DEUTERIODESILYLATION: A MILD AND SELECTIVE METHOD FOR THE SITE-SPECIFIC INCORPORATION OF DEUTERIUM INTO DRUG CANDIDATES AND PHARMACEUTICAL STRUCTURES

Kimberly N. Voronin

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Department of Chemistry and Biochemistry
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Approved by

Advisory Committee

Chris V. Galliford Pamela J. Seaton

John A. Tyrell
Chair

Accepted by

Dean, Graduate School
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ABSTRACT

Silicon is a very useful hetereoelement in synthetic organic and biological chemistry.\textsuperscript{1} In contrast to carbon, silicon posesses 3d orbitals that allow hypervalent chemistry to take place. It is the key component of understanding the reactivity patterns of silicon chemistry and the design of novel reactions.

Deuteriodesilylation is a mild and selective method for the site-specific incorporation of deuterium atoms into pharmaceutical compounds. This methodology involves the direct replacement of a substituted silicon atom with deuterium by first activating the silyl group with a fluoride source as a Lewis base, to form either a pentacoordinate or hexacoordinate silicate complex.\textsuperscript{2} This hypervalent silicate which acts as a masked anion equivalent\textsuperscript{3} then reacts with the deuterium source, replacing the silicon-carbon bond with a deuterium-carbon bond. The reaction is monitored by high performance liquid chromatography (HPLC) and then purified by flash column chromatography, typically giving high yields and chemoselectivity.

Deuterated analogs of pharmaceutical compounds are mainly used to prepare analytical internal standards for drug studies in pharmaceutical industry. They also have been extensively studied for the investigation of biosynthetic pathways, chemical reaction mechanisms, kinetics and analysis of drug metabolism.\textsuperscript{4} The deuteriodesilylation reaction is extremely mild, with excellent functional group tolerance, and appears to have excellent substrate scope, quantitatively generating deuterated product in every substrate tested. Excess TMAF is chosen as a Lewis base, CD\textsubscript{3}OD and D\textsubscript{2}O are used as deuterium sources. The reaction proceeds at 65 °C for 1h to 16 h depends on the substrates giving quantitative conversion of the product by analytical HPLC. The reaction is purified by ISCO flash column chromatography or preparative-HPLC to obtain deuterio- product in high yield.
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I would like to have a special thanks to my parents, my sisters and brother for supporting my decision to continue my education. I am forever grateful to my husband Gregory and my children, for their understanding during this period of my life. They all made sacrifices so that I could succeed in this research work.
DEDICATION

For my step-father Ferdinand Krason, my sister Kim Thuy Nguyen and my brother Tuyen Nguyen, who will be remembered long after the content of this thesis is forgotten.
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LIST OF ABBREVIATIONS

THF: tetrahydrofuran
DMF: dimethylformamide
DMSO: dimethylsulfoxide
MeCN: acetonitrile
TBAF: tetrabutylammonium fluoride
TASF: tris(dimethylamino)sulfonium difluorotrimethylsilicate
TMAF: tetramethylammonium fluoride
TBAT: tetrabutylammonium triphenyldifluorosilicate
EtOAc: ethyl acetate
NMR: nuclear magnetic resonance
MS: mass spectrometry
HPLC: high performance liquid chromatography
TLC: thin layer chromatography
MRI: magnetic resonance imaging
PET: positron emission tomography
KIE: kinetic isotope effect
PTC: phase transfer catalyst
SLA: substituted Lewis acid
HIV: human immunodeficiency virus
DNA: deoxyribonucleic acid
HMPA: hexamethylphosphoramide
cod: 1,5-cyclooctadiene
Cy: cyclohexyl
Py: pyridine
TMSCN: trimethylsilyl cyanide
TFA: trifluoroacetic acid
TBS: tert-butyldimethylphenylsilyl
μ-wave: microwave irradiation
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INTRODUCTION

1.1 Background

The introduction of deuterium atoms into pharmaceutically active compounds is currently an area of significant scientific interest.\(^4\) Although methods exist to synthesize deuterated compounds,\(^5\) many of them suffer from harsh conditions, functional group intolerance or poor generality of substrate scope. Current methods start with alkenes, carbonyl compounds and aryl halides which can all easily be reduced to the protio or deuterio-compounds under standard conditions for deuterium incorporation (i.e. by addition of D\(_2\)(g), borodeuteride or dehalogenation).\(^6\)

A new method for the late stage site-specific incorporation of deuterium atoms via a new deuteriodesilylation reaction has been developed, using a fluoride source as a Lewis base and inexpensive and readily available sources of deuterium such as \(d_4\)-methanol (CD\(_3\)OD) and deuterated water (D\(_2\)O). These reagents are readily available in most laboratories and can be “pulled off the shelf” for immediate use.

A vast amount of chemical and biochemical research has taken advantage of the fact that deuterium (D) from D\(_2\)O can be readily exchanged with hydrogen atoms of organic molecules, especially those bound to O and N atoms. The addition of a neutron makes C-D bonds stronger and more stable than C-H bonds,\(^7\) creating potentially beneficial properties while maintaining almost identical chemical properties.\(^8\) Deuterated compounds are used extensively in spectrophotometric studies, since hydrogen containing water interferes with nuclear magnetic resonance (NMR) signals.\(^9\) This powerful technique for studying molecular structure is often
applied to compounds suspended in D₂O or deuterated organic solvents. Deuterated proteins and other macromolecules maybe especially valuable for NMR and neutron diffraction studies.¹⁰

1.1.1 History of Deuterium

Deuterium was discovered by Harold Clayton Urey, a Professor of Chemistry at Columbia University in 1931. His work on deuterium and the development of methods for production of heavy water were the beginning of introducing stable isotopes for tracer studies in biological research and gave him a Nobel Prize in 1935.¹¹

The deuterium gas was detected in the concentrates through its atomic spectrum via distillation. Large scale production of deuterium has been accomplished by the electrolytic method by E. W. Washburn.¹² In the electrolysis of water, the rate of discharged hydrogen is more rapid than that for deuterium, resulting in a concentration of deuterium in the electrolyte. By continuing the process until the residue of water is sufficiently small, about 1/100000 of the original volume, very near pure D₂O remains. Deuterium has also been produced by Hertz, using a method of diffusion of hydrogen gas through porous tubes.¹³

The chemical properties of hydrogen and deuterium compounds are almost identical, but their physical properties are different in their melting points and boiling points. The biological effects of deuterium oxides are very important. It has been established that both plants and animals cannot live in water containing deuterium oxide of high concentration.

Deuterium is also applied in the study of metabolic processes within living things. It is used to prepare isotope labeled compounds as internal standards for drug metabolism studies and
to trace a variety of chemical entities through living organisms.\textsuperscript{14} Deuterium is also applicable to the study of mechanisms and rates of transfer of biological substances by absorption, secretion and to the study of diffusion and membrane permeability. This study was demonstrated by Hevesy and Hofer, who investigated the rate at which water is eliminated from the human body by using heavy water.\textsuperscript{15} Polanyi and Eyring predicted reactivity differences between isotopomers, the origin of kinetic isotope effects.\textsuperscript{16} Since the first report in 1947, biochemists and chemists have been using the “kinetic isotope effect” (KIE) of deuterium to determine enzyme reactions in metabolism studies, rate limiting steps and transition states.\textsuperscript{17}

The pioneering scientists behind much of the understanding and development of kinetic isotope effect were Jacob Bigeleisen and Maria Goeppert Mayer.\textsuperscript{18} Kinetic isotope effects specifically explore the change in rate of a reaction due to isotopic substitution.

The word “Isotopes” comes from the Greek “Isos and Topos” are the atoms of the same element having same number of protons but different numbers of neutrons. There are ideal combinations of protons and neutrons that allow the nucleus to be stable or not be radioactive. Radioactive decay is the result of the adjustment of the nuclei of atoms from unstable to more stable states. The nucleus can undergo decomposition in a variety of ways. The spontaneous decay process can produce particles as in the case of alpha, beta (electron is ejected from nucleus to give $\text{e}^-$), or positron emission (electron is remained in nucleus to give $\text{e}^+$). The alternate form of emission is that of electromagnetic radiation such as X-rays or gamma-rays. Radioactive decay is a property only of the nucleus. It doesn’t depend on chemical or physical state or temperature and pressure. The discovery of artificial radioactivity by Joliot and Curie in 1934 led to the production of a number of radioactive isotopes which are of value in biological investigation.\textsuperscript{19}
Unlike a radioactive isotope, stable isotopes remain unchanged indefinitely. The most commonly used stable isotope is of hydrogen. There are three isotopes of hydrogen: protium, deuterium and tritium, which are summarized in Table 1-1 below. Isotopes commonly used in heavy atom isotope effects include carbon ($^{12}\text{C}$, $^{13}\text{C}$), nitrogen ($^{14}\text{N}$, $^{15}\text{N}$), oxygen, sulfur and bromine. Not all elements exhibit different isotopes, but those that due serve as powerful tools in isotope effect studies.

Table 1-1. Summarized table of isotopes of hydrogen.

<table>
<thead>
<tr>
<th>Isotope</th>
<th>$^1\text{H}$</th>
<th>$^2\text{H}$</th>
<th>$^3\text{H}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name:</td>
<td>Protium</td>
<td>Deuterium</td>
<td>Tritium</td>
</tr>
<tr>
<td>Symbol:</td>
<td>H</td>
<td>D</td>
<td>T</td>
</tr>
<tr>
<td>Atomic number:</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Number of neutrons:</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Natural abundance</td>
<td>99.9844%</td>
<td>0.0150%</td>
<td>Very small</td>
</tr>
</tbody>
</table>

1.1.1 Kinetic Isotope Effects (KIEs)

When one isotope is substituted for another, a *Kinetic Isotope Effect* (KIE) may be observed in subsequent reactions. Because of differences in their masses, molecules containing isotopes behave differently. Isotopes of hydrogen in particular exhibit pronounced differences in their reaction kinetics.\(^20\) KIEs are used to determine reaction mechanisms by determining rate limiting steps and transition states.\(^21\) KIEs are useful in studying reactions in organic chemistry and enzymatic reactions.\(^22\) The effects are commonly measured using NMR to detect isotope location or GC/MS to detect mass changes.
A common isotope substitution is the replacement of hydrogen with deuterium. The change in reaction is known as the deuterium effect and is expressed by the ratio:

\[
\text{Rate (C-H) breaking/Rate (C-D) breaking} = \frac{k_H}{k_D}, \text{ where } k = \text{rate.}
\]

Normal KIEs for the deuterium effects \((k_H/k_D)\) are in the range of 1 to 7. Large effects are seen because the percentage mass change between hydrogen and deuterium is great (mass of deuterium is double of mass of hydrogen). Heavy atom isotope effects involve the substitution of carbon, oxygen, nitrogen, sulfur and bromine. The measure of the effect is much smaller for heavy isotopes and is usually between 1.02 and 1.10. The difference in size is directly related the percentage change in mass.

An isotopic substitution will have a pronounced effect of the reaction rate when the isotopic substitution (i.e. D for H) is part of a chemical bond that is broken, formed or modified in the rate determining step. Isotopic rate changes are most observable when the relative mass difference is the greatest since the effect is related to vibrational frequencies of the affected bonds. The R-D bond is slightly stronger (lower energy) than the R-H bond, making it harder to break because it requires more input of energy (Figure 1-1).

**Figure 1-1.** Activation energy diagram of C-H and C-D bond homolysis.
1.1.2.1 Primary Kinetic Isotope Effect

Primary kinetic isotope effects\textsuperscript{24} are rate changes due to isotopic substitution at a site of bond breaking and bond making in the rate determining step of a mechanism. In the following E\textsuperscript{2} elimination reactions, there are several examples of a kinetic isotope effects. Figure 1-2 shows the E\textsuperscript{2} elimination reaction of \textbf{1-1} and its deuterated analog \textbf{1-3}:

\begin{itemize}
\item \textbf{1-1} → \textbf{1-2}
\item \textbf{1-3} → \textbf{1-4}
\end{itemize}

Figure 1-2. E\textsuperscript{2} elimination reaction showing a primary deuterium effect. The deuterium-carbon bond is cleaved in the rate determining step.

In the E\textsuperscript{2} reaction of either \textbf{1-1} or \textbf{1-3}, the rate determining step involves breaking a C-H bond or a C-D bond. Since breaking a C-D is harder, the rate will decrease. In this case, the kinetic isotope effect \( k_H/k_D = 6/1 = 6 \). This large isotope effect is due to the C-D bond cleavage occurring in the rate determining step. Isotopic substitution is affected by mass dependent properties. It does not affect the potential energy surface of the reaction or the energies of the electronic states.
1.1.2.2 Secondary Kinetic Isotope Effect

Secondary kinetic isotope effects affect the reaction rate due to isotopic substitutions at a site other than the bond breaking site in the rate determining step of a mechanism (Figure 1-3).

In this example, the ratio $k_H/k_D = 6/4 = 1.5$. In this case, 1-2 is formed 1.5 times faster than 1-6. This is significantly less than the preceding primary isotope effect seen in the formation of 1-4. This is an example of a secondary isotope effect, when deuterium is attached to an atom that is changed somehow in the reaction (in this case the carbon atom that deuterium is bound to undergoes a change in hybridization change), but it is not undergoing bond cleavage in the rate determining step.

Figure 1-3. $E^2$ reaction showing a secondary isotope effect. This time the deuterium-carbon bond is not cleaved in the rate determining step.
1.1.2.3 Zero Isotope Effect

Figure 1-4. Zero kinetic isotope effect. No cleavage or rehybridization at C-D bond.

In this example of zero isotope effect (Figure 1-4), in the transformation 1-7 to 1-8 a deuterium bond is not being cleaved and the hybridization of the carbon atom remains unchanged, therefore there is no deuterium isotope effect observed.

Singleton and co-workers have developed a method for precise measurement of $^{13}$C and $^2$H KIE at natural abundance simultaneously for every atom in the molecule of interest, using atoms that will not have isotope effects as an “internal standard.” This method is general for nearly every type of reaction, making the study of KIEs a practical tool in elucidating even the most ambiguous mechanisms. For example, Singleton’s elegant NMR method allows measurement of $^{13}$C KIEs, providing convincing evidence that the proposed concerted [3+2] pathway of the mechanism of the OsO$_4$ catalyzed dihydroxylation of olefins is likely operative, instead of the alternative, involving an initial [2+2] cycloaddition-ring expansion mechanism.
1.1.2.4 Solvent Effects

Reactions may be affected by the type of solvent used such as H\textsubscript{2}O to D\textsubscript{2}O or ROH to ROD\textsuperscript{28}. Solvents effect reactions in three different ways:

- The solvent can act as a reactant resulting in a primary isotope effect.
- Rapid hydrogen exchange can occur between substrate molecules labeled with deuterium and hydrogen atoms in the solvent. Deuterium may change positions in the molecule resulting in a new molecule that then reacts in the rate determining step of the reaction.
- The interactions between solvent and solute may also change with differing solvents. This could change the energy of transition state. This usually results in a secondary isotope effect.

To summarize, if $k\textsubscript{H}/k\textsubscript{D}$ is greater than 1, there is some sort of normal isotope effect. If $k\textsubscript{H}/k\textsubscript{D}$ is smaller than 1, it is considered an inverse isotope effect. Isotope effects with other atoms like $^{13}$C/$^{12}$C or $^{15}$N/$^{14}$N are always smaller than H/D isotope effects because of the relative size different (D is twice as heavy as H, where a $^{13}$C is only 8% heavier than $^{12}$C).

1.2 Stable Isotope/Radiolabeling

1.2.1 Purpose: Use of Stable Label Compounds and Radiotracers

Stable isotope and radioisotope labeling are used to prepare substrates for the study of reaction mechanism in either an artificial or a biological medium. They can also be used to trace the movement of a molecule, its degradation or metabolic product \textit{in vivo} or \textit{vitro}\textsuperscript{14} and to study
diffusion and membrane permeability. In medicine, a variety of imaging techniques such as Magnetic Resonance Imaging (MRI) or Positron Emission Tomography (PET) have been developed that rely on materials labeled with radioactive isotopes for example fluorine-18, for brain function studies. Use of stable isotopes and radiolabeled compounds are important in metabolic tracers in development and in clinical studies for the treatment of different diseases.

The presence of an isotopic label is assumed to exert no effect in the properties or chemistry of the molecules. Therefore, it serves as a label or marker that allows normal chemical or biochemical processes to be monitored without causing any interference.

Furthermore, as a consequence of the rapid development of higher performance mass spectrometers and their widespread use, the demand for isotopically labeled internal standards has risen. Starting from commercially available, isotopically labeled precursors, both $^2$H, as well as $^{13}$C and $^{15}$N-labeled compounds, can be prepared by conventional synthesis. The latter are also useful in vivo studies, where deuterium labeled compounds sometimes cannot be used because of the possibility of a different metabolism in comparison with the parent compound, or possible metabolic loss of deuterium. However, long synthetic routes and the high costs of $^{13}$C and $^{15}$N-labeled starting materials must often be taken into account. In contrast, a molecule can be labeled considerably more rapidly by the directly exchange of a hydrogen atom with deuterium or tritium. Rapid and efficient labeling is an important goal to meet the urgent demands of research, minimizing the synthesis costs and reducing potential exposure to radioactivity during the course of multi-step syntheses. Compounds labeled with tritium are particular advantageous for researchers since they can be made rapidly.
Since the radioactive labeled precursors are expensive and the use of radioactive compounds can entail a risk of contamination or damage to health, the synthetic methods employed should be optimized to obtain maximum yield and purity. The labeled compound is best introduced at the latest stage in the synthesis route as possible. However, yield can become secondary to expediency, reflected in the speed of conversion and waste minimization.

1.2.2 Motivation For Use of Deuterium in Pharmaceutical Structures

The kinetic isotope effect of deuterium plays an important role in determination of the rate of metabolism and excretion of biologically active drugs in pharmacokinetic studies. Because deuterium and hydrogen exhibit nearly identical physical properties, deuterated drug molecules have been investigated to identify and quantify metabolites in effort to understand metabolism-mediated toxicities in non-clinical settings and used in humans as metabolic or pharmacokinetic probes. One of the most important examples of a primary kinetic isotope effect is in the metabolism of paroxetine™. Paroxetine (also known by the trade name Paxil) is an antidepressant drug. It was first marketed in 1992 by GlaxoSmithKline. The metabolism of paroxetine is well understood and shown in Figure 1-5 below.

**Figure 1-5.** The metabolism of paroxetine.
Paroxetine is metabolized by a cytochrome P450 enzyme residing in liver called CYP2D6. CP2D6 is responsible for metabolism of up to 25% of medication. CYP2D6 reacts with paroxetine at the methylenedioxy unit to form a highly reactive carbene that binds irreversibly to the enzyme’s heme active site and inactivates it. Replacing the pair of hydrogens on the methylenedioxy bridge of paroxetine with a pair of deuteriums dramatically reduces carbene formation and thus lessens the inactivation of the enzyme and enables its broader use with other drugs. As before, this observation can be explained by the difference in strength between C-D and C-H bonds. Since deuterium is heavier than hydrogen, it has lower zero point vibration energy, therefore, it has a higher activation energy to reach the transition state, so more energy is required to break C-D bond than the C-H bond. In other words, it forms a stronger bond. Therefore, the drug is more stable during metabolism or in other words, the heavier deuterium slows down the metabolism process and lasts longer in the body due to a kinetic isotope effect.

In the case of telaprevir™ (1-11), an inhibitor of the hepatitis C virus, the incorporation of deuterium improved the bioavailability, by retarding the epimerization of telaprevir to the low activity (R)-diastereomer (Figure 1-6).

![Figure 1-6. The structure of D₁-telaprevir.](image-url)
Another example of an improved metabolic profile resulting from kinetic isotope effect is the deuteration of Bristol-Myers Squibb’s Antazanavir™ (1-12). CTP-518 (1-13) is a deuterated analog of the HIV drug which is eliminated from the body more slowly and might potentially allow it to be used clinically without the need for boosting by Ritonavir, an effective antiviral agent, that is commonly administered as part of a combination therapy. This could lead to better safety and tolerability for patients (Figure 1-7).

![CTP-518 (1-13) and Atazanavir (Reyataz) (1-12)](image)

**Figure 1-7.** Atazanavir and deuterated Atazanavir

Other drugs show similar effects after deuteration, including amphetamine, which is more readily transported into the brain in deuterated form. Deuterated halogenated anaesthetics such as Selvoflurane™ are no longer oxidized to toxic form within body.

However, deuteration of pharmaceutical compounds doesn’t always work to slow metabolism of the drug substances. Sometimes the organism will simply over express a gene to speed up the metabolic process. An example of an undesired outcome of deuteration is 1,2-dibromoethane, a DNA alkylating reagent. Its tetradeuterated form is indeed metabolized more slowly than the protio version. However, the deuterated compound actually causes more DNA damage than its
protio-counterpart, because reduced metabolism prolongs the existence of the reactive species in the body.

Although deuterium has been extensively used for the quantitation of drugs and metabolites in pharmacokinetic studies, it has not yet been incorporated into a clinical candidate. The challenge of incorporating deuterium into a drug is the possibility of deuterium/hydrogen exchange within the physiological environment, eviscerating the effect of the compound. When deuterium retards metabolism at one site, a phenomenon called “metabolic switching” can occur where the suppression of one metabolic pathway promotes metabolism at another site, leading to metabolites with toxic properties. For a deuterated clinical candidate to be successful, it must overcome the problems of biochemical deuterium exchange and metabolic switching. Deuterating positions that are readily metabolized has the potential to increase bioavailability, reduce level of toxic metabolites, slow metabolism and changing ADME (Absorption, Distribution, Metabolism, Excretion) profile. Thus, synthetic methods to prepare deuterated drug compounds are of critical importance to aid this research.

1.3 Methods for the Incorporation of Deuterium

Compounds can be isotopically labeled by the direct exchange of a hydrogen atom with a deuterium atom. These exchange reactions can often be carried out directly on the target molecule or a late intermediate in the synthesis. Deuterium-containing reagents such as CD$_3$OD, D$_2$O and D$_2$ gas can be used as deuterium source. D$_2$ gas is available commercially in cylinders, and can be used in conjunction with standard atmospheric or pressurized hydrogenation reactors.
This method is efficient for the synthesis of deuterated organic compounds. Deuterium can be incorporated into a molecule via addition reaction, deuterium-halogen exchange.\textsuperscript{6}

1.3.1 Addition to Alkynes or Alkenes

Addition of D\textsubscript{2} to unsaturated carbon-carbon bonds, e.g. \textbf{1-14} was treated with formic acid in D\textsubscript{2}O as the deuterium source and iridium catalyst \textbf{1-16} to give deuterium-labeled compounds \textbf{1-15} in quantitative yield (\textasciitilde 99\%), with high levels of deuterium incorporation (\textasciitilde 96\%).\textsuperscript{6a} The reaction is very mild, generating D\textsubscript{2} gas by decomposition of formic acid and rapid H/D exchange.

\textbf{Scheme 1-1.} Deuterium exchange reaction of mesaconic acid.

An interesting example of \textsuperscript{2}H\textsubscript{2}-labeling is a synthesis of isotopically-labeled chiral acetic acid 1-27 by Melzer and co-workers. This approach successfully utilized tritiation of lithiated acetylide \textbf{1-17} followed by a controlled catalytic deuterogenation. The intermediate \textbf{1-19} was then underwent a stereospecific intramolecular [1,3]-hydride shift, and after ozonolysis afforded the target chiral acetic acid \textbf{1-21}, (Scheme 1-2).\textsuperscript{39}
**Scheme 1-2.** Tritiation of an acetylide, followed by catalytic deuteration.

1.3.2 Reduction of Carbonyl Compounds

Sodium borohydride (NaBH$_4$) is widely used as a selective and relatively mild chemical reducing reagent for organic functional groups. It is often used in place of the much more powerful reagent lithium aluminum hydride LiAlH$_4$, which reduces a wide range of functional groups rapidly and nonselectively. NaBH$_4$ reduces aldehyde and ketone to the corresponding alcohol without affecting carboxylic acid groups or their derivatives.$^{40}$ A particular advantage of NaBH$_4$ is its greater resistance to hydrolysis, which permits reduction to be performed in aqueous or alcoholic media. Because of their widely applicability as reducing agents, deuterium analogues of LiAlH$_4$ and NaBH$_4$ are very useful reagents for the selective introduction of deuterium into organic compounds. NaBD$_4$ can be prepared by the reaction of tetramethoxysodiumborohydride with diborane-d$_6$. 

---

**Scheme 1-2: Tritiation of an acetylide, followed by catalytic deuteration.**

**Reaction Steps:**
1. BuLi, THF (100 mCi/mL)
2. THF (100 mCi/mL)
3. D$_2$, Pd/BaSO$_4$
4. CH$_3$OH, quinoline
5. NaOH, DMF, 80 °C, 15 h, 58%

**Chemical Structures:**
- 1-17
- 1-18
- 1-19
- 1-20
- 1-21
- 1-22
The iminium perchlorate salt 1-24 generated by treatment of 1-23 with perchloric acid, can be reduced by NaBD$_4$ in methanol to give a 96% yield of 1-25 (Scheme 1-4). The reaction occurs stereoselectively, with deuteride delivered from the least hindered face of the bicyclic iminium ring system.

Lithium aluminum deuteride can be prepared by using the existing classical synthesis of lithium aluminum hydride. Specifically, this utilizes lithium deuteride (prepared from deuterium gas with lithium metal. The lithium deuteride reacts with aluminum trichloride to form the desired deuteride reagent (Scheme 1-5, eq 1).
**Scheme 1-5.** Classical synthesis of LiAlD\(_4\) and reduction of a methyl ester.

An example of lithium aluminum deuteride in synthesis is shown in Scheme 1-5, eq 2. Methyl ester 1-26 is reduced by LiAlD\(_4\), followed by quenching with D\(_2\)O under acidic conditions to give deuterated alcohol 1-27, which was then oxidized to ketone 1-28.

LiAlD\(_4\) followed by D\(_2\)O were also used to reduced propargyl alcohol (1-29) at low temperature (5-10 °C) to give *trans*-3-deuterioallyl alcohol (1-30) with high stereoselectivity (Scheme 1-6).\(^{41}\)

**Scheme 1-6.** Reduction of propargyl alcohol by LiAlD\(_4\).
1.3.3 Reduction of Carbon-Halogen bonds

There are numerous methods for the reduction of carbon-halogen bonds. An interesting example is the iodine-deuterium exchange reaction of 1-31 mediated by tributyltin hydride (Scheme 1-7). The reaction uses THF-d$_8$ as the deuterium source and V65 [2,2’-Azobis(2,4-dimethyl valeronitrile)] as an initiator$^{42}$ to give a good yield of compound 1-32 with high deuterium incorporation.

**Scheme 1-7.** Halogen-deuterium exchange of a halo-compound (the number in the bracket, give the percentage fraction of deuterium [%])

![Chemical structure](image)

1.3.4 Protic Exchange Reactions

In addition to the deuteration of organic molecules, H/D exchange reactions are used as models for optimization of the introduction of tritium ($^3$H). Radiolabeled pharmaceutical candidates of this type are used for pharmacokinetic and metabolic studies to support the drug development. There are two methods for H/D exchange: acid-base catalyzed and homogeneous or heterogeneous metal-catalyzed exchange.
1.3.4.1  H/D Exchange with D$_2$O

H/D exchange reaction without the addition of acids or bases are characterized by the acidic $\alpha$-proton position of carbonyl being deuterated by the use of deuterium oxide, because of its autoprotolytic equilibrium can act as either an acid or a base. Thus, for example, in the synthesis of deuterated-2-indanone 1-34 a high degree of monodeuteration (99%) was obtained by heating reaction of ketone 1-33 in D$_2$O (Scheme 1-8).$^{43}$

**Scheme 1-8.** H/D exchange at the $\alpha$-carbonyl position.

Werstiuk and Ju reported that pyridine derivatives in D$_2$O incorporated several deuterium atoms without addition of acid or base.$^{44}$ In the H/D exchange with 2-hydroxypyridine (1-35), or 2-mercaptoypyridine (1-37), for example, the exchange was highly regioselective and the hydrogen atoms in positions C$_3$, C$_5$ and C$_6$ were exchanged preferentially in both compounds 1-36 and 1-38 (Scheme 1-9). The reactions were performed in sealed vessels at high temperatures (200 and 260 °C).
More recently, microwave reactors have been used in exchange reactions, compared to conventional heating conditions, higher or comparable degree of deuteration can be obtained with much shorter reaction times. For example, several analytical standards of glycopeptide bleomycin A2 were prepared by heating in D₂O at 165 °C for only two minutes.⁴⁵

1.3.4.2 Acid-Catalyzed Exchange Methods

In an acid-catalyzed exchange, incorporation of deuterium occurs at aromatic C-H bonds usually by using strong deuterated Brønsted acids or Lewis acids with a deuterium source. For example, according to the research group of Wähälä, deuteration of arenes occurred via H/D exchange of the polyphenols with D₃PO₄/BF₃/D₂O at 20-55 °C for one to four days.⁴⁶,⁴⁷ Positions that are less readily accessible for an electrophilic substitution show a lower tendency for exchange under these conditions. In the case of compound 1-39 below (Scheme 1-10), these
positions can also be deuterated under more forcing conditions (100 °C in an autoclave) to generate 1-40.\textsuperscript{48} In the case of compound 1-41, complete exchange (>99% D) of all protons on the aromatic ring took place in good yield to generate 1-42 even at room temperature, including the unactivated \textit{meta} positions. The hydrogen atoms of aliphatic residues did not exchange under acidic conditions.\textsuperscript{49} H/D-exchange reactions in the presence of Lewis acids such as AlBr\textsubscript{3}, EtAlCl\textsubscript{2} or MoCl\textsubscript{5} and [D\textsubscript{6}]-benzene as the deuterium source, complete exchange of all hydrogen atoms on nonpolar arenes (ie. naphthalene, isopropylbenzene) is observed. In contrast, aromatic rings such as phenol, anisole, aniline, benzaldehyde or benzoic acid are not amenable to H/D exchange, as they inhibit the deuteration of other arenes through the complexation of the Lewis acid.\textsuperscript{50} Deuterated Brønsted acids such as DCl, D\textsubscript{2}SO\textsubscript{4}, AcOD and CF\textsubscript{3}CO\textsubscript{2}D have also used as deuterium sources in microwave-assisted, acid catalyzed exchange reactions.

\textbf{Scheme 1-10.} H/D exchange of polyphenols using an acid catalyst.
Jones and co-workers treated the hydrochloride salt of 2-methylaniline 1-43 with D$_2$O (Scheme 1-11). After heating for only 2 minutes, quantitative deuteration was observed. The method was subsequently applied to aminopyridine derivatives. Deuterium incorporation was complete within a few minutes and depending on the substrate, a high deuterium content was achieved at the positions ortho and para to the amino group.

**Scheme 1-11.** H/D exchange of 2-methylaniline hydrochloride under microwave irradiation.

Lammerhofer et al. exploited the readily achieved racemization of α-amino acids 1-32 for acid-catalyzed deuteration (Scheme 1-12). With an excess of D$_1$-acetic acid and a catalytic amount of salicylaldehyde, the reaction occurred in good yield with a deuterium incorporation of more than 95% via the corresponding Schiff’s base. After N-Boc-protection of the amine, the resulting enantiomeric mixture rac-1-46 was separated by preparative-HPLC on a chiral stationary phase to give (R)-1-47 and (S)-1-48.

**Scheme 1-12.** Acid-catalyzed deuteration of glycine.
Recently, Akiyama and co-workers have introduced a new method to prepare deuterated amines of general structure 1-51 with excellent enantioselectivity by using a chiral phosphoric acid 1-52 with 2-deuterated benzothiazoline (1-50) as a deuterium donor (Scheme 1-13).

Scheme 1-13. Preparation of a deuterated amine.

The proposed mechanism features a highly organized transition state (Figure 1-8), suggesting that carbon-deuterium bond cleavage is the rate-determining step.

Figure 1-8. Proposed reaction mechanism of imine with 2-deuterated benzothiazole.
1.3.4.3 Base-Catalyzed Exchange Methods

Base-catalyzed H/D exchange reactions also provide a facile method for the exchange of acidic hydrogen atoms for deuterium. In carbonyl compounds such as ketones,\textsuperscript{55} aldehydes,\textsuperscript{56} esters\textsuperscript{57} and carboxylic acids,\textsuperscript{58} the acidic C-H hydrogen atoms are exchanged with high selectivity (>90\% D incorporation) and yield. The $\gamma$-hydrogen atoms in $\alpha,\beta$-unsaturated ketones \textbf{1-39} are also accessible for isotope exchange through conjugation, for example treatment of \textbf{1-53} readily leads to \textbf{1-54} (Scheme 1-14). Conversion was effected by alkaline deuteroxides in D$_2$O at temperatures between 25 ℃ and 100 ℃. Sodium methoxide in MeOD also proved to be viable alternative (Scheme 1-14).\textsuperscript{59,61a}

\textbf{Scheme 1-14.} Base-catalyzed exchange of $\alpha,\beta$-unsaturated ketone \textbf{1-53}.

Deuteration of the methyl group of aryl methyl ketones,\textsuperscript{60} and aryl methyl sulfones\textsuperscript{61} with the use of a tertiary amine as a basic catalyst was achieved by Berthelette and Scheigetz. For example, \textbf{1-55} gave deuterated product \textbf{1-56} in 89\% yield (Scheme 1-15).
**Scheme 1-15.** Base-catalyzed exchange of an aryl methyl ketone.

![Scheme 1-15](image)

Exchange of 1-57 using KOD in D$_2$O gave α-carbon deuterium labeled L-α-amino acid 1-58, using the cinchona alkaloid-derived chiral phase transfer catalyst 1-59 (Scheme 1-16).

**Scheme 1-16.** Base-catalyzed H/D exchange of amino acid using PTC catalyst.

![Scheme 1-16](image)

Organometallic compounds can also be employed for the synthesis of deuterated compounds. Compound 1-62 (Scheme 1-17) is generated by deprotonation of compound 1-60 with sec-butyllithium and then the anion is trapped by deuterated with electrophiles such as D$_2$O, CD$_3$OD, give complete ortho-deuteration giving 1-61 with 99% deuterium incorporation.$^{62}$ Interestingly, when a second lithiation is performed on 1-61, anion formation shows a strong preference for ortho-deprotonation vs. ortho-dedeuteronation. 1-62 is formed by trapping with methyl iodide, and remarkably, the isotopic purity only suffers a modest erosion of 1%, with 98% in the final product 1-62.
1.3.5 Homogeneous Catalysis of H/D Exchange

Transition metal-mediated H/D-exchange reactions with soluble catalyst complexes have many advantages over other deuteration methodologies. They have relatively mild reaction conditions and good functional group tolerance. Often, the target compound of interest itself can simply be used as the starting material, negating the need to prepare a more functionalized analog as a precursor for reduction. Undesirable side reactions such as dehalogenation, deuterium addition to multiple bonds, hydrolysis or the cleavage of protecting group can also be avoided. Furthermore, the incorporation of deuterium under these metal catalysis conditions can be used as the model for tritium incorporation. In addition to the use of deuterium gas and deuterium oxide as deuterium sources, deuterated solvents such as [D₆]-acetone or [D₆]-benzene are used in H/D exchange on less polar substrates, although their use is less common.

There are many efficient methods which allow high degree of deuteration in both aromatic and aliphatic substrates, these are primarily based on the early fundamental studies of Garnett\textsuperscript{63} on H/D exchange using homogeneous catalysis. There are many exchange reactions based on different transition-metal complexes such as iridium, platinum and rhodium-catalyzed H/D exchanges.
1.3.5.1 Iridium-Catalyzed Exchange

Cationic iridium complexes are homogeneous metal catalysts that are well suited for the activation of C-H bonds.\(^{64}\) Probably the most investigated area is the ortho-deuteration of aryl ketone 1-63 and acetonilides 1-65 (Scheme 1-18). These serve as model substrates for these reactions, as well as a providing a yardstick for the development of new catalyst systems.

**Scheme 1-18.** Iridium-catalyzed exchange of aryl ketones and acetonilides.

![Diagram of iridium-catalyzed exchange of aryl ketones and acetonilides.](image)

Acetophenone is used as model substrate for H/D exchange by iridium metal catalysis to give completely 2,6-deuterated acetophenone without difficulty. Steric and electronic effects can reduce the degree of deuteration with substituted derivatives. The degree of deuteration may depend on the effects of complex ligands,\(^{65}\) deuterium source,\(^{66}\) the solvent,\(^{67}\) the addition of bases,\(^{68b}\) the amount of catalyst,\(^{70}\) or the temperature and the duration of the reaction.\(^{69}\)

In the postulated mechanism (Figure 1-9), iridium(I) complex 1-67 is drawn in generalized form (L = ligand; S = solvent). After association of the carbonyl oxygen atom and \(\pi\)-system of the aromatic ring (complex 1-68), oxidative addition leads to 1-69, which can only occur at the ortho position to form a highly favored five-membered metallacycle 1-70. For this
reason, 1-69 is the pivotal intermediate for the explanation of ortho regioselectivity. Subsequent H/D exchange at the metal with the deuterium source provides intermediate 1-71, followed by reductive elimination, leading to regeneration of the catalyst 1-67 and to the labeled product 1-72. With acetanilides (conversion of 1-65 into 1-66), the intermediate metallacycle is expanded to form a six-membered metallacycle intermediate.

**Figure 1-9.** Postulated mechanism of the ortho-deuteration of 1-68 (XD = D₂ or D₂O).

In addition to acetophenone, a high degree of deuteration may be achieved with benzamides, benzoic acid derivatives, acetanilides and 2-phenylpyridines, by using Crabtree’s catalyst [Ir(cod)P(Cy)₃(py)]PF₆ (1-73) (cod = 1,5-cyclooctadiene, Cy = cyclohexyl, py = pyridine) in Figure 1-10 below.⁶⁸-⁷⁰
Reactions using Crabtree’s catalyst 1-73 are often very rapid and efficient in the incorporation of the isotope into the molecule. However, they do also have drawbacks and can often fail with complex molecules due to unproductive binding and the need to carry out the exchange reactions in dichloromethane.

Fels and co-workers demonstrated that α,β-unsaturated carbonyl compounds are also excellent substrates, which react through a similar mechanism. Table 1-2 below shows deuteration of α,β-unsaturated and aromatic carboxylic acids in the β and ortho positions with generally good results. Fels and co-workers have also demonstrated that by using [Ir(cod)(acac)] (acac=acetylacetonate) 1-74, the regioselectivity of the labeling is dependent upon the deuterating agent. For example, in the case of 2-methoxybenzoic acid (1-79), instead of using the D₃O/DMA conditions to give 98% ortho-deuteration (table 1-2), 45% deuterium incorporation solely in the position para to the carboxylate group was observed when D₂ gas was employed instead of D₂O. One explanation for this observation is provided by the reduction of the ligand with the concomitant formation of elemental iridium, which then precipitates from the reaction solution and then acts as a heterogeneous catalyst to cause the unusual selectivity.
Table 1-2. Iridium-catalyzed H/D exchange of α, β-unsaturated and aromatic carboxylic acids.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Product[a]</th>
<th>Degree of deuteration[n][%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-75</td>
<td>![Image]</td>
<td>69[c]</td>
</tr>
<tr>
<td>1-76</td>
<td>![Image]</td>
<td>75</td>
</tr>
<tr>
<td>1-77</td>
<td>![Image]</td>
<td>75</td>
</tr>
<tr>
<td>1-78</td>
<td>![Image]</td>
<td>99</td>
</tr>
<tr>
<td>1-79</td>
<td>![Image]</td>
<td>98</td>
</tr>
</tbody>
</table>

[a] Reaction conditions: [Ir(cod)(acac)] 1-74 (4 mol %), D₂O, N,N-dimethyl acetamide (DMA), 90 °C, 2 h. [b] Deuterium uptake relative to the labeled position(s). [c] After 4 h

Bergman and coworkers have reported a catalyst for C-H bond activation,⁶⁷ that is also suitable for deuteration of aliphatic and nonfunctionalized aromatic substrates depending on the ligand. They obtained a very high degree of deuteration with certain hydrocarbons, alcohols, phenols, ethers, carboxylic acids, esters and amides with D₂O, [D₆]-acetone, [D₆]-benzene.⁶⁹
1.3.5.2 Platinum-Catalyzed Exchange

Since the pioneering work of Garnett and co-workers, homogeneous catalytic exchange with platinum (specifically using tetrachloridoplatinate(II) salts), has mainly been used for the deuteration of arenes,\textsuperscript{70} using D\textsubscript{2}O/AcOD as the deuterium source and solvent in a closed vessel at 80-130 °C.\textsuperscript{66} Jones and co-workers achieved quantitative H/D exchange in the position \textit{meta} to the carboxylate group in the benzoic acid derivative \textbf{1-80} with aqueous [Na\textsubscript{2}PtCl\textsubscript{4}] solution as shown in Scheme 1-19.\textsuperscript{54} Activation of this catalyst system with microwave irradiation allows reduced reaction times and acid-free deuteration of arenes.

\textbf{Scheme 1-19}. Platinum-catalyzed H/D exchange of benzoic acid derivatives.

![Scheme 1-19](image)

1.3.5.3 Rhodium-Catalyzed Exchange

Brookhart and co-workers developed rhodium-olefin complex \textbf{1-83},\textsuperscript{71} for the deuteration of substrates such as aniline (\textbf{1-82}) and cyclopentene (\textbf{1-85}) the deuterated compounds \textbf{1-84} and \textbf{1-86} were prepared with excellent incorporation in the case of aniline, and a modest result for cyclopentene (Scheme 1-20).
A solution of rhodium trichloride hydrate in a deuteroacetic acid/deuterated water mixture was found to effectively catalyze the deuteration of alkylbenzenes, halobenzenes and alkanes.\(^7^2\) Rhodium trichloride hydrate was one of several catalysts studied by Jones in tritium labeling of simple aromatic and aliphatic substrates, with \(^3\)H-NMR spectrometry employed to determine the regiospecificity of incorporation.\(^7^3\) In 1982, Lockley reported that rhodium trichloride trihydrate could be used to regiospecifically label chromone-2-carboxylic acids (1-87) in DMF/D\(_2\)O at 105-110 °C (Scheme 1-21).\(^7^4\)

In order to account for high regiospecificity, it was postulated that the carboxylate was directing the catalyst to form a rhodium-carbon bond and thus form a five-membered cyclometallated intermediate. In the presence of D\(_2\)O, dissociation of this intermediate would lead to the regiospecific incorporation of deuterium. Additional studies with both deuterium and tritium in model systems showed broad applicability to regiospecific ortho hydrogen isotope exchange in aromatic carboxylic acids, amides and anilides.\(^7^7\)
Scheme 1-21. Deuteration and tritiation of alkyl benzene and chromone-2-carboxylic acid, using RhCl\textsubscript{3}•3H\textsubscript{2}O.

1.3.5.4 Ruthenium-Catalyzed Exchange

The use of homogeneous ruthenium catalysts for H/D exchange has been investigated in recent years.\textsuperscript{75} Matsubara and co-workers demonstrated that substrates with electron donors such as double bonds, hydroxyl groups and amino groups maybe efficiently deuterated in this way, as shown in Scheme 1-22.


Akenols such as 1-91 are deuterated in good yield in D\textsubscript{2}O by ruthenium-mediated migration of the double bond and isomerization to ketones 1-92 (via an eventual enol
tautomerization). Under similar conditions, primary alcohols and amines are deuterated at the α-position. Scheme 1-23 shows that after deuteration the configuration of β-stereocenter remains unaffected as long as the temperature did not exceed 100 °C.

**Scheme 1-23.** Ruthenium-catalyzed H/D exchange of a primary alcohol.

The use of other metals such as manganese, rhenium, chromium and mercury, or their complexes, have been mentioned, but these have so far made little impact as catalysts for homogeneous H/D exchange.

1.3.6 Heterogenous Catalysis of H/D Exchange

The advantage of heterogeneous catalysis over the corresponding homogeneous process is the potential ability to remove the catalyst by simple filtration at the end of the reaction. Furthermore, the exchange processes occur without side products and no further work-up steps are necessary. However, the formation of dehalogenation, hydrogenation and hydrolysis products as well as harsh conditions, epimerization and racemization must be anticipated in heterogeneous catalyzed processes. Optimization of the reaction conditions for each substrate is usually unavoidable, in spite of the methodological improvements of recent years. High activity
for H/D exchange has been found with palladium, platinum, rhodium, nickel and cobalt catalysts.\textsuperscript{81} No exchange has been observed catalyzed by iridium under heterogeneous conditions.

Since deuterium transfer in high yield is frequently typically observed for substrates that contain a double bond or aromatic ring system, Garnett and co-workers believed that π-complex mechanisms involve in heterogeneous catalyzed exchange,\textsuperscript{82} involving both associative and dissociative mechanisms (Scheme 1-24).\textsuperscript{83} Both mechanisms involve initial adsorption of substrate onto the catalyst surface. The major difference between these two pathways is that associative mechanism I involves direct substitution of deuterium bound to the metal center for hydrogen, whereas the dissociative mechanism II requires a replacement of hydrogen by a metal to give the intermediate aryl metal species 1-97.\textsuperscript{84} Only in the second step does substitution of the metal atom by a deuterium take place to form the product 1-96.

**Scheme 1-24.** Associative (I) and dissociative mechanism (II) of the heterogeneous H/D exchange of an aromatic substrate 1-95.
Apparently, both mechanisms are operative in the formation of the product, depending on the transition metal. In the case of platinum, a dissociated mechanism is proposed, but for palladium, the associated mechanism predominates; in the case of rhodium, both mechanisms appear to be involved equally.\textsuperscript{85} Aliphatic compounds are only deuterated under forcing conditions and no general mechanism has yet been proposed.

1.3.6.1 Palladium-Catalyzed Exchange

Palladium is used often in combination with gaseous deuterium in heterogeneous H/D catalyzed exchange. In the method developed by Azran et al,\textsuperscript{86} a 10\% Pd/C surface was exhaustively purged from adventitious adsorbed hydrogen and protic compounds by repeated treatment with deuterium gas. Benzylic hydrogen atoms could be substituted selectively within an hour at room temperature with this catalyst and deuterium transfer was influenced by the solvent, the substrate structure and the catalyst/substrate ratio.

The investigation by Sajiki et al. on 5-phenylvaleric acid (1-98) (Scheme 1-25) found that the reaction temperature greatly influenced the regioselectivity and deuterium incorporation in H/D exchange.\textsuperscript{87}

Scheme 1-25. Palladium-catalyzed exchange of 5-phenylvaleric acid.
The benzylic hydrogen atoms of compound 1-98 were selectively deuterated at room temperature (1-99), whereas at high temperature (160 °C), the less reactive positions of compound were also deuterated, giving 1-100. The incorporation of deuterium into the side chain decreases with increasing distance from the benzene ring. The H/D exchange was not observed in the absence of H₂ gas or 10% Pd/C.

Faigl and co-workers developed a significantly higher exchange efficiency for the benzylic hydrogen atoms of the piperidine derivatives 1-101 with Pd/C-H₂-D₂O in the presence of deuterated alcohols and DCl (Scheme 1-26). 88

**Scheme 1-26.** Pd-catalyzed H/D exchange of piperidine derivatives.

1.3.6.2 Platinum-Catalyzed Exchange

Both palladium and platinum are widely applied, highly active catalysts for the H/D(T) exchange labeling of organic compounds. The basic exchange reaction is similar and the same activation principles apply to both systems. 89 Platinum catalysts generally have a high tendency towards the deuteration of aromatic positions, whereas palladium catalysts preferentially deuterated aliphatic positions, 90 according to Sajiki and co-workers. The deuteration of phenol was achieved almost quantitatively with 5% Pt/C at room temperature. In contrast, the
palladium-catalyzed reaction had to be heated at 180 °C for deuteration to take place. Palladium and platinum can also be used as a mixed catalyst system for the deuteration of sterically hindered aromatic positions.

The difference in chemoselectivity between palladium and platinum catalysts at lower reaction temperatures has also been reported by Matsubara and co-workers. For example, arylsilanes 1-106 could be selectively deuterated at the aromatic ring in this hydrothermal reaction, in which exchange at the ortho position was disfavored due to steric hindrance (Scheme 1-27).

**Scheme 1-27.** Platinum-catalyzed H/D exchange of arylsilanes.

At lower temperatures, platinum metal forms from PtO₂ (1-103) during an inductive phase and then inserts into D₂O, forming D-Pt-OD complex 1-104, which dissociates with formation of the key cationic platinum species 1-105. This reacts at at the arylsilane 1-106 at the para position. Aryl platinate 1-108 is generated which leads to deuteration at the same carbon atom, generating the product 1-109.
1.3.6.3 Nickel-Catalyzed H/D Exchange

Raney nickel has been used mainly for the deuteration of aromatic substrates, whereas only hydrogen atoms on the aliphatic residue were exchange by heating phenylacetic acid in D$_2$O in a sealed tube. A high degree of deuteration was achieved by using D$_2$O or other deuterated protic solvents.

Under Raney nickel-catalyzed exchange; only the hydrogen atoms at the α-carbon atoms underwent exchange in quinuclidine (1-110) (Scheme 1-28).^94


1.4 Protodesilylation for Hydrogen Incorporation and the Research

1.4.1 Proposed Research

Although there are many methods to prepare deuterated labeled compounds, not all work well for any given substrate. They suffer from harsh conditions, functional group intolerance or poor generality of substrate scopes. There has been no truly general method for the site specific introduction of deuterium atoms into molecules of pharmaceutical interest, so a need exists for a mild and selective method for site-specific deuterium incorporation strategy. This is an exceptionally useful tool to both understand and potentially control the metabolism of drug
substances. The methodology involves the direct replacement of a substituted silicon atom with deuterium by first activating the silyl group with Lewis base to form either penta- or hexacoordinate silicate complex (Figure 1-11). This hypervalent silicate, which acts as masked anion equivalent, then reacts with a deuterium source, replacing the silicon-carbon bond with a deuterium-carbon bond. The analogous protiodesilylation has been previously studied and served as a basis from which to develop the deuteriodesilylation methodology.

\[
\begin{align*}
\text{L}^\text{\textregistered} \text{SiL}^\text{\textregistered} \text{L} & \quad \text{L}^\text{\textregistered} \left[ \text{L} \text{SiL}^\text{\textregistered} \text{L} \right] \quad \text{L}^\text{\textregistered} \left[ \text{L} \text{SiL}^\text{\textregistered} \text{L} \right]^\text{2\textregistered}
\end{align*}
\]

**Figure 1-11.** Activation of tetracoordinated silicon by Lewis base.

This research develops a method for late stage site-specific incorporation of deuterium atoms, using a fluoride source as a Lewis base and inexpensive and readily available sources of deuterium such as \(d_4\)-methanol (CD\(_3\)OD) and deuterated water (D\(_2\)O). The method involves substitution of silicon atom with deuterium. This reaction requires activation of the silicon atom with a Lewis base, a process well-precedented in the chemical literature. The reaction of a range of silyl-substituted compounds with Lewis base have been studied with the goal of identifying optimal conditions for replacing silicon with deuterium.

\[
\begin{align*}
\text{R-SiR}_3 & \quad \xrightarrow{\text{Lewis base}} \quad \text{CD}_3\text{OD or D}_2\text{O} \quad \xrightarrow{\text{R-D}} \quad \text{R}^\text{-D}
\end{align*}
\]

**Figure 1-12.** Deuteriodesilylation of an organosilane promoted by Lewis base.
To investigate the feasibility of this hypothesis, the reaction of a range of silyl-substituted compounds with Lewis base was studied with the goal of identifying optimal conditions for replacing silicon with deuterium.

Optimal conditions would ideally allow for a mild reaction and broad functional group tolerance, which is lacking in current synthetic methods for deuterated compounds. This allows the method to be complementary to existing routes.

The use of silicon substituted compounds as precursors to deuterated analogous is predicated on the analogous protodesilylation reaction.\textsuperscript{97} Silicon has long held a privilege in organic synthesis.\textsuperscript{98a,98} Additionally, the use of silicon protecting groups in the majority of multi-step syntheses, illustrated the necessity, the stability and functional group tolerance of organosilicon compounds, allowing for the silicon atom to act as a “deuterium surrogate”. Compared with other organometallic reagents, silicon compounds are much more moisture and air-stable. Organosilanes are easily to prepare compounds with low toxicity. Silicon substituted building blocks are commercially available, especially trimethyl silyl compounds. The number of the commercial silicon compounds are steadily increasing due to their useful applications in pharmaceutical industry and research applications.

1.4.2 Survey of Literature Precedent for Protodesilylation

Schemes 1-29 and 1-30 are two examples of silicon being replaced by hydrogen by two different ways.\textsuperscript{100a,b}
Roush and co-workers have reported a fluoride-promoted protodesilylation (Scheme 1-29)\textsuperscript{100b}, the dimethylphenylsilyl-substituted tetrahydrofuran \textbf{1-112} undergoes protodesilylation of unactivated C(sp\textsuperscript{3})-SiMe\textsubscript{2}Ph bond to form tetrahydrofuran \textbf{1-114} via isolable dimethylsilanol \textbf{1-113} intermediates by using wet TBAF.\textsuperscript{99} The use of six equivalents of TBAF was the preferred method of activation of the silicon atom. The authors invoke a hexavalent silicate intermediate, and given that the reaction proceeds by first undergoing protodesilylation of the phenyl group to form a silanol, it seems unlikely that this reaction would work without an aromatic silyl substituent.

\textbf{Scheme 1-29.} The protodesilylation of unactivated SiMe\textsubscript{2}Ph via an isolable dimethylsilanol.

In the following example by Silverman and co-workers (Scheme 1-30),\textsuperscript{100a} a silicon atom is used to tether aryl amino ester \textbf{1-115} to a solid support to obtain tripeptide \textbf{1-118}.
**Scheme 1-30.** Polymer-supported synthesis of 3-Aryl-β-alanine-containing tripeptide.

The silicon “linker” is then removed by TFA-promoted protodesilylation and replaced by a hydrogen atom. This is therefore called traceless silicon linker. Numerous synthetic steps are performed prior to cleavage of the linker, demonstrating excellent functional group tolerance.
1.5 Organosilanes

1.5.1 Methods for the Preparation of Organosilicon Compounds

Organosilicon compounds do not occur free in nature, they are prepared synthetically. The first halosilane-silicon tetrachloride was discovered by Berzelius, by reacting elemental chlorine with silica and carbon, in the same year he discovered silicon (Scheme 1-31).

**Scheme 1-31.** Preparation of silicon tetrachloride.

\[
\text{SiO}_2 + \text{C} + 2\text{Cl}_2 \xrightarrow{1000 \, ^\circ\text{C}} \text{SiCl}_4 + \text{CO}_2
\]

Silicon tetrachloride (1-119) then became the fundamental building block for the synthesis of organosilanes. The formation of tetraethylsilane (1-120) was first studied by Friedel and Crafts in 1863 by reacting silicon tetrachloride with diethyl zinc (Scheme 1-32).

**Scheme 1-32.** Synthesis of tetraethylsilane.

Organosilyl halides are important reagents in organic chemistry, especially trimethyl silyl chloride. A classic method called the Flood reaction (Scheme 1-33) for the synthesis of this
compound by heating hexaalkyldisiloxanes $R_3SiOSiR_3$ with concentrated $H_2SO_4$ and sodium or ammonium halide.$^{102}$

**Scheme 1-33.** Synthesis of an organosilyl halide by the Flood reaction.

$$\text{R}_3\text{SiOSiR}_3 \xrightarrow{\text{NH}_4\text{Cl}, \text{H}_2\text{SO}_4} \text{R}_3\text{SiCl}$$

Kipping studied the reaction of organohalosilanes with Grignard reagents allowing the facile synthesis of substituted organosilanes.$^{103}$ This approach is quite general, for example, **1-120** readily reacts with phenylmagnesium bromide (**1-121**) to generate trimethylsilyl benzene (**1-122**) (Scheme 1-34).

**Scheme 1-34.** General synthesis of organosilane **1-122** using Grignard reagents.

Rochow and Muller discovered the copper-catalyzed high temperature “direct reaction” of silicon with chlorinated hydrocarbon (Scheme 1-35) in the presence of a metal catalyst to form organo-halosilanes such as **1-123**.$^{104}$
Many different classes of organosilanes are known. The preparation of the most popular classes of organosilanes are summarized below.

1.5.1.1 Synthesis of Alkylsilanes

a) Nucleophilic substitution

Nucleophilic displacement of a halogen from a halosilane by an alkyl organolithium (or Grignard) reagent is a common method. For example trimethylsilyl chloride (1-120) is a common electrophile when reacted with alkylolithiums in the synthesis of trimethylsilylalkanes such as 1-124 (Scheme 1-36).

Scheme 1-36. General synthesis of alkylsilanes.

b) Hydrosilylation (addition of silanes to multiple bonds)

Scheme 1-37 depicts dichloromethylsilane undergoing addition across an olefin double bond. Silanes that have one or more halogen substituents are more reactive than trialkylsilanes.
In the following example of conventional hydrosilylation of alkene 1-125 catalyzed by H$_2$PtCl$_6$ proceeds by the Chalk-Harrod mechanism,$^{110a}$ and gave 1-126 in 65% yield.

**Scheme 1-37.** Synthesis of alkylsilane 1-126 by hydrosilylation.

1.5.1.2 Synthesis of Alkenylsilanes

a) Nucleophilic substitution reaction

Reaction of 1-hexyne (1-127) (Scheme 1-38) with ethylmagnesium bromide and TMSCl (1-120) in ether generates 1-128, followed by hydroboration-protonolysis in acetic acid at reflux to give cis-vinylsilane (1-129), in 67% yield.$^{107}$

**Scheme 1-38.** Synthesis of alkenylsilane by nucleophilic displacement.
b) Hydrosilylation reaction

Vinylsilane 1-131 (Scheme 1-39) was prepared by the reaction of terminal alkyne 1-130 with triethylsilylhydride in the presence of H₂PtCl₆ catalyst to give the product in 77% yield. This method is general for the hydrosilylation of a variety of silanes with terminal alkynes.


1.5.1.3 Synthesis of Alkynylsilanes

Terminal alkynes 1-132 (Scheme 1-40) can be protected as trimethylsilyl alkynes 1-133 by reaction with n-BuLi in THF, followed by TMSCl in 80% yield.

Scheme 1-40. Reaction of a terminal alkyne with TMSCl.

b) Alkynyl silanes undergo electrophilic attack (ipso substitution) in the presence of Lewis acids such as BF₃, AlCl₃, TiCl₄, followed by elimination. The β-effect of silicon determines the regiochemistry of the electrophile attack (see also Section 1.5.2.1). Scheme 1-41 shows the general mode of reactivity with 1-134 smoothly transformed into 1-136, via 1-135.
Scheme 1-41. Reaction of a trimethylsilylalkyne with electrophiles promoted by Lewis acid.

Needed as a building block in the synthesis of hematoporphoryn and protoporphyrin by Martin and co-workers,\textsuperscript{110} AlCl$_3$-mediated electrophilic substitution of trimethylpropyne (1-137) with acetyl chloride (1-138) proceeds via an acylium ion intermediate, furnishing alkynyl ketone 1-139 in 49% yield:

Scheme 1-42. Synthesis of alkynyl ketone 1-139.

1.5.1.4 Synthesis of Allylsilanes

Allylsilanes are stable and play an important role in organic synthesis, whereas the corresponding Li, Mg, Zn and B species all tend to undergo 1,3-shift of the metal, and even organostannanes exhibit this behavior.\textsuperscript{111} Negishi and co-workers have reported the reaction of
alkenyl iodide 1-140 with trimethylsilylmagnesium chloride (1-141) in the presence of a catalytic amount of Ni(PPh₃)₄ or Pd(PPh₃)₄, giving the allylsilane 1-142 in high yield (Scheme 1-42). There is no reaction in the absence of Ni or Pd complex.

**Scheme 1-43.** Synthesis of an allylsilane.

1.5.2 Overview of Organosilane Chemistry

Silicon is the second most abundant element on the surface of the Earth, after oxygen. Silicon does not occur as a free element in nature, but it is found as silica (quartz, sand) or as silicates. Silicon comes directly below carbon in periodic table and forms tetrahedral compounds. This can be explained using the classic Valence Shell Electron Pair Repulsion (VSEPR) model that silicon with valence electrons 3s² 3p² will form four sp³ hybridized atomic orbitals in order to make four σ-bonds to four ligands, each with single unpaired electrons. In order to add an additional ligand, the silicon atom expands its coordination sphere to give a relatively stable hypervalent pentacoordinate silicon sp³d, due to its vacant 3d-orbital (Figure 1-13).

**Figure 1-13.** Atomic orbital geometries of tetracoordinate and pentacoordinate species.
Unlike carbon, silicon does not form multiple bonds, as the large 3p orbital on Si does not overlap well with 2p orbitals on C, O or N. The Si-Si bond (53 kcal/mol) is weak in comparison to C-C bond (83-88 kcal/mol), whereas the Si-O bond (108 kcal/mol) is much stronger and longer than C-O bond (80 kcal/mol). Many characteristics of silicon differ from those of carbon. For example, the atomic radius of silicon (1.06 Å) is larger than the atomic radius of carbon (0.66 Å), but the electronegativity of silicon (1.7) is much less than that of carbon (2.5) according to Allred-Rochow Scale.\textsuperscript{103} Table 1-3 shows that most silane ligands have higher electron withdrawing abilities than the silicon center.\textsuperscript{114}

In general, atoms with high electronegativities form stronger bonds with Si than with carbon. Si forms very strong bonds to oxygen and fluorine. Much of organosilicon chemistry is driven by the formation of these bonds at the expense of weaker bonds. The C-Si bond is strong enough for trialkyl silyl group to survive a wide variety of synthesis transformations, but it is weak enough to be selectively cleaved under mild conditions.

Table 1-3. Electronegativity values for common silicon ligands.

<table>
<thead>
<tr>
<th>Element</th>
<th>Electronegativity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Si</td>
<td>1.7</td>
</tr>
<tr>
<td>C</td>
<td>2.5</td>
</tr>
<tr>
<td>Cl</td>
<td>3.0</td>
</tr>
<tr>
<td>H</td>
<td>4.0</td>
</tr>
<tr>
<td>F</td>
<td>2.1</td>
</tr>
<tr>
<td>N</td>
<td>3.0</td>
</tr>
<tr>
<td>O</td>
<td>3.5</td>
</tr>
</tbody>
</table>

*= Allred-Rochow Scale
A fluoride source is used to remove the silyl group due to the ability of fluoride to form a strong bond with silicon. The bonds between Si and other atoms are in general longer than the equivalent bonds between carbon and the corresponding atoms. This allows a hard nucleophile (e.g. fluoride ion) to react at sterically hindered at silicon centers. Carbon-silicon bonds are polarized toward carbon because carbon has a higher electronegativity value than Si. This caused Si open to attack by nucleophiles.

1.5.2.1 Silicon β-effect

The stabilization of cations at the carbon atom β- to Si is referred to as the silicon β-effect. It is the result of the overlap between the vacant p-orbital on the carbon β to the Si atom and the filled sp$^3$ orbital between the Si atom and the α-carbon. Maximum stabilization only occurs if the vacant p-orbital and the s-orbital on the C-Si bond are coplanar (Figure 1-14).

![Figure 1-14. β-silicon effect.](image)

An example of the influence the β-effect has in organosilane chemistry is the preference for Ipso-substitution displayed by arylsilanes in electrophilic aromatic substitution reactions. Figure 1-15 shows two possible electrophilic aromatic substitution possibilities. In the first,
trimethylsilylbenzene (1-142) is transformed into 1-144 through an *ipso*-substitution pathway. In the second case, 1-142 becomes 1-146, via normal electrophilic aromatic substitution at the *meta* position. The only product formed in these reactions is 1-144, resulting from direct substitution of the silyl group on aromatic ring (Figure 1-15).\(^\text{115}\) No *ortho*, *meta* or *para*-substitution is observed. This observation can be explained by the β-silyl effect. In the *ipso*-substitution case, orbital overlap between the cation’s empty p-orbital and the adjacent C(sp\(^3\))-silicon bond is possible, conveying significant stabilization through hyperconjugation (1-143). In all other cases (1-145) proper alignment for overlap cannot be achieved, as the p-orbital and the C(sp\(^3\))-silicon bond are orthogonal to each other, and cannot overlap. Therefore 1-144 is the product of the reaction, and not 1-146.

![Figure 1-15. *Ipso*-substitution due to the β-silicon effect.](image)

1.5.2.2 Stabilization of α-Negative Charges

54
Carbanions with an α-silicon group are more stable than their carbon analogs due to three factors:\textsuperscript{116}

1. The empty 3d atomic orbital on Si which allows pπ-dπ bonding.

2. Overlap between the filled σ-orbital of the metal-carbon bond and the unfilled σ\textsuperscript{*}C-Si orbital is energetically favorable (Figure 1-16). The larger coefficient on the silicon atom in the σ\textsuperscript{*} molecular orbital further improves the orbital overlap.

3. Si is a relatively large atom, with a Van der Waals radius is about 2.1 Å, therefore it is readily polarized. Induced dipoles will also stabilize proximal negative charge.

Figure 1-16. α-Silyl effect.

The Peterson olefination reaction exploits this α-silyl effect (Scheme 1-44). In this reaction, an α-silyl carbanion reacts with an aldehyde or ketone to generate an alkene. Scheme 1-44 depicts a recent example of this useful reaction by Waldemar and co-workers. After formation of α-silyl carbanion 1-148, starting from 1-147, 1-148 then reacts with a range of ketones 1-149 to furnish moderate to excellent yields of enamines of general structure 1-150 via a β-silylalkoxide intermediate.\textsuperscript{117}

Scheme 1-44. An example of α-silyl effect in the Peterson olefination reaction.
1.5.2.3 Silicon Groups as Latent Anion Equivalents

According to Scheidt (Scheme 1-45), Chult (Scheme 1-46) and others, activated silicon can act as a masked anion equivalent. In a recent report by Scheidt and co-workers,\textsuperscript{99a} potassium ethoxide acts as a Lewis base, activating triethoxysilylacetylene 1-151. This generates a pentavalent silicate intermediate 1-152, which readily reacts with benzaldehyde as if it was a carbanion to give 1-153.

Scheme 1-45. Silyl groups as anion equivalents.

Chult’s research group have reported an interesting annulation reaction involving activation of a silane with fluoride. Substrate 1-154 undergoes methylation to form quaternary ammonium salt. The Lewis base (fluoride ion in this case) then activates the trimethylsilyl group and generates a carbanion equivalent at the α-carbon. Subsequent 1,4-elimination then leads to diene 1-155, which undergoes intramolecular Diels-Alder reaction to make the steroid core 1-156 (Scheme 1-46),\textsuperscript{99a}
Scheme 1-46. Steroid core synthesis via an intramolecular Diels-Alder reaction.

1.5.3 Reactions of Organosilanes

1.5.3.1 Peterson Olefination Reaction

As mentioned in Section 1.5.2.2, The Peterson olefination reaction allows the preparation of alkenes from decomposition of β-hydroxysilane under either acidic or basic conditions. β-hydroxysilane 1-118 can be prepared by addition of α-silyllithium 1-116 reagents to carbonyl compounds (Scheme 1-47).

Scheme 1-47. The Peterson olefination reaction.
\[ \beta\text{-hydroxysilanes 1-157} \] can undergo elimination to form olefins 1-159 through either a concerted syn-periplanar reaction pathway under basic conditions, or through a stepwise anti-periplanar pathway, typically occurring under acidic conditions.

In this case, syn-periplanar elimination from conformer B is favored, leading to the observed product (Figure 1-17).

**Figure 1-17.** Conformers of Peterson olefination intermediates.

1.5.3.2 Tamao-Fleming Oxidation

Activated organosilanes such as 1-160 undergo direct oxidation to aldehydes or ketones 1-161 when treated with a fluoride source, hydrogen peroxide and base.\(^{119}\) The reaction is thought to proceed through hypervalent silicate intermediates 1-162 and 1-163, with eventual formation of an enol 1-164 that is readily tautomerized to the product. (Scheme 1-47).
1.5.3.3 Hosomi-Sakurai Reaction

The use of o-Benzeneisulfonimide as a Brønsted acid catalyst under mild condition to catalyze the reaction between various acetals or alcohol with allyl(trimethyl)silane.\textsuperscript{120}

**Scheme 1-49.** Hosomi-Sakurai reaction.

Lewis acid-catalyzed addition of allyltrimethylsilane (1-166) with acetal 1-165 in the presence of catalyst 1-167 to give 1-168 (Scheme 1-48) in excellent yield under mild conditions. In this reaction, 1-167 is responsible for converting the acetal into a oxocarbenium ion, which readily undergoes allylation with 1-166, forming 1-168.
Allylsilanes are far more nucleophilic than vinyl silanes. In an allylsilane, the C-Si β-bond can align with the empty p-orbital on the adjacent carbocation. In a vinylsilane, the C-Si β-bond is orthogonal to the empty p-orbital. As a result, it needs to undergo a 60° bond rotation before it can optimally stabilize the β-positive charge.

1.5.3.4 Hiyama Coupling Reaction

Due to the low polarization of the C-Si bond, organosilanes are relatively unreactive nucleophilic coupling partners for Pd(0)-catalyzed cross-coupling reactions. As a result, the reaction is usually performed in the presence of an activator, a fluoride source such as TBAF, TASF, etc. Silanes contain electron withdrawing groups tend to be more active: Me₂FSi-, MeF₂Si- (but not F₃Si-) or Me₂(RO)Si-, Me(RO)₂Si-. The Hiyama coupling reaction is palladium-catalyzed cross-coupling reaction of organosilicons with organic halides or triflates and fluoride source or a base.¹²¹

**Scheme 1-50.** Hiyama Coupling Reaction, General Scheme.

\[
R^*-X + R_3Si-R' \xrightarrow{\text{[Pd]-cat fluoride source}} R^*-R'
\]

One example of Hiyama coupling reaction is the reaction of 1-iodonaphthalene (1-169) with trimethylvinylsilane (1-170) to produce 1-vinynaphthalene (1-171) using Pd(dba)₂ as catalyst and KF as fluoride source. Fluoride is used to activate the silicon compound to form a reactive pentavalent silicate intermediate, analogous to a activation of boron in a Suzuki coupling.
Scheme 1-51. Synthesis of 1-vinylnaphthalene.

The mechanism is proposed in Figure 1-18:

Figure 1-18. Mechanism of Hiyama coupling reaction.

1.5.3.5 Brook Rearrangement

The the [1,2]-silyl migration of α-silyl oxyanions, such as those derived from silyl carbinol 1-172 to α-silyloxy carbanion 1-173 via reversible process involving a pentacoordinate silicon intermediate is known as the Brook rearrangement (Scheme 1-51). The reaction is generally reversible in nature, although the reaction is heavily influenced by the ability of the adjacent groups to stabilize negative charge, and the metal counter ion. For example if one of the R-groups were phenyl and a lithium base is used, the equilibrium in Scheme 1-52 would lie heavily towards 1-173. Conversely, if 1-172 were a zinc salt and R₁ = R₂ = alkyl, the
equilibrium would lie to the left. When stereogenic silicon atoms are used, the chiral configuration is retained after rearrangement.

**Scheme 1-52.** The Brook rearrangement.

![Scheme 1-52](image)

The mechanism of the Brook rearrangement, is shown in Figure 1-19 below:

![Figure 1-19](image)

**Figure 1-19.** Mechanism of Brook rearrangement reaction.

---

1.5.3.6  **Epoxidation-Hydrolysis of Vinylsilanes**

Unactivated vinyl silanes of the general structure 1-74 can undergo oxidation to give the corresponding aldehyde 1-175. This process involves first preparing the silyl epoxide 1-176, then hydrolysis to the aldehyde through a two-step sequence (Scheme 1-53).^{123}
1.5.4 Chemistry of Hypervalent Silicates

Compounds of silicon with coordination numbers greater than four have been known since Gay-Lussac\textsuperscript{124} and J. Davy\textsuperscript{125} independently observed the formation of the \([\text{SiF}_6]^{2-}\) ion and the adduct of \(\text{SiF}_4\) with ammonia.

Hypervalent silicate chemistry continues to be an area of interest and challenge in synthetic organic chemistry.\textsuperscript{126} In the last few years, stereoselective versions of several reactions promoted by silicon-based catalysts have been developed.\textsuperscript{127} Hypervalent silicate intermediates have also been utilized as chiral Lewis bases.\textsuperscript{128} Organosilanes have the ability to form five- (A), six- (B) and even seven-coordinated (C) silicon species (Scheme 1-54) in the presence of donor molecules or ions, many of which have been isolated and/or characterized.\textsuperscript{2a,b} In order to explain how the hypervalency originates, two different theories have been considered: the first involves vacant d-orbitals on Si combined with the effect of \(\sigma^*\) (Si-L) orbitals, in the pentacoordinate species, the silicon orbitals would have a \(sp^3d\) hybridization, while in the hexacoordinate species, the hybridization would be \(sp^3d^2\). The reduced s character of the silicon
orbitals in the extracoordinated species would explain the increased Lewis acidity of the silicon center and the increased electron density at the ligand L and R in the order A<B<C. The magnitude of this polarization is also dependent on the electronegativity of these ligands L and R. The second theoretical approach, in contrast, rules out the participation of the 3d-orbitals in the bonding process, the hypervalent bonding instead involve respectively one or two 3 center 4-electron molecular bonds, each formed by a silicon p-orbital and two p-orbitals of electronegative ligands. That is why virtually all hypervalent compounds bond F, Cl, and OR. More electron withdrawing ligands (ie. OR, NR₂ or halides) on a tetracoordinate silicon, the more likely to form hypervalent silicate complex. Thus, tetrachlorosilane and fluoride ion should form a silicate more easily than tetramethylsilane.

**Scheme 1-54.** Valency and electron density at silicon in organosilicon compounds.

Both theories proved to be helpful in the interpretation of the fundamental properties of hypervalent silicates B and C (Scheme 1-54). This clearly distinguish their reactivity from that of tetracoordinate compounds, such as the increased Lewis acidity of the silicon atom and the transfer of electronic density to the ligands, results in a distinctly enhanced capability of transferring a formally negatively charge R group to an acceptor. (carbanion or hydride equivalent). Thus, transformations involving a pentavalent (B) or hexavalent silicon (C) as the
reactive site generally allow for carbon-carbon as well as carbon-heteroatom bond formation, and not carbon-silicon formation. Conversely, tetravalent compounds (A) exhibit different reactivity patterns. Any carbon atoms bound to silicon in these tetracoordinated silicate are less polarized and hence, more covalent. The most common synthetic application of tetracoordinated silanes is the transition-metal-catalyzed hydrosilylation reaction,\textsuperscript{130} which corresponds to a silicon-hydrogen bond activation. Thus, transformations that are likely to involve a tetravalent silicon center (A) as the reactive site allow for carbon-silicon as well as silicon-heteroatom bond formation, and not carbon-carbon formation.

Coordination of the Lewis base electrons can be by either intermolecular,\textsuperscript{131} or intramolecular addition.\textsuperscript{132} Neutral ligands are either attached via a tether to the silicon in the case of intramolecular coordination or associate to the Lewis acid silicon center in the case of intermolecular case. The neutral ligands usually involved are ketones or trisubstituted amines which donate their unbound electrons to silicon.\textsuperscript{138} The formation of hypervalent silicates 1-177-1-179 by intramolecular addition of a neutral ligand is shown in Scheme 1-55.

\textbf{Scheme 1-55.} The formation of hypervalent silicate by intramolecular ligand addition.

\[
\text{MesN}^+\text{F}_3\text{Si}^-\text{F} \quad \text{F}_3\text{Si}^-\text{F} \quad \text{F}_3\text{Si}^-\text{F}
\]

Intramolecular coordination is more dependent on the remaining substituents on silicon, despite the favorable geometry aiding interaction between ligand and silicon. Both distances and hypervalency confirmed by X-ray analysis.\textsuperscript{133} Intramolecular coordination is aided by the chelate effect by donate electron rich group in close proximity to an electron poor center.
1.5.4.1 Nucleophilic Substitution

As mentioned above, the reactivity of organosilicon compounds is determined by the ability of the silicon atom to expand its valence shell.\textsuperscript{134,133a} Thus, nucleophilic substitution at the silicon atom proceeds by the associative mechanism through hypervalent intermediates E (Scheme 1-55).\textsuperscript{135,133a,139} In contrast to the analogous $S_N2$ substitution at the carbon atom in which the new Nu-Si bond is partially forming at the same time that the old Si-X bond is partially breaking, the silicon intermediate E can exist for sometime before the leaving group is eliminated. However, in some cases, intermediate E could be isolated and characterized.\textsuperscript{133a,139,136}

Scheme 1-56. Nucleophilic substitution of organosilicon compounds.

In general, the position of the equilibrium presented in Scheme 1-56 depends on the nucleophile and the leaving group and on the properties of the substituents A, B and C. These substituents may have a pronounced effect on the kinetics and thermodynamics of the substitution reaction, even though they are not directly involved in the reaction process.

1.5.4.2 Activation by Lewis Base: Hydride Donor

Corriu and co-workers developed a method in which Si-H bond acts as a selective reducing reagent. Cesium fluoride is used to activate the silicon atom, promoting the reduction
of carbonyl compounds. Acetophenone (1-180) is readily reduced to the corresponding alcohol 1-181 in 80% yield (Scheme 1-57).\textsuperscript{137} The advantage of this method is that the reduction is highly chemoselective and mild.

**Scheme 1-57.** Reduction of acetophenone with HSi(OEt)$_3$ and Lewis base.

\[
\begin{align*}
\text{Ph} & \quad \text{CH}_3 \\
\text{O} & \quad \text{Si(OEt)}_3, \text{CsF} \\
\text{1-180} & \quad \text{0 °C} \\
& \quad \text{80\%} \\
\text{Ph} & \quad \text{OH} \\
& \quad \text{CH}_3 \\
& \quad \text{1-181}
\end{align*}
\]

An outline of the proposed mechanism is shown in Scheme 1-58. After activation by fluoride to the hypervalent silicate 1-182, the ketone occupies the remaining coordination site. 1-183 then transfers hydride from the silicon atom to the carbonyl group, leading to 1-184. Siyl hydrolysis then furnishes the final product, alcohol 1-181.

**Scheme 1-58.** Proposed mechanism.
1.5.4.3 Activation Driven by Strain Release Lewis Acidity

According to Denmark,\textsuperscript{138} and Leighton,\textsuperscript{139} cyclobutane strained silacycles \textbf{1-185} and cyclopentane strained with diamine ligands \textbf{1-187} offered enhanced Lewis acidity because ring strain is released when the silicon transitions from tetrahedral to pentavalent, enhancing activation of the silicon atom in \textbf{1-886} and \textbf{1-188} (Figure 1-20).

![Diagram showing activation by strain release Lewis acidity]

\textbf{Figure 1-20.} Activation by strain release Lewis acidity.

The activation driven by strain release Lewis acidity is shown in Scheme 1-59.\textsuperscript{140} Allylsilane \textbf{1-189} doesn’t react with benzaldehyde (\textbf{1-191}) even at high temperature, however, cyclobutane strained silacycle \textbf{1-191} readily reacts with benzaldehyde to give compound \textbf{1-192} in high yield.

\textbf{Scheme 1-59.} Example of activation by strain release Lewis acidity.
1.5.4.4 Hypervalent Silicates as Lewis Acid Catalysts

When treated with a Lewis base, the central atom in a Lewis acid can become more electrophilic.\textsuperscript{141} Hence, the ligand is ionized and the generation of cationic species results in a significant increase in the Lewis acidity (Figure 1-21).

\textbf{Figure 1-21.} Hypervalent silicates as Lewis acids.

1.5.5 Stereoselective Reactions

1.5.5.1 Lewis Base-Catalyzed Allylation Reaction

Corriu, Hosomi and Sarukai\textsuperscript{142} have all independently reported racemic Lewis base-promoted allylation using either fluoride or oxyanions as Lewis bases to activate allylsilanes. For example, the allylation reactions of pentacoordinate allylsilicate \textbf{1-146} with aldehyde \textbf{1-145} was developed to obtain homoallyl alcohol in good yield \textbf{1-147} (Scheme 1-60).\textsuperscript{147}
Scheme 1-60. Allylation reaction of pentacoordinate allysilicate with aldehyde.

In 1991, Kobayashi and co-workers reported that trimethylsilyl cyanide (TMSCN) reacted with aldehydes in the presence of a catalytic amount of Lewis base such as tertiary amines or phosphines to afford cyanohydrin trimethylsilyl ethers in good yield.\textsuperscript{143}

Scheme 1-61. DMF-promoted reaction of crotyltrichlorosilanes.

More recently, they reported that neutral Lewis base such as DMF can activate allyl or crotyltrichlorosilanes at low temperatures to afford the corresponding homoallylic alcohols in high yields and diastereoselectivity (Scheme 1-61).\textsuperscript{144}
The reaction of aldehydes with allyltrichlorosilane \textbf{1-196} in DMF under neutral conditions giving homoallylic alcohol \textbf{1-197} with high regio- and diastereoselective. \textit{Syn}- and \textit{anti}-homoallylic alcohols were stereoselectively obtained from (\textit{Z}) and (\textit{E})-allyltrichlorosilanes, respectively. In these reactions, DMF coordinates to the silicon atom of the allyltrichlorosilane to form the corresponding hexacoordinate organosilicate.\textsuperscript{145} This hypervalent silicate has enough Lewis acidity due to the electron-withdrawing chlorine groups as well as nucleophilicity due to electron-donation from the hypervalent silicon atom to the allyl π systems (s-p conjugation).\textsuperscript{147a} The high stereoselectivities can be explained by a chair-like six-membered cyclic transition state with the crotly methyl group either syn or anti to the hydrogen of the aldehyde in the transition state.\textsuperscript{146} Thus, \textbf{1-196} leads to \textbf{1-197}, and \textbf{1-198} leads to \textbf{1-199}.

1.5.5.2 Hypervalent Silicates for Hydride Transfer

Malkov, Kocovsky and co-workers have reported that the asymmetric reduction of ketimine \textbf{1-200} with trichlorosilane can be catalyzed by \textit{N}-methyl-\textit{L}-valine \textbf{1-202} to afford secondary amine \textbf{1-201} with high enantioselectivity (Scheme 1-62).\textsuperscript{147}

**Scheme 1-62.** Hypervalent silicates for hydride transfer.
Figure 1-22 depicts the proposed transition state in the hydride transfer, with both hydrogen bonding and π-π interactions between the catalyst’s aryl ring and the aniline aryl ring of the imine appearing to be the key elements that determine the enantiofacial selectivity.

![Proposed transition state in the reduction of N-arylimine.](image)

**Figure 1-22.** Proposed transition state in the reduction of $N$-arylimine.

1.5.5.3 Denmark’s Bisphosphoramide Lewis Base Catalyst

Denmark and co-workers have developed a novel approach to carbonyl addition reactions that combine the use of chiral Lewis bases to generate catalytically active chiral Lewis acids (Scheme 1-63).\(^\text{148}\)

**Scheme 1-63.** Hypervalent silicon as chiral Lewis acid.
In the presence of catalytic amounts of chiral biphophoramide \((R,R)-1-204\), the weak Lewis acid \(\text{SiCl}_4\) is activated to form a stronger Lewis acid which promotes the asymmetric addition of a variety of silyl enol ethers to aldehydes in excellent yield (Scheme 1-63).

The addition of amine base as a proton scavenger in this reaction is a key component for high yields. Silyl ketene acetal \(1-203\) rapidly reacts with benzaldehyde \((1-190)\) in the presence of 5 mol\% of the dimeric phosphoramidate \((R,R)-1-204\) low temperature to afford the desired aldol product \(1-205\) in high yield and enantioselectivity.

A simplified catalytic cycle, proposed by the authors is shown in Scheme 1-64 below, which shows the reaction of \(1-203\) with \(1-190\) mediated by \(\text{SiCl}_4\) and catalyzed by hexamethylphosphoramide (HMPA, \(1-209\)). The proposed mechanism is supported by extensive \(^{29}\text{Si}\) NMR studies of the reaction mixtures, which led the authors to propose a pentavalent silyl cation \(1-206\) as the key active species. This is formed by the reaction of reaction HMPA with \(\text{SiCl}_4\). Under the reaction conditions, the cationic species \(1-206\) is formed (based on \(^{29}\text{Si}\) NMR data). This reacts with benzaldehyde \((1-190)\) to generate the hexacoordinate silicate \(1-207\), (in equilibrium with the silyl chlorohydrin \(1-208\)). \(1-203\) then reacts with the activated aldehyde \(1-207\), forming \(1-205\) in very high anti-diastereoselectivity. Desilylation of the TBS and chlorosilyl groups generate product and return the phosphoramide HMPA \((1-209)\) to the catalytic cycle, allowing the active cationic silicon species to continue promoting the reaction.

This reaction is unusual in that it is not, strictly speaking a Lewis acid-catalyzed reaction, rather these reactions are phosphoramide-catalyzed and \(\text{SiCl}_4\)-mediated. The authors point out that examination of the catalytic cycle reveals that each molecule of \(\text{SiCl}_4\) that enters the
catalytic cycle ends up incorporated into the product (until hydrolyzed on work up), while the
Lewis basic phosphoramidate catalyst is released to participate in subsequent turnovers.

Scheme 1-64 explains the formation of product and demonstrates that the product 1-209 is
predominantly trans, even in the absence of the chiral phosphoramidate 1-204. Therefore the
process must be inherently diastereoselective, most likely proceeding via an open, anti-transition
state. This is an interesting result, as many Mukaiyama-type aldol reactions tend to favor the
syn-diastereomer.

The authors also investigated the origin of the enantioselectivity of 1-205. Energy
minimized modelling calculations found that the bis-phosphoramidate catalyst 1-204, when bound as
the now chiral version of intermedante 1-207, effectively blocks one face of the aldehyde,
allowing for very high levels of enantioselectivity to be obtained, without necessarily
attenuating or enhancing the inherent diastereoselectivity of the reaction.

**Scheme 1-64.** Proposed catalytic cycle.
CHAPTER 2: RESULTS AND DISCUSSION

2.1 Selection of a Model Substrate

Silicon-substituted compounds are becoming increasingly easy to access or source commercially, and are therefore useful precursors in synthesis. The heterocyclic precursor 2-1 and protio-analog 2-1b are commercially available, allowing a complete analytical profile to be recorded for each with standard samples of both the starting material and product. The study of the conversion of 2-1 to 2-1a could thus be studied in detail.

Figure 2-1. Model Substrates.

2.1.1 Survey of Reaction Conditions Using a Model Substrate

Table 1 details the results of our model substrate optimization. As described in Section 1.4.1 Lewis bases, especially fluoride sources, are known to promote the reaction of organosilanes, (including protodesilylation reactions). Therefore the initial survey of reaction conditions began with Lewis bases that could promote the conversion of 2-1 to 2-1a. As expected, the reaction is extremely reliable when a fluoride source is employed as the Lewis base, with nearly all the entries showing conversion to the product. Notably, potassium carbonate was also efficient in smoothly promoting conversion of 2-1 to 2-1a. Potassium carbonate also proved to be a competent Lewis
base (Entry 7), but only when two equivalents were used, suggesting a hexacoordinate silicate may be the reactive intermediate for this Lewis base.

Table 2-1. Optimization of model substrate deuterodesilylation reaction.

![Chemical Reaction Diagram](Diagram)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis base</th>
<th>Solvent</th>
<th>Time (t)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TBAF•H₂O (2.0)</td>
<td>MeOH</td>
<td>1 h, 65 °C</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>TBAT (2.0)</td>
<td>CD₃OD</td>
<td>4 h, 65 °C</td>
<td>57</td>
</tr>
<tr>
<td>3</td>
<td>TBAT (4.0)</td>
<td>CD₃OD</td>
<td>6 h, 65 °C</td>
<td>100</td>
</tr>
<tr>
<td>4</td>
<td>TMAF (2.0)</td>
<td>CD₃OD</td>
<td>1 h, 65 °C</td>
<td>100</td>
</tr>
<tr>
<td>5</td>
<td>TMAF (1.0)</td>
<td>CD₃OD</td>
<td>2.5 h, 65 °C</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>CsF (2.0)</td>
<td>CD₃OD</td>
<td>1 h, 65 °C</td>
<td>100</td>
</tr>
<tr>
<td>7</td>
<td>K₂CO₃ (2.0)</td>
<td>CD₃OD</td>
<td>1 h, 65 °C</td>
<td>100</td>
</tr>
<tr>
<td>8</td>
<td>KF (2.0)</td>
<td>CD₃OD</td>
<td>1 h, 65 °C</td>
<td>100</td>
</tr>
<tr>
<td>9</td>
<td>NaF (2.0)</td>
<td>CD₃OD</td>
<td>1 h, 65 °C</td>
<td>91</td>
</tr>
<tr>
<td>10</td>
<td>TMAF (2.0)</td>
<td>D₂O</td>
<td>16 h, 65 °C</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>TMAF (2.0)</td>
<td>D₂O/dioxane</td>
<td>16 h, 65 °C</td>
<td>100</td>
</tr>
<tr>
<td>12</td>
<td>TMAF (2.0)</td>
<td>D₂O/dioxane</td>
<td>2.5 h, 65 °C</td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TBAF:</th>
<th>TBAT:</th>
<th>TMAF:</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-Bu₄NF·xH₂O</td>
<td>Ph₂Si-Ph⁻</td>
<td>Me₄NF⁺</td>
</tr>
</tbody>
</table>

*a Percentage of the conversion was determined by analytical HPLC in 0.2-1M reaction
Despite the wide variety of Lewis bases available to promote the reaction, we were keen to keep the reaction conditions as moisture-free as possible. Thus, hygroscopic fluoride reagents were less desirable as the introduction of competing proton sources could reduce the isotopic purity of the isolated products. I was particularly keen to avoid the use of tetra-\textit{n}-butylammonium fluoride (TBAF),\textsuperscript{102} as this compound is extremely hygroscopic and cannot be dried to the extent that all traces of water are removed. TBAF decomposes under conditions of prolonged drying, via a Hofmann elimination with fluoride serving as base.\textsuperscript{150} Additionally, the salt isolated after dehydration is contaminated with bifluoride ion (HF\textsubscript{2}\textsuperscript{-}) and tributylamine.\textsuperscript{151} Anhydrous TBAF however, can be generated directly in polar aprotic solvent at low temperature by treatment of hexafluorobenzene with tetrabutylammonium cyanide in THF, MeCN or DMSO.\textsuperscript{156} Unfortunately, this method is incompatible with our desired reaction conditions where readily available sources of deuterium such as CD\textsubscript{3}OD or D\textsubscript{2}O are required. Adventitious water from TBAF would reduce the nucleophilicity of fluoride by hydrogen bonding and especially lead to undesired protodesilylation competing with our desired deuterodesilylation process.

Instead, non-hygroscopic tetramethylammonium fluoride (TMAF),\textsuperscript{152} which lack of \textbeta\-hydrogen atoms for Hofmann elimination and the hypervalent silicate tetra-\textit{n}-butylammonium difluorotriphenylsilicate (TBAT)\textsuperscript{153} were preferred (Entries 2-5 & 10-12), along with anhydrous mineral fluoride sources which worked very efficiently (Entries 6, 8 & 9). Crystalline TBAT is stable and less reactive than TBAF, non-hygroscopic and soluble in a wide range of organic solvents. Unfortunately we found it difficult and inconvenient to remove the excess TBAT from the crude reaction mixture. Although TBAT met our criteria for being non-hygroscopic, the need for an excess of this reagent, as well as the longer reaction times, and need to remove the unreacted reagent by crystallization on work-up, led us to examine other sources of fluoride.
Mineral fluoride salts are available in anhydrous forms, but readily form hydrates and are quite hygroscopic. Sodium fluoride is better in this regard than potassium fluoride, but is slightly less efficacious in the reaction (Table 1, Entry 9).

The reaction for the model substrate was monitored by analytical HPLC (Figure 2-2) below.
HPLC trace I: 2-1

HPLC trace II: 2-1b

HPLC trace III: 2-1a (crude)

**Figure 2-2.** HPLC traces: (I) 2-trimethylsilyl-6-iodofuropyridine (II) standard iodofuropyridine (III) deuterated iodofuropyridine.
The crude reaction mixture showed quantitative conversion of the starting material \(2-1\) (Table 2-1, Entry 1) to the product \(2-1a\) with 94.4\% purity. This result was unambiguously confirmed the conversion of compound \(2-1\) to compound \(2-1a\), by \(^1\)H NMR analysis of the crude reaction mixture, and analytical HPLC analysis against a known standard of \(2-1b\). The hydrogen atom at the 2-position next to oxygen of the furan can easily see by \(^1\)H NMR. Deuteriodesilylation of \(2-1\) led to the disappearance of the protons of trimethylsilyl group at \(\delta 0\) ppm. The analogous protodesilylation \(2-1b\) was characterized by the additional appearance of a new proton resonance at the 2-position next to the furo oxygen (\(\delta 7.8\) ppm), a signal not present in \(2-1a\).

### 2.1.2 Choice of Fluoride Source and Reaction Conditions

Although the Lewis bases CsF, KF and TMAF all worked well for the model substrate, TMAF was selected as the reagent of choice over TBAT, TBAF or other mineral fluoride salts. In addition to the reasons advanced in the section above, we also envisaged that TMAF might be a more efficient reagent in biphasic reaction systems, as it resembles tetraalkyl ammonium salts that function well as phase transfer catalysts.\(^{155}\) For example where deuterated water is used as the deuterium source, dioxane is used as a co-solvent to help solubilize the substrate (Entries 11 \& 12). This would be relevant in the event tritiodesilylation were attempted, where \(\text{T}_2\text{O}^6\) or THO could be used as a tritium source (tritiated methanol [or MeOT] is not commercially available). TMAF is the best choice for biphasic reaction conditions (dioxane/water), as it seems to act like a phase transfer catalyst, so reactions are faster with TMAF in these conditions. With efficient reaction conditions in hand, a general procedure was developed involving treatment of the trimethylsilyl compound with 2-6 equivalents of TMAF, and heating in deuterated methanol for 2-16 hours,
(Method A, Section 3.2.2). This protocol would be tested across a variety of organosilanes with the goal of demonstrating a straightforward, selective and mild method for the preparation of deuterated compounds.

It was also desirable to determine whether D$_2$O could be used as a deuterium source. When D$_2$O was employed as the reaction solvent, unreacted starting material was returned (Table 1, entry 10), most likely due to solubility issues (the reaction mixture was not homogeneous and the majority of 2-1 did not dissolve). Use of a co-solvent (1,4-dioxane – Method B, Section 3.2.2), solved this problem, Table 1, entries 11 & 12 showing the reaction is complete after as little as 2.5 hours. Method B provides a second inexpensive and readily available deuterium source to be employed in our reaction manifold.

2-4 Comparison of Protio- and Deuterodesilylation and Kinetics

We were interested in understanding whether the reaction works as well for and whether an obvious kinetic isotope effect would be observed. So a simple experiment to measure the conversion of 2-1 into 2-1a (deuterodesilylation) or 2-1b (protodesilylation) over time was undertaken. For this experiment D$_2$O/H$_2$O were used as the deuterium or hydrogen source, using Method B. The raw data for kinetic experiments is shown in Table 2-2. The reaction conditions for this study utilized two equivalents of TMAF and, 0.032 mmol of 2 in 10 µL of either H$_2$O or D$_2$O (ca. 0.56 mmol). 100 µL of dioxane was the reaction solvent. It was convenient for the reaction to be conducted at the slightly lower temperature of 70 °C, so that the reaction was sufficiently slow to monitor by analytical HPLC effectively.
Table 2-2. Measurement of relative rates for deuterium and hydrogen incorporation.

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>time, (min)</th>
<th>conversion (%) D$_2$O</th>
<th>entry</th>
<th>time, (min)</th>
<th>conversion (%) H$_2$O</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>10.3</td>
<td>8</td>
<td>14</td>
<td>9.0</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>15.5</td>
<td>9</td>
<td>28</td>
<td>14.6</td>
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<tr>
<td>3</td>
<td>43</td>
<td>21.7</td>
<td>10</td>
<td>46</td>
<td>28.9</td>
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<tr>
<td>4</td>
<td>61</td>
<td>40.4</td>
<td>11</td>
<td>60</td>
<td>38.6</td>
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<tr>
<td>5</td>
<td>76</td>
<td>61.5</td>
<td>12</td>
<td>79</td>
<td>75.8</td>
</tr>
<tr>
<td>6</td>
<td>89</td>
<td>85.6</td>
<td>13</td>
<td>102</td>
<td>96.1</td>
</tr>
<tr>
<td>7</td>
<td>103</td>
<td>93.9</td>
<td>14</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Percentage of the conversion was determined by analytical HPLC*

An essentially negligible difference in the time taken for 2-1 into 2-1a or 2-1b was observed. Both reactions are essentially complete after 2 h (>95% conversion). Given the lack of an obvious difference in rate, we concluded that no kinetic isotope effect had occurred, and that it was unlikely that trapping the activated hypervalent silane intermediate was the rate limiting step of the reaction.

Table 2-1 contains a clear trend in the model system reaction with respect to the regarding the stoichiometry of the fluoride Lewis base. According to Table 2-1, when 2 equivalents of TMAF (Entry 4) is used to activate silicon, the reaction rate is faster than when only
one equivalent of TMAF is employed (Entry 5). This trend also holds true for the TBAT-promoted reactions (Entries 2 & 3). This suggests that activating silicon by F is the rate limiting step of the reaction. This data may also suggest that where stoichiometry allows for the formation of a hexavalent over a pentavalent silicate, the hexavalent silicate is able to react more rapidly.

2.2 Scope of Reaction

Tables 2-3 and 2-4 show the substrate scope for this reaction. Gratifyingly, 2-trimethylsilyl furopyridinyl substrates 2-1 to 2-3 are all smoothly converted to deuterated analogs in excellent yield using TMAF-promoted conditions (Table 1, Entries 4,5). The 5-allyl, 5-carboxaldehyde and 5-iodo substituents were chosen to illustrate the mild and selective nature of our approach. Alkenes, carbonyl compounds and aryl halides are all easily reduced to the protio or deuterio-compound under standard conditions for deuterium incorporation (by addition of D2(g), borodeuteride or dehalogenation). These functional groups would therefore normally be incompatible with certain deuterium-incorporation conditions, unless the site of deuteration was at the reactive functional group itself. By siting the silyl group at this 2-position, the labeled deuterium will be incorporated at this site-specific place that doesn’t affect other functional groups in the molecule. Table 2-3, Entries 4-6 show the results for the analogous protodesilylation reaction, accomplished using methanol as the reaction solvent. Very similar yields, reaction times were observed for these transformations.
To demonstrate the broader substrate scope of this reaction manifold, a variety of different organosilanes were subjected to our optimized reaction conditions (Table 2-3):
Table 2-4. General substrate scope

<table>
<thead>
<tr>
<th>entry</th>
<th>Silyl precursor</th>
<th>product</th>
<th>yielda (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2-4</td>
<td>2-4a</td>
<td>90</td>
</tr>
<tr>
<td>2</td>
<td>2-4</td>
<td>2-4b</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>2-5</td>
<td>2-5a</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>n-C4H9&lt;sup&gt;2&lt;/sup&gt; -O-SiMe&lt;sub&gt;3&lt;/sub&gt;</td>
<td>n-C4H9&lt;sup&gt;2&lt;/sup&gt; -D</td>
<td>64</td>
</tr>
<tr>
<td>5</td>
<td>MeO&lt;sup&gt;2&lt;/sup&gt; -SiMe&lt;sub&gt;3&lt;/sub&gt;</td>
<td>MeO&lt;sup&gt;2&lt;/sup&gt; -D</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>2-8</td>
<td>2-8a</td>
<td>N. R.</td>
</tr>
</tbody>
</table>

<sup>a</sup>Isolated yields after chromatography.

Table 2-4, Entry 1 features another example of a high-yielding deuterium incorporation; gratifyingly, the reaction of 2-chloro-4-iodo-3-trimethylsilyl pyridine demonstrated that TMAF was a mild enough reagent not to affect the chlorine atom at the 2-position, whereas TBAF is known to react with 2-chloropyridines or pyrimidines, replacing the chlorine atom with fluorine. This result is pleasing, as it means our reaction works well, without disturbing other
functional groups. The analogous protodesilylation was also performed (Entry 2), again with very similar results.

A bis-trimethylsilylbenzene undergoing double deuterodesilylation (Entry 3), smoothly generating 1,4-dideuterio-2,3,5-trichlorobenzene in 58% yield. Acylsilane 2-6, (Entry 4) was transformed into the corresponding deuterio-benzaldehyde 2-6a in 64% yield. Finally the alkynylsilane 2-7 (Entry 5) was rapidly converted to the deuterio-alkyne 2-7a in excellent yield, showing that C(sp)-Si bonds also participate in the reaction.

2.3 Attempted Deuterodesilylation of C(sp\(^3\))-SiR\(_3\) Substrates

Table 2-4, Entry 6 depicts an attempt to convert 2-8 into the corresponding deuterated compound 2-8a. Under our reaction conditions (Method B) we recovered only starting material in this reaction. We were still interested however, to see if these same conditions could be applied to the deuterodesilylation of C(sp\(^3\))-substituted silanes. We re-applied our own conditions, this time using 6 equivalents of TMAF (Table 2-5, Entry 2), reasoning that in the case of the alkyl substrates, it might be more difficult to activate to the hypervalent silicate intermediate. Once again, starting material was the main peak in the HPLC.

Reaction using Method B was also attempted, using 6.0 equivalents of TMAF and CsF as the flouride source (Entries 3 and 4 respectively), yielding no conversion of the starting material meaningfully to product. In contrast, the trimethylsilylethylether can be removed by using TFA.\(^{157}\)
Table 2-5. Deuteriodesilylation of C(sp³)-silanes.

| Entry | Method | Deuterium Source | Fluoride Source (No. equiv.) | Temperature | Reaction Duration | Result  
|-------|--------|------------------|-----------------------------|-------------|------------------|--------
| 1     | A      | CD₃OD            | TMAF (2.0)                  | 70 °C       | 16 h             | S. M. only |
| 2     | A      | CD₃OD            | TMAF (6.0)                  | 70 °C       | 16 h             | >80% S.M. |
| 3     | B      | D₂O              | TMAF (6.0)                  | 90 °C       | 16 h             | >75% S.M. |
| 4     | B      | D₂O              | CsF (6.0)                   | 90 °C       | 16 h             | >90% S.M. |
| 5     | Roush  | D₂O/DMSO         | TBAF (6.0)                  | 110 °C      | 16 h             | S. M. only |

*aPercentage conversion was determined by analytical HPLC.*

TBAF-promoted protodesilylation of C(sp³)-silanes has been reported by Roush and co-workers, however only dimethylphenylsilyl organosilanes work efficiently as substrates. Interestingly, the reactions proceed via an isolable dimethylsilanol intermediate, where the phenyl substituent reacts rapidly to form a silanol, which is a competent substrate in the desilylation. The conditions reported in this paper were attempted (Table 2-5, Entry 5), but no product formation was observed.

There are only sporadic examples of protodesilylation of trimethylsilyl-C(sp³) substrates in the literature. Hudrlick has reported a t-BuOK/DMSO:H₂O at 25 °C reaction which only appears to work for silanes with an adjacent α or β-hydroxyl group. (Scheme 2-1).
According to Hudrlik and co-workers, α or β-hydrosilanes undergo protodesilylation when treated with t-BuOK in aqueous DMSO at 25 °C. The addition of a small amount of 18-crown-6 facilitates the reactions with unreactive C(sp³)-substrates without increasing the amount of undesired elimination product and shorten reaction time. The presence of hydroxy group was necessary for the reaction to occur and a mechanism involving a four-member ring intermediate for the β-elimination reaction and protodesilylation of β-hydroxysilanes was suggested (Scheme 2-2).¹⁵⁹

**Scheme 2-1.** Deuterodesilylation of 2-trimethylsilylcyclohexanol using Hudrlik’s method.

![Deuterodesilylation of 2-trimethylsilylcyclohexanol using Hudrlik’s method.](image)

**Scheme 2-2.** Proposed mechanism of elimination and protodesilylation of β-hydroxysilanes.

![Proposed mechanism of elimination and protodesilylation of β-hydroxysilanes.](image)
A low water concentration was believed to slow down the elimination reaction and favor protodesilylation. Simple α-hydroxysilanes undergo protodesilylation faster than β-hydroxysilanes.\textsuperscript{16a} When DMSO-d\textsubscript{6}:D\textsubscript{2}O (19:1) was used, a full deuterium incorporation and a high yield of 2-deuteriocyclohexanol was obtained.

### 2.4 Tritidesilylation

After establishing that deuterium can be readily exchanged with trimethylsilyl groups, I then investigated the possibility of expanding the scope of the reaction to include tritium. Tritium decays to \(^3\)He by emitting a β-particle. The energy of β-particles varies from 0 to 18.6 keV. While deuterium model reactions are often conducted with pure deuterium oxide as the isotope source, tritium oxide is rarely used at anything close to nuclidic purity.\textsuperscript{5} Tritiated water at 50 Ci/ml, the highest specific activity normally available commercially, has a tritium/hydrogen ratio of only about 1.6/98.4, therefore the concentration of tritium in THO is usually much slower than that of deuterium in D\textsubscript{2}O and this difference is important in explaining a low level incorporation of tritium in tritiodesilylation reaction.

![Figure 2-5. Tritidesilylation reaction.](image)

A pilot reaction using low specific activity tritiated water (approximately 1% THO in H\textsubscript{2}O) was performed (Figure 4). At the time of writing, I believe this to be the first example of a
tritiodesilylation of any kind. The result of this is modest, starting with 10 millicuries (mCi) of tritiated water, the radioactivity incorporated into the product 2-1c was only ca. 0.1 mCi. This rather modest result, where only 0.1% of the activity was incorporated into the product 2-1c supports my earlier kinetic analysis of the relative rate of deuterium versus hydrogen incorporation. ³H reacts slower than ¹H and the water concentration is much higher than concentration of THO.
CHAPTER 3: CONCLUSION

Isotope labeling of organic compounds continues to be of critical importance in the development of new drugs and therapies. Deuterium is the most accessible and the least expensive stable isotope used to prepare internal standard for the metabolic studies in clinical diagnosis and research. Additionally, deuteration of new drug candidates and existing drugs has also demonstrated the potential for improved metabolic switching to generate active metabolites from prodrugs and longer duration of pharmacological action. These advancements can potentially improve existing drugs and reduce the risk of failure in drug design and development.

A new deuteriodesilylation has been developed for the site-specific incorporation of deuterium to pharmaceutical compounds and drug substances. In this novel approach, deuterium is only introduced at the carbon atom that was bound to silicon allowing for a high degree of site-specificity in the deuterium-containing product. Gratifyingly, the reaction is quite mild and general, tolerating a wide variety of functional groups on the molecule, while also providing a high level of deuterium incorporation. The reaction utilizes $d_4$-methanol (CD$_3$OD) and deuterated water as the source of deuterium atoms. These are relatively inexpensive deuterium sources, and are readily available reagents in most laboratories. Commercially available anhydrous TMAF was chosen as a Lewis base in promoting the desilylation reaction. As a nucleophilic fluoride source, this reagent has similar activity to the more commonly used TBAF, with the added advantage that anhydrous TMAF is readily available, and can be successfully dried by the azeotropic removal of water using cyclohexane or toluene. This provided a relatively cheap source of highly soluble fluoride source containing a chemically inert counter ion. Critically, by
employing non-hygroscopic TMAF, there was no adventitious proton source to lower the isotopic purity of the deuterated products. TMAF had been found to be thermally stable at high temperature.

An interesting trend in the kinetic reaction suggested that the rate of the reaction is dependent on the number of equivalents of TMAF, suggesting a hexacoordinate silicate is the more likely reactive intermediate. No appreciable rate difference was observed when our model substrate underwent protodesilylation in methanol, versus deuterodesilylation in CD$_3$OD. The reaction works in high yield when both D$_2$O and CD$_3$OD were employed as the deuterium source. Organosilanes starting materials, especially trimethylsilyl compounds are commercially available from Sigma-Aldrich and these numbers are continue growing, because organosilanes are low toxic, moisture and air-stable, readily prepared from a wide range of cheap staring materials and useful in pharmaceutical industry. The reactions are very user-friendly, and are easily purified by flash column chromatography or preparative-HPLC, giving high yields and purity of products.

This deuterodesilylation method was general for non-alkyl substrates and was used as a model for the first time to employ the incorporation of tritium, because compounds labeled with tritium are a very common source of radiotracers in early pharmaceutical development. Exposure of tritiated water in air is up to 25,000 times more hazardous than exposure to gaseous tritium due to the body’s readily absorption of tritium in the form of water through the skin, therefore, the handling of tritium compounds (especially THO) requires a special training and precaution, and may only be carried out at facilities with a National Radiochemistry Council (NRC) license. The exchange reaction of model substrate silicon compound with THO gave modest result, where only 0.1% of the tritium was incorporated (the rest was the protio-compound).
concentration of THO in water was low, only 1%. MeOT is not commercially available, but T\textsubscript{2}O can be obtained through Perkin Elmer with much higher concentration (maximum at 95% T\textsubscript{2}O in water), but it couldn’t be used in the reaction because of its extremely high cost. Furthermore, T\textsubscript{2}O is very unstable which is the result of its high specific radioactivity. This instability is due to tritium oxide generating a hydroxyl free radical from radiolytic decomposition of water in addition to extra energy from β-decay impinging on surrounding molecules.

Optimal conditions allowed for a mild reaction and broad functional group tolerance, which is in contrast to existing methods, which often suffer functional group and substrate incompatibility issues. A substrate scope was surveyed using a representative of silyl compounds. A range of C(sp\textsuperscript{2}) or C(sp)-organosilanes were converted to their corresponding deuterated analogs in excellent yield and high selectivity. In addition an acylsilane was converted to deuterated aldehyde, providing a completely novel method for synthesizing these important class of compounds. However, we were unable to effect the transformation of a C(sp\textsuperscript{3})-organosilane to its deuterated analog. In the analogous, and more frequently reported protodesilylation reaction, only certain C(sp\textsuperscript{3})-organosilane substrates appear to undergo reaction. Hudrlik and co-workers reported that protodesilylation appeared to work for silanes with adjacent α or β-hydroxyl group. The authors postulate that this is due to neighboring oxygen activating silicon to form intermolecular coordination siloxane intermediate. Roush and co-workers have reported that unactivated C(sp\textsuperscript{3})-dimethyl phenylsilyl substrate undergo protodesilylation efficiently. In this case, the phenyl group on the silicon atom is critical to the reaction’s success. The phenyl group undergoes protodesilylation first, generating a stable dimethyl silanol intermediate that is a competent substrate for C(sp\textsuperscript{3})-protodesilylation. Both
approaches require very specific organosilane precursors and employ harsher reaction conditions than our deuteriodesilylation protocol.

In summary, a new deuteriodesilylation method has been developed that provides a useful general synthetic tool for the site-specific synthesis of deuterated compounds. The reaction is mild and general, providing a complimentary approach to existing methods for deuterium compound synthesis.
CHAPTER 4: EXPERIMENTAL SECTION

General Information

All deuteriodesilylation reactions were carried out in flame-dried glassware with magnetic stirring. Purification of reaction products was carried out by flash column chromatography using EM Reagent silica gel 60 (230-400 mesh) or by ISCO Rf flash column chromatography, using ISCO pre-packed SiO$_2$ or C18 columns. Analytical thin layer chromatography was performed on Analtech 250 micron plates. Visualization was accomplished with UV light.

Analytical HPLC was performed to monitor the reactions by using a Waters 600 E system controller and Waters 712 WISP auto injector. HPLC column Synergy Polar RP, 15 cm x 3 mm ID, 4µ was used with the solvent system either 70:30 methanol/aqueous formic acid (0.1%) or a gradient of 0-100% acetonitrile/aqueous trifluoroacetic acid (0.1%). The detector was set at 254 nm unless otherwise stated. $^1$H NMR spectra were recorded on a Varian Inova 400 (400 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl$_3$ at 7.26 ppm). Data are reported as (s = singlet, d = doublet, t = triplet, m = multiplet, b = broad); coupling constant(s) in Hz; integration. Proton-decoupled $^{13}$C NMR spectra were acquired on Varian Inova 400 (100 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl$_3$ at 77.0 ppm) unless otherwise noted. Tetramethylsilane (TMS) served as internal ($^1$H, $^{13}$C) standard. Mass spectrometry data were obtained on Waters Acquity LC-MS 277. Na$_2$SO$_4$ purchased from Acros Organics was used to dry organic layers after extraction. CD$_3$OD and D$_2$O were purchased from Sigma-Aldrich or Cambridge Isotope Laboratories and used without
further purification. Tritiated water was purchased from Amersham Biosciences. Chemical purity was determined using Waters 486 single channel detector. UV detector and Radiochemical purity using Radiomatic Flow I radioflow detector with Radiomatic Flo-Scint III liquid scintillation cocktail. The tritium experiment was performed in a high-ventilation hood. All radioactive materials were kept in a hood and handled with extreme care to avoid the contamination. The tritiated materials were transported using a secondary container. Double gloves were used at all times, with the top pair changed frequently. The work area was surveyed frequently for contamination using a Geiger-Muller Counter and liquid scintillation detector was used to monitor for any contamination. All starting materials and solvents were purchased from commercial sources and used without further purification except compound 2-7 which was prepared using literature procedures.

Experimental Procedures

3.2.1 Synthesis of 4-\textit{n}-Butylbenzoylsilane (2-4):

This compound was prepared according to the procedure of Yamamoto and coworkers.\textsuperscript{160}

\begin{center}
\includegraphics[width=0.2\textwidth]{structure.png}
\end{center}

In a screw-capped pressure tube were placed allylpalladium(II) chloride dimer (137 mg, 0.37 mmol) and triethyl phosphite (249 mg, 1.5 mmol). The mixture was stirred for 5 min. Hexamethyldisilane (3.2 mL, 15.3 mmol) was added and the mixture stirred for another 5 min at room temperature. 4-\textit{n}-butylbenzoyl chloride (2.96 g, 15.0 mmol) was then added and the tube sealed, and heated to 110 °C for 18 h, after this time, a silver mirror had precipitated onto the glass vessel. The crude reaction mixture was then purified by vacuum
distillation to yield 1.231 g of product 2-4 (35% yield).  $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm:
7.62 (d, 2H), 7.12 (d, 2H), 2.50 (m, 2H), 1.46 (m, 2H), 1.20 (dq, $J = 14.6, 7.3$ Hz, 2H), 0.77 (t, $J = 7.3$ Hz, 3H), 0.22 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) 149.66, 140.66, 140.66, 129.97, 128.98, 37.03, 34.55, 23.63, 15.20, 0.26, -0.25 $\delta$ ppm; Mass calculated for C$_{11}$H$_{22}$Osi 234.14, Found 234.2 [M]$^+$ . HPLC $R_t = 20.5$ min, 98.7% purity.

3.2.2 Deuterio- or Protodesilylation: General Method A

To a reaction vial was added trimethylsilyl compound (0.40 mmol) and TMAF (0.8-2.4 mmol) in CD$_3$OD or CH$_3$OH (0.4-2.0 mL). The resulting mixture was stirred at 70 °C until monitoring of the reaction (TLC or HPLC) indicated completion had occurred. The reaction mixture was then allowed to cool to room temperature and concentrated to dryness under reduced pressure. The reaction mixture was then diluted with H$_2$O (2 ml) and extracted with EtOAc (2 × 2 ml). The combined organic layers were dried (Na$_2$SO$_4$), and concentrated to dryness. The crude product was purified by flash column chromatography, eluted with 15-20% EtOAc in hexanes to afford the desired product.

3.2.3 Microscale Deuterio- or Protodesilylation: General Method B

To a reaction vial was added trimethylsilyl compound (0.05 mmol) and TMAF (0.10 mmol) in 1,4-dioxane (100 µL). D$_2$O (2-10 µL; 0.11-0.55 mmol), was then added. The resulting mixture was stirred at 90 °C until monitoring of the reaction (TLC or HPLC) indicated
completion had occurred. The reaction mixture was then allowed to cool to room temperature and concentrated to dryness under reduced pressure. The reaction mixture was then diluted with H₂O (2 ml) and extracted with EtOAc (3 × 1 ml). The combined organic layers were dried (Na₂SO₄), and concentrated to dryness. The crude product was purified by flash column chromatography, eluted with 15-20% EtOAc in hexanes or preparative-HPLC to afford the desired product.

3.2.4 Attempted Deuteriodesilylation of Compound 2-9

![Chemical structure](image)

Attempted conversion of 2-8 was carried out as described in Table 2-5.

Disappearance of the starting material was monitored by HPLC, with minimal conversion of the starting material under all conditions tried.

**Conditions attempted:**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Method</th>
<th>Deuterium Source</th>
<th>Fluoride Source (No. equiv.)</th>
<th>Temperature</th>
<th>Reaction Duration</th>
<th>Result¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>CD₂OD</td>
<td>TMAF (2.0)</td>
<td>70 °C</td>
<td>16 h</td>
<td>S. M. only</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>CD₂OD</td>
<td>TMAF (6.0)</td>
<td>70 °C</td>
<td>16 h</td>
<td>&gt;80% S.M.</td>
</tr>
<tr>
<td>3</td>
<td>B</td>
<td>D₂O</td>
<td>TMAF (6.0)</td>
<td>90 °C</td>
<td>16 h</td>
<td>&gt;75% S.M.</td>
</tr>
<tr>
<td>4</td>
<td>B</td>
<td>D₂O</td>
<td>CsF (6.0)</td>
<td>90 °C</td>
<td>16 h</td>
<td>&gt;90% S.M.</td>
</tr>
<tr>
<td>5</td>
<td>Roush</td>
<td>D₂O/DMSO</td>
<td>TBAF (6.0)</td>
<td>110 °C</td>
<td>16 h</td>
<td>S. M. only</td>
</tr>
</tbody>
</table>

¹: Percentage of the conversion was determined by analytical HPLC
3.2.5 Kinetic Studies

The comparison of rate of deuterio- vs. protodesilylation (using D$_2$O vs H$_2$O) was performed using Method B as follows:

To a reaction vial was added 2-8 (15.9 mg, 0.05 mmol) and TMAF (9.3 mg, 0.10 mmol) in 1,4-dioxane (100 µL). Either D$_2$O or H$_2$O (10.0 µL, 55 mmol), was then added using a 5 µL syringe. The resulting mixture was stirred at 70 °C. HPLC monitoring was performed at regular intervals, and the ratio of 2-8 to 2-8a noted at each time point. This was continued until <5% of 2-8 remained. The results are shown in Table 2-5.

3.2.6 Tritiodesilylation

The reaction was carried out according to Method B, as follows:

To a reaction vial was added 2-1 (15.9 mg, 0.05 mmol) and TMAF (9.3 mg, 0.10 mmol) in 1,4-dioxane (100 µL). THO (aq) (10.0 µL, 55 mmol, 10.0 mCi), was then added using a 5 µL syringe. The resulting mixture was stirred at 90 °C for 2 h. At this time radio-HPLC indicated that the reaction was complete. The reaction mixture was then allowed to cool to room temperature and concentrated to dryness under reduced pressure. The reaction mixture was then diluted with H$_2$O (2 ml) and extracted with EtOAc (3 × 1 ml). The combined organic layers were dried (Na$_2$SO$_4$), and concentrated to dryness. Identity of 2-1c was confirmed by HPLC against a standard sample of 2-1b (it’s protio-analog). The compound had the same retention time and also co-eluted as a mixed sample.
Characterization Data

3.3.1 Protodesilylated Compounds 2-1 to 2-1b

Compound 2-1b was prepared using Method A: 6-iodo-2-(trimethylsilyl)furo[3,2-b]pyridine (0.40 mmol), TMAF (0.80 mmol) and 2.0 mL CH$_3$OH. 93.1 mg was isolated as a white solid 2-1b (95%).

Analytical data for Compound 1-1b: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$, ppm: 8.74 (s, 1H), 8.12 (s, 1H), 7.77 (d, $J$ = 2.3 Hz, 1H), 6.96 (d, $J$ = 2.3 Hz 1H); $^{13}$C NMR (400 MHz, CDCl$_3$) $\delta$ ppm: 151.8, 149.5, 149.2, 148.2, 126.7, 108.2; Mass calcd for C$_7$H$_4$INO [M+H]$^+$, 244.93, Found 245.9. $R_f = 0.43$ (15% EtOAc/hexanes).

Compound 2-2b was prepared using the Method A: 6-allyl-2-(trimethylsilyl)furo[3,2-b]pyridine (0.40 mmol), TMAF (0.80 mmol) and 2.0 mL CH$_3$OH. 54.1 mg was isolated as a white solid (85%).

Analytical data for Compound 2-2b: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.41 (s, 1H), 7.80 (d, $J$ = 2.3 Hz, 1H), 7.60 (m, 1H), 6.96 (d, $J$ = 2.3 Hz, 1H), 5.96 (m, 1H), 5.14 (m, 2H), 3.54 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 148.6-148.1 (t), 148.0, 146.6, 145.7, 136.4, 131.4, 118.5, 116.9, 107.7, 37.3; Mass calculated for C$_{10}$H$_9$NO [M+H]$^+$, 159.07. Found 160.07. $R_f = 0.29$ (15% EtOAc/hexanes).
Compound **2-3b** was prepared using Method A: 2-(trimethylsilyl)furo[3,2-b]pyridine-6-carbaldehyde (0.40 mmol), TMAF (0.80 mmol) and 2.0 mL CH$_3$OH. 57.7 mg of **2-3b** was isolated as a colorless waxy solid (98%).

Analytical data for Compound **2-3b**: $^1$H NMR (400 MHz, CDCl$_3$) δ 10.16 (s, 1H), 9.01 (s, 1H), 8.21 (s, 1H), 8.05 (d, $J$ = 2.3 Hz, 1H), 7.06 (d, $J$ = 2.3 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 190.3, 153.2, 152.7, 149.4, 147.4, 128.0, 117.4, 108.7.

Mass calculated for C$_8$H$_5$NO$_2$ 147.03. Found 147.1 [M$^+$]. R$_f$ = 0.26 (15% EtOAc/hexanes).

Compound **2-4b** was prepared using Method A: 2-chloro-4-iodo-3-(trimethylsilyl)pyridine (0.40 mmol), TMAF (0.80 mmol) and 2.0 mL CH$_3$OH. 85.2 mg was isolated as a colorless oil (88%).

Analytical data for Compound **2-4b**: $^1$H NMR (400 MHz, CDCl$_3$) δ 8.08-8.06 (d, $J$ = 5.1 Hz, 1H), 7.74 (s, 1H), 7.58 (d, $J$ = 5.1 Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 152.8, 149.7, 133.1, 131.6, 106.6; Mass calculated for C$_5$H$_3$ClIN [M+H]$^+$, 238.9. Found 239.8 R$_f$ = 0.7 (15%EtOAc/hexanes).
3.3.2 Deuterodesilylated Compounds 2-1 to 2-1a

Compound 2-1a was prepared using Method A: 6-iodo-2-(trimethylsilyl)furo[3,2-b]pyridine (0.40 mmol), TMAF (0.80 mmol) and 2.0 mL CD$_3$OD. 92.5 mg was isolated as a white solid (94%).

Analytical data for Compound 2-1a: $^1$H NMR (400 MHz, CDCl$_3$) δ ppm: 8.74 (s, 1H), 8.13 (s, 1H); 6.96 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 151.8, 149.2-148.9, 148.6, 148.1, 146.4, 126.7, 108.0, 86.2, 76.7; Mass calculated for C$_7$H$_3$DINO 245.94, Found 246.9 [M+H]$^+$. R$_f$ = 0.43 (15% EtOAc/hexanes).

Compound 2-2a was prepared using Method A: 6-allyl-2-(trimethylsilyl)furo[3,2-b]pyridine (0.40 mmol), TMAF (0.80 mmol) and 2.0 mL CD$_3$OD. 52.5 mg was isolated as a colorless waxy solid (82%).

Analytical data for Compound 2-2a: $^1$H NMR (400 MHz, CDCl$_3$) δ ppm: 8.41 (s, 1H), 7.61 (m, 1H), 6.96 (s, 1H), 5.96 (m, 1H), 5.14 (m, 2H), 3.52 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 148.6-148.1, 148.0, 146.6, 145.7, 136.4, 131.4, 118.5, 116.9, 107.7, 37.3; Mass calculated for C$_{10}$H$_8$DNO 160.07, Found 161.08 [M+H]$^+$. R$_f$ = 0.29 (15% EtOAc/hexanes).
Compound 2-3a was prepared using Method A: 2-(trimethylsilyl)furo[3,2-b]pyridine-6-carbaldehyde (0.40 mmol), TMAF (0.80 mmol) and 2.0 mL CD$_3$OD. 57.4 mg was isolated as a colorless waxy solid (97%).

Analytical data for Compound 2-3a: $^1$H NMR (400 MHz, CDCl$_3$) δ ppm: 10.16 (s, 1H), 9.01 (s, 1H), 8.56 (s, 1H), 7.08 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm 190.3, 153.2-153.0, 152.8, 149.4, 147.4, 128.1, 117.4, 108.6; Mass calculated for C$_8$H$_4$DNO$_2$ 148.14, Found 148.1[M]$^+$ R$_f$ = 0.28 (40% EtOAc/hexanes).

Compound 2-4a was prepared using Method A: 2-chloro-4-iodo-3-(trimethylsilyl)pyridine (0.40 mmol), TMAF (0.80 mmol) and 2.0 mL CD$_3$OD. 86.6 mg was isolated as a colorless oil (90%).

Analytical data for compound 2-4a: $^1$H NMR (400 MHz, CDCl$_3$) δ ppm: 8.07 (d, $J$ = 5.1 Hz, 1H), 7.59 (d, $J$ = 5.1 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ ppm: 149.5, 149.3, 132.8, 131.8, 110.2; Mass calculated for C$_5$H$_2$DClIN 239.91, Found 240.89, [M+H]$^+$. R$_f$ = 0.7 (15% EtOAc/hexanes).

Compound 2-6a was prepared using Method A: 4-n-Butylbenzoyltrimethylsilane (0.40 mmol), TMAF (2.40 mmol) and 2.0 mL CD$_3$OD. 41 mg was isolated as a colorless oil (64%).

Analytical data for Compound 2-6a: $^1$H NMR (400 MHz, CDCl$_3$) δ ppm: 7.8 (d, $J$ = 8.2 Hz, 2H), 7.32 (d, $J$ = 8.2 Hz, 2H), 2.68 (m, 2H), 1.6 (m, 2H), 1.36 (dq, $J$ = 14.6, 7.3 Hz, 1H), 0.93 (t, $J$ =
7.3 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ (ppm) 179.2, 150.5, 130.3, 129.9, 128.6, 35.9, 33.2, 22.3, 13.9; Mass calculated for C$_{11}$H$_{13}$DO 163.23, Found 164.1 [M+H]$^+$. $R_f$ = 0.63 (10% EtOAc/hexanes). HPLC $R_t$ = 16.9 min.

Compound 2-7a was prepared using Method A: 3,5-dimethoxyphenyl-ethynyltrimethylsilane (0.40 mmol), TMAF (0.80 mmol) and 2.0 mL CD$_3$OD. 63.4 mg was isolated as an off-white solid (87%).

Analytical data for Compound 2-7a: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm: 6.62 (s, 2H), 6.44 (s, 1H), 3.78 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm: 160.5, 124.4, 109.7, 105.0, 102.3, 93.8, 55.5; Mass calculated for C$_{10}$H$_9$DO$_2$ 163.19, Found 163.1 [M]$^+$. $R_f$ = 0.45 (10% EtOAc/hexanes). HPLC $R_t$ = 14.5 min.

Compound 2-5a was prepared using Method A: 2,3,5-trichloro-1,4-phenylene bistrimethylsilane (0.25 mmol), TMAF (1.50 mmol) and 1.50 mL CD$_3$OD. 26.6 mg was isolated as a colorless oil (58%).

Analytical data for Compound 2-5a: $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ ppm: 7.45 (s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ ppm 133.4, 133.0, 130.1, 131.0, 130.26, 127.96; Mass calculated for C$_6$HD$_2$ 181.45, Found 181.9 [M]$^+$. $R_f$ = 0.85 (pentane). HPLC $R_t$ = 17.1 min.
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