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Strategic Applications of the β-Silicon Effect

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Abstract. Organosilicon reagents are highly versatile and privileged scaffolds in modern synthetic chemistry, largely due to the range of transformations the groups are amenable to. The β-Silicon effect is one of the fundamental phenomena underpinning the inherent reactivity of organosilicon reagents, allowing unsaturated organosilanes to undergo a range of electrophilic substitutions with a variety of nucleophiles. The application of the β-Silicon effect in a range of organic transformations is reviewed with the discussion divided up based on the class of silane. The reactivity of these compounds towards carbon, heteroatom and metallic electrophiles is discussed from classical applications such as the Sakurai allylation to contemporary applications such as cross-coupling chemistry. In addition, examples of these transformations in the context of methodology development and natural product synthesis are provided.

Abstract Text----Continued

Keywords:

1 Introduction

In recent years, organosilicon chemistry has become a vital component of modern synthetic organic chemistry. This is in no small part due to the unique chemistry displayed by these compounds when compared to their carbon analogue. The placement of silicon in the periodic table affords organosilanes increased size,[1] ability to possess an 'expanded valency'[2] and a degree of electrophilic character[3] which in turn opens the door to cross-couplings with suitable electrophiles as with the Hiyama coupling.[4] These hypervalent intermediates can also readily undergo oxidation under a variety of conditions, as exemplified by the Fleming and Tamao oxidations.[5]

One of the most notable features of organosilicon chemistry is the ability of the silyl group to stabilize charges in the vicinity of the group, specifically geminal anions and vicinal cations. These two phenomena are termed the α-effect and β-effect respectively. The α-effect is frequently manifested as the metalation of silanes in this position with strong bases, a key step in the Peterson olefination.[6] This effect is significantly less pronounced than the β-silicon effect, and this is reflected by the multitude of studies which have been carried out on the origin and application of the effect. This intense study has manifested itself in the development of methodologies exploiting the formation of these silyl stabilized cations, and it is the purpose of this review to highlight the advances in the development of these reactions in recent years.

Biographical Sketch

Dean Roberts graduated from Manchester Metropolitan University with a first class MChem degree, completing his research project in the group of Dr Ryan Mewis. He subsequently began his postgraduate studies in the group of Dr Mark McLaughlin at Lancaster University. His current research is regarding the stereoselective synthesis and subsequent applications of organosilicon compounds.

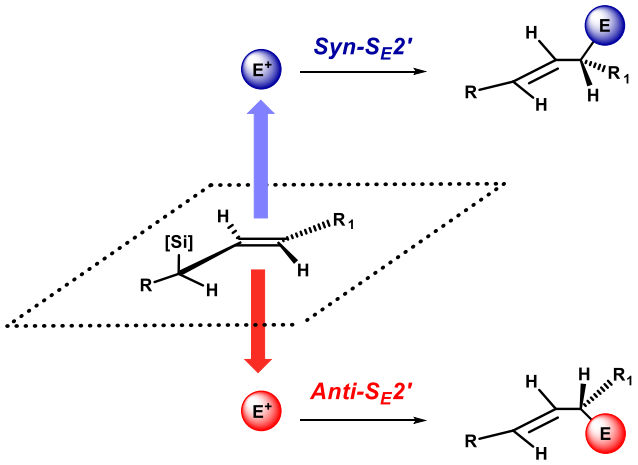
Mark McLaughlin obtained his PhD under the supervision of Dr Matthew Cook from Queen's University Belfast. Following postdoctoral fellowships at the Institute of Cancer Research, London, and The University of Oxford, he began his first independent position at Manchester Metropolitan University in 2018 and moved Lancaster University in 2021. His research interests are focussed on the development of new methodology to access complex scaffolds and using these to interrogate novel protein targets.

2 Silyl Olefins

2.1. Allyl Silanes

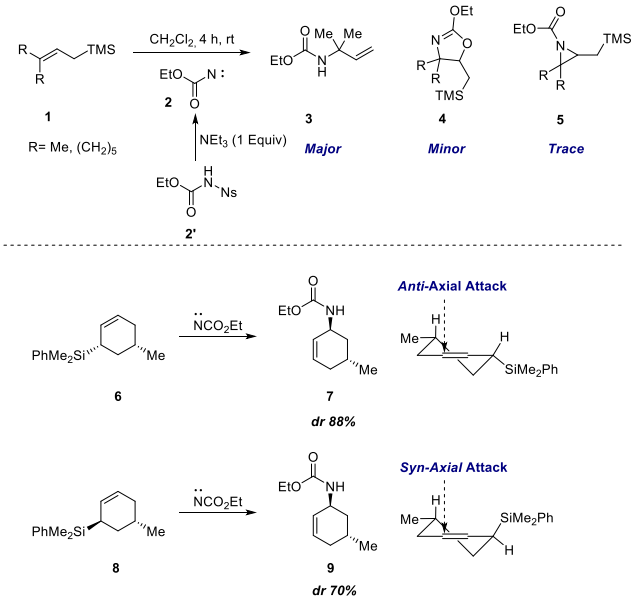
2.1.1 Attack at Heteroatomic Electrophiles

Allyl silanes react as π-nucleophiles with a variety of electrophiles in a stepwise process. The intermediate cation, stabilized through hyperconjugative interactions with the low-lying C-Siσ orbital, is quenched via loss of the silane, resulting in a formal allylation of the electrophile. This addition generally occurs through an *anti*-attack of the electrophile, however in cases of extreme steric bias, *syn* S_E2' reactions are known (Scheme 1). Although loss of silane is the most common reaction pathway for these nucleophiles, loss of other groups, or nucleophilic trapping of the cation are also viable pathways.



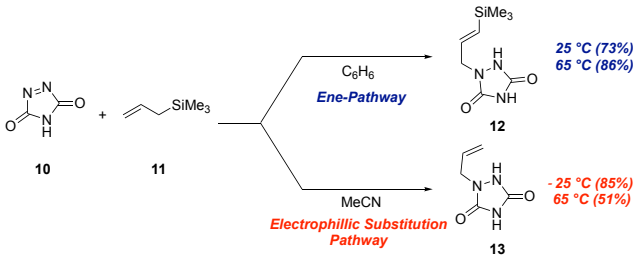
Scheme 1. The two stereochemically distinct reaction pathways for the electrophilic substitution of allyl silanes

While most electrophiles in these reactions are carbon centres with the most well studied being the Hosomi-Sakurai allylation of carbonyl compounds, other electrophiles have frequently been employed in these allylation reactions, including both metallic and heteroatomic electrophiles. Early examples of the reactions of allylsilanes with nitrogen nucleophiles included the desilylative nitration of allyl silanes using NO_2BF_4.[7] Loreto and co-workers demonstrated the nucleophilic attack of allyl silanes at nitrene centers, allowing for access to **3**. **2** was generated *in-situ* from base mediated α-elimination of ethyl N-carbamate **2'** with triethylamine. This work strongly supports the intermediacy of the silyl stabilized cation in these reactions, as the formation of aziridine **5** is also observed in trace amounts via GC-MS analysis, as well as the formation of isolable amounts of 2-alkoxyoxazolines **4**, formed *via 5-endo-dig* cyclisation (Scheme 2.)[8] Further studies by the same group suggest that the attack generally occurs *anti* to the silane in cyclic systems, where permissible by stereoelectronic and conformational factors.[9] Over the following years, several further examples of electrophilic substitution of an allyl silane with a nitrene electrophile were reported by the Tardella group, with the aziridine intermediate again isolated in several cases, confirming the stepwise nature of the reaction.[10]



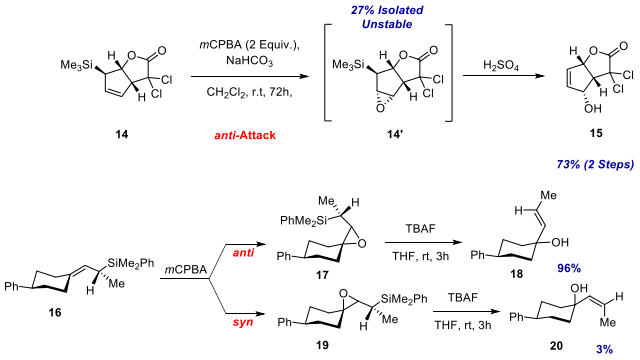
Scheme 2. Reactions of allyl silanes with nitrene electrophiles

11 has been shown to react with 1,2,4-triazoline-3,5-diones (**10**) in both a desilylative electrophilic substitution reaction and in an ene-type reaction (Scheme 3.) The factors influencing the reaction pathway were studied by Butler and co-workers, with more polar solvents favouring the desilylative pathway. This preference is rationalized by the stabilization to the ionic intermediate offered by the more polar solvent. As the ene pathway proceeds through a concerted mechanism, no such stabilization is required, and the pathway is favoured in solvents with low polarity such as benzene. At lower temperatures, the ionic pathway is also favoured, with higher temperatures favouring the pericyclic pathway.[11]



Scheme 3. Reaction pathways for the addition of allyl trimethyl silane to 1,2,4-triazoline-3,5-diones

Allyl silanes have also been shown to also react with oxygen-based electrophiles such as peroxyacids. In their study on an allyl silane derived from a key intermediate in the synthesis of prostaglandin, Fleming *et al* found that treatment of **14** with *m*-CPBA under basic conditions did yield the expected peroxide **14'** derived from an *anti*-attack of the silane. While **14'** could be isolated, upon standing it quickly isomerised *via* Brook rearrangement to the corresponding silyl ether, which is readily hydrolysed to **15**. The transformation can be telescoped to access the allylic alcohol in 73% yield from the allyl silane. Interestingly, while other electrophiles in the study afforded products arising from a *syn*-addition, this sterically unfavourable *anti*-addition provides evidence that these allylic epoxidations can be guided *via* hydrogen bonding interactions with neighbouring functional groups, in this case, the fused lactone.[12] Subsequent studies showed that in the absence of intramolecular direction, the epoxidation occurs *via* an *anti*-attack preferentially when steric hinderance is not a factor (Scheme 4.) [13] While allylic silanes are known to react with other oxygen electrophiles such as singlet oxygen[14] and osmium tetroxide,[15] the behaviour is likely independent of the β-silicon effect, and as such is not discussed in this review.

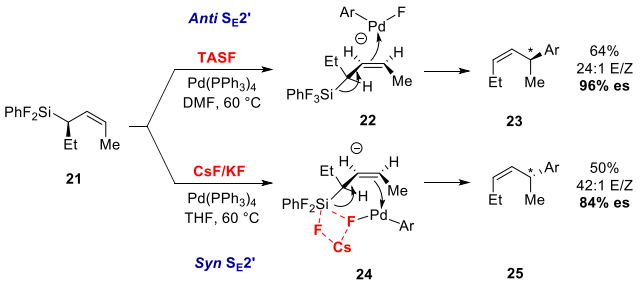


Scheme 4. Epoxidation of allyl dimethyl phenyl silanes with mCPBA and subsequent desilylative epoxide opening

2.1.2 Attack at Metallic Centres

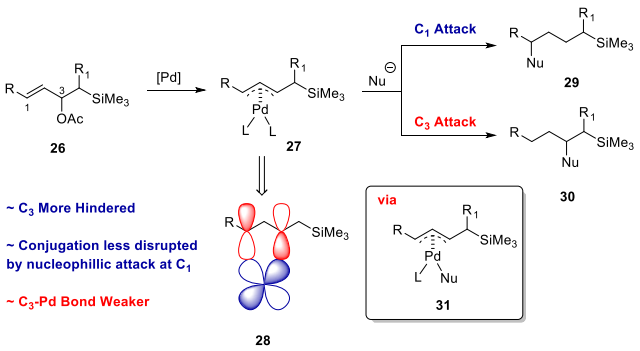
Allyl silanes are known to react with suitably electrophilic metal centers, and in particular, Pd(II) centers have been shown to be highly suitable electrophiles for this type of reaction. Several palladated intermediates have been isolated, characterised and confirmed to arise from the expected *anti*-desilylativepalladation of difluorophenylallyl silanes.[16] Hiyama and co-workers took advantage of this known *anti*-attack in the cross coupling of optically active **21** with aryl triflates. In this work, the Pd(II) center is formed *in-situ via* oxidative addition of $Pd(PPh_3)_4$ into the aryl-triflate bond. The fluoride-activated allyl silane, then undergoes stereospecific S_E2' reaction with this Pd(II) species. Subsequent reductive elimination affords the allylated product in moderate yields and excellent enantiospecificities. Interestingly, this *anti*-selectivity was reversed when the fluoride source was switched from an organic source (TASF) to an inorganic fluoride source (KF, CsF.) This was rationalized *via* interaction between the fluoride of the activated pentavalent silicate species, the metal fluoride and the palladium center, thus forming a closed transition state and anchoring the palladium in place for a *syn*-type attack (Scheme 5.)[17] These findings regarding the stereoselectivity of the Pd(II) catalyzed S_E2' were corroborated in 1996 by Mori and co-workers, along with the confirmation that

the reaction occurs through an S_E2' mechanism rather than a direct S_E2. The regioselectivity of the substitution was confirmed through ^{13}C labelling of the C-Si bond.[18]



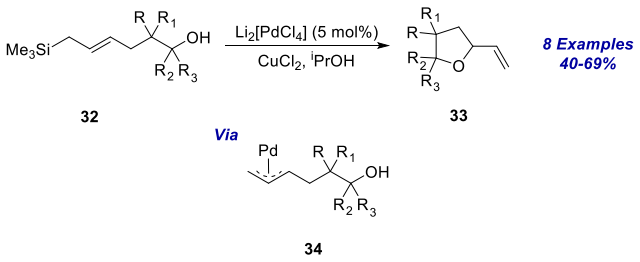
Scheme 5. The influence of F- source on the stereochemical outcome of Pd catalyzed allyl silane/aryl bromide couplings

The scope of external nucleophiles amenable to these reactions was thoroughly explored by Szabó and co-workers with malonates, enoxyborates and sodium cyclopentadienyl sodium all viable as external nucleophiles. So-called internal nucleophiles, where the bond forming process arrives from a reductive elimination from the palladium center after formation of **31** rather than a formal nucleophilic attack, was also explored in the same study. Disilanes and sodium tetraphenylborane proved successful as 'internal' nucleophiles. While the regioselectivity of nucleophilic attack for the external nucleophiles was generally at the C_1 position of **26** affording **28**, the internal nucleophiles showed slightly less regioselectivity in their additions. This was rationalized by several means. The steric bulk of the silane group clearly dissuades attack at the nearby C_3 position by shielding from the approach of an external nucleophile. Any nucleophilic attack at this carbon also relies on the energetically unfavourable disruption of the conjugation between the allylic system and the energetically low-lying C-Siσ orbital. In favour of attack at this position however, is the weakening of the C_3-Pd bond *via* hyperconjugative effects arising from the interaction of the C-Siσ orbital and the unfilled LUMO of the allyl-Pd complex, weakening the C_3-Pd bond. In the case of external nucleophiles, the first two factors heavily outweigh the latter, and thus nucleophilic attack at the allylic position is preferred. For internal nucleophiles, the sterics of the silyl group are less of a factor, and thus the regioselectivity is governed by the first and last factor, lowering regioselectivity (Scheme 6.)[19]



Scheme 6. Differing stereochemical outcomes of intra and intramolecular nucleophilic attack at Pd-Allyl species with an organosilicon functionality

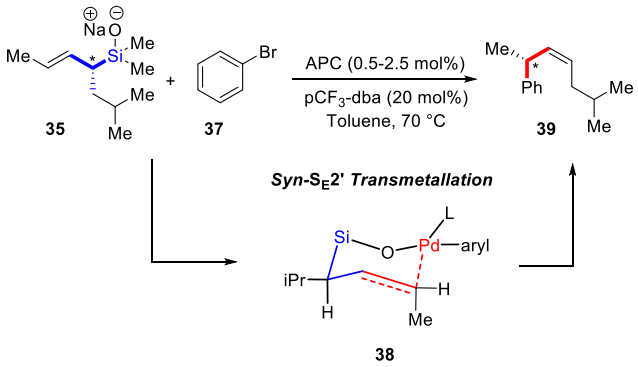
An intramolecular cyclisation of **32** was reported by Szabó and co-workers. This reaction, catalyzed by $Li_2[PdCl_4]$ proceeds through a palladadesilylation of the allyl silane, forming η-3 allyl palladium (II) intermediate **34**, which subsequently undergoes intramolecular nucleophilic attack. Reoxidation of the palladium center with $CuCl_2$ regenerates the initial Pd(II) species and affords **32** as the sole cyclisation product through a 5-exo-dig cyclisation (Scheme 7.) 8 substrates were reported in moderate yields, with substitution at both the 4 and 5 positions of the ring.[20] A similar body of work by the same authors expanded on this initial report, also exploring tosyl sulfonamides as nucleophiles, allowing for the synthesis of N-Tosyl pyrrolidines using the same methodology. Notably, this work also included *in silico* mechanistic studies, which suggests the implication of a weak hyperconjugation between the filled Si-Cσ orbital and a relatively high lying Pd-CCπ* orbital.[21]



Scheme 7. Pd catalyzed cyclization of allyl silanes bearing a tethered hydroxyl group

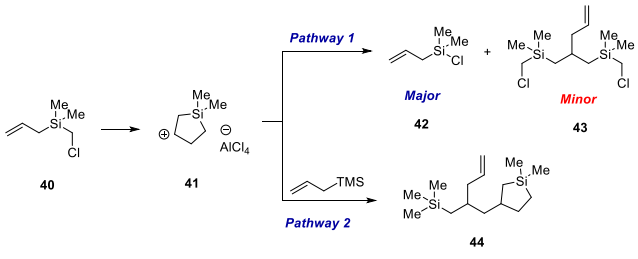
In 2008, Denmark and co-workers studied the palladium catalyzed cross-coupling of **35** with **37**, a method which circumvents the need for fluoride activation of the silane. The reaction proceeded well with a variety of electron rich aromatics with allyl-TMS as the allylating agent, with electron deficient rings proving to be less effective substrates. Applying the same reaction conditions to a branched allylic silanolate resulted in a poor regioselectivity of the allylation, with the α and γ allylated products formed in approximately equal amounts. Thus, the reaction conditions for these branched silanolates were

reoptimized, and the optimal conditions found to be palladium centers bearing olefin ligands, such as $[Pd_2(dba)_3]$. [22] In a later study, Denmark and co-workers then extended this methodology to the coupling of optically active allyl silanes with aryl bromides in an enantiospecific manner. Despite the well-established knowledge of the general *anti* reactivity of allyl silanes, the use of silanolates in this body of work opens up the possibility for the reaction to proceed through closed transition state **38**, with a Si-O-Pd linkage proposed to be crucial in the delivery of the *syn* mechanism, and resultantly the formation of the *R*-(E) product (Scheme 8.)[23]



Scheme 8. Cross coupling of allylic silanolates with aryl bromides through a proposed closed transition state

In 2004, the intramolecular allyl migration reaction of **40** was reported by Il Nam Jung and co-workers. This reaction, catalyzed by $AlCl_3$ proceeds through the cationic intermediate **41**, which is then either attacked intermolecularly by another equivalent of allyl silane affording **43/44**, or is reattacked by a chloride ion, resulting in the formal allyl migration product **42** as shown in Scheme 9. In all cases, the authors noted a competing allylsilylation pathway, although this was observed to be the minor product regardless of the nature of the starting material, due to the predominance of the intramolecular process.[24]

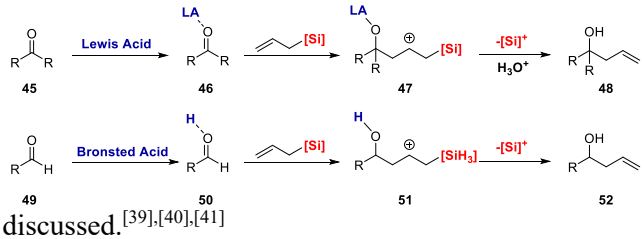


Scheme 9. Allyl migration at aluminium centres

As was initially reported by Hirao in 1981, the β-silicon effect is particularly pronounced in directing the regio chemical outcome in Tsuji-Trost allylic substitutions.[25] This initial report found that a variety of nucleophiles were amenable to the reaction, including several malonates and enamines, with the reaction proceeding well in each case. Regardless of reaction conditions, the resultant vinyl silane was afforded as a mixture of E/Z isomers. Subsequent studies of this reaction employing optically active starting materials, with the reaction proposed to proceed by an inversion-inversion pathway.[26]

2.1.3 Lewis Acid & Lewis Base Mediated Allylation of Carbon Electrophiles

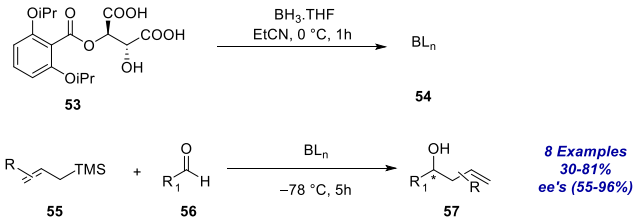
The Hosomi-Sakurai allylation is the acid promoted desilylative-addition of allyl silanes into carbon electrophiles, which notably provides distinct stereochemical outcomes in comparison to other allyl metal reagents, as noted by Denmark.[27] While the initial report utilized a carbonyl electrophile, [28] a variety of electrophiles have been reported including α,β-unsaturated carbonyl compounds,[29] imines/iminium ions,[30] epoxides,[31] acyl halides[32] and oxocarbenium ions.[33] Equally, the scope of the reaction has been thoroughly explored, as have the compounds which are able to catalyze the transformation. The original report utilized titanium tetrachloride as the activating agent, but a variety of other Lewis and Brønsted acids have been shown to mediate the reaction. These include organosilicon compounds,[34] borane derivatives,[35] transition metal salts and complexes,[30] alkali earth metals[36] and main group superacids.[37], [38] The Hosomi-Sakurai allylation is an extensively studied reaction, and as such is already the study of several reviews in itself. As the purpose of this review is to provide a more general overview of the application of silyl stabilized cations, rather than in-depth advancements in a single reaction methodology, only highlighted examples of advances in enantioselective allylations will be discussed.[39],[40],[41]



Scheme 10. Lewis & Brønsted Acid catalyzed Hosomi-Sakurai allylation of ketones

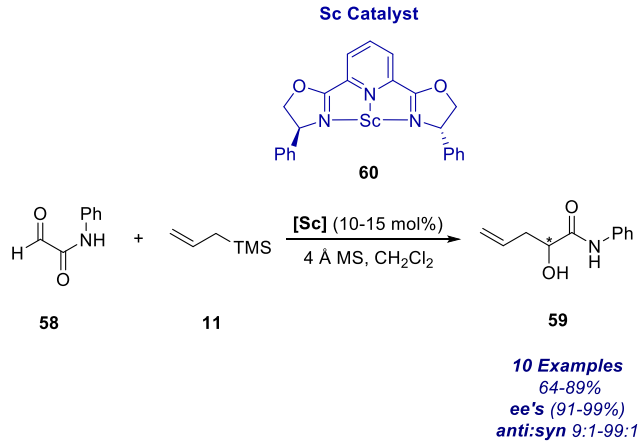
One particularly attractive factor of the Hosomi-Sakurai allylation is the potential for application of chiral Lewis acid activation of the electrophile, allowing for enantioselective allylation of the relevant electrophile. Enantioselective allylation of aldehydes and imines in particular is a well explored process. The first example of enantioselective aldehyde allylation included the report by Yamamoto and co-workers, who utilized the chiral acyloxy borane species **53** to activate a variety of aldehydes towards enantioselective allylation in moderate to good yields with moderate to excellent enantioselectivities (Scheme 11.) It was reported that the reaction of simple allyl-TMS was insufficient to provide high

yields of the desired products, an issue which was overcome *via* application of more reactive silanes of general formula **55**.[42],[43]



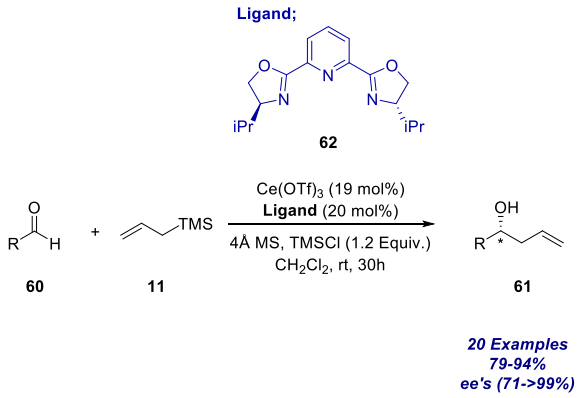
Scheme 11. Enantioselective allylation of aldehydes with allyl-TMS using a chiral Lewis acid

Evans and co-workers later reported the scandium catalyzed addition of allyl-TMS derivatives to glyoxyamide derivatives. This addition, catalyzed by Sc-Pybox complex **60**, affords **59** in both high enantio- and diastereoselectivity (Scheme 12._ This method was applied to the synthesis of *N*-Boc d-Alloisoleucine and d-Isoleucine.[44] Interestingly, whereas previous work had shown the reaction to be stereoconvergent with respect to the alkene geometry in the starting material, E and Z alkenes in this case displayed complementary stereoselectivities in this case.



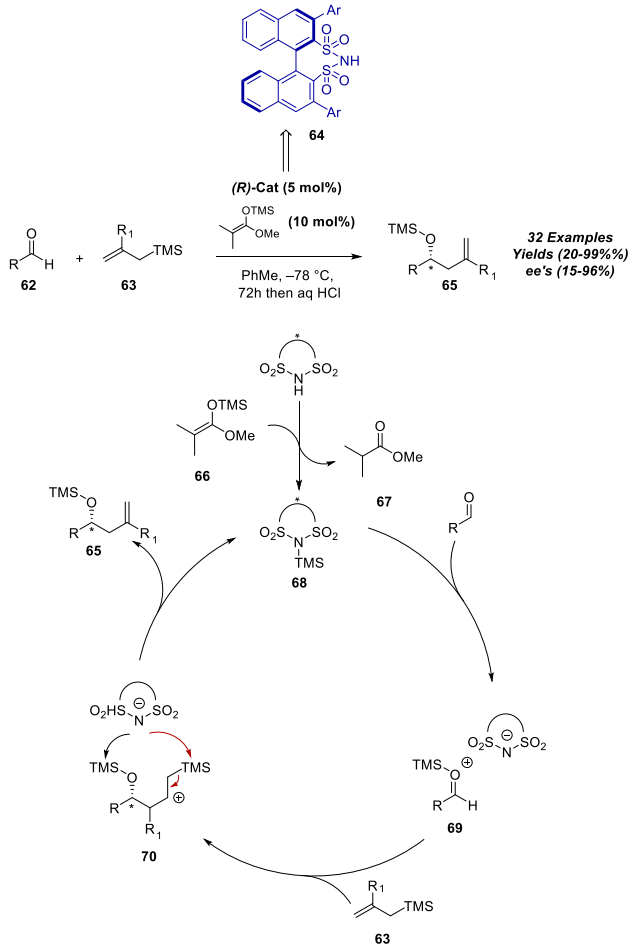
Scheme 12. Enantioselective allylation of glyoxamide using a chiral scandium catalyst

A similar approach was recently used by Du and colleagues, utilising chiral cerium PyBox complex **62** to achieve the enantioselective allylation of aldehydes in good to excellent yields and enantioselectivities (Scheme 13.) Using the optimised conditions, with stoichiometric TMSCl as an activator, a variety of both aliphatic and aromatic aldehydes were successfully allylated.[45] While the reaction is highly successful with both aliphatic, and *para*/unsubstituted aromatics, introducing substitution at the *meta* or *ortho* site on the aromatic ring leads to a dramatic decrease in the enantioselectivity of the reaction.



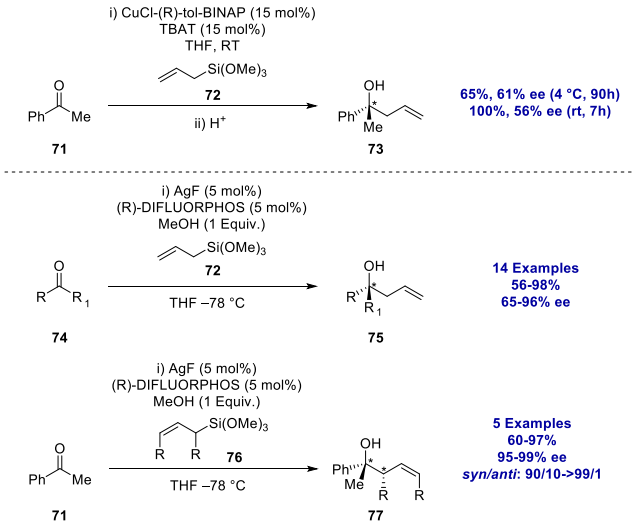
Scheme 13. Enantioselective allylation of aldehydes with a chiral cerium catalyst

A different approach to the asymmetric Sakurai allylation was utilized by List and co-workers in their 2012 study on the counterion directed asymmetric allylation of aldehydes. In this case, rather than a chiral Lewis acid activating the electrophile, chiral sulfinimide **64** reacts as a Brønsted acid with silyl ketene-acetal **67** to form **68** *in-situ*. Coordination of the aldehyde and liberation of the chiral anion generates the activated electrophilic species **69** for subsequent allylation. The overall catalytic cycle for the reaction is shown in Scheme 14.[46]



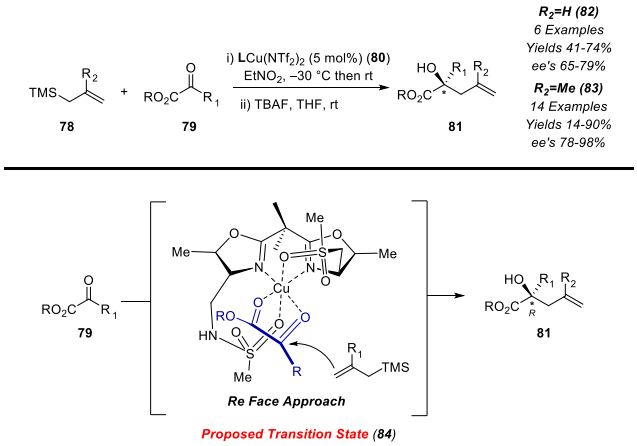
Scheme 14. Enantioselective allylation of aldehydes using a chiral Brønsted acid catalyst

The enantioselective addition of allyl silanes to ketones however, has proven to be more challenging. The first report of an enantioselective addition of an allyl silane to a ketone was reported by Shibasaki in 2002. The copper catalyst system used in this study was initially applied to the non-asymmetric allylation of aldehydes, ketones and imines with only one example of an asymmetric allylation. The allylation of acetophenone was achieved using a Cu-BINAP complex with a moderate yield (65%) and enantioselectivity (ee 61%) achieved when the reaction was carried out at 4 °C. The yield could be improved to >99% with a slight drop in enantiomeric excess (56%) when the reaction was warmed to room temperature.[30] These moderate selectivities were enhanced significantly in the work of Yamamoto in 2005. In this study, the authors utilized a chiral Ag-diphosphine complex to achieve the enantioselective allylation of a variety of simple ketones in moderate to excellent yields with good to excellent enantioselectivities. Notably, when using branched allylic silanes, the catalyst system was able to combine its excellent enantioselectivity with high levels of diastereoselectivity, with the reaction affording the *syn* isomer in both high stereoselectivities and moderate to excellent yields (Scheme 15.)[47]



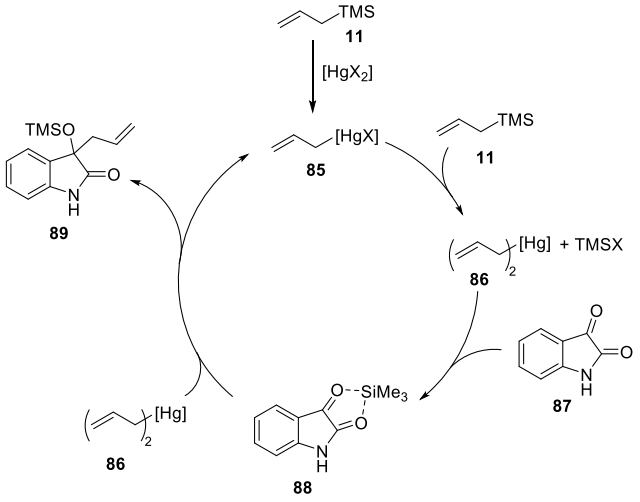
Scheme 15. Enantioselective allylation of ketones by chiral transition metal complexes

More recently, the enantioselective Hosomi-Sakurai reaction of **79** was reported by Sakakura and co-workers. This reaction was shown to be efficiently catalyzed by copper-*bis*-triflimidate complex **80**, with enantioselectivity imparted by the application of a chiral bis(oxazoline) ligand bearing methanesulfonamide groups. The reaction, which proceeded in nitroethane with 5 mol% catalyst at room temperature, was shown to be able to readily proceed with a variety of esters, affording the allylated carbinol **82** in generally moderate to good yields with moderate to good enantioselectivities. When the more reactive methallyltrimethylsilane was employed, both yields and enantioselectivities were significantly improved, presumably due to the increased steric hinderance around the reactive site. The proposed transition state **84** through which the reaction proceeds is shown in Scheme 16. [48]



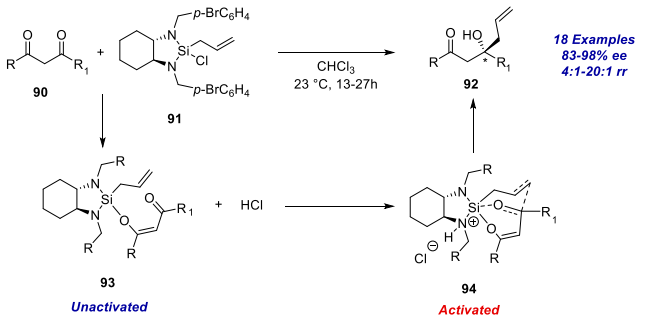
Scheme 16. Cu catalyzed enantioselective allylation of α-ketoesters

While much of the work regarding the enantioselective Lewis acid catalyzed Hosomi-Sakurai employs the use of a chiral metal species to activate the electrophile, Zhou and co-workers utilized the chiral metal species in an alternative manner. In this mercury catalyzed approach, the allyl silane initially reacts with the mercury complex to form allyl mercury species **82**, a much more potent nucleophile (Scheme 17.) This chiral nucleophile then attacks the electrophile, in this case isatins and isatinketoimines, affording **89** in excellent yields.[49] While the initial report used a Hg-BINAP complex, achieving only moderate enantioselectivies (55-63% ee), the subsequent report utilized a Hg-difluorphos complex, with much greater enantioselectivities achieved.[50]



Scheme 17. Allylation of isatinketoimines using a silicon-mercury transmetallation approach

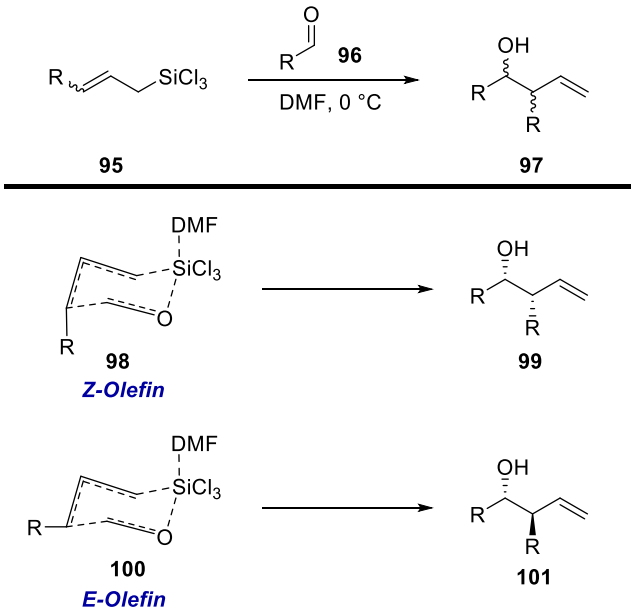
Leighton and co-workers considered a significantly different approach when studying the asymmetric synthesis of allylated tertiary carbinols. They proposed that the allylation of **90**, species notable for their significant degree of enol-like characteristics, could be carried out *via* formation of **93**, which would then undergo intramolecular allylation. The formation of this intermediate would then allow the issue of enol reactivity to be masked. The poor reactivity of these functionalities towards allylation was overcome *via* conversion into **84**, which following β-aminosiloxyenone formation, was activated with the liberated HCl, thus increasing reactivity and rate of reaction towards the ketone (Scheme 18.) Formation of the chiral amino silyl chloride allowed for the operationally simple allylation of 1,3-diketones with moderate to excellent yields, with enantioselectivities generally in the >90% ee range, and high levels of regioselectivity when unsymmetrical diketones were employed.[51]



Scheme 18. Enantioselective Allylation of 1,3-diketones.

Another class of organosilanes frequently applied in allylation chemistry is allyl trichlorosilane and compounds derived thereof. Whilst previous allylation reactions generally require the activation of the electrophile via either Brønsted or Lewis acid activation, in this case, the more Lewis acidic silicon centre is activated by a Lewis base, either the electrophile itself or via addition of an external Lewis basic catalyst. As with the Sakurai allylation in general, these types of reagents have previously been reviewed, and so only a general overview and some notable examples and applications will be provided here.[52]

Early work by Kobayashi demonstrated the activation of the allylating agent by the electrophile in these cases. The 1994 study by Kobayashi and Nishio concerning the synthesis of homoallylic alcohols via allylation of the parent aldehyde afforded the alcohols in a stereoselective manner, with the geometry of the allyl silane dictating the *syn*/*anti* relationship of the product. The reaction was proposed to proceed through a closed transition state, with the authors proposing the intermediacy of a 5 or 6 membered silicate intermediate which could be detected by ^{29}Si NMR. The dependency of the reaction on Lewis basic activation of the silane was shown by the solvent dependency of the reaction. Whilst the reaction readily proceeded in solvents such as DMF, solvents such as toluene and benzene shut down reactivity entirely. Using other solvents in conjunction with DMF as an additive similarly allowed the reaction to proceed. [53]



Scheme 19. Lewis base activation of allyltrichlorosilanes towards carbonyl allylation.

Subsequent work by the Kobayashi group, amongst others, began to explore to scope of Lewis bases which were able to promoto this reaction, beyond DMF. Several other nitrogen derived bases were quickly revealed to be effective, including ureas, formamides and N-Heteroarenes.[54] Lewis bases featuring oxygen donors such as tartrates, phenols and N-Oxides have also successfully been used as additives in these types of reactions.[55] In each case, the reaction was again proposed to proceed through the same 6-membered closed transition state proposed by Kobayashi.

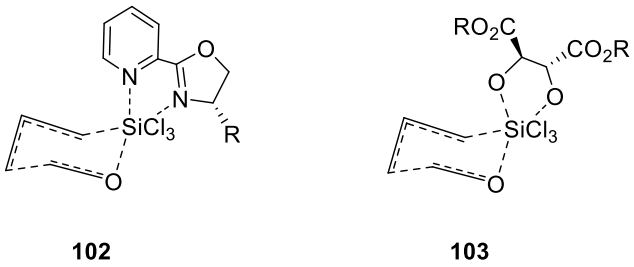
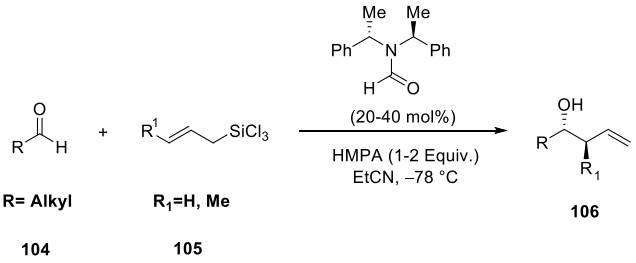


Figure 1. Proposed transition states of N-Heteroarene and tartrate activation of allyltrichlorosilane.

As shown in **Figure 1**, the application of chiral Lewis bases in these types of reactions affords the opportunity for enantioselectivity to be imparted on

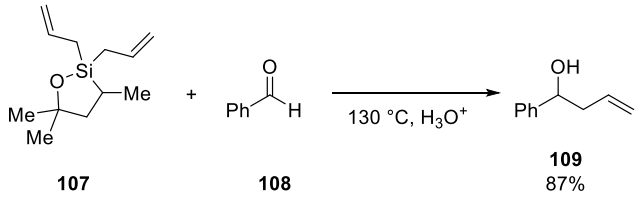
the transformation, a facet of allyltrichlorosilane which has been reviewed in depth by Denmark and Fu.[56] Phosphoramides in particular have found extensive application to these transformations, as first demonstrated by Denmark in 1994, although subsequent studies have dramatically expanded on the scope of phosphoramide catalysts able to promote allylation.[57] Whilst initially tempting to invoke the transition states shown in **Figure 1**, Denmark had previously noted a dependence of enantioselectivity on concentration of phosphoramide, a phenomenon which was explored in a later mechanistic exploration. This revealed two pathways in operation, the more selective pathway in operation at higher concentrations of phosphoramide being second order with respect to promoter.[58]

Unsurprisingly, given the initial observation of DMF promoted allylation, optically active formamides have also found application in the enantioselective allylation of aldehydes. Early examples by the Kobayashi group utilised a (*S*,*S*)-*N*,*N*-Bis(α-methylbenzyl)formamide in conjuction with stoichiometric amounts of hexamethylphosphoramide in order to achieve the asymmetric allylation of a variety of aliphatic aldehydes using allyltrichlorosilane affording the corresponding *anti* allylic alcohols **106**.[54a, 59] Similarly to the case of phosphoramides, multiple reaction pathways are suggested by the dependency of catalyst loading of these reactions.



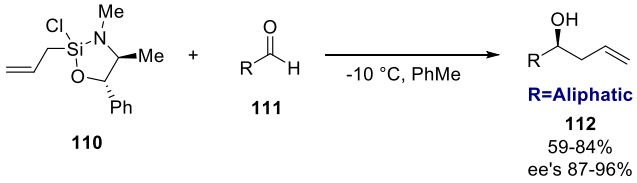
Scheme 20. Proposed transition states of N-Heteroarene and tartrate activation of allyltrichlorosilane.

The Leighton group has contributed extensively to the application of organosilanes in allylation chemistry. In particular, the group has extensively explored the utilisation of strained silacycles as allylating agents. The first example of this was reported by Leighton and Zacuto in 2000. The authors report the pyrolysis of silacycle **107** in the presence of benzaldehyde to afford the allylated product.[60] The efficacy of this reagent in allylation chemistry is due to 'strain release Lewis acidity' as reported by Denmark.[61]



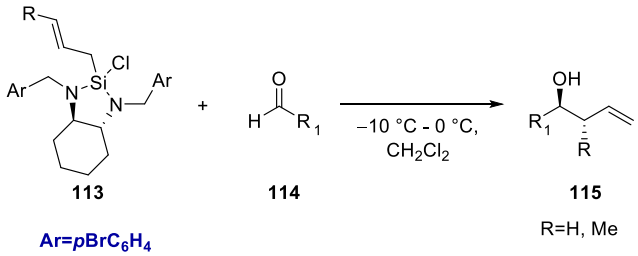
Scheme 21. Allylation of benzaldehyde using a strained, Lewis acidic silicon heterocycle

Subsequent work by the group explored the use of optically active pseudoephedrine derived silacycles **110** in these allylations. The silacycle was formed via reaction of (*1S,2S*)-pseudoephedrine with allyltrichlorosilane and Et_3N in CH_2Cl_2 and afforded the corresponding cyclised product in a 2:1 mixture of diastereomers. Using these chiral silacycles, the authors were able to allylate a variety of aromatic and aliphatic aldehydes in enantioselectivities ranging from 78-96%. Interestingly, by attenuation of the Lewis acidity of the silicon atom, the reaction could now be carried out at −10 ˚C.[62] Further applications were later explored by the same group regarding the enantioselective allylation of acyl and benzoyl hydrazones.[63]



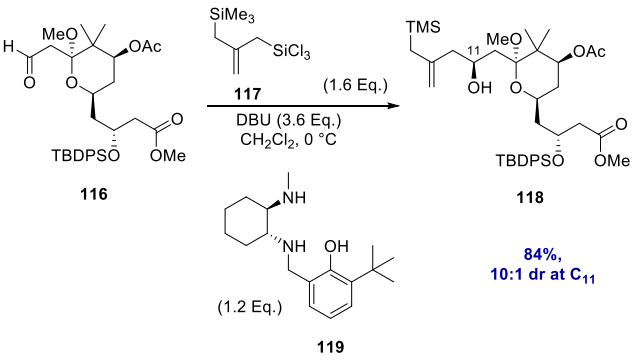
Scheme 22. *(1S, 2S)*-pseudoephedrine derived asymmetric allylating reagents

Related C_2-symmetric compounds derived from N,N-dialkylcyclohexanediamine later showed promise as enantioselective allylation agents, effectively allylating a variety of aldehydes in excellent enantioselectivities. Notably, this reaction could be carried out under very mild conditions, with several examples being carried out at 0 ˚C. Also worth noting is that allylating agents are crystalline, easily prepared and stable under ambient conditions.[64] Subsequent work revealed that the same type of reagent can likewise be applied to the crotylation of aldehydes with excellent levels of enantioselectivity and diastereoselectivity.[65] Imines bearing a 2-hydroxyphenyl directed group are also amenable to allylation and crotylation using these reagents.[66]



Scheme 23. C_2-Symmetric asymmetric allylation reagents

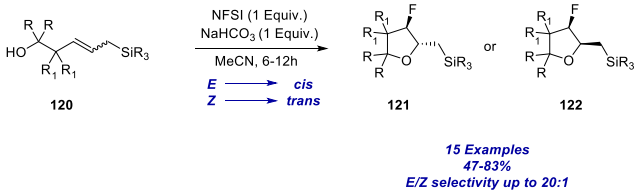
A further class of silanes which has found extensive application in allylation chemistry are allyldisilanes. In particular, orthogonally functionalised allyldisilanes are particularly attractive due to the two distinct modes of activation required to utilise each silyl moiety as an allylating agent. The first reported synthesis of these orthogonally functionalised disilanes was in 2011 by Kočovskỳ and co-workers, who applied the reagent to the stereoselective construction of furan scaffolds through a triple allylation approach. Utilisation of a chiral N-Oxide acting as a Lewis base allowed for high levels of enantioselectivity to be achieved.[67] The rich synthetic utility of these species was demonstrated in 2017 by Stevens and co-workers in their total synthesis of bryostatin 1 and various analogues thereof. The allylation of intermediate **116** using allyldisilane **117** was carried out on a multigram scale (>25 mmol) with a chiral aminophenol catalyst affording the allylated product with high (10:1) levels of diastereoselectivity. Most notably, whilst the initial allylation took place via Lewis base activation, resulting in loss of the trichlorosilane group, the remaining trimethylsilyl group remained intact, allowing several more synthetic manipulations to take place before the second allylation was carried out under acidic conditions. [68]



Scheme 24. Allyldisilane allyation towards the total synthesis of bryostatin 1

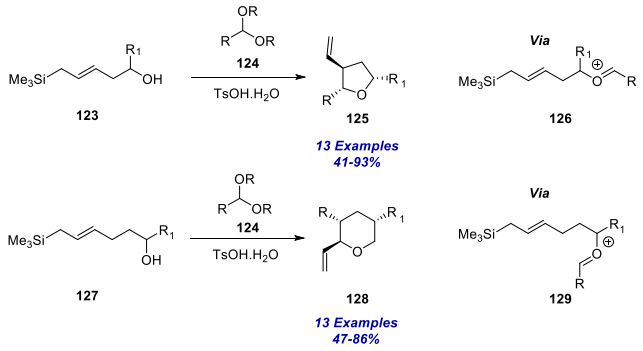
2.1.4 Cyclisation of Allyl Silanes

Silyl stabilized cations arising from electrophilic activation and subsequent cyclization of an allyl silane bearing a tethered nucleophile has proved a fruitful method to access cyclic compounds from stable and easily prepared precursors. Gouverneur and co-workers utilized the silicon directed fluorocyclisation of **120** to access a variety of oxy-heterocycles.[69] In this work, the choice of the silyl group was crucial to the reaction outcome, with dimethyl phenyl silane undergoing desilylative-fluorination exclusively, with no cyclized product observed. Interestingly, this work showed that the major diastereomer produced in the reaction is entirely dependent on the stereochemistry of the starting materials, with *E* alkenes forming **121**, While *Z* alkenes formed **122** (Scheme 25.) While useful, the starting materials, and resultantly the products, contained varying amounts of both alkene isomers, resulting in a mixture of diastereomers in the products. This arises from the use of Grubbs chemistry to access the allylic silanes. Boc and tosyl protected amines also serve as intramolecular nucleophiles in another study by the same group, although in this case, the desilylation pathway could not be entirely shut down, presumably due to the highly deactivated nature of the nucleophiles.[70]



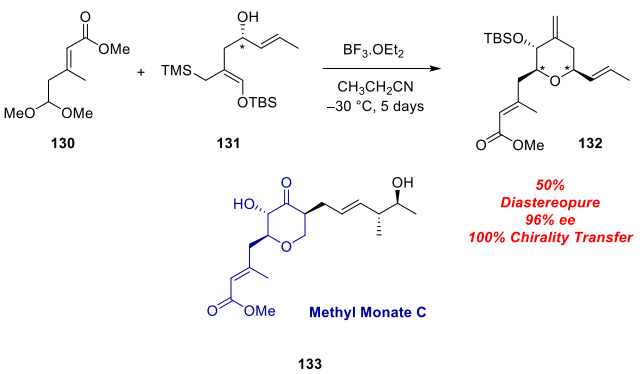
Scheme 25. Fluorocyclisation of Allylic Silanes bearing a Tethered Oxygen Nucleophile

Aside from electrophilic cyclisation, allylic silanes have frequently been employed as nucleophiles in intramolecular Prins cyclisations, affording diverse cyclic scaffolds while minimising the regioselectivity issues and harsh reaction conditions associated with a classical Prins reaction. This was demonstrated in seminal work by Mohr, who demonstrated the reaction between **123**/**127** and **124** under acidic conditions readily affords the corresponding furan or pyran. This reaction occurs *via* initial nucleophilic attack of the hydroxyl group at an oxocarbenium ion generated from the acetal (Scheme 26.) A second acid mediated oxocarbenium formation, and subsequent nucleophilic attack from the allyl silane followed by desilylation affords the cyclic product.[71] The Silyl-Prins cyclisation of allyl silanes, being a mild way to access highly privileged scaffolds, has been the subject of reviews in its own right and as such, a detailed breakdown of advancements in its methodology is outside the scope of this review and therefore only notable examples will be highlighted and discussed.[72]



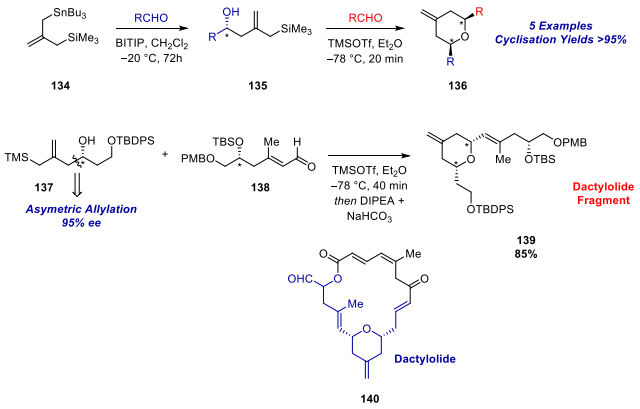
Scheme 26. Prins reactions of allyl silanes towards oxy-heterocycles

As a result of the high value heterocyclic scaffolds afforded by the silyl-Prins reaction, it is of little surprise that significant attention has been directed towards realising an asymmetric variant. Predominantly this has resulted in the utilisation of optically active starting materials, which then display little racemisation through the course of the reaction, providing a method to enantioselectively access the corresponding heterocycle. Such methodology was utilized by Markó and co-workers within their total synthesis of methyl monate C **133**, the methyl ester derivative of pseudomonic acid C shown in Scheme 27. Obtaining enantioenriched alcohol **131** *via* enantioselective reduction of an enone precursor using a BINAL-H derivative, the authors were able to obtain the *Z*-allylic silane in 96% ee. This silane then underwent cyclisation with **130** in the presence of $BF_3.OEt_2$, affording the *2,6-cis-2,3-anti* tetrahydropyran **132** with complete chirality transfer and complete diastereoselectivity. [73]



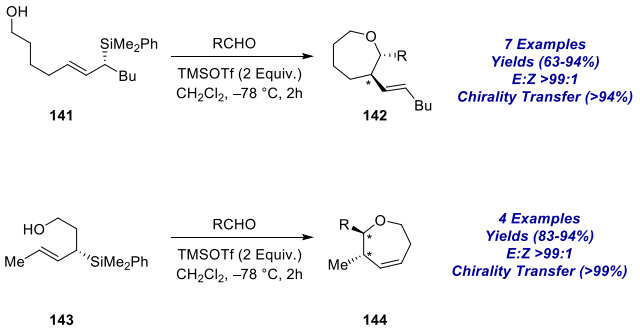
Scheme 27. Application of the silyl-Prins reaction towards the synthesis of Methyl Monate C

A similar approach had been previously utilized by Keck and Sanchez in their total synthesis of (+)-Dactylolide **140**, albeit it with the chirality being set by enantioselective allylation as opposed to enantioselective reduction, and the same methodology was shown by the same group to be broadly applicable to the asymmetric synthesis of several other tetrahydropyrans shown in Scheme 28.[74],[75]



Scheme 28. Application of the silyl-Prins reaction towards the synthesis of Dactylolide

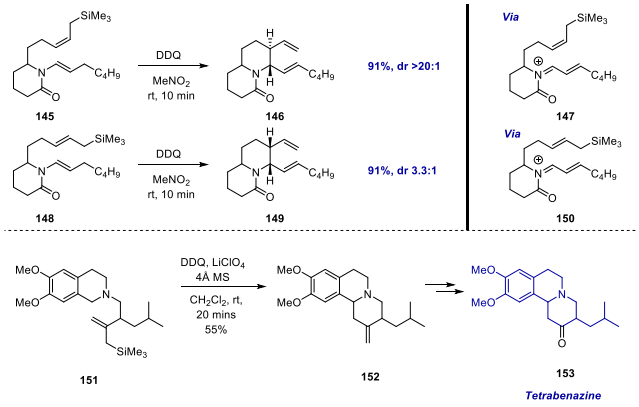
While the Silyl-Prins reaction has predominantly been applied to the synthesis of furans and pyrans, the methodology has been extended to the synthesis of larger oxy-heterocycles including oxepanes and oxocanes. Ito and co-workers applied the methodology to the synthesis of 7-membered rings from optically active allylic silanes (Scheme 29). Treating these allylic silanes with a suitable aldehyde in the presence of 2 equivalents of TMSOTf afforded **142** with excellent chirality transfer and high levels of diastereoselectivity.[76] Simple alteration of the starting alcohol allows the eventual alkene to be formed as either part of the heterocycle, or as an exocyclic functionality (**144**).[77]



Scheme 29. The silyl-Prins reaction in the synthesis of homologated oxy-heterocycles

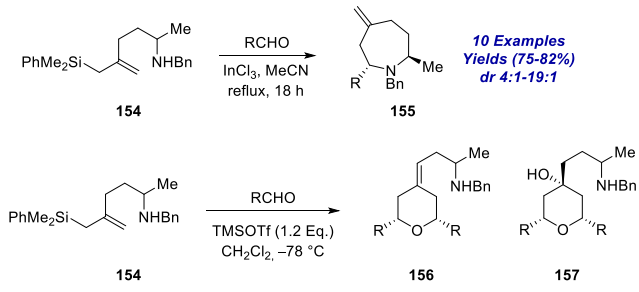
Although the majority of the studies describing the silyl-Prins reaction report the synthesis of oxy-heterocycles, several methods have been reported to access the analogous aza-heterocycles, principally N-protected piperidines and pyrrolidines. The iminium ion can be formed either from a standard acidic amine/aldehyde condensation, or by acid mediated elimination of an N,O-acetal. Both the multicomponent and single component approaches

have proved viable in the synthesis of both pyrrolidines and piperidines.[78],[78b, 79] [80] Another less intuitive way iminium ions have been generated is *via* DDQ mediated oxidation of enamines **145/148**, which following subsequent iminium formation, undergoes intramolecular Prins cyclisation.[81] A similar DDQ mediated imine formation was used previously by Min & co-workers in their synthesis of the vesicular monoamine transporter-2 inhibitor tetrabenazine **153**, with Upjohn dihydroxylation of the resultant alkene and oxidative diol cleavage affording the final product (Scheme 30.)[82]



Scheme 30. The intramolecular trapping of an iminium ion, formed by DDQ oxidation of an enamine, with allyl silanes

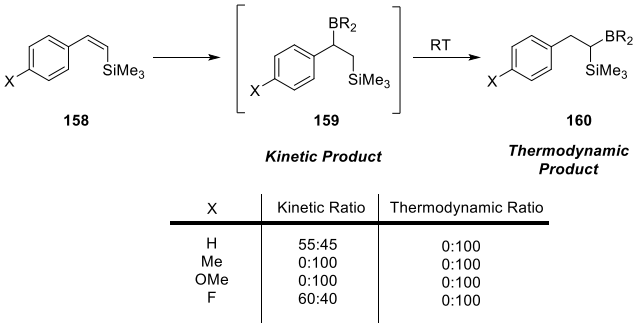
The synthesis of larger homologs of these aza-heterocycles is more scarcely reported. In 2016, González-Ortega *et al* reported the first synthesis of azepane derivatives *via* the silyl-aza-Prins reaction. This work relied on the condensation between an aldehyde and benzylamine derivative **154**, forming an iminium ion *in-situ* which then underwent nucleophilic attack by the tethered allyl silane. Interestingly, the choice of Lewis acid had a significant effect on the course of the reaction. When TMSOTf is employed as the choice of acid, the product arising from a Sakurai/Prins cascade arises, whereas indium (III) chloride proved effective at solely catalysing the desired aza-Prins reaction, affording azepanes **155** in good yields with moderate to good levels of diastereoselectivity (Scheme 31.)[83]



Scheme 31. The silyl-Prins reaction in the synthesis of homologated aza-heterocycles

2.2. Vinyl Silanes

The polarisation of unsaturated C-C bonds as a result of the β-silicon effect plays a key role in the hydroboration of vinyl silanes as reported in 1998 by Piers and Parks. In this work, the authors studied the effect of varying the steric bulk of the vinyl silane in relation to the regiochemical outcome of the hydroboration of **158** with *bis*-pentafluorophenylborane. As boranes are isoelectronic with carbocations, the stabilization of carrying out a hydroboration of an allyl silane affording a 1,1-silylborane is shown to generally override the apparent significant steric clashes that exist within these compounds. While under kinetic control, the less hindered isomer **159** is generally formed, at room temperature the mixture readily isomerises to the more thermodynamically favoured 1,1- isomer **160**. This effect is even more pronounced on internal vinyl silanes, where the discrepancy in steric clashes isn't as pronounced as the terminal olefins (Scheme 32.) In these cases, even under kinetic control with electronics which would favour the kinetic product formation, there is an approximately equal distribution of kinetic and thermodynamic product formed. In cases where electronics are more favourable for the thermodynamic product, no kinetic product was formed.[84]

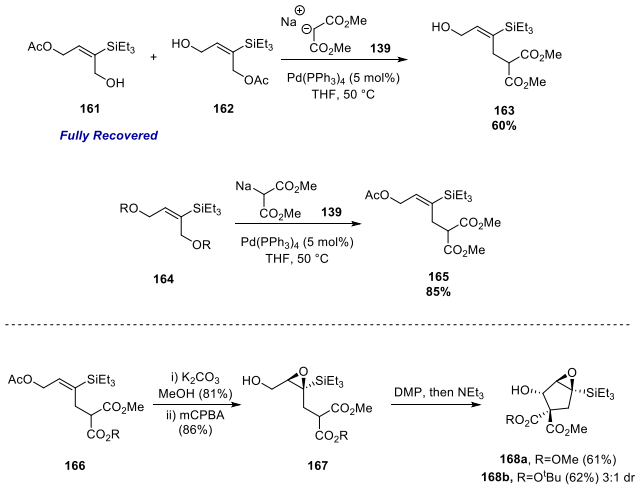


X	Kinetic Ratio	Thermodynamic Ratio
H	55:45	0:100
Me	0:100	0:100
OMe	0:100	0:100
F	60:40	0:100

Scheme 32. The β-silicon directed hydroboration of olefins using HB(C6F5)2

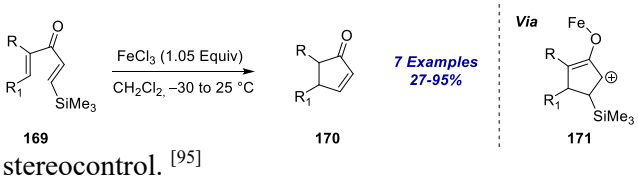
The stabilization of cations formed from leaving groups in an allylic position was shown to be capable of directing a regioselective palladium catalyzed allylic substitution (Scheme 33.) The study, by Malacria and Thorimbert, shows that in competition experiments between **161** and **162** the rate of reaction at the silyl stabilized site is significantly faster than the non-stabilized site, to the extent that the non-stabilized substitution pathway is effectively shut down.[85] Subsequent studies by the same group also demonstrated that the substitution is largely stereo-retentive with respect to the geometry of the double bond,[86] with all experimental observations being supported by subsequent computational calculations.[87] The same group were able to subsequently apply the methodology to the synthesis

of silylated epoxypentanols **168**[88] and polyhydroxylated piperidine based natural products including (±)-Deoxymannojirimycin.[89],[90]



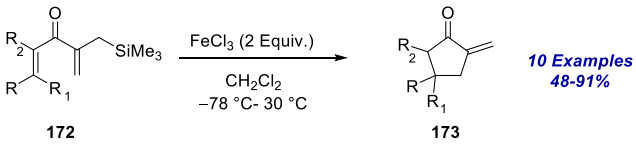
Scheme 33. Competition studies showing the rate increased of silyl stabilized sites in allylic substitution reactions, and the application of this reaction in the synthesis of silylated epoxycyclopentanes

In much the same manner as allyl silanes, vinyl silanes have found widespread application in a variety of cyclisations proceeding through a silicon stabilized cationic intermediate.[91] This was exemplified by early work in the Denmark group, where the application of β-silyl divinyl ketones **169** were utilized in a silicon directed Nazarov cyclisation, where the position of the resultant carbon-carbon double bond is directed by the by loss of silicon, overcoming a considerable drawback of the classical Nazarov cyclisation (Scheme 34.) A variety of Lewis acids were screened, with iron(III) chloride found to be the most efficient promotor of the reaction, with the reaction being broadly tolerant to an array of functional groups, and displaying good levels of stereoselectivity.[92],[93],[94] Further work in the Denmark lab extended the methodology to the synthesis of a variety of fused tricycles affording 6-5-6, 6-5-5 and 5-5-5 fused ring systems using either an $FeCl_3$ or $BF_3.OEt_2$ with excellent levels of regio and stereocontrol. [95]



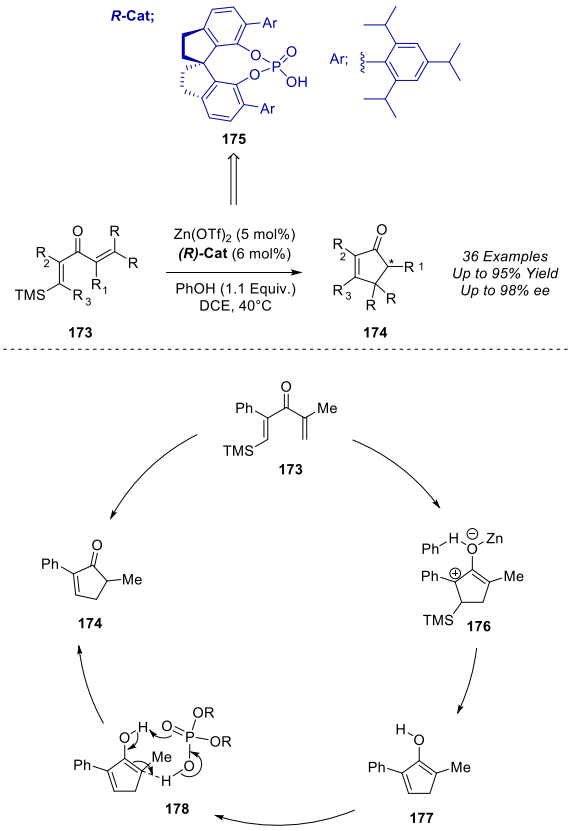
Scheme 34. Iron (III) chloride mediated cyclisation of β-silyl divinyl ketones

Several years after Denmark's initial reports, it was found that alteration of the silylated site allows the position of the final olefin to be controlled. This was shown to be able to direct the subsequent position of the alkene to an exocyclic position 3as with **17**. As with the report by Denmark, it was found that iron chloride most efficiently mediates the process, and the reaction can be applied to the synthesis of bi and tricycles bearing an exocyclic methylene group (Scheme 35.)[96] This process could be applied to the synthesis of fused bi and tricycles in excellent yields from thienyl and napthyl aldehydes, with the intermediate non-aromatic ring system quickly oxidised by trace $FeCl_2$ to regenerate the lost aromaticity.



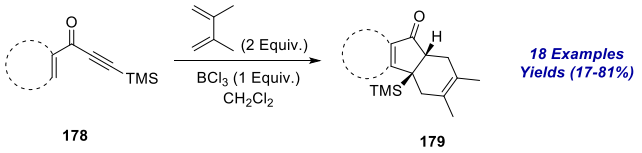
Scheme 35. Iron (III) chloride mediated synthesis of methylene substituted cyclopentanones

Recently, chiral spiro-phosphoric acid **175** in conjunction with $Zn(OTf)_2$ was used to achieve an enantioselective Nazarov cyclisation of **173** in both excellent yields and enantioselectivies. The reaction, which also requires stoichiometric phenol to act as a proton donor, affords a variety of cyclized products in high yields and enantioselectivities. The reaction was shown to be highly dependent on the nature of the silicon substituent, with bulkier groups resulting in decreased yields and enantioselectivities. The reaction in this case proceeds as with a standard silicon-directed Nazarov rearrangement, but with the penultimate enol intermediate **177** undergoing enantioselective proton transfer by virtue of the phosphoric acid in this case, affording the optically active product as depicted in Scheme 36.[97]



Scheme 36. The enantioselective, silicon directed Nazarov rearrangement

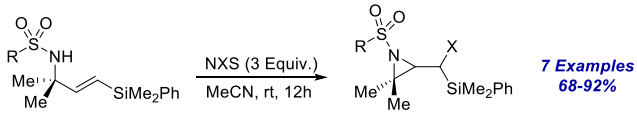
Vinyl silanes, and the silyl stabilized cations derived thereof, were proposed to be key intermediates in the tandem Diels-Alder/Nazarov cyclisation reported by Chalifoux and co-workers (Scheme 37.) In this work, trimethylsilyl-protected aryl-ynones **178** were shown to undergo [4+2] cycloaddition with a suitable diene to yield the expected product, which is primed for silicon-directed Nazarov cyclisation, mediated by BCl_3. Using this approach, several tricyclic cores of general structure **179** were accessed in varying yields, including scaffolds derived from valuable heterocyclic starting materials.[98]



Scheme 37. The tandem Diels-Alder/Nazarov cyclization proceeding through the formation of a silyl stabilized cation

The effect of hydroxylic additives to the silicon directed Nazarov cyclisations was studied by West and co-workers. The work was born out of the observation by the authors that the reaction efficacy is significantly decreased at larger scales, with decreased yields arising for reported oligomerisation of the products. The authors observed that the reaction was more effective when aged $FeCl_3$ was used, and therefore proposed that trace amounts of water in the catalyst actually aided the reaction. As a result, a screen of hydroxylic additives was carried out, resulting in previously low yielding substrates increasing, as well as permitting an increased scale of the reaction. Methanol was found to be the optimal additive, with the authors proposing a Lewis acid mediated Brønsted acid activation of the carbonyl, in addition to increased ease of protonating the dienolate intermediate.[99]

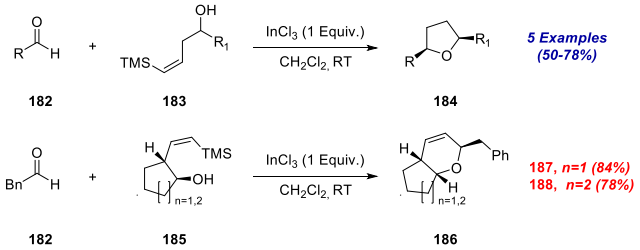
In 2021, McLaughlin and Roberts applied the electrophilic activation of silanes bearing tethered N-Sulfonyl amines (**180**) towards the synthesis of tetrasubstituted aziridines (Scheme 38.) In this case, the silanes were accessed *via* regio and stereoselective hydrosilylation of propargylic amines with a Pt-Xantphos catalyst system, a transformation which had previously proven difficult due to amine inhibition of the active catalyst. While the cyclisation afforded high yields of N-sulfonyl aziridines **181**, amides or amines proved to be less viable substrates, due to competing rearrangement pathways and 5-exo-dig



cyclisations.[100]

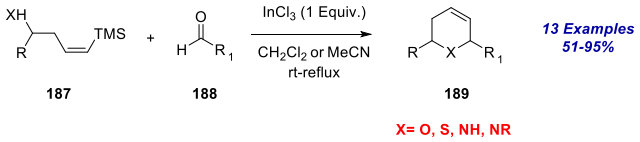
Scheme 38. Electrophilic halogenation/cyclization of N-Sulfonyl amines bearing tethered vinyl silanes

As with allylic silanes, vinyl silanes have been employed as cyclisation precursors in the silyl-Prins reaction, to afford a variety of heterocyclic scaffolds, although significantly more work has been reported on the use of allyl silanes in these reactions.[101] In 2002, Dobbs and co-workers utilized a silyl-Prins reaction to access a range of 1,5-*cis*-substituted dihydropryans **184**. Indium chloride was found to be the best catalyst for the reaction, proposed to proceed through a chair-like transition state, and the reaction was applied to the synthesis of a variety of mono and disubstituted rings, even allows for the synthesis of several fused bicycles **186** as shown in Scheme 39.[102]



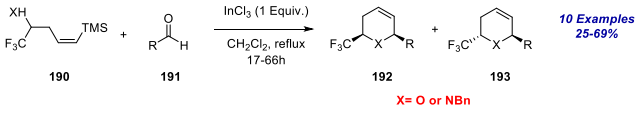
Scheme 39. Prins cyclization of vinyl trimethylsilanes to form 5 & 6 membered oxacycles

Similar methodology was utilized by Dobbs and co-workers in their 2003 study on the synthesis of unsaturated heterocycles via the silyl-Prins reaction. In this work, the authors demonstrated that the intermediate ion generated via indium (III) chloride mediated condensation of **187** with **188** could be intramolecularly trapped to form a variety of unsaturated 6 membered rings of general structure **189** as shown in Scheme 4. Several heterocycles could be formed from starting materials containing both alcohols, thiols and both primary and secondary amines. The products were isolated as a sole diastereomer, with the relationship of these groups proved via SC-XRD. Interestingly, while the thiol and alcohol derived products afforded the syn isomer, the aza-heterocycles were accessed as the anti-isomer, with a complete reversal of diastereoselectivity. The highest yields were afforded by the amine derivatives, with the thiol derived products isolated in generally lower yields.[103]



Scheme 40. Prins cyclization towards a variety of 6-membered heterocycles

The same group were also able to apply the same methodology to **190**, affording trifluoromethylated heterocycles **192** and **193**, scaffolds of high value within medicinal chemistry. As with the previous example, both oxygen and nitrogen heterocycles were accessed using this methodology, starting from the corresponding trifluoromethyl alcohol or amine (Scheme 41.) While the yields for the dihydropyran products were generally lower than the corresponding tetrahydropyridines, in all cases the yields were generally moderate. This decrease in yield versus previous examples of silyl-Prins reactions was attributed to the strongly deactivating effect of the trilfluoromethyl group on the alcohol or amine moiety.[104]

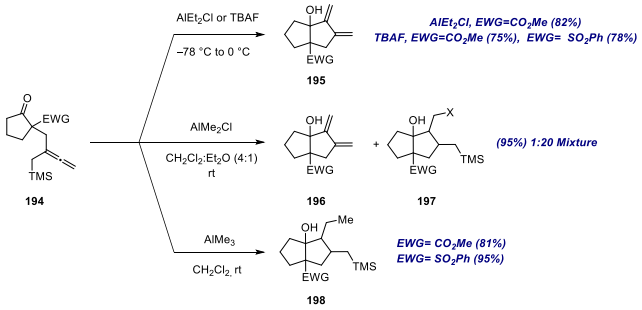


Scheme 41. Prins cyclization towards the synthesis of trifluoromethylated heterocycles

3 Silyl Alkynes

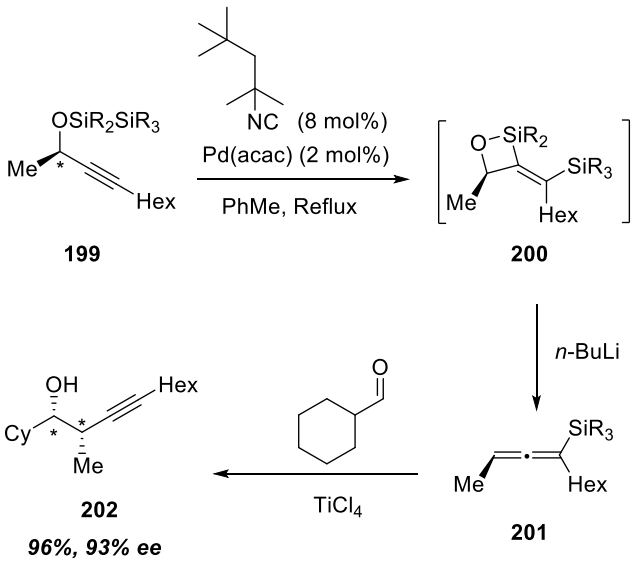
3.1. Allenyl Silanes

Allenyl silanes, isomers of propargyl silanes, have also been thoroughly studied in recent decades.[105] Early work by Trost and co-workers demonstrated the nucleophilicity of **194**, through their addition into carbonyl compounds activated with Lewis acids Scheme 42.) The nature of the reaction was shown to be highly dependent on the nature of the Lewis acid used, with both diethylaluminium chloride and tetrabutylammonium fluoride yielding **195**, while dimethylaluminium chloride resulted in the formation of both the **196** and **197** in a 1:20 ratio. This secondary product arises from group transfer to the intermediary allyl cation from the Lewis acid. Alkyl groups can be transferred to this cation in much the same way when trialkylallanes are the acid applied affording **198**.[106]



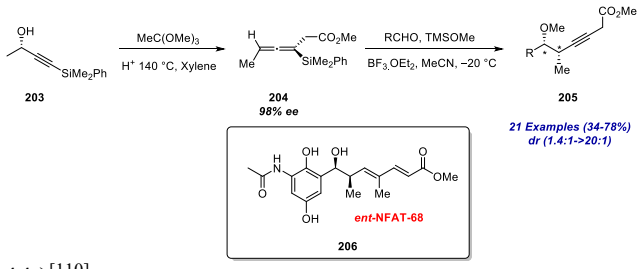
Scheme 42. Nucleophilic addition of allenyl silanes into activated ketones

An interesting facet of allene chemistry in general is the potential for atropisomerism, a feature which has implications in subsequent applications of allenyl silanes as nucleophiles. This was reported by Ito and co-workers in their Pd catalyzed *bis*-silylation of optically active **199**. Treatment of the resultant *bis*-silylated product with *n*-BuLi results in a Peterson-type elimination of the internal silane, forming enantioenriched allene **201**, with retention of stereochemistry from the initial alcohol. This then undergoes stereoselective addition to cyclohexane carboxaldehyde in the presence of titanium tetrachloride to yield **202** (Scheme 43.) The authors propose the selectivity of the addition of the allene into the aldehyde arises from the preference of the carbonyl to approach the π face of the reacting alkene on the face opposite to that of the silyl group, minimising steric repulsions.[107] In a similar study on the addition of allenyl silanes to enantioenriched 2-methyl-3-oxygenated propanals, the nature of the protecting group within the electrophile had a profound effect on the stereochemical outcome of the reaction, rationalized *via* the reaction proceeding *via* Felkin-Anh control in the case of the silyl ether protected alcohols, whereas a chelation controlled model more adequately explained the outcome of the benzyl ether protected propanals.[108]



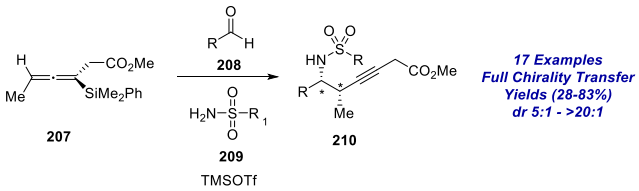
Scheme 43. Addition of enantioenriched allenes into activated carbonyl compounds

Panek and co-workers have carried out several studies on the nucleophilic addition of optically active allenes into electrophiles to afford enantioenriched products. In their 2007 study, Panek and Brawn utilized an oxocarbenium ion, derived from treatment of an aldehyde with TMSOMe in the presence of $BF_3.OEt_2$, as an electrophile, with the subsequent S_E2' yielding ethers of formula **205** in moderate to good yields, and excellent (>97%) ee's. In this case, the enantioselectivity is effectively identical to the ee of **204**, which is synthesized *via* Johnson-Claisen rearrangement of either the *R* or *S* enantiomer of **203**. The enantiopure alcohols are obtained *via* kinetic resolution of the racemic mixture using Amano lipase AK. [109] The method was used by the same group in their total synthesis of (NFAT-68) **206** (Scheme 44.)[110]



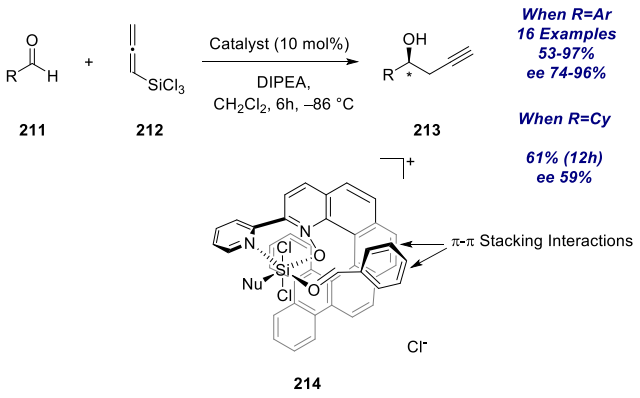
Scheme 44. Enantioselective synthesis of homopropargylic ethers via nucleophilic addition of allenyl silanes to aldehydes

In a similar body of work, the same authors explored the addition of these species into iminium ions derived from **208** and **209** in the presence of TMSOTf (Scheme 45.) Once again, the enantioselectivity is locked in from a kinetic resolution of the initial alcohol, before subsequent rearrangement and addition affords **210**. Again, diastereoselectivity is largely good, although for less encumbered straight chain aliphatic substrates, a notable loss of selectivity is observed. Interestingly, the outcome of this reaction was shown to be highly solvent dependent; when acetonitrile was used, the homopropargylic sulfonamide was the major product, with trace amounts of lactone observed. Upon switching to dichloromethane, the lactone became the sole product, albeit as a racemic mixture. The formation of these lactone products was proposed to proceed through an unprecedented allenyl silyl ketene acetal.[111]



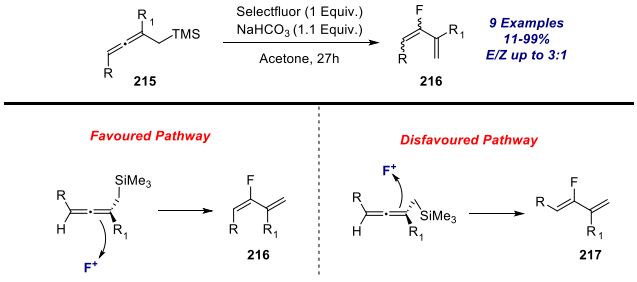
Scheme 45. Enantioselective synthesis of homopropargylic amines via nucleophilic addition of optically active allenes into iminium ions

While enantioselectivity of allene addition can be a consequence of the chirality of the starting allene, Takenaka *et al* demonstrated an alternative approach. Activation of an aldehyde with helically chiral 2,2'-bipyridine-N-oxide followed by addition of **212** allows for the effective preparation of **213** in high yields and enantioselectivities (Scheme 46.)[112] The selectivity of this transformation is governed by the interaction between the helicine, silane and aldehyde, through the formation of hexavalent silicate complex **214**. The delivery of the nucleophile to the *si* face of the aldehyde is then preferential, as this maximises the π-π stacking interactions between the electrophile and the helicene. This is supported by the dramatic decrease in enantioselectivity when aliphatic aldehydes are used in place of the aryl aldehydes. Malkov and co-workers similarly used a set of atropisomerically active bipyridine N,N'-dioxides as a Lewis base catalyst in the enantioselective homopropargylation of aromatic aldehydes. [113] In this case, rather than being helicene based catalysts, the bipyridine compounds are derived from terpene compounds, prepared from simple methyl ketones. The catalyst is proposed to interact with the silane through the formation of a 6-coordinate complex. A variety of aromatic and unsaturated aldehydes were highly successful using this catalyst, although saturated aliphatic substrates demonstrated decreased yields and enantioselectivities.



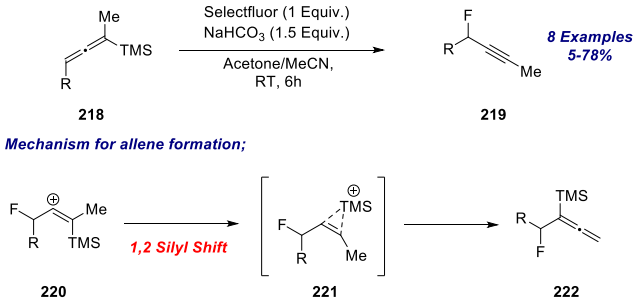
Scheme 46. Enantioselective addition of achiral allenes to aryl aldehydes using a helically chiral bipy-N-oxide based catalyst

Treatment of **215** with Selectfluor™ was shown to be an effective method to access dienes of general structure **216** as reported by Gouverneur and wo-workers. The reaction proceeds through the expected cationic intermediate, generated by nucleophilic attack of the allene. As would be expected, groups that aid in the stabilization of the intermediate cation gave the highest yields, with alkyl and phenyl substituents in this position being particularly successful. Equally, silyl groups in the R^1 position destabilize the intermediate and thus decrease the yield to as low as 11%. The authors observed that the *E*-isomer is preferentially formed, and rationalize this observation by suggesting that the electrophile encounters decreased steric hinderance should it approach from the face of the allene bearing the hydrogen, as shown in Scheme 47.[114]



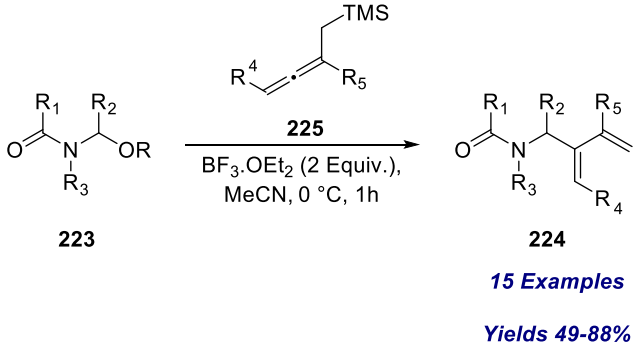
Scheme 47. Electrophilic fluorination of silyl allenes

In a similar study by Gouverneur *et al*, treatment of allenyl silanes not featuring the methylene spacer previously present with Selectfluor yields the corresponding propargylic fluoride **219**, arising from nucleophilic attack of the allene and subsequent desilylation. While a useful transformation, the authors noted competing formation of a fluorinated allene **222** which had retained its silyl group. This was proposed to arise from a 1,2-silyl shift and subsequent deprotonation to reform the allene moiety.[115] The same chemistry can be applied to enantioenriched allenylsilanes to provide chiral propargylic fluorides *via* enantioselective S_E2' reaction with Selectfluor (Scheme 48.) In this case, minimal erosion of the enantiomeric excess of the starting material is observed through the fluorination.[116] The same fluorination/desilylation chemistry was used by Perez-Luna and co-workers to synthesize a range of β-fluoropropargylic fluorides from 4-amino-1-allenyl silanes, once again using Selectfluor as a source of electrophilic fluorine.[117]



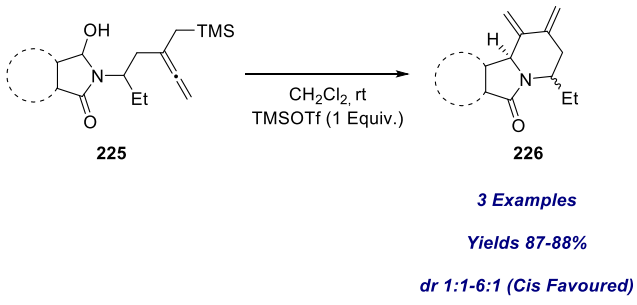
Scheme 48. Synthesis of propargyl fluorides using an electrophilic desilylative fluorination strategy

In addition to reactivity towards inherently electrophilic functionalities, silyl allenes have been shown to be compatible with electrophilic species generated *in-situ* through treatment with a Lewis acid. Hiemstra and co-workers utilized a Lewis acid catalysis approach to generate highly electrophilic N-Acyliminium species from a variety of N,O-acetals **223** *via* treatment with $BF_3.OEt_2$, which subsequently underwent nucleophilic attack in the expected manner from the allenes (Scheme 49.) This yielded a variety of dienylated substrates **224**, which were amenable to further transformation *via* both inter and intramolecular Diels-Alder cycloadditions. The products were also able to be cyclized *via* treatment with both 1st and 2nd generation Grubb's catalysts. A variety of N-Acyliminium ion precursors were used in the study, with both cyclic and acyclic precursors proving viable substrates, providing the expected products in moderate to excellent yields.[118]



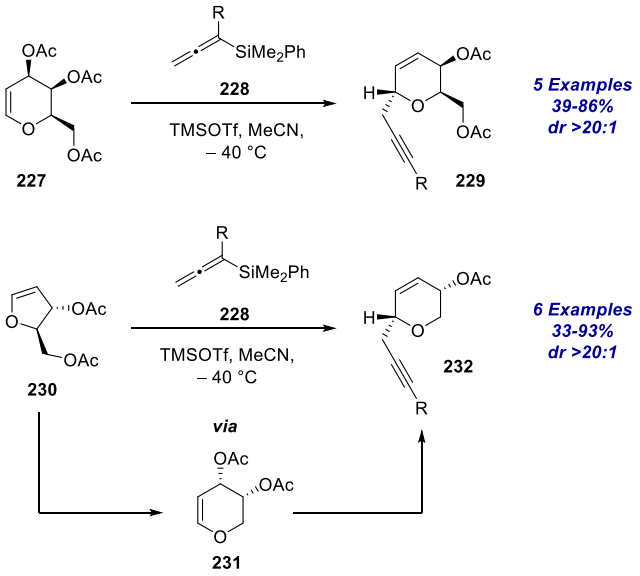
Scheme 49. Addition of silyl allenes into catalytically generated N-Acyl iminium ions

A similar approach was utilized by Kim and co-workers to access a variety of indolizidinone derivatives **226** from cyclisation of allenyl silanes onto an intramolecularly tethered N-Acyliminium ion.[119] In this case, the electrophilic species was generated *via* treatment of the N,O-acetal precursor with stoichiometric amounts of TMSOTf (Scheme 50.) The reaction proceeds through the expected nucleophilic attack at the β position relative to the silane. Subsequent loss of the silane, as in the previous example, affords **226** with an exocyclic 1,3-diene moiety, which can successfully undergo Diels-Alder cycloadditions. Interestingly, in a system with a methylene group removed, the site of nucleophilicity changes, and the silane instead acts as an α-nucleophile. While less common, this α-nucleophilicity has been previously documented.[120]



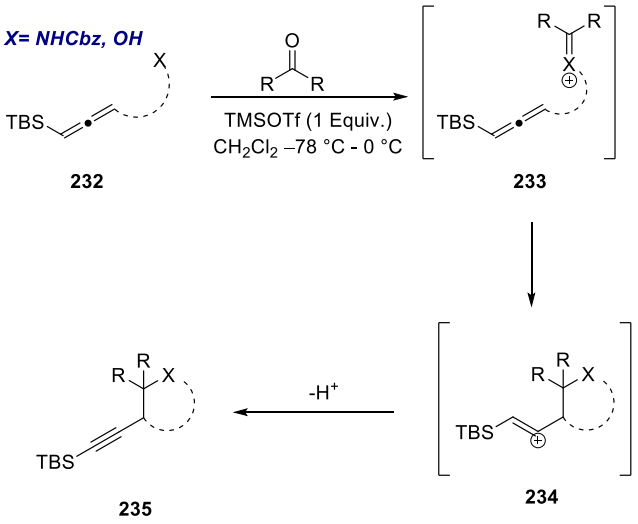
Scheme 50. Intramolecular cyclization of silyl allenes by addition into tethered N-Acyl iminium ions

Allenyl silanes were used as carbon nucleophiles in the stereoselective C-glycosidation reaction reported by Panek and co-workers in 2010. Treatment of tri-*O*-acetyl-d-glucal, tri-*O*-acetyl-d-galactal **227** and several dihydrofuran derivates with **228** in the presence of TMSOTf affords **229**, *via* addition of the allene to the less sterically hindered face of the oxocarbenium ion generated *in-situ* (Scheme 51.) Interestingly, in the case of **230**, these compounds isomerise to a *d-ribose* structure under the reaction conditions, and so even in this case the product is still a 6 membered ring. A variety of allenyl silanes were amenable to these reaction conditions, and the nature of the substrates had seemingly no influence on the stereochemical outcome of the reaction, with the dr in all cases exceeding 20:1.[121]



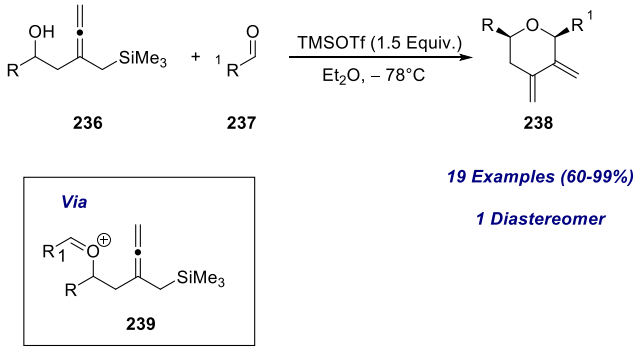
Scheme 51. C-Glycosidation of silyl allenes mediated by trimethylsilyl triflate

As a result of the inherent nucleophilicity of the α-carbon of allenyl silanes, the motif has found application within a variety of Prins type cyclisation to access heterocycles.[122] This was reported by Ohfune and co-workers in 2012, where the reaction between hydroxy or amino containing allenylsilanes **232** and aldehydes in the presence of catalytic amounts of Lewis acid leads to the formation of a variety of 5 membered rings **235** through a 5-*endo-trig* cyclisation. TMSOTf was found to be the optimal acid for the reaction, and the reaction yielded the corresponding heterocycles in moderate to good diastereoselectivities. Equally, a homologous analogue could be applied to the synthesis of pyrans through the same methodology.[123]



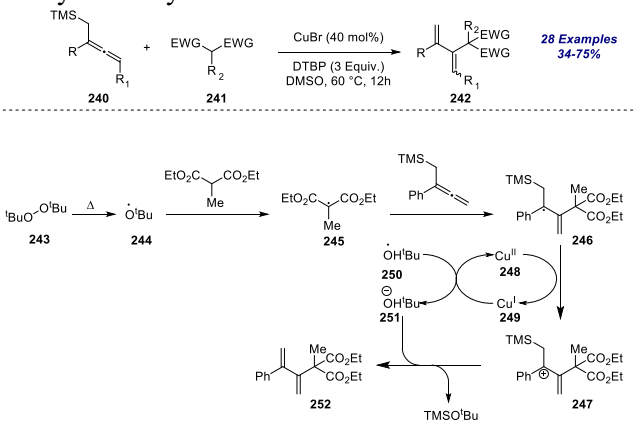
Scheme 52. Formation of heterocycles through the Prins cyclization of silyl allenes

In a related study on the Prins cyclisation with allenylsilanes bearing hydroxyl groups, a variety of tetrahydropyrans of general structure **238** were accessed. The reaction is proposed to proceed through a chair-like transition state, which in turn allows for the products to be formed with a *cis* relationship between the two R groups.[124] The same group further applied this chemistry to homologated oxy-heterocycles bearing the same 3,4-exocyclic methylene substituents. Using this methodology, a variety of oxepanes were synthesized, as well as several bi- and tricyclic polyethers (Scheme 53.)[122]



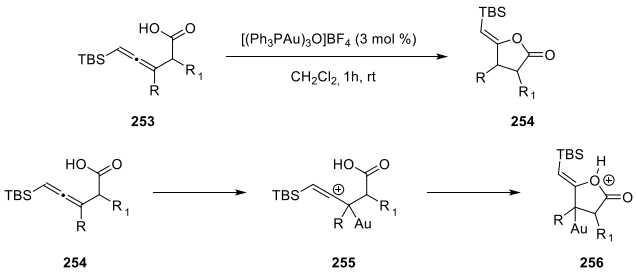
Scheme 53. Tetrahydropyran formation via cyclization of allenyl silanes

Silyl stabilized cations were proposed to be a key intermediate in the copper catalyzed cross-nucleophile coupling reported by Hu *et al*. Here, cation **247** is generated *via* 1 electron oxidation of the corresponding β-silyl radical **246** (Scheme 54.) In this work, a formal 1,3-dienylation of acidic C-H bonds with β-allenylsilanes, di-*tert*-butyl peroxide **243** (DTBP) undergoes thermal homolysis to generate *tert*-butoxyl radicals **244**, which subsequently abstract a hydrogen from the C(sp^3)-H carbon, forming tertiary radical species **245**. This electrophilic species then undergoes addition to the allene, affording an allylic radical species **246**, which following subsequent oxidation to the β-stabilized cation, is readily desilylated to yield **252**.[125]



Scheme 54. Copper catalyzed cross-nucleophile coupling

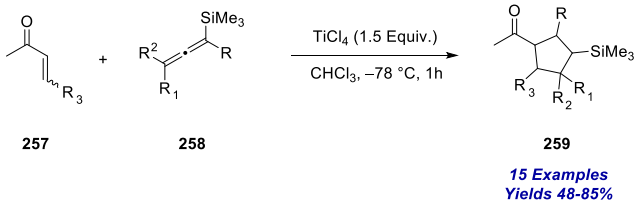
Ohfune and co-workers demonstrated that cationic intermediates could be generated from allenyl silanes through the strategic application of π-acid catalysis. Treatment of **253** with a suitable π acid catalyst allows for cyclisation through the nucleophilic acid in a 5-*endo*-dig cyclisation, which following protodemetallation yields a variety of lactones of general formula **254** in excellent enantioselectivities and yields, and moderate to good diastereoselectivities (Scheme 55.) Highest yields were obtained using $[(Ph_3PAu)_3O]BF_4$ as a catalyst with a 3 mol% catalyst loading, although $AuCl_3$ as well as mercury and silver-based catalysts also produced varying amounts of the cyclized product. The stereochemical outcome of the reaction was found to be highly substrate dependent, with stabilizing effects from NBoc or hydroxyl groups in the R^1 position found to direct towards the selectivity towards *anti* diastereomer, selectivity which was scrambled for more sterically bulky substrates.[126]



Scheme 55. Synthesis of lactones from allenyl silanes via π-acid catalysis

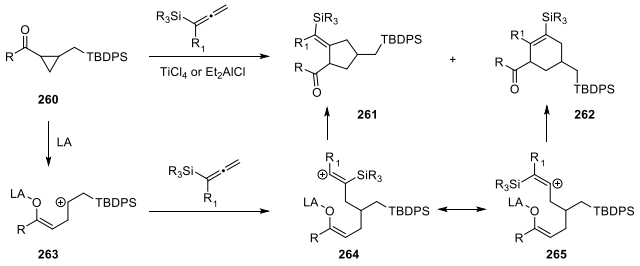
One of the classical applications of allenylsilanes in organic synthesis is their capacity to undergo annulations with α,β-unsaturated carbonyl compounds **257**. This Lewis acid catalyzed reaction, first observed by Danheiser and co-workers, proceeds *via* 1,4 addition of the allene into the enone before subsequent 1,2-silyl shift allows for attack of the transient enolate

at the cationic center, affording the cyclized product **259** (Scheme 56.)[127] Subsequent studies by the same group reveal that the reaction takes place *via suprafacial* addition of the allene to the enone. The reaction has subsequently found widespread application in the total synthesis of natural products containing five-membered ring systems.[128]



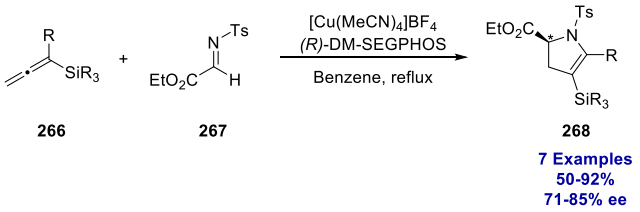
Scheme 56. The formal [3+2] annulation between allenyl silanes and α,β-unsaturated ketones

In 2004, Sriramurthy and co-workers demonstrated an annulation of allenyl silanes with several TBDPS-substituted cyclopropyl ketones **260** in the presence of Lewis acid catalysts (Scheme 57.) This reaction yields both [3+2] (**261**) and [3+3] (**262**) annulated products, allowing access to 5 and 6 membered carbocycles. Both $TiCl_4$ and Et_2AlCl were suitable as catalysts for this transformation, although Et_2AlCl offered two notable benefits; avoidance of a protodesilylation pathway for the products, and the ability to selectively access the [3+3] product at 25 °C. [129]



Scheme 57. Lewis Acid Catalysed Annulation of Cyclopropyl ketones and Silyl Allenes

In subsequent work by Akiyama *et al*, a similarly Lewis acid catalyzed addition was reported, this time using α-imino ester **267** as an electrophile for the formal [3+2] cycloaddition, affording access to a variety of silyl dehydropyrrolidines **268** (Scheme 58.) For this work, $[Cu(MeCN)_4]BF_4$ was used to activate the electrophile, in conjunction with a SEGPHOS based ligand, yielding the corresponding heterocycles in moderate to excellent yields and moderate to good enantioselectivities.[130]

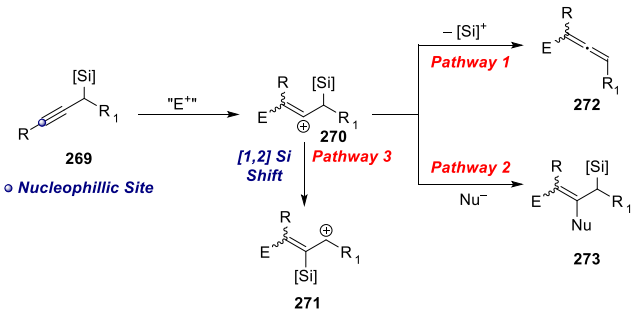


Scheme 58. Copper catalyzed enantioselective synthesis of silyl pyrrolidines

It should be noted that while the chemistry of the imino ene-type reactions of allenyl silanes reported by Weinreb and co-workers initially appear to plausibly proceed through the intermediacy of a cationic species, the high degree of stereospecificity of these reactions means that they likely proceed through a concerted mechanism, and therefore the β-silicon effect is not a factor in these transformations.[131]

3.2. Propargyl Silanes

As a system, propargylic silanes **269** effectively mimic the reactivity of allyl silanes in being nucleophilic at the γ position relative to the silane. This in turn generates the stabilized β-cation which can subsequently be quenched *via* loss of the silane or *via* nucleophilic attack at the cationic site. Pathway 1 generally dominates when a smaller silyl group is used, encouraging nucleophilic attack at the silane, whereas this is discouraged using bulkier silyl groups, resulting in pathway 2 dominating. In certain cases, a third pathway is in operation where the silane undergoes a 1,2-migration in order to generate a more stable cation, with these pathways being outlined in Scheme 59.

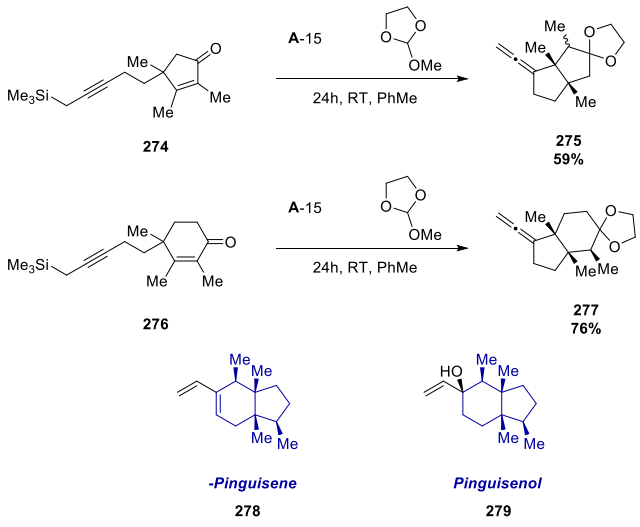


Scheme 59. General nucleophillic reaction pathways of propargylic silanes

The desilylation pathway allows access to a variety of densely functionalised allenes for relatively simple starting materials. A variety of electrophiles have been utilized in these reactions, with iminium ions,[132] acetals,[133] and aldehydes[134] all proving to be viable electrophiles, yielding allenes in good to excellent yields. While the methods used to access allenes are dependent on the loss of silane following the initial nucleophilic attack, when a potential nucleophile is present in the reaction mixture, the potential for nucleophilic attack at the generated cation is then also

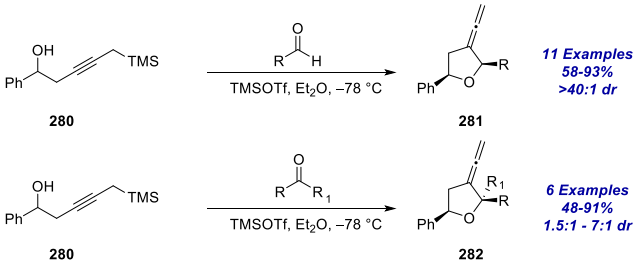
a factor for consideration. This is exemplified by the work of Aragoncillo *et al* wherein the Lewis acid used to activate the electrophile, in this case 4-oxoazetinde-2-carbaldehydes, has profound effect on the outcome of the reaction. Use of boron trifluoride etherate to activate the aldehyde yields the allene in much the same as the previous examples, use of tin tetrachloride yields mixtures of the allene as well as various chlorinated silane derivatives.[134] The competing formation of the allene when a nucleophile is present is significantly diminished when the nucleophilic attack occurs intramolecularly. This is demonstrated by Hirashita wherein the addition of propargyl trimethyl silane into an N-aryl aldimine is subsequently followed by an SE_{Ar} reaction to yield the corresponding 1,2-dihydroquinoline.[135]

The conjugate addition of propargyl silanes into activated electrophiles including Michael acceptors such as **274** and **276** was demonstrated by Schinzer and Ringe in their total syntheses of B-Pinguisine (**278**) and Pinguisinol (**279**) in 1996 (Scheme 60.) This method used Amberlyst 15 in order to activate the electrophile, though in the case of more sterically hindered substrates, a trans-ketalization process was required, and thus the addition of methoxy-dioxolane was required, and the resultant product becomes the ketal protected ketone. The allene resulting from loss of the silyl group was readily cleaved under ozonolysis conditions, and subjected to several further functionalisations.[136]



Scheme 60. Intramolecular conjugate additions of propargyl silanes towards the synthesis of pinguisene and pinguisinol

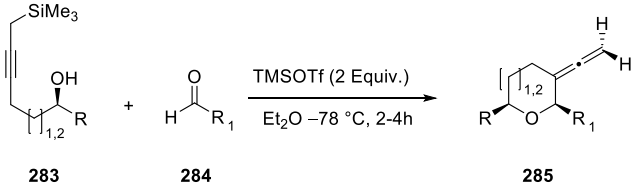
As with other unsaturated silanes, propargyl silanes have frequently been used as intramolecular nucleophiles in Prins cyclisations, with the electrophile being an oxocarbenium ion generated from acid mediated condensation of an alcohol and aldehyde or ketone. In 2005, Cho and co-workers used this method in their stereoselective synthesis of a variety of tetrahydrofurans from **262**. TMSOTf was found to best mediate the transformation, and using this method, a variety of tetrahydrofurans could be accessed, including privelleged spirocyclic scaffolds. In the case of aldehydes, the stereoselectivity was excellent, generally providing only **281**, however with ketones this selectivity was significantly decreased



affording **282**.[137]

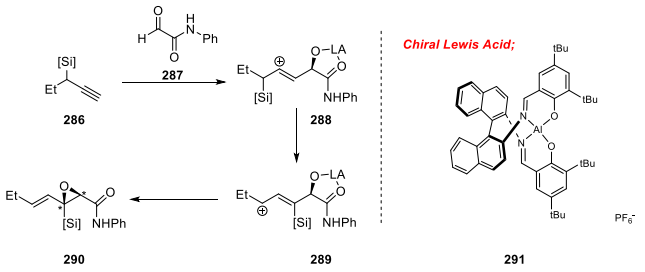
Scheme 61. Prins cyclization of propargylic silanes affording allenyl tetrahydrofurans

Later work by Justyniak and co-workers applied a similar methodology to optically active **283** accessed *via* Corey-Bakshi-Shibata reduction of the parent ketone, to synthesize a range of optically active tetrahydropyran derivatives of general structure **285** (Scheme 62.) In addition to these substrates, a homologated variant also proved highly successful in the synthesis of optically active oxepanes. Enantiomeric excesses of this work were generally greater than 90%, although in the case of benzylic alcohols, a drop of in ee was observed. This was proposed to be a result of the formation of a benzylic cation at this position under the reaction conditions, leading to partial racemisation of the starting material.[138]



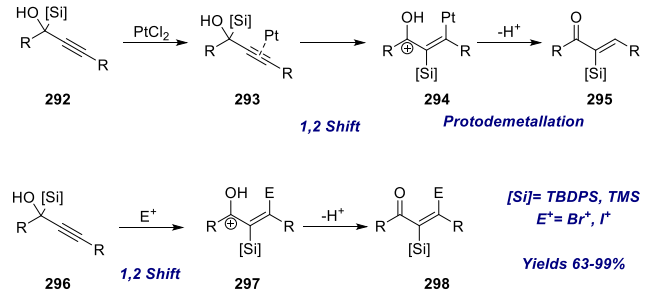
Scheme 62. Prins cyclization of optically active propargylic silanes affording enantioenriched tetrahydropyrans

As discussed, to mitigate competing pathways, larger silyl groups can be used to discourage the formation of the allenyl alcohol. This is exemplified by the work of Evans *et al*, wherein the use of **286** ([Si]=diisopropylphenylsilane) in conjunction with chiral aluminium complex **291**, allows for highly enantioselective addition of the silane into glyoxamide (Scheme 63.) Given the bulky nature of the silane, a 1,3 silicon shift then occurs, with the allylic cation formed then quenched *via* nucleophilic attack of the neighbouring alcohol, resulting in the formation of enantioenriched vinyl epoxides **290**.[139]



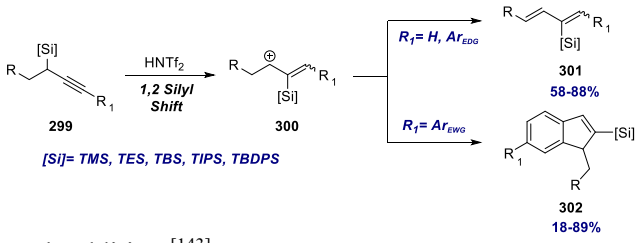
Scheme 63. Aluminium catalyzed enantioselective synthesis of vinyl epoxides from propargyl silanes

The 1,2-silyl shift demonstrated by propargyl silanes is utilized in chemistry beyond that of nucleophilic additions of these compounds, but the underlying driving force of the formation of the allylic cation remains constant. Ferreira and co-workers utilized this driving force to access a series of α-silyl enones (**295**) *via* 1,2 silyl shift of **292**. This first required the activation of the alkyne *via* treatment with a suitable electrophile. Pt(II) salts were shown to effectively promote this reaction through the well-established formation of π acid complexes, other electrophiles such as N-Halosuccinimides were also explored (Scheme 64.) It should be noted that the use of this chemistry has subsequently been further explored by the same group to access tetra functionalised olefins through sequential cross-couplings,[140] and to access polysubstituted furans.[141]



Scheme 64. Electrophile mediated rearrangement of propargylic silyl alcohols

Aside from the activation of propargyl silanes through formation of a π-acid complex or *via* treatment with an electrophilic halide source, superacid catalysis has also been used to protonate the unsaturated C-C bond of these compounds and form the β-silyl cation. This was the method used by Turks and co-workers, where the superacid of choice was bis(trifluoromethylsulfonyl)amine, who applied to method to a variety of propargyl silanes **299** (Scheme 65.) The outcome of the reaction was found to be largely dependent on the nature of the alkyne. Terminal alkynes, having no other way of quenching the allylic cation, readily undergo deprotonation to form the corresponding silyl diene, as did electron rich aromatic groups in the same position. Any aryl group less electron rich than the *p*-OMePh group instead proceeded to cyclize and yield the corresponding indene *via* electrophilic aromatic substitution.[142] Using a similar approach, albeit with tosylic acid, the same group were able to form a variety of cyclic sulfones by 'trapping out' the diene formed *in-situ* with sulfur dioxide through a cheletropic [4+1] cycloaddition.[143]

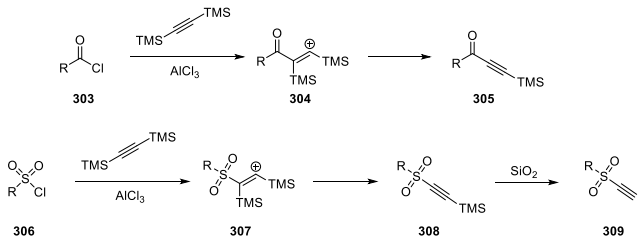


Scheme 65. Triflimide catalyzed rearrangement of propargylic silanes affording 1,3 dienes and indenes.

In 2008, Ito and co-workers utilized an Au(I) catalyst system to catalyze the known [3,3] sigmatropic rearrangement of propargylic esters, with the resultant silyl-stabilized cation then trapped with water. Subsequent tautomerization then affords the product, an α-acyloxy-α′-silyl ketone, in a one-pot procedure. Using this procedure, a variety of ketones were synthesized in yields largely ranging from good to excellent. Interestingly, when using propargylic esters substituted with dialkylaryl silanes, such as dimethyl phenyl silane, the catalyst was deactivated and no reaction observed. This was attributed to an interaction between the π-system of the aryl group and the gold catalyst, shutting down the desired reaction pathway. This issue could be overcome by switching to a less electrophilic gold catalyst. [144]

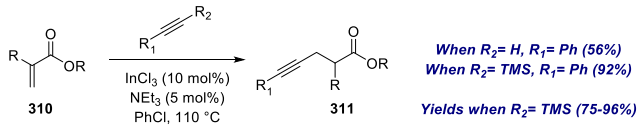
3.3. Alkynyl Silanes

Bis-silylacetylenes have long been known to act as nucleophiles in Friedel-Crafts type reactions with a variety of acyl halides. This reaction proceeds through the intermediacy of a stabilized vinylic cation, which following loss of a silyl group, results in the formation of the silyl protected propargylic ketone.[145] This reaction is dependent on the activation of the acyl chloride with a suitable Lewis acid, typically aluminium trichloride, although indium salts have also been shown to be effective catalysts.[32] In a similar fashion, bis-silylacetylenes can be added into a variety of sulfonyl chlorides, in the presence of a Lewis acid, to access ethynyl sulfones.[146] Although these highly electrophilic species are unable to be deprotected in basic media unlike most silyl protected alkynes, purification *via* silica gel affords the deprotected alkyne in almost quantitative yields (Scheme 66.)[147]



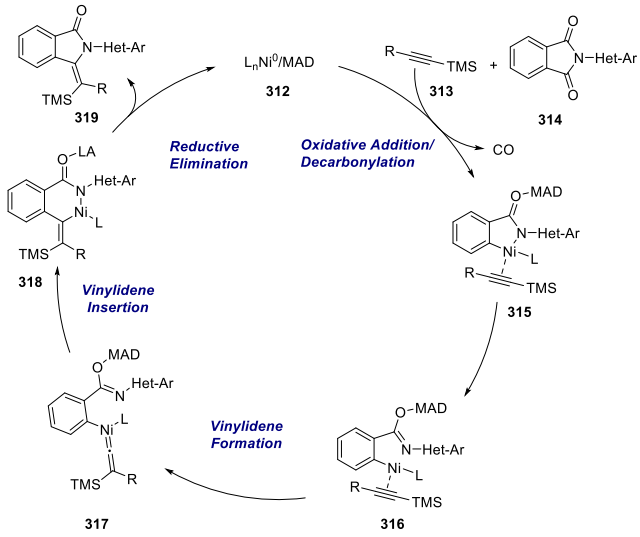
Scheme 66. Friedel-Crafts acylation and sulfonylation of bis-trimethylsilyl acetylene

Although less well explored than their propargylic counterparts, alkynyl silanes have been shown to act as nucleophiles towards activated electrophiles, with the formation of the stabilized cation being crucial to affording high yields of the corresponding alkyne. This was demonstrated by Su *et al* with their study on the addition of trimethylsilyl alkynes into acrylate esters **310** in the presence of an indium chloride catalyst (Scheme 67.) Without the presence of the silyl group to stabilize the intermediate, the yield of alkyne obtained is decreased from 92% to 56%.[148] Reactions of similar Lewis acid catalyzed conjugate additions have similarly been reported.[148-149]



Scheme 67. Indium Catalyzed Addition of Activated Alkynes into Acrylate Esters

In the context of transition metal catalysis, alkynyl silanes have proven to be valuable reagents in the formation of metal-vinylidene complexes with a significant degree of backdonation from the metal center. The formation of these complexes is once again driven by the stability afforded to the vacant p-orbital of the carbene by the increased hyperconjugation with the neighbouring C-Siσ orbital. The energy afforded to the stability of these carbenes was extensively studied by Gordon *et al*.[150] The application of these vinylidene complexes towards the synthesis of isoindolinones bearing an exocyclic alkene via decarbonylation of N-Heteroaryl phthalimides was explored by Kurahashi *et al* (Scheme 68.)[151] This method required the addition of Methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) to facilitate the formation of a cationic nickel species, stabilized by an electron rich ligand, which would in turn help drive the formation of **317**. The bond is determined in the vinylidene insertion into the Ni-Aryl bond, with the preference being for the bulky silyl group to be directed away from the phosphine ligand. A similar mechanism was proposed for the [2+2+1] cyclotrimerization of carboryne, alkenes and trimethylsilylalkynes reported by Xie and co-workers, although further computational studies by the same group suggest that in this case, the pathway is kinetically and thermodynamically unlikely.[152]



Scheme 68. Nickel catalyzed synthesis of isoindolinones from N-Heteroaryl phthalimides and trimethylsilyl protected alkynes.

4 Conclusions and outlook

In conclusion, an overview of the applications of the β-silicon effect in organic chemistry has been provided, with the reactivity of a variety of classes of unsaturated organosilanes discussed. The utilisation of these reagents as allylating agents has been discussed in length, with particular focus placed on more contemporary developments of enantioselective variants of these reactions. The application of unsaturated organosilanes in the synthesis of privelleged carbocyclic and heterocyclic scaffolds, with a variety of activation methods, has also been thoroughly explored. An in depth discussion of the use of application of silyl stabilised cations in transition metal catalysis has also been provided. As transition metal catalysis remains one of the most prevalent areas of research in modern synthetic chemistry, it is envisaged that further examples of these processes employing the β-silicon effect as a lynchpin in the reaction will continue to emerge.

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