SYNTHETIC METHODS IN ORGANIC AND SUPRAMOLECULAR CHEMISTRY

by

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Submitted to the Graduate Faculty of

Arts and Sciences in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2005

UNIVERSITY OF PITTSBURGH

FACULTY OF ARTS AND SCIENCES

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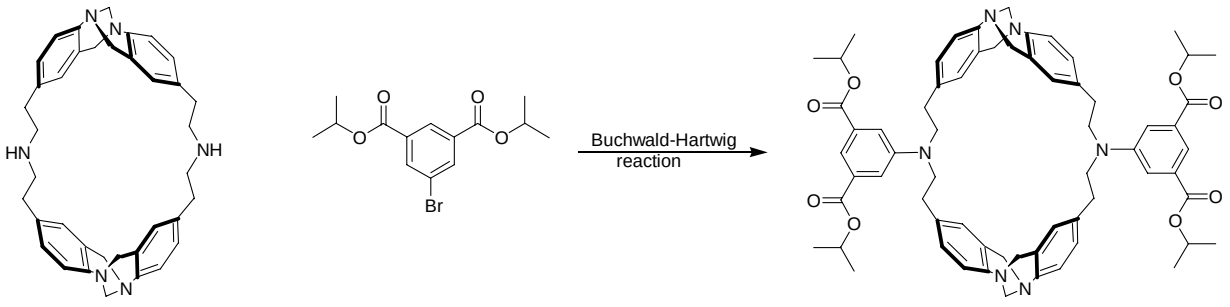
SYNTHETIC METHODS IN ORGANIC AND SUPRAMOLECULAR CHEMISTRY

Colleen Nicola Scott, PhD

University of Pittsburgh, 2005

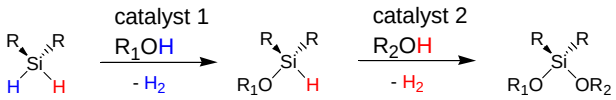
The synthesis of cyclophane **17** (9,10,11,12,26,27,28,29-octahydro-3H,8H,16H,20H,25H, 33H-4,7:21,24- dimetheno -13,19,15:30,2,32-di[1]propane[1]yl[3]ylidine-1H,18H-dipyrimidino [1,2-a;1',6'-o] [1,8,15,22]tetraazacyclo-octacosine) is described. Both isomers of cyclophane **17** were synthesized over nine steps in 46 % overall yield from readily available starting materials. We designed and synthesized a side group for attachment to cyclophane **17**, which we wish to use for the directed-complexation of the cyclophane with a specified aromatic guest. We had hoped to use the Buchwald-Hartwig reaction to attach this side arm to the secondary amines of **17**, but despite our many efforts we were unable to achieve this goal in a reproducible manner.



17 **38** **41a**

We have developed a method which allows the stepwise construction of silyl ketals; silyl ketals may be used as reactive intermediates in the construction of complex molecules. We synthesized silyl ketals **3a – 3i**, **5a – 5f** and **7a – 7e** in moderate to high yields using a combination of $Rh_2(OAc)_4$ followed by 10 % Pd/C or $Mn(CO)_5Br$ as catalysts. We have shown

that diisopropylsilane was crucial to the success of this process and that employing (+)-ethyl lactate as the alcohol in the first step leads to a faster and more efficient reaction in the second step. Silyl ketals **7a**, **7b** and **7d** were used to show that intramolecular radical translocation beyond the 1,5 atom was not only feasible, but efficient.



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PREFACE

I thank my Lord and Savior Jesus Christ for giving me health and strength to complete my Ph.D. degree. I am eternally grateful to you for the things you have allowed me to endure through out these years. Thank you for all the things you have taught me; especially, to have patience and perseverance when things are not going well. I have developed the discipline to endure the rough times and the attitude to enjoy the good times. I have learned that there is always a light at the end of the tunnel, no matter the length of the tunnel. I would like to thank my church family at Pentecostal Temple C.O.G.I.C. for all your prayers and encouragements.

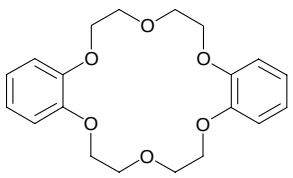
I would like to thank Professor Craig Wilcox for teaching me the skills to become a good scientist. I thank him for having patience for me when I was not patient with myself. Professor Wilcox, I really appreciate all the advice you have given me through out the years. I thank you for allowing me to pursue my dream of becoming an Olympian. I thank all the members of the Wilcox's group both past and present for all your support. I thank all the faculty and staff in the chemistry department who have helped me over the years to achieve my goal. Fran, I would like to thank you for being there to answer my questions and for keeping me on track.

To my family and friends, thank you for all your support and for understanding when I could not be there for you. I love you all. Last but certainly not least, to my dear husband Andre, I love you. Thank you for being patient with me while I pursued this road that has chosen me. I thank you for all your encouragements and for being a wonderful husband.

1. Design and Synthesis of a New Water-Soluble Cyclophane

1.1. Introduction

Molecular recognition is defined as the study of poly-nuclear entities and assemblies of supramolecular complexes formed between two or more intended chemical species which are held together by non-covalent forces.[1] Pioneers in this field include Pedersen,[2a,2b] Lehn[2c,2d] and Cram,[2e,2f] who were awarded the 1987 Nobel Prize in chemistry. Their work has led to tremendous developments in the area of host-guest complexation and has inspired others in this field. Charles Pedersen discovered crown ethers in 1967 and established the first neutral synthetic compound capable of complexing alkali cations (**1**).[2a] Lehn's work focused on macrobicyclic polyethers as ligands that would bind ions, forming inclusion complexes called cryptands.[2c] Compound **2** is one of the many cryptands made in Lehn's group. His work also included the binding of tetrahedral guests (NH_4^+), the synthesis of co-receptor molecules with multiple recognition sites, and the study of cooperative binding, catalysts and transport. Cram's work highlighted in the development of two of the most fundamental theories of molecular recognition.[3] The theories of complementarity and preorganization constitute the basis of host-guest chemistry. Complementarity is described by Cram as "the ability of the host's binding site to contact and attract the binding site of the guest without generating internal strains or strong non-bonded repulsion." This concept is important because complexation can only



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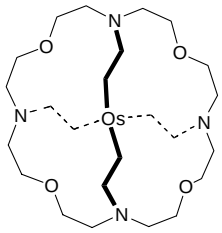

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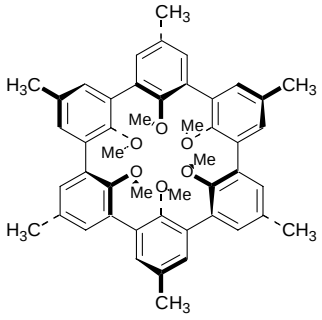
compete with solvation if the binding forces of the complex (the energy for complexation) act cooperatively, and are larger than the energy for solvation. This is similar to the lock and key principle of enzyme recognition. Preorganization governs association energy or binding power. It is described by Cram as "the more highly organized the host and guest are for binding and the lower their solvation prior to their complexation, the greater the stability of the complex formed".[3] If the host is not preorganized, then structural organization must occur during complexation, and this can cost part of or all of the binding free energy. Cram et al. calculated the difference in the association constants (K_as) for a host that is preorganized compared with one that was not.[3] For example, the spherand **3** had a K_a value that is 10^{10} times greater than it's open chain counterpart (**4)** for the same guest. The difference is credited to the preorganization of **3** for binding of the cation. Spherand **3** is presumed to have only one conformation in solution, where as podand **4** is presumed to have many. The lower binding energy for compound **4** is due to a free energy cost for the organization into its binding conformation, where as in compound **3** this cost was paid during the synthesis.



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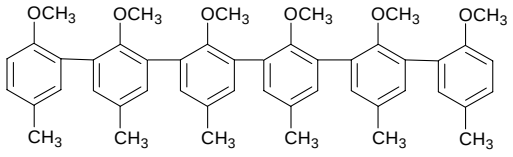

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The forces that drive molecular recognition are made up of a variety of low-energy, non-covalent interactions. These include hydrogen bonding, electrostatic interaction (ion pairing),

metal ion to ligand attraction, π-acid to π-base attraction and van der Waals forces.[3b] The contribution of individual forces to the total interaction energy varies from complex to complex. For example, in the complexation of an apolar substrate into a lipophilic cavity under aqueous conditions, the predominant host-guest interactions are van der Waals forces. Another strong influence on binding is the "Hydrophobic Effect". It is defined by Breslow as "the lowering of the free energy of the system when non-polar molecules or segments cluster together in water so as to minimize the hydrocarbon-water interface."[4] These non-covalent forces are responsible for selectivity and specificity in the binding.

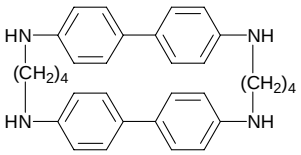
Molecular recognition is a very important process in biological processes. These processes include enzymic catalysis and inhibition, immunological response, storage and retrieval of genetic information, replication, regulatory function, drug action and ion transport.[5] Proteins such as enzymes, antibodies, intracellular and extracellular transport molecules use molecular recognition events to carry out their functions. Receptor sites on proteins and in an enzyme's active site have a precise shape that interacts specifically and selectively with their substrates. Because of their selectivity and specificity, the active sites of proteins have interested scientists all over the world. Most efforts in molecular recognition are concentrated on design and synthesis of systems capable of mimicking biological systems.

Proteins are very large molecules with complex structures that make them difficult to study. Because of their complexity, smaller and simpler molecules are required to effectively study the driving forces behind molecular recognition. These compounds have to be carefully designed to include or resemble that portion of the protein that is responsible for its activity. Cyclophanes are among many compounds used to study the driving forces in molecular recognition.

Cyclophanes are described as macrocyclic compounds with aromatic rings bridged by aliphatic side chains. They contain an open cavity with lipophilic walls in order to help in the binding of apolar guests. The aromatic rings have multiple functions. The main function is to provide a rigid, and organized binding site. Due to the high polarizability of the aromatic rings, they can interact with aromatic guests to stabilize the complex through van der Waals interactions. The aromatic rings also provide a site for attachment of functional groups. As early as 1937, Lüttringhaus synthesized cyclophanes such as **5** and called them "ansa compounds".[6] In the early 1950's, Cram and Steinberg reported the synthesis of [2.2] paracyclophane **6** in which two benzene rings are held face to face by methylene bridges.[7] Independently, Brown and

5

6



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Farthing also reported the synthesis of compound **6**.[8] Advancements in cyclophane receptor chemistry came in 1955, when Stetter and Roos recognized the ability of cyclophanes to form inclusion complexes. They reported what they thought to be cavity inclusion complexation of benzene in cyclophane **7**.[9] This opened the door to the study of inclusion complexation with cyclophanes. However, in the early 1980's when the crystal structure of Stetter's "complex" was solved it was shown that the benzene was located between two host molecules and not inside the

cavity of the host as initially thought.[10] There was now an immense need for chemists to provide proof of inclusion of the aromatic guest inside the cavity of the host and evidence against simple stacking. Whitlock et al. showed an example of such a case when they studied the binding of a series of naphthalenophanes with guests such as 8-phenylamino-1 naphthalenesulfonate (1,8 ANS) and 2-naphthalenesulfonate.[11] The experimental evidence provided by both optical and ^{1}H NMR spectroscopy was inconclusive due to the formation of exo-cavity π–π stacking interactions between receptor and guest, and also strong aggregation of the receptor (Figure 1).

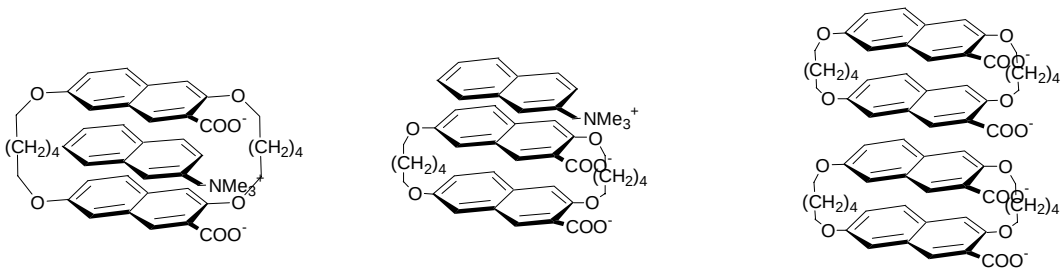


Figure 1. Competing association events in solution of hosts and guests with large apolar surfaces capable of forming intra-and-extra-cavity π-stacking interactions.

In 1980 Koga provided the first unambiguous evidence for inclusion complexation of an apolar guest in a synthetic host in both the solid state and aqueous media.[12] He provided a crystal structure of the complexation of **8** with durene under acidic conditions (Figure 2). The protonated ammonium groups provided solubility in water, and also stabilized the cavity via ion-dipole interactions. The ^{1}H NMR studies indicated a 1:1 inclusion complex with a K_a of 2.8 x 10^3 L/mol.[12b] Calculation of the K_a value was based on changes in the chemical shift of the protons of both the host and guest. These changes are a result of the position of the protons of both host and guest within the shielding or deshielding regions of the aromatic rings in the complex. Koga's work was important for two reasons: the crystal structure showed the inclusion

of an apolar guest in a synthetic host, and he established ^{1}H NMR spectroscopy as a useful method for studying inclusion complexation in solution.

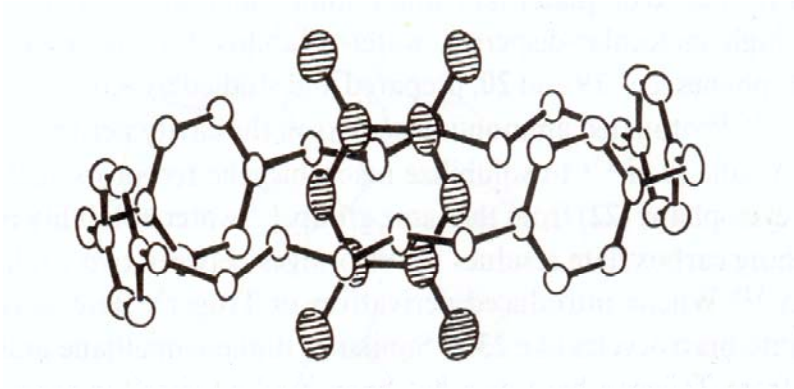
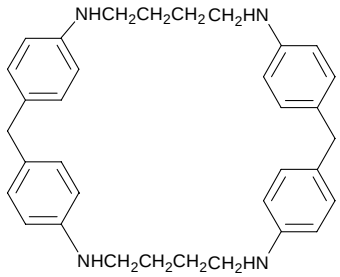


Figure 2. X-ray structure of Koga's cyclophane **8** showing inclusion complexation with durene.

New developments in cyclophane design came from improvements to Koga's cyclophane **8**. Koga synthesized a variety of cyclophane hosts using the diphenylmethane skeleton.[13] He introduced water solubility to host **8** by protonating the nitrogens, but this required that all binding studies be conducted at pH < 2 rather than at physiological pH. Schneider also studied the same cyclophanes as Koga, except he used quaternized nitrogen groups (**9**) in place of protonated ones, allowing binding studies to be done at physiological pH.[14]



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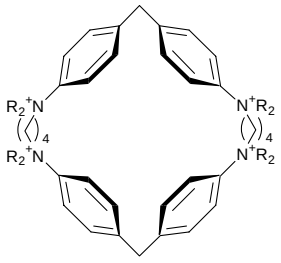
Another way of introducing water solubility was shown by Vögtle et al. and others.[15] They attained water solubility for their hosts by attaching ionizable carboxylic groups. While water solubility is important, it was thought that having the solvated charges in the periphery of the binding site reduces the driving forces for complexation. However, Schneider found that having the charges at the cavity of the host actually stabilized the complexes formed with electron rich arenes and anionic guests.[14] This stabilization resulted from donor-acceptor and



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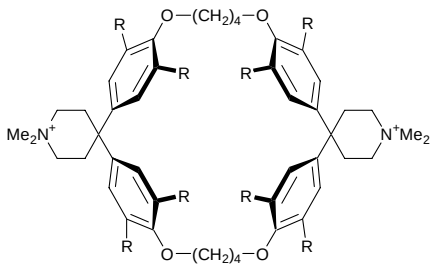

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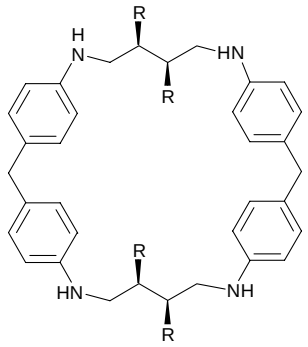
ion-dipole interactions between the host and the guest. François Diederich also addressed the issue of ionic centers at the periphery of the cavity by removing the charges to a remote position.[16] He introduced the spiropiperidium group as the water-soluble entity on the diphenylmethane skeleton (**10**). This change improved the hydrophobic nature of the cavity allowing a more reliable investigation into the nature and strengths of the binding interaction between host and guest. Diederich did extensive thermodynamics studies on these compounds to better understand whether it was enthalpic or entropic forces that were responsible for binding.[16b] The studies revealed surprising results in that the energy of complexation came from favorable enthalpic and not entropic contributions as described in the hydrophobic effect. Actually it was found that entropic factors reduce the free energy of complexation.

Another major improvement in cyclophane design was also made by Koga who introduced chirality to the cavity.[17] This was done by replacing the achiral methylene groups with a four-carbon chain derived from L-tartaric acid (**11**). Data from ^{1}H NMR showed that there was a slight difference in binding of the host to R- and S- isomers of the same guest. This was the first example of a synthetic host showing chiral recognition in water.



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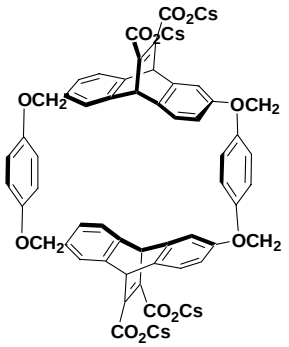
Cyclophanes using the diphenylmethane unit was a good foundation; however because of the floppiness of the diphenylmethane unit, it was thought that there might be other conformations during binding which can lower the free energy of association. Dougherty's[15b] and Wilcox's[18] group addressed this issue of rigidity. Dougherty introduced a bridged anthracene unit with solubilizing carboxylic groups remote from the cavity (**12**). The increased rigidity of the anthracene units gave rise to a more highly preorganized binding site. It also had a larger cavity than the previous diphenylmethane macrocycle, allowing binding of larger guest such as adamantane derivatives. Wilcox also opted for a more rigid spacer and introduced derivatives of the dibenzodiazocine unit commonly known as Tröger's Base to replace one of the diphenylmethane units (**13-16**).



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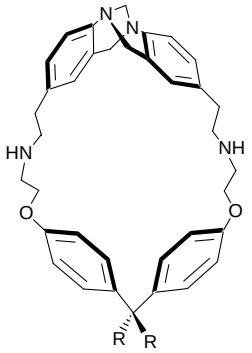
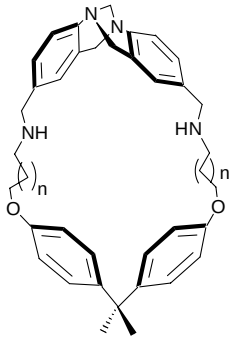


13 R = CH3
14 R = H



15 n = 0
16 n = 1

Tröger's base was first synthesized in 1887 and has been widely used over the years.[19] It can be prepared by acid-catalyzed condensation between formaldehyde and aniline derivatives.[20] It is C_2 symmetric and is chiral due to the inability of the nitrogens to invert. *R* and *S* enantiomers (Figure 3) were resolved in 1944 by Prelog.[21] Wilcox reported the first X-ray structure of Tröger's base in 1985 and it was shown to have substantial folding with dihedral angles between the planes of the aromatic rings of 92.8-97.4 depending on substituents.[22]

Tröger's base was incorporated into the cyclophane structure as a building block to add rigidity to the host. Each host varies in some small structural changes, such as varying the length of the linker and changing the attachments.[23] For example, host **13** has diphenylpropane and host **14** has diphenylmethane linked by six atoms to the dibenzodiazomethane unit. Host **15** and **16** are both benzyl amines with host **16** having one more atom in the linker chain than host **15**.

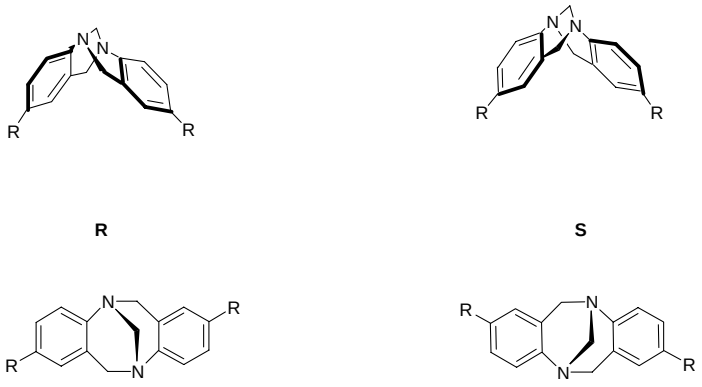


Figure 3. *R* and *S* isomer of Tröger's base.

These hosts were used to study inclusion complexation with aromatic guests in aqueous solution.[23] The differences in binding between the phenethylamines and the benzylamines are shown in Table 1. Host **13** and **14** bound aromatic guests better than host **15** and **16**. It is possible that the ammonium groups of the benzyl amine hosts are directed into the cavity; this reduces its hydrophobicity and results in a low binding constant. There was also a strong

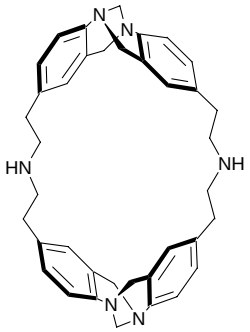
Table 1. Binding Data for Hosts 13-17

	K_a (M^{-1}) /-ΔG (kcal/mol)[#]				
Guest*	**13**	**14**	**15**	**16**	**17**
2,4,6-trimethylphenol	71.4/2.5	100/2.7	12.5/1.5	14.3/1.6	650/3.83
4-toluenesulfonic acid	250/3.2	333/3.4	55/3.4	67/2.5	1020
1,3-dihydroxynaphthalene		333/3.4			4695/4.97
4-methylphenol	43/2.2	52/2.3	11/1.4	16/1.7	
4-cyanophenol	67/2.5	77/2.9	50/2.3	30/2.0	

Guest* concentration was 3-4 mM. [#]Temperature 298 K, D_2O, pD 1.9, 0.1 M KCl-DCl buffer.

preference for the 4-toluenesulfonic acid. This can be explained by the electrostatic charge-charge attraction between anionic guests and protonated amines of the host. This was observed before by Koga,[13c] Schneider[24a] and Diederich.[24b] The small preference of 4-cyanophenol over 4-methylphenol, maybe a result of donor-acceptor interaction between the aromatic rings of the host and the electron deficient guest. This type of interaction was observed by Schneider,[25a,25b] Diederich[16b,25c] and Dougherty.[15b]

Wilcox took this cyclophane to the next level by introducing a second Tröger's base unit to replace the diphenylmethane (**17**).[26] It was hoped that added rigidity would lead to a more preorganized host, which was expected to give improved binding. Host **17** exists as diastereomers because of two chiral molecules being brought together. One of the diastereomers is the meso isomer because the two Tröger's bases that come together are *R* and *S*; the other diastereomer is the d/l isomer because the two Tröger's bases that come together are either *R*, *R* or *S*, *S*. Binding study data for host **17** (Table 1) indicated that it bound better to aromatic guest over the previous hosts, by more than 1 kcal/mol. Wilcox et al. was able to obtain a crystal structure of the meso isomer with xylene (Figure 4).[26] The X-ray structure shows π-stacking interaction between the aromatic groups and an edge to face interaction between the hydrogen of the xylene and the phenyl ring. The improved binding, which was thought to be a result of increased rigidity and a more organized cavity, was good news. Other macrocycles were prepared combining the dibenzodiazocine unit with the ethenoanthracene unit. This host binds aliphatic guests selectively over aromatic ones (**18**).[23,27] Host **17** remains the best host for binding aromatic guest.



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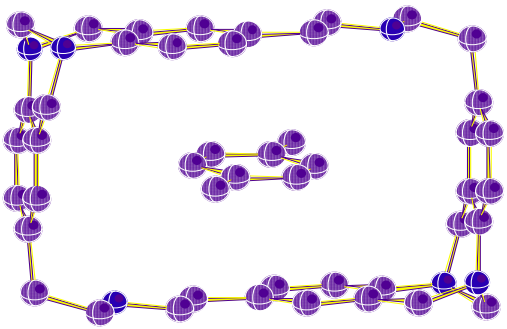
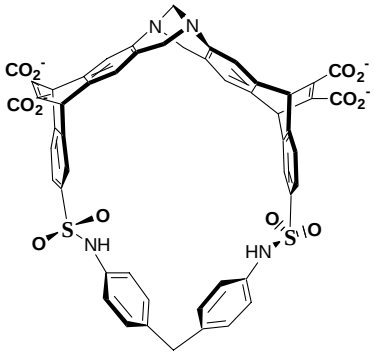


Figure 4. Crystal structure of **17** with xylene.



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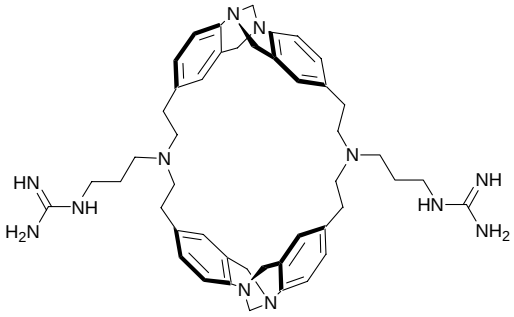
With the increased ability to bind aromatic guests, host **17** was the cyclophane of choice for attaching side arms with different functionalities that can be used to test ideas of biological interest. One such side arm was a three-carbon guanidinium group (**19**) that was used to test the binding to phosphotyrosine, which is a significant target in biological systems.[28] Although this arm was floppy, it provided water solubility in the protonated guanidinium groups positioned away from the cavity. This host showed improved binding to aromatic guests, including those with anionic phosphate groups. No significant binding occurred with the desired guest, phosphotyrosine.



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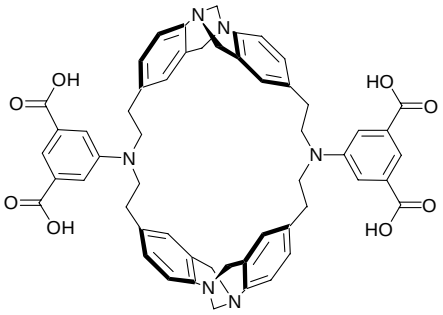
Attachment of a rigid arm to the cyclophane **17** in the form of a functionalized aromatic ring has some advantages (**20**). A more rigid arm is predicted to bring more preorganization to the molecule, which may improve binding. The side arm is designed to contain carboxylic groups to provide water solubility at neutral pH. Host **20** can be functionalized with chiral or phosphate recognition elements to be used accordingly. It could also be of biological importance as a drug delivery agent in binding biological amines such as L-Dopa (**21**), dopamine (**22**) and serotonin (**23**).



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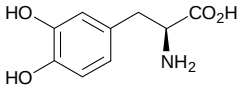

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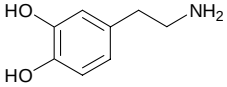

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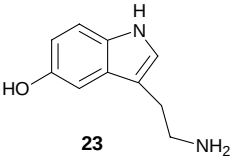
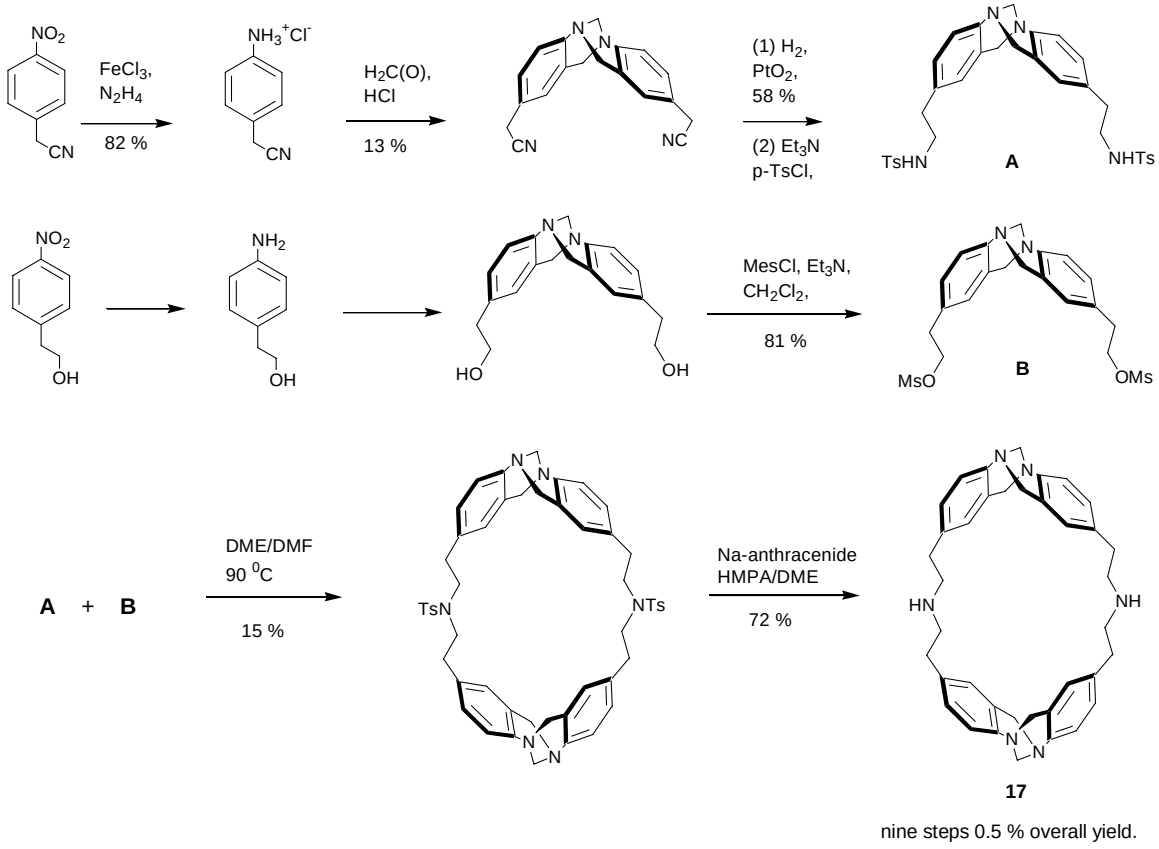


23

Although host **17** was good for binding aromatic guests and to attach side arms for directed binding, there were problems with synthesizing this compound. The goals of this project are to optimize the synthesis of host **17**, and attach rigid arms with ionizable carboxylic groups for water solubility. This new host can be used to investigate the binding of aromatic guests at physiological pH.

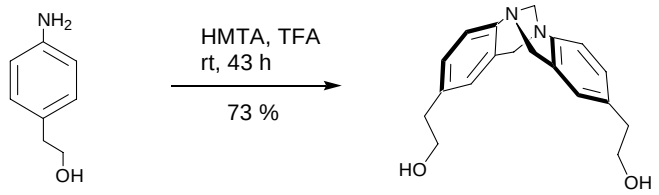
1.2. Synthesis of the Macrocyclic Portion of Host

Although there were several syntheses of host **17**, the yields were often low and the synthetic steps were irreproducible. The first synthesis of host **17** was pursued by Marlon Cowart.[26b] A convergent pathway in which two Tröger's base halves were coupled in the macrocyclic step was used (Scheme 1). There were problems associated with this synthesis; the two Tröger's base pieces were obtained from two different precursors, the yields in the Tröger's base formation and macrocyclization step were low, and the deprotection step was irreproducible.



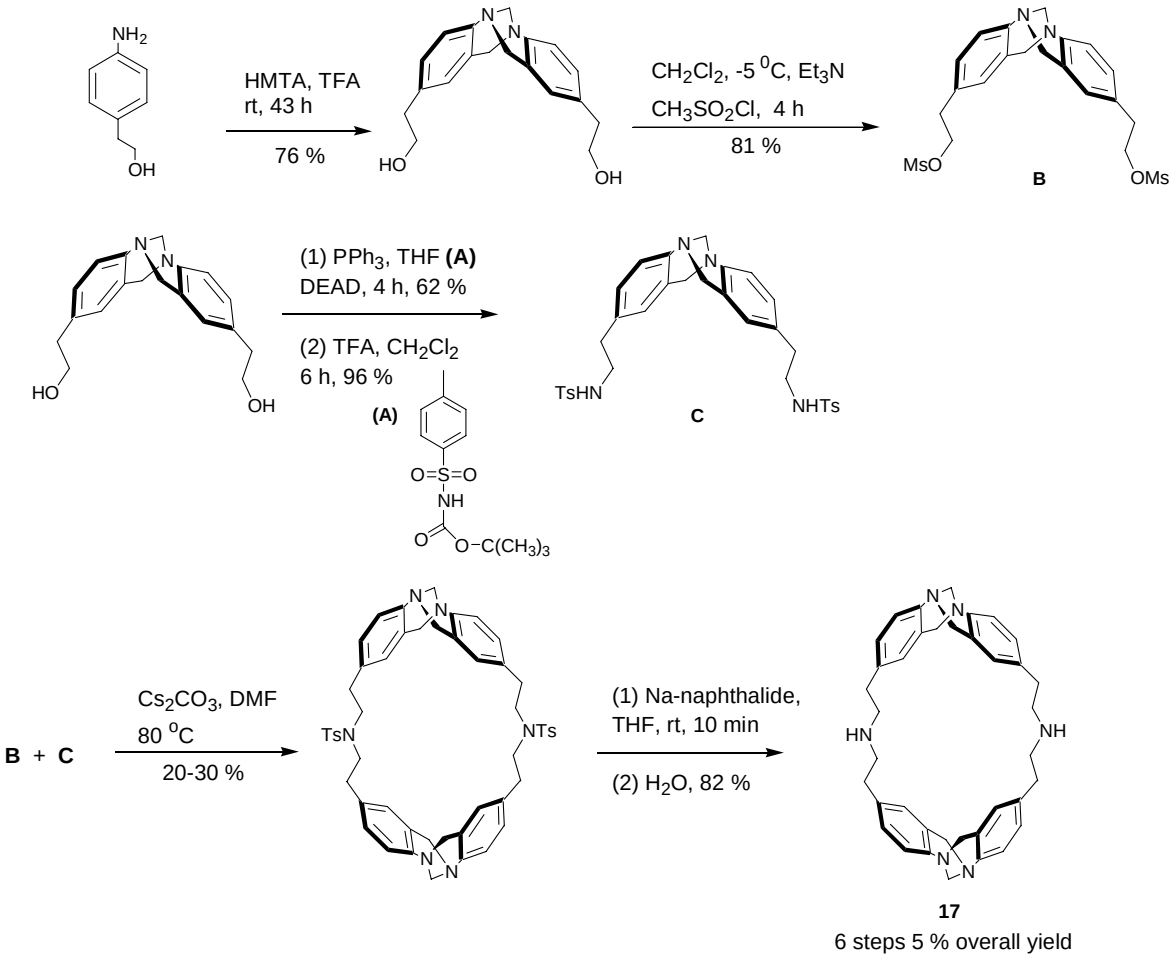
Scheme 1. Cowart's synthesis

Frank Zawacki improved the synthesis by making some strategic changes.[29] The synthesis of the Tröger's base was improved by using Johnson's method of hexamethylenetetraamine (HMTA) and trifluoroacetic acid (TFA) (Scheme 2).[29] Another valuable change was achieved by synthesizing the two Tröger's base halves that are required for the macrocyclization step, from a common precursor (Scheme 3). The challenges that continued to plague the synthesis were the macrocyclization step and the deprotection step. Zawacki discovered that the product from the deprotection of the tosylamine using sodium anthracenide was moisture and air sensitive, and mono-detosylation occurred. Zawacki addressed this problem by using a stronger reducing agent (sodium naphthalide), which was less air sensitive. In this approach the mono-tosyl compound was no longer observed. The strong reducing agent presented another problem; it reduces other parts of the molecule making the reaction sensitive to variation in time and temperature. Zawacki improved the synthesis of **17** to six steps in 5 % overall yield from Cowart's synthesis of nine steps in 0.5 % overall yield.



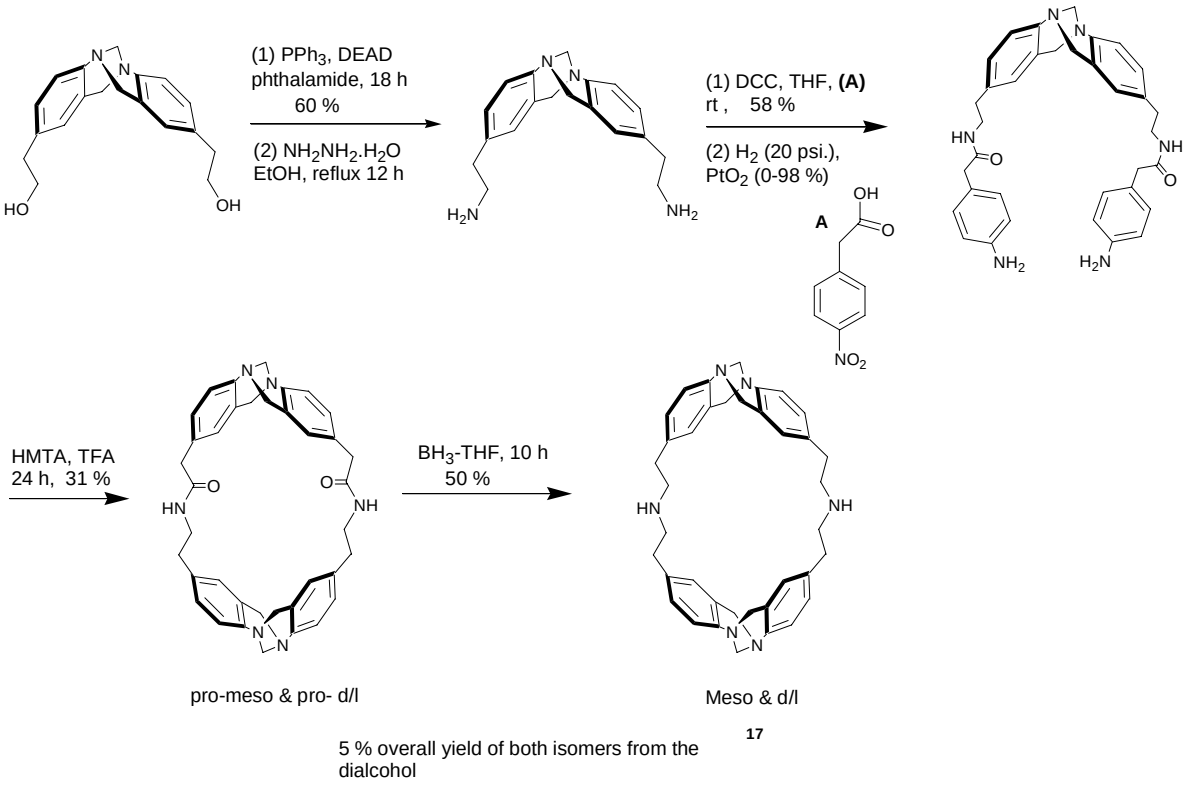
Scheme 2. Johnson's method.

Qingwu Jin repeated Zawacki's synthesis but the overall yields to the macrocycle were too low to continue further studies.[30] Jin developed another route that closed the macrocycle via Tröger's base formation (Scheme 4). The Tröger's base diol was used as a starting material.



Scheme 3. Zawacki's synthesis.

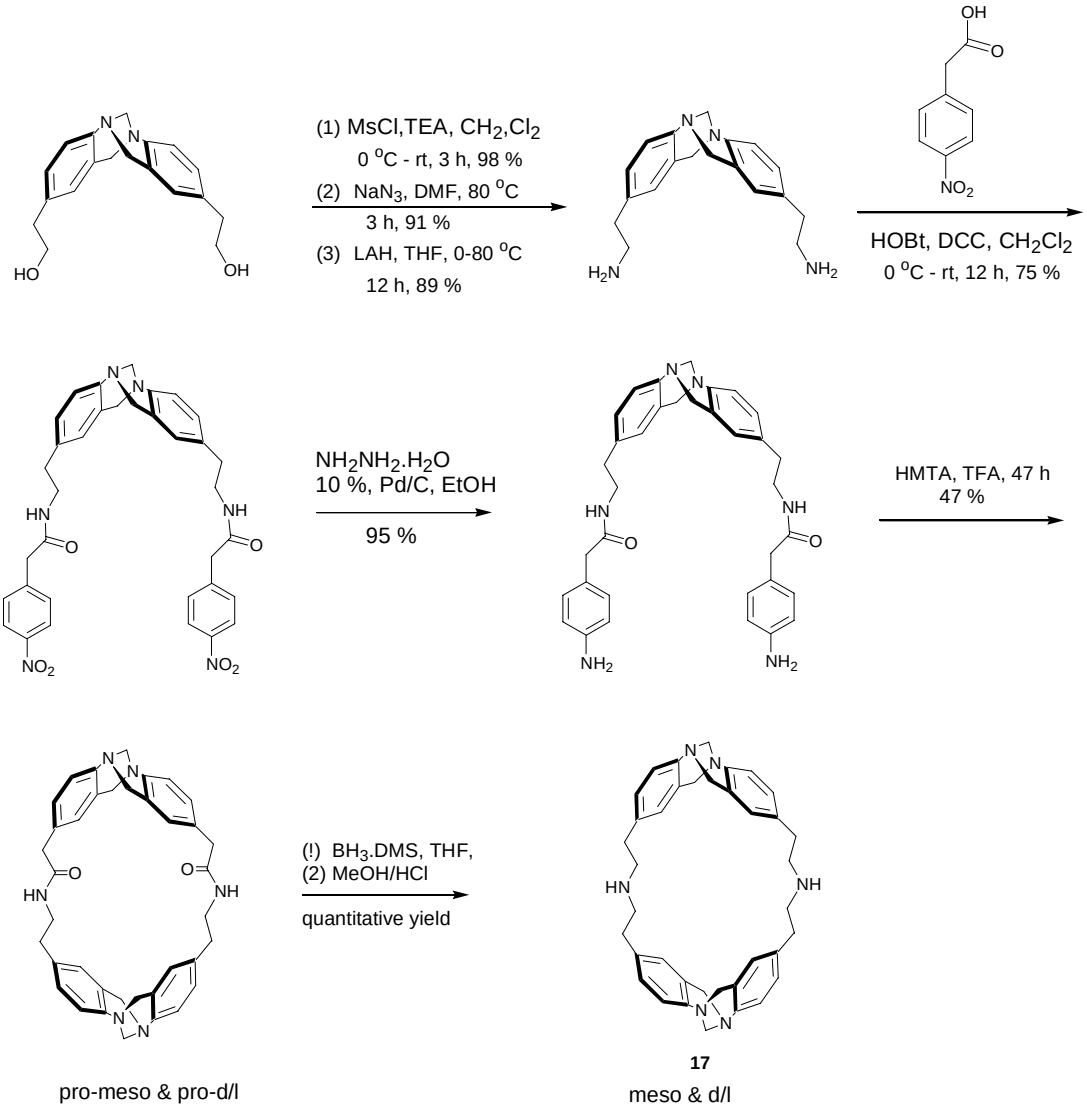
It was converted to the phthalimide via a Mitsunobu reaction, reduced to the amine, and the amine was coupled with *p*-nitrophenylacetic acid to give the precursor to the macrocycle. Macrocylization was done via Tröger's base formation using Johnson's method, which resulted in two isomers of the amide macrocycle. These were separated and reduced to give the cyclophane host. This was the first time two diastereomers were observed in these syntheses and the separation of these diastereomers was very difficult.



Scheme 4. Jin's synthesis

In reproducing Jin's synthesis, Janet Asper came across some difficult steps.28 Apart from the low yields in the macrocyclization step, there were purification problems with the Mitsunobu reaction and low solubility of the starting material in the dicyclohexylcarbodiimide (DCC) coupling step. Asper developed a new route to the Tröger's base diamine. This route, though longer, is more traditional and involves functional group manipulation (Scheme 5). The Tröger's base diol was converted to the mesylate, then to the azide, followed by reduction to the amine. This afforded the amine in 83% overall yield in three steps. The coupling of the amine with *p*-nitrophenylacetic acid was optimized using DCC, HOBt in CH_2Cl_2 to give 75% yield of the product. The reduction of the nitro group by transfer hydrogenation over palladium on carbon, using either ammonium formate or hydrazine as the hydrogen source gave improved

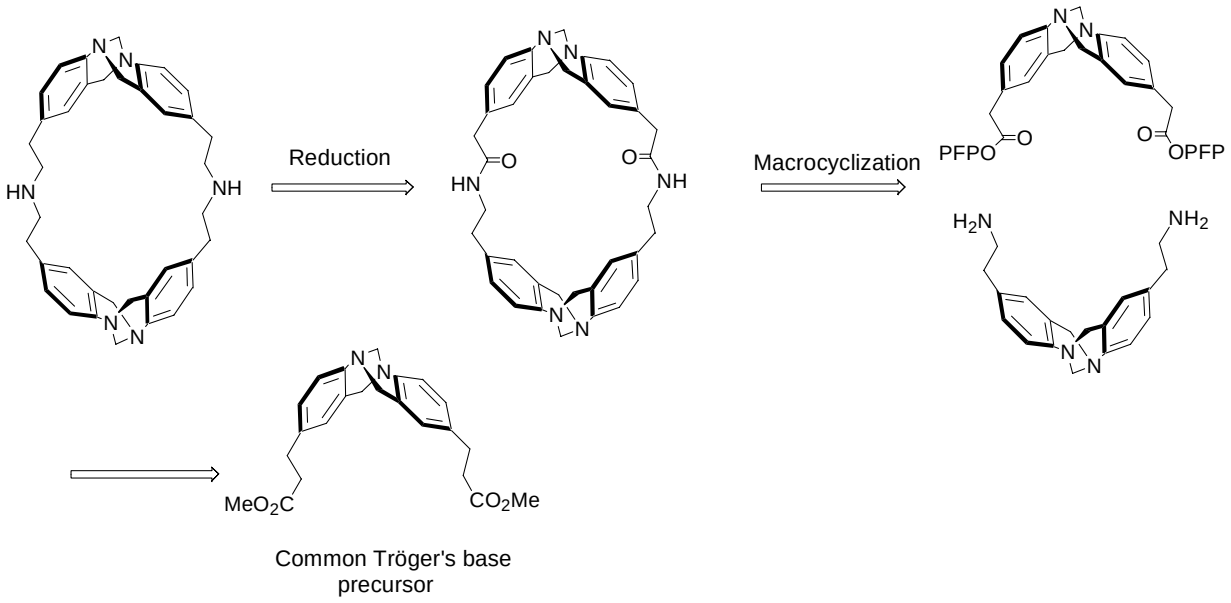
yields. Closing the macrocycle via Tröger's base formation continued to be a challenge. Both diastereomers were being formed and the separation was difficult.



Scheme 5. Asper's synthesis.

It was necessary at this stage to develop a reliable synthesis to host **17**. Dr. Muneharu Miyake developed a new route to **17**. During this time I joined the group and was assigned the

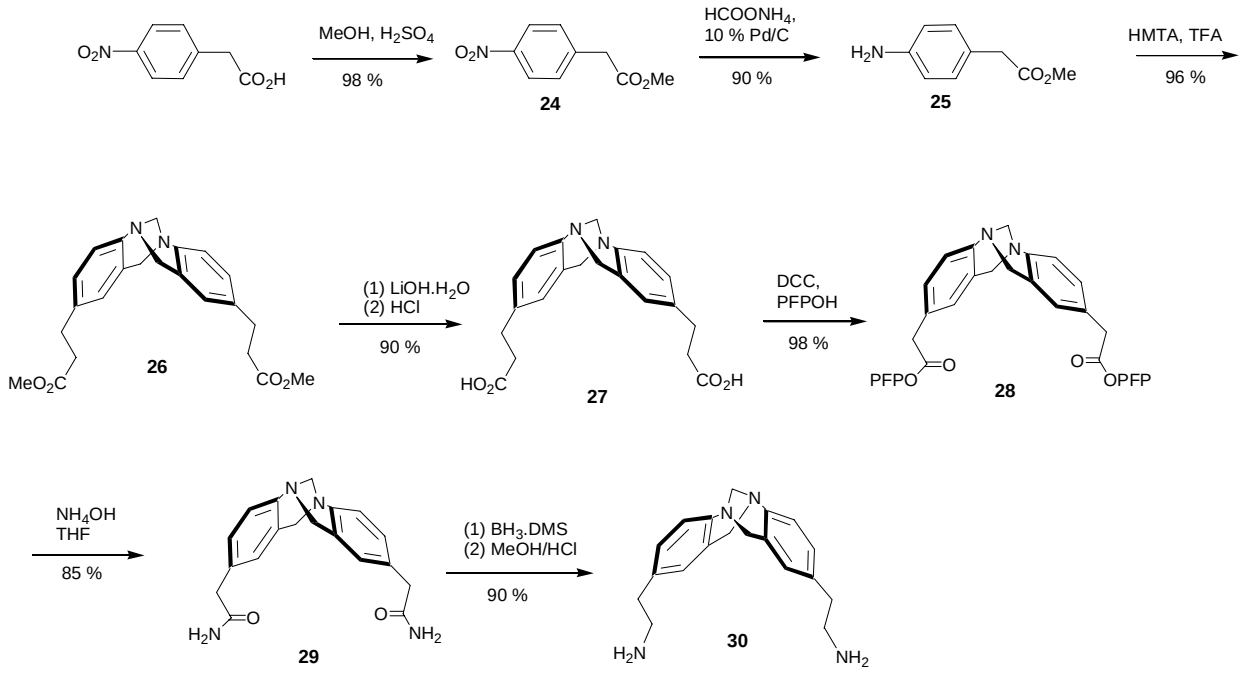
task of working with Dr. Miyake to reproduce and optimize the synthesis of host **17**. Herein is a report of the new synthesis with the optimization steps.



Scheme 6. Retrosynthesis of host **17**.

The new route followed a convergent pathway in which the two Tröger's base halves, which came from a common precursor, are brought together in the macrocyclization step (Scheme 6). This route began with a Fisher esterification of 4-nitrophenylacetic acid to the methyl ester **24** in 97 % yield, then reduction of the nitro-group with ammonium formate on activated palladium gave the corresponding amine **25** in 93 % yield (Scheme 7). Tröger's base formation was accomplished using Johnson's method (hexamethylenetetraamine (HMTA) and trifluoroacetic acid) to give the Tröger's base ester **26** in 96 % yield. Hydrolysis of the ester to acid **27** was done with lithium hydroxide in 91 % yield followed by coupling with pentafluorophenyl alcohol and DCC to form the pentafluorophenyl ester **28** in 95 % yield. At

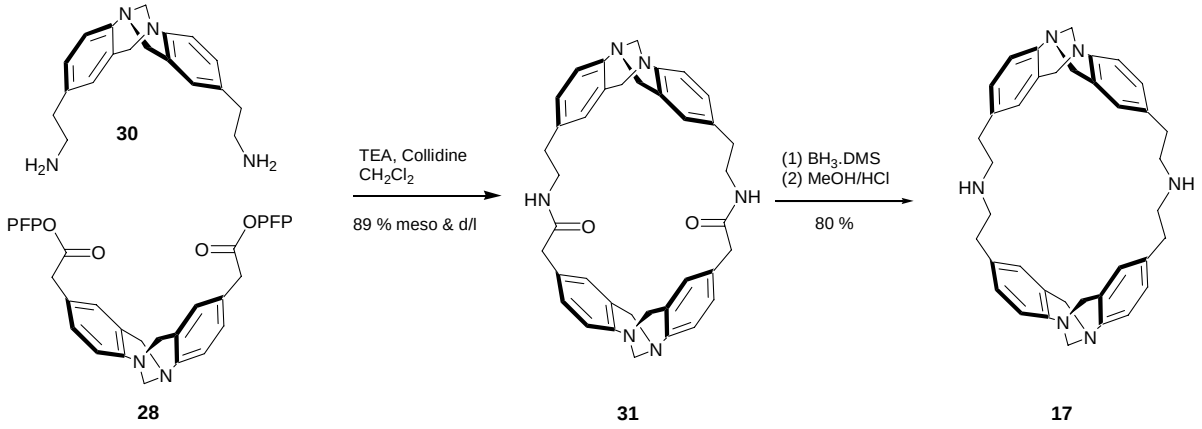
this stage only one half of ester **28** will be carried on in the synthesis. The other one half will be used in the macrocyclization step. Amide formation to give Tröger's base **29** was done with ammonium hydroxide and the resulting amide was reduced with borane- DMS complex (BH_3-DMS) to give the amine **30** in 97 % yield.



Scheme 7. Synthesis of host **17**.

Up to this point, the synthesis is very reliable and high yielding. The macrocyclization step, which is done by coupling of the pentafluorophenol ester of the Tröger's base with the Tröger's base amine in CH_2Cl_2, collidine and TEA, produced 60 % of the macrocyclic product containing the two diastereomers. Although this was an improvement compared to previous synthesis, it was the lowest yielding step in the route and needed to be optimized. This was done by a slow addition of the two Tröger's base reagents (Tröger's base amine, TEA in CH_2Cl_2 and Tröger's base pentafluorophenol ester in CH_2Cl_2) to a refluxing solution of collidine in CH_2Cl_2.

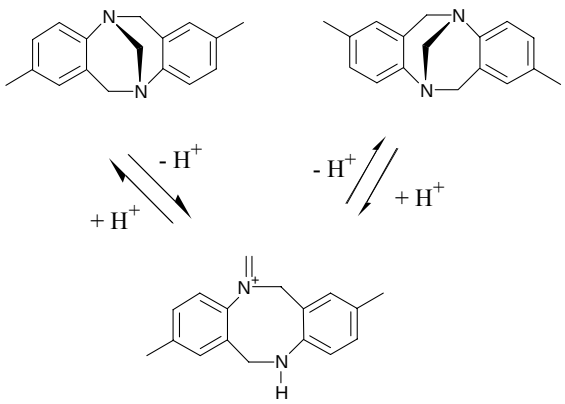
After three experiments the yield improved to 89 % of the two diastereomers **31**. The diastereomers were separated by column chromatography on silica gel of size 40-50 μm, and solvent $CHCl_3$: MeOH: NH_4OH (100:7:1) to give 43 % of pro-meso isomer, 21 % of pro-d/l isomer and 24 % of mixture. The macrocycle amides, pro-meso and pro-d/l isomers, were reduced separately with borane-DMS complex to give **17** meso and **17** d/l both in 80 % yield. We have been successful in synthesizing host **17** in high yields (9 steps and 46 % overall yield). Our synthesis of host **17** was greatly improved over all the previous syntheses. Each step of the synthesis has been repeated many times and each step gave reproducible results.



Scheme 8. Synthesisof host **17** cont'd.

During the final reduction step, isomerization of the meso to a 1:1 mixture of meso and d/l was observed (Scheme 9). We became aware that the quenching process during the reduction of **31** to **17** using MeOH/HCl was very sensitive to moisture; therefore the reagents were purified shortly before using. We developed a method to separate the isomers by column chromatography on silica gel of size 40-50 μm, and solvent $CHCl_3$:MeOH:NH_4OH, (100:5:1).

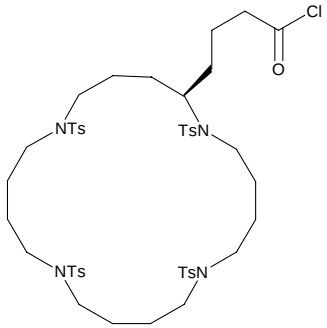
With this optimized synthesis in hand enough macrocycle could be made to test new methods for side arm attachment.



Scheme 9. Proposed mechanism for isomerization.

1.3. Attachment of the Side Arms

A variety of side arms have been attached at the site of the secondary amine of macrocycle **17**. One synthesis involved the attachment of the macrocyclic polyamine **32** through amide formation with the secondary amine of **17**.[30] Another side arm that was attached to **17** was a three-carbon guanidinium group.[28] This was done via a Michael-type addition of **17** to acrylonitrile, followed by reduction of the nitrile with borane dimethylsulfide complex (BH_3.DMS) to give the amine (Scheme 10). This amine was treated with a protected guanidinium group via a reaction with thiourea. The guanidinium group was then deprotected under acidic conditions. It is shown in Table 2 that the presence of the side arm enhances binding to aromatic guests.[28] This led us to explore the idea of attaching a more rigid arm that may improve binding due to greater preorganization.



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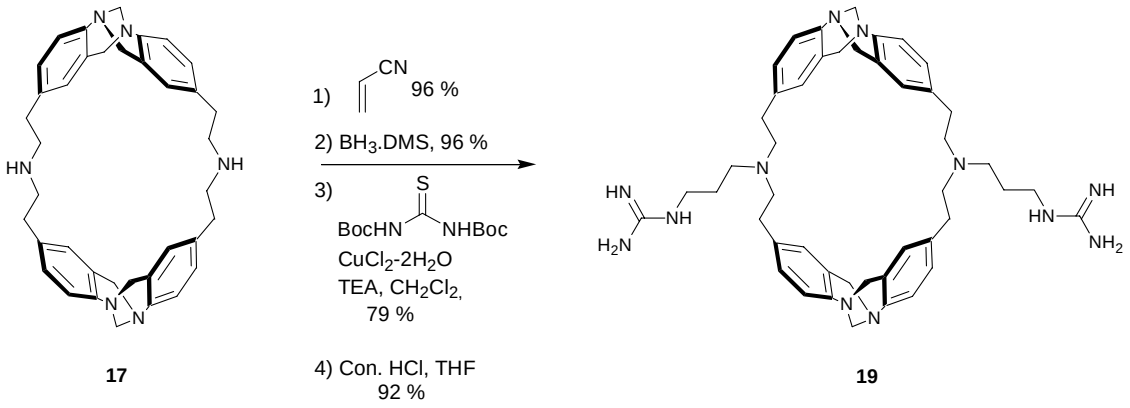


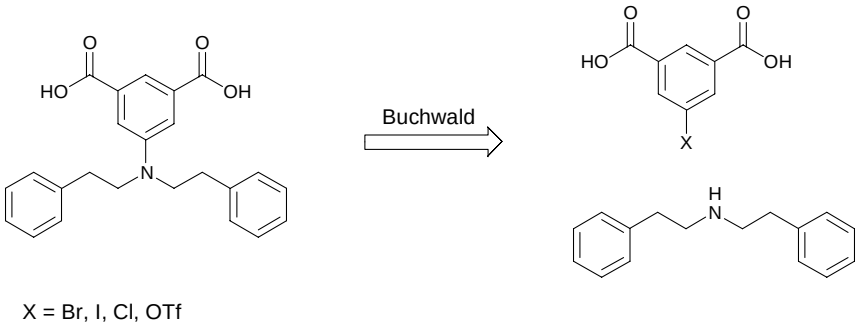
Scheme 10. Attachment of guanidinium arm.

Table 2. Comparing Binding Data of Host **17** with Host **19**.

Host	**17**	**19**
Guest	K_a (M^{-1})	K_a (M^{-1})
2,4,6-trimethylphenol	390	---
cresol	270	480
phosphocresol cycloheyxlammonium salt	45	1460
tyrosine	40	---
phosphotyrosine	Non detectable	Non detectable

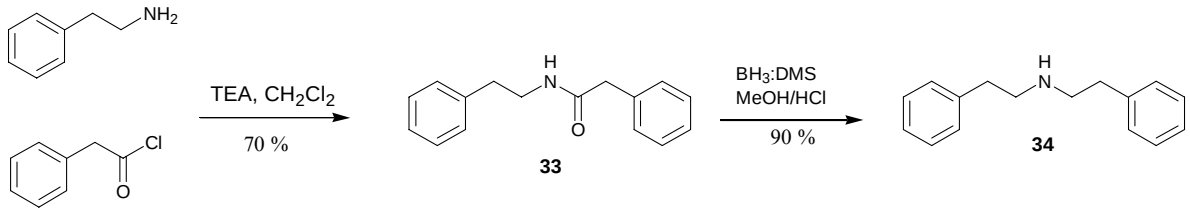
The new side arm was designed to serve multiple purposes. One function is to add rigidity to the cyclophane providing a more preorganized molecule, and another function is to provide for water solubility via the carboxylate groups that would allow binding studies to be done at physiological pH, and to provide a way to further modify the cavity with recognition elements such as chiral groups or phosphate recognition elements.

It was envisioned that the attachment of a functionalized aromatic group could be done via a Buchwald-Hartwig reaction (Scheme 11). This reaction was first studied using diphenethylamine with aryl triflates and halides as model compounds. Diphenethylamine was

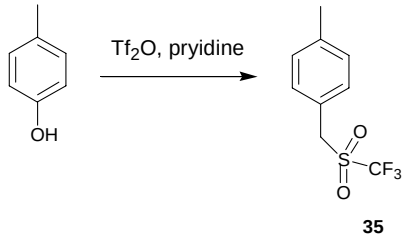


Scheme 11. Buchwald-Hartwig Reaction

synthesized by the reaction of phenethylamine and phenacetylchloride to give amide **33**, which was reduced with BH_3.DMS complex to give amine **34** (Scheme 12). We began our study with aryl triflates compounds because they are readily available from phenolic precursors using Stille's method (Scheme 13).[31] *p*-Cresol was treated with triflic anhydride in pyridine to give the corresponding triflate (**35**).



Scheme 12. Synthesis of diphenethylamine (**34**).



35

Scheme 13. Synthesis of triflate **35**.

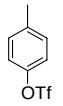
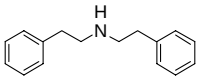
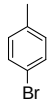
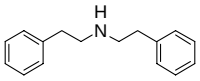
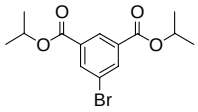
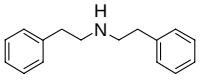
The Buchwald-Hartwig reaction was performed under a variety of conditions starting with the model compounds and leading up to target substrate. The results are shown in Table 3. There was a 70 % yield obtained in the reaction of triflate **35** with the cyclic secondary amine morpholine using condition A (entry 1),[32] however the reaction fails with diphenethylamine (entry 2). Changing the base to sodium *tert*-butoxide (condition B) or the catalyst to $Pd_2(dba)_3$ and ligand (condition C) also resulted in no reaction (entries 3 and 4).

During this time some new ligands (Table 2) were reported by Buchwald that gave improved yields in the reaction of secondary acyclic amines with aryl halides.[33] The conditions were changed substituting aryl bromide for the aryl triflate. Under condition C (2-(di-*tert*-butylphosphino) biphenyl (ligand 1), tris (dibenzylideneacetone) palladium (0) as the catalyst and sodium tert-butyl oxide as the base), 4-Bromo-toluidine reacted with diphenethylamine to give product **36** in 60 % yield (entry 5). The yield improved from 60 % to 96 % upon changing the ligand to 2-(dicyclohexylphosphino) biphenyl (ligand 2) (entry 6).

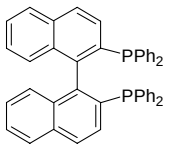
We applied these optimized conditions with aryl bromide **38**. Bromide **38** was prepared from isophthalic acid by bromination in the *meta* position with concentrated sulfuric acid, bromine and silver sulfate to give compound **37**,[34] which was converted to the isopropyl ester with HMPA and isopropyl iodide (Scheme 14). When 5-bromo-isophthalic acid diisopropyl ester **38** was treated with diphenethylamine only starting material and reduced aryl compound

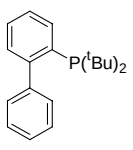
was retrieved (entry 7). Changing the solvent to THF gave no reaction (entry 8). Changing to a milder base (potassium phosphate) the reaction proceeded to give compound **39** in 60 % yield (entry 9). There were no further attempts to optimize the reaction with the diphenethylamine.

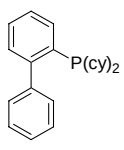
Table 3. Conditions Applied to the Buchwald-Hartwig Reaction.

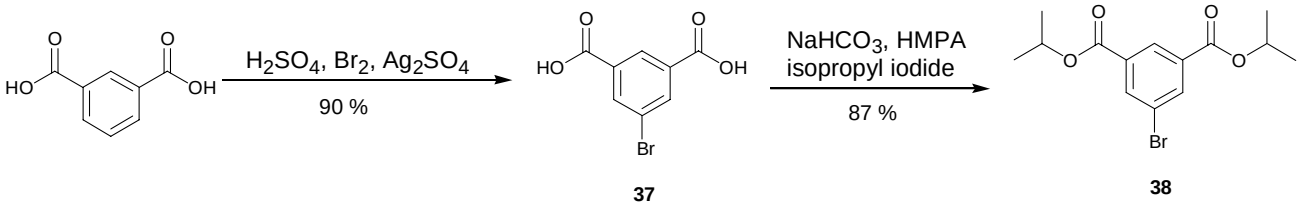
Entry	Aryl Compound	Amine	Condition	Ligand	% yield of Product
1			A	BINAP	70
2			A	BINAP	0
3			B	BINAP	0
4			C	1	0
5			C	1	60
6			C	2	96
7			C	2	0
8			D	2	0
9			E	2	60
10		Host **17** (d/l)	E	2	nmr product
11		Host **17** (meso)	E	2	21

Conditions: A: Cs_2CO_3, $Pd(OAc)_2$, Tol, 80 ºC
B: Na^tOBu, $Pd(OAc)_2$, Tol, 80 ºC
C: Na^tOBu, $Pd_2(dba)_3$, Tol, 80 ºC
D: Na^tOBu, $Pd_2(dba)_3$, THF, 80 ºC
E: K_3PO_4, $Pd_2(dba)_3$, Tol, 80 ºC


R,S-BINAP

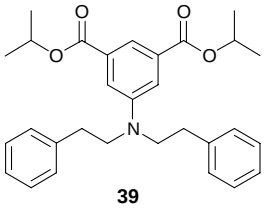

Ligand 1

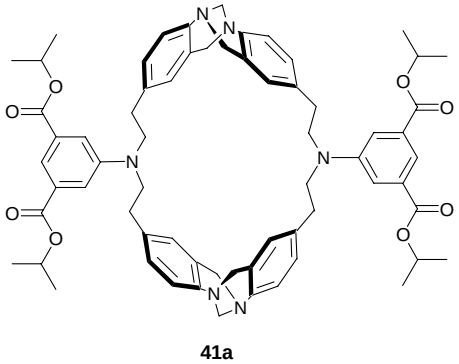

Ligand 2

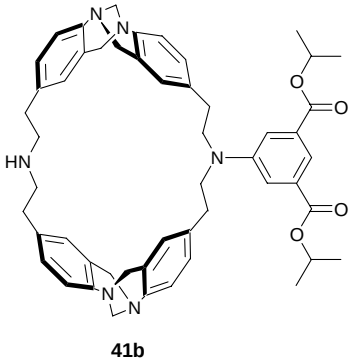


Scheme 14. Synthesis of aryl bromide 38.

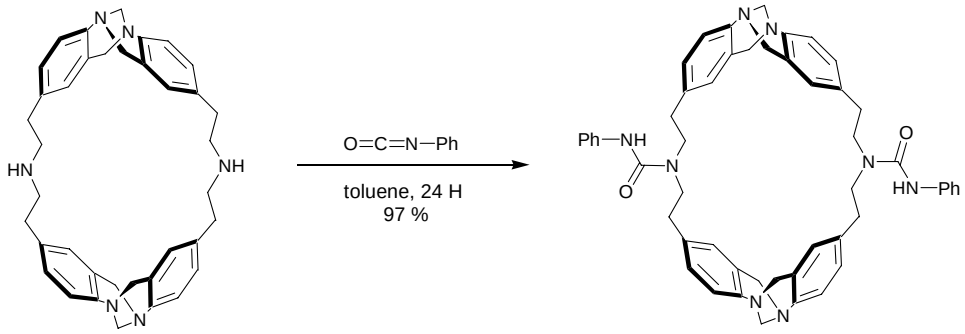
We applied the improved conditions (Condition E) to the macrocycle substrate. The reaction of **38** with the d/l isomer of **17** using Condition E showed some formation of product in the crude NMR, but recovery of pure product was not achieved (entry 10). The reaction condition was then applied to the meso isomer of **17** and 21 % of the diarylated compound **41a** and 19 % of the mono-arylated compound **41b** were isolated (entry 11). Several other attempts gave no improvement in the yield.







Our unsuccessful effort to apply the Buchwald-Hartwig reaction to the macrocycle substrate is not a result of the general unreactivity of secondary amines. As seen in previous reactions to introduce side arms, the reactivity of the secondary amines is usually good, leading to high yield of the product (Scheme 10). Although these reactions are not similar in conditions to the Buchwald-Hartwig reaction, they emphasize the general nucleophilicity of the secondary amines. This was further supported by the observation that both isomers of **17**, when treated with phenyl isocyanate, yield the urea compounds **42a** and **42b** in good yields (Scheme 15).[35] These compounds were synthesized in an effort to grow crystals for an X-ray analysis.

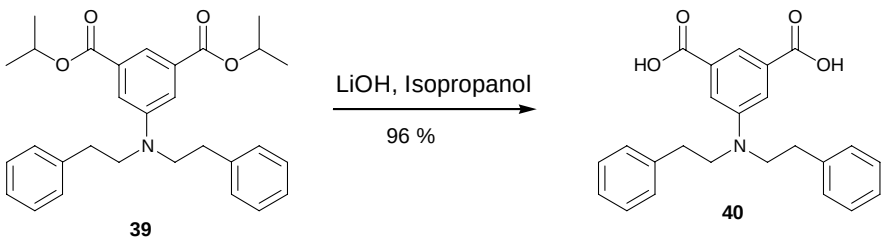


17
Meso siomer
or
d/l isomer

42
meso isomer **42a**
or
d/l isomer **42b**

Scheme 15. Synthesis of macrocyclic compounds **42a** and **42b.**

In order to test conditions for hydrolyzing the isopropyl ester, compound **39** was subjected to hydrolysis condition of lithium hydroxide in isopropanol to give the diacid compound **40** (Scheme 16). Upon subjecting macrocycle **41a** to these conditions, no product was obtained and the starting material could not be retrieved. We were also unsuccessful in making more of **41a**.



Scheme 16. Hydrolysis of model compound **39.**

1.4. Conclusions

The synthesis of macrocycle **17** was optimized to 46 % overall yield of both isomers and 22 % overall yield of the meso isomer in nine steps. During this synthesis a method was developed to separate the pro-meso isomer from the pro-d/l isomer of the amides. This method was very reproducible and there was good recovery of compound from the column. A method was also developed to separate the meso isomer from the d/l isomer that resulted from isomerization of the meso isomer to a 1:1 mixture of meso and d/l during the reduction of pro-meso to the meso isomer. However, this method was tedious and not very reproducible; therefore care must be taken to prevent isomerization during the reduction of the amide. With an optimized synthesis of the macrocycle **17** at hand, enough macrocycle was made available to explore synthesis of the attachment of the side arm.

The side arms were introduced via a Buchwald-Hartwig reaction. While the yield of the reaction was low and the reaction was not reproducible, this was the first example of a Buchwald-Hartwig reaction on a macrocyclic system of this kind. In addition, this was the first example of a Buchwald-Hartwig reaction to di-arylate a diamine system.

1.5. Experimental

General Experimental.

Melting points were determined using a Hoover capillary melting point apparatus and are uncorrected. Infrared spectra (IR) were determined on a Mattson Cygnus 100. IR was taken using Nujol. Proton and Carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on Bruker AF-300 MHz, AC-300 MHz, or AM-500 MHz spectrometer. Chemical shifts are expressed as parts per million (ppm) downfield from tetramethylsilane (TMS). When $CDCl_3$ and DMSO were used (^{13}C-NMR), peak assignments were made relative to TMS (0.00 ppm), $CDCl_3$ (77.00 ppm) and DMSO-d6 (39.5 ppm). The following abbreviation are used: br = broad, s = singlet, d = doublet, t = triplet, dd = doublet of doublets, sept = septet, m = multiplet. Low and high resolution (LRMS & HRMS), chemical ionization (CI), and fast atom bombardment mass spectra (FAB-MS) were obtained on a Varian MAT CH-5 or VG 7070 mass spectrometer.

Analytical thin layer chromatography (TLC) was conducted on pre-coated TLC plates, silica gel 60 F_{254}, layer thickness 0.25 mm, manufactured by E. Merck and Co., Darmstadt, Germany. Silica Gel for flash column chromatography was obtained from Silicycle Chemical Division "Silica Gel, 60" (particle size 0.040 – 0.063 mm); 230-240 mesh ASTM. Silica gel for column chromatography used in the separation of isomers of compounds **31** and **17,** and also compounds **41a** and **41b**, was obtained from Kanto Chemical, "Silica Gel, 60 (spherical)" (particle size 0.036-0.060 mm). For these compounds the columns were prepared, loaded, and fractions collected by gravity flow. For all other compounds the columns were prepared, loaded, and fractions collected according to the specification of Still.[37] Ethyl acetate used for chromatography was dried over 4 Å molecular sieves for at least 24 hours prior to use. Hexanes are the mixed hydrocarbon fraction (bp 60-70 °C), principally *n*-hexanes, which was purified as

follows: the commercial solvent was stirred concentrated sulfuric acid for at least 24 hours, decanted, stirred over anhydrous sodium carbonate for 6 hours, decanted, then distilled.

Solvents were distilled shortly before use from an appropriate drying agent. Diethyl ether, toulene and tetrahydrofuran (THF) were distilled under dry nitrogen from potassium metal in the presence of benzophenone. Benzene and dichloromethane were distilled from calcium hydride. Dimethylformamide (DMF) was dried over 4 Å molecular sieves and distilled under reduced pressure at ~ 40 °C. "Absolute" methanol was methanol distilled from magnesium metal while "dry" methanol was methanol (Reagent Grade) stored over 3 Å molecular sieves. "Absolute" ethanol and 95 % ethanol (Reagent Grade) were used. "Ether" refers to commercially available anhydrous diethyl ether. MeOH/HCl solution was prepared from stirring freshly distilled acetyl chloride (0.500 mL) in dry MeOH (10.0 mL) before using.

Reactions run under a nitrogen atmosphere were arranged with a mercury bubbler so that the system could be alternately evacuated and filled with nitrogen and left under positive pressure. Syringes and reaction flasks were dried at least 12 hours in an oven at 120 °C and cooled in a desiccator over anhydrous calcium sulfate prior to use. Reactions at "room temperature (rt)" were conducted under ambient laboratory conditions: T = 20-27 °C, P = 720-770 mmHg. References to "removal of volatile components" or "concentrated under reduced pressure" refer to rotary evaporation of a sample at 25-65 °C under pressure (15-25 mmHg) at room temperature. Lyophilization of TFA was performed by freezing the reaction mixture in a thin layer in a 1.0 L round bottom flask. The flask was attached to a dry ice-acetone cooled cold finger and placed under reduced pressure (0.1-0.3 mmHg) until the mixture was reduced to a thick oil.

All percent yields reported are for compounds that have a purity of approximately 95% or better as determined by ^{1}H NMR. All chemicals were bought from Acros, Lancaster, Aldrich, and Cambridge and were purified according to conditions of Perin, D. D.; Armarego, W. L. F.; Perin, D. R. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon Press Ltd., 1980.. Compounds **24**-**31** and **17** were all previously characterized.[26,28,29,38] Compounds **33** and **34** were previously characterized.[28]

(4-Nitro-phenyl)-acetic acid methyl ester: (24)

To a solution of 4-nitrophenylacetic acid (3.62 g, 20.0 mmol) in methanol (30.0 mL, 0.670 M) was added concentrated sulfuric acid (0.500 mL) and the reaction was refluxed at 70 °C overnight. The volatile components were removed under reduced pressure and the residue was taken up in EtOAc (100 mL), washed with sat'd $NaHCO_3$ (3 x 50.0 mL), washed with brine, dried over $MgSO_4$ and filtered. The volatile components were removed under reduced pressure to give 3.78 g of crude **24** as a white solid in 97.0 % yield, which was carried on to the next step without further purification.

^{1}H NMR (300 MHz $CDCl_3$) δ 8.21 (2 H, d, J = 7 Hz), 7.47 (2 H, d, J = 7 Hz), 3.77 (2 H, s), 3.75 (3 H, s). HRMS (EI): m/z calcd for $C_9H_9NO_4$ [M^+], 195.0532; found 195.0530. Spectroscopic data were consistent with the compound previously prepared.[39]

(4-Amino-phenyl)-acetic acid methyl ester: (25)

To a solution of (4-nitro-phenyl)-acetic acid methyl ester **24** (8.11 g, 41.6 mmol) in ethanol (208 mL) was added 10% Pd/C (3.20 g) and NH_4HCOO (14.0 g in 10 equal portions every 5 min) while stirring at room temperature. The reaction was stirred for 24 h, followed by

filtration through a 1 inch thick pad of Celite. The volatile components were removed under reduced pressure and residue purified by flash column chromatography on silica gel eluting with Hex: EtOAc (1:1) to give 6.44 g of **25** as a white solid in 93.0 % yield.

^{1}H NMR (300 MHz $CDCl_3$) δ 7.11 (2 H, d, *J* = 8 Hz), 6.75 (2 H, d, *J* = 8 Hz), 3.69 (3 H, s), 3.54 (2 H, s). HRMS (EI): m/z calcd for $C_9H_{11}NO_2$ [M^+], 165.0790; found 165.0788.

(8-Methoxycarbonylmethyl-*6H,12H*-5,11-methano-dibenzo[*bf*][1,5]diazocin-2-yl)-acetic acid methyl ester: (26)

To a solution of (4-amino-phenyl)-acetic acid methyl ester **25** (1.10 g, 6.68 mmol) in TFA (40.0 mL, 0.170 M), was added hexamethyltetraamine (HMTA) (0.947 g, 6.76 mmol) and the resulting solution was stirred at room temperature for 3 days. The TFA was removed by lyophilization and the remaining residual slurry was taken up in 35.0 mL H_2O and basified to pH >10 with concentrated NH_4OH. The aqueous solution was extracted with CH_2Cl_2 (3 x 35.0 mL), washed with brine, dried over $MgSO_4$ and filtered. The volatile components were removed under reduced pressure and the residue was purified by flash column chromatography on silica gel [EtOAc: MeOH (9:1)] to give 1.18 g of **26** as a yellow solid in 96.0 % yield .

^{1}H NMR (300 MHz $CDCl_3$) δ 7.11 (4 H, s), 6.84 (2 H, s), 4.72 (2 H, d, *J* =17 Hz), 4.9 (2 H, s), 4.16 (2 H, d, *J* = 17 Hz), 3.67 (6 H, s), 3.51 (4 H, s). ^{13}C NMR ($CDCl_3$) δ 172.3, 147.3, 129.7, 128.5, 127.8, 125.5, 66.9, 58.7, 52.3, 40.8. HRMS (EI): m/z calcd for $C_{21}H_{22}N_2O_4$[M^+], 366.1579; found 366.1596.

(8-Carboxymethyl-6*H*,12*H*-5,11-methano-dibenzo[*b f*][1,5]diazocin-2-yl)-acetic acid: (27)

To a solution of (8-methoxycarbonylmethyl-*6H,12H*-5,11-methano-dibenzo[bf][1,5] diazocin-2-yl)-acetic acid methyl ester **26** (4.88 g, 133 mmol) in MeOH/H_2O (3: 1 v/v) (17 mL)

was added $LiOH.H_2O$ (1.34 g, 320 mmol) and the solution was stirred at rt for 24 h. Most of the solvent was removed under reduced pressure and 20 mL of H_2O was added to the residue. After acidification with 0.040 M HCl to pH 1.5, the suspension was left to stand overnight at rt, followed by filtration to give 4.47 g of **27** as a white solid in 91.0 % yield.

^{1}H NMR (300 MHz DMSO-d_6) δ 12.21 (2 H, s, br), 7.03-6.96 (4 H, m), 6.84 (2 H, s), 4.55 (2 H, d, *J* = 17 Hz), 4.20 (2 H, s), 4.05 (2 H, d, *J* = 17 Hz), 3.40 (4H, s). ^{13}C NMR (DMSO) δ 172.8 146.6, 130.0, 128.1, 127.8, 127.6, 124.6, 66.3, 58.2. HRMS (EI): m/z calcd for $C_{19}H_{18}N_2O_4$ [M^+], 338.1266; found 338.1254.

(8-Pentafluorophenyloxycarbonylmethyl-6*H*,12*H*-5,11-methano-dibenzo[*b f*][1,5]diazocin-2-yl)-acetic acid pentafluorophenyl ester: (28)

To a solution of (8-carboxymethyl-6H,12H-5,11-methano-dibenzo[bf][1,5]diazocin-2-yl)-acetic acid **27** (3.31 g, 9.79 mmol) in CH_2Cl_2 (450 mL) was added pentafluorophenol (3.64 g, 18.2 mmol) and dicyclohexylcarbodiimide (DCC) (4.05 g, 19.6 mmol) and the reaction mixture was stirred at room temperature for 24 h. The DCU was removed by filtration and the volatile components were removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel [Hex: EtOAc (1:1)] to give 6.24 g of **28** as a white solid in 95 % yield.

^{1}H NMR ($CDCl_3$) δ 7.16 (s, 4 H), 6.91 (s, 2 H), 4.72 (d, *J* = 17 Hz) 4.32 (s, 2 H), 4.19 (d, *J* = 17 Hz), 3.86 (s, 4 H). ^{13}C NMR: ($CDCl_3$) δ 167.7, 147.8, 128.5, 128.0, 127.695, 125.7, 66.9, 58.7, 39.6. HRMS (EI): m/z calcd for $C_{31}H_{16}F_{10}N_2O_4$ [M^+], 670.0944; found 670.0950.

2-(8-Carbamoylmethyl-6*H*,12*H*-5,11-methano-dibenzo[*bf*][1,5]diazocin-2-yl)acetamide: (**29**)

To a solution of (8-pentafluorophenyloxycarbonylmethyl-6*H*,12*H*-5,11-methano-dibenzo[*bf*] [1, 5]dibenzocin-2-yl)-acetic acid pentafluorophenyl ester **28** (0.541 g, 0.807 mmol) in THF (8.00 mL) was added NH_4OH (1.60 mL, 13.2 mmol). The reaction mixture was stirred for 1 h at room temperature followed by addition of sat. $NaHCO_3$ (45.0 mL). The reaction mixture was continued stirring for another 20 min followed by filtration to separate the precipitated product, which was dried to give 0.233 g of **29** as a white solid in 86 % yield.

^{1}H NMR (300 MHz DMSO-d_6) δ 7.37 (2 H, s, br, NH_2), 7.00 (4 H, s), 6.78 (4 H, s, arom-H and NH_2), 4.57 (2 H, d, *J* = 17 Hz), 4.19 (2 H, s), 4.03 (2 H, d, *J* = 17 Hz), 3.20 (4 H, s). ^{13}C NMR (DMSO) δ 172.3, 146.4, 131.5, 127.7, 127.2, 124.5, 58.2, 41.7. HRMS (EI): m/z calcd for $C_{19}H_{20}N_4O_2$ [M^+], 336.1586; found 336.1588.

2-[8-(2-Amino-ethyl)-6*H*,12*H*-5,11-methano-dibenzo[*bf*][1,5]diazocin-2-yl]-ethylamine: (30)

To a suspension of 2-(8-carbamoylmethyl-6*H*,12*H*-5,11-methano-dibenzo[*bf*][1,5]diazocin-2-yl)acetamide **29** (0.155 g, 0.461 mmol) in THF (6.00 mL) under N_2 at 0 °C was added borane-dimethylsulfide (BH_3.DMS) complex (0.700 mL, 7.38 mmol) and reaction was refluxed at 80 °C for 29 h. The reaction was allowed to come to room temperature followed by addition of MeOH/HCl (3.00 mL); the reaction was refluxed for an additional 30 min. The reaction was cooled to room temperature and the volatile components were removed under reduced pressure. The residue was taken up in H_2O (5.00 mL) and basified to pH = 11.5. This mixture was extracted with CH_2Cl_2 (3 x 30 mL), washed with brine, dried over Na_2SO_4, and filtered. The volatile components were removed under reduced pressure and the crude product was purified by flash column chromatography on silica gel [$CHCl_3$: MeOH: NH_4OH (100: 40: 1) to give 0.139 g of **30** as a white solid in 98 % yield.

^{1}H NMR (CD_3OD) δ 7.07 (d, 2 H, *J* = 8 Hz), 7.01 (d, 2 H, *J* = 8 Hz), 6.78 (s, 2 H), 4.62 (d, 2 H, *J* = 17 Hz), 4.29 (s, 4 H), 4.13 (d, 2 H, *J* = 17 Hz), 2.75 (t, 4 H, *J* = 7 Hz), 2.61 (t, 4 H, *J* = 7 Hz). ^{13}C NMR (75 MHz, CD_3OD) 146.6, 137.0, 128.9, 128.1, 125.9, 67.6, 59.4, 43.9, 39.4. HRMS (EI): m/z calcd for $C_{19}H_{24}N_4$[M^+], 308.2000; found 308.2001.

9,10,11,26,28,29-Hexahydro-12,27-dioxo-3H,8H,16H,20H,25H,33H-4,7:21,24-dimetheno-13,19,15:30,2,32-di[1]propane[1]yl[3]ylidine-1H,18H-dipyrimidino[1,2-a;1',6'o][1,8,15,22]-tetraazacyclooctacosine: (31)

To a solution collidine (2.20 mL) in CH_2Cl_2 (460 mL) at reflux was added (8-pentafluorophenyloxycarbonylmethyl-6*H*,12*H*-5,11-methano-dibenzo[*bf*][1,5]diazocin-2-yl) acetic acid pentafluorophenyl ester **28** (1.13 g, 1.66 mmol) in CH_2Cl_2 (20.0 mL) and 2-[8-(2-amino-ethyl)-6*H*,12*H*-5,11-methano-dibenzo[*bf*][1,5]diazocin-2-yl]-ethylamine **30** (0.513 g, 1.66 mmol) in CH_2Cl_2 (20.0 mL) and TEA (2.30 mL) in 1-2 mL portions every 10 min. The remaining CH_2Cl_2 (total of 700 mL) was added and the reaction was refluxed at 80 °C under N_2 for 48 h. The volatile components were removed under reduced pressure and the crude product was purified by gravity column chromatography on silica eluting with $CHCl_3$: MeOH: NH_4OH (100:10:1) to give mixture of the pro-meso and pro-d/l isomers. This mixture was re-subjected to gravity column chromatography on silica gel eluting with $CHCl_3$: MeOH: NH_4OH (100:7:1) to give 0.432 g of the meso isomer in 42.5 % yield, 0.217 g of the d/l isomer in 21.4 % yield, and 0.254 g of the mixture on meso and d/l in 25.0 % yield.

^{1}H NMR (300 MHz $CDCl_3$) (Meso isomer) δ 77.06-6.60 (12 H, m), 5.46 (2 H, br), 4.65 (4 H, d, *J* = 17 Hz), 4.30 (4 H, s), 4.08 (4 H, d, *J* = 17 Hz), 3.29 (8 H, m), 2.57-2.54 (4 H, m). ^{13}C NMR

(300 MHz, $CDCl_3$) δ 146.1, 136.9, 128.0, 128.0, 127.2, 125.0, 67.2, 58.9, 50.4, 35.1. mp 295 °C (decomp). HRMS (EI): m/z calcd for $C_{38}H_{38}N_6O_2$ [M^+], 610.3056; found 610.3064.

^{1}H NMR (300 MHz $CDCl_3$) (d/l isomer) δ 7.05-6.97 (4 H, dd, *J* = 8 Hz, 8 Hz), 6.78 (2 H, d, *J* = 8 Hz), 6.66-6.60 (6 H, m), 5.22 (2 H, br), 4.66 (4 H, d, *J* = 17 Hz), 4.28, (4 H, s), 4.07 (4 H, d, *J* = 17 Hz), 3.47-3.08 (8 H, m), 2.54-2.46 (4 H, m). ^{13}C NMR (300 MHz, $CDCl_3$) δ 171.2, 147.0, 146.5, 134.7, 130.6, 128.4, 128.3, 128.1, 127.9, 127.3, 127,2, 125.2, 124.9, 77.6, 67.2, 59.1, 42.9, 40.1, 35.7.

9,10,11,12,26,27,28,29-Octahydro-3H,8H,16H,20H,25H,33H-4,7:21,24-dimetheno-13,19,15:30,2,32-di[1]propane[1]yl[3]ylidine-1H,18H-dipyrimidino[1,2-a;1',6'o] [1,8,15,22]tetraazacyclooctacosine: (17)

To a solution of 9,10,11,26,28,29-Hexahydro-12,27-dioxo-3H,8H,16H,20H,25H,33H-4,7:21,24-dimetheno-13,19,15:30,2,32-di[1]propane[1]yl[3]ylidine-1H,18H-dipyrimidino[1,2-a;1',6'o] [1,8,15,22]tetraazacyclo-octacosine **31** (0.301 g, 0.493 mmol) in THF (18.0 mL) under N_2, was added BH_3.DMS complex (0.600 mL, 6.33 mmol) and the reaction was refluxed at 80 °C for 48 h. The reaction was allowed to come to room temperature followed by addition of MeOH/HCl (3.00 mL); the reaction was refluxed for an additional 30 min. The reaction was cooled to room temperature and the volatile components were removed under reduced pressure. The residue was taken up in H_2O (5.00 mL) and basified to pH > 10. This mixture was extracted with CH_2Cl_2 (3 x 40 mL), washed with brine, dried over Na_2SO_4, and filtered. The volatile components were removed under reduced pressure and the crude product was purified by gravity column chromatography on silica gel [$CHCl_3$:MeOH:NH_4OH (100:7:1)] to give 0.229 g of **17** as a white solid in 80 % yield.

meso isomer ^{1}H NMR (300 MHz $CDCl_3$): δ 6.99-6.90 (8 H, m), 6.63 (4 H, s), 4.61 (4 H, d, *J* = 17 Hz). 4.29 (4 H, s), 4.00 (4 H, d, *J* = 17 Hz), 2.79-2.53 (16 H, m). ^{13}C NMR ($CDCl_3$) (500 MHz) δ 146, 136, 128, 127.7, 127.1, 124.8, 67.1, 58.9, 50, 34.7.

mp 293 °C (decomp HRMS (EI): m/z calcd for $C_{38}H_{42}N_6$ [M^+], 582.3471; found 582.3442.

d/l isomer ^{1}H NMR (300 MHz $CDCl_3$): δ 6.99 (4 H, d, *J* = 8 Hz), 6.93-6.90 (4 H, dd, *J* = 8 Hz, 2 Hz), 6.61 (4 H, s), 4.60 (4 H, d *J* = 17 Hz), 4.29 (4 H, s), 4.00 (4 H, d, *J* = 17 Hz), 2.79-2.56 (16 H, m). ^{13}C NMR (75 MHz, $CDCl_3$) 146.1, 136.2, 133.5, 128.0, 127.2, 125.087, 67.164, 58.9, 50.4, 35.1.

***N*-Phenethyl-2-phenyl-acetamide:** (**33**)

To a solution of phenethylamine (5.00 mL, 39.8 mmol) in CH_2Cl_2 (50.0 mL) at 0 °C was added a mixture of phenyl acetyl chloride (5.30 mL, 40.0 mmol) in triethylamine (3.00 mL) via an additional funnel with an attaching drying tube. The reaction was stirred at room temperature for 20 h and the mixture was taken up in CH_2Cl_2 (50 mL), washed with 1M HCl (2 x 100 mL), washed with sat. $NaHCO_3$ (2 x100 mL), washed with H_2O (1 x100 mL), washed with brine, dried over K_2CO_3 and filtered. The volatile components were removed under reduced pressure to give a yellow solid, which was purified by recrystallized from hot hexane to give 6.36 g of **33** as light yellow crystals in 66 % yield.

^{1}H NMR (300 MHz $CDCl_3$) δ 7.34-7.03 (10 H, m), 3.55 (2 H, s), 3.50-3.44 (2 H, m), 2.73 (2 H, t, *J* = 6.8 Hz).

Diphenethyl-amine: (**34**)

To a solution of *n*-phenethyl-2-phenyl-acetamide **33** (5.50 g, 23.0 mmol) in THF (24 mL) stirred in an ice-bath under N_2 for 1 h, was added BH_3.DMS complex (4.4 mL, 46.0 mmol) and the reaction mixture was refluxed at 80 °C for 24 h. The reaction was allowed to come to room temperature followed by addition of MeOH/HCl (60.0 mL); the reaction was refluxed for an additional 1 h. The reaction was cooled to room temperature and the volatile components were removed under reduced pressure. The residue was taken up in H_2O (100 mL) and basified to pH > 10. The reaction mixture was extracted with CH_2Cl_2 (3 x150 mL), washed with sat. $NaHCO_3$ (1 x150 mL), washed with brine, dried over K_2CO_3 and filtered. The volatile components were removed under reduced pressure to give an oily liquid which was purified by vacuum distillation to give 4.74 g of **34** as an oily liquid in 91 % yield.

^{1}H NMR (300 MHz $CDCl_3$): δ 7.31-7.16 (10 H, m), 2.91-2.78 (8 H, m). ^{13}C NMR ($CDCl_3$) δ 140.2, 128.8, 128.6, 126.3, 51.2, 36.5.

Trifluoro-methanesulfonic acid *p*-tolyl ester: (**35**) Prepared according to methods of Stille et al. [31]

5-Bromo-isophthalic acid: (**37**)

To a mixture of isophthalic acid (2.50 g, 15.0 mmol) in H_2SO_4 (35.0 mL, 0.440 M) was added Ag_2SO_4 (2.81 g, 9.03mmol) and Br_2 (2.00 mL, 19.5 mmol) and the reaction was refluxed at 110 °C for 48 h. After 48 h the excess Br_2 was distilled off and the crude mixture was taken up in H_2O (100 mL). The precipitate was filtered off by vacuum filtration and dissolved in sat. $NaHSO_4$ (50 mL). The suspension was filtered in a 3.00 M H_2SO_4 solution (100 mL) cooled in

an ice bath. The white precipitate was collected and recrystallized from acetone/water mixture (1:1) to give 3.39 g as white needles in 92 % yield.

^{1}H NMR (300 MHz DMSO-d_6) δ 8.38 (d, 1 H, J = 2 Hz), 8.21 (d, 2 H, J = 1 Hz). ^{13}C NMR (300 MHz DMSO-d_6) δ 166, 136, 134, 129, 123. MP. 282 °C.

5-Bromo-isophthalic acid diisopropyl ester: (**38**)

To a mixture of 5-bromo-isophthalic acid **37** (2.01 g, 8.20 mmol) and $NaHCO_3$ (2.07 g, 24.6 mmol) in HMPA (15.0 mL) stirred under nitrogen for 1 h, was added isopropyl iodide (2.40 mL, 24.6 mmol) and the reaction was stirred at room temperature for 24 h. After 24 h, another 3 equivalent of $NaHCO_3$ and isopropyl iodide was added and stirring was resumed for another 24 h. The reaction mixture was taken up in 2.00 N HCl (150 mL) and extracted with CH_2Cl_2 (3 x 100 mL), washed with 1.00 N NaOH (2 x 100 mL) washed with sat. $NaHCO_3$ (1 x 100 mL), washed with brine, dried over $MgSO_4$ and filtered. The volatile components were removed under reduced pressure to give 16 g of a crude product (mostly HMPA), which was purified by flash column chromatography on silica gel eluting with Hex: EtOAc (20:1) to give 2.32 g of **38** as a white solid in 85.0 % yield.

^{1}H NMR (300 MHz $CDCl_3$) δ 8.59 (1 H, d, J = 1 Hz), 8.33 (2 H, d, J = 1 Hz), 5.28 (2 H septet, J = 6 Hz), 1.40 (12 H, d, J = 6 Hz). ^{13}C NMR (300 MHz $CDCl_3$) δ 164, 136, 133, 129, 122.5, 70, 22. IR (cm^{-1}) 2926, 2926, 2845, 1723, 1724, 1575; HRMS (EI): m/z calcd for $C_{14}H_{17}BrO_4$ [M^+]. 328.0310; found 328.0312. MP 48 ^{o}C. R_f (Hex: EtOAc 20:1) is 0.32.

General procedures for the Buchwald-Hartwig reaction.

Method A:

A dry two-neck flask was charged with amine (1.00 mmol), triflate or bromide (1.20 mmol), base (1.40 mmol), ligand (10 mol%), palladium acetate ($Pd(OAc)_2$) or tris-(dibenzylidene-acetone)dipalladium (0) (Pd_2dba_3) (5 mol%), and toluene (2.00 mL/mmol of amine). The reaction was flushed with N_2 and heated at 80 °C. The mixture was diluted with ether, filtered through a pad of Celite, and the volatile components were removed reduced pressure to give a crude product, which was purified by flash column chromatography on silica gel.

Method B:

A dry two-neck flask was charged with amine (1.00 mmol), bromide (2.40 mmol), base (2.80 mmol), ligand (20.0 mol%), tris (dibenzylideneacetone)dipalladium (0) (Pd_2dba_3) (10 mol%), and toluene (2.00 mL/mmol of amine). The reaction was flushed with N_2 and heated at 90 °C. The mixture was diluted with ether, filtered through a pad of Celite, and the volatile components were removed reduced pressure to give a crude product, which was purified by flash column chromatography on silica gel.

4-*p*-Tolyl-morpholine: (Table 3, entry 1)

Following the general procedure of method A, morpholine (0.132 g, 1.56 mmol), *p*-cresol triflate (0.288 g, 1.26 mmol), Cs_2CO_3 (0.652 g, 2.00 mmol), BINAP (0.040 g, 5 mol%) and $Pd(OAc)_2$ (0.013g, 5 mol%), in toluene (2.00 mL) afforded 0.353 g of a crude product which was purified by flash column chromatography on silica gel eluting with 4:1 hexane: EtOAc to give 0.118 g of the product in 70 % yield.

^{1}H NMR (300 MHz $CDCl_3$) δ 7.10 (2 H, d, *J* = 8 Hz), 6.85 (2 H, d, *J* = 8 Hz), 3.87 (4 H, t, *J* = 5 Hz), 3.12 (4H, t, *J* = 5 Hz), 2.29 (3 H, s). Spectroscopic data were consistent with the compound previously prepared.[32]

Diphenethyl-*p*-tolyl-amine: (Table 3, entry 6)

Following the general procedure of method A, diphenethylamine (0.240 g, 1.07 mmol), 4-bromotoluene (0.219 g, 1.28 mmol), Na^{t}OBu (0.145 g, 1.50 mmol), 2-(dicyclohexylphosphino)biphenyl (0.0270 g, 10 mol%) and Pd_2dba_3 (0.0350 g , 5 mol%) in toluene (2.00 mL) afforded a crude product which was purified by flash column chromatography on silica gel eluting with 20:1 hexane: EtOAc to give 0.323 g of the product in 96% yield.

^{1}H NMR (300 MHz $CDCl_3$) δ 7.35-7.20 (10 H, m), 7.13 (2 H, d, *J* = 8 Hz), 6.75 (2 H, d, J = 8 Hz), 3.48 (4 H, t, *J* = 8 Hz), 2.84 (4 H, t, *J* = 8 Hz), 2.33 (3 H, s). ^{13}C NMR (300 MHz $CDCl_3$) δ 140.0, 130.2, 129.0, 128.7, 126.4, 125.4, 112.5, 53.7, 33.9, 20.5.

5-Diphenethylamino-isophthalic acid diisopropyl ester: (**39**) (Table 3, entry 9)

Following general procedure of method B, 5-bromo-isophthalic diisopropyl ester (0.506 g, 1.54 mmol), diphenethylamine (0.284 g, 1.26 mmol), potassium phosphate (0.390 g, 1.84 mmol), 2-(dicyclohexylphosphoino) biphenyl (0.0450 g, 10 mol%), and Pd_2dba_3 (0.0590 g, 5 mol%) in toluene (0.500 mL) afforded 0.913 g of a crude mixture which was purified by flash column chromatography on silica gel eluting with Hex: EtOAc (20:1) to give 0.427 g of **39** in 60 % yield.

^{1}H NMR (300 MHz $CDCl_3$) δ 7.99 (1 H, t, *J* = 1 Hz), 7.63 (2 H, d, *J* = 1 Hz), 7.34-7.21 (10 H, m), 5.30 (1 H, septet *J* = 6 Hz), 3.54 (4 H, t, *J* = 8 Hz), 2.83 (4 H, t, *J* = 8 Hz), 1.43 (12 H, d, *J* =

6 Hz). ^{13}C NMR (300 MHz $CDCl_3$) δ 166.3, 147.3, 139.3, 132.3, 129.0, 128.8, 126.6, 117.9, 116.6, 68.9, 53.7, 33.6, 22.2; IR (cm^{-1}) 3024, 2923, 2853, 1720, 1594, 1462, 1240. HRMS (EI): m/z calcd for $C_{30}H_{35}NO_4$ [M^+] 473.2566; found 473.2565. MP 71 ^oC;

9,10,11,12,26,27,28,29-Octahydro-10,27-bis(isophthalic acid diisopropyl ester)-3H,8H,16H,20H,25H,33H-4,7:21,24-dimetheno-13,19,15:30,2,32 di[1]propane[1]yl[3]ylidine -1H,18H-dipyrimidino[1,2 a;1',6'o][1,8,15,22]tetraazacyclooctacosine: (41a meso) (Table 3, entry 12)

Following general procedure of method B, 5-bromo-isophthalic diisopropyl ester (0.0660 g, 0.201 mmol), 9,10,11,12,26,27,28,29-Octahydro-3H,8H,16H,20H,25H,33H-4,7:21,24-dimetheno-13,19,15:30,2,32-di[1]propane[1]yl[3]ylidine-1H,18H-dipyrimidino[1,2-a;1',6'o] [1,8,15,22]tetraazacyclooctacosine (meso isomer) (0.0490 g, 0.0840 mmol), potassium phosphate (0.0500 g, 0.235mmol), 2-(dicyclohexylphosphoino) biphenyl (0.00600 g, 20 mol%) and Pd_2dba_3 (0.008 g, 10 mol%) in toluene (0.500 mL) afforded 0.132 g of a crude mixture, which was purified by flash column chromatography on silica gel eluting with $CHCl_3$: MeOH: NH_4OH **(**100: 7: 1) then Hex: EtOAc (1: 10) to give 0.0700 g of **41a** as a yellow oil in 21 % yield.

^1H NMR (300 MHz DMSO-d_6) δ 7.99 (2H, s), 7.53 (4 H, s), 7.07-6.92 (8 H, m), 6.32 (4 H, s), 5.29 (4 H, septet), 4.63 (4 H, d, *J* = 17 Hz), 4.21 (4 H, s), 4.08 (4 H, d, *J* = 17 Hz), 3.31 (8 H, t, *J* = 7 Hz), 2.47-2.38 (4 H, m), 1.66-1.76 (4 H, m). ^{13}C NMR (300 MHz $CDCl_3$) δ 166, 147, 146, 135, 132, 128, 127.5, 127, 125, 118, 116, 69, 67, 58, 33, 22. LRMS found for $C_{66}H_{74}N_6O_8$ [M^+], 1078.5.

5.Diphenethylamino-isophthalic acid: (**40**)

To a solution of 5-diphenethylamino-isophthalic acid diisopropyl ester **39** (0.129 g, 0.272 mmol) in isopropyl alcohol/H_2O mixture (3:1) (4.00 mL) was added $LiOH.H_2O$ (0.0870 g, 2.07 mmol) and the solution was stirred at room temperature for 48 h. The volatile components were removed under reduced pressure and residue was taken up in H_2O (15.0 mL) and acidified with 1.00 N HCl (5.00 mL). The suspension was stirred for 30 min and the residue was collected by filtration and dried in the hood overnight to give 0.102 g of **40** as a white solid in 96% yield.

^{1}H NMR (300 MHz DMSO-d_6) δ 7.75 (1 H, s), 7.49 (2 H, s), 7.32-7.20 (10 H, m), 3.52 (4 H, t, *J* = 7 Hz), 2.76 (4 H, t, *J* = 7 Hz). ^{13}C NMR (300 MHz DMSO-d_6) δ 167.7, 147.6, 139.6, 132.6, 129.2, 128.9, 126.7, 117.4, 116.1, 52.9, 32.9; HRMS (EI): m/z calcd for $C_{24}H_{23}NO_4$ [M^+], 389.1627; found 389.1634. MP 232-233 °C.

9,10,11,12,26,27,28,29-Octahydro-10,27-bis(carboxylic acid phenyl amide)-3H,8H,16H,20H, 25H,33H-4,7:21,24-dimetheno-13,19,15:30,2,32-di[1]propane[1]yl[3]ylidine-1H,18H-dipyrimidino[1,2-a;1',6'o][1,8,15,22]tetraazacyclooctacosine-(d/l): (42b)

To a solution of 9,10,11,12,26,27,28,29-octahydro-3H,8H,16H,20H,25H,33H-4,7:21,24-dimetheno-13,19,15:30, 2,32-di[1]propane[1]yl[3]ylidine-1H,18H-dipyrimidino[1,2-a;1',6'o] [1, 8,15,22]tetraazacyclo-octacosine **17** d/l (0.016 g, 0.028 mmol) in toluene (1 mL) under N_2, was added phenyl isocyanate (0.200 mL) and the reaction mixture was stirred at rt for 12 h. The suspension was filtered and dried to give 0.022 g of **42b** as a white solid in 97% yield.

^{1}H NMR (300 MHz $CDCl_3$) δ 7.33-7.18 (4 H, m), 7.11-6.93 (10 H, m), 6.58-6.49 (8 H, m), 5.44 (2 H, br), 4.64 (4 H, d, *J* = 17 Hz), 4.26 (4 H, s). 4.07 (4 H, d, *J* = 17 Hz), 3.31 (8 H, m), 2.32-

2.25 (4 H, m). ^{13}C NMR (300 MHz $CDCl_3$) δ 155.9, 146.6, 138.9, 129.4, 128.9, 128.2, 127.8, 127.2, 125.1, 124.1, 123.0, 120.9, 119.5, 57.2, 59.1, 54.8, 34.3. IR (cm^{-1}) 3375, 3327, 2923, 2853, 1655, 1594, 1231; MP 250 °C. FAB 821.

9,10,11,12,26,27,28,29-Octahydro-10,27-bis(carboxylic acid phenyl amide)-3H,8H,16H,20H, 25H,33H-4,7:21,24-dimetheno-13,19,15:30,2,32-di[1]propane[1]yl[3]ylidine-1H,18H-dipyrimidino[1,2-a;1',6'o][1,8,15,22]tetraazacyclooctacosine-(meso): **42a**

To a solution of 9,10,11,12,26,27,28,29-Octahydro-3H,8H,16H,20H,25H,33H-4,7:21,24-dimetheno-13,19,15:30,2,32-di[1]propane[1]yl[3]ylidine-1H,18H-dipyrimidino[1,2-a;1',6'o] [1,8,15,22]tetraazacyclo-octacosine **17** meso (0.0167g, 0.0287 mmol) in toluene (1 mL) under N_2, was added phenyl isocyanate (0.210 mL) and the reaction mixture was stirred at rt for 12 h. The suspension was filtered and dried to give 0.023 g of **42** as a white solid in 97% yield.

^{1}H NMR (300 MHz $CDCl_3$) δ7.33 (2 H, m), 7.31-7.03 (10 H, m), 6.96-6.79 (10 H, m), 5.08 (2 H, br), 4.60 (4 H, d, *J* = 17 Hz), 4.29 (4 H, s), 4.08 (4 H. *J* = 17 Hz), 3.47-3.20 (8 H, m), 2.37-2.06 (8 H, m). ^{13}C NMR (300 MHz $CDCl_3$) δ 156.4, 146.4, 138.8, 135.5, 129.3, 128.7, 128.1, 127.8, 127.3, 125.0, 123.9, 122.6, 120.7, 119.4, 67.5, 59.3, 55.0, 34.3. MP 210 ^{0}C;

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2. Synthetic Developments in Unsymmetrical Silyl Ketal Synthesis

2.1. Introduction

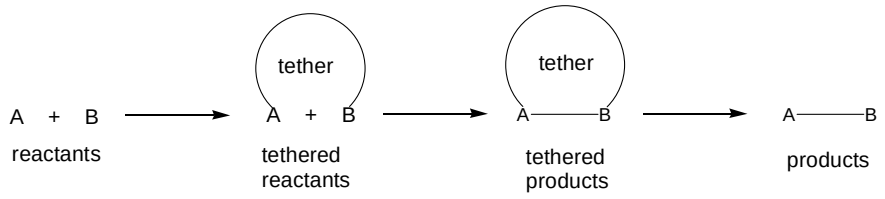
The development of synthetic methods is a very important branch of natural product synthesis, and complex target-oriented synthesis. The new chemical methods that are developed by chemists simplify the process of synthesis. This simplification generally leads to a shorter number of steps in the synthesis and therefore a more efficient synthesis. New synthetic methods are usually developed with simple substrates which highlight the main functional group transformation. These methods can be difficult to be transferred to a more complex molecule; therefore, it is important that a new synthetic method demonstrates the scope and limitation of the method.

Organosilicon compounds have an important role in chemistry. These compounds are used in areas such as molecular and bio-molecular chemistry, medicinal chemistry, coordination and inorganic chemistry, macromolecular chemistry, solid-state and physical chemistry and organic chemistry.[1] One of the primary characteristics of organosilicon compounds is their compatibility with biological systems.[2] This opens the door for their use in the drug industry; organosilicon compounds are being explored for their use as possible drug additives and drug delivery regulators.[3,4] Another area where organosilicon chemistry has left its mark is in organic synthesis. Organosilicon chemistry has provided many fundamental tools in organic synthesis – allylsilanes, enoxysilanes, hydrosilanes, alkoxysilanes, etc.

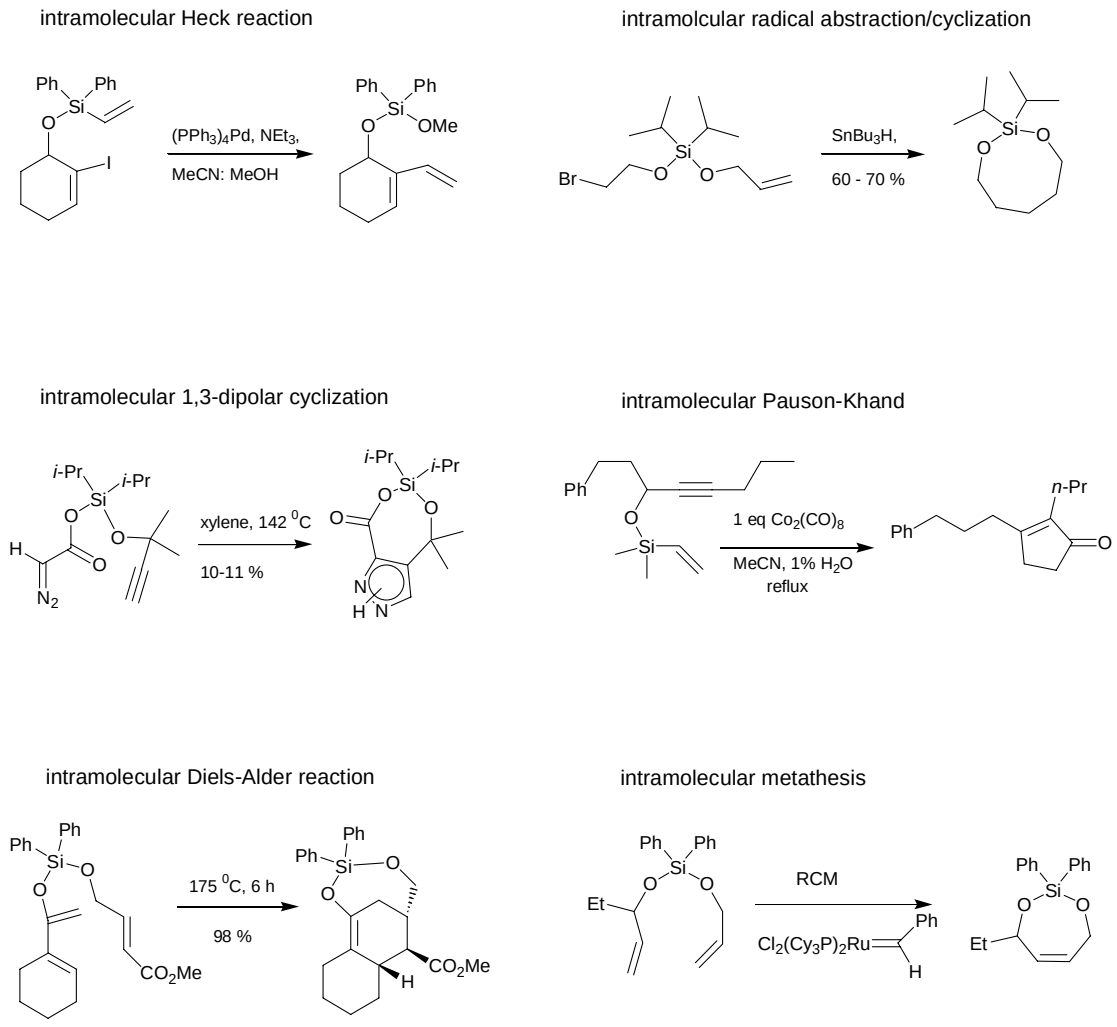
Synthetic methods using organosilanes are vital to organic synthesis. Formation of silyl ethers and silyl ketals are among the examples. There have been significant developments in silyl ether synthesis and applications to organic chemistry over the years. These compounds have proved to be versatile, safe, and compatible with a variety of reaction conditions. For these reasons silyl ethers and silyl ketals have been widely employed in organic synthesis. They are

used in the areas of tethering reactants for stereospecific intramolecular reactions,[5,6] protecting agents for many functional groups,[7] and anchoring reagents and substrates for solid support synthesis.[8]

Research on tethering reactants for stereospecific intramolecular reactions has become a fast growing field in the synthesis of complex compounds.[9] Intramolecular reactions are faster and display high regio- and stereoselectivity, which is important in the synthesis of complex molecules. Whereas this process has been successfully exploited in the synthesis of cyclic molecules, it has not been easily extended to the synthesis of acyclic molecules. One way that intramolecular reactions can be carried out to form acyclic molecules is to tether the reactants, perform the intramolecular reaction and then remove the linker group (Scheme 17). The choices for tethers for many chemists are the silyl ether and the silyl ketal linkers. Apart form the advantages that were mentioned above, silyl ethers and silyl ketals provide a reliable protecting group for the hydroxyl-group which can be easily and selectively removed after the reaction is performed. This is evident in the many examples in the literature where silyl ketals are used as tethers for intramolecular reactions. Scheme 18 lists a few of these examples.



Scheme 17. Tethered reactants for intramolecular reactions.

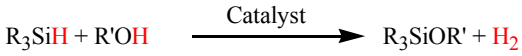


Scheme 18. Examples of silicon tethered intramolecular reactions.

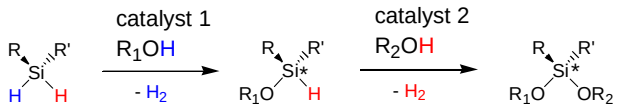
Silicon tethers based on bis-alkoxysilanes (silyl ketals) are commonly prepared from the dichlorosilanes by reaction with an alcohol in the presence of base. These conditions are not compatible with some base labile compounds. To make unsymmetrical bis-alkoxysilanes requires a method for breaking the symmetry of the dichlorosilane. Without such a method, one must accept a statistically determined mixture of mono-alkoxy and bis-alkoxy products. This may be acceptable for inexpensive readily available alcohols, but it precludes the use of bis-alkoxysilane tethers for high-value synthetic intermediates. To overcome these limitations to

bis-alkoxysilane synthesis, we investigated catalysts for the controlled stepwise alcoholysis of dihydridosilanes.

Catalytic alcoholysis of silanes by a variety of transition metal based catalysts is a useful method to form silyl ethers under mild conditions (Scheme 19). The process is atom-economical; hydrogen gas is the only byproduct. This mild method has not been fully exploited for the preparation of unsymmetrical bis-alkoxysilanes. A catalytic synthesis using silicon alcoholysis would circumvent the need of bases (and the attendant formation of protic byproducts), and eliminate the need for excess silicon dichlorides in the first silyl ether formation. We sought catalytic methods that would ultimately allow formation of chiral tethers that are asymmetric at the silicon center (Scheme 20). Our method, once developed, should be easily transferable for use with high-value synthetic intermediates in a complex target-oriented synthesis; therefore, it will be necessary to evaluate the scope and limitation of our new method.



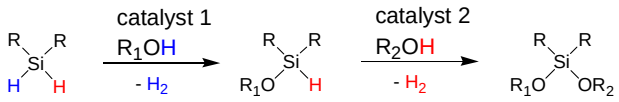
Scheme 19. Catalytic alcoholysis of silanes.



Scheme 20. Proposed stepwise catalytic alcoholysis of dihydridosilanes to form chiral organosilanes.

There have been several reports of catalytic methods for alcoholysis of trialkylsilanes,[10-17] however only a few of these papers have included reactions with dialkyl(dihydrido)silanes.[9a,d,15] Among the more reactive catalysts for the preparation of trialkylsilyl ethers from silyl hydrides

are $Co_2(CO)_8$,[11] $[IrCl(C_8H_{14})_2]_2$,[12] *cis*-$PtCl_2(PhCH{=}CH_2)_2$,[13] Crabtree's and Brookhart's cationic complexes ($[IrH_2(THF)_2(PPh_3)_3]SbF_6$[14] and $[C_5H_5(CO)(PPh_3)Fe^+]$[15] respectively), Wilkinson's catalyst ($Rh(PPh_3)_3Cl$),[9a] Stryker's catalyst ($[PPh_3CuH]_6$),[16] Doyle's rhodium(II) perfluorobutyrate ($Rh_2(pfb)_4$),[17] and Cutler's manganese pentacarbonyl bromide and its dimer ($Mn(CO)_5Br$, $[Mn(CO)_4Br]_2$).[18] A desirable catalyst for silane alcoholysis should fulfill several criteria. The catalyst should be able to couple tertiary alcohols even with less reactive silanes, it should be compatible with carbon-carbon multiple bonds and carbonyl groups, and it should be easily accessible and cost effective. Some of the more reactive catalysts such as ($Co_2(CO)_8$,[10] $[IrCl(C_8H_{14})_2]_2$,[11] *cis*-$PtCl_2(PhCH{=}CH_2)_2$,[12] and ($[IrH_2(THF)_2(PPh_3)_3]SbF_6$)[13]) competitively catalyzed alkene hydrosilylation and/or hydrogenation. The $[PPh_3CuH]_6$, and $Mn(CO)_5Br$ and its dimer $[Mn(CO)_4Br]_2$ are known to be compatible with both alkenes and alkynes,[15,17] and $Rh_2(pfb)_4$ is known to be compatible with alkenes.[16]



Scheme 21. Proposed stepwise catalytic alcoholysis of dihydridosilanes.

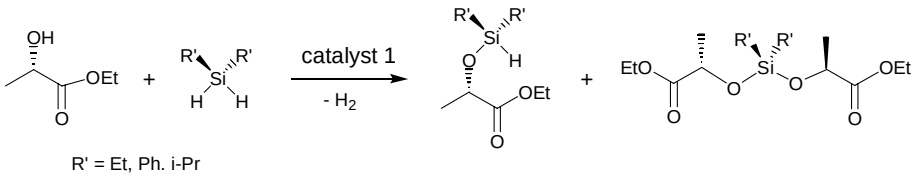
There have been a few reports on the controlled catalytic alcoholysis of dialkylsilanes to produce the mono-hydrido silyl ether.[9a,c,15,16] One such report is by Corriu and Moreau who have illustrated the use of either $(PPh_3)_3RhCl$, $(PPh_3)_3RuCl$ or Raney Ni to execute the controlled alcoholysis of diphenylsilane to give the mono-functional alkoxysilane as the only product.[9a] Doyle attempted to use the $Rh_2(pfb)_4$ catalyst with diphenylsilane and *trans*-1,2-cyclohexanediol to prepare the cyclic silyl ketal,[16] but this was not successful, perhaps because the *trans*-fused

[4.3.0] bicyclic product incorporating two Si-O bonds (1.6 Å) in a 5-membered ring is too unstable. A six-membered cyclic silyl ketal was accessible when 1,3-diols were treated with diphenylsilane or methylphenylsilane in the presence of $[PPh_3CuH]_6$ catalyst.[15] We have evaluated different catalytic methods to explore an efficient synthetic method for creating unsymmetrical bis-alkoxysilanes from dihydridosilanes in two consecutive catalyzed alcoholysis reactions (Scheme 21), and herein we report our results.

2.2. Discussions and Results

2.2.1. $Rh_2(OAc)_4$ Catalyst

We began our search by looking for silanes and catalysts that would allow a single addition of an alcohol to a dihydridosilane under mild conditions. The silanes that were studied are diethylsilane, diphenylsilane and diisopropylsilane. These silanes were treated with (+)-ethyl lactate in the presence of a variety of transition metal catalysts. The silanes were



Scheme 22. Catalytic alcoholysis of various dihydridosilanes with (+)-ethyl lactate.

Table 4. Catalytic Alcoholysis of Diethylsilane, Diphenylsilane and Diisopropylsilane with Various Catalysts.

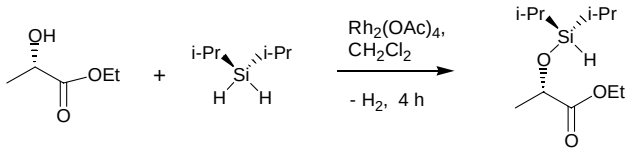
Entry	R'	Time (h)	Catalyst	Ratio[a]	
				$R'_2Si(H)OR^b$	$R_2Si(OR^b)_2$
1	Et	1	$Rh_2(OAc)_4$	0	1
2		1	$Rh_2(pfb)_4$	0	1
3		1	10 % Pd/C	0	1
4		1	$[PPh_3CuH]_6$	0	1
5	Ph	12	$Rh_2(OAc)_4$	1	0
6		1	$Rh_2(pfb)_4$	0.9	0.1
7	*i*-propyl	4	$Rh_2(OAc)_4$	1	0

(a) Ratio of products as observed by NMR of the crude mixture; no starting material was observed.
(b) R = (+)-ethyl lactate.

evaluated in stages with different catalysts. With diethylsilane, 10 % palladium on carbon (10 % Pd/C), rhodium acetate dimer ($Rh_2(OAc)_4$), rhodium perfluorobutyrate ($Rh_2(pfb)_4$) and $[PPh_3CuH]_6$ hexamer were each evaluated. They gave the bis-alkoxy product after only 1 h (Scheme 22, Table 4). The next silane investigated was diphenylsilane. $Rh_2(OAc)_4$ and $Rh_2(pfb)_4$ were the only catalysts evaluated with this silane. $Rh_2(pfb)_4$ gave a 9:1 ratio of the mono-alkoxy product and the bis-alkoxy product, but the $Rh_2(OAc)_4$ dimer gave only the mono-alkoxy product. This result was encouraging; however the excess diphenylsilane could not be removed by vacuum evaporation after the reaction, due to its high boiling point (95-97 ºC at 13 mm). Column chromatography was also ineffective in removing the excess diphenylsilane, because the mono-alkoxysilane substrate was unstable on silica gel. We developed a protocol that was effective in removing the excess diphenylsilane. Treatment of the reaction mixture with Wang resin (in the presence of the catalyst) allowed the removal of the excess diphenylsilane after several hours without reaction of the mono-alkoxysilane. Although this was a good method, we continued to seek a silane-catalyst combination that would be less time consuming to use. We were interested in finding a silane with a boiling point low enough that it could be easily removed by evaporation at the end of the reaction, and a catalyst (such as $Rh_2(OAc)_4$) which could be filtered off.

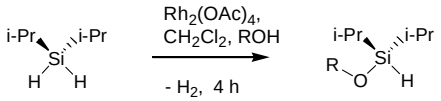
Following our results with diethylsilane and diphenylsilane, we consider the evaluation of diisopropylsilane or di-tert-butylsilane. Diisopropylsilane and di-tert-butylsilane may both be bulky enough that they would allow only one addition; however diisopropylsilane (bp 96 ºC) has a lower boiling point than di-tert-butylsilane (bp 128 ºC) and would be easier to be removed at the end of the reaction by simple evaporation on a rotary evaporation apparatus. Unlike the two previous silanes, diethylsilane and diphenylsilane, diisopropylsilane was not commercially

available. Diisopropylsilane was synthesized from dichlorodiisopropylsilane by reduction with lithium aluminium hydride according to the procedure of Horner and Mathias.[19] To our delight catalytic alcoholysis of diisopropylsilane with (+)-ethyl lactate in the presence of $Rh_2(OAc)_4$ gave only the mono-alkoxysilane product (**1e**) after 4 h (Scheme 23). Diisopropylsilane also met the requirement of being easily removed after the reaction by simple evaporation on a rotary evaporation apparatus. Since this result met our need, the reaction was never attempted with $Rh_2(pfb)_4$.



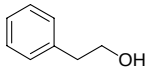
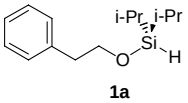
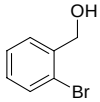
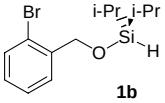
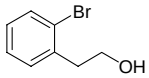
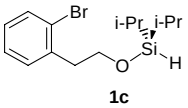
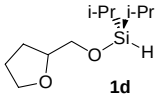
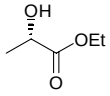
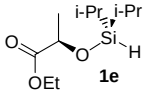
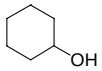
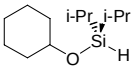
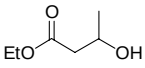
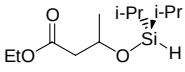
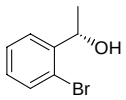
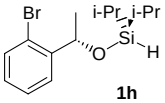
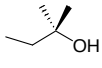
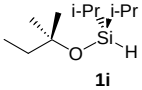
Scheme 23. Controlled catalytic alcoholysis of diisopropylsilane with (+)-ethyl lactate using $Rh_2(OAc)_4$ as the catalyst. The reaction stops after one addition.

After obtaining this encouraging result, the $Rh_2(OAc)_4$ catalyst was evaluated with several other alcohols using diisopropylsilane (Scheme 24). The reaction works with primary, secondary and tertiary alcohols (Table 5). Alcohols with aryl halide functionality also work, however the reaction failed with alcohols containing double and triple bonds because hydrosilylation and/or hydrogenation of double and triple bonds is believed to be a major side reaction as judged by NMR analysis of crude mixture.



Scheme 24. Alcoholysis of diisopropylsilane using $Rh_2(OAc)_4$ as catalyst.

Table 5. Mono-alkoxysilanes **1a-1i**.

Entry	ROH	Time (h)	Product	% Conversion[a]
1		1.5	 **1a**	100
2		1.5	 **1b**	100
3		1.5	 **1c**	100
4		1.5	 **1d**	100
5		4	 **1e**	100
6		4	 **1f**	100
7		4	 **1g**	100
8		4	 **1h**	100
9		4	 **1i**	100

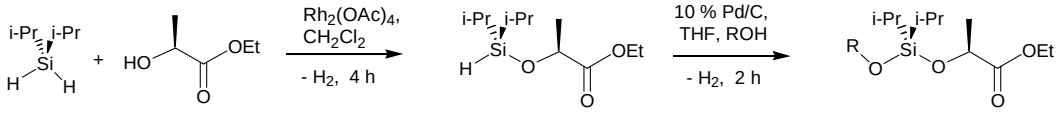
(a) Product was observed in the reaction mixture by NMR analysis; no starting material was observed and there were no other products containing the alcohol moiety.

2.2.2. 10 % Pd/C Catalyst

Following our success in finding a suitable silane and catalyst for the first step in the synthesis of unsymmetrical bis-alkoxysilanes, we set out to evaluate catalysts to achieve the second alcoholysis. We were aware from prior reports in the literature that there were a variety of catalysts capable of performing alcoholysis of silanes.[10-17] From prior evaluation of catalysts in the first step, we knew that 10 % Pd/C, $Rh_2(pfb)_4$, and "CuH" all catalyze the reaction of the second step with diethylsilane and $Rh_2(pfb)_4$ catalyzes the reaction of the second step (10 %) with diphenylsilane (Table 4). $Rh_2(OAc)_4$ was ruled out by our discovery that only one addition of alcohol occurred with diisopropylsilane.

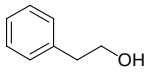
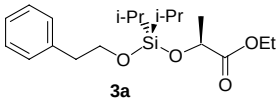
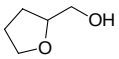
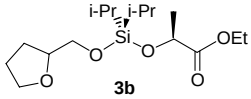
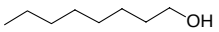
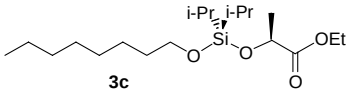
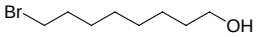
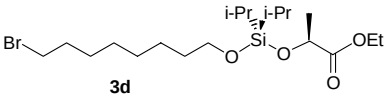
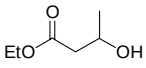
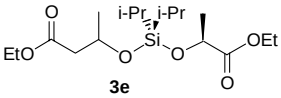
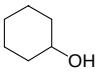
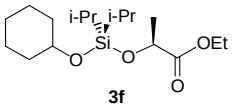
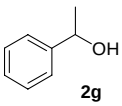
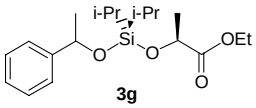
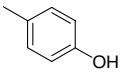
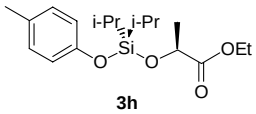
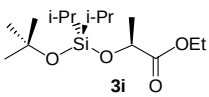
The mono-alkoxy products from the first addition of both diisopropylsilane and diphenylsilane with (+)-ethyl lactate was evaluated with $[PPh_3CuH]_6$, $Rh_2(pfb)_4$ and 10 % Pd/C. When $[PPh_3CuH]_6$ was used as catalyst with the mono-alkoxy product from (+)-ethyl lactate and diisopropylsilane (**1e**), a 30 % yield (isolated by flash chromatography) of the desired silyl ketal product was obtained. The yields rose to up to 70 % for the reaction of the mono-alkoxy diisopropylsilane using $[Rh_2(pfb)_4]$ after 14 h at room temperature.

The best results were obtained for the formation of the bis-alkoxy diisopropylsilane products when 10 % Pd/C was used as the catalyst (Scheme 25). Under these conditions excellent yields were obtained in just 2 h at room temperature. We propose that the use of diisopropylsilane is crucial to the success of the second addition, because the mono-alkoxy product from the reaction of (+)-ethyl lactate with diphenylsilane,[20] when subjected to the conditions of the second addition using any of the three catalysts evaluated, gave only low yields of the unsymmetrical bis-alkoxysilane.



Scheme 25. Two step procedure for the synthesis of unsymmetrical silyl ketals.

Table 6. Alcohol Addition to Ethyl (2S)-2-[(diisopropylsilyl)oxy]propanoate using 10 % Pd/C as the Catalyst.

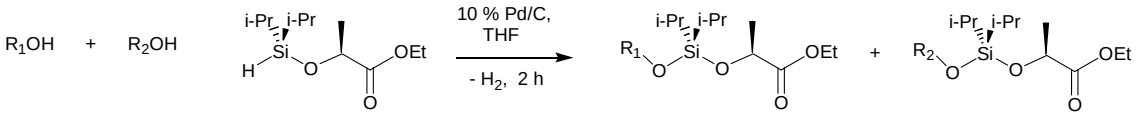
Entry	Alcohol	Product	% isolated yield[a]
1	 **2a**	 **3a**	84
2	 **2b**	 **3b**	82
2	 **2c**	 **3c**	84
3	 **2d**	 **3d**	87
4	 **2e**	 **3e**	84
5	 **2f**	 **3f**	84
6	 **2g**	 **3g**	78
7	 **2h**	 **3h**	91
8	 **2i**	 **3i**	86

(a) % isolated yield over two steps.

The advantages of 10 % Pd/C include the short reaction time and the ease with which the catalyst can be separated from the product after the reaction is completed. The disadvantage is that 10 % Pd/C catalyzes the reduction of double bonds under the reaction conditions, therefore it is not compatible with substrates containing carbon-carbon multiple bonds.

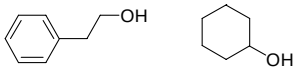
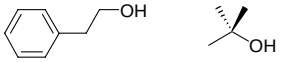
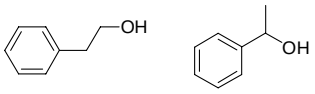
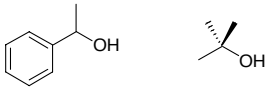
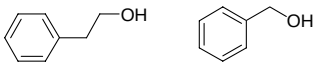
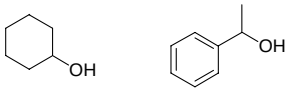
Our optimized method was applied to form several unsymmetrical bis-alkoxysilanes in very good yields over two steps (Table 6). Tertiary alcohols, which can be difficult to protect, readily react under the conditions to give good yields of the unsymmetrical bis-alkoxysilane product.[21]

The influence of the alcohol on the reaction was evaluated (Scheme 26). The results of a competition experiment between the alcohols are shown in Table 7. Both alcohols were treated with mono-alkoxysilane **1e** using 10 % Pd/C as the catalyst. The silyl ketals of both alcohols were isolated as a mixture and the area under the methine protons, from the (+)-ethyl lactate moiety of both silyl ketals, was compared by NMR analysis. The difference in reactivity of primary, versus secondary, versus tertiary alcohol was small. The differences in reactivity range from 1.5:1 for 1º vs 2º, to 3:1 for 1º vs 3º. The reactivity of a benzyl alcohol is slower than the aliphatic alcohol as shown in entries 4 to 6. Entries 4 and 5 show an increase in the ratio of 1º:2º alcohol and a decrease in ratio for the 2º:3º for the secondary benzyl alcohol. Entries 6 and 7 confirm that benzyl alcohols are less reactive than aliphatic alcohols. The inductive electron withdrawing effect of the aryl group in the benzyl alcohol renders it less nucleophillic and this may affect the rate of reaction with the silane. Although the difference in reactivity is small, this trend may be informative. The influence of the alcohol's nucleophilicity on the reaction mechanism will be addressed in a later section.



Scheme 26. The evaluation of alcohols on the rate of reaction.

Table 7. Steric and Electronic Effects on the Reactivity of Alcohols with Ethyl (2S)-2-[(diisopropylsilyl)-oxy]propanoate using 10 % Pd/C as the Catalyst.

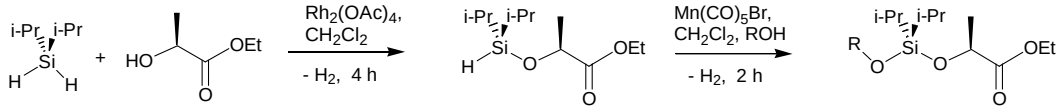
Entry	Alcohols	Ratio of silyl ketals[a]
1	 1° aliphatic vs 2° aliphatic	1.4 : 1
2	 1° aliphatic vs 3° aliphatic	3.0 : 1
3	 2° aliphatic vs 3° aliphatic	2.4 : 1
4	 1° aliphatic vs 2° benzyl	2.6 : 1
5	 2° benzyl vs 3° aliphatic	2.0 : 1
6	 1° aliphatic vs 1° benzylic	1.1 : 1
7	 2° aliphatic vs 2° benzylic	1.2 : 1

(a) Ratio describe the difference in the area under the methine proton for the (+)-ethyl lactate moiety of both silyl ketals by NMR analysis.

2.2.3. $Mn(CO)_5Br$ Catalyst

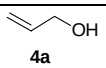
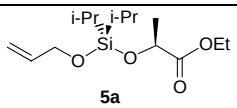
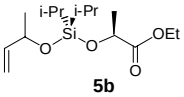
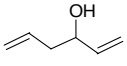
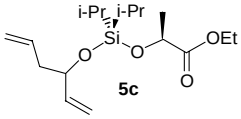
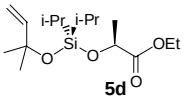
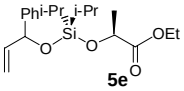
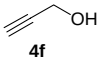
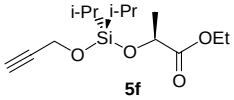
Although we were successful in accomplishing the second addition step using 10 % Pd/C as catalyst, we wanted a catalytic system that was tolerable to a variety of functional groups including alkenes, alkynes and aryl halides. We continued to evaluate other catalysts for the second addition step to find a method compatible with alcohols having alkene, alkyne, or aryl halide functionality. It was reported by Cutler et al. that $Mn(CO)_5Br$ and its dimer $[Mn(CO)_4Br]_2$ catalyze silane alcoholysis with trialkylsilanes and they were compatible with alkenes and alkynes.[17] Upon our evaluation of $Mn(CO)_5Br$ we found that it successfully catalyzes the alcoholysis of the second step. We were pleased to find that the $Mn(CO)_5Br$ catalyst was compatible with alcohols containing alkenes and alkynes functional groups (Scheme 27), and with alcohols containing aryl halide functional group (Scheme 28).

Once again the mono-alkoxy product **1e** was used as our starting point. This mono-alkoxy product was treated with several alcohols using the $Mn(CO)_5Br$ as catalyst in CH_2Cl_2 at room temperature in air. The results are shown in Table 8 and Table 9. The success of this reaction was very encouraging to us because we were able to synthesize unsymmetrical bis-alkoxysilanes containing modifiable functional groups. This will allow us to explore stereospecific intramolecular reactions with chiral silanes.

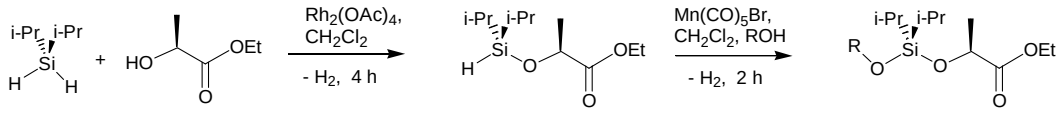


Scheme 27. Two step procedure for the synthesis of unsymmetrical silyl ketals containing alkene and alkyne functionality.

Table 8. Alkenols addition to ethyl (2S)-2-[(diisopropylsilyl)oxy]propanoate using $Mn(CO)_5Br$

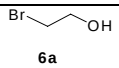
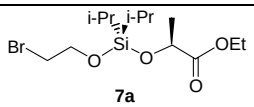
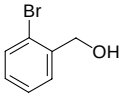
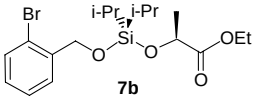
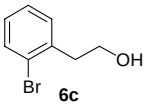
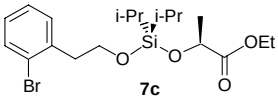
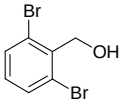
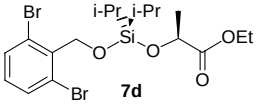
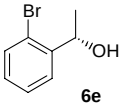
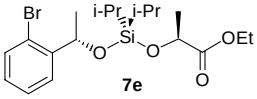
Entry	Alcohol	Product	% Isolated yield[a]
1	 **4a**	 **5a**	68
2	 **4b**	 **5b**	67
3	 **4c**	 **5c**	62
4	 **4d**	 **5d**	56
5	 **4e**	 **5e**	51
6	 **4f**	 **5f**	70

(a) % isolated yield over two steps.



Scheme 28. Two step procedure for the synthesis of unsymmetrical silyl ketals containing aryl bromide functionality.

Table 9. Alcohol Addition to Ethyl (2S)-2-[(diisopropylsilyl)oxy]propanoate using $Mn(CO)_5Br$ as the Catalyst.

Entry	Alcohol	Product	Isolated % yield
1	 **6a**	 **7a**	68
2	 **6b**	 **7b**	75
3	 **6c**	 **7c**	65
4	 **6d**	 **7d**	33
5	 **6e**	 **7e**	59

(a) % isolated yield over two steps

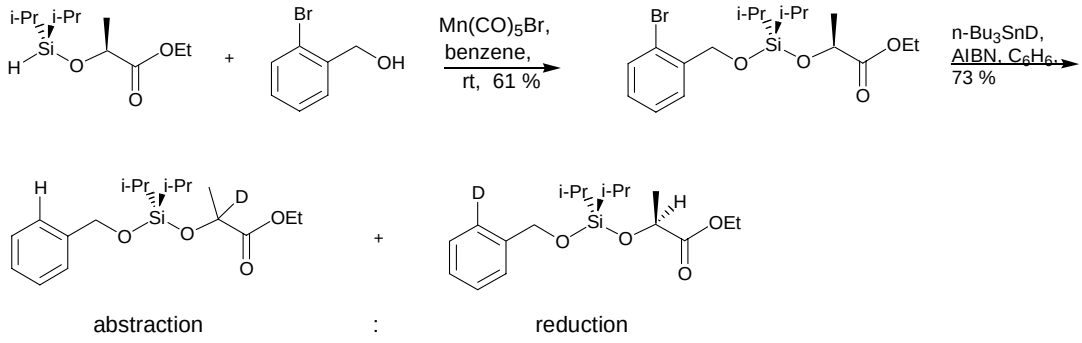
2.2.4. Intramolecular Radical Translocation Reaction

Our success in synthesizing silyl ketals containing an aryl halide with (+)-ethyl lactate led us to explore the intramolecular radical translocation reaction (Scheme 29). The term 'radical translocation' is described by Robertson et al. as "the intramolecular abstraction of an atom (usually hydrogen) or group by a radical center; this results in a repositioning of the site of the unpaired electron which can lead to functionalization at positions normally unreactive towards external reagents or whose selective modification is difficult." In the most common cases the abstraction occurs at a site that is five atoms away from the radical; 1,6 atom abstraction are less common, and 1,n-abstractions where n > 6 are rare. This is because the shortest chain length that can accommodate the trajectory for atom abstraction contains six atoms, as in the case of the 1,5 atom abstraction. Entropic factors usually result in the failure of the process in the cases where n > 6 atoms.

Curran and co-workers have explored the use of silicon tethers to carry out these reactions.[22,23,24] They have successfully demonstrated the 1,5 and 1,6 translocation of a radical that goes on to do intramolecular cyclization reactions. This method was used to synthesize natural product such as crinipellin A[22] and 2-(*o*)-(2-bromoaryl)dimethylsilyl-α-methyl-$_D$-mannopyranoside.[24] One of the nice benefits to the use of silicon tethers is that they serve as a hydroxyl-protecting group before and after the reaction is performed.

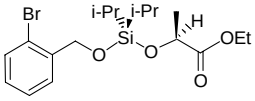
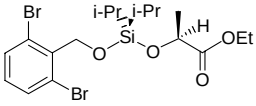
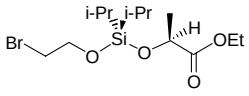
We explored three examples of this reaction. In our first two examples, the abstraction occurs at the 7th position away from the initial radical center (Table 10, entries 1 and 2), and in another example, it occurs at the 6th position away from the radical center (Table 10, entry 3). It is a well established fact that radical quenching is a very fast process; however in all our examples where n > 6 atoms, radical translocation was faster than radical quenching. This result

is remarkable because as mentioned above, radical translocation where n > 6 atoms, is very difficult to achieve. From this result we propose that silicon tethers can be used to accomplish radical translocation reaction for n = 6 and 7 atoms.



Scheme 29. Radical translocation and hydrogen atom abstraction.

Table 10. Hydrogen Atom Abstraction versus Radical Quenching for 1,7 and 1,8 Atom Radical Translocation.

Entry	Substrate	Conditions	Isolated % yield	Abs : Rdn
1		A	73	1.8 : 1
		B	68	2.6 : 1
		C	57	2.5 : 1
2		B	42	5.0 : 1
3		B	41	1.8 : 1

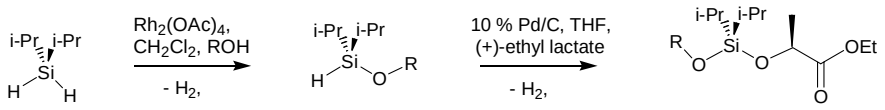
Conditions: A: Substrate 1 equiv.; nBu_3SnD 1.3 equiv.; Benzene [0.05 M]

B: Substrate 1 equiv.; nBu_3SnD 1.3 equiv.; Benzene [0.01 M]

C: Substrate 1 equiv.; nBu_3SnD 1.3 equiv.; Benzene [0.005 M]

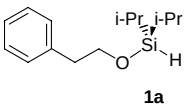
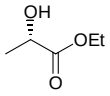
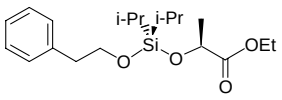
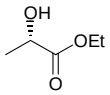
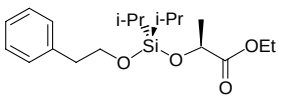
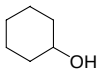
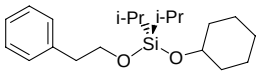
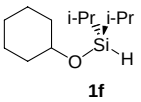
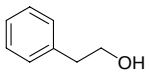
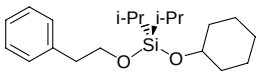
2.2.5. Exploring the Scope and Limitation of Our Method

Thus far we have been using (+)-ethyl lactate as the alcohol in the first step in the synthesis of silyl ketals. As we mentioned in the introduction, in order for our method to be transferred for use with high-value synthetic intermediates in a complex target-oriented synthesis, we must explore the scope and limitation of our method. We began by evaluating the synthesis of silyl ketals by reversing the order of the alcohol addition (Scheme 30).



Scheme 30. Reverse order of silane alcoholysis.

Table 11. Catalytic Alcoholysis with a Reverse Order Addition of the Alcohols.

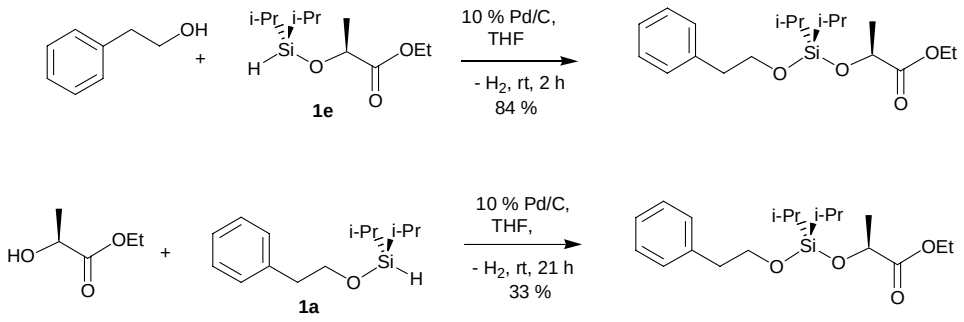
Entry	Mono-alkoxy silane	Alcohol	Time (h)	Silyl ketal	% Isolated yield
1	 **1a**		21		33
2			2[b]		41
3			8		76
4	 **1f**		20		68

(a) Reaction was performed at rt. (b) Reaction was performed at 70 ºC.

The mono-alkoxy product from 2-phenylethanol and diisopropylsilane (**1a**) was used in the evaluation (Table 11). When **1a** was treated with (+)-ethyl lactate using 10 % Pd/C as

catalyst, no product was obtained under the standard reaction condition (rt, 2 h). The reaction was repeated and allowed to go for several hours, and after 21 h only 33 % of product was obtained. The reaction of **1a** with (+)-ethyl lactate was repeated at 70 ºC, and 41 % of the product was obtained after 2h. Subsequently treatment of **1a** with cyclohexanol resulted in 76 % of the product after 8 h. This silyl ketal was synthesized in the reversed order; the reaction of **1f** with 2-phenylethanol yield 68 % of the bis-alkoxy product along with 13 % of the starting silane after 20 h at rt.

The mono-alkoxy product from (+)-ethyl lactate and diisopropylsilane (**1e**) is shown to be more reactive than **1a** and **1f** (Scheme 31). We can only speculate at this time that there may be some intramolecular interactions between the Lewis basic carbonyl oxygen of the (+)-ethyl lactate and the silicon atom, which may either, activate the silane towards oxidative addition to the metal catalyst or increase the rate at which the silane-metal complex is attacked by the nucleophilic alcohol.



Scheme 31. Comparison of the reactivity of **1a** versus **1e**.

2.3. The Mechanism

The mechanism of silane alcoholysis has been the focus of discussions over many years.[10a,14,15,17,25,30] A general mechanism is outlined below. This mechanism begins with oxidative addition of the metal into the Si-H bond to form either a η^2 complex (**Ia)** or a silyl hydride (**Ib**) (Figure 5). The alcohol then coordinates to the silicon forming a new complex (**II**) which can lose silyl ether to form a metal dihydrogen complex (**III**). The catalyst is regenerated when another silane displace molecular hydrogen from the catalyst. There are several minor variations of this mechanism; however this basic mechanism is believed to hold for many catalytic systems.

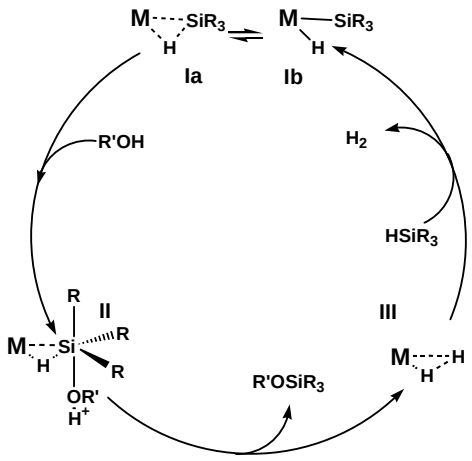


Figure 5. General mechanism of silane alcoholysis.

One example of minor variation in the catalytic cycle above is shown by Brookhart and co-workers, who performed a low temperature NMR study of their catalyst [$Cp(CO)(PR_3)Fe^+$] in the alcoholysis of triethylsilane with ethanol and phenol.[15] They observed catalyst deactivation during the reaction and upon evaluation of the system using low temperature NMR, they discovered that the ethanol disrupts the catalytic cycle in two ways (Figure 6). Ethanol

deprotonates the dihydrogen complex (**III**) reversibly, forming the iron hydride complex (**II**) along with the protonated ethanol. Ethanol also displaces the dihydrogen irreversibly from the metal forming a new metal-ethanol complex (**IV**). The formation of metal-ethanol complex **IV** terminates the catalytic cycle. The authors discovered that phenol, which is both less basic and less nucleophilic than ethanol, does not disrupt the catalytic cycle. They concluded that an alcohol that is basic and nucleophilic can disrupt the catalytic cycle causing deactivation of the catalyst.

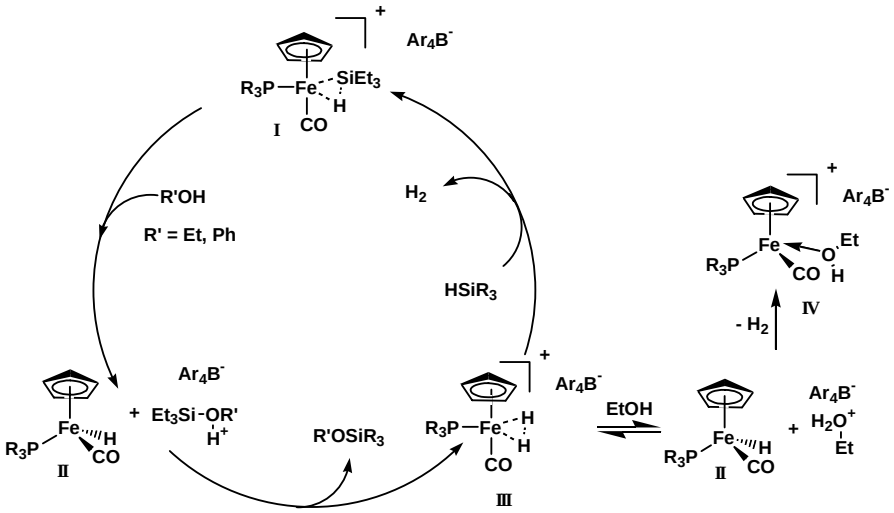


Figure 6. Catalytic cycle for Brookhart's iron catalyst showing disruption of the catalytic cycle by ethanol.

Oxidative addition of a Si-H bond to a metal can be explained using the Dewar-Chatt-Duncanson model. This model describes the σ-donation from the ligand (silane) into the d-orbital of the metal and back donation from the metal's dπ-orbital into the σ* of the ligand (Figure 7).[26] The extent of bonding depends on both the σ-donating ability of the ligand and the ability of the ligand to accept the back donation of electrons from the metal. This back donation of electrons from the metal depends on the valence of the metal center. It has been shown that

silane is a strong σ* accepting ligand because of the weaker Si-H bond,[27] causing oxidative addition on Si-H bonds to be fast and reversible. This is an important fact and we will later discuss its importance to our understanding of the mechanism of our catalytic system.

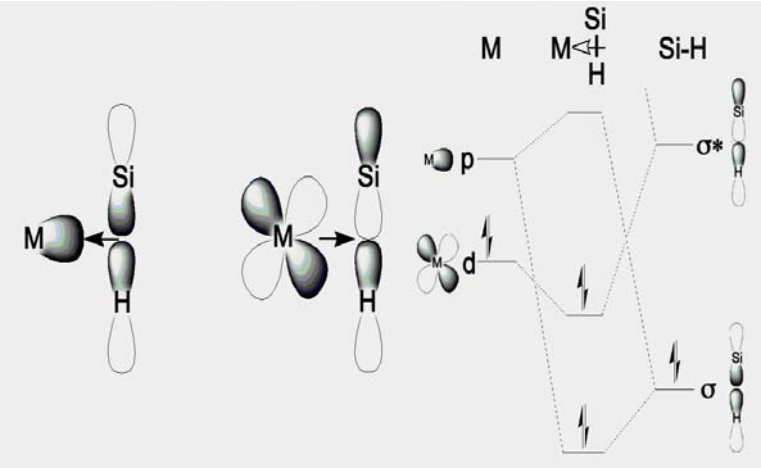
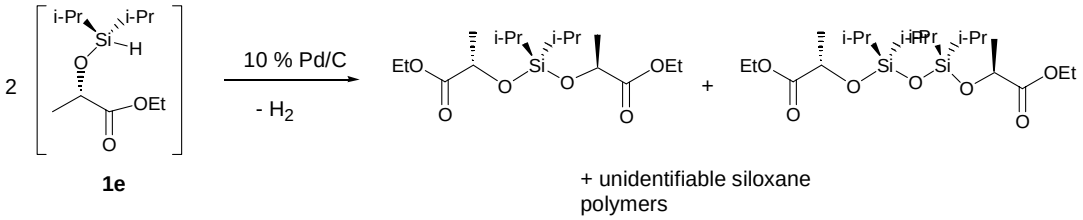


Figure 7. The metal η^2-silane bonding interactions based on the Dewar-Chatt-Duncanson model.

We have utilized three different catalytic systems; however during this investigation we have not thoroughly studied their mechanisms. The $Rh_2(OAc)_4$ system performed as expected, but the 10 % Pd/C and the $Mn(CO)_5Br$ catalytic systems gave us results that presented a need to consider their mechanism.

2.3.1. 10 % Pd/C Catalytic System

During our investigation of the reactivity of the 10 % Pd/C catalyst, we found that **1e** reacts with itself forming dimeric compounds (Scheme 32). This problem was solved by slow addition of the silane to a mixture of the alcohol and catalyst in the second alcoholysis step. We proposed that the silyl ether is activated by the catalyst and intramolecular dimerization occurs on the surface of the catalyst (Figure 8). This reaction is faster than the usual intermolecular reaction of the incoming alcohol with the silane, resulting in the dimeric products.



Scheme 32. Dimerization of **1e** with 10 % Pd/C.

The dimerization reaction could take place in at least two ways. The silyl ether oxygen of one silyl group may be in close proximity to the activated silicon of another, facilitating transfer of the lactate group (Figure 8**A**). A second pathway that could occur is that the transfer of lactate would be assisted by the neighboring hydrogen on the surface of the catalyst (Figure 8**B**). This would lead to the liberation of the free alcohol which could then react with the adjacent silane (Figure 8**C**). At this time we have not done any mechanistic studies to elucidate the pathway for this dimerization. Suggestions for further studies are discussed later.

We have observed that **1e** seems to be more reactive than both **1a** and **1f** (Scheme 33). This is evident in the long reaction times for conversion to the silyl ketals when **1a** or **1f** was treated with another alcohol (Table 11). In order to explain the increased reactivity of the **1e**, we

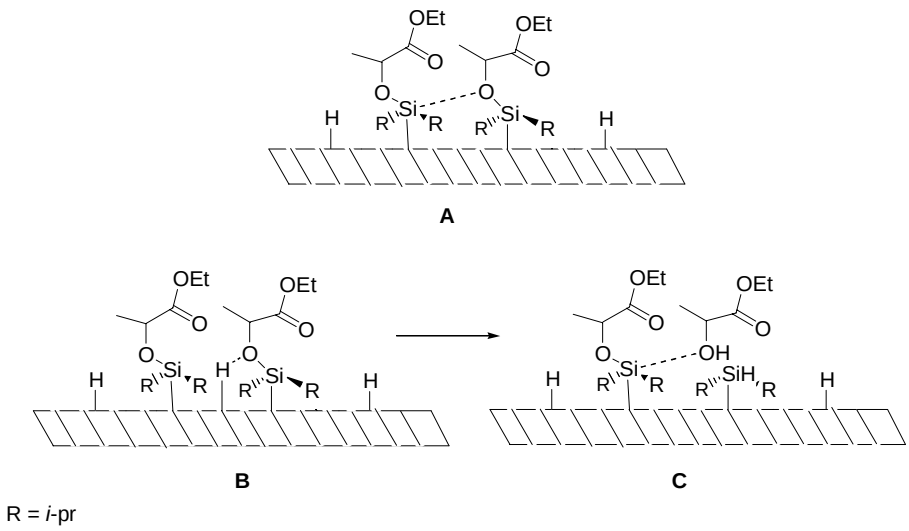
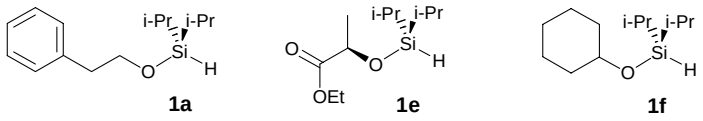


Figure 8. Proposed mechanism of dimerization of **1e** with 10 % Pd/C.

must first understand the mechanism of this reaction. Although a general mechanism has been proposed for silane alcoholysis, the rate determining step, which determines the rate of the reaction, may vary among different catalytic systems. It has been shown that the rate determining step for Brookhart' iron is the dissociation of the dihydrogen-metal complex assisted by the silane (Figure 5, step 4).[15] If this is true for the palladium system, then a more reactive silane would speed up the reaction. The question we have posed is — what makes **1e** more reactive?



Scheme 33. Compounds **1a, 1e** and **1f**.

We propose that the carbonyl oxygen of the (+)-ethyl lactate acts as a Lewis base forming an intramolecular pentacoordinated organosilicon compound. Pentacoordination from a

neighboring Lewis base has been previously described by Corriu et al. who showed that there is a higher reactivity of the pentacoordinated silanes toward nucleophiles than their tetravalent counterparts.[28] Intramolecular pentacoordination by an ester carbonyl group (as in our case) has been described by Voronkov and co-workers.[29] The extent of pentacoordination of the carbonyl oxygen to the silane depends on the substituents on the silane. Upon examination of the infra red spectrum of **1e**, the ν(C=O) stretching vibrations (1757cm^{-1}) indicate that pentacoordination is not occurring to a great extent at this stage. However it is likely that the degree of pentacoordination increases upon formation of the silane-metal complex.

Oxidative addition of the silane to the metal is fast and reversible;[30] therefore unless the pentacoordinated silane drastically slows down the oxidative addition process, pentacoordination will not alter the rate of the reaction at this stage of the cycle. The increased reactivity of **1e** may be explained by the attack of the alcohol on the pentacoordinated silane that would form after oxidative addition (Figure 9A). The rate of the alcohol addition is increased by the higher reactivity of the pentacoordinated silicon center. This may explain the slower reactivity for those alkoxysilanes that cannot form this intramolecular coordination complex due to the absence of a nearby Lewis basic atom. We had observed during the comparison of aliphatic alcohol to benzyl alcohol that the nucleophilicity of the alcohols has an effect on the rate of the reaction. This is evidence that the alcohol and the silane are involved in the rate-determining step with 10 % Pd/C catalytic system.

Our idea that intramolecular pentacoordination may accelerate the reaction was tested by using an alcohol with a neighboring ether group to act as a Lewis base (Figure 9B). Ethers are known to be more basic then the carbonyl of an ester.[31] The mono-alkoxysilane from

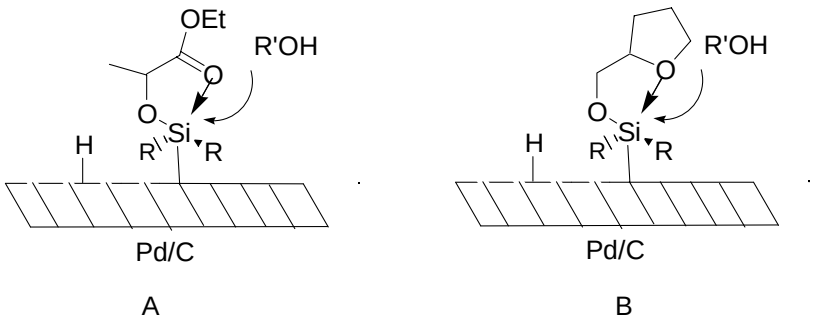
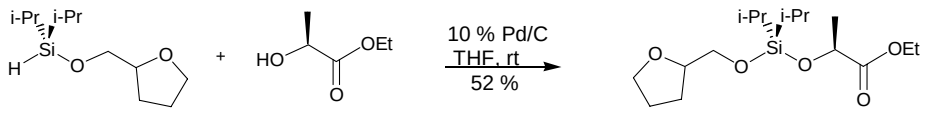


Figure 9. Reaction of alcohol on penta-coordinated metal-silane complex.

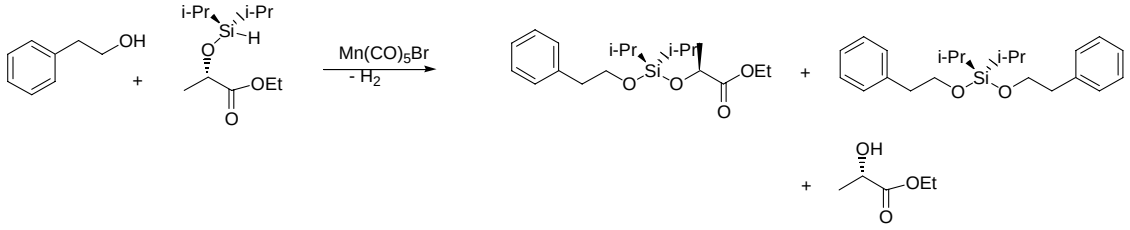
tetrahydrofurfuryl alcohol and diisopropylsilane (**1d**) was treated with (+)-ethyl lactate using 10 % Pd/C as the catalyst (Scheme 34). The silyl ketal was obtained in 52 % yield after 4 h. Although this reaction is faster than the reaction of **1a** with (+)-ethyl lactate, it is still much slower than the reaction of **1e** with other alcohols, including tetrahydrofurfuryl alcohol. Although the ether moiety of tetrahydrofurfuryl alcohol may be more basic than the carbonyl of (+)-ethyl lactate, the carbonyl of (+)-ethyl lactate may be more nucleophilic. In this case basicity does not match nucleophilicity. The result shows however that there is some advantage of having an electron donating group in proximity to the silicon atom to cause enhancement of the reaction. This rate enhancement was also observed in the reaction of mono-alkoxysilane from 3-hydroxy butyrate and diisopropylsilane (**1g)** with homoallyl alcohol using $Mn(CO)_5Br$ as the catalyst. This will be further discussed in the next section.



Scheme 34. Catalytic alcoholysis of **1d** with (+)-ethyl lactate.

2.3.2. $Mn(CO)_5Br$ Catalytic System

Our investigation of silane alcoholysis catalyzed by $Mn(CO)_5Br$ gave us some interesting results. Although we were delighted to find out that this catalytic system is compatible with alkenes, alkynes and aryl halides, the yields of these reactions were lower than in the 10 % Pd/C reactions. These lower yields are due, in some instances, to a side reaction in which exchange of alcohols occurs and formation of a symmetrical product is observed. When primary alcohols are treated with **1e**, symmetrical silyl ketal from the primary alcohol is observed along with the un-symmetrical silyl ketal product (Scheme 35). Although the amount of this side product is usually small (~ 10-20 %), the exchange product in some cases become the major product. This exchange is not observed when 10 % Pd/C is used as the catalyst. For these reasons we became interested in the mechanism of this exchange.



Scheme 35. Reaction of **1e** with 2-phenylethanol using $Mn(CO)_5Br$ as catalyst.

We proposed a mechanistic outline (Figure 10) and carried out several reactions in order to get an insight into the mechanism. We have demonstrated that the silane and alcohol are involved in the rate-determining step for the 10 % Pd/C catalytic system. It was documented with Brookhart's iron catalyst that the rate determining step for that system was the dissociation of molecular hydrogen from the metal assisted by the silane.[15] If the rate determining step is the same for our manganese catalyst as Brookhart's catalyst, then the concentration and lifetime of

the dihydrogen complex (**III**) is increasing over the course of the reaction. This allows time for the dihydrogen complex to engage in side reactions. Metal-dihydrogen complexes are known to be more acidic than the free hydrogen and may be capable of protonating silyl ethers or silyl ketals.[32] We proposed that the metal-dihydrogen complex is effecting the intermolecular protonation of the silyl ketal.

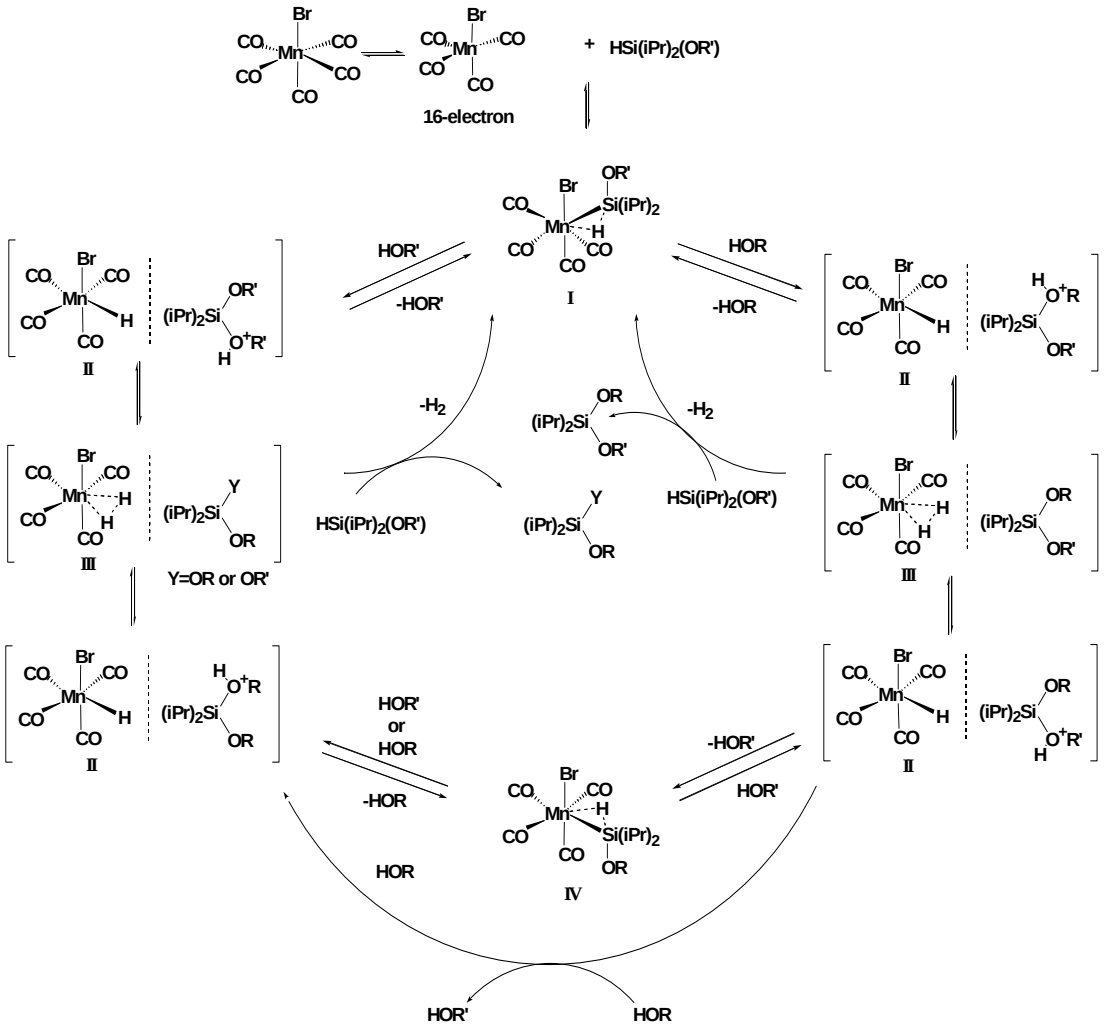


Figure 10. Our first proposed mechanism.

Figure 10 describes our proposed mechanism for protonation and eventually exchange of the alcohols leading to the symmetrical silyl ketal. Some processes are presumed reversible (denoted with the double arrows) but only the forward reactions are discussed. Oxidative addition of the metal into the Si-H bond results in the formation of metal-silane complex **I**. Alcohol addition to **I** leads to the metal hydride complex **II** and the protonated form of the unsymmetrical silyl ketal. Transfer of the proton from the silyl ketal to **II** gives the metal-dihydrogen complex **III**. Complex **III** can lose molecular hydrogen aided by the silane to give the unsymmetrical product and regenerate complex **I**. Complex **III** could also reprotonate the silyl ketal on the opposite oxygen forming the other protonated silyl ketal and the metal hydride complex **II**. This silyl ketal could lose the alcohol and form a new metal-silane complex **IV**. Complex **IV** could now react with the alcohol that is in the highest concentration to give the protonated form of a new symmetrical silyl ketal and regenerate complex **II**. Transfer of the proton to complex **II** leads to the metal-dihydrogen complex **III** and symmetrical silyl ketal. Dissociation of molecular hydrogen, aided by the silane, gives the symmetrical product and regenerates complex **I**.

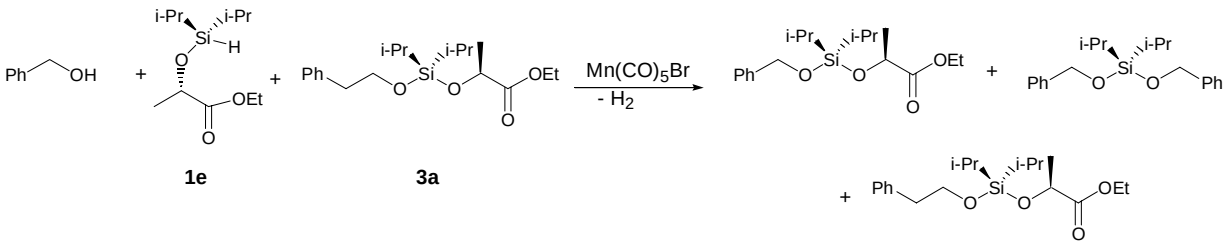
In the case where the silyl ketal is made up of the 2-phenylethanol and (+)-ethyl lactate (**3a**), the more basic oxygen would be the one on the 2-phenylethanol moiety. However protonation and eventually dissociation of this alcohol leads back to the starting silyl ether. Protonation could also occur on the oxygen of the (+)-ethyl lactate moiety. Once the (+)-ethyl lactate is protonated it could dissociate resulting in newly formed silyl ether. This newly formed silyl ether can react with the dissociated (+)-ethyl lactate, or it can go on to react with another 2-phenethyl ethanol which is present in a higher concentration than the dissociated (+)-ethyl

lactate. In order to test the idea that the metal-dihydrogen complex is the species that reprotonates the silyl ketal, we carried out three experiments.

The first experiment was designed to test whether the combination of hydrogen and catalyst could generate the metal-dihydrogen complex. This complex could protonate the silyl ketal causing exchange of alcohols. We treated the catalyst ($Mn(CO)_5Br$) with molecular hydrogen for 2 h, and then added 2-phenylethanol and silyl ketal **3a** in CH_2Cl_2 to the mixture. This was stirred under hydrogen for another 2 h. No exchanged product (the symmetrical silyl ketal from 2-phenylethanol) was observed.

The second experiment was to test the effect of bases on the rate of exchange during the alcoholysis reaction. This was to determine whether the exchange process was taking place by simple proton catalysis. We treated 2-phenylethanol and **1e** under the standard reaction conditions but this time 4 mol % potassium carbonate (K_2CO_3) was added. After the reaction was completed, 16 % of the exchanged product was observed. There was no difference in the extent of exchange by added base. The experiment was also conducted with triethylamine (Et_3N) as the base; however the reaction did not proceed.

The third and most informative experiment was to test whether the silyl ketal, after being formed, was able to lead to exchange products. We treated **1e** with benzyl alcohol under the standard condition for the manganese catalyst in the presence of **3a** (Scheme 36). The products that were obtained from this reaction include the unsymmetrical silyl ketal from benzyl alcohol and (+)-ethyl lactate, the symmetrical silyl ketal from benzyl alcohol, and recovered **3a**. No unsymmetrical silyl ketal from benzyl alcohol and 2-phenylethanol was observed.



Scheme 36. Reaction of benzyl alcohol with **1e** in the presence of **3a** using $Mn(CO)_5Br$ as the catalyst.

We concluded from these experiments that the exchange process must be occurring along the pathway to the product and the final product, once formed, is stable to the reaction conditions. Based on these results we have proposed a new mechanism which will be discussed further in the next section. We will also suggest experiments to test our new hypothesis.

2.3.3. Similarities Between the 10 % Pd/C and the $Mn(CO)_5Br$ Catalysts

The accelerated rate for alcoholysis with **1e**, which was observed for the 10 % Pd/C catalytic system, was also seen with the $Mn(CO)_5Br$ catalyst. Reactions of **1e** with primary, secondary or tertiary alcohols resulted in moderate yields of the corresponding silyl ketals after 2 h (Table 8 and 9). When mono-alkoxy silane from 3-hydroxy butyrate (**1g**) was treated with homoallyl alcohol in the presence of $Mn(CO)_5Br$ as the catalyst under the standard conditions, 76 % of the silyl ketal was obtained. These silyl ethers possess neighboring carbonyl groups that can participate in the reaction by forming a more reactive pentacoordinated silicon center upon addition of the silane to the metal center..

The reaction of **1a** with (+)-ethyl lactate resulted in only 43 % yield of the product after 24 h using the manganese catalyst. Silyl ether **1b** and **1c**, when treated with primary alcohols in the presence of $Mn(CO)_5Br$, resulted in very low yield of the silyl ketal along with desilylated alcohols. Reaction with secondary (excluding (+)-ethyl lactate and 3-hydroxy butyrate) or tertiary alcohols gave no product. Likewise reaction of **1h** with primary alcohols gave low yields of the unsymmetrical silyl ketal along with substantial amount of symmetrical silyl ketal resulting from exchange of the primary alcohols. Reaction of **1h** with secondary alcohols resulted in only recovered starting material and no silyl ketal was observed. The reaction of **1h** and tertiary alcohols was not attempted.

Another similarity between the two catalysts was the small electronic effect observed for 2-phenylethanol versus benzyl alcohol. The same 1.1: 1 ratio in favor of 2-phenylethanol was observed when a competition experiment was performed between the two alcohols.

From these results we concluded that the rate determining steps for both catalytic systems involves the alcohol and the mono-alkoxysilane. This rate is influenced by both the nucleophilicity of the alcohol and the reactivity of the silane.

2.4. Further Developments of Methodology

2.4.1. Understanding the Manganese System.

Progress towards the development of our method has been substantial; however more work is needed in order to widen the scope and determine the limitations of this method. There needs to be an understanding of the mechanism for the manganese catalyzed silane alcoholysis reaction in order to improve the yields. Some important questions to answer are: how is the exchange taking place? At what stage of the reaction cycle is exchange happening? Why is the exchange only limited to primary alcohols? Is there an electronic effect in play separate from a steric effect? In order to address these questions, a detailed look into the mechanism is required.

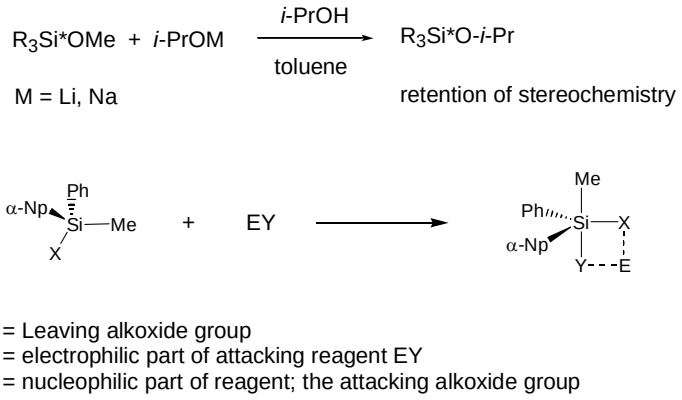
How is the exchange taking place and at what stage?

A low temperature NMR experiment of the reaction at different stages may give some insight to the species that are present and their concentrations. This experiment may reveal the stage at which desilylation of the more sterically demanding alcohol is taking place and the acid component that protonates it. We observed a lower yield for the reactions performed with $Mn(CO)_5Br$ as the catalyst compared to the reactions performed with 10 % Pd/C as catalyst. The lower yield may be attributed to deactivation of the catalyst by the alcohol as seen by Brookhart et al. with the cationic $[Cp(CO)(PR_3)Fe^+]$ catalyst.[14]

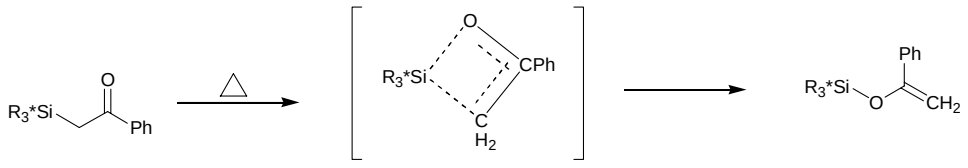
Our results from the experiments with the manganese catalyst indicate that proton transfer may not be intermolecular and the manganese-dihydrogen complex was not able to catalyze the exchange process. Corriu et al. reported that the manganese hydride complex in $[(\eta^5\text{-}CH_3C_5H_4)Mn(CO)_2(H)SiPh_3]$ has a very low acidity and the silylmanganese complex could not be deprotonated by (tetraethylammonium) chloride (Et_4NCl). In comparison, the silyliron hydride in $[(CO)_4Fe(H)SiPh_3]$ is very acidic and is deprotonated by Et_4NCl. Corriu's

manganese complex $[(\eta^5\text{-}CH_3C_5H_4)Mn(CO)_2(H)SiPh_3]$ requires a very strong base such as sodium hydride (NaH) to deprotonate it.[33]

We now propose that the proton transfer process could be occurring via an intramolecular 4-centered transition state between the newly formed silyl ketal (Figure 10). A similar 4-centered transition state has been previously proposed by Sommer and Fujimoto to explain retention of the stereochemistry at an asymmetric silicon center during the exchange of alkoxide groups (Scheme 37).[34] Brook and co-workers also proposed a 4-centered transition state for the thermal rearrangement of β-ketosilanes (Scheme 38).[35]



Scheme 37. Exchange of alkoxy groups via a 4-centered transition state.



Scheme 38. 4-Centered transition state showing the rearrangement of β-ketosilanes.

The intramolecular proton transfer between the incoming alcohol and the silyl ether could be taking place while the silane is still bonded to the metal center, maintaining a pentacoordinated-silicon center. At this stage there are two pathways that could take place that would result in exchanged products (Figure 11).

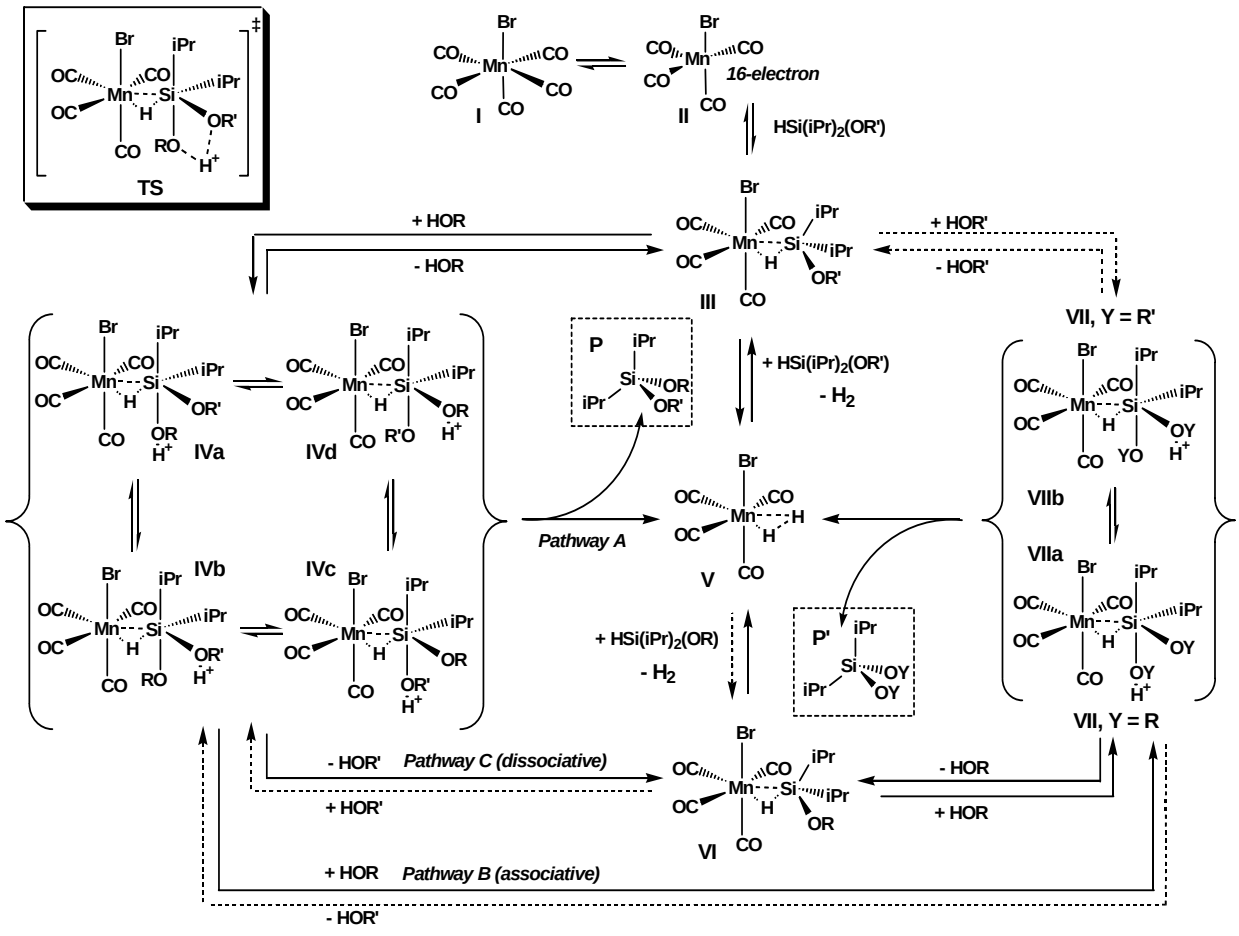


Figure 11. Proposed mechanism for the formation of symmetrical product.

Oxidative addition of the 16-electron manganese center on the silyl ether leads to silyl-manganese complex **III**. Attack on **III** by an incoming alcohol (ROH) leads to complex **IV**. Pseudorotation gives all four possible structures of **IV**. Complex **1V**, having a free proton,

could form a hydrogen bond between the two alkoxy groups via a 4-centered transition state (**TS**); three possible pathways could then occur.

Pathway A is a dissociation of the silyl ketal from the metal center forming a metal-dihydrogen complex **V** and the unsymmetrical silyl ketal product. Once this product is formed, it cannot get reprotonated because the metal-dihydrogen complex **V** is not sufficiently acidic to reprotonate silyl ketal. Hydrogen gas then dissociates from the metal center aided by the silane to regenerate the catalyst (**III**).

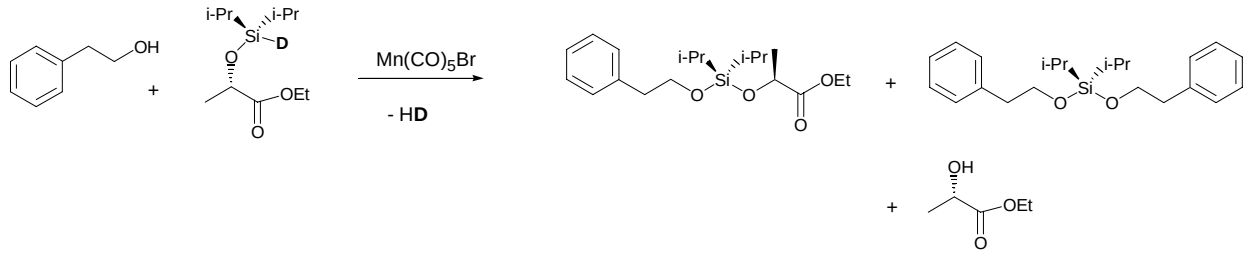
Pathways B and C describe the process that could occur to form the symmetrical silyl ketal. Formation of silyl ketal-metal complex **VII** could occur in one step via an associated pathway B, or in two steps via a dissociative pathway C. Pathway B could occur by attack on the pentacoordinated silyl ketal-metal complex **IV** by alcohol ROH, forcing the dissociation R'OH leading to complex **VII**. The associative pathway would precede through a hexacoordinated silicon species. Hexacoordinated silicon compounds have been shown to be very reactive.[36,23d] The choice of the alcohol that dissociates would be determined by electronic and/or steric factors.

Silyl ketal **VII** could also be formed in two steps by dissociation of R'OH, leading to silane **VI** (pathway C). Silane **VI** can react with ROH which is present in excess leading to the symmetrical silyl ketal **VII**. Dissociation of the silyl ketal from the metal center leads to the metal-dihydrogen complex **V** and the symmetrical silyl ketal product. Regeneration of (**III**) occurs when hydrogen gas dissociates from the metal center aided by the silane.

All these processes, except for dissociation of the silyl ketal from the metal center, are presumed reversible. The dotted arrows signify the possible reactions of R'OH that is present in low concentration.

It should be pointed out that no exchanged product is observed when two secondary alcohols or a secondary and a tertiary alcohol are involved in the reaction; neither is there exchange if the alcohol in the first step is primary and the alcohol in the second step is secondary or tertiary. As is mentioned above, the choice of which alcohol group dissociates may be determined by electronic and/or steric factors. However since we have not isolated any symmetrical silyl ketal containing two secondary alcohols, we are led to believe that the exchange phenomenon is influenced by a steric factor. Protonation occurs on the bulkier alcohol and not necessarily the more basic one. The exchange phenomenon is only limited to primary alcohols in the second step, and there is no steric differentiation between a secondary and a tertiary alcohol. Smaller alcohols lead to exchange.

One way to test our hypothesis in the intramolecular proton transfer is to perform a deuterium labeled experiment. The proton of the silane could be labeled with a deuterium atom and the percent deuterium present in the evolving gas could be measured (Scheme 39). If our hypothesis is correct and the proton that is transferred does not come from the silane, then the amount of deuterium in the evolving gas should be determined by the amount of silane used.

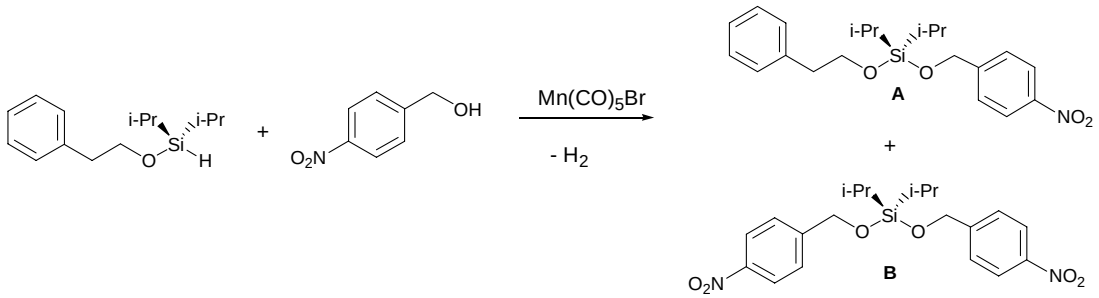


Scheme 39. Deuterium labeled experiment to test for proton transfer.

Why is the exchange phenomenon limited to primary alcohols and is there an electronic effect separate from the steric effect?

We have also proposed two pathways for intermediate **IV**, pathway B and pathway C (Figure 11). We are led to believe that pathway B is the major pathway because we have not observed any symmetrical product containing two secondary alcohols. A secondary alcohol would not be expected to facilitate pathway B. However pathway C could still be a major competing pathway with primary alcohols. A theoretical calculation of the difference in free energy in going from **IV** to **VII**, could give us vital information on the lowest energy pathway.

We have briefly looked at the electronic effects on this mechanism by the competition experiment of two primary alcohols (2-phenethyl ethanol and benzyl alcohol). The information we obtained only explained the importance of the nucleophilicity of the alcohol. In order to determine the electronic effects on the dissociating alcohol, an experiment could be performed that treats the silyl ether of a primary alcohol with a second primary alcohol, both alcohols having different electronic environments (Scheme 40). The ratio of exchange product (**B**) to expected product (**A**) would be an indication of the effect of the electronic environment on the dissociating alcohol in intermediate **IV** of Figure 11.



Scheme 40. Evaluation of electronic factors on the extent of exchange.

2.4.2. Chiral Silanes

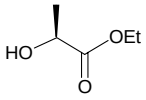
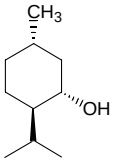
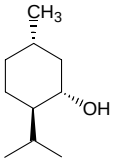
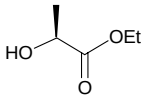
The ability to produce optically active molecules from prochiral precursors by asymmetric induction is an important goal in synthetic organic chemistry. Given the many synthetically useful reactions of organosilanes, it would be very valuable if these reactions could be carried out with transfer of chirality from the silicon to the carbon. Chiral transfer from silicon center to carbon can be done by either of two methods as explained by Paquette.[37] One method is called substrate-controlled transformation, where the chiral silane moiety is covalently bonded to the substrate functioning as a chiral auxiliary. During the reaction no bonds are replaced at the silicon center. The silane auxiliary can be removed after. This process has the advantages of using the silane moiety to serve as a protecting group as well as a chiral auxiliary. The other method is called reagent-controlled transformation, where a covalent bond is replaced by a prochiral substrate at the chiral silicon center during the reaction. The new substrate that is attached to the silane now has a new chiral carbon center, and this new chiral information was transferred from the silicon. In addition, we wish to point out the value of using chiral silanes for kinetic resolution of racemic compounds.

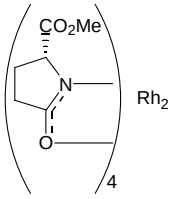
We sought catalytic methods that would allow formation of chiral tethers that are asymmetric at the silicon center. Synthesis of the chiral tether by our method would be advantageous for the reasons we described in the Introduction. Chiral information could be transferred during an intramolecular reaction. This would be an example of substrate-controlled transformation.

We have tried to synthesize chiral silanes using our method and the prochiral silanes methylphenylsilane and methylcyclohexylsilane with (+)-ethyl lactate and *D*-menthol. Both of these silanes gave racemic mono-alkoxy products with the alcohols used (Table 12). The

reaction was tried using Doyle's chiral dirhodium carboxamide catalyst under the standard conditions for the first addition, but not selectivity was observed. Work is presently being pursued in our lab to synthesize a chiral catalyst that could induce selectivity in this reaction.

Table 12. The Evaluation Silane Alcoholysis of Prochiral Silanes with Chiral Alcohols in the First Addition.

Entry	Silane	Alcohol	Ligand	Ratio of Isomers
1			no ligand	1:1
2			no ligand	1:1
3			Doyle's catalyst $Rh_2(5S\text{-}MEPY)_4$	1:1
4			no ligand	1:1

Doyle's chiral dirhodium carboxamide: 

Once a chiral silane is synthesized, intramolecular reaction such as the Heck reaction and the radical cyclization reaction with transfer of chirality from the silicon center can be pursued. Other reactions of interest include the stereoselective hydrosilylation of aldehydes and ketones. Our method could be used to tether chiral silanes to solid support for uses in solid support

synthesis. A solid supported chiral tether could be a potentially powerful tool in the kinetic resolution of racemic alcohols.

2.5. Conclusion

A mild method has been developed to synthesize unsymmetrical bis-alkoxysilanes (silyl ketals). This method utilizes three different catalysts to synthesize a variety silyl ketals in a stepwise manner. We were able to achieve our initial goal of finding catalytic systems that are mild, compatible with carbon-carbon multiple bonds, easily accessible and cost effective. Our method can couple tertiary alcohols in moderate to high yields.

We have synthesized mono-alkoxysilanes **2a-2i** and unsymmetrical bis-alkoxysilanes **3a–3i**, **5a–5f** and **7a–7e** in moderate to high yields using a combination of $Rh_2(OAc)_4$ followed by 10 % Pd/C or $Mn(CO)_5Br$ as catalysts. To our knowledge we are the first to show the compatibility of the manganese catalyst with aryl bromides. We have shown that diisopropylsilane was crucial to this process and that employing (+)-ethyl lactate as the alcohol in the first step allows for a faster and more efficient reaction in the second step.

Silyl ketals **7a**, **7b** and **7d** were used to show that intramolecular radical translocation beyond the 1,5 atom was not only feasible, but efficient.

We have performed several studies on the manganese catalytic system in order to get some insight to the mechanism. We have observed exchange of alcohols during the reactions involving primary alcohols, which we attributed to occur as a result of proton transfer. We have concluded from our results that the proton transfer process could not be taking place by an intermolecular process and therefore we proposed an intramolecular version to account for the proton transfer.

We have established that the nucleophilicity of the alcohol and the reactivity of the mono-alkoxysilanes are very important to the rate of alcoholysis. This effect was observed by both the 10 % Pd/C and the $Mn(CO)_5Br$ catalytic systems. We have concluded from this study

that the alcohol and the mono-alkoxysilane are both involved in the rate-determining step for both the 10 % Pd/C and the $Mn(CO)_5Br$ catalytic systems.

2.6. Experimental

Infrared spectra (IR) were determined on a Mattson Cygnus 100. IR was taken using thin layer preparation. Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on Bruker AF-300 MHz, AC-300 MHz, or AM-500 MHz spectrometer. Chemical shifts are expressed as parts per million (ppm) downfield from tetramethylsilane (TMS). When $CDCl_3$ and DMSO were used (^{13}C-NMR), peak assignments were made relative to TMS (0.00 ppm), CD_2Cl_2 (53.50 ppm) and DMSO-d6 (39.5 ppm). The following abbreviations are used: br = broad, s = singlet, d = doublet, t = triplet, dd = doublet of doublets, sept = septet, m = multiplet. Low and high resolution (LRMS & HRMS), chemical ionization (CI), and fast atom bombardment mass spectra (FAB-MS) were obtained on a Varian MAT CH-5 or VG 7070 mass spectrometer.

Analytical thin layer chromatography (TLC) was conducted on pre-coated TLC plates, silica gel 60 F_{254}, layer thickness 0.25 mm, manufactured by E. Merck and Co., Darmstadt, Germany. Silica Gel for flash column chromatography was obtained from Silicycle Chemical Division "Silica Gel, 60" (particle size 0.040 – 0.063 mm); 230-240 mesh ASTM. All columns were prepared, loaded, and fractions collected according to the specification of Still.[37] Ethyl acetate used for chromatography was dried over 4 Å molecular sieves for at least 24 hours prior to use. Hexanes are the mixed hydrocarbon fraction (bp 60-70 °C), principally n-hexanes, which was purified as follows: the commercial solvent was stirred concentrated sulfuric acid for at least 24 hours, decanted, stirred over anhydrous sodium carbonate for 6 hours, decanted, then distilled.

Solvents were distilled shortly before use from an appropriate drying agent. Diethyl ether and tetrahydrofuran (THF) were distilled under dry nitrogen from potassium metal in the presence of benzophenone. Dichloromethane was distilled from calcium hydride.

Reactions run under a nitrogen atmosphere were arranged with a mercury bubbler so that the system could be alternately evacuated and filled with nitrogen and left under positive pressure. Syringes and reaction flasks were dried at least 12 hours in an oven at 120 °C and cooled in a desiccator over anhydrous calcium sulfate prior to use. Reactions at "room temperature (rt)" were conducted under ambient laboratory conditions: T = 20-27 °C, P = 720-770 mmHg. References to "removal of volatile components" or "concentrated under reduced pressure" refer to rotary evaporation of a sample at 25-65 °C under pressure (15-25 mmHg) at room temperature.

All percent yield reported are for compounds that have a purity of approximately 95 % or better as determined by ^{1}H NMR, and compound used for subsequent reaction with out further purification. Diisopropylsilane was prepared from dichlorodiisopropylsilane according to the procedures described in the literature.[19] All alcohols were dried over calcium hydride and distilled before use. $Rh_2(OAc)_4$, 10 % Pd/C and $Mn(CO)_5Br$ were commercially obtained and used without further treatment.

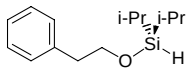
Mono-Alkoxy Silane (**1a-1i**)

General Procedure:

To a solution of alcohol **1a-1i** (2.0 mmol) in CH_2Cl_2 (4.0 mL) was added $Rh_2(OAc)_4$ (0.020 g, 2.0 mol %) followed by diisopropylsilane (0.49 mL 3.0 mmol). The reaction was allowed to stir at room temperature for the appropriate time. The evolving hydrogen was periodically vented. After the reaction was completed, dry CH_2Cl_2 (10 mL) was added and the reaction was filtered through dry Florisil. The volatile components, including excess

diisopropylsilane, were removed under reduced pressure to give a crude yield of the mono-alkoxy silane which was used in the next step without further purification.

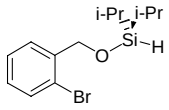
Diisopropyl(2-phenylethoxy)silane: (**1a**)



1a

^{1}H NMR (CD_2Cl_2): δ = 7.31-7.17 (m, 5 H), 4.13 (br s, 1 H, Si-H), 3.90 (t, 2 H, *J* = 7 Hz), 2.85 (t, 2 H, *J* = 7 Hz), 1.01 (d, br 14 H, *J* = 3 Hz). ^{13}C NMR (CD_2Cl_2): δ = 139.2, 129.2, 128.2, 126.1, 66.7, 39.3, 17.3, 17.1, 12.4. IR (cm^{-1}) 3060, 3030, 2949, 2863, 2088, 1499, 1456, 1384, 1103, 1001, 920, 828, 795, 749, 697.

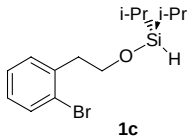
[(2-Bromobenzyl)oxy](diisopropyl)silane: (1b)



1b

^{1}H NMR (CD_2Cl_2): δ = 7.58 (dd, 1 H, *J* = 8 Hz, 1 Hz), 7.53 (dd, 1 H, *J* = 8 Hz, 1 Hz), 7.36 (ddd, 1 H, *J* = 8 Hz, 7 Hz, 1 Hz), 7.15 (ddd, 1 H, *J* = 8 Hz, 7 Hz, 1 Hz), 4.84 (s, 2 H), 4.30 (s, 1 H, Si-H), 1.10-1.08 (m, 14 H). ^{13}C NMR (CD_2Cl_2): δ = 140.0, 132.1, 128.5, 127.8, 127.4, 121.3, 66.9, 17.3, 17.2, 12.5. IR (cm^{-1}): 3068, 2940, 2863, 2095, 1568, 1460, 1440, 1378, 1199, 1117, 1102, 1030, 876, 835, 748, 671.

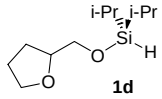
[2-(2-Bromophenyl)ethoxy](diisopropyl)silane: (1c)



1c

^{1}H NMR (CD_2Cl_2): δ = 7.54 (dd, 1 H, *J* = 8 Hz, 1 Hz), 7.30 (dd, 1 H, *J* = 8 Hz, 2 Hz), 7.25 (ddd, 1 H, *J* = 8 Hz, 7 Hz, 1 Hz), 7.09 (ddd, 1 H, *J* = 8 Hz, 7 Hz, 2 Hz), 4.13 (br s, 1 H, Si-H), 2,92 (t, 2 H, J = 7 Hz), 3.02 (t, 2 H, J = 7 Hz), 1.03-1.00 (m, 14 H). ^{13}C NMR (CD_2Cl_2): δ = 138.3, 132.7, 131.6, 128.0, 127.3, 124.6, 64.7, 39.3, 17.3, 17.1, 12.4. IR (cm^{-1}) 3064, 2948, 2867, 2089, 1571, 1470, 1379, 1095, 1038, 1004, 915, 874, 831, 740, 658. HRMS (EI): m/z calcd for $C_{14}H_{22}{}^{79}BrOSi$ [M – H^+], 313.0623; found, 313.0626.

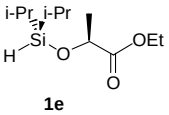
Diisopropyl(tetrahydrofuran-2-ylmethoxy)silane: (1d)



1d

^{1}H NMR (CD_2Cl_2): δ = 4.14 (s, 1 H, Si-H), 3.97-3.89 (m, 1 H), 3.84-3.60 (m, 4 H), 1.97-1.60 (m, 4 H), 1.06-0.98 (m, 14 H). ^{13}C NMR (CD_2Cl_2): δ = 79.3, 68.1, 68.0, 27.7, 25.7, 17.0, 12.3. IR (cm^{-1}): 2942, 2868, 2092, 1463, 1385, 1242, 1091, 997, 911, 878, 837, 800, 662

Ethyl (2S)-2-[(diisopropylsilyl)oxy]propanoate (1e)

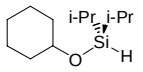


1e

^{1}H NMR (CD_2Cl_2): δ = 4.33 (q, 1 H, *J* = 7 Hz), 4.15 (qd, 2 H, *J* = 7 Hz, 1 Hz), 1.39 (d, 3 H, *J* = 7 Hz), 1.26 (t, 3 H, *J* = 7 Hz), 1.03 – 0.99 (br s, 14 H). ^{13}C NMR (CD_2Cl_2): δ = 173.3, 70.4, 60.6,

20.7, 17.03, 16.95, 16.83, 13.9, 12.4, 12.3. IR (cm^{-1}): 2940, 2863, 2090, 1757, 1731, 1460, 1363, 1153, 1061, 999, 876, 830, 799, 661.

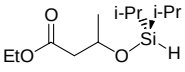
(cyclohexyloxy)(diisopropyl)silane: (1f)



1f

^{1}H NMR (CD_2Cl_2): δ = 4.16 (s, 1 H, Si-H), 3.65-3.60 (m, 1 H), 1.84-1.71 (m, 4 H), 1.56-1.49 (m, 6 H), 1.06–0.98 (m, 14 H). ^{13}C NMR (CD_2Cl_2): δ = 73.1, 35.5, 25.7, 24.1, 17.3, 17.2, 12.6.

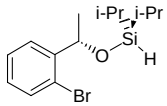
Ethyl 3-[(diisopropylsilyl)oxy]butanoate: (1g)



1g

^{1}H NMR (CD_2Cl_2): δ = 4.34 – 4.24 (m, 1 H), 4.17 (t, 1 H, Si-H, J = 1 Hz), 4.09 (qd, 2 H, J = 7 Hz, 2 Hz), 2.48 (dd, 1 H, J = 15 Hz, 7 Hz), 2.37 (dd, 1 H, J = 15 Hz, 6 Hz), 1.24 (t, 3 H, J = 7 Hz), 1.23 (d, 3 H, J = 6 Hz), 1.04 – 0.96 (m, 14 H). ^{13}C NMR (CD_2Cl_2): δ = 171.1, 67.9, 60.1, 44.5, 23.0, 17.0, 13.9, 12.4. IR (cm^{-1}): 2942, 2868, 2092, 1736, 1463, 1377, 1299, 1181, 1095, 1001, 882, 801, 662.

[(1S)-1-(2-Bromophenyl)ethoxy](diisopropyl)silane: (1h)

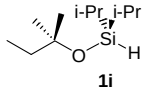


1h

^{1}H NMR (CD_2Cl_2): δ = 7.62 (dd, 1 H, *J* = 8 Hz, 2 Hz), 7.49 (dd, 1 H, *J* = 8, Hz, 1 Hz), 7.34 (ddd, 1 H, *J* = 8 Hz, 8 Hz, 1 Hz), 7.11 (ddd, 1 H, *J* = 8 Hz, 8 Hz, 2 Hz), 5.21 (q, 1 H, *J* = 6 Hz), 4.19 (s,

1 H), 1.42 (d, 3 H, *J* = 6 Hz), 1.01 –0.93 (m, 14 H). ^{13}C NMR (CD_2Cl_2): δ = 145.4, 132.2, 128.4, 127.7, 127.4, 120.9, 71.9, 24.9, 17.3, 17.2, 17.1, 17.0, 12.6, 12.4. IR (cm^{-1}): 3069, 2934, 2862, 1566, 1465, 1364, 1268, 1196, 1124, 1100, 1025, 1001, 957, 873, 837, 749, 665.

(1,1-dimethylpropoxy)(diisopropyl)silane: (1i)



1i

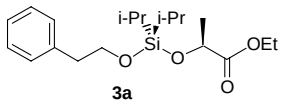
^{1}H NMR (CD_2Cl_2): δ = 4.32 (t, 1 H, *J* = 1 Hz), 1.50 (q, 2 H, *J* = 8 Hz), 1.21 (s, 6 H), 1.05 – 1.00 (br s, 14 H). 0.90 (t, 3 H, *J* = 8 Hz). ^{13}C NMR (CD_2Cl_2): δ = 73.7, 37.1, 28.4, 17.6, 17.3, 13.1. IR (cm^{-1}) 2968, 2940, 2862, 2092, 1464, 1382, 1361, 1233, 1180, 1070, 1027, 882, 843, 818, 800.

Silyl ketals (3a-i)

General Procedure:

To a solution of alcohol **2a-h** (3.0 mmol) in THF (2.0 mL) was added 10% Pd/C (0.015 g) followed by a solution of **1e** (2.0 mmol) in THF (2.0 mL), slowly added over a 1 h period via a syringe pump. After the addition, the reaction was allowed to stir at room temperature for another 1 h after which pentane (20 mL) was added and the reaction was filtered through Celite. The volatile components were removed under reduced pressure to give a colorless liquid which was subjected to flash column chromatography on silica gel eluting with hexane (100 mL) followed by hexane: ethyl acetate (30:1) to give the pure product as a colorless liquid. The yields and characteristic data for **3a-h** are presented below.

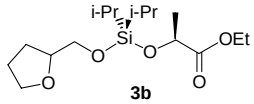
Ethyl (2S)-2-{[diisopropyl(2-phenylethoxy)silyl] oxy}propanoate: (3a)



3a

^{1}H NMR (CD_2Cl_2): δ = 7.30-7.16 (m, 5 H), 4.39 (q, 1 H, *J* = 7 Hz), 4.14 (dq, 2 H, *J* = 1 Hz, 7 Hz), 3.94 (t, 2 H, *J* = 7 Hz), 2.84 (t, 2 H, *J* = 7 Hz), 1.36 (d, 3 H, *J* = 7 Hz), 1.25 (t, 3 H, *J* = 7 Hz), 1.02 – 1.01 (br s, 14 H). ^{13}C NMR (CD_2Cl_2): δ = 173.7, 139.3, 129.2, 128.2, 126.2, 67.8, 64.3, 60.7, 39.4, 21.3, 17.0, 14.1, 12.3. IR (cm^{-1}): 3053, 3022, 2941, 2872, 1750, 1731, 1492, 1461, 1449, 1369, 1280, 1195, 1141, 11.3, 1057, 1022, 976, 883, 741, 694. HRMS (EI): m/z calcd for $C_{16}H_{25}O_4Si$ [M – $CH(CH_3)_2^+$], 309.152213; found, 309.152695.

Ethyl (2S)-2-{[diisopropyl(tetrahydrofuran-2-ylmethoxy)silyl]oxy}propanoate: (3b)

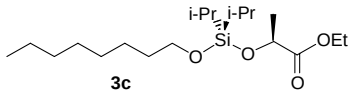


3b

two diastereomers

^{1}H NMR (CD_2Cl_2): δ = 4.53 (qd, 1 H, *J* = 7 Hz, 2 Hz, 2 diastereomers), 4.14 (qd, 2 H, *J* = 7 Hz, 1 Hz, 2 diastereomers), 3,98-3.90 (m, 1 H, 2 diastereomers), 3.83-3.64 (m, 4 H, 2 diastereomers), 1.96-1.60 (m, 4 H. 2 diastereomers), 1.40 (d, 3 H, *J* = 7 Hz, 2 diastereomers), 1.25 (t, 3 H, *J* = 7 Hz, 2 diastereomers), 1.04 – 1.03 (br s, 14 H, 2 diastereomers). ^{13}C NMR (CD_2Cl_2): δ = 173.7, 79.4, 68.3, 67.8, 65.8, 60.6, 27.7, 25.8, 21.3, 17.0, 14.0, 12.2. IR (cm^{-1}): 2942, 2864, 1748, 1732, 1462, 1373, 1270, 1144, 1066, 993, 886, 813, 694. HRMS (EI): m/z calcd for $C_{13}H_{25}O_5Si$ [M – $CH(CH_3)_2^+$], 289.1479; found, 289.1473.

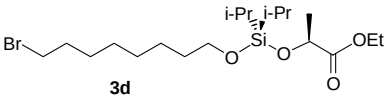
Ethyl (2S)-2-{[diisopropyl(octyloxy)silyl]oxy}propanoate: (3c)



3c

^{1}H NMR (CD_2Cl_2): δ = 4.49 (q, 1 H, *J* = 7 Hz), 4.14 (q, 2 H, *J* = 7 Hz), 3.72 (t, 2 H, *J* = 7 Hz), 1.60 – 1.50 (m, 2 H), 1.40 (d, 3 H, *J* = 7 Hz), 1.29-1.23 (m, 13 H), 1.07 – 1.01 (m, 14 H), 0.88 (t, 3 H, J = 7 Hz). ^{13}C NMR (CD_2Cl_2): δ = 173.8, 67.8, 63.2, 60.7, 32.8, 31.9, 29.5, 29.4, 25.8, 22.8, 21.3, 17.0, 14.1, 14.0, 12.33, 12.28. IR (cm^{-1}): 2930, 2858, 1757, 1455, 1373, 1265, 1137, 1101, 1056, 974, 881, 789, 692. HRMS (EI): m/z calcd for $C_{16}H_{33}O_4Si$ [M – $CH(CH_3)_2^+$], 317.214813; found, 317.214091.

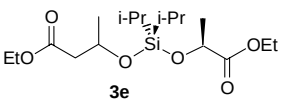
Ethyl (2S)-2-{[[(8-bromooctyl)oxy](diisopropyl) silyl]oxy}propanoate: (3d)



3d

^{1}H NMR (CD_2Cl_2): δ = 4.48 (q, 1 H, J = 7 Hz), 4.14 (dq, 2 H, *J* = 1 Hz, 7 Hz), 3.72 (t, 2 H, *J* = 7 Hz), 3.42 (t, 2 H, *J* = 7 Hz), 1.85 (quint, 2 H, *J* = 7 Hz), 1.59 – 1.48 (m, 2 H), 1.40 (d, 3 H, *J* = 7 Hz), 1.35 -1.28 (m, 8 H), 1.25 (t, 3 H, *J* = 7 Hz), 1.08 – 0.94 (m, 14 H). ^{13}C NMR (CD_2Cl_2): δ = 173.8, 67.8, 63.2, 60.7, 34.3, 33.0, 32.8, 29.3, 28.8, 28.2, 25.7, 21.3, 17.1, 14.1, 12.32, 12.27. IR (cm^{-1}): 2906, 2863, 2724, 1756, 1727, 1463, 1368, 1267, 1243, 1142, 1099, 1061, 883, 792, 682. HRMS (EI): m/z calcd for $C_{16}H_{32}BrO_4Si$ [M – $CH(CH_3)_2^+$], 395.125324; found, 395.125490.

Ethyl (2S)-4,4-diisopropyl-2,6-dimethyl-8-oxo-3,5, 9-trioxa-4-silaundecan-1-oate (3e)



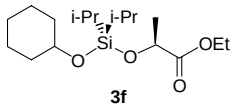
3e

two diastereomers

^{1}H NMR (CD_2Cl_2): δ = 4.49 (q, 1 H, *J* = 7 Hz, 2 diastereomers), 4.47 (ddq, 1 H, *J* = 6 Hz, 6 Hz, 7 Hz, 2 diastereomers), 4.18-3.85 (m, 4 H, 2 diastereomers), 2.52 (dd, 1 H, *J* = 15 Hz, 7 Hz, 2 diastereomers), 2.38 (dd, ½ H, *J* = 15 Hz, 6 Hz, 1 diastereomer), 2.37 (dd, ½ H, *J* = 15 Hz, 6 Hz, 1 diastereomer), 1.40 (d, 3/2 H, *J* = 7 Hz, 1 diastereomer), 1.39 (d, 3/2 H, *J* = 7 Hz, 1 diastereomer), 1.28-1.20 (m, 9 H, 2 diastereomers), 1.03-0.91 (m, 14 H, 2 diastereomers).

^{13}C NMR (CD_2Cl_2): δ = 173.7, 171.2, 67.9, 66.0, 60.7, 44.7, 23.7, 23.6, 21.4, 17.0, 14.1, 12.7, 12.5. . IR (cm^{-1}): 2945, 2869, 1736, 1639, 1465, 1377, 1302, 1249, 1185, 1148, 1098, 1012, 977, 885, 784, 690. HRMS (EI): m/z calcd for $C_{14}H_{27}O_6Si$ [M – $CH(CH_3)_2^+$], 319.157692; found, 319.157777.

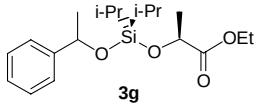
Ethyl (2S)-2-{[(cyclohexyloxy)(diisopropyl)silyl] oxy}propanoate (3f)



3f

^{1}H NMR (CD_2Cl_2): δ = 4.40 (q, 1 H, *J* = 7 Hz), 4.14 (q, 2 H, *J* = 7 Hz), 3.86-3.79 (m, 1 H), 1.76-1.71 (m, 4 H), 1.39 (d, 3 H, *J* = 7 Hz), 1.25 (t, 3 H, *J* = 7 Hz), 1.49-1.16 (m, 6 H), 1.06-0.91 (m, 14H). ^{13}C NMR (CD_2Cl_2): δ = 173.9, 70.5, 67.8, 60.6, 35.8, 25.7, 23.9, 21.4, 17.1, 14.1, 12.7. IR (cm^{-1}): 2935, 2863, 1752, 1726, 1460, 1440, 1368, 1265, 1137, 1107, 1056, 1020, 999, 968, 861, 887. HRMS (EI): m/z calcd for $C_{14}H_{27}O_4Si$ [M – $CH(CH_3)_2^+$], 287.167863; found, 287.168055.

Ethyl (2S)-2-{[diisopropyl(1-phenylethoxy)silyl] oxy}propanoate: (3g)



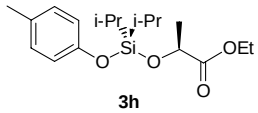
3g

two diastereomers

^{1}H NMR (CD_2Cl_2): δ = 7.37-7.20 (m, 5 H, 2 diastereomers), 5.01 (q, ½ H, *J* = 6 Hz, 1 diastereomer), 5.08 (q, ½ H, *J* = 6 Hz, 1 diastereomer), 4.40 (q, ½ H, *J* = 7 Hz, 1 diastereomer), 4.39 (q, ½ H, *J* = 7 Hz, 1 diastereomer), 4.14 (q, 1 H, *J* = 7 Hz, 1 diastereomer), [4.08 (dq, ½ H, *J* = 11 Hz, 7 Hz), 4.00 (dq, ½ H, *J* = 11 Hz, 7 Hz, 1 diastereomer)], 1.44 (d, 3/2 H, *J* = 6 Hz, 1 diastereomer), 1.42 (d, 3/2 H, *J* = 6 Hz, 1 diastereomer), 1.36 (d, 3/2 H, *J* = 7 Hz, 1 diastereomer), 1.26 (d, 3/2 H, *J* = 7 Hz, 1 diastereomer), 1.26 (t, 3/2 H, *J* = 6 Hz, 1 diastereomer), 1.20 (t, 3/2 H, *J* = 7 Hz, 1 diastereomer), 1.07-0.95 (m, 14 H, 2 diastereomers).

^{13}C NMR (CD_2Cl_2): δ = 173.7, 146.8, 128.2, 126.9 & 126.8, 125.2, 70.8 & 70.7, 67.9, 60.7, 27.4 & 27.3, 21.3 & 21.2, 17.0, 14.1 & 14.0, 12.6. IR (cm^{-1}): 3088, 3068, 3025, 2970, 2945, 2895, 2868, 1754, 1735, 1465, 1453, 1207, 1146, 1094, 1067, 1035, 961, 799, 700. HRMS (EI): m/z calcd for $C_{16}H_{25}O_4Si$ [M – $CH(CH_3)_2^+$], 309.152213; found, 309.152231.

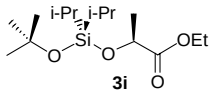
Ethyl (2S)-2-{[diisopropyl(4-methylphenoxy)silyl] oxy}propanoate: (3h)



3h

^{1}H NMR (CD_2Cl_2): δ = 7.02 (d, 2 H, *J* = 6 Hz), 6.83 (d, 2 H, *J* = 6 Hz), 4.57 (q, 1 H, *J* = 7 Hz), 4.13 (q, 2 H, *J* = 7 Hz), 2.26 (s, 3 H), 1.41 (d, 3 H, *J* = 7 Hz), 1.24 (t, 3 H, *J* = 7 Hz), 1,20-1.11 (m, 2 H), 1.08-1.-5 (m, 12 H). ^{13}C NMR (CD_2Cl_2): δ =173.5, 152.9, 131.0, 130.0, 119.6, 68.6, 61.0, 21.4, 20.5, 17.1, 14.2, 12.9. IR (cm^{-1}): 3025, 2934, 2872, 1758, 1729, 1623, 1508, 1465, 1369, 1259, 1153, 1052, 971, 941, 889, 817, 798, 697. HRMS (EI): m/z calcd for $C_{15}H_{23}O_4Si$ [M – $CH(CH_3)_2^+$], 295.136563; found, 295.136963.

Ethyl (2S)-2-{[tert-butoxy(diisopropyl)silyl]oxy} propanoate: (3i)



3i

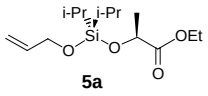
^{1}H NMR (CD_2Cl_2): δ = 4.50 (q, 1 H, *J* = 7 Hz), 4.14 (q, 2 H, *J* = 7 Hz), 1.39 (d, 3 H, *J* = 7 Hz), 1.29 (s, 9 H), 1.25 (t, 3 H, *J* = 7 Hz), 1.05- 1.01 (m, 12 H), 0.98-0.87 (m, 2 H).

^{13}C NMR (CD_2Cl_2): δ = 174.0, 72.2, 67.9, 60.6, 31.7, 21.5, 17.3, 14.1, 13.6. IR (cm^{-1}): 2944, 2973, 2867, 1753, 1734, 1460, 1393, 1359, 1239, 1268, 1196, 1134, 1057, 1024, 961, 884, 817, 774. HRMS (EI): m/z calcd for $C_{12}H_{25}O_4Si$ [M – $CH(CH_3)_2^+$], 261.152213; found, 261.152398.

Silyl ketals **(5a – 5f)** and **(7a – 7e)**

To a solution of alcohol **4a-4f** and **6a-6e** (3.0 mmol) and mono-alkoxy silane **1e** (2.0 mmol) in CH_2Cl_2, was added $Mn(CO)_5Br$ (0.022 g, 4.0 mol%) and the reaction was allowed to stir at room temperature for 2 h. The volatile components were removed under reduced pressure and the crude mixture was purified by flash column chromatography on silica gel eluting with hexane (100 mL) followed by hexane: ethyl acetate (25: 1) to give the pure product as a colorless liquid. The yields and characteristic data for **5a-5f** and **7a-7e** are presented below.

Ethyl (2S)-2-{[(allyloxy)(diisopropyl)silyl]oxy}propanoate: (5a)

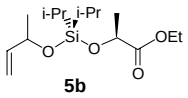


5a

^{1}H NMR (CD_2Cl_2): δ = 5.91 (ddt, 1 H, J = 17 Hz, 11 Hz, 4 Hz), 5.28 (dq, 1 H, J = 17 Hz, 2 Hz), 5.07 (dq, 1 H, J = 11 Hz, 2 Hz), 4.48 (q, 1 H, J = 7 Hz), 4.28 (dt, 2 H, J = 4 Hz, 2 Hz), 4.13 (q, 2 H, J = 7 Hz), 1.39 (d, 3 H, J = 7 Hz), 1.26 (t, 3 H, J = 7 Hz), 1.04 – 1.02 (m, 14 H). ^{13}C NMR (CD_2Cl_2): δ = 173.8, 137.5, 113.7, 68.1, 63.9, 60.8, 21.4, 17.21, 17.17, 17.13, 14.2, 12.54, 12.49.

IR (cm^{-1}): 2946, 2864, 1752, 1736, 1462, 1372, 1270, 1144, 1033, 886, 809, 694. HRMS (EI): m/z calcd for $C_{11}H_{21}O_4Si$ [M – $CH(CH_3)_2^+$], 245.1209; found, 245.1216.

Ethyl (2S)-2-({diisopropyl[(1-methylpro-2-en-1-yl)oxy]silyl}oxy)propanoate: (5b)

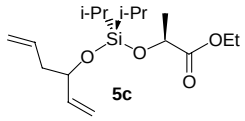


5b

two diastereomers

^{1}H NMR (CD_2Cl_2): δ = 6.01–5.88 (m, 1 H, 2 diastereomers), 5.28 (dt, ½ H, J = 5 Hz, 2 Hz, 1 diastereomer), 5.22 (dt, ½ H, J = 5 Hz, 2 Hz, 1 diastereomer), 5.08 (dt, ½ H, J = 6 Hz, 2 Hz, 1 diastereomer), 5.05 (dt, ½ H, J = 6 Hz, 2 Hz, 1 diastereomer), 4.75 (q, 2 H, 7 Hz, 2 diastereomers), 4.22 (qd, 2 H, 7 Hz, 4 Hz, 2 diastereomers), 1.47 (d, 3/2 H, 7 Hz, 1 diastereomer), 1.46 (d, 3/2 H, 7 Hz, 1 diastereomer), 1.36 – 1.29 (m, 6 H, 2 diastereomers), 1.11 (br s, 14 H, 2 diastereomers). ^{13}C NMR (CD_2Cl_2): δ = 173.74 & 173.68, 142.7 & 142.6, 112.4 & 112.3, 69.5 & 69.4, 67.84 & 67.80, 60.6, 24.20 & 24.16, 21.34 & 21.28, 17.0, 14.0, 12.59, 12.56, 12.52. IR (cm^{-1}): 2940, 2868, 1737, 1639, 1465, 1378, 1306, 1178, 1096, 1009, 912, 886, 810, 758, 687. HRMS (EI): m/z calcd for $C_{12}H_{23}O_4Si$ [M – $CH(CH_3)_2^+$], 259.1366; found, 259.1366.

Ethyl (2S)-2-({diisopropyl[(1-vinylbut-3-en-1-yl)oxy]silyl}oxy)propanoate: (5c)



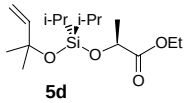
5c

two diastereomers

^{1}H NMR (CD_2Cl_2): δ = 5.94 – 5.73 (m, 2 H, 2 diastereomers), 5.17 (dddd, 1 H, J =17 Hz, 5 Hz, 2 Hz, 2 Hz, 1 diastereomer), 5.10 – 5.00 (m, 2 H, 1 diastereomer, 1 H, 1 diastereomer), 4.50 (q, 1

H, 7 Hz, 1 diastereomer), 4.43 – 4.36 (m, 1 H, 2 diastereomers), 4.14 (qd, 2 H, 7 Hz, 4 Hz, 2 diastereomers), 2.41 – 2.23 (m, 2 H, 2 diastereomers), 1.40 (d, 3/2 H, 7 Hz, 1 diastereomer), 1.38 (d, 3/2 H, 7 Hz, 1 diastereomer) 1.26 (t, 3/2 H, J = 7 Hz, 1 diastereomer), 1.25 (t, 3/2 H, J = 7 Hz, 1 diastereomer), 1.08 – 0.95 (m, 14 H, 2 diastereomers). ^{13}C NMR (CD_2Cl_2): δ = 173.7, 140.8 & 140.7, 134.5, 116.9, 114.0 & 113.9, 73.3 & 73.2, 67.9, 60.6, 42.7, 21.4, 17.0, 14.0 & 13.9, 12.62, 12.56. HRMS (EI): m/z calcd for $C_{14}H_{25}O_4Si$ [M – $CH(CH_3)_2^+$], 285.1522; found, 285.1517.

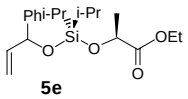
Ethyl (2S)-2-{[[(1,1-dimethylprop-2-en-1-yl)oxy](diisopropyl)silyl]oxy}propanoate: (5d)



5d

^{1}H NMR (CD_2Cl_2): δ = 5.99 (dd, 1 H, J = 17 Hz, 11 Hz), 5.15 (dd, 1 H, J = 17 Hz, 2 Hz), 4.92 (dd, 1 H, J = 11, 2), 4.50 (q, 1 H, J = 7 Hz), 4.14 (q, 2 H, J = 7 Hz), 1.38 (d, 3 H, J = 7 Hz), 1.25 (t, 3 H, J = 7 Hz), 1.05 – 0.95 (m, 14 H). ^{13}C NMR (CD_2Cl_2): δ = 173.8, 146.6, 110.3, 73.9, 67.9, 60.5, 29.8, 21.4, 17.3, 14.0, 13.6, 13.5. IR (cm^{-1}): 2980, 2945, 2865, 1755, 1731, 1462, 1372, 1143, 1059, 880, 775, 680. HRMS (EI): m/z calcd for $C_{13}H_{25}O_4Si$ [M – $CH(CH_3)_2^+$], 273.1522; found, 273.1522.

Ethyl (2S)-2-({diisopropyl[(1-phenylprop-2-en-1-yl)oxy]silyl}oxy)propanoate: (5e)



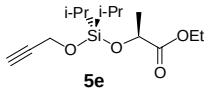
5e

2-diastereomers

^{1}H NMR (CD_2Cl_2): δ = 7.55 – 7.34 (m, 5 H, 2 diastereomers), 6.11 (ddd, ½ H, J = 10 Hz, 6 Hz, 3 Hz, 1 diastereomer), 6.05 (ddd, ½ H, J = 10 Hz, 6 Hz, 3 Hz 1 diastereomer), 5.53 (d, 1 H, J = 6 Hz, 1 diastereomer), {5.46 (dt, ½ H, J = 7 Hz, 2 Hz), 5.41 (dt, ½ H, J = 7 Hz, 2 Hz) 1

daistereomer}, 5.20 (dt, ½ H, J = 6 Hz, 2 Hz, 1 diastereomer), 5.17 (dt, ½ H, J = 6 Hz, 2 Hz, 1 diastereomer), 4.54 (q, ½ H, J = 7 Hz, 1 diastereomer), 4.53 (q, ½ H, J = 7 Hz, 1 diastereomer), 4.26 (qd, 1 H, J = 7 Hz, 1.3 Hz, 1 diastereomer), {4.21 (dq, ½ H, J = 11, Hz, 7 Hz), 4.13 (dq, ½ H, J =11 Hz, 7 Hz) 1 diastereomer}, 1.49 (d, 3/2 H, J = 7 Hz, 1 diastereomer), 1.40 (d, 3/2 H, J = 7 Hz, 1 diastereomer), 1.39 (t, 3/2 H, J = 7 Hz, 1 diastereomer), 1.33 (t, 3/2 H, J = 7 Hz, 1 diastereomer), 1.22 – 1.08 (m, 14 H, 2 diastereomers). ^{13}C NMR (CD_2Cl_2): δ = 173.7 & 173.6, 143.7 & 143.6, 141.7 & 141.6, 128.30 & 128.26, 127.24 & 127.15, 126.0 & 125.9, 113.1 & 112.9, 75.5, 67.9 & 67.8, 60.7, 21.3 & 21.2, 17.07, 17.01, 16.96, 16.91, 14.1 & 14.0, 12.61, 12.54, 12.50. IR (cm^{-1}): 3086, 3063, 2942, 2867, 1754, 1734, 1466, 1371, 1270, 1191, 1139, 1064, 1034, 988, 026, 884, 857, 753, 700. HRMS (EI): m/z calcd for $C_{17}H_{25}O_4Si$ [M – $CH(CH_3)_2^+$], 321.1522; found, 321.1524.

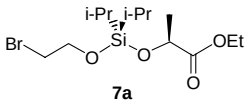
Ethyl (2S)-2-{[diisopropyl(prop-2-yn-1-yloxy)silyl]oxy}propanoate: (5f)



5e

^{1}H NMR (CD_2Cl_2): δ = 4.52 (q, 1 H, J = 7 Hz), 4.43 (d, 2 H, J = 2 Hz), 4.30 (q, 2 H, J = 7 Hz), 2.44 (t, 1 H, 2 Hz), 1.42 (d, 3H, J = 7 Hz), 1.26 (t, 3 H, J = 7 Hz), 1.05 (br s, 14 H). ^{13}C NMR (CD_2Cl_2): δ = 173.5, 82.1, 72.6, 68.0, 60.8, 51.2, 21.2, 17.0, 14.0, 12.2. IR (cm^{-1}): 3313, 3273, 2942, 2868, 1752, 1462, 1372, 1266, 1197, 1144, 1091, 1066, 1005, 886, 800, 698. HRMS (EI): m/z calcd for $C_{11}H_{19}O_4Si$ [M – $CH(CH_3)_2^+$], 243.1053; found, 243.1051.

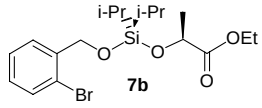
Ethyl (2S)-2-{[(2-bromoethoxy)(diisopropyl)silyl]oxy}propanoate: 7a



7a

^{1}H NMR (CD_2Cl_2): δ = 4.52 (q, 1 H, J = 7 Hz), 4.15 (q, 2 H, J = 7 Hz), 4.03 (t, 2 H, J = 6 Hz), 3.44 (t, 2 H, J = 6 Hz), 1.41 (d, 3 H, J = 7 Hz), 1.26 (t, 3 H, J = 7 Hz), 1.05 – 1.04 (m, 14 H). ^{13}C NMR (CD_2Cl_2): δ = 173, 68.2, 63.6, 60.9, 21.4, 17.1, 14.2, 12.5. IR (cm^{-1}): 2938, 2868, 1753, 1462, 1377, 1283, 1140, 1017, 976, 882, 788, 739, 690. HRMS (EI): m/z calcd for $C_{10}H_0{}^{79}BrO_4Si$ [M – $CH(CH_3)_2{}^+$], 311.0314; found, 311.0313.

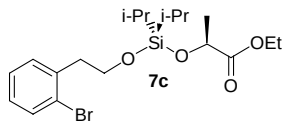
Ethyl (2S)-2-{[[(2-bromobenzyl)oxy](diisopropyl)silyl]oxy}propanoate: (7b)



7b

^{1}H NMR (CD_2Cl_2): δ = 7.60 (dd, 1 H, J = 8 Hz, 1 Hz), 7.52 (dd, 1 H, J = 8 Hz, 1 Hz), 7.36 (ddd, 1 H, J = 8 Hz, 7 Hz, 1 Hz), 7.15 (ddd, 1 H, J = 8 Hz, 7 Hz, 1 Hz), 4.90 (s, 2 H), 4.54 (q, 1 H, J = 7 Hz), 4.11 (dq, 2 H, J = 3 Hz, 7 Hz), 1.42 (d, 3 H, J = 7 Hz), 1.22 (t, 3 H, J = 7 Hz), 1.12 – 1.09 (m, 14 H). ^{13}C NMR (CD_2Cl_2): δ = 173. 5, 140.0, 132.1, 128.3, 127.4, 121.0, 68.0, 64.5, 60.8, 33.6, 21.2, 17.12, 17.09, 17.03, 14.0, 12.4, 12.3 IR (cm^{-1}) 3064, 2945, 2865, 2725, 1751, 1571, 1462, 1442, 1367, 1268, 1203, 1138, 1093, 1028, 879, 820, 745, 691. HRMS (EI): m/z calcd for $C_{15}H_{22}{}^{79}BrO_4Si$ [M – $CH(CH_3)_2{}^+$], 373.0484; found, 373.0471.

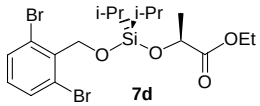
Ethyl (2S)-2-{[[2-(2-bromophenyl)ethoxy](diisopropyl)silyl]oxy}propanoate: (7c)



7c

^{1}H NMR (CD_2Cl_2): δ = 7.53 (dd, 1 H, J = 8 Hz, 1 Hz), 7.31 (dd, 1 H, J = 8 Hz, 2 Hz), 7.24 (ddd, 1 H, J = 8 Hz, 7 Hz, 1 Hz), 7.09 (ddd, 1 H, J = 8 Hz, 7 Hz, 2 Hz), 4.38 (q, 1 H, J = 7 Hz), 4.13 (q, 2 H, 7 Hz), 3.96 (t, 2 H, J = 7 Hz), 3.00 (t, 2 H, J = 7 Hz), 1.36 (d, 3 H, J = 7 Hz), 1.24 (t, 3 H, J = 7 Hz), 0.99 (br s, 14 H). ^{13}C NMR (CD_2Cl_2): δ = 173. 7, 138.4, 132.7, 131.8, 128.1, 127.3, 124.6, 67.8, 62.4, 60.7, 39.4, 21.3, 17.0, 14.1, 12.3. IR (cm^{-1}): 2940, 2863, 1747, 1737, 1470, 1440, 1368, 1281, 1194, 1143, 1096, 1061, 1040, 886, 743, 687. HRMS (EI): m/z calcd for $C_{16}H_{24}{}^{79}BrO_4Si$ [M – $CH(CH_3)_2^+$], 387.0627; found, 387.0627.

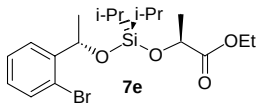
Ethyl (2S)-2-{[[(2,6-dibromobenzyl)oxy]diisopropyl)silyl]oxy}propanoate: (7d)



7d

^{1}H NMR (CD_2Cl_2): δ = 7.56 (d, 2 H, J = 8 Hz), 7.03 (t, 1 H, J = 8 Hz), 5.15 (d, 1 H, J = 11 Hz), 5.11 (d, 1 H, J = 11 Hz), 4.64 (q, 1 H, J = 7 Hz), 4.15 (q, 1 H, J = 7 Hz), 4.14 (q, 1 H, J = 7 Hz), 1.45 (d, 3 H, J = 7 Hz), 1.25 (t, 3 H, J = 7 Hz), 1.09 (br s, 14 H). ^{13}C NMR (CD_2Cl_2): δ = 173. 7, 138.3, 132.6, 130.5, 126.1, 68.0, 65.8, 60.7, 21.4, 17.1, 14.1, 12.54, 12.46. IR (cm^{-1}): 2935, 2863, 1742, 1588, 1557, 1424, 1373, 1276, 1204, 1143, 1102, 974, 886, 784, 718. HRMS (EI): m/z calcd for $C_{15}H_{21}{}^{79}Br_2O_4Si$ [M – $CH(CH_3)_2^+$], 450.9576; found, 450.9574.

Ethyl (2S)-2-{[[(1S)-1-(2-bromophenyl)ethoxy](diisopropyl)silyl]oxy}propanoate: (7e)

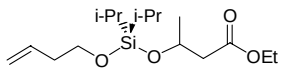


7e

^{1}H NMR (CD_2Cl_2): δ = 7.65 (dd, 1 H, J = 8 Hz, 2 Hz), 7.48 (dd, 1 H, J = 8, Hz, 1 Hz), 7.34 (ddd, 1 H, J = 8 Hz, 8 Hz, 1 Hz), 7.11 (ddd, 1 H, J = 8 Hz, 8 Hz, 2 Hz), 5.39 (q, 1 H, J = 6 Hz), 4.43 (q,

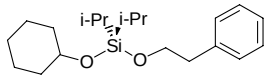
1 H, J = 7 Hz), 4.10 (dq, 1 H, J = 11 Hz, 7 Hz), 4.04 (dq, 1 H, J = 11 Hz, 7 Hz), 1.44 (d, 3 H, J = 6 Hz), 1.38 (d, 3 H, J = 7 Hz), 1.22 (t, 3 H, J = 7 Hz), 1.07 –0.98 (m, 14 H). ^{13}C NMR (CD_2Cl_2): δ = 173. 5, 145.6, 132.3, 128.4, 127.7, 127.1, 120.7, 69.7, 67.9, 60.7, 25.5, 21.3, 17.02, 16.96, 16.92, 14.0, 12.4. IR (cm^{-1}): 3063, 2940, 2863, 1747, 1568, 1455, 1368, 1265, 1148, 1096, 1030, 958, 876, 794, 748. HRMS (EI): m/z calcd for $C_{15}H_{24}{}^{79}BrO_4Si$ [M – $CH(CH_3)_2{}^+$], 387.0627; found, 387.0626.

Ethyl 3-{[(but3-en-1-yloxy)(diisopropyl)silyl]oxy}butanoate



^{1}H NMR (CD_2Cl_2): δ = 5.95 – 5.79 (m, 1 H), 5.12 – 5.01 (m, 2 H), 4.50 – 4.40 (m, 1 H), 4.09 (qd, 2 H, J = 7.1 Hz, 1.1 Hz), 3.78 (t, 2 H, J = 6.7 Hz), 2.52 (dd, 1 H, J = 14.6 Hz, 6.8 Hz), 2.38 (dd, 1 H, J = 14.6 Hz, 6.1 Hz), 2.31 (qt, 2 H, J = 6.8 Hz, 1.2 Hz), 1.25 (d, 3 H, J = 6.1 Hz), 1.23 (t, 3 H, J = 7.1 Hz), 1.03 – 0.99 (m, 14 H). ^{13}C NMR (CD_2Cl_2): δ = 171.2, 135.6, 116.1, 65.8, 62.5, 60.2, 44.8, 37.4, 23.7, 17.2, 14.0, 12.4, 12.3. IR (cm^{-1}): 2940, 2868, 1737, 1639, 1465, 1378, 1306, 1178, 1096, 1009, 012, 886, 810, 758, 687. HRMS (EI): m/z calcd for $C_{13}H_{25}O_4Si$ [M – $CH(CH_3)_2{}^+$], 273.1522; found, 273.1523.

(Cyclohexyloxy)(diisopropyl)(2-phenylethoxy)silane



^{1}H NMR (CD_2Cl_2): δ = 7.28 – 7.22 (m, 5 H), 3.94 (t, 2 H, J = 7.0 Hz), 3.78 – 3.71 (m, 1 H), 2.85 (t, 2 H, J = 7.0 Hz), 1.80 – 1.71 (m, 4 H), 1.38 – 1.18 (m, 6 H), 1.07 – 0.93 (m, 14 H). ^{13}C NMR (CD_2Cl_2): δ = 139.4, 129.2, 128.2, 126.1, 70.3, 64.1, 39.5, 35.9, 25.7, 24.0, 17.3, 17.2, 12.4. IR

(cm^{-1}): 3068, 3027, 2914, 2863, 2095, 1603, 1491, 1455, 1373, 1245, 1107, 999, 891, 856. HRMS (EI): m/z calcd for $C_{17}H_{27}O_2Si$ $[M - CH(CH_3)_2^+]$, 291.1780; found, 291.1774.

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[20] **Ethyl (2S)-2-[(diphenylsilyl)oxy]propanoate**
^{1}H NMR (CD_2Cl_2): δ = 7.71-7.67 (m, 4 H), 7.52-7.39 (m, 6H), 5.53 (s, 1H), 4.49 (q, 1 H, *J* = 7 Hz), 4.14 (dq, 2H, *J* = 1 Hz, 7 Hz), 1.50 (d, 3H, *J* = 7 Hz), 1.23 (t, 3H, *J* = 7 Hz).
^{13}C NMR (CD_2Cl_2): δ = 173.4, 134.9, 130.7, 130.6, 128.3, 128.2, 70.1, 61.2, 20.9, 14.2.
HRMS (EI): m/z calcd for $C_{17}H_{20}O_3Si$ [M – H^+], 299.110348; found, 299.111653.

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