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MECHANISTIC INVESTIGATIONS OF [1,4]-WITTIG REARRANGEMENTS OF α-ALKOXYSILANES

presented by

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Major Professor's Signature

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MECHANISTIC INVESTIGATIONS OF [1,4]-WITTIG REARRANGEMENTS OF α-ALKOXYSILANES

By

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ABSTRACT

MECHANISTIC INVESTIGATIONS OF
[1,4]-WITTIG REARRANGEMENTS OF α-ALKOXYSILANES
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The [1,4]-Wittig rearrangement pathway has remained a mechanism of many questions. Whether it is a one step concerted process or a stepwise radical-radical anion dissociation-recombination event and its synthetic capabilities are not fully explored.

This dissertation centers on the Wittig rearrangements of α-trimethylsilyl allyl ethers. Key to this study was optimizing the [1,4]-Wittig rearrangement over competing Wittig rearrangements. In the course of this study, we have demonstrated that by employing a suitable substrate, reaction conditions could be tuned to give excellent selectivity of the [1,4]- over the [1,2]-pathway. We have also shown that the [1,4]-Wittig rearrangement of α-alkoxysilanes could be made efficient in terms of yield.

In pursuing our goal in understanding the mechanism of [1,4]-Wittig rearrangement of α-alkoxysilanes, we showed that α deprotonation and bond reorganization were separate events by generating and trapping the intermediate carbanions prior to rearrangement. We also found that substitution at the migrating carbon erodes the [1,4]/[1,2] selectivity, from almost exclusive (>100:1) [1,4]-product for the reaction of unsubstituted substrate, to approximately 2:1 [1,4]/[1,2] when a substituent is present. Substitution at the terminal sp^2 carbon of the allyl moiety also impacts the [1,4]/[1,2] selectivity, albeit to a lower degree than substitution at the migrating carbon, from > 100:1 [1,4]/[1,2] in the absence of any substituent to

approximately 5:1 [1,4]/[1,2] when the terminal sp^2 carbon of the allyl moiety is substituted.

Among the interesting observations we made is the fact that stereochemistry of the Wittig substrate impacts the rearrangement. It was observed that for a pair of diastereomeric α-trimethylsilyl allyl ethers, the *syn* diastereomer undergoes the Wittig rearrangement readily, whereas the *anti* diastereomer reacts very sluggishly, requiring severe conditions. A base such as *n*-BuLi allows the reactive *syn*-isomer to be completely consumed with no significant transformation of the less-reactive *anti*-isomer, kinetic resolution of diastereomeric ethers is feasible.

With respect to the stereochemistry, we determined that both the [1,2] and the [1,4] pathways occurred predominantly with a retention of stereochemistry at the migrating carbon. That said, enantiomeric ratio observed for the [1,4]-Wittig was lower than for the [1,2]-Wittig. The [1,2]-pathway occurred with lower retention of configuration (83% ee retention/92% er retention) than those typically found in [1,2]-Wittig of allyl ethers (> 90%). On the other hand, the [1,4]-pathway occurred with 75% ee (88% er) retention. In addition, the [1,4]-Wittig for both *syn* and *anti* substrates occurred with similar levels of retention of configuration (75% and 74% respectively) whereas there was significant difference in the levels of retention obtained for the [1,2]-pathway (88% and 69% respectively). This result was viewed as evidence of different mechanisms for both pathways.

To my parents
Late Clement Chukwuneke Ndubuaku
And
Paulina Nwannediuru Ndubuaku

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LIST OF SYMBOLS AND ABBREVIATIONS

Ac	acetyl
acac	acetylacetonate
AIBN	2,2'-azobisisobutyronitrile
aq	aqueous
CI	chemical ionization
Cy	cyclohexyl
DCC	dicycloheylcarbodiimide
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
De	diastereomeric excess
DIAD	diisopropyl azodicarboxylate
DIBAL	disiobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DME	dimethoxylethane
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
EI	electric ionization
eq	equivalent
FAB	fast atom bombardment
h	hour
HMPA	hexamethyl phosphoramide
HRMS	high resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons reaction
KHMDS	potassium bis(trimethylsilyl)amide
LHMDS	lithium bis(trimethylsilyl)amide
mCPBA	m-chloroperbenzoic acid

Mes	2,4,6-trimethyl phenyl
Mesyl	methanesulfonyl
min	minute
mL	milliliter
mmol	millimole
MOM	methoxymethyl
MS	molecular sieves
NaHMDS	sodium bis(trimethylsilyl)amide
NBS	*N*-bromosuccinimide
NMP	N-methyl prolidinone
NOE	nuclear Overhauser effect
PMB	*p*-methoxybenzyl
Py	pyridine
RCM	ring closing metathesis
rt	room temperature
TBAF	tetrabutylammonium fluoride
TBS	*t*-butyldimethylsilyl
TCT	2,4,6-trichloro-[1,3,5]triazine
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TMS	trimethylsilyl
Tosyl	toluenesulfonyl
Tr	triphenylmethyl
TSA	*p*-toluenesulfonic acid

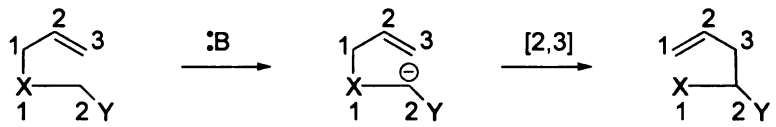
CHAPTER 1

INTRODUCTION

1.1. Background to study

Bond reorganizations of α-lithiated ethers to lithio alkoxides[2] were first described by Wittig and Löhmann in 1942. Termed Wittig rearrangements, these reactions have proven to be of importance in synthetic organic chemistry. Among these rearrangements the [2,3]-pathway (Scheme 1.1) has been most studied and has seen wide use as a tactic in organic synthesis.[3] In recent years, the [2,3]-Wittig rearrangement has been most often employed in the stereoselective formation of homoallylic alcohols from the corresponding α-metalated allyl ethers.[4]

Scheme 1.1. Representative [2,3]-Wittig rearrangement[3a]



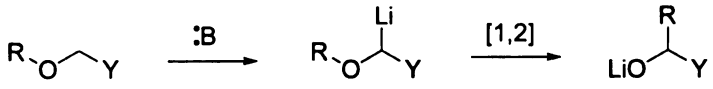
X = heteroatom, Y = anion stabilizing group

The utility of the [2,3]-Wittig rearrangement in synthetic organic chemistry arises from its ability to proceed with (a) regiospecific carbon-carbon bond formation and allylic transposition of the oxygen function, (b) stereospecific generation of olefins (c) the stereoselective creation of vicinal chiral centers, and (d) the transfer of chiralty.[3a]

The [1,2]-Wittig rearrangement, in contrast, has received less attention. Early studies on this isomerization pathway were mainly mechanistic in origin, with the synthetic utility of the [1,2]-Wittig rearrangement limited by the restricted range of

substrates and the tendency toward low product yields.[5] Over the past two decades, however, chemists have made the observation that this rearrangement proceeds with high diastereofacial selectivity.[6,7] This observation has drawn more attention to the [1,2]-Wittig rearrangement as a potential tool in forming *syn*-1,3-diol derivatives preferentially.[7]

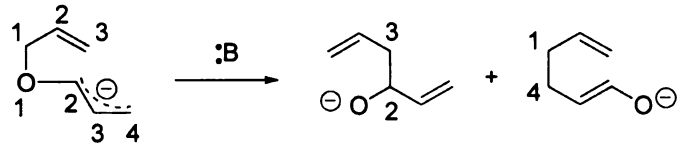
Scheme 1.2. Representative [1,2]-Wittig rearrngement[5a]



X = heteroatom, Y = anion stabilizing group

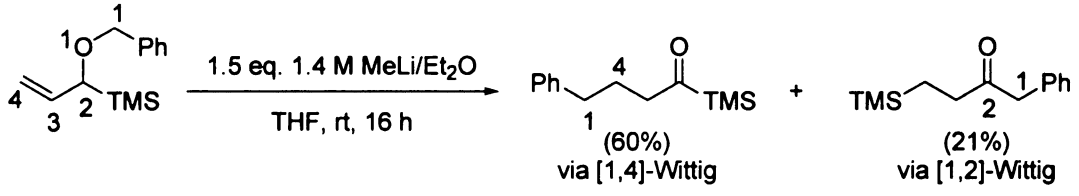
In addition to the [2,3] and [1,2]-Wittigs allylic ethers are capable of a [1,4]-rearrangement. Even relative to the [1,2]-Wittig rearrangement, the [1,4]-pathway remains a reaction of many questions. For example, whether the mechanism is concerted or involves radical-radical anion dissociation-recombination is still debated.[8] Some reports suggest the [1,4]-Wittig is likely to proceed via a stepwise mechanism similar to that of the [1,2]-rearrangement,[3] while other reports describe the [1,4]-rearrangement of allylic ethers as a symmetry allowed, concerted process.[3b,8] The substrate scope of the [1,4]-Wittig is also not well documented and thus its potential in synthetic organic chemistry is unclear.

Scheme 1.3. Representative [1,4]-Wittig rearrangement [3a]



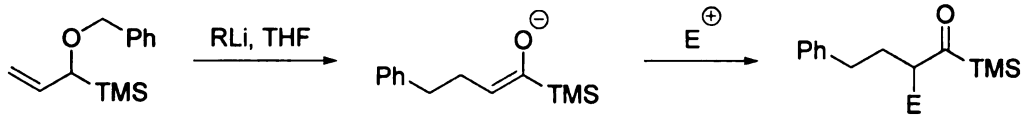
In the course of ongoing research on Wittig rearrangements in our laboratory, it was discovered[9] that an α-alkoxysilane rearranged via the [1,2]- and [1,4]-pathways, with a bias toward formation of the [1,4] derived acysilanes (Scheme 1.4). This was interesting essentially given the synthetic utility documented for acylsilanes[1] and the [1,2]-derived β-silyl ketones also .[10]

Scheme 1.4. Wittig rearrangement of α-alkoxysilane via the [1,2]- and [1,4]-pathways, with a bias toward the [1,4]: formation of acysilanes and β-silyl ketones



Since the [1,4]-Wittig proceeds via an enolate intermediate, the rearrangement could be followed by electrophilic trapping, affording access to diversely α-functionalized acylsilanes (Scheme 1.5). These features, if harnessed, could confer upon the α-alkoxysilanes and the [1,4]-Wittig rearrangement a high level of synthetic utility.

Scheme 1.5. [1,4]-Wittig rearrangement/electrophilic trapping



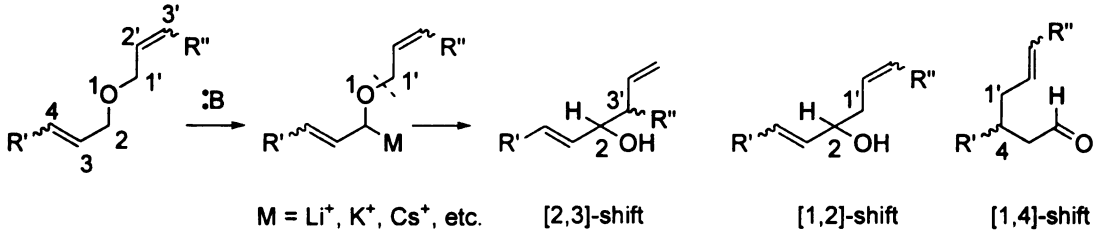
Given the mechanistic uncertainties surrounding the [1,4]-Wittig and the yet untapped synthetic potential of the [1,4]-Wittig, we decided to explore the [1,4]-Wittig rearrangement of α-alkoxysilanes further.

1.2. Relevant previous studies on Wittig rearrangements of ethers

Wittig rearrangements of allylic ethers are typically initiated by the formation of an α-metalated ether which undergoes a subsequent bond reorganization. Several pathways for this rearrangement exist but usually come in the form of a [2,3]-, [1,2]-, or [1,4]-shift. The process of bond reorganization involves the breaking of a C–O bond and formation of a C–C bond (Scheme 1.6).[3] The [2,3]-Wittig rearrangement has long been established as a concerted, thermally allowed sigmatropic reaction, following the Woodward-Hoffman rules.[3] As previously stated, the [1,2]-rearrangement is generally accepted to proceed in a stepwise manner, through a radical-radical anion dissociation-recombination process.[6] Again, less is known about [1,4]-rearrangement, and whether its mechanism is concerted[3] or involves a radical-radical anion dissociation-recombination.[8]

Irrespective of the pathway, [1,2], [2,3], or [1,4], Wittig rearrangements are generally preceded by formation of an α-metalated ether often through direct deprotonation at the ether's α-carbon. This process is usually facilitated by the presence of anion stabilizing groups such as carbonyls, nitriles, as well as vinyl, phenyl, or alkynyl moieties (Scheme 1.6).[2b,11]

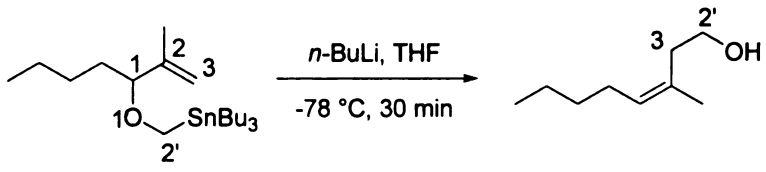
Scheme 1.6. Generation of α-metalated ethers by direct deprotonation at the α-carbon



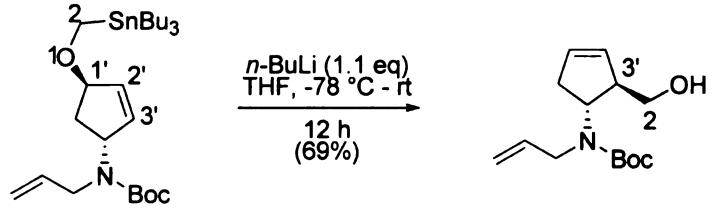
Generation of α-metalated ethers by direct deprotonation at the α-carbon requires the presence of a conjugated diene or an electron withdrawing group to stabilize α-anion.

A limitation to this direct deprotonation approach is that it is only applicable to those compounds possessing sufficiently acidic α-hydrogens. This restriction can be overcome by generating the α-alkoxy carbanion via tin-lithium exchange[4d] as shown by Still and Mitra in 1978 (Scheme 1.7).

Scheme 1.7. Wittig-Still rearrangement: initiation by Sn-Li exchange[4d]



Scheme 1.8. Application of the Wittig-Still rearrangement in the stereoselective synthesis of protected thymine polyoxin C[12f]

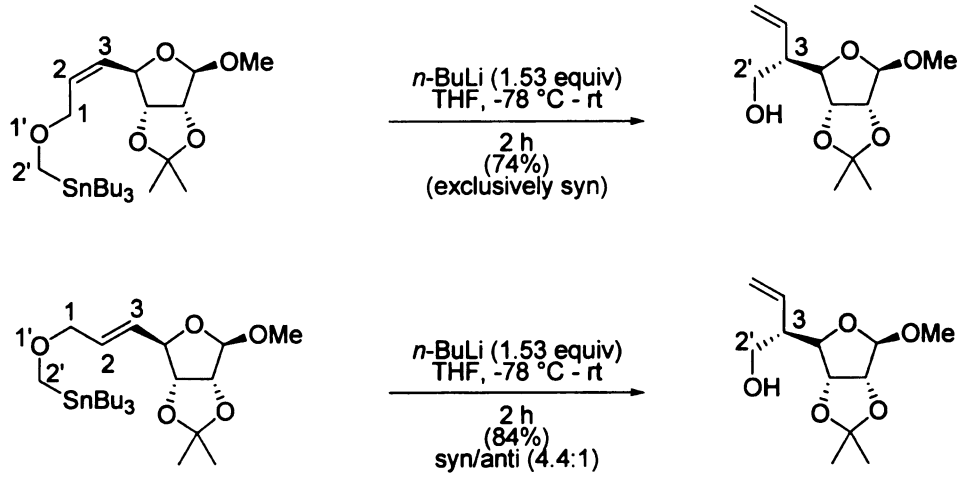


This Wittig-Still rearrangement has since attained the status of a useful synthetic tool,[12] and has enjoyed a number of impressive applications in the area of natural product synthesis.[13] For example, the Wittig-Still rearrangement was employed as a key transformation in the stereoselective synthesis of protected thymine polyoxin C[12f] (Scheme 1.8).

Another example of the application of the Wittig-Still rearrangement in synthetic organic chemistry is in the total synthesis of (+)-astrophylline by Schaudt and Blechert[12b]

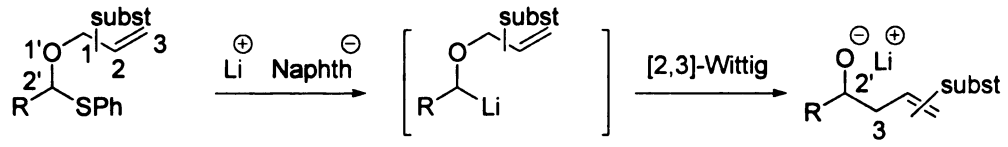
(Scheme 1.9). In this instance the authors employed this rearrangement as a critical transformation in the stereocontrolled generation of the 1,2-trans configuration of a key cyclopentene intermediate.

Scheme 1.9. Application of the Wittig-Still rearrangement in the total synthesis of (+)-astrophylline[12b]

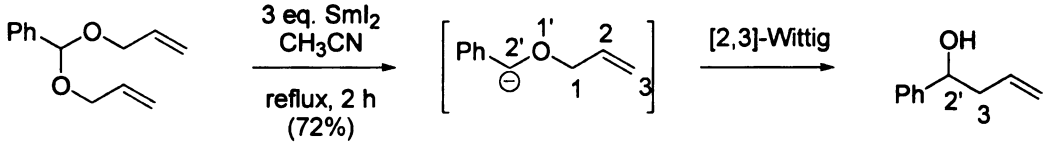


Despite its demonstrated potential, broad application of the Wittig-Still protocol has been governed by its call for use of relatively toxic organostannanes.[14] To get around this limitation, several research groups have sought "tin free" alternatives to the regioselective generation of α-ethereal carbanions. Successful solutions to this problem include the reductive cleavage of *O,S*-acetals with lithium naphthalenide (Scheme 1.10);[15] SmI_2 mediated[16] reduction of diallyl acetals (Scheme 1.11); and vinyl halides capable of 1,5-hydrogen transfer (Scheme 1.12).[17]

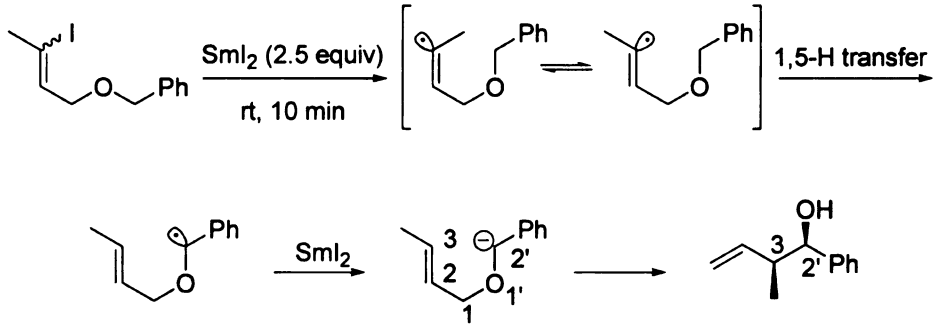
Scheme 1.10. Wittig rearrangement of O,S-acetals initiated by lithium naphthalenide



Scheme 1.11. Wittig rearrangement initiated by SmI_2 mediated reduction of diallyl acetals

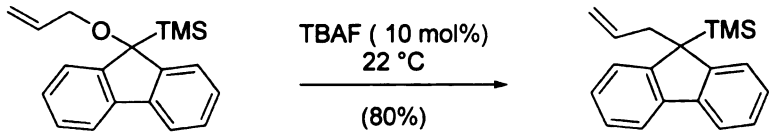


Scheme 1.12. Wittig rearrangement initiated by [1,5]-H transfer



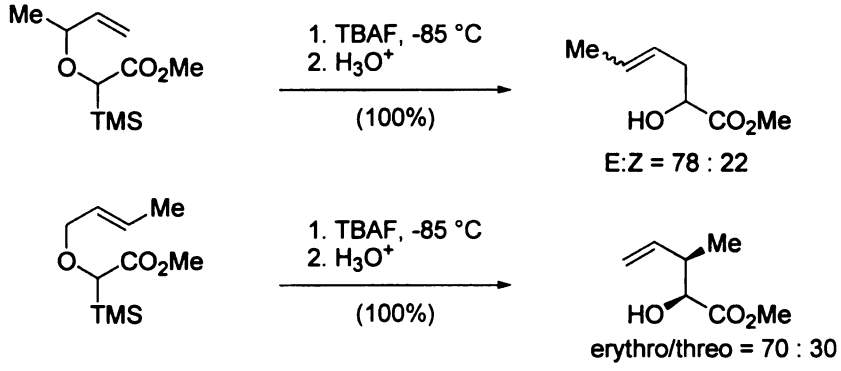
In the search for 'tin-free' alternatives to the regioselective generation of α-ethereal carbanions, the possibility of replacing tin with silicon had been considered.[18] However, this approach had received very limited consideration in the past. Reetz and Greif showed that the thermal rearrangement of fluorine derivatives could be facilitated by catalytic amounts (10 mol%) of tetrabutylammonium fluoride (TBAF) (Scheme 1.13).[18a]

Scheme1.13. Fluoride-promoted thermal rearrangement of α-alkoxysilanes by Reetz and Greif[18a]



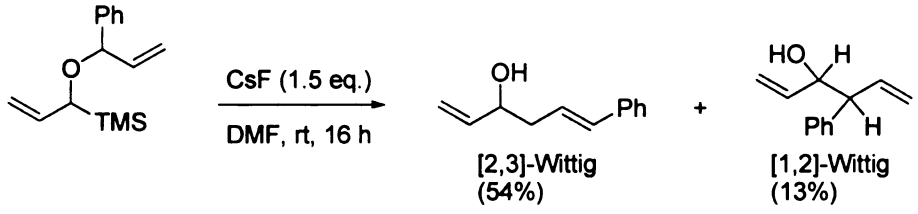
Nearly a decade following Reetz's report, Nakai reported that Wittig rearrangement in α-silylallyloxy esters could be initiated by the action of the fluoride ion (Scheme 1.14).[18b] Both Reetz's and Nakai's systems are activated (in addition to the α-silyl group, both contain groups capable of stabilizing an anion).

Scheme1.14. Fluoride-promoted Wittig rearrangements of α-alkoxysilanes prior to Maleczka's



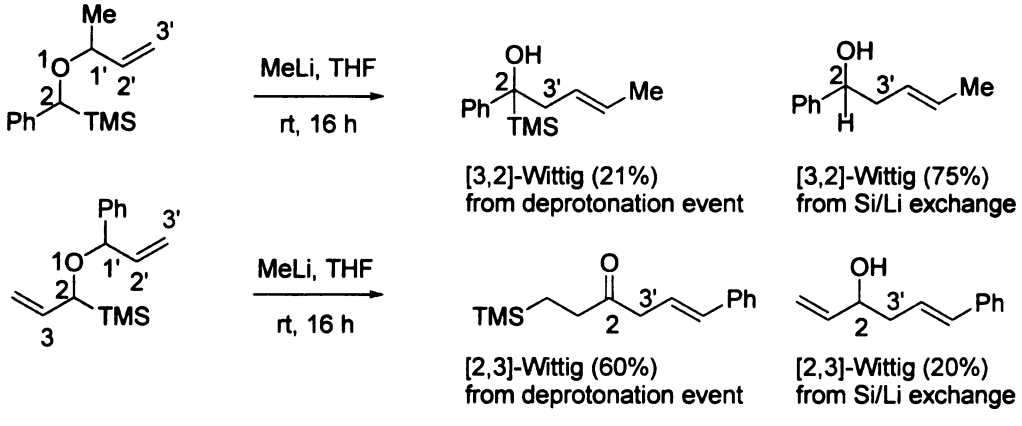
Several years later Maleczka and Geng[19] extended these studies and showed that the action of fluoride could trigger the desired rearrangements even in relatively unactivated substrates (Scheme 1.15).[6e,6f]

Scheme 1.15. Fluoride-promoted Wittig rearrangements of α-alkoxysilanes by Maleczka



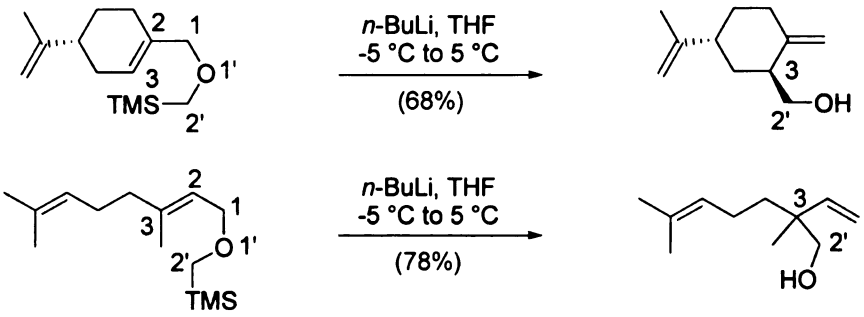
In addition to serving as a carbanion mask, the silyl moiety in α-alkoxysilanes can also function as an anion-stabilizing group.[20] Thus there are two Wittig rearrangement manifolds available to α-alkoxysilanes in the presence of lithium bases, with deprotonation (e.g. by alkyl lithium bases) and Si/Li exchange being plausible ways to initiate the Wittig rearrangements on this class of compounds. Indeed, Maleczka and Geng[9] reported the Wittig rearrangement of α-alkoxysilanes initiated by the direct metalation of the substrates as well as by Si/Li exchange (Scheme 1.16).

Scheme 1.16. Wittig rearrangement of α-alkoxysilanes initiated by Si-Li exchange and direct α-deprotonation manifolds

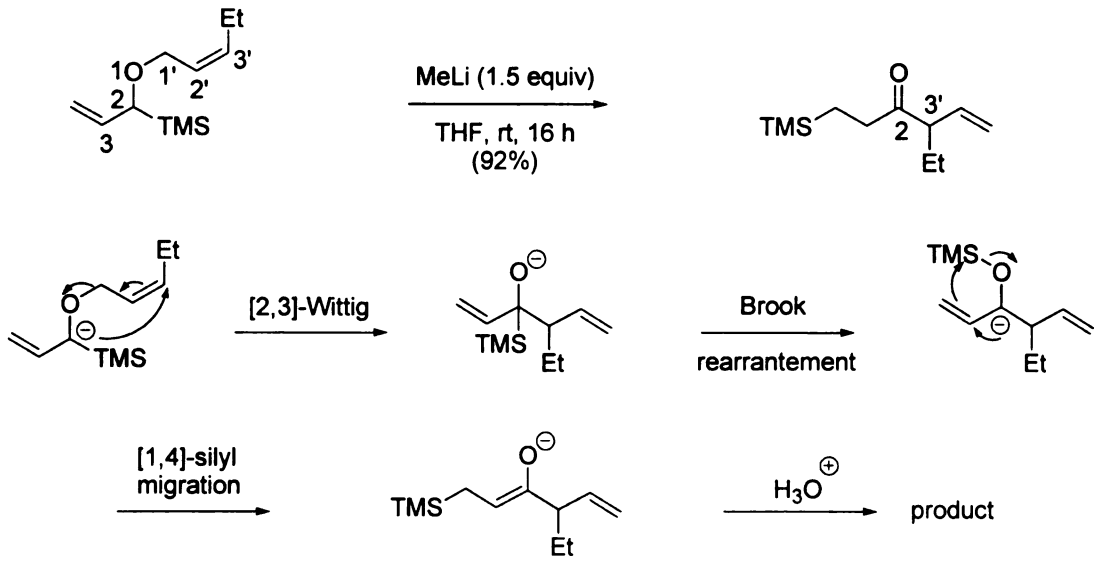


While the Si/Li exchange of α-alkoxytrimethylsilanes appears to be a straightforward alternative to the Wittig-Still rearrangement, this approach has received little attention, despite such exchange reactions being well precedented.[20b,c,d] Prior to the work by Maleczka and Geng,[9] only two examples (Scheme 1.17), both reported by Muzler and List,[20b] stood alone as the only [2,3]-Wittig rearrangements triggered by Si/Li substitution.

Scheme 1.17. Wittig rearrangement of α-alkoxysilanes initiated by Si-Li exchange prior to Maleczka and Geng



Scheme 1.18. Wittig rearrangement of α-alkoxysilanes initiated by direct deprotonation



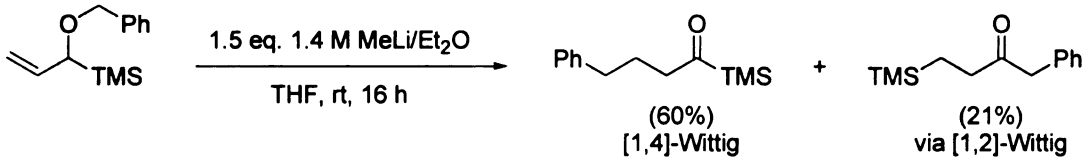
Similarly, prior to the work by Maleczka and Geng (Scheme 1.18),[9] few examples of initiating Wittig rearrangements of α-silyl ethers by direct deprotonation were reported.[21] This is surprising, in view of the fact that the deprotonation path would afford a unique access to the synthetically malleable silanes.[22] Despite the lack of precedent, Maleczka and Geng[9] showed that upon deprotonation by MeLi (Scheme 1.18), α-alkoxysilanes underwent Wittig rearrangement via [2,3]-pathway, which was then followed by Brook's rearrangement and subsequent [1,4]-silyl migration to furnish a β-silyl ketone(Scheme 1.18).

1.3. Previous synthetic studies on [1,4]-Wittig rearrangement

As already mentioned earlier in this dissertation, relative to the [1,2]-Wittig rearrangement, the [1,4]-rearrangement has received very little attention. The substrate scope of the [1,4]-Wittig is not yet well documented and thus its potential in synthetic organic chemistry is unclear.

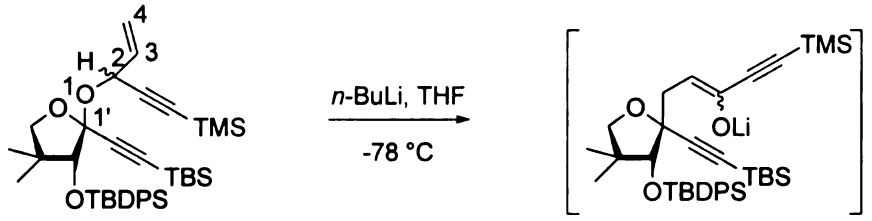
As just discussed, Maleczka and Geng[9] reported the Wittig rearrangement of an α-alkoxysilane, initiated by α-deprotonation (Scheme 1.4). The substrate rearranged via the [1,2]- and the [1,4]-pathways to furnish a β-silyl ketone and an acylsilane in 1:2 ratio in a combined 80% yield. To the best of our knowledge, this report represented the first efficient and selective [1,4]-Wittig rearrangement of α-alkoxysilanes.

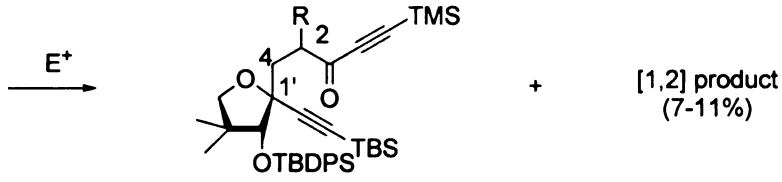
Scheme 1.4. Wittig rearrangement of an α-alkoxysilane



Subsequent to the reactions above, Wittig rearrangement of an α-metalated *O*-glycoside system was documented by Tomooka and co-workers.[23] The authors reported that treatment of a racemic 1-ethynylated propargyl acetal (both (*S*)-**42** and (*R*)-**42**, R'=H) with *n*-BuLi (3.0 equiv) in THF at -78 °C afforded the [1,2] product as the major product (78%) and only 17-19% of the [1,4] product (Scheme 1.19). However, the introduction of a *tert*-butyldimethylsilyl group to the ethynyl unit at the C1 position (R'=TBDPS) led to a reversal in product distribution, affording the [1,4]-rearrangement product as the major product (73% yield), and the [1,2]-rearrangement product as the minor product (7-11%). This report represents the most selective and efficient [1,4]-Wittig documented to date.

Scheme 1.19. [1,4]-Wittig rearrangement of
4-oxa-5-hexenyllithiums mediated by *t*-BuLi[23]



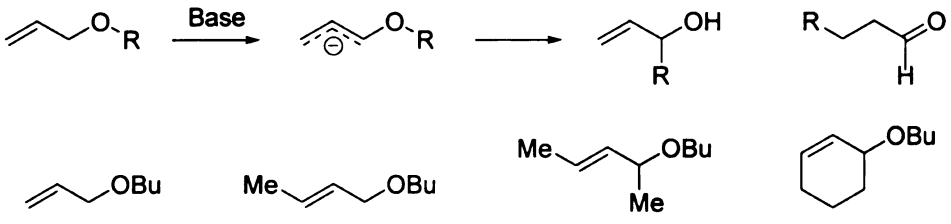


[1,4-product

$E^+ = H_3O^+$ β-ketone, R = H (73%)
E^+ = HCHO β-hydroxyketone, R = CH_2OH (60% d.r. at C2') (60%)

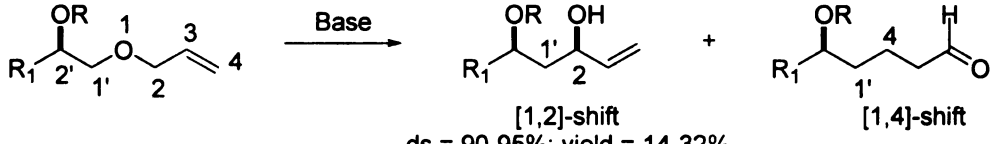
Prior to the studies by Maleczka[9] and Tomooka,[23] Felkin and Tambute[24] had explored the Wittig rearrangements of metalated allyl aryl and allyl alkyl ethers and found that on treatment with an excess (30%) of an equimolar mixture of propyllithium and *N,N,N,'N'*-tetramethylethylenediamine (TMEDA) in pentane (or THF in place of TMEDA), a series of ethers afforded aldehydes and ketones (via [1,4] rearrangement), and 1-alken-3-ol (via [1,2] rearrangement) (Scheme 1.20). The yields, however, did not exceed 30% for either component. The authors observed that the yields of the [1,4] products were insensitive to the substitution pattern in the allylic moiety of the ethers.

Scheme 1.20. Wittig rearrangement of allyl ethers by Felkin and Tambute[23]



Similarly, α-alkoxyalkyl allyl ethers have been shown to rearrange via the [1,2] and [1,4] pathways[7a] to afford secondary allyl alcohols (via the [1,2]-Wittig) and aldehydes (via the [1,4]-Wittig) respectively (Scheme 1.21). The *syn* [1,2] products were obtained in 14-32% yield with 90-95% diastereoselectivity. The [1,4]-product was found to predominate at low temperature, whereas at 0 °C the [1,2]-product was favored but the absolute yield remained the same. The authors noted however, that the extent of formation of the [1,4]-Wittig product was markedly dependent on reaction temperature and solvent polarity.

Scheme 1.21. Wittig rearrangement of α-alkoxyalkyl allyl ethers



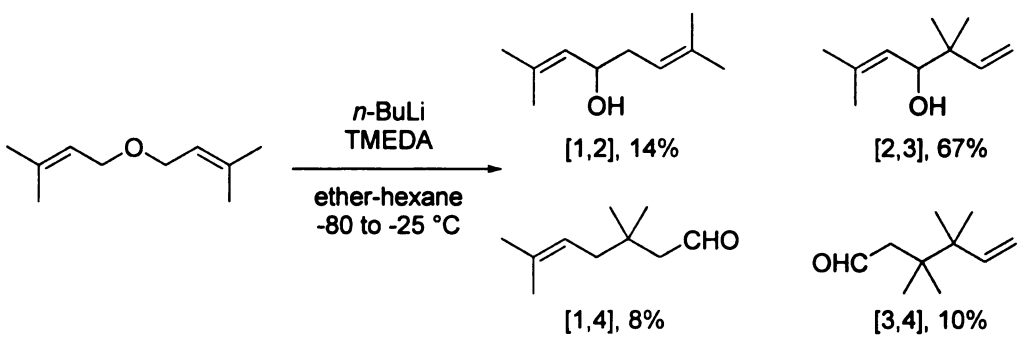
1.4. Previous mechanistic studies on [1,4]-Wittig rearrangement

As mentioned in the introductory part of this Chapter, whether the [1,4]-Wittig involves a one-step concerted process or a two-step radical-radical anion dissociation-

recombination event, or both remains an open question. Indeed, there have been reports in support of either mechanism and for both mechanisms being operative, depending on the substrate.

Some α-metalated ether systems are capable of undergoing rearrangement via all four Wittig pathways viz [2,3]-, [1,2]-, [3,4]-, or [1,4]-shift. However, in general such systems (e.g. bis(allyl) and allyl 2-alkynyl ethers)[3] find the 2,3-mode of rearrangement is electronically[25] and geometrically,[26] favorable, and thus predominant over the 1,2-mode[26b] with the 1,4-[26a] and the 3,4-paths[26b] becoming competitive only in exceptional cases. This trend is illustrated by bis-γ,γ-(dimethyl)allyl ether (Scheme 1.22), which rearranges by all four pathways.[26b,27]

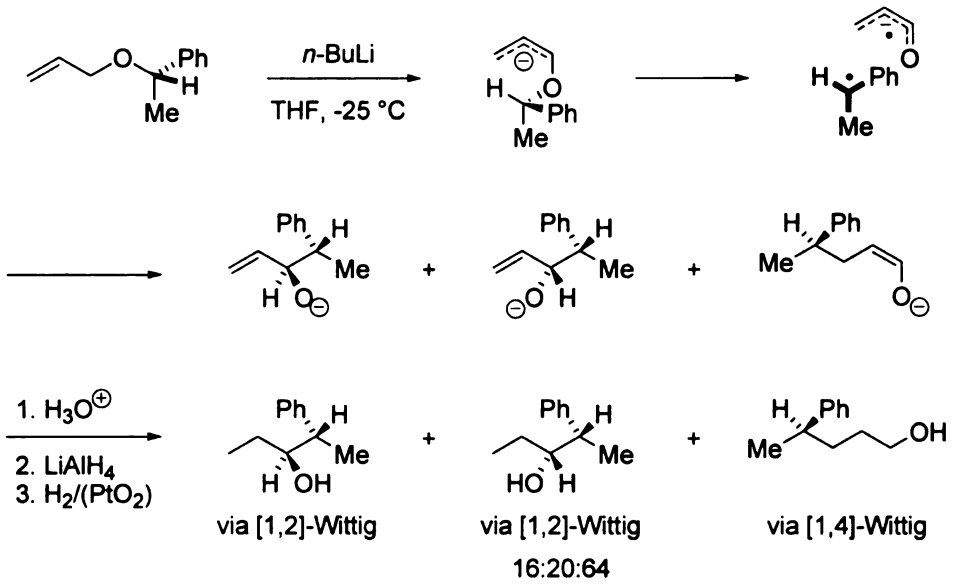
Scheme 1.22. Wittig rearrangement of bis-γ,γ-(dimethyl)allyl ether[3]



Felkin published the results of his mechanistic studies on the [1,4]-Wittig rearrangement in 1977,[8d] in which he showed that, on treatment with excess butyl lithium in THF at -25 °C, optically active allyl α-phenylethyl ether underwent rearrangement to afford a mixture of anionic products via [1,2]- and [1,4]-rearrangements. Saturation of these products afforded a mixture of [1,2] and [1,4] derived isomers in 60% overall yield with a ratio of 16:20:64 in favor of the [1,4]-Wittig (Scheme 1.23). The authors observed

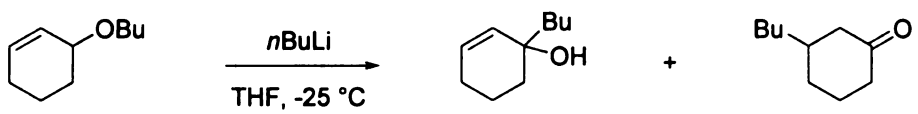
that all three rearrangement products favored retention of configuration with a similar extent of racemization (30±5%) observed for all products. This was said to suggest that reactions leading to both [1,2] and [1,4] products occurred via a non-concerted radical-radical anion cleavage-recombination mechanism.

Scheme 1.23. Wittig rearrangement of allyl α-phenylethyl[8d]



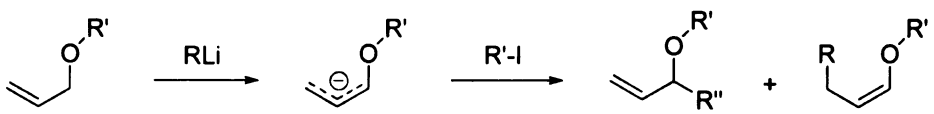
Further support for this conclusion was derived from observations made during the rearrangement of a cyclic allylic ether (Scheme 1.24). Despite its inability to adopt the cisoid conformation necessary for a concerted [1,4] alkyl shift, the compound afforded appreciable amounts of the [1,4] rearrangement product.[8d]

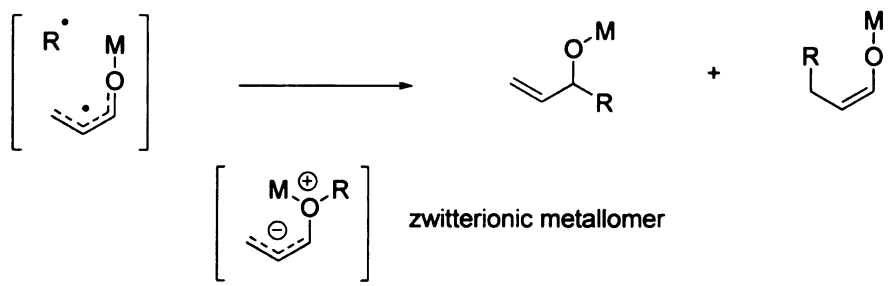
Scheme 1.24. Wittig rearrangement of cyclic allylic ether[8d]



In 1989, Schlosser and Strunk[28] reported that the rearrangement of metalated allyl alkyl ethers in the presence of potassium *tert*-butoxide, involves preferential migration of primary alkyl groups to the unsubstituted allylic terminus (γ-position), accompanied by alkyl migration to the α-position adjacent to the oxygen atom. This resulted in the formation of [1,4] and [1,2] products in an approximate ratio of 9:1 (Scheme 1.25). They obtained enolates [M=Si(CH_3)$_3$] with high (~90%) regioisomeric purity only when a resonance inactive primary alkyl group (such as butyl, 3-methylbutyl, or nonyl) was allowed to migrate. The migration of secondary or tertiary alkyl groups (1-ethylpropyl, *tert*-butyl) or even the cyclopropylmethyl moiety led to 2:3 or 1:1 mixtures of 1-alken-3-olates and enolates.

Scheme 1.25. Previous studies by Schlosser and Strunk[28]





Based on these data, they proposed a solvent caged 1-(alkoxy)-allyl radical/alkyl radical pair as a major transient species in the Wittig rearrangement of the allyl alkyl ethers (Scheme 1.25). They further proposed that this pair might be preceded by the

zwitterionic metallomer, an *O*-lithio(oxonia)-propenide, which could either collapse to the radical pair or, in borderline cases, directly isomerize to provide the rearrangement products.

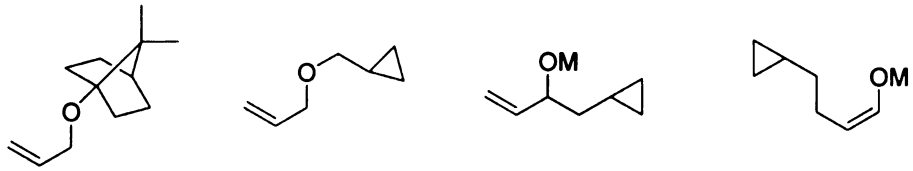


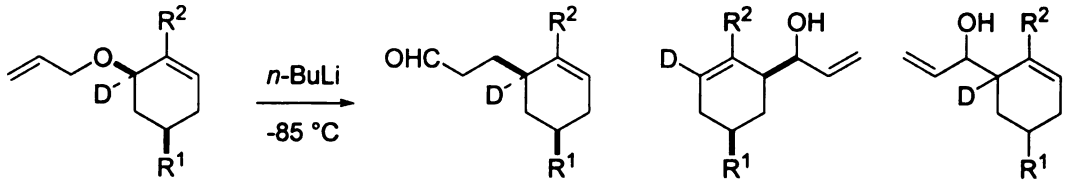
Figure 1.1. Substrates studied by Schlosser and Strunk[28]

The authors pointed out that a concerted process would imply the nucleophilic displacement of the migrating group from the alkoxy moiety, a process that would result in its transfer to the α- or γ-allylic carbon atom without its bonding electrons and with retention of configuration. They argued this would be disfavored and provided the rational why the lithiated allyl 1-(7,7-dimethyl)bicyclo[2.2.1]heptyl ether (allyl 1-apocamphyl ether) (Figure 1.1) was unable to undergo Wittig rearrangement. Additional evidence for the radical-radical anion dissociation-recombination mechanism came from "radical clock" experiments, namely the isomerization of the cyclopropylmethyl allyl ether radical to a 3-butenyl ("homoallyl") radical. In these experiments the exclusive formation of cyclopropane derivatives (isolated as the *O*-silyl ethers, M=Si$(CH_3)_3$) (Figure 1.1) supported the radical mechanism.

In contrast to the above reports in support of the radical-radical anion dissociation-recombination mechanism for the [1,4]-Wittig rearrangement of ethers, Nakai has reported that this reaction pathway is likely to be a one-step, symmetry-

allowed, concerted process.[29] In his investigation of the stereochemistry of the sigmatropic rearrangement of stereodefined *cis*-allyl cyclohexenyl ethers (*n*-BuLi, THF, -85 °C), he obtained a stereoisomeric mixture of secondary alcohols (via [2,3]- and [1,2]-alkyl shifts) in 62% isolated yield along with 14% of a *syn*-aldehyde (Scheme 1.26). The aldehyde is the result of [1,4]-rearrangement of the substrate ether, a process that occurred with retention of stereochemistry as required by orbital symmetry considerations. Based on the data from their stereochemical studies, the regio- and stereochemical outcomes of the [1,4]-shift are exactly the same as those of a tandem [2,3]-Wittig-oxy-Cope sequence of the same substrate. The authors also showed that the proportion of the [1,4]-product varies with the type of substituent, increasing with complexity of the substituent (Scheme 1.26).

Scheme 1.26. Wittig rearrangement of stereochemically defined allyl cyclohexenyl ether by Nakai[29]

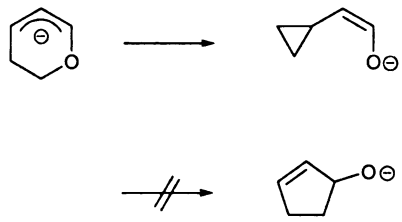


R^1	R^2	[1,4]/[2,3]/[1,2]
H	H	12 : 24 : 64
CH_3	H	18 : 54 : 28
$C(CH_3)=CH_2$	CH_3	48 : 6 : 46

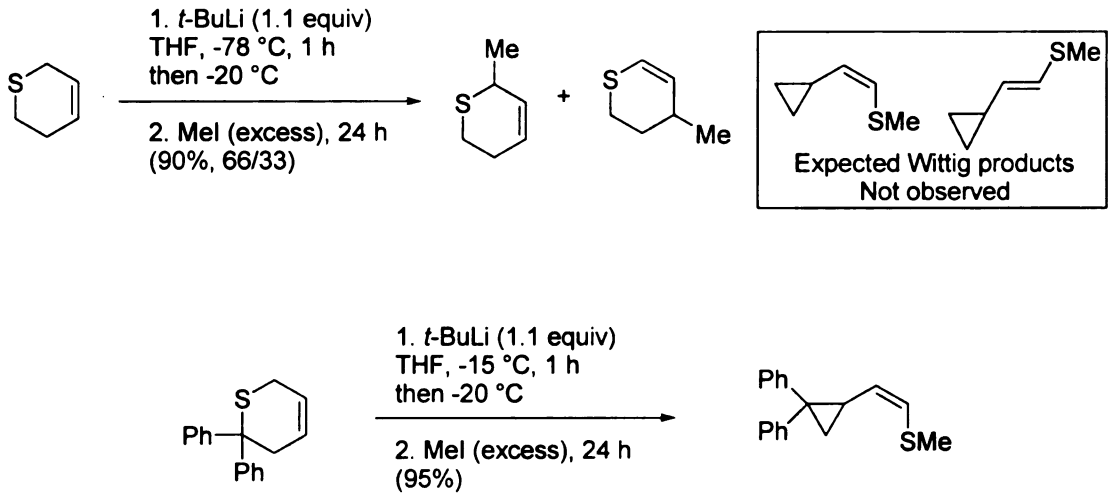
Despite these earlier studies, the case for either a radical-radical anion dissociation-recombination or a concerted process cannot always be made. Indeed an admixture of pathways may operate depending on the substrate. The rearrangement of a

dihydropyranyl anion was reported to occur via [1,4]-pathway to give exclusively the (*Z*)-cyclopropyl enolate (Scheme 1.27).[30] The [1,4]-pathway for this substrate would require that the dihydropyranyl anion adopt a cis orientation to ensure that the two interacting ends are in close proximity for a concerted process. This requirement is fulfilled as the ring structure enforces a cis orientation of the allylic anion. The complete absence of cyclopentenyl ring ([1,2]-product) was taken as evidence for a concerted pathway. On the other hand, the analogous thioether compound did not afford the expected rearranged product.[31] However, on placement of resonance-stabilizing groups at C5 of this substrate, it rearranged to afford the expected product. The fact that resonance-stabilizing groups facilitated the bond reorganization suggested a stepwise mechanism (Scheme 1.28).

Scheme 1.27. Wittig rearrangement of dihydropyranyl anion via [1,4]-Wittig pathway[30]

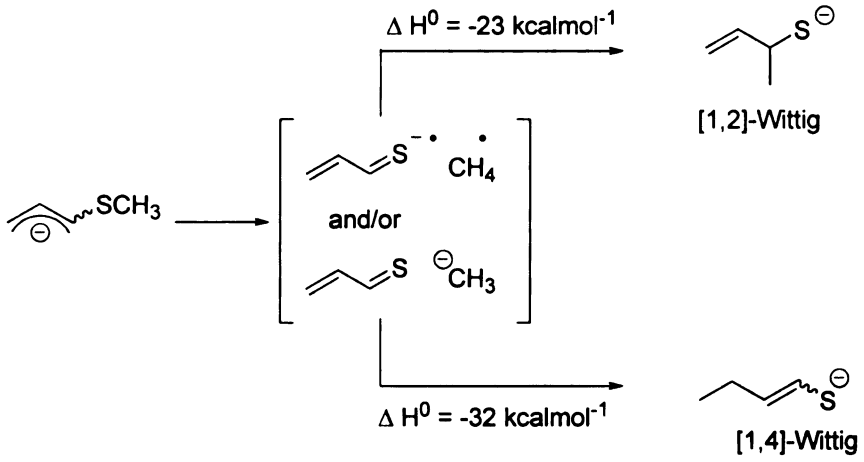


Scheme 1.28. Wittig rearrangement of carbanions from 4-thiacyclohexenyl systems[31]



Kass and cowokers[32] tried to provide a rationale for the mechanistic contradictions and inconsistencies regarding these Wittig rearrangement pathways. They carried out an extensive gas-phase study on the thio-Wittig rearrangement of deprotonated allyl methyl sulfide, and found that 1-thiomethylallyl anion predominantly isomerizes to 1-butenyl thiolate, a [1,4]-Wittig product. In contrast methyl deprotonation in the gas phase leads to 3-butene-1-thiolate, a [2,3]-Wittig product. These authors found that both [1,2] and [1,4] pathways have similar energy requirements, and are thermodynamically accessible to allyl methyl sulfide on the basis of calculations at a high level of theory (QCISD(T)/6-331++G(d,p)/HF/6-31+G(d)). However, by these calculations, the [1,4] rearrangement is favored by 9 kcal mol^{-1} (Scheme 1.29). They also explained that the observed selectivity for [1,2] and [1,4] could be most easily accommodated by a concerted process, but that the stepwise radical mechanism could also be operative.

Scheme 1.29. Gas-phase Wittig-rearrangement of allyl methyl sulfide by Kass[32]



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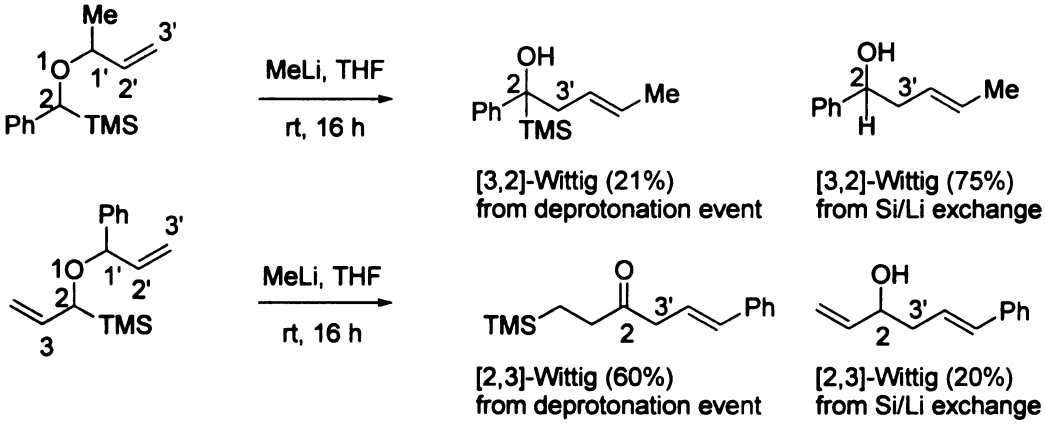
CHAPTER 2

OPTIMIZATION OF [1,4]-WITTIG REARRANGEMENT OF MODEL SUBSTRATE

2.1. Introduction

In the course of their study on the MeLi-promoted Wittig rearrangements of α-alkoxysilanes, Maleczka and Geng[1] found that the Wittig rearrangements of α-alkoxybenzysilanes were initiated by both direct metalation and Si/Li exchange (Scheme 1.16). For example, the rearrangement of compound **1** afforded product **3** arising from Si/Li exchange was obtained in 75% yield while the yield for compound **2** resulting from initiation by α-deprotonation was 21%. They further observed that on moving from α-alkoxylbenzylsilanes to α-alkoxylallylsilanes, the extent of Si/Li exchange was significantly diminished. This is clearly demonstrated in the second reaction of Scheme 1.16 (rearrangement of **4**). Si/Li exchange afforded **6**, accounting for 20% of the product mixture and α-deprotonation gave 60% of the corresponding β-silyl ketone product **5**.

Scheme 1.16. Wittig rearrangement of α-alkoxysilanes initiated by Si-Li exchange and direct α-deprotonation manifolds



In addition, the Wittig rearrangements of two of their substrates were initiated exclusively by deprotonation (Scheme 1.4 and Scheme 1.18). One of these substrates, **10**, rearranged exclusively via the [2,3]-Wittig pathway to afford **11** (Scheme 1.18). The other substrate **7** rearranged via a mixture of both [1,4]- and [1,2]-Wittig pathways, with the [1,4]-product **8**[1,2] favored by a ratio of 3:1 (Scheme 1.4). Given the synthetic utility reported for both acylsilanes[3] and β-silyl ketones,[4] we decided to explore the Wittig rearrangement or this substrate further, focusing on optimizing the [1,4]-Wittig pathway.

The reaction of Scheme 1.4 formed the basis/starting point of this dissertation. At the start of our study we posed the following questions as a guide: (1) could the rearrangement be made to generally to favor the [1,4]- over the [1,2]-rearrangement? (2) Could the [1,4]-Wittig be made more efficient in terms of yield? (3) Could the synthetic utility of the [1,4]-Wittig rearrangement be expanded? (4) What is a plausible mechanism of this rearrangement? We believed that finding answers to the above questions would give insight into the mechanism and synthetic utility of the [1,4]-Wittig rearrangement of α-alkoxysilanes.

2.2. Yield Optimization

Introduction

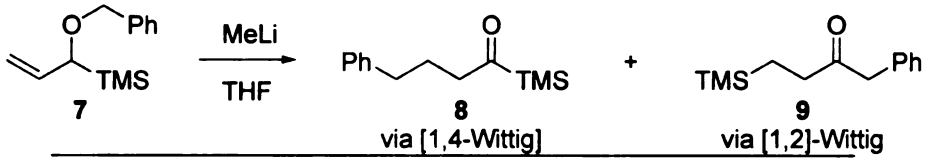
Our initial research focused on optimizing for the [1,4]-Wittig. On the basis of existing literature reports on the Wittig rearrangement of ethers[1,3,4] we reasoned that attempts at achieving selectivity of the Wittig rearrangement of α-alkoxysilanes would be aided by a good knowledge of how reaction variables such as base (type and concentration), reaction temperature, solvent[1] and substrate structure,[3] (sterics and

electronics) impact the reaction. Using model compound **7**, we systematically investigated the reaction under various base, temperature, and solvent conditions.

2.2.1. Wittig rearrangement of model substrate 7: Effect of temperature

Employing MeLi as base, the effect of temperature on the Wittig rearrangement of **7** was studied. On treatment with MeLi (1.5 eq), α-alkoxysilane **7** underwent a facile isomerization reaction via both [1,4]- and [1,2]-pathways to afford **8** and **9**. The results obtained (Table 2.1) showed that the rearrangement of **7**, mediated by MeLi, was mildly selective for the [1,4]-pathway and that the selectivity is highly temperature dependent.

Table 2.1. MeLi-mediated Wittig rearrangement reaction of **7**- Effect of temperature.



Entry	Base equiv	Temp (°C)	Time (h)	Yield (%)	[1,4]/[1,2]
1	1.5-2.0	18 to 20	1.0	69	1.4:1 to 2:1
2	3.0	-80 to -37	72	68	4:1
3	3.0	-80 to -50	72	68	>12:1
4	3.0	-80 to -50	120	66	>12:1
5	4.0	-80 to -37	65	68	4:1
6	4.0	-80 to -50	72	60	>12:1

Our findings can be summarized as follows: (1) the [1,2]-Wittig pathway was effectively suppressed when the reaction temperature was kept below (-60 °C). However,

at this temperature, the rate of conversion of the substrate to product was very slow and did not go to completion even after 72 h. (2) Complete consumption of the starting material took 65 to 72 hours with 3 to 4 equivalents of MeLi respectively, and required warming the reaction to -37 °C. Under these conditions the selectivity was 4:1 in favor of the [1,4]-Wittig product. (3) Use of less than 3 equivalents of base at temperatures below -60 °C resulted in less than 50% conversion of the substrate, and using more than 3 equivalents of MeLi did not give any additional advantage (compare entries 2 and 5, 3 and 6 of Table 2.1).

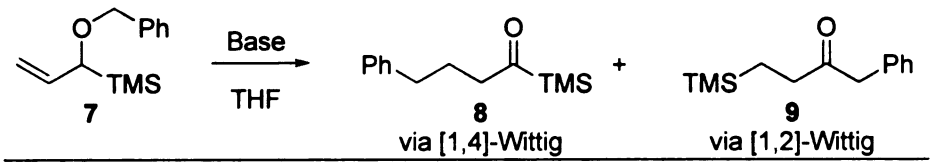
Employing 3 and 4 equivalents of MeLi at different temperatures -80 to -37 °C and -80 to -50 °C respectively for the same length of time resulted in [1,4]/[1,2] ratios of 4:1 (compare entries 2 and 3, 5 and 6 of Table 2.1), but the absolute yield of products remained the same. It is pertinent to mention that in these experiments, reproducibility of results was an issue. The outcome of the rearrangements varied with the rate of addition of the base. In summary, the rearrangement of compound **7**, mediated by MeLi, is selective for the [1,4]-pathway and the degree of this selectivity is highly temperature dependent.

2.2.2. Effect of base on the Wittig rearrangement of model substrate 7

With our initial temperature studies complete, we turned to the effect of base on the rearrangement of model substrate **7**. We tested different alkyllithium bases in the reaction. Our results are summarized in Table 2.2. *n*-BuLi, unlike MeLi afforded the [1,4]-product selectively at -78 °C (the [1,2]-product could not be detected by ^{1}HNMR). Adding *n*-BuLi at -78 °C and allowing the reaction to slowly warm up to -37 °C afforded

the [1,2] and [1,4]-Wittig products **8** and **9**. These compounds were obtained in a combined 83% yield and 9:1 ratio in favor of the [1,4] product. However, at room temperature, the [1,4]/[1,2] selectivity was not improved over MeLi, and the yields were comparable. Nevertheless, *n*-BuLi proved to superior to MeLi. With 1.5 eq. of *n*-BuLi, at -78 °C, reaction was complete in about 5 h, as compared to MeLi that gave an incomplete reaction even beyond 72 h (compare entries 7 and 8 of Table 2.2). *s*-BuLi was found to be superior to both *n*-BuLi and MeLi in initiating the Wittig rearrangements of α-alkoxysilanes (results are shown in Table 2.2). Upon treatment of a cold (-78 °C) THF solution of the substrate ether with 1.5 equiv of *sec*-BuLi (1.3M in cyclohexane), Wittig rearrangement was complete in 30 min to afford the [1,4]-rearrangement product exclusively and in good yield (79-82%). The presence of the [1,2]-Wittig product was not detected (by using TLC, NMR and GC-MS). From these experiments, our optimum conditions for the Wittig rearrangements of our model substrate **7** were treatment with 1.5 eq. of *s*-BuLi at -75 °C in THF solvent for 30 minutes, and quenching of reaction with NH_4Cl (sat. aq.). Table 2.2 also illustrates the effect of temperature on the Wittig rearrangement of our model substrate with all three bases. In general, [1,4]/[1,2] selectivity was greatest at lower temperature, with selectivity being eroded at warmer temperatures. To the best of our knowledge, this is the most selective and most efficient [1,4]-Wittig rearrangement of α-alkoxysilanes in particular, and allyl benzyl ethers in general, to be reported.

Table 2.2. Effect of base on the selectivity of Wittig rearrangement of **7**



Entry	Base	Base equiv	Temp (°C)	Time (h)	Yield (%)	[1,4]/[1,2]
1	MeLi	1.5-2.0	18 to 20	1.0	69	1.4:1 to 2:1
2	*n*-BuLi	1.5	18 to 20	1.0	68	2.45:1
3	*s*-BuLi	-	-	-	-	-
4	MeLi	3.0	-80 to -37	72	68	4:1
5	*n*-BuLi	1.5	-80 to -37	2	83	9.1:1
6	*s*-BuLi	1.5	-50 to -37	<0.1	79-83	>20:1
7	MeLi	3.0	-80 to -50	72	68	>12:1
8	*n*-BuLi	1.5	-80 to -75	<5	79-83	>100:1[a]
9	*s*-BuLi	1.5	-80 to -75	<0.5	79-83	>100:1[a]

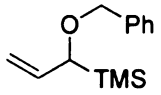
a No [1,2]-Wittig product could be detected by ^{1}H NMR

2.3. Conclusions

In summary, we have demonstrated that the [1,4]-Wittig rearrangement of simple, unsubstituted α-alkoxysilanes, representated by **7**, could be efficient in terms of yield, and that the selectivity of the rearrangement could be improved to favor the [1,4]- over the [1,2]-pathway. Furthermore, the differential selectivities we obtained in the Wittig rearrangement of model substrate **7** could be an indication that [1,4-] and [1,2]-rearrangements of α-alkoxysilanes probably have completely different mechanisms.

The [1,4]-Wittig of **7** results in the formation of an enolate imtermediate, which on protonation undergoes keto-enol tautomerism to afford the resultant acylsilane **8**. Instead of protonating the enolate, the reaction could be quenched with a variety of electrophiles, an event that would put the electophile either on the oxygen to give a vinyl ether derivative or on α carbon to afford α-functionalized acylsilane. Chapter 2 will discuss the electrophilic trapping of the intermediate enolate in the [1,4]-Wittig pathway.

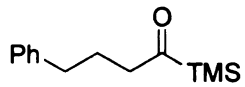
EXPERIMENTAL



7

Preparation of α-alkoxysilane 7: Trichloroacetimidate of benzyl alcohol (2.0 equiv, 4.85 g, 19.20 mmol) (prepared following literature procedure)[5] was added to a stirred solution of α-(trimethylsilyl)allyl alcohol (1.0 equiv, 1.32 g (10.13 mmol) in cyclohexane (0.2 M) at room temperature. A TMSOTf (0.055 equiv, 0.12 g, 0.55 mmol, 0.10 mL) solution in cyclohexane (0.1 mL/1.0 mL cyclohexane) was then added. White precipitate formed upon addition of the Lewis acid. The reaction mixture was stirred at room temperature overnight and filtered. The precipitate was then washed with pentane or hexane (precipitate is soluble in ether) and the filtrate diluted with ether. The diluted filtrate was subsequently washed with $NaHCO_3$ (sat. aq.) (x 2), 1N HCl (x 2), and lastly with brine (x 2). The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated to furnish the crude product. Note: the product was always accompanied by an ester by-product, which was removed by base hydrolysis (usually stirring with 2M NaOH at room temperature for about 2 h). Purification by column chromatography on silica gel (0-1% EtOAc in hexane gradient) afforded 56% of pure **7** as a colorless oil. [Geng Feng, Michigan State University, Ph.D. dissertation 2001]. IR (neat) 2959, 1454, 1383, 1248 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.24 (m, 5H), 5.89-5.77 (m, 1H), 5.12-5.04 (m, 2H), 4.71 (d, J = 12.4 Hz, 1H), 4.32 (d, J = 12.4 Hz, 1H), 3.64-3.60 (dt, J = 7.1, 1.4 Hz, 1H), 0.02 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 137.2, 128.1, 127.5,

127.1, 112.5, 75.9, 71.8, -3.8. **7** is a known compound and has spectral data in accord with the reported ones.[1a]



8

Wittig rearrangement reaction of 7- preparation of acylsilane 8. A solution of 76 mg (0.34 mmol) of silane **7** in 4.5 mL of THF was cooled to -78 °C under nitrogen. *s*-BuLi (1.3 M in cyclohexane, 0.4 mL, 0.52 mmol) was added dropwise via syringe. The reaction mixture was stirred for 30 min. at -78 °C, and then quenched with saturated aqueous NH_4Cl, diluted with diethyl ether, washed with water and brine. The organic phase was dried over $MgSO_4$ and concentrated. Silica gel chromatography (0 to 2% EtOAc in hexane gradient) afforded 63 mg (82%) of **8** as a light yellow oil. IR (neat) 2955, 1717, 1643, 1497, 1454, 1250 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.27-.14 (m, 5H), 2.62-2.59 (apparent t, J = 7.3, 6.8 Hz, 2H), 2.58-2.55 (apparent t, J = 7.8, 7.3 Hz, 2H), 1.87-1.81 (m, 2H), 0.16 (s, 9H). ^{13}C (125 MHz, $CDCl_3$) δ 248.1, 141.8, 128.4, 128.3, 125.8, 47.5, 35.2, 23.6, -3.2. **8** is a known compound and has spectral data in accord with the reported ones.[1,2]

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4. For a general review see Weber, W. P. In *Silicone Reagents for Organic Synthesis*; Springer-Verlag: New York, 1983. (a) Fleming,I.; Mandal, A. K. *Chem. Commun.* **1999**, 923-924. (b) Furin, G. G.; Vyazankina, O. A.; Gostevsky, B. A.; Vyazankin, N. S. *Tetrahedron* **1988**, *44*, 2675-2749. (c) Hsiao, C. N.; Shechter, H. *J. Org. Chem.* **1988**, *53*, 2688-2699, and referenced cited therein.

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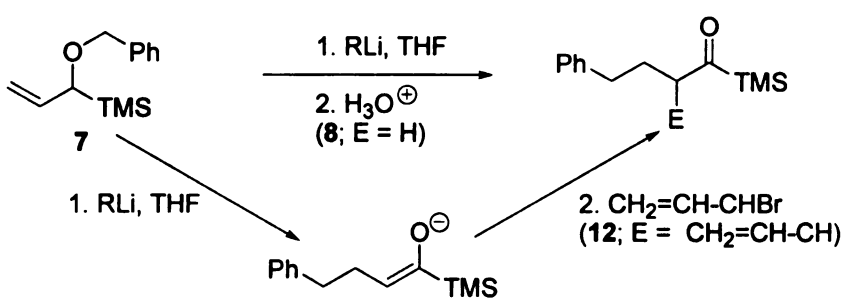
CHAPTER 3

PREPARATION OF ACYLSILANES: TRAPPING OF ENOLATE OF MODEL SUBSTRATE

3.1. Introduction

In Chapter 2 of this dissertation we showed that α-alkoxysilanes, typified by model compound **7**, undergo efficient and very selective [1,4]-Wittig rearrangement to afford affords acylsilanes via an enolate intermediate.[1] This discovery was made by Maleczka and Geng,[1] who, during the course of their study on the Wittig rearrangements of α-alkoxylsilanes, isolated an acylsilane [Scheme 3.1, E = H, **8**], from compound **7** that rearranged via both [1,4]- and [1,2]- pathways. This was the first time an acylsilane was prepared via a Wittig rearrangement of α-alkoxylsilanes. The intermediacy of an enolate offers an attractive access to a variety of novel acylsilanes by trapping the enolate with suitable electrophiles. This was first demonstrated by Maleczka and Geng when they generated and trapped the [1,4]-enolate with allyl bromide to obtain the α-allyl acylsilane in 15% yield (Scheme 3.1, E = allyl).

Scheme 3.1. Eletrophilic trapping of enolate of model compound **7**-formation of acylsilanes

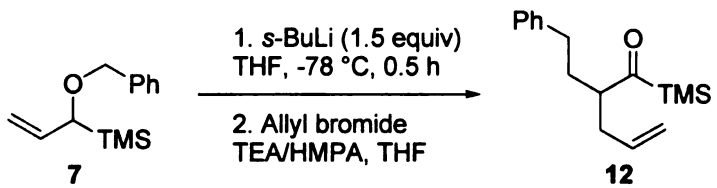


This discovery opened the door for a new route to these useful compounds, and we thus decided to develop viable and more efficient routes to the acylsilanes via the Wittig rearrangement reactions of α-alkoxylsilanes (Scheme 3.1). Having gained control of the Wittig rearrangements of our model compound, we then turned our attention on the prospects of introducing various substituents at the α-position of the carbonyl compounds resulting from the [1,4]-pathway

3.2. Electrophilic trapping of intermediate 7 enolate

We started enolate trapping studies by optimizing for the reaction illustrated in Scheme 3.1. After generating the enolate of **7** under our optimum conditions, it was transferred by canula into a THF solution of an appropriate electrophile. With allyl bromide as the electrophile, we observed that the mode of addition of the electrophile and the reaction temperature are two important factors that control the formation of as well as the yield of product (Table 3.1).

Table 3.1. Allylation of the enolate of compound **7**



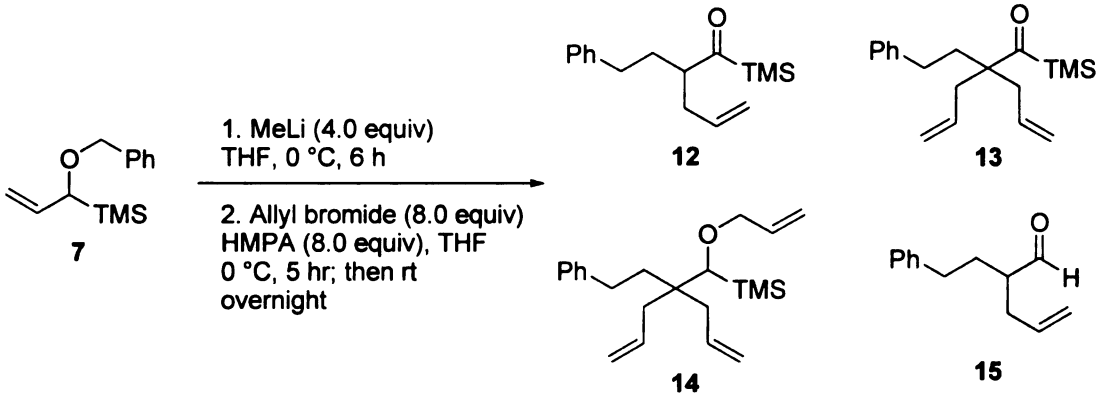
7 **12**

Entry	Allyl bromide (equiv)	TEA (equiv)	HMPA (equiv)	Temp (°C)	Time (h)	Yield (%)
1	6.0	6.0	3.0	-75 to rt	14	No product isolated
2	4.0	4.0	-	-75 to rt	6	55

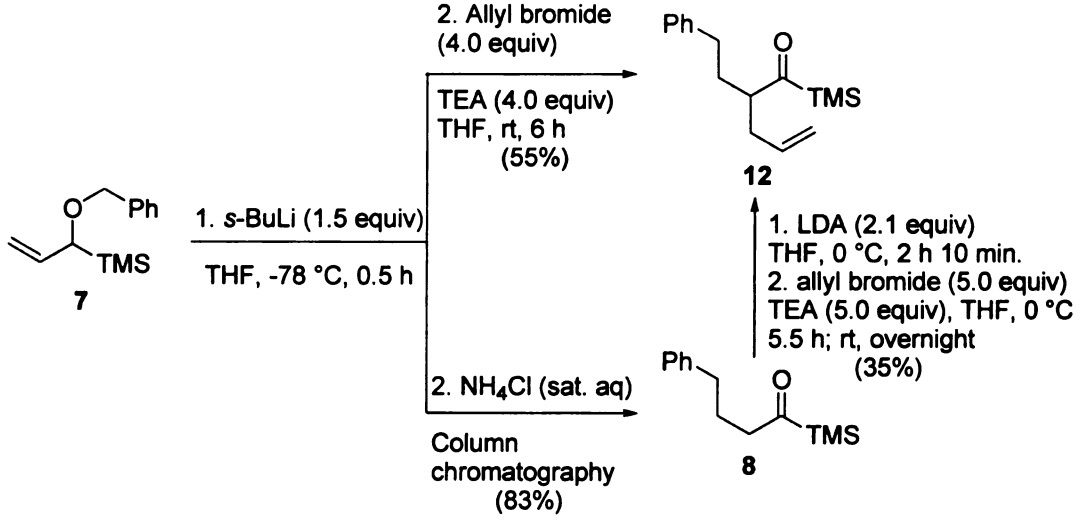
Addition of allyl bromide directly to the reaction mixture at 0 °C led to the recovery of the rearranged products, with little or no evidence of the expected allylated product. Use of TEA at room temperature proved advantageous, affording the desired product, **12**, in 55% yield (Table 3.1, entry 2), with just some detection of a second product, which, from ^{1}H-NMR and ^{13}C-NMR, was an aldehyde. Substituting HMPA for TEA under the prevailing reaction conditions resulted in the reverse result, the aldehyde being obtained as the major product and **12** obtained in only 14% yield. However, addition of the electrophile in the presence of HMPA at lower temperature (0 °C) resulted in both **12** and this aldehyde being obtained in 2:1 ratio,[2] accompanied by other by-products. Two of these by-products (tentative structures given as **12** and **14**) resulted from multiple allylations of the enolate and one (**15**) a monoallylation/desilylation compound (Scheme 3.2). These by-products could not be isolated and the NMR spectra of the product mixture were very complex. However, we were able to at least partially identify them by high resolution mass spectrometry[3] and the tentative structures in Scheme 3.2 suggested. As shown in Table 3.1, employing a 2:1 mixture of TEA and HMPA resulted in a messy reaction and no product was isolated (Table 3.1, entry 1).

A two-pot Wittig rearrangement/LDA deprotonation-allylation was carried out to compare to our one-pot process (Scheme 3.3). In this process, compound **7** was subjected to Wittig rearrangement and **8** isolated (83%). Acylsilane **8** was then deprotonated with LDA at low temperatures and the resulting enolate trapped with allylbromide. Our results indicate that the one-pot process is synthetically more efficient than the two-pot Wittig rearrangement/deprotonation-allylation route, both in terms of time and yield.

Scheme 3.2. Allylation of enolate of compound **7** in the presence of HMPA

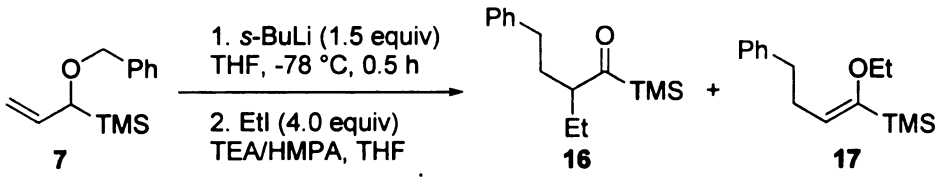


Scheme 3.3. One-pot vs. two-pot Wittig rearrangement/allylation of **7**



Ethylation was achieved by use of EtI and resulted in a mixture of *C*- and *O*-alkylated products (**16** and **17**) in a 3:1 ratio in favor of *C*-alkylation. Ethylation required the use of an additive, and HMPA proved to be superior to TEA in this case (Table 3.2).

Table 3.2. Ethylation of the enolate of **7**[a]



Entry	TEA (eq.)	HMPA (eq.)	Temp (°C)	Time (h)	Yield (%)
1	4.0	-	-75 to rt	3.75	48
2	-	4.0	-75 to rt	5	81

(a) Ratio of *C*-alkylation/*O*-alkylation was 3:1.

The methyl group was successfully installed at the α-carbon using MeI as the electrophile (Scheme 3.4). This reaction was optimized, and the results are shown in Table 3.3. Slow addition of the trapping mixture (MeI/TEA) to a cold (0 °C) solution of the enolate resulted in the formation of three carbonyl compounds, one silylated compound **18**, and two aldehydes **19** and **20**[4], respectively (Scheme 3.4). On the other hand, slow addition of a cold (-75 °C) THF-solution of the enolate to the trapping mixture (MeI (4.0 equiv.)/TEA (4.0 equiv.) in THF) at room temperature, and stirring for 50 min, afforded the desired α-methylated acylsilane as a single product in 72% yield (Table 3.3, entry 2). Trapping at low temperatures (-75 to -45 °C) required a longer reaction time (7 h) and led to diminished yield (59%) (Table 3.3, entry 1). The feasibility of this reaction in the absence of TEA was also investigated, and it was found that at room temperature, and in the absence of TEA, trapping of the enolate was feasible and rate comparable to that with TEA; however, the yield was significantly lower (56%) (Table 3.3, entry 3). It

is apparent from Table 3.6 that low temperatures and prolonged reaction time are unfavorable for this reaction, and that TEA was an essential additive.

Scheme 3.4. Methylation of enolate of **7**

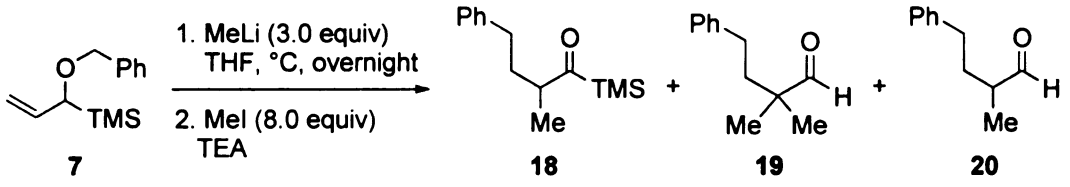
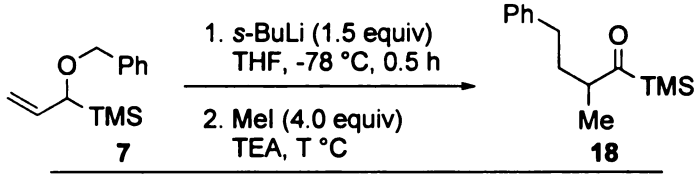


Table 3.3. Methylation of the enolate of **7**



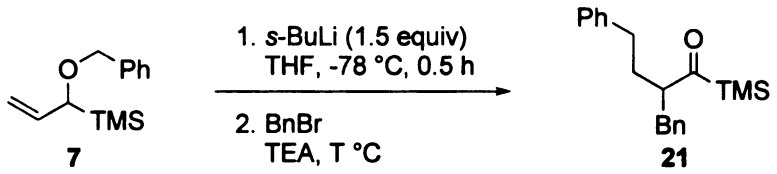
Entry	TEA (equiv)	Temp (°C)	Time (h)	Yield (%)
1	4.0	-75 to 20[a]	7	59
2	4.0	20	0.83	72
3	-	20	1	56

(a)After addition at -78 °C, reaction was allowed to warm to -45 °C first. When no reaction was observed (by GC-MS) after 1 h 25 min, it was then allowed to warm to room temperature.

Reaction of the enolate with benzyl bromide was also found to be temperature dependent. Whereas the α-benzylated product, **21**, was obtained in 66% yield in the presence of TEA at 20 °C ($PhCH_2Br$ (4.0 equiv.)/TEA (4.0 equiv.)) (Table 3.4, entry 2), carrying out the reaction at lower temperatures (-75 to -45 °C) resulted in an incomplete reaction even after 24 h, affording the product in only 36% yield (Table 3.4, entry 4). It was also determined that TEA is beneficial for this reaction, because, even though a 60%

yield of product was obtained in the absence of TEA (Table 3.4, compare entries 2 and 3), the reaction required 7 h to go to completion. TBAI also proved to be an effective additive, allowing a low temperature (-75 °C) trapping and affording the product in 59% yield. No *O*-alkylation was observed in these reactions. From the results in Table 3.4, HMPA is not a requirement in this reaction (Table 3.4, compare entries 1 and 2). The use of HMPA resulted in the formation of the desired product (in only 32% yield), accompanied by the formation of by-products (Table 3.4, entry 1).

Table 3.4. Benzylation of the enolate of **7**.



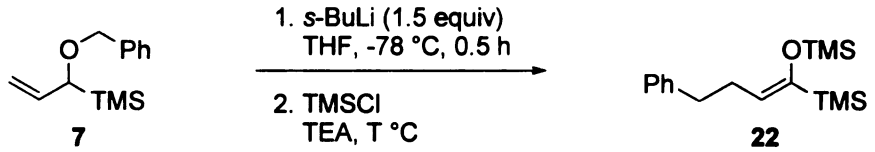
Entry	BnBr (eq.)	TEA (eq.)	Temp (°C)	Time (h)	Yield (%)
1[a]	6.0	6.0	0 to 20	4	32
2	4.0	4.0	20	1.5	66
3	4.0	-	20	7	60
4	4.0	4.0	-75 to 20	24	36[b,c]
5[d]	4.0	-	-78	3.5	59

(a) 3.0 eq. of HMPA was employed. (b) The crude reaction mixture contained the rearranged and trapped products in 1:2.8 ratio. (c) 22% of [1,4] product **8** was isolated. (d) 4.0 eq. of TBAI added.

The silyl derivative **22** was prepared by trapping the enolate intermediate with TMSCl. The trapping was investigated under various reaction conditions and the results obtained are given in Table 3.5. The reaction afforded the *O*-silylated product, which was

expected. No *C*-silylation was detected. The reaction was facile at low temperatures (-75 to -45 °C), being complete in 50 minutes, and affording the desired product **22** in 85% yield (Table 3.5, entry 4). It is also clear from the Table that TMSCl was a good enough electrophile, so as not to require the use of any additives.

Table 3.5. Silylation of the enolate of **7**.

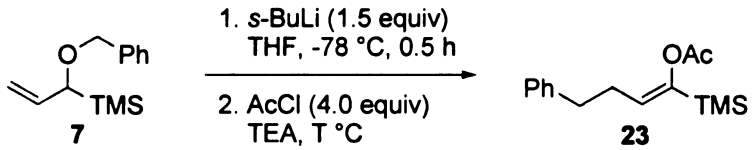


7 **22**

Entry	*s*-BuLi (equiv)	Time (h)	TMSCl (equiv)	TEA (equiv)	HMPA (equiv)	Temp (°C)	Time (h)	Yield (%)
1	3.0	4	6.0	6.0	3.0	-75 to -45	1	71
2	1.5	0.5	6.0	6.0	3.0	-75 to 20	0.83	48
3	1.5	0.5	4.0	4.0	-	20	0.67	54
4	1.5	0.5	4.0	4.0	-	-75 to -45	1.33	85

Acetylation of the enolate was accomplished with acetyl chloride (Table 3.6). The best conditions appeared to be addition of the cold (-75 °C) enolate solution to a solution of CH_3COCl in THF at room temperature for 1 h 20 min. Under these conditions, the ester **(23)** was obtained in 69% yield (Table 3.6, entry 2). Trapping at low temperature was detrimental, as was the use of TEA.

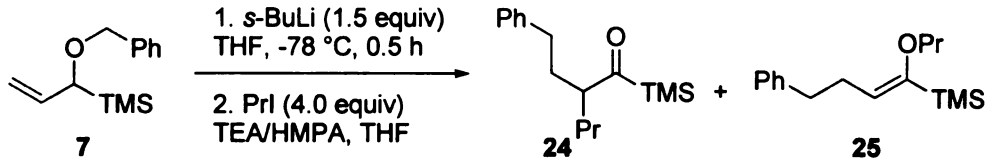
Table 3.6. Acetylation of the enolate of **7**



Entry	TEA (equiv)	Temp (°C)	Time (h)	Yield (%)
1	-	-75 to -45	24	59
2	-	20	1.33	69
3	4.0	20	5	50

The propyl derivatives **24** and **25** were prepared by trapping the enolate with *n*-propyl iodide and the results obtained are given in Table 3.7. *n*-Propyl iodide proved to be a poor electrophile, requiring the use of an additive. In this case reaction gave a 3:1 mixture of both *C*- (**24**) and *O*-alkylation (**25**) products. Use of TEA (4.0 eq) significantly shortened the reaction time (from 52 h without to 24 h with TEA), but did not give much yield enhancement (Table 3.7, entry1). However, HMPA gave better results in terms of reaction time and product yield (Table 3.7, entries 3 and 4).

Table 3.7. Trapping of the enolate of **7** with propyl iodide.

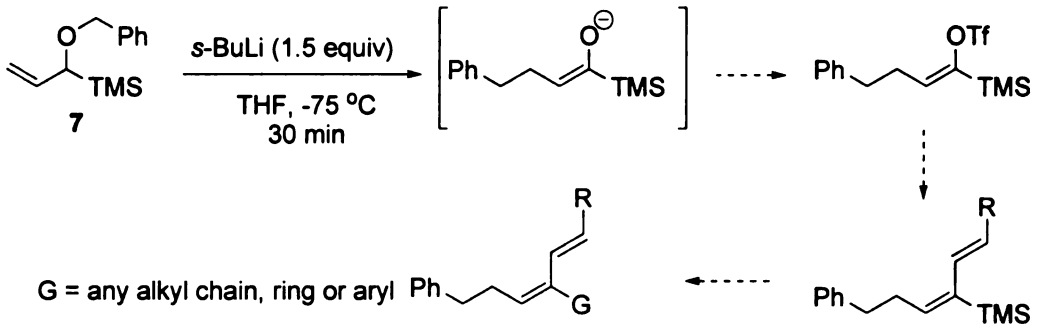


Entry	TEA (equiv)	HMPA (equiv)	Temp (°C)	Time (h)	Yield (%)	Ratio
1	4.0	-	20	24	39	3:1
2	-	-	20	52	32	2.6:1
4	-	4.0	20	17	66	3:1

Benzaldehyde was also investigated as an electrophile for the trapping of the enolate. Trapping was facile at low temperatures (-78 °C) and resulted in the formation of **29** in 68% yield. This reaction did not require the use of Lewis acid catalysts.[5]

Vinyl perfluoroalkanesulfonates, e.g. vinyl triflates and vinyl nonaflates are widely utilized in organic synthesis due to the high leaving-group ability of the perfluoroalkanesulfonyloxy group. These compounds have often been used in transition metal-catalyzed cross-coupling reactions.[6] We envisaged that trapping the enolate generated from the Wittig rearrangement of model compound **7** would lead to a vinyl perfluoroalkanesulfonate, which when coupled with a suitable partner would result in a vinyl silyl compound. This could be amenable to further transformations (Scheme 3.5).

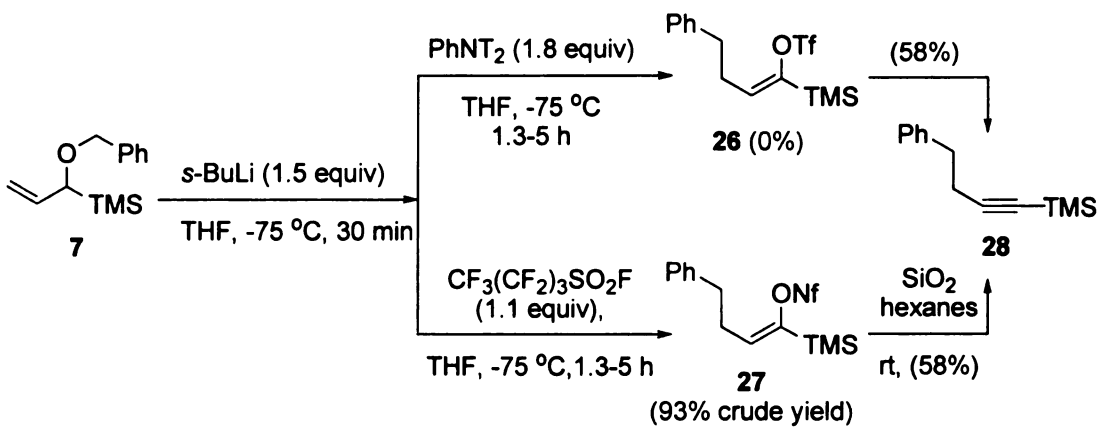
Scheme 3.5. Schematic of envisaged [1,4]-Wittig/electrophilic trapping/coupling reactions of model substrate **7**



Attempts were also made to prepare the triflate by quenching a cold (-75 °C) solution of the enolate with a variety of triflating agents. With triflic anhydride, only the [1,4]-rearranged product **8** was isolated, with no evidence of the expected vinyl triflate. The use of $PhNTf_2$ did not allow for the isolation of the vinyl triflate **26**, but gave trimethyl-(4-phenyl-but-1-ynyl)-silane, **28** (Scheme 3.6). The formation of **28** is envisaged to result from the expected vinyl triflate, which very likely underwent

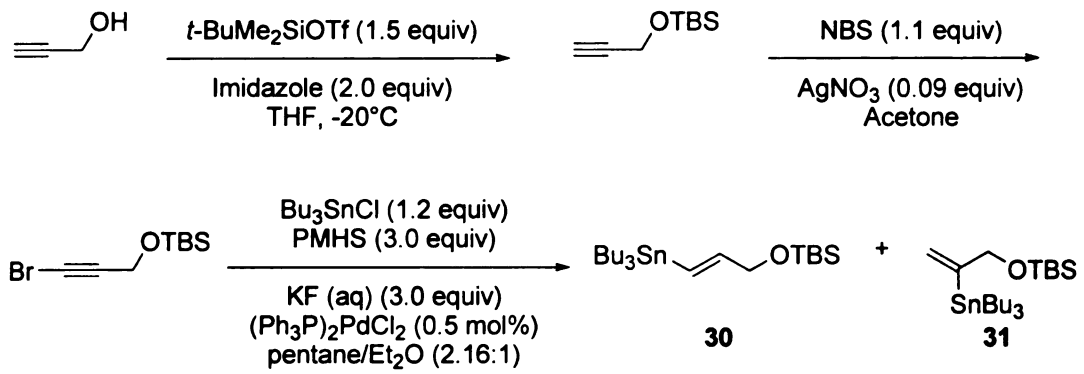
elimination of the triflate and a vinyl proton to give the observed alkynylsilane (Scheme 3.6). Use of the nonaflating reagent ($CF_3(CF_2)_3SO_2F$) under similar reaction conditions resulted in the formation of the vinyl nonaflate, **27** (Scheme 3.6) (^{1}H-NMR of the crude product was obtained). However, the nanoflate was sensitive to acidic conditions, and attempted purification by silica gel column chromatography resulted in the elimination of the nonaflate group to give **28**. In all cases, product identification was by ^{1}H-NMR, ^{13}C-NMR, and high resolution GC-MS.

Scheme 3.6. Attempted synthesis of Vinyl triflate and vinyl nonaflate

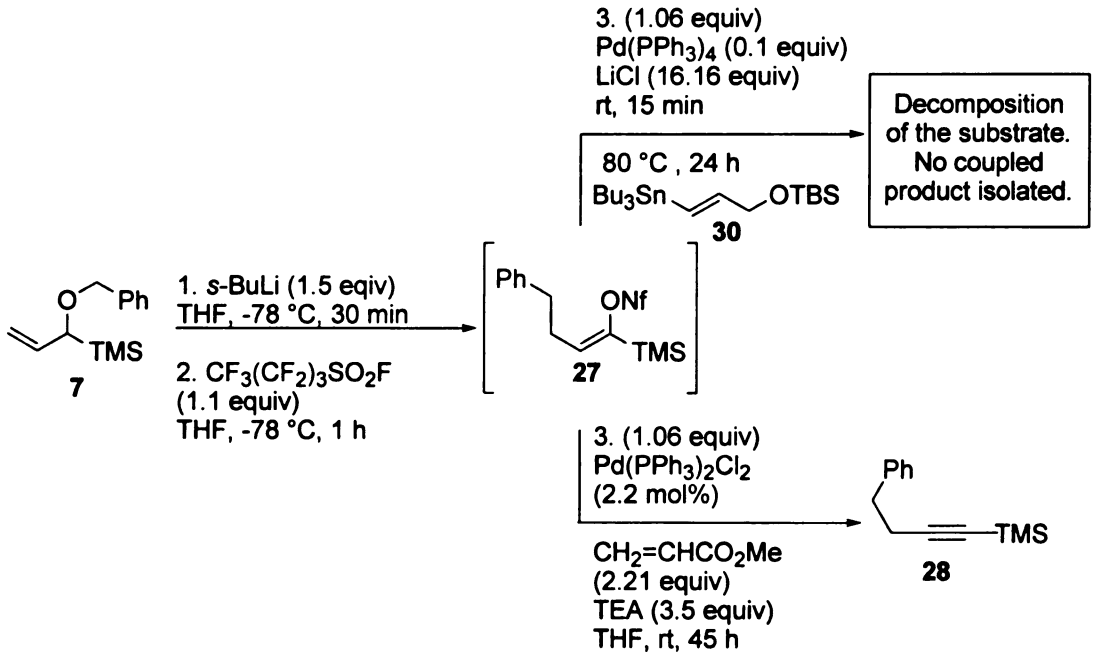


As mentioned above, vinyl triflates and nanoflates are known to be good coupling partners in coupling reactions.[9] Since our vinyl triflates (or vinyl nonaflate) were unstable, we wanted to trap these species in situ, in a Stille or Heck coupling reaction. This however, was not realized as the attempted Stille coupling (Scheme 3.8) (for preparation of the stannane partner see Scheme 3.6) and Heck reaction (Scheme 3.8) failed to occur.

Scheme 3.7. Synthesis of the stannane coupling partner

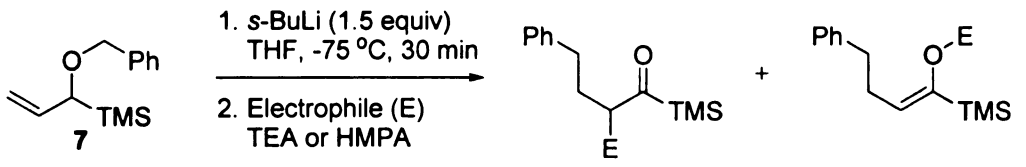


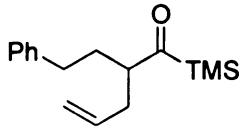
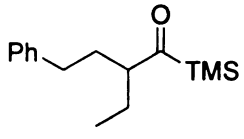
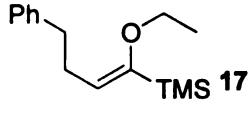
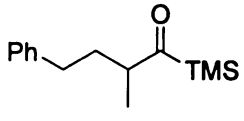
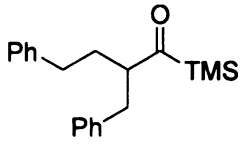
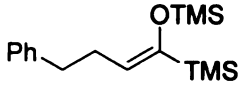
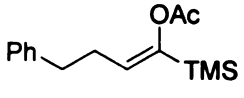
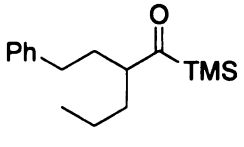
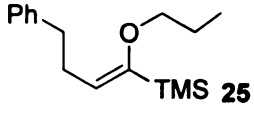
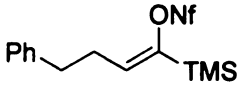
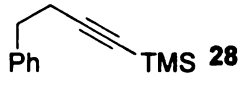
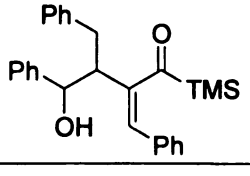
Scheme 3.8. Attempted Wittig/nonaflation/Pd(0)-mediated coupling of model substrate **7**



The summary of the results of the trapping experiments is given in Table 3.8.

Table 3.8. One-pot Electrophilic Trapping of Enolate of **7**: Preparation of Acylsilanes



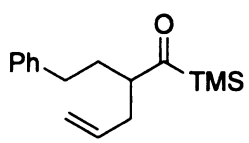
Entry	Electrophile	Product(s)	Yield (%)
1	CH_2=$CHCH_2Br$	 **12**	55
2	CH_3CH_2I	 **16** +  **17**	81 (3:1)
3	CH_3I	 **18**	73
4	$PhCH_2Br$	 **21**	66
5	TMSCl	 **22**	73
6	CH_3COCl	 **23**	69
7	$CH_3CH_2CH_2I$	 **24** +  **25**	66 (3:1)
8	$CF_3(CF_2)_2SO_2F$	 **27** →  **28**	58
9	PhCHO	 **29**	68

3.3. Conclusions

We have shown that the [1,4]-Wittig rearrangement of allyl ethers can be coupled with electrophilic trapping of the resultant enolate intermediate. This procedure provides unique access to α-functionalized acylsilanes, which are synthetically versatile building blocks in organic chemistry. In some cases such as trapping with ethyl iodide and propyl iodide, the vinyl silyl ether resulting from *O*-alkylation features a vinyl silyl group and thus is a masked umpolung anion.

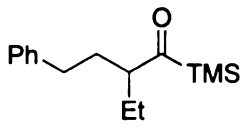
In Chapter 2 of this dissertation, we showed that for simple unsubstituted α-alkoxysilanes such as **7** Wittig rearrangement could be very selective with careful control of reaction conditions. We also showed that the reaction could be efficient in terms of yield. In the present chapter, the efficiency of the [1,4]-Wittig of α-alkoxysilanes was effectively harnessed, establishing the utility of the [1,4]-Wittig of this class of compounds. At this point an appropriate questions becomes "what would be the effect of substitution on the Wittig rearrangement of α-alkoxysilanes?" This topic will be discussed in the next chapter.

Preparation of acylsilanes. Representative procedure: A solution of **7** in THF (0.065 M) was cooled to -78 °C under nitrogen. *s*-BuLi (1.3 M in cyclohexane, 1.5 equiv) was added dropwise via syringe. The reaction mixture was stirred for 30 min. at -78 °C. The resultant enolate solution was transferred via cannula to a THF solution of the appropriate electrophile at the appropriate temperature. Reaction was stirred for the required time, then quenched with saturated aqueous NH_4Cl and diluted with diethyl ether. Phases were separated and the organic phase washed with water and brine. The organic phase was then dried over $MgSO_4$ and concentrated. Silica gel chromatography (0 to 2% EtOAc in hexane gradient) afforded the pure acylsilane.

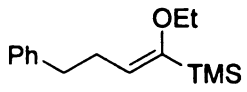


12

Trapping of enolate of 7 with allyl bromide, preparation of acylsilane 12: Applying the **Representative procedure** to 106 mg (0.48 mmol) of **7**, 323 mg (1.92 mmol) of allyl bromide, 195 mg (1.92 mmol, 0.27 mL) of TEA at -78 °C, and allowing the reaction to warm to room temperature for 7 h, after silica gel chromatography (0-2% EtOAc in hexane gradient), afforded 69 mg (55%) of pure **12** as a clear oil. IR (neat) 2953, 1715, 1640, 1454, 1250 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.11 (m, 5H), 5.70-5.61 (m, 1H), 5.01-5.61 (m, 2H), 3.03-2.97 (m, 1H), 2.53-2.43 (m, 2H), 2.39-2.33 (m, 1H), 1.98-1.89 (m, 1H), 1.62-1.55 (m, 1H), 0.16 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 250.5, 141.8, 135.8, 128.4, 128.3, 125.9, 116.6, 77.2, 54.6, 33.5, 30.6, -2.8. HRMS (EI) *m/z* 259.1528 [$(M-H)^+$; calcd for $C_{16}H_{23}OSi$, 259.1518].

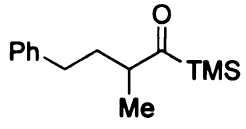


16



17

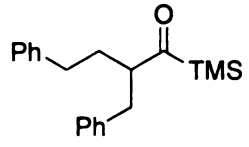
Trapping of enolate of 7 with ethyl iodide- preparation of compounds 16 and 17: Applying the **Representative procedure** to 121 mg (0.55 mmol) of **7**, 343 mg (2.2 mmol) of ethyl iodide, and 394 mg (2.2 mmol, 0.25 mL) of HMPA, after silica gel chromatography (0-2% EtOAc in hexane gradient), afforded 84 mg (61%) of **16** as a light yellow oil, and 28 mg (21%) of **17** as a clear oil (82% combined yield, 3:1 ratio). **16**: IR (neat) 2961, 1713, 1639, 1454, 1250 cm^{-1}. ^1H NMR (500 MHz $CDCl_3$) δ 7.30-7.16 (m, 5H), 2.85-2.78 (m, 1H), 2.52-2.42 (m, 2H), 1.97-1.89 (m, 1H), 1.71-1.62 (m, 1H), 1.59-1.51 (m, 1H), 1.43-1.34 (m, 1H), 0.85 (t, J = 7.8, 6.8 Hz, 3H), 0.21 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 251.2, 142.0, 128.4, 128.3, 125.8, 57.1, 33.7, 30.6, 22.3, 11.7, -2.7. HRMS (NH_3 CI) *m/z* 249.1676 [$(M+H)^+$; calcd for $C_{15}H_{25}OSi$, 249.1675]. **17**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.33-7.16 (m, 5H), 5.10 (t, J = 7.3, 6.8 Hz, 1H), 3.67-3.62 (q, J = 7.3, 6.8 Hz, 2H), 2.39-2.25 (m, 2H), 1.86-1.78 (m, 2H), 1.20-1.17 (t, J = 7.3, 6.8 Hz, 3H), 0.12 (s, 9H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 161.2, 142.2, 128.4, 128.2, 128.1, 125.6, 66.2, 35.9, 27.2, 15.8, -0.66.



18

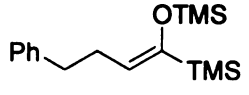
Trapping of enolate of 7 with methyl iodide preparation of acylsilane 18: Applying the **Representative procedure** to 98 mg (0.445 mmol) of **7**, 252 mg (1.78 mmol) of methyl iodide, 180 mg (1.78 mmol, 0.25 mL) of TEA for 50 min, after silica gel chromatography (0-2% EtOAc in hexane gradient), afforded 92 mg (73%) of **18** as a

light yellow oil. IR (neat) 2963, 1713, 1639, 1604, 1454, 1250 cm^{-1}. ^1H NMR (500MHz $CDCl_3$) δ 7.27-7.13 (m, 5H), 2.94-2.87 (m, 1H), 2.60-2.47 (m, 2H), 2.03-1.96 (m, 1H), 1.51-1.1.44 (m, 1H), 1.00 (d, J = 6.8 Hz, 3H), 0.16 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 250.4, 141.9, 128.3, 125.8, 49.6, 33.4, 32.6, 14.3, -2.7. HRMS (EI) *m/z* 233.1356 [$(M-H)^+$; calcd for $C_{14}H_{21}OSi$, 233.1362].



21

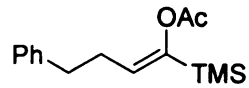
Trapping of enolate of 7 with benzyl bromide-preparation of acylsilane 21: Applying the **Representative procedure** to 99 mg (0.45 mmol) of **7**, 307 mg (1.8 mmol) of benzyl bromide, 182 mg (1.8 mmol, 0.25 mL) of TEA for 1.5 h, after silica gel chromatography (0-2% EtOAc in hexane gradient), afforded 92 mg (66%) of **21** as a light yellow oil. IR 3026, 2951, 1713, 1639, 1603, 1496, 1454, 1250 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.13 (m, 10H), 3.43-3.33 (m, 1H), 3.12-2.94 (dd, J = 13.7, 7.8 Hz, 1H), 2.63-2.47 (m, 3H), 2.02-1.90 (m, 1H), 1.69-1.57 (m, 1H), 0.08 (s, 9H). ^{13}C (125 MHz, $CDCl_3$) δ 251.8, 141.7, 139.9, 129.0, 128.4, 128.3, 126.1, 125.9, 56.3, 35.9, 33.4, 31.3, -3.2. HRMS (EI) *m/z* 309.1669 [$(M-H)^+$; calcd for $C_{20}H_{25}OSi$, 309.1675].



22

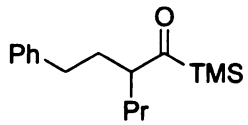
Trapping of enolate of 7 with TMSCl-preparation of vinyl silyl ether 22: Applying the **Representative procedure** to 126 mg (0.572 mmol) of **7**, 248 mg (2.29 mmol) of TMSCl, 231 mg (2.29 mmol, 0.32 mL) of TEA for 1.5 h, after silica gel chromatography (hexanes neat), afforded 142 mg (85%) of **22** as clear oil. IR (neat)

3028, 2959, 1614, 1496, 1454, 1250, 1121 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.29-7.16 (m, 5H), 5.07-5.02 (t, *J* = 6.7 Hz, 1H), 2.66-2.60 (t, *J* = 8.5, 7.4 Hz, 2H), 2.40-2.35 (m, 2H), 0.16 (s, 9H), 0.07 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 142.2. 128.4, 128.3, 125.7, 124.4, 35.7, 27.6, 0.9, -1.7. HRMS (NH_3 CI) *m/z* 293.1747 [$(M+H)^+$; calcd for $C_{16}H_{29}OSi_2$, 293.1757].

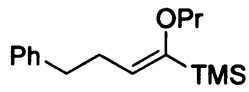


23

Trapping of enolate of 7 with acetyl chloride-preparation of vinyl acetate 23: Applying the **Representative procedure** to 89 mg (0.404 mmol) of **7**, and 127 mg (1.62 mmol) of acetyl chloride for 1.5 h, after silica gel chromatography (0-2% EtOAc in hexane gradient), afforded 73 mg (69%) of **23** as a clear oil. IR 3086, 3026, 2955, 2922, 2849, 1745, 1603, 1496, 1454, 1369, 1230, 1089, 1039 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.30-7.15 (m, 5H), 5.51-5.48 (t, *J* = 7.1, 6.8 Hz, 1H), 2.68-2.64 (t, *J* = 8.4, 7.5 Hz, 2H), 2.36-2.31 (quintet, *J* = 8.4, 7.5, 7.1 Hz, 2H), 2.11 (s, 3H), 0.11 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 155.3, 141.6, 130.5, 128.4, 128.3, 125.9, 35.0, 27.6, 20.5, -1.5. HRMS (EI) *m/z* 262.1387 [(M); calcd for $C_{15}H_{22}O_2Si$, 262.1389].



24



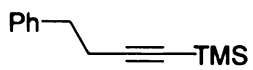
25

Trapping of enolate of 7 with propyl iodide-preparation of compounds 24 and 25: Applying the **Representative procedure** to 129 mg (0.59 mmol) of **7**, 398 mg (2.34 mmol) of propyl iodide, and 420 mg (2.34 mmol, 0.41 mL) of HMPA for 17 h,

after silica gel chromatography (0-2% EtOAc in hexane gradient), afforded pure 102 mg (66%) of **24** and **25** (3:1 ratio by ^{1}HNMR) as a light yellow oil.

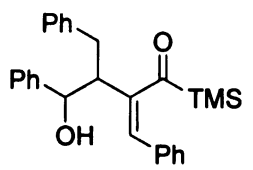
24: IR (neat) 2957, 1717, 1638, 1454, 1250 cm^{-1}. ^{1}H NMR (500MHz $CDCl_3$) δ 7.29-7.12 (m, 5H), 2.92-2.86 (m, 1H), 2.52-2.44 (m, 2H), 1.95-1.88 (m, 1H), 1.65-1.51 (m, 2H), 1.32-1.17 (m, 3H), 0.86 (t, J = 6.8 Hz, 3H), 0.16 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 251.2, 142.0, 128.34, 128.32, 125.8, 55.3, 33.7, 31.5, 31.0, 20.6, 14.3, -2.7. HRMS (NH_3 CI) *m/z* 263.1821 [$(M+H)^+$; calcd for $C_{16}H_{27}OSi$, 263.1831].

25 was not isolated after chromatography.



III-15

Trapping of enolate of 7 with nonaflating agent-preparation of silyl acetylene 28: Applying the **Representative procedure** to 85 mg (0.39 mmol) of **7**, and 128 mg (0.43 mmol) of perfluoro-1-butanesulfonyl fluoride for about 5 h, after silica gel chromatography (0-2% EtOAc in hexane gradient), afforded 45 mg (58%) of pure **28** as a clear oil. IR (neat) 2959, 2175, 1603, 1496, 1454, 1250 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.20 (m, 5H), 2.85-2.80 (t, J = 7.7 Hz, 2H), 2.51-2.46 (t, J = 7.7 Hz, 2H), 0.13 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.6, 128.5, 128.3, 126.2, 106.6, 85.2, 35.1, 22.1, 0.1. HRMS (EI) *m/z* 202.1174 [(M); calcd for $C_{13}H_{18}Si$, 202.1178].



29

Trapping of enolate of 7 with benzaldehyde-preparation of compound 29: Applying the **Representative procedure** to 286 mg (1.3 mmol) of **7**, 276 mg (2.6 mmol)

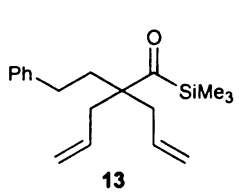
benzaldehyde and 3 mg (0.13 mmol) of TMSOTf for 4 h, after silica gel chromatography (0-10% EtOAc in hexane gradient), afforded 287 g (68%) of pure **29** as a clear oil. IR (neat) 3486, 2955, 1717, 1603, 1495, 1453, 1315, 1273, 1250 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.0 H, 2H), 7.59-7.56 (t, *J* = 7.5 Hz, 1H), 7.47-7.44 (t, *J* = 7.5 Hz, 2H), 7.39-7.26 (m, 6H), 7.23-7.20 (t, *J* = 7.5 Hz, 2H) 7.15-7.12 (apparent t, *J* = 7.5, 7.1 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 2H), 4.51 (t, *J* = 7.1, 5.7 Hz, 1H), 3.90-3.88 (dd, *J* = 5.7, 5.3, 3.1 Hz, 1H), 2.43-2.37 (m, 1H), 2.26-2.20 (dt, *J* = 12.4, 4.4 Hz, 1H), 2.06-2.03 (t, *J* = 7.5, 5.7 Hz, 1H), 0.06 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 142.8, 142.2, 133.2, 129.9, 129.7, 128.5, 128.4, 128.3, 127.6, 126.8, 125.8, 74.2, 47.6, 30.4, -2.7. HRMS (EI) *m/z* 415.2079 [$(M+H)^+$; calcd for $C_{27}H_{31}O_2Si$, 415.2093].

REFERENCES

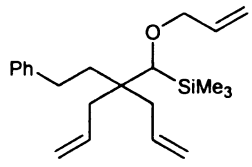
1. Maleczka, R. E. Jr.; Geng, F. *Org. Lett.* **1999**, *1*, 1115-1118.

2. **12** was obtained accompanied by a second product, which, based on ^{1}H-NMR and ^{13}C-NMR, was an aldehyde **15**. Use of HMPA either alone or in combination with TEA (at 0 °C) resulted in more of this accompanying aldehyde being formed.

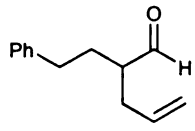
3. HRMS results for compounds **13**, **14** and **15**:



13



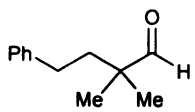
14



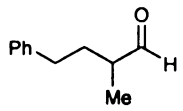
15

13: HRMS (EI) *m/z* 300.1911[(M); calcd for $C_{19}H_{28}OSi$, 300.1909].
14: HRMS (EI) *m/z* 340.2238 [(M); calcd for $C_{22}H_{32}OSi$, 340.2222].
15: HRMS (EI) *m/z* 204.1174 [(M); calcd for $C_{13}H_{16}O_2Si$, 204.1150].

4. HRMS results for compounds **19** and **20**:



19



20

19: HRMS (EI) *m/z* 176.1207 [(M); calcd for $C_{12}H_{16}O$, 176.1201].
20: HRMS (EI) *m/z* 162.1055 [(M); calcd for $C_{11}H_{14}O$ 162.1045].

5. We sought to improve on the yield of this reaction by employing TMSOTf as catalyst (0.01 equiv), however, this did not give any advantage.

6. For enol triflates in coupling reactions, see: (a) Li, ShengJian,; Dieter, R. K. *J. Org. Chem.* **2003**, *68*, 969-973 and references therein. (b) Scott, J. W.; McMurry, J. E. *Acc. Chem. Res.* **1988**, *21*, 47-54. For enol nonaflates in coupling reactions, see: (c) Lyapkalo, I. M.; Hogermeier, J.; Reissig, H-U. *Tetrahedron* **2004**, *60*, 7721-7729 and references therein. (d) Lyapkalo, I.M.; Webel, M.; Reissig, H-U. *Eur. J. Org. Chem.* **2002**, *21*, 3646-3658. (e) Wada, A.; Leki, Y.; Ito, M. *Synlett* **2002**, *7*, 1061-1064. (f) Ritter, K. *Synthesis* **1993**, 735. (g) Stang, P. J.; Hanack, M.; Subramanian, L. R. *Synthesis* **1982**, 85. (g) Stille, J. K. *Angew. Chem. Int. Ed.* 1986, 25, 508.

CHAPTER 4

IMPACT OF SUBSTITUTIONS ON WITTIG REARRANGEMENTS OF α-ALKOXYSILYL ETHERS

4.1. Preparation of of α-alkoxysilanes

4.1.1. Introduction: Design of substrates

In chapter 2, we mentioned that attempts to achieve selective Wittig rearrangement of α-alkoxysilanes would be highly dependent on understanding the reaction variables that impact the reaction such as base (type and concentration), reaction temperature, solvent[1] and substrate structure,[2] (sterics and electronics) impact the reaction. We then studied the effects of base, temperature and solvent and established optimum conditions for our substrates. Employing these optimum conditions, we were able to generate and trap the enolate of model compound **7** to functionalize the resultant acylsilane at the α-carbon. In this chapter, we will discuss the results of our studies on the structural requirements for α-alkoxysilanes in the Wittig rearrangement.

Model substrate **7** rearranged selectively via the [1,4]-Witttig pathway at low temperatures. However, as the temperature rose, there was gradual erosion in selectivity and at room temperature, [1,4]/[1,2] selectivity reached a ratio of 2:1 (Chapter 2). This result clearly showed that elevated temperature favors the [1,2]-Wittig. We wondered whether we could still control the [1,4]/[1,2] selectivity if we made structural changes (sterics and electronics) in the structure of model substrate **7**.

From the beginning, we recognized that proper design of substrates was of key importance to the study of structural requirement[2] in this reaction. Tomooka and co-workers,[2f] established that in general, the scope and limitations of the [1,2]-Wittig

rearrangement are determined principally by the migratory aptitude of the alkyl group and the reactivity of the carbanion terminus as dictated by the nature of the carbanion stabilizing group (Scheme 4.1). They also determined that the migratory aptitude of the alkyl group increases in the order primary<secondary<tertiary-ally<benzyl. This trend is consistent with the stability order of the corresponding radicals. Previous reports have also shown that the [1,2]-alkyl shift is promoted by a radical stabilizing migrating group and/or a terminal radical stabilizing group (Figure 4.1).[2,3] On the other hand, the yield of [1,4]-product has been reported to be remarkably insensitive to the substitution pattern within the allylic moiety of the ethers.[1] In a different study, it was shown that the concerted pathways available to a substrate are primarily determined by the geometry of the system and thus may be sensitive to steric effects.[4] In contrast these two factors have little or no effect on the stepwise pathways.[4]

Given the nature of these previous studies, we sought substrates to allow investigations of the different factors that are most likely to control the course of the Wittig rearrangements of α-alkoxysilanes. These factors would include the influence of sterics, stereochemistry, and electronics and could be independently studied by the proper choice of R_1 and R_2 (Figure 4.1).

In investigating the structural requirements for the α-alkoxysilanes in the Wittig rearrangement, we recognized that electronically, migrating alkyl groups that are activated (bearing an electron donating group), deactivated (bearing an electron withdrawing group) as well as unactivated (e.g. a simple alkyl group) would have different impacts on the Wittig rearrangement of this class of compounds.

Secondly, sterics could be introduced at either the migrating carbon, the terminal sp^2 carbon of the allyl moiety, or at both. We anticipated that at whatever position, sterics would alter the ratio of the [1,4]/[1,2]-rearrangement products, however, the magnitude of this impact could not be estimated.

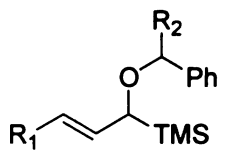
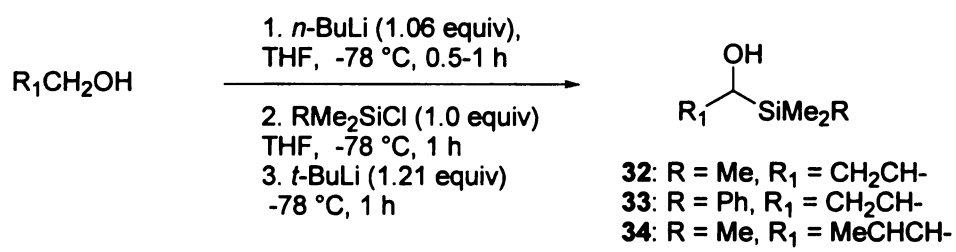


Figure 4.1. Generalized Structure of α-alkoxysilanes

4.1.2. Preparation of α-alkoxysilanes

To study a variety of Wittig substrates we first needed to prepare the precursor silyl-alcohols. α-(Hydroxyallyl)silanes **32-34** were prepared following a procedure of Danheiser and co-workers[5] that involves the retro-Brook rearrangement[6] of appropriate alkylsilyl ethers (Scheme 4.1).

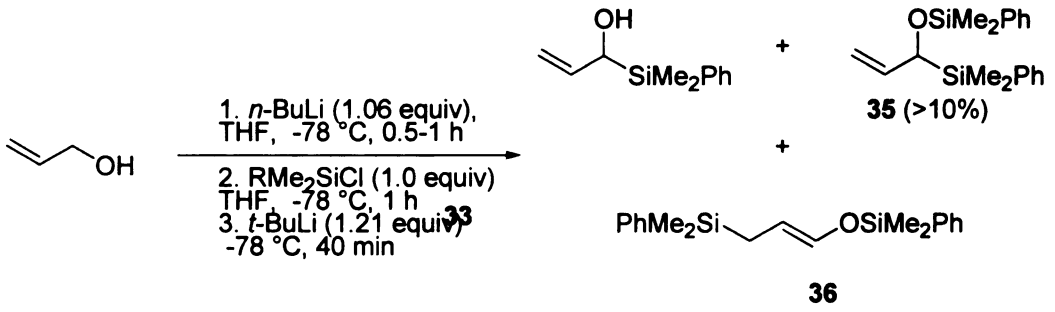
Scheme 4.1. Preparation of various α-hydroxysilanes



The syntheses of **32**[7] and **34**[8] were uneventful, with both alcohols being obtained in 93% and 53% yields, respectively. However, the synthesis of **33** proved to be more complicated and was studied in some detail. Deprotonation of allyl alcohol with 1.06

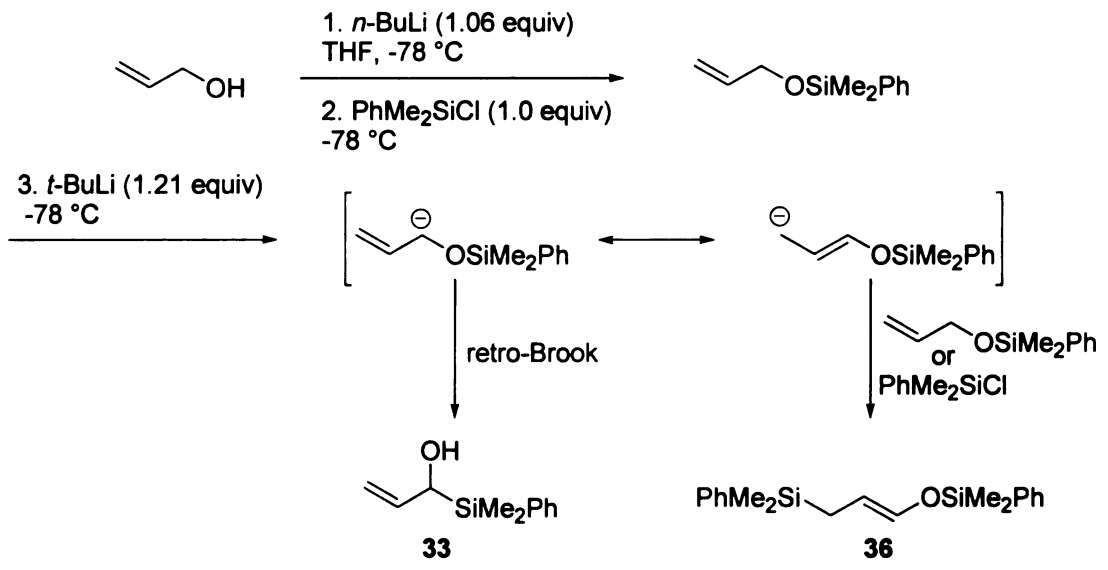
equiv of *n*-BuLi in THF at -78 °C and trapping with phenyldimethylsilyl chloride proceeded reasonably well. However, we found that this reaction was highly dependent on the rate of addition of *t*-BuLi and the time following this addition. Variation in these conditions resulted in a mixture of three products **33**, **35**, **36** (Scheme 4.2).

Scheme 4.2. Preparation of α-(hydroxydimethylphenylallyl)silane **33**



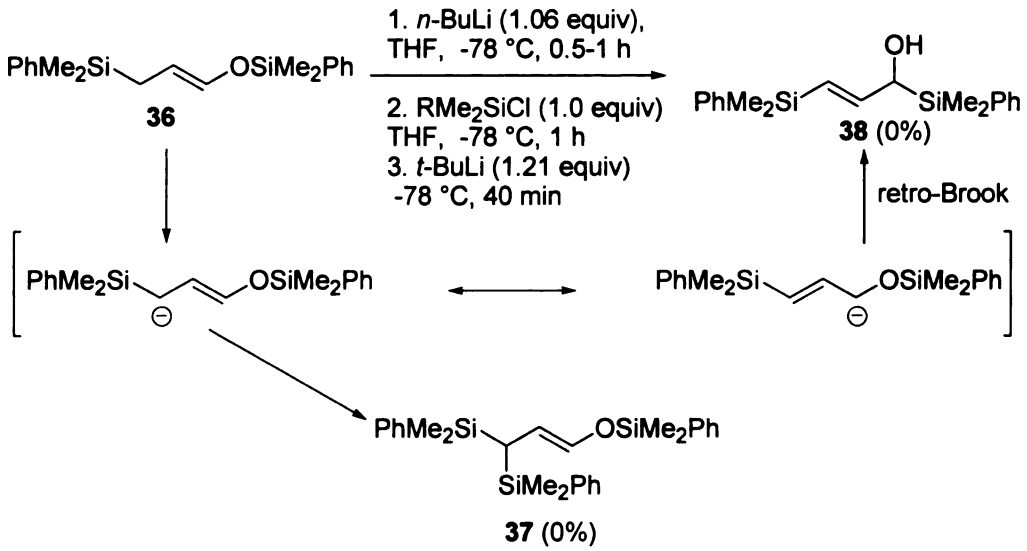
Following addition of *t*-BuLi with long reaction times (1.5 h or more) gave approximately a 1:1 to 2:1 mixture of the desired α-hydroxisilane **33** and vinyl silyl ether **36** (Scheme 4.2). Rapid addition of *t*-BuLi was also not favorable for formation of the desired alcohol. Arresting the reaction five minutes after a rapid addition of base afforded the vinyl silyl ether **36** as the only product and in near quantitative yield. As illustrated in Scheme 4.3, the more stable resonance structure (featuring the more substituted double bond) either abstracts a silyl group from allyl silyl ether or is trapped by the $PhMe_2SiCl$ in the reaction mixture to give the observed product. Our best result (11:1 alcohol to vinyl silyl ether, 71% yield) was obtained when *t*-BuLi was added fairly slowly at 0.35 ml/min, with the subsequent reaction being allowed to stir at -78 °C for 40 minutes.

Scheme 4.3. Formation of α-(dimethylphenylsilyl)allyl alcohol **33** and vinyl silyl ether **36**



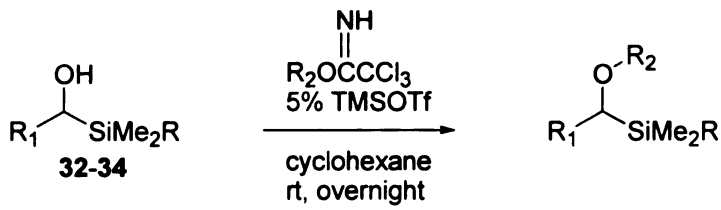
It is worth mentioning that when the vinyl silyl ether **36** was subjected to the reaction conditions of Scheme 4.2 it was recovered unchanged. Deprotonation of the vinyl silyl ether **36** would result in the formation of an allyl carbanion stabilized by an α-silyl group, which could be captured by $PhMe_2SiCl$ to give **37** or result in the formation of an α-hydroxysilane **38** bearing a vinyl silyl group (Scheme 4.4). However, none of these products were observed. This could mean that either the deprotonation did not happen or the α-silyl carbanion is stable toward further reaction.

Scheme 4.4. Subjection of vinyl silyl ether to deprotonation/silylation/retro-Brook reaction conditions



Our model substrate **7** and the other Wittig substrates employed in this work[9] were prepared following the general method for the synthesis of α-alkoxysilanes developed in our laboratory by Maleczka and Geng.[10] Their preparation involves Lewis acid catalyzed etherification of α-hydroxysilanes (**32-34**) via the trichloroacetimidates[11] of the appropriate alcohols.[12] The Wittig substrates prepared are shown in Table 4.1.

Table 4.1. Preparation of various α-alkoxysilanes[a]

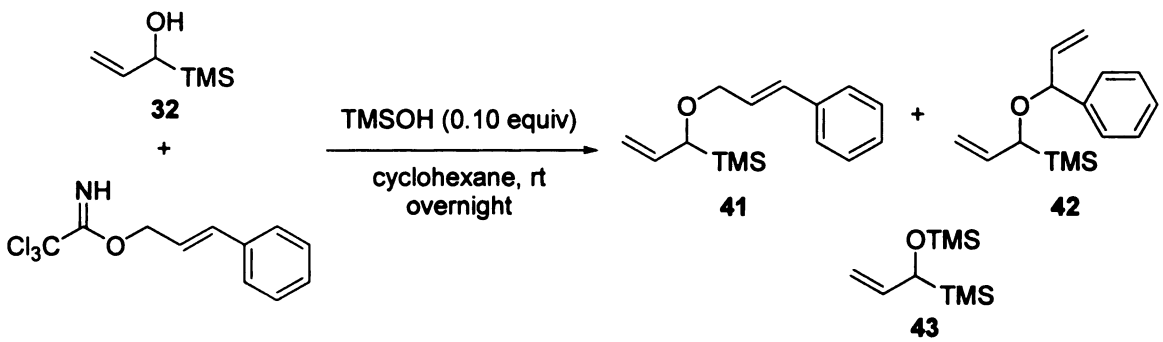


Entry	R	R_1	R_2	silane	Yield (%)
1	Ph	-CH=CH_2	-CH_2Ph	**39**	35
2	Me	-CH=CH_2	-CH_2CH=CHSiMe_3	**40**	59
3	Me	-CH=CH_2	-CH_2CH=CHPh	**41**	24
4	Me	-CH=CH_2	-CH(Ph)CH=CH_2	**42**	22
5	Me	-CH=CH_2	-CH(Me)Ph	**44**	78
6	Ph	-CH=CH_2	-CH(Me)Ph	**45**	28
7	Ph	-CH=CH_2	-CH(Me)*p*-$NO_2C_6H_4$	**46**	35
8	Me	-CH=CH_2	-CH(Me)*p*-$MeOC_6H_4$	**47**	92[b]
9	Me	-CH=CH_2	-CH(Ph)CH_2Me	**48**	37
10	Ph	-CH=CH_2	-CH(Ph)CH_2Me	**49**	38
11	Me	-CH=CH_2	-CH(Ph)CH_2CH_2Me	**50**	75
12	Ph	-CH=CH_2	-CH(Ph)CH_2CH=CH_2	**51**	77
13	Me	-CH=CH_2	-CH(Ph)CH_2CH=CH_2	**52**	80[c]
14	Me	-CH=CH_2	-CH(Ph)$CHMe_2$	**53**	59
15	Me	-CH=CH_2	-CH(Ph)$(CH_2)_3$CH=CH_2	**54**	15
16	Me	(*E*)-CH=$CHCH_3$	-CH_2Ph	**55**	36
17	Me	(*E*)-CH=$CHCH_3$	-CH(Me)Ph	*E*-**56**	49
18	Me	(*Z*) -CH=$CHCH_3$	-CH(Me)Ph	*Z*-**56**	<10
19	Me	(E) -CH=$CHCH_3$	-CH(Ph)CH_2CH=CH_2	**58**	69

(a) Unless otherwise stated, α-alkoxysilanes were obtain in approximate ratio of 1:1 (reactive *syn*:less reactive *anti*). (b) 3.3:1 ratio of less reactive:reactive diastereomeric **47** was obtained. (c) 2.6:1 ratio of less reactive:reactive diastereomeric **52** was obtained.

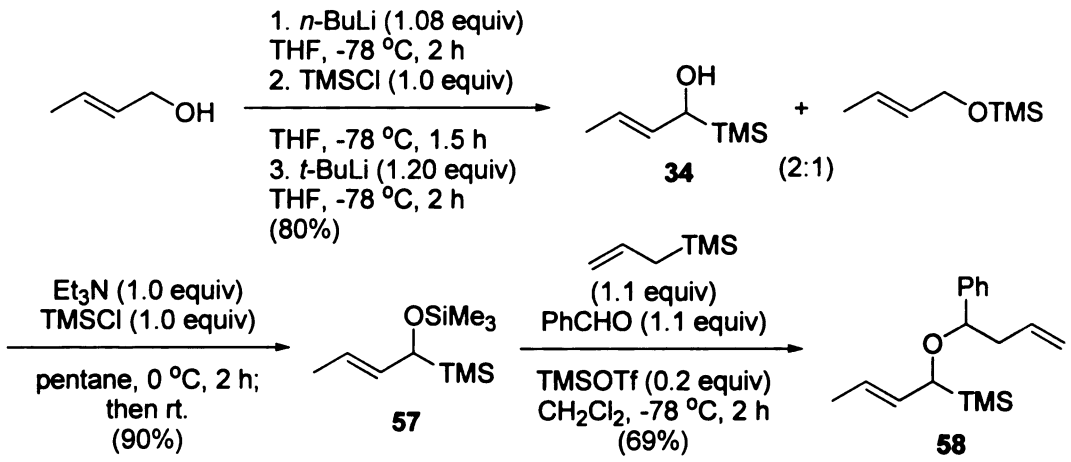
Etherification of **32** with the trichloroacetimidate of cinnamyl alcohol, catalyzed by both TMSOTf and triflic acid, respectively, afforded a mixture of four products.[13] These were **41** (23%), a near 1:1 pair of diastereomeric **42** (20%), and TMS-protected **32** (5%). All the compounds were fully characterized (^{1}H NMR, ^{13}C NMR, DEPT) (Scheme 4.5).

Scheme 4.5. Etherification of α-hydroxysilane **32** with trichloroacetimidate of cinnamyl alcohol



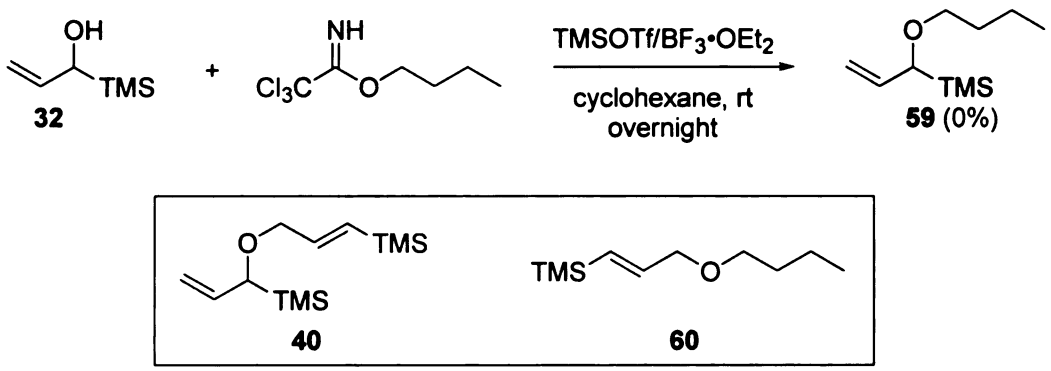
Compounds **51**, **52**, and **58** were not accessed via the previously described route, but rather via Rychnovsky's protocol.[9] As illustrated in Scheme 4.6, the silylation of **34** afforded the crotyl silyl ether **57** (90% yield). This compound was employed in a three component coupling reaction with allylsilane and benzaldehyde, catalyzed by TMSOTf to afford **58** as a 1:1 pair of diastereomers in 68% yield. Compound **51** was a clear oil obtained as a 1:1 pair of diastereomers in 77% yield and **52** was also a clear oil, obtained as a 1:2.6 pair of diastereomers in 80% yield.

Scheme 4.6. Preparation of substrate **58** via Rychnovsky's protocol



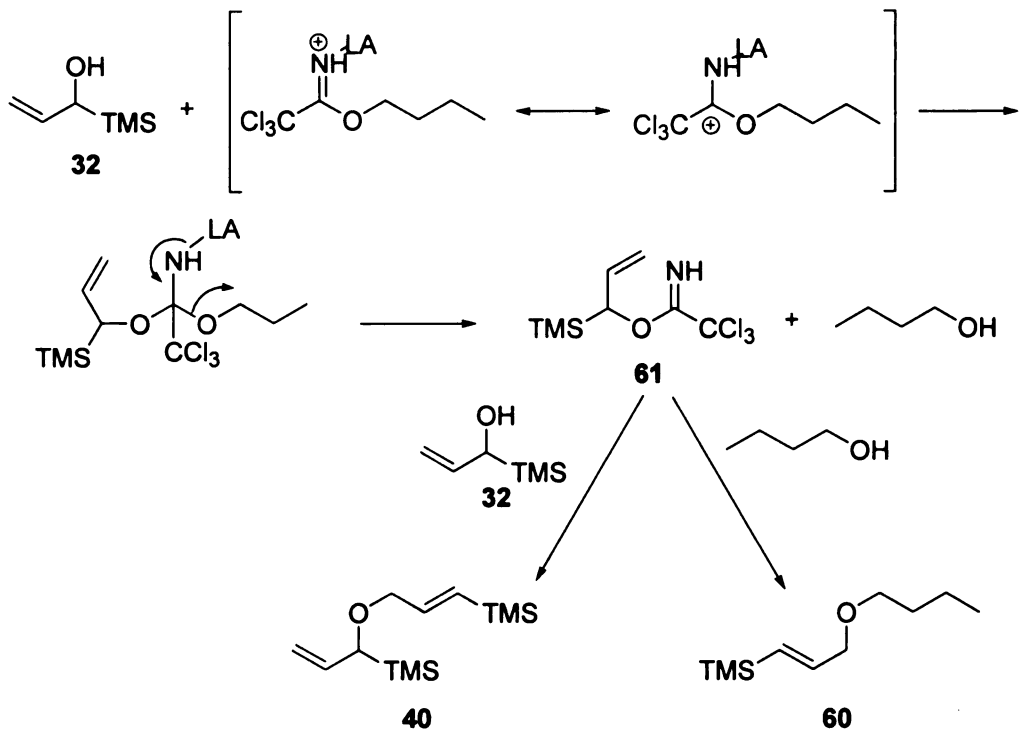
As illustrated in Table 4.1 we prepared a variety of α-alkoxysilanes including those bearing activated migrating groups (e.g. benzyl and substituted benzyl), as well as those bearing substituents at the terminal carbon of the allyl moiety. However, this first set of compounds contained no substrates bearing unactivated migrating groups (simple alkyls). To investigate the behavior of simple unactivated alkyl groups, we decided to employ α-(trimethylsilyl)allyl butyl ether as a prototype. The synthesis of α-(trimethylsily)allyl butyl ether was attempted by Lewis acid-catalyzed etherification of α-hydroxyallylsilane, **32**, with the trichloroacetimidate of *n*-butyl alcohol[11] (Scheme 4.7). Unfortunately the target compound **59** was not observed. Nevertheless, two silylated compounds were isolated, **40** and **60**, albeit in low yields.

Scheme 4.7. Attempted synthesis of α-(trimethylsilyl)allyl butyl ether



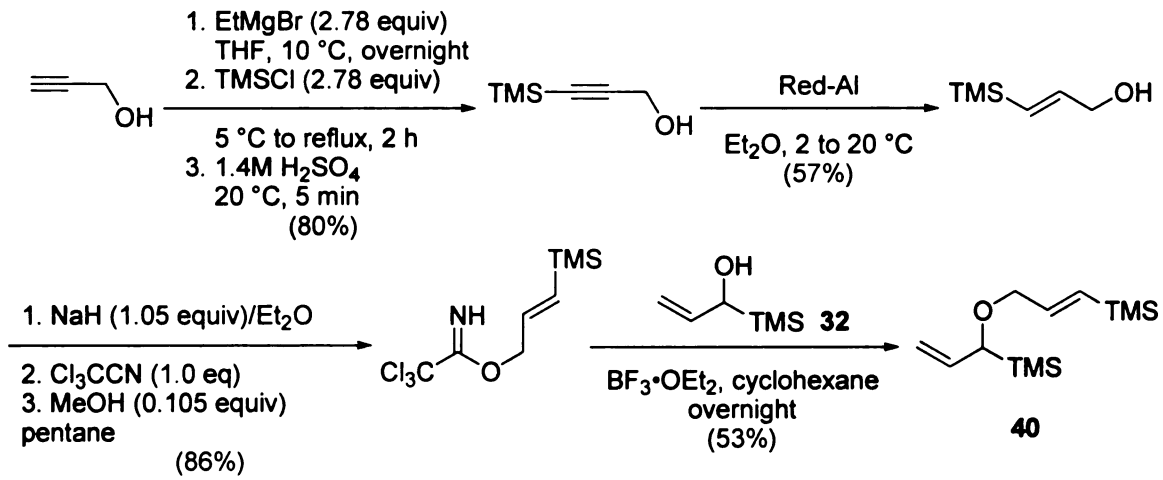
In order to explain the formation of the observed compounds, the mechanism illustrated in Scheme 4.8 is proposed. Coordination of the Lewis acid to the acetimidate nitrogen makes the iminium carbon more electrophilic. The incoming nucleophile (**32**) would attack at the iminium carbon to form activated allylic acetimidate intermediate **61**, liberating butanol in the process. A nucleophilic attack at the terminal olefinic carbon by another molecule of **32** would result in the formation of **40**. On the other hand, a nucleophilic attack on the terminal olefinic carbon by a butanol molecule would lead to the formation of **60**. The formation of the target compound would demand attack of a molecule of α-hydroxysilane **32** at the α-carbon of the butyltrichloroacetimidate. This process would require some kind of activation of the α-carbon (e.g. by resonance stabilization), which is not possible with the butyl system. Though somewhat disappointing this result was interesting given the unique nature of compound **40**.

Scheme 4.8. Attempted synthesis of α-(trimethylsilyl)allyl butyl ether-Plausible mechanism



Considering the unique nature of compound **40**, we sought further confirmation of its structure. Independent synthesis of **40** was accomplished in 53% yield by the $BF_3 \cdot OEt_2$ mediated etherification of **32** with the trichloroacetimidate of γ-silylalcohol (3-trimethylsilyl-2-propen-1-ol), which was itself prepared following the method of Denmark and Jones (Scheme 4.9).[14]

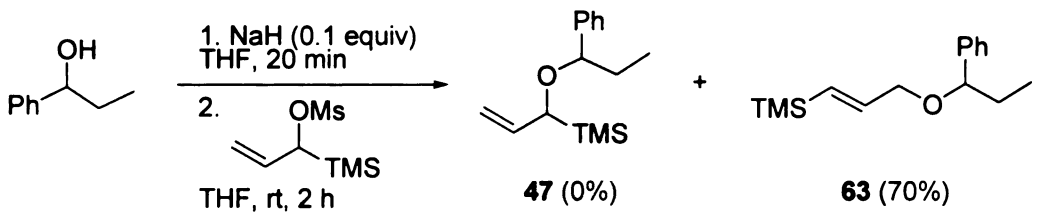
Scheme 4.9. Independent synthesis of Wittig substrate **40**



4.2. In search of new methods for accessing α-alkoxysilanes

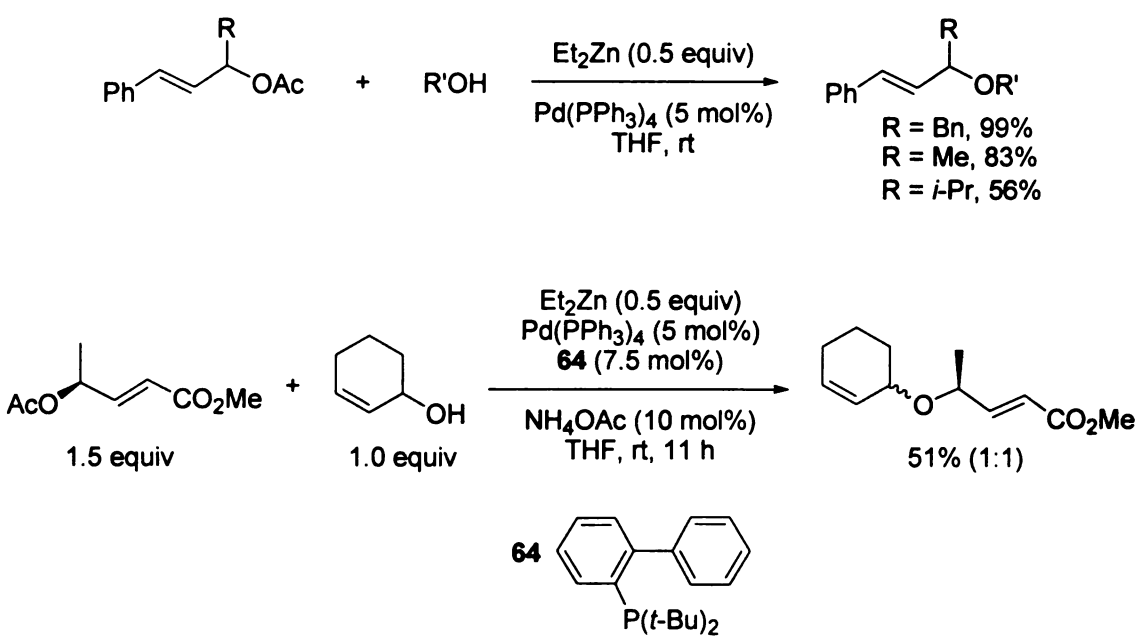
We still desired to investigate the behavior of non-activated migrating centers under our Wittig rearrangement conditions. As the previous protocol for accessing the Wittig substrates was not amenable to the syntheses of α-(trimethylsilyl)allyl alkyl ethers,[15] a nucleophilic substitution reaction between the alkoxide of 1-phenyl-1-propanol and the mesylate of **32** was considered (Scheme 4.10). The formation of **62**, mesylate of **32** was very efficient, affording the desired mesylate in 96% yield.[16] However, reaction with a preformed acetimidate of 1-phenylpropan-1-ol in THF resulted in an S_N2'-displacement of the mesylate group to afford **62** in 70%, with no evidence of the desired S_N2 product **47** observed.

Scheme 4.10. Attempted synthesis of **47** via an S_N2 displacement of a mesylate group



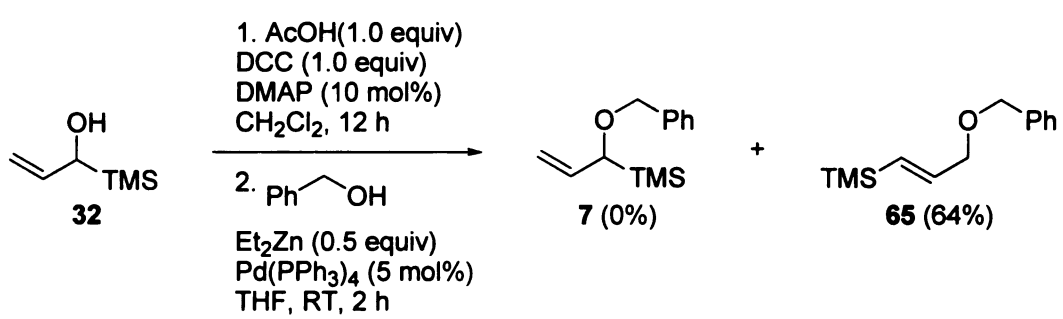
Kim and Lee[17] reported a mild and efficient method for the stereoselective formation of C–O bonds via an S_N2 type process, based on Pd-catalyzed allylic etherification using Zn(II) alkoxides as nucleophiles (Scheme 4.11). Fundamental to their protocol was the use of allylic acetate and a wide variety of alcohols (primary, secondary acyclic, secondary cyclic, allylic, propargylic, and aromatic). In this protocol, Et_2Zn served as the source of base and counter ion.

Scheme 4.11. Pd(0)-mediated stereoselective formation of C–O bonds via S_N2 type process



The above protocol was adapted to acetyl ester of **32** and benzyl alcohol as coupling partners. Treating a THF solution of benzyl alcohol with Et_2Zn at room temperature and stirring for 50 min preformed the Zn benzyl oxide. Subsequent addition of the allyl acetate and $Pd(PPh_3)_4$ and stirring for 2 h resulted in the complete consumption of the allyl acetate. However, the expected coupled product was not obtained. Instead, **65**, resulting from an E2′ elimination of the acetate group was isolated in 64% yield (Scheme 4.12). This result is similar to that obtained with the corresponding α-(trimethylsilyl)allyl mesylate (Scheme 4.10). These results are clear indications that allylsilanes possessing substituents that are good leaving groups prefer to react by elimination of the leaving group via an E2′ mode.

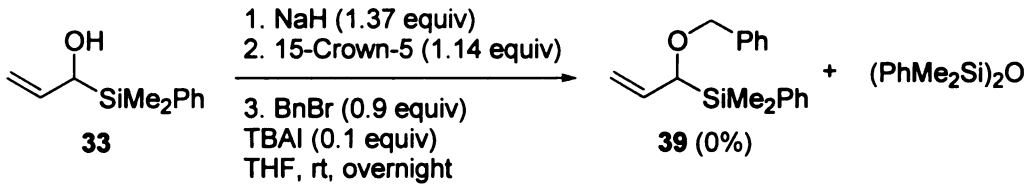
Scheme 4.12. Pd-catalyzed allylic etherification using Zn(II) alkoxide as nucleophile



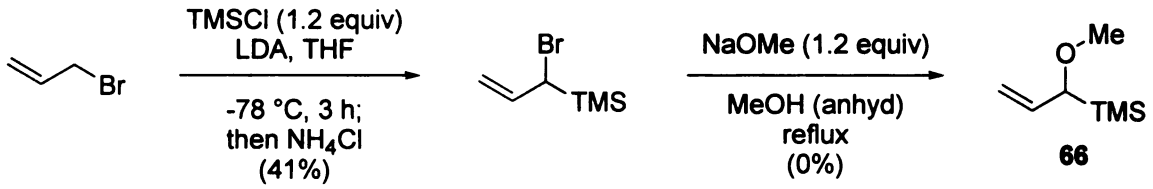
An attempt was also made to access the α-alkoxysilanes via the classical Williamson's ether synthesis (Scheme 4.13). The caveat of this method is that deprotonation of the starting alcohol will very likely trigger a Brook rearrangement. However, we reasoned that a bulky group (such as phenyl) on silicon might help slow down this process and lead to the desired product. Thus,[18] $PhMe_2Si-$ was substituted for Me_3Si- group. A catalytic amount of TBAI was also employed to facilitate benzylation.

Regretably, the expected α-alkoxysilane was again not obtained. The reaction afforded $(PhMe_2Si)_2O$ as the only product (quantitative crude yield). We also tried a direct S_N2 displacement of a *sec*-bromide with a methoxide ion (Scheme 4.14). However, the expected allyl methyl ether was not isolated and neither was the starting *sec*-allyl bromide recovered.

Scheme 4.13. Attempt at accessing α-alkoxysilanes via the Williamson's ether synthesis

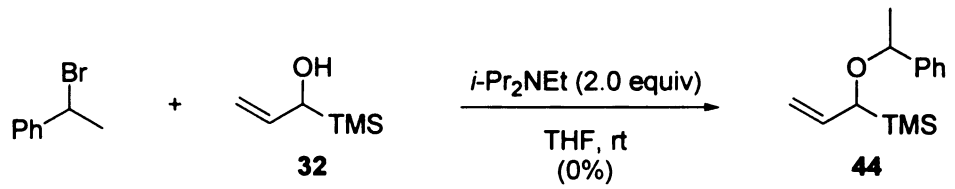


Scheme 4.14. Attempted preparation of α-alkoxysilanes by direct S_N2 displacement



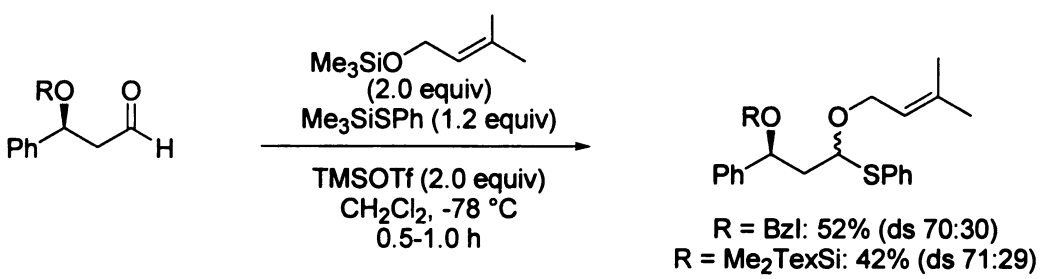
In an attempt to get around the use of a strong base we contemplated accessing α-alkoxysilanes via direct S_N2 reaction between **32** and 1-bromoethyl benzene in the presence of a weak base (2.0 equiv of *i*-Pr_2NEt, THF, rt). In the end though, this protocol did not give the expected product (Scheme 4.15).

Scheme 4.15. Attempt at accessing α-alkoxysilanes via direct S_N2 reaction

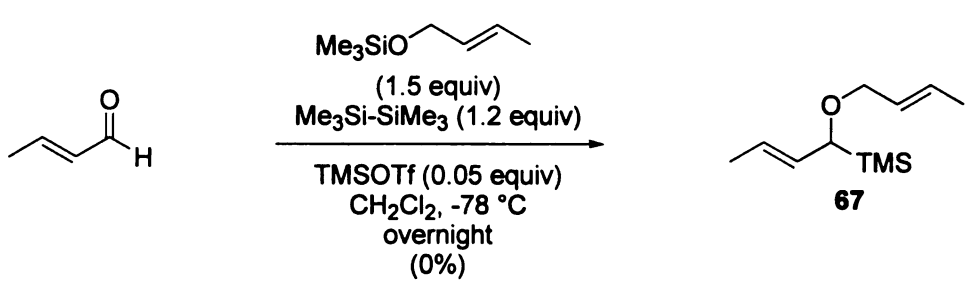


In 1992, Hoffmann and Brückner[19] reported the synthesis of two functionalized O-S acetals by a one-pot thioacetalization of the requisite aldehydes when they reacted the aldehydes, (trimethylsilyl)-prenol, (trimethylsilyl)thiophenol, and 2 equiv. of TMSOTf at -78°C in CH_2Cl_2 (Scheme 4.16). When we tried to adapt this protocol to our system comprising crotonaldehyde, trimethylsilyl-protected crotyl alcohol, hexamethyl disilazane, and a catalytic amound (0.05 equiv) of TMSOTf, the desired compound **67** was not observed (Scheme 4.17).

Scheme 4.16. Hoffmann and Brückner one-pot synthesis of O-S acetals



Scheme 4.17. Attempted adaptation of Hoffmann and Bruckner protocol



In conclusion, due to our inability to access requisite substrates, we were unable to investigate the Wittig rearrangements of trimethylsilylallyl alkyl ethers possessing non-activated migrating alkyl groups and which are set up to undergo [1,4]-Wittig rearrangement.

4.3. Impact of substitutions on Wittig rearrangements of α-alkoxysilanes

4.3.1. Introduction

With substrates in hand, we started to look at their rearrangement under our Wittig conditions. The purpose of this part of the research was to investigate the effect of sterics on the Wittig rearrangement of α-alkoxysilanes. Toward this end we placed a substituent at (1) the migrating carbon, (2) the terminal olefinic carbon, and (3) both the migrating and the terminal olefinic carbons in some of these compounds. In the first two scenarios, if the reaction goes via both the [1,2] and the [1,4]-pathways, one stereocenter will be formed in each of the Wittig products. Installing substituents at both sites would in theory give a pair of diastereomeric products with two adjacent stereogenic centers. In both cases the issue of stereoselectivity has not been well addressed to date.

4.3.2. Effect of groups on silicon on the Wittig rearrangement of α-alkoxysilanes

In Chapter 2 we presented our results on the Wittig rearrangement of our model substrate **7** featuring α-trimethylsilyl group. Compound **7** underwent facile bond reorganization under our Wittig conditions. We desired to establish whether or not the groups on silicon have any effect on the Wittig rearrangement of α-alkoxysilanes. Thus, compound **39** (possessing $PhMe_2Si$ group) was subjected to our conditions as already

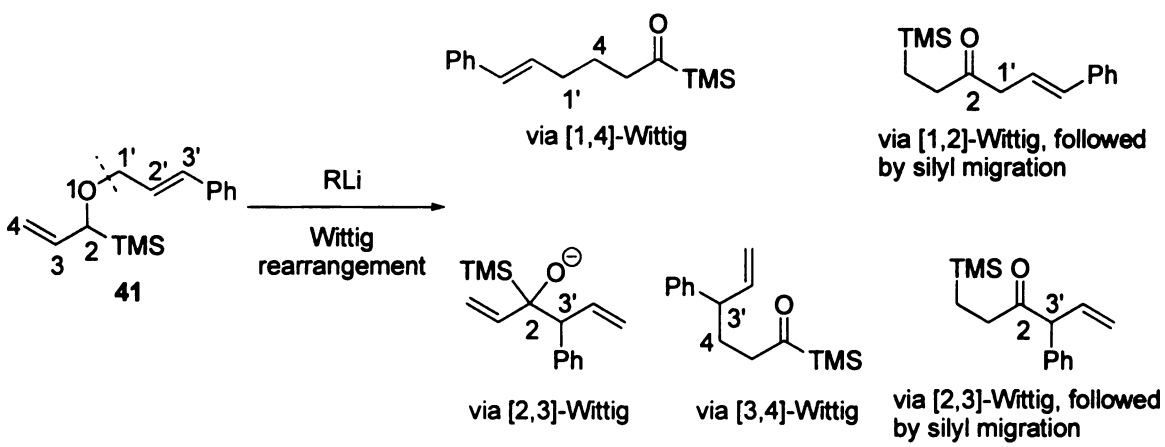
described for **7**. We were pleased to note that the substrate reacted very readily. At low temperatures (-78 °C) the rearrangement of **39** afforded only the [1,4]-Wittig product **68** in 69% yield (Table 4.2, entry 1). At elevated temperatures however the reaction proceeded via both [1,4] and [1,2]-pathways to give **68** and **69**. As was observed for model substrate **7**, the ratio of [1,4]/[1,2] products varied depending on the reaction temperature. In addition both **7** and **39** had comparable reaction rates (both reactions were done in about 30 minutes).

4.3.3. Effect of Electronics on the Wittig rearrangements of α-alkoxysilanes

4.3.3.1. Wittig rearrangement reaction of 41

Compound **41** is set up to undergo bond reorganization via the [1,2], [1,4], and [2,3] pathways as illustrated in Scheme 4.18. Theoretically, one would expect a mixture of some or all of the possible products.

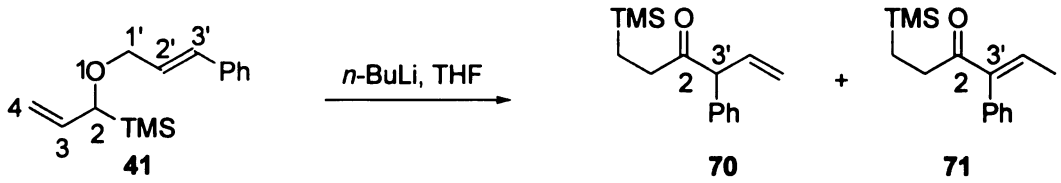
Scheme 4.18. Wittig rearrangement of **41**: expected [1,2], [1,4], and [2,3] products



Upon subjecting **41** to our standard Wittig conditions, it underwent facile bond reorganization. This resulted in an inseparable mixture of two products **70** and **71**

(Scheme 4.19). We observed however that the outcome of this reaction was dependent upon the temperature at which the reaction was carried out. Treatment of a solution of **41** in THF with 1.5 equiv of *n*-BuLi (1.6 M solution in hexanes) at room temperature resulted in a very fast reaction that was complete in approximately 5 min to afford **70** and **71** (> 1:10 ratio). At low temperatures (-78 °C), this reaction took 2.5 h to go to completion and gave the reverse outcome, affording the [2,3] product as the major product (**70/71** >10:1). Addition of base at -78 °C, and then allowing the reaction to warm to room temperature resulted in varying ratios of the products. Both **70** and **71** resulted from [2,3]-Wittig rearrangement of **41**. No [1,2] and [1,4] products were observed in this reaction.

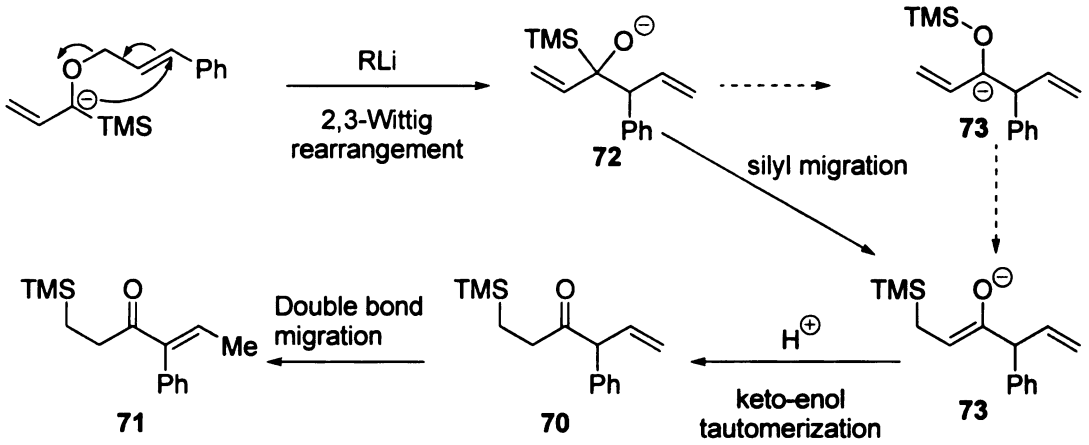
Scheme 4.19. Wittig rearrangement of **41** mediated by *n*-BuLi



We propose the mechanism in Scheme 4.20 to account for the products of this reaction. α-Deprotonation at low temperatures was followed by a facile [2,3] bond reorganization to give the [2,3] intermediate **72**, which was accompanied by silyl migration to give **73** (possibly via [1,2]-migration of the silyl moiety from carbon to oxygen). At low temperatures, the isomerization of **70** (the kinetic product) to **71** (the thermodynamic product) was slow, and quenching the reaction at this temperature afforded **70** as the major product. However, at elevated temperatures, bond isomerization

was facile, an event driven by conjugation with the aromatic ring (Scheme 4.20), resulting in **71** as the major product. These reactions were clean and the crude yield was quantitative, however, upon purification by silica gel, the yield dropped significantly (~51%), indicating sensitivity of the products to silica.

Scheme 4.20. Wittig rearrangement of **41**: A Putative Mechanism.

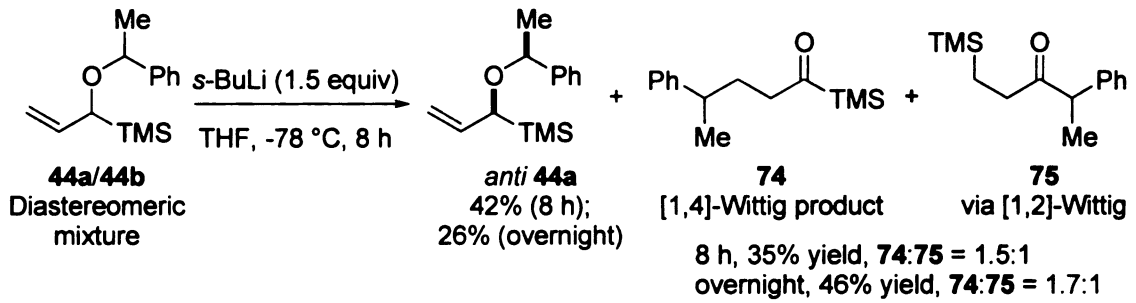


4.4. Wittig rearrangements of α-alkoxysilanes: Effect of substitution at the migrating carbon

Our study of steric effects on the Wittig rearrangements of α-alkoxysilanes started with diastereomeric α-(trimethylsilyl)allyl *sec*-phenethyl ethers **44a** and **44b**. These compounds were synthesized as a 1:1.13 (anti/syn) mixture of diastereomers in 79% yield from α-hydroxysilane **32** and the trichloroacetimidate of *sec*-phenethyl alcohol following our standard method. The pair of diastereomers were not separable by column chromatography, thus the product mixture was employed in the study. Though inconvenient, some of the proton signals were well resolved [δ (Me_3SiCH- 3.38-3.42, (td,

J = 6.8, 1.4 Hz, 1H); 3.77-3.81 (td, J = 5.5, 1.4 Hz, 1H) and $CH_2CHCHSiMe_3$ 4.90-5.00 (tq, J = 10.4, 7.9, 1.4 Hz, 2H); 5.02-5.09 (m, J = 3.5, 1.4 Hz, 2H)], thus, it was possible to monitor the rearrangement.

Scheme 4.21. Substitution at the migrating carbon: Wittig rearrangement of **44a/44b**



44a/44b Diastereomeric mixture

anti **44a** 42% (8 h); 26% (overnight)

74 [1,4]-Wittig product

75 via [1,2]-Wittig

8 h, 35% yield, **74**:**75** = 1.5:1
overnight, 46% yield, **74**:**75** = 1.7:1

When a cold (-78 °C) THF solution of **44a/44b** was treated with 1.5 equiv of *sec*-BuLi, the clear solution turned deep purple, and after eight hours we were surprised to find that one diastereomer was completely consumed, as evidenced by the disappearance of one set of ^{1}H NMR signals (δ 3.77-3.81 (td, J = 5.5, 1.4 Hz, 1H) and 4.90-5.0 (tq, J = 10.4, 7.9, 1.4 Hz, 2H)). Separation of the unreacted diastereomer from the Wittig products was trivial, and afforded the [1,2] and [1,4] products (**74** and **75**) in a ratio of 1:1.5, in a combined 35% yield, with 42% recovery of the unreacted 'less reactive' *anti* **44a** (Scheme 4.21) (details of determination of the relative stereochemistry of the reactive and less reactive diastereomers will be presented in Chapter 5). We observed that allowing the reaction to stir overnight resulted in increased yield (46%) as well as an increase in the [1,2]/[1,4] ratio from 1:1.5 to 1:1.7, with a corresponding decrease in the recovery of the unreacted diastereomer (26%). We were very surprised to observe the near complete erosion of the [1,4]-selectivity (> 100:1 in the **7**). Also, the introduction of

a substituent at the migrating carbon resulted in reduced reactivity, as evidenced by a longer reaction time (approximately 8 h; **7** reacted completely within 30 min.).

The observed variations in product yield and percent recovery of unreacted **44a** noted in the preceding paragraph could be due to one of two reasons: either that the other diastereomer reacted but very slowly (less reactive) or that it was undergoing some unproductive processes. To find out which, we carried out a qualitative NMR-tube experiment in which the pure unreactive **44a** diastereomer was subjected to our Wittig conditions and the reaction was monitored by ^{1}H NMR. Here we observed a slow decrease in the signal at (δ 3.38-3.42), but the reaction reached a point where no further decrease in starting material could be detected. Thus, diastereomer **44a** does undergo the Wittig rearrangement reaction under our conditions, albeit very sluggishly. This process offers a good route to kinetic separation of the pair of diastereomers (Scheme 4.21, after 8 h reaction time, 35% yield of product mixture and 42% of less reactive isomer recovered, compare with 46% yield of product mixture and 26% recovery of less reactive isomer after about 20 h).

Just as with our model substrate **7** (no substituent at the migrating carbon), we desired to establish the effect of silyl substituent on the Wittig rearrangement of a substrate bearing a substituent on the migrating carbon. Thus compound **45a** and **45b** were subjected to the Wittig conditions. The reactive diastereomer **45b** readily underwent Wittig rearrangement to afford **76** and **77** (Table 4.2, entry 5). Thus establishing one more time that substitution on silicon was no issue on these reactions.

4.4.1. Wittig rearrangements of 46 and 47: Electronic factor

The presence of a substituent capable of stabilizing a negative charge (e.g., *p*-NO_2) will lead to increased kinetic acidity of the benzylic proton, and its abstraction could become competitive with the tertiary α-proton. This situation might be unfavorable for the cleavage of the C-O bond. On the other hand, the presence of an electron-donating substituent (e.g., *p*-OMe) would attenuate the kinetic acidity of the benzylic proton, and hence forestall dianion formation. To investigate this hypothesis, substrates **46** (bearing an electron withdrawing *p*-NO_2 group) and **47** (bearing an electron donating *p*-OMe group) were designed (Figure 4.2). **47** was synthesized in 92% yield as a 3.25:1 (GC-FID) mixture of diastereomers. The minor product (reactive **47**) readily underwent the Wittig rearrangement to afford both [1,4] and [1,2] products **78** and **79** in 22% in approximately 1.8:1 ratio based on total starting mixture (93% based on amount of starting reactive isomer). On the other hand, the rearrangement of **46** was very sluggish at low temperatures (-78 °C) and gave a complex mixture of compounds.

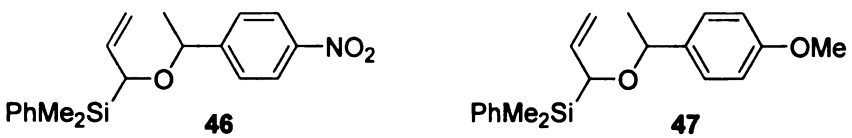


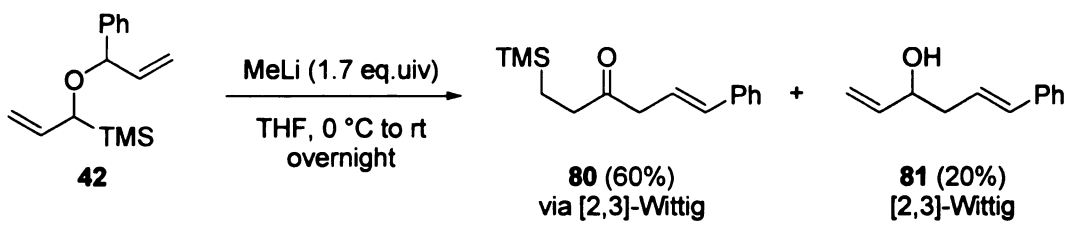
Figure 4.2. Substrates designed to study electronic effects on the Wittig rearrangement of α-alkoxysilanes

The facile rearrangement of **47** (*p*-MeO-C_6H_4-) and the sluggish rearrangement of **47** could be indicative of a developing negative charge at the migrating center, which would be highly stabilized in the case of **46**. To a first approximation, the feasibility of cleavage of the C—O bond would be expected to be less for a highly stabilized migrating group.

4.4.2. Wittig rearrangement of 42

Maleczka and Geng[20] reported that **42** readily underwent the Wittig rearrangement mediated by MeLi to afford the 2,3-rearrangement products selectively (Scheme 4.22). We decided to revisit the Wittig rearrangements of this substrate under our reaction conditions.

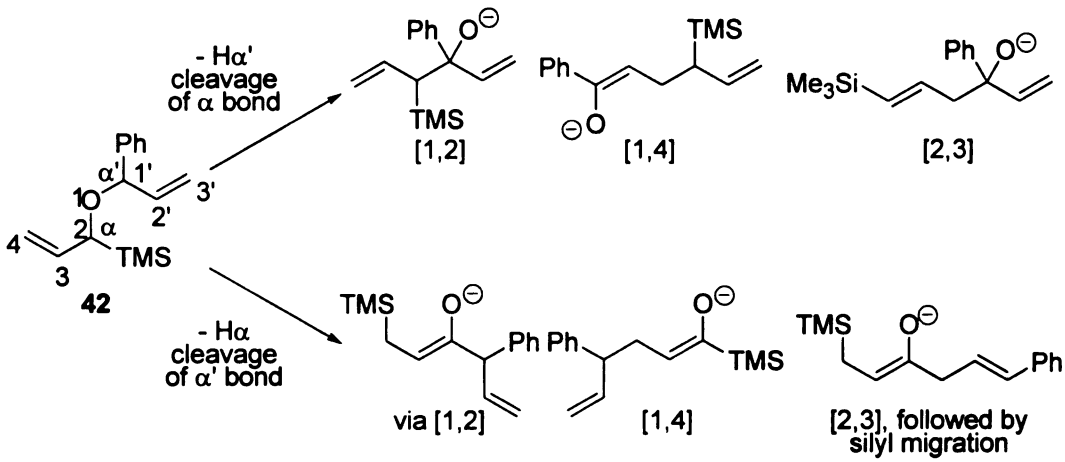
Scheme 4.22. MeLi-mediated Wittig rearrangement of **42** by Maleczka and Geng[1]



Compound **42** is an analog of **44**, with a vinyl group in place of a methyl group at the migrating carbon. Compound **42** did not undergo the Wittig rearrangement at low temperatures. Above -20 °C, the reaction required 4 equiv of *n*-BuLi and twelve hours for the complete consumption of the starting material. The reaction however afforded an intractable mixture of products. **42** has two acidic protons, thus, there arises the question of regioselective deprotonation. In the event that both protons (α and α′) were abstracted under the reaction condition, then one would expect each carbanion to react as an independent entity, resulting in a mixture of products (Scheme 4.23). However, in the event that α-deprotonation was favored over α′-deprotonation, it would result in a migrating carbon that is benzylic as well as allylic. Such a structure would be expected to lead to increased kinetic acidity of the benzylic/allylic proton and stability for a developing negative charge, a situation that would be expected to lead to a decrease in the migratory ability of the C–O bond. If this was indeed the case, then moving the double

bond further away from the migrating center would be expected to give a different outcome.

Scheme 4.23. Plausible pathways for the Wittig rearrangement of **42**



This was the case with substrate **48** (R = Et; synthesized in 64% yield as a 1:1.2 mixture of separable diastereomers) (Figure 4.5), which underwent facile Wittig rearrangement at low temperatures (-78 °C) to afford a mixture of both [1,4] and [1,2] rearranged products (**82** and **83**) in 47-63% yield and in the ratio of 1.5:1 to 1.8:1(Table 4.2, entry 7). Similarly, **49** (R = Et, R'_3Si = $PhMe_2Si$) (Figure 4.5) underwent the Wittig rearrangement to give **84** and **85** (Table 4.2, entry 7), illustrating that substitution on silicon is no issue in the Wittig rearrangement of our substrates. Under forcing (3.0 eq of *sec*-BuLi, THF, -78 °C to rt, 4 d), less reactive **48** underwent rearrangement to afford 14% of the rearranged products, with 43% recovery of the starting material.

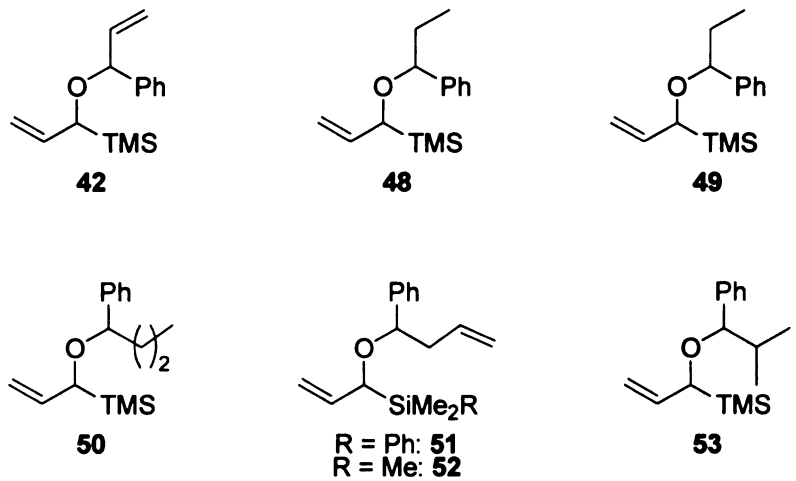


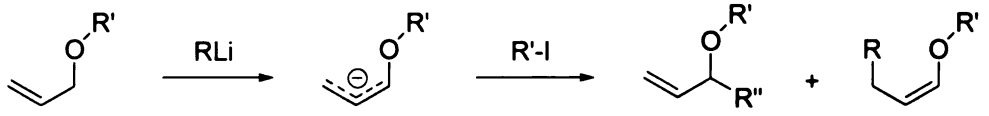
Figure 4.5. Wittig substrates bearing various substituents at the migrating carbon

To further investigate the effect of the proximity of olefin functionality to the migrating center, we studied the behaviors of substrates **50** and **52** (Figure 4.5) under our Wittig conditions. Both compounds underwent the Wittig rearrangement when treated with of *n*-BuLi in THF, to give the rearranged products, along with recovery of the unreactive diastereomers in each case. The Wittig rearrangement of **50** was facile, requiring only 1.5 equiv of base, and at -78 °C, goes to completion within 24 h to afford **86** and **87** (Table 4.2, entry 8). On the other hand, **52** required 4 equiv of base, elevated temperature conditions (-30 °C) and long reaction times (>24 h) to give **88** and **89** (Table 4.2, entry 9; 32% based on total 2.64:1 (unreactive *anti*/reactive *syn*) mixture of starting material). However, at room temperature, **52** underwent complete rearrangement in less than ten hours to afford the [1,2] and [1,4] products. The lower reactivity of **52** could be the result of the migrating carbon being benzylic and homoallylic, situations that would stabilize developing negative charge as well or a radical species.

Replacing the *n*-propyl group in substrate **50** with an isopropyl group in **53** (Figure 4.5) had a marked effect on reactivity. Compound **53** did not rearrangement at

low temperatures. However, at elevated temperatures (above -20 °C), the compound underwent the Wittig rearrangement to afford the [1,2] and [1,4] products **90** and **91** in 23% yield and 1.8:1 ratio (Table 4.2, entry 10).

Scheme 4.24. Wittig rearrangement of metalated allyl alkyl ether by Schlosser and Strunk[21]



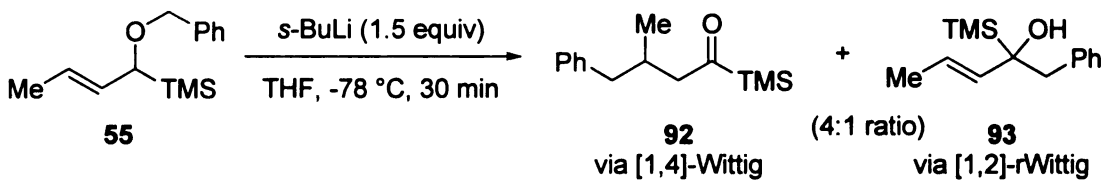
OR' = OC_4H_9, $OCH_2CH_2CH(CH_3)$ (23:77); OC_9H_{19}, OCH_2cPr (75:25); $OCH(C_2H_5)_2$ (50:50); $OC(CH_3)_3$ (70:30); yields = 73-85

So far we had shown that substitution at the migrating carbon of the α-alkoxysilanes resulted in erosion of the [1,4]/[1,2] selectivity. The loss of selectivity in the Wittig rearrangement of allyl ethers on placement of substitution at the migrating carbon is precedented. Schlosser and Strunk[21] reported the loss of regioisomeric purity in the Wittig rearrangement of metalated allyl alkyl ethers upon substitution at the migrating carbon. They observed that in the presence of potassium *tert*-butoxide, their substrates afforded [1,4] and [1,2] products in an approximate ratio of 9:1 (90% regioisomeric purity) (Scheme 4.24), but only when a resonance inactive primary alkyl group (such as butyl, 3-methylbutyl or nonyl) was allowed to migrate. They reported that the migration of secondary or tertiary alkyl groups (1-ethylpropyl, *tert*-butyl) or even the cyclopropylmethyl moiety led to 2:3 or 1:1 mixtures of 1-alken-3-olates and enolates. Thus our results were consistent with those of Schlesser and Strunk.[21]

4.5. Wittig rearrangement reaction of α-alkoxysilanes: Effect of substitution at the terminal sp^2 carbon of the allyl moiety

Next, we studied the effect of a substituent at the terminal sp^2 carbon of the allyl moiety. Here we studied α-alkoxysilane **55**, which was prepared following our general protocol from α-hydroxysilane **34** and the trichloroacetimidate of benzyl alcohol in 36% yield.

Scheme 4.25. Substitution at the terminal sp^2 carbon: Wittig rearrangement reaction of **55**

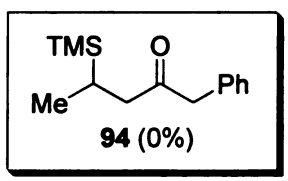


55

92 via [1,4]-Wittig

(4:1 ratio)

93 via [1,2]-rWittig



94 (0%)

When subjected to our Wittig conditions (1.5 equiv *s*-BuLi, THF, -78 °C, 40 min), **55** afforded a 4:1 ratio of two new compounds **92** and **93**, resulting from [1,4]- and [1,2]-Wittig respectively, with a combined yield of 74% (Scheme 4.25). The observed (4:1) ratio shows an erosion of the [1,4]/[1,2] selectivity. We also observed that reaction time is significantly less than for **44a** (40 min vs. 8 h). This decreased rate of reaction with substitution at the migrating carbon could be attributed to sterics (secondary vs. tertiary carbon). With **55** (featuring a substitution at the terminal sp^2 carbon of the allyl moiety), we did not observe the silyl migration that usually accompanies the [1,2]-Wittig of α-alkoxysilanes bearing no such substituent (Scheme 4.25, compound **94**).

From these data, we can conclude that substitution at the migrating center as well as the terminal sp^2 carbon of the allyl moiety significantly impacts the [1,4]-Wittig rearrangement of α-alkoxysilanes but to different degrees. Our results seem to be in disagreement with the literature report that [1,4]-alkyl shift is insensitive to the substitution pattern in the allylic moiety of the ethers.[22]

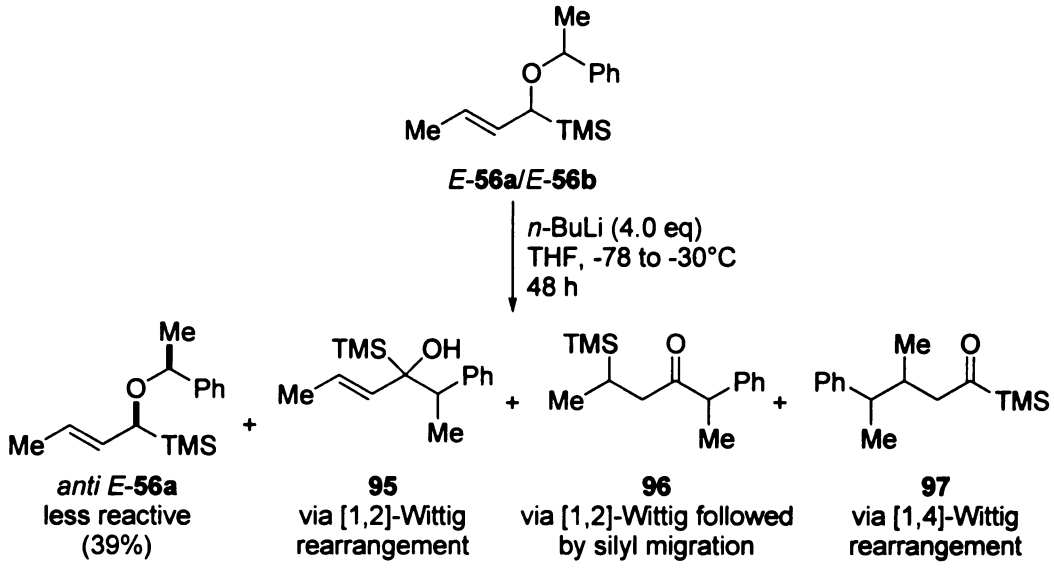
4.6. Wittig rearrangement of α-alkoxysilanes: Substitution at both the migrating carbon and the terminal sp^2 carbon of the allyl moiety.

An appropriate question at this point became, "What would be the effect of substitution at both the migrating center and the terminal sp^2 carbon of the allyl moiety?" To answer this question, α-alkoxysilanes *E*-**56a** and *E*-**56b** were prepared from α-hydroxysilane **34** and the trichloroacetimidate of *sec*-phenethyl alcohol following our general protocol. Here though TMSOTf catalysis did not work well for this system, giving less than 10% yield of the desired compound, $BF_3 \bullet OEt_2$ proved to be a better Lewis acid in this case and employing 0.15 equiv of this catalyst afforded the desired compound as a 1:1.7 (*anti E*-**56a**/*syn E*-**56b**) pair of diastereomers in a combined 49% yield. We studied the rearrangement of *E*-**56a** and *E*-**56b** (Scheme 4.26) under various reaction conditions of temperature and base equivalents.

In theory, six compounds (three pairs of diastereomers) are expected from this reaction, a pair of diastereomeric [1,4]-products, a pair of [1,2]-products, and a pair of [1,2]-silyl migration products. On carrying out this reaction, it was found that this substrate reacted sluggishly, requiring up to 4.0 equiv of *n*-BuLi base, elevated

temperature (-30 °C), and up to 48 h reaction time. As before only one diastereomer underwent the Wittig rearrangement and 39% of the less reactive isomer was recovered. All six expected compounds were formed making the product isolation very tedious. The mixture of products **95**, **96** and **97** were obtained in a combined 35-57% yield (Scheme 4.26). We were nevertheless able to obtain analytically pure samples of the products by silica gel chromatography, followed by preparatory HPLC. It was not possible to obtain the ratios of products from either ^{1}HNMR or HPLC, as the spectrum and chromatogram were too complex to allow for accurate measurements.

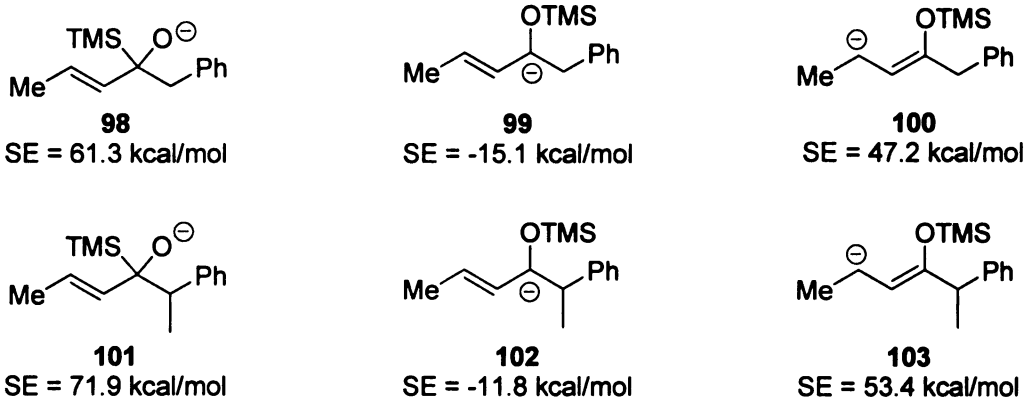
Scheme 4.26. Substitution at both the migrating center and the terminal sp^2 carbon



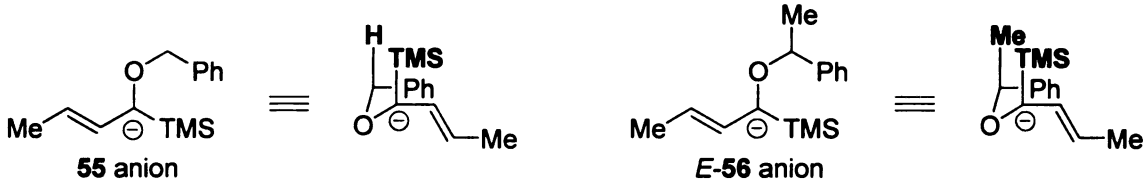
The isolation of [1,2]-Wittig/silyl migration products **96** from the reaction of *E*-**56** contrasted our earlier observation with **55**, where no migration product was observed (Scheme 4.25). We sought an explanation to these conflicting results and considered the stability of the retro-Brook intermediate. Ab initio calculations (Geometry Optimization

using RHF/6-31G* model)[23] employing two models, molecular mechanics and density functional, reveal that the Brook rearrangement of both **55** and *E*-**56** have the same energy requirement. However, the retro-Brook intermediate **100** from α-alkoxysilane **55** was lower in energy (6 kcal/mol) than the retro-Brook intermediate **103** from α-alkoxysilane *E*-**56** (Scheme 4.27). This could explain in part the absence of silyl migration event accompanying the [1,2]-Wittig of **55** (Scheme 4.25). One could also argue steric difference in the pre-Brook intermediates from α-alkoxysilanes **55** and *E*-**56** (Scheme 4.28, structures **98** and **101**) was responsible for this distinction. Sterics at the two adjacent stereogenic centers might provide enough driving force for the silyl migration in the 'presumed' intermediate for *E*-**56**.

Scheme 4.27. Energy calculations for pre-Brook, Brook and retro-Brook for **55** and *E*-**56**

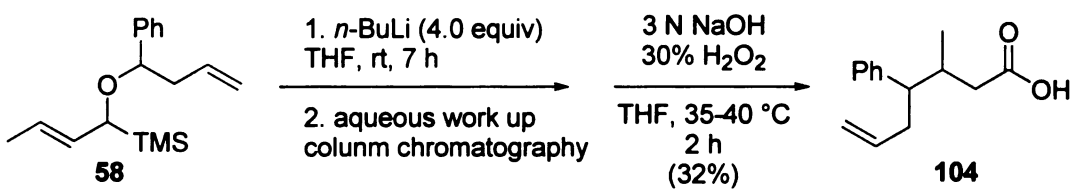


Scheme 4.28. Sterics in the 'intermediate' structures for **55** and *E*-**56**



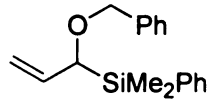
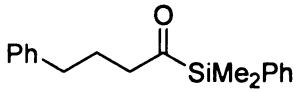
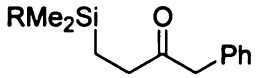
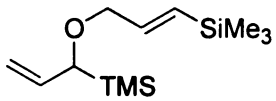
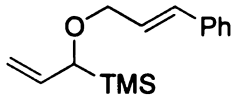
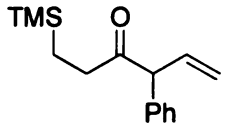
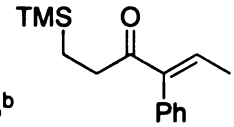
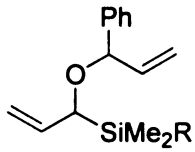
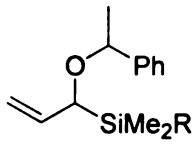
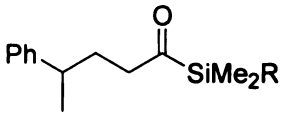
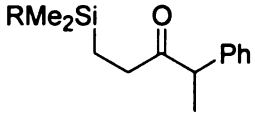
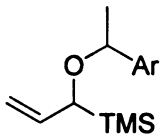
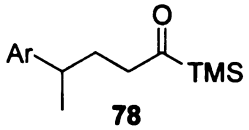
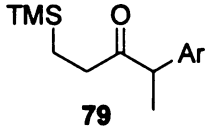
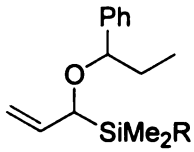
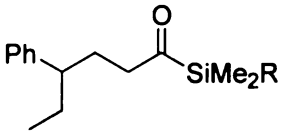
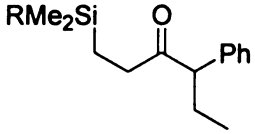
Compound **58** required 4.0 eq. of *n*-BuLi, room temperature and a 7 h reaction time to undergo the Wittig rearrangement. Like the substrates bearing a substituent at the migrating carbon, only one diastereomer reacted to afford a complex mixture of products, which except for the unreacted starting material proved very difficult to separate. Thus, following the Wittig rearrangement reaction, aqueous workup, and column chromatography on silica gel, the products were collected as a mixture. Since our main interest was in the [1,4]-products, we decided to subject the mixture of products to oxidation condition (3 N NaOH, 30% H_2O_2, THF, 35 to 40 °C, 2 h) (Scheme 4.29).

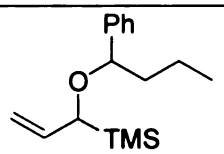
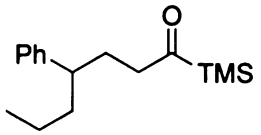
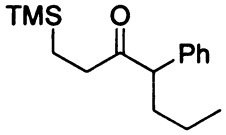
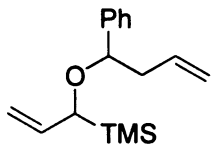
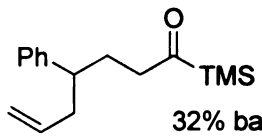
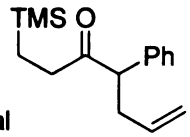
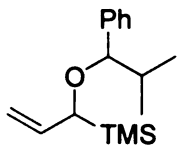
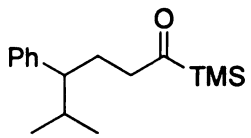
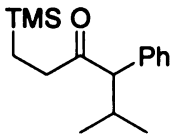
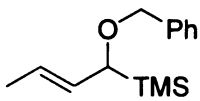
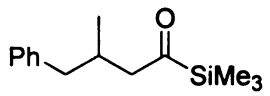
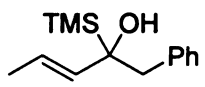
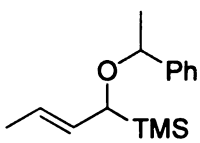
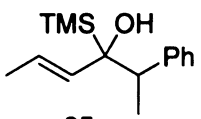
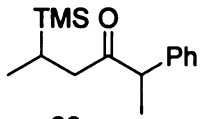
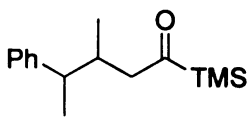
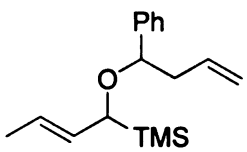
Scheme 4.29. Wittig rearrangement of compound **58**/oxidation of [1,4] product



We observed that the yield of the carboxylic acid products **104** was low (32%). It is pertinent to mention here that the low yield of **104** was due to loss of material during work up and isolation, and is not inherent to the reaction. We also observed that the mixture of compounds isolated from the organic phase was intractable and upon column chromatography, the alcohol **34** was isolated. From our results, it was obvious that the olefin functionality in all the products was being oxidized. The summary of the Wittig rearrangements of all the substrates is given in Table 4.2.

Table 4.2. Wittig rearrangements of all substrates[a]

Entry	Wittig substrate	Wittig products
1	 **39**	 **68** (69%)  product not observed at low temperatures
2	 **40**	Reaction very sluggigh and was not investigated further. However, the substrate was employed in mechanistic experiments.
3	 **41**	 **70** 51%[b] (10:1 at -78 °C) (1:10 at 20 °C)  **71**
4	 **42**	Reaction gave a complex mixture of products
5	 **44**: R=Me **45**: R=Ph	 **74** R=Me: 35 - 42% (1:1.5 to 1>7) **75** **76** R=Ph: 58.24% **77** 
6	 **46**: Ar=*p*-$NO_2C_6H_4$ **47**: Ar=*p*-$MeOC_6H_4$	 **78**  **79** **46**: reaction sluggish; no products isolated. **47**: 22% based on 3.25:1 mixture of diastereomers, 92% based on the reactive **47**
7	 **48**: R=Me **49**: R=Ph	 **82** R=Me: 35 - 42% (1:1.5 to 1>7) **83** **84** R=Ph: 58.24% **85** 

Entry	Wittig substrate	Wittig products
8	 **50**	 **86** 35 to 41% (~1.7:1)  **87**
9	 **52**	 **88** 32% based on total 2.64:1 (less reavtive/reactive) mixture of starting materal  **89**
10	 **53**	 **90** 23% (1.8:1)  **91**
11	 **55**	 **92** 74% yield (4:1)  **93**
12	 *E*-**56**	 **95**  **96** **97** (syn/anti 1:3)  35-57% combined yield
13	 **58**	The products of this reaction were not isolated. The crude reaction mixture was oxidized (3N NaOH/30% H_2O_2) and the carboxylic acids resulting from the [1,4]-Wittig products isolated.

(a) All reactions were carried out in THF employing *s*-BuLi or *n*-BuLi (1.5 to 4.0 equiv depending on the substrate). Reaction temperature also depended on the substrate (see experimental). (b) Reaction was clean and crude yield was quantitative. However, when the compound was put on silica gel, yield decreased to 51%.

4.7. Conclusions

Substitution at the terminal sp^2 carbon of the allyl moiety (**55**) does not seem to have a significant effect on the rate of the reaction; rearrangement is complete in 40 min. Nevertheless, selectivity is drastically eroded, with a mixture of both [1,4]- and [1,2]-Wittig products obtained in approximately 4:1 ratio (74% yield). We observed that with this substrate, the subsequent silyl migration that usually accompanies the [1,2]-rearrangement of our model substrate **7** does not occur, and a tertiary alcohol [1,2]-rearrangement product is obtained (Schemes 4.25).

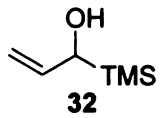
Introducing sterics at the migrating carbon (**44**) seems to have a far more reaching effect. We observed a longer reaction time (5-8 h), and erosion of [1,4]/[1,2] selectivity in favor of [1,2]- rearrangement ([1,4]/[1,2] = 1.7:1). With substitution at both the migrating and terminal sp^2 carbons (*E*-**56**), Wittig rearrangement becomes sluggish, and requires more forcing conditions (4.0 equiv of base, -30 °C, 24 h or more), and only one diastereomer rearranges to afford a mixture of six compounds (three pairs of diastereomers). As is observed with substitution at the migrating carbon, there is serious erosion of [1,4]/[1,2] regioselectivity (approx. 3:1), accompanied by a significant drop in yield. All the possible products were observed and isolated, amongst them the product resulting from [1,2]-rearrangement/silyl migration events.

The size and nature of substituent at the migrating carbon are factors to reckon with. The larger the group, the more difficult the reaction. Groups capable of stabilizing a developing negative charge at the migrating carbon are not favorable since they tend to retard the reaction. Radical stabilizing groups at the migrating carbon center, and or at the terminal sp^2 carbon of the allyl moiety promote [1,2]-Wittig.

Having established the existence of differential reactivities between a pair of diastereomeric α-alkoxysilane (relative stereochemistry (*anti*) and (*syn*))under our Wittig conditions, we wanted to determine which of the two diastereomers was undergoing the Wittig rearrangement. The issue of stereochemistry of the Wittig substrates will be dealt with in Chapter 5 of this dissertation.

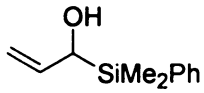
EXPERIMENTAL

Preparation of α-(trimethylsilyl)allyl alcohols: [Danheiser, R. L.; Fink, D. M.; Okano, K.; Tsai, Y-M.; Szczepanski, S. W. *J. Org. Chem.* **1985**, *50*, 5393-5396.]



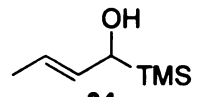
32

Preparation of 32: **Representative Procedure A**. To a cold (-78 °C), stirred solution of allyl alcohol (1.0 eq, 8.2 g, 141.18 mmol) in THF (350 mL) was added dropwise via cannula *n*-BuLi (1.6 M in hexanes, 1.08 eq, 95.3 mL, 152.48 mmol). Upon complete addition of base the reaction mixture was stirred for 1 h. Then, TMSCl (freshly distilled over CaH, 1.0 eq, 15.34 g, 141.34 mmol, 17.92 mL) was added dropwise via syringe. Following this addition, reaction was stirred further for 1.5 h, and then *t*-BuLi (1.7 M in hexanes, 1.2 equiv, 99.66 mL, 169.42 mmol) was added dropwise via cannula. After stirring for an additional 1.5 h, reaction was quenched by addition of sat. aq. NH_4Cl, and diluted with ether. Phases were separated, and the aqueous phase extracted with ether (150 mL x 3). Combined organic phases were washed with H_2O, and brine, and dried over anhydrous Na_2SO_4. Distillation at atmospheric pressure afforded 17.05 g (93%) of alcohol **32**. Compound data match literature report.[5] IR (neat) 3430, 2959, 1634, 1250 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.06-5.95 (m, 1H), 5.08-5.01 (apparent dt, J = 17.0, 2.2, 1.6 Hz, 1H), 4.99-4.94 (apparent dt, J = 11.0, 2.2, 1.6 Hz, 1H), 3.97-4.01 (dt, J = 5.5, 2.2, 1.6 Hz, 1H), 0.029 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7, 109.2, 68.9, -4.2. **32** is a known compound and has spectral data in accord with the reported ones.[5,10,24]



33

Preparation of 33: Applying the Representative Procedure **A** for **32** to allyl alcohol (10.0 g, 11.7 mL, 138.7 mmol), *n*-BuLi (1.6 M in hexanes, 146.3 mmol, 91.44 mL), chlorodimethylphenylsilane $PhMe_2SiCl$ (15.85 g, 145.8 mmol, 18.51 mL) and *t*-BuLi (1.7 M in pentane, 166.4 mmol, 97.89 mL) afforded 10.50 g (53%) of **33**. IR (neat) 2959, 1642, 1493, 1452,1248, 1078, 1053 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.58-7.55 (m, 2H), 7.39-7.34 (m, 3H), 6.04-5.93 (m, 1H), 5.09-5.27 (d, J = 17.8, 1H), 5.01-4.97 (d, J = 10.7 Hz, 1H), 4.23-4.20 (dt, J = 5.2 H, 1H), 0.35 (s, 3H), 0.33 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2, 135.9, 134.1, 129.4, 127.7, 110.0, 68.4, -5.6, -5.9. **32** is a known compound and has spectral data in accord with the reported ones.[25,26]



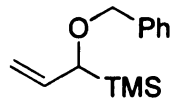
34

Preparation of 34: Applying the Representative Procedure **A** to *trans*-crotyl alcohol (10.0 g, 138.7 mmol), *n*-BuLi (1.6 M in hexanes, 146.3 mmol, 91.44 mL), TMSCl (15.85 g, 145.8 mmol, 18.51 mL) and *t*-BuLi (1.7 M in pentane, 166.4 mmol, 97.89 mL) afforded 10.50 g (53%) of **34**. IR (neat) 3395, 2959, 2856, 1452, 1248 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 5.61-5.43 (m, 2H), 3.87 (m, 1H), 1.70-1.68 (dt, J = 6.3, 1.5 Hz, 3H), 0.01 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 132.3, 122.3, 68.5, 17.9, -4.2. **32** is a known compound and has spectral data in accord with the reported ones.[27]

Preparation of trichloroacetimidates: General Procedure **B**. [Wessel, H-P.; Iversen, T.; Bundle, D. R. J. *Chem. Soc. Perkin Trans.I* 1985, 2247-2250.] NaH (60% dispersion in oil, 0.105 eq) was suspended in anhydrous ether, and a solution of the appropriate alcohol (1.0 eq) in ether added dropwise with stirring. The reaction mixture was stirred for 20 to 30 min, and then cooled to 0 °C with a salt-ice bath. Trichloroacetonitrile (1.0 equiv) was added dropwise during 15 min and reaction mixture allowed to warm to 20 °C over 60 min, then concentrated to a syrup using rotary evaporator. A solution of anhydrous methanol (0.105 eq) in pentane (1.05 M) was then added to the syrup and the mixture shaken vigorously, filtered and the filtrate concentrated to afford the crude product which was used without further purification. Yields are generally in the range 73-100%. The trichloroacetimidates were usually stored as a solution in hexane in the freezer.

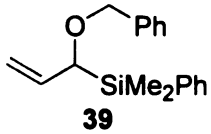
Preparation of α-alkoxysilanes: General procedure **C**. Trichloroacetimidate of the appropriate alcohol (prepared according to literature procedure)[11] (2.0 eq) was added to a stirred solution of the requisite α-(trimethylsilyl)allyl alcohol (1.0 equiv) in cyclohexane (0.2 M) at room temperature. A TMSOTf (0.055 equiv) solution in cyclohexane (usually 0.1 mL/1.0 mL cyclohexane) was then added. White precipitate formed upon addition of the Lewis acid. The reaction mixture was stirred at room temperature overnight and filtered. The precipitate was then washed with pentane or hexane (precipitate is soluble in ether) and the filtrate diluted with ether. The diluted filtrate was subsequently washed with $NaHCO_3$ (sat. aq.) (x 2), 1N HCl (x 2), and lastly with brine (x 2). The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated to furnish the crude product. Purification by column chromatography on

silica gel (0-2% EtOAc in hexane gradient) afforded the pure product. Note: for the synthesis of the model substrate **7** and **39**, the products were always accompanied by an ester byproduct, which was removed by base hydrolysis (usually stirring with 2 M NaOH at room temperature for about 2 h).



7

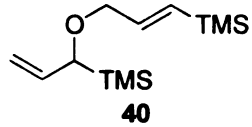
Preparation of 7: Applying general procedure **C** to 1.32 g (10.13 mmol) of α-hydroxysilane **32**, 4.85 g (19.20 mmol) of the trichloroacetimidate of benzyl alcohol (prepared following General procedure **B**)[11] and 0.12 g (0.55 mmol, 0.10 mL) of TMSOTf afforded 1.23 g (5.59 mmol), 56% of pure **7** as a colorless oil: IR (neat) 2959, 1454, 1383, 1248 cm^{-1}, ^1H NMR (300 MHz, $CDCl_3$) δ 7.24-7.37 (m, 5H), 5.77-5.89 (m, 1H), 5.04-5.00 (dt, J = 9.3, 1.6 Hz, 2H),4.97 (m, 1H), 4.68-4.73 (d, J = 12.4 Hz, 1H), 4.30-4.34 (d, J = 12.4 Hz, 1H), 3.60-3.64 (dt, J = 7.1, 1.4 Hz, 1H), 0.02 (s, 9H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 139.1, 137.2, 128.1, 127.5, 127.1, 112.5, 75.9, 71.8, -3.8. 7 is a known compound and have spectral data in accord with the reported ones. **7** is a known compound and has spectral data in accord with the reported ones.[20]



39

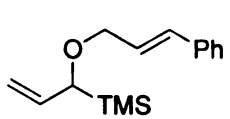
Preparation of 39: Applying general procedure **C** to 0.24 g (2.33 mmol) of α-hydroxysilane **33**, 1.17 g (4.65 mmol) of the trichloroacetimidate of benzyl alcohol (prepared following General procedure **B**)[11] and 0.03 g (0.13 mmol, 0.02 mL) of TMSOTf overnight, afforded 0.23 g (35%) of the **39**. IR (neat) 2959, 1628, 1496, 1454,

1248 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.55-7.21 (m, 10H), 5.84-5.72 (m, 1H), 5.10-5.06 (apparent dt, J = 8.2, 7.7, 1.6 Hz, 1H), 5.04 (d, J = 1.4 Hz, 1H), 4.70-4.66 (d, 1H, J = 12.1 Hz, 1H), 4.32-4.27 (d, J = 12.1 Hz, 1H), 3.84-3.81 (apparent dt, J = 7.1, 1.6, 1.1 Hz, 1H), 0.31 (s, 3H), 0.28 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 136.7, 136.6, 134.2, 129.1, 128.0, 127.5, 127.5, 127.1, 113.1, 75.4, 71.9, -5.3, -5.6. HRMS (EI) *m/z* 282.1433 [$(M-H)^+$; calcd for $C_{18}H_{22}OSi$, 282.1440].

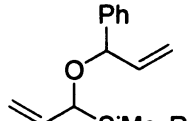


40

Preparation of 40: Applying general procedure **C** to 0.78 g (6.03 mmol) of α-hydroxysilane **32**, 2.0 g (7.24 mmol) of the trichloroacetimidate of trimethylsilylallyl alcohol (prepared following General procedure **B**)[11] and 0.05 g (0.36 mmol, 0.05 mL) of BF_3•OEt_2 afforded 0.77 g (52%) of pure **40** as a colorless oil. IR (neat) 2957, 1624, 1248 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.07-5.98 (dt, J = 18.7, 4.9 Hz, 1H), 5.87-5.70 (m, 2H), 5.05-4.96 (m, 2H), 4.18-4.11 (ddd, J = 13.7, 4.1, 1.6 Hz, 1H), 3.82-3.75 (apparent dd, J = 11.4, 7.1, 5.2 Hz, 1H), 3.59-3.56 (dt, J = 6.9, 1.4 Hz, 1H), 0.04 (s, 9H), 0.01 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4, 137.5, 130.9, 112.1, 76.3, 73.3, 1.31, -3.9. HRMS (EI) *m/z* 242.1515 [(M);calcd for $C_{12}H_{26}OSi_2$, 242.1522].



41



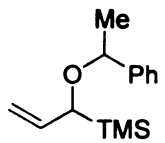
42

Preparation of 41 and 42: Applying general procedure **C** to 2.53 g (19.42 mmol) of α-hydroxysilane **32**, 10.82 g (38.84 mmol) of the trichloroacetimidate of cinnamyl alcohol (prepared following General procedure **B**)[11] and 0.24 g (0.19 mL, 1.07 mmol) of

TMSOTf overnight gave a near 1:1 mixture of **41** and **42** which was readily separable by column chromatography on silica gel to afford 1.14 g (24%) of **41** and 1.07 g (22%) of a 1:1 diastereomeric pair of **42** as clear oils.

41: IR (neat) 2957, 1628, 1495, 1248 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.41-7.21 (m, 5H), 6.61-6.55 (d, J = 15.9 Hz, 1H), 6.31-6.22 (m, 1H), 5.89-5.77 (m, 1H), 5.13-5.05 (t, J = 14.3, 9.3 Hz, 2H), 4.36-4.30 (dd, J = 13.2, 4.9 Hz, 1H), 4.02-3.96 (dd, J = 12.6, 6.6, 6.0 Hz, 1H), 3.72-3.69 (d, J = 6.6 Hz, 1H), 0.07 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.4, 137.0, 131.6, 128.5, 127.4, 127.2, 126.4, 112.3, 76.0, 70.8, -4.0. HRMS (APCI) *m/z* 247.1516 [$(M+H)^+$; calcd for $C_{15}H_{23}OSi$, 247.1518].

42: IR (neat) 2959, 1628, 1495, 1452, 1248 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.20 (m, 5H), 5.84-5.66 (m, 2H), 5.30-5.22 (m, 2H), 5.07-4.98 (m, 2H), 4.85-4.82 (d, J = 8.2 Hz, 1H), 3.93-3.90 (dt, J = 7.1, 6.6, 1.6 Hz, 1H), 0.07 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 139.1, 137.3, 128.1, 127.0, 126.3, 117.3, 112.4, 80.81, 72.9, -3.9. HRMS (APCI) *m/z* 247.1522 [$(M+H)^+$; calcd for $C_{15}H_{23}OSi$, 247.1518].

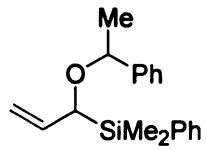


44

Preparation of 44: Applying general procedure **C** to 4.01 g (30.82 mmol) of α-hydroxysilane **32**, 15.61 g (58.57 mmol) of the trichloroacetimidate of *sec*-phenethyl alcohol (prepared following General procedure **B**)[11] and stirring the reaction overnight afforded and 0.38 g (1.70 mmol) of TMSOTf, afforded 5.7 g (79%) of pure 1:1 diastereomeric pair of **44** as clear oils. IR (neat) 2972, 2928, 2899, 1628, 1493, 1452, 1248 cm^{-1}.

Mixture of *syn/anti* **44a/44b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ7.36-7.10 (m, 10H), 5.83-5.68 (m, 2H), 5.06-4.87 (m, 4H), 4.56-4.46 (m, 2H), 3.82-3.80 (dt, *J* = 6.9, 1.4 Hz, 1H), 3.43-3.41 (dt, J = 6.9, 1.4 Hz, 1H), 1.40-1.32 (dd, 6H), 0.06 (s, 9H), 0.02 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3, 144.2, 137.6, 128.4, 128.0, 127.9, 127.1, 126.7, 126.6, 125.8, 112.1, 111.7, 76.0, 75.6, 74.1, 73.2, 24.8, 22.3, -3.7, -3.8. HRMS (EI) *m/z* 234.1434 [(M); calcd for $C_{14}H_{22}OSi$, 234.1440].

Less reactive *anti*- **44a**: ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.35-7.21 (m, 5H), 5.82-5.70 (m, 1H), 5.05-4.95 (m, 2H), 4.56-4.49 (q, *J* = 6.6, 6.2 Hz, 1H), 3.43-3.40 (dt, *J* = 7.1, 1.3 Hz, 1H), 1.39-1.37 (d, *J* = 6.6 Hz, 3H), -0.001 (s, 9H). ^{13}C NMR (125 MHz, CDCl3) δ 144.4, 137.8, 128.2, 127.2, 126.8, 112.2, 75.7, 73.3, 24.6, -3.9. HRMS (EI) *m/z* 234.1428 [(M); calcd for $C_{14}H_{22}OSi$, 234.1440].

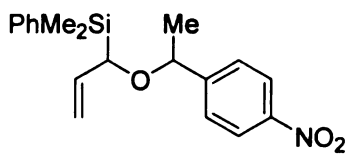


45

Preparation of 45: Applying general procedure **C** to 0.37 g (1.91 mmol) of α-hydroxysilane **33**, 1.02 g (3.83 mmol) of the trichloroacetimidate of (*S*)-*sec*-phenethyl alcohol (prepared following General procedure **B**)[11] and 0.02 g (0.02 mL, 0.105 mmol) of TMSOTf overnight afforded 0.40 g (21%) of a 1.45:1 mixture of **45** as clear oils. IR (neat) 2972, 2928, 1628, 1452, 1248 cm^{-1}; Mixture of *syn/anti* **45a/45b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61-7.06 (m, 20H), 5.77-5.63 (m, 2H), 5.05-5.45 (m, 4H), 4.55-4.48 (q, *J* = 6.6, 6.3 Hz, 1H), 4.45-4.38 (q, *J* = 6.3 Hz, 1H), 4.00-3.97 (dt, *J* = 6.6, 1.4 Hz, 1H), 3.62-3.59 (dt, *J* = 6.9, 1.4 Hz, 1H), 1.37-1.34 (d, *J* = 6.6 Hz, 3H), 1.28-1.26 (d, *J* = 6.3 Hz, 3H), 0.35 (s, 3H), 0.31 (s, 3H), 0.27 (s, 3H), 0.24 (s, 3H). ^{13}C NMR (125 MHz,

$CDCl_3$) δ 145.2, 144.0, 137.2, 136.9, 134.3, 134.2, 129.1, 129.0, 128.1, 128.0, 127.6, 127.5, 127.1, 126.7, 125.9, 112.8, 112.3, 76.2, 75.6, 73.7, 73.7, 72.7, 24.6, 22.3, -5.4, -5.4, -5.6, -5.9.

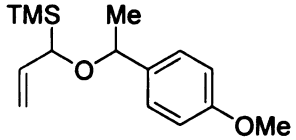
Less reactive *anti*-**45a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49-7.06 (m, 10H), 5.77-5.65 (m, 1H), 5.03-4.93 (m, 2H), 4.55-4.48 (q, J = 6.6, 6.3 Hz, 1H), 3.62-3.58 (dt, J = 6.9, 1.4 Hz, 1H), 1.35 (d, J = 6.6 Hz, 3H), 0.27 (s, 3H), 0.23 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.9, 137.2, 134.3, 128.9, 128.0, 127.5, 127.4, 127.0, 126.7, 112.8, 75.7, 72.8, 24.7, -5.3, -5.8.



46

Preparation of 46: The trichloroacetimidate of *p*-nitrophenethyl alcohol was prepared from 1.2 g (7.17 mmol) of *p*-nitrophenethyl alcohol, 0.03 g (0.72 mmol) NaH 0.98 g (6.81 mmol) of trichloroacetonitrile, 0.02 g (0.72 mmol) anhydrous methanol prepared following general procedure **B**.[11] Applying general procedure **C** to 0.69 g (3.59 mmol) of α-hydroxysilane **33**, the in situ generated trichloroacetimidate, and 0.08 g (0.36 mmol, 0.07 mL) of TMSOTf and stirring the reaction overnight afforded **46** as a 1:1 mixture of diastereomers which were obtained in a combined 0.43 g (36%) yield as colorless oils after purification by column chromatography on silica gel. IR (neat) 2975, 1628, 1607, 1523, 1427, 1348, 1248 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19-8.16 (d, J = 8.8 Hz, 2H), 8.15-8.12 (d, J = 8.8 Hz, 2H), 8.01-7.98 (d, J = 8.8 Hz, 2H), 7.59-7.33 (m, 10H), 7.13-7.10 (d, J = 8.8 Hz, 2H), 5.80-5.60 (m, 2H), 5.08-4.87 (m, 4H), 4.63-4.57 (q, J = 6.6, 6.3 H, 1H), 4.53-4.47 (q, J = 6.6, 6.3 Hz, 1H), 4.0-3.98 (d, J = 6.8 H, 1H), 3.51-

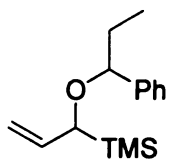
3.49 (d, J = 6.8 Hz, 1H), 1.34 (d, J = 6.6 H, 3H), 1.27 (d, J = 6.3 Hz, 3H), 0.36 (s, 3H), 0.33 (s, 3H), 0.31 (s, 3H), 0.24 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 151.8, 147.0, 146.8, 136.7, 136.6, 136.5, 136.4, 134.3, 134.2, 129.3, 127.64, 127.62, 127.2, 126.7, 126.5, 123.5, 123.4, 123.3, 113.4, 112.9, 75.4, 75.1, 74.4, 73.9, 24.5, 22.1, -5.4, -5.5, -5.8, -6.6. Calculated for HRMS (FAB+) *m/z* 341.1445 [$(M)^+$; calcd for $C_{19}H_{23}NO_3Si$, 341.1447].



47

Preparation of 47: The trichloroacetimidate of *p*-methoxyphenethyl alcohol was prepared from 2.00 g (13.14 mmol) of *p*-methoxyphenethyl alcohol, 0.06 g (1.38 mmol) NaH, 1.90 g (13.14 mmol) of trichloroacetonitrile, and 0.04 g (1.38 mmol) anhydrous methanol prepared following General procedure **B**.[11] Then applying general procedure **C** to 0.85 g (6.52 mmol) of α-hydroxysilane **32**, the in situ generated trichloroacetimidate, and 0.087 g (0.07 ml, 0.39 mmol) of TMSOTf, afforded **47** as a 3.25:1 mixture of *anti/syn* diastereomers which, after silica gel chromatography (0-2% EtOAc gradient in hexanes), was obtained in a combined 1.59 g (92%) yield as colorless oils. IR (neat) 2972, 1612, 1512, 1466, 1442, 1248 cm^{-1}. Reactive*syn* **47**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.23 (d J = 8.8 Hz, 2H), 6.84-6.82 (d, J = 8.8 Hz, 2H), 5.78-5.69 (m, 1H), 4.96-4.94 (d, J = 11.7 Hz, 1H), 4.90-4.87 (d, J = 11.7 Hz, 1H), 4.45-4.41 (q, J = 6.8, 5.8 Hz, 1H), 3.78 (s, 3H), 3.76 (d, part of the doublet buried in the singlet at 3.78, 1H), 1.33-1.31 (d, J = 6.8 Hz, 3H), 0,03 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 137.7, 137.5, 127.1, 113.3, 111.5, 75.6, 74.0, 55.2, 22.2, -3.9. Less reactive *anti* **47**: ^{1}H NMR (300

MHz, $CDCl_3$) δ 7.18-7.16 (d, *J* = 7.8 Hz, 2H), 6.85-6.83 (d, *J* = 7.8 Hz, 2H), 5.78-5.69 (m, 1H), 5.02-4.97 (t, J = 13.7, 10.7 Hz, 2H), 4.49-4.43 (q, *J* = 6.8, 5.8 Hz, 1H), 3.79 (s, 3H), 3.39-3.38 (d, *J* = 6.8 Hz, 1H), 1.36-1.35 (d, *J* = 6.8 Hz, 3H), -0.06 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 137.7, 136.3, 127.9, 113.4, 112.0, 75.0, 72.9, 55.2, 24.6, -4.0. HRMS (CI) *m/z* 265.1617 [$(M+H)^+$; calcd for $C_{15}H_{25}O_2Si$, 265.1624].



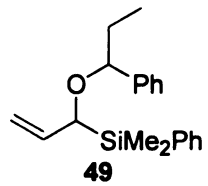
48

Preparation of 48: The trichloroacetimidate of α-phenylpropyl alcohol was prepared from 1.89 g (13.84 mmol) of α-phenylpropyl alcohol, 0.033 g (1.38 mmol) NaH, 1.90 g (13.15 mmol) of trichloroacetonitrile, and 0.044 g (1.90 mmol) anhydrous methanol prepared following general procedure **B**.[11] Then applying general procedure **C** to 0.90 g (6.92 mmol) of α-hydroxysilane **32**, the in situ generated trichloroacetimidate, and 0.015 g (0.01 mL, 0.069 mmol) of TMSOTf overnight afforded 0.612 g (36%) of a 1:1 mixture *anti/syn* **48** as a clear oil. IR 3069, 2961, 2934, 1626, 1491, 1452, 1427, 1253, 1118, 1049, 1026 cm^1.

Less reactive *anti*-**48a**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.15 (m, 5H), 5.80-5.68 (m, 1H), 5.04-4.93 (m, 2H), 4.31-4.26 (dd, *J* = 7.7, 7.4, 1.1 Hz, 1H), 3.42-3.39 (dt, *J* = 7.4, 1.4, 1.1 Hz, 1H), 1.81-1.52 (m, 2H), 0.90-0.85 (t, *J* = 7.4 Hz, 3H), -0.03 (s, 9H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 143.1, 137.8, 127.9, 127.2, 127.0, 112.6, 80.9, 72.8, 31.6, 10.6, -3.8.

Reactive *syn*-**48b**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.19 (m, 5H), 5.75-5.63 (m, 1H), 4.96-4.82 (m, 2H), 4.31-4.27 (t, *J* = 6.0, 5.8 Hz, 1H), 3.80-3.76 (dt, *J* = 7.1, 6.9,

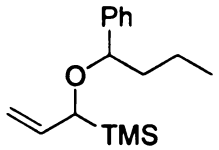
1.6, 1.4 Hz, 1H), 1.85-1.64 (m, 2H), 0.84-0.79 (t, J = 7.1 Hz, 3H), 0.08 (s, 9H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 143.8, 137.9, 127.7, 126.6, 126.5, 111.53, 8.25, 75.4, 29.5, 9.5, -3.6. HRMS (APCI) *m/z* 249.1675 [$(M+H)^+$; calcd for $C_{15}H_{24}OSi$, 249.1674].



49

Preparation of 49: The trichloroacetimidate of α-phenylpropyl alcohol was prepared from 1.10 g (8.09 mmol) of α-phenylpropyl alcohol, 0.032 g (0.81 mmol) NaH, 1.11 g (7.68 mmol) of trichloroacetonitrile, and 0.03 g (0.81 mmol) anhydrous methanol prepared following general procedure **B**.[11] Applying general procedure **C** to 0.78 g (4.05 mmol) of α-hydroxysilane **33**, the in situ generated trichloroacetimidate, and 0.09 g (0.40 mmol) of TMSOTf and stirring overnight afforded 0.47 g (38%) of a 1:1.2 mixture of **49a** and **49b** as clear oils. IR (neat) 2963, 1628, 1427, 1248 cm^{-1}. Reactive *syn*-**49b**: ^1H NMR ($CDCl_3$, 300 MHz) δ 7.60-7.16 (m, 10H), 5.68-5.56 (m, 1H), 4.92-4.78 (m, 2H), 4.16 (t, J = 6.0, 5.8 Hz, 1H), 3.95-3.92(dt, J = 6.9, 1.6, 1.4 Hz, 1H), 1.80-1.52 (m, 2H), 0.67 (t, J = 7.4 Hz, 3H) 0.36 (s, 3H), 0.31 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 143.5, 137.4, 136.9, 134.2, 132.9, 129.0, 127.67, 127.6, 127.5, 126.6, 126.5, 112.1, 82.39, 74.8, 29.5, 9.4, -5.1, -5.5. HRMS (CI) *m/z* 295.1517 [$(M-CH_3)^+$; calcd for $C_{20}H_{26}OSi$, 295.1518].Less reactive *anti*-**49a**: ^1H NMR ($CDCl_3$, 300 MHz) δ7.50-7.12 (m, 10H), 5.74-5.62 (m, 1H), 5.01-4.90 (t, 2H), 4.28 (t, J = 6.9, 6.3 Hz, 1H), 3.6-3.57 (d, J = 7.4 Hz, 1H), 1.80-1.66 (m, 1H), 1.64-1.50 (m, 1H), 0.85 (t, J = 7.4 Hz, 3H), 0.26 (s, 3H), 0.23 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 142.6, 137.3, 136.8, 134.3, 128.9, 127.9, 127.3,

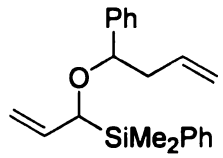
127.2, 127.0, 113.2, 80.8, 72.4, 31.6, 10.6, -5.1, -5.8. HRMS (CI) *m/z* 295.1521[(M-CH_3)$^+$; calcd for $C_{19}H_{23}OSi$, 295.1518].



50

Preparation of 50: Applying general procedure **C** to 0.88 g (6.73 mmol) of **32**, 3.96 g (13.45 mmol) of the acetimidate of 1-phenylbutan-1-ol (prepared following general procedure **B**)[11] and TMSOTf (catalyst) (0.07 mL, 0.04 mmol) and stirring the reaction mixture overnight afforded **50** as a 1:1 mixture of diastereomers which were readily separable by silica gel chromatography (0-2% EtOAc gradient in hexanes), and obtained in a combined 1.32 g (75%) yield as colorless oils, accompanied by 0.33 g, 37% of 1-phenylbut-1-ene. IR (neat) 2959, 1628, 1454, 1248 cm^{-1}.

Less reactive *anti*-**50a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.20 (m, 5H), 5.79-5.67 (m, 1H), 5.03-4.91 (m, 2H), 4.38-4.34 (dd, *J* = 8.0, 7.7, 5.2 Hz, 1H), 3.40-3.37 (dt, *J* = 7.4, 1.4 Hz), 1.80-1.68 (m, 1H), 1.57-1.34 (m, 2H), 1.32-1.15 (m, 1H), 0.87 (t, *J* = 7.1 Hz, 3H), 0.04 (s, 9H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 143.3, 137.8, 127.9, 127.2, 127.0, 112.7, 79.3, 72.8, 41.0, 19.4, 14.2, -3.8. HRMS (EI) *m/z* 263.1844 [(M+H)$^+$; calcd for $C_{16}H_{26}OSi$, 263.1831]. Reactive *syn*-**50b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.19 (m, 5H), 5.74-5.62 (m, 1H), 4.94-4.81 (ddt, *J* = 17.6, 13.7, 10.4, 2.2, 1.65 Hz, 2H), 4.34-4.30 (t, *J* = 6.0 Hz, 1H), 3.78-3,75 (dt, *J* = 7.1, 1.6 Hz, 1H), 1.83-1.71 (m, 1H), 1.68-1.56 (m, 1H), 1.37-1.18 (m, 2H), 0.91-0.86 (t, *J* = 7.7, 7.1 Hz, 3H), 0.08 (s, 9H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 144.2, 138.0, 127.7, 126.6, 126.5, 111.4, 81.4, 75.5, 39.4, 18.5, 14.3, -3.4. HRMS (EI) *m/z* 263.1840 [(M+H)$^+$; calcd for $C_{16}H_{27}OSi$, 263.1831].

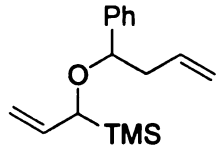


51

Preparation of 51: General procedure **D**. Allyltrimethylsilane (0.12 g, 0.16 mL, 1.02 mmol), benzaldehyde (0.11 g, 0.10 mL, 1.02 mmol), and TMSOTf ((0.04 g, 0.03 mL, 0.19 mmol) were successively added to a stirred cold (-78 °C) solution of α-(dimethylphenylsilyl)allyl dimethylphenylsilyl ether (0.30 g, 0.93 mmol) in CH_2Cl_2 (9.3 mL). The reaction was stirred for 70 min and then quenched with $NaHCO_3$ (aq. sat.). The aqueous phase was extracted with CH_2Cl_2 (10 mL x 4), and the combined organic layers were washed with $NaHCO_3$ (10 mL x 2), brine (10 mL x 2), and then dried ($MgSO_4$). Filtration and concentration afforded the crude product as a 1:1 mixture of diastereomers which were readily separated by silica gel chromatography (0-1% EtOAc gradient in hexanes) to give a combined 0.21 g (77%) yield of pure **51** as colorless oils.

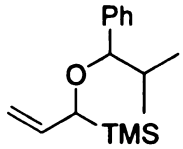
IR (neat) 3063, 1628, 1248 cm^{-1}. Reactive *syn*-**51**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.59-7.56 (m, 2H), 7.38-7.32 (m, 3H), 7.27-7.18 (m, 5H), 5.64-5.53 (m, 2H), 4.90-4.79 (m, 4H), 4.27 (t, J = 6.3, 5.9 Hz, 1H), 3.98-3.96 (dt, J = 6.8, 1.5 Hz, 1H), 2.46-2.41 (m, 1H), 2.37-2.31 (m, 1H), 0.35 (s, 3H), 0.30 (s, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 143.3, 137.4, 136.9, 134.7, 129.15, 127.8, 127.6, 126.9, 126.6, 116.8, 112.3, 81.0, 75.1, 41.5, -5.3, -5.6. HRMS (APCI) *m/z* 323.1830 [$(M+H)^+$; calcd for $C_{21}H_{26}OSi$, 323.1831]. Less reactive *anti*-**51**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.50-7.02 (m, 10H), 5.81-5.73 (m, 1H), 5.70-5.63 (m, 1H), 5.00-4.91 (m, 4H), 4.43-4.40 (dd, J = 7.8, 5.8 Hz, 1H), 3.60-3.58 (dt, J = 7.3, 1.5 Hz, 1H), 2.52-2.46 (m, 1H), 2.33-2.28 (m, 1H), 6, 0.26 (s, 3H), 0.23 (s, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 142.1, 137.1, 136.8, 135.4, 134.4, 129.0, 128.1, 127.4,

127.3, 127.2, 116.4, 113.5, 79.1, 72.4, 43. 1, -5.3, -6.0. HRMS (APCI) *m/z* 323.1834 [$(M+H)^+$; calcd for $C_{21}H_{26}OSi$, 323.1831].



52

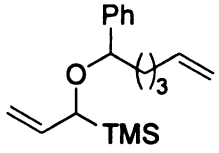
Preparation of 52: Applying the general procedure **D** described for the preparation of **51** to allyltrimethylsilane 1.26 g, (11.0 mmol, 1.75 mL), benzaldehyde 1.67 g (11.0 mmol, 1.12 mL), and TMSOTf 0.36 mL (2.0 mmol, 0.44 g) and α-(trimethylsilyl)allyl trimethysilyl ether 2.0 g (10.0 mmol) in CH_2Cl_2 (100 mL), gave a1:2.56 mixture of diastereomers. After silica gel chromatography 1.96 g (7.58 mmol) of the pure products were obtained in a combined yield of 69%. The pair of diastereomers is separable by column chromatography on silica gel. IR (neat) 2959, 1641, 1248, 1060 cm^{-1}. Less reactive *anti*-**52**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.22 (m, 5H), 5.88-5.69 (m, 2H), 5.05-4.95 (m, 4H), 4.46-4.42 (dd, *J* = 13.5, 7.7, 5.8 Hz, 1H), 3.44-3.42 (d, *J* = 7.4 Hz, 1H), 2.59-2.49 (quintet, *J* = 7.7 Hz, 1H), 2.39-2.30 (quintet, *J* = 6.86, 1H), -0.01 (s, 9H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 142.5, 137.7, 135.4, 128.1, 127.4, 127.4, 116.3, 112.9, 79.3, 73.0, 43.03, -4.0. HRMS (CI) *m/z* 261.1664 [$(M+H)^+$; calcd for $C_{16}H_{24}OSi$, 261.1675. Reactive *syn*-**52**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.20 (m, 5H), 5.79-5.60 (m, 2H), 5.01-4.80 (m, 4H), 4.39-4.35 (t, *J* = 6.2 Hz, 1H), 3.82-3.78 (dt, *J* = 7.1, 1.3 Hz, 1H), 2.54-2.40 (m, 2H), 0.05 (s, 9H). ^{13}C NMR (500 MHz, $CDCl_3$) δ143.6, 137.9, 134.9, 127.8, 126.9, 126.6, 116.8, 111.9, 81.1, 75.8, 41.5, -3.7. HRMS (CI) *m/z* 261.1681 [$(M+H)^+$; calcd for $C_{16}H_{24}OSi$, 261.1675].



53

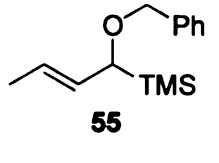
Preparation of 53: The trichloroacetimidate of α-phenylisopropyl alcohol was prepared from 2.88 g (19.19 mmol) of α-phenylisopropyl alcohol, 0.08 g (1.92 mmol) NaH, 2.63 g (18.23 mmol) of trichloroacetonitrile, 0.06 g (1.92 mmol) anhydrous methanol following general procedure **B**.[11] Then applying general procedure **C** to 1.25 g (9.59 mmol) of α-hydroxysilane **32**, the in situ generated trichloroacetimidate, and 0.03 mL (0.04 g, 0.19 mmol) of TMSOTf, afforded **53** as a 1:1 mixture of diastereomers which were readily separable by silica gel chromatography (0-2% EtOAc gradient in hexanes), and obtained in a combined 1.47 g (5.62 mmol), 59% as colorless oils. IR (neat) 2959, 1628, 1452, 1248 cm^{-1}.

Less reactive *anti*-**53a**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.31-7.19 (m, 5H), 5.77-5.70 (m, 1H), 5.03-4.92 (dd, J = 17.2, 11.48, 10.6 Hz, 2H), 4.07-4.06 (d, J = 7.5 Hz, 1H), 3.39-3.37 (d, J = 8.0 Hz, 1H), 1.91-1.85 (m, 2H), 1.01-1.00 (d, J = 6.6 Hz, 3H), 0.72-0.70 (d, J = 7.1 Hz, 3H), -0.01 (s, 9H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 141.8, 138.0, 128.7, 128.1, 127.8, 127.1, 113.1, 84.7, 72.6, 35.0, 19.2, 19.0, -4.0. HRMS (APCI) *m/z* 263.1821 [$(M+H)^+$; calcd for $C_{16}H_{26}OSi$, 263.1831]. Reactive *syn*-**53b**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.17 (m, 5H), 5.64-5.53 (m, 1H), 4.89-4.72 (dd, J = 16.7, 10.7 Hz, 2H), 4.01-3.99 (d, J = 6.0 Hz, 1H), 3.72-3.68 (d, J = 7.4 Hz, 1H), 1.89-1.99 (m, 1H), 0.93-0.91 (d, J = 6.9 Hz, 3H), 0.77-0.74 (d, J = 6.9 Hz, 3H), 0.05 (s, 9H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 142.6, 138.2, 127.4, 127.3, 126.5, 111.4, 87.5, 76.6, 34.5, 18.7, -3.5. HRMS (APCI) *m/z* 263.1821 [$(M+H)^+$; calcd for $C_{16}H_{26}OSi$, 263.1831].



54

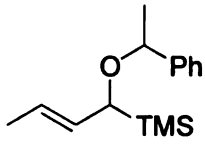
Preparation of 54: Applying general procedure **C** to 0.74 g (5.68 mmol) **32**, 3.46 g (10.79 mmol) of the trichloroacetimidate of 1-phenyl-5-hexen-1-ol (prepared following general procedure **B**)[11] and TMSOTf (catalyst) (0.10 mL, 0.57 mmol) in cyclohexane and stirring reaction overnight afforded a 1:1 pair of diastereomeric **54** as colorless oils in a combined 0.25 g (15%) yield. IR (neat) 2941, 1641, 1454, 1248 cm^{-1}. Reactive *syn*-**54**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.20 (m, 105H), 5.82-5.58 (m, 4H), 5.04-4.78 (m, 8H), 4.39-4.35 (dd, 1H), 4.32-4.28 (t, 1H), 3.74-3.72 (d, 1H), 3.41-3.38 (d, 1H), 2.07-1.97 (m, 4H), 1.81-1.51 (m, 6H), 1.42-1.24 (m, 2H), -0.33 (s, 9H), -0.05 (s, 9H). Less reactive *anti*-**54**: ^1H NMR (500 MHz, $CDCl_3$) δ (7.33-7.20 (m, 5H), 5.80-5.69 (m, 2H), 5.02-4.88 (m, 4H), 4.37-4.34 (dd, J = 7.8, 4.9 Hz, 1H), 3.39-3.37 (dt, J = 4.9, 2.4 Hz, 1H), 2.05-2.00 (q, J = 8 .3, 6.3 Hz, 2H), 1.79-1.70 (m, 1H), 1.62-1.48 (m, 2H), 1.37-1.27 (m, 1H), -0.05 (s, 9H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 143.2, 138.9, 137.8, 128.1, 127.2, 127.2, 114.3, 112.8, 79.3, 72.8, 38.07, 33.7, 25.3, -4.0. HRMS (APCI) *m/z* 289.1983 [$(M+H)^+$; calcd for $C_{18}H_{29}OSi$, 289.1987].



55

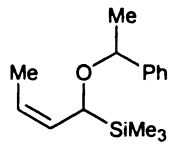
Preparation of 55: Applying general procedure **C** to 6.75 g (46.86 mmol) of **34**, 17.75 g (70.29 mmol) of the trichloroacetimidate of benzyl alcohol (prepared following

literature procedure),[11] and BF_3•OEt_2 (catalyst) (0.65 mL, 5.15 mmol) in cyclohexane afforded 2.11 g (34%) of **55** as a colorless oil. IR (neat) 2959, 1497, 1454, 1246 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.55-5.39 (m, 2H), 4.69-4.65 (d, *J* = 12.4, 1H), 4.37-4.28 (d, *J* = 12.4, 1H), 3.52-3.50 (d, *J* = 7.1, 1H), 1.74-1.72 (d, *J* = 4.7, 3H), 0.01 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4, 129.7, 128.0, 127.5, 127.0, 125.1, 75.1, 71.3, 18.0, -3.7. HRMS (CI) *m/z* 252.1775 [$(M+NH_4)^+$; calcd for $C_{14}H_{22}OSi$, 252.1784].



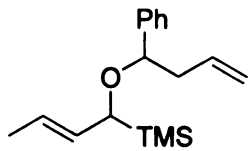
E-**56**

Preparation of *E*-56: Applying general procedure **C** to 3.60 g (24.98 mmol) of α-hydroxysilane **34**, 13.32 g (49.50 mmol) of the trichloroacetimidate of phenethyl alcohol (prepared following general procedure **B**)[11] and 0.47 mL (0.53 g, 3.74 mmol) of BF_3•OEt_2, afforded 3.07 g (49%) of *E*-**56** as a 1:1 mixture of *anti*/*syn* diastereomers. IR (neat) 2963, 1493, 1452, 1246, 1082, cm^{-1}. Mixture of *anti*/*syn* *E*-**56**: Less reactive *anti* *E*-**56**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.21 (m, 5H), 5.43-5.33 (m, 2H), 4.55-4.49 (q, *J* = 6.6, 6.3 Hz, 1H), 3.30-3.28 (d, *J* = 6.0 Hz, 1H), 1.72-1.70 (d, *J* = 4.9 Hz, 3H), 1.36-1.34 (d, *J* = 6.3 Hz, 3H), -0.5 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.5, 130.1, 128.0, 126.9, 126.7, 124.5, 75.0, 72.3, 24.8, 18.1, -3.7. HRMS (CI) *m/z* 248.1591 [(M); calcd for $C_{15}H_{24}OSi$, 248.1596].



Z-**56**

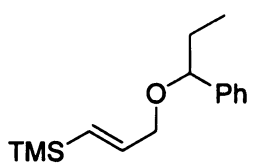
Preparation of (*Z*)-56: Applying general procedure **C** to 1.50 g (10.41 mmol) of α-hydroxysilane (*Z*)-**34**, 5.55 g (20.82 mmol) of the trichloroacetimidate of *sec*-phenethyl alcohol,[11] and 0.17 mL (0.14 g, 0.62 mmol) of TMSOTf afforded 0.91 g of a mixture of products including (*Z*)-**56**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.19 (m, 10H), 5.92-5.87 (apparent dd, *J* = 11.8, 11.0, 6.6, 5.2 Hz, 1H),5.86-5.80 (apparent dd, *J* = 11.8, 11.0, 6.6, 5.2 Hz, 1H), 5.71 (dd, *J* = 3.2, 1.1 Hz, 1H), 5.64 (dd, *J* = 3.2, 1.1 Hz, 1H), 4.54-4.47 (q, *J* = 6.5 Hz, 1H), 4.48-4.41 (q, *J* = 6.5 Hz, 1H), 1.41 (d, *J* =6.3 Hz, 3H), 1.39 (d, *J* = 6.3 Hz, 3H), 1.22 (d, *J* = 6.3 Hz, 3H), 1.15 (d, *J* = 6.3 Hz, 3H), 0.07 (s, 9H), -0.3 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.2, 147.5, 144.6, 144.2, 131.1, 129.4, 128.2, 128.1, 127.1, 127.0, 126.2, 76.1, 75.7, 75.1, 74.5, 24.8, 24.0, 21.7, 20.4, -1.1, -1.3.



58

Preparation of 58: Applying the general **D** to 0.59 g (0.82 mL, 5.18 mmol) of allyltrimethylsilane, 0.55 g (0.53 mL, 5.18 mmol) of benzaldehyde, 0.21 g (0.17 mL, 0.94 mmol) of TMSOTf, and 1.02 g (4.71 mmol) of α-(trimethylsilyl)allyl trimethylsilyl ether in CH_2Cl_2 (47 mL), after about 3 h reaction time afforded **58** as a 1:1 mixture of diastereomers, which were readily separable by silica gel chromatography (0-1% EtOAc gradient in hexanes), and obtained in a combined 0.65 g (51%) yield as colorless oils. IR (neat) 2959, 1642, 1493, 1452,1248, 1078, 1053 cm^{-1}. Less reactive *anti*-**58**: ^{1}H NMR

(300 MHz, $CDCl_3$) δ 7.34-7.17 (m, 5H), 5.85-5.64 (m, 1H), 5.42-5.20 (m, 2H), 5.01-4.93 (tm, 2H), 4.44-4.35 (m, 1H), 3.31-3.29 (d, J = 6.0 Hz, 1H), 2.55-2.38 (m, 2H), 1.71-1.69 (d, J = 5.5 Hz, 3H), –0.4 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.6, 135.5, 129.9, 127.9, 127.2, 127.1, 125.1, 116.1, 78.6, 72.0, 43.1, 18.1, -3.7. Reactive *syn*-**58**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.28-7.17 (m, 5H), 5.80-5.64 (m, 1H), 5.38-5.20 (m, 2H), 4.99-4.93 (t, J = 2H), 4.43-4.30 (m, 1H), 3.7 (d, J = 7.4 Hz, 1H), 2.54-2.36 (m, 2H), 1.54 (d, J = 5.5 Hz, 3H), 0.02 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 134.8, 130.4, 127.7, 126.6, 126.5, 124.1, 116.6, 80.1, 74.7, 41.3, 17.9, -3.5. HRMS (CI) *m/z* 275.1823 [$(M+H)^+$; calcd for $C_{17}H_{26}OSi$, 275.1831].

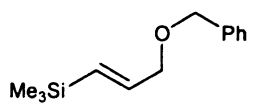


63

Preparation of 63: formation of mesylate of **32** - to a cold (0 °C) THF solution of **32** (0.1 M) were added MsCl (0.87 g, 0.59 mL, 7.59 mmol), followed by Et_3N (0.77 g, 1.05 mL, 7.59 mmol), and the mixture stirred for 2.5 h. Then, the reaction was quenched with $NaHCO_3$ (sat, aq), diluted with ether, phases separated. The organic phase was washed with NH_4Cl (sat, aq), dried over $MgSO_4$ and concentration with rotary evaporator to afford 0.76 g (96%) of the crude product which was employed in the next step without purification.

To a stirred suspension of NaH (0.02 g, 0.40 mmol) in THF (1.5 mL) at room temperature, was added a solution of α-phenylpropyl alcohol (0.53 g, 3.9 mmol) in THF (2.0 mL) via syringe, followed by a THF wash (1.0 ml; total volume of THF became 3.0 ml). The reaction mixture was stirred at room temperature for 30 min, and transferred via

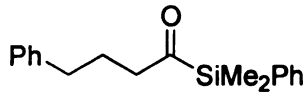
syringe, to a solution of the crude mesylate in THF (7.0 mL; 0.5 M) at room temperature. The reaction was stirred for additional 2 h, quenched with NH_4Cl, washed with brine, dried over $MgSO_4$, and concentrated to give 1.15 g of crude product. Purification on silica gel afforded 0.61 g (2.44 mmol, 70%) of **63** as a colorless oil. IR (neat) 2963(s), 2934(m), 1622(m), 1452(s), 1248(m) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.15 (m, 5H), 6.09-6.00 (dt, J = 18.8, 5.2, 4.6 Hz, 1H), 5.87-5.80 (dt, J = 18.7, 1.5 Hz, 1H), 3.94-3.87 (ddd, J = 4.4, 1.6 Hz, 1H), 3.80-3.74 (ddd, J = 12.9, 5.2, 1.4 Hz, 1H), 1.90-1.50 (m, 2H), 0.89 (t, J?, 3H), 0.04 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.6, 142.4, 131.4, 128.1, 127.3. 126.7, 83.3, 71.7, 31.1, 10.4, -1.2.



65

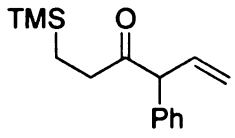
Preparation of 65: To a solution of BnOH (0.31 g (2.88 mmol) in THF at room temperature was added dropwise Et_2Zn (1.0 M in heptane, 1.44 mmol, 1.44 mL) via syringe. The resulting mixture was stirred for about 50 min, resulting in the formation of cloudy white precipitate. To this suspension were added the acetate of **32** (0.50 g, 2.89 mmol) and $Pd(PPh_3)_4$ (5 mol%, 0.17 g, 0.15 mmol), and reaction stirred at room temperature for 2 h. The reaction mixture was passed through a short plug of silica gel, elute concentrated, and product purified by flash chromatography on silica gel (0 to 2% EtOAc in hexane gradient) to afford 0.41 g (64%) of **65** as a clear oil. IR (neat) 2955, 1622, 1496.95, 1454, 1248 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ ^{13}C NMR (300 MHz, $CDCl_3$) δ 142.1, 138.2, 132.0, 128.3, 127.7, 127.6, 127.5, 73.1, 72.4, -1.24. 65 is a known compound and have spectral data in accord with the reported ones.[28]

Wittig rearrangements of α-alkoxysilanes- Representative procedure E. A solution of α-alkoxysilane (1.0 equiv) in freshly distilled anhydrous THF (0.06 – 0.07 M) was cooled to the desired temperature under nitrogen. The required amount of *s*-BuLi (1.5 – 4.0 equiv, 1.3 M in cyclohexane) was added dropwise via syringe. The reaction mixture was stirred at the reaction temperature for the desired length of time, then quenched with saturated aqueous NH_4Cl and diluted with ether. Phases separated and the organic phase was washed with water and brine. The organic phase was dried over $MgSO_4$ and concentrated. Silical gel chromatography (0 to 2% EtOAc in hexane gradient) afforded the rearranged products usually as a light yellow oil.



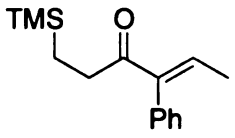
68

Wittig rearrangement of 39: preparation of 68: Applying the representative procedure **E** for the Wittig rearrangement of α-alkoxysilanes to 57 mg (0.20 mmol) of silane **39**, 0.37 mL (0.30 mmol) s-BuLi and THF (3.0 mL) at –78 °C for 45 min afforded, after silical gel chromatography (2% EtOAc in hexanes), 39 mg (69%) of pure **II-05** as a clear oil. IR cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.56-7.54 (m, 2H), 7.45-7.38 (m, 3H), 7.26-7.07 (m, 5H), 2.62-2.59 (apparent t, J = 7.5, 7.1 Hz, 2H), 2.51 (apparent t, J = 8.0, 7.5 Hz, 2H), 1.82-1.79 (quintet, J = 8.0, 7.5, 7.1 Hz, 2H), 0.49 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 245.9, 141.8, 133.9, 129.9, 128.4, 128.3, 128.2, 128.1, 125.8, 47.9, 35.7, 23.7, -4.8. 68 is a known compound and have spectral data in accord with reported ones.[29]



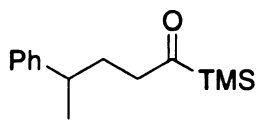
70

Applying representative procedure **E** for Wittig rearrangement of α-alkoxysilanes to 93 mg (0.34 mmol) of **41** and 0.35 mL (1.5 equiv, 0.49 mmol) of *n*-BuLi (1.6 M in hexane) at -78 °C fo5 2.5 h, afforded 47 mg (51%) of **70** as a colorless oil. IR (neat) 2955, 2897, 1717, 1635, 1495, 1454, 1410, 1250 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.20 (m, 5H), 6.27-6.20 (m, 1H), 5.20-5.17 (dt, *J* = 10.2, 1.1 Hz, 1H), 5.08-5.03 (d, *J* = 17.1, 1.2 Hz, 1H), 4.41-4.39 (d, *J* = 8.2 Hz, 1H), 2.41-2.38 (dd, *J* = 10.1, 8.8 Hz, 2H), 0.73-0.66 (m, 2H), -0.09 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.7, 136.3, 128.9, 128.2, 127.3, 117.3, 62.5, 36.2, 10.2, -1.9.

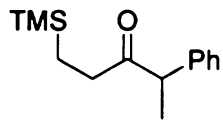


71

Applying representative procedure **E** for Wittig rearrangement of α-alkoxysilanes to 153 mg (0.621 mmol) of **41** and 0.58 mL (1.5 equiv, 0.932 mmol) of *n*-BuLi (1.6 M in hexane) at room temperature, after silica gel chromatography (1% EtOAc in hexanes) afforded 80 mg (52%) of pure **71** as light yellow oil. IR (neat) 2953, 2895, 1694, 1624, 1493, 1445, 1410, 1354, 1248 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.33-7.19 (m, 5), 6.02-5.98 (q, *J* = 7.2 Hz, 1H), 2.41-2.37 (dd, *J* = 8.7, 8.1 Hz, 2H), 1.88 (d, *J* = 7.2 Hz, 3H), 0.76-0.73 (t, *J* = 8.7, 8.1 Hz, 2H), 0.09 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.0, 144.0, 138.1, 129.4, 128.6, 127.6, 126.8, 37.5, 15.5, 10.2, -1.9. HRMS (EI) *m/z* 246.1433 [$(M-H)^+$; calcd for $C_{15}H_{22}OSi$, 246.1440].



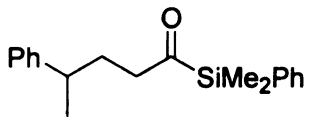
74



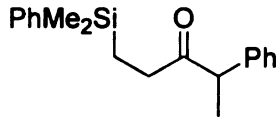
75

Wittig rearrangement of 44: Applying representative procedure **E** for Wittig rearrangement of α-alkoxysilanes to 360 mg (1.53 mmol) of **44** and 1.8 mL (2.30 mmol) of *s*-BuLi (1.3 M in cyclohexane) at -78 °C overnight, afforded 162 mg (46%) of a 1.68:1 mixture of **74** and **75** as a colorless oil. **74**: IR (neat) 2957, 2899, 1643, 1603, 1495, 1452, 1410, 1375, 1250 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.12 (m, 5H), 2.67-2.57 (m, 1H), 2.54-2.41 (m, 1H), 1.89-1.67 (m, 2H), 1.24-1.21 (d, J = 7.1 Hz, 3H), 0.11 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 248.2, 146.6, 128.4, 127.0, 126.0, 46.4, 39.3, 30.2, 22.4, -3.2. HRMS (EI) *m/z* 233.1358 [$(M-H)^+$; calcd for $C_{14}H_{21}OSi$, 233.1362].

75: IR (neat) 2955, 2895, 1717, 1601, 1495, 1452, 1414, 1373, 1248, 1180 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.19 (m, 5H), 3.82-3.75 (q, J = 7.1, 6.9 Hz, 1H), 2.34-2.28 (m, 2H), 1.38 (d, J = 6.9 Hz, 3H), 0.77-0.55 (m, 2H), -0.11 (s, 9H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 211.8, 140.8, 128.8, 127.8, 127.0, 52.3, 35.6, 17.7, 10.3, -1.9. HRMS (CI) *m/z* 234.1466 [(M); calcd for $C_{14}H_{22}OSi$, 234.1440].



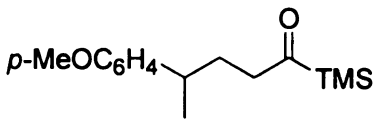
76



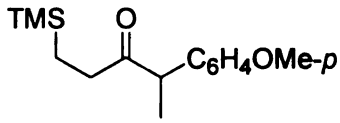
77

Applying representative procedure **E** for Wittig rearrangement of α-alkoxysilanes to 76 mg (0.25 mmol) of **45** and 0.38 mL (0.38 mmol) of *s*-BuLi (1.0 M in cyclohexane) and stirring for 4 h at -78 °C afforded 37 mg (49%) of a 1.3:1 mixture of **76** and **77** as light yellow oils. ^1H NMR (300 MHz, $CDCl_3$) δ 7.49-7.02 (m, 20H), 3.75-3.68 (q, J =

7.1, 6.8 Hz, 1H), 2.59-2.20 (m, 4H), 1.96-1.60 (m, 2H), 1.35, d, J = 7.1, 3H), 1.16 (d, J = 6.8 Hz, 3H), 1.05-0.95 (m, 1H), 0.91-0.80 (m, 1H), 0.42 (s, 3H), 0.41 (s, 3H), 0.18 (s, 3H), 0.16, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 246, 211.3, 146.4, 140.6, 138.3, 133.8, 133.4, 129.7, 128.8, 128.7, 128.4, 128.2, 128.0, 127.7, 127.6, 126.9, 126.8, 125.9, 52.4, 46.8, 39.2, 35.6, 30.4, 22.3, 17.7, 9.5, -3.0, -3.2, -4.6.



78

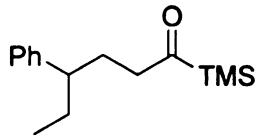


79

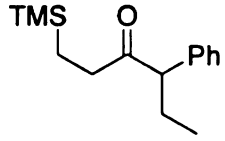
Wittig rearrangement of 47: Applying representative procedure **E** for the Wittig rearrangement of α-alkoxysilanes to 154 mg (0.582 mmol) of a 1:3.25 (reactive *syn*/less reactive *anti*) mixture of **47** afforded a mixture of both [1,2]- and [1,4]-rearrangement products **78** and **79** in approximately 1.8:1 ratio and in 93% yield IR (neat) 2959, 1717(w), 1643, 1613, 1515, 1456, 1248 cm^{-1}. **78**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (d, J = 8.8 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 3.77 (s, 3H), 2.62-2.55 (m, 1H), 2.52-2.46 (m, 1H), 2.43-2.37 (m, 1H), 1.82-1.75 (m, 1H), 1.72-1.65 (m, 1H), 1.20-1.18 (d, J = 6.8 Hz, 3H), 0.11 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 248.3, 157.8, 138.7, 127.8, 113.7, 55.2, 46.5, 38.5, 30.4, 22.6, -3.2. HRMS (EI) *m/z* 264.1542 [$(M)^+$; calcd for $C_{15}H_{24}O_2Si$, 264.1546].

79: IR (neat) 2953, 1715, 1611, 1513, 1456, 1250, 1178 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11 (d, J = 8.3 Hz, 2H), 6.8 (d, J = 8.8 Hz, 2H), 3.77 (s, 3H), 3.75-3.70 (q, J = 7.3, 6.8 Hz, 1H), 2.35-2.24 (m, 2H), 1.34 (d, J = 6.8 Hz, 3H), 0.73-0.67 (m, 1H), 0.63-0.56 (m, 1H), -0.11 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.1, 158.6, 132.9,

128.8, 114.2, 55.2, 51.4, 35.5, 17.8, 10.4, -1.9. HRMS (EI) *m/z* 264.1547 [$(M)^+$; calcd for $C_{15}H_{24}O_2Si$, 264.1546].



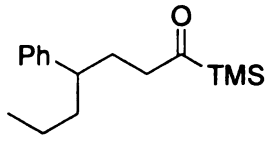
82



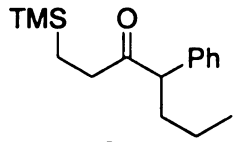
83

Applying representative procedure **E** for Wittig rearrangement of α-alkoxysilanes to 530 mg (2.15 mmol) of reactive **48** and 2.30 mL (3.23 mol) of *s*-BuLi (1.4 M in cyclohexane) and stirring overnight at -78 °C afforded 347 mg (65%) of **82** and **83** in approximately 2:1 ratio. IR (neat) cm^{-1}. **82**: IR (neat) 2957, 2930, 1717, 1643, 1495, 1452, 1250 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.27-7.06 (m, 5H), 2.49-2.42 (m, 1H), 2.37-2.31 (m, 1H), 1.95-1.88 (m, 1H), 1.70-1.60 (m, 2H), 1.58-1.49 (m, 1H), 0.74 (t, *J* = 7.5 Hz, 3H), 0.08 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 248.5, 144.9, 128.3, 128.2, 127.7, 126.0, 47.1, 46.4, 29.7, 28.4, 12.1, -3.2. HRMS (FAB+) *m/z* 249.1677 [$(MH)^+$; calcd for $C_{15}H_{25}OSi$, 249.1675].

83: IR (neat) 2957, 1715, 1601, 1493, 1454, 1248 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.19 (m, 5H), 3.56-3.53 (t, *J* = 7.5, 7.1 Hz, 1H), 2.33-2.25 (m, 2H), 2.06-2.00 (m, 1H), 1.72-1.66 (m, 1H), 1.41-0.81-0.78 (t, *J* = 7.5, 7.1 Hz, 3H), 0.74-0.68 (m, 1H), 0.61-0.55 (m, 1H), -0.11 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.5, 139.2, 128.7, 128.2, 127.0, 60.1, 36.5, 25.5, 12.2, 10.1, -1.9. HRMS (CI) *m/z* 248.1590 [$(M)^+$; calcd for $C_{15}H_{24}OSi$, 248.1596].

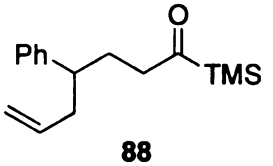


86

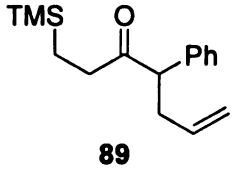


87

Applying representative procedure **E** for Wittig rearrangement of α-alkoxysilanes to 156 mg (0.60 mol) of a 1:1.35 mixture of **50** and 0.6 mL *n*-BuLi (1.6 M in hexane, 0.90 mmol) at -78 °C for 24 h afforded 65 mg (41%) of a mixture of **86** and **87** as light yellow oils. **86**: IR (neat) 2957, 2930, 1719, 1643, 1459, 1452, 1250 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.27-7.07 (m, 5H), 2.48-2.42 (m, 2H), 2.37-2.32 (m, 1H), 1.93-1.86 (m, 1H), 1.69-1.62 (m, 1H), 1.60-1.48 (m, 2H), 1.22-1.10 (m, 2H), 0.81 (t, J = 7.3 Hz, 3H), 0.08 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 248.4, 145.1, 128.3, 127.7, 126.0, 46.4, 45.0, 39.2, 28.8, 20.6, 14.1, -3.2. HRMS (CI) *m/z* 263.1824 $[(M+H)^+$; calcd for $C_{16}H_{27}OSi$, 263.1831]. **87**: IR (neat) 2957, 1717, 1493, 1454, 1248 cm^{-1}. ^1H NMR (500 MHz, CDCl3) δ 7.32-7.20 (m, 5H), 3.67 (t, J = 7.8, 7.3 Hz, 1H), 2.38-2.27 (m, 2H), 2.03-1.96 (m, 1H), 1.72-1.64 (m, 1H), 1.27-1.14 (m, 2H), 0.88 (t, J = 7.3 Hz, 3H), 0.76-0.69 (m, 1H), 0.64-0.57 (m, 1H), -0.09 (s, 9H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 211.5, 139.4, 128.7, 128.2, 127.0, 58.1, 36.5, 34.5, 20.7, 14.0, 10.2, -1.9. HRMS (CI) *m/z* 262.1756 $[(M)^+$; calcd for $C_{16}H_{26}OSi$, 262.1753].



88



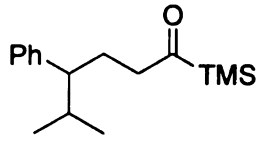
89

Applying representative procedure **E** for Wittig rearrangement of α-alkoxysilanes to 165 mg (0.638 mmol) of **52** and 1.6 mL (2.55 mmol) of *n*-BuLi (1.6 M in hexanes) at –78 °C, allowing the reaction to warm to –30 °C and stirring at this temperature for about 30 h, after purification by column chromatography on silica gel afforded 45 mg (32%) of

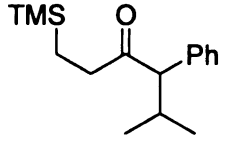
a 4.53:1 mixture of **88** and **89** as light yellow oils. Note: the reported yield is based on 2.64:1 ratio of less reactive *anti*/reactive *syn* starting mixture of substrates.

88: IR (neat) 2955, 2926, 1717, 1643, 1495, 1452, 1248 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.16 (m, 5H), 5.78-5.60 (m, 1H), 5.00-4.89 (m, 2H), 2.58-2.52 (m, 1H), 2.50-2.45 (m, 1H), 2.39-2.31 (m, 3H), 2.00-1.93 (m, 1H), 1.72-1.64 (m, 1H), 0.09 (6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 248.1, 144.4, 136.8, 128.4, 127.7, 126.2, 116.0, 46.1, 45.1, 41.4, 27.9, -3.2.

89: ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.08 (m, 5H), 5.68-5.60 (m, 1H), 5.00-4.91 (m, 2H), 3.72 (t, J = 7.7, 7.4 Hz, 1H), 2.81-2.75 (m, 1H), 2.65-2.59 (m, 1H), 2.09-2.02 (m, 1H), 1.86-1.78 (m, 1H), 0.74-0.68 (m, 1H), 0.62-0.56 (m, 1H), -0.11 (s, 9H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 210.6, 135.9, 128.8, 128.2, 128.1, 127.2, 116.6, 58.1, 36.7, 36.5, 10.1, -1.9.



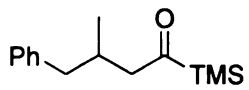
90



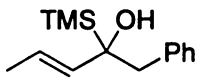
91

Applying representative procedure **E** for Wittig rearrangement of α-alkoxysilanes to 66 mg (0.252 mmol) of **53** and 0.39 mL (0.63 mmol) of *n*-BuLi (1.6 M in hexane) at –78 °C and allowing the reaction to warm up to 4 °C for 24 h afforded 22 mg (33%) of a 1.8:1 mixture of **90** and **91** as light yellow oils. **90**: IR (neat)2957, 1719(w), 1643, 1493, 1452, 1250 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.26-7.03 (m, 5H), 2.39-2.35 (m, 1H), 2.30-2.24 (m, 1H), 2.20-2.15 (m, 1H), 2.08-2.02 (m, 1H), 1.80-1.73 (m, 1H), 1.71-1.63 (m, 1H), 0.94 (d, J = 6.8 Hz, 3H), 0.68 (d, J = 6.8 Hz, 3H), 0.06 (s, 9H). ^{13}C NMR (125

MHz, $CDCl_3$) δ 248.6, 143.8, 128.4, 128.1, 126.0, 52.4, 33.7, 25.2, 20.9, 15.3, -3.3. HRMS (APCI) *m/z* 263.1840 [$(M+H)^+$; calcd for $C_{16}H_{27}OSi$, 263.1831]. **91**: IR (neat) 2957, 1715, 1454, 1248 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.29-7.20 (m, 5H), 3.3 (d, *J* = 10.2 Hz, 1H), 2.42-2.25 (m, 3H), 0.94 (d, *J* = 6.3 Hz, 3H), 0.74-0.67 (m, 1H), 0.63 (d, *J* = 6.8 Hz, 3H), 0.61-0.54 (m, 1H), -0.11 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.7, 138.4, 128.7, 128.6, 127.0, 66.4, 37.8, 30.7, 21.7, 20.4, 9.9, -1.9. HRMS (CI) *m/z* 262.1755 [$(M)^+$; calcd for $C_{16}H_{26}OSi$, 262.1753].



92



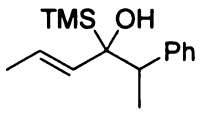
93

Applying representative procedure **E** for Wittig rearrangement of α-alkoxysilanes to 141 mg (0.60 mmol) of **55** and 0.69 mL (0.90 mmol) of *s*-BuLi (1.3 M in cyclohexane) at –78 °C for for 30 min, after purification by column chromatography on silica gel, afforded 106 mg (75%) of a 4:1 mixture of both [1,4]- and [1,2]-rearrangement products **92** (a light yellow oil) and **93** as a colorless oil.

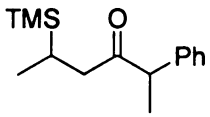
92: 2959, 2928, 1709, 1641, 14961454, 1250 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.32-7.17 (m, 5H), 2.61-2.50 (m, 2H), 2.47-2.30 (m, 3H), 0.84-0.81 (d, J = 6.6 Hz, 3H), -0.13 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 248.59, 140.59, 129.20, 128.17, 125.91, 54.94, 43.28, 29.58, 19.90, -3.25. HRMS (EI) *m/z* 233.1355 [$(M-H)^+$; calcd for $C_{14}H_{21}OSi$, 233.1362].

93: IR 3432, 2978, 2926, 1454, 1381, 1248, 1121 (neat) cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.26-7.10 (m, 5H), 5.60-5.56 (dq, *J* = 15.4, 1.6 Hz, 1H), 5.19-5.12 (apparent dq, J = 15.4, 6.6, 6.0 Hz, 1H), 2.88-2.79 (apparent q, *J* = 13.2, 7.7 Hz, 2H),

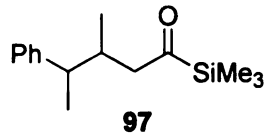
1.64-1.62 (dd, J = 6.6, 1.6 Hz, 3H), 0.05 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.2, 135.4, 130.6, 127.9, 126.3, 121.62, 70.4, 43.1, 17.8, -4.2. HRMS (EI) *m/z* 234.1435 [$(M)^+$; calcd for $C_{14}H_{22}OSi$, 234.1440].



95



96



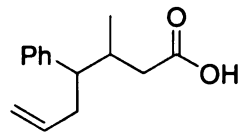
97

Applying representative procedure **E** for Wittig rearrangement of α-alkoxysilanes to 2.91 g (11.62 mmol) of *E*-**56** and 29.05 mL (4.0 equiv, 46.48 mmol) of *n*-BuLi (1.6 M in hexanes) at –78 °C and allowing the reaction to warm to –30 °C for 4 d, after purification by column chromatography on silica gel, afforded 1.66 g (57%) of a mixture **95** and **96** and **97** as colorless oils.

95 (mixture of diastereomers): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33-7.13 (m, 10H), 5.76-5.69 (dq, J = 15.4, 1.6 Hz, 1H), 5.62-5.57 (dq, J = 15.4, 1.6 Hz, 1H), 5.33-5.22 (dq, J = 15.4, 6.6, 6.0 Hz, 1H), 5.18-5.06 (dq, J – 15.4, 6.6, 6.0 Hz, 1H), 3.08-3.00 (q, J = 7.1 Hz, 2H), 3.03-2.96 (q, J = 7.1 Hz, 2H), 1.73-1.70 (dd, J = 6.6, 1.6 Hz, 3H), 1.61 (dd, J = 6.0, 1.6 Hz, 3H), 1.37 (d, J = 7.1 Hz, 3H), 1.32 (d, J = 7.1 Hz, 3H), -0.3 (s, 9H), -0.09 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ HRMS (CI) *m/z* 249.1666 [$(M+H)^+$; calcd for $C_{15}H_{24}OSi$, 249.1675].

96: IR 2955, 1715, 1495, 1452, 1250 (neat) cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32-7.18 (m, 10H), 3.80-3.76 (q, J = 7.3, 6.8 Hz, 1H), 3.74-3.70 (q, J = 7.3, 6.8 Hz, 1H), 2.38-2.36 (dd, J = 3.9, 3.4 Hz, 1H), 2.34-2.33 (dd, J = 3.9, 3.4 Hz, 1H), 2.10-2.06 (m, 2H), 1.39-1.36 (t, J = 6.8, 6.3 Hz, 6H), 1.35-1.10 (m, 2H), 0.82 (d, J = 7.3 Hz, 3H), 0.69 (d, J = 7.3 Hz, 3H), -0.11 (s, 9H), -0.16 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.4, 210.8, 140.58, 140.55, 128.81, 128.76, 127.95, 127.88, 127.03, 127.01, 53.5, 52.1, 43.4,

43.3, 17.5, 17.4, 15.4, 15.2, 14.6, 14.0, -3.57, -359. HRMS (EI) *m/z* 248.1594 [$(M)^+$; calcd for $C_{15}H_{24}OSi$, 248.1596]. **97** was oxidized to the corresponding carboxylic acid and data are given in Chapter 6.



104

Preparation of 104: Applying representative procedure **E** for Wittig rearrangement of α-alkoxysilanes to 6.66 g (2443 mmol) of *E*-**58** and 61.10 mL (4.0 equiv, 97.74 mmol) of *n*-BuLi (1.6 M in hexanes) at –78 °C and allowing the reaction to warm to –30 °C for 4 d, after purification by column chromatography on silica gel, afforded 2.49 g (37%) of a mixture of all possible Wittig products. 0.60 g of this mixture was dissolved in THF (4.40 mL) and 3N NaOH (0.4 mL/mmol starting material, 0.88 mL) added. The mixture was heated to 35-40 °C, and then oxidized by adding dropwise 30% H_2O_2 (0.20 mL/mmol starting material, 0.44 mL), while maintaining the reaction temperature below 50 °C for 2 h. The aqueous phase was cooled to 0 °C, and acidified to pH of 1-2 with 6 N HCl.. The resulting aqueous material was extracted with ether (5 x 20 mL), and the ether solution dried with $MgSO_4$. Filtration and concentration afforded 69 mg of **104** as a thick colorless oil. Purification by column chromatography on silica gel (hexane/EtOAc (0-10%) afforded **104a** and **104b** as a near 1:1 mixture of diastereomers (ratio by ^{1}HNMR). IR (neat) 3100-2500 (vs, v br), 2973, 1709, 1642, 1495, 1452, 1414, 1296, 1250 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.70 (br, 1H), 7.29-7.12 (m, 10H), 5.65-5.01 (m, 2H), 4.99-4.85 (m, 4H), 2.67-2.63 (m, 1H), 2.56-2.22 (m, 9H), 2.08-2.03 (dd, J = 15.1, 8.8 Hz, 1H), 1.95-1.90 (dd, J = 15.1, 9.3 Hz, 1H), 1.05 (d, J = 6.3 Hz, 3H),

0.83 (d, J = 6.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.9, 179.8, 142.7, 141.5, 136.8, 136.7, 128.9, 128.5, 128.3, 128.1, 126.4, 126.37, 116.1, 116.0, 51.0, 49.8, 39.7, 39.3, 37.1, 36.9, 35.0, 34.2, 17.9, 16.3. HRMS (FAB+) *m/z* 219.1383 [$(MH)^+$; calcd for $C_{14}H_{19}O_2$, 218.1307].

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7. α-Hydroxyallylsilane **32** was obtained in 93% yield when the alcohol was isolated by distillation at atmospheric pressure.

8. The yield of this alcohol is generally moderate. Kamimura prepared **34** in 43% yield, see Kamimura, A.; Kaneko, Y.; Ohta, A.; Matsuura, K.; Fujimoto, Y.; Kakehi, A.; Kanemasa, S. *Tetrahedron* **2002**, 9613-9620.

9. Compounds **51**, **52** and **58** were prepared following Rychnovsky's protocol: Cossrow, J.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 147-150.

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12. In the preparation of *E*-**56** we found that $BF_3 \cdot OEt_2$ gave better results than TMSOTf.

13. Maleczka and Geng reported that this same reaction catalyzed by TMSOTf-catalyzed afforded 67% of **42** and the formation of any other compounds was not reported. Maleczka, R. E. Jr.; Geng, F. *Org. Lett.* **1999**, *1*, 1115-1118.

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15. The etherification of an alcohol via the trichloroacetimidate requires for the alcohol part of the trichloroacetimidate to be activated (benzyl or allyl).

16. Reaction of alcohol **32** with MsCl in the presence of Et_3N in THF at 0 °C afforded the corresponding mesylate (96%).

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23. Ab initio calculations (Geometry Optimization using RHF/6-31G* Model) were performed by Courtney Olmsted; Chemistry Department, Michigan State University.

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CHAPTER 5

STEREOCHEMICAL REQUIREMENTS IN THE WITTIG REARRANGEMENTS OF α-ALKOXYSILYL ETHERS

5.1. Stereochemical requirements for Wittig substrates

Introduction

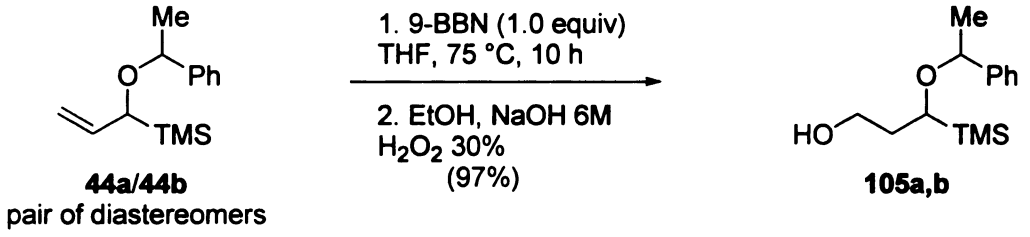
As noted in Chapter 4, those Wittig substrates with substitution at the migrating center were prepared as diastereomeric pairs, in near equal amounts (ratios ranging from 1:1 to 1.3:1.)[1] It was also noted in the same chapter that under our conditions, a pair of diastereomers have differential reactivities, with only one diastereomer readily undergoing the Wittig rearrangement. The appropriate question at this point became, "Which diastereomer (*syn* or *anti*) was undergoing the Wittig rearrangement?" In an effort to identify the two isomers we resorted to derivatization.

5.2. Derivatization of α-alkoxysilanes 44a and 44b

5.2.1. Synthesis of 2,4-dinitrophenylhydrazone derivatives of 44a and 44b

Carbonyl compounds (aldehydes and ketones) are known to form crystalline hydrazone derivatives with 2,4-dinitrophenylhydrazine, which are often employed in the identification of this class of compounds. In order to convert compounds **44a** and **44b** into their corresponding 2,4-dinitrophenylhydrazones, we oxidized the double bond to primary alcohols **105a** and **105b** (97% yield) by hydroboration/oxidation[2] (Scheme 5.1).

Scheme 5.1. Hydroboration/oxidation of diastereomeric **44a/44b**



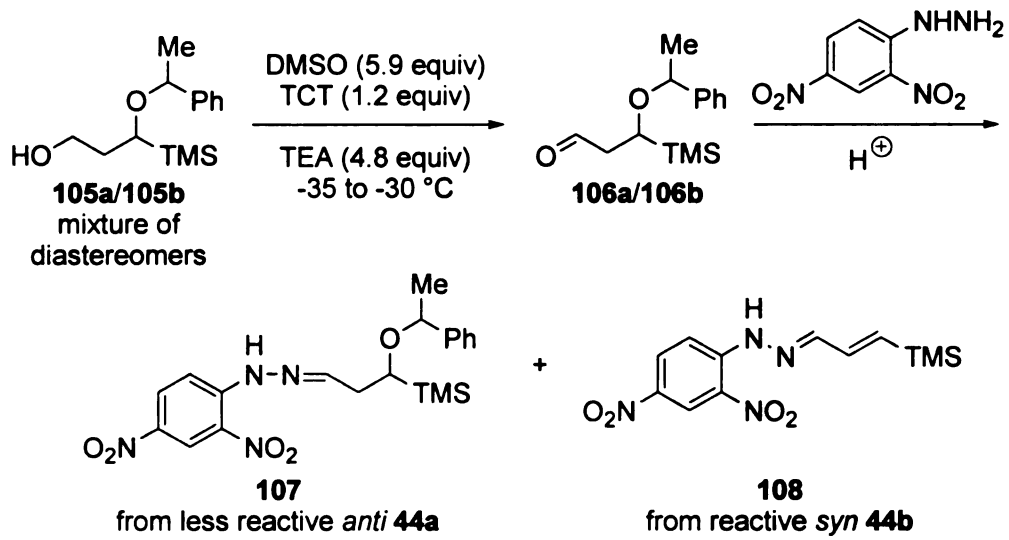
44a/44b
pair of diastereomers

105a,b

Diastereomeric alcohols **105a** and **105b** were converted into their corresponding aldehydes **106a** and **106b** via a modified Swern oxidation.[3] The crude aldehydes were subsequently converted into hydrazones by reaction with acidified 2,4-dinitrophenyl-hydrazine at room temperature (Scheme 5.2).[4]

The two diastereomeric α-alkoxysilanes *anti*-**44a** and *syn*-**44b** showed different behaviors with regard to hydrazone formation. Of the two hydrazones formed, one was the expected product (**107**) and the other (**108**) was an elimination product in which the benzyloxy group was lost. Since **44a** could be obtained pure from the Wittig rearrangement reaction, it was converted to the corresponding alcohol **105a**, and subsequently into the 2,4-dinitrophenyl hydrazone derivatize. We observed that the less reactive **44a** afforded the desired hydrazone **107** as an amorphous solid in 58% yield (mp 129-130 °C) (Scheme 4.31). The reactive **44b**, on the other hand, formed the conjugated hydrazone **108** in 32% yield (reaction was not optimized), bearing a vinyl silyl group (Scheme 5.2). Recrystallization of **108** from EtOAc afforded the pure compound (m.p. 199.5-200.5 °C). NMR, and single crystal x-ray analysis[5] revealed the presence of the two double bonds (see Figure 5.1 for ORTEP of **108**).

Scheme 5.2. Derivatization of **44a/44b**: conversion to 2,4-dinitrophenylhydrazone



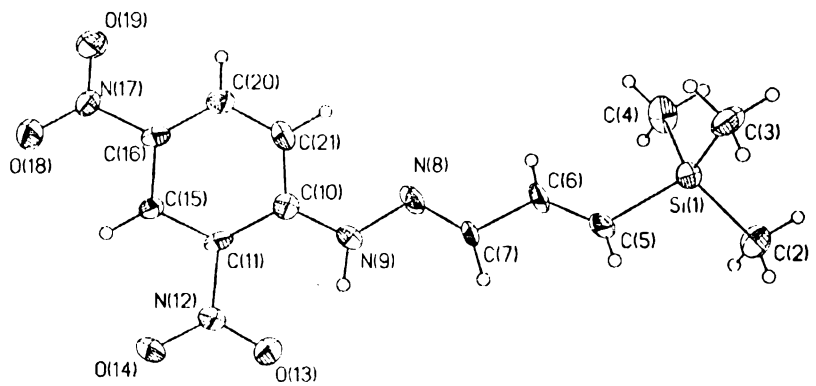
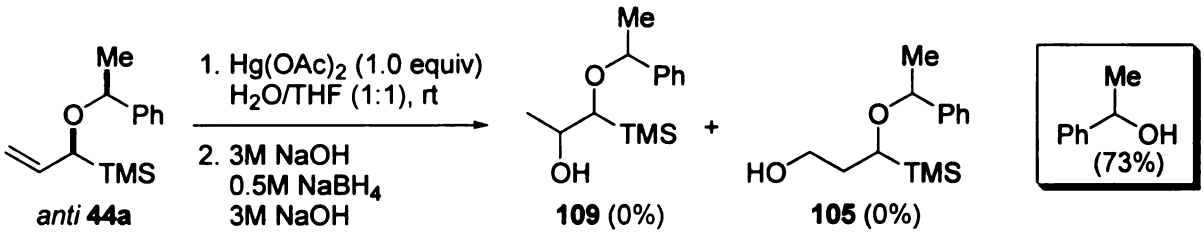


Figure 5.1. Single x-ray crystal structure analysis ORTEP view of **108**, 2,4-dintrophenylhydrazone derivative of reactive *syn* **44b**

The difficulty in recrystallizing compound **107** (hydrazone of the less reactive *anti* **44a**) was an impetus to explore alternatives. We hoped that the hydrazone of the ketone derivative (rather than the aldehyde derivative) might give better crystals for single crystal x-ray analysis. Thus, pure *anti* **44a** was subjected to oxymercuration/demercuration conditions for the purpose of making the secondary alcohol. However, this venture only led to the hydrogenolysis of the ether to give *sec*-

phenethyl alcohol in 73% yield. The desired secondary alcohol **109** was not obtained (Scheme 5.3).

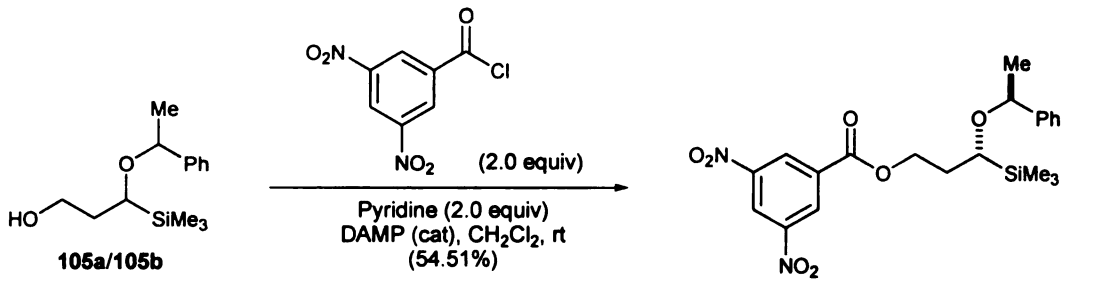
Scheme 5.3. Attempted oxymercuration/demercuration of *anti* **44a**



5.2.2. Synthesis of 3,5-dinitrobenzoyl ester of α-alkoxysilanes 44a and 44b

In a further attempt towards establishing the stereochemistry of the reactive and less reactive Wittig substrates via single crystal x-ray analysis, we converted the diastereomeric alcohol **105a,b** into the corresponding 3,5-dinitrophenyl ester[6] **110a,b**, in 55% yield (Scheme 5.4). The ester products **110a,b** were obtained as a oil/solid mixture. Recrystallization from a 1:1 mixture of absolute ethanol:hexanes[7] afford colorless crystals of **110a** (ester of the reactive **44**) and an oily mother liquor containing **110b** (ester of the less reactive **44**). Converting the alcohol from less reactive **44** to the corresponding ester gave an oil. This established that the reactive diastereomer gave the crystalline ester product (mp 74.5-75.5 °C). We obtained the single crystal X-ray structure of this compound (Figure 5.2), which revealed the relative stereochemistry of reactive **44** to be *syn* (*syn* with respect to TMS and Me groups).

Scheme 5.4. Derivatization of **44a/44b**: conversion to 3,5-dinitrophenylbenzoyl ester



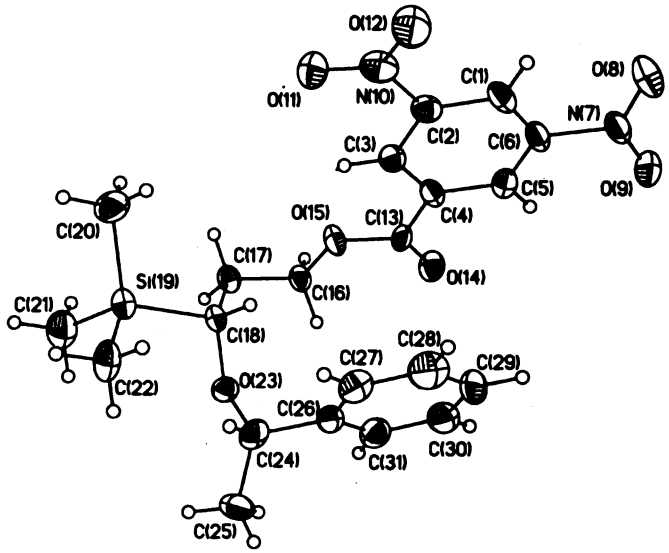
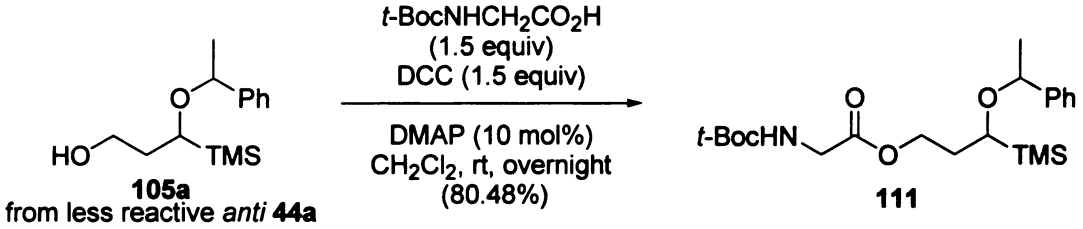


Figure 5.2. X-ray crystal structure analysis ORTEP view of **110b**, the 3,5-dinitrobenzoyl ester derivative of reactive *syn* **44b**

Though we had secured the relative stereochemistry of reactive **44b** and could infer the opposite relative stereochemistry for the less reactive diastereomer, we still wished to obtain solid evidence to corroborate our results. Amino acids are known to give crystalline ester derivatives with organic alcohols. Thus, we hoped that the ester from *N*-(tert-butoxycarbonyl)glycine and the alcohol from the less reactive **44a** would be

crystalline, enabling us get the single crystal x-ray analysis on that diastereomer. DCC mediated esterification of **105a** with *N*-(tert-butoxycarbonyl)glycine in the presence of a catalytic amount of DMAP afforded the desired ester **111** in 81% yield (Scheme 5.5). However we were unable to obtain the sought after single crystal x-ray as the ester was a thick oil.

Scheme 5.5. *Boc*-glycine ester derivative of less reactive **105a**

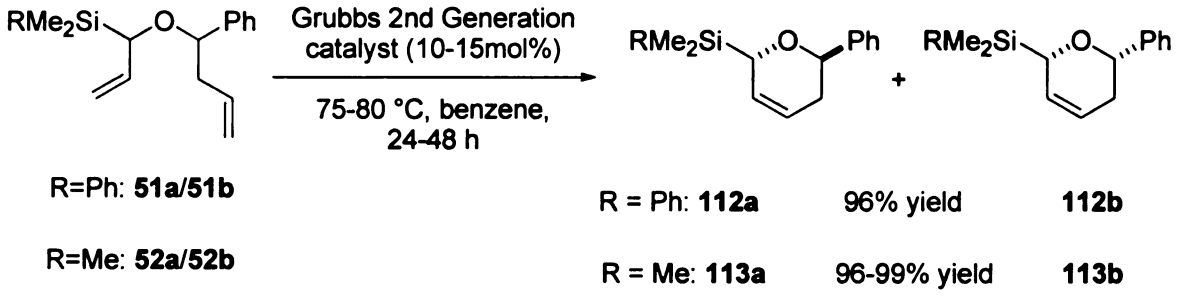


5.3. NOE Experiment

In a further attempt to establish the stereochemical requirement for the Wittig rearrangements of α-alkoxysilanes, we reasoned that if we could tie up an acyclic Wittig substrate into a ring, then we could use NMR experiments (NOE) to determine the stereochemistries of the reactive and less reactive pair of diastereomers. Toward this aim we utilized compounds **51** and **52**. Compound **52**, as reported in section 4.4.2 (and Table 4.2) undergoes rearrangement when its solution in THF is treated with 4.0 equiv. of *n*-BuLi at temperatures above -40 °C for 48 h. Only one diastereomer reacts under these conditions, furnishing the [1,2] and [1,4] products. We found that when a dilute solution (0.1-0.2 M) of **51** in benzene was heated to 70-80 °C in the presence of a catalytic amount (10-15 mol%) of Grubbs second generation catalyst, it underwent ring closing metathesis

(RCM) to afford six-membered cyclic ethers **112a/b** in 94-96% yield (Scheme 5.6). Diastereomeric **52** was similarly converted to the corresponding six-membered cyclic ethers **113a/b** in 97-99% yield. Then, each of the diastereomers, *syn*-**52** and *anti*-**52**, was subjected to the ring closing metathesis conditions. The spectral data from their respective products were compared. Stereochemical evidence was obtained from NOESY1D experiments (Figure 5.3) that revealed NOE (1%) between Ha and Hb in the RCM product resulting from the less reactive diastereomer (**113b**), an indication of *syn* stereochemistry (both protons are on the same face of the molecule). On the other hand, there was no NOE seen between Ha and Hb in the cyclic ether resulting from the RCM of the reactive isomer (**113b**), indicating that the two protons are *anti* (Figure 5.3).

Scheme 5.6. Ring closing metathesis of **51** and **52**



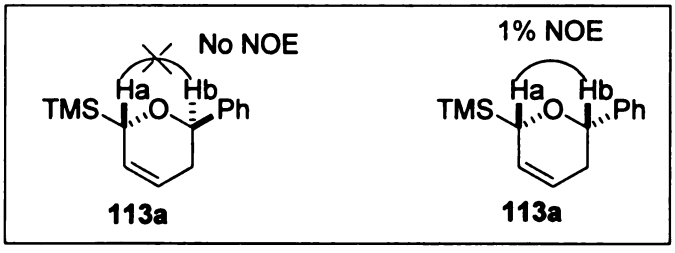
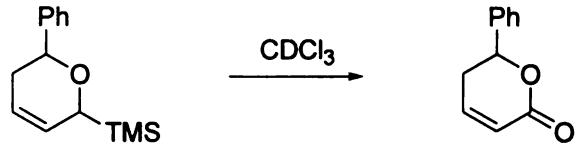


Figure 5.3. NOSEY1D result showing relative stereochemistries in **113a/b**

Compound **113** stored well in the freezer (no evidence of decomposition was seen after three months). However, we observed that the cyclic ether was acid sensitive, decomposing completely within seven days when left in $CDCl_3$ (from NMR analysis). Upon isolation of the decomposition product **114**[8], we were able to elucidate its structure by NMR spectroscopy, and it is as shown in Scheme 5.7. The new product is a cyclic enol ether which features a carbonyl functionality (incorporation of an extra oxygen atom). The mechanism of this reaction is not clear to us at this point.

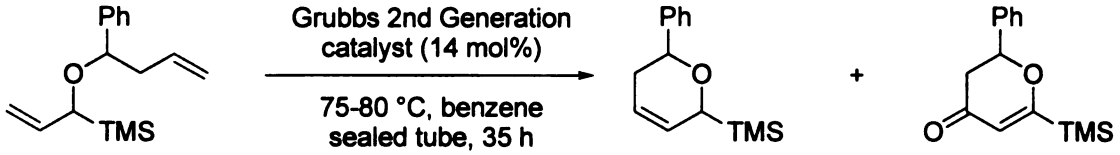
Scheme 5.7. Decomposition of metathesis product in the presence of $CDCl_3$



113 **114**

In the course of our investigation of the ring closing metathesis reaction of **52**, we found that carrying out the reaction in a sealed tube afforded **113** (45%) and a second product **115** (34%) yield. We elucidated the structure of **115** by ^1H NMR, ^{13}C NMR, and DEPT experiments and is as shown in Scheme 5.8. This compound shows incorporation of an extra oxygen atom. It also features a carbonyl group conjugated to a double bond and a vinyl trimethylsilyl group.

Scheme 5.8. Cross metathesis reaction of **52** in sealed tube



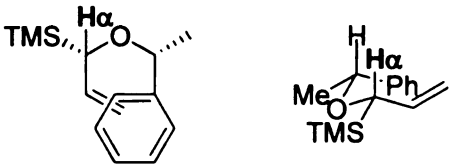
52 **113** (45%) **115** (34%)

5.4. Relative reactivities of a pair of diastereomeric α-alkoxysilanes

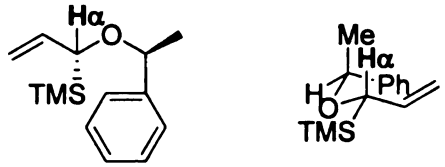
In an effort to understand the marked difference in reactivity between the *syn* and *anti* diastereomers under our Wittig rearrangement reaction conditions, a modeling study was undertaken. For this study, α-alkoxysilane **44** was employed for simplicity and modeled using the Spartan Ab initio program.[9]

Geometry Optimization using RHF/6-31G* Model showed that the *anti* isomer is lower in energy by 1.44 kcal/mol. The modeling study did not reveal much in terms of the conformations of the pair of *anti*/*syn* diastereomeric **44a**/**44b**. However, analysis of the data from this study showed that the two diastereomers have slightly different conformations (Figure 5.4). The dihedral angles were similar ($C_1C_2C_3\alpha H$ of 6° in the *syn* conformer and $C_1C_2C_3\alpha H$ of 11° in the *anti* conformer), thus no deductions could be made base on it. However, the data revealed that the aromatic ring and the double bond are on the same side of the molecule in *syn* **44b** (Figure 5.4). This suggests a possibility of π-stacking (C_1-C_7 = 3.2 Å; C_2-C_6 = 4.3 Å) (Figure 5.4). On the other hand, in the *anti* diastereomer **44a**, the aromatic ring and the double bond are on opposite sides of the molecule, with no possibility of π-stacking (C_1-C_7 = 4.4 Å; C_2-C_6 = 6.1 Å) (Figure 5.4). It appears there is some steric interaction between the TMS group and the aromatic ring that could result in the molecule being slightly out of plane. Non-planarity means that the negative charge on the α-carbon (from deprotonation) will not be effectively delocalized over the pi system (little or no resonance stabilization). The implication of this is that the α-H in the less reactive *anti* **44a** (dihedral angle $C_1C_2C_3\alpha H$ = 11°) will be less acidic than in the reactive *syn* diastereomer (dihedral angle $C_1C_2C_3\alpha H$ of 6°). It also would appear

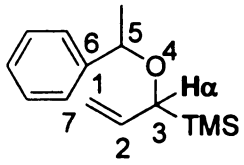
that there is some crowding around the α-H that could possibly result in the alkyllithium base having less access to that proton.



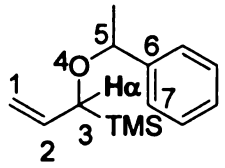
Reactive *syn* **44b** (*syn* with respect to TMS and Me groups). Structure shows possibility of *pi* stacking and the accessibility ofHα proton to base. Minimum steric interaction illustrated.



Less reactive anti **44a** (*anti* with respect to TMS and Me groups). TMS and phenyl ring on same face of the molecule. Structureshows no possibility of pi stacking. Steric interaction betweenTMS and phenyl groups as well as diaxial interaction between Me and Hα are also illustrated.



(*syn*)-**44b**
$C_1C_2C_3H\alpha$ dihedral angle = 6°
C_1-C_7 = 3.2 Å
C_2-C_6 = 4.3 Å



(*anti*)-**44a**
$C_1C_2C_3H\alpha$ dihedral angle = 11°
C_1-C_7 = 4.4 Å
C_2-C_6 = 6.1 Å

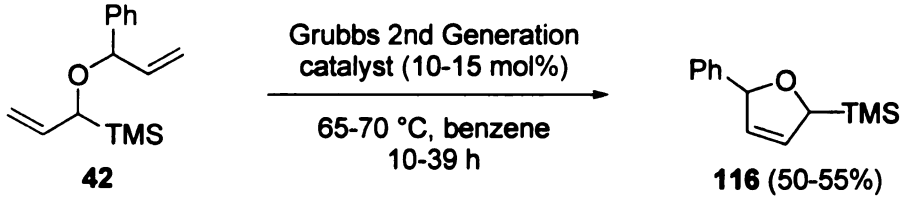
Figure 5.4. Modeling studies of the Wittig substrates **44a** and **44b**

The single crystal x-ray picture of the ester **110b** show the two aromatic rings facing each other, a conformation that would promote *pi*-stacking in the molecule, and corroborates the result from the ab initio calculations for the *syn* isomer in the preceding paragraph. However, we were unable to obtain the single crystal x-ray analysis of the less reactive *anti* diastereomer for comparison. Nevertheless, from our NOE and single x-ray analysis results, we can say with certainty that the reactive diastereomer is the *syn* isomer (TMS and alkyl groups on same side of the molecule).

5.5. Cross metathesis of α-hydrosilanes and α-alkoxysilanes

We would like to point out from the start that this part of the report has little or nothing to do with the stereochemical requirements of α-akoxysilanes in the Wittig rearrangement. The opportunity presented itself and we could not let it pass. Following our success with the ring closing metathesis of compounds **51** and **52**, we subjected **42** to similar metathesis reaction conditions and we were pleased to observe that this substrate underwent cyclization to afford the expected five-membered cyclic ether **116** in 50-55% yield (Scheme 5.9). The formation of the five-membered ring product, however, was less efficient than the formation of six-membered counterparts **112** and **113** from the cyclization of **51** and **52**, respectively (Scheme 5.6, over 95% yield in each case).

Scheme 5.9. Ring closing metathesis of **42**

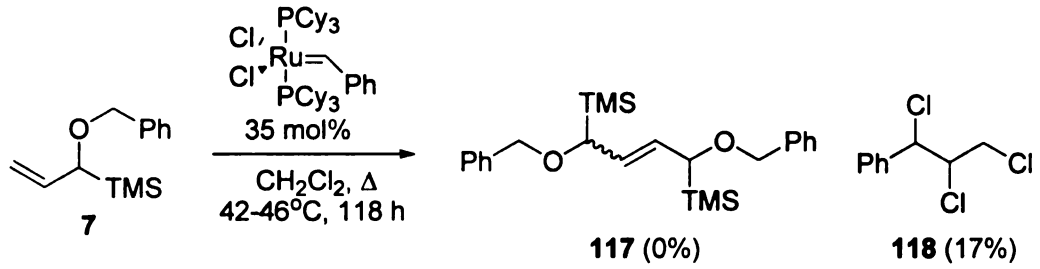


42 **116** (50-55%)

We were encouraged by the above results and we wanted to apply cross metathesis to one of the aims of this research, which was to expand the synthetic utility of α-alkoxysilanes by developing methods for generating a wide variety of these compounds for use in Wittig rearrangement reactions. Cross-metathesis with the terminal olefin of monosubstituted α-silyl ethers would generate α-alkoxysilanes with internal olefins. Several attempts were made at dimerizing our model substrate **7**, as well as cross-metathesis of this substrate with a number of partners. Dimerization using first generation Grubbs catalyst (bis(tricyclohexylphosphine) benzylidine ruthenium (IV)

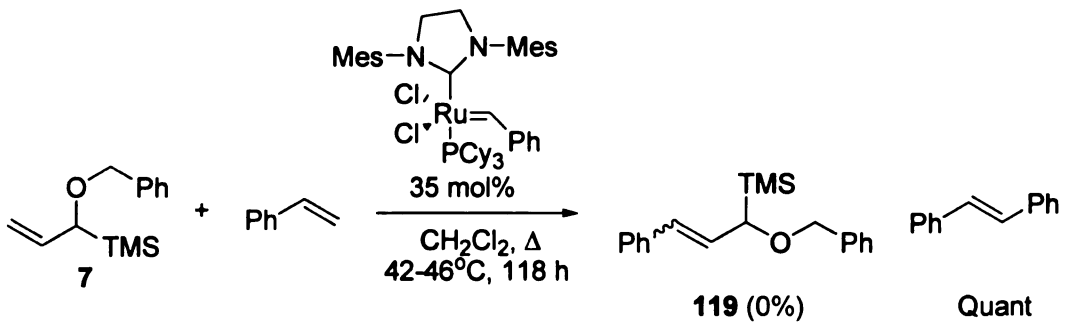
dichloride) did not give the expected dimer **117**, instead a non-silylated, heavily chlorinated compound **118** was isolated, the structure of which was elucidated by ^{1}H NMR, ^{13}C NMR and DEPT and is as shown in Scheme 5.10.

Scheme 5.10. Attempted Dimerization of model substrate **7**



Cross-metathesis of compound **7** with styrene[10] in the presence of second generation Grubbs catalyst (tricyclohexylphosphine[1,3-bis(2,4,6,-trimethylphemyl)-4,5-dihydroimidazol-2-ylidene][benzylidine]ruthenium(IV)dichloride) resulted in the quantitative formation of trans-stilbene. No crossed product **119** was observed (Scheme 5.11).

Scheme 5.11. Cross-Metathesis of model substrate **7** with Styrene

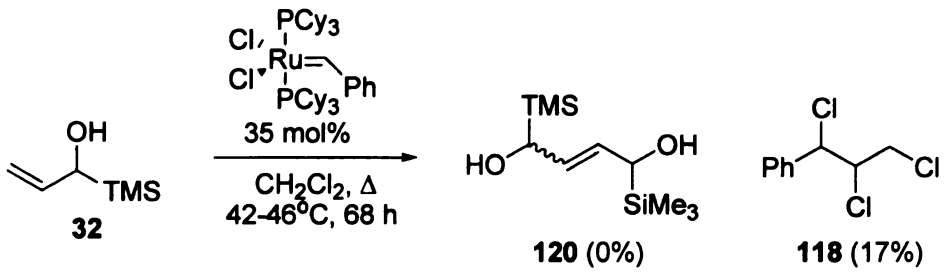


Cross-metathesis of compound **7** with acrylonitrile[11] was also attempted, but no product was observed.

We thought that a good alternative route to α-alkoxysilanes possessing internal double bonds would be to employ α-hydroxysilanes **32** in the cross-metathesis reaction to produce new α-hydroxysilanes featuring internal double bonds, which we could then etherify to obtain the α-alkoxysilanes. When **32** was treated with first generation Grubbs catalyst (10 mol%, 0.005M in CH_2Cl_2, 40-44 °C), the product isolated was identical (^{1}H-NMR, ^{13}C-NMR and GC-MS) to the product (**118**) isolated from the attempted dimerization of **7** (Scheme 5.12). This time, the formation of the product required less catalyst loading (10 mol%) and shorter reaction time (78 h), than with **7** (35 mol% and 118 h).

The observation that the attempted dimerization of both α-alkoxysilane **7** and α-hydroxysilane **32**, mediated by the same catalyst, gave the same product, seemed to indicate that the product might be either coming from the catalyst, and since the product is heavily chlorinated (from GC-MS), the solvent, CH_2Cl_2, might be participating in the reaction.

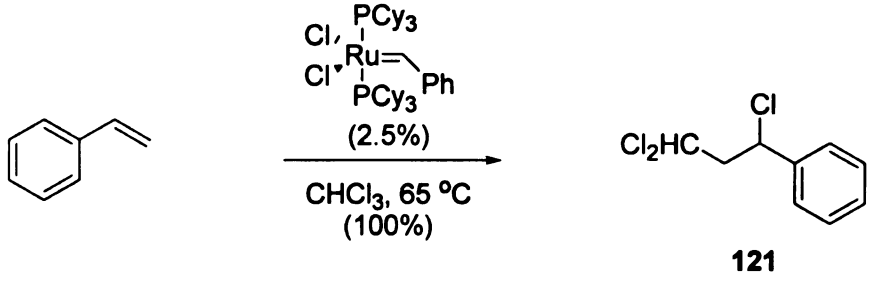
Scheme 5.12. Metathesis Dimerization of **32**



32 **120** (0%) **118** (17%)

A search of the literature revealed the ability of low-valent ruthenium complexes to catalyze electron transfer reactions is known.[12-16] Ru(II) catalyzes the radical addition of carbon tetrachloride or chloroform to olefins (Kharasch addition reaction).[12] The first report of this reaction employed $(Ph_3P)_2RuCl_2$ as the catalyst.[13] Subsequently Grubbs ruthenium catalyst,[14] $Cp^*Ru(Ph_3P)_2Cl$,[15] and ruthenium-carborane phosphine complexes have been used.[16] For example, Grubbs first generation catalyst has been reported to catalyze the addition of chloroform to styrene to afford the product **121** quantitatively (Scheme 5.13).

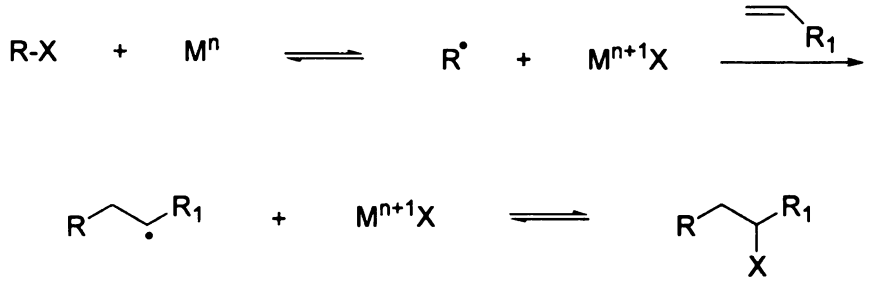
Scheme 5.13. Ruthenium Catalyzed Addition of Chloroform to Styrene



121

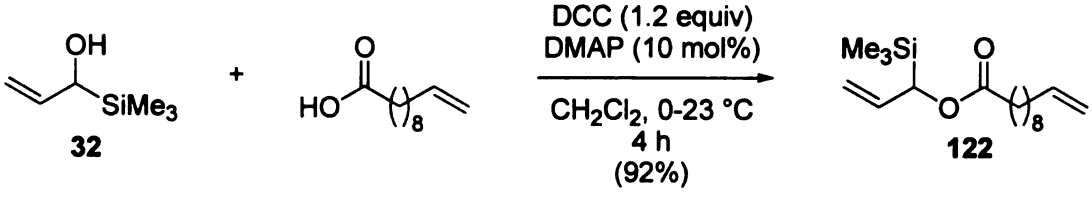
In Kharasch addition reaction, the ruthenium acts as the carrier of the halogen in a reversible redox process. Initially, the transition metal species, M^n, abstracts a halogen atom X from the organic halide, R-X, to form the oxidized species, $M^{n+1}X$, and the carbon-centered radical R*. Subsequently, the radical, R*, reacts with alkene with the formation of the intermediate radical species $R\text{-}R_1^*$. The reaction between $M^{n+1}X$ and $R\text{-}R_1^*$ results in the target product $R\text{-}R_1\text{-}X$, and regeneration of the reduced transition-metal species, M^n, which further reacts with R-X and promotes a new redox cycle (Scheme 5.14).

Scheme 5.14. Mechanism of the Kharasch Addition Reaction



One of the coupling partners we investigated in the cross-metathesis reaction is undec-10-enoic acid ethyl ester. However, this too, did not undergo the desired cross-metathesis. Following our success in the ring closing metathesis of **42**, **51**, and **52**, we decided to lock the two reacting olefins in one molecule and look to effect an RCM of the resulting compound. The requisite substrate **122**[17] was prepared in two steps starting from undec-10-enoic acid ethyl ester. Hydrolysis of the ester with 10% NaOH, followed by coupling of the resulting carboxylic acid and **32** afforded the desired ester **122** in 92% yield (Scheme 5.15). However, when this ester was employed in the cross metathesis reaction, the expected reaction failed to occur. A plausible explanation could be the ring size of the expected lactone product. If the intramolecular cross metathesis occurred, the resulting product would be a 13-membered ring lactone, which in our opinion would not be very favorable.

Scheme 5.15. Preparation of undecanoic acid ester of **32**



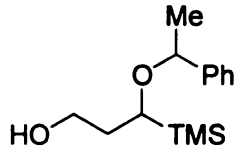
5.6. Conclusions

We have been able to establish the relatively stereochemistry of the pair of diastereomeric α-alkoxysilanes undergoing the Wittig rearrangement. The reactive diastereomer has the *syn* relative stereochemistry (α-TMS and benzylic alkyl substituent on the same face of the molecule) while the less reactive diastereomer has the *anti* relative stereochemistry. We could do this as a result of the differential reactivities of a pair of diastereomers which we observed in the course of this research. Under our standard Wittig conditions, the *anti* diastereomer undergoes the rearrangement while the *syn* diastereomer does so only very sluggishly, thus affording an efficient tool for separation of the two diastereomers. The difference in the chemical properties between the pair of diastereomers also extends to their reactions with other compounds. In this chapter, we noted that the reactive **44b** formed a crystalline hydrazone after eliminating the *sec*-phenethyl group whereas the less reactive diastereomer formed the expected hydrazone as an amorphous solid. With regard to the formation of 3,5-dinitrobenzoate, the reactive diastereomer (anti stereochemistry) formed a crystalline solid whereas the ester of the less reactive diastereomer (syn stereochemistry) was a clear oil.

We were also able to accomplish the Ru-catalyzed ring closing metathesis of α-alkoxysilanes using Grubbs catalyst efficiently. This is an important addition to literature considering that such cyclizations are usually difficult to effect under Ru catalysis.

At this point in our study we thought that we were ready to tackle the issue of the mechanism of the Wittig rearrangements of α-alkoxysilanes. We were particularly interested in the mechanism of the [1,4]-Wittig. As mentioned in Chapter 1 of this dissertation, very little is known about the mechanism of the [1,4]-Wittig rearrangement

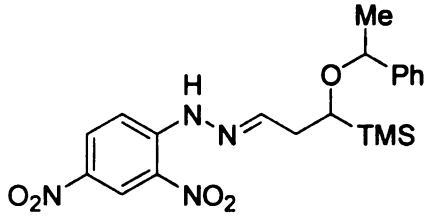
of allyl alkyl ethers as this pathway is still beclouded by many controversies. In Chapter 6 we will discuss our results in this regard.



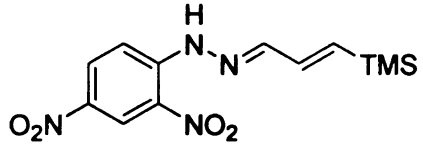
105a/b

Preparation of 105a/b: A 100 mL round-bottomed flask equipped with a magnetic stir bar and a N_2 line was charged with 9-BBN (0.5 M solution in THF, 2.04 mL, 1.02 mmol) and the mixture refluxed. The substrate **44** (671 mg, 2.85 mmol) was then added as a THF solution (0.57 M) and the reaction refluxed at oil bath temperature of 90 °C, for 10 h. Reaction mixture was cooled to 55 to 65 °C and EtOH (2.0 mL), NaOH (6 M, 0.5 mL) and H_2O_2 (30%, 1.0 mL) added. The reaction was stirred at 55 to 65 °C for 1 h and cooled to room temperature. The aqueous phase was saturated with K_2CO_3, phases were separated, organic phase dried over anhydrous K_2CO_3 and concentrated to afford the crude product. Purification by silica gel (hexanes/EtOAc (0-10%)) gave 702 mg of pure **105a/b** in combined 97% yield. IR (neat) 3370, 2955, 2928, 1452, 1371, 1248 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.26 (m, 10H), 4.59-4.53 (q, J = Hz, 1H), 4.39-4.32 (q, J = Hz, 1H), 3.89-3.75 (m, 2H), 3.52-3.44 (m, 2H), 3.20-3.20 (m, 2H), 2.21-2.09 (m, 3H), 1.68-1.59 (m, 5H), 1.43-1.41 (d, 7H), 0.09 (s, 9H), -0.07 (s, 9H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 143.53, 143.47, 128.5, 128.2, 127.8, 127.5, 126.8, 126.7, 77.9, 76.4, 70.0, 69.0, 62.3, 61.3, 34.6, 33.7, 31.7, 27.4, 23.6, 23.5, 22.6, -2.5, -2.8. Reactive: HRMS (EI) *m/z* 253.1627 [$(M+H)^+$; calcd for $C_{14}H_{25}O_2Si$, 253.1624]. Less reactive *anti*-**105b**: IR (neat) 3358, 2955, 2928, 1493, 1452, 1371, 1248 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.22 (m, 5H), 4.58-4.54 (apparent q, J = 6.8, 6.3 Hz, 1H),

3.89-3.84 (m, 1H), 3.80-3.75 (m, 1H), 3.23 (t, J = 5.4, 4.9 Hz, 1H), 2.20-2.12 (m, 1H), 1.67-1.60 (m, 1H), 1.42 (d, J = 6.8 Hz, 3H), -0.7 (s, 9H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 143.5, 128.2, 127.5, 126.8, 76.4, 70.1, 62.5, 34.6, 31.7, 23.7, -2.8. HRMS (EI) *m/z* 253.1618 [$(M+H)^+$; calcd for $C_{14}H_{25}O_2Si$, 253.1624].



107



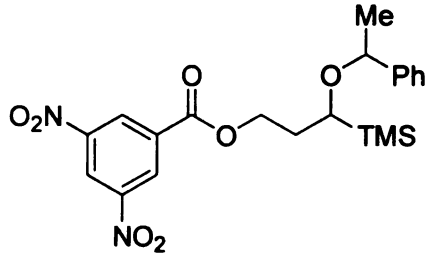
108

Preaparation of hydrazone 107 and 108: To a cold (-35 to -30 °C) solution of 2,4,6-trichloro[1,3,5]-triazine(cyanuric chloride) (158 mg, 0.86 mmol) in THF, was added DMSO (0.30 mL, 328 mg, 4.20 mmol) and the mixture stirred for 30 min. A 0.1M THF solution of the substrate **105** (181 mg, 0.72 mmol) was added very slowly and the reaction stirred for 30 min. Then TEA (0.48 mL, 345 mg, 3.41 mmol) was added. After stirring for additional 20 min, the reaction was warmed to room temperature. The solvent was removed under vacuum and Et_2O added to the solid formed. Reaction was quenched by adding HCl (1 M, 2.0 mL). Phases were separated and the organic phase washed with $NaHCO_3$ (aq, sat), followed by brine, dried over Na_2SO_4 and the solvent evaporated to yield an aldehyde intermediate, which was treated with an acidic solution of 2,4-dinitrophenylhydrazine to afford 80 mg (25%) of a mixture of hydrazones (yellow amorphous and orange crystals). Recrystallization from EtOAc afforded orange crystals.

107: IR (neat) 3287, 2955, 2918, 1618, 1593, 1520, 1335, 1306, 1271, 1072 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.02 (s, 1H), 9.11 (d, J = 2.7 Hz, 1H), 8.30-8.27 (dd, J = 9.5, 2.6 Hz, 1H), 7.92-7.89 (d, J = 9.5 Hz, 1H), 7.54 (t, J = 6.0, 5.7 Hz, 1H), 7.34-7.26

(m, 5H), 4.54-4.50 (q, J = 6.6, 6.4 Hz, 1H), 3.24 (t, J = 5.7, 5.5 Hz, 1H), 2.89-2.83 (m, 1H), 2.62-2.56 (m, 1H), 1.39 (d, J = 6.4 Hz, 3H), -0.04. ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.5, 130.0, 128.4, 127.7, 126.9, 123.5, 116.4, 76.6, 67.4, 33.5, 24.2, -3.1. HRMS (EI) *m/z* 431.1749 [$(MH)^+$; calcd for $C_{20}H_{27}N_4O_5Si$, 431.1751]. (mp 199.5-200.5 °C).

108: IR (neat) 3291, 1618, 1516, 1416. 1371, 1321, 1267, 1080 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.10 (s, 1H), 9.11 (d, J = 2.4 Hz, 1H), 8.31-8.29 (dd, J = 10.2, 8.8, 1.9 Hz, 1H), 7.94 (d, J = 9.3 Hz, 1H), 7.72 (d, J = 9.3 Hz, 1H), 6.79-6.73 (dd, J = 19.0, 18.5, 9.3, 8.8 Hz, 1H), 6.52-6.48 (d, J = 18.5 Hz, 1H), 0.15 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.0, 146.2, 144.7, 138.9, 130.0, 123.4, 116.7, -1.7. HRMS (EI) *m/z* 308.0935 [$(M)^+$; calcd for $C_{12}H_{16}N_4O_4Si$, 308.0941]. (mp 129-130 °C)

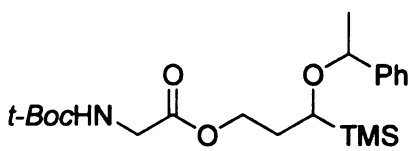


110a/110b
Mixture of diastereomers

Preparation of the ester 110 (mixture of diastereomers): A mixture of the substrate alcohol, **105** (201 mg, 0.80 mmol), 3,5-dinitrobenzoyl chloride (366 mg, 1.59 mmol) in pyridine as solvent, was heated to reflux for 52-55 h. Then the solvent was removed under reduced pressure and the crude product purified by chromatography on silica gel (hexanes/EtOAc (0-10%) to afford 194 mg, 55% of the expected ester **110** as a solid/oil mixture. Separation by crystallization from a 1:1 EtOH/hexane mixed solvent afforded product as colorless crystals. IR 2961 1732, 1630, 1547, 1462, 1344, 1279, 1250, 1167 cm^{-1}.

Reactive *syn* **110b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.22-9.16 (m, 2H), 8.88 (d, J = 2.2 Hz, 1H), 7.33-6.96 (m, 10H), 4.59-4.46 (m, 3H), 4.37-4.29 (m, 2H), 4.19-4.10 (m, 1H), 3.25-3.20 (dd, J = 8.2, 7.7 Hz, 1H), 3.16-3.13 (apparent t, J = 6.6, 5.0 Hz, 1H), 2.30-2.20 (m, 1H), 2.03-1.95 (m, 1H), 1.90-1.83 (m, 2H), 1.43-1.40 (dd, J = 6.6, 6.0 Hz, 6H), 0.15 (s, 9H), 0.02 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.2, 148.4, 143.8, 134.0, 129.2, 128.2, 127.4, 126.7, 122.0, 78.1, 66.7, 64.4, 30.6, 23.6, -2.7. (Mp. 74.5 – 75.5 °C).

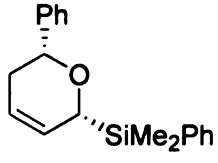
Less reactive *anti*-**110a**: m.p. 74.5-75.5 °C. IR (neat) 2957, 1728, 1630,1543, 1348, 1279, 1246 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (t, J = 2.2 Hz, 1H), 8.88 (d, J = 2.2 Hz, 2H), 7.29-6.99 (m, 5H), 4.36-4.29 (m, 2H), 4.18-4.10 (m, 1H), 3.25-3.20 (dd, J = 8.0, 6.0 Hz, 1H), 1.90-1.83 (m, 2H), 1.41 (d, J = 6.3 Hz, 3H), 0.15 (s, 9H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 162.2, 148.4, 143.9, 134.0, 129.2, 128.2, 127.4, 126.7, 122.1, 78.1, 66.7, 64.4, 30.6, 23.6, -2.7. HRMS (Electrospray) *m/z* 447.1599 [$(M+H)^+$; calcd for $C_{21}H_{27}N_2O_7Si$, 447.1587].



111

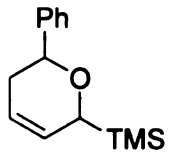
Preparation of ester 111: A solution of less reactive *anti*-**105** (128 mg, 0.506 mmol), *N*-(*tert*-butoxycarbonyl)glycine (1.5 equiv, 133 mg, 0.758 mmol), and DMAP (10 mol%, 6 mg, 0.051) in CH_2Cl_2 57.0mL) was cooled to 0 °C. Then a solution of DCC (1.5 equiv, 157 mg, 0.758 mmol) in CH_2Cl_2 (2.0 mL) was added slowly via syringe. Following this addition, the cold bath was removed and reaction warmed to room temperature. Reaction was stirred at room temperature overnight, then filtered to remove the urea by-product. The filtrate was washed with 0.5 M HCl and $NaHCO_3$ (aq. sat.), and

dried over $MgSO_4$. Filtration and removal of solvent in vacuo, and then purification by column chromatography on silica gel afforded 167 mg of *anti*-**111** as a thick colorless oil in 81% yield. IR (neat) 3374, 2976, 2932, 1753, 1721, 1512, 1454, 1368, 1250, 1169 cm^{-1}. 7.31-7.24 (m, 5H), 5.00 (bs, 1H), 4.45-4.39 (q, J = 12.9, 6.6, 6.3 Hz, 1H), 4.27-4.22 (t, J = 7.4, 7.1 Hz, 2H), 3.90 (d, J = 5.5 Hz, 2H), 3.05-3.01 (t, J = 6.3, 5.5 Hz, 1H), 2.09-1.97 (m, 1H), 1.87-1.76 (m, 1H), 1.44 (s, 9H), 1.37, (d, J = 6.6 Hz, 3H), -0.9 (s, 9H). 170.2, 155.5, 143.8, 128.1, 127.3, 126.7, 80.0, 76.5, 66.5, 63.3, 42.5, 29.6, 28.4, 23.9, -2.9. HRMS (EI) *m/z* 410.2370 [$(M+H)^+$; calcd for $C_{21}H_{35}NO_5Si$, 410.2363].



112

Preparation of 112: **General method F for metathesis reactions**. A mixture of less reactive *anti*-**51** (89 mg, 0.28 mmol) and Grubbs second generation Ru catatyst (15 mol%, 35 mg, 0.04 mmol) in benzene (2.0 mL, 0.14 M) was heated to 70-77 °C for 10 h. Reaction mixture was allowed to cool to room temperature, concentrated on the rotavap and purified on silica gel to afford 88 mg (0.26 mmol, 94%) of trimethyl-(6-phenyl-5,6-dihydro-2H-pyran-2-yl)-silane, **112**. IR (neat) 3069, 3028, 2957, 2920, 1620, 1495, 1452, 1427, 1248, 1113 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.40, (s, 3H), 0.42 (s, 3H), 2.11-2.29 (m, 2H), 4.42-4.46 (m, 2H), 5.75-5.96 (m, 2H), 7.23-7.75 (m, 10H). ^{13}C NMR (300 MHz, $CDCl_3$) δ -5.79, -5.00, 34.10, 71.25, 75.49, 121.46, 125.54, 126.89, 127.59, 127.63, 128.03, 129.14, 134.11, 136.61, 143.76. HRMS (FAB+) *m/z* [(M^+) 294.1441; calcd for $C_{19}H_{22}OSi$, 294.1440].

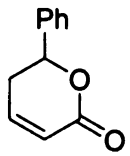


113

Preparation of 113: Applying general method **F** to 162 mg (0.63 mmol) of a 2.64:1 (*cis/trans*) diastereomeric **52** (ratio determined by GC-FID), and 80 mg (15 mol%, 0.094 mmol) of catalyst in 6.0 mL of benzene (0.104 M) at 75-80 °C for 10 h afforded, after silica gel chromatography, 146 mg (quant) of 3.31:1 diastereomeric **113**. IR 2957, 2774, 1604, 1493, 14521383, 1248 (neat) cm^{-1}.

Less reactive *anti*-**113a**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.23 (m, 5H), 5.85-5.76 (m, 2H), 4.75-4.71 (t, J = 5.7, 5.3 Hz, 1H), 4.04-4.02 (m, 1H), 2.43-2.39 (m, H), 0.1 (s, 9H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 142.0, 128.1, 128.0, 127.1, 126.5, 119.9, 72.3, 70.1, 30.2, -2.8. HRMS (FAB+) *m/z* [$(M-H)^+$ 231.1206; calcd for $C_{14}H_{19}OSi$, 231.1205].

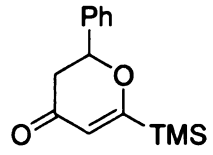
Reactive *syn*-**113b**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.21 (m, 5H), 5.85-5.57 (m, 2H), 4.42-4.37 (dd, J = 9.7, 3.5 Hz, 1H), 4.19-4.15 (m, 1H), 2.28-2.10 (m,2H), 0.09 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 128.02, 127.97, 126.9, 125.5, 121.0, 75.3, 711.6, 34.2, -3.9.



114

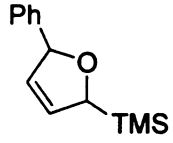
Formation of 114: Allowing a $CDCl_3$ solution of **113** to sit on the bench for about 7 days resulted in complete conversion to decomposition product **114**.[8] IR 2912, 1721, 1495, 1454, 1383, 1248 (neat) cm^{-1}. ^{1}HNMR ($CDCl_3$, 500 MHz) δ 7.41-7.32 (m, 5H), 6.97-6.93 (m, 1H), 6.14-6.11 (ddd, J = 9.9, 2.5, 1.1 Hz, 1H), 5.45-5.42 (dd, J = 11.3,

4.7 Hz, 1H), 2.57-2.69 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 164.2, 145.1, 138.3, 128.6, 128.5, 125.9, 121.4, 79.2, 31.5. HRMS (Methane CI) *m/z* 174.0680 [$(M)^+$; calcd for $C_{11}H_{10}O_2$ 174.0681].



115

Cyclization product 115: Applying representative procedure **F** to 235 mg (0.91 mmol) of **52** and 110 mg (0.130 mmol) of Grubbs second generation Ru catalyst in C_6H_6 in a sealed tube and heating to 80 °C for about 30 h, gave a mixture of 113 and 115 which was readily separable by column chromatography on silica gel (hexanes/EtOAc 0-5%) to afford 94 mg (45%) of **113** and 75 mg (34%) of **115** as colorless oils. **115**: IR (neat) 2959, 1667, 1557, 1497, 1454, 1304, 1250, 1234 1070 (neat) cm^{-1}. ^{1}HNMR ($CDCl_3$, 300 MHz) δ 7.41-7.33 (m, 5H), 5.72 (d, *J* = 1.0 Hz, 1H), 5.33-5.30 (dd, *J* = 14.6, 3.5 Hz, 1H), 2.81-2.74 (dd, *J* = 16.8, 14.1 Hz, 1H), 2.64-2.0 (ddd, *J* = 16.8, 3.5, 1.3 Hz, 1H), 0.21 (s, 9H). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 191.7, 185.7, 139.0, 128.7, 128.4, 125.9, 114.1, 80.6, 43.4, -3.02. HRMS (EI) *m/z* 246.1068 [$(M)^+$; calcd for $C_{14}H_{18}O_2Si$, 246.1076].



116

Preparation of 116: Applying the above representative method to 325 mg (1.32 mmol) of **42**, and 112 mg (0.132 mmol) of catalyst in 7.0 mL of benzene (0.19 M) at 75-78 °C for 36-48 h afforded 198 mg (69%) of the five-membered cyclic ether **116**.

116a: A clear oil. IR (neat) 2957, 2929, 1599, 1493, 1449, 1250, 1097 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.39-7.21 (m, 5H), 5.54-5.47 (dd, *J* = 10.7, 7.7 Hz, 1), 5.14 (t, *J* = 2.5 Hz, 1H), 3.14-3.04 (ddd, *J* = 11.0, 2.5 Hz, 1H), 2.59-2.50 (dd, *J* = 8.0, 7.7, 2.7 Hz, 1H), 0.20 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1, 144.1, 128.3, 127.2, 125.3, 109.9, 82.9, 39.8, -2.1. HRMS (FAB+) *m/z* [$(M+H)^+$ 219.1204; calcd for $C_{13}H_{19}OSi$, 219.1205].

116b: A shiny white fluffy solid. IR (neat) 2957, 1597, 1495, 1452, 1248, 1072 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.27 (m, 5H), 6.05-6.01 (dt, *J* = 6.04, 2.0 Hz, 1H), 5.73-5.70 (dt, *J* = 7.1, 6.7, 2.2 Hz, 1H), 5.67-5.63 (ddd, *J* = 3.0, 2.7 Hz, 1H), 4.80-4.75 (ddd, *J* = 3.9, 2.8, 1.9 Hz, 1H), 0.09 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 128.9, 128.3, 127.5, 126.5, 126.4, 88.6, 82.7, -3.7.

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15. Simal, F.; Wlodarczk, L.; Demonceau, A. *Tetrahedron Lett.* **2000**, *41*, 6071.

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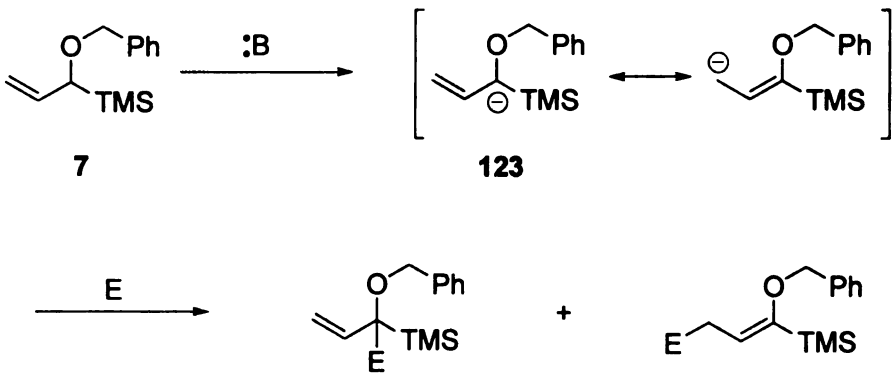
CHAPTER 6

ON THE MECHANISM OF [1,4]-WITTIG REARRANGEMENT OF α-ALKOXYSILANES

6.1. Trapping of Carbanion of model substrate 7

In Chapter 2 of this dissertation we showed that the Wittig rearrangement of α-alkoxysilane **7** was initiated by deprotonation of the α-proton with alkyllithium bases. Thus we asked if deprotonation was concurrent with rearrangement? If the two events were not concurrent, the next question would be if it were possible to hold the intermediate carbanion **123** (Scheme 6.1) long enough to trap it with an electrophile?

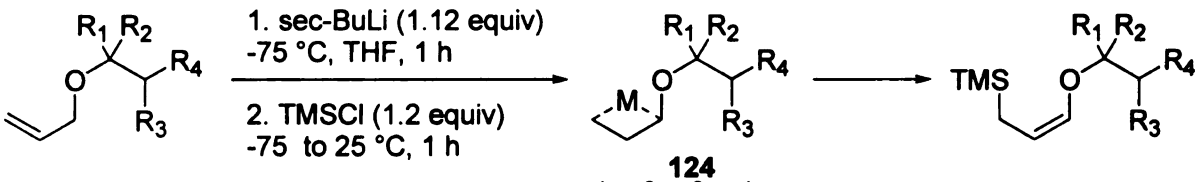
Scheme 6.1. Generating and trapping the carbanion of model substrate **7**



To answer the question of whether or not deprotonation and rearrangement of α-alkoxysilanes are concurrent or separate events we searched the literature for precedence. We found that in 1989 Schlosser and Strunk[1] had reported experimental conditions that allow virtually quantitative metalation of allyl ethers without simultaneous [1,2] and [1,4] rearrangements. This involved generating organometallic intermediates **124** [M = Li] with *sec*-BuLi in THF at -75 °C for 1 h, and trapping with TMSCl (addition of TMSCl at

-75 °C and allowing to warm to 25 °C for 1 h) to afford alkyl 3-trimethylsilyl-1-propenyl ethers with high yields (Scheme 6.2). They also reported that when the solutions containing intermediate **124** were stored 2 h at -25 °C before being acidified, no allyl or propenyl ethers remained. However in these cases only small quantities of the putative product aldehydes or alcohols were detected. Moreover many attempts to improve the mass balance failed.

Scheme 6.2. Trapping of carbanion of allyl ethers by Schlosser and Strunk[1]



124

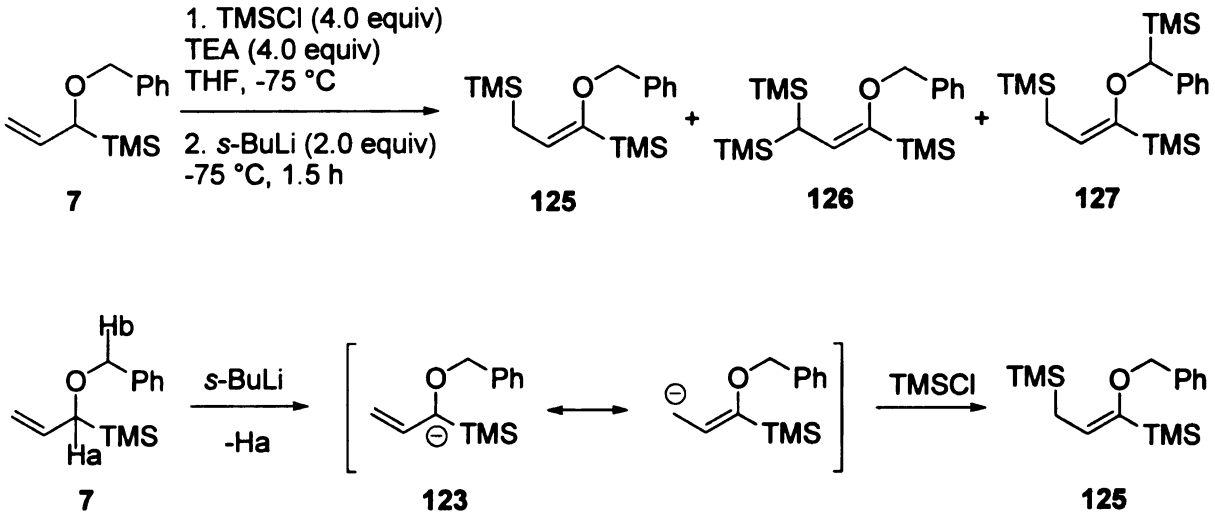
M = Li; R^1, R^2, R^3, R^4 = H or alkyl

Taking a lead from the above named authors, we decided to employ TMSCl as our elecrophile. However, the rearrangement of **7** at -78 °C was very facile, being complete in about 30 min, and attempted trapping only afforded **8**. We were able to get around this problem by initiating the Wittig rearrangement reaction in the presence of the electrophile (Scheme 6.3). Thus, treatment of a cold (-78 °C) mixture of **7**, and TMSCl (2.0 equiv)/TEA (2.0 equiv) with *sec*-BuLi (2.0 equiv; very slow addition), stirring at this temperature for 1 h, followed by an aqueous workup, resulted in the formation of three products. The ratio of these products depended on the mode of addition of the base.

Slow addition of base (1.0 mL/70 min) gave a very clean reaction that resulted in the formation of a single product **125** in 55% yield (Scheme 6.3). Formation of the observed product could be rationalized as arising from α-deprotonation leading to a

resonance-stabilized allylic anion, followed by selective capture of the electrophile at the less hindered carbon (second reaction of Scheme 6.3).

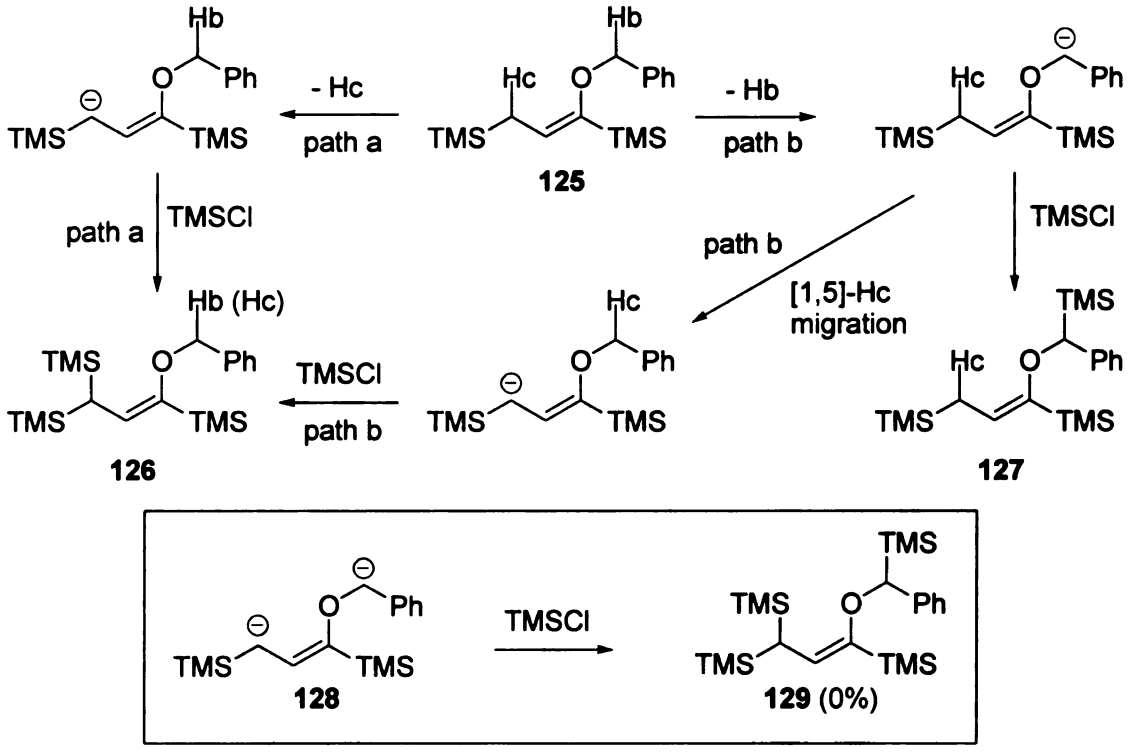
Scheme 6.3. Deprotonation and Trapping of carbanion of **7**



More rapid addition of base (approximately 1.0 mL/35 min) resulted in the formation of a mixture of three compounds, **125**, **126**, and **127** in a combined 66% yield, with **125** as the major product. However, fast addition of the base (beyond 1.0 mL/35 min) under similar reaction conditions led to the formation of a mixture of three compounds, with **127** as the major product, followed by **126**. It is likely that on slow addition of base, compound **125** is formed initially, and subsequently undergoes further deprotonation to afford **126** and **127** (Scheme 6.3). Once **125** is formed, there seems to be competition for the removal of protons Hb and Hc (refer to Scheme 6.4). Compound **126** could result from two pathways (Scheme 6.4): (1) selective removal of Hc followed by silylation (path a) or (2) selective removal of Hb, [1,5]-Hc migration, perhaps promoted by the ability of the two silyl groups to stabilize the resulting anion followed by silylation (path b). It should be noted that formation of a dianion from **125** is a possibility

that we are not ruling out at this time. However, generation of a dianion would result in the formation of a tetrasilylated product **128**, which was not observed (Scheme 6.4).

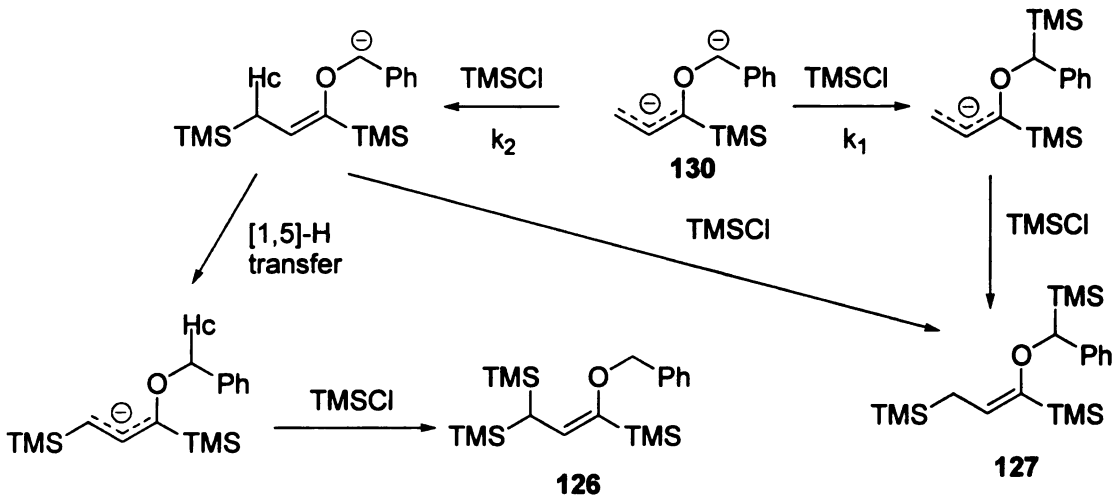
Scheme 6.4. Plausible fate of compound **125**



The selective formation of **127** following fast addition of base prompted us to propose the intermediacy of a dianionic species **130**, which could be generated if $k_1 > k_2$. Also as shown in Scheme 6.5, compound **127** could result from two possible pathways both of which could be operative at the same time. Compounds **126** and **127** were unexpected, but helped shed some light on the deprotonation process and that was the possibility of dianion formation. Dianion formation could account for the problems we had earlier in this study, which was non-reproducibility of the Wittig rearrangement results of our model substrate **7** when the study was carried out with excess of base (in this case MeLi).

We ran a parallel control experiment consisting of **7**, TMSCl (4.0 eq)/TEA (4.0 eq), THF, -78 °C, but excluding *sec*-BuLi, and no reaction occurred, ruling out the possibility that TEA might, in anyway, be involved/aiding the initiation of the Wittig rearrangement reaction.

Scheme 6.5. Plausible pathway for the observed products

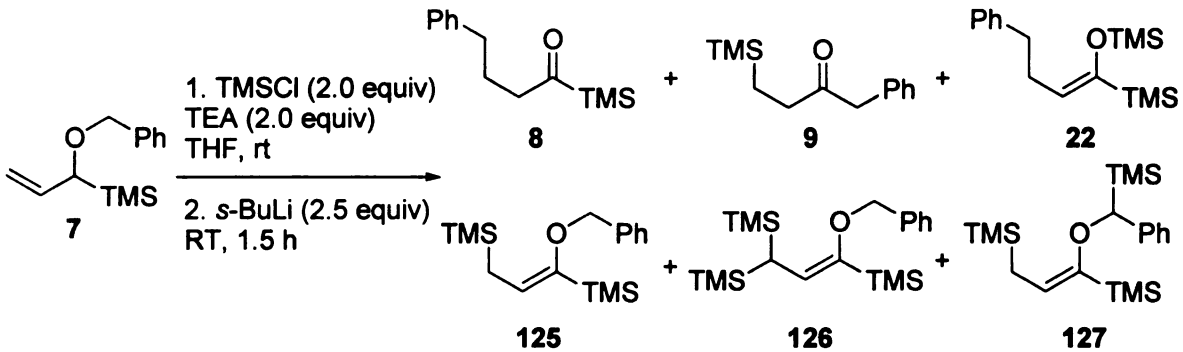


In all the above experiments, Wittig products were not evident. In addition, the complete absence of rearranged products suggests that at low temperatures, rearrangement was not fast enough to compete with electrophile capture, thus permitting trapping of the deprotonated species before it can rearrange. This observation could be interpreted to imply that the breaking of the O–C bond is the slow (rate limiting) step in this reaction. This experiment was conclusive evidence that in the Wittig rearrangement of our model substrate, α-deprotonation and cleavage of C–O bond, and hence rearrangement, are not concurrent events.

A pertinent question at this point then became[2] "could rearrangement compete favorably with electrophilic trapping at elevated temperatures?" The above experiment

was repeated at room temperature, and resulted in the formation of all three compounds **125**, **126**, and **127**, in addition to the [1,4]-, [1,2]-products (**8**, **9**), and vinylsilyl ether **22** resulting from the electrophilic trapping of the enolate from the [1,4]-Wittig pathway (Scheme 6.6). From these results, it was apparent that at room temperature, the breaking of the O–C bond was more facile, and Wittig rearrangement of **7** competes favorably with electrophilic capture of the intermediate carbanion. The structures of these compounds were assigned based on data from ^{1}H NMR, ^{13}C NMR, HRMS, and DEPT.

Scheme 6.6. Room temperature electrophilic trapping of carbanion of **7**



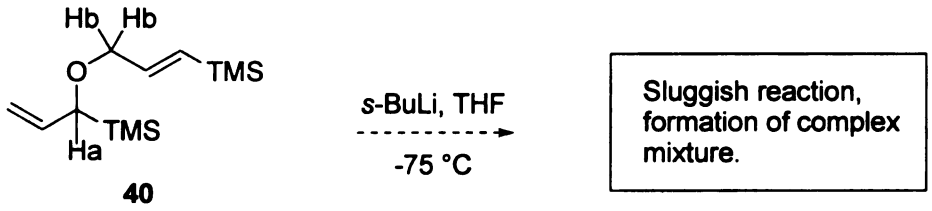
8/9 = 28% (>4:1); **22/125** = 6%; **126** = trace; **127** = 17%

6.2. Trapping of the carbanion of compound 40

We wanted to obtain further evidence in support of our results which showed that deprotonation and bond reorganization of α-alkoxysilanes were separate events. Compound **40** was employed for this purpose. Compound **40** was generated during our attempt to prepare α-(trimethylsilyl)-allyl butyl ether via the TMSOTf-mediated etherification of α-hydroxysilane **32** with the trichloroacetimidate of butyl alcohol (Scheme 4.8). Even though its formation was unexpected, **40** nevertheless is a potential

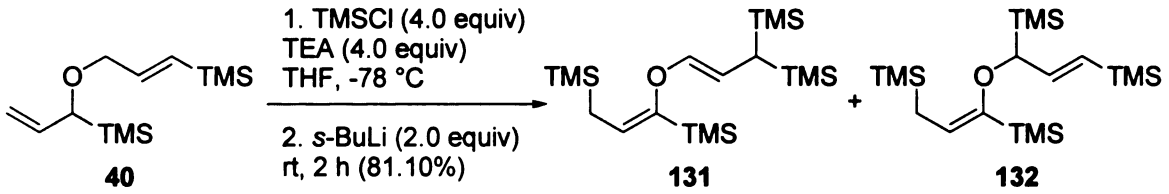
Wittig substrate. Considering the unique nature of **40**, there is the question of the relative acidities of protons Ha and Hb (Scheme 6.7), and of selective deprotonation by a base, or whether, in fact, both protons could be removed simultaneously.

Scheme 6.7. Attempted Wittig rearrangement reaction of **40**



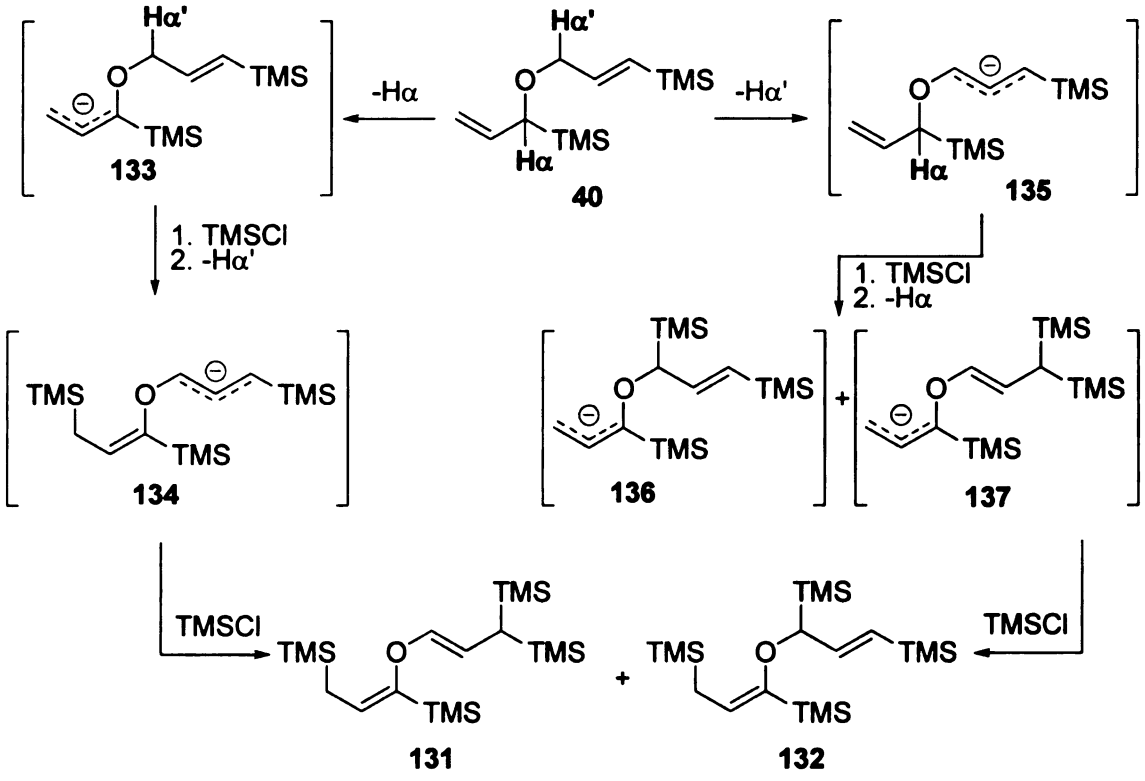
The rearrangement of **40** under our conditions was sluggish, even at room temperature and produced a complex mixture of products (from ^{1}H NMR). The sluggishness of **40** to undergo the Wittig rearrangement may be due to the stabilization of the resulting carbanion. We sought to understand the nature of the species undergoing the rearrangement by trapping the carbanion with a suitable electrophile. Thus, treatment of a cold (-78 °C) mixture of **40**, TMSCl, and TEA in THF under N_2 atmosphere with *s*-BuLi, for 2 h afforded compounds **131** and **132** (1:3.44), which were isolated in a combined 86% yield after column chromatography on $AgNO_3$-impregnated silica gel[3] (Scheme 6.8). This result reveals that **40** undergoes deprotonation under our Wittig conditions; however, the event is not accompanied by concomitant bond reorganization. This result thus provided further evidence that deprotonation and C–O bond breaking are separate events.

Scheme 6.8. Electrophilic trapping of the carbanion of **40**



The formation of the two observed products **131** and **132** could be explained in two ways: (1) stepwise deprotonation-electrophilic trapping process and (2) formation of a dianionic species, followed by electrophilic attack (Scheme 6.9). Both routes are possible; however, dianion formation (Figure 6.1) would explain the inability of this particular compound to undergo the Wittig rearrangement reaction readily. We speculate that formation of a dianionic intermediate, which is resonance stabilized, would very likely suffer from a high-energy demand for the breaking of the O–C bond following deprotonation.

Scheme 6.9. Plausible explanation for the formation of **131** and **132** from **40**



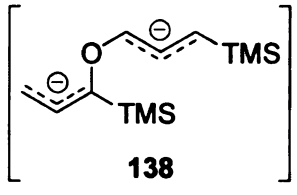


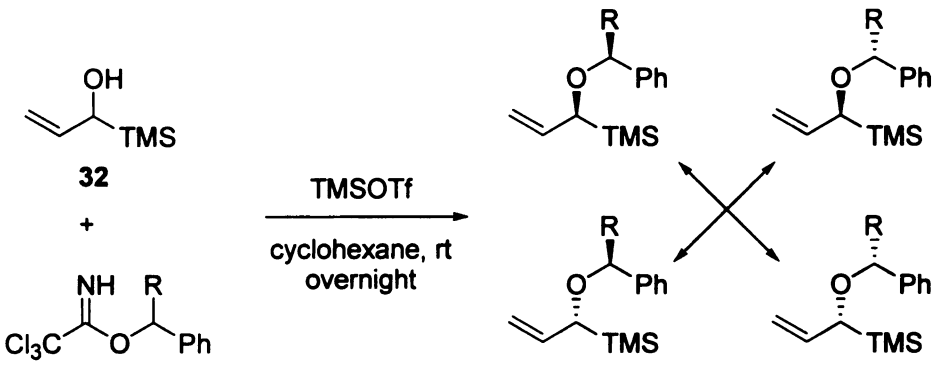
Figure 6.1. Formation of dianion **138** from compoun **40**

6.3. Stereochemistry of the [1,4]-Wittig rearrangement of α-alkoxysilyl ethers

Having established that deprotonation and bond reorganization are not concurrent but separate events in the Wittig rearrangement of α-alkoxysilanes, we then addressed the next question regarding the mechanism of the [1,4]-Wittig, which was "does the [1,4]-

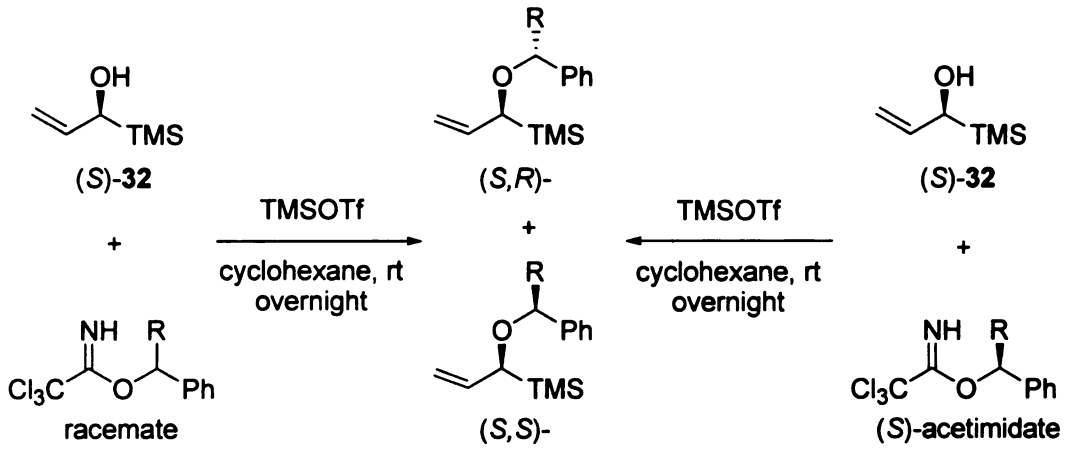
Wittig rearrangement of α-alkoxysilanes occur with retention or inversion of configuration at the migrating center?" Answering this question would require a substrate bearing a stereodefined migrating center which could be accessed via an enantiomerically pure α-hydroxysilane.

Scheme 6.10. Preparation of α-alkoxysilanes bearing substituent at the migrating carbon



We already determined that the coupling of a racemic α-hydroxysilane and the trichloroacetimidate of a secondary alcohol produces a set of diastereomers in an approximate ratio of 1:1 to 1:1.3 in favor of the less reactive *anti* isomer (Scheme 6.10). In theory, employing an enantiopure α-hydroxysilane, for instance (*S*)-**32**, and a racemic trichloroacetimidate would result in only one pair of optically active diastereomers (*S,S* and *S,R*) (Scheme 6.11). During our earlier studies, if R = Et, Pr, *i*-Pr, or allyl the two diastereomers were separable by column chromatography on silica gel. Thus we could access enantiomerically pure substrate either by employing enantiomerically pure starting materials (alcohol and acetimidate) or an enantiopure α-hydroxysilane and a racemic trichloroacetimidate. Each of these two routes would in principle result in only one pair of optically active α-alkoxysilanes (Scheme 6.11).

Scheme 6.11. Preparation of α-alkoxysilanes from enantiopure starting materials



6.4. Efforts towards accessing enantiopure Wittig substrate for mechanistic studies

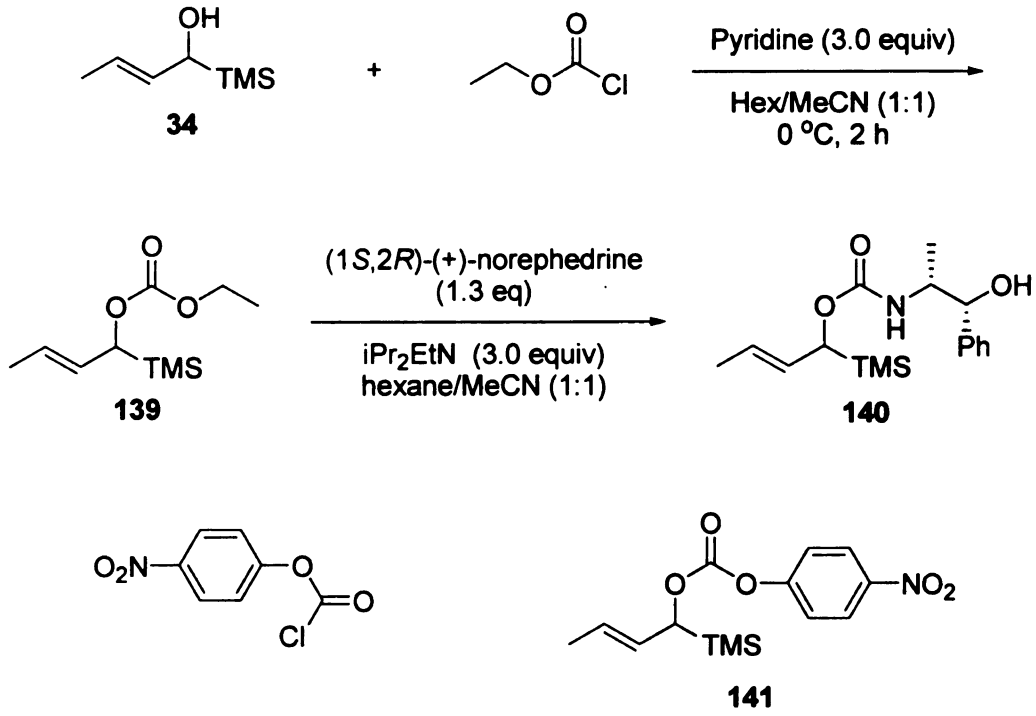
6.1.2.1. Exploratory ventures into accessing enantiopure α-hydroxysilanes

We explored a number of routes to access enantiomerically pure α-hydroxysilanes. Kells et al[4] reported the successful resolution of α-hydroxystannanes via norephedrine carbamates in a two-phase acetonitrile-hexanes solvent system. In this case, α-hydroxystannanes were converted into mixed carbonates with *p*-nitrophenyl chloroformate. Treatment with norephedrine then afforded the carbamates which were converted back to α-hydroxystannane by reduction with AlH_3.

We carried out a model study to determine the compatibility of the trimethylsilyl group with the above procedure. In doing so we substituted ethylchloroformate for *p*-nitrophenylchloroformate. Thus, stirring a mixture of α-hydroxysilane **34**, ethylchloroformate, and pyridine in hexane/acetonitrile at 0 °C for 2 h, and then quenching with water, afforded the carbonate derivative **139**. The first step of this reaction proceeded well (Scheme 6.12). However, the subsequent step, which involves

the replacement of the carbonate functionality with a carbamate, did not proceed, and only **139** was recovered.

Scheme 6.12. Attempted kinetic resolution of α-hydroxysilane **34** by Kells' protocol[4]

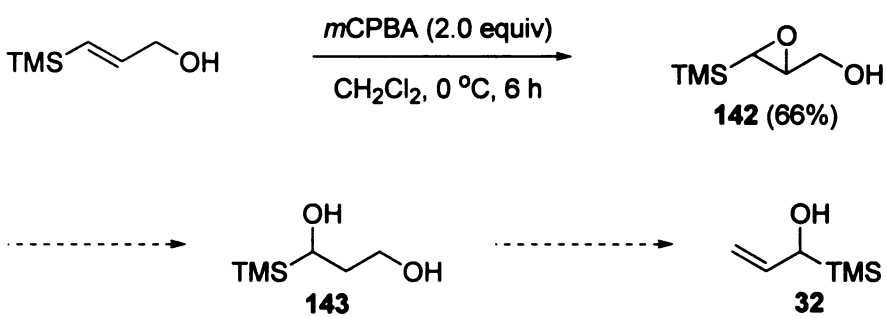


The failure of the second step may be due to the poor leaving ability of the ethoxide group. To overcome this problem *p*-nitrophenyl chloroformate was employed in step one of the reaction, affording the mixed carbonate **141** as a dirty white solid after 45 minutes. A mixture of this crude carbonate **141**, (1S,2R)-(+)-norephedrine, and diisopropyl amine, in hexane/acetonitrile (1:1 v/v) was stirred at room temperature for 24 h, followed by aqueous workup to give **140** (Shemen 6.12) as an inseparable mixture of diastereomers (Scheme 6.12). The difficulty in separation forced us to abandon this route.

Next we explored the possibility of employing an elimination reaction to install the terminal double bond in α-hydroxysilanes. We reasoned that elimination of a

suitably derivatized diol **143** could lead to the desired alcohol (Scheme 6.13). Compound **143** could be derived from the epoxy alcohol (glycidol) **142**, which would come from the epoxidation of *E*-3-trimethylsilanyl-prop-2-en-1-ol. Thus, silylation of propargyl alcohol (2.0 equiv *n*-BuLi, Et_2O, -20 °C, 2.2 equiv TMSCl, H_2O/AcOH), followed by reduction of the triple bond with Red-Al afforded the requisite allyl alcohol, *E*-3-trimethylsilanyl-prop-2-en-1-ol[5]. Epoxidation of this was readily accomplished by reacting the alcohol with 2.0 equiv of *m*CPBA in CH_2Cl_2 to obtain the glycidol in 66% yield (Scheme 6.13).

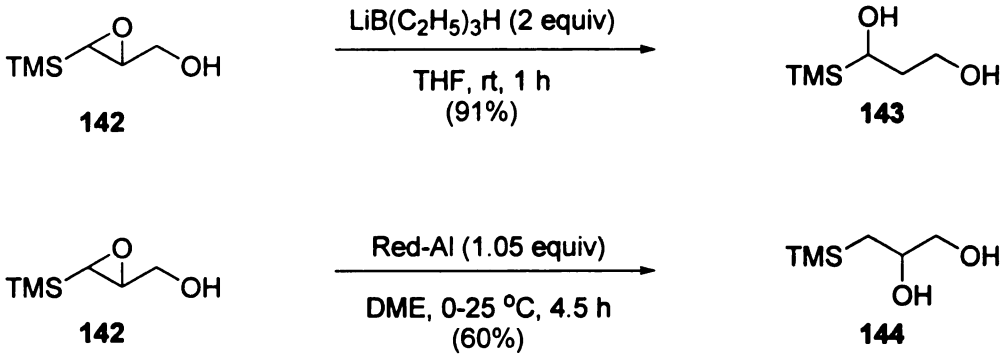
Scheme 6.13. Epoxidation of *E*-3-trimethylsilanyl-prop-2-en-1-ol with *m*CPBA



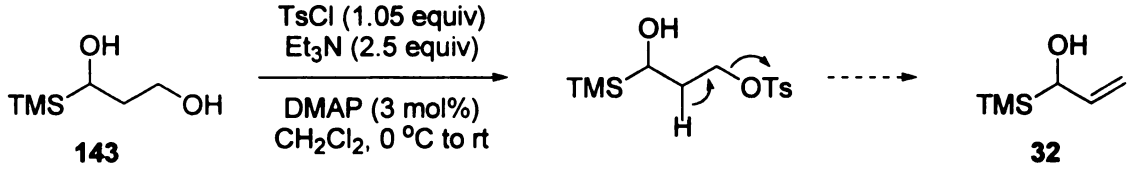
We then explored conditions for selective opening of the epoxide to furnish the desired diol **143**. Red-Al has been reported to react with epoxy cinnamyl alcohol in dimethylethane, and open the epoxide from the less hindered side to furnish the corresponding 1,3-diol.[6] However, when a DME solution of glycidol **142** was treated with 1.05 equiv of Red-Al at 0-25 °C for 4.5 h, 1,2-diol **144** was obtained in 60% yield (Scheme 6.14). The expected 1,3-diol was not observed under this reaction condition. Interestingly, an entirely different result was obtained with $LiB(C_2H_5)_3H$ (superhydride). Treatment of a THF solution of **142** with 2.0 equiv of superhydride at room temperature for 1 h, resulted in the opening of the epoxide from the less hindered side to afford the desired 1,3-diol **143** in 91% yield (Scheme 6.14). The next step was tosylation of the

primary hydroxyl group of diol **143**. However, selective tosylation was not achieved (Scheme 6.15) and we did not pursue this procedure any further.

Scheme 6.14. Regioselective opening of epoxide **142**

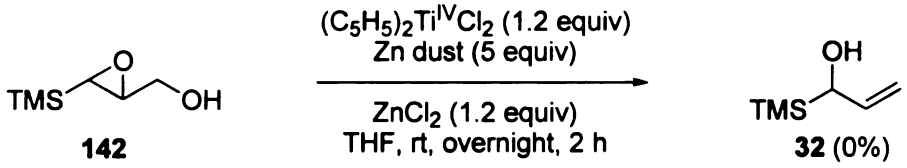


Scheme 6.15. Proposed derivatization and elimination reactions of **143**



The conversion of glycidols to allyl alcohols bearing terminal olefins by Ti (IV)$(C_5H_5)_2Cl_2$/Zn/$ZnCl_2$ has been reported in the literature.[7] This process involves the Ti(IV) induced homolysis of the C—O bond of a 2,3-epoxy alcohol, with deoxygenation occurring exclusively from the least substituted carbon end to produce terminal alkenic alcohol in high yield. However, when this protocol was adapted to glycidol **142** (Scheme 6.16), the expected product was not obtained.

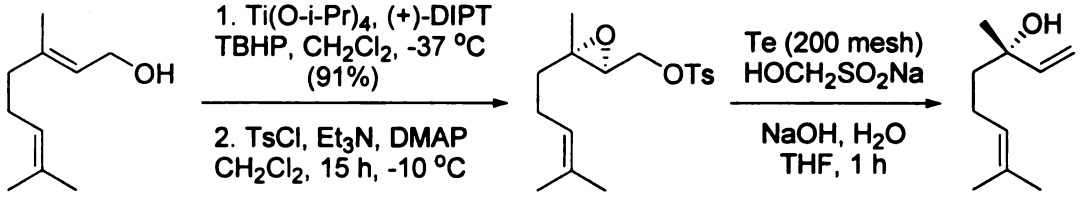
Scheme 6.16. Attempted conversion of **142** to **32** mediated by Ti(IV) system



142 **32** (0%)

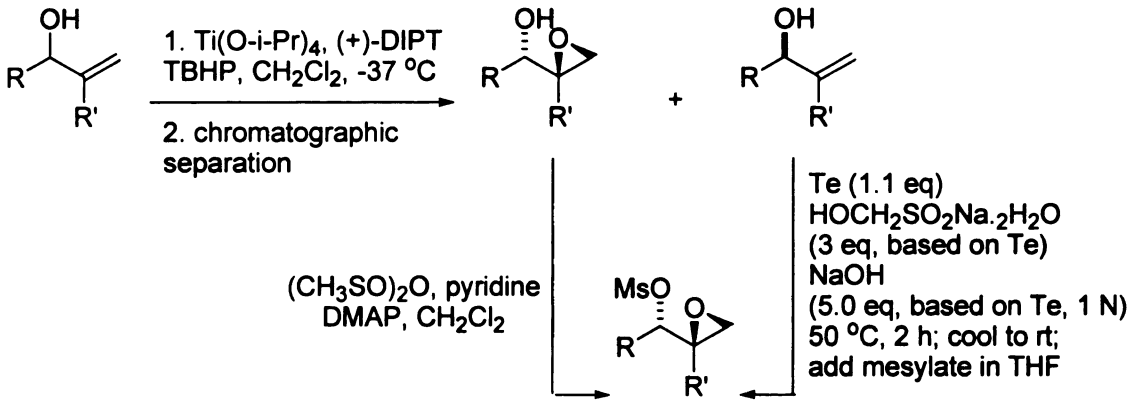
Also documented in the literature[8] is the finding that the telluride ion (generated by in situ reduction of elemental Te by sodium hydroxymethanesulfinate dihydrate (Rongalite) or by $NaBH_4$) can mediate the transposition of a primary allylic alcohol to a tertiary homochiral allylic alcohol via the tosylate ester of a homochiral glycidol obtained by the Sharpless asymmetric epoxidation (Scheme 6.17). The site of attack of the tellurium ion is at the carbon atom of a primary tosylate. The authors of this report also reported successful application of this protocol to a terminal allylic alcohol[8] via the mesylate of the glycidol (Scheme 6.18)

Scheme 6.17. Telluride mediated double bond transposition in primary allylic alcohols



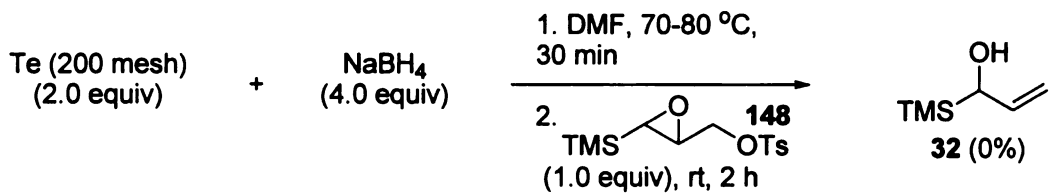
145 **146** **147**

Scheme 6.18. Telluride mediated double bond transposition in secondary allylic alcohols



In adapting the above protocol, the telluride ion[9] was first preformed by reacting 2 equiv of Te (200 mesh) and 4 equiv of $NaBH_4$ in DMF at 70-80 °C for 30 min. The glycidyl tosylate **148** reacted readily with the preformed telluride complex at room temperature. Sampling after 2 h revealed the complete absence of the starting tosylate (Scheme 6.19). However, upon quenching (exposure to air, followed by treatment with a few drops of H_2O_2 to to oxidize the telluride) and aqueous work up, no product was isolated.

Scheme 6.19. Attempted preparation of **32** via telluride ion mediated reduction of glycidyl tosylate

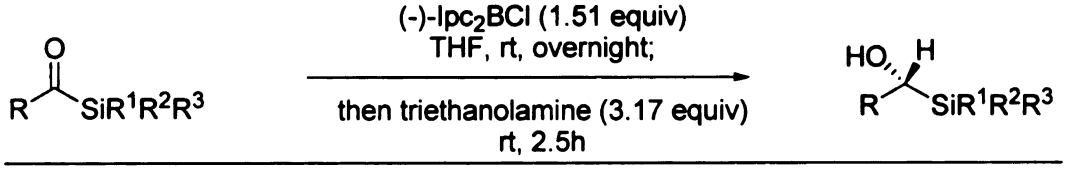


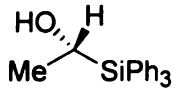
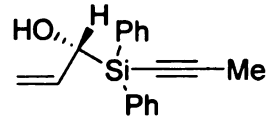
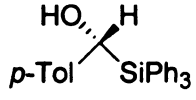
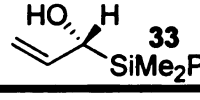
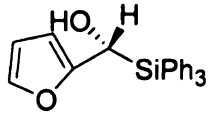
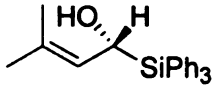
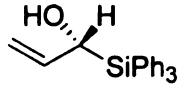
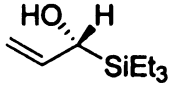
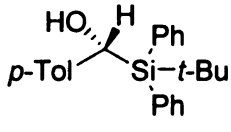
6.5. Accessing enantiopure α-hydroxysilane 33

So far, our efforts toward accessing enantiopure α-hydroxysilane **32** had proved unsuccessful. In prior studies on asymmetric reductions of acylsilanes with chiral borane reagents,[10,11,12] high enantiomeric purities (95% ee or better) were obtained with substrates in which the α-carbon bore a phenyl ring or saturated alkyl groups. α,β-Unsaturated acylsilanes were reduced effectively provided they contain bulky groups on silicon. However α,β-unsaturated acylsilanes with small groups on silicon afforded alcohols with lower enantiomeric purity (80-89% ee).[9,10,11] Such trends are evident in the work of Buynak and coworkers,[10] who explored the reduction of acylsilanes by (-)-Ipc_2BCl.[14] Their results are shown in Table 6.1 below (Table 6.1, compare entries 4 and 8 to entries 6, 7 and 9). α-Silyl allyl alcohols bearing a TMS group are clearly missing from Table 6.1.

Nonetheless we were happy to find that alcohol **33** was one of the α-hydroxysilanes formed by Buynak (Table 6.1, entry 7).[10] Although its enantiomeric excess was not very high, it afforded us a starting point for our work. Buynak[10] reported making the α-hydroxysilane **33** in 35% yield via a sequence of reactions involving synthesis,[15] silylation, and finally acid hydrolysis[16] of allenyl ether **152** to give the α,β-unsaturated acylsilane **153**, which was subsequently subjected to asymmetric reduction of (Scheme 6.20).

Table 6.1. Buynak's asymmeric reductions of acylsilanes using (-)-Ipc_2BCl[10]

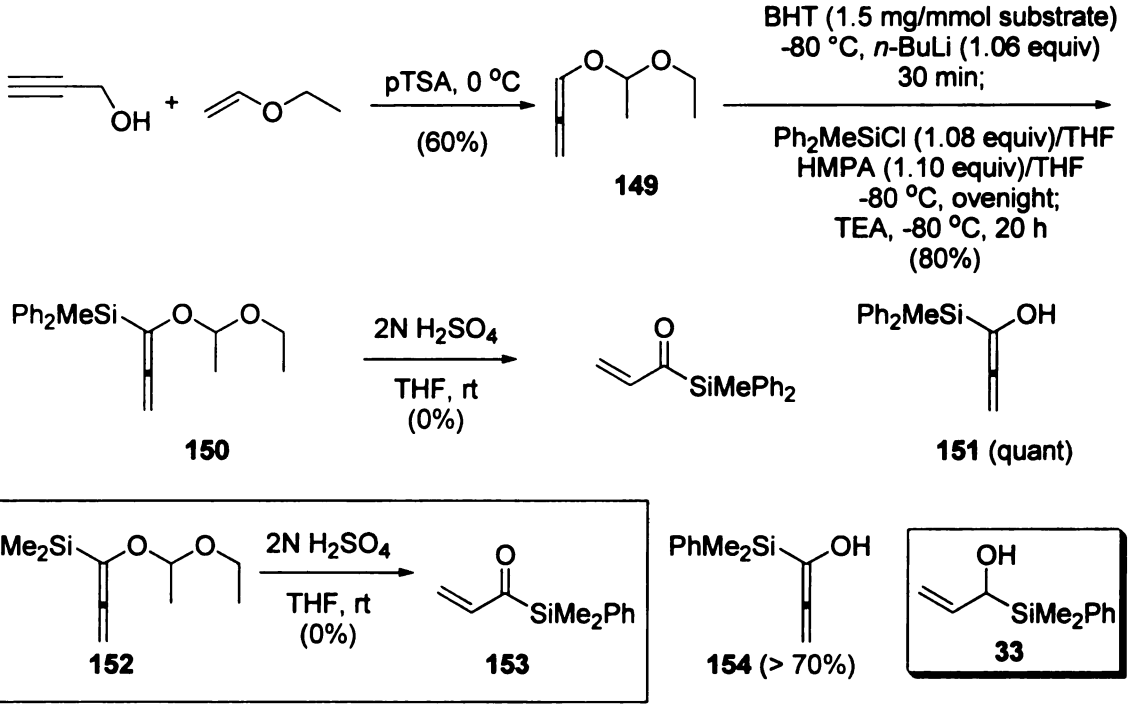


Entry	α-silyl alcohol	% ee	Entry	α-silyl alcohol	% ee
1		95	6		89
2		96	7	 **33**	83
3		95	8		97
4		97	9		80
5		95			

We needed alcohol **33** as a substrate in our work, thus we wanted to repeat Buynak's protocol. We prepared 1-(1-ethoxy-ethoxy)-propa-1,2-diene **149** by stirring a cold (0 °C) mixture of propargyl alcohol and vinyl ether in the presence of *p*-toluenesulfonic acid (*p*TSA) under an atmosphere of N_2 for 30 min. After quenching with a saturated solution of K_2CO_3, phase separation and distillation of the crude product under reduced pressure gave the compound **149** in 60% yield. Silylation of **149** with chloromethyldiphenylsilane ($Ph_2MeSiCl$) was carried out in the presence of radical inhibitor BHT (1.5 mg/mmol substrate)[16] and quantitatively afforded the expected product **150** as a thick brown oil. However, acid hydrolysis of **150** with 2N H_2SO_4 failed to give the expected α,β-unsaturated α-silyl ketone. Instead, the α-silylallenyl alcohol

151 was isolated quantitatively (Scheme 6.20) (IR (neat) 3323 cm^{-1} HO–C=•=C and 2178 cm^{-1} C=•=C). Compound **151** was subjected to chromatography on silica gel with the expectation of possible isomerization to the α,β-unsaturated carbonyl isomer. However, no isomerization was observed and we recorded over 90% recovery of the pure compound.[13]

Scheme 6.20. Attempted preparation of α,β-unsaturated α-silyl ketone **153**-a repeat of Buynak's protocol

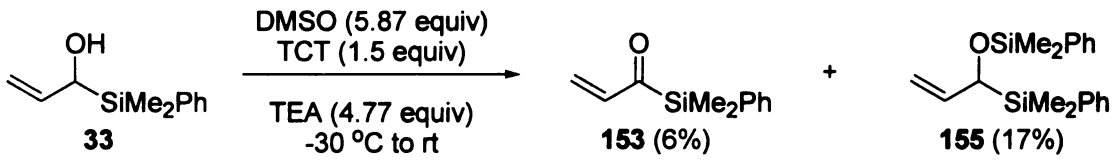


An attempt was also made at silylating the 1-(1-ethoxy-ethoxy)-propa-1,2-diene **149** with chlorodimethylphenylsilane. However, like the above case, acid hydrolysis of **152** failed to afford the desired α,β-unsaturated α-silyl ketone **153** (Scheme 6.20). The reaction of Scheme 6.20 afforded the 1-(dimethylphenylsilanyl)-propa-1,2-dien-1-ol, **154**,

in over 70% yield after purification by silica gel chromatography. The structures of these compounds were elucidated by NMR (^{1}H and ^{13}C), DEPT, and IR data.

With no success from the above route, we next considered making racemic α-hydroxysilane **33**, oxidizing the racemic alcohol to the acylsilane **153** and subsequently carrying out asymmetric reduction of acylsilane **153** to obtain the requisite chiral **33**. We explored several methods to oxidize alcohol **33**. DeLuca's protocol,[17] which involves the use of cyanuric acid (TCT) in the activation of DMSO (Scheme 6.21) was first attempted. However, this route afforded the desired enone **153** in only 6% yield, accompanied by other by-products including **155** which was obtained in 17% yield.

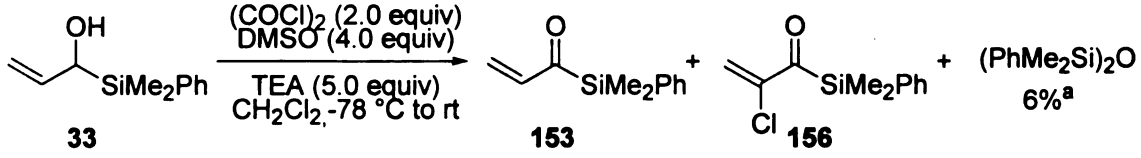
Scheme 6.21. Oxidation of α-hydroxysilane **33** via the DeLuca protocol



α-Silyl alcohols have been shown to undergo facile Swern oxidation to afford the corresponding enones in good to excellent yields.[18] However, Swern oxidation was not our first choice method because of concern over how the phenyldimethylsilyl group would behave under such conditions. Despite these reservations, our lack of progress in this endeavor prompted us to take α-hydroxysilane **33** through the typical Swern reaction.[19] Disappointingly this resulted in the formation of α-chloro-α,β-unsaturated acyl silane **156** (22%) accompanied by some disilyl ether $(PhMe_2Si)_2O$ (6%). No trace of the desired product **153** was observed (Scheme 6.22). α-Chlorination during Swern oxidation is documented in the literature. Smith and Leenay[20] and Kende and co-

workers[21] have independently reported observing α-chlorination during the Swern oxidation of secondary alcohols.

Scheme 6.22. Swern oxidation of racemic α-hydroxysilane **33**



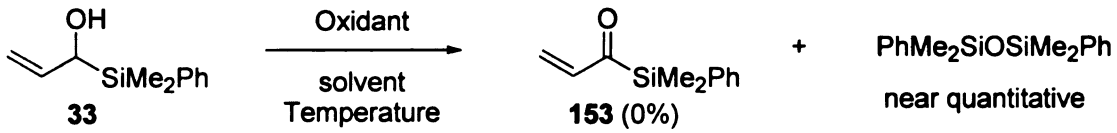
T (°C)	**153**:**156**	Yield (%)
-78 to rt	**156** only	22[a]
-55 to rt	3:1	77
-50 to rt	10:1	91

(a) Reaction was accompanied by formation of $(PhMe_2Si)_2O$ obtained in 6% yield

While the α-chlorination product posed a problem, we were somewhat encouraged by the fact that the oxidation did take place. Thus we decided to study the reaction conditions further in an effort to make the desired alcohol without the adventitious chlorination. Our results are summarized in Scheme 6.22. We were pleased to observe that by simply varying the reaction temperature from -78 to -55 °C, the above procedure afforded a 3:1 mixture of the desired product and the α-chlorinated acylsilane in 77% yield. We obtained our best result, combined 91% yield of **153** and **156**, and 10:1 ratio in favor of the desired acylsilane, by carrying out the Swern oxidation at -50 °C.

We also explored other oxidation methods, including use of PCC,[22] IBX,[23] and chemical MnO_2[24] (Scheme 6.23). The generally observed pattern with all these reagents was that the substrate got completely consumed, but that the only isolable product was $PhMe_2SiOSiMe_2Ph$.

Scheme 6.23. Attempted oxidation of α-hydroxysilane **33** via other routes



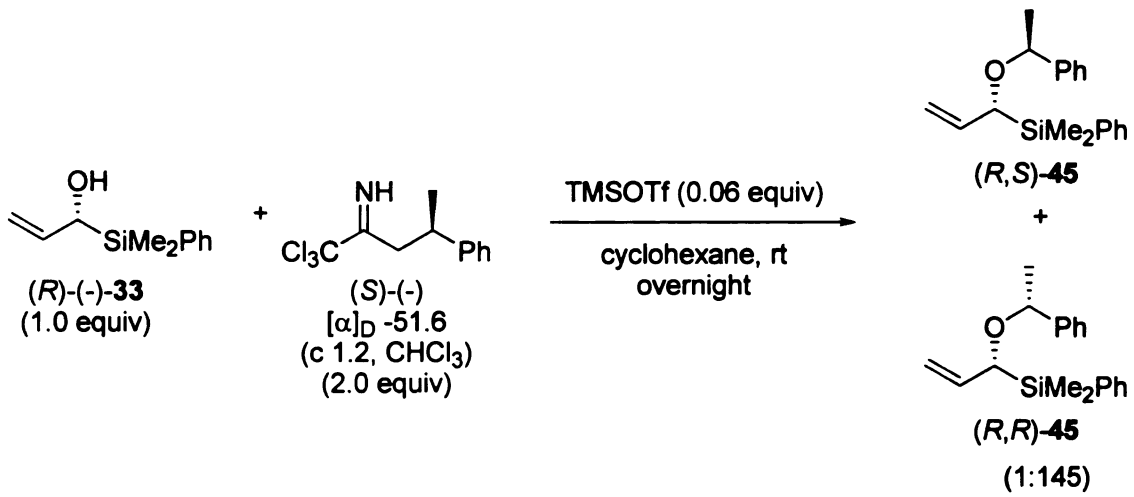
Oxidant	Solvent	Temperature
PCC	CH_2Cl_2	rt
IBX	EtOAc	80 °C
MnO_2	CH_2Cl_2	rt

6.6. Asymmetric reduction of acylsilane

Reduction of α,β-unsaturated acylsilane **153** was achieved (-)-Ipc_2BCl by applying literature procedure[10] (treatment of an approximately 0.34 M solution of the acylsilane in THF (at -35 °) with 1.1 equiv of (-)-Ipc_2BCl). The downside to this method is the very low yield associated with it. Buynak[10] reported a 25% yield of alcohol (*R*)-**33** (83% ee). We obtained the desired alcohol **33** in 39% yield (Scheme 6.24). The alcohol was converted to its MPA ester[25] and the diastereomeric excess (84% de) was established by ^1H NMR.

Although the level of enantiomeric purity of the (-)-Ipc_2BCl reduction was lower than we would have liked for our mechanistic study, it was good enough for us to investigate the etherification of enantioenriched α-hydroxysilane with enantioenriched trichloroacetimidate.

Scheme 6.24. Preparation of enantioenriched **45**



The TMSOTf catalyzed etherification of (*R*)-(-)-**33** with the (*S*)-(-)-benzyl trichloroacetimidate[26] afforded a 1:1.45 mixture of diastereomeric ethers **45** (Scheme 6.24). At this point, it was clear to us that all we needed was enantiopure α-hydroxysilane and we could access both diastereomers of α-alkoxysilane in optically pure form.

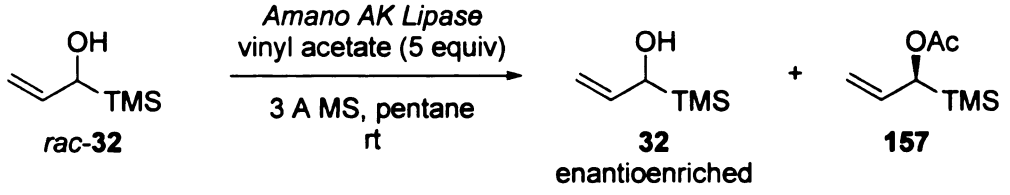
6.7. Kinetic resolution of α-hydroxysilane 32 by *Lipase*

The problems associated with the Swern oxidation of **33** and the low enantiomeric purity offered by the asymmetric reduction of same made us look for alternative routes to the enantioenriched Wittig substrates. This search took on a particular urgency given the yet to be resolved problem of reducing α,β-unsaturated acylsilane where the silicon bears non-bulky groups such as Me, Et, and Pr.

As part of this search we considered kinetic resolution of **32**. Most of the work on kinetic resolution of α-silyl alcohols has been done with α-silyl benzyl alcohol, and α-

silyl allyl alcohols in which the silicon bears bulky groups such as *t*-Bu, Ph, and *i*-Pr.[10] In addition, Lipase-mediated resolutions of secondary propargyl alcohols bearing silyl substituents leading to high enantiomeric purity are documented in the literature.[27] Even though the substrates in these previous studies are significantly different from ours, we thought that kinetic resolution was worth investigating since this would offer a useful route to the less studied α-silyl alcohols. We investigated the enzymatic resolution of α-hydroxysilane **32** under various conditions (enzyme loading, acylating agent, and temperature). The process involves stirring a mixture of the substrate alcohol, the enzyme, vinyl acetate and 3Å MS in pentane, and monitoring the reaction by chiral GC. Our results are summarized in Table 6.2 below. From Table 6.2, it is clear that *Amano AK Lipase* effectively resolves α-hydroxysilane **32** with synthetically useful levels of enantiomeric differentiation. In the course of this study, we established that 1.0 wt. equiv of *Amano AK Lipase* was optimal, and anything beyond this did not afford any advantage. For instance, use of 2.0 wt. equiv of the enzyme under similar conditions gave 81-83% ee at best. Temperature is a very important factor in this process. The reaction is facile at elevated temperatures (33 h at 35-38 °C). It is worth noting that when this reaction was run neat, it was slower than when run in solvent.

Table 6.2. Lipase resolution of α-hydroxysilane **32**

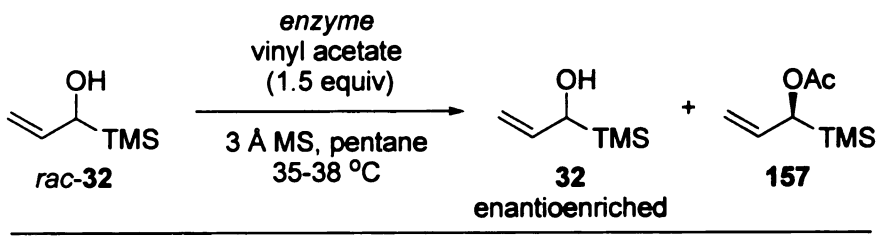


0.5 wt. equiv				0.75 wt. equiv				1.0 wt. equiv			
Entry	Time (h)	Ratio of acetates	% ee	Entry	Time (h)	Ratio of acetates	% ee	Entry	Time (h)	Ratio of acetates	% ee
1	47	1:8	79	1	45	1:10	82	1	23	1:6	73
2	72	1:10	82	2	72	1:9	80	2	96	1:9	81
3	120	1:10	82	3	120	1:9	80	3	120	1:9	80
4	144	1:9	80	4	144	1:9	80	4	168	1:9	80
								5	192	1:10	82
								6	240	1:11	84

Two other enzymes, *Amano PS Lipase* and *Novozym 435*, were also investigated in the kinetic resolution of **32** (Table 6.3). *Amano PS Lipase* (1.0 wt equiv of *Lipase*, 5.0 equiv of vinyl acetate, pentane 3 Å MS, rt, 168 h) afforded the desired acetate of 96% ee. *Novozym 435* proved to be the best of the three enzymes investigated. Employing 0.015 g of *Novozym 435* per mmol of alcohol (5.0 equiv of vinyl acetate,[27] pentane 3Å MS, rt, 168 h) gave acetic acid 1-trimethylsilanyl-allyl ester of 98% ee (Table 6.3). It was observed that very long reaction time is detrimental to the level of enantiomeric excess of the resulting acetate, and secondly, we determined that the use of a large excess of vinyl acetate is not necessary in the reaction. Thus, carrying out this reaction at elevated temperatures (35-38 °C), employing 1.5 equiv of vinyl acetate afforded the desired acetate **157** in 30% yield and 98-99% ee after 33 h (Table 6.3). The enriched alcohol was recovered in 33% yield. On the other hand, employing only 0.01 g of *Novozym 435*/mmol alcohol afforded similar results in terms of enantiomeric excess (99% ee), but

the reaction required 84 h, and product yield was 26%, and the enriched alcohol was obtained in 24% yield after chromatographic separation on silica gel.

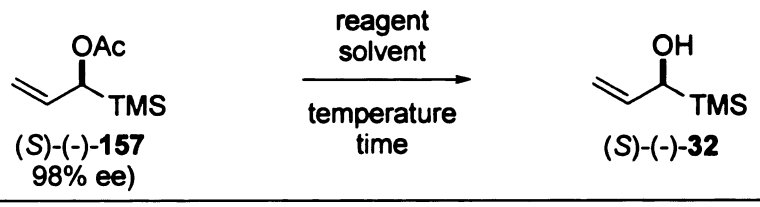
Table 6.3. Kinetic resolution α-hydroxysilane **32** by *Amano PS Lipase* and *Novozym 435*



1.0 wt. equiv *Amano PS Lipase*				15 mg *Novozym 435*/mmol *rac*-ROH			
Entry	Time (h)	Ratio of acetates	% ee	Entry	Time (h)	Ratio of acetates	% ee
1	22	1:16	88	1	8	1:166	99
2	24	1:29	93	2	13	1:172	99
3	48	1:34	94	3	22	1:150	99
4	96	1:25	92	4	27	1:116	98
5	169	1:57	96	5	33	1:112	98

With the requisite chiral acetate **157** in hand, we turned our attention to finding procedures for its hydrolysis to obtain the desired chiral alcohol. The results of this investigation are summarized in Table 6.4 below. A variety of reagents were investigated for the hydrolysis. Many of these led to erosion of enantiomeric excess (Table 6.4, entries 1-6). A look at Table 6.4 reveals DIBALH as the reagent of choice, and the best conditions for the hydrolysis of the silyl acetate to be 1.05 to 1.1 equiv of DIBALH, hexane, -78 °C, 2 h 20 min. (entries 8 and 9). Beyond 3 h reaction times erosion of enantiomeric excess was observed (entry 10), and it is also worth mentioning that use of excess DIBALH resulted in erosion of % ee of the resulting alcohol (entry 11; 3.15 equiv of DIBALH, hexane, -78 °C; 86% ee).

Table 6.4. Hydrolysis of acetic acid 1-trimethylsilyl ester **157**



(*S*)-(-)-**157** 98% ee)

(*S*)-(-)-**32**

Entry	Reagent	Equiv	Solvent	T (°C)	Time (h)	% ee	Yield (%)
1	K_2CO_3	5	MeOH	20	4	85	a
2	LiOH	5	MeOH-H_2O	20	5	85	a
3	LAH	1.2	Ether	reflux	2	80	a
4	$LiBH(C_2H_5)_3$	2	THF	0	2	Inconclusive	a
5	Red-Al	1.05	THF	0 to rt	1.75	81	a
6	$LiAlH(Ot\text{-}Bu)_3$	1.05	THF	-78 to rt	48	87	a
7	DIBALH	1.1	CH_2Cl_2	-78	3	84	a
8	DIBALH	1.05	Hexane	-78	2.5	98	82
9	DIBALH	1.1	Hexane	-78	2.33	98	90
10	DIBALH	1.2	Hexane	-78	5	94	b
11	DIBALH	1.5	Hexane	-78	20	94	b

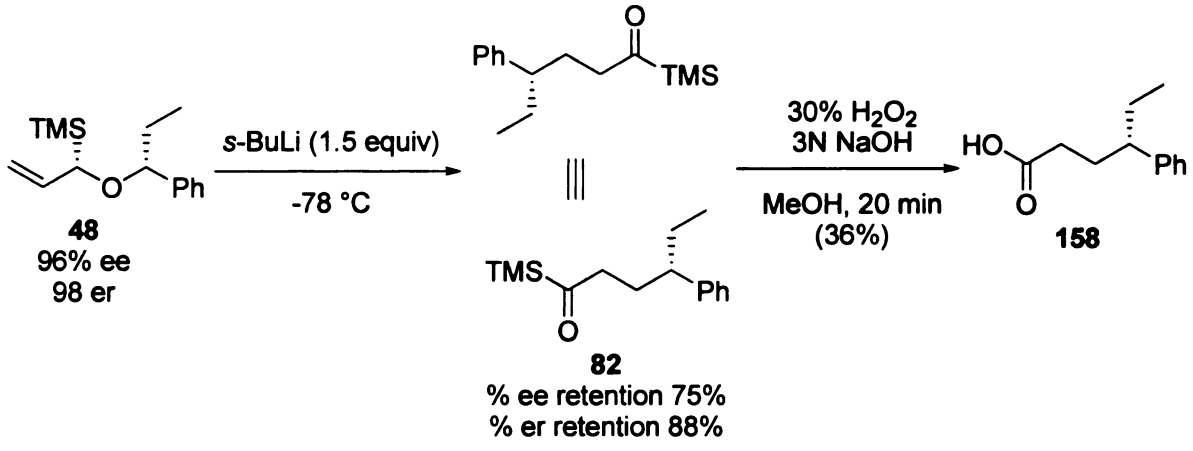
a. The experiments in entries 1 through 7 were qualitative in nature and the yields were not determined
b. The experiments in entries 10 and11 were carried out to determine the effect of long reaction time on the enantiomeric excess of the chiral alcohol product

6.8. Stereochemistry of the Wittig products.

Compound (*S*)-(-)-**32** was employed in the preparation of desired diastereopure substrate (*S,R*)-**48**. TMSOTf-mediated etherification of enantiomerically pure (*S*)-(-)-**32** with the trichloroacetimidate of *sec*-phenylpropyl alcohol afforded a 1:1 mixture of (*S,R*)-**48** and (*S,S*)-**48**, which were readily separable by column chromatography on silica gel. The reactive isomer (*S,R*)-**48**, on treatment with 1.5 equiv of *n*-BuLi in THF at -78 °C

overnight, afforded the Wittig products, which were separated by column chromatography on silica gel. We had earlier determined that the racemic [1,4]-Wittig product *rac*-**82** (Table 4.2, entry 7) was not resolvable by chiral GC and chiral HPLC. However, we were pleased to observe that after oxidation of the acylsilane (Scheme 6.25), the resulting carboxylic acid **158** was resolvable by chiral HPLC.[28]

Scheme 6.25. Conversion of the [1,4]-Wittig product **82** into 3-Phenyl-pentanoic acid

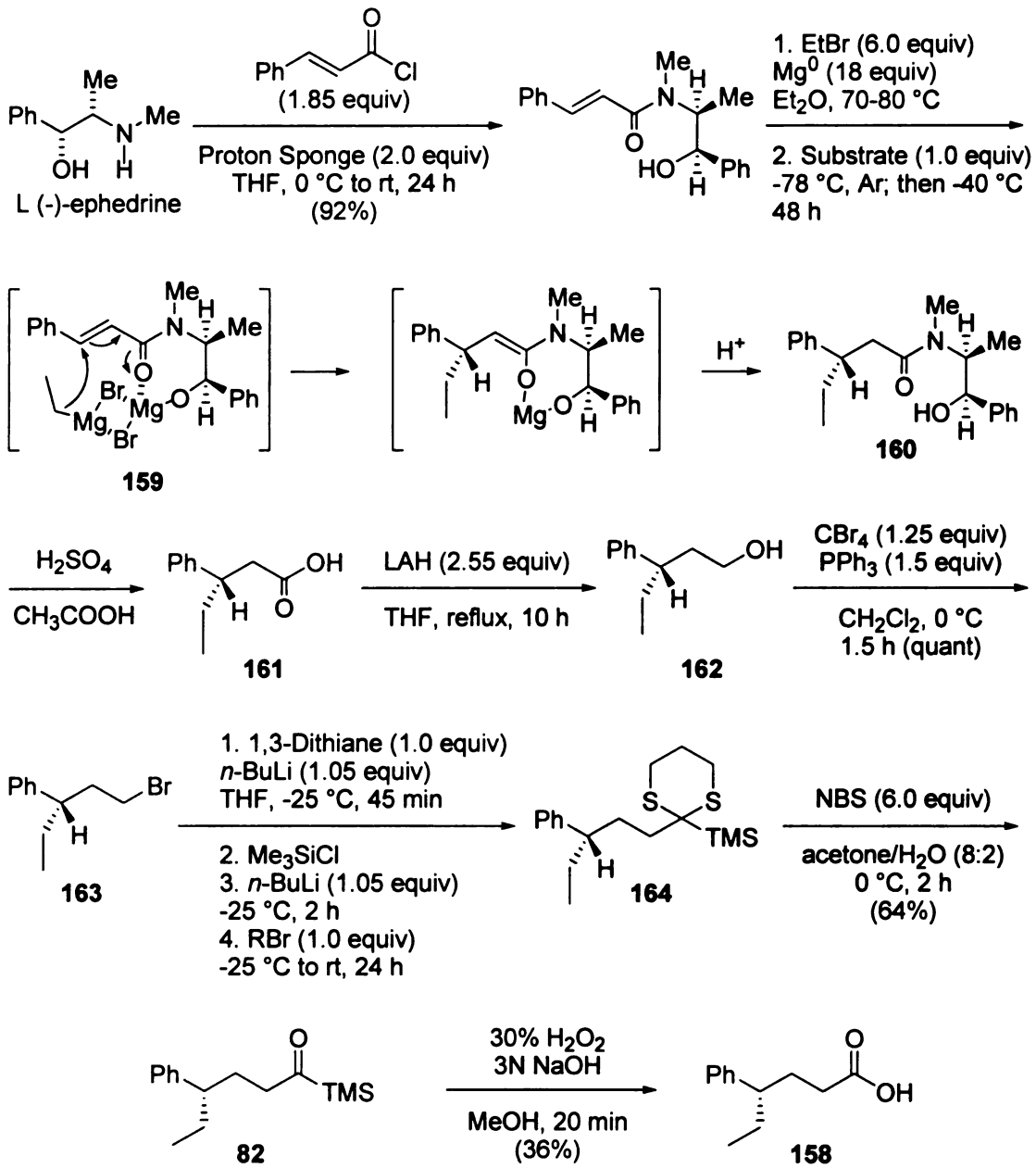


We also subjected the less reactive anti diastereomer (*S,S*)-**48** to our Wittig conditions, and the reaction took about 3 days at –10 to 5 °C to go to completion. The [1,4]-product from this reaction was also converted into the corresponding carboxylic acid and analyzed by chiral HPLC.

For reference, we accessed the [1,4]-Wittig product via an independent route starting from L-(-)-ephedrine (Scheme 6.26). The reaction of L-(-)-ephedrine and trans-cinnammoyl chloride in the presence of Proton Sponge® followed by treatment of the resulting amide with EtMgBr in ether, afforded the corresponding adduct via 1,4-conjugate addition of the Grignard reagent to the amide. Mukaiyama[29] has presented a plausible mechanism to explain the stereoselectivity of the reaction. The reaction between

the amide and the Grignard reagent forms an initial internal chelate complex **159** (Scheme 6.26) that would rigidly fix the conformation of the molecule owing to the planarity of the amide group. Excess Grignard reagent would approach the molecule from the less sterically hindered side (i.e. opposite side of the phenyl and methyl groups on the asymmetric carbon) by means of strong interaction with the Mg salt. Quenching of this Mg complex with dilute acid solution afforded the addition product, and removal of the chiral auxiliary by acid hydrolysis (H_2SO_4/AcOH, heat) furnished the carboxylic acid, which was subsequently converted in two steps to the corresponding alkyl bromide (Scheme 6.26). Reaction of this alkyl bromide with 1-timethylsilyl-1,2-dithiane lithium species afforded the corresponding 1,1-disubstituted 1,3-dithiane. Deprotection with NBS and oxidation of the resulting acylsilane converted the 1,3-dithiane into the corresponding carboxylic acid. The [1,4]-products from the two different routes were analyzed by chiral HPLC and compared. By this analysis, we determined that the [1,4]-Wittig product from the rearrangement of reactive (*S,R*)-**48** was obtained with retention of configuration at the migrating carbon (% ee retention = 75%; % er retention = 88%). The [1,4]-product from the less reactive (*S,S*)-**48** was also obtained with predominant retention of configuration (% ee retention = 74%; % er retention = 87%). Comparison of the results obtained with both (*S,R*)-**48** and (*S,S*)-**48** show that both substrates afforded [1,4] products with similar level of retention of configuration at the migrating carbon.

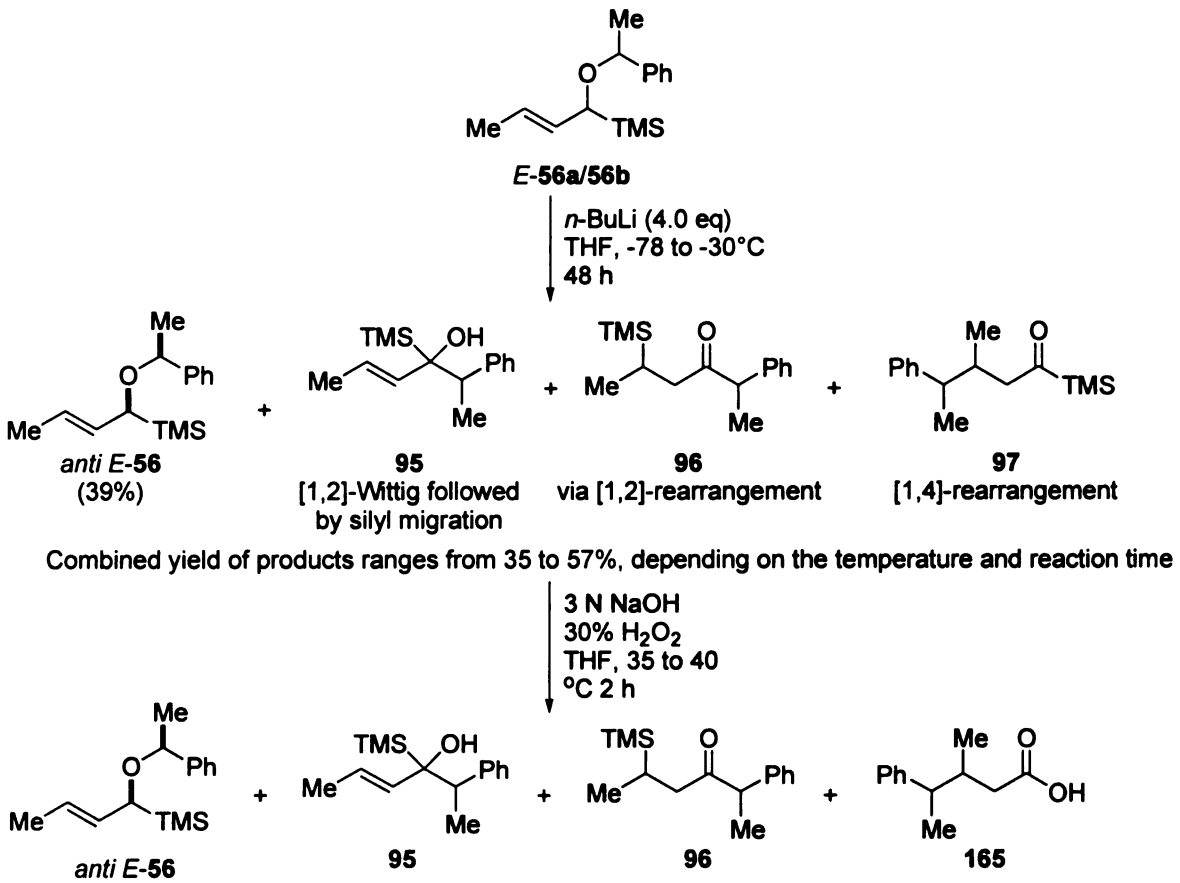
Scheme 6.26. Preparation of **82** via an independent route



6.9. Stereoselection in the [1,4]-Wittig rearrangement of α-alkoxysilanes: Relative stereochemistry of the newly formed adjacent stereocenters.

We were next interested in determining the relative stereochemistry of two newly formed stereogenic centers (Scheme 6.27) in cases where substituent was present at the terminal sp^2 carbon of the allyl moiety. α-Alkoxysilane *E*-**56** was employed in this investigation. The diastereomeric [1,4]-Wittig product **97** resulting from the rearrangement reaction of *E*-**56** was oxidized to the known[30] diastereomeric carboxylic acid **165** (Scheme 6.27). The diastereomeric acids were not separable by column chromatography on silica gel. Nevertheless, the methyl signals were well resolved by ^1H NMR spectroscopy and by integrating the signal peaks, the *anti*/*syn* acids were formed in a ratio of 2.8:1 to 3:1 in favor of the *anti* isomer.

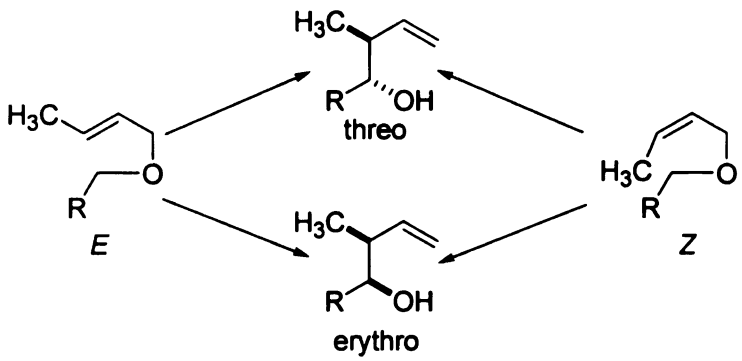
Scheme 6.27. Wittig rearrangement of *E*-**56**/oxidation of [1,4]-Wittig product **165**



In 1983, Nakai and co-workers[31] reported their efforts in acyclic diastereoselection in the [2,3]-Wittig rearrangement of a series of isomeric crotyl ethers (Scheme 6.28). The authors noted such general trends in terms of the sense and degree of diastereoselection as: (1) Erythro selection by *Z* substrates (with low erythro selectivity when R is Ph group) and threo selection by *E* substrates; (2) the dependence of the degree of stereoselection upon the kind of substituent (R), which according to the authors indicates that carbanion structure conferred by a given R plays a significant role in dictating reaction stereoselectivity, and (3) the decrease in threo selectivity with

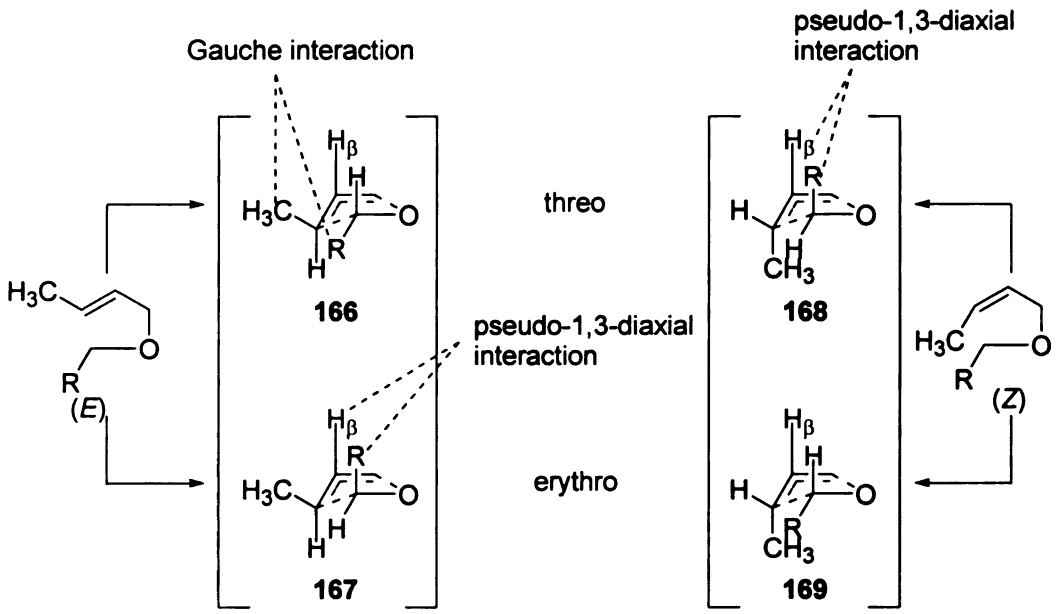
changing R for *E* substrates in the order: C≡C>CH=CR' (R' = H, Ph) >CR'=CH_2 (R' = CH_3, Me_3Si) > Ph.

Scheme 6.28. Diastereoselection in [2,3] Wittig rearrangement by Mikami et al[31]



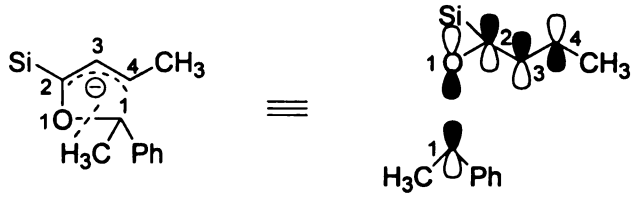
On the basis of the widely accepted postulate that the [2,3]-sigmatropic rearrangement proceeds via envelope transition state, the authors proposed the transition-state model shown in Scheme 6.29, which best accommodates both the sense and degree of stereoselection described in the preceding paragraph, and which provides a logical basis for explaining and predicting the stereoselection over a range of substrates. In their system, they explained the observed sense of stereoselection in terms of the pseudo-1,3-diaxial interaction between R and H_β in **167** and **168** (Scheme 6.29). The marked dependence of the threo selectivity on the R group was rationalized by assuming an additional R↔CH_3 steric parameter (gauche interaction) in the preferred transition state **166**. The gauche interaction is enhanced by a bulky R group. Furthermore, based on the postulate that the oxybenzylic carbanion possesses preferentially a pyramidal configuration (depending largely on the solvent),[32] for R = Ph, the CH_3↔Ph gauche interaction would be greatly enhanced, eventually leading to very low stereoselectivities as the authors actually observed in their systems.

Scheme 6.29. Proposed transition-state model for stereoselection by Mikami et al [31]



We have tried to adapt the above model to our system in an effort to explain the observed stereochemical outcome of the [1,4]-alkyl shift in the Wittig rearrangement of *E*-**56** (Scheme 6.31). In doing so we presumed that the [1,4]-pathway is a one-step concerted process, which is allowed by orbital symmetry[33] as illustrated in Scheme 6.30. The orbitals and methyl groups on silicon are left out for simplicity of presentation.

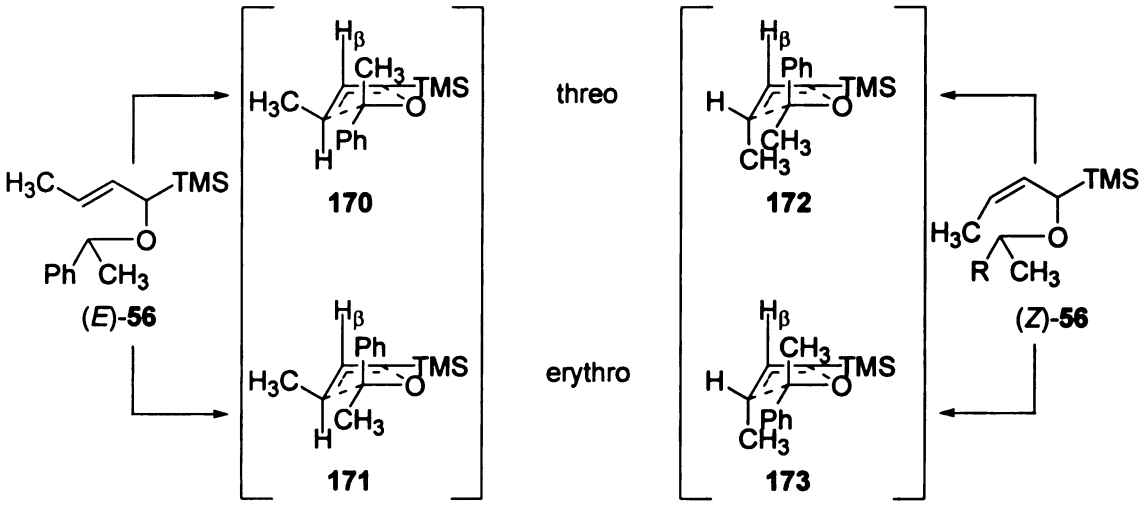
Scheme 6.30. Frontal orbital representation of *E*-**56**



Pseudo-1,3-diaxial interaction exists in both transitions states **170** and **171**. However, the effect is greater in **171** (Ph↔H_β) than in **170** (CH_3↔H_β), thus favoring **170** Now, assuming an additional R-R' gauche interaction, this would be enhanced in **170**

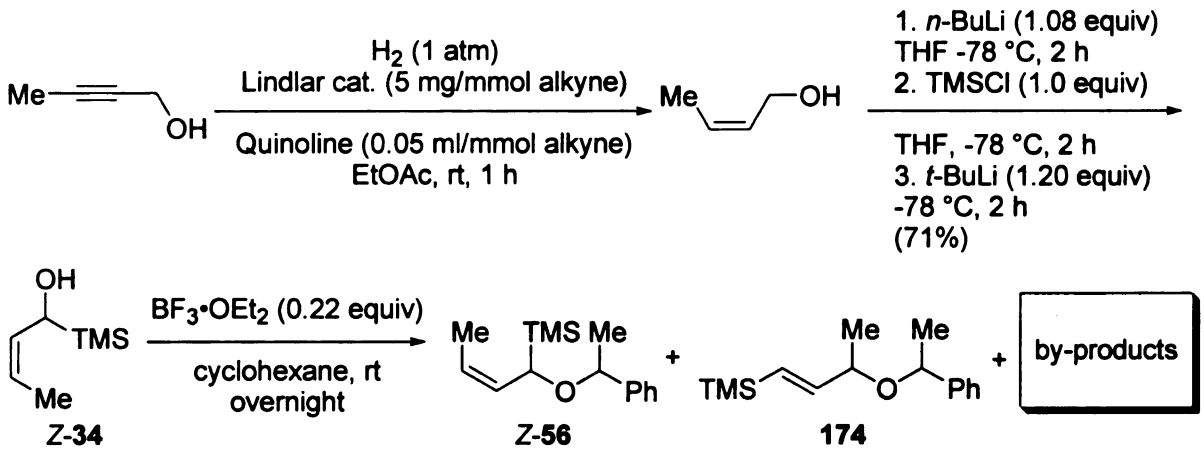
(Ph↔CH_3) relative to **171** (CH_3↔CH_3), making transition state **171** more favorable. The fact that the Wittig rearrangement reaction of *E*-**56** gives *anti*/*syn* selectivity of 2.8:1 would suggest that the pseudo-1,3-diaxial interaction outweighs the effect of gauche interaction. However, the gauche effect would explain the low selectivity observed.

Scheme 6.31. Proposed transition-state model for stereoselection in the [1,4]-alkyl migration in *E*-**56**



In the case of *Z*-**56**, pseudo-1,3-diaxial intearaction favors **173** (CH_3↔H_β) over **172** (Ph↔H_β). On the other hand, steric parameters (gauche interactions) favor **172** (CH_3↔CH_3) over **173** (Ph↔CH_3). Assuming that the pseudo-1,3-diaxial interaction outweighs the gauche interaction, then, we would expect a reversal in the outcome of the reaction employing *Z*-**56**, that is, a reversal in *anti*/*syn* stereoselection, if the mechanism of the [1,4]-alkyl shift were a concerted event. Thus, our next plan was to employ the geomeric *Z*-**56** in the Wittig rearrangement reaction.

Scheme 6.32. Preparation of *Z*-α-alkoxysilane *Z*-**56**



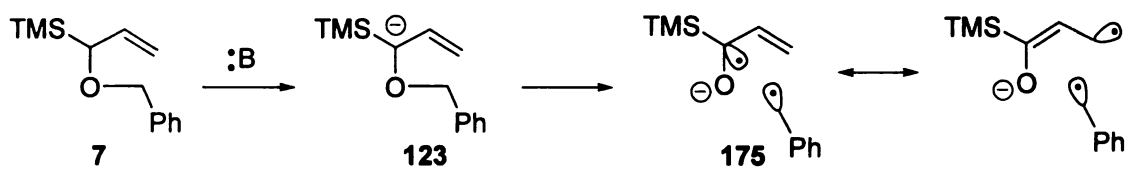
The synthesis of *Z*-**56** as outlined in Scheme 6.32 started with reduction of propargyl alcohol with Lindlar catalyst to afford the *Z*-crotyl alcohol (85% crude yield), which was employed in the next step without purification. The *Z*-crotyl alcohol was converted to trimethylsilyl ether by deprotonation with 1.08 equiv of *n*-BuLi and trapping with TMSCl. Subsequent treatment with *t*-BuLi afforded the desired *Z*-α-hydroxysilane *Z*-**34** in 71% yield. Etherification with the trichloroacetimidate of *sec*-phenethyl alcohol, mediated by BF_3•OEt_2 afforded less than 10% of the desired product *Z*-**56**, accompanied by numerous by-products which included **174**, which presumably is the result of transacetimidation/S_N2' by the liberated *sec*-phenethyl alcohol (Scheme 6.32). Given the difficulty in accessing *Z*-**56** no attempt was made to optimize the reaction conditions at this point. This will be for future studies.

6.10. On the mechanism of the [1,4]-alkyl shift in the Wittig rearrangement reaction of α-alkoxysilanes

Although we recognize that more work has to be done before we can make conclusive statement on the mechanism of the [1,4]-Wittig pathway, we venture to draw some tentative conclusions based on the results of the present research.

In the Wittig rearrangement of our model substrate **7**, the [1,2]-alkyl shift is effectively suppressed at low temperatures, and the [1,4] product is obtained as a single product. However, at elevated temperatures, the [1,2]-pathway becomes competitive and the [1,4]/[1,2] ratio increases to 2:1. We submit that if both rearrangement pathways were proceeding via the radical-radical anion dissociation-recombination mechanism, implicating a common intermediate **175** (Scheme 6.33), then complete suppression of the [1,2]-alkyl shift at low temperatures is unlikely. The two rearrangement pathways most likely have different mechanisms.

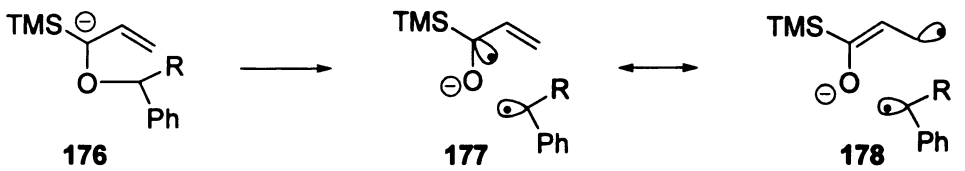
Scheme 6.33. Radical-radical anion dissociation-recombination in **7**



On introducing a substituent at the migrating carbon, [1,2]-Wittig becomes competitive even at low temperatures (-78 °C). This observation is in agreement with the generally observed characteristics of this reaction pathway, which is that the [1,2]-alkyl shift is promoted by a radical stabilizing migrating group and / or a terminal radical stabilizing group.[34] R ≠ H implies a relatively stable secondary benzylic radical **176** which is a good intermediate and promotes [1,2]-alkyl shift (Scheme 6.34). This is

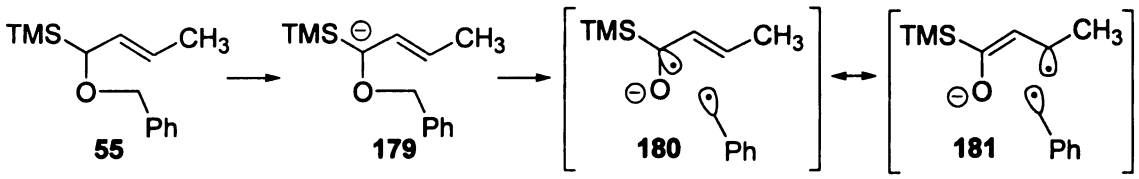
evident in the rearrangement reaction of compound **44**, in which a [1,4]/[1,2] ratio of (1.5:1 to 1.7:1) was observed, contrary to a ratio of >100:1 for **7**.

Scheme 6.34. Radical-radical anion dissociation-recombination in α-alkoxysilane bearing a substituent at the migrating carbon

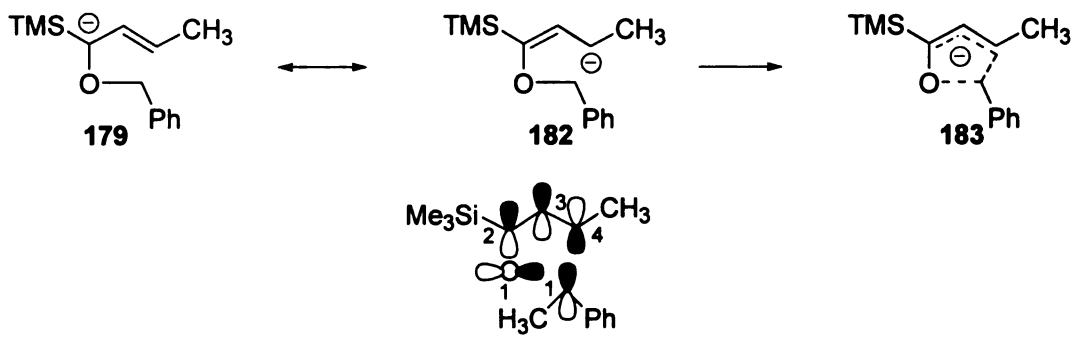


On introduction of a substituent at the terminal sp^2 carbon of the allyl moiety as in α-alkoxysilane **55**, the [1,2]-alkyl shift becomes competitive even at low temperatures (at -78 °C, [1,4]/[1,2] ratio is 4:1). Even though the migrating radical intermediate is benzylic, the allylic radical is resonance stabilized (Scheme 6.35). Theoretically, one would expect that the radical α to TMS (**180**) would be the less contributing resonance structure relative to the structure in which the radical is β to TMS (**181**) (β-effect of silicon). If this argument is reasonable, then one will expect a higher ratio of [1,4]/[1,2] than the observed 4:1. On the other hand, if the [1,4] shift is a concerted event, then, the reaction would involve a carbanionic intermediate (**182**) as shown in Scheme 6.36. **179** is expected to be the more stable resonance contributor (α-anion stabilization by silicon) than **182** and is invariably expected to furnish more [1,2]-Wittig product. That this was not the observation could be taken as further evidence that both [1,2] and [1,4] processes follow different pathways. Evidently the anionic nature of the [1,4]-Wittig pathway was supported.

Scheme 6.35. Radical-radical anion dissociation-recombination in α-alkoxysilanes bearing substituent at the terminal sp^2 carbon of the allyl moiety



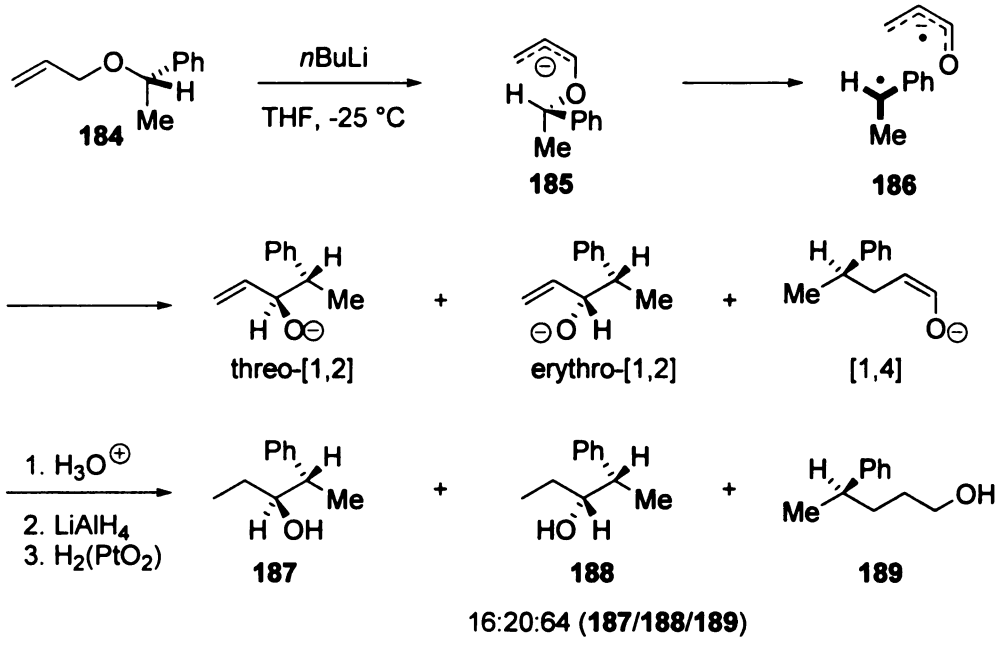
Scheme 6.36. Carbanion formation in the [1,4]-pathway in α-alkoxysilanes bearing a substituent at the terminal sp^2 carbon of the allyl moiety



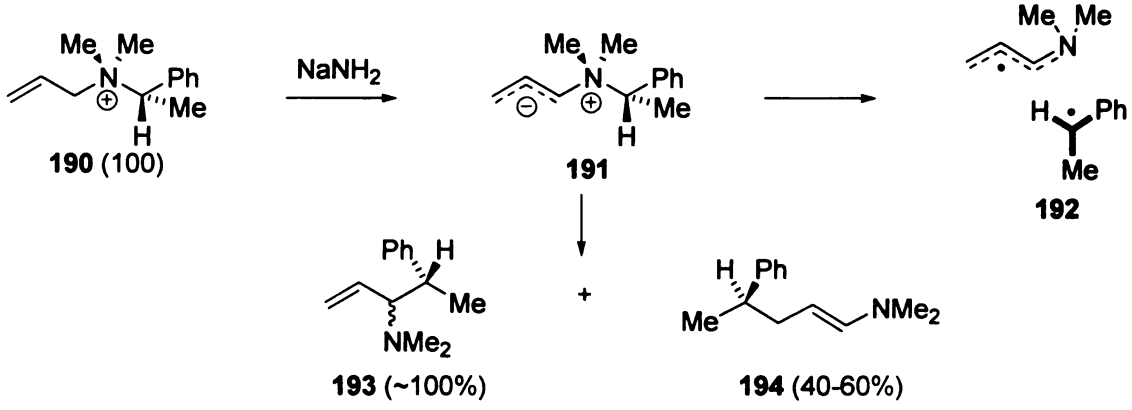
Felkin reported in 1977[35] that, on treatment with excess butyl lithium in THF at -25 °C, optically active allyl α-phenylethyl ether **184** underwent rearrangement to afford a mixture of anionic products via [1,2]- and [1,4]-rearrangements, which were converted to a mixture of the saturated products in 60% overall yield in a ratio of 16:20:64 (Scheme 6.37). The authors observed that all three rearrangement products **187**, **188**, and **189** were predominantly formed with retention of configuration and the extent of racemization was similar (30±5%). This suggested that reactions leading to both [1,2] and [1,4] products occurred via the non-concerted radical-radical anion cleavage-recombination mechanism. This observation is in contrast to our results- [1,2] and [1,4] products were formed with different levels of retention of configuration (95% ee and

97% er retention for [1,2] and 73% ee and 88% er retention for [1,4]). This too could be interpreted as suggesting different mechanisms for both types of Wittig rearrangements.

Scheme 6.37. Wittig rearrangement of allyl α-phenylethyl by Felkin[35]



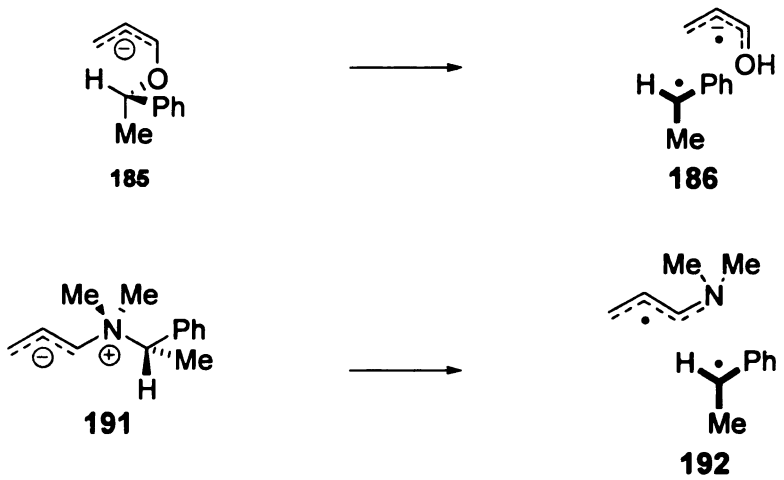
Scheme 6.38. Stevens rearrangement of optically active allylic ammonium salt by Jenny and Druey



In contrast to Felkin's system, the Stevens rearrangement of optically active allylic ammonium salt **190**, analogous to Felkin's *S*-allyl α-pheneyethyl ether **184**, was studied by Jenny and Druey,[36] who found that the [1,4]-shift of the phenylethyl group is accompanied by considerable racemization, whereas the [1,2]-migration, the major process, is stereospecific (Scheme 6.38).

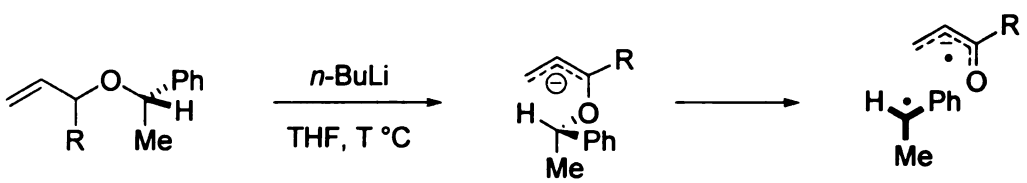
Felkin[35] explained that the difference in the stereochemical course of the two reactions could be due to a difference in the configurations of the two ions **185** and **191** and hence of the radical pairs **186** and **192** (Scheme 6.39). The authors[35] argued that the preference of allylic anions for the cis configuration[37] leads to a radical pair **186** in which the migrating α-phenylethyl radical is situated somewhere near the middle of the allylic moiety, a situation that results in approximately equal amounts of [1,2] and [1,4] rearrangement products and a similar racemization. The ammonium zwitterion in the Stevens rearrangement, on the other hand, adopts the trans configuration **191**. This scenario leads to a radical pair **192** in which the migrating radical is placed close to the carbon atom bearing the nitrogen, and remote from the terminal carbon of the allyl moiety, resulting in a predominance of [1,2] over [1,4] rearrangement[36] and a greater racemization in the [1,4] product. According to Felkin[35] the migrating radical has farther to go in order to react.

Scheme 6.39. Felkin's comparison of his and Jenny and Druey's systems



Our system is analogous to Felkin's (Scheme 6.40), however, we obtained results very different from his. Our [1,4]-rearrangement product is obtained with 73% (ee) retention/88% (er) retention and our [1,2] product with approximately 95% (ee) retention/97% (er) retention of configuration at the migrating carbon. If Felkin's argument on the position of the migrating α-phenylethyl radical held in our case, then we could argue that the [1,2] and [14]-alkyl shifts in α-alkoxysilanes do not have the same mechanism. This is additional evidence in support of different reaction mechanisms for the two types of alkyl shifts.

Scheme 6.40. Comparison of Felkin's and our systems



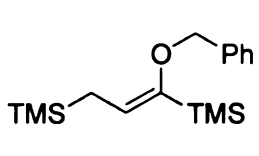
184: R = H, T = -25 °C: Felkin's
44: R = Me_3Si, T = -78 °C: ours

6.11. Conclusions

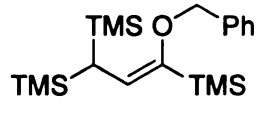
From our electrophilic trapping experiments we obtained conclusive evidence that in the Wittig rearrangement of α-alkoxysilanes, α-deprotonation and cleavage of C–O bond, and hence rearrangement, are not concurrent events. Our results could also be interpreted to imply that the breaking of the O–C bond is the slow (rate limiting) step in the Wittig rearrangement of this class of compounds.

In the Wittig rearrangement of a stereodefined α-alkoxysilane, the [1,4]-pathway occurred with predominant retention of configuration at the migrating carbon. We observed that the [1,4]-pathway in a pair of diastereomeric α-alkoxysilanes occurred with similar levels of retention of configuration. On the other hand, the [1,2]-Wittig in the same pair of diastereomeric substrates occurred with different levels of retention of configuration (details to be presented in Chapter 7). This result is evidence that the [1,2] and the [1,4]-Wittig rearrangements of α-silyl ethers proceed via different mechanisms.

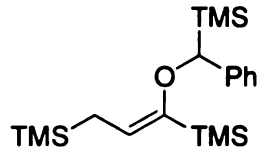
[2,3]-Alkyl migration is a concerted, thermally allowed sigmatropic process following the Woodward Hoffmann rule[28a] or the Fukui's frontier orbital theory.[33] In the [2,3]-alkyl shift in *E* substrates, the resulting [2,3] product has predominantly anti stereochemistry at the two newly formed stereocenters. We made a similar observation in the [1,4]-Wittig rearrangement reaction of α-alkoxysilane *E*-**56**. However, the experiment with *Z*-substrate would be very necessary for an unequivocal statement on the mechanism of the [1,4]-Wittig rearrangement of α-alkoxysilanes. This part of the study remains on of the areas for future study.



125



126



127

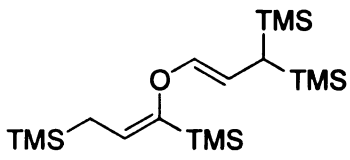
Electrophilic trapping of carbanion of 7-preparation of 125, 126, and 127: A mixture of 612 mg (2.78 mmol) of **7**, 1208 mg (11.12 mmol) of TMSCl, and 1124 mg (11.12 mmol) of TEA in 43 mL of THF, was cooled to below –78 °C. Then, 7.40 mL (6.95 mmol) of *s*-BuLi (0.94 M in cyclohexane) was added slowly via syringe. Following the addition of base, reaction was stirred at -78 °C for 3-4 h, and then quenched by adding saturated aqueous solution of NH_4Cl. Phases were separated and the organic phase was washed with water, and brine, then dried over anhydrous $MgSO_4$. Filtration, followed by concentration gave the crude product as a mixture, which, after silica gel chromatography (0 to 1% EtOAc in hexane gradient) afforded **125**, **126** and **127** in a combined 82% yield. Compounds **125**, **126** and **127** were readily separable by column chromatography on silica gel (hexanes neat).

125: IR (neat) 2955, 1609 1454, 1248 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.42-7.25 (m, 5H), 5.25-5.21 (t, J = 8.4 Hz, 1H), 4.75 (s, 2H), 1.68-1.66 (d, J = 8.4 Hz, 2H), 0.21 (s, 9H), 0.03 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 139.0, 128.3, 127.3, 127.1, 123.7, 72.3, 16.5, -0.3, -1.7. HRMS (EI) *m/z* 292.1686 [$(M)^+$; calcd for $C_{16}H_{28}OSi_2$, 292.1679].

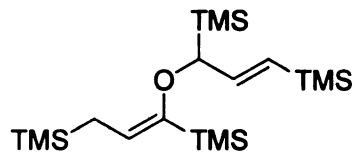
126: IR (neat) 2955, 1591, 1304, 1250 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.26 (m, 5H), 5.06-5.03 (d, J = 12.7 Hz, 1H), 4.71 (s, 2H), 1.93-1.91 (d, J = 12.2 Hz, 1H),

0.16 (s, 9H), 0.00 (s, 18H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.0, 139.2, 128.2, 127.2, 126.9, 125.5, 72.0, 18.3, -0.2, -0.4. HRMS (EI) *m/z* 364.2078 [$(M)^+$; calcd for $C_{19}H_{36}OSi_3$, 364.2074].

127: A white semi solid, melting near room temperature. IR (neat) 2955, 1601, 1495, 1448, 1408, 1248 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.26-7.03 (m, 5H), 4.97-4.91 (dd, J = 9.7 Hz, 1H), 4.70 (s, 1H), 2.07-2.00 (dd, J = 12.8, 9.7 Hz, 1H), 1.43-1.36 (dd, J = 12.4, 12.8 Hz, 1H), 0.01 (s, 9H), 0.00 (s, 9H), -0.02 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 141.9, 127.7, 125.3, 125.2, 120.1, 76.5, 16.9, 0.2, -1.5, -3.8. HRMS (EI) *m/z* 364.2078 [$(M)^+$; calcd for $C_{19}H_{36}OSi_3$, 364.2074].



131



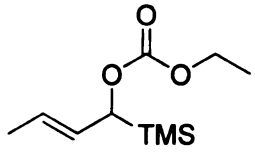
132

A mixture of 187 mg (0.77 mmol) of **40**, 333 mg (3.07 mmol) of TMSCl, and 310 mg (3.07 mmol) of TEA in 43 mL of THF, was cooled to below –78 °C. Then, 1.48 mL (1.92 mmol) of *s*-BuLi (1.3 M in cyclohexane) was added slowly via syringe. Follow addition of base, reaction was stirred at -78 °C for 3-4 h, then quenched by adding saturated aqueous solution of NH_4Cl. Phases were separated, the organic phase washed with water, and brine, then dried over anhydrous $MgSO_4$ and concentrated to give the crude product as a mixture, which, after silica gel chromatography (0 to 1% EtOAc in hexane gradient) afforded the **131** and **132** in a combined 86% yield. IR (neat) 2955, 1640, 1616, 1377, 1248 cm^{-1}.

131: ^1H NMR (500 MHz, $CDCl_3$) δ 6.00 (d, J = 5.7 Hz, 1H), 5.24 (t, J = 8.8, 8.4 Hz, 1H), 4.19-4.15 (dd, J = 12.4, 5.7 Hz, 1H), 1.60-1.58 (d, J = 8.8 Hz, 2H), 1.57-1.55 (d,

J = 12.4 Hz, 1H) 0.11 (s, 9H), 0.03 (s, 18H), -0.01 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.6, 142.4, 125.0, 103.2, 16.7, 15.6, -0.3, -1.1, -1.7. HRMS (EI) *m/z* 386.2321 [$(M)^+$; calcd for $C_{18}H_{42}OSi_4$, 386.2313].

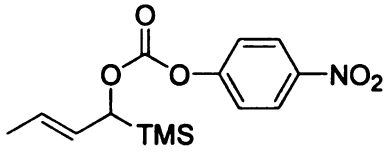
132: ^1H NMR (500 MHz, $CDCl_3$) δ 6.0-5.94 (dd, J = 19.0, 5.7 Hz, 1H), 5.54-5.50 (dd, J = 19.0, 1.8 Hz, 1H), 4.96-4.92 (apparent dd, J = 9.3, 8.8, 7.9, 7.5 Hz, 1H), 4.19-4.17 (dd, J = 5.7, 1.8 Hz, 1H), 1.82-1.77 (dd, J = 12.8, 9.3 Hz, 1H), 1.42-1.38 (dd, J = 13.2, 12.8, 8.0, 7.5 Hz, 1H), 0.07 (s, 9H), 0.03 (s, 9H), 0.01 (s, 9H), -0.02 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 146.4, 125.6, 120.1, 77.9, 16.5, 0.2, -1.1, -1.5, -3.8. HRMS (EI) *m/z* 386.2309 [$(M)^+$; calcd for $C_{18}H_{42}OSi_4$, 386.2313].



139

Preparation of 139: Ethylchloroformate (1.13 g, 10.41 mmol) was added to a cold (0 °C) solution of **34** (1.0 g, 6.94 mmol) in hexane/acetonitrile (1:1 v/v, 20 mL), followed by pyridine (1.70 mL, 20.82 mmol), and the reaction stirred at 0 °C for 2 h (TLC showed absence of starting material). The reaction was quenched by the addition of H_2O (30 mL), diluted with CH_3CN (50 mL), and then hexanes (150 mL). Layers separated and the hexane/acetonitrile layer was washed with brine (30 mL), dried with Na_2SO_4, and concentrated under reduced pressure to give the crude product, which was employed in the second step without further purification. To a solution of the crude carbonate in hexane/acetonitrile (1:1 v/v, 30 mL) at 0 °C, was added (1*R*,2*S*)-(+)-norephedrine (1.3 equiv, 1.36 g, 9.0 mmol), followed by diisopropylethylamine (3.63 mL, 20.82 mmol). The reaction was allowed to warm to room temperature overnight,

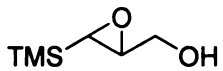
then quenched by the addition of H_2O. Phases were separated and the organic phase (hexane/acetonitrile) washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure to yield the desired product as a clear oil. The second step did not go, and after purification by column chromatography on silica gel (3% EtOAc in hexanes), 632 mg (42%) of **139**, the product of the first step, was obtained as a clear oil. IR (neat) 2961, 1744, 1451, 1370, 1277, 1252 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.58-5.41 (m, 2H), 4.87-4.85 (d, J = 6.3 Hz, 1H), 4.18-4.11 (q, J = 7.1 Hz, 2H), 1.67 (d, J = 5.5 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 0.03 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 127.1, 125,6, 74.5, 63.8, 17.9, 14.3, -4.0. HRMS (EI) *m/z* 216.1184 [$(M+H)^+$; calcd for $C_{10}H_{20}O_3Si$, 216.1182].



141

Preparation of carbonate 141: *p*-Nitrophenylchloroformate (629 mg, 3.12 mmol) was added to a cold (0 °C) solution of **34** (300 mg, 2.08 mmol) in hexane/acetonitrile (1:1 v/v, 11 mL), followed by pyridine (0.51 mL, 6.25 mmol), and the reaction stirred at 0 °C for 2 h (TLC showed absence of starting material). The reaction was quenched by the addition of H_2O (5 mL), diluted with CH_3CN (10 mL), and then hexanes (20-25 mL). Layers separated and the hexane/acetonitrile layer was washed with brine (30 mL), dried with Na_2SO_4, and concentrated under reduced pressure to afford 294 mg (0.95 mmol, 46% yield) of the pure carbonate **141** (mp 58.5-59.5 °C). IR (neat) 2961, 1763, 1616, 1595, 1526, 1493, 1348, 1252, 1213 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.26-8.23 (d, J = 9.1 Hz, 2H), 7.37-7.34 (d, J = 9.3 Hz, 2H), 5.68-5.61 (m, 1H),

5.59-5.50 (m, 1H), 4.99-4.96 (d, J = 7.7 Hz, 1H), 1.72 (d, J = 6.3 Hz, 3H), 0.09 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.9, 152.9, 145.2, 127.4, 126.2, 125.2, 121.8, 77.1, 17.9, -4.0. HRMS (FAB+) *m/z* 308.0957 [$(M-H)^+$; calcd for $C_{14}H_{18}NO_5Si$, 308.0955].

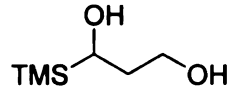


142

Preparation of 3-trimetylsilanyl-oxiranyl)-methanol 142: To a cold (-20 °C) solution of *n*-BuLi (1.6 M in hexanes, 2.0 equiv, 160.0 mmol, 100 mL) in a round-bottom flask was added propargyl alcohol (1.0 equiv, 80 mmol, 4.66 mL) as a solution in THF (5 M, 16 mL Et_2O). Subsequently TMSCl (2.2 equiv, 176 mmol, 19.12 g, 22.34 mL) was added over 30 min (-15 to -20 °C). Reaction was stirred for additional 2 h at room temperature, poured into an excess of 1N H_2SO_4 solution, and stirred for 2 h at room temperature. Phases were separated and the aqueous phase was extracted with Et_2O (4 x 50 mL). The combined ethereal solutions were washed with $NaHSO_4$ (sat, aq) to neutralize the H_2SO_4, then dried over anhydrous $MgSO_4$, filtered, and the solvent removed under reduced pressure to give the crude product, (*E*)-3-Trimethylsilanyl-prop-2-en-1-ol. Distillation through a 40-cm Vigreux column under reduced pressure gave 3.77 g (37%) of the desired allyl alcohol employed in the oxidation step.

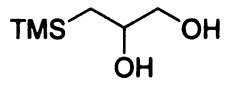
m-CPBA (2.0 equiv, 3.0 g, 23.03 mmol) solution in CH_2Cl_2 (140 mL) was added to a cold (0 °C), stirred solution of the *E*-3-trimethylsilanylprop-2-en-1-ol from step one above (1.0 equiv, 0.22 g, 1.66 mmol) in CH_2Cl_2 (50 mL) via syringe, and the reaction mixture stirred at 0 °C and monitored by GC-FID and TLC. After 6 h, the reaction mixture was filtered to remove precipitated *m*-chlorobenzoic acid. The solvent was removed in vacuo; the resultant massive white solid was dissolved in the minimal amount

of hexanes, filtered and washed with a minimal amount of hexanes. The solvent was removed in vacuo to give a colorless oil, which was purified by silica gel column chromatography using hexanes/EtOAc (20%) as eluent to give the pure epoxide **142** in 66% yield. IR (neat) 3418, 2959, 1720, 1410, 1250 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.00-3.94 (d, J = 13.0 Hz, 1H), 3.56 (d, J = 12.1 Hz, 1H), 3.01 (m, 1H), 2.25 (d, J = 3.7 Hz, 1H) 0.05 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 63.5, 56.1, 48.3, -3.8. **142** is a known compound and has spectral data in accord with the reported ones.[39]



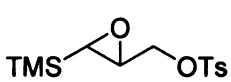
143

Preparation of 1-trimetylsilanyl-propane-1,3-diol 143: To a solution of 3-trimethylsilanyl-2,3-epoxypropan-1-ol (1.0 equiv, 220 mg, 1.50 mmol) in THF (2.0 ml) was added dropwise via syringe, a 1.0 M solution of $LiB(C_2H_5)_3H$ (superhydride) (2.0 equiv, 3.01 mmol, 3.0 ml) in THF. The reaction was stirred at room temperature for 1 h, at which time sampling by GC-MS revealed the complete consumption of the starting epoxyalcohol. Then water was added to quench the reaction, followed by washing with $NaHSO_4$ (sat, aq), and brine. The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated to furnish the crude product. Purification by silica gel column chromatography using hexanes/EtOAc (20%) afforded 200 mg (90% yield) of **143** as a clear oil. IR (neat) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 4.52-4.46 (m, 1H), 4.23-4.20 (dd, J = 8.8, 7.5 Hz, 1H), 3.64-3.61 (dd, J = 8.8, 7.5 Hz, 1H), 1.10-1.06 (dd, J = 14.1, 7.1 Hz, 1H), 0.89-0.84 (dd, J = 14.1, 7.9 Hz, 1H), 0.02 (s, 9H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 73.0, 25.4, 7.6, -1.0. **143** is a known compound and has spectral data in accord with the reported ones.[40]



144

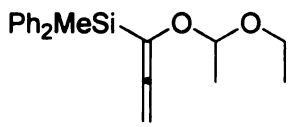
Preparation of 3-trimethylsilanyl-propane-1,2-diol 144: To a cold (0 °C) solution of 3-trimethyl-silanyl-2,3-epoxypropan-1-ol (1.0 equiv, 0.10 g, 0.684 mmol) in dimethoxyethane (DME) (3.5 ml) was added a 65+% solution of sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) in toluene (1.05 equiv, 0.718 mmol) dropwise under N_2. Following this addition, the reaction was allowed to warm to room temperature and stirred for 4.5 h. The reaction mixture was diluted with ether and quenched with 5% HCl solution. Phases were separated and the aqueous phase washed with ether. The combined organic phase was dried with anhydrous $MgSO_4$, filtered, and concentrated to give the crude product, which was clean (60% yield). Purification by silica gel column chromatography using hexanes/EtOAc (20%) as eluent afforded **144** in almost the same condition as the crude. This reaction was not optimized. IR (neat) 3358, 2952, 2919, 1420, 1250 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.89-3.77 (m, 1H), 3.61-3.56 (dd, J = 11.0, 2.7 Hz, 1H), 3.35-3.29 (dd, J = 11.0, 8.2 Hz, 1H), 2.58 (bs, 2H), 0.83-0.76 (dd, J = 14.3, 8.2 Hz, 1H), 0.72-0.65 (dd, J = 14.8, 14.3 Hz, 1H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 70.3, 69.1, 21.6, -0.8. **144** is a known compound and has spectral data in accord with the reported ones.[41]



148

Preparation of toluene-4-sulfonic acid 3-trimethylsilanyl-oxiranylmethyl ester 148: To a cold (0 °C) solution of 3-trimethylsilanyl-2,3-epoxypropan-1-ol 1.0 equiv, 0.40 g, 2.74 mmol) in CH_2Cl_2 (5 mL) were added TsCl (1.05 equiv, 0.55 g, 2.87

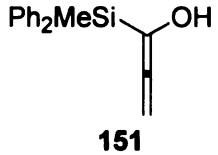
mmol), followed by Et_3N (2.5 equiv, 0.69 g, 6.83 mmol). The reaction mixture was allowed to warm to room temperature and stirred overnight. Reaction was quenched with $NaHCO_3$ (sat, aq), and diluted with CH_2Cl_2. Phased separated and the organic phase was washed with NH_4Cl (sat, aq) and brine, then dried over $MgSO_4$. Filtration and concentration under reduced pressure afforded 0.73 g (89%) of tosylate **148**. IR (neat) 2957, 1599, 1450, 1364, 1250, 1176 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 8.2 Hz, 2H), 7.33 (d, J = 7.7 Hz, 2H), 4.27-4.24 (dd, J = 11.2, 3.3 Hz, 1H), 3.90-3.87 (apparent dd, J = 11.5, 11.0, 6.6, 6.1 Hz, 1H), 3.03-3.00 (m, 1H), 2.43 (s, 3H), 2.03 (d, J = 3.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.0, 132.8, 129.9, 127.9, 72.3, 52.4, 49.0, 21.6, -3.8.



150

Preparation of [1-(1-ethoxy-ethoxy)-propa-1,2-dienyl]-methyldiphenylsilane 150: A dry 100 mL round-bottomed flask was flushed with N_2, and charged with ethyl vinyl ether (20.94 g, 0.29 mmol, 28 mL) and cooled to 0 °C. Then *p*-toluenesulfonic acid (13 mg, 0.07 mmol) was added with stirring, followed by dropwise addition of propargyl alcohol (11.63 g, 0.21 mol, 12.08 mL) over 20 min, while keeping the reaction temperature close to 0 °C. After stirring for additional 30 min, K_2CO_3 (sat, aq) was added with vigorous stirring. Phases were separated and the organic phase was dried over anhydrous K_2CO_3, filtered and excess vinyl ether removed by evaporation on a rotavap. The residue was then distilled under reduced pressure (oil bath temperature approx. 60 °C) to afford 16.02 g, 60% of the pure 1-(1-ethoxy-ethoxy)-propa-1,2-diene.

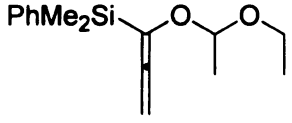
A solution of 1-(1-ethoxy-ethoxy)-propa-1,2-diene (10.18 g, 79.45 mmol) and BHT (1.5 mg/mmol substrate, 0.12 g, 0.54 mmol) in 320 mL THF in a 1 L round bottom flask was cooled to –80 °C, with stirring, and *n*-BuLi (1.5M solution in hexanes, 84.22 mmol, 56.15 mL) was added dropwise via a syringe over 1.5 h. After stirring for additional 30 min, a solution of $Ph_2MeSiCl$ (19.98 g, 85.81 mmol, 18 mL) in THF (30 mL) was added dropwise via a syringe, followed by addition of a solution of HMPA (15.66 g, 87.40 mmol, 15.2 mL) in THF (30 ml). The reaction mixture was stirred at –80 °C overnight, then Et_3N (12 mL) was added and the mixture stirred vigorously for 10 min, then poured into $NaHCO_3$ (sat, aq) (200 mL) and ether/pentane (1:1 v/v) added. Phases were separated and the aqueous phase washed with ether/pentane (1:1) (x 2). The combined organic phases were subsequently washed with H_2O and brine, passed through anhydrous Na_2SO_4, and then dried over K_2CO_3. Filtration, evaporation of solvent with a rotavap, and removal of the rest of the volatile components by distillation gave quantitative yield (29.22 g) of the product **150** as a thick brown oil. IR: (neat) 2978, 2178, 1589, 1429, 1385, 1254 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.64-7.34 (m, 10H), 4.90-4.87 (q, J = 5.3 Hz, 1H), 4.35-4.27 (q, J = 5.0 Hz, 2H), 3.70-3.63 (m, 1H), 3.53-3.47 (m, 1H), 1.35-1.34 (d, J = 5.3 Hz, 3H), 1.20-1.17 (t, J = 7.1 Hz, 3H), 0.70 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.0, 134.5, 129.7, 127.9, 105.4, 98.8, 87.1, 61.1, 53.4, 19.8.15.2, -2.1.



151

Preparation of 1-(methyldiphenylsilanyl)-propa-1,2-dien-1-ol 151: [1-(1-ethoxy-ethoxy)-propa-1,2-dienyl]-dimethylphenylsilane **150** (28.58 g, 88 mmol) was

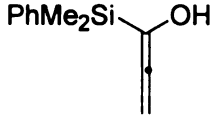
added to 2N H_2SO_4 (13.2 mL in 88 mL THF) and stirred at room temperature overnight. Reaction was poured into H_2O and extracted with ether/pentane (1:1). The combined organic fractions were washed with H_2O (x 3) and brine (x 1), poured through anhydrous Na_2SO_4, dried over Na_2SO_4 and concentrated under reduced pressure to give the crude 1-(diphenylmethylsilanyl)-propa-1,2-dien-1-ol **151**, which was purified by chromatography on silica gel (0-5% EtOAc in hexane gradient) to give a quantitative yield of the pure product. IR (neat) 3327, 2961, 2178, 1429, 1254, 1115, 1041 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.70-7.40 (m, 10H), 4.34 (s, 2H), 2.23 (bs, 1H), 0.76 (s, 3H). ^{13}C NMR (300 MHz, $CDCl_3$) δ 134.74, 134.42, 129.73, 127.93, 107.17, 86.94, 51.55, -2.24. HRMS (EI) *m/z* 252.0959 [$(M)^+$; calcd for $C_{16}H_{16}OSi$, 252.0970].



152

Preparation of [1-(1-ethoxy-ethoxy)-propa-1,2-dienyl]-dimethylphenylsilane, 152: A dry 100 ml round-bottomed flask was flushed with N_2, and charged with ethyl vinyl ether (20.94 g, 0.29 mol, 28 mL) and cooled to 0 °C. Then *p*-toluenesulfonic acid (13 mg, 0.07 mmol) was added with stirring, followed by dropwise addition of propargyl alcohol (11.63 g, 0.21 mol, 12.08 mL) over 20 min, while keeping the reaction temperature close to 0 °C. After stirring for additional 30 min, K_2CO_3 (sat, aq) was added with vigorous stirring. The organic phase was dried over anhydrous K_2CO_3, filtered and excess vinyl ether removed by rotavap. The residue was then distilled under reduced pressure (oil bath temperature approx. 60 °C) to afford 16.02 g, 60% of the pure 1-(1-ethoxy-ethoxy)-propa-1,2-diene. A solution of 1-(1-ethoxy-ethoxy)-propa-1,2-diene

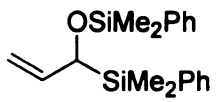
(5.10 g, 39.73 mmol) and BHT (1.5 mg/mmol substrate, 0.06 g, 0.27 mmol) in 160 mL THF was cooled to –80 °C, with stirring, and *n*-BuLi (1.5 M solution in hexanes, 42.11 mmol, 28.1 mL) was added dropwise via a syringe over 1 h. After stirring for additional 30 min, a solution of $PhMe_2SiCl$ (7.33 g, 42.90 mmol, 7.20 mL) in THF (15 mL) was added dropwise via a syringe, followed by addition of a solution of HMPA (7.831 g, 43.70 mmol, 7.6 mL) in THF (15 mL). The reaction mixture was stirred at –80 °C overnight, then Et_3N (6 mL) was added and the mixture stirred vigorously for 10 min, then poured into $NaHCO_3$ (sat, aq) (100 mL) and ether/pentane (1:1 v/v) added. Phases were separated and the aqueous phase washed with ether/pentane (1:1) (x 2). The combined organic phases were subsequently washed with H_2O and brine, passed through anhydrous Na_2SO_4, and then dried over K_2CO_3. Filtration, removal of solvent by rotavap, and removal of the rest of the volatile components by distillation gave 8.35 g (80%) of the product **152** as thick brown oil. IR (neat) 2974, 2176, 1428, 1384, 1251, 1116, 1056 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.63-7.35 (m, 5H), 4.89-4.83 (q, 1H), 4.24 (s, 2H), 3.71-3.43 (m, 2H), 1.34-1.32 (d, 3H), 1.21-1.17 (m, 3H), 0.41 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.6, 133.62, 129.45, 127.84, 103.60, 98.61, 88.64, 60.88, 53.32, 19.71, 15.21, -1.05. **152** is a known compound.[19a]



154

Preparation of 1-(dimethylphenylsilanyl)-propa-1,2-dien-1-ol 154: [1-(1-ethoxy-ethoxy)-propa-1,2-dienyl]-dimethylphenylsilane was added to 2N H_2SO_4 (4.7 mL in 31 mL THF) and stirred at room temperature overnight. Reaction was poured into

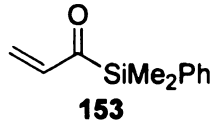
H_2O and extracted with ether/pentane (1:1). The combined organic fractions were washed with H_2O (x 3) and brine (x 1), poured through anhydrous Na_2SO_4, dried over Na_2SO_4 and concentrated under reduced pressure to give 6.65 g (88%) of the crude 1-(dimethylphenylsilanyl)-propa-1,2-dien-1-ol, which was purified by chromatography on silica gel (0-5% EtOAc in hexane gradient) to give the product **154** in 71% yield. IR (neat) 3324, 2961, 2178, 1492, 1250 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.63-7.36 (m, 5H), 4.28 (s, 2H), 1.78 (bs, 1H), 0.42 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.4, 133.6, 129.5, 127.9, 105.4, 88.7, 51.7, -1.1. HRMS (EI) *m/z* 190.0817 [$(M)^+$; calcd for $C_{11}H_{14}OSi$, 190.0814].



155

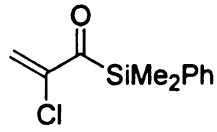
Preparation of 153 and 155-oxidation of oxidation of α-hydroxysilane 33: To a cold (-35 to -30 °C) solution of 2,4,6-trichloro[1,3,5]-triazine (cyanuric chloride) (8.23 g, 44.65 mmol) in THF (150 mL), was added DMSO (12.4 mL, 174.74 mmol) and the mixture stirred for 40 min. A 0.1 M THF solution of 1-(dimethylphenylsilanyl)-prop-2-en-1-ol (5.72 g, 29.76 mmol) was added very slowly and the reaction stirred for 2 h, followed by the addition of TEA (19.80 mL, 142 mmol). After stirring for an additional 1 h, the reaction was warmed to room temperature. The solvent was removed under vacuum and Et_2O added to the resulting solid residue. Reaction was quenched by adding HCl (1M, 2.0 mL). Phases were separated and the organic phase washed with $NaHCO_3$ (aq, sat), followed by brine, dried over Na_2SO_4 and the solvent evaporated to give the oxidation products **153** (371 mg, 6% yield) and **155** (1.61 g, 17% yield). **155**: IR (neat)

2959, 1630, 1427, 1252 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.55-7.31 (m, 10H), 5.87-5.80 (m, 1H), 5.04-5.00 (d, *J* = 17.8 Hz, 1H), 4.91-4.88 (d, *J* = 10.3 Hz, 1H), 4.18 (d, *J* = 2.4 Hz, 1H), 0.27 (s, 3H, 0.26 (s, 6H), 0.23 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 134.3, 133.6, 129.3, 129.1, 127.7, 127.6, 110.5, 69.3, -1.1, -1.2, -5.9, -6.0. HRMS (FAB+) *m/z* 326.1521 [$(M)^+$; calcd for $C_{19}H_{26}OSi_2$, 326.1522].



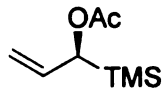
153

Preparation of 153: **Swern oxidation of 33**: To a cold (-50 °C) solution of oxalyl chloride (1.32 mL, 15.06 mmol) in CH_2Cl_2 (18.30 mL) was added via syringe, DMSO (2.15 mL, 30.13 mmol) solution in CH_2Cl_2 (4.56 mL) and the reaction stirred for 20 min. Then, the substrate alcohol **33** (2.63 g, 13.70 mmol) solution in CH_2Cl_2 (4.56 mL) was added via syringe and the reaction stirred at -50 °C for 20 min. Et_3N (7.63 mL, 54.79 mmol) was added by syringe (reaction turned yellow and massive precipitate formed). The cold bath was removed and the reaction allowed to warm to room temperature over 1 h. Aqueous workup, and purification by column chromatography on silica gel (0 to 2% EtOAc in hexane gradient) afforded **153** and **155** (10:1) in 91% yield. IR (neat) 2961, 1726, 1640, 1601. 1429, 1252 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.54-7.35 (m, 5H), 6.44-6.38 (dd, *J* = 18.0, 11.0 Hz, 1H), 5.95 (d, *J* = 17.2), 5.81 (d, *J* = 11.0, 1H), 0.52 (s, 6). ^{13}C NMR (75 MHz, $CDCl_3$) δ 235.5, 141.1, 135.2, 133.9, 129.8, 128.9, 128.2, -3.7. **153** is a known compound and have spectral data in accord with the reported ones.[10]



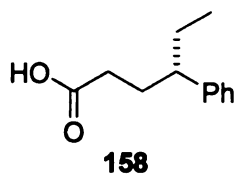
156

156: IR (neat) 2963, 1699, 1626,1429, 1252, 1111 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.53-7.36 (m, 5H), 6.25 (d, *J* = 2.2 Hz, 1H), 6.11 (d, *J* = 2.2 Hz, 1H), 0.57 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 224.5, 144.4, 134.5, 133.9, 130.2, 128.4, 127.8, -3.2.



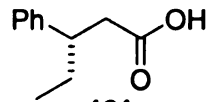
157

Enzymatic resolution of 1-trimethylsilanyl-prop-2-en-1-ol 32-preparation of (*S*)-(-)-32: To a solution of racemic α-hydroxysilane **32** (7.71 g, 59.27 mmol) in pentane (20 mL, 4.0 M) were added *Novozym 435* (0.015 g/mmol racemic alcohol, 0.89 g) and vinyl acetate (1.5 equiv, 7.65 g, 88.90 mmol, 8.2 mL). The reaction was stirred at to 38 °C and monitored by chiral GC (BETA DEX TM 325 capillary column, 30 m x 0.25 mm x 0.25 um film thickness, Catalog No. 24308; Program 30 to 100 °C, at 5 °C/min, hold at 100 °C for 2 min.). Then reaction mixture was filtered through a pad of Celite 503, concentrated, and purified by silica gel column chromatography. Optical rotation IR (neat) 2961, 1742, 1636, 1370, 1235 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 5.84-5.77 (m, 1H), 5.26-5.14 (dt, *J* = 6.0, 2.0 Hz, 1H), 4.98-4.93 (m, 1H), 2.05 (s, 3H), 0.02 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6, 134.9, 111.2, 70.6, 20.9, -4.1. **157** is a known compound and has spectral data in accord with the reported ones.[42]



158

Preparation of 4-phenyl-hexanoic acid 158. 30% H_2O_2 (1.0 mL) and 3N NaOH (0.50 mL) were added to a solution of 4-phenyl-1-trimethylsilanyl-hexan-1-one (0.32 mmol, 0.08 g) in MeOH (3.0 mL) and the mixture turned cloudy, which dissipated on stirring at room temperature for 20 min. The mixture was extracted with ether, and concentrated. Purification by column chromatography on silica gel (hexane/EtOAc (0-10%) gave 0.022 g (0.116 mmol, 36%) of 4-phenyl-hexanoic acid **158**. IR (neat) cm^{-1}. ^{1}HNMR ($CDCl_3$, 300 MHz) δ 0.76 (t, 3H), 1.50-1.72 (m, 2H 3H), 1.75-1.88 (m, 1H), 1.95-2.07 (m, 1H), 2.15 (t, 2H), 2.37-2.47 (m, 1H). ^{13}CNMR ($CDCl_3$, 125 MHz) δ 179.1, 144.2, 128.4, 127.7, 126.3, 47.1, 32.0, 31.1, 29.6, 12.1. **158** is a known compound and have spectral data in accord with the reported ones.[43]

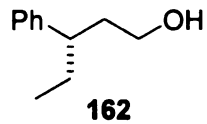


161

Preparation of 3-phenyl-pentanoic acid 161. *N*-(2-Hydroxy-1-methyl-2-phenyl-ethyl)-*N*-methyl-3-phenyl-acrylamide: A solution of cinnamoyl chloride (1.15 equiv, 22.80 mmol, 3.8 g) in THF (8.0 mL, 2.85 M) was added via cannula over 10 min to an ice-cold solution of L-(-)-ephedrine•HCl (1.0 equiv, 19.83 mmol, 4.0 g) and proton-sponge in THF (47 M, 0.42 M L-(-)-ephedrine). Reaction was stirred at 0 °C and allowed to warm to rt for 24 h. The reaction mixture was partitioned between EtOAc (79 mL) and brine (6.0 mL). Phases were separated and the aqueous phase extracted with EtOAc to afford 6.95 g of the crude product, which was passed through silica gel column to give 6.03 g (18.17 mmol, 92%) of and excess phenylacetyl *N*-(2-Hydroxy-1-methyl-2-phenyl-ethyl)-*N*-methyl-3-phenyl-acrylamide. This amide was employed in the following step.

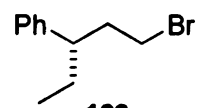
Alkylation of *N*-(2-hydroxy-1-methyl-2-phenyl-ethyl)-*N*-methyl-3-phenyl-acrylamide: A 3-necked round-bottomed flask equipped with a condenser (carrying a drying tube), an addition funnel, and a magnetic stir bar was charged with Mg (7.95 g, 327.12 mmol) and ether (80 mL). The flask was immersed in an oil bath and a solution of EtBr (11.88 g, 109.04 mmol) in ether (50 mL) added slowly. Reaction was stirred at reflux for 3 h and transferred via cannula to a cold (-78 °C) solution of *N*-(2-hydroxy-1-methyl-2-phenyl-ethyl)-*N*-methyl-3-phenyl-acrylamide (from step one above) (6.03 g, 18.17 mmol) in ether/THF (1:1.5 v/v, 280 mL). Following the transfer, reaction was allowed to warm from -78 to -40 °C and stirred at this temperature for 48 h. The reaction was filtered (to remove insoluble materials), residue washed with EtOAc. The aqueous phase was extracted with EtOAc, combined organic extract dried over MgSO4, filtered, concentrated, and purified by column chromatography on silica gel (hex/EtOAc (0-40%) to afford **160** in >100% yield. **Acid hydrolysis**: Compound **160** was dissolved in AcOH (43 mL) and 6N H_2SO_4 (86 mL), and refluxed for 3 h. The reaction mixture was cooled to room temperature, diluted with ether, and phases separated. The aqueous phase was extracted with ether (40 mL x 3) and the combined ethereal extracts was washed with brine, and dried over $MgSO_4$. Filtration and concentration under reduced pressure afforded 2.63 g of the crude **161**. Purification by column chromatography on silica gel (hexanes/EtOAc (0-50%) afforded 1.87 g (10.52 mmol, 58% yield) of the pure acid (yield was over 2 steps). IR (neat) 3400-2500, 1709, 1933, 1605, 1495, 1452, 1412, 1285 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 11.31 (bs, 1H), 7.32-7.16 (m, 5H), 3.04-2.94 (m, 1H), 2.71-2.56 (m, 2H), 1.80-1.53 (m, 2), 0.78 (apparent t, J = 7.7, 7.1 Hz, 3H). ^{13}C NMR (75

MHz, $CDCl_3$) δ 178.7, 143.4, 128.3, 127.3, 126.4, 43.5, 41.2, 29.1, 11.9. **161** is a known compound and have spectral data in accord with the reported ones.[44]



162

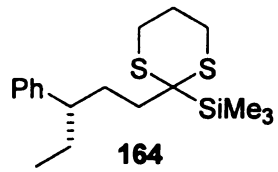
Preparation of 3-phenyl-pentan-1-ol 162. To a solution of LAH (0.98 g, 25.87 mmol) in THF (80 mL) was added a solution of 3-phenyl-pentanoic acid **161** (1.80 g, 10.14 mmol) in THF (50 mL), and the reaction refluxed for 18-20 h. The reaction was quenched by very careful addition of H_2O. Phases were separated and the aqueous phase was extracted with ether (50 mL x 3). The combined ethereal layer was washed with H_2O and brine, dried over $MgSO_4$, filtered and concentrated to give 1.88 g of crude 3-phenyl-pentan-1-ol as a light yellow, thick oil. Purification by column chromatography on silica gel (hexanes/EtOAc (0-10%) afforded 1.28 g (7.81 mmol, 74%) of alcohol **162** as a thick colorless oil. $[a]_D^{20}$+11, (c. 1.21, PhH). IR (neat) 3331, 2963, 2930, 1603, 1495, 1452, 1372 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.12 (m, 5H), 3.54-3.39 (m, 2H), 2.62-2.51 (m, 1H), 1.99-1.87 (m, 1H), 1.83-1.72 (m, 1H), 1.70-1.50 (m, 3H), 0.77 (t, J = XX Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8, 128.3, 127.5, 126.0, 61.2, 44.3, 39.3, 29.8, 12.2. **162** is a known compound and have spectral data in accord with the reported ones.[45]



163

Preparation of (3-Bromo-1-ethyl-propyl)-benzene 163. A 100 mL 2-necked round-bottomed flast was charged with 3-phenyl-pentan-1-ol **162** (1.0 equiv, 3.05 mmol,

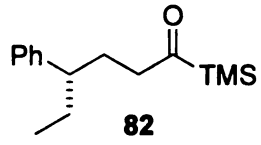
0.50 g), CBr_4 (1.25 equiv, 3.81 mmol, 1.26 g) and CH_2Cl_2 (to make a 0.1 M solution of 3-phenyl-pentan-1-ol. The flask was capped under N_2 and cooled to 0 °C. Then, a solution of PPh_3 (1.5 equiv, 4.57 mmol, 1.2 g) in CH_2Cl_2 (10 mL, 0.45 M) was added at the rate of 0.86 ml/min, and reaction stirred at 0 °C for 1.5 h. Reaction mixture was allowed to warm to room temperature, and diluted with ether. White precipitates formed. Filtration, concentration of the filtrate, and purification by column chromatography on silica gel afforded 0.69 g (3.04 mmol, 99.80%) of (3-Bromo-1-ethyl-propyl)-benzene **163**.[46] IR (neat) 2961, 2926, 1603, 1493, 1452, 1254 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.13 (m, 5H), 3.31-3.23 (m, 1H), 3.14-3.05 (m, 1H), 2.7-2.60 (m, 1H), 2.24-2.01 (m, 2H), 1.73-1.51 (m, 2H), 0 78 (t, J = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 128.4, 127.6, 126.3, 46.1, 39.5, 32.3, 29.4, 12.2. $[a]_D^{20}$



164

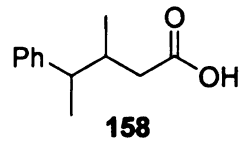
Preparation of trimethyl-[2-(3-phenyl-pentyl)-[1,3]dithian-2-yl]-silane 164. To a cold (-25 °C) THF solution of 2-silyl-1,3-dithiane (0.5 M, 1.0 equiv, 2.55 mmol, 0.49 g, 0.5 M in THF) was added dropwise over 20 min, *n*-BuLi (1.6 M solution in hexane, 1.05 equiv). Reaction was stirred for 2 h, and transferred to a THF solution of 3-bromo-1-ethyl-propyl)-benzene **163** (1.0 equiv, 2.55 mmol, 0.58 g, 0.5 M in THF). Reaction was stirred at -25 °C for 58 h, and allowed to warm to room temperature for 10 h, and quenched by the addition of ether/water (4:3 v/v). Phases were separated, and the organic layer washed with brine (x 2), dried over $MgSO_4$ and concentrated on the rotavap to give crude trimethyl-[2-(3-phenyl-pentyl)-[1,3]dithian-2-yl]-silane **164**. Purification

by column chromatography on silica gel (hexanes/EtOAc (0-1%) delivered 0.68g (2.03 mmol, 80%) of the pure product. IR (neat) 2959, 1603, 1493, 1452, 1423, 1250 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.14 (m, 5H), 2.84-2.74 (m, 1H), 2.66-2.56 (m, 1H), 2.41-2.21 (m, 3H), 2.10-2.00 (m, 2H), 1.90-1.57 (m, 6H), 0.78 (t, J = 7.7, 7.1 Hz, 3H), 0.13 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.3, 128.2, 127.8, 125.9, 48.3, 38.8, 34.6, 34.3, 29.8, 25.5, 23.1, 22.9, 12.2, -2.6. HRMS (EI) *m/z* 338.1544 [$(M)^+$; calcd for $C_{18}H_{30}S_2Si$, 338.1558]. $[a]_D^{20}$



82

Preparation of 4-phenyl-1-trimethylsilanyl-hexan-1-one 82. A solution of trimethyl-[2-(3-phenyl-pentyl)[1,3]- dithian-2-yl]-silane **164** (1.0 equiv, 0.88 mmol, 0.30 g) in acetone (8.0 mL) was added slowly to a cold (0 °C) stirred suspension of *N*-bromosuccinimide (6.0 equiv, 5.29 mmol, 0.94 g) in 80% aqueous acetone. Reaction was stirred at 0 °C for 2 h. The ice bath was removed and Na_2S solution wa rapidly added, and product extracted with ether. The combined organic layers were washed with H_2O, brine, dried with $MgSO_4$, and concentrated on the rotary evaporator. Purification by column chromatography on silica gel (hexanes/EtOAc (0-1%) afforded 0.14 g (0.56 mmol, 64%) of 4-Phenyl-1-trimethylsilanyl-hexan-1-one **82**. IR (neat) cm^{-1}. ^1HNMR ($CDCl_3$, 300 MHz) δ 7.29-7.06 (m, 5H), 2.49-2.42 (m, 1H), 2.38-2.31 (m, 2H), 1.95-1.88(m, 1H), 1.70-1.61 (m, 2H), 1.5801.49 (m, 1H), 0.76-0.73 (t, J = 7.5 Hz, 3H), 0.08 (s, 9H). $^{13}CNMR$ ($CDCl_3$, 125 MHz) δ 248.5, 144.8, 128.3, 127.7, 126.0, 47.1, 46.4, 29.8, 28.4, 12.1, -3.2. $[a]_D^{20}$



158

Preparation of 158: The [1,4]-Wittig product **97** from the Wittig rearrangement of α-alkoxysilane of *E*-**56** (217 mg, 0.87 mmol) was dissolved in THF (0.24 M, 3.6 mL), and 3N NaOH (0.83 mL/mmol starting material, 0.72 mL) added. The mixture was heated to 35-40 °C, and then oxidized by adding dropwise 30% H_2O_2 (0.42 mL/mmol starting material, 0.36 mL), while maintaining the reaction temperature below 50 °C for 2 h. The aqueous phase was cooled to 0 °C, and acidified to pH of 1-2 with 6 N HCl.. The resulting aqueous material was extracted with ether (5 x 20 mL), and the ether solution dried with $MgSO_4$. Filtration and concentration afforded 158 mg (94% yield) of **158a** and **158b** as thick colorless oils. Purification by column chromatography on silica gel (hexane/EtOAc (0-10%) afforded **158a** and **158b** as a 2.8:1 mixture of diastereomers (ratio by ^{1}HNMR). IR (neat) 3100-2500 (s, v br), 2967, 1707, 1495, 1452, 1412, 1290 cm^{-1}.

Major *anti*-**158a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.49 (br s, 1H), 7.31-7.18 (m, 5H), 2.72-2.65 (quintet, *J* = 7.1, 6.6 Hz, 1H), 2.53-2.48 (dd, *J* = 14.8, 4.4 Hz, 1H), 2.28-2.18 (m, 1H), 2.14-2.09 (dd, *J* = 15.1, 9.1 Hz, 1H), 1.28-1.26 (d, *J* = 7.1 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.8, 144.8, 128.2, 127.6, 126.2, 44.4, 38.9, 36.2, 18.3, 17.5. HRMS (EI) *m/z* xxx.yyyy [$(M-H)^+$; calcd for $C_{12}H_{16}O_2$, xxx.yyyy].

Minor *syn*-**158b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.49 (br s, 1H), 7.33-7.18 (m, 5H), 2.63-2.56 (quintet, *J* = 7.1, 6.6 Hz, 1H), 2.35-2.31 (apparent dd, *J* = 15.4, 14.8, 4.4, 3.8 Hz, 1H), 2.28-2.18 (m, 1H), 2.04-1.99 (dd, J = 14.8, 9.3 Hz, 1H), 1.27-1.24 (d, *J* = 7.1

Hz, 3H), 1.04 (d, J = 6.6 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.8, 145.7, 128.2, 127.5, 126.1, 44.7, 39.8, 36.4, 18.3, 17.2. *Anti* **158a** and *syn* **158b** are known compounds and have spectral data in accord with the reported ones.[47]

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26. Resolution of sec-phenethyl alcohol was done by stirring a mixture of the racemic alcohol, 1.0 equiv of acetic anhydride and Amano AK Lipase in benzene at room temperature for 55 h [($[a]_D^{20}$ –51.6 ° (c 1.294, $CHCl_3$); Lit$[a]_D^{25}$ –41.0 ° (neat)).] This

reaction also afforded 45.81 of (*R*)-(+)-1-phenylethanol acetate $[a]_D^{20}$ +94.4 ° (c 1.104, $CHCl_3$); Lit. $[a]_D^{25}$ +106 °, (c 1, ether)). The trichloroacetimidate of (*S*)-(-)-phenethyl alcohol was prepared following literature procedure and obtained in 88% enantiomeric excess ($[a]_D^{20}$ –51.6 ° (c 1.2, $CHCl_3$)).

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CHAPTER 7

[1,2]-WITTIG REARRANGEMENT OF α-ALKOXYSILANES

7.1. Introduction

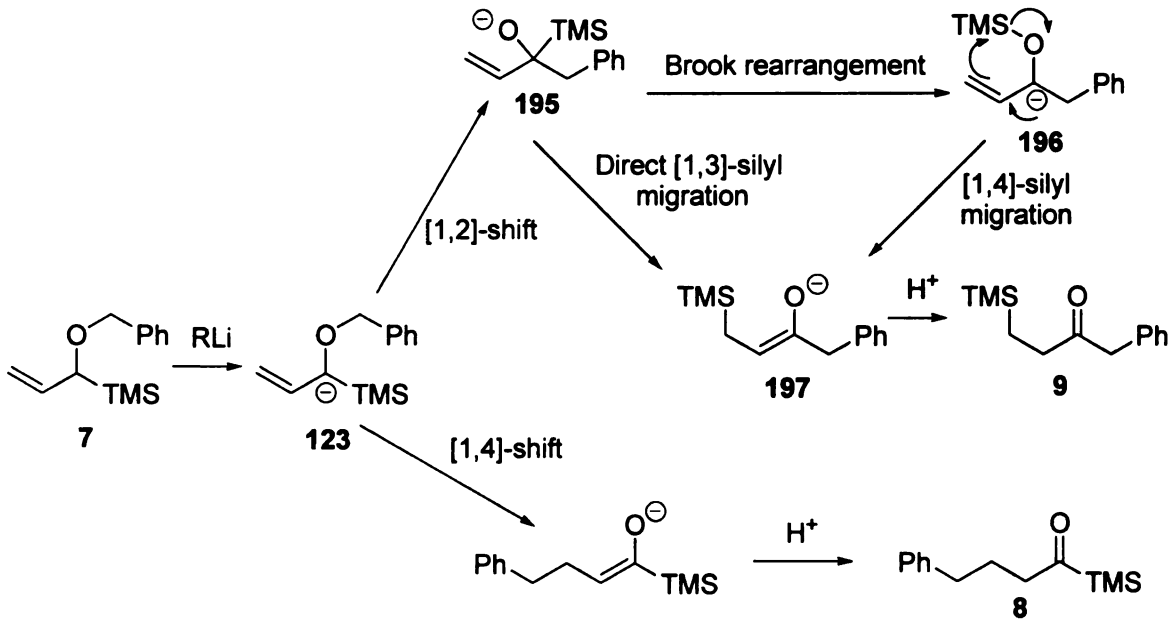
As reported in previous chapters of this dissertation, the Wittig rearrngements of α-alkoxysilanes studied in this work were initiated by deprotonation α to the silyl group and afforded [1,2] and [1,4] products. Product distribution depended largely on the structure of the starting alkoxy ether and the temperature of the reaction. We showed that for a simple α-alkoxysilane **7** bearing no substituent at the migrating carbon center and at the terminal sp^2 carbon of the allyl moiety, product formation could be controlled simply by careful control of reaction temperature and that the [1,2]-rearrangement pathway could be effectively suppressed. We also showed that compounds featuring a substituent either at the migrating center or at the terminal sp^2 carbon, or at both sites, afforded the [1,2] and [1,4] products in approximately 1:2 ratio, regardless of the reaction temperature.

As reported in Chapter 4, substitution at the migrating carbon resulted in a pair of diastereomeric compounds with different reactivities. We also reported that the Wittig products formed a new chiral center. We reported the determination of the relative stereochemistries of the reactive and less reactive diastereomer pair of α-alkoxysilanes in Chapter 5 and in Chapter 6 we discussed the mechanism of the [1,4]-Wittig. At this point we were poised to investigate further the [1,2]-Wittig reaction of α-alkoxysilanes.

7.2. Observed [1,2]-alkyl shift/silyl migration in some α-alkoxysilanes

Maleczka and Geng[1] first showed that the Wittig rearrangement of our model substrate **7** afforded the products **8** and **9** via the [1,4] and [1,2] pathways (Scheme 7.1). A close look at this Scheme reveals that while **8** is the [1,4]-Wittig product, **9** is not the expected [1,2]-product, but is obtained via the [1,2]-pathway.

Scheme 7.1. Plausible pathway for the [1,2]-Wittig rearrangement/silyl migration observed in compound **7**

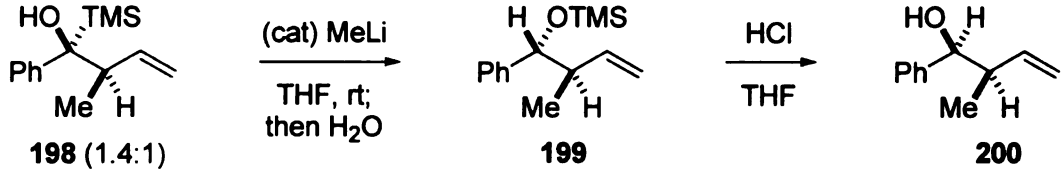


Scheme 7.1 shows our explanation of the observed [1,2]-products from the Wittig rearrangement of compound **7**. The [1,2]-Wittig pathway for the carbanion of **7** (**123**) via radical-radical anion dissociation-recombination event would afford the tertiary alkoxide **195**, which could undergo a subsequent silyl migration via two possible routes. First, the silyl group could do a 1,2-Brook rearrangement, placing the negative charge on the carbon, and a subsequent 1,4-shift to give an enolate intermediate **197**. The second route would involve a direct [1,3]-silyl migration, also

giving the enolate **197**. Looking at these two scenarios more closely, the first route involves breaking a weaker Si–C bond (Si–C bond in Me_4Si is 318 $kJmol^{-1}$/75.967 $kcalmol^{-1}$, bond length 0.189 nm) and making a stronger O–Si bond [approximate bond dissociation energies: Si–O bond in Me_3SiOMe is 531 $kJmol^{-1}$/126.851 $kcalmol^{-1}$; in $(Me_3Si)_2O$ 812 kJmol-1/193.98 $kcalmol^{-1}$; bond length in $(H_3Si)_2O$ is 0.163 $kJmol^{-1}$/)].[2] However, this process would result in going from an alkoxide anion to a carbanion. The question here is whether the gain in energy (ΔE) could offset the loss in going from an alkoxide to a carbanion. In the second route, there is breaking of a C–C bond and making of a new C–C bond, a process that is energetically neutral, but maintains an alkoxide anion throughout.

In their previous work, Maleczka and Geng[1] reported isolation of an alkyl silyl ether **199**, which would arise from a [1,2]-Brook rearrangement on deprotonation of the tertiary alcohol **198** (Scheme 7.2). This result seems to support the first pathway as the operative mechanism.

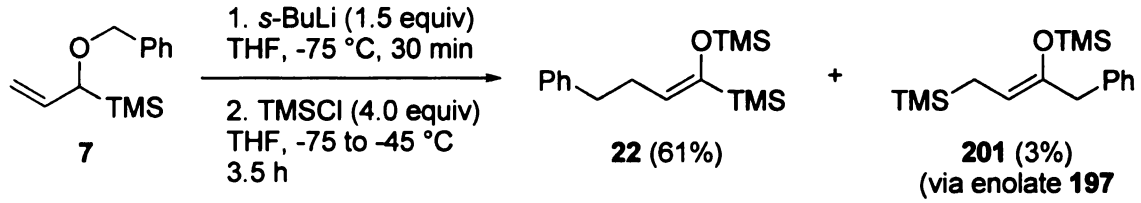
Scheme 7.2. Previous work by Maleczka and Geng



In the present work, we isolated a vinyl trimethylsilyl ether **201** from the Wittig rearrangement/electrophilic trapping of **7** (Scheme 7.3). The formation of compound **201** could be explained by either Brook rearrangement/[1,4]-silyl migration or direct [1,3]-silyl migration, as both routes result in the requisite enolate intermediate **197**

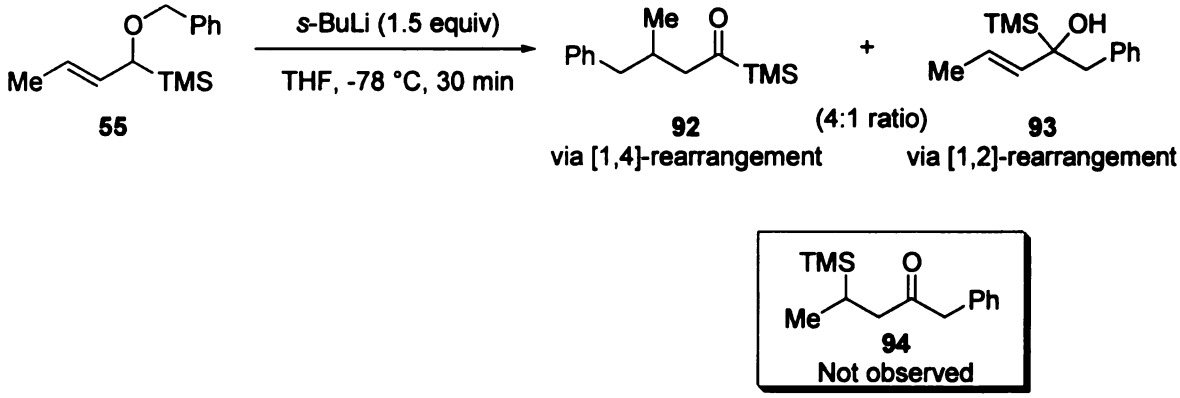
(Scheme 7.1). Thus, this result does not give information as to which mechanism is operative.

Scheme 7.3. Present work: isolation of vinyl silyl ether **201** in the Wittig rearrangement/electrophilic trapping of **7**



In Chapter 4, we reported the Wittig rearrangement of **55**, featuring a substitution at the terminal sp^2 carbon of the allyl moiety. Here, we did not observe the silyl migration that usually accompanies the [1,2]-Wittig of α-alkoxysilanes bearing no such substituent (Scheme 4.26).

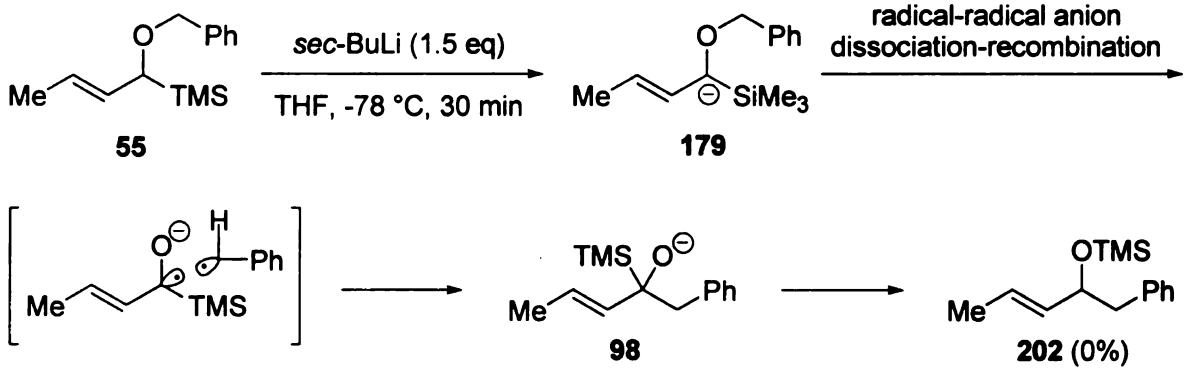
Scheme 4.26. Substitution at the terminal sp^2 carbon: Wittig rearrangement reaction of **55**



The isolation of **92** from the Wittig rearrangement of **55** seems to support the second route. If Brooks rearrangement precedes silyl migration, and if substitution at the terminal sp^2 carbon of the allyl moiety suppresses silyl migration, then one would

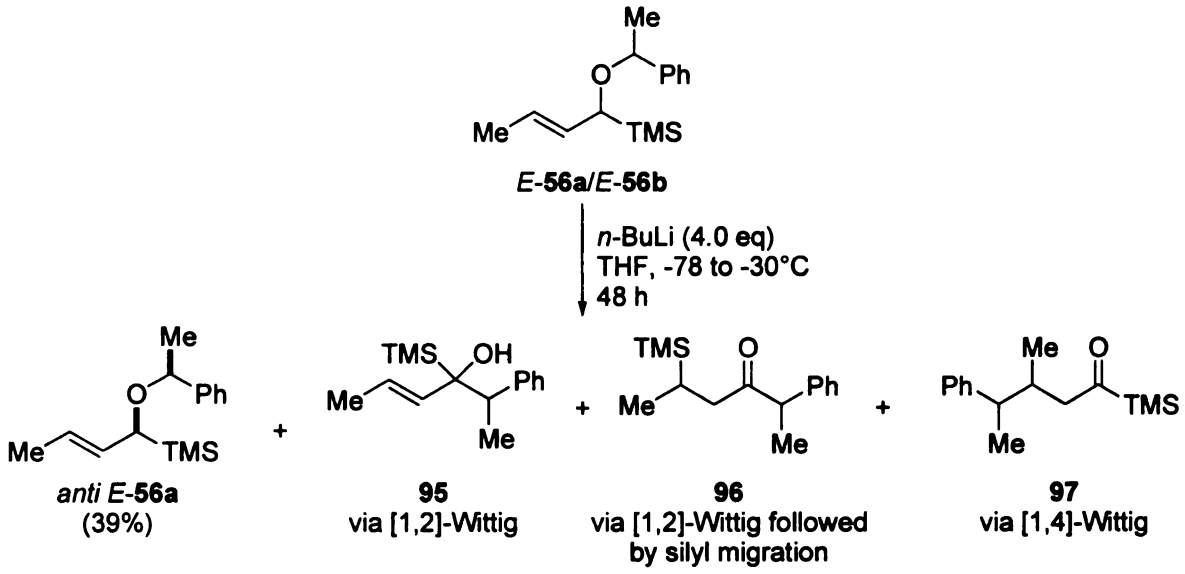
expect the formation of the allyl trimethylsilyl ether **202** (Scheme 7.4), which we did not observe. Although we have no direct evidence of any *O*-silyl products, we are not completely ruling out the possibility that the [1,3]-silyl migration could occur via Brook rearrangement of **195** (Scheme 7.1).[3]

Scheme 7.4. Plausible mechanism of the [1,2]-Wittig rearrangement of α-alkoxysilanes



In the Wittig rearrangement of *E*-**56** (Scheme 4.26), we isolated two products arising from [1,2]-rearrangement **95** and [1,2]-rearrangement/silyl migration **96**. Steric congestion at the two vicinal stereocenters could be the driving force for the silyl migration leading to **96**.

Scheme 4.26. Substitution at both the migrating center and the terminal sp^2 carbon

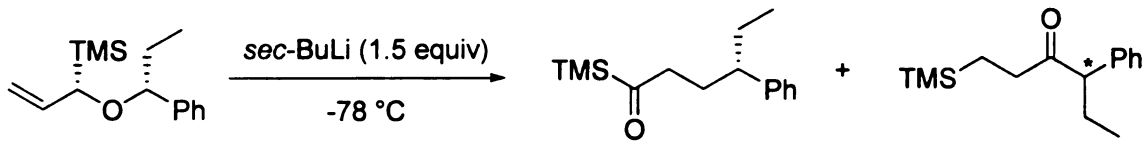


Combined yield of products **95**, **96** and **97** ranges from 35 to 57% depending on the temperature and reaction time

7.3. Stereochemistry of the [1,2]-Wittig rearrangement of α-alkoxysilanes

For an α-alkoxysilane bearing an alkyl substituent at the migrating center, there arises the question of stereochemistry at the newly formed stereocenter of the [1,2]-Wittig product. The Wittig rearrangement of enantiodefined substrate **48** afforded **82** and **83**, arising from [1,4] and [1,2]-Wittig pathways respectively (Scheme 7.5). Unlike the [1,4]-Wittig product **82, 83** was amenable to analysis by chiral HPLC.[4] The racemic [1,2] product was analyzed first to determine the retention times for the two enantiomers (for reference purposes).

Scheme 7.5. Wittig rearrangement reaction of **48** mediated by *sec*-BuLi



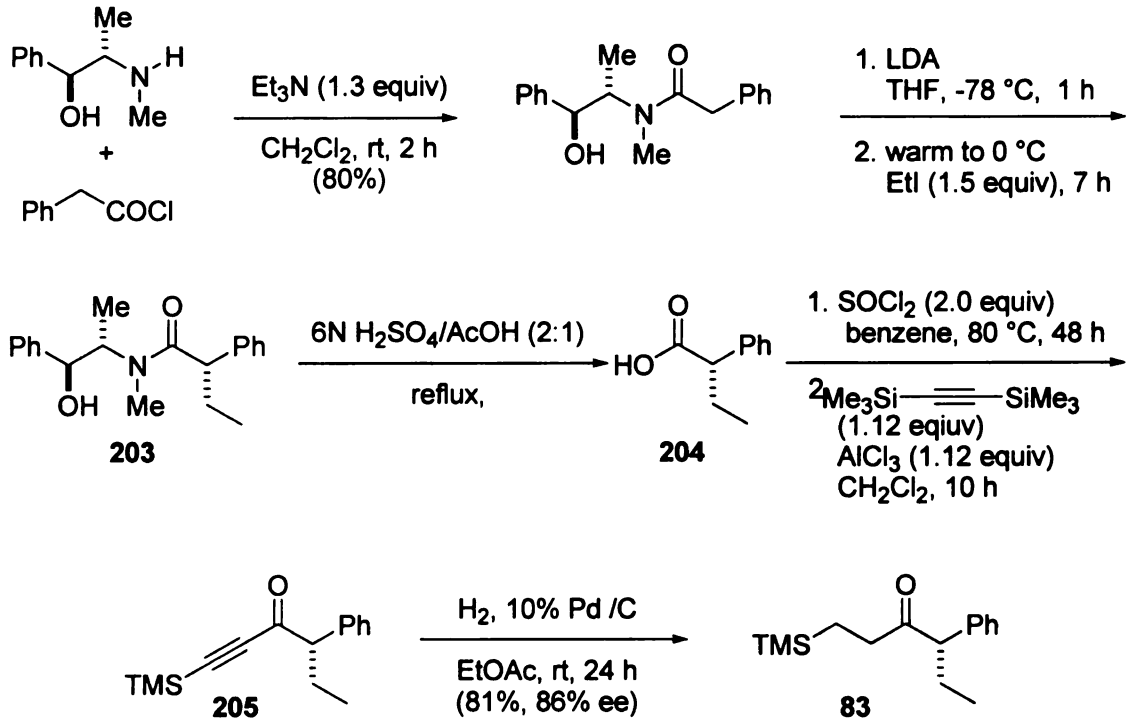
48
96% ee/98% er

82
% ee retention 75%
% er retention 88%

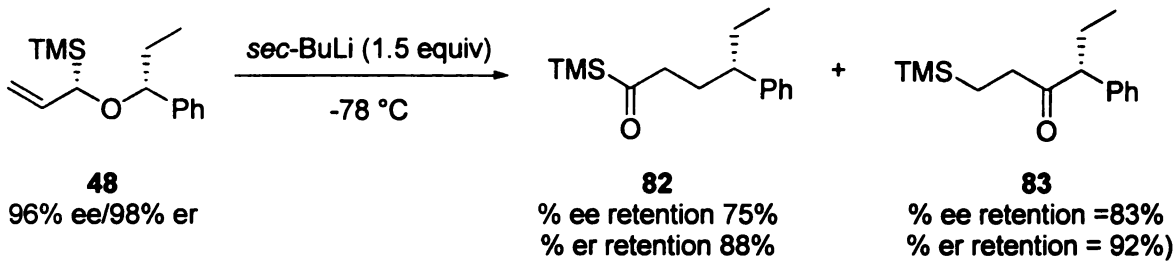
83

Next enantiomerically enriched [1,2] product **83** was prepared by an independent route as illustrated in Scheme 7.6. The preparation started with the formation of the amide **203**[5] (81% yield), by the reaction between pseudoephedrine and phenylacetyl chloride, in the presence of TEA. Deprotonation of this amide by LDA, trapping with EtI, and removal of the chiral auxiliary by acid hydrolysis afforded the expected 2-phenyl-butyric acid (42%). This compound was subsequently converted to the corresponding 2-phenyl-butyryl chloride. Lewis acid mediated acetylation of 2-phenyl-butyryl chloride[6] followed by catalytic hydrogenation afforded the expected [1,2]-Wittig product **83** (81% yield, 87% ee). The HPLC traces of the [1,2]-Wittig products (from both sources) were obtained and compared. It was found that the [1,2]-pathway proceeded with retention of configuration at the migrating carbon (% ee retention = 83%, % er retention = 92%) (Scheme 7.7).

Scheme 7.6. Synthesis of [1,2]-Wittig product by an independent route



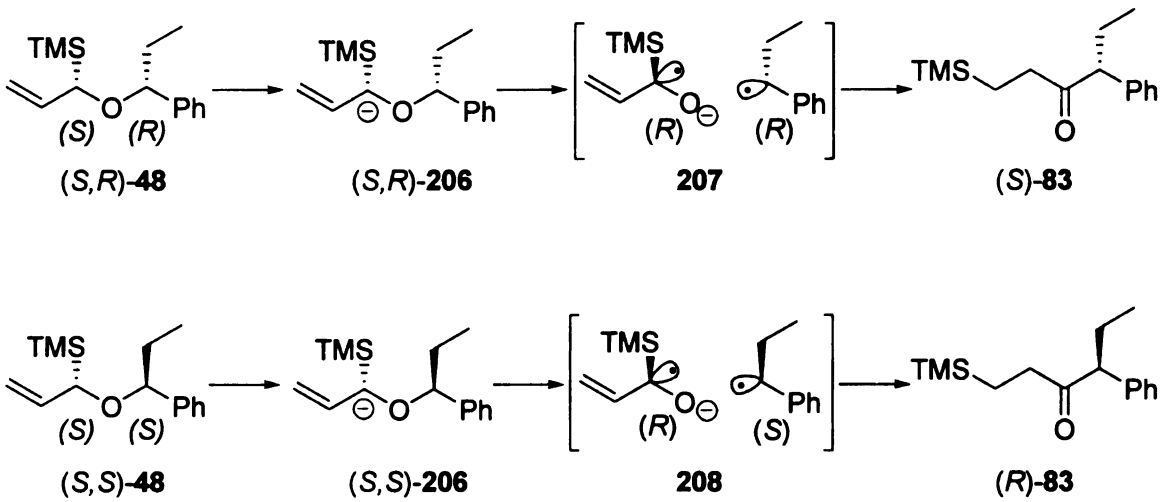
Scheme 7.7. Determination of the stereochemistry of the [1,2]-Wittig product



We subjected the less reactive (*S,S*)-**48** to the Wittig conditions and it reacted completely in about three days to give the [1,2] and [1,4] rearranged products. On analysis by chiral HPLC, we found that the [1,2]-Wittig product was obtained with a lower level of retention of stereochemistry (69% ee retention/85% er retention) than the

level obtained with the reactive diastereomer (*S,R*)-**48** (83% ee retention/~92% er retention).

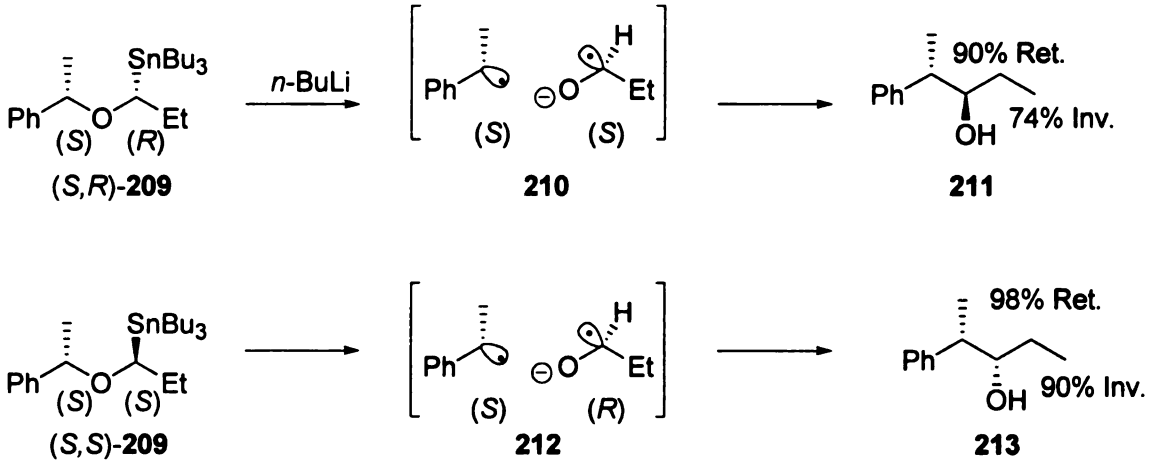
Scheme 7.8. Comparison of the [1,2]-Wittig of (*S,R*)-**48** and (*S,S*)-**48**



[1,2]-Wittig rearrangement of allyl alkyl ethers is known to occur with inversion of configuration at the metal bearing center and with retention of configuration at the migrating carbon.[7] In the Wittig rearrangement of α-alkoxysilanes investigated in this study, we observed predominant retention of configuration at the migrating carbon. Following deprotonation, there is weakening and breaking of the C—O bond. With the breaking of the C-O bond there is inversion of configuration at the α carbon (metal-bearing center) from (*S*) to (R) in both the reactive and less reactive diastereomers. It would appear that recombination between (*R*)-**207** and (*R*)-benzylic radical is more rapid in the reactive (*S,R*)-**48** than recombination between (*R*)-**208** and (*S*)-benzylic radical in less reactive (*S,S*)-**48**. This is evident in the different levels of retention of configuration observed for both cases. This observation is in contrast to the results obtained by Nakai (Scheme 7.9).[8]

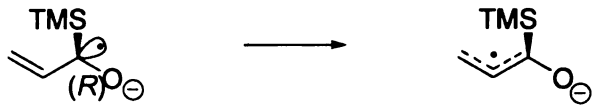
Wittig rearrangement of compound **209** was studied by Nakai and co-workers who found that the (*S,R*)-**209** afforded **211** with lower level of retention at the migrating center (90%) and lower level of inversion at the metal-bearing center (74%) than (*S,S*)-**209** that afforded 213 with 98% retention at the migrating center and 90% inversion at the metal-bearing center.[8] According to the authors, the difference in stereospecificity means that a substantial level of mutual recognition of radical enantiomers takes place during the recombination process.

Scheme 7.9. Wittig rearrangement of a pair of optically defined diastereomers by Nakai and co-workers



The lower degree on retention of configuration at the migrating carbon observed for α-alkoxysilanes relative to Nakai's results could be explained by resonance (Scheme 7.10). Resonance in the carbanion could result in partial racemization, and thus lower level of retention. The metal-bearing center in Nakai's study is resonance inactive.

Scheme 7.10. Possible racemization in the [1,2]-Wittig rearrangement of α-alkoxysilanes as a resonance of resonance

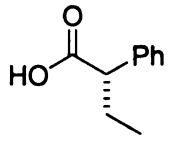


207 **207**

7.4. Conclusions

[1,2]-Wittig rearrangement of α-alkoxysilanes occurred with predominant retention of configuration at the migrating center. We obtained 83% ee/92% er retention with the reactive *syn* diastereomer and 69% ee/85% er retention with the less reactive *anti* diastereomer. The lower level of retention we obtained with the *syn* **48b** compared to literature reports[8] for allyl alkyl ethers could be accounted for by the significant difference in the structures studied. The metal-bearing center in the literature subtrates were resonance inactive in contrast to our systems that were susceptible to resonance. The significant difference in stereoselectivity observed for the *syn* **48b** and *anti* **48a** was in disagreement with Nakai's results.[8] Whereas his system showed mutual recognition of radical enantiomers during the recombination, our system gave the opposite outcome.

EXPERIMENTAL

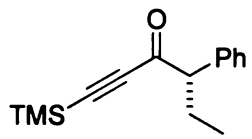


204

Preparation of 2-phenyl-butyric acid 204: A 3-necked round-bottomed flask (500 mL) equipped with a mechanical stirrer was charged with LiCl (6.0 equiv, 132.98 mmol, 5.63 g), iPr$_2$NH (2.25 equiv, 49.87 mmol, 5.04 g, 7.0 ml), and THF (27 mL, 0.8 M substrate). The resulting suspension was cooled to -78 °C, and *n*-BuLi (1.6 M in hexane, 2.08 equiv, 46.10 mmol, 30.73 mL) was added via syringe. The reaction was warmed hriefly to 0 °C and cooled back to -78 °C. An ice-cold solution of *N*-(2-hydroxy-1-methyl-2-phenyl-ethyl)-*N*-methyl-2-phenyl-acetamide (1.0 equiv, 22.16 mmol, 6.28 g) in a minimal amount of THF was added to the reaction via cannula. The reaction mixture was stirred at -78 °C for 1 h, at 0 °C for 15 min, and at room temperature for 5 min, and cooled back to 0 °C. Then EtI (1.5 equiv, 33.24 mmol, 5.18 g, 2.66 mL) was added and the reaction stirred at -78 °C for 7 h.

The crude product was taken up in 10 M H_2SO_4 (50 mL) and 1,4-dioxane (50 mL). The biphasic mixture was heated at reflux (oil bath temperature 130 °C) for 3 h and then cooled to 0 °C. The mixture was adjusted to pH $\geq$ 10 by the slow addition of 50% aqueous NaOH solution, and the resulting mixture was portioned between H_2O and CH_2Cl_2 (2 x 100 mL). The aqueous layer was acidified to pH $\leq$ 2 by the slow addition of 6 N H_2SO_4 (aq) and then extracted with CH_2Cl_2 (100 mL x 3). The combined organic extract was concentrated to about 50 mL, the concentrate washed with 1 N HCl (aq) to remove residual dioxane, dried over Na_2SO_4, and concentrated to afford crude 2-phenyl-

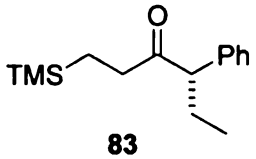
butyric acid. Purification by column chromatography on silica gel, eluting with hexanes/EtOAc (100-90%) afforded 0.92 g (5.62 mmol, 25%) of the pure acid. Note: A repeat of this reaction starting from (+)-norephedrine afford the pure acid **204** in 42% starting from (+)-norephedrine. $[a]_D^{20}$ +54.5 (c. 1.63, $CHCl_3$). IR (neat) 3400-2400, 2969, 1707, 1601, 1497, 1456, 1414, 1287, 1223 cm^{-1}. ^{1}HNMR ($CDCl_3$, 300 MHz) δ 11.54 (bs, 1H), 7.34-7.21 (m, 5H), 3.46-3.41 (t, J = 7.7 Hz, 1H), 2.16-2.01 (m, 1H), 1.87-1.72 (m, 1H), 0.91-0.86 (t, J = 7.4 Hz, 3H). ^{1}HNMR ($CDCl_3$, 75 MHz) δ 180.3, 138.2, 128.5, 128.0, 127.3, 53.3, 26.3, 12.2. $[a]_D^{20}$ +55 (c.1.63, $CHCl_3$). **204** is a known compound and has spectral data in accord with the reported one.[9]



205

Preparation of 205: A mixture of 2-phenyl-butyric acid (1.0 equiv, 3.20 mmol, 0.52 g) and $SOCl_2$ (2.0 equiv, 6.39 mmol, 0.76 g, 0.47 mL) in benzene was stirred at 80 °C for 48 h, and excess solvent removed under reduced using a rotavap. The resulting 2-phenyl-butyryl-chloride was taken up in CH_2Cl_2 and bis(trimethylsilyl)acetylene (1.12 equiv, 3.58 mmol, 0.61g, 0.81 mL) added. This mixture was cooled in ice water and anhydrous $AlCl_3$ (1.12 equiv, 3.58 mmol, 0.48 g) added in portions. After stirring for about 5.0 min, the cold bath was removed, and reaction stirred at RT for 10 h. The reaction mixture was poured into 20 ml of ice-cold water, and extracted with ether (50 mL x 4). The ethereal extract was dried over anhydrous $MgSO_4$, filtered and concentrated on a rotary evaporator to five the 0.60 of crude product. Purification by silica column chromatography on silica gel (2% EtOAc in hexanes) afforded 0.60 mg

(77%) of pure **205**. $[a]_D^{20}$ +45.0 (c. 1.092, $CHCl_3$). IR (neat) 2964, 2151, 2093, 1676, 1454, 1254 1140 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.21 (m, 5H), 3.63-3.57 (t, J = 7.7, 7.4 Hz, 1H), 3.24-2.09 (m, 1H), 1.88-1.73 (m, 1H), 0.90-0.85 (t, 7.4 Hz, 3H), 0.14 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 187.6, 137.3, 128.6, 128.5, 127.3, 101.4, 99.9, 62.5, 24.6, 12.1, -0.8. OR +45 (c. 1.0925, $CHCl_3$). HRMS (CI) *m/z* 244.1279 [$(M)^+$; calcd for $C_{15}H_{20}OSi$, 244.1283].



83

Preparation of 83: 10% Pd/C was added to a solution of 4-phenyl-1-trimethylsilanyl-hex-1-yn-3-one (1.73 mmol, 0.42 g) in EtOAc at RT. The flask was evacuated, and filled with H_2 gas at 1 atm (H_2 balloon). The flask was evacuated and this process repeated 4 times. The reaction was then stirred under H_2 atmosphere for 36 h. The reaction was filtered on Celite 503, the Celite thoroughly washed, and the combined organic phases concentrated to give the crude product. Purification by column chromatography on silica gel (hexanes/EtOAc (0-1%) afforded 0.30 g (1.35 mmol, 78%) of pure product 4-phenyl-1-trimethylsilanyl-hexan-3-one **83**. IR (neat) 2957, 1715, 1601, 1493, 1454, 1248 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.31-7.19 (m, 5H), 3.56-3.53 (t, J = 7.5, 7.1 Hz, 1H), 2.33-2.25 (m, 2H), 2.06-2.00 (m, 1H), 1.72-1.66 (m, 1H), 1.41-0.81-0.78 (t, J = 7.5, 7.1 Hz, 3H), 0.74-0.68 (m, 1H), 0.61-0.55 (m, 1H), -0.11 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.5, 139.2, 128.7, 128.2, 127.0, 60.1, 36.5, 25.5, 12.2, 10.1, -1.9.

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CHAPTER 8

CONCLUSIONS

We have demonstrated that the [1,4]-Wittig rearrangement of simple, unsubstituted α-alkoxysilanes, representated by **7**, could be efficient. The selectivity of the rearrangement was improved to favor the [1,4]- over the [1,2]-pathway. We also showed that the [1,4]-Wittig rearrangement of allyl ethers could be coupled with electrophilic capture of the resultant enolate intermediate. This procedure provides unique access to α-functionalized acylsilanes, which are synthetically versatile building blocks in organic chemistry.

The relative stereochemistries of a pair of diastereomeric α-alkoxysilanes undergoing Wittig rearrangement were established employing such techniques as 1H NMR (NOE) experiments and single crystal x-ray analysis. We determined that the reactive diastereomer has the *syn* relative stereochemistry and the less reactive has the anti relative stereochemistry. We also showed that a pair of diastereomeric α-alkoxysilanes have different chemical properties with regard to the formation of hydrazone and ester derivatives.

Efficient ring closing metathesis of α-alkoxysilanes using Grubbs second generation Ru catalyst was achieved. We made five and six-membered cyclic ethers and observed the formation of six-membered silyl ethers to be more efficient than the formation of five-membered ones. This is an important contribution to the field considering that cyclization of α-alkoxysilanes is not trivial.

In the area of mechanism of the Wittig rearrangement, we found that α deprotonation and cleavage of C–O bond in the Wittig rearrangement of α-alkoxysilanes are not concurrent but separate events. That the [1,2]-pathway could be effectively suppressed at low temperatures was evidence that the [1,4-] and the [1,2]-rearrangements of α-alkoxysilanes have different mechanisms. The [1,4]-Wittig rearrangement of stereochemically defined α-alkoxysilanes occurred with predominant retention of configuration (75% ee ret.) at the migrating carbon as required by orbital symmetry considerations. The [1,4]-Wittig rearrangement of α-alkoxysilanes bearing substituents at the migrating center and the terminal olefinic carbon formed acysilanes with approximately 3:1 anti selectivity. This result is in agreement with Nakai's results for the [2,3]-Wittig rearrangement of *E* allyl ethers. This could interpreted as implying the concertedness of the [1,4]-Wittig of α-alkoxysilanes. That [1,4]-pathway for the *syn* and the *anti* substrates acylsilanes occur with similar levels of retention of configuration (75% and 74% respectively) on one hand and [1,2]-products with significantly different levels of retention of configuration (83% and 69%) on the other hand is conclusive evidence that these two rearrangement pathways have different mechanisms. At low temperatures, the less reactive *anti* diastereomer was undergoing deprotonation as evidenced by the formation of yellow reaction mixture, however, at this temperature, no rearrangement occurred. This provided further conclusive evidence that the breaking of the C–O bond is the limiting step of this reaction.

APPENDIX 1

ORTEP REPRESENTATION AND X-RAY DATA FOR COMPOUND **108**

Table 1. Crystal data and structure refinement for p1

Identification code	p1
Empirical formula	C24 H32 N8 O8 Si2
Formula weight	616.76
Temperature	173(2) K
Wavelength	0.71073 A
Crystal system	Triclinic
Space group	P1
Unit cell dimensions	a = 6.2212(12) A b = 11.574(2) A c = 11.576(2) A alpha = 110.73(3) deg. beta = 99.03(3) deg. gamma = 95.56(3) deg.
Volume	759.3(3) A^3
Z	1
Density (calculated)	1.349 Mg/m^3
Absorption coefficient	0.176 mm^-1
F(000)	324
Crystal size	? x ? x ? mm
Theta range for data collection	1.91 to 28.26 deg.
Index ranges	-8<=h<=8, -15<=k<=11, -14<=l<=14
Reflections collected / unique	4723 / 4022 [R(int) = 0.0117]
Completeness to theta = 28.26	90.1%
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4022 / 3 / 411
Goodness-of-fit on F^2	0.779
Final R indices [I>2sigma(I)]	R1 = 0.0329, wR2 = 0.0951
R indices (all data)	R1 = 0.0436, wR2 = 0.1029
Absolute structure parameter	0.0(3)
Largest diff. peak and hole	0.235 and -0.253 e.A^-3

Table 2. Atomic coordinates (x 10^4), equivalent isotropic displacement parameters (A^2 x 10^3), and occupancies for p1

	x	y	z	U(eq)	Occ.
Si(1)	14281(2)	1821(1)	6722(1)	28(1)	1
C(2)	16559(12)	3071(7)	7870(7)	44(2)	1
C(3)	15381(10)	442(6)	5784(7)	39(2)	1
C(4)	12257(10)	1311(7)	7571(6)	38(2)	1
C(5)	12733(11)	2481(6)	5600(6)	28(1)	1
C(6)	10638(10)	2144(6)	5161(6)	28(1)	1
C(7)	9430(9)	2568(6)	4199(5)	20(1)	1
N(8)	7416(9)	2102(5)	3717(5)	29(1)	1
N(9)	6428(9)	2544(5)	2806(5)	27(1)	1
C(10)	4352(9)	2091(6)	2212(5)	23(1)	1
C(11)	3183(9)	2536(5)	1361(5)	22(1)	1
N(12)	4187(9)	3545(5)	1036(5)	27(1)	1
O(13)	6158(8)	3937(5)	1437(4)	37(1)	1
O(14)	3014(8)	4008(5)	419(4)	35(1)	1
C(15)	977(9)	2062(5)	741(5)	23(1)	1
C(16)	-74(9)	1067(6)	1019(5)	23(1)	1
N(17)	-2367(8)	580(5)	395(5)	28(1)	1
O(18)	-3264(8)	976(5)	-357(5)	46(1)	1
O(19)	-3299(7)	-256(5)	646(5)	39(1)	1
C(20)	987(10)	613(6)	1865(6)	27(1)	1
C(21)	3159(10)	1117(6)	2436(5)	26(1)	1
Si(22)	2166(2)	7036(1)	-2327(1)	26(1)	1
C(23)	4177(13)	7492(9)	-3160(8)	52(2)	1
C(24)	-149(12)	5842(8)	-3417(7)	45(2)	1
C(25)	1118(10)	8467(6)	-1372(6)	34(1)	1
C(26)	3605(10)	6389(6)	-1239(6)	28(1)	1
C(27)	5840(9)	6686(5)	-725(6)	27(1)	1
C(28)	6959(10)	6280(6)	168(6)	31(1)	1
N(29)	9044(8)	6733(5)	681(5)	26(1)	1
N(30)	9950(8)	6286(5)	1549(5)	24(1)	1
C(31)	12122(9)	6778(6)	2181(5)	22(1)	1
C(32)	13294(10)	6330(5)	3076(5)	24(1)	1
N(33)	12289(8)	5316(5)	3342(5)	26(1)	1
O(34)	13451(8)	4870(5)	3991(5)	41(1)	1
O(35)	10249(8)	4920(5)	2941(5)	41(1)	1
C(36)	15483(9)	6839(6)	3636(5)	24(1)	1
C(37)	16525(9)	7745(6)	3408(5)	24(1)	1
N(38)	18822(9)	8301(5)	4032(5)	32(1)	1
O(39)	19772(8)	9116(5)	3739(5)	38(1)	1
O(40)	19732(8)	7879(6)	4799(5)	49(2)	1
C(41)	15428(10)	8254(6)	2569(5)	25(1)	1

C(42)	13293(10)	7782(6)	1964(6)	26(1)	1

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Table 3. Bond lengths [A] and angles [deg] for p1

Si(1)-C(3)	1.848(7)
Si(1)-C(2)	1.876(7)
Si(1)-C(4)	1.885(6)
Si(1)-C(5)	1.911(6)
C(5)-C(6)	1.289(9)
C(6)-C(7)	1.498(7)
C(7)-N(8)	1.268(8)
N(8)-N(9)	1.412(6)
N(9)-C(10)	1.323(8)
C(10)-C(11)	1.404(7)
C(10)-C(21)	1.412(8)
C(11)-C(15)	1.402(7)
C(11)-N(12)	1.463(7)
N(12)-O(13)	1.220(7)
N(12)-O(14)	1.230(6)
C(15)-C(16)	1.428(7)
C(16)-C(20)	1.378(7)
C(16)-N(17)	1.451(7)
N(17)-O(18)	1.207(7)
N(17)-O(19)	1.225(7)
C(20)-C(21)	1.377(8)
Si(22)-C(23)	1.840(8)
Si(22)-C(24)	1.840(8)
Si(22)-C(26)	1.843(6)
Si(22)-C(25)	1.878(6)
C(26)-C(27)	1.382(8)
C(27)-C(28)	1.398(8)
C(28)-N(29)	1.310(8)
N(29)-N(30)	1.357(7)
N(30)-C(31)	1.390(7)
C(31)-C(42)	1.430(8)
C(31)-C(32)	1.445(7)
C(32)-C(36)	1.386(8)
C(32)-N(33)	1.427(7)
N(33)-O(34)	1.236(6)
N(33)-O(35)	1.260(7)
C(36)-C(37)	1.308(8)
C(37)-C(41)	1.425(7)

C(37)-N(38)	1.466(7)
N(38)-O(40)	1.246(7)
N(38)-O(39)	1.239(7)
C(41)-C(42)	1.360(8)
C(3)-Si(1)-C(2)	111.2(3)
C(3)-Si(1)-C(4)	109.0(3)
C(2)-Si(1)-C(4)	110.8(4)
C(3)-Si(1)-C(5)	108.7(3)
C(2)-Si(1)-C(5)	108.9(3)
C(4)-Si(1)-C(5)	108.2(3)
C(6)-C(5)-Si(1)	121.7(5)
C(5)-C(6)-C(7)	122.4(5)
N(8)-C(7)-C(6)	118.9(5)
C(7)-N(8)-N(9)	114.8(5)
C(10)-N(9)-N(8)	119.9(5)
N(9)-C(10)-C(11)	124.0(5)
N(9)-C(10)-C(21)	120.2(5)
C(11)-C(10)-C(21)	115.8(5)
C(10)-C(11)-C(15)	123.9(4)
C(10)-C(11)-N(12)	122.4(4)
C(15)-C(11)-N(12)	113.7(4)
O(13)-N(12)-O(14)	122.1(5)
O(13)-N(12)-C(11)	118.4(5)
O(14)-N(12)-C(11)	119.4(5)
C(11)-C(15)-C(16)	115.9(5)
C(20)-C(16)-C(15)	122.4(5)
C(20)-C(16)-N(17)	121.2(5)
C(15)-C(16)-N(17)	116.4(5)
O(18)-N(17)-O(19)	122.7(5)
O(18)-N(17)-C(16)	120.3(5)
O(19)-N(17)-C(16)	117.0(5)
C(16)-C(20)-C(21)	118.6(5)
C(20)-C(21)-C(10)	123.3(5)
C(23)-Si(22)-C(24)	112.2(4)
C(23)-Si(22)-C(26)	108.0(3)
C(24)-Si(22)-C(26)	108.6(3)
C(23)-Si(22)-C(25)	109.2(4)
C(24)-Si(22)-C(25)	110.3(3)
C(26)-Si(22)-C(25)	108.4(3)
C(27)-C(26)-Si(22)	124.8(4)
C(26)-C(27)-C(28)	126.3(5)
N(29)-C(28)-C(27)	120.3(6)
C(28)-N(29)-N(30)	115.2(5)
N(29)-N(30)-C(31)	118.3(5)
N(30)-C(31)-C(42)	119.8(5)
N(30)-C(31)-C(32)	123.1(5)

C(42)-C(31)-C(32)	117.1(5)
C(36)-C(32)-N(33)	118.7(4)
C(36)-C(32)-C(31)	119.8(5)
N(33)-C(32)-C(31)	121.5(5)
O(34)-N(33)-O(35)	121.8(5)
O(34)-N(33)-C(32)	118.6(5)
O(35)-N(33)-C(32)	119.6(5)
C(37)-C(36)-C(32)	121.9(5)
C(36)-C(37)-C(41)	120.7(5)
C(36)-C(37)-N(38)	121.5(5)
C(41)-C(37)-N(38)	117.7(5)
O(40)-N(38)-O(39)	123.8(6)
O(40)-N(38)-C(37)	117.0(5)
O(39)-N(38)-C(37)	119.1(5)
C(42)-C(41)-C(37)	120.6(5)
C(41)-C(42)-C(31)	119.9(5)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for p1

	U11	U22	U33	U23	U13	U12
Si(1)	27(1)	28(1)	27(1)	13(1)	1(1)	3(1)
C(2)	43(4)	31(3)	38(3)	2(3)	-19(3)	-6(3)
C(3)	29(3)	37(3)	46(4)	17(3)	2(3)	-9(2)
C(4)	32(3)	64(4)	32(3)	30(3)	17(2)	15(3)
C(5)	35(3)	28(3)	24(3)	18(2)	-3(2)	3(2)
C(6)	28(3)	35(3)	25(3)	20(2)	-2(2)	11(2)
C(7)	20(2)	25(3)	20(3)	15(2)	-1(2)	7(2)
N(8)	36(3)	34(3)	24(3)	20(2)	2(2)	9(2)
N(9)	32(2)	28(3)	28(3)	19(2)	2(2)	3(2)
C(10)	22(3)	23(3)	23(3)	6(2)	6(2)	6(2)
C(11)	23(2)	17(3)	24(3)	6(2)	7(2)	-5(2)
N(12)	31(3)	24(3)	29(3)	15(2)	3(2)	1(2)
O(13)	27(2)	41(3)	44(3)	25(2)	-3(2)	-6(2)
O(14)	34(2)	37(3)	43(3)	30(2)	1(2)	-1(2)
C(15)	24(2)	18(2)	22(3)	7(2)	1(2)	-3(2)
C(16)	25(3)	18(2)	26(3)	8(2)	8(2)	-2(2)
N(17)	23(3)	28(3)	27(3)	10(2)	-1(2)	-4(2)
O(18)	30(2)	54(3)	56(3)	36(3)	-11(2)	-11(2)
O(19)	23(2)	38(3)	56(3)	25(2)	3(2)	-4(2)
C(20)	26(3)	26(3)	31(3)	13(3)	9(2)	1(2)
C(21)	30(3)	29(3)	20(3)	11(2)	4(2)	13(2)
Si(22)	23(1)	31(1)	25(1)	13(1)	0(1)	6(1)
C(23)	48(4)	69(5)	51(4)	39(4)	0(3)	15(4)
C(24)	45(4)	44(4)	45(4)	19(3)	-2(3)	13(3)
C(25)	38(3)	28(3)	40(3)	12(3)	11(3)	19(2)
C(26)	22(2)	30(3)	34(3)	12(3)	9(2)	3(2)
C(27)	30(3)	19(3)	31(3)	10(2)	9(2)	-3(2)

C(28)	35(3)	25(3)	31(3)	7(2)	9(3)	0(2)
N(29)	19(2)	28(3)	31(3)	12(2)	2(2)	2(2)
N(30)	17(2)	27(3)	29(2)	14(2)	-1(2)	2(2)
C(31)	26(3)	24(3)	21(3)	12(2)	5(2)	4(2)
C(32)	29(3)	26(3)	24(3)	16(2)	3(2)	12(2)
N(33)	27(3)	25(3)	25(3)	12(2)	0(2)	1(2)
O(34)	38(2)	35(3)	54(3)	30(3)	-9(2)	2(2)
O(35)	28(2)	45(3)	55(3)	37(3)	-6(2)	-9(2)
C(36)	28(3)	29(3)	22(3)	15(2)	6(2)	13(2)
C(37)	21(2)	29(3)	21(3)	9(2)	0(2)	7(2)
N(38)	31(3)	29(3)	38(3)	14(2)	8(2)	7(2)
O(39)	37(3)	31(2)	43(3)	17(2)	4(2)	-10(2)
O(40)	35(3)	61(4)	55(3)	37(3)	-13(2)	1(2)
C(41)	32(3)	20(3)	27(3)	13(2)	9(2)	5(2)
C(42)	27(3)	23(3)	36(3)	20(2)	8(2)	1(2)

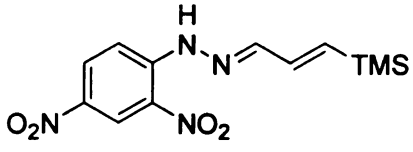
The anisotropic displacement factor exponent takes the form:

-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

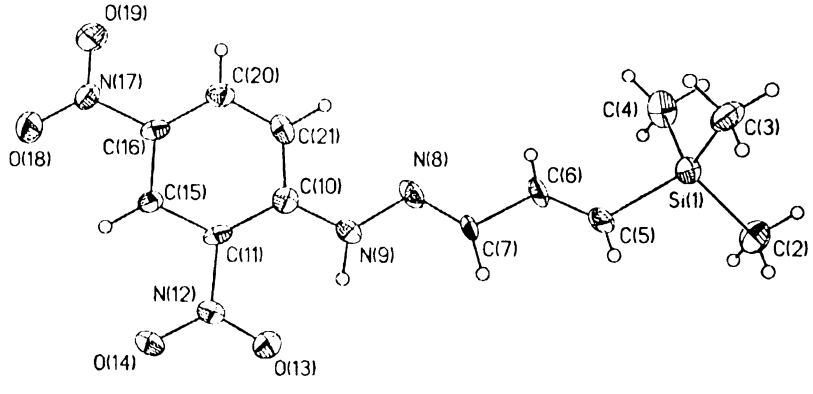
Table 5. Hydrogen coordinates (x 10^4), isotropic displacement parameters (A^2 x 10^3), and occupancies for p1

	x	y	z	U(eq)	Occ.
H(2A)	15943	3772	8349	66	1
H(2B)	17543	3336	7417	66	1
H(2C)	17358	2744	8431	66	1
H(3A)	14186	-175	5194	58	1
H(3B)	16141	93	6337	58	1
H(3C)	16388	691	5334	58	1
H(4A)	11100	677	6968	56	1
H(4B)	11635	2017	8035	56	1
H(4C)	13005	980	8144	56	1
H(5)	13630(110)	2870(70)	5420(60)	50(20)	1
H(6)	9750(80)	1710(50)	5430(40)	15(13)	1
H(7)	10550(90)	3090(60)	3990(50)	56(19)	1
H(9)	6980(150)	3160(90)	2570(80)	150(30)	1
H(15)	243	2377	183	27	1
H(20)	252	-21	2046	32	1
H(21)	3875	800	2997	31	1
H(23A)	5339	8125	-2560	78	1
H(23B)	3455	7814	-3749	78	1
H(23C)	4788	6773	-3607	78	1
H(24A)	-1180	5652	-2948	68	1
H(24B)	399	5096	-3859	68	1
H(24C)	-873	6154	-4014	68	1
H(25A)	2344	9092	-827	52	1
H(25B)	178	8249	-872	52	1
H(25C)	297	8791	-1928	52	1
H(26)	2810(80)	5690(50)	-920(40)	26(12)	1
H(27)	6790(100)	7520(60)	-860(50)	79(19)	1
H(28)	6330(60)	5640(40)	420(30)	7(8)	1
H(30)	9150(50)	5730(30)	1680(30)	0(6)	1
H(36)	16234	6526	4192	29	1
H(41)	16179	8914	2434	30	1
H(42)	12594	8113	1410	32	1

Table 6. Torsion angles [deg] for p1


H
N
N
TMS
O2N
NO2

108


O(19)
N(17)
C(20)
C(21)
O(18)
C(16)
C(15)
C(10)
N(8)
C(6)
C(4)
C(3)
Si(1)
C(11)
N(9)
C(7)
C(5)
C(2)
N(12)
O(14)
O(13)

APPENDIX 2

ORTEP REPRESENTATION AND X-RAY DATA FOR COMPOUND **110b**

Table 1. Crystal data and structure refinement for p1

Identification code	p1
Empirical formula	C21 H26 N2 O7 Si
Formula weight	446.53
Temperature	293(2) K
Wavelength	0.71073 A
Crystal system	?
Space group	?
Unit cell dimensions	a = 8.3919(17) A b = 12.006(2) A c = 12.492(3) A alpha = 112.91(3) deg. beta = 93.78(3) deg. gamma = 91.95(3) deg.
Volume	1154.3(4) A^3
Z	2
Density (calculated)	1.285 Mg/m^3
Absorption coefficient	0.145 mm^-1
F(000)	472
Crystal size	? x ? x ? mm
Theta range for data collection	1.85 to 28.28 deg.
Index ranges	-8<=h<=11, -15<=k<=15, -15<=l<=16
Reflections collected / unique	7332 / 6098 [R(int) = 0.0095]
Completeness to theta = 28.28	90.4%

Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6098 / 3 / 559
Goodness-of-fit on F^2	0.925
Final R indices [I>2sigma(I)]	R1 = 0.0326, wR2 = 0.1051
R indices (all data)	R1 = 0.0390, wR2 = 0.1119
Absolute structure parameter	0.0(2)
Largest diff. peak and hole	0.247 and -0.221 e.A^-3

Table 2. Atomic coordinates (x 10^4), equivalent isotropic displacement parameters (A^2 x 10^3), and occupancies for p1

	x	y	z	U(eq)	Occ.
C(1)	-336(6)	3490(4)	6289(5)	31(1)	1
C(2)	-82(6)	4535(4)	6081(4)	28(1)	1
C(3)	906(6)	5540(4)	6853(4)	26(1)	1
C(4)	1613(6)	5471(4)	7830(4)	26(1)	1
C(5)	1382(6)	4417(4)	8061(4)	28(1)	1
C(6)	408(6)	3467(4)	7271(4)	28(1)	1
N(7)	205(6)	2347(3)	7498(4)	34(1)	1
O(8)	-831(6)	1594(3)	6887(4)	49(1)	1
O(9)	1050(6)	2273(3)	8306(4)	46(1)	1

N(10)	-847(5)	4645(4)	5044(3)	35(1)	1
O(11)	-796(5)	5615(3)	4953(3)	37(1)	1
O(12)	-1508(6)	3692(3)	4262(4)	51(1)	1
C(13)	2608(5)	6504(4)	8711(4)	27(1)	1
O(14)	3266(5)	6528(3)	9628(3)	34(1)	1
O(15)	2676(4)	7460(3)	8385(3)	30(1)	1
C(16)	3582(6)	8571(4)	9156(4)	26(1)	1
C(17)	3615(6)	9378(4)	8465(4)	26(1)	1
C(18)	4553(6)	8843(4)	7381(4)	23(1)	1
Si(19)	4224(1)	9629(1)	6312(1)	28(1)	1
C(20)	2025(7)	9450(6)	5805(5)	43(1)	1
C(21)	4837(8)	11267(5)	7061(5)	48(1)	1
C(22)	5453(8)	8916(5)	5040(4)	40(1)	1
O(23)	6232(4)	8973(3)	7796(3)	28(1)	1
C(24)	7189(6)	7987(4)	7086(5)	34(1)	1
C(25)	8921(7)	8514(5)	7439(7)	52(2)	1
C(26)	6819(6)	6847(3)	7290(4)	27(1)	1
C(27)	6000(7)	5853(4)	6369(5)	36(1)	1
C(28)	5633(8)	4797(5)	6517(6)	52(2)	1
C(29)	6050(8)	4686(5)	7566(7)	47(1)	1
C(30)	6849(7)	5712(5)	8513(5)	42(1)	1
C(31)	7222(7)	6739(5)	8315(5)	38(1)	1
C(32)	1832(6)	6640(4)	2757(5)	31(1)	1

C(33)	1045(6)	6676(4)	1739(4)	30(1)	1
C(34)	79(6)	5706(4)	935(4)	28(1)	1
C(35)	-146(6)	4666(4)	1148(4)	25(1)	1
C(36)	603(6)	4624(4)	2188(4)	29(1)	1
C(37)	1544(6)	5576(4)	2926(4)	29(1)	1
N(38)	1304(6)	7789(4)	1518(4)	37(1)	1
O(39)	440(5)	7892(3)	738(4)	43(1)	1
O(40)	2315(5)	8577(3)	2150(4)	48(1)	1
N(41)	2337(5)	5534(3)	4016(4)	34(1)	1
O(42)	3005(6)	6431(4)	4723(4)	56(1)	1
O(43)	2264(5)	4528(3)	4088(3)	40(1)	1
C(44)	-1177(5)	3591(3)	282(4)	25(1)	1
O(45)	-1799(5)	3599(3)	-595(3)	34(1)	1
O(46)	-1224(4)	2706(3)	642(3)	30(1)	1
C(47)	-2171(6)	1591(4)	-106(4)	31(1)	1
C(48)	-2179(6)	795(4)	576(4)	27(1)	1
C(49)	-3083(6)	1299(4)	1672(4)	26(1)	1
Si(50)	-2756(1)	525(1)	2713(1)	28(1)	1
C(51)	-621(7)	699(5)	3243(5)	41(1)	1
C(52)	-3863(7)	1280(5)	4042(4)	36(1)	1
C(53)	-3408(7)	-1126(4)	1954(5)	36(1)	1
O(54)	-4768(4)	1187(3)	1243(3)	29(1)	1
C(55)	-5689(6)	2123(4)	1910(4)	30(1)	1

C(56)	-7424(7)	1654(5)	1556(7)	49(2)	1
C(57)	-5311(6)	3309(4)	1768(4)	30(1)	1
C(58)	-5731(7)	3388(5)	677(5)	34(1)	1
C(59)	-5346(7)	4495(5)	583(6)	47(1)	1
C(60)	-4591(8)	5416(6)	1420(7)	51(2)	1
C(61)	-4139(7)	5372(4)	2482(6)	43(1)	1
C(62)	-4514(7)	4290(5)	2639(5)	37(1)	1

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Table 3. Bond lengths [A] and angles [deg] for p1

C(1)-C(6)	1.350(8)
C(1)-C(2)	1.390(7)
C(2)-C(3)	1.412(6)
C(2)-N(10)	1.462(7)
C(3)-C(4)	1.355(7)
C(4)-C(5)	1.413(6)
C(4)-C(13)	1.480(6)
C(5)-C(6)	1.378(7)
C(6)-N(7)	1.485(6)
N(7)-O(9)	1.229(7)
N(7)-O(8)	1.215(6)
N(10)-O(11)	1.213(6)
N(10)-O(12)	1.260(5)
C(13)-O(14)	1.227(6)
C(13)-O(15)	1.361(5)
O(15)-C(16)	1.456(5)
C(16)-C(17)	1.529(6)
C(17)-C(18)	1.538(6)
C(18)-O(23)	1.451(6)
C(18)-Si(19)	1.924(4)
Si(19)-C(21)	1.855(6)
Si(19)-C(20)	1.888(6)
Si(19)-C(22)	1.881(5)
O(23)-C(24)	1.474(5)
C(24)-C(26)	1.512(7)
C(24)-C(25)	1.530(8)
C(26)-C(31)	1.359(7)
C(26)-C(27)	1.412(6)
C(27)-C(28)	1.378(8)
C(28)-C(29)	1.392(10)
C(29)-C(30)	1.439(8)
C(30)-C(31)	1.379(7)
C(32)-C(37)	1.390(7)
C(32)-C(33)	1.410(8)
C(33)-C(34)	1.393(7)
C(33)-N(38)	1.477(6)
C(34)-C(35)	1.384(6)
C(35)-C(36)	1.426(7)
C(35)-C(44)	1.516(6)
C(36)-C(37)	1.342(7)
C(37)-N(41)	1.495(6)
N(38)-O(40)	1.230(6)
N(38)-O(39)	1.225(7)

N(41)-O(42)	1.186(6)
N(41)-O(43)	1.245(5)
C(44)-O(45)	1.186(6)
C(44)-O(46)	1.304(6)
O(46)-C(47)	1.467(5)
C(47)-C(48)	1.507(7)
C(48)-C(49)	1.529(7)
C(49)-O(54)	1.462(6)
C(49)-Si(50)	1.883(5)
Si(50)-C(51)	1.845(6)
Si(50)-C(53)	1.877(4)
Si(50)-C(52)	1.878(5)
O(54)-C(55)	1.404(6)
C(55)-C(56)	1.516(8)
C(55)-C(57)	1.527(6)
C(57)-C(62)	1.368(7)
C(57)-C(58)	1.425(7)
C(58)-C(59)	1.408(7)
C(59)-C(60)	1.297(9)
C(60)-C(61)	1.377(10)
C(61)-C(62)	1.416(7)
C(6)-C(1)-C(2)	117.1(4)
C(1)-C(2)-C(3)	122.3(5)
C(1)-C(2)-N(10)	120.9(4)
C(3)-C(2)-N(10)	116.8(4)
C(4)-C(3)-C(2)	118.1(4)
C(3)-C(4)-C(5)	120.9(4)
C(3)-C(4)-C(13)	121.5(4)
C(5)-C(4)-C(13)	117.6(4)
C(6)-C(5)-C(4)	118.2(5)
C(1)-C(6)-C(5)	123.4(4)
C(1)-C(6)-N(7)	118.4(4)
C(5)-C(6)-N(7)	118.1(5)
O(9)-N(7)-O(8)	125.4(4)
O(9)-N(7)-C(6)	117.9(4)
O(8)-N(7)-C(6)	116.7(5)
O(11)-N(10)-O(12)	123.0(4)
O(11)-N(10)-C(2)	120.1(4)
O(12)-N(10)-C(2)	116.9(4)
O(14)-C(13)-O(15)	123.4(4)
O(14)-C(13)-C(4)	125.9(4)
O(15)-C(13)-C(4)	110.7(4)
C(13)-O(15)-C(16)	118.6(3)
O(15)-C(16)-C(17)	105.1(3)
C(16)-C(17)-C(18)	112.1(4)
O(23)-C(18)-C(17)	106.8(4)

O(23)-C(18)-Si(19)	110.0(3)
C(17)-C(18)-Si(19)	113.1(3)
C(21)-Si(19)-C(20)	109.0(3)
C(21)-Si(19)-C(22)	109.7(3)
C(20)-Si(19)-C(22)	110.7(3)
C(21)-Si(19)-C(18)	109.8(2)
C(20)-Si(19)-C(18)	108.6(2)
C(22)-Si(19)-C(18)	109.2(2)
C(18)-O(23)-C(24)	114.5(3)
O(23)-C(24)-C(26)	110.5(4)
O(23)-C(24)-C(25)	104.1(4)
C(26)-C(24)-C(25)	114.9(4)
C(31)-C(26)-C(27)	118.6(5)
C(31)-C(26)-C(24)	123.3(4)
C(27)-C(26)-C(24)	118.0(5)
C(28)-C(27)-C(26)	120.0(5)
C(29)-C(28)-C(27)	121.3(5)
C(28)-C(29)-C(30)	118.5(5)
C(31)-C(30)-C(29)	118.0(5)
C(26)-C(31)-C(30)	123.4(5)
C(37)-C(32)-C(33)	115.4(4)
C(34)-C(33)-C(32)	122.9(4)
C(34)-C(33)-N(38)	119.4(5)
C(32)-C(33)-N(38)	117.7(5)
C(35)-C(34)-C(33)	118.9(5)
C(34)-C(35)-C(36)	119.1(4)
C(34)-C(35)-C(44)	120.1(4)
C(36)-C(35)-C(44)	120.8(4)
C(37)-C(36)-C(35)	119.7(4)
C(36)-C(37)-C(32)	124.1(5)
C(36)-C(37)-N(41)	119.9(4)
C(32)-C(37)-N(41)	116.1(4)
O(40)-N(38)-O(39)	123.6(4)
O(40)-N(38)-C(33)	119.0(5)
O(39)-N(38)-C(33)	117.3(5)
O(42)-N(41)-O(43)	125.3(4)
O(42)-N(41)-C(37)	118.8(4)
O(43)-N(41)-C(37)	115.9(4)
O(45)-C(44)-O(46)	127.6(4)
O(45)-C(44)-C(35)	122.1(4)
O(46)-C(44)-C(35)	110.4(4)
C(44)-O(46)-C(47)	117.1(3)
O(46)-C(47)-C(48)	105.8(4)
C(47)-C(48)-C(49)	113.5(4)
O(54)-C(49)-C(48)	105.1(4)
O(54)-C(49)-Si(50)	111.2(3)

C(48)-C(49)-Si(50)	114.8(3)
C(51)-Si(50)-C(53)	109.8(3)
C(51)-Si(50)-C(52)	105.9(3)
C(53)-Si(50)-C(52)	111.5(2)
C(51)-Si(50)-C(49)	109.9(2)
C(53)-Si(50)-C(49)	109.6(2)
C(52)-Si(50)-C(49)	110.1(2)
C(55)-O(54)-C(49)	115.2(4)
O(54)-C(55)-C(56)	106.3(4)
O(54)-C(55)-C(57)	112.5(4)
C(56)-C(55)-C(57)	113.2(4)
C(62)-C(57)-C(58)	118.3(5)
C(62)-C(57)-C(55)	122.2(5)
C(58)-C(57)-C(55)	119.4(4)
C(59)-C(58)-C(57)	117.4(5)
C(60)-C(59)-C(58)	123.3(6)
C(59)-C(60)-C(61)	121.2(5)
C(60)-C(61)-C(62)	118.2(5)
C(57)-C(62)-C(61)	121.5(5)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for p1

	U11	U22	U33	U23	U13	U12
C(1)	32(2)	21(2)	36(3)	7(2)	6(2)	-6(2)
C(2)	26(2)	26(2)	28(2)	5(2)	0(2)	-1(2)
C(3)	27(2)	21(2)	26(2)	5(2)	0(2)	-1(2)
C(4)	27(2)	20(2)	31(2)	10(2)	8(2)	-1(2)
C(5)	32(2)	27(2)	27(2)	12(2)	7(2)	6(2)
C(6)	30(2)	21(2)	37(3)	13(2)	11(2)	0(2)
N(7)	35(2)	25(2)	44(2)	15(2)	10(2)	-3(2)
O(8)	60(3)	30(2)	55(3)	16(2)	5(2)	-12(2)
O(9)	48(2)	39(2)	64(3)	35(2)	6(2)	5(2)
N(10)	34(2)	38(2)	24(2)	2(2)	-2(2)	-3(2)
O(11)	45(2)	31(2)	35(2)	13(2)	2(2)	5(2)
O(12)	63(3)	39(2)	42(2)	11(2)	-18(2)	-10(2)
C(13)	28(2)	31(2)	33(2)	23(2)	7(2)	8(2)
O(14)	42(2)	34(2)	28(2)	16(1)	-4(2)	0(2)
O(15)	40(2)	26(2)	27(2)	15(1)	-6(2)	-11(1)
C(16)	30(2)	21(2)	26(2)	10(2)	-4(2)	-6(2)
C(17)	32(2)	23(2)	22(2)	9(2)	7(2)	1(2)
C(18)	27(2)	19(2)	24(2)	10(2)	2(2)	-2(2)
Si(19)	35(1)	25(1)	28(1)	14(1)	3(1)	0(1)
C(20)	36(3)	58(3)	38(3)	25(2)	-5(2)	2(2)
C(21)	56(4)	49(3)	47(3)	27(2)	6(3)	5(2)
C(22)	59(3)	36(2)	33(2)	21(2)	10(2)	10(2)
O(23)	25(2)	23(1)	34(2)	8(1)	4(1)	4(1)
C(24)	36(3)	30(2)	37(3)	12(2)	14(2)	16(2)
C(25)	29(3)	44(3)	88(5)	29(3)	17(3)	3(2)
C(26)	27(2)	18(2)	32(2)	4(2)	1(2)	1(2)
C(27)	37(3)	27(2)	33(2)	1(2)	-4(2)	4(2)
C(28)	48(3)	28(2)	60(4)	-4(2)	0(3)	2(2)
C(29)	44(3)	23(2)	78(4)	21(2)	13(3)	4(2)
C(30)	36(3)	51(3)	47(3)	26(2)	3(2)	2(2)
C(31)	35(3)	34(2)	42(3)	13(2)	2(2)	4(2)
C(32)	30(2)	30(2)	31(2)	8(2)	2(2)	4(2)
C(33)	28(2)	27(2)	37(3)	14(2)	4(2)	4(2)
C(34)	25(2)	30(2)	34(2)	17(2)	4(2)	0(2)
C(35)	23(2)	30(2)	25(2)	12(2)	1(2)	2(2)
C(36)	31(2)	31(2)	31(2)	18(2)	7(2)	4(2)
C(37)	31(2)	32(2)	28(2)	15(2)	4(2)	4(2)
N(38)	39(2)	29(2)	48(3)	18(2)	11(2)	9(2)

O(39)	44(2)	40(2)	53(2)	26(2)	5(2)	7(2)
O(40)	46(2)	31(2)	65(3)	19(2)	1(2)	-7(2)
N(41)	35(2)	32(2)	37(2)	18(2)	-2(2)	3(2)
O(42)	72(3)	47(2)	39(2)	12(2)	-22(2)	-19(2)
O(43)	41(2)	44(2)	39(2)	23(2)	-4(2)	3(2)
C(44)	26(2)	20(2)	22(2)	0(1)	2(2)	-5(1)
O(45)	39(2)	32(2)	34(2)	15(2)	-4(2)	-1(1)
O(46)	36(2)	28(2)	28(2)	14(1)	-3(1)	-6(1)
C(47)	35(2)	32(2)	21(2)	7(2)	3(2)	-7(2)
C(48)	26(2)	23(2)	32(2)	10(2)	-1(2)	-1(2)
C(49)	24(2)	24(2)	30(2)	9(2)	1(2)	0(2)
Si(50)	33(1)	25(1)	29(1)	14(1)	4(1)	2(1)
C(51)	44(3)	37(2)	42(3)	16(2)	3(2)	8(2)
C(52)	39(2)	39(2)	32(2)	15(2)	11(2)	-5(2)
C(53)	50(3)	16(2)	40(3)	11(2)	5(2)	-7(2)
O(54)	28(2)	25(1)	33(2)	9(1)	1(1)	1(1)
C(55)	36(3)	24(2)	35(2)	15(2)	6(2)	0(2)
C(56)	39(3)	30(2)	85(4)	26(3)	25(3)	10(2)
C(57)	28(2)	33(2)	35(2)	19(2)	7(2)	11(2)
C(58)	36(3)	36(2)	34(2)	19(2)	-4(2)	3(2)
C(59)	49(3)	47(3)	66(4)	43(3)	11(3)	21(2)
C(60)	42(3)	45(3)	83(4)	41(3)	20(3)	13(2)
C(61)	35(3)	27(2)	64(3)	14(2)	10(2)	-2(2)
C(62)	35(3)	39(2)	38(3)	17(2)	5(2)	7(2)

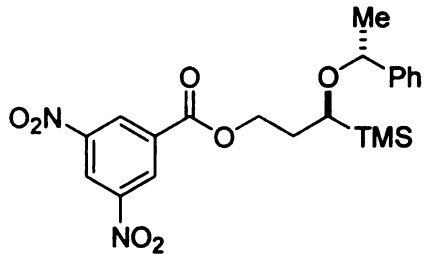
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

Table 5. Hydrogen coordinates (x 10^4), isotropic displacement parameters (A^2 x 10^3), and occupancies for p1

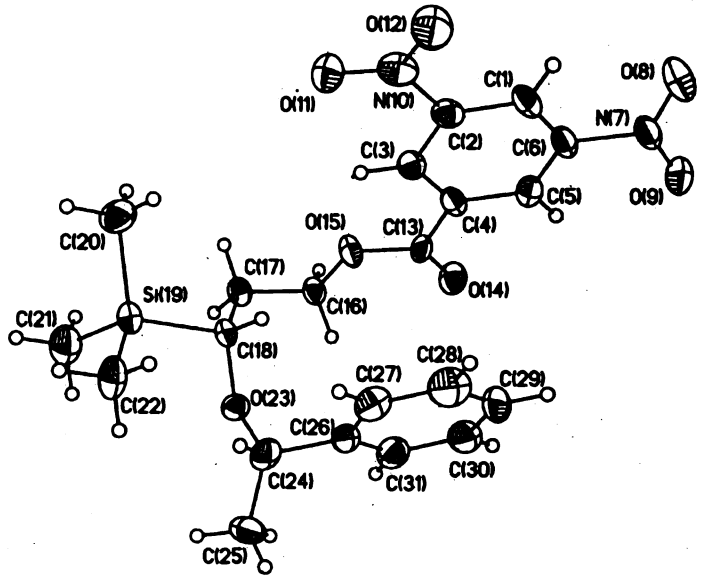
	x	y	z	U(eq)	Occ.
H(1)	-991	2834	5773	37	1
H(3)	1066	6230	6695	31	1
H(5)	1875	4366	8728	33	1
H(16A)	4659	8403	9355	31	1
H(16B)	3064	8957	9869	31	1
H(17A)	4101	10171	8965	31	1
H(17B)	2526	9480	8223	31	1
H(18)	4228	7979	6974	27	1
H(20A)	1694	8604	5429	64	1
H(20B)	1845	9832	5264	64	1
H(20C)	1419	9824	6464	64	1
H(21A)	5950	11365	7334	72	1
H(21B)	4210	11627	7711	72	1
H(21C)	4668	11656	6525	72	1
H(22A)	6566	9018	5313	60	1
H(22B)	5283	9300	4499	60	1
H(22C)	5138	8068	4657	60	1
H(24)	6930	7821	6259	41	1
H(25A)	9050	9235	7287	78	1
H(25B)	9629	7930	6996	78	1
H(25C)	9170	8709	8255	78	1
H(27)	5707	5910	5662	43	1
H(28)	5097	4146	5903	62	1
H(29)	5817	3965	7654	57	1
H(30)	7106	5684	9237	51	1
H(31)	7779	7392	8914	45	1
H(32)	2498	7284	3279	38	1
H(34)	-407	5757	266	34	1
H(36)	441	3940	2355	34	1
H(47A)	-1690	1195	-834	37	1
H(47B)	-3253	1769	-280	37	1
H(48A)	-1082	695	802	33	1
H(48B)	-2663	1	76	33	1
H(49)	-2755	2162	2086	32	1
H(51A)	-298	1544	3640	61	1
H(51B)	7	342	2594	61	1
H(51C)	-463	301	3772	61	1

H(52A)	-3494	2119	4416	55	1
H(52B)	-3672	889	4574	55	1
H(52C)	-4989	1218	3815	55	1
H(53A)	-2814	-1487	1286	54	1
H(53B)	-4530	-1212	1708	54	1
H(53C)	-3215	-1523	2480	54	1
H(55)	-5455	2265	2733	36	1
H(56A)	-7595	919	1679	74	1
H(56B)	-7672	1495	747	74	1
H(56C)	-8104	2250	2020	74	1
H(58)	-6241	2734	52	41	1
H(59)	-5648	4570	-115	56	1
H(60)	-4350	6118	1300	61	1
H(61)	-3601	6036	3081	52	1
H(62)	-4213	4245	3351	44	1

Table 6. Torsion angles [deg] for p1


Me
O
O
Ph
O_2N
O
TMS
NO_2

110b


O(12)
O(11)
N(10)
C(1)
O(8)
N(7)
C(2)
C(6)
C(3)
C(5)
O(9)
C(4)
O(15)
C(13)
C(20)
C(17)
O(14)
Si(19)
C(16)
C(21)
C(18)
C(28)
C(27)
C(29)
C(22)
O(23)
C(26)
C(31)
C(30)
C(24)
C(25)