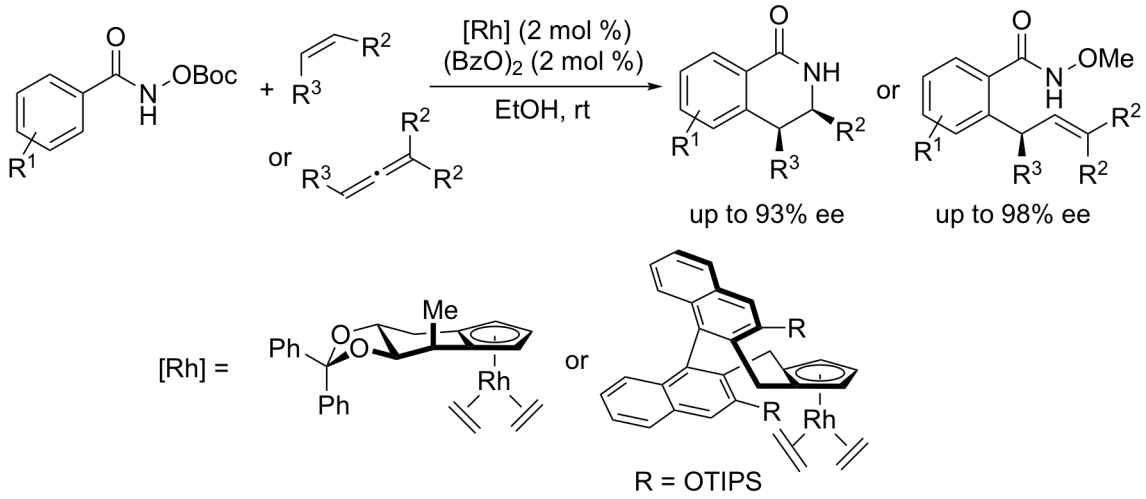
*a) Early report by Murai*




*b) A representative example of intramolecular processes*



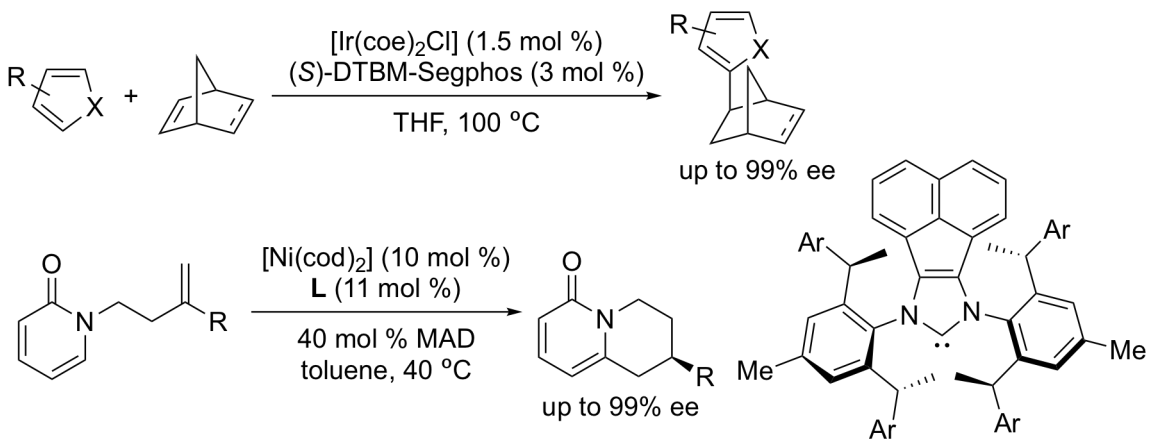

*c) A representative example of intermolecular processes*



This catalyst enabled C–H bond activation directed by hydroxamic acid and intermolecular addition to alkenes and allenes. Yamamoto reported an asymmetric, intramoleuclar hydroarylation of α-ketoamides by using this strategy with an iridium catalyst.[61]

In addition, methods have been developed in which site-selectivity of the first C–H functionalization was determined by the electronic property of the substrate without the presence of a directing group (Scheme 1.6). For example, Hartwig and coworkers reported an Ir-catalyzed heteroarylation of bicycloalkenes in which functionalization of heteroarene occurs *ortho* to the heteroatom.[62] Cramer reported a related transformation of pyridones catalyzed by a Ni complex containing a NHC ligand.[63]

**Scheme 1.6** Representative examples of *undirected* C–H bond functionalization followed by addition to prochiral functional groups

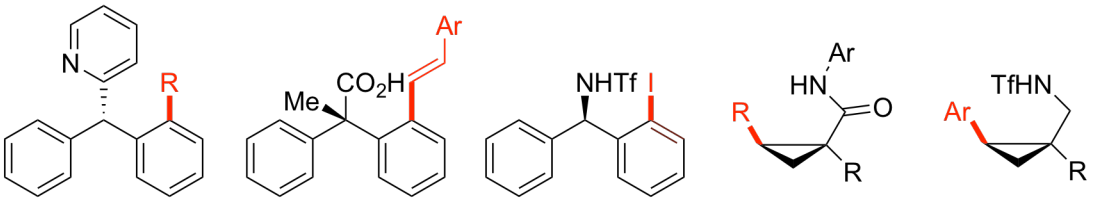



Introduction of a stereogenic center through desymmetrization of a prochiral molecule has been a long-standing interest to synthetic chemists.[64,65] This strategy has been adopted into transition metal-catalyzed C–H bond functionalization (Scheme 1.4b).

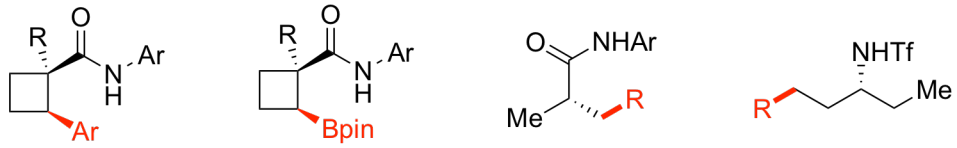
For example, Yu and coworkers have reported a series of enantioselective, directed C-H activation reactions of this class with Pd catalysts with protected amino acid or aminomethyl oxazoline ligands (Scheme 1.7a). Reactions of both aryl and aliphatic C–H bonds have been reported. The transformations include cross-coupling with organoboron reagents[66-70] or aryl and alkenyl iodides,[71,72] oxidative olefination,[73] oxidation,[74] and iodination.[75] They also have developed kinetic resolution of chiral substrates to address the issue of limited structural diversity inherent in desymmetrization processes.[76-78] In addition, reactions that introduce planar chirality have been developed by others.[79-81]

**Scheme 1.7** Representative examples of the products from desymmetrizing C–H bond functionalizations

*a) Catalyzed by Pd complexes with protected amino acid or aminomethyl oxazoline ligands*

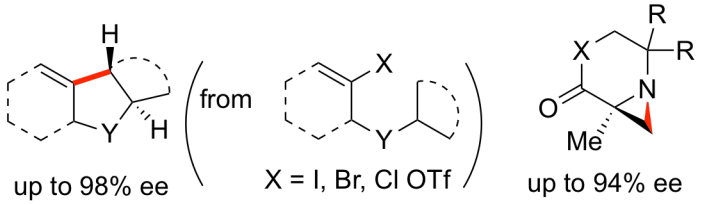



up to 95% ee, R = alkyl | up to 97% ee | up to 99% ee | up to 99% ee, R = aryl, vinyl, alkyl | up to 99% ee



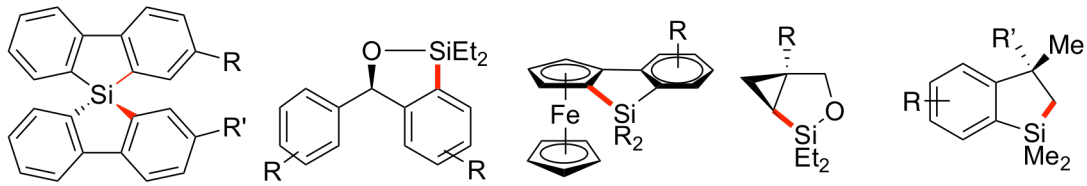

up to 95% ee | up to 99% ee | up to 96% ee, R = aryl, vinyl, akynyl | up to 99% ee, R = aryl, vinyl

*b) Catalyzed by Pd catalysts with chiral phosphine, phosphoramidite, NHC, or phosphoric acid*



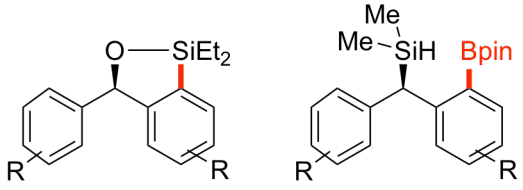

up to 98% ee | up to 94% ee

*c) Catalyzed by Rh cataysts with phosphine ligands*




up to 88% ee | up to 99% ee | up to 97% ee | up to 95% ee | up to 96% ee

*d) Catalyzed by Ir catalysts with pyrox ligands*




up to 93% ee | up to 92% ee

In some cases, a catalyst reacts with a pre-existing functional group within the substrate and then cleaves the C–H bond. Intramolecular reactions in which metal catalysts react with organic halides or pseudohalides have been reported to occur in the

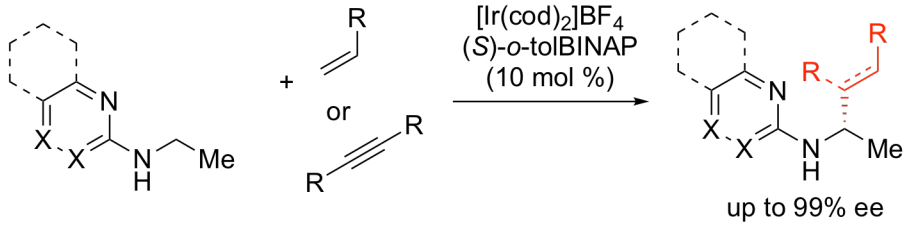
presence of palladium catalysts with bisphosphine, phosphoramidite, or NHC ligands (Scheme 1.7b).[82-90] Reactions of aryl, vinyl, and aliphatic C–H bonds to form C–C bonds have been studied. In addition, an intramolecular C–N bond formation through activation of aliphatic C–H bonds has been developed towards the synthesis of aziridines with a palladium catalyst with a chiral phosphoric acid.[91]

Hartwig, Takai, He, and Shibata have investigated rhodium and iridium complexes for the construction of C–Si and C–B bonds (Scheme 1.7c and 1.7d).[92-102] Enantioselective silylation of C–H bonds will be discussed more in detail in the following section.

In the last class of asymmetric C–H bond functionalization, the catalyst differentiates two C–H bonds in a methylene group to introduce a stereogenic center at the carbon that is functionalized (Scheme 1.4c). For the reaction in which the metal catalyst directly inserts into the carbon–hydrogen bond, the development of this class of reaction has met limited success until very recently. This limited success is because the oxidative addition of a transition metal to a secondary C–H bond and the following reductive elimination to form the C–X bond are not as facile as those to a primary C–H

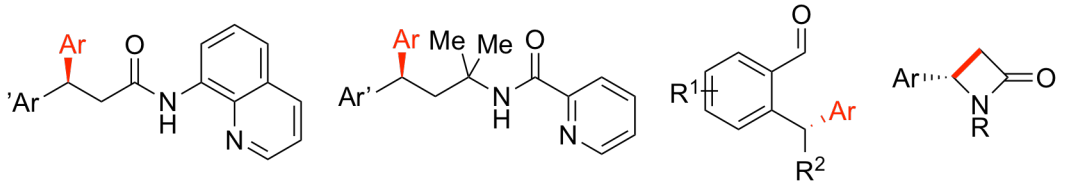
**Scheme 1.8** Representative examples of enantioselective functionalization of methylene C–H bonds

a) Functionalization of methylene C–H bonds α to nitrogen



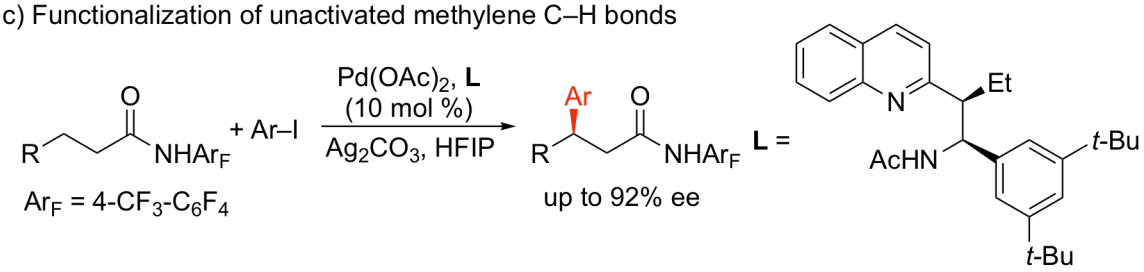

up to 99% ee

b) Products formed from Pd-catalyzed functionalization of benzylic C–H bonds




up to 82% ee | up to 97% ee | up to 96% ee | up to 98% ee

c) Functionalization of unactivated methylene C–H bonds

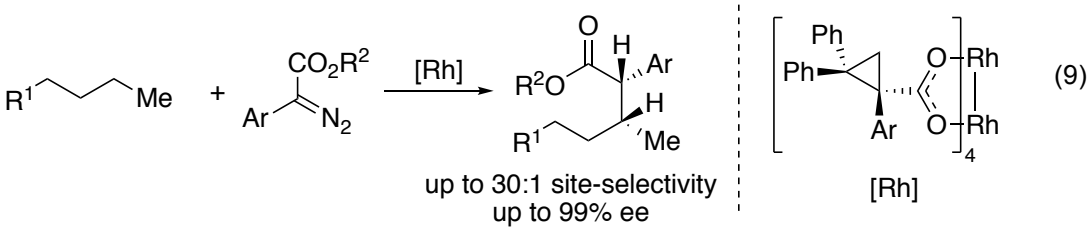



$Ar_F$ = 4-$CF_3$-$C_6F_4$

up to 92% ee

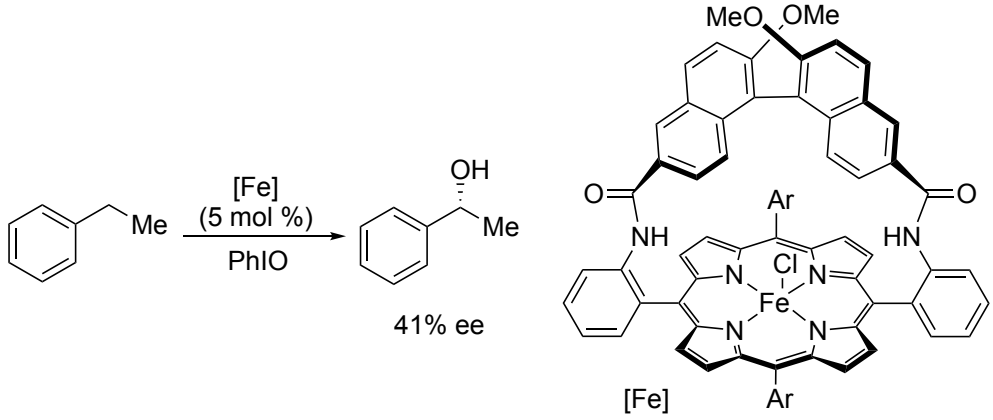
bond.[103] For this reason, early efforts focused on the cleavage of C–H bonds that are activated (Scheme 1.8a and 1.8b). For example, Shibata and coworkers reported alkylation and alkenylation of C–H bonds α to nitrogen in the presence of a iridium catalyst with a bisphosphine ligand (Scheme 1.8a).[104-106] In addition, Cramer, Duan, He, Chen, and Yu reported directed intermolecular arylation or intramolecular alkylation of benzylic C–H bonds catalyzed by Pd complexes containing chiral phosphoric amides, phosphoric acids, or amino acids (Scheme 1.8b).[107-110] Asymmetric functionalization of unactivated methylene C¬H bonds of this class is rare. Recently, Yu and coworkers conducted a systematic modification of chiral ligands to develop a highly enantioselective Pd-catalyzed arylation of unactivated methylene C–H bonds with a catalyst containing an acetyl-protected aminoethyl quinolone ligand (Scheme 1.8c).[111]

In addition to reactions occurring by a mechanism involving the formation of a metal–carbon bond, asymmetric C–H bond functionalizations occur through mechanisms that do not form a metal-carbon bond. One of the most successful examples is carbene and nitrene insertions.[112-115] This area has been intensively studied, and one of the most recent reports by Davies group showed that even C–H bonds in linear hydroalkanes can be functionalized in exceptional site-, diastereo-, and enantioselectivity.[116]

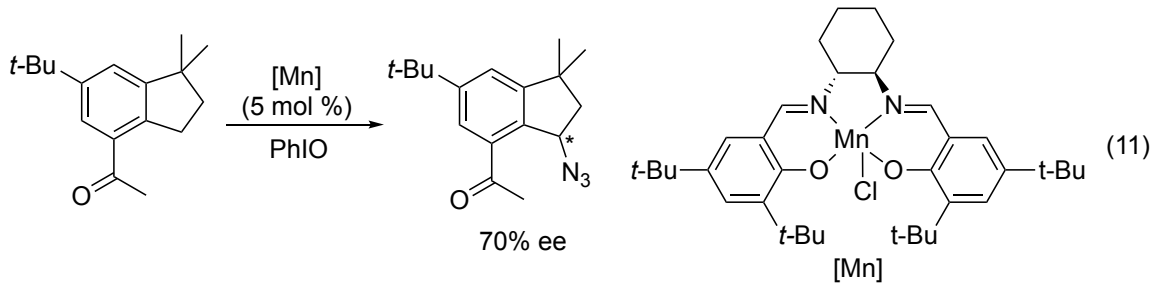



(9)

Asymmectric transformations that occur through radical abstraction of C–H bonds by metal-oxo complexes have been reported, although these reactions do not occur in high enantioselectivity. For examples, Groves and coworkers reported asymmetric hydroxylation and azidation catalyzed by iron or manganese complexes that occur low-to-moderate enantioselectivity (eq 10 and 11).[117,118]



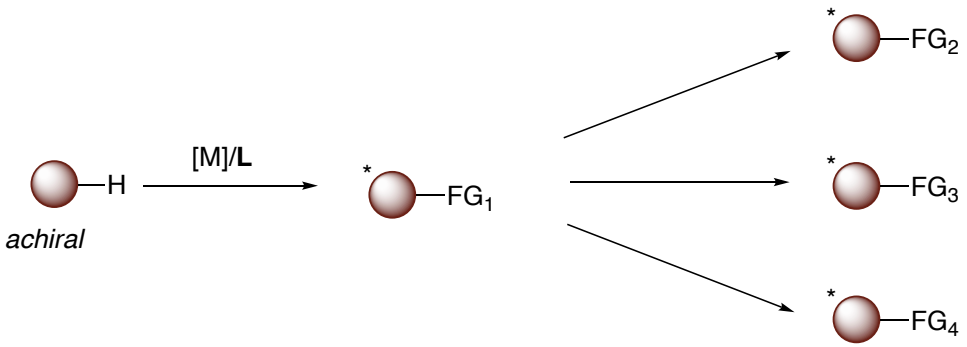

(10)




## 1.3 Transition metal-catalyzed enantioselective silylation of C–H bonds

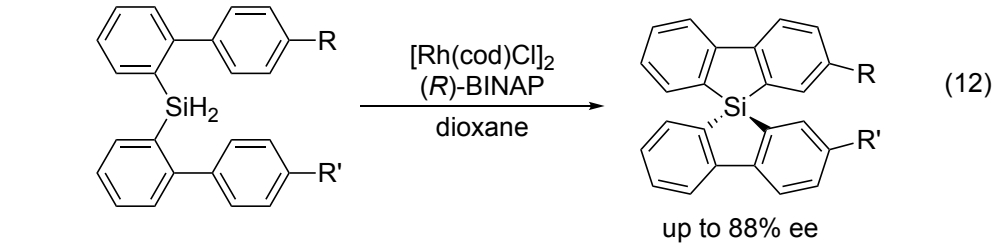
As described in the previous section, the majority of enantioselective functionalizations of C–H bonds form carbon–carbon bonds. Despite the importance of the construction of carbon-carbon bonds in organic synthesis, one of the drawbacks of these methods is that the installed group is not often amenable to further functionalization; therefore the development of different catalysts is required to introduce different functional groups into similar substrates. We envisioned that the asymmetric introduction of a functional group that can be easily transformed into other functional groups would be advantageous to previous approaches. If the subsequent transformation occurs without erosion of enantiomeric excess, this protocol would allow rapid access to a wide range of chiral, nonracemic compounds in high enantiopurity (Scheme 1.9).

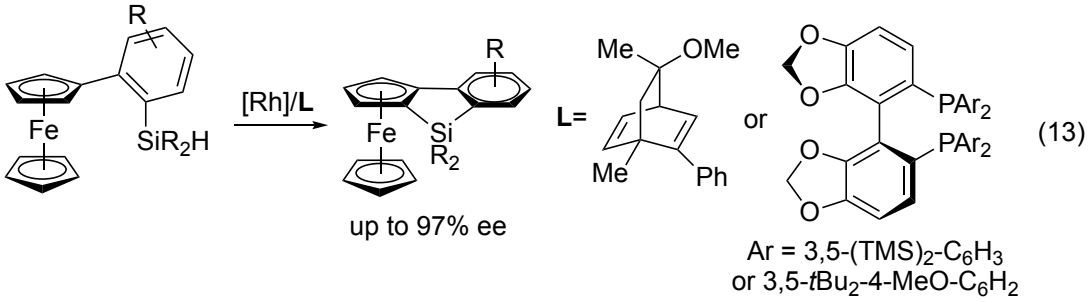
**Scheme 1.9** Asymmetric C–H bond functionalization that introduces a functional group that is suitable for further functionalization




In order to develop such reactions, we sought to develop asymmetric silylations of C–H bonds. Organosilane compounds are inexpensive, stable and nontoxic.[119] Silyl groups can be easily transformed into other functional groups by following standard literature protocols. Organosilanes can undergo cross-coupling with electrophiles to form carbon-carbon bonds,[120,121] oxidations,[122,123] halogenations,[124,125] aminations,[126,127] and trifluoromethylation.[128] For these reasons, many groups have investigated catalytic silylation of aryl and alkyl C−H bonds. The scope, mechanism, and applications of the silylation of C−H bonds have been previously reviewed.[33] However, the development of asymmetric version of this process has lagged.

Prior to our contributions that will be discussed in the following chapters, only two asymmetric silylations of C–H bonds have been reported. Takai and coworkers reported an asymmetric Rh-catalyzed silylation of C–H bonds to set a stereogenic silicon center of a spirocyclic silane with up to 88% ee (eq 12).[92,93] Shibata, He and Takai reported the silylation of C–H bonds in ferrocenes to generate planar chiral compounds with moderate to high ee's (eq 13).[95-97] However, these reports have not demonstrated the potential of enantioenriched organosilanes as a precursor to more conventional chiral compounds that contain stereogenic carbon. Therefore, these prior reactions are unlikely to be useful in medicinal chemistry, and the tetraalkylsilanes products formed in these reports are not amenable to further transformations.




The following chapters describe our contributions to the development of enantioselective silylation of unactivated C–H bonds and demonstrate the synthetic utility of these compounds.

## 1.4 References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# CHAPTER 2

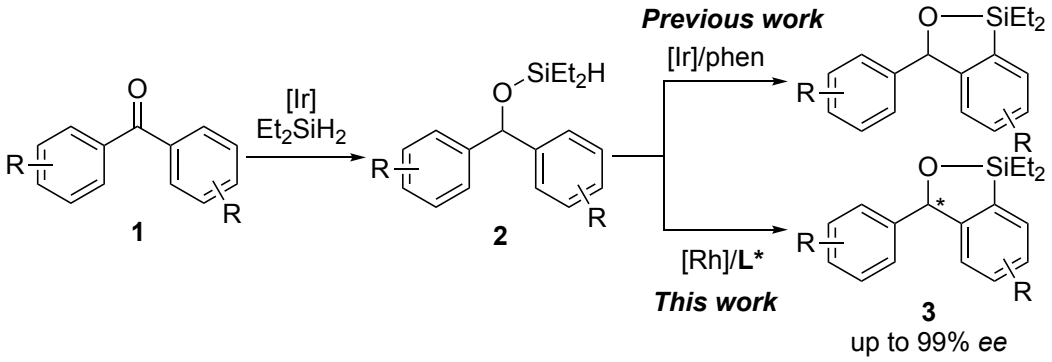
## Rhodium-Catalyzed Enantioselective Silylation of Aryl C–H bonds: Desymmetrization of Diarylmethanols

## 2.1 Introduction

The functionalization of C–H bonds with main group reagents, such as boranes and silanes, has become a commonly practiced synthetic method due to the high regioselectivity of the reaction and diverse applications of the products.[1,2] Although some of these reactions generate chiral products, setting stereogenic carbon atoms by the enantioselective functionalization of a C–H bond with such main group reagents has not been achieved. As described in Chapter 1, Takai reported an asymmetric Rh-catalyzed C–H silylation reaction to set a stereogenic silicon center of a spirocyclic silane with up to 88% ee,[3,4] and Shibata, He and Takai reported the silylation of C–H bonds in ferrocenes to generate planar chiral compounds with moderate to high ee's.[5-7] However, the application of the silylation to enantioselective formation of molecules related to products more commonly used in medicinal chemistry has not been reported.

In 2010, Simmons and Hartwig reported the iridium-catalyzed silylation of aromatic C–H bonds to form benzoxasiloles[8]. In this reaction, a (hydrido)silyl group is generated *in situ* from dehydrogenative silylation of an alcohol or hydrosilylation of a ketone and serves as the directing element for C–H activation of the arene (Scheme 1). Benzophenone, a substrate containing enantiotopic phenyl rings, underwent the C-H silylation, creating the potential to develop an enantioselective version of this process. With the appropriate combination of a metal precursor and chiral ligand, an enantioselective C–H silylation could be performed to set the stereogenic carbon of a diarylmethanol.

**Scheme 2.1** (Hydrido)silyl-directed functionalization of aryl C–H bonds




Chiral diarylmethanols are an important pharmacophore and can be found in biologically active compounds such as lapaquistat[9] and KAT 2003[10] (Figure 2.1). Enantioenriched diarylmethanols can be synthesized by asymmetric reduction of benzophenone derivatives or by asymmetric addition of aryl organometallic reagents to aldehydes.[11-17] Enantioselecitve C–H bond functionalization of diarylmethanols with silane reagents would be an alternative, mild, catalytic route to this class of compound.

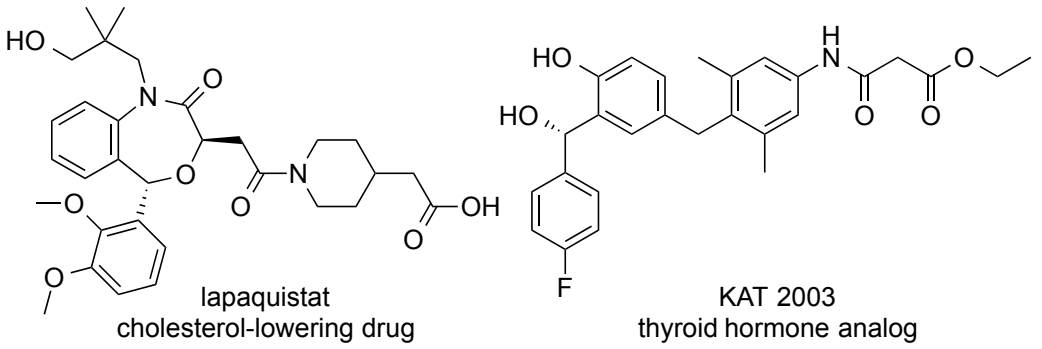


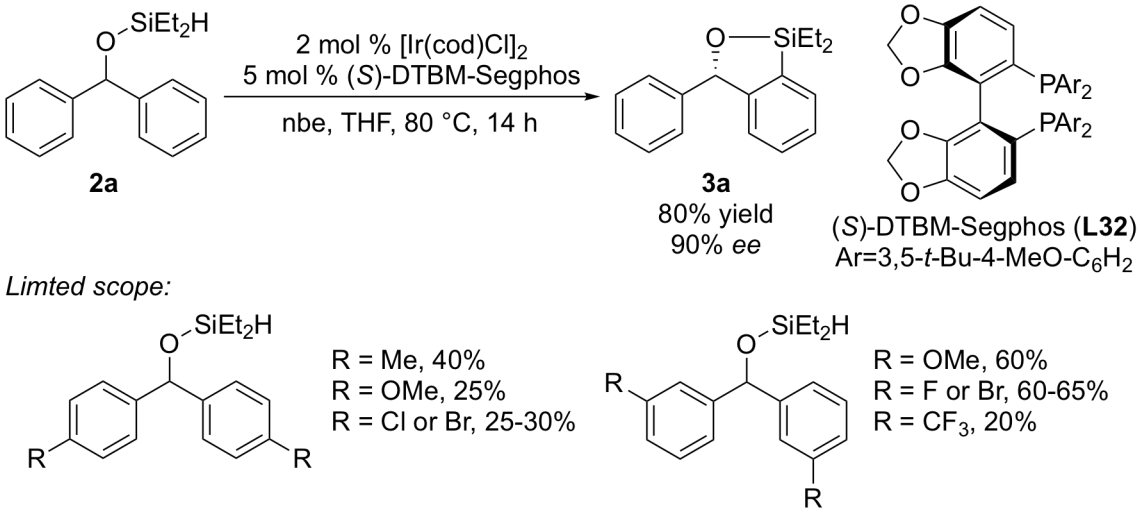

**Figure 2.1** Two enantiopure medicinally active compounds containing chiral diarylmethanol motifs.

We report catalysts and conditions for such enantioselective silylation. The combination of hydrosilylation of benzophenone or its derivatives and intramolecular silylation of the resulting silyl ether creates chiral, non-racemic diarylmethanols in high enantiopurity. This stereoselective process also enables the site-selective functionalization of enantioenriched chiral diaryl methanols. The products of these functionalization reactions are suitable for a range of transformations at the C-Si bond.

## 2.2 Results and Discussion

On the basis of previous iridium-catalyzed intramolecular silylation of C–H bonds, we focused initially on potential iridium catalysts containing chiral nitrogen, phosphine-nitrogen and bisphosphine ligands for enantioselective C–H silylation (Scheme 2.2). We found that the combination of $[Ir(cod)Cl]_2$ and (*S*)-DTBM-Segphos (**L32**) provided **3a** in 90% ee and 80% yield. However, this system required temperatures higher than 80 °C with 4 mol % catalyst loading to form the desired product in good

**Scheme 2.2** Initial results on iridium-catalyzed asymmetric silylation of aryl C–H bonds



yields. In addition, the reaction under these conditions gave high yields and ee's only with unsubstituted benzophenone.

To address these limitations, we tested rhodium catalysts, instead of iridium catalysts, based on prior intramolecular silylations of arenes and alkanes, albeit at high temperatures, published by Takai.[18,19] Indeed, we found that the combination of $[Rh(cod)Cl]_2$ and DTBM-Segphos (**L32**) catalyzes the silylation of **2a** at 50 °C to give **3a** in 90% ee with complete conversion. This preliminary result led to the finding that Rh-bisphosphine complexes catalyze intermolecular silylations of aromatic C–H bonds at only 45 °C with 2 mol % catalyst.[20] However, the scope of the reaction catalyzed by $[Rh(cod)Cl]_2$ and DTBM-Segphos was similarly narrow, even though the reaction occurred at lower temperature.

To identify a catalyst that would react with a broader range of diarylmethanols, we evaluated the reaction of substituted and unsubstituted diarylmethyl silyl ethers (**2a** and **2j**) catalyzed by 5 mol % $[Rh(cod)Cl]_2$ and 58 commercially available bisphosphines, phosphine-nitrogen ligands and dinitrogen ligands (Figures 2.2 and 2.3) The reactions were conducted with 2 equivalents of norbornene as a hydrogen acceptor at 50 °C in THF. In contrast to the catalyst generated from DTBM-Segphos (**L32**), which was active and selective for reaction of only substrate **2a**, the rhodium complexes derived from members of the Walphos (**L15-L22**) and catASium (**L46-47**) classes of ligands generated catalysts that formed the desired silylation products with high ee's for both of the test

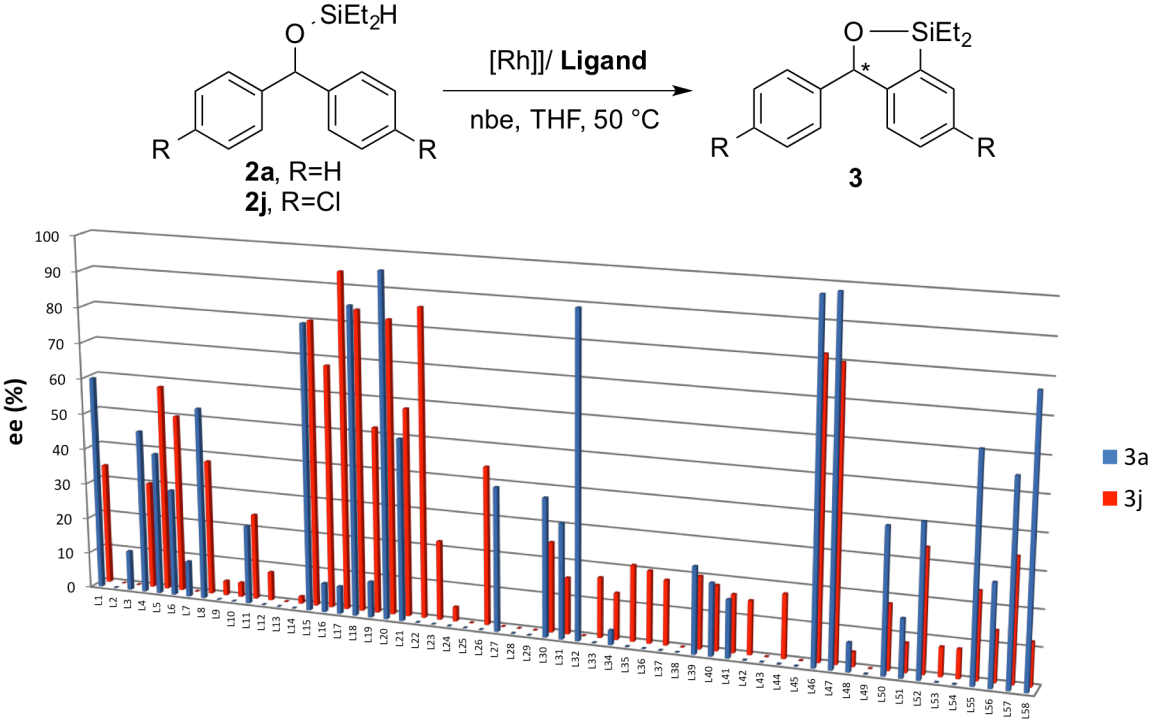



**Figure 2.2** Results from evaluation of 58 ligands for the asymmetric silylation of diaryl methanols **2a** and **2j** (% ee). Conditions: $[Rh(cod)Cl]_2$ (2.5 mol %), ligand (5 mol %), nbe (2 equiv), THF, 50 °C. List of selected ligand categories: Josiphos class (**L1**–**L12**), Walphos class (**L15**–**L22**), Segphos class (**L30**–**L33**), catASium class (**L46**–**L47**)

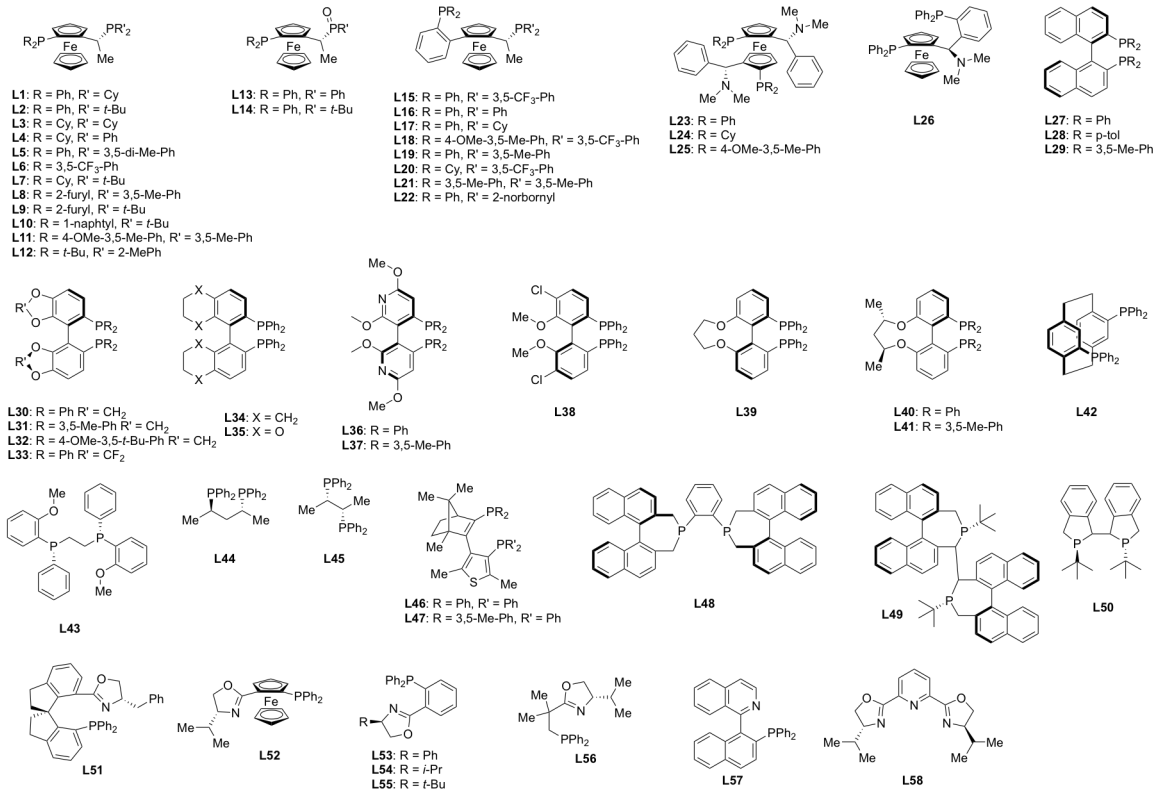


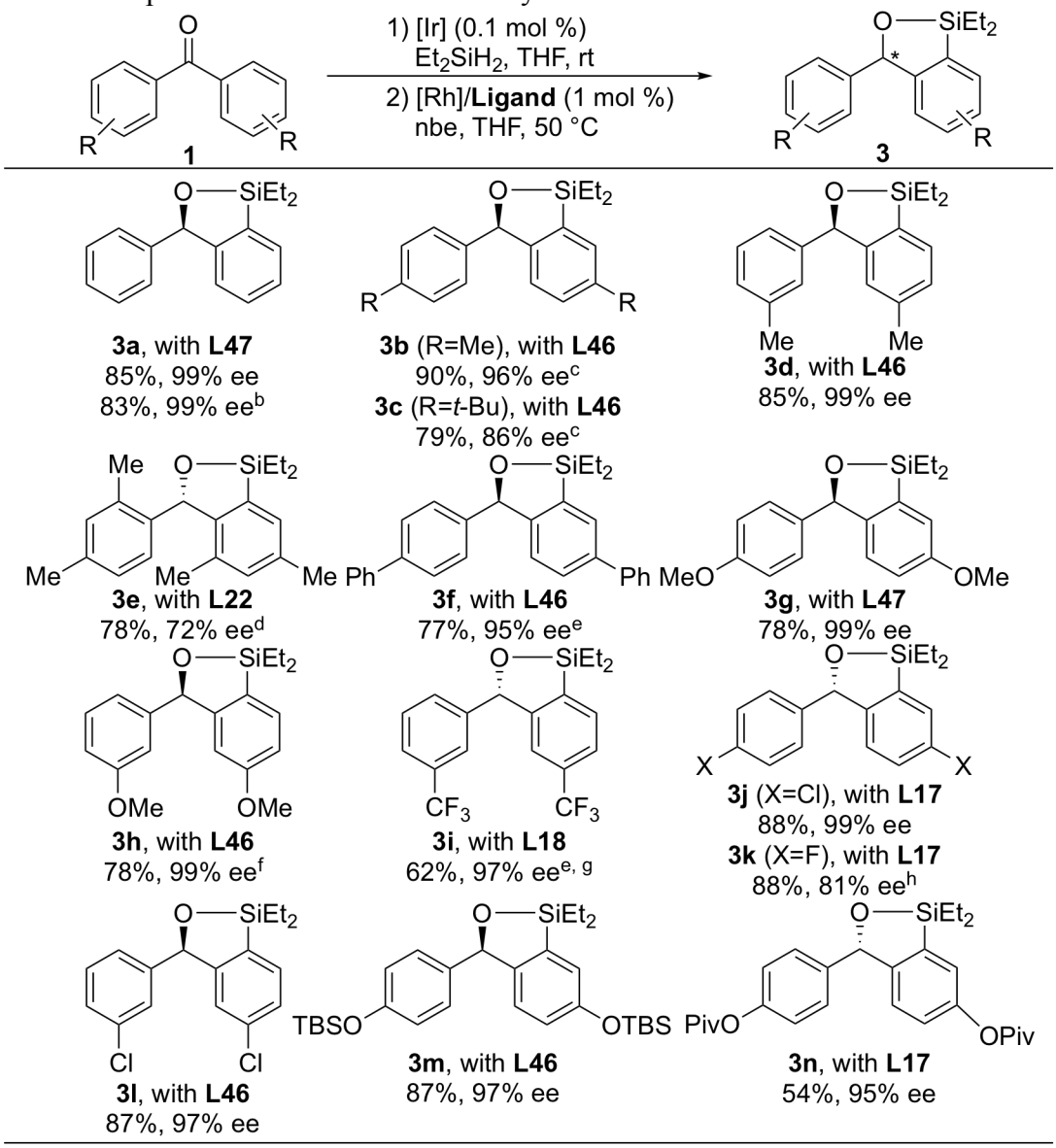

**Figure 2.3** Structures of the ligands used for the Rh-catalyzed enantioselective C–H silylation

substrates and a range of additional diarylmethyl silyl ethers (*vide infra*). The highest enantioselectivity (99% ee) for reaction of diarylmethyl silyl ether **2a** was obtained with catalysts containing the catASium ligands (**L46**, **L47**), but when the catalyst containing the catASium ligands gave the product in low yield or stereoselectivity, those containing the Walphos ligands (**L17**, **L18**, **L22**) gave the desired products in high yields and enantioselectivities. In general, we observed that the catalysts generating large amounts of byproducts also reacted with low ee.[21] Finally, the reaction occurred with equivalent enantioselectivities and yields when it was conducted with a lower loading of catalyst (1 mol %) and a smaller number of equivalents of norbornene (1.2 equiv) as when it was conducted with 5 mol % of catalyst and 2 equiv of norbornene.

The scope of the Rh-catalyzed asymmetric silylation is shown in Table 2.1. Hydrosilylation of benzophenones **1a**–**n** with diethylsilane catalyzed by 0.05 mol % $[Ir(cod)OMe]_2$ formed (hydrido)silyl ethers **2a**–**n**. In the presence of 1.0 mol % of both $[Rh(cod)Cl]_2$ and ligand with 1.2 equiv of norbornene as an $H_2$ acceptor, a wide range of the silyl ethers were converted to benzoxasiloles (**3a-n**) in good-to-excellent yields with excellent enantioselectivity (Table 2.1).[22] For the reaction of each substrate, ligands **L17**, **L18**, **L22, L46** and **L47** were examined to determine which ligand provided the highest yield and ee. Unsubstituted benzophenone (**1a**) and alkyl or aryl-substituted benzophenones containing *meta* and *para* substituents (**1b-1d**, **1f**) yielded the desired products in high yields (77-90%) and good-to-excellent enantioselectivities (86-99% ee) with either **L46** or **L47**. Variation of the electronic properties of the arene had little

influence on the yield and ee (**1g-1i**). Although silyl ethers containing aryl bromides formed substantial amounts of byproducts resulting from protodebromination, those substituted with a chloro group (**1j**, **1l**) or a fluoro group (**1k**) reacted in good yield and good-to-excellent ee. In addition, functional groups containing oxygen, such as silyl ethers (**1m**) and esters (**1n**), were tolerated under the reaction conditions. However,

**Table 2.1** Scope of enantioselective C–H silylation[a]

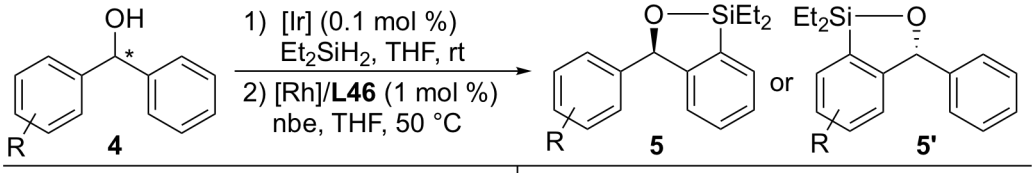


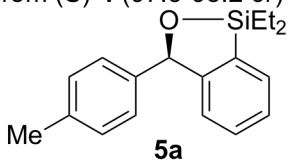
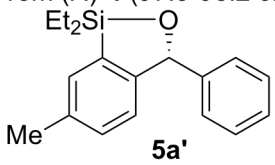
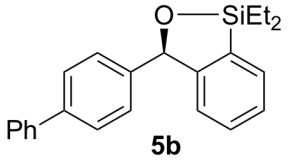
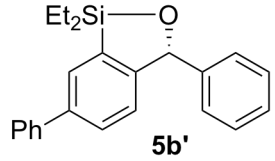
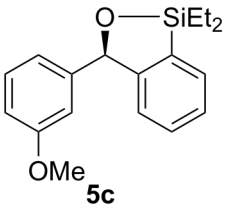
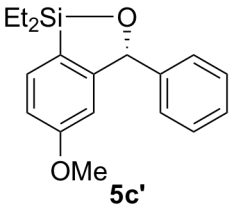
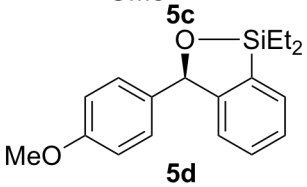
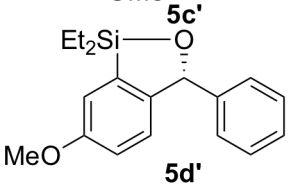
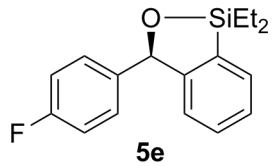
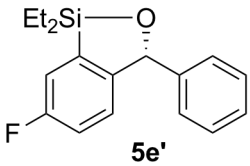

[a]Isolated yields for reactions conducted on a 1.0 mmol scale following purification by silica gel chromatography. The ee values were determined by chiral HPLC analysis. The absolute configuration was assigned by analogy. [b]5.0 mmol scale. [c]The ee values were determined after iodination. [d]The reaction was conducted at 80 °C. [e]0.1 mol % $[Ir(cod)OMe]_2$ was used for the first step. [f]The corresponding diarylmethanol was used as a substrate. [g]The ee value was determined after Tamao-Fleming oxidation. [h]The reaction was conducted at room temperature.

reactions with a substrate bearing substituents at the *ortho*- positions (**1e**) required a higher temperature to reach full conversion, and a lower ee of 72% was observed. Finally, this reaction occurred with 5 mmol of substrate to provide more than 1 g of the enantioenriched benzoxasilole (**3a**) in a yield and ee similar to those of the reactions conducted on a 1 mmol scale.

Nonracemic chiral catalysts can react with two enantiomers of a substrate to form two constitutional isomers of the products selectively.[23,24] We exploited the high

**Table 2.2** Scope of site-selective C–H silylation[a]




| From (*S*)-**4** (97:3-98:2 *er*) | | From (*R*)-**4** (97:3-98:2 *er*) | |
|---|---|---|---|
|  **5a** | 77%[b] **5a**:**5a'** = 96:4 |  **5a'** | 73%[b] **5a**:**5a'** = 4:96 |
|  **5b** | 84%[c] **5b**:**5b'** = 96:4 |  **5b'** | 78%[c] **5b**:**5b'** = 7:93 |
|  **5c** | 79%[c] **5c**:**5c'** = 97:3[d] |  **5c'** | 84%[c] **5c**:**5c'** = 5:95[d] |
|  **5d** | 68%, 99% *ee*[c,e] **5d**:**5d'** = 92:8 |  **5d'** | 53%, 99% *ee*[c,e] **5d**:**5d'** = 9:91 |
|  **5e** | 72%[c] **5e**:**5e'** = 95:5[d] |  **5e'** | 81%[c] **5e**:**5e'** = 5:95[d] |

[a]Isolated yields of for reactions conducted on a 0.25 mmol scale following purification by silica gel chromatography. Combined yields of both constitutional isomers are reported. Regioisomeric ratio was determined by GC analysis of the crude reaction mixture unless otherwise noted. [b]The enantiomeric ratio (er) value of the starting material was 98:2. [c]The er value of the starting material was 97:3. [d]Regioisomeric ratio was determined by $^1$H NMR spectroscopy of the crude reaction mixture. [e]Isolated yield of the single isomer.

stereoselectivity of our C–H silylation reactions for site-selective silylations of enantioenriched diarylmethanols (Table 2.2). Selective C–H bond functionalization at one aryl group over the other of a chiral diarylmethanol in the absence of distinct steric properties is challenging. However, reaction of a (hydrido)silyl ether, prepared by dehydrogenative silylation of chiral diarylmethanol enantiomers **4**, in the presence of a highly enantioselective catalyst should convert the two enantiomers into the two different constitutional isomers **5** and **5'**, respectively. As shown in Table 2, the reaction of a variety of enantioenriched diarylmethanols occurs with high site selectivity controlled by the configuration of the catalyst. The (*S*)-enantiomer of **4** was transformed into **5** with high site-selectivity, while the (*R*)-enantiomer of **4** was transformed selectively into **5'**.

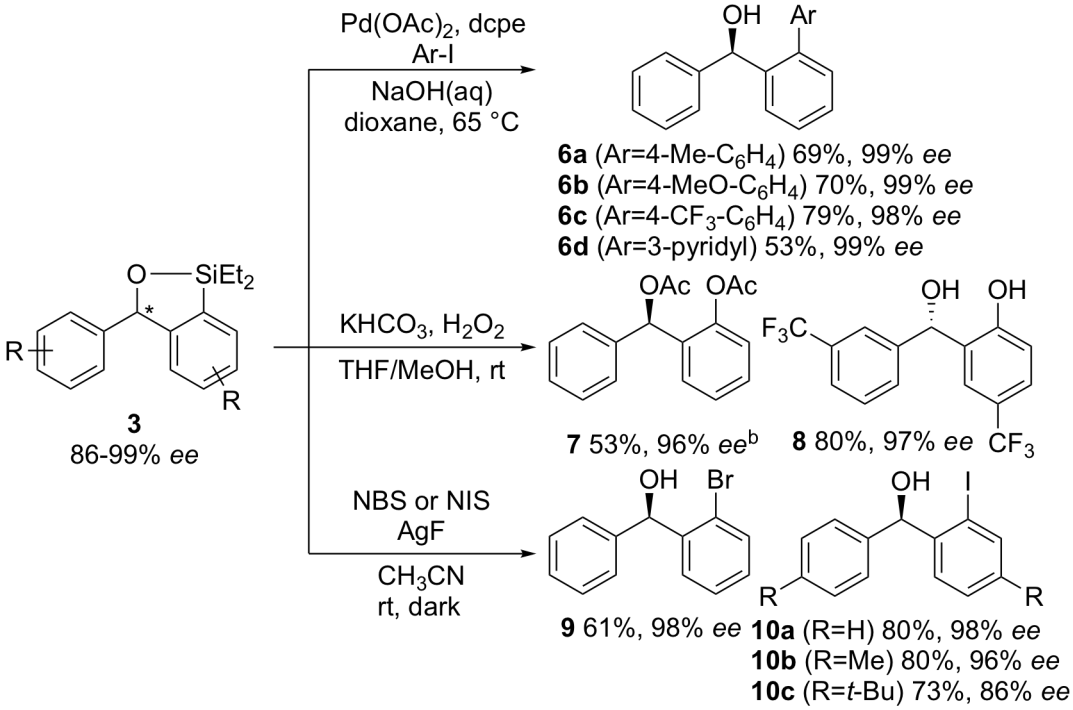
According to the Horeau principle, the enantiomeric excess amplifies as two enantioselective operations occur on the same substrate successively.[25] In our case, the synthesis of enantioenriched substrate **4** can be considered the first enantioselective operation of this scenario, and our silylation reaction the second enantioselective operation that improves the enantiomeric excess of the diarylmethanol **4**. Consistent with this reasoning, the enantiomeric excess of the constitutional isomers of products **5d** and **5d'** (>99% ee) were higher than those of the starting materials (94% ee). Thus, this method can be used to upgrade the enantiomeric excess of enantioenriched diarylmethanols.

The enantioenriched benzoxasiloles formed in these reactions are useful synthetic intermediates because the Ar–Si linkage can be converted into carbon–carbon or carbon–heteroatom bonds without any erosion of enantiomeric excess (Scheme 2.3). Under conditions developed for the coupling of silyl ethers,[8,26] Pd-catalyzed Hiyama cross-coupling of the enantioenriched products with aryl iodides formed benzoxasilole **3a** in good yields without any erosion of enantiomeric purity (98–99% ee). Electron-neutral (**6a**), electron-rich (**6b**) and electron-poor (**6c**) aryl iodides and a heteroaryl iodide (**6d**) were suitable coupling partners. In addition, the enantioenriched benzoxasiloles underwent Tamao-Fleming oxidation to form carbon–oxygen bonds. The treatment of benzoxasilole **3** with aqueous $H_2O_2$ and $KHCO_3$ gave diol products. Benzoxasiloles **3a** and **3i** were converted to diacetate **7** and diol **8**, respectively without any significant change in ee. Finally, halogenation of **3** in the presence of silver fluoride and *N*-halosuccinimide formed the brominated and iodinated diarylmethanols **9** and **10** in good yields while maintaining high ee.

## 2.3 Conclusions

In summary, we have shown that the silylation of aryl C–H bonds can create a new class of enantioselective C–H bond functionalization. The enantioselective silylation of aromatic C–H bonds directed by a (hydrido)silyl group we developed occurs in high yield with excellent enantioselectivity when catalyzed by the combination of $[Rh(cod)Cl]_2$ and chiral bisphosphine ligands from the Walphos and catASium family. In addition, we showed that this catalyst system is capable of the site-selective silylation of enantioenriched chiral diarylmethanols due to its strong catalyst control. Lastly, we

**Scheme 2.3** Functionalization of enantioenriched benzoxasiloles[a]




[a]Isolated yields for reactions following purification by silica gel chromatography. The ee values were determined by chiral HPLC analysis. The absolute configuration was assigned by analogy. [b]Diol product was acetylated with $Ac_2O$ before isolation.

demonstrated that the C–Si bond of the enantioenriched benzoxasiloles can be converted to C–C, C–O, C–I or C–Br bonds without erosion of enantiomeric excess.

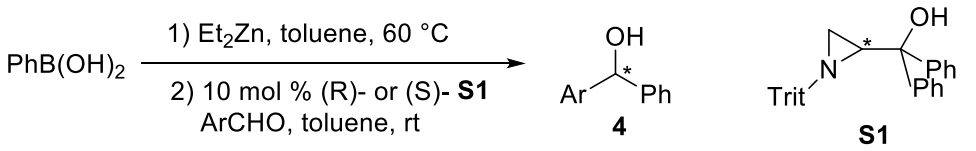
## 2.4 Experimental

### *2.4.1 Methods and Materials*

The silylation reactions were assembled in an $N_2$-filled glovebox using oven-dried glassware and were stirred with Teflon-coated magnetic stirring bars. $[Ir(cod)OMe]_2$ was obtained as a gift from Johnson Matthey or purchased from Strem and was used as received. $[Rh(cod)Cl]_2$ was either obtained as a gift from Johnson Matthey, purchased from Strem, or prepared from $[RhCl_3 \cdot xH_2O]$ according to the standard procedure.[27] CatASium® and Walphos ligands were purchased from Strem and were used as received. Diethylsilane ($Et_2SiH_2$) was purchased from Gelest and was used as received. Norbornene (nbe) was purchased from Aldrich and was used as received. Compounds **1h**, **1k**, **1l** and **S1** were prepared according to the literature procedures.[28-31] Tetrahydrofuran (THF) was degassed by purging with nitrogen and then dried with a solvent purification system containing activated alumina. All other solvents and reagents were used as received.

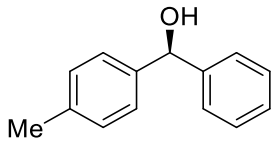
Reaction temperatures above 23 °C refer to temperatures of an aluminum heating block, which were controlled by an electronic temperature modulator. Silica gel chromatography was performed using a Teledyne Isco CombiFlash® $R_f$ system with Redi*Sep* $R_f$ Gold™ columns. $^1$H and $^{13}$C NMR spectra were recorded on Bruker AVB-400, AV-500 and AV-600 with $^{13}$C operating frequencies of 101 MHz, 125 MHz and 150 MHz, respectively. $^{19}$F NMR spectra were recorded on a Bruker AVQ-400 spectrometer with a $^{19}$F operating frequency of 376 MHz. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ = 7.26 for $^1$H NMR and δ = 77.0 for $^{13}$C NMR). High-resolution mass spectral data were obtained from the QB3/Chemistry Mass Spectrometry Facility, University of California, Berkeley. Chiral HPLC analysis was conducted on Waters or Shimadzu chromatography system. Racemic samples were obtained following the procedure reported by our group. [8]

*2.4.2 Synthesis of enantioenriched diarylmethanols*




The general conditions developed by Braga and modified by Jarvo were employed.[31,32] To a solution of phenylboronic acid (ca. 4.8 mmol) in toluene (10 mL) was added diethylzinc (14 mL, 15 mmol, 1.1 M in toluene), and the resulting solution was heated at 60 °C for 12 h. After cooling to room temperature, a solution of (*S*)- or (*R*)-(1-tritylaziridin-2-yl)diphenylmethanol **S1** (93.5 g, 0.200 mmol) in toluene (5 mL) was added. The reaction mixture was allowed to stir for 10 minutes before a solution of the corresponding aldehyde (ca. 2.0 mmol) in toluene (5 mL) was added. The reaction was stirred for 12 h at room temperature, at which time it was quenched by careful addition of 1 N HCl (10 mL). The resulting mixture was diluted with water (20 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$) and concentrated. The crude product was purified by silica gel chromatography.

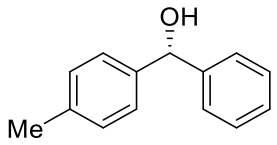
**(*S*)-(4-Tolyl)phenylmethanol 4a**




Following the general procedure, 4-tolualdehyde (241 mg, 2.01 mmol) was allowed to react with phenyl boronic acid and (*S*)-**S1**. The crude product was purified by silica gel chromatography (100:0→80:20 hexanes/EtOAc) to give 353 mg (89% yield) of (*S*)-**4a** as a white solid. **HPLC analysis**: 98:2 er, Chiralcel OD-H column, 10% isopropanol in hexane, 1.0 mL/min flow rate, 220 nm UV lamp, $t_R$ = 20.5 min (major), $t_R$ = 21.6 min

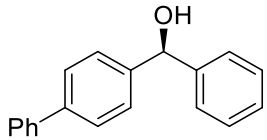
(minor). $[\alpha]_D^{25}$ = -8.1 (c 1.05, $CHCl_3$). **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.38 (d, J = 7.4 Hz, 2H), 7.33 (t, J = 7.6 Hz, 2H), 7.28 – 7.24 (m, 3H), 7.15 (d, J = 7.9 Hz, 2H), 5.83 (d, J = 3.3 Hz, 1H), 2.33 (s, 3H), 2.15 (d, J = 3.5 Hz, 1H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 143.9, 140.9, 137.0, 129.0, 128.3, 127.2, 126.4, 126.4, 75.8, 21.0. ($^1$H and $^{13}$C NMR data and $[\alpha]_D^{25}$ value were consistent with previously reported values.[31])

**(*R*)-(4-Tolyl)phenylmethanol 4a**



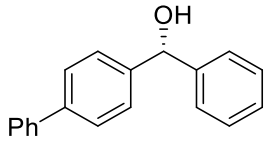

Following the general procedure, 4-toluadehyde (242 mg, 2.01 mmol) was allowed to react with phenyl boronic acid and (*R*)-**S1**. The crude product was purified by silica gel chromatography (100:0→80:20 hexanes/EtOAc) to give 372 mg (94% yield) of (*R*)-**4a** as a white solid, which gave $^1$H and $^{13}$C NMR data data identical to that of (*S*)-**4a**. **HPLC analysis**: 98:2 er, Chiralcel OB-H column, 10% isopropanol in hexane, 1.0 mL/min flow rate, 220 nm UV lamp, $t_R$ = 10.9min (major), $t_R$ = 13.3 min (minor). $[\alpha]_D^{25}$ = +7.8 (c 0.98, $CHCl_3$).

**(*S*)-(4-Biphenyl)phenylmethanol 4b**



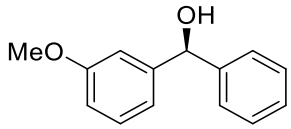

Following the general procedure, biphenyl-4-carboxaldehyde (368 mg, 2.02 mmol) was allowed to react with phenyl boronic acid and (*S*)-**S1**. The crude product was purified by silica gel chromatography (100:0→80:20 hexanes/EtOAc) and then recrystallized from ethyl acetate and hexanes to give 437 mg (84% yield) of (*S*)-**4b** as a white solid. **HPLC analysis**: 97:3 er, Chiralcel OD-H column, 6% isopropanol in hexane, 0.8 mL/min flow rate, 220 nm UV lamp, $t_R$ = 33.7 min (major), $t_R$ = 36.3 min (minor). $[\alpha]_D^{25}$ = +7.1 (c 1.05, $CHCl_3$). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.61 – 7.54 (m, 4H), 7.50 – 7.39 (m, 6H), 7.39 – 7.33 (m, 3H), 7.33 – 7.26 (m, 1H), 5.91 (d, J = 2.9 Hz, 1H), 2.25 (s, 1H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 143.7, 142.8, 140.7, 140.4, 128.7, 128.5, 127.6, 127.3, 127.2, 127.0, 126.9, 126.5, 76.0. ($^1$H and $^{13}$C NMR data and $[\alpha]_D^{25}$ value were consistent with previously reported values.[32])

**(*R*)-(4-Biphenyl)phenylmethanol 4b**



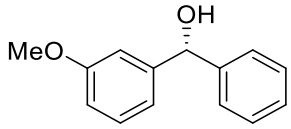

Following the general procedure, biphenyl-4-carboxaldehyde (370 mg, 2.03 mmol) was allowed to react with phenyl boronic acid and (*R*)-**S1**. The crude product was purified by silica gel chromatography (100:0→80:20 hexanes/EtOAc) to give 455 mg (87% yield) of (*S*)-**4b** as a white solid, which gave $^{1}$H and $^{13}$C NMR data data identical to that of (*S*)-**4b**. **HPLC analysis**: 97:3 er, Chiralcel OB-H column, 5% isopropanol in hexane, 1.0 mL/min flow rate, 220 nm UV lamp, $t_R$ = 42.4 min (major), $t_R$ = 67.0 min (minor). $[\alpha]_D^{25}$ = -6.8 (c 1.02, $CHCl_3$).

**(*S*)-(3-Methoxyphenyl)phenylmethanol 4c**




Following the general procedure, 3-anisaldehyde (272 mg, 2.00 mmol) was allowed to react with phenyl boronic acid and (*S*)-**S1**. The crude product was purified by silica gel chromatography (100:0→80:20 hexanes/EtOAc) to give 320 mg (75% yield) of (*S*)-**4c** as a pale colorless oil. **HPLC analysis**: 97:3 er, Chiralpak IB column, 5% isopropanol in hexane, 0.8 mL/min flow rate, 220 nm UV lamp, $t_R$ = 17.5 min (minor), $t_R$ = 23.7 min (major). $[\alpha]_D^{25}$ = +15.3 (c 1.01, $CHCl_3$). **$^{1}$H NMR** (600 MHz, $CDCl_3$) δ 7.39 (d, J = 7.6 Hz, 2H), 7.34 (t, J = 7.2 Hz, 2H), 7.29 – 7.23 (m, 2H), 6.98 – 6.93 (m, 2H), 6.81 (d, J = 8.2 Hz, 1H), 5.82 (s, 1H), 3.79 (s, 3H), 2.19 (s, 1H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 159.5, 145.4, 143.6, 129.4, 128.4, 127.4, 126.4, 118.8, 112.8, 112.0, 75.9, 55.1. ($^{1}$H and $^{13}$C NMR data and $[\alpha]_D^{25}$ value were consistent with previously reported values.[33])

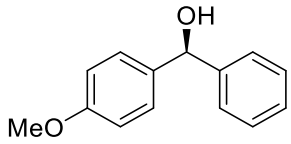
**(*R*)-(4-Methoxyphenly)phenylmethanol 4c**




Following the general procedure, 3-anisadehyde (243 mg, 2.01 mmol) was allowed to react with phenyl boronic acid and (*R*)-**S1**. The crude product was purified by silica gel chromatography (100:0→80:20 hexanes/EtOAc) to give 396 mg (92% yield) of (*R*)-**4c** as a pale colorless oil, which gave $^{1}$H and $^{13}$C NMR data identical to that of (*S*)-**4c**. **HPLC analysis**: 97:3 er, Chiralpak IB column, 10% isopropanol in hexane, 1.0 mL/min flow

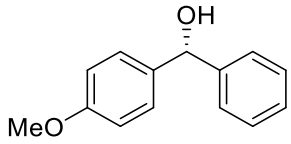
rate, 220 nm UV lamp, $t_R$ = 17.8 min (minor), $t_R$ = 24.0 min (major). $[\alpha]_D^{25}$ = -14.9 (c 1.02, $CHCl_3$).

**(*S*)-(4-Methoxyphenyl)phenylmethanol 4d**



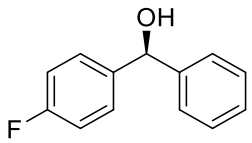

Following the general procedure, 4-anisaldehyde (273 mg, 2.01 mmol) was allowed to react with phenyl boronic acid and (*S*)-**S1**. The crude product was purified by silica gel chromatography (100:0→80:20 hexanes/EtOAc) to give 321 mg (75% yield) of (*S*)-**4d** as a pale colorless oil. **HPLC analysis**: 97:3 er, Chiralcel AD-H column, 10% isopropanol in hexane, 1.0 mL/min flow rate, 220 nm UV lamp, $t_R$ = 10.9 min (minor), $t_R$ = 11.8 min (major). $[\alpha]_D^{25}$ = -15.1 (c 1.01, $CHCl_3$). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 4H), 7.31 – 7.24 (m, 3H), 6.87 (d, J = 8.7 Hz, 2H), 5.82 (d, J = 2.8 Hz, 1H), 3.79 (s, 3H), 2.14 (d, J = 3.3 Hz, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 158.8, 144.0, 136.1, 128.3, 127.8, 127.3, 126.3, 113.7, 75.6, 55.1. ($^1$H and $^{13}$C NMR data and $[\alpha]_D^{25}$ value were consistent with previously reported values.[33])

**(*R*)-(4-Methoxyphenly)phenylmethanol 4d**




Following the general procedure, 4-anisadehyde (242 mg, 2.01 mmol) was allowed to react with phenyl boronic acid and (*R*)-**S1**. The crude product was purified by silica gel chromatography (100:0→80:20 hexanes/EtOAc) to give 338 mg (79% yield) of (*R*)-**4d** as a pale colorless oil, which gave $^1$H and $^{13}$C NMR data data identical to that of (*S*)-**4d**. **HPLC analysis**: 97:3 er, Chiralcel AD-H column, 10% isopropanol in hexane, 1.0 mL/min flow rate, 220 nm UV lamp, $t_R$ = 11.0 min (major), $t_R$ = 11.8 min (minor). $[\alpha]_D^{25}$ = +14.3 (c 1.04, $CHCl_3$).

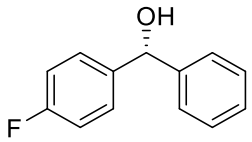
**(*S*)-(4-Fluorophenyl)phenylmethanol 4e**




Following the general procedure, 4-fluorobenzaldehyde (248 mg, 2.00 mmol) was allowed to react with phenyl boronic acid and (*S*)-**S1**. The crude product was purified by silica gel chromatography (100:0→80:20 hexanes/EtOAc) to give 343 mg (85% yield) of (*S*)-**4e** as a colorless oil, which solidified upon seating. **HPLC analysis**: 97:3 er,

Chiralpak IB column, 5% isopropanol in hexane, 0.8 mL/min flow rate, 220 nm UV lamp, $t_R$ = 15.0 min (minor), $t_R$ = 15.6 min (major). $[\alpha]_D^{25}$ = +7.1 (c 1.05, $CHCl_3$). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 6H), 7.31 – 7.26 (m, 1H), 7.02 (t, J = 8.7 Hz, 2H), 5.84 (d, J = 2.7 Hz, 1H), 2.22 (d, J = 3.3 Hz, 1H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 162.1 (d, *J* = 246 Hz), 143.6, 139.5 (d, *J* = 3.0 Hz), 128.5, 128.2 (d, *J* = 8.1 Hz), 127.7, 126.4, 115.2 (d, *J* = 21.4 Hz), 75.6. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -114.23. ($^1$H and $^{13}$C NMR data and $[\alpha]_D^{25}$ were consistent with previously reported values.[33])

**(*R*)-(4-Fluorophenyl)phenylmethanol 4e**

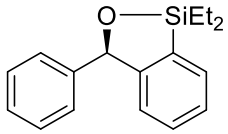



Following the general procedure, 4-fluorobenzaldehyde (249 mg, 2.01 mmol) was allowed to react with phenyl boronic acid and (*R*)-**S1**. The crude product was purified by silica gel chromatography (100:0→80:20 hexanes/EtOAc) to give 347 mg (86% yield) of (*R*)-**4e** as a colorless oil, which gave $^1$H and $^{13}$C NMR data data identical to that of (*S*)-**4e**. **HPLC analysis**: 97:3 er, Chiralcel OB-H column, 20% isopropanol in hexane, 1.0 mL/min flow rate, 220 nm UV lamp, $t_R$ = 15.5 min (major), $t_R$ = 21.2 min (minor). $[\alpha]_D^{25}$ = –6.8 (c 1.02, $CHCl_3$).

*2.4.3 General procedure for enantioselective intramolecular arene silylation*

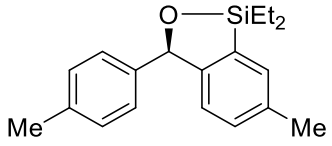
In an $N_2$-filled glovebox, ca. 1.0 mmol of the benzophenone was weighed into a 1 dram screw-top vial. A stir bar was added, and the substrate was dissolved in THF (0.50 mL). The resulting solution was treated first with a freshly prepared stock solution of $[Ir(cod)OMe]_2$ (0.5 μmol, 0.05 mol %) in THF (0.50 mL) and then neat $Et_2SiH_2$ (1.20 mmol). The vial was capped with a Teflon-lined screw-cap, and the resulting solution was stirred in the glovebox at rt until complete conversion to the corresponding diethyl(hydrido)silyl ether was observed, as determined by GC-MS analysis (typically 12 h). The volatile materials were then removed by placing the reaction mixture directly under high-vacuum for 1 h (the stir bar was temporarily removed during this operation to prevent bumping). The stir bar was replaced, and the concentrated diethyl(hydrido)silyl ether was then sequentially treated with norbornene (1.20 mmol), THF (1.0 mL) and a freshly prepared stock solution of $[Rh(cod)Cl]_2$ (5 μmol, 0.50 mol %) and the corresponding ligand (12.5 μmol, 1.25 mol %) in THF (1.0 mL) . The Teflon-lined screw-cap was replaced, and the resulting solution was stirred in the glovebox for 1 h (to ensure complete formation of the active Rh species). The vial was then removed from the glovebox, placed in a pre-heated aluminum heating block at 50 °C. After the cyclization was complete (as determined by GC-MS analysis), the reaction mixture was allowed to cool to rt, and the solvent was removed via rotary evaporation. The crude product was purified by silica gel chromatography.

**Benzoxasilole 3a**



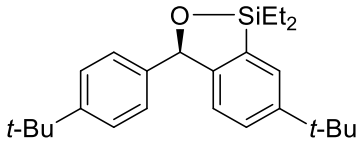

Following the general procedure, benzophenone (182 mg, 1.00 mmol) was converted to the corresponding diethyl(hydrido)silyl ether using $[Ir(cod)OMe]_2$ (0.05 mol %) at rt. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/**L47** (1.0 mol %) at 50 °C for 5 h. Concentration of the reaction mixture, adsorption of the resulting residue onto Celite, and purification by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 229 mg (85%) of **3a** as a colorless oil, which solidified during the storage. Following the general procedure for silylation on 5.0 mmol scale with $[Rh(cod)Cl]_2$/**L47** (1.0 mol %) as catalyst, 917 mg (5.03 mmol) of benzophenone was converted to the corresponding diethyl(hydrido)silyl ether and allowed to cyclize at 50 °C for 9 h. Purification by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 1.13 g (83%) of **3a** as a colorless oil. **HPLC analysis**: 99% *ee*, Chiralcel OJ-H column, 1% isopropanol in hexane, 1.0 mL/min flow rate, 220 nm UV lamp, $t_R$ = 11.0 min (major), $t_R$ = 17.5 min (minor). $[\alpha]_D^{25}$ = -111 (c 1.00, $CHCl_3$). **$^1$H NMR** (400 MHz, Chloroform-d) δ 7.61 (dd, *J* = 5.6, 2.6 Hz, 1H), 7.38 – 7.23 (m, 7H), 7.02 (dd, *J* = 5.6, 2.6 Hz, 1H), 6.16 (s, 1H), 1.07 (t, *J* = 7.6 Hz, 3H), 1.03 – 0.82 (m, 7H). **$^{13}$C NMR** (101 MHz, CDCl3) δ 153.0, 143.7, 133.4, 131.2, 129.7, 128.4, 127.8, 127.3, 126.9, 123.7, 84.2, 7.2, 6.9, 6.8, 6.5. ($^1$H and $^{13}$C NMR data were consistent with previously reported values.[8])

**Benzoxasilole 3b**



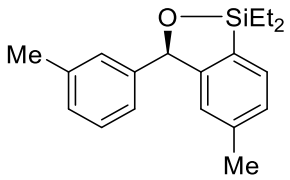

Following the general procedure, 4,4'-dimethylbenzophenone (211 mg, 1.00 mmol) was converted to the corresponding diethyl(hydrido)silyl ether at rt using $[Ir(cod)OMe]_2$ (0.05 mol %) as catalyst. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/**L46** (1.0 mol %) at 50 °C for 6 h. Concentration of the reaction mixture, adsorption of the resulting residue onto Celite, and purification by silica gel chromatography (100:0→ 90:10 hexanes/EtOAc) gave 267 mg (90%) of **3b** as an yellow oil. The enantiomeric excess was determined after iodination (96% *ee*, see below). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.21 – 7.13 (m, 5H), 6.92 (d, *J* = 7.9 Hz, 1H), 6.12 (s, 1H), 2.40 (s, 3H), 2.35 (s, 3H), 1.08 (t, *J* = 7.1 Hz, 3H), 1.05 – 0.83 (m, 7H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 150.4, 141.0, 137.2, 136.2, 133.5, 131.4, 130.7, 129.0, 127.2, 123.5, 83.9, 21.0 (*two overlapping resonances*), 7.2, 6.9, 6.8, 6.5. **HRMS** (EI+) calcd for $[C_{19}H_{24}OSi]^+$: *m/z* 296.1596, found 296.1598.

**Benzoxasilole 3c**



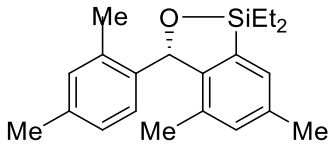

Following the general procedure, 4,4'-di-*tert*-butylbenzophenone (244 mg, 1.00 mmol) was converted to the corresponding diethyl(hydrido)silyl ether at rt using $[Ir(cod)OMe]_2$ (0.05 mol %) as catalyst. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/**L46** (1.0 mol %) at 50 °C for 16 h. Concentration of the reaction mixture, adsorption of the resulting residue onto Celite, and purification by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 300 mg (79%) of **3c** as an yellow oil. The enantiomeric excess was determined after iodination (86% *ee*, see below). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.62 (d, J = 1.7 Hz, 1H), 7.43 – 7.34 (m, 3H), 7.26 (d, *J* = 8.3 Hz, 2H), 7.01 (d, *J* = 8.2 Hz, 1H), 6.14 (s, 1H), 1.37 (s, 9H), 1.33 (s, 9H), 1.11 (t, *J* = 7.6 Hz, 3H), 1.07 – 0.86 (m, 7H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 150.5, 150.3, 149.5, 140.9, 133.3, 127.4, 127.2, 126.9, 125.3, 123.2, 83.8, 34.6, 34.5, 31.5, 31.3, 7.3, 7.0, 6.9, 6.6. **HRMS** (EI+) calcd for $[C_{25}H_{36}OSi]^+$: *m/z* 380.2535, found 380.2526.

**Benzoxasilole 3d**



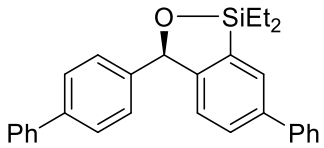

Following the general procedure, 3,3'-dimethylbenzophenone (209 mg, 0.996 mmol) was converted to the corresponding diethyl(hydrido)silyl ether at rt using $[Ir(cod)OMe]_2$ (0.05 mol %) as catalyst. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/**L46** (1.0 mol %) at 50 °C for 17 h. Concentration of the reaction mixture, adsorption of the resulting residue onto Celite, and purification by silica gel chromatography (100:0→95:5 hexanes/EtOAc) gave 251 mg (85%) of **3d** as a clear oil **HPLC analysis**: 99% *ee*, LUX Amylose-2 150 x 2 mm 3µ column, 5mM ammonioum acetate 63% in acetonitrile, 0.3 mL/min flow rate, 220 nm UV lamp, $t_R$ = 22.5 min (minor), $t_R$ = 24.9 min (major). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 7.5Hz, 1H), 7.24 (t, *J* = 7.5Hz, 1H), 7.17-7.05 (m, 4H), 6.85 (m, 1H), 6.09 (s, 1H), 2,35 (s, 3H), 2.31 (s, 3H), 1.12-1.05 (m, 3H), 1.04-0.80 (m, 7H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 153.7, 143.9, 139.9, 138.2, 131.2, 130.2, 128.7, 128.5, 128.3 (*two overlapping resonances*), 124.6, 124.5, 84.4, 21.7, 21.6, 7.5, 7.2, 7.0, 6.7. **HRMS** (EI+) calcd for $[C_{19}H_{22}OSi]^+$: *m/z* 296.1596, found 296.1602.

**Benzoxasilole 3e**



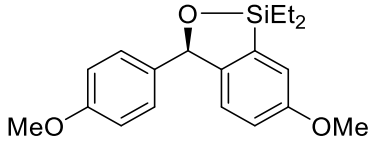

Following the general procedure, 2,2',4,4'-tetramethylbenzophenone (241 mg, 1.01 mmol) was converted to the corresponding diethyl(hydrido)silyl ether at rt using $[Ir(cod)OMe]_2$ (0.05 mol%) as catalyst. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/**L22** (1.0 mol %) at 80 °C for 48 h. Concentration of the reaction mixture, adsorption of the resulting residue onto Celite, and purification by silica gel chromatography (100:0→95:5 hexanes/EtOAc) gave 255 mg (78%) of **3e** as a clear oil **HPLC analysis**: 72% *ee*, LUX Amylose-2 150 x 2 mm 3µ column, 5mM ammonioum acetate 55% in acetonitrile, 0.3 mL/min flow rate, 220 nm UV lamp, $t_R$ = 27.8 min (major), $t_R$ = 32.2 min (minor). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.35 (s, 1H), 7.07 (s, 1H), 7.04 (s, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 6.57 (bs, 1H), 6.44 (s, 1H), 2.65 (s, 3H), 2.44 (s, 3H), 2.33 (s, 3H), 1.87 (s, 3H), 1.05-0.98 (m, 6H), 0.93-0.82 (m, 4H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 148.4, 138.3, 137.1, 136.8, 136.4, 135.1, 132.7, 132.6, 131.2, 129.1, 126.8 (*two overlapping resonances*), 79.3, 21.2, 21.1, 19.3, 19.1, 7.7, 7.3, 7.1, 6.8. **HRMS** (EI+) calcd for $[C_{21}H_{28}OSi]^+$: *m/z* 324.1909, found 324.1915.

**Benzoxasilole 3f**



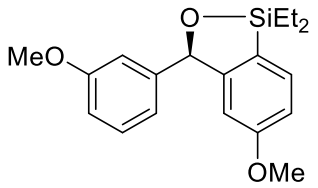

Following the general procedure, 4,4'-diphenylbenzophenone (334 mg, 1.00 mmol) was converted to the corresponding diethyl(hydrido)silyl ether at rt using $[Ir(cod)OMe]_2$ (0.1 mol %) as catalyst and 2.80 equiv of $Et_2SiH_2$ as reagent (otherwise identical condition). The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/**L46** (1.0 mol %) at 50 °C for 60 h. Concentration of the reaction mixture, adsorption of the resulting residue onto Celite, and purification by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 322 mg (77%) of **3f** as a clear foam. **HPLC analysis**: 95% *ee*, Chiralpak IA column, 1% isopropanol in hexane, 1.0 mL/min flow rate, 220 nm UV lamp, $t_R$ = 6.0 min (minor), $t_R$ = 8.2 min (major). **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.93 (d, *J* = 1.4 Hz, 1H), 7.72 – 7.63 (m, 7H), 7.55 – 7.47 (m, 6H), 7.41 (dt, *J* = 14.6, 7.4 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 1H), 6.35 (s, 1H), 1.22 (t, *J* = 7.7 Hz, 3H), 1.17 – 0.95 (m, 7H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 152.0, 142.7, 141.1, 140.9, 140.7, 140.1, 134.4, 129.8, 129.0, 128.72, 128.67, 127.8, 127.3, 127.22 (*two overlapping resonances*), 127.19, 127.1, 124.1, 83.8, 7.3, 7.0, 6.9, 6.5. **HRMS** (EI+) calcd for $[C29H28OSi]^+$: *m/z* 420.1909, found 420.1906.

**Benzoxasilole 3g**



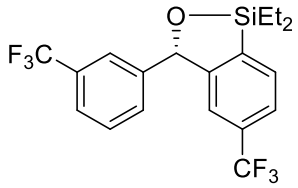

Following the general procedure, 4,4'-dimethoxybenzophenone (243 mg, 1.00 mmol) was converted to the corresponding diethyl(hydrido)silyl ether at rt using $[Ir(cod)OMe]_2$ (0.05 mol %) as catalyst. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/**L47** (1.0 mol %) at 50 °C for 6 h. Concentration of the reaction mixture, adsorption of the resulting residue onto Celite, and purification by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 258 mg (78%) of **3g** as a colorless oil. **HPLC analysis**: 99% *ee*, Chiralcel OJ-H column, 1% isopropanol in hexane, 1.0 mL/min flow rate, 220 nm UV lamp, $t_R$ = 51.7 min (major), $t_R$ = 79.8 min (minor). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.6 Hz, 2H), 7.10 (d, *J* = 2.1 Hz, 1H), 6.97 – 6.84 (m, 4H), 6.11 (s, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 1.08 (t, *J* = 7.6 Hz, 3H), 1.05 – 0.83 (m, 7H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 159.1, 158.6, 145.4, 136.3, 135.0, 128.5, 124.7, 116.3, 114.6, 113.6, 83.3, 55.1, 55.0, 7.1, 6.8, 6.7, 6.4. **HRMS** (EI+) calcd for $[C_{19}H_{24}O_3Si]^+$: *m/z* 328.1495, found 328.1493.

**Benzoxasilole 3h**



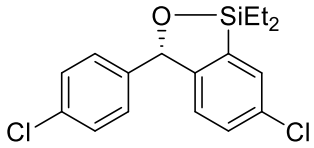

Following the general procedure, bis(3-methoxyphenyl)methanol (244 mg, 0.998 mmol) was converted to the corresponding diethyl(hydrido)silyl ether at rt using $[Ir(cod)OMe]_2$ (0.05 mol %) as catalyst. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/**L46** (1.0 mol %) at 50 °C for 19 h. Concentration of the reaction mixture, adsorption of the resulting residue onto Celite, and purification by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 258 mg (78%) of **3h** as a colorless oil. **HPLC analysis**: 99% *ee*, Chiralpak IA column, 0.1% isopropanol in hexane, 0.5 mL/min flow rate, 220 nm UV lamp, $t_R$ = 21.2 min (major), $t_R$ = 24.3 min (minor). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.0 Hz, 1H), 7.28 (t, *J* = 7.9 Hz, 1H), 6.98 – 6.82 (m, 4H), 6.59 (d, *J* = 1.7 Hz, 1H), 6.11 (s, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 1.11 (t, *J* = 7.7 Hz, 3H), 1.05 – 0.84 (m, 7H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 161.3, 159.7, 155.1, 145.2, 132.2, 129.4, 124.2, 119.6, 114.1, 113.3, 112.6, 108.6, 83.9, 55.0, 55.0, 7.4, 7.1, 6.8, 6.5. **HRMS** (EI+) calcd for $[C_{19}H_{24}O_3Si]^+$: *m/z* 328.1495, found 328.1499.

**Benzoxasilole 3i**



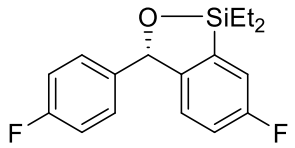

Following the general procedure, 3,3'-bis(trifluoromethyl)benzophenone (319 mg, 1.00 mmol) was converted to the corresponding diethyl(hydrido)silyl ether at rt using $[Ir(cod)OMe]_2$ (0.1 mol%) as catalyst (under otherwise identical condition). The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/**L18** (1.0 mol %) at 50 ° C for 18 h. Concentration of the reaction mixture, adsorption of the resulting residue onto Celite, and purification by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 252 mg (62%) of **3i** as a colorless oil. The enantiomeric excess was determined after Tamao-Flemming oxidation (97% *ee*, see below). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.75 (d, J = 7.6 Hz, 1H), 7.59 (m, 3H), 7.50 (t, J = 7.7 Hz, 1H), 7.45 (d, J = 7.7 Hz, 1H), 7.23 (s, 1H), 6.23 (s, 1H), 1.11 – 0.85 (m, 10H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 152.9, 143.9, 138.5, 132.3 (q, *J* = 32.1 Hz), 132.1, 131.2 (q, *J* = 32.4 Hz), 130.5, 129.2, 125.1 (q, *J* = 3.6 Hz), 124.2 (q, *J* = 3.3 Hz), 124.1 (q, *J* = 3.7 Hz), 124.0 (q, *J* = 272.5 Hz, *two overlapping resonances*), 120.2 (q, *J* = 3.8 Hz), 83.4, 7.0, 6.8, 6.6, 6.3. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -62.75, -62.79. **HRMS** (EI+) calcd for $[C_{19}H_{18}F_6OSi]^+$: *m/z* 404.1031, found 404.1032.

**Benzoxasilole 3j**



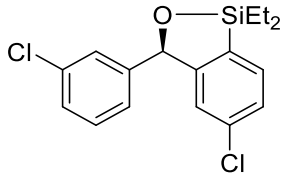

Following the general procedure, 4,4'-dichlorobenzophenone (251 mg, 1.00 mmol) was converted to the corresponding diethyl(hydrido)silyl ether at rt using $[Ir(cod)OMe]_2$ (0.05 mol %) as catalyst. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/**L17** (1.0 mol %) at 50 °C for 10 h. Concentration of the reaction mixture, adsorption of the resulting residue onto Celite, and purification by silica gel chromatography (100:0→ 90:10 hexanes/EtOAc) gave 267 mg (88%) of **3j** as a colorless oil. **HPLC analysis**: 99% *ee*, Chiralcel OD-H column, 1% isopropanol in hexane, 0.5 mL/min flow rate, 220 nm UV lamp, $t_R$ = 8.1 min (major), $t_R$ = 8.9 min (minor). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 2.0 Hz, 1H), 7.31 – 7.20 (m, 3H), 7.15 (d, *J* = 6.7 Hz, 2H), 6.87 (d, *J* = 8.3 Hz, 1H), 6.04 (s, 1H), 1.01 (t, *J* = 7.6 Hz, 3H), 0.97 – 0.77 (m, 7H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 150.7, 141.8, 136.1, 133.7, 133.5, 130.8, 129.9, 128.7, 128.6, 125.0, 83.0, 7.0, 6.8, 6.7, 6.3. **HRMS** (EI+) calcd for $[C_{17}H_{18}Cl_2OSi]^+$: *m/z* 336.0504, found 336.0502.

**Benzoxasilole 3k**



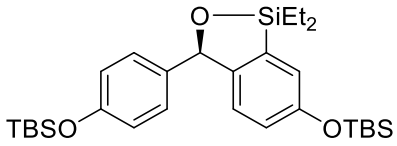
Following the general procedure, 4,4'-difluorobenzophenone (219 mg, 1.00 mmol) was converted to the corresponding diethyl(hydrido)silyl ether at rt using $[Ir(cod)OMe]_2$ (0.05 mol %) as catalyst. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/**L17** (1.0 mol %) at rt for 72 h (under otherwise identical condition). Concentration of the reaction mixture, adsorption of the resulting residue onto Celite, and purification by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 267 mg (88%) of **3k** as a colorless oil. **HPLC analysis**: 81% *ee*, Chiralcel OJ-H column, 1% isopropanol in hexane, 1.0 mL/min flow rate, 220 nm UV lamp, $t_R$ = 6.7 min (major), $t_R$ = 8.7 min (minor). **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.30 – 7.24 (m, 3H), 7.07 – 7.00 (m, 3H), 6.95 (dd, J = 8.5, 4.5 Hz, 1H), 6.14 (s, 1H), 1.08 (t, J = 7.8 Hz, 3H), 1.03 – 0.84 (m, 7H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 162.4 (d, *J* = 246.2 Hz), 162.3 (d, *J* = 247.3 Hz), 148.2 (d, *J* = 2.2 Hz), 139.4 (d, *J* = 3.1 Hz), 136.3 (d, *J* = 5.5 Hz), 129.0 (d, *J* = 8.2 Hz), 125.4 (d, *J* = 7.7 Hz), 117.2 (d, *J* = 23.0 Hz), 116.9 (d, *J* = 19.8 Hz), 115.4 (d, *J* = 21.5 Hz), 83.1, 7.1, 6.8, 6.7, 6.3. **$^{19}$F NMR** (376 MHz, CDCl3) δ -113.46, -115.58. **HRMS** (EI+) calcd for $[C_{17}H_{18}F_2OSi]^+$: *m/z* 304.1095, found 304.1097.

**Benzoxasilole 3l**



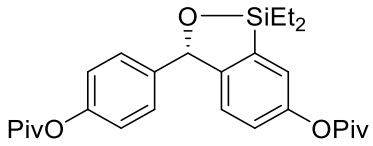
Following the general procedure, 3,3'-dichlorobenzophenone (251 mg, 1.00 mmol) was converted to the corresponding diethyl(hydrido)silyl ether at rt using $[Ir(cod)OMe]_2$ (0.05 mol%) as catalyst. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/**L46** (1.0 mol %) at 50 °C for 17 h. Concentration of the reaction mixture, adsorption of the resulting residue onto Celite, and purification by silica gel chromatography (100:0→95:5 hexanes/EtOAc) gave 279 mg (83%) of **3l** as a clear oil **HPLC analysis**: 97% *ee*, LUX Amylose-2 150 x 2 mm 3μ column, 5mM ammonioum acetate 63% in acetonitrile, 0.3 mL/min, 220 nm UV lamp, $t_R$ = 38.3 min (minor), $t_R$ = 39.6 min (major). Alternatively, Chiralcel OD-H column, 0.1% isopropanol in hexane, 0.5 mL/min flow rate, 220 nm UV lamp, $t_R$ = 12.6 min (minor), $t_R$ = 7.4 min (major). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.55 (d, J = 7.9Hz, 1H), 7.35-7.25 (m, 4H), 7.20 (m, 1H), 7.03 (m, 1H), 6.09 (s, 1H), 1.14-1.07 (m, 3H), 1.04-0.84 (m, 7H). **$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 154.4, 145.0, 136.4, 134.6, 132.5, 131.8, 129.9, 128.3, 127.8, 127.4, 125.4, 123.9, 83.1, 7.2, 6.9, 6.7, 6.4. **HRMS** (EI+) calcd for $[C_{17}H_{18}Cl_2OSi]^+$: *m/z* 336.0504, found 336.0514.

**Benzoxasilole 3m**




Following the general procedure, 4,4'-bis(di-*tert*-butyldimethylsilyloxy)benzophenone (443 mg, 1.00 mmol) was converted to the corresponding diethyl(hydrido)silyl ether at rt using $[Ir(cod)OMe]_2$ (0.05 mol%) as catalyst. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/**L46** (1.0 mol %) at 50 ° C for 25 h. Concentration of the reaction mixture, adsorption of the resulting residue onto Celite, and purification by silica gel chromatography (100:0→95:5 hexanes/EtOAc) gave 461 mg (87%) of **3m** as a colorless oil. **HPLC analysis**: 97% *ee*, Chiralcel AD-H column, 0.1% isopropanol in hexane, 0.5 mL/min flow rate, 220 nm UV lamp, $t_R$ = 7.1 min (minor), $t_R$ = 7.4 min (major). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 2.2 Hz, 1H), 6.89 – 6.74 (m, 4H), 6.05 (s, 1H), 1.09 – 0.79 (m, 28H), 0.21 (s, 6H), 0.18 (s, 6H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 155.2, 154.6, 146.0, 137.0, 135.1, 128.6, 124.8, 122.0, 121.5, 119.9, 83.6, 25.7 (*two overlapping resonances*), 18.2 (*two overlapping resonances*), 7.2, 7.0, 6.8, 6.5, -4.4 (*two overlapping resonances*). **HRMS** (EI+) calcd for $[C_{29}H_{48}O_3Si_3]^+$: *m/z* 528.2911, found 528.2912.

**Benzoxasilole 3n**

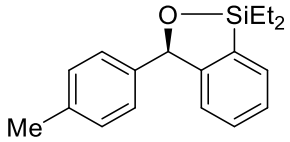



Following the general procedure, 4,4'-bis(trimethylacetoxy)benzophenone (381 mg, 0.996 mmol) was converted to the corresponding diethyl(hydrido)silyl ether at rt using $[Ir(cod)OMe]_2$ (0.05 mol%) as catalyst. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/**L17** (1.0 mol %) at 50 ° C for 17 h. Concentration of the reaction mixture, adsorption of the resulting residue onto Celite, and purification by silica gel chromatography (100:0→95:5 hexanes/EtOAc) gave 254 mg (54%) of **3n** as a clear foam **HPLC analysis**: 95% *ee*, Chiralpak IC column, 5% isopropanol in hexane, 1.0 mL/min flow rate, 220 nm UV lamp, $t_R$ = 4.9 min (minor), $t_R$ = 5.7 min (major). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.34 – 7.25 (m, 3H), 7.06 – 7.01 (m, 4H), 6.16 (s, 1H), 1.38 (s, 9H), 1.35 (s, 9H), 1.05 (t, *J* = 7.5 Hz, 3H), 1.02 – 0.85 (m, 7H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 177.0, 176.8, 150.7, 150.3, 149.7, 140.8, 135.3, 128.4, 124.8, 123.3, 123.2, 121.4, 83.3, 39.0, 39.1, 27.1, 27.0, 7.09, 6.81, 6.73, 6.40. **HRMS** (EI+) calcd for $[C_{27}H_{36}O_5Si]^+$: *m/z* 468.2332, found 468.2326.

*2.4.4 General procedure for site-selective intramolecular arene silylation*

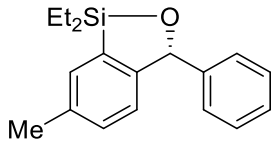
In an $N_2$-filled glovebox, ca. 0.25 mmol of the enantioenriched diarylmethanol substrate was weighed into a 1 dram screw-top vial. A stir bar was added. A freshly prepared stock solution of $[Ir(cod)OMe]_2$ (0.13 μmol, 0.05 mol %) in THF (0.25 mL) and then neat $Et_2SiH_2$ (0.375 mmol). The vial was capped with a Teflon-lined screw-cap, and the resulting solution was stirred in the glovebox at rt until complete conversion to the corresponding diethyl(hydrido)silyl ether was observed, as determined by GC-MS analysis (typically 12 h). The volatile materials were then removed by placing the reaction mixture directly under high-vacuum for 1 h (the stir bar was temporarily removed during this operation to prevent bumping). The stir bar was replaced, and the concentrated diethyl(hydrido)silyl ether was then sequentially treated with norbornene (0.30 mmol), THF (0.25 mL) and a freshly prepared stock solution of $[Rh(cod)Cl]_2$ (1.3 μmol, 0.50 mol %) and the corresponding ligand (3.1 μmol, 1.25 mol %) in THF (0.25 mL) . The Teflon-lined screw-cap was replaced, and the resulting solution was stirred in the glovebox for 1 h (to ensure complete formation of the active Rh species). The vial was then removed from the glovebox, placed in a pre-heated aluminum heating block at 50 °C. After the cyclization was complete (as determined by GC-MS analysis), the reaction mixture was allowed to cool to rt, and the solvent was removed via rotary evaporation. The crude product was purified by silica gel chromatography.

**Benzoxasilole 5a**



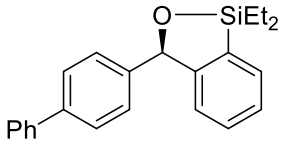

Following the general procedure, (*S*)-(4-tolyl)phenylmethanol **4a** (50.0 mg, 0.252 mmol) was converted to the corresponding diethyl(hydrido)silyl ether at rt using $[Ir(cod)OMe]_2$ (0.05 mol %) as catalyst. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/**L46** (1.0 mol %) at 50 °C for 12 h. Concentration of the reaction mixture, adsorption of the resulting residue onto Celite, and purification by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 54.5 mg (77%) of a mixture of **5a** and its constitutional isomer **5a'** as a colorless oil. The ratio between **5a** and **5a'** was determined to be 96:4 by GC analysis of the crude mixture. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.66 (d, *J* = 6.0 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.06 (d, *J* = 6.9 Hz, 1H), 6.19 (s, 1H), 2.38 (s, 3H), 1.12 (t, *J* = 7.8 Hz, 3H), 1.07 – 0.88 (m, 7H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 153.2, 140.9, 137.4, 133.5, 131.1, 129.6, 129.1, 127.3, 126.8, 123.7, 84.1, 21.1, 7.2, 6.9, 6.8, 6.5. **HRMS** (EI+) calcd for $[C_{18}H_{22}OSi]^+$: *m/z* 282.1440, found 282.1434.

**Benzoxasilole 5a'**



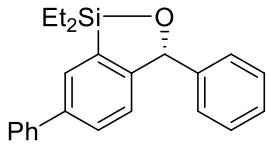

Following the general procedure, (*R*)-(4-tolyl)phenylmethanol **4a** (49.4 mg, 0.250 mmol) was converted to the corresponding diethyl(hydrido)silyl ether at rt using $[Ir(cod)OMe]_2$ (0.05 mol %) as catalyst. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/**L46** (1.0 mol %) at 50 °C for 12 h. Concentration of the reaction mixture, adsorption of the resulting residue onto Celite, and purification by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 51.8 mg (73%) of a mixture of **5a'** and its constitutional isomer **5a** as a colorless oil. The ratio between **5a'** and **5a** was determined to be 96:4 by GC analysis of the crude mixture. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.34 (d, *J* = 7.3 Hz, 2H), 7.33 – 7.27 (m, 3H), 7.16 (d, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.15 (s, 1H), 2.40 (s, 3H), 1.10 (t, *J* = 7.8 Hz, 3H), 1.05 – 0.86 (m, 7H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 150.3, 143.9, 136.4, 133.6, 131.5, 130.8, 128.4, 127.7, 127.3, 123.5, 84.1, 21.2, 7.3, 6.9, 6.8, 6.5. **HRMS** (EI+) calcd for $[C_{18}H_{22}OSi]^+$: *m/z* 282.1440, found 282.1439.

**Benzoxasilole 5b**



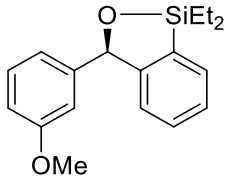

Following the general procedure, (*S*)-(4-biphenyl)phenylmethanol **4b** (65.5 mg, 0.252 mmol) was converted to the corresponding diethyl(hydrido)silyl ether at rt using $[Ir(cod)OMe]_2$ (0.05 mol %) as catalyst. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/**L46** (1.0 mol %) at 50 °C for 14 h. Concentration of the reaction mixture, adsorption of the resulting residue onto Celite, and purification by silica gel chromatography (100:0→95:5 hexanes/EtOAc) gave 72.5 mg (84%) of a mixture of **5b** and its constitutional isomer **5b'** as a colorless oil. The ratio between **5b** and **5b'** was determined to be 96:4 by GC analysis of the crude mixture. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.64 (d, *J* = 6.8 Hz, 1H), 7.58 (t, *J* = 7.7 Hz, 4H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.39 – 7.32 (m, 5H), 7.09 (d, *J* = 7.5 Hz, 1H), 6.22 (s, 1H), 1.10 (t, *J* = 7.8 Hz, 3H), 1.05 – 0.97 (m, 5H), 0.96 – 0.86 (m, 2H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 152.9, 142.8, 140.9, 140.7, 133.6, 131.3, 129.8, 128.7, 127.8, 127.3, 127.2, 127.1, 127.0, 123.8, 84.0, 7.3, 7.0, 6.9, 6.5. **HRMS** (EI+) calcd for $[C_{23}H_{24}OSi]^+$: *m/z* 344.1596, found 344.1602.

**Benzoxasilole 5b'**



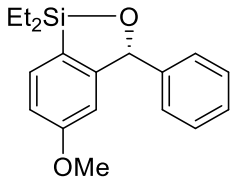

Following the general procedure, (*R*)-(4-biphenyl)phenylmethanol **4b** (65.5 mg, 0.252 mmol) was converted to the corresponding diethyl(hydrido)silyl ether at rt using $[Ir(cod)OMe]_2$ (0.05 mol %) as catalyst. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/**L46** (1.0 mol %) at 50 °C for 14 h. Concentration of the reaction mixture, adsorption of the resulting residue onto Celite, and purification by silica gel chromatography (100:0→95:5 hexanes/EtOAc) gave 67.4 mg (78%) of a mixture of **5b'** and its constitutional isomer **5b** as a colorless oil. The ratio between **5b'** and **5b** was determined to be 93:7 by GC analysis of the crude mixture. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.82 (s, 1H), 7.62 (d, *J* = 7.5 Hz, 2H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.46 (t, *J* = 7.3 Hz, 2H), 7.39 – 7.30 (m, 6H), 7.10 (d, *J* = 8.0 Hz, 1H), 6.22 (s, 1H), 1.12 (t, *J* = 7.8 Hz, 3H), 1.07 – 0.99 (m, 5H), 0.99 – 0.88 (m, 2H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 152.1, 143.7, 141.1, 140.1, 134.3, 129.8, 129.0, 128.7, 128.5, 127.9, 127.3, 127.3, 127.2, 124.1, 84.1, 7.3, 7.0, 6.9, 6.5. **HRMS** (EI+) calcd for $[C_{23}H_{24}OSi]^+$: *m/z* 344.1596, found 344.1594.

**Benzoxasilole 5c**



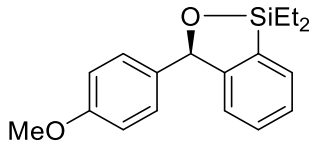

Following the general procedure, (*S*)-(3-methoxyphenyl)phenylmethanol **4c** (54.1 mg, 0.252 mmol) was converted to the corresponding diethyl(hydrido)silyl ether at rt using $[Ir(cod)OMe]_2$ (0.05 mol %) as catalyst. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/**L46** (1.0 mol %) at 50 °C for 14 h. Concentration of the reaction mixture, adsorption of the resulting residue onto Celite, and purification by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 52.9 mg (79%) of a mixture of **5c** and its constitutional isomer **5c'** as a colorless oil. The ratio between **5c** and **5c**' was determined to be 97:3 by GC analysis of the crude mixture. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.62 (d, *J* = 6.5 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 7.4 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 6.87 – 6.81 (m, 2H), 6.15 (s, 1H), 3.77 (s, 3H), 1.10 (t, *J* = 7.7 Hz, 3H), 1.01 (t, *J* = 7.6 Hz, 5H), 0.95-0.85 (m, 2H).. **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 159.7, 152.8, 145.3, 133.3, 131.2, 129.7, 129.4, 127.0, 123.7, 119.7, 113.4, 112.7, 84.1, 55.1, 7.2, 6.9, 6.8, 6.5. **HRMS** (EI+) calcd for $[C_{18}H_{22}O_2Si]^+$: *m/z* 298.1389, found 298.1395.

**Benzoxasilole 5c'**



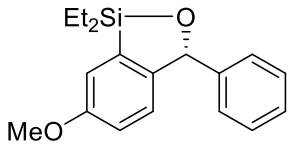

Following the general procedure, (*R*)-(3-methoxyphenyl)phenylmethanol **4c** (53.9 mg, 0.252 mmol) was converted to the corresponding diethyl(hydrido)silyl ether at rt using $[Ir(cod)OMe]_2$ (0.05 mol %) as catalyst. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/**L46** (1.0 mol %) at 50 °C for 14 h. Concentration of the reaction mixture, adsorption of the resulting residue onto Celite, and purification by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 56.1 mg (84%) of a mixture of **5c'** and its constitutional isomer **5c** as a colorless oil. The ratio between **5c'** and **5c** was determined to be 95:5 by GC analysis of the crude mixture. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.52 (d, *J* = 8.0 Hz, 1H), 7.38 – 7.33 (m, 2H), 7.32 – 7.28 (m, 3H), 6.89 (dd, *J* = 8.1, 2.1 Hz, 1H), 6.53 (d, *J* = 1.9 Hz, 1H), 6.12 (s, 1H), 3.72 (s, 3H), 1.07 (t, *J* = 7.8 Hz, 3H), 1.02 – 0.94 (m, 5H), 0.92 – 0.83 (m, 2H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 161.3, 155.3, 143.7, 132.3, 128.5, 127.8, 127.4, 124.4, 114.1, 108.7, 84.1, 55.1, 7.4, 7.1, 6.8, 6.5. **HRMS** (EI+) calcd for $[C_{18}H_{22}O_2Si]^+$: *m/z* 298.1389, found 298.1387.

**Benzoxasilole 5d**



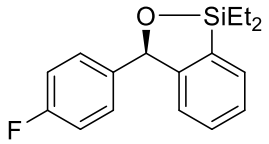

Following the general procedure, (*S*)-(4-methoxyphenyl)phenylmethanol **4d** (53.9 mg, 0.252 mmol) was converted to the corresponding diethyl(hydrido)silyl ether at rt using $[Ir(cod)OMe]_2$ (0.05 mol %) as catalyst. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/**L46** (1.0 mol %) at 50 °C for 33 h. Concentration of the reaction mixture, adsorption of the resulting residue onto Celite, and purification by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 45.5 mg (68%) of **5d** as a colorless oil. The ratio between **5d a**nd **5d'** was determined to be 92:8 by GC analysis of the crude mixture. **HPLC analysis**: 99% *ee*, Chiralcel OJ-H column, 1% isopropanol in hexane, 1.0 mL/min flow rate, 220 nm UV lamp, $t_R$ = 22.1 min (minor), $t_R$ = 36.1 min (major). **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.36 – 7.32 (m, 2H), 7.31 – 7.26 (m, 3H), 7.10 (d, J = 2.4 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 1H), 6.90 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.13 (s, 1H), 3.84 (s, 3H), 1.09 (t, *J* = 7.8 Hz, 3H), 1.01 (t, *J* = 7.7 Hz, 3H), 1.00 – 0.86 (m, 4H). **$^{13}$C NMR** (151 MHz, CDCl3) δ 158.8, 145.2, 144.0, 135.2, 128.4, 127.7, 127.3, 124.8, 116.5, 114.9, 83.9, 55.3, 7.2, 6.9, 6.8, 6.5. **HRMS** (EI+) calcd for $[C_{18}H_{22}O_2Si]^+$: *m/z* 298.1389, found 298.1383.

**Benzoxasilole 5d'**



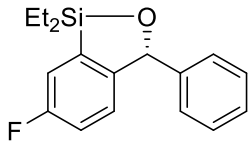

Following the general procedure, (*R*)-(4-methoxyphenyl)phenylmethanol **4d** (53.1 mg, 0.248 mmol) was converted to the corresponding diethyl(hydrido)silyl ether at rt using $[Ir(cod)OMe]_2$ (0.05 mol %) as catalyst. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/**L46** (1.0 mol %) at 50 °C for 24 h. Concentration of the reaction mixture, adsorption of the resulting residue onto Celite, and purification by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 36.0 mg (53%) of **5d'** as a colorless oil. The ratio between **5d' a**nd **5d** was determined to be 91:9 by GC analysis of the crude mixture. **HPLC analysis**: 99% *ee*, Chiralpak IA column, 0.1% isopropanol in hexane, 1.0 mL/min flow rate, 220 nm UV lamp, $t_R$ = 7.4 min (major), $t_R$ = 8.6 min (minor). Alternatively, Chiralcel AD-H column, 0.1% isopropanol in hexane, 0.5 mL/min flow rate, 220 nm UV lamp, $t_R$ = 14.1 min (minor), $t_R$ = 14.9 min (major). **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.63 (dd, J = 6.2, 1.6 Hz, 1H), 7.37 – 7.29 (m, 2H), 7.22 (d, J = 8.7 Hz, 2H), 7.02 (d, *J* = 7.3 Hz, 1H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.15 (s, 1H), 3.81 (s, 3H), 1.08 (t, *J* = 7.8 Hz, 3H), 1.04 – 0.85 (m, 7H). **$^{13}$C NMR** (151 MHz, CDCl3) δ 159.2, 153.2, 136.2, 133.5, 131.1, 129.6, 128.7, 126.9, 123.8, 113.8, 83.8, 55.2, 7.3, 6.9, 6.8, 6.5. **HRMS** (EI+) calcd for $[C_{18}H_{22}O_2Si]^+$: *m/z* 298.1389, found 298.1387.

**Benzoxasilole 5e**




Following the general procedure, (*S*)-(4-fluorophenyl)phenylmethanol **4e** (51.4 mg, 0.254 mmol) was converted to the corresponding diethyl(hydrido)silyl ether at rt using $[Ir(cod)OMe]_2$ (0.05 mol %) as catalyst. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/**L46** (1.0 mol %) at 50 °C for 14 h. Concentration of the reaction mixture, adsorption of the resulting residue onto Celite, and purification by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 51.7 mg (72%) of a mixture of **5e** and its constitutional isomer **5e'** as a colorless oil. The ratio between **5e a**nd **5e'** was determined to be 95:5 by the NMR analysis of the crude mixture. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.0 Hz, 1H), 7.38 – 7.31 (m, 2H), 7.30 – 7.25 (m, 2H), 7.06 – 7.01 (m, 2H), 7.00 (d, *J* = 7.1 Hz, 1H), 6.16 (s, 1H), 1.08 (t, *J* = 7.7 Hz, 3H), 1.05 – 0.95 (m, 5H), 0.95 – 0.85 (m, 2H). **$^{13}$C NMR** (151 MHz, CDCl3) δ 162.4 (d, *J* = 246 Hz), 152.7, 139.7, 133.5, 131.3, 129.8, 129.1 (d, *J* = 8.1 Hz), 127.1, 123.7 , 115.3 (d, *J* = 22 Hz), 83.5, 7.2, 6.9, 6.8, 6.5. **$^{19}$F NMR** (376 MHz, CDCl3) δ -113.86. **HRMS** (EI+) calcd for $[C_{17}H_{19}FOSi]^+$: *m/z* 286.1189, found 286.1190.

**Benzoxasilole 5e'**

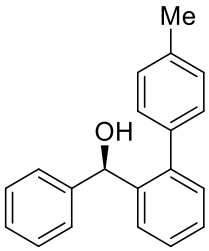



Following the general procedure, (*R*)-(4-fluorophenyl)phenylmethanol **4e** (49.7 mg, 0.246 mmol) was converted to the corresponding diethyl(hydrido)silyl ether at rt using $[Ir(cod)OMe]_2$ (0.05 mol %) as catalyst. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/**L46** (1.0 mol %) at 50 °C for 14 h. Concentration of the reaction mixture, adsorption of the resulting residue onto Celite, and purification by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 57.8 mg (81%) of a mixture of **5e'** and its constitutional isomer **5e** as a colorless oil. The ratio between **5e' a**nd **5e** was determined to be 96:4 by the NMR analysis of the crude mixture. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.35 (t, *J* = 7.3 Hz, 2H), 7.32 – 7.24 (m, 4H), 7.04 – 6.96 (m, 2H), 6.13 (s, 1H), 1.08 (t, *J* = 7.8 Hz, 3H), 1.02 – 0.97 (m, 5H), 0.94 – 0.84 (m, 2H). **$^{13}$C NMR** (151 MHz, CDCl3) δ 162.2 (d, *J* = 247 Hz), 148.4, 143.5 , 136.3 (d, *J* = 5.0 Hz), 128.5 , 128.0, 127.3, 125.4 (d, *J* = 7.7 Hz), 117.2 (d, *J* = 22.9 Hz), 116.8 (d, *J* = 19.7 Hz), 83.9, 7.1, 6.9, 6.7, 6.4. **$^{19}$F NMR** (376 MHz, CDCl3) δ -116.00 **HRMS** (EI+) calcd for $[C_{17}H_{19}FOSi]^+$: *m/z* 286.1189, found 286.1193.

*2.4.5 General procedure for Hiyama coupling of benzoxasilole products*

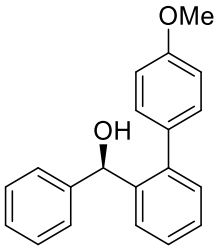
In an $N_2$-filled glovebox, a 1 dram screw-top vial was charged with $Pd(OAc)_2$ (2.3 mg, 10 $\mu$ mol, 4 mol %), 1,2-bis(dicyclohexylphosphino)ethane (4.7 mg, 11 μmol, 4.5 mol %) and a stir bar. A solution of the benzoxasilole (0.25 mmol) and the aryl iodide (0.30 mmol) in dioxane (1.25 mL) was then added. The vial was capped with a screw cap containing a PTFE-lined septum and removed from the glovebox. After being stirred at rt for 5-10 min, the light yellow/golden solution was treated with 2 M aq NaOH (0.63 mL, 1.25 mmol), and the resulting biphasic mixture was stirred at rt for an additional 30 min. The vial was then placed in a pre-heated aluminum block at 65 °C and stirred for 14 h. The reaction mixture was allowed to cool to rt and then diluted with EtOAc, filtered through $SiO_2$ and concentrated. The residue was adsorbed onto Celite and purified by silica gel chromatography to provide the biaryl alcohol product.

**Biarylmethanol 6a**



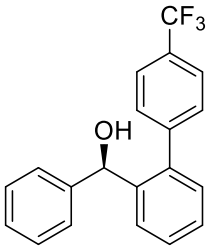

Following the general procedure, benzoxasilole **3a** (67.3 mg, 0.251 mmol) was coupled with 4-iodotoluene (67.5 mg, 0.310 mmol) with $Pd(OAc)_2$/dcpe at 65 °C. The crude product was purified by silica gel chromatography (100:0→80:20 hexanes/EtOAc) to give 47.4 mg (69%) of **3a** as a white oil. **HPLC analysis**: 99% *ee*, Chiralcel OD-H column, 3% isopropanol in hexane, 0.5 mL/min flow rate, 220 nm UV lamp, $t_R$ = 23.4 min (minor), $t_R$ = 26.0 min (major). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.53 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.37 (td, *J* = 7.5, 1.6 Hz, 1H), 7.33 (td, *J* = 7.4, 1.6 Hz, 1H), 7.30 – 7.15 (m, 10H), 5.96 (s, 1H), 2.41 (s, 3H), 2.13 (br s, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 143.9, 141.3, 141.1, 137.8, 136.8, 130.1, 129.2, 128.8, 128.2, 127.7, 127.4, 127.3, 127.1, 126.6, 72.3, 21.2. ($^1$H and $^{13}$C NMR data were consistent with previously reported values.[34])

**Biarylmethanol 6b**



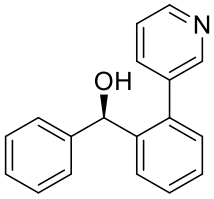

Following the general procedure, benzoxasilole **3a** (67.3 mg, 0.251 mmol) was coupled with 4-iodoanisole (74.8 mg, 0.320 mmol) with $Pd(OAc)_2$/dcpe at 65 °C. The crude product was purified by silica gel chromatography (100:0→80:20 hexanes/EtOAc) to give 51.0 mg (70%) of **3b** as a white foam. **HPLC analysis**: 99% *ee*, Chiralcel OD-H column, 10% isopropanol in hexane, 0.5 mL/min flow rate, 220 nm UV lamp, $t_R$ = 15.8 min (major), $t_R$ = 18.4 min (minor). **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.54 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.37 (td, *J* = 7.6, 1.3 Hz, 1H), 7.32 (td, *J* = 7.4, 1.4 Hz, 1H), 7.30 – 7.17 (m, 8H), 6.92 (d, *J* = 8.8 Hz, 2H), 5.96 (s, 1H), 3.85 (s, 3H), 2.14 (br s, 1H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 158.8, 143.9, 141.3, 141.0, 133.1, 130.4, 130.2, 128.2, 127.6, 127.4, 127.2, 127.2, 126.6, 113.6, 72.5, 55.3. **HRMS** (EI+) calcd for $[C_{20}H_{18}O_2]^+$: *m/z* 290.1307, found 290.1307.

**Biarylmethanol 6c**




Following the general procedure, benzoxasilole **3a** (67.2 mg, 0.250 mmol) was coupled with 4-iodobenzotrifluoride (81.9 mg, 0.301 mmol) with $Pd(OAc)_2$/dcpe at 65 °C. The crude product was purified by silica gel chromatography (100:0→80:20 hexanes/EtOAc) to give 65.3 mg (79%) of **3c** as a colorless foam. **HPLC analysis**: 98% *ee*, Chiralcel OD-H column, 3% isopropanol in hexane, 0.5 mL/min flow rate, 220 nm UV lamp, $t_R$ = 20.9 min (minor), $t_R$ = 28.6 min (major). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.9 Hz, 3H), 7.44 (td, *J* = 7.6, 1.3 Hz, 1H), 7.40 – 7.33 (m, 3H), 7.30 – 7.19 (m, 4H), 7.15 – 7.10 (m, 2H), 5.84 (s, 1H), 2.16 (br s, 1H) **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 144.5, 143.5, 140.8, 139.9, 129.7, 129.4 (q, *J* = 32.6 Hz), 128.5, 128.3, 127.6, 127.5, 127.3, 126.7, 126.5, 125.0 (q, *J* = 3.7 Hz), 124.2 (q, *J* = 272.1 Hz), 72.6. **$^{19}$F NMR** (376 MHz, CDCl3) δ -61.62. **HRMS** (EI+) calcd for $[C_{20}H_{15}F_3O]^+$: *m/z* 328.1075, found 328.1077.

**Biarylmethanol 6d**



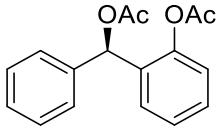

Following the general procedure, benzoxasilole **3a** (67.1 mg, 0.250 mmol) was coupled with 3-iodopyridine (63.7 mg, 0.311 mmol) with $Pd(OAc)_2$/dcpe at 65 °C. The crude product was purified by silica gel chromatography (100:0→20:80 hexanes/EtOAc) to give 34.4 mg (53%) of **6d** as a white solid. **HPLC analysis**: 99% *ee*, Chiralcel OD-H column, 10% isopropanol in hexane, 0.5 mL/min flow rate, 220 nm UV lamp, $t_R$ = 20.6 min (major), $t_R$ = 26.1 min (minor). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 8.52 – 8.35 (br, 2H), 7.63 (d, *J* = 7.6 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.43 (t, *J* = 7.5 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.29 – 7.16 (m, 5H), 7.16 – 7.11 (m, 2H), 5.81 (s, 1H), 3.64 (br s, 1H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 149.4, 147.9, 143.7, 141.6, 137.3, 137.0, 130.1 (*two overlapping resonances*), 128.7 (*two overlapping resonances*), 128.3, 127.6, 127.6, 127.3, 126.7, 72.3. **HRMS** (EI+) calcd for $[C_{18}H_{15}NO]^+$: *m/z* 261.1154, found 261.1150.

*2.4.6 General procedure for Tamao-Fleming oxidation of benzoxasilole products*

A solution of benzoxasilole (0.25 mmol) in 1:1 THF/MeOH (1.0 mL) was treated sequentially with $KHCO_3$ (0.50 mmol) and $H_2O_2$ (30% solution in $H_2O$, 2.0 mmol). The resulting mixture was stirred at rt until complete consumption of the benzoxasilole was observed, as judged by TLC analysis. The reaction was carefully quenched by slow addition of the reaction mixture (via pipette) to a solution of aq $NaHSO_3$ (10 mL), and the resulting mixture was extracted with EtOAc (3 x 10 mL). The combined organic layers were washed (10 mL water, then 10 mL sat. $NaHCO_3$), dried ($Na_2SO_4$), and concentrated. The resulting diol was either purified by silica gel chromatography to provide the diol or acetylated to form the corresponding diacetate**.**

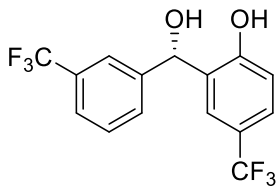
*Procedure for Diacetylation*: Without further purification, the crude phenol was dissolved in $CH_2Cl_2$ (0.8 mL) and $Et_3N$ (0.4 mL), and the resulting solution was treated with $Ac_2O$ (3 equiv). After being stirred at rt overnight, the reaction mixture was concentrated. The resulting residue was adsorbed onto Celite and purified by silica gel chromatography to provide the diacetate product.

**Diacetate 7**




Following the general procedure, benzoxasilole **3a** (67.7 mg, 0.252 mmol) was oxidized with $KHCO_3/H_2O_2$ at rt. The crude phenol was acylated with $Ac_2O/Et_3N$ according to the general procedure, and the resulting diactate was purified by silica gel chromatography (100:0→80:20 hexanes/EtOAc) to give 37.5 mg (53% over 2 steps) of **7** as a colorless oil. **HPLC analysis**: 96% *ee*, Chiralcel OJ-H column, 5% isopropanol in hexane, 1.0 mL/min flow rate, 220 nm UV lamp, $t_R$ = 18.3 min (major), $t_R$ = 34.4 min (minor). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.41 (d, *J* = 7.6 Hz, 1H), 7.38 – 7.22 (m, 7H), 7.14 – 7.06 (m, 2H), 2.21 (s, 3H), 2.15 (s, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 169.7, 168.9, 148.2, 138.9, 131.9, 129.1, 128.5, 128.4, 128.0, 127.0, 126.0, 123.0, 71.7, 21.0, 20.8. ($^1$H NMR data were consistent with previously reported values. $^{13}$C NMR data were not reported.[35])

**Diol 8**



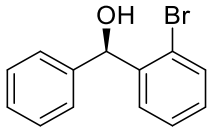

Following the general procedure, benzoxasilole **3i** (67.8 mg, 0.168 mmol) was oxidized with $KHCO_3/H_2O_2$ at rt. The resulting diol was purified by silica gel chromatography (100:0→65:35 hexanes/EtOAc) to give 45.4 mg (80%) of **8** as a white solid. **HPLC**

**analysis**: 97% *ee*, Chiralcel AD-H column, 10% ethanol in hexane, 1.0 mL/min flow rate, 220 nm UV lamp, $t_R$ = 5.6 min (major), $t_R$ = 6.1 min (minor). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.70 (s, 1H), 7.61 (d, J = 6.7 Hz, 1H), 7.55 – 7.45 (m, 3H), 7.22 (s, 1H), 6.97 (d, J = 8.5 Hz, 1H), 6.10 (s, 1H), 3.14 (s, 1H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 158.0, 142.0, 131.2 (q, *J* = 32.5 Hz), 130.0, 129.4, 127.0 (q, *J* = 3.7 Hz), 126.4, 125.4 (*two overlapping quartets*), 124.1 (q, J = 272.6 Hz), 123.9 (q, J = 271.5 Hz), 123.5 (q, *J* = 3.8 Hz), 122.6 (q, *J* = 32.8 Hz), 117.8, 75.8. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -60.68, -61.81. **HRMS** (EI+) calcd for $[C_{15}H_{10}F_6O_2]^+$: *m/z* 336.0585, found 336.0585.

*2.4.7 General procedure for halogenation of benzoxasilole products*

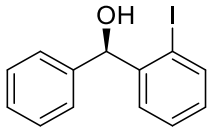
In an $N_2$-filled glovebox, a 1 dram screw-top vial was charged with *N*-bromosuccinimide or *N*-iodosuccinimide (1.1 equiv) and AgF (4 equiv). To this vial was added a solution of benzoxasilole in acetonitrile (0.1 M). The vial was capped with a Teflon-lined screw-cap, and the resulting heterogeneous solution was stirred in the glovebox at rt in the dark until complete conversion was observed, as determined by TLC analysis (30 min – 1 h). The reaction mixture was poured onto aq. $NaHCO_3$ (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated. The crude product was adsorbed onto Celite and purified by silica gel chromatography to provide the halogenated biaryl product.

**(2-Bromophenyl)phenylmethanol 9**



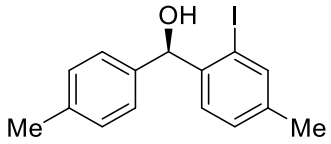

Following the general procedure, benzoxasilole **3a** (67.1 mg, 0.250 mmol) was brominated with NBS/AgF at rt. The resulting product was purified by silica gel chromatography (100:0→80:20 hexanes/EtOAc) to give 44.7 mg (61%) of **9** as a colorless oil. **HPLC analysis**: 98% *ee*, Chiralcel OD-H column, 10% isopropanol in hexane, 1.0 mL/min flow rate, 220 nm UV lamp, $t_R$ = 9.8 min (major), $t_R$ = 13.5 min (minor). $[\alpha]_D^{25}$ = +40.1 (c 1.05, $CHCl_3$). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.41 (d, *J* = 7.1 Hz, 2H), 7.38 – 7.26 (m, 4H), 7.16 (td, *J* = 7.8, 1.6 Hz, 1H), 6.19 (s, 1H), 2.49 (br s, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 142.5, 142.1, 132.8, 129.1, 128.4 (*two overlapping resonances*), 127.7, 127.7, 127.0, 122.7, 74.7. ($^1$H and $^{13}$C NMR data were consistent with previously reported values.[36])

**(2-Iodophenyl)phenylmethanol 10a**



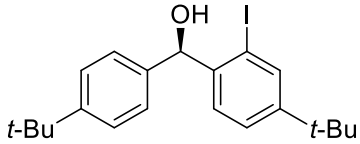

Following the general procedure, benzoxasilole **3a** (67.0 mg, 0.250 mmol) was iodinated with NIS/AgF at rt. The resulting product was purified by silica gel chromatography (100:0→80:20 hexanes/EtOAc) to give 67.6 mg (80%) of **7a** as a colorless oil. **HPLC analysis**: 98% *ee*, Chiralcel OD-H column, 10% isopropanol in hexane, 0.5 mL/min flow rate, 220 nm UV lamp, $t_R$ = 19.7 min (major), $t_R$ = 27.3 min (minor). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 7.9, 1.1 Hz, 1H), 7.53 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.45 – 7.28 (m, 6H), 7.00 (td, *J* = 7.7, 1.7 Hz, 1H), 6.05 (s, 1H), 2.64 (br s, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 145.3, 142.0, 139.4, 129.3, 128.5, 128.4, 128.3, 127.7, 127.2, 98.6, 78.9. ($^1$H and $^{13}$C NMR data were consistent with previously reported values.[37])

**Diarylmethanol 10b**




Following the general procedure, benzoxasilole **3b** (29.4 mg, 0.0992 mmol) was iodinated with NIS/AgF at rt. The resulting product was purified by silica gel chromatography (100:0→80:20 hexanes/EtOAc) to give 29.6 mg (80%) of **10b** as a colorless oil. **HPLC analysis**: 96% *ee*, Chiralcel OD-H column, 10% isopropanol in hexane, 0.5 mL/min flow rate, 220 nm UV lamp, $t_R$ = 14.3 min (major), $t_R$ = 15.2 min (minor). **$^1$H NMR** (400 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.39 (d, *J* = 7.9 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.20 – 7.11 (m, 3H), 5.99 (s, 1H), 2.33 (s, 3H), 2.29 (overlapping s, 4H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 142.5, 139.9, 139.4, 139.36, 137.35, 129.4, 129.1, 127.9, 127.1, 98.5, 78.6, 21.1, 20.4. **HRMS** (EI+) calcd for $[C_{15}H_{15}IO]^+$: *m/z* 338.0168, found 338.0168.

**Diarylmethanol 10c**




Following the general procedure, benzoxasilole **3c** (38.2 mg, 0.100 mmol) was iodinated with NIS/AgF at rt. The resulting product was purified by silica gel chromatography (100:0→80:20 hexanes/EtOAc) to give 31.0 mg (73%) of **10c** as a colorless foam. **HPLC analysis**: 86% *ee*, Chiralcel OD-H column, 10% isopropanol in hexane, 1.0 mL/min flow

rate, 220 nm UV lamp, $t_R$ = 5.6 min (minor), $t_R$ = 6.3 min (major). **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.82 (d, *J* = 1.9 Hz, 1H), 7.44 (d, *J* = 8.2 Hz, 1H), 7.39 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.36 (s, 4H), 6.02 (d, *J* = 2.5 Hz, 1H), 2.30 (d, *J* = 3.1 Hz, 1H), 1.31 (s, 9H), 1.29 (s, 9H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 152.7, 150.6, 142.6, 139.4, 136.5, 127.8, 126.8, 125.8, 125.3, 98.9, 78.7, 34.5, 34.4, 31.3, 31.2. **HRMS** (EI+) calcd for $[C_{21}H_{27}IO]^+$: *m/z* 422.1107, found 422.1107.

*2.4.8 Assignment of the absolute configuration of the benzoxasilole products*

The absolute configuration of the products was assigned based on the following observations. First, the bromination of **3a** yielded (2-bromophenyl)phenylmethanol **9** whose optical rotation value $[\alpha]_D^{25}$ was +40.1 (c 1.05, $CHCl_3$). The (*S*)-enantiomer of **9** was reported to have an $[\alpha]_D^{22}$ value of -41.9 (c 1.19, $CHCl_3$).[13] Therefore, the compounds **3a** and **9** were assigned to have the (*R*) absolute configuration. Because **3a** was prepared using the catalyst derived from a catASium ligand **L47**, the compounds that were formed from the catalyst containing catASium ligands (**L46**, **L47**) were assigned to be (*R*). Second, the silylation of enantioenriched diarylmethanols occurs with site-selectivity that is consistent with the formation of (*R*)-enantiomers. Lastly, the benzoxasiloles formed with the catalyst containing the Walphos ligands (**L17**, **L18**, **L22**) were assigned to be the (*S*)-enantiomers because the absolute configuration of the major enantiomers formed from those catalysts had the opposite configuration to that formed from the catalyst containing **L46** and **L47.**

## 2.5 References

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Lee, T.; Wilson, T. W.; Berg, R.; Ryberg, P.; Hartwig, J. F. Rhodium-Catalyzed Enantioselective Silylation of Arene C−H Bonds: Desymmetrization of Diarylmethanols. *J. Am. Chem. Soc.* **2015**, *137*, 6742. 

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# CHAPTER 3

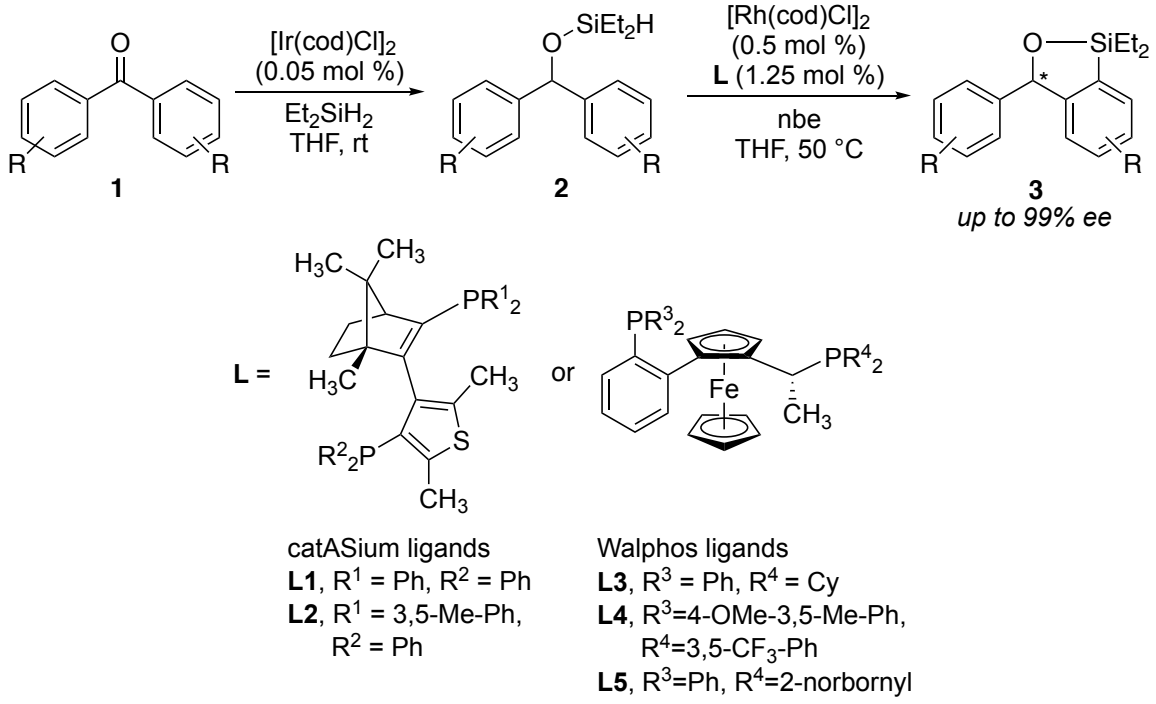
## Mechanistic Studies on Rhodium-Catalyzed Enantioselective Silylation of Aryl C–H Bonds

## 2.1 Introduction

The functionalization of C–H bonds with main group reagents, such as boranes and silanes, has become a synthetically valuable process because of the high regioselectivity of the reactions and the widespread utility of the products.[1-3] Mechanistic studies on these reactions have provided insight into the catalyst resting states, rate-determining steps, and origins of selectivities.[4-9] However, little information on the mechanism of enantioselective variants of these reactions is available.[10-18] Preliminary mechanistic data on enantioselective silylation of C–H bonds have been reported,[11,17,18] but systematic mechanistic studies involving the isolation of reaction intermediates and kinetic analysis of the process have not been conducted. Most relevant to the work reported here, little information on the origins of enantioselectivities has been gained.

In Chapter 2, we described a highly enantioselective silylation of C–H bonds catalyzed by the combination of a rhodium precatalyst and a chiral bisphosphine ligand.[15] In this reaction, (hydrido)silyl ethers **2**, which are formed *in situ* by hydrosilylation of benzophenone or its derivatives **1**, undergo asymmetric C–H silylation in high yield with excellent enantioselectivity to form enantioenriched benzoxasilole products **3** (Scheme 3.1). This reaction proceeds in the presence of $[Rh(cod)Cl]_2$ and catASium (**L1**–**L2**) or Walphos (**L3**–**L5**) ligands with norbornene (nbe) as a hydrogen acceptor.

**Scheme 3.1** Rh-catalyzed enantioselective silylation of aryl C-H bonds

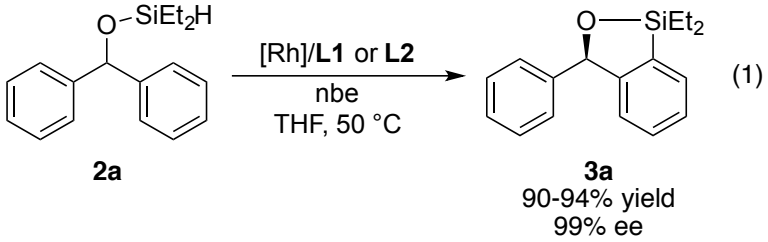



Here we describe detailed mechanistic studies on these enantioselective C–H silylation reactions. We show that the catalyst resting state is a mixture of a rhodium silyl dihydride and a rhodium norbornyl complex, the ratio of which depends on the relative concentrations of silane and norbornene. We prepared these complexes independently

and showed that they are competent to be reaction intermediates. Measurements of inter- and intramolecular kinetic isotope effects (KIE) indicated that the C–H cleavage step is not rate-determining and is partially reversible. Our studies indicate that both C–H oxidative addition and C–Si reductive elimination steps influence the enantioselectivity. DFT calculations suggest that the enantioselectivity results from steric repulsion between the alkyl substituent on silicon of the substrate and the aryl group of the ligand in the transition state that forms the minor enantiomer.

## 3.2 Results and Discussion

As stated in the introduction, the enantioselective silylation of diarylmethyl silyl ethers **2** occurs in the presence of $[Rh(cod)Cl]_2$ and catASium (**L1**–**L2**) or Walphos (**L3**–**L5**) ligands with norbornene as hydrogen acceptor (Scheme 3.1). To gain detailed information on the mechanism of this process, we chose to study the reaction of **2a** catalyzed by $[Rh(cod)Cl]_2$ and catASium ligands **L1** or **L2** (eq 1). The reaction yields the silylated product **3a** in 90-94% yield, as determined by $^1H$ NMR analysis, with an enantiomeric excess of 99% with both ligands. The reaction conducted with $[Rh(C_2H_4)_2Cl]_2$ as the rhodium precursor occurred with the same level of reactivity and enantioselectivity.




*3.2.1 Characterization of the catalyst resting states*

The silylation of **2a** with $[Rh(C_2H_4)Cl]_2$ or $[Rh(cod)Cl]_2$ as the source of rhodium, **L1** as the ligand, and 1.2 equivalent of norbornene as hydrogen acceptor was monitored in THF-$d_8$ at 50 °C (eq 1). We observed two phosphine-ligated rhodium species **4a** and **5** during the reaction (Figure 1). The $^{31}P$ NMR signals corresponding to **4a** consisted of two doublets of doublets at 29.4 ppm ($J_{Rh–P}$ = 123 Hz, $J_{P–P}$ = 22.6 Hz) and 25.1 ppm ($J_{Rh–P}$ = 131 Hz, $J_{P–P}$ = 22.6 Hz), and those corresponding to complex **5** consisted of two broad doublets at 36.6 ppm ($J_{Rh–P}$ = 264 Hz) and 24.5 ppm ($J_{Rh–P}$ = 178 Hz).

Two hydride species were observed in the $^1H$ spectrum. A broad singlet at –8.62 ppm and a broad doublet at –3.12 ppm were observed at 50 °C. Correlations between protons at –8.62 ppm in the $^1H$ spectrum and $^{31}P$ nuclei of complex **4a** and correlations between the proton at –3.12 ppm in the $^1H$ spectrum and the $^{31}P$ nuclei of complex **5** were observed in the $^{31}P–^1H$ HMBC NMR spectrum.

The relative concentrations of **4a** and **5** varied during the course of the reaction. At the beginning of the reaction, the concentration of **4a** was higher than that of **5**. However, the concentration of **5**, relative to that of **4a**, increased as the reaction progressed, and complex **4a** became undetectable at greater than 90% conversion.

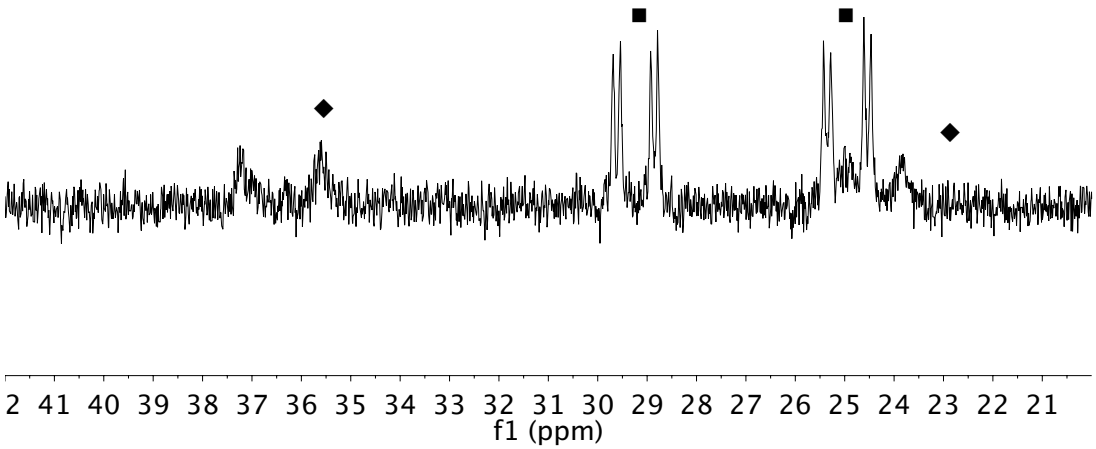
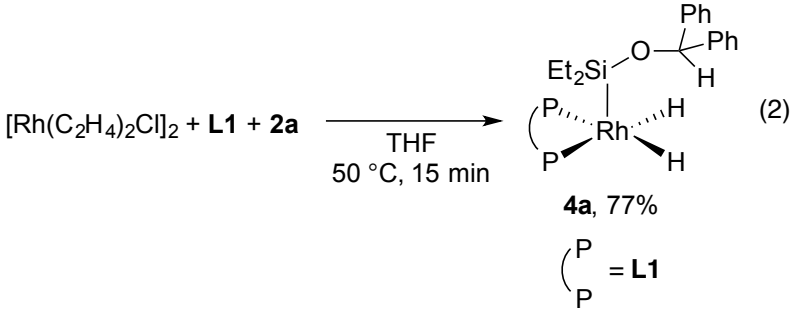



**Figure 3.1** $^{31}$P NMR spectrum at 50 °C of silylation reaction of 2a conducted with $[Rh(C_2H_4)Cl]_2$ (2.5 mol %) and L1 (5 mol %) as the catalyst precursors and 1.2 equivalent of norbornene at ca. 40% conversion of **2a**. **4a** (■), **5** (◆).

Monitoring of the reactions with **L2** in place of **L1** led to the same general observations. The $^{31}$P NMR spectrum contained two sets of signals, one of which was sharp and one of which was broad. The $^{1}$H NMR spectrum also contained two hydride signals. Finally, a similar interconversion of the two phosphine-ligated rhodium hydride complexes occurred during the course of the reaction catalyzed by the complex of **L2** as occurred during the reaction catalyzed by the complex of **L1**, and the relative amounts of the two complexes ligated by **L2** varied as did the amounts of the two complexes ligated by **L1**. Thus, the mechanistic data on these two catalyst systems are generally interchangeable.[19]

To identify complexes **4a** and **5**, we prepared them independently. We synthesized a complex having NMR signals that matched those of rhodium hydride species **4**. We generated this complex by the reaction of $[Rh(C_2H_4)Cl]_2$ and **L1** with 10 equivalents of silane **2a** and isolated it as a yellow solid in 77% yield (eq 2). Complex **4a** was a rhodium silyl dihydride species that is analogous to the complex we observed as the resting state in the rhodium-catalyzed intermolecular silylation of aryl C–H bonds.[5,20] However, **4a** is distinct from the previously reported complex because **4a** contains aryl C–H bonds that can react.[21]




(2)

The solid-state structure of **4a** was determined to be a distorted square-based pyramid by single-crystal X-ray analysis (Figure 3.2). The phenyl groups on the silyl

ether are positioned far from the rhodium center. The two hydrides are non-equivalent, but the two rhodium−hydride protons resonate as a single signal in the $^1$H NMR spectrum at 50 °C. Complex **4a** is likely to undergo pseudorotation of the ligands in solution at that temperature, and this pseudorotation leads to the site exchange between the two rhodium hydrides. The broad hydride signal in the $^1$H NMR spectrum was fully resolved into two sharp signals at –20 °C. Each of the two signals is a doublet of doublets of doublets of doublets due to the *J* couplings with rhodium nucleus, two phosphorus nuclei, and the other hydride proton. An energy barrier ($\Delta G^{\ddagger}_{310K}$) for the exchange of the hydrides of **4a** was calculated to be ca. 14 kcal/mol from the coalescence temperature ($T_c$) of 37 °C and the extrapolated peak separation of $\Delta\nu$ = 452 Hz at $T_c$ in the $^1$H NMR spectrum.

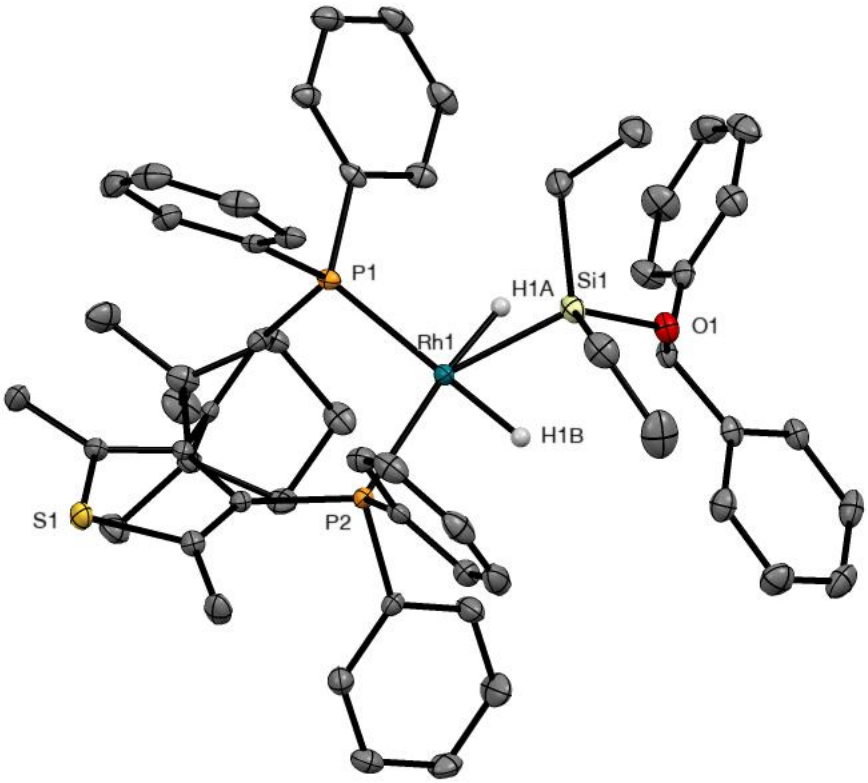
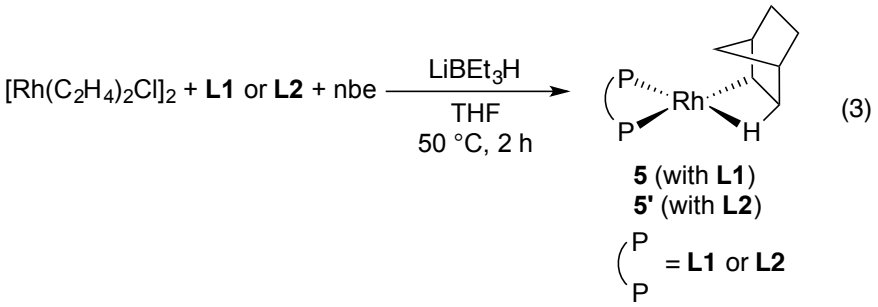



**Figure 3.2** ORTEP diagram of **4a** (thermal ellipsoids at the 50% probability level). Hydrogen atoms have been omitted except for the hydrides bound to rhodium. Selected bond lengths (Å): Rh1−P1 = 2.2763(8), Rh1−P2 = 2.3456(8), Rh1−H1A = 1.48(3), Rh1−H1B = 1.49(3), Rh1−Si1 = 2.3126(8), Si1−H1A = 1.85(3). Selected bond angles (°): P1− Rh1−Si1 = 115.52(3), P2−Rh1−Si1 = 129.64(3), H1A−Rh1−Si1 = 53(1), H1B− Rh1−Si1 = 63(1).

In addition, we independently prepared a complex with NMR signals that matched those of rhodium complex **5**, which is the major species observed during the catalytic reaction at high conversion of silane **2a**. This complex was generated by the addition of lithium triethylborohydride to a solution of $[Rh(C_2H_4)Cl]_2$, **L1** and norbornene (eq 3), followed by heating at 50 °C for 2 hours.[22] Complex **5'**, containing **L2** in place of **L1**, was prepared in the same manner. We were unable to isolate complexes **5**

and **5'** in pure form because of their high solubility, but they were generated in approximately 70% yields, as determined by $^1$H NMR spectroscopy with an internal standard.




(3)

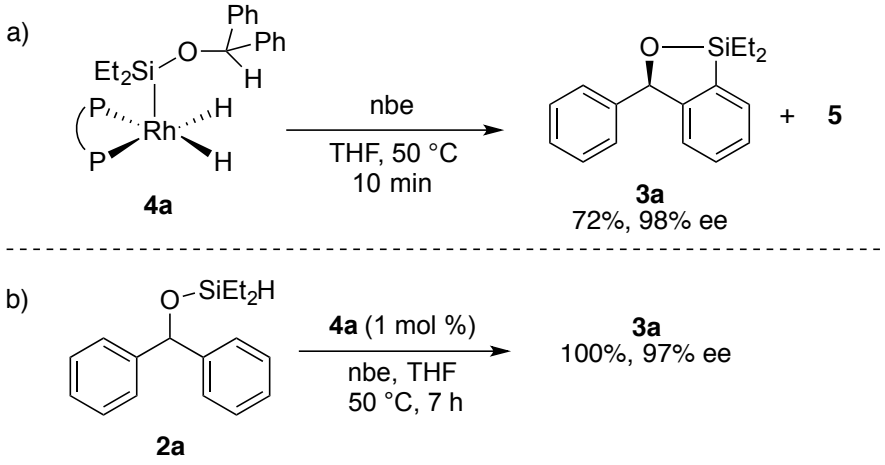
We assigned **5** and **5'** to be norbornyl rhodium complexes containing β-agostic interactions between the rhodium and a C–H bond of the norbornyl ligand. The signals at the chemical shift of –3.12 ppm (**5**) and –3.24 ppm (**5'**) were assigned to the agostic protons. These chemical shifts are more downfield than those of terminal rhodium hydride complexes[23-25] and are similar to those of other metal complexes that contain norbornyl ligands with agostic interactions.[26-31] The $^1J_{C–H}$ coupling constant of the agostic C–H bond of **5'** was ~60 Hz at –80 °C, as determined by 2D *J*-resolved $^{13}$C NMR spectroscopic analysis. This value is significantly lower than those of the analogous free C–H bonds and agrees with the previously reported values for C–H bonds engaged in agostic interactions.[32] In addition, the infrared spectrum of **5'** did not contain any bands attributable to Rh–H stretches, which further supports the assertion that **5'** is not a rhodium species containing a terminal metal hydride.[33]

Considering the structures of **4a** and **5**, we propose that the resting state of the catalytic reaction changes from **4a** to **5** during the catalytic process because the relative concentration of norbornene to the substrate **2a** increases. The change in the relative concentrations occurs because norbornene was used in slight excess, relative to **2a** and because a pathway for the catalytic conversion of **2a** to **3a** that does not require norbornene is followed in parallel with a pathway that requires norbornene. Consistent with this proposal, complex **5** was the major species at all times when the reaction was conducted with a larger excess (2.2 equiv) of norbornene.

*3.2.2 Evaluation of the kinetic competency of **4a***

The reactivity of the isolated complex **4a** was investigated to assess the relevance of the complex to the catalytic system (Scheme 3.2). The reaction of **4a** with norbornene in THF at 50 °C formed **3a** in 72% yield with 98% ee. The enantiomeric excess of this stoichiometric reaction was comparable to that of the catalytic reaction (99% ee). In addition, complex **5** formed as a product in this reaction. This result suggests that **4a** and **5** are potential intermediates in the catalytic reaction. The intermediacy of **4a** was further demonstrated by the reaction catalyzed by **4a**. The catalytic reaction of **2a** by complex **4a** resulted in the formation of **3a** in quantitative yield and 97% ee.

**Scheme 3.2** Reactivity of Complex **4a**




*3.2.3 Determination of the experimental rate law*

We determined the rate law of the silylation process by the method of initial rates with $[Rh(cod)Cl]_2$ and **L1** (Rh:**L1**=1:1.25) as the catalyst. The reaction was first order in catalyst and first order in silane **2a** when the concentration of **2a** was below ~0.33 M (0.83 equiv to nbe) and was zeroth order in **2a** when the concentration of **2a** was higher than ~0.33 M (Figure 3.3a). The dependence of the rate on the concentration of norbornene was more complex (Figure 3.3b). The reaction proceeded in the absence of norbornene,[34] but the reaction in the presence of norbornene was faster than that in the absence of norbornene. The rate was first order in norbornene up to ~0.40 M of norbornene (1.2 equiv to **2a**). However, the rate decreased with increasing concentrations of norbornene when the concentration of norbornene was higher than ~0.40 M.

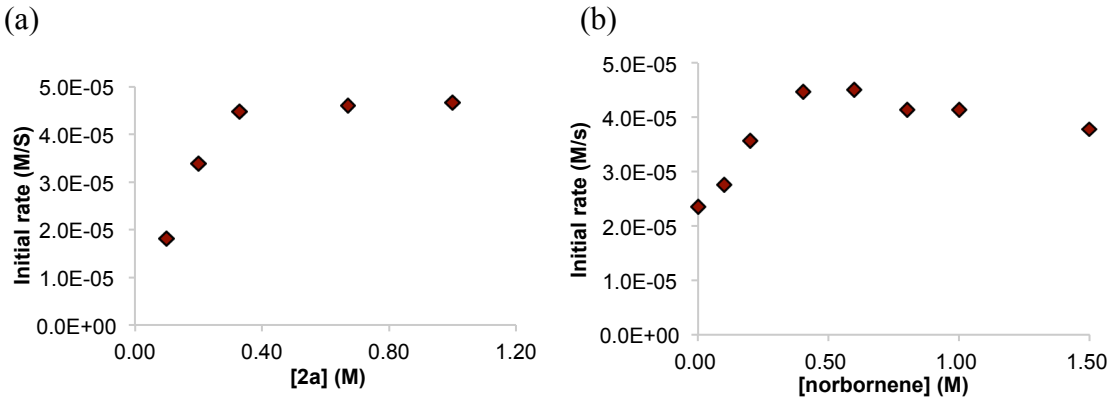



**Figure 3.3** Dependence of the rate of C−H silylation on the concentration of **2a** (a) and norbornene (b). Reactions were conducted with 3.3 mM of catalyst, 0.40 M of nbe (a), and 0.33 M of **2a** (b).

These findings are consistent with our proposal that the resting state of the reaction depends on the ratio of **2a** to norbornene. When [**2a**] was higher than [nbe], silyl complex **4a** was the major species, and this resting state led to a zeroth-order dependence

of the rate on [**2a**] and positive-order dependence of the rate on [nbe].[35] On the other hand, when [**2a**] was lower than [nbe], norbornyl complex **5** was the major rhodium species, and this change in the resting state led to a first-order dependence on [**2a**] and a partial inverse-order dependence on [nbe].

The partial inverse-order dependence on [nbe] when complex **5** was major rhodium species is likely to result from competitive pathways with different rate dependences on the concentration of norbornene (Figure 3.4). For the one pathway that is inversely dependent on the concentration of norbornene, complex **5** would react by reversible dissociation of norbornene to generate a 14-electron Rh(I) hydride **6**. For the pathway that is independent of the concentration of norbornene, complex **5** could react directly with silane to form silyl hydride complex **7a** or **5** could react in a multi-step sequence involving release of norbornene to form **6**, addition of silane to **6** to form dihydride silyl complex **4a**, and insertion of norbornene into the hydride of **4a** to generate **7a**. This multi-step process would be zero-order in norbornene because it dissociates and adds prior to the rate-limiting transition state. If pathways with inverse and zero-order dependences on norbornene occur competitively, then the complex kinetic behavior in Figure 3b would be observed.

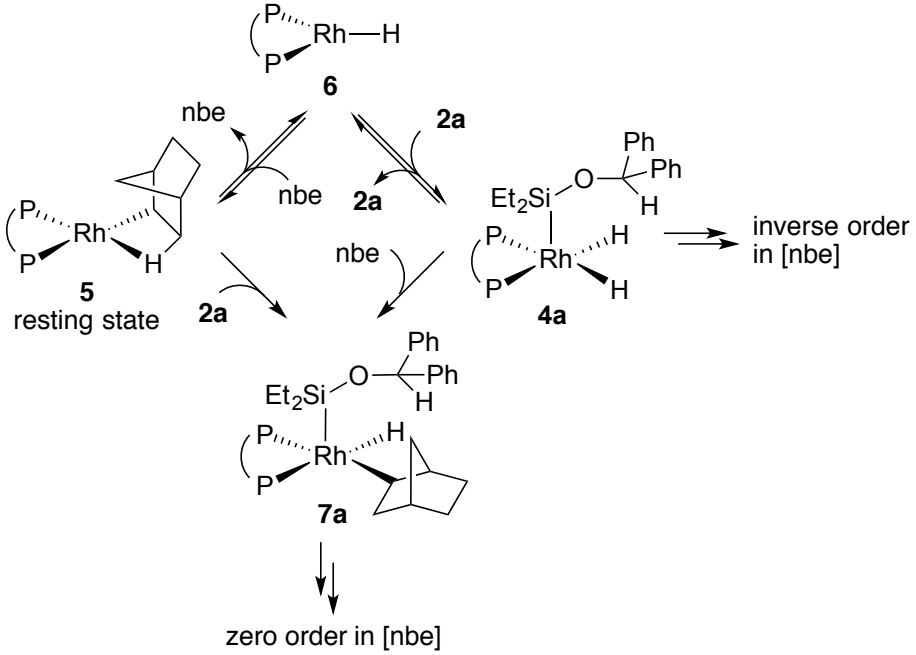



**Figure 3.4** Competitive pathways responsible for the partial inverse-order rate dependence on [nbe] when complex **5** is the resting state.

As shown in Figure 3.4, the insertion of norbornene into rhodium silyl dihydride **4a** or the addition of silane **2a** into **5** leads to formation of complex **7a**. The distinction between these two pathways is subtle because they are indistinguishable by the kinetic analysis of the catalytic reaction. Therefore, we conducted DFT calculations to determine which pathway is preferred (Figure 3.5).

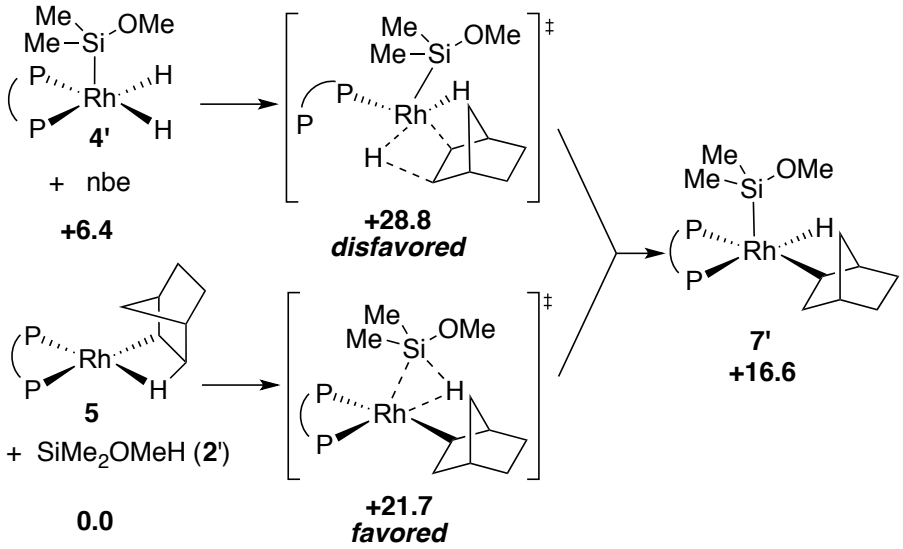



**Figure 3.5** Computed pathways for the formation of **7'**.

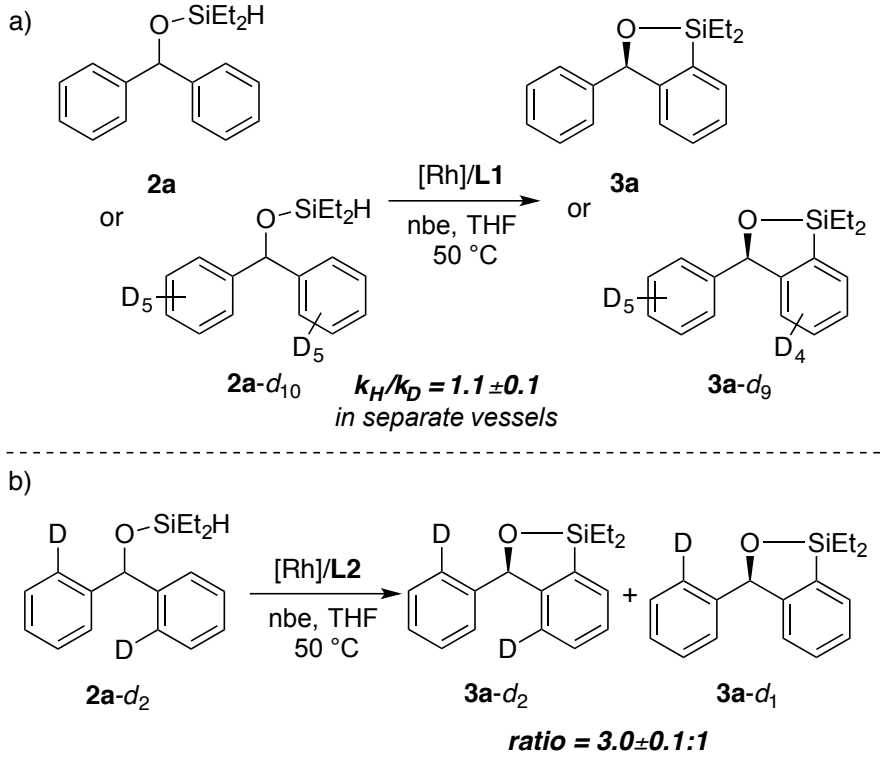
This calculation was performed on model compounds **2'**, **4'**, and **7'** to simplify the calculation while maintaining the electronic environment on the silicon. The structures of intermediates and transition states were optimized using the B3LYP functional with the lanl2dz basis set for rhodium and the 6-31G** basis set for all other atoms. Single-point energy calculations with solvent correction (THF, SMD) were conducted using the M06 functional with the lanl2tz basis set for rhodium and the 6-311++G** basis set for all other atoms.[36]

As shown in Figure 3.5, the computed transition state for the insertion of norbornene into **4'** to form **7'** was 7.1 kcal higher than that for the oxidative addition of the Si–H of **2'** into **5**. These calculations imply that complex **7a** is likely to be generated from the reaction between **5** and **2a**, not from the reaction between **4a** and norbornene.

*3.2.4 Measurement of kinetic isotope effect*

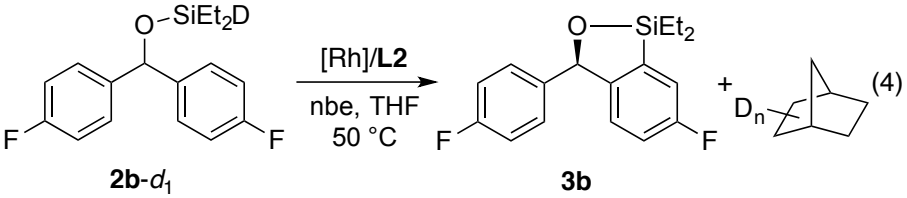
We determined the kinetic isotope effect (KIE) by measuring the initial rates of the silylation of **2a** and **2a**-$d_{10}$ in separate vessels (Figure 3.3a). The KIE from this set of experiments was 1.1 ± 0.1. This value indicates that C–H bond cleavage is not the rate-determining step.[37] To assess the reversibility of the C–H bond cleavage step, we measured an intramolecular KIE. The reaction of **2a**-$d_2$ (Scheme 3.3b) gave a mixture of **3a**-$d_2$ and **3a**-$d_1$ in a 3.0 ± 0.1 : 1 ratio. This KIE is primary, but the modest value suggests that the C–H bond oxidative addition step could be partially reversible[38] and that both the oxidative addition of the C–H bond and reductive elimination to form the C–Si bond could affect the enantioselectivity.

**Scheme 3.3** Kinetic isotope effects



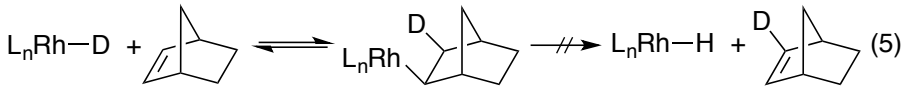

*3.2.5 Deuterium labeling study*

We studied reactions of a substrate **2b**-$d_1$ to gain further insight into the reaction mechanism (eq 4). When the silylation of **2b**-$d_1$ was conducted with the catalyst containing **L2** and norbornene, deuterium was incorporated only into norbornane. The absence of deuterium in aryl C–H bonds of the remaining **2b**-$d_1$ at partial conversion or in **3b** at partial or full conversion indicates that the rhodium deuteride species does not cleave the C–H bond to generate an intermediate with two equivalent or interconverting hydrides. Because the C–H cleavage step is likely to be partially reversible, according to the moderate intramolecular KIE value and computational studies described in the next section, incorporation of deuterium into the aryl C-H bonds in **2b**-$d_1$ or **3b** would be observed if a rhodium deuteride species undergoes oxidative addition of the C–H bond.

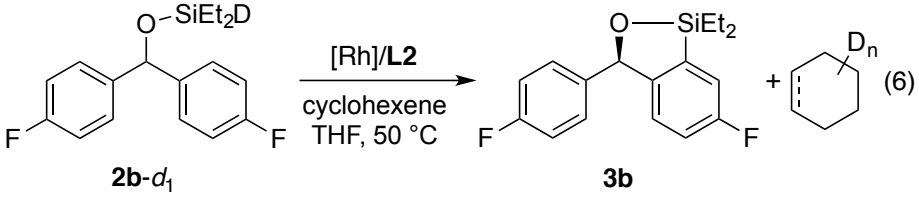



We sought to investigate the reversibility of insertion of the hydrogen acceptor into the rhodium hydride by testing for the incorporation of deuterium into the remaining hydrogen acceptor. Although we used norbornene in our synthetic studies, norbornene is not a suitable hydrogen acceptor for this study because deuterium would not be

incorporated into norbornene, even if the insertion process were reversible. The insertion occurs by *syn*-insertion, and the reverse reaction occurs by *syn*-β-H elimination. Thus, deuterium would not be present in nobornene after the β-H elimination (eq 5).




Instead, we conducted the silylation of **2b**-$d_1$with cyclohexene as a hydrogen acceptor (eq 6). In this experiment, we observed the incorporation of deuterium into both cyclohexene and cyclohexane.[39] This result suggests that the insertion of the rhodium hydride into the hydrogen acceptor is reversible.




*3.2.6 Computational study of the origin of enantioselectivity*

We conducted DFT calculations to investigate the origin of enantioselectivity. We calculated the energies of intermediates and transition states involved in the oxidative addition of the C–H bond and reductive elimination to form the C–Si bond (Figure 3.6).[40] The computational method described previously in 3.2.3 was used in this calculation.

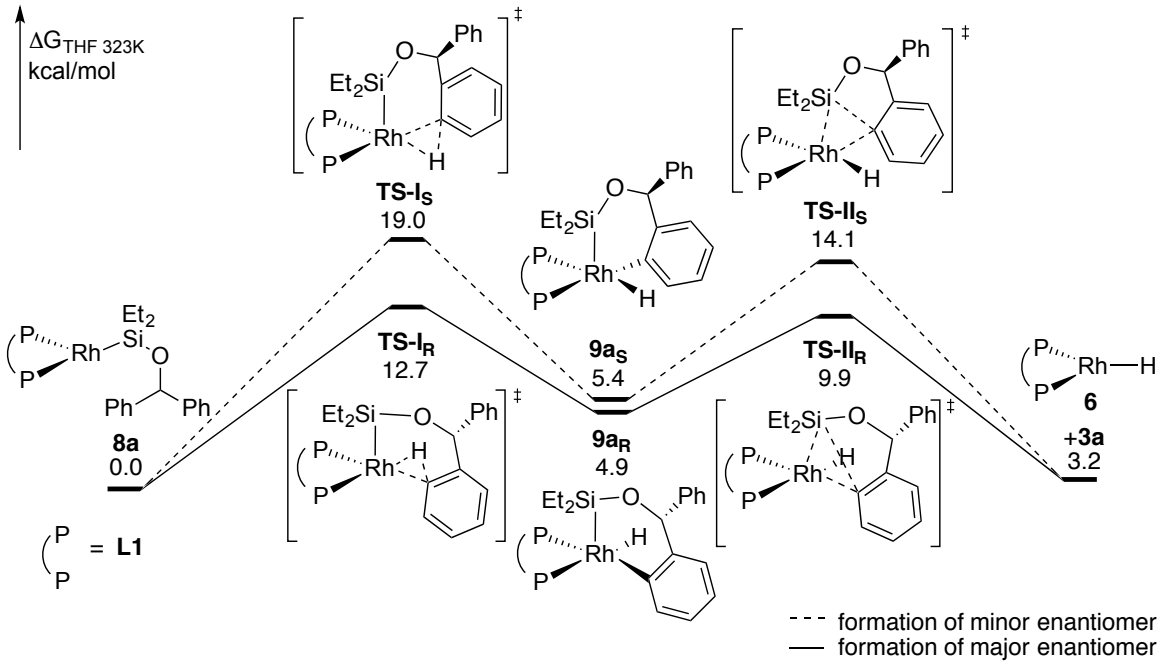



**Figure 3.6** Computed pathways for the C–H oxidative addition and C–Si reductive elimination.

As shown in Figure 3.6, the computed transition state for the oxidative addition of the C–H bond in the pathway to form the major enantiomer was 2.8 kcal higher than that

for the reductive elimination of the C–Si bond in the same pathway. This result suggests that oxidative addition could be the enantioselectivity-determining step. However, the intramolecular KIE was calculated to be 4.2, and this value is higher than the experimental value of 3.0. This difference implies that the difference in energy between the two steps could be overestimated by the DFT calculation. If the barrier for the C–H oxidative addition step were reduced by 3.0 kcal or the barrier for the C–Si reductive elimination were increased by 3.0 kcal without changing the KIE's of each elementary step, the computed KIE would be 3.5 (See the Experimental for the details). Based on this analysis, we suggest that the energy barriers for the oxidative addition of the C–H bond and reductive elimination to form the C–Si bond are likely to be similar to each other, and both steps are likely to affect the enantioselectivity of the silylation process.

The difference in free energy between the transition states to form the major and minor enantiomers was calculated to be 6.3 kcal for the C–H oxidative addition step and 4.2 kcal for the C–Si reductive elimination step. These values are line with the observed enantiomeric excess of 99%.

Comparison of the diastereomeric transition states leading to the formation of two enantiomers revealed the origin of the enantioselectivity (Figure 3.7). Three phenyl groups of **L1** project toward the coordination sites of the bound substrate, rendering quadrants II, III and IV less accessible than quadrant I (Figure 3.7a). In **TS-I$_R$** and **TS-I$_S$**, an ethyl group on the silicon of the substrate points towards **L1** (Figure 3.7b and 3.7c). In **TS-I$_R$**, the silyl group is placed in quadrant I, minimizing the steric repulsion between the ethyl group of the substrate and the phenyl group of the ligand. A similar arrangement exists in the experimental solid-state structure of the silyl complex **4a**. In this structure, the silyl group resides in quadrant I, presumably to avoid unfavorable interaction with the ligand (Figure 3.2). In **TS-I$_S$**, however, the silyl group lies in quadrant II to avoid the steric interaction between **L1** and the phenyl group of the substrate that is not reacting. This conformation places the ethyl group proximal to the phenyl group in quadrant II, causing an unfavorable steric interaction. Similar analysis of the transition states **TS-II$_R$** and **TS-II$_S$** indicates that an analogous interaction causes the energy of **TS-II$_S$** to be higher than that of **TS-II$_R$**. Thus, these calculations indicate that the difference in orientations of the substrate in the diastereomeric transition states gives rise to the high level of enantioselectivity.

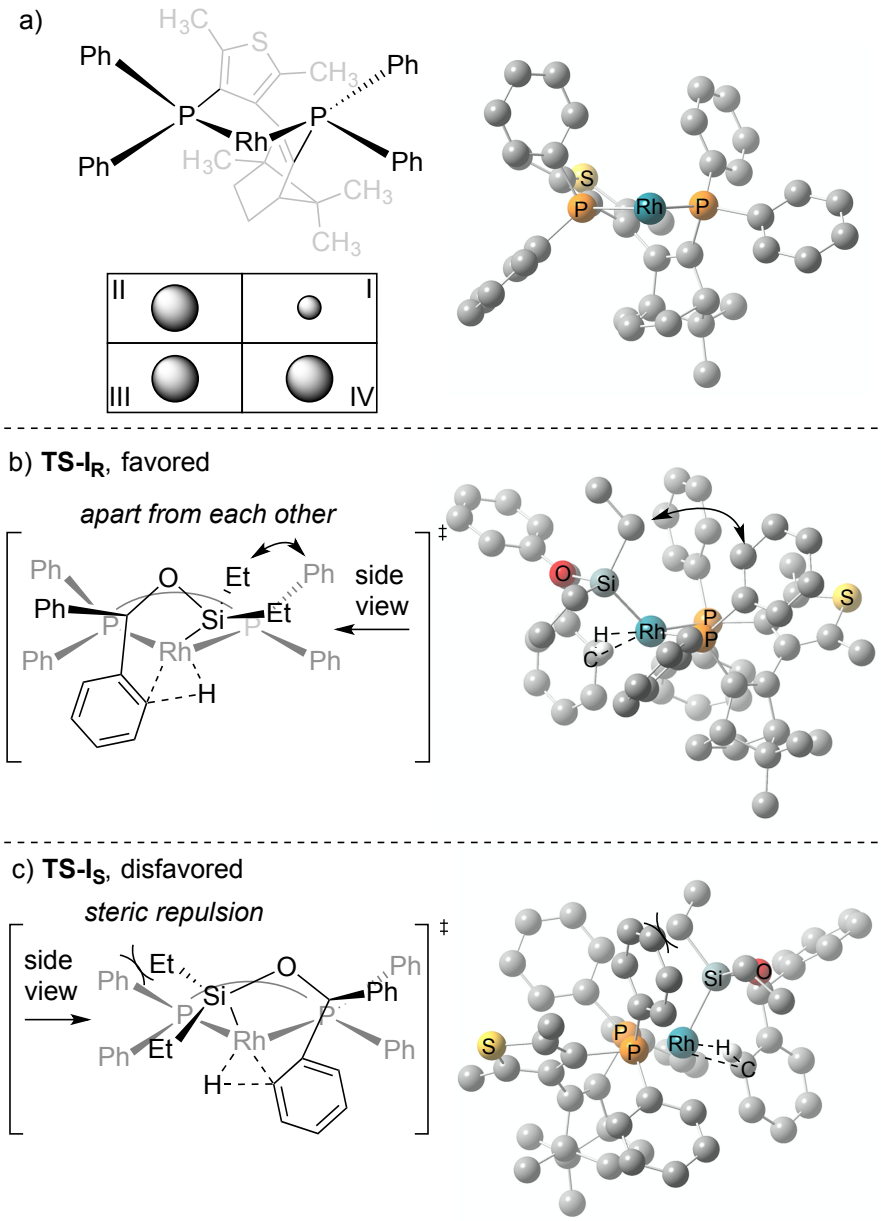
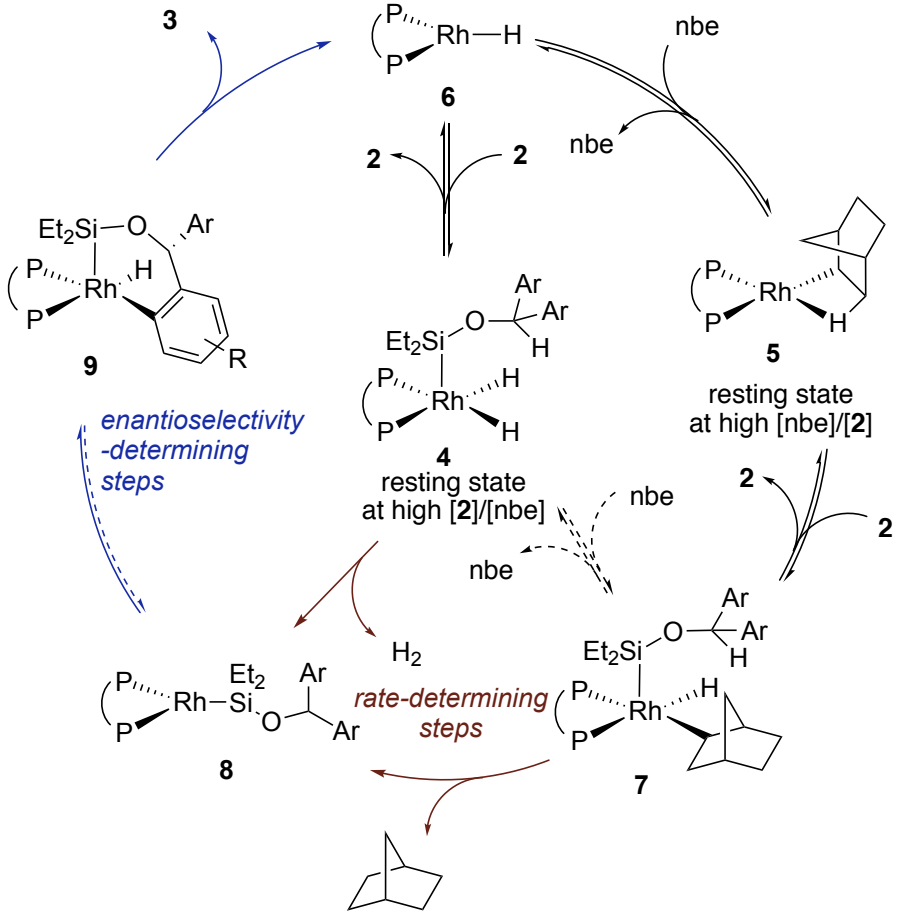



**Figure 3.7** Computed structures of the transition states of the C–H oxidative addition step: a) Rhodium ligated by **L1** in **TS-I$_R$**, b) **TS-I$_R$** and c) **TS-I$_S$**. Hydrogen atoms have been omitted except for the ones in C–H bonds being cleaved.

*3.2.7 Proposed mechanism*

Based on the results described above, we propose that the rhodium-catalyzed enantioselective silylation of aryl C–H bonds occurs by the mechanism shown in Scheme 3.4.

**Scheme 3.4** Proposed mechanism of enantioselective silylation of aryl C-H bonds




In this mechanism, the catalyst resting state is either **4** or **5**, and the identity of the resting state depends on the relative concentrations of the silane **2** and norbornene. The addition of silane **2** into **5** generates **7**. Although intermediate **7** can be formed by the insertion of norbornene into rhodium silyl dihydride **4**, we disfavor this alternative mechanism based on the higher barrier computed by DFT for this pathway than that computed for the addition of **2** into **5**. Either process that forms **7** is likely to be reversible because we observed the incorporation of deuterium into a hydrogen acceptor, cyclohexene, when a silane containing a Si–D bond was used.

Intermediate **7** can then undergo reductive elimination to generate intermediate **8** and norbornane. Alternatively, **8** can be formed by the reductive elimination of $H_2$ from **4**. Intermediate **8** would then undergo oxidative addition of the C–H bond. Oxidative addition of the C–H bond by complex **8** is consistent with the lack of deuterium

incorporation into the aryl C–H bonds from reactions with the substrate containing an Si–D bond. If other intermediates, such as **4** or **7**, cleaved the C–H bond, incorporation of deuterium into the aryl C–H bonds in **2** or **3** would occur because the oxidative addition of the C–H bond is partially reversible.

Reductive elimination occurs to form the C–Si bond of silylation product **3** and rhodium hydride species **6**. The transition-state energy for this step is likely to be similar to that of the previous step (oxidative addition of the C–H bond) and to influence the enantioselectivity together with the preceding C–H bond cleavage step, according to the results from the measurement of the KIE from an intramolecular competition between the silylations of C–H and C–D bonds and DFT calculations. Intermediate **6** then can be converted to the catalyst resting states **4** or **5** by addition into the Si–H bond of **2** or by insertion of norbornene.

Because the C–H bond cleavage step is not rate-determining, according to the KIE value of 1.1 for side-by-side reactions, and the energies of the transition states for oxidative addition of the C–H bond and reductive elimination to form the C–Si bond are likely to be similar to each other, for the reasons discussed above, we propose that reductive elimination of norbornane or dihydrogen to generate a Rh(I) silyl complex **8** is the rate-determining step for this silylation process. The generation of a Rh(I) silyl complex is the same process proposed to be rate-determining in the mechanism of intermolecular silylation of aryl C–H bonds.[5]

## 2.3 Conclusions

The identity of the resting states of the catalyst, the kinetic data, and the results of DFT calculations provide detailed insights into the mechanism of intramolecular enantioselective silylation of aryl C-H bonds and the origin of enantioselectivity. We showed that the rhodium silyl dihydride and the rhodium norbornyl complex are the catalyst resting states. The kinetic isotope effect measured in separate vessels was close to 1, implying that oxidative addition of the C–H bond is not the rate-determining step. However, the KIE from an intramolecular competition between the silylations of C–H and C–D bonds was 3.0. This value and the results from the DFT calculation suggest that the transition-state energies of the C–H bond cleavage step and the C–Si bond forming step are close to each other and, therefore, affect the enantioselectivity of this silylation process together. In addition, the examination of calculated diastereomeric transition states indicates that the steric interaction between the alkyl substituent of the silicon on the substrate and the aryl group on the bisphosphine ligand lead to the high level of enantioselectivity.

This work constitutes a rare systematic mechanistic study on enantioselective C–H bond functionalization[41-44] and the first on the enantioselective functionalization of C–H bonds with main group reagents. By conducting a combination of experimental and theoretical studies, we elucidated the enantioselectivity-determining steps and the origin of the high enantioselectivity. We envision that insights obtained from this study may serve as a guideline for the design of catalysts for enantioselective C–H functionalization.

## 3.4 Experimental

*2.4.1 Methods and Materials*

All air-sensitive manipulations were assembled in an $N_2$-filled glovebox using oven-dried glassware. $[Rh(cod)Cl]_2$ was prepared according to the standard procedure.[45] $[Rh(C_2H_4)Cl]_2$ , **L1**, and **L2** were purchased from Strem and were used as received. Silanes **2a**, **2a**-$d_{10}$, and **2a**-$d_2$ were prepared from the hydrosilylation of benzophenone and benzophenone-$d_{10}$[46] and the dehydrogenative silylation of benzhydrol-$d_2$[47] according to the procedure described in Chapter 2.[15] The silane **2b**-$d_1$ was prepared according to a literature procedure.[18] Norbornene (nbe) was purchased from Aldrich and was used as received. Tetrahydrofuran (THF) was degassed by purging with nitrogen and then dried with a solvent purification system containing activated alumina. All other solvents and reagents were used as received.

Reaction temperatures above 23 °C refer to the temperature of an aluminum heating block, which was controlled by an electronic temperature modulator. NMR spectra were recorded on Bruker AVQ-400, AV-500, DRX-500 and AV-600 instruments. $^1$H NMR chemical shifts (δ) are reported in ppm relative to the residual solvent signal. $^{31}$P NMR chemical shifts were reported relative to an external $H_3PO_4$ (85% aqueous) sample. Elemental analysis was conducted at the Micro Analytical Facility in the College of Chemistry, University of California, Berkeley. Chiral SFC analysis was conducted on a Waters chromatography system.

*3.4.2 Observation of the Resting States*

Diethyl(hydrido)silyl ether **2a** (54.1 mg, 0.200 mmol) was treated with norbornene (22.6 mg, 0.240 mmol), and a freshly prepared stock solution of a rhodium precursor ($[Rh(C_2H_4)Cl]_2$ or $[Rh(cod)Cl]_2$, 5 μmol, 2.5 mol %) and **L1** (10 μmol, 5.0 mol %) in THF (0.4 mL) in a 4 mL vial. The solution was transferred to a J-Young NMR tube. The reaction was monitored by $^{31}$P NMR spectroscopy at 50 °C. A higher catalyst loading of 5 mol % (in contrast to 1 mol % used in preparative reactions) was used to facilitate the observation of the resting states.

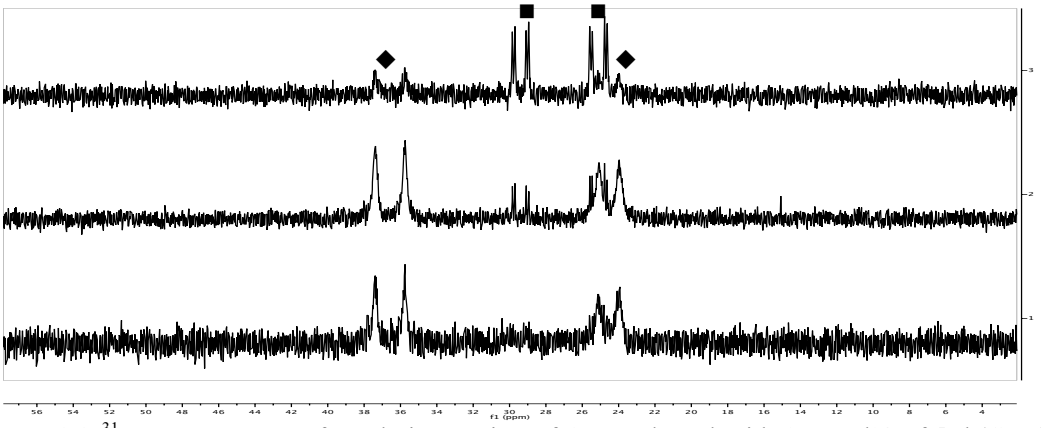


**Figure 3.8** $^{31}$P NMR spectra of catalytic reaction of **2a** conducted with 2.5 mol% of $[Rh(C_2H_4)Cl]_2$, 5 mol% of **L1**, and 1.2 equivalent of norbornene at (a) 5 min (~40% conversion), (b) 10 min (~70% conversion) and (c) 15 min (~90% conversion). **4a** (■), **5** (◆).

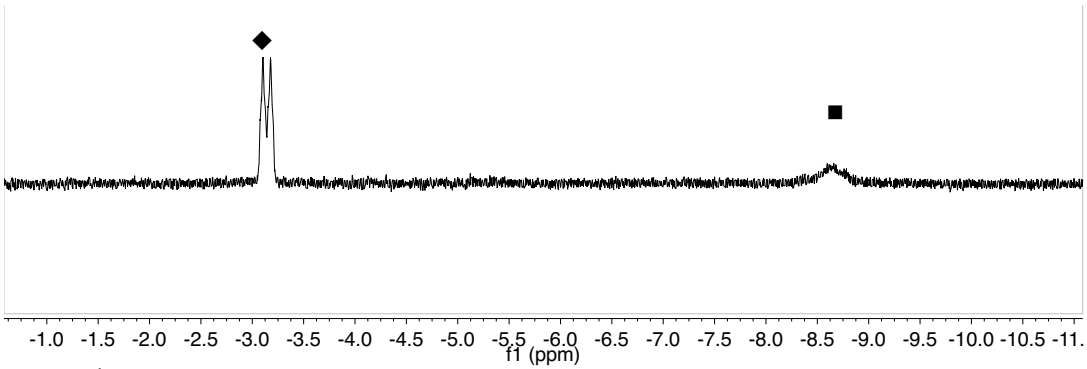



**Figure 3.9** $^{1}$H NMR spectrum of catalytic reaction of **2a** conducted with 2.5 mol % of $[Rh(C_2H_4)Cl]_2$, 5 mol% of **L1**, and 1.2 equivalent of norbornene at 10 min (71% conversion). **4a** (■), **5** (◆).

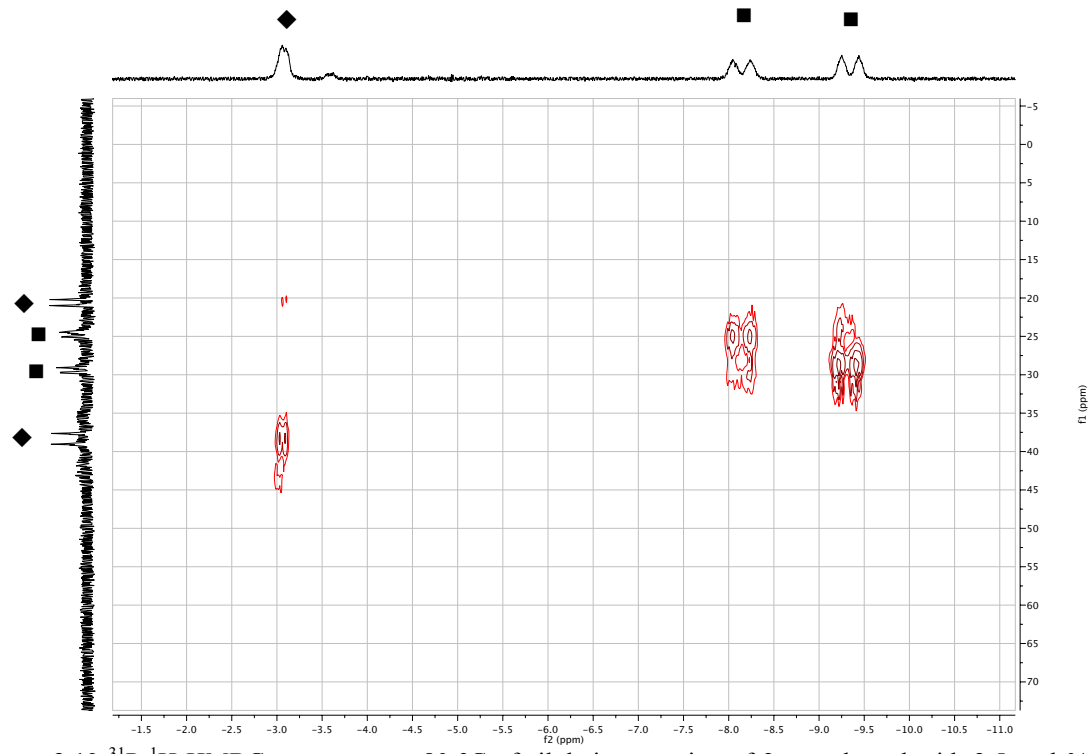
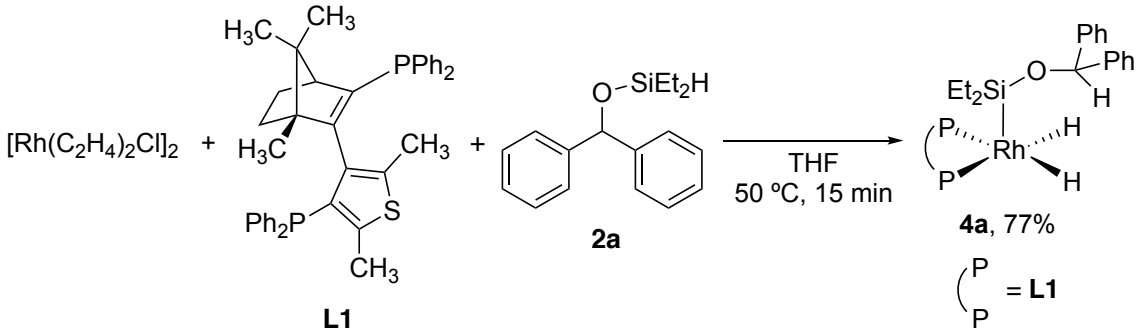



**Figure 3.10** $^{31}$P-$^{1}$H HMBC spectrum at –80 °C of silylation reaction of **2a** conducted with 2.5 mol % of $[Rh(C_2H_4)Cl]_2$, 5 mol % of **L1**, and norbornene. **4a** (■), **5** (◆, major isomer labeled).

*3.4.4 Synthesis and Characterization of Complex **4a***




To a solution of $[Rh(C_2H_4)_2Cl]_2$ (11.7 mg, 0.0301 mmol) and **L1** (36.9 mg, 0.0600 mmol) in THF (1.2 mL) was added **2a** (163 mg, 0.603 mmol), and the mixture was stirred at 50 °C for 15 min, during which time the mixture turned from dark red to orange. The volatile materials were evaporated, and the residual mixture was washed with pentane to afford complex **4a** as a yellow solid (45.5 mg, 77% yield). **$^1$H NMR** (600 MHz, THF-$d_8$) δ 7.90 (t, J=7.2 Hz, 2H), 7.85 (t, *J*=9.3 Hz 2H), 7.74 (t, *J*=8.1 Hz, 2H), 7.41 (s, 3H), 7.34 – 6.93 (m, 21H), 6.09 (s, 1H), 2.48 (s, 3H), 2.00 (s, 1H), 1.91 (t, *J* = 9.9 Hz, 1H), 1.61 (td, *J* = 8.7, 4.4 Hz, 1H), 1.23 (s, 3H), 1.13 (s, 3H), 0.84 (t, *J* = 10.6 Hz, 1H), 0.77 (s, 3H), 0.71 – 0.59 (m, 9H), 0.44 – 0.35 (m, 1H), 0.35 – 0.28 (m, 1H), 0.11 (t, *J* = 10.1 Hz, 1H), 0.08 – 0.01 (m, 1H), -0.07 – -0.17 (m, 1H), -8.21 (br d, *J* = 76.1 Hz, 1H), -9.16 (br d, *J* = 78.0 Hz, 1H). **$^{31}$P NMR** (243 MHz, THF-$d_8$) δ 29.39 (dd, $J_{P\text{-}Rh}$ = 122.6, $J_{P\text{-}P}$ = 22.6 Hz), 25.11 (dd, $J_{P\text{-}Rh}$ = 131.2, $J_{P\text{-}P}$ = 22.6 Hz). Anal. Calcd (%) for $C_{57}H_{63}OP_2RhSSi$ : C, 69.22, H, 6.42, S 3.24. Found: C, 69.14, H, 6.56, S 3.56.

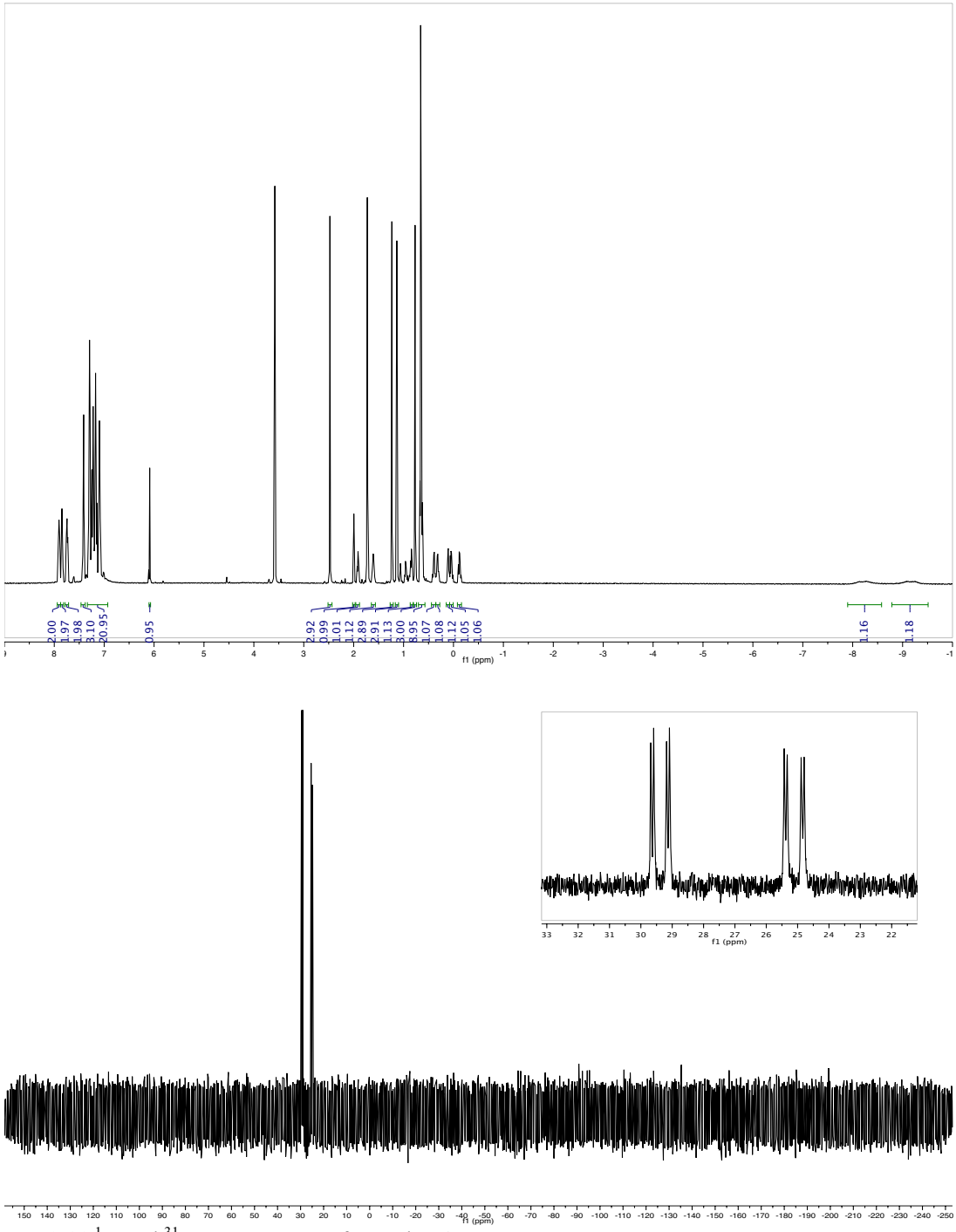



**Figure 3.11** $^{1}H$ and $^{31}P$ NMR spectra of complex **4a**.

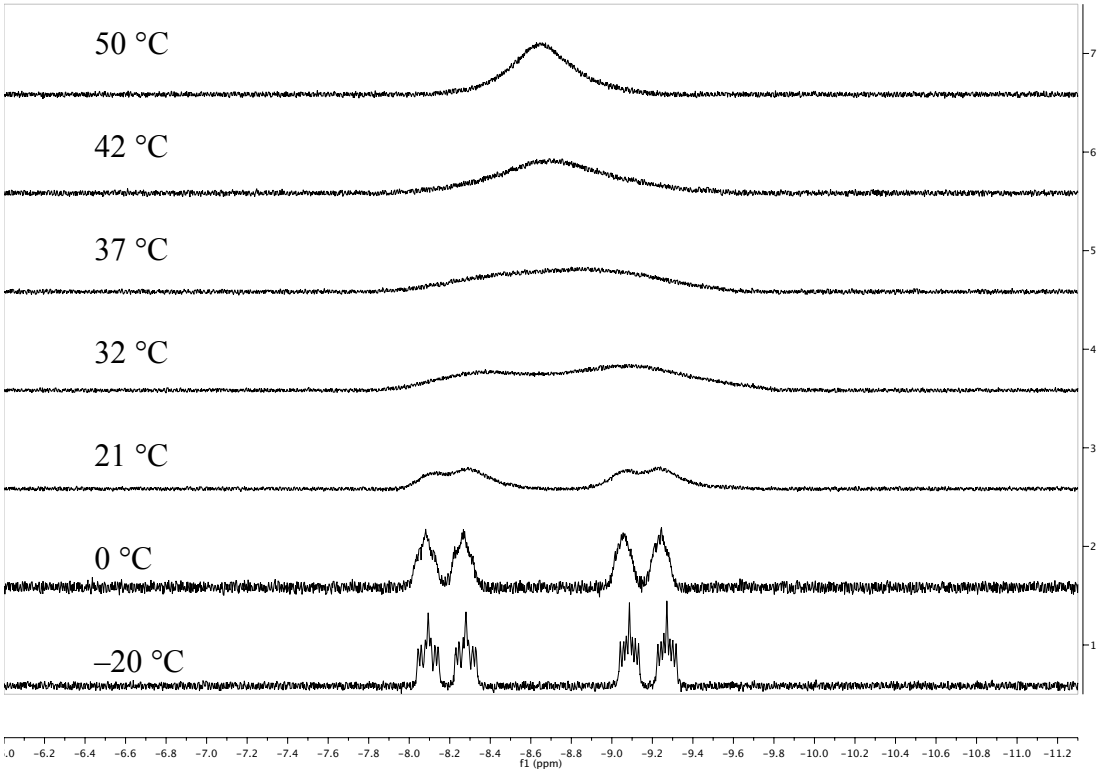



**Figure 3.12** Variable-temperature $^{1}$H spectra of complex **4a** (hydride region) between 50 °C and –20 °C, measured by a 500 MHz NMR spectrometer. Hydride signals at –20 °C: $^{1}$H NMR (500 MHz, THF-$d_8$) δ -8.19 (dddd, $J$ = 93.2, 24.9, 17.7, 8.0 Hz, 1H), -9.18 (dddd, $J$ = 92.7, 22.7, 15.0, 8.0 Hz, 1H).

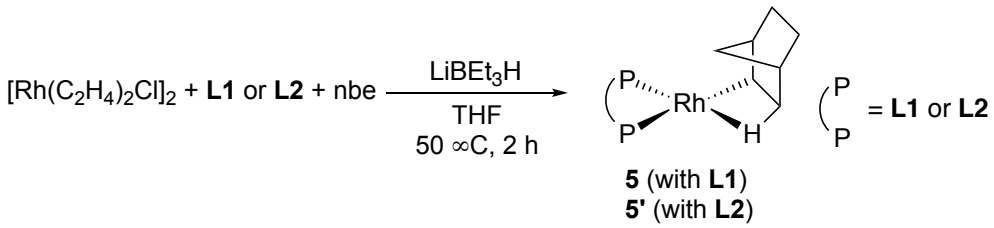
Single crystals of **4a** suitable for X-ray diffraction were obtained from a dilute solution of **4a** and **2a** in pentane at 25 °C. A yellow rod 0.060 x 0.040 x 0.030 mm in size was mounted on a cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using phi and omega scans. Crystal-to-detector distance was 40 mm and exposure time was 10 seconds per frame using a scan width of 0.5°. Data collection was 100.0% complete to 25.000° in q. A total of 71036 reflections were collected covering the indices, -26<=*h*<=26, -25<=*k*<=27, -11<=*l*<=11. 9051 reflections were found to be symmetry independent, with an $R_{int}$ of 0.0342. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be P $2_1$ $2_1$ 2 (No. 18). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. The absolute stereochemistry was unambiguously determined to be *R* at C16 and *S* at C14, respectively.

**Table 3.1** Crystal data and structure refinement for **4a**.

| | | |
|---|---|---|
| Empirical formula | $C_{57}H_{63}OP_2RhSSi$ | |
| Formula weight | 989.07 | |
| Temperature | 100(2) K | |
| Wavelength | 0.71073 Å | |
| Crystal system | Orthorhombic | |
| Space group | P $2_1$ $2_1$ 2 | |
| Unit cell dimensions | a = 22.1200(17) Å | α = 90°. |
| | b = 22.8814(16) Å | β = 90°. |
| | c = 9.7523(7) Å | γ = 90°. |
| Volume | 4936.0(6) $Å^3$ | |
| Z | 4 | |
| Density (calculated) | 1.331 $Mg/m^3$ | |
| Absorption coefficient | 0.517 $mm^{-1}$ | |
| F(000) | 2072 | |
| Crystal size | 0.060 x 0.040 x 0.030 $mm^3$ | |
| Theta range for data collection | 1.280 to 25.392°. | |
| Index ranges | -26<=h<=26, -25<=k<=27, -11<=l<=11 | |
| Reflections collected | 71036 | |
| Independent reflections | 9051 [R(int) = 0.0342] | |
| Completeness to theta = 25.000° | 100.0 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.928 and 0.852 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 9051 / 0 / 581 | |
| Goodness-of-fit on $F^2$ | 1.048 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0207, wR2 = 0.0457 | |
| R indices (all data) | R1 = 0.0224, wR2 = 0.0466 | |
| Absolute structure parameter | -0.022(5) | |
| Extinction coefficient | n/a | |
| Largest diff. peak and hole | 0.474 and -0.274 $e.Å^{-3}$ | |

*3.4.4 Synthesis and Characterization of Complex **5** and **5'***

To a solution of $[Rh(C_2H_4)_2Cl]_2$ (1.9 mg, 0.0050 mmol) and **L1** (6.1 mg, 0.010 mmol, for complex **5**) or **L2** (6.7 mg, 0.010 mmol, for complex **5'**) in THF (0.4 mL) was added norbornene (37.7 mg, 0.400 mmol), and the mixture was stirred at 50 °C for 2 hours. The volatile materials were evaporated to afford a mixture containing complex **5** or **5'** as a brown solid.




*NMR spectra data of **5** or **5'**:*

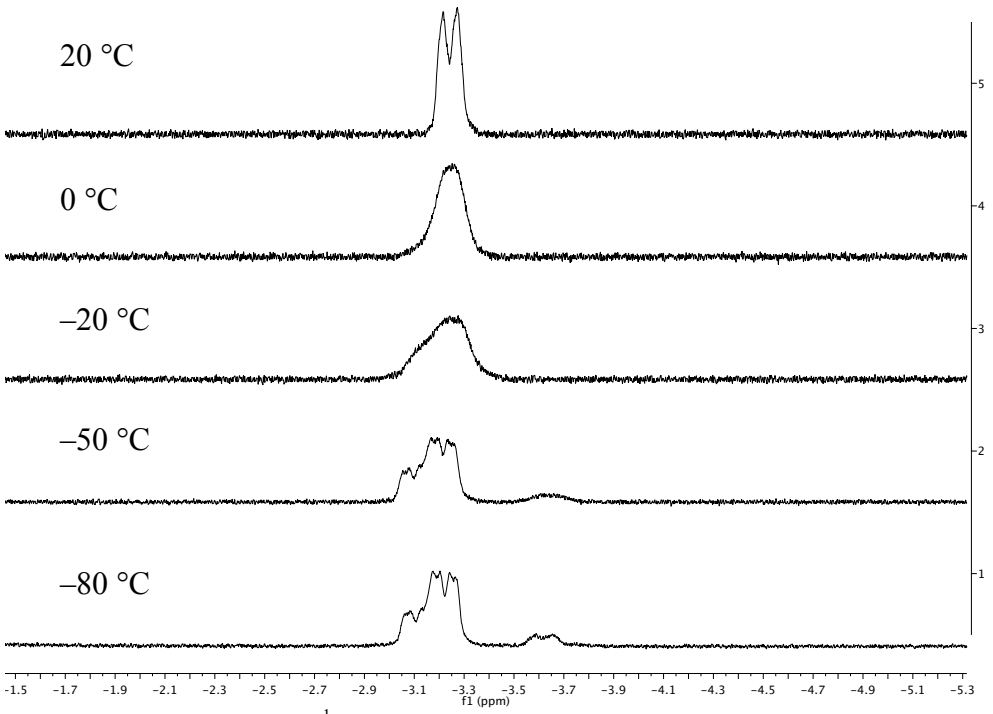



**Figure 3.13** Variable-temperature $^1$H spectra of complex **5'** (hydride region) between 19 °C and –80 °C. Three hydride signals corresponding to three isomers were observed at –80 °C: δ -3.11 (dd, $J$ = 33.7, 13.3 Hz), -3.22 (dd, $J$ = 32.8, 12.9 Hz), -3.62 (br d, $J$ = 35 Hz).

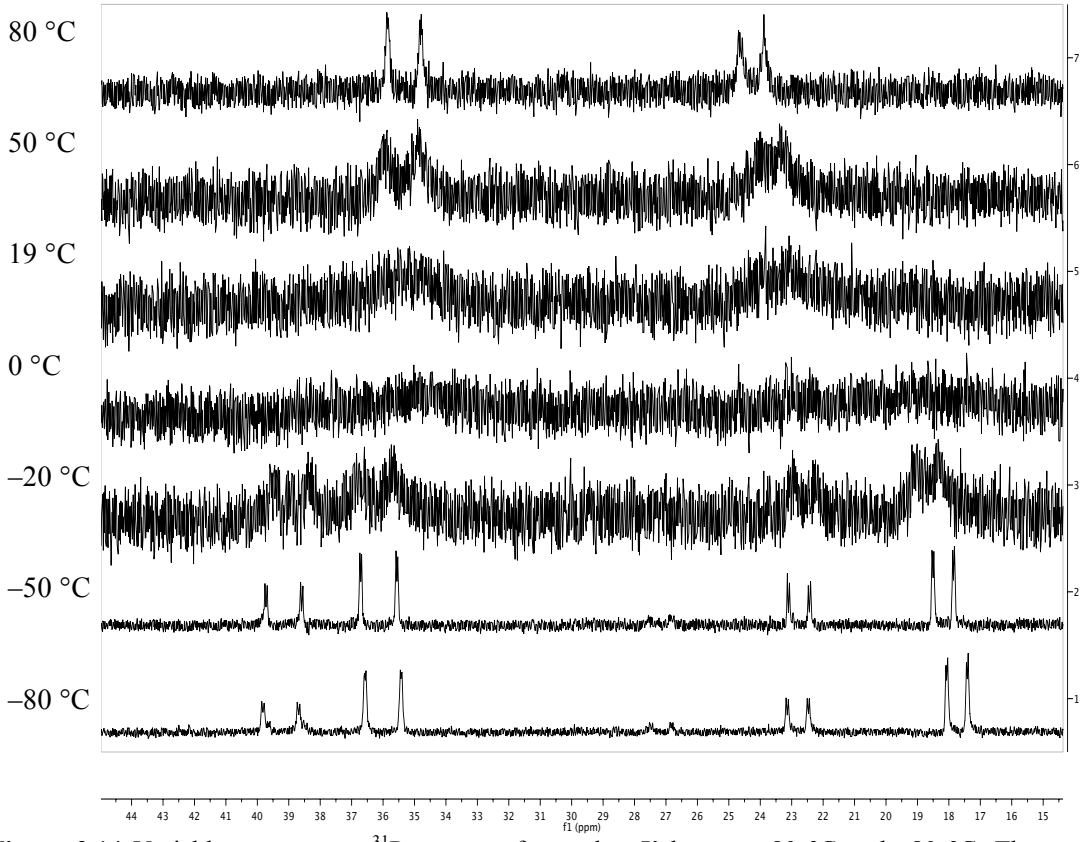



**Figure 3.14** Variable-temperature $^{31}P$ spectra of complex **5'** between 80 °C and –80 °C. Three sets of signals corresponding to three isomers were observed at –80 °C.

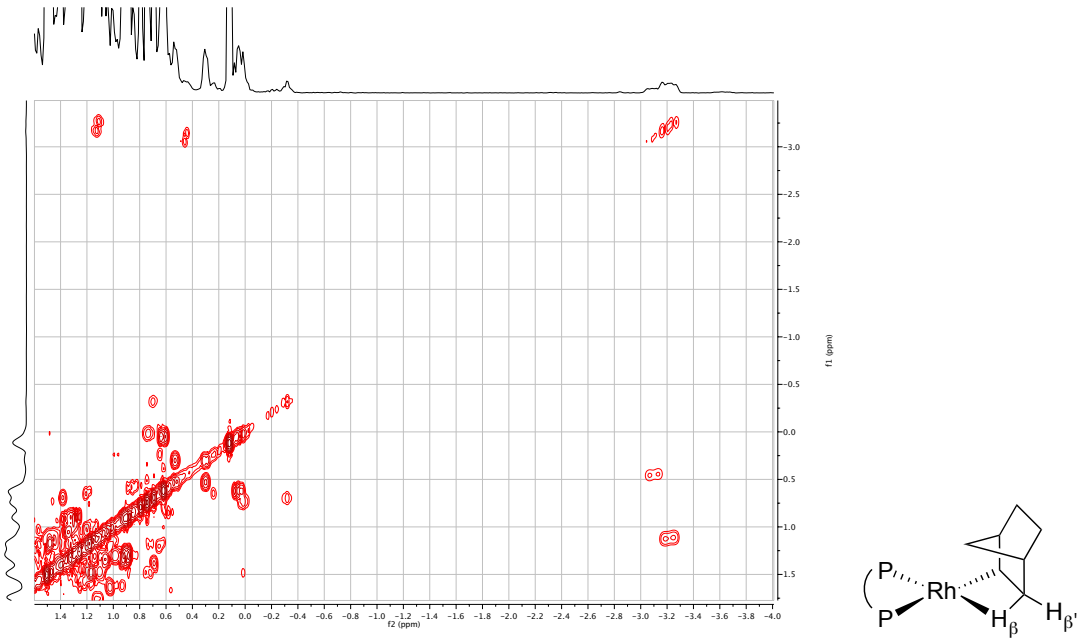



**Figure 3.15** $^{13}C$-$^{1}H$ COSY spectrum of **5'** at –80 °C showing the correlation between agostic $H_\beta$ and non-agostic $H_{\beta'}$ resonances.

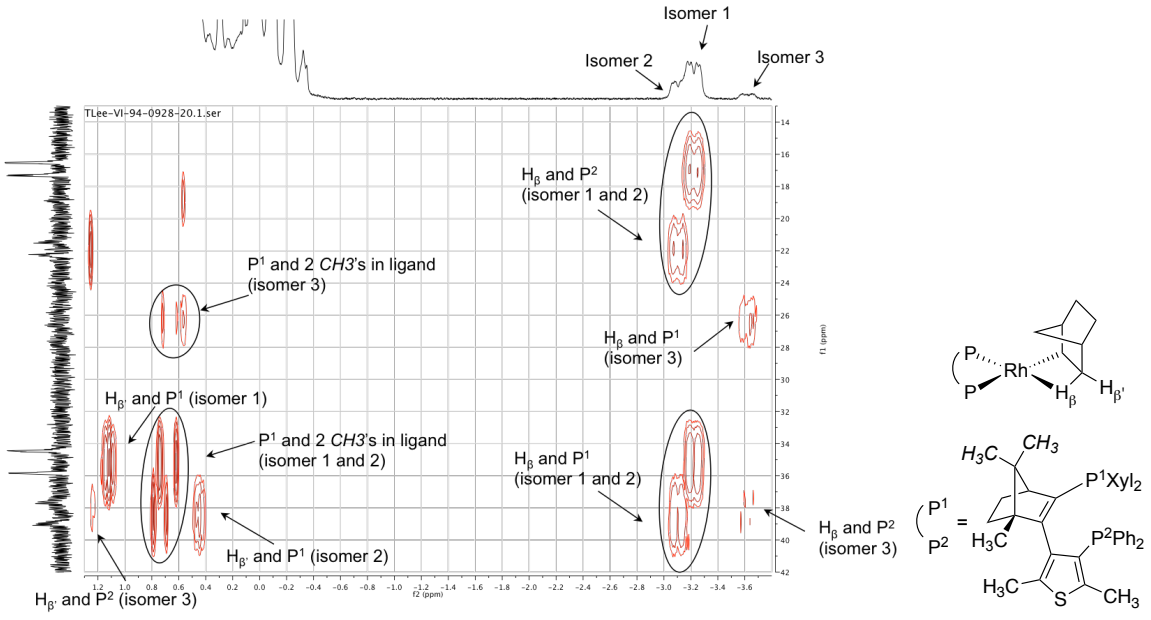
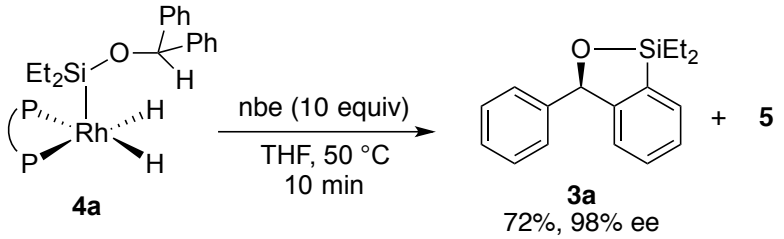
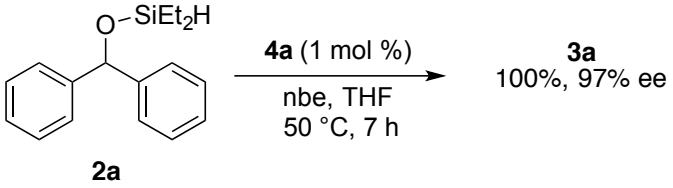



**Figure 3.16** $^{31}P$-$^{1}H$ HMBC spectrum of **5'** at –80 °C showing the correlation between the agostic $H_\beta$ and the ligand resonances.

*3.4.4 Examination of the Reactivity of Complex **4***




To a J-Young NMR tube was added complex **4a** (9.9 mg, 0.010 mmol), norbornene (9.6 mg, 0.10 mmol) and THF-$d_8$ (0.30 mL). The resulting mixture was heated at 50 °C for 10 min. The $^1$H NMR spectrum of this reaction mixture showed that **4a** was fully consumed and that **3a** and **5** formed in an equal amounts at this time. The yield of **3a** was determined by $^1$H NMR spectroscopy using 1,3,5-trimethoxybenzene as the internal standard added at the end of the reaction, and the enantiomeric excess was determined by chiral SFC analysis.




Diethyl(hydrido)silyl ether **2a** (41.1 mg, 0.153 mmol) was treated with norbornene (16.4 mg, 0.174 mmol), and a solution of **4a** (1.5 mg, 1.5 μmol, 1.0 mol %) in THF (0.4 mL) in a 4 mL vial. The resulting mixture was heated at 50 °C for 7 hours. The formation of **3a** was monitored by GC analysis with dodecane as the internal standard. The enantiomeric excess was determined by chiral SFC analysis.

*3.4.4 Determination of the Experimental Rate Law*

Silylation of **2a** was conducted in THF with a total volume of 300 μL by using the combination of $[Rh(cod)Cl]_2$ and **L1** (Rh:L ratio = 1:1.25) as the catalyst. The concentrations of each reagent under the standard conditions for the catalytic silylation are: 0.33 M **2a**, 0.40 M norbornene, and 3.3 mM catalyst. To determine the rate dependence on one reagent, the concentration of that reagent was varied while the concentration of other reagents and the total volume (300 μL) were held constant. The concentration of **2a** was varied between 0.10 and 1.0 M. The concentration of norbornene was varied between 0 and 1.5 M. The concentration of the catalyst was varied between 0.20 and 6.7 mM. The rate law of the reaction was determined by the method of initial rates at 50 °C monitored by GC analysis with dodecane as the internal standard.

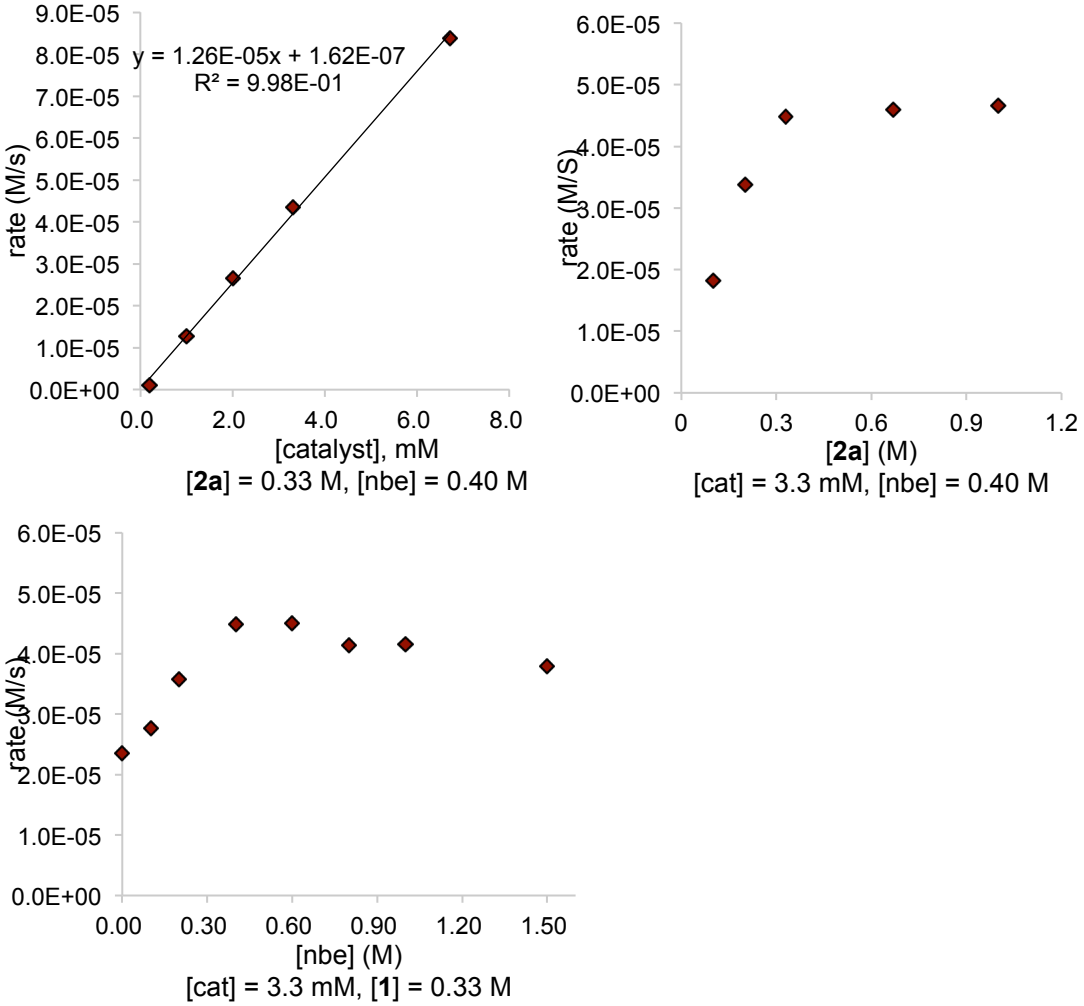



**Figure 3.17** Determination of the rate law for the silylation of **2a**.

Additional sets of data points were obtained to illustrate the saturation of the rate at high [**2a**] and [nbe] (Figure 3.18). The rate dependence on [**2a**] at [nbe] = 0.20 M and on [nbe] at [**2a**] = 0.20 M were measured.

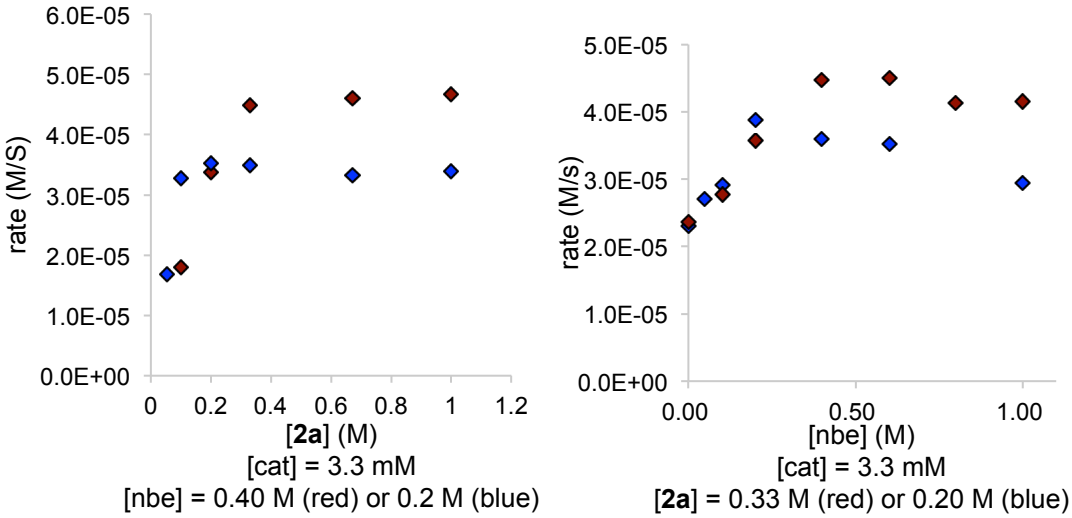



**Figure 3.18** Determination of the rate law for the silylation of **2a** illustrating the saturation of the rate at high [**2a**] at two concentrations of nbe, and the saturation of the rate at high [nbe] at two concentrations of **2a**.

The rate dependence on [**2a**] at [nbe] = 0 M was measured (Figure 3.19).

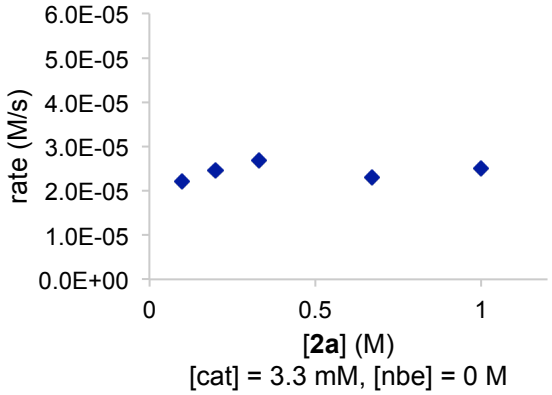
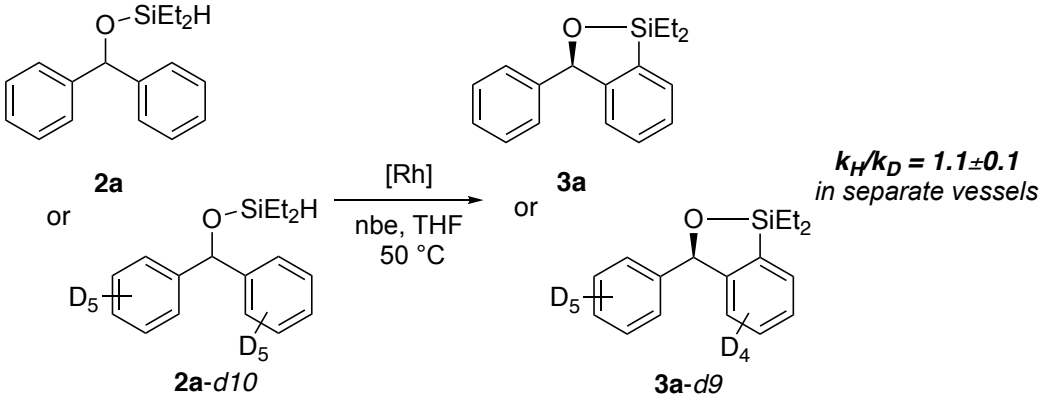
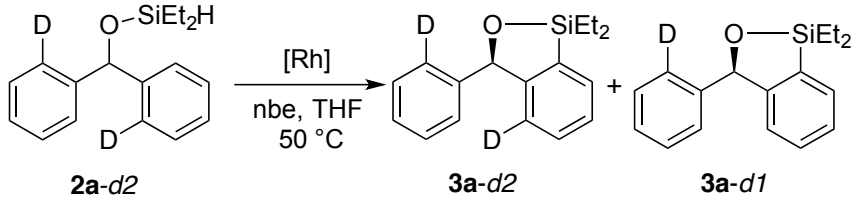



**Figure 3.19** Determination of the rate law for the silylation of **2a** at [nbe] = 0 M

### *3.4.4 Determination of the Kinetic Isotope Effect*



Silylation of **2a**–$d_{10}$ was conducted in THF with a total volume of 300 μL under the standard conditions. The concentrations of each reagent under the standard conditions were 0.33 M **2a**-$d_{10}$, 0.40 M norbornene and 3.3 mM catalyst. The initial rate of the reaction at 50 °C was determined by GC analysis with dodecane as the internal standard. From the initial rates for the silylation of **2a** and **2a**-$d_{10}$, the kinetic isotope effect was determined to be $k_H/k_D$ = 1.1±0.1 (average of two experiments).




***ratio = 3.0±0.1:1***

Diethyl(hydrido)silyl ether **2a**-$d_2$ (27.2 mg, 0.100 mmol) was treated with norbornene (11.3 mg, 0.120 mmol), and a solution of [Rh(cod)Cl]$_2$ (1.0 μmol, 1.0 mol %) and **L2** (2.5 μmol, 2.5 mol %) in THF (0.4 mL) in a 4 mL vial. The resulting mixture was heated at 50 °C for 24 h. The ratio of **3a**-$d_2$ and **3a**-$d_1$ was determined to be 3.0±0.1 : 1 by $^1$H NMR analysis (average of two experiments).

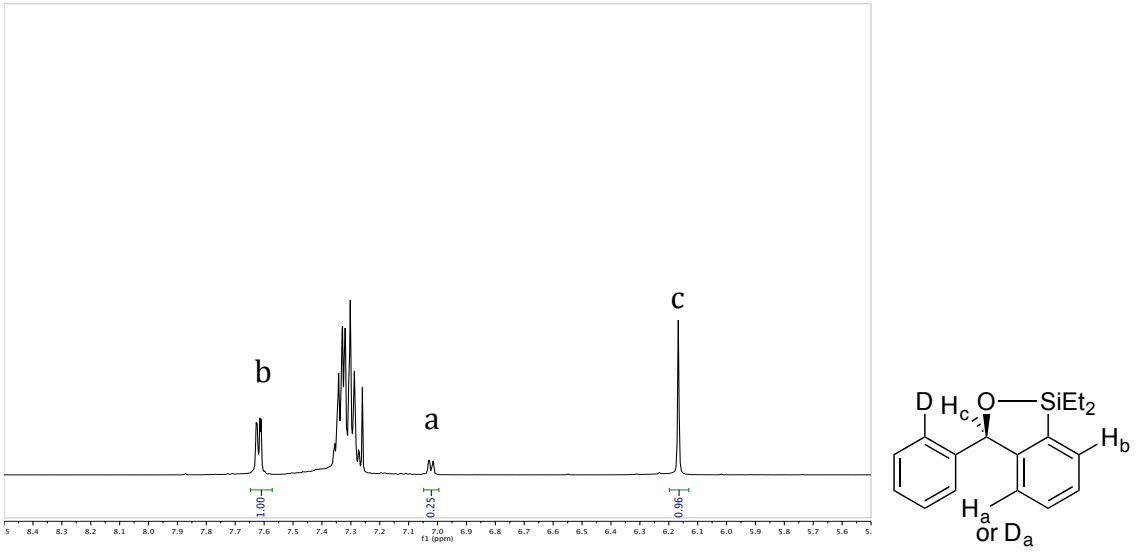
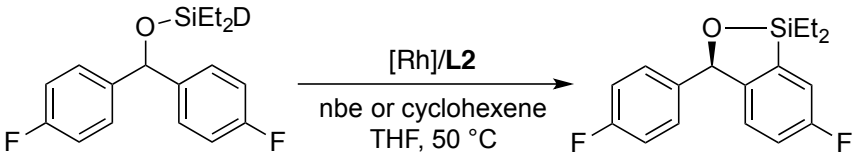



**Figure 3.20** $^1$H spectrum of the mixture of **3a**-$d_2$ and **3a**-$d_1$.

*3.4.5 Deuterium Labeling Study*




**2b**-$d_1$ **3b**

To a J-Young NMR tube was added diethyl(hydrido)silyl ether **2b**-$d_1$ (30.7 mg, 0.100 mmol), norbornene (11.3 mg, 0.120 mmol) or cyclohexene (12 μL, 0.12 mmol), and a solution of $[Rh(cod)Cl]_2$ (2.0 μmol, 2.0 mol %) and **L2** (5.0 μmol, 5.0 mol %) in THF (0.4 mL) and THF-$d_8$ (2 μL, standard) in a 4 mL vial. The resulting mixture was heated at 50 °C. The incorporation of deuterium was determined by $^2$H NMR analysis.

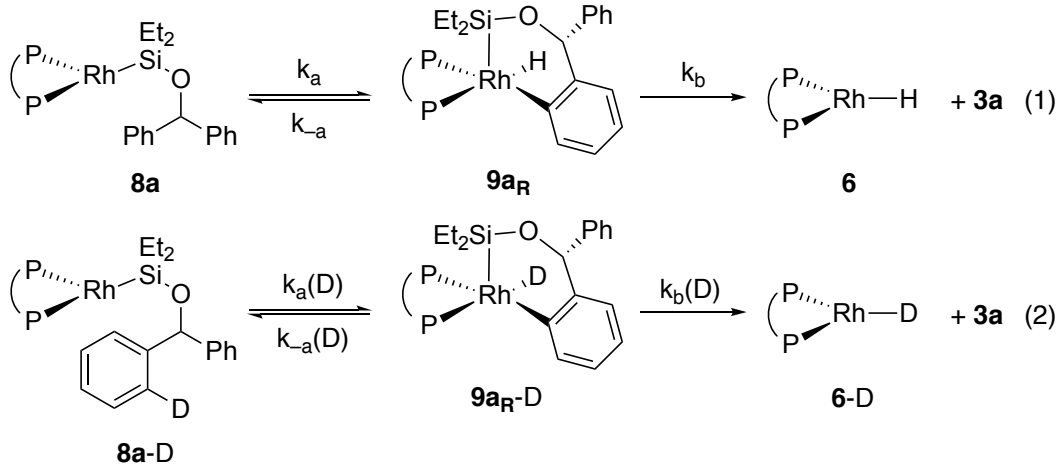
*3.4.5 Computational Studies*

All DFT calculations were performed with the Gaussian 09 software package.[37] Geometries for intermediates and transition states were optimized with the lanl2dz basis set[38] for rhodium and the 6-31G(d,p) basis set[39] for all other atoms with the B3LYP functional.[40] Frequency calculations were conducted on these structures at the same level of theory (at 323 K) to obtain thermodynamic energy corrections and to ensure that all transition states had only one imaginary frequency and all ground states had only positive frequencies. Single-point energy calculations were conducted with the lanl2tz basis set[5] for rhodium and the 6-311++G** basis set[41-44] for all other atoms with the M06 functional.[45] A solvent correction (THF, SMD)[46] was included for the single-point energy calculations.

Multiple isomers can be envisioned for each structure. For example, $\mathbf{9a_R}$, a five-coordinate rhodium complex with a non-C2 symmetric bisphosphine ligand **L1**, can have two diasteromers based on whether phosphorus (P1) of **L1** is trans or cis to the hydride (See Figure 3.2 to see which phosphorus is P1), and each diasteromer has at least two rotamers based on how the backbone is oriented. At the beginning of the study, we focused on $\mathbf{9a_R}$ and $\mathbf{9a_S}$, and we calculated 8 structures for each. We found that the structures that resembled the experimental solid-state structure of **4a** were lowest in the energy among the calculated structures. Because of this similarity between the computational and experimental data, we focused on the structures similar to the experimental solid-state structure of **4a** for other intermediates and transition states.

*3.4.5.1 Calculation of Theoretical intramolecular KIE*

The intramolecular KIE was calculated by DFT using the following assumptions: 1) only the C–H/D oxidative addition and C–Si reductive elimination steps described in the Figure S13 affect the ratio between C–D and C–H silylation products, 2) the pathway that forms the minor enantiomer is negligible, and 3) the concentration of intermediate **IIa** can be treated with the steady-state approximation. Based on these assumptions, the comparison of the rates of reactions in equation 1 and 2 provides the intramolecular KIE.




From equation 1,

$$\frac{d[9a_R]}{dt} = k_a[8a] - k_{-a}[9a_R] - k_b[9a_R] = 0$$

$$[9a_R] = \frac{k_a[8a]}{k_{-a} + k_b}$$

From equation 2,

$$\frac{d[9a_R\text{-}D]}{dt} = k_a(D)[8a\text{-}D] - k_{-a}(D)[9a_R\text{-}D] - k_b(D)[9a_R\text{-}D] = 0$$

$$[9a_R\text{-}D] = \frac{k_a(D)[8a\text{-}D]}{k_{-a}(D) + k_b(D)}$$

Thus,

$$intramolecular\ KIE = \frac{rate\ of\ reation\ in\ Eq.1}{rate\ of\ reaction\ in\ Eq.2} = \frac{k_b[9a_R]}{k_b(D)[9a_R\text{-}D]}$$

$$= \frac{\frac{k_b k_a}{k_{-a} + k_b}}{\frac{k_b(D)k_a(D)}{k_{-a}(D) + k_b(D)}}$$

Microscopic rate constants $k_a$, $k_{-a}$, and $k_b$ were calculated by using the Eyring equation:

$$k_a = 1.59\times10^4\ s^{-1}$$

$$k_{-a} = 3.14\times10^7\ s^{-1}$$

$$k_b = 2.57\times10^9\ s^{-1}$$

$k_a$(D), $k_{-a}$(D), and $k_b$(D) were calculated by dividing each microscopic rate constant $k_a$, $k_{-a}$, and $k_b$ by its corresponding KIE. The KIE's for each step were calculated from the zero-point energy difference in the reactants ($\Delta ZPE_{reactant}$) and the zero-point energy difference in the transition state ($\Delta ZPE_{TS}$). $\Delta$ZPE is the difference of the zero-point energy between the protiated structure and the deuterated structure. The expression for the microscopic KIE's is:

$$KIE = e^{\frac{\Delta ZPE_{reactant} - \Delta ZPE_{TS}}{RT}}$$

Zero-point energies for deauterated structures were determined from frequency calculations. The corresponding hydrogen atoms were substituted with deuterium in optimized structures of **8a**, **TS-I$_R$**, **9a$_R$**, and **TS-II$_R$** in these frequency calculations. The microscopic KIE's are:

$$KIE_a = 4.21$$

$$KIE_{-a} = 1.39$$

$$KIE_b = 0.962$$

From these values, the theoretical intramolecular KIE was calculated to be 4.20.

*3.4.5.2 Calculation with the M06 functional*

We optimized the geometry of the structures by using the M06 functional to ensure the consistency of results from different functionals. The computational details are identical as described above except the use of the M06 functional for geometry optimization. We were unable to calculate **TS-II$_R$** and **TS-II$_S$** in this set of calculation.

Comparison of the energies from these calculations with M06 to those with the B3LYP functionals suggested that the discrepancy between the two functionals is not significant enough to affect the conclusion in our study. Both calculations suggest that **TS-I$_S$** is 6-7 kcal/mol higher than **TS-I$_R$** (Figure 3.6 and 3.21). Differences of the lengths of the bonds that break and form during **TS-I$_S$** and **TS-I$_R$** between the two functionals are within 0.05 Å (Figure 3.22).

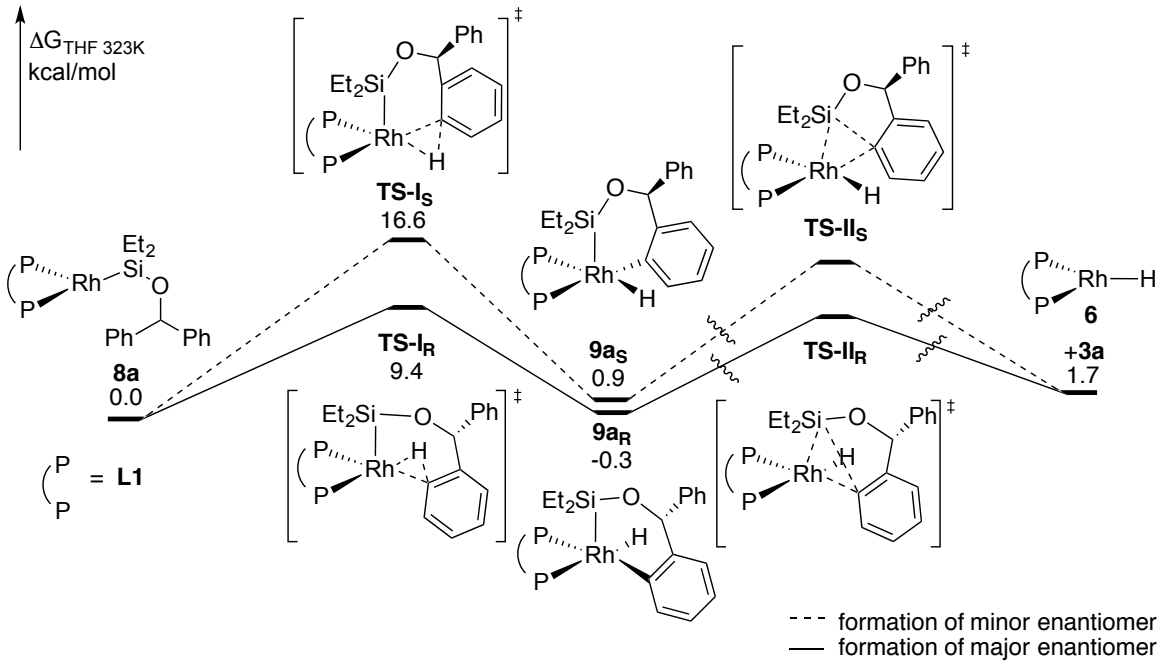



**Figure 3.21** Computed pathways for the C–H oxidative addition and C–Si reductive elimination (M06 functional).

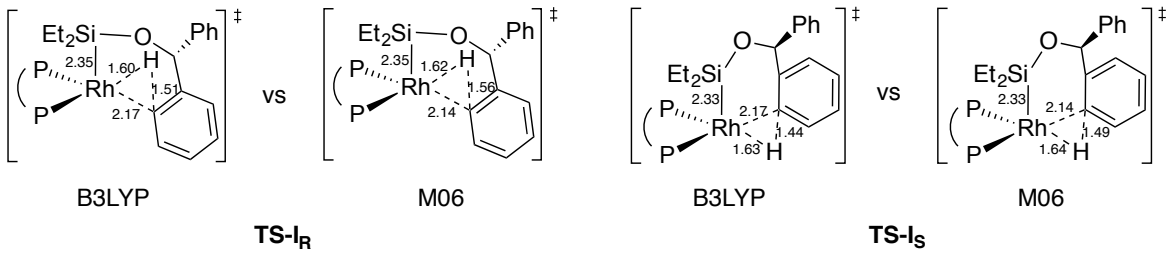



**Figure 3.22** Comparison of **TS-I$_R$** and **TS-I$_S$** computed with the B3LYP and M06 functionals (All distances are in Å.)

## 2.5 References

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Lee, T.; Hartwig, J. F. Mechanistic Studies on Rhodium-Catalyzed Enantioselective Silylation of Aryl C−H Bonds. *J. Am. Chem. Soc.* **2017**, *139*, 4879. Copyright 2017 American Chemical Society.

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(33) In the IR spectrum of the C−D analogue of **5**, this band shifted, confirming that they originated from stretching modes of the agostic C–H bond.
(34) The reaction of **2a** catalyzed by $[Rh(cod)Cl]_2$ (0.5 mol %) and **L1** (1.25 mol %) in the absence of norbornene formed **3a** in 87% yield and 97% ee.
(35) The reaction rate is zero order in [**2a**] in the absence of nbe.
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(39) Trace amount of deuterium (less than 1%) was incorporated into **3b**.
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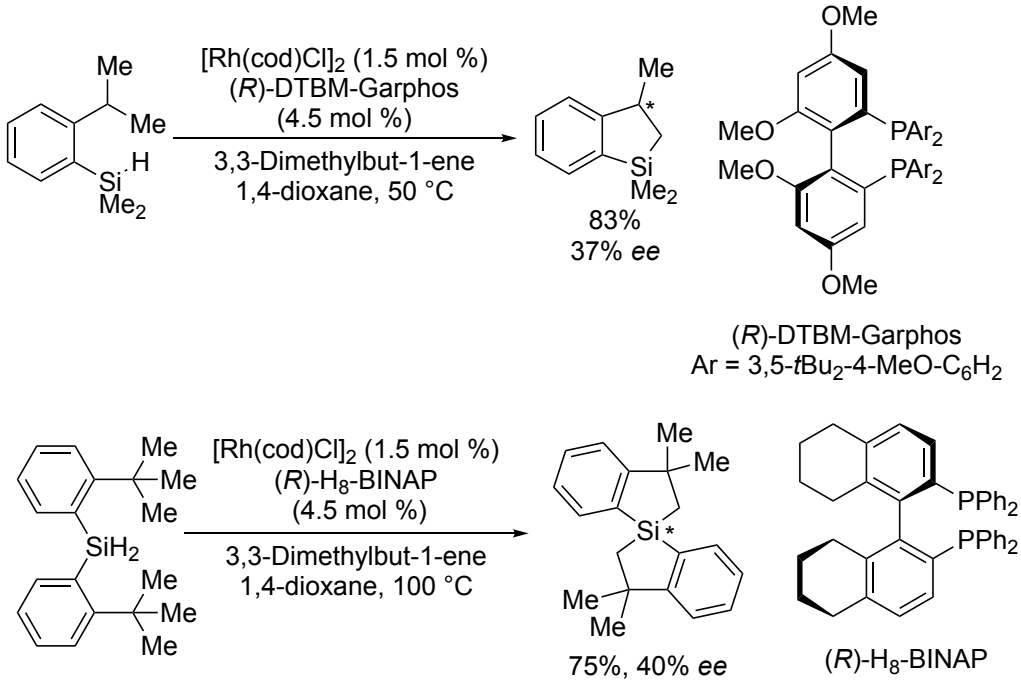
# CHAPTER 4

## Rhodium-Catalyzed Enantioselective Silylation of Cyclopropyl C–H bonds

## 4.1 Introduction

In previous chapters, we discussed enantioselectiove silylation of *aryl* C–H bonds. These reactions generate a stereogenic silicon center,[1,2] introduce planar chirality by asymmetric C–H silylation of ferrocenes.[3-5], and set a carbon stereogenic center in diarylmethanol.[6] Although these reactions can occur with high enantioselectivity, they are limited to the functionalization of aryl C–H bonds. Prior to the work that will be discussed in this Chapter, the only published set of enantioselective silylations of alkyl C–H bonds occurs with low ee (37-40% ee) and with limited scope (Scheme 1).[7]

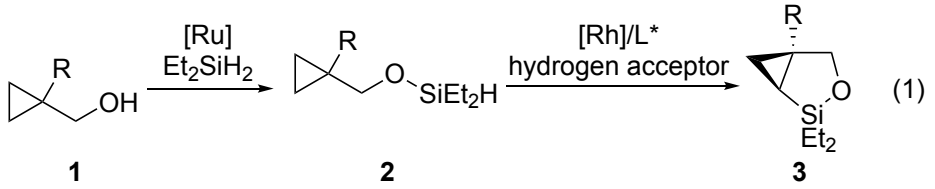
**Scheme 4.1** Previous work on enantioselective silylation of aliphatic C–H Bonds[7]




To create the first silylations of alkyl C–H bonds that occur with high enantioselectivity, we investigated systems for the reactions of cyclopropanes. C–H bonds of cyclopropanes are more reactive than $sp^3$ C–H bonds of unstrained rings or alkyl chains,[8] and the rigid conformation of a cyclopropane could allow for high stereoselectivity. Yu and co-workers reported enantioselective, palladium-catalyzed arylation and alkylation reactions of cyclopropanes containing *N*-aryl or triflyl amide as a directing group with organoborane or iodoarene reagents.[9,10] In addition, Cramer and co-workers reported Pd-catalyzed intramolecular arylations and alkylation of cyclopropyl C–H bonds to form tetrahydroquinolines, dihydroquinolones, dihydroisoquinolones and γ-lactams.[11-13] However, enantioselective functionalization to form products containing a new carbon-heteroatom bond was not reported prior to this work. [14] Enantioselective silylation would generate a product containing a new carbon-oxygen bond after oxidation

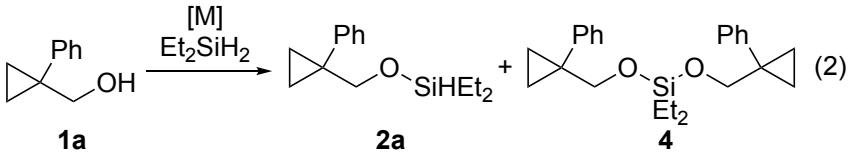
of the C–Si bond in the silylation product.[15] Although two silylations of cyclopropyl C–H bonds have been reported,[16,17] no enantioselective variant of this reaction has been reported.

We report a rhodium-catalyzed, enantioselective silylation of cyclopropanes directed by a (hydrido)silyl group (eq 1). The reaction is initiated by formation of silyl ether **2** from cyclopropylmethanol **1** and leads to the silylation of a cyclopropyl C–H bond to form the silylcyclopropane product **3** in high yield and ee. This process is a rare example of the silylation of secondary C–H bonds,[16-20] and the product undergoes oxidation with full conservation of the enantiomeric excess of the silylation product to form a diol containing a secondary carbinol stereocenter that would be difficult to set by more classical hydrogenation of the corresponding ketone.[21]




## 2.2 Results and Discussion

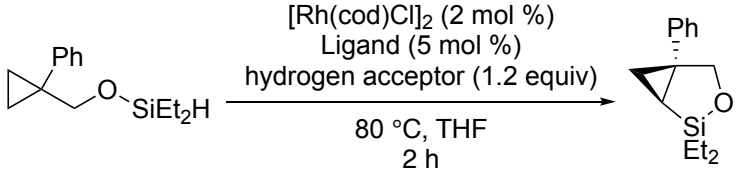
We began our investigation of the enantioselective silylation of cyclopropanes by examining the reactions of (1-phenylcyclopropyl)methanol (**1a**). The dehydrogenative coupling of **1a** with diethylsilane catalyzed by $[Ir(cod)Cl]_2$ or $[Ir(cod)OMe]_2$ under conditions we reported previously for the dehydrogenative silylation of alcohols and amines[20,22-24] formed a a mixture of hydrosilyl ether **2a** and dialkoxysilane **4** (eq 2). In contrast, the reaction catalyzed by 0.2 mol % $Ru(PPh_3)_3Cl_2$ at 50 °C formed **2a** exclusively. The ruthenium complex did not catalyze the silylation of alcohol **1a** with the silyl ether **2a**.[23,25] Silyl ether **2a** formed by the Ru-catalyzed process was used without further purification for the silylation of a cyclopropyl C–H bond after the removal of the solvent and remaining diethylsilane.




Having identified a simple synthesis of **2a**, we sought conditions for the asymmetric, intramolecular silylation (Table 4.1). Based on previous reports of Rh-catalyzed silylations of C–H bonds,[4-7] we examined the Rh catalyst derived from $[Rh(cod)Cl]_2$ and (*S*)-DTBM-SEGPHOS (**L1**) with cyclohexene as a hydrogen acceptor[26] at 80 °C (entry 1). The functionalization of cyclopropyl C–H bonds occurred in 2 hours under these conditions, yielding the cyclized product **3a** in 93% yield and 83% ee. Other SEGPHOS derivatives, such as (*S*)-SEGPHOS (**L2**), (*R*)-DM-SEGPHOS (**L3**) and (*R*)-DMM-SEGPHOS (**L4**) formed catalysts with lower reactivity and enantioselectivity

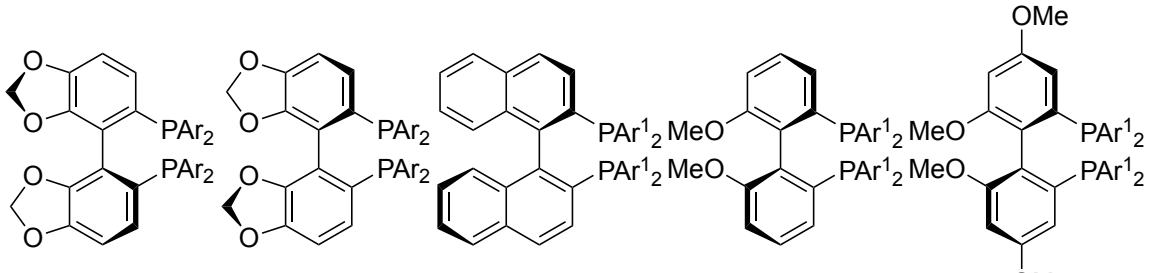
toward the silylation than did (*S*)-DTBM-SEGPHOS (**L1**) (entries 2-4). These results suggest that bulky substituents on the ligands are important for achieving both high reactivity and selectivity. Complexes generated from related bisphosphine ligands, such as (*R*)-DTBM-BINAP (**L5**), (*R*)-DTBM-MeOBIPHEP (**L6**) and (*R*)-DTBM-GARPHOS (**L7**) (entries 5-7), formed less selective catalysts.

**Table 4.1** Evaluation of reaction conditions




**2a** **3a**

| entry | ligand | hydrogen acceptor | yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|
| 1 | **L1** | cyclohexene | 93 | 83 |
| 2[c] | **L2** | cyclohexene | 9 | nd |
| 3[c] | **L3** | cyclohexene | 25 | nd |
| 4[c] | **L4** | cyclohexene | 35 | -11 |
| 5[c] | **L5** | cyclohexene | 55 | -39 |
| 6 | **L6** | cyclohexene | 60 | -45 |
| 7 | **L7** | cyclohexene | 48 | -36 |
| 8 | **L1** | norbornene | 81 | 84 |
| 9[c] | **L1** | none | 54 | 70 |
| 10[d] | **L1** | cyclohexene | 90 | 87 |




L1, Ar = $Ar^1$
L2, Ar = $Ar^2$

L3, Ar = $Ar^3$
L4, Ar = $Ar^4$

**L5** **L6** **L7**

$Ar^1$ = 3,5-*t*-Bu-4-MeOPh
$Ar^2$ = Ph
$Ar^3$ = 3,5-MePh
$Ar^4$ = 3,5-Me-4-MeOPh

[a]Determined by GC analysis with dodecane as the internal standard. [b]Determined by SFC analysis on a chiral stationary phase. A negative ee value indicates *ent*-**3a** was formed as the major enantiomer. nd = not determined. [c]12 h. [d]50 °C, 24 h.

The presence of a hydrogen acceptor in the reaction and the proper identity of this accepter were critical to achieve high yield and good enantioselectivity, and the temperature substantially affected enantioselectivity. In the absence of a hydrogen acceptor, competing processes occurred, including the disproportionation of **2a** to form **4** (entry 9), and low yield and ee of the silylcyclopropane were observed. The reaction with norbornene instead of cyclohexene as hydrogen acceptor also occurred in lower yield than did that with cyclohexene, due to the hydrosilylation and dehydrogenative silylation of norbornene (entry 8). Reactions run at 50 °C occurred with higher enantioselectivity than those run at 80 °C, and high conversion was maintained (entry 10).

With cyclohexene as hydrogen acceptor, **L1** as ligand, and 50 °C as the reaction temperature (entry 10), the competing processes were suppressed. For example, products from silylation of aryl C–H bonds were not observed, although the conditions we developed are similar to those used for the silylation of aryl C–H bond.[6] In addition, ring opening of the cyclopropane by the (hydrido)silyl group was not observed. Opening of a cyclopropane ring by hydrosilane in the presence of Rh catalysts has been reported previously.[27-29]

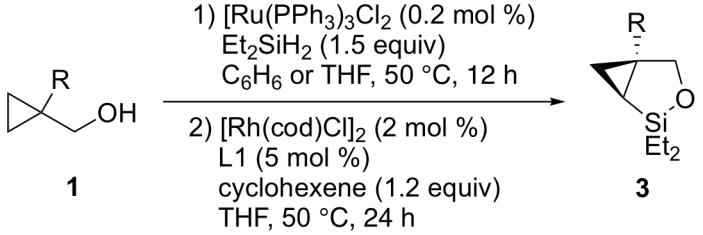
Having established conditions for the enantioselective silylation of cyclopropane **2a**, we investigated the scope of the reaction. Table 4.2 shows yields of isolated products and representative yields determined by GC or $^1$H NMR spectroscopy.[30] In general, the enantioselectivity of this reaction correlated with the steric properties of the aryl ring in the substrate. The enantioselectivity from substrates containing *meta* (**1b**, **c**) or *ortho* (**1d**) substituents on the aryl rings was higher than that from those lacking any substituents (**1a**) or those containing only *para* (**1g**) substituents on the aryl ring. A similar correlation between enantioselectivity and the steric properties was observed for the reactions of cyclopropylmethanols substituted with naphthyl groups (**1e**, **f**). For example, the enantioselectivity of the reaction of (1-naphtylcyclopropyl)methanol (**1f**) was higher than that from reaction of the less sterically demanding (2-naphtylcyclopropyl)methanol (**1e**).

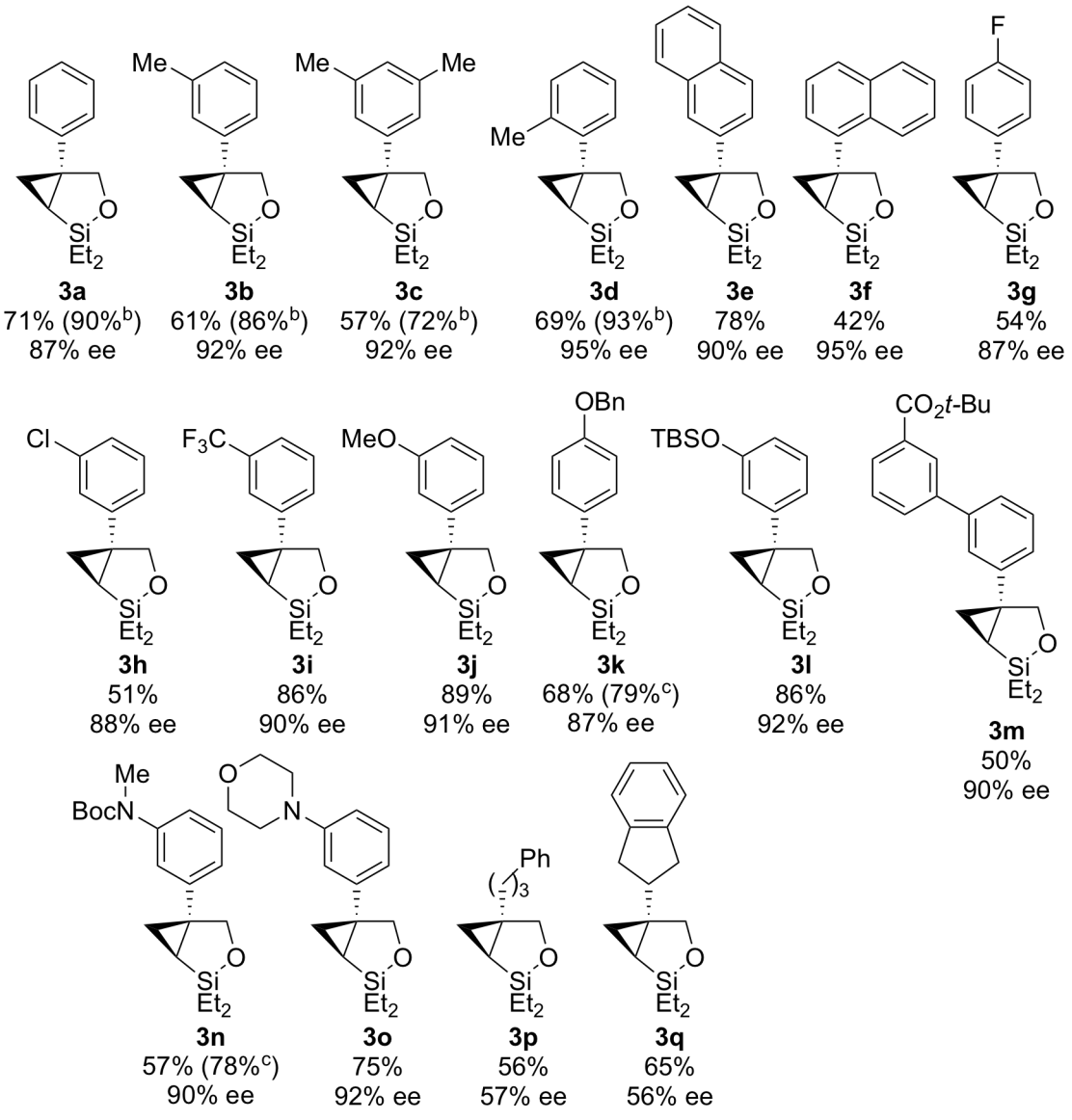
Further reactions probed the functional-group tolerance of the silylation process. Aryl halides (**1g-h**) and a trifluoromethylarene (**1i**) were both compatible with the reaction conditions. Oxygen-based functional groups, such as methoxy (**1j**), benzyloxy (**1k**), silyloxy (**1l**) and alkoxycarbonyl (**1m**) groups, were also compatible with the silylation process. Although nitro groups were not tolerated under the reaction conditions, carbamates (**1n**) and tertiary amino groups (**1o**) were tolerated.

The enantioselectivity from cyclopropanes substituted with alkyl groups (**3p**, **q**) was lower than that from cyclopropanes substituted with aryl groups. This trend does not correlate with the steric environment imposed by the alkyl groups because the enantioselectivity of the reaction of a cyclopropane bearing a primary alkyl substituent was almost identical to that of the reaction of a cyclopropane bearing a secondary alkyl substituent. The high enantioselectivity for arylcyclopropanes could result from an interaction between the aryl rings of the catalyst and the aryl substituents on the substrate.

In addition to controlling the enantioselectivity, the chiral catalyst could control the diastereoselectivity of the silylation of an enantioenriched cyclopropane, such as substrate **5** in Table 4.3. To determine the inherent diastereoselectivity controlled by the

**Table 4.2** Scope of enantioselective C–H silylation[a]



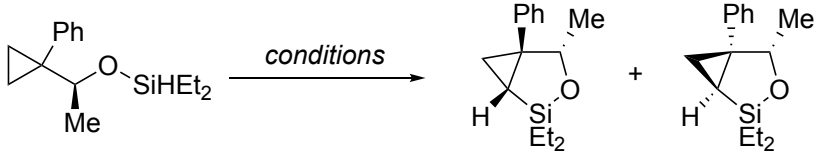




[a]Isolated yields for reactions conducted on a 0.25–1.0 mmol scale following purification by bulb-to-bulb

substrate, we conducted a silylation reaction of **5** with the achiral catalyst generated from $[Ir(cod)OMe]_2$ and 3,4,7,8-tetramethyl-1,10-phenanthroline ($me_4$phen) at 80 °C (entry 1).

This reaction yielded a mixture of **6a** and **6b** in 10:1 ratio. This result suggests that there is a strong preference to form **6a** over **6b**, presumably to avoid the unfavorable steric interaction between the phenyl and methyl groups. In the matched combination of catalyst and substrate, the reaction of **5** catalyzed by the combination of $[Rh(cod)Cl]_2$ and *ent*-**L1** yielded a mixture of **6a** and **6b** in a ratio over 20:1 (entry 2) and with enantiomeric excess for **6a** exceeding 99%. Thus, this silylation protocol forms an enantiopure compound possessing three consecutive stereocenters from a readily accessible enantioenriched secondary alcohol.[31,32] The reaction of **5** conducted with the combination of $[Rh(cod)Cl]_2$ and **L1** as the catalyst formed a mixture of **6a** and **6b** in a 1:1.6 ratio with **6b** as the major diasteromer (entry 3). Although the diastereoselectivity was low, the catalyst did override the substrate bias and formed the isomer that was strongly disfavored with an achiral catalyst as the major product.

**Table 4.3** Diastereoselective C–H silylation on a chiral substrate




**5**
95% ee

**6a** **6b**

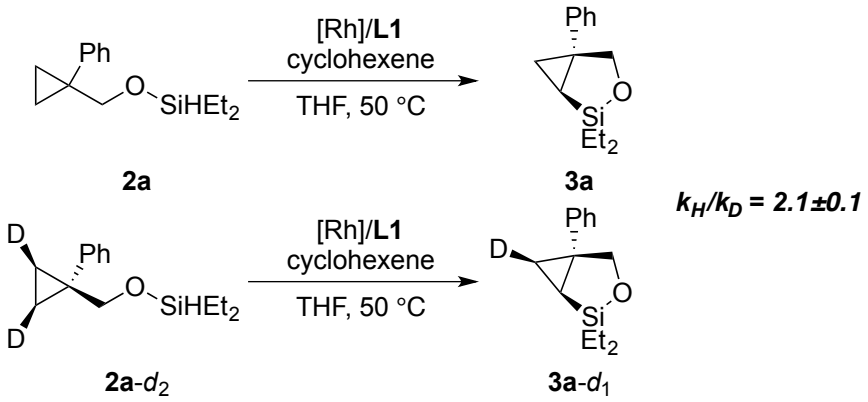
| entry | condition | yield[a] | **6a**:**6b**[b] |
|---|---|---|---|
| 1 | $[Ir(cod)OMe]_2$/$me_4$phen (2 mol %)<br>norbornene, 80 °C, 6 h | 78% | 10:1 |
| 2 | [Rh]/*ent*-**L1** (4 mol %)<br>cyclohexene, 50 °C, 24 h | 66%<br>>99% ee[c] | >20:1 |
| 3 | [Rh]/**L1** (4 mol %)<br>cyclohexene, 50 °C, 24 h | 57%[d] | 1:1.6 |

[a]Isolated yields for reactions conducted on a 0.25 mmol scale following purification by silica gel chromatography. [b]Determined by GC analysis [c]The ee value corresponds to the major isomer **6a** and was determined by chiral HPLC analysis. The absolute configuration was assigned by analogy. [d]The isolated product contained ~5% of inseparable impurities.

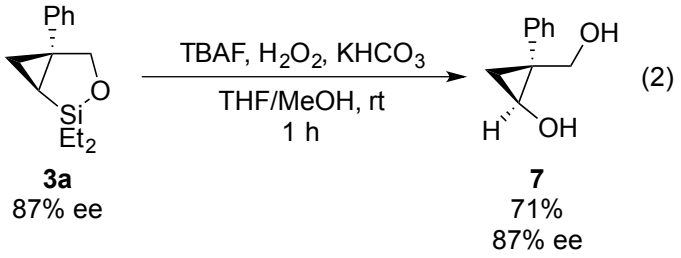
To gain insight into the mechanism of this reaction, we measured the kinetic isotope effect (KIE). The KIE was determined by measuring the initial rates of the silylation of non-deuterated and deuterated substrates **2a** and **2a**-$d_2$ in separate vessels. The KIE from this set of experiments was 2.1 (Scheme 2). This value is similar to that we observed for the Ir-catalyzed silylation of secondary C–H bonds[20] and implies that C–H cleavage may be the turnover-limiting step.[33] Assuming this KIE, although modest, implies that the C–H bond is cleaved irreversibly, this value would also imply that the

configuration at the C-Si bond in the product is set by C–H bond cleavage, not by the C-Si bond-forming reductive elimination.

**Scheme 2.** Kinetic isotope effect on the silylation of cyclopropyl C–H bonds.




Enantioenriched oxasilolanes are easily converted into cyclopropanols, a useful building block in organic synthesis.[34] For example, the treatment of oxasilolane **3a** with TBAF, aqueous $H_2O_2$, and $KHCO_3$ formed cyclopropanol **7** without any erosion in ee (eq 2).[35] The absolute configurations of the stereogenic centers in **7** were unambiguously determined by single-crystal X-ray analysis.




## 2.3 Conclusions

In summary, we have developed an enantioselective silylation of cyclopropanes, which constitutes the first highly enantioselective silylation of an alkyl C–H bond and the first catalytic, enantioselective functionalization of the C–H bond in a cyclopropane to form a carbon-heteroatom bond. The silylation process occurs in high yield and enantioselectivity and tolerates a wide range of functional groups when catalyzed by a Rh complex containing a chiral bisphosphine. Tamao-Fleming oxidation of the enantioenriched oxasilolanes yields cyclopropanols with the same ee as the oxasiloles precursors. The observed KIE of 2.1 suggests that the C–H cleavage step is turnover limiting and enantioselectivity determining.

## 2.4 Experimental

### *2.4.1 Methods and Materials*

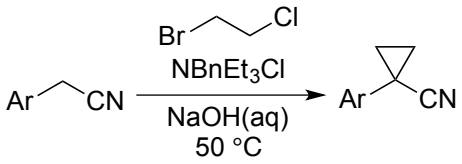
The silylation reactions were assembled in an $N_2$-filled glovebox using oven-dried glassware and were stirred with Teflon-coated magnetic stirring bars. $Ru(PPh_3)_3Cl_2$ was purchased from Strem and was used as received. $[Rh(cod)Cl]_2$ was prepared from $[RhCl_3 \cdot xH_2O]$ according to a standard procedure.[36] (*S*)-DTBM-SEGPHOS was obtained as a gift from Takasago and was used as received. Diethylsilane ($Et_2SiH_2$) was purchased from Gelest and Alfa Aesar and was used as received. Cyclohexene was purchased from Spectrum and subjected to molecular sieves prior to use. Tetrahydrofuran (THF) and benzene were degassed by purging with nitrogen and then dried with a solvent purification system containing activated alumina. All other solvents and reagents were used as received.

Reaction temperatures above 23 °C refer to temperatures of an aluminum heating block, which were controlled by an electronic temperature modulator. Silica gel chromatography was performed using a Teledyne Isco CombiFlash® $R_f$ system with Redi*Sep* $R_f$ Gold™ columns. $^1H$ and $^{13}C$ NMR spectra were recorded on Bruker AV-300, AVB-400, AV-500 and AV-600 spectrometers with $^{13}C$ operating frequencies of 76 MHz, 101 MHz, 125 MHz and 151 MHz, respectively. $^{19}F$ NMR spectra were recorded on a Bruker AVQ-400 spectrometer with a $^{19}F$ operating frequency of 376 MHz. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ = 7.26 for $^1H$ NMR and δ = 77.0 for $^{13}C$ NMR). High-resolution mass spectral data were obtained from the QB3/Chemistry Mass Spectrometry Facility at the University of California, Berkeley and the Lawrence-Berkeley National Laboratory Catalysis Center. Chiral SFC analysis was conducted on Waters chromatography system. Chiral HPLC analysis was conducted on Waters or Shimadzu chromatography systems. Racemic samples were obtained by following the procedures reported here with a racemic catalyst or the procedures previously reported.[22,23]

*2.4.2 Synthesis of cyclopropylmethanols*

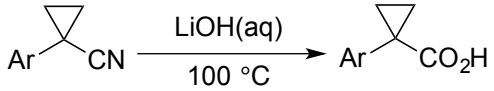
(1-Arylcyclopropyl)methanols (**1b-1o**) were synthesized following the general procedures A-E with additional steps if necessary.

*General Procedure A: Synthesis of 1-Arylcyclopropanecarbonitrile* [9,37]



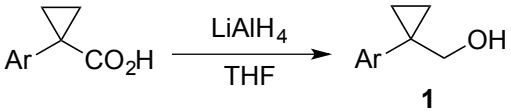

To a 20 mL vial charged with arylacetonitrile (1.0 equiv), 1-bromo-2-chloroethane (2.6 equiv) and benzyltriethylammonium chloride (0.020 equiv) was added 50% aqueous sodium hydroxide (6 equiv). The vial was capped with a Teflon-lined screw cap, and the resulting solution was stirred at 50 °C under ambient atmosphere until complete consumption of the aryacetonitrile was observed, as determined by GC-MS analysis (typically 12 h). The solution was poured into water and extracted with dichloromethane three times. The combined organic layers were washed with 1 N HCl, saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$), and concentrated. The crude product was purified by column chromatography if necessary.

*General Procedure B: Hydrolysis of 1-Arylcyclopropanecarbonitrile*[9,37]




To a flask containing 1-aryl-1-cyanocyclopropane (1.0 equiv) was added a slurry of lithium hydroxide (30 equiv) in water ([cyclopropane] = 1 M). The flask was fitted with reflux condenser and heated at 100 °C until complete consumption of the carboxylic acid was observed, as determined by TLC analysis (typically 24 h). The reaction was allowed to cool to room temperature. 1 N HCl was then added until the pH of the solution reached 1, as measured by pH paper. The solution was extracted with ethyl acetate three times. The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography if necessary.

*General Procedure C: Reduction of 1-Arylcyclopropanecarboxylic Acid*

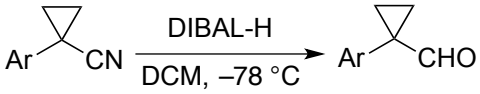



**1**

To a solution of 1-arylcyclopropanecarboxylic acid (1 equiv) in THF (0.2 M) was added a solution of $LiAlH_4$ (1.6 equiv, 1.0 M in THF) dropwise at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 2 h, at which time it was

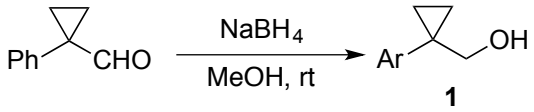
quenched by careful addition of saturated $NH_4Cl$ solution and extracted with diethyl ether three times. The combined organic layers were washed with water and brine, dried ($MgSO_4$) and concentrated. The crude product was purified by silica gel chromatography.

*General Procedure D: Reduction of 1-Arylcyclopropanecarbonitrile*



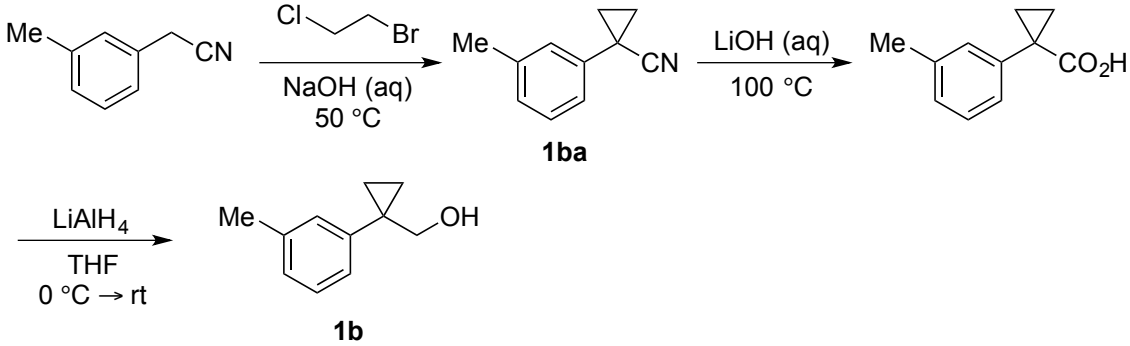

To a solution of 1-arylcyclopropanecarbonitrile (1 equiv) in DCM (0.13 M) was added a solution of DIBAL-H (2.1 equiv, 1.0 M in hexane) dropwise at –78 °C. The resulting solution was stirred for 2 h, at which time it was quenched by careful addition of saturated $NH_4Cl$ solution and extracted with diethyl ether three times. The combined organic layers were washed with water and brine, dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography if necessary.

*General Procedure E: Reduction of 1-Arylcyclopropanecarbaldehyde*




To a solution of 1-arylcyclopropanecarbaldehyde (1 equiv) in MeOH (0.25 M) was added $NaBH_4$ (1.5 equiv) at room temperature. The resulting solution was stirred for 1 h, at which time it was quenched by careful addition of saturated $NH_4Cl$ solution and extracted with diethyl ether three times. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography to provide (1-arylcyclopropyl)methanol.

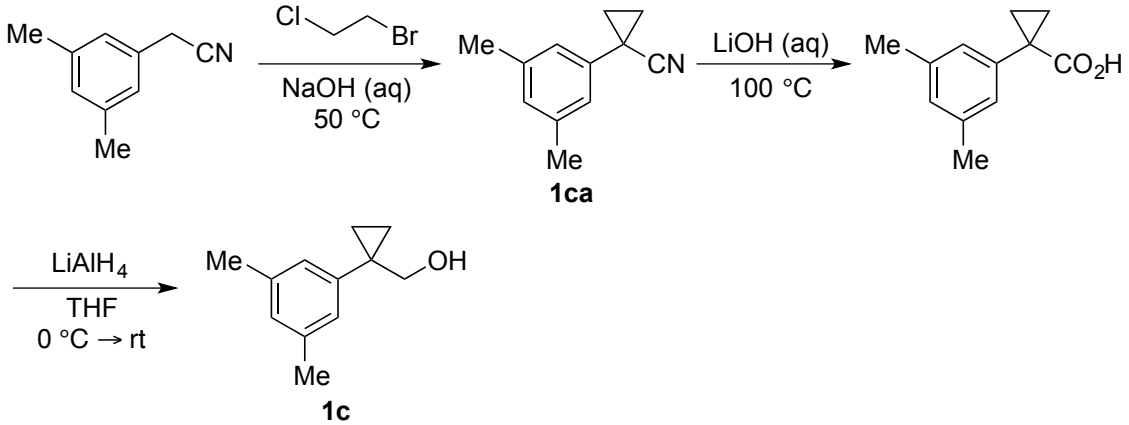
**(1-(*m*-Tolyl)cyclopropyl)methanol 1b**




Following the general procedure A, 2-(*m*-tolyl)acetonitrile (656 mg, 5.00 mmol) was allowed to react with 1-bromo-2-chloroethane. The crude reaction mixture was purified by silica gel chromatography (100:0→75:25 hexanes/$Et_2O$) to give 613 mg (78%) of cyclopropane **1ba** as a yellow oil. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 7.22 (d, $J$ = 7.6 Hz,

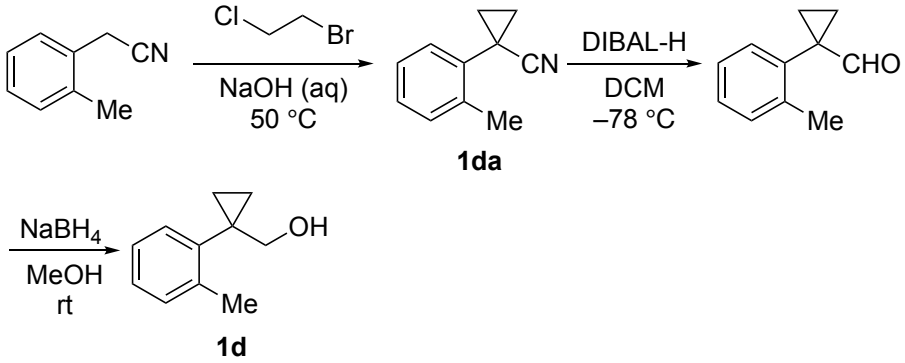
1H), 7.17 – 7.02 (m, 3H), 2.36 (s, 3H), 1.79 – 1.61 (m, 2H), 1.49 – 1.30 (m, 2H). Following the general procedures B and C, **1ba** (593 mg, 3.77 mmol) was allowed to react with LiOH(aq) and then $LiAlH_4$. The crude reaction mixture was purified by silica gel chromatography (100:0→60:40 hexanes/$Et_2O$) to give 398 mg (60% in 2 steps) of **1b** as a colorless oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.25 – 7.20 (m, 2H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.06 (d, *J* = 7.4 Hz, 1H), 3.65 (s, 3H), 2.37 (s, 2H), 1.77 (s, 1H), 0.90 – 0.87 (m, 2H), 0.86 – 0.82 (m, 2H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 142.6, 137.9, 129.7, 128.2, 127.3, 126.0, 70.7, 27.9, 21.4, 11.2. **HRMS** (ESI+) calcd for $C_{11}H_{14}NaO$ $[M+Na]^+$ 185.0937, found 185.0930.

**(1-(3,5-Dimethylphenyl)cyclopropyl)methanol 1c**



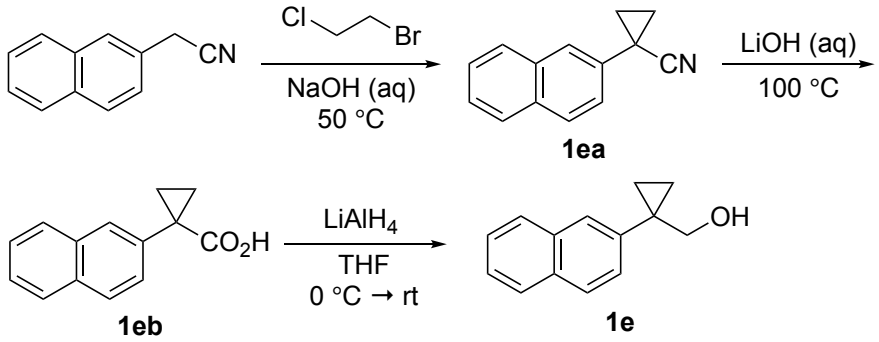

Following the general procedure A, 2-(3,5-dimethylphenyl)acetonitrile (726 mg, 5.00 mmol) was allowed to react with 1-bromo-2-chloroethane. The crude reaction mixture was purified by silica gel chromatography (100:0→75:25 hexanes/$Et_2O$) to give 653 mg of a mixture containing cyclopropane **1ca** and unknown impurity (ca. 10%) as a brown oil (ca. 70% yield). Following the general procedures B and C, the mixture obtained above (627 mg, ca. 3.39 mmol) was allowed to react with LiOH(aq) and then $LiAlH_4$. The crude reaction mixture was purified by silica gel chromatography (100:0→60:40 hexanes/$Et_2O$) to give 308 mg (54% in 2 steps) of **1c** as a colorless oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.00 (s, 2H), 6.89 (s, 1H), 3.64 (s, 2H), 2.32 (s, 6H), 1.60 (s, 1H), 0.89 – 0.85 (m, 2H), 0.85 – 0.81 (m, 2H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 142.5, 137.9, 128.3, 126.8, 70.9, 27.9, 21.3, 11.2. **HRMS** (EI+) calcd for $C_{12}H_{16}O$ $[M]^+$ 176.1201, found 176.1199

**(1-(*o*-Tolyl)cyclopropyl)methanol 1d**




Following the general procedure A, 2-(*o*-tolyl)acetonitrile (1.31 g, 10.0 mmol) was allowed to react with 1-bromo-2-chloroethane. The crude reaction mixture was purified by silica gel chromatography (100:0→75:25 hexanes/$Et_2O$) to give 1.06 g (67%) of cyclopropane **1da** as a colorless oil. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.29 – 7.22 (m, 3H), 7.21 – 7.16 (m, 1H), 2.57 (s, 3H), 1.72 – 1.68 (m, 2H), 1.34 – 1.29 (m, 2H). Following the general procedures D and E, **1da** (989 mg, 6.29 mmol) was allowed to react with DIBAL-H and then $NaBH_4$. The crude reaction mixture was purified by silica gel chromatography (100:0→60:40 hexanes/$Et_2O$) to give 424 mg (41% in 2 steps) of **1d** as a colorless oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.32 (d, $J$ = 6.3 Hz, 1H), 7.19 – 7.13 (m, 3H), 3.58 (s, 2H), 2.45 (s, 3H), 1.54 (s, 1H), 0.93 – 0.87 (m, 2H), 0.87 – 0.82 (m, 2H). **$^{13}$C NMR** (151 MHz, CDCl3) δ 139.9, 138.2, 131.6, 130.4, 126.9, 125.7, 69.6, 27.3, 19.2, 11.1. **HRMS** (ESI–) calcd for $C_{11}H_{13}O$ $[M–H]^-$ 161.0972, found 161.0977.

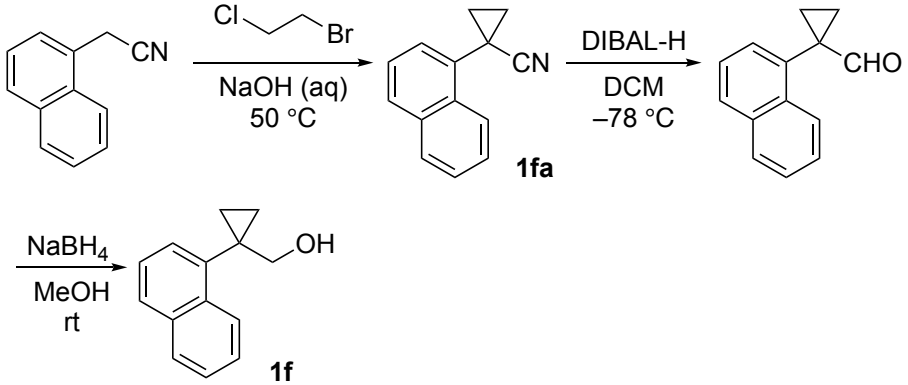
**(1-(2-Naphthyl)cyclopropyl)methanol 1e**




Following the general procedure A, 2-naphthylacetonitrile (836 mg, 5.00 mmol) was allowed to react with 1-bromo-2-chloroethane. The crude reaction mixture was purified by silica gel chromatography (100:0→75:25 hexanes/$Et_2O$) to give 766 mg (79%) of cyclopropane **1ea** as a yellow oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.87 – 7.76 (m, 4H), 7.55 – 7.46 (m, 2H), 7.32 (d, $J$ = 8.4 Hz, 1H), 1.84 – 1.75 (m, 2H), 1.55 – 1.48 (m, 2H). Following the general procedure B, **1ea** (707 mg, 3.66 mmol) was allowed to react with

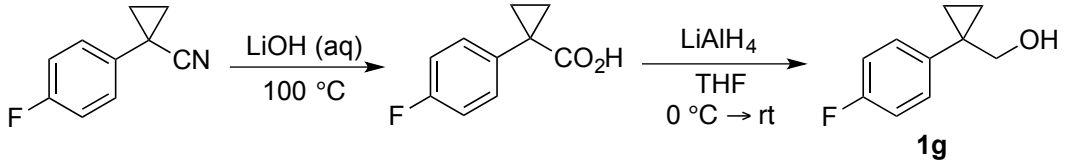
LiOH(aq). The crude reaction mixture was washed with cold $Et_2O$ to give 545 mg (70%) of acid **1eb** as a white solid. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.83 – 7.77 (m, 3H), 7.76 (s, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.48 – 7.42 (m, 2H), 1.78 – 1.68 (m, 2H), 1.43 – 1.31 (m, 2H). Following the general procedure C, **1eb** was allowed to react with $LiAlH_4$. The crude reaction mixture was purified by silica gel chromatography (100:0→60:40 hexanes/$Et_2O$) to give 379 mg (98%) of **1e** as a white solid. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.84 – 7.77 (m, 4H), 7.52 – 7.42 (m, 3H), 3.77 (s, 2H), 1.52 (s, 1H), 1.04 – 0.97 (m, 2H), 0.97 – 0.90 (m, 2H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 140.0, 133.4, 132.3, 128.1, 127.7, 127.6, 127.5, 127.1, 126.1, 125.6, 70.8, 28.3, 11.4. **HRMS** (EI+) calcd for $C_{14}H_{14}O$ $[M]^+$ 198.1045, found 198.1046.

**(1-(1-Naphthyl)cyclopropyl)methanol 1f**




Following the general procedure A, 2-(1-naphthyl)acetonitrile (1.67 g, 10.0 mmol) was allowed to react with 1-bromo-2-chloroethane. The crude reaction mixture was purified by silica gel chromatography (100:0→75:25 hexanes/$Et_2O$) to give 1.69 g (87%) of cyclopropane **1fa** as a white solid. **$^1$H NMR** (300 MHz, $CDCl_3$) δ 8.40 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.61 – 7.53 (m, 1H), 7.52 – 7.39 (m, 2H), 1.95 – 1.75 (m, 2H), 1.52 – 1.36 (m, 2H). Following the general procedures D and E, **1fa** (1.67 g, 8.65 mmol) was allowed to react with DIBAL-H and then $NaBH_4$. The crude reaction mixture was purified by silica gel chromatography (100:0→60:40 hexanes/$Et_2O$) to give 818 mg (48% in 2 steps) of **1f** as a colorless oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.6 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.57 – 7.52 (m, 2H), 7.50 (t, *J* = 7.1 Hz, 1H), 7.45 – 7.41 (m, 1H), 3.76 (s, 2H), 1.46 (s, 1H), 1.14 – 1.04 (m, 2H), 1.03 – 0.95 (m, 2H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 138.1, 134.0, 132.5, 128.8, 128.7, 127.9, 125.8, 125.6, 125.3, 124.6, 70.5, 26.9, 11.2. **HRMS** (ESI+) calcd for $C_{14}H_{14}NaO$ $[M+Na]^+$ 221.0937, found 221.0941.

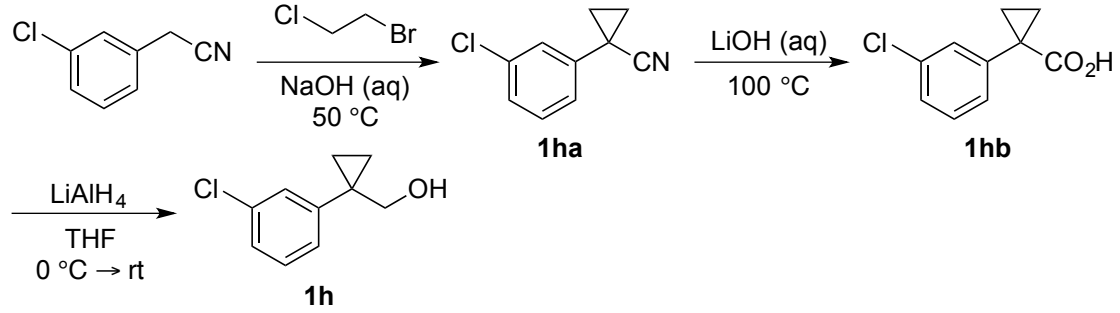
**(1-(4-Fluorophenyl)cyclopropyl)methanol 1g**




**1g**

Following the general procedures B and C, 1-(4-fluorophenyl)cyclopropanecarbonitrile (806 mg, 5.00 mmol) was allowed to react with LiOH(aq) and then $LiAlH_4$. The crude reaction mixture was purified by silica gel chromatography (100:0→60:40 hexanes/$Et_2O$) to give 469 mg (56% in 2 steps) of **1g** as a colorless oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.33 – 7.29 (m, 2H), 6.98 (t, *J* = 8.7 Hz, 2H), 3.59 (s, 2H), 1.83 (s, 1H), 0.82 (s, 4H). **$^{13}$C NMR** (151 MHz, CDCl3) δ 161.5 (d, *J* = 245 Hz), 138.5 (d, *J* = 3.1 Hz), 130.6 (d, *J* = 8.0 Hz), 115.0 (d, *J* = 21 Hz), 70.7, 27.4, 11.2. **HRMS** (ESI–) calcd for $C_{10}H_{10}FO$ $[M–H]^-$ 165.0721, found 165.0743.

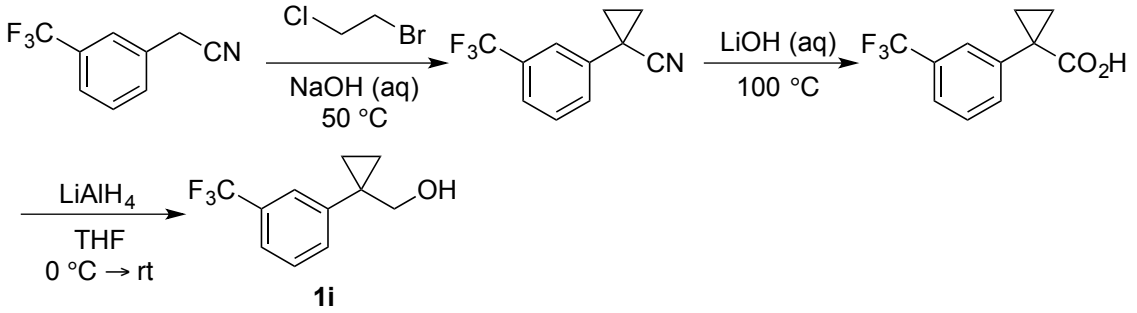
**(1-(3-Chlorophenyl)cyclopropyl)methanol 1h**




**1ha** **1hb** **1h**

Following the general procedure A, 2-(3-chlorophenyl)acetonitrile (775 mg, 5.11 mmol) was allowed to react with 1-bromo-2-chloroethane. The crude reaction mixture was purified by silica gel chromatography (100:0→80:20 hexanes/$Et_2O$) to give 790 mg (78%) of cyclopropane **1ha** as a yellow oil. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.31 – 7.27 (m, 2H), 7.27 – 7.24 (m, 1H), 7.20 (dt, *J* = 7.1, 1.9 Hz, 1H), 1.81 – 1.70 (m, 2H), 1.47 – 1.36 (m, 2H). Following the general procedures B and C, **1ha** (765 mg, 4.31 mmol) was allowed to react with LiOH(aq) and then $LiAlH_4$. The crude reaction mixture was purified by silica gel chromatography (100:0→70:30 hexanes/$Et_2O$) to give 583 mg (74% in 2 steps) of **1h** as a colorless oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.34 (s, 1H), 7.24 – 7.20 (m, 2H), 7.20 – 7.17 (m, 1H), 3.62 (s, 2H), 1.84 (s, 1H), 0.88 – 0.83 (m, 4H). **$^{13}$C NMR** (151 MHz, CDCl3) δ 145.0, 134.0, 129.5, 129.0, 127.0, 126.6, 70.3, 27.7, 11.5. **HRMS** (ESI+) calcd for $C_{10}H_{13}ClNaO$ $[M+Na]^+$ 205.0391, found 205.3082.

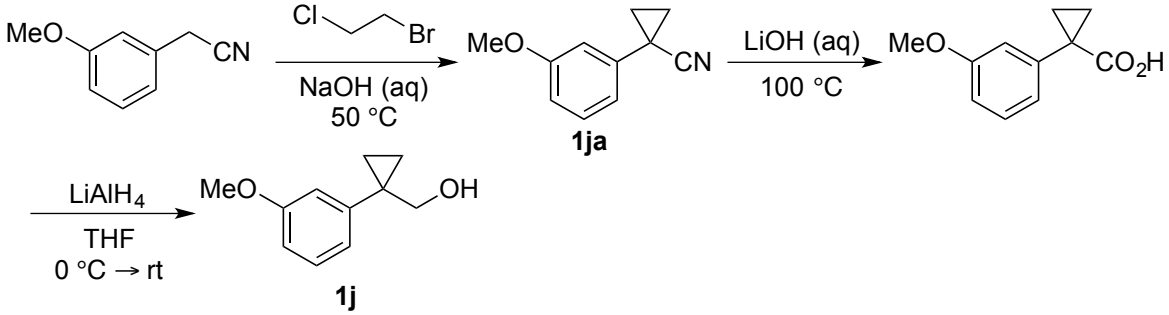
**(1-(3-(Trifluoromethyl)phenyl)cyclopropyl)methanol 1i**




**1i**

Following the general procedures A, B and C, 2-(3-(trifluoromethyl)phenyl)acetonitrile (926 mg, 5.00 mmol) was allowed to react with 1-bromo-2-chloroethane, LiOH(aq), and then $LiAlH_4$. The crude reaction mixture was purified by silica gel chromatography (100:0→60:40 hexanes/$Et_2O$) to give 641 mg (59% in 3 steps) of **1i** as a colorless oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.41 (t, *J* = 7.7 Hz, 1H), 3.66 (s, 2H), 1.79 (s, 1H), 0.90 (s, 4H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 143.9, 132.4, 130.6 (q, *J* = 32 Hz), 128.7, 125.6 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 272 Hz), 123.3 (q, *J* = 3.8 Hz), 70.3, 27.8, 11.5. **HRMS** (ESI–) calcd for $C_{11}H_{10}F_3O$ $[M–H]^-$ 215.0689, found 215.0698.

**(1-(3-Methoxyphenyl)cyclopropyl)methanol 1j**

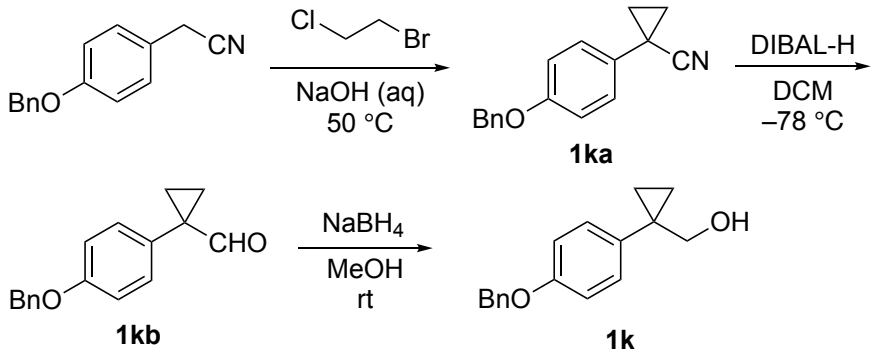



**1ja** **1j**

Following the general procedure A, 2-(3-methoxyphenyl)acetonitrile (736 mg, 5.00 mmol) was allowed to react with 1-bromo-2-chloroethane. The crude reaction mixture was purified by silica gel chromatography (100:0→75:25 hexanes/$Et_2O$) to give 496 mg (57%) of cyclopropane **1ja** as a colorless oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.25 (t, *J* = 7.4 Hz, 1H), 6.89 – 6.80 (m, 3H), 3.82 (s, 3H), 1.76 – 1.66 (m, 2H), 1.46 – 1.35 (m, 2H). Following the general procedures B and C, 1-(3-methoxyphenyl)cyclopropanecarbonitrile (477 mg, 2.75 mmol) was allowed to react with LiOH(aq) and then $LiAlH_4$. The crude reaction mixture was purified by silica gel chromatography (100:0→50:50 hexanes/$Et_2O$) to give 482 mg (98% in 2 steps) of **1j** as a colorless oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.23 (t, *J* = 7.9 Hz, 1H), 6.96 (d, *J* = 7.6 Hz, 1H), 6.92 (t, *J* = 2.2 Hz, 1H), 6.77 (dd, *J* = 8.2, 2.5 Hz, 1H), 3.80 (s, 3H), 3.65 (s, 2H), 1.69 (s, 1H), 0.92 – 0.86 (m, 2H), 0.86 – 0.80

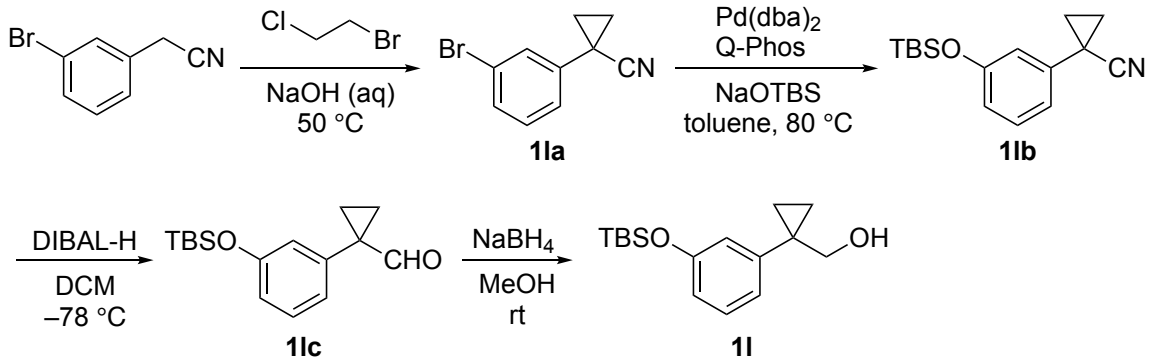
(m, 2H). **$^{13}$C NMR** (151 MHz, CDCl3) δ 159.5, 144.3, 129.3, 121.2, 114.8, 111.8, 70.6, 55.1, 28.1, 11.4. **HRMS** (EI+) calcd for $C_{11}H_{14}O_2$ $[M]^+$ 178.0994, found 178.0991.

**(1-(4-Benzyloxyphenyl)cyclopropyl)methanol 1k**



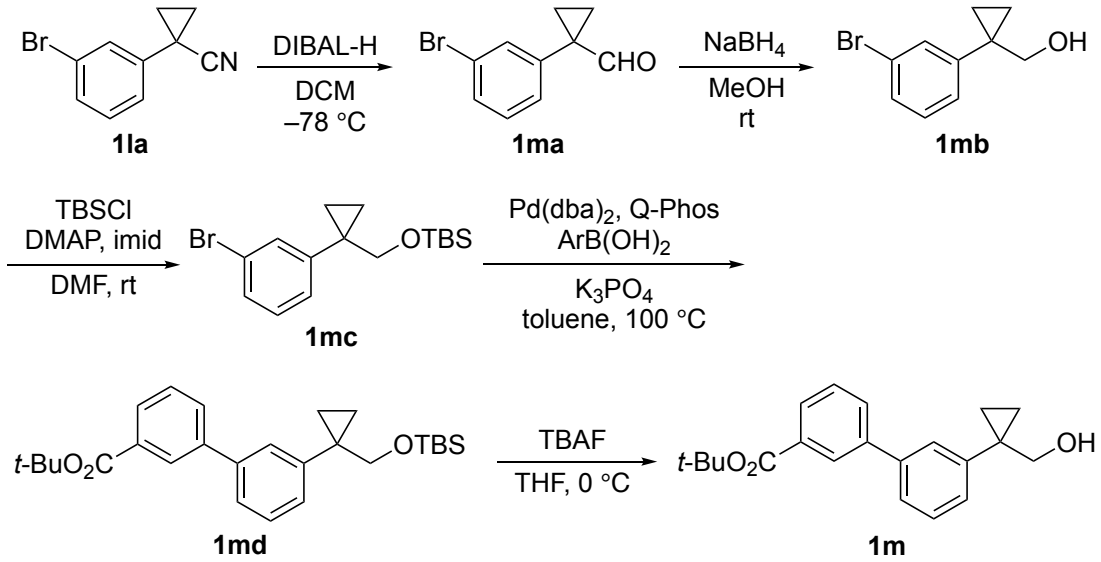

Following the general procedure A, 2-(4-benzyloxyphenyl)acetonitrile[38] (1.23 g, 5.51 mmol) was allowed to react with 1-bromo-2-chloroethane. The crude reaction mixture was purified by silica gel chromatography (100:0→80:20 hexanes/EtOAc) to give 629 mg of a 2.5:1 mixture of cyclopropane **1ka** and 2-(4-benzyloxyphenyl)acetonitrile as a yellow oil (ca. 36% yield). Following the general procedures D, the mixture obtained above was allowed to react with DIBAL-H. . The crude reaction mixture was purified by silica gel chromatography (100:0→80:20 hexanes/EtOAc) to give 278 mg (62%) of aldehyde **1kb**. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 9.23 (s, 1H), 7.43 (d, $J$ = 7.2 Hz, 2H), 7.39 (t, $J$ = 7.5 Hz, 2H), 7.33 (t, $J$ = 7.3 Hz, 1H), 7.22 (d, $J$ = 8.7 Hz, 2H), 6.97 (d, $J$ = 8.6 Hz, 2H), 5.07 (s, 2H), 1.59 – 1.50 (m, 2H), 1.42 – 1.32 (m, 2H). Following the general procedures E, **1kb** (261 mg, 1.03 mml) was allowed to react with $NaBH_4$. The crude reaction mixture was purified by silica gel chromatography (100:0 → 65:35 hexanes/EtOAc) to give 233 mg (89%) of **1k** as a white solid. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.44 (d, $J$ = 7.6 Hz, 2H), 7.40 (t, $J$ = 7.5 Hz, 2H), 7.34 (t, $J$ = 7.2 Hz, 1H), 7.30 (d, $J$ = 8.5 Hz, 2H), 6.94 (d, $J$ = 8.5 Hz, 2H), 5.06 (s, 2H), 3.62 (s, 2H), 1.54 (s, 1H), 0.86 – 0.79 (m, 4H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 157.5, 137.0, 134.9, 130.2, 128.5, 127.9, 127.4, 114.7, 71.0, 70.0, 27.4, 11.1. **HRMS** (ESI+) calcd for $C_{17}H_{18}NaO_2$ $[M+Na]^+$ 277.1199, found 277.1210.

**(1-(3-((*tert*-Butyldimethylsilyl)oxy)phenyl)cyclopropyl)methanol 1l**




Following the general procedure A, 2-(3-bromophenyl)acetonitrile (1.96 g, 10.0 mmol) was allowed to react with 1-bromo-2-chloroethane. The crude reaction mixture was purified by silica gel chromatography (100:0→75:25 hexanes/$Et_2O$) to give 1.99 g (89%) of cyclopropane **1la** as a brown oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.45 – 7.38 (m, 2H), 7.29 – 7.19 (m, 2H), 1.82 – 1.69 (m, 2H), 1.48 – 1.35 (m, 2H). The conditions described by our group were used for the following Pd-catalyzed C-O bond-forming cross coupling.[39] In an $N_2$-filled glovebox, **1la** (666 mg, 3.00 mmol) and NaOTBS (555 mg, 3.6 mmol)[40] were weighed into a 20 mL screw-top vial. A solution of $Pd(dba)_2$ (86.3 mg, 0.150 mmol) and Q-Phos (107 mg, 0.150 mmol) in toluene (12 mL) was added to the vial. The vial was capped with a Teflon-lined screw cap, and the resulting solution was stirred at 80 °C for 5 h. The crude reaction mixture was filtered through Celite, concentrated and purified by silica gel chromatography (100:0→90:10 hexanes/EtOAc) to give 829 mg (92%) of silyloxyarene **1lb** as a red oil. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.19 (t, $J$ = 8.0 Hz, 1H), 6.86 (ddd, $J$ = 7.8, 1.9, 0.9 Hz, 1H), 6.77 (t, $J$ = 2.0 Hz, 1H), 6.75 (ddd, $J$ = 8.0, 2.3, 0.9 Hz, 1H), 1.76 – 1.64 (m, 2H), 1.44 – 1.32 (m, 2H), 0.98 (s, 9H), 0.20 (s, 6H). Following the general procedures D, **1lb** (663 mg, 2.42 mmol) was allowed to react with DIBAL-H. The crude reaction mixture was purified by silica gel chromatography (100:0→90:10 hexanes/EtOAc) to give 547 mg (68%) of aldehyde **1lc** as a red oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 9.35 (s, 1H), 7.21 (t, 1H), 6.90 (d, $J$ = 7.8 Hz, 1H), 6.81 – 6.74 (m, 2H), 1.60 – 1.51 (m, 2H), 1.42 – 1.32 (m, 2H), 0.98 (s, 9H), 0.20 (s, 6H). Following the general procedures E, **1lc** (519 mg, 1.88 mml) was allowed to react with $NaBH_4$. The crude reaction mixture was purified by silica gel chromatography (100:0→85:15 hexanes/EtOAc) to give 418 mg (94%) of **1l** as a colorless oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.16 (t, $J$ = 7.8 Hz, 1H), 6.95 (d, $J$ = 7.7 Hz, 1H), 6.84 (s, 1H), 6.70 (d, $J$ = 8.0Hz, 1H), 3.64 (s, 2H), 1.53 (s, 1H), 0.99 (s, 9H), 0.89 – 0.85 (m, 2H), 0.85 – 0.80 (m, 2H), 0.20 (s, 6H). **$^{13}$C NMR** (151 MHz, CDCl3) δ 155.6, 144.2, 129.3, 121.8, 120.7, 118.2, 70.7, 27.9, 25.7, 18.2, 11.5, -4.4. **HRMS** (ESI–) calcd for $C_{16}H_{26}NaO_2Si$ $[M+Na]^+$ 301.1594, found 301.1621.

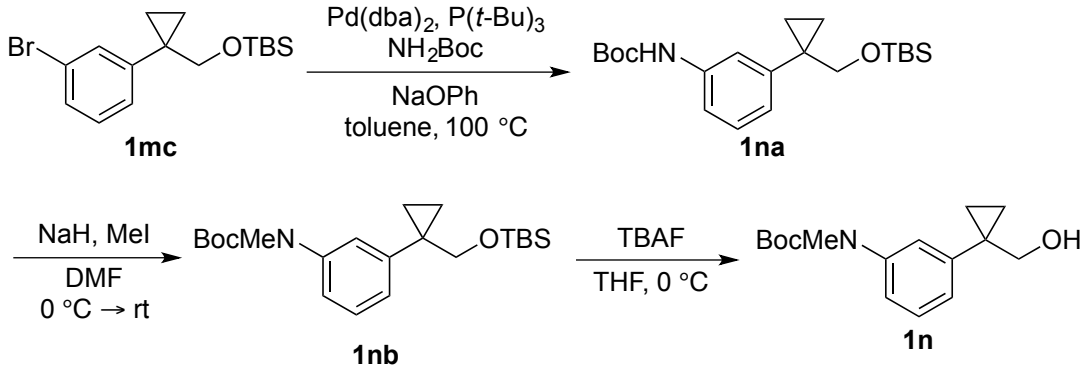
***tert*-Butyl 3'-(1-(hydroxymethyl)cyclopropyl)-[1,1'-biphenyl]-3-carboxylate 1m**




Following the general procedures D, cyclopropane **1la** (3.83 g, 17.3 mmol) was allowed to react with DIBAL-H. . The crude reaction mixture was purified by silica gel chromatography (100:0→60:40 hexanes/$Et_2O$) to give 3.14 g (81%) of aldehyde **1ma** as a yellow oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 9.18 (s, 1H), 7.47 – 7.42 (m, 2H), 7.28 – 7.22 (m, 2H), 1.63 – 1.54 (m, 2H), 1.46 – 1.37 (m, 2H). Following the general procedures E, **1ma** (3.01 g, 13.4 mml) was allowed to react with $NaBH_4$. The crude reaction mixture was purified by silica gel chromatography (100:0→85:15 hexanes/$Et_2O$) to give 2.53 g (83%) of alcohol **1mb** as a colorless oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.35 (d, $J$ = 7.1 Hz, 1H), 7.29 (d, $J$ = 7.7 Hz, 1H), 7.18 (t, $J$ = 7.8 Hz, 1H), 3.66 (d, $J$ = 6.0 Hz, 2H), 1.44 (t, $J$ = 6.1 Hz, 1H), 0.91 – 0.84 (m, 4H). To a round bottom flask was added **1mb** (1.50 g, 6.61 mmol), TBSCl (1.40 g, 9.25 mmol), DMAP (49 mg, 0.060 mmol) and imidazole (675 mg). The flask was sealed with a septum, and dry DMF (7 mL) was added at room temperature under $N_2$. The mixture was stirred for 6 h. The reaction was quenched with a saturated $NH_4Cl$ solution and extracted with diethyl ether three times. The combined organic layers were washed with water and brine, dried ($MgSO_4$) and concentrated. The crude reaction mixture was purified by silica gel chromatography (100:0→90:10 hexanes/EtOAc) to give 2.03 g (90%) of alkoxysilane **1mc** as a colorless oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.32 (d, $J$ = 7.9 Hz, 1H), 7.25 (d, $J$ = 7.5 Hz, 1H), 7.13 (t, $J$ = 7.8 Hz, 1H), 3.64 (s, 2H), 0.89 – 0.81 (m, 11H), 0.81 – 0.73 (m, 2H). -0.08 (s, 6H). The conditions described by our group were used for the following Pd-catalyzed C-C bond-forming cross coupling.[39] In an $N_2$-filled glovebox, **1mc** (683 mg, 2.00 mmol), (3-(*tert*-butoxycarbonyl)phenyl)boronic acid (666 mg, 3.00 mmol) and $K_3PO_4$ (1.27 g, 6.00 mmol) were weighed into a 20 mL screw-top vial. A solution of $Pd(dba)_2$ (5.8 mg, 0.010 mmol) and Q-Phos (14.2 mg, 0.020 mmol) in toluene (8 mL) was added to the vial. The vial was capped with a Teflon-lined screw cap, and the resulting solution was stirred at 100 °C for 3 h. The crude reaction mixture was filtered

through Celite, concentrated and purified by silica gel chromatography (100:0→90:10 hexanes/EtOAc) to give 942 mg (100%) of biaryl **1md** as a colorless oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.96 (d, *J* = 7.7 Hz, 1H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.61 (s, 1H), 7.51 – 7.42 (m, 2H), 7.37 (d, *J* = 4.5 Hz, 2H), 3.73 (s, 2H), 1.62 (s, 9H), 0.96 – 0.88 (m, 2H), 0.88 – 0.79 (m, 11H), -0.07 (s, 6H). To a solution of **1md** (942 mg, 2.00 mmol) in THF (8 mL), TBAF (4.0 mL, 1.0 M in THF) was added dropwise at 0 °C and stirred for 3 h. The reaction was quenched with a saturated $NH_4Cl$ solution and extracted with diethyl ether three times. The combined organic layers were washed with water and brine, dried ($MgSO_4$) and concentrated. The crude reaction mixture was purified by silica gel chromatography (100:0→80:20 hexanes/EtOAc) to give 606 mg (93%) of **1m** as a colorless oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.97 (d, *J* = 7.8 Hz, 1H), 7.74 (d, *J* = 7.7 Hz, 1H), 7.61 (s, 1H), 7.51 – 7.46 (m, 2H), 7.43 – 7.37 (m, 2H), 3.72 (s, 2H), 1.62 (s, 9H), 1.57 (s, 1H), 0.97 – 0.93 (m, 2H), 0.93 – 0.88 (m, 2H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 165.7, 143.4, 141.2, 140.6, 132.5, 131.1, 128.9, 128.6, 128.4, 128.2, 128.1, 127.9, 125.5, 81.2, 70.8, 28.22, 28.20, 11.4. **HRMS** (ESI+) calcd for $C_{21}H_{24}NaO_3$ $[M+Na]^+$ 347.1618, found 347.1617.

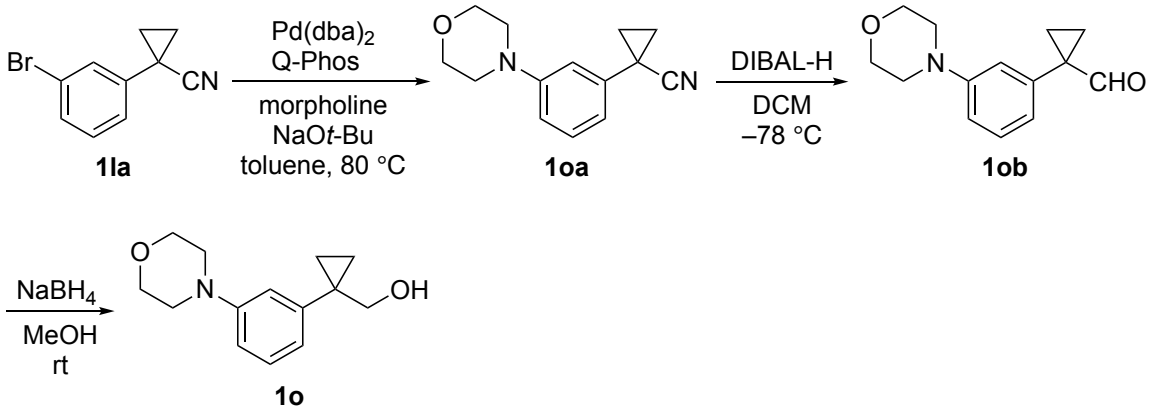
***tert*-Butyl (3-(1-(hydroxymethyl)cyclopropyl)phenyl)(methyl)carbamate 1n**




The conditions described by our group were used for the following Pd-catalyzed C-N bond-forming cross coupling.[41] In an $N_2$-filled glovebox, arylbromide **1mc** (683 mg, 2.00 mmol), *tert*-butyl carbamate (351 mg, 3.00 mmol) and NaOPh (348 mg, 3.00 mmol) were weighed into a 20 mL screw-top vial. A solution of $Pd(dba)_2$ (28.8 mg, 0.0500 mmol) and P(*t*-Bu)$_3$ (20.2 mg, 0.100 mmol) in toluene (6 mL) was added to the vial. The vial was capped with a Teflon-lined screw cap, and the resulting solution was stirred at 100 °C for 2 h. The crude reaction mixture was filtered through Celite, concentrated and purified by silica gel chromatography (100:0→50:50 hexanes/DCM) to give 680. mg (90%) of arylcarbamate **1na** as a yellow oil. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.31 (s, 1H), 7.25 – 7.14 (m, 2H), 7.03 (d, *J* = 6.9 Hz, 1H), 6.41 (s, 1H), 3.67 (s, 2H), 1.52 (s, 9H), 0.87 – 0.79 (m, 11H), 0.79 – 0.70 (m, 2H), -0.08 (s, 6H). To a solution of **1na** (566 mg, 1.50 mmol) in DMF (4.5 mL), NaH (43.2 mg) was added portionwise at rt and stired for 1.5 h. The solution was cooled to 0 °C, and MeI (0.112 mL, 1.80 mmol) was added dropwise to

the mixture. The resulting solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with a saturated $NH_4Cl$ solution and extracted with diethyl ether three times. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The crude reaction mixture was purified by silica gel chromatography (100:0→90:10 hexanes/EtOAc) to give 469 mg (87%) of **1nb** as a yellow oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.24 – 7.17 (m, 2H), 7.13 (d, *J* = 7.7 Hz, 1H), 7.05 (d, *J* = 7.7 Hz, 1H), 3.67 (s, 2H), 3.24 (s, 3H), 1.44 (s, 9H), 0.89 – 0.80 (m, 11H), 0.79 – 0.72 (m, 2H), -0.08 (s, 6H). To a solution of **1nb** (392 mg, 1.00 mmol) in THF (4 mL), TBAF (2.0 mL, 1.0 M in THF) was added dropwise at 0 °C and stirred for 2 h. The reaction was quenched with a saturated $NH_4Cl$ solution and extracted with diethyl ether three times. The combined organic layers were washed with water and brine, dried ($MgSO_4$) and concentrated. The crude reaction mixture was purified by silica gel chromatography (100:0→65:35 hexanes/EtOAc) to give 270. mg (93%) of **1n** as a colorless oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.30 – 7.22 (m, 2H), 7.16 (d, *J* = 7.7 Hz, 1H), 7.09 (d, *J* = 7.9 Hz, 1H), 3.67 (s, 2H), 3.26 (s, 3H), 1.56 (s, 1H), 1.45 (s, 9H), 0.90 – 0.87 (m, 2H), 0.87 – 0.84 (m, 2H). **$^{13}$C NMR** (151 MHz, CDCl3) δ 154.7, 143.7, 143.3, 128.4, 126.3, 126.0, 123.4, 80.2, 70.4, 37.3, 28.3, 28.0, 11.3. **HRMS** (ESI–) calcd for $C_{16}H_{22}NO$ $[M–H]^-$ 276.1605, found 276.1604.

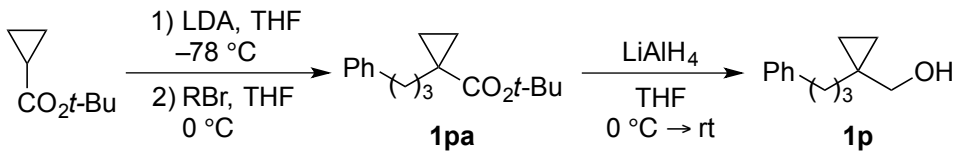
**(1-(3-3-Morpholinophenyl)cyclopropyl)methanol 1o**




The conditions described by our group were used for the following Pd-catalyzed C-N bond-forming cross coupling.[39] In an $N_2$-filled glovebox, arylbromide **1la** (666 mg, 3.00 mmol) and NaO*t*-Bu(432 mg, 4.50 mmol) were weighed into a 20 mL screw-top vial. A solution of $Pd(dba)_2$ (12.7 mg, 0.0300 mmol) and Q-Phos (42.6 mg, 0.0600 mmol) in toluene (12 mL) and morpholine (0.29 mL, 3.3 mmol) were added to the vial. The vial was capped with a Teflon-lined screw cap, and the resulting solution was stirred at 80 °C for 5 h. The crude reaction mixture was filtered through Celite, concentrated and purified by silica gel chromatography (100:0→65:35 hexanes/EtOAc) to give 775 mg (94%) of arylmorpholine **1oa** as a red oil. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.24 (t, *J* = 8.0 Hz, 1H), 6.93 (s, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 3.90 – 3.82 (m, 4H), 3.22 – 3.14 (m, 4H), 1.75 – 1.64 (m, 2H), 1.44 – 1.35 (m, 2H). Following the general

procedures D, **1oa** (572 mg, 2.51 mmol) was allowed to react with DIBAL-H. . The crude reaction mixture was purified by silica gel chromatography (100:0 → 65:35 hexanes/EtOAc) to give 529 mg (76%) of aldehyde **1ob** as a yellow oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 9.31 (s, 1H), 7.25 (t, *J* = 7.8 Hz, 1H), 6.89 – 6.83 (m, 2H), 6.81 (d, *J* = 7.5 Hz, 1H), 3.90 – 3.76 (m, 4H), 3.21 – 3.08 (m, 4H), 1.59 – 1.49 (m, 2H), 1.43 – 1.33 (m, 2H). Following the general procedures E, **1ob** (501 mg, 2.17 mml) was allowed to react with $NaBH_4$. The crude reaction mixture was purified by silica gel chromatography (100:0→45:55 hexanes/EtOAc) to give 400. mg (79%) of **1o** as a colorless oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.22 (t, *J* = 7.9 Hz, 1H), 6.98 – 6.94 (m, 1H), 6.89 (d, *J* = 7.6 Hz, 1H), 6.78 (dd, *J* = 8.2, 2.4 Hz, 1H), 3.89 – 3.82 (m, 4H), 3.64 (s, 2H), 3.19 – 3.14 (m, 4H), 1.56 (s, 1H), 0.90 – 0.85 (m, 2H), 0.85 – 0.81 (m, 2H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 151.3, 143.7, 129.2, 120.8, 116.6, 113.9, 70.9, 66.9, 49.4, 28.5, 11.2. **HRMS** (ESI–) calcd for $C_{14}H_{18}NO_2$ $[M–H]^-$ 232.1343, found 232.1352.

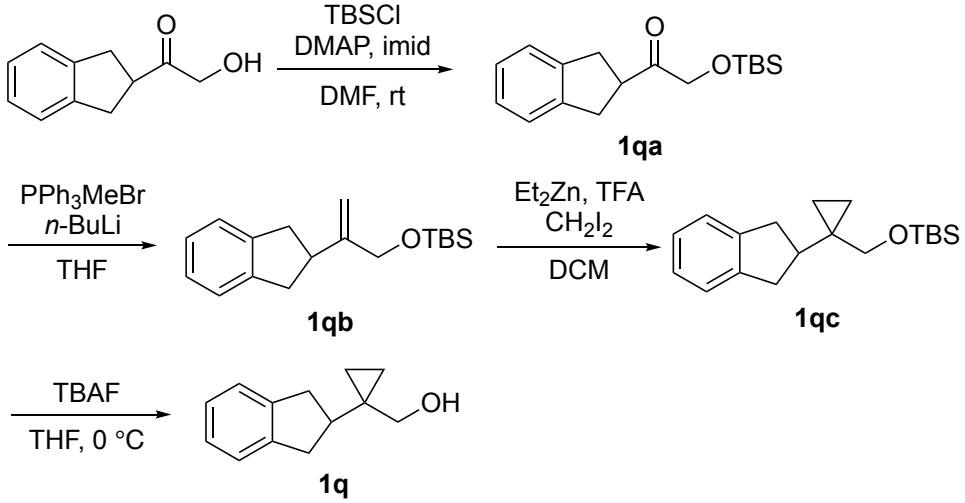
**(1-(3-phenylpropyl)cyclopropyl)methanol 1p**




The conditions developed by Seebach and modified by Yu were employed.[9,42] To a freshly prepared solution of lithium diispropylamide (0.40 M, 6.0 mmol) in THF was added a solution of *tert*-butyl cyclopropanecarboxylate (711 mg, 5.00 mmol) in THF (1.4 mL) over 10 min –78° C. The resulting solution was stirred at –78 °C for 6 h. A solution of (3-bromopropyl)benzene (2.28 mL, 15.0 mmol) in THF (5 mL) was added over 10 min. The solution was allowed to warm to 0 °C slowly over 5 h, after which the solution was removed from the cooling bath, quenched by addition of saturated $NH_4Cl$ solution and extracted with diethyl ether three times. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The crude reaction mixture was purified by silica gel chromatography (100:0→95:5 hexanes/$Et_2O$) to give 780. mg (60%) of cyclopropane **1pa** as a colorless oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.6 Hz, 2H), 7.22 – 7.17 (m, 3H), 2.62 (t, *J* = 7.8 Hz, 2H), 1.84 – 1.75 (m, 2H), 1.57 – 1.51 (m, 2H), 1.43 (s, 9H), 1.16 – 1.06 (m, 2H), 0.65 – 0.54 (m, 2H). To a solution of **1pa** (673 mg, 2.58 mmol) in THF (13 mL) was added a solution of $LiAlH_4$ (4.1 mL, 1.0 M in THF) dropwise at 0 °C. The resulting solution was allowed to warm to room temperature and stirred for 2 h, at which time it was quenched by careful addition of saturated $NH_4Cl$ solution and extracted with diethyl ether three times. The combined organic layers were washed with water and brine, dried ($MgSO_4$) and concentrated. The crude reaction mixture was purified by silica gel chromatography (100:0→60:40 hexanes/$Et_2O$) to give 369 mg (75%) of **1p** as a colorless oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.7 Hz, 2H), 7.21 – 7.16 (m, 3H), 3.42 (s, 2H), 2.61 (t, *J* = 7.8 Hz, 2H), 1.77 – 1.69 (m, 2H), 1.48 – 1.43 (m, 2H), 1.40 (s, 1H), 0.40 – 0.36 (m, 2H), 0.35 – 0.32 (m, 2H). **$^{13}$C NMR** (151

MHz, $CDCl_3$) δ 142.5, 128.3, 128.2, 125.6, 68.5, 36.2, 33.7, 28.5, 22.3, 10.0. **HRMS** (ESI–) calcd for $C_{13}H_{17}O$ $[M–H]^-$ 189.1285, found 189.1293.

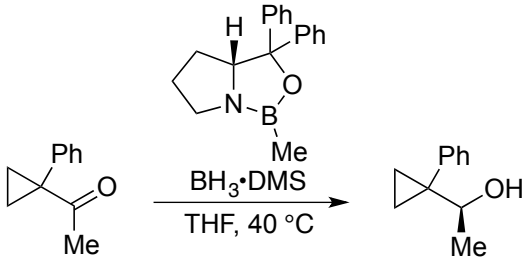
**(1-(2,3-dihydro-1*H*-inden-2-yl)cyclopropyl)methanol 1q**




To a round bottom flask was added 1-(2,3-dihydro-1*H*-inden-2-yl)-2-hydroxyethan-1-one[37] (980. mg, 5.60 mmol), TBSCl (1.18 g, 7.86 mmol), DMAP (49 mg, 0.34 mmol) and imidazole (572 mg, 8.40 mmol). The flask was sealed with a septum, and dry DMF (6 mL) was added at room temperature under $N_2$. The mixture was stirred for 2 h. The reaction was quenched with a saturated $NH_4Cl$ solution and extracted with diethyl ether three times. The combined organic layers were washed with water and brine, dried ($MgSO_4$) and concentrated. The crude reaction mixture was purified by silica gel chromatography (100:0→90:10 hexanes/EtOAc) to give 1.47 g (90%) of alkoxysilane **1qa** as a yellow oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.24 – 7.18 (m, 2H), 7.18 – 7.13 (m, 2H), 4.32 (s, 2H), 3.74 (p, $J$ = 8.6 Hz, 1H), 3.23 (dd, $J$ = 15.7, 8.1 Hz, 2H), 3.16 (dd, $J$ = 15.7, 9.1 Hz, 2H), 0.94 (s, 9H), 0.12 (s, 6H). To a solution of $Ph_3PMeBr$ (3.57 g, 10.0 mmol) in THF (25 mL) was added *n*-BuLi (3.6 mL, 2.5 M in hexanes) dropwise at 0 °C. To the resulting mixture was added a solution of **1qa** (1.44 g, 4.96 mmol) in THF (5 mL) at –78 °C. The resulting solution was allowed to warm to room temperature and stirred overnight. The reaction was quenched with a saturated $NH_4Cl$ solution and extracted with hexanes three times. The combined organic layers were dried ($MgSO_4$) and concentrated. The crude reaction mixture was purified by silica gel chromatography (hexanes only) to give 1.28 g (89%) of alkene **1qb** as a colorless oil. **$^1$H NMR** (600 MHz, $CDCl_3$ δ 7.23 – 7.18 (m, 2H), 7.18 – 7.11 (m, 2H), 5.12 (s, 1H), 4.95 (s, 1H), 4.19 (s, 2H), 3.14 – 3.05 (m, 3H), 2.96 – 2.86 (m, 2H), 0.92 (s, 9H), 0.09 (s, 6H). The conditions previously reported were used for the following cyclopropanation.[43] To a solution of $Et_2Zn$ (8.74 mL, 8,74 mmol, 1.0 M in hexanes) in $CH_2Cl_2$ (20 mL) was added a solution of trifluoroacetic acid (0.67 mL, 8.7 mmol) in $CH_2Cl_2$ (5 mL) was added dropwise under $N_2$ at 0 °C. After stirring for 20 min, a solution of $CH_2I_2$ (0.69 mL, 8.7 mmol) in $CH_2Cl_2$ (5

mL) was added. After an additional 20 minutes of stirring, a solution of **1qb** (1.26 g, 4.37 mmol) in $CH_2C1_2$ (5 mL) was added, and the reaction mixture was slowly warmed to room temperature. After an additional 30 min of stirring, the reaction mixture was quenched with a saturated $NH_4Cl$ solution and extracted with diethyl ether three times. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The crude reaction mixture was purified by silica gel chromatography (hexanes only) to give 1.24 g (93%) of cyclopropane **1qc** as a colorless oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.20 – 7.14 (m, 2H), 7.14 – 7.08 (m, 2H), 3.52 (s, 2H), 2.90 (dd, *J* = 14.6, 8.1 Hz, 2H), 2.82 – 2.72 (m, 1H), 2.63 (dd, *J* = 15.0, 9.9 Hz, 2H), 0.88 (s, 9H), 0.48 – 0.44 (m, 2H), 0.43 – 0.40 (m, 2H), 0.02 (s, 6H). To a solution of **1qc** (1.09 g, 3.60 mmol) in THF (14 mL), TBAF (7.2 mL, 1.0 M in THF) was added dropwise at 0 °C and stirred for 2 h. The reaction was quenched with a saturated $NH_4Cl$ solution and extracted with diethyl ether three times. The combined organic layers were washed with water and brine, dried ($MgSO_4$) and concentrated. The crude reaction mixture was purified by silica gel chromatography (100:0→50:50 hexanes/$Et_2O$) to give 607 mg (90%) of **1q** as a colorless oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.23 – 7.17 (m, 2H), 7.18 – 7.12 (m, 2H), 3.51 (s, 2H), 2.97 (dd, *J* = 14.6, 7.6 Hz, 2H), 2.83 – 2.72 (m, 1H), 2.69 (dd, *J* = 15.3, 8.9 Hz, 2H), 1.61 (s, 1H), 0.61 – 0.51 (m, 2H), 0.50 – 0.40 (m, 2H). **$^{13}$C NMR** (151 MHz, CDCl3) δ 143.0, 126.1, 124.3, 69.1, 42.3, 36.2, 24.8, 8.1. **HRMS** (ESI–) calcd for $C_{13}H_{15}O$ $[M–H]^-$ 187.1128, found 187.1139.

**(*S*)-1-(1-phenylcyclopropyl)ethanol 5'**

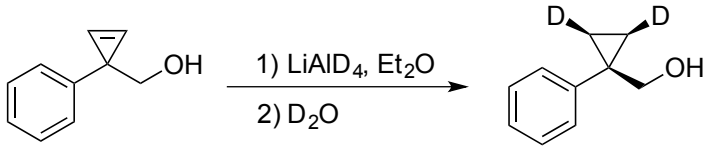



**5'**

The conditions previously reported were used for the enantioselective reduction of ketone with slight modification.[44,45] To a solution of (*R*)-tetrahydro-l-methyl-3,3-diphenyl-l*H*,3*H*-pyrrolo[l,2-c]-1,3,2-oxazaborole (69.3 mg, 0.250 mmol) in THF (3 mL) was added borane-methyl sulfide complex in THF (0.50 mL, 2.0 M in THF) and the solution was warmed to 40 °C. To the resulting solution was added a solution of 1-(1-phenylcyclopropyl)ethanone[46] (160. mg, 1.00 mmol) in THF (3 mL) over 2 h. The reaction mixture was stirred for an additional hour. The reaction mixture was cooled to 0 °C and carefully quenched with MeOH and then 1M HCl. The aqueous layer was separated and extracted with diethyl ether three times. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. The crude reaction mixture was purified by silica gel chromatography (100:0→65:35 pentane/$Et_2O$) to give 132 mg

(81%) of **5'** as a colorless oil. **HPLC analysis**: 95% *ee*, Chiralpak AD-H column, 10% isopropanol in hexane, 1.0 mL/min flow rate, 220 nm UV lamp, $t_R$ = 5.9 min (minor), $t_R$ = 6.4 min (major). $[\alpha]_D^{25}$ = –22.6 (c 1.03, $CH_2Cl_2$). **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.25 (t, *J* = 7.3 Hz, 1H), 3.39 (q, *J* = 6.4 Hz, 1H), 1.81 (s, 1H), 1.12 (d, *J* = 6.4 Hz, 3H), 0.89 – 0.85 (m, 1H), 0.85 – 0.79 (m, 2H), 0.78 – 0.74 (m, 1H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 141.2, 131.1, 127.9, 126.7, 74.3, 32.0, 20.5, 11.2, 9.8. ($^1$H and $^{13}$C NMR data were consistent with previously reported values.[47])

**(1-phenylcyclopropyl)methanol-*d*$_2$ 1a-*d*$_2$**



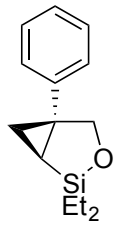

**1a**-*d*$_2$

The conditions previously reported were used with slight modification for the directed reduction of cyclopropene with $LiAlD_4$.[16] To a slurry of $LiAlD_4$ (56.0 mg, 1.30 mmol) in diethyl ether (0.8 mL) was added a solution of (1-phenylcycloprop-2-enyl)methanol[48] (94.9 mg, 0.649 mmol) in diethyl ether (0.5 mL) over 1 h. The reaction mixture was stirred overnight. The reaction was quenched by a careful addition of $D_2O$. The resulting mixture was stirred for another 30 min, at which time it was treated with NaOD (40 wt% in $D_2O$) and additional $D_2O$. The aqueous layer was separated and extracted with diethyl ether three times. The combined organic layers were dried over $MgSO_4$, purified by elution through a plug of silica gel and concentrated to give 50.0 mg (51%) of **1**-*d*$_2$ (>98% D incorporation).

*2.4.3 General procedure for enantioselective silylation of cyclopropanes*

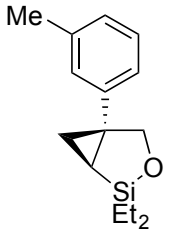
In an $N_2$-filled glovebox, cyclopropyl methanol (1.0 equiv) was weighed into a 4 mL screw-top vial. A freshly prepared stock solution of $Ru(PPh_3)_3Cl_2$ (0.2 mol %) in benzene or THF ([alcohol] = 1 M) was added, and then neat $Et_2SiH_2$ (1.5 equiv) was added dropwise. The vial was capped with a Teflon-lined screw cap, and the resulting solution was stirred at 50 °C for 12 h. The volatile materials were then removed by placing the reaction mixture directly under high vacuum for 1 h (the stir bar was temporarily removed during this operation to prevent bumping). The stir bar was replaced, and the concentrated diethyl(hydrido)silyl ether was then sequentially treated with a freshly prepared stock solution of $[Rh(cod)Cl]_2$ (2.0 mol %) and (S)-DTBM-Segphos (5.0 mol %) in THF ([silyl ether] = 0.5 M) and cyclohexene (1.2 equiv). The Teflon-lined screw cap was replaced, and the vial was then removed from the glovebox and placed in a pre-heated aluminum heating block at 50 °C. After 24 hours, the reaction mixture was allowed to cool to rt, and the solvent was removed via rotary evaporation. The crude product was purified by Kugelrohr distillation or silica gel chromatography.

**Oxasilolane 3a**




Following the general procedure, cyclopropylmethanol **1a**[49] (74.0 mg, 0.499 mmol) was converted to the corresponding diethyl(hydrido)silyl ether using $Ru(PPh_3)_3Cl_2$ (0.2 mol %) in THF (0.50 mL) at 50 °C for 12 h. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/(*S*)-DTBM-SEGPHOS (4.0 mol %) in THF (1.0 mL) at 50 °C for 24 h. Concentration of the reaction mixture and purification by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 82.0 mg (71%) of **3a** as a colorless oil. **SFC analysis**: 87% *ee*, Chiralpak AD-H column, 0.5% isopropanol, 2.5 mL/min flow rate, 220 nm UV lamp, $t_R$ = 2.1 min (major), $t_R$ = 3.2 min (minor). $[\alpha]_D^{25}$ = +84.4 (c 1.00, $CHCl_3$). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.30 (t, *J* = 7.5 Hz, 2H), 7.26 (d, *J* = 6.8 Hz, 2H), 7.21 (t, *J* = 7.1 Hz, 1H), 4.21 (d, *J* = 9.4 Hz, 1H), 4.19 (d, *J* = 9.4 Hz, 1H), 1.21 (dd, *J* = 10.5, 3.9 Hz, 1H), 1.12 – 1.02 (m, 6H), 0.95 (dd, *J* = 6.7, 3.9 Hz, 1H), 0.83 – 0.69 (m, 4H), 0.57 (dd, *J* = 10.5, 6.7 Hz, 1H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 142.5, 128.3, 127.7, 126.3, 71.8, 32.3, 14.8, 9.1, 7.0, 6.9, 6.3, 4.3. **HRMS** (EI+) calcd for $C_{14}H_{20}OSi$ $[M]^+$ 232.1283, found 232.1284.

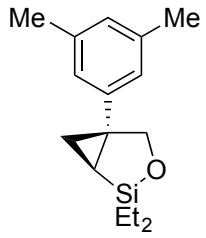
**Oxasilolane 3b**




Following the general procedure, cyclopropylmethanol **1b** (168 mg, 1.04 mmol) was converted to the corresponding diethyl(hydrido)silyl ether using $Ru(PPh_3)_3Cl_2$ (0.2 mol %) in benzene (1.0 mL) at 50 °C for 12 h. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/(*S*)-DTBM-SEGPHOS (4.0 mol %) in THF (2.0 mL) at 50 °C for 24 h. Concentration of the reaction mixture and purification by Kugelrohr distillation (1 Torr, 130 °C), followed by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 150. mg (61%) of **3b** as a colorless oil. **SFC analysis**: 92% *ee*, Chiralpak AD-H column, 0.5% isopropanol, 1.5 mL/min flow rate, 220 nm UV lamp, $t_R$ = 2.8 min (major), $t_R$ = 4.0 min (minor). $[\alpha]_D^{25}$ = +87.8 (c 1.07, $CHCl_3$). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.20 (t, *J* = 7.9 Hz, 1H), 7.09 – 7.05 (m, 2H), 7.03 (d, *J* = 7.6 Hz, 1H), 4.20 (d, *J* = 9.4 Hz, 1H), 4.18 (d, *J* = 9.4 Hz, 1H), 2.34 (s, 3H), 1.19 (dd, *J* = 10.5, 3.9 Hz, 1H), 1.11 – 1.03 (m, 6H), 0.94 (dd, *J* = 6.8, 3.9 Hz, 1H), 0.82 – 0.70 (m, 4H), 0.56 (dd, *J* = 10.5, 6.6 Hz, 1H). **$^{13}$C**

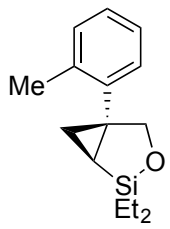
**NMR** (151 MHz, $CDCl_3$) δ 142.4, 137.9, 128.4, 128.2, 127.1, 124.7, 71.8, 32.2, 21.4, 14.8, 9.0, 7.0, 6.9, 6.3, 4.3. **HRMS** (EI+) calcd for $C_{15}H_{22}OSi$ $[M]^+$ 246.1440, found 246.1438.

**Oxasilolane 3c**




Following the general procedure, cyclopropylmethanol **1c** (146 mg, 0.828 mmol) was converted to the corresponding diethyl(hydrido)silyl ether using $Ru(PPh_3)_3Cl_2$ (0.2 mol %) in benzene (0.80 mL) at 50 °C for 12 h. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/(*S*)-DTBM-SEGPHOS (4.0 mol %) in THF (1.7 mL) at 50 °C for 24 h. Concentration of the reaction mixture and purification by Kugelrohr distillation (1 Torr, 150 °C), followed by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 122 mg (57%) of **3c** as a colorless oil. **SFC analysis**: 92% *ee*, Chiralcel OZ-H column, 0.5% isopropanol, 2.5 mL/min flow rate, 220 nm UV lamp, $t_R$ = 4.1 min (minor), $t_R$ = 6.0 min (major). $[\alpha]_D^{25}$ = +83.7 (c 1.00, $CHCl_3$). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.86 (overlapping s, 3H), 4.19 (d, *J* = 9.5 Hz, 1H), 4.16 (d, *J* = 9.4 Hz, 1H), 2.30 (s, 6H), 1.17 (dd, *J* = 10.5, 3.8 Hz, 1H), 1.11 – 1.02 (m, 6H), 0.92 (dd, *J* = 6.5, 4.1 Hz, 1H), 0.81 – 0.70 (m, 4H), 0.55 (dd, *J* = 10.4, 6.7 Hz, 1H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 142.4, 137.8, 128.0, 125.5, 71.9, 32.1, 21.3, 14.9, 8.9, 7.0, 6.9, 6.3, 4.3. **HRMS** (EI+) calcd for $C_{16}H_{24}OSi$ $[M]^+$ 260.1596, found 260.1595.

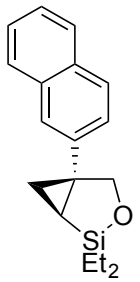
**Oxasilolane 3d**




Following the general procedure, cyclopropylmethanol **1d** (82.2 mg, 0.507 mmol) was converted to the corresponding diethyl(hydrido)silyl ether using $Ru(PPh_3)_3Cl_2$ (0.2 mol %) in THF (0.50 mL) at 50 °C for 12 h. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/(*S*)-DTBM-SEGPHOS (4.0 mol %) in THF (1.0 mL) at 50 °C for 24 h. Concentration of the reaction mixture and purification by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 86.9 mg (69%) of **3d** as a colorless oil. **SFC analysis**: 95% *ee*, Chiralcel OZ-H column, 0.5% isopropanol, 2.5 mL/min flow rate, 220

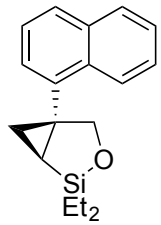
nm UV lamp, $t_R$ = 3.2 min (major), $t_R$ = 4.6 min (minor). $[\alpha]_D^{25}$ = +90. (c 0.54, $CHCl_3$). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.30 – 7.27 (m, 1H), 7.15 (q, *J* = 3.5, 2.6 Hz, 3H), 4.16 (d, *J* = 9.5 Hz, 1H), 3.91 (d, *J* = 9.5 Hz, 1H), 2.43 (s, 3H), 1.16 – 1.11 (m, 4H), 1.07 (t, *J* = 8.0 Hz, 3H), 1.01 (dd, *J* = 6.5, 3.8 Hz, 1H), 0.84 (q, *J* = 7.7 Hz, 2H), 0.80 – 0.69 (m, 2H), 0.56 (dd, *J* = 10.5, 6.5 Hz, 1H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 140.1, 138.4, 130.3, 130.1, 126.9, 125.8, 71.3, 32.5, 19.6, 14.0, 8.2, 7.0, 6.9, 6.3, 4.3. **HRMS** (EI+) calcd for $C_{15}H_{22}OSi$ $[M]^+$ 246.1440, found 246.1441.

**Oxasilolane 3e**




Following the general procedure, cyclopropylmethanol **1e** (155 mg, 0.782 mmol) was converted to the corresponding diethyl(hydrido)silyl ether using $Ru(PPh_3)_3Cl_2$ (0.2 mol %) in benzene (0.80 mL) at 50 °C for 12 h. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/(*S*)-DTBM-SEGPHOS (4.0 mol %) in THF (1.6 mL) at 50 °C for 24 h. Concentration of the reaction mixture and purification by Kugelrohr distillation (1 Torr, 160 °C) gave 176 mg (78%) of **3e** as a colorless oil. **SFC analysis**: 90% *ee*, Chiralcel OZ-H column, 5% isopropanol, 1.5 mL/min flow rate, 220 nm UV lamp, $t_R$ = 3.3 min (minor), $t_R$ = 3.9 min (major). $[\alpha]_D^{25}$ = +86.9 (c 1.03, $CHCl_3$). **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.82 – 7.76 (m, 3H), 7.68 (s, 1H), 7.49 – 7.41 (m, 2H), 7.37 (dd, *J* = 8.5, 1.7 Hz, 1H), 4.31 (d, *J* = 9.4 Hz, 1H), 4.29 (d, *J* = 9.4 Hz, 1H), 1.33 (dd, *J* = 10.5, 4.0 Hz, 1H), 1.14 – 1.06 (m, 6H), 1.04 (dd, *J* = 6.7, 4.0 Hz, 1H), 0.85 – 0.73 (m, 4H), 0.68 (dd, *J* = 10.5, 6.7 Hz, 1H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 139.8, 133.3, 132.1, 128.0, 127.5, 127.5, 126.1, 126.0, 125.9, 125.5, 71.7, 32.4, 15.0, 9.4, 7.0, 6.9, 6.3, 4.3. **HRMS** (EI+) calcd for $C_{18}H_{22}OSi$ $[M]^+$ 282.1440, found 282.1437.

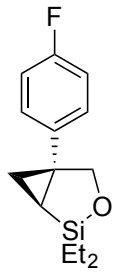
**Oxasilolane 3f**




Following the general procedure, cyclopropylmethanol **1f** (101 mg, 0.509 mmol) was converted to the corresponding diethyl(hydrido)silyl ether using $Ru(PPh_3)_3Cl_2$ (0.2 mol

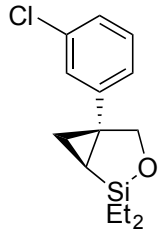
%) in THF (0.50 mL) at 50 °C for 12 h. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/(*S*)-DTBM-SEGPHOS (4.0 mol %) in THF (1.0 mL) at 50 °C for 24 h. Concentration of the reaction mixture and purification by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 59.6 mg (42%) of **3f** as a colorless oil. **SFC analysis**: 95% *ee*, Chiralpak AD-H column, 3% isopropanol, 2.5 mL/min flow rate, 220 nm UV lamp, $t_R$ = 3.9 min (minor), $t_R$ = 5.3 min (major). $[\alpha]_D^{25}$ = +91.8 (c 1.04, $CHCl_3$). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.36 (d, *J* = 8.3 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.77 (d, *J* = 8.1 Hz, 1H), 7.58 – 7.51 (m, 1H), 7.53 – 7.46 (m, 2H), 7.46 – 7.39 (m, 1H), 4.40 (d, *J* = 9.4 Hz, 1H), 4.05 (d, *J* = 9.6 Hz, 1H), 1.30 (dd, *J* = 10.5, 3.7 Hz, 1H), 1.26 – 1.17 (m, 4H), 1.12 (t, *J* = 8.0 Hz, 3H), 0.94 (q, *J* = 7.9 Hz, 2H), 0.88 – 0.78 (m, 2H), 0.71 (dd, *J* = 10.5, 6.5 Hz, 1H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 138.7, 133.7, 133.2, 128.6, 127.6, 127.2, 125.8, 125.6, 125.5, 124.8, 72.5, 32.0, 14.4, 8.2, 7.03, 6.96, 6.4, 4.4. **HRMS** (EI+) calcd for $C_{18}H_{22}OSi$ $[M]^+$ 282.1440, found 282.1439.

**Oxasilolane 3g**



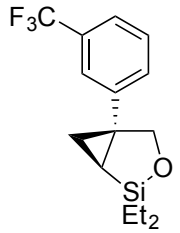

Following the general procedure, cyclopropylmethanol **1g** (41.6 mg, 0.251 mmol) was converted to the corresponding diethyl(hydrido)silyl ether using $Ru(PPh_3)_3Cl_2$ (0.2 mol %) in benzene (0.25 mL) at 50 °C for 12 h. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/(*S*)-DTBM-SEGPHOS (4.0 mol %) in THF (0.50 mL) at 50 °C for 24 h. Concentration of the reaction mixture and purification by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 33.4 mg (54%) of **3f** as a colorless oil. **SFC analysis**: 87% *ee*, Chiralpak AD-H column, 0.5% isopropanol, 1.5 mL/min flow rate, 220 nm UV lamp, $t_R$ = 2.3 min (major), $t_R$ = 3.4 min (minor). $[\alpha]_D^{25}$ = +80.9 (c 0.983, $CHCl_3$). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.25 – 7.19 (m, 2H), 7.02 – 6.94 (m, 2H), 4.16 (d, *J* = 9.4 Hz, 1H), 4.11 (d, *J* = 9.4 Hz, 1H), 1.17 (dd, *J* = 10.5, 3.9 Hz, 1H), 1.11 – 1.01 (m, 6H), 0.93 (dd, *J* = 6.7, 4.0 Hz, 1H), 0.83 – 0.68 (m, 4H), 0.50 (dd, *J* = 10.5, 6.7 Hz, 1H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 161.4 (d, *J* = 245 Hz), 138.1, 129.5, 115.1 (d, *J* = 21 Hz), 72.0, 31.8, 14.5, 9.1, 6.92, 6.89, 6.3, 4.3. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ –115.54. **HRMS** (EI+) calcd for $C_{14}H_{19}FOSi$ $[M]^+$ 250.1189, found 250.1189.

**Oxasilolane 3h**



Following the general procedure, cyclopropylmethanol **1h** (143 mg, 0.783 mmol) was converted to the corresponding diethyl(hydrido)silyl ether using $Ru(PPh_3)_3Cl_2$ (0.2 mol %) in benzene (0.80 mL) at 50 °C for 12 h. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/(*S*)-DTBM-SEGPHOS (4.0 mol %) in THF (1.6 mL) at 50 °C for 24 h. Concentration of the reaction mixture and purification by Kugelrohr distillation (400 mTorr, 120 °C), followed by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 109 mg (51%) of **3h** as a colorless oil. **SFC analysis**: 88% *ee*, Chiralpak AD-H column, 0.5% isopropanol, 2.5 mL/min flow rate, 220 nm UV lamp, $t_R$ = 2.7 min (major), $t_R$ = 4.2 min (minor). $[\alpha]_D^{25}$ = +80. (c 0.35, $CHCl_3$). **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.22 (t, *J* = 7.7 Hz, 1H), 7.21 – 7.17 (m, 2H), 7.12 (dt, *J* = 7.5, 1.5 Hz, 1H), 4.19 (d, *J* = 9.3 Hz, 1H), 4.16 (d, *J* = 9.5 Hz, 1H), 1.19 (dd, *J* = 10.3, 4.3 Hz, 1H), 1.09 – 1.03 (m, 6H), 0.97 (dd, *J* = 6.8, 4.1 Hz, 1H), 0.80 – 0.70 (m, 4H), 0.58 (dd, *J* = 10.5, 6.8 Hz, 1H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 144.7, 134.2, 129.6, 127.7, 126.5, 125.8, 71.4, 32.0, 15.2, 9.5, 6.92, 6.85, 6.2, 4.3. **HRMS** (EI+) calcd for $C_{14}H_{19}ClOSi$ $[M]^+$ 266.0894, found 266.0893.

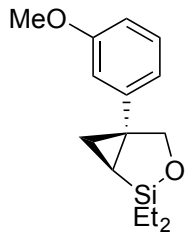
**Oxasilolane 3i**



Following the general procedure, cyclopropylmethanol **1i** (216 mg, 1.00 mmol) was converted to the corresponding diethyl(hydrido)silyl ether using $Ru(PPh_3)_3Cl_2$ (0.2 mol %) in benzene (0.80 mL) at 50 °C for 12 h. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/(*S*)-DTBM-SEGPHOS (4.0 mol %) in THF (1.6 mL) at 50 °C for 24 h. Concentration of the reaction mixture and purification by Kugelrohr distillation (500 mTorr, 140 °C) gave 258 mg (86%) of **3i** as a colorless oil. **HPLC analysis**: 90% *ee*, Chiralpak IC column, 0.1% isopropanol in hexane, 1.0 mL/min flow rate, 220 nm UV lamp, $t_R$ = 5.1 min (minor), $t_R$ = 5.9 min (major). $[\alpha]_D^{25}$ = +70.3 (c 1.05, $CHCl_3$). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.48 – 7.44 (m, 2H), 7.44 – 7.39 (m, 2H), 4.23 (d, *J* = 9.4 Hz, 1H), 4.18 (d, *J* = 9.4 Hz, 1H), 1.23 (dd, *J* = 10.6, 4.0 Hz, 1H), 1.10 – 1.03 (m, 6H), 1.01 (dd, *J* = 6.8, 4.1 Hz, 1H), 0.83 – 0.70 (m, 4H), 0.62 (dd, *J* = 10.5, 6.8 Hz, 1H). **$^{13}$C**

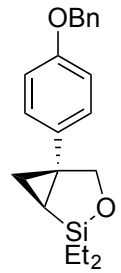
**NMR** (151 MHz, $CDCl_3$) δ 143.6, 131.0, 130.8 (q, *J* = 32 Hz), 128.8, 124.2 (q, J = 3.8 Hz), 124.1 (q, *J* = 272 Hz), 123.1 (q, J = 3.7 Hz), 71.4, 32.1, 15.1, 9.6, 6.9, 6.8, 6.2, 4.2. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ –61.79. **HRMS** (EI+) calcd for $C_{15}H_{19}F_3OSi$ $[M]^+$ 300.1157, found 300.1162.

**Oxasilolane 3j**




Following the general procedure, cyclopropylmethanol **1j** (180. mg, 1.01 mmol) was converted to the corresponding diethyl(hydrido)silyl ether using $Ru(PPh_3)_3Cl_2$ (0.2 mol %) in benzene (1.0 mL) at 50 °C for 12 h. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/(*S*)-DTBM-SEGPHOS (4.0 mol %) in THF (2.0 mL) at 50 °C for 24 h. Concentration of the reaction mixture and purification by Kugelrohr distillation (1 Torr, 140 °C) gave 237 mg (89%) of **3j** as a colorless oil. **SFC analysis**: 91% *ee*, Chiralcel OZ-H column, 1% isopropanol, 2.5 mL/min flow rate, 220 nm UV lamp, $t_R$ = 3.1 min (minor), $t_R$ = 3.8 min (major). $[\alpha]_D^{25}$ = +82.1 (c 1.08, $CHCl_3$). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.22 (t, *J* = 7.9 Hz, 1H), 6.85 (ddd, *J* = 7.7, 1.5, 0.9 Hz, 1H), 6.82 – 6.77 (m, 1H), 6.76 (ddd, *J* = 8.2, 2.5, 0.8 Hz, 1H), 4.19 (ABq, *J* = 9.4 Hz, 2H), 3.80 (s, 3H), 1.20 (dd, *J* = 10.5, 3.9 Hz, 1H), 1.10 – 1.02 (m, 6H), 0.94 (dd, *J* = 6.8, 4.0 Hz, 1H), 0.80 – 0.69 (m, 4H), 0.57 (dd, *J* = 10.5, 6.8 Hz, 1H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 159.6, 144.2, 129.3, 120.0, 113.8, 111.2, 71.7, 55.1, 32.3, 15.0, 9.3, 6.9, 6.9, 6.3, 4.3. **HRMS** (EI+) calcd for $C_{15}H_{22}O_2Si$ $[M]^+$ 262.1389, found 262.1387.

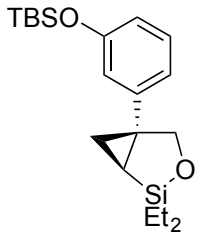
**Oxasilolane 3k**




Following the general procedure, cyclopropylmethanol **1k** (125 mg, 0.492 mmol) was converted to the corresponding diethyl(hydrido)silyl ether using $Ru(PPh_3)_3Cl_2$ (0.2 mol %) in benzene (0.50 mL) at 50 °C for 12 h. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/(*S*)-DTBM-SEGPHOS (4.0 mol %) in THF (1.0 mL) at 50 °C for 24 h. Concentration of the reaction mixture and purification by silica gel chromatography

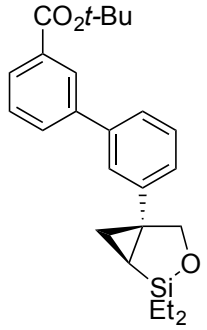
(100:0→90:10 hexanes/EtOAc) gave 129 mg (68%) of **3k** as a colorless oil. **HPLC analysis**: 87% *ee*, Chiralcel OD-H column, 1% isopropanol in hexane, 1.0 mL/min flow rate, 254 nm UV lamp, $t_R$ = 8.6 min (major), $t_R$ = 9.7 min (minor). $[\alpha]_D^{25}$ = +67.7 (c 0.964, $CHCl_3$). **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.5 Hz, 2H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.94 (d, *J* = 8.6 Hz, 2H), 5.06 (s, 2H), 4.17 (d, *J* = 9.4 Hz, 1H), 4.14 (d, *J* = 9.4 Hz, 1H), 1.20 (dd, *J* = 10.4, 3.7 Hz, 1H), 1.14 – 1.04 (m, 6H), 0.93 (dd, *J* = 6.6, 3.9 Hz, 1H), 0.84 – 0.72 (m, 4H), 0.50 (dd, *J* = 10.4, 6.7 Hz, 1H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 157.4, 137.0, 134.7, 129.1, 128.5, 127.9, 127.4, 114.7, 72.2, 70.0, 31.8, 14.2, 8.9, 7.0, 6.9, 6.3, 4.3. **HRMS** (EI+) calcd for $C_{21}H_{26}O_2Si$ $[M]^+$ 338.1702, found 338.1705.

**Oxasilolane 3l**



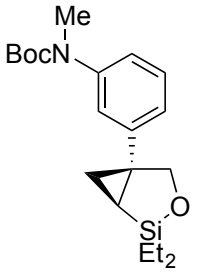

Following the general procedure, cyclopropylmethanol **1l** (168 mg, 0.603 mmol) was converted to the corresponding diethyl(hydrido)silyl ether using $Ru(PPh_3)_3Cl_2$ (0.2 mol %) in benzene (0.60 mL) at 50 °C for 12 h. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/(*S*)-DTBM-SEGPHOS (4.0 mol %) in THF (1.2 mL) at 50 °C for 24 h. Concentration of the reaction mixture and purification by Kugelrohr distillation (500 mTorr, 160 °C) gave 187 mg (86%) of **3l** as a colorless oil. **SFC analysis**: 92% *ee*, Chiralcel OD-H column, 0.1% isopropanol, 2.5 mL/min flow rate, 220 nm UV lamp, $t_R$ = 4.0 min (minor), $t_R$ = 4.7 min (major). $[\alpha]_D^{25}$ = +59.8 (c 1.03, $CHCl_3$). **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.14 (t, *J* = 7.8 Hz, 1H), 6.85 (d, *J* = 7.7 Hz, 1H), 6.72 (s, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 4.18 (s, 2H), 1.20 (dd, *J* = 10.5, 3.9 Hz, 1H), 1.11 – 1.03 (m, 6H), 0.99 (s, 9H), 0.93 (dd, *J* = 6.7, 3.9 Hz, 1H), 0.81 – 0.69 (m, 4H), 0.54 (dd, *J* = 10.4, 6.8 Hz, 1H), 0.20 (s, 6H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 155.6, 144.1, 129.2, 120.6, 119.4, 118.0, 71.8, 32.1, 25.7, 18.2, 14.9, 9.3, 7.0, 6.9, 6.3, 4.4, -4.4. **HRMS** (EI+) calcd for $C_{20}H_{34}O_2Si_2$ $[M]^+$ 362.2097, found 362.2096.

**Oxasilolane 3m**




Following the general procedure, cyclopropylmethanol **1m** (158 mg, 0.487 mmol) was converted to the corresponding diethyl(hydrido)silyl ether using $Ru(PPh_3)_3Cl_2$ (0.2 mol %) in benzene (0.50 mL) at 50 °C for 12 h. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/(*S*)-DTBM-SEGPHOS (4.0 mol %) in THF (1.0 mL) at 50 °C for 24 h. Concentration of the reaction mixture and purification by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 103 mg (50%) of **3m** as a colorless oil. **HPLC analysis**: 90% *ee*, Chiralcel OD-H column, 1% isopropanol in hexane, 1.0 mL/min flow rate, 254 nm UV lamp, $t_R$ = 4.9 min (minor), $t_R$ = 8.5 min (major). $[\alpha]_D^{25}$ = +59.8 (c 1.04, $CHCl_3$). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.21 (t, *J* = 1.8 Hz, 1H), 7.98 (dt, *J* = 7.7, 1.4 Hz, 1H), 7.73 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.52 – 7.44 (m, 3H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 7.7 Hz, 1H), 4.27 (d, *J* = 9.4 Hz, 1H), 4.24 (d, *J* = 9.4 Hz, 1H), 1.62 (s, 9H), 1.27 (dd, *J* = 10.5, 3.9 Hz, 1H), 1.15 – 1.04 (m, 6H), 1.00 (dd, *J* = 6.7, 4.0 Hz, 1H), 0.86 – 0.71 (m, 4H), 0.64 (dd, *J* = 10.5, 6.7 Hz, 1H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 165.7, 143.2, 141.2, 140.6, 132.5, 131.1, 128.9, 128.6, 128.3, 128.1, 127.1, 126.6, 125.3, 81.1, 71.8, 32.4, 28.2, 15.0, 9.2, 7.0, 6.9, 6.3, 4.3. **HRMS** (EI+) calcd for $C_{25}H_{32}O_3Si$ $[M]^+$ 408.2121, found 408.2121.

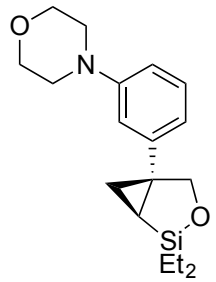
**Oxasilolane 3n**




Following the general procedure, cyclopropylmethanol **1n** (99.8 mg, 0.360 mmol) was converted to the corresponding diethyl(hydrido)silyl ether using $Ru(PPh_3)_3Cl_2$ (0.2 mol %) in benzene (0.36 mL) at 50 °C for 12 h. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/(*S*)-DTBM-SEGPHOS (4.0 mol %) in THF (0.72 mL) at 50 °C for 24 h. Concentration of the reaction mixture and purification by silica gel chromatography

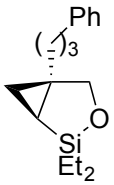
(100:0→80:20 hexanes/EtOAc) gave 73.9 mg (57%) of **3n** as a colorless oil. **HPLC analysis**: 90% *ee*, Chiralcel OD-H column, 1% isopropanol in hexane, 1.0 mL/min flow rate, 220 nm UV lamp, $t_R$ = 6.2 min (minor), $t_R$ = 7.2 min (major). $[\alpha]_D^{25}$ = +60.2 (c 1.05, $CHCl_3$). **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.24 (t, *J* = 7.8 Hz, 1H), 7.11 (s, 1H), 7.09 – 7.03 (m, 2H), 4.19 (d, *J* = 9.4 Hz, 1H), 4.16 (d, *J* = 9.4 Hz, 1H), 3.25 (s, 3H), 1.44 (s, 9H), 1.20 (dd, *J* = 10.5, 3.9 Hz, 1H), 1.11 – 1.01 (m, 6H), 0.94 (dd, *J* = 6.7, 4.0 Hz, 1H), 0.82 – 0.68 (m, 4H), 0.55 (dd, *J* = 10.5, 6.8 Hz, 1H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 154.6, 143.8, 142.9, 128.4, 125.2, 124.7, 123.2, 80.2, 71.8, 37.3, 32.2, 28.3, 14.8, 9.2, 6.9, 6.9, 6.2, 4.3. **HRMS** (EI+) calcd for $C_{20}H_{31}NO_3Si$ $[M]^+$ 361.2073, found 361.2075.

**Oxasilolane 3o**



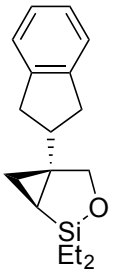

Following the general procedure, cyclopropylmethanol **1o** (165 mg, 0.707 mmol) was converted to the corresponding diethyl(hydrido)silyl ether using $Ru(PPh_3)_3Cl_2$ (0.2 mol %) in benzene (0.70 mL) at 50 °C for 12 h. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/(*S*)-DTBM-SEGPHOS (4.0 mol %) in THF (1.4 mL) at 50 °C for 24 h. Concentration of the reaction mixture and purification by Kugelrohr distillation (1 Torr, 160 °C) gave 166 mg (75%) of **3o** as a colorless oil. **SFC analysis**: 92% *ee*, Chiralcel OZ-H column, 5% isopropanol, 2.5 mL/min flow rate, 220 nm UV lamp, $t_R$ = 3.8 min (minor), $t_R$ = 4.4 min (major). $[\alpha]_D^{25}$ = +65.3 (c 0.955, $CHCl_3$). **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.21 (t, *J* = 7.9 Hz, 1H), 6.82 (d, *J* = 2.0 Hz, 1H), 6.80 (d, *J* = 7.6 Hz, 1H), 6.77 (dd, *J* = 8.2, 2.0 Hz, 1H), 4.19 (d, *J* = 9.4 Hz, 1H), 4.17 (d, *J* = 9.4 Hz, 1H), 3.88 – 3.84 (m, 4H), 3.18 – 3.14 (m, 4H), 1.20 (dd, *J* = 10.5, 3.8 Hz, 1H), 1.12 – 1.02 (m, 6H), 0.93 (dd, *J* = 6.7, 3.9 Hz, 1H), 0.82 – 0.69 (m, 4H), 0.55 (dd, *J* = 10.5, 6.7 Hz, 1H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 151.3, 143.5, 129.2, 119.7, 115.4, 113.7, 72.0, 66.9, 49.4, 32.7, 14.8, 9.0, 7.0, 6.9, 6.3, 4.4. **HRMS** (EI+) calcd for $C_{18}H_{27}NO_3Si$ $[M]^+$ 317.1811, found 317.1813.

**Oxasilolane 3p**




Following the general procedure, cyclopropylmethanol **1p** (79.1 mg, 0.416 mmol) was converted to the corresponding diethyl(hydrido)silyl ether using $Ru(PPh_3)_3Cl_2$ (0.2 mol %) in THF (0.40 mL) at 50 °C for 12 h. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/(*S*)-DTBM-SEGPHOS (4.0 mol %) in THF (0.80 mL) at 50 °C for 24 h. Concentration of the reaction mixture and purification by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 63.7 mg (56%) of **3p** as a colorless oil. **SFC analysis**: 57% *ee*, Chiralcel OD-H column, 1% isopropanol, 2.5 mL/min flow rate, 220 nm UV lamp, $t_R$ = 4.6 min (minor), $t_R$ = 6.1 min (major). $[\alpha]_D^{25}$ = +25.0 (c 1.03, $CHCl_3$). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.5 Hz, 2H), 7.21 – 7.14 (m, 3H), 3.91 (d, *J* = 9.3 Hz, 1H), 3.88 (d, *J* = 9.3 Hz, 1H), 2.66 – 2.55 (m, 2H), 1.74 – 1.61 (m, 3H), 1.46 – 1.38 (m, 1H), 1.03 – 0.95 (m, 6H), 0.73 (dd, *J* = 10.2, 3.9 Hz, 1H), 0.68 – 0.59 (m, 4H), 0.55 (dd, *J* = 6.5, 3.9 Hz, 1H), -0.06 (dd, *J* = 10.2, 6.4 Hz, 1H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 142.3, 128.3 (*two overlapping resonances*), 125.7, 70.9, 36.1, 34.8, 29.2, 28.0, 13.2, 7.0, 6.8, 6.7, 6.3, 4.3. **HRMS** (EI+) calcd for $C_{17}H_{26}OSi$ $[M]^+$ 274.1753, found 274.1758.

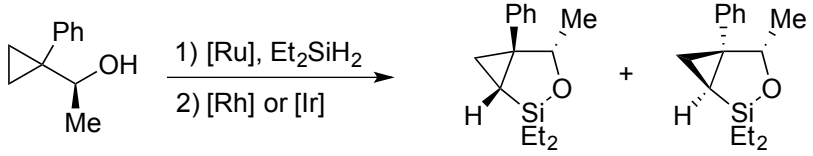
**Oxasilolane 3q**




Following the general procedure, cyclopropylmethanol **1q** (149 mg, 0.791 mmol) was converted to the corresponding diethyl(hydrido)silyl ether using $Ru(PPh_3)_3Cl_2$ (0.2 mol %) in benzene (0.80 mL) at 50 °C for 12 h. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/(*S*)-DTBM-SEGPHOS (4.0 mol %) in THF (1.6 mL) at 50 °C for 24 h. Concentration of the reaction mixture and purification by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 143 mg (65%) of **3q** as a colorless oil. **SFC analysis**: 56% *ee*, Chiralpak AD-H column, 0.1% isopropanol in hexane, 1.0 mL/min flow rate, 254 nm UV lamp, $t_R$ = 7.0 min (major), $t_R$ = 10.2 min (minor). $[\alpha]_D^{25}$ = +40.7 (c 1.25, $CHCl_3$). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.21 – 7.16 (m, 2H), 7.16 – 7.11 (m, 2H), 4.00 (d, *J* = 9.4 Hz, 1H), 3.94 (d, *J* = 9.3 Hz, 1H), 3.03 – 2.96 (m, 1H), 2.93 (dd, *J* = 15.3,

7.8 Hz, 1H), 2.73 (dd, *J* = 15.3, 9.8 Hz, 1H), 2.69 – 2.58 (m, 2H), 1.07 – 0.98 (m, 6H), 0.90 (dd, *J* = 10.4, 4.1 Hz, 1H), 0.74 – 0.62 (m, 4H), 0.59 (dd, *J* = 6.5, 4.2 Hz, 1H), 0.14 (dd, *J* = 10.3, 6.5 Hz, 1H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 142.9, 142.7, 126.2 (*two overlapping resonances*), 124.29, 124.28, 69.9, 43.2, 36.4, 36.3, 30.8, 11.7, 7.0, 6.9, 6.3, 5.1, 4.3. **HRMS** (EI+) calcd for $C_{17}H_{24}OSi$ $[M]^+$ 272.1596, found 272.1600.

*2.4.4 Diastereoselective silylation of cyclopropanes*




**5'**
95% ee

**6a** **6b**

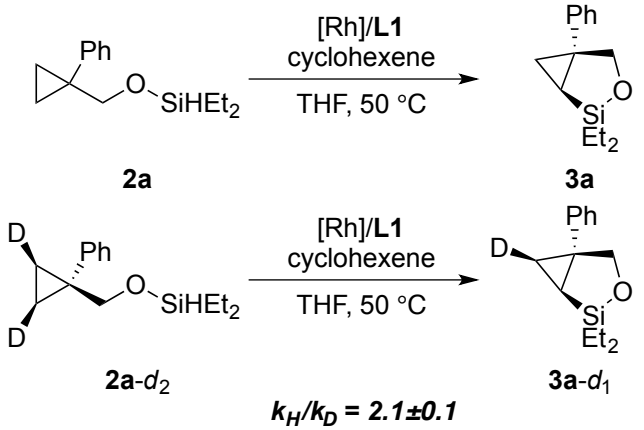
Entry 2, Table 4.3: Following the general procedure, cyclopropylmethanol **5'** (40.1 mg, 0.247 mmol) was converted to the corresponding diethyl(hydrido)silyl **5** ether using $Ru(PPh_3)_3Cl_2$ (0.2 mol %) in THF (0.25 mL) at 50 °C for 12 h. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/(*R*)-DTBM-SEGPHOS (4.0 mol %) in THF (1.2 mL) at 50 °C for 24 h. Concentration of the reaction mixture and purification by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 40.6 mg (66%) of a mixture of **6a** and **6b** as a colorless oil. The ratio of **6a** and **6b** was >20:1 as determined by GC and NMR analysis. **HPLC analysis**: >99% *ee* (**6a**), Chiralcel OD-H column, 0.1% isopropanol in hexane, 0.50 mL/min flow rate, 220 nm UV lamp, $t_R$ = 10.4 min (major), $t_R$ = 11.3 min (minor). $[\alpha]_D^{25}$ = –32.1 (c 1.07, $CHCl_3$). **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 4H), 7.22 (t, *J* = 6.9 Hz, 1H), 4.47 (q, *J* = 6.0 Hz, 1H), 1.21 – 1.10 (m, 7H), 1.05 (t, *J* = 8.0 Hz, 3H), 0.90 (dd, *J* = 6.7, 4.2 Hz, 1H), 0.80 (qd, *J* = 7.9, 2.3 Hz, 2H), 0.73 (qd, *J* = 8.0, 1.8 Hz, 2H), 0.38 (dd, *J* = 10.4, 6.6 Hz, 1H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 142.7, 129.4, 128.3, 126.5, 77.3, 37.8, 19.1, 10.7, 9.5, 7.0 (*two overlapping resonances*), 6.4, 4.4. **HRMS** (EI+) calcd for $C_{15}H_{22}OSi$ $[M]^+$ 246.1440, found 246.1438.

Entry 3, Table 4.3: Following the general procedure, cyclopropylmethanol **5'** (40.7 mg, 0.251 mmol) was converted to the corresponding diethyl(hydrido)silyl ether **5** using $Ru(PPh_3)_3Cl_2$ (0.2 mol %) in THF (0.25 mL) at 50 °C for 12 h. The subsequent cyclization was conducted with $[Rh(cod)Cl]_2$/(*S*)-DTBM-SEGPHOS (4.0 mol %) in THF (0.50 mL) at 50 °C for 24 h. Concentration of the reaction mixture and purification by silica gel chromatography (100:0→90:10 hexanes/EtOAc) gave 35.0 mg (74%) of a mixture of **6a** and **6b** as a colorless oil. The ratio of **6a** and **6b** was 1:1.6 prior to the purification and 1:1.5 after the purification as determined by GC and NMR analysis. (The isolated product contained ~5% of inseparable impurities.) **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 4H), 7.25 – 7.19 (m, 1H) , 4.48 (q, *J* = 6.0 Hz, 1H, **6a**), 4.44 (q, *J* = 6.4 Hz, 1H, **6b**), 1.18 (d, *J* = 6.0 Hz, 3H, **6a**), 1.17 – 1.11 (m, 4H for **6a**, 3H for **6b**), 1.09 – 1.00 (m, 3H for **6a**, 4H for **6b**), 0.99 – 0.93 (m, 4H, **6b**), 0.91 (dd, *J* = 6.7, 4.6 Hz, 1H,

**6a**), 0.86 – 0.78 (m, 2H), 0.78 – 0.69 (m, 2H), 0.65 (dd, *J* = 10.3, 6.5 Hz, 1H, **6b**), 0.38 (dd, *J* = 10.3, 6.7 Hz, 1H, **6a**).**$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 142.7 (**6a**), 142.5 (**6b**), 130.0 (**6b**), 129.3 (**6a**), 128.3 (**6a**), 128.0(**6b**), 126.52 (**6b**), 126.49 (**6a**), 77.5 (**6b**), 77.3 (**6a**), 37.8 (**6a**), 37.6 (**6b**), 23.6 (**6b**), 19.1 (**6a**), 15.4 (**6b**), 10.7 (**6a**), 9.6 (**6a**), 8.0 (**6b**), 7.2 (**6b**), 7.13 (**6b**), 7.10 (**6b**), 7.0 (**6a**, *two overlapping resonances*), 6.5 (**6a**), 4.4 (**6a**), 4.3 (**6b**). **HRMS** (EI+) calcd for $C_{17}H_{24}OSi$ $[M]^+$ 246.1440, found 246.1441.

Entry 1, Table 4.3: Following the general procedure, cyclopropylmethanol **5'** (40.1 mg, 0.247 mmol) was converted to the corresponding diethyl(hydrido)silyl ether **5** using $Ru(PPh_3)_3Cl_2$ (0.2 mol %) in THF (0.25 mL) at 50 °C for 12 h. The volatile materials were then removed by placing the reaction mixture directly under high-vacuum for 1 h (the stir bar was temporarily removed during this operation to prevent bumping). The stir bar was replaced, and the concentrated diethyl(hydrido)silyl ether **5** was then sequentially treated with norbornene (28.2 mg, 0.250 mmol) and a freshly prepared stock solution of $[Ir(cod)OMe]_2$ (1 mol %) and 3,4,7,8-tetramethyl-1,10-phenanthroline (2.5 mol %) in THF (0.5 mL). The Teflon-lined screw cap was replaced, and the vial was then removed from the glovebox and placed in a pre-heated aluminum heating block at 80 °C. After 6 hours, the reaction mixture was allowed to cool to rt, and the solvent was removed via rotary evaporation. The crude product was purified by silica gel chromatography (100:0 →90:10 hexanes/EtOAc) gave 47.8 mg (78%) of a mixture of **6a** and **6b** as a colorless oil. The ratio of **6a** and **6b** was 10:1 as determined by GC and NMR analysis. $^1$H and $^{13}$C NMR data were consistent with values reported above.

*2.4.5 Measurement of the kinetic Isotope effect of enantioselective silylation*




The diethyl(hydrido)silyl ethers were prepared from the dehydrogenative silylation of **1a** and **1a**-$d_2$ in the presence of 0.2 mol % of $Ru(PPh)_3Cl_2$ according to the general procedure. In an $N_2$-filled glovebox, the diethyl(hydrido)silyl ether **2a** (0.10 mmol) was sequentially treated with dodecane (10. μL), a freshly prepared stock solution of $[Rh(cod)Cl]_2$ (1.0 mol %) and (*S*)-DTBM-SEGPHOS (2.5 mol %) in THF (0.2 mL) and cyclohexene. The vial was removed from the glove box and placed in a pre-heated

aluminum block at 50 °C. Aliquots were taken every hour for 5 hours and analyzed by GC. The silylation of **2a**-$d_2$ was conducted in the same way as the silylation of **2a**. From the chromatograms, the initial rate for the formation of **3a** or **3a**-$d_1$ was determined. From the initial rates for the silylation of **2a** and **2a**-$d_2$, the kinetic isotope effect was determined. (Note: reactions conducted for kinetic measurements were run with lower catalyst loadings than those for evaluating the reaction scope to obtain reproducible data.)

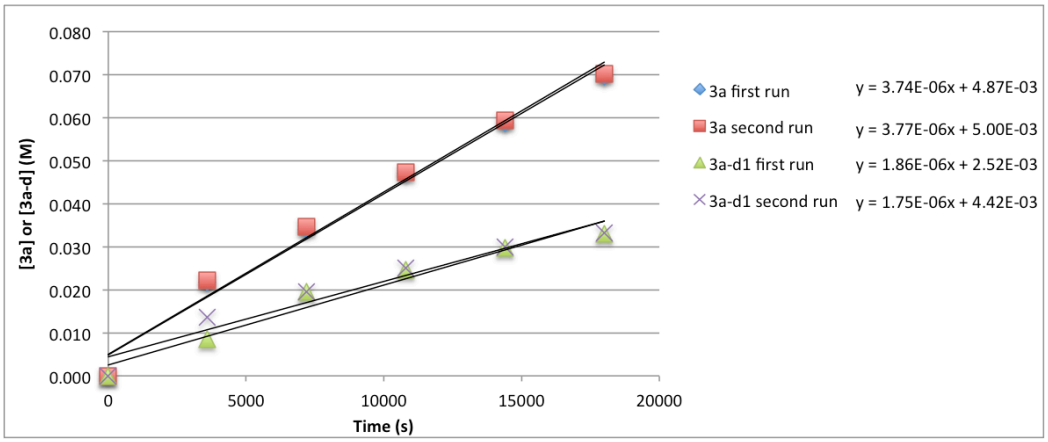
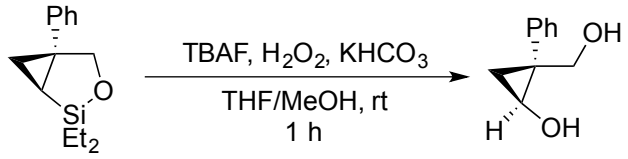



**Figure 4.1** Measurement of the kinetic isotope effect

*2.4.6 Oxidation of enantioenriched oxasilolane*




**3a** **7**

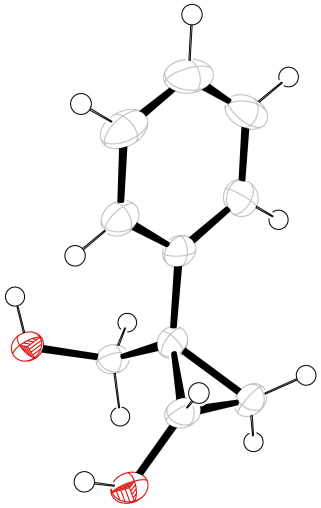
The conditions previously reported for the oxidation of cyclopropylsilane were used.[35] To a solution of **3a** (31.2 mg, 0.134 mmol) in THF (1.0 mL), a solution of TBAF (1.0 mL, 1.0 M) was added under $N_2$ at room temperature. After 30 min of stirring, methanol (1.0 mL), $KHCO_3$ (50. mg, 0.50 mmol), and $H_2O_2$ (30 % in water, 0.50 mL, 4.4 mmol) were added to the reaction mixture. After stirring for 30 min, the reaction mixture was diluted with water and extracted three times with ethyl acetate. The combined organic layers were washed with a 1% aqueous solution of $Na_2S_2O_3$ and brine, dried ($Na_2SO_4$), and concentrated. The crude reaction mixture was purified by silica gel chromatography (100:0→50:50 hexanes/EtOAc) gave 15.6 mg (71%) of **7** as a white solid. **HPLC analysis**: 87% *ee*, Chiralcel OJ-H column, 20% isopropanol in hexane, 1.0 mL/min flow rate, 220 nm UV lamp, $t_R$ = 6.6 min (major), $t_R$ = 8.1 min (minor). $[\alpha]_D^{25}$ = +23. (c 0.15, MeOH). **$^1$H NMR** (600 MHz, $CD_3OD$) δ 7.32 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.27 (t, *J* = 7.8 Hz, 2H), 7.17 (tt, *J* = 6.9, 1.3 Hz, 1H), 4.88 (s, 2H), 3.96 (d, *J* = 12.0 Hz, 1H), 3.91 (d, *J* = 11.6 Hz, 1H), 3.60 (dd, *J* = 6.8, 3.7 Hz, 1H), 1.11 (t, *J* = 6.4 Hz, 1H), 0.97 (dd, *J* = 5.9,

3.7 Hz, 1H). **$^{13}$C NMR** (151 MHz, $CD_3OD$) δ 144.4, 129.9, 129.3, 127.2, 65.9, 57.7, 34.3, 19.7. **HRMS** (EI+) calcd for $C_{10}H_{12}O_2$ $[M]^+$ 164.0837, found 164.0835.

*2.4.7 Determiniation of absolute stereochemistry*

A single crystal suitable for X-ray crystallography was obtained by slow diffusion of pentane into a solution of **7** in EtOAc at room temperature. On the basis of structure determination by X-ray crystallography, the absolute stereochemistry was assigned to be *R* at C3 and *S* at C1. The configurations of the stereocenters in **7** are assumed to be identical to those in **3a** because 1) inversion of configuration would lead to the formation of diastereomers of **7**, not the enantiomer of **6** and 2) retention of configuration during Tamao-Flemming oxidation has been established.

X-ray data:



A colorless plate 0.050 x 0.040 x 0.020 mm in size was mounted on a Cryoloop with Paratone oil. Data were collected in a nitrogen gas stream at 100(2) K using and scans. Crystal-to-detector distance was 60 mm and exposure time was 10 seconds per frame using a scan width of 2.0°. Data collection was 99.6% complete to 67.000° in q. A total of 39189 reflections were collected covering the indices, -6<=*h*<=5, -13<=*k*<=13, -32<=*l*<=32. 3198 reflections were found to be symmetry independent, with an $R_{int}$ of 0.0469. Indexing and unit cell refinement indicated a primitive, orthorhombic lattice. The space group was found to be $P2_12_12_1$ (No. 19). The data were integrated using the Bruker SAINT software program and scaled using the SADABS software program. Solution by iterative methods (SHELXT-2014) produced a complete heavy-atom phasing model consistent with the proposed structure. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares (SHELXL-2014). All hydrogen atoms were placed using a riding model. Their positions were constrained relative to their parent atom using the appropriate HFIX command in SHELXL-2014. The absolute configuration was unambiguously determined to be *R* at C3 and C13, and *S* at C1 and C11, respectively.

**Table 4.4** Crystal data and structure refinement for **7**.

| | | |
|---|---|---|
| Empirical formula | $C_{10}H_{12}O_2$ | |
| Formula weight | 164.20 | |
| Temperature | 100(2) K | |
| Wavelength | 1.54178 Å | |
| Crystal system | Orthorhombic | |
| Space group | P $2_1$ $2_1$ $2_1$ | |
| Unit cell dimensions | a = 5.7680(3) Å | α= 90°. |
| | b = 11.2667(6) Å | β= 90°. |
| | c = 27.1370(15) Å | γ = 90°. |
| Volume | 1763.53(16) $Å^3$ | |
| Z | 8 | |
| Density (calculated) | 1.237 $Mg/m^3$ | |
| Absorption coefficient | 0.687 $mm^{-1}$ | |
| F(000) | 704 | |
| Crystal size | 0.050 x 0.040 x 0.020 $mm^3$ | |
| Theta range for data collection | 3.257 to 68.449°. | |
| Index ranges | -6<=h<=5, -13<=k<=13, -32<=l<=32 | |
| Reflections collected | 39189 | |
| Independent reflections | 3198 [R(int) = 0.0469] | |
| Completeness to theta = 67.000° | 99.6 % | |
| Absorption correction | Semi-empirical from equivalents | |
| Max. and min. transmission | 0.929 and 0.799 | |
| Refinement method | Full-matrix least-squares on $F^2$ | |
| Data / restraints / parameters | 3198 / 0 / 221 | |
| Goodness-of-fit on $F^2$ | 1.123 | |
| Final R indices [I>2sigma(I)] | R1 = 0.0448, wR2 = 0.1052 | |
| R indices (all data) | R1 = 0.0461, wR2 = 0.1057 | |
| Absolute structure parameter | 0.07(7) | |
| Extinction coefficient | n/a | |
| Largest diff. peak and hole | 0.229 and -0.154 $e^-Å^{-3}$ | |

## 4.5 References

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Lee, T.; Hartwig, J. F. Rhodium-Catalyzed Enantioselective Silylation of Cyclopropyl C H Bonds. *Angew. Chem., Int. Ed.* **2016**, *55*, 8723. Copyright 2016 Wiley-VCH.

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# CHAPTER 5

## Iridium-Catalyzed Silylation of C–H Bonds in Aliphatic Amines for the Synthesis of 1,2-Amino Alcohols

## 5.1 Introduction

Amines are commonly found in natural products and pharmaceutical agents.[1] Therefore, methods that enable selective functionalization of C–H bonds of amines will present opportunities to access useful moieties. However, the development of functionalization of C–H bonds of amines, especially aliphatic amines, has been limited because of the challenges associated with this process. First, the C–H functionalization of aliphatic amines often occur at highly activated C–H bonds α to nitrogen.[2-4] This inherent preference needs to be circumvented to gain an alternate site-selectivity. In addition, the reaction conditions of many C–H bond functionalization processes are oxidative, and therefore can cause by-product formation involving *N*-oxidation. Lastly, amines can bind to a metal catalyst and lead to the deactivation of a catalyst.

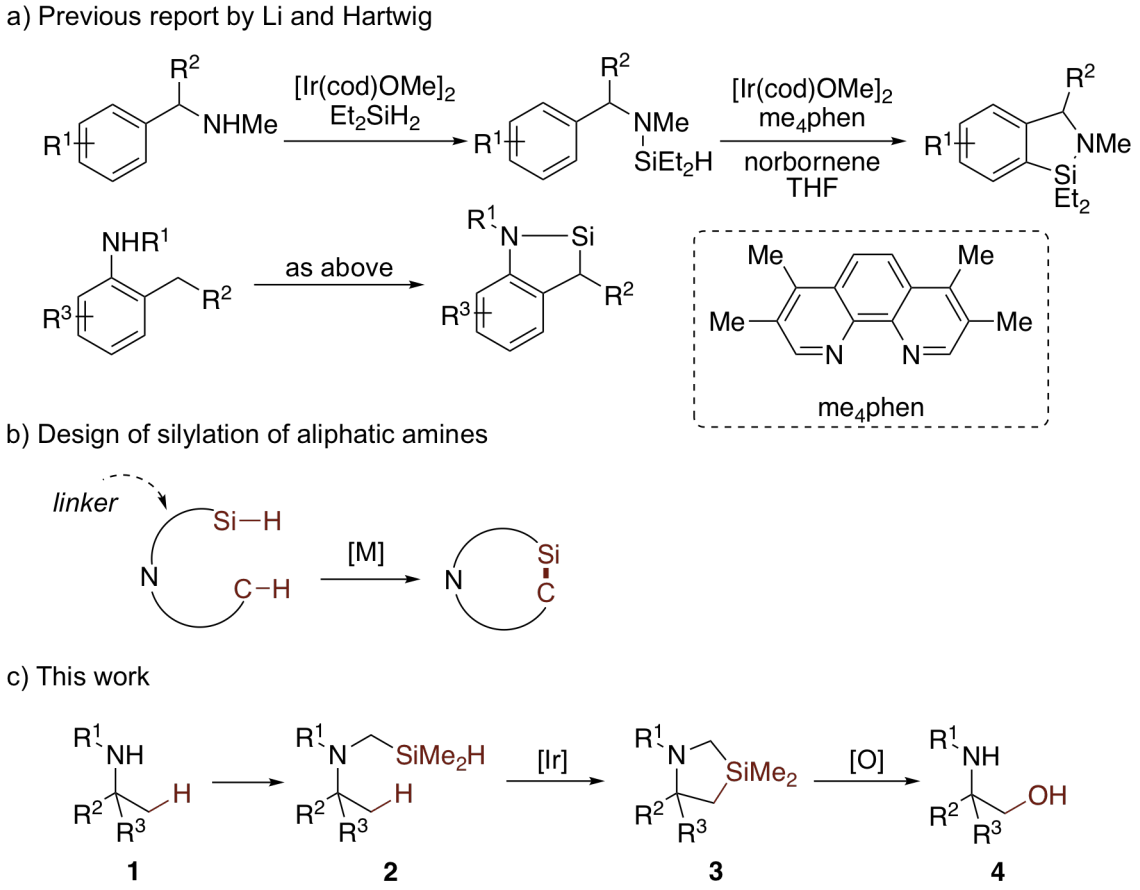
Despite these challenges, selective functionalization of aliphatic C–H bonds in amines has been achieved. One of the most common strategies to obtain a site-selectivity is the incorporation of a nitrogen-protecting group.[5-13] The catalyst coordinates to this functional group and directs the functionalization to occur at the C-H bonds β or γ to nitrogen. A second strategy involves the complexation of amine with a Brønsted acid or Lewis acid.[14-16] This strategy has been used to deactivate C–H bonds proximal to nitrogen and allow for the functionalization of C–H bonds remote to nitrogen. A third strategy is to render the reactions intramolecular by the incorporation of removable tethers between the nitrogen and the functional group that is being introduced such as oxygen.[17,18]

The silylation of C–H bonds could provide a platform for a selective functionalization of amines (Scheme 5.1). Li and Hartwig previously reported the silylation of aryl and benzyl C–H bonds of amines (Scheme 5.1a).[19] However, the reported system was not applicable to the functionalization of unactivated $sp^3$ C–H bonds because of the instability of N–Si bonds under the reaction conditions. We envisioned that the placement of a linker between nitrogen and silicon could increase the stability of the substrate and render the reaction selective for a site proximal to nitrogen (Scheme 5.1b). *N*-oxidations could be avoided because the C–H silylation occurs under non-oxidative conditions. This method could be rendered enantioselective with the appropriate combination of a metal precursor and chiral ligand. Although asymmetric functionalizations of C–H bonds in amines have been reported,[4,20-26] most of the examples of the functionalization of aliphatic C–H bonds have focused on carbon–carbon bond formation.

Here, we report an iridium-catalyzed silylation of aliphatic amines (Scheme 5.1c). (Silylmethyl)amime **2** can be easily prepared from alkylation of secondary amine **1**,[27,28] and the silylation process leads to the functionalization of C–H bonds β to nitrogen to form silapyrrolidine **3**. Synthesis of a saturated heterocycle containing a (silylmethyl)amino group by the silylation of activated C–H bonds α to nitrogen was reported previously,[29] but a process that involves the functionalization of an unactivated aliphatic C–H bond was not. Silapyrrolidines are useful moieties for drug discovery because the lipophilicity of the compounds containing silapyrrolidines is higher than that of compounds containing pyrrolidines.[30-32] In addition, we show that the silapyrrolines can serve as substrates for Tama-Flemming oxidation to form 1,2-amino alcohols.[33] This

process is a rare example of oxidation of β-C–H bonds in aliphatic amines.[10-12] Finally, we show that this reaction can be conducted enantioselectively to set a stereogenic center α to nitrogen. Appropriately substituted 2-pyridine imidazoline ligands, an unusual class of chiral framework, formed active and enantioselective catalysts for this transformation.

**Scheme 5.1** Design of silylation of unactivated $sp^3$ C–H bonds of amines

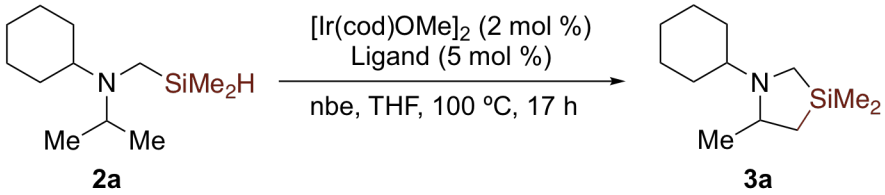



## 5.2 Results and Discussion

To develop site-selective silylation of aliphatic amines, we evaluated various conditions for the cyclization of (silylmethyl)amine **2a** (Table 5.1). Based on previous reports of iridium-catalyzed silylation of C–H bonds,[19,34-40] we examined iridium catalysts derived from $[Ir(cod)OMe]_2$ and various dinitrogen ligands with norbornene as a hydrogen acceptor at 100 °C. The reaction in the absence of any dinitrogen ligand led to the formation of the silylation product in 6% yield, suggesting that the (silylmethly)amine substrate itself cannot serve as a ligand to iridium to form an active catalyst. In the presence of an Ir catalyst containing 4,4′-di-*tert*-butylbipyridine **L1**, intramolecular cyclization provided the silapyrrolidine **3a** in 46% yield. The reaction yields were higher when the reactions were conducted with phenanthroline derivatives (entry 3–6). We

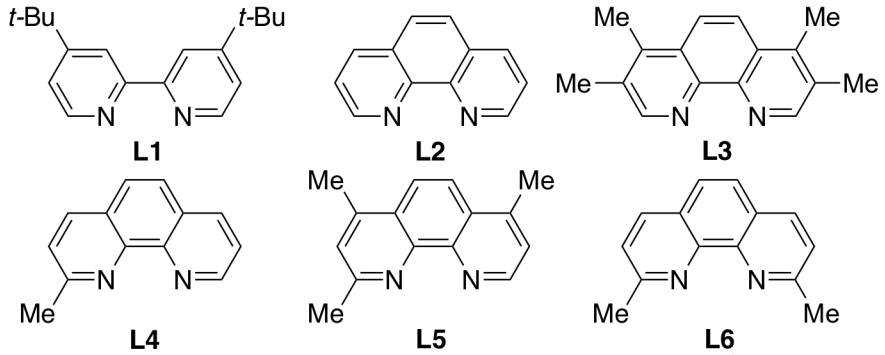
found that 2-methylphenanthrolines formed the most active catalysts to provide the silylated product **3a** in 90% yields (entry 5–6). This result is consistent with the previous results from Ir-catalyzed silylation of aryl C–H bonds reported by Cheng and Hartwig.[38] The ligand containing an additional substituent at the 9-position led to the formation of a much less productive catalyst (entry 7). Although we typically assembled our silylation reactions in an $N_2$-filled glovebox, a high yield of the silapyrrolidine product was obtained from the reactions conducted by standard air-free methods without a glovebox (entry 8; see the Experimental for details).

**Table 5.1** Evaluation of reaction conditions for the intramolecular silylation of **2a**[a]




**2a** **3a**

| entry | ligand | conversion (%)[b] | yield (%)[b] |
|---|---|---|---|
| 1 | none | 70 | 6 |
| 2 | **L1** | >99 | 46 |
| 3 | **L2** | >99 | 85 |
| 4 | **L3** | >99 | 86 |
| 5 | **L4** | >99 | 90 |
| 6 | **L5** | >99 | 90 |
| 7 | **L6** | 98 | 26 |
| 8[c] | **L5** | >99 | 91 |



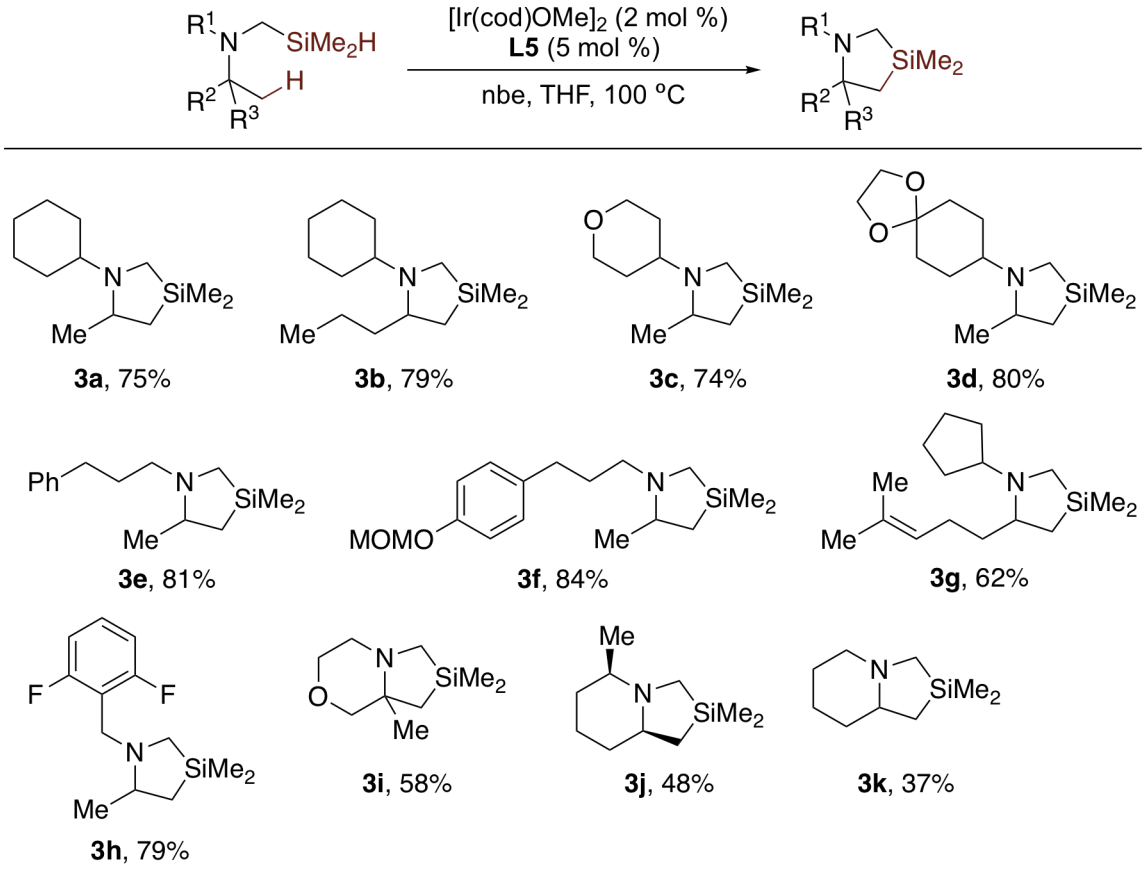

**L1** **L2** **L3** **L4** **L5** **L6**

[a]Reactions were assembled on a 0.10 mmol scale in an $N_2$-filled glovebox. [b]Determined by $^1$H NMR analysis with 1,3,5-trimethoxybenzene as an internal standard added after the reaction. [c]Reactions were assembled on a 0.25 mmol scale using a standard air-free technique outside an $N_2$-filled glove box.

Having established conditions for the silylation of (silylmethyl)amine **2a**, we investigated the scope of the reaction (Table 5.2). Structurally diverse amines underwent the silylation process smoothly. Both *sec*- and *tert*-alkylamines were tolerated under the reaction conditions. Linear amines (**2a**–**2h**) and cyclic amines (**2i**–**2k**) both were compatible with the reaction conditions. Isopropyl amines with both linear (**2e**, **2f**, **2h**) and branched *N*-alkyl groups (**2a**, **2c**, **2d**) were suitable substrates for this process. A

series of functional groups, including ethers (**2c**, **2i**), an acetal (**2d**), a MOM aryl ether (**2f**) and an internal olefin (**2g**), were tolerated.

**Table 5.2** Scope of the C–H silylation of aliphatic amines[a]



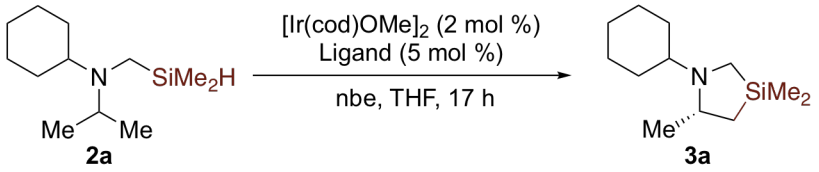

[a]Isolated yields for reactions conducted on a 0.10–0.25 mmol scale following purification by silica gel chromatography.

Development of methods that set stereogenic centers α to nitrogen is highly desirable because existing methods, such as hydrogenation or Strecker-type reactions, furnish amines with limited structural diversity.[41,42] In general, these methods proceed in high enantioselectivity only when the nitrogen or the prochiral carbon of the substrate is substituted with an aryl group. Therefore, we pursued the development of enantioseletive silylations of aliphatic amines that can provide a method that is complementary to previous protocols for the synthesis of nonracemic chiral amines.

On the basis of a previous report on asymmetric silylation of aliphatic C–H bonds,[40] we examined a variety of chiral *N*,*N*-ligands with iridium precursors for asymmetric silylation of **2a** (Table 5.3). An initial survey with chiral ligands that are commonly used in asymmetric catalysis, such as a bis(oxazoline) ligand (e.g. **L6**, entry 1) or a pyridine oxazoline ligand (e.g. **L7**, entry 2), showed that the reactivity and

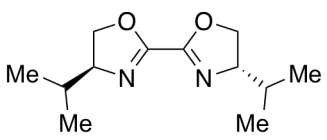
enantioselectivity of catalysts formed from these classes of ligands was low. We hypothesized that ligands containing an imidazoline unit might generate more active catalysts than those containing an oxazoline unit. Because imidazoline is more electron-donating than oxazoline is, the ligands containing an imidazoline unit could lead to the formation of more electron-rich catalysts than those containing an oxazoline unit, and oxidative additions of C–H bonds to more electron-rich catalysts tend to be faster than those to less electron-rich catalysts. Because both yields and enantioselectivity of the

**Table 5.3** Evaluation of reaction conditions for the asymmetric silylation of **2a**

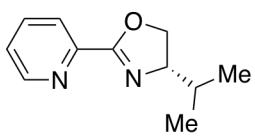



**2a** **3a**

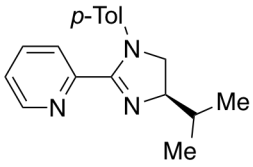
| entry | ligand | temperature (°C) | yield (%)[a] | ee (%)[b] |
|---|---|---|---|---|
| 1 | **L6** | 80 | 9 | <5 |
| 2 | **L7** | 80 | 19 | 27 |
| 3 | **L8** | 80 | 69 | –59 |
| 4 | **L8** | rt | 85 | –70 |
| 5 | **L9** | rt | 86 | 79 |
| 6 | **L10** | rt | 57 | 67 |
| 7 | **L11** | rt | 90 | 49 |
| 8 | **L12** | rt | 68 | –76 |
| 9 | **L13** | rt | 65 | 80 |
| 10 | **L14** | rt | 23 | 18 |
| 11 | **L15** | rt | <5 | nd |
| 12 | **L16** | rt | 29 | 80 |
| 13 | **L17** | rt | 87 | 79 |
| 14[c] | **L17** | 4 | 76 | 83 |
| 15[c] | **L9** | 4 | 63 | 82 |
| 16[c,d] | **L17** | 4 | 82 | 83 |



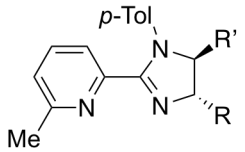

**L6**



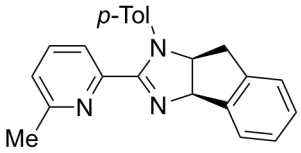

**L7**



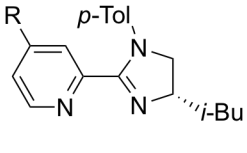

**L8**



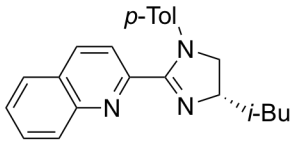

**L9**, R = *i*-Bu, R' = H
**L10**, R = Bn, R' = H
**L11**, R = Ph, R' = Ph



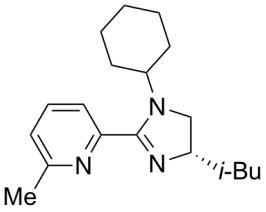

**L12**




**L13**, R = H
**L14**, R = OMe
**L15**, R = $CF_3$




**L16**




**L17**

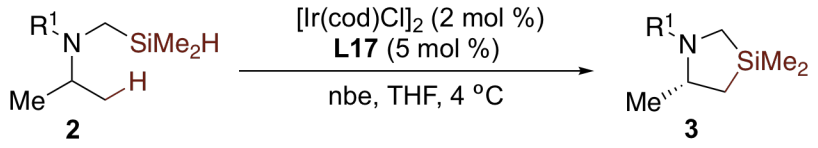
[a]Determined by $^1$H NMR analysis with 1,3,5-trimethoxybenzene as an internal standard added after the reaction. [b]Determined by GC analysis on a chiral stationary phase. A negative ee value indicates *ent*-**3a** was formed as the major enantiomer. nd = not determined. [c]72 h. [d]$[Ir(cod)Cl]_2$ instead of $[Ir(cod)OMe]_2$.

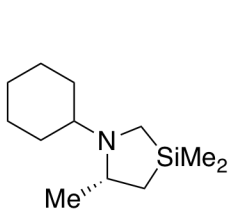
reactions catalyzed by iridium complexes from pyridine oxazoline ligands were higher than those from bis(oxazoline) ligands, we prepared pyridine imidazoline ligands to test this hypothesis. Indeed, the ligand containing imidazoline led to the formation of a catalyst with significantly higher reactivity and enantioselectivity than the ligand containinig oxazoline did (compare entries 2 and 3). In addition, the silylation reaction occurred in a high yield, even at room temperature, to afford **3a** in a higher yield and ee than at 80 °C (entry 4). This reactivity at room temperature is unprecedented for any type of metal-catalyzed C–H silylation process.

A further survey of the effect of substituents on the imidazoline fragment of the ligand (entry 5–8) revealed that the silylation proceeds with good enantioselectivity with the pyridine imidazoline ligand containing an isobutyl group (**L9**). The modification of other parts of the ligand scaffold did not result in the formation of a catalyst (entry 9–13, **L13**–**17**) that is more enantioselective than that containing **L9** at room temperature. However, we found that the complex formed from an *N*-alkyl imidazoline (**L17**) catalyzed the silylation at 4 °C with good enantioselectivity in a higher yield than the complex from **L9** did (entry 14–15). Investigation of other reaction parameters showed that silapyrrolidine **3a** forms in a higher yield when $[Ir(cod)Cl]_2$ was used as a pre-catalyst than $[Ir(cod)OMe]_2$ was (entry 17). This work is the first example in which pyridine imidazoline ligands were used for a catalytic reaction with a high enantioselectivity.[43,44]

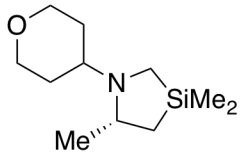
The scope of enantioseletive silylation of aliphatic amines is summarized in Table 5.4. The silapyrrolidine was formed in high yield and good enantioselectivity when the isoproylamine was substituted with a cyclohexyl or 2,6-disubstituted benzyl group.

**Table 5.4** Scope of the asymmetric C–H silylation of aliphatic amines[a]

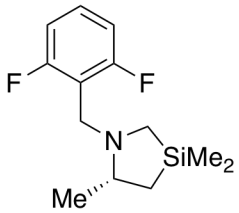



**3a**, 80%, 81% ee




**3c**, 81%, 81% ee

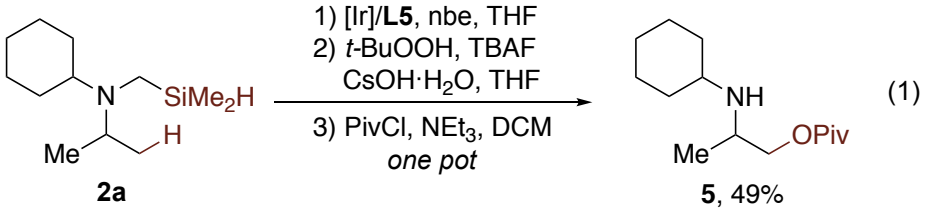



**3h**, 74%, 75% ee

[a]Isolated yields for reactions conducted on a 0.25 mmol scale following purification by silica gel chromatography. The ee values were determined by chiral GC analysis or $^1$H NMR analysis with (*S*)-*O*-acetylmandelic acid.

To demonstrate the synthetic utility of the silylation process, we sought to develop conditions for Tamao-Fleming oxidation of the silapyrrolidne products to form 1,2-amino alcohols. Although oxidation of tetraalkylsilane is usually a challenging process, the oxidation of an (aminomethyl)silane has been reported.[33] We found that

treatment of silapyrrolidne **3a** with *tert*-butyl hydroperoxide, cesium hydroxide monohydrate, and tetrabutylammonium fluoride in THF gave the amino alcohol product **4a**. These conditions were based on those reported previously for the oxidation of sterically hindered silanes.[36,45] The silylation of **2a**, oxidation, and protection of the hydroxyl group all could be performed in one pot to furnish protected amino alcohol **5** in 49% yield (eq 1).




**2a** **5**, 49% (1)

## 5.3 Conclusions

In summary, we have developed an iridium-catalyzed silylation of unactivated aliphatic C–H bonds in amines. The introduction of silylmethyl group on a secondary amine allowed a site-selective functionalization of β-C–H bonds of amines to form silapyrrolidines. The silylation process occurs in high yield and tolerates a wide range of structurally diverse amines when catalyzed by an iridium complex containing a phenanthroline ligand. An iridium catalyst formed from a chiral pyridine imidazoline ligand is highly active towards C–H silylation process even at below room temperature and enables the enantioselective synthesis of a chiral amine with a stereogenic center α to nitrogen. This method is complementary to previously reported methods because the presence of an aryl group near the prochiral center is not required to obtain high enantioselectivity. The silapyrrolidne product serves as a precursor to 1,2-amino alcohols by the oxidation of the silapyrrolidines, leading to an overall site-selective, and even enantioselective, oxidation of amines at the β-C–H bonds.

## 5.4 Experimental

### *5.4.1 Methods and Materials*

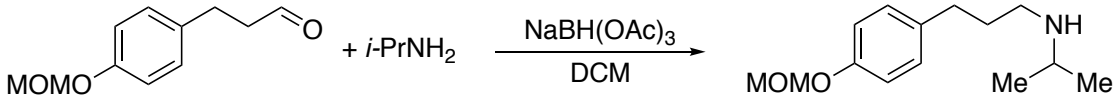
The silylation reactions were assembled in an $N_2$-filled glovebox using oven-dried glassware unless otherwise noted and were stirred with Teflon-coated magnetic stirring bars. $[Ir(cod)Cl]_2$ and $[Ir(cod)OMe]_2$ were prepared according to a standard procedure.[46] Tetrahydrofuran (THF) was degassed by purging with nitrogen and then dried with a solvent purification system containing activated alumina. All other solvents and reagents were used as received.

Reaction temperatures above 23 °C refer to temperatures of an aluminum heating block, which were controlled by an electronic temperature modulator. Silica gel chromatography was performed using a Teledyne Isco CombiFlash® $R_f$ system with Redi*Sep* $R_f$ Gold™ columns. $^1H$ and $^{13}C$ NMR spectra were recorded on Bruker AVB-

400, AV-500 and AV-600 spectrometers with $^{13}C$ operating frequencies of 101 MHz, 125 MHz and 151 MHz, respectively. $^{19}F$ NMR spectra were recorded on a Bruker AVQ-400 spectrometer with a $^{19}F$ operating frequency of 376 MHz. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal ($CDCl_3$: 7.26 ppm for $^1H$ NMR and 77.2 ppm for $^{13}C$ NMR; $C_6D_6$: 7.16 ppm for $^1H$ NMR and 128.1 ppm for $^{13}C$ NMR). High-resolution mass spectral data were obtained from the QB3/Chemistry Mass Spectrometry Facility at the University of California, Berkeley and the Lawrence-Berkeley National Laboratory Catalysis Center. Chiral GC analysis was conducted on an Agilent system.

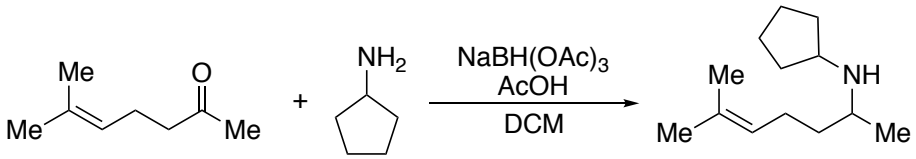
*5.4.2 Synthesis of Secondary Amines **1***

**Amine 1f**




To a solution of 3-(4-(methoxymethoxy)phenyl)propanal[47] (1.54 g, 7.94 mmol) and isopropylamine (1.72 mL, 20.0 mmol) in dichloromethane (40 mL) was added sodium triacetoxyborohydride (3.52 g, 16.6 mmol) at 0 °C. The mixture was allowed to warm to room temperature and then stirred overnight. The reaction was quenched with saturated $NaHCO_3$ aqueous solution and extracted with dichloromethane. The organic phase was washed with brine, dried with $Na_2SO_4$ and concentrated *in vacuo*. The crude product was purified by Kugelrohr distillation to give 1.26 g (67%) of amine **1f** as a colorless oil. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 5.15 (s, 2H), 3.48 (s, 3H), 2.80 (hept, *J* = 6.4 Hz, 1H), 2.67 – 2.56 (m, 4H), 1.80 (p, *J* = 7.5 Hz, 2H), 1.06 (d, *J* = 6.2 Hz, 6H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 155.5, 135.7, 129.4, 116.3, 94.7, 56.0, 48.8, 47.2, 33.1, 32.3, 23.2. **HRMS** (ESI+) calcd for $C_{14}H_{24}NO_2$ $[M+H]^+$ 238.1802, found 238.1797.

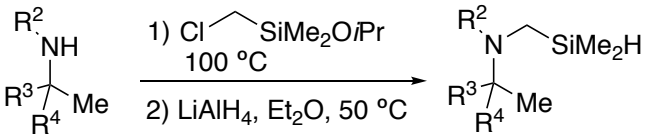
**Amine 1g**




To a solution of 6-methyl-5-hepten-2-one (2.23 mL, 15.0 mmol) and cyclopentylamine (1.78 mL, 18.0 mmol) in dichloromethane (50 mL) was added sodium triacetoxyborohydride (4.77 g, 22.5 mmol) and acetic acid (0.86 mL, 15 mmol) at 0 °C. The mixture was allowed to warm to room temperature, and then stirred overnight. The reaction was quenched with saturated $NaHCO_3$ solution and extracted with dichloromethane. The organic phase was washed with brine, dried with $Na_2SO_4$ and concentrated *in vacuo*. The crude product was purified by Kugelrohr distillation to give 2.66 g (91%) of amine **1g** as a colorless oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 5.10 – 5.06 (m, 1H), 3.13 (p, *J* = 7.1 Hz, 1H), 2.66 (h, *J* = 6.3 Hz, 1H), 2.05 – 1.91 (m, 2H), 1.89 – 1.78 (m, 2H), 1.70 – 1.60 (m, 5H), 1.58 (s, 3H), 1.54 – 1.41 (m, 3H), 1.35 – 1.18 (m, 3H),

1.02 (d, $J$ = 6.2 Hz, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 131.5, 124.5, 57.0, 51.2, 37.4, 33.9, 33.3, 25.8, 24.8, 23.99, 23.96, 20.8, 17.8. **HRMS** (ESI+) calcd for $C_{13}H_{26}N$ $[M+H]^+$ 196.2060, found 196.2059.

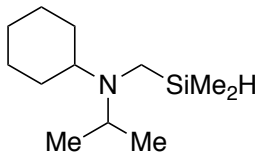
*5.4.3 Synthesis of (Silylmethyl)amines **2***




**1** **2**

In an $N_2$-filled glovebox, amine **1** (2 equiv) and (chloromethyl)-isopropoxyl-dimethylsilane (1 equiv) were added to a 20 mL screw-top vial. Alternatively, amine **1** (1 equiv), (chloromethyl)-isopropoxyl-dimethylsilane (1 equiv), and triethylamine (1 equiv) were added to the vial. The vial was capped with a Teflon-lined screw cap, and the resulting mixture was stirred at 100 °C overnight. The mixture was filtered, and the filter cake was washed with dry diethyl ether. Amine **1** that was used in excess as a base in this $S_N2$ reaction can be recovered from the filter cake containing ammonium chloride salt if necessary. The filtrate was concentrated. The mixture was brought back into the glove box and dissolved into diethyl ether ([silane] = 2 M). This solution was added dropwise to a slurry of $LiAlH_4$ (1 equiv) in diethyl ether (final concentration of silane = 1 M) in a 20 mL screw-top vial. If this reaction requires more than 5 mL of solvent, the reaction was conducted in multiple vials to allow enough head space. The vial was capped with a Teflon-lined screw cap, and the resulting mixture was stirred at 50 °C overnight. The mixture was brought into the glovebox and slowly filtered through Celite to remove the majority of residual lithium hydride. The filtrate was concentrated. The residue was carefully purified by kugelrohr distillation with minimum exposure to moisture. If the distilled sample contains visible white impurities, it was filtered through a 0.2 μm PTFE membrane or basic alumina.

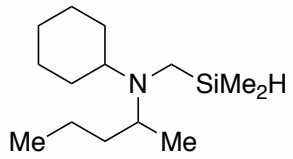
**(Silylmethyl)amine 2a**




Following the general procedure, *N*-cyclohexylisopropylamine **1a** (6.6 mL, 40. mmol) was allowed to react with (chloromethyl)-isopropoxyl-dimethylsilane (3.6 mL, 20. mmol). The crude reaction mixture was purified by kugelrohr distillation to give 1.91 g (45%) of (silylmethyl)amine **2a** as a colorless oil. **$^1$H NMR** (500 MHz, $C_6D_6$) δ 4.30 – 4.18 (m, 1H), 3.00 (hept, $J$ = 6.5 Hz, 1H), 2.51 (tt, $J$ = 10.8, 2.7 Hz, 1H), 2.09 (d, $J$ = 3.0 Hz, 2H), 1.77 – 1.64 (m, 4H), 1.60 – 1.52 (m, 1H), 1.28 – 1.12 (m, 4H), 1.07 – 0.92 (m,

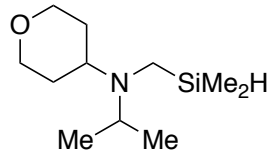
7H), 0.14 (d, *J* = 3.6 Hz, 6H). **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 59.7, 49.5, 34.0, 31.7, 27.0, 26.8, 20.8, -4.8. **HRMS** (ESI+) calcd for $C_{12}H_{28}N^+$ [M+H$^+$] 214.1986, found 214.1985.

**(Silylmethyl)amine 2b**



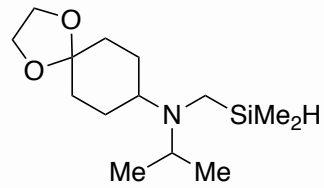

Following the general procedure, amine **1b** (1.67 g, 9.88 mmol) was allowed to react with (chloromethyl)-isopropoxyl-dimethylsilane (1.79 mL, 9.88 mmol) and triethylamine (1.38 mL, 9.88 mmol). The crude reaction mixture was purified by kugelrohr distillation to give 464 mg (20%) of (silylmethyl)amine **2b** as a colorless oil. **$^1$H NMR** (400 MHz, $C_6D_6$) δ 4.30 – 4.20 (m, 1H), 2.78 (tq, *J* = 7.8, 6.4 Hz, 1H), 2.53 (tt, *J* = 11.1, 3.3 Hz, 1H), 2.17 (dd, *J* = 14.9, 2.0 Hz, 1H), 2.05 (dd, *J* = 14.8, 4.0 Hz, 1H), 1.87 – 1.62 (m, 4H), 1.61 – 0.87 (m, 16H), 0.16 (d, *J* = 3.6 Hz, 3H), 0.10 (d, *J* = 3.6 Hz, 3H). **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 60.0, 53.40, 38.7, 33.9, 33.4, 30.2, 27.2, 7.0, 26.8, 20.9, 17.7, 14.7, -4.6, -4.9. **HRMS** (EI+) calcd for $C_{14}H_{31}NSi$ [M] 241.2226, found 241.2229.

**(Silylmethyl)amine 2c**



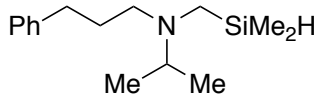

Following the general procedure, amine **1c**[48] (1.26 g, 8.80 mmol) was allowed to react with (chloromethyl)-isopropoxyl-dimethylsilane (0.80 mL, 4.4 mmol). The crude reaction mixture was purified by kugelrohr distillation to give 573 mg (60%) of (silylmethyl)amine **2c** as a colorless oil. **$^1$H NMR** (500 MHz, $C_6D_6$) δ 4.23 – 4.15 (m, 1H), 3.98 – 3.90 (m, 2H), 3.18 (td, *J* = 11.9, 2.0 Hz, 2H), 2.94 (hept, *J* = 6.5 Hz, 1H), 2.57 (tt, *J* = 11.6, 3.8 Hz, 1H), 1.97 (d, *J* = 3.1 Hz, 2H), 1.60 – 1.49 (m, 2H), 1.37 – 1.30 (m, 2H), 0.91 (d, *J* = 6.6 Hz, 6H), 0.09 (d, *J* = 3.6 Hz, 6H). **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 68.1, 56.9, 49.7, 33.9, 32.1, 20.4, -4.9. **HRMS** (EI+) calcd for $C_{11}H_{25}NOSi$ [M] 215.1705, found 215.1710.

**(Silylmethyl)amine 2d**



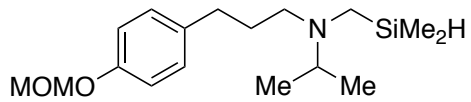
Following the general procedure, amine **1d**[49] (1.76 g, 8.83 mmol) was allowed to react with (chloromethyl)-isopropoxyl-dimethylsilane (0.80 mL, 4.4 mmol). The crude reaction mixture was purified by kugelrohr distillation to give 176 mg (15%) of (silylmethyl)amine **2d** as a colorless oil. **$^1$H NMR** (500 MHz, $C_6D_6$) δ 4.26 – 4.18 (m, 1H), 3.59 – 3.49 (m, 4H), 3.03 (hept, *J* = 6.6 Hz, 1H), 2.60 (tt, *J* = 11.5, 3.3 Hz, 1H), 2.08 (d, *J* = 3.1 Hz, 2H), 1.88 – 1.78 (m, 4H), 1.70 – 1.60 (m, 4H), 0.94 (d, *J* = 6.6 Hz, 6H), 0.09 (d, *J* = 3.6 Hz, 6H). **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 108.78, 64.37, 64.25, 58.33, 49.80, 35.08, 34.17, 28.21, 20.61, -4.90. **HRMS** (ESI+) calcd for $C_{14}H_{30}NO_2Si^+$ [M+H$^+$] 272.2040, found 272.2038.

**(Silylmethyl)amine 2e**



Following the general procedure, amine **1e**[48] (1.23 g, 6.94 mmol) was allowed to react with (chloromethyl)-isopropoxyl-dimethylsilane (1.26 mL, 6.94 mmol) and triethylamine (0.97 mL, 6.9 mmol). The crude reaction mixture was purified by kugelrohr distillation to give 479 mg (28%) of (silylmethyl)amine **2e** as a colorless oil. **$^1$H NMR** (500 MHz, $C_6D_6$) δ 4.23 – 4.15 (m, 1H), 3.98 – 3.90 (m, 2H), 3.18 (td, *J* = 11.9, 2.0 Hz, 2H), 2.94 (hept, *J* = 6.5 Hz, 1H), 2.57 (tt, *J* = 11.6, 3.8 Hz, 1H), 1.97 (d, *J* = 3.1 Hz, 2H), 1.60 – 1.49 (m, 2H), 1.37 – 1.30 (m, 2H), 0.91 (d, *J* = 6.6 Hz, 6H), 0.09 (d, *J* = 3.6 Hz, 6H). **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 143.09, 128.79, 128.64, 125.99, 51.82, 51.67, 38.93, 34.00, 30.86, 17.45, -4.84. **HRMS** (EI+) calcd for $C_{15}H_{27}NSi$ [M] 249.1913, found 249.1918.

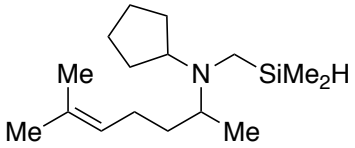
**(Silylmethyl)amine 2f**



Following the general procedure, amine **1f** (1.11 g, 4.68 mmol) was allowed to react with (chloromethyl)-isopropoxyl-dimethylsilane (0.42 mL, 2.3 mmol). The crude reaction mixture was purified by kugelrohr distillation to give 93.0 mg (13%) of (silylmethyl)amine **2f** as a colorless oil. **$^1$H NMR** (500 MHz, $C_6D_6$) δ 7.13 – 7.04 (m, 4H), 4.89 (s, 2H), 4.26 – 4.13 (m, 1H), 3.15 (s, 3H), 2.91 (hept, *J* = 6.6 Hz, 1H), 2.60 – 2.52 (m, 2H), 2.38 – 2.30 (m, 2H), 1.92 (d, *J* = 3.1 Hz, 2H), 1.77 – 1.66 (m, 2H), 0.90 (d, *J* = 6.6 Hz, 6H), 0.10 (d, *J* = 3.6 Hz, 5H). **$^{13}$C NMR** (151 MHz, $C_6$D6) δ 156.24, 136.35,

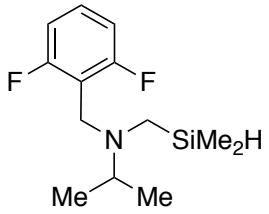
129.68, 116.65, 94.68, 55.49, 51.85, 51.74, 38.98, 33.16, 31.09, 17.47, -4.83. **HRMS** (ESI+) calcd for $C_{17}H_{32}NO_2Si^+$ [M+H$^+$] 310.2197, found 310.2193.

**(Silylmethyl)amine 2g**



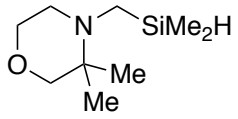

Following the general procedure, amine **1g** (1.95 g, 10.0 mmol) was allowed to react with (chloromethyl)-isopropoxyl-dimethylsilane (0.91 mL, 5.0 mmol). The crude reaction mixture was purified by kugelrohr distillation to give 666 mg (50%) of (silylmethyl)amine **2f** as a colorless oil. **$^1$H NMR** (600 MHz, $C_6D_6$) δ 55.29 (t, *J* = 7.2 Hz, 1H), 4.26 – 4.20 (m, 1H), 3.12 – 3.04 (m, 1H), 2.83 (h, *J* = 6.7 Hz, 1H), 2.28 – 2.18 (m, 1H), 2.13 – 2.04 (m, 1H), 2.03 – 1.95 (m, 2H), 1.74 – 1.34 (m, 15H), 1.27 (ddt, *J* = 13.4, 9.5, 6.2 Hz, 1H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.16 (d, *J* = 3.7 Hz, 3H), 0.10 (d, *J* = 3.7 Hz, 3H). **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 130.9, 125.8, 61.2, 56.0, 35.7, 35.1, 31.7, 28.7, 26.3, 25.9, 24.9, 24.1, 17.9, 15.8, -4.5, -4.7. **HRMS** (EI+) calcd for $C_{16}H_{33}NSi$ [M] 267.2382, found 267.2387.

**(Silylmethyl)amine 2h**



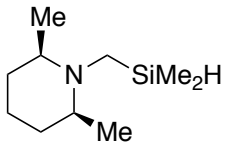

Following the general procedure, amine **1h**[48] (2.35 g, 12.7 mmol) was allowed to react with (chloromethyl)-isopropoxyl-dimethylsilane (1.15 mL, 6.34 mmol). The crude reaction mixture was purified by kugelrohr distillation to give 1.00 g (61%) of (silylmethyl)amine **2h** as a colorless oil. **$^1$H NMR** (400 MHz, $C_6D_6$) δ 6.70 – 6.43 (m, 3H), 4.25 – 4.15 (m, 1H), 3.59 (s, 2H), 2.94 (hept, *J* = 6.8 Hz, 1H), 2.00 (d, *J* = 3.0 Hz, 2H), 0.95 (d, *J* = 6.6 Hz, 6H), 0.06 (d, *J* = 3.7 Hz, 6H). **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 162.85 (dd, *J* = 248.5, 8.6 Hz), 128.86 (t, *J* = 10.2 Hz), 116.7 (t, *J* = 18.5 Hz), 111.2 (dd, *J* = 21.3, 5.1 Hz), 51.7, 44.0, 38.2, 17.2, -5.1. **$^{19}$F NMR** (376 MHz, $C_6$D6) δ -113.12 **HRMS** (EI+) calcd for $C_{13}H_{21}F_2NSi$ [M] 257.1411, found 257.1414.

**(Silylmethyl)amine 2i**



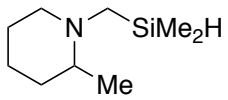

Following the general procedure, amine **1i** (1.00 g, 8.68 mmol) was allowed to react with (chloromethyl)-isopropoxyl-dimethylsilane (1.5 mL, 8.7 mmol) and triethylamine (1.21 mL, 8.68 mmol). The crude reaction mixture was purified by kugelrohr distillation to give 714 mg (44%) of (silylmethyl)amine **2i** as a colorless oil. **$^1$H NMR** (400 MHz, $C_6D_6$) δ 4.17 – 4.06 (m, 1H), 3.63 – 3.54 (m, 2H), 3.30 (s, 2H), 2.41 – 2.31 (m, 2H), 1.74 (d, *J* = 2.9 Hz, 2H), 0.83 (s, 6H), 0.05 (d, *J* = 3.7 Hz, 6H). **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 78.0, 68.4, 54.0, 50.0, 37.9, 18.4, -5.0. **HRMS** (EI+) calcd for $C_9H_{21}NOSi$ [M] 187.1392, found 187.1392.

**(Silylmethyl)amine 2j**




Following the general procedure, amine **1j** (0.67 mL, 5.0 mmol) was allowed to react with (chloromethyl)-isopropoxyl-dimethylsilane (0.70 mL, 5.0 mmol) and triethylamine (0.70 mL, 5.0 mmol). The crude reaction mixture was purified by kugelrohr distillation to give 279 mg (30%) of (silylmethyl)amine **2i** as a colorless oil. **$^1$H NMR** (500 MHz, $C_6D_6$) δ 4.34 – 4.22 (m, 1H), 2.29 – 2.18 (m, 2H), 2.14 (d, *J* = 3.4 Hz, 2H), 1.57 – 1.50 (m, 1H), 1.47 – 1.38 (m, 2H), 1.34 – 1.19 (m, 3H), 1.07 (d, *J* = 6.2 Hz, 6H), 0.11 (d, *J* = 3.7 Hz, 6H). **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 59.8, 40.5, 35.3, 24.7, 22.8, -3.8. **HRMS** (EI+) calcd for $C_{10}H_{23}NSi$ [M] 185.1600, found 185.1592.

**(Silylmethyl)amine 2k**

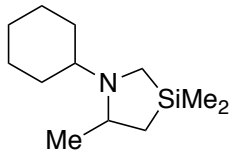



Following the general procedure, amine **1k** (1.18 mL, 10.0 mmol) was allowed to react with (chloromethyl)-isopropoxyl-dimethylsilane (1.81 mL, 10.0 mmol) and triethylamine (1.39 mL, 10.0 mmol). The crude reaction mixture was purified by kugelrohr distillation to give 561 mg (33%) of (silylmethyl)amine **2k** as a colorless oil. **$^1$H NMR** (500 MHz, $C_6D_6$) δ 4.30 – 4.20 (m, 1H), 2.98 – 2.87 (m, 1H), 2.39 (dd, *J* = 14.4, 4.1 Hz, 1H), 2.04 – 1.95 (m, 2H), 1.62 – 1.42 (m, 5H), 1.36 – 1.26 (m, 1H), 1.25 – 1.15 (m, 1H), 1.01 (d, *J* = 6.2 Hz, 3H), 0.14 (d, *J* = 3.6 Hz, 3H), 0.07 (d, *J* = 3.6 Hz, 3H). **$^{13}$C NMR** (151 MHz, $C_6D_6$) δ 60.00, 56.11, 43.99, 35.11, 27.03, 24.49, 19.64, -4.54, -4.76. **HRMS** (EI+) calcd for $C_9H_{21}NSi$ [M] 171.1443, found 171.1443.

*5.4.4 General Procedure for Silylation of Aliphatic Amines*

In an $N_2$-filled glovebox, (silylmethyl)amine **2** (1.0 equiv) was weighed into a 4 mL screw-top vial. The amine was then sequentially treated with norbornene (1.5 equiv) and a freshly prepared stock solution of $[Ir(cod)OMe]_2$ (2.0 mol %) and 2,4,7-trimethylphenanthroline **L5** (5.0 mol %)[38] in THF ([silane] = 0.5 M). The vial was capped with a Teflon-lined screw cap and placed in a pre-heated aluminum heating block at 100 °C. After 17 hours, the reaction mixture was allowed to cool to room temperature, and the solvent was removed via rotary evaporation. The crude product was absorbed to Celite and purified by silica gel chromatography.

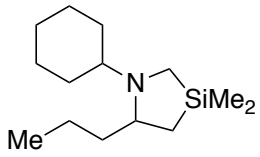
**Silapyrrolidine 3a**




Following the general procedure, (silylmethyl)amine **2a** (54.4 mg, 0.255 mmol) was reacted with $[Ir(cod)OMe]_2$/2,4,7-trimethylphenanthroline in THF (0.5 mL) at 100 °C for 17 h. Concentration of the reaction mixture and purification by silica gel chromatography (hexanes with 1% $NEt_3$ : EtOAc 100:0→90:10) gave 39.4 mg (75%) of **3a** as a colorless oil. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 2.98 – 2.87 (m, 1H), 2.62 (tt, *J* = 10.7, 3.2 Hz, 1H), 2.01 (d, *J* = 12.8 Hz, 1H), 1.82 (d, *J* = 12.8 Hz, 1H), 1.80 – 1.58 (m, 5H), 1.41 – 1.07 (m, 5H), 1.05 (d, *J* = 6.2 Hz, 3H), 0.94 (dd, *J* = 14.2, 5.7 Hz, 1H), 0.57 (dd, *J* = 14.2, 8.5 Hz, 1H), 0.18 (s, 3H), 0.11 (s, 3H). **$^{13}$C NMR** (101 MHz, $CDCl_3$) δ 58.4, 55.1, 35.7, 33.3, 26.7, 26.5, 25.8, 23.6, 23.4, 19.6, -1.6, -2.0. **HRMS** (ESI+) calcd for $C_{12}H_{26}NSi^+$ $[M+H^+]$ 212.1829, found 212.1831.

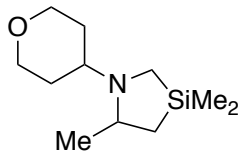
*Glovebox-free procedure*: $[Ir(cod)OMe]_2$ (3.3 mg, 0.0050 mmol, 2.0 mol %), **L5** (2.8 mg, 0.013 mmol, 5.0 mol%), and a solution of **2a** (53.4 mg, 0.250 mmol) and norbornene (35.3 mg, 0.375 mmol, 1.5 equiv) in THF (0.5 mL) were quickly added in this order on the benchtop to a cooled, flame-dried Schlenk tube. The reaction vessel was degassed by reducing pressure briefly and backfilling with nitrogen (three cycles). The Schlenk tube was immersed in a preheated oil bath at 100 °C and stirred at this temperature for 17 h. After this time, the reaction was cooled to room temperature, and the yield was determined by $^1$H NMR analysis with 1,3,5-trimethoxybenzene (8.2 mg, 0.049 mmol, 0.20 equiv) as an internal standard added after the reaction (91%).

**Silapyrrolidine 3b**



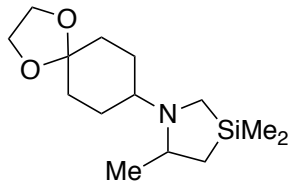

Following the general procedure, (silylmethyl)amine **2b** (60.3 mg, 0.250 mmol) was reacted with [Ir(cod)OMe]$_2$/2,4,7-trimethylphenanthroline in THF (0.5 mL) at 100 °C for 17 h. Concentration of the reaction mixture and purification by silica gel chromatography (hexanes with 1% $NEt_3$ : EtOAc 100:0→95:5) gave 47.4 mg (79%) of **3a** as a colorless oil. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 2.98 – 2.87 (m, 1H), 2.62 (tt, *J* = 10.7, 3.2 Hz, 1H), 2.01 (d, *J* = 12.8 Hz, 1H), 1.82 (d, *J* = 12.8 Hz, 1H), 1.80 – 1.58 (m, 5H), 1.41 – 1.07 (m, 5H), 1.05 (d, *J* = 6.2 Hz, 3H), 0.94 (dd, *J* = 14.2, 5.7 Hz, 1H), 0.57 (dd, *J* = 14.2, 8.5 Hz, 1H), 0.18 (s, 3H), 0.11 (s, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 59.9, 57.9, 36.0, 35.3, 33.3, 26.8, 26.6, 25.8, 23.4, 20.1, 19.7, 14.7, -1.7, -2.0. **HRMS** (ESI+) calcd for $C_{14}H_{30}NSi^+$ [M+H$^+$] 240.2142, found 240.2152.

**Silapyrrolidine 3c**



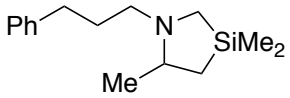

Following the general procedure, (silylmethyl)amine **2c** (53.6 mg, 0.249 mmol) was reacted with [Ir(cod)OMe]$_2$/2,4,7-trimethylphenanthroline in THF (0.5 mL) at 100 °C for 17 h. Concentration of the reaction mixture and purification by silica gel chromatography (hexanes with 1% $NEt_3$ : EtOAc 100:0→90:10) gave 39.3 mg (74%) of **3c** as a colorless oil. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 4.04 – 3.97 (m, 2H), 3.42 (td, *J* = 11.2, 3.4 Hz, 1H), 3.36 (ddd, *J* = 14.5, 6.5, 4.3 Hz, 1H), 3.06 – 2.97 (m, 1H), 2.82 (tt, *J* = 10.1, 5.2 Hz, 1H), 1.95 (d, *J* = 12.7 Hz, 1H), 1.88 (d, *J* = 12.7 Hz, 1H), 1.77 – 1.66 (m, 2H), 1.64 – 1.55 (m, 2H), 1.04 (d, *J* = 6.2 Hz, 3H), 0.98 (dd, *J* = 14.2, 6.0 Hz, 1H), 0.58 (dd, *J* = 14.2, 7.5 Hz, 1H), 0.20 (s, 3H), 0.14 (s, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 68.1, 67.4, 56.3, 54.7, 35.6, 33.2, 25.4, 23.1, 18.8, -1.5, -2.0. **HRMS** (ESI+) calcd for $C_{11}H_{24}NOSi^+$ [M+H$^+$] 214.1622, found 214.1628.

**Silapyrrolidine 3d**



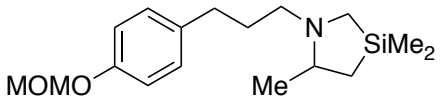

Following the general procedure, (silylmethyl)amine **2d** (67.4 mg, 0.248 mmol) was reacted with [Ir(cod)OMe]$_2$/2,4,7-trimethylphenanthroline in THF (0.5 mL) at 100 °C for 17 h. Concentration of the reaction mixture and purification by silica gel chromatography (hexanes with 1% $NEt_3$ : EtOAc 100:0→90:10) gave 54.0 mg (80%) of **3d** as a colorless oil. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 3.93 (s, 4H), 2.88 (tq, *J* = 8.5, 6.0 Hz, 1H), 2.73 (tt, *J* = 10.2, 3.9 Hz, 1H), 2.03 (d, *J* = 12.7 Hz, 1H), 1.84 – 1.69 (m, 5H), 1.67 – 1.46 (m, 4H), 1.06 (d, *J* = 6.1 Hz, 3H), 0.95 (dd, *J* = 14.2, 5.7 Hz, 1H), 0.56 (dd, *J* = 14.2, 8.5 Hz, 1H), 0.17 (s, 3H), 0.10 (s, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 109.0, 64.40, 64.35, 56.8, 55.5, 35.7, 34.2, 33.6, 29.8, 23.5, 20.3, 19.7, -1.7, -2.1. **HRMS** (ESI+) calcd for $C_{14}H_{28}NO_2Si^+$ [M+H$^+$] 270.1884, found 270.1887

**Silapyrrolidine 3e**




Following the general procedure, (silylmethyl)amine **2e** (63.6 mg, 0.255 mmol) was reacted with [Ir(cod)OMe]$_2$/2,4,7-trimethylphenanthroline in THF (0.5 mL) at 100 °C for 17 h. Concentration of the reaction mixture and purification by silica gel chromatography (hexanes with 1% $NEt_3$ : EtOAc 100:0→95:5) gave 51.4 mg (81%) of **3e** as a colorless oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.28 (t, *J* = 7.6 Hz, 2H), 7.20 (d, *J* = 7.3 Hz, 2H), 7.17 (t, *J* = 7.3 Hz, 1H), 2.84 (ddd, *J* = 11.7, 8.9, 6.6 Hz, 1H), 2.69 – 2.63 (m, 1H), 2.62 – 2.55 (m, 1H), 2.52 – 2.46 (m, 1H), 2.30 (d, *J* = 12.9 Hz, 1H), 2.15 (ddd, *J* = 11.7, 8.9, 6.0 Hz, 1H), 1.90 – 1.77 (m, 2H), 1.49 (d, *J* = 12.9 Hz, 1H), 1.08 (d, *J* = 6.1 Hz, 3H), 0.98 (dd, *J* = 14.3, 5.9 Hz, 1H), 0.57 (dd, *J* = 14.3, 8.9 Hz, 1H), 0.19 (s, 3H), 0.13 (s, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 142.8, 128.56 128.4, 125.7, 60.2, 55.8, 42.9, 34.1, 29.6, 23.5, 20.6, -1.8, -2.0. **HRMS** (ESI+) calcd for $C_{15}H_{26}NSi^+$ [M+H$^+$] 248.1829, found 248.1835.

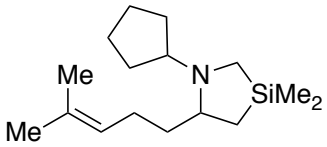
**Silapyrrolidine 3f**




Following the general procedure, (silylmethyl)amine **2f** (30.6 mg, 0.0989 mmol) was reacted with [Ir(cod)OMe]$_2$/2,4,7-trimethylphenanthroline in THF (0.2 mL) at 100 °C for 17 h. Concentration of the reaction mixture and purification by silica gel chromatography (hexanes with 1% $NEt_3$ : EtOAc 100:0→95:5) gave 25.5 mg (84%) of **3f** as a colorless

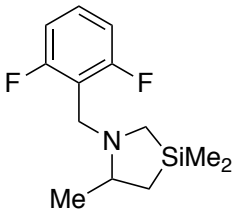
oil. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 5.15 (s, 2H), 3.48 (s, 3H), 2.82 (ddd, *J* = 11.7, 8.9, 6.7 Hz, 1H), 2.65 – 2.41 (m, 3H), 2.29 (d, *J* = 13.0 Hz, 1H), 2.13 (ddd, *J* = 11.7, 8.8, 6.0 Hz, 1H), 1.89 – 1.72 (m, 2H), 1.48 (d, *J* = 12.9 Hz, 1H), 1.08 (d, *J* = 6.1 Hz, 3H), 0.97 (dd, *J* = 14.3, 5.8 Hz, 1H), 0.57 (dd, *J* = 14.3, 8.9 Hz, 1H), 0.18 (s, 3H), 0.12 (s, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 155.4, 136.2, 129.4, 116.3, 94.8, 60.2, 56.0, 55.8, 42.9, 33.3, 29.8, 23.5, 20.6, -1.8, -2.0. **HRMS** (EI+) calcd for $C_{17}H_{29}NO_2Si$ [M] 307.1968, found 307.1968.

**Silapyrrolidine 3g**



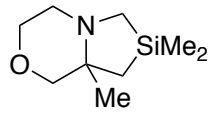

Following the general procedure, (silylmethyl)amine **2g** (68.1 mg, 0.255 mmol) was reacted with $[Ir(cod)OMe]_2$/2,4,7-trimethylphenanthroline in THF (0.5 mL) at 100 °C for 17 h. Concentration of the reaction mixture and purification by silica gel chromatography (hexanes with 1% $NEt_3$) gave 42.1 mg (62%) of **3g** as a colorless oil. **$^1$H NMR** (500 MHz, $CDCl_3$) δ δ 5.15 – 5.08 (m, 1H), 3.11 (p, *J* = 8.1, 7.4 Hz, 1H), 2.92 – 2.83 (m, 1H), 2.07 – 1.92 (m, 2H), 1.91 – 1.77 (m, 3H), 1.75 – 1.36 (m, 14H), 1.04 (dtd, *J* = 12.8, 10.0, 5.1 Hz, 1H), 0.92 (dd, *J* = 14.3, 6.5 Hz, 1H), 0.66 (dd, *J* = 14.3, 5.2 Hz, 1H), 0.18 (s, 3H), 0.15 (s, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 131.40, 124.69, 62.63, 61.97, 37.44, 31.98, 30.15, 26.44, 25.73, 25.57, 24.55, 24.05, 18.87, 17.68, -1.24, -1.80. **HRMS** (ESI+) calcd for $C_{16}H_{32}NSi^+$ $[M+H^+]$ 266.2299, found 266.2298.

**Silapyrrolidine 3h**



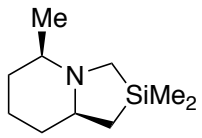

Following the general procedure, (silylmethyl)amine **2h** (64.9 mg, 0.252 mmol) was reacted with $[Ir(cod)OMe]_2$/2,4,7-trimethylphenanthroline in THF (0.5 mL) at 100 °C for 17 h. Concentration of the reaction mixture and purification by silica gel chromatography (hexanes with 1% $NEt_3$) gave 50.6 mg (79%) of **3h** as a colorless oil. **$^1$H NMR** (500 MHz, $CDCl_3$) δ δ 7.20 (tt, *J* = 8.3, 6.4 Hz, 1H), 6.90 – 6.81 (m, 2H), 4.02 (d, *J* = 12.4 Hz, 1H), 3.49 (d, *J* = 12.4 Hz, 1H), 2.63 – 2.53 (m, 1H), 2.18 (d, *J* = 13.0 Hz, 1H), 1.55 (d, *J* = 13.0 Hz, 1H), 1.28 (d, *J* = 5.9 Hz, 3H), 0.98 (dd, *J* = 14.4, 6.0 Hz, 1H), 0.58 (dd, *J* = 14.4, 9.1 Hz, 1H), 0.12 (s, 3H), 0.07 (s, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 162.4 (dd, *J* = 248.0, 8.8 Hz), 128.6 (t, *J* = 10.4 Hz), 115.1 (t, *J* = 19.8 Hz), 111.1 (dd, *J* = 21.6, 5.1 Hz), 59.8, 46.6, 43.0, 23.6, 21.6, -1.9, -2.1. **$^{19}$F NMR** (376 MHz, $CDCl_3$) δ -112.5. **HRMS** (ESI+) calcd for $C_{13}H_{20}F_2NSi^+$ $[M+H^+]$ 256.1328, found 256.1334.

**Silapyrrolidine 3i**



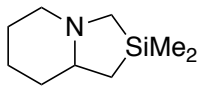

Following the general procedure, (silylmethyl)amine **2i** (46.1 mg, 0.246 mmol) was reacted with [Ir(cod)OMe]$_2$/2,4,7-trimethylphenanthroline in THF (0.5 mL) at 100 °C for 17 h. Concentration of the reaction mixture and purification by silica gel chromatography (hexanes with 1% $NEt_3$ : EtOAc 100:0→90:10) gave 26.3 mg (58%) of **3i** as a colorless oil. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 3.86 – 3.74 (m, 1H), 3.67 – 3.53 (m, 2H), 3.20 (d, *J* = 10.6 Hz, 1H), 2.72 (td, *J* = 11.7, 3.6 Hz, 1H), 2.54 (d, *J* = 11.9 Hz, 1H), 2.20 (d, *J* = 12.9 Hz, 1H), 1.81 (d, *J* = 12.8 Hz, 1H), 0.96 (s, 3H), 0.59 (d, *J* = 13.6 Hz, 1H), 0.52 (d, *J* = 13.9 Hz, 1H), 0.23 (s, 3H), 0.21 (s, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 79.6, 67.5, 59.9, 51.0, 42.2, 24.8, 13.6, -1.2, -1.6. **HRMS** (ESI+) calcd for $C_9H_{20}NOSi^+$ [M+H$^+$] 186.1309, found 186.1313.

**Silapyrrolidine 3j**




Following the general procedure, (silylmethyl)amine **2j** (46.9 mg, 0.253 mmol) was reacted with [Ir(cod)OMe]$_2$/2,4,7-trimethylphenanthroline in THF (0.5 mL) at 100 °C for 17 h. Concentration of the reaction mixture and purification by silica gel chromatography (hexanes with 1% $NEt_3$ : EtOAc 100:0→95:5) gave 22.2 mg (48%) of **3j** as a colorless oil. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 2.64 (d, *J* = 13.0 Hz, 1H), 1.99 – 1.88 (m, 2H), 1.86 – 1.75 (m, 1H), 1.70 – 1.61 (m, 1H), 1.60 – 1.51 (m, 1H), 1.37 – 1.18 (m, 4H), 1.11 (d, *J* = 6.3 Hz, 3H), 0.89 (dd, *J* = 14.2, 4.8 Hz, 1H), 0.59 (dd, *J* = 14.2, 11.8 Hz, 1H), 0.20 (s, 3H), 0.10 (s, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 65.5, 62.9, 44.5, 36.4, 34.8, 25.0, 22.4, 21.8, -2.0, -2.1. **HRMS** (ESI+) calcd for $C_{10}H_{22}NSi^+$ [M+H$^+$] 184.1516, found 184.1519.

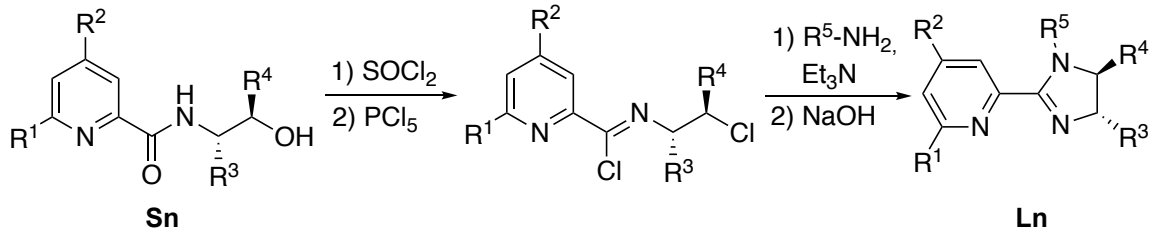
**Silapyrrolidine 3k**




Following the general procedure, (silylmethyl)amine **2j** (42.1 mg, 0.246 mmol) was reacted with [Ir(cod)OMe]$_2$/2,4,7-trimethylphenanthroline in THF (0.5 mL) at 100 °C for 17 h. Concentration of the reaction mixture and purification by silica gel chromatography (hexanes with 1% $NEt_3$ : EtOAc 100:0→95:5) gave 15.5 mg (37%) of **3k** as a colorless oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 3.13 – 3.02 (m, 1H), 2.43 (d, *J* = 13.0 Hz, 1H), 2.00 – 1.91 (m, 1H), 1.86 – 1.75 (m, 2H), 1.74 – 1.66 (m, 1H), 1.63 – 1.54 (m, 2H), 1.39 (d, *J* = 13.1 Hz, 1H), 1.26 – 1.15 (m, 2H), 0.90 (dd, *J* = 14.1, 4.9 Hz, 1H), 0.51 (dd, *J* = 14.2,

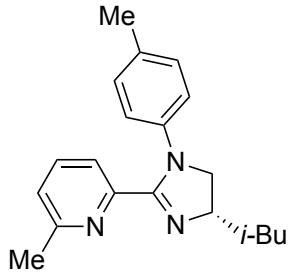
11.4 Hz, 1H), 0.21 (s, 3H), 0.11 (s, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 65.0, 59.3, 48.1, 36.2, 26.4, 25.2, 22.4, -2.05, -2.07. **HRMS** (ESI+) calcd for $C_9H_{20}NSi^+$ [M+H$^+$] 170.1360, found 170.1368.

*5.4.5 Synthesis of Pyridine Imidazoline Ligands (**L8**–**L17**)*




General conditions developed by Casey were employed with slight modifications. [50] To a solution of *N*-(pyridinoyl)-amino alcohol (1 equiv) in chloroform (1 M solution), thionyl chloride (1.1 equiv) was added dropwise at room temperature, and the resulting mixture was stirred at reflux for 2 h. The completion was confirmed by $^1$H NMR analysis. Phosphorus pentachloride (1 equiv) was added at room temperatue, and the resulting suspension was refluxed for 2 h. Reaction was monitored by $^1$H NMR analysis. If the reaction is not complete in 2 h, additional amount of $PCl_5$ was added to the reaction mixture, and the suspension was heated for an additional 2 h. (Optional: Upon completion of this step, the solvent was evaporated, and $POCl_3$ was removed under high vacuum. The resulting residue was dissolved in chloroform again.) The solution was cooled to 0 °C and a solution of *p*-toluidine (1.2 equiv) in triethylamine (3 equiv) and chloroform was added dropwise. The solution was stirred at 0 °C for 30 min and then refluxed for 12 h. The chloroform was evaporated, and 20% NaOH (10 mL) was added to the mixture. The aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with brine and dried over $Na_2SO_4$. The solvent was evaporated, and the crude product was purified by silica gel chromatography. (Synthesis of **L8** and **L13** was previously reported.[50])

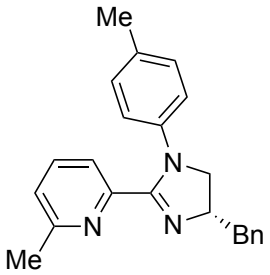
**Pyridine Imidazoline L9**




Following the general procedure, amide **S9** (473 mg, 2.00 mmol) was converted into **L9**. Purification by silica gel chromatography (first run with DCM : MeOH 100:0→80:20, then second run with hexanes : EtOAc 50:50→00:100) gave 151 mg (25%) of **L9** as a tan

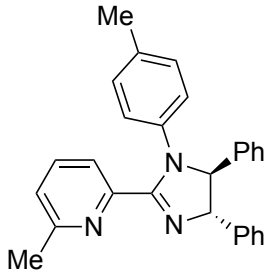
solid. **$^1$H NMR** (500 MHz, $CDCl_3$) 7.51 (t, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 7.7 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 2H), 6.63 (d, *J* = 8.4 Hz, 2H), 4.33 (dtd, *J* = 9.8, 8.4, 5.8 Hz, 1H), 4.09 (dd, *J* = 10.2, 9.0 Hz, 1H), 3.64 (t, *J* = 9.0 Hz, 1H), 2.47 (s, 3H), 2.24 (s, 3H), 1.90 – 1.79 (m, 2H), 1.50 – 1.41 (m, 1H), 0.98 (d, *J* = 6.4 Hz, 3H), 0.96 (d, *J* = 6.3 Hz, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 160.7, 158.5, 150.3, 140.8, 136.6, 132.7, 129.2, 123.9, 122.1, 121.3, 63.5, 59.9, 46.4, 25.5, 24.6, 23.2, 22.8, 20.9. **HRMS** (ESI+) calcd for $C_{20}H_{26}N_3^+$ [M+H$^+$] 308.2121, found 308.2121. $[\alpha]_D^{25}$ = –127 (c 0.858, $CHCl_3$).

**Pyridine Imidazoline L10**




Following the general procedure, amide **S10** (624 mg, 2.31 mmol) was converted into **L10**. Purification by silica gel chromatography (first run with DCM : MeOH 100:0→ 80:20, then second run with hexanes : EtOAc 50:50→00:100) gave 125 mg (18%) of **L10** as a viscous oil. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.52 (t, *J* = 7.7 Hz, 1H), 7.33 – 7.26 (m, 5H), 7.24 – 7.19 (m, 1H), 7.11 (d, *J* = 7.7 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 2H), 6.55 (d, *J* = 8.4 Hz, 2H), 4.60 (tdd, *J* = 9.8, 8.0, 4.5 Hz, 1H), 3.94 (t, *J* = 9.8 Hz, 1H), 3.75 (dd, *J* = 9.5, 8.0 Hz, 1H), 3.36 (dd, *J* = 13.7, 4.5 Hz, 1H), 2.84 (dd, *J* = 13.7, 9.4 Hz, 1H), 2.47 (s, 3H), 2.22 (s, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 161.3, 158.5, 149.9, 140.4, 138.6, 136.6, 133.1, 129.5, 129.2, 128.5, 126.4, 124.1, 122.4, 121.3, 66.0, 58.5, 42.4, 24.6, 20.9. **HRMS** (ESI+) calcd for $C_{23}H_{24}N_3^+$ [M+H$^+$] 342.1965, found 342.1969. $[\alpha]_D^{25}$ = –11 (c 0.18, $CHCl_3$).

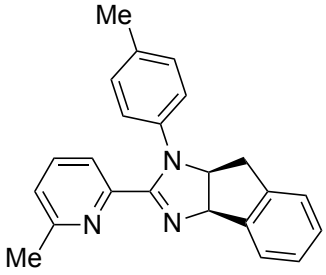
**Pyridine Imidazoline L11**




Following the general procedure, amide **S11** (447 mg, 1.34 mmol) was converted into **L11**. Purification by silica gel chromatography (first run with DCM : MeOH 100:0→ 80:20, then second run with hexanes : EtOAc 50:50→00:100) gave 37.2 mg (7%) of **L11** as a viscous oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.55 (d, *J* = 4.6 Hz, 2H), 7.43 – 7.27 (m,

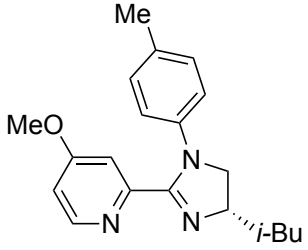
10H), 7.14 – 7.11 (m, 1H), 6.84 (d, *J* = 8.0 Hz, 2H), 6.65 (d, *J* = 8.0 Hz, 2H), 5.17 (d, *J* = 7.8 Hz, 1H), 4.88 (d, *J* = 7.8 Hz, 1H), 2.47 (s, 3H), 2.18 (s, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 162.5, 158.5, 149.7, 143.3, 142.6, 140.2, 136.4, 134.2, 129.2, 129.0, 128.7, 127.8, 127.4, 127.2, 127.0, 124.2, 124.1, 121.7, 78.8, 78.4, 24.6, 20.9. **HRMS** (ESI+) calcd for $C_{28}H_{26}N_3^+$ [M+H$^+$] 404.2121, found 404.2115. $[\alpha]_D^{25}$ = +110 (c 0.33, $CHCl_3$).

**Pyridine Imidazoline L12**




Following the general procedure, amide **S12** (509 mg, 1.90 mmol) was converted into **L12**. Purification by silica gel chromatography (first run with DCM : MeOH 100:0→ 80:20, then second run with hexanes : EtOAc 50:50→00:100) gave 120 mg (19%) of **L12** as a tan soild. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 7.66 (d, *J* = 6.9 Hz, 1H), 7.44 (t, *J* = 7.7 Hz, 1H), 7.30 – 7.21 (m, 4H), 7.04 (d, *J* = 7.7 Hz, 1H), 6.99 (d, *J* = 7.9 Hz, 2H), 6.77 (d, *J* = 7.8 Hz, 2H), 5.83 (d, *J* = 9.2 Hz, 1H), 5.05 – 4.95 (m, 1H), 3.42 (dd, *J* = 17.1, 7.1 Hz, 1H), 3.35 (d, *J* = 16.9 Hz, 1H), 2.41 (s, 3H), 2.27 (s, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 161.2, 158.4, 149.7, 143.0, 140.5, 139.5, 136.4, 134.2, 129.5, 128.2, 127.4, 126.1, 125.1, 124.3, 124.0, 121.6, 75.8, 68.5, 40.1, 24.5, 21.0. **HRMS** (ESI+) calcd for $C_{23}H_{22}N_3^+$ [M+H$^+$] 340.1808, found 340.1808. $[\alpha]_D^{25}$ = +360 (c 0.46, $CHCl_3$).

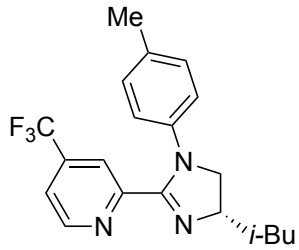
**Pyridine Imidazoline L14**




Following the general procedure, amide **S14** (73.7 mg, 0.290 mmol) was converted into **L14**. Purification by silica gel chromatography (DCM : MeOH 100:0→80:20) gave 26.4 mg (28%) of **L14** as a colorless oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 8.29 (d, *J* = 5.6 Hz, 1H), 7.21 (d, *J* = 2.4 Hz, 1H), 6.93 (d, *J* = 7.9 Hz, 2H), 6.76 (dd, *J* = 5.8, 2.5 Hz, 1H), 6.63 (d, *J* = 7.9 Hz, 2H), 4.35 – 4.26 (m, 1H), 4.13 (t, *J* = 9.6 Hz, 1H), 3.83 (s, 3H), 3.62 (t, *J* = 8.9 Hz, 1H), 2.23 (s, 3H), 1.92 – 1.75 (m, 2H), 1.48 – 1.40 (m, 1H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.96 (d, *J* = 6.6 Hz, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 166.1, 160.6, 152.5, 150.5, 140.7, 132.7, 129.3, 121.9, 111.1, 109.9, 63.3, 59.9, 55.4, 46.3, 25.4, 23.1,

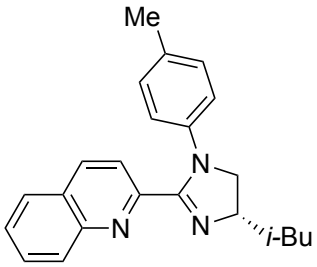
22.8, 20.9. **HRMS** (ESI+) calcd for $C_{20}H_{26}N_3O^+$ [M+H$^+$] 324.2070, found 324.2074. $[\alpha]_D^{25}$ = –74 (c 0.26, $CHCl_3$).

**Pyridine Imidazoline L15**



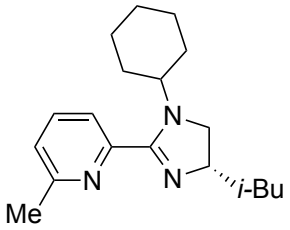

Following the general procedure, amide **S15** (678 mg, 2.34 mmol) was converted into **L15**. Purification by silica gel chromatography (DCM : MeOH 100:0→80:20) gave 191 mg (23%) of **L15** as a colorless oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 8.65 (d, *J* = 5.0 Hz, 1H), 7.98 (s, 1H), 7.46 (d, *J* = 5.0 Hz, 1H), 6.96 (d, *J* = 7.9 Hz, 2H), 6.64 (d, *J* = 7.9 Hz, 2H), 4.35 (p, *J* = 8.5 Hz, 2H), 4.17 (t, *J* = 9.6 Hz, 1H), 3.63 (t, *J* = 8.9 Hz, 1H), 2.25 (s, 3H), 1.94 – 1.74 (m, 2H), 1.49 – 1.43 (m, 1H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.98 (d, *J* = 6.6 Hz, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 159.7, 152.3, 150.2, 140.6, 139.0 (q, *J* = 34.4 Hz), 133.5, 129.5, 122.7 (q, *J* = 273 Hz), 122.5, 120.1 (q, *J* = 3.6 Hz), 120.1 (q, *J* = 3.6 Hz), 119.8 (q, *J* = 3.6 Hz), 63.7, 60.4, 46.3, 25.4, 23.1, 22.8, 20.9. **HRMS** (ESI+) calcd for $C_{20}H_{23}F_3N_3^+$ [M+H$^+$] 362.1839, found 362.1837. $[\alpha]_D^{25}$ = –80 (c 0.32, $CHCl_3$).

**Pyridine Imidazoline L16**




Following the general procedure, amide **S16** (757 mg, 2.34 mmol) was converted into **L16**. Purification by silica gel chromatography (first run with DCM : MeOH 100:0→ 80:20, then second run with hexanes : EtOAc 100:00→50:50) gave 279 mg (29%) of **L16** as a yellow viscous oil. **$^1$H NMR** (600 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.70 – 7.63 (m, 2H), 7.54 (t, *J* = 7.5 Hz, 1H), 6.90 (d, *J* = 7.9 Hz, 2H), 6.68 (d, *J* = 7.9 Hz, 2H), 4.46 – 4.36 (m, 1H), 4.17 (t, *J* = 9.6 Hz, 1H), 3.70 (t, *J* = 9.0 Hz, 1H), 2.21 (s, 3H), 1.95 – 1.85 (m, 2H), 1.55 – 1.46 (m, 1H), 1.01 (d, *J* = 6.1 Hz, 3H), 0.99 (d, *J* = 6.1 Hz, 3H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 160.8, 150.9, 147.7, 140.9, 136.5, 133.0, 130.3, 129.7, 129.4, 128.2, 127.6, 127.4, 122.3, 121.4, 63.8, 60.2, 46.4, 25.5, 23.2, 22.8, 20.9. **HRMS** (ESI+) calcd for $C_{23}H_{26}N_3^+$ [M+H$^+$] 344.2121, found 344.2125. $[\alpha]_D^{25}$ = –130. (c 1.13, $CHCl_3$).

**Pyridine Imidazoline L17**

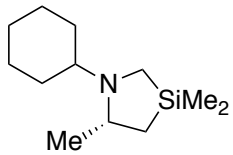



Following the general procedure, amide **S17** (823 mg, 6.00 mmol) was converted into **L17**. Purification by silica gel chromatography (DCM : MeOH 100:0→90:10) gave 290 mg (20%) of **L17** as a colorless oil. **$^1$H NMR** (500 MHz, $C_6D_6$) δ 8.03 (d, *J* = 7.8 Hz, 1H), 7.02 (t, *J* = 7.7 Hz, 1H), 6.55 (d, *J* = 7.7 Hz, 1H), 4.57 (tt, *J* = 11.7, 3.7 Hz, 1H), 4.21 (dddd, *J* = 10.3, 9.1, 7.7, 6.4 Hz, 1H), 3.44 (dd, *J* = 10.3, 8.7 Hz, 1H), 2.98 (t, *J* = 9.0 Hz, 1H), 2.33 (s, 3H), 2.17 – 2.06 (m, 1H), 1.92 – 1.81 (m, 2H), 1.81 – 1.74 (m, 1H), 1.69 – 1.58 (m, 2H), 1.53 – 1.45 (m, 1H), 1.41 (dt, *J* = 13.6, 7.0 Hz, 1H), 1.30 (pd, *J* = 11.7, 11.3, 3.3 Hz, 2H), 1.25 – 1.13 (m, 2H), 1.06 (d, *J* = 6.6 Hz, 3H), 1.01 (d, *J* = 6.7 Hz, 3H), 0.95 (qt, *J* = 12.8, 3.9 Hz, 1H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 163.6, 157.7, 151.1, 136.8, 123.7, 121.3, 62.6, 54.6, 51.0, 46.6, 31.5, 30.5, 26.0, 25.8, 25.8, 25.4, 24.6, 23.2, 22.8. **HRMS** (ESI+) calcd for $C_{19}H_{30}N_3^+$ [M+H$^+$] 300.2434, found 300.2433. $[\alpha]_D^{25}$ = –73 (c 0.55, $CHCl_3$).

*5.4.6 General Procedure for Enantioselective Silylation of Aliphatic Amines*

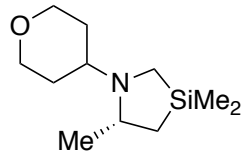
In an $N_2$-filled glovebox, (silylmethyl)amine **2** (1.0 equiv) was weighed into a 4 mL screw-top vial. The amine was then sequentially treated with norbornene (2 equiv) and a cold stock solution of $[Ir(cod)Cl]_2$ (2.0 mol %) and **L17** (5.0 mol %) in THF ([silane] = 0.5 M). The vial was capped with a Teflon-lined screw cap and stirred at 4 °C. After 72 hours, the solvent was removed via rotary evaporation, and the crude product was absorbed to Celite and purified by silica gel chromatography.

**Silapyrrolidine (*S*)-3a**



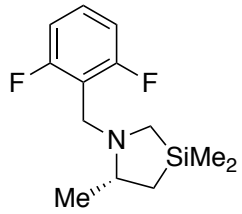

Following the general procedure, (silylmethyl)amine **2a** (52.9 mg, 0.248 mmol) was reacted with $[Ir(cod)Cl]_2$/**L17** in THF (0.5 mL) at 4 °C for 72 h. Concentration of the reaction mixture and purification by silica gel chromatography (hexanes with 1% $NEt_3$ : EtOAc 100:0→90:10) gave 42.0 mg (80%) of **(*S*)-3a** as a colorless oil. **Chiral GC analysis**: 81% ee, Cyclodex-B column (30 m x 0.25 mm ID x 0.25 um film), 120 °C, FID detector, $t_R$ = 14.5 min (minor), $t_R$ = 14.9 min (major). $[\alpha]_D^{25}$ = +48 (c 0.68, $CHCl_3$). $^1$H and $^{13}$C NMR data were consistent with the values reported above.

**Silapyrrolidine (*S*)-3c**



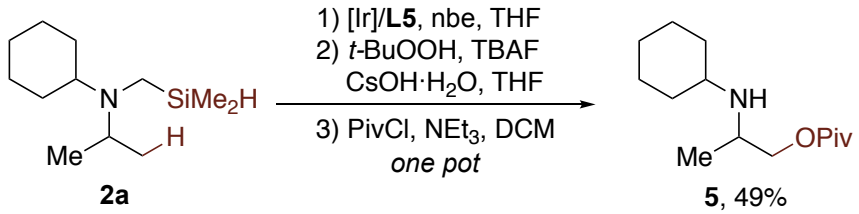

Following the general procedure, (silylmethyl)amine **2c** (53.4 mg, 0.248 mmol) was reacted with [Ir(cod)Cl]$_2$/**L17** in THF (0.5 mL) at 4 °C for 72 h. Concentration of the reaction mixture and purification by silica gel chromatography (hexanes with 1% $NEt_3$ : EtOAc 100:0→90:10) gave 43.0 mg (81%) of **(*S*)-3c** as a colorless oil. **Chiral GC analysis**: 81% ee, Cyclodex-B column (30 m x 0.25 mm ID x 0.25 um film), 120 °C, FID detector, $t_R$ = 25.5 min (minor), $t_R$ = 25.8 min (major). $[\alpha]_D^{25}$ = +51 (c 0.72, $CHCl_3$). $^1$H and $^{13}$C NMR data were consistent with the values reported above.

**Silapyrrolidine (*S*)-3h**




Following the general procedure, (silylmethyl)amine **2c** (64.6 mg, 0.253 mmol) was reacted with [Ir(cod)Cl]$_2$/**L17** in THF (0.5 mL) at 4 °C for 72 h. Concentration of the reaction mixture and purification by silica gel chromatography (hexanes with 1% $NEt_3$ : EtOAc 100:0→90:10) gave 39.4 mg (73%) of **(*S*)-3h** as a colorless oil. Enantiomeric excess of 75% ee was determined by $^1$H NMR analysis with (*S*)-*O*-acetylmandelic acid in $C_6D_6$. $[\alpha]_D^{25}$ = +38 (c 0.65, $CHCl_3$). $^1$H and $^{13}$C NMR data were consistent with the values reported above.

*5.4. Oxidation of Silapyrrolidnes*




In an $N_2$-filled glovebox, (silylmethyl)amine **2a** (53.1 mg, 0.249 mml) was weighed into a 4 mL screw-top vial. The amine was then sequentially treated with norbornene (35.3 mg, 0.375 mmol) and a freshly prepared stock solution of [Ir(cod)OMe]$_2$ (2.0 mol %) and 2,4,7-trimethylphenanthroline **L5** (5.0 mol %) in THF (0.5 mL). The vial was capped with a Teflon-lined screw cap and placed in a pre-heated aluminum heating block at 100

°C. After 17 hours, the reaction mixture was allowed to cool to rt, and the volatile materials were removed via rotary evaporation. The crude reaction mixture was dissolved in THF (2.5 mL) and sequentially treated with $CsOH \cdot H_2O$ (505 mg, 3.37 mmol), *t*-BuOOH (0.70 mL, 5.0–6.0 M in decane), and TBAF (2.5 mL, 1M in THF). The vial was sealed with a Teflon-lined screw cap, and the resulting mixture was stirred overnight at room temperature. The reaction was carefully quenched with aqueous $Na_2SO_3$ solution, and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over $Na_2SO_4$, filtered through Celite, and concentrated via rotary evaporation. The crude mixture was dissolved in DCM (3.75 mL) and triethylamine (0.88 mL) and treated with pivaloyl chloride (0.31 mL, 2.5 mmol). The vial was sealed with a Teflon-lined screw cap, and the resulting mixture was stirred overnight at room temperature. The reaction mixture was quenched with water, and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried with $Na_2SO_4$ and concentrated via rotary evaporation. Purification by silica gel chromatography (DCM : MeOH 100:0→90:10) gave 29.6 mg (49%) of **5** as a yellow oil. **$^1$H NMR** (500 MHz, $CDCl_3$) δ 4.00 – 3.89 (m, 2H), 3.06 (h, $J$ = 6.2 Hz, 1H), 2.51 (tt, $J$ = 10.5, 3.8 Hz, 1H), 1.92 – 1.80 (m, 2H), 1.76 – 1.66 (m, 2H), 1.64 – 1.55 (m, 1H), 1.31 – 1.10 (m, 12H), 1.09 – 0.96 (m, 5H). **$^{13}$C NMR** (151 MHz, $CDCl_3$) δ 178.5, 68.6, 53.9, 48.6, 39.0, 34.6, 34.2, 27.4, 26.3, 25.3, 25.3, 18.7. $^1$H and $^{13}$C NMR data were consistent with the previously reported values.[48]

*5.4. Assignment of absolute stereochemistry*

Asymmetric silylation, oxidation and protection of **2a** yielded protected amino alcohol **5** whose optical rotation value $[\alpha]_D^{25}$ was +7.8 (c 0.35, $CHCl_3$). An authentic sample of (*S*)-enantiomer of **5** was prepared according to a literature protocol[48] and determined to have an $[\alpha]_D^{25}$ value of +6.6 (c 0.48, $CHCl_3$). Therefore, the compounds **5** and **3a** were assigned to have the (*S*) absolute configuration.

## 5.5 References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