ABSTRACT

APPLICATION OF 1-HYDROSILATRANE AS A ROBUST REDUCING REAGENT

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In this work 1-Hydrosilatrane has shown great potential to be a commodity reducing reagent in organic synthesis. Initially, 1-hydrosilatrane was investigated as a reducing reagent in the transformation of aldehydes to corresponding alcohols. Although initial investigations did not confirm previously published work, after addition of a Lewis base activator 1-hydrosilatrane demonstrated speedy reductions of many functionalized aryl aldehydes to alcohols with good yields. Next, 1-hydrosilatrane was used in a direct reductive amination reaction between primary amines and aldehydes/ketones. Reaction proceeded in the presence of a Brønsted acid, and resulted in excellent yields. This reaction was then expanded to chiral Brønsted acids and demonstrated the potential of 1-hydrosilatrane as a reagent in chiral reactions with enantiomeric excess of up to 84%. This work demonstrates versatility of 1-hydrosilatrane and presents it as a must have reagent in every organic chemistry lab.
APPLICATION OF 1-HYDROSILATRANE AS A ROBUST REDUCING REAGENT

BY

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CHAPTER 1

INTRODUCTORY TOPICS

1.1.1 Hypercoordinate silanes

Silicon is a unique element. Although in the same group as carbon, it has an affinity to form penta- or hexacoordinate species. The first discovery of hypercoordinate silane was made in the 19th century by Gay-Lussac and Davy by reacting silicon tetrafluoride and ammonia to give \( \text{SiF}_4(\text{NH}_3)_2 \) (Figure 1.1). This ability to have expanded valency gives silicon unique reactivity and structural characteristics.

![Figure 1.1. First example of hypercoordinate silane.](image)

Although hypercoordination of silicon has been known for quite some time, the silicon chemistry community is yet to come to a consensus on the way silicon achieves hypercoordination. One camp supports the older idea of silicon atoms utilizing \( d \)
orbitals to achieve hypercoordination. This theory is consistent with the molecular geometry of penta- and hexacoordinate silanes and valence bond theory. Yet, the idea of three center four electron bonding has been gaining momentum since the 1960’s because of its better fit with the energetics of orbitals. The electrons reside on the ligand in the non-bonding orbital; thus more electronegative atoms like F, Cl, and OR stabilize the overall system (Figure 1.2).

Formation of hypercoordinate silanes is straightforward (Figure 1.3). In a) organosilanes readily react with anions like $\text{F}^-$, $\text{Cl}^-$ and OR to form anionic penta- and hexacoordinate silicon complexes. In b) neutral high coordinate silane complexes are also possible, with the addition of a neutral donor to a silane containing good electron withdrawing substitutions, as in $\text{SiF}_4(\text{NH}_3)_2$. In c) hypercoordination can be internal, as in the case of silatrane. This forms from reaction of triethanolamine with
trialkoxydisilane. These caged molecules are extremely stable and can be used for a variety of applications.

Although hypercoordinate silanes exceed the octet rule, they exhibit a large spectrum of reactivity. Chemists have examined very reactive molecules like the tetraalkoxyhydrosilanes that reduce alkyl halides and carbonyls. On the other hand, they have also prepared water stable compounds like silatranes that can undergo atom transfer and coupling reactions, and silicon phthalocyanines that are used in photolytic drug therapy.

1.2.1 Silatranes

Silatranes are a class of pentacoordinate silicon compounds with history spanning the past fifty years. From the first synthesis by Frye et. al., to present day, silatranes continue to be a focus point for many organic silicon chemists such as...
Corriu, Frye, Hencsei, Lukevics, Verkade, Voronkov and others, focusing on structure investigations\textsuperscript{15,16}, reactivity\textsuperscript{17–20}, and biological activity\textsuperscript{21–24}.

Structurally, silatranes are a unique pentacoordinate silane with a nearly trigonalbipyramidal silicon and a nitrogen lone pair pointing at the silicon creating a Si-N dative bond. The dative bond has been a source of much interest and investigation. Manipulation of the Si-X substitution can lead to a notable change in the Si-N distance. Electron withdrawing groups tend to shorten the Si-N dative bond, like in the case of 1-fluorosilatrane\textsuperscript{25} with Si-N = 2.042Å, while electron donating substitutions are prone to Si-N bond elongation, with the longest reported being silatranylosmium complex\textsuperscript{26} with Si-N = 3.176Å.

The most common method of synthesizing silatranes is the reaction of triethanolamine with a trisubstituted silane, typically a trialkoxysilane. This method is preferred because of the ready availability of trialkoxysilanes and the simplicity of the procedure. For a successful reaction, one uses a high boiling inert solvent, usually xylene or toluene, and a hydroxide or alkoxide base catalyst. The byproducts are typically volatile alcohols like ethanol or methanol and are easily driven off with distillation. This method produces a variety of different silatranes, including 1-hydro-\textsuperscript{27}, 1-alkyl\textsuperscript{28}, 1-aryl\textsuperscript{29} and other silatranes.

Despite the hypercoordinate nature of the silicon silatranes is quite stable. This can be attributed to the cage skeleton and the dative bond to the nitrogen, this essentially blocks the possibility of a backside attack on the silicon. Unlike tetracoordinate silanes, silatranes rarely undergo nucleophilic substitution at the silicon, exceptions envolving Grignard and organolithium\textsuperscript{30} substrates. Moreover, the
nitrogen does not undergo reactions with electrophiles like MeI\textsuperscript{31} or even strong acids\textsuperscript{32}, although super acids react with almost exo-silatranes like the silatranylosmium complex.\textsuperscript{26}

![Figure 1.4. Hydrolysis of silatrane.](image)

Although much more slowly than do the parent tetracoordinate alkoxy silanes, silatranes do undergo hydrolysis (Figure 1.4). Experimental and computational study suggests that, in the first step of this twostep process, oxygen of water coordinates reversibly to the silicon atom while the hydrogen coordinates to the cage oxygen atom. Subsequently, in the rate-determining step, one of the arms of the triethanolamine dissociates from Si, opening the cage. This is then followed by the similar addition at the other Si-O bonds until full liberation of the triethanolamine.\textsuperscript{31} The rate of hydrolysis increases with decrease in pH.\textsuperscript{31, 33} Furthermore, the rate of the hydrolysis can be influenced by a variety of factors such as Si-N distance, substitution on the cage, and the nature of the Si-X interaction.\textsuperscript{34}
1.2.2 1-Hydrosilatrane

![1-Hydrosilatrane](image)

Figure 1.5. 1-Hydrosilatrane.

The simplest silatrane, 1-hydrosilatrane (1), undergoes a variety of chemical transformations (Figure 1.6). It rapidly reacts with dihalides and halonic acids to produce halosilatranes\(^{32}\) (5) in excellent yields. A related point to consider is that the reaction can only produce bromo- and chlorosilatranes while iodosilatrane cannot be obtained by this method. The only known way of obtaining iodosilatrane (6) is by the reaction of 1-hydrosilatrane with perfluoroalkyl iodides\(^ {35}\) under ultraviolet light irradiation with the product forming in almost quantitative yields. Reaction of 1 with an alcohol or phenol produces the respective silatrane alkoxy or phenoxy silatrane\(^ {36}\) (7). This reaction is prominent at reflux in high boiling solvents like xylene and often catalyzed by an alkoxide ion. Like the reaction with alcohols, 1 can react with carboxylic acids to form carboxysilatranes (8), giving excellent yields when ZnCl\(_2\) is used as a catalyst.\(^ {31}\)
Figure 1.6. Exchange reactions with 1-Hydrosilatrane.

Being a hypercoordinate silicon hydride, 1 can be utilized as a reducing agent.

Eaborn et al. reported the potential of 1-hydrosilatrane to reduce a variety of functional groups (Figure 1.7). Although quite harsh conditions were used, (refluxing xylene over 72h), the reaction yields were low. Nevertheless, the 1-hydrosilatrane was reported to reduce acetone, 4-hydroxybenzaldehyde, benzyl bromide, benzoyl chloride, azoxybenzene and nitrobenzene\(^\text{37}\).
Like some in its family, 1-hydrosilatrane can undergo an exchange reaction with trialkyl halo silanes. This is a peculiar reaction where the hydride and the halide switch places. It is not well understood, but the typical trend is in formation of a shorter Si-N bond\textsuperscript{31}.

A special mention must be made on the reactivity of 1-hydrosilatrane with the metal salts of mercury, silver and copper (Figure 1.8). 1-Chlorosilatrane is formed within several hours at ambient temperature by reacting copper chloride with 1-
hydrosilatrane in 79% yield. Silver nitrate and chloride react rapidly with 1-hydrosilatrane to produce metallic silver and corresponding chloro- or nitrato-silatrane. The mercury salt reacts similarly the selectively producing a variety of silatrane derivatives with NO₃, OCOMe, OCOCF₃, OCOCCL₃, SCN and Br substituents in excellent yields.

Figure 1.8. Reaction of 1-Hydrosilane with metal salts.

Some transition metal complex with 1-hydrosilatrane to produce crystalline adducts. Those solids are unusual in structure and special mention must be made regarding the length of the Si-N bond. The platinum complex exhibits Si-N distance of 2.89 Å the osmium complex 3.176 Å and the ruthenium complex 3.000 Å.

Transition metal-catalyzed coupling reactions are possible with 1-hydrosilatrane and an aryl halide. This was shown with the example of iridium catalyzed coupling by Miyaura. Also, rhodium catalyzed coupling was successful with electronically deficient iodoaryl rings in good yields.
1.3.1 Reduction using hydrosilanes

In recent years reductions using silicon have hydrides become a widely explored topic. Any compound with one or more Si-H bonds can act as a hydride donor under set conditions. This is possible because in the Si-H bond the hydrogen is slightly hydridic. This can be explained when looking at the electronegativity values of Si (1.90) and H (2.20)\textsuperscript{45}. Although the difference in electronegativity is small this still makes the Si-H bond weakly polarized, making silane reagents less reactive and more selective reducing reagents.

$$\text{R}_3\text{Si}-\text{H} + \overset{\text{C}^+}{\text{R}^\text{C}} \rightarrow \overset{\text{R}''\text{H}}{\text{R}'\text{C}'}$$

$$\text{R}_3\text{Si}-\text{H} + \text{LB}^- \rightarrow \overset{\text{X \text{R}''\text{R}'}}{\text{R}'\text{C}'}$$

Figure 1.9. Hydride transfer with hydrosilanes.

Unlike the majority of other reducing reagents like sodium borohydride and lithium aluminum hydride, silane reducing reagents do not typically react spontaneously with weakly polarized functional groups like aldehydes, ketones, or amines, making them mild reducing reagents. For the reaction to occur the silane needs one of two things: a) a sufficiently electrophilic center like a carbocation\textsuperscript{46} or b) a silane center with expanded coordination\textsuperscript{47-49} (Figure 1.9). The formation of carbocation is usually forced by addition of a strong Lewis or Brønsted acid to the
reaction mixture forcing the formation of a charged species; this is possible due to a slow reactivity of silicon hydrides with acids. On the other hand, the coordination number can be expanded which increasing the nucleophilicity of the silicon peripheral groups making the hydride more reactive. This method uses strong Lewis bases like alkoxy\(^5\) or fluoride ions\(^\text{51}\).

### 1.3.2 Reduction of aldehydes using hydrosilane

As stated earlier, tetracoordinated hydrosilanes do not spontaneously react with aldehydes. Reduction is still possible (Figure 1.10), providing a good Brønsted acid like trifluoroacetic\(^\text{52,53}\) acid or sulfuric acid\(^\text{54}\) is used with triethylsilane (Figure 1.10a). This is done thru protonation of an aldehyde oxygen resulting in an electron deficient carbonyl carbon that is attacked by the silicon hydride. Lewis acids can also be used. BF\(_3\) with triethylsilane is an example\(^\text{55,56}\) (Figure 1.10b) it coordinates to the carbonyl oxygen drawing electron density away from the carbonyl carbon allowing attack by hydride. This method has its limitations in that acid-sensitive functional groups cannot be present.

![Figure 1.10. Acid activated reductions using hydrosilanes.](image-url)

\[ \text{R}_3\text{SiH} + \text{RCHO} \xrightarrow{\text{H}^+} \text{RCH(OH)R} \]

\[ \text{R}_3\text{SiH} + \text{RCHO} \xrightarrow{\text{BF}_3} \text{RCH(OH)R} \]
When using hydrosilanes, the more common and selective method for reduction of aldehydes is with the use of Lewis base nucleophiles (Figure 1.11). This method has been explored in depth. The reaction occurs with or without solvent, with a fluoride or alkoxy anion activator, under heterogeneous or homogenous conditions. These types of reactions have good chemoselectivity and functional group tolerance. When looking at activators, fluoride anions are one of the more widely used. Fluoride has a naturally strong attraction towards silicon. The driving force behind this is the Si-F bond being one of the strongest bonds in chemistry\(^{86}\). The source of the fluoride can vary. For example, reaction of aryl aldehyde with triethoxy silane in presence of fluoride activator gives different yields depending on the activator. Cesium fluoride (CsF) is deemed to be the most effective (95% yield) while tetraethylammonium fluoride results in 36% yield\(^{57}\). Alkoxy anions are popular activators for reductions of aldehydes. Lithium, sodium, and potassium salts of many alcohols and phenols can be used in activation\(^9,48,58\). The reaction works by a mechanism similar to that of fluoride anion activation, through coordination with the silicon hydride, resulting in formation of a more hydridic hydride.

\[
R_3\text{Si-H} + X^- \rightarrow \begin{bmatrix} R''_1\text{Si}^{-}\text{H} \, & \, \, \text{Si}^{-}\text{R} \end{bmatrix}^- + R'O\, R'^{-}\, R''^+ \rightarrow \text{OH} \, R'^{-}\, R''^+
\]

Figure 1.11. Lewis base activated reduction with hydrosilane.
1.3.3 Direct reductive amination

Direct reductive amination (DRA) is a process by which aldehyde or a ketone reacts with an amine resulting in formation of imine in the case of primary amines, or an iminium ion when the secondary amines are used. After the formation of the imine or iminium ion the reducing species donates hydride resulting in formation of an amine. This is a preferred method for synthesis of many pharmaceutical, agricultural, and fine chemical compounds.

\[
\begin{align*}
\text{R}^\alpha\text{R}' & + \text{R''N}^+\text{R'''} - \text{H}_2\text{O or O}^- \rightarrow \text{R''N}^+\text{R'''R'} \\
& \xrightarrow{\text{R}_3\text{Si-H}} \text{R''N}^+\text{R'''R'} \rightarrow \text{R''N}^+\text{R'''}\text{R'}
\end{align*}
\]

Figure 1.12. Direct reductive amination using a hydrosilane.

In the literature, hydrosilanes are common reagents in reductive amination reactions (Figure 1.12). Use of transition metal catalysts like titanium, tin, and zinc is ubiquitous among DRA examples\textsuperscript{54,59,62}. Although a limited range of catalysts has been employed, the hydrosilanes that can be used are quite diverse. The most commonly used hydride source is triethylsilane\textsuperscript{54,61,63}, a moisture and air stable molecule that only reacts if a strong carbocation is present. Another commonly used silane is polymethylhydrosiloxane (PMHS)\textsuperscript{59}. Unfortunately, it has a major drawbacks: when exposed to Lewis bases it produces extremely pyrophoric silane gas, making this reagent unsuitable for large scale synthetic applications. Aminosilanes, where the amine and the silicon hydride are on the same molecule\textsuperscript{60}, are another interesting
hydride source. These aminosilanes require strong Lewis acid catalysts and long reaction time. Another common reagent is trichlorosilane\textsuperscript{62}, which is an abundant cheap reagent, although 1) its use creates a large amount of halogenated waste and 2) it reacts violently with water and if stored incorrectly has a short shelf life.

1.3.4 Chiral direct reductive amination

Chiral direct reductive amination is the most useful method for synthesis of optically active amines. There are many methods available for this transformation. Many of them involve transition metals\textsuperscript{64}, Hantzsch ester\textsuperscript{65,66}, frustrated Lewis pairs\textsuperscript{67} and silicon hydrides. Silicon hydrides are one of the least used. The majority of examples use trichlorosilane with a chiral Lewis base activator\textsuperscript{68,69}. This method results in good enantiomeric excesses (ee) and high yields, but as discussed previously it generates a large amount of halogenated waste. PMHS, when used with a strong chiral Lewis acid, results in high ee and yield, although the reaction requires high silane loading, low temperatures and long reaction times\textsuperscript{69,70}.

1.4.1 Chiral Brønsted acid catalysts

Catalysis using organic catalysis has become a big part of chemistry. The idea of using inexpensive, easily synthesized, and effective small organic molecules instead of expensive, toxic, and/or rare transition metals is appealing. Chiral Brønsted acids are a good example: the first use of a chiral Brønsted acid as a catalyst was by Jacobsen et al. in 1998 for the enantioselective Strecker reaction\textsuperscript{71}. Since then the field has expanded tremendously. In recent years use of 1.1’-bi-2-naphthol (BINOL)-
derived phosphoric acids by Akiyama et al. and Terada et al. have become popular. The versatility of these catalysts is truly remarkable; they use in a variety of different chiral reactions: Mannich reactions, Aza-Henry reactions, Friedel-Craft reactions, Aza-Ene-type reactions, Diels-Alder reactions, direct reductive aminations, and others.

Figure 1.13. BINOL and BINOL-phosphoric acid.

BINOL (Figure 1.13a) type catalysts are well known for their use in transition metal catalysis. The C2-symmetry is the key to the success of BINOL-derived phosphoric acids (Figure 1.13b), because when the proton migrates to the phosphorus oxygen the catalyst is then reformed. Another benefit of using BINOL derived catalysts is its availability from chemical vendors; both R and S variations are available at relatively low prices. Furthermore, functionalization of the BINOL backbone is not synthetically challenging. Functional groups at 3,3’-positions (Figure 1.13c) can be substituted in simple reactions.

The most popular method of synthesis of optically active amines is the use of chiral transition metal hydrogenation catalysts and hydrogen gas. Recently the use of chiral Brønsted acids became popular after List et al. (Figure 1.14). and MacMillan
et al.\textsuperscript{81} independently used Hantzsch ester (HEH) (6) in a DRA reaction with a catalytic amount of Brønsted acid. After these publications, 6 became a popular tool in chiral reductive amination reaction.

![Reaction scheme](image)

Figure 1.14. Hantzsch ester (HEH) direct reductive amination.
CHAPTER 2

REDUCTION OF ALDEHYDES USING 1-HYDROSILATRANE

*This chapter is adapted in part from our publication^82

2.1.1. General strategies

To investigate previous reductions using 1 we examined the literature. As discussed in previous sections the only reported use of 1 as a reducing agent came from Eaborn et al.\textsuperscript{37} This explored a limited number of examples involving aldehydes, ketones, acid chlorides, alkyl halides etc. To start our investigation we thought to optimize the reaction conditions and expand the scope of reduction of aldehydes.

When looking at reaction conditions presented by Eaborn et al. three areas merited investigation: 1) concentration of the reaction components, 2) choice of reaction solvent, 3) and use of an activator.

2.1.2 Activator free conditions

Repeating the literature procedure was the first step in the investigation of optimal conditions. Direct reaction using literature conditions (Table 2.1, entries 1-2) gave no alcohol product and only starting material, \( p \)-hydroxybenzaldehyde (7), was isolated. Attempts involving increased concentrations also did not yield any reduction product (Table 2.1, entries 3-4). This suggests that reaction does not proceed as the literature outlines and other optimizations were required.
Table 2.1 Attempts to repeat literature reports.

<table>
<thead>
<tr>
<th>entry</th>
<th>1-hydrosilatrane mmol</th>
<th>concentration mmol</th>
<th>temperature</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.02</td>
<td>0.005</td>
<td>140</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>0.02</td>
<td>0.006</td>
<td>140</td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td>0.4</td>
<td>0.1</td>
<td>reflux</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>0.11</td>
<td>0.4</td>
<td>reflux</td>
<td>NR</td>
</tr>
</tbody>
</table>

With unsuccessful initial results we investigated a variety of different solvents in hopes of forcing the reaction to proceed. The solubility of 1-hydrosilatrane in xylene is quite poor, and even at reflux temperatures a large quantity of xylene is needed to solubilize a small quantity of 1-hydrosilatrane. We started by changing the aldehyde from $p$-hydroxybenzaldehyde (7) to $p$-methoxybenzaldehyde (10). With this change we hoped to eliminate a phenolic proton, but still maintain an electron-donating group in the para position thus mimicking the electronic characteristics of the original investigation. During the solvent investigation, use of nonpolar solvents like benzene (Table 2.2, entry 1) diglyme (entry 2) tetrahydrofuran (THF) (entry 5) and polar solvents like methanol (entry 3) acetonitrile (entry 6) and dimethyl formamide (DMF) (entry 7) all gave no product formation. The exception to this was water (entry 4), providing small amounts of product. During the course of this solvent investigation it was determined that 1-hydrosilatrane is poorly soluble in non-polar solvents like benzene, diglyme, and THF and very soluble in polar solvents like DMF,
water, methanol and acetonitrile. However, as mentioned previously, 1-hydrosilatrane undergoes hydrolysis in water, and it is especially fast at the elevated temperature of the reaction, essentially destroying the reducing reagent prior to the reaction with aldehyde.

Table 2.2 Solvent screening.

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Benzene</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>Diglyme</td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td>Methanol</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>Water</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>Acetonitrile</td>
<td>NR</td>
</tr>
<tr>
<td>7</td>
<td>DMF</td>
<td>NR</td>
</tr>
</tbody>
</table>

Although reactions in water gave some product, the majority of 1-hydrosilatrane was hydrolyzed. This being the dominant reaction, we thought that varying the concentration of water in different polar solvents would slow the hydrolysis of 1-hydrosilatrane and increase our desired reduction product (Table 2.3). All of the reaction were run at room temperature to decrease the rate of hydrolysis and to normalize the reaction conditions. Pure solvents like isopropanol, ethanol, methanol and DMF (Table 2.3, entries 1-4) showed no conversion to desired alcohol. With the addition of 10% water (entries 5-8) no significant conversions were observed.
With the further increase to 25% water (entries 9-12) all solvent system with, exception of DMF, showed less than 1 percent conversion. Increasing the water concentration to 50% (entries 13-16) show further small increases in conversion, with the highest being 50/50 ethanol/water mixture 1.8% conversion. Further increase to 90% water (entry 17) showed conversion of 3.4% in methanol/water mix.

Table 2.3 Mixture of solvents screening.

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Isopropanol(1.0)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Ethanol(1.0)</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Methanol(1.0)</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>DMF(1.0)</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Ethanol/H$_2$O(0.9/0.1)</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Ethanol/H$_2$O(0.75/0.25)</td>
<td>0.4%</td>
</tr>
<tr>
<td>7</td>
<td>Ethanol/H$_2$O(0.5/0.5)</td>
<td>1.7%</td>
</tr>
<tr>
<td>8</td>
<td>i-propanol/H$_2$O(0.9/0.1)</td>
<td>0.7%</td>
</tr>
<tr>
<td>9</td>
<td>i-propanol/H$_2$O(0.75/0.25)</td>
<td>0.7%</td>
</tr>
<tr>
<td>10</td>
<td>i-propanol/H$_2$O(0.5/0.5)</td>
<td>1.8%</td>
</tr>
<tr>
<td>11</td>
<td>DMF/H$_2$O(0.5/0.5)</td>
<td>0.0%</td>
</tr>
<tr>
<td>12</td>
<td>DMF/H$_2$O(0.5/0.5)</td>
<td>0.0%</td>
</tr>
<tr>
<td>13</td>
<td>DMF/H$_2$O(0.5/0.5)</td>
<td>0.9%</td>
</tr>
<tr>
<td>14</td>
<td>Methanol/H$_2$O(0.5/0.5)</td>
<td>0.0%</td>
</tr>
<tr>
<td>15</td>
<td>Methanol/H$_2$O(0.5/0.5)</td>
<td>0.5%</td>
</tr>
<tr>
<td>16</td>
<td>Methanol/H$_2$O(0.5/0.5)</td>
<td>0.6%</td>
</tr>
<tr>
<td>17</td>
<td>Methanol/H$_2$O(0.25/0.75)</td>
<td>0.0%</td>
</tr>
<tr>
<td>18</td>
<td>Methanol/H$_2$O(0.1/0.9)</td>
<td>3.4%</td>
</tr>
</tbody>
</table>
2.1.3 Lewis base activator selection

The next approach was to use an activator to enhance reaction. As discussed in previous sections, there are two ways to activate silicon hydrides to reduce aldehydes: 1) using strong acids, Lewis or Brønsted, creating a sufficiently electron-deficient carbon, or 2) using Lewis bases creating a hypercoordinate silane species.

Based on literature reports, the most effective acid catalyzed reduction reactions use expensive and reactive boron Lewis acids like \(\text{B}(\text{C}_6\text{F}_5)_3\), a strategy unfit for large scale applications. With that we decided that the best course of action was to investigate Lewis base activators.

In choosing the solvent for Lewis base testing, we required two criteria: 1) the solvent must dissolve 1-hydrosilatrane efficiently at room temperature and 2) 1-hydrosilatrane must not react with the solvent. With those criteria we selected DMF as a model solvent.

First sodium hydroxide, a readily available strong Lewis base, was tested. Using an overabundance of activator (Table 2.4, entry 1) efficient reduction was observed in 30 minutes and the desired alcohol was isolated in 95% yield. Decreasing the activator loading to 1 equivalent (entry 2) and increasing the reaction time to 24 hours significantly decreased the yield. Switching to potassium hydroxide, another common Lewis base, in hopes of seeing different effects showed a slight decrease in the yield (entry 3). Use of stoichiometric amounts of potassium tert-butoxide resulted in quick reaction with good yield (entry 4). Next, in hopes of using a more mild activator, amine Lewis bases were tested (entries 5-7) but these resulted in no conversion. This suggests that a strong negatively charged Lewis base is required to
activate the silatrane in this reaction. Sodium carbonate, bicarbonate and acetate were tested unsuccessfully (entries 8-10), further supporting the hypothesis that a more nucleophilic activator is required.

Table 2.4 Activator selection for reduction of $p$-methoxybenzyl aldehyde using 1-hydrosilatrane

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>additive</th>
<th>eq. of additive</th>
<th>time (h)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMF</td>
<td>NaOH</td>
<td>30</td>
<td>0.5</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>NaOH</td>
<td>1</td>
<td>24</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>KOH</td>
<td>20</td>
<td>0.5</td>
<td>84</td>
</tr>
<tr>
<td>4</td>
<td>DMF</td>
<td>tBuOK</td>
<td>1</td>
<td>0.5</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>iPrNH$_2$</td>
<td>1.5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>DMF</td>
<td>HNEt$_2$</td>
<td>1.5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>DMF</td>
<td>NEt$_3$</td>
<td>1.5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>THF</td>
<td>NaOH</td>
<td>30</td>
<td>0.5</td>
<td>87</td>
</tr>
<tr>
<td>9</td>
<td>THF</td>
<td>NaHCO$_3$</td>
<td>10</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>THF</td>
<td>Na$_2$CO$_3$</td>
<td>10</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>THF</td>
<td>HCO$_2$Na</td>
<td>1.5</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

With the desired activator chosen, solvents were re-investigated. Both DMF and THF gave good results in the reduction of $p$-methoxybenzaldehyde (9) (Table 2.5, entries 1-2). Non-polar solvents like diethyl ether and hexane gave very low yields (entries 3, 5), while acetonitrile and methanol gave modest yields (entries 4, 6). Finally dichloromethane was used to test chlorinated solvents, resulting in good conversion (entry 7).
### Table 2.5 Solvent screening with activated 1-hydrosilatrane

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>yield(^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMF</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>diethyl ether</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>acetonitrile</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>hexane</td>
<td>3</td>
</tr>
<tr>
<td>6</td>
<td>methanol</td>
<td>35</td>
</tr>
<tr>
<td>7</td>
<td>dichloromethane</td>
<td>81</td>
</tr>
</tbody>
</table>

\(^a\) Yields determined by NMR spectroscopy.

---

#### 2.2.1 Investigation of the scope of aldehyde reduction

The optimized reaction conditions, derived above, were employed on a variety of different benzaldehydes; results are summarized in Table 2.6. The parent benzaldehyde (11) was efficiently reduced in high yield (entry 1). Benzaldehydes with electron donor substituents were reduced efficiently regardless of substituent position (entries 2, 5-7).

While electron donating substituents were well tolerated and resulted in high-yield reduction reactions, attempts to reduce benzaldehydes bearing electron withdrawing groups resulted in formation of small to moderate amounts of corresponding benzoic acid byproduct, in some cases significantly lowering the yield (entries 3, 11, 13-14, 17, and 19). This could be caused by a competing Cannizzaro reaction, aerobic oxidation, or both. As we could not control the Cannizzaro reaction,
the logical step was to limit the aerobic oxidation\textsuperscript{87}. This was done by first deoxygenating the solvent using either a freeze vacuum technique or by bubbling inert gas (argon or nitrogen) through the solvent over a period of 30 minutes. The reactions were re-run under these oxygen-free conditions and resulted in clean formation of desired alcohols with no observable benzoic acid (entries 4, 12, 15, 16, 18, and 20).

Under these optimized conditions 1 does not react with other potentially reducible functional groups, including nitriles (Table 2.6, entries 11, 12), nitro (entry 15), benzyl (entry 9), oxyallyl (entry 10) and halide groups (entry 14-20).

Although other oxygen containing donating groups were reduced efficiently, hydroxyl substituted benzaldehydes showed low yield in the case of 3-hydroxy (27) (Table 2.6, entry 23) and no reduction in the case of 4-hydroxy (26) (entry 21).

This behavior can be explained with simple resonance structures (figure 2.1). As the phenolic proton is acidic, it is rapidly deprotonated by strong bases like sodium or potassium hydroxide. In the case of 4-hydroxybenzaldehyde the charge resonates through the conjugated benzene ring to the carbonyl oxygen. This resonance form resists reduction, because the buildup of negative charge on the carbonyl carbon renders it unreactive to the incoming similarly negative hydride. In the case of 3-hydroxybenzaldehyde the negative charge builds up in position 2 and 6 of the benzene ring and cannot resonate effectively all the way to the carbonyl. Thus reduction of the carbonyl is still possible. It is worth noting that the reaction did not benefit from increasing the time of the reaction, nor from increasing the amount of 1-hydrosilatrane added (Table 2.6, entry 22, 24).
Table 2.6 Scope of aryl aldehyde reductions using 1-hydrosilatrane

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>compound number</th>
<th>Yield(^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>11</td>
<td>98(^b)</td>
</tr>
<tr>
<td>2</td>
<td>4-tBu</td>
<td>12</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>4-Me</td>
<td>13</td>
<td>66(^c)</td>
</tr>
<tr>
<td>4</td>
<td>4-OMe</td>
<td>14</td>
<td>92(^b,d)</td>
</tr>
<tr>
<td>5</td>
<td>3-OMe</td>
<td>15</td>
<td>95</td>
</tr>
<tr>
<td>6</td>
<td>2-OMe</td>
<td>16</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>4-OPh</td>
<td>17</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>4-OBn</td>
<td>18</td>
<td>99</td>
</tr>
<tr>
<td>9</td>
<td>4-OAll</td>
<td>19</td>
<td>98</td>
</tr>
<tr>
<td>10</td>
<td>4-CN</td>
<td>20</td>
<td>60(^c)</td>
</tr>
<tr>
<td>11</td>
<td>4-CN</td>
<td>20</td>
<td>93(^b,d)</td>
</tr>
<tr>
<td>12</td>
<td>3-NO₂</td>
<td>21</td>
<td>88(^c)</td>
</tr>
<tr>
<td>13</td>
<td>4-Cl</td>
<td>22</td>
<td>76(^c)</td>
</tr>
<tr>
<td>14</td>
<td>4-F</td>
<td>23</td>
<td>98(^b,d)</td>
</tr>
<tr>
<td>15</td>
<td>3-F</td>
<td>24</td>
<td>96(^b,d)</td>
</tr>
<tr>
<td>16</td>
<td>2-F</td>
<td>25</td>
<td>28(^c)</td>
</tr>
<tr>
<td>17</td>
<td>4-OH</td>
<td>26</td>
<td>46(^c)</td>
</tr>
<tr>
<td>18</td>
<td>3-OH</td>
<td>27</td>
<td>44</td>
</tr>
<tr>
<td>19</td>
<td></td>
<td></td>
<td>0(^e)</td>
</tr>
<tr>
<td>20</td>
<td></td>
<td></td>
<td>0(^e)</td>
</tr>
<tr>
<td>21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Yield determined by NMR unless otherwise noted. \(^b\) Yield determined by GC-FID. \(^c\) Product mixture contained significant amounts (> 5 %) of corresponding benzoic acid. \(^d\) Reaction run under oxygen-free conditions. \(^e\) Reaction run with 2.5 equiv. of 1 for 24 h.
Figure 2.1 Proposed mechanism for the lack of reactivity of hydroxybenzaldehydes.

Next the optimized reaction conditions were tested on a variety of heterocyclic and polycyclic aryl aldehydes (figure 2.2). In all cases reaction proceeded as expected with excellent yields and no observed byproducts. The optimized reaction conditions also work well with aliphatic aldehydes (figure 2.3).

We propose the following mechanism for this base activated reduction of aldehydes using 1-hydrosilatrane (Figure 2.4). In the first step of the reaction 1-hydrosilatrane reacts with the Lewis base sodium hydroxide, creating a new hexa-coordinate silicon species. Next the aldehyde coordinates to the silicon atom, thereby dissociating the nitrogen atom and keeping the silicon atom hexacoordinate.
Figure 2.2 Reduction of polyaromatic and heteroaromatic aldehydes.

This is followed by hydride transfer to the carbonyl carbon resulting in formation of a penta-coordinate silicon center. Then the nitrogen reforms the dative bond, forcing dissociation of the bulkier alkoxy group and forming a pentacoordinate silatrane hydroxide.
2.2.2 Conclusion

We were able to accomplish the reduction of aldehydes to alcohols using 1-hydrosilatranes and a Lewis base activator. All the aldehydes examined underwent efficient reduction without requiring excluding moisture from the reaction. Only rarely did reductions, particularly the ones involving aldehydes bearing electron-withdrawing groups, need inert atmosphere and degassed solvents to achieve high yields. The only other exceptions involved reducing phenolic aldehydes. In the case of 4-hydroxybenzaldehyde (26) the reaction produced no reduction product and in the case of 3-hydroxybenzaldehyde (25) only partial reduction was observed.
2.3.1 Experimental and Supplemental Information

General Information

All reactions were carried out under ambient conditions in an open vessel, with no special effort to exclude water or air from reaction mixtures unless otherwise noted. Chemicals and reagents were purchased from Sigma-Aldrich and/or Fisher, and were used without further purification unless otherwise noted. $^1$H NMR spectra were recorded at 500 MHz at ambient temperature using a Bruker Avance III spectrometer. The chemical shifts in $^1$H NMR spectra are reported relative to residual CHCl$_3$ in CDCl$_3$ (7.27 ppm). The yields were determined using mesitylene as an internal standard in CDCl$_3$. IR data was acquired using an ATI Mattson FTIR.

Synthesis of 1-hydrosilatrane (1)

To a 25mL flask was added boric acid (50 mmol) and triethanolamine (50 mmol). Water (3 mL) was added to facilitate solubility. The flask was equipped with a short path distillation apparatus and heated to 120°C until no more water condensed. The isolated boratrane was recrystallized from acetonitrile and used directly in the next step. The experimental data collected are in agreement with those described in the literature.$^{82}$ To an oven-dried, argon-flushed 100 mL flask containing boratrane (5 mmol) in mixed xylenes (40 mL), was added triethoxysilane (6 mmol) and anhydrous AlCl$_3$ (0.05 mmol). The reaction was refluxed over 4h and then cooled to room temperature. The resulting solids were filtered and further recrystallized from xylene to give silatrane as white fibrous crystals. The experimental data collected are in agreement with those described in the literature.$^{82}$
Results for Attempted Additive-Free Reduction of Aryl Aldehydes

To a flame-dried 250 mL round-bottom two-neck flask flushed with argon was added 1-hydrosilatrane (0.07 g, 0.4 mmol), 4-hydroxybenzaldehyde (0.012 g, 0.1 mmol) and 50 mL of degassed xylene. The mixture was then heated to reflux temperature over 72h, after which the reaction was cooled to room temperature, quenched with 4 mL 1 M HCl then extracted three times with dichloromethane. The extracts were isolated from dichloromethane under reduced pressure and the resulting concentrate was purified via column chromatography (5:1 hexanes/ethyl acetate). Only starting materials was recovered.

Additive Screening for the Reduction of para-Methoxybenzaldehyde

To a 2 dram vial containing a stir bar was added 1-hydrosilatrane (0.15 mmol), p-methoxybenzaldehyde (0.1 mmol), and solvent (1 mL). The solution was stirred for 5 min to allow for all the silatrane to dissolve, after which additive was added. After stirring in ambient conditions for the indicated time the solution was washed once with 1 M HCl, then extracted three times with dichloromethane and once with diethyl ether. The resulting organic extract was concentrated under reduced pressure. Yield was determined by NMR with an internal standard (mesitylene).
General Method for the Reduction of Aldehydes

To a 2 dram vial containing a stir bar was added 1-hydrosilatrane (0.15 mmol), aldehyde (0.1 mmol), and DMF (1 mL). The solution was stirred for 5 min to allow for all the silatrane to dissolve, after which 1 pellet of NaOH, finely ground, was added. After 30 min of stirring in ambient conditions the solution was washed once with 1 M HCl, then extracted three times with dichloromethane and once with diethyl ether. The resulting organic extract was concentrated under reduced pressure and used to determine yield without any further purification.
1-Hydrosilatrane (1)

\[
\begin{array}{c}
\text{\(\text{N} \text{Si-O\text{O}}\)} \\
\text{\(\text{H}\)}
\end{array}
\]

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 3.92 \text{ (s, 1H), 3.82 (t, J = 6 Hz, 6H), 2.89 (t, J = 6 Hz, 6H).} \)

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 57.2, 51.2.\) IR (ATR): 2937, 2887, 2087, 1487, 1456, 1348, 1269, 1090, 1047, 1020, 926, 860, 748, 631, 592 cm\(^{-1}\).

Phenylmethanol (11)

\[
\begin{array}{c}
\text{\(\text{C} \text{H}_3\text{OH}\)}
\end{array}
\]

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.39 - 7.28 \text{ (m, 4H), 4.70 (s, 2H), 1.90 (b, 1H).} \)

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 140.87, 128.57, 127.66, 127.00, 65.36.\) IR (ATR): 3299, 1454, 1207, 1010, 732, 696 cm\(^{-1}\).
**p-tolylmethanol (13)**

![Chemical structure](attachment:image.png)

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.27 (d, $J$ = 8 Hz, 2H), 7.19 (d, $J$ = 8 Hz, 2H), 4.66 (s, 2H), 2.37 (s, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 138.12, 137.62, 129.46, 127.33, 65.50, 21.36. IR (ATR) 3357.96, 3287.18, 2950.88, 2920.74, 1517.11, 1445.10, 1348.60, 1202.49, 1028.96, 1013.51, 836.60, 804.71, 743.38, 650.86 cm$^{-1}$.

**4-(tert-butyl)phenyl)methanol (12)**

![Chemical structure](attachment:image.png)

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.41 (d, $J$ = 8 Hz, 2H), 7.32 (d, $J$ = 8.5 Hz, 2H), 4.68 (s, 2H), 1.34 (s, 10H). $^{13}$C NMR (75 MHz, CDCl$_3$) δ 150.86, 138.19, 127.09, 125.66, 65.31, 31.54. IR (ATR) 3367.67, 2959.98, 2866.80, 1665.26, 1512.82, 1461.31, 1387.50, 1362.41, 1268.10, 1214.15, 1106.54, 1013.43, 833.44, 666.05, 575.40 cm$^{-1}$.
(4-methoxyphenyl)methanol (14)

\[
\begin{align*}
\text{\text{O}} & \quad \text{OH} \\
\end{align*}
\]

\( ^1 \text{H NMR} \ (500 \text{ MHz, CDCl}_3) \delta 7.30 \text{ (d, } J = 8.5 \text{ Hz, } 2\text{H), 6.90 \text{ (d, } J = 8.5 \text{ Hz, } 2\text{H), 4.63 \text{ (s, } 2\text{H), 3.82 \text{ (s, } 3\text{H).} } \)

\( ^13 \text{C NMR} \ (125 \text{ MHz, CDCl}_3) \delta 159.46, 133.33, 128.87, 114.19, 65.31, 55.52. \text{ IR (ATR) } 3354.59, 2934.08, 2835.74, 2360.34, 2341.42, 1611.99, 1511.31, 1462.76, 1300.97, 1243.38, 1173.02, 1030.53, 1004.96, 814.24, 575.67 \text{ cm}^{-1}. \)

(3-methoxyphenyl)methanol (15)

\[
\begin{align*}
\text{\text{O}} & \quad \text{OH} \\
\end{align*}
\]

\( ^1 \text{H NMR} \ (500 \text{ MHz, CDCl}_3) \delta 7.29 \text{ (t, } J = 8 \text{ Hz, } 1\text{H), 6.95 \text{ (d, } J = 8 \text{ Hz } 1\text{H), 6.94 \text{ (s, } 1\text{H), 6.85 \text{ (dt, } J = 8, 1.5 \text{ Hz, } 1\text{H), 4.68 \text{ (s, } 2\text{H), 3.83 \text{ (s, } 3\text{H).} } \)

\( ^13 \text{C NMR} \ (125 \text{ MHz, CDCl}_3) \delta 160.08, 142.77, 129.82, 119.31, 113.51, 112.47, 65.50, 55.45. \text{ IR (ATR) } 3370.57, 2937.85, 2835.69, 1662.23, 1597.10, 1585.91, 1488.31, 1455.84, 1435.50, 1260.32, 0151.98, 1036.87, 857.51, 857.51, 780.23, 736.42, 692.12 \text{ cm}^{-1}. \)
(2-methoxyphenyl)methanol (16)

\[
\text{\begin{center}
\includegraphics[width=0.5\textwidth]{molecule1.pdf}
\end{center}}
\]

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.31-7.27 (m, 2H), 6.96 (td, \(J = 7.25, 0.5\) Hz, 1H), 6.90 (d, \(J = 8.5\) Hz, 1H), 4.70 (s, 2H), 3.88 (s, 3H). \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 157.61, 129.10, 128.89, 120.81, 110.37, 62.22, 55.43. IR (ATR) 3376.16, 2935.70, 1661.99, 1601.77, 1588.96, 1491.55, 1461.14, 1437.87, 1386.72, 1287.73, 1237.84, 1193.78, 1115.56, 1096.78, 1027.77, 811.44, 752.45, 662.19, 606.70, 579.29 cm\(^{-1}\).

(4-phenoxyphenyl)methanol (17)

\[
\text{\begin{center}
\includegraphics[width=0.5\textwidth]{molecule2.pdf}
\end{center}}
\]

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.36-7.33 (m, 4H), 7.11 (t, \(J = 8.5, 1\) Hz, 1H), 7.02 (d, \(J = 14\) Hz, 4H), 4.67 (s, 2H). \(^13\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 157.41, 157.05, 135.93, 129.97, 128.91, 123.51, 119.16, 119.08, 65.13. IR (ATR) 3389.47, 1589.65, 1504.51, 1487.71, 1420.16, 1254.72, 1164.06, 1107.77, 1071.51, 996.63, 872.71, 842.06, 762.48, 737.56, 690.07, 571.28 cm\(^{-1}\).
(4-(benzyloxy)phenyl)methanol (18)

\[
\begin{align*}
&\text{H NMR (500 MHz, CDCl}_3\text{) } \delta \text{ 7.45 (d, } J = 7 \text{ Hz, 2H), 7.40 (t, } J = 5.5 \text{ Hz, 2H), 7.35 (d, } J = 7 \text{ Hz, 1H), 7.31 (d, } J = 8.5 \text{ Hz, 2H), 6.99 (d, } J = 9 \text{ Hz, 2H), 5.09 (s, 2H), 4.64 (s, 2H).} \\
&\text{C NMR (125 MHz, CDCl}_3\text{) } \delta \text{ 158.61, 137.18, 133.63, 128.88, 128.82, 128.20, 127.67,} \\
&115.15, 70.26, 65.20. \text{ IR (ATR) 3372.24, 3061.74, 3034.56, 2945.85, 2916.11, 2868.00,} \\
&1608.95, 1584.92, 1509.45, 1454.51, 1381.28, 1297.92, 1237.18, 1171.60, 1111.61,} \\
&995.46, 916.60, 860.86, 834.50, 810.35, 777.21, 740.00, 695.51, 613.54, 558.50 \text{ cm}^{-1}. 
\end{align*}
\]
(4-(allyloxy)phenyl)methanol (19)

\[
\begin{align*}
\text{H NMR (500 MHz, CDCl}_3\text{)} & \quad \delta 7.29 (d, J = 8.5, 2H), 6.92 (d, J = 8.5 \text{ Hz}, 2H), 6.10-6.03 (m, 1H), 5.43 (dq, J = 17.5, 1.5 \text{ Hz}, 1H), 5.30 (dq, J = 11, 1.5 \text{ Hz}, 1H), 4.62 (s, 2H), 4.55 (dt, J = 3.5, 1.5 \text{ Hz}, 2H). \\
\text{C NMR (125 MHz, CDCl}_3\text{)} & \quad \delta 158.35, 133.40, 129.58, 128.78, 117.86, 114.95, 69.00, 65.13 \text{ IR (ATR) } 3354.78, 2868.48, 1610.23, 1584.56, 1509.42, 1456.83, 1422.43, 1363.05, 1299.75, 1239.31, 1219.97, 1173.18, 1111.73, 1019.19, 995.03, 925.52, 824.73, 778.14, 571.98 \text{ cm}^{-1}.
\end{align*}
\]
4-(hydroxymethyl)benzonitrile (20)

\[
\text{\textsuperscript{1}H NMR (500 MHz, CDCl}_3\text{) } \delta 7.68 (d, J = 8.5, 2H), 7.51 (d, J = 8 Hz, 2H), 4.82 (d, J = 5.5, 2H). \text{\textsuperscript{13}C NMR (125 MHz, CDCl}_3\text{) 146.33, 132.55, 127.22, 119.05, 111.44, 64.47}
\]

IR (ATR) 3415.79, 2923.73, 2870.62, 2228.29, 1609.16, 1505.28, 1450.96, 1413.66, 1203.77, 1044.29, 1016.31, 814.72, 690.74, 546.84 cm\textsuperscript{-1}.

(3-nitrophenyl)methanol (21)

\[
\text{\textsuperscript{1}H NMR (500 MHz, CDCl}_3\text{) } \delta 8.13 (dd, J = 8 Hz, 1.5 Hz, 1H), 8.03 (s, 1H), 7.70 (d, J = 8 Hz, 1H), 7.53 (t, J = 8 Hz, 1H), 4.82 (s, 2H). \text{\textsuperscript{13}C NMR (125 MHz, CDCl}_3\text{) 148.64, 143.05, 132.81, 129.66, 122.72, 121.73, 64.21 IR (ATR) 3330.95, 2870.21, 1522.64, 1480.49, 1346.87, 1202.16, 1092.08, 1040.00, 918.69, 891.13, 801.83, 730.07, 670.04, 604.56 cm}\textsuperscript{-1}.
\]
(4-chlorophenyl)methanol (22)

\[
\text{Cl} \quad \text{OH}
\]

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 7.35-7.31\) (m, 4H), 4.68 (s, 2H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta 139.45, 133.60, 128.90, 128.49, 64.79\). IR (ATR) 3340.57, 2959.57, 2924.19, 1684.25, 1491.12, 1450.75, 1404.72, 1341.69, 1296.68, 1260.09, 1208.12, 1085.35, 1009.63, 906.76, 829.49, 797.54, 730.75, 652.25 cm\(^{-1}\).

(4-fluorophenyl)methanol (23)

\[
\text{F} \quad \text{OH}
\]

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 7.34\) (q, \(J = 5.5\) Hz, 2H), 7.05 (t, \(J = 8.5\) Hz, 2H), 4.67 (s, 2H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta 163.39, 161.44, 136.89, 136.87, 128.92, 128.86, 115.55, 115.39, 64.67\). IR (ATR) 3369.81, 2932.76, 2872.91, 1661.55, 1603.10, 1508.67, 1387.33, 1217.88, 1155.27, 1096.22, 1011.88, 821.67, 662.76, 558.29 cm\(^{-1}\).
(3-fluorophenyl)methanol (24)

\[
\begin{align*}
\text{F} & \quad \text{OH} \\
& \quad \quad \text{H}
\end{align*}
\]

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.35-7.31 (m, 1H), 7.14 (d, \(J = 7.5\) Hz, 1H), 7.11 (d, \(J = 9.5\) Hz, 1H), 6.99 (td, \(J = 8.5, 2.5\) Hz, 1H), 4.72 (s, 2H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\)

164.19, 162.23, 143.71, 143.65, 130.26, 130.19, 122.38, 122.36, 114.66, 114.49, 113.93, 113.76, 64.73, 64.71 IR (ATR) 3319.81, 2872.96, 1662.63, 1617.13, 1590.40, 1487.20, 1449.73, 1251.70, 1134.61, 1019.84, 915.40, 866.72, 780.45, 742.06, 683.43, 629.28 cm\(^{-1}\).

(2-fluorophenyl)methanol (25)

\[
\begin{align*}
& \quad \text{OH} \\
& \quad \quad \text{F}
\end{align*}
\]

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.44 (td, \(J = 7.25, 1.5\) Hz, 1H), 7.32-7.27 (m, 1H), 7.16 (td, \(J = 7.5, 1\) Hz, 1H), 7.07 (t, \(J = 7.75\) Hz, 1H), 4.78 (s, 2H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\)

161.80, 159.85, 129.57, 129.51, 129.47, 128.10, 127.98, 124.44, 124.41, 115.53, 115.36, 59.56, 59.53. IR (ATR) 3345.00, 2933.79, 2880.52, 1661.83, 1615.11, 1586.06, 1489.31, 1455.62, 1387.18, 1225.35, 1180.38, 1103.44, 1011.86, 832.28, 753.77 cm\(^{-1}\).
3-(hydroxymethyl)phenol (27)

\[
\begin{align*}
&\text{HO} \quad \text{OH} \\
&\text{H} \quad \text{C} \\
&\text{H} \quad \text{C} \\
&\text{H} \quad \text{C} \\
&\text{H} \quad \text{C} \\
&\text{H}
\end{align*}
\]

\(^1\text{H NMR} (500 \text{ MHz}, \text{CDCl}_3) \delta 7.21 (t, \ J = 8 \text{ Hz}, 1\text{H}), 6.89 (s, 2\text{H}), 6.81 (s, 1\text{H}), 6.79 (dd, \ J = 8, 2.5 \text{ Hz}, 1\text{H}), 4.64 (s, 2\text{H}). \ ^{13}\text{C NMR} (75 \text{ MHz}, \text{CDCl}_3) \delta 156.09, 142.97, 130.09, 119.39, 114.82, 113.97, 65.29. \ \text{IR (ATR)} 3374.52, 1653.57, 1589.52, 1483.74, 1457.00, 1410.56, 1334.99, 1273.01, 1215.51, 1154.34, 1021.64, 997.39, 920.94, 861.73, 783.19, 748.22, 691.13 \text{ cm}^{-1}.

naphthalen-1-ylmethanol (31)

\[
\begin{align*}
&\text{OH} \\
&\text{H} \quad \text{C} \\
&\text{H} \quad \text{C} \\
&\text{H} \quad \text{C} \\
&\text{H} \quad \text{C} \\
&\text{H} \quad \text{C}
\end{align*}
\]

\(^1\text{H NMR} (500 \text{ MHz}, \text{CDCl}_3) \delta 8.14 (d, \ J = 8.5 \text{ Hz}, 1\text{H}), 7.90 (d, \ J = 8 \text{ Hz}, 1\text{H}), 7.83 (d, \ J = 8 \text{ Hz}, 1\text{H}), 7.58-7.53 (m, 3\text{H}), 7.47 (t, \ J = 7.5 \text{ Hz}, 1\text{H}), 5.17 (s, 2\text{H}). \ ^{13}\text{C NMR} (75 \text{ MHz}, \text{CDCl}_3) \delta 136.26, 133.82, 131.24, 128.68, 128.61, 126.36, 125.89, 125.40, 125.36, 123.65, 63.73. \ \text{IR (ATR)} 3314.17, 3046.77, 1686.51, 1597.12, 1510.47, 1391.91, 1328.66, 1218.05, 1164.50, 1079.12, 994.26, 790.69, 770.80, 710.69, 649.39, 594.74 \text{ cm}^{-1}.
**naphthalen-2-ylmethanol (32)**

![Image of naphthalen-2-ylmethanol](image)

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.86-7.82 (m, 4H), 7.50-7.49 (m, 3H), 4.87 (s, 2H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 138.51, 133.58, 133.16, 128.55, 128.09, 127.92, 126.40, 126.11, 125.65, 125.37, 65.70. IR (ATR) 3243.72, 3051.45, 2909.48, 1601.32, 1507.85, 1438.99, 1389.02, 1332.16, 1260.35, 1169.04, 1117.26, 1038.52, 963.07, 893.96, 856.86, 810.61, 737.58, 689.94 cm$^{-1}$.

**anthracen-9-ylmethanol (33)**

![Image of anthracen-9-ylmethanol](image)

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.47 (s, 1H), 8.42 (dd, $J$ = 8.25, 0.5 Hz, 2H), 8.04 (d, $J$ = 8.5 Hz, 2H), 7.57 (td, $J$ = 7.25, 1.5 Hz, 2H), 7.50 (td, $J$ = 7.5, 1 Hz, 2H), 5.66 (s, 2H).

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 131.76, 131.23, 130.46, 129.36, 128.60, 126.67, 125.31, 124.10, 57.63. IR (ATR) 3447.70, 1671.80, 1622.56, 1445.47, 1330.03, 1306.47, 1259.13, 1159.16, 1046.65, 977.94, 883.97, 841.98, 791.31, 731.90, 699.26, 651.83, 603.76 cm$^{-1}$.
furan-2-ylmethanol (28)

\[
\begin{align*}
\text{\textsuperscript{1}H NMR (300 MHz, CDCl}_3) & \delta 7.41 (dd, J = 1.8, 0.9 Hz, 1H), 6.35 (d, J = 3 Hz, 1H), 6.30 (d, J = 3 Hz, 1H), 4.61 (d, J = 2.4 Hz, 2H). \\
\text{\textsuperscript{13}C NMR (75 MHz, CDCl}_3) & \delta 154.03, 142.56, 110.36, 107.75, 57.43. \\
\text{IR (ATR)} & 3376, 1504, 1220, 1147, 1006, 914, 885, 811, 732 \text{ cm}^{-1}.
\end{align*}
\]

thiophen-2-ylmethanol (29)

\[
\begin{align*}
\text{\textsuperscript{1}H NMR (500 MHz, CDCl}_3) & \delta 7.30 (dd, J = 5, 1 Hz, 1H), 7.04 (dd, J = 3.5, 1 Hz, 1H), 7.00 (t, J = 4.25 Hz, 1H), 4.86 (s, 2H). \\
\text{\textsuperscript{13}C NMR (125 MHz, CDCl}_3) & \delta 144.56, 126.91, 125.45, 125.36, 59.96. \\
\text{IR (ATR)} & 3384.62, 2929.07, 2866.66, 1655.97, 1436.36, 1385.93, 1254.57, 1210.08, 1159.86, 1096.10, 1016.08, 851.96, 830.50, 699.99, 661.24 \text{ cm}^{-1}.
\end{align*}
\]
thiophen-3-ylmethanol (30)

\[
\begin{array}{c}
\text{H} \\
\text{C} \\
\text{S} \\
\text{H}
\end{array}
\]

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.35 (dd, $J = 5$, 3 Hz, 1H), 7.26 (dd, $J = 3$, 1 Hz, 1H), 7.13 (dd, $J = 5$ Hz, 1 Hz, 1H), 4.74 (s, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 142.60, 126.97, 126.34, 121.99, 60.78. IR (ATR) 3384.76, 3099.84, 2928.49, 2867.42, 1656.55, 1493.29, 1435.98, 1385.94, 1253.24, 1153.36, 1095.55, 1024.26, 854.95, 829.93, 777.12, 691.54, 660.90 cm$^{-1}$.

Cyclohexylmethanol (34)

\[
\begin{array}{c}
\text{C} \\
\text{H}_2 \\
\text{H}
\end{array}
\]

$^1$H NMR (300 MHz, CDCl$_3$) δ 3.44 (dd, $J = 6.3$, 2.7 Hz, 2H), 1.77 - 1.66 (m, 4H), 1.53 - 1.50 (m, 2H), 1.49 - 1.46 (m, 4H), 1.45 - 1.42 (m, 2H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 68.71, 40.44, 29.56, 26.58, 25.83. IR (ATR) 3313, 2919, 2852, 1448, 1334, 1089, 1022, 890 cm$^{-1}$.
CHAPTER 3

BRØNSTED ACID-MEDIATED DIRECT REDUCTIVE AMINATION USING 1-HYDROSILATRANE

*This chapter is adapted in part from our publication83

3.1.1 Introduction

With the positive outcome of our previous work on reduction of aldehydes, we were optimistic about reducing other functional groups. First, to compliment the aldehyde work, reduction of ketones was successfully performed using 1-hydrosilatrane and a Lewis base. Next, we investigated reduction of iminium ions. An aldehyde or a ketone reacts under neat conditions with a secondary amine on a bed of 1-hydrosilatrane. This is a speedy reaction resulting in good yields and proceeds under ambient atmosphere with no exclusion of moisture. That work was done by Varjosaari et al and is discussed elsewhere83,84. The work discussed in this chapter complements the iminium ion reduction work and further expands the scope of reductive amination using 1-hydrosilatrane.

Excited by the results from direct reductive amination of secondary amines and aldehydes, we hoped similar reactivity would be observed with aldehydes and primary amines. Unfortunately, when an aldehyde and a primary amine were reacted in the presence of 1-hydrosilatrane only the imine product was isolated. The reactions were
also tested at elevated temperatures with no reduction product. Consequently testing and optimization of reaction condition had to be performed.

### 3.2.1 Direct reductive amination of aldehydes and primary amines

First we set out to repeat previous work, using a Lewis base activator and a preformed imine (Table 3.1, entry 2). Unfortunately no reduction was observed. Next, we examined the possibility of adding a weak acid to the reaction mixture to create an iminium ion that would be electrophilic enough for the reduction by 1-hydrosilatrane. For this we used commonly available acetic acid. It is inexpensive, environmentally friendly and readily available chemical. When using it as a solvent we saw speedy reduction and excellent conversion (Table 3.1, entry 3).

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>DMF</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Acetic acid</td>
<td>88</td>
</tr>
</tbody>
</table>

*a Potassium t-butoxide used as activator.

As the reaction was fast and showed excellent yields, no further optimization was done. The reaction conditions were repeated with a variety of aldehydes and primary amines, results of which are shown in figure 3.1. Optimized conditions
showed good to excellent results when \( p \)-tolualdehyde was reacted with aliphatic, aromatic and benzylic amines (compounds 35-37). Electron rich aldehydes like \( p \)-dimethylaminobenzaldehyde and \( p \)-methoxybenzaldehyde demonstrated excellent reactivity with benzyl amine resulting in high yields with no observable byproducts 38, 39. Excellent reactivity was also observed with electron poor \( p \)-fluorobenzaldehyde and benzyl amine (41). Reaction with cinnamaldehyde, a possible Michael acceptor proceeded smoothly under our reaction conditions resulting in a good yield 42.

\[
\begin{array}{ccc}
R^1 & + & \text{1-hydrosilatrane (2 eq.)} \\
\text{H} & \text{AcOH, r.t.} & \text{R^1-N-R^2}
\end{array}
\]

![Chemical structures](image)

Figure 3.1 Scope of direct reductive amination of aryl aldehydes with 1-hydrosilatrane and primary amines.
Furthermore aliphatic aldehydes react just as efficiently as the aromatic aldehydes 43. Finally, a special mention must be made with the respect to the reaction of \( p \)-tolualdehyde and a methoxide ester of amino acid phenylalanine (compound 40). Under our reaction conditions product was isolated in excellent yields with no reduction of a potentially reducible ester functional group.

3.2.2 Direct reductive amination of ketones and primary amines

After a successful series of direct reductive aminations with aldehydes, we wanted to see if the same conditions could be applied to ketones. Indeed, the reaction works well with ketones and primary amines.

\[
\begin{align*}
\text{R}^1\text{C}=\text{O} & \quad + \quad \text{H}_2\text{N}^+\text{R}^2 & \text{1-hydrosilatrane (2 eq.)} & \text{AcOH, 70°C} & \text{R}^1\text{N}^+\text{R}^2
\end{align*}
\]

Figure 3.2 Scope of direct reductive amination of ketones with 1-hydrosilatrane and primary amines.
Figure 3.3 Expanding the reaction scope of the direct reductive amination with aryl primary amines and aryl ketones.

As might be expected, the increase in steric hindrance of the ketones required longer reaction times, and in some cases, higher temperatures. Acetophenone reacted
with both benzyl amine and aniline, with aniline giving a much higher yield (44, 45). Cyclic and acyclic ketones reacted well with aniline and benzyl amine (46-49).

To further screen the potential of this reaction, we focused on reactions of aryl ketones with aryl amines. Figure 3.3 demonstrates the scope of this reaction. The reaction works well with sterically hindered propiophenone and isobutyrophenone, resulting in excellent yields. It also works with both electron rich and electron poor ketones (54, 55). Bromo and fluoro substituted ketones react in excellent yields (58, 59). Special mention must be made with the respect towards keto esters reacted with aniline and o-methoxyaniline (52, 56). Those reactions show lower yield and produce a small amount of alcohol byproduct, based on the GCMS data analysis.

3.2.3 Synthesis of biologically active molecules

Many significant pharmaceutically relevant compounds are alkaloids, and for this reason the synthesis of amines is of great practical interest in this field. To highlight this application, we applied our method for reductive amination using 1 in the synthesis of two 2-substituted isoindoline derivatives of alpha-amino acids. The compounds are selective COX-2 and COX-1 inhibitors, respectively, of which 63 has been singled out for further study as an anti-inflammatory agent85. Both compounds have also shown moderate antiproliferative activity towards HeLa cells. To form the isoindoline structure, one aldehyde of an o-dialdehyde arene would have to undergo intermolecular reductive amination, whereupon the remaining aldehyde would have to undergo intramolecular reductive amination. Phthaldialdehyde reacted with the
two corresponding amino acid methyl esters to give the isoindoline products in one step, in very good yield.

Figure 3.4 Synthesis of biologically active molecules using a direct reductive amination with 1-hydrosilatrane.

3.3.1 Proposed mechanism

Next a brief discussion of the Brønsted acid mediated direct reductive amination is in order. We propose a mechanism illustrated in figure 3.5. First step in the reaction is the formation of the imine and liberation of a water molecule. Next, the imine is protonated with Brønsted acid resulting in an iminium ion formation. The iminium ion increases the positive charge on the carbonyl carbon allowing 1-hydrosilatrane to transfer its hydride resulting in formation of amine.
3.4.1 Conclusion

In conclusion we developed an efficient route to secondary amines using 1-hydrosilatrane. In a direct reductive amination reaction an aldehyde or a ketone is combined with a primary amine in the presence of a Brønsted acid. Reactions proceed smoothly and efficiently, and products rarely require more than extraction to be purified. The reactions are all run under ambient atmosphere with no exclusion of moisture or air. Most reactions are completed in under 12 hours at room temperature and in only rare cases require elevated temperatures. It is also important to note that aryl amines, although are less nucleophilic than the alkyl amines, react efficiently and the reactions result in excellent yields.
3.5.1 Experimental and Supplemental Information

**General information**

All chemicals were obtained from commercial sources and used without further purification. Column chromatography was performed using silica gel from Macherey-Nagel (60 M, 0.04-0.063 mm). $^1$H NMR, and $^{13}$C NMR were recorded on either a 300 or 500 MHz Bruker Avance III spectrometer. Chemical shifts were reported in ppm with the solvent resonance as internal standard ($^1$H NMR CDCl$_3$ $\delta = 7.28$, $^{13}$C NMR CDCl$_3$ $\delta = 77.01$, $^{13}$C NMR (CD$_3$)$_2$SO $\delta = 39.99$). IR spectra were acquired using an ATI Mattson FTIR spectrophotometer on neat samples.

**General procedure for synthesis of secondary amines (aldehydes)**

To a 5 dram vial containing aldehyde (1 mmol), primary amine (1.2 mmol) and acetic acid (1 mL) was added 1-hydrosilatrane (2 mmol). The reaction mixture was stirred using a magnetic stir bar for 1.5 hours upon which the reaction was neutralized using 1M NaOH and extracted using dichloromethane three times. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under low pressure. The resulting residue was analyzed with no further purification unless otherwise stated.

**General procedure for synthesis of secondary amines (ketone)**

To a 5 dram vial containing ketone (1 mmol), primary amine (1.2 mmol) and acetic acid (1 mL) was added 1-hydrosilatrane (2 mmol). The reaction mixture was stirred
using a magnetic stir bar for 2 hours upon which the reaction was neutralized using 1M NaOH and extracted using dichloromethane three times. The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under low pressure. The resulting residue was analyzed with no further purification unless otherwise stated.

General procedure for synthesis of isoindoles 62 63

To a 5 dram vial containing amino acid methyl ester hydrochloride (1 mmol) phthalaldehyde (1 mmol) and 1 mL of acetic acid was added 1-hydrosilatran (2 mmol). The resulting mixture was stirred at room temperature for 2 hours, and quenched with 1M NaOH. The resulting mixture was extracted three times with dichloromethane, combined organic layers were dried over anhydrous sodium sulfate and concentrated under low pressure. The residue was then purified using column chromatography with hexane/ethyl acetate (4/1) to give the isoindole derivative.
N-(4-methylbenzyl)propan-1-amine (35)

\[
\begin{align*}
\text{H NMR (500 MHz, CDCl}_3\text{): } & \delta = 7.46 (d, J = 8.0 \text{ Hz}, 2H), 7.20 (d, J = 8.0 \text{ Hz}, 2H), 3.98 \\
& (s, 2H), 2.74 (t, J = 8.0 \text{ Hz}, 2H), 2.32 (s, 3H), 1.84 (dt, J = 7.5, 15.0 \text{ Hz}, 2H), 0.94 (t, J \\
& = 7.5 \text{ Hz}, 3H). \quad ^{13}\text{C NMR (125 MHz, CDCl}_3\text{): } \delta = 139.3, 130.2, 129.8, 127.4, 50.5, 47.7, \\
& 21.2, 19.5, 11.2. \quad \text{IR (ATR): } 2933, 2769, 2708, 2409, 1435, 1009, 810, 731, 559 \text{ cm}^{-1}.
\end{align*}
\]

N-benzyl-1-(p-tolyl)methanamine (36)

\[
\begin{align*}
\text{H NMR (500 MHz, CDCl}_3\text{): } & \delta = 7.40-7.36 (m, 4H), 7.28 (d, J = 7.5 \text{ Hz}, 2H), 7.19 (d, J = \\
& 7.5 \text{ Hz}, 2H), 2.85 (s, 2H), 3.83 (s, 2H), 2.39 (s, 3H). \quad ^{13}\text{C NMR (125 MHz, CDCl}_3\text{): } \delta = \\
& 140.4, 137.3, 136.5, 129.1, 128.4, 128.2, 128.1, 126.9, 53.1, 52.9, 21.1. \quad \text{IR (ATR): } \\
& 3024, 2920, 2362, 1738, 1452, 1103, 802, 735, 696 \text{ cm}^{-1}.
\end{align*}
\]
N-(4-methylbenzyl)aniline (37)

![Structure of N-(4-methylbenzyl)aniline]

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.30$ (s, 1H), 7.29 (s, 1H), 7.22-7.17 (m, 4H), 6.74 (t, $J = 7.5$ Hz, 1H), 6.67 (dd, $J = 1.0$, 8.5 Hz, 2H), 4.31 (s, 2H), 2.37 (s, 3H).

$^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 148.2$, 136.9, 136.4, 129.3, 129.2, 127.5, 117.5, 112.8, 48.1, 21.1. IR (ATR): 1597, 1500, 1273, 1095, 841, 785, 688, 594 cm$^{-1}$.

4-((benzylamino)methyl)-N,N-dimethylaniline (38)

![Structure of 4-((benzylamino)methyl)-N,N-dimethylaniline]

$^1$H NMR (300 MHz, CDCl$_3$): $\delta = 7.37$ (s, 4H), 7.35 (d, $J = 2.4$ Hz, 1H), 7.24 (d, $J = 8.7$ Hz, 2H), 6.75 (d, $J = 8.7$ Hz, 2H), 3.83 (s, 2H), 3.75 (s, 2H), 2.96 (s, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 149.9$, 140.5, 129.1, 128.4, 128.3, 128.2, 126.8, 112.7, 53.0, 52.7, 40.8. IR (ATR): 2802, 1614, 1520, 1452, 1342, 1163, 947, 800, 733, 698 cm$^{-1}$.
N-benzyl-1-(4-methoxyphenyl)methanamine (39)

\[
\text{O} \quad \text{N} \quad \text{H} \quad \text{O} \\
\text{H} \quad \text{N} \quad \text{H} \quad \text{O}
\]

\[^1H\text{ NMR (500 MHz, CDCl}_3): \delta = 7.38-7.37 (m, 4H), 7.30 (d, J = 8.5 Hz, 3H), 6.91 (d, J = 8.5 Hz, 2H), 3.84 (s, 5H), 3.79 (s, 2H). \[^{13}C\text{ NMR (125 MHz, CDCl}_3): \delta = 158.7, 140.4, 132.5, 129.9, 129.4, 128.4, 128.2, 126.9, 113.8, 55.3, 53.1, 52.6. IR (ATR): 2833, 1610, 1510, 1454, 1244, 1034, 810, 737, 698 \text{ cm}^{-1}.\]

methyl 2-((4-methylbenzyl)amino)-3-phenylpropanoate (40)

\[
\text{O} \quad \text{N} \quad \text{H} \quad \text{O} \\
\text{H} \quad \text{N} \quad \text{H} \quad \text{O}
\]

\[^1H\text{ NMR (500 MHz, CDCl}_3): \delta = 7.32-7.29 (m, 2H), 7.27-7.24 (m, 1H), 7.20-7.18 (m, 2H), 7.15-7.11 (m, 4H), 3.92-3.84 (m, 1H), 3.80 (d, J = 13 Hz, 1H), 3.68 (s, 3H), 3.63 (d, J = 16 Hz, 1H), 3.58 (t, J = 6.5 Hz), 2.99 (d, J = 6.5 Hz, 2H), 2.35 (s, 3H). \[^{13}C\text{ NMR (125 MHz, CDCl}_3): \delta = 175.1, 137.4, 136.6, 136.5, 129.2, 129.0, 128.4, 128.1, 126.7, 62.0, 51.7, 51.6, 39.8, 21.1. IR (ATR): 2947, 2879, 1734, 1454, 1107, 800, 700 \text{ cm}^{-1}.\]
N-benzyl-1-(4-fluorophenyl)methanamine (41)

\[
\text{\includegraphics[width=0.5\textwidth]{n-benzyl-1-(4-fluorophenyl)methanamine.png}}
\]

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.38-7.28\) (m, 8H), 7.05 (t, \(J = 8.0\) Hz, 2H), 3.83 (s, 2H), 3.81 (s, 2H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 161.9\) (d, \(J = 242.5\) Hz, C-1), 140.2, 136.1, 129.7 (d, \(J = 8.75\) Hz, C-3 and C-5), 128.5, 128.2, 127.0, 115.1 (d, \(J = 21.3\) Hz, C-2 and C-6), 53.1, 52.4. IR (ATR): 2821, 1603, 1508, 1454, 1219, 1155, 822, 737, 696 cm\(^{-1}\).

(E)-N-benzyl-3-phenylprop-2-en-1-amine (42)

\[
\text{\includegraphics[width=0.5\textwidth]{e-n-benzyl-3-phenylprop-2-en-1-amine.png}}
\]

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.41\) (d, \(J = 7.0\) Hz, 2H), 7.38 (d, \(J = 5.0\) Hz, 4H), 7.35 (t, \(J = 7.5\) Hz, 2H), 7.32-7.29 (m, 1H), 7.26 (tt, \(J = 1.5, 7.0\) Hz, 1H), 6.58 (d, \(J = 16\) Hz, 1H), 6.36 (dt, \(J = 6.0, 16.0\) Hz, 1H), 3.88 (s, 2H), 3.48 (dd, \(J = 1.5, 6.5\) Hz, 2H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 140.3, 137.2, 131.4, 128.6, 128.5, 128.4, 128.3, 127.4, 127.0, 126.3, 53.4, 51.2\). IR (ATR): 3026, 2808, 1495, 1450, 1120, 966, 731, 692 cm\(^{-1}\).
\[\text{N-benzyl-1-cyclohexylmethanamine (43)}\]

\[\text{\H NMR (500 MHz, CDCl}_3\text{): } \delta = 7.36 \text{ (s, 2H), 7.35 \text{ (s, 2H), 7.29-7.26}\text{ (m, 1H), 3.81\text{ (s, 2H), 2.50 (d, } J = 6.5 \text{ Hz, 2H), 1.81-1.68 \text{ (m, 6H), 1.53-1.51\text{ (m, 1H), 1.30-1.18 \text{ (m, 4H), 0.95 (qd, } J = 6.5, 11.5 \text{ Hz, 2H).} \text{ 13C NMR (125 MHz, CDCl}_3\text{): } \delta = 140.8, 128.4, 128.1, 126.8, 56.3, 54.2, 38.1, 31.5, 26.7, 26.1. IR (ATR): 2920, 2848, 1450, 1122, 733, 696 \text{ cm}^{-1}.}\]

\[\text{N-benzyl-1-phenylethanamine (44)}\]

\[\text{\H NMR (500 MHz, CDCl}_3\text{): } \delta = 7.36 \text{ (s, 2H), 7.35 \text{ (s, 2H), 7.29-7.26}\text{ (m, 1H), 3.81\text{ (s, 2H), 2.50 (d, } J = 6.5 \text{ Hz, 2H), 1.81-1.68 \text{ (m, 6H), 1.53-1.51\text{ (m, 1H), 1.30-1.18 \text{ (m, 4H), 0.95 (qd, } J = 6.5, 11.5 \text{ Hz, 2H).} \text{ 13C NMR (125 MHz, CDCl}_3\text{): } \delta = 140.8, 128.4, 128.1, 126.8, 56.3, 54.2, 38.1, 31.5, 26.7, 26.1. IR (ATR): 2920, 2848, 1450, 1122, 733, 696 \text{ cm}^{-1}.}\]
N-(1-phenylethyl)aniline (45)

\[
\begin{align*}
\text{N} & \quad \text{NH} \\
\text{Ph} & \quad \text{Ph}
\end{align*}
\]

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.41\) (d, \(J = 7.5\) Hz, 2H), 7.36 (t, \(J = 7.5\) Hz, 2H), 7.26 (tt, \(J = 1.5, 7.5\) Hz, 1H), 7.13 (dd, \(J = 7.5, 8.5\) Hz, 2H), 6.68 (t, \(J = 7.0\) Hz, 1H), 6.55 (dd, \(J = 1.0, 8.5\) Hz, 2H), 4.52 (q, \(J = 6.5\) Hz, 1H), 4.1 (s, 1H), 1.55 (d, \(J = 7.0\) Hz, 3H).

\(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 147.3, 145.3, 129.1, 128.7, 126.9, 125.9, 117.2, 113.3, 53.5, 25.1\). IR (ATR): 3408, 3022, 2972, 1599, 1502, 1317, 1257, 746, 690 cm\(^{-1}\).

N-benzylcyclopentanamine (49)

\[
\begin{align*}
\text{H} & \quad \text{NH} \\
\text{Cyclopentane} & \quad \text{Ph}
\end{align*}
\]

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.37-7.36\) (m, 4H), 7.30-7.26 (m, 1H), 3.81 (d, \(J = 2.5\) Hz, 2H), 3.16 (td, \(J = 3.0, 6.5\) Hz, 1H), 1.93-1.86 (m, 2H), 1.78-1.71 (m, 2H), 1.62-1.54 (m, 2H), 1.45-1.37 (m, 2H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 140.8, 128.4, 128.2, 126.8, 59.2, 52.8, 33.2, 24.2\). IR (ATR): 2951, 2866, 2360, 1452, 1344, 731, 696, 669 cm\(^{-1}\).
N-benzylhexan-2-amine (47)

\[
\begin{align*}
\text{\textsuperscript{1}H NMR (500 MHz, CDCl}_3\text{): } & \delta = 7.35 (d, J = 4.5 \text{ Hz}, 4H), 7.28-7.25 (m, 1H), 3.86 (d, J = 13.0 \text{ Hz}, 1H), 3.77 (d, J = 13.0 \text{ Hz}, 1H), 2.69 (m, 1H), 1.54-1.50 (m, 1H), 1.37-1.29 (m, 6H), 1.11 (d, J = 6.0 \text{ Hz}, 3H), 0.92 (t, J = 7.0 \text{ Hz}, 3H). \\
\text{\textsuperscript{13}C NMR (125 MHz, CDCl}_3\text{): } & \delta = 141.0, 128.4, 128.1, 126.8, 52.6, 51.5, 36.9, 28.2, 22.9, 20.4, 14.1. \text{ IR (ATR): } 3258, 2956, 2927, 1601, 1504, 1375, 731, 696 \text{ cm}^{-1}. 
\end{align*}
\]

N-(hexan-2-yl)aniline (48)

\[
\begin{align*}
\text{\textsuperscript{1}H NMR (500 MHz, CDCl}_3\text{): } & \delta = 7.19 (td, J = 2.0, 7.5 \text{ Hz}, 2H), 6.69 (t, J = 7.5 \text{ Hz}, 1H), 6.61 (dd, J = 1.0, 7.5 \text{ Hz}, 2H), 3.48 (m, 2H), 1.65-1.58 (m, 1H), 1.51-1.32 (m, 6H), 1.21 (d, J = 6.5 \text{ Hz}, 3H), 0.94 (t, J = 7.0 \text{ Hz}, 3H). \\
\text{\textsuperscript{13}C NMR (125 MHz, CDCl}_3\text{): } & \delta = 147.7, 129.3, 116.7, 113.07, 48.5, 37.0, 28.4, 22.8, 20.8, 14.1. \text{ IR (ATR): } 3404, 2958, 2927, 1601, 1504, 1317, 746, 690 \text{ cm}^{-1}. 
\end{align*}
\]
methyl 2-(isoindolin-2-yl)-3-phenylpropanoate (62)

\[
\text{\includegraphics[width=0.2\textwidth]{methyl_2-(isoindolin-2-yl)-3-phenylpropanoate}}
\]

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 7.34-7.31\) (m, 2H), 7.29-7.25 (m, 3H), 7.24 (s, 4H), 4.27 (d, \(J = 10.5\) Hz, 2H), 4.19 (d, \(J = 10.5\) Hz, 2H), 3.84 (dd, \(J = 6.5, 8.5\) Hz, 1H), 3.64 (s, 3H), 3.21 (dd, \(J = 9.0, 13.5\) Hz, 1H), 3.16 (dd, \(J = 7.0, 13.5\) Hz, 1H). \(^1\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 172.6, 139.3, 137.8, 129.0, 128.5, 126.8, 126.6, 122.4, 66.6, 55.5, 51.3, 37.4\). IR (ATR): 3028, 2949, 1730, 1198, 1161, 741, 698 cm\(^{-1}\).
methyl 3-(4-hydroxyphenyl)-2-(isoindolin-2-yl)propanoate (63)

\[
\text{HO} \quad \begin{array}{c}
\text{N} \\
\text{O}
\end{array} \\
\text{O}
\]

\(^1\text{H NMR}\ (500\text{ MHz, CDCl}_3): \delta = 7.23\ (s, 4\text{H}), 7.09\ (d, J = 8.5\text{ Hz, 2H}), 6.72\ (d, J = 8.5\text{ Hz}), 5.16\ (s, 1\text{H}), 4.27\ (d, J = 10.5\text{ Hz, 2H}), 4.17\ (d, J = 10.5\text{ Hz, 2H}), 3.78\ (dd, J = 6.5, 8.5\text{ Hz, 1H}), 3.64\ (s, 3\text{H}), 3.1\ (m, 2\text{H}). \ \ ^{13}\text{C NMR}\ (125\text{ MHz, CDCl}_3): \delta = 172.8, 154.6, 139.1, 130.1, 129.4, 127.3, 126.8, 122.4, 121.0, 115.4, 73.6, 67.1, 55.6, 51.5, 36.6. \text{IR (ATR): 3363, 3026, 2951, 1732, 1516, 1219, 1171, 742, 540 cm}^{-1}.
N-(1-cyclohexylethyl)aniline (46)

\[
\begin{align*}
\text{H NMR (300 MHz, CDCl}_3\text{): } & \delta = 7.16 (t, J = 7.8 \text{ Hz, } 2\text{H}), 7.09 (t, J = 7.2 \text{ Hz, } 1\text{H}), 6.72 \\
& (dd, J = 8.5, 1 \text{ Hz, } 2\text{H}), 3.49 (s, 1\text{H}), 3.34 (p, J = 6 \text{ Hz, } 1\text{H}), 1.86 - 1.68 (m, 5\text{H}), 1.55 - \\
& 1.42 (m, 1\text{H}), 1.33 - 1.19 (m, 3\text{H}), 1.13 (d, J = 6 \text{ Hz 3H}), 1.05 (d, J = 12 \text{ Hz, } 1\text{H}). \\
\text{C NMR (75 MHz, CDCl}_3\text{): } & \delta = 147.96, 129.25, 116.49, 112.94, 52.97, 42.98, 29.79, 28.41, \\
& 26.65, 26.49, 26.35, 17.42. \text{ IR (ATR): } 3413, 2921, 2850, 1600, 1504, 1448, 1429, 1373, \\
& 1317, 1253, 1155, 1074, 991, 863, 744, 690 \text{ cm}^{-1}.
\end{align*}
\]
2-methoxy-N-(1-phenylpropyl)aniline (51)

\[ \text{H NMR (300 MHz, CDCl}_3\text{): } \delta = 7.37 - 7.29 (m, 4H), 7.26 - 7.23 (m, 1H), 6.77 (dd, } J = 7.8, 1.5 \text{ Hz, 1H), } 6.72 (\text{td, } J = 7.5, 1.5 \text{ Hz, 1H), } 6.61 (\text{td, } J = 7.5, 1.5 \text{ Hz, 1H), } 6.36 (\text{dd, } J = 7.8, 1.5 \text{ Hz, 1H), } 4.71 (s, 1H), 4.23 (t, } J = 6.5 \text{ Hz, 1H), } 3.91 (s, 3H), 1.89 (p, } J = 7.5 \text{ Hz, 2H), 0.99 (t, } J = 7.2 \text{ Hz, 3H). } \]

\[ ^{13}\text{C NMR (75 MHz, CDCl}_3\text{): } \delta = 146.62, 144.19, 137.48, 128.42, 126.77, 126.48, 121.15, 116.12, 110.86, 109.27, 59.60, 55.47, 31.77, 10.90. \]

IR (ATR): 3432, 2962, 2929, 1602, 1509, 1454, 1427, 1344, 1303, 1238, 1220, 1176, 1139, 1106, 1049, 1027, 900, 732, 700 cm\(^{-1}\).
ethyl 2-((2-methoxyphenyl)amino)-2-phenylacetate (52)

$\text{H NMR (300 MHz, CDCl}_3$: $\delta = 7.53 \text{ (dd, J = 8, 1.5 2H), 7.39 - 7.31 (m, 3H), 6.82 - 6.66 (m, 3H), 6.37 \text{ (dd, J = 7.5, 1.5 Hz, 1H), 5.50 (d, J = 6 Hz, 1H), 5.08 (d, J = 6.3, 1H), 4.313 - 4.10 (m, 2H), 3.91 (s, 3H), 1.23 (t, J = 7.2 Hz, 3H). 13C NMR (75 MHz, CDCl}_3$: $\delta = 171.80, 147.05, 137.84, 136.04, 128.76, 128.14, 127.23, 121.02, 117.29, 110.67, 109.56, 61.67, 60.80, 55.48, 14.05. \text{ IR (ATR): 3423, 2937, 1733, 1602, 1511, 1456, 1429, 1315, 1247, 1222, 1178, 1139, 1025, 730, 696 cm}^{-1}.$
2-methoxy-N-(1-phenylethyl)aniline (50)

\[
\begin{align*}
\text{H NMR (300 MHz, CDCl}_3\text{): } & \delta = 7.40 - 7.30 (m, 4H), 7.25 - 7.21 (m, 1H), 6.78 (dd, J = 7.2, 1.5 Hz, 1H), 6.73 (td, J = 7.5, 1.5 Hz, 1H), 6.62 (td, J = 7.5, 1.5 Hz, 1H), 6.36 (dd, J = 7.2, 1.5 Hz, 1H), 4.63 (s, 1H), 4.47 (t, J = 6.5 Hz, 1H), 1.57 (d, J = 6.6 Hz, 3H). \\
\text{C NMR (75 MHz, CDCl}_3\text{): } & \delta = 146.55, 145.45, 137.22, 128.57, 126.75, 125.83, 121.15, 116.27, 111.02, 109.27, 55.43, 53.30, 25.14. \text{ IR (ATR): } 3424, 3062, 2962, 2832, 1735, 1685, 1602, 1509, 1454, 1427, 1349, 1249, 1222, 1176, 1143, 1108, 1049, 1025, 900, 759, 734, 700 \text{ cm}^{-1}.
\end{align*}
\]
N-(1-(4-nitrophenyl)ethyl)aniline (54)

\[ \text{O} \begin{array}{c} \text{N} \\ \text{O} \\ \text{N} \end{array} \]

\[ \begin{array}{c} \text{O} \\ \text{N} \end{array} \]

\(^1\text{H}\) NMR (300 MHz, CDCl\(_3\)): \( \delta = 8.20 \text{ (dd, } J = 6.9, 1.5 \text{ Hz, 2H)}, 7.57 \text{ (d, } J = 8.7 \text{ Hz, 2H)}, 7.11 \text{ (t, } J = 7.5 \text{ Hz, 2H)}, 6.70 \text{ (t, } J = 7.5 \text{ Hz, 1H)}, 6.46 \text{ (dd, } J = 8.5, 1.2 \text{ Hz, 1H)}, 4.58 \text{ (q, } J = 6.3 \text{ Hz, 1H)}, 4.09 \text{ (s, 1H)}, 1.56 \text{ (d, } J = 6.3 \text{ Hz, 3H}). \(^{13}\text{C} \) NMR (75 MHz, CDCl\(_3\)): \( \delta = 153.15, 147.09, 156.51, 129.24, 126.69, 124.09, 118.00, 113.29, 53.33, 24.95. \) IR (ATR): 3409, 3052, 2971, 2927, 1598, 1513, 1504, 1450, 1430, 1340, 1317, 1280, 1257, 1205, 1180, 1143, 1106, 1012, 854, 748, 692 cm\(^{-1}\).
N-(1-(4-methoxyphenyl)ethyl)aniline (55)

\[
\text{\ding{69} NMR (300 MHz, CDCl}_3\text{: }\delta = 7.34 \text{ (d, } J = 6.3 \text{ Hz, 2H), 7.15 \text{ (t, } J = 8.4 \text{ Hz, 2H), 6.91}
\]
\[
\text{d, } J = 6.3 \text{ Hz, 2H), 6.70 \text{ (t, } J = 7.2 \text{ Hz, 1H), 6.57 \text{ (dd, } J = 8.4, 0.9 \text{ Hz, 2H), 4.51 \text{ (q, } J}
\]
\[
\text{= 6.3 Hz, 1H), 4.04 \text{ (s, 1H), 3.83 \text{ (s, 3H), 1.55 \text{ (t, } J = 6.3 \text{ Hz, 3H). }} \text{\ding{69}C NMR (75 MHz,}
\]
\[
\text{CDCl}_3\text{: }\delta = 158.52, 147.41, 137.31, 129.13, 126.94, 117.21, 114.05, 113.35, 55.27,
\]
\[
52.85, 25.04. \text{IR (ATR): 3405, 2962, 1602, 1504, 1461, 1317, 1284, 1241, 1176, 1105,}
\]
\[
1031, 993, 829, 748, 692, 545 \text{ cm}^{-1}.
\]
N-(1-(2-fluorophenyl)ethyl)aniline (53)

\[
\text{\begin{center}
\includegraphics[width=0.1\textwidth]{image}
\end{center}}
\]

\[^1\text{H NMR (500 MHz, CDCl}_3\text{): } \delta = 7.40 \text{ (td, } J = 7.8, 2 \text{ Hz, 1H), 7.25 - 7.20 (m, 1H), 7.15 - 7.05 (m, 4H), 6.69 (t, } J = 7.5 \text{ Hz, 1H), 6.55 (dd, } J = 8.5, 1, \text{Hz, 2H), 4.84 (q, } J = 7 \text{ Hz, 1H), 4.07 (s, 1H), 1.57 (d, } J = 7 \text{ Hz, 3H). \text{^13C NMR (125 MHz, CDCl}_3\text{): } \delta = 161.46, 159.51, 146.86, 131.70 (d, } J_{CF} = 12.5 \text{ Hz), 129.16, 128.30 (d, } J_{CF} = 8.75 \text{ Hz), 127.19 (d, } J_{CF} = 5 \text{ Hz), 124.39 (d, } J_{CF} = 3.75 \text{ Hz), 117.5, 115.49 (d, } J_{CF} = 21.25 \text{ Hz), 113.21, 47.51 (d, } J_{CF} = 2.5 \text{ Hz), 23.37. IR (ATR): 3411, 3052, 3019, 2971, 2927, 1602, 1504, 1484, 1448, 1375, 1317, 1259, 1220, 1182, 1087, 823, 748, 692, 609 \text{ cm}^{-1}.\]


ethyl 2-phenyl-2-(phenylamino)acetate (56)

\[
\text{\begin{tikzpicture}
    \draw[thick,->] (0,0) -- (1,1);
    \draw[thick,->] (1,0) -- (0,1);
    \draw[thick,->] (1,1) -- (1.5,1);
    \draw[thick,->] (1.5,1) -- (2,0);
    \draw[thick,->] (2,0) -- (1.5,-1);
    \draw[thick,->] (1.5,-1) -- (1,-1);
    \draw[thick,->] (1,-1) -- (0,0);
    \end{tikzpicture}}
\]

\[\text{H} \quad \text{N} \quad \text{O} \quad \text{O} \quad \text{H} \]

\[\text{\begin{tikzpicture}
    \draw[thick,->] (0,0) -- (1,1);
    \draw[thick,->] (1,0) -- (0,1);
    \draw[thick,->] (1,1) -- (1.5,1);
    \draw[thick,->] (1.5,1) -- (2,0);
    \draw[thick,->] (2,0) -- (1.5,-1);
    \draw[thick,->] (1.5,-1) -- (1,-1);
    \draw[thick,->] (1,-1) -- (0,0);
    \end{tikzpicture}}\]

\[\text{\begin{tikzpicture}
    \draw[thick,->] (0,0) -- (1,1);
    \draw[thick,->] (1,0) -- (0,1);
    \draw[thick,->] (1,1) -- (1.5,1);
    \draw[thick,->] (1.5,1) -- (2,0);
    \draw[thick,->] (2,0) -- (1.5,-1);
    \draw[thick,->] (1.5,-1) -- (1,-1);
    \draw[thick,->] (1,-1) -- (0,0);
    \end{tikzpicture}}\]

\[^1\text{H NMR (300 MHz, CDCl}_3\): \delta = 7.53 (dd, J = 8, 1.2 \text{ Hz}, 1H), 7.40 - 7.32 (m, 3H), 7.15 (td, J = 7, 1.8 \text{ Hz}, 2H), 6.72 (t, J = 7.5 \text{ Hz}, 1H), 6.59 (dd, J = 8.7, 1 \text{ Hz}, 2H), 5.09 (d, J = 6, 1H), 4.99 (d, J = 5.5 \text{ Hz}, 1H), 4.32 - 4.11 (m, 2H), 1.25 (t, J = 7.2 \text{ Hz}, 3H). \]^1\text{C NMR (75 MHz, CDCl}_3\): \delta = 171.83, 146.01, 137.74, 129.23, 128.81, 128.21, 127.21, 118.04, 113.41, 61.81, 60.81, 14.05. IR (ATR): 3396, 1722, 1689, 1602, 1506, 1454, 1365, 1313, 1251, 1214, 1178, 1139, 1018, 873, 840, 748, 694, 626 cm\(^{-1}\).\]
N-(1-(4-bromophenyl)ethyl)aniline (59)

\[ \text{1H NMR (300 MHz, CDCl}_3\text{): } \delta = 7.47 (dd, J = 6.6, 1.8 Hz, 2H), 7.28 (d, J = 8.4 2H), 7.13 (td, J = 7, 1.8 Hz 2H), 6.50 (dd, J = 8.5, 1.2 Hz, 2H), 4.47 (q, J = 6.6 Hz, 1H), 4.03 (s, 1H), 1.52 (d, J = 7 Hz, 3H). \]

\[ \text{13C NMR (75 MHz, CDCl}_3\text{): } \delta = 146.96, 144.38, 131.75, 129.16, 127.65, 120.50, 117.55, 113.32, 53.06, 25.08. \]

IR (ATR): 3415, 2966, 1600, 1502, 1429, 1402, 1317, 1255, 1180, 1139, 1070, 1008, 908, 821, 748, 690 cm\(^{-1}\).
N-(1-(pyridin-2-yl)ethyl)aniline (57)

\[
\begin{align*}
&\text{H NMR (300 MHz, CDCl}_3\text{): }\delta = 8.60 (\text{dd}, J = 4.2, 0.6 \text{ Hz, 1H}), 7.63 (\text{td}, J = 7.65, 1.2 \text{Hz, 1H}), 7.37 (\text{d}, J = 7.8 \text{ Hz, 1H}), 7.14 (\text{q}, J = 7.5 \text{ Hz, 3H}), 6.68 (\text{t}, J = 7.2 \text{ Hz, 1H}), 6.58 (\text{d}, J = 8.4 \text{ Hz, 2H}), 4.64 (\text{q}, J = 6.6 \text{ Hz, 1H}), 4.47 (\text{ s, 1H}), 1.57 (\text{d}, J = 6.6 \text{ Hz, 3H}). \\
&\text{C NMR (75 MHz, CDCl}_3\text{): }\delta = 163.89, 149.32, 147.10, 136.80, 129.16, 121.95, 121.95, 120.30, 117.39, 113.41, 54.75, 23.21. \text{IR (ATR): } 3403, 2969, 1600, 1502, 1471, 1432, 1317, 1259, 1180, 1153, 1025, 993, 869, 784, 746, 692 \text{ cm}^{-1}.
\end{align*}
\]
N-(2-methyl-1-phenylpropyl)aniline (60)

\[
\begin{align*}
\text{H NMR (300 MHz, CDCl}_3\text{): } & \delta = 7.32 \text{ (d, } J = 4.2 \text{ Hz, 4H), } 7.26 - 7.20 \text{ (m, 1H), } 7.09 \text{ (t, } J = 7.5 \text{ Hz, 2H), } 6.63 \text{ (t, } J = 7.5 \text{ Hz, 1H), } 6.52 \text{ (dd, } J = 8.4 \text{, 1 Hz, 2H), } 4.15 \text{ (d, } J = 6 \text{ Hz, 2H), } 2.06 \text{ (oc, } J = 6.3 \text{ Hz, 1H), } 1.01 \text{ (d, } J = 7 \text{ Hz, 3H), } 0.95 \text{ (d, } J = 7 \text{ Hz, 3H).} \\
\text{C NMR (75 MHz, CDCl}_3\text{): } & \delta = 147.73, 142.59, 129.05, 128.19, 127.17, 126.76, 116.99, 113.21, \\
& 63.77, 34.89, 19.73, 18.61. \text{ IR (ATR): } 3421, 3021, 2958, 2871, 1600, 1502, 1452, 1367, \\
& 1313, 1267, 1178, 1078, 1027, 756, 690 \text{ cm}^{-1}.
\end{align*}
\]
N-(1-(4-fluorophenyl)ethyl)aniline (58)

\[
\begin{align*}
\text{F} & \quad \text{N} \\
& \quad \text{H}
\end{align*}
\]

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 7.38 - 7.34 (m, 2H), 7.13 (t, J = 8 \text{ Hz}, 2H), 7.03 (t, J = 8.7 \text{ Hz} 2H), 6.69 (t, J = 7.2 \text{ Hz}, 1H), 6.52 (d, J = 7.8 \text{ Hz}, 2H), 4.50 (q, J = 7 \text{ Hz}, 1H), 4.03 (s, 1H), 1.53 (d, J = 6.6 \text{ Hz}, 3H)\). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \(\delta = 147.1, 140.89, 129.14, 127.32 (d, J_{CF} = 12.5 \text{ Hz}), 117.44, 115.44 (d, J_{CF} = 36.25 \text{ Hz}), 113.32, 52.90, 25.19\). IR (ATR): 3411, 3050, 2969, 1600, 1504, 1429, 1373, 1315, 1257, 1218, 1155, 1139, 1093, 1014, 833, 748, 690 cm\(^{-1}\).
N-(1-phenylpropyl)aniline (61)

\[ 
\text{H NMR (300 MHz, CDCl}_3\text{): } \delta = 7.40 - 7.37 \text{ (m, 4H), 7.29 - 7.26 (m, 1H), 7.13 (dd, } J = 7.5 \text{ Hz, 2H), 6.67 (t, } J = 7.2 \text{ Hz, 1H), 6.56 (d, } J = 7.5 \text{ Hz, 2H), 4.27 (t, } J = 7.5 \text{ Hz, 1H), 4.10 (br, 1H), 1.87 (pd, } J = 7 \text{ Hz, 3H), 1.00 (t, } J = 7.2 \text{ Hz, 3H). } \text{\textsuperscript{13}C NMR (75 MHz, CDCl}_3\text{): } \delta = 147.55, 143.95, 129.11, 128.52, 126.90, 126.51, 117.14, 113.26, 59.74, 31.69, 10.85. \text{ IR (ATR): 3407, 2964, 2929, 2873, 1600, 1504, 1452, 1317, 1180, 1105, 1027, 1004, 902, 867, 746, 692 cm}^{-1}. \]
CHAPTER 4

CHIRAL BRØNSTED ACID CATALYZED DIRECT REDUCTIVE AMINATION

4.1.1 Introduction

After a successful series of direct reductive amination reactions, our goal was to further explore potential applications of 1-hydrosilatrane. Primarily our interest was piqued by the reaction of a ketone and an aryl amine. This efficient, high yielding reaction formed a chiral center at the carbonyl carbon. Chirality with 1-hydrosilatrane was previously explored by our group with the reduction of ketones using a chiral Lewis base as an activator for 1-hydrosilatrane. To explore potential chiral direct reductive amination with 1-hydrosilatrane we investigated a variety of chiral Brønsted acids that are commercially available and are readily synthesized.

4.2.1 Testing chiral Brønsted acids

We started our investigation into optimized conditions with the reaction of aniline and acetophenone. Initially we investigated chiral Brønsted acids, focusing on ones that are readily available and inexpensive. First we tested tartaric acid (Table 4.1, entry 1), giving us a conversion of 25% with an enantiomeric ratio (er) of -1. Another similar carboxylic acid was tested (Table 4.1, entry 2) with no improvement in er. With initially unsuccessful results we tested more commonly used chiral BINOL-
derived phosphoric acid. The parent catalyst showed a good conversion and a slight er (Table 4.1, entry 4). Next we tested a bulkier derivative resulting in slightly here er (Table 4.1, entry 5).

Table 4.1 Chiral Brønsted acid screening

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>er</th>
<th>conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Image" /></td>
<td>acetonitrile 50:50</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Image" /></td>
<td>acetonitrile 50:50</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Image" /></td>
<td>ethyl acetate 50:50</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Image" /></td>
<td>ethyl acetate 48:52</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Image" /></td>
<td>benzene 46:54</td>
<td>50</td>
<td></td>
</tr>
</tbody>
</table>

R = 3,5-trifluoromethyl phenyl

4.2.2 Synthesis of chiral Brønsted acids

The preliminary results showed that the BINOL phosphoric acid derivatives were the way to proceed. We set out to synthesize bulkier derivatives. Previous work done by MacMillan et al. demonstrated the potential for catalyst 72 to
be a good starting point for further investigation. Figure 4.1 outlines our reaction pathway. The first step the BINOL was protected with MOM protecting groups. Next the 3 and 3’ positions were deprotonated using n-butyllithium, followed by the addition of triphenylchlorosilane resulted in formation of disilylated product. The MOM protecting groups were then removed using strong acid and heat, resulting in formation of deprotected product. This was then sequentially reacted with phosphorus oxychloride and water to produce 72.

![Figure 4.1 Synthesis of (R)-(-)-3,3’-Bis(triphenylsilyl)-1,1’-binaphthyl-2,2’-diyl hydrogenphosphate 72.](image)

The bulkier phosphate BINOL 77 was synthesized using a literature procedure outlined in figure 4.2. In the first step BINOL was protected with methyl iodide. Next the protected BINOL was sequentially reacted with n-butyllithium and iodine resulting in a diiodinated product. This underwent Kumada coupling with the Grignard reagent
and nickel catalyst to form disubstituted intermediate. This was then deprotected using boron tribromide and then further reacted with phosphorus oxychloride and water to form 77.

![Chemical structures](image)

**Figure 4.2 Synthesis of \((R)-3,3′\text{-Bis(2,4,6-triisopropylphenyl)}-1,1′\text{-binaphthyl-2,2′-diyl hydrogenphosphate} 77.**

4.3.1 Optimization of reaction conditions

With the two chiral catalysts in hand we tested their chiral activity. Benzene was selected as solvent of choice because of its known ability to increase er. The catalyst 72 (Table 4.2, entry 1), although used extensively in other work, provided
little increase in the er under our conditions. On the other hand catalyst 77 provided a great increase in er and conversion (Table 4.2, entry 2).

Table 4.2 Synthesized BINOL-phosphoric acid screening

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>er</th>
<th>conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72</td>
<td>benzene</td>
<td>44:56</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R = SiPh₃</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>77</td>
<td>benzene</td>
<td>84:16</td>
<td>95</td>
</tr>
</tbody>
</table>

R = 2,4,6-triisopropylphenyl

In hopes of making the reaction more environmentally friendly, acetonitrile and ethyl acetate was used (entries 2 and 3). Acetonitrile showed no significant er and good conversion while ethyl acetate showed moderate er and good conversion. Toluene behaved almost identical to benzene with 85:15 er.

Table 4.3 Solvent optimization for chiral direct reductive amination

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>sieves</th>
<th>er</th>
<th>conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Benzene</td>
<td>5Å</td>
<td>84:16</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>Acetonitrile</td>
<td>5Å</td>
<td>47:53</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>Ethyl Acetate</td>
<td>5Å</td>
<td>75:25</td>
<td>77</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>5Å</td>
<td>85:15</td>
<td>99</td>
</tr>
</tbody>
</table>
Catalyst loading was investigated next. Going from 1 to 0.3 equivalent (eq.) of catalyst showed almost no impact on er or conversions. When less than 0.3 eq. was used, the conversion and er dropped. Finally, the attempts were made to optimize the reaction temperature, it is worth noting that during temperature optimization no significant change in er or conversion was detected from 50°C to room temperature, although when cooled below 0°C the conversion and er dropped significantly.

4.4.1 Scope of chiral direct reductive amination

With the optimized conditions, we investigated the potential of this chiral reaction. We tested a variety of ketones (figure 4.3). Reaction of aniline and acetophenone proceeded smoothly with a complete conversion to the corresponding amine in 72% ee. A bulkier propiophenone and isobutyrophenone gave good to excellent conversions, and in the case of propiophenone increased the ee to 76%. Election poor p-nitroacetophenone showed quantitative conversion but ee of only 56%. Electron rich p-methoxyacetophenone reacted with aniline in excellent conversion with 66% ee. 2-Acetylpyridine reacted with aniline in good conversion although the ee was unable to be determined precisely due to the limitation of chiral GC/MS column that was unable to separate the two enantiomer effectively. Reaction of para-substituted halides gave excellent conversion and ee, with p-fluoroacetophenone giving an ee of 84%. Aliphatic ketones gave good conversion, although the ee was low. Finally, we tested the reaction on a ketoester. Although the racemic reaction (discussed in chapter 3) gave a relatively good conversion, the chiral counterpart resulted in negligible conversion to the amine with no ee.
Figure 4.3 Scope of chiral direct reductive amination using 1-hydrosilatrane.
4.4.2 Conclusion

We have developed a method using 1-hydrosilatrane as a reducing agent in a chiral direct reductive amination. Furthermore this is the first method using an alkoxyhydrosilane. Using Brønsted acid catalyst 77 we were able to obtain er of 92/8 under 30% catalyst loading. This reaction works well with a variety of functionalized aryl ketones, activating and deactivating groups, halides, and even ketoesters. Although aromatic ketones performed exceptionally well, aliphatic counterparts showed low er but high conversions.

4.5.1 Experimental and Supplementary information

General information

All chemicals were obtained from commercial sources and used without further purification. Column chromatography was performed using silica gel from Macherey-Nagel (60 M, 0.04-0.063 mm). $^1$H NMR, and $^{13}$C NMR were recorded on either a 300 or 500 MHz Bruker Avance III spectrometer. Chemical shifts were reported in ppm with the solvent resonance as internal standard ($^1$H NMR CDCl$_3$ δ = 7.28, $^{13}$C NMR CDCl$_3$ δ = 77.01, $^{13}$C NMR (CD$_3$)$_2$SO δ = 39.99). IR spectra were acquired using an ATI Mattson FTIR spectrophotometer on neat samples.

Synthesis of chiral phosphoric acid 72

a) 1.81g of (R)-BINOL was dissolved in 15 mL of dimethyl formamide (DMF) and cooled to 0°C. Sodium hydride (0.575 g) was added in one portion to the stirring solution and let stir for 20 minutes at 0°C. MOMCl was added dropwise
over the course of 5 min and the solution was let to warm up to room
temperature and stirred for an additional hour. The reaction was quenched
with water and extracted three times with diethyl ether. Organic fractions
were concentrated and used without further purification.

b) The MOM-protected (R)-BINOL (2.26 g) from (a) was dissolved in diethyl ether
(104 mL) followed by a dropwise addition of n-butyllithium (8.75 mL of 1.5 M)
over the course of 10 minutes. The resulting solution was stirred at room
temperature for 1.5 hours. The mixture was then cooled to 0°C and 50mL of
tetrahydrofuran (THF) was added. After a further 15 minutes of stirring a
solution of Ph₃SiCl (4.15 g in 10 mL of THF) was added. The resulting suspension
was allowed to warm up to room temperature and stirred for 30 hours. The
reaction was quenched by addition of saturated NH₄Cl followed by extraction
with dichloride methane. The organic fractions were concentrated and purified
by column chromatography (1:1:20 CH₂Cl₂:Et₂O:Hexane).

c) Concentrated HCl was added to a solution of MOM protected (R)-BINOL from (b)
in dioxane. The resulting solution was heated at 70°C for 24 hours. The
reaction mixture was then cooled and acid was neutralized with sodium
carbonate solution. The product was extracted with ethyl acetate and
concentrated. The product was purified by trituration with hot CH₂Cl₂:Et₂O
(1:10).

d) The diol from (c) was suspended in pyridine. Phosphorous oxychloride was
added dropwise at room temperature with rapid stirring and the resulting
suspension was heated to 95°C. Upon reaching 95°C the reaction was stirred at
the temperature for 24 hours. The solution was then cooled to 0°C and water was added slowly. The resulting suspension was heated at 95°C for 6 hours. The reaction was then quenched with 1M HCl and extracted with dichloromethane and the organic phases were concentrated. The resulting solid was purified by column chromatography (98:2 CH₂Cl₂:MeOH).

**Synthesis of chiral phosphoric acid 77**

a) (R)-BINOL (2.6g) was heated in acetone (80 mL) until dissolved. To the solution potassium carbonate (4.15 g) was added followed by methyl iodide (5 g) and the resulting mixture was heated at reflux for 24 hours. Additional methyl iodide was added and the reaction was heated for additional 12 hours. The solution was evaporated until only 30 mL of solvent remained. Water (80 mL) was added, and the heterogeneous mixture was allowed to stir for 8 hours. The resulting solid was filtered, washed 3 times with water, then collected and dried at reduced pressure.

b) To a mixture of methoxy protected (R)-BINOL (2.53 g) in 30 mL of diethyl ether was added tetramethylethylenediamine (2.9 g) at room temperature. To the resulting mixture n-butyllithium (11.33 mL of 1.5 M) was added dropwise. The reaction mixture was allowed to stir at room temperature for 4 hours. The reaction was cooled to -78°C and I₂ in 30 mL of ether was added and stirred for 5 hours. The reaction mixture was then warmed to room temperature, and a saturated solution of Na₂S₂O₃ was added and stirred for 30 minutes. The organic layer was then separated and the
aqueous phase was extracted with dichloromethane three times. The
combined organic layers were concentrated and purified by column
chromatography (4:1 hexane:CH₂Cl₂).

c) To a well-stirred suspension of diiodo (R)-BINOL (2.169 g) and NiCl₂(Ph₃P)₂
(0.432 g) in 40 mL of diethyl ether was slowly added Grignard solution over
10 minutes. The solution was then refluxed over 16 hours after which the
mixture was diluted with 1 M HCl. The aqueous layer was extracted three
times with diethyl ether and the combined organic phases were
concentrated. The resulting solid was purified by column chromatography
(100:1 hexane:Et₂O).

d) To a solution of protected BINOL (3.0 g) in 100mL of dichloromethane at
0°C was slowly added BBr₃ (30 mL of 1 M CH₂C₂). After the full addition the
resulting solution was left stirring at room temperature for 24 hours. Upon
completion the reaction was cooled back to 0°C and water (84 mL) was
added slowly. Resulting suspension was extracted three times with
dichloromethane and the combined extracts were concentrated and purified
by column chromatography (99:1 hexane:Et₂O).

e) Diol (2 g) was suspended in 6 mL of pyridine. Phosphorous oxychloride was
added dropwise at room temperature with rapid stirring and the resulting
suspension was heated to 95°C. Upon reaching 95°C the reaction was stirred
at the temperature for 24 hours. The solution was cooled to 0°C and water
was added slowly. The resulting suspension was heated at 95°C for 6 hours.
The reaction was then quenched with 1M HCl and extracted with
dichloromethane and the organic phases were concentrated. The resulting solid was purified by column chromatography (98:2 CH<sub>2</sub>Cl<sub>2</sub>:MeOH).

**General procedure for synthesis of chiral secondary amines**

In a 5 dram vial a mixture of molecular sieves (5 Å), 1-hydrosilatrane (0.035 g) acetophenone (0.036 mL), aniline (0.01 mL) and chiral activator (0.3 eq) in 1 mL of toluene was stirred at room temperature overnight. A small portion of the mixture was then tested using a chiral GC/MS for enantiomeric excess. Enantiomeric ratio was determined using chiral DEX-CB GC column.
(R)-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (69)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.98$ (d, $J = 9$ Hz, 2H), 7.90 (d, $J = 8.5$ Hz, 2H), 7.60 (d, $J = 9$ Hz, 2H), 7.37 (t, $J = 7.5$ Hz, 2H), 7.25 (t, $J = 8.5$ Hz, 2H), 7.18 (d, $J = 8.5$ Hz, 2H), 5.11 (d, $J = 6.5$ Hz, 2H), 5.00 (d, $J = 6.5$ Hz, 2H), 3.17 (s, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 152.66, 134.03, 129.89, 129.39, 127.86, 126.29, 125.56, 124.06, 121.33, 117.32, 95.24, 55.83$. IR (ATR): 2921, 2852, 1619, 1592, 1506, 1463, 1240, 1147, 1068, 1031, 1010, 921, 809, 754 cm$^{-1}$. 
(R)-(2,2′-bis(methoxymethoxy)-[1,1′-binaphthalene]-3,3′-diyl)bis(triphenylsilane)

(70)

\[
\begin{align*}
\text{Ph}_3\text{Si} & \quad \text{Ph} \\
\text{Si} & \quad \text{Ph} \\
\end{align*}
\]

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta = 8.00\) (d, \(J = 9\), 2H), 7.93 (d, \(J = 8\) Hz, 2H), 7.78 (dd, \(J = 8, 1.5\) Hz, 2H), 7.64 (d, \(J = 9\) Hz, 2H), 7.47 - 7.38 (m, 5H), 7.28 (td, \(J = 7, 1.5\) Hz, 2H), 7.23 (d, \(J = 8.5\) Hz, 2H), 5.14 (d, \(J = 6.5\) Hz, 2H), 5.03 (d, \(J = 6.5\) Hz, 2H), 3.20 (s, 6H), 1.14 (s, 4H). \(^1\)C NMR (125 MHz, CDCl\(_3\)): \(\delta = 152.70, 135.31, 134.86, 134.08, 129.94, 129.69, 129.45, 127.92, 127.77, 126.35, 125.61, 124.12, 121.36, 117.33, 95.23, 55.85, 26.63, 19.07\). IR (ATR): 2954, 2931, 1427, 1240, 1197, 1147, 1106, 1074, 1033, 1004, 958, 923, 740, 698 cm\(^{-1}\).
(R)-4-hydroxy-2,6-bis(triphenylsilyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide (72)

$^1$H NMR (300 MHz, CDCl$_3$): $\delta = 7.94$ (s, 2H), 7.73 (d, $J = 8.2$ Hz, 2H), 7.63 - 7.61 (m, 12H), 7.40 - 7.16 (m, 24H). $^{13}$C NMR (75 MHz, CDCl$_3$): $\delta = 152.67, 152.55, 142.07, 136.81, 134.74, 134.62, 130.30, 129.46, 128.52, 127.73, 127.16, 126.82, 125.66, 124.82, 121.75$. IR (ATR): 1427, 1253, 1216, 1101, 983, 956, 856, 744, 698, 676, 613 cm$^{-1}$. 
(R)-2,2'-dimethoxy-1,1'-binaphthalene (73)

\[
\text{\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): } \delta = 8.01 (d, J = 9 \text{ Hz}, 2H), 7.90 (d, J = 8.5 \text{ Hz}, 2H), 7.50 (d, J = 9 \text{ Hz}, 2H), 7.35 (td, J = 8, 1.5 \text{ Hz}, 2H), 7.24 (td, J = 8, 1.5 \text{ Hz}, 2H), 6.95 (dd, J = 8.5, 1.5 \text{ Hz}, 2H), 3.80 (s, 6H). \text{\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): } \delta = 155.00, 134.03, 129.41, 129.24, 127.93, 126.31, 125.28, 123.52, 119.64, 114.29, 56.93. \text{IR (ATR): } 1617, 1589, 1506, 1459, 1353, 1263, 1249, 1089, 1064, 896, 809, 746 \text{ cm}^{-1}.
\]
(R)-3,3’-diiodo-2,2’-dimethoxy-1,1’-binaphthalene (74)

![Chemical Structure](image.png)

$^1$H NMR (500 MHz, CDCl$_3$): δ = 8.56 (s, 2H), 7.82 (d, $J$ = 8 Hz, 2H), 7.83 (s, 2H), 7.53 (td, $J$ = 8, 1.5 Hz, 2H), 7.43 (dd, $J$ = 8.5, 1.5 Hz, 2H), 7.29 (dd, $J$ = 8.5, 1.5 Hz, 2H), 7.10 (dd, $J$ = 8.5, 0.5 Hz, 2H), 3.45 (s, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$): δ = 154.49, 139.90, 133.86, 132.19, 127.08, 126.97, 125.78, 125.66, 125.38, 92.35, 61.12. IR (ATR): 2935, 1560, 1492, 1454, 1386, 1346, 1230, 1041, 1018, 968, 906, 883, 727 cm$^{-1}$. 
(1R,3r)-2,2'-dimethoxy-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthalene (75)

\[
\begin{align*}
\text{1H NMR (500 MHz, CDCl}_3): \ & \delta = 7.88 \ (d, \ J = 8 \ Hz, \ 2H), \ 7.77 \ (s, \ 2H), \ 7.44 \ (dd, \ J = 8, \ 1.5 \ Hz, \ 2H), \ 7.38 - 7.31 \ (m, \ 7H), \ 7.12 \ (dd, \ J = 8.5, \ 1.5 \ Hz, \ 4H), \ 3.17 \ (s, \ 6H), \ 2.99 \ (sp, \ J = 7 \ Hz, \ 2H), \ 2.89 \ (sp, \ J = 6.5 \ Hz, \ 2H), \ 2.83 \ (sp, \ J = 6.5 \ Hz, \ 2H), \ 1.36 \ (d, \ J = 7 \ Hz, \ 12H), \\
& \ 1.23 \ (d, \ J = 7 \ Hz, \ 6H), \ 1.20 \ (d, \ J = 7 \ Hz, \ 6H), \ 1.16 \ (d, \ J = 7 \ Hz, \ 6H), \ 1.11 \ (d, \ J = 7 \ Hz, \ 6H). \\
\text{13C NMR (125 MHz, CDCl}_3): \ & \delta = 155.09, \ 148.06, \ 147.03, \ 146.74, \ 134.11, \ 133.87, \\
& \ 133.68, \ 133.24, \ 130.90, \ 130.22, \ 128.53, \ 128.47, \ 127.86, \ 125.88, \ 125.78, \ 124.69, \\
& \ 124.53, \ 120.63, \ 59.78, \ 34.24, \ 30.99, \ 30.82, \ 25.49, \ 25.27, \ 24.15, \ 24.10, \ 23.39, \ 23.32. \\
\text{IR (ATR):} \ & 2960, \ 2867, \ 1457, \ 1402, \ 1361, \ 1243, \ 1213, \ 1149, \ 1020, \ 906, \ 730, \ 649 \ cm^{-1}. 
\end{align*}
\]
(1R,3r)-3,3'-bis(2,4,6-triisopropylphenyl)-[1,1'-binaphthalene]-2,2'-diol (76)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta = 7.90$ (d, $J = 8$ Hz, 2H), 7.79 (s, 2H), 7.41 (td, $J = 8$, 1.5 Hz, 2H), 7.36 - 7.31 (m, 4H), 7.16 (dd, $J = 8$, 1.5 Hz, 4H), 4.95 (s, 2H), 2.99 (sp, $J = 7$ Hz, 2H), 2.88 (sp, $J = 6.5$ Hz, 2H), 2.72 (sp, $J = 6.5$ Hz, 2H), 1.34 (d, $J = 7$ Hz, 12H), 1.23 (d, $J = 6.5$ Hz, 6H), 1.14 (d, $J = 7$ Hz, 6H), 1.12 (d, $J = 7$ Hz, 6H), 1.06 (d, $J = 7$ Hz, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta = 150.64, 149.14, 147.80, 147.75, 133.46, 130.65, 130.37, 129.11, 129.05, 128.23, 126.62, 124.52, 123.76, 121.23, 121.17, 113.11, 34.35, 30.89, 30.85, 24.31, 24.29, 24.07, 24.00, 23.92, 23.72. IR (ATR): 3521, 2960, 2867, 1604, 1457, 1421, 1382, 1361, 1255, 1232, 1170, 1114, 908, 730 cm$^{-1}$. 
(R)-4-hydroxy-2,6-bis(2,4,6-triisopropylphenyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide (77)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta =$ 7.91 (d, $J =$ 8.5 Hz, 2H), 7.83 (s, 2H), 7.53 (td, $J =$ 8, 1.5 Hz, 2H), 7.38 - 7.33 (m, 4H), 6.95 (dd, $J =$ 18.5, 1.5 Hz, 4H), 2.86 (sp, $J =$ 7 Hz, 2H), 2.61 (sp, $J =$ 6.5 Hz, 2H), 2.53 (sp, $J =$ 6.5 Hz, 2H), 1.26 (d, $J =$ 2.5 Hz, 6H), 1.24 (d, $J =$ 2.5 Hz, 6H), 1.03 (d, $J =$ 6.5 Hz, 6H), 1.00 (d, $J =$ 7 Hz, 6H), 0.93 (d, $J =$ 6.5 Hz, 6H), 0.68 (d, $J =$ 6.5 Hz, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta =$ 148.30, 147.92, 147.36, 145.88, 145.81, 132.60, 132.37, 132.25, 131.27, 130.96, 128.12, 127.36, 126.14, 125.58, 122.00, 121.09, 120.23, 34.21, 30.95, 30.63, 26.31, 24.97, 24.14, 23.91, 23.23, 22.81. IR (ATR): 2960, 2867, 1606, 1459, 1409, 1361, 1278, 1238, 1207, 1149, 1020, 970, 904, 730, 647, 611, 551 cm$^{-1}$. 
CHAPTER 5

CONCLUSIONS

The work discussed in this dissertation shows the process behind developing new reduction reactions with 1-hydrosilatrane. First, investigation of reduction of aldehydes to alcohols was conducted. With an addition of a Lewis base, 1-hydrosilatrane showed great potential as a reducing reagent. Reactions with many aryl aldehydes resulted in high yield and rapid reaction times. Furthermore, 1-hydrosilatrane demonstrated good chemoselectivity, avoiding potentially reducible functional groups like halides, nitro, allyl and benzyl groups. The majority of the reactions were run under ambient conditions with no exclusion of moisture from reaction vesicle.

Moreover, 1-hydrosilatrane was investigated as a reducing reagent in direct reductive amination reaction. Primary amines were reacted with ketones or aldehydes in the presence of acetic acid, a common Brønsted acid. This reaction proceeded at room temperature and resulted in excellent yields and functional group tolerance.

With the success of Brønsted acid-mediated reductive amination reaction, we investigated the potential use of catalytic amounts of chiral acids to achieve enantioselectivity. To date these kind of reactions have not been possible with other silane reducing reagents. Our work showed that using a bulky chiral BINOL-phosphoric acid lead to good enantioselectivity. In our hands, we were able to reach 82% ee, and we believe that further work with manipulation of catalysts can lead to even high ee.
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APPENDIX A

CHIRAL GC/MS RESULTS
N-(1-phenylethyl)aniline (45)
N-(1-cyclohexylethyl)aniline (46)
ethyl 2-((2-methoxyphenyl)amino)-2-phenylacetate (52)
2-methoxy-N-(1-phenylethyl)aniline (50)
N-(1-(4-nitrophenyl)ethyl)aniline (54)
N-(1-(4-methoxyphenyl)ethyl)aniline (55)
N-(1-(4-bromophenyl)ethyl)aniline (59)
N-(1-(pyridin-2-yl)ethyl)aniline (57)
N-(2-methyl-1-phenylpropyl)aniline (60)
N-(1-(4-fluorophenyl)ethyl)aniline (58)
N-(1-phenylpropyl)aniline (51)
APPENDIX B

$^1$H AND $^{13}$C NMR SPECTRA OF REDUCED ALCOHOLS
1-Hydrasilatrane (1)
Phenylmethanol (11)
$p$-tolylmethanol (13)

\[
\begin{align*}
&\text{Chemical Shifts:} \\
7.279 & \quad 7.279 & \quad 7.188 & \quad 7.119 \\
-4.088 & \quad -2.367 \\
120 & \quad 65.30 & \quad 21.86
\end{align*}
\]
(4-(tert-butyl)phenyl)methanol (12)
(4-methoxyphenyl)methanol (14)
(3-methoxyphenyl)methanol (15)
(2-methoxyphenyl)methanol (16)
(4-phenoxypyphenyl)methanol (17)
(4-(benzyloxy)phenyl)methanol (18)
(4-(allyloxy)phenyl)methanol (19)
4-(hydroxymethyl)benzonitrile (20)
(3-nitrophenyl)methanol (21)
(4-chlorophenyl)methanol (22)
(4-fluorophenyl)methanol (23)
(3-fluorophenyl)methanol (24)
(2-fluorophenyl)methanol (25)
3-(hydroxymethyl)phenol (27)
naphthalen-1-ylmethanol (31)
naphthalen-2-ylmethanol (32)
anthracen-9-ylmethanol (33)
furan-2-ylmethanol (28)
thiophen-2-ylmethanol (29)
thiophen-3-ylmethanol (30)
Cyclohexylmethanol (34)
APPENDIX C

$^1$H AND $^{13}$C NMR SPECTRA OF REDUCTIVE AMINATION PRODUCTS
N-(4-methylbenzyl)propan-1-amine (35)
N-benzyl-1-(p-tolyl)methanamine (36)
N-(4-methylbenzyl)aniline (37)
4-((benzylamino)methyl)-N,N-dimethylaniline (38)
N-benzyl-1-(4-methoxyphenyl)methanamine (39)
methyl 2-((4-methylbenzyl)amino)-3-phenylpropanoate (40)
N-benzyl-1-(4-fluorophenyl) methanamine (41)
(E)-N-benzyl-3-phenylprop-2-en-1-amine (42)
N-benzyl-1-cyclohexylmethanamine (43)
N-benzyl-1-phenylethananine (44)
N-(1-phenylethyl)aniline (45)
N-benzylcyclopentanamine (49)
N-benzylhexan-2-amine (47)

Proton
N-(hexan-2-yl)aniline (48)
methyl 2-(isoindolin-2-yl)-3-phenylpropanoate (62)
methyl 2-(isoindolin-2-yl)-3-(p-tolyl)propanoate (63)
N-(1-cyclohexylethyl)aniline (46)
2-methoxy-N-(1-phenylpropyl)aniline (51)
ethyl 2-((2-methoxyphenyl)amino)-2-phenylacetate (52)
2-methoxy-N-(1-phenylethyl)aniline (50)
$N$-(1-(4-nitrophenyl)ethyl)aniline (54)
N-(1-(4-methoxyphenyl)ethyl)aniline (55)
N-(1-(2-fluorophenyl)ethyl)aniline (53)
ethyl 2-phenyl-2-(phenylamino)acetate (56)
N-(1-(4-bromophenyl)ethyl)aniline (59)
N-(1-(pyridin-2-yl)ethyl)aniline (57)
N-(2-methyl-1-phenylpropyl)aniline (60)
N-(1-(4-fluorophenyl)ethyl)aniline (58)
N-(1-phenylpropyl)aniline (61)
(R)-2,2'-bis(methoxymethoxy)-1,1'-binaphthalene (69)
(R)-(2,2'-bis(methoxymethoxy)-[1,1'-binaphthalene]-3,3'-diyl)bis(triphenylsilane) (70)
(R) 4-hydroxy-2,6-bis(triphenylsilyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide (72)
(R)-2,2'-dimethoxy-1,1'-binaphthalene (73)
(R)-3,3'-diiodo-2,2'-dimethoxy-1,1'-binaphthalene (74)
(1R,3r)-2,2'-dimethoxy-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthalene (75)
(1R,3r)-3,3′-bis(2,4,6-triisopropylphenyl)-[1,1′-binaphthalene]-2,2′-diol (76)
(R) 4-hydroxy-2,6-bis(2,4,6-triisopropylphenyl)dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide (77)