DEVELOPMENT OF ORGANOSILICON CROSS-COUPLING REACTION

BY

ZAIN YOUSAF

THESIS

Submitted in partial fulfillment of the requirements for the degree of Master of Science in Chemistry in the Graduate College of the University of Illinois at Urbana-Champaign, 2015

Urbana, Illinois

Adviser:

Professor Scott E. Denmark
Abstract

Use of palladium catalyzed cross-couplings have found widespread use in the pharmaceutical industry and there is a significant ongoing effort to either improve or devise new synthetic strategies to help build complex biologically active compounds. This is a study for advancing the use of silanols and silanolate cross-coupling in modern organic chemistry.
# Table of Contents

Chapter 1: Silanolate Cross-Coupling ................................................................................................. 1

1.1 Introduction .................................................................................................................................. 1

1.2 Nickel-Catalyzed Silanolate Cross-Coupling ............................................................................... 1

1.2.1 Background ............................................................................................................................. 1

1.2.2 Results and Discussion ........................................................................................................... 3

1.3 Palladium-Catalyzed Enantioselective Cross-Coupling ............................................................... 8

1.3.1 Background ............................................................................................................................. 8

1.3.2 Results and Discussion ........................................................................................................... 16

Chapter 2: Silanol Cross-Coupling and Synthesis of Oximidine II .................................................. 27

2.1 Introduction .................................................................................................................................. 27

2.2 Background .................................................................................................................................. 27

2.3 Results and Discussion .................................................................................................................. 32

2.4 Future Directions ............................................................................................................................ 36

Chapter 3: Stereoselective Synthesis of Tetrasubstituted Alkenes .................................................... 39

3.1 Introduction and Background ......................................................................................................... 39

3.2 Results and Discussion .................................................................................................................. 40

Chapter 4: Intramolecular Sulfenoamination of Olefins ..................................................................... 43

4.1 Introduction and Background ......................................................................................................... 43

4.2 Results and Discussion .................................................................................................................. 43

Chapter 5: Experimental .................................................................................................................. 46

5.1 General Experimental .................................................................................................................... 46
5.2 Literature Preparations .................................................................................................................. 46

5.3 Experimental Procedures .............................................................................................................. 47

Chapter 6: References .......................................................................................................................... 90
Chapter 1: Silanolate Cross-Coupling

1.1 Introduction

Palladium-catalyzed cross-coupling of silanols has proven to be a competent synthetic strategy for making C-C bonds. Previous work in silanol-mediated cross-coupling required fluoride sources as activators thus reducing the functional group tolerance and the breadth of substrates that can be utilized. Use of fluoride in particular leads to incompatibility with other silicon based functional groups. However, it has been shown that this limitation can easily be overcome by use of silanlates as coupling partners, which can be utilized directly in palladium-catalyzed cross-coupling (Scheme 1).

Scheme 1

Organosilanols or silanoates are excellent candidates as transferable groups in cross-coupling reactions for the following reasons: (i) silanols are stable and not hydrolytically labile; (ii) silanols are amenable to purification; (iii) silanols are low molecular weight compared to some of the commonly used organoboron analogues thus enhancing atom economy (iv) silanols can be readily installed into organic structures by a myriad of well-established reactions and (v) the byproducts of silanol mediated cross-coupling are innocuous and can be easily be removed by standard chromatography or distillation. These characteristics not only make silanols or silanlates excellent coupling partners in palladium-catalyzed cross-coupling but also act as excellent precursors in synthetic chemistry.

1.2 Nickel-Catalyzed Silanolate Cross-Coupling

1.2.1 Background

While the scope of organosilicon reagents as coupling partners for cross-coupling by palladium has been extensively studied, the use of other transition metals for cross-coupling remain relatively unexplored. Although there is no direct proof that organosilicon compounds can transfer their organic groups to organonickel complexes, it was implied in multiple studies by Fu and coworkers, and later the work was expanded on by Miura and coworkers. These pioneering studies involve the use of super stoichiometric amounts of fluoride salts, but demonstrated that aryl trifluorosilanes and aryl- and alkenyltrimethoxysilanes can be used to construct sp²-sp² and sp²-sp³ bonds. Since nickel is a readily available cheap transition metal
it would be highly desirable to access nickel catalyzed cross-coupling chemistry using organosilanoates. In light of the advances made by Denmark and coworkers it is hypothesized that the same strategies that helped achieve transmetalation in palladium silanol coupling could potentially be used to achieve the same result in nickel catalyzed cross-coupling reactions because of the similarities in the reactivity of the two metals.

Previous work in the Denmark group has focused on the preparation of standard complexes which represent the pre- and post- transmetalated complexes with the catalytic cycle. Attempts at isolating the post transmetalated complexes results in the isolation of cross-coupled product which gives credence to the idea that once a transmetalated complex is formed it should readily give the cross-coupled product (Scheme 2).

Scheme 2

Organonickel-silanolate complexes 5-10 were prepared which are analogous to the intermediate in the palladium-catalyzed cross-coupling reaction (Figure 1). Unfortunately, any attempts to transmetalate these complexes by heating proved unsuccessful. The X-ray crystal structures show that these complexes are square planar at Ni with slightly smaller dihedral angles in comparison to organopalladium silanolate complexes (Pd-O-Si = 142.2°, Ni-O-Si = 141.5°), lending support to the idea that similar methodology for transmetalation should be possible.

Figure 1. Pre-transmetalation complexes
A preliminary survey done by Dr. Milicevic of solvents, additives and ligands provided a maximum yield of 30% using 50 mol % of Ni(cod)$_2$, styryl silanolate and iodocyclohexane (Scheme 3).\(^8\)

**Scheme 3**

```
  11 + 12 \rightarrow 13 (30%)  
  \[ \text{50 mol \% Ni(COD)$_2$} \]
  \[ \text{Bipy, Dioxane, rt, 15 h} \]
```

Though the metal complexes made by Dr. Milicevic did not transmetalate to give sp$^2$-sp$^2$ coupling product, she did showed in her survey that sp$^2$-sp$^3$ cross coupling is possible through the use of nickel. Since the catalyst loading is much higher than the maximum yield observed by GC the reaction cannot not be categorized as catalytic. With these results in mind the aim of the project was set to explore nickel mediated cross-coupling using different nickel sources, solvents, temperature and ligands using silanate 15 and alkyl halide 14a (Scheme 4).

**Scheme 4.**

```
  TMS$\stackrel{\text{Cl}}{\longrightarrow}$Cl + C$_9$H$_{17}$\(\text{Si}\text{OK}\)
  \[ \text{Ni(0)/Ni(2), Ligand} \]
  \[ \text{Solvent, T, time} \]
  \[ \text{Me$_3$Si$\longrightarrow$C$_9$H$_{17}$} \]
```

**1.2.2 Results and Discussion**

In order to avoid side reactions commonly associated with metal-mediated cross coupling such as β-hydride elimination, the alkyl halide chosen initially for this study did not have β-hydrogens. The silanol 19 was synthesized from alkyne 17 in two simple steps. Diisobutylaluminium hydride reduction of dec-1-ynyl and capture with iodine gave alkenyl iodide 18. Lithiation and capture with 2,2,4,4,6,6-hexamethyl-1,3,5,2,4,6-trioxatrisilinane gave silanol 19 (Scheme 5).\(^9\) The silanol can be simply converted to the potassium silanolate 15 by reacting with KH under inert atmosphere in the solvent of choice.

**Scheme 5.**

```
  C$_9$H$_{17}$\(\text{\longrightarrow}^{-}\)
  17
  1. DIBAL (1 equiv)
  hexane, 0 °C to 50 °C, 2 h
  2. I$_2$ (1 equiv)
  THF, -78 °C to rt
  C$_9$H$_{17}$\(\text{\longrightarrow}^{-}\)
  18 (53%)
  1. t-BuLi (2 equiv)
  Et$_2$O, -78 °C, 1 h
  2. \(\text{SiO}_2\)
  \(-78 \text{°C to rt, 3 h} \)
  C$_9$H$_{17}$\(\text{\longrightarrow}^{-}\)
  19 (84%)
  19 (84%)
```

For the initial screening, a set of ligands and solvents most commonly associated with nickel catalysis were chosen to include a range of sterically and electronically diverse properties (Table 1) (See
In toluene and THF, the silanolate almost exclusively converted into disiloxane 20 (entries 1-4). Dioxane was chosen for further optimization because it showed traces of product and it did not have the major problem of disiloxane formation (entries 5-11) associated with other solvents (See Supporting information, S23 for further details). As seen in the work done by Dr. Milicevic once transmetalation occurs the product forms readily but the intermediate nickel-silanolate complexes when subjected to heat showed no sign of transmetalation, thus it is reasonable to assume that the transmetalation is the rate determining step. Due to this reason, higher temperature was used for the initial survey but due to disiloxane formation across all solvents the temperature for later studies was reduced to room temperature.

Table 1 Solvent Screen

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>Ligand</th>
<th>15 (%)</th>
<th>16 (%)</th>
<th>Disiloxane 20 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>PCy₃</td>
<td>10</td>
<td>0.0</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>JohnPhos</td>
<td>0</td>
<td>0.0</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>PCy₃</td>
<td>0.0</td>
<td>trace</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>JohnPhos</td>
<td>0.0</td>
<td>0.0</td>
<td>91</td>
</tr>
<tr>
<td>5</td>
<td>Dioxane</td>
<td>PCy₃</td>
<td>80</td>
<td>trace</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>Dioxane</td>
<td>JohnPhos</td>
<td>87</td>
<td>0.0</td>
<td>10</td>
</tr>
<tr>
<td>7</td>
<td>Dioxane</td>
<td>XPhos</td>
<td>77</td>
<td>0.0</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>Dioxane</td>
<td>RuPhos</td>
<td>84</td>
<td>trace</td>
<td>14</td>
</tr>
<tr>
<td>9</td>
<td>Dioxane</td>
<td>dppe</td>
<td>81</td>
<td>trace</td>
<td>13</td>
</tr>
<tr>
<td>10</td>
<td>Dioxane</td>
<td>dpdf</td>
<td>85</td>
<td>0.0</td>
<td>11</td>
</tr>
<tr>
<td>11</td>
<td>Dioxane</td>
<td>rac-BINAP</td>
<td>91</td>
<td>0.0</td>
<td>6</td>
</tr>
</tbody>
</table>

a All reactions were performed on 0.1 mmol of 15 and 14a unless otherwise noted. b Yield based on GC analysis relative to an internal standard (dodecane).

To study the effect of the halide on the cross coupling, 14b and 14c were synthesized by simple displacement of chlorine in 14a using the appropriate halogen salt and phase transfer catalyst (Scheme 6).
The survey employed the same set of ligands for better comparison to initial study (Table 2) (See page 88 for full details). The study yielded no desired product under the tested conditions.

**Table 2 Screen of Coupling Partner**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Halogen</th>
<th>Ligand</th>
<th>15 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>16 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Disiloxane 20 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>PCy&lt;sub&gt;3&lt;/sub&gt;</td>
<td>41.2</td>
<td>0.0</td>
<td>57.4</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>JohnPhos</td>
<td>30.3</td>
<td>0.0</td>
<td>65.4</td>
</tr>
<tr>
<td>3</td>
<td>I</td>
<td>PCy&lt;sub&gt;3&lt;/sub&gt;</td>
<td>55.6</td>
<td>0.0</td>
<td>40.3</td>
</tr>
<tr>
<td>4</td>
<td>I</td>
<td>JohnPhos</td>
<td>48.9</td>
<td>0.0</td>
<td>48.7</td>
</tr>
</tbody>
</table>

<sup>a</sup> All reactions were performed on 0.1 mmol of 15 and 14b-c unless otherwise noted. <sup>b</sup>Yield based on GC analysis relative to an internal standard (dodecane).

Since a trimethylsilyl methyl group is similar in size to a neopentyl group, it is reasonable to assume that the steric bulk could be inhibiting the reaction. The coupling partner was changed to a more reactive and less sterically encumbered benzyl substituent, which also does not have β hydrogens to avoid β hydride elimination (Table 3). Changing the substituent from trimethylsilyl methyl to benzyl had no effect on the amount of product observed, but changing chlorine to bromine there is a large increase in disiloxane formation (entries 1-4) (See page 88 for full detail).

**Table 3 Screen with Benzyl Halides**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Halogen</th>
<th>Ligand</th>
<th>15 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>22 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Disiloxane 20 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>PCy&lt;sub&gt;3&lt;/sub&gt;</td>
<td>0.0</td>
<td>trace</td>
<td>95.2</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>JohnPhos</td>
<td>0.0</td>
<td>trace</td>
<td>94.3</td>
</tr>
<tr>
<td>3</td>
<td>Cl</td>
<td>PCy&lt;sub&gt;3&lt;/sub&gt;</td>
<td>32.6</td>
<td>0.0</td>
<td>66.3</td>
</tr>
<tr>
<td>4</td>
<td>Cl</td>
<td>JohnPhos</td>
<td>62.3</td>
<td>trace</td>
<td>30.5</td>
</tr>
</tbody>
</table>

<sup>a</sup> All reactions were performed on 0.1 mmol of 15 and 21a-b unless otherwise noted. <sup>b</sup>Yield based on GC analysis relative to an internal standard (dodecane).

Due to limited success and products only found in trace amounts, different sources of nickel were explored. A survey with all the previous halides was performed with Hartwig’s catalyst [(dppf)Ni(cinnamyl)]Cl which has been used previously in Suzuki coupling though employing very different coupling partners than are used for this study (Table 4) (See page 89 for full detail).<sup>11</sup> This survey also yielded no product.
Table 4 Survey of cross coupling using Hartwig’s Catalyst as nickel source

<table>
<thead>
<tr>
<th>entry</th>
<th>Halogen</th>
<th>R</th>
<th>15 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Disiloxane 20 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Product (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I</td>
<td>Me₃SiCH₂</td>
<td>42.5</td>
<td>55.8</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>Me₃SiCH₂</td>
<td>47.5</td>
<td>51.6</td>
<td>0.0</td>
</tr>
<tr>
<td>3</td>
<td>Cl</td>
<td>Me₃SiCH₂</td>
<td>68.1</td>
<td>29.5</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>PhCH₂</td>
<td>33.4</td>
<td>65.3</td>
<td>trace</td>
</tr>
<tr>
<td>5</td>
<td>Cl</td>
<td>PhCH₂</td>
<td>66.9</td>
<td>31.7</td>
<td>0.0</td>
</tr>
</tbody>
</table>

<sup>a</sup> All reactions were performed on 0.1 mmol of 15 and 14a-c or 21a-b unless otherwise noted. <sup>b</sup> Yield based on GC analysis relative to an internal standard.

NiBr₂·diglyme was also employed because of its use in Suzuki coupling for the generation of sp²-sp³ C-C bonds (Table 5) (See page 89 for further detail).<sup>12</sup> The GC analysis of the reaction mixtures showed only traces of the desired product.

Table 5 NiBr₂·Diglyme Screen<sup>a</sup>

<table>
<thead>
<tr>
<th>entry</th>
<th>Halogen</th>
<th>Ligand</th>
<th>15 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>22 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Disiloxane 20 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>PCy₃</td>
<td>10.2</td>
<td>0.0</td>
<td>85.3</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>JohnPhos</td>
<td>14.3</td>
<td>trace</td>
<td>83.8</td>
</tr>
<tr>
<td>3</td>
<td>Cl</td>
<td>PCy₃</td>
<td>55.3</td>
<td>trace</td>
<td>42.5</td>
</tr>
<tr>
<td>4</td>
<td>Cl</td>
<td>JohnPhos</td>
<td>64.1</td>
<td>trace</td>
<td>34.9</td>
</tr>
</tbody>
</table>

<sup>a</sup> All reactions were performed on 0.1 mmol of 15 and 21a-b unless otherwise noted. <sup>b</sup> Yield based on GC analysis relative to an internal standard.

Nickel catalyzed silanolate cross-coupling, though challenging, is still open to further exploration. Dr. Milicevic’s work has shown that sp²-sp³ cross coupling using nickel is possible but different conditions and substrates still need to be tested. So far the conditions tested have been inspired from palladium catalyzed silanolate cross-coupling but a possible future direction is the use of conditions that have been employed in other cross-coupling reactions employing nickel as the metal catalyst.<sup>13-23</sup> Some of the nickel sources, solvents, and additives employed in nickel based cross-coupling, categorized by the specific cross-coupling reaction are as follows:
• Negishi conditions:
  \( \text{NiBr}_2 \cdot \text{diglyme/iPrPyBox/DMA} \)
  \( \text{NiCl}_2 \cdot \text{glyme/BnCH2PyBox/NaCl/DMA/DMF} \)
  \( \text{Ni(acac)}_2 / \text{LiI/THF} \)
• Suzuki conditions:
  \( \text{NiI}_2 / \text{aminocyclohexanol/NaHMDS/iPrOH} \)
  \( \text{NiCl}_2 \cdot \text{glyme/dimethylcyclohexanediamine/KOtBu/iBuOH/Dioxane} \)
  \( \text{Ni(cod)}_2 / \text{dimethylbis(p-CF}_3\text{C}_6\text{H}_4)\text{ethanediamine/KOtBu/iBuOH/iPr}_2\text{O} \)
• Hiyama conditions:
  \( \text{NiCl}_2 \cdot \text{glyme/norephedrine/LiHMDS/H}_2\text{O/CsF/DMA} \)
  \( \text{NiCl}_2 \cdot \text{glyme/dimethylbisphenylethanediamine/TBAT/Dioxane} \)
  \( \text{NiBr}_2 \cdot \text{diglyme/bathophenanthroline/CsF/DMSO} \)

These conditions could act as a good starting point for future investigation into silanolate cross-coupling using nickel. The successful combination of solvent, nickel sources and additives could be used to survey different coupling partners for \( \text{sp}^2 \)-\( \text{sp}^3 \) cross coupling reactions. Unfortunately due to the lack of any product being observed during the course of this survey, the project was put on hold.
1.3 Palladium-Catalyzed Enantioselective Cross-Coupling

1.3.1 Background

The biaryl structural motif is a widely used structural element which is found in various ligands used for asymmetric catalysis and found in various biologically active natural products such as vancomycin. The chirality possessed by these compounds originates from the restricted rotation of the two aromatic rings along the Caryl-Caryl single bond. Because of their widespread use, a variety of synthetic methods have been employed for their atroposelective construction. The major strategies that are most commonly used are desymmetrization, catalytic asymmetric synthesis, and kinetic resolution. Although the catalytic construction of biaryl systems is the most efficient and atom economical approach, no single protocol exists that can be effectively applied in all scenarios to give high yields and enantioselectivities.

The most common catalytic approaches to form the chiral biaryls reported in the literature include SNAr, Kumada, Negishi and Suzuki coupling. The Suzuki reaction is currently the most practiced reaction because of broad functional group tolerance, ease of handling of reagents and low levels of toxicity.

The first ligand-controlled catalytic asymmetric synthesis of biaryls was reported by Kumada and coworkers in 1975 and 1977 using chiral phosphines and nickel catalysis. The best results the authors reported was a poor ee of 4% but it inspired later work in the field (Scheme 7).

Scheme 7.

In 1988, Ito and coworkers showed that a monodentate phosphine ligand (S)-(R)-PPFOMe with a ferrocene framework increased the yields and enantiopurity of nickel catalyzed cross-coupling (Scheme 8). The ligand imparts stereoselectivity presumably by the organized coordination of magnesium in the Grignard reagent with the methoxy group during the transmetalation step. In the absence of the methoxy group on the ligand all asymmetric induction is lost. It was also found that the steric bulk around the newly formed C-C bond increases the enantiomeric composition of the product.
Crepy and coworkers in 2000, reported the use of Suzuki coupling for the synthesis of biaryls (Scheme 9). The authors found that the dimethylamino analogue of the (S)-(R)-PPFOMe was more effective for asymmetric induction due to stronger coordinating ability of nitrogen as opposed to oxygen but the authors could not explain the lower yields associated with the new ligand as compared to the work of Ito and coworkers.

The same dimethylamino moiety also appeared in an independent paper published by Buchwald and coworkers (Scheme 10). For the first time sensitive functional groups such as phosphonates and nitro groups could be tolerated but the substrate scope was only limited to compounds that contained those functionalities.
In 2001, Miura reported the palladium-catalyzed cross-coupling using aryl halides and α,α-disubstituted arylmethanols (Scheme 11).\(^{38}\) The cleavage of the disubstituted arylmethanols produce acetone as a side product and an enantiomerically-enriched, hindered biaryl as the desired product.

**Scheme 11.**

![Scheme 11 Diagram](image)

A C\(_2\)-symmetric bishydrazones ligand was employed by Fernandez and coworkers for Suzuki coupling to form biaryls in excellent yields and enantioselectivities (Scheme 12).\(^{37}\) The reactions were performed at room temperature to increase enantioselectivity and avoid deborylation and homocoupling, however the reaction time was significantly increased.

**Scheme 12.**

![Scheme 12 Diagram](image)

A detailed mechanistic study of the formation of biaryls in Suzuki coupling using KenPhos as the ligand was published by Buchwald and coworkers in 2010 (Scheme 13).\(^{39}\) In an alternative mechanistic hypothesis the authors propose that the electron rich phosphonate in the model system at α-position on one of the substituents binds to the palladium in the transition state and is essential for asymmetric induction.

**Scheme 13.**

![Scheme 13 Diagram](image)
The main limitations in these methods is the long reaction time. At higher temperature, the reaction rates improve dramatically but in view of the low rotational barrier, atropisomerization becomes a major problem. If temperatures are lowered the enantioselectivity improves but often leads to lowering of yield. Keeping these limitations in mind new ligand design for the construction of these versatile and important systems is clearly required to advance the field.

Previous work in the group done by Dr. Chang using organosilanolates is summarized below. Compared to the Suzuki coupling the silanolate coupling greatly reduces the reaction time while matching or improving the reaction yields and enantioselectivity. The 2,5-diphenylpyrrolidine hydrazone ligand afforded the highest yield and stereoselectivity and thus was chosen for further optimization (Scheme 14).

Scheme 14.

New C2-symmetric ligands were synthesized based on 2,5-diphenylpyrrolidine hydrazone ligand by adding electron donating, electron withdrawing groups and changing the substitution pattern on the phenyl group. These ligands were then tested for correlation between these changes to yields or enantioselectivities (Scheme 15). Unfortunately, no clear pattern was immediately evident from the results.
Mechanistic insights were gained with regards to the catalytic cycle and the stereodetermining step by doing donor acceptor reversal experiments (Scheme 16). Binaphthyl 39a is obtained as (R)-configured isomer by both reactions with the exact same er 95:5 (Scheme 16, Eq 1-2). Furthermore the exact same er is observed when the transmetalating agent is an aryl-borate in the Suzuki coupling reaction (Scheme 16, Eq 3). These observations lead to the conclusion that the reaction must be proceeding through a common intermediate. This step is the stereodetermining step and must be after the transmetalation step since the er is same going from a silicon transmetalating agent to a boronate coupling partner.

Scheme 16.
The proposed catalytic cycle (Figure 2) consistent with Pd(II)/Pd(0) chemistry reveals that the reductive elimination step is the only intermediate in which the naphthyl groups have no memory of origin either from donor or acceptor. On this basis it is proposed that the reductive elimination step is the stereodetermining step.

![Proposed mechanism for palladium catalyzed biaryl silanolate cross-coupling.](image)

**Figure 2.** Proposed mechanism for palladium catalyzed biaryl silanolate cross-coupling.

Based on the results of these ligand screens and mechanistic insights a high level computational study was performed on the diastereomeric complexes that are invoked as intermediates in the stereodetermining steps by Houk and Liu at UCLA. The minimum free energy analysis shows that electron withdrawing groups on the phenyl compared with just phenyl on the ligand have a more pronounced π-π interaction in the transition state that leads to the minor product between the aromatic ring on the ligand and the substituents (Figure 3).
Figure 3. Transition structures for diarylpalladium complex of 4-trifluorophenyl substituted bis-hydrazone ligand and phenyl bis hydrazine ligand.

The Hammett plot with respect to arylsilanolate was shown to have a negative gradient ($\rho = -1.11$) which means there is a partial positive charge developing in the transition state. Withdrawal of electron density through the $\pi-\pi$ interaction likely leads to lowering of the transition stage energy of the intermediate that leads to the minor product which is responsible for lower er. If this interaction could be further reduced, the enantioselectivity should increase. With that information in mind it is envisioned that a cyclohexyl-substituted ligand 41 would be able to further increase the selectivity by removing the $\pi-\pi$ interaction (Figure 4).

Figure 4. The 2,5-dicyclohexylpyrrolidine based bishydrazone ligand.

The retrosynthesis of 2,5-dicyclohexylpyrrolidine based bishydrazone ligands was envisioned as a hydrogenation step being introduced before or after Corey-Itsuno reduction or after capture of mesylate 45 with hydrazine in the synthesis of 2,5-diphenylpyrrolidine hydrazone ligand and rest of the synthesis carried out as shown (Scheme 17).
First strategy employed was the synthesis of cyclohexyl diketone and its reduction using Corey-Ituno reduction (Scheme 18). The reduction of cyclohexyl diketone afforded 57:43 enantiomeric ratio which is surprising because phenyl reduction affords >99:1 enantiomeric ratio. This is counter intuitive because cyclohexyl is more bulky than a phenyl group. However similar discrepancies have been reported previously in the literature.

The strategy was therefore changed to reducing the phenyl groups in one of the intermediate steps. The hydrogenation of 1-aminopyrrolidline 46 failed due to extrusion of nitrogen resulting in the formation of a four membered ring. Any attempts to protect the amine made it too bulky which led to no reaction. (Scheme 19). However previous work in the group showed that diol 44 could be hydrogenated using rhodium catalysis.
With these results in mind the aim of the project is to successfully synthesize the 2,5-dicyclohexylpyrrolidine based bishydrazone ligand and test it with palladium catalyzed cross-coupling of aryl silanlates. If an increase in er is observed the steric space around the cyclohexyl ligand could be explored to further improve er and yields.

1.3.2 Results and Discussion

The reaction conditions for hydrogenation of 44 were optimized to give 74% yield of the cyclohexyl diol 54 with >99:1 er and 93:7 dr (the er and dr of the cyclohexyl diol 54 was measured by forming a Mosher’s ester derivative) followed by converting to the corresponding mesylate 55 (Scheme 20).

Scheme 20.

The diphenyl mesylate 55 is extremely reactive and decomposes upon heating up to 40°C or when put under high vacuum whereas the dicyclohexyl mesylate 55 is stable up to 80°C and does not decompose even when put under high vacuum. Displacement of dimesylate 55 with hydrazine was attempted for formation of the five-membered pyrrolidine ring. This required high temperatures and the disubstituted hydrazines are sensitive functional groups which can eliminate nitrogen resulting in a variety of side products. Attempts to capture with pure hydrazine resulted in a mixture of products which decomposes on silica. Without the ability to individually identify the side products further optimizations were not attempted.

An alternative strategy is to use the bistriflate of the diol 54 which is a much better leaving group and should make trapping with hydrazine easier. Because triflates are better leaving groups, after the first triflate is formed the intramolecular displacement by the second hydroxyl group is much faster and results almost exclusively in the formation of dicyclohexyl tetrahydrofuran (Scheme 21). Consequently the bistosylate of the diol 54 which has similar leaving group potential as the mesylate was envisioned but the
second tosylation is too slow and like the triflate derivative the second hydroxyl does an intramolecular displacement forming the dicyclohexyl tetrahydrofuran.

Scheme 21.

![Scheme 21](image)

To overcome this problem thionyl chloride was used for capturing the diol to cyclic sulfate 56 which could be oxidized to form the corresponding cyclic sulfate 57 (Scheme 22).\(^{43}\)

Scheme 22.

![Scheme 22](image)

Deprotonated hydrazine was tested to promote the displacement of sulfate 57 under mild conditions. Hydrazine can be deprotonated using \(n\)-BuLi to form the lithium hydrazine but attempts to displace sulfate 57 with lithium hydrazine failed because of its low solubility in THF or because the lithium-nitrogen bond is too covalent.\(^{44}\) Reaction of 57 with simple hydrazine resulted in complex mixtures with lots of decomposition observed by \(^1\)H NMR and even after some optimization did not yield any product and instead yielded 59 in 15% yield (Scheme 23). Lowering the temperature should decrease the number of side products and N-N cleavage but the starting material is insoluble below 65 °C.

Scheme 23.

![Scheme 23](image)

Mass spectroscopy analysis of the crude reaction mixture showed a mass peak corresponding to the hydrazine product 58 (Scheme 23). A test reaction was performed on the crude reaction mixture of sulfate displacement with hydrazine using glyoxal and a small amount of mono glyoxal product 60 was isolated.
giving only a 4% yield over two steps (Scheme 24). Thus synthesizing hydrazine 58 neatly with little to no N-N cleavage is the challenge in the synthesis of C2-symmetric dicyclohexyl bishydrazone ligand.

Scheme 24.

![Scheme 24](image)

It was envisioned that the cyclic sulfate 56 and mesylate 55 could be subjected to a range of alternative nitrogen containing nucleophiles to install the proper functionality which could be converted by first a deprotection followed by installation of a nitroso group and reduction of the nitroso group should reveal the dicyclohexyl pyrrolidine hydrazine 58 (Figure 5).

![Figure 5](image)

Figure 5. Proposed synthesis of hydrazine 58 by displacement.

Allyl amine was first employed for opening up cyclic sulfate 57 or displacing the mesylate 55 at room temperature using triethylamine as base but only starting materials were recovered from the reactions. Heating the solutions at 55 °C for extended amounts of time only resulted in decomposition of the starting material but no product was observed by 1H NMR at any point during the reaction.

The same strategy was employed using benzylamine but even under optimized conditions benzyl protected cyclohexyl pyrrolidine 61 was isolated in only 4% yield (Scheme 25).

Scheme 25.

![Scheme 25](image)
Other nucleophiles tested were TsNHNa and NaN₃ but in all cases no product was observed. Despite all the efforts no viable method could be identified for the synthesis of the desired product so alternate routes for accessing the biscyclohexyl pyrrolidine were explored.

Previous attempts to hydrogenate the diphenyl pyrrolidine hydrazine 46 failed due to elimination of nitrogen gas from hydrazine or lack of reactivity for protected hydrazine analogue 51. It was envisioned that protected diphenyl pyrrolidine amine could be tested for hydrogenation. The resulting amine could then be deprotected, nitrosated, and reduced to give the desired hydrazine product 58 (Figure 6).

![Figure 6. Proposed synthesis of hydrazine 58 from phenyl pyrrolidine.](image)

Capture of the diphenyl mesylate 45 worked extremely well with allyl amine to give the diphenyl pyrrolidine 62 in 82% yield and subsequently the protected amine was deallylated using Wilkinson’s catalyst to give pyrrolidine 63 in 86% yield (Scheme 26). But when this unprotected amine was subjected to hydrogenation using rhodium on alumina no hydrogenation product was observed.

Scheme 26.

The free amine could be poisoning the catalyst, a protecting group that decreases the nucleophilicity of the basic amine should help with the hydrogenation. So the pyrrolidine 63 was protected with a Boc group using Boc anhydride and DMAP to give the protected pyrrolidine 64 in 88% yield and optimized conditions for the hydrogenation of the diphenyl pyrrolidine gave the dicyclohexyl pyrrolidine 65 in 82% yield using 10% rhodium trichloride as a catalyst (Scheme 27).

Scheme 27.
The Boc group was removed using TMSI which gave cyclohexyl pyrrolidine \(59\) in 52\% yield. Though when TMSI was replaced with TFA it gave near quantitative yield of the cyclohexyl pyrrolidine \(59\) (Scheme 28). The pyrrolidine \(59\) was then successfully nitrosated using sodium nitrite and p-toluenesulfonic acid to give the nitrosoamine \(66\) in 76\% yield as a white crystalline solid (Scheme 28).

Scheme 28.

Unfortunately the reduction of the nitroso compound was not as easy as envisioned. When attempted to reduce the nitrosoamine with diisobutylaluminum hydride or lithium aluminum hydride at room temperature there was no reaction and only starting material was recovered. When refluxed with LAH there was significant N-N cleavage but a small amount of hydrazine product was observed. After significant optimization of the equivalence and concentration the desired product was only obtained in 2:1 mixture of hydrazine \(58\) and amine \(59\) along with some decomposition side products which could not be purified because hydrazine product \(58\) is not amenable to alumina or silica column.

Similar results were obtained when the nitrosamine \(66\) was reacted with different reducing agents such as Zn/AcOH, LAH with microwave irradiation and TiCl\(_3\) at different pH (Table 6).\(^{46}\) It has been shown in the literature previously that the presence of a bulky substituent \(\alpha\) to the nitrosamine functional group results in the inactivation of the group towards reduction and instead results predominantly in cleavage of the N-N bond.\(^{47,48}\) It is hypothesized that the process of N-N cleavage involves first the protonation of the basic nitrogen followed by elimination of NO\(^-\) though there are reports of N-N cleavage over NO reduction in neutral conditions using palladium on carbon or palladium on alumina.\(^ {47}\)
Table 6. Nitrosamine 66 reduction

<table>
<thead>
<tr>
<th>entry</th>
<th>Reductant (equiv)</th>
<th>solvent</th>
<th>Temp(°C)</th>
<th>66:58:59&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Zn/conc. HCl (4/8)</td>
<td>H₂O-EtOH (1/10)</td>
<td>rt</td>
<td>50:25:25</td>
</tr>
<tr>
<td>2</td>
<td>Zn/conc. HCl (8/32)</td>
<td>H₂O-EtOH (1/4)</td>
<td>rt</td>
<td>33:33:33</td>
</tr>
<tr>
<td>3</td>
<td>Zn/1M HCl (100/26)</td>
<td>H₂O-EtOH (1/1)</td>
<td>rt</td>
<td>67:0:33</td>
</tr>
<tr>
<td>4</td>
<td>Zn/6M HCl (8/32)</td>
<td>H₂O-EtOH (2/3)</td>
<td>rt</td>
<td>0:75:25</td>
</tr>
<tr>
<td>5</td>
<td>Zn/AcOH (8/6)</td>
<td>EtOH</td>
<td>rt</td>
<td>67:0:33</td>
</tr>
<tr>
<td>6</td>
<td>DIBAL (3)</td>
<td>DCM</td>
<td>rt</td>
<td>100:0:0</td>
</tr>
<tr>
<td>7</td>
<td>LAH (1.5)</td>
<td>THF</td>
<td>rt</td>
<td>100:0:0</td>
</tr>
<tr>
<td>8</td>
<td>LAH (1.5)</td>
<td>THF</td>
<td>66</td>
<td>29:71:0</td>
</tr>
<tr>
<td>9</td>
<td>LAH (3)</td>
<td>THF</td>
<td>66</td>
<td>0:66:33</td>
</tr>
<tr>
<td>10</td>
<td>TiCl₃ pH 1 (4)</td>
<td>MeOH</td>
<td>0</td>
<td>100:0:0</td>
</tr>
<tr>
<td>11</td>
<td>TiCl₃ pH 6.8 (4)</td>
<td>MeOH</td>
<td>rt</td>
<td>100:0:0</td>
</tr>
<tr>
<td>12</td>
<td>TiCl₃ pH 1 (4)</td>
<td>MeOH</td>
<td>rt</td>
<td>73:0:27</td>
</tr>
</tbody>
</table>

<sup>a</sup> Relative ratio estimated by ¹H NMR spectroscopy normalized to a sum of 100.

Nitrosamine 66 has two bulky cyclohexyl substituents α to the nitrosamine functional group so it is not surprising that it does not react with LAH and DIBAL at room temperature and predominantly gives the amine product 59 (Table 6, entries 6-7). In the literature successful reduction of bulky α substituted nitrosamines were achieved using Zn dust with concentrated acids at low temperatures.<sup>47,48</sup> The reaction of nitrosamine 66 with Zn dust in ethanol with concentrated HCl at best showed a 1:1:1 mixture of desired product, starting material, and N-N cleavage side product (Table 6, entries 1-2). Lowering the concentrated of the acid only resulted in more N-N cleavage (Table 6, entries 3-5). Since it is a biphasic mixture the stirring rate and shape and size of vessel had a great impact on the product and side product ratio. It was a great relief when the same reaction gave the desired product almost exclusively with a small amount of amine side product 59 when the reaction was performed at -78°C in methanol (Scheme 29). The product is temperature sensitive so the quench and extraction is done with cold solutions. The hydrazine is used in the subsequent step without purification because it could not be columned, distilled, or crystalized away from the amine side product.
With a way to synthesize hydrazine 58 in almost quantitative yields the monoglyoxal condensation product 60 can easily be synthesized by stirring crude hydrazine 58 with excess glyoxal in water and THF to give the desired compound in 64% yield over 2 steps (Scheme 30). The monoglyoxal condensation product 60 when reacted with hydrazine 58 in the presence of sodium sulfate did not yield any product but when sodium sulfate is replaced with magnesium sulfate the desired product is isolated in 47% yield (Scheme 30).

With the cyclohexyl ligand finally synthesized in twelve total steps it was tested for cross coupling with the standard reagents and conditions but the reaction stalled after four hours producing the binaphthyl 39a in 15% yield and 64:36 er. Since the hydrazine product was temperature sensitive it would not be surprising if the cyclohexyl ligand was also temperature sensitive and might be decomposing under reaction conditions but when tested the ligand was stable at 70 °C for 5 hours without any decomposition. The solution changes from brown to black which is indicative that the ligand might be falling off of palladium. Increasing the ligand loading from 5% to 10% does result in complete consumption of starting material to give the binaphthyl 39a in 75% yield and 72:28 er but it takes longer for the reaction to go to full completion (Scheme 31).
Since the ligand might be falling off of palladium which could lower er, lowering the temperature could in theory increase the er. The ligand was tested again with the temperature lowered to 40 °C but resulted in very long reaction time and significant lowering of the yield to 44% and er of 55:45. The low er could be the result of the background reaction caused by palladium without the ligand since the reaction time has increased to 40 h. Alternatively (MeCN)$_2$PdCl$_2$ was used as the palladium(II) source which is known to have no background reaction thus resulting in better er but it usually gives lower yield which is hypothesized to be due to slow transmetalation of the bis-silanolate complex to convert Pd(II) to Pd(0). The use of (MeCN)$_2$PdCl$_2$ results in only 13% yield but the er is only improved to 76:24 which is not significantly different when allyl palladium chloride is used as palladium source at 70 °C (Scheme 32).

Scheme 32.

In conclusion the cyclohexyl ligand did not perform as expected resulting in lower yield and er than the previously reported highest yield of 86% and 95:5 er.

The computational studies done by the Houk group suggested that the steric bulk attached to the pyrrolidine ring is responsible for the free energy difference in two transition states for both the major and minor product. One can envision a 5,5,5-tricyclic system with limited rotation outside the plane containing the pyrrolidine ring should offer greater steric bulk and prevent the rotation of binaphthyls once the transmetalation step has taken place (Figure 7).

Figure 7. 5,5,5-tricyclic bishydrazone ligand.

Dicyclopentylpyrrolidine can be synthesized from cyclopentanone by first forming diketone 68 using copper triflate which gave the highest yield 57% (Scheme 33). Other oxidants tried were copper chloride, iron trichloride and TBACAN all of which give <20% yield. The oxidative synthesis of 1,4-
diketones is well preceded with high yields for ketones with α aryl substituents but the yields are low if the α substituent is an alkyl group especially in the case of cyclic ketones.\(^{49}\) Condensation of diketone 68 with formamide followed by reduction results in the formation of cyclopentyl formamide 69 as a 2:1 mixture of cis and trans product (Scheme 33).\(^{50}\) The two isomers can be separated using the difference in the reactivity towards hydrolysis of the amide bond to obtain racemic pyrrolidine amine 70 in 24% yield (Scheme 33). The enantiomers can be separated by forming a salt with (-)-mandelic acid as demonstrated by Ramamurthy and coworkers.\(^{50}\)

**Scheme 33.**

The racemic dicyclopentylpyrrolidine ligand was synthesized in a small amount from racemic pyrrolidine 70 by first forming the nitrosate 71 in 65% yield and conversion to corresponding hydrazine 72 in 30% yield (Scheme 34). Attempts to optimize the synthesis of hydrazine were met with failure and use of varying concentrations of HCl and acetic acid with zinc dust at -78 °C did not improve the yield of the hydrazine product. The impure reaction mixture from the reduction of nitrosamine 71 was stirred with glyoxal in THF/H\(_2\)O to give the mono condensation product 73 in 57% yield. The synthesis of the racemic ligand 67 is completed by stirring the mono condensation product 73 with of hydrazine 72 to give the desired compound in 36% yield (Scheme 34).
Due to low yields in oxidative copper coupling, material loss due to cis isomer of formamide 69 and separation of the stereoisomers, combined with difficulty in achieving clean reduction of nitrosamine 72, the scale up for further testing was deemed unviable. That coupled with disappointing results from the screening of 2,5-dicyclohexylpyrroldine bishydrazone based ligand 41, further testing on the hypothesis that decrease in π-π interaction should increase the er of the palladium catalyzed cross-coupling of binaphthyls was halted.

In conclusion it has been shown that the arene-arene interaction as predicted by the computational study might not be responsible for the low er. Though the new cyclohexyl ligand seem to be weakly coordinating so it might be binding in a monodentate fashion or rapidly equilibrating between monodentate and bidentate complexation resulting in lowering of the er. It is also possible that the presence of aromatic functionality might be necessary for the successful assembly of the binaphthyls by π-π stacking interaction and by switching to cyclohexyl ligand that interaction is lost thus resulting in longer reaction times. It might be possible to increase the er by rigidifying the pyrrolidine backbone in the form of a 5,5,5-tricyclic ligand. As seen in cyclohexyl ligand case the change in electronic space of the ligand might be an issue so a biphenyl substituted 5,5,5-tricyclic ligand 74 might be a better candidate for synthesis and testing (Figure 8). Since the ligand has an aromatic group α to it, it should not suffer from the same reactivity issues as seen in the 2,5-dicyclohexylpyrroldine bishydrazone ligand and it should be possible to synthesize the ring using similar synthetic strategies used for the synthesis of 2,5-arylpyrroldine bishydrazone ligand.
Figure 8. Biphenyl substituted 5,5,5-tricyclic ligand

Alternatively the chemical space around the cyclohexyl groups could be explored by using substituted cycloalkyl groups. Recently Fu and coworkers have shown that 2-alkyl substituted pyrrolidines can be accessed easily via nickel catalyzed Negishi coupling to generate mono substituted pyrrolidines in excellent yields and er (Scheme 35). The chemistry could be extended to generate 2,5-disubstituted pyrrolidines and the corresponding bishydrazone ligands could be synthesized using the strategies employed earlier.

Scheme 35.
Chapter 2: Silanol Cross-Coupling and Synthesis of Oximidine II

2.1 Introduction

Functionalized macromolecules, such as benzolactone macrocycles are an interesting structural motif found in biologically active compounds. Many structurally related benzolactone enamides have been isolated recently, including compounds such as oximidine, lobatamides, salicylihalamides, and other similar natural products (Figure 9). Oximidine II was first isolated and reported in the literature by Hayakawa in 1999 and exhibited selective cytotoxicity against many human cancer cell lines at ng/mL levels by inhibiting vacuo lar-type proton ATPase enzymes. Oximidine II has generated significant interest due to the difficulty in making large functionalized macrocycles and potential to serve as a basis for the discovery of chemotherapeutic anticancer agents. To date, there are two literature reports of its total synthesis, one formal synthesis, and three studies on the formation of the 12-membered macrocyclic core of oximidine II.

Figure 9. Benzolactone macrocyclic enamides.

2.2 Background

The first enantioselective total synthesis of Oximidine II was reported by Porco in 2003 (Figure 10). The key step involved a ruthenium-catalyzed ring closing metathesis to construct the macrocyclic triene core in 48% yield.
In 2004 Molander devised a formal synthesis of the same compound using a similar retrosynthetic analysis to reach common intermediate 78, but instead of using an RCM to form the macrolactone, the group reported the use of a Suzuki-Miyura cross coupling of potassium alkenyltrifluoroborate to form the benzolactone 82 in 42% yield (Scheme 36).\(^{55}\)

A second total synthesis was recently reported by Georg in 2011 after publishing his initial studies on the synthesis of oximidine II in 2003.\(^{56}\) The key step in the synthesis involved a copper-mediated reductive enyne macrocyclization to form the benzolactone core 83 in 67% yield to get to a similar intermediate as the Porco’s synthesis and finish the total synthesis using the already established pathway. (Scheme 37).\(^{56}\)
Macrocycles ranging from 8-14 membered rings are generally hard to synthesize for a number of reasons. The acyclic precursors usually have more degrees of freedom than the product which is unfavorable thus giving rise to what is known as the entropic effect. The structure and substitution pattern of the acyclic precursor also plays an important role by influencing the nonbonding interactions which can favor or disfavor the intermediate assembly. The enthalpic contributions come from: (i) Pitzer strain or torsional strain which arises from resistance to bond twisting, (ii) Baeyer strain, or angle strain that arises from deformation of bond angles, and (iii) Prelog strain or transannular strain from repulsive interactions due to eclipsing interactions during bond rotation. Presence of double or triple bonds in the acyclic precursor and the product result in reduction of degrees of freedom thus reducing the contributions of the entropic effect and transannular strain.

Macrocyclization based upon C-C bond formation was initially achieved with nucleophile- and electrophile-promoted methods. Radical and metal catalyzed cyclizations have also been reported later in the literature. Metal catalyzed cyclization include ring closing metathesis (RCM) and palladium-catalyzed cross coupling reactions using Stille, Suzuki and Hiyama reactions. The earliest reports of using cross-coupling reactions for the formation of macrocycles involved organoboron and organostannanes as the transmetalating agents. But more recently use of organosilicon has emerged as a viable alternative. The work done by our group has shown that 11-14 membered rings can be constructed with good yields using palladium catalyzed cross-coupling of organosilanol reagents (Scheme 38).

Scheme 38.

With the ability to construct 12 membered rings it was envisioned that the oximidine core can be synthesized using palladium catalyzed organosilanol cross-coupling. A test study within our group was
performed by Dr. Muhuhi to study the formation of 12-membered benzolactones containing 8-\(E\) and 10-\(Z\) diene to give the core product in 74% yield (Scheme 39).\(^{62}\)

**Scheme 39**

Synthesizing the (8\(E\), 10\(Z\))-diene containing macrolactone 91 in 74% yield is far better than Porco’s and Molander’s below 50% yield and marginally better than Georg’s 67% yield for the key step. It was envisioned that a similar strategy can be utilized for a more efficient synthesis of Oximidine II which contains an (8\(E\), 10\(Z\), 12\(Z\)) -triene. Since the Oximidine II core has a triene the cyclization yield should be even higher due to fewer degrees of freedom. In addition all the previous syntheses of Oximidine II generate the diastereomically pure diol fragment 80 from precursors that utilize asymmetric addition of an allylborane or alkyne into an aldehyde to give 92 and 93 (Scheme 40). These additions requires the use of expensive chiral additives ($3,378/mol for (+)-Ipc\(_2\)BOMe and and $4159/mol for (+)-\(N\)-Methylephedrine from Sigma Aldrich) stoichiometrically.

**Scheme 40.**

A retrosynthetic analysis was designed to intercept an advance intermediate 78 common to both the previous total syntheses and formal synthesis (Figure 11). Oximidine II can be synthesized from this intermediate by simply converting the protected alcohol to vinyl iodide followed by a Cu-mediated coupling of amide diene, as was demonstrated by Porco.\(^ {54}\) Our proposed synthesis not only has the potential to synthesize the 12-membered Oximidine II core in higher yields but can generate the same diol fragment in same number of steps using extremely cheap \(L\)-malic acid ($89/mol from Sigma Aldrich).
Figure 11. Retrosynthesis of Oximidine II.

One of the key late stage intermediates involves the formation of a seven-membered diene using ring closing metathesis (RCM). In order to ensure that such late stage RCM would work a test case study was designed using 104 as a model substrate (Figure 12). Since the product is a seven-membered ring containing a diene the RCM should predominantly result in the Z,Z-diene because the incorporation of an E-olefin would be energetically disfavored in a small ring. In order to access the intermediate compound 104, 99, 106, and 97a must first be synthesized and stitched together by forming an ester and silyl ether.

Figure 12. Retrosynthesis of model substrate 104.
Once intermediate 104 has been synthesized it can be tested for RCM using 108 and 109 (Figure 13). First generation Grubs catalyst 107 and second generation 108 were chosen because they have previously been used to make dienes.63-67

![Grubbs Catalysts](image)

**Figure 13.** Potential Grubbs Catalysts to be tested.

Danishefsky et al. in the total synthesis of Radiciol and Monocillin I demonstrated the use of 108 for the formation of a Z,E-conjugated diene 110 in 60% yield (Scheme 41).64 Use of 107 gave very low yields and the authors argue that is because of the presence of vinyl epoxide and range of functionality in the ring. The synthesis of Oximidine II by Porco also utilized 108 for ring closing of a triene to give the desired compound in 48% yield.54

**Scheme 41.**

A common problem that occurs in RCM in the presence of a dienes is a side product formation due to RCM with the internal olefin as opposed to terminal olefin, in that case usually first generation Grubb’s catalysts are known to give better yields because of their lower reactivity.63 In 2002 Paquette published a study where he analyzed the two competing pathways and concluded that the side product is formed from a ring contraction RCM on the desired product which is influenced significantly by how reactive the catalyst is.67 Since Grubb catalysts are more sensitive to sterics they are the only catalysts employed in literature for diene or triene synthesis using RCM.

### 2.3 Results and Discussion

Vinyl iodide 99 can be synthesized in 54% overall yield over 4 steps from a known literature procedure (Scheme 42).62
Retrosynthesis of the protected diol 106 was envisioned as a mono protection with TBS of ethylene glycol followed by the oxidation of unprotected alcohol. Addition of commercially available vinyl magnesium bromide should generate protected diol 119. Protection by PMB and removal of TBS should yield the desired compound with an unprotected primary alcohol (Scheme 43).

Protection and oxidation of ethylene glycol proceeds as expected to give aldehyde 116 in 69% yield over two steps (Scheme 44). The Grignard addition at 0 °C results in a low yield of only 45% but when the addition of Grignard is performed at -78 °C the desired product 119 is obtained in 69% yield (Scheme 44).

Protection of secondary alcohol 119 with PMBCl and 1.05 equivalence of NaH resulted in only 61% yield but optimization of NaH equivalence to 1.5 and use of PMBBBr instead of PMBCl results in the
desired product being isolated in 86% yield (Scheme 45). Treatment of the protected diol 120 with 1.0 M solution of TBAF results in the mono protected diol 106 isolated in 94% yield (Scheme 45).

Scheme 45.

The synthesis of dimethyl silyl chloride 97 was envisioned as an elimination from dibromobutene to generate Z-bromodiene 121 as reported in the literature. Lithium halogen exchange and capture with dimethyl silyl chloride followed by chlorination of the Si-H bond should result in the desired product 97 (Scheme 46).

Scheme 46.

However the synthesis of the diene 97 was more problematic than anticipated. The bromodiene was synthesized successfully using literature precedent to give Z/E mixture of 84:16. Because dimethyl silane is a sensitive functionality which is hydrolytically labile it was thought that the capture of lithiated diene should be first done using TMSCl for optimization. The knowledge from this study could then be applied to a more sensitive system. But lithiation of the diene followed by capture with TMSCl resulted in E/Z isomerization (Table 7, entries 1-2). In order to ensure if the isomerization is not substrate dependent the electrophile was replaced with the desired electrophile but still results in the isomerization of the diene (Table 7, entries 3-4). Similar work previously done in the group using E-diene showed retention of configuration. But when the Z-diene was used, isomerization was observed which leads to the conclusion that Z is the less thermodynamically stable isomer. Lithium species are known to be stable at the temperatures used so isomerization must be occurring during the electrophile capture.
Table 7. Testing for isomerization of Z diene in electrophile capture

<table>
<thead>
<tr>
<th>entry</th>
<th>Electrophile (equiv)</th>
<th>Temp(°C)</th>
<th>Z:E</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMSCl (2)</td>
<td>-78</td>
<td>1:1</td>
</tr>
<tr>
<td>2</td>
<td>TMSCl (2)</td>
<td>-95</td>
<td>1.5:1</td>
</tr>
<tr>
<td>3</td>
<td>(Me)₂SiHCl (1)</td>
<td>-78</td>
<td>2:1</td>
</tr>
<tr>
<td>4</td>
<td>(Me)₂SiHCl (1)</td>
<td>-95</td>
<td>2:1</td>
</tr>
</tbody>
</table>

An alternate retrosynthesis was envisioned starting from TMS alkyne and vinyl bromide and performing a Sonogashira coupling to give a protected enyne intermediate 125 (Scheme 47). The enyne 125 could then be brominated followed by lithium halogen exchange and capture with chlorodimethylsilane. The resultant alkyne could then be reduced using DIBAL to selectively give Z-diene 122b which could be chlorinated to give the desired compound 97 (Scheme 47).

Scheme 47.

The Sonagashira coupling works as expected yielding the desired compound in 62% yield (Scheme 48). However, attempts to brominate the ene-yne intermediate 125 resulted in bromination of the terminal alkene (Scheme 48). Since the bromination proceeds through a radical pathway it is not surprising that bromination predominantly occurs at the least hindered unsubstituted olefin. Attempts at iodination and chlorination of the compounds also failed to give any useful yield of the product.
In order to overcome this issue and difficulty of dealing with low molecular weight compounds 1-bromo-1-propene could be used instead of vinyl bromide 124. It will not only increase the mass thus making compounds easier to handle but also allow for easier bromination as preceded in the literature. Since the terminal alkene is going to be part of the RCM having the extra methyl group would not change the final product.

Sonogashira coupling using bromo-1-propene and TMS alkyne give the desired enyne intermediate 128 in 74% yield. Bromination of the intermediate give the desired compound 129 in a modest yield of 53% which could be lithiated and captured with chlorodimethylsilane to give silane 130 in 52% yield (Scheme 49). DIBAL reduction of the enyne results in the formation of the desired diene dimethylsilane 131 in 30% yield with Z/E ratio of 4:1 (Scheme 49). Chlorination of the silane 131 using sulfuryl chloride gives a mixture of products including the desired compound. The chlorinating agent and reaction conditions need to be optimized to predominantly give the desired product. Further optimizations are also necessary to improve the yield of lithiation followed by capture with chlorodimethylsilane and DIBAL reduction.

Scheme 49.

2.4 Future Directions

If the RCM study is successful the synthesis of Oximidine II will proceed via the retrosynthesis provided earlier (Figure 11). The silyl diene and the acetonide fragment is already part of RCM study, the only compounds that needs to be prepared are aldehyde 102 and zinc reagent 101 (Figure 11).

The aldehyde 102 can be synthesized from naturally occurring L-(-)-malic acid by first preferentially forming an ester on the carboxylic acid β to the alcohol (Scheme 49). Protection of the alcohol with TBSCI and subsequent reduction of the acid using BH₃SMe₂ should give the primary alcohol
Protection with PMBBr\textsuperscript{74} and reduction of the ester 135 to using DIBAL should yield aldehyde 102 (Scheme 50).\textsuperscript{74}

Scheme 50.

The zinc reagent 101 could be synthesized easily by doing a metal exchange with vinyl magnesium bromide.\textsuperscript{76} Alcohol 136 can be synthesized from zinc reagent 101 by addition of the organozinc reagent to the aldehyde 25 under an anti-Felkin-Ahn chelation control method developed by Walsh which uses the stereo center present in the molecule to set the newly formed stereocenter (Scheme 51).\textsuperscript{77} The TBS protecting group is important because studies by Walsh showed that the diastereomeric ratio was dependent on the steric bulk on the protecting group and high yield and dr was observed when TBS was used as a protecting group. Protection of the resulting alcohol with a MOM group followed by removal of the TBS protecting group using TBAF should generate intermediate 100.

Scheme 51.

Taking precedent from the work of Muhuhi\textsuperscript{62} and Georg\textsuperscript{56} NaHMDS can be used to form the sodium alkoxide of 100 followed by ring opening of the cyclic lactone 99 to form the ester 137 and subsequent protection of the phenol with TBSCl and imidazole. Deprotection of the MOM ether using CBr\textsubscript{4} should give intermediate 98 (Scheme 52).\textsuperscript{9}
Once compound 98 is successfully synthesized, an analogue of silyl ether 96b can be synthesized using simple amine bases, vinyl dimethylsilyl chloride 97b and unprotected alcholol 98. A ring closing metathesis employing the catalysts and optimization conditions learned from the earlier study should give 95 as a precursor to the key fluoride-activated silanol cross-coupling reaction. Once the core structure 95 is synthesized, it will be subjected to the reaction conditions optimized earlier in the model study by Muhuhi to form 6 (Scheme 53). Optimizations with respect to the fluoride source and solvent might be necessary because in the previous study THF also showed product but gave slightly lower yields and changing the hydration of the fluoride source had significant impact on the yield and selectivity of the reaction.

Scheme 53.

Oximidine II can be synthesized from compound 6 by protection of the alcohol and the total synthesis completed by simply converting the side chain alcohol to vinyl iodide followed by a Cu-mediated coupling of amide diene, as was demonstrated by Porco.54

In conclusion studies in our group have shown that Oximidine II core can be synthesized using the palladium catalyzed silanol chemistry developed in our lab. The preliminary studies also show that the key macrocycle forming reaction could give a higher yield compared to previous methods that have been applied so far. If the RCM study is successful Oximidine II could be synthesized from much cheaper starting materials and in higher yields for the key macrocyclization step than have been reported so far.
Chapter 3: Stereoselective Synthesis of Tetrasubstituted Alkenes

3.1 Introduction and Background

The alkene moiety is one of the most important functional groups in small molecules. Their versatility as useful synthetic intermediates as well as presence in important small molecules makes them an end target for a lot of synthetic transformations. And though many methods exist for stereoselective synthesis of di- and trisubstituted alkenes the synthesis of all carbon tetrasubstituted alkenes with a high degree of selectivity is still a challenging problem in organic synthesis. To this end it was envisioned that selective addition of silylborane to an asymmetric alkyne could provide access to a tetrasubstituted alkene which could then later be further functionalized by Suzuki and Hiyama cross-coupling reactions. Suginome and coworkers have previously shown that silylborane 139 can be added to phenyl-1-propyne with 93:7 selectivity (Scheme 54).

Scheme 54.

While the pinacolborane is a commonly used nucleophile in cross-coupling reactions to the best of our knowledge there is no literature report for the use of phenyldimethylsilane as a cross-coupling partner. The phenyl group could be replaced with a masked silanol which could potentially be revealed after the silaboration step thus activating the compound for a Hiyama-Denmark cross-coupling. Tertbutyl ester 142 was chosen for the steric bulk which should allow for the high selectivity of silaboration addition and the ease of removal of a tertbutyl group. This organoboron reagent can be accessed from commercially available chloro(dimethyl) phenylsilane. Lithiation of the commercially available chlorosilane and subsequent addition gives the silylborane 139. This silylborane could be treated with hydrogen chloride in the presence of aluminum chloride without cleavage of the Si-B bond. The silyl chloride could then be easily converted to the desired ester 142 by treating with the corresponding alcohol (Scheme 55).
3.2 Results and Discussion

Masked silanol 142 was synthesized over 4 steps with 47% overall yield. The silanol was then subjected to the reaction conditions described by Suginome but disappointingly the standard conditions only gave the desired alkene 143 in 67% yield and 78:22 selectivity (Scheme 56).

Suginome in 2008, showed that (allyl)PdCp could be used to selectively install silylboranes containing silylesters on terminal alkynes. Following the precedent we attempted to install silylborane 142, however no product was observed.

The low selectivity of the silylborane suggests that the phenyl group is essential for differentiating the alkyne. Previous work our lab has shown that methoxy group installed at the 2 and 4 position of the phenyl group can activate it towards cleavage and formation of silanol under mild conditions. In our system use of substituted silylboranes could give high selectivity like the parent silylborane and then cleaved off using mild acidic conditions. Silylboranes could be made by starting off from 4- or 2,4- disubstituted phenyl bromides 144a-b. Lithiation and subsequent addition to dichlorodimethylsilane results in formation of chlorosilanes 145a-b (Scheme 57). Unfortunately lithiation of the Si-Cl bond would only occur at room temperature which resulted in a rearrangement to form the more stable oxyanion.
In 2008, Hartwig showed that [Ir(cod)OMe]$_2$ complex could be used to couple silanes with B$_2$pin$_2$ but the substrates only included silanes with alkyl groups because the iridium complex is known for aromatic C-H activation and borylation.\textsuperscript{85} It was envisioned that sterically hindered 2,4,6-trisubstituted phenyl silane 147 might be bulky enough to prevent any C-H activation and could result in the formation of desired silyl borane 148. Unfortunately the strategy failed as significant C-H activation was observed (Scheme 58).

Due to lack of success in silaboration of a masked silanol the strategy was changed to exploring the use of dimethylphenylsilane as a masked silanol. In 2004, Anderson showed that vinyl silanes could be converted in situ into silanolates for Hiyama-Denmark cross-coupling.\textsuperscript{86} With this in mind the silaboration was carried out as described in literature followed by coupling with 2-bromotoluene to give the vinyl silane 149 in 63\% yield (Scheme 59).

The vinyl silane 149 was subjected to the conditions described by Anderson and co but it resulted only in protodesylation of the starting material and desired tetrasubstituted product 150 was not observed (Scheme 60).
Previous work from our lab has shown that copper(I) salts could be used to stabilize the anion generated by the desylation and the resulting complex could successfully take part in palladium catalyzed cross coupling. Unfortunately, attempts to use copper(I)iodide in conjugation with fluoride sources such as TBAF, CsF, KF.2H2O and TBAT either resulted in no observed reaction or protodesylation of the vinylsilane 149.

Due to little success in silaboration of masked silanols and failed attempts at using phenyldimethylsilane in Hiyama cross-coupling the project was not pursued any further.
Chapter 4: Intramolecular Sulfenoamination of Olefins

4.1 Introduction and Background

Nitrogen containing heterocycles are one of the most commonly found moieties in natural products and active pharmaceutical compounds.\(^{88-89}\) Size of the rings and the configuration of carbon and heteroatom substituents have a great influence on the biological properties of these compounds. Thus efforts to develop and explore strategies for selective construction of these rings have been a major focus of research in both academia and industry. As part of ongoing research in our group, the role of Lewis bases is being explored as activating agents for Lewis acids. One such Lewis base \(151\) was identified as an excellent catalyst for enantioselective sulfenoamination of olefins (Scheme 61).\(^{90}\)

Scheme 61.

Currently the role of anilines is being explored as nucleophiles for the sulfenoamination reaction. A diverse set of anilines are currently under investigation with the standard conditions to explore the substrate scope of the Lewis base catalyzed enantioselective sulfenoamination methodology. Four substrates \(153, 154, 155\) and \(156\) were identified for synthesis because of their electronic and steric properties (Figure 14)

Figure 14. Target anilines.

4.2 Results and Discussion

Dimethyl vinyl substituted aniline \(153\) was synthesized by first addition of ethynyltrimethylsilane to acetone and conversion of the resulting alcohol to its chloride equivalent \(158\) (Scheme 62).\(^{91}\)
Scheme 62.

Alkylation of aniline with propargyl chloride 158 gave the propargylaniline 159 in 72% yield. Reduction of the terminal alkyne with lindlars catalyst resulted in the formation of aniline 160 (Scheme 63).\(^{91}\)

Scheme 63.

Aniline 160 is subjected to amino-Claisen rearrangement to give the free amine 161 which was then protected with tosyl chloride to give the desired compound 153 in 15% yield over 6 steps (Scheme 64).\(^ {91-92}\)

Scheme 64.

Aniline 154, 155 and 156 were prepared via similar strategy where the corresponding aniline was first condensed with benzaldehyde to give the imine 163a-c. The imines were vinylated using a modification of the methodology developed by Ishihara and coworkers to give disubstituted anilines 164a-c (Scheme 65).\(^ {93}\)

Scheme 65.
The allyl amines 164a-c were subjected to amino-Claisen rearrangement conditions developed by Cooper and coworkers\textsuperscript{91} to give the corresponding free anilines 165a-c which were then protected with tosyl chloride to give the desired compounds 154, 155 and 156 (Scheme 66).

Scheme 66.
Chapter 5: Experimental

5.1 General Experimental

All reactions were performed in flame dried or oven dried glassware sealed under argon. All solvents used for extraction were reagent grade, and chromatography solvents were technical grade. Reaction solvents tetrahydrofuran (Fischer, HPLC grade), diethylether (Fischer, BHT stabilized ACS grade) and methylene chloride (Fischer, unstabilized HPLC grade) were dried by percolation through two columns packed with neutral alumina under positive pressure of argon. Reaction solvents hexane (Fischer, OPTIMA grade) and toluene (Fischer, ACS grade) were dried by percolation through a column packed with neutral alumina and a column packed with Q5 reactant, a supported copper catalyst for scavenging oxygen, under a positive pressure of argon. Analytical thin-layer chromatography was performed on Merck silica gel plates with phosphomolybdic acid (PMA) or aqueous KMnO$_4$ as indicator. Column chromatography was performed using Merck silica gel. Mass spectrometry (MS) was performed by the University of Illinois Mass Spectrometry Laboratory.

$^1$H, $^{13}$C, $^{31}$P and $^{19}$F NMR were recorded on Varian Unity 400 (400 MHz, $^1$H; 202 MHz, $^{31}$P), Varian Unity 500 (500 MHz, $^1$H; 125 MHz, $^{13}$C; 470 MHz, $^{19}$F), and Varian VXR 500 (499 MHz, $^1$H; 125 MHz, $^{13}$C) spectrometer. Spectra were referenced to residual chloroform (7.26 ppm, $^1$H). Chemical shifts are reported in ppm, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (hextet), dd (doublet of doublet), dt (doublet of triplet), dq (doublet of quartet) m (multiplet) and br (broad). The University Of Illinois Mass Spectrometer Center 68 performed Mass spectroscopy. ESI mass spectra were performed on a Micromass Quattro spectrometer. Data are reported in the form of (m/z). GC analysis was performed on Hewlett Packard 5890 series II and HPLC analysis on Agilent 1100 series. Analytical supercritical fluid chromatography (SFC) was performed on a Berger Instruments Packed-Column SFC with built in photometric detector (220 nm) using a Daicel Chiralpak OJ column.

Commercial Chemicals

1-decyne was bought from GFS chemicals. Rhodium trichloride was bought from pressure chemicals. All other commercial chemicals were bought from Aldrich or Alfa-Aesar.

5.2 Literature Preparations

E-1-Iododecanee 18, and silanols 19 was prepared as described in unpublished results.$^9$ Trimethylsilyl methylbromide 14b and Trimethylsilylmethyliodide 14c were prepared using the method reported in literature.$^{10}$ Hartwig’s catalyst [(dppf)Ni(Cinnamyl)Cl] was prepared using literature
procedure. Compounds 43, 44, 45, 46, 47, 48 were prepared using method reported by Fernandez group. 1-bromonaphthalene, CBS catalyst, potassium dimethyl(2-methylnaphthalen-1-yl)silanolate and TMSmethyl magnesium chloride were provided by Timothy W. Chang. Lithium hydrazine was prepared using method described in the literature. Mesylate 55 was prepared using method described in Timothy W. Chang’s thesis. 1-allyl-2,5-diphenyl pyrrolidine 62 and 2,5-diphenyl pyrrolidine amine 63 were synthesized using literature procedures. Preparation of 5,5,5-tricycloc formamide 69 and amine 70 were prepared using method described by Ramamurthy and coworkers. Acetonide 111, 112, 113, 114, and 99 was synthesized using procedures described by Muhuhi. TBS protected ethylene glycol 115 and aldehyde 116 were synthesized using a known literature procedure. Vinyl magnesium addition product 119 was prepared as described in the literature. Z-bromodiene 121, enyne 125, enyn 128, and bromo enyne 129 were prepared using known procedures. Compounds 140 was prepared as described in literature. Compounds 139, 141 and 142 were prepared as described in literature. Compounds 157, 159, 160 and 161 were prepared as reported. Compound 153 was synthesized as described. Compounds 163a, 163b and 163c were made as reported in literature.

5.3 Experimental Procedures

Preparation of (E)-Trimethyl(undec-2en-1-yl)silane (16)

![Chemical Reaction Diagram]

To a 15 mL flame dried schlenk flask in a dry box was added 58 mg (0.05 mmol, 0.05 equiv) of tetrakis(triphenylphosphine)palladium. Taken out of the dry box and cannulaed in a solution of (E)-1-iododec-1-ene (266 mg, 1.0 mmol) in 3.5 mL of THF followed by 1.25 mL of a 0.8 M solution of trimethylsilylmethyl magnesium chloride (1.0 mmol, 1.0 equiv) in ether, and the resulting mixture was stirred at room temperature for 62 h. Sat. aq. NH₄Cl (2 mL) was added followed by Et₂O (2 mL), and the layers were separated. The organic layer was washed with sat. aq. NaHCO₃ (2 mL), water (2 mL), and brine (2 mL), dried over MgSO₄ (2g), passed through florisil (2g) and concentrated to dryness in vacuo to give 250mg of a yellow oil. The residue was purified by distillation at 60°C / 0.5 mmHg and flash chromatography (silica 2 cm x 14 cm; hexanes), to afford 69 mg (31%) of 16 as a clear liquid.
Data for 16:

Mol.Formula: \( \text{C}_{14}\text{H}_{30}\text{Si} \)

\(^{1}H\) NMR: (400 MHz, CDCl\(_3\))
\( \delta \) -0.02 (s, 9 H, SiCH\(_3\)(4)), 0.88 (t, \( J = 6.4 \) Hz, 3 H, H\(_3\)C(5)) 1.18-1.36 (m, 12 H, H\(_2\)C(6-11)), 1.39 (d, \( J = 7.6 \) Hz, 2 H, H\(_2\)C(3)), 1.96 (q, \( J = 6.72, 6.80 \) Hz, 2 H, H\(_2\)C(12)), 5.24 (dt, \( J = 15.0, 7.8, 6.8 \) Hz, 1 H, HC(2)), 5.36 (dt, \( J = 15.0, 7.7, 7.0 \) Hz, 1 H, HC(1)).

TLC: \( R_f \) 0.74 (hexanes)

Preparation of (E)-undec-2en-1-ylbenzene (22)

To a 15 mL flame dried schkelnk flask in a dry box was added 58 mg (0.05 mmol, 0.05 equiv) of tetrakis(triphenylphosphine)palladium. Taken out of the dry box and cannulaed in a solution of (E)-1-iododec-1-ene (266 mg, 1.0 mmol) in 4 mL of THF followed by 1.14 mL of a 1.05 M solution of Benzyl magnesium chloride in ether (1.2 mmol, 1.2 equiv), and the resulting mixture was stirred at room temperature for 24 h. Sat. aq. NH\(_4\)Cl (2 mL) was added followed by Et\(_2\)O (2 mL), and the layers were separated. The organic layer was washed with sat. aq. NaHCO\(_3\) (2 mL), water (2 mL), and brine (2 mL), dried over MgSO\(_4\) (2g), passed through florisil (2g) and concentrated to dryness in vacuo to give 224 mg of a yellow oil. The residue was purified by distillation at 225\(^\circ\)C / 0.8 mmHg, to afford 100 mg (44%) of 22 as a clear liquid.

Data for 22:

Mol.Formula: \( \text{C}_{17}\text{H}_{26} \)

\(^{1}H\) NMR: (400 MHz, CDCl\(_3\))
\( \delta \) 0.88 (t, \( J = 6.6 \) Hz, 3 H, H\(_3\)C(4)) 1.24-1.42 (m, 12 H, H\(_2\)C(5-10)), 2.01 (q, \( J = 6.7 \) Hz, 2 H, H\(_2\)C(11)), 3.33 (d, \( J = 5.7 \) Hz, 2 H, H\(_2\)C(3)), 5.53 (dt, \( J = 9.7, 6.0 \) Hz, 2 H, HC(1-2)), 7.19 (q, \( J = 4.0, 3.5 \) Hz, 3 H, HC(14-16)), 7.33 – 7.26 (m, 2 H, HC(13) and HC(17)).

TLC: \( R_f \) 0.34 (hexanes)
Procedure for Screening ligands and solvents.

To a solution of silanol 19 (214 mg, 1.0 mmol) in 0.5 mL of the solvent used for a particular screen inside a glove box was added KH (48 mg, 1.2 mmol). Stirred until no bubbling is observed and decanted to remove excess KH. Filled up to 1 mL mark to generate 1M solution of silanolate 15. To oven dried vial added 10 mol% of Ni source and 20 mol% of ligand. Injected solution of silanolate 15 (21.4 mg, 0.1 mmol, 0.1 mL) followed by coupling partner (0.1 mmol), dodecane (15 mg) and 1 mL of solvent. The vial closed under argon with Teflon stopper and stirred for 24 h. Passed through florisil to remove metal and diluted with Et$_2$O for GC analysis.

Preparation of (1R,4R)-1,4-Dicyclohexylbutane-1,4-diol (54)

To a 100 mL glass container was added a solution of rhodium trichloride (191 mg, 0.912 mmol, 0.1 equiv) in 20 mL of H$_2$O followed by a solution of Aliquat 336 (1.76 g, 3.65 mmol, 0.4 equiv) in 10 mL of CH$_2$Cl$_2$ followed by (1R,4R)-1,4-diphenylbutane-1,4-diol (2.21 g, 9.12 mmol) in 30 mL of CH$_2$Cl$_2$. Sealed in a bomb and pressurized to 70 PSI with H$_2$. Stirred for 26 h and the remaining gas was slowly released and glass container removed from the bomb. Added H$_2$O (50 mL) and CH$_2$Cl$_2$ (50 mL) and the organic layer separated and the aqueous layer was back extracted with Et$_2$O (3 x 50 mL). The combined organic layer washed with H$_2$O (50 mL) and brine (50 mL), dried over MgSO$_4$ (5 g), concentrated to dryness in vacuo to give white black solid. The residue was purified by flash chromatography (silica, 13 cm x 5.5 cm; gradient elution, 8:1, 4:1, 2:1, 0:1, hexanes/EtOAc, 360 mL, 250 mL, 225 mL and 200 mL respectively), to afford 1.71 g (74%) of 54 as white powder.

Data for 54:

Mol.Formula: C$_{16}$H$_{30}$O$_2$

$^1$H NMR: (400 MHz, CDCl$_3$) δ 0.93-1.86 (m, 26 H, CH(2-8)), 1.99 (s, 2 H, OH(9)), 3.37 (dd, $J = 8.5, 5.4$ Hz, 2 H, HC(1)).

TLC: $R_f$ 0.12 (hexanes/EtOAc 8:1) [KMnO$_4$]
Preparation of (4R,7R)-4,7-Dicyclohexyl-1,3,2-dioxathiepane 2-oxide (56)

In a 5 mL flame dried 3-necked round bottom flask was added thionyl chloride (0.218 mL, 3.0 mmol, 1.5 equiv) followed by a solution of chiral diol 54 (509 mg, 2.0 mmol) in CCl₄ (1.5 mL). The resulting mixture was then stirred at 60 °C for 3 h. After the complete consumption of 54 on TLC, the solution was cooled to room temperature. Water (5 mL) was added followed by Et₂O (10 mL) and organic layer was separated. The aqueous layer was back extracted with Et₂O (3 x 5 mL), and the combined organic layer was washed with H₂O (3 x 5 mL), dried over MgSO₄, concentrated to dryness in vacuo to give white solid. The residue was purified by flash chromatography (silica, 21 cm x 2 cm; 18:1, hexanes/EtOAc), to afford 446 mg (74%) of 56 as a white powder.

Data for 56:

Mol. Formula: C₁₆H₂₈O₃S

¹H NMR: (400 MHz, CDCl₃)
δ 0.95-1.90 (m, 26 H, CH(2-8)), 3.86 (dd, J = 10.3, 5.5 Hz, 1 H, HC(1)), 4.72 (dd, J = 10.9, 5.7 Hz, 1H, HC(1)).

TLC: Rf 0.65 (Hexane/EtOAc 18:1) [KMnO₄]

Preparation of (4R,7R)-4,7-Dicyclohexyl-1,3,2-dioxathiepane 2,2-dioxide (57)

To a 15ml flame dried round bottom flask was added a solution of 56 (446 mg, 1.49 mmol) in CH₃CN (1.4 mL), CCl₄ (1.4 mL), H₂O (2.1 mL) and RuCl₃•nH₂O (6.15 mg, Ru = 2 mol %) and NaIO₄ (477 mg, 2.23 mmol, 1.5 equiv) and allowed to stir at room temperature for 6 h. Water (10 mL) was added followed by Et₂O (10 mL) and organic layer was separated. The aqueous layer was back extracted with Et₂O (3 x 10 mL) and the combined organic layer washed with H₂O (5 mL) and brine (2 x 5 mL), dried over MgSO₄, concentrated to dryness in vacuo to give white solid. The residue was purified by flash
chromatography (silica, 16 cm x 2 cm; 30:1, hexanes/EtOAc), to afford 390 mg (83%) of 57 as white powder.

Data for 57:

Mol. Formula: \( \text{C}_{16}\text{H}_{28}\text{O}_{3}\text{S} \)

\(^{1}H\) NMR: (400 MHz, CDCl\(_3\))
\[ \delta 1.32 \text{ – 1.03} (m, 10 H), 1.99 \text{ – 1.63} (m, 16 H), 4.42 \text{ (dq, } J = 9.1, 6.0, 5.0 \text{ Hz, 2H, OCH(1-2)}) \].

TLC: \( R_f 0.1 \) (hexane/EtOAc 30:1) [PMA]

**Determination of Stereochemistry of (1R,4R)-1,4-dicyclohexylbutane-1,4-diol (ZY2-027)**

\[
\begin{align*}
\text{Cy} & \quad \text{OH} & \quad \text{Ph} & \quad \text{O} & \quad \text{F}_3\text{C} & \quad \text{OMe} \\
\text{OH} & \quad \text{Cy} & \quad \text{N} & \quad \text{CY} & \quad \text{Ph} & \quad \text{F}_3\text{C}
\end{align*}
\]

To a 1 mL flame dried Schlenk flask was added diol 15 (4 mg, 0.016 mmol) followed by N,N-dimethylpyridin-4-amine (0.39mg, 0.003 mmol, 0.2 equiv) and 0.08 mL of Pyridine. To this solution was added (R)-(+)α-Methoxy-α-trifluoromethylphenylacetyl chloride (24 mg, 0.096 mmol, 6equiv) followed by 0.08 mL of Pyridine. Stirred at 95 °C in an oil bath for 42 h, after the complete consumption of 15 on TLC. The solution was cooled to room temperature and added CH\(_2\)Cl\(_2\) (5 mL) and 1M HCl (5 mL). the organic layer was separated and the aqueous layer was back extracted with CH\(_2\)Cl\(_2\) (3x5 mL). The combined organic layer was washed with sat. aq. NaHCO\(_3\) (3 x 5 mL), dried over Na\(_2\)SO\(_4\), concentrated to dryness in vacuo to give clear liquid (~100% yield). HPLC analysis using 99:1 Hex/i-PrOH, at room temperature, 1 mL flow on AD-H column.
Preparation of (2S,5S)-2,5-dicyclohexylpyrrolidin (61)

To a flame dried 5 mL round bottom flask was added cyclic sulphate 57 (316 mg, 1.0 mmol) and benzylamine (1.607 g, 15 mmol, 15 equiv). Stirred at 75 °C in an oil bath for 24 h. Cooled to room temperature and added 1M NaOH (50 mL) and CH₂Cl₂ (3 x 50 mL). The combined organic layer was washed with H₂O (2 x 50 mL), brine (2 x 50 mL), dried over MgSO₄ and concentrated to dryness in vacuo to give pale liquid. The residue was purified by flash chromatography (silica, 26 cm x 2 cm; gradient elution, 9:1, 4:1, hexanes/EtOAc, 400 mL and 200 mL respectively), to afford 10 mg (15%) of 61 as pale yellow liquid.

Data for 61:

Mol.Formula: C₂₂H₃₅N

¹H NMR: (400 MHz, CDCl₃)
δ 0.86 (m, 5 H), 1.20 – 1.02 (m, 6 H), 1.42 (tdt, J = 8.7, 6.2, 32.9 Hz, 3 H), 1.80 – 1.55 (m, 13 H), 2.73 (q, J = 5.5, 2 Hz, 2 H, HC(1)), 3.53 (d, J = 14.2 Hz, 1 H, HC(9)), 3.79 (d, J = 14.2 Hz, 1 H, HC(9)), 7.17 (t, J = 7.2 Hz, 1 H, HC(13)), 7.30 (dd, J = 26.3, 7.5 Hz, 4 H, HC(11-12)).

TLC: Rf 0.85 (hexane/EtOAc 9:1)

Preparation of (2S,5S)-1-allyl-2,5-Diphenylpyrrolidine (62)

To a 100 mL flame dried Schlenk flak under argon was added 1.052 g of 45 (2.64 mmol) and 39 mL of allylamine (517.44 mmol, 196 equiv) in i-PrOH bath cooled to 0 °C using a cryo cool. The solution was stirred for 20h at 0°C. Warmed to room temperature and excess allyl amine was removed under reduced pressure. To the residue was added Et₂O (70mL) and organic layer washed with sat. aq. NaHCO₃ (20 mL), brine (20 mL), dried over MgSO₄ and concentrated to dryness in vacuo to give yellow oil plus white solid.
The residue was purified by flash chromatography (silica, 16 cm x 3.5 cm; 97:3, hexanes/Et₂O), to afford 575 mg (82%) of 62 as pale yellow liquid.

**Data for 62:**

Mol. Formula: C₁₉H₂₁N

**¹H NMR:** (500 MHz, CDCl₃)

δ 1.91 (dddd, J = 13.6, 10.0, 4.9, 2.0 Hz, 2 H, HC(2)), 2.59 – 2.45 (m, 2 H, HC(2)), 2.71 (dd, J = 14.7, 7.4 Hz, 1 H, HC(3)), 2.98 (ddt, J = 14.7, 4.2, 2.0 Hz, 1 H, HC(3)), 4.33 (ddt, J = 7.7, 6.0, 3.0 Hz, 2 H, HC(1)), 4.97 – 4.85 (m, 2 H, HC(5)), 5.64 (dddd, J = 17.4, 10.3, 7.4, 4.4 Hz, 1 H, HC(3)), 7.25 (dd, J = 5.3, 2.7, 1.1 Hz, 2 H, HC(8)), 7.33 (m, 8 H, HC(6-7)).

**TLC:** Rf 0.45 (hexane/Et₂O 97:3)

**Preparation of (2S,5S)-2,5-Diphenylpyrroolidine (63)**

To a 25 mL round bottom flask under argon was added 575 mg of 62 (2.174 mmol), 10.3 mg of Wilkinson catalyst (0.022 mmol, 0.01 equiv) and a mixture of 7 mL of acetonitrile and 2 mL of water. The solution was refluxed and monitored with TLC. After 5 h the solution was cooled to room temperature and added Et₂O (20 mL) and water (10 mL). The organic layer was washed with brine (10 mL), and combined aqueous layer was back extracted with Et₂O (2 x 20mL), combined organic layer was dried over MgSO₄ and concentrated to dryness in vacuo to give yellow oil. The residue was purified by flash chromatography (silica, 16 cm x 3.5 cm; 9:1, hexanes/EtOAc), to afford 485 mg (100%) of 63 as pale liquid.
Data for 63:

**Mol.Formula:** C₁₆H₁₇N

**¹H NMR:** (500 MHz, CDCl₃)
δ 1.97 – 1.85 (m, 2 H, HC(2)), 2.08 (s, 1 H, HN(3)), 2.47 – 2.35 (m, 2 H, HC(2)), 4.60 – 4.52 (m, 2 H, HC(1)), 7.26 – 7.22 (m, 2 H, HC(6)), 7.35 (dd, J = 8.5, 6.9 Hz, 4 H, HC(5)), 7.44 – 7.40 (m, 4 H, HC(4)).

**TLC:** Rf 0.11 (hexane/EtOAc 9:1)

---

**Preparation of tert-butyl (2S,5S)-2,5-Diphenylpyrrolidine-1-carboxylate (64)**

![Chemical Structure]

To a 5 mL flame dried Schlenk flask under argon was added 112 mg of 63 (0.5 mmol), 0.5 mL of CH₂Cl₂, 6.1 mg of DMAP (0.05 mmol, 0.1 equiv) and 163.5 mg of Boc anhydride (0.75 mmol, 1.5 equiv) and the mixture was solution was stirred at room temperature for 14 h. The solution was diluted with Et₂O (20 mL) and washed with sat. aq. NaHCO₃ (2 x 10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated to dryness in vacuo to give a yellow oil. The residue was purified by flash chromatography (silica, 26 cm x 1.5 cm; 9:1, hexanes/EtOAc), to afford 143 mg (88%) of 64 as pale liquid.

Data for 64:

**Mol.Formula:** C₂₁H₂₅NO₂

**¹H NMR:** (500 MHz, CDCl₃)
δ 1.30 (s, 9 H, HC(3)), 1.88 – 1.77 (m, 2 H, HC(2)), 2.55 – 2.45 (m, 2 H, HC(2)), 5.28 (d, J = 6.8 Hz, 1 H, HC(1)), 5.36 (d, J = 7.0 Hz, 1 H, HC(1)), 7.26 (d, J = 2.2 Hz, 2 H, HC(6)), 7.27 (dt, J = 4.6, 1.8 Hz, 4 H, HC(5)), 7.36 (ddd, J = 8.5, 7.0, 2.1 Hz, 4 H, HC(4)).

**TLC:** Rf 0.07 (hexane/EtOAc 9:1)
Preparation of tert-butyl (2S,5S)-2,5-Dicyclohexylpyrrolidine-1-carboxylate (65)

To a 50 mL glass container was added a solution of rhodium trichloride (74 mg, 0.35 mmol, 0.1 equiv) in 18 mL of \( \text{H}_2\text{O} \) followed by a solution of Aliquat 336 (680 mg, 1.41 mmol, 0.4 equiv) in 8 mL of \( \text{CH}_2\text{Cl}_2 \) followed by pyrrolidine 64 (1.14 g, 3.53 mmol) in 24 mL of \( \text{CH}_2\text{Cl}_2 \). Sealed in a bomb and pressurized to 80 PSI with \( \text{H}_2 \). Stirred for 24 h and the remaining gas was slowly released and glass container removed from the bomb. Added \( \text{H}_2\text{O} \) (30 mL) and \( \text{CH}_2\text{Cl}_2 \) (60 mL) and the organic layer separated and the aqueous layer was back extracted with \( \text{CH}_2\text{Cl}_2 \) (3 x 60 mL). The combined organic layer washed with \( \text{H}_2\text{O} \) (30 mL) and brine (30 mL), dried over MgSO\(_4\), concentrated to dryness in vacuo to give black oil. The residue was purified by flash chromatography (silica, 12 cm x 3.5 cm; 8:1, hexane/s/EtOAc), to afford 970 mg (82%) of 65 as a colorless oil.

Data for 65:

Mol.Formula: \( \text{C}_{21}\text{H}_{37}\text{NO}_2 \)

\(^1\text{H NMR:} \) (400 MHz, CDCl\(_3\))
\[ \delta \text{ 1.29 – 0.91 (m, 10 H), 1.51 (s, 9 H, HC(3)), 1.87 – 1.59 (m, 14 H), 1.97 (ddt, } J = 12.5, 9.1, 4.9 \text{ Hz, 1 H, HC(2)), 2.24 (tq, } J = 12.3, 3.3 \text{ Hz, 1 H, HC(2)), 3.71 (ddd, } J = 7.0, 4.4, 2.6 \text{ Hz, 1 H, HC(1)), 3.81 (dt, } J = 6.6, 2.4 \text{ Hz, 1 H, HC(1)).} \]

TLC: \( R_f \) 0.43 (hexane/EtOAc 8:1) [KMnO\(_4\)]

Preparation of (2S,5S)-2,5-Dicyclohexylpyrrolidine (59)

To a 25 mL flame dried Schlenk flask under argon in an ice bath was added 970 mg of pyrrolidine 65 (2.89 mmol), 9 mL of \( \text{CH}_2\text{Cl}_2 \), and 1.33 mL of trifluoroacetic acid (20.24 mmol, 7 equiv). The ice bath
was removed and the solution was stirred at room temperature for 4 h. The solution was diluted with CH$_2$Cl$_2$ (10 mL) and 1M NaOH (5 mL). The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 10 mL) and combined organic layer was dried over Na$_2$SO$_4$ and concentrated to dryness in vacuo to give a yellow oil. The residue was purified by flash chromatography (silica, 12 cm x 1.5 cm; 98:1.8:0.2, CH$_2$Cl$_2$/MeOH/aq. NH$_3$), to afford 680 mg (100%) of 59 as pale liquid.

Data for 59:

Mol. Formula: C$_{16}$H$_{29}$N

$^1$H NMR: (500 MHz, CDCl$_3$)

δ 1.18 – 0.91 (m, 7 H), 1.67 – 1.56 (m, 5 H), 1.78 – 1.68 (m, 9 H), 2.03 – 1.91 (m, 5 H), 3.24 (q, $J = 8.0$ Hz, 2 H, HC(1)), 3.46 (s, 1 H, HC(3)).

MS (ESI)

236.4 (100, M+H), 234.3 (20), 205.2 (3)

TLC: $R_f$ 0.1 (CH$_2$Cl$_2$/MeOH/aq. NH$_3$ 98:1.8:0.2) [KMnO$_4$]

Preparation of (2S,5S)-2,5-dicyclohexyl-1-nitrosopyrrolidine (66)

To a 25 mL flame dried Schlenk flask under argon was added 680 mg of pyrrolidine 59 (2.89 mmol), 230 mg of sodium nitrite (3.32 mmol, 1.15 equiv), 632 mg of $p$-Toluenesulfonic acid (3.32 mmol, 1.15 equiv) and 12 mL of CH$_2$Cl$_2$. A yellow precipitate forms after ten minutes, stirred at room temperature for 5 h. The solution was diluted with CH$_2$Cl$_2$ (10 mL) and 1M NaOH (25 mL). The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 10 mL) and combined organic layer was dried over Na$_2$SO$_4$ and concentrated to dryness in vacuo to give a yellow oil. The residue was purified by flash chromatography (silica, 14 cm x 3.5 cm; 9:1, hexane/EtOAc), to afford 580 mg (76%) of 66 as a white powder.
Data for 66:

Mol. Formula: C\textsubscript{16}H\textsubscript{28}NO

\textsuperscript{1}H NMR: (500 MHz, CDCl\textsubscript{3}) 
δ 1.39 – 0.91 (m, 13H), 1.51 (s, 2H), 1.71 – 1.61 (m, 3H), 1.88 – 1.74 (m, 5H), 2.05 (dddd, J = 29.3, 11.4, 8.0, 3.6 Hz, 2H, HC(2)), 2.30 (dp, J = 12.0, 4.3, 3.5 Hz, 1H, HC(2)), 4.08 (dd, J = 6.8, 4.7 Hz, 1H, HC(1)), 4.34 (q, J = 6.5, 6.0 Hz, 1H, HC(1)).

\textsuperscript{13}C NMR: (126 MHz, CDCl\textsubscript{3}) 
δ 67.5 (C(1)), 63.0 (C(1)), 41.2 (C(2)), 38.1 (C(2)), 30.8, 29.8, 27.3, 26.9, 26.4, 25.6, 23.6

TLC: R\textsubscript{f} 0.35 (hexane/EtOAc 9:1)

Preparation of (((2S,5S)-2,5-dicyclohexylpyrrolidin-1-yl)imino)acetaldehyde (60)

To a 5 mL flame dried Schlenk flask under argon was added 100 mg of nitrosoamine 66 (0.38 mmol), 198 mg of zinc dust (3.03 mmol, 8 equiv), and 4 mL of methanol. The flask was cooled to -78 °C in an IPA/dry ice bath and slowly pipetted 0.252 mL of conc. HCl (3.03 mmol, 8 equiv). The mixture was stirred at -78 °C for 2 hours and then warmed up to 0 °C in an ice bath. Diluted with cold CH\textsubscript{2}Cl\textsubscript{2} (5 mL) and cold 1M NaOH (5 mL). The organic layer was separated and the aqueous layer was extracted with cold CH\textsubscript{2}Cl\textsubscript{2} (2 x 5 mL) and combined organic layer was dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated to dryness in vacuo to give 95mg of a yellow oil. Used immediately in next step without further purification.

To a 25 ml flame dried Schlenk flask was added 95 mg of pyrrolidine 58 (0.38 mmol) from previous step and added 5 mL THF and 1.3 mL of 40% w/w glyoxal in water (11.38 mmol, 30 equiv). The reaction mixture was stirred at room temperature for 24 h. Diluted with CH\textsubscript{2}Cl\textsubscript{2} (20 mL) and sat. aq. NaHCO\textsubscript{3} (5 mL). The organic layer was separated and the aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (2 x 20 mL) and combined organic layer was dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated to dryness in vacuo to give a pale liquid. The residue was purified by flash chromatography (silica, 26 cm x 0.5 cm; 9:1, hexane/EtOAc), to afford 70 mg (64%) of 60 as a pale oil.
Data for **60**:

Mol. Formula: \( \text{C}_{18}\text{H}_{30}\text{N}_{2}\text{O} \)

\[^{1}\text{H} \text{NMR}:\] (400 MHz, CDCl\(_3\))

\(\delta 1.41 – 0.95 (m, 13 \text{ H}), 1.51 (s, 2 \text{ H}), 1.82 – 1.63 (m, 8 \text{ H}), 1.92 (m, 4 \text{ H}), 2.10 (d, \text{ J} = 13.2 \text{ Hz}, 1 \text{ H}, \text{ HC(4)}), 3.66 (s, 2 \text{ H}, \text{ HC(3)}), 6.78 (d, \text{ J} = 7.6 \text{ Hz}, 1 \text{ H}, \text{ HC(2)}), 9.35 (d, \text{ J} = 7.6 \text{ Hz}, 1 \text{ H}, \text{ HC(1)})\).

\[^{13}\text{C} \text{ NMR}:\] (126 MHz, CDCl\(_3\))

\(\delta 191.2 (\text{C}(1)), 129.7 (\text{C}(2)), 86.1 (\text{C}(2)), 64.4 (\text{C}(3)), 39.7 (\text{C}(4)), 31.6, 30.1, 27.1, 26.6, 26.2, 24.7\)

MS (ESI)

291.5 (100, M+H), 292.5 (25), 236.4 (25), 119.3 (13)

TLC: \(R_f 0.35\) (hexane/EtOAc 9:1)

**Preparation of \(N,N'\)-bis((2S,5S)-2,5-dicyclohexylpyrrolidin-1-yl)ethane-1,2-diimine (41)**

![Chemical Structure](image)

To a 25 ml flame dried Schlenk flask was added 70 mg of mono glyoxal product \(60\) (0.24 mmol) followed by 95 mg of freshly prepared pyrrolidine \(x\) (0.38 mmol, 1.56 equiv) and 7 mL CH\(_2\)Cl\(_2\). To this solution was added 63 mg of magnesium sulfate (0.52 mmol, 2.17 equiv). The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was filtered and concentrated to dryness in vacuo to give a pale liquid. The residue was purified by flash chromatography (silica, 16 cm x 0.5 cm; 9:1, hexane/EtOAc), to afford 58 mg (47%) of \(41\) as a pale oil.
Data for **41**:

**Mol. Formula:** \( C_{34}H_{58}N_4 \)

**\( ^1H \) NMR:** (400 MHz, CDCl\(_3\))
\[ \delta 1.24 - 0.90 (m, 22 H), 1.45 (d, J = 12.4 Hz, 4 H), 1.61 - 1.52 (m, 6 H), 1.70 (dd, J = 12.8, 8.3 Hz, 13H), 1.90 - 1.76 (m, 7 H), 1.96 (ddq, J = 12.3, 10.3, 3.4 Hz, 4 H, HC(3) 3.60 (dt, J = 6.3, 2.9 Hz, 4 H, HC(2)), 6.98 (s, 2 H, HC(1)). \]

**\( ^13C \) NMR:** (126 MHz, CDCl\(_3\))
\[ \delta 130.7 (C(1)), 65.4 (C(2)), 40.2 (C(3)), 31.8, 30.9, 26.9, 25.8, 24.8, 22.9 \]

**MS** (ESI)

524.1 (100, M+H), 525.0 (50).

**TLC:** \( R_f 0.32 \) (hexane/EtOAc 9:1)

**Procedure for Screening ligand in biaryl cross-coupling.**

To an oven dried 5 mL one piece round bottom flask and condenser in a dry box was added palladium source, cyclohexyl ligand \( \mathbf{x} \). Added 0.25 mL of toluene and 1-bromo naphthalene at which point solution turns yellow. 2-methyl naphthyl-1-potassiumsilanolate was added followed by 0.25 mL of toluene resulting in a slight brown heterogeneous mixture. The reaction flask was sealed and brought outside and stirred at specified temperature for specified amount of time. Cooled to room temperature and filtered through a silica pad and eluted with Et\(_2\)O. The resulting solution was concentrated to dryness in vacuo to give a dark brown liquid. The residue was purified by flash chromatography (silica, 26 cm x 0.5 cm; hexanes), to afford desired product \( \mathbf{x} \) as a white solid. Determination of \( \mathbf{er} \) was done by SFC chromatography using Daicel Chiralpak OJ column: 2.0 mL/min, 200 bar, 5% MeOH, 40 °C 220 nm.
<table>
<thead>
<tr>
<th>entry</th>
<th>Palladium source</th>
<th>Ligand (equiv)</th>
<th>Temp(°C)</th>
<th>t (h)</th>
<th>Yield</th>
<th>er</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[allylPdCl]_2</td>
<td>0.05</td>
<td>70</td>
<td>4</td>
<td>15%</td>
<td>64:36</td>
</tr>
<tr>
<td>2</td>
<td>[allylPdCl]_2</td>
<td>0.1</td>
<td>70</td>
<td>16</td>
<td>75</td>
<td>72:28</td>
</tr>
<tr>
<td>3</td>
<td>[allylPdCl]_2</td>
<td>0.1</td>
<td>40</td>
<td>30</td>
<td>44</td>
<td>55:45</td>
</tr>
<tr>
<td>4</td>
<td>(MeCN)_2PdCl_2</td>
<td>0.05</td>
<td>40</td>
<td>26</td>
<td>13</td>
<td>76:24</td>
</tr>
</tbody>
</table>

**Preparation of [1,1'-bi(cyclopentane)]-2,2'-dione (68)**

In a 100 mL flame dried schlenk flask was added 2.94g of LiHMDS (17.6 mmol, 1.1 equiv) inside a dry box. The flask was sealed and brought outside. Under argon added 8 mL THF and cooled to -78 °C at which point the solution turned yellow. A solution of cyclohexanone in 6 mL THF was cannuled into the flask while keeping the T < -65 °C and washed with 2 mL THF. The solution was stirred for 15 min. In a flame dried 25 mL schlenk flask was added copper(II)triflate inside a dry box. The flask was sealed and brought outside. The copper salt was dissolved in 8 mL acetonitrile. The blue copper solution in cannuled into the 100 mL schlenk flask while keeping T < -60°C washed with 2 mL acetonitrile. The solution turned brown/black. The mixture was stirred at -78°C for 0.5h and then at room temperature for 0.5h. A yellow precipitate forms after ten minutes. Continue stirring at room temperature for another 5 h. The solution was diluted with Et₂O (25 mL) and 1M HCl (25 mL). The organic layer was separated and the aqueous layer was extracted with Et₂O (3 x 30 mL) and combined organic layer was dried over MgSO₄ and concentrated to dryness in vacuo to give a black oil. The crude was passed through a florasil plug to remove any remaining copper in the mixture and eluted with Et₂O. The residue was purified by flash chromatography (silica, 14 cm x 2.5 cm; 4:1, hexane/Et₂O), to afford 757 mg (57%) of 68 as a colorless oil. The spectroscopic data matches literature values.
Data for 68:

**Mol. Formula:** C\(_{10}\)H\(_{14}\)O\(_2\)

\(^1\)H NMR: (500 MHz, CDCl\(_3\))
\(\delta 1.69 – 1.52 (m, 2 \text{ H}), 1.85 – 1.71 (m, 2 \text{ H}), 2.24 – 1.98 (m, 6 \text{ H}), 2.40 – 2.28 (m, 2 \text{ H}), 2.71 – 2.49 (m, 2 \text{ H, HC(1)}).

**TLC:** \(R_f 0.1\) (hexane/Et\(_2\)O 4:1)

---

Preparation of rac-4-nitrosodecahydro-1H-dicyclopenta[b,d]pyrrole (71)

![Chemical Structure](image)

To a 25 mL flame dried Schlenk flask under argon was added 128 mg of pyrrolidine 70 (0.85 mmol), 67 mg of sodium nitrite (0.97 mmol, 1.15 equiv), 185 mg of p-Toluenesulfonic acid (0.97 mmol, 1.15 equiv) and 3.5 mL of CH\(_2\)Cl\(_2\). A yellow precipitate forms after ten minutes, stirred at room temperature for 5 h. The solution was diluted with CH\(_2\)Cl\(_2\) (10 mL) and 1M NaOH (5 mL). The organic layer was separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (2 x 10 mL) and combined organic layer was dried over Na\(_2\)SO\(_4\) and concentrated to dryness in vacuo to give a pale oil. The residue was purified by flash chromatography (silica, 14 cm x 3.5 cm; 9:1, hexane/EtOAc), to afford 99 mg (65%) of 71 as a colorless liquid.

Data for 71:

**Mol. Formula:** C\(_{10}\)H\(_{16}\)N\(_2\)O

\(^1\)H NMR: (500 MHz, CDCl\(_3\))
\(\delta 1.73 – 1.36 (m, 7 \text{ H}), 2.02 – 1.74 (m, 3 \text{ H}), 2.10 (dddd, J = 14.1, 9.3, 7.9, 6.3 Hz, 1 \text{ H, HC(2)}), 2.40 (dddt, J = 20.6, 10.6, 5.6, 4.8, 2.3 Hz, 2 \text{ H, HC(5)}), 2.56 – 2.47 (m, 1 \text{ H, HC(2)}), 4.54 (tdd, J = 7.9, 3.3, 1.5 Hz, 1 \text{ H, HC(1)}), 4.73 (tt, J = 6.6, 1.8 Hz, 1 \text{ H, HC(1)}).

**TLC:** \(R_f 0.39\) (hexane/EtOAc 9:1)
Preparation of rac-((decahydro-4H-dicyclopenta[b,d]pyrrol-4-yl)imino)acetaldehyde (73)

To a 5 mL flame dried Schlenk flask under argon was added 30 mg of nitrosoamine 71 (0.17 mmol), 87 mg of zinc dust (1.33 mmol, 8 equiv), and 1.7 mL of methanol. The flask was cooled to -78 °C in an IPA/dry ice bath and slowly pipetted 0.111 mL of conc. HCl (1.33 mmol, 8 equiv). The mixture was stirred at -78 °C for 4 hours and then warmed up to 0 °C in an ice bath. Diluted with cold CH₂Cl₂ (5 mL) and cold 1M NaOH (5 mL). The organic layer was separated and the aqueous layer was extracted with cold CH₂Cl₂ (2 x 5 mL) and combined organic layer was dried over Na₂SO₄ and concentrated to dryness in vacuo to give 10mg of a pale oil. Used immediately in next step without further purification.

To a 5 ml flame dried Schlenk flask was added 10 mg of pyrrolidine 72 (0.06 mmol) from previous step and added 0.9 mL THF and 0.21 mL of 40% w/w glyoxal in water (1.8 mmol, 30 equiv). The reaction mixture was stirred at room temperature for 24 h. Diluted with CH₂Cl₂ (10 mL) and sat. aq. NaHCO₃ (5 mL). The organic layer was separated and the aqueous layer was extracted with cold CH₂Cl₂ (2 x 10 mL) and combined organic layer was dried over Na₂SO₄ and concentrated to dryness in vacuo to give a pale liquid. The residue was purified by flash chromatography (silica, 32 cm x 0.5 cm; 9:1, hexane/EtOAc), to afford 7 mg (57%) of 73 as a pale oil.

Data for 73:

**Mol.Formula:** C₁₂H₁₈N₂O

**¹H NMR:** (400 MHz, CDCl₃) δ 1.96 – 1.45 (m, 11 H), 2.21 (d, J = 13.6 Hz, 1 H, HC(4)), 2.41 (s, 1 H), 2.51 (d, J = 8.2 Hz, 1 H, HC(4)), 4.00 (d, J = 8.3 Hz, 1 H, HC(3)), 4.21 (d, J = 6.9 Hz, 1 H, HC(3)), 6.69 (dd, J = 12.5, 7.6 Hz, 1 H, HC(2)), 9.36 (dd, J = 7.6, 4.7 Hz, 1 H, HC(1)).

**TLC:** Rₚ 0.17 (hexane/EtOAc 9:1)
Preparation of rac-(2,5-dicyclohexylpyrrolidin-1-yl)ethane-1,2-diimine (67)

To a 5 ml flame dried Schlenk flask was added 7 mg of mono glyoxal product 73 (0.03 mmol) followed by 10 mg of freshly prepared pyrrolidine 72 (0.06 mmol, 1.74 equiv) and 1 mL CH$_2$Cl$_2$. To this solution was added 9 mg of magnesium sulfate (0.0.07 mmol, 2.17 equiv). The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was filtered and concentrated to dryness in vacuo to give a pale liquid. The residue was purified by flash chromatography (silica, 20 cm x 0.5 cm; 9:1, hexane/EtOAc), to afford 4 mg (33%) of 67 as a pale oil.

Data for 67:

\[
\text{Mol.Formula: } C_{22}H_{34}N_4
\]

$^1$H NMR: (500 MHz, CDCl$_3$)
$\delta$ 1.61-1.42 (m, 16 H), 1.92 – 1.62 (m, 12 H), 2.76 – 2.22 (m, 4 H, HC(3)), 4.15-3.6 (m, 4 H, HC(2)), 7.23 – 6.92 (m, 2 H, HC(1)).

$^{13}$C NMR (126 MHz, CDCl$_3$)
$\delta$ 134.5 (C(1)), 66.9 (C(2)), 48.7 (C(3)), 33.9 (C(4) or C(6)), 33.8 (C(4) or C(6)), 25.0 (C(5)).

MS (ESI)

355.8 (100, M+H), 356.8.0 (26), 207.5 (5).

TLC: $R_f$ 0.1 (hexane/EtOAc 9:1)
Preparation of \textit{tert}-butyl((2-((4-methoxybenzyl)oxy)but-3-en-1-yl)oxy)dimethylsilane (120)

To a 25 mL flame dried Schlenk flask in a dry box was added 320 mg of NaH (13.34 mmol, 1.5 equiv), sealed under argon and brought outside. To the flask was added 9 mL of THF and cooled to 0 °C. A solution of secondary alcohol 119 (1.8 g, 8.9 mmol) in 9 mL THF was cannulaed slowly into the schlenk flask and some bubbling was observed. The mixture was stirred for 15 min until the bubbling has subsided and 1.878 g of 1-(bromomethyl)-4-methoxybenzene (9.34 mmol, 1.05 equiv) was added. Stirred at room temperature for 3 h. After complete consumption of starting material by TLC the solution was diluted with EtOAc (30 mL) and sat. aq. NH$_4$Cl (30 mL). The organic layer was separated and the the aqueous layer was extracted with EtOAc (2 x 30 mL) and combined organic layer was washed with brine (30 mL), dried over Na$_2$SO$_4$ and concentrated to dryness in vacuo to give a pale oil. The residue was purified by flash chromatography (silica, 16 cm x 3.5 cm; 9:1, hexane/EtOAc), to afford 2.44 g (86%) of 120 as a colorless liquid.
Data for 120:

**Mol. Formula:** C_{18}H_{30}O_{3}Si

**{^1}H NMR:** (500 MHz, CDCl₃)  
δ 0.11 – 0.03 (m, 6 H, HC(5)), 0.91 – 0.88 (m, 9 H, HC(6)), 3.39 (dd, J = 5.8, 3.1 Hz, HC(1)), 3.59 (dd, J = 10.5, 5.2 Hz, HC(1)), 3.71 (dd, J = 10.5, 6.5 Hz, HC(1)), 3.82 – 3.79 (m, 3 H, HC(10)), 3.86 (q, J = 6.4 Hz, HC(1)), 4.31 (q, J = 5.4 Hz, HC(2)), 4.40 (d, J = 11.6 Hz, HC(2)), 4.50 (d, J = 11.2 Hz, 1 H, HC(7)), 4.58 (d, J = 11.6 Hz, 1 H, HC(7)), 5.13 (dt, J = 10.5, 1.7 Hz, HC(4)), 5.34 – 5.23 (m, 2 H, HC(4)), 5.76 (ddd, J = 17.4, 10.4, 7.1 Hz, HC(3)), 5.85 (dd, J = 10.6, 5.3 Hz, HC(3)), 5.89 (dd, J = 10.7, 5.4 Hz, HC(3)), 6.89 – 6.85 (m, 2H, HC(9)), 7.30 – 7.24 (m, 2H, HC(8))

**{^{13}C NMR:** (126 MHz, CDCl₃)  
δ 159.23 (C(12)), 138.8-136.5 (C(11)), 130.6-129.5 (C(8 or 9)), 118.3 (C(4),114.4-113.9 (C(8 or 9)), 81.0 (C(7)), 74.9-73.2 (C(2)), 66.5 (C(1)), 55.5 (C(10)), 34.21 (C(6)), 31.8 (C(6)), 26.1 (C(6)), 18.6 (C(13)), -5.0 (C(5)).

**MS**  
(ESI)  
345.2 (100, M+Na), 346.2 (26), 347.2 (8).

**TLC:**  
R_f 0.75 (hexane/EtOAc 9:1)

Preparation of 2-((4-methoxybenzyl)oxy)but-3-en-1-ol (106)

To a 5 mL flame dried Schlenk flask was added 110 mg of protected diol 120 (0.34 mmol) and 1 mL of THF and cooled to 0 °C. To the cooled solution was added 0.51 mL of 1M TBAF (0.51 mmol, 1.5 equiv). The mixture was stirred at room temperature for 4 h. After complete consumption of starting material by TLC the solution was diluted with CH₂Cl₂ (10 mL) and sat. aq. NaHCO₃ (5 mL). The organic layer was separated and the the aqueous layer was extracted with CH₂Cl₂ (2 x 10 mL) and combined organic layer was washed with sat. aq. NaHCO₃ (10 mL) dried over Na₂SO₄ and concentrated to dryness in vacuo
to give a pale oil. The residue was purified by flash chromatography (silica, 16 cm x 2 cm; 400 mL of 9:1 hexane/EtOAc, flush with CH$_2$Cl$_2$), to afford 67 mg (94%) of 106 as a colorless liquid.

Data for 106:

Mol.Formula: C$_{12}$H$_{16}$O$_3$

$^1$H NMR: (500 MHz, CDCl$_3$)
$\delta$ 1.79 – 1.59 (m, 1 H, HO(1)), 3.36 (dt, $J$ = 9.6, 5.6 Hz, HC(2)), 3.56 (ddt, $J$ = 32.5, 9.6, 4.1 Hz, 1 H, HC(2)), 3.92 – 3.80 (m, 3 H, HC(11)), 3.95 (qd, $J$ = 7.0, 6.5, 3.3 Hz, HC(2)), 4.36 (dt, $J$ = 11.0, 8.7, 7.7, 3.4 Hz, 1 H, HC(3)), 4.68 – 4.50 (m, 2 H, HC(6)), 5.43 – 5.16 (m, 2 H, HC(5)), 5.89 – 5.72 (m, 1 H, HC(4)), 6.90 (ddt, $J$ = 8.4, 5.6, 3.3 Hz, 2 H, HC(9)), 7.35 – 7.28 (m, 2H, HC(8)).

$^{13}$C NMR (126 MHz, CDCl$_3$)
$\delta$ 135.4 (C(4)), 129.7 (C(7)), 128.9 (C(8)), 119.5 (C(5)), 116.7 (9), 81.0 (C(6)), 73.3 (C(3)), 71.8 (C(3)), 65.5 (C(2)), 55.5 (C(3)).

MS (ESI)
231.0 (100, M+Na), 121.4 (55).

TLC: $R_f$ 0.2 (CH$_2$Cl$_2$)

Procedure for lithiation and capture with electrophile of z-bromodiene

To a 5 mL flame dried Schlenk flask was added 0.27 g of z-bromodiene 121 (2.0 mmol) and 1 mL of Et$_2$O and cooled to specified temperature either using IPA/cryo cool bath or hexane/liquid nitrogen bath. To it was added 2.35 mL of a 1.7 M solution of t-BuLi in pentane (4 mmol, 2 equiv), dropwise keeping temperature always below T -5 where T is the intended temperature. Let it stir for 2 h and then add the specified electrophile. Stir for another 2 hours at the intended temperature and then half an hour at room temperature. The excess solvent was distilled off and the residue filtered and washed using pentane. The pentane was removed under 350 mmHg to give an oil. The E/Z isomers were determined via $^1$H NMR.

Preparation of dimethyl(pent-3-en-1-yn-1-yl)silane (130)

To a 15 mL flame dried Schlenk flask was added 385 mg of enyne 129 (2.66 mmol) and 5 mL of THF and cooled to -78 °C using IPA/dry ice bath. To the cooled solution was added 1.31 mL of 2.54M
solution of \( n \)-BuLi (3.32 mmol, 1.25 equiv). The mixture was stirred at -78 °C for 2 hours and added 0.38 mL of chloro dimethylsilane (3.45 mmol, 1.3 equiv). Let it stir for 30 min at -78 °C and then warmed to room temperature and let it stir for another 2 h. The solution was diluted with \( \text{Et}_2\text{O} \) (20 mL) and sat. aq. \( \text{NH}_4\text{Cl} \) (20 mL). The organic layer was separated and washed with brine (10 mL) dried over \( \text{MgSO}_4 \) and concentrated to dryness in 350 mmHg to give a pale oil. The residue was purified by flash chromatography (silica, 16 cm x 2 cm; pentane), to afford 158 mg (52%) of 130 as a colorless liquid.

Data for 130:

- **Mol. Formula:** \( \text{C}_7\text{H}_{12}\text{Si} \)
- **\( ^1\text{H} \) NMR:**
  - (400 MHz, CDCl\(_3\))
  - \( \delta \) 0.26 (dd, \( J = 10.5, 3.8 \text{ Hz}, 6 \text{ H}, \text{HC}(1) \)), 1.95 – 1.74 (m, 3 H, HC(5)), 4.26 – 4.12 (m, 1 H, HSi(2)), 5.57 – 5.47 (m, 1 H, HC(4)), 6.32 – 6.00 (m, 1 H, HC(3)).
- **\( ^{13}\text{C} \) NMR:**
  - (126 MHz, CDCl\(_3\))
  - \( \delta \) 141.95 (C(4)), 110.84 (C(7)), 105.6 (C(3)), 77.54 (C(6)), 18.9 (C(5), -2.7 (C(1)).
- **TLC:** \( R_f \) 0.52 (pentane)

**Preparation of dimethyl((1Z)-penta-1,3-dien-1-yl)silane (131)**

[Diagram of the reaction]

To a 5 mL flame dried Schlenk flask was added 621 mg of enyne silane 130 (5 mmol) and 10 mL of pentane and cooled to 0 °C using ice bath. To the cooled solution was added 6 mL of 1M solution of DIBAL (6 mmol, 1.2 equiv). The mixture was stirred at 0 °C for 4. Warmed up to room temperature and added 5 mL of sat. aq. \( \text{NH}_4\text{Cl} \) and white solid filtered off. The organic layer was separated and dried over \( \text{MgSO}_4 \) and concentrated to dryness in 100 mmHg to give 189 mg of 131 as a yellow oil. \( ^1\text{H} \) NMR of the product shows Z/E mixture of 8:2.
Data for 131:

Mol. Formula: C₇H₁₅Si

¹H NMR: (500 MHz, CDCl₃)
δ 0.31 – 0.16 (m, 6 H, HC(2)), 1.92 – 1.77 (m, 4 H, HC(7)), 4.34 – 4.29 (m, 1 H, HSi(1)), 5.55 – 5.42 (m, 1 H, HC(3)), 5.78 (dq, J = 14.3, 6.8 Hz, 1 H, HC(6)), 6.41 – 6.31 (m, 1 H, HC(5)), 6.81 (dd, J = 14.0, 11.0 Hz, 1 H, HC(4)) for Z isomer, 6.56 (dd, J = 18.3, 10.0 Hz, HC(4)) for E isomer

TLC: Rf 0.36 (pentane)

Preparation of Tert-butoxy-dimethyl-[(E)-1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)prop-1-enyl]silane (143)

To a one piece 0.5 mL round bottom flask with condenser and a stir bar under argon was added 2 mg of Pd(OAc)₂ (0.008 mmol, 0.02 equiv), 17 mg of t-OcNC (0.12 mmol, 0.3 equiv) and 0.1 mL of toluene. Stirred for 5 min and added 65 mg of phenyl-1-propyne (0.56 mmol, 1.4 equiv) and 103 mg of silylborane 142 (0.4 mmol). The flask was submerged in a heated oil bath and let it stir at reflux for 18 hours. The apparatus was cooled to room temperature and filtered through 1 inch of silica in a glass pipette using diethyl ether. The volatiles were removed under reduced pressure to give a black oil. The residue was concentrated to dryness in 0.7 mmHg at 150 °C to give afford 101 mg (67%) of 143 as a brown oil.
Data for **143**:

**Mol. Formula**: \( \text{C}_{21}\text{H}_{35}\text{BO}_{3}\text{Si} \)

\( ^1\text{H NMR} \) (400 MHz, CDCl\(_3\))

\( \delta \) 0.17 (s, 1 H, HC(12)), 1.24 (1.24 (dd, \( J = 2.3, 1.1 \) Hz, 12H, HC(9)), 1.27 (s, 8H HC(12)), 2.05 (s, 3H, HC(7)), 7.33 – 7.27 (m, 3H, HC(4,6)), 7.38 (dd, \( J = 6.7, 3.0 \) Hz, 2H, HC(5))

\( ^{11}\text{B NMR} \) (128 MHz, CDCl\(_3\))

\( \delta \) 20.66, 22.57.

**Preparation of Chloro-(2,4-dimethoxyphenyl)-dimethyl-silane (145a)**

To a flame dried 200 ml round bottom flask with a stir bar under argon was added 6.5g of 1-bromo-2,4-dimethoxybenzene (30 mmol) and 30 mL of hexane. The solution was cooled to –78 °C and treated with 37.9 mL of 1.60 M \( \text{t-BuLi} \) in pentane (60.6 mmol, 2.05 equiv) over 15 min and stirred for 30 min. To the solution was slowly added 4.7 mL of TMEDA (31.5 mmol, 1.05 equiv) via syringe and the resulting suspension was cannulated into a solution of 10.8 mL of dichlorodiethylsilane (90 mmol, 3 equiv) in 20 mL hexane at –78 °C. The original flask was rinsed with hexane (3 x 10 mL). The mixture was warmed to room temperature and stirred for 30 min. The resulting suspension was filtered on a medium glass frit funnel to partially remove the Li salts. The solvent was removed under reduced pressure; the residual dichlorodiethylsilane and TMEDA were removed under high vacuum over 12 h. The residue was purified by distillation at 124 °C / 1 mmHg to afford 5.9 g (86%) of **145a** as a colorless liquid.
Data for 145a:

Mol. Formula: \( \text{C}_{10}\text{H}_{15}\text{ClO}_{2}\text{Si} \)

\(^1\text{H NMR:}\) (400 MHz, CDCl\(_3\))
\( \delta \) 7.52 (d, \( J = 8.1 \text{ Hz} \), 1 H, HC(2)), 6.58 – 6.52 (m, 1 H, HC(1)), 6.42 (d, \( J = 2.1 \text{ Hz} \), 1 H, HC(4)), 3.83 (s, 3 H, HC(8)), 3.81 (s, 3 H, HC(7)), 0.63 (s, 6 H, HC(9)).

\(^{13}\text{C NMR}\) (126 MHz, CDCl\(_3\))
\( \delta \) 165.4 (C(5)), 163.7 (C(3)), 136.7 (C(1)), 115.5 (C(2)), 100.6 (C(4)), 97.9 (C(6)), 55.6 (C(7)), 55.4 (C(8)), 3.2 (C(9)).

Preparation of Chloro-(4-methoxyphenyl)-dimethyl-silane (145b)

To a flame dried 250 mL round bottom flask with a stir bar under argon was added 1.25 mL of 1-bromo-4-methoxy-benzene (10 mmol) and 10 mL of hexane. The solution was cooled to –78 °C and treated with 12.8 mL of 1.60 M \( \text{t-BuLi} \) in pentane (20.5 mmol, 2.05 equiv) over 15 min and stirred for 30 min. To the solution was slowly added 1.6 mL of TMEDA (10.5 mmol, 1.05 equiv) via syringe and the resulting suspension was cannulated into a solution of 3.6 mL of dichlorodiethylsilane (30 mmol, 3 equiv) in 7.5 mL hexane at –78 °C. The original flask was rinsed with hexane (3 x 10 mL). The mixture was warmed to room temperature and stirred for 30 min. The resulting suspension was filtered on a medium glass frit funnel to partially remove the Li salts. The solvent was removed under reduced pressure; the residual dichlorodiethylsilane and TMEDA were removed under high vacuum over 12 h. The residue was purified by distillation at 112 °C / 1 mmHg to afford 1.3 g (65%) of 145b as a colorless liquid.
Data for 145b:

Mol.Formula: C₉H₁₃ClOSi

¹H NMR: (500 MHz, CDCl₃)
δ 7.60 – 7.53 (m, 2 H, HC(2)), 6.99 – 6.90 (m, 2 H, HC(1)), 3.83 (d, J = 0.7 Hz, 3 H, HC(5)), 0.67 (d, J = 0.6 Hz, 6 H, HC(6)).

¹³C NMR: (126 MHz, CDCl₃)
δ 135.0 (C(1)), 114.1 (C(2)), 55.38 (C(5)), 2.5 (C(6)).

Preparation of Dimethyl-(2,4,6-trimethoxyphenyl)silane (147)

To a flame dried 100 ml round bottom flask with a stir bar under argon was added 1.68 g of 1,3,5-trimethoxybenzene (10 mmol) and 10 mL of hexane. The solution was cooled to −78 °C and treated with 6.5 mL of 1.60 M n-BuLi in pentane (10.5 mmol, 1.05 equiv) and stirred for 30 min. To the solution was slowly added 1.5 mL of TMEDA (10.2 mmol, 1.02 equiv) and 1.7 mL of chlorodiethylsilane (15 mmol, 1.5 equiv). The mixture was warmed to room temperature and stirred for 3 hours. The resulting suspension was filtered on a medium glass frit funnel to partially remove the Li salts. The solvent was removed under reduced pressure; the residual chlorodiethylsilane and TMEDA were removed under high vacuum over 12 h. The residue was purified by distillation at 137 °C / 0.2 mmHg to afford 2.1 g (93%) of 147 as a white solid.

Data for 147:

Mol.Formula: C₁₁H₁₈O₃Si

¹H NMR: (400 MHz, CDCl₃)
δ 6.09 (s, 2 H, HC(2)), 4.50 (h, J = 3.8 Hz, 1 H, HSi(8)), 3.79 (d, J = 21.9 Hz, 9 H, HC(5,6)), 0.29 (dd, J = 3.8, 1.3 Hz, 6 H, HC(7)).

¹³C NMR: (126 MHz, CDCl₃)
δ 166.4 (C(1)), 163.6 (C(3)), 128.5 (C(4)), 90.6 (C(2)), 55.7 (C(6)), 55.4 (C(5)), -2.3 (C(7)).
Preparation of 2-((4-methoxybenzyl)oxy)but-3-en-1-ol (149)

To a one piece 5 mL round bottom flask with condenser and a stir bar under argon was added 0.04 mL of 1-bromo-2-methyl-benzene (0.35 mmol, 1.5 equiv), 19 mg of Pd(dppf)Cl₂ (0.024 mmol, 0.1 equiv), 0.11 mL of 3 M solution of KOH in water (0.35 mmol, 1.5 equiv) and a solution of 89 mg of vinyl silane 140 (0.235 mmol) in 1 mL of Dioxane. The flask was heated up to 90°C in an oil bath and stirred for 16 hours. The flask was cooled to room temperature and extracted with 20 mL diethyl ether. The volatiles removed under reduced pressure to give a dark brown oil. The residue was purified by flash chromatography (silica, 16 cm x 3.5 cm; with 200:1 hexane/EtOAc), to afford 361 mg (63%) of 149 as a brown liquid.

Data for 149:

Mol. Formula: C₂₄H₂₆Si

¹H NMR: (400 MHz, CDCl₃)
δ 7.32 – 6.93 (m, 17 H, 4,5,6,9,10,11,12,13,17,18,19), 2.18 (d, J = 2.2 Hz, 3 H, HC(14)), 1.71 (d, J = 0.7 Hz, 3 H, HC(7)), -0.14 (d, J = 56.5 Hz, 6 H, HC(15)).

TLC: Rf 0.67 (Hexanes/EtOAc 200:1)

Preparation of 4-fluoro-N-(1-phenylallyl)aniline (164a)

In a flame dried 50 mL schlenk flask was injected 18.8 mL of 1.6 M solution of vinylmagnesium chloride in THF (30 mmol, 2 equiv) and 3 mL of 1 M solution of ZnCl₂ in THF (3 mmol, 0.2 equiv). Stirred for 20 min and then added 2.99 g of imine 163a (15 mmol) under positive argon pressure. The solution was
stirred at room temperature for 16 hours. The reaction was quenched with 30 mL aq. NH₄Cl and extracted with EtOAc (3 x 40 mL). Combined organic layer washed with 30 mL brine and dried with MgSO₄. Solvent removed under reduced pressure to give 3.05g of crude material. The residue was purified by flash chromatography (silica, 16 cm x 5 cm; 800 mL of 93:5:2, hexane/EtOAc/Triethylamine, 200 mL of 90:10 hexane/EtOAc, 200 mL of 85:15 hexane/EtOAc, 200 mL of 80:20 hexane/EtOAc), to afford 2.84 g (83%) of 164a as a brown liquid. The spectroscopic data matches the literature reported values.97

Data for 164a:

Mol.Formula: C₁₅H₁₄FN

\( ^1H \text{NMR:} \) (400 MHz, CDCl₃)

δ 7.43 – 7.36 (m, 4H, HC(10,11)), 7.31 (ddd, \( J = 7.6, 4.2, 2.3 \) Hz, 1 H, HC(12)), 6.92 – 6.83 (m, 2 H, HC(7)), 6.59 – 6.52 (m, 2 H, HC(6)), 6.06 (ddd, \( J = 17.0, 10.2, 5.9 \) Hz, 1 H, HC(4)), 5.34 – 5.23 (m, 2 H, HC(5)), 4.89 (d, \( J = 6.0 \) Hz, 1 H, HC(3)), 3.97 (s, 1 H, HN(2)).

\( ^13C \text{NMR} \) (126 MHz, CDCl₃)

δ 157.1, 155.3, 143.9, 142.0, 139.4, 129.1, 127.8, 127.4, 116.5, 115.9, 115.7, 114.8, 114.7, 61.8 (C(3)).

TLC: \( R_f \) 0.54 (9:1 Hexanes/Ethylacetate)

Preparation of 4-methoxy-N-(1-phenylallyl)aniline (164b)

In a flame dried 100 mL schlenk flask was injected 18.8 mL of 1.6 M solution of vinylmagnesium chloride in THF (30 mmol, 2 equiv) and 3 mL of 1 M solution of ZnCl₂ in THF (3 mmol, 0.2 equiv). Stirred for 20 min and then added 3.17 g of imine 163b (15 mmol) under positive argon pressure. The solution was stirred at room temperature for 16 hours. The reaction was quenched with 30 mL aq. NH₄Cl and extracted with EtOAc (3 x 30 mL). Combined organic layer washed with 30 mL brine and dried with MgSO₄. Solvent removed under reduced pressure to give dark brown oil. The residue was purified by flash chromatography (silica, 18 cm x 5 cm; 1000 mL of 93:5:2, hexane/EtOAc/Triethylamine, 500 mL of 95:5 hexane/EtOAc, 300 mL of 93:7 hexane/EtOAc, 300 mL of 90:10 hexane/EtOAc), to afford 2.93 g (82%) of 164b as a brown liquid. The spectroscopic data matches the literature reported values.97
Data for 164b:

Mol.Formula: C_{16}H_{17}NO

\[ ^1H \text{ NMR:} \]
\( \delta \) 7.42 – 7.32 (m, 4 H, HC(10,11)), 7.31 – 7.24 (m, 1 H, HC(12)), 6.78 – 6.72 (m, 2 H, HC(7)), 6.61 – 6.54 (m, 2 H, HC(6)), 6.04 (ddd, \( J = 17.2, 10.2, 6.0 \) Hz, 1 H, HC(4)), 5.32 – 5.19 (m, 2 H, HC(5)), 4.87 (d, \( J = 6.1 \) Hz, 1 H, HC(3)), 3.82 (s, 1 H, HN(2)), 3.73 (s, 3 H, HC(13)).

\[ ^{13}C \text{ NMR} \]
\( \delta \) 170.6 (C(8)), 152.4 (C(1)), 142.3 (C(9)), 141.7 (C(4)), 139.7 (C(4)), 128.9 (C(11)), 127.6 (C(12)), 127.4 (C(10)), 116.1 (C(6)), 115.1 (C(5)), 114.9 (C(7)), 61.0 (C(3)), 55.9 (C(13)).

TLC: \( R_f \) 0.44 (4:1 Hexanes/Ethylacetate)

Preparation of N-(1-phenylallyl)naphthalen-2-amine (164c)

In a flame dried 50 mL schlenk flask was injected 18.8 mL of 1.6 M solution of vinylmagnesium chloride in THF (30 mmol, 2 equiv) and 3 mL of 1 M solution of ZnCl\(_2\) in THF (3 mmol, 0.2 equiv). Stirred for 20 min and then added 3.47 g of imine 163c (15 mmol) under positive argon pressure. The solution was stirred at room temperature for 16 hours. The reaction was quenched with 30 mL aq. NH\(_4\)Cl and extracted with EtOAc (3 x 40 mL). Combined organic layer washed with 30 mL brine and dried with MgSO\(_4\). Solvent removed under reduced pressure to give brown oil. The residue was purified by flash chromatography (silica, 16 cm x 5 cm; 800 mL of 93:5:2, hexane/EtOAc/Triethylamine, 200 mL of 90:10 hexane/EtOAc, 200 mL of 85:15 hexane/EtOAc, 200 mL of 80:20 hexane/EtOAc), to afford 3.70 g (95\%) of 164c as a brown liquid. The spectroscopic data matches the literature reported values.\(^98\)
Data for 164c:

Mol. Formula: C_{19}H_{17}N

^1H NMR: (400 MHz, CDCl_3)
δ 7.65 (d, J = 8.1 Hz, 1 H), 7.62 (d, J = 8.8 Hz, 1 H), 7.54 (dd, J = 8.3, 1.1 Hz, 1 H), 7.54 (d, J = 8.2 Hz, 1 H), 7.45 – 7.41 (m, 2 H), 7.37 (t, J = 7.6 Hz, 2 H), 7.34 – 7.27 (m, 2 H), 7.18 (ddd, J = 8.1, 6.8, 1.2 Hz, 1 H), 6.92 (dd, J = 8.8, 2.4 Hz, 1 H), 6.77 (d, J = 2.4 Hz, 1 H), 6.10 (ddd, J = 17.1, 10.2, 5.8 Hz, 1 H, HC(4)), 5.33 (dt, J = 17.1, 1.4 Hz, 1 H, HC(5)), 5.27 (dt, J = 10.2, 1.3 Hz, 1 H, HC(5)), 5.08 (t, J = 5.5 Hz, 1 H, (C(3)), 4.22 (d, J = 5.2 Hz, 1 H, HN(2)).

TLC: Rf 0.35 (4:1 Hexanes/Ethylacetate)

Preparation of 4-fluoro-N-(1-phenylallyl)aniline (165a)

In a 500 ml flame dried schlenk flask was added 2.05g 4-fluoro-N-(1-phenylallyl)aniline (9 mmol) followed by 352 mg of p-Toluenesulfonic acid monohydrate (1.8 mmol, 0.2 equiv). To this was added 90 mL of acetonitrile and 10 mL of water. The solution was heated to 65°C in an oil bath for 36 hours. The reaction was monitored by NMR (the reaction stalled after 36 hours). Volatiles were removed under reduced pressure and the residue was extracted with diethyl ether (3 x 30 mL). Combined organic layer was washed with 1M NaOH (30 mL) and H_2O (30 mL). The organic phase was dried with Na_2SO_4 and solvent removed under reduced pressure. The residue was purified by flash chromatography (silica, 9.5 cm x 5 cm; 500 mL of 88:10:2, hexane/EtOAc/Triethylamine, 200 mL of 90:10 hexane/EtOAc, 200 mL of 80:20 hexane/EtOAc, 250 mL of 50:50 hexane/EtOAc), to afford 1.45 g (71%) of 165a as a brown liquid. The spectroscopic data matches the literature reported values.\(^9\)
Data for 164a:

Mol. Formula: \( \text{C}_{15}\text{H}_{14}\text{FN} \)

\(^1\text{H NMR:} \) (400 MHz, CDCl\(_3\))
\( \delta \) 7.45 – 7.23 (m, 5 H, (C(11,12,13)), 6.88 (ddt, \( J = 19.9 \), 8.5, 2.7 Hz, 2 H, HC(2,6)), 6.65 (dd, \( J = 8.7 \), 4.9 Hz, 1 H, HC(3)), 6.50 (d, \( J = 15.9 \) Hz, 1 H, HC(9)), 6.35 (dt, \( J = 15.8 \), 6.3, 1.8 Hz, 1 H, HC(8)), 3.59 (s, 2 H, HN(14)), 3.45 (d, \( J = 6.3 \) Hz, 2 H, HC(7)).

\(^{13}\text{C NMR} \) (101 MHz, CDCl\(_3\))
\( \delta \) 156.7 (d, \( J = 235.9 \) Hz, C(1)), 141.1 (C(4)), 137.3 (C(10)), 132.0 (C(13)), 128.9 (C(12)), 127.8 (C(9 or 11)), 127.0 (C(9 or 11)), 126.5 (C(8)), 126.2 (d, \( J = 6.6 \) Hz, C(5)), 116.9 (d, \( J = 5.7 \) Hz, C(3)), 116.7 (d, \( J = 20.4 \) Hz, C(6)), 114.1 (d, \( J = 22.1 \) Hz, C(2)), 35.6 (C(7)).

TLC: \( R_f \) 0.26 (4:1 Hexanes/Ethylacetate)

Preparation of 2-[(E)-cinnamyl]-4-methoxy-aniline (165b)

In a 100 ml flame dried schlenk flask was added 239 mg 4-methoxy-N-(1-phenylallyl)aniline (1 mmol) followed by 39 mg of \( p \)-Toluensulfonic acid monohydrate (0.2 mmol, 0.2 equiv). To this was added 10 mL of acetonitrile and 1 mL of water. The solution was heated to 65°C in an oil bath for 36 hours. The reaction was monitored by NMR (the reaction stalled after 36 hours). Volatiles were removed under reduced pressure and the residue was extracted with diethyl ether (3 x 10 mL). Combined organic layer was washed with 1M NaOH (10 mL) and H\(_2\)O (10 mL). The organic phase was dried with MgSO\(_4\) and solvent removed under reduced pressure. The residue was purified by flash chromatography (silica, 16 cm x 2 cm; 500 mL of 95:5:2, hexane/EtOAc/Triethylamine, 200 mL of 90:10 hexane/EtOAc, 200 mL of 50:50 hexane/EtOAc), to afford 195 mg of brown liquid. The residue was dissolved in ~0.5 mL boiling diethylther, to it slowly added ~3 mL of pentane. The solution was cooled to room temperature and then to -20°C in a freezer. Filtered to give 170 mg of 165b as white needle like crystals.
Data for 164b:

Mol. Formula: C_{16}H_{17}NO

m.p.: 63-64 °C

\(^1\)H NMR: (500 MHz, CDCl\(_3\))
\[\delta 3.45 (d, J = 7.3 \text{ Hz}, 4\text{H}, \text{HC}(7) \text{ and } \text{HN}(15)), 3.75 (s, 3\text{H}, \text{HC}(14)), 6.33 (dt, J = 15.8, 6.2 \text{ Hz}, 1\text{H}, \text{HC}(8)), 6.45 (dt, J = 16.0, 1.4 \text{ Hz}, 1\text{H}, \text{HC}(9)), 6.65 (d, J = 8.5 \text{ Hz}, 1\text{H}, \text{HC}(3)), 6.67 (dd, J = 8.4, 2.9 \text{ Hz}, 1\text{H}, \text{HC}(2)), 6.72 (d, J = 2.8 \text{ Hz}, 1\text{H}, \text{HC}(6)), 7.24 – 7.17 (m, 1\text{H}, \text{HC}(13)), 7.31 – 7.27 (m, 2\text{H}, \text{HC}(12)), 7.35 (d, J = 7.0 \text{ Hz}, 2\text{H}, \text{HC}(11))\]

\(^{13}\)C NMR (125 MHz, CDCl\(_3\))
\[\delta 153.2 (\text{C}(1)), 138.5 (\text{C}(4)), 137.4 (\text{C}(5)), 131.6 (\text{C}(9)), 128.8 (\text{C}(12)), 127.7 (\text{C}(8)), 127.5 (\text{C}(13)), 126.4 (\text{C}(11)), 126.2 (\text{C}(10)), 117.3 (\text{C}(3)), 116.3 (\text{C}(6)), 113.0 (\text{C}(2)), 56.0 (\text{C}(14)), 36.0 (\text{C}(7))\]

FTIR: 3358 (w), 3024 (w), 2998 (w), 2936 (w), 2906 (w), 2831 (w), 1607 (w), 1500 (s), 1465 (m), 1448 (m), 1432 (m), 1323 (w), 1286 (w), 1242 (s), 1211 (w), 1189 (w), 1154 (m), 1075 (w), 1040 (m), 969 (m) 940 (w), 870 (w), 854 (w), 811 (m), 747 (m), 732 (m), 692 (s), 566 (m), 498 (w), 475 (m).

LR MS (ESI): 136 (M-Styrene\(^+\), 51), 239 (12), 240 (M+H\(^+\), 100), 241 (17).

HR MS (ESI): calcd for C\(_{16}\)H\(_{18}\)NO: 240.1383, found: 240.1391

Elemental Analysis: Calcd: C, 80.30%; H, 7.16%; N, 5.85%. Found: C, 80.25%; H, 7.05%; N, 5.93%.

TLC: \(R_f\) 0.25 (4:1 Hexanes/Ethylacetate)

Preparation of 1-[(E)-cinnamyl]naphthalen-2-amine (165c)

In a 50 ml flame dried schlenk flask was added 259 mg N-(1-phenylallyl)naphthalen-2-amine (1 mmol) followed by 39 mg of \(p\)-Toluenesulfonic acid monohydrate (0.2 mmol, 0.2 equiv). To this was added 10 mL of acetonitrile and 1 mL of water. The solution was heated to 65°C in an oil bath for 6 hours.
The solution was cooled to room temperature at which point a solid started to form. To this suspension was added 2 M NaOH (10 mL) and diethylether (20 mL). The organic layer was washed with brine (10 mL), dried with MgSO₄ and solvent removed under reduced pressure. The residue was purified by flash chromatography (silica, 16 cm x 2 cm; 300 mL of 95:5 hexane/EtOAc, 200 mL of 90:10 hexane/EtOAc, 250 mL of 50:50 hexane/EtOAc), to afford 210 mg of brown liquid. The residue was dissolved in ~0.5 mL boiling diethylther, to it slowly added ~2 mL of pentane. The solution was cooled to room temperature and then to -20 °C in a freezer. Filtered to give 192 mg of 165c as white crystals.

**Data for 164b:**

- **Mol. Formula:** C₁₉H₁₈N
- **m.p.** 66-68 °C
- **¹H NMR:** (500 MHz, CDCl₃)
  \[ \delta \ 3.86 \ (d, J = 4.5 \text{ Hz}, \ 4H, \ \text{HC}(7) \text{ and } \text{HN}(18)), \ 6.44 \text{ – } 6.34 \ (m, \ 2H, \ \text{HC}(8,9)), \ 6.99 \ (d, \ J = 8.7 \text{ Hz}, \ 1H, \ \text{HC}(3)), \ 7.17 \ (tt, \ J = 7.2, \ 2.2 \text{ Hz}, \ 1H, \ \text{HC}(17)), \ 7.26 \text{ – } 7.22 \ (m, \ 2H, \ \text{HC}(16)), \ 7.28 \ (tt, \ J = 5.4, \ 1.5 \text{ Hz}, \ 3H, \ \text{HC}(12,15)), \ 7.45 \ (dd, \ J = 8.5, \ 6.8, \ 1.4 \text{ Hz}, \ 1H, \ \text{HC}(11)), \ 7.64 \ (d, \ J = 8.7 \text{ Hz}, \ 1H, \ \text{HC}(2)), \ 7.75 \ (dt, \ J = 8.1, \ 0.7 \text{ Hz}, \ 1H, \ \text{HC}(13)), \ 7.88 \ (d, \ J = 8.6 \text{ Hz}, \ 1H, \ \text{HC}(10)). \]
- **¹³C NMR** (125 MHz, CDCl₃)
  \[ \delta \ 142.3 \ (C(4)), \ 137.4 \ (C(14)), \ 133.6 \ (C(6)), \ 130.7 \ (C(9)), \ 128.9 \ (C(13)), \ 128.8 \ (C(1)), \ 128.7 \ (C(16)), \ 128.3 \ (C(2)), \ 127.4 \ (C(17)), \ 127.3 \ (C(8)), \ 126.8 \ (C(11)), \ 126.3 \ (C(12)), \ 122.5 \ (C(10)), \ 122.4 \ (C(15)), \ 119.1 \ (C(3)), \ 114.7 \ (C(5)), \ 29.9 \ (C(7)). \]
- **FTIR**
  3023 (w), 1622 (s), 1600 (m), 1496 (m), 1473 (m), 1446 (m), 1435 (m), 1393 (m), 1356 (w), 1282 (m), 1259 (m), 1222 (w), 1164 (w), 964 (s), 908 (m), 857 (w), 811 (s), 782 (m), 731 (s), 691 (s), 672 (m), 648 (m), 617 (m), 599 (m), 586 (m), 545 (m), 518 (m), 500 (m), 477 (m).
- **LR MS (ESI)**
  156 (M-Styrene*, 100), 157 (11), 260 (M+H*), 261 (10)
- **HR MS (ESI)**
calcd for C₁₉H₁₈N: 260.1434, found: 260.1441
- **Elemental Analysis**
  Calcd: C, 80.30%; H, 7.16%; N, 5.85%. Found: C, 80.25%; H, 7.05%; N, 5.93%.
- **TLC:**
  \[ R_f \ 0.4 \ (4:1 \text{ Hexanes/Ethylacetate}) \]
Preparation of 1-[(E)-cinnamyl]naphthalen-2-amine (154)

To a 50 ml flame dried schlenk flask under argon with a stir bar and a septum was added 1.13 g of aniline 165a (5 mmol) and 15 mL DCM. The solution was cooled to 0°C and added 2 ml of pyridine (25 mmol, 5 equiv) and 1.43 g of 4-Toluenesulfonyl chloride (7.5 mmol, 1.5 equiv). Warmed to room temperature and stirred for 12h. To the solution was added brine (30 mL) and extracted with DCM (3 x 30 mL). Combined organic layer dried with MgSO₄ and solvent removed under reduced pressure. The residue was purified by flash chromatography (silica, 8 cm x 5 cm; 500 mL of 90:10 hexane/EtOAc, 200 mL of 85:15 hexane/EtOAc, 200 mL of 80:20 hexane/EtOAc, 200 mL of 75:25 hexane/EtOAc, 200 mL of 50:50 hexane/EtOAc), to afford 1.88 g of brown liquid. The residue was dissolved in ~10 mL boiling ethyl acetate. The solution was cooled to room temperature and then to -20 °C in a freezer. Filtered and mother liquor concentrated and recrystallized using ~5 mL of boiling ethyl acetate to give 1.63g of 154 as white fluffy solid.
Data for 154:

Mol. Formula: \( \text{C}_{22}\text{H}_{20}\text{FNO}_2\text{S} \)

m.p. 128-129 °C

\(^1\text{H NMR}: \) (500 MHz, CDCl\(_3\))
\[ \delta 2.39 (s, 3H, HC(19)), 3.18 (d, J = 6.01Hz, 2H, HC(7)), 6.04 (dt, J = 15.9, 6.5 Hz, 1H, HC(8)), 6.27 (dt, J = 16.2, 0.9 Hz, 1H, HC(9)), 6.32 (s, 1H, HN(14)), 6.89 (ddd, J = 19.0, 8.6, 3.0 Hz, 2H, HC(2 and 6)), 7.21 (d, J = 8.1 Hz, 2H, HC(17)), 7.31 – 7.26 (m, 6H, HC(3,11,12,13)), 7.57 (d, J = 8.3 Hz, 2H, HC(16)) \]

\(^13\text{C NMR}: \) (125 MHz, CDCl\(_3\))
\[ \delta 162.3 (\text{C}(1)), 144.2 (\text{C}(18)), 136.7 (\text{C}(15)), 136.6 (\text{C}(4)), 132.7 (\text{C}(9)), 130.6 (\text{C}(5) \text{ or C}(10)), 130.5 (\text{C}(5) \text{ or C}(10)), 129.9 (\text{C}(17)), 128.8 (\text{C}(6)), 128.0 (d, J = 6.0 Hz, \text{C}(3)), 127.9 (\text{C}(12)), 127.8 (\text{C}(13)), 127.4 (\text{C}(16)), 126.5 (\text{C}(11)), 126.4 (\text{C}(8)), 117.3 (d, J = 22.7 Hz, \text{C}(6)), 114.6 (d, J = 22.2 Hz, \text{C}(2)), 35.2 (\text{C}(7)), 21.8 (\text{C}(19)). \]

\(^19\text{F NMR}: \) (470 MHz, CDCl\(_3\))
\[ \delta -115.22 \]

FTIR
3270 (w), 3028 (w), 2924 (w), 1614 (w), 1598 (w), 1494 (m), 1448 (w), 1435, (w), 1392 (w), 1328 (w), 1305 (w), 1273 (w), 1200 (w), 1184 (w), 1157 (s), 1120 (w), 1092 (w), 1019 (w), 963 (w), 904 (w), 814 (w), 754 (w), 730 (w), 706 (w), 692 (w), 664 (m), 595 (w), 548 (m), 527 (m), 493 (w).

LR MS (ESI)
226 (21), 227 (M-Ts\text{*}, 100), 228 (18), 382 (M+H\text{*}, 72), 399 (36), 404 (17)

HR MS (ESI)
calcld for \( \text{C}_{22}\text{H}_{21}\text{FNO}_2\text{S} (\text{M+H}^+)\): 382.1271, found: 382.1273

Elemental Analysis
Calcd: C, 69.27%; H, 5.28%; N, 3.67%. Found: C, 69.36%; H, 5.20%; N, 3.70%.

TLC:
\( R_f \) 0.32 (4:1 Hexanes/Ethylacetate)
Preparation of N-[2-[(E)-cinnamyl]-4-fluoro-phenyl]-4-methyl-benzenesulfonamide (154)

To a 50 ml flame dried schlenk flask under argon with a stir bar and a septum was added 1.13 g of aniline 165a (5 mmol) and 15 mL DCM. The solution was cooled to 0°C and added 2 mL of pyridine (25 mmol, 5 equiv) and 1.43 g of 4-Toluenesulfonyl chloride (7.5 mmol, 1.5 equiv). Warmed to room temperature and stirred for 12h. To the solution was added brine (30 mL) and extracted with DCM (3 x 30 mL). Combined organic layer dried with MgSO$_4$ and solvent removed under reduced pressure. The residue was purified by flash chromatography (silica, 8 cm x 5 cm; 500 mL of 90:10 hexane/EtOAc, 200 mL of 85:15 hexane/EtOAc, 200 mL of 80:20 hexane/EtOAc, 200 mL of 75:25 hexane/EtOAc, 200 mL of 50:50 hexane/EtOAc), to afford 1.88 g of brown liquid. The residue was dissolved in ~10 mL boiling ethyl acetate. The solution was cooled to room temperature and then to -20 °C in a freezer. Filtered and mother liquor concentrated and recrystallized using ~5 mL of boiling ethyl acetate to give 1.63g of 154 as white fluffy solid.
Data for 154:

Mol. Formula: C_{22}H_{20}FNO_{2}S

m.p. 128-129 °C

^{1}H NMR: (500 MHz, CDCl_{3})
δ 2.39 (s, 3H, HC(19)), 3.18 (d, J = 6.01 Hz, 2H, HC(7)), 6.04 (dt, J = 15.9, 6.5 Hz, 1H, HC(8)), 6.27 (dt, J = 16.2, 0.9 Hz, 1H, HC(9)), 6.32 (s, 1H, HN(14)), 6.89 (ddd, J = 19.0, 8.6, 3.0 Hz, 2H, HC(2 and 6)), 7.21 (d, J = 8.1 Hz, 2H, HC(17)), 7.31 – 7.26 (m, 6H, HC(3,11,12,13)), 7.57 (d, J = 8.3 Hz, 2H, HC(16))

^{13}C NMR (125 MHz, CDCl_{3})
δ 162.3 (C(1)), 144.2 (C(18)), 136.7 (C(15)), 136.6 (C(4)), 132.7 (C(9)), 130.6 (C(5) or C(10)), 130.5 (C(5) or C(10)), 129.9 (C(17)), 128.8 (C(6)), 128.0 (d, J = 6.0 Hz, C(3)), 127.9 (C(12)), 127.8 (C13)), 127.4 (C(16)), 126.5 (C(11)), 126.4 (C(8)), 117.3 (d, J = 22.7 Hz, C(6)), 114.6 (d, J = 22.2 Hz, C(2)), 35.2 (C(7)), 21.8 (C(19)).

^{19}F NMR (470 MHz, CDCl_{3})
δ -115.22

FTIR
3270 (w), 3028 (w), 2924 (w), 1614 (w), 1598 (w), 1494 (m), 1448 (w), 1435, (w), 1392 (w), 1328 (w), 1305 (w), 1273 (w), 1200 (w), 1184 (w), 1157 (s), 1120 (w), 1092 (w), 1019 (w), 963 (w), 904 (w), 814 (w), 754 (w), 730 (w), 706 (w), 692 (w), 664 (m), 595 (w), 548 (m), 527 (m), 493 (w).

LR MS (ESI)
226 (21), 227 (M-Ts^{+}, 100), 228 (18), 382 (M+H^{+}, 72), 399 (36), 404 (17)

HR MS (ESI)
calcd for C_{22}H_{21}FNO_{2}S (M+H^{+}): 382.1271, found: 382.1273

Elemental Analysis
Calcd: C, 69.27%; H, 5.28%; N, 3.67%. Found: C, 69.36%; H, 5.20%; N, 3.70%.

TLC: R_{f} 0.32 (4:1 Hexanes/Ethylacetate)
Preparation of N-[2-[(E)-cinnamyl]-4-methoxy-phenyl]-4-methyl-benzenesulfonamide (155)

To a 50 ml flame dried schlenk flask under argon with a stir bar and a septum was added 1.17 g of aniline 165b (4.9 mmol) and 15 mL DCM. The solution was cooled to 0°C and added 1.97 ml of pyridine (24.5 mmol, 5 equiv) and 1.4 g of 4-Toluenesulfonyl chloride (7.35 mmol, 1.5 equiv). Warmed to room temperature and stirred for 12h. To the solution was added brine (30 mL) and extracted with DCM (3 x 30 mL). Combined organic layer dried with MgSO$_4$ and solvent removed under reduced pressure. The residue was dissolved in ~10 mL boiling ethyl acetate. The solution was cooled to room temperature and then to -20 °C in a freezer. Filtered and mother liquor concentrated and recrystallized using ~5 mL of boiling ethyl acetate to give 1.6 g of 155 as white solid.
Data for 155:

Mol. Formula: $\text{C}_{23}\text{H}_{23}\text{ONO}_3\text{S}$

m.p.: 114-115 °C

$^1$H NMR: (500 MHz, CDCl$_3$)
$\delta$ 2.39 (s, 3H, HC(19)), 3.17 (dd, $J$ = 6.5, 1.6 Hz, 2H, HC(7)), 3.77 (s, 3H, HC(20)), 6.06 (dt, $J$ = 15.9, 6.5 Hz, 1H, HC(8)), 6.26 (dt, $J$ = 15.8, 1.7 Hz, 1H, HC(9)), 6.31 (s, 1H, HN(14)), 6.69 (d, $J$ = 2.9 Hz, 1H, HC(6)), 6.72 (dd, $J$ = 8.7, 3.0 Hz, 1H, HC(2)), 7.19 (d, $J$ = 8.7 Hz, 1H, HC(3)), 7.24 – 7.20 (m, 3H, HC(17,13)), 7.31 – 7.27 (m, 4H, HC(11,12)), 7.58 (d, $J$ = 8.2 Hz, 2H, HC(16))

$^{13}$C NMR: (125 MHz, CDCl$_3$)
$\delta$ 158.68 (C(1)), 143.92 (C(18)), 137.02 (C(10)), 136.99 (C(5)), 132.03 (C(9)), 129.85 (C(17)), 128.79 (C(12)), 128.50 (C(3)), 127.73 (C(13)), 127.69 (C(10) or C(15)), 127.49 (C(16)), 127.41 (C(10) or C(15)), 127.30 (C(8)), 126.46 (C(11)), 116.04 (C(6)), 112.59 (C(2)), 55.63 (C(20)), 35.36 (C(7)), 21.82 (C(19))

FTIR:
3271 (w), 3027 (w), 2957 (w), 2837 (w), 1599 (m), 1581 (w), 1496 (s), 1464 (w), 1448 (w), 1433 (w), 1399 (m), 1327 (m), 1304 (m), 1290 (m), 1215 (m), 1185 (w), 1159 (s), 1092 (m), 1038 (m), 968 (m), 945 (w), 899 (m), 814 (m), 753 (m), 731 (m), 693 (m), 665 (m), 596 (w), 550 (m).

LR MS (ESI):
239 (M-Ts+, 100), 240 (18), 394 (M+H+, 45), 395 (12), 411 (10)

HR MS (ESI):
calcd for C23H24ONO3S: 394.1471, found: 394.1479

Elemental Analysis:
Calcd: C, 70.20%; H, 5.89%; N, 3.56%. Found: C, 69.85%; H, 5.81%; N, 3.59%.

TLC: $R_f$ 0.30 (4:1 Hexanes/Ethylacetate)
Preparation of N-[1-[(E)-cinnamyl]-2-naphthyl]-4-methyl-benzenesulfonamide (156)

To a 50 ml flame dried schlenk flask under argon with a stir bar and a septum was added 1.43 g of aniline 165c (5.5 mmol) and 17 mL DCM. The solution was cooled to 0°C and added 2.2 ml of pyridine (27.5 mmol, 5 equiv) and 1.57 g of 4-Toluenesulfonyl chloride (8.25 mmol, 1.5 equiv). Warmed to room temperature and stir red for 12h. To the solution was add ed brine (30 mL) and extracted with DCM (3 x 30 mL). Combined organic layer dried with MgSO₄ and solvent removed under reduced pressure to give dark brown oil. The residue was dissolved in diethyl ether and yellow solid immediately crashed out. It was filtered and dissolved in ~10 mL boiling ethyl acetate. The solution was cooled to room temperature and then to -20 °C in a freezer. Filtered and mother liquor concentrated and recrystallized using ~5 mL of boiling ethyl acetate to give 1.9 g of 156 as yellow solid.
Data for 156:

Mol. Formula: \( \text{C}_{26}\text{H}_{23}\text{ONO}_2\text{S} \)

m.p. 148-149 °C

\(^1\)H NMR: (500 MHz, CDCl\(_3\))
\[ \delta \] 2.31 (s, 3H, HC(23)), 3.65 (dd, \( J = 5.4, 1.3 \) Hz, 2H, HC(7)), 6.13 (d, \( J = 16.1 \) Hz, 1H, HC(9)), 6.19 (dt, \( J = 16.1, 5.1, 1.1 \) Hz, 1H, HC(8)), 6.64 (s, 1H, HN(18)), 7.13 (d, \( J = 7.9 \) Hz, 2H, HC(21)), 7.22 – 7.17 (m, 3H, HC(15,17)), 7.24 (dd, \( J = 7.2, 1.2 \) Hz, 2H, HC(16)), 7.53 – 7.42 (m, 2H, HC(11,3)), 7.61 (d, \( J = 8.1 \) Hz, 2H, HC(20)), 7.66 (d, \( J = 8.8 \) Hz, 1H, HC(12)), 7.75 (d, \( J = 8.8 \) Hz, 1H, HC(13)), 7.84 (d, \( J = 8.1 \) Hz, 1H, HC(2)), 7.92 (d, \( J = 8.5 \) Hz, 1H, HC(10)).

\(^{13}\)C NMR: (125 MHz, CDCl\(_3\))
\[ \delta \] 144.1 (C(22)), 136.9 (C(14)), 136.8 (C(19)), 132.7 (C(6)), 132.6(C(1)), 132.4 (C(5)), 131.6 (C(9)), 129.9 (C(21)), 129.8 (C(4)), 128.9 (C(2)), 128.7 (C(16)), 128.4 (C(13)), 127.7 (C(17)), 127.5 (C(5)), 127.4 (C(20)), 127.0 (C(11)), 126.8 (C(8)), 126.4 (C(15)), 125.8 (C(3)), 124.5 (C(10)), 123.6 (C(12)), 30.0 (C(7)), 21.8 (C(23)).

FTIR 3283 (w), 1598 (m), 1512 (w), 1496 (w), 1468 (w), 1447 (w), 1407 (m), 1367 (m), 1320 (m), 1304 (m), 1234 (w), 1185 (w), 1159 (s), 1092 (m), 1067 (w), 1019 (w), 966 (m), 907 (m), 864 (w), 847 (w), 813 (m), 763 (m), 733 (s), 706 (m), 691 (m), 669 (s), 598 (m), 552 (s), 532 (m), 494 (w).

LR MS (ESI) 258 (22), 259 (M-Ts+, 100), 260 (18), 436 (M+Na+, 25)

HR MS (ESI) calcd for C26H23ONO2SNa: 436.1342, found: 436.1347

Elemental Analysis Calcd: C, 75.52%; H, 5.61%; N, 3.39%. Found: C, 75.19; H, 5.63%; N, 3.51%.

TLC: \( R_f \) 0.38 (4:1 Hexanes/Ethylacetate)
# Table of Screens

## Table 8 Solvent Screen

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>Ligand</th>
<th>15 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>16 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Disiloxane 20 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>PCy&lt;sub&gt;3&lt;/sub&gt;</td>
<td>10.2</td>
<td>0.0</td>
<td>89.8</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>JohnPhos</td>
<td>0</td>
<td>0.0</td>
<td>100.0</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>XPhos</td>
<td>5.0</td>
<td>0.0</td>
<td>95.0</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>RuPhos</td>
<td>0.0</td>
<td>0.0</td>
<td>100.0</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>dppe</td>
<td>0.0</td>
<td>0.0</td>
<td>100.0</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
<td>rec-BINAP</td>
<td>10.2</td>
<td>0.0</td>
<td>89.8</td>
</tr>
<tr>
<td>7</td>
<td>THF</td>
<td>rec-BINAP</td>
<td>10.2</td>
<td>0.0</td>
<td>89.8</td>
</tr>
<tr>
<td>8</td>
<td>Toluene</td>
<td>PCy&lt;sub&gt;3&lt;/sub&gt;</td>
<td>0.0</td>
<td>trace</td>
<td>100.0</td>
</tr>
<tr>
<td>9</td>
<td>Toluene</td>
<td>JohnPhos</td>
<td>0.0</td>
<td>0.0</td>
<td>90.6</td>
</tr>
<tr>
<td>10</td>
<td>Toluene</td>
<td>XPhos</td>
<td>0.0</td>
<td>0.0</td>
<td>100.0</td>
</tr>
<tr>
<td>11</td>
<td>Toluene</td>
<td>RuPhos</td>
<td>0.0</td>
<td>0.0</td>
<td>100.0</td>
</tr>
<tr>
<td>12</td>
<td>Toluene</td>
<td>dppe</td>
<td>22.8</td>
<td>0.0</td>
<td>77.2</td>
</tr>
<tr>
<td>13</td>
<td>Toluene</td>
<td>dppe</td>
<td>14.5</td>
<td>0.0</td>
<td>85.5</td>
</tr>
<tr>
<td>14</td>
<td>Toluene</td>
<td>rec-BINAP</td>
<td>0.0</td>
<td>0.0</td>
<td>92.8</td>
</tr>
<tr>
<td>15</td>
<td>Dioxane</td>
<td>PCy&lt;sub&gt;3&lt;/sub&gt;</td>
<td>80.4</td>
<td>trace</td>
<td>15.2</td>
</tr>
<tr>
<td>16</td>
<td>Dioxane</td>
<td>JohnPhos</td>
<td>87.3</td>
<td>0.0</td>
<td>10.2</td>
</tr>
<tr>
<td>17</td>
<td>Dioxane</td>
<td>XPhos</td>
<td>77.2</td>
<td>0.0</td>
<td>20.8</td>
</tr>
<tr>
<td>18</td>
<td>Dioxane</td>
<td>RuPhos</td>
<td>84.2</td>
<td>trace</td>
<td>14.6</td>
</tr>
<tr>
<td>19</td>
<td>Dioxane</td>
<td>dppe</td>
<td>81.9</td>
<td>trace</td>
<td>13.2</td>
</tr>
<tr>
<td>20</td>
<td>Dioxane</td>
<td>dppe</td>
<td>85.6</td>
<td>0.0</td>
<td>11.4</td>
</tr>
<tr>
<td>21</td>
<td>Dioxane</td>
<td>rec-BINAP</td>
<td>91.3</td>
<td>0.0</td>
<td>5.6</td>
</tr>
</tbody>
</table>

<sup>a</sup> All reactions were performed on 0.1 mmol of 15 and 14a unless otherwise noted. <sup>b</sup>Yield based on GC analysis relative to an internal standard (dodecane).
Table 9 Coupling Partner

<table>
<thead>
<tr>
<th>entry</th>
<th>Halogen</th>
<th>Ligand</th>
<th>15 (%)</th>
<th>16 (%)</th>
<th>Disiloxane 20 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>PCy₃</td>
<td>41.2</td>
<td>0.0</td>
<td>57.4</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>JohnPhos</td>
<td>30.3</td>
<td>0.0</td>
<td>65.4</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>dpf</td>
<td>0.0</td>
<td>0.0</td>
<td>95.0</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>dppe</td>
<td>64.2</td>
<td>0.0</td>
<td>32.9</td>
</tr>
<tr>
<td>5</td>
<td>Br</td>
<td>rac-binap</td>
<td>66.5</td>
<td>0.0</td>
<td>31.2</td>
</tr>
<tr>
<td>6</td>
<td>Br</td>
<td>phenanthroline</td>
<td>54.3</td>
<td>0.0</td>
<td>42.6</td>
</tr>
<tr>
<td>7</td>
<td>Br</td>
<td>BPy</td>
<td>62.4</td>
<td>0.0</td>
<td>36.8</td>
</tr>
<tr>
<td>8</td>
<td>I</td>
<td>PCy₃</td>
<td>55.6</td>
<td>0.0</td>
<td>40.3</td>
</tr>
<tr>
<td>9</td>
<td>I</td>
<td>JohnPhos</td>
<td>48.9</td>
<td>0.0</td>
<td>48.7</td>
</tr>
<tr>
<td>10</td>
<td>I</td>
<td>dpf</td>
<td>25.2</td>
<td>0.0</td>
<td>62.0</td>
</tr>
<tr>
<td>11</td>
<td>I</td>
<td>dppe</td>
<td>0.0</td>
<td>0.0</td>
<td>100.0</td>
</tr>
<tr>
<td>12</td>
<td>I</td>
<td>rac-binap</td>
<td>0.0</td>
<td>0.0</td>
<td>100.0</td>
</tr>
<tr>
<td>13</td>
<td>I</td>
<td>phenanthroline</td>
<td>0.0</td>
<td>0.0</td>
<td>100.0</td>
</tr>
<tr>
<td>14</td>
<td>I</td>
<td>BPy</td>
<td>0.0</td>
<td>0.0</td>
<td>96.8</td>
</tr>
</tbody>
</table>

All reactions were performed on 0.1 mmol of 15 and 14 unless otherwise noted. Yield based on GC analysis relative to an internal standard (dodecane).

Table 10 Screen with Benzyl substituent

<table>
<thead>
<tr>
<th>entry</th>
<th>Halogen</th>
<th>Ligand</th>
<th>15 (%)</th>
<th>22 (%)</th>
<th>Disiloxane 20 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>PCy₃</td>
<td>0.0</td>
<td>trace</td>
<td>95.2</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>JohnPhos</td>
<td>0.0</td>
<td>trace</td>
<td>94.3</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>dpf</td>
<td>0.0</td>
<td>0.0</td>
<td>96.6</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>dppe</td>
<td>0.0</td>
<td>0.0</td>
<td>92.3</td>
</tr>
<tr>
<td>5</td>
<td>Br</td>
<td>rac-binap</td>
<td>10.2</td>
<td>trace</td>
<td>84.5</td>
</tr>
<tr>
<td>6</td>
<td>Br</td>
<td>phenanthroline</td>
<td>8.5</td>
<td>0.0</td>
<td>86.3</td>
</tr>
<tr>
<td>7</td>
<td>Br</td>
<td>BPy</td>
<td>8.6</td>
<td>trace</td>
<td>85.7</td>
</tr>
<tr>
<td>8</td>
<td>Cl</td>
<td>PCy₃</td>
<td>32.6</td>
<td>0.0</td>
<td>66.3</td>
</tr>
<tr>
<td>9</td>
<td>Cl</td>
<td>JohnPhos</td>
<td>62.3</td>
<td>trace</td>
<td>30.5</td>
</tr>
<tr>
<td>10</td>
<td>Cl</td>
<td>dpf</td>
<td>69.8</td>
<td>0.0</td>
<td>25.4</td>
</tr>
<tr>
<td>11</td>
<td>Cl</td>
<td>dppe</td>
<td>64.5</td>
<td>0.0</td>
<td>31.9</td>
</tr>
<tr>
<td>12</td>
<td>Cl</td>
<td>rac-binap</td>
<td>42.3</td>
<td>0.0</td>
<td>54.7</td>
</tr>
<tr>
<td>13</td>
<td>Cl</td>
<td>phenanthroline</td>
<td>59.1</td>
<td>0.0</td>
<td>38.3</td>
</tr>
<tr>
<td>14</td>
<td>Cl</td>
<td>BPy</td>
<td>61.3</td>
<td>0.0</td>
<td>37.2</td>
</tr>
</tbody>
</table>

All reactions were performed on 0.1 mmol of 15 and 21 unless otherwise noted. Yield based on GC analysis relative to an internal standard (dodecane).
**Table 11** Hartwig’s Catalyst

\[
\text{C}_9\text{H}_{17} \xrightarrow{\text{OK}} \text{Si} \xrightarrow{\text{R-X}} \text{(dppf)Ni(cinnamyl)Cl} \xrightarrow{\text{dodecane, Dioxane, rt, 24 h}} \text{C}_9\text{H}_{17} \xrightarrow{\text{R}} \text{Si} \xrightarrow{\text{O}} \text{Si} \xrightarrow{\text{C}_9\text{H}_{17}} \\
15 + R \rightarrow X
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>Halogen</th>
<th>R</th>
<th>15 (%)</th>
<th>Disiloxane 20 (%)</th>
<th>Product (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I</td>
<td>TMSmethyl</td>
<td>42.5</td>
<td>55.8</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>TMSmethyl</td>
<td>47.5</td>
<td>51.6</td>
<td>0.0</td>
</tr>
<tr>
<td>3</td>
<td>Cl</td>
<td>TMSmethyl</td>
<td>68.1</td>
<td>29.5</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>Benzyl</td>
<td>33.4</td>
<td>65.3</td>
<td>trace</td>
</tr>
<tr>
<td>5</td>
<td>Cl</td>
<td>Benzyl</td>
<td>66.9</td>
<td>31.7</td>
<td>0.0</td>
</tr>
</tbody>
</table>

\(^a\) All reactions were performed on 0.1 mmol of 15 and 14a-c or 21a-b unless otherwise noted. \(^b\) Yield based on GC analysis relative to an internal standard.

**Table 12** NiBr<sub>2</sub>.Diglyme Screen

\[
\text{C}_9\text{H}_{17} \xrightarrow{\text{Ph-X}} \text{OK} \xrightarrow{\text{21a-b}} \xrightarrow{\text{10 mol % NiBr}_2, \text{Diglyme, 20 mol % ligand}} \text{Dodecane, Dioxane, rt, 24 h} \xrightarrow{\text{C}_9\text{H}_{17}} \text{Ph} \xrightarrow{\text{Si}} \text{Si} \xrightarrow{\text{C}_9\text{H}_{17}} \\
15 + Ph \rightarrow X
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>Halogen</th>
<th>Ligand</th>
<th>15 (%)</th>
<th>22 (%)</th>
<th>Disiloxane 20 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Br</td>
<td>PCy&lt;sub&gt;3&lt;/sub&gt;</td>
<td>10.2</td>
<td>0.0</td>
<td>85.3</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>JohnPhos</td>
<td>14.3</td>
<td>trace</td>
<td>83.8</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>dppf</td>
<td>6.3</td>
<td>trace</td>
<td>92.3</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>dppe</td>
<td>20.9</td>
<td>trace</td>
<td>78.4</td>
</tr>
<tr>
<td>5</td>
<td>Br</td>
<td>rac-binap</td>
<td>6.2</td>
<td>trace</td>
<td>95.5</td>
</tr>
<tr>
<td>6</td>
<td>Br</td>
<td>phenanthroline</td>
<td>6.4</td>
<td>trace</td>
<td>91.3</td>
</tr>
<tr>
<td>7</td>
<td>Br</td>
<td>BPY</td>
<td>12.2</td>
<td>trace</td>
<td>86.8</td>
</tr>
<tr>
<td>8</td>
<td>Cl</td>
<td>PCy&lt;sub&gt;3&lt;/sub&gt;</td>
<td>55.3</td>
<td>trace</td>
<td>42.5</td>
</tr>
<tr>
<td>9</td>
<td>Cl</td>
<td>JohnPhos</td>
<td>64.1</td>
<td>trace</td>
<td>34.9</td>
</tr>
<tr>
<td>10</td>
<td>Cl</td>
<td>dppf</td>
<td>65.4</td>
<td>trace</td>
<td>33.5</td>
</tr>
<tr>
<td>11</td>
<td>Cl</td>
<td>dppe</td>
<td>56.2</td>
<td>trace</td>
<td>42.3</td>
</tr>
<tr>
<td>12</td>
<td>Cl</td>
<td>rac-binap</td>
<td>51.8</td>
<td>0.0</td>
<td>48.3</td>
</tr>
<tr>
<td>13</td>
<td>Cl</td>
<td>phenanthroline</td>
<td>48.3</td>
<td>0.0</td>
<td>51.3</td>
</tr>
<tr>
<td>14</td>
<td>Cl</td>
<td>BPY</td>
<td>41.5</td>
<td>0.0</td>
<td>48.2</td>
</tr>
</tbody>
</table>

\(^a\) All reactions were performed on 0.1 mmol of 15 and 21a-b unless otherwise noted. \(^b\) Yield based on GC analysis relative to an internal standard.
Chapter 6: References


(45) Li, X.; Zhao, G.; Cao, W., Chinese Journal of Chemistry, **2006**, 24, 1402—1405.


