BALANCING PROTECTION AND ACTIVATION: SILYL ETHERS AND DICOBALT COMPLEXES AS CONTROLLING ELEMENTS IN ORGANIC SYNTHESIS

By

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SILYL ETHERS AND DICOBALT COMPLEXES IN ORGANIC SYNTHESIS

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ABSTRACT

The tris(trimethylsilyl)silyl (sisyl) ether is photolabile, and possesses the potential to be used as a hydroxyl protecting group which can be photolytically cleaved selectively, in the presence of other silyl ethers. In order to compare its hydrolytic stability with that of a *t*-butyldimethylsilyl (TBS) ether, the rates of acidic hydrolysis of a series of sisyl and TBS ethers were determined under pseudo-first-order conditions. The sisyl ethers were found to be more hydrolytically stable in $CDCl_3$ containing *p*-TsOH·H_2O, but less hydrolytically stable in a AcOH/THF/H_2O solvent mixture.

The hydrolysis studies were extended to the corresponding series of alkoxyallyl-*t*-butylmethylsilanes, which were determined to be more hydrolytically stable than either the sisyl or the TBS ethers. The ability of the alkoxyallyl-*t*-butylmethylsilanes to function as both allylsilanes (undergoing silicon-carbon bond cleavage), and alkoxysilanes (undergoing silicon-oxygen bond cleavage), was examined under conditions that could lead to both processes. In the presence of Brønsted acids, silicon-oxygen bond cleavage occurred exclusively. Electrophilic substitution of the allyl group was only observed in the presence of the very sterically hindered triphenylcarbenium ion.

Allylsilanes were also originally envisioned as ideal nucleophilic partners for the development of a method of forming carbon-carbon bonds at the propargylic carbon atom of dicobalt-complexed acetylenic aldehydes or ketones, diastereoselectively. Allyl transfer onto racemic mixtures of chiral dicobalt pentacarbonyl(triarylphosphine)-

complexed acetylenic aldehydes, leading to the formation of the hexa-1,5-enyne system, was accomplished with modest diastereoselectivity.

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^{13}C NMR	Carbon Nuclear Magnetic Resonance Spectroscopy
CI	Chemical Ionization Mass Spectrometry
CCl_4	Carbon Tetrachloride
CO	Carbon Monoxide
d	Doublet (^1H NMR)
dd	Doublet of doublets (^1H NMR)
ddd	Doublet of doublets of doublets (^1H NMR)
DCM	Dichloromethane
DMF	Dimethylformamide
EI	Electron Impact Mass Spectrometry
+ve ES	Positive Mode Electrospray Mass Spectrometry
-ve ES	Negative Mode Electrospray Mass Spectrometry
h	Hour(s)
^1H NMR	Proton Nuclear Magnetic Resonance Spectroscopy
$h\nu$	Irradiation with Light
IR	Infrared Spectroscopy
J	Coupling Constant
m	Multiplet (^1H NMR)

min	Minute(s)
MS	Mass Spectrometry
m/z	Mass to Charge Ratio of an Ion (Mass Spectrometry)
ppm	Parts Per Million
s	Singlet (^{1}H NMR)
TBDMS	*tert*-Butyldimethylsilyl
TBMS	*tert*-Butylmethylsilyl
TMS	Trimethylsilyl
THF (-d_8)	Tetrahydrofuran (fully deuterated)
t	Triplet (^{1}H NMR)
TLC	Thin Layer Chromatography
UV	Ultraviolet
q	Quartet (^{1}H NMR)

PREFACE

This research was initiated by an interest in determining the degree of stability of the silicon-oxygen-carbon linkage of several alkoxysilanes to acid-catalyzed hydrolysis by varying the degree of steric bulk at both silicon and the alcohol carbon. The application of this "protecting group methodology" would allow one to control the hydrolytic cleavage of an alkoxy-bearing hydrophilic moiety from oligosiloxanes. This was extended to an examination of the relative reactivity of alkoxy and allyl groups bonded to the same silicon atom, since the allyl group provides a route for the introduction of oligosiloxanes via hydrosilylation. Chapter One contains an overview of the properties that affect the acid-catalyzed hydrolysis of silyl ethers, followed by a discussion of the observed rates of hydrolysis of several alkoxysilanes. Chapter Two contains an overview of the mechanism of electrophilic substitution of allylsilanes, followed by a discussion of the observed regioselectivity of reaction of several alkoxyallylsilanes with proton and carbon electrophiles.

Our studies on allylalkoxysilanes led to an interest in developing a methodology for stereoselective allyl transfer onto acetylenic carbonyl compounds for the preparation of 3,4-disubstituted-hexa-1,5-enyne systems. Allyl and crotylsilanes were originally envisioned as ideal nucleophilic organometallic reagents due to their ease of preparation, stability, and low toxicity. However, it was found that the more reactive allylstannanes were required to effect allyl transfer onto the desired dicobalt-complexed acetylenic aldehydes and ketones.

Chapter Three contains a description of the dynamic processes which are believed to occur in dicobalt-complexed acetylenic systems, and the methods that have been advanced to circumvent them, in order to achieve diastereoselectivity during carbon-carbon bond formation at the propargylic site. In this context, an overview of the approaches to achieving diastereoselectivity in the carbon-carbon bond forming reactions of allylsilanes with carbonyl compounds, has been included, although it has been placed in the introduction to Chapter Two. This was deemed more appropriate, as it follows a description of the mechanism and stereochemistry of allylic transposition onto electrophiles from allyl and crotylsilanes. The experimental results obtained from diastereoselective allyl transfer reactions between allyltributylstannane and chiral dicobalt-complexed acetylenic aldehydes are discussed in Chapter Three.

CHAPTER 1

THE HYDROLYTIC STABILITY OF TRIS(TRIMETHYLSILYL)SILYL ETHER, A PHOTOLABILE HYDROXYL PROTECTING GROUP

INTRODUCTION

1.1.1 Strategies for the Introduction and Removal of Silyl Groups

The silyl ether has become the most commonly used alcohol protecting group in organic synthesis due to its ease of formation and the selectivity with which it can be removed. Conversion of an alcohol to a silyl ether is typically carried out by addition of the corresponding chlorosilane to the alcohol in the presence of a base, as shown in equation (1).[1]

$$R_1R_2R_3SiCl + R_4OH + \text{Imidazole} \rightarrow R_1R_2R_3SiOR_4 + \text{Imidazole-HCl} \qquad (1)$$

As the steric bulk of the substituents bonded to silicon increases, the reactivity toward nucleophilic substitution at silicon decreases, and is reduced even further with increased steric bulk at the alcohol carbon atom.[2] This can be used to synthetic advantage for the selective protection of a less sterically hindered alcohol in the presence of a more hindered one.[3] An ordering of decreasing steric bulk at silicon of some of the more prevalent silyl groups was compiled and is given by:[4]

$(t\text{-Bu})_3Si > (t\text{-Bu})Ph_2Si > (i\text{-Pr})_3Si > (i\text{-Bu})_3Si > (n\text{-Bu})_3Si > (t\text{-Bu})Me_2Si > (n\text{-Pr})_3Si > (s\text{-Bu})Me_2Si > (i\text{-Pr})Me_2Si > (Et)_3Si > (\text{cyclopentyl})Me_2Si > (i\text{-Bu})Me_2Si > (Me_3Si)Me_2Si > (n\text{-Bu})Me_2Si > (Ph)_3Si > (Et)Me_2Si > (Ph)Me_2Si > Me_3Si$.

Figure 1 - 1: Ordering of Silyl Groups Based on Steric Bulk

Deprotection to regenerate the original alcohol can then be carried out either with a fluoride source such as tetrabutylammonium fluoride, or via acidic or basic hydrolysis. Both the electronic and steric properties of substituents influence the stability of silyl ethers to hydrolysis.[5] In general, electron donating groups bonded to either the silicon atom or the alcohol carbon atom, lead to an acceleration of the rate of acidic hydrolysis, whereas electron withdrawing groups have the opposite effect.

The hydrolytic stability is also proportional to the degree of steric hindrance at both silicon and the alcohol carbon atom, although the former has been shown to have a greater influence on the rate. The observed rate constants, obtained from acidic hydrolysis of a series of silyl ethers in a 45 % acetone-containing aqueous buffer solution, decreased by four orders of magnitude when a primary methyl group on silicon in compound **1** was replaced with the *tertiary*-butyl group to give compound **3**, as shown in **Figure 1 - 2**.[6] In contrast, the observed rate constant only decreased by one order of magnitude when the primary alkoxy group in compound **4** was replaced with the *tert*-butoxy group to give compound **6**, as shown in **Figure 1 - 2**.

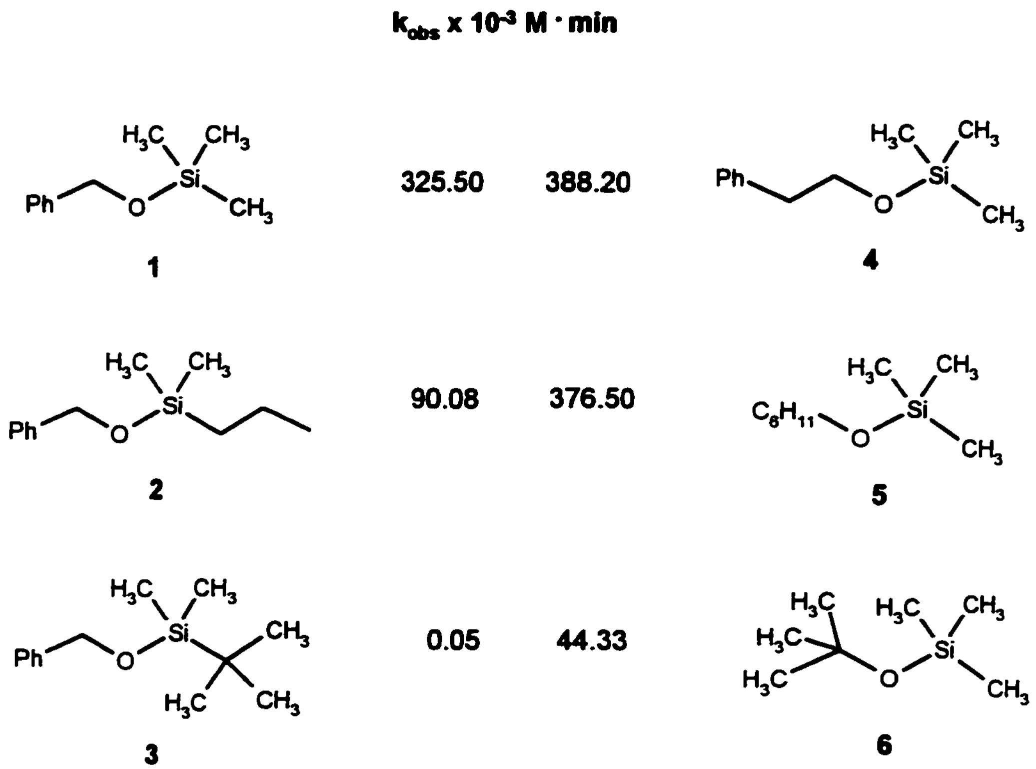


Figure 1 - 2: Hydrolysis of Silyl Ethers in a 45 % Acetone-Aqueous AcOH-AcONa Buffer Solvent Mixture

1.1.2 Quantitative Structure-Reactivity Relationships

In an attempt to separate and quantify the polar and steric effects of substituents for the purpose of correlating structure with reactivity of organic compounds, Taft derived the linear free energy relationship shown in equation (2).[7] This has a similar form to the Hammett equation, whereby the relative rate of two reactions can be correlated with the polar effect of a substituent.[8] The Taft equation (3) is an extension of equation (2) with an additional term, E_s, corresponding to the steric effect of a substituent, for those reaction series where both electronic and steric effects influence the rate.[9]

$$\log (k/k_o) = \sigma^*\rho^* \tag{2}$$

$$\log (k/k_o) = \sigma^*\rho^* + \delta E_s \tag{3}$$

The definition of the polar substituent constant σ^* is given in equations (6) and (7), which were obtained from equations (4) and (5):

$$\log (k/k_o)_b = \sigma^*\rho^*_b + \delta E_{s,b} \tag{4}$$

$$\log (k/k_o)_a = \sigma^*\rho^*_a + \delta E_{s,a} \tag{5}$$

$$[\log (k/k_o)_b - \log (k/k_o)_a] = \sigma^*\rho^* \tag{6}$$

$$[\log (k/k_o)_b - \log (k/k_o)_a]\ 1/\rho^* = \sigma^* \tag{7}$$

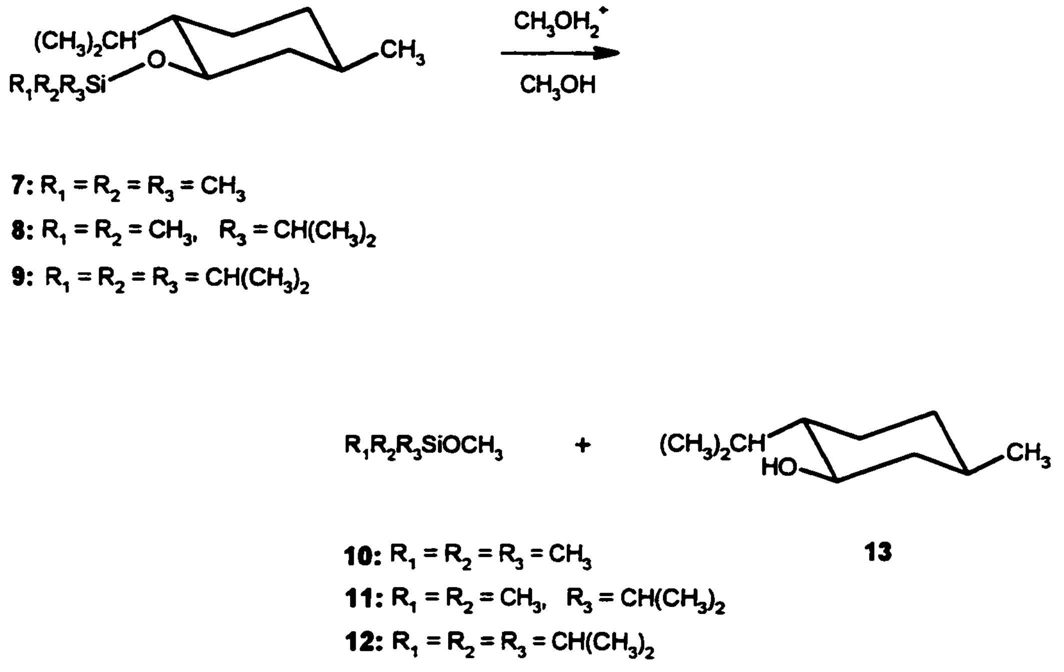
The term $(k/k_o)_b$ in equation (4) was proposed to be a measure of the steric and polar effects of a substituent X under alkaline hydrolysis of aliphatic esters of the type XCOOR, relative to the reference compound CH_3COOR. Values of σ^* and E_s were defined to be zero for CH_3. The term $(k/k_o)_a$ in equation (5) was proposed to be a measure of only the steric effect of the substituent X under acidic hydrolysis of the esters XCOOR, also relative to CH_3COOR. The assumption was made that the term $\sigma^*\rho^*_a$ corresponding to acidic hydrolysis of the aliphatic esters XCOOR was negligible. This was based on the small values of ρ reported by Hammett for acidic hydrolysis of aromatic esters, as compared with the much larger values of ρ reported for alkaline hydrolysis of aromatic esters. The difference between the expressions for $(k/k_o)_b$ and $(k/k_o)_a$ was used to define the polar effects as shown in equations (6) and (7), based on a further assumption that the steric effects under acidic and basic hydrolysis were equivalent, that is, $\delta E_{s,b} = \delta E_{s,a}$. The substituent constants σ^*, so derived, could then be used with equation (3) to correlate a difference between two reaction rates with a change in the overall steric environment caused by changing one of the substituents on the reference compound.

A linear relationship was found to exist between log (k/k_o) - obtained from rate constants for acidic solvolysis of a number of silanes possessing substituents of similar steric bulk, but different polar effects - and Taft substituent constant σ^* values. The reaction is depicted in equation (8).[10]

$$R_1R_2R_3SiH + R_4OH_2^+ + R_4OH \rightarrow R_1R_2R_3SiOR_4 + H_2 + R_4OH_2^+ \tag{8}$$

Based on this empirical relationship for substitution reactions of alkylsilanes, where the only variable is change of the substituents bonded to silicon, deviations from linearity can be attributed to steric effects. These steric effects can then be quantified with the use of Taft's equation (3).

Sommer and coworkers used the Taft equation (3) to assess the steric effect of substituents at silicon on the rates of acidic methanolysis of trialkylsilyl ethers, where (-)-menthoxytrimethylsilyl ether 7 served as the reference compound (**Figure 1 - 3**).[11]



7: $R_1 = R_2 = R_3 = CH_3$
8: $R_1 = R_2 = CH_3$, $R_3 = CH(CH_3)_2$
9: $R_1 = R_2 = R_3 = CH(CH_3)_2$

10: $R_1 = R_2 = R_3 = CH_3$
11: $R_1 = R_2 = CH_3$, $R_3 = CH(CH_3)_2$
12: $R_1 = R_2 = R_3 = CH(CH_3)_2$

13

Figure 1 - 3: Hydrolysis of Silyl Ethers in MeOH Containing a Pyridine-Pyridine Hydrochloride Buffer System

The rate constants of methanolysis of the reference compound 7 and compound **8** were obtained. These values along with the Taft substituent constant $\sigma^* = -0.19$ for isopropyl, $\delta = 1.0$, and the reaction constant $\rho^* = -1.20$ for acidic methanolysis of the (-)-menthoxysilyl ethers (which had been previously determined) were substituted into equation (3) to calculate a value of -2.17 for the steric substituent constant E_s of an isopropyl group. This value represents a relative measure of the increase in steric hindrance upon replacing a methyl group on silicon in compound 7 with an isopropyl group, leading to an attenuation of the rate of reaction. A similar calculation using the rate constant of methanolyis of the triisopropylsilyl ether **9** yielded a value of $E_s = -6.57$. Since this relates to three isopropyl groups, division by three gives a value of $E_s = -2.19$

for a single isopropyl group. Thus, a comparison of the value of E_s corresponding to replacement of one methyl group by an isopropyl group, with that corresponding to replacement of all three methyl groups by isopropyl groups, reveals that the steric effects of the substituents on silicon have a nearly-quantitative additive effect on the rate of acidic methanolysis.

1.1.3 Mechanism of Acidic Hydrolysis of Silyl Ethers

The actual mechanism of nucleophilic substitution at silicon that occurs during hydrolysis remains elusive, and the subject of much controversy. Nevertheless, detailed kinetic studies of the alcoholysis of silyl ethers carried out by Dietze and co-workers, provide some insight for an understanding of the mechanism itself, and the properties which affect the rate of reaction.

Pseudo-first-order rate constants were obtained for the trifluoroethanolysis of dimethylphenylphenoxysilane in trifluoroethanol containing either an acidic or a basic buffer system.[12] From the rate constants obtained in different buffer concentrations, it was determined that both general acid catalysis and general base catalysis were operational. Thereby, these researchers concluded that trifluoroethanolysis proceeded through an S_N2-like mechanism where bond formation to the attacking solvent molecule occurred simultaneously with cleavage of the silicon-oxygen leaving group bond. During this process, the acid catalyst participated by donating a proton to the leaving group, while the base catalyst abstracted a proton from the attacking solvent molecule, as shown in **Figure**

1 - 4. Such a mechanism is consistent with the well-documented dependence of the rate of hydrolysis on the steric crowding at silicon.

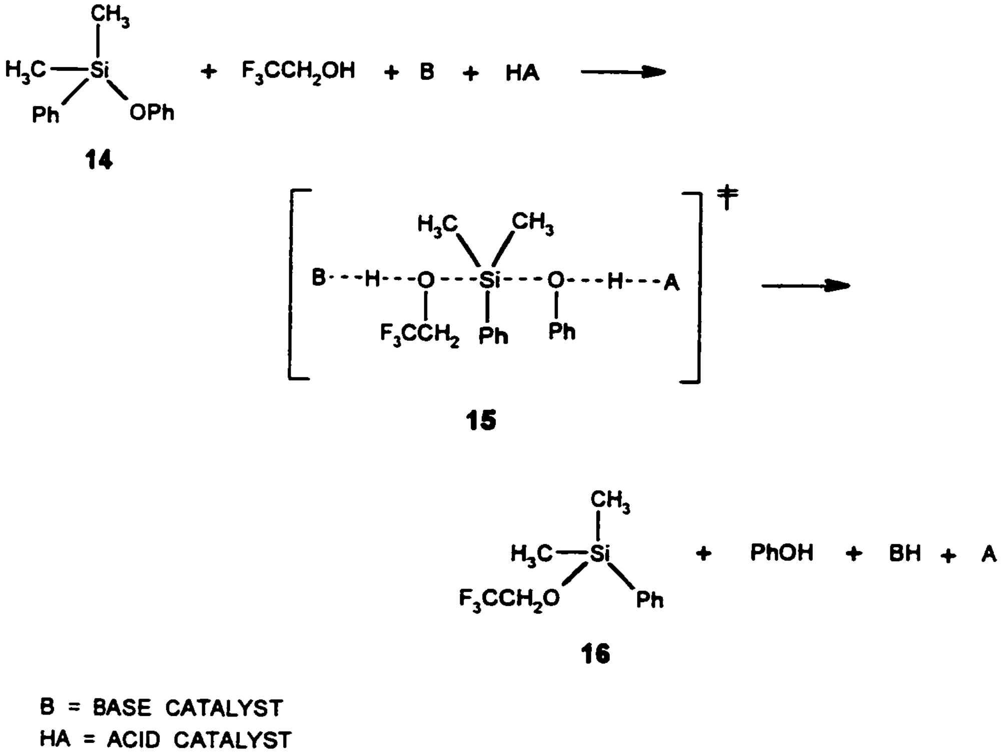
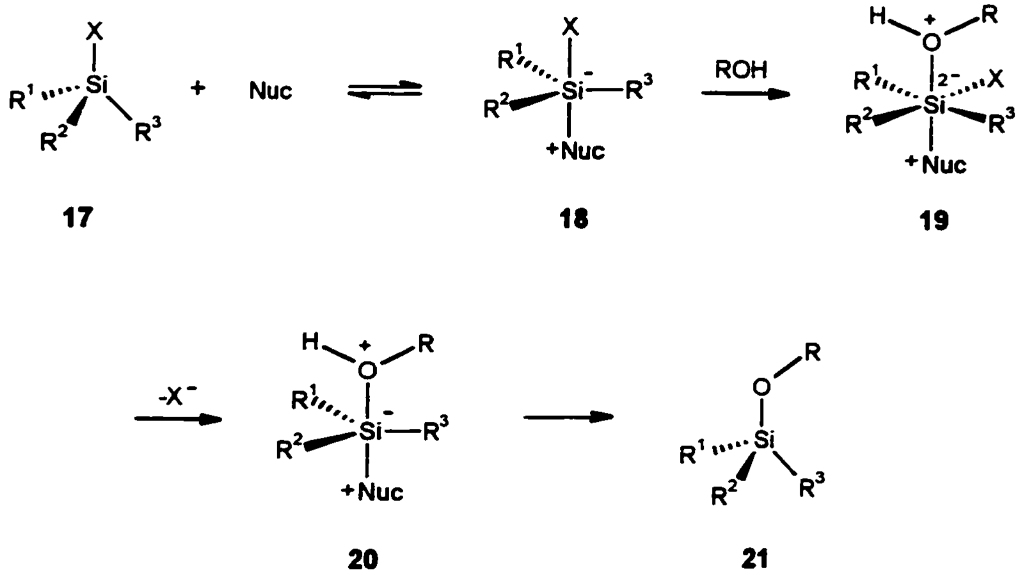


Figure 1 - 4: Mechanism of Hydrolysis Proposed by Dietze and Co-workers

Corriu and coworkers proposed a different mechanism for hydrolysis and alcoholysis of methyl-1-naphthylphenylchlorosilane in aprotic solvents including anisole.[13] These reactions were activated by the presence of nucleophiles such as HMPA, DMSO and DMF.[14] The mechanism is believed to involve rapid and reversible attack by a molecule of nucleophile to form a pentacoordinate intermediate **18**, followed by rate-determining attack of an alcohol molecule at an extracoordinate silicon species, as shown in **Figure 1 - 5.**[15] An acceleration of rate was found in solvents of increased polarity such as THF, which were shown to allow more rapid formation of the pentacoordinate species.[16] A decrease in the rate of reaction was also observed with increased steric crowding at silicon.[17]



X = Cl
Nuc = DMSO, HMPA, DMF

Figure 1 - 5: Mechanism of Hydrolysis Proposed by Corriu and Co-workers

Both of the mechanisms advanced by Dietze and Corriu involve nucleophilic substitution at silicon proceeding through rate-determining addition of an alcohol molecule to silicon. While Dietze's mechanism describes conditions that allow hydrogen bonding to participate, Corriu's mechanism relates the ease of substitution at silicon to its ability to form an extracoordinate species, under conditions in which the extent of hydrogen bonding is limited by the concentration of alcohol present in the medium. Although a vast number of reports have appeared in the literature concerning the mechanism of nucleophilic substitution at silicon, these two studies have been emphasized here since they most closely resemble the experimental conditions used in this study for hydrolysis of silyl ethers.

1.1.4 Alternative Strategies for Deprotection of Silyl Ethers

Since the first report of its application in masking a hydroxyl group,[18] the *tert*-butyldimethylsilyl group has become the most frequently utilized member of the repertoire of silanes for the protection of alcohols, and its cleavage by acidic hydrolysis has become the paradigm of silyl ether deprotection methodology. A large number of silyl groups that differ in the structure of the substituents bonded to silicon were later introduced, taking advantage of the additive nature of the steric effects of groups at silicon, to span a broad range of stability to acidic hydrolysis (see **Figure 1 - 1**).

This has allowed for two or more different silyl groups to be used as alcohol protecting groups within the same molecule. Strategies for the selective deprotection of one silyl ether in a molecule which also contains a different silyl ether, have been predominantly based on placement of the more hydrolytically labile silyl ether at the alcohol which is to be deprotected first, during the synthetic sequence.[19] The extensive series of silanes available allows for selection of groups whose hydrolytic stability varies considerably, when a small number of different silyl ethers are to be present within the same molecule. However, utilization of many different silyl ethers within the same molecule becomes problematic when the combined effects of the steric environment at both silicon and the alcohol carbon atom lead to more subtle differences in hydrolytic susceptibility, and decreased selectivity of deprotection. Thus, there is a need for methods that override the general trends of hydrolysis rates based on steric bulk.

The photolytic cleavage of silyl ethers provides an alternative approach to selective deprotection that does not rely on steric bulk for discrimination between silyl groups, and which has received little attention.[20] It has been observed that photolysis of trisilanes, oligosilanes or polysilanes, can give rise to silyl radicals via homolytic silicon-silicon bond cleavage, or extrusion of silylenes (the silicon analogues of carbenes).[21] The formation of silylenes from the tris(trimethylsilyl)silyl ether of methanol was inferred from the products recovered in the presence of 1,3-butadiene as a trapping agent, as shown in **Figure 1 - 6**.[22]

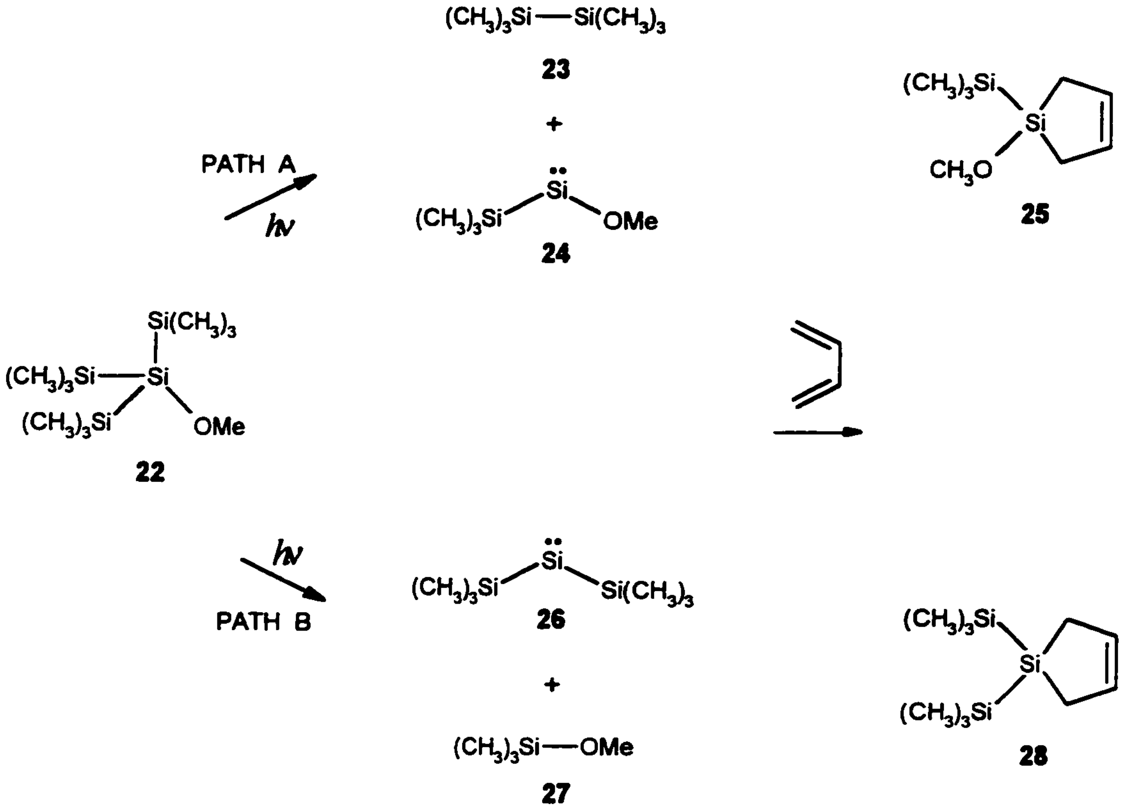


Figure 1 - 6: Photolytic Extrusion of Silylenes from Tris(Trimethylsilyl)Silyl Ether

RESEARCH PROPOSAL

The tris(trimethylsilyl)silyl (sisyl) group was predicted to function as a photolabile alcohol protecting group based on the known cleavage pathways of silicon-silicon bonds. The preparation of sisyl chloride would allow for the formation of sisyl ethers from alcohols by typical methods. Photolytic cleavage of the sisyl ethers would then give rise to a hydrolytically more labile silyl ether upon insertion of either of the two silylenes, formed via Path A and Path B shown in **Figure 1 - 6**, into the hydrogen-oxygen bond of an alcohol molecule present in solution. Finally, regeneration of the original alcohol would occur under very mild conditions.

In order to determine whether the sisyl group could be cleaved selectively by photolysis while remaining stable to conditions that are employed to cleave commonly used alcohol protecting groups, the hydrolytic stability of the sisyl ether of a primary, benzylic and secondary alcohol under aqueous acidic conditions was studied. Its hydrolytic stability under acidic conditions was compared with that of the corresponding *tert*-butyldimethylsilyl (TBDMS) ethers in both protic and aprotic solvents.

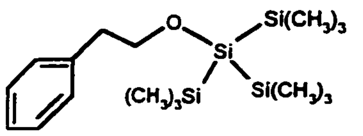
RESULTS

1.2.1 Synthesis of Silyl Ethers

Tris(trimethylsilyl)silyl chloride was prepared from tris(trimethylsilyl)silane by stirring in CCl_4 according to a procedure established by Bürger and coworkers.[23] Sisyl ethers of the primary and secondary alcohols (**29** - **31**) shown in **Figure 1 - 7** were then prepared by the reaction of sisyl chloride with the alcohol in the presence of imidazole in DMF or 4-dimethylaminopyridine in CH_2Cl_2. Although attempts to prepare the ether of a tertiary alcohol were unsuccessful, this is a common problem of sterically hindered alcohols that can usually be overcome with the use of the more reactive silyltriflate, rather than the chlorosilane.[24]

The corresponding *t*-butyldimethylsilyl (TBDMS) ethers (**32** - **34**) were prepared from the same alcohols to allow comparison of the sisyl ethers. In addition, the allyl-*t*-butylmethylsilyl (allyl-TBMS) ethers of these alcohols (**35** - **37**) were prepared from allyl-*t*-butylchloromethylsilane.

SISYL ETHER SERIES:



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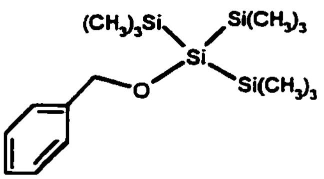

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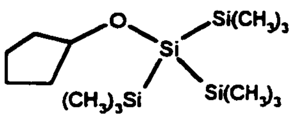

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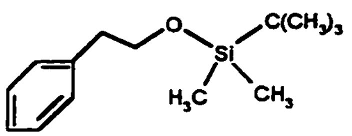
TBDMS ETHER SERIES:



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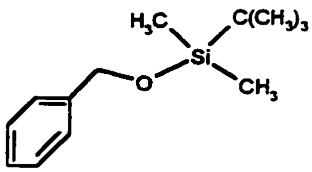

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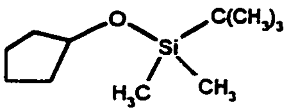

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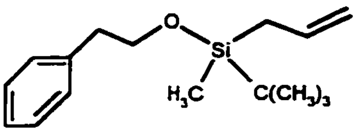
ALLYL-TBMS ETHER SERIES:



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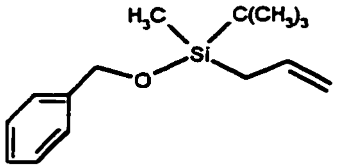

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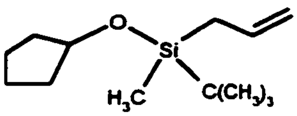

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Figure 1 - 7: Silyl Ethers Prepared for Rate Studies

1.2.2 Acidic Hydrolysis in a Protic Medium

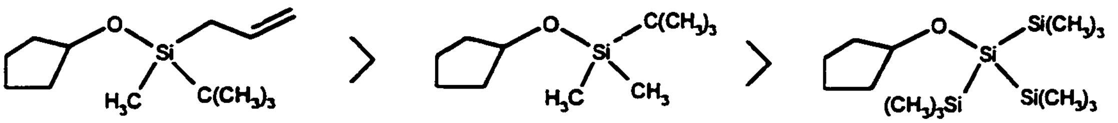
In order to determine the hydrolytic stability of the sisyl group relative to that of the TBDMS group, the rates of acid-catalyzed hydrolysis of both the sisyl and TBDMS ethers were measured. A modification of the procedure established by Corey and co-workers,[18] which employed an aqueous solution of THF and acetic acid, was found suitable to allow hydrolysis of all the compounds to occur within a 12 hour period. Rate constants were obtained under pseudo-first-order conditions wherein both CD_3CO_2D and D_2O were in large excess. Loss of the silyl ether was monitored over time using ^1H NMR, and the concentrations of products and starting material were determined by integrating the peaks corresponding to each. The observed rate constants, k_{obs}, were then calculated from a least squares linear regression analysis of silane concentration *versus* time data.

In all cases, hydrolysis led to regeneration of the original alcohol and the silanol (or disiloxane). The ^1H and ^{13}C NMR spectra were compared before and after addition of an authentic sample of the appropriate alcohol to the reaction mixture to confirm its formation. The observed rate constants for hydrolysis of the sisyl, TBDMS and allyl-TBMS ethers are given in **Table 1 - 1**.

Table 1 - 1. Observed Rate Constants (k_{obs}) and Correlation Coefficients (r) for Acidic Hydrolysis of Silyl Ethers $R_1OSiR_2R_3R_4$

$R_1OSiR_2R_3R_4$	k_{obs}	r
$PhCH_2CH_2OSi(Si(CH_3)_3)_3$	$(3.74 \pm 0.20) \times 10^{-2}\ s^{-1}$	0.98
$PhCH_2OSi(Si(CH_3)_3)_3$	$(1.94 \pm 0.06) \times 10^{-2}\ s^{-1}$	0.99
$C_5H_9OSi(Si(CH_3)_3)_3$	$(1.30 \pm 0.05) \times 10^{-2}\ s^{-1}$	0.99
$PhCH_2CH_2OSi(CH_3)_2t$-Bu	$(6.04 \pm 0.13) \times 10^{-3}\ s^{-1}$	0.99
$PhCH_2OSi(CH_3)_2t$-Bu	$(3.53 \pm 0.03) \times 10^{-3}\ s^{-1}$	0.99
$C_5H_9OSi(CH_3)_2t$-Bu	$(3.49 \pm 0.05) \times 10^{-3}\ s^{-1}$	0.99
$PhCH_2CH_2OSi(CH_3)(CH_2CH{=}CH_2)t$-Bu	$(2.94 \pm 0.03) \times 10^{-3}\ s^{-1}$	0.99
$PhCH_2OSi(CH_3)(CH_2CH{=}CH_2)t$-Bu	$(1.11 \pm 0.02) \times 10^{-3}\ s^{-1}$	0.99
$C_5H_9OSi(CH_3)(CH_2CH{=}CH_2)t$-Bu	$(8.26 \pm 0.12) \times 10^{-4}\ s^{-1}$	0.99

The decreasing rate found on proceeding from compounds **29** to **31**, **32** to **34**, and **35** to **37**, is consistent with the previously reported correlation of decreased rate of acidic hydrolysis with increased steric bulk at the alcohol carbon, for each of the sisyl, TBDMS, and allyl-TBMS ether series.[5] A comparison of the three secondary alcohols (where the steric bulk at the alcohol carbon is kept constant) reveals that the decreasing order of hydrolytic stability is given by allyl-TBMS > TBDMS > sisyl ether, as shown in **Figure 1 - 8**. This order is also found for the primary and benzylic alcohols.



37 **34** **31**

k_{obs} = 8.26×10^{-4} s^{-1} 3.49×10^{-3} s^{-1} 1.30×10^{-2} s^{-1}

Figure 1 - 8: Hydrolytic Stability of Different Silyl Groups Derived from Cyclopentanol, in CD_3CO_2D/D_2O/THF

Electronic as well as steric perturbations of the substituents bonded to silicon in silyl ethers have been reported to affect the rate of acidic hydrolysis, and both factors are expected to have influenced the rates of hydrolysis of compounds **29** to **37**. Since the individual contributions of the electronic and steric effects on the rates cannot be quantified based on the results obtained, some simplifying assumptions must be made in order to draw conclusions regarding the relative reactivity of the three different silyl ethers within each of the primary, benzylic and secondary alcohol series.

1.2.3 Steric Effects of the Three Different Silyl Groups

The methyl, *tert*-butyl, allyl and trimethylsilyl groups have all been classified as inductive electron donor substituents according to the Hammett σ_m and Taft σ^* substituent series. Since electron-donating groups on silicon have been shown to accelerate the rate of acidic hydrolysis, the electronic effects of the substituents bonded to silicon in compounds **29** to **37** are expected to have influenced the reaction in the same direction, that is, rate enhancement. Furthermore, the hydrolytic stability of trialkylsilyl ethers derived from the same alcohol is known to parallel the steric bulk around the silicon nucleus. If the simplifying assumption is initially made that the magnitude of the electronic effects on the rate is smaller than the magnitude of the steric effects, then based on the observed reactivity order, we arrive at the conclusion that the central silicon atom in sisyl ethers must be more accessible to nucleophilic attack than the silicon atom in either TBDMS or allyl-TBMS ethers.

An analysis of the Taft linear free energy relationship shown in equation (3) provides indirect evidence in support of this last point.

$$\log (k/k_o) = \sigma^*\rho^* + \delta E_s \qquad (3)$$

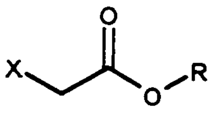
Based on values of the steric substituent constant E_s calculated from rates of acid-catalyzed methanolysis of trialkylsilyl ethers of the secondary alcohol (-)-menthol, the argument was put forth by Sommer and co-workers that the steric effects of alkyl substituents bonded to silicon have a nearly-quantitative additive effect on the rates of methanolysis. Hence, the total steric effect of all three substituents on silicon in the sisyl, TBDMS and allyl-TBMS ethers can be compared by calculating a value for E_s for each of the silyl ethers in a similar manner. With the trimethylsilyl ether of cyclopentanol serving as a reference compound, the steric effect of replacing one methyl group with a *tert*-butyl group can be estimated from a calculated value of E_s. Similarly, the steric effect of replacing two methyl groups with one *tert*-butyl and one allyl group, and the effect of replacing all three methyl groups with trimethylsilyl substituents, can be estimated from calculated values of E_s.

As the trimethylsilyl and *tert*-butyldimethylsilyl groups correspond to low steric hindrance and high steric hindrance at silicon, respectively, the TMS and TBDMS ethers of several alcohols were prepared in order to compare the hydrolytic stability of the sisyl and allyl-TBMS ethers. The TMS ethers were hydrolyzed too quickly to obtain proper rate data under the reaction conditions employed for acidic hydrolysis of compounds **29** to **37**, and are not reported in **Table 1 - 1**. However, it was found that their rate of hydrolysis was at least twice the value of that of the analogous sisyl ethers. Thus, for cyclopentanoxytrimethylsilane, the pseudo-first-order rate constant was taken to be 2.60 x 10^{-2} s^{-1} (2 x k_{obs} (**31**)). The reaction constants δ and ρ^* were both arbitrarily assigned a value of -1.0. Even though the exact value of ρ^* for this reaction series did not need to be known as it was used to calculate relative values of E_s, a value of -1.0 is not unreasonable when compared to the value of $\rho^* = -1.2$ obtained by Sommer and co-workers for the acidic methanolysis of menthoxysilyl ethers.

The substituent constants were obtained from the Taft σ_I scale, which was originally defined as given in equation (9) where $\sigma^*_{XCH_2}$ corresponds to hydrolysis of the esters **38** shown in **Figure 1 - 9**, and σ' corresponds to the bicyclo[2.2.2]octane system **39**.[25] The scaling factor of 0.450 was calculated from experimental values of both $\sigma^*_{XCH_2}$ and σ', and reflects the attenuation of inductive effects as a result of the intervening methylene group of **38**.

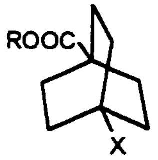
$$\sigma_I = (0.450)\sigma^*_{XCH_2} = \sigma' \qquad (9)$$

Although the bicyclo[2.2.2]octane system is regarded as an excellent measure of the inductive effect of substituents X relative to the reference compound having X = H, the range of the scale has been limited by the difficulty of synthesizing derivatives with different X groups. By contrast, the σ_I scale has the advantage of being more comprehensive, so σ_I values for *tert*-butyl (-0.07), trimethylsilyl (-0.12) and allyl (-0.14) were used to determine steric parameters E_s, as described below.



38

$\sigma^*_{XCH_2}$



39

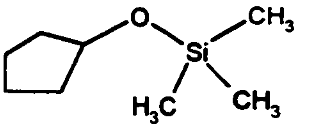
σ'

Figure 1 - 9: Reference Compounds for Determination of Polar Substituent Constants

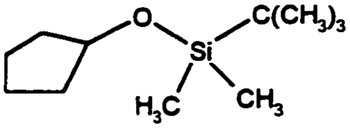
1.2.4 Calculation of Steric Effects of the Silyl Groups

The increase in steric hindrance at silicon experienced during hydrolysis upon replacing one of the methyl groups of cyclopentanoxytrimethylsilane with a *tert*-butyl group, giving compound **34**, is represented by the value of E_s = -0.94 calculated according to equations (10) to (12). This reflects the total steric effect of all three substituents on silicon. A value of E_s = -0.66 was calculated for the replacement of all three methyl groups of cyclopentanoxytrimethylsilane with trimethylsilyl groups, giving compound **31**, as shown in equations (13) to (15). In a similar manner, E_s = -1.71 was calculated according to equations (16) to (18) for the replacement of two methyl groups with one *tert*-butyl and one allyl group, giving rise to compound **37**. Since an increase in the magnitude of the E_s value reflects an increase in steric effects, a decreasing order of steric crowding at silicon based on E_s values calculated in equations (10) to (18) is given by **37** > **34** > **31**. Thus, if hydrolytic stability under acidic conditions were governed primarily by steric effects, the decreasing order of stability would be given by **37** > **34** > **31**, which is exactly what is observed experimentally, as shown in **Figure 1 - 8**.

*Replacement of One Si-CH_3 In **40** With $C(CH_3)_3$:*



40



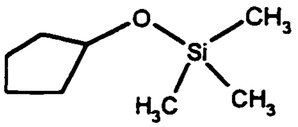
34

$$\log(\mathbf{34}/\mathbf{40}) = \sigma'_{(t\text{-Butyl})}\rho^* + \delta E_s \qquad (10)$$

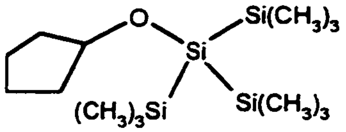
$$\log(3.49 \times 10^{-3}/2.60 \times 10^{-2}) = (-0.07)(-1.0) + E_{s(t\text{-Butyl})} \qquad (11)$$

$$-0.94 = E_{s(t\text{-Butyl})} \qquad (12)$$

Replacement of All Three Si-CH_3's With Si$(CH_3)_3$:[26]



40



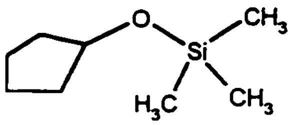
31

$$\log(\mathbf{31}/\mathbf{40}) = \rho^{*}\Sigma\sigma'_{(TMS)} + \delta E_s \qquad (13)$$

$$\log(1.30 \text{ x } 10^{-2}/2.60 \text{ x } 10^{-2}) = (-1.0)(3)(-0.12) + E_{s(TMS)} \qquad (14)$$

$$-0.66 = E_{s(TMS)} \qquad (15)$$

Replacement of Two Si-CH_3's With One $C(CH_3)_3$ and One $CH_2CH{=}CH_2$:



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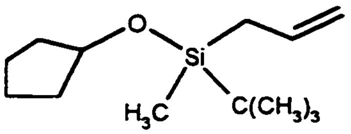


37

$$\log(\mathbf{37}/\mathbf{40}) = \rho^{*}[\sigma'_{(t\text{-Butyl})} + \sigma'_{(Allyl)}] + \delta E_s \qquad (16)$$

$$\log(8.26 \text{ x } 10^{-4}/2.60 \text{ x } 10^{-2}) = (-1.0)[(-0.07) + (-0.14)] + E_{s(t\text{-Butyl + Allyl})} \qquad (17)$$

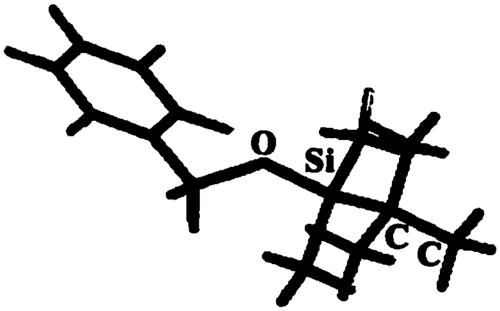
$$-1.71 = E_{s(t\text{-Butyl + Allyl})} \qquad (18)$$

1.2.5 Calculation of Volume and Examination of Steric Crowding at Silicon

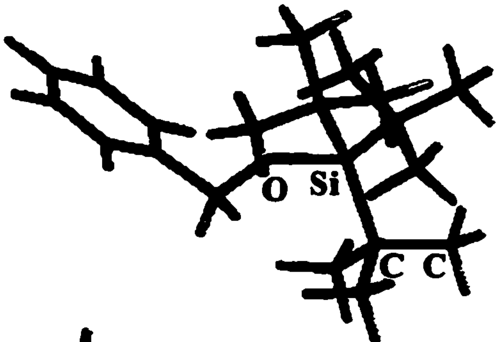
An inspection of the volumes of the sisyl and TBDMS ethers could provide clues about the differences in the steric environment of the two different silyl ethers. The volume of compounds **33**, **30** and 1-(tris(*tert*-butyl)silyl)benzyl alcohol **41** were calculated after conformational analyses were carried out using the Merck Molecular Force Field (MMFF94).[27] Compound **41** is structurally similar to **30**, with the exception that the external silicon atoms in the latter have been replaced with carbon atoms in the former. The structures **33**, **41** and **30**, and their calculated volumes of 294, 414 and 450 Å^3 respectively, are shown in **Figure 1 - 10**.

The difference in volume between **33** and **41** corresponds to the increased number of methyl groups that comprise the three *tert*-butyl substituents of the latter, as compared with the two methyl and one *tert*-butyl substituents of the former. By contrast, the increased volume of **30** as compared with **41** cannot be attributed solely to the replacement of quaternary carbon atoms in **41** with silicon atoms. Two differences between these structures are noteworthy. Firstly, the silicon-silicon bond length of 2.39 Å in **30** is greater than the silicon-carbon bond length of 1.97 Å in **41**. Secondly, the silicon-carbon bond length of 1.88 Å in **30** is greater than the carbon-carbon bond length of 1.56 Å in **41**. Both of these features place the bulky trimethylsilyl substituents of **30** at a farther distance than the bulky *tert*-butyl substituents of **41** from the central silicon atom. Therefore, the central silicon atom of **30** is expected to be more accessible to nucleophilic attack than the silicon atom of **41**. This can be extended to a comparison of **30** and **33**,

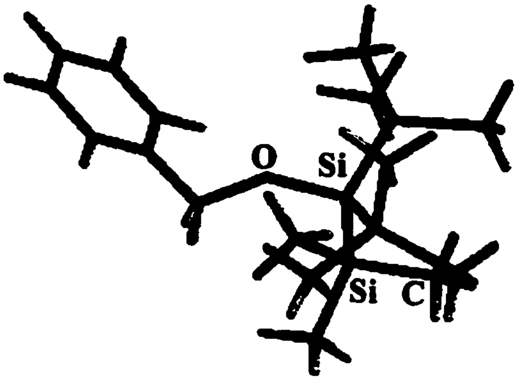
30 and 33, whereby the central silicon atom in 30 is also expected to be less sterically hindered and more accessible to nucleophilic attack than the silicon atom in 33.



33
V = 294 Å^3



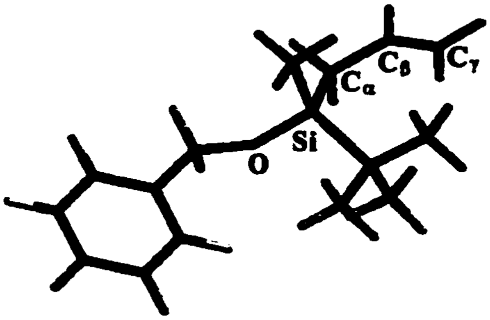
41
V = 414 Å^3



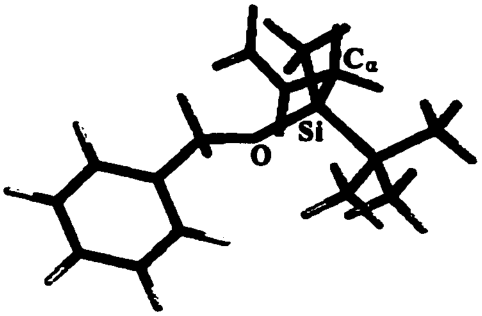
30
V = 450 Å^3

Figure 1 - 10: Calculated Volumes (V) for Structures 30, 33 and 41

A similar conformational analysis and volume calculation was carried out for compound **36**, yielding a value of 328 Å^3, shown in **Figure 1 - 11**. Whereas the accessibility of the silicon atom to nucleophiles in compound **33** should be unaffected by rotation about any of the silicon-carbon bonds, this does not hold true for compound **36**. Rotation about the silicon-carbon bond corresponding to the allylic substituent of **36** (labeled Si-C$_\alpha$) gives rise to a conformation depicted as **36'** in **Figure 1 - 11**. This illustrates the additional factor in **36**, which contributes to steric crowding at silicon, namely, its conformation.



36
V = 328 Å



36'

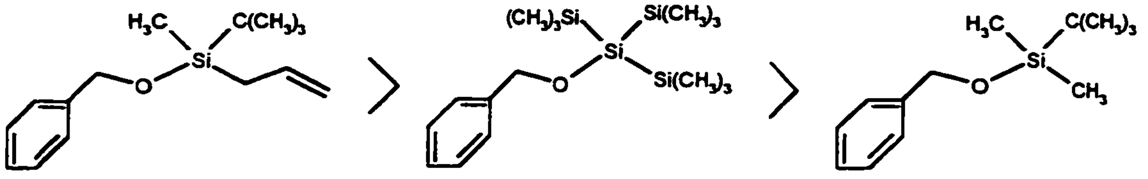
Figure 1 - 11: Calculated Volume (V) for Structure 36

Based on calculations of the volumes and the steric parameters E_s, the decreasing order of steric crowding at silicon is given by allyl-TBMS > TBDMS > sisyl ethers. That this order parallels the decreasing order of hydrolytic stability found with all three alcohol series under protic conditions, leads to the conclusion that the reactivity in a protic medium was determined primarily by steric effects.

1.2.6 Acidic Hydrolysis in Aprotic Solvent

The tremendous utility of silyl ethers in synthetic organic chemistry as alcohol protecting groups has been unparalleled due to the breadth of their stability towards hydrolysis, a chemical property which can be controlled to a large extent, through selection of the substituents bonded to silicon. This has allowed for the selective hydrolysis of a particular silyl ether in the presence of one or more different silyl ethers in the same molecule, simply by controlling experimental conditions. As such, it was of interest to compare the rates of hydrolysis of compounds **29** to **37** in a non-polar solvent that would be more representative of the medium that is often required to dissolve large organic molecules.

When the rates of hydrolysis of compounds **30**, **33** and **36** were measured using *p*-toluenesulfonic acid in $CDCl_3$, the decreasing order of hydrolytic stability was found to be allyl-TBMS > sisyl > TBDMS ether as shown in **Figure 1 - 12** for benzyl alcohol. Although rate constants could not be measured under pseudo-first-order conditions due to the low solubility of *p*-toluenesulfonic acid in $CDCl_3$, the relative rates of hydrolysis of **33**, **30** and **36** were determined to be 2.5, 0.9 and 0.8 (x 10^{-4}) mol L^{-1} min^{-1}, respectively. This surprising reversal of reactivity between the sisyl and TBDMS ethers, and the smaller difference in rates found when the medium was changed from the protic aqueous-THF mixture to aprotic chloroform, warrants closer examination of the previous inferences regarding steric and electronic effects.



36 **30** **33**

Figure 1 - 12: Hydrolytic Stability of Different Silyl Groups Derived from Benzyl Alcohol, in $CDCl_3$/pTsOH·H_2O

1.2.7 Analysis of Electronic Effects

The order of hydrolytic stability determined in an aprotic solvent does not appear to follow the order of steric crowding at silicon. Since the steric environment at silicon is independent of solvent, some other property must be responsible for the reversal of reactivity between sisyl and TBDMS ethers observed within each of the primary, benzylic and secondary alcohol series. This would imply that a change of mechanism had occurred upon changing the solvent. In fact, such a phenomenon was previously observed by Sommer who reported a dramatic stereochemical crossover from retention to inversion of configuration at silicon during alkoxide exchange of 1-naphthylphenylmethylmethoxysilane with increasing alcoholic content of a benzenebutanol solvent mixture, as shown in equation (19).[28] This was interpreted to reflect a changeover in mechanism as a result of increased activation of the leaving group via hydrogen bonding with the alcoholic solvent.

$$R_3Si^*OCH_3 + n\text{-}BuOLi \rightarrow R_3Si^*O\text{-}n\text{-}Bu \qquad (19)$$

If the mechanism proposed by Corriu for nucleophilic substitution at silicon were operational in aprotic solvents (see **Figure 1 - 5**), then the factors which facilitate that process, including the silyl ether's ability to undergo expansion of coordination, should influence the rate of reaction. It is well documented that the tendency for silicon to form extracoordinate species is enhanced by the presence of electron-withdrawing substituents at silicon.[29] We can, therefore, estimate the relative ability of the silicon atom in sisyl and TBDMS ethers to undergo coordination expansion based on their respective electronic environments, which can be deduced from ^{29}Si chemical shifts. These are given in **Table 1 - 2**.

Table 1 - 2. ^{29}Si Chemical Shift Values (δ) of the Central Silicon Atom in $R_1OSiR_2R_3R_4$

$SiR_2R_3R_4$		**R_1**	
	CH_2CH_2Ph	CH_2Ph	C_5H_9
$Si(CH_3)_2t$-Bu	18.80	19.44	15.82
$Si[Si(CH_3)_3]_3$	-16.55	-15.61	-2.72

The central silicon atom of a sisyl ether is more electron rich than the silicon atom of TBDMS ethers, as judged by its ^{29}Si chemical shift value which falls in a range that corresponds to increased shielding at silicon.[30] Thus, sisyl ethers are expected to undergo coordination expansion with lesser ease than TBDMS ethers, and it may have been this property which was responsible for the reversal of reactivity between sisyl and TBDMS ethers in an aprotic solvent. Our original assumption that the magnitude of electronic effects of substituents at silicon on the rate of substitution is smaller than the magnitude of steric effects is likely only applicable in protic media.

1.2.8 Photolytic Cleavage of Sisyl Ethers

Photodegradation of the sisyl ethers was performed by a co-worker.[31] Upon irradiation of a sample of the sisyl ether in a CH_2Cl_2-MeOH mixture at 254 nm, the original alcohol was indeed recovered in yields of 82 to 88 %.[32]

1.3.1 Summary

The sisyl group proved to be a very versatile alcohol protecting group which could be made more stable or less stable to acidic hydrolysis than the frequently utilized *tert*-butyldimethylsilyl group, simply by selection of the reaction conditions. It can also be cleaved selectively by photolysis in the presence of other silyl ethers which are not photoactive. The allyl-TBMS ethers were shown to be more hydrolytically stable than both the TBDMS and sisyl ethers in both protic and aprotic media.

EXPERIMENTAL

1.4.1 General Procedures and Instrumentation

^{1}H NMR spectra were recorded on a Bruker AC-200 spectrometer at 200.133 MHz using the residual $CHCl_3$ present in $CDCl_3$ as internal reference. ^{13}C NMR spectra were recorded on the same instrument at 50.323 MHz, also using $CDCl_3$ as internal reference. ^{29}Si NMR spectra were recorded on a Bruker AC-300 spectrometer at 59.6 MHz.

Chemical ionization (CI), with ammonia as the reagent gas, and electron impact (EI) mass spectra were recorded on a VG Analytical ZAB-R mass spectrometer equipped with a VG 11-250 data system. Typical experimental conditions included electron energy of 70 eV and source temperature of 200 °C.

Infrared spectra were recorded on a Bio Rad FTS-40 Fourier transform spectrometer. Liquid samples were used as neat films on NaCl discs and solid samples were prepared as KBr pellets.

1.4.2 Molecular Mechanics Calculations

Conformational analysis of compounds **30**, **33**, **36** and **41** was carried out using the Merck Molecular Force Field (MMFF94). The volumes were calculated using the program SPARTAN, based on the structures generated with MMFF94.

1.4.3 Reagents and Solvents

Benzyl alcohol, cyclopentanol, 2-phenylethanol, 4-dimethylaminopyridine, imidazole, *t*-butylmagnesium chloride in THF, tris(trimethylsilyl)silane, THF d_8 and CD_3CO_2D were purchased from Aldrich and used without purification. Allyldichloromethylsilane and *t*-butylchlorodimethylsilane were purchased from Gelest and used without further purification. D_2O and $CDCl_3$ were obtained from Cambridge Isotope Labs and used without purification.

CH_2Cl_2 was distilled from CaH_2 prior to use, and DMF was distilled from $CaSO_4$.

1.4.4 Compounds Prepared

Tris(trimethylsilyl)silyl chloride:

This was prepared according to the procedure of Bürger *et al.*[23] To 5 mL of CCl_4 at 0 °C was added 2 mL (6.4 mmol) of tris(trimethylsilyl)silane. Stirring was continued overnight, followed by removal of solvent under reduced pressure to yield 1.72 g, 95 % of a colorless oil. ^{1}H NMR ($CDCl_3$): δ 0.20 (s, 27 H); ^{13}C NMR ($CDCl_3$,): δ -0.7; ^{29}Si NMR ($CDCl_3$): δ -11.84, 10.81; IR (neat, NaCl): ν 2953, 2895, 1439, 1398, 1246, 1072, 837, 745, 691, 622 cm^{-1}.

*Allyl-t-butylchloromethylsilane, **103**:*

A solution of *t*-butylmagnesium chloride in THF (1.0 M, 100 mL, 100 mmol) was added dropwise to a flask containing allyldichloromethylsilane (13 mL, 90.1 mmol) and copper (I) cyanide (0.45 g, 5.0 mmol) in THF (90 mL) at 0 °C, over a period of 2 h. After stirring at 0 °C for 2 h, the solution was warmed to 25 °C and stirring was continued for an additional 24 h. After filtration of the precipitate under N_2, distillation under reduced pressure yielded 7.1 g, 40 % of a colorless oil (b.p. 55 °C/25 mmHg). ^{1}H NMR ($CDCl_3$): δ 5.78 (m, 1H), 4.99 (m, 2H), 1.82 (dd, J = 1.3, 1.7 Hz, 1H), 1.78 (dd, J = 1.4, 1.8 Hz, 1H), 0.97 (s, 9H), 0.32 (s, 3H); ^{13}C NMR ($CDCl_3$): 132.7, 115.1, 25.6, 22.3, 19.6, -3.7; ^{29}Si NMR ($CDCl_3$): δ 32.14; IR (neat, NaCl): ν 2959, 2934, 2862, 1633, 1471, 1256, 901, 826, 776 cm^{-1}; MS (EI, m/z): 176 (10), 135 (20), 119 (20); MS (CI, NH_3, m/z): 194 (50), 176 (30), 152 (50); HRMS (m/z) calcd for $C_8H_{17}Si_1Cl_1$ (M^+): 176.0788, found: 176.0778.

General Procedure for Protection of the Alcohol:

To a stirring solution of the alcohol (1 mmol) and 4-dimethylaminopyridine (DMAP) (1.20 mmol) in CH_2Cl_2 was added a solution of tris(trimethylsilyl)silyl chloride (1 mmol) in CH_2Cl_2 (1 M). The solution was stirred overnight at room temperature under N_2. Water was added and the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried over anhydrous sodium sulfate, filtered and the solvent was removed under reduced pressure. Separation by flash chromatography gave the products in 80-90% yields.

1-[Tris(trimethylsilyl)silyl]cyclopentanol, 31:

Cyclopentanol (0.12 mL, 1.3 mmol), DMAP (0.18 g, 1.6 mmol), CH_2Cl_2 (2.0 mL), tris(trimethylsilyl)silyl chloride (0.38 g, 1.3 mmol). Purification by chromatography with eluent pentane yielded 0.33 g, 90 % of a colorless oil. ^1H NMR ($CDCl_3$): δ 3.90 (m, 1H), 1.64 (m, 4H), 1.46 (m, 4H), 0.16 (s, 27H); ^{13}C NMR ($CDCl_3$): δ 78.9, 35.8, 36.0, 23.3; ^{29}Si NMR ($CDCl_3$): δ -2.72, 11.30; IR (neat, NaCl): ν 2952, 2895, 1439, 1246, 1060, 836 cm^{-1}; UV (hexane) λ_{max} = 196 nm, ε_{254} = 1425; MS (EI, m/z): 263 (20), 191 (20), 175 (30), 131 (35), 73 (100); MS (CI, NH_3, m/z): 264 ($Si(TMS)_3^+ + NH_3$, 8).

1-[Tris(trimethylsilyl)silyl]-2-phenylethanol, 29:

2-Phenyethanol (0.24 mL, 2.1 mmol), DMAP (0.29 g, 2.5 mmol), CH_2Cl_2 (3.0 mL), tris(trimethylsilyl)silyl chloride (0.61 g, 2.1 mmol). Purification by chromatography with eluent pentane:diethyl ether = 9:1 yielded 0.50 g, 80 % of a colorless oil. ^1H NMR ($CDCl_3$): δ 7.27 (m, 5H), 3.74 (t, J = 6.9 Hz, 2H), 2.85 (t, J = 6.9 Hz, 2H), 0.24 (s, 27H); ^{13}C NMR ($CDCl_3$): δ 139.0, 129.0, 128.0, 126.0, 69.0, 39.8, 0.3; ^{29}Si NMR ($CDCl_3$): δ 1.47, -16.55; IR (neat, NaCl): ν 3029, 2950, 2893, 1396, 1376, 1245, 1088, 1078, 836.9 cm^{-1}; UV (hexane) λ_{max} = 194 nm, ε_{254} = 1207; MS (EI, m/z): 263 (15), 175 (10), 131 (15), 105 (100), 73 (60); MS (CI, NH_3, m/z): 369 (100), 263 (50), 138 (50), 122 (60), 105 (70), 90 (50).

1-[Tris(trimethylsilyl)silyl]benzyl alcohol, 30:

Benzyl alcohol (0.85 mL, 8.1 mmol), DMAP (1.33 g, 10.9 mmol), CH_2Cl_2 (8.0 mL), tris(trimethylsilyl)silyl chloride (2.29 g, 8.1 mmol). Purification by chromatography with eluent petroleum ether:diethyl ether = 39:1 yielded 2.33 g, 82 % of a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.26 (m, 5H), 4.59 (s, 2H), 0.18 (s, 27H); ^{13}C NMR ($CDCl_3$,): δ 141.6, 128.1, 126.7, 125.5, 69.3, -0.1; ^{29}Si NMR ($CDCl_3$,): δ 3.47, -15.61; IR (neat, NaCl): ν 2952, 2893, 2857, 1245, 1085, 1063, 836, 690 cm^{-1}; UV (hexane) λ_{max} = 193 nm, ε_{254} = 1263; MS (EI, m/z): 339 (10), 263 (90), 248 (15), 189 (30), 175 (40), 131 (25), 117 (25), 91 (100), 73 (75); MS (CI, NH_3, m/z): 372 (15), 355 (100), 264 (70), 108 (20), 90 (25); HRMS (m/z): calcd for $C_{15}H_{31}O_1Si_1$ (M^+ - CH_3): 339.1451, found: 339.0750.

1-(t-Butyldimethylsilyl)-2-phenylethanol, 32:

2-Phenylethanol (1.5 mL, 12.5 mmol), DMAP (1.84 g, 15.0 mmol), CH_2Cl_2 (13.0 mL), *t*-butylchlorodimethylsilane (1.88 g, 12.5 mmol). Purification by chromatography with eluent pentane:diethyl ether = 19:1 yielded 2.6 g, 88 % of a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.20 (m, 5H), 3.78 (t, J = 7.1 Hz, 2H), 2.80 (t, J = 7.1 Hz, 2H), 0.85 (s, 9H), -0.03 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 139.2, 129.1, 128.2, 126.1, 64.5, 39.6, 25.9, 18.3, -5.4; ^{29}Si NMR ($CDCl_3$): δ 18.80; IR (neat, NaCl): ν 3023, 2953, 2930, 2854, 1474, 1254, 1102, 827, 781, 692 cm^{-1}; MS (EI, m/z): 221 (10), 179 (100), 161 (25), 105 (50), 75 (25); MS (CI, NH_3, m/z): 254 (35), 237 (100), 196 (35), 179 (15), 122 (15), 105 (15); HRMS (m/z): calcd for $C_{13}H_{21}O_1Si_1$ (M^+ - CH_3): 221.1361, found: 221.1361.

1-(t-Butyldimethylsilyl)benzyl alcohol, 33:

Benzyl alcohol (2 mL, 19.3 mmol), imidazole (1.57 g, 23.1 mmol), DMF (20.0 mL), *t*-butylchlorodimethylsilane (2.9 g, 19.3 mmol). Purification by chromatography with eluent petroleum ether:diethyl ether = 39:1 yielded 3.69 g, 86 % of a colorless oil. ^1H NMR ($CDCl_3$): δ 7.29 (m, 5H), 4.73 (s, 2H), 0.92 (s, 9H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 141.3, 128.1, 126.8, 125.9, 64.9, 25.9, 18.4, -5.2; ^{29}Si NMR ($CDCl_3$): δ 19.44; IR (neat, NaCl): ν 2955, 2930, 2857, 1470, 1254, 1096, 1070, 838, 776, 728 cm^{-1}; MS (EI, m/z): 222 (18), 165 (100), 135 (40), 91 (45); MS (CI, NH_3, m/z): 240 (75), 223 (15), 182 (15), 108 (100), 91 (20); HRMS (m/z): calcd for $C_{13}H_{22}Si_1O_1$ (M^+): 222.1439, found: 222.1429.

1-(t-Butyldimethylsilyl)cyclopentanol, 34:

Cyclopentanol (1.6 mL, 17.6 mmol), DMAP (2.58 g, 21.1 mmol), CH_2Cl_2 (18.0 mL), *t*-butylchlorodimethylsilane (2.65 g, 17.6 mmol). Purification by chromatography with eluent pentane yielded 2.61 g, 75 % of a colorless oil. ^1H NMR ($CDCl_3$): δ 4.20 (m, 1H), 1.66 (m, 4H), 1.47 (m, 4H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 74.4, 35.7, 25.9, 23.1, 18.1, -4.7; ^{29}Si NMR ($CDCl_3$): δ 15.82; IR (neat, NaCl): ν 2951, 2930, 2855, 1468, 1252, 1060, 832, 775 cm^{-1}; MS (EI, m/z): 185 (5), 143 (50), 75 (100), 59

(10), 43 (15); MS (CI, NH_3, m/z): 201 (100), 162 (20), 133 (35), 92 (55), 74 (15); HRMS (m/z): calcd for $C_{10}H_{21}O_1Si_1$ (M^+ - CH_3): 185.1361, found: 185.1361.

1-(Allyl-t-butylmethylsilyl)-benzyl alcohol, 36:

Benzyl alcohol (0.75 mL, 7.2 mmol), imidazole (1.0 g, 14.7 mmol), DMF (8.0 mL), allyl-*t*-butylchloromethylsilane (1.26 g, 7.2 mmol). Purification by chromatography with eluent pentane:diethyl ether = 19:1 yielded 1.32 g, 74 % of a colorless oil. ^1H NMR ($CDCl_3$): δ 7.27 (m, 5H), 5.84 (m, 1H), 4.86 (m, 2H), 4.75 (s, 2H), 1.66 (m, 2H), 0.92 (s, 9H), 0.09 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 141.2, 134.5, 128.1, 126.8, 125.9, 113.7, 65.2, 26.2, 20.7, 18.9, -7.45; ^{29}Si NMR ($CDCl_3$): δ 15.12; IR (neat, NaCl): ν 2956, 2930, 2858, 1631, 1470, 1255, 1096, 1070, 833, 770, 728 cm^{-1}; MS (EI, m/z): 248 (3), 207 (55), 191(15), 91 (85); MS (CI, NH_3, m/z): 266 (5), 224 (100); HRMS (m/z): calcd for $C_{15}H_{24}O_1Si_1$ (M^+): 248.1596, found: 248.1600.

1-(Allyl-t-butylmethylsilyl)-2-phenylethanol, 35:

2-Phenylethanol (0.65 mL, 5.4 mmol), DMAP (0.86 g, 7.0 mmol), CH_2Cl_2 (6.0 mL), allyl-*t*-butylchloromethylsilane (0.95 g, 5.4 mmol). Purification by chromatography with eluent pentane:diethyl ether = 9:1 yielded 1.10 g, 78 % of a colorless oil. ^1H NMR (CD_2Cl_2): δ 7.23 (m, 5H), 5.82 (m, 1H), 4.85 (m, 2H), 3.83 (t, J = 6.9 Hz, 2H), 2.79 (t, J = 6.9 Hz, 2H), 1.60 (m, 2H), 0.88 (s, 9H), 0.01 (s, 3H); ^{13}C NMR (CD_2Cl_2): δ 139.7, 135.2, 129.5, 128.5, 126.3, 113.5, 65.1, 39.8, 26.3, 20.9, 19.1, -7.4; ^{29}Si NMR ($CDCl_3$): δ

14.36; IR (neat, NaCl): ν 3076, 3022, 2953, 2928, 2887, 2859, 1733, 1633, 1473, 1254, 1105, 896, 832, 768, 693, 610 cm^{-1}; MS (EI, m/z): 221 (40), 179 (75), 163 (50), 105 (75), 75 (60), 41 (100); MS (CI, NH_3, m/z): 238 (20), 221 (100), 179 (40), 105 (40).

1-(Allyl-t-butylmethylsilyl)-cyclopentanol, 37:

Cyclopentanol (0.50 mL, 5.5 mmol), DMAP (0.90 g, 7.4 mmol), CH_2Cl_2 (5 mL), allyl-*t*-butylchloromethylsilane (0.97 g, 5.5 mmol). Purification by chromatography with eluent pentane:diethyl ether = 9:1 yielded 1.0 g, 80 % of a colorless oil. ^{1}H NMR (CD_2Cl_2): δ 5.84 (m, 1H), 4.85 (m, 2H), 4.27 (m, 1H), 1.65 (m, 8H), 1.52 (m, 2H), 0.89 (s, 9H), 0.06 (s, 3H); ^{13}C NMR (CD_2Cl_2): δ 135.5, 113.3, 75.1, 36.1, 26.3, 23.5, 21.5, 19.0, 6.9; ^{29}Si NMR ($CDCl_3$): δ 11.63; IR (neat, NaCl): ν 3075, 2955, 2929, 2895, 2858, 1633, 1474, 1362, 1248, 1054, 895, 824, 767, 610 cm^{-1}; MS (EI, m/z): 185 (25), 143 (30), 101 (20), 75 (100), 41 (70); MS (CI, NH_3, m/z): 227 (10), 202 (100), 185 (25), 134 (40), 92 (40), 75 (40); HRMS (m/z): calcd for $C_{13}H_{26}OSi$ (M^+): 226.1752, found: 226.1752.

*Cyclopentanoxytrimethylsilane, **40**:*

Cyclopentanol (0.50 mL, 5.5 mmol), imidazole (0.75 g, 11.0 mmol), DMF (6.0 mL) chlorotrimethylsilane (0.70 mL, 5.5 mmol). Purification by chromatography with eluent petroleum ether:diethyl ether = 9:1 yielded 0.74 g, 85 % of a colorless oil. ^{1}H NMR ($CDCl_3$): δ 4.15 (m, 1H), 1.65 (m, 4H), 1.52 (m, 4H), 0.01 (s, 9H).

1.4.5 General Procedure For Acidic Hydrolysis

In Aqueous Media:

To an NMR tube containing the silyl ether (0.076 mmol) under N_2 at 25 °C was added THF d_8 (0.26 mL), D_2O (0.12 mL), and CD_3CO_2D (0.38 mL), to make a 0.1M solution of silyl ether. The ^{1}H NMR spectra were acquired initially within 2 minutes of addition of CD_3CO_2D, and subsequently every 10 minutes.

A linear relationship was found to exist when the natural logarithm of the silyl ether concentration was plotted as a function of time. The raw data is provided in the Appendix of this chapter. The method of least squares linear regression analysis was used to find a line of best fit, the slope of which corresponded to the observed rate constant under pseudo-first-order conditions.

In Organic Media:

To the silyl ether (0.07 mmol) in $CDCl_3$ (3 mL), was added *p*-toluenesulfonic acid monohydrate (0.28 mmol). The reaction was monitored by TLC and ^{1}H NMR every 10 minutes.

APPENDIX

Table 1 - 3. Concentration *versus* Time Data for Hydrolysis in $CD_3CO_2D/D_2O/THF$

1-[Tris(trimethylsilyl)-silyl] 2-phenylethanol		**1-[Tris(trimethylsilyl)-silyl] benzyl alcohol**		**1-[Tris(trimethylsilyl)-silyl] cyclopentanol**	
Time (min.)	ln [Silane][a]	Time (min.)	ln [Silane]	Time (min.)	ln [Silane]
3.5	-2.43	3.5	-2.42	11	-2.44
5	-2.48	6.5	-2.56	17	-2.47
8	-2.65	9.5	-2.64	29	-2.63
11	-2.75	12.5	-2.71	41	-2.76
14	-2.93	15.5	-2.77	53	-2.90
17	-2.91	18.5	-2.89	65	-3.03
20	-3.05	20	-2.95	77	-3.18
23	-3.16	23	-3.07	89	-3.28
24.5	-3.26	26	-3.14	101	-3.48
35	-3.31	29	-3.16	113	-3.68
41	-3.37	37	-3.34	125	-3.87
47	-3.45	48	-3.46	150	-4.14
53	-3.50	54	-3.53	161	-4.31
59	-3.68	60	-3.61	173	-4.46
101	-3.89	72	-3.89	185	-4.64
123	-3.95	78	-4.02	209	-4.94
		84	-4.11	221	-5.18
		102	-4.46		

[a] Only the first nine data points were used for linear regression analysis; phase separation of the reaction mixture was observed approximately 30 min. after the addition of reagents to the alkoxysilane.

Table 1 - 4. Concentration *versus* Time Data for Hydrolysis in $CD_3CO_2D/D_2O/THF$

1-(*t*-Butyldimethylsilyl)-2-phenylethanol		**1-(*t*-Butyldimethylsilyl)-benzyl alcohol**		**1-(*t*-Butyldimethylsilyl)-cyclopentanol**	
Time (min.)	ln [Silane]	Time (min.)	ln [Silane]	Time (min.)	ln [Silane]
2	-2.33	9	-2.34	6	-2.44
8	-2.36	33	-2.41	12	-2.50
14	-2.39	69	-2.52	24	-2.54
20	-2.43	93	-2.59	36	-2.56
32	-2.50	123	-2.70	48	-2.61
44	-2.56	153	-2.79	60	-2.67
56	-2.65	183	-2.88	120	-2.90
62	-2.66	213	-2.98	180	-3.12
92	-2.88	243	-3.11	240	-3.26
122	-3.06	273	-3.22	300	-3.51
152	-3.22	342	-3.43	360	-3.62
182	-3.40	384	-3.61	390	-3.84
212	-3.62	426	-3.78	450	-3.97
242	-3.83	468	-3.89	510	-4.29
272	-4.00	510	-4.06	570	-4.47
302	-4.15	552	-4.23	630	-4.63
332	-4.31	594	-4.34		
392	-4.62	636	-4.48		
422	-4.86	678	-4.71		
		720	-4.85		
		762	-4.91		
		804	-5.14		

Table 1 - 5. Concentration *versus* Time Data for Hydrolysis in $CD_3CO_2D/D_2O/THF$

1-(Allyl-*t*-butylmethylsilyl)-2-phenylethanol		**1-(Allyl-*t*-butylmethylsilyl)-benzyl alcohol**		**1-(Allyl-*t*-butylmethylsilyl)-cyclopentanol**	
Time (min.)	ln [Silane]	Time (min.)	ln [Silane]	Time (min.)	ln [Silane]
17	-2.36	30	-2.33	35	-2.32
32	-2.41	106	-2.41	95	-2.37
39	-2.42	226	-2.58	155	-2.42
62	-2.50	346	-2.68	215	-2.47
92	-2.60	466	-2.84	275	-2.52
122	-2.69	586	-2.95	335	-2.57
152	-2.77	768	-3.21	395	-2.62
182	-2.87	978	-3.40	455	-2.67
212	-2.96	1140	-3.54	515	2.72
242	-3.04			575	-2.77
272	-3.14			635	-2.82
290	-3.22			695	-2.87
334	-3.35				
389	-3.52				
444	-3.68				
499	-3.87				
554	-4.01				
609	-4.19				
664	-4.35				
719	-4.49				
774	-4.60				
829	-4.85				

Table 1 - 5 cont'd.

1-(Allyl- *t*-butylmethylsilyl)- 2-phenylethanol		**1-(Allyl- *t*-butylmethylsilyl)- benzyl alcohol**		**1-(Allyl- *t*-butylmethylsilyl)- cyclopentanol**	
Time (min.)	ln [Silane]	Time (min.)	ln [Silane]	Time (min.)	ln [Silane]
884	-5.00				
939	-5.06				
994	-5.22				
1049	-5.29				

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[31] The deprotection of silyl ethers **29** and **31** was performed by Mustafa Mohamed according to the following procedure which appeared in a joint publication (see ref. 32). A 0.1 M solution of the protected alcohol in methylene chloride containing methanol, placed within a quartz cell, was irradiated in a Rayonet photochemical reactor at 254 nm, until the reaction was judged by TLC to be complete. The solvent was then removed under reduced pressure and the alcohol was purified by flash chromatography. The deprotection yields of **29** and **31** were found to be 82 % and 88 %, respectively

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CHAPTER 2

ALKOXYALLYLSILANES AS REACTIVE PROTECTING GROUPS

INTRODUCTION

2.1.1 Mechanism and Stereochemistry of Electrophilic Substitution of Allylsilanes

Allylsilanes react with electrophiles in the sense shown in **Figure 2 - 1**, undergoing S_E2' substitution. A wide range of electrophiles have been studied, including protons (referred to as protodesilylation), heteroatoms, and carbon electrophiles such as carbonyl compounds, acetals, ketals, and iminium ions, among others.[1]

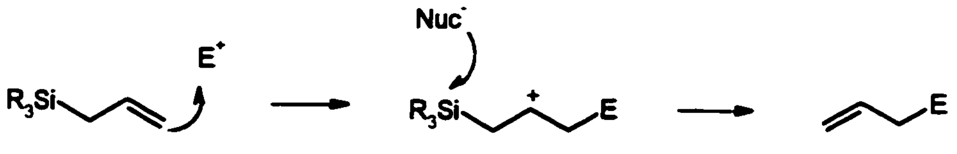


Figure 2 - 1: Electrophilic Substitution of an Allylsilane

Since the first report of the addition of allyltrimethylsilane to activated carbonyl compounds such as α-chloroacetone in the presence of Lewis acids by Calas and co-workers in 1974,[2] allylsilanes have filled a very important niche in synthetic organic chemistry as reagents for stereoselective carbon-carbon bond formation.

One of the advantages of allylsilanes over other organometallic compounds, such as allyllithium and allylGrignard reagents, is the regiospecificity of allylic transposition.[3] Electrophilic attack on the π-bond always occurs at the terminus of the allyl unit remote from the silyl group as shown in **Figure 2 - 2**, to generate the cation **43**. The allylsilane itself is thermally stable with respect to allylic shift of the silyl group.[4] In a final step, nucleophilic displacement of the silyl group leads to formation of an alkene.

The high levels of (*E*)-double bond geometry found in the alkene product have been rationalized as having arisen from the expected lowest energy conformation of the allylsilane. This places the smallest substituent at the α-carbon in a position eclipsing the adjacent double bond, as illustrated in structure **42** of **Figure 2 - 2**.[5] Approach of the electrophile towards the π-system occurs from the face opposite to the one occupied by the bulky silicon group, to generate the intermediate cation **43**, which is believed to retain its configuration due to hyperconjugative overlap of the silicon-carbon bond with the empty *p* orbital on the β-carbon.[6] Loss of the silyl group then leads predominantly to formation of a *trans* double bond.

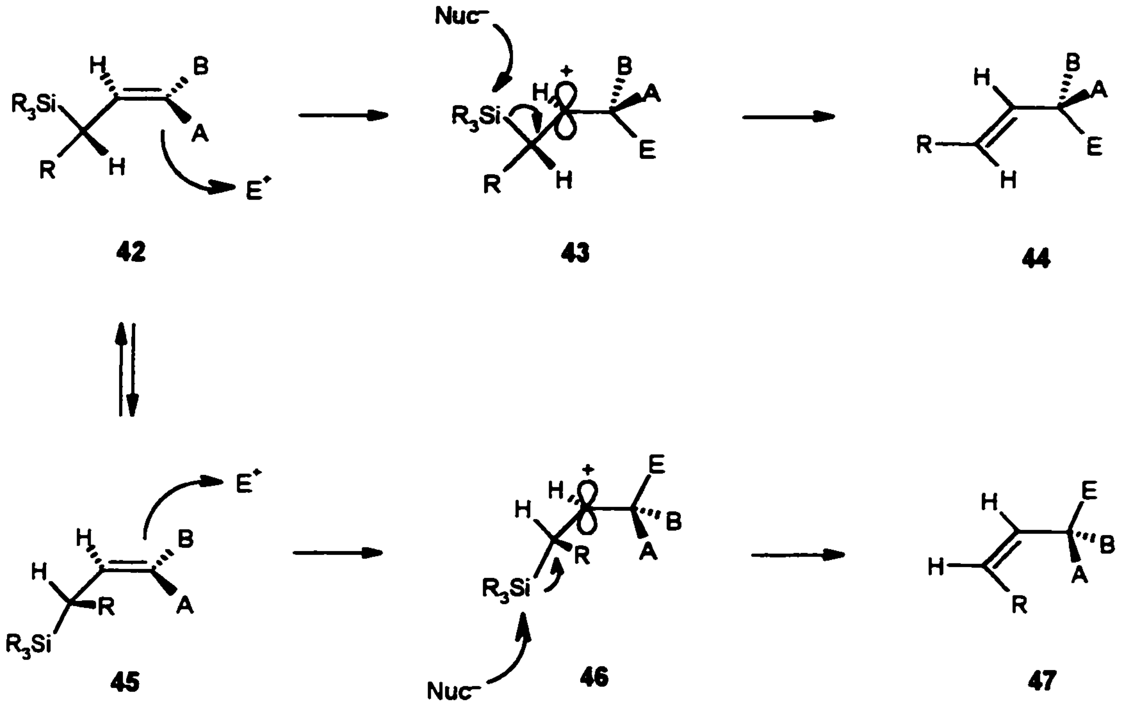


Figure 2 - 2: Stereochemistry of Electrophilic Substitution of an Allylsilane

A significant proportion of product having a *cis* double bond was recovered from reactions where the electrophile was very large, or from the *E*-isomer of allylsilanes having a 1,2-disubstituted double bond.[7] An extension of the above rationale predicts that the allylsilane could, alternatively, adopt an orientation in which the R group of the α-carbon is eclipsed with the adjacent double bond in the transition state when the R group is not very large, and particularly, when the double bond of the allylsilane has the *E*-configuration. This orientation, depicted in structure **45**, where **A** represents a hydrogen atom (**Figure 2 - 2**), leads to a minimization of the steric interaction between a bulky electrophile and the R group. Thus, based on the assumption that the intermediate cation retains its configuration once formed, the preference for formation of a *cis* or *trans* alkene appears to be determined by whether the magnitude of steric interaction between the incoming electrophile and the α-carbon substituent (which is oriented in the direction of electrophilic approach), is greater than, or less than, the steric repulsion between the two eclipsed allylic substituents.

Although evidence has been presented recently that suggests the addition of an electrophile to an allylsilane is stereoselectively rather than stereospecifically *anti* to the silyl group,[8] the mechanistic interpretation described above provides an excellent tool for predicting the stereochemical outcome of electrophilic substitution reactions of allylsilanes.

2.1.2 Transition State Models for Diastereoselectivity of Electrophilic Substitution

In their reaction with carbonyl compounds as electrophiles, both (*E*)- and (*Z*)-crotylsilanes give rise to two new chiral centers with a preference for the formation of a *syn* relationship in both cases between the hydroxy substituent and the methyl substituent that was originally on the allylic γ-carbon. An open transition state model, termed antiperiplanar, in which the two reacting π-bonds are coplanar and the angle between them is 180°, has been proposed to account for the observed stereoselectivity.[9] The transition structures corresponding to (*E*)-crotylsilane based on this model are shown in **Figure 2 - 3**.

In accordance with the *anti* stereochemistry that has been observed in the reaction of allylsilanes with simple electrophiles (see **Figure 2 - 2**), the aldehyde is expected to be oriented towards the alkene π-face that is *anti* to the silyl group. The observed diastereoselectivity of the products is consistent with a π-facial selectivity of the aldehyde leading to the least amount of steric repulsion between the aldehyde substituent **R**, and the vinyl methyl group. This corresponds to structure **48** in **Figure 2 - 3**, leading to formation of the *syn* diastereomer **49** preferentially.

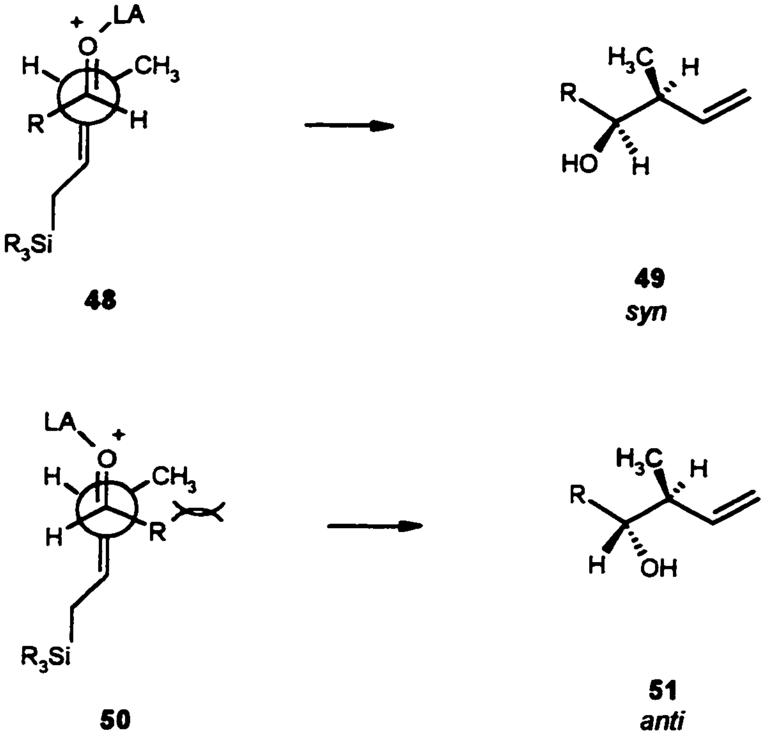
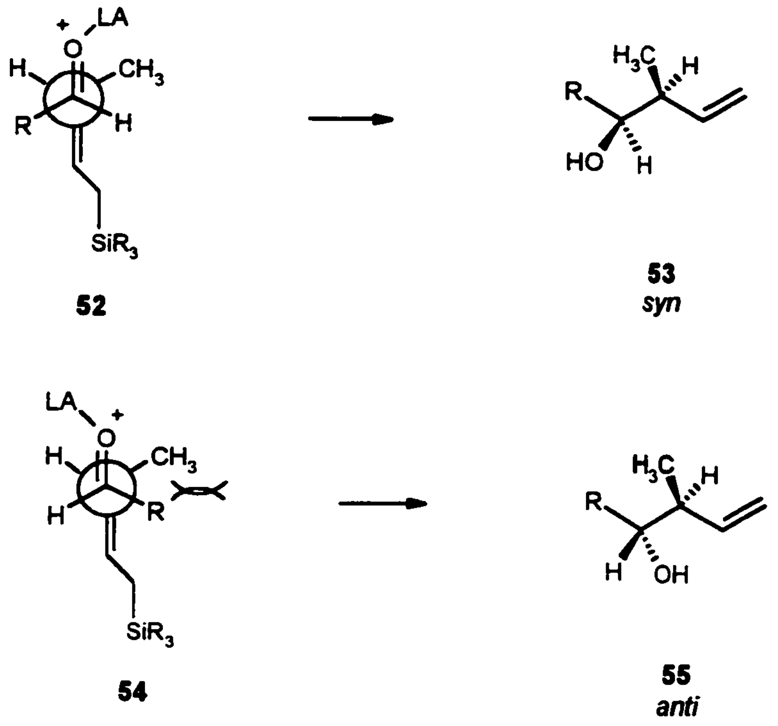


Figure 2 - 3: Antiperiplanar Transition State Model for (*E*)-Crotylsilanes

The transition structures corresponding to (*Z*)-crotylsilane are shown in **Figure 2 - 4**. Again, the preference for the *syn* diastereomer **53** has been attributed to a minimization of the steric repulsion between the aldehyde substituent **R** and the vinyl methyl group, illustrated in structure **54**. A second transition state model in which the carbonyl and allyl π-bonds are positioned at an angle of approximately 30° to each other, termed synclinal, has also been proposed to account for the *syn* diastereoselectivity found in numerous reactions of substituted allylsilanes with carbonyl compounds.[10] However, the antiperiplanar model seems to be more widely applicable in explaining the observed stereoselectivity. A more detailed comparison of the ability of the two transition state models to describe a typical reaction will be postponed to Section 2.1.4.



52

53
syn

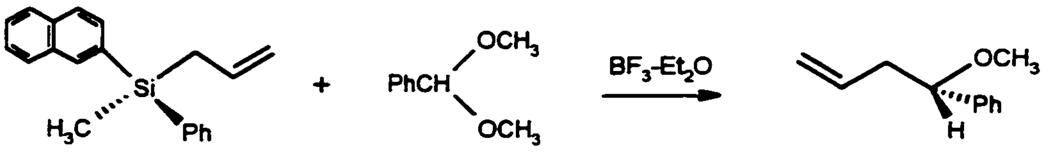
54

55
anti

Figure 2 - 4: Antiperiplanar Transition State Model for (*Z*)-Crotylsilanes

2.1.3 Control of Stereochemistry via a Silicon-Centered Chiral Allylsilane

Initial attempts to induce chirality transfer during allylic transposition involved the use of a silicon-centered chiral silane, as shown in **Figure 2 - 5**. The authors did not have any success with several aldehydes, but did manage to find conditions to effect allyl transfer onto a dimethyl acetal with a reported enantiomeric excess of 5 %.[11] Although the discussion here will be focused mainly on the use of aldehydes as electrophiles in the presence of Lewis acids, this result is relevant since it is the only reported example of the use of a silicon-centered chiral silane in such reactions.



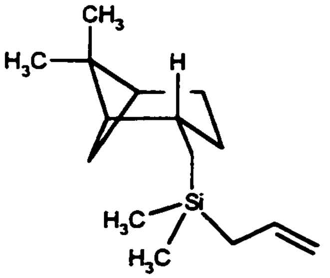
56 **57** **58**

Figure 2 - 5: Enantioselectivity via a Silicon-Centered Chiral Allylsilane

2.1.4 Control of Stereochemistry via Carbon-Centered Chiral Allylsilanes

The methodologies that followed involved chiral silanes with carbon-centered chirality. One approach utilized chiral auxiliary groups bonded to allyldimethylsilane for the purpose of transferring chiral information during allylic transposition onto aldehydes. These groups were derived from optically active compounds[12,13] such as (1*S*)-(-)-*β*-

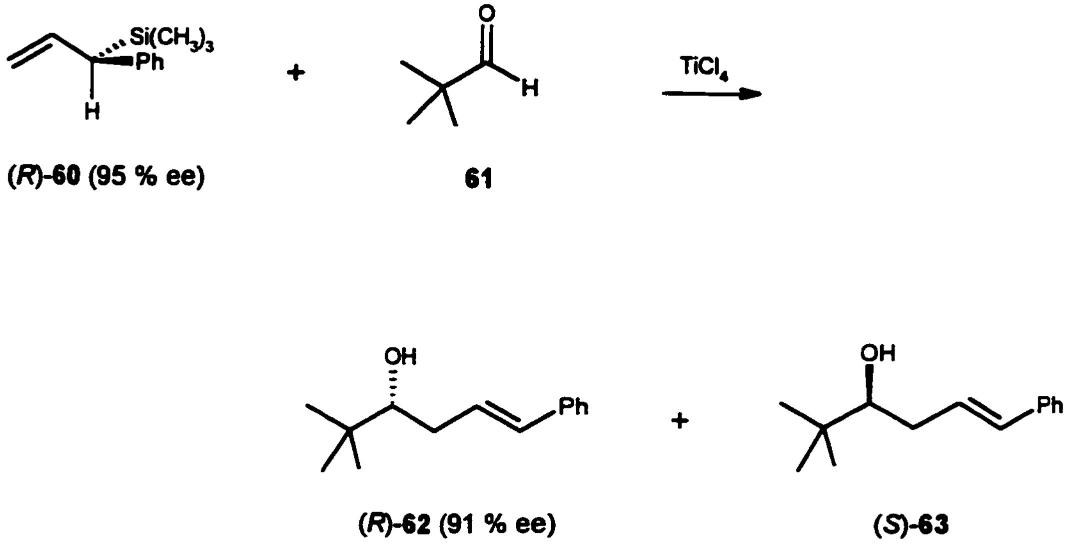
pinene.[14] The recovered homoallylic alcohols had enantiomeric excesses in the range of 4 to 23 %. Based on the supposition of a mechanism proceeding through an antiperiplanar transition state, chirality, at silicon or bonded to silicon, would have little influence on the stereochemical outcome of the reaction when it is remote from the bonds that are forming in the transition state. The chiral allylsilane derived from (1*S*)-(-)-*β*-pinene is shown in **Figure 2 - 6**.



59

Figure 2 - 6: Chiral Allylsilane Derived from (1*S*)-(-)-*β*-pinene

An improvement in the enantioselectivity was achieved with the use of a carbon-centered chiral allylsilane in which the substituents at the chiral carbon had the potential to influence the π-facial selectivity of the aldehyde through steric effects, due to their proximity to the bonds being formed in the transition state. The homoallylic alcohol product (*R*)-**62** was obtained with an enantiomeric excess of 91 % from allylic transposition of the chiral allylsilane (*R*)-**60** (of high optical purity) onto the sterically hindered pivalaldehyde, as shown in **Figure 2 - 7**.[15]



(R)-60 (95 % ee)

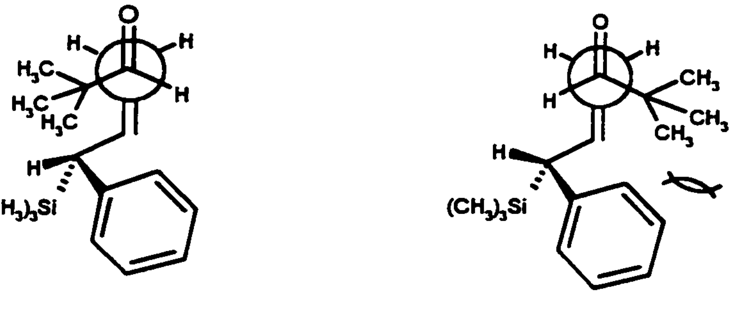
61

(R)-62 (91 % ee)

(S)-63

Figure 2 - 7: Enantioselectivity via Carbon-Centered Chiral Allylsilane (*R*)-**60**

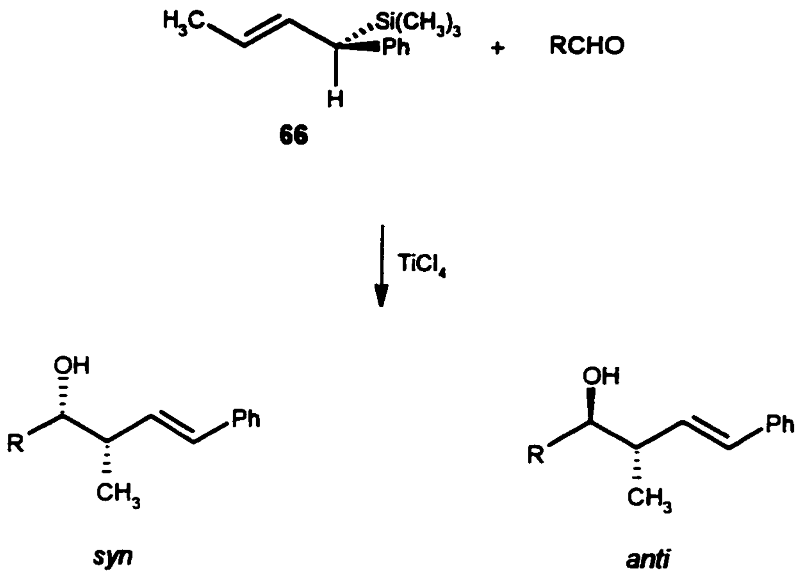
Based on a determination of the absolute configuration of the chiral center in the alcohol **62**, it was concluded that the aldehyde **61** had reacted selectively at its *Re* face. This aldehyde π-facial selectivity is shown in the antiperiplanar transition structure **64** in **Figure 2 - 8**, and is believed to have been the result of destabilization of transition structure **65**, arising from steric repulsion between the aldehyde *tert*-butyl group and the aromatic group. Formation of the isomer (*S*)-**63** was proposed to have arisen not via a transition structure **65**, but rather, from the small amount of (*S*)-**60** that was initially also present.



64 **65**

Figure 2 - 8: π-Facial Selectivity of Aldehyde **61**

When the same reaction was carried out with acetaldehyde, the enantiomeric excess of the homoallylic alcohol product dropped to 64 %. High levels of stereoselectivity via single asymmetric induction depend on the presence of sterically hindered substituents on both the aldehyde and the allyl group, leading to a more pronounced preference for reaction to occur at one of the aldehyde's π-faces. This is further illustrated by the allyl transfer reaction of the corresponding (*E*)-crotylsilane **66**, having yielded diastereoselectivities of 99:1, 95:5, and 92:8 for the *syn*:*anti* homoallylic alcohol products obtained from pivalaldehyde, isobutyraldehyde, and acetaldehyde respectively, as shown in **Figure 2 - 9**.[16] This correlation of increasing selectivity with increasing size of the aldehyde substituent **R**, is consistent with the increasing magnitude of steric repulsion between itself and both the aromatic and vinyl methyl group, that would be predicted from an antiperiplanar transition state model. The antiperiplanar structures **70** and **73**, leading to formation of the *syn* and *anti* diastereomeric alcohols respectively, are shown in **Figure 2 - 10** and **Figure 2 - 11**.



	RCHO	*syn* : *anti*
67	$(CH_3)_3CCHO$	99 : 1
68	$(CH_3)_2CHCHO$	95 : 5
69	CH_3CHO	92 : 8

Figure 2 - 9: Diastereoselectivity via Chiral (*E*)-Crotylsilane **66**

The two synclinal transition structures **71** and **72**, which also relate the *syn* diastereoselectivity of the alcohol product to reaction having occurred at the aldehyde *Re* face, are shown in **Figure 2 - 10**. Since these structures convey greater total steric repulsion than the corresponding antiperiplanar structure **70**, the latter model was used to explain the observed stereochemistry. Similarly, the two synclinal transition structures that depict formation of the *anti* diastereomer are shown in **Figure 2 - 11**. Although the synclinal structure **75** should possess less steric repulsion than the antiperiplanar structure

73, the antiperiplanar model was favored. This example illustrates, quite nicely, the inadequacy of either transition state model to explain all the stereochemical results, and the inconsistency with which the models are employed.

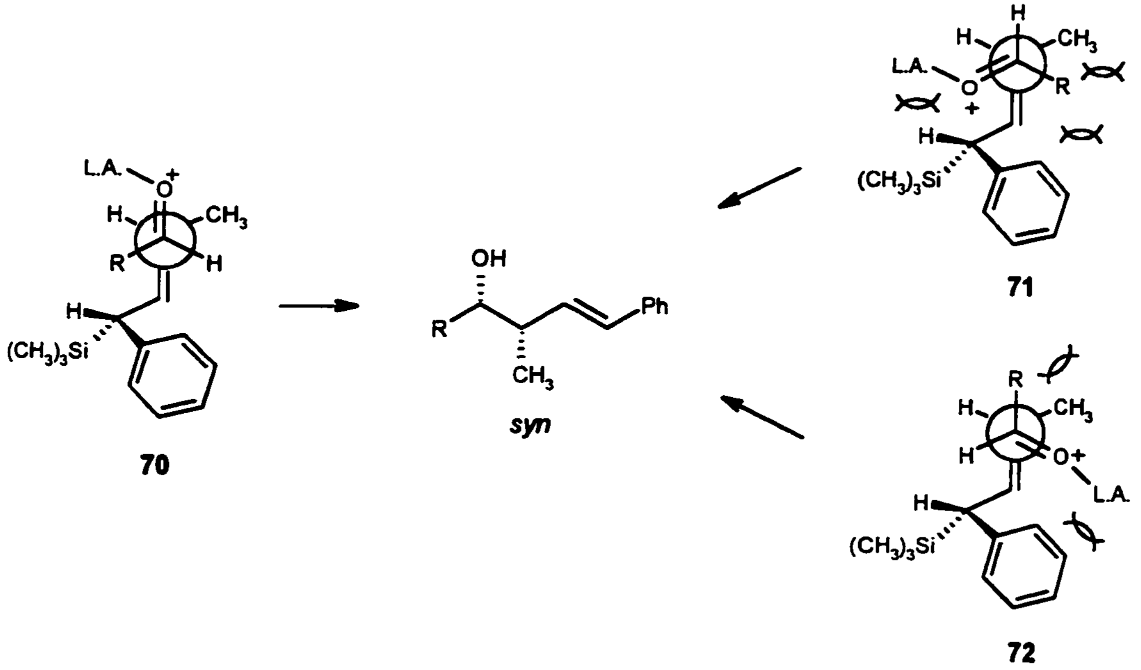


Figure 2 - 10: Antiperiplanar and Synclinal Transition Structures leading to *syn* Diastereomers 67-69

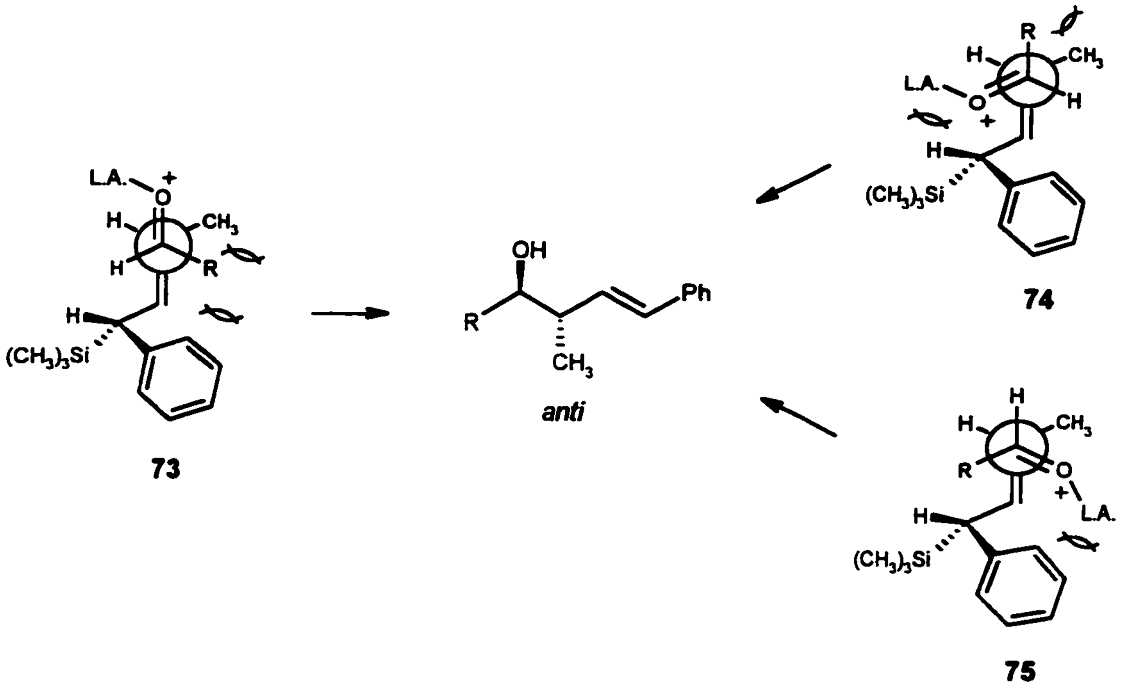


Figure 2 - 11: Antiperiplanar and Synclinal Transition Structures leading to *anti* Diastereomers **67-69**

2.1.5 Control of Stereochemistry through Chelation of the Aldehyde with the Allylsilane

A different approach to improving the enantioselectivity of the homoallylic alcohol product involves chelation of an aldehyde with a chiral allylsilane through a bidentate Lewis acid.[17] This was the premise for the reaction carried out between allylsilane **76**, possessing a chiral auxiliary group derived from optically active (1*R*)-(-)-myrtenal, and butanal in the presence of $TiCl_4$.[18] However, poor enantiomeric excesses of the alcohol **79** (up to 46 %) were obtained. In addition, the reaction was plagued by very low yields of alcohol due to formation of the tetrahydropyran **80**, and incomplete hydrolysis of the silyl ether **78**, upon aqueous work-up.

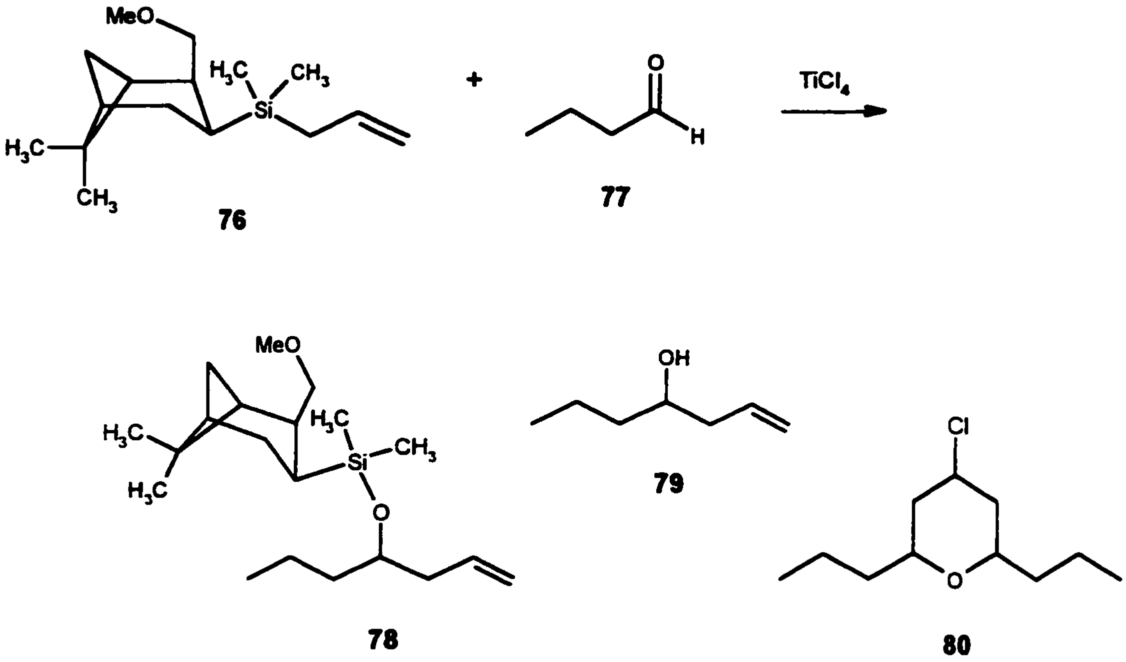
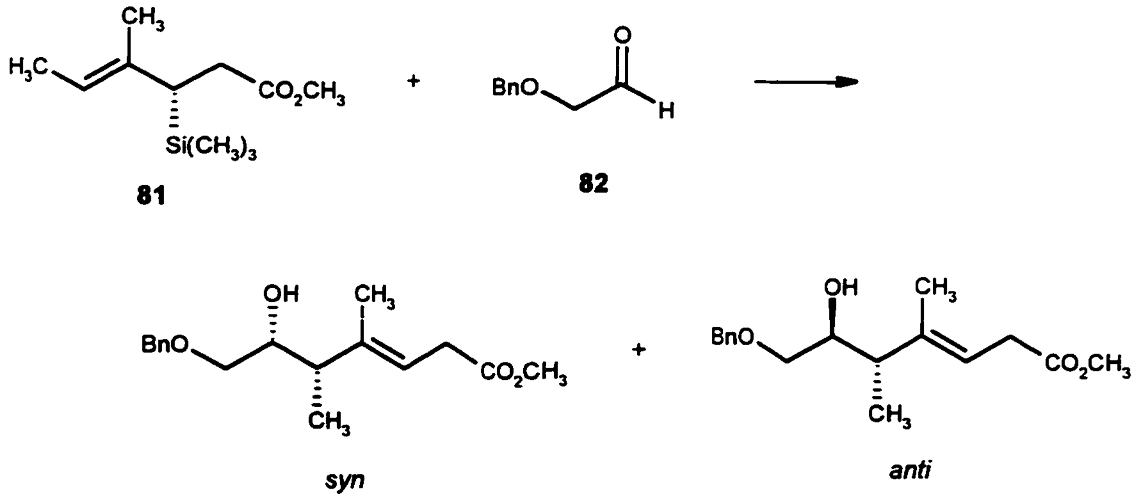


Figure 2 - 12: Enantioselectivity via Chiral Allylsilane **76**

2.1.6 Control of Stereochemistry through Chelation of the Aldehyde

It was found with aldehydes, which had the ability to participate in bidentate chelation, that the diastereoselectivity of the homoallylic alcohol product of allyl transfer could be reversed through selection of the Lewis acid.[19] In the presence of the monodentate Lewis acid $BF_3{\cdot}Et_2O$, allyl transfer from the carbon-centered chiral allylsilane **81** onto α-(benzyloxy)acetaldehyde **82** gave rise to the homoallylic alcohol products **83** and **84**, shown in **Figure 2 - 13**. The *syn* diastereoselectivity of the reaction is that which would be predicted on the basis of an antiperiplanar transition model with bond formation occurring at the *Re* face of the aldehyde, as illustrated in structure **85** in **Figure 2 - 14**.

The same allylsilane and aldehyde yielded the *anti* diastereomer **84** preferentially when the bidentate Lewis acid $MgBr_2{\cdot}Et_2O$ was used. This reversal in facial selectivity of the aldehyde, which gave rise to the *anti* product, was attributed to a change in steric requirements of the transition state as a result of chelation of the aldehyde with the Lewis acid. Addition of the allyl group to the *Si* face of the aldehyde can be rationalized with the aid of either the synclinal transition model **86** or the antiperiplanar model **87**.[20] Although it is not obvious *a priori* which one might comprise lower total steric repulsion, the authors chose structure **86** to explain their results.



81

82

syn

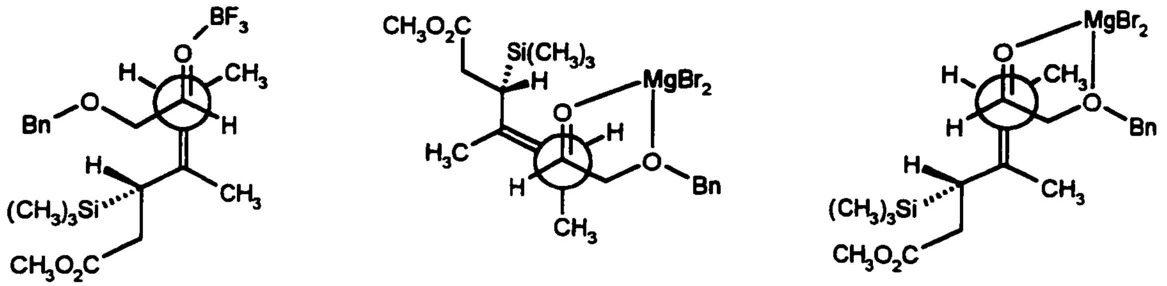
83

anti

84

	syn : *anti*
BF_3-Et_2O	87:13
$MgBr_2$-Et_2O	8:92

Figure 2 - 13: Effect of Lewis Acid on Diastereoselectivity of Homoallylic Alcohols



85 **86** **87**

Figure 2 - 14: Antiperiplanar and Synclinal Transition Structures Leading to Formation of Homoallylic Alcohols **83** and **84**

2.1.7 Control of Stereochemistry via Chiral Aldehydes

An alternative approach to achieving stereoselectivity is to have the chiral information on the aldehyde. The modest diastereoselectivities, observed in the homoallylic alcohol product of allyl transfer onto aldehydes possessing a chiral center at the α-carbon, have been rationalized in the context of the Felkin-Anh model.[21] Nucleophilic attack occurs from a direction approaching the least bulky substituent (S), when the largest substituent (L) is oriented perpendicular to the plane of the carbonyl group, as shown in **Figure 2 - 15**. This is referred to as Cram addition, since the product **89**, is the same product that would be predicted on the basis of the Cram model, which predates the Felkin-Anh model. The Cram model predicts nucleophilic attack from a direction approaching the smallest substituent (S), when the largest substituent (L) is oriented *anti* to the carbonyl group oxygen atom.[22] When the difference in size between the substituents L and M is small, nucleophilic attack at the other aldehyde π-face, typically referred to as *anti*-Cram addition, also takes place.

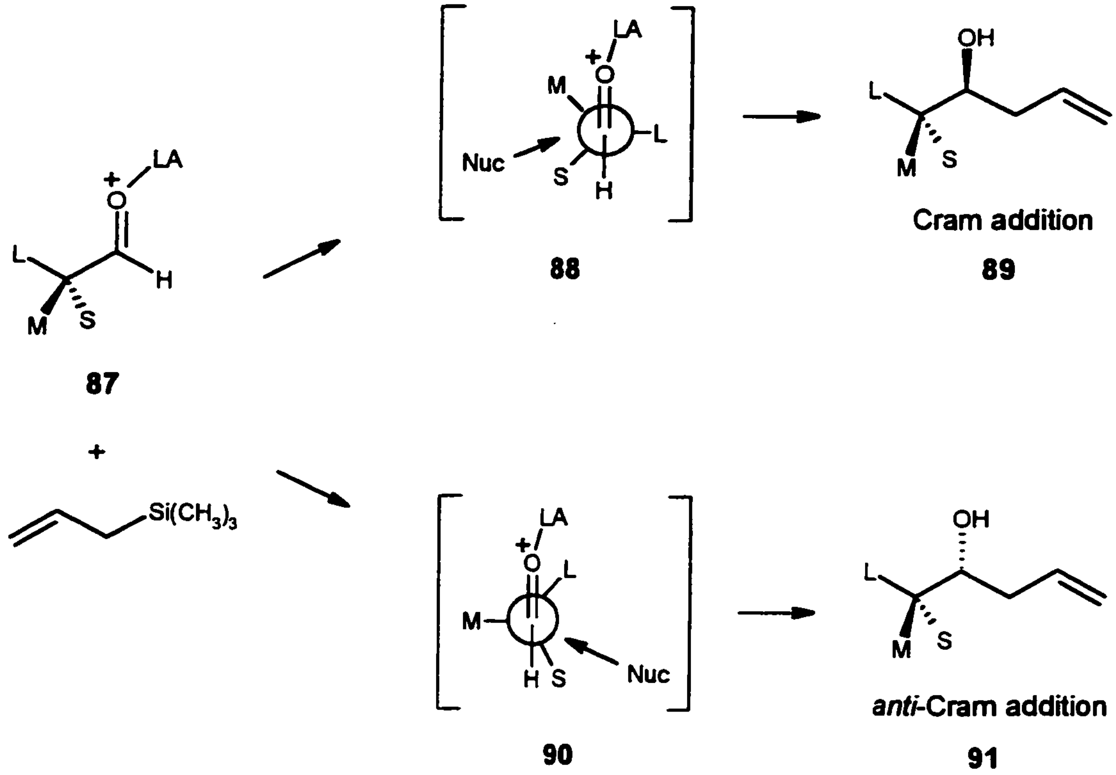
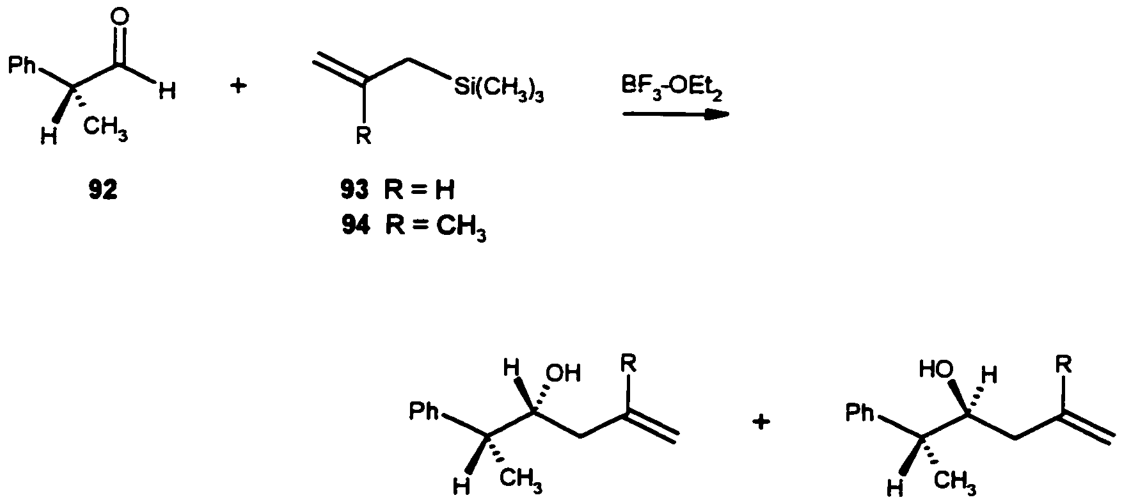


Figure 2 - 15: Felkin-Anh Model for Allyl Transfer onto α-Chiral Aldehyde

This approach to enantioinduction, suffers from the requirement that a large size difference must exist between the substituents at the α-carbon, and a bulky Lewis acid must be employed in order to achieve good stereoselectivity. Utilization of a chiral aldehyde is most effective at producing very high levels of diastereoselectivity when combined with asymmetric induction from a chiral allyl reagent, or with a substituted allyl reagent (such as a crotylmetal reagent) that can discriminate between the two aldehyde faces based on steric effects.[23]

Addition of allyltrimethylsilane to the chiral aldehyde **92** shown in **Figure 2 - 16** illustrates the moderate stereoselectivity that is imparted by the presence of the chiral center alone.[24] Substitution at the β-carbon of the allylsilane markedly improves the preference for Cram-addition to the aldehyde *Re* face, leading to formation of the *syn* diastereomer **95**, as would be predicted based on an antiperiplanar transition model.



92

93 R = H
94 R = CH$_3$

syn
(Cram addition)
95

anti
(*anti*-Cram addition)
96

	syn : *anti*
R = H	2 : 1
R = CH$_3$	7 : 1

Figure 2 - 16: Diastereoselectivity of Allyl Transfer onto Chiral Aldehyde **92**

RESEARCH PROPOSAL

Silyl ethers have proven to be invaluable in synthetic applications for the protection of alcohol groups, as described in the previous chapter. Allylsilanes have likewise, proven to be extremely useful synthons for the 2-propene group. We were interested in determining if the utility of silyl ethers could be combined with that of allylsilanes; that is, whether the reactivity of each of the functional groups would remain unchanged when both were present within the same molecule.

Two related applications were envisioned for such alkoxyallylsilanes, both involving the use of these silanes as "reactive" alcohol protecting groups. The alkoxyallylsilanes themselves can be prepared from the reaction between a hydroxy-containing compound and an allylsilane possessing a good leaving group on silicon. Upon formation, there exists the potential to effect allylic transposition intermolecularly if a suitable electrophile exists, or intramolecularly upon activation of a functional group present within the same molecule, in addition to masking the hydroxy group.

Alkoxyallylsilanes could also serve as a route for the introduction of ether groups onto oligosiloxanes, via hydrosilylation onto the allyl group. When derived from a hydroxy-containing hydrophilic molecule, they provide a method of interfacing hydrophilic moieties with hydrophobic ones, in analogy to the silane coupling agents utilized for binding organic resins to mineral surfaces.[25] Since the silicon-oxygen-silicon linkage is more stable to hydrolysis than the silicon-oxygen-carbon linkage,[26] the latter site can be used to cleave the hydrophobic moiety from the hydrophilic one. Protecting group methodology can be applied to control the stability of the silicon-oxygen-carbon linkage by varying the steric bulk at silicon, or less effectively, at carbon.

Toward this end, several alkoxyallylsilanes were prepared and the relative reactivity of the silicon-oxygen bond and the allylic carbon-silicon bond were examined under conditions that typically lead to hydrolysis of silyl ethers, and allylic transposition. These results were compared with the stability of the silicon-oxygen-carbon bond of an alkoxy-functionalized disiloxane derived from one of the aforementioned alkoxyallylsilanes, serving as a model compound for oligosiloxane-modified ethers, when subjected to the same reaction conditions.

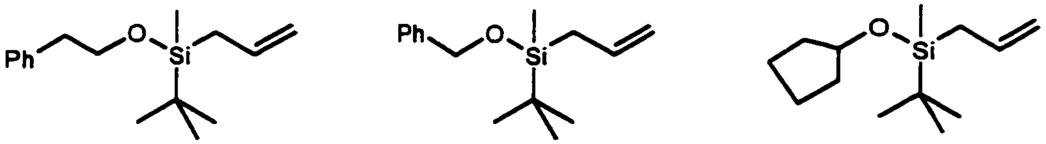
RESULTS

2.2.1 Synthesis of the Alkoxyallylsilanes

Initially, the silane chosen for study contained a methyl and a *tert*-butyl group bonded to silicon, in addition to the alkoxy and allyl functional groups. This was expected to provide a steric environment at silicon comparable to that found in the *tert*-butyldimethylsilyl group, a frequently utilized alcohol protecting group.[27] The degree of steric hindrance at silicon was one of the variables that would affect the ease of cleavage of both silicon-oxygen and silicon-carbon bonds. Its effect could then be studied further by incorporating either increased steric bulk, as found in bis-*tert*-butylalkoxyallylsilane, or decreased bulk, as found in dimethylalkoxyallylsilane.

Allyl-*t*-butylchloromethylsilane was prepared by the reaction of *t*-butylmagnesium chloride with allyldichloromethylsilane in the presence of catalytic quantities of CuCN, the latter compound having previously been reported to afford high yields of organosilanes from the reaction of organomagnesium reagents and chlorosilanes under very mild conditions.[28] KCN is a reagent typically used for the transformation of chorosilanes to cyanosilanes.[29] Based on the finding that the rate of nucleophilic substitution at silicon was accelerated by the addition of anions which can form pentavalent silicon species, it is conceivable that the cyanide ion served to enhance the rate of reaction by coordination to allyl-*t*-butylchloromethylsilane in a similar manner. This allowed for the alkoxysilanes to be prepared by nucleophilic substitution of the chlorosilane with the corresponding alcohol, by the same procedure that is used to protect alcohols in the form of silyl ethers.[30]

The primary, benzylic and secondary alcohols, 2-phenylethanol, benzyl alcohol and cyclopentanol respectively, were chosen in order to determine the effect of steric hindrance around the alcohol carbon, on the lability of the silicon-oxygen bond. The three alkoxyallylsilanes prepared are shown in **Figure 2 - 17**.



35 **36** **37**

Figure 2 - 17: Primary, Secondary and Benzylic Alkoxyallylsilanes Prepared

2.2.2 Regioselectivity of Acidic Hydrolysis with a Weak Acid

Initially, the relative reactivity of the alkoxy and allyl groups on silicon in the presence of a weak Brønsted acid was examined. Both cleavage of the silicon-oxygen bond and cleavage of the allyl group via protodesilylation were possible. Each of the three alkoxyallylsilanes was separately added to an excess of CD_3CO_2D in a THF-d_8-D_2O solvent mixture. The progress of the reaction in an NMR tube was monitored over time using TLC, ^1H NMR and ^{13}C NMR, as described in Chapter One.

The two possible reaction pathways for allylbenzyloxy-*t*-butylmethylsilane are shown in **Figure 2 - 18**. Path A depicts formation of a β-silyl cation from electrophilic attack on the allylic π-bond, while Path B depicts nucleophilic substitution of an alkoxy group bonded to silicon. For all three alkoxyallylsilanes, hydrolysis of the silyl ethers occurred exclusively. This was confirmed by comparison of the R_f values of the product mixture with that of an authentic sample of the parent alcohol, using thin layer chromatography, and by the addition of an authentic sample of the parent alcohol to the reaction mixture, and observing the increase in peak intensity. A transition structure consistent with the S_N2-like mechanism proposed by Dietze and co-workers, for hydrolysis of alkoxysilanes involving general acid catalysis in a protic medium, is also illustrated in **Figure 2 - 18**.

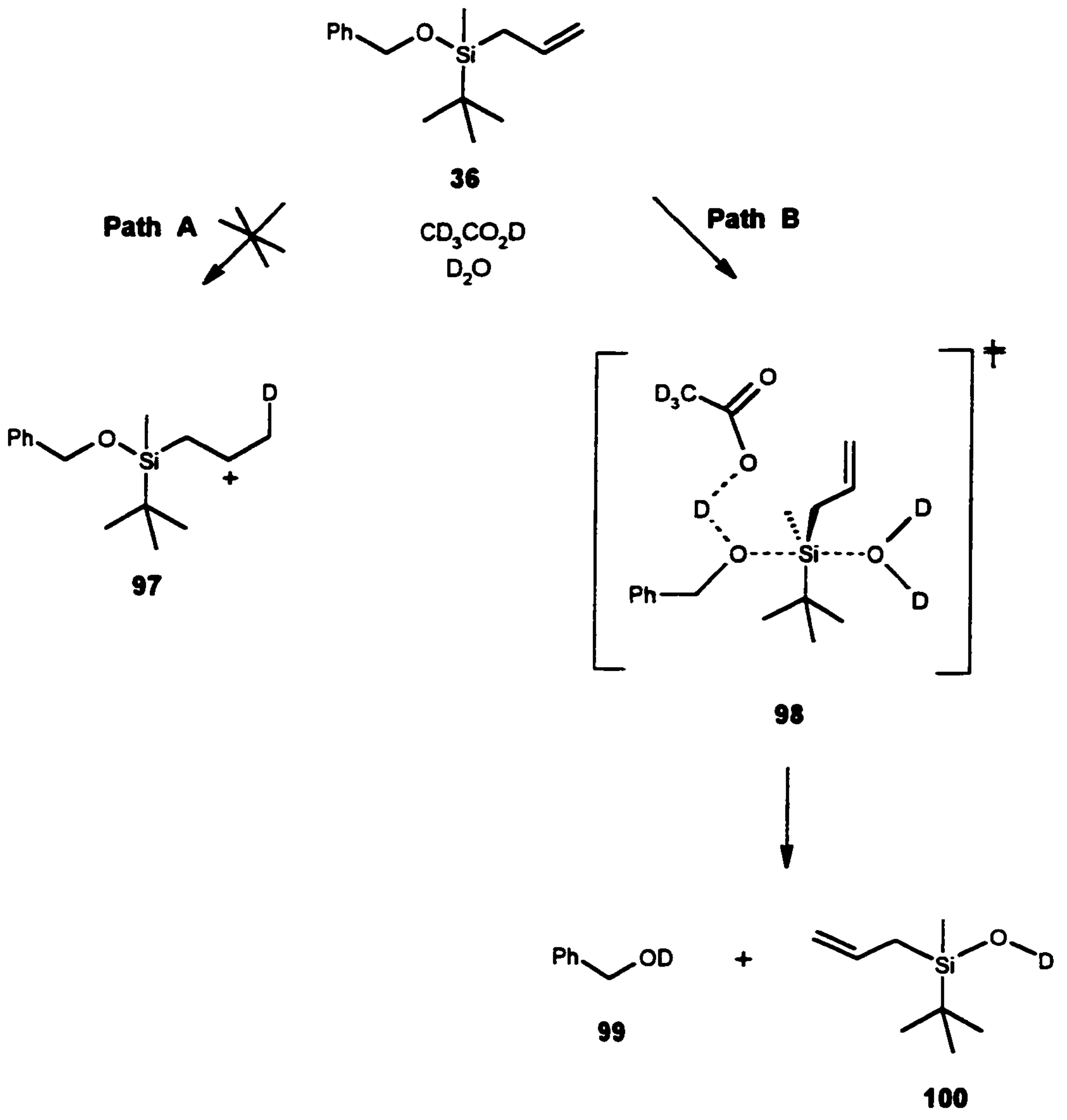
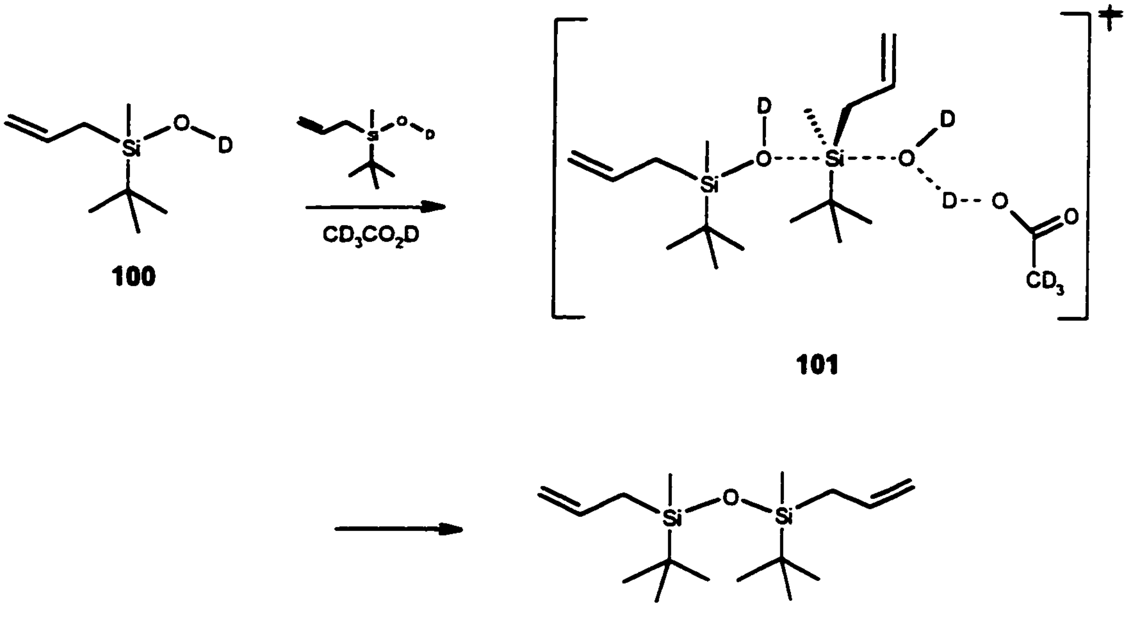


Figure 2 - 18: Cleavage Pathways of 36 with a Weak Brønsted Acid

The first formed allyl-*t*-butylmethylsilanol **100** was not actually observed, but was assumed to have undergone condensation, a characteristic transformation of silanols,[26] to generate allyl-*t*-butylmethyldisiloxane **102** in a subsequent, presumably analogous S_N2-like process, as shown in **Figure 2 - 19**. The formation of the disiloxane was ascertained from the presence of diastereomeric peaks in the ^{1}H NMR and ^{13}C NMR spectra of the product mixture, and by comparison with a sample previously prepared. The disiloxane itself remained indefinitely stable to protodesilylation of the allyl unit in the presence of excess CD_3CO_2D, based on the constant peak area ratios obtained over time using ^{1}H NMR, of the allylic methylene protons to the *tert*-butyl methyl protons, and the allylic methylene protons to the silyl methyl protons. Thus, acetic acid was not a strong enough Brønsted acid to effect protodesilylation from either the original alkoxyallylsilane, or the resulting disiloxane.



100

101

102

Figure 2 - 19: Disiloxane Formation via Condensation of **100**

A related result was obtained from the hydrolysis of allyl-*t*-butylchloromethylsilane **103**, monitored over time using ^{1}H NMR and ^{13}C NMR. The initially formed silanol **104** also underwent condensation to form the disiloxane **106**, which was ascertained by the presence of diastereomeric peaks in both the ^{1}H NMR and ^{13}C NMR spectra. Eventually, protodesilylation of the disiloxane gave rise to the silanols **107** and **108**, which then formed oligo- and/or poly-*t*-butylmethylsiloxanes by further condensation, likely with the HCl liberated upon hydrolysis of the chlorosilane, as shown in **Figure 2 - 20**.

The appearance of a near-Gaussian distribution of multiple resonances corresponding to the silyl methyl and silyl *t*-butyl methyl groups, and the disappearance of the allylic resonances, was indicative of the formation of oligosiloxanes **109** and compound **110**. The formation of structures **107** and **108** were not actually observed, but inferred, based on the formation of **109**. From these observations, one would conclude that condensation of the silanol was more rapid than protodesilylation of the silanol under conditions where the concentration of acid was low. In addition, HCl is a strong enough Brønsted acid to effect protodesilylation from the disiloxane, whereas CD_3CO_2D is not. In general, weak acids such as acetic acid, only lead to protodesilylation of allyl groups bonded to trialkylsilanes when the β-silyl cation formed from the allyl group is tertiary.[31] It was predicted, then, that protodesilylation might be made to occur from an alkoxyallylsilane with the use of a much stronger acid such as *p*-toluenesulfonic acid, as has been applied successfully to the protodesilylation of simple allylsilanes giving rise to secondary β-silyl cations.[32]

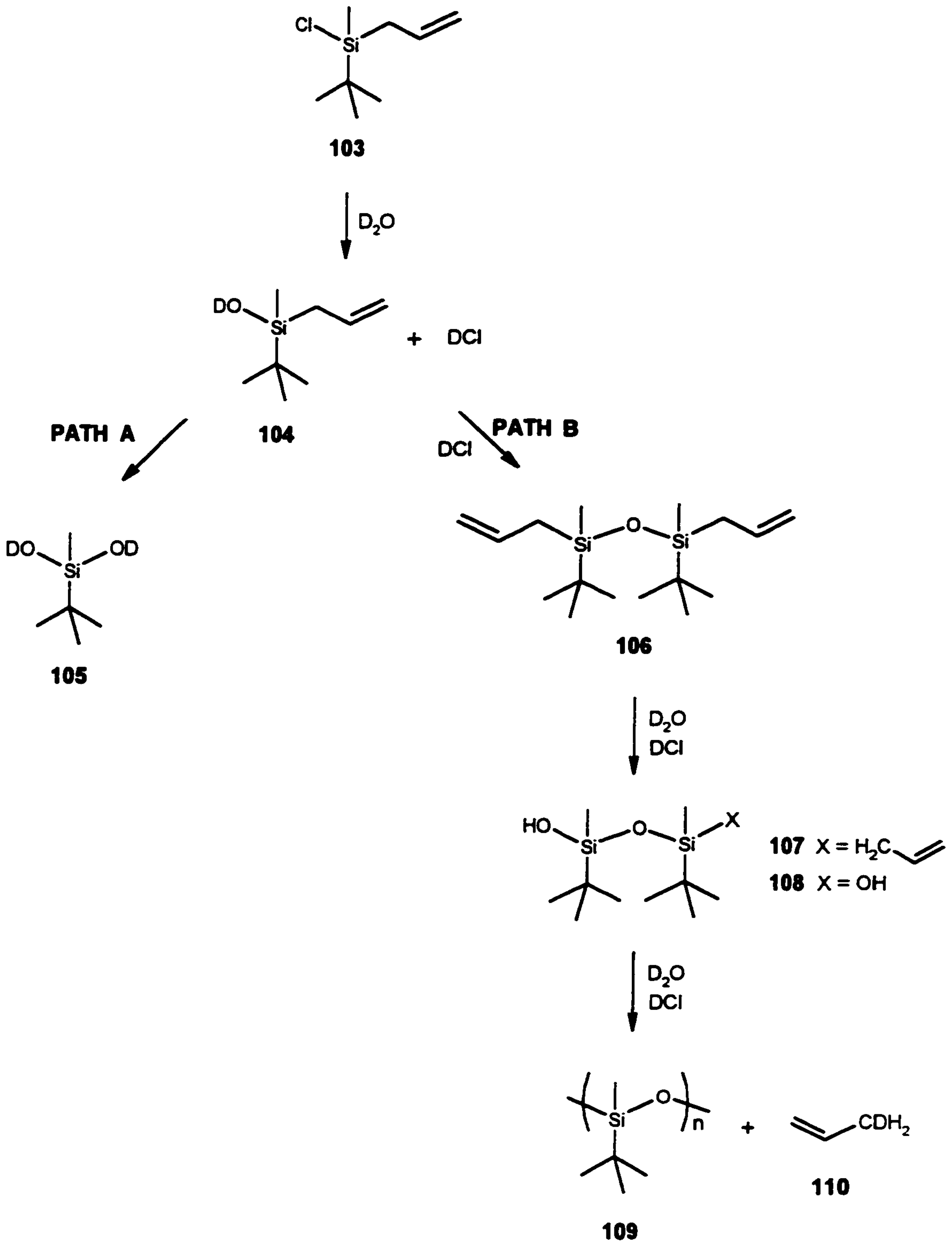


Figure 2 - 20: Hydrolysis and Condensation Pathways of **103**

2.2.3 Regioselectivity of Acidic Hydrolysis with a Strong Acid

The regioselectivity of reaction with *p*-toluenesulfonic acid (which had been dried by azeotropic distillation) was examined by adding 0.4 molar equivalents of the acid to an NMR tube containing allylbenzyloxy-*t*-butylmethylsilane in CD_2Cl_2. This was repeated using 0.8, 1.0, 1.5 or 2.0 molar equivalents of the acid to determine the effect of its concentration on the products formed. Analysis of the product mixture over time using ^1H NMR and ^{13}C NMR revealed that the first-formed products were the result of cleavage of the silicon-oxygen bond, regardless of the concentration of acid, as depicted in Path B of **Figure 2 - 21**. The concentration of *p*-toluenesulfonic acid only affected the rate at which the silicon-oxygen bond was cleaved.

The formation of benzyl alcohol was confirmed by comparison of the R_f values of the product mixture with that of an authentic sample, and by observing an increase in peak intensity in the ^1H NMR spectrum, after addition of an authentic sample of the alcohol to the reaction mixture. The resulting allyl-*t*-butylmethylsilyl product is predicted to have been the silanol **114**. Comparison of its ^1H NMR spectrum with that of allyl-*t*-butylmethyldisiloxane described in Section 2.2.3 indicated that it was not the disiloxane **115**. The silyl tosylate **113** can be ruled out since tosylate is a very good leaving group, imparting greater reactivity to **113** toward hydrolysis than the original alkoxyallylsilane **36**. Oligo- and/or poly-*t*-butylmethylsiloxanes were concluded to have formed in the presence of adventitious water at long reaction times, based on the appearance of a near-Gaussian distribution of multiple resonances corresponding to the silyl methyl and silyl *t*-butyl methyl groups, along with the disappearance of the allylic resonances.

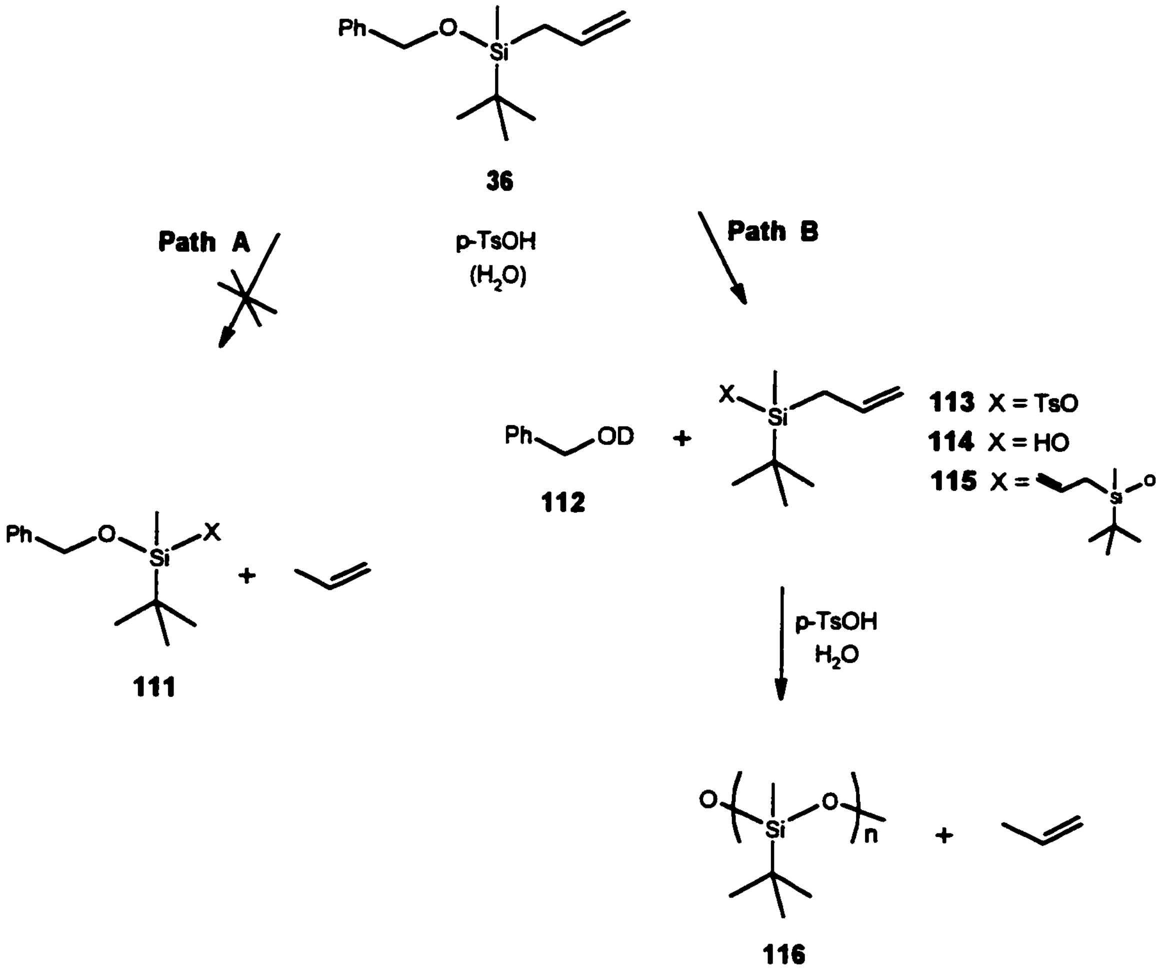
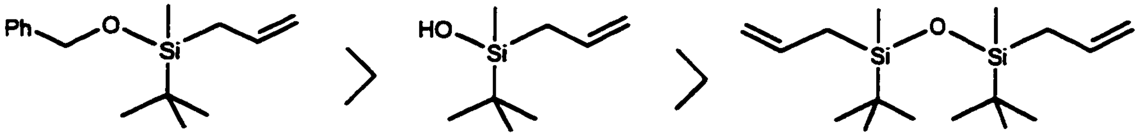


Figure 2 - 21: Cleavage Pathways of **36** with a Strong Brønsted Acid

It is conceivable that condensation of **114** was followed by rapid protodesilylation such that the disiloxane **115** was not detected. Alternatively, protodesilylation could have occurred from **114** directly, followed by condensation to give the oligosiloxanes **116**. Regardless of which path was followed, protodesilylation occurred from a species in which the basicity of the oxygen had been reduced relative to that in allylbenzyloxy-*t*-butylmethylsilane. Based upon the relative basicity of the oxygen in C-O-Si, H-O-Si and Si-O-Si systems,[33] the decreasing order of basicity of the oxygen in three different allylsilanes is given by:



Several conclusions can be drawn from all three sets of experiments. Upon addition of either a weak or a strong Brønsted acid to allylbenzyloxy-*t*-butylmethylsilane, the products recovered indicate that the first step involved cleavage of the silicon-oxygen bond. Based on these results, the β-silyl cation is assumed to be destabilized by the presence of an inductive electron-withdrawing alkoxy substituent bonded to silicon, allowing nucleophilic substitution at silicon to occur instead. A reduction in the rate of electrophilic substitution of the allyl group of allylchlorosilanes, which similarly possess electron-withdrawing halogen substituents on silicon, relative to allyltrimethylsilane, has previously been reported.[34]

In general, the rates of hydrolysis of alkoxysilanes and condensation of the resulting silanols are both dependent on the pH of the medium and the amount of available water. Under acidic conditions, condensation proceeds at a slower rate than hydrolysis.[35] Thus, once formed, allyl-*t*-butylmethylsilanol can condense to form allyl-*t*-

butylmethyldisiloxane, or undergo protodesilylation to form *t*-butylmethyldisilanol in the case that condensation is even slower than protodesilylation. Which of these two processes predominates will be determined by the pH of the medium, the concentration of acid in solution, and the strength of the acid participating in electrophilic addition to the allyl π-bond.

Based on the selectivity with which the different Brønsted acids effected protodesilylation, it appears that only upon reduction of the basicity of the oxygen in an alkoxyallylsilane, as in the transformation of allylbenzyloxy-*t*-butylmethylsilane to allyl-*t*-butylmethyldisiloxane, can electrophilic substitution of the allyl group become a competitive reaction pathway.

2.2.4 Regioselectivity of Reaction with a Carbenium Ion as Electrophile

Since there appeared to be a preference for protonation to occur at oxygen rather than at the γ-carbon of the allyl group, the possibility of using the different steric environments around oxygen and around the allylic γ-carbon to direct electrophilic substitution to the latter site was examined. The sterically hindered and electrophilic triphenylcarbenium hexafluorophosphate was chosen as a carbon electrophile. The reaction between allylbenzyloxy-*t*-butylmethylsilane and 0.5, 1.0, 2.0 or 4.0 molar equivalents of this electrophile in CD_2Cl_2, was monitored over time using TLC, ^1H NMR and ^{13}C NMR.

The first products to form, allyl-*t*-butylmethylsilanol **124** and triphenylmethyl benzyl ether **123**, were again the result of silicon-oxygen bond cleavage, regardless of the concentration of electrophile, as shown in Path B of **Figure 2 - 22**. The presence of the latter compound was confirmed by comparison with the ^{1}H NMR spectrum of an authentic sample of it, which had been prepared by an independent synthesis. The concentration of electrophile only affected the rate at which triphenylmethyl benzyl ether was formed.

Following the onset of formation of triphenylmethyl benzyl ether, the benzyloxy-*t*-butylmethylsilyl product **118** and 4,4,4-triphenyl-1-butene **119**, resulting from electrophilic substitution of the allyl group (Path A), appeared concomitantly with formation of compounds **123** and **124**, regardless of the concentration of carbenium ion. Formation of compound **119** was confirmed by comparison with an authentic sample, also prepared independently. At low conversions, it was clear from the integration of peaks in the ^{1}H NMR spectra that **119** had originated from silicon-carbon bond cleavage of structure **36**. However, at higher conversions, it is unclear whether it continued to form from **36**, **124**, or both. At very long reaction times, benzyl alcohol was detected and its presence was confirmed using TLC and by the addition of an authentic sample to the reaction mixture. Oligo- and/or poly-*t*-butylmethylsiloxanes were concluded to have formed in the presence of adventitious water, based on the appearance of a near-Gaussian distribution of multiple resonances corresponding to the silyl methyl and silyl *t*-butyl methyl groups, along with loss of compound **124**.

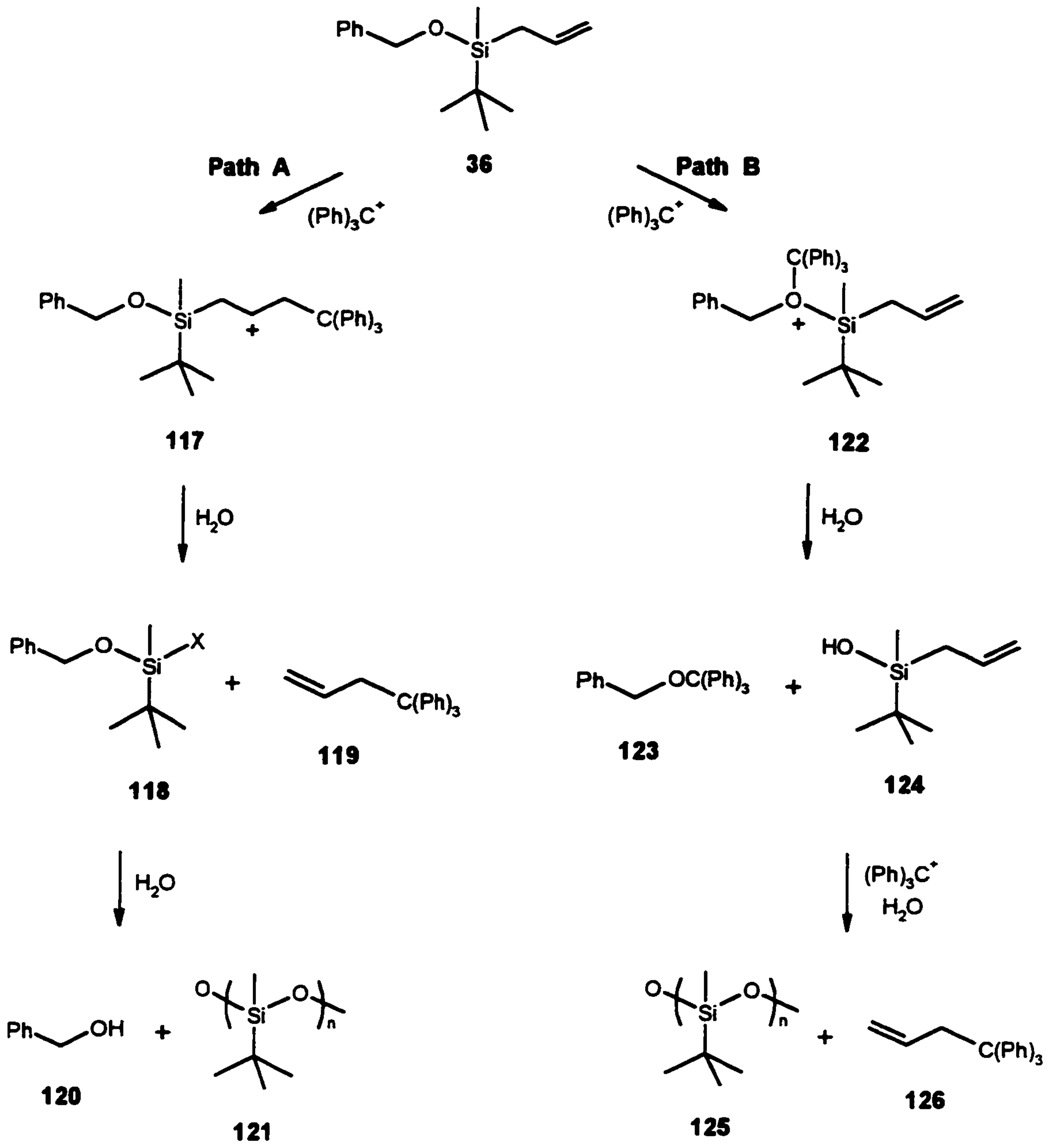


Figure 2 - 22: Cleavage Pathways of 36 with a Carbenium Ion as Electrophile

If the rationale that was used to explain the regioselectivity of reaction of allylbenzyloxy-*t*-butylmethylsilane with Brønsted acids is extended to these results, then the initial formation of triphenylmethyl benzyl ether would have arisen from a transition state in which the electrophilic triphenylcarbenium ion participated in assisting departure of the alkoxy substituent. As illustrated in **Figure 2 - 23**, the steric crowding in the transition structure **127** would be considerably greater than that in structure **39**. This would allow electrophilic substitution of the allyl group to become a competitive reaction pathway. Thus, there seems to be a trade-off between destabilization of the β-silyl cation as a result of inductive electron-withdrawal at silicon, and steric hindrance in the transition state for nucleophilic substitution at silicon. However, it should be emphasized that this is presumed to be different from steric hindrance of nucleophilic attack at silicon caused by the bulky silyl substituents themselves. Had that been the case, electrophilic addition to the allyl group would have occurred instead of electrophilic substitution,[36] as reported by Mayr and co-workers for allyl-*t*-butyldimethylsilane **128**, shown in **Figure 2 - 24**.[37]

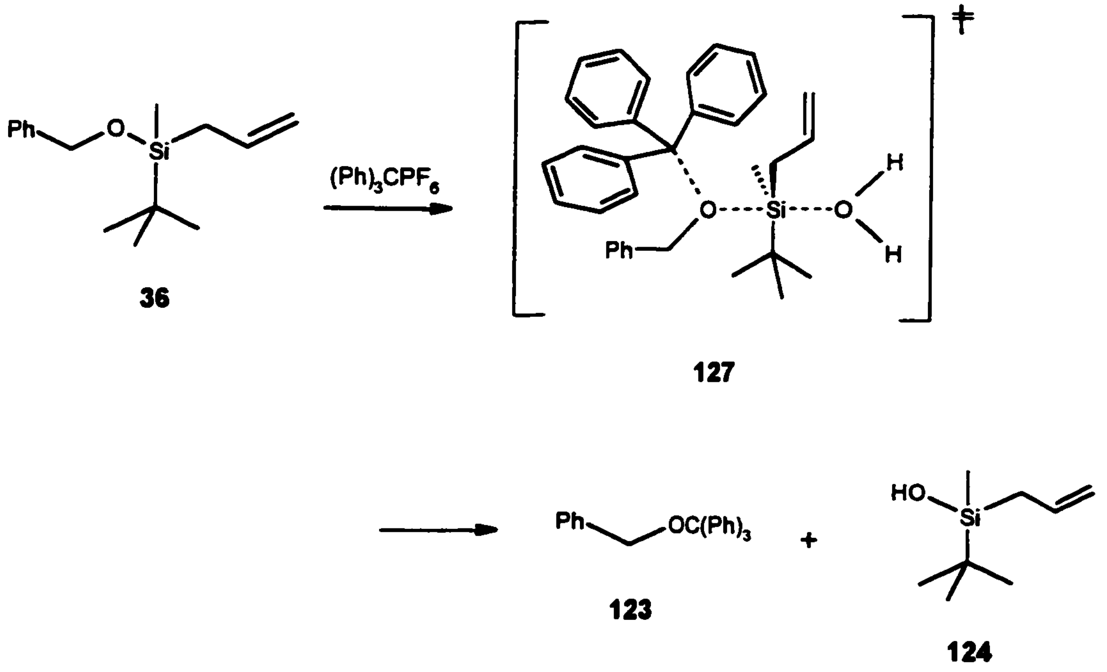


Figure 2 - 23: Silicon-Oxygen Bond Cleavage of 36 via S_N2-Like Transition State

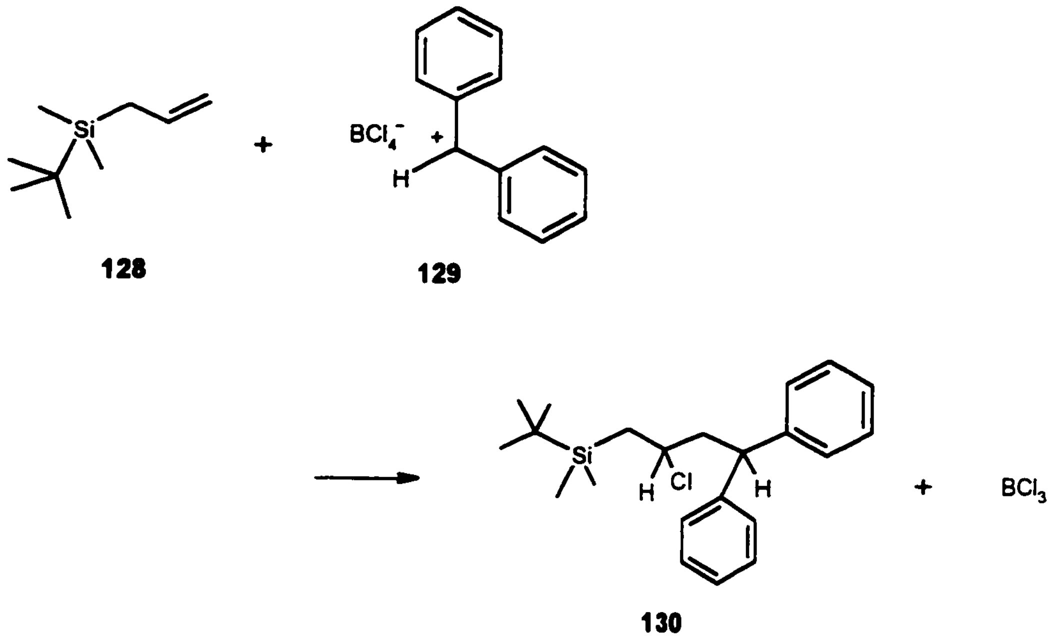


Figure 2 - 24: Electrophilic Addition to Allylsilane 128

2.2.5 Regioselectivity of Reaction with an Aldehyde as Electrophile

In order to determine whether electrophilic substitution of the allyl group would occur with a carbon electrophile that would be more typically found in syntheses of organic compounds, the regioselectivity of reaction of allylbenzyloxy-*t*-butylmethylsilane with benzaldehyde was examined. Although trialkylallylsilanes typically react with aldehydes and ketones in the presence of Lewis acids to give homoallylic alcohols, no reaction could be detected using TLC and ^{1}H NMR after addition of allylbenzyloxy-*t*-butylmethylsilane to a solution of benzaldehyde and $BF_3 \cdot OEt_2$. Only the unreacted alkoxyallylsilane was recovered from the reaction mixture.

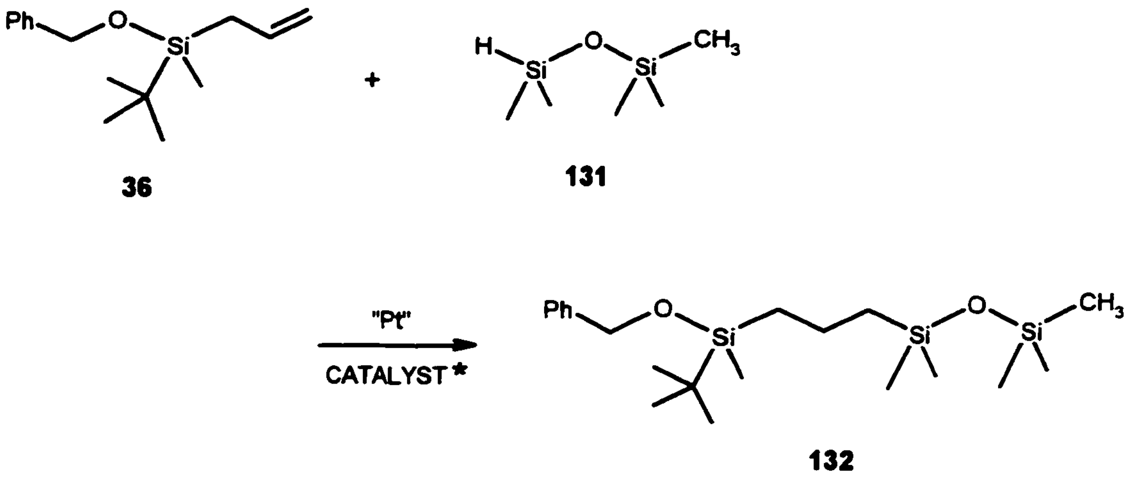
These results are similar to those from a related study published by Chan and co-workers involving allylic transposition via alkoxyallylsilanes.[38] $BF_3 \cdot OEt_2$ was chosen as the Lewis acid in this study since Chan and co-workers reported that it did not lead to cleavage of the silicon-oxygen bond, unlike $AlCl_3$, $SnCl_4$ and $TiCl_4$.

The tetrahydropyrans **80** (shown in **Figure 2 - 12**) were the major by-products recovered along with homoallylic alcohols from the reaction of allylsilanes with aldehydes, as reported by several researchers.[18] Since none of the tetrahydropyran product was obtained when benzaldehyde was reacted with allylbenzyloxydimethylsilane,[38] it was chosen as the aldehyde in this study. However, it proved to be too weak an electrophile to react with allylbenzyloxy-*t*-butylmethylsilane. No yield of homoallylic alcohol derived from benzaldehyde was actually reported by Chan and co-workers, suggesting that they may have obtained a similar result. It remains as future research to examine the possibility of allylic transposition onto aliphatic and more electrophilic aldehydes.

Finally, in a competition reaction involving one equivalent of each of allylbenzyloxy-*t*-butylmethylsilane, allyltrimethylsilane and benzaldehyde in the presence of $BF_3 \cdot OEt_2$, only allyltrimethylsilane gave allylic transposition onto benzaldehyde. This merely served to verify the expected difference in reactivity between an alkoxydialkylallylsilane and a trialkylallylsilane toward electrophiles.

2.2.6 Stability of Alkoxy-Functionalized Disiloxane

Since utilization of the alkoxyallylsilanes as a route for the introduction of oligosiloxanes onto hydrophilic moieties was one of the applications envisioned, it remained to carry out hydrosilylation of allylbenzyloxy-*t*-butylmethylsilane with pentamethyldisiloxane **131** serving as a model oligosiloxane, catalyzed by Karstedt's catalyst. This is illustrated in **Figure 2 - 25**. A mechanism which has been proposed for the hydrosilylation reaction, involves coordination of both the hydrosilane and the double bond of the allylsilane to a platinum species, before addition of the hydrosilane across the double bond.[39] As this mechanism is different from that elucidated for electrophilic substitution of an allylsilane, and does not involve generation of a β-silyl cation, the reactivity of allylbenzyloxy-*t*-butylmethylsilane was not expected to be attenuated as a result of the electron-withdrawing substituent at silicon. And indeed, the hydrosilylation reaction proceeded in very high yield.



* $Pt_n[(CH_2{=}CHSiMe_2)_2O]_m$
where n = 2, m = 3

Figure 2 - 25: Hydrosilylation of Pentamethyldisiloxane onto 36

In order to compare the stability of the silicon-oxygen-carbon linkage in compound **132** with that found in the parent allylbenzyloxy-*t*-butylmethylsilane **36** from which it was derived, compound **132** was subject to the same hydrolysis conditions used to determine the pseudo-first-order rate constants for the alkoxysilanes described in the previous chapter. However, this proved impossible since compound **132** was insoluble in that solvent mixture. Instead, the relative reactivity order was determined in $CDCl_3$ using *p*-toluenesulfonic acid monohydrate. The change in concentration of the starting material was followed as a function of time, using TLC and ^{1}H NMR.

Cleavage of the silicon-oxygen bond in allylbenzyloxy-*t*-butylmethylsilane could be followed to near complete conversion before any protodesilylation of the allyl group commenced, as judged from the integration of peaks in the ^{1}H NMR spectra. Similarly, cleavage of the Si-O-Si silicon-oxygen bonds was not detected during cleavage of the Si-O-C silicon-oxygen bond of compound **132**. It was found that the rate of Si-O-C cleavage was approximately the same in both compounds. This indicates that the steric and electronic properties of the silyl group, separated by a propyl unit from the silicon at which hydrolysis takes place, does not affect the rate of alkoxysilane hydrolysis. Consequently, the hydrolytic stability of the silicon-oxygen-carbon linkage in a "silicone"-modified ether, once formed, should be controlled predominantly by the steric and electronic properties of the substituents at silicon and the alcohol carbon atom, as it is in silyl ethers. Therefore, protecting group methodology can be used to tailor the properties of a "silicone"-modified ether.

2.3.1 Summary

In their reaction with protic acids, the alkoxyallylsilanes were found to undergo silicon-oxygen bond cleavage in preference to electrophilic substitution of the allyl group, which was attributed to decreased stability of the β-silyl cation. Protodesilylation of the allyl group became a competitive reaction only after reduction of the basicity of the oxygen.

The bulky electrophile triphenylcarbenium ion similarly led to preferential cleavage of the silicon-oxygen bond. In this case, the product ratio obtained is believed to reflect a balance between destabilization of the β-silyl cation, and destabilization of a transition state leading to nucleophilic substitution at silicon, as a result of steric crowding.

Furthermore, although alkoxyallyldimethylsilanes have previously been reported to yield homoallylic alcohols from their reaction with aldehydes as carbon electrophiles, no allylic transposition occurred between allylbenzyloxy-*t*-butylmethylsilane and benzaldehyde. These results seem to indicate that regioselectivity might only be accomplished with alkoxy groups that are bulkier than benzyloxy, and perhaps, with electrophiles that are as sterically hindered as the triphenylcarbenium ion. These requirements clearly preclude the use of alkoxyallylsilanes as both alkoxysilanes and allylsilanes.

Utilization of the alkoxyallylsilanes as reagents for the introduction of oligosiloxanes, in an effort to couple hydrophilic moieties with hydrophobic ones, can be accomplished via hydrosilylation onto the allyl group. The hydrolytic stability of the Si-O-C linkage can then be controlled through selection of appropriate silyl substituents in much the same way as would be done for an alcohol protecting group.

EXPERIMENTAL

2.4.1 General Procedures and Instrumentation

^1H NMR spectra were recorded on a Bruker AC-200 spectrometer at 200.133 MHz using the residual $CHCl_3$ present in $CDCl_3$ as internal reference. ^{13}C NMR spectra were recorded on the same instrument at 50.323 MHz, also using $CDCl_3$ as internal reference. ^{29}Si NMR spectra were recorded on a Bruker AC-300 spectrometer at 59.6 MHz.

Chemical ionization (CI), with ammonia as the reagent gas, and electron impact (EI) mass spectra were recorded on a VG Analytical ZAB-R mass spectrometer equipped with a VG 11-250 data system. Typical experimental conditions included electron energy of 70 eV and source temperature of 200 °C.

Infrared spectra were recorded on a Bio Rad FTS-40 Fourier transform spectrometer. Liquid samples were used as neat films on NaCl discs and solid samples were prepared as KBr pellets.

2.4.2 Reagents and Solvents

Pentamethyldisiloxane, *p*-toluenesulfonic acid monohydrate, triphenylcarbenium hexafluorophosphate, benzaldehyde and $BF_3{\cdot}OEt_2$ were purchased from Aldrich and used without purification. Allyltrimethylsilane and platinum-divinyltetramethyldisiloxane complex were purchased from Gelest and used without purification. D_2O, CD_2Cl_2 and $CDCl_3$ were obtained from Cambridge Isotope Labs and used without purification.

2.4.3 Compounds Prepared

Allyl-*t*-butylchloromethylsilane, allylbenzyloxy-*t*-butylmethylsilane, allyl-*t*-butyl(2-phenylethanoxy)methylsilane and allyl-*t*-butylcyclopentanoxymethylsilane were prepared as described in Chapter One.

1-(Benzyloxy-t-butylmethylsilyl)-3-(pentamethyldisiloxane)-propane, 132:

To a flask containing pentamethyldisiloxane (0.28 g, 2 mmol) and allylbenzyloxy-*t*-butylmethylsilane (0.5 g, 2 mmol) in hexanes (5 mL), was added platinum-divinyltetramethyldisiloxane complex (1 drop) at 25 °C. After stirring overnight, purification by chromatography with eluent pentane:ether (19:1) yielded 0.75 g, 96% of a colorless oil. ^{1}H NMR ($CDCl_3$): δ 7.46 (m, 5H), 4.92 (s, 2H), 1.65 (m, 2H), 1.12 (s, 9H), 1.05 (m, 2H), 0.79 (m, 2H), 0.27 (s, 3H), 0.23 (s, 9H), 0.20 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 141.5, 128.1, 126.8, 126.0, 65.3, 26.4, 23.2, 18.8, 17.8, 17.1, 2.0, 0.5, -7.0; ^{29}Si NMR ($CDCl_3$): δ 18.43, 9.07, 6.55; IR (neat, NaCl): ν 2957, 2930, 2859, 1254, 1064, 842 cm^{-1}; MS (EI, m/z): 181 (12), 91 (100); MS (CI, NH_3, m/z): 207 (26), 91 (100), 72 (22), 43 (16); HRMS (m/z): calcd for $C_{20}H_{39}O_2Si_3$ (M^+ - H): 395.2257, found: 395.2215.

2.4.4 General Procedure for Acidic Hydrolysis

In Aqueous Media:

To an NMR tube containing the silyl ether (0.076 mmol) under N_2 at 25 °C was added THF-d_8 (0.26 mL), D_2O (0.12 mL), and CD_3CO_2D (0.38 mL), to make a 0.1M solution of the silyl ether. The ^1H NMR spectra were acquired initially within 2 min of addition of CD_3CO_2D, and subsequently every 10 min. The presence of benzyl alcohol was confirmed by injecting an authentic sample into the NMR tube containing the reaction mixture. The presence of allyl-*t*-butylmethyldisiloxane was confirmed by comparison with an authentic sample of both diastereomers. ^1H NMR ($CDCl_3$): δ 5.84 (m, 2H), 4.91 (m, 4H), 1.63 (m, 4H), 0.91 (s, 9H), 0.89 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (CD_2Cl_2): δ 134.1, 133.2, 115.7, 115.3, 25.5, 25.2, 23.0, 22.7, 18.8, 18.5, -4.2, -4.5.

In Organic Media ($CDCl_3$):

To the silyl ether in a flask (0.07 mmol) with $CDCl_3$ (3 mL), was added *p*-toluenesulfonic acid monohydrate (0.28 mmol). The reaction was monitored by TLC and ^1H NMR every 10 min.

In Organic Media (CD_2Cl_2):

To an NMR tube containing allylbenzyloxy-*t*-butylmethylsilane (0.022 g, 0.091 mmol) in CD_2Cl_2 (0.5 mL) under N_2 at 25 °C was added *p*-toluenesulfonic acid, which had been dried by azeotropic distillation (0.091 mmol in 0.5 mL CD_2Cl_2). The ^{1}H NMR spectra were acquired initially within 5 min, and subsequently every 15 min. This was then repeated using 0.4, 0.8, 1.5 and 2.0 molar equivalents of *p*-toluenesulfonic acid. The absence of benzyl *p*-toluenesulfonate was confirmed by comparison with an authentic sample which had been prepared by the method of Tipson.[40] ^{1}H NMR (CD_2Cl_2): δ 7.78 (m, 2H), 7.32 (m, 7H), 5.02 (s, 2H), 2.44 (s, 3H).

2.4.5 Reactions with electrophiles

Triphenylcarbenium Ion:

To an NMR tube containing allylbenzyloxy-*t*-butylmethylsilane (0.02 g, 0.08 mmol) in CD_2Cl_2 (0.8 mL) under N_2 at 25 °C was added triphenylcarbenium hexafluorophosphate (0.031 g, 0.08 mmol). The ^{1}H NMR spectra were acquired initially within 5 min, and subsequently every 15 min. This was then repeated using 0.5, 2.0 and 4.0 molar equivalents of triphenylcarbenium hexafluorophosphate. The presence of 4,4,4-triphenyl-1-butene was confirmed by comparison with an authentic sample that was prepared according to the procedure of Bachmann and co-workers.[41] ^{1}H NMR (CD_2Cl_2): δ 7.21 (m, 15 H), 5.65 (m, 1H), 4.95 (m, 2H), 3.46 (m, 2H). The presence of triphenylmethyl benzyl ether was confirmed by comparison with an authentic sample that was prepared according to the procedure of Chaudhary and co-workers.[42] ^{1}H NMR (CD_2Cl_2): δ 7.30 (m, 20H), 4.19 (s, 2H).

Benzaldehyde:

To a flask containing benzaldehyde (0.1 mL, 0.98 mmol) and $BF_3 \cdot OEt_2$ (0.12 mL, 0.98 mmol) in CD_2Cl_2 (10 mL) was added allylbenzyloxy-*t*-butylmethylsilane (0.24 g, 0.96 mmol) at 0 °C. After stirring at 25 °C for 24 h, only starting material was detected by TLC and ^1H NMR.

Competition Reaction with Allyltrimethylsilane:

To a flask containing benzaldehyde (0.1 mL, 0.98 mmol) and $BF_3 \cdot OEt_2$ (0.12 mL, 0.98 mmol) in CD_2Cl_2 (5 mL) was added a solution of allylbenzyloxy-*t*-butylmethylsilane (0.23 g, 0.93 mmol) and allyltrimethylsilane (0.15 mL, 0.93 mmol) in CD_2Cl_2 (5 mL) at 0 °C. When benzaldehyde could no longer be detected using TLC, a saturated aqueous solution of $NaHCO_3$ was added at 0 °C, followed by extraction using CH_2Cl_2, drying over $MgSO_4$, and removal of solvent under reduced pressure. The presence of 1-phenyl-3-buten-1-ol was confirmed by comparison with an authentic sample. This had been prepared by the reaction of benzaldehyde with allytrimethylsilane in the presence of $BF_3 \cdot OEt_2$, and compared with previously reported characterization. ^1H NMR (CD_2Cl_2): δ 7.34 (m, 5H), 5.71 (m, 1H), 4.95 (m, 2H), 4.09 (t, $J = 6.5$ Hz, 1H), 2.53 (m, 2H), 1.78 (s, 1H).

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CHAPTER 3

ALLYL TRANSFER ONTO DICOBALT-COMPLEXED ACETYLENIC KETONES AND ALDEHYDES

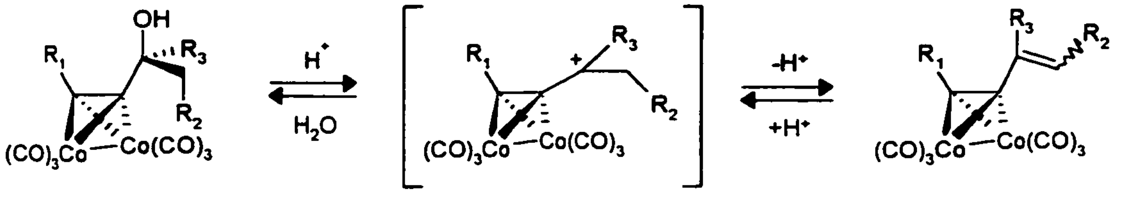
INTRODUCTION

DICOBALT-COMPLEXED PROPARGYL ALCOHOLS AND DYNAMIC PROCESSES OF THE TRANSITION METAL CLUSTER

3.1.1 Dicobalt-Complexed Acetylenes

The complexation of dicobalt hexacarbonyl to acetylenes was originally investigated as a method of protecting the triple bond in order to carry out addition reactions such as reduction or hydroboration of a double bond in the presence of the more reactive triple bond.[1] When complexed, the triple bond has been shown to be relatively inert under these and a variety of other reaction conditions.

Studies on both the acid-promoted hydration of alkene groups adjacent to dicobalt-complexed alkynes, and the dehydration of dicobalt-complexed propargyl alcohols, led to the proposal of a hydration/dehydration equilibrium proceeding through an intermediate carbocation **134** of exceptional stability, which connects the dicobalt hexacarbonyl complexes of propargyl alcohol and 1,3-enyne as shown in **Figure 3 - 1**.[2]



133 **134** **135**

Figure 3 - 1: Acid-Promoted Equilibration of Propargyl Alcohol and 1,3-Enyne

The [(propargylium)$Co_2(CO)_6$]BF_4 complex, which was generated from the corresponding propargyl alcohol, was then introduced as a regioselective propargyl cation synthon for the formation of carbon-carbon bonds at the propargylic site. This route to carbon-carbon bond formation circumvents the isomerization characteristic of propargyl and allenyl organometallics, which can lead to product mixtures.[3]

3.1.2 Charge Stabilization by Transition Metal Clusters

Early studies on trimetallic tetrahedral cluster compounds have provided a framework within which the structure and properties of dicobalt hexacarbonyl-complexed acetylene compounds can be understood. The carbenium hexafluorophosphate salts of alkylidynetricobalt nonacarbonyl complexes were prepared by treatment of the parent alcohols with hexafluorophosphoric acid, as shown in equation (20).[4]

$$(OC)_9Co_3CCH(OH)R \xrightarrow{H^+PF_6^-,\ (EtCO)_2O} [(OC)_9Co_3CCHR]^+\ [PF_6]^- \qquad (20)$$

Two limiting resonance structures can be drawn to represent these cations, in which the charge is localized on either carbon (shown upright in structure **136**), or on the cobalt (shown bent in **137** and **138**) in **Figure 3 - 2.** It was suggested by Seyferth that the stabilization of positive charge at the position α to the trimetallic cluster could be the result of a direct interaction with the metal center, allowing the charge to be delocalized onto the CO ligands.[5]

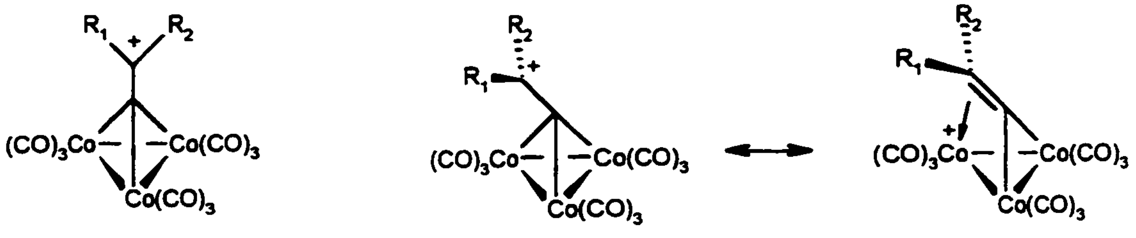
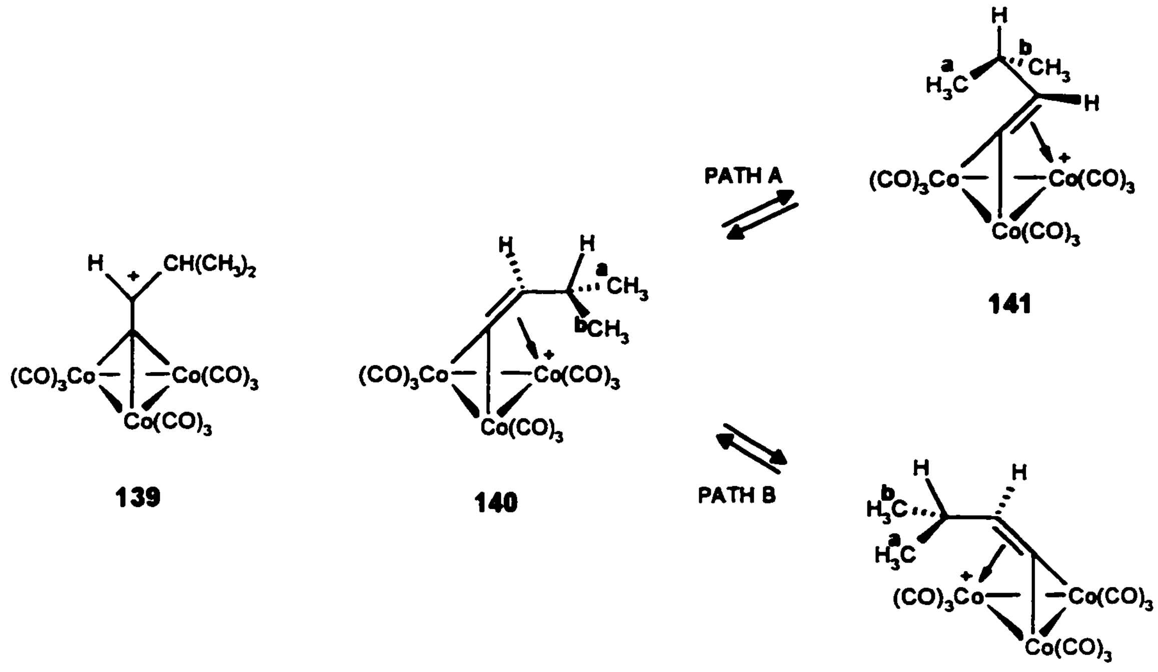


Figure 3 - 2: Charge Delocalization on Carbon *versus* Cobalt

This was later corroborated by Edidin and co-workers in an experiment designed to distinguish between the chiral environment of the bent structure **140** and the achiral environment expected of the upright structure **139** shown in **Figure 3 - 3**.[6] The methyl groups of the isopropyl substituent in **139** are expected to be enantiotopic and show magnetic equivalence on the NMR timescale. In contrast, the methyl groups in **140** are diastereotopic, and magnetically non-equivalent. Variable temperature ^{13}C NMR spectroscopy revealed that the single resonance corresponding to the isopropyl methyl groups observed at room temperature separated into two sets of doublets as the temperature was lowered to -65 °C. This was interpreted as evidence in support of a bent structure having charge delocalized onto the metal vertex, which undergoes a dynamic process that interconverts the diastereotopic groups. Two different mechanisms exist for interconversion of the diastereotopic methyl groups. One involves 180 ° rotation about the C1-C2 bond (Path A) yielding **141**, as depicted in **Figure 3 - 3**. The other involves migration of the alkylidene ligand from one cobalt vertex to the other with simultaneous rotation about the C1-C2 bond (Path B) yielding **142**. For this particular compound, the two different processes actually lead to the same product. Thus, structures **141** and **142** are in fact two representations of the same molecule.



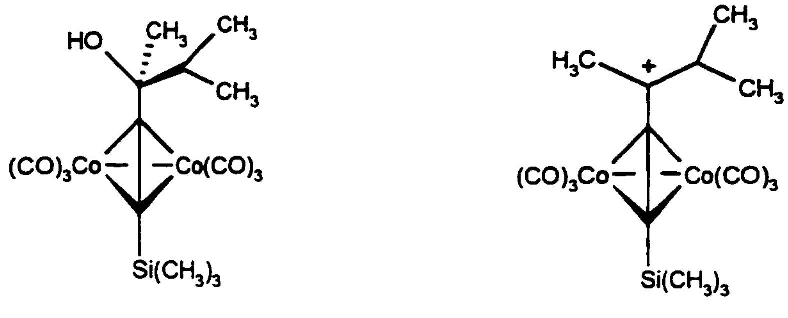
139 **140** **141** **142**

Figure 3 - 3: Mechanisms for Interconversion of the Diastereotopic Methyl Groups

3.1.3 Dynamic Behaviour of Dicobalt Hexacarbonyl-Complexed Propargyl Cations

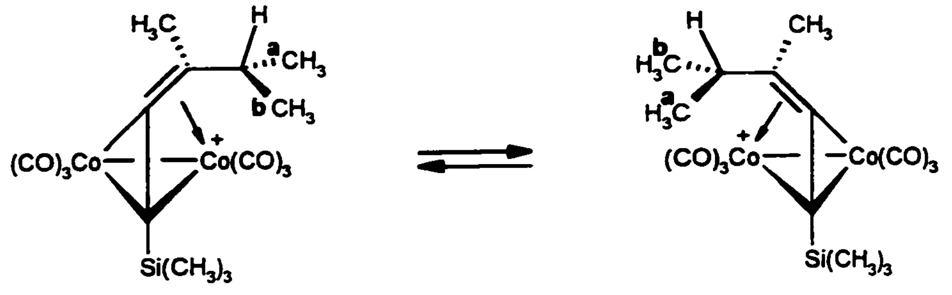
These early studies have provided insight into the elucidation of a dynamic process that can occur in cations derived from dicobalt hexacarbonyl-complexed acetylene compounds, the latter of which are obtained by isolobal replacement of a $Co(CO)_3$ vertex in alkylidynetricobalt nonacarbonyl cluster compounds by a carbynyl (RC≡) moiety.[7]

Two distinct fluxional processes[8] in the propargyl cation generated from the parent alcohol **143** (**Figure 3 - 4**) have been detected by variable temperature ^1H and ^{13}C NMR.[9] The ^{13}C NMR spectrum of the cation **144** at 183 K consisted of four resonances corresponding to the isopropyl methyl groups, but only two sets of resonances for every other carbon. As the temperature was increased to 233 K, the four isopropyl methyl signals coalesced into two, while all others remained unaffected. This was interpreted as evidence of the presence of two diastereomers, each of which contained diastereotopic isopropyl methyl groups, whose interconversion had been frozen out at 183 K. Upon warming, interconversion of the isopropyl methyl groups in each of the two diastereomers occurred. Based on prior studies on trimetallic systems, this was attributed to a process whereby the vinylidene group migrated from one cobalt vertex to the other, with simultaneous rotation about the C1-C2 bond, termed "antarafacial migration". This process is depicted in **Figure 3 - 5** for one diastereomer. The methyl groups have been labeled to show how they are exchanged.



143 **144**

Figure 3 - 4: Parent Alcohol and Corresponding Propargyl Cation



145 **146**

Figure 3 - 5: Antarafacial Migration of the Cation **144**

As the temperature was further increased to 253 K, the two isopropyl methyl resonances in the ^{13}C NMR spectrum coalesced with the two resonances corresponding to the propargyl methyl group, resulting in a single peak. This second higher energy process exchanged the environments of the two substituents on the propargyl carbon, and can be described by two mechanisms. The first mechanism, termed "suprafacial migration", involves migration of the vinylidene group from one cobalt vertex to the other. This is depicted in **Figure 3 - 6** (the conversion of **145** to **147**, and the conversion of **146** to **148**), where the propargyl methyl substituent is converted from a conformation in which it is "*syn*" to a cobalt-cobalt bond (**145** and **146**), to one in which it is "*syn*" to a carbon-cobalt bond (**147** and **148**). Alternatively, the environment of the two substituents on the propargyl carbon could be exchanged by simple rotation about the vinylidene carbon-carbon bond. This would convert **145** to its diastereomer **148**. The experimental results do not allow for a distinction to be made between suprafacial migration and rotation.

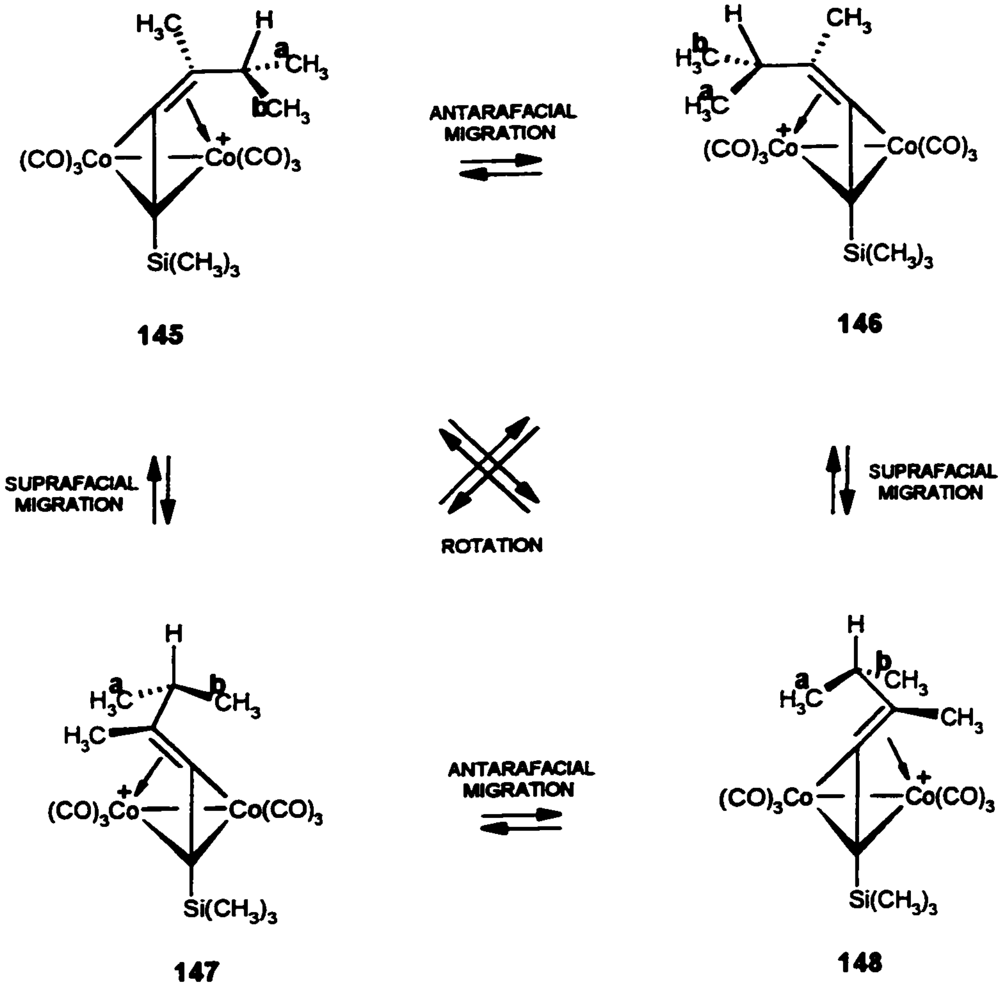
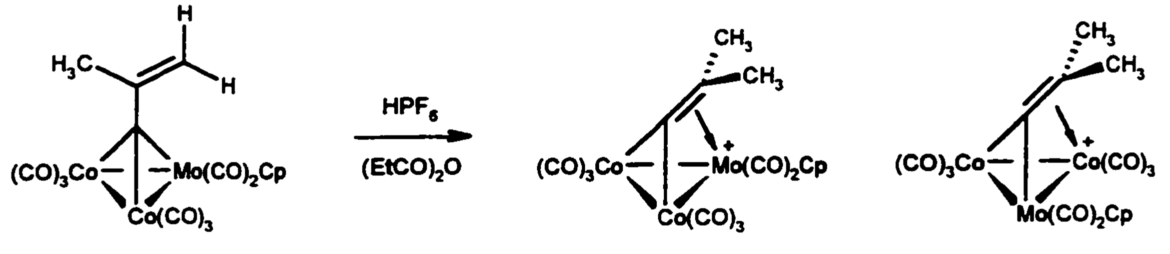


Figure 3 - 6: Dynamic Processes of the Cation **144**

3.1.4 Charge Stabilization in Bimetallic-Complexed Propargyl Cations

Considerable spectroscopic data supports the hypothesis that positive charge can be preferentially delocalized onto one metal vertex in tetrahedral cluster compounds containing two different metal vertices.[10] Upon protonation, the bimetallic cluster compound **149** could, in principle, give rise to the cation **150**, having positive charge delocalized onto the molybdenum vertex (**Figure 3 - 7**).[11] This structure has C_s symmetry, and the two methyl groups are magnetically equivalent. It could also give rise to the cation **151** with charge delocalized onto the cobalt vertex. In the latter structure, the methyl groups are rendered magnetically non-equivalent by the chiral nature of the cluster. Following protonation of compound **149**, the ^{13}C NMR spectrum of the cation generated revealed only a single methyl resonance which did not change over the temperature range of 273 K to 183 K. This was interpreted as evidence that the charge was delocalized onto the molybdenum vertex, and the molecule was not fluxional on the NMR time scale, within the temperature limits of the study.



149 **150** **151**

Figure 3 - 7: Charge Delocalization onto either Molybdenum or Cobalt Vertex

3.1.5 Stereochemical Influence of Dicobalt-Complexed Propargyl Cation

The ability of one vertex to stabilize the charge preferentially can be used to synthetic advantage, since it precludes the formation of all possible stereoisomeric propargylic cations through fluxional processes. This subsequently reduces the number of stereoisomeric products that are formed by nucleophilic attack at the propargyl cation. As an illustrative example, four possible stereoisomers can be formed when a CO ligand on cobalt is replaced with triphenylphosphine, starting from a racemic mixture of the alcohol **152** (R_1 = H; R_2 = alkyl or Ph), as shown in **Figure 3 - 8**.[12] Experimentally, it was found that when the substituent R_2 was methyl or phenyl, both sets of diastereomeric alcohols (the enantiomeric **153**, **154** and **155**, **156**) were formed by replacement of a cobalt CO ligand with PPh_3.

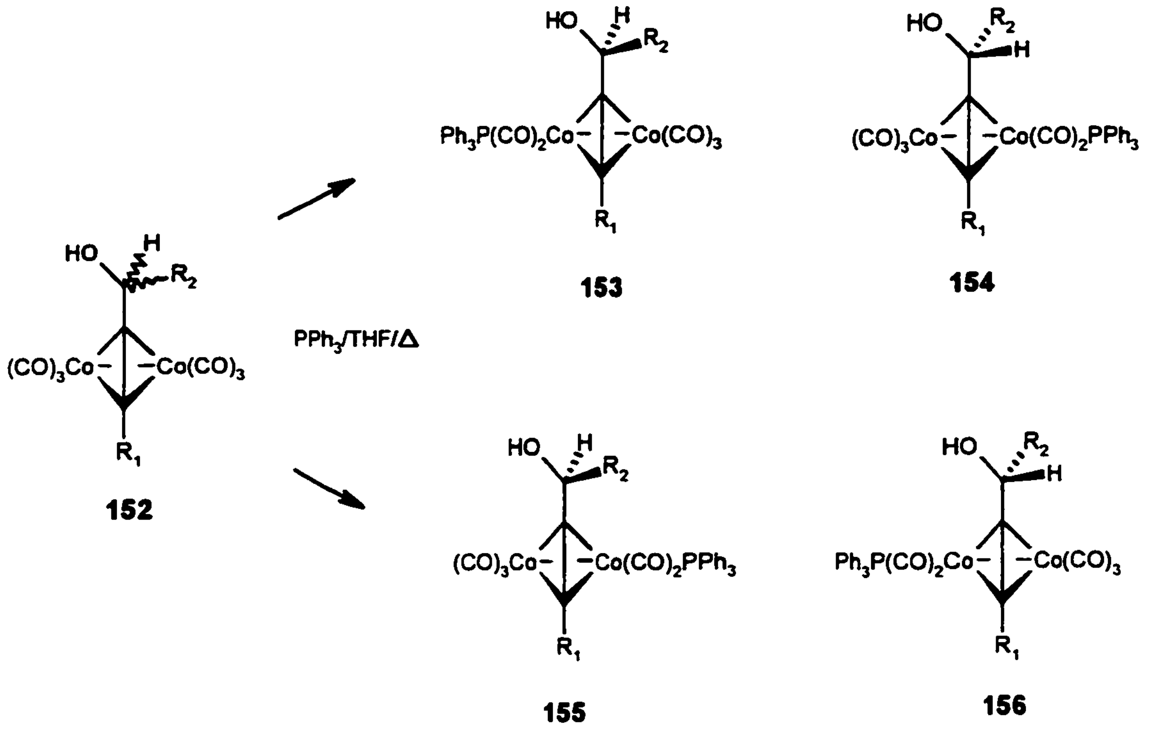
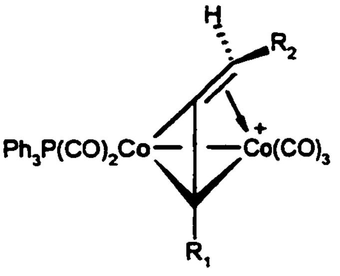


Figure 3 - 8: Stereoisomers Formed from Ligand Substitution on Cobalt

Upon protonation of this alcohol, of the four possible diastereomeric cations that could be formed (shown in **Figure 3 - 9**), only two were detected using ^1H and ^{13}C NMR spectroscopy.[13] The two cationic diastereomers formed were predicted to have structures **158** and **159**, based on their spectroscopic properties and reactivity. That is, on proceeding from the complexed alcohols **153 - 156** to their corresponding cations **157 - 160**, the carbonyl stretching band was observed in their infrared spectra to shift to higher frequencies. The smaller magnitude of this shift, relative to that found when the analogous dicobalt hexacarbonyl-complexed propargyl alcohols were converted to cations, was attributed to increased back-bonding, as a result of replacing the CO ligand with the more strongly σ-donating PPh_3 ligand.[8c,d] In addition, the increased hydrolytic stability and decreased reactivity of the phosphine-substituted cationic complexes **157 - 160** with nucleophiles which had been shown to react with the parent dicobalt hexacarbonyl-complexed cations, such as allyltrimethylsilane, points to a more electron-rich complex, with charge delocalized onto the phosphine-substituted cobalt vertex.



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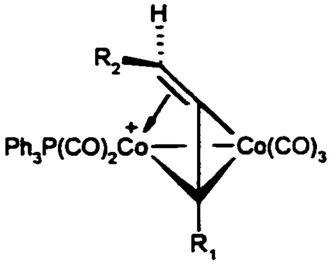

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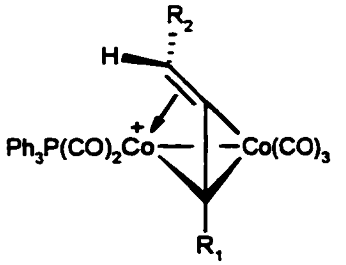

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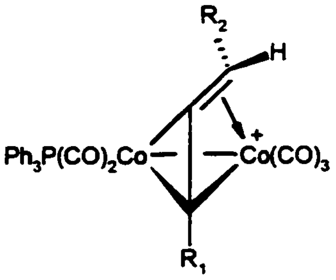


160

Figure 3 - 9: Diastereomeric Cobalt Cations

When R_2 was a sterically hindered substituent such as isopropyl or *t*-butyl, only one of the four possible diastereomeric alcohols was formed upon replacement of a carbonyl ligand in **152** with PPh_3.[12] This was attributed to unfavorable steric interactions between the bulky **R** group and PPh_3. Subsequently, only one of the four possible diastereomeric cations was detected after protonation of the alcohol, and nucleophilic quenching of that cation generated only one diastereomeric product.[13] The nucleophilic quenching of cations is depicted in **Figure 3 - 10**.

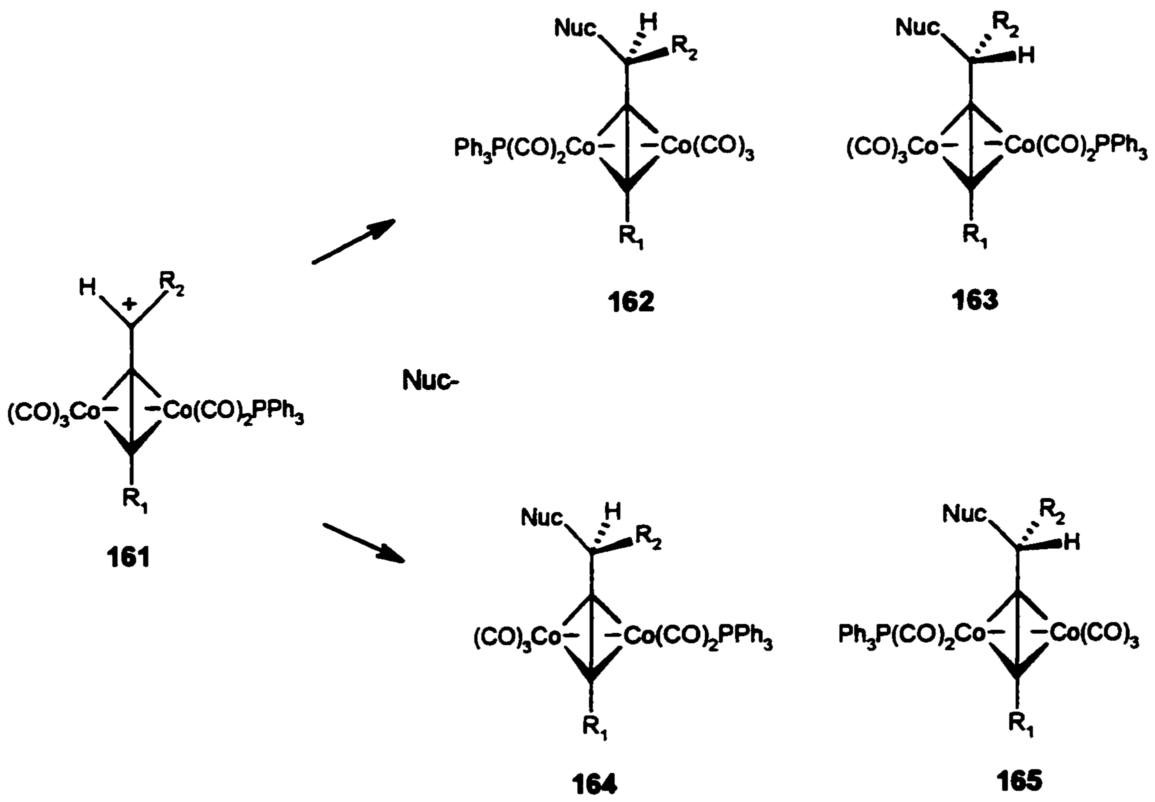


Figure 3 - 10: Nucleophilic Quenching of Cation **161**

DIASTEREOSELECTIVITY OF ALLYL TRANSFER ONTO ACETYLENIC ALDEHYDES VIA DICOBALT CLUSTER

3.2.1 The Hexa-1,5-Enyne System in Organic Synthesis

The development of methods for the formation of highly functionalized acyclic structures containing multiple asymmetric centers, to serve as chiral building blocks, is of continued interest for the convergent synthesis of more complex biologically active molecules. Synthesis of the hexa-1,5-enyne system was originally developed as a method of creating a carbon framework which, after selective reduction of the triple bond, would provide an alternative approach to the preparation of the hexa-1,5-diene system.[14] Numerous procedures have been reported for the direct formation of 1,5-dienes based on the coupling of an allylic halide with either an organometallic allyl reagent (derived from either alkali or alkaline earth metals), or a transition metal π-allyl complex.[15] For the most part, however, these methods suffer from poor stereoselectivity, poor regioselectivity as a result of 1,3-allylic transposition, and poor coupling specificity as a result of ligand exchange when two unlike allyl groups were coupled.

In addition to the intrinsic synthetic value of the hexa-1,5-enyne system, the 3,4-disubstituted-hexa-1,5-enyne fragment containing two adjacent asymmetric centers is a particularly versatile fragment. For instance, the 3,4-disubstituted-hexa-1,5-enyne fragment has found application in the formation of polycyclic structures via radical cascade reactions,[16] and in the formation of cyclopentenes containing an *exo*-olefin as part of a conjugated 1,3-diene system, via transition metal-catalyzed intramolecular coupling of the alkyne and alkene.[17] The resulting 1,3-dienes are themselves synthetically very useful, having found application in procedures such as the Diels-Alder reaction.[18] In addition, the 3,4-disubstituted-hexa-1,5-enyne fragment can also be transformed to the 3,4-disubstituted-1,5-diene system that is required for a Cope rearrangement.

A retrosynthetic analysis of the 3,4-disubstituted-hexa-1,5-enyne carbon skeleton reveals that a bond disconnection can be made at either C3-C4 or at C4-C5, as shown in **Figure 3 - 11**. Both of these strategies have been applied to the synthesis of these compounds with limited success. Coupling of a propargylic anion with an allylic halide (C3-C4 disconnection) can lead to a mixture of both acetylenic and allenic products,[19] whereas coupling of a metal acetylide with a homoallylic halide (C4-C5 disconnection) is often thwarted by a competing elimination.[20]

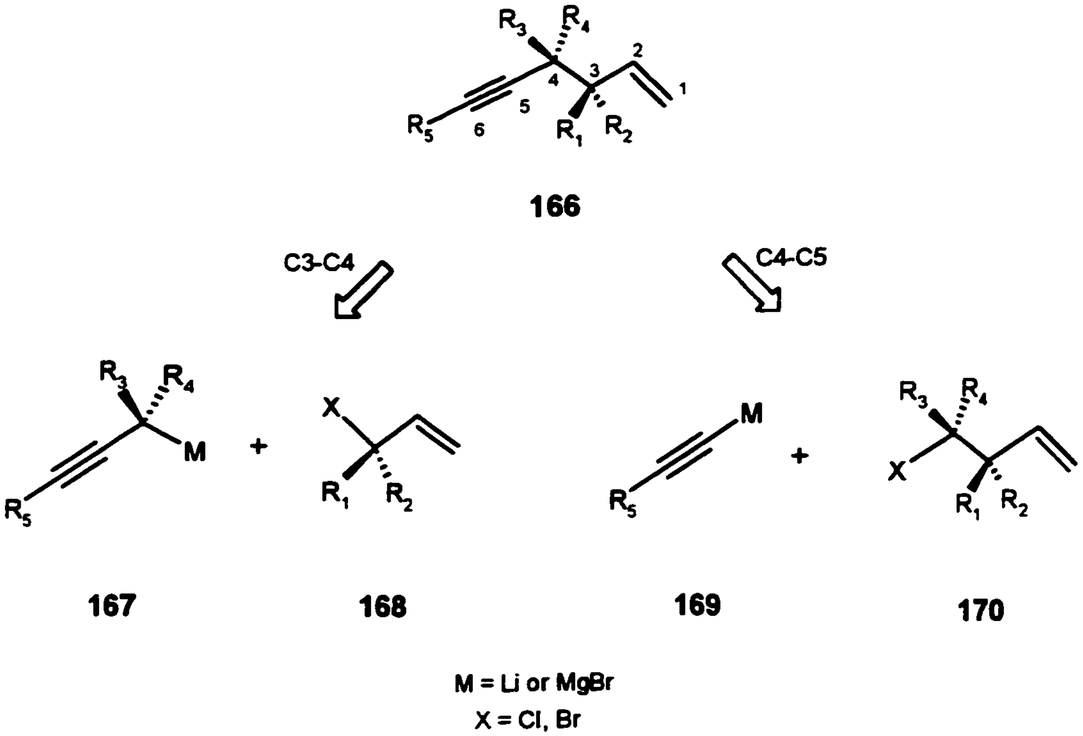
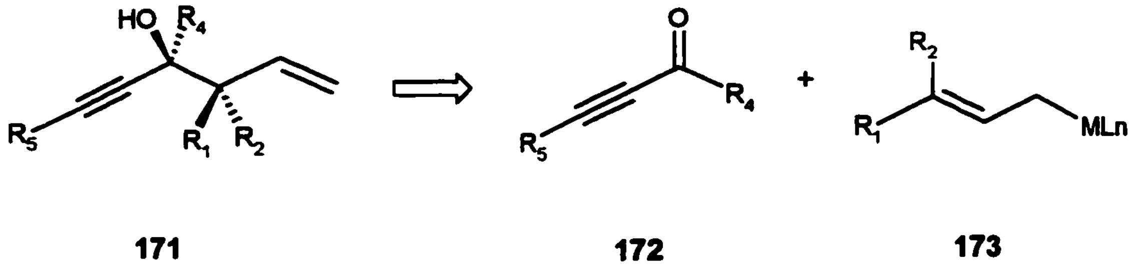


Figure 3 - 11: Retrosynthetic Analysis of the 1,5-Enyne System

3.2.2 Stereoselective Formation of the 3,4-Disubstituted-1,5-Enyne System

An alternative retrosynthetic route to preparation of the 3,4-disubstituted-hexa-1,5-enyne system involves disconnection of the C3-C4 bond, where the allylic component functions as the nucleophile, and the alkynyl component functions as the electrophile. The actual C3-C4 bond formation could be accomplished by nucleophilic addition to an acetylenic aldehyde with a (γ-alkylallyl)metal reagent (for compounds having R_1 or R_2 = alkyl, R_3 = OH, R_4 = H as shown in **Figure 3 - 12**). This has been achieved with simple diastereoselectivity as high as 90:10 (presumably the result of steric effects in an anti-periplanar transition structure, as described in Chapter Two), using the acetylenic aldehyde **174** and allylstannane compound **175**, shown in **Figure 3 - 13.**[14a]



M = Si, Sn

Figure 3 - 12: Bond Formation via Nucleophilic Addition to an Alkynal

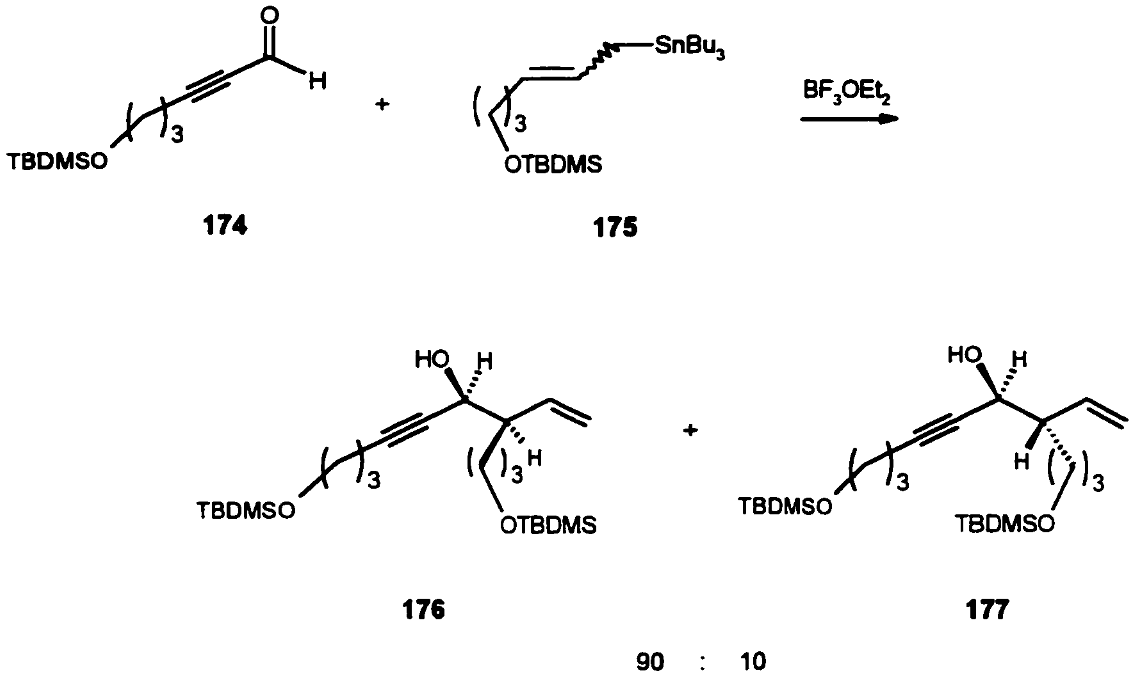


Figure 3 - 13: Diastereoselectivity Obtained from Nucleophilic Addition to Alkynal 174

For compounds defined by R_1 or R_2 = OR, R_3 = OH, R_4 = H (in **Figure 3 - 11**), bond formation at C3-C4 can be carried out by nucleophilic addition with a (γ-alkoxyallyl)metal reagent to an acetylenic aldehyde. This has been achieved with a *syn* diastereoselectivity of 90:10 using the dicobalt hexacarbonyl-complexed acetylenic aldehyde **178** and [(*Z*)-γ-methoxyallyl]-diisopinocampheylborane **179**, shown in **Figure 3 - 14**.[21] However, this transformation was limited to the use of the (*Z*)-allyl reagent; yields in the range of 20 % of **180** and **181** were obtained with the (*E*)-γ-methoxyallylborane reagent. Even lower yields of homoallylic alcohol products were obtained (5-10 %) when either the (*Z*)-allyl or the (*E*)-allyl reagent was added to the corresponding non-complexed acetylenic aldehyde.

The dicobalt cluster only played a small role in improving the diastereoselectivity that was controlled to a large extent by the presence of bulky substituents on boron. As with other reactions involving allyl transfer from boron, the stereoselectivity was rationalized within the context of a Zimmerman-Traxler transition state model.[22] In this closed, chair-like transition structure, the dominant steric interaction was assumed to be the 1,3-diaxial interaction between the aldehyde **R** substituent and the isopinocampheyl group, as shown in **Figure 3 - 15**. A bulky, dicobalt hexacarbonyl-complexed acetylene **R** group would have amplified the preference for a transition structure such as **182**, leading to the syn diastereomer (from the (*Z*)-allylboron reagent), in which the 1,3-diaxial interaction is minimized.

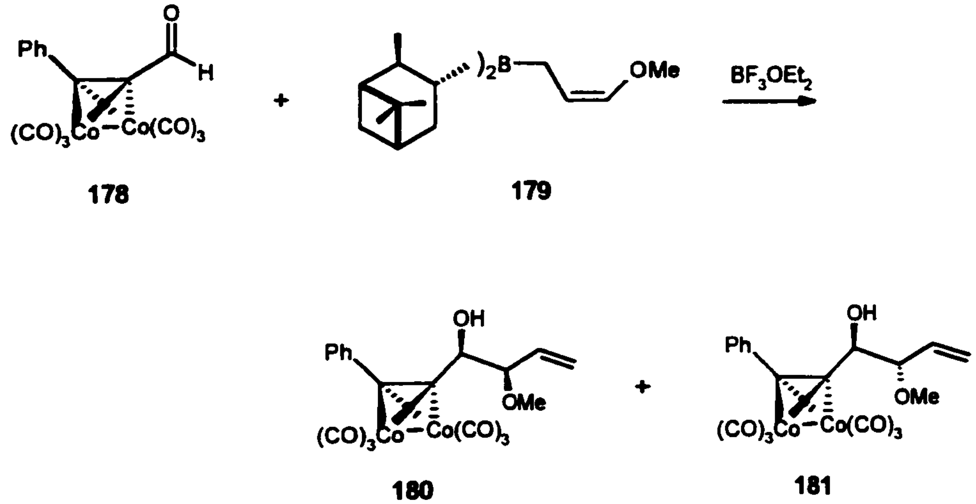


Figure 3 - 14: Diastereoselectivity of Nucleophilic Addition to 178 Using Chiral Allylboron Reagent

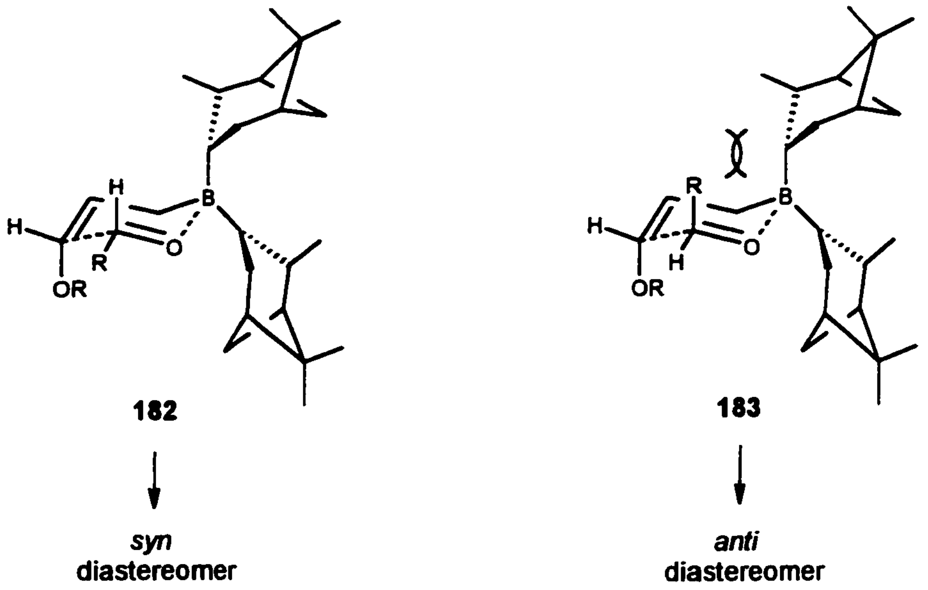


Figure 3 - 15: Zimmerman-Traxler Transition Structures for Allyl Transfer onto 178

3.2.3 Utilization of the Dicobalt Cluster to Control Stereochemistry

In a method reported by Schreiber and co-workers, unlike the one described above, the cobalt cluster of a dicobalt-complexed propargyl ether was made to play a more active role in controlling the stereochemistry of nucleophilic attack at the propargylic carbon atom.[9] Allylation of two diastereomeric ethers **186** and **187** which had been chromatographically separated following their preparation from (+)-isopinocampheol **184** and a racemic mixture of the propargyl alcohol **185**, yielded in both cases a racemic mixture of allylated product **188**, as illustrated in **Figure 3 - 16**. That both diastereomers led to the same product mixture was concluded to have arisen from a common cobalt cation intermediate that underwent racemization via antarafacial migration at a rate that was faster than the rate of allylation. This introduced the possibility of achieving stereoselectivity with a suitable chiral, nonracemic nucleophile which could undergo alkylation at a rate comparable to, or greater than, that of racemization of the cobalt cation. Indeed, very good diastereoselectivity was attained from alkylation of the achiral dicobalt-complexed propargyl ether **189** with Evans' enolate, as shown in **Figure 3 - 17**. Although the products do not contain the 3,4-disubstituted-hexa-1,5-enyne system, this example illustrates the potential of using the cobalt cluster to control the stereochemistry of nucleophilic addition, in addition to protecting the triple bond.

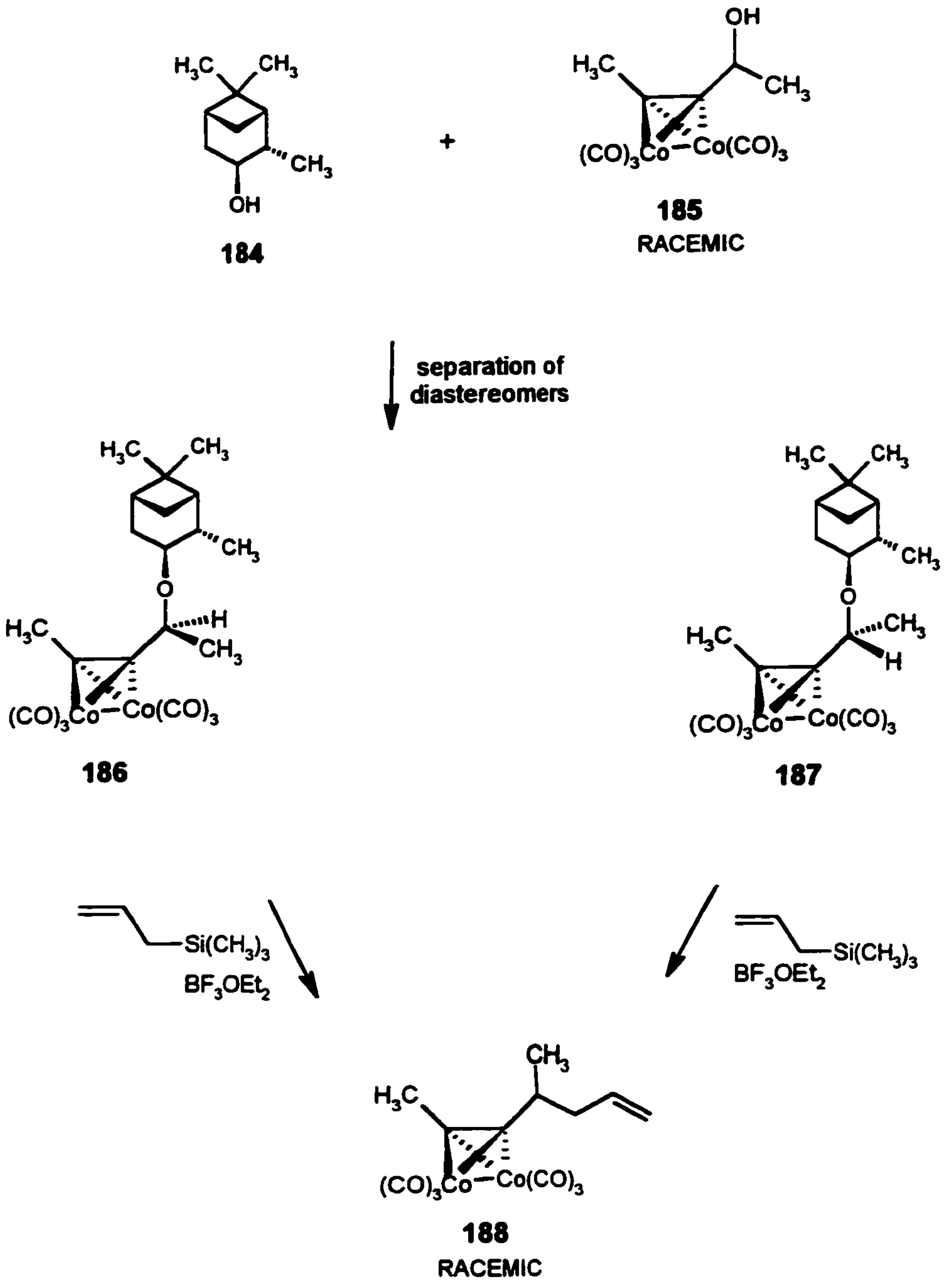


Figure 3 - 16: Allyl Transfer onto a Cobalt-Stabilized Cation

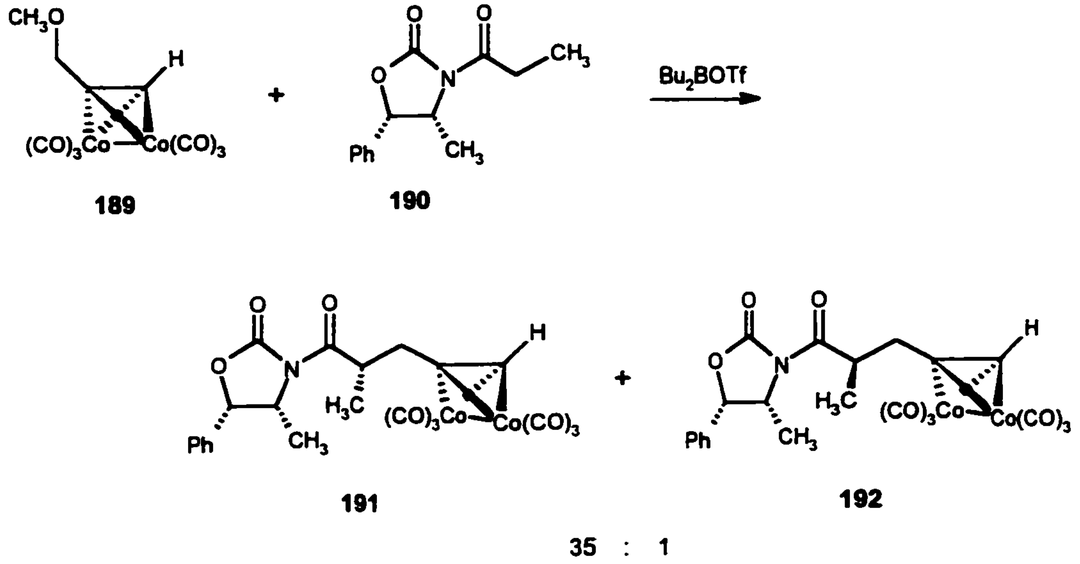


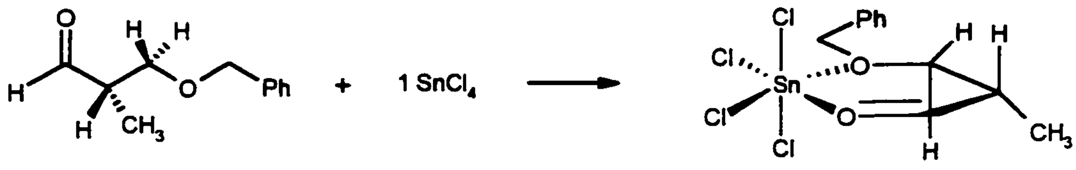
Figure 3 - 17: Chirality Transfer during Alkylation of the Cobalt-Stabilized Cation

DIASTEREOSELECTIVITY OF NUCLEOPHILIC ADDITION TO A CARBONYL GROUP VIA INTRAMOLECULAR CHELATION

3.3.1 Intramolecular Chelation of β-Alkoxyaldehydes

The temporary conversion of a conformationally mobile system to a rigid and cyclic one, has been invoked to account for the pronounced increase in diastereoselectivity of nucleophilic addition upon activation of an α- or β-alkoxy aldehyde with a bidentate Lewis acid, as compared with a monodentate Lewis acid.[23] As an example, the diastereomeric ratio of the homoallylic alcohol product of the addition of allyltributylstannane to 2-methyl-3-benzyloxypropanal **193a** increased from 52:48 to 98:2 when the Lewis acid was switched from monodentate $BF_3{\cdot}OEt_2$ to bidentate $SnCl_4$.[24]

Evidence in support of a chelated complex of 2-methyl-3-benzyloxypropanal and one equivalent of a bidentate Lewis acid includes a change in coupling constants and a marked downfield shift of protons adjacent to both the carbonyl and ether oxygen, obtained via variable-temperature ^{1}H NMR spectroscopy.[25] The observed coupling constants for the C2 methine proton and the adjacent diastereotopic C3 methylene protons are characteristic of protons situated in an axial-axial and axial-equatorial relationship to each other. Based on these values, the researchers concluded that the methyl group at C2 occupied a pseudo-equatorial position in the chelated form and proposed a solution structure **194**, shown in **Figure 3 - 18**. The stability of chelated complexes was also found to have a temperature dependence that varied with the structure of the aldehyde; chelated 2-methyl-3-benzyloxypropanal persisted in the temperature range of –80 °C to –20 °C.



193a **194**

Figure 3 - 18: Solution Structure Involving Intramolecular Chelation of **193a**

A study of the formation of this chelated structure was carried out with a titration experiment that was followed using variable-temperature ^{119}Sn NMR spectroscopy.[26] In principle, after addition of 0.5 molar equivalents of aldehyde to a solution of $SnCl_4$, formation of an intramolecularly chelated complex will leave an equivalent amount of free $SnCl_4$, whose ^{119}Sn NMR chemical shift is known. The absence of free $SnCl_4$ would suggest that the carbonyl and alkoxy oxygen atoms were each coordinated to one molecule of $SnCl_4$. Experimentally, two peaks were observed; one at –155 ppm corresponding to free $SnCl_4$, and a second at –577 ppm which was attributed to the chelate structure **194** shown in **Figure 3 - 18**.

A 2:1 complex having the gross structure **195** depicted in **Figure 3 - 19** was postulated for aldehydes that do not possess additional substituents which can chelate. In the absence of chelation, addition of 0.5 molar equivalents of aldehyde relative to Lewis acid would also result in a peak corresponding to free $SnCl_4$, and an additional peak corresponding to the 2:1 complex **195**. In order to differentiate between a 1:1 complex such as **194** and a 2:1 complex such as **195**, the solution was titrated with aldehyde until one molar equivalent had been added relative to the initial concentration of $SnCl_4$. The disappearance of free $SnCl_4$ and the persistence of the peak at –577 ppm was taken as evidence of a chelated complex **194**.

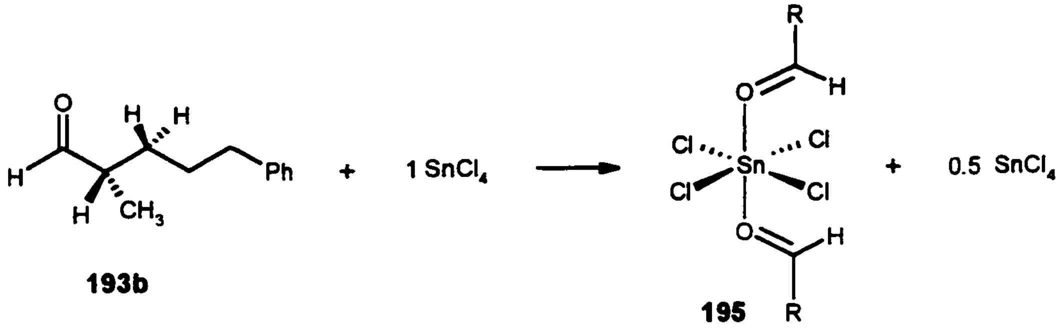
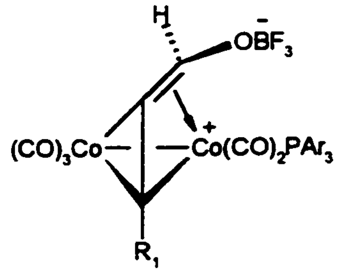


Figure 3 - 19: Solution Structure when Chelation is Precluded

RESEARCH PROPOSAL

It was envisioned that the cobalt cluster of a dicobalt-complexed acetylenic aldehyde or ketone could serve as both a protecting group for the triple bond, as well as a removable chiral auxiliary group, controlling the stereochemistry of nucleophilic addition to the carbonyl group. Ideally, the cobalt cluster would be used to force the propargylic carbon to adopt an orientation that would allow access to only one of the two prochiral carbonyl faces for nucleophilic attack. This could be accomplished in part by incorporating a dicobalt cluster where one of the two vertices provides greater charge stabilization than the other. The result would be a reduction in the number of diastereomeric cationic intermediates (or transition structures) formed upon complexation of the carbonyl group with a Lewis acid, from four to two. The preferential charge stabilization by one vertex in dicobalt pentacarbonyl(triphenylphosphine)-complexed propargylic cations was described in Section 3.1.5.

With (3-phenylpropynal)dicobalt hexacarbonyl serving as a representative acetylenic aldehyde, triarylphosphine was chosen for ligand substitution on cobalt to create different environments at the two vertices, since a number of substituted triarylphosphines are commercially available and are stable to hydrolysis. Assuming that intermediates are in fact formed, both enantiomers of the two diastereomeric cationic intermediates that were predicted to form upon complexation with the monodentate Lewis acid $BF_3 \cdot OEt_2$ are depicted in **Figure 3 - 20**. The dicobalt pentacarbonyl(triarylphosphine) cluster is itself one chiral element. Upon nucleophilic addition to the propargyl carbon, a new chiral center is then created. The four possible stereoisomers that can be formed from nucleophilic addition (both enantiomers of two diastereomers) are shown in **Figure 3 - 21**.



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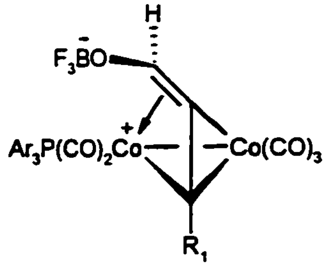

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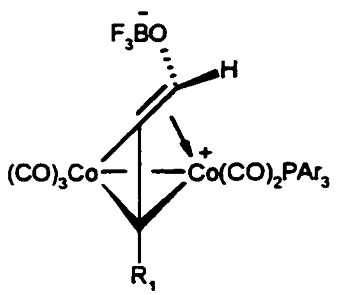

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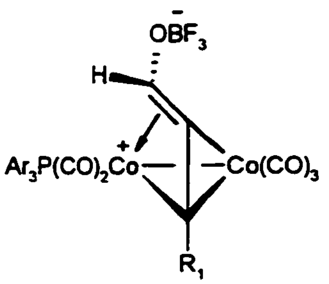
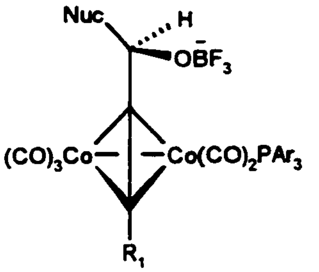
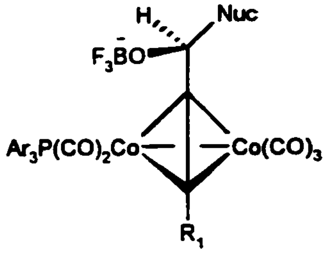


199

Figure 3 - 20: Proposed Stereoisomeric Intermediates Formed with a Lewis Acid



200



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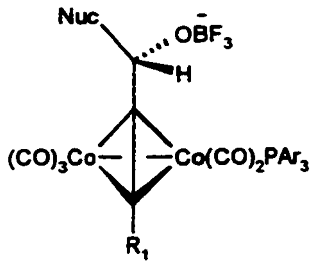

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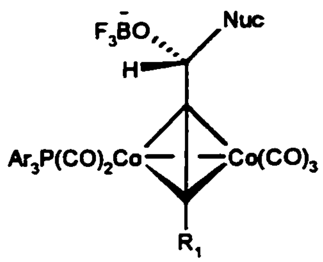
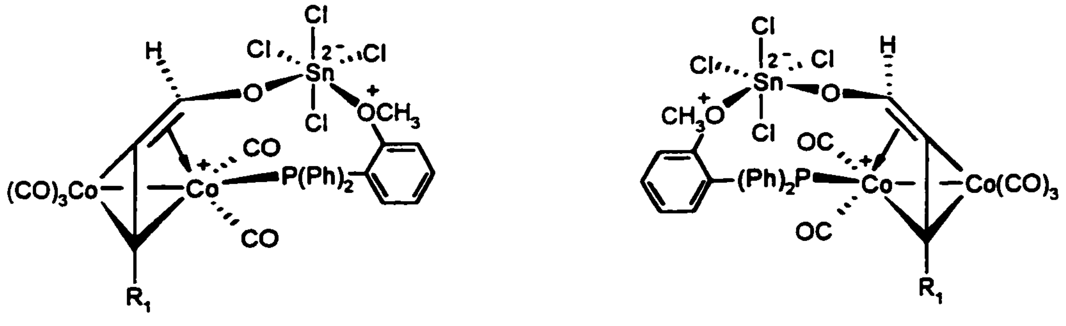


203

Figure 3 - 21: Stereoisomers Formed from Nucleophilic Addition to the Dicobalt-Complexed Acetylenic Aldehyde

It was also envisioned that the number of possible diastereomeric cationic intermediates **196** – **199** could be further reduced from two to one, in an effort to control the alkylidene facial selectivity during nucleophilic addition, via chelation of the carbonyl oxygen along with one of the ligands on cobalt, to a bidentate Lewis acid. It was anticipated that the use of diphenyl(2-methoxyphenyl)phosphine as a ligand on cobalt would allow the possibility of coordination of the ortho methoxy group to a Lewis acid. Therefore, it was of interest to determine if experimental conditions could be found, that would favor formation of the diastereomeric intermediate (racemic mixture) shown in **Figure 3 - 22**. The formation of such a chelated structure would have been manifested as an increase in diastereoselectivity of the products obtained upon replacement of a monodentate Lewis acid with a bidentate Lewis acid.



204 **205**

Figure 3 - 22: Chelated Diastereomeric Intermediate

Allylsilanes were chosen to be the nucleophilic partners for two reasons. Firstly, they provided an extension to the allyl transfer studies described in Chapter Two, and secondly, substitution at any of the allylic α, β, or γ positions would provide a route to a wealth of compounds containing the substituted hexa-1,5-enyne system, all of which possess considerable synthetic value. A process involving a chelated structure would provide the advantage over previously reported procedures that utilized dicobalt clusters, of being a general method for stereoselective bond formation at the propargylic site. The potential also exists to expand this methodology to achieve enantioselectivity of nucleophilic addition to the carbonyl group, with the use of a chiral bidentate Lewis acid in conjunction with a dicobalt cluster which can coordinate to the Lewis acid.

RESULTS

3.4.1 Synthesis and Allyl Transfer onto Acetylenic Ketones and Ketals

Initially, we were interested in the possibility of effecting allyl transfer from a crotylsilane onto a dicobalt hexacarbonyl-complexed acetylenic ketone as this would lead to the 3,4-dialkyl-4-hydroxyhexa-1,5-enyne system. In order to determine whether this transformation would occur at all, the readily available allyltrimethylsilane and the dicobalt hexacarbonyl-complexed ketone 4-trimethylsilyl-3-butyn-2-one were chosen as reaction partners. However, only starting material was recovered from the addition of one molar equivalent of each of allyltrimethylsilane and $BF_3{\cdot}OEt_2$ as Lewis acid to the ketone at -78 °C, followed by gradual warming to room temperature. Under identical reaction conditions, the corresponding non-complexed acetylenic ketone **206** gave rise to the conjugated compound 4-methyl-6-trimethylsilyl-5-hexyn-1,3-diene **209**, presumably as a result of elimination from the homoallylic alcohol product of allyl transfer **208**, shown in **Figure 3 - 23**. The configuration of the double bond could not be determined from its ^{1}H NMR spectrum alone.

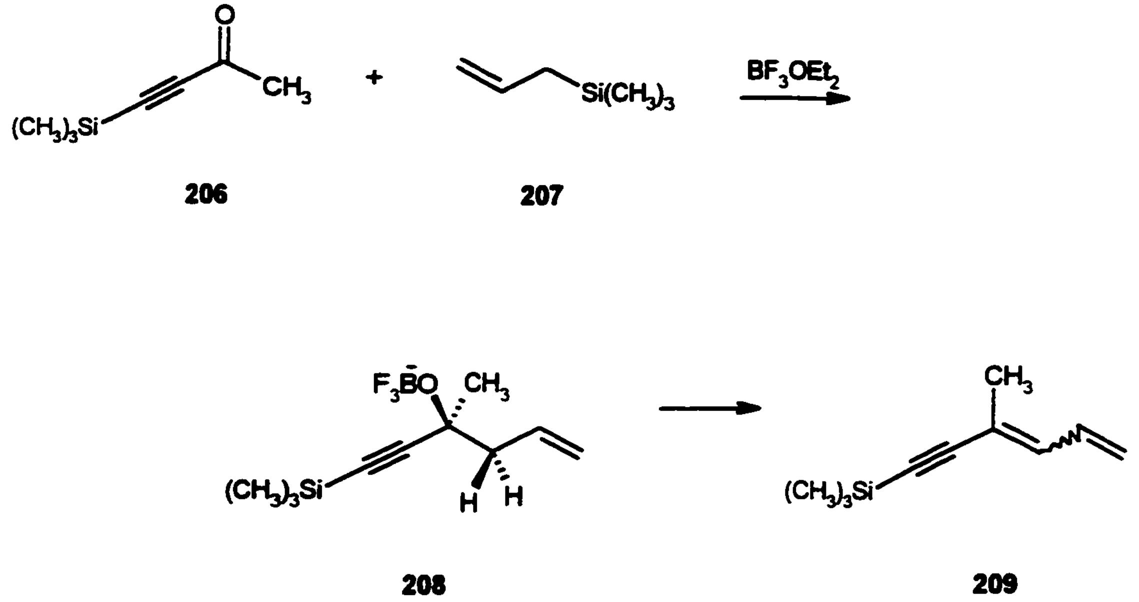


Figure 3 - 23: Allyl Transfer onto Alkynone **206**

As the tertiary alcohols produced from allylation of ketones frequently undergo elimination, ketals can be used in the place of ketones.[27] This method has the advantage that elimination from the resulting ether is much less likely to occur, and when the ketal is derived from a 1,3-diol, the resulting ether can be converted to a hydroxy group subsequent to nucleophilic addition to the ketal.[28] Oxidation of the primary alcohol in compound **212** to a carboxylic acid would allow for intramolecular proton transfer and decarboxylation to occur, in a manner analogous to the 1,3-decarboxylation of β-keto acids. This process is illustrated in **Figure 3 - 24**.

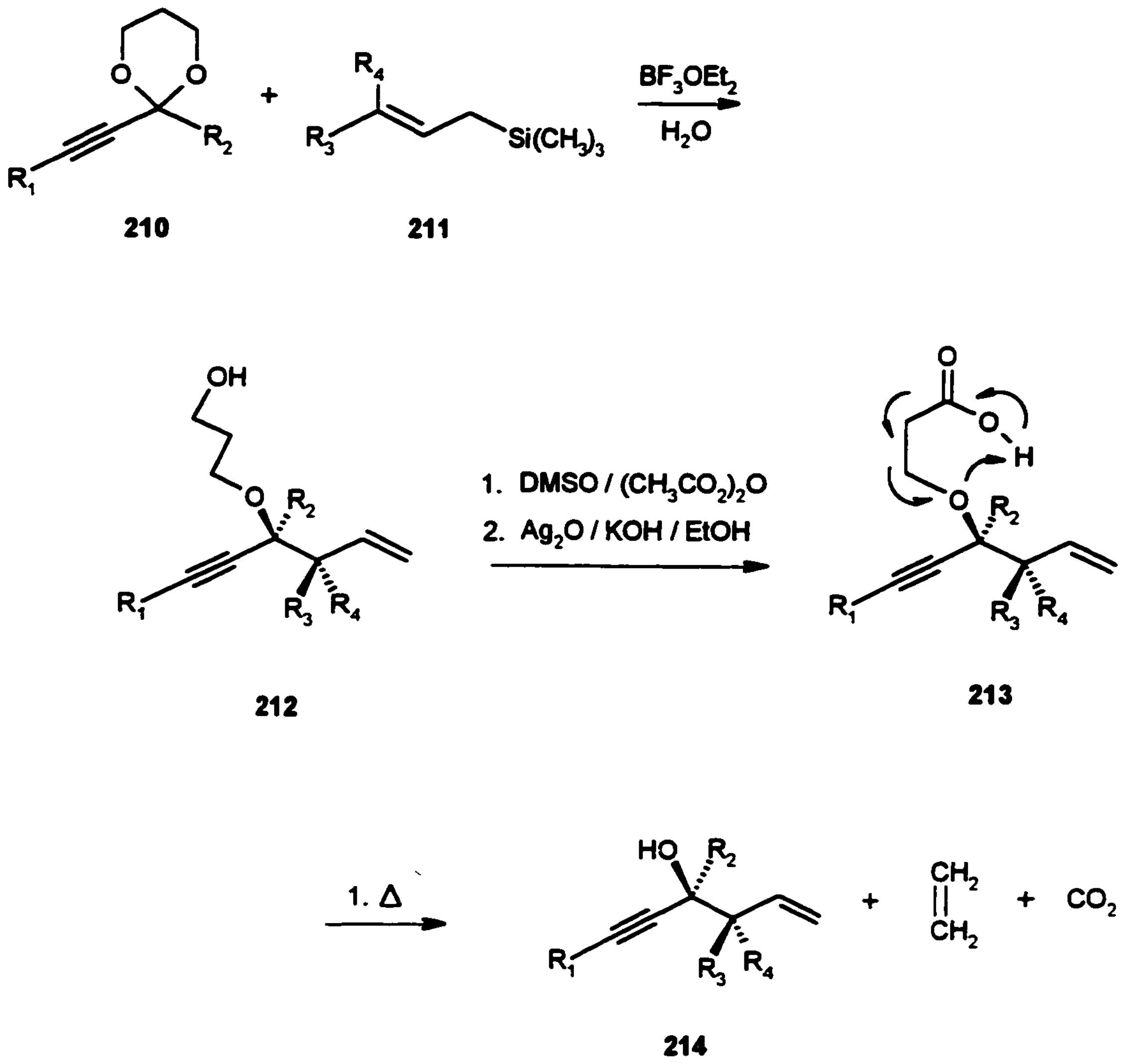


Figure 3 - 24: General Procedure of Allyl Transfer onto Acetylenic Acetal

In order to compare the reactivity of a simple acetylenic ketal with the acetylenic ketone described above, the dicobalt hexacarbonyl complex of 4-trimethylsilyl-2,2-ethylenedioxy-3-butyne and the corresponding non-complexed acetylenic ketal were prepared. The compounds were subjected to the same reaction conditions described above, with either $BF_3{\cdot}OEt_2$ or $CF_3SO_3Si(CH_3)_3$ as Lewis acid. Again, only starting material was recovered from the reaction involving the dicobalt-complexed ketal, whereas the non-complexed ketal **215** gave rise to the homoallylic ether product expected from nucleophilic addition, as shown in **Figure 3 - 25**.

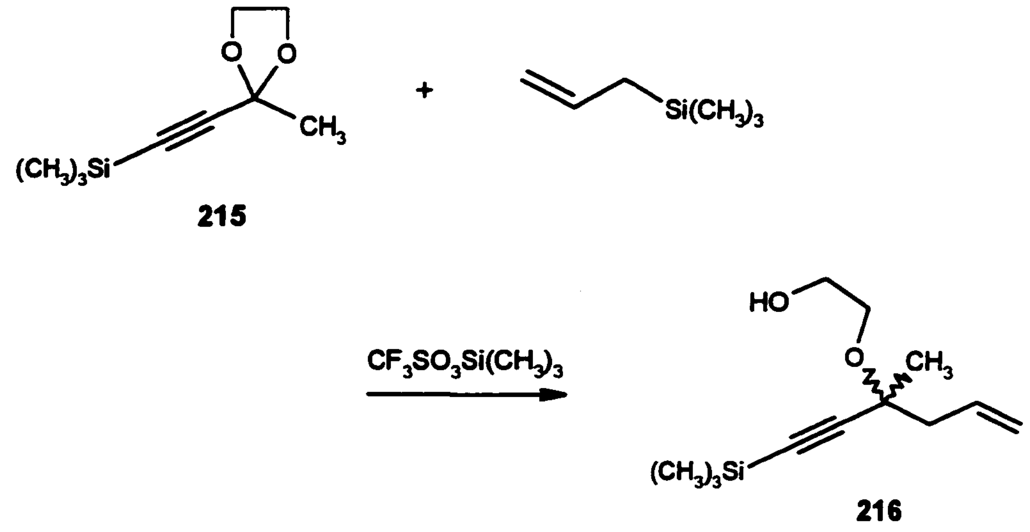


Figure 3 - 25: Allyl Transfer onto Acetylenic Ketal **215**

A more nucleophilic allylmetal reagent was then sought to effect allyl transfer onto the dicobalt hexacarbonyl-complexed acetylenic ketone. Allyltributylstannane proved to be such a reagent, having previously been reported to be approximately four orders of magnitude more reactive than allyltrimethylsilane towards diarylcarbenium ions.[29] However, allylic transposition was followed by elimination to give (4-methyl-6-trimethylsilyl-5-hexyn-1,3-diene)dicobalt hexacarbonyl **219** shown in **Figure 3 - 26**. The homoallylic alcohol itself was not isolated; a discussion of elimination from dicobalt-complexed compounds has been postponed to Section 3.4.3.

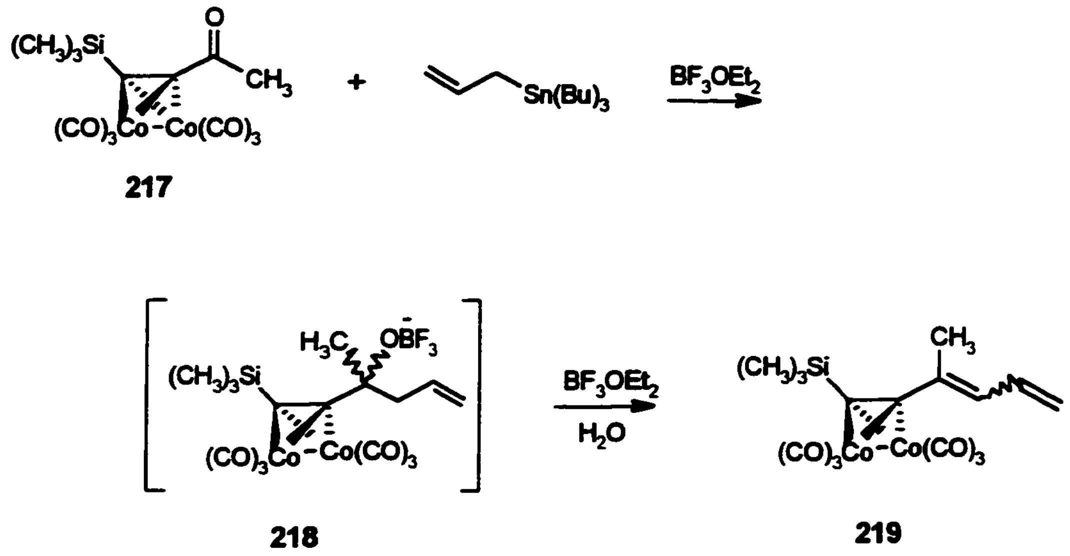
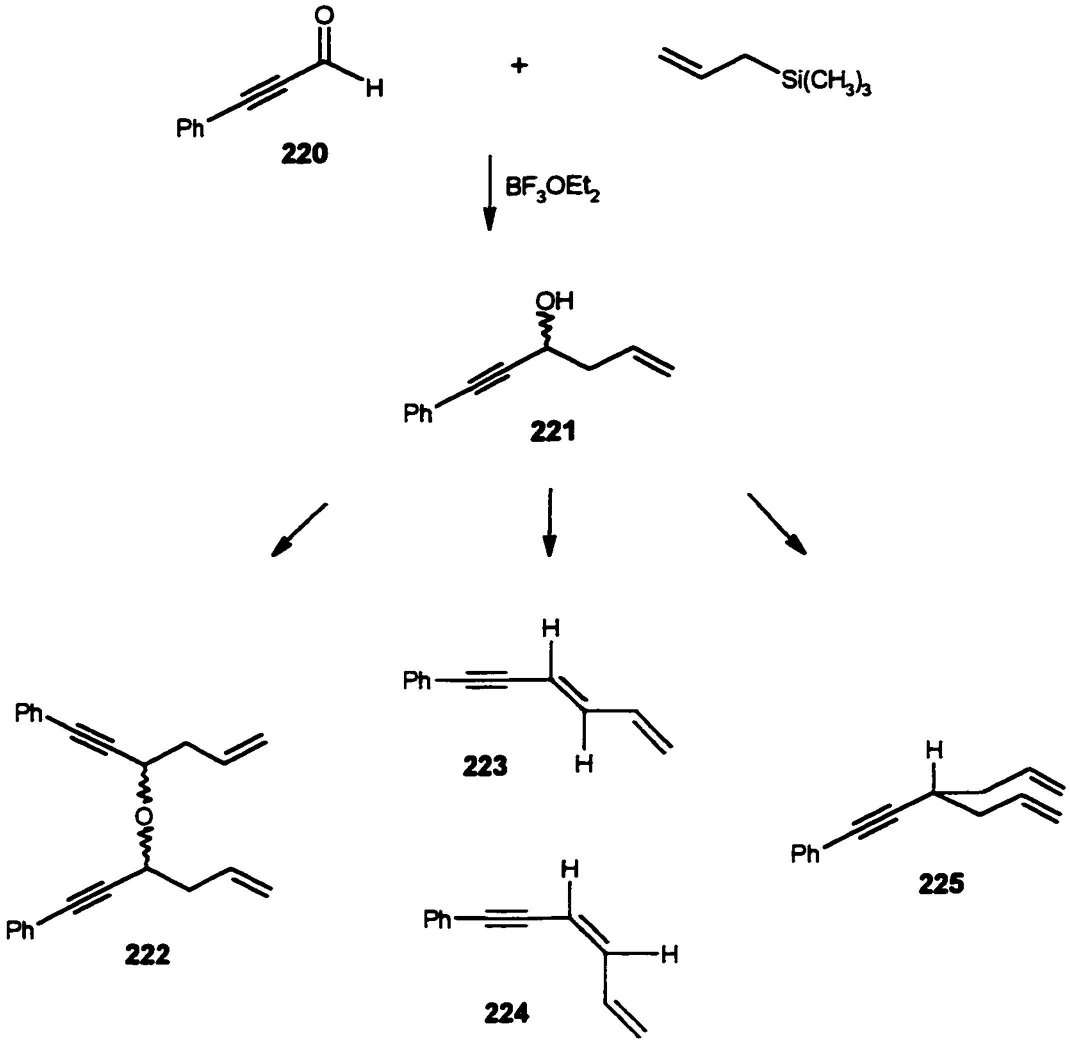


Figure 3 - 26: Allyl Transfer onto Dicobalt-Complexed Alkynone 217

3.4.2 Synthesis and Allyl Transfer onto an Acetylenic Aldehyde

In an effort to avoid the problem of elimination from both the complexed and non-complexed ketones, the focus of the intermolecular allyl transfer study was changed from acetylenic ketones to acetylenic aldehydes. The aldehyde 3-phenylpropynal **220** was chosen and prepared by addition of *N*-formylmorpholine as the formylating agent, to a solution of lithium phenylacetylide. The reaction of this aldehyde with one molar equivalent of both allyltrimethylsilane and $BF_3{\cdot}OEt_2$ indeed produced the homoallylic secondary alcohol 1-phenyl-5-hexenyn-3-ol **221**. Compound **221** underwent subsequent elimination, disubstitution and coupling in the presence of allyltrimethylsilane and $BF_3{\cdot}OEt_2$, to form the isolated compounds **223** + **224**, **225** and **222**, respectively, shown in equivalents of allyltrimethylsilane and $BF_3 \cdot OEt_2$ were added to aldehyde **220**, the product ratio **221**:**222**:**223**+**224**:**225** was determined to be 75:8:16: < 1. The relative quantities of products did not vary considerably regardless of whether or not the Lewis acid was in excess.



221 : **222** : **223** : **224** : **225** = 70 : 14 : 4 : 11 : 1

Figure 3 - 27: Allyl Transfer onto Alkynal **220**

3.4.3 Allyl Transfer onto a Dicobalt Hexacarbonyl-Complexed Acetylenic Aldehyde

The yield of homoallylic alcohol was improved dramatically (to 90 %) by employing the dicobalt hexacarbonyl complex of 3-phenylpropynal under the same reaction conditions. In fact, it was the only product recovered when the reaction mixture was subject to work-up conditions immediately following the disappearance of the starting aldehyde, as judged by thin layer chromatography. Decomplexation with $(NH_4)_2Ce(NO_3)_6$ then led to recovery of 1-phenyl-5-hexen-1-yn-3-ol **228**.

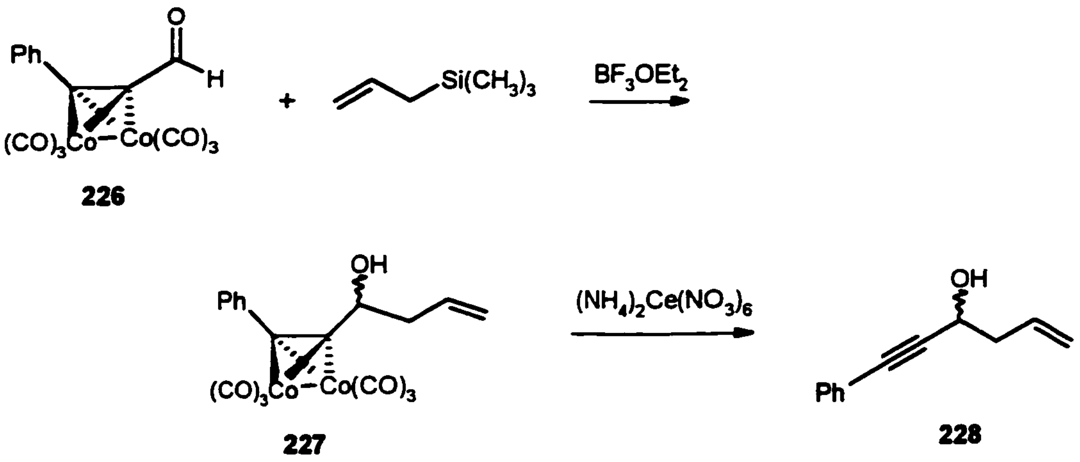


Figure 3 - 28: Allyl Transfer onto Dicobalt-Complexed Alkynal **226**

When allylation conditions involved two molar equivalents of each of allyltrimethylsilane and $BF_3{\cdot}OEt_2$, the initially produced dicobalt hexacarbonyl-complexed homoallylic alcohol underwent a second allylation to form the dicobalt hexacarbonyl-complexed 4-(phenylacetylene)-1,6-heptadiene **231**, as shown in **Figure 3 - 29**. The structure was confirmed by characterization of the compound **232** after decomplexation with $(NH_4)_2Ce(NO_3)_6$. Less than 10 % of the (*E*)- and (*Z*)-dienes **230** were also produced.

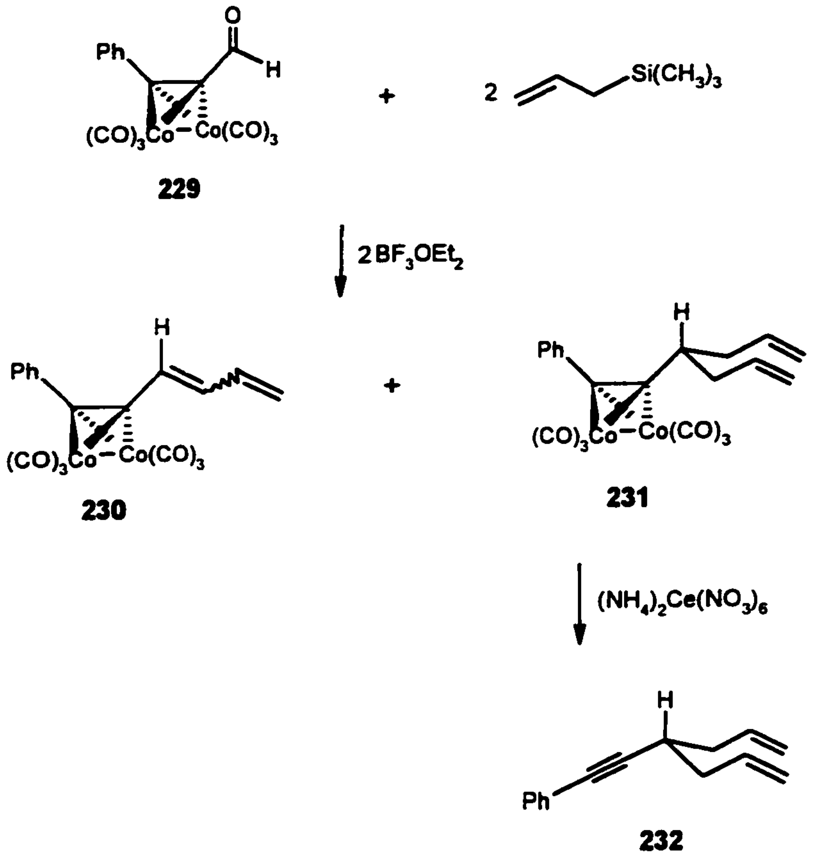


Figure 3 - 29: Allyl Transfer onto Dicobalt-Complexed Alkynal **229**

It was thought that the reaction had proceeded via nucleophilic addition to the dicobalt-stabilized cation generated from loss of boron etherate. To verify this, (1-phenyl-5-hexen-1-yn-3-ol)dicobalt hexacarbonyl **233** was independently synthesized, and reacted with one molar equivalent of allyltrimethylsilane and $BF_3{\cdot}OEt_2$ under the same reaction conditions. Indeed, 4-(phenylacetylene)-1,6-heptadiene dicobalt hexacarbonyl **236** was obtained along with approximately 10 % of elimination products, as shown in **Figure 3 – 30.**

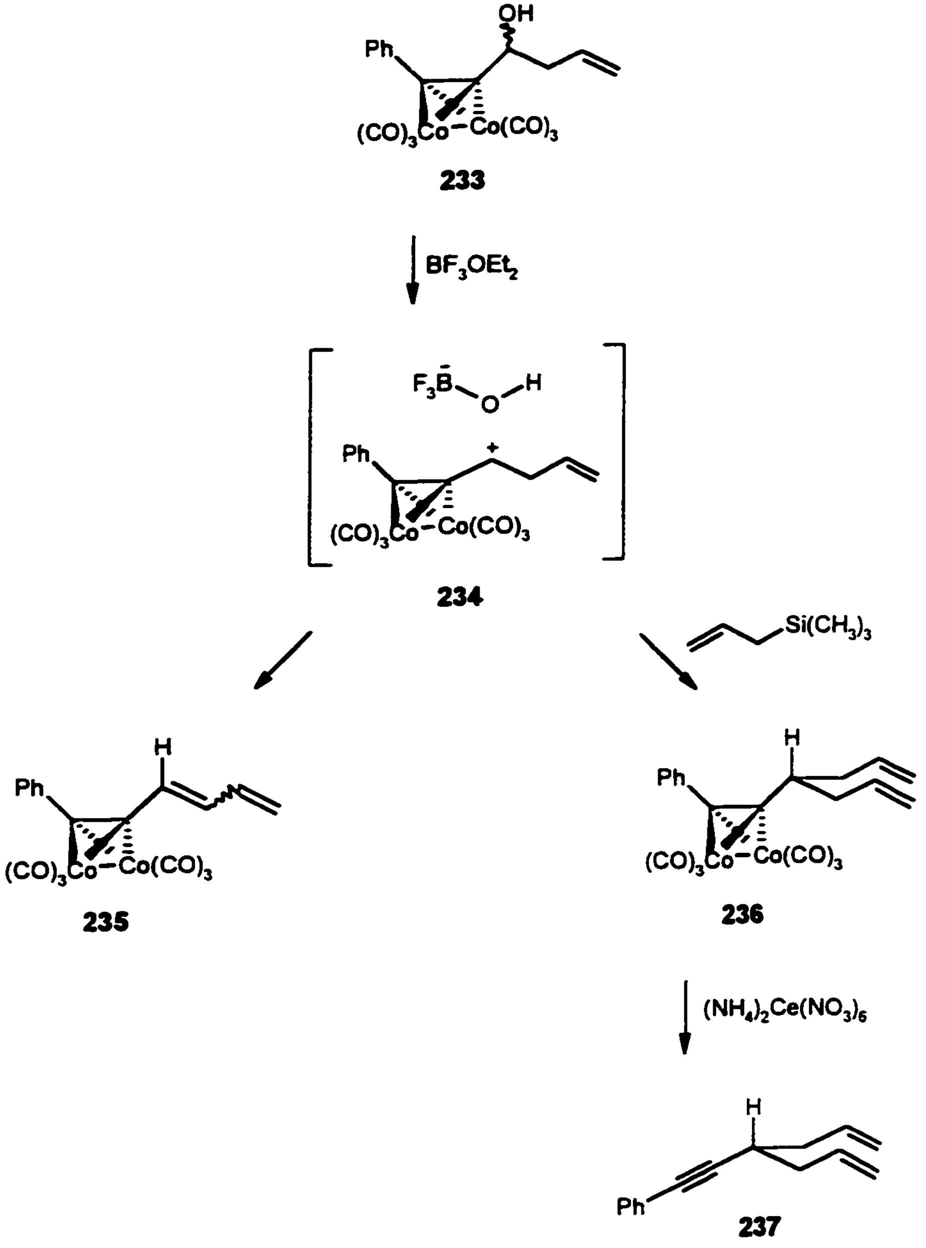
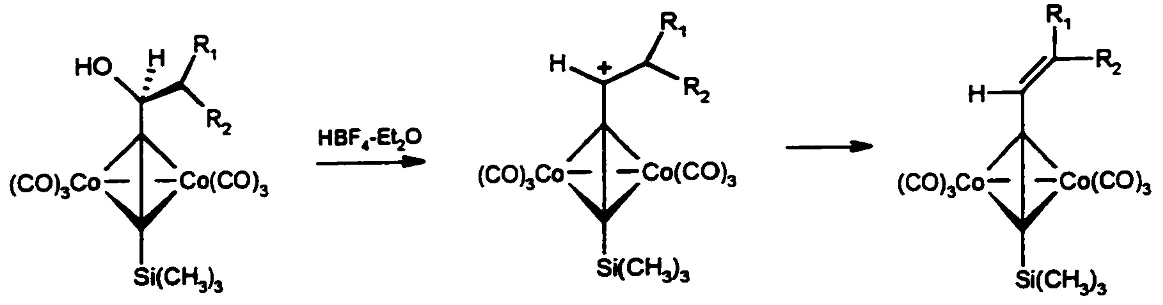


Figure 3 - 30: Allyl Transfer onto Dicobalt-Complexed Homoallylic Alcohol **233**

It can be seen that elimination from the initially formed non-complexed homoallylic alcohol **221** was a competing reaction pathway, and the disubstituted compound **225** was formed in minimal quantities, regardless of whether or not the Lewis acid and allyl reagent were present in excess. In contrast, elimination from the initially formed dicobalt-complexed homoallylic alcohol comprised less of the total product mixture, and the disubstituted compound **231** was recovered as the major product when an excess of Lewis acid and allylmetal reagent were present. This decreased reactivity of a dicobalt-complexed aldehyde in secondary reaction pathways provides evidence supporting the intermediacy of a dicobalt-stabilized cation. The process of disubstitution introduces the possibility of incorporating two different nucleophiles at the propargylic site, giving rise to a trialkylsubstituted carbon atom from an acetylenic aldehyde, and a tetraalkylsubstituted carbon atom from an acetylenic ketone.

These results are also consistent with the findings of Schreiber and co-workers, who have previously reported that the principal competing pathway in the formation of a dicobalt hexacarbonyl-stabilized propargyl cation from the parent propargyl alcohol, was elimination of a proton to give a dicobalt hexacarbonyl-stabilized propargyl alkene, as shown in **Figure 3 - 31**.[9] Elimination was presumed to occur from the dicobalt-stabilized cation rather than through a concerted process of carbon-oxygen bond cleavage and proton abstraction, based on the ease of formation of several alkenes. For example, the cation **240** was generated from the secondary alcohol **238** and was stable in the temperature range –90 °C to –20 °C. Only above –20 °C did the olefin product **242** of elimination begin to form. In contrast, the cation **241** could not be isolated in the temperature range –90 °C to 0 °C after protonation of the secondary alcohol **239**; the more highly substituted alkene **243** was produced exclusively.



238 $R_1, R_2 = H$
239 $R_1, R_2 = CH_3$

240 $R_1, R_2 = H$
241 $R_1, R_2 = CH_3$

242 $R_1, R_2 = H$
243 $R_1, R_2 = CH_3$

Figure 3 - 31: Elimination from Dicobalt Hexacarbonyl Stabilized Cations

3.4.4 Dicobalt Pentacarbonyl(triaryl)Phosphine-Complexed Acetylenic Aldehydes

With (3-phenylpropynal)dicobalt hexacarbonyl in hand, ligand substitution at cobalt was carried out under conditions of gentle reflux in a THF/ether solvent mixture containing one molar equivalent of diphenyl(2-methoxyphenyl)phosphine. The racemic mixture of monosubstituted phosphine complexes (**246** and **247**) was then separated from the disubstituted phosphine complex by flash chromatography. Since chelation to a bidentate Lewis acid would involve the carbonyl oxygen and the aromatic ortho-methoxy substituent, it was necessary to prepare a second acetylenic aldehyde containing triphenylphosphine as a ligand on cobalt that did not contain substituents able to participate in chelation. This would allow a direct comparison of products obtained from a substrate which was capable of undergoing chelation, with those obtained from a substrate which was not. Thus, the procedure described above was repeated using triphenylphosphine. Both enantiomers of each of the two different monophosphine complexes are shown in **Figure 3 - 32**.

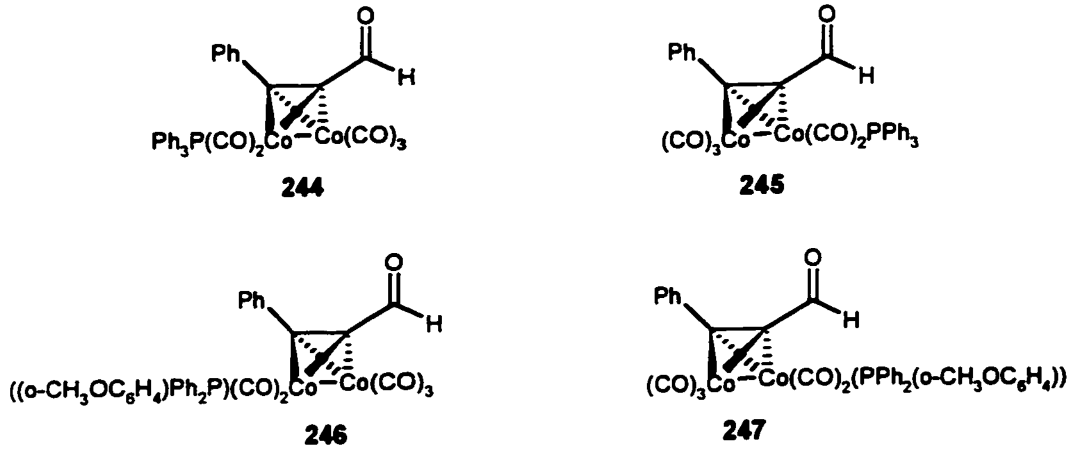


Figure 3 - 32: Dicobalt Pentacarbonyl(triarylphosphine)-Complexed Acetylenic Aldehyde Compounds Synthesized

3.4.5 Effects of Lewis Acid on Allyl Transfer - 1.0 Equivalent of Monodentate BF_3

Initial studies involved finding the experimental conditions required to effect allyl transfer onto the dicobalt pentacarbonyl(triphenyl)phosphine-complexed aldehydes in the presence of a monodentate Lewis acid. The attempted allyl transfer onto compounds **244** + **245** and **246** + **247** using allyltrimethylsilane in the presence of $BF_3 \cdot OEt_2$ yielded only starting materials. An attenuated reactivity of the related dicobalt pentacarbonyl(triphenyl)phosphine-complexed propargylic cations relative to their dicobalt hexacarbonyl analogues has previously been reported, and was attributed to increased stability of the cation as a result of replacement of a weakly σ-donating/strongly π-accepting CO ligand with the strongly σ-donating/weakly π-accepting PPh_3.[30] A similar effect may have been exerted on the development of positive charge at the carbonyl carbon of the acetylenic aldehyde upon complexation with a Lewis acid, reducing its reactivity towards nucleophiles, relative to the corresponding dicobalt hexacarbonyl-complexed aldehyde.

The more nucleophilic allyltributylstannane was again required to effect allyl transfer onto aldehydes **244** + **245** and **246** + **247**. The progress of the reaction between either **244** + **245**, or **246** + **247** and one molar equivalent of each of allyltributylstannane and $BF_3{\cdot}OEt_2$ at –78 °C was monitored using thin layer chromatography (TLC) as the cooling bath temperature was allowed to gradually warm to 25 °C. The diastereomeric products were easily discernible from the starting aldehyde using TLC. A mixture of the diastereomeric dicobalt-complexed homoallylic alcohols **248** - **251** was formed from aldehydes **244** + **245**, as well as two additional products which appeared following the onset of the former. These were determined to be dicobalt-complexed (*E*)-3,5-hexadien-1-ynylbenzene **256** + **257** and 1-phenyl-5-hexenyn-3-ol **260**. The product mixture is shown in **Figure 3 - 33**. Decomplexation of compounds **256** + **257** with $(NH_4)_2Ce(NO_3)_6$ was then carried out to verify the structural assignment. Similarly, a mixture of the diastereomeric dicobalt-complexed homoallylic alcohols **252** - **255** was formed from aldehydes **246** + **247**. Dicobalt-complexed (*E*)-3,5-hexadien-1-ynylbenzene **258** + **259** and 1-phenyl-5-hexenyn-3-ol **260**, were also recovered as part of the reaction mixture, shown in **Figure 3 - 33**.

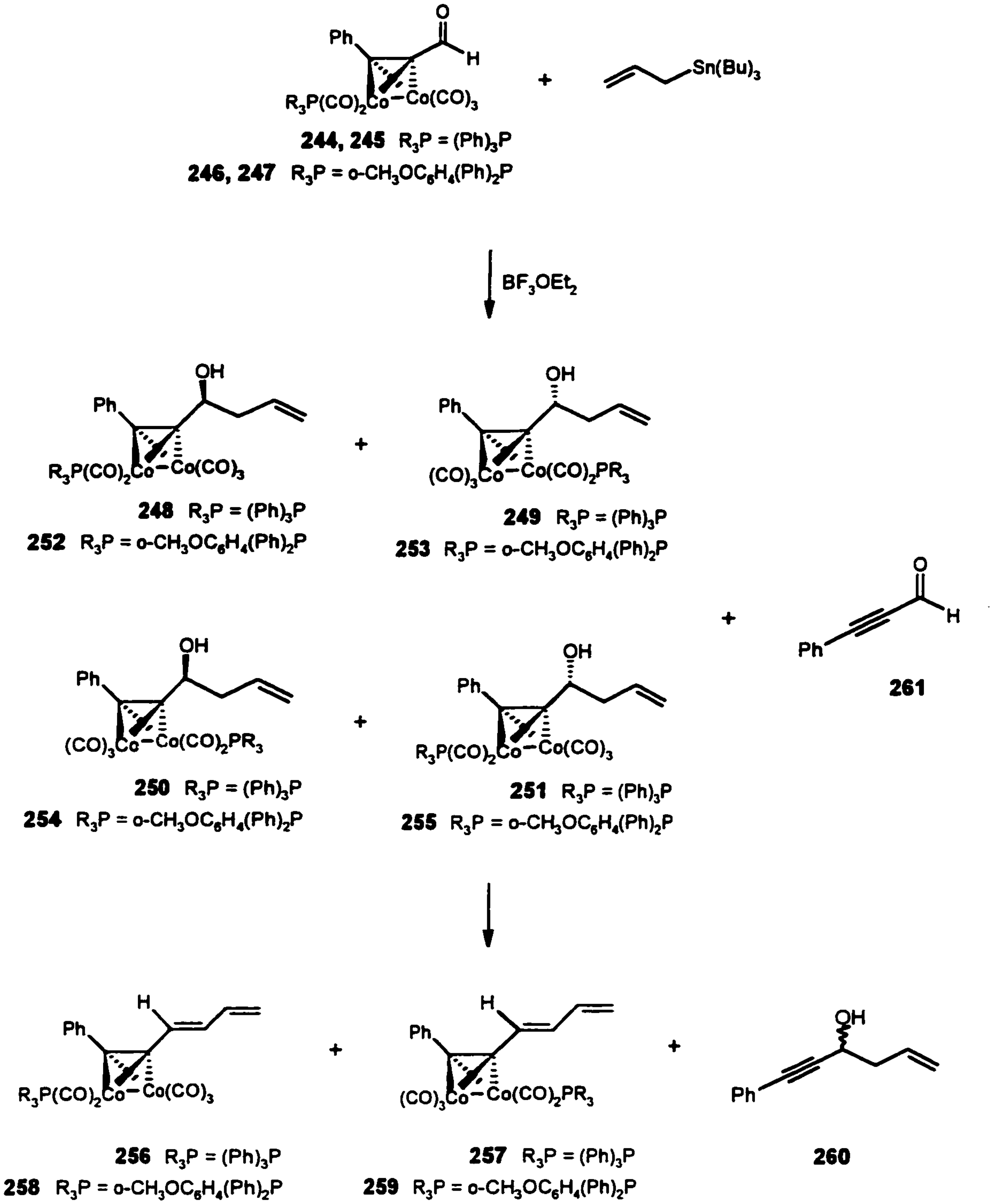


Figure 3 - 33: Allyl Transfer onto Alkynals 244 – 247

A summary of quantities of products isolated from the reactions of aldehydes **244** + **245** and aldehydes **246** + **247**, and the ratios of diastereomeric homoallylic alcohols, is given in **Table 3 - 1** and **Table 3 - 2**, respectively. Each entry in both tables corresponds to an individual allyl transfer reaction involving addition of the allylstannane to the aldehyde at –78 °C, followed by gradual warming, which required a period of 4 - 6 hours to reach 25 °C. The entries differ in the length of time that the mixtures were kept at 25 °C before quenching. The time of work-up ranged from approximately 6 hours following the time of addition of reagents (and applies to entries 1 and 4), to approximately 12 hours following the time of addition of reagents (and applies to entries 3 and 6). Thus, there is a correlation between an increased length of time of standing at 25 °C before quenching, and the "reversal" of diastereoselectivity found in entries 4 and 6, relative to that found in entries 1 and 3. The formation of compounds **256** - **259** is presumed to have been the result of elimination from the homoallylic alcohols **248** - **255**, as described in Section 3.4.3. This was confirmed by mixing an authentic sample of both diastereomers of (1-phenyl-5-hexenyn-3-ol)dicobalt pentacarbonyl(triphenylphosphine), which had been prepared by an independent synthesis, with $BF_3{\cdot}OEt_2$ at -78 °C and monitoring the formation of **256** + **257** with thin layer chromatography and ^1H NMR during the time period in which the temperature gradually rose to 25 °C. Eventually, both diastereomers were completely converted to **256** + **257**, commencing when the cooling bath temperature was in the range of -10 to -5 °C.

The homoallylic alcohol **260**, isolated after chromatographic separation of the reaction mixture, is the product of decomplexation of the dicobalt cluster of compounds **248** - **255**. The decomplexation itself may have been mediated by the Lewis acid during the reaction, or it may have occurred thermally, as the reaction mixture was allowed to reach 25 °C before quenching. The same process would have given rise to acetylenic aldehyde **261** from compounds **244** – **247**. Thermal decomplexation has previously been observed in both dicobalt-complexed alkynes and in octacarbonyldicobalt [$Co_2(CO)_8$], from which they are derived.[7] At 25 °C, carbon monoxide is slowly lost from octacarbonyldicobalt, leaving behind cobalt metal

Table 3 - 1. Quantities of all products obtained and the corresponding diastereomeric ratio of **248** - **251** from the addition of 1 molar equivalent of allyltributylstannane and 1 molar equivalent of $BF_3{\cdot}OEt_2$ at -78 °C to compounds **244** and **245**.

Entry	Aldehyde	Products Obtained (mol %)					
		244 + **245**	**261**	**248** - **251**	**260**	**256** + **257**	Diast. Ratio[a]
1	**244** + **245**	16	0	70	0	14	30 : 70
2	**244** + **245**	16	0	25	0	59	40 : 60
3	**244** + **245**	0	0	23	0	77	95 : 5

[a] The diastereomeric ratio of **248** - **251** is given as X : Y where X and Y correspond to the compound having a chemical shift of C4-H, observed using ^{1}H NMR, at 4.0 and 3.83 ppm respectively.

Table 3 - 2. Quantities of all products obtained and the corresponding diastereomeric ratio of **252 - 255** from the addition of 1 molar equivalent of allyltributylstannane and 1 molar equivalent of $BF_3{\cdot}OEt_2$ at -78 °C to compounds **246** and **247**.

Entry	Aldehyde	Products Obtained (mol %)					
		246 + 247	**261**	**252 - 255**	**260**	**258 + 259**	Diast. Ratio[b]
4	**246 + 247**	32	5	19	27	17	17 : 83
5	**246 + 247**	11	0	33	0	56	51 : 49
6	**246 + 247**	0	2	6	12	80	95 : 5

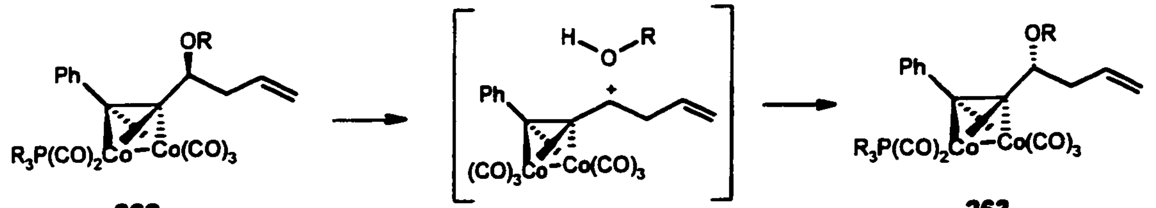
[b] The diastereomeric ratio of **252 - 255** is given as X : Y where X and Y correspond to the compound having a chemical shift of C4-H, observed using ^1H NMR, at 4.23 and 3.79 ppm respectively.

3.4.6 Elimination from Diastereomeric Homoallylic Alcohols 248 - 255

An examination of the values reported in **Table 3 - 1** and **Table 3 - 2** reveals that from both aldehydes **244** + **245** (entries 1-3) and **246** + **247** (entries 4-6), the diastereomeric excess obtained was found to be highest when the amount of elimination products **256 - 259** was either quite low (entries 1 and 4) or quite high (entries 3 and 6). In addition, as the amount of elimination product was found to increase on proceeding from entries 1 through 3, and entries 4 through 6, a seemingly reversal of diastereoselectivity was also obtained.

Since **256 - 259** were derived directly from the diastereomers **248 - 255**, the effect of their formation on the diastereoselectivity warranted further analysis. Following a typical procedure of addition of allyltributylstannane to a solution of **244** + **245** and $BF_3{\cdot}OEt_2$ at -78 °C, the progress of the reaction was monitored with TLC and ^1H NMR as the contents of the flask were allowed to gradually warm to room temperature. When formation of the diastereomers **248 - 251** was first detected using TLC, at a cooling bath temperature of -20 °C, a small aliquot was removed from the flask and the diastereomeric ratio was determined by ^{1}H NMR to be 20:80.[31] The presence of **256 + 257** was not detected until the bath temperature had reached -5 °C, and while it rose to 25 °C, products **248 - 251** and **256 + 257** continued to form, as determined by TLC. At this point, another aliquot was taken from the flask and the diastereomeric ratio of **248 - 251** was determined by ^{1}H NMR to be 40:60.[31] Eventually, the diastereoselectivity was observed (by ^{1}H NMR) to have been reversed. Thus, it seems that although the diastereoselectivity was initially high, preferential or exclusive elimination from the diastereomer that was originally in excess may have led to the observed low diastereomeric excess followed by a reversal of diastereoselectivity. Furthermore, the reversal of diastereoselectivity found in reactions where large quantities of **256 + 257** were also formed, would be consistent with loss of the diastereomer which was initially more abundant.

It is also possible that the conversion of one dicobalt-complexed diastereomer to another, via Lewis acid-promoted loss of alkoxide followed by re-addition, had contributed to the change in diastereomeric ratio to lower values of diastereomeric excess over time, as illustrated in **Figure 3 - 34**. This epimerization would not necessarily have occurred independently of the elimination described above, since it is expected to have proceeded through a dicobalt-stabilized propargyl cation, which is a common intermediate to both the processes of elimination and epimerization. The stability of dicobalt-complexed propargyl cations and their tendency to undergo elimination (and other subsequent reactions including re-addition of an alkoxide), was previously observed by Schreiber and co-workers,[9] to be temperature dependent (described in Section 3.4.3).



262 **264** **263**

OR = OBF_3 or $OSnCl_4$

Figure 3 - 34: Epimerization at the Propargyl Stereocenter

A related temperature dependence of diastereoselectivity was previously reported by Nicholas and co-workers, in a study of Lewis acid mediated addition of the enol silane **265** to the dicobalt-complexed acetylenic acetal **264** shown in **Figure 3 - 35**.[32] Whereas a 6:1 *syn* diastereoselectivity of the β-ethoxyacetylenic cyclohexanones **266** + **267** was obtained at –78 °C, the *syn* selectivity increased to 9:1 when the reaction was carried out at 25 °C. The authors found that while separate samples of *syn*-**266** and *anti*-**267** remained stable at –78 °C, warming to 25 °C did not affect *syn*-**266**, but resulted in elimination from *anti*-**267** to form compound **268** *and* conversion of *anti*-**267** to *syn*-**266**.

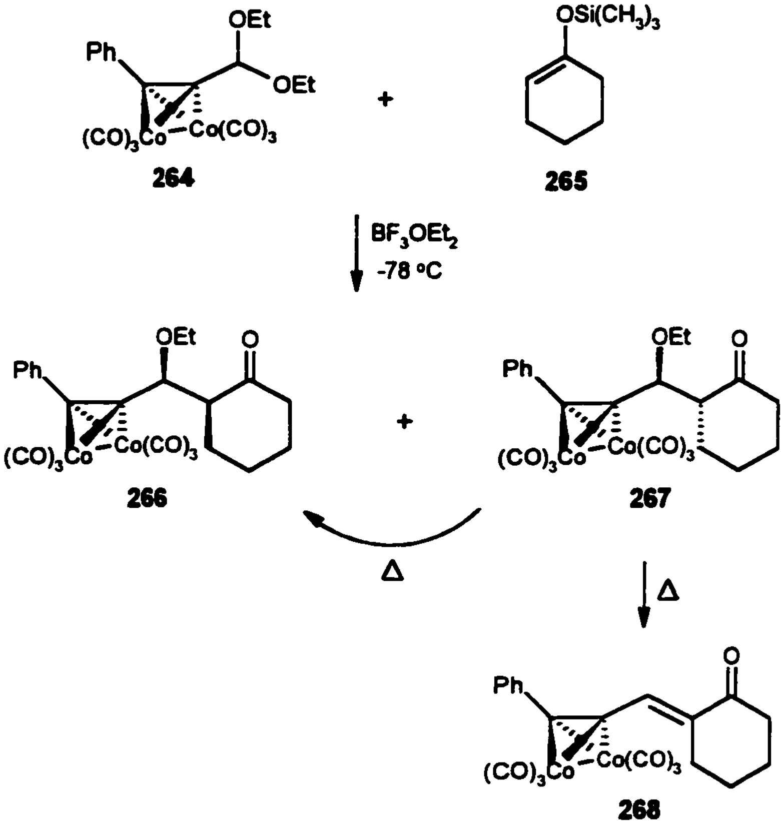


Figure 3 - 35: Temperature-Dependent Reactions of Dicobalt-Stabilized Cation

3.4.7 Thermal Decomposition of Diastereomeric Homoallylic Alcohols 248 - 255

It was observed during the preparation of authentic samples of (1-phenyl-5-hexen-1-yn-3-ol)dicobalt hexacarbonyl and both of the (1-phenyl-5-hexen-1-yn-3-ol)dicobalt pentacarbonyl(triarylphosphine)s, that thermal decomplexation of the cobalt cluster to give the non-complexed homoallylic alcohol **260** had occurred on standing at room temperature. The ^{1}H NMR spectra of several of the purified product mixtures (corresponding to entries 1-16 in **Tables 3 - 1** to **3 - 6**) involving aldehydes **244** – **247**, were then acquired at various periods after the original purification, ranging from two days to two months. They revealed that complete decomplexation of the cobalt cluster eventually occurred from all diastereomers (with minimal change to the diastereomeric ratio during the process), when a comparison was made with spectra acquired at the original time of reaction. Thus, the assumption was made that the processes which affected the diastereomeric ratio, subsequent to allylic transposition, were limited to those involving cleavage of the propargylic carbon-oxygen bond.

3.4.8 Effects of Lewis Acid on Allyl Transfer - 1.0 Equivalent of Bidentate $SnCl_4$

In order to compare the diastereoselectivity of allyl transfer onto aldehydes **244** – **247** in the presence of a bidentate Lewis acid, a second series of reactions were set up using $SnCl_4$ as the Lewis acid. To a mixture of the aldehyde and 1.0 molar equivalent of $SnCl_4$ at -30 °C, was added 1.0 molar equivalent of allyltributylstannane. Each of the reaction mixtures was allowed to warm to 25 °C before quenching. The time of work-up ranged from approximately 6 hours following the time of addition of reagents (and applies to entries 7 and 13), to approximately 24 hours following the time of addition of reagents (and applies to entry 9). This temperature was chosen since product formation was not detected, using TLC, at cooling bath temperatures below -20 °C. The product mixture contained aldehydes **244** - **247**, aldehyde **261**, homoallylic alcohols **248** - **255**, elimination products **255** - **259** and alcohol **260**. The results of addition to aldehydes **244** + **245** and **246** + **247** are given in **Table 3 - 3** and **Table 3 - 4**, respectively, wherein each entry corresponds to an individual reaction. The results of those reactions carried out with $BF_3{\cdot}OEt_2$ are also presented in **Table 3 - 3** and **Table 3 - 4** for comparison.

Table 3 - 3. Quantities of all products obtained and the corresponding diastereomeric ratio of **248 - 251** from the addition of 1 molar equivalent of allyltributylstannane and 1 molar equivalent of Lewis Acid at -30 °C to compounds **244** and **245**.

Entry	Lewis Acid	Products Obtained (mol %)					
		244 + 245	**261**	**248 - 251**	**260**	**256 + 257**	Diast. Ratio[a]
7	$SnCl_4$	7	11	21	34	27	16 : 84
8	$SnCl_4$	0	5	18	59	18	21 : 79
9	$SnCl_4$	5	8	5	11	71	75 : 25
10	$BF_3{\cdot}OEt_2$	16	0	70	0	14	30 : 70
11	$BF_3{\cdot}OEt_2$	16	0	25	0	59	40 : 60
12	$BF_3{\cdot}OEt_2$	0	0	23	0	77	95 : 5

[a] The diastereomeric ratio of **248 - 251** is given as X : Y where X and Y correspond to the compound having a chemical shift of C4-H, observed using ^1H NMR, at 4.0 and 3.83 ppm respectively.

Table 3 - 4. Quantities of all products obtained and the corresponding diastereomeric ratio of **252 - 255** from the addition of 1 molar equivalent of allyltributylstannane and 1 molar equivalent of Lewis Acid at -30 °C to compounds **246** and **247**.

Entry	Lewis Acid	Products Obtained (mol %)					
		246 + 247	**261**	**252 - 255**	**260**	**258 + 259**	Diast. Ratio[b]
13	$SnCl_4$	8	13	43	16	20	13 : 87
14	$SnCl_4$	0	7	22	29	42	35 : 65
15	$SnCl_4$	0	4	25	22	49	48 : 52
16	$BF_3{\cdot}OEt_2$	32	5	19	27	17	17 : 83
17	$BF_3{\cdot}OEt_2$	11	0	33	0	56	51 : 49
18	$BF_3{\cdot}OEt_2$	0	2	6	12	80	95 : 5

[b] The diastereomeric ratio of **252 - 255** is given as X : Y where X and Y correspond to the compound having a chemical shift of C4-H, observed using ^1H NMR, at 4.23 and 3.79 ppm respectively.

An examination of the products obtained from the reactions in which $SnCl_4$ was used reveals that a considerably larger amount of compound **260** and less unreacted aldehyde was recovered, as compared with those reactions in which $BF_3{\cdot}OEt_2$ was used (**Table 3 - 3** and **Table 3 - 4**). This was attributed to a slight difference in experimental conditions where $SnCl_4$ was employed; in an attempt to achieve higher conversions of starting material, a longer delay period was incurred between the time at which the cooling bath had reached 25 °C, and the time at which the reaction mixture was worked-up.

An analysis of entries 7, 8 and 9 in **Table 3 - 3**, reveals the seemingly reversal of diastereoselectivity of dicobalt-complexed homoallylic alcohols **248** – **251** accompanying the formation of a large quantity of **256** + **257** from aldehydes **244** + **245** in entry 9, as compared with entries 7 and 8. This correlation of reversal of diastereoselectivity with very large percentages of **256** + **257** was previously observed when $BF_3{\cdot}OEt_2$ was employed as the Lewis acid, and can be seen from a comparison of entries 10 and 12 in **Table 3 - 3**. A similar reduction in the diastereomeric excess of dicobalt-complexed homoallylic alcohols **252** - **255** with an increased quantity of compounds **258** + **259** was obtained from allyl transfer onto aldehydes **246** + **247**, as can be seen from a comparison of entries 13 and 15 in **Table 3 - 4**. Thus, the tendency of the dicobalt-complexed homoallylic alcohols to undergo elimination appears to be independent of the nature of the Lewis acid.

3.4.9 Origins of Stereoselectivity

One of the objectives of this research endeavor was to determine if the aromatic methoxy substituent of aldehydes **246** + **247** could participate in intramolecular chelation to a bidentate Lewis acid, along with the carbonyl oxygen. The marked improvement in the stereoselectivity of nucleophilic addition to a carbonyl group upon replacement of a monodentate Lewis acid such as $BF_3{\cdot}OEt_2$, with a bidentate Lewis acid such as $SnCl_4$, is one of the qualitative features that is indicative of a process having involved chelation. Accordingly, a comparison of entry 13 (derived from $SnCl_4$) and entry 16 (derived from $BF_3{\cdot}OEt_2$) in **Table 3 - 4**, wherein the amount of **258** + **259** was less than 20 %, reveals that modest diastereoselectivity was obtained from allyl transfer onto aldehydes **246** + **247**, regardless of whether a monodentate or a bidentate Lewis acid was employed. Since intramolecular chelation of aldehyde **246** + **247** is not possible with $BF_3{\cdot}OEt_2$, the diastereoselectivity obtained with the monodentate Lewis acid must be the result of some other determinant.

The allyl transfer reactions onto aldehydes **244** + **245** served to provide information regarding the inherent diastereoselectivity of the transformation, in the absence of chelation. A comparison of entries 8 (derived from $SnCl_4$) and 1 (derived from $BF_3{\cdot}OEt_2$) in **Table 3 - 3**, wherein the amount of **256** + **257** was also less than 20 %, reveals that modest diastereoselectivity was also obtained from allyl transfer onto aldehydes **244** + **245** when either a monodentate or a bidentate Lewis acid was employed. These results indicate that in the absence of chelation, the intrinsic diastereoselectivity of allylic transposition onto **244** + **245** had likely been controlled by some characteristic of the aldehyde, such as a steric biasing of the direction of nucleophilic attack at the carbonyl group.

The triarylphosphine ligand on cobalt in both aldehydes **244** + **245** and **246** + **247** is presumed to have provided steric crowding in both sets of compounds. Evidence in support of this was obtained during the preparation of authentic samples of the diastereomeric homoallylic alcohols **248** - **255**. Replacement of one CO ligand on cobalt in (1-phenyl-5-hexen-1-yn-3-ol)dicobalt hexacarbonyl **227** with triphenylphosphine produced a mixture of monophosphinated diastereomers **248** - **251** in a ratio of 30:70.[31] Similarly, replacement of one CO ligand on cobalt in **227** with diphenyl(2-methoxyphenyl)phosphine produced a mixture of monophosphinated diastereomers **252** - **255** in a ratio of 22:78.[33]

The triarylphosphine ligand on cobalt in both sets of aldehydes **244** + **245** and **246** + **247** may have also influenced the stereoselectivity of allylic transposition through steric effects. This would explain the diastereoselectivity of the dicobalt-complexed homoallylic alcohols obtained from aldehydes **244** + **245**. However, based only on the diastereoselectivity of the homoallylic alcohols obtained from aldehydes **246** + **247**, which possessed a substituent that was able to participate in chelation to $SnCl_4$, a distinction cannot be made between a process which had been controlled by chelation, and one which had been controlled by steric effects alone.

3.4.10 Effects of Lewis Acid on Allyl Transfer - 0.5 Equivalents of Bidentate $SnCl_4$

A second qualitative feature, albeit much less reliable, which could provide clues regarding the possibility that allylic transposition had occurred via a chelated aldehyde, is the quantity of unreacted dicobalt-complexed aldehyde relative to the quantity of Lewis acid employed. Based on the ^1H, ^{13}C and ^{119}Sn NMR studies of the stoichiometry of complexation of 2-methyl-3-benzyloxypropanal with $SnCl_4$ (described in Section 3.3.1), intramolecular chelation of aldehydes **246** + **247** with $SnCl_4$ would have given rise to a 1:1 complex, in analogy to **194** in **Figure 3 - 18**. Upon reduction of the stoichiometry of Lewis acid from 1.0 molar equivalent (relative to the aldehyde), to 0.5 equivalents, a 1:1 complex would have, in principle, resulted in 50 % unreacted aldehyde. In contrast, if chelation had been precluded and a 2:1 complex analogous to **195** in **Figure 3 - 19** had formed, both 0.5 and 1.0 molar equivalents of $SnCl_4$ would have been sufficient to allow 100 % conversion of the aldehyde. However, in this case, 50 % of the 1.0 molar equivalent of Lewis acid would have remained unreacted.

A third series of allyl transfer reactions were then carried out with aldehydes **244** - **247** and allyltributylstannane under identical experimental conditions as those described in Section 3.4.8, with the exception that 0.5 molar equivalents of $SnCl_4$ (relative to the aldehyde) were used. As with the previous two reaction series, the product mixture was comprised of unreacted aldehydes **244** - **247**, decomplexed aldehyde **261**, homoallylic alcohols **248** - **255**, elimination products **255** - **259** and alcohol **260**. The results are given in **Table 3 - 5** and **Table 3 - 6**, wherein each entry corresponds to one individual reaction, along with the data first tabulated in Section 3.4.8, for comparison. Each of the reaction mixtures was allowed to reach 25 °C before quenching, and the time of work-up ranged from 6 – 12 hours following the time of addition of reagents.

Table 3 - 5. Quantities of all products obtained and the corresponding diastereomeric ratio of **248** - **251** from the addition of 1 molar equivalent of allyltributylstannane and 0.5 (or 1.0) molar equivalent of $SnCl_4$ at -30 °C to compounds **244** and **245**.

Entry	Equiv. of $SnCl_4$	Products Obtained (mol %)					
		244 + 245	**261**	**248 - 251**	**260**	**256 + 257**	Diast. Ratio[a]
19	0.5	7	10	16	42	25	10 : 90
20	0.5	3	11	33	30	23	37 : 63
21	1.0	7	11	21	34	27	16 : 84
22	1.0	0	5	18	59	18	21 : 79
23	1.0	5	8	5	11	71	75 : 25

[a] The diastereomeric ratio of **248** - **251** is given as X : Y where X and Y correspond to the compound having a chemical shift of C4-H, observed using ^{1}H NMR, at 4.0 and 3.83 ppm respectively.

Table 3 - 6. Quantities of all products obtained and the corresponding diastereomeric ratio of **252** - **255** from the addition of 1 molar equivalent of allyltributylstannane and 0.5 (or 1.0) molar equivalent of $SnCl_4$ at -30 °C to compounds **246** and **247**.

Entry	Equiv. of $SnCl_4$	Products Obtained (mol %)					
		246 + 247	**261**	**252 - 255**	**260**	**258 + 259**	Diast. Ratio[b]
24	0.5	4	14	31	49	2	20 : 80
25	0.5	5	10	48	21	16	20 : 80
26	1.0	8	13	43	16	20	13 : 87
27	1.0	0	7	22	29	42	35 : 65
28	1.0	0	4	25	22	49	48 : 52

[b] The diastereomeric ratio of **252** - **255** is given as X : Y where X and Y correspond to the compound having a chemical shift of C4-H, observed using ^{1}H NMR, at 4.23 and 3.79 ppm respectively.

The very low quantity of unreacted aldehydes **246** + **247** recovered from the reaction mixture, regardless of whether 1.0 or 0.5 equivalents of $SnCl_4$ were used, could be interpreted as evidence in support of a process that involved a 2:1 complex between the aldehyde and Lewis acid. In addition, greater quantities of the elimination products **258** + **259** were obtained with 1.0 rather than 0.5 equivalents of Lewis acid, which would be consistent with a 2:1 complex between the aldehyde and Lewis acid, whereby excess $SnCl_4$ would have been available to effect elimination from the diastereomeric homoallylic alcohols **252** - **255**. Taken together, these results would seem to be indicative of a process that did not involve intramolecular chelation of aldehydes **246** + **247**. In all cases, however, the total yield of all products recovered was less than would be expected from 100 % conversion of the aldehyde (see **Tables 3 - 7** to **3 - 12** in the Experimental Section). In addition, a small quantity of an intractable residue, which could not be solubilized, was also found in every product mixture. If this residue contained a polymer that had formed from either the complexed or the non-complexed aldehyde, then the values reported for unreacted aldehydes **246** + **247** (in terms of allyl transfer) would correspond to underestimated quantities. The polymerization of aldehydes using $SnCl_4$ has previously been reported.[34] Therefore, no conclusion can be made regarding whether or not allyl transfer onto aldehydes **246** + **247** had proceeded through an intramolecularly chelated structure, based on the quantities of unreacted aldehyde recovered.

3.5.1 Summary

The dicobalt hexacarbonyl-complexed acetylenic ketone and aldehyde allowed for the formation of the 3-hydroxy-hexa-1,5-enyne system from allyl transfer. Although elimination occurred from the former to give a conjugated diene, experimental conditions might be found which prevent elimination. The dicobalt pentacarbonyl(triarylphosphine)-complexed acetylenic aldehydes allowed for the formation of the dicobalt-complexed 3-hydroxy-hexa-1,5-enyne system with good diastereoselectivity at low conversions. However, based on the results obtained, it cannot be determined to what extent the diastereomeric ratios obtained at higher conversions were skewed as a result of the competing elimination, decomplexation and possibly epimerization reactions of the first formed homoallylic etherate. Therefore, a conclusion cannot be made as to whether the stereoselectivity was controlled by steric effects caused by the phosphine ligand alone, or was the outcome of a process having involved intramolecular chelation (in the case of aldehydes **246** + **247**).

The processes of elimination and decomplexation have been observed in this study, and have been previously reported by other researchers, to be temperature dependent. In addition, the stability of the chelated intermediates of acyclic α- and β-hydroxy aldehydes, described in Section 3.3.1, was shown to be temperature-dependent, typically in the range of -90 °C to -20 °C. It is conceivable that the experimental conditions required, in order for allyl transfer onto a chelated aldehyde to be a favorable pathway, fall within narrow ranges of temperature and concentration. It is possible then, that the reaction conditions employed were not optimal for chelation; elimination, decomplexation and possibly epimerization, became competing pathways as the bath temperature was allowed to gradually increase from the temperature of addition of reagents.

FUTURE RESEARCH

The experimental conditions of temperature, concentration and solvent, which are required for the formation of a stable chelate of aldehydes **246** + **247** with a bidentate Lewis acid, need to be found, if they exist at all. This might be accomplished by monitoring product formation with variable-temperature ^{119}Sn NMR spectroscopy while titrating a solution of $SnCl_4$ with the aldehyde, as described in Section 3.3.1.

In order to reduce the steric contribution of the aromatic groups on phosphine, and more importantly, to determine if a change in the size of the expected cyclic, chelated structure would affect its ability to form, a trialkylphosphine ligand could be employed on cobalt, rather than a triarylphosphine. The size of the chelated structure could be varied with the use of ligands of the type $R_2P(CH_2)_nOCH_3$ where $n \geq 1$. Two such ligands include $(CH_3)_2PCH_2OCH_3$ and $P(CH_2OCH_3)_3$, whose syntheses have been reported.[35]

An alternative approach would involve utilization of an alkylphosphine ligand derived from a chiral nonracemic compound. This might allow both diastereoselectivity and enantioselectivity to be accomplished in one step, but has the disadvantage that the chiral moiety must be used in a stoichiometric quantity, in contrast to the method of chelation, wherein the chiral Lewis acid could be catalytic.

EXPERIMENTAL

3.6.1 General Procedures and Instrumentation

^1H NMR spectra were recorded on a Bruker AC-200 spectrometer at 200.133 MHz using the residual $CHCl_3$ present in $CDCl_3$ as internal reference. ^{13}C NMR spectra were recorded on the same instrument at 50.323 MHz, also using $CDCl_3$ as internal reference.

Chemical ionization (CI), with ammonia as the reagent gas, and electron impact (EI) mass spectra were recorded at 70 eV with a source temperature of 200 °C on a VG Analytical ZAB-R mass spectrometer equipped with a VG 11-250 data system. Electrospray ionization mass spectra were obtained with a Fisons Platform quadrupole instrument using a CH_3CN/H_2O (50/50) mixture as the mobile phase, with the addition of CF_3CO_2H for samples analyzed in the positive mode (+ve ES), and NH_4OH or NH_4Cl for samples analyzed in the negative mode (-ve ES).

Infrared spectra were recorded on a Bio Rad FTS-40 Fourier transform spectrometer. Liquid samples were used as neat films on NaCl discs and solid samples were prepared as KBr pellets.

3.6.2 Reagents and Solvents

Acetyl chloride, allyltributylstannane, phenylacetylene, *N*-formyl morpholine, triphenylphosphine, diphenyl(2-methoxyphenyl)phosphine, n-butyllithium in hexanes,

$(NH)_4Ce(NO_3)_6$, $AlCl_3$, $BF_3{\cdot}OEt_2$, $SnCl_4$ and trimethylsilyl trifluoromethanesulfonate were purchased from Aldrich and used without purification. Allyltrimethylsilane, bis(trimethylsilyl)acetylene and 1,2-bis(trimethylsilyloxy)ethane were purchased from Gelest and used without further purification. Dicobalt octacarbonyl was purchased from Acros Organics and used without further purification. $CDCl_3$ was obtained from Cambridge Isotope Labs and used without purification.

CH_2Cl_2 was distilled from CaH_2 prior to use, THF and diethyl ether were distilled from sodium prior to use.

3.6.3 Compounds Prepared and Reactions

4-Trimethylsilyl-3-butyn-2-one, 206:

To a suspension of $AlCl_3$ (0.78 g, 5.86 mmol) in CH_2Cl_2 (25 mL) was added acetyl chloride (0.42 mL, 5.86 mmol) at 0 °C under N_2. After stirring for 30 min, a solution of bis(trimethylsilyl)acetylene (1.00 g, 5.86 mmol) in CH_2Cl_2 (10 mL) was added dropwise at 0 °C. After stirring for an additional 4 h, the reaction mixture was quenched by the careful addition of cold H_2O at 0 °C. After the mixture had warmed to room temperature, the organic phase was separated, dried over $MgSO_4$, and concentrated under reduced pressure to give a yellow oil. Purification by flash chromatography (85:15 pentane:diethyl ether) yielded 0.72 g (5.14 mmol, 88%) of a yellow oil. ^1H NMR ($CDCl_3$, 200 MHz) δ 2.32 (s, 3 H), 0.21 (s, 9H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 183.8, 102.1, 96.8, 32.2, -1.0; IR (neat) 2966, 2153, 1680, 1254, 867, 847 cm^{-1}; MS (EI, m/z) 125 (M^+

- CH_3, 95), 97 (M^+ - C(O)CH_3, 26), 43 (100); MS (CI, NH_3, m/z) 158 (M + NH_4, 100), 125 (23), 43 (31).

(4-Trimethylsilyl-3-butyn-2-one)dicobalt hexacarbonyl, 217:

To a solution of dicobalt octacarbonyl (0.36 g, 1.05 mmol) in CH_2Cl_2 (25 mL) at 0 °C under N_2 was added a solution of 4-trimethylsilyl-3-butyn-2-one (0.10 g, 0.71 mmol) in CH_2Cl_2 (10 mL). The mixture was allowed to gradually warm to room temperature and after 4 h of stirring, the solvent was concentrated under reduced pressure and the reaction mixture was purified by flash chromatography (8:2 pentane:diethyl ether) to yield 0.28 g (0.65 mmol, 92%) of a red solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.47 (s, 3H), 0.32 (s, 9H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 199.4, 198.7, 100.2, 80.6, 31.3, 0.6; IR (neat) 2963, 2098, 2061, 2028, 1671, 1252, 839 cm^{-1}; MS (EI, m/z) 398 (M^+ - CO, 5), 370 (M^+ - 2 CO, 9), 342 (M^+ - 3 CO, 15), 314 (M^+ - 4 CO, 14), 286 (M^+ - 5 CO, 33), 258 (M^+ - 6 CO, 30), 125 (71), 43 (100); MS (CI, NH_3, m/z) 427 (M + H^+, 100), 399 (15), 43 (29).

*4-Methyl-6-trimethylsilyl-5-hexyn-1,3-diene, **209**, via allyl transfer onto acetylenic ketone*

To a solution of 4-trimethylsilyl-3-butyn-2-one (0.50 g, 3.57 mmol) and $BF_3 \cdot OEt_2$ (0.44 mL, 3.57 mmol) in CH_2Cl_2 (35 mL) at -78 °C under N_2, was added allyltrimethylsilane (0.56 mL, 3.57 mmol). The reaction mixture was allowed to gradually warm to room temperature overnight, followed by quenching with cold aqueous $NaHCO_3$

at -78 °C. After the mixture had warmed to room temperature, the organic layer was separated, extracted with a saturated aqueous NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure to give a yellow oil. Purification by flash chromatography (9:1 pentane:diethyl ether) yielded 0.15 g (0.91 mmol, 26%) of a yellow volatile oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.76 (ddd, J = 17.1, 10.9, 10.2 Hz, 1H), 6.22 (d, J = 10.9 Hz, 1H), 5.22 (dd, J = 17.1, 1.5 Hz, 1H), 5.12 (dd, J = 10.2, 1.5 Hz, 1H), 1.88 (s, 3H), 0.19 (s, 9H).

4-Trimethylsilyl-2,2-ethylenedioxy-3-butyne, 215:

To a solution of 1,2-bis(trimethylsilyloxy)ethane (0.87 mL, 3.56 mmol) and trimethylsilyl trifluoromethanesulfonate (0.06 mL, 0.35 mmol) in CH_2Cl_2 (7 mL) at -78 °C under N_2 was added 4-trimethylsilyl-3-butyn-2-one (0.5 g, 3.56 mmol). After stirring for 3 h, the reaction mixture was quenched by the addition of a cold aqueous $NaHCO_3$ solution at -78 °C. After the mixture had warmed to room temperature, the organic layer was separated, extracted with a saturated aqueous NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure to give a yellow oil. Purification by flash chromatography (9:1 pentane:diethyl ether) yielded 0.55 g (2.99 mmol, 84%) of a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.00 (m, 4H), 1.65 (s, 3H), 0.14 (s, 9H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 103.0, 100.4, 87.4, 64.5, 26.2, -0.2; IR (neat) 3001, 2962, 2897, 2171, 1252, 1177, 1034, 923, 861, 843 cm^{-1}; MS (EI, m/z) 169 (M^+ - CH_3, 58), 125 (M^+ - CH_3 - CH_2CH_2O, 68), 97 (M^+ - $C(OCH_2CH_2O)CH_3$, 37), 87 (M^+ - $C_2Si(CH_3)_3$, 100), 73 (M^+ - $C_2C(OCH_2CH_2O)CH_3$, 41), 43 (100); MS (CI, NH_3, m/z) 185 ($M + H^+$, 100), 169 (M^+ - CH_3, 11).

(4-Trimethylsilyl-2,2-ethylenedioxy-3-butyne)dicobalt hexacarbonyl:

To a solution of dicobalt octacarbonyl (0.25 g, 0.72 mmol) in CH_2Cl_2 (10 mL) at 0 °C under N_2 was added a solution of 4-trimethylsilyl-2,2-ethylenedioxy-3-butyne (0.10 g, 0.56 mmol) in CH_2Cl_2 (5 mL). After stirring overnight, the solvent was concentrated under reduced pressure and the reaction mixture was purified by flash chromatography (19:1 pentane:diethyl ether) to yield 0.24 g (0.52 mmol, 93%) of a red solid. ^1H NMR ($CDCl_3$, 200 MHz) δ 4.04 (s, 4H), 1.67 (s, 3H), 0.30 (s, 9H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 200, 111.7, 110.3, 78.4, 65.5, 28.6, 0.8; IR (neat) 2960, 2893, 2092, 2053, 2017, 1248, 1180, 1041, 839 cm^{-1}; MS (EI, m/z) 442 (M^+ - CO, 2), 414 (M^+ - 2 CO, 3), 386 (M^+ - 3 CO, 3), 358 (M^+ - 4 CO, 4), 330 (M^+ - 5 CO, 6), 302 (M^+ - 6 CO, 7), 87 (M^+ - $C_2Si(CH_3)_3$, 69), 43 (100); MS (CI, NH_3, m/z) 471 ($M + H^+$, 43), 443 ($M + H^+$ - CO, 9), 415 ($M + H^+$ - 2 CO, 10), 387 ($M + H^+$ - 3 CO, 6), 87 (M^+ - $C_2Si(CH_3)_3$, 44).

2-(1-Trimethylsilylalkynyl-1-but-3-enoxy)-1-ethanol, 216, via allyl transfer onto acetylenic acetal:

To a solution of 4-trimethylsilyl-2,2-ethylenedioxy-3-butyne (0.05 g, 0.26 mmol) in CH_2Cl_2 (1.3 mL) was added trimethylsilyl trifluoromethanesulfonate (a 0.2 M solution in CH_2Cl_2; 0.13 mL, 0.02 mmol) at 0 °C under N_2. Then, allyltrimethylsilane (0.04 mL, 0.26 mmol) was added and the reaction mixture was stirred overnight. After quenching the reaction mixture by the addition of a cold aqueous $NaHCO_3$ solution at 0 °C and allowing it to warm to room temperature, the organic layer was separated, extracted with a saturated aqueous NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure to give a yellow oil. Purification by flash chromatography (9:1 pentane:diethyl ether) yielded 0.029 g (0.13 mmol, 50%) of a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.84 (m, 1H), 5.10 (m, 2H), 3.68 (m, 4H), 2.42 (d, $J = 6.1$ Hz, 2H), 2.01 (s, 1H), 1.37 (s, 3H), 0.14 (s, 9H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 133.2, 118.3, 106.7, 73.1, 65.0, 62.2, 45.7, 26.0, 0.0; IR (neat) 3408, 3073, 2959, 2165, 1644, 1251, 1083, 843 cm^{-1}.

(4-Methyl-6-trimethylsilyl-5-hexyn-1,3-diene)dicobalt hexacarbonyl, ***219****, via allyl transfer onto dicobalt hexacarbonyl-complexed acetylenic ketone:*

To a solution of (4-trimethylsilyl-3-butyn-2-one)dicobalt hexacarbonyl (0.11 g, 0.25 mmol) and $BF_3{\cdot}OEt_2$ (0.03 mL, 0.25 mmol) in CH_2Cl_2 (9 mL) at -78 °C under N_2, was added allyltributylstannane (0.08 mL, 0.25 mmol). The reaction mixture was allowed to gradually warm to room temperature overnight, followed by quenching with cold aqueous $NaHCO_3$ at -78 °C. After the mixture had warmed to room temperature, the organic layer was separated, extracted with a saturated aqueous NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure to give a black oil. Purification by flash chromatography (19:1 pentane:diethyl ether) yielded 0.09 g (0.20 mmol, 80%) of a black solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.61 (m, 2H), 5.18 (m, 2H), 2.10 (s, 3H), 0.33 (s, 9H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 200.3, 134.7, 133.2, 132.2, 118.6, 110.0, 80.4, 19.3, 0.8; IR (neat) 3085, 2963, 2088, 2048, 2020, 1672, 1561, 1251, 839 cm^{-1}; MS (EI, m/z) 422 (M^+ - CO, 3), 394 (M^+ - 2 CO, 7), 366 (M^+ - 3 CO, 9), 338 (M^+ - 4 CO, 17), 310 (M^+ - 5 CO, 28), 282 (M^+ - 6 CO, 46), 73 (100); MS (CI, NH_3, m/z) 451 (M + H^+, 10), 423 (M + H^+ - CO, 14), 395 (M + H^+ - 2 CO, 15), 367 (M + H^+ - 3 CO, 17), 311 (M + H^+ - 5 CO, 8), 73 (100); HRMS (m/z) calcd for $C_{15}H_{16}O_5SiCo_2$ (M^+ - CO): 421.9440, found 421.9431.

*3-Phenylpropynal, **220:***

To a solution of phenylacetylene (2 mL, 18.21 mmol) in diethyl ether (7 mL) at -78 °C under N_2 was added n-butyllithium in hexanes (a 1.6 M solution; 11.4 mL, 18.2 mmol). After stirring for 2 h, *N*-formyl morpholine (1.85 mL, 18.39 mmol) in diethyl ether (17 mL) was added, and the reaction mixture was allowed to gradually warm to room temperature overnight. Following addition of a 3 M aqueous solution of HCl, the organic layer was separated, extracted with a saturated aqueous NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure to give a yellow oil. Purification by flash chromatography (19:1 pentane:diethyl ether) yielded 1.82 g (14.0 mmol, 77%) of a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.40 (s, 1H), 7.44 (m, 5H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 176.1, 132.6, 130.8, 128.2, 118.8, 94.3, 88.0; IR (neat) 3063, 2858, 2190, 1691, 978, 759 cm^{-1}; MS (EI, m/z) 129 (M^+ - H, 100), 29 (M^+ - $C_6H_5C_2$, 8); MS (CI, NH_3, m/z) 148 (M + NH_4^+, 100), 129 (M^+ - H, 68).

Allyl transfer onto 3-phenylpropynal:

To a solution of 3-phenylpropynal (0.2 g, 1.53 mmol) and $BF_3{\cdot}OEt_2$ (0.20 mL, 1.58 mmol) in CH_2Cl_2 (30 mL) was added allyltrimethylsilane (0.24 mL, 1.53 mmol) at -78 °C under N_2. Stirring was continued for 6 h while the mixture was allowed to gradually warm to room temperature. The mixture was then quenched by the addition of a cold aqueous $NaHCO_3$ solution at -78 °C. After the mixture had warmed to room temperature, the organic layer was separated, extracted with a saturated aqueous NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure to give a yellow oil. Separation by flash chromatography (19:1 pentane:diethyl ether) yielded the following:

1. 6-Phenyl-1-hexen-5-yn-4-ol, 221:

Isolated 0.10 g (0.60 mmol) of a colorless oil. ^1H NMR ($CDCl_3$, 200 MHz) δ 7.35 (m, 5H), 5.94 (m, 1H), 5.22 (m, 2H), 4.64 (t, $J = 6.1$ Hz, 1H), 2.56 (dd, $J = 6.8, 6.1$ Hz, 2H), 2.11 (s, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 133.0, 131.5, 128.2, 128.1, 122.4, 118.7, 89.4, 85.0, 61.9, 42.0; IR (neat) 3397, 3080, 2981, 2913, 2232, 1642, 1490, 1442, 1031, 757, 692 cm^{-1}; MS (EI, m/z) 131 (M^+ - $CH_2CH{=}CH_2$, 100), 77 (36); MS (CI, NH_3, m/z) 190 ($M + NH_4^+$, 48), 172 (M^+, 62), 155 (M^+ - OH, 100).

2. Di-4-(6-Phenyl-1-hexen-5-ynl) ether - (enantiomers (4R,4'R and 4S,4'S) or meso compound), 222a:

Isolated 0.023 g (0.13 mmol) of a colorless oil. ^1H NMR ($CDCl_3$, 200 MHz) δ 7.37 (m, 10H), 6.00 (m, 2H), 5.19 (m, 4H), 4.77 (t, $J = 6.3$ Hz, 2H), 2.61 (m, 4H); ^{13}C NMR

($CDCl_3$, 50.3 MHz) δ 133.6, 131.7, 128.3, 128.2, 122.8, 117.9, 88.0, 86.2, 68.6, 40.1; IR (neat) 3079, 2980, 2918, 2865, 2231, 1490, 1070, 917, 756 cm^{-1}; MS (EI, m/z) 285 (M^+ - $CH_2CH{=}CH_2$, 10), 155 (M^+ - $C_6H_5C_2CH(O)CH_2CH{=}CH_2$, 100), 77 ($C_6H_5^+$, 16), 41 (14); MS (CI, NH_3, m/z) 344 ($M + NH_4^+$, 33), 172 (M^+ - $C_6H_5C_2CHCH_2CH{=}CH_2 + H^+$, 58), 155 ($M^+$ - $C_6H_5C_2CH(O)CH_2CH{=}CH_2$, 100).

*3. Di-4-(6-Phenyl-1-hexen-5-ynl) ether - (enantiomers (4R,4′R and 4S,4′S) or meso compound), **222b**:*

Isolated 0.022 g (0.13 mmol) of a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.37 (m, 10H), 6.00 (m, 2H), 5.19 (m, 4H), 4.57 (t, *J* = 6.3 Hz, 2H), 2.58 (m, 4H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 133.5, 131.7, 128.2, 128.1, 122.7, 117.6, 87.5, 86.2, 67.4, 40.1; IR (neat) 3079, 2980, 2918, 2865, 2231, 1490, 1070, 917, 756 cm^{-1}; MS (EI, m/z) 285 (M^+ - $CH_2CH{=}CH_2$, 8), 155 (M^+ - $C_6H_5C_2CH(O)CH_2CH{=}CH_2$, 100), 77 ($C_6H_5^+$, 63), 41 (46); MS (CI, NH_3, m/z) 344 ($M + NH_4^+$, 69), 172 (M^+ - $C_6H_5C_2CHCH_2CH{=}CH_2 + H^+$, 65), 155 ($M^+$ - $C_6H_5C_2CH(O)CH_2CH{=}CH_2$, 100).

*4. (E)-3,5-Hexadien-1-ynylbenzene, **223** and (Z)-3,5-hexadien-1-ynylbenzene, **224**:*

Isolated 0.02 g (0.11 mmol) of a colorless oil containing both (*E*) and (*Z*) isomers. (*E*) isomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.28 (m, 5H), 6.67 (dd, *J* = 15.4, 10.8 Hz, 1H), 6.40 (ddd, *J* = 16.6, 10.8, 10.0 Hz, 1H), 5.82 (d, *J* = 15.4 Hz, 1H), 5.31 (dd, *J* = 16.6, 1.2 Hz, 1H), 5.19 (dd, *J* = 10.0, 1.2 Hz, 1H). (*Z*) isomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ

7.35 (m, 5H), 6.97 (ddd, J = 16.6, 10.6, 10.0 Hz, 1H), 6.43 (dd, J = 10.8, 10.6 Hz, 1H), 5.68 (d, J = 10.8 Hz, 1H), 5.40 (dd, J = 16.6, 1.4 Hz, 1H), 5.31 (dd, J = 10.0, 1.4 Hz, 1H).

5. 4-(Phenylalkynyl)-1,6-heptadiene, 225:

Isolated 0.01 g (0.01 mmol) of a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.31 (m, 5H), 5.90 (m, 2H), 5.10 (m, 4H), 2.67 (q, J = 7.0 Hz, 1H), 2.29 (dd, J = 7.0, 6.7 Hz, 4H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 135.8, 131.6, 128.1, 127.5, 123.8, 116.7, 92.2, 82.2, 38.6, 32.0; MS (EI, m/z) 196 (M^+, 7), 155 (M^+ - $CH_2CH{=}CH_2$, 100), 77 ($C_6H_5^+$, 44); MS (CI, NH_3, m/z) 197 (M + H^+, 100), 155 (M^+ - $CH_2CH{=}CH_2$, 60).

(3-Phenylpropynal)dicobalt hexacarbonyl, 226:

To a solution of dicobalt octacarbonyl (0.31 g, 0.91 mmol) in CH_2Cl_2 (18 mL) was added 3-phenylpropynal (0.10 g, 0.76 mmol) in CH_2Cl_2 (15 mL) at 0 °C under N_2. Stirring was continued overnight, followed by concentration of the solvent under reduced pressure and purification by flash chromatography (19:1 pentane:diethyl ether) to yield 0.31 g (0.74 mmol, 97%) of a red solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 10.50 (s, 1H), 7.45 (m, 5H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 197.6, 190.8, 136.3, 129.7, 129.0, 128.8, 92.1, 85.6; IR (neat) 2101, 2065, 2032, 1666, 1484, 1442 cm^{-1}; MS (EI, m/z) 388 (M^+ - CO, 21), 360 (M^+ - 2 CO, 31), 332 (M^+ - 3 CO, 29), 304 (M^+ - 4 CO, 53), 276 (M^+ - 5

CO, 68), 248 (M^+ - 6 CO, 100); MS (CI, NH_3, m/z) 417 (M + H^+, 100), 389 (M + H^+ - CO, 56).

(6-Phenyl-1-hexen-5-yn-4-ol)dicobalt hexacarbonyl, 227, via allyl transfer onto dicobalt hexacarbonyl-complexed acetylenic aldehyde:

To a solution of (3-phenylpropynal)dicobalt hexacarbonyl (0.15 g, 0.37 mmol) and $BF_3{\cdot}OEt_2$ (0.05 mL, 0.39 mmol) in CH_2Cl_2 (18 mL) at -78 °C under N_2 was added allyltrimethylsilane (0.06 mL, 0.37 mmol). After stirring for 5 h, the mixture was quenched by the addition of a cold aqueous $NaHCO_3$ solution at -78 °C. After the mixture had warmed to room temperature, the organic layer was separated, extracted with a saturated aqueous NaCl solution, concentrated under reduced pressure, and purified by flash chromatography (19:1 pentane:diethyl ether) to yield 0.15 g (0.33 mmol, 90%) of a red solid. ^1H NMR ($CDCl_3$, 200 MHz) δ 7.43 (m, 5H), 5.95 (m, 1H), 5.24 (m, 2H), 5.06 (m, 1H), 2.65 (m, 1H), 2.43 (m, 1H), 2.21 (d, J = 3.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 199.3, 137.6, 134.1, 129.6, 128.8, 127.9, 118.9, 100.2, 90.8, 71.5, 43.9; IR (neat) 3467, 3080, 2942, 2092, 2053, 2021, 1612, 1483, 1442, 1050, 760, 692 cm^{-1}; MS (EI, m/z) 430 (M^+ - CO, 5), 402 (M^+ - 2 CO, 35), 374 (M^+ - 3 CO, 12), 346 (M^+ - 4 CO, 26), 318 (M^+ - 5 CO, 48), 290 (M^+ - 6 CO, 100); MS (CI, NH_3, m/z) 441 (M^+ - OH, 100), 413 (M^+ - OH – CO, 68), 385 (M^+ - OH – 2 CO, 80), 346 (M^+ - 4 CO, 63), 290 (M^+ - 6 CO, 72); MS (-ve ES, m/z) 456.9 (100) $[M - 1H]^-$, 457.9 (24) [M].

Decomplexation of the above cobalt cluster for structural confirmation:

To a solution of (6-phenyl-1-hexen-5-yn-4-ol)dicobalt hexacarbonyl (0.09g, 0.20 mmol) in acetone (20 mL) at -78 °C was added dropwise a solution of $(NH)_4Ce(NO_3)_6$ (0.87 g, 1.6 mmol) in acetone (10 mL). After stirring for 2 h, the reaction mixture was allowed to warm to room temperature, extracted with a saturated aqueous solution of NaCl, dried over $MgSO_4$, and the solvent removed under reduced pressure to yield 0.01 g (0.06 mmol, 33%) of a yellow oil which was confirmed by ^1H NMR to be 1-phenyl-5-hexen-1-yn-3-ol.

(4-(Phenylacetylene)-1,6-heptadiene)dicobalt hexacarbonyl, ***231****, via allyl transfer onto dicobalt hexacarbonyl-complexed acetylenic aldehyde:*

To a solution of (3-phenylpropynal)dicobalt hexacarbonyl (0.22 g, 0.52 mmol) and $BF_3{\cdot}OEt_2$ (0.15 mL, 1.19 mmol) in CH_2Cl_2 (11 mL) at -78 °C under N_2 was added allyltrimethylsilane (0.19 mL, 1.19 mmol). After stirring for 8 h, the mixture was quenched by the addition of a cold aqueous $NaHCO_3$ solution at -78 °C. After the mixture had warmed to room temperature, the organic layer was separated, extracted with a saturated aqueous NaCl solution, concentrated under reduced pressure, and purified by flash chromatography (8:2 pentane:diethyl ether) to yield 0.08 g (0.40 mmol, 77%) of a red solid. ^1H NMR ($CDCl_3$, 200 MHz) δ 7.34 (m, 5H), 5.84 (m, 2H), 5.05 (m, 4H), 3.23 (q, J = 6.6 Hz, 1H), 2.44 (dd, J = 6.6, 6.1 Hz, 4H). Decomplexation with $(NH)_4Ce(NO_3)_6$ as described above was then carried out for structural confirmation, which yielded 0.04 g

(0.20 mmol, 50%) of a yellow oil which was determined by ^1H NMR to be 4-(phenylacetylene)-1,6-heptadiene.

*(4-(Phenylalkynyl)-1,6-heptadiene)dicobalt hexacarbonyl, **236**, via second allyl transfer onto dicobalt hexacarbonyl-complexed acetylenic homoallylic alcohol:*

To a solution of (6-phenyl-1-hexen-5-yn-4-ol)dicobalt hexacarbonyl (0.09 g, 0.20 mmol) and $BF_3 \cdot OEt_2$ (0.03 mL, 0.23 mmol) in CH_2Cl_2 (11 mL) at -78 °C under N_2 was added allyltrimethylsilane (0.04 mL, 0.25 mmol). After stirring for 6 h, the mixture was quenched by the addition of a cold aqueous $NaHCO_3$ solution at -78 °C. After the mixture had warmed to room temperature, the organic layer was separated, extracted with a saturated aqueous NaCl solution, concentrated under reduced pressure, and purified by flash chromatography (8:2 pentane:diethyl ether) to yield 0.07 g (0.15 mmol, 75%) of a red solid which was determined by ^1H NMR to be (4-(phenylacetylene)-1,6-heptadiene)dicobalt hexacarbonyl.

*(3-Phenylpropynal)dicobalt pentacarbonyl (triphenylphosphine), **244** + **245**:*

To a solution of (3-phenylpropynal)dicobalt hexacarbonyl (0.19 g, 0.45 mmol) in diethyl ether (4.5 mL) and THF (4.5 mL) at 60 °C under N_2 was added triphenylphosphine (0.12 g, 0.45 mmol) in diethyl ether (4.5 mL) and THF (4.5 mL). After gentle reflux for 4 h, the solution was cooled to room temperature, and the solvent concentrated under reduced pressure. Purification by flash chromatography (6:4 pentane:diethyl ether) yielded 0.24 g (0.37 mmol, 81%) of a red solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 9.93 (s, 1H), 7.21 (m, 20H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 199.5, 190.9, 137.9, 133.0, 132.8, 130.3, 130.1, 128.5, 128.3, 127.3, 88.2, 79.6; IR (neat) 2068, 2022, 2005, 1971, 1652, 1480, 1438, 753, 699 cm^{-1}; MS (+ve ES, m/z) 651.0 (7) $[M + 1H]^+$.

(3-Phenylpropynal)dicobalt pentacarbonyl (diphenyl(2-methoxyphenyl)phosphine), ***246*** *+* ***247****:*

To a solution of (3-phenylpropynal)dicobalt hexacarbonyl (0.60 g, 1.44 mmol) in diethyl ether (15 mL) and THF (15 mL) at 60 °C under N_2 was added diphenyl(2-methoxyphenyl)phosphine (0.42 g, 1.44 mmol) in diethyl ether (15 mL) and THF (15 mL). After gentle reflux for 4 h, the solution was cooled to room temperature, and the solvent concentrated under reduced pressure. Purification by flash chromatography (6:4 pentane:diethyl ether) yielded 0.84 g (1.23 mmol, 86%) of a red solid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 10.01 (s, 1H), 6.95 (m, 19H), 3.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 199.8, 191.4, 159.4, 138.3, 133.9, 133.7, 133.2, 133.0, 132.9, 132.4, 130.1, 128.2, 126.9, 120.4, 120.3, 119.7, 110.9, 88.3, 79.3, 54.2; IR (neat) 2068, 2026, 1999, 1979, 1648, 1480, 1438, 1019, 753, 699 cm^{-1}; MS (+ve ES, m/z) 681.0 (80) $[M + 1H]^+$.

(6-Phenyl-1-hexen-5-yn-4-ol)dicobalt pentacarbonyl (triphenylphosphine), ***248*** *–* ***251****, via allyl transfer onto dicobalt-complexed acetylenic aldehyde:*

Three variations of this general procedure were employed. 1) The first one involved addition of 1.0 molar equivalent of $BF_3{\cdot}OEt_2$ (relative to the aldehyde) to **244** + **245** at -78 °C. The molar ratios of products obtained are given in **Table 3 - 1**, and the actual molar quantities are given in **Table 3 - 7**. 2) The second procedure involved addition of 1.0 molar equivalent of $SnCl_4$ (relative to the aldehyde) to **244** + **245** at -30 °C. This is described in detail below. The molar ratios of products obtained are given in **Table 3 - 3**, and the actual molar quantities are given in **Table 3 - 8**. 3) The third procedure involved addition of 0.5 molar equivalents of $SnCl_4$ (relative to the aldehyde) to **244** + **245** at -30 °C. The molar ratios of products obtained are given in **Table 3 - 5**, and the actual molar quantities are given in **Table 3 - 9**. In all three procedures, the reaction mixture was allowed to gradually warm to 25 °C (which required approximately 4 – 6 hours), followed by quenching at either -78 °C (in the case of $BF_3{\cdot}OEt_2$) or -30 °C (in the case of $SnCl_4$). The time at which the reaction mixtures were worked-up, following the time of addition of reagents, ranged from approximately 6 hours (applies to entries 1, 7 and 19), to approximately 12 hours (applies to entry 12) and 24 hours (applies to entry 9). Entries 2, 8 and 20 correspond to reactions that were worked up at various times between 6 and 12 hours following the time of addition of reagents.

To a solution of (3-phenylpropynal)dicobalt pentacarbonyl(triphenylphosphine) (0.06 g, 0.09 mmol) in CH_2Cl_2 (9 mL) was added $SnCl_4$ (a 1.0 M solution in CH_2Cl_2; 0.09

mL, 0.09 mmol) at -30 °C under N_2 and stirred for 1.5 h. Allyltributylstannane (0.03 mL, 0.09 mmol) was then added and the reaction was monitored using TLC to determine when the starting material had been completely consumed. Analysis of the product mixture using TLC (8:2 pentane:diethyl ether) revealed: **256** + **257** R_f = 0.68 (green spot); **244** + **245** R_f = 0.34 (red spot); **248** - **251** R_f = 0.30 and 0.38 (both red spots); **260** R_f = 0.24 (UV active). The mixture was quenched by the addition of a cold aqueous $NaHCO_3$ solution at -30 °C. After the reaction mixture had warmed to room temperature, the organic layer was separated, extracted with a saturated aqueous NaCl solution, concentrated under reduced pressure, and then separated by flash chromatography (8:2 pentane:diethyl ether) to yield the following:

1. (6-Phenyl-1-hexen-5-yn-4-ol)dicobalt pentacarbonyl (triphenylphosphine), diastereomeric mixture, 248 – 251:

The diastereomers that are shown in **Figure 3 - 33** have been arbitrarily assigned compound numbers **248** - **251**, however, it has not been established yet whether the major diastereomer (see below) corresponds to structures **248** + **249** or structures **250** + **251**. Using entry 1 of **Table 3 - 7** as an example, the diastereomer ratio 30:70 corresponds to:

Minor diastereomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.27 (m, 20H), 5.98 (m, 1H), 5.12 (m, 2H), 4.0 (m, 1H), 2.65 (M, 1H), 2.31 (m, 1H), 1.61 (s, 1H);

Major diastereomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.27 (m, 20H), 5.74 (m, 1H), 5.12 (m, 2H), 3.83 (m, 1H), 2.31 (m, 1H), 2.03 (m, 1H), 1.31 (s, 1H);

Diastereomeric Mixture: ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 205.4, 201.3 (CO), 135.3, 135.1 (CH=), 139.2 and 134.3 – 126.5 (C_6H_5), 117.8, 117.1 (=CH_2), 96.1, 94.0, 86.8, 84.0 (C≡C), 70.2, 70.0 (CHOH), 44.1, 42.2 (CH_2); IR (neat) 3311, 3078, 3059, 2058, 2008, 1961,1642, 1488, 1438, 1182, 1120, 723, 694 cm^{-1}; MS (-ve ES, m/z) 726.8 (62) [M + ^{35}Cl]$^-$, 728.8 (27) [M + ^{37}Cl]$^-$.

2. ((E)-3,5-Hexadien-1-ynylbenzene)dicobalt pentacarbonyl(triphenylphosphine), ***256 + 257:***

^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.19 (m, 20H), 6.31 (m, 3H), 5.12 (m, 2H).

After decomplexation of the compound using $(NH)_4Ce(NO_3)_6$, structural confirmation was obtained by comparison of the compound's ^{1}H NMR spectrum with that of (*E*)-3,5-hexadien-1-ynylbenzene.

3. 6-Phenyl-1-hexen-5-yn-4-ol, ***260:***

A comparison of the ^{1}H NMR spectrum confirmed the structure.

EXPERIMENTAL QUANTITIES:

Table 3 - 7. Quantities of all products obtained and the corresponding diastereomeric ratio of **248** - **251** from the addition of 1 molar equivalent of allyltributylstannane and 1 molar equivalent of $BF_3 \cdot OEt_2$ at -78 °C to compounds **244** and **245**.

Entry	**244** + **245**	Products Obtained (mmol)					
	(mmol)	**244** + **245**	**261**	**248** - **251**	**260**	**256** + **257**	Diast. Ratio[a]
1	0.212	0.043	0	0.184	0	0.038	30 : 70
2	0.061	0.009	0	0.014	0	0.034	40 : 60
3	0.169	0	0	0.047	0	0.159	95 : 5

[a] The diastereomeric ratio of **248** - **251** is given as X : Y where X and Y correspond to the compound having a chemical shift of C4-H, observed using ^1H NMR, at 4.0 and 3.83 ppm respectively.

Table 3 - 8. Quantities of all products obtained and the corresponding diastereomeric ratio of **248** - **251** from the addition of 1 molar equivalent of allyltributylstannane and 1 molar equivalent of Lewis Acid at -30 °C to compounds **244** and **245**.

Entry	**244** + **245**	Products Obtained (mmol)					
	(mmol)	**244** + **245**	**261**	**248** - **251**	**260**	**256** + **257**	Diast. Ratio[a]
7	0.186	0.016	0.025	0.048	0.079	0.063	16 : 84
8	0.074	0	0.005	0.018	0.060	0.019	21 : 79
9	0.080	0.005	0.008	0.005	0.011	0.073	75 : 25
10	0.212	0.043	0	0.184	0	0.038	30 : 70
11	0.061	0.009	0	0.014	0	0.034	40 : 60
12	0.169	0	0	0.047	0	0.159	95 : 5

[a] The diastereomeric ratio of **248** - **251** is given as X : Y where X and Y correspond to the compound having a chemical shift of C4-H, observed using ^1H NMR, at 4.0 and 3.83 ppm respectively.

Table 3 - 9. Quantities of all products obtained and the corresponding diastereomeric ratio of **248** - **251** from the addition of 1 molar equivalent of allyltributylstannane and 0.5 (or 1.0) molar equivalents of $SnCl_4$ at -30 °C to compounds **244** and **245**.

Entry	**244** + **245**	Products Obtained (mmol)					
	(mmol)	**244** + **245**	**261**	**248** - **251**	**260**	**256** + **257**	Diast. Ratio[a]
19	0.065	0.005	0.007	0.011	0.028	0.017	10 : 90
20	0.103	0.003	0.015	0.044	0.038	0.031	37 : 63
21	0.186	0.016	0.025	0.048	0.079	0.063	16 : 84
22	0.074	0	0.005	0.018	0.060	0.019	21 : 79
23	0.080	0.005	0.008	0.005	0.011	0.073	75 : 25

[a] The diastereomeric ratio of **248** - **251** is given as X : Y where X and Y correspond to the compound having a chemical shift of C4-H, observed using ^1H NMR, at 4.0 and 3.83 ppm respectively.

(6-Phenyl-1-hexen-5-yn-4-ol)dicobalt pentacarbonyl(diphenyl(2-methoxyphenyl)-phosphine), 252 - 255, via allyl transfer onto dicobalt-complexed acetylenic aldehyde:

Three variations of this general procedure were employed. 1) The first one involved addition of 1.0 molar equivalent of $BF_3{\cdot}OEt_2$ (relative to the aldehyde) to **246** + **247** at -78 °C. The molar ratios of products obtained are given in **Table 3 - 2**, and the actual molar quantities are given in **Table 3 - 10**. 2) The second procedure involved addition of 1.0 molar equivalent of $SnCl_4$ (relative to the aldehyde) to **246** + **247** at -30 °C. This is described in detail below. The molar ratios of products obtained are given in **Table 3 - 4**, and the actual molar quantities are given in **Table 3 - 11**. 3) The third procedure involved addition of 0.5 molar equivalents of $SnCl_4$ (relative to the aldehyde) to **246** + **247** at -30 °C. The molar ratios of products obtained are given in **Table 3 - 6**, and the actual molar quantities are given in **Table 3 - 12**. In all three procedures, the reaction mixture was allowed to gradually warm to 25 °C (which required approximately 4 – 6 hours), followed by quenching at either -78 °C (in the case of $BF_3{\cdot}OEt_2$) or -30 °C (in the case of $SnCl_4$). The time at which the reaction mixtures were worked-up, following the time of addition of reagents, ranged from approximately 6 hours (applies to entries 4 and 13), to approximately 12 hours (applies to entry 6). Entries 5, 14, 15, 24, and 25 correspond to reactions that were worked-up at various times between 6 and 12 hours following the time of addition of reagents.

To a solution of (3-phenylpropynal)dicobalt pentacarbonyl(diphenyl(2-methoxyphenyl)phosphine) (0.08 g, 0.11 mmol) in CH_2Cl_2 (12 mL) was added $SnCl_4$ (a 1.0 M solution in CH_2Cl_2; 0.11 mL, 0.11 mmol) at -30 °C under N_2 and stirred for 1.5 h. Allyltributylstannane (0.04 mL, 0.12 mmol) was then added and the reaction was monitored by TLC to determine when the starting material had been completely consumed. Analysis of the product mixture using TLC (7:3 pentane:diethyl ether) revealed: **258** + **259** $R_f = 0.75$ (green spot); **246** + **247** $R_f = 0.53$ (red spot); **252** - **255** $R_f = 0.45$ (red spot); **260** $R_f = 0.40$ (UV active). The mixture was quenched by the addition of a cold aqueous $NaHCO_3$ solution at -30 °C. After the mixture had warmed to room temperature, the organic layer was separated, extracted with a saturated aqueous NaCl solution, concentrated under reduced pressure, and then separated by flash chromatography (7:3 pentane:diethyl ether) to yield the following:

1. (6-Phenyl-1-hexen-5-yn-4-ol)dicobalt pentacarbonyl (diphenyl(2-methoxyphenyl)-phosphine), diastereomeric mixture, 252 – 255:

The diastereomers that are shown in **Figure 3 - 33** have been arbitrarily assigned compound numbers **252 - 255**, however, it has not been established yet whether the major diastereomer (see below) corresponds to structures **252** + **253** or structures **254** + **255**. Using entry 4 of **Table 3 - 10** as an example, the diastereomer ratio 17:83 corresponds to:

Minor diastereomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.19 (m, 19H), 5.83 (m, 1H), 5.13 (m, 2H), 4.23 (m, 1H), 3.53 (s, 3H), 2.77 (s, 1H), 2.23 (m, 2H);

Major diastereomer: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.19 (m, 19H), 5.72 (m, 1H), 4.97 (m, 2H), 3.79 (m, 1H), 3.42 (s, 3H), 2.17 (s, 1H), 2.08 (m, 2H);

Diastereomeric Mixture: ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 205.3, 201.5 (CO), 134.0, 133.9 (CH=), 139.5 - 126.2 (C_6H_5), 120.9, 120.6 (=CH_2), 96.6, 94.1, 86.6, 83.5 (C≡C), 70.5, 70.2 (CHOH), 54.6, 54.2 (OCH_3), 44.1, 43.4 (CH_2); IR (neat) 3450, 3064, 2060, 2007, 1982, 1963, 1619, 1476, 1434, 1093, 1018, 756, 696 cm^{-1}; MS (-ve ES, m/z) 757.0 (63) $[M + {}^{35}Cl]^-$, 759.0 (26) $[M + {}^{37}Cl]^-$.

2. ((E)-3,5-Hexadien-1-ynylbenzene)dicobalt pentacarbonyl (diphenyl(2-methoxyphenyl)-phosphine), 258 + 259:

^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.16 (m, 19H), 6.20 (m, 3H), 5.13 (m, 2H), 3.39 (s, 3H).

After decomplexation of the compound using $(NH)_4Ce(NO_3)_6$, structural confirmation was obtained by comparison of the compound's ^{1}H NMR spectrum with that of (*E*)-3,5-hexadien-1-ynylbenzene.

*3. 6-Phenyl-1-hexen-5-yn-4-ol, **260**:*

A comparison of the ^{1}H NMR spectrum confirmed the structure.

EXPERIMENTAL QUANTITIES:

Table 3 - 10. Quantities of all products obtained and the corresponding diastereomeric ratio of **252** - **255** from the addition of 1 molar equivalent of allyltributylstannane and 1 molar equivalent of $BF_3 \cdot OEt_2$ at -78 °C to compounds **246** and **247**.

Entry	**246** + **247** (mmol)	Products Obtained (mmol) **246** + **247**	**261**	**252** - **255**	**260**	**258** + **259**	Diast. Ratio[b]
4	0.172	0.070	0.10	0.041	0.058	0.036	17 : 83
5	0.522	0.076	0	0.229	0	0.389	51 : 49
6	0.094	0	0.002	0.007	0.014	0.095	95 : 5

[b] The diastereomeric ratio of **252** - **255** is given as X : Y where X and Y correspond to the compound having a chemical shift of C4-H, observed using ^{1}H NMR, at 4.23 and 3.79 ppm respectively.

Table 3 - 11. Quantities of all products obtained and the corresponding diastereomeric ratio of **252** - **255** from the addition of 1 molar equivalent of allyltributylstannane and 1 molar equivalent of Lewis Acid at -30 °C to compounds **246** and **247**.

Entry	**246** + **247** (mmol)	Products Obtained (mmol) **246** + **247**	**261**	**252** - **255**	**260**	**258** + **259**	Diast. Ratio[b]
13	0.143	0.016	0.027	0.089	0.033	0.043	13 : 87
14	0.119	0	0.010	0.032	0.042	0.061	35 : 65
15	0.047	0	0.004	0.023	0.020	0.044	48 : 52
16	0.172	0.070	0.10	0.041	0.058	0.036	17 : 83
17	0.522	0.076	0	0.229	0	0.389	51 : 49
18	0.094	0	0.002	0.007	0.014	0.095	95 : 5

[b] The diastereomeric ratio of **252** - **255** is given as X : Y where X and Y correspond to the compound having a chemical shift of C4-H, observed using ^{1}H NMR, at 4.23 and 3.79 ppm respectively.

Table 3 - 12. Quantities of all products obtained and the corresponding diastereomeric ratio of **252** - **255** from the addition of 1 molar equivalent of allyltributylstannane and 0.5 (or 1.0) molar equivalents of $SnCl_4$ at -30 °C to compounds **246** and **247**.

Entry	**246** + **247**	Products Obtained (mmol)					
	(mmol)	**246** + **247**	**261**	**252** - **255**	**260**	**258** + **259**	Diast. Ratio[b]
24	0.044	0.002	0.008	0.017	0.026	0.001	20 : 80
25	0.068	0.002	0.004	0.020	0.009	0.007	20 : 80
26	0.143	0.016	0.027	0.089	0.033	0.043	13 : 87
27	0.119	0	0.010	0.032	0.042	0.061	35 : 65
28	0.047	0	0.004	0.023	0.020	0.044	48 : 52

[b] The diastereomeric ratio of **252** - **255** is given as X : Y where X and Y correspond to the compound having a chemical shift of C4-H, observed using ^{1}H NMR, at 4.23 and 3.79 ppm respectively.

((E)-3,5-hexadien-1-ynylbenzene)dicobalt pentacarbonyl (triphenylphosphine), ***256*** *+* ***257****, via elimination from the dicobalt-complexed homoallylic alcohol:*

To a solution of (1-phenyl-5-hexen-1-yn-3-ol)dicobalt pentacarbonyl(triphenylphosphine) (0.05 g, 0.07 mmol) in CH_2Cl_2 (7 mL) was added $SnCl_4$ (a 1.0 M solution in CH_2Cl_2; 0.07 mL, 0.07 mmol) at -30 °C under N_2. The disappearance of the starting material was monitored using TLC, and when the reaction was deemed to be complete, the mixture was quenched by the addition of a cold aqueous $NaHCO_3$ solution at -30 °C. After the mixture had warmed to room temperature, the organic layer was separated, extracted with a saturated aqueous NaCl solution, concentrated under reduced pressure, and then the single product formed was purified by flash chromatography (8:2 pentane:diethyl ether) and determined by ^{1}H NMR to be the elimination products **256** + **257**.

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