Allylsilanes in Organic Synthesis − Recent Developments

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Allylsilanes have been used extensively over the last 30 years. A survey of the most recent advances in this field is described, including transformations of allylsilanes through electrophilic, radical and organometallic processes. Particular emphasis will be placed on the stereocontrol arising from these processes.

1. Introduction

Allylsilanes are widely used in organic synthesis.[1] The weak polarisation of the C−Si bond allows an easy handling of these stable organometallic-type reagents which therefore occupy a unique place in the armoury of the organic chemist. Although acid-, fluoride- and metal-catalyzed allylation reactions still constitute one of the major applications of these useful synthons,[2] additions of electrophilic species and free radicals as well as neutral precursors in cycloaddition processes to the double bond of allylsilanes have also been intensively studied. This review describes some significant results in this field, including some of our own results. It is not intended to cover all aspects of allylsilane chemistry but will restrict itself to the most recent studies on allylsilane reactivity. We will particularly focus our attention on the stereochemical induction arising from transformation of cyclic and acyclic chiral allylsilanes. As several previous reviews[3] have dealt with this important subject, only key points will be addressed. Allylsilanes can be prepared in a number of ways and their synthesis has been investigated in depth. For the synthesis of simple and

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Philippe James (left) was born in Montluçon (France) in 1978. During his undergraduate studies he worked in the laboratory of Prof. Husson in the University René Descartes (Paris V) under the guidance of Dr. A. Blommaert and Dr. J. Royer on (R)-phenylglycinol-derived chiral scaffolds in the solid phase. Since 2001, he has been studying for a Ph.D. in synthetic organic chemistry under the supervision of Prof. Y. Landais at the University Bordeaux-I (France). His thesis is currently focused on the synthesis and radical functionalisation of chiral allylsilanes.

Yannick Landais (centre) was born in Angers (France) in 1962. He received his Ph.D. in chemistry from the University of Orsay (Paris XI) under the supervision of Dr. Jean-Pierre Robin. After carrying out postdoctoral work with Prof. Ian Fleming at Cambridge University (1988−1990), he took up a position of Maître-Assistant at the University of Lausanne (1990−1997). He was then appointed at the University Bordeaux-I where he is currently Professor of organic chemistry. His research interests are in synthetic organic chemistry, asymmetric synthesis, and radical chemistry, with a special emphasis on organosilicon chemistry and its applications in total synthesis of natural products. In 1997, he was awarded the Werner prize by the New Swiss Chemical Society. Since 2000, he is a member of the Institut Universitaire de France.

Laurent Chabaud (right) was born in Bordeaux (France) in 1978. In 2001, he spent a few months in the laboratory of Prof. Philippe Renaud (Bern, Switzerland) working on the development of organoborane-mediated radical reactions. Since 2002, he has been pursuing his Ph.D. studies under the supervision of Prof. Yannick Landais, in collaboration with Prof. Philippe Renaud. His research interest is the stereocontrolled radical functionalisation (including carboazidation) of chiral allylsilanes.

MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.

more complex allylsilanes, the reader should refer to recent exhaustive reviews.[4]

1.1. Electronic Effects of R_3Si

A knowledge of the intrinsic electronic properties of silicon[5] is important to have a good understanding of the unique reactivity of allylsilanes as compared with simple olefins.[6] These effects can be classified into two main classes: α-[7,8] and β-effects[9,10] (Figure 1).

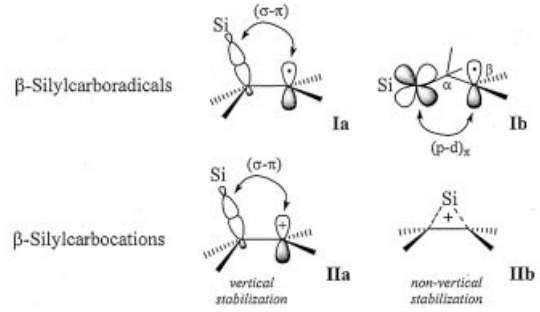
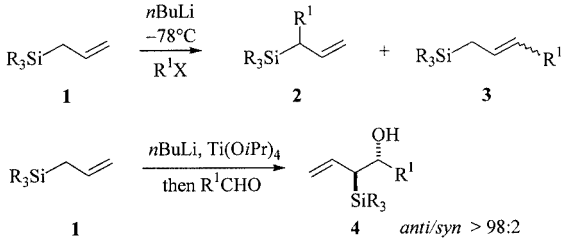


Figure 1. Silicon β-effects: stabilization of carbocations and carboradicals

It is well known that silicon shows a strong tendency to stabilize adjacent negative charges.[5,8] This has often been rationalized by invoking $(p\text{-}d)_\pi$ bonding, but more recent experiments and calculations indicate that hyperconjugation offers a more plausible explanation.[8c,8d] An SiH_3 group was thus shown, by calculations, to stabilize a carbanion by 31.5 kcal/mol relative to a methyl group, which is in good agreement with experimental values. Interestingly, silicon also stabilizes α-carboradicals, but to a much lesser extent.[7] Although the exact value is not known with certainty, stabilizations ranging between 0.4 and 2.6 kcal/mol have been measured using different techniques. The α-effect is illustrated in allylsilane chemistry by the ease of deprotonation of the allylic position α to the silicon atom. Carbanions can thus be generated by simple deprotonation using strong bases (*n*BuLi, *s*BuLi). The presence of phenyl groups on the silicon atom usually facilitates the deprotonation. Subsequent reactions of these ambident carbanions with electrophiles have been well studied.[8] In alkylation with alkyl halides, α and γ regioisomers **2** and **3** are formed in unequal amounts, with the product ratio varying with the size and the nature of the substituent on the silicon group and the nature of the alkyl halides (Scheme 1). More reliable results are obtained through coupling of these carbanions with aldehydes, after transmetallation of the lithio species with titanium alkoxides (vide infra).[8a,11] β-Hydroxysilanes **4** are thus prepared in excellent yields with a high level of stereocontrol (Scheme 1). Use of an optically active titanium complex[12a] or organoborane derivatives[12b,12c] also allows the reaction to be carried out enantioselectively. The latter approach has enjoyed a renewed interest recently as it is an efficient and reliable method for constructing a chiral allylsilane framework.



Scheme 1

The silicon β-effect is a prominent feature of the reactivity of allylsilanes, and many illustrations of such an effect can be found in the literature[1,2,5] (Figure 1). Silicon is well known to stabilize β-carbocations[10] as well as β-carboradicals,[9] but again to a very different degree. While hyperconjugative stabilization of a β-silylcarbonium ion (e.g. **IIa**, Figure 1) is estimated at 29−30 kcal/mol, stabilization of the analogous radical species is assessed to be 2.6−4.5 kcal/mol. As a consequence, the former stabilization has been more extensively used to promote a large variety of reactions, as illustrated below; σ-π hyperconjugation (also called vertical stabilization, **IIa**) is generally used to describe the stabilization of β-carbocations and the required coplanarity usually accounts well for the regiochemistry observed in a number of electrophilic reactions of organosilanes. Non-vertical stabilization, as in **IIb**, has also been invoked but gas-phase experiments and ab initio calculations suggest that such a stabilization is isoenergetic with the open β-silyl cation **IIa**.[13] The silacyclopropylium cation **IIb** is often proposed as an intermediate in electrophilic reactions of organosilanes involving a 1,2-silicon shift (e.g. [3+2]-annulation, vide infra).[14] Recent investigations by Lambert et al.,[10e] using secondary deuterium isotope effects, however, established unambiguously that the β-silicon effect only involves the open, unbridged species **IIa**.

The origin of the β-effect for β-carboradicals is still subject to controversy.[9] Two types of models have been invoked for stabilization of β-carboradicals. Homoconjugation $[(p\text{-}d)_\pi]$ between the odd electron and the 3d orbitals of the silicon atom as in **Ib** is usually preferred, even if MO calculations tend to favour σ-π hyperconjugation as in **Ia**.[9d] Hyperconjugation necessarily implies certain conformational requirements (coplanarity of the involved orbitals), which is not the case with $(p\text{-}d)_\pi$ bonding, where overlapping is continuous due to the symmetry of the 3d orbitals. ESR measurements showed that the magnitude of the homoconjugative delocalization of the odd electron into 3d orbitals of the silicon atom was of the same order as the delocalization of the odd electron into the σ^*_{C-Si} orbital.[9a]

As a conclusion, it is worth mentioning that even if electronic factors are important in reactions of organosilanes, they should not be overestimated. They often work in the same direction as steric effects and are thus difficult to estimate on their own. The fact that steric and electronic factors are additive certainly contributes to the high selectivity of the reactions with organosilanes.

Finally, it is worth underlining that allylsilanes are versatile synthetic equivalents, depending on the nature of the process in which they are involved. In electrophilic processes, the site of attack of the electrophile (e.g. C-γ or C-3) is controlled by the fact that the resulting cation

at C-β (C-2) is stabilized by hyperconjugation (e.g. **IIa**, Figure 1). Synthetic equivalents (**IIIb**) may thus be considered for addition and S_E' reactions, where this regioselectivity is well established.[2,3] The dipole may also be located between C-1 and C-3 (e.g. **IIIc**), resulting from a 1,2-silicon shift, as observed in the Lewis acid mediated [3+2]-annulation between allylsilanes and carbonyl compounds (vide infra).[14] Allylsilanes have also recently been used as diradical equivalents such as **IIId**. Various combinations of the synthetic equivalents below are also allowed, illustrating the diversity of functionalization which can be envisioned, starting from simple allylsilanes **1**. Finally, it is worth noting that, as a silicon group can be unmasked under oxidative conditions,[15] allylsilanes may also be considered as the oxygenated equivalents (OH) of the intermediates in Figure 2.

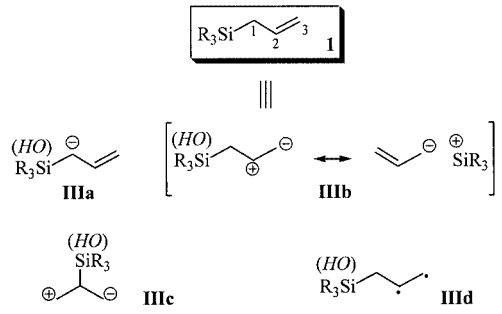


Figure 2. Allylsilanes as synthetic equivalents

2. Functionalization of Allylsilanes

2.1. Electrophilic Additions and Substitutions on Allylsilanes

2.1.1. Introduction

Electrophilic additions and substitution reactions (S_E') on chiral allylsilanes have been intensively studied over the last two decades.[2,3] Electrophilic species (e.g. X−Y in Figure 3) generally react with chiral allylsilanes in an *anti* fashion, with or without loss of the silicon group, along with generation of one or two new stereocenters. Regioselectivity problems may be encountered with unsymmetrical electrophiles such as boranes or amino-hydroxylation reagents, although regiocontrol is generally high with sterically demanding electrophiles. We have summarized in here the recent progress which has been made in the area of dihydroxylation, amino-hydroxylation, epoxidation and cyclopropanation of chiral allylsilanes. Other examples of electrophilic processes such as hydroboration and nitration are also covered although they have been more scarcely used. Reactivity of allylsilanes towards nitrenes, hydroperoxides, thioacetals and propargylic acetals will also be discussed. Finally, electrophilic substitution reactions in the context of annulation and cycloaddition reactions have also been mentioned, but not allylation reaction of aldehydes or imines, which have been exhaustively reviewed.[2,3]

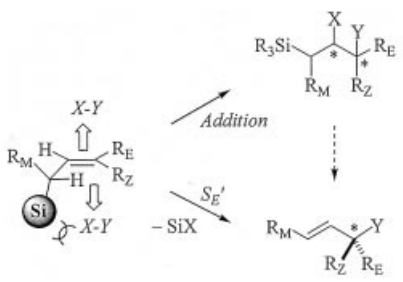


Figure 3. Addition and S_E' reactions of chiral allylsilanes

Diastereocontrol arising from electrophilic functionalization of chiral allylsilanes is well documented, and a reliable model that predicts the stereochemical outcome of these processes has been developed (Figure 4).[2,3] The high diastereocontrol generally observed in these reactions is rationalized by invoking an antiperiplanar attack of the electrophile onto the acyclic allylsilane in a conformation such as **IVa**, where the smallest group (e.g. H) eclipses the double bond (*inside* position), the silicon−carbon bond thus being perpendicular to the olefin, allowing the stabilization of the incipient carbocation (σ-π stabilization; e.g. **IIa**, Figure 1). It is interesting to note that the transition state conformation **IVa** closely resembles that of the allylsilane in the ground state. Calculations have shown that ground-state interactions between the σ_{C-Si} bond and the olefin raise the HOMO of the allylsilane, making it more reactive towards electrophiles.[16a] Calculations of electrostatic potentials corresponding to the diastereotopic faces also led to the conclusion that the face opposite to the silicon atom is more reactive towards electrophiles.[16b] Therefore, it appears that electronic and steric effects reinforce each other in chiral allylsilanes, both contributing to the high level of stereocontrol generally observed in their reactions with electrophiles.[2] To what extent this stereocontrol is steric or electronic in origin remains a matter of debate, in spite of studies which have carefully addressed this problem.[17] Conformation **IVb**, with the medium-sized group R_M *inside*, experiences strong $A_{1,3}$ interactions between R_M and R_Z, thus explaining the generally higher diastereocontrol observed with (*Z*)-allylsilanes than with (*E*)-allylsilanes.[2,3] In cyclic systems, locked conformations provide sufficient

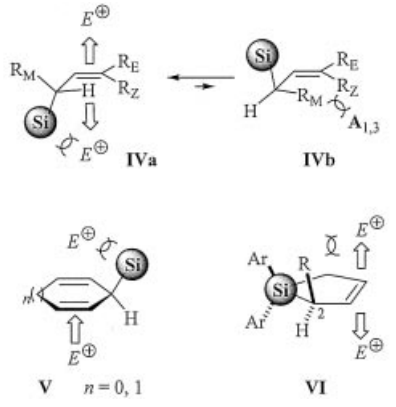


Figure 4. Stereochemistry of addition and S_E' reactions of chiral allylsilanes

steric differentiation to lead to high *anti* stereocontrol, whatever the nature of the silicon group. Cyclohexadienyl and pentadienyl systems such as **V** are thus known to provide quasi exclusively *anti*-diastereofacial selectivities.[18] More recently, we investigated epoxidation and dihydroxylation of cyclic allylsilanes in which the silicon group was part of the ring (model **VI**, Figure 4).[19] In those substrates, the C−Si bond is nearly perpendicular to the π-system and hence has no effect on the stereocontrol. The stereofacial differentiation is thus only governed by the size and the nature of the R chain at the allylic stereogenic centre C-2.

A high degree of 1,2-stereocontrol may also be obtained using heteroatom-directed processes.[20] Coordination of the incoming electrophile (E^+) by a chelating group (OH, NHR) present on the olefinic framework allows better facial stereodifferentiation, through conformations of type **VIIa** and **VIIb** (Figure 5). A few examples of such processes have been reported, which demonstrate that substrate-directable electrophilic functionalization of chiral allylsilanes effectively provides excellent levels of stereocontrol (vide infra).[3]

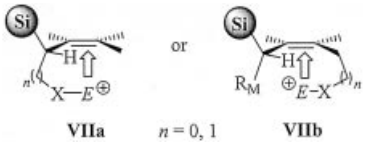
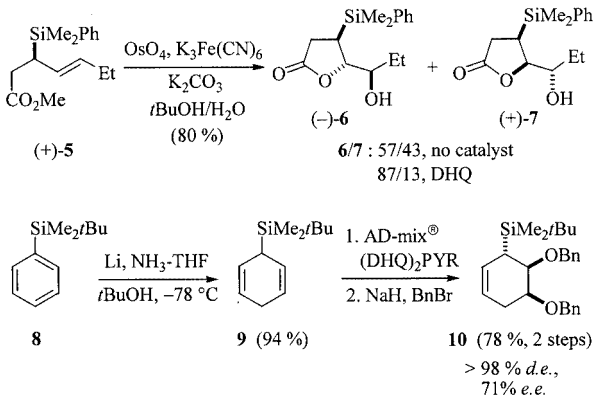


Figure 5. Substrate-directable addition reactions on chiral allylsilanes

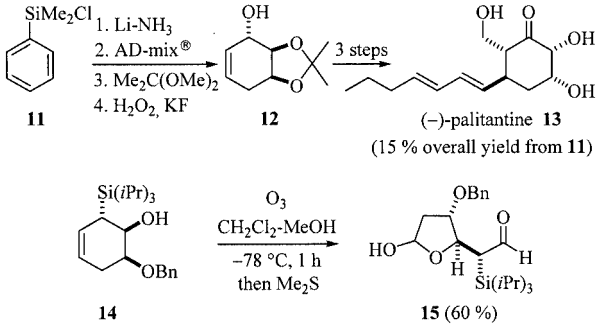
2.1.2. Dihydroxylation of Allylsilanes

Dihydroxylation of chiral allylsilanes is a simple method to gain access in a limited number of steps to lactones and cyclic and acyclic polyols. The enantiomerically pure (*E*)-allylsilane **5** with a β-ester function thus undergoes dihydroxylation and in situ lactonisation to afford diastereomeric γ-lactones **6** and **7** in good yields, but with a low level of diastereocontrol (Scheme 2).[21] A more satisfying *anti*/*syn* selectivity was obtained through double diastereodifferentiation, using dihydroquinidine *p*-chlorobenzoate (DHQ) as chiral ligand. As already shown by Fleming,[22] (*E*)-allylsilanes afford low levels of stereocontrol in dihydroxylation. On the contrary, complete diastereofacial selectivity was observed during Sharpless dihydroxylation[23] of cyclic dienylsilane **9**, readily available from arylsilanes **8**.[24] Using AD-mix® and $(DHQ)_2PYR$ (Hydroquinine-2,5-diphenyl-4,6-pyrimidinediyl diether) as chiral ligand the enantiotopic double bonds were relatively well differentiated, affording allylsilane **10** in 71% e.e. The diastereocontrol may be explained by invoking conformation **V** depicted above (Figure 4).



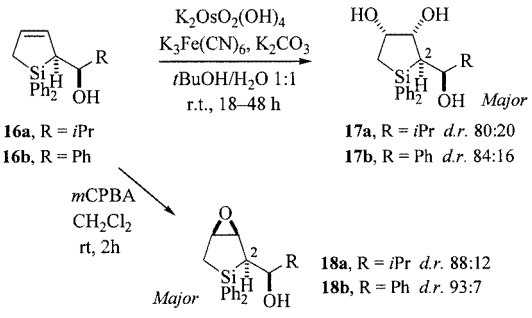
Scheme 2

Highly functionalized cyclic synthons are thus available starting from allylsilanes such as **10** (vide infra).[18,25] Unmasking of the C−Si bond by oxidation[15] provides an allylic alcohol that can then be epoxidized or simply transformed into an enone. Such a sequence has been applied with success in the total synthesis of (−)-palitantine (**13**), an antibiotic from *Penicillum palitans*,[25a] which was obtained enantiomerically pure in only seven steps and 15% overall yield from commercially available $PhMe_2SiCl$ (**11**) via the key intermediate **12** (Scheme 3). At about the same time a Birch reduction-dihydroxylation-ozonolysis sequence starting from arenes was developed to access acyclic polyols and lactols.[26] For instance, a selective monobenzylation of the diol resulting from Sharpless dihydroxylation [away from the TIPS (triisopropylsilyl) group] was used to access to alcohol **14**, which, upon reductive ozonolysis, furnished the lactol **15** as a single diastereoisomer.



Scheme 3

Dihydroxylation has also been studied on simple cyclic allylsilanes **16a**,**b** (Scheme 4).[19] As expected, OsO_4 approached *anti* relative to the chain at C-2, according to model **VI** (Figure 4 and 6), to provide diols **17a**,**b** with reasonable diastereocontrol. It is interesting to note that a reversal of the diastereoselectivity is observed during epoxidation of **16a**,**b** with *m*CPBA (*m*-chloroperbenzoic acid),



Scheme 4

which may be explained by the known tendency of alcohols to hydrogen bond with peracids.[20] The oxidant is thus delivered from the sterically most hindered face, providing the complementary diastereomer to that formed through dihydroxylation (e.g. **18a**,**b** in Scheme 4 and Figure 6).

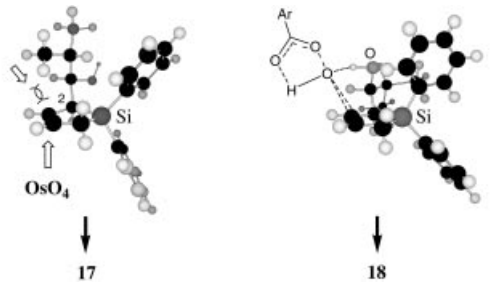
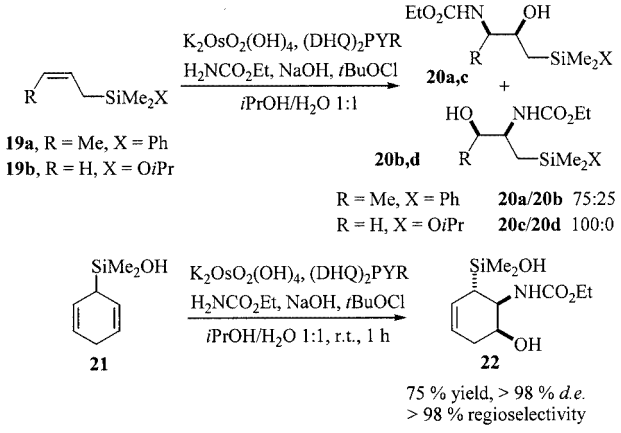


Figure 6. Transition-state models for dihydroxylation and epoxidation of allylsilanes **16**

2.1.3. Aminohydroxylation of Allylsilanes

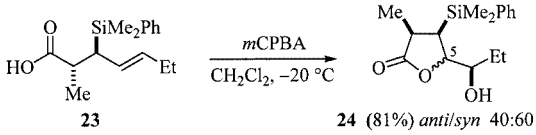
Aminohydroxylation of allylsilanes has recently been investigated. Good levels of regiocontrol may be observed depending on the nature of the allylsilanes.[25a,26b,27] For instance, in acyclic systems it appears that, with monosubstituted allylsilanes, the carbamate group prefers the less-substituted end of the olefin (e.g. **20c/20d**, Scheme 5), whereas with disubstituted olefins the picture is not so clear-cut, the carbamate reacting away from the silicon group (C-γ), but with modest regiocontrol (e.g. **20a/20b**). It is noteworthy that a similar regiocontrol was observed with the corresponding allylic alcohols. In contrast, complete regio- and diastereocontrol was found during aminohydroxylation of cyclohexadienylsilane **21**, leading to amino alcohol **22** in excellent yield and reasonable enantioselectivity.[25a,27] Oxidation of the C−Si bond and protection of the amino alcohol moiety led to a crystalline compound, eventually isolated in enantiomerically pure form after a single recrystallization. Compound **22** was then elaborated further into various aminocyclitols. In these systems, the regiocontrol varies with the nature of the silicon group and particularly with that of the tertiary amine present in the medium. For instance, with dienylsilane **9** under the same conditions, 8% of the other regioisomer was formed, and changing the ligand from $(DHQ)_2PYR$ to quinuclidine then iPr_2NEt led to the formation of 30% and 50%, respectively, of the second regioisomer.[25a]



Scheme 5

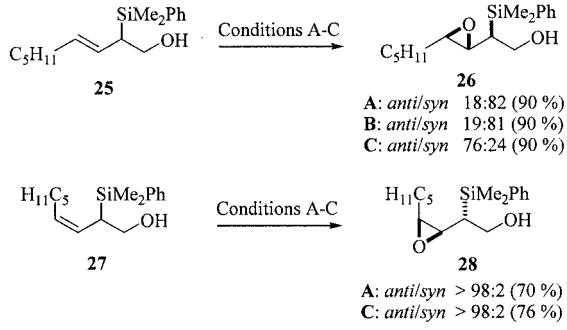
2.1.4. Epoxidation of Allylsilanes

Epoxidation of allylsilanes provides β,γ-epoxysilanes that are often unstable under the reaction conditions and decompose into the corresponding allylic alcohol with transposition, after a Peterson-type elimination, thus resulting overall in an S_E' reaction.[3b,28] When a nucleophile is present in the starting allylsilane, intramolecular displacement may occur, as demonstrated by the epoxidation of **23** with *m*CPBA, which is followed by a lactonization to give **24** (Scheme 6).[21] The epoxidation proceeds with virtually complete diastereocontrol, according to transition-state model **IVa** (Figure 4), but the stereochemistry at the stereogenic centre C-5 is lost upon lactonisation, which presumably occurs through the intermediacy of a β-silyl carbocation.[21a]



Scheme 6

The epoxidation reaction has also been studied on allylsilanes such as **25** having a coordinating β-hydroxy group (Scheme 7).[29] Three different conditions were examined for epoxidation: **A**: $Ti(OiPr)_4$, *t*BuOOH, CH_2Cl_2, −10 °C; **B**: $VO(acac)_2$, *t*BuOOH, CH_2Cl_2, 20 °C; and **C**: *m*CPBA, K_2HPO_4, CH_2Cl_2, 20 °C (Scheme 7).[29a] As in non-directed reactions,[22] (*Z*)-allylsilanes were shown to provide better selectivities than (*E*)-allylsilanes, although reasonable diastereocontrol was still observed with an (*E*)-allylsilane such as **25**. Remarkably, during Ti- and V-catalyzed epoxidation, (*E*)- and (*Z*)-allylsilanes **25** and **27** led to opposite face selectivity, affording *syn*- and *anti*-epoxides **26** and **28**, respectively. These results contrast with those obtained with closely related analogues lacking a hydroxy group in the vicinity of the allylic stereogenic centre, in which both (*Z*)- and (*E*)-allylsilanes led to the *anti*-epoxide.[22] This indicates the profound effect of the OH group on the stereocontrol. It must be added that this behaviour only concerned metal-catalyzed epoxidation (conditions **A** or **B**), since epoxidation with *m*CPBA (conditions **C**) led to the *anti* product, irrespective of the stereochemistry of the olefin.



Scheme 7

The stereoselectivity was rationalized by the chair-like transition states **VIIIa**, **VIIIb** and **VIIIc**, depending on the reaction conditions (Figure 7).[29a] In each model, the OH group coordinates to the metal atom (or H with *m*CPBA), and the bulky silicon group occupies the pseudoequatorial position to minimize the $A_{1,3}$ interaction.[20,30] With (*Z*)-allylsilanes under metal-catalyzed epoxidation conditions, the chair-transition state **VIIIa** prevails over **VIIIb**, due to steric interactions occurring in **VIIIb** between R_Z and the metal ligands (ligands on the metal atom have been omitted for clarity). As *m*CPBA induces few steric interactions, (*Z*)-allylsilanes react in these conditions through **VIIIc**, which closely resembles the transition-state model **IVa** that is governed by $A_{1,3}$ strain (Figure 4). With (*E*)-allylsilanes, the chair-like transition state **VIIIb** is favoured over **VIIIa** due to important steric interactions in the latter between R_E and the oxometal complex.

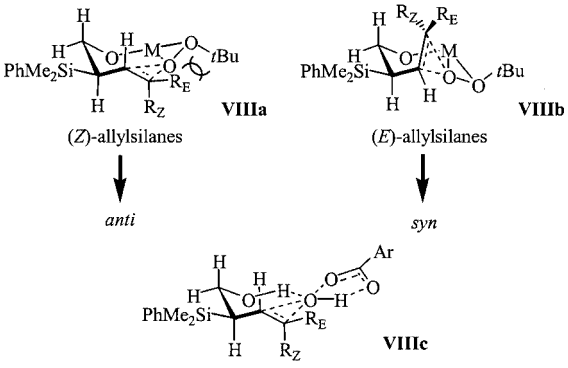
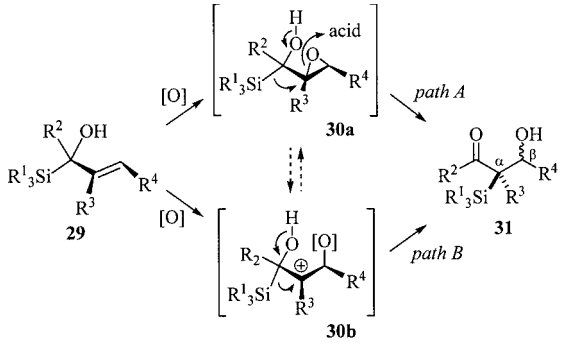


Figure 7. Transition-state models for epoxidation of allylsilanes **25** and **27**

Epoxidation of allylsilanes containing an α-hydroxy group has also been reported (Scheme 8). In this case, a cascade reaction takes place transforming α-silylated allylic alcohols **29** into α-silylated aldols **31**.[31] This cascade involves an epoxidation, followed by a pinacol-type rearrangement of intermediate **30a** in which the silicon group undergoes a [1,2]-shift to form the aldol species (*path A*). An alternative path (*path B*) may also be followed, involving the intermediate **30b**, eventually leading to the α-silyl-β-hydroxy ketone **31**.



Scheme 8

As a consequence of the β-effect, it is likely that the rearrangement of species **30a** proceeds via an intermediate of type **30b**. It was found that (*E*)-olefins provide exclusively the corresponding *anti* products, whereas (*Z*)-olefins lead to the *syn*-α-silylated alcohols. Finally, it has been shown that the stereochemical course of this transformation is independent of the nature of the oxidizing reagents [*t*BuOOH/$Ti(OiPr)_4$ (cat.), *t*BuOOH/$VO(acac)_2$ (cat.), *m*CPBA or dimethyldioxirane].

In conformation **IXa**, the OH group in the *inside* position may direct the epoxidation either by transition-metal coordination or by H-bonding (Figure 8). To efficiently stabilize the evolving carbocation in the β-position relative to the silyl group, the C−Si bond must be parallel to the π-system. Such a coordination with the OH group would not be possible in transition state **IXb** and, furthermore, repulsive steric interactions between the reagent and the R^2 group disfavour an *anti* approach of the reagent through this conformation. Calculations (MM2) finally indicate that, even in the ground state, the conformation of the precursor leading to **IXa** is preferred by 3 kJ/mol over that leading to **IXb**.[32]

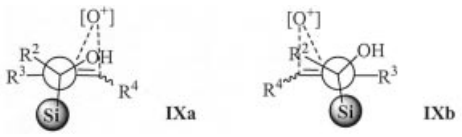
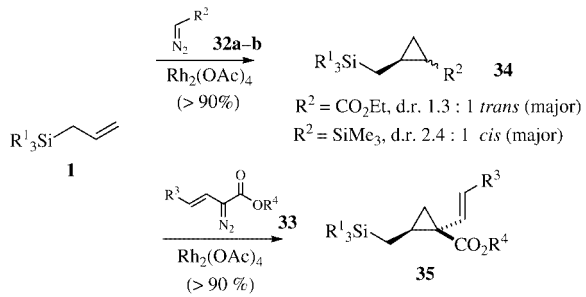


Figure 8. Transition-state models for epoxidation of allylsilanes **29**

2.1.5. Cyclopropanation of Allylsilanes

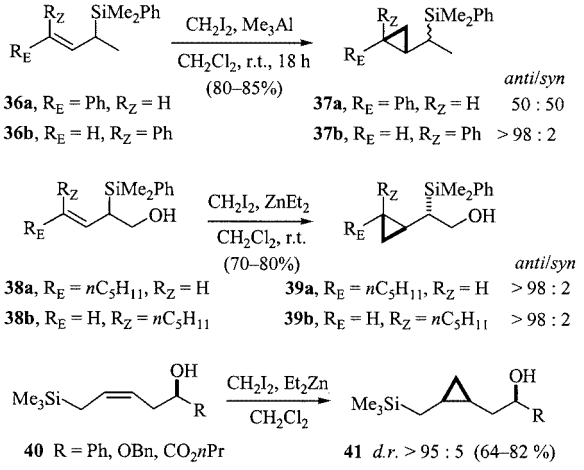
The cyclopropanation of simple allylsilanes such as **1** has recently been studied by Turos et al.[33] The reaction was carried out using different diazo compounds **32a**,**b** and **33** in the presence of $Rh_2(OAc)_4$ (Scheme 9). In the first two cases, the diastereoselectivity was low, giving mainly the *trans* and *cis* products **34**, respectively. Conversely, rhodium-catalyzed cyclopropanation using disubstituted diazo compound **33** occurred with excellent diastereocontrol to provide the *trans*-cyclopropane as the unique product. The stereochemical course of this process is consistent with an open transition-state model wherein the rhodium carbenoid species approaches the allyl−metal π-bond from an antiperiplanar orientation with respect to the allylic carbon−SiR_3 bond. Whilst the C−Si bond may help to stabilize the developing β-cationic charge in the transition state, hyperconjugation appears to play a minor role, if at all, in directing the stereochemical course of the cyclopropanation.

Cyclopropanation of acyclic chiral allylsilanes follows the same trend as dihydroxylation and epoxidation,[2,3,22a] and



Scheme 9

the stereochemical outcome of these processes is generally well rationalized by transition-state models **IVa** and **IVb** based on $A_{1,3}$ strain (Figure 4). Cyclopropanation of (*Z*)-allylsilane **36b** was thus shown to produce only the *anti* product **37b**, while (*E*)-allylsilane **36a** gave a 50:50 mixture of *anti*- and *syn*-**37a** (Scheme 10).[22a] The problem of low diastereocontrol observed with (*E*)-allylsilanes may be circumvented using substrate-directable reactions.[20,29b,34] Allylsilanes bearing a homoallylic hydroxy group such as in **38a**,**b** are thus cyclopropanated under Furukawa conditions in good yields (71−88%) and with excellent *anti* diastereocontrol (> 98:2), irrespective of the stereochemistry of the olefin.[34] This was rationalized by considering a chair-like transition-state model **X** (Figure 9). Steric hindrance around the iodine atom on the metal atom probably prevents the cyclopropanation of (*E*)-olefin if it was to proceed through a conformation similar to **VIIIb** (Figure 7), explaining the absence of *syn* products. Therefore, as noticed before for transition-metal-catalyzed epoxidation, steric interactions between R_Z or R_E and the ligands on the zinc atom (including iodine) govern the diastereofacial selectivity of the cyclopropanation. The homoallylic alcohols **40** developed by Mohr showed the same behaviour (Scheme 10).[35] The stereochemical outcome could be rationalized assuming a chair-like transition state, closely related to that of **VIIIb** (Figure 7), in which the R substituent adopts a pseudoequatorial position.



Scheme 10

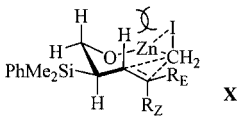
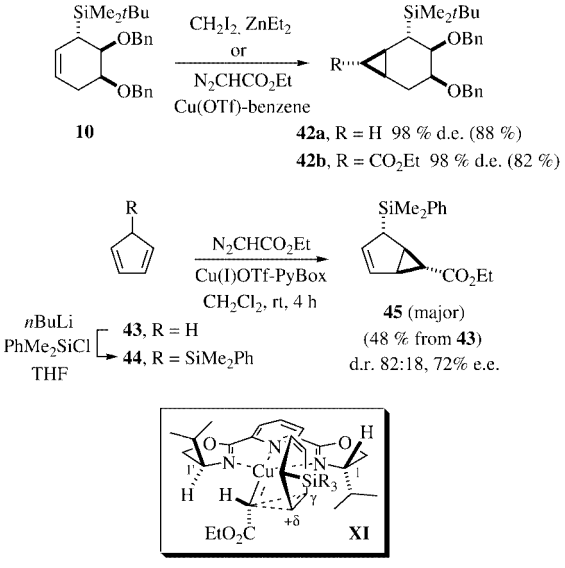


Figure 9. Transition-state models for cyclopropanation of allylsilanes **38**

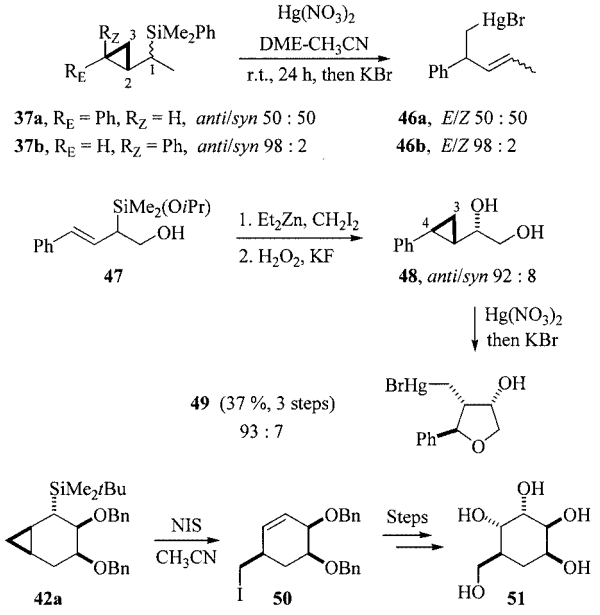
Cyclic allylsilanes such as cyclohexadienyl- or cyclopentadienylsilanes **10** and **44** have also been cyclopropanated with success (Scheme 11).[24b,34,36] Cyclopropanation of allylsilane **10** afforded **42a** under Furukawa conditions or **42b** when treated with ethyl diazoacetate in the presence of a catalytic amount of $Cu^{I}OTf$/Schiff base. In both cases a single diastereomer was detected. Again, the metallocarbene reagent was shown to approach *anti* relative to the silicon group. Excellent diastereocontrol (95:5) was also observed for the cyclopropanation of the analogous cyclopentadienylsilane **44**.[34,36b,36c] An enantioselective approach has recently been developed, in which PyBox asymmetric ligands were found to afford the best results.[36a] To the best of our knowledge, this is the first example of a desymmetrisation process using an asymmetric cyclopropanation. Surprisingly, the reaction was less diastereoselective with PyBox than with achiral Schiff bases used in racemic series. Enantiomeric excesses of up to 72% were obtained for the major cyclopropane **45** and its diastereomer, which remarkably arises from a *syn*-cyclopropanation. A transition state **XI** was thus proposed to rationalize the stereochemistry of **45**. It is likely that bonding between the γ-carbon atom of the allylsilane and the carbenoid centre occurs first, leaving a partial positive charge β to the silicon group that is stabilized through hyperconjugation (Scheme 11).[37] The enantioselectivity of the process is thought to be governed by steric interactions developing between substituents on the carbene (carboxylate) and those on the chiral ligand (*i*Pr groups) during carbenoid pyramidalization.[37,38] The preferential attack of the carbenoid species onto the pro-(*S*) double bond (*anti* relative to the SiR_3 group, Scheme 11) would thus prevent steric interactions developing between the *i*Pr group at C-1 and the carboxylate.



Scheme 11

Ring opening of cyclopropanated allylsilanes has also been investigated.[24b,34,36b,36c,39] Mercury-mediated ring-opening-desilylation of (cyclopropylmethyl)silanes such **37a** or **37b** has been shown to occur with high regioselectivity, the C-2−C-3 bond being broken exclusively as a result of the stabilization of the developing positive charge β to the silicon atom (Scheme 12).[34] The sequence also proceeds stereospecifically to afford the corresponding olefins in good yields; *anti*- and *syn*-cyclopropanes **37a** and **37b** were thus shown to provide (*E*)- and (*Z*)-olefins **46a** and **46b**,

respectively, in excellent yields (> 80%). Interestingly, the analogous cyclopropyl alcohol **48**, prepared by cyclopropanation of the corresponding allylsilane **47** and C−Si bond oxidation, led regioselectively to C-3−C-4 bond cleavage, providing stereospecifically, after 5-*endo* cyclization, the trisubstituted tetrahydrofuran **49** (Scheme 12).[34a] This dichotomy between allylic alcohols and allylsilanes is noteworthy and has already been observed in other processes.[29a,34a,40] Finally, *N*-iodo- and *N*-bromosuccinimide were also shown to efficiently open cyclopropane **42a**, in order to access homoallylic halides **50**, which are useful intermediates in the total synthesis of carba-sugars such as **51**.[18,24b,25b,34a]

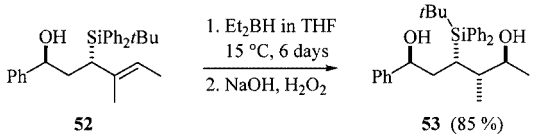


Scheme 12

3. Miscellaneous Electrophilic Reactions

3.1. Hydroboration

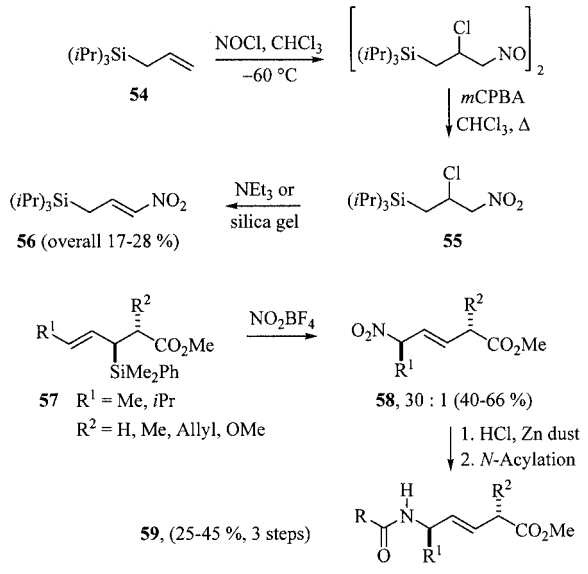
Hydroboration of allylsilanes has originally been shown by Fleming et al. to proceed with excellent regio- and diastereocontrol.[41] The best results are usually obtained with sterically hindered boranes (9-BBN), with the boron group approaching the γ-carbon atom, *anti* relative to the silicon group. As mentioned previously for epoxidation and dihydroxylation, transition-state model **IVa** (Figure 4) was used to rationalize the stereochemical outcome of such hydroborations.[41] Such a useful transformation has recently been employed in the course of the synthesis of the "western" fragment of amphotericin-B.[42] Hydroboration of the trisubstituted olefin **52** with Et_2BH (6 equiv.) gave, after oxidative workup, the alcohol **53**, resulting from an *anti* addition (Scheme 13). Hydroboration proceeded with excellent diastereocontrol, as only 3% of the other diastereomer was isolated. The starting olefin was shown to be inert to the classical reagents 9-BBN, (thexyl)BH_2, BH_3·SMe_2 or $BHBr_2$·SMe_2.



Scheme 13

3.2. Nitrosylation and Nitration

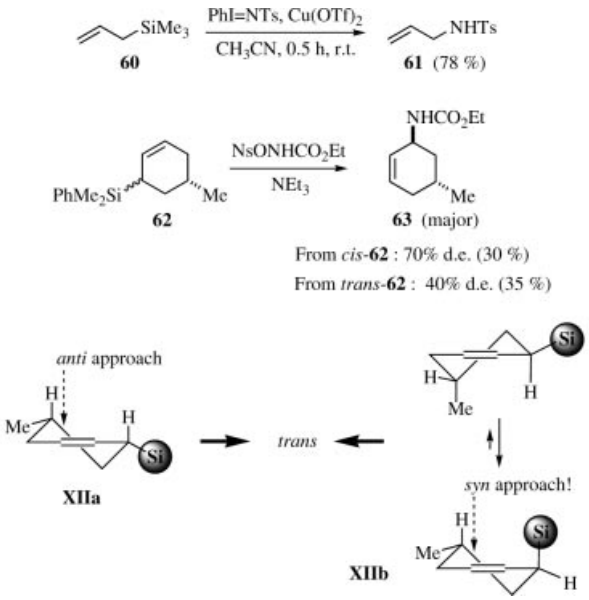
Hwu et al. have developed the synthesis of 1-nitro-3-organosilyl-1-propenes **56** through nitrosylation of allylsilanes.[43] The first investigations were carried out by allowing allyltriisopropylsilane **54** to react with nitrosyl chloride in chloroform at −60 °C (Scheme 14). Oxidation with *m*CPBA and dehydrochlorination of the intermediate **55**, in the presence of triethylamine or silica gel, produced **56** with an overall yield ranging between 17 and 28%. An improved protocol was then developed involving sonication of the allylsilane in the presence of $NaNO_2$, $Ce(NH_4)_2(NO_3)_6$, and acetic acid, which afforded 1-nitro-3-organosilyl-1-propenes **56** in 51−86% yields. The mechanism, although unknown, is likely to be a radical and not a cationic addition of the NO_2 group onto the allylsilane. A new approach towards (*E*)-olefin dipeptide isosters **59** has been described by Panek et al., and is based on an asymmetric C−N bond formation through nitronium tetrafluoroborate (NO_2BF_4) promoted electrophilic nitrations of chiral (*E*)-crotylsilanes **57**.[44] Analogous work has been carried out by Procter et al. by a multi-step dihydroxylation-nucleophilic substitution sequence.[45] Formation of the allylic nitro compounds **58** occurs in reasonable yields, with subsequent reduction and *N*-acetylation affording the desired dipeptide isosters **59**. The S_E' process occurs with high stereocontrol, NO_2^+ approaching the chiral allylsilanes *anti* relative to the silicon atom in a conformation probably close to that of transition-state model **IVa** mentioned above (Figure 4).



Scheme 14

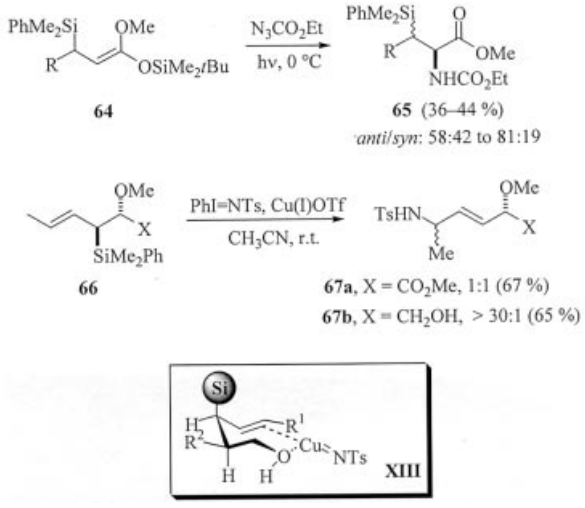
3.3. Reactivity of Allylsilanes towards Nitrenes

S_E' reactions on allylsilanes with electrophilic nitrogen sources such as nitrenes constitute a straightforward access to allylamines. For instance, treatment of allyltrimethylsilane (**60**) with iodinane derivative PhI=NTs in the presence of a catalytic amount of Lewis acid has been shown to afford the corresponding allylamine **61** in moderate to good yields (Scheme 15).[46] The reaction is faster in acetonitrile and **60** is converted into allylamine **61** in 78% yield in only 30 min. Loreto et al. have used (ethoxycarbonyl)nitrene, generated by α-elimination of $NsONHCO_2Et$ with Et_3N, to obtain chiral *N*-substituted allylic amines **63**.[47] The stereochemical outcome of this S_E' process is worth commenting on. When *cis*-allylsilane **62** (e.g. 80:20 mixture *cis*/*trans*) was submitted to the S_E' reaction, the *trans* product **63** was obtained as the major product, probably through an aziridine intermediate. The formation of *trans*-**63** corresponds to an axial approach of the reagent, *anti* to the silicon group, according to model **XIIa**. On the other hand, when *trans*-allylsilane **62** (e.g. 10:90 mixture *cis*/*trans*) was submitted to the same conditions, **63** was obtained as a mixture of diastereomers, in which the *trans* isomer was again the major product. This result is rather surprising, since it implies that the reagent approached the allylsilane *syn* relative to the bulky silicon group according to model **XIIb**. It is believed that in this conformation the pseudoaxial Si group would be suitably placed as to favour σ_{C-Si}-π interactions.



Scheme 15

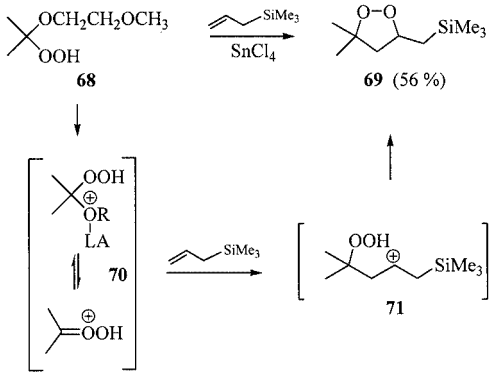
The reaction of β-silylated silylketene acetals **64** with (ethoxycarbonyl)nitrene, generated by photolysis of N_3CO_2Et, was shown to produce β-silylated *N*-(ethoxycarbonyl)amino esters **65**, albeit with modest yields and diastereoselectivities (Scheme 16).[48] The major *anti* diastereomer is thought to be generated through an attack of the electrophile *anti* relative to the silicon group, according to transition-state model **IV** (Figure 4). A similar reactivity was observed by Panek et al. during reactions of chiral allylsilanes **66** having a nondirecting group (X = CO_2Me) with PhI=NTs in the presence of copper(I) triflate.[49] However, when a coordinating group (X = CH_2OH) was present on the substrate, the diastereocontrol was dramatically improved. Aziridines are probably formed as intermediates, although they have not been isolated; aziridine ring-opening followed by desilylation would then provide the desired allylamines **67**. A transition-state model **XIII** (similar to models **VIIa,b**, Figure 5) was proposed, in which the copper nitrenoid species is coordinated to both the double bond and to the oxygen atom in a chair-like conformation, with the silicon group occupying a pseudoaxial position.



Scheme 16

3.4. Reaction with Hydroperoxides

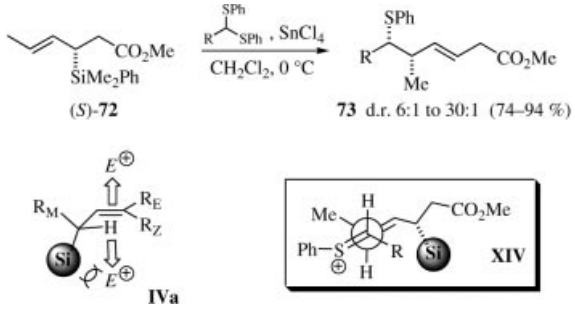
Lewis-acid activation of hydroperoxy ketals such as **68** (derived from ozonolysis) affords the hydroperoxycarbenium ions intermediate **70** (equivalent to protonated carbonyl oxides), which react with allyltrimethylsilane to afford 1,2-dioxolanes **69** (Scheme 17).[50] The β-silylcarbocation intermediate **71** is trapped intramolecularly by the peroxide to form **69**. Similar reactions have been performed with ozonides, forming metalated carbonyl oxide by $SnCl_4$ activation.[51]



Scheme 17

3.5. Reaction with Thioacetals

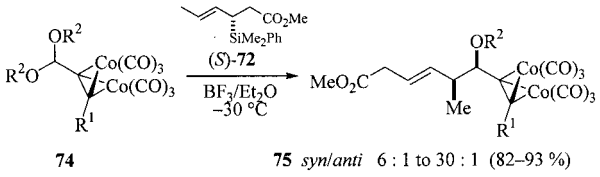
Reaction of enantioenriched (*E*)-crotylsilane reagents **72** with thioacetals affords, under Lewis-acid catalysis, the corresponding S_E' product **73** with good to excellent diastereocontrol (Scheme 18).[52] The addition proceeds with predictable diastereofacial selectivity through an open transition-state model **XIV**, consistent with a stereospecific *anti*-S_E' pathway, as already mentioned above (transition-state model **IVa**, Figure 4). Cyclic and acyclic aliphatic thioacetals generally gave higher levels of selectivity than their aromatic analogues.



Scheme 18

3.6. Reactivity towards Propargylic Derivatives

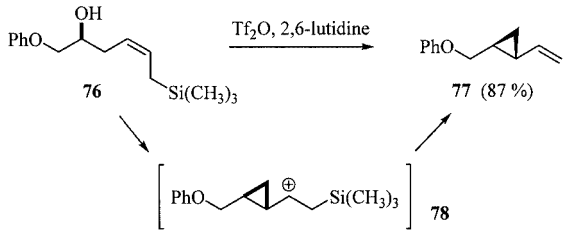
The chiral allylsilane (*S*)-**72** has also been submitted to Lewis-acid-catalyzed reaction with propargyl acetals, which unfortunately led to low levels of diastereocontrol (1:1 to 2:1 *syn*/*anti*).[53] However, increasing the steric bulk of the propargylic reagent through protection of the alkyne with hexacarbonyldicobalt, as in **74**, led to a dramatic improvement of the diastereoselectivity in favour of the *syn* isomer (Scheme 19). The propargylic ether derivative could then be recovered by oxidation of **75**. The origin of the diastereocontrol may be explained by a transition-state model similar to model **XIV**, used for the addition of thionium species (Scheme 18).



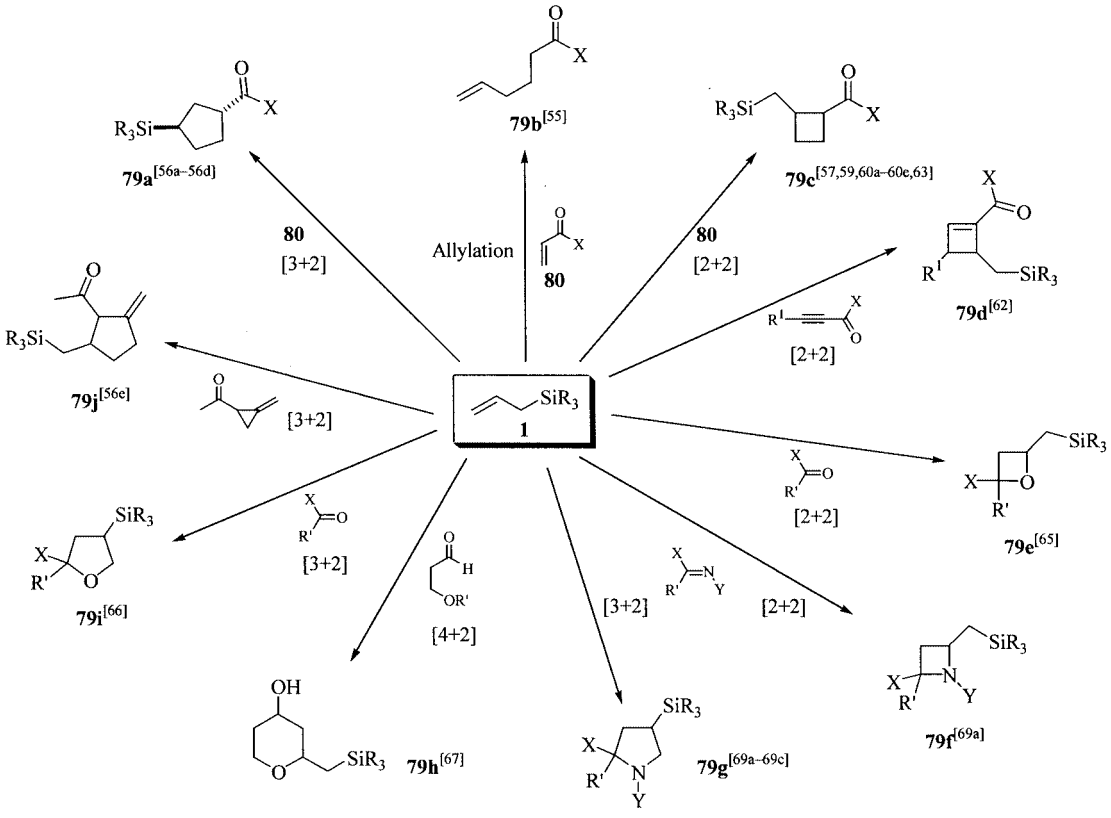
Scheme 19

3.7. Intramolecular S_E' Processes

An intramolecular S_E' reaction of allylsilanes has been elegantly used for the diastereocontrolled preparation of cyclopropanes starting from homoallylic alcohols **76** (Scheme 20). The reaction proceeds through the formation



Scheme 20



Scheme 21

of a triflate which is displaced by the allylsilane moiety, thus forming a β-silylcarbocation intermediate **78**, which then loses its silyl group to provide the cyclopropane **77** as a unique diastereomer having the *trans* configuration.[54]

4. S_E' versus Annulation Processes

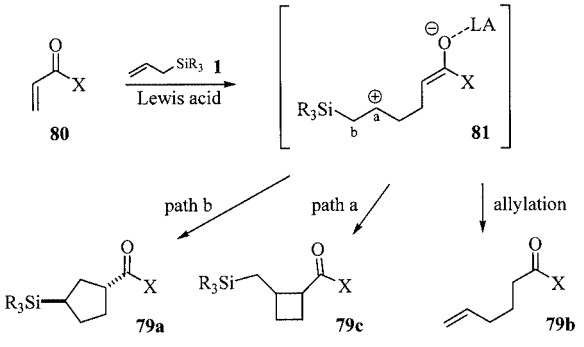
4.1. Introduction

The introduction of allyl groups by Lewis-acid-promoted 1,2- or 1,4-addition of an allylsilane to α,β-unsaturated aldehydes or ketones (Hosomi−Sakurai or S_E' reaction[55]) has found many applications in stereoselective synthesis.[56] Furthermore, cycloaddition reactions of allylsilanes with electron-deficient olefins, carbonyl compounds and imines have been developed for the stereoselective construction of carbocycles as well as four-, five- and six-membered heterocycles (Scheme 21).

In most cases, the reaction pathway depends on the size of the silyl group. Indeed, increasing the size of the ligands on the silicon atom increases the rate of product formation and the proportion of annulation relative to allylation (vide infra).[57] Several examples of solvent,[58a] reactant,[58b] or substrate[59] effects on the chemoselectivity have also been reported. When a bulky silyl group is employed [generally Si(*i*Pr)$_3$] in order to avoid formation of the Sakurai product, the oxidative cleavage has proven to be difficult.[15] To overcome this problem, novel allylsilanes that give high yields of cycloadducts and are easily oxidable into hydroxy moieties have been developed.[60] As a large variety of carbocycles and heterocycles are accessible through cycloaddition with allylsilanes, we will focus our attention on the stereochemical outcome of this reaction through selected examples. Some applications of this reaction in total synthesis will also be described.

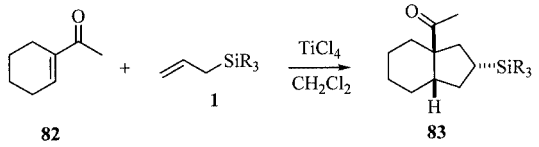
4.2. Access to Carbocycles

Lewis-acid-mediated [2+2]- and [3+2]-annulation of allylsilanes with electron-deficient olefins has been shown to be a useful method for the preparation of cycloalkanes. This process involves a conjugate addition of allylsilanes **1** onto unsaturated substrates **80** (Scheme 22).



Scheme 22

The open β-silyl cation intermediate **81** is central to all possible products (vide supra). First, a halide issued from the Lewis acid may displace the silicon group, resulting in a net allyl transfer product **79b**. The enolate moiety in **81** may react (at C-a) in an intramolecular fashion (4-*exo* process) to afford the cyclobutane **79c**, or through a 5-*endo* process (at C-b) by a sila-Wagner−Meerwein shift to give the cyclopentane **79a**. Pathways a and b are usually dominant when the R group on the silicon atom is larger than methyl (*i*Pr, Ph, *t*Bu; Scheme 23, Table 1).[61]

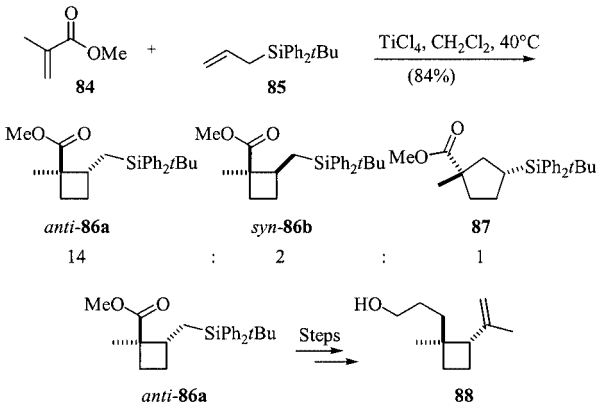


Scheme 23

Table 1. [3+2]-annulation reactions of allylsilanes (see also Scheme 23)

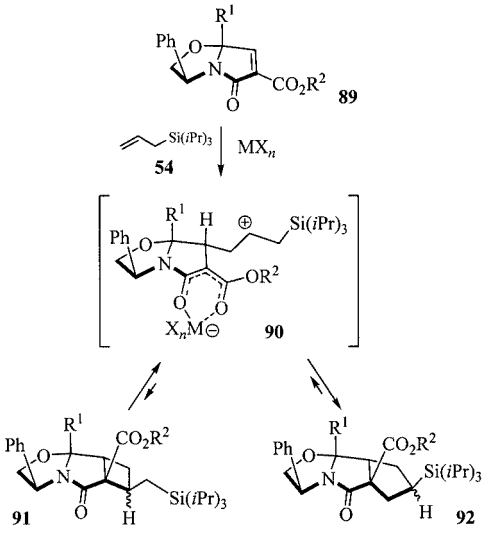
SiR_3 in **83**	Yield (%)
$SiMe_3$	18
$SiPh_3$	51
$SitBuPh_2$	69
$Si(iPr)_3$	86

Access to cyclobutenes such as **79d** (Scheme 21) has also been accomplished by using electron-deficient alkynes with cyclic[62a] or acyclic allylsilanes.[62b] For example, Knölker et al. have shown that (*Z*)- and (*E*)-crotylsilanes react with methyl propynoate to provide stereospecifically *cis*- and *trans*-3,4-disubstituted cyclobutenes, respectively.[62b] When olefins were used instead of alkynes, a Lewis-acid-promoted [2+2]-cycloaddition occurred to afford cyclobutane **79c**.[59,60a−60c] This methodology has been employed by the same authors in order to achieve a stereoselective total synthesis of (±)-fragranol (**88**) (Scheme 24).[60a] Cycloaddition of allyl-*tert*-butyldiphenylsilane (**85**) and methyl methacrylate (**84**) thus afforded the two diastereoisomeric silylmethylcyclobutanes *anti*-**86a** and *syn*-**86b** along with the silylcyclopentane **87** in a 14:2:1 ratio and 84% total yield. Compound **86a** was then elaborated further en route to fragranol (**88**) which was obtained in 7% overall yield and 11 steps from **84**.



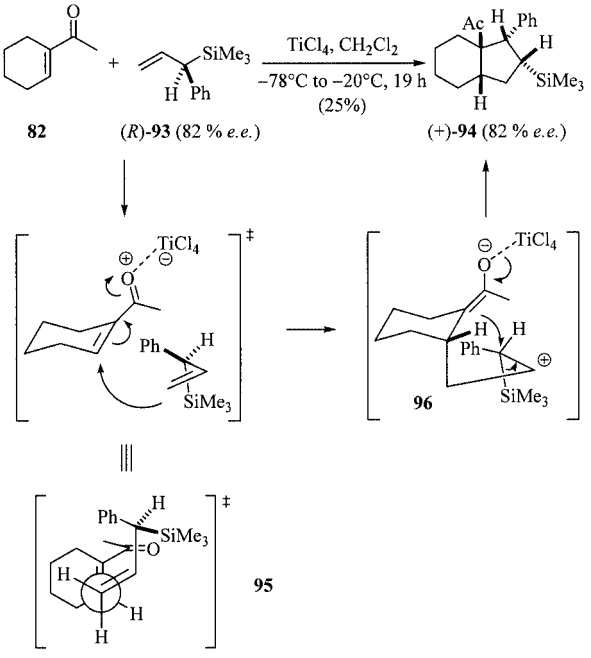
Scheme 24

Experimental observations made by Meyers et al.[63a] suggest that the cyclobutane **91** is the kinetic product whereas the cyclopentane **92** is the thermodynamic product. It has been demonstrated, by treating the pure cyclobutane **91** (R^1 = Ph, R^2 = *t*Bu) with $TiCl_4$ at −78 °C that, upon warming, it immediately rearranges to the corresponding cyclopentane derivative **92** (Scheme 25).[60e,63]



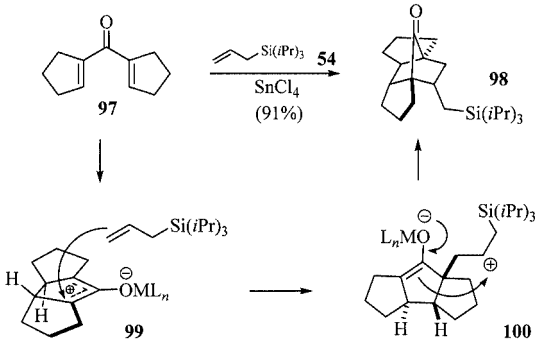
Scheme 25

In contrast to [2+2]-annulation, [3+2]-cycloaddition is a highly diastereoselective reaction, and in most cases it provides exclusively the *anti* stereoisomer **79a**. This stereoselectivity can be attributed to the preference of the electron-withdrawing group and the silicon group to align themselves to produce a *synclinal* transition state such as **95** (Scheme 26).[61] Knölker et al. have shown that when the chiral, non-racemic allylsilane (*R*)-**93** was used, the [3+2]-cycloaddition proceeded enantiospecifically to generate the chiral annulated cyclopentane (+)-**94** with four stereogenic centres.



Scheme 26

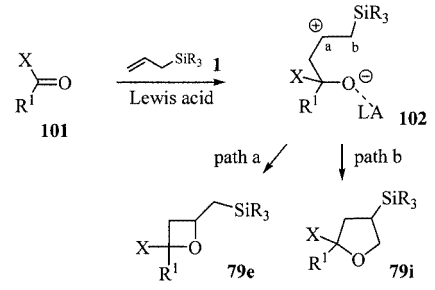
A [3+2]-annulation reaction was recently introduced within a cascade of cationic processes involving a Nazarov cyclization (Scheme 27).[64] Nazarov electrocyclization of **97** was thus shown to lead to the tricyclic oxyallyl intermediate **99**, which was trapped by allylsilane **54** to furnish the β-silylcarbocation intermediate **100** that finally cyclized to produce the annulated polycyclic system **98**. This remarkable transformation generates three new carbon−carbon bonds and up to five contiguous stereocenters during the construction of the functionalised bicyclo[2.2.1]heptanone **98** from the simple dienone **97** and allylsilane precursor **54**.



Scheme 27

4.3. Access to Heterocycles

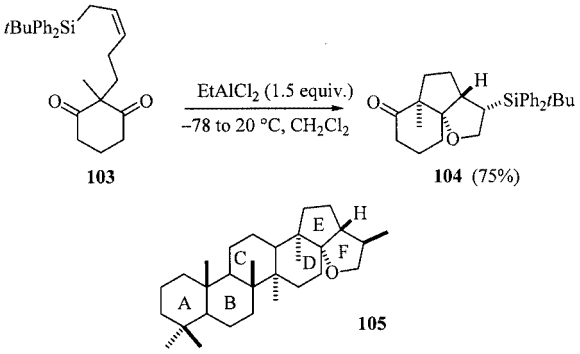
Formation of heterocycles through cycloadditions of allylsilanes with aldehydes or imines has been intensively studied.[58,60c,60h,65−69] From a mechanistic point of view, the reaction involves an activation of the carbonyl function of **101** by a Lewis acid, before reaction with the allylsilane **1**, to afford the β-silylcarbocation intermediate **102** (Scheme 28). The oxygen centre in this intermediate can then attack the cation, either by pathway a to afford the oxetane **79e**[65] or by pathway b to furnish tetrahydrofuran **79i**.[66]



Scheme 28

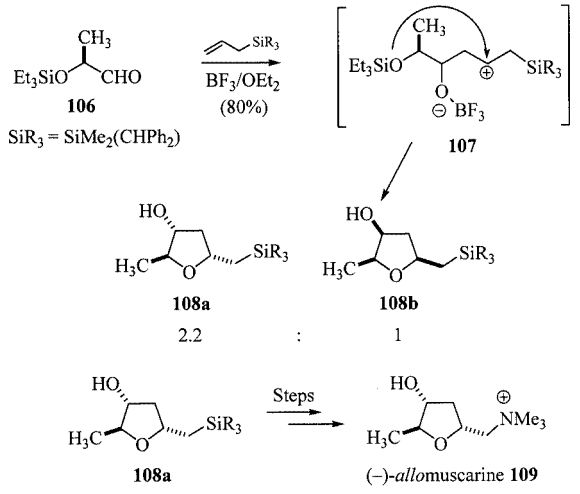
Akiyama et al.[65a] have described the first example of a highly stereoselective construction of oxetanes by $TiCl_4$-mediated [2+2]-cycloaddition of allylsilanes and α-oxo esters (path a). In comparison with carbocycles, they observed that oxetanes are the kinetic products whereas tetrahydrofurans are the thermodynamic products (vide supra). They reported that oxetanes can also be synthesized from α-siloxy aldehydes using $ZrCl_4$ as the Lewis acid.[65b]

Further examples of the formation of tetrahydrofurans by path b have been reported,[66] such as that described by Schinzer et al., who developed a novel tandem reaction using a silicon-terminated cyclization of allylsilanes with cyclic 1,3-diketones (Scheme 29).[66a–66b] The tricyclic furan system **104** is formed in a stereoselective manner from allylsilane **103** (*synclinal* transition state), by an intramolecular [3+2]-heteroannulation reaction. Compounds of type **104** are useful precursors for the D-E-F tricyclic subunit of complex triterpenes **105** of the hopane family.



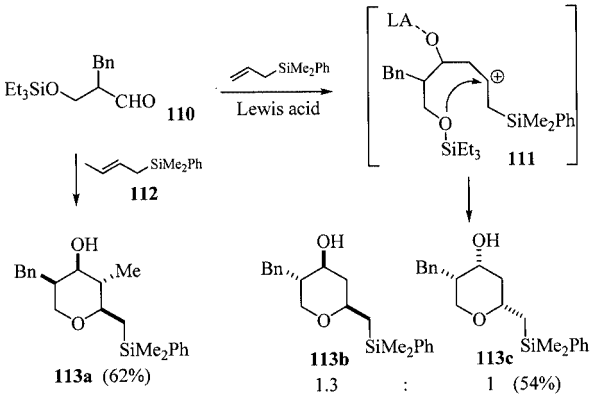
Scheme 29

In the previous example, the alkoxide oxygen atom in **102** intercepted the β-silyl cation intermediate (Scheme 28). There are some examples where this is not the case, and a nucleophile other than the alkoxide oxygen atom may react with this cation.[66c–66e] By using the α-triethylsilyloxy aldehyde **106**, Angle et al.[66c] have achieved the stereoselective preparation of tetrahydrofurans by formal [3+2]-cycloaddition of allyl- and crotylsilanes (Scheme 30). The triethylsilyl ether oxygen atom seems to be more nucleophilic than the Lewis-acid-complexed alkoxide, and thus it is this internal nucleophile which participates in the cyclization of **107**. This new approach was applied to the formal syntheses of (−)-*allo*-muscarine **109** and (+)-*epi*-muscarine from the tetrahydrofurans **108a** and **108b**, respectively.



Scheme 30

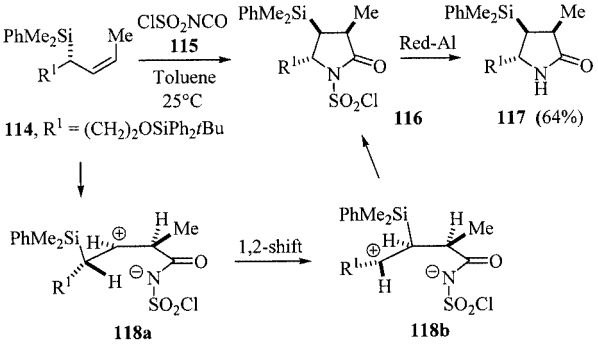
As an extension, reaction of a series of β-triethylsilyloxy aldehydes **110** with several allylsilanes and crotylsilanes was also described by the same authors.[67a] They observed that aldehydes possessing an α-stereocenter, such as **110**, react with allylsilanes to afford tetrahydropyrans **113b** and **113c** as a mixture of two diastereomers with low stereocontrol, whereas a single diastereomer **113a** was obtained in the case of (*E*)-crotylsilanes **112** (Scheme 31).



Scheme 31

With regard to the synthesis of heterocycles containing an oxygen atom, the preparation of original cycles such as 1,2-dioxolanes[50] and 1,3-dioxanes[68] has also been reported by the cycloaddition of allylsilanes.

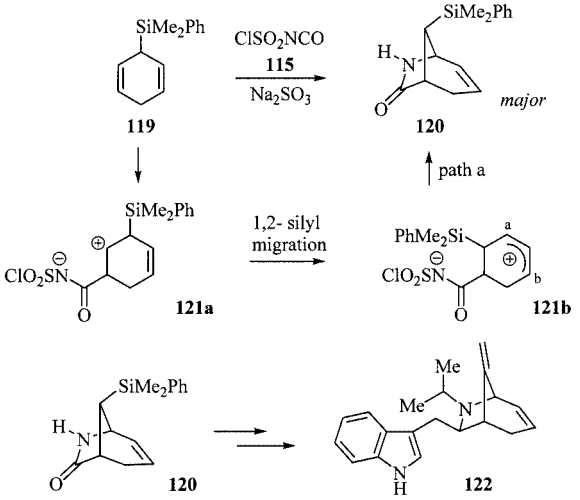
Finally, we will describe the formation of four- and five-membered heterocycles containing one nitrogen atom, such as **79f** and **79g** (Scheme 21).[69] The [3+2]-annulation of acyclic[69a,69b] or cyclic[69c] allylsilanes with chlorosulfonyl isocyanate (CSI, **115**) is an efficient, and stereospecific method for the synthesis of highly substituted 2-pyrrolidones **117** (Scheme 32), and β-lactams.[69a] Interestingly, unlike the reactions of allylsilanes with most electrophiles, the annulation with CSI requires no Lewis acid activation.



Scheme 32

The [3+2]-cycloaddition of enantiomerically pure allylsilane **114** [> 99% (*Z*), >98% *ee*] occurred with retention of enantiomeric purity to afford pyrrolidinone **117** (*dr* > 95:5, > 98% *ee*) in good yield. Since the [3+2]-annulation with CSI is stereospecific and highly diastereoselective, it was concluded that the initial electrophilic attack was diastereoselective (the electrophile approaching *anti* relative to the silicon atom as in transition-state model **IVa** (Figure 4), the silyl migration (1,2-shift) was stereospecific, and both β-silyl carbocation intermediates **118a** and **118b** were configurationally stable (Scheme 32).[69a] This methodology has been extended successfully to the reaction of cyclohexadien-

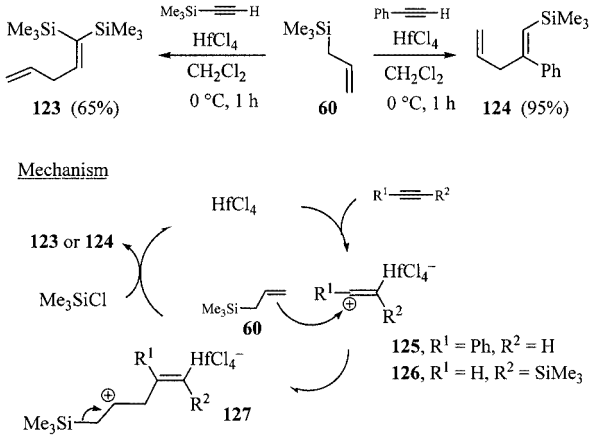
ylsilane **119** with CSI to afford the bicyclic lactam **120**, which was found to be a valuable intermediate for the total synthesis of (±)-peduncularine (**122**; Scheme 33).[69c] As above in the acyclic series, a silyl migration occurs to generate a well-stabilized allylic carbocation **121b**, which then cyclises to give bicyclic **120** as the major product (path a).



Scheme 33

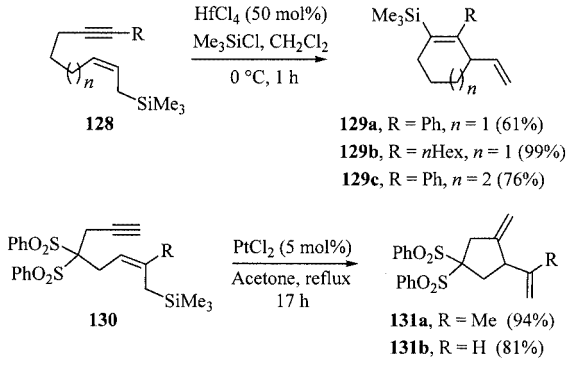
4.4. Addition of Allylsilanes to Alkenes and Alkynes

Allylsilylation of alkenes, alkynes and dienes has recently been developed both in inter- and intramolecular series. As with the allylation of carbonyl compounds, the reaction is catalyzed by Lewis acids such as $AlCl_3$,[70] $GaCl_3$,[71] $EtAlCl_2$ [72a] and $HfCl_4$,[72b] which are the most efficient catalysts for this process. These new processes have recently been reviewed up to 1999 by Jung,[70a] one of the pioneers in this field. Two examples illustrate the value of such a simple process for organic chemists. $HfCl_4$-mediated addition of allylsilane **60** to phenylacetylene provides diene **124** in excellent yield with complete regiocontrol (Scheme 34).[72b] It is interesting to note that addition of **60** to trimethylsilylacetylene provides **123** with a reversal of regioselectivity. This is well accounted for by a stepwise mechanism, involving coordination of the Lewis acid to the acetylenic substrate which generates the most stable vinylic carbocation **125** and **126** (**126** is stabilized by a β-silicon effect). The latter then adds to the allylsilane to give rise to a β-silylcarbocation species **127**, which then loses its silicon group. Transmetallation of $HfCl_4$ with Me_3Si then provides the desired products **123** or **124**. It is noteworthy that addition of Me_3SiCl to the reaction mixture improves the process by accelerating the transmetallation of **127**.



Scheme 34

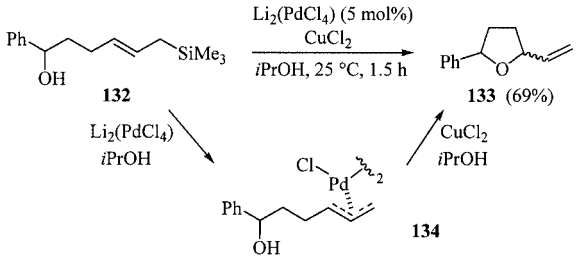
The intramolecular analogue of this allylsilylation of alkynes was originally developed by the same group and led to an unusual but exclusive *endo-dig* carbocylisation, as illustrated by the transformation of enyne **128** into the six- and seven-membered ring systems **129a**–**c** (Scheme 35).[73] Subtle steric and electronic features of the vinylic carbocation intermediate (resembling cations **125** and **126**; Scheme 34) is believed to account for this unusual ring closure. A regio-complementary process is available using Pt^{II}, Pd^{II}, Ru^{II} and Ag^{I} catalysts;[74,75] 5-*exo-dig* cyclizations were thus carried out as illustrated by the conversion of enyne **130** into the five-membered-ring compounds **131a**,**b** (Scheme 35).[74] $PtCl_2$ was found to be the most efficient catalyst for these reactions, which are believed to proceed through complexation of the metal atom by the alkyne that then triggers the *anti*-nucleophilic attack of the soft allylsilane nucleophile onto a vinylic cation such as **125**. A related study was reported earlier by Forsyth[76] using stoichiometric quantities of mercury(II) salts, which corroborates Echavarren's hypothesis.[74] Mercury(II) chloride was also shown to activate the alkynyl group, with the allylsilane moiety attacking the carbomercurinium intermediate in an *anti* fashion to provide the vinylmercurial products in moderate to good yields with complete stereocontrol; 5-*exo*, and to a lesser extent 6-*exo* products were produced, but no seven-membered ring carbocycles were available using this approach.



Scheme 35

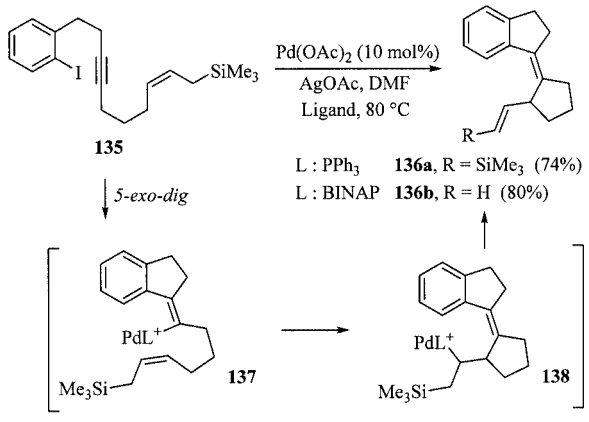
Allylsilanes have also been shown earlier to add to dienes[75,77] in the presence of Pd^{II} catalysts. According to a mechanism similar to that depicted in Scheme 34, the metal atom probably coordinates to the diene, which is then attacked by the allylsilane that acts as a nucleophile.[78] Umpolung reactivity may also be observed in reactions of allylsilanes with certain Pd^{II} complexes.[75,79] Allylpalladium species are thus formed through palladadesilylation to give

an (η^3-allyl)palladium intermediate that can then be attacked by nucleophiles such as alkoxy and amino groups. Szabo et al.[79] have used this approach to prepare tetrahydrofurans (e.g. **133**), piperidines and pyrrolidines through cyclization of hydroxy- and aminoallylsilanes such as **132** (Scheme 36). Interestingly, they were also able to isolate the (η^3-allyl)palladium intermediate **134**, which then led to **133** upon treatment with $CuCl_2$. The latter activates the allylpalladium species towards nucleophilic attack and reoxidizes Pd^0 into Pd^{II}. The reaction was shown to be facilitated by the presence of chloride ions in MeOH; density-functional calculations provided a clear mechanistic picture of the process and established that Cl^- assists the C−Si cleavage after the complexation of the double bond of the allylsilane by the Pd catalyst.



Scheme 36

Finally, the nucleophilicity of allylsilanes has been elegantly exploited by Tietze in allylsilane-terminated domino-Heck reactions.[80] This strategy has been used in several enantioselective syntheses of carbocycles and heterocycles, including natural products. An illustration of such a process is the transformation of enyne **135** into polycyclic indanes **136a**,**b** (Scheme 37).[81] The process probably involves a 5-*exo-dig* cyclization of a cationic palladium species to the alkyne to produce the intermediate **137**, which is stable enough to be trapped by the nucleophilic allylsilane and to lead to **138**. Depending on the nature of the phosphane — PPh_3 or BINAP — β-hydride or β-silyl elimination takes place to give indanes **136a** and **136b**, respectively, in excellent yield.

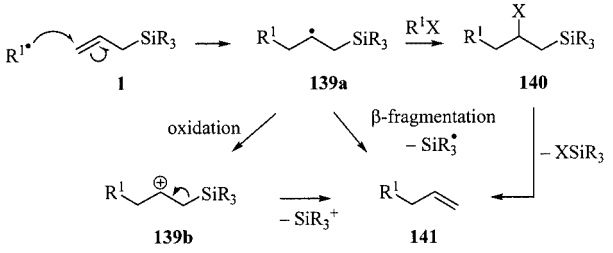


Scheme 37

5. Reactivity of Allylsilanes towards Free Radicals

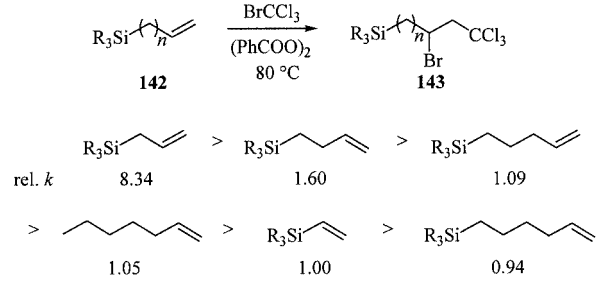
5.1. Introduction

Addition of radical species onto allylsilanes **1** has long been recognized as a valuable transformation,[1a] enabling both the formation of a carbon−carbon bond under mild conditions and leaving a stabilized radical β to the silicon group.[9] As illustrated in the general scheme (Scheme 38), this radical may then evolve in different directions depending on the reaction medium, the nature of the silicon group and the reagents. Addition or allylation products **140** and **141** are usually produced, similar to what is observed in ionic processes. β-Fragmentation is usually observed with an $(Me_3Si)_3Si$ group[82] and not with other alkyl- and aryl-substituted silanes. Radical **139a** may also be oxidized in the medium to afford the stabilized β-silylcarbocation **139b**, which can then lose the silyl group to provide the allylation product **141**.[58]



Scheme 38

Although hydrosilylation of allylsilanes using $HSiCl_3$ under radical conditions was reported as early as 1957 by Topchiev et al.,[83] a general survey of the reactivity of allylsilanes towards free-radical species was not produced until 1969, in a report by Sakurai et al.[84] They showed that addition of $BrCCl_3$ to vinylsilanes, allylsilanes and related olefins **142** in an atom-transfer process afforded excellent yields of addition products **143** (Scheme 39). This study revealed that a maximum of reactivity was attained with allylsilanes, which were found to be between five and nine times more reactive than vinylsilanes and their homologous silyl olefins. Such an enhancement of reactivity towards trichloromethyl radicals was at the time attributed to both $(p\text{-}d)_\pi$ homoconjugation[9d] and inductive effects. As the trichloromethyl radical is electrophilic in nature, the relative reactivity towards this species is likely to decrease with decreasing nucleophilic character of the olefin, and it is probable that

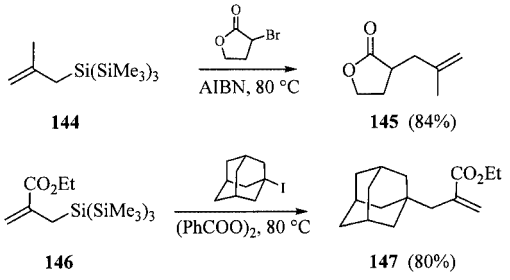


Scheme 39

the relatively low reactivity of vinylsilanes as compared to allylsilanes is also steric in origin.[85]

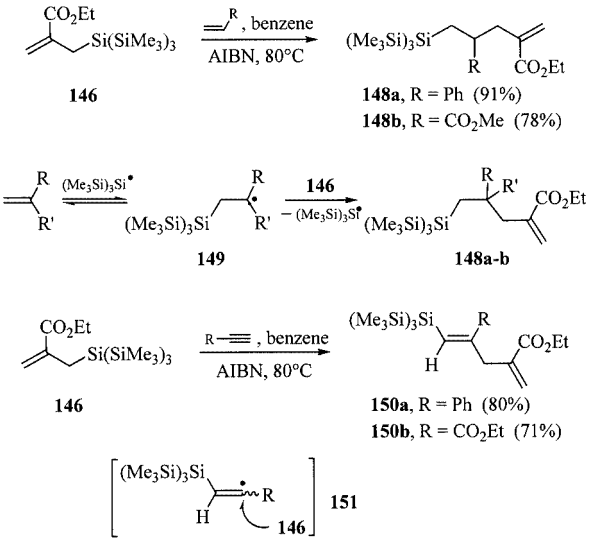
5.2. Radical Allylations

Allylsilanes have been extensively utilized as allylating agents. Although this process is very common under ionic conditions, it is only recently that a radical version has been devised, exploiting the remarkable reactivity of allyltris(trimethylsilyl)silanes such as **144** and **146** (Scheme 40).[82] Addition of radical species onto these allylsilanes produces a β-silyl carboradical (e.g. **139a**; Scheme 38), which can then β-fragment into the allylation product (e.g. **141**; Scheme 38) and the stabilized $(Me_3Si)_3Si$ radical. The latter can then abstract an halogen from the alkyl halide to regenerate the alkyl radical and complete the cycle of this chain reaction. Allylation with such organosilanes is sensitive to polar effects, hence a matched reactivity between the substrate and the allylsilane reagent is a pre-requisite to obtaining good yields of allylation products. For instance, electron-rich allyl, or methallylsilanes, such as **144**, react well with moderately or strongly electrophilic agents, while electron-poor (2-cyano- or 2-carboxyallyl)silanes, such as **146**, react with nucleophilic radicals (Scheme 40).



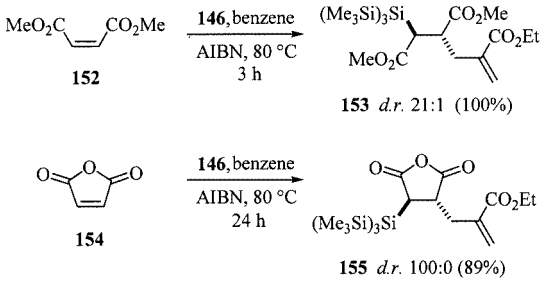
Scheme 40

Allylsilane **146** was also found to add to α,β-unsaturated esters, alkynes and aldehydes to provide allylsilylation products with generally good yields (Scheme 41).[86] With olefins, the reaction is believed to proceed through the addition of the tris(trimethylsilyl)silyl radical to the olefin to generate a β-silyl carboradical **149**, which is stable enough to add intermolecularly to **146** to provide addition products **148a**,**b** and regenerate the silyl radical. The reaction is restricted to electron-poor allylsilanes such as **146**, but performs equally well with electron-rich and electron-poor olefins. When applied to acetylenic compounds, the addition proceeds solely with terminal alkynes, but with high levels of regioselectivity, the silicon group adding on the terminal carbon atom and the allylation then occurring on a vinyl radical intermediate **151**, on the opposite side to the bulky silyl group.



Scheme 41

The process can also be extended to non-terminal but activated olefins such as **152** and **154** (Scheme 42), where allylsilylation interestingly gives rise to the desired products with excellent levels of diastereocontrol.



Scheme 42

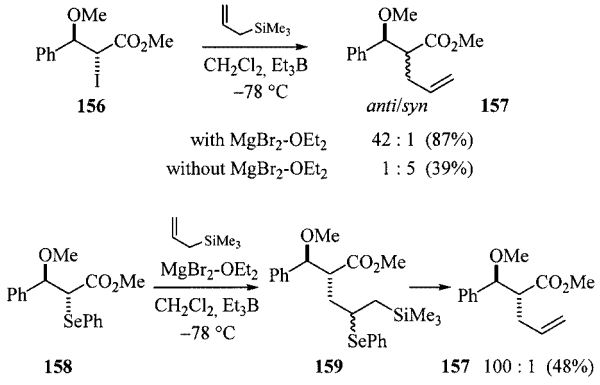
The formation of major diastereomers **153** and **155** in cyclic and acyclic systems, respectively, was rationalized invoking transition states **XV** and **XVI**, in which allylsilane **146** approaches *anti* relative to the silicon group (Figure 10).

Figure 10. Stereochemistry of radical allylation of olefins

5.3. Radical Additions

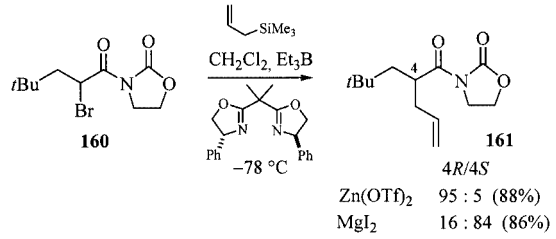
Alkylation of allylsilanes through an atom-transfer process, as reported earlier by Sakurai[84] (Scheme 39), has recently received a great deal of attention in asymmetric synthesis. In this process, the β-silyl carboradical **139a** (Scheme 38) does not fragment, but, instead, abstracts an X group from the alkylating agent RX (X = halogen, SePh). The resulting β-halosilane **140** is not stable and directly affords the corresponding olefin through β-elimination. Although the process is mechanistically distinct from the allylation with allyltris(trimethylsilyl)silane,[82,86] the reaction product is the same (i.e. **141**; Scheme 38). Radical allylation under chelation and non-chelation control has been studied extensively by Guindon et al. (Scheme 43).[87] Allylation of α-iodo ester **156** with allyltrimethylsilane in

the presence of $MgBr_2$ thus affords essentially the *anti* isomer of **157**, while the same reaction carried out in the absence of Lewis acid led to the *syn* isomer, albeit in lower yield. It is noteworthy that starting from α-selenyl ester **158** they were able to prove that an atom-transfer mechanism was operative by isolating the selenyl-transfer product **159**, which decomposed on silica to produce *anti*-**157** (Scheme 43). It is believed that the same pathway is valid for allylation of analogous α-bromo and α-iodo esters.



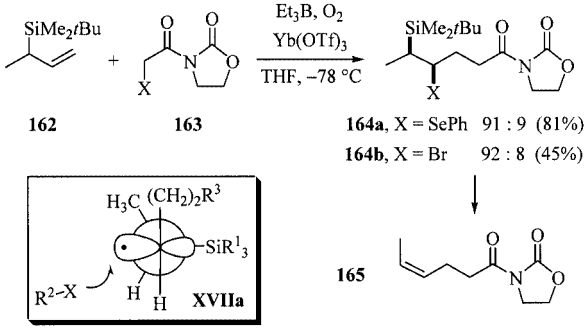
Scheme 43

An enantioselective version of this allyl-transfer reaction has recently been reported by Porter et al. using bis(oxazolines) as chiral inductors (Scheme 44).[88] α-Bromooxazolidinones **160** are good substrates in these processes catalyzed by various Lewis acids. Magnesium iodide and zinc triflate were shown to catalyze the process efficiently, affording the allylation products **161** in excellent yields and high enantioselectivities, but surprisingly with the opposite topicity in the presence of the same chiral inductor. The nature of the substituents on the silicon centre was also varied, revealing that trimethyl, trimethoxy and triethoxy groups performed equally well, while the triphenyl analogue led to poor results.



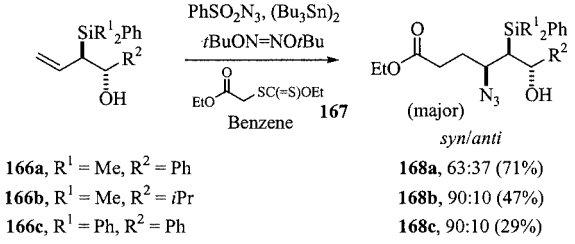
Scheme 44

Porter also extended this process to chiral allylsilanes **162**, demonstrating that an excellent level of 1,2-stereocontrol could be attained, with a diastereomeric ratio of up to 94:6 in favour of the *syn* isomer (Scheme 45).[89] A Felkin−Anh-type model **XVIIa** was proposed to account for this 1,2-stereocontrol. β-Elimination of the β-seleno- or -halosilane **164a**,**b** led stereospecifically to olefin **165** having a (*Z*) configuration. Assuming an *anti* stereochemistry for this elimination,[90] a *syn* configuration was hence proposed for **164a**,**b**. As far as we know, this is the first study on the 1,2-stereocontrol issued from radical functionalization of chiral allylsilanes.



Scheme 45

More recently, we and Renaud[91] described the first stereocontrolled carboazidation of chiral allylsilanes. Addition of xanthates **167** onto a series of allylsilanes **166a**−**c** possessing one or two stereogenic centres (in the α- and β-positions relative to the silicon atom) led to the generation of a β-silyl carboradical intermediate that was trapped by a sulfonyl azide (Scheme 46). This led to the formation of β-azidosilanes **168a**−**c** with a level of diasterecontrol ranging from 7:3 to 9:1. As mentioned above, fluoride-mediated elimination of the major isomers led exclusively to the (*Z*)-olefins. Based on a study on the stereochemistry of fluoride-mediated elimination of β-azidosilanes,[90b] we were able to demonstrate that, similarly to Porter's atom-transfer reaction,[89] the carboazidation led to the *syn* isomer as the major product.



Scheme 46

We rationalized our results by invoking a pyramidalization of the transition state into a quasi-staggered conformation **XVIIb** to avoid gauche interactions between large groups (here between SiR_3 and $CH_2CH_2CO_2Et$ groups; Figure 11). Such non-stabilized radicals are known to be pyramidalized already in the ground state,[92] and consequently the sulfonyl azide would approach *anti* relative to the bulky silicon group, on the side of the smallest group (H). In the diastereomeric transition-state conformation **XVIIc**, a larger steric interaction would exist between the sulfonyl azide and the medium-sized group R^2CHOH (R^3). This is corroborated by the higher stereocontrol observed when R^2 is *i*Pr as compared with Ph. Moreover, as a consequence of the electrophilic nature of the sulfonyl azide, a partial positive charge is likely to develop β to the silicon group. This partial positive charge would be stabilized by the quasi-coplanar electron-rich C−Si bond (silicon β-ef-

fect), thus adding to the intrinsic steric effect of the silicon group.

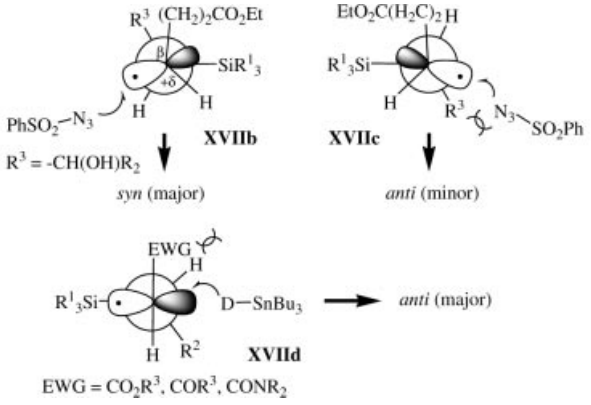
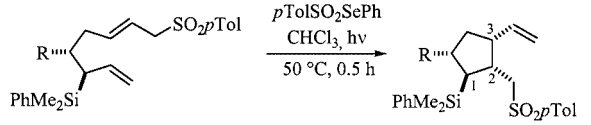


Figure 11. Stereochemistry of azidation and deuteration of β-silyl radicals

This transition-state model is to be compared with a model **XVIId**, proposed for radical deuterations and allylations of closely related β-silyl carboradicals "conjugated" with a carbonyl group (Figure 11).[93] Such radical enolates led mainly to the *anti* product with similar diastereocontrol; this *anti* stereoselectivity was rationalized by considering a transition-state model **XVIId** based on allylic strain. Clearly, allylic strain cannot be involved in the carboazidation process, and the Felkin−Anh-type model **XVIIb** is in better agreement with our experimental results.[94] A refinement of the models above, and firm conclusions, are expected to follow from further experiments and high level calculations.

As a continuation of our investigations into free-radical functionalization of allylsilanes, we have recently studied the sulfonyl radical addition-5-*exo-trig* cyclization-β-fragmentation cascade onto allylsilanes **169a**,**b** (Scheme 47).[95] Tri- and tetrasubstituted cyclopentanes **170a**,**b** were obtained in excellent yields with unexpectedly high levels of diastereocontrol. Several related cyclizations were also conducted on analogues bearing allylic methyl and hydroxy groups, to explore the generality of the method. It was eventually concluded that only a silicon group at the allylic stereogenic centre is able to induce such high levels of stereocontrol. Reaction rates with allylsilanes were also much higher than those with non-silylated analogues, which was attributed to the electrophilic nature of pTolSO$_2$ radical that reacts faster with electron-rich olefins such as allylsilanes.



Scheme 47

The stereoinduction was rationalized using the Beckwith−Houk model **XVIII** (Figure 12).[96] The major diastereomer is likely to be formed through a chair-like transition state in which the bulky silicon group occupies a pseudoequatorial position. It is noteworthy that in such a conformation the electron-rich C−Si bond is nearly aligned with the incipient bond and can therefore stabilize the developing positive charge at C-1, in the β-position. This is reminiscent of the β-silicon effect discussed above for ionic processes.[9,10] Using this approach, it was possible to efficiently control the relative configuration between C-1, C-2 and C-3 (1,2- and 1,5-stereocontrol), usually a difficult task to achieve. As far as we know, this is the first report on a successful control of the three contiguous stereogenic centres in such systems, using radical 5-*exo-trig* cyclizations. Recent investigations in our laboratory using other radical processes have also shown that such a high stereocontrol is a general trend with these substrates.

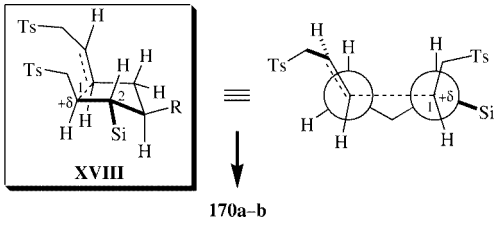
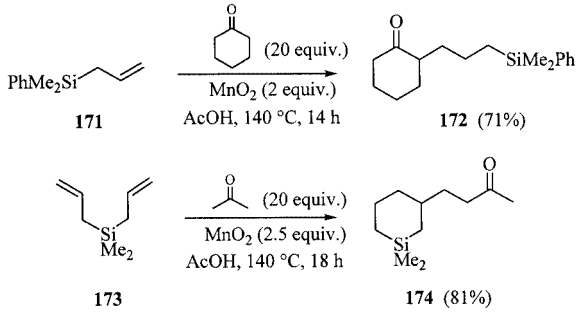


Figure 12. Stereochemistry of 5-*exo-trig* cyclization of allylsilanes **169a**,**b**

Ketones can also be added to allylsilanes through a radical pathway, but under oxidative conditions.[97] When using MnO_2 as oxidant, a purely radical process operated with hydrogen-atom transfer. The reaction of the ketone with MnO_2 (used in large excess) is believed to generate a radical centre α to the carbonyl group, which can then add at the terminal sp^2-carbon atom of allylsilane **171** to form a β-silyl carboradical intermediate (Scheme 48). Hydrogen-atom transfer from a second molecule of ketone to this β-silyl carboradical then produces the desired addition product **172** and regenerates the α-carbonyl radical, which can propagate the radical chain. When applied to diallylsilane **173**, the process led selectively to the ketone **174** in good yield. Formation of this silacycle probably results from the addition of acetone to one allyl group, thus generating a β-silyl carboradical which then adds in a 6-*endo-trig* fashion to the second allylic group. This indicates that an intermolecular addition of two ketones cannot compete with the intramolecular process. Several general trends also emerge from this investigation. In good agreement with earlier reports,[98] it was observed that allylsilanes always gave higher

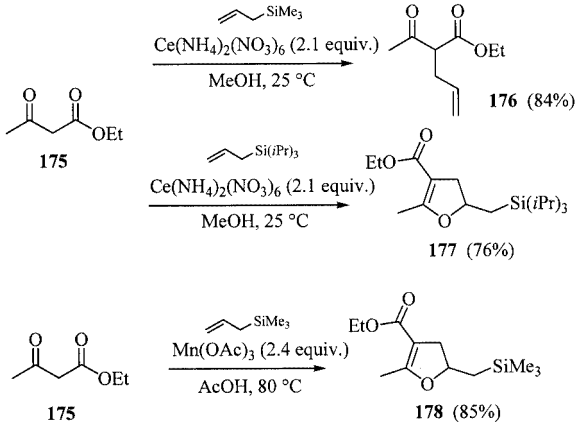


Scheme 48

yields than simple olefins, indicating that the silicon centre has a promoting effect. The nature of the substituents on the silicon atom also plays a role: electron-donating groups have a promoting effect, but steric hindrance retards the addition process.[97b]

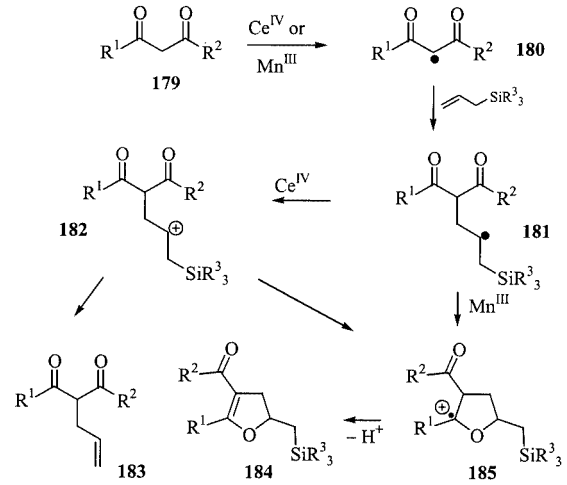
5.4. Radical Allylation versus Addition Processes

This work can be extended to the addition of 1,3-dioxo compounds, such as β-oxo esters and malonates.[58b] Oxidants such as $[Ce(NH_4)_2(NO_3)_6]$ (CAN) and $Mn(OAc)_3$ have been used in this context and were found to provide distinct products (Scheme 49). Oxidation of β-oxo ester **175** with 2 equiv. of CAN in the presence of allyltrimethylsilane produced the allylation product **176**, while the same reaction in the presence of allyltriisopropylsilane gave only the dihydrofuran **177**. Interestingly, oxidation of **175** by manganese(III) acetate in the presence of allyltrimethylsilane produced exclusively the dihydrofuran **178**, indicating the influence of both the nature of the oxidant and that of the silicon group.



Scheme 49

This was rationalized as depicted in Scheme 50. In the presence of the oxidant, a radical **180** is formed from the 1,3-dioxo compound, which then adds onto the allylsilane fragment to generate a β-silyl carboradical **181**. CAN is a stronger oxidant than Mn^{III} and can therefore further oxidize **181** to a stabilized β-silyl carbocation **182** (e.g. **139b**; Scheme 38). This then evolves in one of two directions, depending on the nature of the silicon group. With a small SiR_3 group, β-fragmentation occurs to produce the allylation product **183**, while a bulky TIPS group that is more difficult to eliminate allows one oxygen atom of the 1,3-dioxo moiety to trap the positive charge to produce the corresponding dihydrofuran **184**. Conversely, Mn^{III} cannot oxidize **181**, and therefore an intramolecular reaction occurs to give an α-oxy radical intermediate which is then easier to oxidize into oxonium compound **185**. This oxonium compound then produces the dihydrofuran **184** by proton elimination. A related investigation has recently appeared which further extends this methodology.[58a] $[Ce^{IV}(nBu_4N)_2(NO_3)_6]$ (CTAN), which is more soluble in organic solvents than CAN, has been used in this context and was shown to provide different chemoselectivities in CH_3CN and CH_2Cl_2. In the former, allylation products **183** are produced, while in the latter dihydrofurans are formed, both starting from allyltrimethylsilane. This intriguing result was rationalized by recognizing the stabilization of carbocation **182** in CH_3CN, which then produced allylation product **183**. In less polar CH_2Cl_2 (no stabilization), cyclization would be favoured through the proximity of a carbonyl group to form **185**, then **184**.

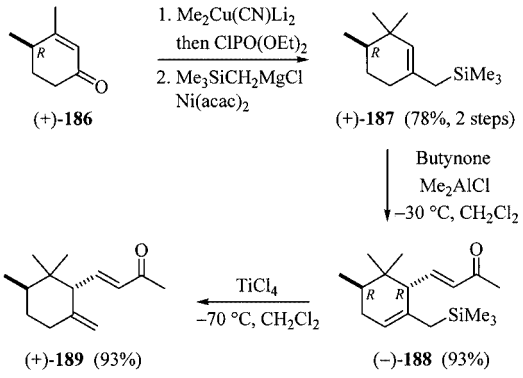


Scheme 50

6. Cycloadditions

6.1. Ene Reactions

As mentioned above, ynones can react with allylsilane to furnish cyclobutenes **79d** (Scheme 21). Interestingly, by choosing the appropriate Lewis acid, the course of the reaction can be changed to give exclusively an H-ene reaction.[62a] According to this strategy, Monti et al.[99] have reported the first enantioselective synthesis of (+)-(2*R*,6*R*)-*trans*-γ-irone (**189**) starting from ketone (+)-**186**. This synthesis is based on the Lewis-acid-promoted H-ene reaction of cyclohexenic allylsilane (+)-**187** with butynone to give the corresponding ene adduct (−)-**188** (Scheme 51).

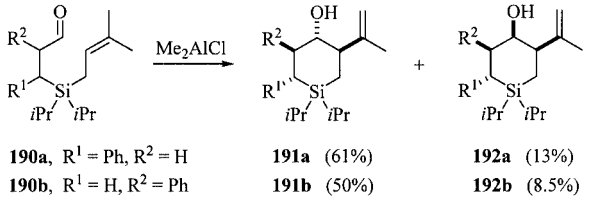


Scheme 51

The total synthesis of (+)-**189** has been achieved by a straightforward four-step procedure, giving an overall yield of 68% starting from (+)-**186**, and a similar H-ene reaction

with an ynone has been used for the elaboration of the C-1−C-16 fragment of brystatins.[100]

The H-ene reaction can also be performed between an allylsilane and a carbonyl derivative.[101−103] In some cases, the silicon atom can be used as a link between the two fragments to provide ene cyclization (Scheme 52).[101] Treatment of allylsilanes **190a** and **190b** with a Lewis acid such as Me_2AlCl initiates the ene reaction to produce 1,2-*trans*- and 1,2-*cis* adducts **191a**,**b** and **192a**,**b**, respectively.



Scheme 52

The observed relative stereochemistry was rationalized on the basis of a *trans*-decalin-like transition state **XIXa** to give 1,2-*trans* adducts **191a**,**b** or a *cis*-decalin-like arrangement **XIXb** to afford 1,2-*cis* isomers **192a**,**b** (Figure 13); in both cases the phenyl substituents adopt pseudoequatorial positions during cyclization.

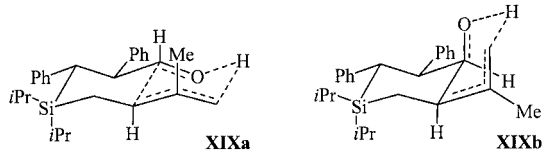
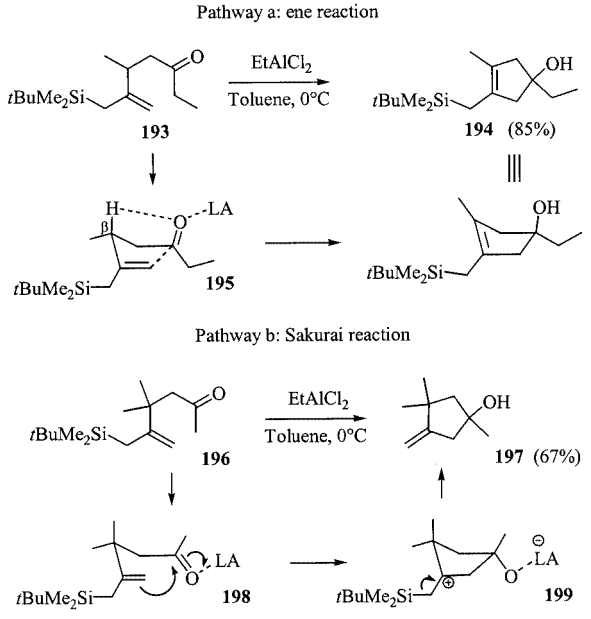


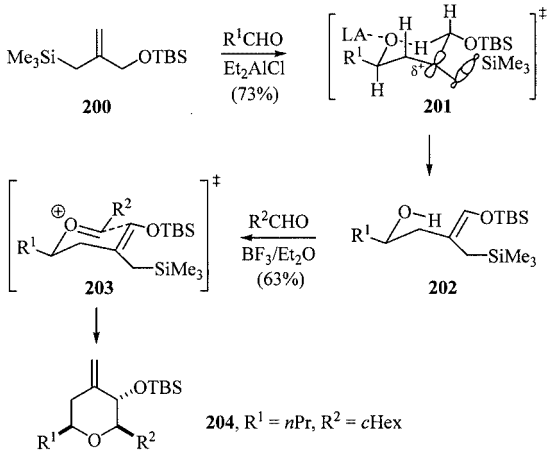
Figure 13. Stereochemistry of intramolecular H-ene reactions

Another interesting intramolecular ene reaction has been reported by Pulido et al.,[102] who found that oxo-allylsilanes **193** and **196** bearing a bulky *tert*-butyldiphenylsilyl group undergo highly selective intramolecular cyclizations when treated with Lewis acid, to afford unsaturated cyclopentanes adducts **194** and **197** (Scheme 53). Two reactivity patterns were observed: an ene reaction without loss of the silyl group, which furnished cyclopentene **194** (pathway a), or allylsilane-terminated cyclization involving elimination of silicon (Sakurai reaction), providing *exo*-methylenecyclopentane **197** (pathway b). The pattern followed depends on the ability of the hydrogen atom β to the carbonyl group to be removed during the ene process. When the structure of the precursor does not allow a low-energy transition state for the ene reaction, then an intramolecular allylsilane-terminated cyclization is observed. It must be added that the *tert*-butyldiphenylsilyl group has a lower nucleofugacity than $PhMe_2Si$, which always provides the Sakurai product under similar conditions.



Scheme 53

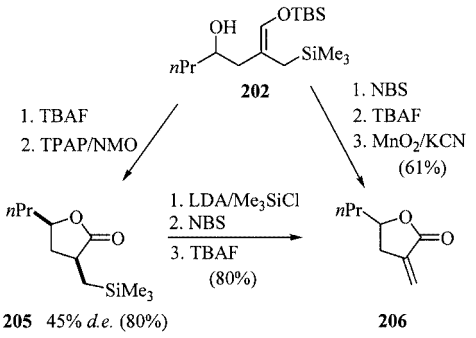
In contrast with these results, Markó et al. have developed a tandem ene reaction/intramolecular Sakurai cyclization (IMSC) using allylsilane **200** in order to prepare polysubstituted tetrahydropyrans **204** (Scheme 54).[103] Upon activation of the first aldehyde by a suitable Lewis acid, an initial ene reaction takes place with allylsilane **200** to produce the ene adduct **202**. Transition state **201**, in which R^1 and the silyloxy groups occupy pseudoequatorial positions, experiences no 1,3-diaxial interactions and benefits from the stabilizing β-silicon effect. Subsequent Lewis-acid-catalysed condensation of adduct **202** with the second aldehyde generates the oxocarbonium cation **203**, which undergoes an intramolecular Sakurai reaction to afford diastereomerically pure *exo*-methylenetetrahydropyrans **204**.



Scheme 54

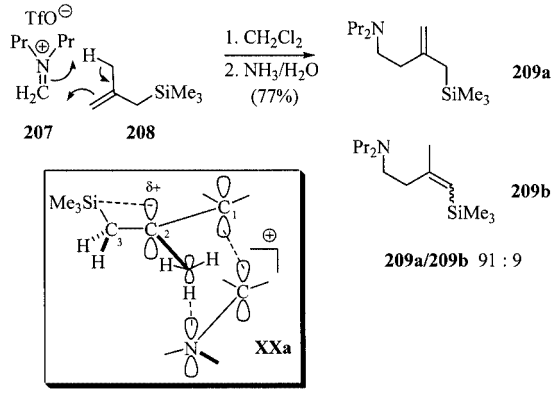
Ene adduct **202** (R^1 = *n*Pr) also proved to be a useful precursor for lactone synthesis (Scheme 55).[103d]—[103g] Recognizing that adduct **202** is equivalent to an aldehyde homoenolate addition product, two simple routes towards γ-butyrolactones **205** and *exo*-methylene-γ-butyrolactones **206** were established.

In ordinary ene reactions such as those previously described, the electron-rich species (allylsilane) play the role of the ene fragment while the electron-deficient partner acts as the enophile. It appears that the same process occurs in the reaction between allylsilane **208** and iminium salt **207** to produce the unsaturated tertiary amines **209a** and **209b** (Scheme 56).[104] In a concerted but non-synchronous per-



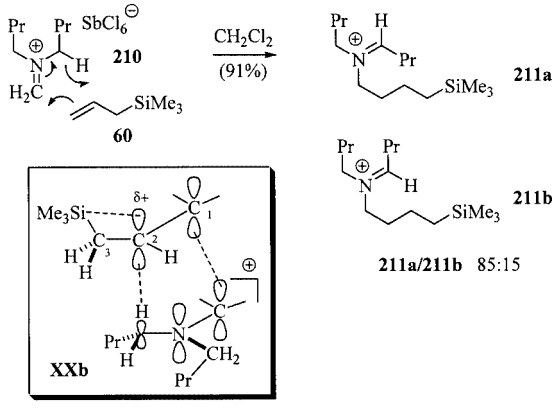
Scheme 55

icyclic reaction, transition state **XXa** is favoured because the partial positive charge developing at C-2 on the allylsilane moiety can be stabilized through hyperconjugation with the neighbouring C−Si bond (β-silyl effect).[10]



Scheme 56

Unlike allylsilane **208**, allyltrimethylsilane (**60**) reacts with the iminium salt **210** to give iminium compounds **211a** and **211b** by ene reactions with inverse electron demand. In this case, **60** behaves as the enophile and **210** as the ene partner (Scheme 57). In the sterically least hindered transition state **XXb**, the (trimethylsilyl)methyl substituent is directed away from the iminium salt. In this way, the nitrogen atom is not in the proximity of the allylic hydrogen atom required for the regular ene reaction. Instead, an H transfer

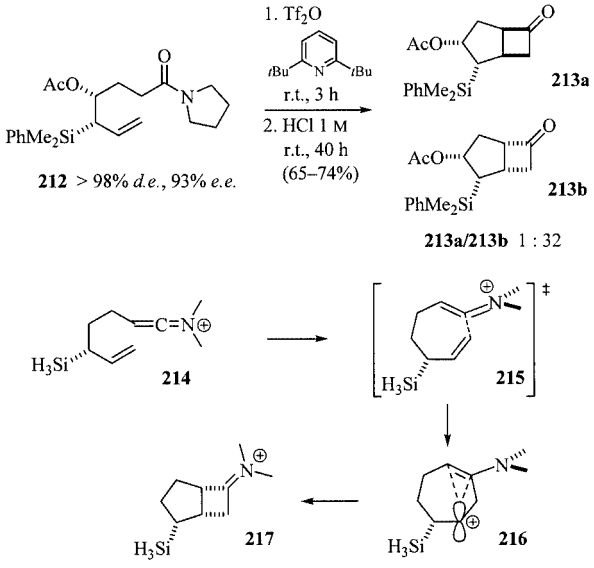


Scheme 57

from the iminium salt to the carbon atom C-2 of the allylsilane fragment occurs. Other transition states, which might give rise to the regular ene reaction, are disfavoured as they suffer from destabilizing steric interactions and the lack of hyperconjugative β-silyl stabilization.

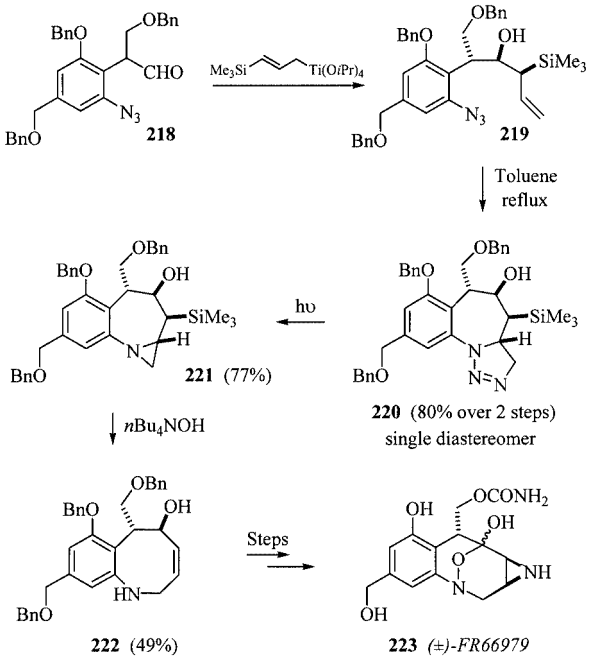
6.2. Cycloaddition Reactions

Cycloaddition reactions of allylsilanes have been used to construct a range of four-,[105,106] five-[107,108] and six-membered rings.[109] In these processes the silyl substituent activates the double bond towards electrophilic attack and, in some cases, can also control the facial selectivity, as shown by the synthesis of bicyclic compounds **213a**,**b** (Scheme 58).[105] It was observed that intramolecular [2+2]-cycloaddition of the keteniminium ion, generated from amide **212**, gave a 1:32 mixture of bicyclo[3.2.0]heptanones **213a** and **213b**. This high facial selectivity is in good agreement with the calculated transition state **215**, which has a nearly perfectly staggered arrangement between the alkene and the keteniminium group and the C−Si bond aligned with the alkene π orbitals (close to conformation **IVb**; Figure 4). This alignment provides a stabilization of the transition state by a β-effect which explains the formation of the iminium ion **217**.



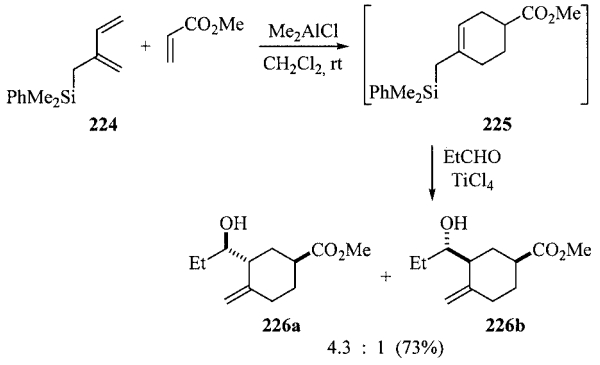
Scheme 58

During the course of their total synthesis of (±)-FR66979 (**223**), Ciufolini et al. have used a diastereoselective intramolecular cycloaddition involving the azidoaryl group and the double bond of the allylsilane moiety of intermediate **219** (Scheme 59).[107] Compound **219** was obtained as a single diastereomer by coupling of an allyltitanate intermediate with aldehyde **218** (e.g. Scheme 1). The intramolecular 1,3-dipolar cycloaddition of **219** then afforded a triazoline **220**, as a single stereoisomer, which then underwent dediazonation upon irradiation to give aziridine **221**. Cycloadduct **221** was then converted through homo-Brook fragmentation into the eight-membered ring heterocycle **222**, a required intermediate en route to (±)-FR66979 (**223**).[107b]



Scheme 59

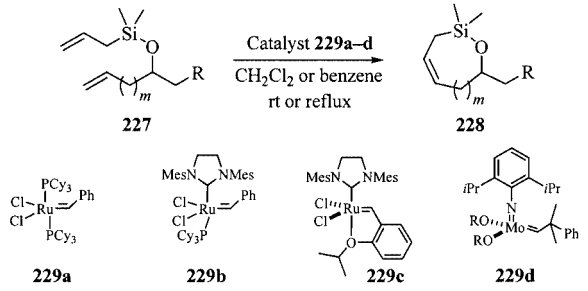
It is also worth noting that allylsilanes are useful partners in Diels–Alder reactions.[109] Organ et al. have developed a tandem transformation that combines pericyclic and electrophilic substitution reactions (Scheme 60). When Lewis-acid-catalysed cycloaddition between diene **224** (bearing the allylsilane moiety) and methyl acrylate was complete, aldehyde and $TiCl_4$ were added to the solution. In this way, the allylsilane **225** formed during the cycloaddition underwent an electrophilic substitution reaction (S_E') with an aldehyde (propanal) to provide *exo*-methylenecyclohexanes **226a** and **226b** with a reasonable diastereocontrol. In each case, the tandem reaction provided a higher yield of the final product than the non-tandem sequence.



Scheme 60

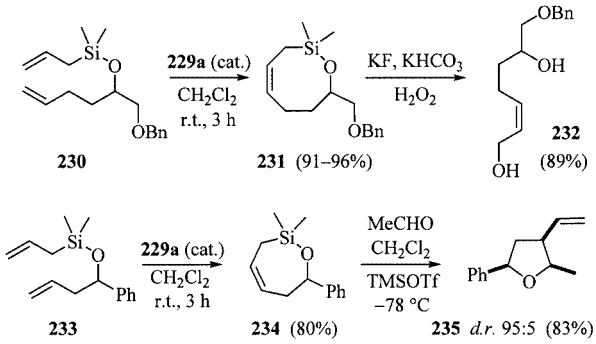
7. Allylsilanes in Ring-Closing and Cross-Metathesis Processes

Allylsilanes have been used as olefinic partners in ring-closing metathesis (RCM) and cross-metathesis (CM) catalyzed by ruthenium and molybdenum complexes **229a–d** (Scheme 61). This gives access to useful allylsilanes that may be difficult to prepare using other methods. The electron-rich C–Si bond probably enhances the nucleophilicity of the olefin through hyperconjugation, but has no effect on the stability of the alkylidene intermediate.[110] In the pioneering work on RCM reactions of allylsilanes, the silicon atom was mainly used to connect dienes through a siloxane (Si–O) linkage (e.g. **227**; Scheme 61).[111] These siloxanes are easily available through reaction of an alcohol with the corresponding chlorosilane. Grubbs' first-generation catalyst **229a** was thus shown to initiate the RCM process, leading to medium-sized rings **228** in excellent yields, under mild conditions (room temperature).[112] Six- to ten-membered rings were thus at hand for further elaboration.



Scheme 61

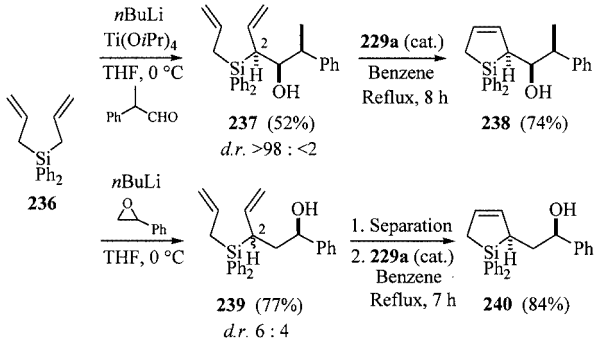
The resulting cyclic siloxanes **231** and **234** were used in various transformations (Scheme 62), including C–Si bond oxidation according to Tamao's procedure[15] to provide the corresponding diols **232** in good yield.[112a] Similarly, Sakurai reaction between siloxanes of type **234** and aldehydes were shown to lead to tri- and tetrasubstituted tetrahydrofurans with a high level of stereocontrol.[112b,112c] A Lewis acid such as TMSOTf was found to be the best choice (better than BF_3),[112b] providing a unique stereoisomer, while $BF_3{\cdot}OEt_2$ led to mixtures of diastereomers.[112c]



Scheme 62

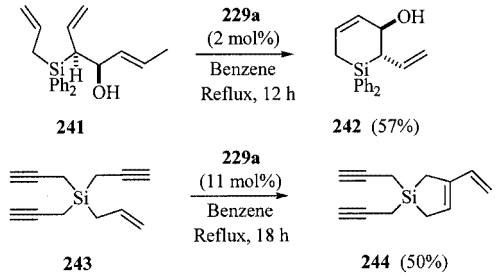
Silicon may also connect dienes through a more robust C–Si linkage. This strategy has been investigated in our laboratory and was shown to offer a rapid and stereocontrolled access to C-2-functionalized silacyclopent-3-enes **238** and **240** from commercially available diene **236** (Scheme 63).[19] Combining the *anti* stereoselective coupling between (γ-silylallyl)titanium intermediates and aldehydes,[11] followed by RCM of the resulting diene **237**, led to **238** in two steps, with overall yields ranging from 40 to

78% depending on the C-2 chain substitution pattern. Similarly, coupling between (γ-silylallyl)lithium and epoxides gave alcohol **239** as a mixture of two diastereomers which were separated by chromatography. RCM independently on both alcohols led to silacyclopent-3-enes such as **240** in good yields. It is interesting to note that ring-closure of the *syn* diastereomer was more sluggish than with the *anti* diastereomer, indicating that the free hydroxy group probably coordinates with the (carbene)ruthenium intermediate. Electrophilic functionalization of the resulting silacycles **238** and **240** through dihydroxylation and epoxidation then led to highly oxygenated synthons with good to excellent levels of stereocontrol (Scheme 4).



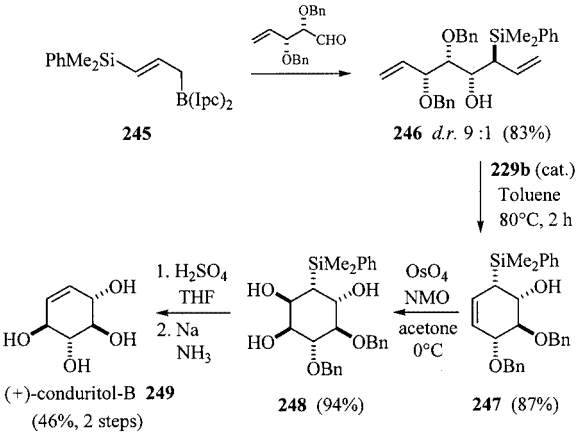
Scheme 63

The relative ease of silacycle formation was found to be in the order: six- > seven- > five-membered rings. Therefore, RCM of diene **241** led to silacyclohex-3-ene **242** and not to the corresponding five-membered ring (Scheme 64).[19b,19c] Undheim[113] has shown that allylsilanes also react as the olefinic partner in enyne metathesis as illustrated by RCM of the tris(propargylic) silane **243**, which afforded, under rather drastic conditions, the diene **244** in moderate yield. Finally, the same authors have reported a few examples of silaspirenes obtained by RCM of the corresponding diallylsilacycles.[113]



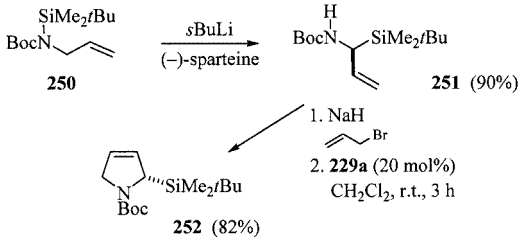
Scheme 64

In the examples reported above, silicon was part of the ring formed during RCM. Recently, several reports have emphasized RCM of dienes in which one of the olefins is an allylsilane.[12,19,113,114] Roush has devised an elegant route to cyclopentenes and cyclohexenes possessing an allylsilane moiety using RCM of suitable dienes.[12b,12c] The diene precursors (e.g. **246**; Scheme 65) are easily available, in an enantiomeric fashion and with high stereocontrol, through coupling between (γ-silylallyl)boronates **245** and suitable aldehydes. Closely related precursors may also be prepared using TADDOL/(γ-silylallyl)titanates.[12a,105] RCM of dienes **246** using Grubbs' second-generation catalyst **229b** (Scheme 61) afforded tetrasubstituted cyclohexenes **247**, which were then elaborated further en route to conduritols and inositols.[12c] As an example, dihydroxylation of allylsilane **247** led to the diol **248** as a single diastereomer, and acid-mediated Peterson elimination and removal of the benzyl protective groups led to optically pure (+)-conduritol-B (**249**). Similarly, base-mediated Peterson elimination on **248** led, after deprotection, to (+)-conduritol-F. Oxidation of the C−Si bond under Fleming conditions[15] afforded, in turn, D-(+)-*chiro*-inositol, thus showing the versatility of this approach as a unique route towards cyclitol sugar mimics.



Scheme 65

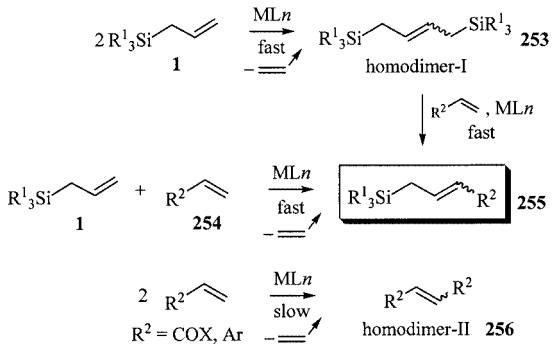
Dihydropyrroles are also available using a similar approach. Sieburth recently reported an enantioselective access to α-silyl-dihydropyrroles through a three-step sequence starting from the simple *N*-silylated allylamine **250** (Scheme 66).[115] Reverse aza-Brook rearrangement of **250** led to allylsilane **251**, which was then allylated to give the diene precursor. RCM of the diene using Grubbs' catalyst **229a** finally led to the sensitive dihydropyrrole **252** in excellent overall yield.



Scheme 66

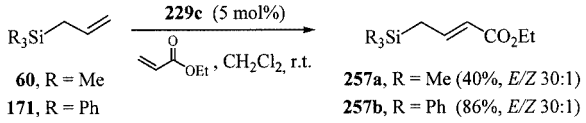
Allylsilanes have also been used in cross-metathesis (CM), and a general empirical model has recently been proposed by Grubbs to predict the outcome of the cross-metathesis process (product selectivity and stereoselectivity),

depending on the nature of the olefins.[116] This classification is based on the reactivity of the olefins with respect to their ability to homodimerize, and then on the susceptibility of their homodimers to enter into a secondary metathesis process. Allylsilanes **1** have been classified as type-I olefins, whatever the nature of the catalyst (i.e. Schrock and Grubbs' first- and second-generation catalysts **229a**−**d**). It has been demonstrated that allyltrimethylsilane is slightly more reactive than simple alkyl olefins but the steric hindrance of the SiR_3 group decreases the reactivity of the alkylidene.[110,117] Allylsilanes, however, lead to rapid homodimerization, their homodimers **253** being then rapidly consumed in secondary cross-metathesis processes (Scheme 67). A good reactivity profile for cross-metathesis of olefins is found when both olefinic partners belong to two different classes: for example, electron-rich allylsilanes **1** were found to react well with electron-deficient acrylates **254** (R^2 = CO_2R) using a 1:1 stoichiometry.[118] Acrylates and acrylamides belong to type-II olefins and are known to homodimerize to a small extent, their homodimers being moderately consumable. Such a matched reactivity pattern is illustrated in Scheme 67.



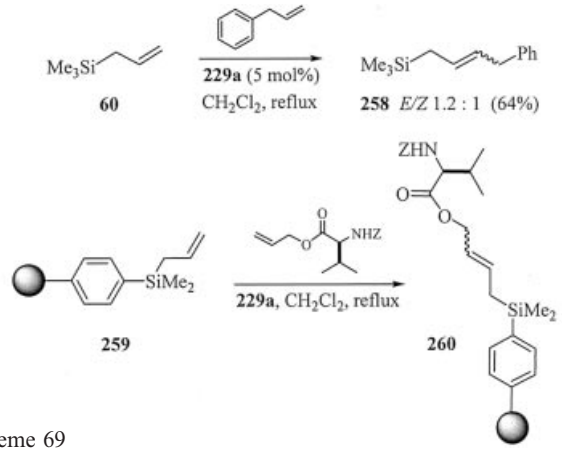
Scheme 67

In line with the predictions of this model, excellent results were obtained through the cross-metathesis reaction between allylsilanes **60** or **171** and ethyl acrylate in the presence of Hoveyda's catalyst **229c** (Scheme 68).[118a] Interestingly, the reaction also works well with unsaturated aldehydes and carboxylic acids, but not with amides. This was rationalized by considering the chelation of the (alkylidene-)metal by the carbonyl group during the catalytic process; the electron-rich carbonyl group in amides gives rise to a stronger chelation which is likely to inhibit the metathesis process.



Scheme 68

When olefins of similar reactivities are used, homodimerization occurs at a similar rate and the cross-product is in equilibrium with homodimerization products. Grubbs' model, however, predicts that cross-metathesis of two type-I olefins may proceed, providing that one olefin is in excess.[106b,116,119] This is illustrated by the cross-metathesis between allylsilane **60** and allylbenzene, in a 2:1 ratio, which provides the desired olefin **258** in good yield, albeit with low selectivity (Scheme 69).[119a] Similar results were obtained when **60** was coupled with alkenyl epoxides.[119b] In both cases, the reaction occurred in CH_2Cl_2 under reflux, although the use of Schrock's catalyst **229d** (Scheme 61) allows a similar cross-metathesis to occur at room temperature with generally shorter reaction times.[110] A striking example of cross-metathesis between a supported allylsilane **259** and a series of densely functionalized olefins has been reported by Blechert.[120a] Protodesilylation of the resulting supported olefin **260** then released the corresponding carboxylic acid. This methodology was then extended to enyne cross-metathesis, to provide the corresponding supported dienylsilanes.[120b] Finally, ring-opening cross-metathesis (ROCM or ROM-CM) using allylsilanes may also be mentioned, although it has remained so far relatively unexplored. Ring-opening of a strained azanorbornene, followed by cross-metathesis with allyltrimethylsilane (**60**), has, however, been reported to give access to γ-lactams in good yields.[121]



Scheme 69

8. Conclusion

Allylsilanes encompass the reactivity of both olefins and organometallic complexes and have thus enjoyed a widespread use in organic chemistry. Elaboration of simple allylsilanes, using electrophilic, radical, and organometallic processes has recently led to the straightforward construction of complex target molecules of biological interest.[1c,12c,18,25,66c,69c,107b] Domino reactions involving allylsilanes have been reported recently,[80,81] providing a good illustration of the many facets of the reactivity of allylsilanes. It is therefore expected that the diversity of transformations allowed with such simple substrates will be useful in the context of cascade and multi-component reactions. However, although complex chiral allylsilanes are now available in a few steps starting from readily available precursors,[12,18] efficient access to optically pure functionalized allylsilanes is still a challenging task. Efforts in this direction will be pursued in the future. As an indication, tuning

of the reactivity of allylsilanes by changing the nature of the substituents on the silicon centre[60,69c] has proved to be a valuable strategy that can certainly be exploited further.

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