Recent Advances in Organosilicon Chemistry

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Contents

Silicon – Fundamental Properties

Silicon

Position in Periodic Table: **Period 3, Group 14 (old group IV)**

Electronegativity: **1.90 (Pauling scale)**

more electropositive than carbon (2.55) and hydrogen (2.2)

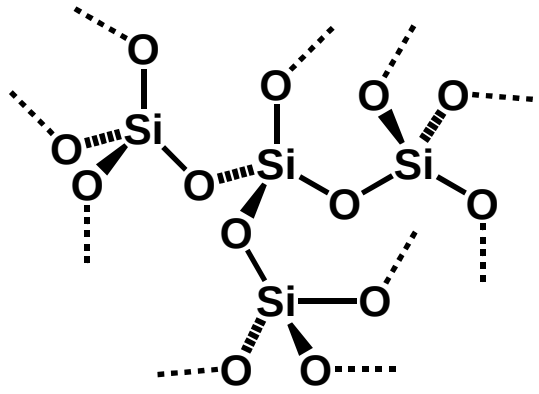
metallic in character

C–Si and H–Si bonds are polarised:

Silicon

Electron Configuration: **$1s^2$, $2s^2$, $2p^6$, $3s^2$, $3p^2$**

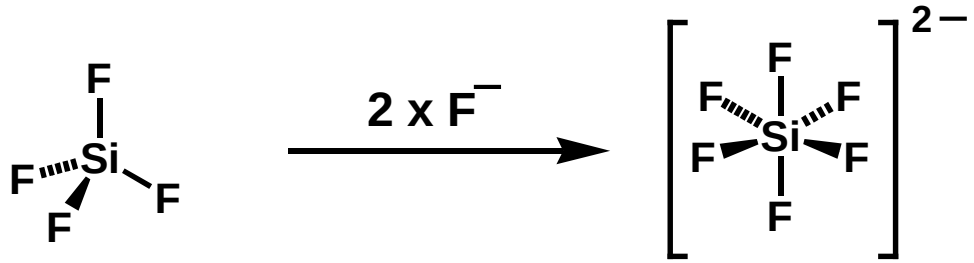
Four electrons in the valence shell and, like carbon, can form four covalent bonds (after hybridisation):



Silicon

The availability of relatively low energy empty 3d AOs allows Si to attain higher coordination numbers (hypervalent silicon compounds).

Electronegative substituents lower the energy of the 3d AOs, which facilitates the formation of hypervalent silicon compounds.



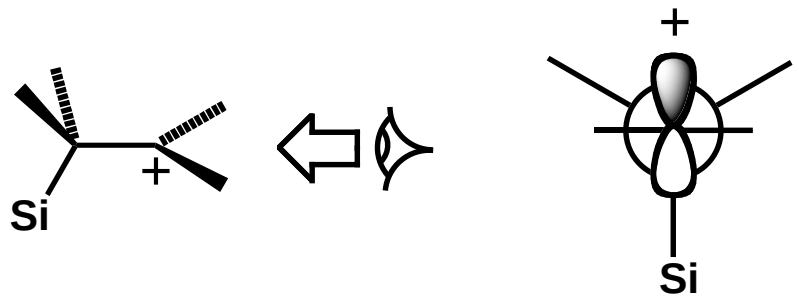
hexafluorosilicate dianion

We will see later how the ability of Si to expand its valence state has ramifications on the mechanisms of many reactions proceeding at Si.

Stabilisation of β-Positive Charge

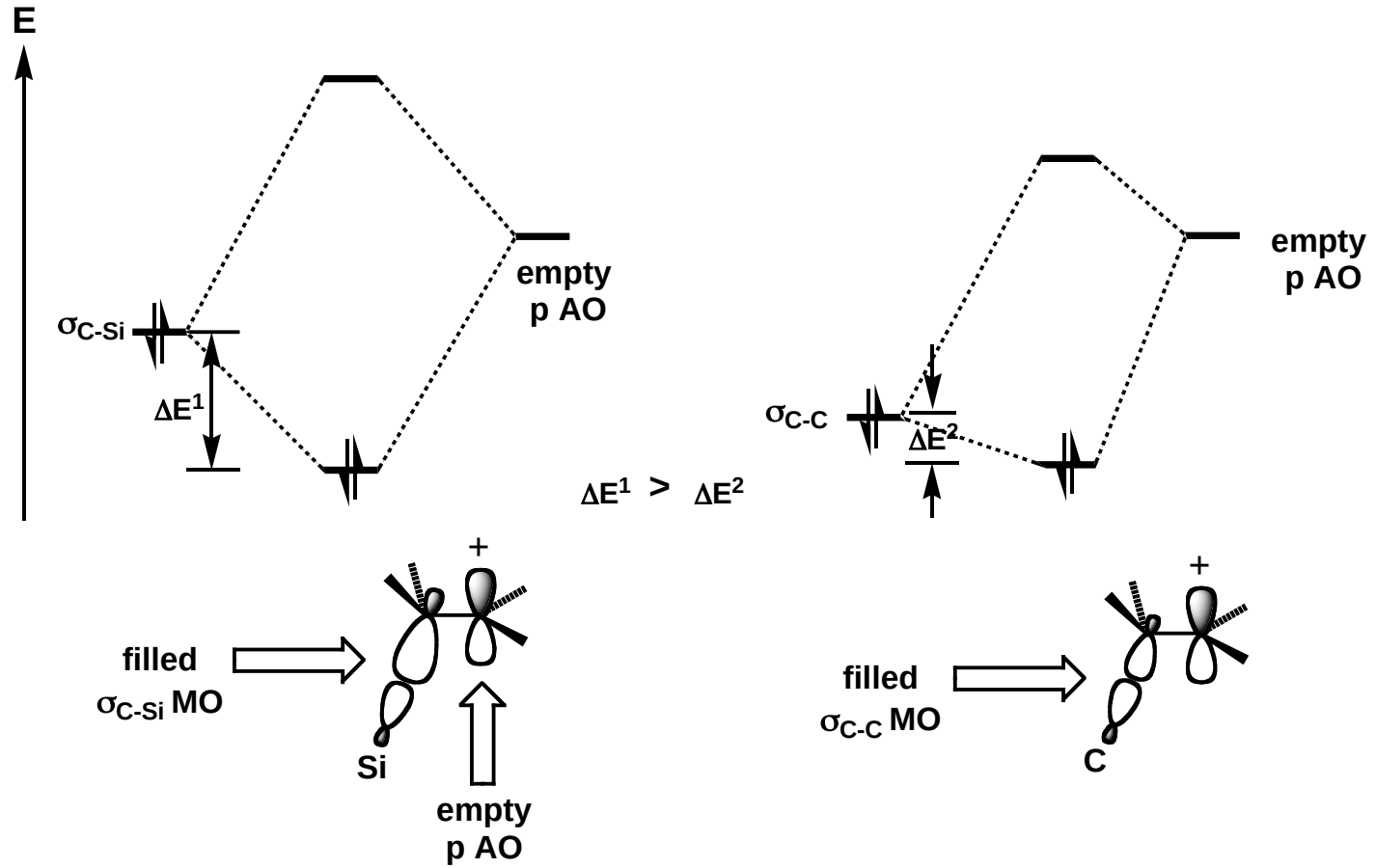
Silicon is better at stabilising β-positive charge than is carbon.

This stabilisation effect is stereoelectronic in origin and often known as the β-Si-effect.[1]



Maximum stabilisation requires the σ_{C-Si} MO to align with the empty p AO on the adjacent carbocationic centre.

β-Silicon Effect



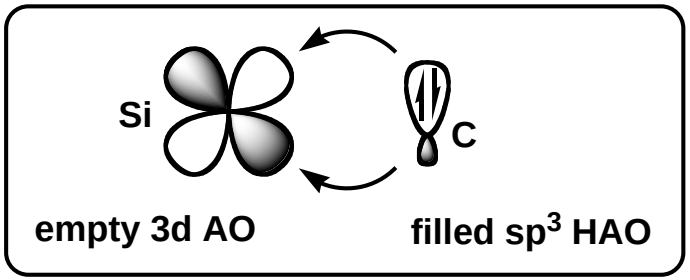
The higher energy $\sigma_{C\text{-}Si}$ MO and the larger coefficient on the carbon in this MO (as a result of the more electropositive Si) lead to more effective orbital overlap and increased stabilisation.

Stabilisation of α-Negative Charge

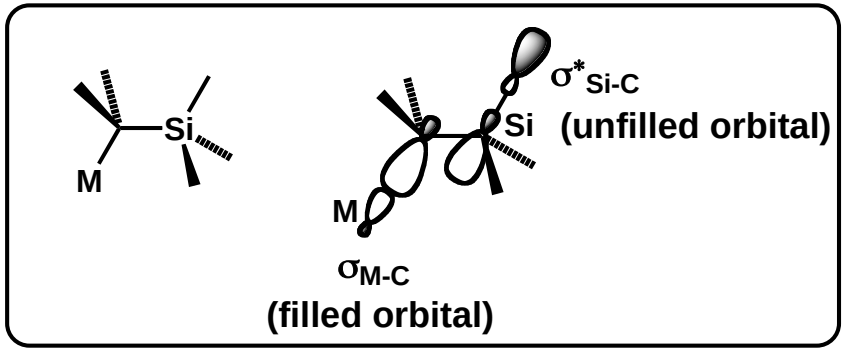
Carbanions with an α-silicon group are more stable than their carbon analogues:

Si exerts a weak +*I* inductive effect through the σ-framework – but this should destabilise α-negative charge. This effect is over-ridden by a number of factors:

1. Empty 3d AOs allow pπ-dπ bonding.

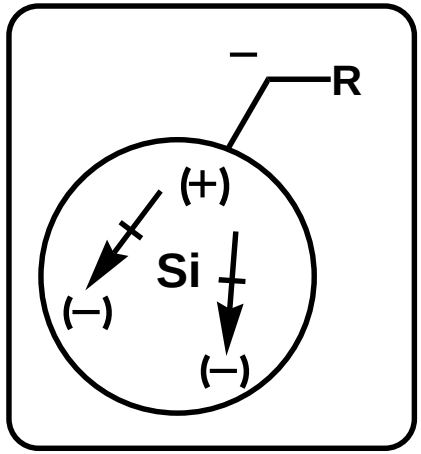


2. Overlap between the filled σ orbital of the metal-carbon bond and the unfilled σ^*_{C-Si} orbital is energetically favourable. The larger coefficient on the silicon atom in the σ* MO further improves the orbital overlap.



Stabilisation of α-Negative Charge

3. Si is a relatively large atom (van der Waals radius ~2.1 Å) and therefore readily polarised. *Induced dipoles* will also stabilise proximal negative charge.



This effect is probably the most important mechanism for stabilising α-negative charge.

Bond Strengths and Bond Lengths

bond	bond strength (kJ $mol^{-1)}$	bond length (Å)
Si–H	318 (in Me_3SiH)	1.48
Si–C	318 (in Me_4Si)	1.85
Si–O	452 (in Me_3SiOMe)	1.66
Si–F	565 (in Me_3SiF)	1.57

Key points:

1) Bonds to Si are approximately 25% longer than the same bonds to C;
2) Si–O and Si–F bonds are much stronger than Si–C and Si–H bonds.

Why Silicon?

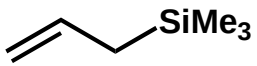
Attractive Features of Organosilicon Chemistry

Organosilanes display many attractive properties:

- **compared with other organometallic reagents they are much more moisture- and air-stable**
- **readily prepared from a wide range of often cheap starting materials**
- **low toxicity**
- **rich and diverse chemistry that can usually be rationalised by understanding a relatively small number of fundamental properties of Silicon**

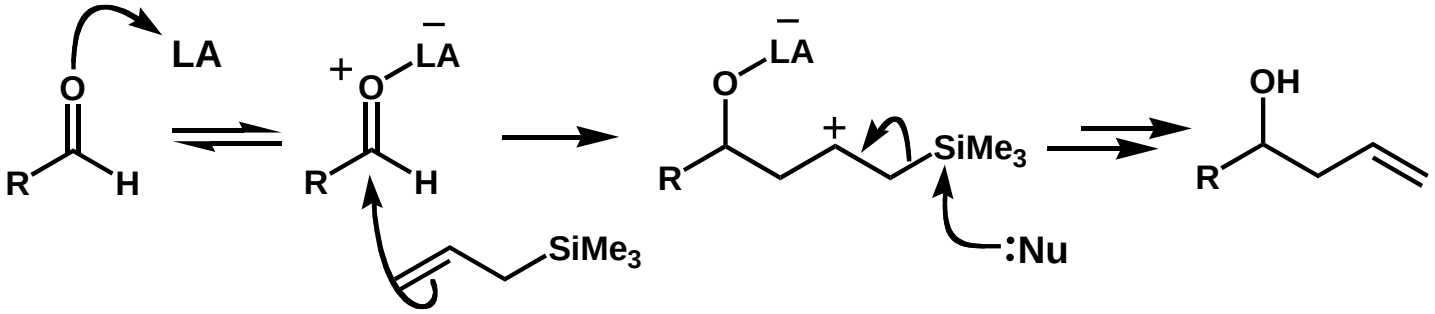
Allylsilanes and Related Nucleophiles

Allyltrialkylsilanes

allyltrimethylsilane 

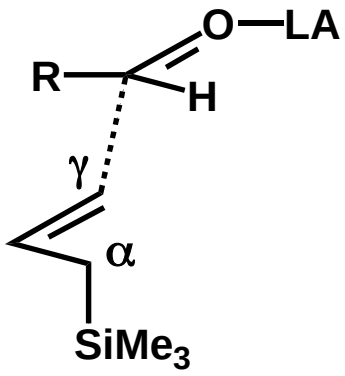
cheap and commercially available

not a strong nucleophile;[1] thus reaction with aldehydes generally requires an external Lewis acid.[2,3]

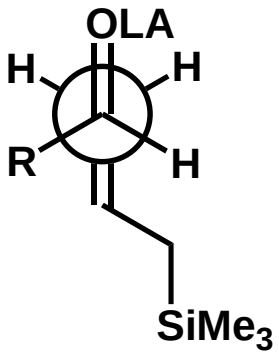


Mechanism

Reaction proceeds through an *anti* S_E2' reaction pathway.[4,5]

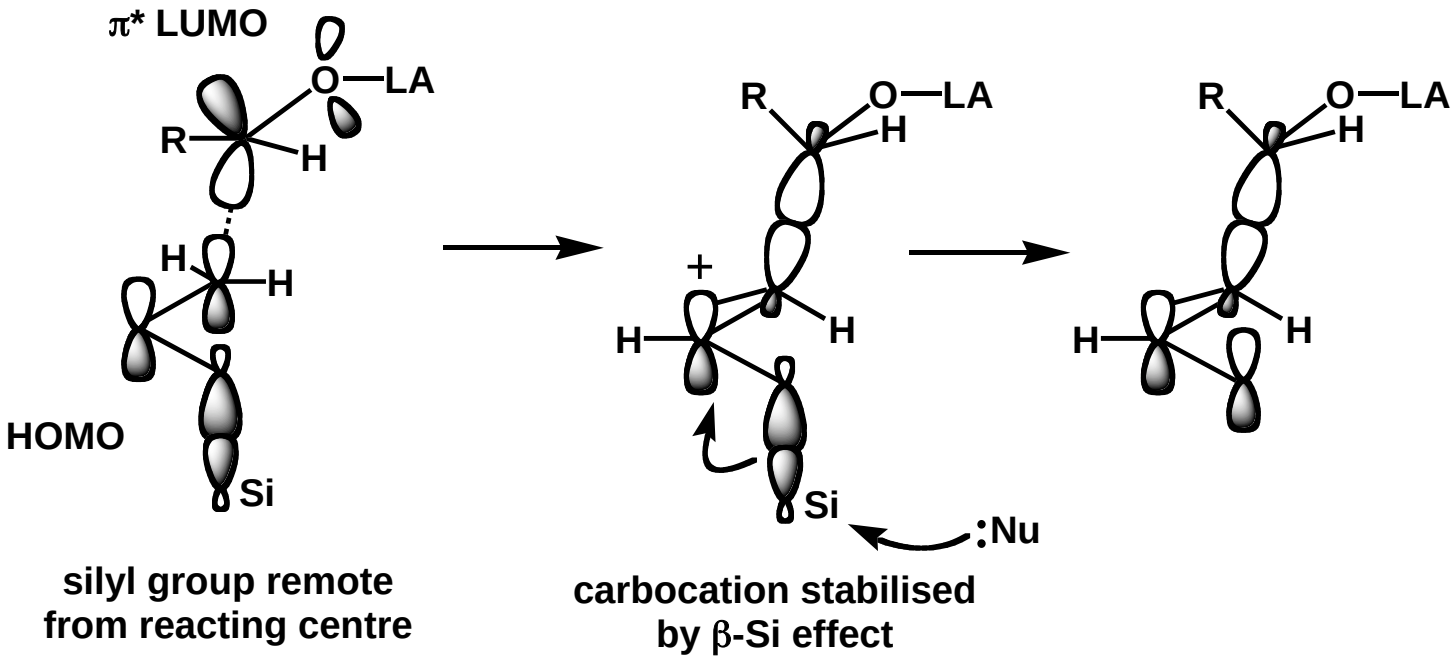


reaction proceeds through the γ-carbon



open T.S. (range of staggered reactive conformations need to be considered)

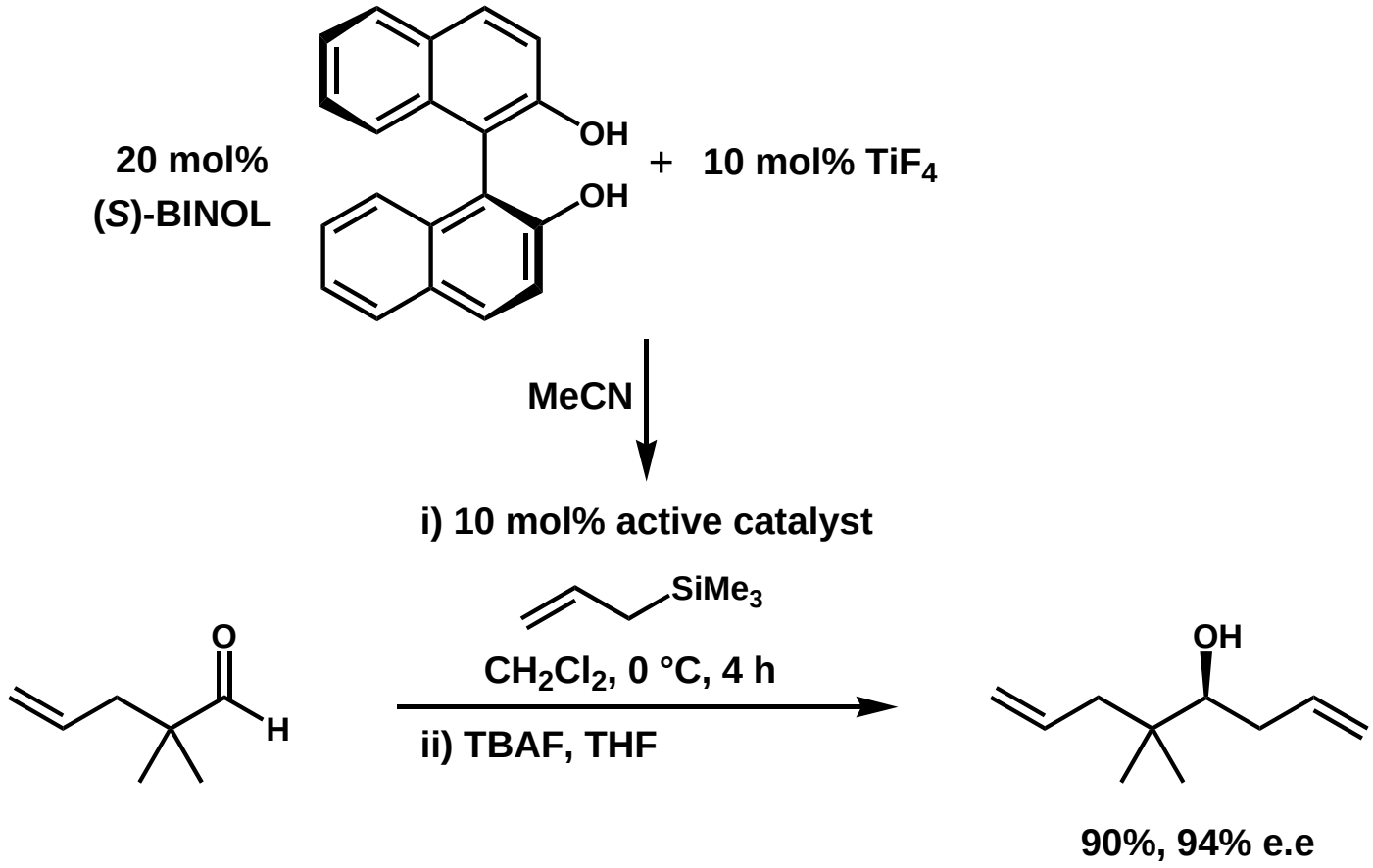
Mechanism


π* LUMO
O—LA
R
H
H
H
HOMO
Si
silyl group remote
from reacting centre
R
O—LA
H
+
H
H
Si
:Nu
carbocation stabilised
by β-Si effect
R
O—LA
H
H
H

Enantioselective Allylation

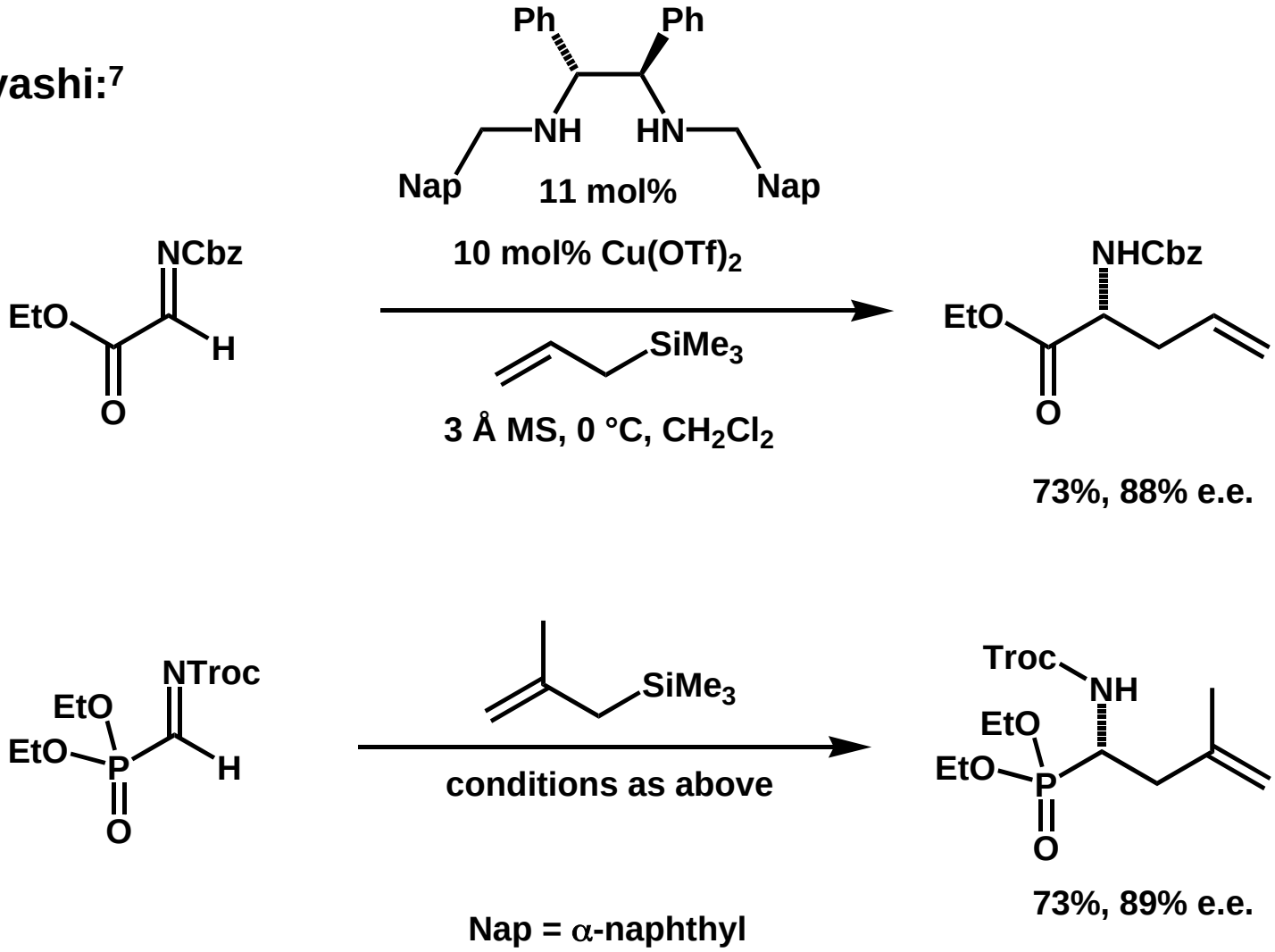
Enantioselective Allylation of Aldehydes

Use a *chiral Lewis acid* to differentiate the enantiotopic faces of the electrophile:[6]



Enantioselective Allylation of Imines

Kobayashi:[7]



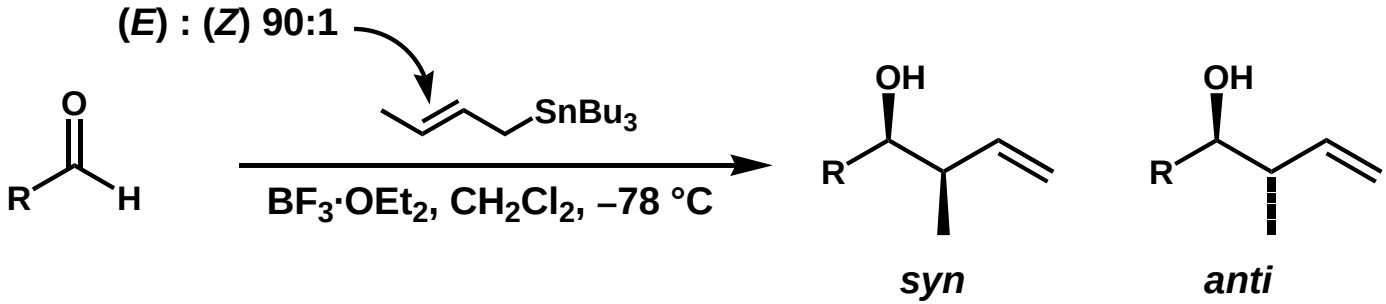
Nap = α-naphthyl

Stereoselective Crotylation

Type II allylating agents[8] have traditionally not been used widely to effect the stereoselective crotylation of aldehydes: reactions with crotylsilanes are particularly rare.[9]

The analogous reaction with crotylstannanes is usually *syn*-selective.[10,11]

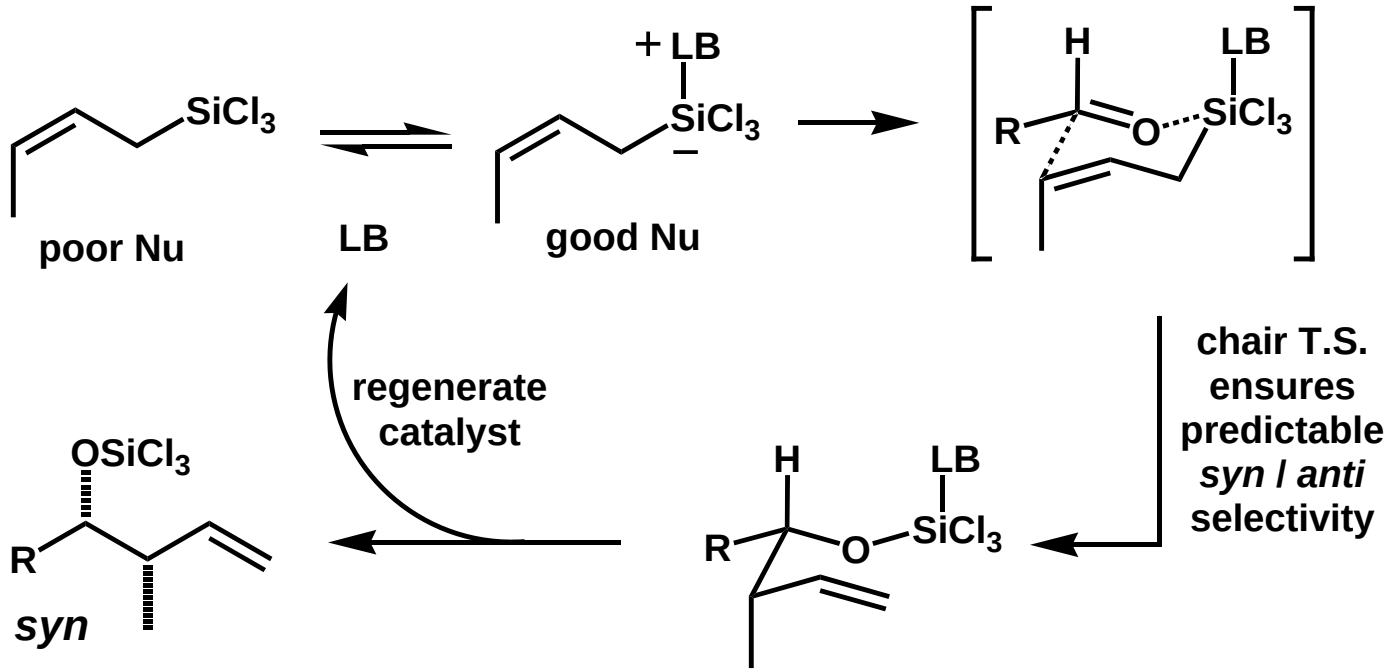
Effective enantioselective variants have not been developed.[9]



R = Ph, *syn:anti* 98:2 (85%)
R = Cy, *syn:anti* 94:6 (88%)

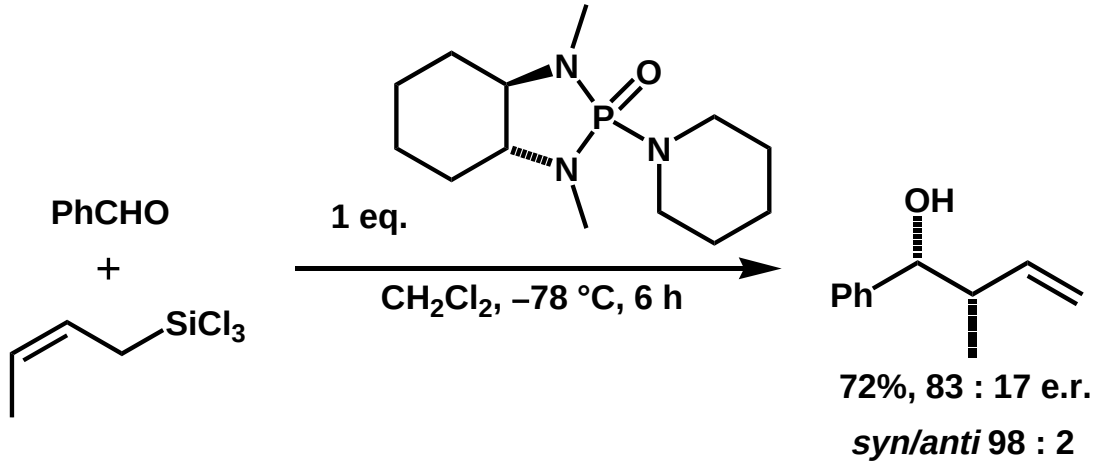
Allyltrichlorosilanes

Used on their own, allyltrichlorosilanes are poor allylating agents. However, their reactivity can be significantly increased when used in the presence of DMF,[12] which acts as a Lewis base activator[13] (remember, Si can expand its valence state). This observation opened up the possibility of using *chiral* Lewis bases to effect the enantioselective allylation of aldehydes using allyltrichlorosilanes.



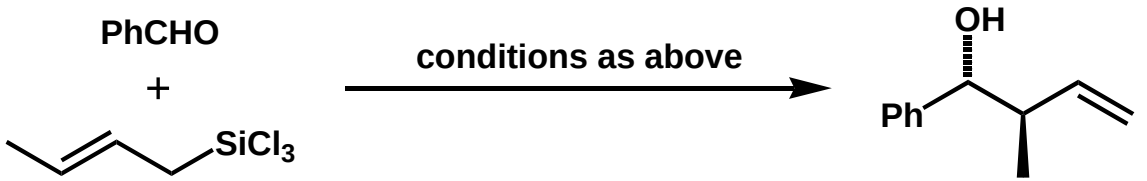
Chiral Phosphoramides

Denmark was the first to exploit *chiral* Lewis bases as catalysts for the enantio-selective crotylation of aldehydes with allyltrichlorosilanes:[14]



72%, 83 : 17 e.r.

***syn/anti* 98 : 2**

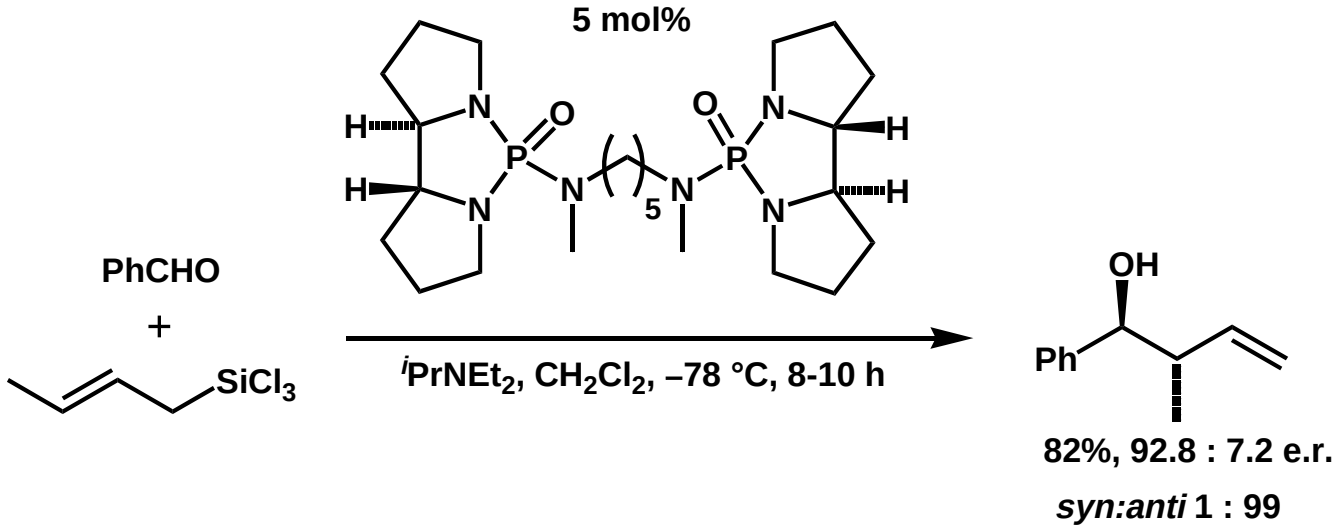


68%, 80 : 20 e.r.

***syn/anti* 2 : 98**

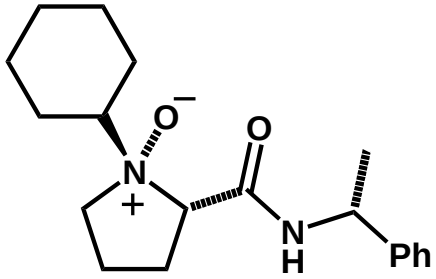
Chiral Phosphoramides

Careful analysis of the mechanism of the reaction and consideration of the reactive transition state structures led to the development of improved catalysts based on a bis-phosphoramide scaffold:[15,16]

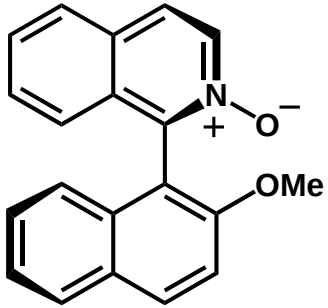


Aliphatic aldehydes are not good substrates for the reaction. Under the reaction conditions, rapid formation of the α-chloro silyl ether occurs. Inclusion of $HgCl_2$ as an additive improves the yield of the allylation; however enantioselectivity is compromised.[15]

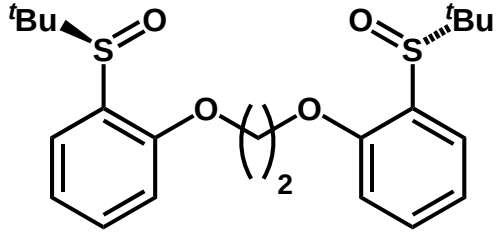
Other Chiral Lewis Base Catalysts



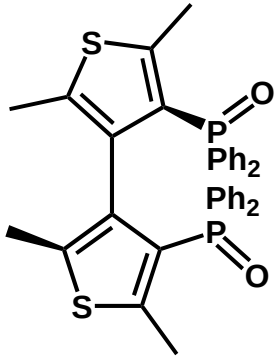
amine oxides[17]



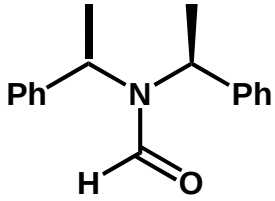
pyridine *N*-oxides and related systems[18]



sulfoxides[19]



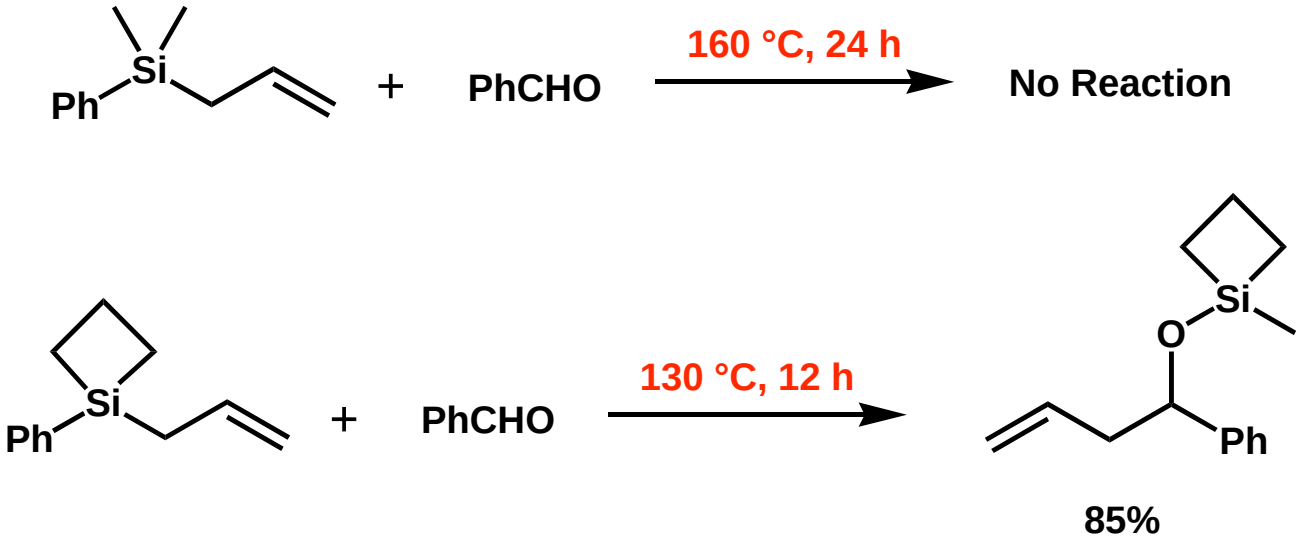
diphosphine oxides[20]



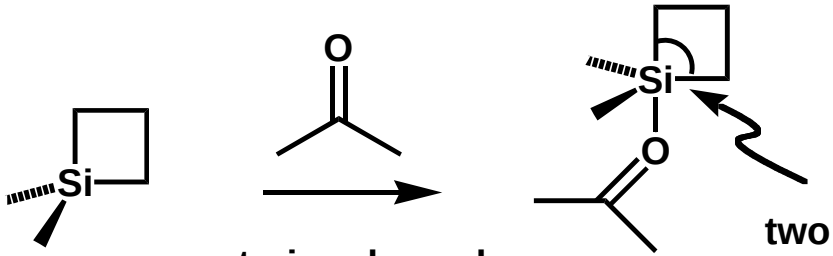
formamides[21]

Strain-Induced Lewis Acidity

We have seen how the stereoselectivity of an allylation can be improved and predicted by forcing the reaction to proceed *via* a closed chair-like T.S. by making the Si atom more Lewis acidic. Another way of increasing the Lewis acidity of the Si centre is to include the Si atom in a small ring:[22]



Strain-Induced Lewis Acidity

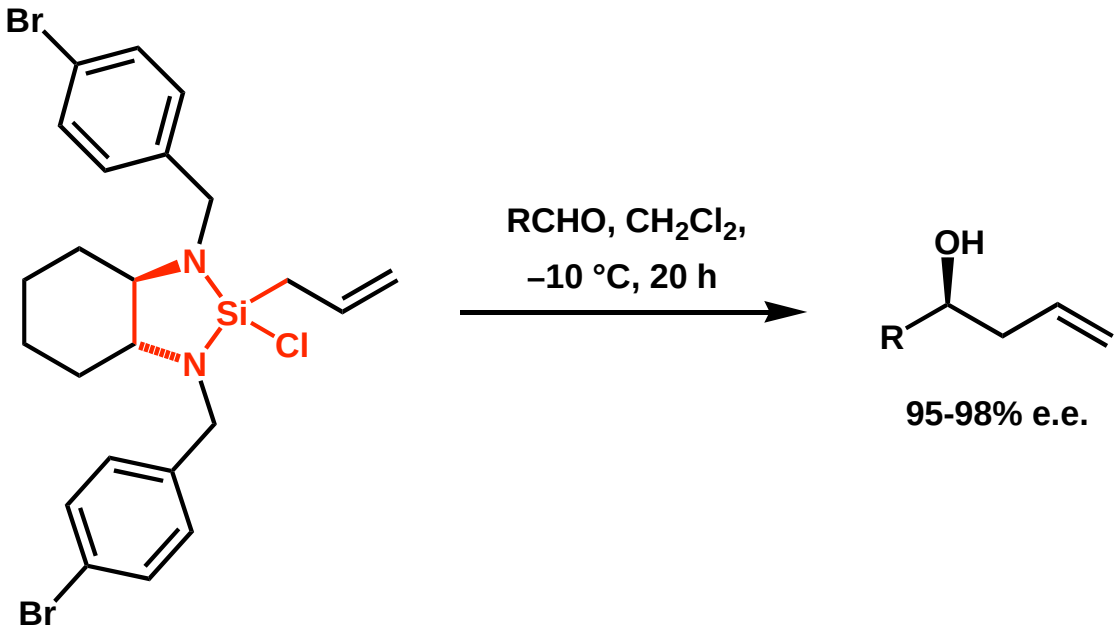


strain released on coordination

90° (ideal for two groups occupying apical and equatorial positions in a trigonal bipyramid)

Leighton's Allylsilanes

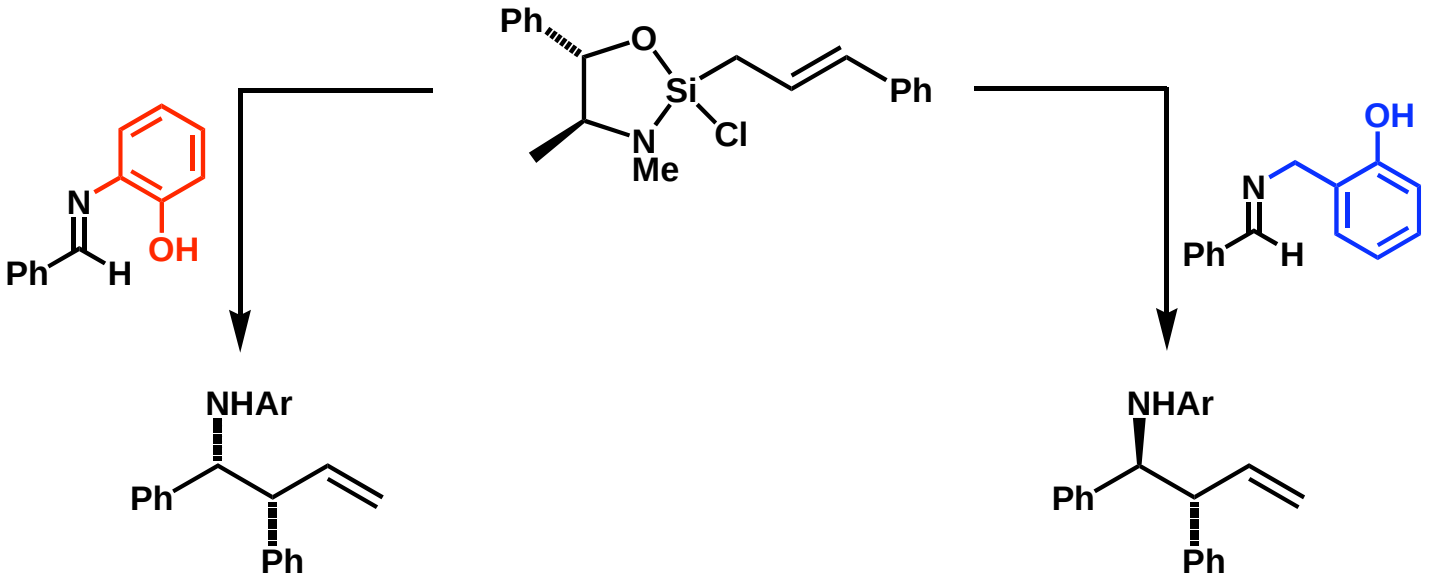
Leighton has introduced a range of allylsilanes in which the Si atom is contained within a *five-membered ring*. The long Si–N and short C–N bonds ensure the silacycle is still strained. The electronegative N and Cl substituents further enhance the Lewis acidity of the Si centre.[23, 24]



reagents are crystalline, shelf-stable, and easy to prepare

Enantioselective Allylation of Imines

Leighton has recently used a related class of chiral γ-substituted allylsilane, readily prepared from the simple allylsilane by cross metathesis, in enantioselective imine allylation.[25]



68%, 7:1 d.r., 96% e.e.

***syn*-selective**

64%, >20:1 d.r., 96% e.e.

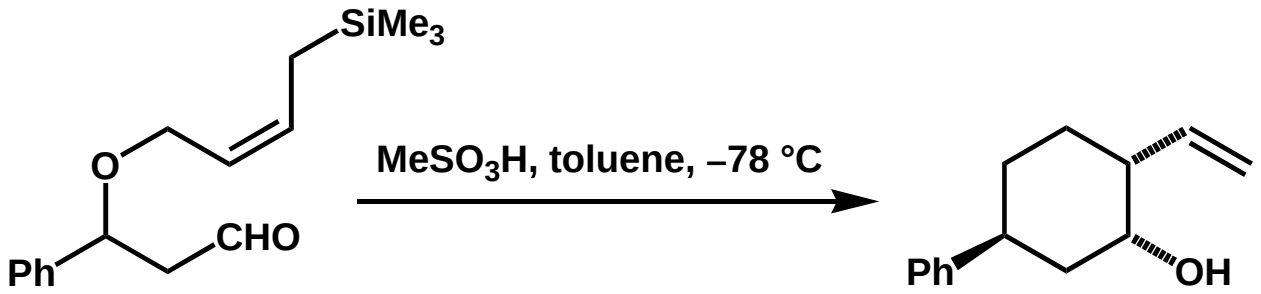
***anti*-selective**

Of particular note in these examples, the choice of nitrogen substituent in the imine determines the diastereoselectivity of the reaction.[26]

More Allylsilane Chemistry

Substrate-Controlled Stereoselective Allylations in Ring Synthesis

Intramolecular allylation provides an excellent opportunity for generating rings. Since cyclisation frequently proceeds through well-defined transition states, levels of stereo-selectivity can be excellent.



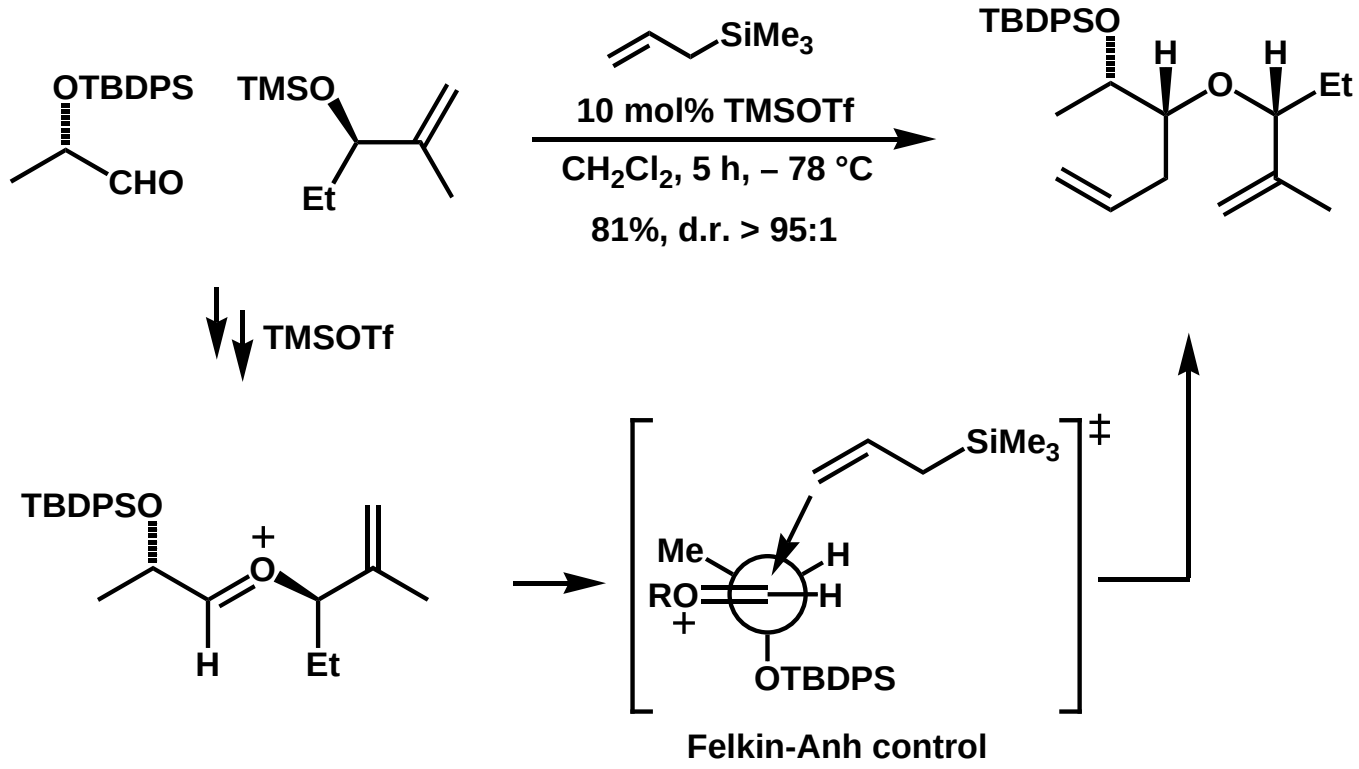
88%, d.e. > 95%

Brønsted acids are not commonly used as activators for reactions involving allylsilanes owing to the propensity for these reagents to undergo protodesilylation.

This was not a problem in this example however; indeed in this case, the use of Lewis acid activators led to a reduction in diastereoselectivity.[27]

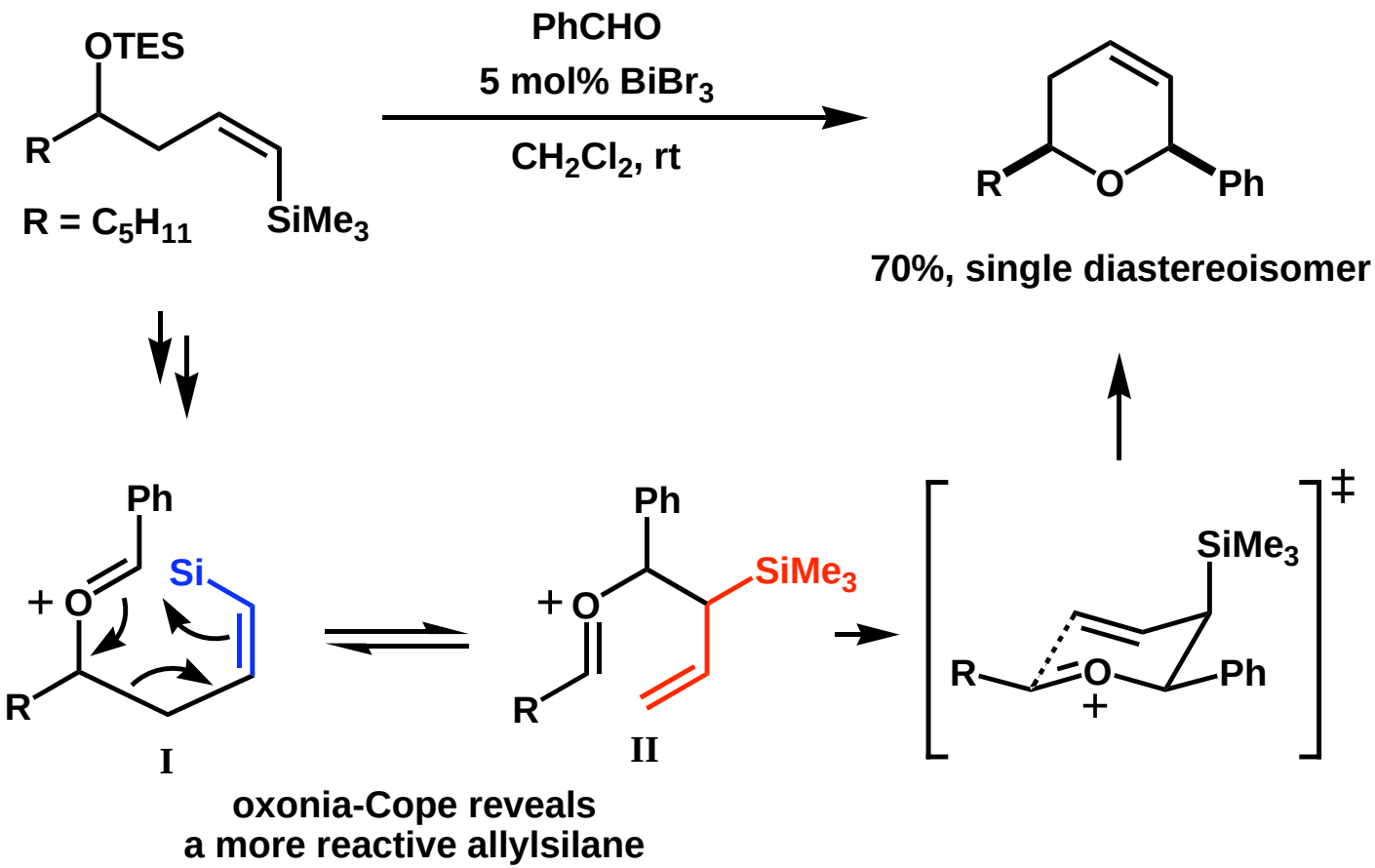
Allylsilanes in Multicomponent Reactions

Lewis- or Brønsted acid-mediated reaction of alcohols or silyl ethers with aldehydes and ketones affords oxacarbenium cations. These reactive electrophiles react readily with allylsilanes. Both inter- and intramolecular variants have been reported.[28]



Markó[28a]

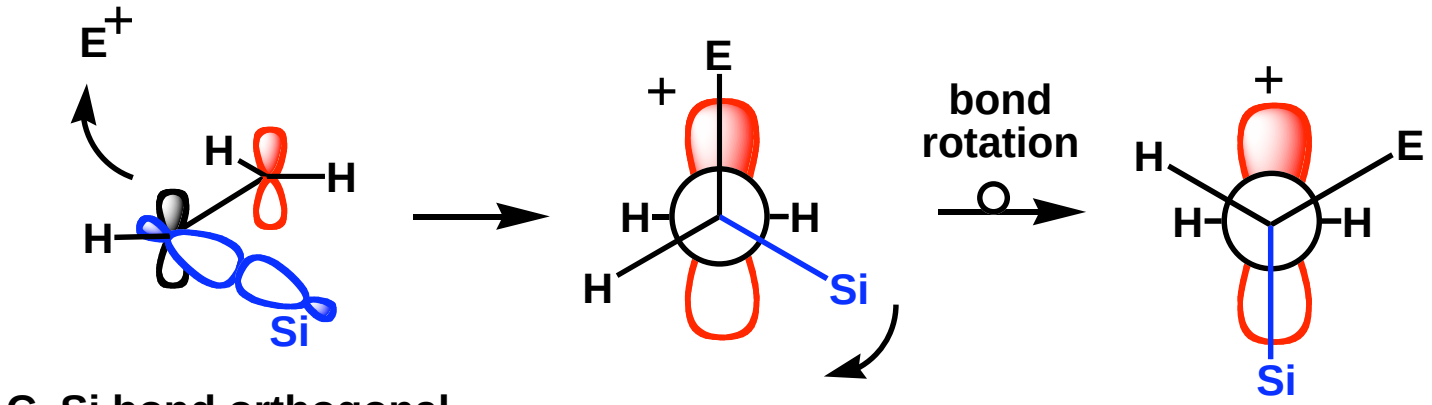
Allylsilanes in Multicomponent Reactions



In this example, condensation of the TES ether with PhCHO generates oxacarbenium ion I. Further rearrangement to a second oxacarbenium II reveals an allylsilane, which undergoes cyclisation.[28b]

Vinylsilanes are Poor Nucleophiles

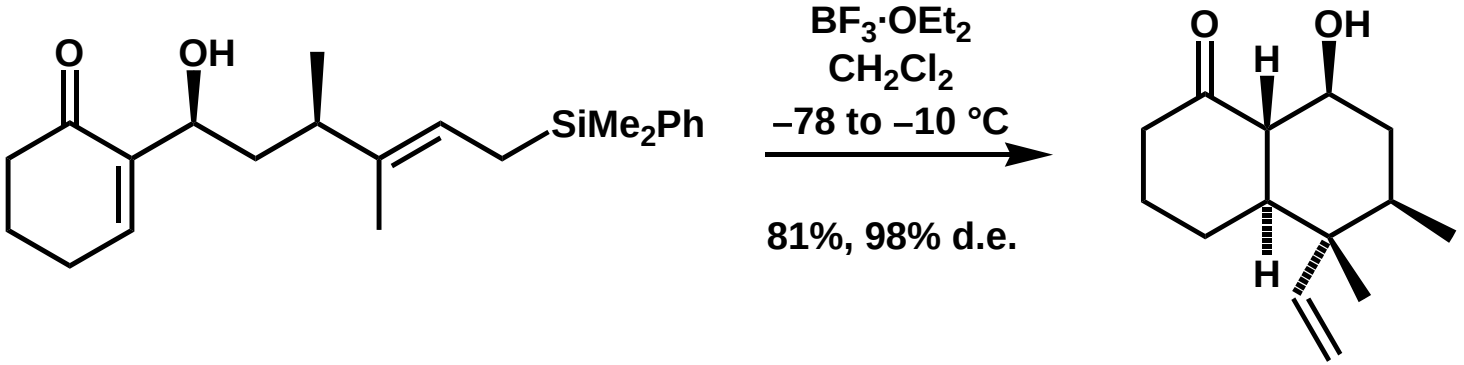
Allylsilanes are far more nucleophilic than vinylsilanes. In an allylsilane, the C–Si bond can align with the developing β-positive charge. In a vinylsilane, the C–Si bond is initially orthogonal to the empty p AO. As a result, the C–Si bond needs to undergo a 60° bond rotation before it can optimally stabilise the β-positive charge. As a consequence, vinylsilanes are not much more nucleophilic than standard olefins.

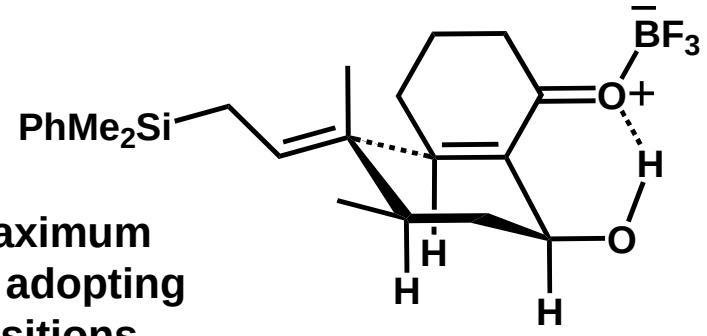


C–Si bond orthogonal to π bond

Intramolecular Hosomi Sakurai Reaction

Under Lewis acid-activation, allylsilanes are good nucleophiles for conjugate addition reactions to α,β-unsaturated carbonyl compounds. Schauss used an intramolecular version of this reaction in a synthesis of the *trans* decalin scaffold found in the clerodane diterpenoid natural products.[29,30]

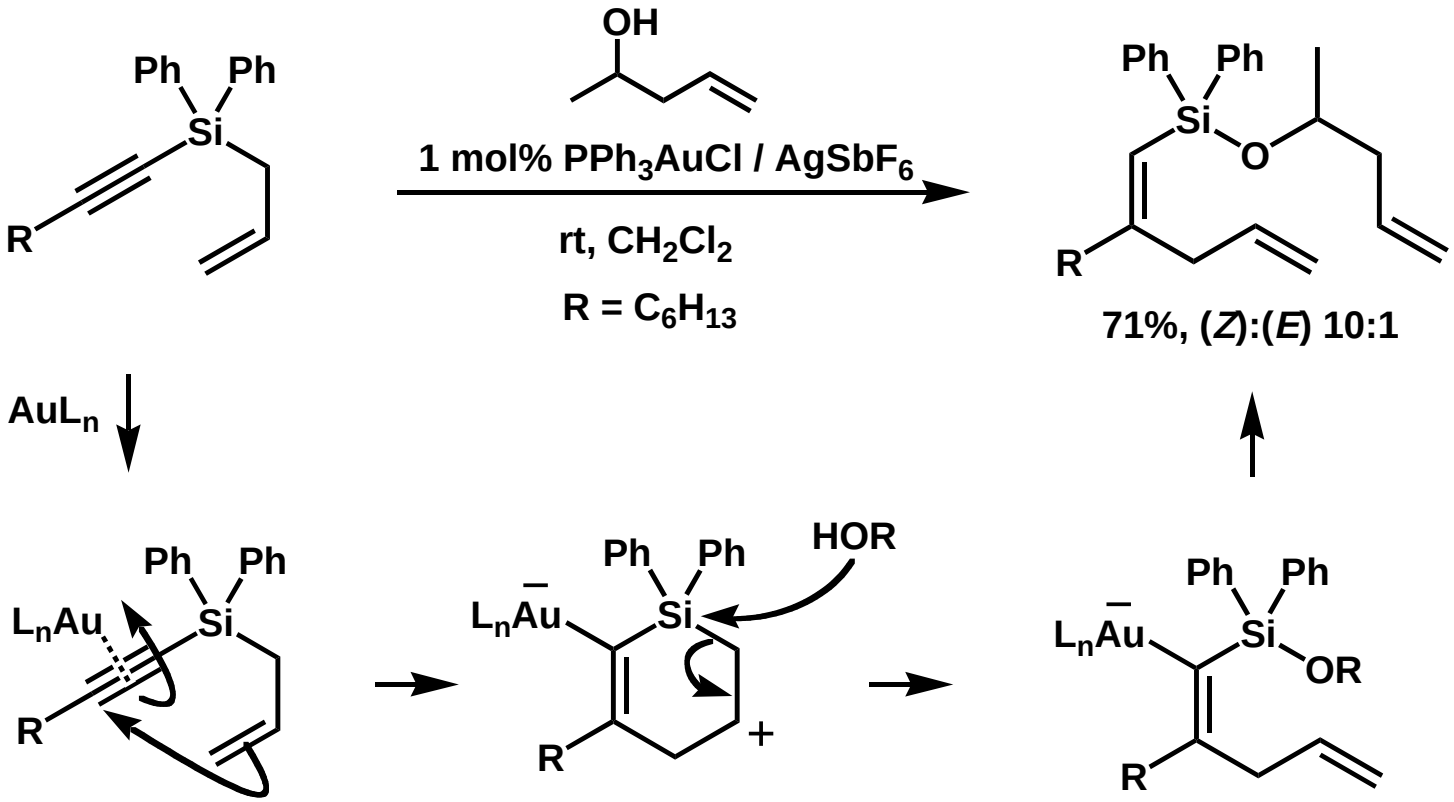




chair-like T.S. with maximum number of substituents adopting pseudoequatorial positions

Reactions of Allylsilanes with other Electrophiles

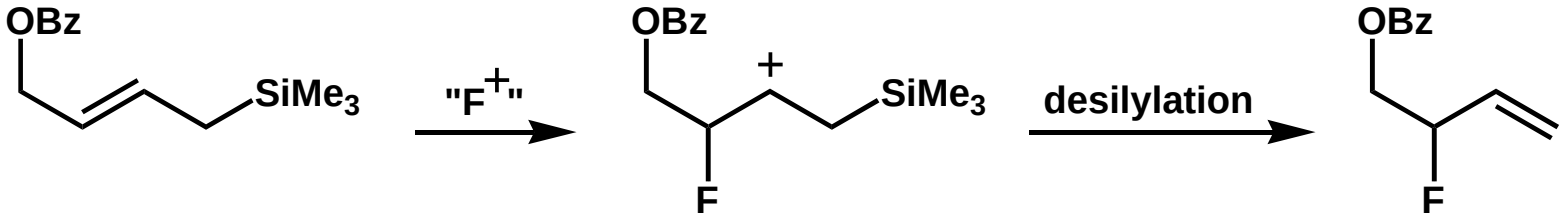
Activated alkynes[31]

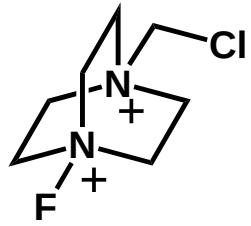


Reactions of Allylsilanes with Electrophilic Fluorine Sources

Regio- and stereoselective fluorination strategies

Allylsilanes react with electrophilic halogen sources. Of particular interest is the use of 'F^{+}' electrophiles as a means for generating organofluorines in a controlled manner.[32] As expected, fluorination occurs regiospecifically at the γ-terminus of the allylsilane to provide a cationic intermediate that collapses to provide an allyl fluoride (S_E2') product.



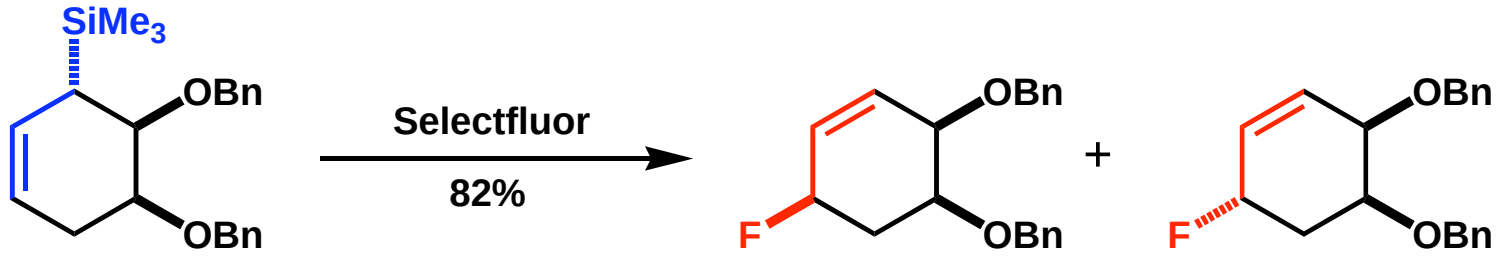


$2\ \overline{B}F_4$

Selectfluor is the most commonly used electrophilic fluorine source.

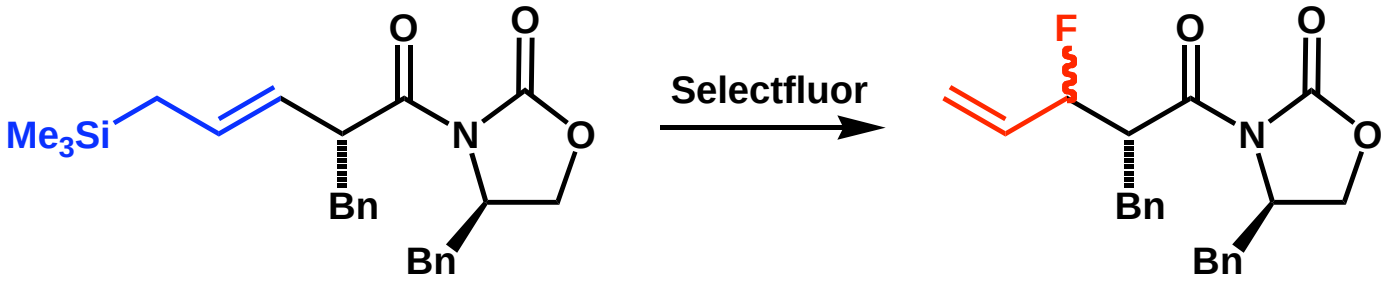
Stereoselective Electrophilic Fluorination of Allylsilanes

Substrate control:[33]



82 : 18

Auxiliary control:[34]

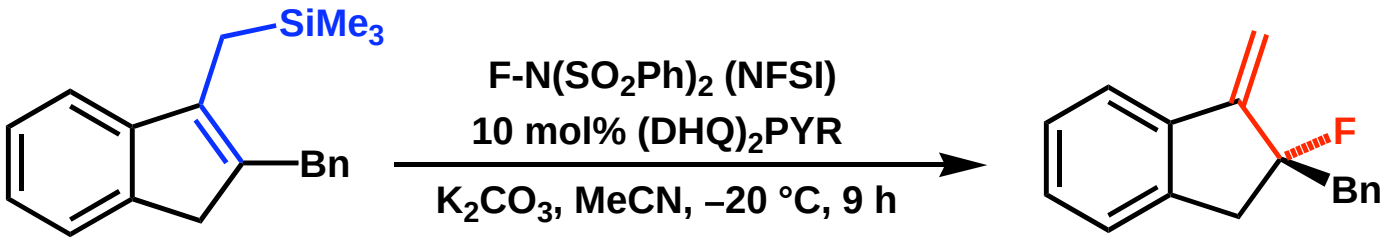


***syn* : *anti* = 1 : 2**

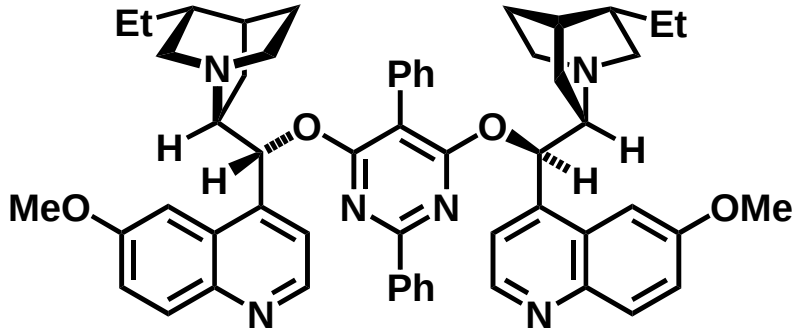
(diastereoisomers separable)

Enantioselective Electrophilic Fluorination of Allylsilanes

Reagent control: ***Catalytic*** **enantioselective fluorination of allylsilanes has recently also been disclosed:[35]**



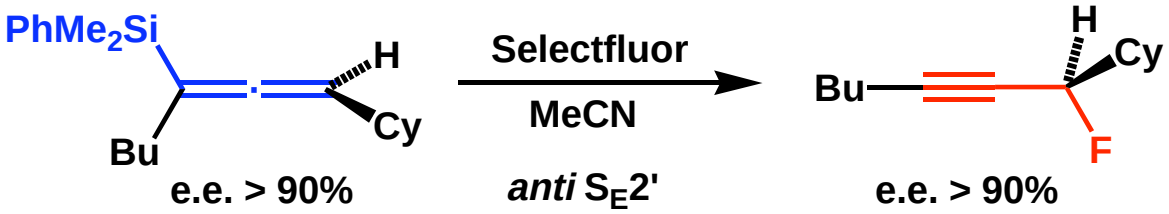
63%, 93% e.e.



$(DHQ)_2PYR$

Electrophilic Fluorination of other Organosilanes

allenylsilanes[36]

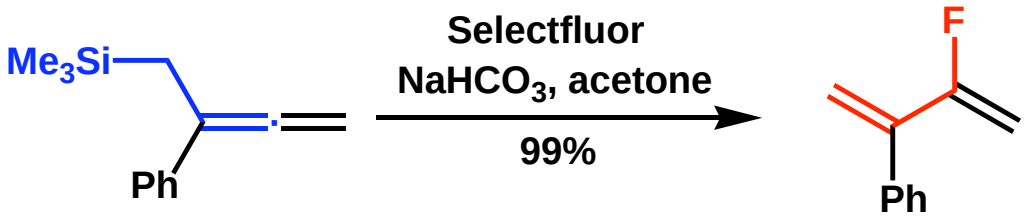


e.e. > 90%

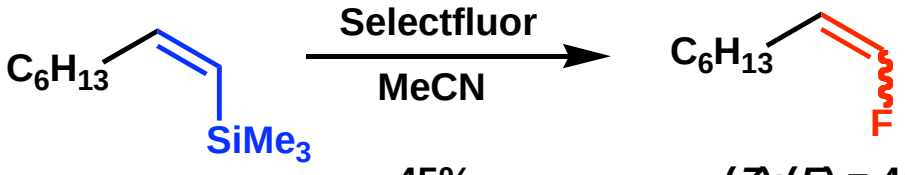
e.e. > 90%

47%

allenylmethylsilanes[37]



vinylsilanes[38]



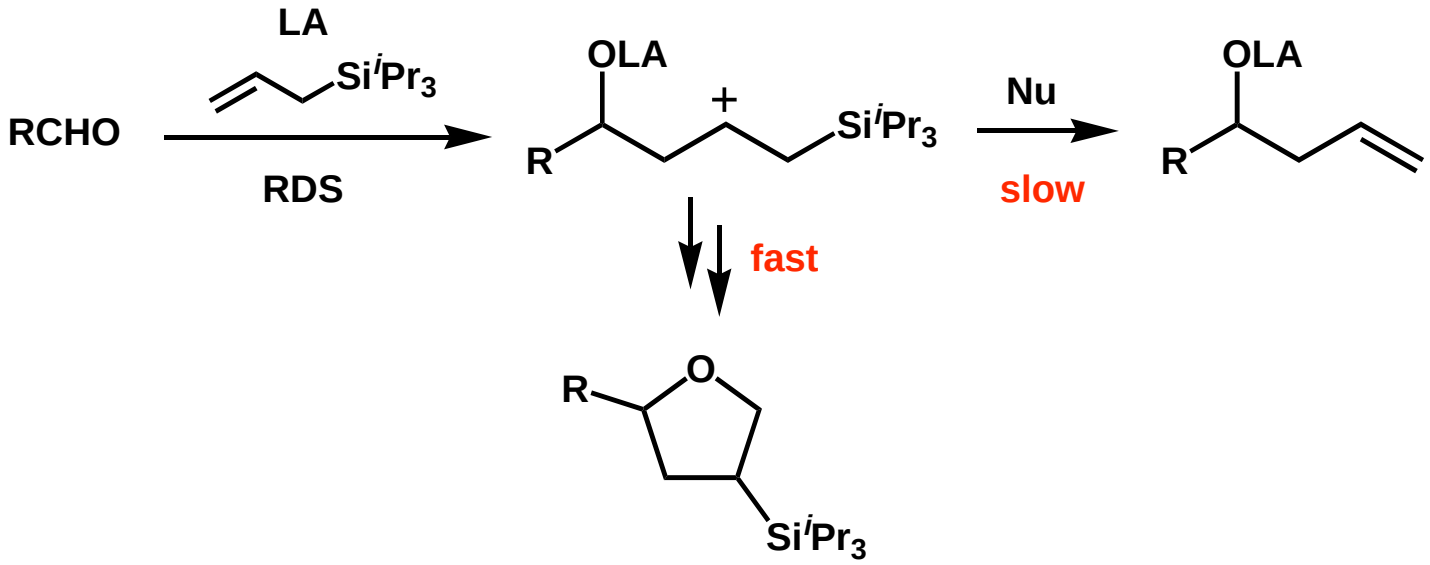
45%

(*Z*):(*E*) = 4:1

[3+2] Annulation Approaches

Allylsilanes in Annulation Reactions

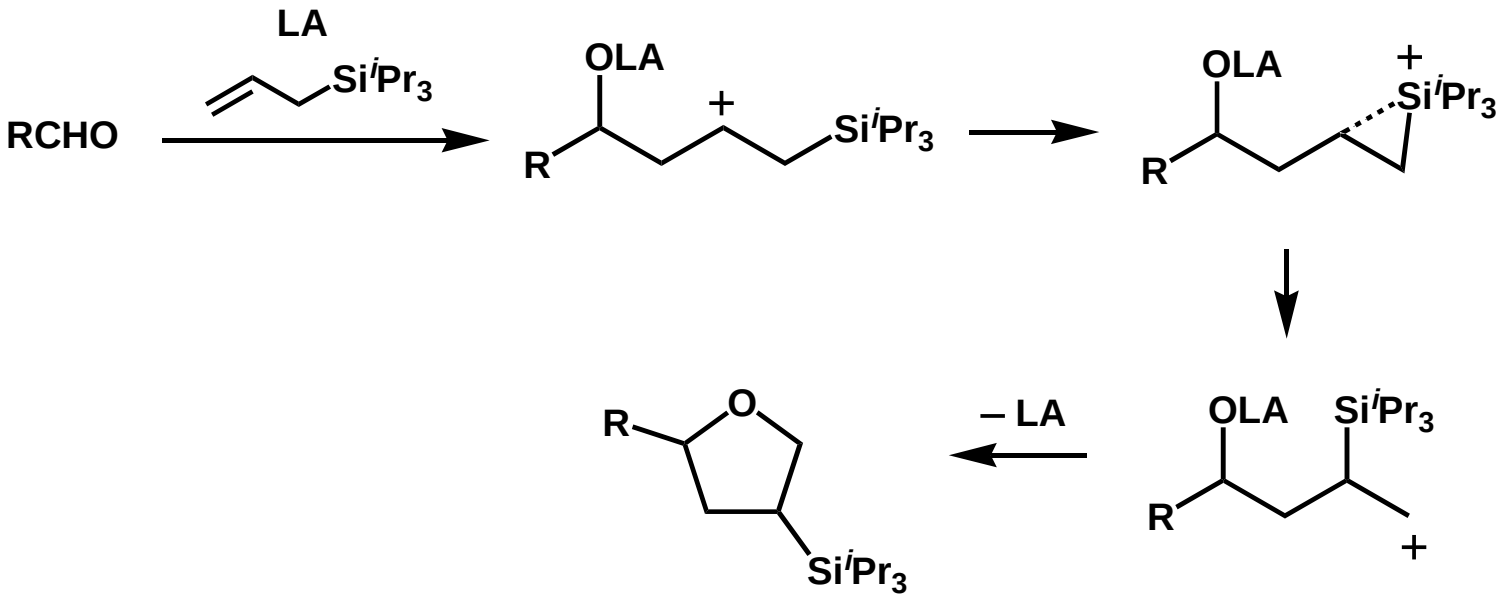
Allylation of aldehydes is a step-wise process, proceeding *via* a carbocationic intermediate. Normally, attack of an external nucleophile on the silyl group in this intermediate is rapid, leading to a homoallylic alcohol product.



However, if the second step of this allylation can be *slowed down* or *disfavoured*, alternative reaction pathways can be followed leading to different products. One of the easiest ways to redirect the allylation reaction is to replace the methyl substituents on the silyl group with bulkier groups. In this case, intramolecular trapping of a carbocationic intermediate provides ring products.

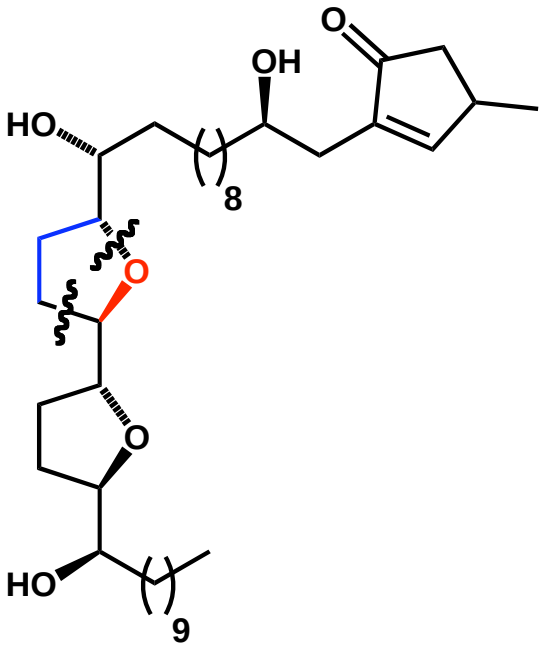
Allylsilanes in Annulation Reactions

Although the product outcome is rather substrate-dependent, a tetrahydrofuran product is particularly common.[39] This outcome requires rearrangement of the initially formed cationic intermediate:

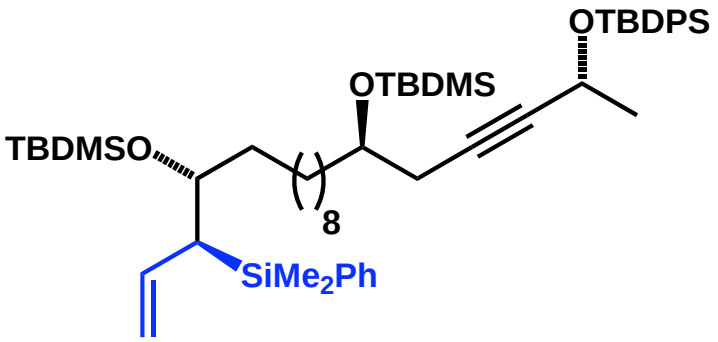


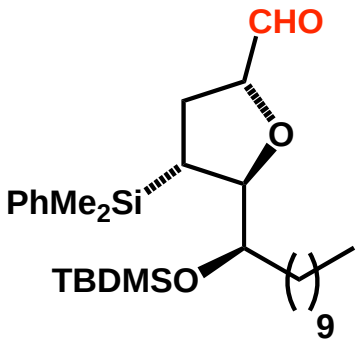
Roush's Synthesis of Asimicin

Roush employed the [3+2] annulation of allylsilanes and aldehydes in the synthesis of the two tetrahydrofuran rings of asimicin.[40]

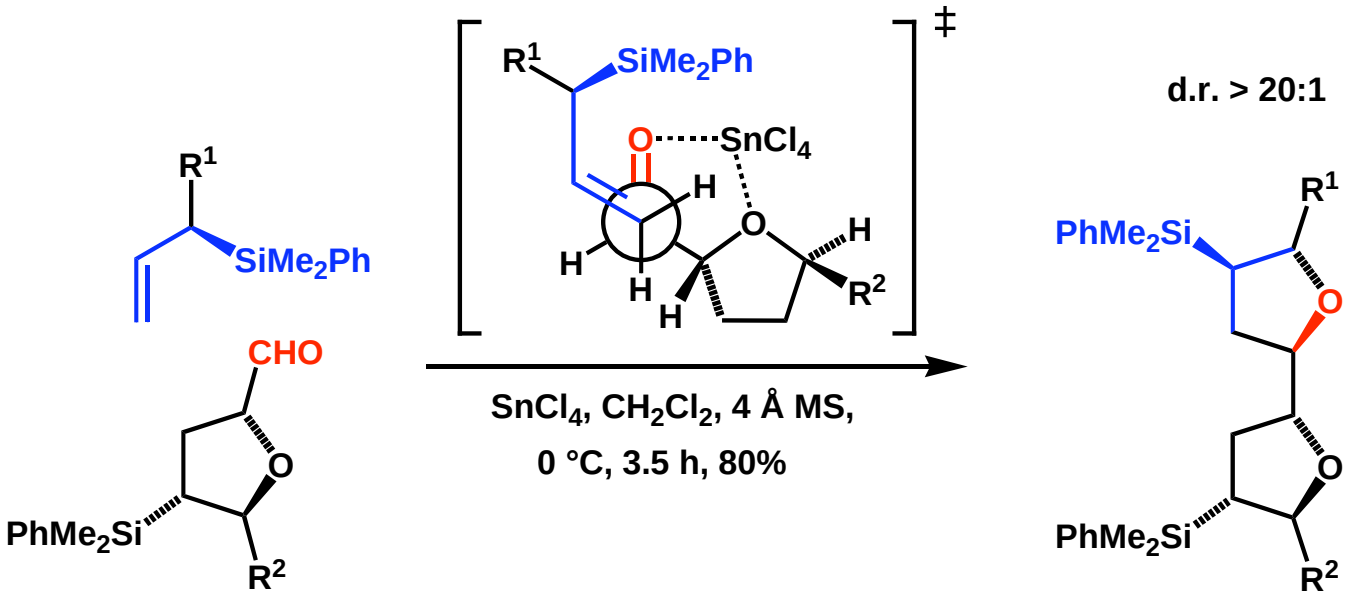


asimicin





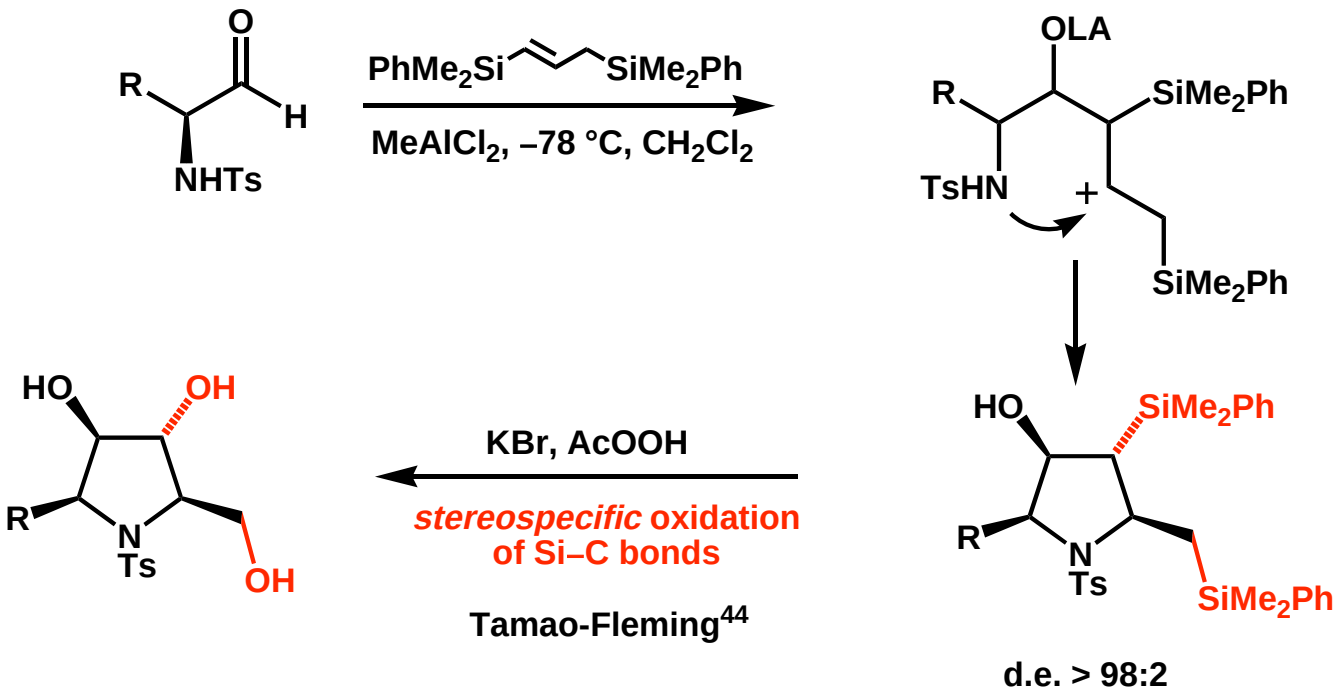
Roush's Synthesis of Asimicin



The excellent diastereoselectivity of this reaction was attributed to the *matched* facial selectivity associated with using a chiral allylsilane (*anti* S_E2') and $SnCl_4$-chelated chiral aldehyde reacting through a *syn* synclinal T.S. as proposed by Keck.[41]

[3+2] Annulation Route to Pyrrolidines

A 1,2-silyl shift of the silyl group in the initially formed carbocationic intermediate is sometimes unnecessary, as in Somfai's synthesis of highly functionalised pyrrolidines where the sulfonamide functions as an internal nucleophile trap:[42,43]

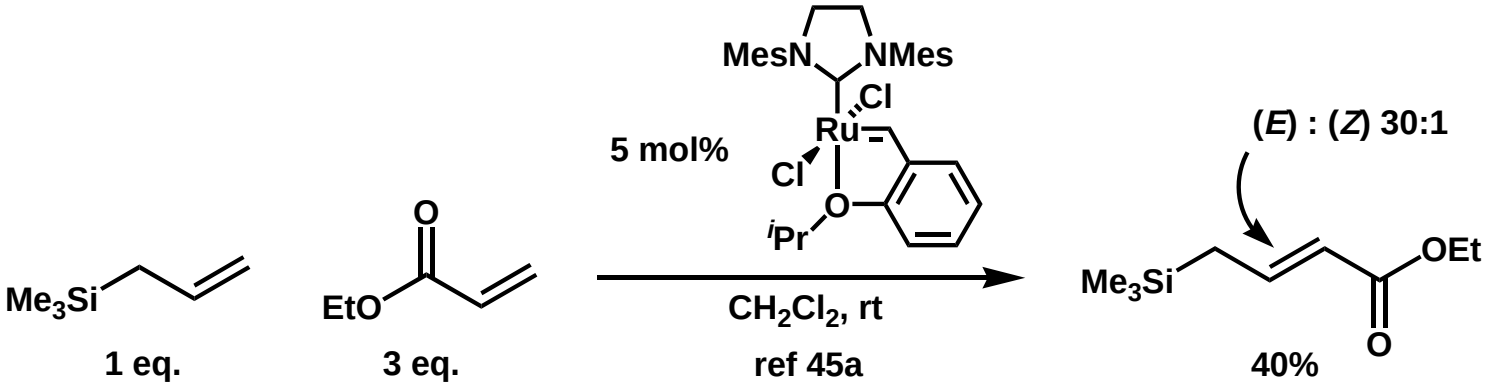


d.e. > 98:2

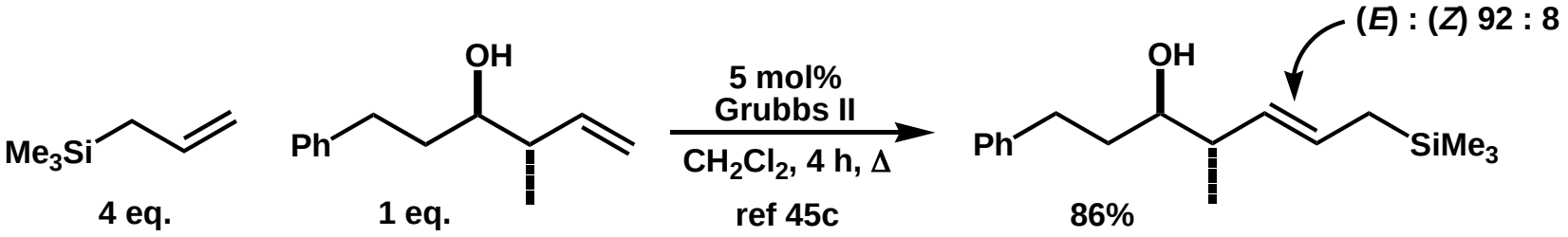
Synthesis of Allylsilanes

Cross Metathesis Approach

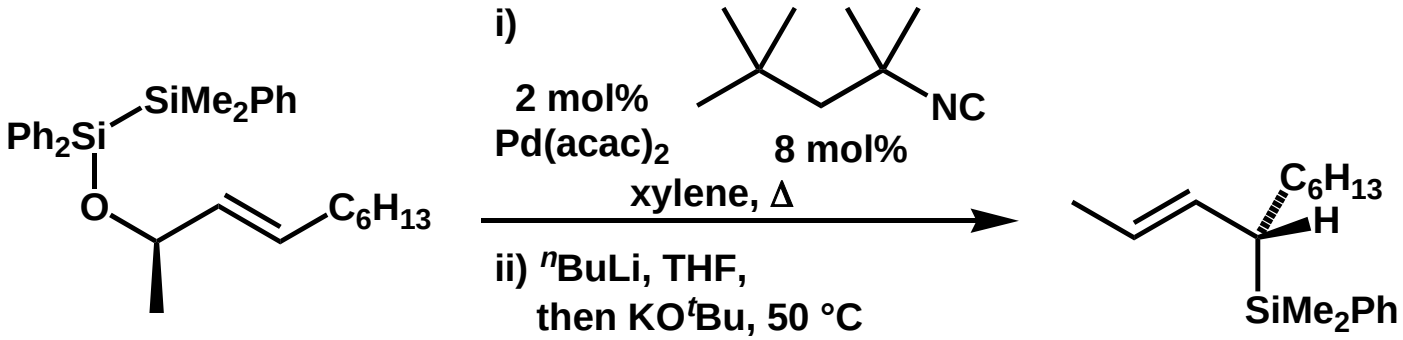
Cross-metathesis provides an efficient route to γ-substituted allylsilanes.[45] Allyltrimethylsilane is a Type I alkene according to Grubbs' classification[46] and homodimerises readily. The homodimer readily takes part in secondary cross-metathesis processes. Particularly good results are obtained with Type II olefins:[45a]



If the cross-metathesis product is required from an allylsilane and an alkene of similar reactivity, the best yields of product are obtained by employing the allylsilane in excess:[45c]



A Silylsilylation Approach

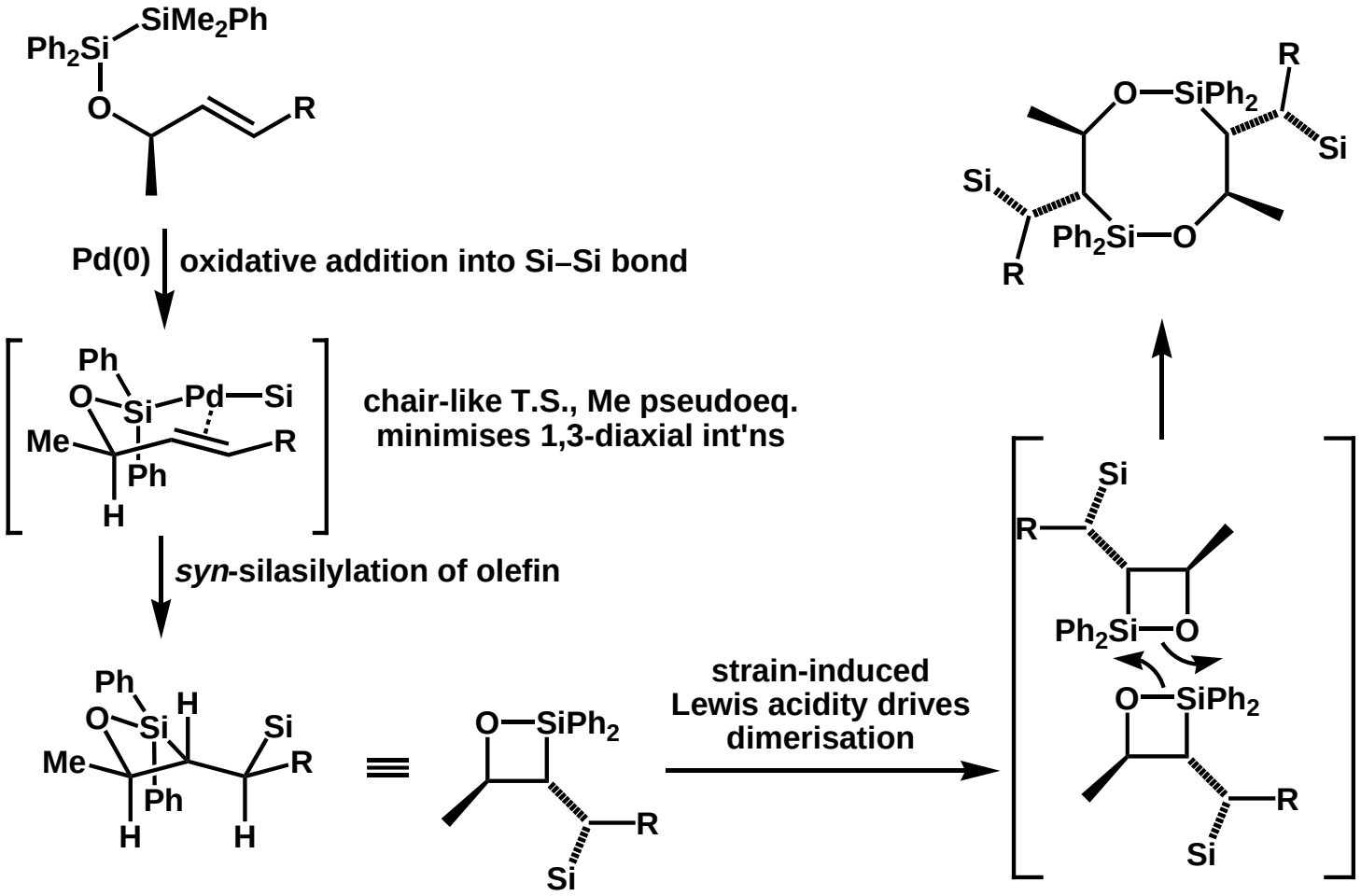


99.7% e.e.

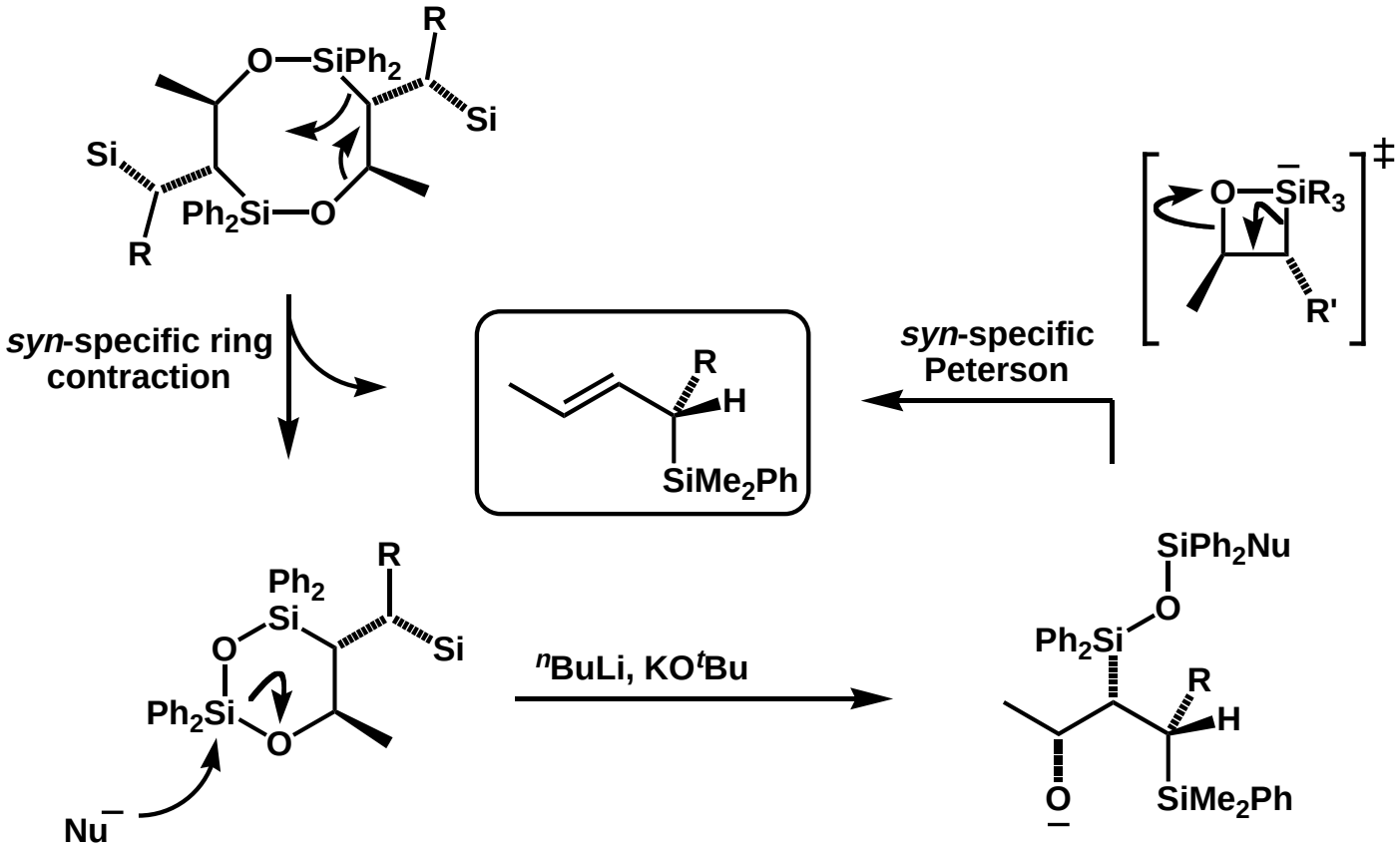
90%, 99.1% e.e.

Use of a temporary silyl ether connection[47] enables an intramolecular bis-silylation of the proximal olefin. In the second step, *syn*-specific Peterson[48] of an intermediate oxesiletane unveils the allylsilane product.[49]

Mechanism


SiMe2Ph
Ph2Si
O
R
Pd(0)
oxidative addition into Si–Si bond
Ph
O
Si
Pd
Si
Me
R
Ph
H
chair-like T.S., Me pseudoeq.
minimises 1,3-diaxial int'ns
syn-silasilylation of olefin
Ph
O
Si
H
Si
Me
R
Ph
H
H
O
SiPh2
R
Si
strain-induced
Lewis acidity drives
dimerisation
Si
R
Ph2Si
O
O
SiPh2
R
Si
R
O
SiPh2
Si
R
Ph2Si
O
Si

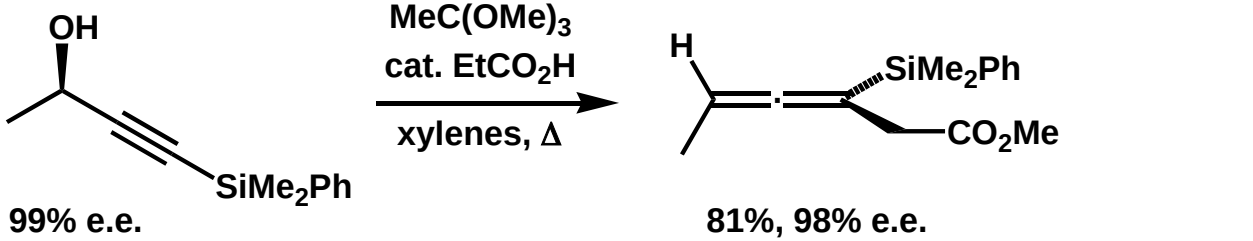
Mechanism

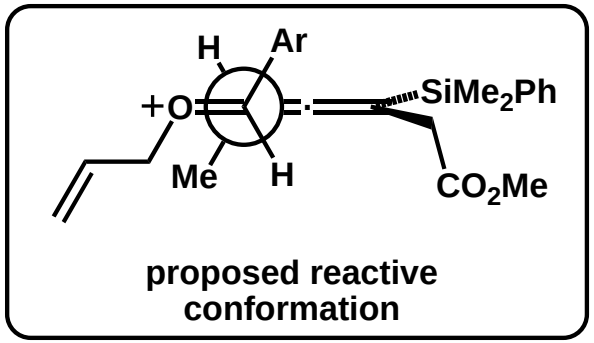

R
O—SiPh2
Si
Si
Ph2Si—O
R
syn-specific ring contraction
R
H
SiMe2Ph
syn-specific Peterson
O—SiR3
R'
Ph2
Si
R
Si
O
Ph2Si
O
Nu−
nBuLi, KOtBu
SiPh2Nu
O
Ph2Si
R
H
O
SiMe2Ph

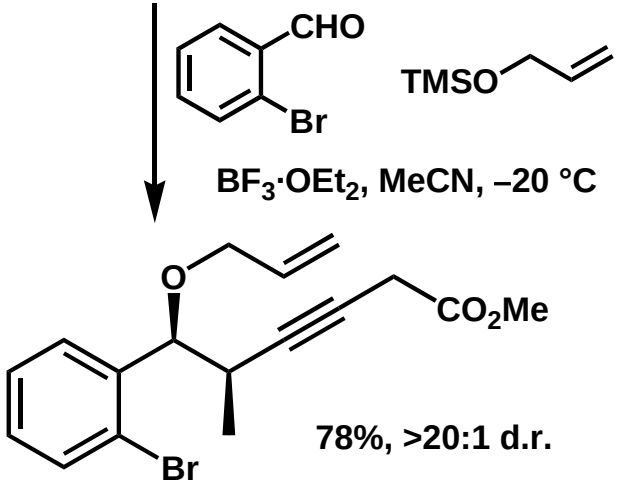
Allenyl, Propargyl and Vinylsilanes

Allenylsilanes

Since the C–Si bond can align with the nucleophilic π-bond, allenylsilanes react in an *anti* S_E2' fashion similar to allylsilanes.[51] Chiral allenylsilanes can also be prepared enantioselectively, often by S_N2' displacement of a propargyl mesylate by a silyl nucleophile, or in this example,[52] by a Johnson orthoester Claisen rearrangement.

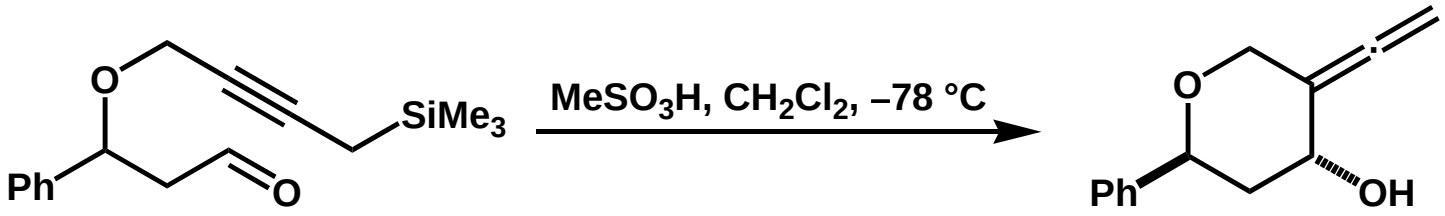






Propargylsilanes

Propargylsilanes also react in an S_E2' fashion although *anti* selectivity is not as high as is observed with allyl- and allenylsilanes.[51] Reaction with aldehydes, and related electrophiles, proceeds under Lewis- or Brønsted acid activation to afford allenyl alcohol products.

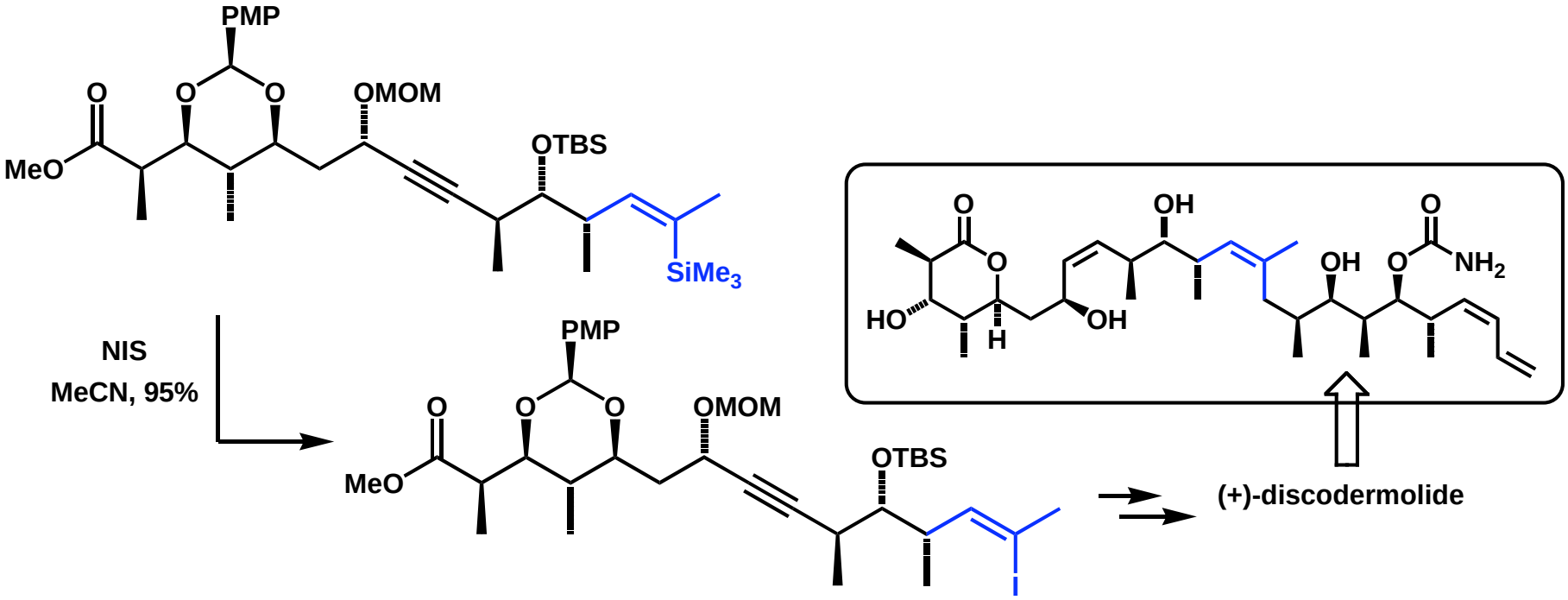


ref 27

single diastereoisomer

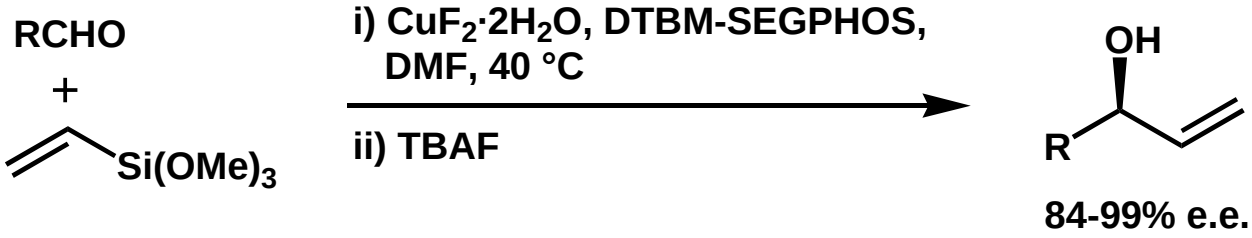
Vinylsilanes

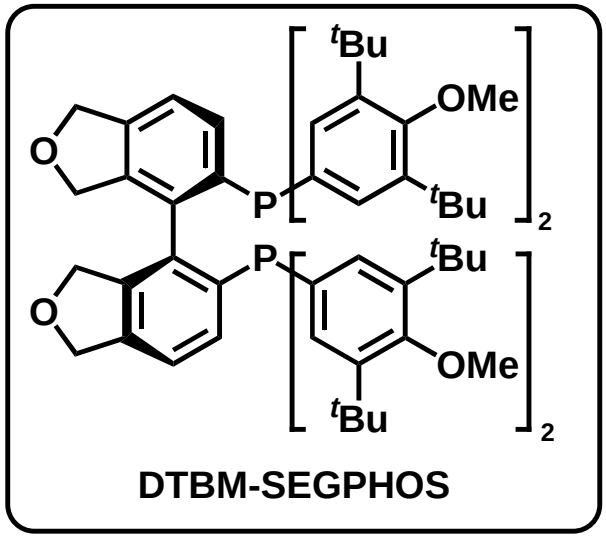
We have already explained why vinylsilanes are far less nucleophilic than allyl-, allenyl- and propargylsilanes. Nevertheless this class of organosilane still reacts with electrophiles with predictable regioselectivity. Panek used a stereodefined vinylsilane as a masked vinyl iodide in his synthesis of discodermolide. The trisubstituted vinyl iodide was unmasked upon treatment with NIS. This iododesilylation proceeded with complete retention of configuration.[53]



Enantioselective Vinylation of Aldehydes

Shibasaki used vinyltrimethoxysilane as a starting reagent in an enantioselective vinylation of aldehydes in the presence of CuF_2 and a chiral bis-phosphine.[54]





DTBM-SEGPHOS

Enantioselective Vinylation of Aldehydes

The likely nucleophile in this reaction is a vinylcopper reagent, which is generated *in situ* by transmetallation of a fluoride-activated vinylsilane intermediate.

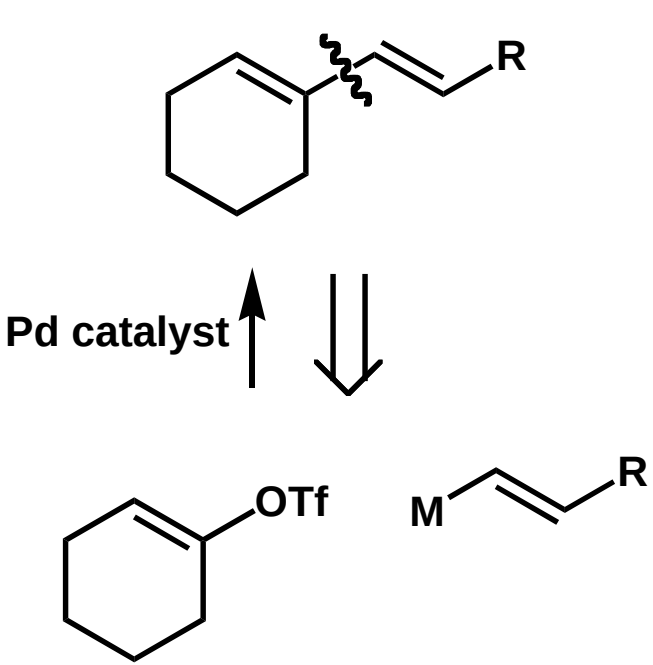
The formation of the hypervalent silyl species is important as transmetallation from standard organosilanes to other vinyl metal species is less efficient.

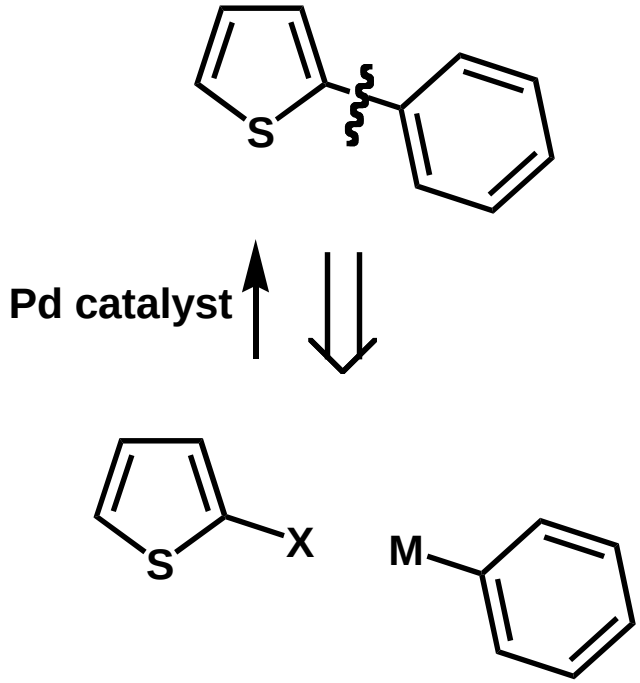
Evans has since reported an enantioselective vinylation of aldehydes that proceeds in the presence of a chiral scandium catalyst *directly* from a vinylsilane nucleophile.[55]

Organosilanes in Cross-Coupling Reactions

Disconnection

Pd-catalysed cross-coupling strategies require an 'electrophilic' coupling partner, usually an organohalide or pseudohalide (sulfonate, phosphate, diazonium sp *etc*) and a 'nucleophilic' coupling partner. Commonly used organometallic reagents include B, Sn, Zn, Cu, Mg, Zr *and* Si species.





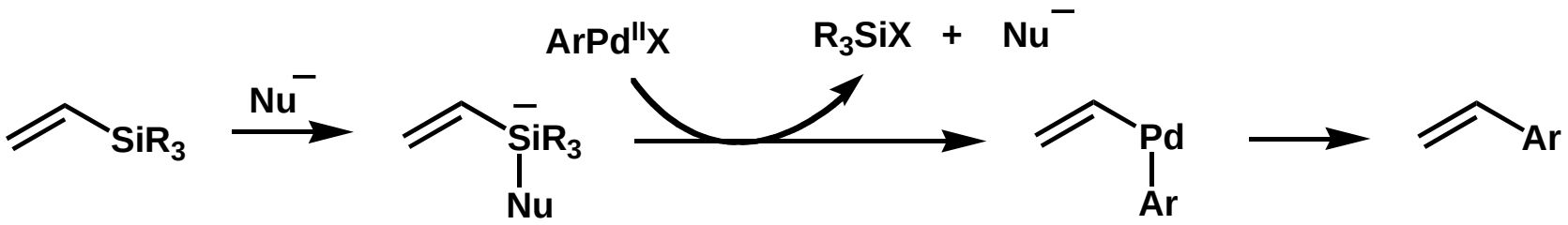
Reactions which employ organosilanes in this type of cross-coupling are commonly referred to as *Hiyama couplings.*[1]

Hiyama Coupling

Owing to the low polarisation of the C–Si bond, organosilanes are relatively unreactive nucleophilic coupling partners for Pd(0)-catalysed cross-coupling reactions.

As a result, reaction is usually performed in the presence of an activator, typically a fluoride source (TBAF, TASF *etc*).

In the presence of an activator, reaction proceeds more readily owing to the *in situ* formation of a pentacoordinate siliconate species, which undergoes more rapid transmetallation.

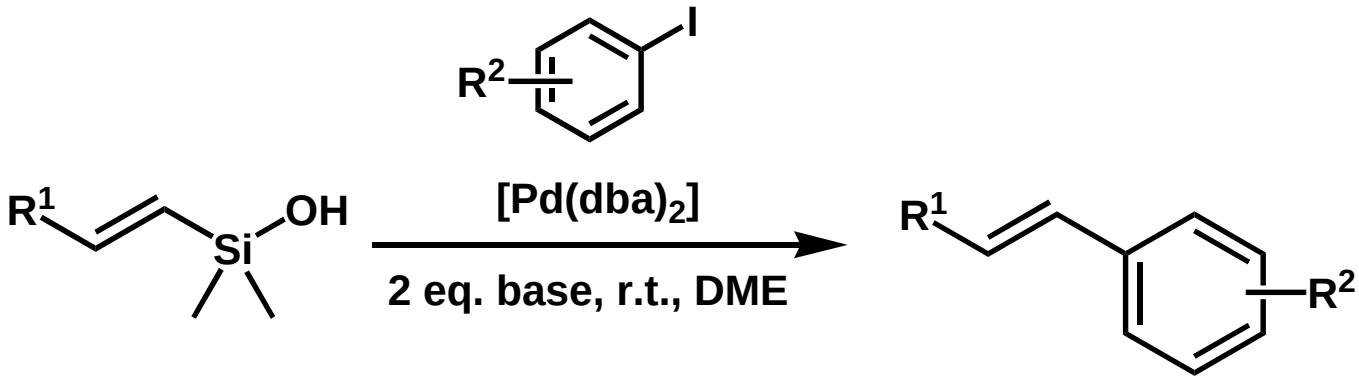


The substituents on the silyl group are also important. Silanes containing electron-withdrawing groups tend to be most useful: $Me_2FSi–$, $MeF_2Si–$ (but not $F_3Si–$) are good, as are alkoxysilanes ($Me_2(RO)Si–$ and $Me(RO)_2Si–$ better than $(RO)_3Si–$).[2]

Recent Developments

Alkoxysilanes and silanols are particularly attractive coupling partners for Hiyama couplings. Reactions proceed efficiently in the presence of a fluoride source.[1,3]

Hiyama couplings under fluoride-free conditions are also possible. Denmark has made significant contributions to this field,[1,4] showing that organosilanols undergo Pd-catalysed cross-coupling in the presence of a base.[1,4]

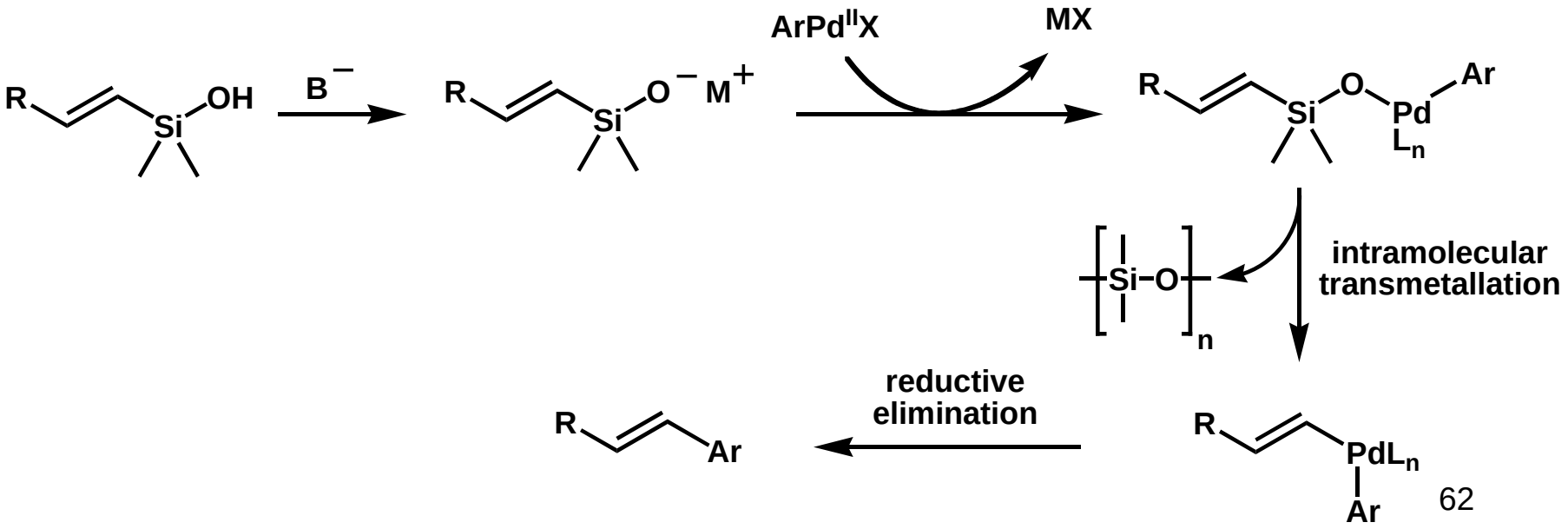


Denmark Modifications

A range of bases can be employed including: NaO^tBu, NaH and Cs_2CO_3. $KOSiMe_3$ is a particularly mild alternative.

In all cases, the reactive species is the corresponding silanolate.

Mechanistic studies have revealed a different mechanistic pathway for this base-mediated Hiyama coupling. Specifically, reaction does not require the formation of a pentavalent siliconate species, rather transmetallation proceeds in a direct, intramolecular fashion on an intermediate *tetracoordinate* Pd^{II} species:



Effect of Silicon Substituents

Denmark has studied the effect of silicon substituents on the efficiency of Hiyama cross-coupling reactions.[2]

For fluoride-activated cross-couplings, the order of reactivity is:

$(CF_3CH_2CH_2)MeSiOH > Me_2SiOEt > Me_2SiOH > Ph_2SiOH > Et_2SiOH > MeSi(OEt)_2 > {}^{i}Pr_2SiOH > Si(OEt_3) >> {}^{t}Bu_2SiOH$

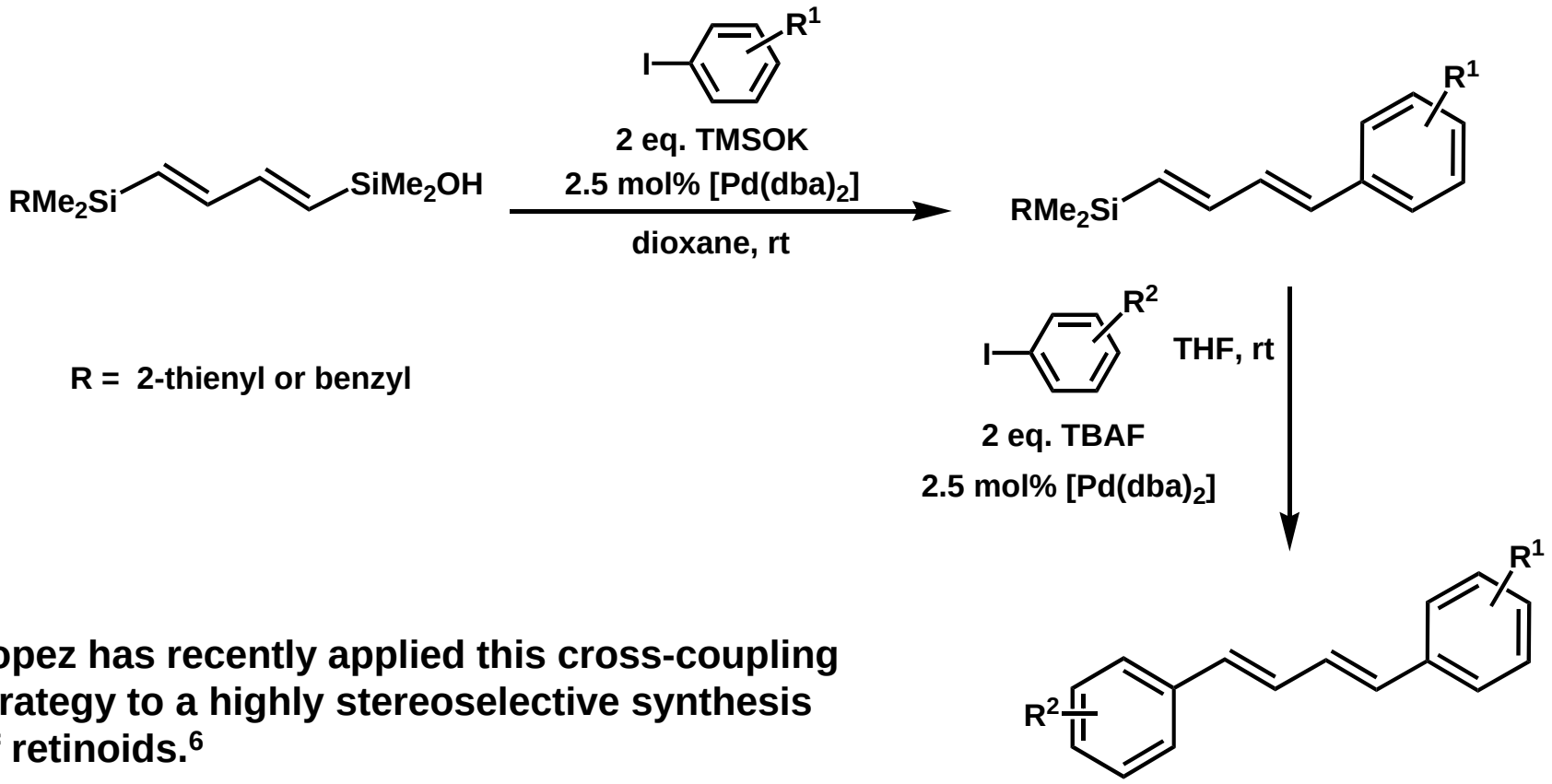
For TMSOK-activated cross-couplings, the order of reactivity is:

$Ph_2SiOH > (CF_3CH_2CH_2)MeSiOH > MeSi(OEt)_2 > Me_2SiOH > Si(OEt_3) \sim Me_2Si(OEt) >> {}^{i}Pr_2SiOH$

Fluoride-activated cross-couplings tend to be faster and less sensitive to structural and electronic features of the substrates than base-mediated couplings.

Applications

The different activity of organosilanes can be exploited in sequential Hiyama coupling reactions:[5]

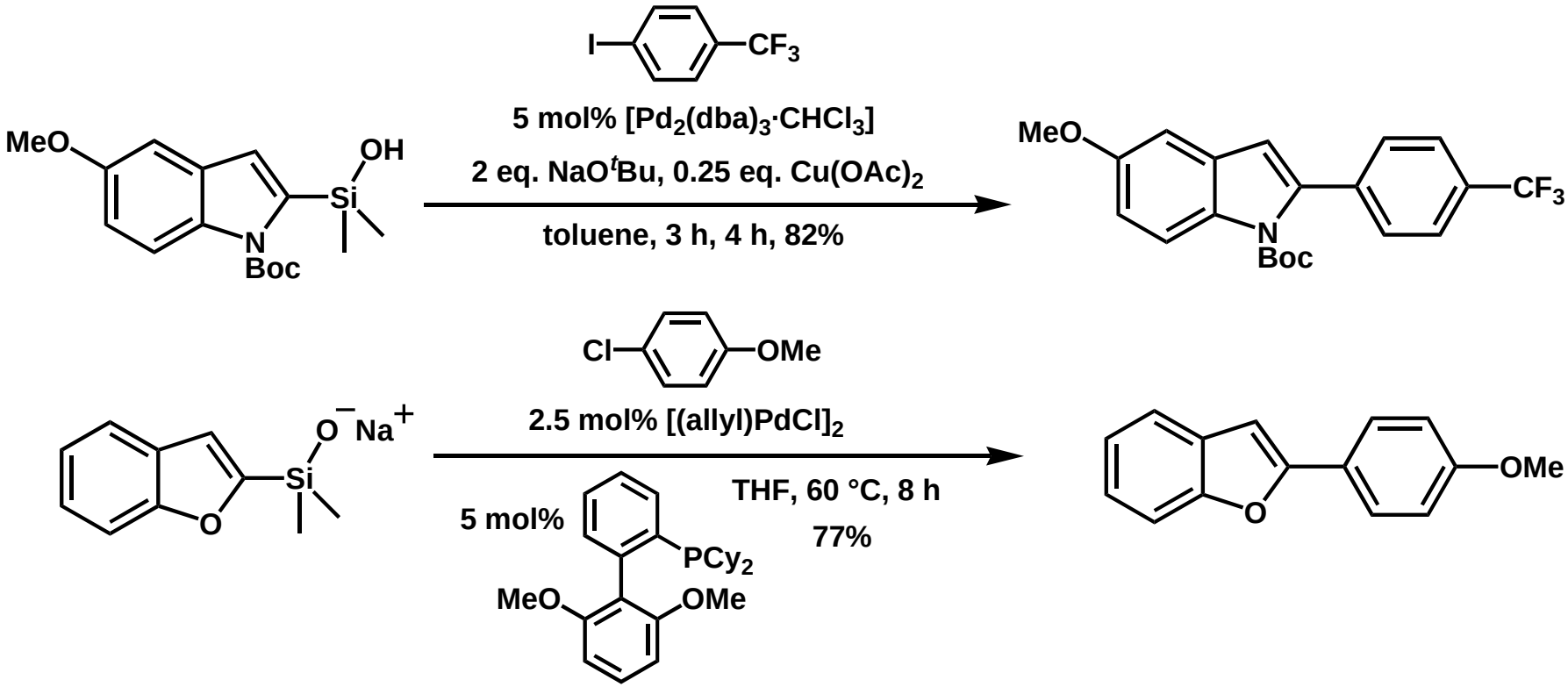


R = 2-thienyl or benzyl

Lopez has recently applied this cross-coupling strategy to a highly stereoselective synthesis of retinoids.[6]

Biaryl Synthesis

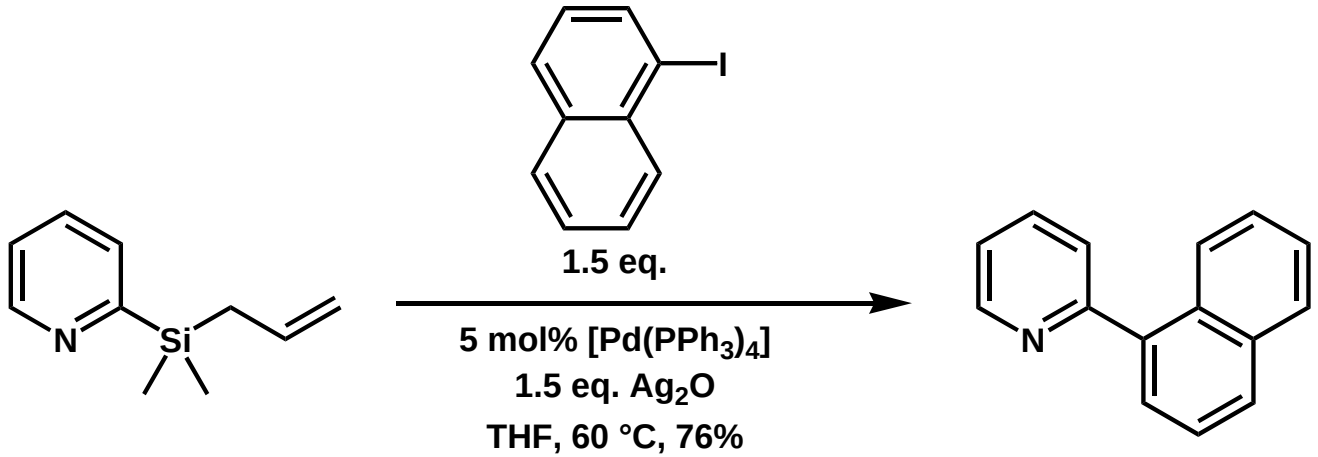
Hiyama couplings have been used to prepare biaryls, including, after optimisation, particularly challenging 2-aryl heterocycles:[7]



These couplings require careful optimisation of the reaction conditions. Choice of protecting group on the indole nitrogen, pre-forming the sodium silanolate prior to reaction, judicious choice of Pd catalyst and ligand, and in some cases the inclusion of a copper salt all need to be considered.[7]

All-Carbon Substituted Organosilanes for Hiyama Couplings

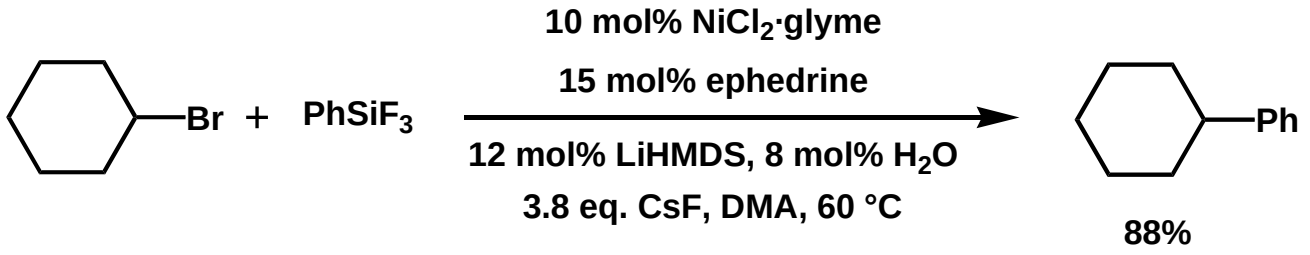
Although silanols, fluorosilanes and alkoxysilanes are the most commonly employed cross-coupling agents for Hiyama couplings, a range of latent silane coupling partners, which generate the reactive coupling agent *in situ* can also be used. These include, 2-pyridyl-, 2-thienyl, benzyl and allylsilanes:[8]



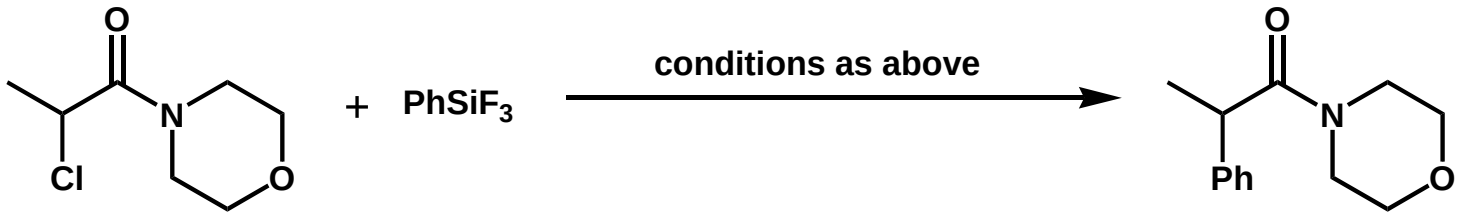
Yoshida has previously shown that 2-pyridylsilanes are useful alkenyl, alkynyl and benzyl transfer agents; however in this example, in the presence of a Ag(I) salt, the allyldimethylsilyl group functions as a 2-pyridyl transfer agent.[8a]

Ni-Catalysed Hiyama Reactions

Fu recently reported a Ni-catalysed variant of the Hiyama coupling between 2° alkyl halides and aryltrifluorosilanes.[9] The inclusion of norephedrine as a ligand was important for obtaining good yields of product.



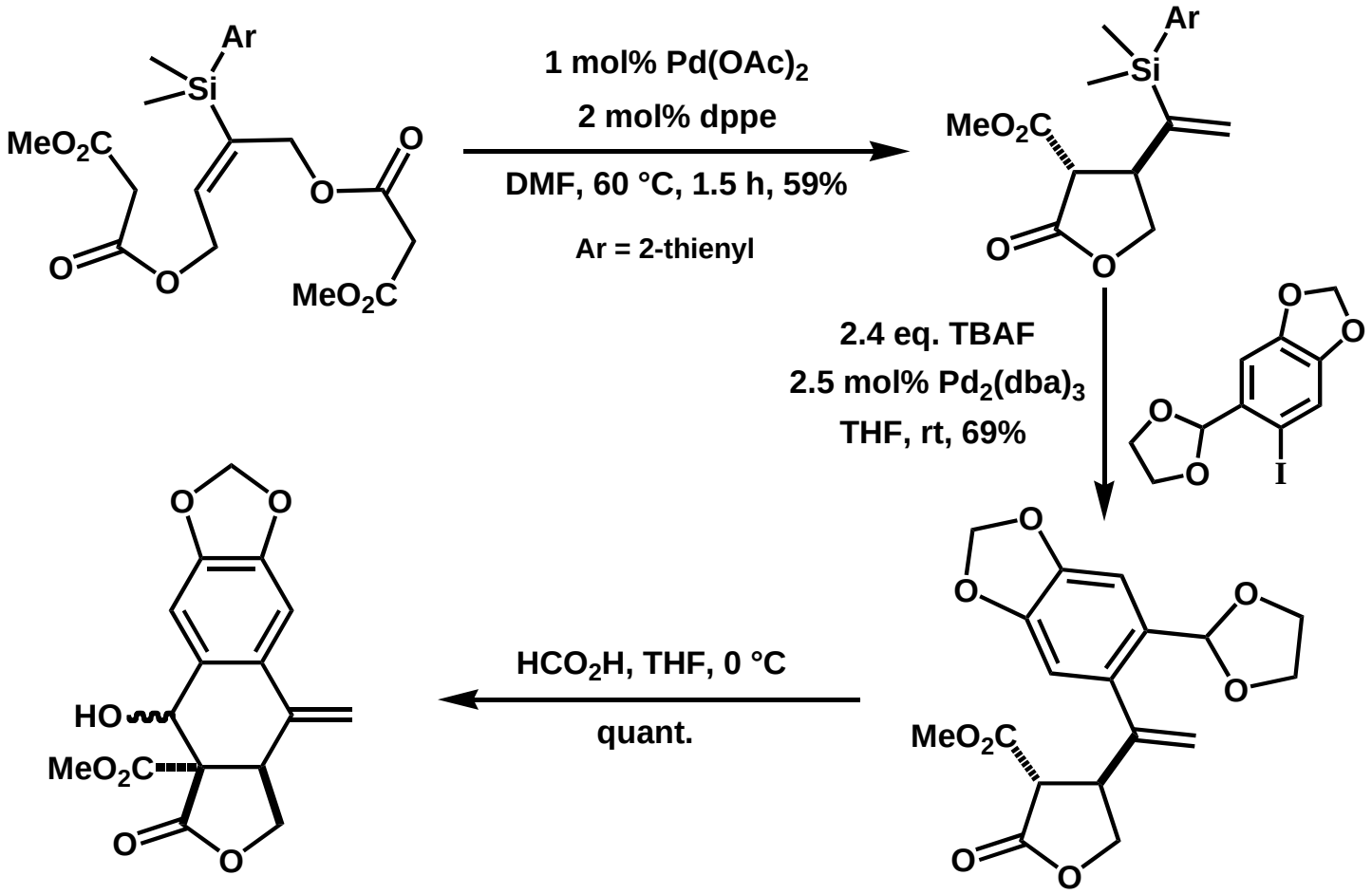
88%



86%

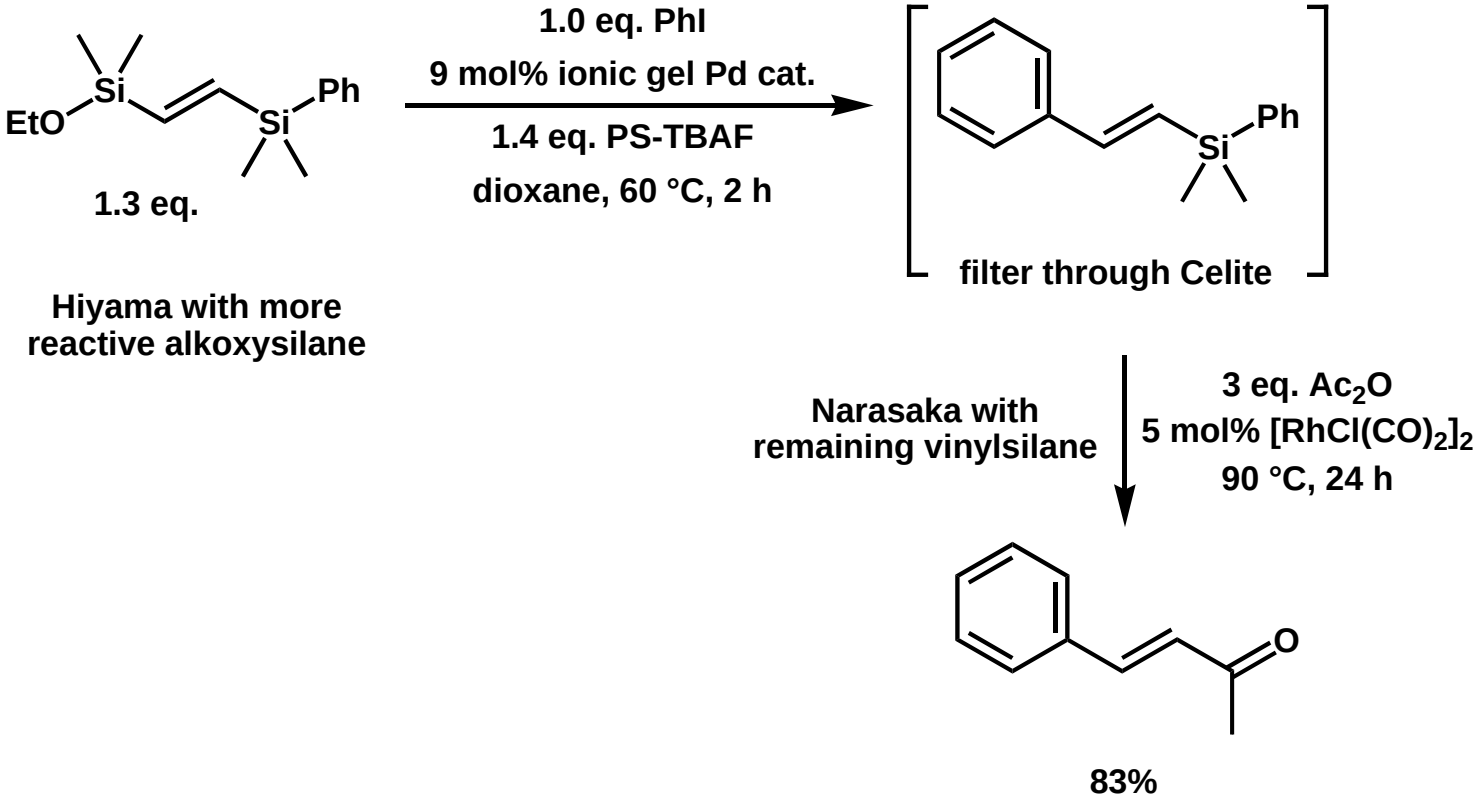
Hiyama Couplings in Pd-Catalysed Sequences

Prestat and Poli used a Pd-catalysed intramolecular allylic alkylation – Hiyama cross-coupling sequence in their synthesis of a series of picropodophyllin analogues:[10]



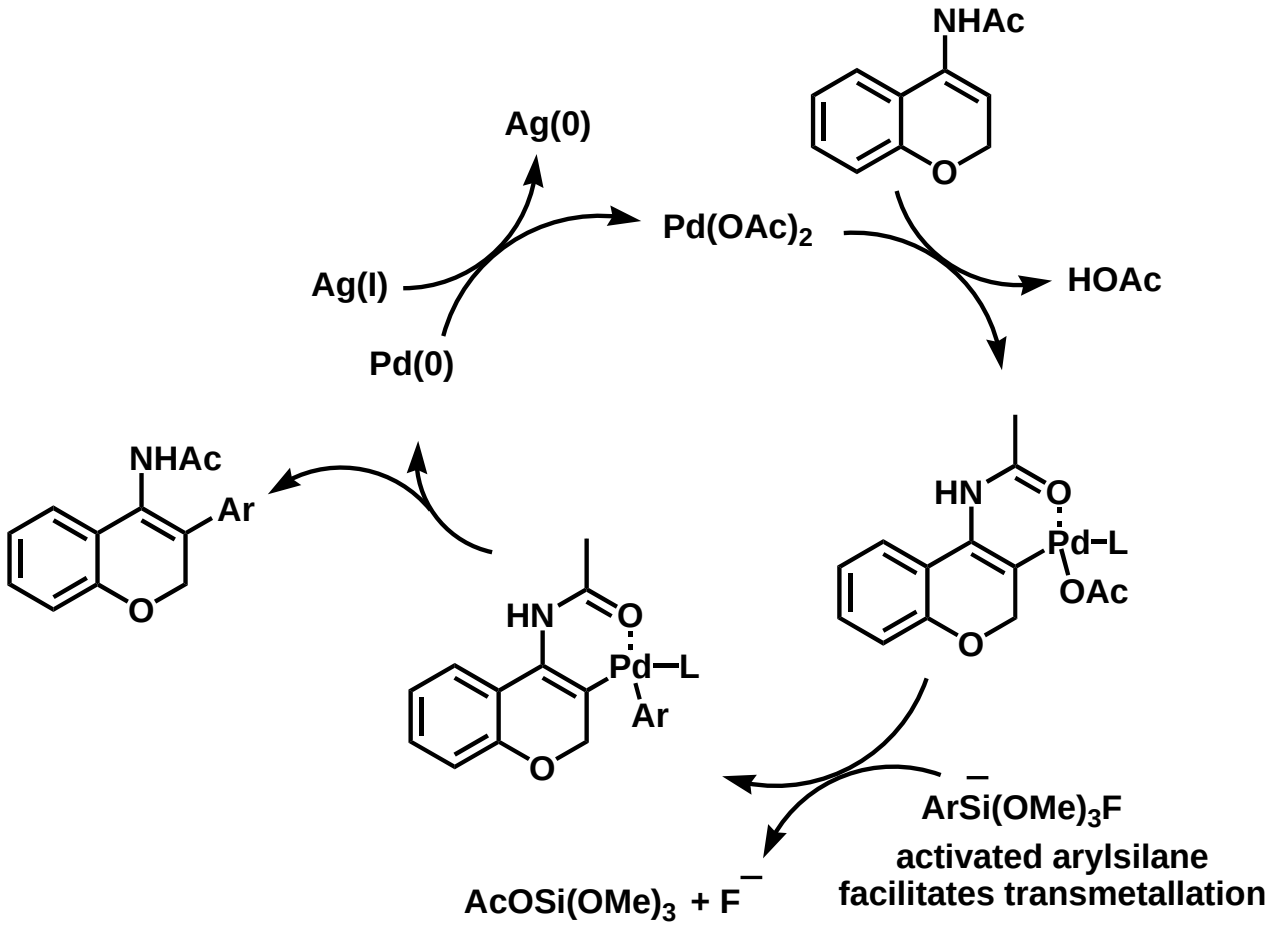
One-Pot Hiyama / Narasaka Coupling

Mioskowski exploited the different reactivity of differentially substituted vinylsilanes in a synthesis of stereodefined enones:[11,12]



Direct Arylation of Cyclic Enamides

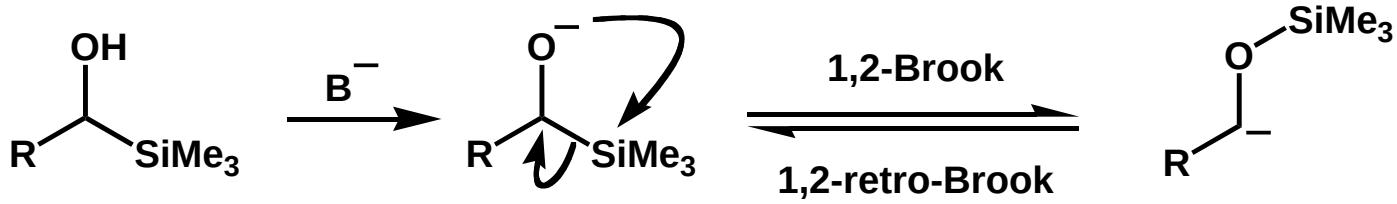
In contrast to standard Hiyama couplings, which employ halide coupling partners, this example uses C–H activation to generate the vinyl-Pd transmetallation precursor. The AgF additive is proposed to play a dual role, activating the alkoxysilane towards transmetallation, and as an oxidant in regenerating Pd(II) at the end of the catalytic cycle.[13]



Brook (and related) Chemistry

Brook Rearrangement

Si–F and Si–O bonds are notably stronger than Si–H and Si–C bonds. This difference in bond strength can be a strong driving force for chemical reactions, and has been particularly widely exploited to generate carbanions from alkoxides through the so-called Brook rearrangement:[1]

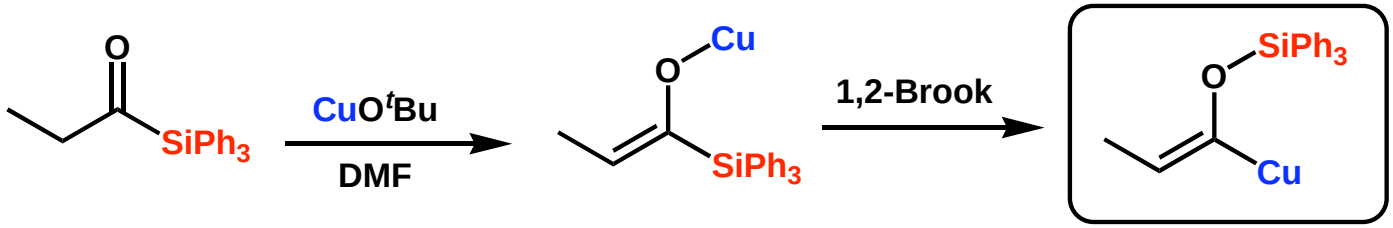


The rearrangement is reversible. The position of the equilibrium depends on a number of factors including: i) solvent polarity, ii) anion-stabilising ability of the carbon substituents, and iii) strength of the oxygen-metal bond.

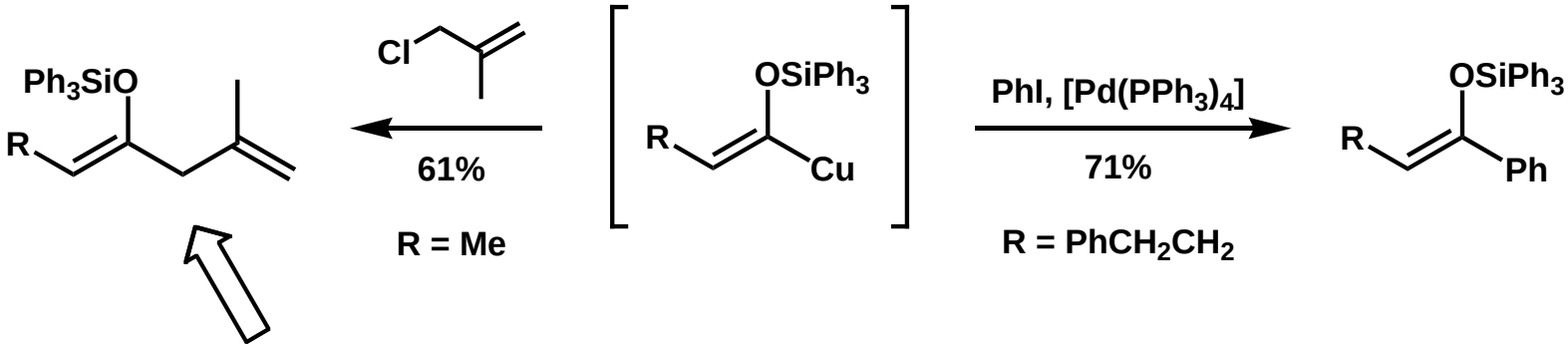
Whilst the original report was of a [1,2]-rearrangement, the reaction is rather general. A range of [1,n]-silyl group to oxygen migrations have been reported and where investigated, been shown to proceed *via* intramolecular silyl group transfer.

Novel Silyl Enol Ether Synthesis

Treatment of acyl silanes with a copper alkoxide affords the corresponding copper enolate, which undergoes a 1,2-Brook rearrangement to afford the corresponding alkenylcopper species with high stereoselectivity. The use of DMF as solvent and a copper rather than alkali metal alkoxide is important to ensure smooth 1,2-silyl migration.[2,3]



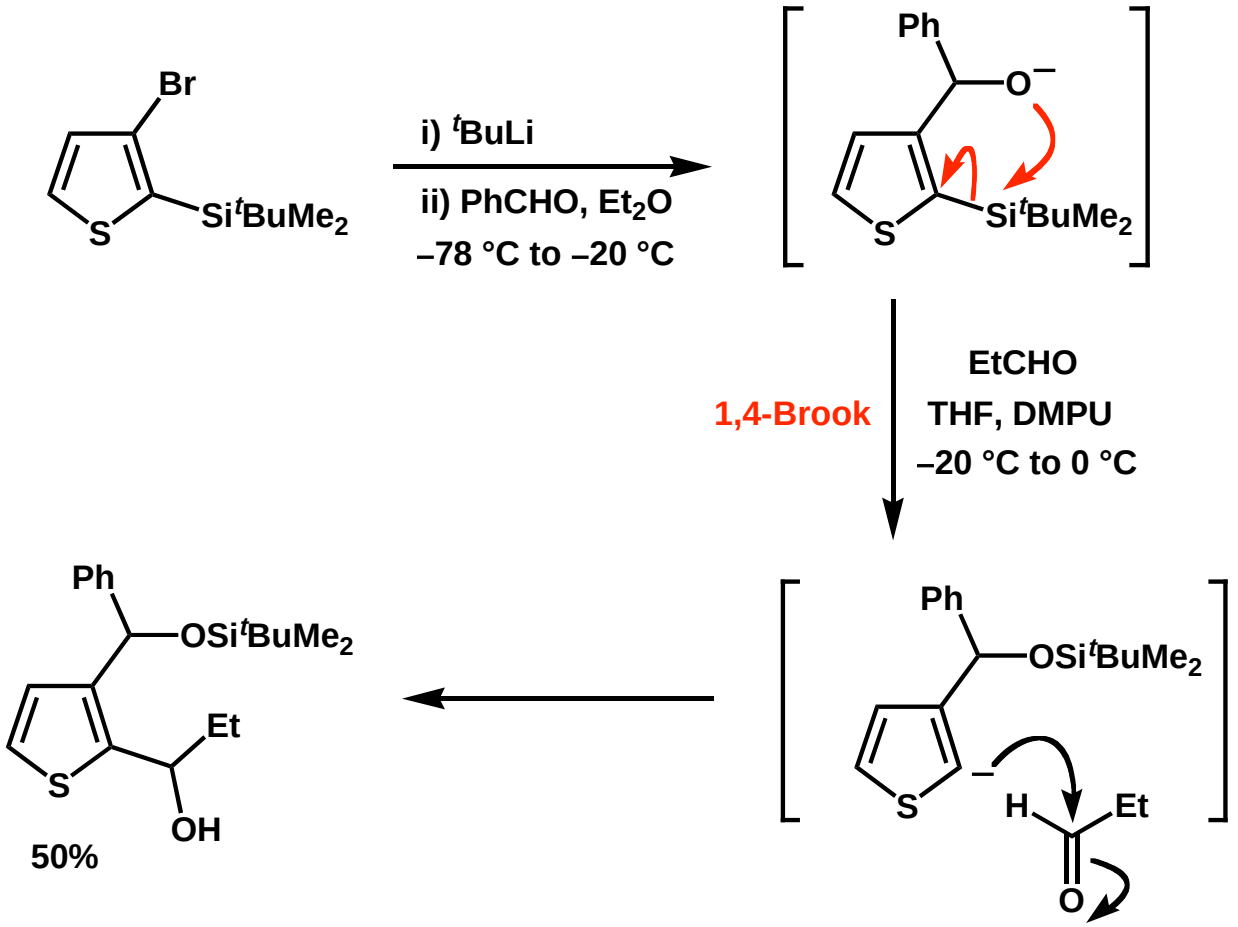
The generated alkenyl copper species is ripe for further elaboration:



regioselective synthesis from ketone using standard deprotonation chemistry would be difficult

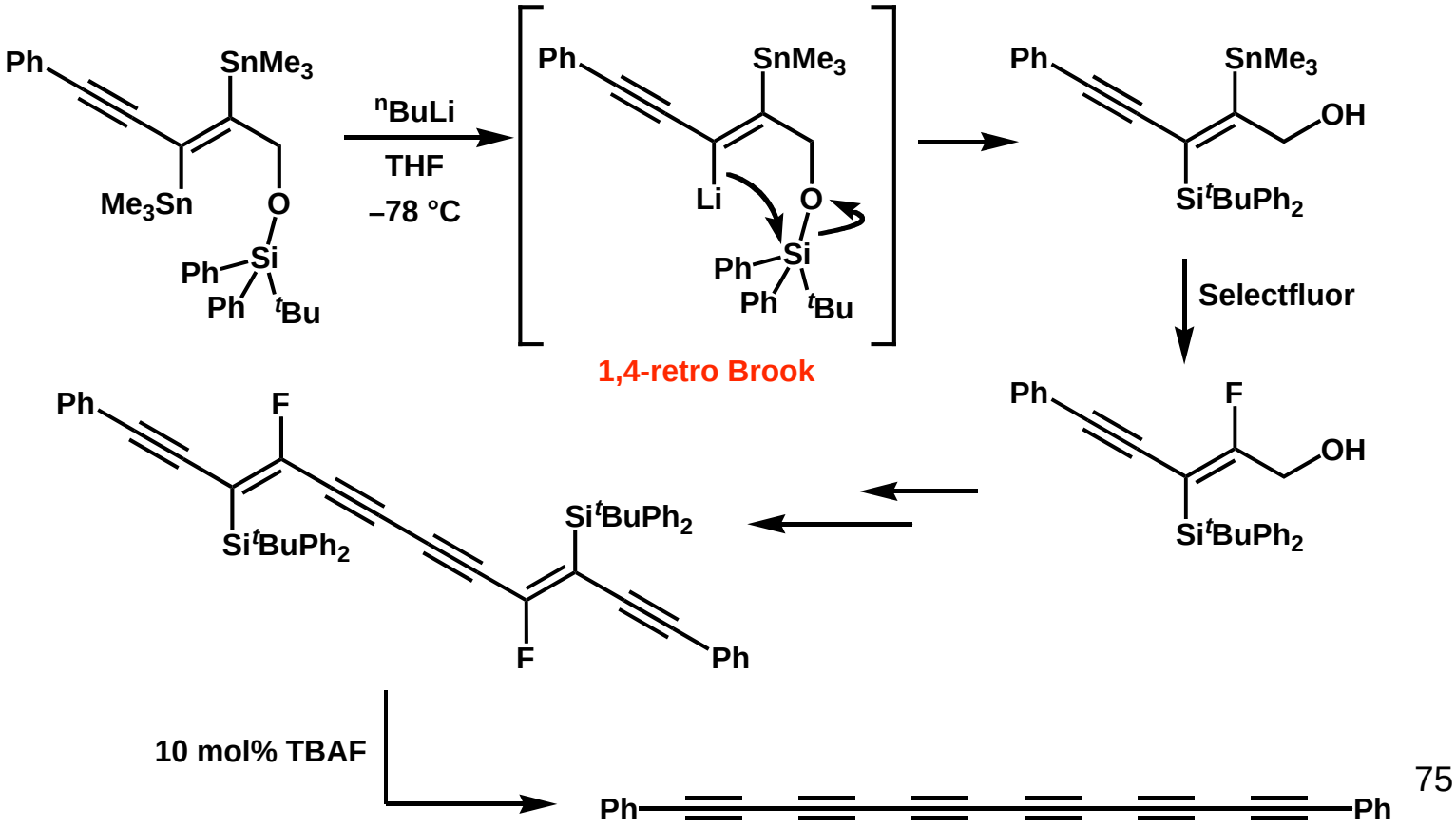
One-Pot Synthesis of 2,3-Disubstituted Thiophenes

In this example from Xian, the inclusion of DMPU as a co-solvent was important to ensure a smooth 1,4-Brook rearrangement:[4,5]



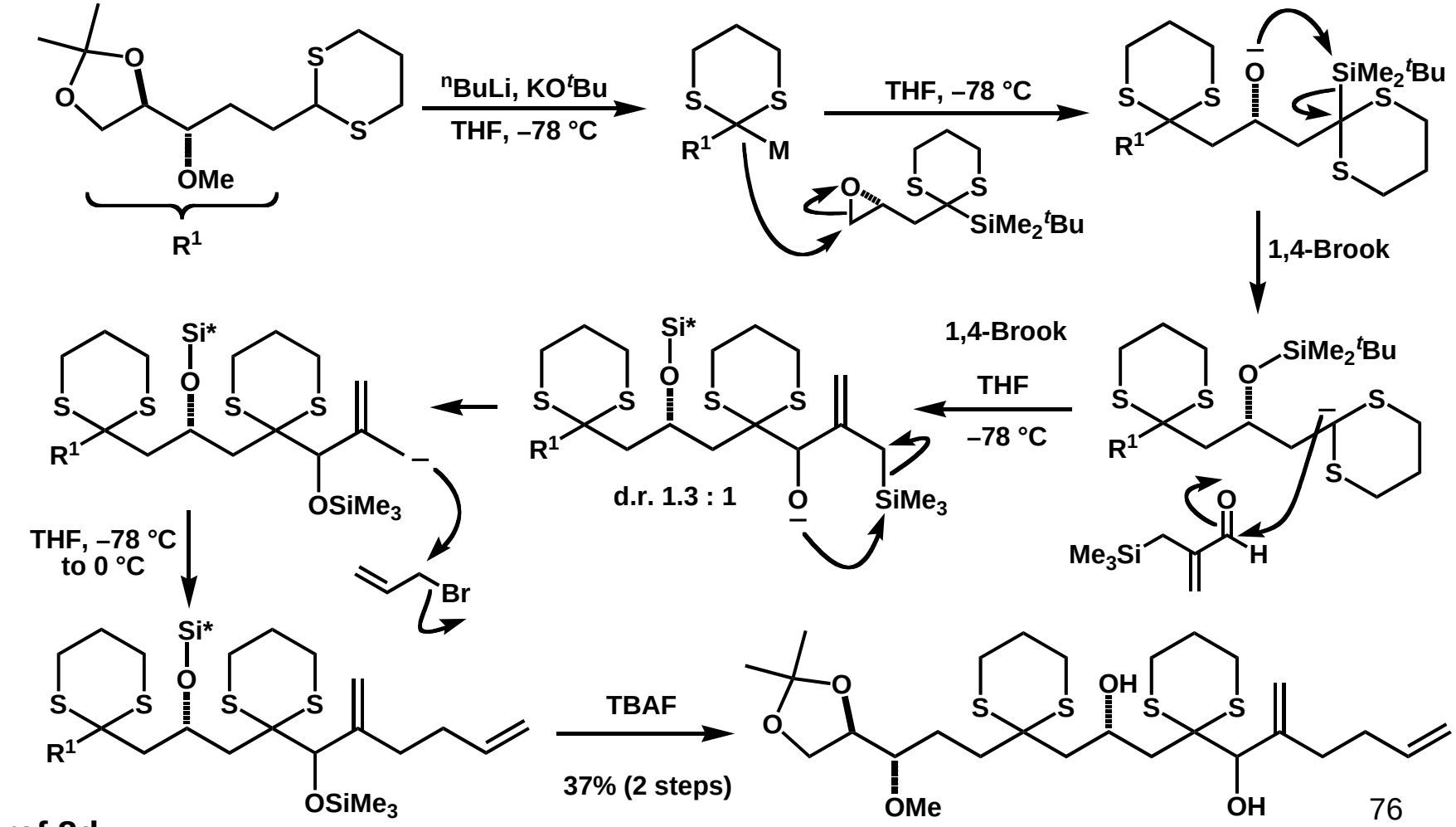
Retro Brook Rearrangements

When used in its reverse sense, the retro-Brook rearrangement provides a useful method for preparing organosilanes. Cox used a 1,4-retro-Brook rearrangement to generate stereodefined tetrasubstituted β-halovinylsilanes, which serve as masked alkynes for oligoyne assembly. *Intra*molecular silyl group transfer allowed the incorporation of bulky silyl groups, which would be difficult to introduce by standard intermolecular trapping methods.[6,7]



Anion Relay Chemistry

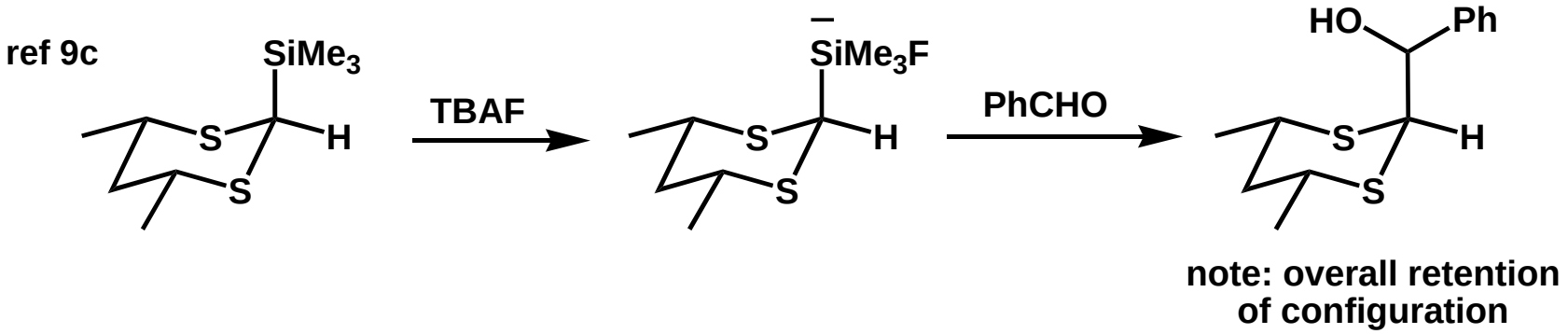
Organosilanes and Brook-type rearrangements have been employed to great effect in multicomponent synthesis. Recent work from Smith is particularly noteworthy:[8]



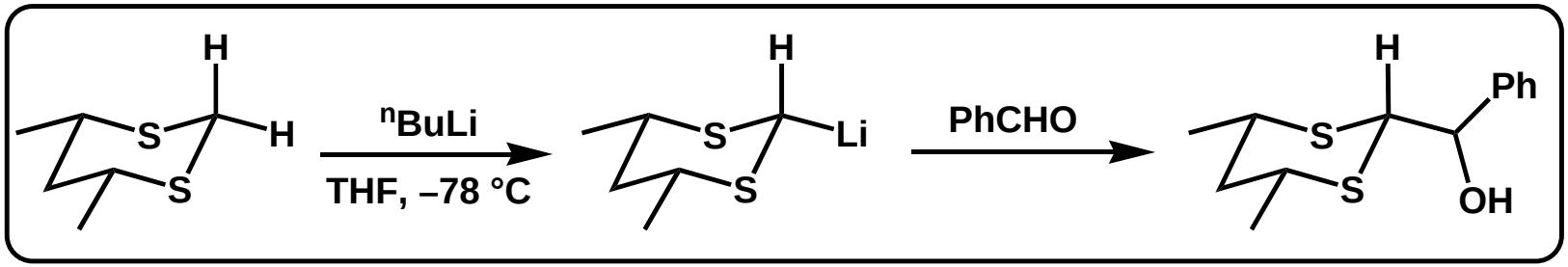
ref 8d

Fluoride Activation of Latent Carbanions

Other carbanionic nucleophiles can be unmasked from organosilanes, often providing an alternative to using a strong base on the corresponding protonated precursor.[9] Silylated 1,3-dithianes provide a nice illustration:[8,9]



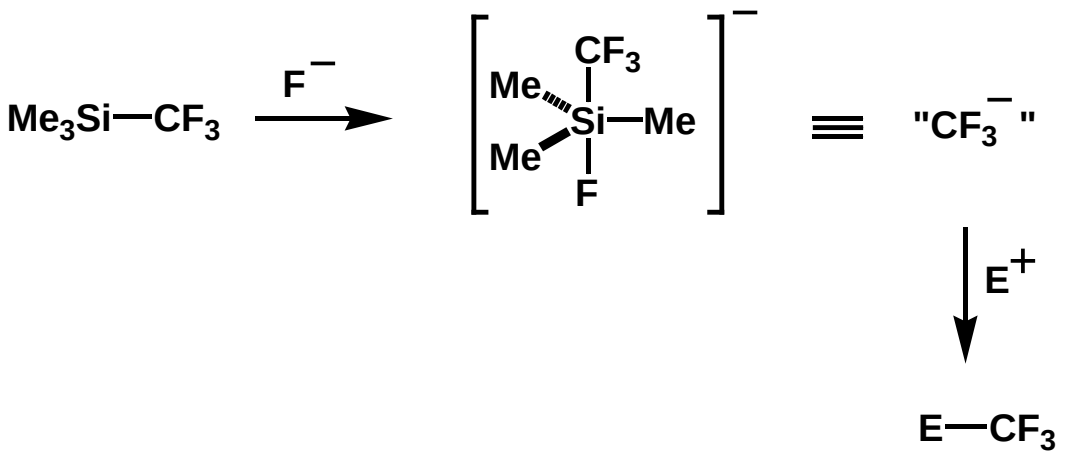
cf:



Fluoride-Mediated Carbanion Generation

Trifluoromethylation:

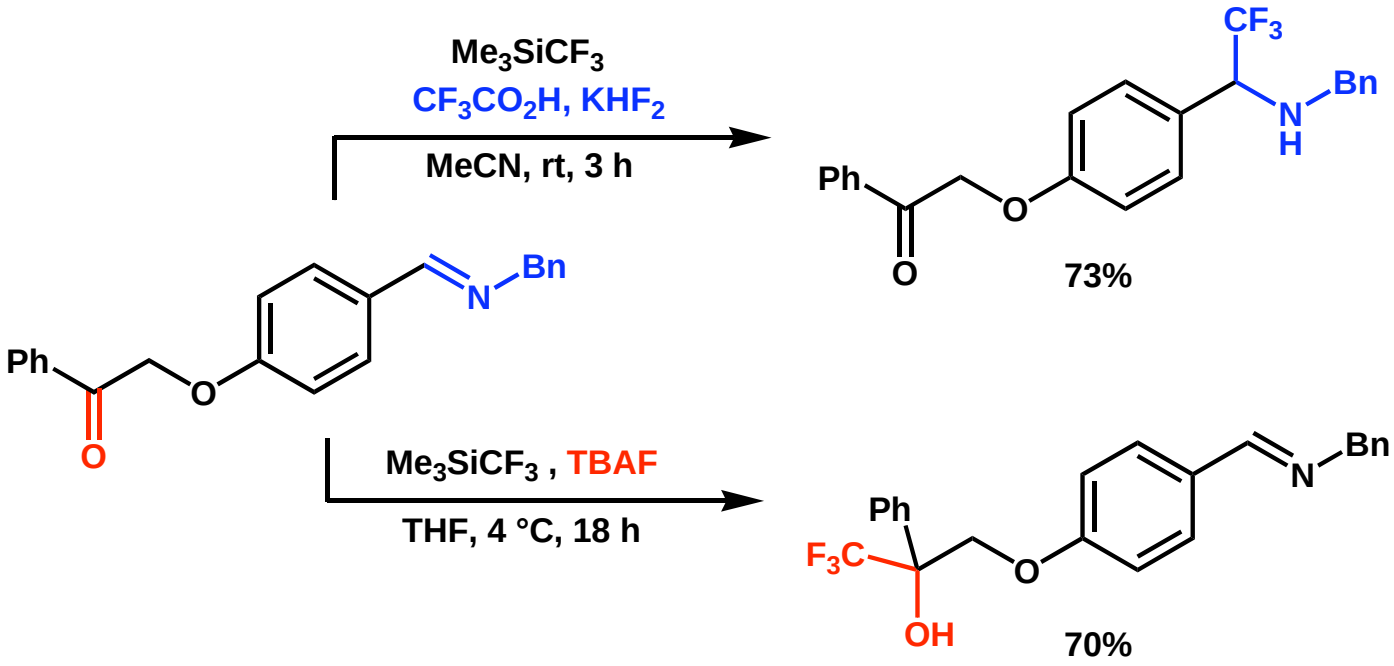
The formation of a thermodynamically stable Si–F bond allows a range of organosilanes to be used as latent carbanions. For example, the Ruppert-Prakash reagent Me_3SiCF_3 is a useful source of the CF_3^- anion.[10]



Trifluoromethylation of Imines

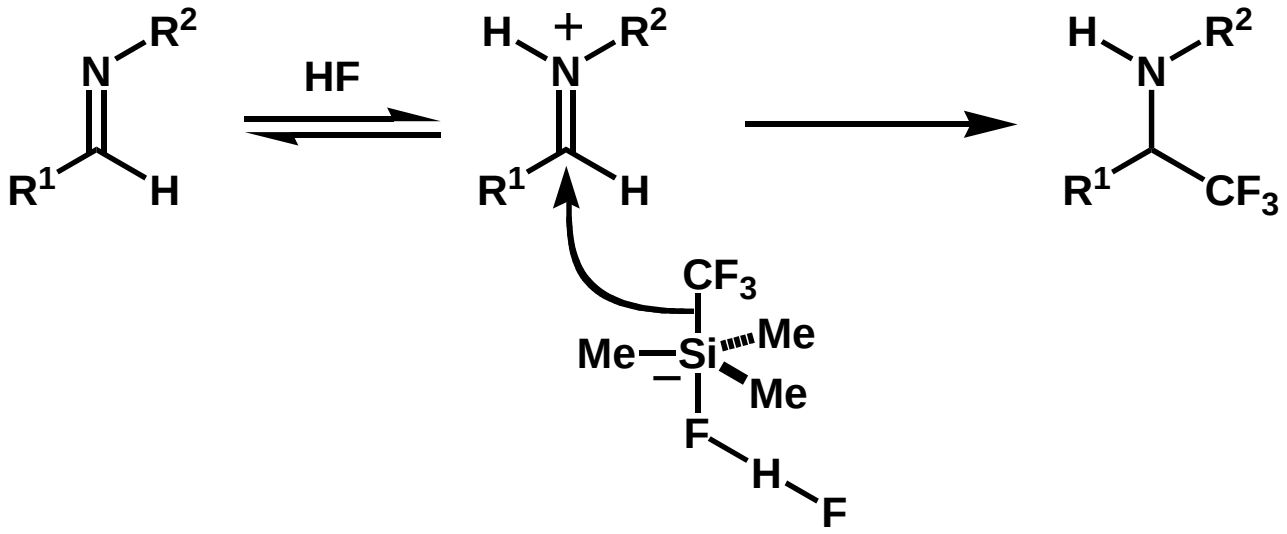
Whilst the fluoride-mediated trifluoromethylation of carbonyl compounds is widespread, the corresponding reaction with imines has received less attention.[10]

Activated imines bearing electron-withdrawing substituents react readily with Me_3SiCF_3 in the presence of a fluoride source such as TBAF. Tartakovsky recently showed that trifluoromethylation of simple imines proceeds under *acidic* conditions under optimised conditions.[11]



Trifluoromethylation of Imines

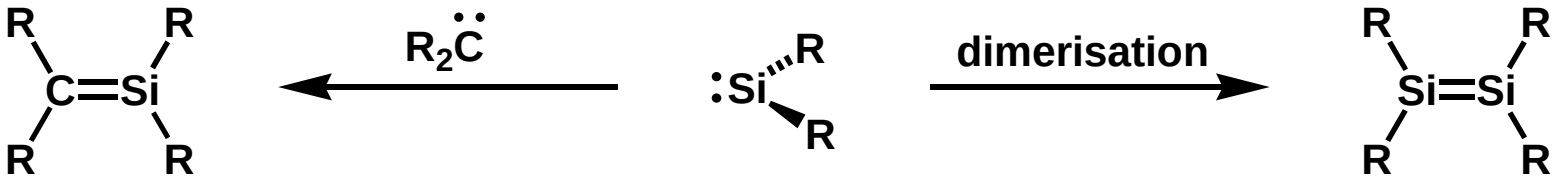
The authors proposed the reaction was mediated by HF, generated *in situ* from KHF_2 and the Brønsted acid additive. CF_3^- anion transfer proceeds *via* a hypervalent silyl species, rather than the free CF_3^- anion, which would be quenched under the acidic reaction conditions.



Low-Coordinate Silicon Compounds

Silylenes, Silenes and Related Species

Since Silicon lies immediately below Carbon in the Periodic Table, much effort has focused on preparing the Silicon analogues of carbenes, olefins and related unsaturated species.[1]



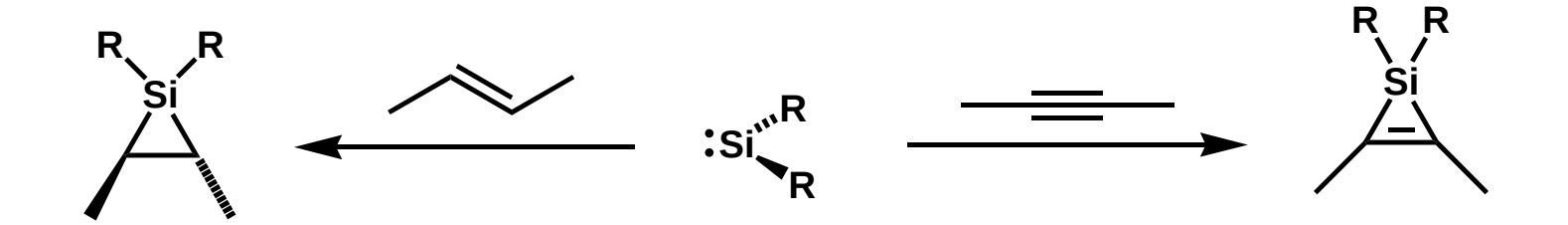
silene **silylene** **disilene**

Silenes, disilenes and silylenes and related low-coordinate Silicon species tend to be highly reactive; however this instability can be tempered by using sterically very bulky substituents and donor groups. Metal coordination offers another important stabilisation strategy.

Silylenes

Silylenes are the Silicon analogues of carbenes. They invariably possess *singlet* ground states and as a consequence of the vacant orbital on the Silicon, are highly electrophilic in character.

In analogy with singlet carbenes, the chemistry of silylenes is typified by addition to π bonds:

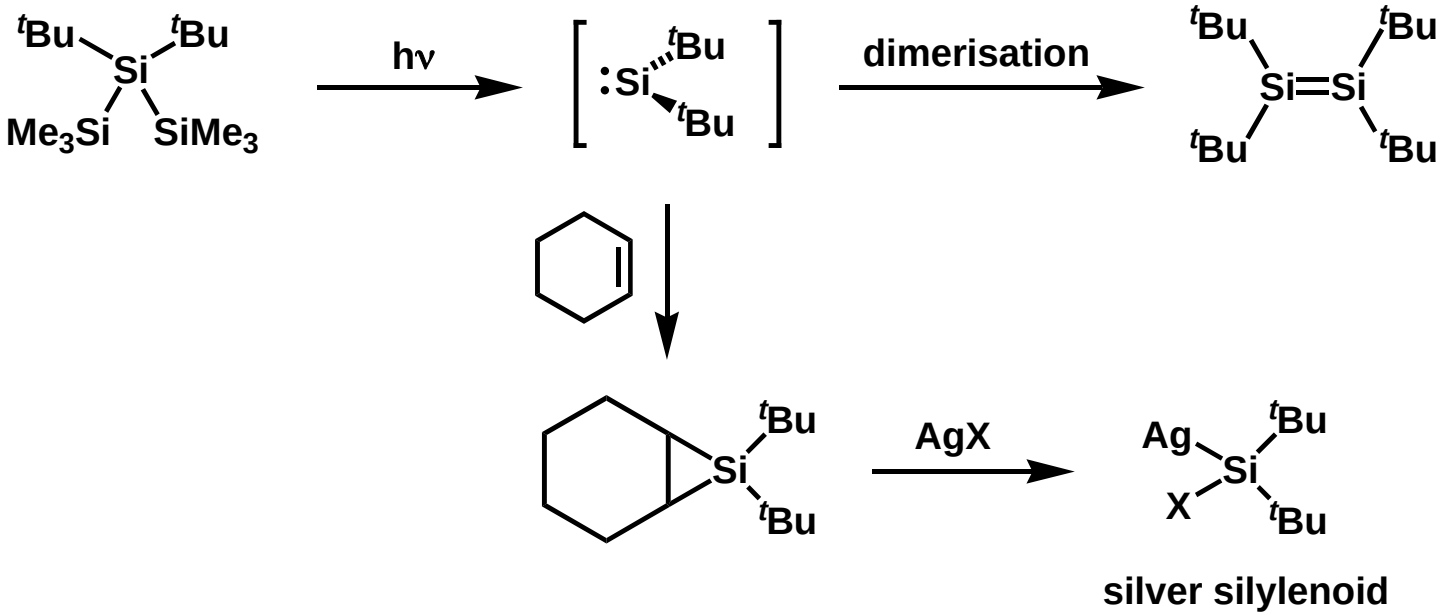


silacyclopropane **silacyclopropene**

Insertion reactions into σ bonds (*e.g.* O–H, Si–H, Si–O) are also common. In these cases, reaction often proceeds *via* a nucleophilic addition-rearrangement mechanism.

Silylene Preparation

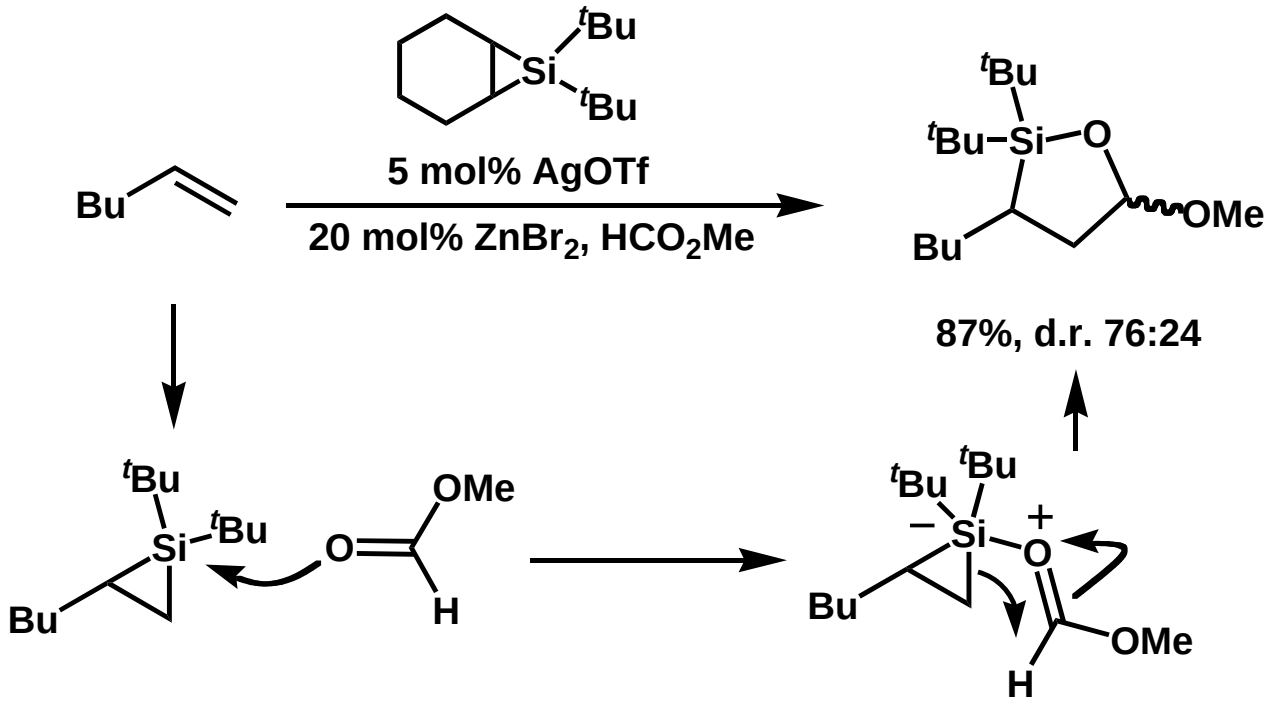
Silylenes have commonly been accessed by thermolysis- or photolysis-induced fragmentation or rearrangement processes. They dimerise readily to the corresponding disilene; however in the presence of a suitable trapping agent, such as cyclohexene, the silylene can react to afford the corresponding silacyclopropane. With bulky *tert*-butyl substituents on the silicon, this species exhibits sufficient stability for its application as a silylene transfer agent under metal catalysis.[2]



Metal-Catalysed Silylene Transfer

In the presence of metal salts, commonly Ag(I) salts, silacyclopropanes react to afford a metal silylenoid species, (*cf.* metal carbenoids formed from diazo compounds and Rh or Cu species). The resulting silver silylenoid displays a rich chemistry that has been investigated in significant detail by Woerpel.[2-4]

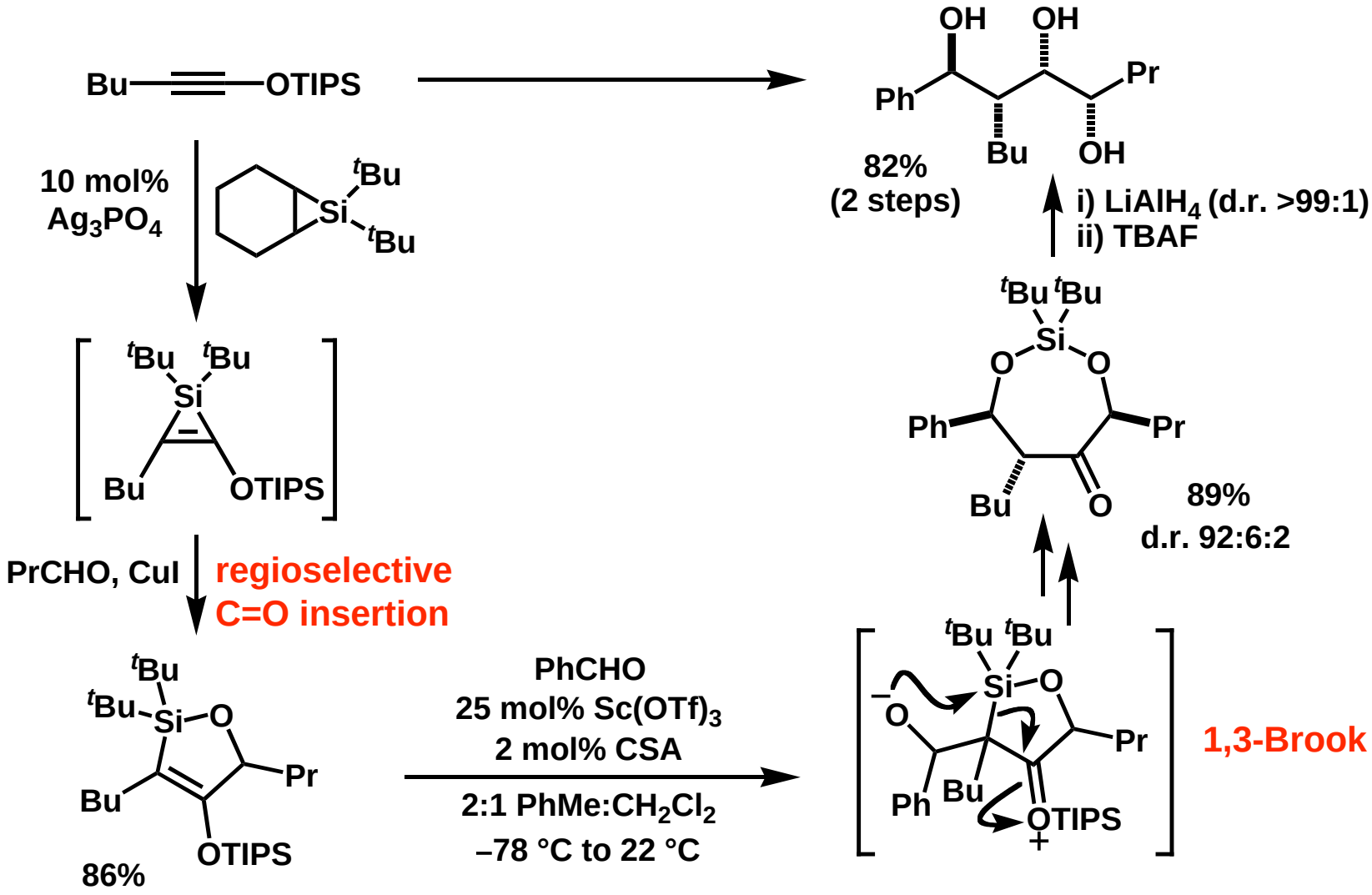
ref 3



strain-induced Lewis acidity

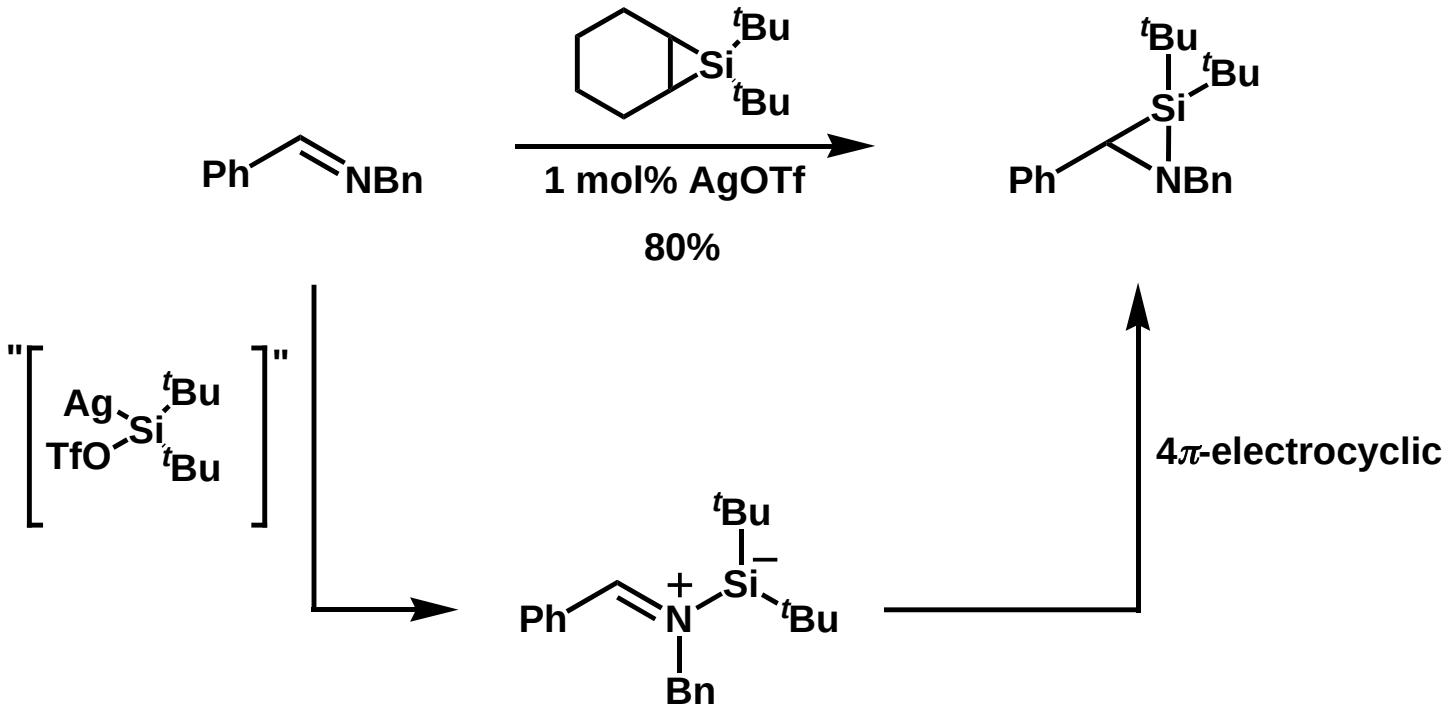
regioselective insertion into C=O group

Application to 1,2,4-Triol Synthesis[5,6]



Metal-Catalysed Silylene Transfer to Imines

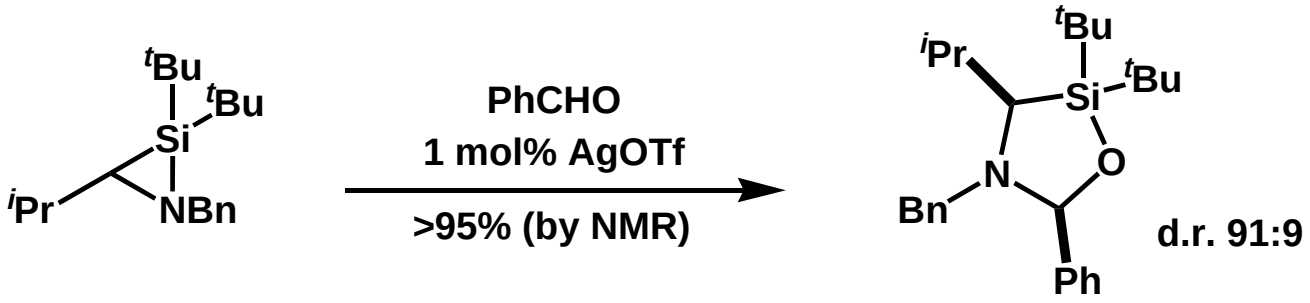
Silylene transfer to imines is also possible.[7] The mechanism of silaaziridine formation likely proceeds *via* nucleophilic addition of the imine nitrogen to the electrophilic silylenoid to provide an ylide which undergoes a 4π-electrocyclisation to provide the strained product.



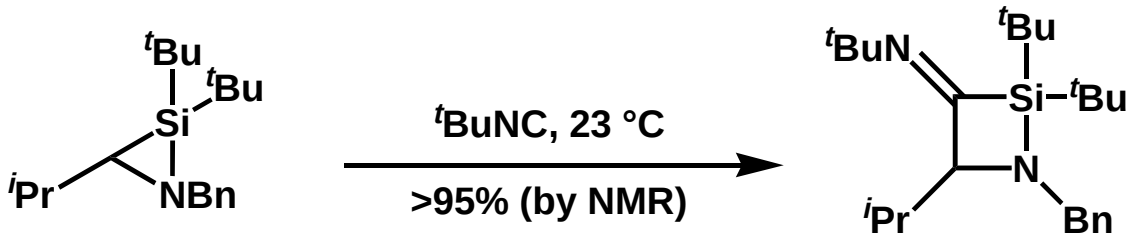
Silaaziridines

Silaaziridines are sensitive to air and moisture; they can be isolated (with care) by distillation. More commonly, they are used directly in further transformations.

They undergo ring-expansion reactions with aldehydes to afford the corresponding *N,O*-acetal resulting from insertion into the more ionic Si–N bond.[7]

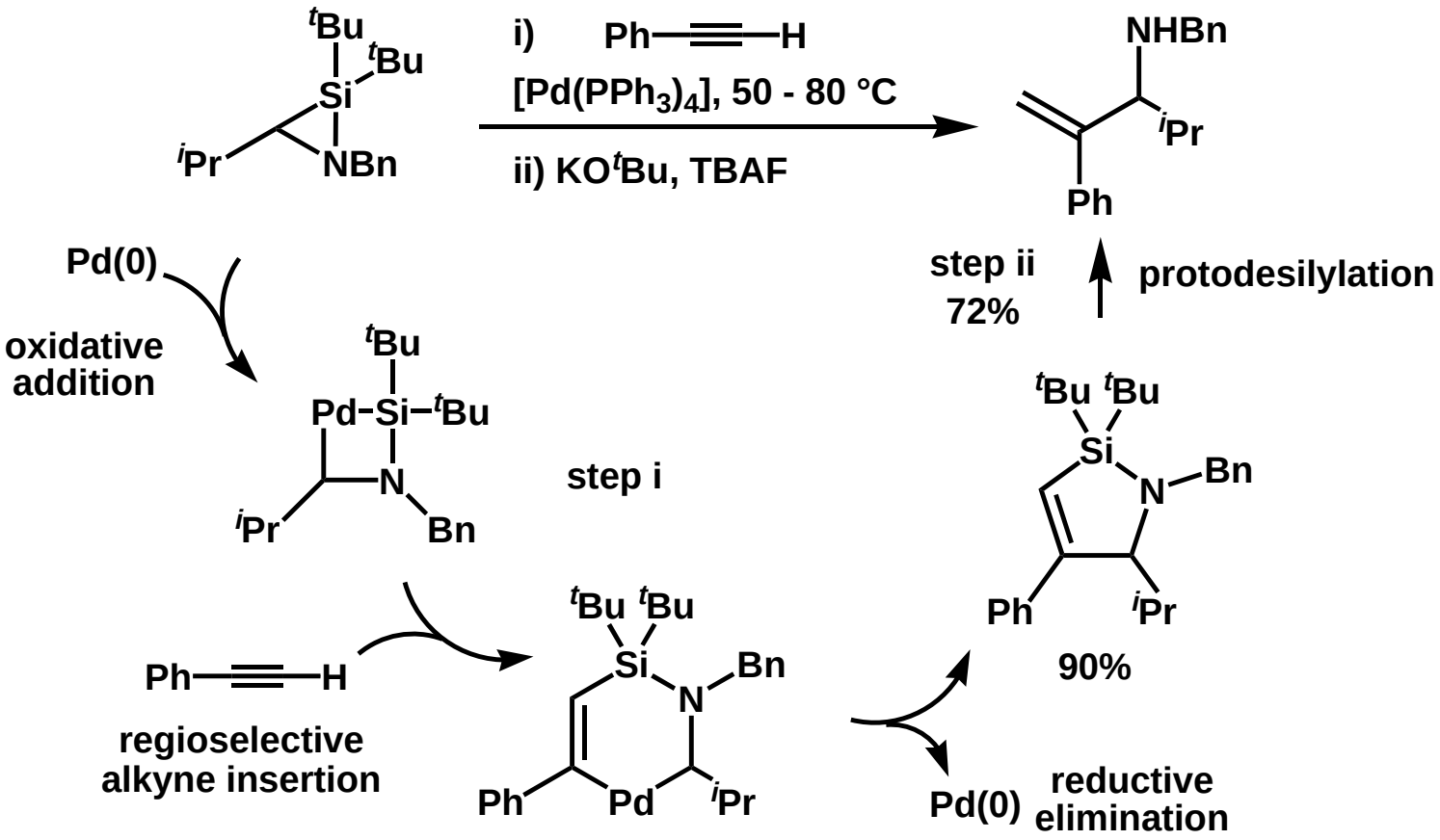


In contrast, reaction with *tert*-butylisocyanide (a softer E^+) proceeds *via* insertion into the more covalent Si–C bond.[7]



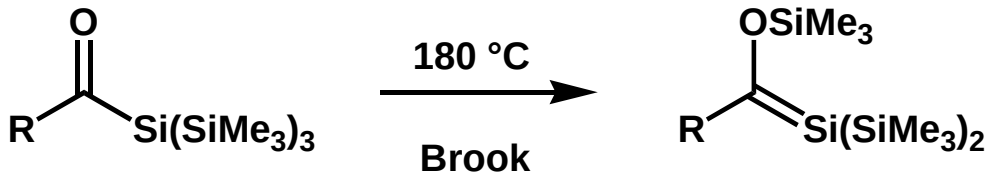
Silaaziridines

Alkynes undergo regioselective insertion into the Si–C bond under Pd-catalysis to provide an azasilacyclopentene ring-expanded product. Subsequent protodesilylation affords an allylic amine product.[7]

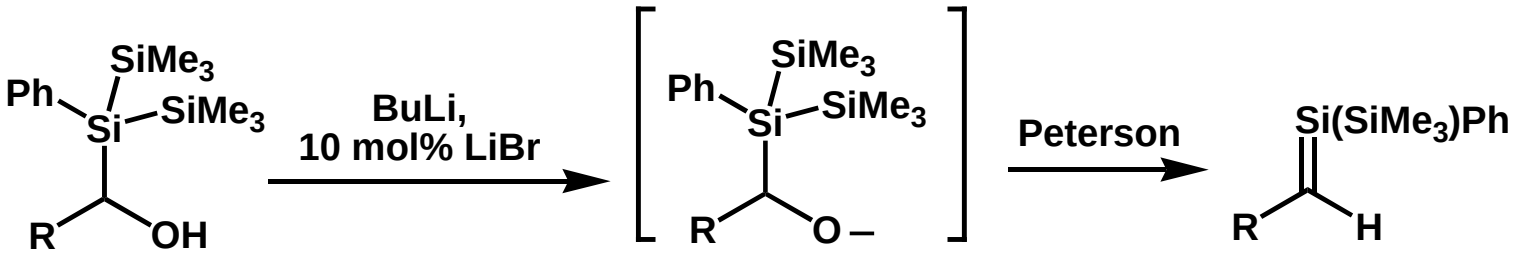


Silenes

Silenes are also reactive species. Traditionally, they have been generated by thermolysis processes:[1]

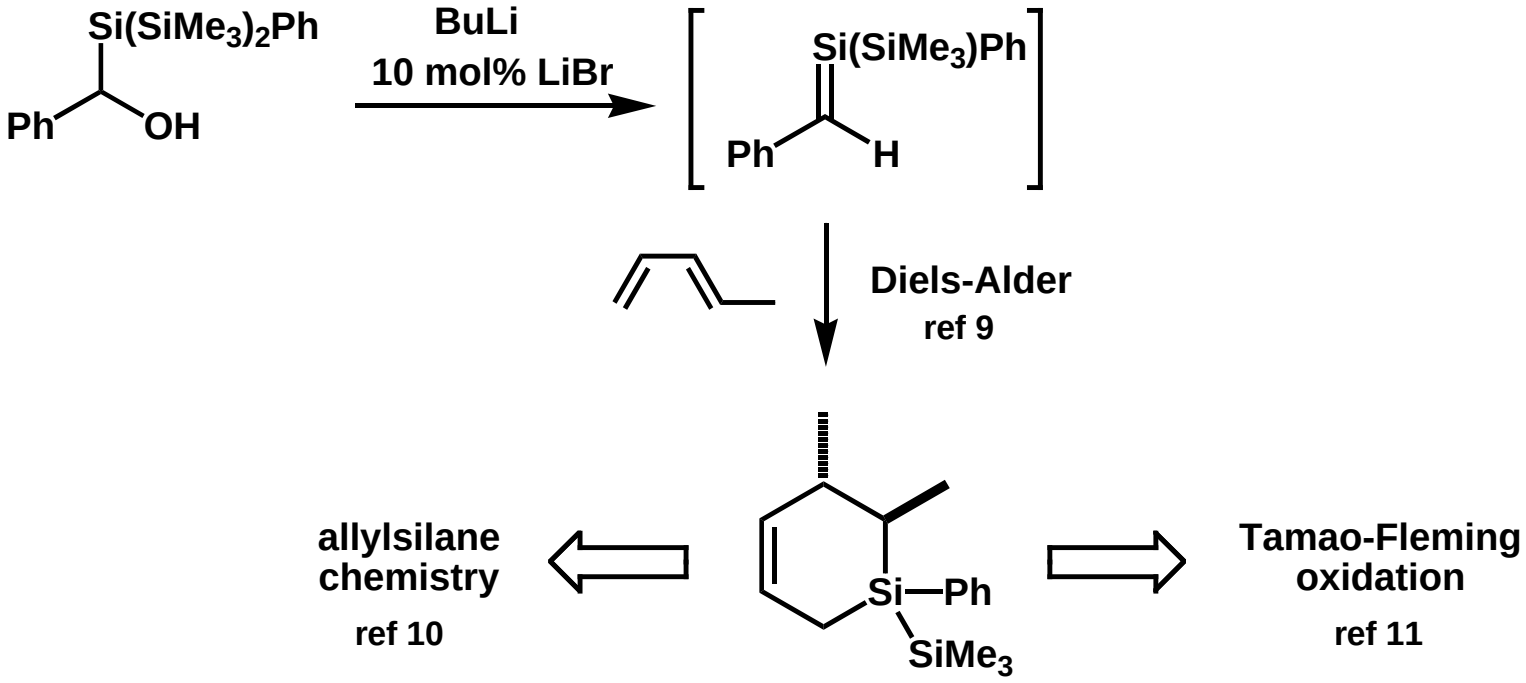


More recently, anionic approaches have allowed silenes to be generated under much milder conditions:[1,8]



Silenes

Silenes are reactive species. For example, they react in a [2+2] cycloaddition fashion with carbonyl compounds, imines, alkenes and alkynes, whilst [4+2] cycloaddition pathways are (usually) observed with dienes and α,β-unsaturated carbonyls.



d.r. 74:20:6

45%

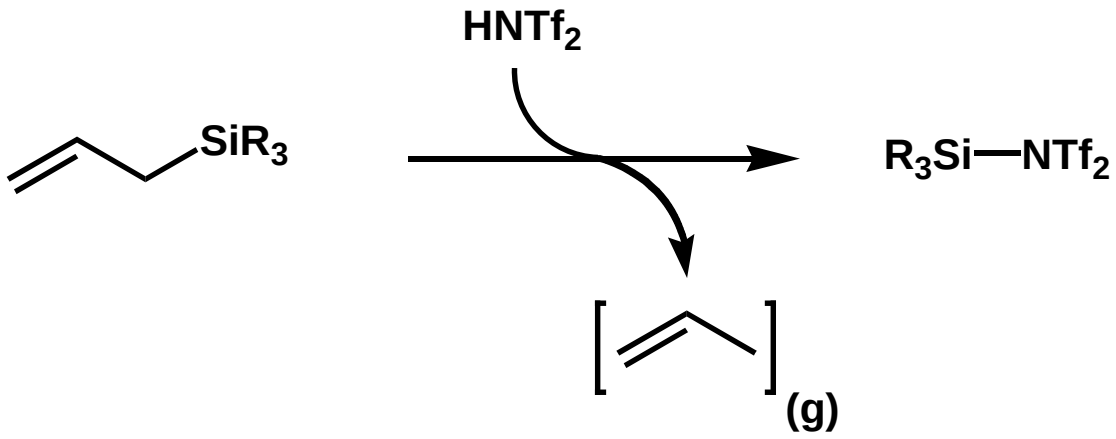
cycloadduct ripe for elaboration

Silicon Lewis Acids

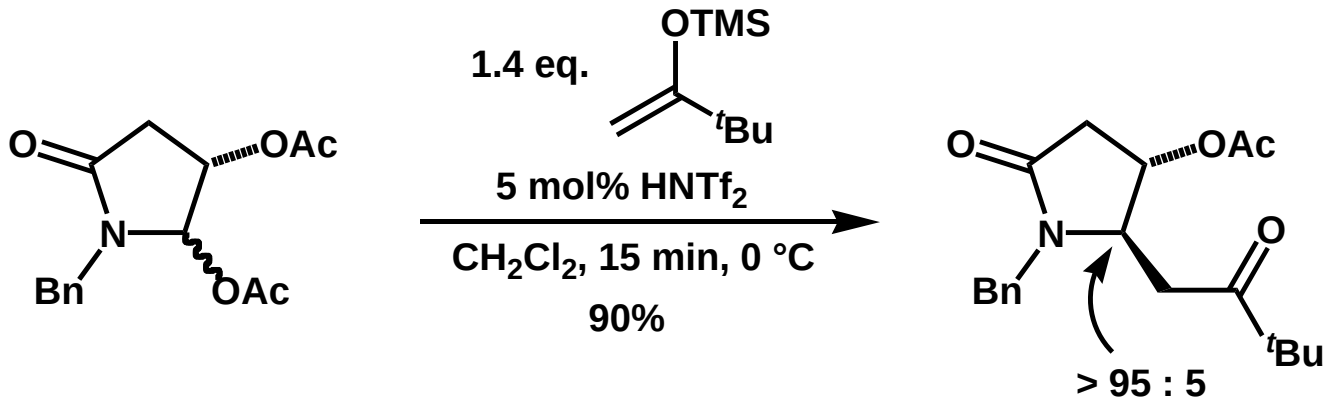
Strong Lewis Acids

TMSOTf, and to a lesser extent TMSCl, are synthetically Lewis acids. Recent variants that exhibit increased Lewis acidity have been introduced. Of these, trialkylsilyl bistrifluoromethanesulfonamides (R_3SiNTf_2), developed by Ghosez[1] and Mikami,[2] are proving particularly useful.

In light of their very high reactivity, R_3SiNTf_2 Lewis acids are most conveniently prepared *in situ* from the corresponding Brønsted acid and an allylsilane or related species:



Application[3]



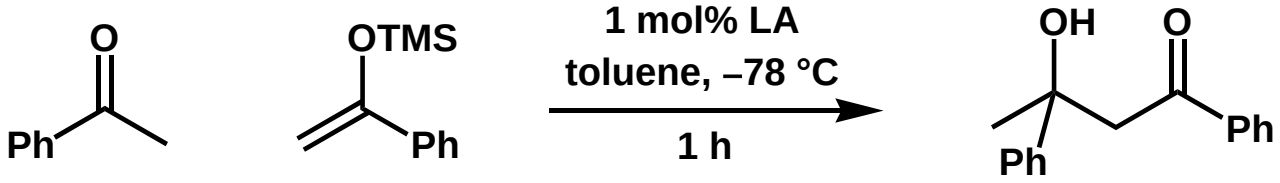
$TMSNTf_2$ is formed *in situ* from the acid $HNTf_2$ and silyl enol ether.

The Lewis acid generates an *N*-acyl iminium species that is trapped in a diastereoselective fashion by the silyl enol ether.

Reaction is 10^8 times faster than the TIPSOTf-catalysed process.

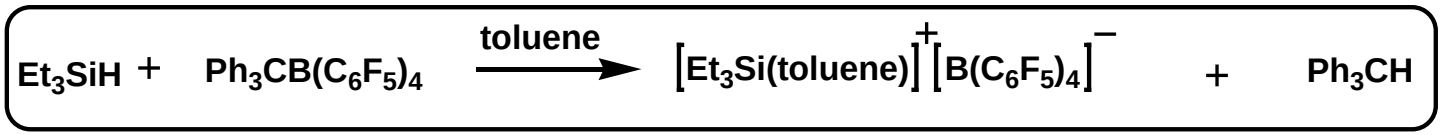
Even Stronger Lewis Acids

The effect of the counteranion on the strength of silyl Lewis acids was studied by Sawamura.[4] Silyl borates of the form $R_3Si(L)BAr_4$, which contain a very weakly coordinating counteranion, were shown to be even more powerful Lewis acids than silyl bistrifluoromethanesulfonamides.



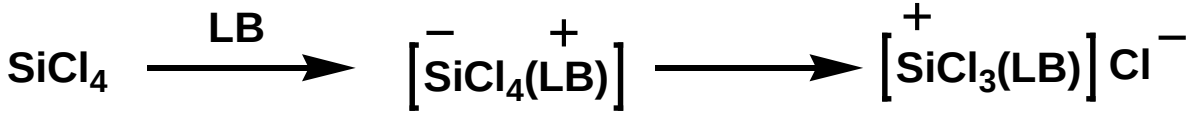
$[Et_3Si(toluene)]^+[B(C_6F_5)_4]^-$	97%
$TMSNTf_2$	12%
TMSOTf	0%

Preparation:

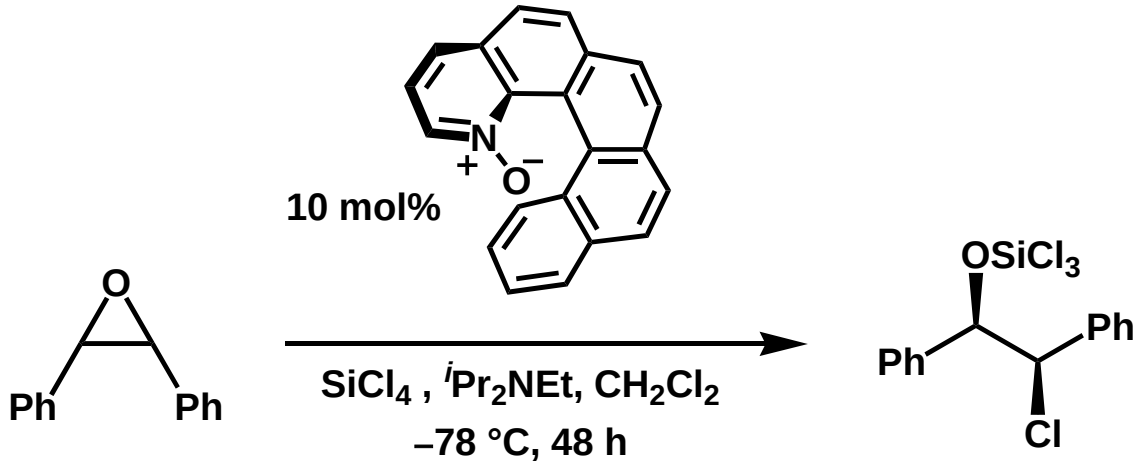


Lewis Base Activation of $SiCl_4$

Whilst $SiCl_4$ is a very weak Lewis acid, we have already seen how Lewis base additives can generate much more reactive Lewis acidic species:



In a nice illustration of this strategy, Takenaka recently used helical chiral pyridine *N*-oxide Lewis bases with $SiCl_4$ in an efficient desymmetrisation of *meso* epoxides:[5]

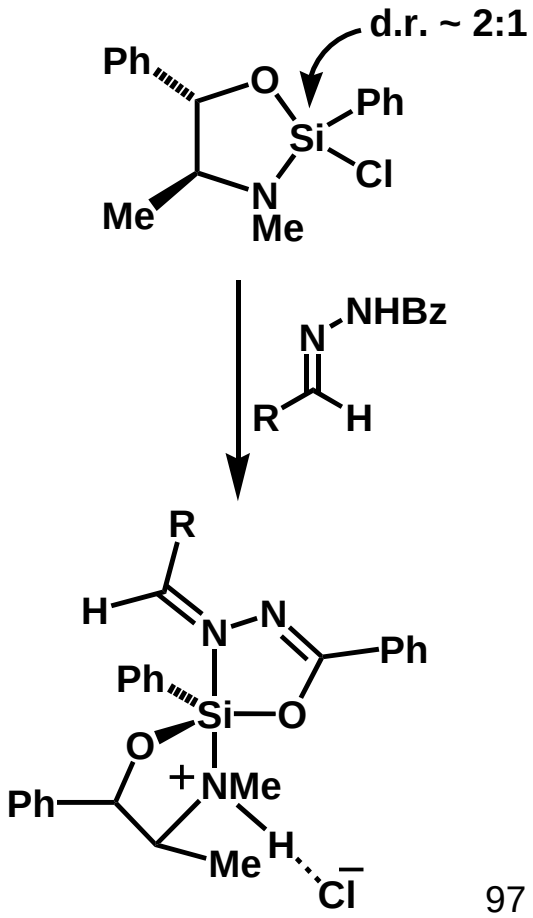


77%, 93% e.e.

Strain-Induced Lewis Acidity

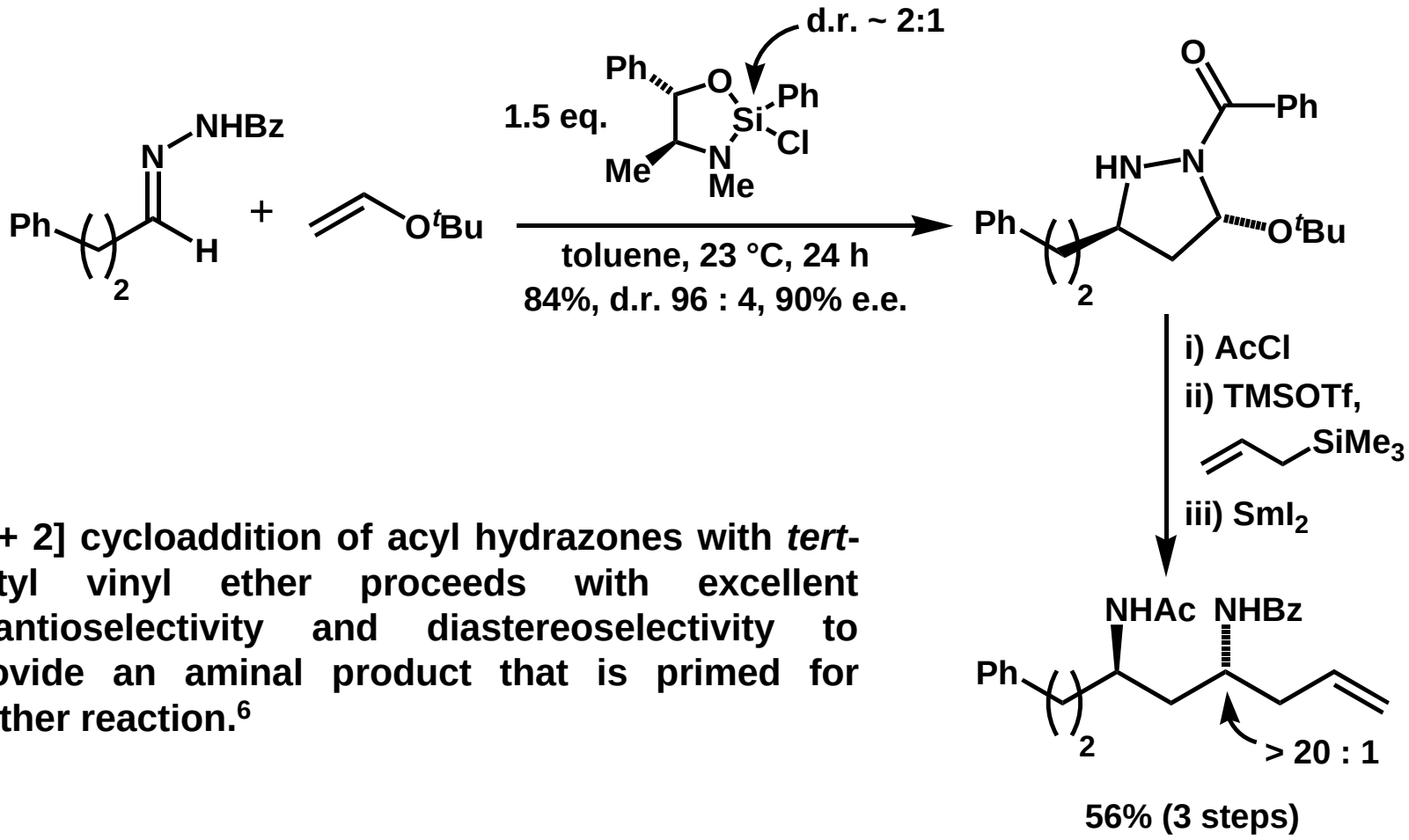
We have already seen how Leighton has used strain-induced Lewis acidity in enantioselective allylation reactions with allylsilanes. Using a similar concept, he has introduced a new class of Silicon Lewis acids for enantioselective synthesis using acyl hydrazones:[6]

The Lewis acid is readily prepared from pseudoephedrine and $PhSiCl_3$ as an inconsequential 2:1 mixture of diastereoisomers.



Reaction with the acyl hydrazone generates an activated intermediate in which the faces of the electrophile are sterically differentiated.

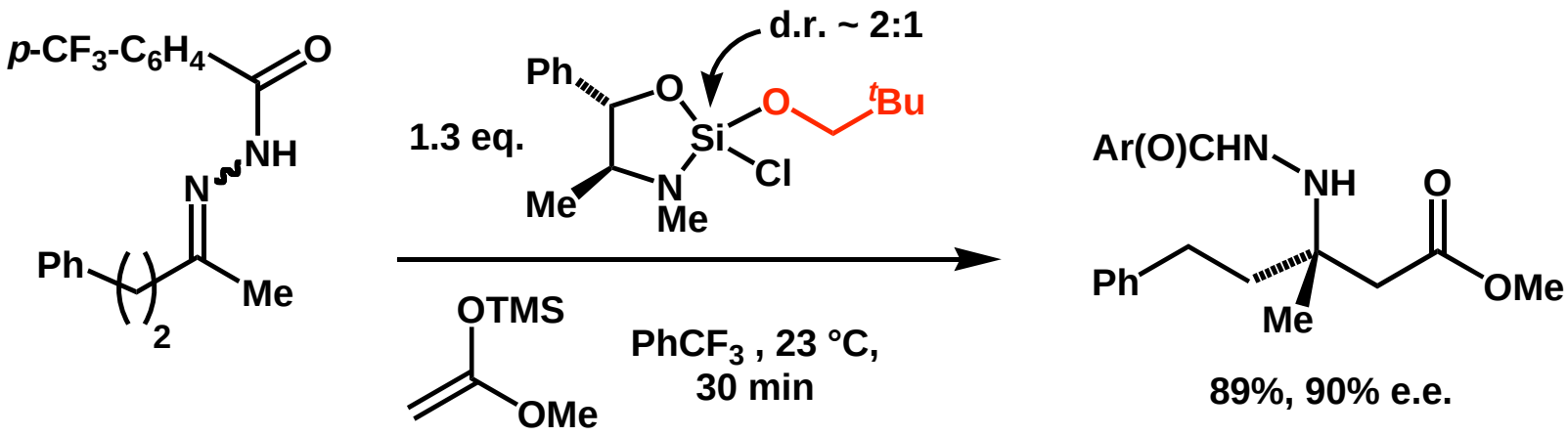
Synthetic Application



[3 + 2] cycloaddition of acyl hydrazones with *tert*-butyl vinyl ether proceeds with excellent enantioselectivity and diastereoselectivity to provide an aminal product that is primed for further reaction.[6]

A More Active Leighton LA

Leighton has recently shown that replacing the Ph substituent in his 1st gen LA with an alkoxy group provides a more straightforward method for catalyst tuning. Moreover the more electron-withdrawing alkoxy group generates a more reactive activator, which allowed its application in an enantioselective Mannich reaction involving aliphatic ketone-derived acyl hydrazones.[7,8]

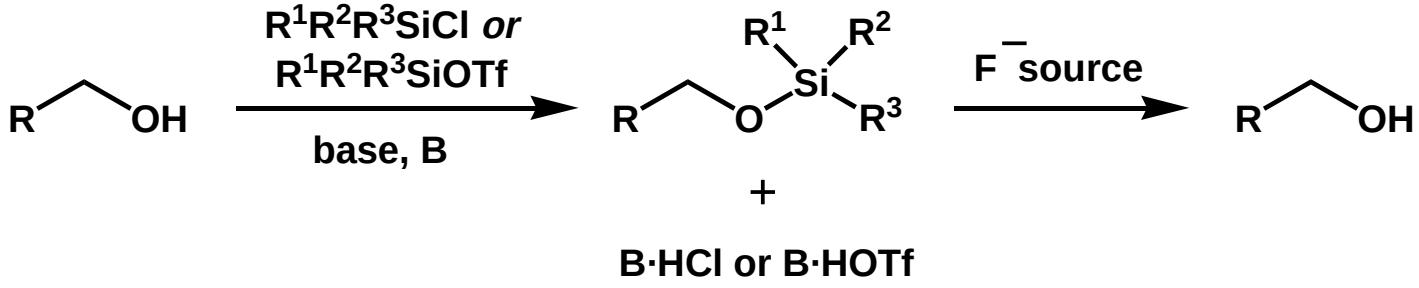


Silyl Protecting Groups

Silyl Ethers as Alcohol Protecting Groups

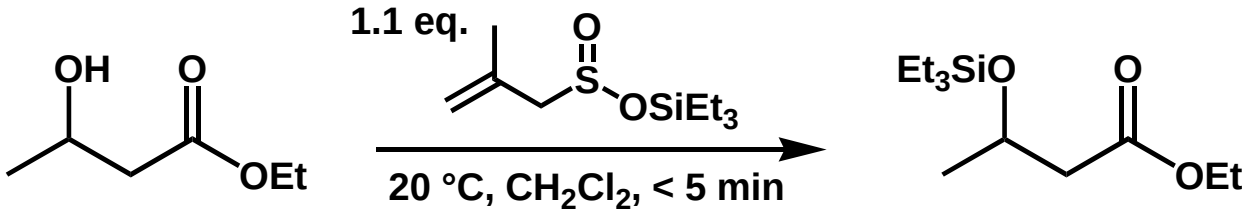
Silyl ethers are important alcohol protecting groups. They are particularly useful because they can be cleaved with a fluoride source, which leaves other protecting groups intact. Moreover, the size of the substituents on the silyl group can be used to modulate their stability.

Silyl ethers are usually formed by treating the alcohol with a silyl chloride or triflate. A base is invariably included to scavenge the acid by-product.

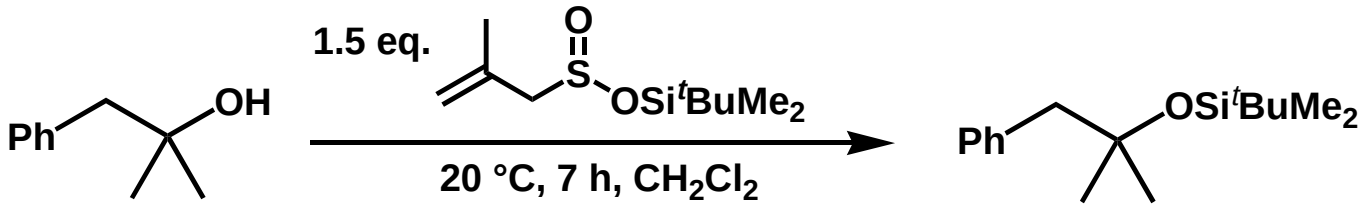


Formation of Silyl Ethers

New methods for forming silyl ethers that avoid the formation of HX·amine salts have been developed. For example, Vogel has introduced silyl methallylsulfinates as silylating agents for alcohols, phenols and carboxylic acids.[1] The reaction proceeds under mild and non-basic reaction conditions. Volatile by-products (SO_2 and isobutene) facilitate work-up:



quant (^{1}H-NMR)

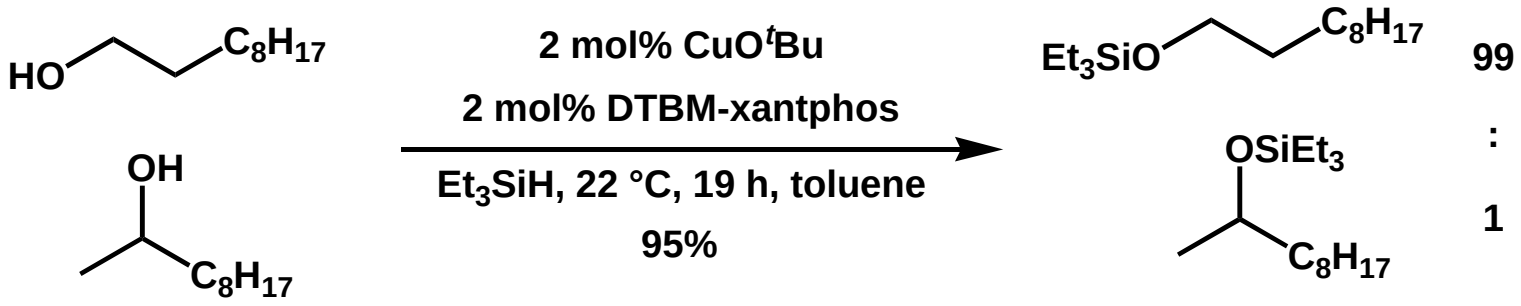


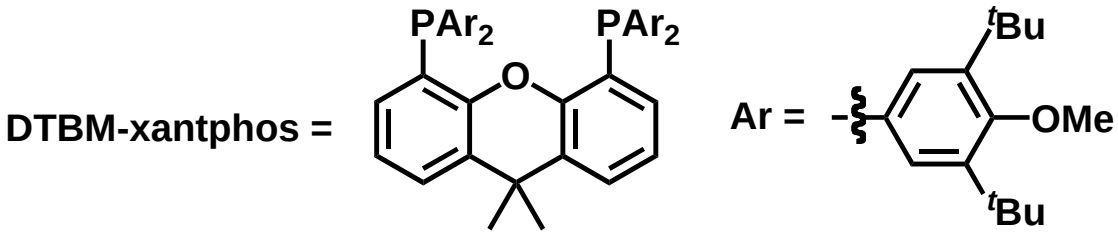
quench excess reagent with MeOH to generate volatiles side-products

quant (^{1}H-NMR)

Formation of Silyl Ethers

The dehydrogenative coupling of a silane with an alcohol is an attractive method for silyletherification since the only by-product is H_2. Ito and Sawamura have developed one of the best reagent systems for effecting this type of silyletherification.[2a]

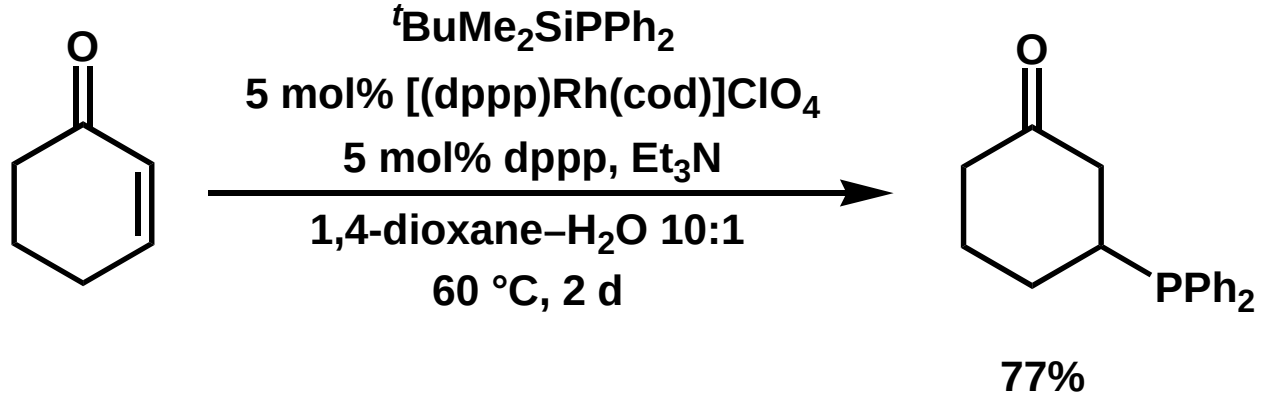




Under the optimised conditions, a range of silanes can be employed, although poor results are observed with very hindered silanes such as $^{i}Pr_3SiH$. Excellent levels of selectivity are observed in the selective silylation of 1° over 2° alcohols. A related Au(I)-xantphos catalyst system has also been developed.[2b]

Modifying Reactivity by Silylation

Silylation can be used to modify the reactivity of a range of reagents:

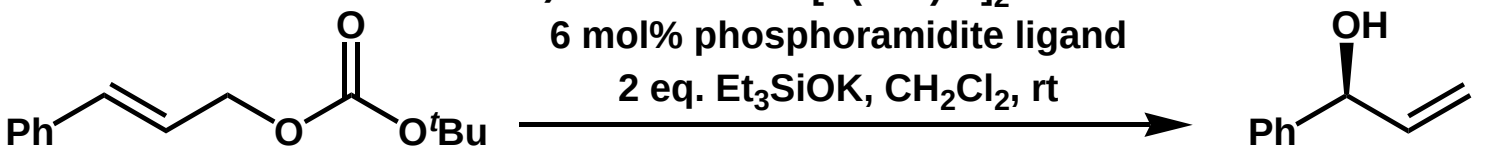


77%

In this example from Oestreich, the silyl phosphine functions as a masked phosphinide in a Rh(I)-catalysed phosphination of cyclic enones.[4]

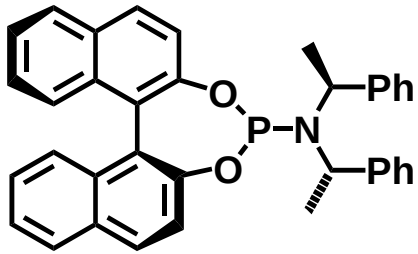
Modifying Reactivity by Silylation

Carreira has introduced silanolates as hydroxide equivalents in an Ir-catalysed enantioselective synthesis of allylic alcohols:[5]



88%, 97% e.e.

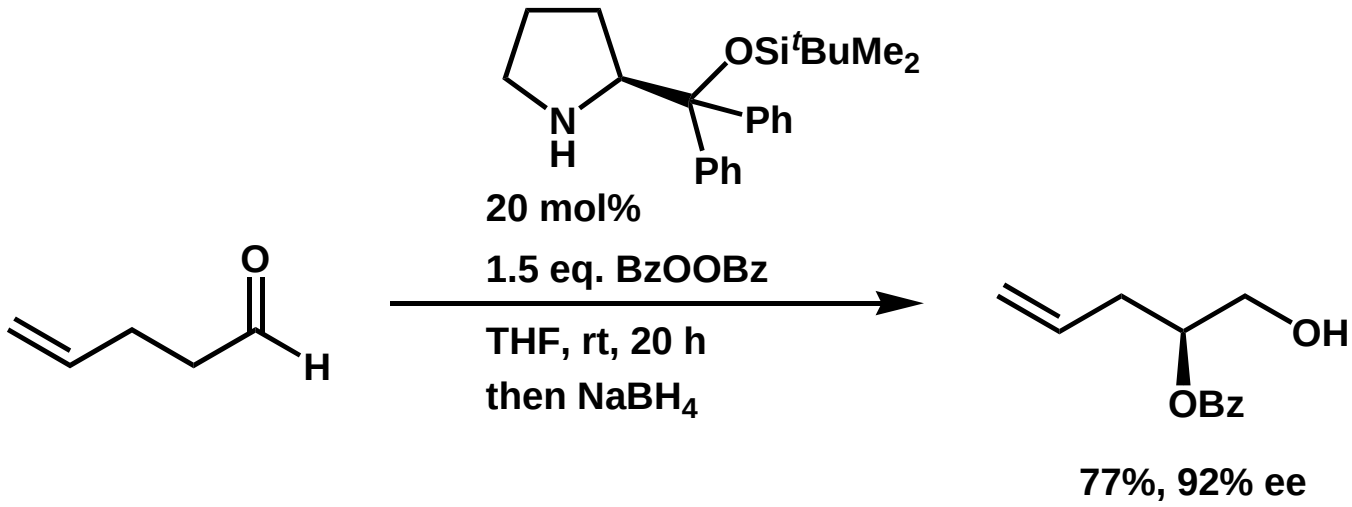
ligand =



^{t}BuMe$_2$SiOK and ^{i}Pr$_3$SiOK could also be used if the the desired product is a alcohol that is protected as a more robust silyl ether.

Modifying Activity by Silylation

Proline derivatives have emerged as powerful organocatalysts for mediating a range of transformations. Diarylprolinol silyl ethers, introduced by Hayashi and Jørgensen, have been used particularly widely, for example in this recent example of a direct enantioselective α-benzoylation of aldehydes.[6]



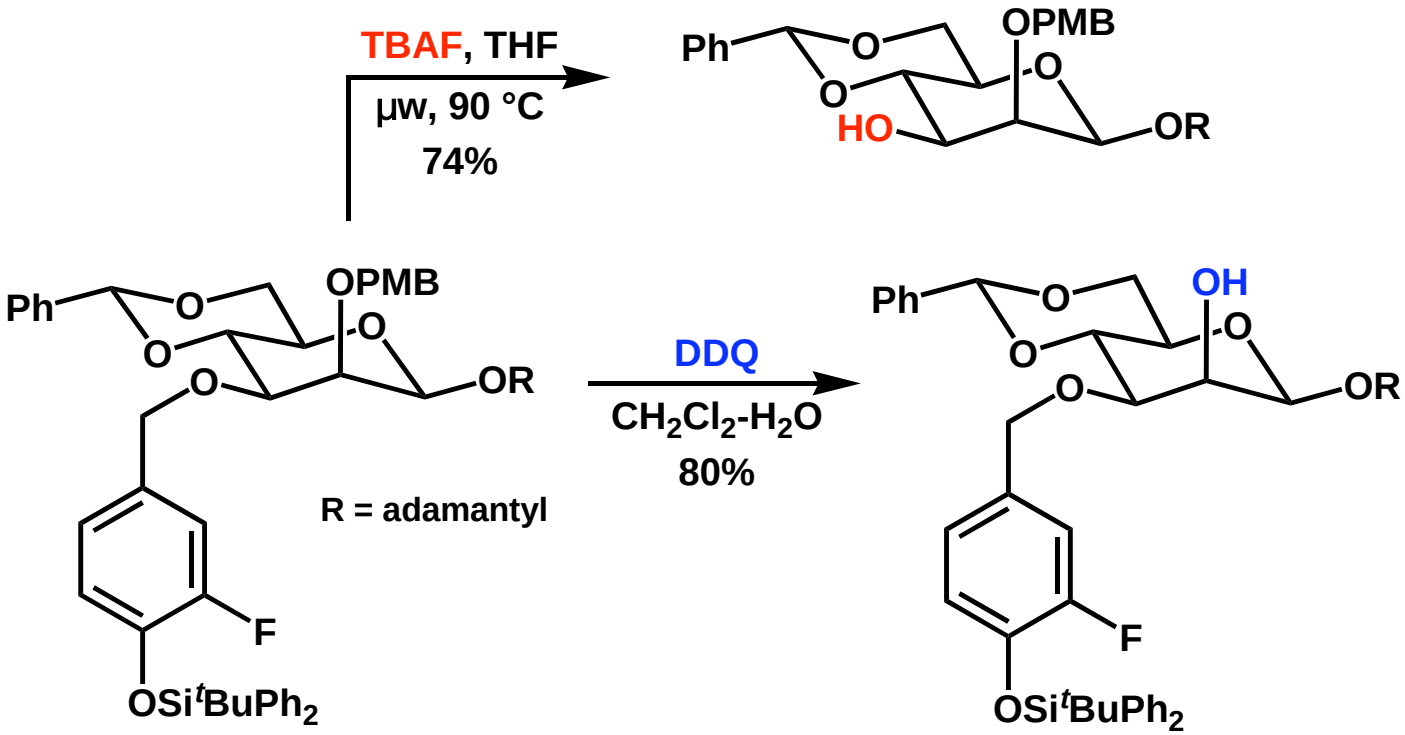
77%, 92% ee

The silyl protecting group in this class of organocatalyst generates a sterically bulky substituent off the pyrrolidine and is important for achieving high levels of asymmetric induction.

New Silyl Protecting Groups

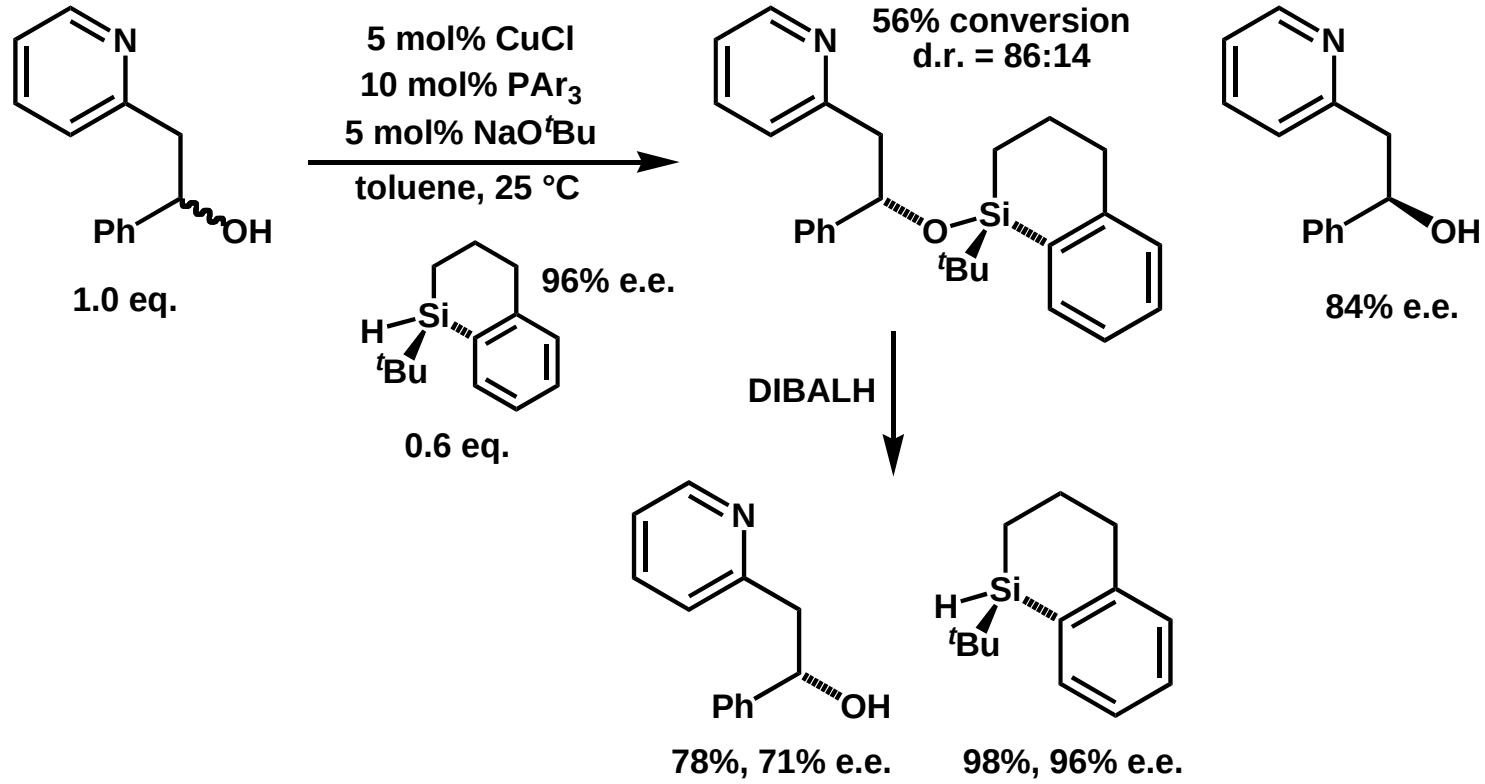
Crich has introduced the 3-fluoro-4-silyloxy-benzyl ether protecting group. The group is readily introduced and can be removed by treatment with TBAF in THF under microwave irradiation.[7]

The electron-withdrawing fluoro substituent imparts enhanced stability to acid and the oxidative reaction conditions used to remove PMB protecting groups, which allows these two types of benzyl ethers to be used as orthogonal alcohol protecting groups.



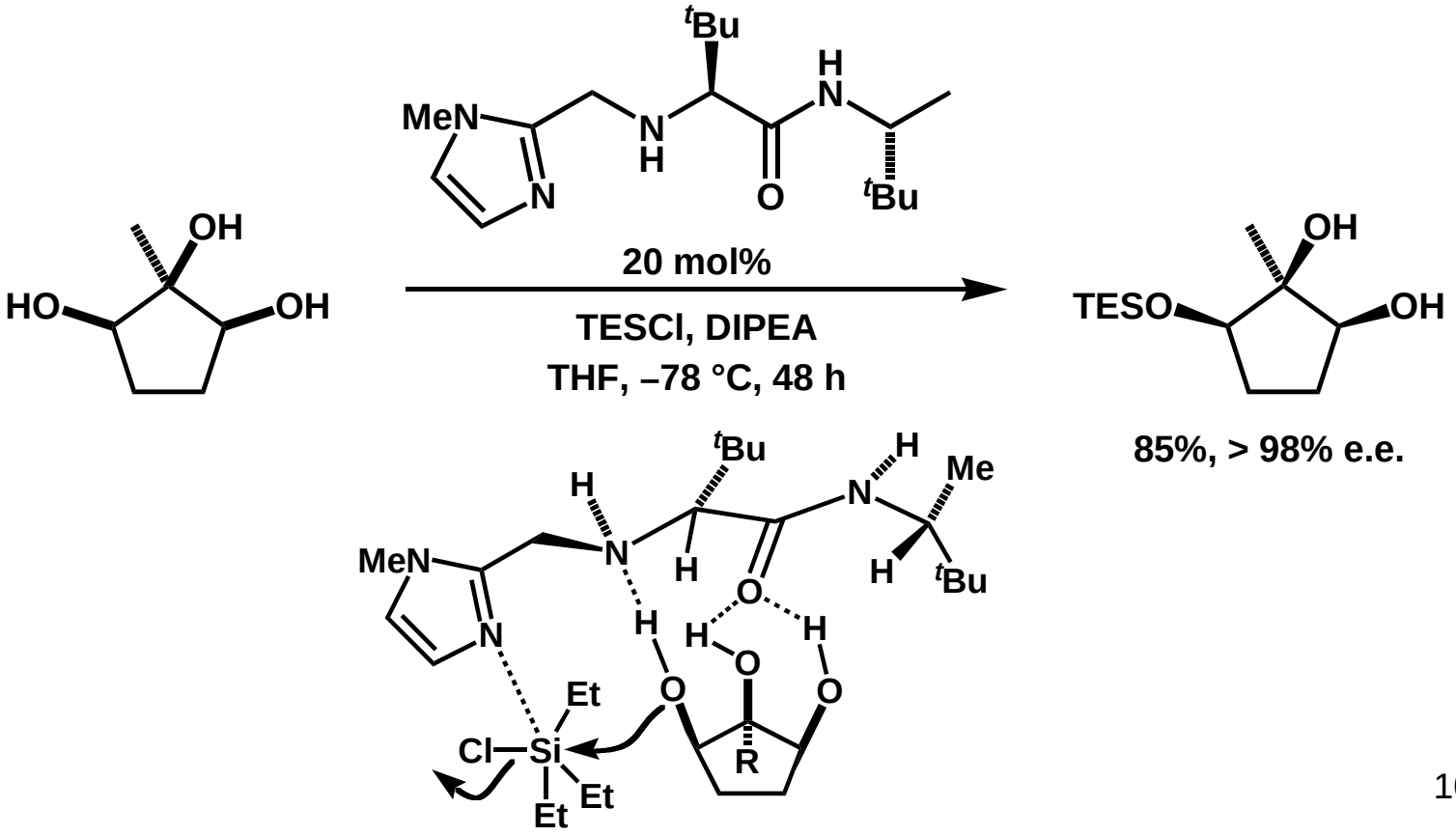
Chiral Silylating Agents in Kinetic Resolutions

Oestreich has used a chiral silane to effect the kinetic resolution of racemic 2° alcohols.[9] Silylation proceeds with retention of configuration at the silicon centre. The silane resolving agent can be recovered (retention of configuration) from the silyl ether by treatment with DIBALH.



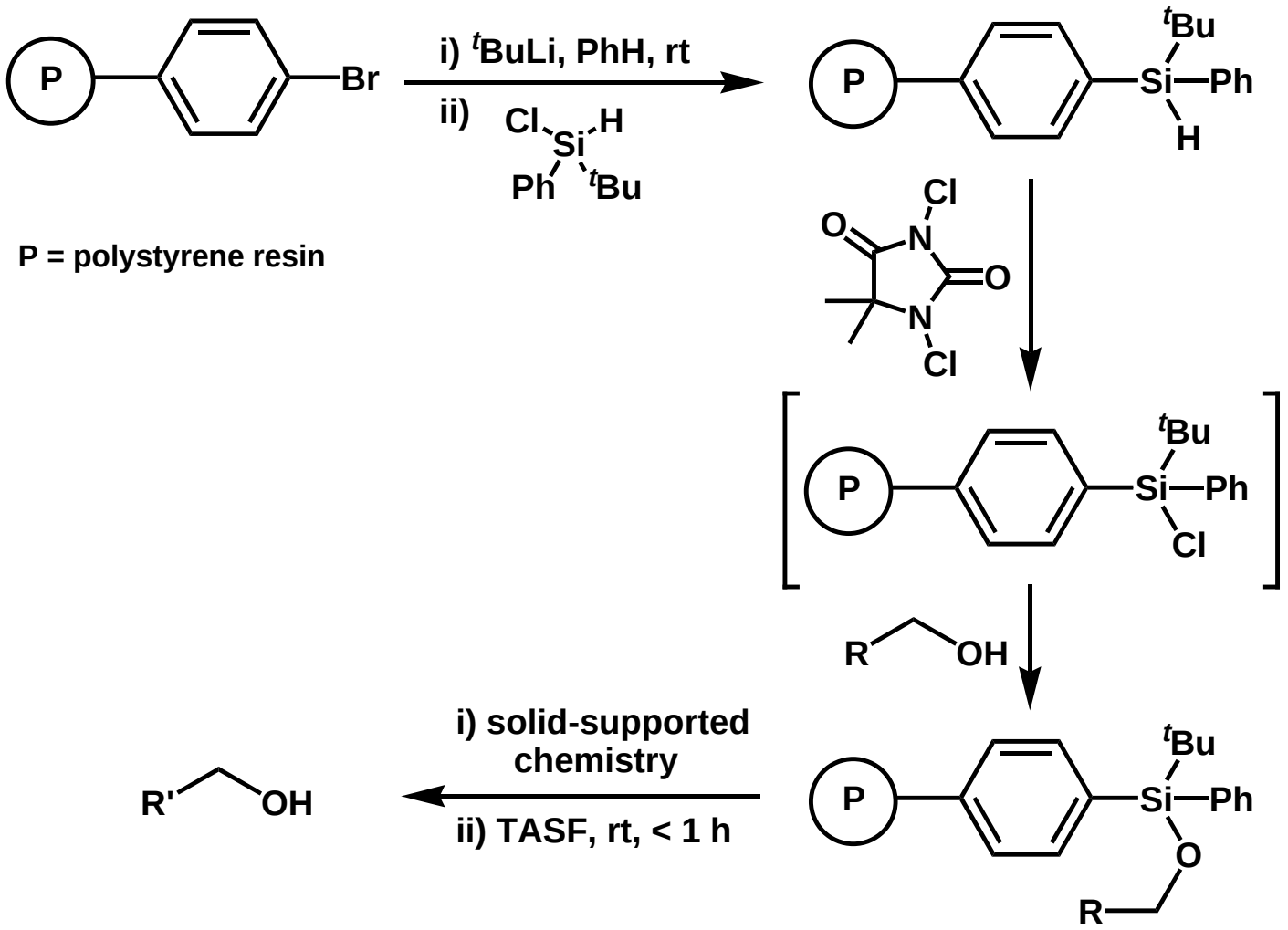
Catalytic Enantioselective Silylation of Triols

Imidazole is commonly used as a nucleophilic catalyst (as well as an acid scavenger) in silylation reactions involving silyl chlorides. Hoveyda and Snapper have developed a chiral imidazole catalyst for the enantioselective silylation of alcohols.[10] They recently extended this strategy to the desymmetrisation of *meso* 1,2,3-triols:[11,12]



Silyl Linkers for Solid-Supported Synthesis

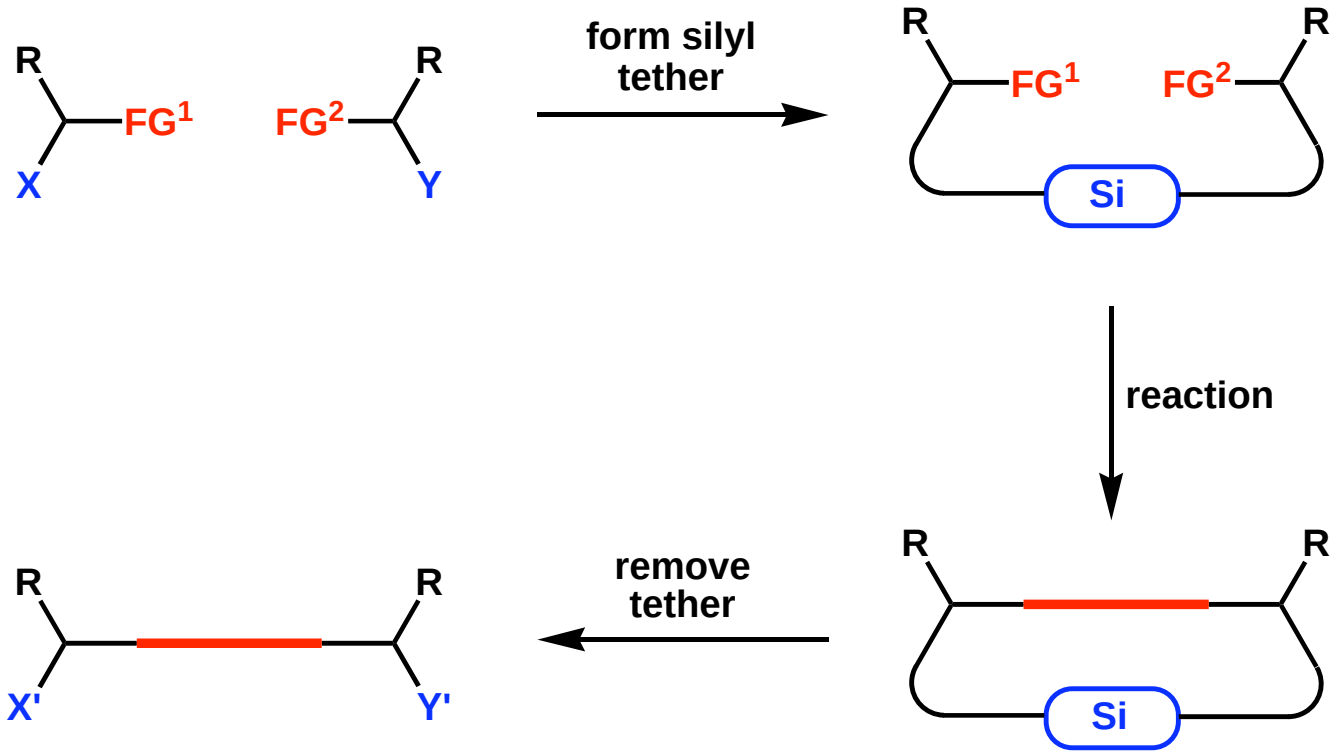
Silyl groups have been used as traceless linkers for solid-supported synthesis.[14] Tan showed that a *tert*-butyldiarylsilyl linker exhibited increased stability to acids than previously used di*iso*propylsilyl-based linkers.[14a]



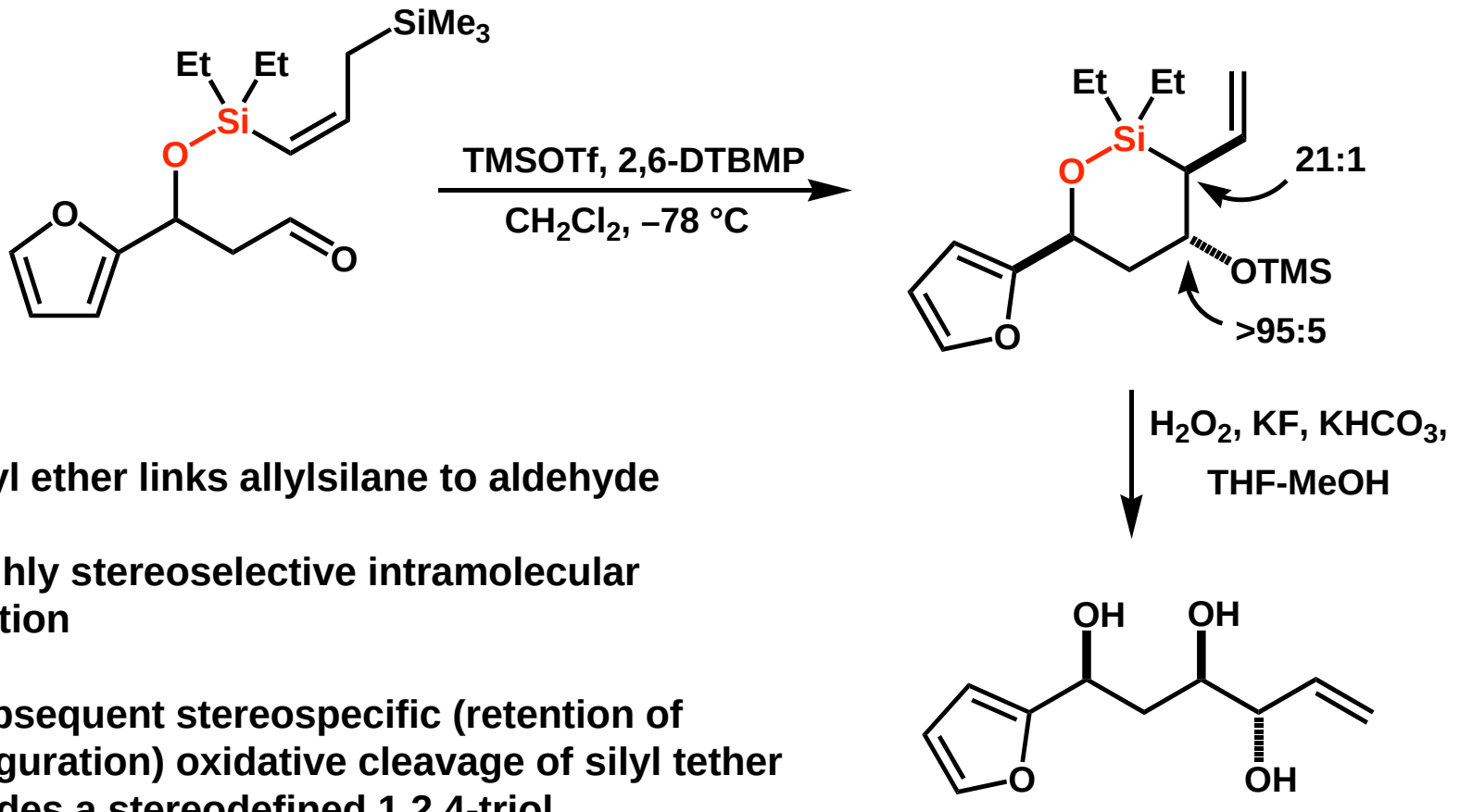
Temporary Silicon Connection

Silyl Tethers

Silyl groups have been used widely to tether two reacting species. Subsequent reaction can then occur in an intramolecular fashion and therefore benefit from all the advantages associated with intramolecular processes. Cleavage of the tether *post* reaction provides a product of an overall net intermolecular process.[1]



Silyl Ether Connection in Intramolecular Allylation[2]



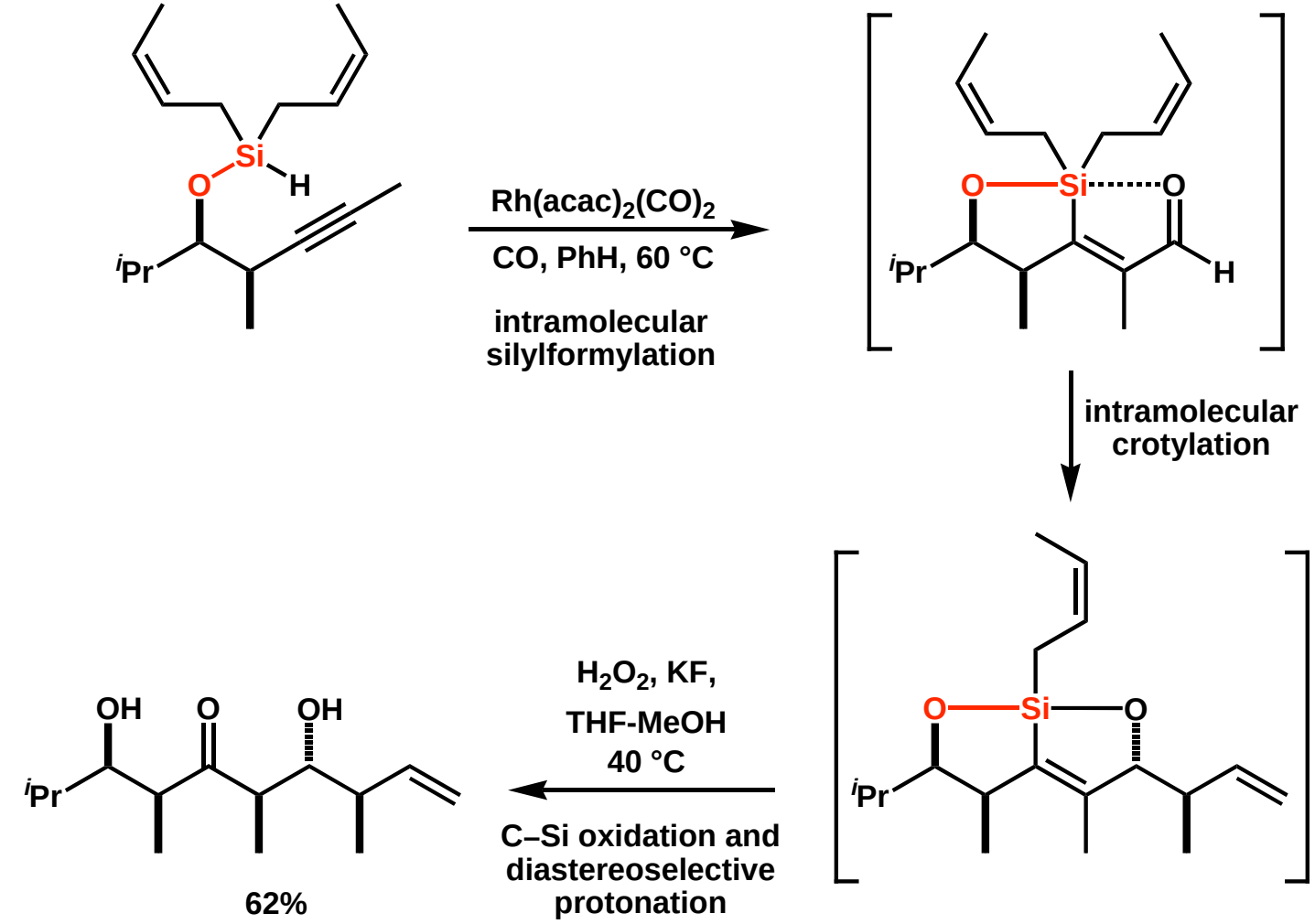
1. silyl ether links allylsilane to aldehyde

2. highly stereoselective intramolecular allylation

3. subsequent stereospecific (retention of configuration) oxidative cleavage of silyl tether provides a stereodefined 1,2,4-triol

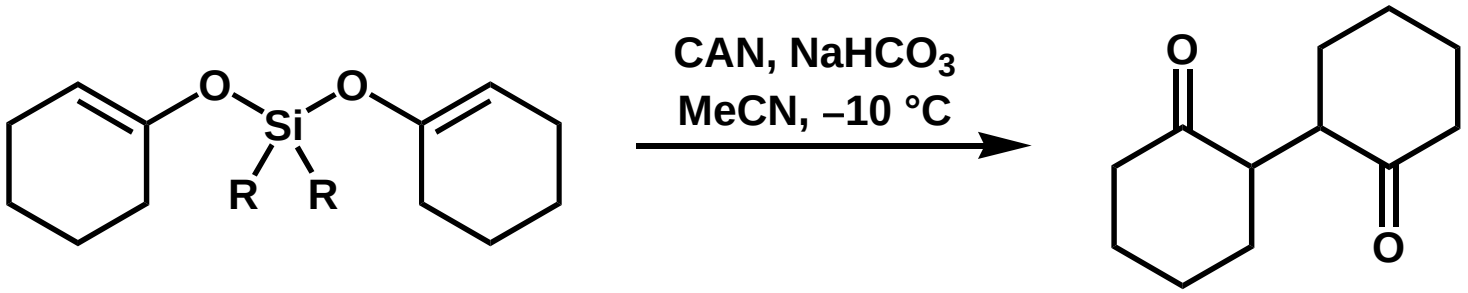
Tandem Silylformylation-Crotylation-Oxidation Route to Polyketides[4]

ref 4a



15 : 1 (major: all minor diastereoisomers)

Diastereoselective Oxidative Coupling of Bis-Silyl Enol Ethers[5]



d/l* : *meso

R = Me 29% 2.4 : 1

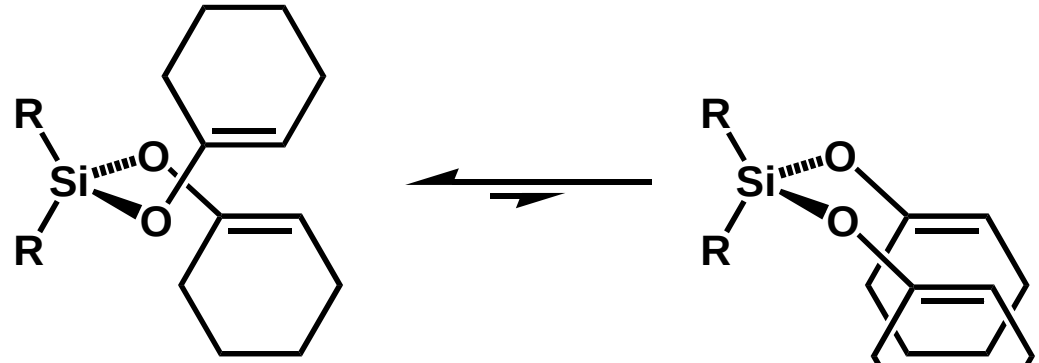
R = ^{i}Pr 57% 10 : 1

isolated yield of *d/l* diastereoisomer

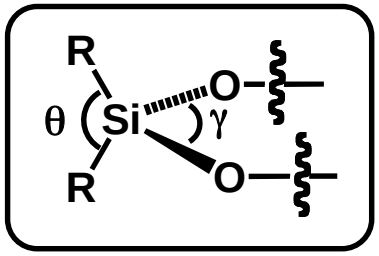
The R substituents in the silyl tether were important in governing the yield and diastereoselectivity of the reaction.

Unsymmetrical bis-silyl enol ethers can also be used.

Origins of Diastereoselectivity

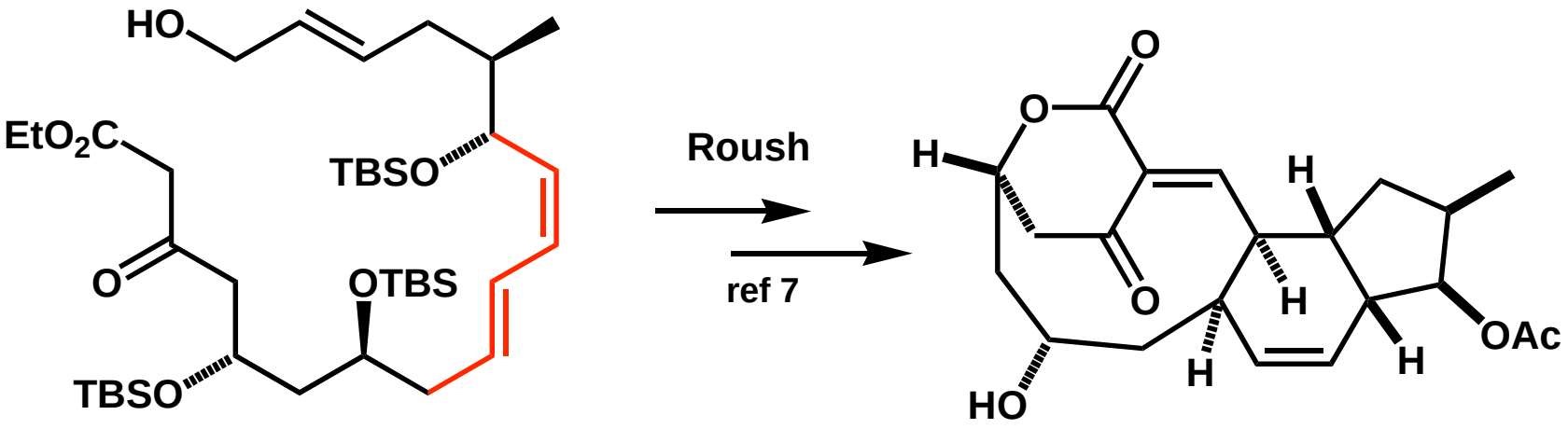


d / l ***meso***



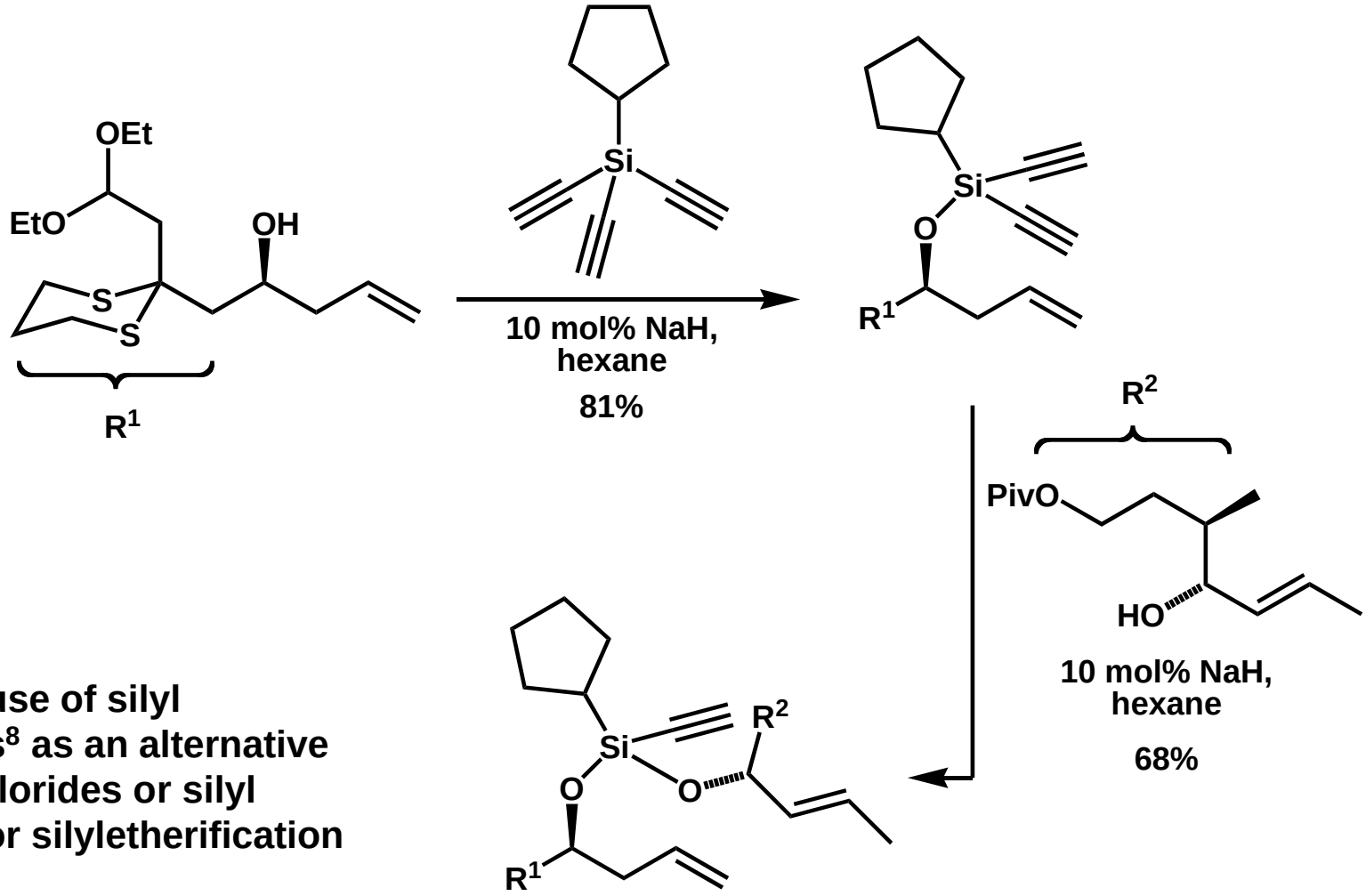
increase size of R ⇨ **increase size of θ** ⇨ **decrease size of γ** ⇨ **destabilise T.S. leading to *meso***

Silyl-Tethered Tandem Ring-Closing Metathesis[6]



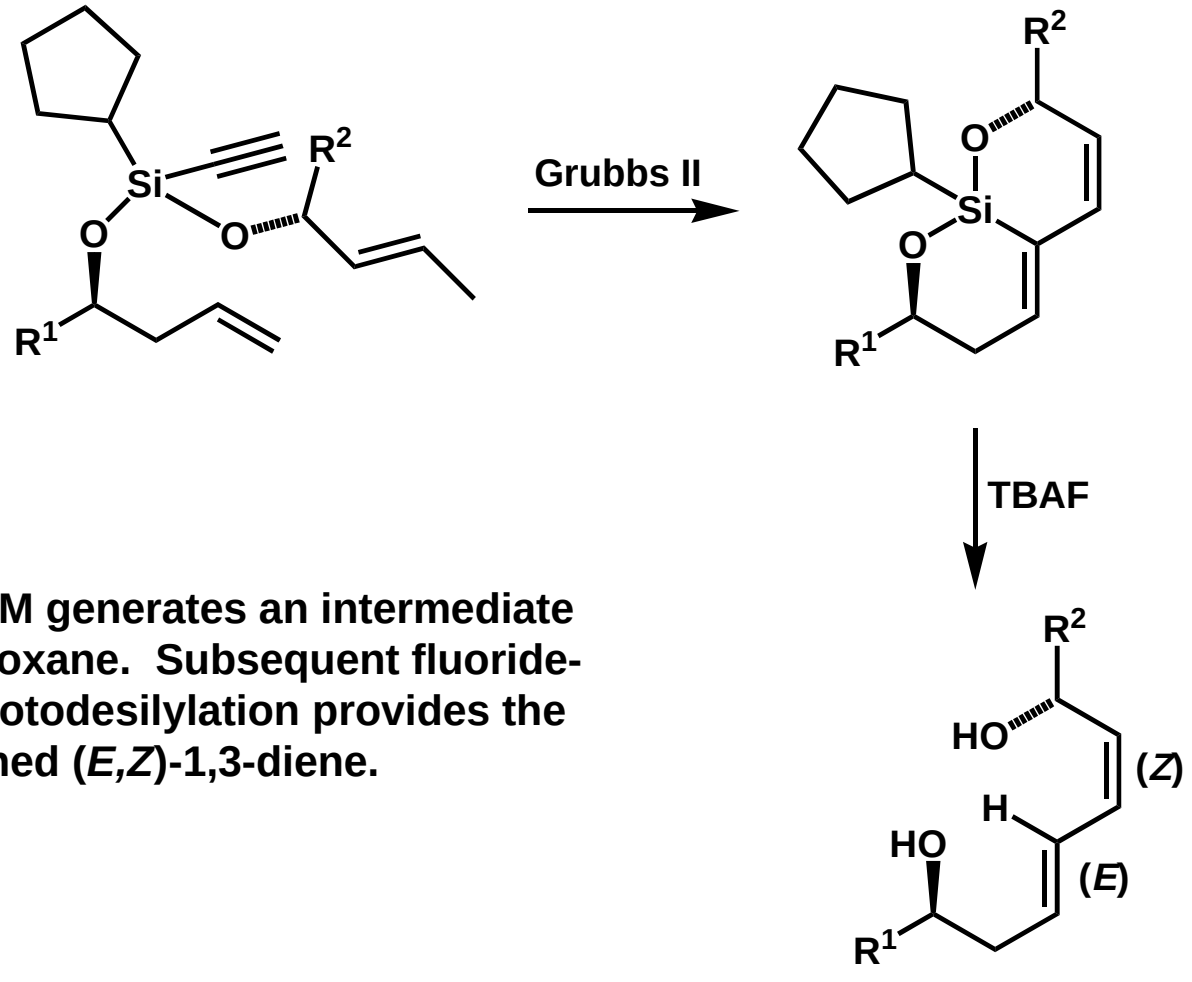
(–)-cochleamycin A

Formation of Metathesis Precursor



Note the use of silyl acetylides[8] as an alternative to silyl chlorides or silyl triflates for silyletherification

Double RCM - Protodesilylation Synthesis of (*E,Z*)-1,3-Diene



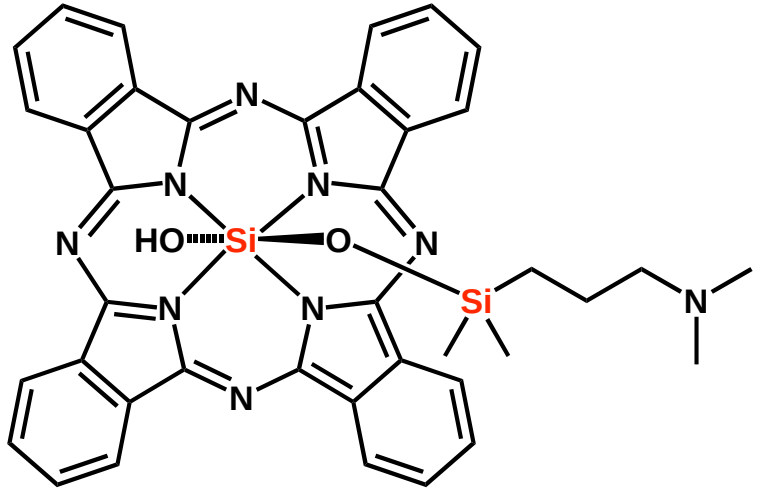
Double RCM generates an intermediate bicyclic siloxane. Subsequent fluoride-induced protodesilylation provides the stereodefined (*E,Z*)-1,3-diene.

61% over two steps

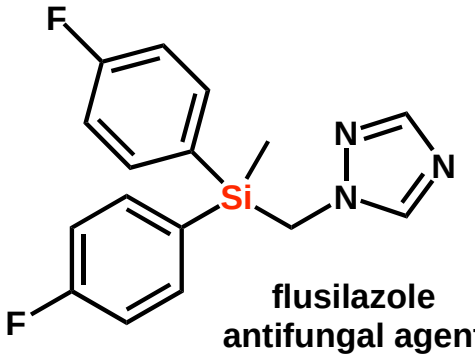
Biological Applications of Organosilanes

Bioactive Organosilanes

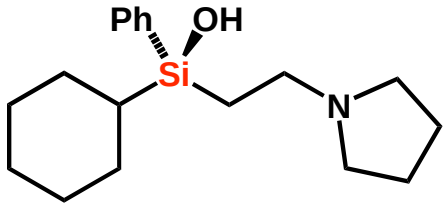
In spite of the similarity of Silicon and Carbon, silicon-containing organic compounds are relatively rare in biological chemistry research programmes. However, bioactive organosilanes are known and in some cases have been commercialised:



Pc4 (photodynamic agent for application in cancer treatment)



flusilazole antifungal agent ($$$)

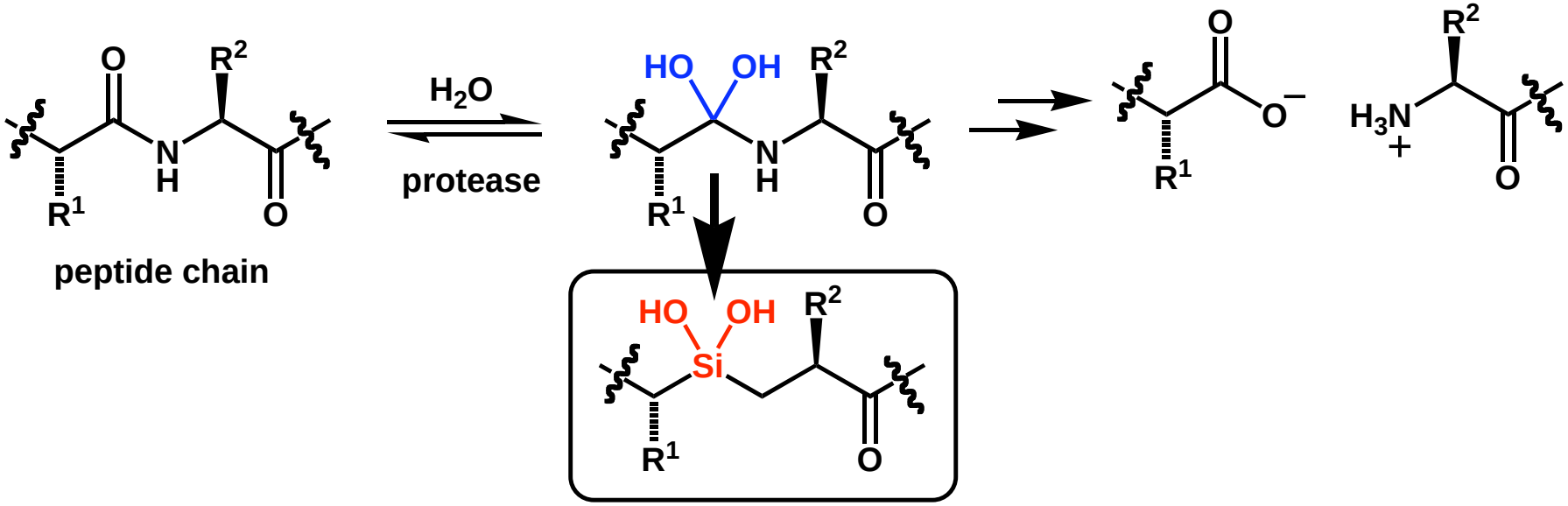


muscarinic receptor agonist

silafluofen insecticide ($$$)

Silanediols as Protease Inhibitors

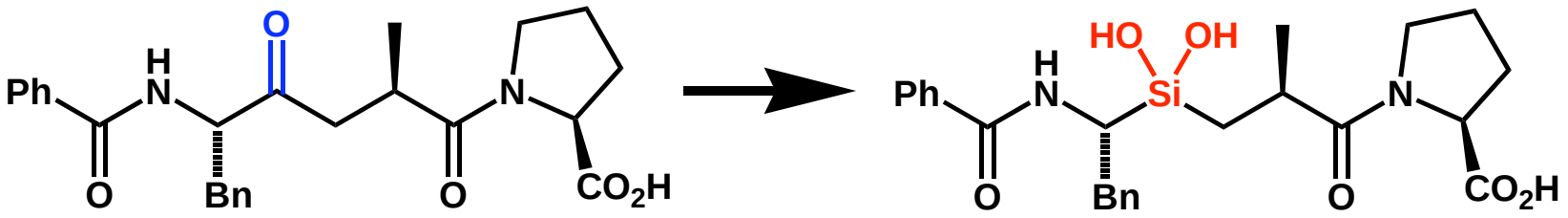
Proteases are enzymes that catalyse the hydrolysis of a peptide bond. Aspartic acid proteases and metalloproteases both catalyse the addition of a water molecule to the amide carbonyl group. Molecules that mimic the hydrated form of the hydrolysing amide bond have therefore been used as inhibitors of these two classes of enzymes.



Silanediols have recently come to the fore as potentially useful isosteres of the tetrahedral intermediate in this type of hydrolysis reaction. Providing their propensity to oligomerise to siloxanes can be controlled (*e.g.* by steric blocking), they are potentially very attractive stable hydrate replacements since they are neutral at physiological pH.[1,2]

Silanediol Inhibitors of Angiotensin-Converting Enzyme (ACE)

Sieburth prepared the silanediol analogue of a known ACE inhibitor.[1b]



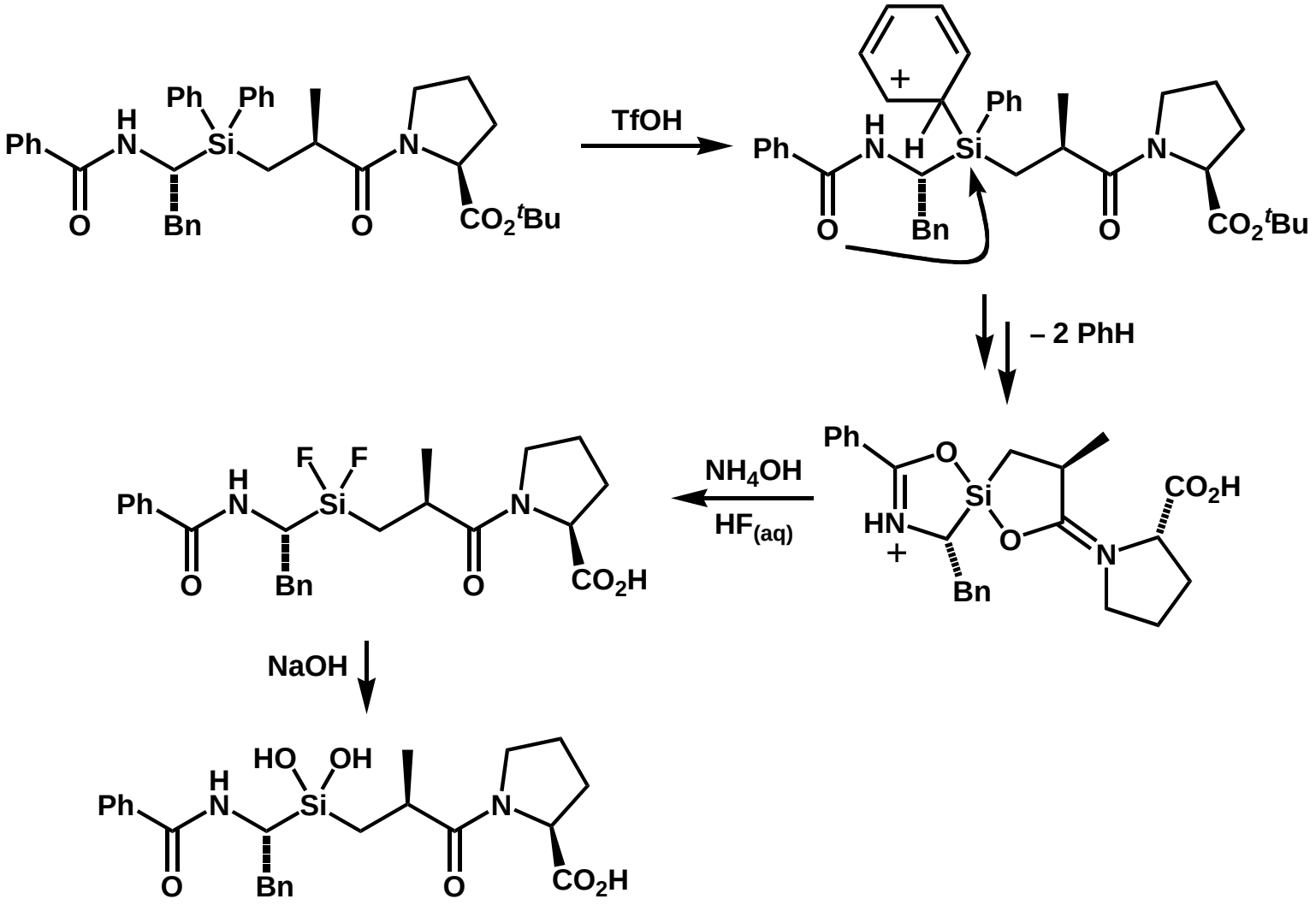
known ACE inhibitor
IC_{50} 1.0 nM

IC_{50} 3.8 nM

Significantly, the inhibitory activity of the silanediol analogue compared favourably with the keto lead.

The synthesis of the silanediol is noteworthy.

Silanediol Synthesis



Some Conclusions

The chemistry of organosilicon compounds is rich and diverse and finds application in many aspects of modern organic synthesis. Most of it, however, can still be rationalised by considering the basics:

electronegativity: Si is more electropositive than C and H

size: Si is a relatively large and polarisable atom compared with C, H, O *etc*

electron config'n: $1s^2$, $2s^2$, $2p^6$, $3s^2$, $3p^2$

pos'n in Periodic Table: Period 3, therefore capable of expanding its valence state

stereoelectronics: C–Si bond is good at stabilising β-positive charge

bond strengths: Si–O and Si–F bonds are significantly stronger than Si–C and Si–H bonds.

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