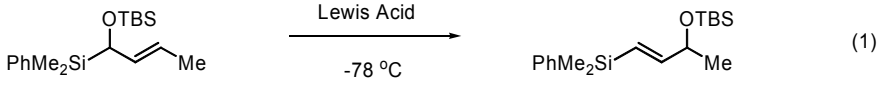
Mechanistic Studies of Allylsilane Rearrangement

Thesis:

The goal of our project is to determine the operating mechanism in the transformation of α-siloxy allylsilanes to vinyl silanes. Elucidating the mechanism will provide valuable information about this rearrangement, which will enable us to fully utilize the synthetic scope of chiral allylsilanes.

Background:

Allylsilanes which possess a siloxy group in the α position have been shown to rearrange under Lewis acid catalysis to afford vinyl silanes (eq 1). To understand this reaction completely, we need to know the exact mechanism by which it occurs. Currently two mechanisms may be postulated for the rearrangement; one involves a concerted pericyclic process and the second involves a stepwise discrete ion formation pathway. Both possibilities will be discussed in this text.



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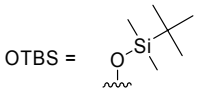
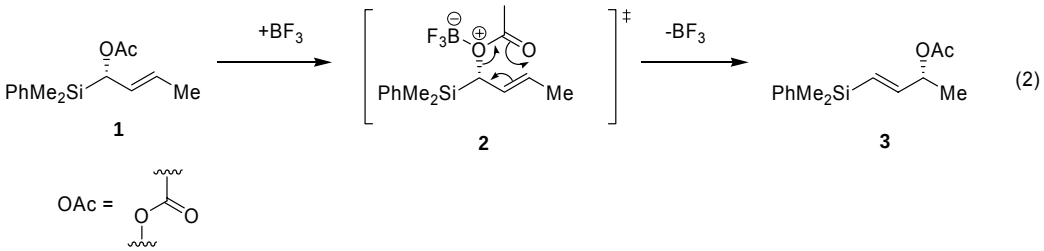
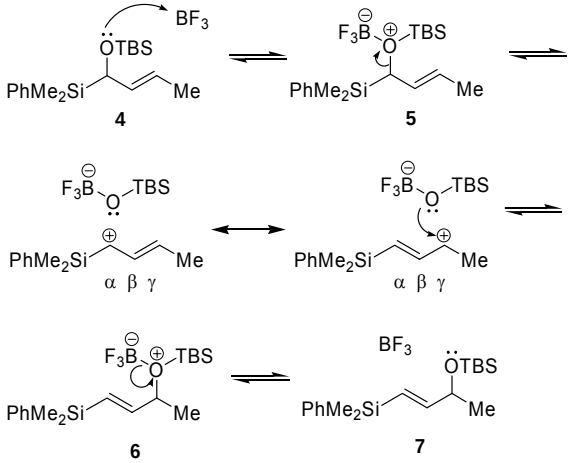


One possible mechanism involves a concerted pericyclic rearrangement of electrons. The fact that similar molecules, like α-acetoxy allylsilane **1,** undergo concerted reactions[1] with boron triflouride (Lewis acid) may suggest that the mechanism for this reaction is concerted and pericyclic (eq 2). Equation 2 shows that if the mechanism is concerted, chirality will be transferred. The net reaction of $\tilde{\alpha}$siloxy allylsilanes is the same as that of α-acetoxy allylsilanes. However, there are important differences between α-acetoxy allylsilanes and $\tilde{\alpha}$siloxy allylsilanes, suggesting that even though the net reaction is the same, the two processes occur by different mechanisms. An α-acetoxy allylsilane has two oxygen atoms: carbonyl and carboxyl oxygen. When the carbonyl oxygen attacks the electrophilic *sp*^{2} carbon, it forms a six-membered ring transition state **2**. The six-membered ring transition state makes it favorable for the α-acetoxy allylsilane to react through a concerted pathway. By contrast, α-siloxy allylsilanes do not have a carbonyl oxygen available for bonding, so they cannot proceed through six-membered ring transition states. For this rearrangement to occur via this mechanism, a strained four membered ring transition state would have to be employed. This transition state would not provide optimal orbital overlap, which makes this pathway unlikely.

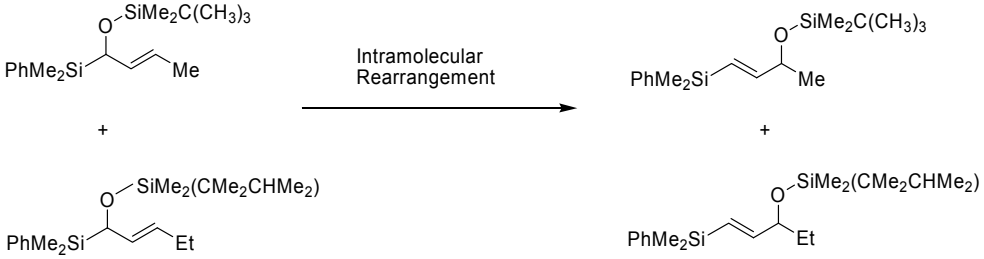


Another possibility for the rearrangement of α-siloxy allylsilanes is that it proceeds through a stepwise mechanism with ion formation. The first step is the formation of a Lewis acid-base complex **5**. The most basic site on the allylsilane is the lone pair electrons on the siloxy oxygen which would complex with the electron deficient boron triflouride. The next step is the dissociation of the complex siloxy group and the formation of ions. Ionization of the molecule forms an allylic carbocation and a complex siloxy anion. After separation, the ions may recombine in two ways. The recombination can take place at the original α-carbon to regenerate starting material or at the respective γ-carbon to afford the vinyl silane. Two modes of recombination are observed because the resonance hybrid of the allylic carbocation has positive charge delocalized over two carbon atoms. In the last step, boron triflouride leaves, and the product vinyl silane is formed. The step-wise mechanism is shown below.



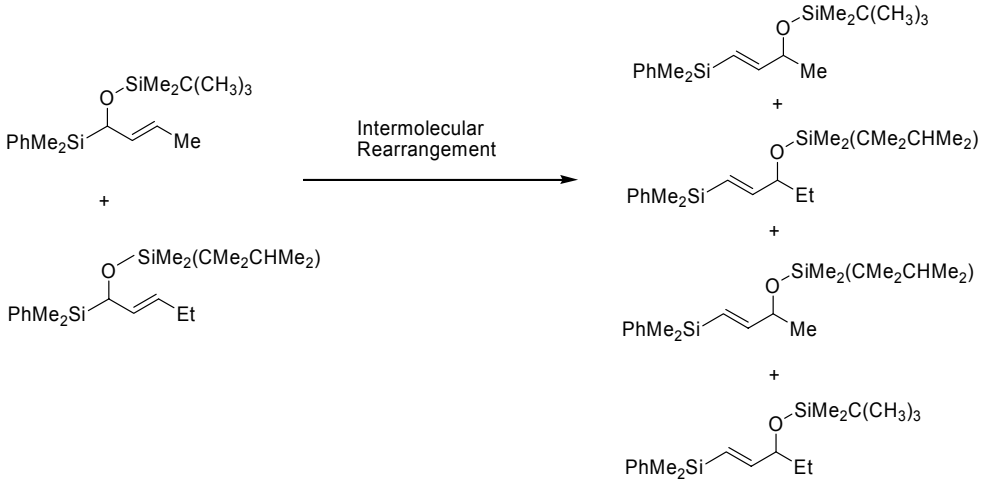
In the stepwise mechanism, the molecule separates into ions, and theoretically, if the ions are completely separate, the reaction should be intermolecular. We set out, based on this rationale, to devise an experiment that would tell us whether the reaction was intermolecular or intramolecular. An intramolecular reaction implies a concerted mechanism, and an intermolecular reaction implies a stepwise mechanism. The experiment we devised is called a "cross-over" or "double-labeling" experiment. The principle of a "cross-over" experiment is to determine whether a reaction is intramolecular or intermolecular by using sets of differentially substituted reactants. If the products contain new combinations of substituents, the reaction is intermolecular, and if not, it is intramolecular. For our experiment, we used two differentially substituted α-siloxy allylsilanes. For an intramolecular rearrangement, we expect to see only two different vinyl silanes, because each allylsilane should only form the corresponding vinyl silane (Scheme 1).

Scheme 1. Intramolecular rearrangement in crossover experiment.



By contrast, in an intermolecular rearrangement, we expect to see four different vinyl silanes, because each combination of ions should produce a different vinyl silane (Scheme 2). After characterizing all possible combinations of allylsilanes and vinyl silanes with gas chromatography, we carried out the reaction and identified the products.

Scheme 2. Intermolecular rearrangement in crossover experiment.



The results of the cross-over experiment were surprising, yet very clear. We obtained only two vinyl silanes in our product, and they corresponded perfectly to the reactant allylsilanes. There was no molecular cross-over. The results of our cross-over experiment clearly show that the reaction is intramolecular. Our discovery implies that the rearrangement is concerted. However, we still cannot discount the possibility of a stepwise mechanism, because the intramolecular reaction may be explained by solvent interactions. Solvent molecules have been shown to surround the solute ions and prevent them from leaving the vicinity of the substrate. A wall of solvent molecules that prevents solute molecules from escaping is called a “solvent cage.” The reaction may be intramolecular because the intermediates are contained by the solvent. Therefore, the cross-over experiment did not conclusively tell us the mechanism of rearrangement, but it did prove that the rearrangement is intramolecular.

Though it did provide valuable information, the cross-over experiment did not disprove either of the possible mechanisms, so we designed a second experiment. There is only one thing that will definitively differentiate the two

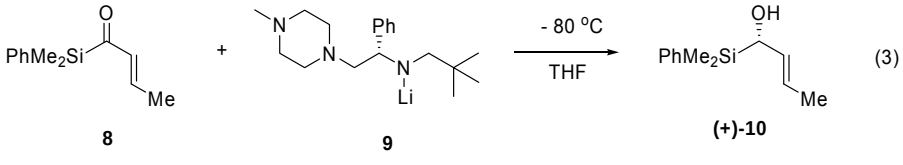
mechanisms: chirality. If the mechanism is concerted and pericyclic, the molecule will have no chance to rearrange its internal structure. Therefore, the stereochemical configuration must remain the same. In a stepwise reaction, formation of ions will cause the molecule to lose chirality. By conducting a stereochemistry experiment, we can determine definitively whether or not the mechanism is concerted.

The objective of our experiment is to synthesize a chiral α-siloxy allylsilane with a high enantiomeric excess, run the rearrangement with boron triflouride, and determine the enantiomeric excess of the product vinyl silane. The chirality of the product will help us determine the mechanism of the reaction. The stepwise mechanism involves the formation of an allylic carbocation and a complex siloxy anion. Free rotation of the allylic carbocation allows the siloxy anion to approach from either side with equal ease. A mixture of enantiomers indicates a loss of enantiomeric excess, which allows us to conclude that the mechanism is stepwise. Conversely, if chirality is transferred, it suggests a concerted mechanism.

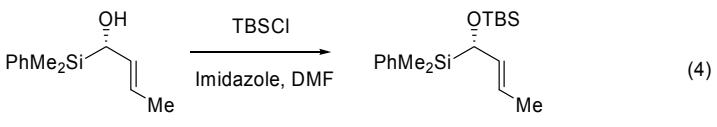
The purpose of this project is to determine the mechanism of the rearrangement of α-siloxy allylsilanes to vinyl silanes. Understanding this reaction will allow us to understand similar reactions, and it will thus give us a general knowledge about the reactions of chiral silanes. Reactions of chiral compounds are extremely useful to synthetic chemists, especially for medicinal purposes. Therefore, new knowledge about the reactions of chiral silanes could significantly benefit the field of medicinal science.

Approach and Methodology:

Our first and primary concern is to synthesize the chiral α-siloxy allylsilane from reagents that are commercially available. We plan on utilizing recent methodology developed by Takeda and coworkers in which they employ chiral lithium amides in asymmetric reductions of acylsilanes[2] (eq 3). The chiral lithium amide **9** provides a source of chirality for the desired α-siloxy allylsilane **11**. The chiral carbon in the reactant lithium amide creates a chiral carbon in the product allylsilane. The other reactant for this transformation,α,β-unsaturated acylsilane **8**, is important because it has a carbonyl carbon that can be reduced asymmetrically by the lithium amide. When an acylsilane is reduced, it affords α-hydroxy silane **10**, which is subsequently silylated to afford the desired α-siloxy allylsilane **11** (eq 4).

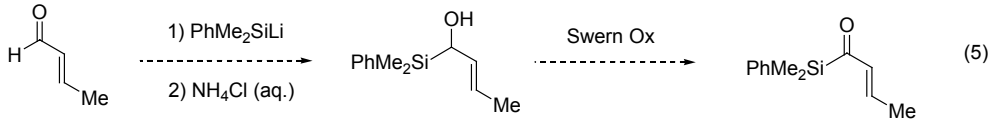


8 **9** **(+)-10**



(+)-10 **11**

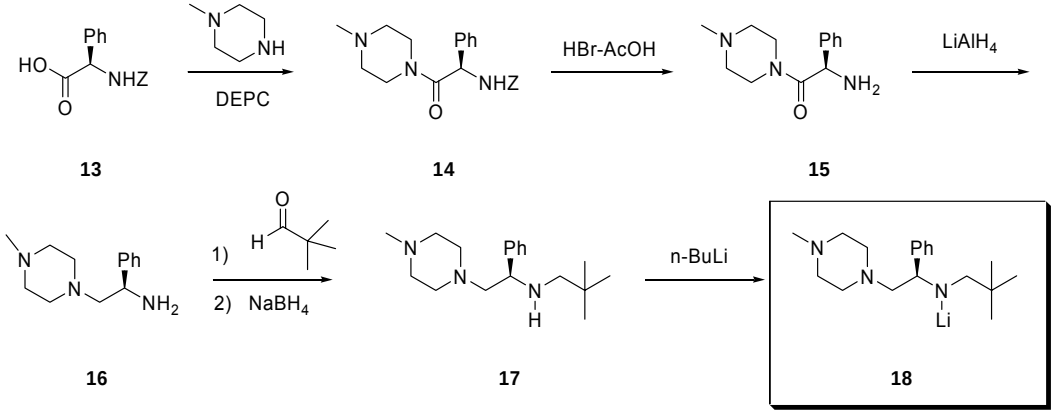
The chiral lithium amide and α,β-unsaturated acylsilane are not commercially available, and must be synthesized in the laboratory. The acylsilane can by synthesized in two steps from the commercially available crotonaldehyde **12** (eq. 5). Nucleophilic addition of the silyl lithium reagent to the crotonaldehyde affords an alkoxide which is subsequently trapped with aqueous NH_4Cl to afford α-hydroxy allylsilane **10**. The second step is the oxidation of the α-hydroxy silane to the corresponding α,β-unsaturated acylsilane **8**, using Swern conditions. The α-hydroxy allylsilane cannot be oxidized by using conventional methods, Manganese Dioxide or any variety of chromium-based reagents, because the resulting acylsilane is very sensitive and harsh conditions decompose it. We oxidize it with a mild method called "Swern Oxidation," which involves the use of alkoxysulfonium species[3].



12 **10** **8**

Chiral lithium amides can be prepared in six steps[4] from the commercially available amino acid phenylglycine **13** (Scheme 3). The first step is the coupling of 1-methylpiperazine with amino acid **13** utilizing coupling agent diethylphosphorocyanidate (DEPC). The net reaction replaces a hydroxyl group with 1-methylpiperazine. Next we remove the amino protecting group substituent, and the piperazine-substituted carbonyl compound **15** is ready for reduction. Complete reduction of the carbonyl compound is carried out with Lithium Aluminum Hydride ($LiAlH_4$), transforming the amide to amine **16**. The mechanism for reduction of an amide with $LiAlH_4$ is widely known and relatively simple to understand. After the amide is reduced to an amine, the primary amine formed must be converted into a secondary amine. This operation is called "reductive amination," because it reduces the aldehyde and converts it to an imide. Subsequent addition of sodium borohydride converts the imide to secondary amine **17**. The secondary amine can then be converted to a lithium amide by adding butyl lithium. The product of this last step is the desired compound, chiral lithium amide **18**.

Scheme 3. Synthesis of chiral lithium amide **18**.



13 **14** **15** **16** **17** **18**

After each step in the synthesis, we will verify that we have synthesized the correct compound using mass spectrometry, infrared spectroscopy, and ^{1}H NMR spectroscopy. With our primary reactant, the α-siloxy allylsilane **11**, we will use High-Performance Liquid Chromatography (HPLC) to determine the enantiomeric excess. If the enantiomeric purity is sufficiently high, we can move on to the next step.

We are then ready to run our primary reaction: the reaction of the α-siloxy allylsilane with boron triflouride in diethyl ether. The reaction may be carried out at a temperature of -78C and it will take approximately three hours to complete. The product obtained will be a vinyl silane with unknown chirality. We will test the product vinyl silane for enantiomeric purity. Using this data, we will determine which mechanism is operating. If the product has lost chirality, we can conclude the mechanism at work is stepwise and involves discrete formation of ions. If the product retains chirality, we can conclude the actual mechanism is a concerted process.

Responsibilities:

My responsibilities will include: synthesis of each intermediate target from reagents that are commercially available; verification of the identity of each intermediate compound by mass spectrometry, infrared spectroscopy, and ^{1}H NMR spectroscopy; synthesis and evaluation of the reactant allylsilane for chirality, stereochemistry, and enantiomeric excess; completion of the intramolecular reaction of the allylsilane with boron triflouride in diethyl ether; examination of the product vinyl silane using mass spectrometry, infrared spectroscopy, ^{1}H NMR spectroscopy, and HPLC; data entry and graphing; examination of data and assessment of results. Ultimately, I will be responsible for reaching a justifiable conclusion about the validity of our hypothesis and explaining why it is or isn't correct. After the experiment is done, I will be responsible for reporting my findings in a final report that will include my objective, procedures, results, and conclusion. I will be working under the supervision of 3rd year graduate student Antonio Romero. I will regularly check in and discuss my progress with Dr. Keith Woerpel.

Timeline:

Week Number	Task to be completed
1 & 2	Synthesize an α,β-unsaturated acylsilane
3 & 4	Synthesize a chiral lithium amide
5	Synthesize an α-siloxy allylsilane
6	Test reactant stereochemistry and %ee
6	Run reaction with boron triflouride in diethyl ether

7 & 8	Identify product using MS, IR, and ^{1}HNMR; test stereochemistry & %ee
9 & 10	Analyze data; draw conclusions; write final report

References:

(1) Panek, J. S.; Sparks, M. A. *J. Org. Chem;* **1990;** *55*, 5564-5566.

(2) Koizumi, T.; Ohnishi, Y.; Takeda, K. *Org. Lett;* **1999;** *1*, 237-239.

(3) Danheiser, R. L.; Fink, D. M.; Okano, K.; Tsai, Y.; Szczepanski, S. W. *J. Org. Chem;* **1985;** *50*, 5393-5396.

(4) Shirai, R.; Aoki, K.; Sato, D.; Kim, H.; Murakata, M.; Yasukata, T.; Koga, K. *Chem. Pharm. Bull;* **1994;** *42*, 690-693.