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Robert E Maleczka

Major Professor's Signature

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Preparation of Optically Active α-Alkoxysilanes

By

IL HWAN AN

A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Chemistry

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ABSTRACT

PREPARATION OF OPTICALLY ACTIVE α-ALKOXYSILANES

By

Il Hwan An

We have studied on developing new method for the generation of optically active α-hydroxysilanes. The ring opening of epoxy alcohols bearing a TMS group with both aluminum and boron hydrides provided the unfavoured1,2-diol . This result shows that silicon plays an important role in determining the regioselectivity and that cyclic boronic esters are formed in the ring opening reaction. The scope and limitation of enzymatic kinetic resolution of α-hydroxysilanes in combination with different solvents, temperatures and acetylation reagents were investigated. The reactions are sensitive to the structures of both the silyl group and the organic side chain. In the non enzymatic kinetic resolution, the absolute stereochemical outcomes complement our enzymatic results.

ACKNOWLEDGEMENT

First, I would like to express my appreciation to Professor Robert E Maleczka for his thoughtful and kind guidance for the last six years. I learned a lot of things from him that I need to be an independent researcher. I feel extremely lucky to be his student.

Also, I would like to thank former and current group members. All of them are very nice to me and they are really diligent and smart people. I also enjoyed the experience of working with them.

I could not have finished my PhD study without the love and support from my parents, Mr. Kyoungsik An and Mrs. Youngae Lee. I would also like to dedicate this humble thesis to my beloved wife, Hua Shao and my son, Edward Inkyoo An.

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Chapter 1. Introduction

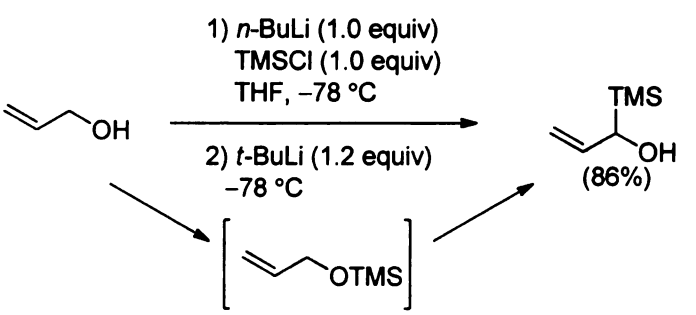
α-Hydroxysilianes have emerged as an important functional group in organic synthesis.[1,2,3,4,5] Many reactions involving α-hydroxysilanes proceed by activation of the silyl group thanks to high Si-O and Si-F bond energies. The carbon-silicon bond is relatively long and tends not hinder reactions. Silyl groups can also stabilize an α-anion and a β-cation and exchange with other metals. These features make the silyl group a powerful C-C bond forming tool in organic synthesis.

1.1. Synthesis of α-Hydroxysilianes

1.1.1. Retro Brook Rearrangement[3,4,5,6]

Many procedures have been developed for the preparation of α-hydroxysilianes. In 1985, Danheiser and coworkers reported that reacting an α,β-unsaturated alkylsily ether with base can initiate retro Brook rearrangement (Scheme 1). An allyl alcohol is converted to the corresponding trimethylsilyl ether followed by retro Brook rearrangement with *t*-BuLi to produce the 1-hydroxyalyltrimethylsilane in 86% yield. This method is useful for preparation of α-hydroxysilianes bearing vinyl and alkyne groups.

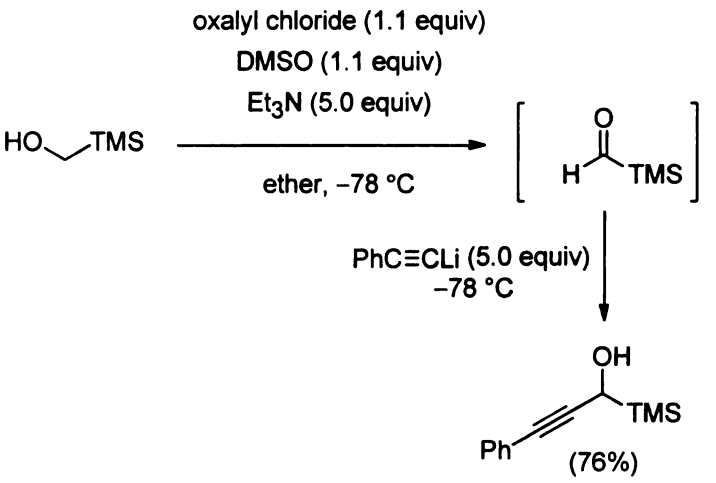
Scheme 1. Preparation of α-Hydroxysiliane by Retro Brook Rearrangement



1.1.2. Swern Oxidation and Alkylation[7,8,9]

α-Hydroxysilianes also can be prepared by Swern oxidation of (trimethylsilyl)methanol followed by alkylation. Nucleophiles can include Grignard reagents such as PhMgBr or alkyl lithiums such as *n*-BuLi. In the first step, (trimethylsilyl)methanol is oxidized to afford formyltrimethylsilane (Scheme 2). When (2-phenylethynyl)-lithium is used as a nucleophile, the condensation product 3-phenyl-1-(trimethylsilyl)-2-propyn-1-ol was obtained in 76% yield.

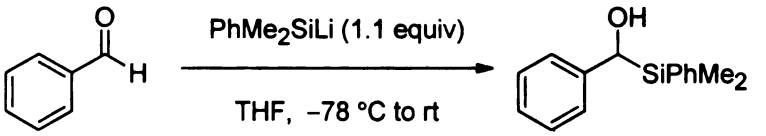
Scheme 2. Preparation of α-Hydroxysiliane by Swern Oxidation



1.1.3. Nucleophilic Addition[10,11,12]

An alternative approach to α-hydroxysilianes is direct addition of a silyl group to aldehydes or ketones. Dimethylphenylsilyl lithium ($PhMe_2SiLi$) is readily available from chlorodimethylphenlysilane and lithium metal (Scheme 3). $PhMe_2SiLi$ can react with various aldehydes such as hexanal, benzaldehyde, cyclohexanecarboxaldehyde to afford α-hydroxysilianes. Unfortunately, trimethylsilyllithium (TMSLi) cannot be prepared by this method because it is not stable.

Scheme 3. Preparation of α-Hydroxysiliane with $PhMe_2SiLi$



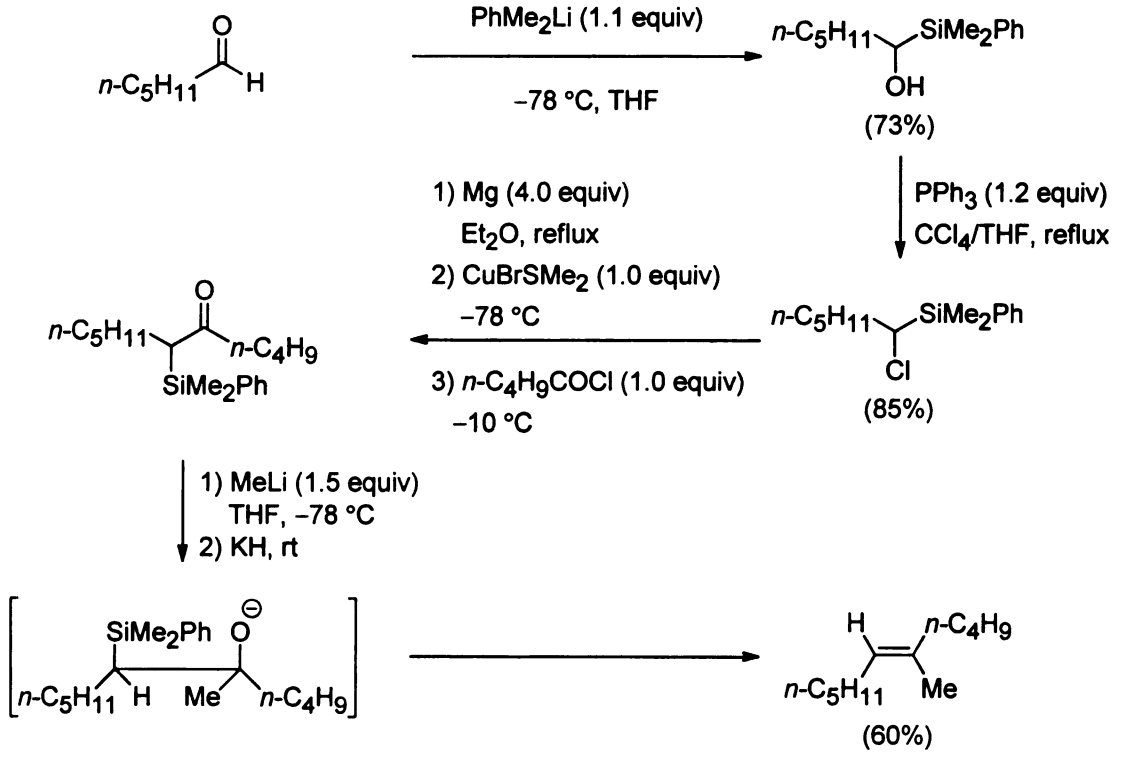
(67%)

1.2. Application of of α-Hydroxysilianes

1.2.1. Peterson Olefination[13,14]

α-Hydroxysilanes can be used for formation of olefins. As mentioned before, the silyl group on α-hydroxysilanes can be easily removed by formation the strong Si-O bond and this can be used for olefin synthesis (Peterson olefination, Scheme 4).

Scheme 4. Peterson Olefination using α-Hydroxysilane

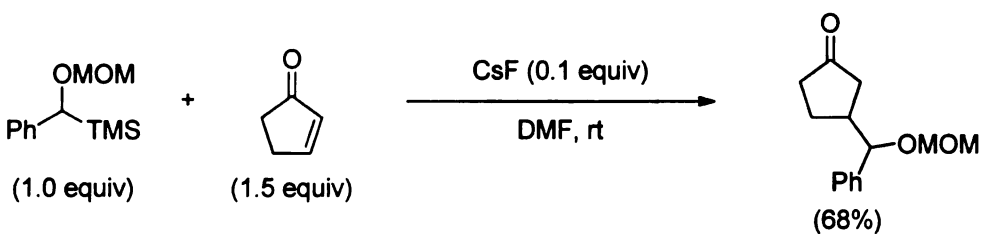


Grignard reagents derived from organochlorides are transmetalated with copper and this substance attack the acylchloride to form the α-silyl ketone. Addition of a nucleophile to the carbonyl group followed by elimination under basic condition affords olefinic product

1.2.2. 1,4-Addition to α,β-Saturated Ketones[15,16]

Silyl groups can also be easily removed by CsF to form aryl α-alkoxy anions. These newly formed weak nucleophiles can undergo 1,4-addition to form C-C bonds. For example, the regioselective 1,4-addition of MOM protected (α-hydroxybenzyl)trimethylsilane to cyclopentenone shown in Scheme 5 was reported.

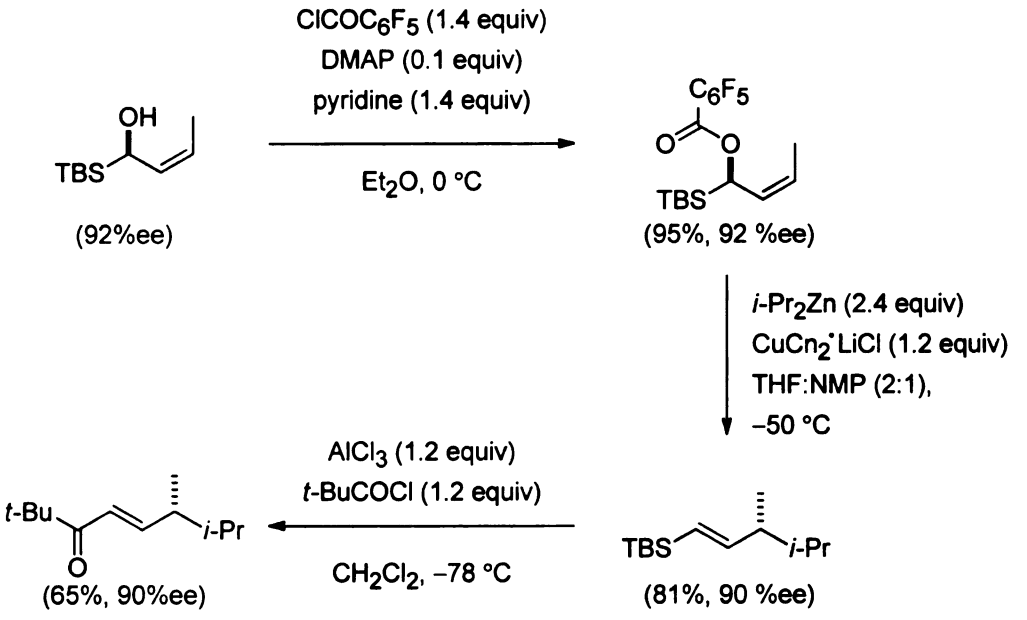
Scheme 5. Regioselective 1,4-Addition of Protected α-Hydroxysiliane



1.2.3. Friedel-Craft Type Alkylation[2,17]

Silyl groups can also stabilize a β-cation. Vinyl silanes prepared from α-hydroxysilanes can undergo Friedel-Craft acylation type reactions to afford α,β-saturated ketones. The copper-mediated allylic substitution reaction allows for the stereoselective preparation of alkenylsilanes bearing a chiral center (Scheme 6). Importantly, the chirality is almost completely transferred to the product during the reaction. The formed alkenylsilane can undergo Friedel-Craft acylation type reaction to afford the α,β-saturated ketone.

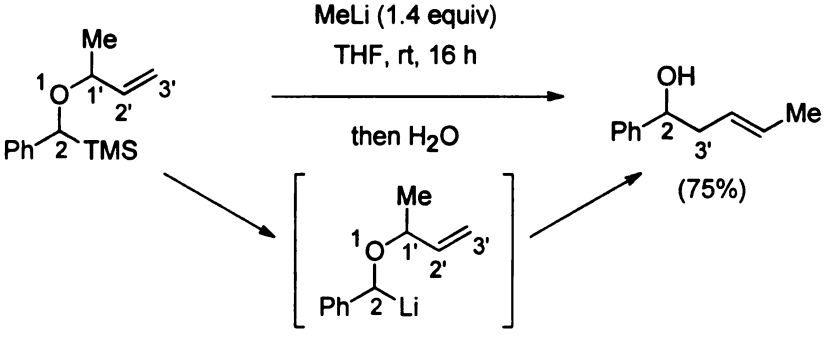
Scheme 6. Fridel-Craft Type Alkylation



1.2.4. [2,3]-Wittig Rearrangement[18]

Our group also uses α-hydroxysilanes as Wittig rearrangement precursors. Because the silyl group can stabilized the negative charge at the α-position or exchange with a metal, two Wittig rearrangement routes are possible (Scheme 7).

Scheme 7. MeLi-promoted [2,3]-Wittig Rearrangement



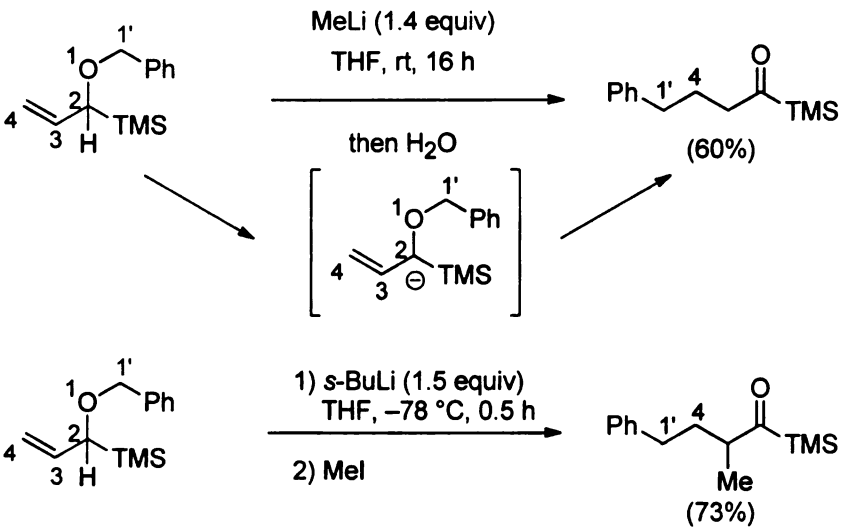
Si/Metal exchange generates a negative charge on the α-position of the α-alkoxysilane and the intermediate can act as a nucleophile. In [2,3]-Wittig rearrangements, the silyl group can exchange with methyl lithium to form a

negative charge on the α to oxygen. This negative charge attacks C3 position to give [2,3]-Wittig rearrangement product.

1.2.5. [1,4]-Wittig Rearrangement[19]

We have also reported on [1,4]-Wittig rearrangements of α-alkoxysilianes derived from allyl α-hydroxysilane. In this case, the negative charge is stabilized by the silyl group and the allyl group and [1,4]-Wittig rearrangement products are obtained as major products (Scheme 8).

Scheme 8. [1,4]-Wittig rearrangement



1.3. Synthesis of Acylsilanes[20,21]

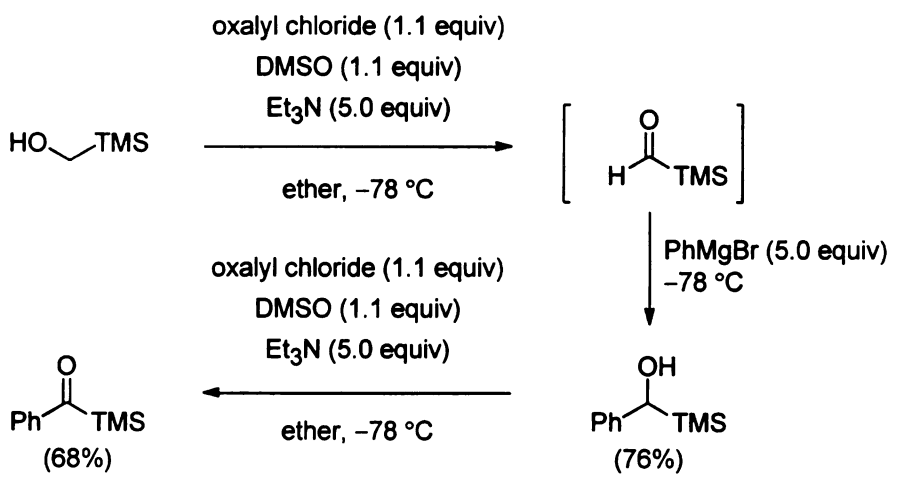
Acylsilanes are carbonyl derivatives which have the silicon directly attached to the carbonyl group. Acylsilanes have unusual reactivity because of the silicon located α to the carbonyl group. They can act as acyl anion precursors and ordinary ketones. Also, the Brook rearrangement is common in the reaction of acylsilanes with nucleophiles. The use of acylsilanes in organic synthesis has

increase significantly due to the discovery of new reactions and improvements in acylsilane syntheses.

1.3.1. Swern Oxidation of α-Hydroxysilanes[10,22, 23]

Functionalized acylsilanes can be simply prepared by Swern oxidation of α-hydroxysilanes, which are prepared by Swern oxidation of trimethylsilylmethanol followed by alkylation (Scheme 9). Interestingly, this method uses the same chemistry for the synthesis of α-hydroxysilanes shown in Chapter 1.1.3. In the first step, (trimethylsilyl)methanol is oxidized to afford formyltrimethylsilane. When phenyl magnesiumbroimde is used as a nucleophile, the condensation product (α-(trimethylsilyl)-benezenemethanol) was obtained in 46% yield. Oxidation to the corresponding acylsilane affords phenyl(trimethylsilyl)-methanone in 68% yield.

Scheme 9. Preparation of Acylsilanes from α-Hydroxysilans by Swern Oxidation

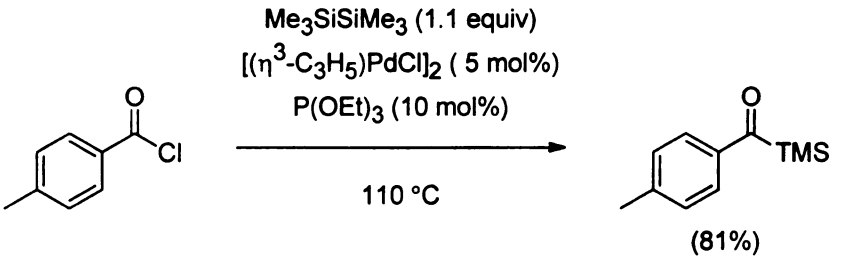


1.3.2. Palladium-catalyzed Acylation of hexamethyldisilane[24,25]

Benzyoltrimethylsilanes can be prepared by palladium catalyzed acylation reactions from hexamethyldisilane with aryl chlorides (Scheme 10). The reaction

could provide ortho, meta, and para substitued benzyoltrimethylsilanes. However, ortho substituted products were obtained with lower yields. 4-Methyl-benzoyl chloride was treated with palladium catalyst and hexamethyldisilane to afford (4-methylphenyl)(trimethylsilyl)-methanone in 81% yield.

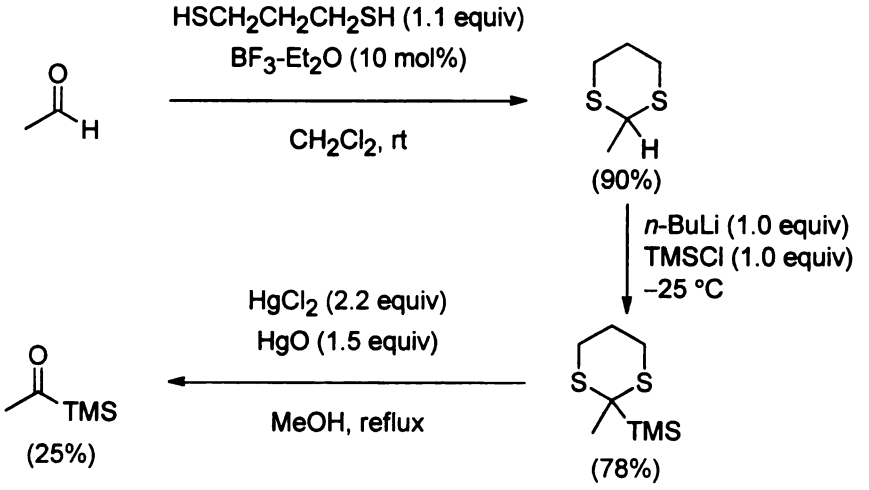
Scheme 10. Preparation of Acylsilanes by Hiyama Type Reaction



1.3.3. Silylation of Dithianes[26,27]

Silylation of dithiane compounds followed by hydrolysis gives acylsilanes (Scheme 11). This dithiane route provides a general method for preparation of acylsilanes bearing aryl and alkyl substituents. In the first step, dithiane is prepared by protection of aldehydes. Deprotonation of the dithianes followed by addition of TMSCl and deprotection of dithianes affords acylsilanes.

Scheme 11. Preparation of Acylsilanes by Dithianes

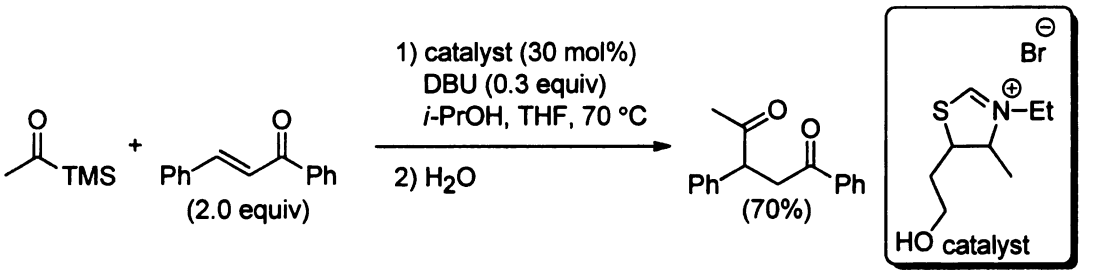


1.4. Application of Acylsilanes

1.4.1. Sila-Stetter Reaction[28,29]

Stetter reactions between acylsilanes and α,β-conjugated ketones can be catalyzed by thiazolium to afford 1,4-dicarbonyl products (Scheme 12). In this reaction, acylsilanes are tunable and various substituted α,β-conjugated ketones produce their corresponding products. The reaction proceeds via 1,4-addition to chalocone (α,β-conjugated ketone). Acetyltrimethylsilane reacts with 1,3-diphenyl-2-propen-1-one to afford 1,3-diphenyl-1,4,-pentanedione.

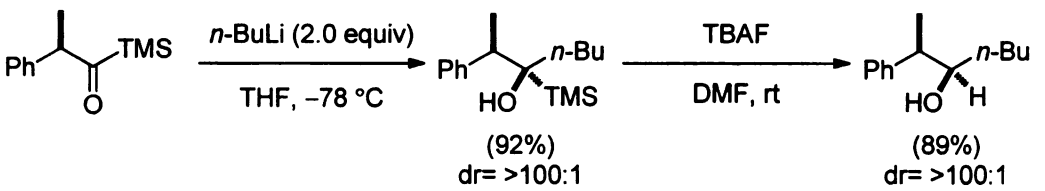
Scheme 12. Thiazolium-Catalyzed Stetter Reaction



1.4.2. Nucleophilic Addition to Acylsilanes[30,31]

Acylsilanes can be considered as aldehyde equivalents because a silyl group can be removed easily by fluoride ion. Addition of a nucleophile to acylsilanes affords α-hydroxysilanes (Scheme 13) and the large silyl group may increase stereodifferentiation.

Scheme 13. Nucleophilic Addition to Acylsilanes

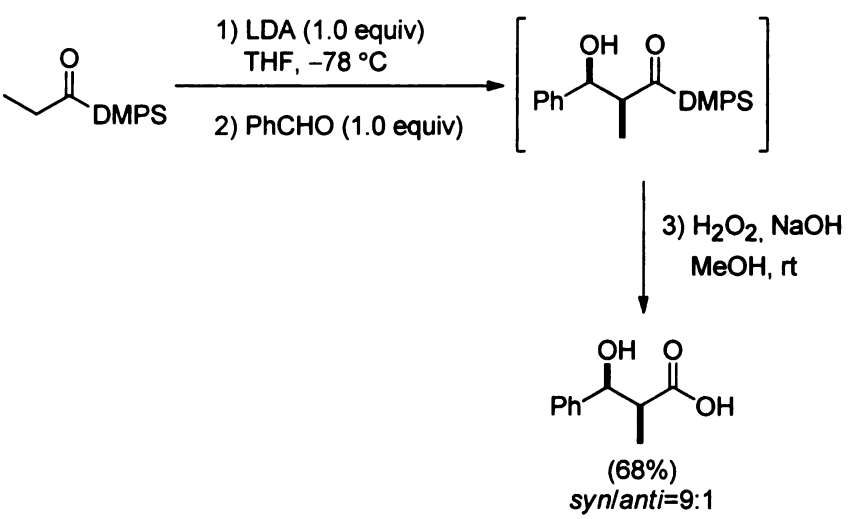


The silyl group can be converted to a hydrogen by TBAF. In this reaction, alkyl lithiums and Grignard reagents can be act as nucleophiles and thus various α-hydroxysilanes can be formed and converted to alcohols.

1.4.3. Aldol Reactions[32, 33]

Lithium enolates from various acylsilanes can react with aryl and alkyl aldehydes to afford β-hydroxyacylsilanes, which can be converted to β-hydroxycarboxylic acid by oxidation (Scheme 14). During the reaction, the large silyl group may also increase the *syn* preference. Aldol reaction between 1-(dimethylphenylsilyl)-1-propanone and benzaldehyde followed by oxidation affords β-hydroxy-α-methyl-benzene propanoic acid in 68% yield.

Scheme 14. An Aldol Reaction with an Acylsilane

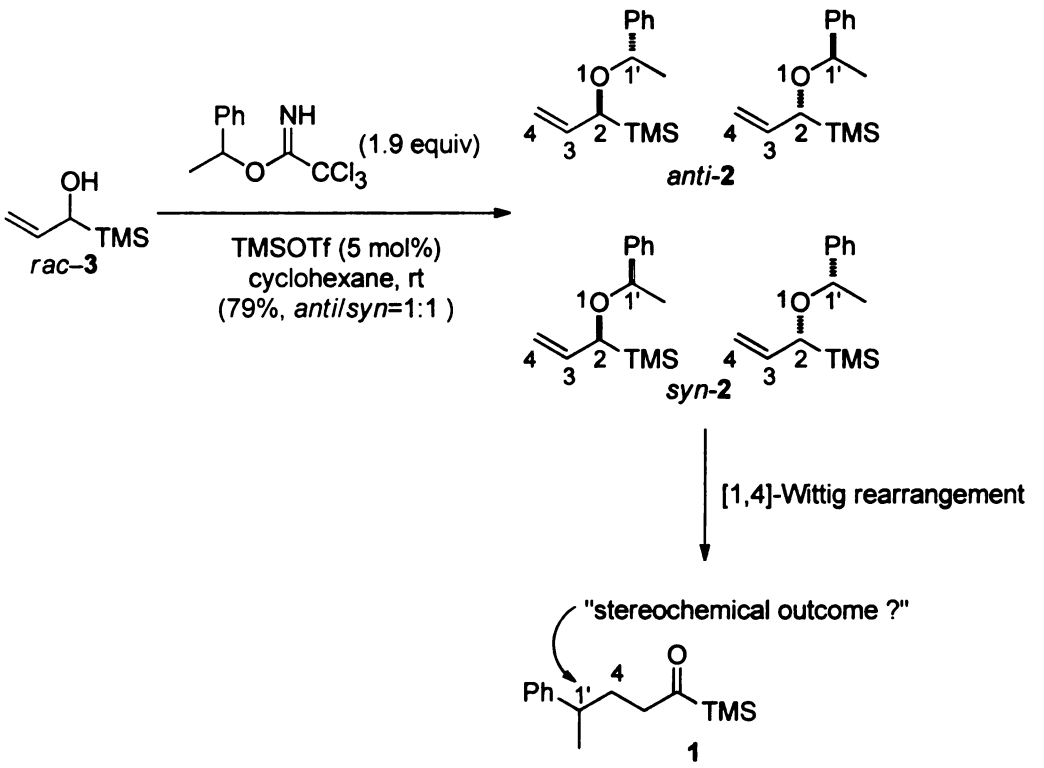


1.5. Requirement of Optically Pure α-alkoxysilane for [1,4]-Wittig Rearrangement Study

As shown before, our group studied the [1,4]-Wittig rearrangement of α-alkoxysilanes. In the course the research, we became interested in determining the stereochemical consequences of these silyl-Wittig rearrangements. Past

results showed that the *syn* isomer reacts faster than the *anti* isomer. We also wondered if this reaction occurs with retention or inversion of configuration at the migrating center. To answer this question, there was need to access optically pure α-hydroxysilianes (Scheme 15). A bottleneck in the synthesis of substrate **2** was the availability of enantiopure compound **3**.

Scheme 15. [1,4]-Wittig Rearrangement



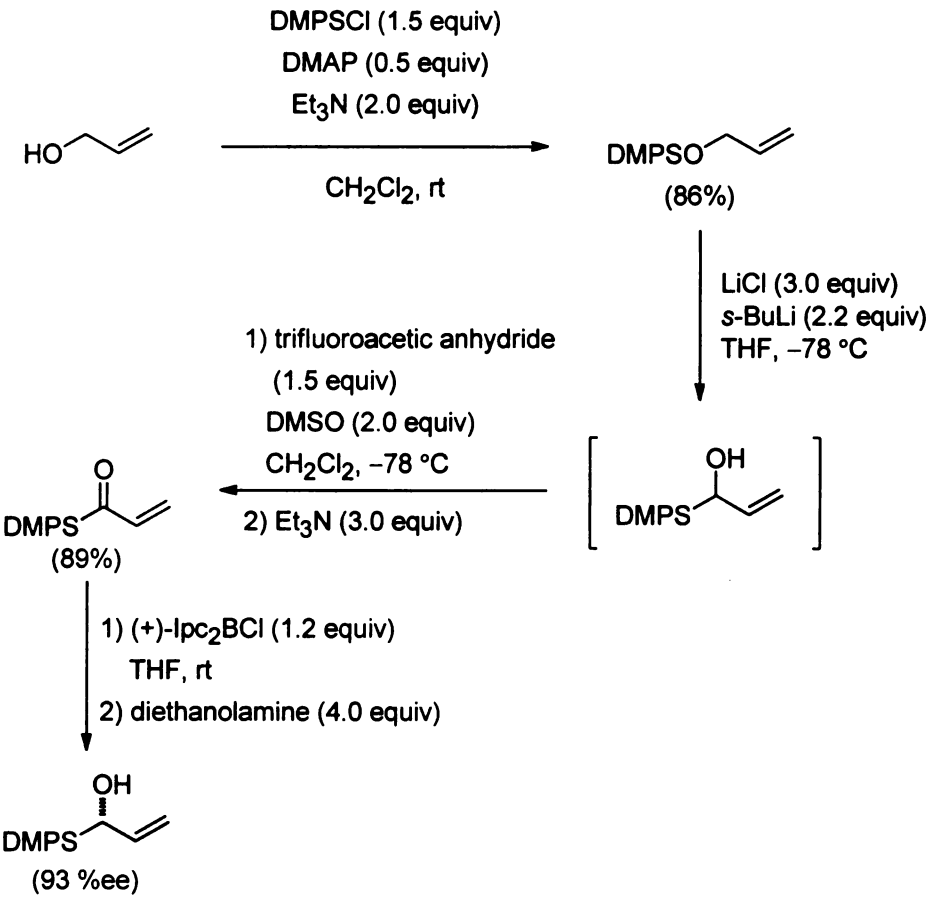
My research focused on development of method for preparation of optically pure α-hydroxysiliane for [1,4]-Wittig rearrangement.

Chapter 2. Synthesis of Optically Pure α-Hydroxysilane - Prior Art

2.1. Reduction of Acylsilanes

The preparation of optically pure α-hydroxysilane compounds is still challenging. A literature search revealed asymmetric reduction as the most common approach to such compounds. Specifically, organoborane hydride additions,[34] asymmetric hydrogenations,[35] chiral lithium amide reactions,[36] and biocatalytic transformations[37] of acylsilanes have afforded a variety of α-hydroxysilanes with high levels of enantioselectivity.

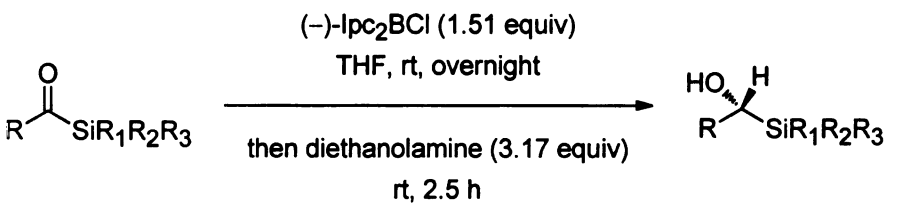
Scheme 16. Preparation of Optically Pure 1-(Dimethylphenylsilyl)-2-proen-1-ol

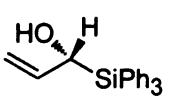
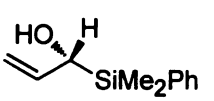
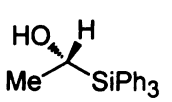
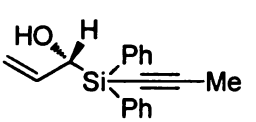
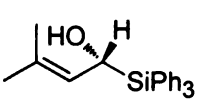
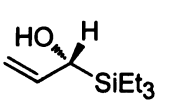


In many of these examples, the starting acylsilanes are generated by the oxidation of racemic α-hydroxysilanes, which themselves are produced via Brook

rearrangement-based processes (Scheme 16). [38] Among the asymmetric reagents for acylsilane reductions, chiral borane reagents are most commonly used. However, most of the work on the synthesis of α-silyl alcohols has been done with α-silyl benzyl and allyl alcohols in which the silicon bears bulky groups such as *t*-Bu, Ph, or *i*-Pr and the terminal sp^2 carbon is substituted. Such trends are evident in the work of Buynak and coworkers, who explored the reduction of acylsilanes by (–)-Ipc_2BCl.[34] Table 1 shows their results. Comparing entries 1, 2 and 3 to entries 4, 5 and 6, one can see that if acylsilanes have a big silyl group such as a triphenylsilyl, the corresponding products are obtained in high optical purity. As the size of the silyl group gets smaller (from triphenyl to dimethyl phenyl to triethyl), enantioselectivity is deceased. Cleary, α-hydroxysilanes bearing a TMS group are missing from the table.

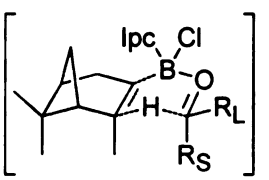
Table 1. Buynak's Asymmetric Reductions[34]



Entry	α-Hydroxysilane	%ee	Entry	α-Hydroxysilane	%ee
1		97	4		83
2		95	5		89
3		97	6		80

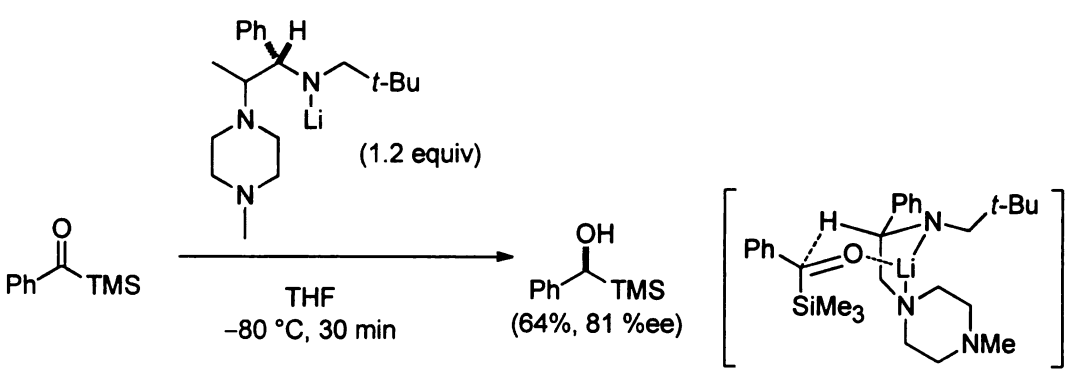
Products from the reduction of acylsilanes using (–)-Ipc_2BCl have the *R* configuration. The proposed reaction mechanism involves a six-membered transition state with the small group occupying the axial position and the large group in the equatorial position so as to minimize unfavorable steric effects (Figure 1).

Figure 1. Transition State Model for the Reduction of Acylsilanes by (–)-Ipc_2BCl



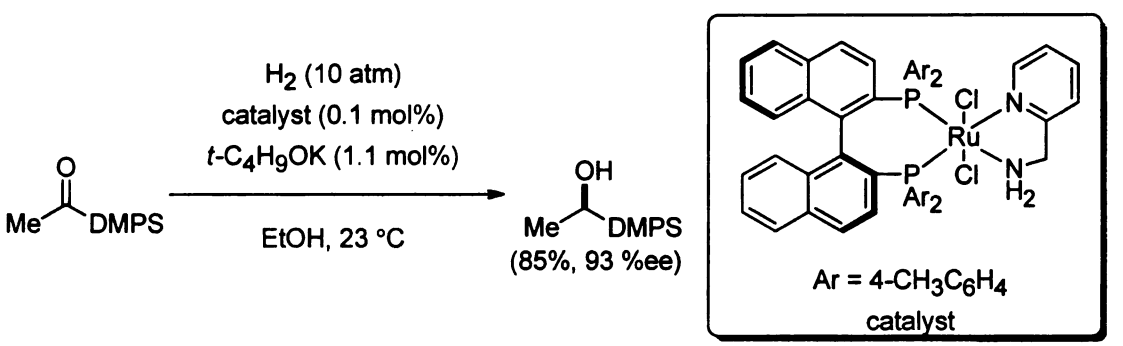
Another possible asymmetric reagent for acylsilane reductions is chiral lithium amides (Scheme 17).[36] The mechanism for these reactions is not clearly understood yet. However, it has been proposed that the bulkier phenyl group occupies the equatorial position and the carbonyl group forms a complex with lithium. This explains the formation of (*S*)-alcohols as the major products. As such, for optimal results a large difference in the size of the two substituents flanking the carbonyl is best.

Scheme 17. Chiral Lithium Amide Reduction



Optically pure α-hydroxysilanes can also be obtained by asymmetric hydrogenation. Recently, Ohkuma reported Tol-binap/pica ruthenium (II) catalyzed asymmetric hydrogenation of α-hydroxysilanes (Scheme 18).[35] (Acetyldimethylsilyl)-benzene was reduced to 1-(dimethylphenylsilyl)-ethanol with good enantiomeric excess. However, this protocol still required large silyl groups such as DMPS or TBS for good enantioselectivity. There were no examples ofsubstrates bearing a TMS group.

Scheme 18. Asymmetric Hydrogenation with Ruthenium Catalyst

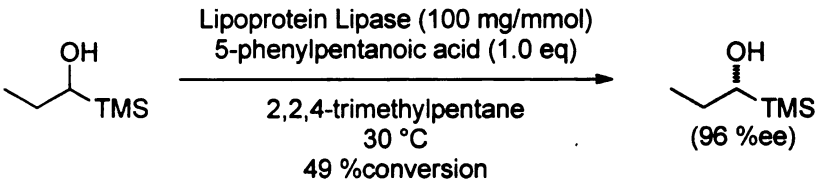


2.2. Enzymatic Kinetic Resolution

Enzymatic Kinetic Resolution of α-hydroxysilanes would be a useful method to prepare optically pure α-hydroxysilanes. Although the kinetic resolution of secondary alcohols via esterification has been extensively explored with various lipases, kinetic resolution of α-hydroxysilane is less studied. To the best of our knowledge, only a few reports on the enzymatic kinetic resolution α-hydroxysilanes exist and in those reports only a limited number of substrates have been examined.

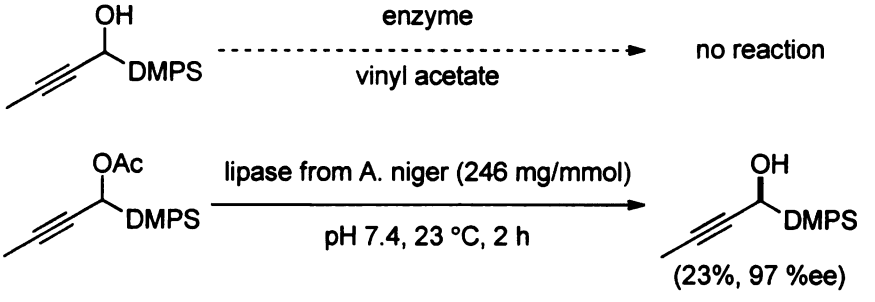
For example, Uejima et al. resolved 1-trimethylsilylpropanol with excellent enantioselectivity by a hydrolase-promoted esterification in 1993 (Scheme 19).[39] No other substrates were tested.

Scheme 19. Kinetic Resolution of 1-Trimethylsilylpropanol



In 2004, Guintchin and Bienz found that treatment of (±)-1-[(dimethyl)(phenyl)silyl]but-2-yn-1-ol with a variety of lipases (lipases from Pseudomonas Fluorescens, Candida cylindracea, Aspergilus niger, Chromobacterium viskosum or hog pancreas) failed to give any acylated material. Partial success was realized when they reacted the corresponding racemic acetate with A. niger (Scheme 20).[40]

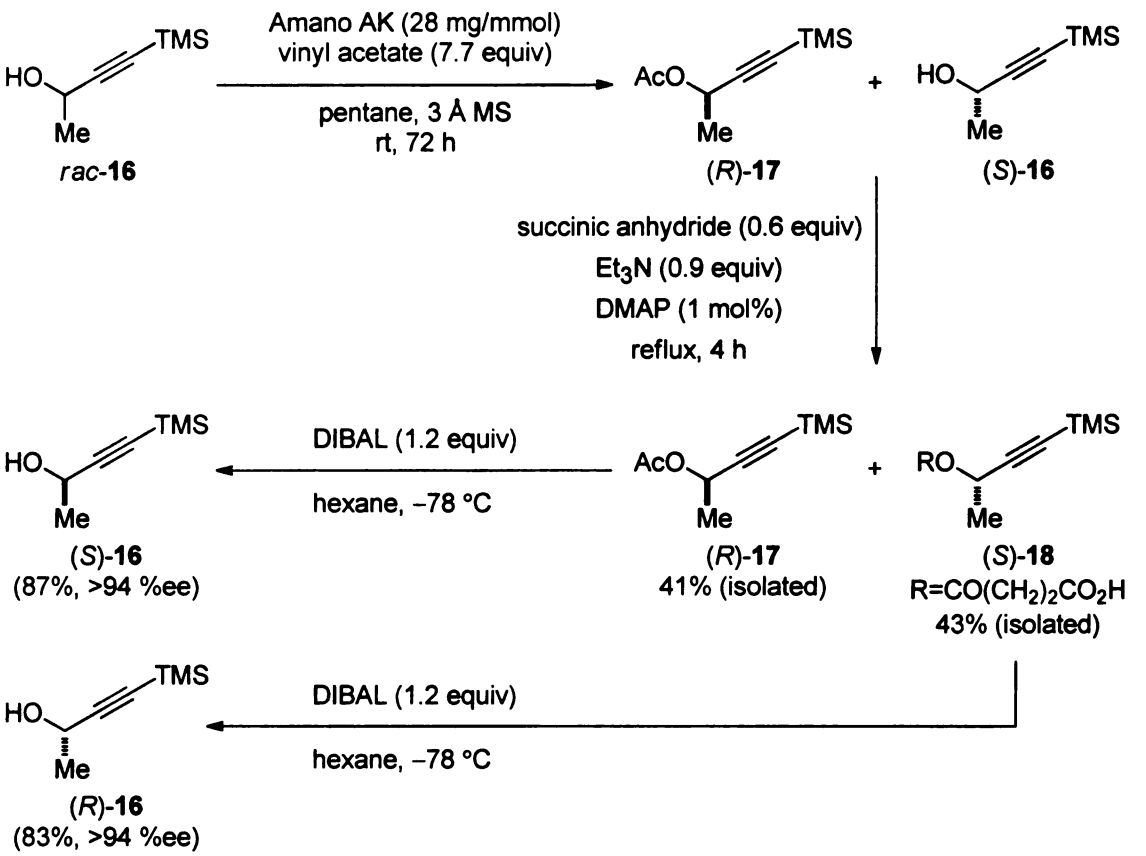
Scheme 20. Hydrolysis and Acylation using Enzyme



Marshall and coworkers also reported lipase-mediated resolutions of secondary propargyl alcohols bearing silyl substituents that lead to high enantiomeric purity (Scheme 21).[41] Even though the substrates in this study are not α-hydroxysilanes, their data indicate the ability of Amano AK to catalyze the esterifcation of silyl containing substrates. In practice, the kinetic resolution of

rac-**16** gave acylated (*R*)-**17** and unreacted (*S*)-**16**. Without further purification, both (*R*)-**17** and (*S*)-**16** were subjected to succinic anhydride so as to esterify (*S*)-**16**. (*R*)-**17** was isolated in 45% yield and (*S*)-**18** in 43% yield. Independently, treatment of (*R*)-**17** and (*S*)-**18** with DIBAL afforded (*S*)-**16** and (*R*)-**16** in good yield with good %ee's.

Scheme 21. Kinetic Resolution of 4-TMS-3-butyn-2-ol



As shown in this chapter, optically pure α-hydroxysilanes can be prepared by acylsilane reductions or enzymatic kinetic resolution of α-hydroxysilanes. In the case of the acylsilane reductions, the size of the two groups flanking on the carbonyl group should be very different. In the most examples, large TBS or TPS groups have been used in the reaction. Kinetic resolution would provide the

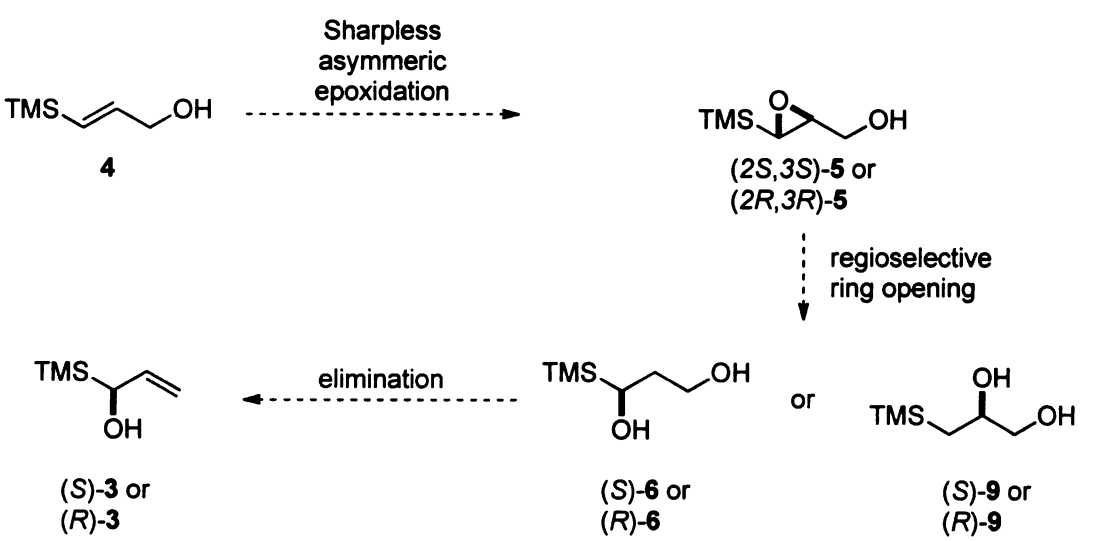
optically pure α-hydroxysilanes bearing a small TMS group. A few of examples do show that α-hydroxysilanes bearing a small TMS group can be resolved with excellent %ee, however, these are few in number and of limited structural diversity.

Chapter 3. Attempted Preparation for Optically Pure α-Hydroxysilanes by Ring Opening of Epoxyalcohol

3.1. Introduction

As mentioned in Chapter 2, several methods exist for the preparation of optically active α-hydroxysilanes. Among these methods the reduction of acylsilanes is the most common, but such reactions typically require large silyl groups (larger than TMS). Kinetic resolution of α-hydroxysilanes, as well as other methods, have not been widely studied in terms of substrate scope. Owing in part to what we viewed as a limited number of available methods and our anticipated need for various optically active α-hydroxysilanes for our Wittig studies (vide supra), we set out to develop new approaches to these compounds and/or to advance existing protocols.

Scheme 22. Our Synthetic Plan for Optically Active α-Hydroxysilane via Ring Opening Reaction



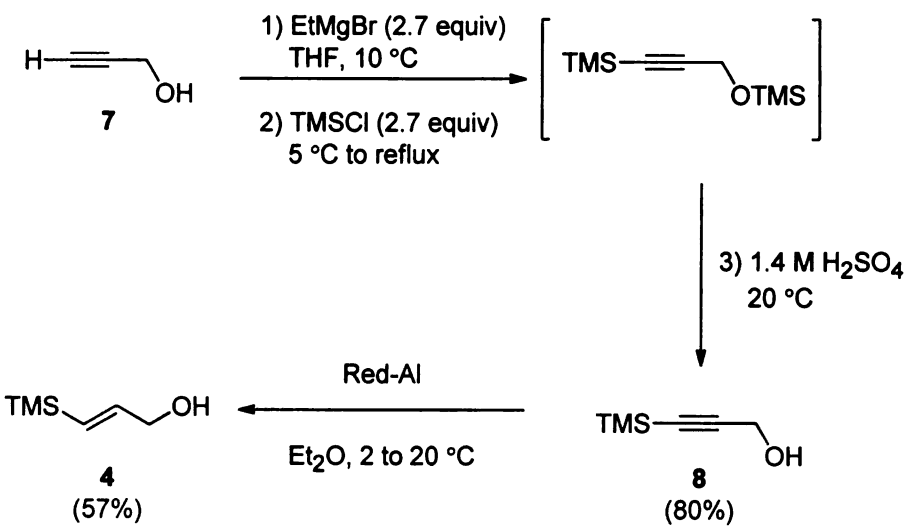
Given our particular need for allylic α-hydroxysilanes, one new approach envisaged involved asymmetric epoxidation of TMS substituted allylic alcohols

followed by ring opening and elimination of the intermediates to install the double bond in the allylic α-hydroxysilane (Scheme 22). This synthetic plan is relatively simple and relies on well established Sharpless asymmetric epoxidations to install chirality through reagent control. Another useful feature is that the final vinyl group or the primary hydroxyl on the intermediate 1,3-diol, could be used for introduction or other functional groups via cross metathesis or other methods.

Importantly, our synthetic plan also allows us to address a synthetic question pertaining to the regioselectivity of the proposed epoxide opening. While TMS groups and free alcohols are known to direct epoxide openings, to our best knowledge, there is no report on the regioselectivity of Red-Al hydride delivery to an epoxyalcohol bearing a silyl group as present in **6**. Therefore, investigating the reaction of **5** with Red-Al will provide new information as to the relative directing strengths of these two groups.

3.2. Ring Opening of Epoxyalcohol

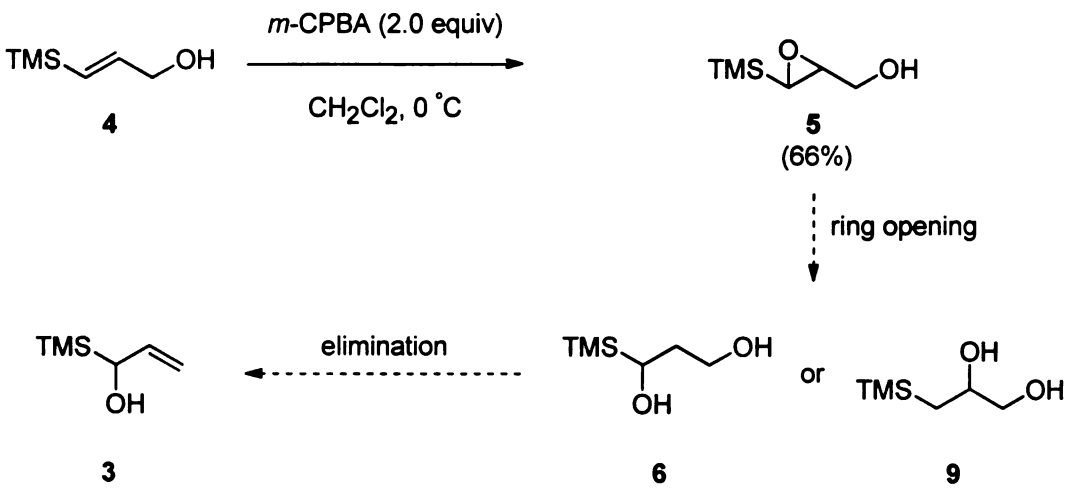
Scheme 23. Synthesis of Compound **4**



The starting material (**4**) for this chemistry was prepared as shown in Scheme 23. Propagylic alcohol reacted with ethylmagnesium bromide to form the dianion, which was quenched with TMSCl to afford trimethyl-[3-[(trimethylsilyl)oxy]-1-propyn-1-yl]-silane. Deprotection of the alcohol followed by reduction of the triple bond with Red-Al afforded the requisite allyl alcohol **4**.

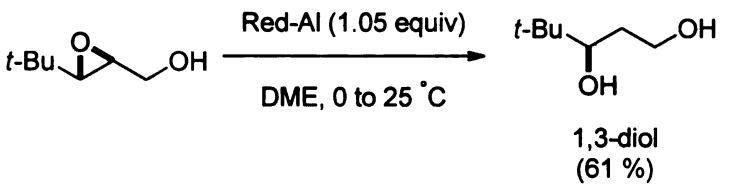
Before implementing our synthetic plan on optically active material, the feasibility and regio chemistry of the key reaction in question was studied with (±)-epoxyalcohol **5** (Scheme 24). Epoxidation of allylic alcohol (**4**) was readily accomplished by treatment with 2.0 equivalents of *m*-CPBA in CH_2Cl_2 to obtain the epoxyalcohol (**5**) in 66% yield.

Scheme 24. Regioselective Opening of Epoxyalcohol



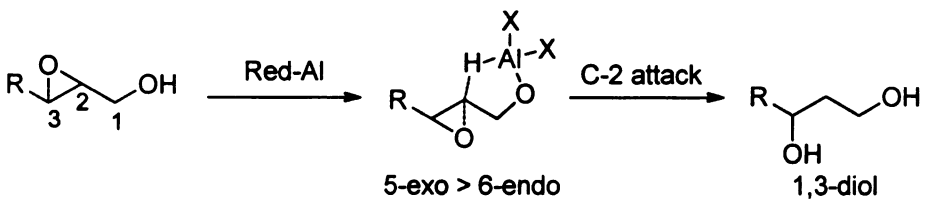
We then explored conditions for the regioselective ring opening of the epoxyalcohol to furnish the desired 1,3-diol (**6**). Red-Al has been reported to react with epoxy alcohols in 1,2-dimethoxyethane to open the epoxide from the less hindered side and furnish the corresponding 1,3-diol (Scheme 25).[42]

Scheme 25. Ring Opening Reaction with Red-Al



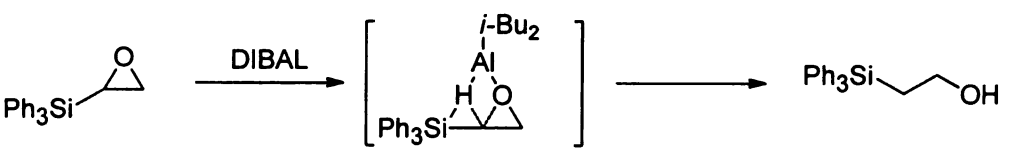
The reaction is thought to involve an initial complexation of the aluminum species with the alcohol followed by internal hydride delivery (Scheme 26). Because 5-exo ring formation is preferred over the 6-endo alternative, the product is a 1,3-diol.

Scheme 26. Ring Opening Reaction for Epoxyalcohol



Interestingly, Liu reported complementary regioselectivity with DIBAL. If an epoxide bears only a silyl group, the regioselectivity is explained by the transition state shown in Scheme 27.[43] Silicon is partially pentancoordinated and hydride is directed to the sterically more crowded carbon to give the product.

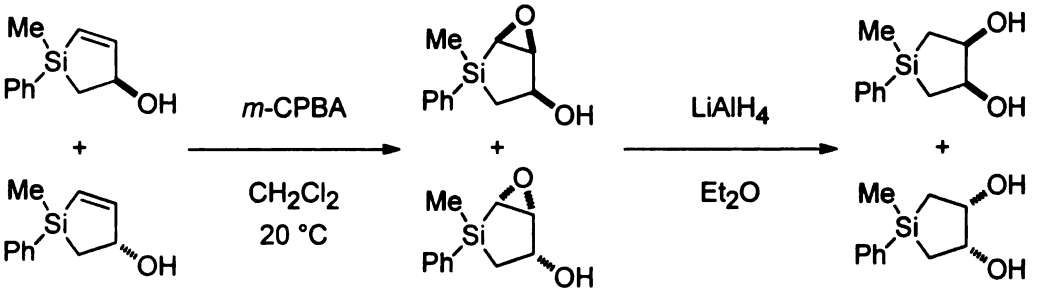
Scheme 27. Ring Opening Reaction for Epoxysilane



A similar ring opening reaction of epoxyalcohol bearing silyl group with a reducing reagent was reported by Manual and coworkers in 1993. However, they used LAH instead of Red-Al. This report shows that LAH can open the

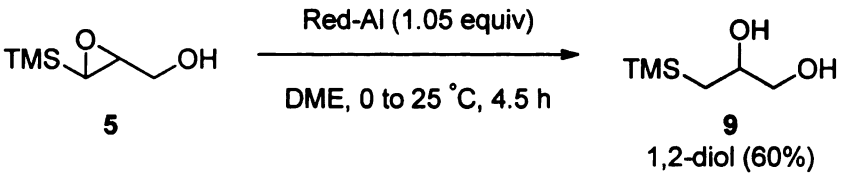
epxoyalchol bearing the silyl group regioselectively (Scheme 28).[44] In the reaction, observed product is the 1,2-diol.

Scheme 28. Ring Opening Reaction of Similar Substrates with LAH



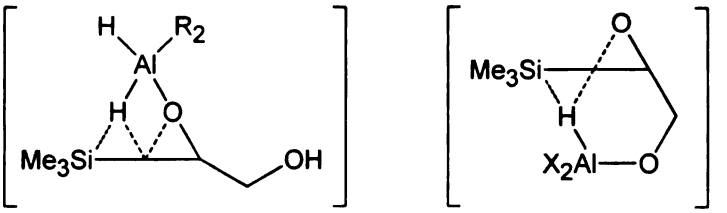
With this information, we first decided to react Red-Al and our substrate. A DME solution of compound **5** was treated with 1.05 equivalent of Red-Al at 0 to 25 °C for 4.5 h. The 1,2-diol (**9**) was exclusively obtained in 60% yield (Scheme 29), and the expected 1,3-diol was not observed under those conditions.

Scheme 29. Ring Opening Reaction using Red-Al



This experiment showed that silicon overrides the directing effects of the OH group. The possible transition state for our ring opening reaction with Red-Al is shown in Figure 2. To obtained the 1,2-diol, the hydride might be strongly coordinated to silicon (a) or the substrate might form a six-membered ring by silicon-hydride coordination (b). In both cases, the silicon plays an important role for the ring opening reaction with Red-Al.

Figure 2. Possible Transition State for Ring Opening with Red-Al

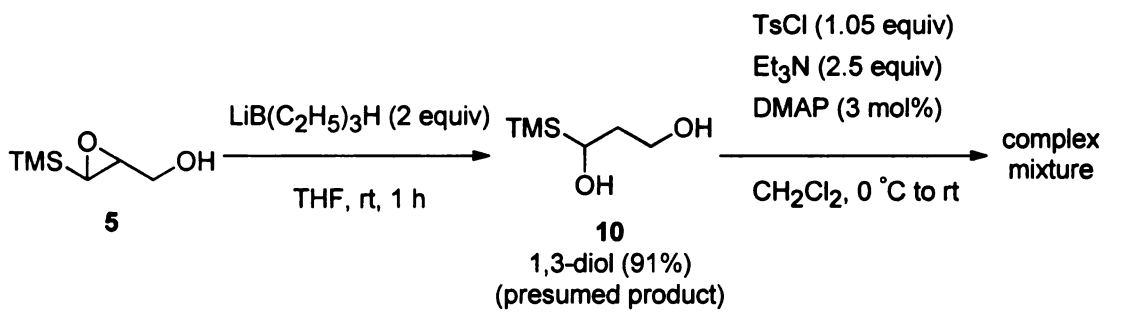


(a) Si group >> OH group

(b) six-membered ring

Whereas Red-Al did not afforded 1,3-diol, we wondered if the regioselectivity in the epoxide ring opening reaction would be changed by using a larger or less coordinating hydride source to maximize the steric effect between silyl group and the reducing reagent. Super-Hydride ($LiB(C_2H_5)_3H$) containing three ethyl groups was selected.

Scheme 30. Ring Opening Reaction using Super-Hydride

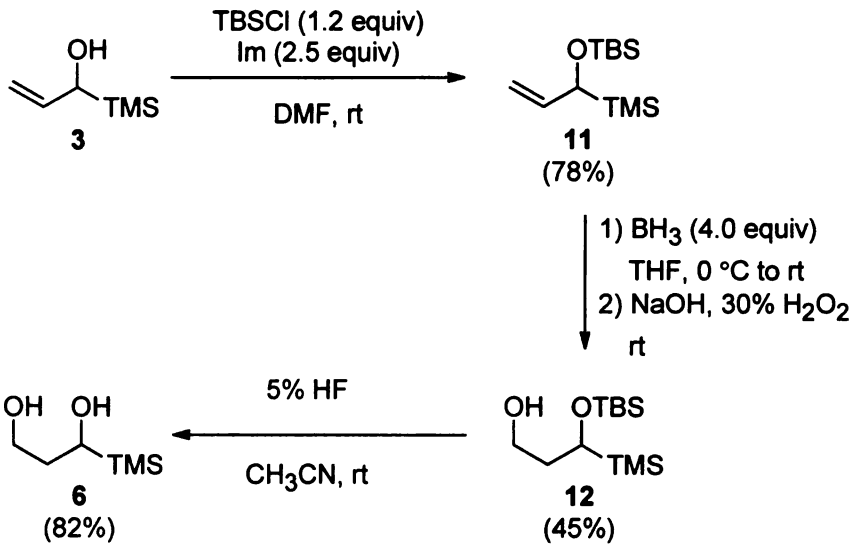


Treatment of a THF solution of compound **5** with 2.0 equivalents of Super-Hydride at room temperature for 1 h gave an unknown product (Scheme 30). The ^1H and ^{13}C NMR spectra obtained were not identical to 1,2-diol (**9**). We postulated that the product might be the desired 1,3-diol, resulting from opening of the epoxide from the less hindered side. However, structural determination was complicated by an impurity that remained after silica gel column

chromatography. Moreover, the next proposed step, tosylation of the primary hydroxyl group, of 'presumed-compound (**10**)', was not achieved.

Other attempts at reacting the impure and presumed **10** also failed. For example, in an effort to form the acetal, the presumed 1,3-diol (**10**) was treated with 4.0 equivalents of benzaldehyde dimethyl acetal and 0.6 equivalent of camphor-10-sulfonic acid in CH_2Cl_2 at room temperature or 10 equivalents of 2,2-diemthyoxypropane and 0.01 equivalent of camphor-10-sulfonic acid in CH_2Cl_2 at room temperature. In the end through, no acetal was formed. Likewise, presumed 1,3-diol **10** did not acylate upon treatment with 2.3 equivalents of acetyl chloride and 2.3 equivalents of triethylamine in THF at room temperature.

Scheme 31. Synthesis of 1,3-Diol (**11**)

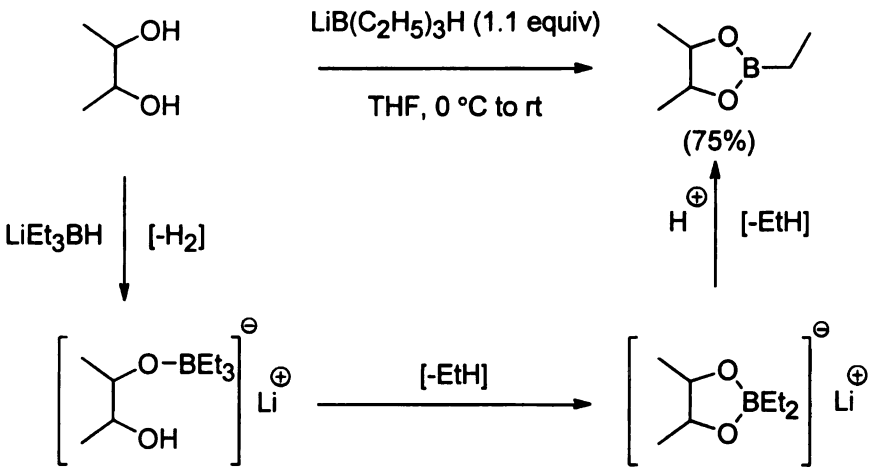


At this point, we doubted our tentative assignments of **10** as the 1,3-diol. To address this question directly, 1,3-diol **6** was prepared independently as illustrated by Scheme 31. Protection of α-hydroxysilane **3** with TBSCl followed by hydroboration/oxidation afforded compound **12**. The last step was removal of the TBS group under acidic conditions to form the 1,3-diol compound. Comparing the

spectroscopic data of 1,3-diol (**6**) and presumed-compound (**10**) showed that the compounds were in fact different.

As this point we considered the work of Vidari and coworkers who, in 1989 reported similar reactions between Super-Hydride and 1,2-diols (Scheme 32).[45] They showed that Super-Hydride could be used not only as a reducing reagent, but also as a reagent for the protection of 1,2-diols. This reaction is general, allowing for the preparation of cyclic ethylboronic esters from acyclic 1,2-diols in high yield. In the reaction, Super-Hydride abstracts hydrogen from the 1,2-diol and forms an O-B bond. Ethane is released and the ethylboronic ester is obtained.

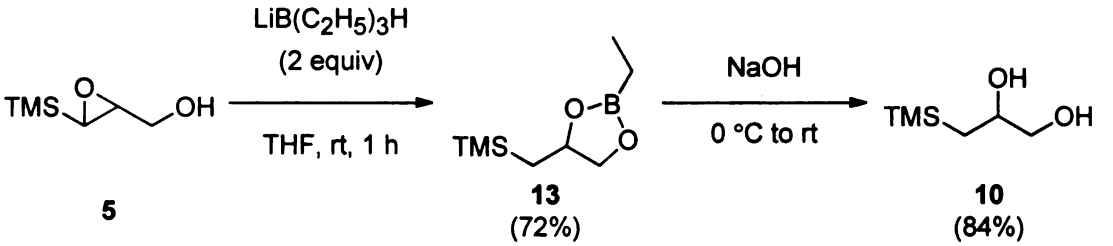
Scheme 32. Formation of Ethylboronic Ester



We recognized that presumed product **10** (Scheme 30) also could be a boronic ester of the type Vidari reported. Conformation of this was made possible by purifying compound **10** by distillation. One compound was obtained and the IR, ^{1}H, ^{13}C and ^{11}B NMR, COSY, HMQC and HRMS spectra revealed that the product was ethylboronic ester **13** (Scheme 33). IR of compound **13** showed that there were no hydroxyl groups and ^{11}B NMR showed the presence of a boron. To

further elucidate the structure, the boron was removed with sodium hydroxide to form 1,2-diol (**10**). We compared the ^{1}H NMR spectrum of compound **10** formed by Red-Al with that of compound **10** from **13**. They were identical and supported the structure of compound **13**.

Scheme 33. Observed Product



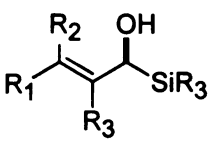
We have studied the ring opening of epoxy alcohols bearing a TMS group with both aluminum and boron hydrides. In all cases, formation of the 1,2-diol was favored. This result shows that silicon plays an important role in determining the regioselectivity and that cyclic boronic esters are formed in the ring opening reaction. Unfortunately, we did not obtained the 1,3-diol needed for the preparation of optically active α-hydroxysilanes. Therefore, we decided to move to the enzymatic kinetic resolution of α-hydroxysilane as described in Chapter 4.

Chapter 4. Enzymatic Kinetic Resolution of α-Hydroxysilanes

4.1. Introduction

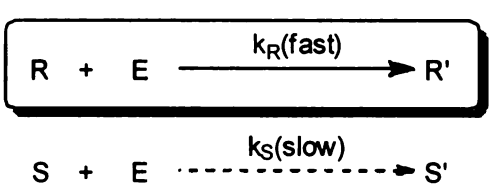
So far, our efforts toward accessing enantiopure α-hydroxysilanes had proven unsuccessful, therefore our attention turned to kinetic resolution (Figure 3). As shown in Chapter 2.2, enzymatic kinetic resolution is an alternative method for preparing α-hydroxysilanes. The advantage of enzymatic esterifications or ester hydrolyses is that they provide ready access to both α-hydroxysilane enantiomers.

Figure 3. α-Hydoxysilane



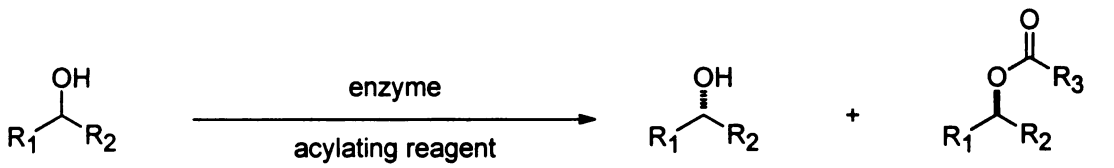
A kinetic resolution is "The achievement of partial or complete resolution by virtue of unequal rates of reaction of the enantiomers in a racemate with a chiral agent (reagent, catalyst, etc.)".[46] Enzymes are widely used in kinetic resolutions. Because enzymes have a chiral active site, one enantiomer of the racemates is transformed to the product at a faster rate than the other. This process is illustrated in Figure 4 where R and S are substrate enantiomers, R' and S' are corresponding product enantiomers and E is enzyme. After the reaction, R' and S are recovered.

Figure 4. Kinetic Resolution



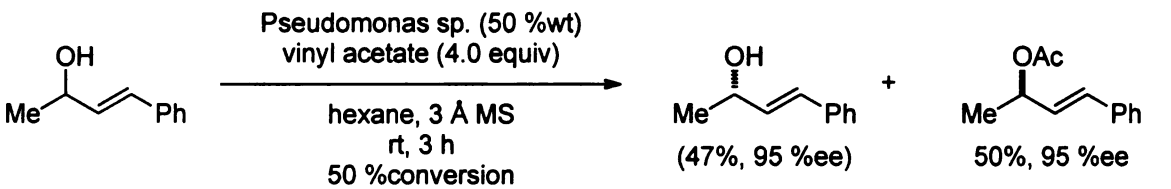
One of the most developed enzymatic kinetic resolutions is the esterification of secondary alcohols (Scheme 34). Treatment of racemic secondary alcohols with acylating reagents and an enzyme can give two products. One is the unreacted secondary alcohol and the other is the acetate.

Scheme 34. Kinetic Resolution of Secondary Alcohol



For example, Pseudomonas sp. resolves (3*E*)-4-phenyl-3-buten-2-ol to afford unreacted (*S*)-alcohol and (*R*)-acetate in good yields with excellent selectivity (Scheme 35).[47] The (*R*)-alcohol was acylated in 47% yield with 95 %ee, while the (*S*)-alcohol was recovered in 50% yield with 95 %ee.

Scheme 35. Kinetic Resolution of Secondary Alcohol with Pseudomonas sp.

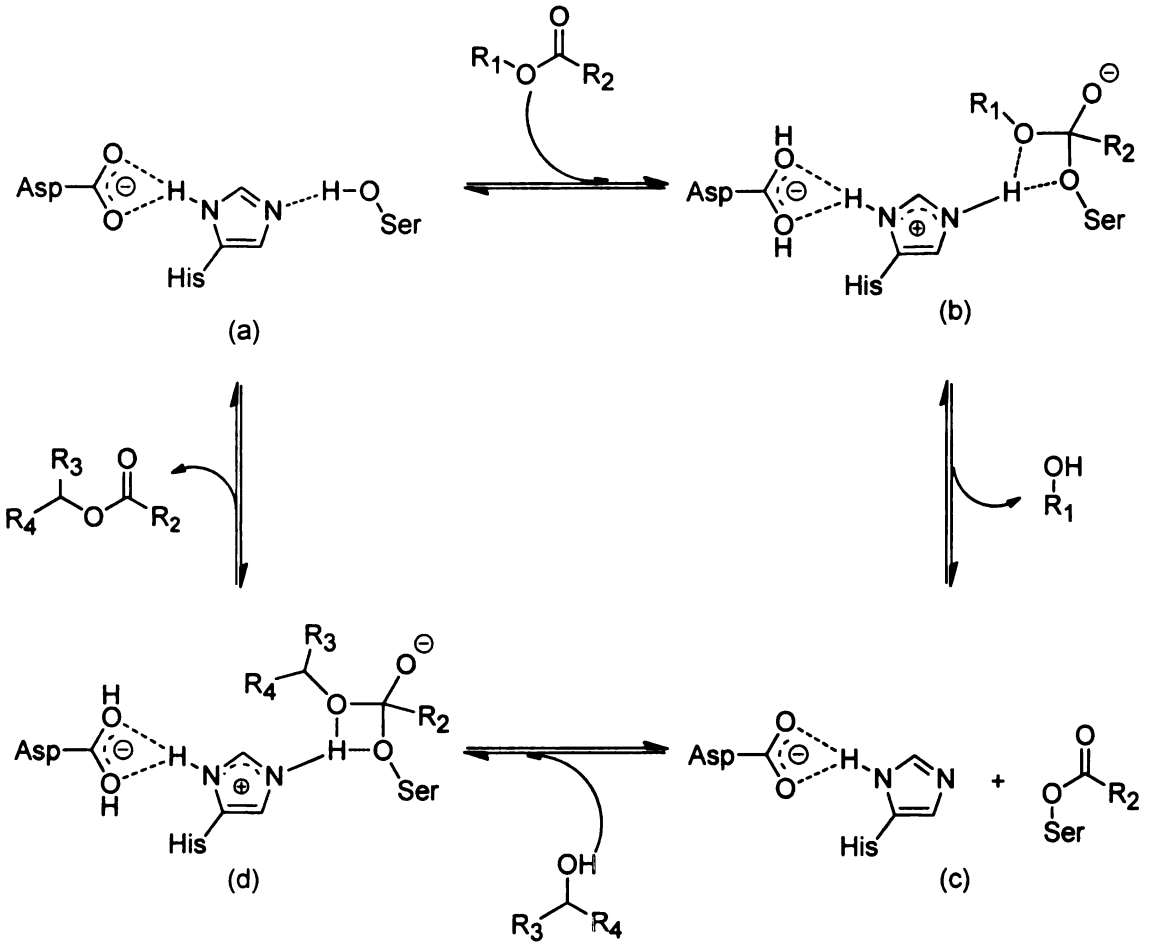


4.2. Mechanism of Kinetic Resolution

Enzymes determine the enantioselection through their chiral active site and also proceeded the acylation process. Acylation of secondary alcohols involves a serin, histidine, aspartate triad (Scheme 36).[48] Serine is activated by the hydrogen bonding of the three amino acids and the nucleophilicity of oxygen on serine increases (a). The oxygen attacks the carbonyl group of the acylating reagent to form transition state (b). The alcohol (R_1OH) is then released (c) and

the secondary alcohol attacks the carbonyl group on serine. Finally, the acetate is afforded and the enzyme is released for the next catalytic cycle (d).

Scheme 36. Mechanism of Kinetic Resolution

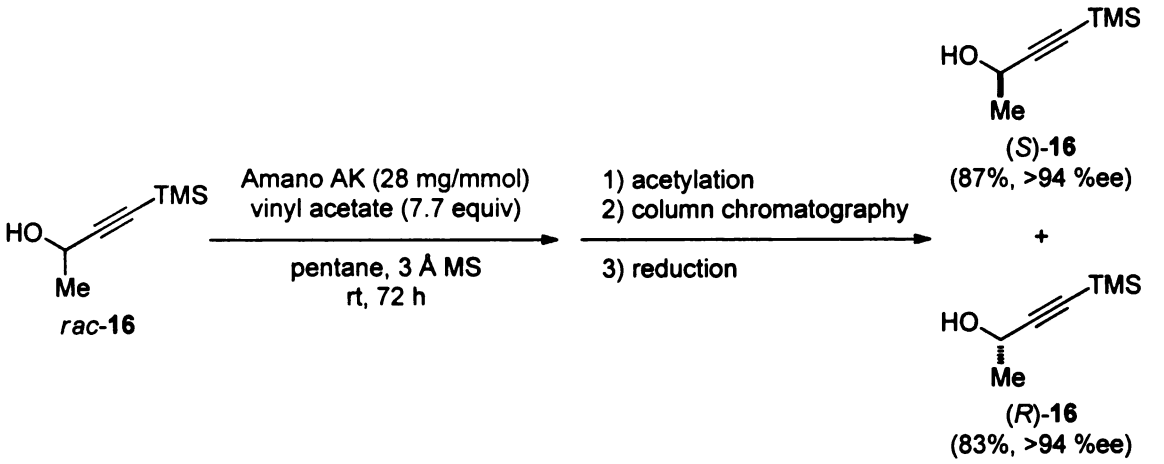


4.3. Enzymatic Kinetic Resolution of α-Hydroxysilanes

As shown in Chapter 2.2, the kinetic resolutions of silicon containing alcohols have been also reported before and 1-trimethylsilylpropanol, 1-acetate-1-(dimethylphenylsilyl)-2-butyn-1-ol and 4-trimethylsilyl-3-butyn-2-ol were resolved successfully. We decided to apply the conditions that had previously been employed during the kinetic resolution of 4-trimethylsilyl-3-butyn-2-ol because the reaction provided both enantiomers with excellent enantiomeric

excess and kinetic resolution of secondary alcohols with Amano AK are well known (Scheme 37).

Scheme 37. Kinetic Resolution of 4-TMS-3-butyn-2-ol with Amano AK



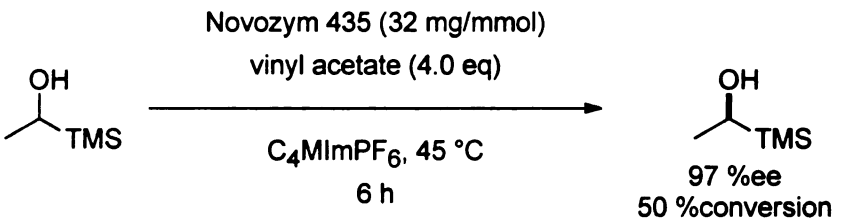
Owing in part to the limited literature precedent (see Chapter 2.2), we set out to conduct our own study on the enzymatic kinetic resolution of α-hydroxysilanes that varied at both the silicon and the organic group flanking the carbinol.

Initially, three different enzymes (Amano AK lipase, Amano PS lipase, and Novozym 435) were investigated in the kinetic resolution of (±)-1-hydroxyallyltrimethylsilane (*rac*-**3**). Reactions were run in a sealed tube filled with substrate, enzyme, vinyl acetate, and 3 Å molecular sieves as a mixture in pentane. The results of these screening experiments are summarized in Table 2.

In all cases, (*S*)-**3** reacted faster than (*R*)-**3**, as determined by a Trost-modified Mosher analysis of the unreacted alcohol using *O*-methylmandelate (vide infra, Chapter 4.4).[49] However, Zong and coworkers reported the remaining alcohols were *S* enantiomers in Novozym 435 catalyzed esterifications of 1-trimethylsilylethanol in both organic solvents and ionic liquids (Scheme 38).[50]

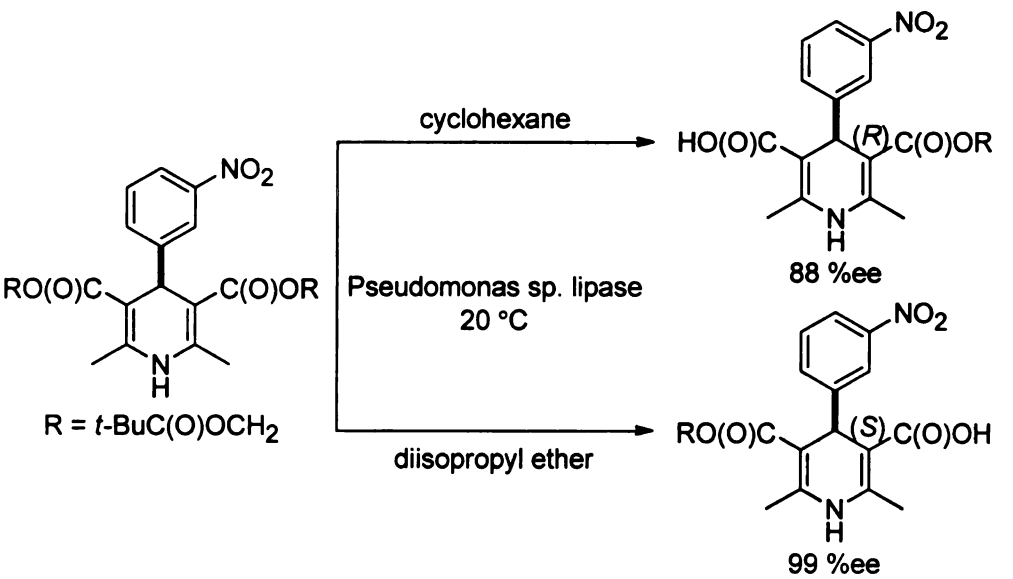
Although Novozym 435 and vinyl acetate were used in our study and Zong's study the product reported by Zong exhibits an opposite sense of absolute stereochemistry to that seen by us. These results obviously show that solvents can play an important role in the stereochemical course of enzymatic kinetic resolutions.

Scheme 38. Kinetic Resolution of 1-Trimethylsilyethanol in Ionic Liquid



Interestingly, the sense of our enantioselection was similar to that observed by Uejima in the resolution of 1-trimethylsilylpropanol with lipoprotein lipase in water-saturated 2,2,4-trimethylpentane (Scheme 19)[39].

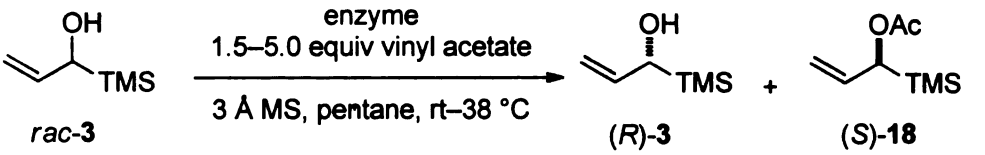
Scheme 39. Solvent Effect in Kinetic Resolution



Scheme 39 shows one of the most drastic examples of solvent influence on the enantioselectivity of an enzymatic kinetic resolution. As reported by Hirose

and coworkers in 1992, [51] in Pseudomonas sp. lipase resolution of dihydropyridine dicarboxylates, (*R*)-monoester was obtained with 88 %ee in cyclohexane and (*S*)-monoester was obtained with 99 %ee in diisoproyl ether. In this reaction, the solvents influence the absolute enantioselectivity, however, the cause of such solvent effects on enantioselectivty is not been fully understood.

Table 2. Kinetic Resolution of *rac*-**3**



rac-**3** (*R*)-**3** (*S*)-**18**

130 mg Amano AK Lipase/mmol[a]			130 mg Amano PS Lipase/mmol[b]			15 mg Novozym 435/mmol[c]		
Entry	Time (h)	(*S*)-**18** (%ee)[c]	Entry	Time (h)	(*S*)-**18** (%ee)[c]	Entry	Time (h)	(*S*)-**18** (%ee)[c]
1	23	73	1	22	88	1	8	99
2	96	81	2	24	93	2	13	99
3	120	80	3	48	94	3	22	99
4	168	80	4	96	92	4	27	98
5	192	82	5	169	96	5	33	98

[a]Reactions using Amano AK Lipase were performed at rt with 5.0 equiv of vinyl acetate in pentane containing 3Å molecular sieves.

[b]Reactions using Amano PS Lipase and Novozym 435 were performed at 38 °C with 1.5 equiv of vinyl acetate in pentane containing 3Å molecular sieves.

[c]The absolute configuration was assigned by Mosher analysis and chiral GC analysis determined the %ee.

It was clear that Amano AK (130 mg/mmol of Amano AK, 5.0 equivalents of vinyl acetate, pentane, 3 Å molecular sieve) could effectively resolve α-

hydroxysilanes with synthetically useful levels of enantioselectivity. However, 130 mg of Amano AK per mmol of *rac*-**3** was necessary and the reaction time was over 192 h. Thus, we continued to our kinetic resolution study in the search of better results. Amano PS was therefore investigated in the kinetic resolution of *rac*-**3**. *Rac*-**3** was treated with 130 mg of Amano PS and 1.5 equivalent of vinyl acetate in pentane with 3 Å molecular sieves. The desired acetate was afforded in 169 h with 96 %ee.

In our kinetic resolution study, Novozym 435 provided even better result. It was superior to Amano AK lipase and Amano PS lipase in that it afforded the best selectivity and shortest reaction times. Also, only 15 mg of Novozym 435 per mmol of *rac*-**3** was need in the reaction. As such, the best conditions to emerge out of these first experiments were to place a sealed tube containing a pentane solution of the *rac*-**3**, 15 mg Novozym 435/mmol *rac*-**3**, 1.5 equivalent of vinyl acetate, and 3 Å molecular sieves under a nitrogen atmosphere into an oil bath heated to 38 °C for 33 h. This protocol afforded (*S*)-acetic acid 1-(trimethylsilyl)-allyl ester (*S*)-**18** in 30% isolated yield with 98 %ee as well as unreacted (*R*)-**3**, which was isolated in 33% yield with 73 %ee.

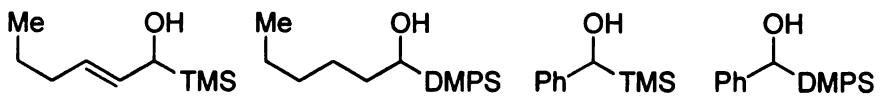
Additional testing showed that increasing the amount of vinyl acetate (up to 5 equivalents) did not improve the selectivity or yield. Likewise, lowering the Novozym 435 loading to 10 mg/mmol *rac*-**3** only resulted in longer reaction times, lower yields, and little change in the selectivity. Notably, if Novozym 435 was excluded no formation of the acetate product was observed.

On the basis of the above results, we applied our established procedure to a series of α-hydroxysilanes. The results from these reactions are summarized in Table 3. Unfortunately, substrate scope proved narrow. Exchanging the TMS group for a dimethylphenylsilyl (DMPS) group (**19**) improved the performance of the reaction (entry 2), whereas the *tert*-butyldimethylsilyl (TBS) analogue (**21**) failed to react (entry 3). Substrates with an additional methyl group at either the α- or β-vinyl positions (entries 4 and 6) did not acylate at 38 °C, even with increased catalyst loadings.

As Novozym 435 is stable at 70–80 °C,[52] *rac*-**22** was exposed to higher oil bath temperatures. At 78 °C and with increased catalyst loading, (*E*)-1-(trimethylsilyl)-2-buten-1-ol (*rac*-**22**) did react, albeit slowly and with low yield and poor selectivity (entry 5). Other solvents, including CH_2Cl_2, THF, benzene, toluene, and *t*-amyl alcohol, were examined, but none proved superior to pentane for the resolutions of **22** and **24**.

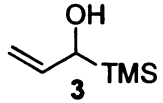
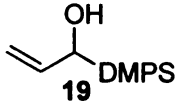
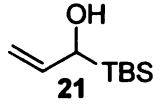
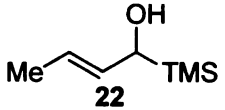
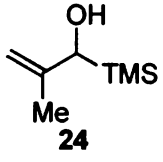
All other α-hydroxysilanes screened (Figure 5) failed to react. Even raising the amount of Novozym 435 to 130 mg/mmol of silane, upping the equivalents of vinyl acetate, and/or running the reactions at elevated temperatures did not promote acylation.

Figure 5. Failed α-Hydroxysilanes



25 **26** **27** **28**

Table 3. Kinetic Resolution of α-Hydroxysilanes

Entry	Starting α-hydroxysilane	mg/mmol Novozym 435	Time (h)	Temp (°C)	(*R*)-Hydroxysilane %ee[b]	(*R*)-Hydroxysilane % yield	(*S*)-Acetate %ee[b]	(*S*)-Acetate % Yield
1	 **3**	15	33	38	73[b]	33% (*R*)-**3**	>98[b]	30% (*S*)-**18**
2	 **19**	15	49	38	>99[b]	43% (*R*)-**19**	>99[b]	37% (*S*)-**20**
3	 **21**	15	24	38	n/a	no reaction	n/a	no reaction
4	 **22**	15	192	38	n/a	no reaction	n/a	no reaction
5		75	85	78	9[c]	11% (*R*)-**22**	—[d]	12% (*S*)-**23**
6	 **24**	75	17	38	n/a	no reaction	n/a	no reaction

[a]Reactions were run in a sealed tube containing substrate, Novozym 435, 1.5 equiv of vinyl acetate, 3Å MS, and pentane.

[b]The absolute stereochemistry was assigned by Mosher analysis and either chiral GC or HPLC analysis determined the %ee.

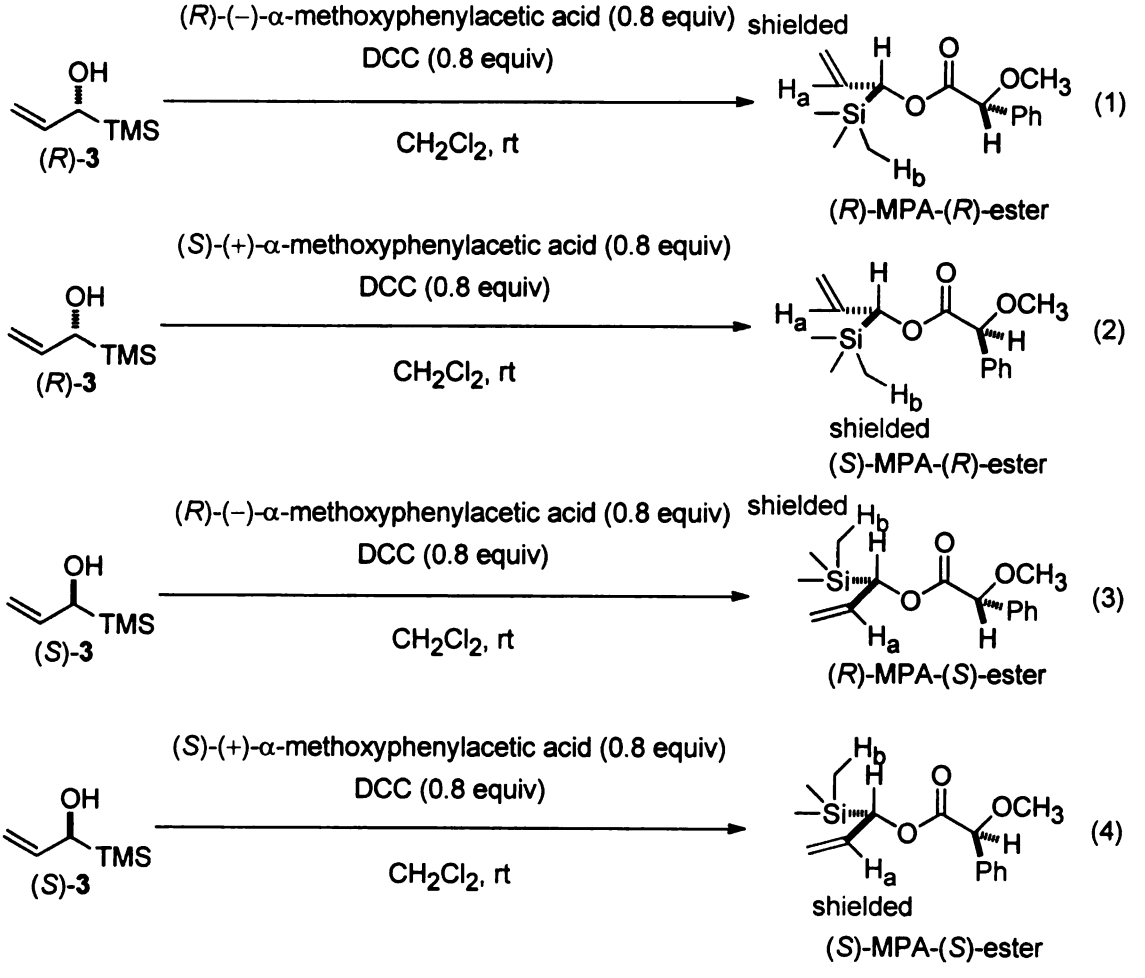
[c]The absolute stereochemistry and %ee was determined by comparing optical rotations of the unreacted alcohol to the literature $[\alpha]_D$.[1]

[d]All chromatographic and spectroscopic attempts to resolve the enantiomers and thus determine the %ee failed.

4.4. Determination of Absolute Stereochemistry

As previously mentioned, the absolute stereochemistry of unreacted α-hydroxysilanes was determined by Mosher ester analysis.[31] These remaining α-hydroxysilanes from the kinetic resolution of *rac*-**3** were treated with (*R*) or (*S*)-α-methoxyphenylacetic acid (MPA), DCC and DMAP in CH_2Cl_2. For such a reaction there are four possible derivatives; the (*R*)-MPA-(*R*)-ester, (*S*)-MPA-(*R*)-ester, (*R*)-MPA-(*S*)-ester, and (*S*)-MPA-(*S*)-ester (Scheme 40).

Scheme 40. Possible Structure in Mosher Ester Analysis

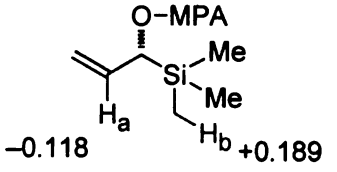


From the Mosher model, it is assumed that the methoxy, carbonyl and H (from the α-hydroxysilane) are in the same plane. If *R*-**3** is the unreacted α-

hydroxysilane, we consider equations (1) and (2). In case of (*R*)-MPA-(*R*)-ester, the phenyl group shields H_a of the vinyl group and the H_a peak moves upfield in the ^{1}HNMR (Eq. 1). For the (*S*)-MPA-(*R*)-ester, the H_b of the methyl group on silicon is shielded by the phenyl group and H_b moves upfield in the ^{1}HNMR (Eq. 2). Thus, the $\Delta\delta H_a$ of δ(*R*)-MPA-(*R*)-ester–δ(*S*)-MPA-(*R*)-ester is negative and the $\Delta\delta H_b$ by δ(*R*)-MPA-(*R*)-ester–δ(*S*)-MPA-(*R*)-ester should be positive. Were unreacted α-hydroxysilane **3** of the *S* absolute stereochemistry an opposite chemical shift and $\Delta\delta$ values would be observed (Eq 3 and 4). Therefore, the $\Delta\delta H_a$ from δ(*R*)-MPA-(*S*)-ester–δ(*S*)-MPA-(*S*)-ester would be positive and the $\Delta\delta H_b$ from δ(*R*)-MPA-(*S*)-ester–δ(*S*)-MPA-(*S*)-ester would be negative.

The ^{1}HNMR spectra of the two derivatives were compared. $\Delta\delta H_a$ was –0.118 and $\Delta\delta H_b$ was +0.189. Therefore, we assigned the absolute stereochemistry of the remaining α-hydroxysilane as *R* (Figure 6). The same procedure was applied to the α-hydroxysilane remaining after the kinetic resolution of *rac*-**19**. Again, the absolute stereochemistry was assigned as *R*.

Figure 6. Determination of Absolute Stereochemistry of (*R*)-**3**



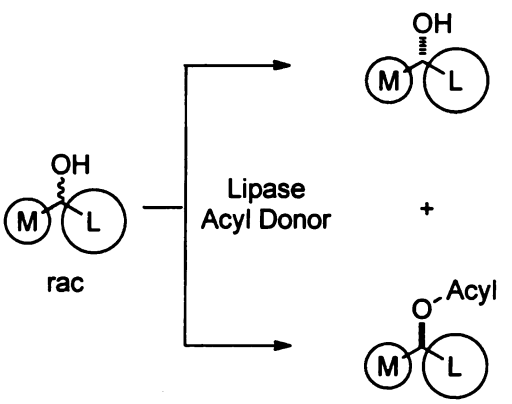
$\delta_{(R)\text{-MPA-}(R)\text{-ester}} - \delta_{(S)\text{-MPA-}(R)\text{-ester}}$

The assigned absolute stereochemistry of the α-hydroxysilanes from the enzymatic kinetic resolution are those that would be expected by an empirical rule called "Kazlauskas' rule".[54] Kazlauskas' rule predicts which alcohol will react faster in an acylation of secondary alcohols. This rule is based on size

differences of the substituents at the stereocenter (one large and one medium group). According to their size, substituents are placed in two different pockets.

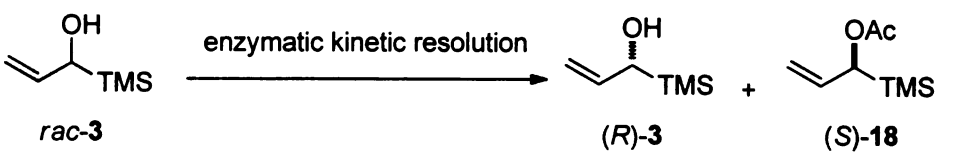
Kazlauskas' rule can be illustrated as shown in Figure 7. The secondary alcohol arranges itself with the larger group on the right and medium group on the left. After the reaction, the alcohol with the OH group orientated toward the back of the plane is unreacted and the alcohol with the OH group orientated to the front of the plane is acylated. The size difference between the two substituents is important for reliably predicting absolute stereochemistry. Usually, lager size differences give better predictability and enantioselectivity.

Figure 7. Kazlauska's Rule



We can clearly see that *rac*-**3** follows Kazlauskas' rule (Scheme 41). The medium size vinyl group is placed on the left side and lager TMS group is on the right side. After the reaction, (*R*)-**3** remains and (*S*)-**3** was acylated. Kazlauskas' rule was also applied to the kinetic resolution of *rac*-**19**.

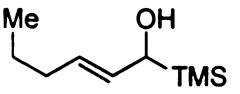
Scheme 41. Enzymatic Kinetic Resolution of α-Hydroxysilane



4.5. Determination of %ee using ^{29}Si NMR

One of the problems we met during the project was to determine enantiomeric excess of the products. Chiral HPLC and GC are useful tools in terms of accuracy and generality, but their use can be time consuming and not always workable. For example, *rac*-**25** did not give good separation under the HPLC and GC conditions we explored (Figure 8).

Figure 8. Difficulty Determinating %ee



25

Mosher ester analysis can be also used for this purpose. However, α-hydroxysilanes were sensitive to the conditions of ester formation and erosion of enantiomeric excess was observed in all cases. As such we continued to search for alternative methods. In 1999, Picard and coworkers reported the use of lanthanide shift reagent to α-*C*-silylated amines and alcohols for determination of enantiomeric excess using ^{29}Si NMR (Figure 9).[55] In the presence of Eu(tfc)$_3$, *rac*-**27** shows two peaks with ratio of 50.3:49.7.

We applied this ^{29}Si NMR analysis to some of our substrates. We ran a series of spectra in the presence of 1–20 mol% of the chemical shift reagent in order to find the optimal conditions. Table 4 shows the best results. Applying this method to *rac*-**27**, **3** and **25** allowed for the determination of the enantiomeric excess with reasonable accuracy and precision. In the case of *rac*-**22,** partial separation of the two peaks was observed but it was not baseline, limiting the use of ^{29}Si NMR in this instance.

Figure 9. ^{29}Si NMR of *Rac*-**27** with $Eu(tfc)_3$

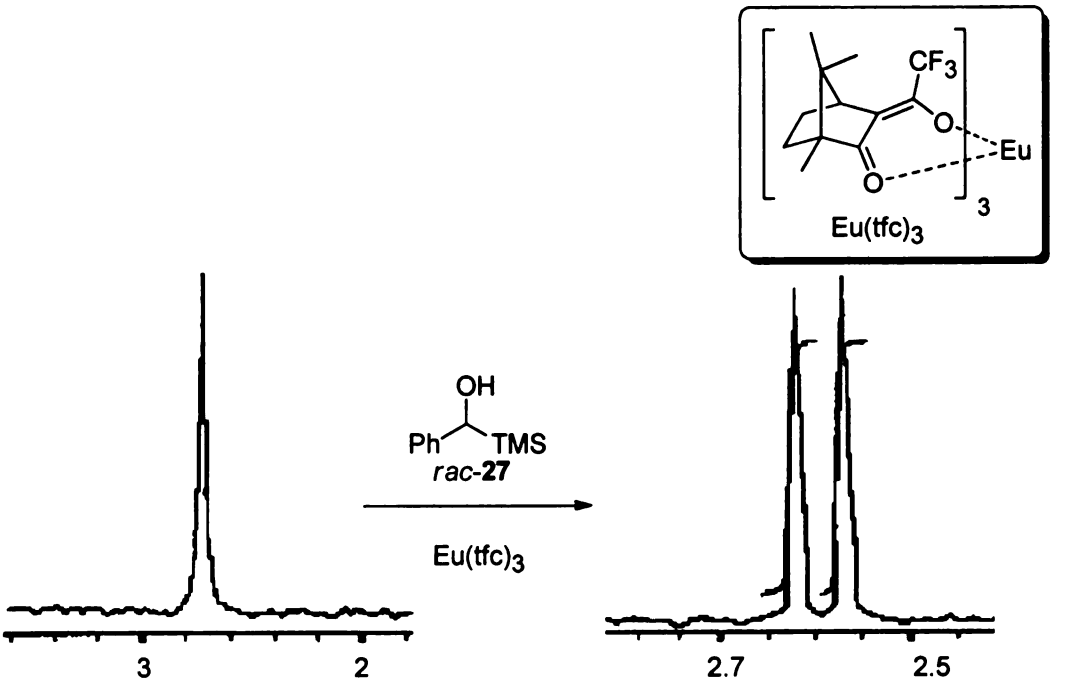
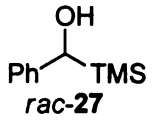
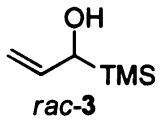
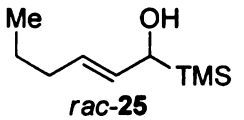
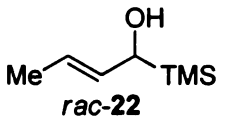


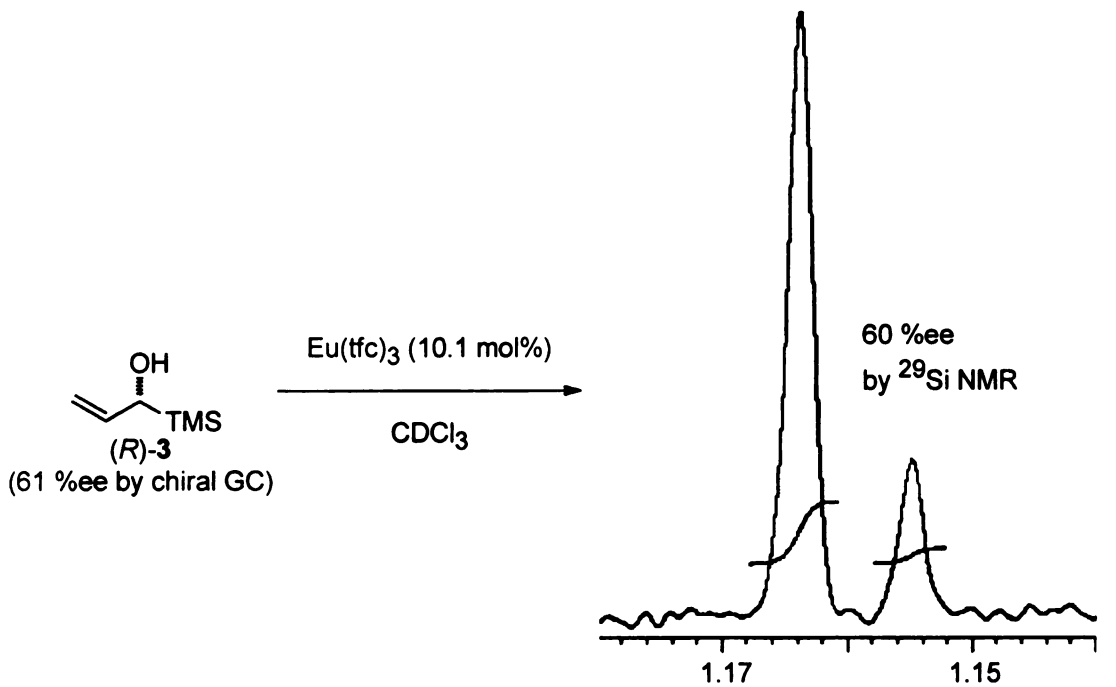
Table 4. Enantiomeric Ratio by ^{29}Si NMR

α-Hydroxysilanes	$Eu(tfc)_3$ (mol%)	Δδ (ppm)	Ratio
 *rac*-**27**	10.1	0.0075	52.1:47.9
 *rac*-**3**	10.1	0.0102	52.2:47.2
 *rac*-**25**	9.7	0.0073	48.0:52.0
 *rac*-**22**	12.0	0.0051	overlapped

To check the accuracy of these measurements, the enantiomeric excess of non racemic mixture **3** was measured by chiral GC and ^{29}Si NMR (Figure 10).

The results were in good agreement. Even though this ^{29}Si NMR method has substrate limitations, the enantiomeric excess can be determined quickly and reliably.

Figure 10. ^{29}Si NMR Spectrum of *R*-**3** with $Eu(tfc)_3$

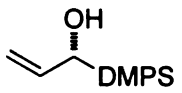


4.6. Conflict Optical Rotation Value of (*R*)-19

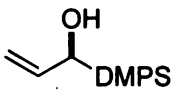
During the kinetic resolution reaction of *rac*-**19**, $[\alpha]_D$ results that were inconsistent with previous reports were obtained. We measured the optical rotation of the remaining alcohol (Figure 11) and a negative value ($[\alpha]_D$ = –8.9 (*c* 1.04, $CHCl_3$)) was obtained (*R*-**19**-a). However, assuming Kauzlaskas' rule and that the unreacted alcohol should be of the *R* configuration, this negative rotation for (*R*)-**19** would be in conflict with a previous report[38, 56] Namely, Woerpel described the preparation of (*S*)-**19** by reduction of 1-(dimethylphenylsilyl)-2-propen-1-one with (+)-Ipc_2BCl and reported a negative $[\alpha]_D$ value for the *S* enantiomer (*R*-**19**-b). Curiously, Marsden reported the preparation of (*R*)-**19**

using (–)-Ipc_2BCl and he also reported a negative $[\alpha]_D$ rotation for his *R* enantiomer (*R*-**19**-c). Obviously, having negative $[\alpha]_D$ values for both *R* and *S* enantiomers is improbable.

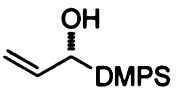
Figure 11. Conflict $[\alpha]_D$ Values



(*R*)-19-a
(99 %ee)
$[\alpha]_D$ = –8.8 (*c* 1.04, $CHCl_3$)
Our result



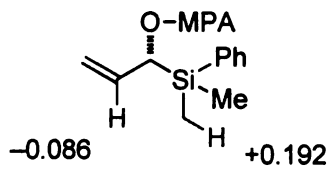
(*S*)-19-b
(93 %ee)
$[\alpha]_D$ = –10.5 (*c* 0.50, $CHCl_3$)
Woerpel's result



(*R*)-19-c
(91 %ee)
$[\alpha]_D$ = –6.8 (*c* n/a, n/a)
Marsden's result

Mosher ester analysis of our material after the kinetic resolution of *rac*-**19** indicated that the unreacted alcohol was (*R*)-**19** and (*S*)-**19** was acylated (Figure 12). However, Mosher ester analysis is an empirical method, and given the conflicting literature, we sought a more definitive conformation of our assignment.

Figure 12. Determination of Absolute Stereochemistry of (*R*)-**19**



$\delta_{(R)\text{-MPA-}(R)\text{-ester}} - \delta_{(S)\text{-MPA-}(R)\text{-ester}}$

In a private communication, we learned that Woerpel and Marsden did not have any material left to recheck the $[\alpha]_D$ values of their materials. To make matters more confusing the original paper on the preparation of optically pure **19**, which was referred to by Woerpel and Marsden, did not report any $[\alpha]_D$ values.[38,56] Thus we were left with no choice other than to repeat the previously reported reductions (Scheme 42). Acylsilanes (**29**) were prepared by Swern oxidation of *rac*-**19** (1.5 equivalent of trifluoroacetic anhydride, 2.0 equivalents of

DMSO and 3.0 equivalents of Et_3N in CH_2Cl_2, –78 °C). (*R*)-**19** and (*S*)-**19** were prepared by reduction of **29** using (–)-Ipc_2BCl and (+)-Ipc_2BCl. In our hands, (*R*)-**19** gave a negative $[\alpha]_D$ and (*S*)-**19** gave a positive $[\alpha]_D$. This result is consistent with our $[\alpha]_D$ value of (*R*)-**19** prepared by enzymatic kinetic resolution.

Scheme 42. Reduction of Acylsilane **29**

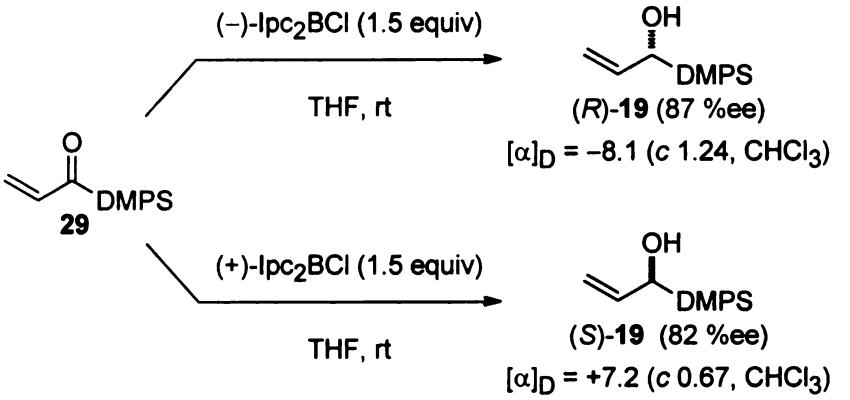


Table 5. Retention Times of Optically Pure **19**

Preparation method for optically pure **19**	HPLC Condition	Retention time (min)
(–)-Ipc_2BCl reduction	Column: OD-H Eluent: 0.5 % IPA/hexane Flow rate: 1.0 mL/min (Woerpel's condition)[38]	9.0
(+)-Ipc_2BCl reduction		8.1
Kinetic resolution		9.0

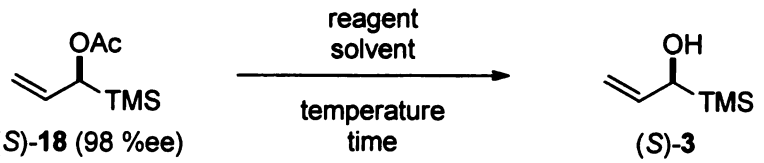
We also compared our enzymatically generated (*R*)-**19** with both (+)-Ipc_2BCl and (–)-Ipc_2BCl reduction products following the HPLC conditions described in Woerpel's paper (Table 5).[38] The retention time of enzymatic product (*R*)-**19** is the same as that of the (–)-Ipc_2BCl reduction product (*R*)-**19**. We thus confirmed the absolute configuration of remaining α-hydroxysilane as *R*

enantiomer and $[\alpha]_D$ value of (*R*)-**19** is negative. (*S*)-**19** prepared by Woerpel should have a positive $[\alpha]_D$ rotation.

4.7. Reduction of Optically Pure Acetate

As the advantage of a resolution is the ability to access both enantiomers, we next investigated procedures for converting the enantioenriched acetates into their corresponding chiral α-hydroxysilanes. Experimenting on (*S*)-**18**, a variety of reagents were investigated, but many of these lead to erosion of enantiomeric excess (Table 6). The most efficient results were achieved with DIBAL. For example, when essentially enantiopure (*S*)-**18** (98 %ee) was treated with 1.0 equivalent of DIBAL in hexane at –78 °C, the corresponding (*S*)-1-hydroxyallyltrimethylsilane ((*S*)-**3**) was obtained in 78% isolated yield with only modest loss of %ee (99:1 to 94.5:5.5 er).

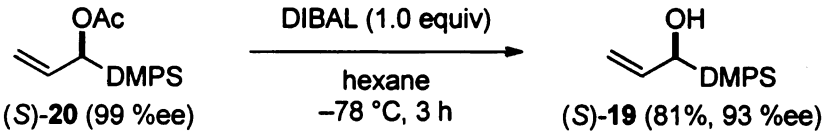
Table 6. Reduction of Optically Pure Acetate (*S*)-**18**



Entry	Reagent	Equiv	Solvent	Temp (°C)	Time (h)	%ee	Yield (%)
1	K_2CO_3	5.0	MeOH	20	4	85	-
2	LAH	1.2	Et_2O	Reflux	2	80	-
3	KCN	1.0	MeOH	rt	24	76	-
4	LiOH	5.0	MeOH-H_2O	20	5	85	-
5	Red-Al	1.05	THF	0 to rt	1.75	81	-
6	DIBAL	1.1	CH_2Cl_2	–78	3	84	-
7	DIBAL	1.0	Hexane	–78	3	89	78

The same procedure could be applied to (*S*)-**20**, with even less loss of enantiopurity. In this way, (*S*)-**19** was obtained in 81% yield with 93 %ee (Scheme 43).

Scheme 43. Reduction of Optically Pure Acetate by DIBAL



(*S*)-**20** (99 %ee) (*S*)-**19** (81%, 93 %ee)

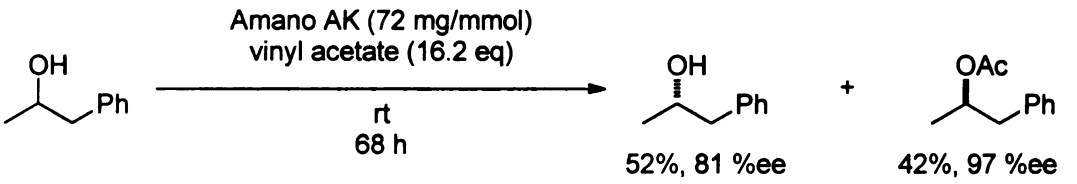
Chapter 5. Enzymatic Kinetic Resolution of Methylated α-Hydroxysilanes

5.1. Introduction

In an attempt to overcome the poor reactivity exhibited by the methylated substrates (Table 3, entries 4 to 6), we turned to commercially available enzymes that are known to effect the transesterification of secondary alcohols. Several such enzymes are documented in the literature.

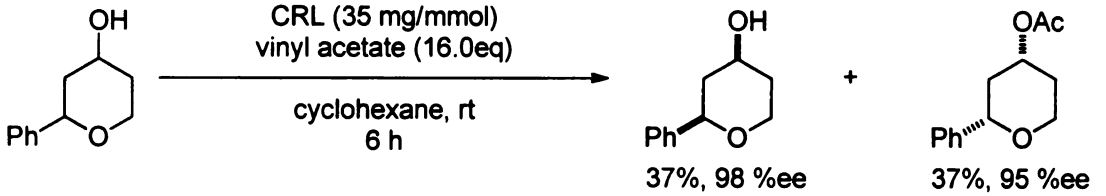
For example, Amano AK resolves α-methyl-benzeneethanol to afford the (*S*)-unreacted alcohol and the (*R*)-acetate in good yields with good enantiomeric excesses (Scheme 44).[57] The acetate was obtained in 42% yield with 97 %ee and the (*S*)-alcohol was recovered in 52% yield with 81 %ee.

Scheme 44. Kinetic Resolution of with Amano AK



Similarly, CRL was reported for the efficient kinetic resolution of tetrahydro-2-pheyl-2H-pyran-4-ol to afford the unreacted alcohol and the corresponding acetate (Scheme 45).[58]

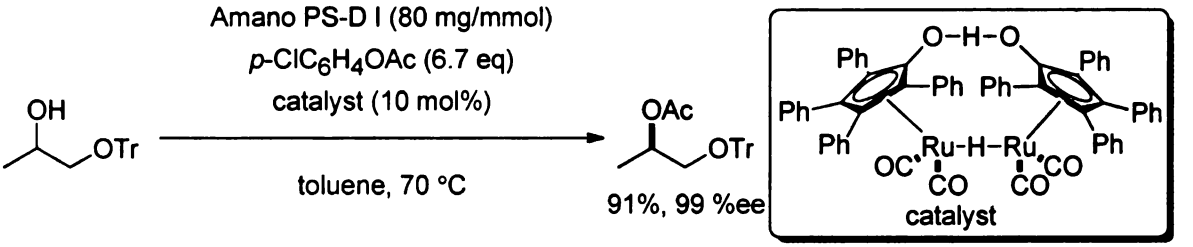
Scheme 45. Kinetic Resolution with CRL



Also there are some examples of the dynamic kinetic resolution of secondary alcohols with a ruthenium cocatalyst. Using a ruthenium racemization

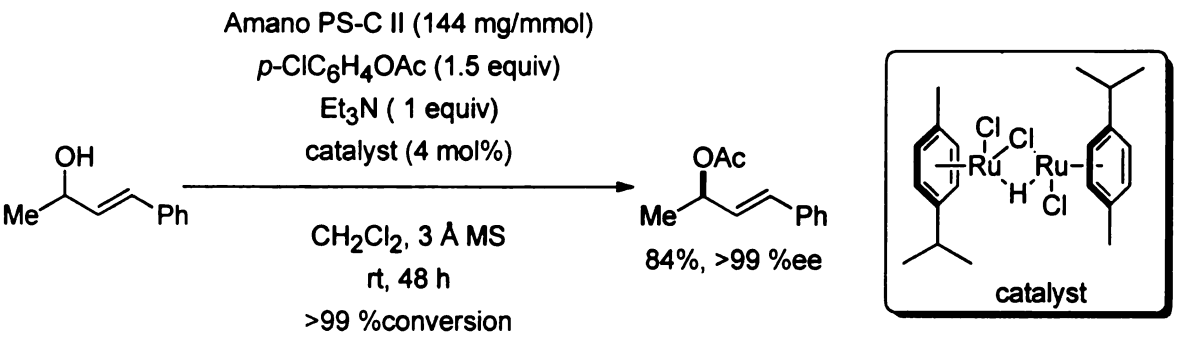
catalyst and PS-D I as an acylating catalyst, a series of secondary alcohols were resolved with excellent enantioselectivities and in good yields (Scheme 46).[59]

Scheme 46. Kinetic Resolution with Amano PS-D I



Kim and coworkers have also reported a novel ruthenium catalyst that can racemiz allylic alcohols (Scheme 47).[60] In the presence of this catalyst, Amano PS-C II catalyzed transesterification using *p*-ClC_6H_4OAc as an acylating reagent afforded (*R*)-acylated product in 84% yield with >99 %ee.

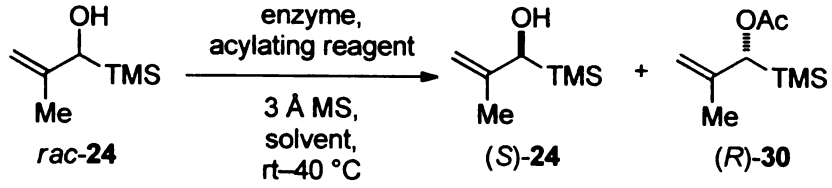
Scheme 47. Kinetic Resolution with Amano PS-C II



5.2. Kinetic Resolution of *Rac*-24

We tested Amano AK, Amano PS-D I, Amano PS-C II and CRL in the kinetic resolution of 2-methyl-1-(trimethylsilyl)-2-propen-1-ol (*rac*-**24**) (Table 7). Amano AK, Amano PS-C II and CRL afforded some level of reactivity but the reaction times were long and enantioselectivity was low. Amano PS-D I gave the best results in terms of enantioselectivity.

Table 7. Kinetic Resolution of α-Hydroxysilanes



Entry	Lipase (mg/mmol)	Acylation reagent (equiv)	Solvent	Time (h)	Temp (°C)	Conv (%)	(*S*)-**24** %ee[b]	(*S*)-**24** % yield[c]	(*R*)-**30** %ee[b]	(*R*)-**30** % yield[c]
1[d]	Amano PS-C II (144)	*p*-ClC_6H_4OAc (1.5)	CH_2Cl_2	209	rt–40	8	2	14	66	2
2	Amano AK (72)	vinyl acetate (16.2)	neat	209	rt–40	13	>1[e]	81	21	13
3	CRL (30)	vinyl acetate (16.0)	cyclohexane	352	rt–40	9	>48[e]	57	9	5
4	Amano PS-D I (72)	*p*-ClC_6H_4OAc (6.7)	toluene	209	70	57	22	33	64	18
5	Amano PS-D I (144)	vinyl acetate (1.5)	toluene	115	40	17	56	89	74	10
6	Amano PS-D I (144)	vinyl acetate (1.5)	CH_2Cl_2	239	40	11	-	65	69	7
7	Amano PS-D I (144)	vinyl acetate (1.5)	THF	239	40	15	-	80	68	13

Table7. Kinetic Resolution of α-Hydroxysilanes (cont'd)

Entry	Lipase (mg/mmol)	Acylation reagent (equiv)	Solvent	Time (h)	Temp (°C)	Conv (%)	(*S*)-**24** %ee[b]	(*S*)-**24** % yield[c]	(*R*)-**30** %ee[b]	(*R*)-**30** % yield[c]
8	Amano PS-D I (144)	vinyl acetate (1.5)	*t*-amylalcohol	115	40	19	-	84	73	16
9	Amano PS-D I (288)	vinyl acetate (1.5)	toluene	140	rt	49	>99	10	87	9.2
10	Amano PS-D I (288)	vinyl acetate (1.5)	*t*-amylalcohol	115	rt	37	-	56	60	13
11	Amano PS-D I (144)	vinyl acetate (1.5)	toluene	306	10	54	>99	2	87	5
12	Amano PS-D I (288)	vinyl acetate (3.0)	toluene	112	rt	44	>99	19	87	13
13	Amano PS-D I (432)	vinyl acetate (1.5)	toluene	140	rt	47	90	22	87	16

[a]Reactions were run in a sealed tube containing the substrate, enzyme, acylation reagent, 3Å MS, and the solvent.

[b]The absolute configuration was determined by Mosher analysis and chiral GC analysis determined the %ee.

[c]Yields were determined by GC using decane as an internal standard.

[d]1.0 equiv triethylamine added.

[e]GC peaks corresponding to (*R*)- and (*S*)-**24** were partially overlapping.

[f]Stirring was difficult because of too much Amano PS-D I.

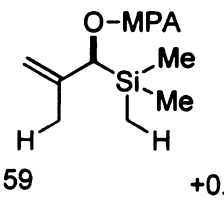
As shown in entry 12, the optimized conditions were *rac*-**24**, 288 mg Amano PS-D I/mmol *rac*-**24**, 3.0 equivalents of vinyl acetate and 3 Å molecular sieves in toluene under a nitrogen atmosphere at room temperature in a sealed tube. Acetate (*R*)-**30** was obtained in 13% yield with 87 %ee, with the alcohol (*S*)-**24** being recovered in 19% yield with 99 %ee. Again, adjustments in the amount of Amano PS-C I lipase and vinyl acetate and/or solvent did not improve the resolution results. If Amano PS-D I was excluded, no formation of acetate product was observed.

From these reactions, we made two important observation. First, (*S*)-**24** was unreacted and (*R*)-**24** was acylated in the reaction. Second, the yield of both products was lower than those from the kinetic resolution with Novozym 435.

5.3. Determination of Absolute Stereochemistry

Again, the absolute stereochemistry of the unreacted α-hydroxysilane **24** was determined by Mosher ester analysis (Figure 13).[31] Interestingly, the stereochemical preference was *opposite* to that observed during the resolution of *rac*-**3** with Novozym 435.

Figure 13. Determination of the Absolute Stereochemistry of (*S*)-**24**

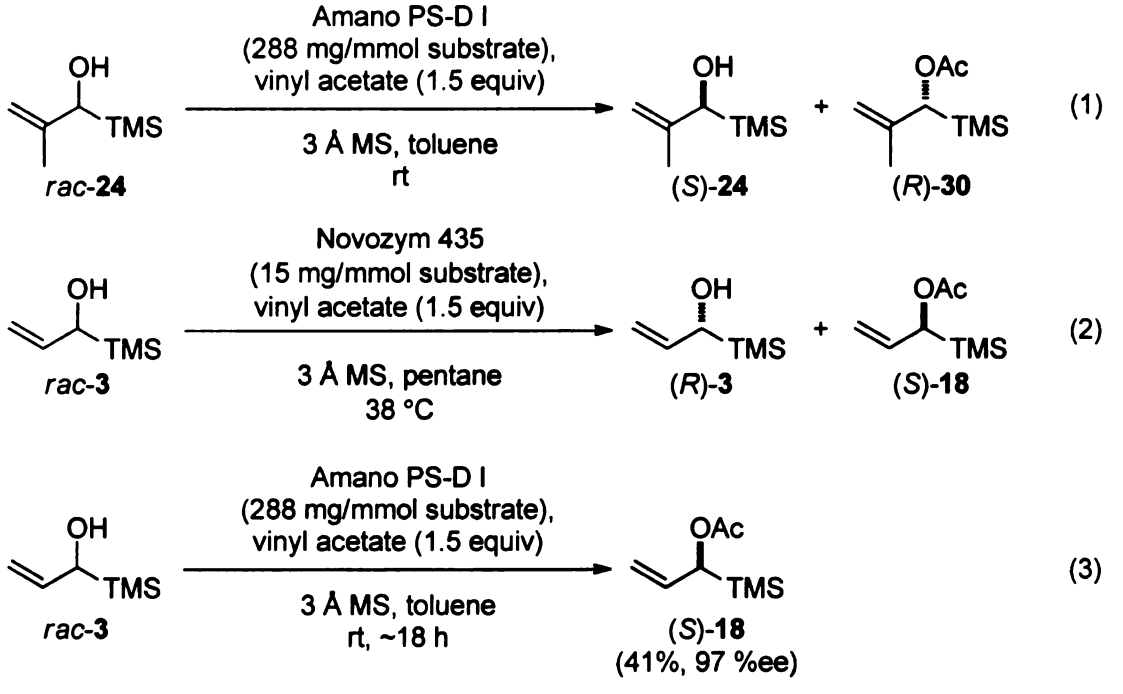


$\delta_{(R)\text{-MPA-}(R)\text{-ester}} - \delta_{(R)\text{-MPA-}(S)\text{-ester}}$

Scheme 48 shows the absolute stereochemistry of the remaining α-hydroxysilane and acetated product after the kinetic resolution. In the case of the kinetic resolution of *rac*-**24** with Amano PS-D I, the unreacted α-hydroxysilane

was the *S* enantiomer (Eq 1). However, the *R* enantiomer was recovered after the kinetic resolution of *rac*-**3** with Novozym 435 (Eq 2). To more directly compare the selectivity of Amano PS-D I vs. Novozym 435, *rac*-**3** was resolved with Amano PS-D I in the presence of 1.5 equivalent of vinyl acetate in toluene at room temperature (Eq 3). After ~18 h, *rac*-**3** was completely consumed and acetate (*S*)-**18** was formed in 41% yield with 97 %ee.

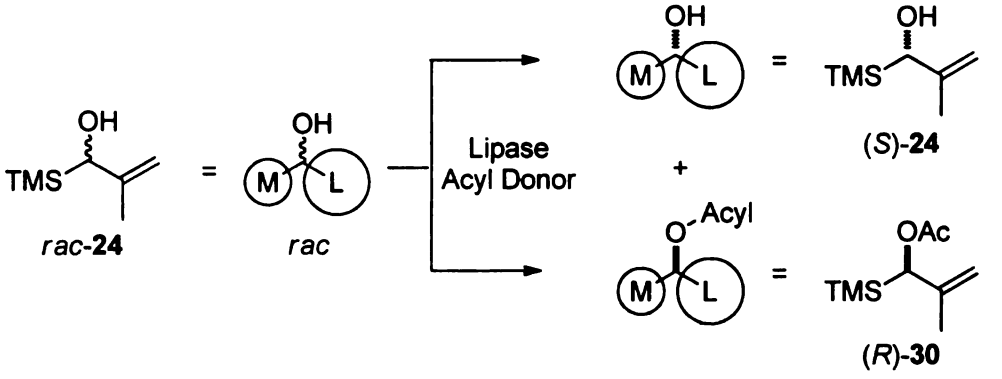
Scheme 48. Comparison of Absolute Stereochemistry



It seems that *rac*-**24** does not follow Kazlauskas' rule. However, *rac*-**24** is different from *rac*-**3** in term of the size of substituents. *Rac*-**24** has a methyl group on the α-position of the vinyl group (isopropenyl group). Unfortunately, we could not find an A value of the isopropenyl group so as to make the direct size comparison of the two groups (A value of TMS= 2.5). For an indirect comparison of the two groups, a similar isopropyl group was selected and it has a smaller A value than TMS (A value of isopropyl= 2.1). We could not decide which group

between TMS and isopropyl group is larger. However, if we assume that the isopropenyl group is larger than the TMS group, Kazlauskas' rule could be apply to the kinetic resolution of *rac*-**24** (Figure 14). Importantly, what can be concluded though is that the observed absolute stereochemistry is highly influenced by even relatively small changes to the side chain structure of the α-hydroxysilane.

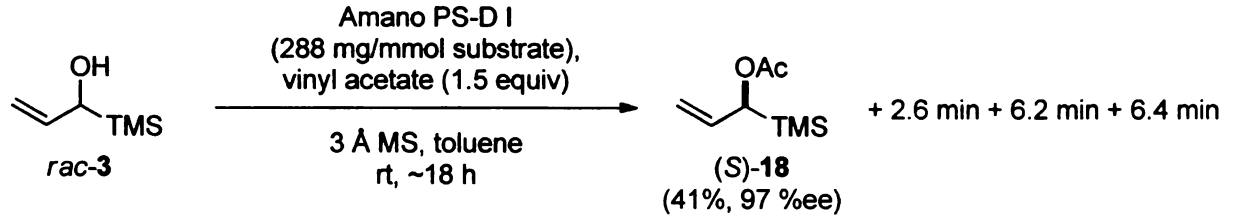
Figure 14. Kazlauskas' Rule for *Rac*-**24**

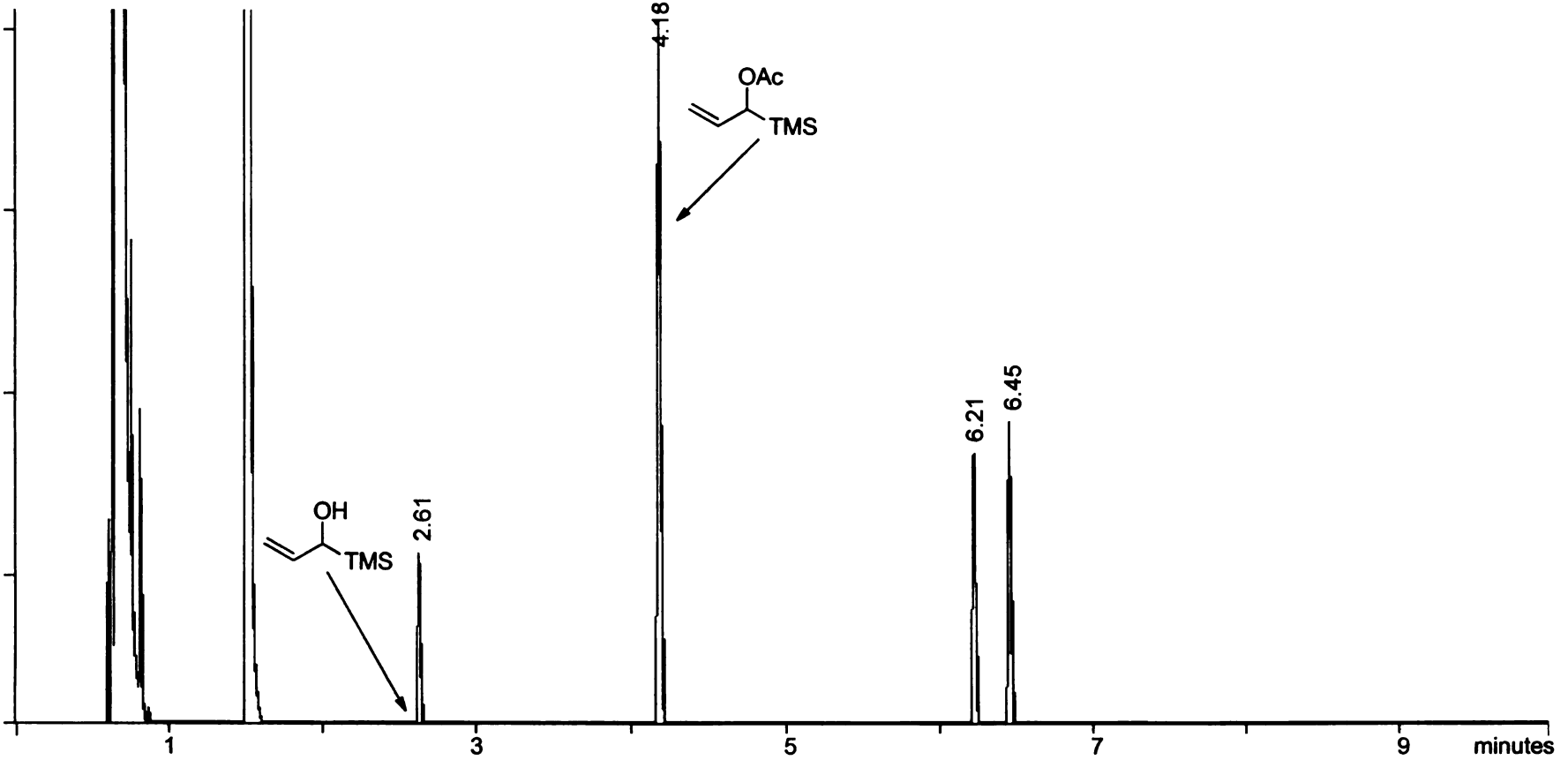


5.4. Formation of Acetylated Hemiacetal

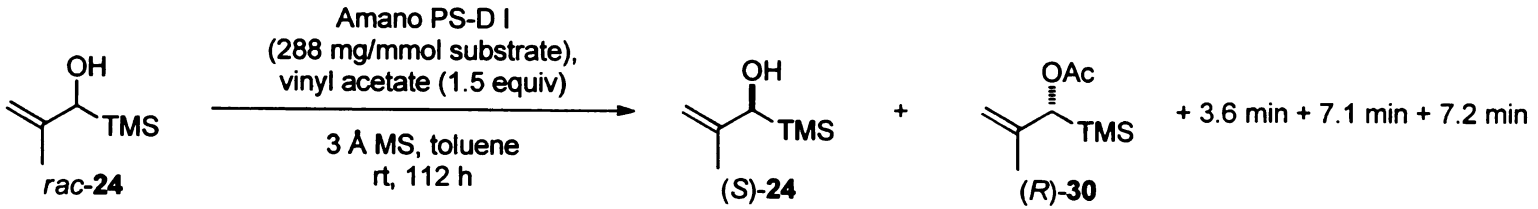
As mentioned before, the kinetic resolution of *rac*-**24** afforded products in low yield (Chapter 5.2). The low yields of (*R*)-**30** and (*S*)-**24** were partly due to formation of unknown compounds as main products of the reaction. While the reactions of *rac*-**3** and *rac*-**24** with Amano PS-D I afforded different stereochemical outcomes, they were similar in that both afforded side products. After the kinetic resolution of *rac*-**24**, three newly formed peaks (3.6 min, 7.1 min and 7.2 min, ratio= 18:43:38) were observed for the unreacted α-hydroxysilane and acetate product by GC (Scheme 49). Similarly, GC of the crude material gave three peaks at 2.6, 6.2, and 6.4 minutes (ratio= 22:38:48) for the acylated products peak from the kinetic resolution of *rac*-**3** (Scheme 50).

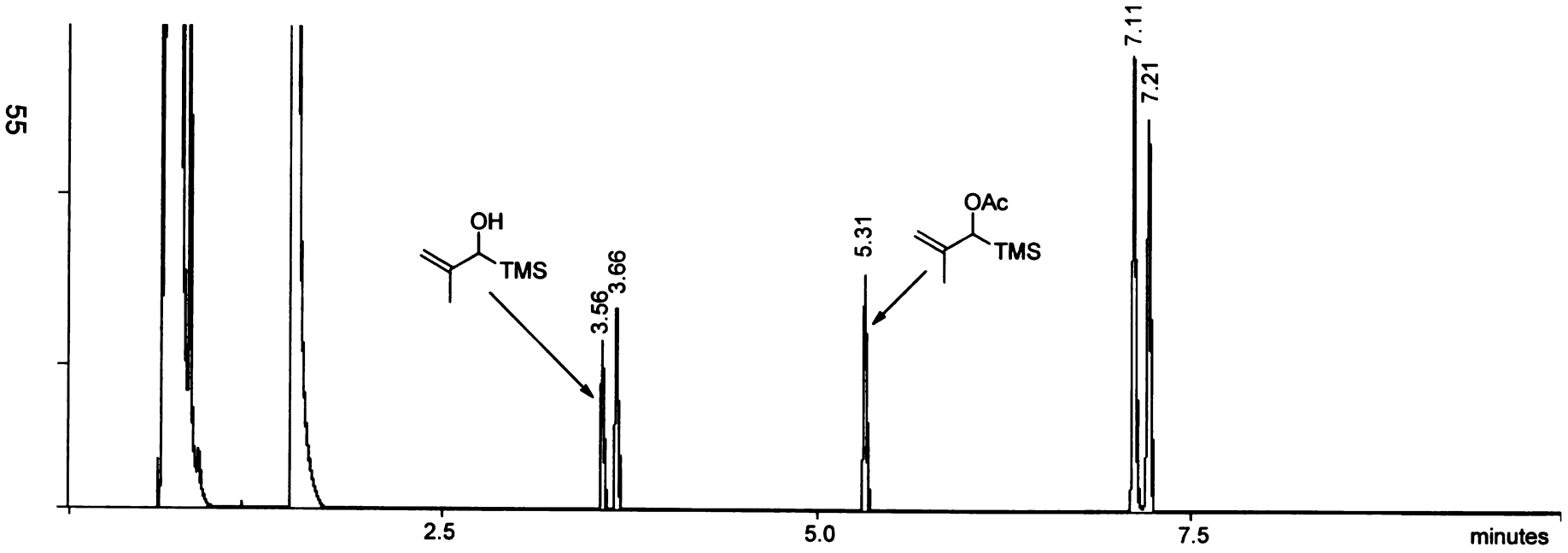
Scheme 50. GC data for Kinetic Resolution of *Rac*-**3**





Scheme 49. GC data for Kinetic Resolution of *Rac*-**24**

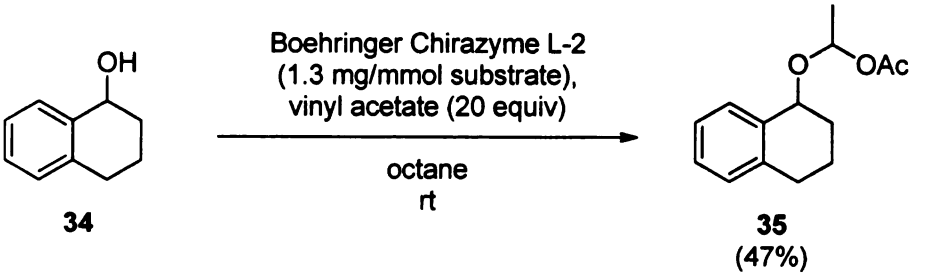




We decided to elucidate the structure of the side product of the kinetic resolution of *rac*-**3**. Acetate (*S*)-**18** was easily removed from the crude material by rotary evaporation. However, a mixture (2.6 min, 6.2 min and 6.4 min on GC) of unknowns was inseparable by silica gel column chromatography or fractional distillation. Furthermore, the compound that eluted at 2.6 min partially decomposed during silica gel column chromatography (ratio of 2.6 min:6.2 min:6.4 min = 9:32:59).

A possible explanation for the byproducts from the enzymatic kinetic resolution of *rac*-**3** is formation of an acylated hemiacetal by reaction between the starting racemic α-hydroxysilanes and the aldehyde formed from the acylating reagent. Recall that all of *rac*-**3** was consumed in the reaction with Amano PS-D I. Forthermore, Högberg and coworkers reported the kinetic resolution of sterically hindered secondary alcohols with vinyl acetates gave acylated hemiacetal as the major product (Scheme 51).[61] Usually, more sterically hindered substrates form these acetals in such reactions.

Scheme 51. Kinetic Resolution of Sterically Hindered Secondary Alcohol **34**



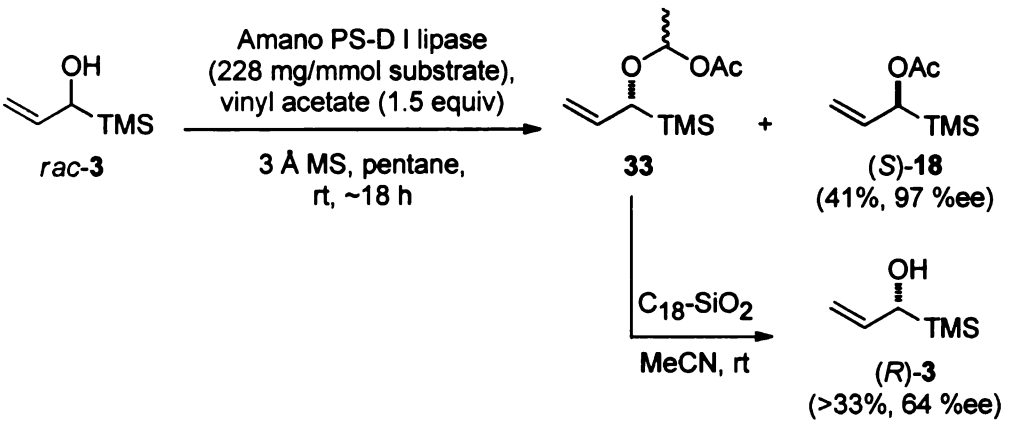
34

35
(47%)

We tentatively assigned the structure of the impure material from the kinetic resolution of *rac*-**3** based on ^{1}H, ^{13}C, HMQC, HMBC, TOCSY, COSY, IR, and HRMS analysis. These data suggested that the peaks occurring at 6.2, and

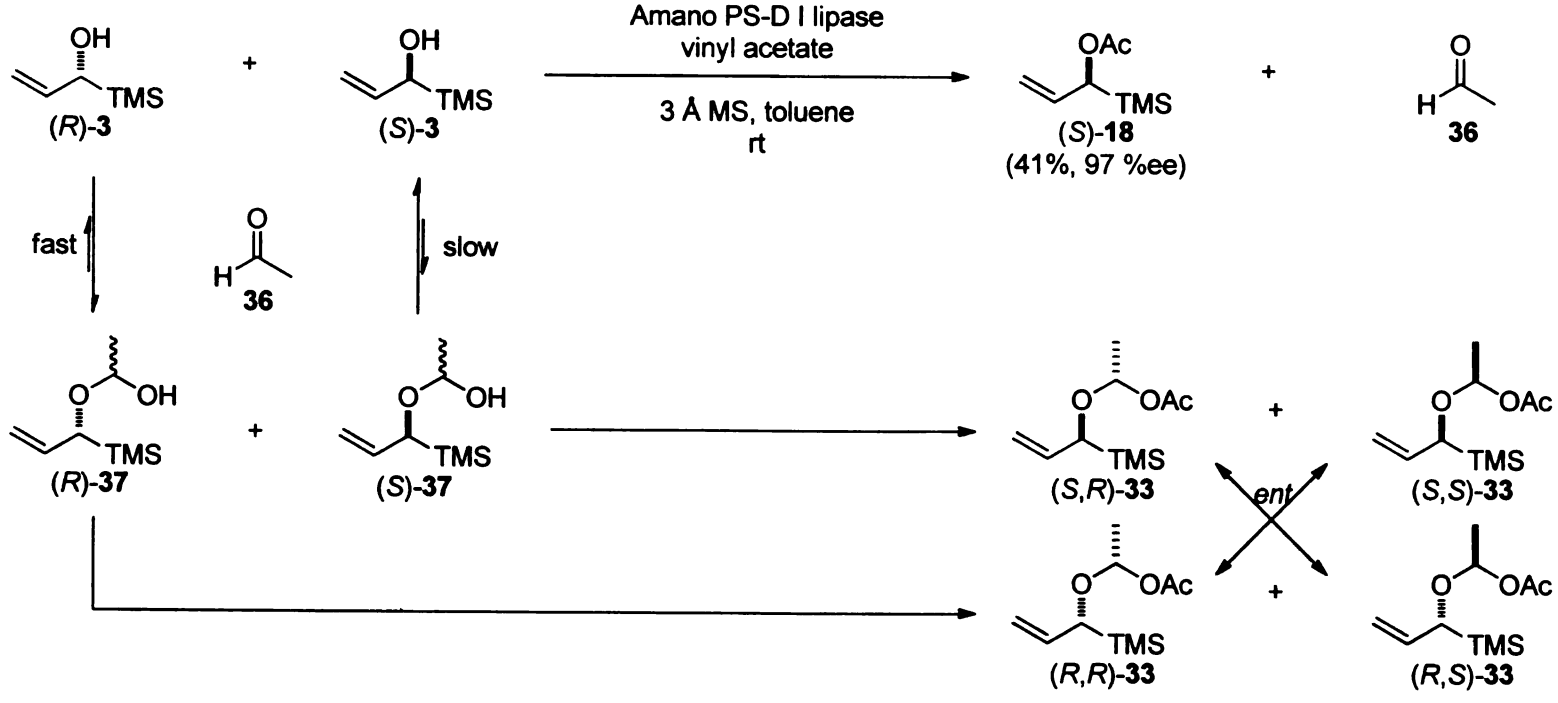
6.4 minutes was diastereomers of **33**. Treatment of the impure acetal **33** with C_{18} silica gel in CH_3CN at room temperature gave (*R*)-**3** with 64 %ee in >33% yield (Scheme 52). This result showed that (*R*)-**3** is converted to the acetal **33** during the kinetic resolution.

Scheme 52. Enzymatic Resolution of *Rac*-**3** with Amano PS-D I lipase and Hydrolysis of **33**



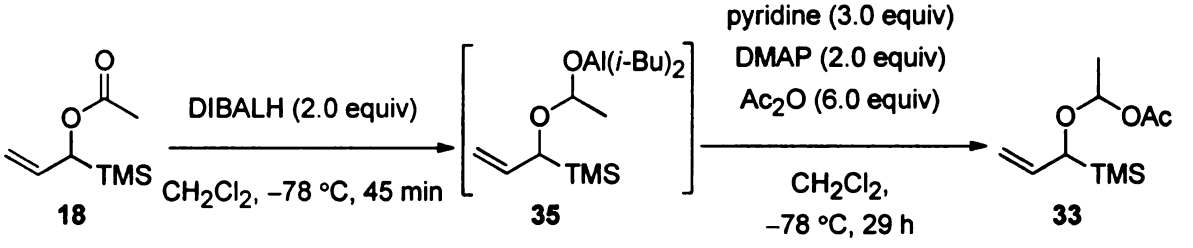
The formation of acylated hemiacetal **33** can be explained by the following mechanism (Scheme 53). The reaction initially affords (*S*)-**18**. During the reaction, aldehyde **36** is also produced by enol-keto tautomerization of the enol side product (from (b) to (c) in Scheme 36). Compound **36** can react with both (*R*) and (*S*)-**3** at different rates. It is assumed that acetylation of (*S*)-**3** is faster than formation of hemiacetal (*S*)-**37**, because (*S*)-**18** is recovered in good yield with excellent enantiomeric excess. In the case of (*R*)-**3**, formation of hemiacetal is faster than acetylation. Subsequently, hemiacetal **37** forms (from (*R*)-**3**), which can be esterified to give (*R*,*R*)- and (*R*,*S*)-**33**.

Scheme 53. Possible Mechanism for Formation of Acetylated Hemiacetal **33**



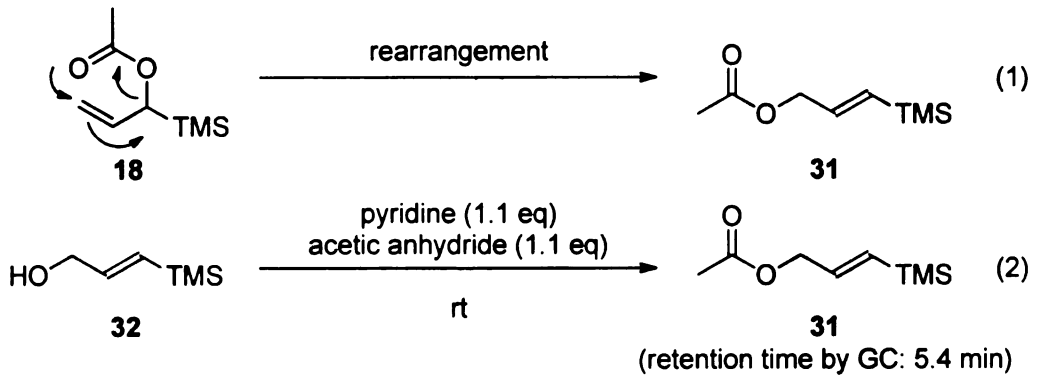
To further support our conclusion, we independently prepared **33** by the reduction of **18** with DIBAL followed by acylation of the resultant hemiacetal (Scheme 54).[62] Interestingly, this newly prepared material had the same impurity profile of **33** made during the kinetic resolution of *rac*-**3**. A GC of the material gave peaks at 2.6, 6.2 and 6.4 minutes, albeit in a different ratio (1:59:40). The material was also spectroscopically similar to that formed during the kinetic resolution. We confirmed the formation of acetal **33** in the kinetic resolution of *rac*-**3**.

Scheme 54. Synthesis of Acetal **33**



The last unknown side product from the kinetic resolution of *rac*-**3** was a compound that eluted at 2.6 min on GC. However, this side product is not separable by silicagel column chromatography or by fractional distillation. We thought that the side product might be a rearrangement product from acetate **18** (Eq 1, Scheme 55), because an extra CH_3 (from the acetate), TMS and vinyl ^1H NMR peaks were presented in the ^1H NMR spectrum of the crude material. With this information, compound **31** was prepared from commercially available **32** (Eq 2) and its GC retention time was determined. This established that **31** was not the side product from the enzymatic kinetic resolution. We still do not know the structure of this minor side product.

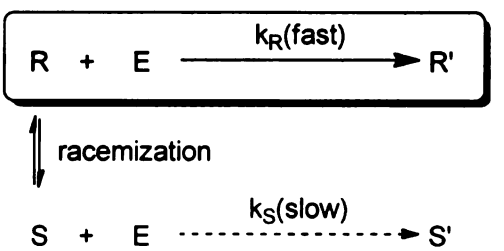
Scheme 55. Possible Rearrangement of **18**



5.5. Future Work

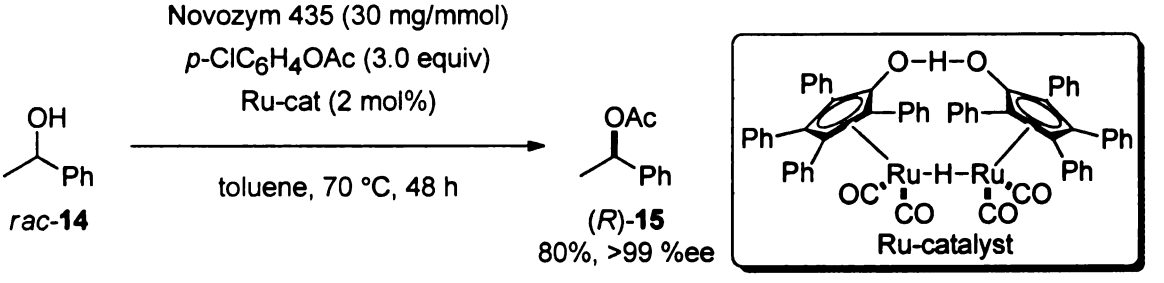
Our research shows the viability of the enzymatic kinetic resolution of α-hydroxysilanes to prepare optically pure α-hydroxysilanes. However, kinetic resolution allows for a maximum of only 50% yield of a single enantiomer. In our study, unreacted α-hydroxysilane was recovered in 43% and the acetate was isolated in 37%. To overcome the maximum of 50% yield in kinetic resolution, a dynamic kinetic resolution (DKR) can be used (Figure 15). During a DKR, *R* and *S* enantiomers react at different rates but they are in equilibrium by way of a racemization event that happens during the kinetic resolution. In this way, all the starting material can be used and the product can be obtained in 100% yield.

Figure 15. Dynmaic Kinetic Resolution



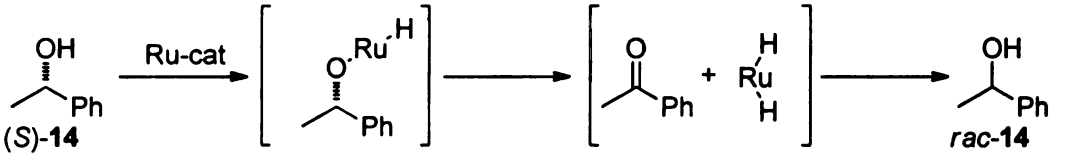
For example, Bäckvall and coworkers have studied the dynamic kinetic resolution of *rac*-**14** with ruthenium-catalysts (Scheme 56).[52] In this case, (*R*)-**15** was obtained in 80% with >99 %ee.

Scheme 56. Dynamic Kinetic Resolution of *Rac*-**14**



In the reaction, the ruthenium catalyst is used for racemization. During the reaction, the *S* enantiomer is racemized and the *R*/*S* ratio is reequilibrated (Scheme 57).

Scheme 57. Racemization of (*S*)-**14**



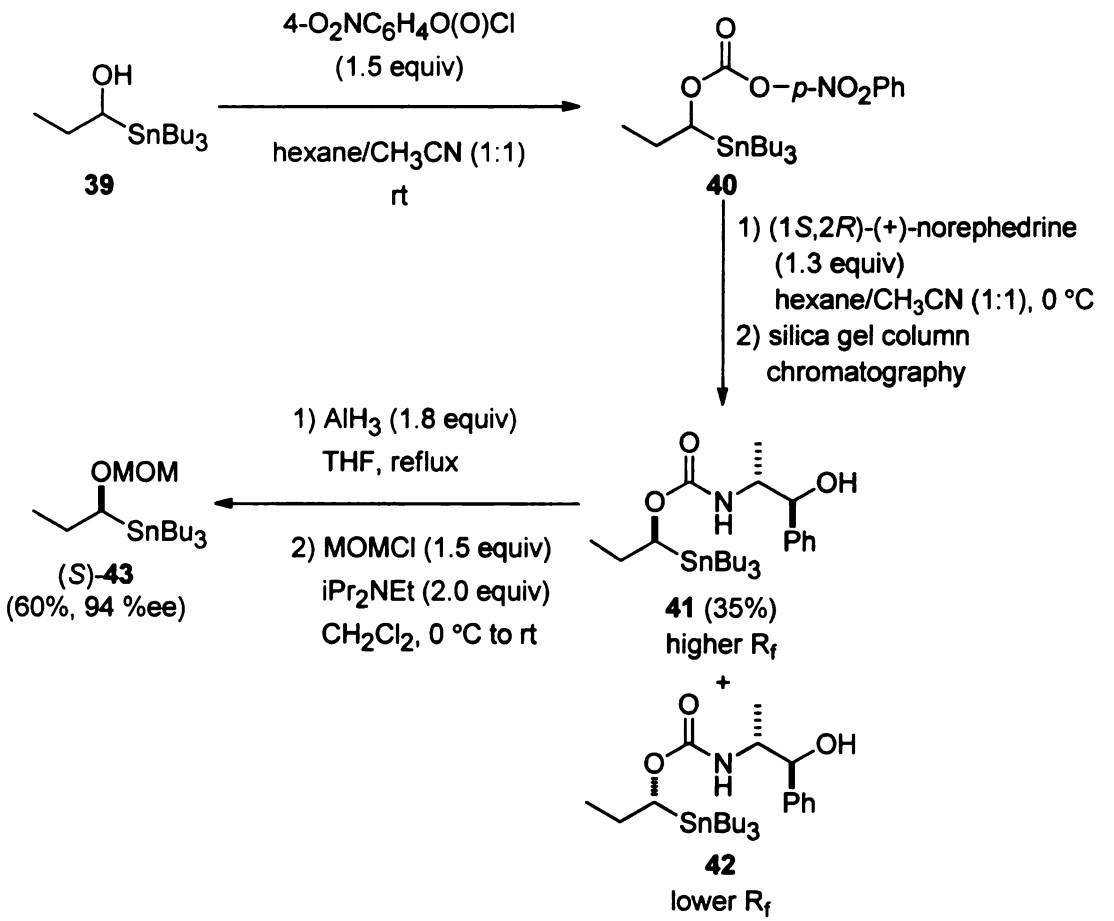
DKR is one of the methods to maximize the yield of the kinetic reaction. We already optimized the conditions for the enzymatic kinetic resolution α-hydroxysilanes. Applying ruthenium catalysts for racemization to our system would allow us to obtained higher throughput of a single enantiomer.

Chapter 6. Preparation of α-Hydroxysilanes by Kinetic Resolution with Phosphabicyclooctane (PBO)

6.1. Attempted Preparation of α-Hydroxysilane

We had investigated the scope and limitation of enzymatic kinetic resolution of α-hydroxysilanes in combination with different enzymes, solvents, temperatures and acylating reagents. However, the substrate scope was not as broad as we had hoped. Therefore we sought even more methods to prepare enantiomerically pure methylated α-hydroxysilanes.

Scheme 58. Resolution of α-Hydroxystannes via Norephedrine Carbamate



One of our trials was the resolution of *rac*-**24** via (1*S*,2*R*)-(+)-norephedrine carbamate. Kelly et al. reported the successful resolution of α-hydroxystannes via

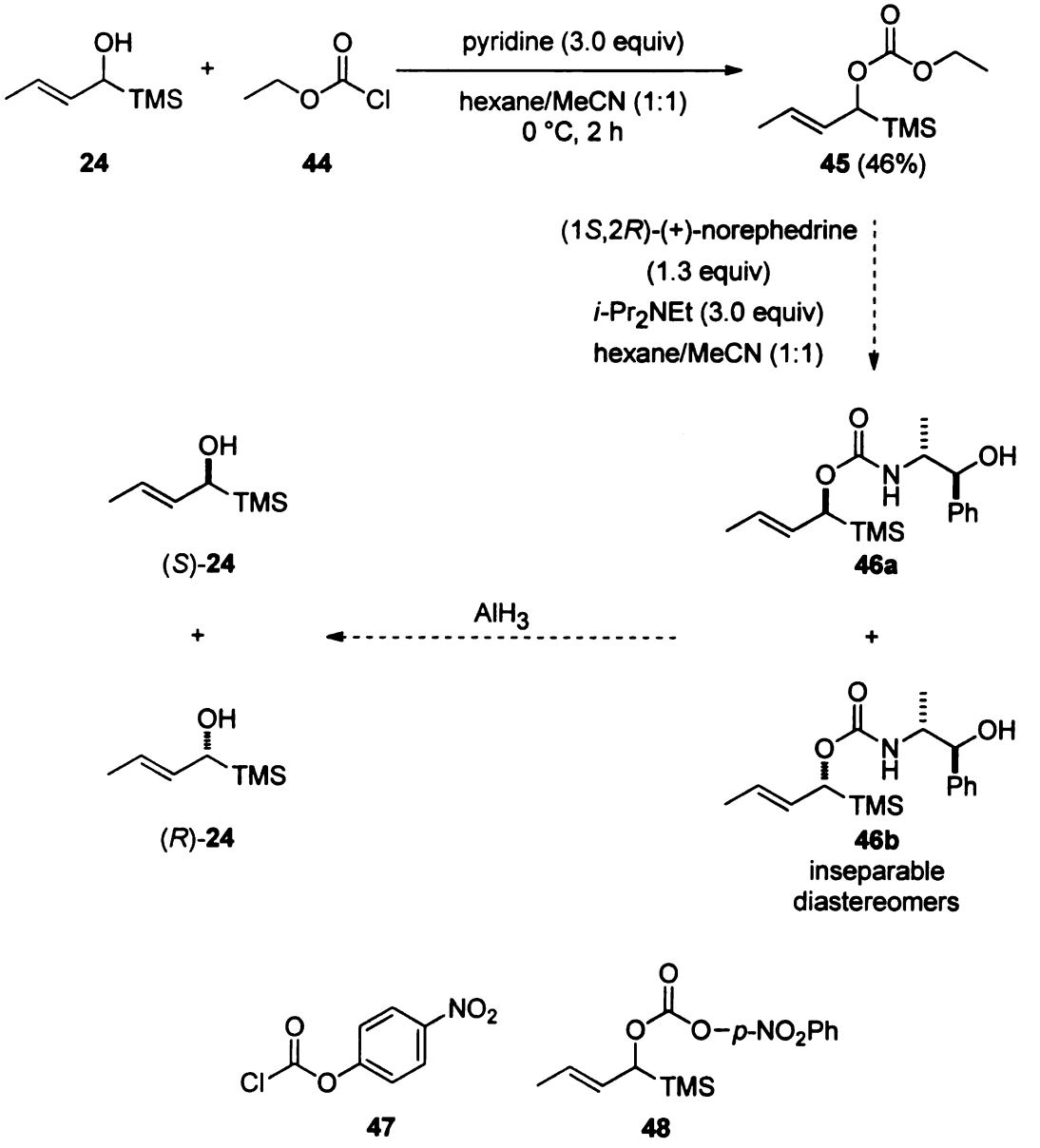
(1*S*,2*R*)-(+)-norephedrine carbamates in a two-phase acetonitrile-hexanes solvent system.[63] In this case, α-hydroxystannes (**39**) were converted into mixed carbonates with *p*-nitrophenyl chloroformate (Scheme 58). Treatment the carbonate (**40**) with (1*S*,2*R*)-(+)-norephedrine then afforded the carbamates (**41** and **42**). Diastereomers **41** and **42** were separable by silica gel column chromatography. Isolated **41** was converted back to optically pure MOM protected α-hydroxystanne by reduction with AlH_3 followed by protection of alcohol. The optically pure protected α-hydroxystannes (*S*)-**43** was obtained in 60% yield with 94 %ee.

We decided to apply this protocol to our methylated α-hydroxysilane (*rac*-**24**), which could not be resolved by enzymatic kinetic resolution with Novozym 435. The modified Kells' procedure was performed on *rac*-**24** (Scheme 59).[64] In doing so, we substituted ethyl chloroformate for *p*-nitrophenyl chloroformate. Thus, stirring a mixture of α-hydroxysilane **24**, ethylchloroformate, and pyridine in hexane/acetonitrile at 0 °C for 2 h, and then quenching with water, afforded the carbonate derivate **45** in 46 %yield. The first step of this reaction proceeded well. However, the subsequent step, which involves the replacement of the carbonate functionality with a carbamate, did not proceed and only **45** was recovered. The failure of the second step may be due to the poor leaving ability of the ethoxide group.

To try and overcome this problem *p*-nitrophenyl chloroformate (**47**) was employed in step one of the reaction, affording the mixed carbonate (**48**) as a dirty white solid after 45 minutes. A mixture of this crude carbonate **48**, (*1S*,*2R*)-

(+)-norephedrine, and diisopropyl amine, in hexane/acetonitrile (1:1 v/v) was stirred at room temperature for 24 h, followed by aqueous workup to give the corresponding carbamate as an inseparable mixture of diastereomers (**46a/46b**) by silica gel column chromatography. The difficulty in separation forced us to abandon this route.

Scheme 59. Attempted Resolution of α-Hydroxysilane by Kells' Protocol

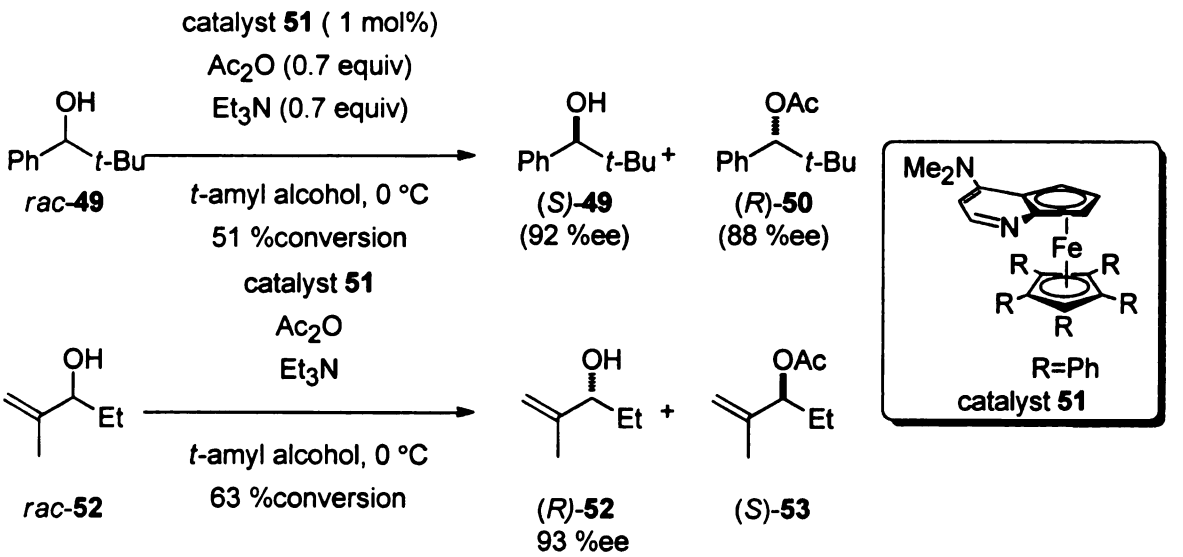


6.2. Non Enzymatic Kinetic Resolutions – Prior Art

We turned our attention to non-enzymatic catalytic kinetic resolutions. Several non-enzyme catalysts for kinetic resolution of secondary alcohols are documented in the literature.

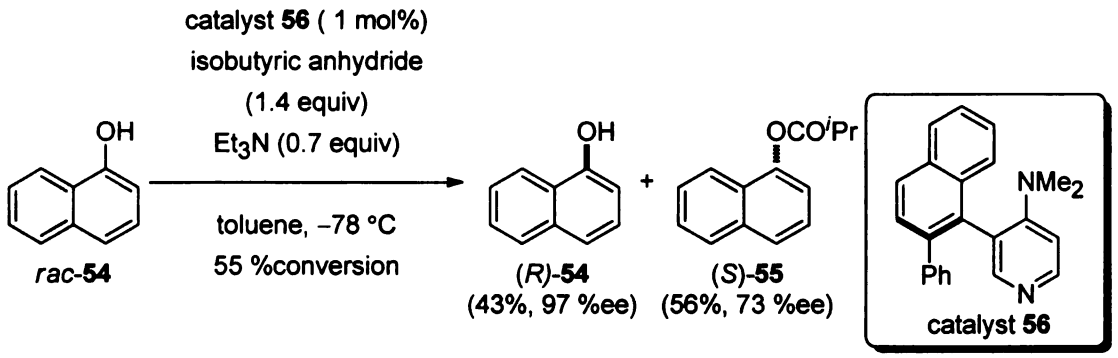
Fu and coworkers reported the kinetic resolution of secondary alcohols with a planar-chiral derivative of 4-(dimethylamino)pyridine (DMAP) **51** (Scheme 60). [65] 2,2-Dimethyl-1-phenylpropan-1-ol (*rac*-**49**) was resolved to unreacted alcohol (*R*)-**49** and acetylated product (*S*)-**50** with excellent enantiomeric excess. A similar protocol was applied to the resolution of a series of racemic allylic alcohols. After kinetic resolution of *rac*-**52**, the remaining (*R*)-**52** was obtained with good enantiomeric excess.

Scheme 60. Kinetic Resolution with Planar-Chiral DMAP Derivate **51**



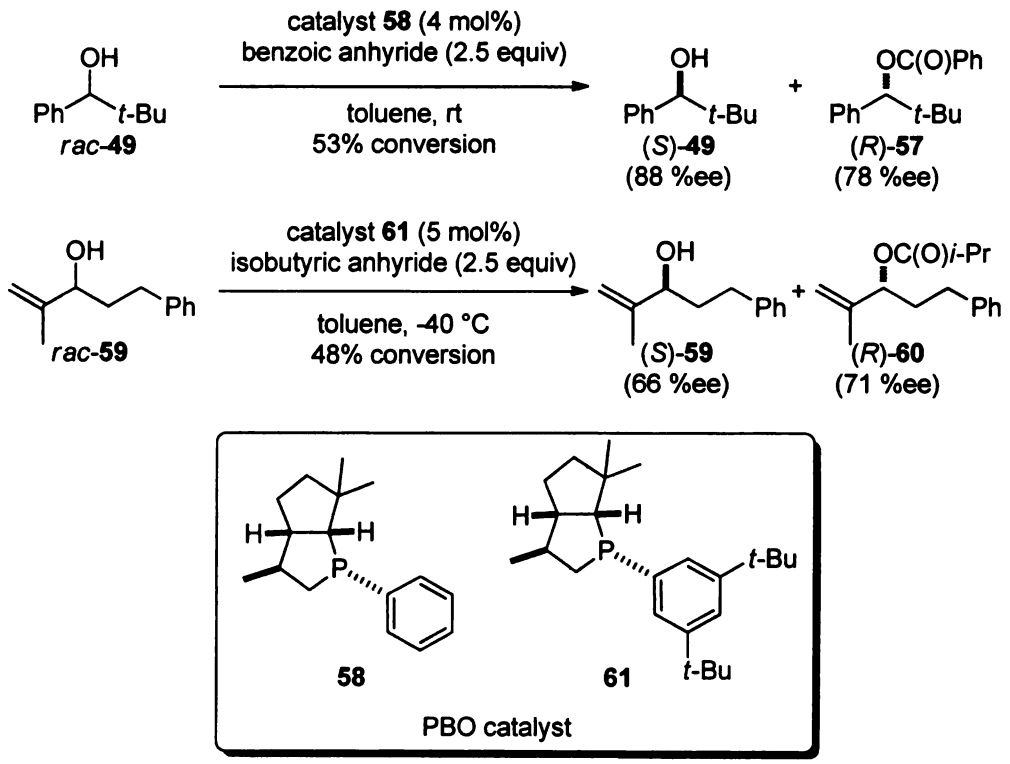
In 2000, Spey and coworkers reported on the development of catalyst **56** for the kinetic resolution of sterically hindered secondary alcohols (Scheme 61).[66] Treatment of 1-naphthol (*rac*-**54**) with **56** and isobutyric anhydride afforded (*R*)-**54** in 43% with 97 %ee as well as (*S*)-**55** in 56 % with 73 %ee.

Scheme 61. Kinetic Resolution with Catalyst **56**



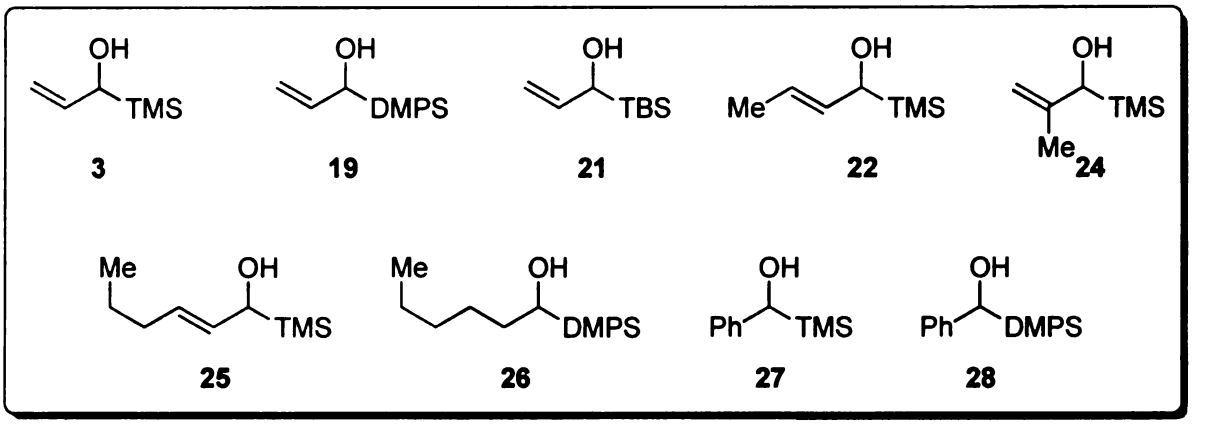
Phosphabicyclooctanes had also previously proven successful in the resolution of alcohols bearing a *t*-butyl group (**35**) and allylic alcohols (**36**) (Scheme 62).[67] In the both cases, unreacted alcohols and acetated products were obtained in reasonable enantiomeric excess.

Scheme 62. Kinetic Resolution with PBO Catalyst **58** and **61**



Given the structural similarities to our silyl substrates, we hypothesize that planar-chiral DMAP derivative or phosphabicyclooctanes could provide a novel route to optically active α-hydroxysilanes (Figure 16). We first chose to investigate the resolution of α-hydroxysilanes via phosphabicyclooctane (PBO) catalyst.

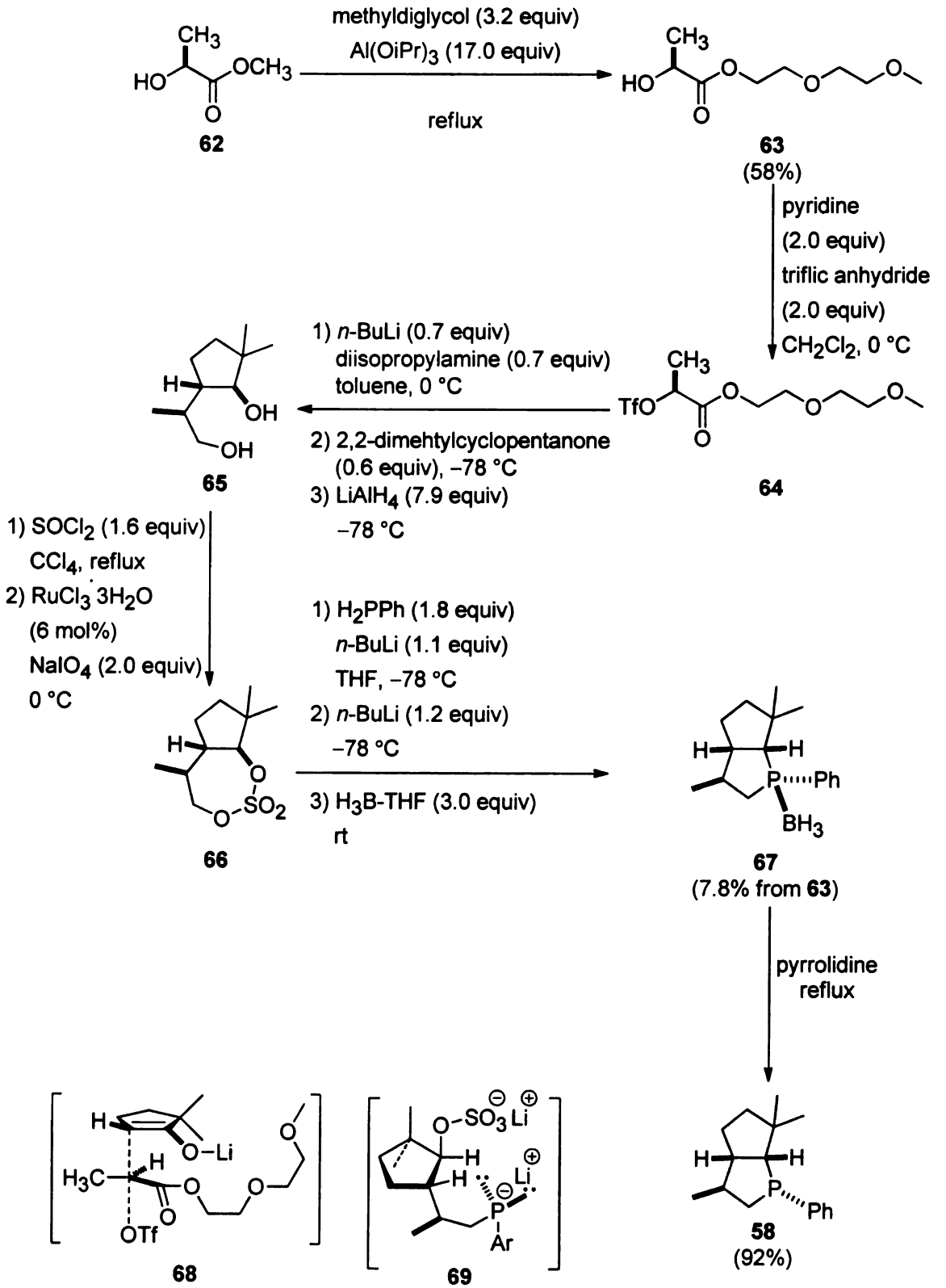
Figure 16. Our Substrates for Kinetic Resolution



6.3. Preparation of Phosphabicyclooctane Catalyst (58)[67]

We decided to prepare catalyst **58** by the following procedure (Scheme 63). The synthesis of catalyst **58** initiated with transesterification of **62** followed by triflation to give **64**. 2,2-Dimethylcyclopentane formed its enolate with LDA and the enolate reacted with triflate **64** in THF (transition state **68**). During the alkylation, the enolatelithium may be coordinated to the oxygens of **64**. To minimize steric effects, the hydrogen should occupy the place below the cyclopentane. After alkylation of **64**, the ester was converted to the corresponding alcohol by LAH. Cyclization of the 1,4-diol **65** followed by oxidation to the corresponding sulfate gave **66**.

Scheme 63. Preparation of Catalyst **58**

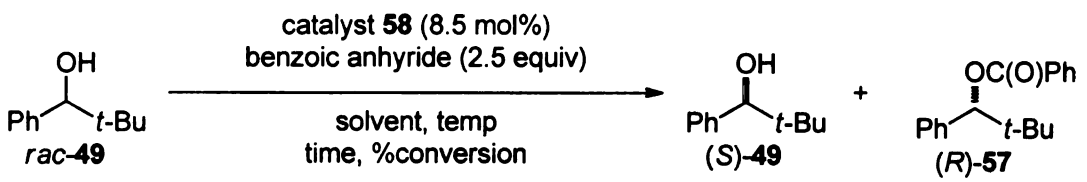


The next step is a double S_N2 reaction. The first S_N2 reaction happens at the less sterically hindered primary carbon on **66**. In second S_N2 reaction, the phenyl group should be away from the reaction center to give the *endo*-phenyl diastereomer (transition state **69**). BH_3 was installed for purification and determination of the diastereomeric ratio (**67**). The final product (**58**) was obtained by removal of the BH_3 group.

6.4. Kinetic Resolution of α-Hydroxysilanes by Phosphabicyclooctane Catalyst (58)

In our hands, catalyst **58** prepared in this manner contained a small amount (60:1) of the *P*-epimer after removal of the BH_3 group. Fortunately, recrystalization of **58** in CH_3CN at –20 °C afforded material that was diastereomerically pure by NMR.

Table 8. Test Reaction for Kinetic Resolution of *Rac*-**49**



Entry	**58** (mol%)	Solvent	Time (h)	Temp(°C)	Conv(%)	(*S*)-**49** (%ee)
1	8.5	heptane	1.6 (5)	r.t.	50 (53)	58 (87)
2	4.0	toluene	5.5 (12)	r.t.	47 (53)	55 (88)
3	4.0	toluene	19.5 (65)	–40	51 (45)	61 (78)
4	4.0	toluene	26	–30	59	85

[a]The number in parenthesis are reported by Vedejs and coworkers

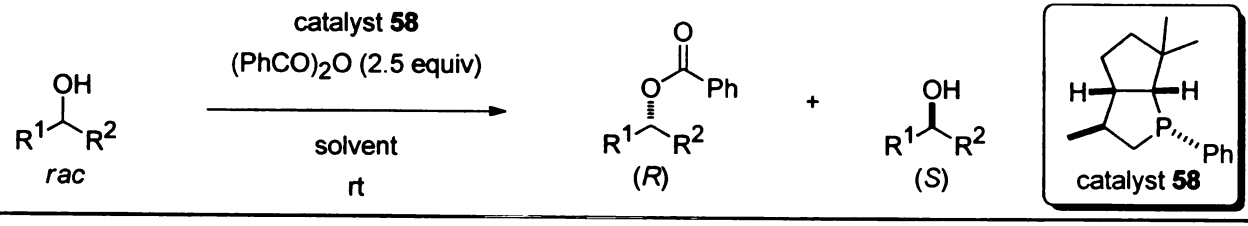
[b]The chiral HPLC analysis determined the %ee.

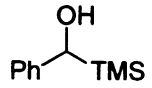
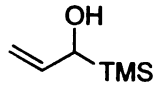
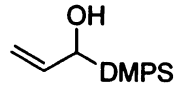
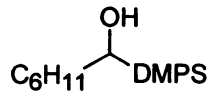
To test synthesized catalyst **58**, we ran the same reactions reported before by Vedejs. Applying this catalyst to the resolution of *rac*-**49** under previously reported conditions gave lower %ee's than expected (Table 8). We obtained (*S*)-**49** with 58 %ee at 50% conversion (Entry 1). In contrast, the literature reported that the kinetic resolution of *rac*-**49** afforded (*S*)-**57** with 87 %ee at 53% conversion (Entry 1 in parenthesis). Changing the conditions did not improve selectivity in the reaction (Entries 2 and 3).

At –40 °C, a white solid was observed during the reaction (Entry 3). We presume that at this temperature the benzoic anhydride did not completely dissolve in the toluene. So we increased the temperature to –30 °C and the kinetic resolution of the *rac*-**66** was tested. This modification improved the outcome of the reaction affording up to 85 %ee at 59% conversion (Entry 4). Notably, the reaction was slow especially past 50% conversion. Nonetheless, more than 50% conversion was necessary to get higher enantiomeric excesses of **49**.

Confident in the quality of the catalyst and our own protocol, we set out to screen the resolutions of a set of α-hydroxysilanes (Table 9). The distinction between a *t*-Bu and TMS group became immediately apparent (compare entry 2 in Table 8 to entry 1 in Table 9). While we were able to achieve the first resolution of an α-hydroxysilanes with catalyst **58**, after 47% conversion the unreacted **27** possessed an enantiomeric excess of only 46 %ee (Entry 1).

Table 9. Kinetic Resolution of α-Hydroxysilanes



Entry	Starting α-hydroxysilane	58 (mol%)	Solvent	Time	Con (%)	α-Hydroxysilane (%ee)
1	 **27**	6.0	toluene	10 min	47	46
2	 **3**	5.0	toluene	2 h	47	19 (*S*)
3	 **19**	5.0	toluene	1 h	54	5 (*S*)
4	 **70**	8.5	heptane	30 min	43	4

[a]The chiral GC and HPLC analysis determined the %ee.

The corresponding allylic alcohol behaved similarly affording *S*-**3** in 19 %ee after 47% conversion (Entry 2). Interestingly, the stereochemical preference was *opposite* to that observed during the resolution of *rac*-**3** with Novozym 435.

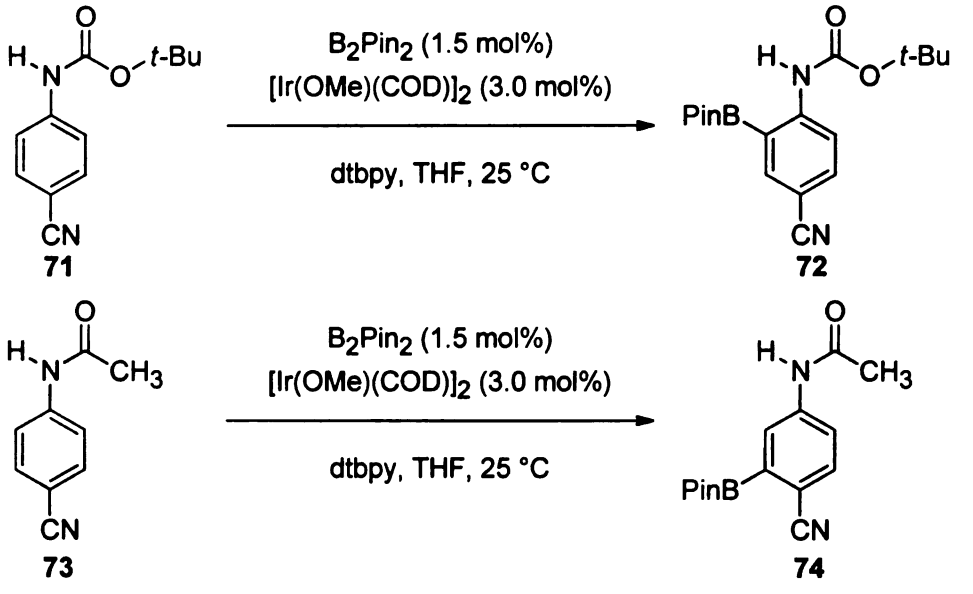
To examine a change in both steric bulk of the silyl and carbon substituent, as well as the hybridization of the carbon substituent, we examined *rac*-**19** and *rac*-**70** (Entries 3 and 4). Both of these substrates responded poorly providing the α-hydroxysilanes with 5 %ee and 4 %ee respectively.

While reaction optimization remains necessary, these results are significant in that they represent the first kinetic resolution of α-hydroxysilanes with phosphabicyclooctanes and in that the absolute stereochemical outcomes complement our enzymatic results.

Chapter 7. Designed and Synthesized a series of Novel *N*-Boc amines

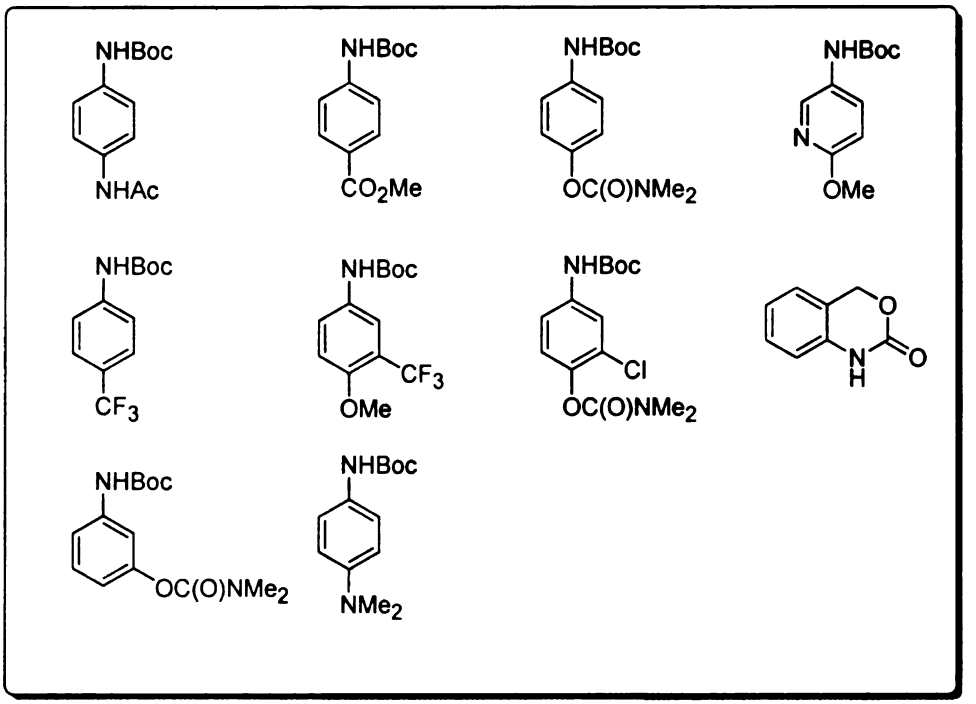
During my PhD studies on the generation of optically active α-hydroxysilanes, I also became involved in a short term side projects when these projects demanded additional and immediate attention. For example, during a study on the C-H activation/borylation of protected anilines, our group working in collaboration with Professor Mitch Smith (MSU) found that **71** borylated at the 2-position (Scheme 64).

Scheme 64. Regioselective Borylation of **71** and **73**



This was unexpected because Ir-catalyzed borylations are generally governed by sterics. For example, NHAc substrate (**73**) borylates at the 3-position under the same conditions.[68] In an attempt to understand the observed regioselectivity, I was called upon to rapidly synthesize of novel *N*-Boc anilines (Figure 17). My compounds are currently being used to complete this study.

Figure 17. Synthesized *N*-Boc Amines



Conclusion

We have studied on developing new method for the generation of optically active α-hydroxysilanes. The ring opening of epoxy alcohols bearing a TMS group with both aluminum and boron hydrides provided the unfavoured1,2-diol . This result shows that silicon plays an important role in determining the regioselectivity and that cyclic boronic esters are formed in the ring opening reaction. The scope and limitation of enzymatic kinetic resolution of α-hydroxysilanes in combination with different solvents, temperatures and acetylation reagents were investigated. The reactions are sensitive to the structures of both the silyl group and the organic side chain. In the non enzymatic kinetic resolution, the absolute stereochemical outcomes complement our enzymatic results.

Appendix. Experimental Details

Materials and Methods

Tetrahydrofuran was freshly distilled from sodium/benzophenone under nitrogen. Benzene and chlorotrimethylsilane were freshly distilled from calcium hydride under nitrogen. Benzene-d6, DMSO-d6, and chloroform-d were purchased from the Cambridge Isotope Labs and used without further purification. Deionized water was used unless otherwise noted. Enzymes were purchased from Aldrich or Novozym. (Amano PS: Lipase from Burkholderia cepacia), Novozym 435: Lipase B from Candida antarctica immobilized on acrylic resin, Amano AK: Lipase from Pseudomonas Fluorescens, Amano PS-D I: Lipase from Pseudomonas cepacia immobilized on diatomite, Amano PS-C II: Lipase from Pseudomonas cepacia immobilized on ceramic, CRL: Lipase from candida rugosa or candida cylindracea)

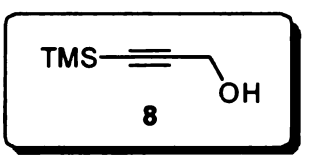
All other commercial reagents were used without purification unless otherwise noted. Flash chromatography was performed with silica gel 60 Å (230–400 mesh) purchased from Silicycle. TLC was performed on aluminum backed TLC plates by Silicycle. All other yields refer to chromatographically and spectroscopically pure compounds. Melting points were determined on a Thomas-Hoover Apparatus, uncorrected. Infrared spectra were recorded on a Nicolet IR/42 spectrometer. 1H, 11B, 13C, 29Si and 31P NMR spectra were recorded on 300 and 500 MHz spectrometer with chemical shifts reported relative to the residue peaks of solvent chloroform (δ 7.24 for 1H and δ 77.0 for 13C). The enantiomeric excess (*ee*) values were determined on an Agilent 1100

series HPLC using a Chiralcel OJ, OD or OD-H columns or on a Varian 3900 GC using a β-dex tm 325 column. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. High-resolution mass spectra (HRMS) were obtained on a Waters QTOF Ultima mass spectrometer at the Michigan State University Mass Spectrometry Facility by Luis Sanchez.

Standard Reaction Method

All reactions were carried out in oven-dried glassware, with magnetic stirring, and monitored by thin-layer chromatography with 0.25-mm precoated silica gel plates, unless otherwise noted. Visualization of reaction progress was achieved by UV lamp, phosphomolybdic acid stain or potassium permanganate stain.

Ring Opening Reaction

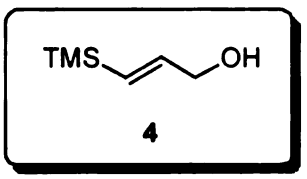


8

3-(Trimethylsilyl)-2-propyn-1-ol (8)[64]

A solution of Mg turnings (4.87 g, 0.2 mol) in THF (100 mL) was stirred while maintain the reaction temperature below 50 °C and bromoethane (14.9 mL, 0.2 mol) was added dropwise over 3 h. The reaction mixture was stirred for 1 h at 50 °C and cooled to 0 °C. A solution of propargyl alcohol (4.16 mL, 72 mmol) in THF (4.2 mL) was added dropwise over 2.25 h below 10 °C. The reaction was stirred overnight and cooled to 0 °C. TMSCl (25.4 mL, 200 mmol) was added dropwise by addition funnel while the reaction temperature below 25 °C. The reaction mixture was heated to reflux for 2 h, the suspension cooled to room temperature and aqueous H_2SO_4 (1.4 M, 80 mL) added over 0.75 h. The reaction mixture was stirred for 5 min and extracted with

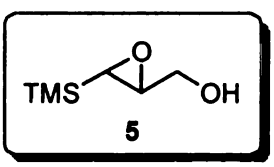
ether. Combined organic phases were washed with water and brine and dried over $MgSO_4$. After filtration and evaporation, the residue was purified by distillation to afford 8.0 g of **8** (80%).



4

(3*E*)-4-(Trimethylsilyl)-3-buten-1-ol (4)[64]

To a cold (0 °C), stirred solution of sodium bis(2-methoxyethoxy) aluminum hydride (7.35 mL, 37.6 mmol) in ether (20 mL) under nitrogen conditions was added a solution of **8** (3.4 mg, 26.8 mmol) in ether (9 mL) dropwise over 1.3 h. The reaction mixture was stirred for 10 min and the cold bath was removed. The reaction mixture was stirred for an additional 1 h at room temperature and then cooled back down to 0 °C. The reaction was quenched by addition of aqueous H_2SO_4 (3.4 M, 50 mL) and extracted with ether. Combined organic phases were washed with water and brined and dried over $MgSO_4$. After filtration and evaporation, the residue was purified by silica gel column chromatography using EtOAc/hexane (1:99) to afford 1.1 g of **4** (56%).

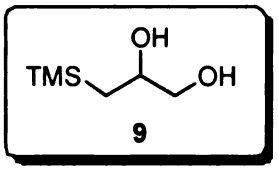


5

3-(Trimethylsilyl)-2-oxiranemethanol (5)

To a cold (0 °C), stirred solution of allyl alcohol **4** (8.7 g, 67 mmol) in CH_2Cl_2 (470 mL) under nitrogen conditions was added a solution of *m*-CPBA (23.1 g, 134 mmol) in CH_2Cl_2 (470 mL) via syringe and stirred at 0 °C. After the complete consumption of the starting allyl alcohol, the reaction mixture was filtered to remove precipitated *m*-chlorobenzoic acid. After evaporation, the residue was purified by silica gel column chromatography using hexane/EtOAc (9:1) to afford 5.6 g of **5** as a pale yellow oil (58%). ^1H NMR (300 MHz, $CDCl_3$) δ

3.94 (ddd, J = 12.4, 6.0, 2.2 Hz, 1 H), 3.57–3.47 (m, 1 H), 3.01–2.97 (m, 1 H), 2.23 (d, J = 3.6 Hz, 1 H), 0.03 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 64.2, 56.8, 48.9, –3.2. The spectroscopic data were consistent with the literature values.[69]



9

3-(Trimethylsilyl)-1,2-propanediol (9)

1) by Super-Hydride[70]

To a cold (0 °C), stirred solution of **13** (223 mg, 1.2 mmol) in THF (1.2 mL) was added sodium hydroxide (101 mg, 2.5 mmol) in water (1.0 mL). After stirring for 1 h at 0 °C and 2 h at 25 °C, the reaction mixture was diluted with water and extracted with ether. Combined organic phases were washed with brine and dried over $MgSO_4$. After filtration and evaporation, the residue was purified by silica gel column chromatography using EtOAc/hexane (7:3) to afford 150 mg of **9** (84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.89–3.82 (m, 1 H), 3.52 (d, J = 10.9 Hz, 1 H), 3.31 (m, 1 H), 0.78 (dd, J = 14.5, 8.1 Hz, 1 H), 0.68 (dd, J = 14.5, 6.1 Hz, 1 H), 0.04 (s, 9 H); ^{13}C NMR (125 MHz , $CDCl_3$) δ 71.1, 69.7, 22.3, –0.1; IR (neat) 3370 cm^{-1}The spectroscopic data were consistent with the literature values.[71]

2) by Red-Al[72]

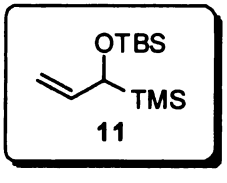
To a cold (0 °C), stirred solution of epoxyalcohol **5** (185 mg, 1.2 mmol) in dimethoxyethane (7 mL) under nitrogen conditions was added a Red-Al (0.38 mL of a 3.5 M solution in toluene, 1.3 mmol) dropwise. The reaction was allowed to warm to room temperature and stirred for 4.5 h. The reaction mixture was diluted with ether and quenched with addition of 5% HCl (3 mL). The phases were separated and the aqueous phase was extracted with ether. The combined

organics were washed with water and brine and then dried over $MgSO_4$. After filtration and evaporation, the product was purified by distillation to afford 120 mg of **9** (63 %).

3) by Dihydroxylation[73]

A mixture of *t*-Butyl alcohol (25 mL), water (25 mL) and AD-mix-alpha (7.0 g) was stirred at room temperature. The reaction mixture was cooled to 0 °C and some of the dissolved salts precipitated. Allyltrimethylsilane (0.79 mL, 5.0 mmol) was added at once and the heterogeneous slurry was stirred vigorously at 0 °C for 38 h. Solid sodium sulfite (7.5 g) was added at the same temperature. The reaction mixture was allowed to warm to room temperature and stirred for an additional 1 h. The reaction mixture was diluted with CH_2Cl_2. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. Combined organic layers were washed with brine and dried over $MgSO_4$. After filtration and evaporation, 224 mg of **9** were obtained (30%).

Synthesis of 1,3-Diol 6 (Scheme 31)

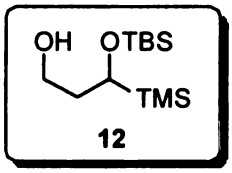


11

[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2-propen-1-yl]trimethylsilane (11)

To a solution of 1-hydroxyallyltrimethylsilane (391 mg, 3.0 mmol) in DMF (4.5 mL) was added TBSCl (0.6 mL, 3.7 mmol) and imidazole (1.0 mL, 7.5 mmol). The reaction mixture was stirred for 24 h before being quenched by addition of water (5 mL) and diluted with EtOAc. The phases were separated and the aqueous phase was extracted with EtOAc. Combined organic layers were washed with saturated aqueous $NaHCO_3$ and brine and dried over $MgSO_4$.

After filtration and evaporation, the residue was purified by silica gel column chromatography using hexane to afford **11** as a pale yellow but the columned material contained impurity. After second silica gel column chromatography, 574 mg of the impure **11** were obtained and in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (ddd, *J* = 17.0, 10.6, 5.3 Hz, 1 H), 5.00 (dt, *J* = 17.0, 2.1 Hz, 1 H), 4.92 (dt, *J* = 10.6, 2.0 Hz, 1 H), 3.97 (dt, *J* = 5.3, 1.9 Hz, 1 H), 0.93 (s, 9 H), 0.02 (d, *J* = 3.2 Hz, 6 H), 0.01 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.6, 109.6, 69.0, 25.8, 18.2, –4.0, –4.4, –5.1; IR (neat) 1270 cm^{-1}; HRMS (EI) (*m/z*) calcd for $C_{12}H_{28}BOSi_2$ $[M+CH_3CN+NH_4]^+$ 303.2288, found 303.2282.

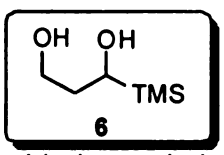


12

3-((tert-Butyldimethylsilyl)oxy)-3-(trimethylsilyl)propan-1-ol (12)[74]

To a cold (0 °C), stirred solution of **11** (245 mg, 1.0 mmol) in THF (4 mL) under nitrogen conditions was added BH_3 (4.0 mL of a 1.0 M solution in THF, 4.0 mmol) dropwise. After stirring for 3 h, aqueous NaOH (4 mL of a 2 N solution) was added dropwise to maintain gentle H_2 evolution. 30 % H_2O_2 (4 mL) was then added and the mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with H_2O and extracted with $CHCl_3$. Combined organic phases were washed with brine and dried over $MgSO_4$. After filtration and evaporation, the residue was purified by silica gel column chromatography using EtOAc/hexane (1:4) to afford 0.119 g of **12** as a colorless oil (45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.85-3.61 (m, 2 H), 3.65 (dd, *J* = 5.8, 4.9 Hz, 1 H), 2.02–1.90 (m, 1 H), 1.77–1.66 (m, 1 H), 0.87 (s, 9 H), 0.08 (s, 3 H), 0.03 (s, 9 H),

0.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 66.3, 62.4, 36.7, 26.6, 18.7, –2.1, –3.7, –4.0; IR (neat) 3340 cm^{-1}; HRMS (EI) (*m/z*) calcd for $C_{12}H_{30}O2Si_2$ $[M+H]^+$ 263.1863, found 263.1859.

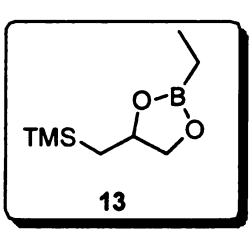


6

1-(Trimethylsilyl)-1,3-propanediol (6)

To a solution of **12** (118 mg, 0.45 mmol) in CH_3CN (1 mL) was added a solution of 5 % aqueous HF (0.1 mL) in CH_3CN (0.5 mL) at room temperature. The reaction mixture was stirred for 40 min and then quenched by the addition of saturated aqueous $NaHCO_3$. The reaction was diluted with ether. The phases were separated and the aqueous phase was extracted with ether. Combined organic phases were washed with brine and dried over $MgSO_4$. After filtration and evaporation, the residue was purified by silica gel column chromatography using hexane/ethyl acetate (1:4) to afford 55 mg of **6** (82%) as a colorless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 3.94–3.72 (m, 2 H), 3.58 (dd, *J* = 11.2, 2.5 Hz, 1 H), 1.82–1.76 (m, 1 H), 1.70–1.60 (m, 1 H), 0.02 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 66.0, 63.4, 35.0, –3.4; IR (neat) 3322 cm^{-1}; HRMS (EI) (*m/z*) calcd for $C_6H_{16}O_2Si$ $[M+H]^+$ 149.1003, found 149.0998.

Ring Opening of 5 with Red-Al (Scheme 33)



13

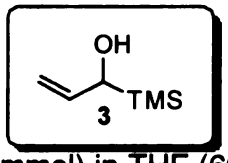
((2-Ethyl-1,3,2-dioxaborolan-4-yl)methyl)trimethylsilane (13)[75]

To a solution of **5** (2.2 g, 15.6 mmol) in THF (1 mL) under nitrogen conditions was added Super-Hydride (1.5 mL of 1.0 M solution in THF, 31.3 mmol) dropwise via syringe pump (1.4 mL/hr). The reaction mixture was stirred for 2.5 h at room temperature before being quenched by addition of water

(10 mL). The reaction was extracted twice with ether. The combined organics were washed with saturated aqueous $NaHCO_3$ and brine and then dried over $MgSO_4$. After filtration and evaporation, the residue was purified by fractional distillation (20 mmHg, 38 °C) to afford 2.253 g of **13** (77%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 4.56–4.44 (m, 1 H), 4.20 (dd, *J* = 8.7, 7.6 Hz, 1 H), 3.62 (dd, *J* = 8.7, 7.5 Hz, 1 H), 1.07 (dd, *J* = 14.2, 6.8 Hz, 1 H), 0.92 (t, *J* = 7.8 Hz, 3 H), 0.86 (dd, *J* = 14.2, 7.7 Hz, 1 H), 0.75 (q, *J* = 7.7 Hz, 2 H), 0.02 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 75.3, 73.0, 25.4, 7.7, 0.1; ^{11}B NMR (160 MHz, CDCl3) δ 43.5. IR (neat) 1340 cm^{-1}; HRMS (EI) (*m/z*) calcd for $C_8H_{19}BO_2Si$ $[M+H]^+$ 187.1326, found 187.1322.

Kinetic Resolution of α-Hydroxysilanes with Novozym 435

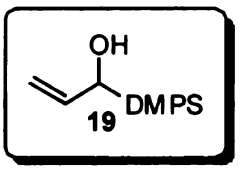
Preparation of α-Hydroxysilanes



1-Hydroxyallyltrimethylsilane (3)[6]

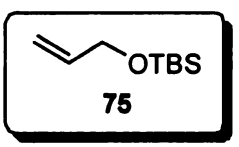
To a cold (–78 °C), stirred solution of allyl alcohol (5.4 mL, 80.0 mmol) in THF (60 mL) under nitrogen conditions was added *n*-BuLi (52.8 mL of a 1.6 M solution in hexane, 84.0 mmol) dropwise via a syringe. Upon complete addition of base, the reaction mixture was stirred for 1 h. Next, TMSCl (10.1 mL, 80.0 mmol) was added dropwise via a syringe. Following this addition, the reaction mixture was stirred for 1.5 h and then *t*-BuLi (56.8 mL of a 1.7 M solution in hexane, 97.0 mmol) was added dropwise via a syringe. After stirring for an additional 1.5 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl and then diluted with ether. The phases were separated and the aqueous phase was extracted with ether. The combined organics were washed with brine

and dried over anhydrous Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography using Et_2O/hexane (1:9) to afford 6.4 g of **3** as a colorless oil (61%). ^1H NMR (500 MHz, $CDCl_3$) δ 6.00 (ddd, J = 17.2, 10.7, 5.3 Hz, 1 H), 5.04 (ddd, J = 17.2, 2.1, 1.6 Hz, 1 H), 4.96 (ddd, J = 10.7, 1.9, 1.6 Hz, 1H), 3.99–3.97 (m, 1 H), 1.35 (br s, 1H), 0.03 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.9, 109.4, 69.0, –4.3. The spectroscopic data were consistent with the literature values.[6]



1-(Dimethylphenylsilyl)-2-propen-1-ol (19)

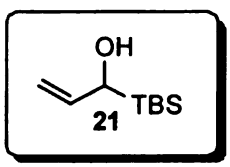
The reaction was carried out on allyl alcohol (2.7 mL, 40.0 mmol) as described in the preparation of **3** except that chlorodimethylphenylsilane (7.0 mL, 42.0 mmol) was used as the silylating agent and that following its addition, the reaction mixture was stirred for 1.25 h and that after the *t*-BuLi addition, it was stirred for an additional 2.0 h. This modified protocol afforded 3.2 g of **19** as a pale yellow oil (42%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.5–7.54 (m, 2 H), 7.39–7.33 (m, 3 H), 5.98 (ddd, J = 17.2, 10.7, 5.3 Hz, 1 H), 5.07–5.03 (m, 1 H), 5.00–4.97 (m, 1 H), 4.21 (ddd, J = 5.3, 2.1, 2.1 Hz, 1 H), 1.28 (br s, 1 H), 0.34 (s, 1 H), 0.32 (s, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3, 136.0, 134.2, 129.5, 127.8, 110.0, 68.4, –5.8, –6.1; IR (neat) 3420 cm^{-1}; HRMS (EI) (*m/z*) calcd for $C_{11}H_{16}OSi$ $[M]^+$ 192.0970, found 192.0963. The spectroscopic data were consistent with the literature values.[56]



(1,1-Dimethylethyl)dimethyl(2-propen-1-yloxy)-silane

A mixture of allyl alcohol (4.0 mL, 60 mmol), TBSCl (10.8 g, 72.0 mmol) and imidazole (6.1 g, 90.0 mmol) in DMF (20 mL) under nitrogen

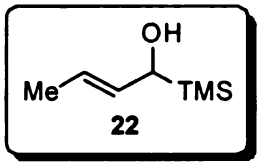
conditions was stirred for 1 h at room temperature. The reaction mixture was extracted with ether. Combined organic phases were washed with water and brine and dried over $MgSO_4$. The residue was purified over silica gel column chromatography using Et_2O/hexane (1:25) to afford 8.5 g of the desired product as a colorless oil (83%). ^1H NMR (500 MHz, $CDCl_3$) δ 5.93 (ddt, *J* = 17.1, 10.4, 4.6, 1 H), 5.25 (dddd, *J* = 17.1, 1.9, 1.9, 1.9 Hz, 1 H), 5.06 (ddd, *J* = 10.5, 1.8, 1.8 Hz, 1 H), 4.16 (dt, *J* = 4.5, 1.8 Hz, 2 H), 0.09 (s, 9 H), 0.06 (s, 6 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5, 113.9, 64.1, 25.9, 18.4, -5.2. The spectroscopic data were consistent with the literature values.[76]



1-[(1,1-Dimethylethyl)dimethylsilyl]-2-propen-1-ol (21)[77]

To a cold (–78 °C), stirred solution of (1,1-dimethylethyl)dimethyl(2-propen-1-yloxy)silane (8.3 g, 48.6 mmol) in THF (200 mL) under nitrogen condition were added tetramethylethylenediamine (13.1 mL, 88.0 mmol) and then *sec*-BuLi (59.7 mL, 1.4 M in cyclohexane, 84.0 mmol) dropwise. The reaction mixture was warmed up to –40 °C and then stirred for 3.5 h. It was recooled to –78 °C and the reaction was quenched by the addition of AcOH (17.9 mL, 314.0 mmol) in THF (53 mL). The reaction mixture was warmed to room temperature and extracted with ether. Combined organic phases were washed with water and brine and dried over $MgSO_4$. The residue was purified over silica gel column chromatography using EtOAc/hexane (1:30) to afford 0.7 g of **21** as a colorless oil (9%). ^1H NMR (500 MHz, CDCl3) δ 6.05 (ddd, *J* = 17.2, 10.7, 5.3 Hz, 1 H), 5.06 (ddd, *J* = 17.2, 2.1, 1.6 Hz, 1 H), 4.97 (ddd, *J* = 10.7, 3.5, 1.6 Hz, 1 H), 4.16 (ddd, *J* = 5.3, 2.1, 2.1 Hz,

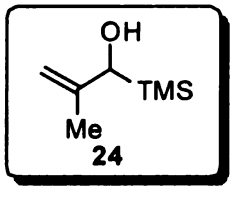
1 H), 0.94 (s, 9 H), 0.11 (s, 3 H), –0.06 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7, 109.4, 67.6, 26.0, 17.0, –7.6, –9.2. The spectroscopic data were consistent with the literature values.[78]



22

(2*E*)-1-(Trimethylsilyl)-2-buten-1-ol (22)

The reaction was carried out as described for the preparation of **3** except that (2*E*)-2-buten-1-ol (5.7 mL, 67.5 mmol) served as the alcohol and reaction times following the addition of TMSCl and *t*-BuLi addition were 2.5 h and 2.0 h, respectively. This modified protocol afforded 5.3 g of **22** as a pale yellow oil (54%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.61–5.42 (m, 2 H), 3.86 (doublet of pentets, J = 6.8, 1.4 Hz, 1 H), 1.68 (dt, J = 6.3, 1.4 Hz, 3 H), 1.27 (br s, 1 H), 0.01 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.4, 122.2, 68.4, 17.8, –4.2; IR (neat) 3416 cm^{-1}; HRMS (EI) (*m/z*) calcd for $C_7H_{16}OSi$ $[M]^+$ 144.0970, found 144.0970. The spectroscopic data were consistent with the literature values.[79]

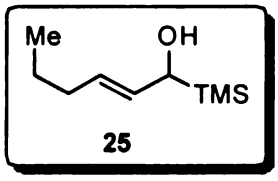


24

2-Methyl-1-(trimethylsilyl)-2-propen-1-ol (24)

The reaction was carried out as described for the preparation of **3** except that 2-methyl-2-propen-1-ol (6.6 mL, 79.0 mmol) served as the alcohol and that following the addition of TMSCl the reaction stirred for 1.0 h, before *t*-BuLi (55.6 mL 1.7 M in hexane, 95.0 mmol) was added dropwise via syringe. After stirring for an additional 3 h at –33 °C, the cold bath was removed and a solution of acetic acid (5.4 mL, 95.0 mmol) in THF (5 mL) was added. After the reaction mixture was stirred for 30 min, saturated aqueous $NaHCO_3$ (60 mL) and pentane (100 mL) were added. Workup and

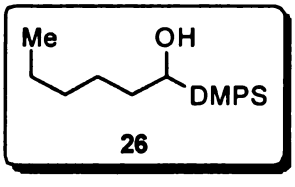
chromatography as previously described afforded 9.1 g of **24** as a colorless oil (81%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.77 (oct, *J* = 0.8 Hz, 1 H), 4.74 (dq, *J* = 3.0, 1.5 Hz, 1 H), 3.86 (s, 1 H), 1.69 (t, *J* = 0.7 Hz, 3 H), 1.29 (br d, *J* = 2.60, 1 H), 0.06 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 106.3, 71.6, 20.7, –3.4. The spectral data were consistent with literature values.[80]



25

(2*E*)-1-(Trimethylsily)-2-hexene-1-ol (25)

The reaction was carried out as described for the preparation of **3** except that (2*E*)-2-hexen-1-ol (2.3 mL, 20.0 mmol) served as the alcohol, *sec*-BuLi (17.1 mL 1.4 M in cyclohexane, 24.0 mmol) was used in place of *t*-BuLi, and reaction times following the addition of TMSCl and *s*-BuLi addition were 2.5 h and 2.0 h respectively. This modified protocol afforded 1.9 g of **25** as a pale yellow oil (57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.57 (dddd, *J* = 1.3, 1.3, 6.6, 15.4 Hz, 1 H), 5.47 (dddd, *J* = 1.5, 6.8, 6.8, 15.1 Hz, 1 H), 3.89–3.87 (m, 1 H), 2.02–1.97 (m, 2 H), 1.37 (sext, *J* = 7.3 Hz, 2 H), 1.27 (br s, 1 H), 0.87 (t, *J* = 7.4 Hz, 3 H), 0.01 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 131.4, 127.5, 68.4, 34.6, 22.8, 13.6, –4.2. The spectral data were consistent with literature values.[81]

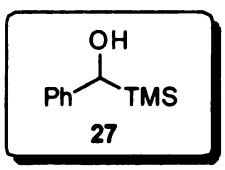


26

1-(Dimethylphenylsilyl)-1-hexanol (26)

Chlorodimethylphenylsilane (9.7 mL, 57.9 mmol) was added to a rapidly stirring mixture of lithium wire (0.9 g, 135.0 mmol (fine cut)) in THF (60 mL) at room temperature. The reaction mixture was stirred for 31 h at room temperature, giving a deep red solution of $PhMe_2SiLi$. This $PhMe_2SiLi$ solution was then added dropwise via cannula to a cold (–78 °C)

stirred solution of hexanal (0.7 mL, 5.8 mmol) in THF (6 mL). The reaction mixture was stirred for 30 min at the same temperature before being quenched by addition of saturated aqueous NH_4Cl solution. The reaction was extracted twice with ether. The combined organics were washed with water and brine and then dried over $MgSO_4$. After filtration and evaporation, the residue was purified over silica gel column chromatography using Et_2O/hexane (1:9) to afford 0.6 g of **26** as a pale yellow oil (44%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.55–7.53 (m, 2 H), 7.37–7.34 (m, 3 H), 3.50–3.47 (m, 1 H), 1.55–1.47 (m, 3 H), 1.30–1.18 (m, 6 H), 0.85 (t, J = 7.04 Hz, 3 H), 0.32 (s, 3 H), 0.31 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.8, 134.1, 129.2, 127.9, 65.5, 33.4, 31.7, 26.5, 22.6, 14.0, –5.3, –5.7. The spectral data were consistent with literature values.[82]

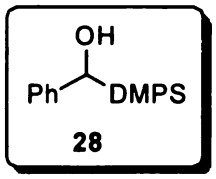


27

α-(Trimethylsilyl)-benzenemethanol (27)[7]

DMSO (0.7 mL, 11.0 mmol) was added dropwise by syringe to a stirred a cold (–78 °C) solution of oxalyl chloride (0.8 mL, 10.5 mmol) in anhydrous ether under nitrogen. The reaction mixture was warmed to –35 °C and then stirred for 1 h. The reaction mixture was then cooled back down to –78 °C and (trimethylsilyl)methanol (1.2 mL, 10.0 mmol) was added dropwise. The reaction mixture was warmed to –35 °C and stirred for 2 h. The reaction mixture was again cooled to –78 °C and triethylamine (6.9 mL, 50.0 mmol (freshly distilled over CaH_2)) was added dropwise. The reaction mixture was stirred for 2 h at the same temperature and then warmed to 0 °C and stirred for 4 h. The reaction mixture was recooled to –78 °C and bromophenylmagnesium (9.0 mL, 50.0 mmol) was added dropwise. After the reaction mixture was stirred

for 2 h at –78 °C, water (20 mL) and ether (90 mL) were added and the mixture was allowed to warm to room temperature. The phases were separated and the aqueous phase extracted with ether. Combined organics were washed with brine and dried over anhydrous $MgSO_4$. After filtration and evaporation, the residue was purified over silica gel column chromatography using Et_2O/hexane (1:9) to afford 0.8 g of **27** as a colorless oil (47%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.30–7.26 (m, 2 H), 7.18–7.13 (m, 3 H), 4.51 (s, 1 H), 1.65 (br s, 1 H), 0.00 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2, 128.1, 125.8, 124.9, 70.6, –4.2. The spectral data were consistent with literature values.[83]

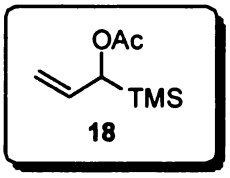


28

α-(Dimethylphenylsilyl)-benzenemethanol (28)

The reaction was carried out as described for the preparation of **26** except that that $PhMe_2SiLi$ was formed over 36 h and benzaldehyde (0.4 mL, 4.3 mmol) served as the aldehyde. This modified protocol afforded 0.4 g of **28** as a colorless oil (40%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.47–7.45 (m, 2 H), 7.39–7.31 (m, 3 H), 7.25–7.21 (m, 2 H), 7.16–7.12 (m, 1 H), 7.08–7.05 (m, 2 H), 4.69 (s, 1 H), 1.64 (br s, 1 H), 0.28 (s, 3 H), 0.25 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 135.9, 134.3, 129.4, 128.0, 127.8, 125.9, 125.1, 70.0, –5.4, –6.3. The spectral data were consistent with literature values.[81]

Acylation of α-Hydroxysilanes

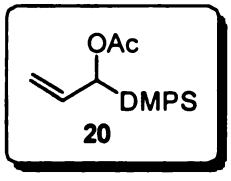


18

Acetic acid 1-(trimethylsilyl)-allyl ester (18)

To a solution of 1-hydroxyallyltrimethylsilane (0.6 g, 4.81 mmol) and pyridine (0.3 mL, 4.8 mmol) was added acetic anhydride (0.4 mL, 4.8 mmol). The reaction mixture was stirred at room temperature

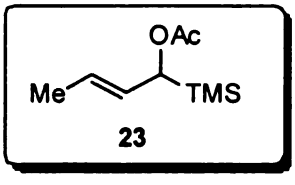
overnight. The reaction mixture was diluted with Et_2O, and then sequentially extracted with 1M HCl, saturated aqueous $NaHCO_3$ and brine. The ethereal layer was dried over $MgSO_4$, filtered, and evaporated to afford 0.5 g **18** as a pale yellow oil (67%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (ddd, J = 17.0, 10.9, 5.8 Hz, 1 H), 5.17 (ddd, J = 5.8, 1.8, 1.8 Hz, 1 H), 4.98 (ddd, J = 9.3, 1.7, 1.7 Hz, 1 H), 4.96 (m, 1 H), 2.07 (s, 3 H), 0.07 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 134.9, 111.3, 70.6, 20.9, –4.0; IR 1734 (s) cm^{-1}; HRMS (EI) (*m/z*) calcd for $C_8H_{16}O_2Si$ $[M]^+$ 172.0920, found 172.0923. The spectral data were consistent with literature values.[84]



20

Acetic acid 1-(dimethylphenylsilyl)-prop-2-enyl ester (20)

Applying the acylation procedure described in preparation of **18** to 1-(dimethylphenylsilyl)-2-propen-1-ol (0.4 g, 2.6 mmol) afforded 0.5 g of **20** as a pale yellow oil (85%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53–7.50 (m, 2 H), 7.40–7.33 (m, 3 H), 5.82–5.75 (m, 1 H), 5.39 (ddd, J = 5.7, 1.9, 1.9 Hz, 1 H), 4.98 (ddd, J = 4.6, 1.6, 1.6 Hz, 1 H), 4.95–4.94 (m, 1 H), 2.04 (s, 3 H), 0.34 (d, J = 0.8 Hz 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 135.5, 134.9, 134.3, 129.8, 128.1, 112.1, 70.2, 21.2, –5.3, –5.4; IR (neat) 1740 cm^{-1}; HRMS (EI) (*m/z*) calcd for $C_{13}H_{18}O_2Si$ $[M]^+$ 234.1076, found 234.1078. The spectral data were consistent with literature values.[34]

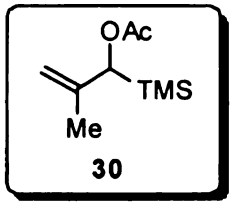


23

Acetic acid 1-(trimethylsilyl)-but-2(*E*)-enyl ester (23)

Applying the acylation procedure described in preparation of **18** to (2*E*)-1-(trimethylsilyl)-2-buten-1-ol (0.7 g, 5.0 mmol) 0.5 g of **23** as a colorless oil (61%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.49–

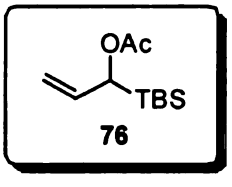
5.39 (m, 2 H), 5.09–5.06 (m, 1 H), 2.02 (s, 3 H), 1.65 (dd, J = 4.8, 1.1 Hz, 3 H), 0.00 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 127.5, 124.5, 70.3, 21.0, 17.8, –3.9; IR (neat) 1742 cm^{-1}; HRMS (EI) (*m/z*) calcd for $C_9H_{18}O_2Si$ $[M]^+$ 186.1076, found 186.1079. The spectral data were consistent with literature values.[80]



30

Acetic acid 2-methyl-1-(trimethylsilyl)-allyl ester (30)

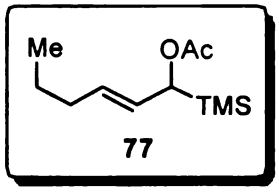
Applying the acylation procedure described in preparation of **18** to 2-methyl-1-(trimethylsilyl)-2-propen-1-ol (0.1 g, 0.7 mmol) afforded 0.07 g of **30** as a pale yellow oil (55%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01 (s, 1 H), 4.72–4.71 (m, 1 H), 4.69–4.67 (m, 1 H), 2.06 (s, 3 H), 1.71–1.69 (m, 3 H), 0.06 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 143.3, 107.9, 72.7, 21.0, 20.7, –3.3; IR (neat) 1770 cm^{-1}; HRMS (EI) (*m/z*) calcd for $C_9H_{18}O_2Si$ $[M]^+$ 186.1076, found 186.1078. The spectral data were consistent with literature values.[85]



76

Acetic acid 1-(t-butyldimethylsilyl)-prop-2-enyl ester

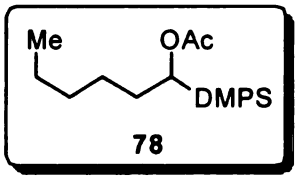
Applying the acylation procedure described in preparation of **18** to 1-[(1,1-dimethylethyl)dimethylsilyl]-2-propen-1-ol (100 mg, 0.5 mmol) afforded 78 mg of the desired product as a pale yellow oil (63%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 (ddd, J = 16.8, 11.0, 5.6 Hz, 1 H), 5.37 (td, J = 5.6, 1.9 Hz, 1 H), 4.97 (td, J = 7.3, 1.6 Hz, 1 H), 4.94 (d, J = 1.8 Hz, 1 H), 2.07 (s, 3 H), 0.90 (s, 9 H), 0.00 (s, 3 H), –0.02 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 135.6, 111.1, 68.7, 26.8, 21.1, 16.9, –7.5, –8.6; IR (neat) 1760 cm^{-1}; HRMS (EI) (*m/z*) calcd for $C_{11}H_{22}O_2Si$ $[M]^+$ 214.1389, found 214.1389.



77

Acetic acid 1-(trimethylsilyl)-hex-2(*E*)-enyl ester

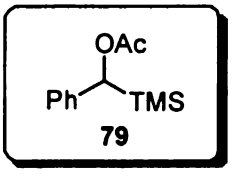
Applying the acylation procedure described in preparation of **18** to (2*E*)-1-(trimethylsilyl)-2-hexene-1-ol (517 mg, 3.0 mmol) afforded 573 mg of the desired product as a pale yellow oil (89%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.45 (m, 2 H), 5.10 (dd, *J* = 4.8, 1.7 Hz, 1 H), 2.02 (s, 3 H), 1.97 (m, 2 H), 1.35 (dt, *J* = 14.7, 7.5 Hz, 2 H), 0.85 (t, *J* = 7.4 Hz, 3 H), 0.00 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 129.7, 126.5, 70.3, 34.5, 22.5, 21.1, 13.5, –3.9; IR (neat) 1740 (s) cm^{-1}; HRMS (EI) (*m/z*) calcd for $C_{11}H_{22}O_2Si$ $[M]^+$ 214.1389, found 214.1389.



78

1-Acetate-1-(dimethylphenylsilyl)-1-hexanol

Applying the acylation procedure described in preparation of **18** to 1-(dimethylphenylsilyl)-1-hexanol (70 mg, 0.29 mmol) afforded 57 mg of the desired product as a colorless oil (69%).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51–7.49 (m, 2 H), 7.36–7.32 (m, 3 H), 4.94 (dd, *J* = 10.8, 3.7 Hz, 1 H), 1.98 (s, 3 H), 1.61–1.12 (m, 8 H), 0.83–0.79 (m, 3 H), 0.30 (d, *J* = 5.8 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 136.1, 134.0, 129.3, 127.7, 68.4, 31.4, 30.9, 26.6, 22.4, 20.9, 13.9, –4.9, –5.2. The spectral data were consistent with literature values.[16]

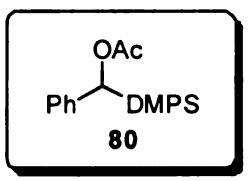


79

1-Acetatae-α-(trimethylsilyl)-benzenemethanol

Applying the acylation procedure described in preparation of **18** to α-(trimethylsilyl)-benzenemethanol (270 mg, 1.5 mmol) afforded 309 mg of the desired product as a pale yellow oil (93%). ^{1}H NMR

(500 MHz, $CDCl_3$) δ 7.30 (m, 2 H), 7.18 (m, 3 H), 5.71 (s, 1 H), 2.15 (s, 3 H), 0.04 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 140.1, 128.1, 126.0, 125.2, 71.6, 21.1, –3.9; IR (neat) 1746 (s) cm^{-1}; HRMS (EI) (*m/z*) calcd for $C_{12}H_{18}O_2Si$ $[M]^+$ 222.1076, found 222.1076.



80

1-Acetate- α-(dimethylphenylsilyl)-benzenemethanol

Applying the acylation procedure described in preparation of **18** to α-(dimethylphenylsilyl)-benzenemethanol (93 mg, 0.38 mmol) afforded 72 mg of the desired product as a pale yellow oil (65%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.43–7.35 (m, 3 H), 7.33–7.29 (m, 2 H), 7.22–7.18 (m, 2 H), 7.15–7.11 (m, 1 H), 7.00–6.97 (m, 2 H), 5.84 (s, 1 H), 2.05 (s, 3 H), 0.30 (s, 3 H), 0.26 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 139.4, 135.0, 134.3, 129.5, 128.0, 127.6, 126.1, 125.4, 76.7, 71.0, 21.0, –5.3, –5.6; IR (neat) 1747 (s) cm^{-1}; HRMS (ESI+) (*m/z*) calcd for $C_{17}H_{21}O_2Si$ $[M+H]^+$ 285.1311, found 285.1317.

Kinetic Resolution of α-Hydroxysilanes with Novozym 435

Resolution of (±)-1-hydroxyallyltrimethylsilane (3) (Table 3, entry 1)

Novozym 435 (30 mg; 15 mg/mmol (*rac*)-alcohol) and vinyl acetate (0.3 mL, 3.0 mmol) were added to a tube containing a mixture of (±)-1-hydroxyallyltrimethylsilane (3) (261 mg, 2.0 mmol) and activated 3Å molecular sieves in pentane (1.0 mL). The tube was purged with N_2 and sealed. The sealed tube was placed in a 38 °C an oil bath and the reaction mixture was stirred with the reaction progress being monitored by GC (VF-1ms column). After ~50% of the starting material was consumed, the reaction mixture was filtered through a pad of Celite 503, concentrated, and purified by silica gel column

chromatography using Et_2O/hexane (1:9) to afford optically active acetate (*S*)-**18** (104 mg, 30%, $[\alpha]_D$ = –17.5 (*c* 1.03, $CHCl_3$, >98 %ee)) and unreacted optically active alcohol (*R*)-**3** (86 mg, 33%, $[\alpha]_D$ = –7.1 (*c* 1.05, $CHCl_3$, 73 %ee)).

Resolution of (±)-1-(dimethylphenylsilyl)-2-propen-1-ol (19) (Table 3, entry 2)

Applying the kinetic resolution procedure described on *rac*-**3** to (±)-1-(dimethylphenylsilyl)-2-propen-1-ol (**19**) (385 mg, 2.0 mmol) afforded after ~49% conversion optically active acetate (*S*)-**20** (174 mg, 37%, $[\alpha]_D$ = –10.1 (*c* 1.26, $CHCl_3$, 99 %ee)) and unreacted optically active alcohol (*R*)-**19** (167 mg, 43%, $[\alpha]_D$ = –8.8 (*c* 1.04, $CHCl_3$, 99 %ee)).

Resolution of (±)-(2*E*)-1-(trimethylsilyl)-2-buten-1-ol (22) (Table 3, entry 5)

Applying the kinetic resolution procedure described on *rac*-**3** to (±)-(2*E*)-1-(trimethylsilyl)-2-buten-1-ol (**22**) (300 mg, 2.1 mmol) at 78 °C, afforded after ~46% conversion acetate **23** (46 mg, 12%, (all chromatographic and spectroscopic attempts to resolve the enantiomers and thus determine the %ee failed) and unreacted optically active alcohol (*R*)-**22** (34 mg, 11%, $[\alpha]_D$ = +4.1 (*c* 1.12, $CHCl_3$, 9 %ee)).

^{29}Si NMR Experiment (Table 5)

Representative procedure for *rac*-3

Rac-**3** (20 mg) was dissolved in $CDCl_3$ (2.0 mL) and $Eu(tfc)_3$ (42 mg) was dissolved in $CDCl_3$ (4.2 mL). The *rac*-**3** solution (0.375 mL) was placed in a NMR tube and then the $Eu(tfc)_3$ solution (5–20 mol%) was added. $CDCl_3$ was added to up to totally 0.75 mL. The tube was sealed under nitrogen with cling-film and

shaken briskly by hand to ensure complete dissolution. After 30 min, the ^{29}Si NMR spectrum was collected at room. Refocused-decoupled INEPT sequence was applied. The FIDs were Fourier transformed and phased automatically, the same phase corrections being applied for each sample.

The experiment results

Table 10. ^{29}Si and ^{1}H Experiments for *Rac*-**22**

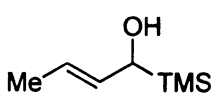
α-Hydroxysilanes	$Eu(tfc)_3$ (mol%)	^{29}Si NMR	Δδ (ppm)	Ratio	^{1}H NMR
	1.2	Not separated	–	–	Not separated
	3.0	Not separated	–	–	Not separated
	6.0	Not separated	–	–	Not separated
	9.0	Not separated	–	–	Not separated
 *rac*-**22**	10.0	Not separated	–	–	Not separated
	12.0	Partial separation	0.0051	Overlapped	Not separated
	13.0	Partial separation	0.0064	Overlapped	Not separated
	14.6	Not separated	–	–	Not separated
	17.1	Not separated	–	–	Not separated

Table 11. ^{29}Si and ^{1}H Experiments for *Rac*-**3**

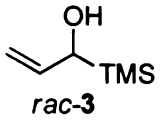
α-Hydroxysilanes	$Eu(tfc)_3$ (mol%)	^{29}Si NMR	Δδ (ppm)	Ratio	^{1}H NMR
 *rac*-**3**	5.0	Not separated	–	–	Not separated
	10.1	Separated	0.0102	52.2:47.2	Not separated
	15.1	Not separated	–	–	Not separated
	20.1	Not separated	–	–	Not separated

Table 12. ^{29}Si and ^{1}H Experiments for *Rac*-**25**

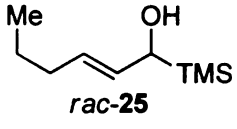
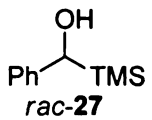
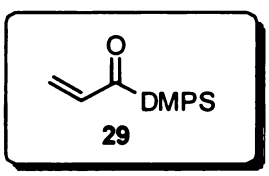
α-Hydroxysilanes	$Eu(tfc)_3$ (mol%)	^{29}Si NMR	Δδ (ppm)	Ratio	^{1}H NMR
	0.9	Not separated	–	–	Not separated
	2.4	Not separated	–	–	Not separated
	4.8	Not separated	–	–	Not separated
 *rac*-**25**	7.2	Partial Separated	0.0078	Overlapped	Not separated
	9.7	Separated	0.0073	48.0:52.0	Not separated
	12.8	Not separated	–	–	Not separated
	15.4	Not separated	–	–	Not separated
	20.1	Not separated	–	–	Not separated

Table 13. ^{29}Si and ^{1}H Experiments for *Rac*-**27**

α-Hydroxysilanes	$Eu(tfc)_3$ (mol%)	^{29}Si NMR	Δδ (ppm)	Ratio	^{1}H NMR
 *rac*-**27**	10.1	Separated	0.0075	52.1:47.9	Not separated

The best result was obtained for *rac*-**27** with 10.1 mol% of $Eu(tfc)_3$, *rac*-**3** with 10.1 mol% of $Eu(tfc)_3$, *rac*-**25** with 9.7 mol% of $Eu(tfc)_3$ and *rac*-**22** with 12.0 mol% of $Eu(tfc)_3$ (Table 10 to Table 13). For *rac*-**27**, *rac*-**3** and *rac*-**25**, this experiment gave good separation. However, *rac*-**22** showed just partially separated two peaks. During the experiment, we also collected the ^{1}H NMR for these substrates at room temperature. Unfortunately, none of them showed any separated peaks.

$[\alpha]_D$ value Experiment for 1-(Dimethylphenylsilyl)-2-propen-1-ol (19) (Scheme 42)

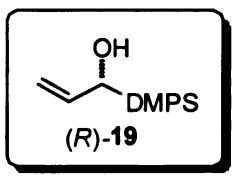


29

1-(Trimethylsilyl)-2-propen-1-one (29)

To a cold (–78 °C), stirred solution of trifluoroacetic anhydride (1.0 mL, 7.5 mmol) in CH_2Cl_2 (8 mL) under nitrogen conditions was added a solution of DMSO (0.71 mL, 10 mmol) in CH_2Cl_2 (6 mL) dropwise via syringe. After stirring for 0.5 h at the same temperature, a solution of **19** (962 mg, 5 mmol) in CH_2Cl_2 (8 mL) was added over 20 min by syringe. The reaction mixture was stirred for 1 h at –78 °C and Et_3N (2.0 mL, 15 mmol) was added dropwise. After stirring for 1 h at the same temperature, the reaction mixture was diluted with water (15 mL), allowed to warm to room

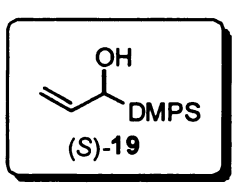
temperature and extracted with CH_2Cl_2. Combined organic phases were washed with water and brine and dried over $MgSO_4$. After filtration and evaporation, the residue was purified over silica gel column chromatography using EtOAc/hexane (5:95) to afford **29** (735 mg) but the columned material contained impurity. Without further purification, the material was used for the next step. ^1H NMR (500 MHz, $CDCl_3$) δ 7.58–7.55 (m, 2 H), 7.44–7.38 (m, 3 H), 6.44 (dd, *J* = 17.9, 10.8 Hz, 1 H), 6.00 (dd, *J* = 17.9, 0.8 Hz, 1 H), 5.88 (10.8, 0.8 Hz, 1 H), 0.55 (s, 6 H). The spectral data were consistent with literature values.[38]



(*R*)-**19**

(*R*)-1-(Dimethylphenylsilyl)-2-propen-1-ol (*R*-19)

To a solution of (–)-Ipc_2BCl (288 mg, 0.89 mmol) in THF (3 mL) was added a solution of 1-(trimethylsilyl)-2-propen-1-one (113 mg, 0.59 mmol) in THF (1 mL) dropwise at room temperature. The reaction mixture was stirred for overnight at room temperature and THF was removed in *vacuo*. The residue was dissolved in Et_2O (5 mL) and diethanolamine (180 μL, 1.89 mmol) was added. The reaction mixture was stirred for 2.5 h at room temperature, filtered and extracted with ether. The combined organics were washed with water and brine and dried over Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography using Et_2O/hexane (1:9) to afford 52 mg of (*R*)-**19** (42%). $[\alpha]_D$ = –8.1 (*c* 1.24, $CHCl_3$, 87 %ee)



(*S*)-**19**

(*S*)-1-(Dimethylphenylsilyl)-2-propen-1-ol (*S*-19)

The reaction was carried out on **29** (141 mg, 0.74 mmol) as described in the preparation of (*R*)-**19** except that (+)-Ipc_2BCl

(358 mg, 1.1 mmol) was used as the reducing reagent. This modified protocol afforded 59 mg of (*S*)-**19** (41%). $[\alpha]_D$ = +7.2 (*c* 0.67, $CHCl_3$, 82 %ee)

8.4.6. Reductive Cleavage of Optically Active Acetates

Reduction of (*S*)-18 (Table 6, entry 7)

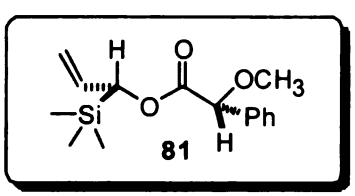
A solution of compound (*S*)-**18** (138 mg, 0.8 mmol, >98 %ee) in hexane (3 mL) was cooled to –78 °C. To that cold solution, DIBAL (0.8 mL of a 1.0 M solution in hexane, 0.8 mmol) was added dropwise. The reaction mixture was then stirred at the same temperature for 2.5 h. The cold bath removed and the reaction mixture was quenched with saturated aqueous Rochellet Salt (1.5 mL) and diluted with ether. The phases were separated, the aqueous phase extracted with ether, and the combined organics were dried over Na_2SO_4. After filtration and evaporation, the residual oil was purified by silica gel column chromatography using Et_2O/hexane (1:9) to afford 82 mg of (*S*)-**18** (78%; $[\alpha]_D$ = +8.3 (*c* 1.21, $CHCl_3$, 89 %ee).

Reduction of (*S*)-20 (Scheme 43)

Applying the conditions described for (*S*)-**18** to (*S*)-**20** (73 mg, 0.3 mmol) in hexane (1.5 mL) using 1.1 equiv of DIBAL (0.3 mL of a 1.0 M solution in hexane, 0.3 mmol) afford 49 mg of (*S*)-**19** (81%; $[\alpha]_D$ = +8.2 (*c* 1.12, $CHCl_3$, 93 %ee).

Mosher's Ester Analyses (Figrue6 and Figure 12)

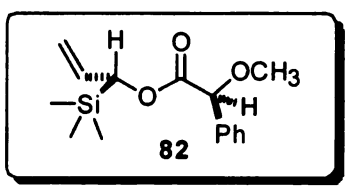
(*R*)-1-Hydroxyallyltrimethylsilane Mosher esters



81

To a solution of (*R*)-1-hydroxyallyltrimethylsilane (46 mg, 0.35 mmol), (*R*)-(–)-α-methoxyphenylacetic acid

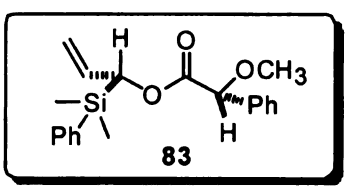
(47 mg, 0.28 mmol) and DCC (65 mg, 0.31 mmol) in CH_2Cl_2 (3.5 mL) under nitrogen was added DMAP (4 mg, 0.032 mmol) in a single portion. The reaction mixture was stirred at room temperate for 4 h. The precipitate formed was removed by filtration and the filtrate was washed with cold 1M HCl, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated to afford the crude Mosher ester, which was immediately analyzed by ^1H NMR (300 MHz, $CDCl_3$, pertinent peaks only) δ 5.75–5.62 (m, 1 H), –0.04 (d, J = 0.8 Hz, 9 H).



82

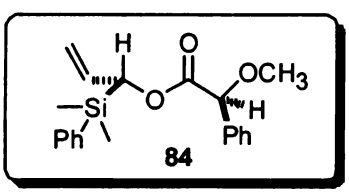
Applying the same procedure to (*R*)-1-hydroxyallyltrimethylsilane (46 mg, 0.35 mmol) and (*S*)-(+)-α-methoxyphenylacetic acid (47 mg, 0.28 mmol) afforded the crude Mosher ester, which was immediately analyzed by ^1H NMR (300 MHz, $CDCl_3$, pertinent peaks only) δ 5.89–5.74 (m, 1 H), –0.22 (d, J = 0.7 Hz, 9 H).

(*R*)-1-(Dimethylphenylsilyl)-2-propen-1-ol Mosher esters



83

Applying the Mosher's procedure to (*R*)-1-(dimethylphenylsilyl)-2-propen-1-ol (72 mg, 0.37 mmol) and (*R*)-(–)-α-methoxyphenylacetic acid (50 mg, 0.30 mmol) (7 h reaction time) afforded the crude Mosher ester, which was immediately analyzed by ^1H NMR (300 MHz, $CDCl_3$, pertinent peaks only) δ 5.71–5.58 (m, 1 H), –0.27 (d, J = 2.8 Hz, 6 H).



84

Applying the Mosher's procedure to (*R*)-1-(dimethylphenylsilyl)-2-propen-1-ol (72 mg, 0.37 mmol)

and (*S*)-(+)-α-methoxyphenylacetic acid (50 mg, 0.30 mmol) (7 h reaction time) afforded the crude Mosher ester, which was immediately analyzed by ^{1}H NMR (300 MHz, $CDCl_3$, pertinent peaks only) δ 5.79–5.66 (m, 1 H), –0.08 (d, *J* = 4.3 Hz, 6 H).

Chiral GC and HPLC Analyses

1-Hydroxyallyltrimethylsilane (3)

GC Column: β-dex tm 325 (30 m x 0.25 mm x 0.25 μm film thickness). Program 30 to 150 °C, at 5 °C/min, hold at 150 °C for 2 min. t_r-(*R*) enantiomer (min) = 10.0 min, t_r-(*S*) enantiomer (min) = 9.8 min.

Acetic acid 1-(trimethylsilyl)-allyl ester (18)

GC Column: β-dex tm 325 (30 m x 0.25 mm x 0.25 μm film thickness). Program: 30 to 150 °C, at 5 °C/min, hold at 150 °C for 2 min. Results: t_r-(*R*) enantiomer (min) = 12.9 min, t_r-(*S*) enantiomer (min) = 13.0 min.

1-(Dimethylphenylsilyl)-2-propen-1-ol (19)

HPLC column: Chiralcel OJ. Eluent: IPA/hexane (90:10), 0.18 mL/min. Results: t_r-(*R*) enantiomer (min) = 23.6 min, t_r-(*S*) enantiomer (min) = 30.9 min.

HPLC column: Chiralcel OD-H. Eluent: IPA/hexane (95:5), 1.0 mL/min. Results: t_r-(*R*) enantiomer (min) = 9.0 min, t_r-(*S*) enantiomer (min) = 8.1 min.

Acetic acid 1-(dimethylphenylsilyl)-prop-2-enyl ester (20)

HPLC column: Chiralcel OJ. Eluent: IPA/hexane (90:10), 0.18 mL/min. Results: t_r-(*R*) enantiomer (min) = 31.2 min, t_r-(*S*) enantiomer (min) = 35.4 min.

(2*E*)-1-(Trimethylsilyl)-2-buten-1-ol (22)

GC Column: β-dex tm 325 (30 m x 0.25 mm x 0.25 μm film thickness). Program: 30 to 150 °C, at 1 °C/min, Results: t_r-(*R*) enantiomer (min) = 29.2 min, t_r-(*S*) enantiomer (min) = 29.9 min.

2-Methyl-1-(trimethylsilyl)-2-propen-1-ol (24)

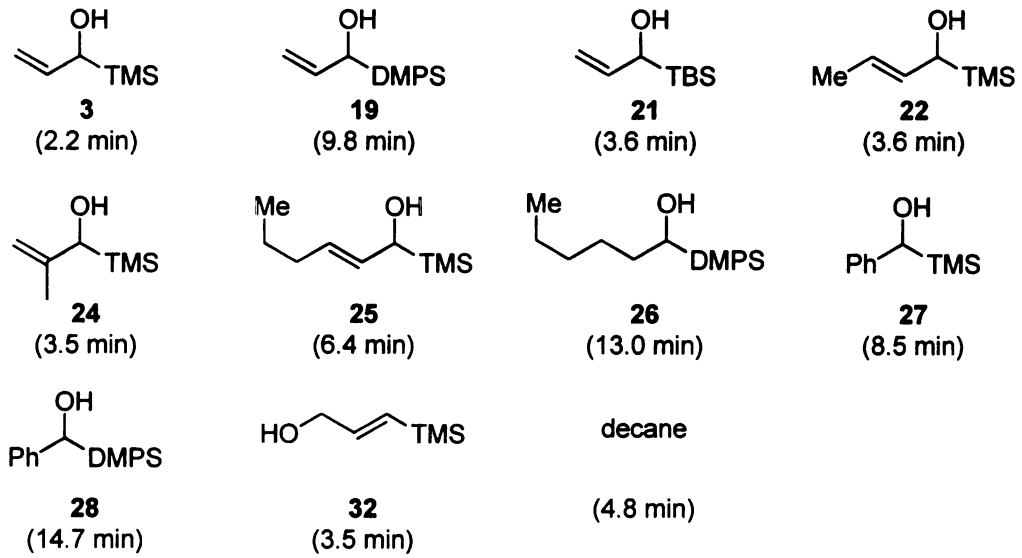
GC Column: β-dex tm 325 (30 m x 0.25 mm x 0.25 μm film thickness). Program: 45 °C for 20 min, 45 to 150 °C, at 2 °C/min. Results: t_r-(*R*) enantiomer (min) = 27.7 min, t_r-(*S*) enantiomer (min) = 28.1 min.

Acetic acid 2-methyl-1-(trimethylsilyl)-allyl ester (30)

GC Column: β-dex tm 325 (30 m x 0.25 mm x 0.25 μm film thickness). Program: 45 °C for 20 min, 45 to 150 °C, at 2 °C/min. Results: t_r-(*R*) enantiomer (min) = 36.0 min, t_r-(*S*) enantiomer (min) = 35.8 min.

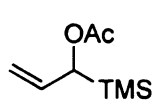
GC Analyses

Figure 18. Retention Times of α-Hydroxysilanes

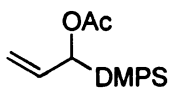


GC Column: VF-1ms column (15 m x 0.25 mm x 0.25 μm film thickness). Program: 50 °C for 2 min, 50 to 200 °C, at 10 °C/min.

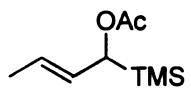
Figure 19. Retention times of Acetated Product



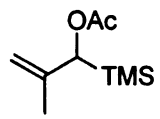
18
(4.1 min)



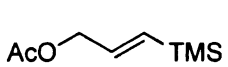
20
(11.0 min)



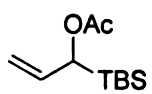
23
(5.5 min)



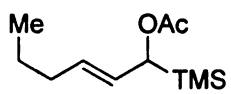
30
(5.3 min)



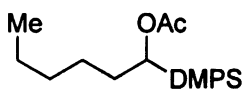
31
(5.4 min)



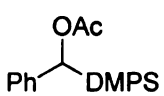
76
(5.8 min)



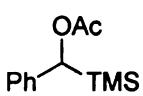
77
(7.9 min)



78
(13.7 min)



79
(15.2 min)



80
(9.8 min)

GC Column: VF-1ms column (15 m x 0.25 mm x 0.25 μm film thickness). Program: 50 °C for 2 min, 50 to 200 °C, at 10 °C/min.

Enzymatic Kinetic Resolution of Methylated α-Hydroxysilanes

Kinetic Resolution of *Rac*-24 and *Rac*-3

Amano PS-C II resolution of *rac*-24 (Table 7, entry 1)

A mixture of *rac*-**24** (144 mg, 1 mmol), *p*-ClC_6H_4OAc (256 mg, 1.5 mmol), Et_3N (0.13 mL, 1.0 mmol) and PS-C II (144 mg) in CH_2Cl_2 under nitrogen conditions was stirred at room temperature. The reaction mixture was stirred with the reaction progress being monitored by GC (VF-1ms column). After stirring for 64 h, temperature was increased to 40 °C and stirred for an additional 145 h. After ~8% of the starting material was consumed, the reaction mixture was filtered through a pad of Celite. Analysis of the filtrate was analyzed by GC (VF-1ms column) using decane as an internal standard indicated that the optically

active acetate (*R*)-**30** to be formed in 2% yield (66 %ee) and the unreacted optically active alcohol (*S*)-**24** was formed in 14% yield (2 %ee).

Amano AK resolution of *rac*-24 (Table 7, entry 2)

A mixture of *rac*-**24** (144 mg, 1 mmol) and Amano AK (72 mg) in vinyl acetate (1.5 mL) under nitrogen conditions was stirred at room temperature. The reaction mixture was stirred with the reaction progress being monitored by GC (VF-1ms column). After stirring for 65 h, temperature was increased to 40 °C and stirred for an additional 144 h. After ~13% of the starting material was consumed, the reaction mixture was filtered through a pad of Celite. Analysis of the filtrate was analyzed by GC (VF-1ms column) using decane as an internal standard indicated that the optically active acetate (*R*)-**30** to be formed in 13% yield (21 %ee) and the unreacted optically active alcohol (*S*)-**24** was formed in 81% yield (>1 %ee).

CRL resolution of *rac*-24 (Table 7, entry 3)

A mixture of *rac*-**24** (144 mg, 1 mmol), CRL (30 mg), vinyl acetate (1.4 mL, 16.0 mmol) in cyclohexane (3 mL) under nitrogen conditions was stirred at room temperature. The reaction mixture was stirred with the reaction progress being monitored by GC (VF-1ms column). After stirring for 16 h, temperature was increased to 40 °C and stirred for an additional 169 h. The temperature was increased to 60 °C and stirred for an additional 167 h. After ~9% of the starting material was consumed, the reaction mixture was filtered through a pad of Celite. Analysis of the filtrate was analyzed by GC (VF-1ms column) using decane as an internal standard indicated that the optically active acetate (*R*)-**30** to be formed in

5% yield (9 %ee) and the unreacted optically active alcohol (*S*)-**24** was formed in 57% yield (>48 %ee).

Amano PS-D I resolution of *rac*-24 (Table 7, entry 12)

To a sealed tube containing a solution of racemic 2-methyl-1-(trimethylsilyl)-2-propen-1-ol (**24**) (144 mg, 1.0 mmol) and activated 3Å molecular sieves in toluene (1 mL) was added PS-D I (288 mg) and vinyl acetate (0.3 mL, 3.0 mmol). The tube was purged with N_2 and sealed. The tube was purged with N_2, sealed, and the reaction mixture was stirred with the reaction progress being monitored by GC (VF-1ms column). After ~44% of the starting material was consumed, the reaction mixture was filtered through a pad of Celite. Analysis of the filtrate was analyzed by GC (VF-1ms column) using decane as an internal standard indicated that the optically active acetate (*R*)-**30** to be formed in 13% yield (87 %ee) and the unreacted optically active alcohol (*S*)-**24** was formed in 19% yield (>99 %ee).

Amino PS-D I resolution of *rac*-3 (Scheme 48, eq 3)

PS-D I (288 mg) and vinyl acetate (0.14 mL, 1.5 mmol) were added to a tube containing a mixture of racemic 1-hydroxyallyltrimethylsilane (0.13 g, 1.0 mmol) and activated 3Å molecular sieves in toluene (1 mL). The tube was purged with N_2, sealed, and the reaction mixture was stirred with the reaction progress being monitored by GC (VF-1ms column). After ~100% of the starting material was consumed, the reaction mixture was filtered through a pad of Celite 503. Analysis of the filtrate was analyzed by GC (VF-1ms column) using decane

as an internal standard indicated that the optically active (*S*)-**18** to be formed in 41% yield (97 %ee) as well as presumed **33** and an impurity.

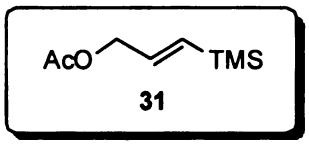
Identification of Acetal 33

Hydrolysis of acetal 33 by C_{18} silica gel (Scheme 52)

PS-D I (2.88 g) and vinyl acetate (1.4 mL, 15.0 mmol) were added to a sealed tube containing a mixture of racemic 1-hydroxyallyltrimethylsilane (1.39 g, 10.6 mmol) and activated 3Å molecular sieves in toluene (10 mL). The sealed tube was purged with N_2 and the mixture was stirred at room temperature and monitored by GC. The tube was purged with N_2, sealed, and the reaction mixture was stirred with the reaction progress being monitored by GC (VF-1ms column). After ~100% of the starting material was consumed, the reaction mixture was filtered through a pad of Celite 503, concentrated, and subjected to silica gel column chromatography using Et_2O/hexane (1:9), which afforded a mixture of (*S*)-**18**, presumed acetal **33** and an unidentified impurity. Compound (*S*)-**18** was removed by rotary evaporation, leaving 117 mg acetal **33** and the impurity. This mixture provided the following data: Major (GC peak at 6.4 min) ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.96 (q, *J* = 5.3 Hz, 1 H), 5.92–5.87 (m, overlapped), 5.07–4.96 (m, 2 H), 3.83–3.80(m, 1 H), 2.00 (s, 3 H), 1.38 (d, *J* = 5.3 Hz, 3 H), 0.03 (s, overlapped); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 137.8, 110.7, 98.1, 78.3, 21.4, 21.1, –4.2; IR (neat) 1740 cm^{-1}; Minor (GC peak at 6.2 min) ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92–5.87 (m, overlapped), 4.93–4.88 (m, 2 H), 3.93–3.89 (m, 1 H), 2.06 (s, 3 H), 1.40 (d, *J* = 5.2 Hz, 3 H), 0.04 (s, overlapped); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 136.2, 112.6, 96.1, 74.6, 21.2, 20.9, –4.0 ; IR (neat) 1740 cm^{-1}; HRMS (ESI+) (*m/z*) calcd for $C_8H_{17}OSi$ $[M + H - CH_3CO_2H]^+$ 157.1049, found

157.1052. These data suggest that the peaks occurring at 6.2, and 6.4 minutes are diastereomers of **33**. In addition the structure of acetal **33** was consistent with HMQC, HMBC, TOCSY, and COSY data acquired on the mixture. Acetal **33** and the impurity (48 mg) were dissolved in CH_3CN (2 mL) to which C_{18} silica gel (500 mg) was added. The mixture was stirred at room temperature for 20 min, filtered, concentrated, and purified by silica gel column chromatography using Et_2O/hexane (1:9) to afford 10 mg of (*R*)-**3** as a colorless oil (>33%, 64 %ee).

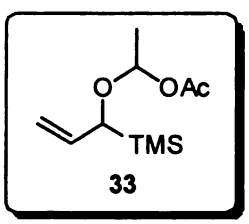
Possible rearrangement product (Scheme 55)



31

(2*E*)-1-acetate-3-(trimethylsilyl)-2-propen-1-ol (31)

To a solution of (2*E*)-3-(trimethylsilyl)-2-propen-1-ol (11 μL, 0.76 mmol) and pyridine (68 μL, 0.84 mmol) was added acetic anhydride (80 μL, 0.84 mmol). The reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with Et_2O, and then sequentially extracted with 1M HCl, saturated aqueous $NaHCO_3$ and brine. The ethereal layer was dried over $MgSO_4$, filtered, and evaporated to afford 134 mg **31** as a pale yellow oil (100%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.04 (dt, *J* = 18.7, 5.0 Hz, 1 H), 5.92 (dt, *J* = 18.7, 1.5 Hz, 1 H), 4.57 (dd, *J* = 5.0, 1.5 Hz, 2 H), 2.08 (s, 3 H), 0.06 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 139.3, 133.5, 66.9, 20.9, –1.5; IR (neat) 1745 (s) cm^{-1}; HRMS (EI) (*m/z*) calcd for $C_8H_{16}O_2Si$ $[M]^+$ 172.0920, found 172.0920.



33

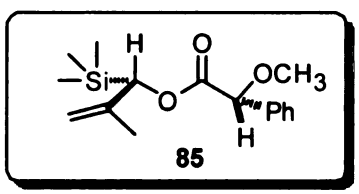
Synthesis of acetal 33 (Scheme 54)[62]

To a cold (–78 °C), stirred solution of (±)-1-trimethylsilylallyl acetate (**18**) (155 mg, 0.9 mmol) in CH_2Cl_2 (5 mL) under nitrogen condition was added DIBAL (1.8 mL of a 1.0 M solution in hexane, 1.8

mmol) dropwise. The resulting reaction mixture was then stirred for 45 min and after which pyridine (0.2 mL, 2.7 mmol), a solution of DMAP (221 mg, 1.8 mmol) in CH_2Cl_2 (2 mL), and acetic anhydride (0.5 mL, 5.4 mmol) were added dropwise. After stirring an additional 29 h, the reaction mixture was warmed to 0 °C and stirred for 0.5 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and sodium potassium tartrate at 0 °C. The resulting solution was warmed to room temperature, stirred for additional 0.5 h and then diluted with CH_2Cl_2. Phases were separated and the aqueous phase extracted with CH_2Cl_2. The combined organics were washed with ice cooled 1 M sodium bisulfate, saturated aqueous $NaHCO_3$, and brine to afford 61 mg (< 31%) of presumed acetal **33**.

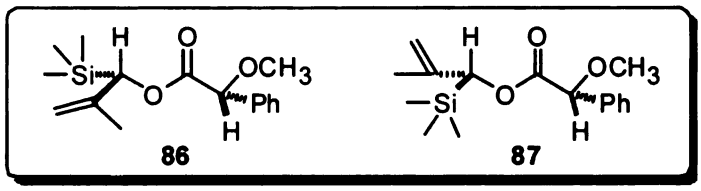
Mosher's Ester Analyses (Figure 13)

(*S*)-2-Methyl-1-(trimethylsilyl)-2-propen-1-ol (8) Mosher esters



85

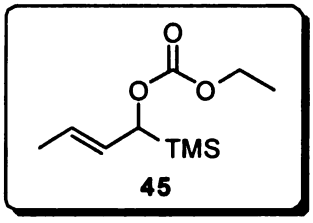
To a solution of (*S*)-2-methyl-1-(trimethylsilyl)-2-propen-1-ol (30 mg, 0.21 mmol), (*R*)-(–)-α-methoxyphenylacetic acid (28 mg, 0.17 mmol) and DCC (39 mg, 0.19 mmol) in CH_2Cl_2 (2.0 mL) under nitrogen was added DMAP (2 mg, 0.019 mmol) in a single portion. The reaction mixture was stirred at room temperate for 7 h. The precipitate formed was removed by filtration and the filtrate was washed with cold 1M HCl, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated to afford the crude Mosher ester, which was immediately analyzed by ^1H NMR (300 MHz, $CDCl_3$, pertinent peaks only) δ 1.67 (s, 3 H), –0.19 (s, 9 H).



86 87

Applying the Mosher's procedure to (*rac*)-2-methyl-1-(trimethylsilyl)-2-propen-1-ol (100 mg, 0.69 mmol) and (*R*)-(–)-α-methoxyphenylacetic acid (94 mg, 0.56 mmol) (7 h reaction time) afforded the crude Mosher ester, which was immediately analyzed by ^{1}H NMR (300 MHz, $CDCl_3$, pertinent peaks only) δ 1.67 (s, 3 H), 1.51 (s, 3 H), 0.00 (s, 9 H), –0.19 (s, 9 H).

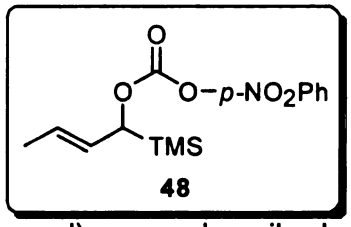
Resolution of α-Hydroxysilanes via Norephedrine Cabamate (Scheme 59)[64]



45

(*E*)-Ethyl(1-(trimethylsilyl)but-2-en-1-yl)carbonate (45) Ethylcholoformate (1.13 g, 10.4 mmol) was added to cold (0 °C) solution of **24** (1.0 g, 6.9 mmol) in hexane/acetonitrile (1:1 v/v, 20 mL), followed by pyridine (1.7 mL, 20.8 mmol), and the reaction stirred at 0 °C for 2 h. The reaction was quenched by the addition of water (30 mL), diluted with CH_3CN (50 mL), and then hexanes (150 mL). Layers separated and the hexane/acetonitrile layer was washed with brine (30 mL), dried with Na_2SO_4, and concentrated under reduced pressure to give the crude product, which was employed in the second step without further purification. To a solution of the crude carbonate in hexane/acetonitrile (1:1 v/v, 30 mL) at 0 °C, was added (1*R*,2*S*)-(+)-norephedrine (1.36g, 9.0 mmol), followed by diisopropylethylamine (3.6 mL, 20.8 mmol). The reaction was allowed to warm to room temperature overnight, and then quenched by the addition of water. Phases were separated and the organic phase (hexane/acetonitrile) washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure to yield the

desired product as a colorless oil. The second step did not go, and after purification by silica gel column chromatography on using EtOAc/hexane (3:97), 632 mg of **45**, the product of the first step, was obtained as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.58–5.41 (m, 2 H), 4.87–4.85 (d, *J* = 6.3 Hz, 1 H), 4.18–4.11 (q, *J* = 7.1 Hz, 2 H), 1.67 (d, *J* = 5.5 Hz, 3 H), 1.27 (t, *J* = 7.1 Hz, 3 H), 0.03 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 127.1, 125.6, 74.5, 63.8, 17.9, 14.3, –4.0; IR (neat) 1744 cm^{-1}; HRMS (EI) (*m/z*) calcd for $C_{10}H_{20}O_3Si$ $[M+H]^+$ 216.1182, found 216.1184.



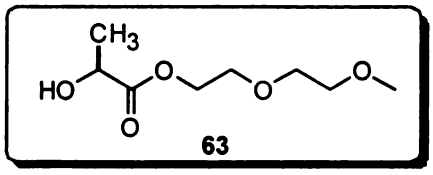
48

(*E*)-*p*-Nitrophenyl(1-(trimethylsilyl)but-2-en-1-yl)-carbonate (48).

The reaction was carried out on **24** (300 mg, 2.0 mmol) as described in the preparation of (*R*)-**19** except that *p*-nitropheylchloroformate (629 mg, 3.1 mmol) was used to form carbonate. This modified protocol afforded 294 mg of **48** (46%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26–8.23 (d, *J* = 9.1 Hz, 2 H), 7.37–7.34 (d, *J* = 9.3 Hz, 2 H), 5.68–5.61 (m, 1 H), 5.59–5.50 (m, 1 H), 4.99–4.96 (d, *J* = 7.7 Hz, 1 H), 1.72 (d, *J* = 6.3 Hz, 3 H), 0.09 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 152.9, 145.2, 127.4, 126.2, 125.2, 121.8, 77.1, 17.9, –4.0; IR (neat) 1763 cm^{-1}; HRMS (FAB+) (*m/z*) calcd for $C_{14}H_{18}NO_5Si$ $[M-H]^+$ 308.0955, found 308.0957.

Kinetic Resolution of α-Hydroxysilanes using PBO Catalyst

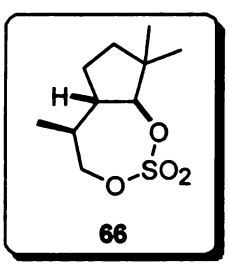
Synthesis of 58 (Scheme 63)



63

(2*S*)-2-(2-methoxyethoxy)ethyl ester-2-hydroxy-propanoic acid (63)

Methyl (*S*)-lactate (33.0 mL, 0.34 mol), di(ethylene glycol) methyl ether (138 mL, 1.1 mol) and $Al(O\textit{i}Pr)_3$ (1.2 g, 5.8 mmol) were stirred under nitrogen conditions and refluxed until 8 mL of methanol was collected (65 °C, 1 atm). The crude material was purified by distillation under reduced pressure (117–120 °C, 1–2 torr) but obtained product contained impurity. The impure **63** was purified by redistillation (97 °C, 1 torr) to afford 38.6 g of **63** as a colorless oil (58%). $[\alpha]_D = -11.9$ (*c* 5.56, EtOAc). ^1H NMR (500 MHz, $CDCl_3$) δ 4.34–4.26 (m, 3 H), 3.72–3.69 (m, 2 H), 3.63–3.60 (m, 2 H), 3.54–3.51 (m, 2 H), 3.35 (s, 3 H), 1.40 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.6, 71.8, 70.5, 68.9, 66.7, 64.5, 59.0, 20.3. The spectral data were consistent with literature values.[67]



66

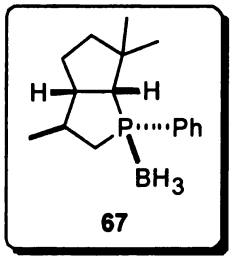
(*5S,5aS,8aS*)-2,2-dioxide-hexahydro-5,8,8-trimethyl-4H-cyclopenta[d]-1,3,2,-dioxathiepin (66)

To a cold (0 °C), stirred solution of **63** (12.3 g, 34.4 mmol) in CH_2Cl_2 (180 mL) under nitrogen conditions was added triflic anhydride (11.9 g, 70.8 mmol) dropwise over 5 min. The reaction mixture was stirred for 5 min at 0 °C and pyridine (5.6 mL, 70.2 mmol) was added dropwise over 5 min at 0 °C. The reaction mixture was stirred for an additional 5 min at the same temperature before removal of ca 2/3 of the solvent by rotary evaporator. Hexane was added and extraction with water. The water layers were washed with hexane and the combined hexane layers were dried over $MgSO_4$. After filtration and evaporation, 14.2 g of impure ethoxyethoxyethyl (*S*)-α-trifluoromethyl-sulfonyloxypropionate (**64**) was obtained. As the literature

mentioned, the crude material was used for the next step without further purification.

To a cold (0 °C), stirred solution of diisopropylamine (3.5 mL, 25.4 mmol) in toluene (200 mL) under nitrogen conditions was added *n*-BuLi (15.8 mL of 1.6 M solution in hexane, 25.2 mmol) and stirred for 5 min. The reaction mixture was cooled to –78 °C and 2,2-diemthyl cyclopentanone (2.9 mL, 23.2 mmol) was added dropwise over 5 min. The reaction mixture was stirred at the same temperature for 1.2 h and then impure **64** (14.2 g, 44 mmol) was added dropwise over 5 min. After stirring for 1 h, the reaction mixture was allowed to warm to –55 °C and stirred for an additional 23 h. The reaction mixture was recooled to –78 °C, THF (150 mL) was added dropwise over 1 h and a suspension of $LiAlH_4$ (10.3 g, 272 mmol) in THF (120 mL) was added by syringe. After stirring for 20 h at –78 °C, the reaction mixture was warmed to –35 °C and stirred for 3 h. The cold bath was removed and warmed to room temperature. The reaction was quenched with saturated NH_4Cl and the phases were separated. The aqueous phase extracted with ether, and the combined organics were dried over Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography using EtOAc/hexane (4:6) to afford (*1S*,5*S*)-5-((*2'S*)-1'-hydroxyprop-2'-yl)-2,2-dimethyl-1-cyclopentanol (**65**) containing an impurity. After subsequently the impure material to two additional silica gel columns, 2.9 g of the impure **65** was obtained and it was used for the next step without further purification.

To a solution of Impure **65** (1.04 g, 6.0 mmol) in CCl_4 (12 mL) under nitrogen conditions was added $SOCl_2$ (0.71 mL, 9.7 mmol) and refluxed for 1 h. The reaction mixture was cooled to room temperature, the solvent was removed by N_2 stream and the residue was dissolved in mixture of CH_3CN, CCl_4 and water (8 mL: 8 mL: 12 mL). The reaction mixture was cooled to 0 °C and $RuCl_3 \cdot H_2O$ (11 mg, 0.4 mmol) and $NaIO_4$ (2.6 g, 12.1 mmol) were added. After stirring for 5 min at 0 °C, the reaction mixture was stirred for an additional 1 h at room temperature. The reaction was quenched by the addition of water and then diluted with ether. The phases were separated and the aqueous phase was extracted with ether. The combined organics were washed with brine and dried over anhydrous $MgSO_4$. After filtration and evaporation, the residue was purified by silica gel column chromatography using Et_2O/hexane (2:8) to afford **66** containing an impurity. After subsequently the impure material to two additional silica gel columns, 633 mg of impure **66** was obtained and it was used for the next step without further purification. ^1H NMR (300 MHz, $CDCl_3$) δ 4.09 (d, J = 10.1, 1 H), 3.92–3.85 (m, 1 H), 3.48 (dd, J =12.1, 3.4 Hz, 1 H), 1.54–1.02 (m, 5 H), 1.00 (s, 3 H), 0.83 (s, 3 H), 0.68–0.53 (m, 1 H), 0.21 (d, J = 6.8 Hz, 3 H). The spectral data were consistent with literature values.[67]



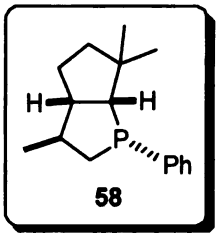
67

(*1R,2R,4S,5S*)-4,8,8-Triemthyl-2-(phenylphospha)-bicyclo-[3.3.0]octane borane complex (67)

To a cold (0 °C), stirred solution of phenylphosphine (5.0 mL of 10 wt% solution in hexane, 3.1 mmol) in THF (21 mL) under nitrogen conditions was added *n*-BuLi (1.8 mL of 1.6 M solution in hexane, 3.0

mmol) dropwise. After stirring for 5 min at 0 °C, a solution of impure **66** (633 mg, 2.7 mmol) in THF (14 mL) was added dropwise at –78 °C. After stirring for an additional 15 min, the cold bath was removed and the reaction mixture was warmed to room temperature. After stirring for 15 min at room temperature, the reaction mixture was recooled to –78 °C and *n*-BuLi (2.0 mL of 1.6 M solution in hexane, 3.3 mmol) was added dropwise. The reaction mixture was stirred for 15 min at –78 °C, warmed to room temperature and stirred for an additional 2 h. After addition of borane-THF (8.1 mL of 1.0 M solution in THF, 8.1 mmol), the reaction mixture was stirred for 1 h at room temperature. The solvent was removed by N_2 stream and aqueous 1M HCl (21 mL) was added. The reaction was diluted with CH_2Cl_2. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organics were washed with brine and dried over anhydrous Na_2SO_4. After filtration and evaporation, the residue was purified by silica gel column chromatography using toluene/hexane (1:1) to afford 444 mg of **67** as a white crystal (7.8 % from **63**). HPLC column: Chiralpak AS. Eluent: EtOH/hexane (0.25:99.75), 1.0 mL/min. Results: 11.1 min (single peak). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82–7.77 (m, 2 H), 7.46–7.41 (m, 3 H), 2.64 (d, *J* = 10.4 Hz, 1 H), 2.56–2.40 (m, 2 H), 2.30–2.20 (m, 1 H), 2.1–1.84 (m, 2 H), 1.52–1.39 (m, 3 H), 1.17 (d, *J* = 6.3 Hz, 3 H), 0.98 (s, 3 H), 0.48 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.8 (d, *J* = 9.1 Hz), 131.1 (d, *J* = 2.1 Hz), 128.68 (d, *J* = 41.5 Hz), 128.60 (d, *J* = 9.7 Hz), 56.8 (d, *J* = 30.0 Hz), 54.8 (d, *J* = 2.45 Hz), 44.5 (d, *J* = 5.5 Hz), 44.2 (s), 43.2 (d, *J* = 4.8 Hz), 35.9 (d, *J* = 35.9 Hz), 30.6 (d, *J* = 4.4 Hz), 29.1 (d, *J* = 4.5 Hz), 24.5 (d, *J* = 24.5 Hz), 20.6 (d, *J* = 9.9 Hz); ^{11}B NMR

(160 MHz, $CDCl_3$)) δ –31.2– –38.2 (m); ^{31}P NMR (200 MHz, $CDCl_3$) δ 33.0–30.9 (m); IR (neat) 2368 cm^{-1}; HRMS (ESI+) (*m/z*) calcd for $C_{16}H_{26}BP$ $[M+Na]^+$ 283.1766, found 283.1763; $[\alpha]_D$ = +29.1 (*c* 2.18, EtOAc); mp = 138–139 °C. The spectral data were consistent with literature values. [67]

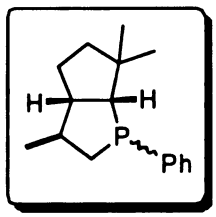


58

(*1S,2R,4S,5S*)-4,8,8-Trimethyl-2-phenyl-2-phosphabicylco-[3.3.0]ocatane (58)

A solution of **67** (435 mg, 1.6 mmol) in pyrrolidine (24 mL) was refluxed for 4 min 30 sec and cooled to room temperature for 20 min. Pyrrolidine was removed by N_2 stream and the residue was filtered through silica gel in toluene under nitrogen conditions. The columned material contained a small amount (60:1) of the *P*-epimer of **58** by ^{31}P NMR. Recrystalization of the material in CH_3CN at –20 °C afforded 379 mg of diastereomerically pure **58** as a white crystal (92%). ^1H NMR (500 MHz, C_6D_6) δ 7.67–7.63 (m, 2 H), 7.11–7.03 (m, 3 H), 2.61 (dd, *J* = 26.7, 9.2 Hz, 1 H), 2.27 (dd, *J* = 14.4, 5.7 Hz, 1 H), 2.21–2.03 (m, 2 H), 1.83-1.74 (m, 1 H), 1.53 (ddd, *J* = 19.4, 14.4, 11.0 Hz, 1 H), 1.35–1.17 (m, 3 H), 0.98 (d, *J* = 6.3 Hz, 3 H), 0.98 (s, 3 H), 0.71 (s, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 139.0 (d, *J* = 31.6 Hz), 134.4 (d, *J* = 20.3 Hz), 128.3 (d, *J* = 21.9 Hz), 128.2 (s, it might be overlapped with C_6D_6), 58.5 (d, *J* = 24.6 Hz), 56.0 (d, *J* = 3.4 Hz), 45.3 (d, *J* = 3.4 Hz), 44.0 (d, *J* = 1.5 Hz), 43.9 (d, *J* = 4.6 Hz), 36.3 (d, *J* = 8.8 Hz), 31.3 (d, *J* = 3.4 Hz), 30.1 (s), 25.6 (d, *J* = 5.5 Hz), 21.5 (d, *J* = 3.4 Hz); ^{31}P NMR (200 MHz, C_6D_6) δ –1.7 (s); IR (neat) 1456 cm^{-1}; HRMS (ESI+) (*m/z*) calcd for $C_{16}H_{24}P$ $[M+H]^+$ 247.1616, found 247.1618; $[\alpha]_D$ = –15.1 (*c*

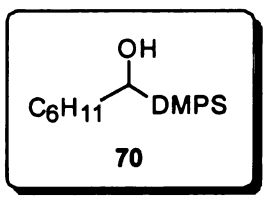
1.07, THF); mp = 49 °C. The spectral data were consistent with literature values.[67]



***P*-epimerization of 58 experiment**

The reaction was carried out on **67** (5.1 mg, 0.502 mmol) as described in the preparation of (*1S,2R,4S,5S*)-4,8,8-trimethyl-2-phenyl-2-phosphabicylco-[3.3.0]ocatane except that the reaction mixture was refluxed for 2 h. ^{1}H NMR (300 MHz, C_6D_6) δ 7.66–7.62 ppm and 7.47–7.43 ppm (ratio of 1.5:1.0), 2.36 pm and 2.25 ppm (ratio of 1.0:1.6); ^{31}P NMR (120 MHz, C_6D_6) δ –2.01 ppm and –15.74 ppm (ratio of 1.0: 1.6).

Preparation of α-Hydroxysilanes

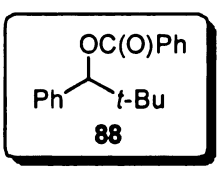


α-(Dimethylphenylsilyl)-cyclohexanemethanol (70)

Chlorodimethylphenylsilane (24.8 mL, 148 mmol) was added to a rapidly stirring mixture of lithium wire (3.2 g, 466 mmol (fine cut)) in THF (120 mL) at room temperature. The reaction mixture was stirred for 28 h at room temperature, giving a deep red solution of $PhMe_2SiLi$. This $PhMe_2SiLi$ solution was then added dropwise via cannula to a cold (–78 °C) stirred solution of cyclohexanecarboxaldehyde (2.4 mL, 20 mmol). The reaction mixture was stirred for 30 min at the same temperature and allowed to warm to 0 °C. The reaction mixture was stirred for an additional 1.5 h at the same temperature before being quenched by addition of saturated aqueous NH_4Cl solution. The reaction was extracted twice with ether. The combined organics were washed with water and brine and then dried over $MgSO_4$. After filtration and evaporation, the residue was purified over silica gel column chromatography

using Et_2O/hexane (1:25) to afford 3.6 g of **70** as a pale yellow oil (73%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.58–7.54 (m, 2 H), 7.36–7.34 (m, 3 H), 3.33 (d, *J* = 5.9 Hz, 1 H), 1.85–1.49 (m, 6 H), 1.25–0.99 (m, 6 H), 0.36 (d, *J* = 4.8 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 134.2, 129.3, 128.0, 71.1, 42.2, 31.0, 29.7, 26.6, 26.5, 26.4, –3.5, –4.0. The spectral data were consistent with literature values.[35]

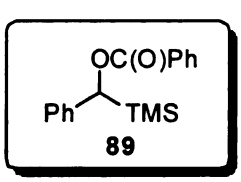
Acylation of α-Hydroxysilanes



88

1-Benzoate-α-(1,1-dimethylethyl)-benzenemethanol

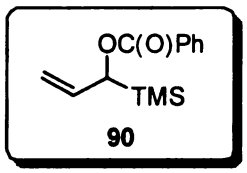
To a solution of α-(1,1-dimethylethyl)-benzenemethanol (100 mg, 0.60 mmol) and pyridine (50 μL, 0.61 mmol) was added benzoic anhydride (139 mg, 0.61 mmol). The reaction mixture was stirred at 80 °C for 48 h. The reaction mixture was diluted with Et_2O, and then sequentially extracted with 1M HCl, saturated aqueous $NaHCO_3$ and brine. The ethereal layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by silica gel column chromatography using EtOAc/hexane (5:95) to afford to 103 mg the desired product (63%). ^1H NMR (500 MHz, $CDCl_3$) δ 8.11–8.08 (m, 2 H), 7.58–7.53 (m, 1 H), 7.47–7.42 (m, 2 H), 7.35–7.32 (m, 2 H), 7.30–7.26 (m, 2 H), 7.26–7.22 (m, 1 H) 5.70 (s, 1 H), 1.01 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 138.4, 132.8, 130.6, 129.5, 128.3, 127.69, 127.64, 127.5, 83.4, 35.4, 26.2. IR (neat) 1722 cm^{-1}; HRMS (ESI+) (*m/z*) calcd for $C_{18}H_{20}O_2$ $[M+Na]^+$ 291.1361, found 291.1358.



89

Phenyl(trimethylsilyl)methyl benzoate

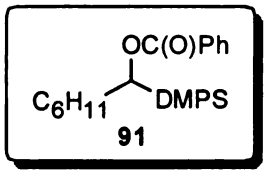
The reaction was carried out on **27** (100 mg, 0.55 mmol) as described in the preparation of 1-benzoate-α-(1,1-dimethylethyl)-benzenemethanol except that the reaction mixture was stirred for 24 h at 50 °C. The residue was purified by silica gel column chromatography using EtOAc/hexane (5:95) to afford to 35 mg the desired product (22%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13–8.09 (m, 2 H), 7.78–7.53 (m, 1 H), 7.49–7.43 (m, 2 H), 7.31–7.26 (m, 2 H), 7.25–7.20 (m, 2 H), 7.19–7.14 (m, 1 H) 5.91 (s, 1 H), 0.08 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 140.0, 132.8, 130.6, 129.5, 128.4, 128.2, 126.1, 125.1, 72.1, –3.7. IR (neat) 1720 cm^{-1}; HRMS (ESI+) (*m/z*) calcd for $C_{17}H_{20}O_2Si$ $[M+Na]^+$ 307.1130, found 307.1136.



90

1-(Trimethylsilyl)allyl benzoate

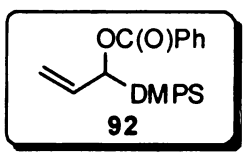
The reaction was carried out on **3** (200 mg, 1.5 mmol) as described in the preparation of 1-benzoate-α-(1,1-dimethylethyl)-benzenemethanol except that the reaction mixture was stirred for 14 h at 50 °C. The residue was purified by silica gel column chromatography using Et_2O/hexane (5:95) to afford to 173 mg the desired product (48%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07–8.04 (m, 2 H), 7.57–7.52 (m, 1 H), 7.46–7.41 (m, 2 H), 5.94 (ddd, *J* = 17.1, 10.8, 5.6 Hz, 1 H), 5.43 (dt, *J* = 5.6, 1.8 Hz, 1 H), 5.10-4.99 (m, 2 H), 0.11 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 134.8, 132.7, 130.6, 129.5, 128.3, 111.4, 70.9, –3.8; IR (neat) 1720 cm^{-1}; HRMS (ESI+) (*m/z*) calcd for $C_{13}H_{19}O_2Si$ $[M+H]^+$ 235.1154, found 235.1159.



91

The reaction was carried out on **70** (113 mg, 0.45 mmol) as described in the preparation of 1-benzoate-α-(1,1-

dimethylethyl)-benzenemethanol except that the reaction mixture was stirred for 48 h at 50 °C. The residue was purified by silica gel column chromatography using EtOAc/hexane (10:90) to afford to 109 mg the desired product (68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02–8.00 (m, 2 H), 7.58–7.51 (m, 3 H), 7.45–7.41 (m, 2 H), 7.35–7.31 (m, 3 H), 5.10 (d, *J* = 7.1 Hz, 1 H), 1.77–1.52 (m, 6 H), 1.17–0.93 (m, 5 H), 0.37 (d, *J* = 17.1 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 136.8, 133.9, 132.5, 130.7, 129.4, 129.2, 128.3, 127.8, 73.6, 40.4, 30.7, 30.0, 26.16, 26.11, 26.0, –3.4, –4.0; IR (neat) 1713 cm^{-1}; HRMS (ESI+) (*m/z*) calcd for $C_{22}H_{28}O_2Si$ $[M+NH_4]^+$ 370.2210, found 370.2202.



92

1-(Dimethyl(phenyl)silyl)allyl benzoate

The reaction was carried out on **18** (200 mg, 1.04 mmol) as described in the preparation of 1-benzoate-α-(1,1-dimethylethyl)-benzenemethanol except that the reaction mixture was stirred for 46 h at 50 °C. The residue was purified by silica gel column chromatography using EtOAc/hexane (10:90) to afford to the desired product but the columned material contained impurity. After second silica gel column chromatography, 160 mg of impure product was obtained. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04–8.00 (m, 2 H), 7.57–7.52 (m, 3 H), 7.45–7.41 (m, 2 H), 7.38–7.32 (m, 3 H), 5.87 (ddd, *J* = 17.1, 10.8, 5.5 Hz, 1 H), 5.62 (dt, *J* = 5.5, 1.8 Hz, 1 H), 5.05–4.96 (m, 2 H), 0.40 (d, *J* = 2.0 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3, 135.4, 134.8, 134.3, 133.0, 130.7, 129.8, 129.7, 128.6, 128.1, 112.1, 70.6, –5.0, –5.3; IR (neat) 1717 cm^{-1}; HRMS (ESI+) (*m/z*) calcd for $C_{18}H_{24}O_2Si$ $[M+NH_4]^+$ 314.1578, found 314.1576.

Kinetic Resolution of α-Hydroxysilanes with PBO Catalyst

Resolution of (±)-α-(1,1-dimethylethyl)-benzenemethanol (49) (Table 8, entry 4)

To a cold (–30 °C) solution of **58** (3.3 mg, 4 mol%) in toluene (1.0 mL) under nitrogen conditions was added (±)-α-(1,1-dimethylethyl)-benzenemethanol (55 mg, 0.33 mmol) and benzoic anhydride (189 mg, 0.83 mmol). The reaction mixture was stirred with the reaction progress being monitored by GC (VF-1ms column). After ~59% of the starting material was consumed, the reaction mixture was filtered through a pad of Celite. Analysis of the filtrate was analyzed HPLC (Chiralcel OD) and indicated that the optically active (*S*)-**49** to be formed with 85 %ee.

Resolution of (±)-α-(trimethylsilyl)-benzenemethanol (Table 9, entry 1)

Applying the kinetic resolution procedure described on *rac*-**49** to (±)-α-(trimethylsilyl)-benzenemethanol (**27**) (18 mg, 0.1 mmol) with **58** (1.5 mg, 6 mol%) at room temperature afforded after ~47% conversion unreacted optically active alcohol with 46 %ee.

Resolution of (±)-1-hydroxyallyltrimethylsilane (Table 9, entry 2)

Applying the kinetic resolution procedure described on *rac*-**49** to (±)-1-hydroxyallyltrimethylsilane (**3**) (13 mg, 0.1 mmol) with **58** (1.2 mg, 5 mol%) at room temperature afforded after ~47% conversion unreacted optically active alcohol (*S*)-**3** with 19 %ee.

Resolution of (±)-1-(dimethylphenylsilyl)-2-propen-1-ol (Table 9, entry 3)

Applying the kinetic resolution procedure described on *rac*-**49** to (±)-1-(dimethylphenylsilyl)-2-propen-1-ol (**19**) (21 mg, 0.1 mmol) with **58** (1.4 mg, 5

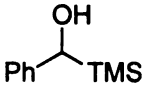
mol%) at room temperature afforded after ~54% conversion unreacted optically active alcohol (*S*)-**19** to be formed with 5 %ee.

Resolution of (±)-α-(dimethylphenylsilyl)-cyclohexanemethanol (Table 9, entry 4)

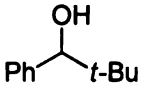
Applying the kinetic resolution procedure described on *rac*-**49** to (±)-α-(dimethylphenylsilyl)-cyclohexanemethanol (38 mg, 0.16 mmol) with **58** (3.5 mg, 8.5 mol%) in heptanes at room temperature afforded after ~43% conversion unreacted optically active alcohol **70** to be formed with 5 %ee.

GC Analyses

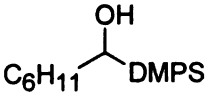
Figure 20. Retention times of α-Hydroxysilanes



27
(8.5 min)



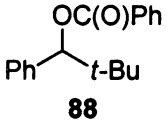
49
(8.4 min)



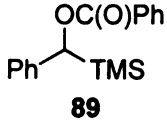
70
(14.5 min)

GC Column: VF-1ms column (15 m x 0.25 mm x 0.25 μm film thickness). Program: 50 °C for 2 min, 50 to 200 °C, at 10 °C/min.

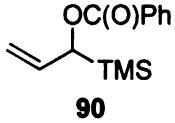
Figure 21. Retention times of Acetated Products



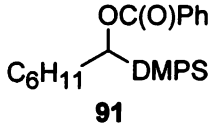
88
(15.8 min)



89
(15.9 min)



90
(9.7 min)



91
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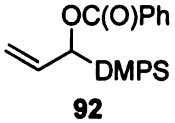


92
(16.6 min)

GC Column: VF-1ms column (15 m x 0.25 mm x 0.25 μm film thickness). Program: 50 °C for 2 min, 50 to 200 °C, at 10 °C/min.

Chiral GC and HPLC Analyses

α-(Trimethylsilyl)-benzenemethanol (27)

HPLC column: Chiralcel OD. Eluent: IPA/hexane (3:97), 1.0 mL/min. Results: 8.3 min, 10.3 min (absolute stereochemistry is not determined yet).

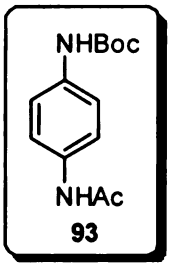
α-(1,1-Dimethylethyl)-benzenemethanol (49)

HPLC column: Chiralcel OD. Eluent: IPA/hexane (3:97), 1.0 mL/min. Results: t_r-(*S*) enantiomer (min) = 7.8 min, t_r-(*R*) enantiomer (min) = 12.2 min.

α-(Dimethylphenylsilyl)-cyclohexanemethanol (70)

HPLC column: Chiralcel OD. Eluent: IPA/hexane (1:400), 1.0 mL/min. Results: 11.1 min, 13.2 min. (absolute stereochemistry is not determined yet)

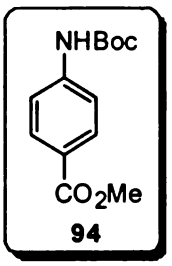
8.8. Designed and Synthesized a series of Novel *N*-Boc amines (Figure 17)



93

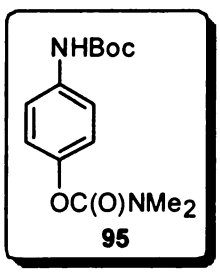
1,1-Dimethylethyl ester-[4-(acetylamino)phenyl]-carbamic acid

A mixture of 4'-aminoacetanilide (5.0 g, 33.3 mmol), Boc_2O (9.4 g, 43.3 mmol), $Zn(ClO_4)_2{\cdot}6H_2O$ (0.62 g, 1.66 mmol) in *t*-BuOH (50 mL) under nitrogen conditions was stirred for 20 h at 30 °C. The solvent was removed in *vacuo* and the residual solid was extracted with brine and CH_2Cl_2. The combined organics were washed with water and brine and then dried over $MgSO_4$. After filtration and evaporation, the residue was washed with ether and hexane to afford 2.02 g of the desired product as a white crystal (23%). ^{1}H NMR (500 MHz, DMSO) δ 9.76 (br s, 1 H), 9.18 (br s, 1 H), 7.45–7.30 (m, 4 H), 1.98 (s, 3 H), 1.45 (s, 9 H); ^{13}C NMR (125 MHz, DMSO) δ 167.7, 152.7, 134.6, 133.8, 119.4, 118.4, 78.7, 28.1, 23.7; IR (neat) 3426, 3334, 1695, 1660 cm^{-1}; HRMS (ESI+) (*m/z*) calcd for $C_{13}H_{18}N_2O_3$ $[M+Na]^+$ 273.1207, found 273.1215. The spectral data were consistent with literature values.[86]



Methyl 4-((*tert*-butoxycarbonyl)amino)benzoate

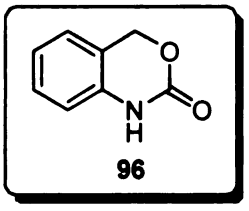
A mixture of methyl 4-aminobenzoate (5.0 g, 33.1 mmol), Boc_2O (9.3 g, 43.0 mmol), $Zn(ClO_4)_2{\cdot}6H_2O$ (0.61 g, 1.65 mmol) in CH_2Cl_2 (50 mL) under nitrogen conditions was stirred for 47.5 h at 30 °C. The solvent was removed in *vacuo* and the residual solid was washed with hexane and CH_2Cl_2. The desired product was purified by recrystalization using EtOAc/hexane to afford 3.01 g of the desired product as a white crystal (36%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.97–7.93 (m, 2 H), 7.43–7.39 (m, 2 H), 6.65 (s, 1 H), 3.86 (s, 3 H), 1.50 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 152.1, 142.6, 130.8, 124.4, 117.3, 81.2, 51.8, 28.2; IR (neat) 3408, 3331, 1711, 1597 cm^{-1}; HRMS (ESI+) (*m/z*) calcd for $C_{13}H_{17}NO_4$ $[M+Na]^+$ 274.1055, found 274.1049.



4-((*tert*-Butoxycarbonyl)amino)phenyl dimethylcarbamate[87]

To a solution of *N*-Boc-4-hydroxyaniline (1.5 g, 7.1 mmol) in pyridine (2.2 mL) was added dimethyl carbamyl chloride (0.85 mL, 9.3 mmol) at room temperature. The reaction mixture was stirred for 46.7 h at room temperature and dimethylcarbamyl chloride (0.85 mL, 9.3 mmol) and pyridine (3.0 mL) were added. The reaction mixture was warm to 50 °C and stirred for 21 h at the same temperature. The reaction was diluted with EtOAc and 1M HCl. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organics were washed with brine and dried over anhydrous $MgSO_4$. After filtration and evaporation, the residue was washed with hexane and purified by recrystalization using EtOAc/hexane. The material was dried over vacuum at 50 °C to afford 1.3 g of the desired product as a white

crystal (65%). mp = 182 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.5, 2 H), 7.03–6.99 (m, 2 H), 6.41 (br s, 1 H), 3.06 (s, 3 H), 2.98 (s, 3 H), 1.49 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 152.7, 146.8, 135.4, 122.0, 119.3, 80.4, 36.6, 36.4, 28.3; IR (neat) 3425, 3298, 1695, 1606 cm^{-1}; HRMS (ESI+) (*m/z*) calcd for $C_{14}H_{20}N_2O_4$ $[M+H]^+$ 281.1501, found 281,149.

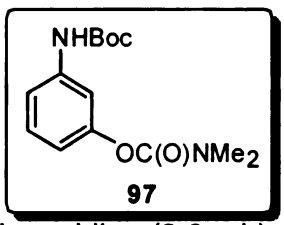


96

1,4-Dihydro-1-benzoxazin-2-one-2H-3[88]

To a solution of ethylchloroformate (3.1 mL, 3.5 g) and pyridine (2.6 mL, 32.5 mmol) in CH_3CN (35 mL) was added 2-aminobenzyl alcohol (4.0 g, 32.5 mmol). The reaction mixture was stirred for 17 h at room temperature and refluxed for 4.5 h. The solution was diluted with CH_2Cl_2 and brine. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organics were washed with brine and dried over anhydrous $MgSO_4$. After filtration and evaporation, the crude material was dissolved toluene (35 mL) and DBU (0.97 mL, 6.5 mmol) was added. The reaction mixture was refluxed for 2.4 h and the solvent was removed in vacuo. The residue was diluted with CH_2Cl_2 and brine. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organics were washed with brine and dried over anhydrous $MgSO_4$. After filtration and evaporation, the residue was washed with hexane and purified by recrystalization using CH_2Cl_2/hexane to afford 1.5 g of the desired product as a white crystal (31%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (br s, 1 H), 7.26–7.23 (m, 1 H), 7.11–7.09 (m, 1 H), 7.07–7.02 (m, 1 H), 6.79–6.76 (m, 1 H), 5.30 (s, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.1, 135.5, 129.2, 124.2, 123.3, 117.9, 114.0, 68.6; IR

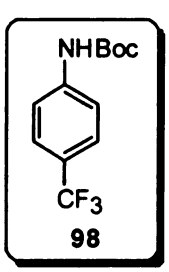
(neat) 1716 cm^{-1}; HRMS (ESI+) (*m/z*) calcd for $C_8H_8N_1O_2$ $[M+H]^+$ 150.0555, found 150.0549. The spectral data were consistent with literature values.[89]



97

3-((*tert*-Butoxycarbonyl)amino)phenyl dimehtyl-carbamate[88]

To a solution of *N*-Boc-3-hydroxyaniline (2.0 g, 9.5 mmol) in pyridine (3.0 mL) was added dimethyl carbamyl chloride (1.14 mL, 12.4 mmol). After stirring for 86 h at 50 °C, the reaction was diluted with EtOAc and 1M HCl. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organics were washed with brine and dried over anhydrous $MgSO_4$. After filtration and evaporation, the residue was washed with hexane and purified by recrystalization using EtOAc/hexane to afford 1.0 g of the desired product as a white crystal (40%). mp = 139 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (br s, 1 H), 7.2 (t, *J* = 8.14 Hz, 1 H), 7.01–6.98 (m, 1 H), 6.79–6.75 (m, 1 H), 6.47 (br s, 1 H), 3.05 (s, 3 H), 2.97 (s, 3 H), 1.48 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 152.4, 152.0, 139.2, 129.3, 116.3, 115.0, 112.1, 80.6, 36.6, 36.4, 28.3; IR (neat) 3308, 1707, 1612 cm^{-1}; HRMS (ESI+) (*m/z*) calcd for $C_{14}H_{20}N_2O_4$ $[M+H]^+$ 281.1501, found 281.1499.

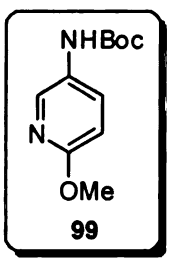


98

1,1-Dimethylethyl ester-N-[4-(trifluoromethyl)phenyl]-carbamic acid[90]

To a solution of 4-(trifluoromethyl)aniline (0.75 mL, 6.0 mmol) in dioxane (3 mL) added to a solution of NaOH (0.24 g, 6.0 mmol) in water (6 mL). The reaction mixture was cooled to 0 °C and a solution of Boc_2O (1.3 g, 6.0 mmol) in dioxane (3 mL) was added dropwise. After stirring for 43 h at

room temperature, the reaction mixture was cooled to 0 °C and solutions of NaOH (0.24 g, 6.0 mmol) in water (6 mL) and Boc_2O (1.3 g, 6.0 mmol) in dioxane (3 mL) were added. The reaction mixture was stirred 73 h at room temperature. The phases were separated and the organic layers were sequentially extracted with 1M HCl, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$, filtered and evaporated. The residue was washed with hexane to afford 584 mg of the desired product as a white crystal (37%). mp = 120 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.53–7.50 (m, 2 H), 7.46–7.43 (m, 2 H), 6.58 (br s, 1 H), 1.51 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3, 141.5, 126.2 (q, J = 3.8 Hz), 124.7 (q, J = 32.7 Hz), 124.2 (q, J = 271.3 Hz), 117.8, 81.2, 28.2. The spectral data were consistent with literature values.[91]

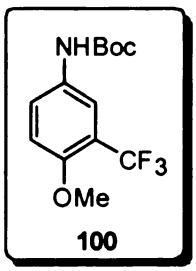


99

1,1-Dimethylethyl ester-N-(4-methoxyphenyl)-carbamic acid[92]

To a solution of 5-amino-2-methoxypyridine (2.0 g, 16.1 mmol) in dioxane (8 mL) was added to a solution of Boc_2O (4.5 g, 20.9 mmol) in dioxane (8 mL). The reaction mixture was stirred for 22 h at room temperature. The reaction mixture was sequentially extracted with 1M HCl, saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by silica gel column chromatography using from 100% CH_2Cl_2 to 100% acetone but the columned material contained impurity. After evaporation, the residue was purified by sublimation (0.2 atm, 85 °C) to afford 863 mg of the desired product as a white crystal (23%). mp = 81 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 2.7 Hz, 1 H), 7.79 (br s, 1 H), 6.60 (d, J = 8.8 Hz, 1 H), 6.30 (br s, 1 H), 3.87 (s, 3 H), 1.48 (s, 9

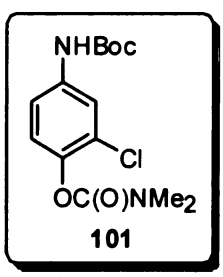
H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.5, 153.2, 137.5, 131.5, 128.9, 110.5, 80.7, 53.4, 28.2; IR (neat) 3325, 1726, 1701 cm^{-1}; HRMS (ESI+) (*m/z*) calcd for $C_{11}H_{16}N_2O_3$ $[M+H]^+$ 225.1239, found 225, 1240. The spectral data were consistent with literature values.[93]



100

1,1-Dimehtylethyl ester-[4-methoxy-3-(trifluoromethyl)-phenyl]carbamic acid[94]

To a solution of 5-methoxy-3-trifluromethyaniline (2.0 g, 10.4 mmol) in THF (7.5 mL) was added to Boc_2O (2.5 g, 11.5 mmol). The reaction mixture was refluxed overnight, cooled and the solvent was removed in vacuo. The residue was purified by silica gel column chromatography using EtOAc/hexane (1:9) to afford 2.8 g of the desired product as a white crystal (92%). mp = 138 °C; ^1H NMR (500 MHz, DMSO) δ 9.40 (br s, 1 H), 7.78 (s, 1 H), 7.59 (d, *J* = 8.3 Hz, 1 H), 7.16 (d, *J* = 9.0 Hz, 1 H), 3.81 (s, 3 H), 1.45 (s, 9 H); ^{13}C NMR (125 MHz, DMSO) δ 152.8, 151.9, 132.4, 123.5 (q, *J* = 272 Hz), 123.4 (br s), 116.6 (q, *J* = 29.9 Hz), 116.3 (br s), 113.4, 79.2, 56.1, 28.0; IR (neat) 3323, 1699 cm^{-1}. The spectral data were consistent with literature values.

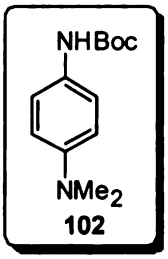


101

4-((tert-Butoxycarbonyl)amino)-2-chlorophenyl dimethyl-carbamate[88]

The reaction was carried out on 1,1-dimethylethyl ester-N-(3-chloro-4-hydroxyphenyl)-carbamic acid (2.0 mg, 8.2 mmol) as described in the preparation of 3-((*tert*-butoxycarbonyl)amino)phenyl dimethyl-carbamate except that the reaction mixture was stirred for 25 h at 70 °C. This modified protocol afforded 1.9 g of the desired product as a white crystal but it

contained impurity (74%). mp = 162 °C; ^{1}H NMR (500 MHz, DMSO) δ 7.55 (br s, 1 H), 7.15–7.05 (m, 2 H), 6.58–6.45 (m, 1 H), 3.11 (s, 3 H), 3.00 (s, 3 H), 1.49 (s, 9 H); ^{13}C NMR (125 MHz, DMSO) δ 154.2, 152.6, 142.5, 136.7, 127.0, 123.7, 119.8, 117.5, 80.5, 36.8, 36.4, 28.2; IR (neat) 3429, 3321,1718,1518 cm^{-1}; HRMS (ESI+) (*m/z*) calcd for $C_{14}H_{19}N_2O_4Cl$ $[M+H]^+$ 315.1112, found 315.1118.



102

1,1-Dimethylethyl ester-[4-(dimethylamino)phenyl]-carbamic acid[95]

To a solution of *N*-Boc-*p*-phenylene diamine (2.0 g, 9.6 mmol) in EtOAc (40 mL) was added formaldehyde (1.5 mL of 37% solution in water, 21.1 mmol) and 10% Pd/C (192 mg). The reaction mixture was hydrogenated at atmospheric pressure for 63 h. The reaction mixture was filtered and the solvent was evaporated. The residue was purified by silica gel column chromatography using EtOAc/hexane (3:7) to afford 513 mg of the desired product as a white solid (22%). mp = 98 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (br d, *J* = 7.7 Hz, 2 H), 6.67 (d, *J* = 8.9 Hz, 2 H), 6.23 (br s, 1 H), 2.87 (s, 6 H), 1.48 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.3, 147.4, 128.3, 120.7, 113.4, 79.8, 41.1, 28.3. The spectral data were consistent with literature values.[96]

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