



Contemporary organosilicon chemistry

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Contemporary organosilicon chemistry

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Editorial

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Abstract

Editorial for the Thematic Series on Contemporary Organosilicon Chemistry.

The field of organosilicon chemistry has a rich and varied history, and has long since made the progression from chemical esoterica to its position as a mainstay of modern synthetic chemistry. In his 1980 Tilden lectures [1], Professor Ian Fleming of Cambridge University, himself one of the major practitioners of the discipline, identified the year 1968 as a watershed in the popularisation of organosilicon chemistry. Notwithstanding the earlier, pioneering work of chemists such as Eaborn, 1968 was notable for many innovations we now take for granted, including the development of silyl enol ether chemistry by Stork and Hudrlik, and the eponymous olefination reaction by Peterson. These landmark papers triggered a massive growth in interest in the area which continues to this day.

Nearly 40 years on from those landmark publications, one could be forgiven for assuming that organosilicon chemistry has reached such a state of maturity that there remain few areas ripe for new development. A brief survey of the modern literature quickly dispels this notion. Far from atrophying, organosilicon chemistry continues to be an area of expansion, with an average of over 550 papers being published per year in the decade to date – an increase of over 30% by comparison with

the 1990s, and equivalent to the number appearing in the much longer established field of organoboron chemistry [2]. This expansion in activity reflects not only the sustained popularity of traditional silicon-based reactions and reagents, but also newer departures such as the effective application of organosilicon compounds in transition metal-catalysed cross-coupling reactions, and the use of silanes as stoichiometric reductants in a range of chemo-, stereo- and enantioselective catalytic reductions.

It is therefore a pleasure to serve as Guest Editor for this first "Thematic Series" in the Beilstein Journal of Organic Chemistry, on "Contemporary Organosilicon Chemistry". We have contributions from some of the leading practitioners in the area, covering a wide range of topics including the stereoselective construction of oxygen and nitrogen-containing heterocycles, the use of tethered silicon reagents to deliver acyclic stereocontrol, chiral-at-silicon reagents for asymmetric synthesis, and a new method for the electrochemical generation of silyl cations. Additionally, the unique nature of internet-based publishing means that the Series can grow as additional contributions are received: future papers in areas including allylation chemistry, stereoselective fluorination, cyclopropane chemistry and the

development of silicon-containing drug candidates should be available shortly. Be sure to check back to keep abreast of the latest developments as the Series grows.

Steve Marsden

Guest Editor

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2. Search on ISI Web of Science for articles related to organic chemistry with search terms "silicon or silyl or silane", versus "boron or borane or boronyl or boronic or Suzuki" records 3,871 hits for the former and 3,884 for the latter in the period 2000–2006.

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Reaction of benzoxasilocines with aromatic aldehydes: Synthesis of homopterocarpanes

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Abstract

Condensation of 2*H*-benzo[*g*][1,2]oxasilocines with aromatic aldehydes in the presence of boron trifluoride affords mixtures of *cis/trans* 2-phenyl-3-vinylchromans with moderate yields. These can be transformed into homopterocarpanes, a synthetic group of substances homologous to the natural isoflavonoid pterocarpanes.

Background

The Sakurai-Hosomi is a useful variant of allylation reactions, [1] which has been used for the formation of carbo- and heterocycles. [2,3] We have applied it to the stereoselective synthesis of dihydrobenzofurans by means of the condensation of benzoxasilopines with aromatic aldehydes in the presence of Lewis acids. [4,5] Using this methodology and through convergent synthetic routes, we have prepared pterocarpanes [6] and neolignans. [7] These good results have encouraged us to undertake the extension of the method to the use of benzo[*g*][1,2]oxasilocines for the preparation of chromans. This heterocyclic system constitutes the core skeleton of several biologically active natural products [8-11] and it is also present in the basic structure of the homopterocarpanes. [12] These are a group of non natural substances whose total synthesis [13] has been stim-

ulated by their interesting biological activities, like antitumor [14] or potential anti-HIV. [15] A theoretical study of their structure has also been published. [16] Here we describe a concise and convergent approach to this skeleton (**1**) based on a Sakurai condensation between a benzoxasilocine (**2**) and a protected *ortho*-hydroxybenzaldehyde (Scheme 1).

Results and discussion

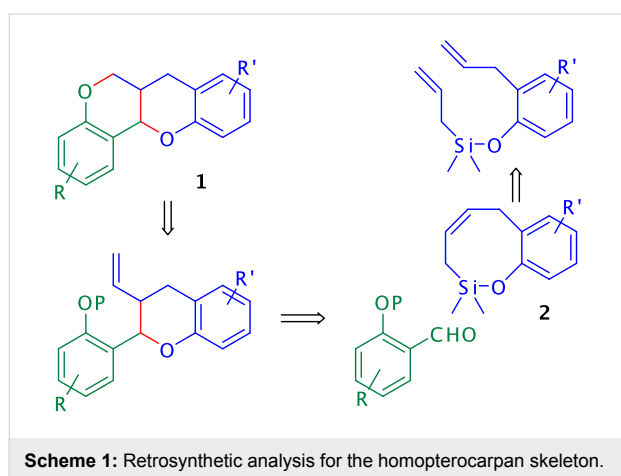
Starting materials

The starting material required for this synthesis is the novel heterocycle 3,6-dihydro-2,2-dimethyl-2*H*-benzo[*g*][1,2]oxasilocine (**5**), which can be prepared through ring closing metathesis (RCM), as has been previously reported for the non-benzofused system. [17-19] Thus, silylation of 2-allylphenol

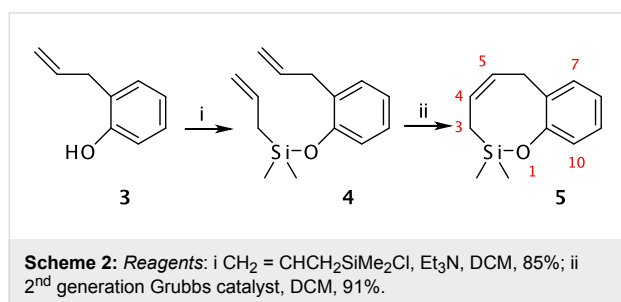
Table 1: Condensation of substituted benzaldehydes with **5**.

benzaldehyde substituent	product	diastereomeric ratio (<i>cis/trans</i>) ^a	yield (DCM) ^b	yield (CHCl ₃) ^c
H	7a	1 : 3	49	56
2-OMe	7b	1 : 1	51	58
3-OMe	7c	1 : 3	30	36
4-OMe	7d	1 : 5	48	60
2-OPiv	7e	1 : 3	48	62
3-OPiv	7f	1 : 5	42	44
4-OPiv	7g	1 : 3	47	58

^a: As deduced by analysis of ¹H NMR spectra or after CC separation ^b: reflux; ^c: 20°C.



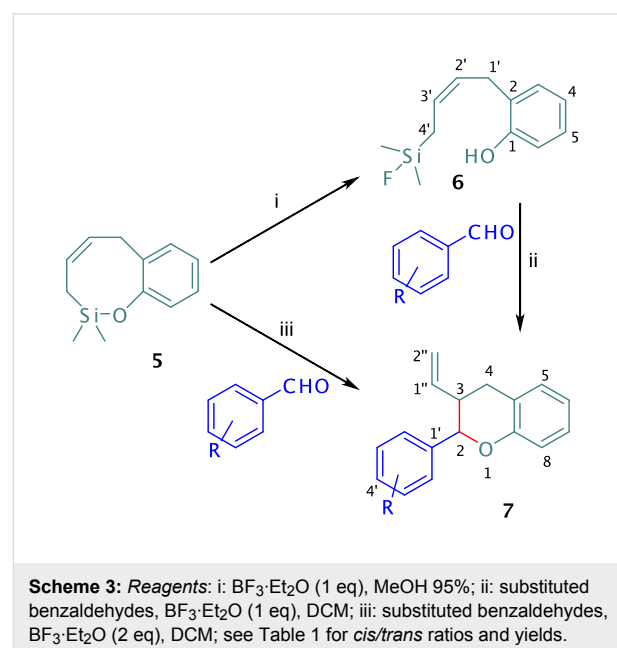
(3) (or conveniently functionalized derivatives) with allylchlorodimethylsilane followed by RCM with 2nd generation Grubbs catalyst [20] leads to the cyclic siloxane with high yields (Scheme 2). The good results in the cyclization step make this approach an excellent way of synthesising of this heterocycle.



Reaction of benzoxasilocines with aromatic aldehydes in the presence of BF₃·Et₂O

We had previously observed [4] that the treatment of the seven membered cyclic allylsiloxane 2,3-dihydro-2,2-dimethylbenzo[*j*][1,2]oxasilolepine with boron trifluoride yielded a ring-opened fluorinated derivative. This derivative was able

to perform the condensation with aromatic aldehydes to generate the dihydrobenzofuran final products in the presence of a second equivalent of BF₃·Et₂O. In a similar way, when **5** is treated with BF₃·Et₂O in MeOH, the fluorinated species **6** is formed quantitatively (Scheme 3). The ¹H NMR is very similar to that of the starting material, but for the methyl groups on silicon, which appear now as doublets due to their coupling with the ¹⁹F (³J_{H-F} = 7.3 Hz). This coupling is also observed for the methylene on silicon H4', which exhibits now an additional splitting (³J_{H-F} = 6.5 Hz) (for details see Supporting Information File 1). ¹³C NMR also reveals the presence of the fluorine on the silicon, because the signal due to the methyl groups appears as a doublet (²J_{C-F} = 14.8 Hz) as well as the signal due to C4' (²J_{C-F} = 13.5 Hz). ¹⁹F NMR shows only one signal at -160.73 ppm (hept t, ³J_{F-H} = 7.3 Hz, ³J_{F-H} = 6.5 Hz) with satellite bands due to the ¹⁹F-²⁹Si coupling (²J_{F-Si} = 283 Hz). A similar spectroscopic behaviour has been reported for other fluorosilanes. [4,21]



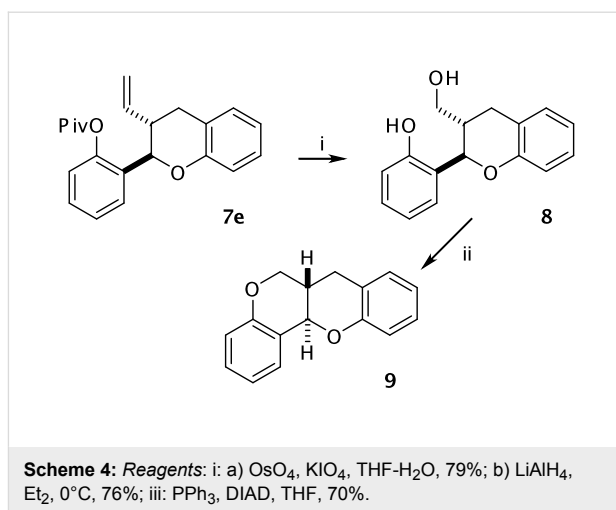
In order to study whether the electronic nature of the aldehyde had any influence on the diastereochemical outcome of the reaction, as observed before with the benzoxasilepines, [4] a selection of benzaldehydes with strongly (OMe) or weakly (OPiv) electron donating groups in *ortho*, *meta* and *para* positions were assayed (Table 1). Under the same experimental conditions used for the preparation of dihydrobenzofurans, the reaction is never diastereospecific, as *cis/trans* mixtures are always observed, the *trans* isomer being the major one. In addition, no clear influence of the electron density of the carbonyl on the diastereomeric ratio can be established. The yields are also considerably lower than those for the dehomologous system. The lack of conjugation between the allylsiloxane double bond in **5** or in **6** when compared with the analogous seven-membered benzoxasilepine could enhance the reactivity and instability of these compounds, accelerating the reaction but also increasing its rate of decomposition. When the reaction is performed in CHCl_3 , a slight increase in the yields is observed, but the diastereoselection levels are basically the same.

We have also described that benzoxasilepines can be condensed with benzaldehydes in the presence of a stoichiometric amount of KF and 18-crown-6 and a catalytic amount of a complex formed with AgOTf and (\pm) -BINAP to give good yields of dihydrobenzofurans. [5] Under the same reaction conditions, the eight membered benzoxasilocines did not react.

The *cis/trans* diastereoisomers could be easily distinguished by means of the coupling constants between the protons H2 and H3 in ^1H NMR, which range from 1.6 Hz to 3.5 Hz for the *cis* isomers and 8.4 Hz to 9.5 Hz for the *trans*.

Compound **7e** was used for the preparation of the core skeleton of homopterocarpan (Scheme 4). Degradation of the olefinic double bond with $\text{OsO}_4/\text{KIO}_4$ afforded an aldehyde which was reduced with LiAlH_4 . Under these conditions the pivaloyl protecting group was removed, affording the dihydroxylated derivative **8**. Application of the Mitsunobu conditions (DIAD, PPh_3) to **9** promoted the cyclization to give the homopterocarpan **8**.

Therefore, following this five steps route, we have accessed the skeleton of homopterocarpan in a convergent approach. We plan to use this strategy for the preparation of a variety of derivatives conveniently substituted on both aromatic rings through an appropriate selection of the starting benzoxasilocine and aromatic aldehyde. In addition, access to the *cis* isomers would allow the study of structure-activity relationships when compared with the *trans* isomers.



Conclusion

The condensation of benzoxasilocines with aromatic aldehydes in the presence of boron trifluoride has been studied. Yields are lower than those for the benzoxasilepines, and the diastereoselectivity is not directly influenced by the electronic density of the aldehydes. Mixtures of *cis/trans* 2-phenyl-3-vinylchromans are always formed, but the *trans* isomer dominates.

It is also described a new total synthesis of homopterocarpan skeleton, which is based on an appropriate transformation of the *trans*-2-(2-pivaloyloxyphenyl)-3-vinylchroman prepared through Sakurai reaction. In this way we have outlined an alternative synthetic strategy for the preparation of non natural analogs of the pterocarpan with promising biologic activities.

Supporting Information

Supporting Information File 1

Experimental data. This file contains all experimental methods and analytical data belonging to the compounds described in the article.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-3-5-S1.doc>]

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Tether-directed synthesis of highly substituted oxasilacycles *via* an intramolecular allylation employing allylsilanes

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Full Research Paper

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Abstract

Background

Using a silyl tether to unite an aldehyde electrophile and allylsilane nucleophile into a single molecule allows a subsequent Lewis-acid-mediated allylation to proceed in an intramolecular sense and therefore receive all the benefits associated with such processes. However, with the ability to cleave the tether *post* allylation, a product that is the result of a net intermolecular reaction can be obtained. In the present study, four diastereoisomeric β -silyloxy- α -methyl aldehydes, which contain an allylsilane tethered through the β -carbinol centre, have been prepared, in order to probe how the relative configuration of the two stereogenic centres affects the efficiency and selectivity of the intramolecular allylation.

Results

Syn-aldehydes, ***syn*-4a** and ***syn*-4b**, both react poorly, affording all four possible diastereoisomeric oxasilacycle products. In contrast, the *anti* aldehydes ***anti*-4a** and ***anti*-4b** react analogously to substrates that lack substitution at the α -site, affording only two of the four possible allylation products.

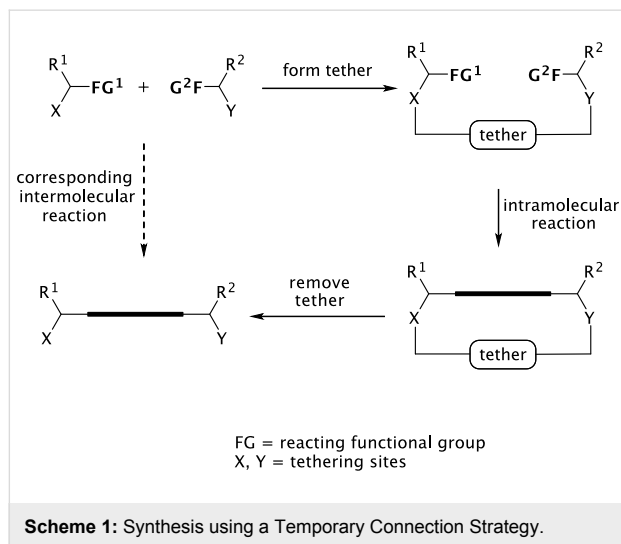
Conclusion

The outcome of the reaction with *anti*-aldehydes is in accord with reaction proceeding through a chair-like transition state (T.S.). In these systems, the sense of 1,3-stereoiduction can be rationalised by the aldehyde electrophile adopting a pseudoaxial orientation, which will minimise dipole-dipole interactions in the T.S. The 1,4-stereoiduction in these substrates is modest and seems to be modulated by the R substituent in the starting material. In the case of the *syn*-substrates, cyclisation through a chair T.S. is unlikely as this would require the methyl substituent α to the reacting carbonyl group to adopt an unfavourable pseudoaxial position. It is therefore proposed that these substrates react through poorly-defined T.S.s and consequently exhibit essentially no stereoselectivity.

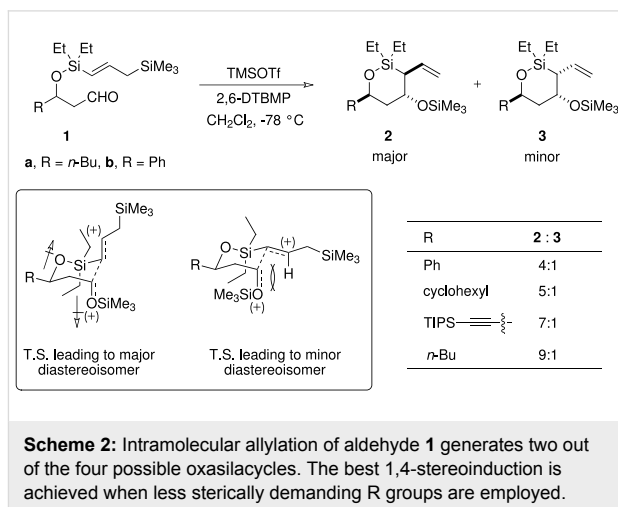
Background

Intramolecular reactions offer distinct advantages over their intermolecular counterparts providing the tethering unit, which connects the reacting functionalities, is neither too long such that the reaction resembles an intermolecular process, nor too short, in which case geometrical constraints can physically prevent the reaction. When these conditions on the tether are satisfied, however, the proximity of the reacting partners, combined with a reduction in the degrees of freedom in the system, render the intramolecular reaction more entropically and kinetically favourable. This can result in a more stereo-, regio- and chemoselective process, which is often reflected in an increased yield of the desired product.

We have been investigating the use of a *temporary* tether to link two reacting partners. [1-3] By using such a transient linker, which can be cleaved *post* reaction, it is possible to accrue the benefits associated with an intramolecular process and yet still obtain a product that derives from a net intermolecular reaction (Scheme 1). [4] Silyl groups have proven to be particularly popular tethering units for this purpose. [4-6] They can be attached to carbon, oxygen and nitrogen functionalities in a variety of ways, and are often stable to a diverse array of reaction conditions. [4] Furthermore, the silyl tether can be manipulated *post* reaction in a range of ways. [7,8] The silyl reagents that are required to prepare the tether are also relatively cheap, exhibit low toxicity and are widely available.



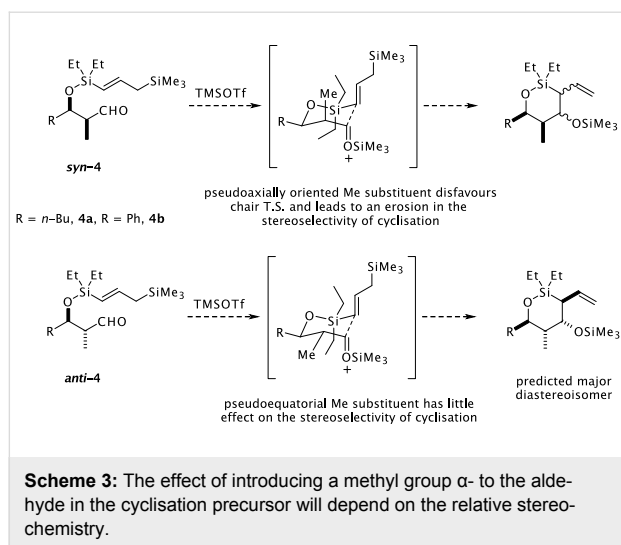
A number of groups have used the silyl group embedded in an allylsilane as the temporary connection for studying intramolecular allylation reactions. [9-14] We have taken a different approach, choosing to append an additional silyl group to the γ -position of the allylsilane nucleophile and use this as the tethering site instead (Scheme 2). This modification



confers a number of advantages on the resulting system: first, it ensures that the allylsilane is exocyclic in the T.S. allowing a direct comparison with the analogous intermolecular reaction; second, the size of the cyclic T.S. is two atoms smaller – and should therefore be better defined – than if the silyl connection were contained within the allylsilane itself; third, the silyl tether remains intact *post* allylation, to provide a product that can be elaborated in a wide variety of ways.

We recently showed that this Temporary Silicon Connection strategy provides a useful method for the stereoselective allylation of aldehydes (Scheme 2). [3] In this study, Lewis acid-mediated allylation of aldehyde **1**, provided the oxasilacycle allylation products **2** and **3** in good yield. More significantly, owing to the complete 1,3-stereoselection that is observed in this cyclisation, only these two – out of a possible four – oxasilacycles were obtained. We have rationalised the sense of 1,3-induction observed in this reaction on electrostatic grounds using a modification of Evans' dipole model, [15] in which the dipole moments across the polar C=O and C-O bonds oppose one another in a chair-like T.S. (Figure inset in Scheme 2). The levels of 1,4-stereoselection in the reaction of aldehyde **1** are more modest. We have argued that the selectivity for the major product **2** arises from minimising steric interactions, principally those between the allylsilane and the ethyl substituents contained within the silyl tether (we have recently shown[16] that replacing the diethylsila-component for a methylene group reverses the sense of 1,4-stereoselection). This is best achieved by placing the reacting allylsilane in a pseudoaxial orientation in a chair-like T.S. (Figure inset in Scheme 2).

It would be expected that large R groups in the cyclisation precursor **1**, such as phenyl and cyclohexyl substituents, would serve as the most effective conformational anchors for our



proposed chair-like T.S. (A values:[17] cyclohexyl: 2.2 kcal mol⁻¹; phenyl: 2.8 kcal mol⁻¹). These groups should occupy a pseudoequatorial position in order to minimise 1,3-diaxial interactions across the ring. Interestingly, these substrates display some of the lowest levels of 1,4-stereoiduction (Entries 1,2, Table in Scheme 2); indeed, the highest levels of 1,4-induction are obtained when substrates containing *less* sterically demanding substituents, such as *n*-Bu and TIPS-C \equiv C-groups, are employed (Entries 3,4, Table in Scheme 2) (A values:[17] ethynyl = 0.41–0.52 kcal mol⁻¹; ethyl = 1.79 kcal mol⁻¹). We acknowledge that analysing steric interactions and predicting favoured conformations for such heavily substituted six-membered cyclic T.S.s is not straightforward, especially for substrates with substituents (*i.e.* small R groups) that are not strong conformational anchors. However, we postulate that when R is large (*e.g.* R = Ph), the reaction proceeds through a standard Zimmerman-Traxler chair T.S. For those substrates that possess small R substituents, however, the R group provides less of a conformational lock for a chair T.S. Consequently, this allows for small structural changes away from a chair conformation, which serve to alleviate the unfavourable interactions associated with placing the allylsilane in

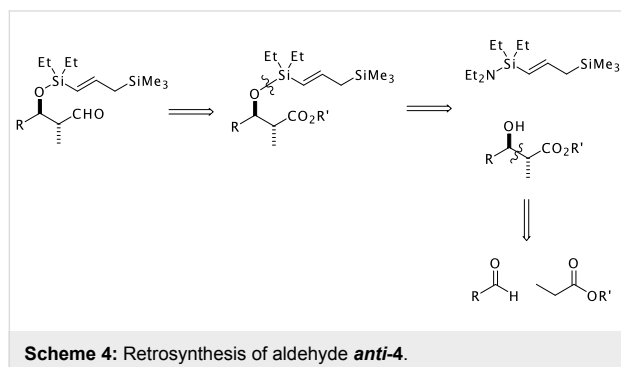
a pseudoaxial orientation and lead to the improved levels of 1,4-induction that are observed in these systems. The presence of relatively long C-Si and O-Si bonds and a relatively flexible O-Si-C bond angle, in the cyclic T.S. means that such deviations from the classical Zimmerman-Traxler T.S. are likely to be readily accommodated.

In light of the interesting substituent effect on 1,4-induction, we were keen to investigate how incorporating additional substituents into the substrate might influence the stereoselectivity of the reaction. Specifically we wanted to assess how incorporating an additional methyl group α to the aldehyde functionality would affect the stereoselectivity of the reaction. We hypothesised that if intramolecular allylation proceeds through a chair-like T.S., then the α -methyl group in *syn*-aldehyde *syn*-4 will occupy a pseudoaxial position. Since this would lead to additional unfavourable 1,3-diaxial interactions, we postulated that cyclisation would likely proceed through alternative reactive conformations with a less predictable stereochemical outcome (Scheme 3). In contrast, a pseudoequatorially orientated methyl substituent, which would result from cyclisation of *anti*-aldehyde *anti*-4, might be expected to exert little impact on the stereoselectivity of the reaction (Scheme 3). To test our hypothesis, we chose to carry out these transformations on the *n*-Bu substrate, **4a**, as a representative of aldehydes possessing a substituent that imposes a relatively poor conformational lock, and compare the results with those for the Ph substrate, **4b**, which represents one of the more sterically demanding substituents.

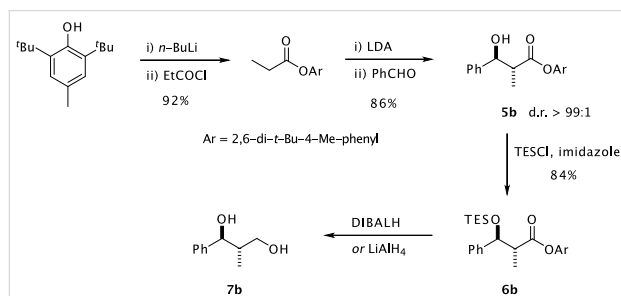
Results and discussion

The desired cyclisation precursors **4a** and **4b** were prepared using our well-established method. [3] The retrosynthetic analysis for the *anti* series of products is outlined in Scheme 4.

We first required access to both *syn*- and *anti*- β -hydroxy ester diastereoisomers of our two test substrates. *Anti*- β -hydroxy ester, *anti*-5b, was prepared with complete diastereoselectivity (the minor diastereoisomer was not observed in the crude reaction mixture on analysis by 300 MHz ¹H-NMR spectroscopy) by a method described by Heathcock *et al.* (Scheme 5). [18] We were concerned, however, that the steric bulk of the aryl ester in **5b**, which is required to impart the complete *anti* selectivity on the aldol reaction, would make unmasking of the aldehyde difficult owing to unfavourable steric clashes between the carbonyl group and one of the *tert*-butyl groups in the aryl ring forcing the aromatic group to rotate out of the plane of the ester, leaving the bulky *tert*-butyl groups to flank the faces of the carbonyl and block the Bürgi-Dunitz approach trajectory of the reducing agent. We therefore chose to investigate this reduction step on the model substrate **6b**, where the TES-ether would



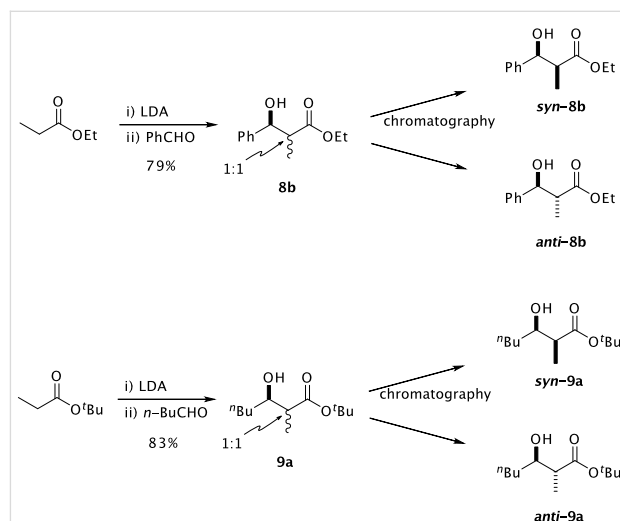
function as a cheaper mimic of the tethered allylsilane in our desired system. As expected, under the reaction conditions which had to be employed to effect reduction (LiAlH_4 in Et_2O or DIBALH in CH_2Cl_2 at reflux), it was neither possible to prevent Si-O bond cleavage, nor were we able to halt the reaction at the aldehyde stage, and consequently diol **7b** was the only product isolated (Scheme 5).



Scheme 5: Attempts to reduce the bulky aryl ester resulted in Si-O bond cleavage and over-reduction to the primary alcohol.

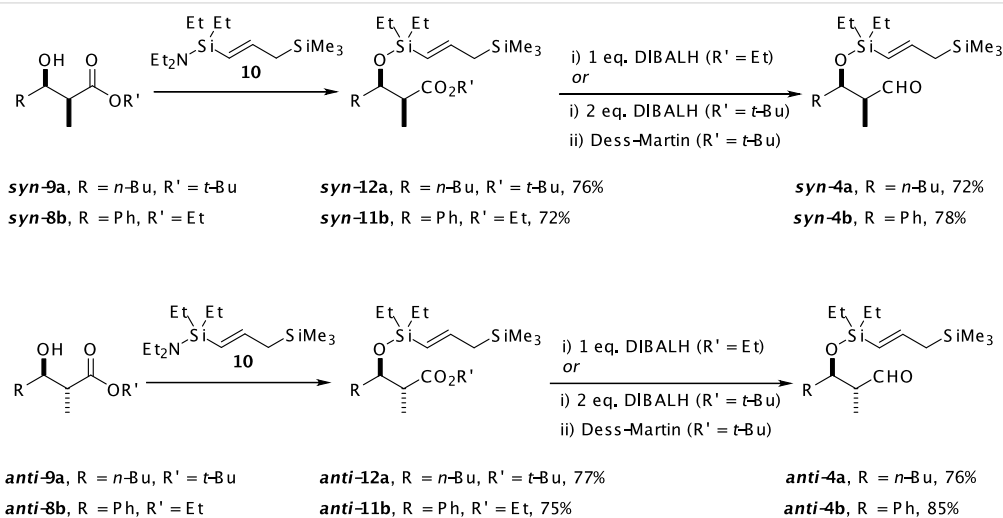
We therefore switched our attention back to ethyl esters, which we knew from previous studies could be reduced directly to the required aldehyde with DIBALH at low temperature. [3] The reaction between the lithium enolate of ethyl propionate and benzaldehyde produced a 1:1 mixture of aldol products, **syn-8b** and **anti-8b**, in good yield (Scheme 6). [19] These were readily separated by flash column chromatography to afford the two required aldol diastereoisomers in gramme quantities. The same reaction employing valeraldehyde also led to the desired two diastereoisomeric products **syn-8a** and **anti-8a** in good yield (1:1 ratio); however this time, the two products proved to be inseparable by flash column chromatography. Fortunately, when *t*-butyl propionate was employed as the enolate

precursor, we were able to access the readily separable *t*-butyl ester aldol products **syn-9a** and **anti-9a** in good yield (Scheme 6). The relative stereochemistry of these products was confirmed by comparison with literature ^1H -NMR data. [20,21] The relative stereochemistry of **anti-8b** was further verified by comparing its diol reduction product with that obtained from the reduction of aryl ester **anti-5b** prepared earlier, which was of known *anti* configuration.



Scheme 6: Preparation of *syn*- and *anti*- β -hydroxy esters.

γ -(Amino)silyl-substituted allylsilane **10** was synthesised according to our standard procedure, [3] and used to tether our allylsilane to the hydroxyl groups of both *syn*- and *anti*- β -hydroxy esters, **9a** and **8b**, by simply stirring the two reagents in the absence of solvent (Scheme 7). The by-product from this reaction is Et_2NH , which can be easily removed by evaporation



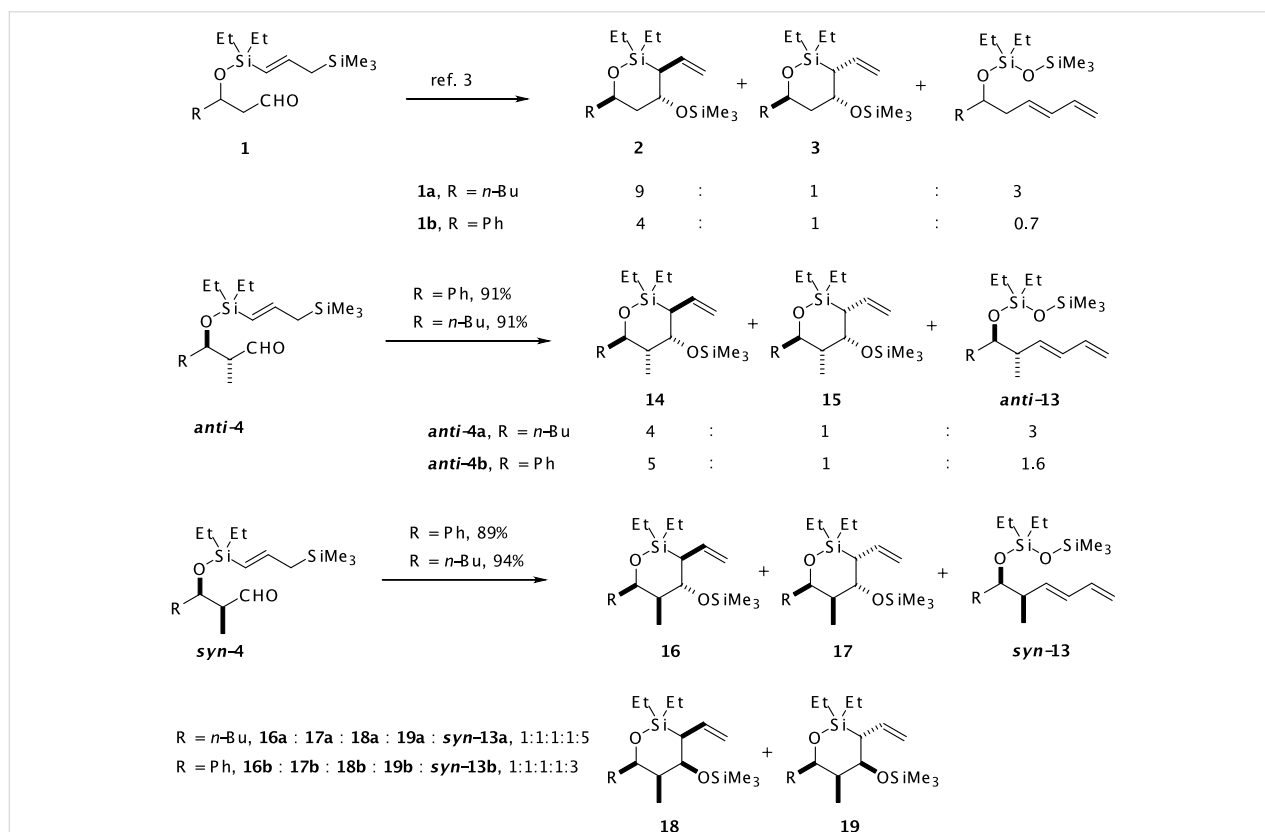
Scheme 7: Preparation of the *syn*- and *anti*-aldehyde cyclisation precursors **4**.

under reduced pressure at the end of the reaction. Subsequent DIBALH reduction of ethyl esters **syn-11b** and **anti-11b** produced the desired cyclisation precursors, aldehydes **syn-4b** and **anti-4b**, respectively. In the case of the two *t*-butyl esters **syn-12a**, and **anti-12a**, we were unable to effect direct reduction to the aldehyde in high yield owing to the propensity for the intermediate aldehyde to be reduced further to the corresponding primary alcohol. Presumably in the case of these *t*-butyl esters, increased steric compression in the initial tetrahedral intermediate causes this to collapse to the aldehyde, even at low temperature, allowing further reduction to the corresponding primary alcohols. Fortunately, the two alcohol products could be oxidised to the desired aldehydes **syn-4a** and **anti-4a**, using Dess-Martin periodinane[22,23] without epimerisation of the α -stereogenic centre (Scheme 7).

With all four cyclisation precursors in hand, we were ready to conduct our intramolecular allylation study. Each aldehyde substrate (>95:5 d.r. in all four cases) was treated with TMSOTf in the presence of 2,4,6-tri-*t*-butyl pyrimidine (TTBP), [24] which acts as a Brønsted acid scavenger, in CH₂Cl₂ as solvent, conditions that had proved successful in our previous cyclisation studies. [3] The results from these reactions are summarised in Scheme 8.

The first point to note is that the reactions of aldehydes **syn-4a** and **syn-4b** were poorly stereoselective; all four diastereoisomers were formed in both cases, as well as a significant amount of the corresponding side-product diene **syn-13a** and **syn-13b** (the diene may be formed in a variety of ways; we favour a mechanism involving a vinylogous silicon-mediated olefination as this best accounts for the excellent (*E*)-stereoselectivity observed). [25-27] The relative stereochemistry of each diastereoisomer in both cases was elucidated by extensive NMR experiments (see the Experimental Section in the Additional Files for full details). The two *syn*-aldehydes reacted not only with poor stereoselectivity, they also cyclised at a much slower reaction rate (24 h reaction time) than was observed with the corresponding α -unsubstituted aldehydes **1**. The results with both Ph and *n*-Bu substrates, **syn-4a** and **syn-4b**, respectively, are consistent with the *syn*-methyl group disfavoured chair-like T.S.s, owing to the fact that the additional methyl group would be forced to adopt a pseudoaxial orientation. Consequently we believe that cyclisation for these substrates proceeds through poorly defined T.S.s, resulting in the observed erosion in the stereoselectivity of the reaction.

In marked contrast to the two *syn* aldehydes, cyclisation of *anti*-aldehydes, **anti-4a** and **anti-4b**, provided results which were



Scheme 8: Intramolecular allylation results.

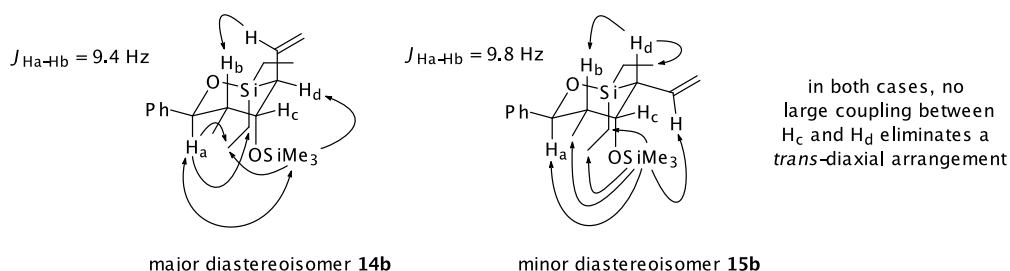


Figure 1: nOe data for the two oxasilacycles obtained from allylation of aldehyde **anti-4b**.

more comparable with those obtained using the corresponding α -unsubstituted aldehydes **1a** and **1b**. The reaction times, 10 h for **anti-4a**, and 6 h for **anti-4b**, were much closer to those required for substrates lacking the α -Me substituent (8 h for both *n*-Bu and Ph substrates, **1a** and **1b**, respectively), and in line with our previous observations (Scheme 2), only two out of the possible four oxasilacycles were formed in both cases. Once again, extensive NMR experiments confirmed the relative stereochemistry in the two diastereoisomers and showed that complete 1,3-stereoselection is obtained in both cyclisations. As expected, the sense of 1,3-induction was the same as was observed with the α -unsubstituted analogues **1a** and **1b** (Figure 1). The two allylation products in each case therefore arise from the modest level of 1,4-stereoselection observed in both cyclisations.

Qualitatively, the observations with the two *anti*-aldehydes, **anti-4a** and **anti-4b**, are consistent with cyclisation proceeding through a chair-like T.S. in which the α -methyl group provides a further conformational lock by adopting a pseudoequatorial orientation. More careful analysis of the levels of 1,4-stereoselection in these cyclisations, and comparison with the results obtained using the corresponding α -unsubstituted aldehydes, **1** (Scheme 2), reveals an erosion of stereoselectivity when cyclising the *n*-Bu substrate (9:1 for **1a** to 4:1 for **anti-4a**), whereas the stereoselectivity obtained when cyclising the phenyl substrate **anti-4b**, is essentially unchanged (4:1 for **1b**, 5:1 for **anti-4b**). We can interpret these results in two ways. One possibility is that the additional methyl group in **anti-4a** provides an additional conformational anchor for a chair-like T.S. The reactive conformation for **anti-4a** therefore deviates towards a more chair-like T.S., as is observed for substrates possessing bulkier substituents such as **anti-4b** and **1b**. This serves to bring down the stereoselectivity for **anti-4a** to similar levels to those observed for systems that react through more chair-like T.S.s. An alternative explanation is that **anti-4a** reacts through a similar T.S. to its α -unsubstituted analogue **1a**, which deviates from a chair-like conformation. The additional

α -methyl group in **anti-4a** then introduces additional unfavourable interactions in this favoured T.S., which leads to the erosion in the level of 1,4-induction.

Summary

We have previously shown that allylsilanes tethered through a γ -silyl substituent to a series of β -hydroxy aldehydes cyclise with complete 1,3-stereoselection but afford two diastereoisomeric products owing to the more modest levels of 1,4-stereoselection. In the present study we have incorporated an α -methyl substituent into the substrate to probe how this affects the stereoselectivity of the reaction. We have shown that the relative stereochemistry of the two stereogenic centres in the starting aldehyde **4** has a profound effect on the efficiency of the reaction. *Syn*-aldehydes react poorly, affording mixtures of all four possible oxasilacycles in addition to appreciable quantities of a diene side-product. The results with *anti*-aldehydes are more interesting. In line with our prediction, substrates possessing this relative stereochemistry provide results which are comparable to those from aldehydes that lack a substituent at the α -site. That a slight reduction in 1,4-stereoselection is observed with the *n*-Bu substrate **anti-4b** supports the idea that substrates, which lack substituents that provide a strong conformational anchor on the reactive conformation, react through a T.S. that deviates from a classical Zimmerman-Traxler chair conformation. Studies are now focusing on how the geometry of the double bond in the tethered allylsilane also influences the stereoselectivity of this reaction.

Additional Material

Detailed experimental procedures and full characterisation data (Supporting Information File 1) and scanned ^1H - and ^{13}C -NMR spectra for all new compounds (Supporting Information File 2, Supporting Information File 3, Supporting Information File 4, Supporting Information File 5, Supporting Information File 6, Supporting Information File 7, Supporting Information File 8) are included as additional files.

Supporting Information

Supporting Information File 1

Experimental details and characterisation data.
[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-3-6-S1.pdf>]

Supporting Information File 2

¹H-NMR and ¹³C-NMR Spectra for the following compounds: **5b**, **6b**, **7b**, *syn*-**8b**, *anti*-**8b**, *syn*-**11b**, *anti*-**11b**, *syn*-**4b**, *anti*-**4b**, *syn*-**9a**, *anti*-**9a**, *syn*-**12a**, *anti*-**12a**, *syn*-**4a**, *anti*-**4a**, *syn*-**13b**, *anti*-**13b**, *syn*-**13a**, *anti*-**13a**.
[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-3-6-S2.pdf>]

Supporting Information File 3

¹H-NMR and ¹³C-NMR Spectra for the following compounds: **16a**, **17a**.
[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-3-6-S3.pdf>]

Supporting Information File 4

¹H-NMR and ¹³C-NMR Spectra for the following compounds: **18a**, **19a**.
[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-3-6-S4.pdf>]

Supporting Information File 5

¹H-NMR and ¹³C-NMR Spectra for the following compounds: **14a**, **15a**.
[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-3-6-S5.pdf>]

Supporting Information File 6

¹H-NMR and ¹³C-NMR Spectra for the following compounds: **16b**, **17b**.
[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-3-6-S6.pdf>]

Supporting Information File 7

¹H-NMR and ¹³C-NMR Spectra for the following compounds: **18b**, **19b**.
[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-3-6-S7.pdf>]

Supporting Information File 8

¹H-NMR and ¹³C-NMR Spectra for the following compounds: **14b**, **15b**.
[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-3-6-S8.pdf>]

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Generation of pyridyl coordinated organosilicon cation pool by oxidative Si-Si bond dissociation

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Preliminary Communication

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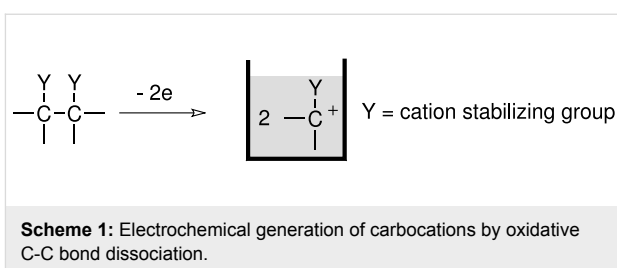
Abstract

An organosilicon cation stabilized by intramolecular pyridyl coordination was effectively generated and accumulated by oxidative Si-Si bond dissociation of the corresponding disilane using low temperature electrolysis, and was characterized by NMR and CSI-MS.

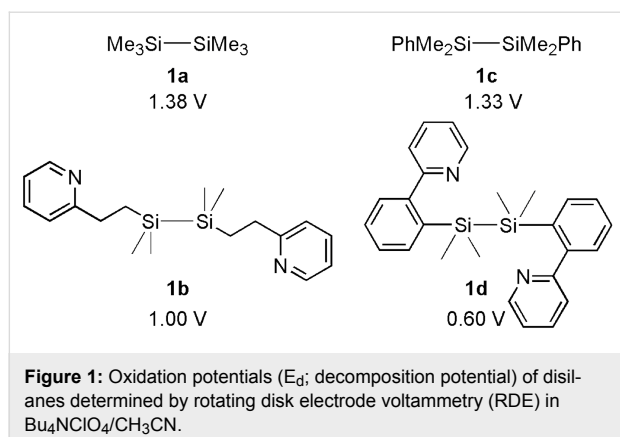
Findings

We have recently developed the "cation pool" method, which involves the irreversible oxidative generation and accumulation of highly reactive cations in the absence of nucleophiles [1-5]. Heteroatom-stabilized carbocations, such as *N*-acyliminium ion pools and alkoxy-carbenium ion pools have been generated based on oxidative C-H, C-Si, and C-S bond dissociation. Very recently, the oxidative C-C bond dissociation has been found to be effective for generation of a pool of a carbocation having a stabilizing group as shown in Scheme 1[6].

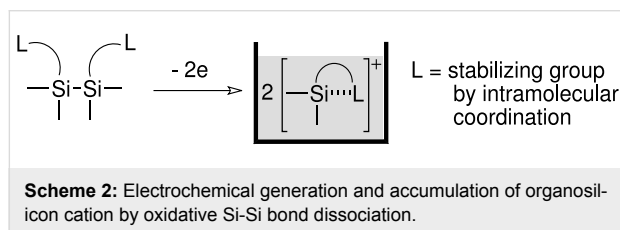
We have been interested in generation and accumulation of cations of other elements such as silicon using the "cation pool" method. Organosilicon cations are known to be extremely unstable and difficult to accumulate in solution [7-11]. Organo-



silicon cations having appropriate donor ligands are, however, reasonably stable to accumulate in solution and many examples of such donor-stabilized organosilicon cations have been reported in the literature [12-18]. Herein, we report the generation and accumulation of a donor-stabilized organosilicon



cation by the electrochemical oxidative Si-Si bond dissociation (Scheme 2) [19-21].



Symmetrical disilanes having coordinating groups on both silicon atoms were used as starting materials for electrochemical generation and accumulation of organosilicon cations, because oxidative dissociation of the Si-Si bond leads to the formation of two equivalents of organosilicon cations and no other product is formed.

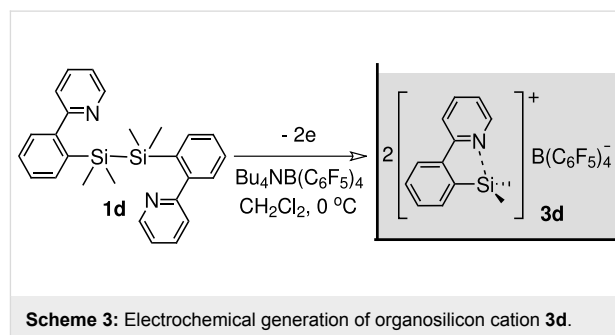
In our earlier study, it was found that the introduction of a coordinating group such as a pyridyl group decreased the oxidation potential of tetraalkylstannanes, although there is no indication of the coordination in the neutral molecule. Dynamic intramolecular coordination to tin seems to facilitate electron transfer [22]. The coordination also stabilizes the thus-generated radical cation and weakens the C-Sn bond. A similar effect of intramolecular coordination was observed in the case of silicon [23]. Another important point is that pyridyl group is rather inactive toward the anodic oxidation. Thus, we chose to use a pyridyl group as a donor ligand.

First, we prepared disilanes having pyridyl groups in appropriate positions and measured their oxidation potentials [24, 25]. The oxidation potential of 2-pyridylethyl substituted disilane **1b** was slightly less positive than hexamethyldisilane **1a**. On the other hand, the oxidation potential of 2-pyridylphenyl substituted disilane **1d** was much less positive than the corresponding disilane **1c** having phenyl groups (Figure 1).

^{29}Si NMR chemical shifts of **1b** and **1d** were similar to those of **1a** and **1c**, indicating that no coordination of the pyridyl groups on silicon existed in the neutral molecules (Supporting Information File 1). Therefore, the significant effect of the 2-pyridyl group on the oxidation potential may be ascribed to effective intramolecular coordination to stabilize the radical cation intermediate. The conformationally less flexible 2-pyridylphenyl group seems to be more effective than the 2-pyridylethyl group.

The intramolecular coordination in the radical cation is supported by the DFT calculations as shown in Figure 2. It is also important to note that such coordination elongates the Si-Si bond and facilitates its dissociation.

Preparative electrochemical oxidation of **1d** was carried out to generate and accumulate the corresponding organosilicon cation **3d** (Scheme 3). Nature of the counter anion was very important. When **1d** was oxidized in the presence of Bu_4NBF_4 , which is a common supporting electrolyte for the "cation pool" method, fluoride was introduced on the silicon atom. Eventually, $\text{Bu}_4\text{NB}(\text{C}_6\text{F}_5)_4$ was found to be an appropriate supporting electrolyte to generate and accumulate the organosilicon cation **3d**.



The ^1H NMR spectrum of the solution obtained by the electrochemical oxidation of **1d** in CH_2Cl_2 (containing 10% CD_2Cl_2) using $\text{Bu}_4\text{NB}(\text{C}_6\text{F}_5)_4$ at 0°C showed complete conversion of disilane **1d** to one species, *i.e.* organosilicon cation **3d**. The Si-CH₃ groups in **3d** exhibited a signal at 0.87 ppm, whereas those in **1d** were observed at -0.05 ppm. Significant low field shift of the protons on the pyridyl ring was also observed. **3d** exhibited a ^{29}Si signal at 37.7 ppm [26-28]. These results strongly suggest the generation of an electron deficient silicon species. Therefore, it is reasonable to consider that the organosilicon cation stabilized by the pyridyl coordination was generated.

The formation of organosilicon cation **3d** was also confirmed by CSI-MS (cold-spray ionization mass spectroscopy) (spray

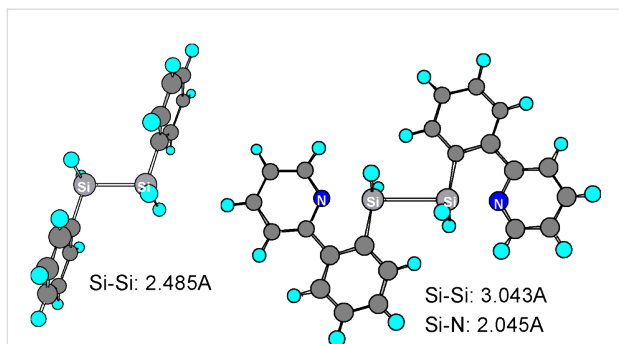


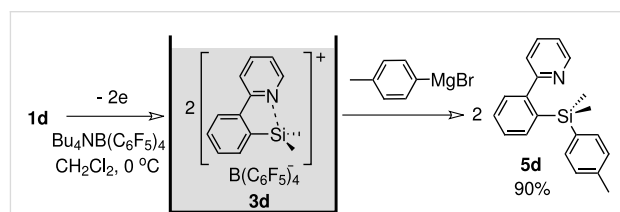
Figure 2: Optimized structures of radical cations of 1,2-diphenyldisilane and 1,2-bis[o-(2-pyridyl)-phenyl]disilane obtained by DFT calculation (B3LYP/LANL2DZ).

temperature; 0°C) [29]. The parent peak was observed at $M/Z = 212.08963$ (Calcd: 212.08955) as shown in Figure 3. A complex of **3d** with HF was also observed, although the mechanism of its formation is not clear at present.

The mechanism shown in Figure 4 seems to be reasonable. The initial one-electron oxidation of disilane **1d** gives radical cation **2d**. The pyridyl coordination in the radical cation facilitates the electron transfer. In the next step, the dissociation of the Si-Si bond in radical cation **2d** takes place to give organosilicon cation **3d** and silyl radical **4d**. DFT calculations indicated that

the pyridyl group coordination to silicon takes place both in cation and radical. Radical **4d** seems to be easily oxidized on the surface of the electrode to give cation **3d**. Therefore, two moles of **3d** should be formed from one mole of **1d** by net two-electron oxidation.

The organosilicon cation **3d** can be trapped by *p*-tolylmagnesium bromide as a nucleophile and the corresponding product **5d** was obtained in 90% yield based on disilane **1d** (Scheme 4) [30]. The observation indicates that two moles of the cation is formed from one mole of the disilane with the consumption of two moles of electrons, being consistent with the mechanism shown in Figure 4.



Scheme 4: Reaction of organosilicon cation **3d** with *p*-tolylmagnesium bromide.

Effective formation of **5d** indicates that organosilicon cation **3d** acted as a silicon centered cation. The carbon nucleophile

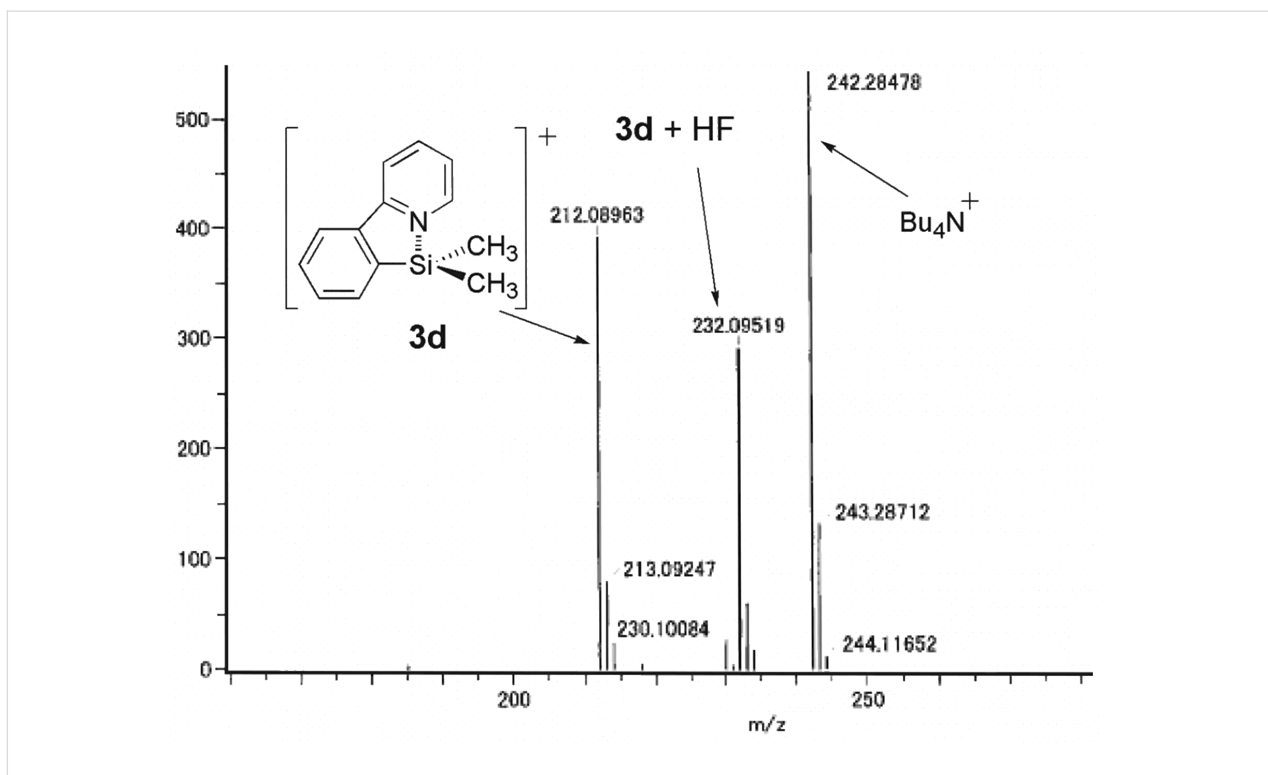
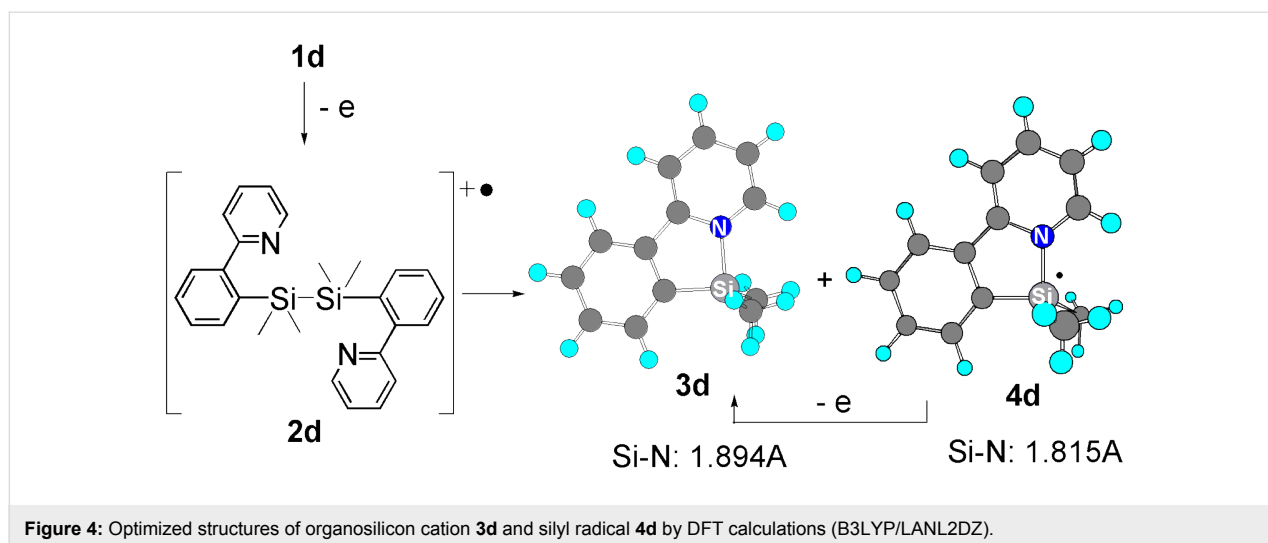


Figure 3: CSI-MS of organosilicon cation **3d** at 0°C.



attacked the silicon atom selectively, although a positive charge should also be delocalized on the nitrogen atom.

The present observations speak well for possibilities of the "cation pool" method in organosilicon chemistry. Donor-stabilized organosilicon cations can be effectively generated and accumulated at 0°C by the electrochemical oxidative Si-Si bond dissociation. It is also noteworthy that the presence of a donor ligand on the silicon atom facilitates the oxidation. Further work aimed at generating other organosilicon cations and exploring their stability and reactivity is currently in progress.

Supporting Information

Supporting Information File 1

Supporting information. Experimental procedures, spectrum data of new compounds, details of DFT calculation, and $^1\text{H}/^{13}\text{C}$ NMR spectra.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-3-7-S1.pdf>]

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30. 90% yield means that 1.8 mole of **5d** was obtained from 1 mole of **1d**.

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Pd-catalysed [3 + 3] annulations in the stereoselective synthesis of indolizidines

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Preliminary Communication

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Abstract

A [3 + 3] annelation of enantiomerically pure aziridine **7** provides the functionalised piperidine **8** that can be elaborated to the indolizidine skeleton in only 4 steps with good stereocontrol.

Introduction

Indolizidine alkaloids represent one of the most structurally diverse classes of natural products and have attracted considerable attention because of their varied biological activity (some examples are illustrated in Scheme 1) [1]. Recent studies in our labs have demonstrated that a range of piperidine alkaloids, [2-6] including quinolizidine based targets, [7,8] can be prepared stereoselectively through the employment of a [3 + 3] annelation strategy [9]. This approach exploits the commercially available reagent **1** developed by Trost [10] that employs a nucleophilic allylsilane motif in conjunction with an allylic acetate moiety. In an effort to expand our studies to new structural classes, we have turned our attention to the employment of this technique in the synthesis of indolizidines. Specifically, and as outlined in Scheme 1, we envisaged that a key piperidine intermediate **3** could be prepared in enantiomerically pure form and converted into a functionalised indolizidine inter-

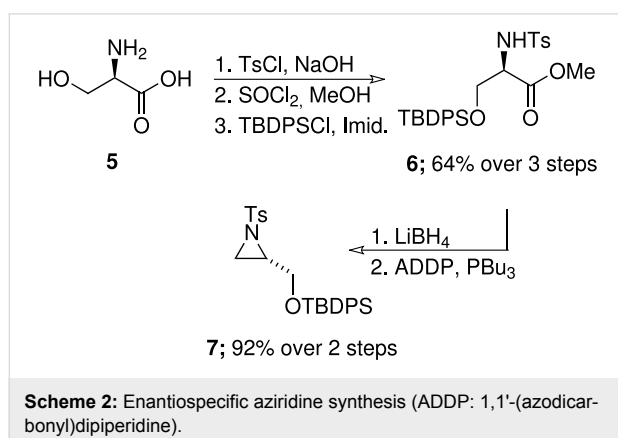
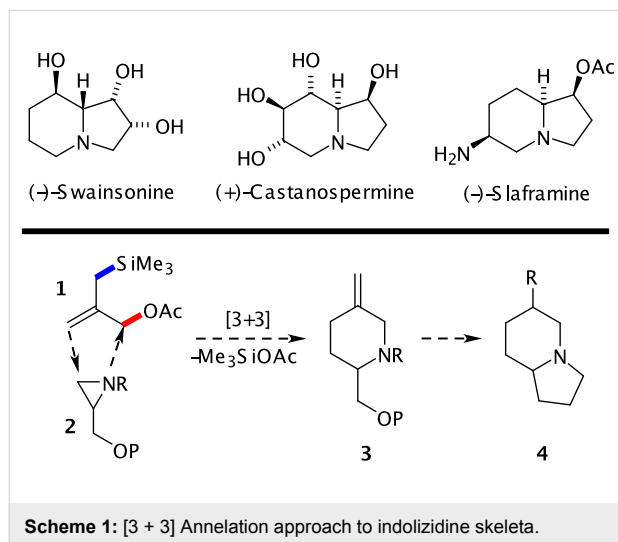
mediate **4** within a few steps. We wish to report herein our recent progress towards this goal.

Our studies began with the preparation of an appropriate precursor to the desired functionalised piperidine (Scheme 2). Specifically, we prepared an enantiomerically pure silyl protected aziridine **7** using a modification of the route described by Righi and co-workers [11]. Accordingly, tosyl protection of (*R*)-serine **5** followed by esterification and TBDPS-protection provided **6** in good overall yield. Ester reduction was carried out conveniently on multigram scale using LiBH₄ to give an amino alcohol that was smoothly transformed to aziridine **7** after Mitsunobu condensation.

Having arrived at the key [3+3] annelation step, we decided to employ our standard conditions for the Pd-catalysed reaction.

Table 1: Investigation of the [3 + 3] annelation reaction

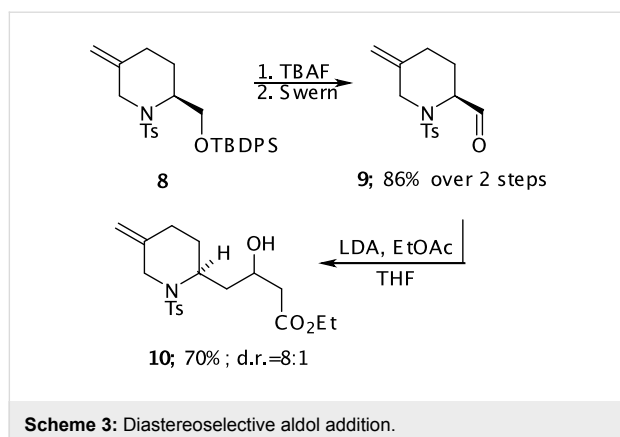
Entry	Reductant	mol% P(OPr) ₃	Yield	
1	<i>n</i> BuLi	60	74%	
2	-	60	38%	
3	-	40	25%	
4	-	80	11%	



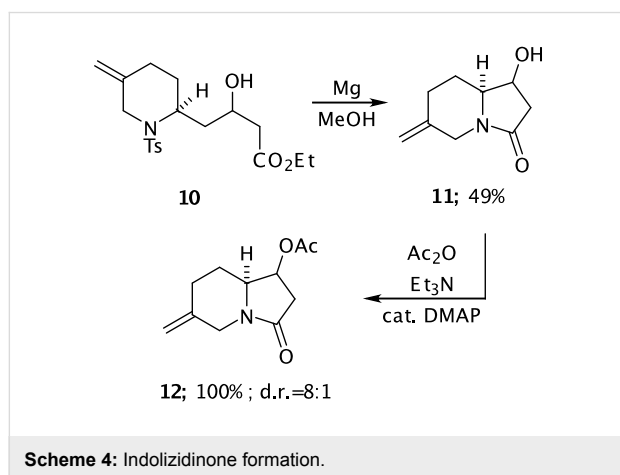
Indeed, we were pleased to find that the desired piperidine **8** could be furnished in high yield and that this reaction allowed 2–3 g of material to be made available at this stage (Table 1, Entry 1). Moreover, we took the opportunity to carry out a study into the role of *n*-BuLi in this process. Specifically, Trost

described the use of this reagent as a reductant for the generation of low valent Pd required for generation of the intermediate TMM-reagent [12]. However, the ability of phosphite to carry out the reduction of Pd(II) to Pd(0) suggested to us that the annelation should proceed equally well in the absence of *n*-BuLi [13]. In an effort to clarify this issue we carried out a study of the [3 + 3] reaction in the absence of the alkyl lithium reagent. As outlined in Table 1, Entries 2–4, the annelation was found to proceed in the absence of *n*-BuLi, however, in all cases the yield of cyclisation product was significantly lower than with catalyst generated by the organolithium reagent. Whilst the underlying reasons for this difference in catalyst activity are unclear at present, we speculate that *n*-BuLi may be responsible for the formation of hitherto uncharacterised phosphine ligands $\text{Bu}_n\text{P}(\text{O}^i\text{Pr})_{3-n}$ that promote the annelation over simple $\text{P}(\text{O}^i\text{Pr})_3$. Indeed, analogous alkoxide substitution reactions of phosphites have been reported using Grignard reagents [14]. In addition, ^{31}P NMR studies showed that the addition of 1 equivalent of *n*-BuLi to $\text{P}(\text{O}^i\text{Pr})_3$ gave a mixture of $\text{P}(\text{O}^i\text{Pr})_3$ and P^nBu_3 after 15 minutes (See Supporting Information File 1 for details). Interestingly however, we have found P^nBu_3 to be inefficient in [3 + 3] reactions as it appears to promote by-product formation [8]. Studies into the nature of the catalyst in the presence of *n*-BuLi are ongoing.

With the key piperidine **8** in hand, we turned our attention to the assembly of the indolizidine skeleton. Deprotection of the silyl ether proceeded smoothly and the alcohol was oxidised to the corresponding aldehyde **9** under Swern conditions. Addition of the Li-enolate of EtOAc to the crude aldehyde provided the aldol product **10** in high yield and with good diastereocontrol (Scheme 3). Notably, reduction of **9** (NaBH_4 , MeOH) followed by formation of the corresponding Mosher's ester showed a single resonance in the ^{19}F NMR spectrum (235 MHz, CDCl_3 ; δ -72.0) suggesting that minimal epimerisation had taken place during the oxidation process.

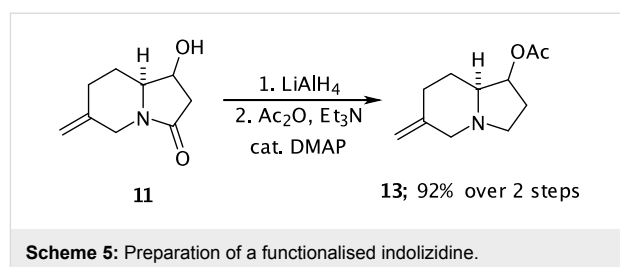


We next decided to investigate the formation of the azabicyclic via the deprotection of the Ts-amine moiety followed by cyclisation onto the ester. Previous work in the quinolizidine area had shown that these transformations could be achieved in one-pot by the use of Mg turnings in methanol at ambient temperature [7,8]. Indeed, subjecting **10** to these conditions provided the desired indolizidine **11**, albeit in modest yield. Finally, acetylation of the hydroxyl group provided **12** and allowed the diastereoisomers to be separated and individually characterised (Scheme 4). Unfortunately however, we were unable to determine the product stereochemistry unequivocally in either case (the ^1H NMR data for the minor diastereomer of **12** compares well with a close analogue reported by Knapp and co-workers suggesting that the aldol addition reaction proceeds under Felkin-Anh control [see Supporting Information File 1]).



In conclusion, we have shown that functionalised indolizidinone intermediates can be generated through the Pd-catalysed [3 + 3] annelation of aziridines and Trost's conjunctive allylsilane reagent. We have also found that reduction of the lactam unit of **11** and acetylation of the hydroxyl group takes place smoothly to provide **13**, demonstrating the potential of

these intermediates for the synthesis of slaframine and related indolizidines (Scheme 5).



Supporting Information

Supporting Information File 1

Supporting information. Experimental procedures and compound characterisation.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-3-8-S1.doc>]

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Conformational rigidity of silicon-stereogenic silanes in asymmetric catalysis: A comparative study

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Full Research Paper

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Abstract

In recent years, cyclic silicon-stereogenic silanes were successfully employed as stereoinducers in transition metal-catalyzed asymmetric transformations as exemplified by (1) the hydrosilylation of alkenes constituting a chirality transfer from silicon to carbon and (2) the kinetic resolution of racemic mixtures of alcohols by dehydrogenative silicon-oxygen coupling. In this investigation, a cyclic and a structurally related acyclic silane with silicon-centered chirality were compared using the above-mentioned model reactions. The stereochemical outcome of these pairs of reactions was correlated with and rationalized by the current mechanistic pictures. An acyclic silicon-stereogenic silane is also capable of inducing excellent chirality transfer (*ct*) in a palladium-catalyzed intermolecular carbon-silicon bond formation yet silicon incorporated into a cyclic framework is required in the copper-catalyzed silicon-oxygen bond forming reaction.

Findings

Within the last decade, several asymmetric transformations based on silicon-stereogenic reagents or substrates were revisited or invented. [1-4] Aside from the use of silicon-stereogenic chiral auxiliaries in substrate-controlled reactions, [5] a still limited number of remarkable stereoselective processes with a stereogenic silicon as the reactive site were reported, [6] namely the inter- [7] as well as intramolecular [8] chirality transfers from silicon to carbon. Moreover, we had demonstrated that chiral silanes resolve racemic mixtures of alcohols

in a non-enzymatic, transition metal-catalyzed kinetic resolution. [9]

During our ongoing investigations directed towards the mechanistic elucidation of the origin of the chirality transfer in a palladium-catalyzed hydrosilylation, [10] we had to perform an extensive screening of silicon-stereogenic tertiary silanes. On that occasion, we became aware that a similar level of stereoselection was obtained when privileged cyclic system **1a** [11]

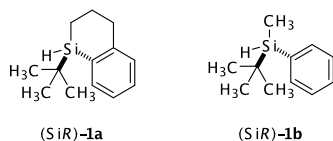


Figure 1: Cyclic and acyclic sterically encumbered silanes.

was exchanged for the important acyclic congener **1b** [12-15] (Figure 1). We had erroneously missed this known tertiary silane. This was particularly unfortunate in the light of the fact that these silanes are both decorated with three substituents of different steric demand and, therefore, display marked stereochemical differentiation around silicon.

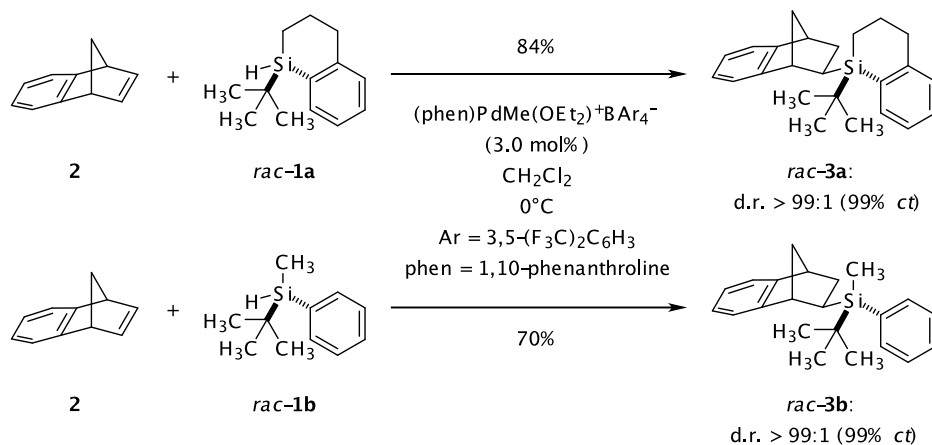
In this preliminary communication, we wish to report a comparison of cyclic **1a** and acyclic **1b** as stereoinducers in the palladium-catalyzed chirality transfer from silicon to carbon and in the copper-catalyzed kinetic resolution of donor-functionalized alcohols capable of two-point binding.

The reagent-controlled hydrosilylation of norbornene derivative **2** with silane **1a** proceeds with a perfect chirality transfer (*rac*-**1a** → *rac*-**3a**, Scheme 1). [8] Mechanistic investigation of the nature of the stereochemistry-determining step in this catalysis required a silane, which would produce slightly diminished diastereoselectivity and, hence, attenuated chirality transfer from silicon to carbon. [10] It was that situation that prompted us to investigate a considerable range of silicon-stereogenic silanes initially varied in ring size and exocyclic substituent; this was not met with satisfactory success. Based on the assumption that less rigid acyclic silanes would induce lower levels of diastereoselection, previously reported silane

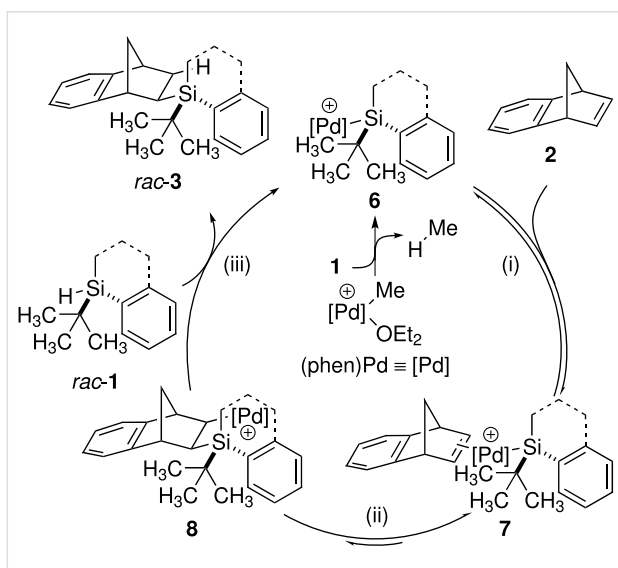
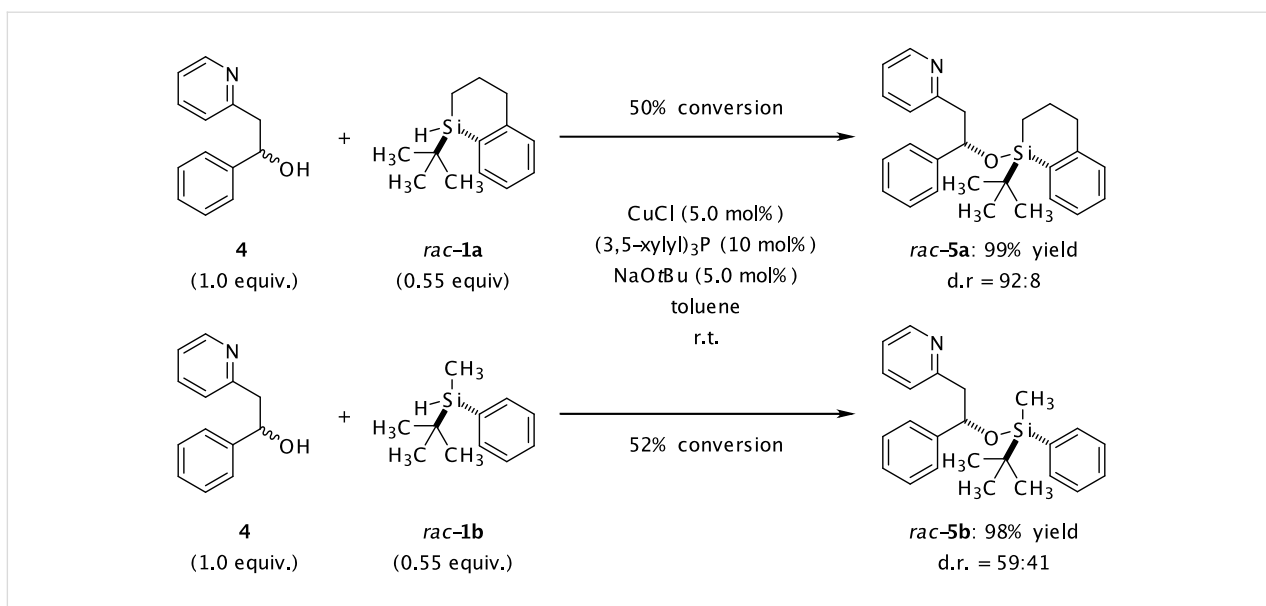
rac-**1b** – readily prepared in its racemic form [13] – was then supposed to serve such purpose. To our surprise, the palladium-catalyzed hydrosilylation of **2** with *rac*-**1b** gave almost perfect diastereoselectivity and good yield (*rac*-**1b** → *rac*-**3b**, Scheme 1).

This unexpected result inevitably introduced the pivotal question whether conformational rigidity of chiral silanes is a dispensable characteristic for asymmetric transformations. Thus, we subsequently tested *rac*-**1b** as resolving reagent in the kinetic resolution of an alcohol with a pending nitrogen donor (Scheme 2). In an earlier report, enantiomerically enriched silane **1a** (96% *ee*) was applied in this diastereoselective copper-catalyzed dehydrogenative silicon-oxygen coupling affording promising optical purities for the unreacted alcohol *ent*-**4** (84% *ee*) along with **5** (d.r. = 84:16) at 56% conversion. [9] For the present study, the diastereoselectivity of the formed ethers **5** is conclusive, which, in turn, allows for working with racemic silanes *rac*-**1** (*rac*-**1a** → *rac*-**5a** versus *rac*-**1b** → *rac*-**5b**, Scheme 2). This is sufficient since the d.r. of **5** will be identical to the e.r. of the remaining alcohol **4** at exactly 50% conversion when using enantiopure silane **1**. It must be noted that that diastereoselectivity is not dependent on conversion when using racemic silanes *rac*-**1**; conversely, using enantioenriched **1** it is.

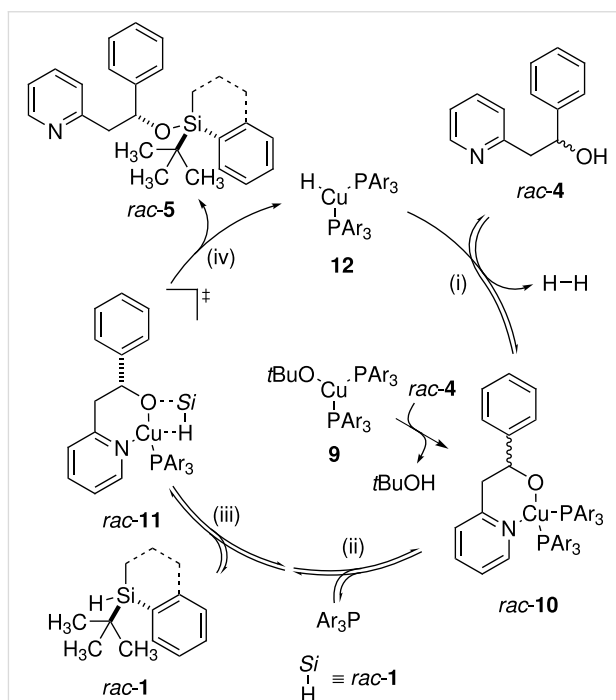
Whereas *rac*-**5a** was formed highly diastereoselectively (d.r. = 92:8) at 50% conversion, [9] the analogous reaction of *rac*-**1b** yielded *rac*-**5b** in a poor diastereomeric ratio (d.r. = 59:41) at comparable conversion. In sharp contrast to the results obtained in the hydrosilylation, embedding the asymmetrically substituted silicon into a cyclic framework appears to be an essential feature.



Scheme 1: Cyclic and acyclic chiral silanes as potent reagents for the silicon-to-carbon chirality transfer.



A comparison of the mechanisms of each reaction might serve as an explanation for this unexpected divergence. As outlined in Scheme 3, the hydrosilylation proceeds via a three-step catalytic cycle: (i) Reversible coordination of cationic silyl palladium species **6** by the alkene **2** (**6** \rightarrow **7**), followed by (ii) fast and reversible migratory insertion forming β -silyl alkyl palladium intermediate **8** (**7** \rightarrow **8**), and (iii) the involvement of a second silane moiety in the irreversible σ -bond metathesis. [10, 16] Recent results clearly indicate step (ii) as diastereoselectivity-determining, revealing a thermodynamically controlled, reversible but highly diastereoselective migratory insertion step. [10]



A different scenario might apply to the copper-catalyzed kinetic resolution of alcohols (Scheme 4). The phosphine-stabilized copper hydride **12** [17] is likely to be the catalytically active species, which is generated by alkoxide exchange (**9** \rightarrow **10**) followed by a single catalytic turnover. The actual catalytic cycle then proceeds in a four-step propagation: (i) Coordination of pyridyl alcohol *rac-4* accompanied by liberation of dihydrogen (**12** \rightarrow **10**), (ii) rate-limiting dissociation of one

phosphine ligand to generate a free coordination site, [18] (iii) coordination of the weakly donating chiral silane (**10** → **11**), followed by (iv) an exothermic and irreversible σ -bond metathesis [19] establishing the silicon-oxygen linkage in **5** and regenerating copper hydride **12** after coordination of another phosphine ligand (**11** → **12**). With steps (ii) and (iii) being reversible and chelate **10** being capable of alkoxide exchange, that is exchange of the optical antipodes of **4**, one enantiomer of **4** is preferentially funnelled out via diastereomeric transition states (**11** → **12**).

There is one major difference between the diastereoselectivity-determining steps in these catalytic cycles: (ii) in Scheme 3 and (iv) in Scheme 4. In the migratory insertion (ii, **7** → **8**), carbon-silicon bond formation occurs between the stereogenic silicon and the prochiral carbon therefore entailing their close proximity. The newly formed stereogenic carbon is directly connected to the former source of chiral information. In contrast, the decisive asymmetrically substituted carbon atom in the alcohol substrate is more remote from the stereoselectivity-controlling silicon moiety in the silicon-oxygen bond formation (iv, **11** → **5**). The stereogenic carbon in the alcohol is not directly involved in the actual bond formation. This mechanistic picture might account for the more demanding requirements to chiral silane **1**: A cyclic framework leading to a locked conformation [11] improving the degree of organization in the stereochemistry-determining transition state **11**.

In summary, we have shown for the first time that an excellent chirality transfer from silicon to carbon is also realized with suitably substituted acyclic silanes such as **1b**. Our survey, however, underscores once more that cyclic silane **1a** is a privileged structure and certainly generally more applicable to catalytic asymmetric processes than **1b**. The current mechanistic pictures provide a rather simple explanation for the observed stereochemical outcome of both diastereoselective carbon-silicon and silicon-oxygen bond formation. Based on this insight, further research will be devoted to the extension of chiral silicon-based asymmetric catalysis.

Supporting Information

Supporting Information File 1

Supporting Information. Experimental procedures and characterization data for all new compounds described in this manuscript.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-3-9-S1.doc>]

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Allylsilanes in the synthesis of three to seven membered rings: the silylcuprate strategy

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Review

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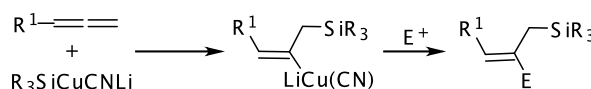
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Abstract

Addition of low order phenyldimethylsilylcyanocuprates to allenes followed by "*in situ*" reaction of the intermediate silylcuprate with electrophiles ("the silylcuprate strategy") provides new routes for the synthesis of functionalised allylsilanes, which undergo highly stereocontrolled silicon-assisted intramolecular cyclizations leading to three to seven membered ring-formation.

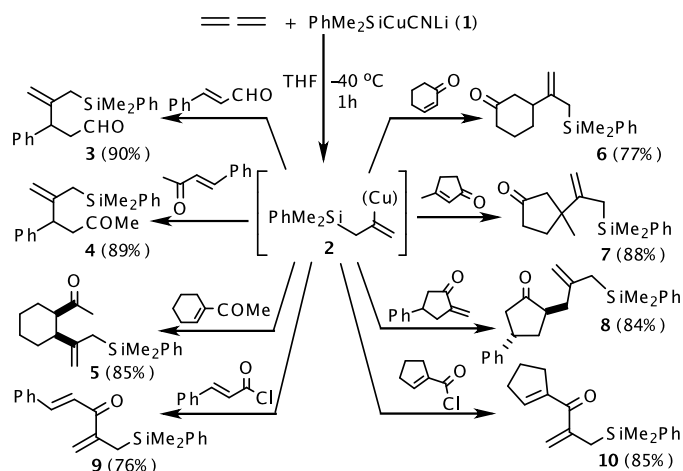
Background

Organosilicon compounds and in particular allylsilanes have attracted considerable attention due to the increasing number of new methodologies that allow useful synthetic transformations. [1,2] Over the last decade allenes have emerged as one of the best sources for the synthesis of allylsilanes. [3] Although unactivated allenes do not easily undergo organometallic addition – and do not react with carbocuprates – they are readily attacked by metalocuprates. [4] In particular, simple allenes react with silylcuprates and stannylcuprates giving rise to a great variety of allyl- and vinylsilanes and stannanes with different substitution patterns. [5,6] The stoichiometry of the silylcuprate (higher or lower order) is responsible for the final regioselectivity of the reaction, leading selectively to allylsilanes when a lower order cyanosilylcuprate ($R_3SiCuCNLi$) is used. [7] Moreover, the high reactivity of the intermediate allylsilane-vinylcuprate species toward electrophiles increases their synthetic potential (Scheme 1). [7,8]



Scheme 1: The silylcupration of allenes.

A large number of electrophiles (alkyl and allyl halides, epoxides, ketones, α,β -unsaturated oxo compounds and acid chlorides, unsaturated nitriles and imines) have been successfully used in this reaction, leading to a wide range of functionalised allylsilanes, which are valuable intermediates for carbocyclic annulations. Effectively, the former substrates (containing a nucleophilic allylsilane unit and an electrophilic function) undergo "*intramolecular allylsilane terminated*" cyclizations when treated with Lewis acid, affording cyclic structures of different size.



Scheme 2: Silylcupration of 1,2-propadiene and reaction with oxo compounds.

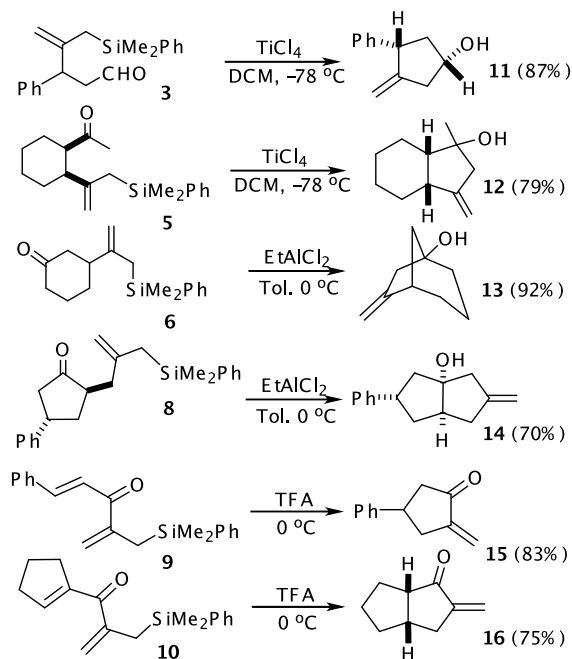
In this account, we show a general survey of the recent advances in allylsilane chemistry and their significance as precursors for the synthesis of three to seven membered rings. We also highlight the contribution of our group to this field.

Five and Six Membered Carbocycles

Phenyldimethylsilylcyanocuprate **1**, prepared by mixing one equivalent of phenyldimethylsilyllithium and one equivalent of copper(I) cyanide, reacts with 1,2-propadiene (bubbled from lecture bottles) at -40°C leading to the intermediate copper species **2**, which on quenching with D_2O undergoes deuterio-decupration introducing deuterium exclusively in the vinylic position C-2. As mentioned in the introduction, the use of lower order cuprates such as silylcyanocuprate **1** leads selectively to allylsilanes. Trapping of the intermediate vinylcuprate **2** with α,β -unsaturated oxo compounds provides an easy entry to the synthesis of oxoallylsilanes **3–8** which are useful synthons for cyclopentane annulations (Scheme 2). [7,9] Acid chlorides react with **2** affording divinyl ketones **9–10**.

Allylsilanes **3–8** carrying an electrophilic carbonyl moiety readily undergo intramolecular cyclization under Lewis acid catalysis. [10] Thus, silicon assisted cyclization of oxoallylsilanes **3–8** in the presence of TiCl_4 or EtAlCl_2 results in the formation of 3-methylene-1-cyclopentanol **11–14** with a high degree of stereocontrol (Scheme 3). [7] The *cis* stereochemistry observed in **11** might indicate a preference for a transition state where the bulky groups attain an equatorial conformation for minimal repulsions. Moreover, the reaction shows a high level of stereoselectivity in the formation of fused bicyclopentanol. Cyclization seems to proceed through a classical S_E mechanism involving stabilized carbocations β to silicon (the so-called β -effect). A unique feature of the reaction is the invariable formation of an exocyclic double bond by loss of the silicon

group. The methylenecyclopentanol moiety is present in the skeleton of some naturally occurring terpene families.

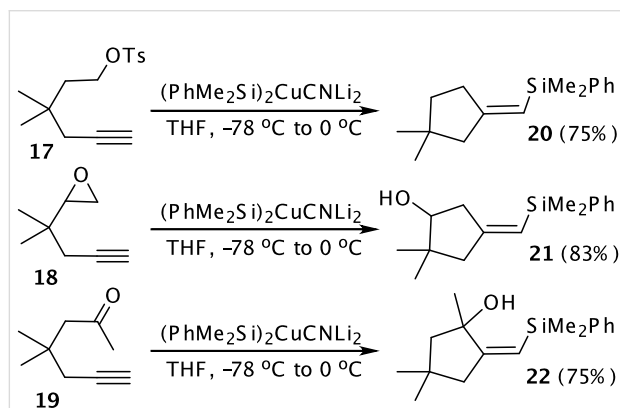


Scheme 3: Silicon assisted cyclization of oxoallylsilanes.

Recent work has shown that the nature of the silyl group may cause important modifications in the mechanism pathway and therefore may change the final outcome. This is the case of analogous allylsilanes bearing the bulky *t*-butyldiphenylsilyl group, which give 3-cyclopenten-1-ols maintaining the hindered silyl group. [11,12]

The reaction between **2** and α,β -unsaturated acid chlorides provides an easy approach to silylated divinyl ketones **9–10** (Scheme 2), which are excellent precursors for silicon-directed Nazarov cyclizations. Acid catalysed electrocyclic closure (TFA, 0–20°C) allows the formation of exocyclic 2-methylene-cyclopentan-1-ones **15–16** (Scheme 3), which are not easily prepared by classical methods, and for which few methods of synthesis have been reported in the literature. [7,13]

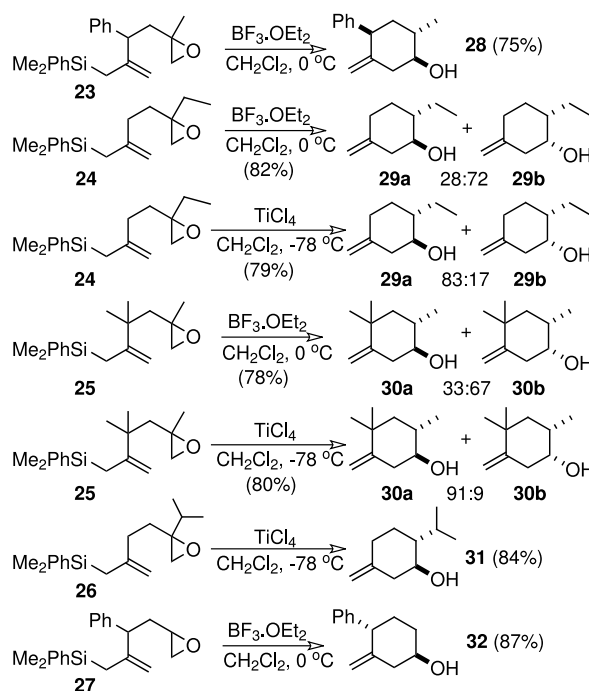
Silylcupration of acetylenes is also a powerful tool for cyclopentane annulations. Terminal alkynes **17–19** bearing electron-withdrawing groups in appropriate positions undergo silylcupration-ring formation, when treated with higher order cyanocuprates as $(\text{PhMe}_2\text{Si})_2\text{CuCNLi}_2$. Intramolecular trapping of the vinylcuprate intermediate allows the synthesis of methylenecyclopentanes **20–22** (Scheme 4). [14]



Scheme 4: Silylcupration of terminal alkynes bearing electron-withdrawing functions.

Epoxidation of the oxoallylsilanes obtained from the "silylcuprate methodology" provides a rapid access to epoxyallylsilanes. Thus, capture of intermediate **2** with enones and later treatment with sulfur ylides afford the epoxyallylsilanes **23–27** (Scheme 5). Despite its synthetic potential, the cyclization of epoxyallylsilanes has not been widely reported. Although Baldwin's rules predict that 5-*exo* attack, leading to cyclopentanol, is favoured over 6-*endo* attack, none of the former cyclization mode is observed when epoxyallylsilanes **23–27** are submitted to Lewis acidic conditions. Instead of this, a rearrangement-cyclization process, giving rise to 3-methylene-cyclohexan-1-ols **28–32**, is observed when reaction is carried out in the presence of BF_3 or TiCl_4 (Scheme 5). [15]

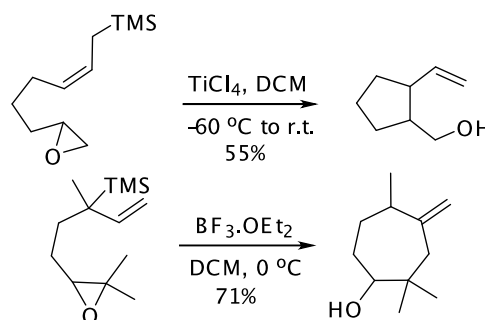
The diastereoselectivity of the reaction depends on the Lewis acid used. Boron and aluminum-based catalysts show a preference for the *cis* isomer (**29b** and **30b**) whereas TiCl_4 gives almost exclusively *trans* isomers (**29a** and **30a**). According to



Scheme 5: The acid-catalyzed cyclization of epoxyallylsilanes.

Schlosser, the preference for the *cis* isomer, when BF_3 is used, might be due to the countercurrent flow of electrons in the $\text{Csp}^2\text{-C(Si)}$ and C=O bonds, which is favoured when these structural elements are aligned parallel. [16]

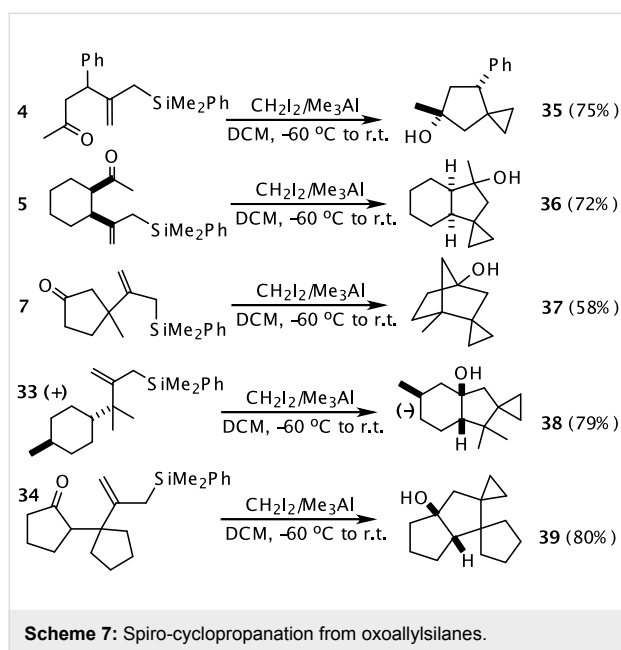
Cyclization of epoxyallylsilanes containing the bulky *t*-butyldiphenylsilyl group takes place without loss of silicon giving cyclohexenols bearing the *t*-butyldiphenylsilyl group. [17] By contrast, the behaviour reported in the bibliography for trimethylsilyl epoxyallylsilanes is frequently different from that observed for phenyldimethylsilyl epoxyallylsilanes of type **23**, giving nucleophilic substitution at the most substituted carbon of the epoxide (Scheme 6). [18,19]



Scheme 6: Intramolecular cyclization of TMS-epoxyallylsilanes.

Three and Four Membered Carbocycles

Oxoallylsilanes **4–7**, **33** and **34**, readily available *via* silylcuprate addition of **2** to enones, react with $\text{CH}_2\text{I}_2/\text{Me}_3\text{Al}$ at low temperature (-60°C to room temperature, then 48 h at r.t.) giving spiro-cyclopropanes **35–39** containing the spiro[2,4]heptanol moiety (Scheme 7). [20] High levels of stereoselectivity were found in all the examples studied. Formation of the spirocycle proceeds by a two-step pathway involving firstly, Me_3Al -catalysed intramolecular cyclization of the oxoallylsilane and subsequent formation of a methylenecyclopentanolate, and then cyclopropanation. This unique mechanism enables the construction of hydroxylated bi-tri- and tetra-cyclic skeletons, bearing the spiro-cyclopropane moiety, from open chain allylsilanes in just one step. The high stereocontrol associated to the ring formation allows the synthesis of enantiomerically pure spiro-tricyclic alcohols containing an angular OH-group, such as **38** (Scheme 7). [20]

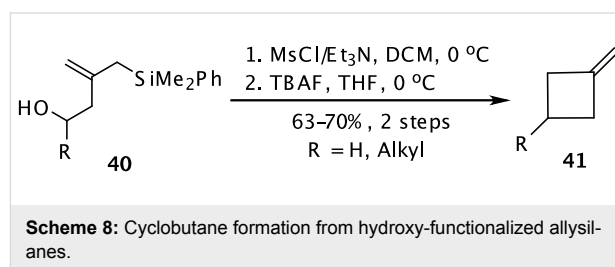


The use of reagents different from organoaluminum compounds resulted in poor efficiency and low stereoselectivity. For example, the Simmons-Smith reagent or the Furukawa modification ($\text{Et}_2\text{Zn}/\text{CH}_2\text{I}_2$) is much less effective than the reported procedure. [21]

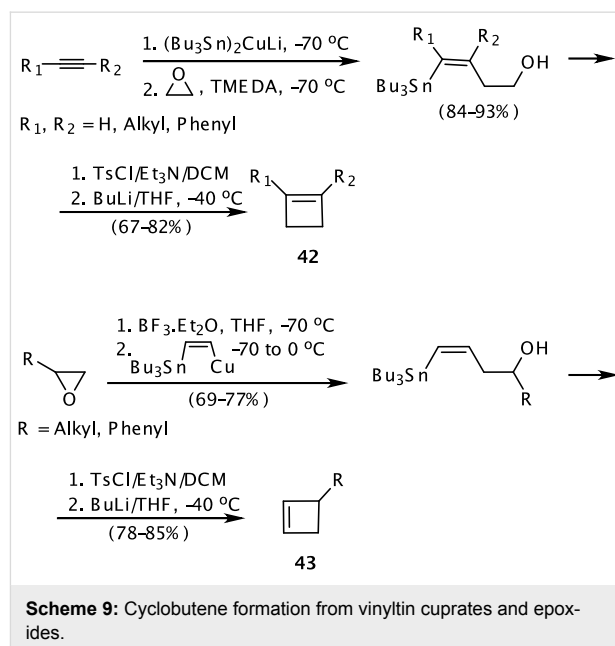
Unfortunately, this route cannot be used to synthesize spiro[2,5]octanes from epoxyallylsilanes of the type **23**, due to the high reactivity of the epoxide group towards Me_3Al , the latter giving $\text{S}_\text{N}1$ attack resulting in the formation of methyl alcohols to a great extent. Future work will show if cyclopropanating reagents with a weaker Lewis acid character can be appropriate to direct the reaction toward the synthesis of spiro[2,5]octanes,

an structural moiety of interest in the synthesis of natural products.

Alcohols as **40** containing an allylsilane unit, which can be readily obtained by reaction of epoxides with the silylcuprate **2**, are excellent synthons for cyclobutane ring-formation. Formation of the corresponding mesylate and fluoride-induced intramolecular displacement led to methylenecyclobutanes **41** in good yields (Scheme 8). [22]



A different approach, starting from acetylenes instead of allenes and using silyl- or stannylcuprates followed by addition of an epoxide as electrophile, led to substituted cyclobutenes after cyclization of the vinylsilane or vinylstannane intermediate. [23] Cyclization of the corresponding vinylsilanes gave poor results of no synthetic utility, however the vinylstannane strategy results in formation of 1- and 3-substituted cyclobutenes **42** and **43** in good yield (Scheme 9).

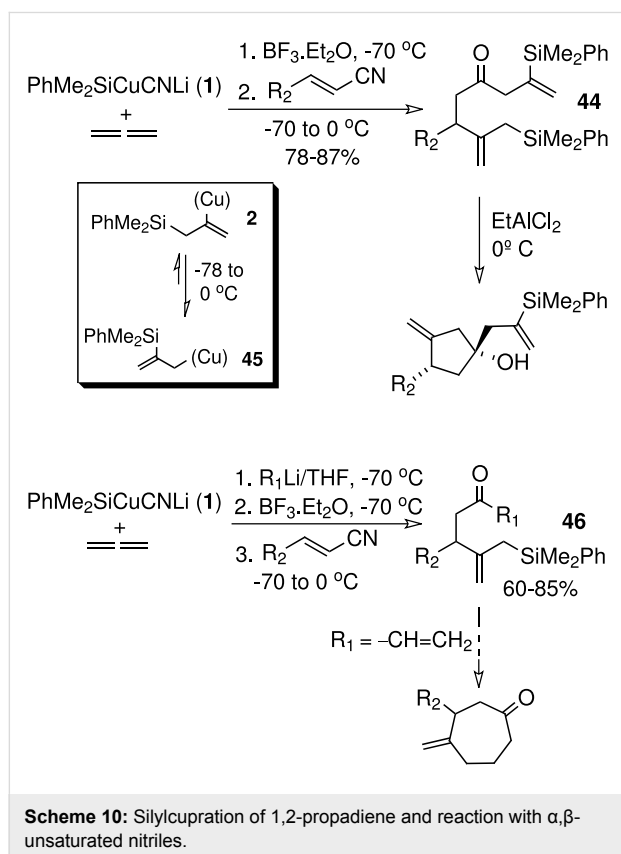


As shown in Scheme 9, the strategy employed allows the selective formation of 1- or 3-substituted derivatives, where the coupling of a C_2 acetylenic synthon and a C_2 epoxide synthon

provides a new and useful [2+2] annulation strategy for the preparation of the strained cyclobutene ring. The key step is the *syn* addition of the tin cuprate to the acetylene, which controls the *cis* stereochemistry required for cyclization. [23]

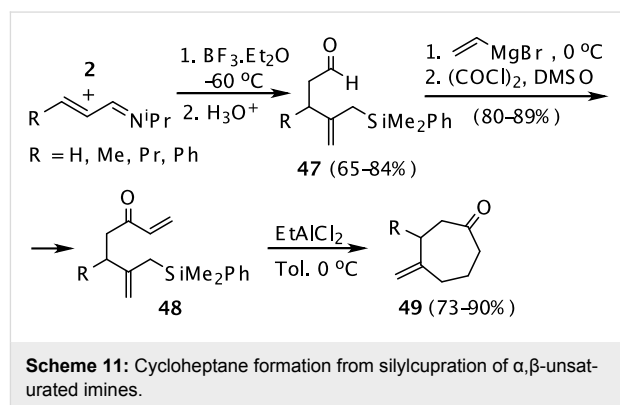
Seven Membered Carbocycles

The use of nitriles and imines as electrophiles in the silylcupration of allene provides new alternatives for carbocyclization. Recently, we showed that α,β -unsaturated nitriles undergo a double addition process when treated with the cuprate species resulting from addition of **1** to allene, giving ketones **44** containing both an allylsilane group and a vinylsilane moiety (Scheme 10). [24] Equilibration between species **2** and **45** as the temperature rises from -70°C to 0°C must be the explanation for this surprising result. Whatever is the reason, this tandem process allows the introduction of two silylated functions, which display a markedly different reactivity. Effectively, allylsilane terminated cyclization, in the same conditions as before (see Scheme 3), gives chemoselectively methylenecyclopentanols, while the vinylsilane unit remains unchanged (Scheme 10). [24] Recent work revealed that addition one equivalent of organolithium reagent (R_1Li) to the reaction mixture leads to the formation of ketones of type **46** (Scheme 10), which result from the addition of the two organometallic species present in the solution (silylcuprate and R_1Li).

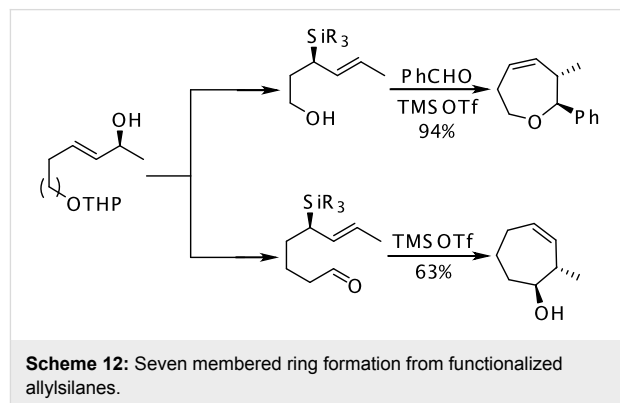


When R_1Li is an alkenyllithium this reaction opens new alternatives for preparation of 7-membered rings by intramolecular Michael addition of the allylsilane group to the enone (Scheme 10).

Similarly, silylcupration of imines [25] provides a simple and efficient route for the preparation of seven membered carbocycles with different substitution patterns. Thus, reaction of **2** with α,β -unsaturated imines, at low temperature, affords allylsilane-containing aldehydes **47**, which upon addition of vinylmagnesium bromide followed by Swern oxidation lead to enones **48**. Lewis acid catalysed cyclization of **48** gives methylenecycloheptanones **49** in high yield (Scheme 11). [25] Consequently, oxoallylsilanes **47** can be considered as useful precursors for cycloheptane annulation. Moreover, the presence of an exocyclic double bond joined to the cycloheptanone core is a structural feature very common in many naturally occurring terpenes (Scheme 11).



Other allylsilane-based strategies have been recently developed to build up cycloheptane derivatives. Thus, the synthesis of seven membered hydroxycycloalkenes and oxacycloalkenes has been achieved by intramolecular cyclization of functionalised allylsilanes obtained from optically active allylic alcohols (Scheme 12). [26]



Conclusion

In summary, the metallocupration (Si-Cu and Sn-Cu) of allenes and acetylenes has proven to be extremely useful for the construction of cyclic structures ranging from three to seven membered rings, through processes which imply addition of the intermediate silylcuprate to an electrophile (enone, epoxide, nitrile, imine, etc) followed by Lewis-acid catalysed intramolecular cyclization, where the electrophile used determines the type of process and the size of the ring.

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The use of silicon-based tethers for the Pauson-Khand reaction

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Preliminary Communication

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Abstract

A range of silicon-based tethers and promoters have been investigated for use in the development of a silyl-tethered Pauson-Khand reaction.

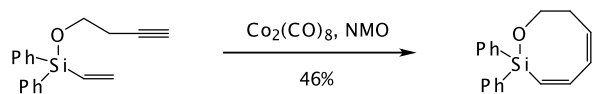
Background

Since its discovery in 1973, the Pauson-Khand (P-K) reaction has become one of the principal methods for the construction of cyclopentenones.[1,2]

Temporary tethers have long been used to convert an intermolecular reaction to an intramolecular one and thus favour reaction. Silicon is by far the most popular choice of element when considering forming a temporary tether to link two reaction components.[3] This popularity is due to several factors. First, the acyclic silicon containing chains are simple to synthesise, such as through the formation of either silyl ethers or acetals, may contain a wide range of functionalities and are stable to a range of different reaction conditions and purification techniques. Second, the silicon tethers remain inert in most

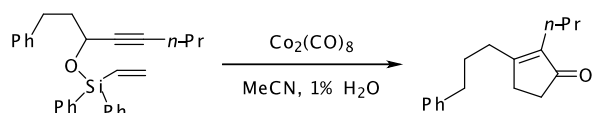
reactions but they can be easily and selectively removed using fluoride containing compounds, such as tetrabutylammonium fluoride (TBAF), or by using the Tamao-Fleming oxidation procedure. In addition, the silicon may also be used simultaneously to protect functionalities during the reaction sequences. Recent examples of the use of silicon-containing tethers have centred upon the Diels-Alder reaction,[4,5] radical reactions[6] and olefin metathesis reactions.

There have been reports of applying the temporary tethering methodology of silicon species to the P-K reaction, but with limited success. Saigo reported that the attempted P-K cyclisation of a variety of 3-sila-1,7-enynes underwent cycloisomerisation instead of the cycloaddition (Scheme 1).[7]



Scheme 1: Saigo's cycloisomerisation reaction under Pauson-Khand conditions.

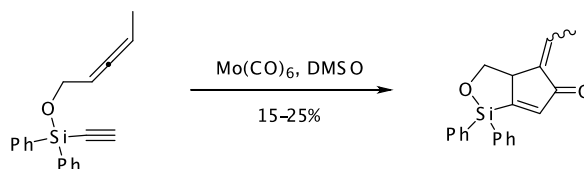
Saigo's work showed that this cycloisomerisation was only applicable to 3-sila-1,7-enynes and any other chain length would undergo decomposition. Pagenkopf has shown that when the P-K cyclisation is carried out in 'wet' acetonitrile the cyclisation would proceed to give the cyclopentenones (Scheme 2).[8, 9] The tethering strategy was not however successful in that although cyclisation gave the correct regiochemistry, the silicon tether is cleaved from the molecule by the reaction conditions and leaves no functionality for further synthetic modifications.



Scheme 2: Pauson-Khand reaction and tether-cleavage in wet acetonitrile.

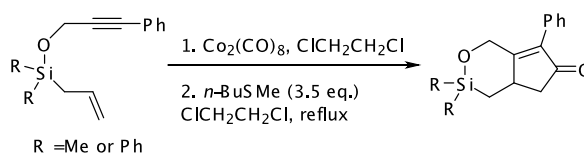
There are only two examples of silicon tethers being successfully applied to a Pauson-Khand type reaction. Brummond researched a large variety of potential systems but found that silicon tethers did not seem to be compatible with the Pauson-Khand reaction. Fortunately her research discovered that by combining the silicon tether with the allenic Pauson-Khand reaction mediated by molybdenum hexacarbonyl the corre-

sponding bicyclic cyclopentenone could be formed although with poor yields (Scheme 3).[10,11]



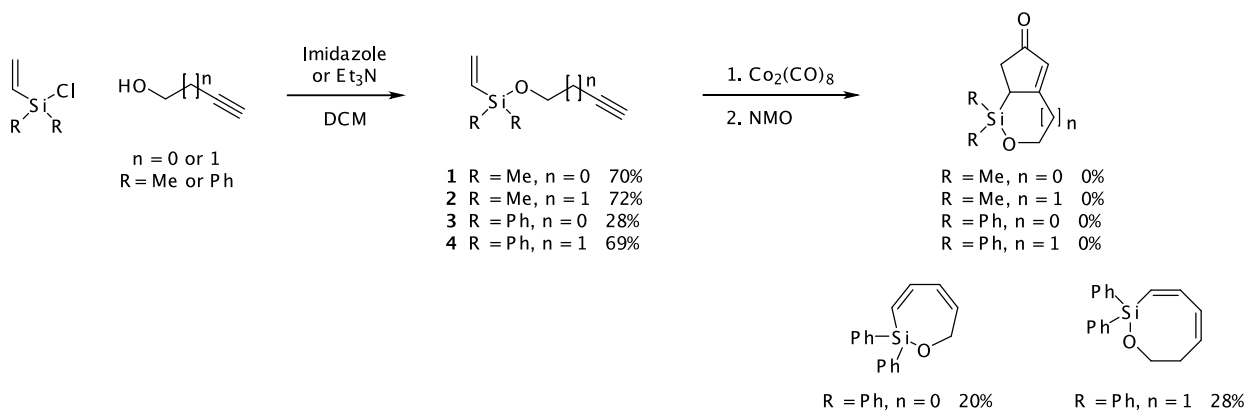
Scheme 3: Silyl-tethered allenic Pauson-Khand reaction reported by Brummond.

Finally, in a recent report, Porter has described the intramolecular Pauson-Khand reaction of allyldimethyl- and allyldiphenylsilyl propargyl ethers promoted by dicobalt octacarbonyl and *n*-butyl methyl sulphide as a promoter to give the bicycles in modest to good yields (Scheme 4).[12]

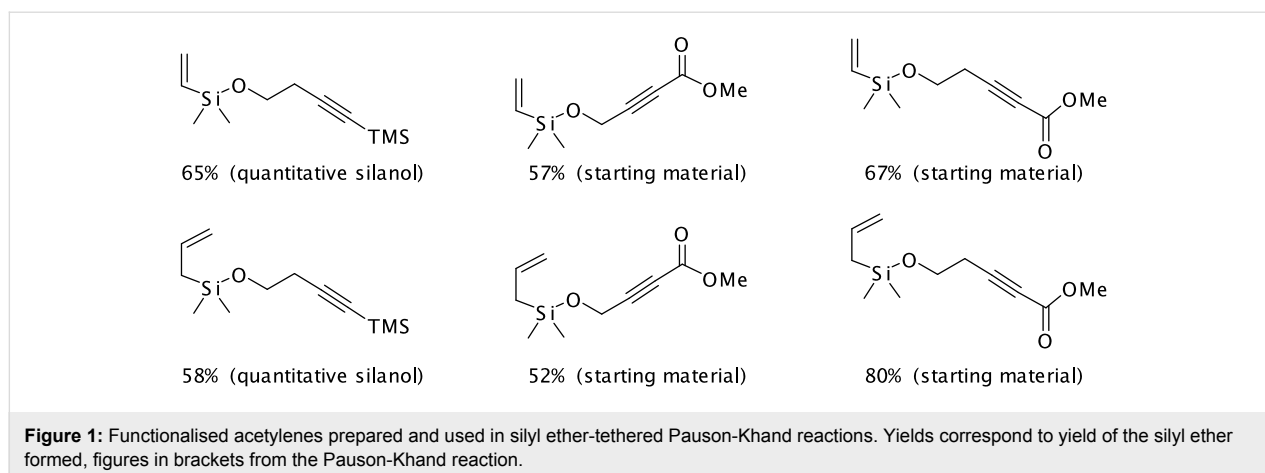


Scheme 4: Intramolecular Pauson-Khand reaction of allyldimethyl- and allyldiphenylsilyl propargyl ethers reported by Porter.

It can be seen that although the silicon methodology has been applied to the P-K reaction no group has been able to combine the synthetic diversity of silicon tethers with the synthetic benefits of the dicobalt octacarbonyl mediated cyclisation of alkynes and alkenes.



Scheme 5: Synthesis and attempted Pauson-Khand reactions of vinyldimethylsilyl- and vinylphenylsilyl ethers.



Results and Discussion

We decided to carry out a thorough investigation of the potential for development of a silicon-tethered Pauson-Khand reaction, using three different types of tether.

i) Silyl ether tethers

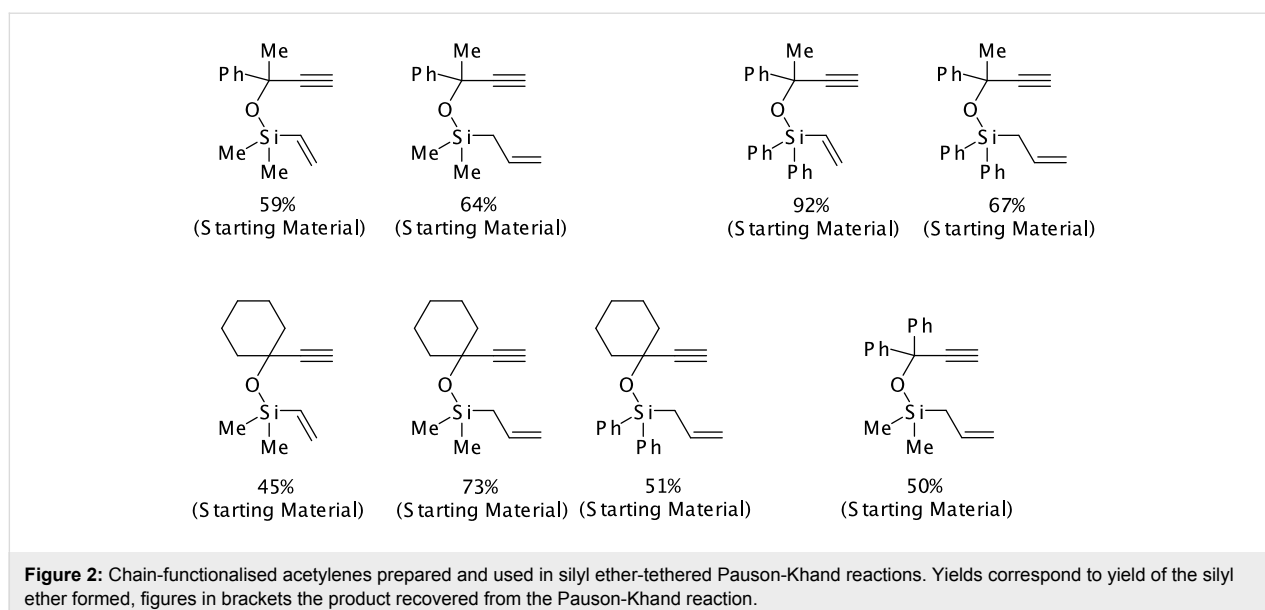
Both vinyltrimethylchlorosilane and vinyltriphenylchlorosilane are commercially available and were chosen as the initial starting materials for this part of the study. A range of silyl ethers were formed, which were then subjected to the 'standard' Pauson-Khand reaction conditions of dicobalt octacarbonyl and *N*-methylmorpholine *N*-oxide.

Although the silyl ethers were formed in good yields, no Pauson-Khand adducts were obtained, only the cycloisomerisation products predicted by Saigo.[7] Repeating the reactions under 1 atm pressure of carbon monoxide also gave only the

isomerisation products, albeit in higher yields and more rapidly. In every example, the main product, accounting for the bulk of the mass balance, were silanols derived from decomposed corresponding silyl ethers.

The P-K reaction is known to be affected by steric and electronic effects within the cyclisation precursors. Therefore we prepared the following dimethyl vinyl- and allyl-silyl ethers with various groups attached to the terminus of the alkyne (Figure 1).[13-15] Once again, all the ethers were formed in good yields, but unfortunately either the silanol or starting materials were recovered in each case, as indicated, from the Pauson-Khand reaction.

Fearing that the lack of cyclisation may have been due to the two arms of the tether simply not coming together, substituents were introduced to the tether chains, in an attempt to produce a



Thorpe-Ingold-type effect and force the two ends of the chain together (Figure 2).

There now exist a plethora both of alternative metal carbonyls and promoters for the Pauson Khand reaction. Using each of the compounds **1–4**, we first tested five alternative promoters to NMO. These were cyclohexylamine[16]; 1,4-dioxane/2M ammonium hydroxide[17]; trimethylamine *N*-oxide, 4 molecular sieves[18]; *n*-butylmethylsulfide[19] and microwave irradiation[20]. As previously, the dicobalt octacarbonyl complexes of each compound were first prepared and characterised, prior to addition of the promoter. Unfortunately, none of the promoters gave any of the desired products but simply de-complexed starting materials were recovered in each case.

Alternative metal carbonyls were also investigated, with compounds **1–4** being reacted with each of molybdenum hexacarbonyl/DMSO[21]; tungsten pentacarbonyl/THF[22]; chromium hexacarbonyl and rhodium cyclooctadiene chloride dimer/pentafluorobenzaldehyde[23,24]. None of the promoters gave any Pauson-Khand adducts, although an interesting THF-insertion adduct was obtained from the reaction of allyldimethylpent-4-ynyloxysilane with tungsten pentacarbonyl, possibly formed *via* oxidation of THF to give an oxonium ion followed by addition of the alcohol cleaved from the silyl ether (Figure 3).

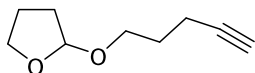
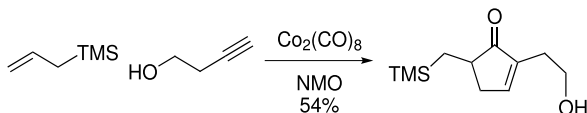


Figure 3: Possible structure of THF-oxidation/insertion product.

In order to investigate if the presence of the silicon linker was preventing the Pauson-Khand reaction occurring, a test reaction between allyltrimethylsilane and 3-butyne-1-ol was performed using dicobalt octacarbonyl and NMO (Scheme 6). A mixture of cyclopentenone regioisomeric isomers were obtained, with the principal regioisomer being the one shown in Scheme 6.

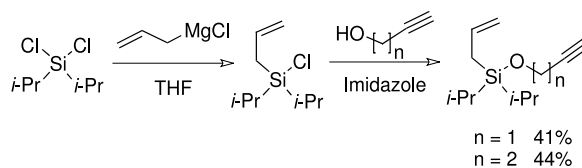


Scheme 6: Model Pauson-Khand reaction of allyltrimethylsilane.

One possible explanation for the failure of all these reactions was that the 'arms' of the silyl ethers were too far apart for

cyclisation to occur. We had already attempted to overcome this potential hurdle by the introduction of functionality within the side chains. Work by Denmark[25] on tethered nitron cycloadditions has shown that for cycloaddition reactions to occur, the non-reactive substituents around the silicon centre must be more bulky than the Me or Ph groups employed in these studies. Denmark's work demonstrated that the angles at the silicon centre between the two 'arms' of the silyl ether can be up to 180°. This large angle would mean that the 'arms' would never be close enough together to undergo cycloaddition. Therefore the angle must be decreased and this can be accomplished by increasing the size of the non-reactive substituents as stated by the Thorpe-Ingold effect. Denmark stated that the substituents on silicon should either be two *isopropyl* or two *tert*-butyl groups in order to achieve reaction. *Diter*tbutyl silanes were found to be impractical because vinyl- or allyl*di*tertbutyl chlorosilanes will not undergo nucleophilic substitution to yield the silyl ethers due to the large steric crowding, preventing the formation of the penta coordinate intermediates. However, *diisopropyl*silanes were successful in Denmark's studies.

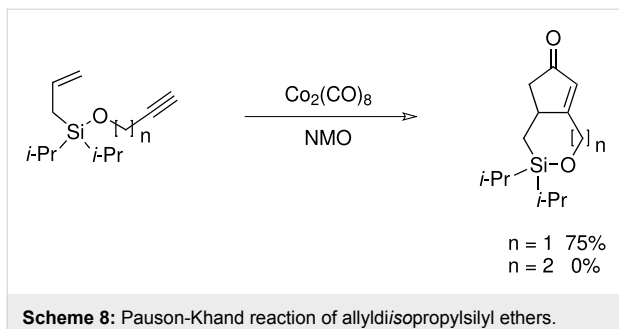
The preparation of *diisopropyl* silyl ethers presented a greater synthetic challenge than the previous silyl ethers. Starting from *diisopropyl*dichlorosilane, a two-step, one-pot procedure was developed, initially adding the allyl arm *via* the allyl Grignard reagent, followed by a more standard silyl ether formation using an acetylenic alcohol and imidazole (without isolating the intermediate silyl chloride). (Isolation of the intermediate *diisopropyl*allylsilyl chloride was impossible, since any attempt to work-up the Grignard reaction resulted in hydrolysis of the silyl chloride to the allyl*diisopropyl*silanol).



Scheme 7: Preparation of allyldiisopropylsilyl ethers.

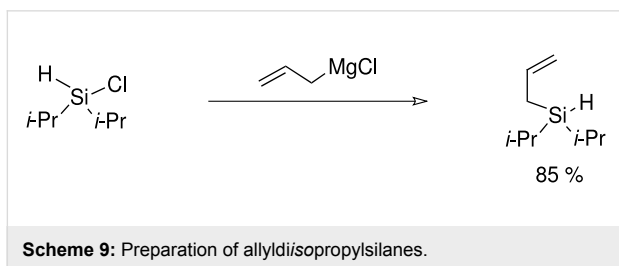
The cyclisation of these two materials was then performed using the standard Pauson-Khand reactions that had previously been successful in our model studies – dicobalt octacarbonyl and NMO.

Under these conditions, a very pleasing 75% yield was obtained for the fused 6,5-ring system ($n = 1$). This is the first example of a *diisopropyl*silyl ether-tethered Pauson-Khand reaction successfully taking place. See Supporting Information File 1 for full experimental details. Unfortunately, no reaction product



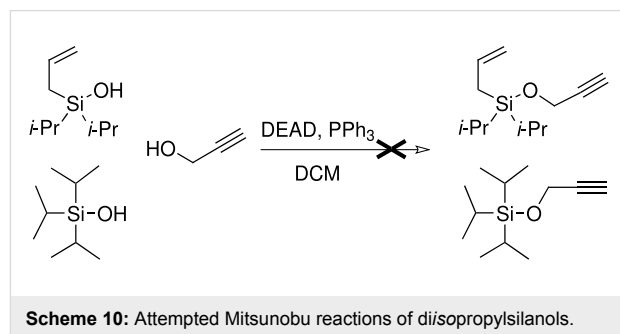
was obtained for the 5,7-ring system ($n = 2$), although this is not quite so surprising, given the general difficulty in forming 5,7-bicyclic systems.[26]

Efforts to prepare further, more substituted allyldiisopropyl silyl ethers by this two-step, one-pot procedure failed to give cyclisation precursors in any appreciable yield and not sufficient for use in the Pauson-Khand reaction. The previous method had shown that the Grignard addition to a dichlorosilane had worked well but that the work-up had hydrolysed the remaining silyl chloride bond. Therefore replacing the second chlorine atom with a group that could not be hydrolysed would allow the work-up and isolation of the products after the Grignard addition had taken place. Due to the restricted number of chlorodiisopropylsilanes available meant that this group had to be a proton. Therefore it was decided to start this new methodology from chlorodiisopropylsilane.



The synthesis of allyldiisopropylsilane proceeded easily and with high yield. Next a variety of methods were attempted for the conversion of the silicon-hydrogen bond to a silicon-chloride bond: chlorine in carbon tetrachloride; copper (II) chloride and Hunig's base; tin (IV) chloride[27] and *N*-bromosuccinimide[28] were all tested but none were successful as either no reaction occurred or the alkene was halogenated as well as the conversion of the silane to the silyl chloride. Further, given that the major product from many of the methods attempted both for the formation of the silyl ethers and from the Pauson-Khand reaction were the corresponding silanols, we wondered if it would be possible to use these compounds for the preparation of our desired ethers *via* a Mitsunobu reaction.

There are examples in the chemical literature in which silanols may be used analogously to alcohols in the Mitsunobu reaction.[29] Unfortunately, neither triisopropylsilanol (synthesised by the hydrolysis of commercially available triisopropylsilyl chloride) or diisopropyl(1-methylallyl)-silanol and but-2-enyldiisopropylsilanol gave any product and quantitative starting materials were recovered (Scheme 10).

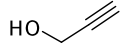
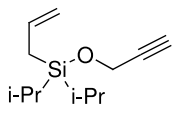
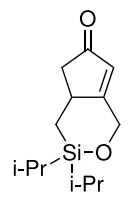
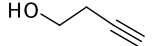
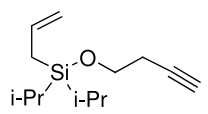
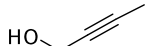
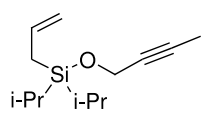
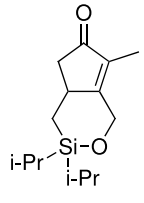
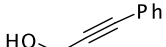
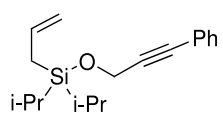
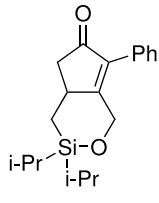

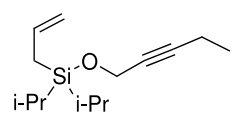
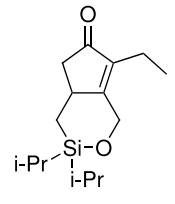

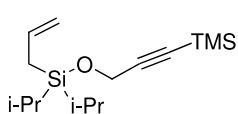

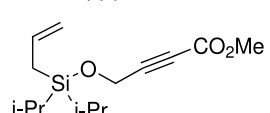
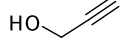
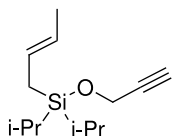
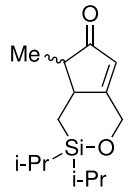
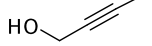
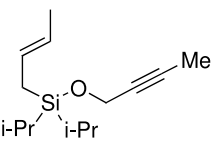
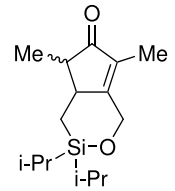


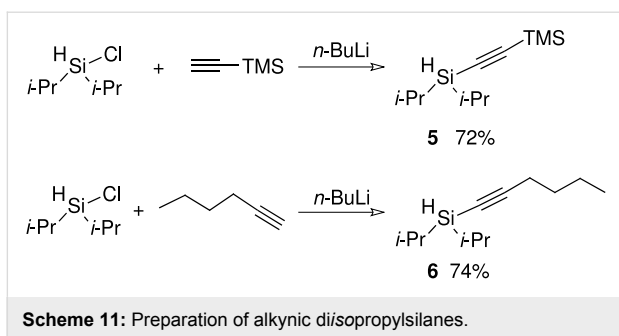
Following the failure of the different methods of forming the silyl ethers it was decided to find a procedure for the direct conversion of the easily synthesised allyldiisopropylsilane to the silyl ethers. The first reaction used a neat mixture of the silane and alcohol with the addition of a catalytic amount of Wilkinson's catalyst.[30] A test reaction using this procedure was carried out to couple allyldiisopropylsilane and propargyl alcohol, but the formation of the silyl ether did not occur and the starting materials were recovered in quantitative amounts.

The second method involved dissolving the silane and alcohol in *N*-methylpyrrolidinone (NMP) followed by the addition of a catalytic amount of a 1 M solution of tetrabutylammonium fluoride (TBAF) in THF.[31] This proved to be successful and a number of different alcohols were tried and the results, together with those from the Pauson-Khand reaction are shown in Table 1.

The application of the TBAF catalyst to the formation of silyl ethers showed mixed results. Entries 1–5 proceeded with moderate to good yields. These yields were much better than those obtained from the one-pot synthesis starting from dichlorodiisopropylsilane described previously. These successful reactions used the simple hydroxyl containing alkynes; when these alkynes had more functionalised substituents (entries 6 and 7) the reaction failed. In the case of entry 7 the only compound recovered from the reaction was the allyldiisopropylsilanol. However in the case of the TMS derivatised alkyne, the major product was the de-silylated silyl ether consistent with entry 1. The reaction proved to be very unreliable and the purity of the substrates had to be very high. Impurities, especially water, were thought to interfere with the mech-

Table 1: Diiso propylsilyl ether formation and subsequent Pauson-Khand reactions

	Alcohol	Silyl Ether	Yield (%)	Pauson-Khand Adduct	Yield (%)
1.			41		75
2.			44	-	0
3.			51		46
4.			49		31
5.			44		34
6.			0	-	-
7.			0	-	-
8.			17		Traces
9.			-		0



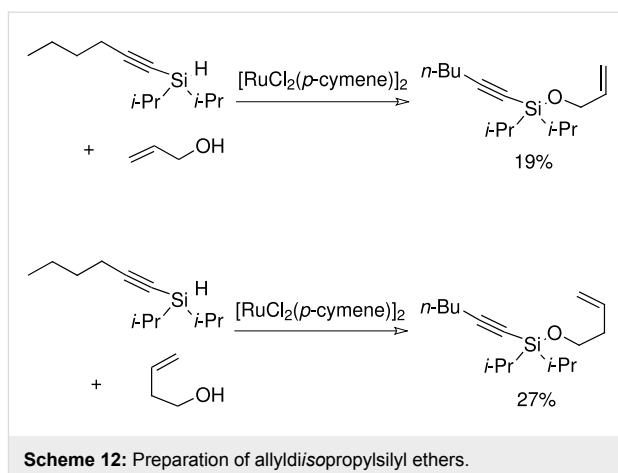
anism of catalysis.

The successfully prepared silyl ethers (Table 1, entries 1–5, 8) were then used as substrates for the P-K cyclisation. The standard conditions, used previously, of one equivalent of dicobalt octacarbonyl and ten equivalents of *N*-methylmorpholine *N*-oxide (NMO) were employed. In all cases except for the longer chain (entry 2) the P-K adduct was obtained in poor to moderate yield. Only traces of product (by GCMS) were observed for entry 8, presumably due to very small scale reaction owing to the poor yield of starting material. The cyclised silyl ether tethered cyclopentenone was again synthesised proving the reaction could be repeated and was not an anomaly. The results for the other silanes did not show the product of the reaction as cyclopentenones. The only identifiable product isolated from any of the other reactions was the silanol associated with hydrolysis of the silicon-oxygen bond. It was impossible to improve on these reaction yields, despite varying the amount of NMO (1, 5 or 10 eq.) and reaction temperature (r.t., 40°C or 80°C).

Finally, it was decided to swap the alkene and alkyne substituents on the silyl ethers around. In order to achieve the formation of these new silyl ethers an alternative methodology had to be applied to both the formation of the silanes and the subsequent formation of the silyl ethers.

Simple deprotonation of the alkyne with *n*-butyllithium and reaction with chlorodiisopropylsilane led to the formation of the desired silanes in good yields.

The formation of the silyl ethers was attempted using the TBAF catalyst procedure that had proven to be successful previously but neither compound gave the desired silyl ethers. GCMS data suggested that the TBAF catalyst had attacked the bond between the TMS group and the alkyne in the case of silane (5) and in the case of silane (6) the reaction had simply not worked, although no clear results were obtained by NMR. It has been shown that a ruthenium catalyst can cause the direct formation of silyl ethers from the silane and an alcohol. The procedure

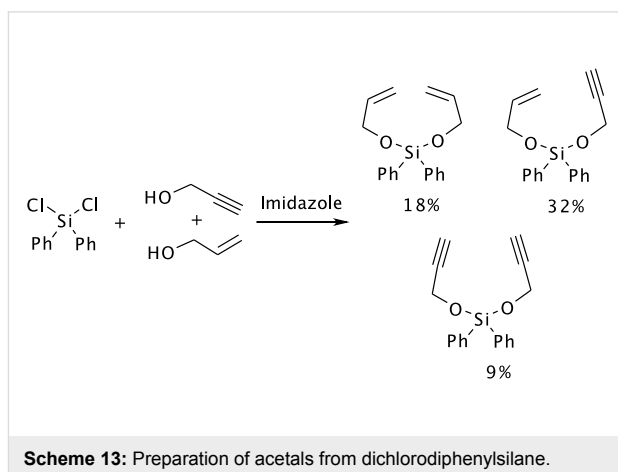


was successful for hex-1-ynyldiisopropylsilane.

The reaction proceeded with low yields but the un-reacted silane was recovered intact at the end of the reaction. The yields for the reactions were significantly below the near quantitative yields reported in the literature but these reactions were never optimised. These two silyl ethers were subjected to the standard P-K reaction conditions. Analysis of the reaction solution showed that cyclisation had not occurred and the only compound recovered was a quantitative amount of the starting material.

ii) Silyl acetal tethers

Although silyl ethers have been the predominant ether of choice, silyl acetals have been applied as temporary tethers in reactions.[32] Silyl acetals have, for example, been applied to any reactions to which silyl ether have been applied, such as radical, Diels Alder reaction or ring closing metathesis, albeit with varying degrees of success. The advantage of silyl acetals over silyl ethers is their greater stability to hydrolysis. The results obtained from the research into silyl ethers suggested

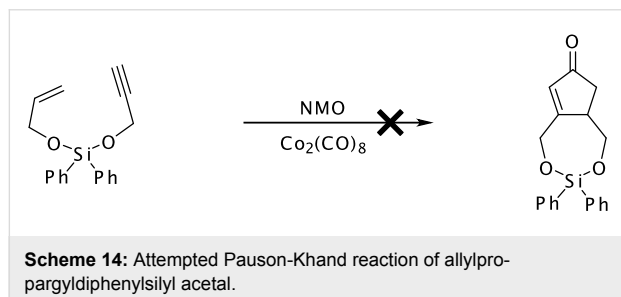


that if, as we believe, hydrolysis was the major problem, this potentially could be overcome using silyl acetals.

First, we attempted to form the required mixed silyl acetal from propargyl and allyl alcohols using diphenyldichlorosilane and imidazole as the base and allowing the reaction to proceed to equilibrium, hopefully allowing for the optimum yield of the mixed acetal.

The result shows that the desired mixed acetal is the major product of the reaction as expected. However, given the similarity in the three products, purification of the acetals by column chromatography proved to be particularly difficult and complete purification could not be achieved (yields given are of pure products obtained; the remaining mass of the reaction could not be completely purified and remained as two mixtures of the acetals).

The cyclisation of the purified mixed acetal was attempted using the standard reaction conditions which had been employed for the successful silyl ether cyclisation reactions (Scheme 14).

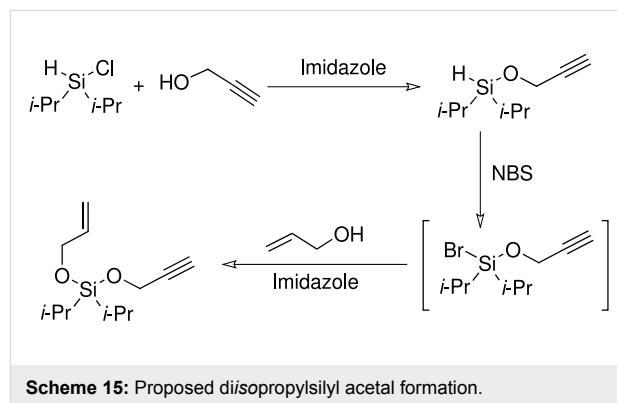


The cyclisation failed to yield any of the bicyclic cyclopentenone predicted. This result is consistent with the literature evidence and our previous results that the 5,7 systems are known not to be synthesised through the cobalt mediated methodology. The unsymmetrical acetal was recovered in near quantitative yield with no trace of any products of decomposition or hydrolysis. Therefore silyl acetal did not undergo hydrolysis thus proving that the silyl acetal is more stable to the P-K reaction conditions than the silyl ethers.

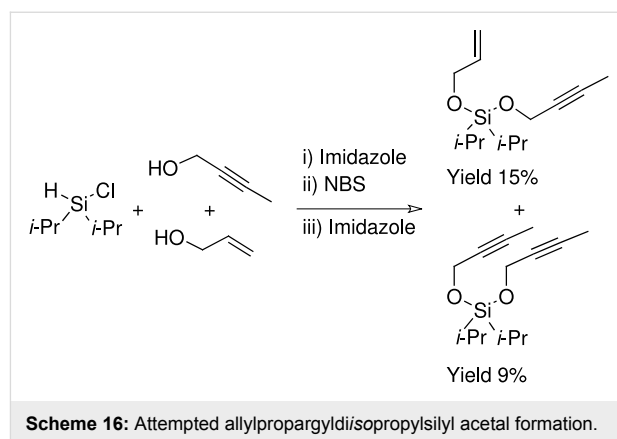
In order to try to achieve cyclisation, the length of each 'arm' of the silyl acetal was increased by 1 carbon unit. It was hoped that the increase in chain lengths would allow the larger ring system (5,9) to be synthesised. This was accomplished by employing 3-butyne-1-ol and 3-buten-1-ol in place of propargyl and allyl alcohol respectively. The same experimental procedure was used and the three acetals were formed in roughly the same ratio as the previous attempt. Unfortunately, on this occasion,

purification by chromatography was completely unable to isolate any of the pure mixed acetal. It was found that the increased chain length had decreased the differences in polarity to such a degree that separation by chromatography was impossible. Purification by distillation proved to be similarly impossible.

Following the work of Denmark and our moderate success in the silyl ether series, it was decided to attempt to use diisopropylsilanes as the base for the acetals. Secondly it was decided to find a methodology that allowed for the formation of only the mixed acetal. In order to achieve this it was thought to form each of the 'arms' of the acetal in separate synthetic steps (Scheme 15).

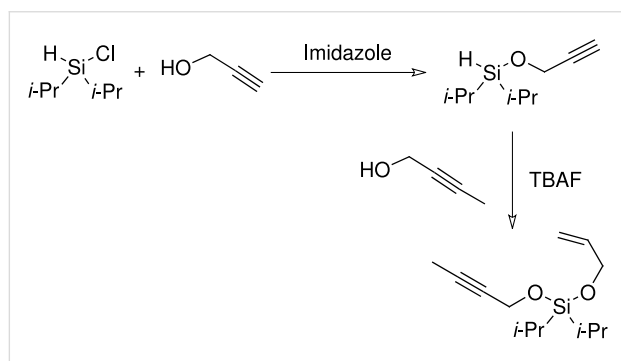


The first stage of the reaction was silyl ether formation. The alkyne 'arm' of the acetal was introduced first, as it was feared that during the next, halogenation step, halogenation of the alkene might occur, if present. This proved to be a successful approach and it was not necessary to purify the first reaction, but simply continue to perform the silyl acetal. The first reaction was attempted using 2-butyne-1-ol and allyl alcohol (Scheme 16).



The result demonstrates that the synthesis of the mixed acetal is successful. However the symmetrical di-alkyne acetal is also formed. This is due to the formation first of the silyl acetal 'arm' not going to completion. Thus after bromination there is still some 2-butyne-1-ol remaining in solution and this reacts with the bromosilane. The low yields could be improved by optimizing the reaction conditions and finding a better way to add the second arm to the acetal, such as a catalytic method, avoiding the need for the bromosilane intermediate. This reaction was repeated using 3-butyne-1-ol to yield the isomeric, terminal alkyne product. However only the symmetrical, di-alkyne acetal was isolated from the reaction mixture and the yield was poor (14%). The poor yield was again due to the bromosilane hydrolysing under the reaction conditions.

The final methodology for synthesising the silyl acetals hoped to combine the silyl ether formation utilised in the NBS procedure with the TBAF methodology which had been so successful for the silyl ethers (Scheme 17).

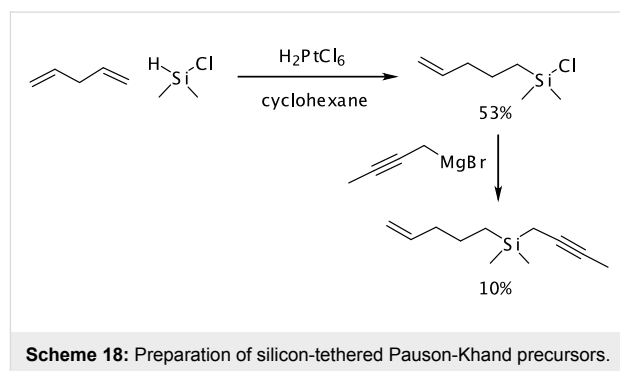


The formation of the alkene 'arm' of the acetal proceeded well using the methodology outlined above. The TBAF catalysed addition of the alkyne 'arm' however did not occur and after the reaction time neither the acetal product or silyl ether intermediate could be isolated. NMR and GCMS studies showed that the TBAF reaction had caused decomposition of the silyl ether intermediate but the decomposition products could not be isolated or identified.

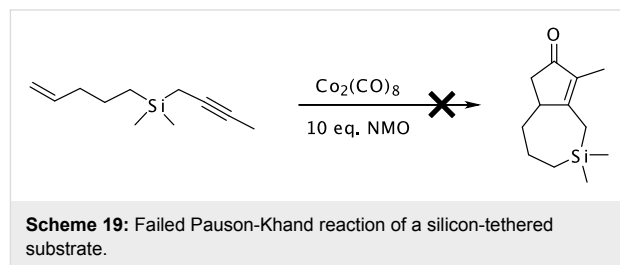
The successfully synthesised silyl acetal was subjected to the P-K reaction conditions. Again the cyclisation was not successful and all that was recovered from the reaction was the un-reacted starting material. Following the difficulties with the synthesis of the silyl acetals and the failure of the silyl acetals to undergo cyclisation it was decided to stop the research into these temporary tethers.

iii) Silicon as the tethering atom

It was decided that the final silicon tethering species that should be investigated was analogous to the first intramolecular P-K cyclisation demonstrated by Schore and co-workers.[34] The idea was to replace directly the carbon atom with a Si(Me)₂ unit. This could provide results on both whether the P-K cyclisation of these species could be achieved and whether the Si-C bond was more stable towards the reaction conditions. There are three primary methods for the synthesis of silicon-carbon bonds: lithium-halogen exchange, Grignard-based methodologies and catalytic hydrosilylation. The approach decided upon used the Grignard and hydrosilylation reactions. Work by Swisher and Chen showed that by using a solution of chloroplatinic acid (H₂PtCl₆ in isopropyl alcohol) compounds containing terminal double bonds could be added catalytically to silane species to yield the substituted chlorosilanes.[33,34] This methodology was coupled with a Grignard reaction to attempt to cyclise the substituted silane (Scheme 18).



The catalytic hydrosilylation using chloroplatinic acid as the catalyst proved to be successful yielding the desired chlorosilane with a yield of 53% which is significantly more than that stated by Swisher and Chen for the same compound. However the Grignard reaction could only be accomplished in very low yield (10%). Nevertheless, the material obtained was subjected to the P-K reaction conditions, and, as before, failed to give any of the 5,7 tethered adduct. Starting material and some decomposed material was recovered.



Conclusion

In conclusion it can easily be seen from the results that silyl ethers and silyl acetals are not good substrates for the P-K reaction when using the standard stoichiometric NMO promoted conditions. Only diisopropylsilanes based silyl ethers have shown any potential as a tethered substrate for the reaction. However, further work is required to optimise the reactions using the diisopropylsilyl tethers and to develop an efficient route for their cleavage.

Supporting Information

Supporting Information File 1

Representative Experimental Procedures and Characterisation Data for Si-tethered P-K reactions.
[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-3-21-S1.doc>]

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The majority of this work was performed at the Department of Chemistry at the University of Exeter. Sadly, the Department was closed by the University on 31/7/2005 and ceased to exist, with all staff and students having to relocate. Please address all correspondence to the author's new institution.

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Single and double stereoselective fluorination of (*E*)-allylsilanes

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Preliminary Communication

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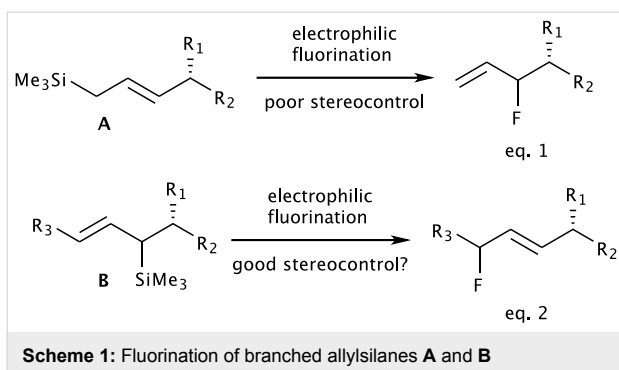
Abstract

Acyclic allylic monofluorides were prepared by electrophilic fluorination of branched (*E*)-allylsilanes with Selectfluor. These reactions proceeded with efficient transfer of chirality from the silylated to the fluorinated stereocentre. Upon double fluorination, an unsymmetrical ethyl *syn*-2,5-difluoroalk-3-enoic ester was prepared, the silyl group acting as an *anti* stereodirecting group for the two C-F bond forming events.

Findings

Asymmetric C-F bond formation continues to challenge chemists, inspiring the development of increasingly effective protocols for stereocontrolled fluorination. [1-11] Studies from our laboratory illustrated that allylsilanes undergo electrophilic fluorination to afford allylic fluorides with clean transposition of the double bond. Using chiral cyclic allylsilanes, these experiments have culminated in efficient methods for the asymmetric synthesis of monofluorinated cyclitols or vitamin D3 analogues. [12-15] The key step of these syntheses is a highly efficient diastereoselective fluorodesilylation. We encountered more difficulties with the fluorination of acyclic allylsilanes **A** constructed by metathetic coupling of allyltrimethylsilane with chiral olefinic partners (eq. 1, Scheme 1). Although high yielding, the electrophilic fluorination of these substrates suffered from a poor level of diastereocontrol, thereby limiting the synthetic value of these reactions. [16,17] The absence of a

silylated stereogenic centre is likely to be responsible for the poor stereocontrol observed upon fluorination of these substrates. We envisaged that the fluorination of (*E*)-allylsilanes **B**, featuring a silylated stereogenic centre, might be a superior transformation to control the configuration of the emerging fluorine-bearing centre (eq. 2, Scheme 1). This working hypothesis is supported by the well-accepted model, which accounts for the observed transfer of chirality when reacting allylsilanes **B** with electrophiles other than fluorine. [18-21] Chiral allylsilanes **B** are known to act as useful carbon nucleophile equivalents in highly stereoselective condensation reactions with a large range of electrophiles leading to the construction of C-C, C-O, C-N or C-S bonds. [22-27] With the nitrogen-based electrophile NO₂BF₄, this methodology delivers acyclic (*E*)-olefin dipeptide isosteres featuring two allylic stereocentres. [28,29]



Herein, we report our investigation into the fluorination of (*E*)-allylsilanes of general structure **B**. A highly efficient and stereoselective synthesis of alkenes featuring bis-allylic stereocentres, one of them being fluorinated, emerged from this study. Significantly, alkenes flanked by two allylic fluorinated stereogenic centres are also accessible upon double electrophilic fluorination of (*E*)-allylsilanes substituted with an ester group.

The synthesis of the allylsilanes (\pm)-**1a-i** featuring an ester or alcohol group was carried out according to the procedure reported by Panek and co-workers.[30] See Supporting Information File 1 for full experimental data. The fluorinations were carried out at room temperature in CH₃CN in the presence of 1.0 eq. of NaHCO₃ and 1.5 eq. of Selectfluor [1-chloromethyl-4-fluoro-1,2-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)]. The reactivity of the (*E*)-allylsilanes **1a-d** possessing a single stereogenic centre was surveyed in priority to probe how structural variations on these substrates influence the *E/Z* selectivity of the resulting allylic fluorides (Table 1). For the (*E*)-allylsilane **1a**, the allylic fluoride **2a** was obtained in

81% yield as a roughly 1/1 mixture of *E/Z* geometrical isomers (entry 1). The structurally related (*E*)-allylsilane **1b** possessing the primary alcohol group underwent fluorination with a lower yield of 64%, delivering preferentially the *E*-isomer with poor selectivity (entry 2). The fluorination of allylsilanes featuring the primary alcohol gave, in addition to the desired product, various amounts of O-trimethylsilylated 5-fluoroalk-3-enols. The presence of the *gem*-dimethyl group on the starting silanes **1c** and **1d** drastically improved the stereochemical outcome of the fluorination. Compounds *E*-**2c** and *E*-**2d** were formed in 95% and 70% yield respectively, with no trace of *Z*-isomer detectable in the crude reaction mixture (entries 3 and 4).

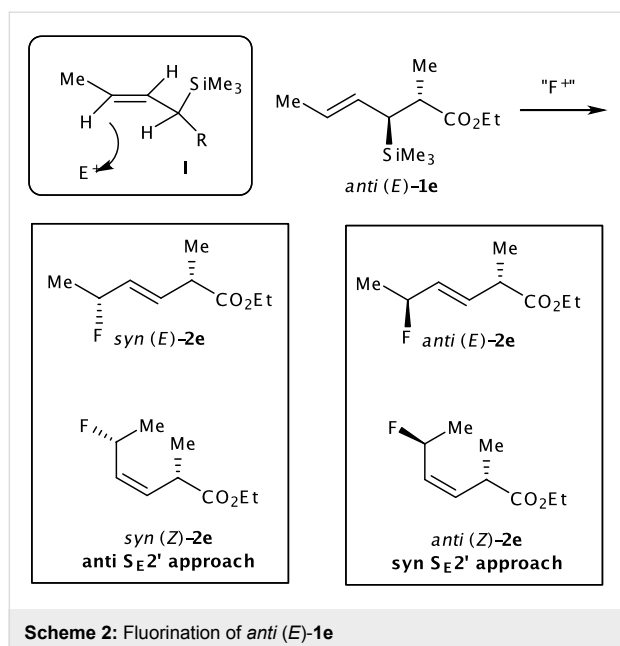
When a second stereogenic centre is present on the starting (*E*)-allylsilane, up to four stereoisomers may be formed upon fluorination. This is illustrated in Scheme 1 with the fluorodesilylation of *anti* (*E*)-**1e**. For substitution reactions (S_E2') of allylsilanes such as *anti* (*E*)-**1e**, with electrophiles other than "F⁺", an *anti* approach with respect to the silyl group prevails with preferential formation of the *syn* (*E*) isomer. [18-21] This stereochemical outcome suggests that the major reaction pathway involves the reactive conformer I leading, after addition of the electrophile, to a carbocationic intermediate which undergoes rapid elimination prior to bond rotation (Scheme 2).

Subsequent experiments focused on the fluorination of *anti* and *syn* (*E*)-allylsilanes **1e-i** to study the effect of silane configuration on diastereoselection (Table 2). Upon fluorination of *anti*-**1e**, the allylic fluoride **2e** was formed in 95% yield as a diastereomeric mixture of both *syn*-**2e** and *anti*-**2e** isomers. The high d.r. [19:1] suggested that the transfer of chirality (*anti* approach of Selectfluor) from the silylated to the fluorinated stereocentre

Table 1: Fluorodesilylation of (*E*)-allylsilanes (\pm)-**1a-d**^a

Entry	(<i>E</i>)-Allylsilane	Major product	Yield	<i>E:Z</i> ^b
1	 1a	 2a	81%	1.3:1
2	 1b	 2b	64%	3:1
3	 1c	 2c	95%	>20:1
4	 1d	 2d	70%	>20:1

a: 1eq. NaHCO₃, 1.5 eq. Selectfluor, CH₃CN, rt; b: ratio determined by ¹⁹F NMR on crude reaction mixtures



was very efficient. A third allylic fluoride was detected in the crude mixture and its structure was tentatively assigned as *syn* (*Z*)-**2e** (entry 1). The benzyl-substituted allylsilane *anti*-**1f** was

fluorinated in 90% yield with a similar sense and level of stereocontrol (entry 2). Excellent transfer of chirality was also observed for the fluorination of *anti* (*E*)-**1g** featuring the primary alcohol group but the yield was significantly lower (entry 3). *Syn*-**1h**, which was used contaminated with *anti*-**1h** [d.r. = 9:1], was fluorinated with an overall yield of 96% delivering a mixture of four stereoisomeric allylic fluorides (entry 4). For this reaction, erosion of stereointegrity resulting from alternative reacting conformation, *syn* approach of the fluorinating reagent with respect to the silyl group, or bond rotation prior to elimination, was detectable but minimal. A similar stereochemical trend was observed for the alcohol *syn* (*E*)-**1i** (entry 5). The stereochemical assignment of compounds **2a-i** was assigned by analogy with the nitration of identical (*E*)-allylsilanes as reported by Panek. [22-27]

This chemistry offers the unique opportunity to access alkenes flanked with two allylic and stereogenic fluorinated centres upon double electrophilic fluorination of (*E*)-allylsilanes featuring an ester group. Although undoubtedly versatile for further functional manipulation, this structural motif is extremely rare with only two symmetrical variants reported in the literature. [31,32] The prospect of validating a more general

Table 2: Fluorodesilylation (*E*)-allylsilanes **1e-i**^a

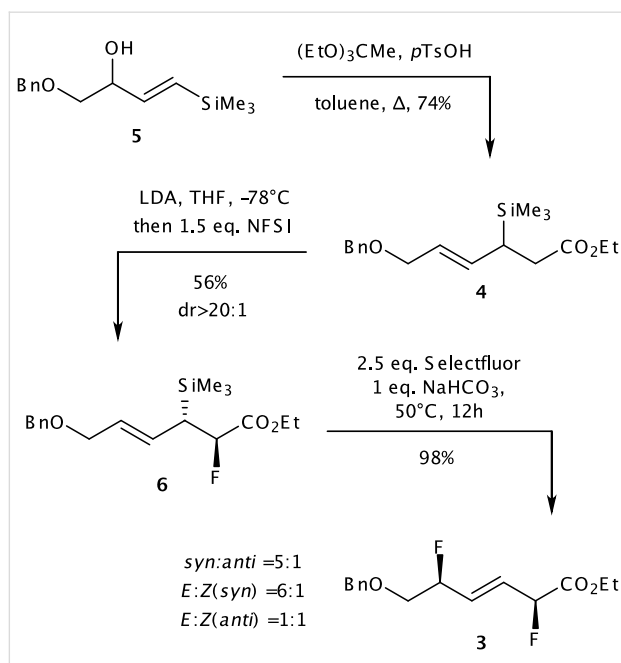
Entry	(<i>E</i>)-Allylsilane <i>anti</i> : <i>syn</i>	Major product	Yield	Syn: <i>anti</i> ^b <i>E</i> : <i>Z</i> (<i>syn</i>) ^b <i>E</i> : <i>Z</i> (<i>anti</i>) ^b
1	 $\text{Me-CH=CH-CH(SiMe}_3\text{)-CH}_2\text{-CO}_2\text{Et}$ $>20:1$ 1e	 $\text{Me-CH=CH-CH(F)-CH}_2\text{-CO}_2\text{Et}$ 2e	95%	19:1 15:1 >20:1
2	 $\text{Me-CH=CH-CH(SiMe}_3\text{)-CH}_2\text{-CO}_2\text{Et}$ $>20:1$ 1f	 $\text{Me-CH=CH-CH(F)-CH}_2\text{-CO}_2\text{Et}$ 2f	90%	>20:1 11:1 >20:1
3	 $\text{Me-CH=CH-CH(SiMe}_3\text{)-CH}_2\text{-OH}$ $>20:1$ 1g	 $\text{Me-CH=CH-CH(F)-CH}_2\text{-OH}$ 2g	66%	>20:1 15:1 >20:1
4	 $\text{Me-CH=CH-CH(SiMe}_3\text{)-CH}_2\text{-CO}_2\text{Et}$ $1:9$ 1h	 $\text{Me-CH=CH-CH(F)-CH}_2\text{-CO}_2\text{Et}$ 2h	96%	1:6 >20:1 11:1
5	 $\text{Me-CH=CH-CH(SiMe}_3\text{)-CH}_2\text{-OH}$ $1:9$ 1i	 $\text{Me-CH=CH-CH(F)-CH}_2\text{-OH}$ 2i	86%	1:8 14:1 10:1

a: 1eq. NaHCO₃, 1.5 eq. Selectfluor, CH₃CN, rt; b: ratio determined by ¹⁹F NMR on crude reaction mixtures

strategy for the preparation of both symmetrical and unsymmetrical alkenes doubly flanked by fluorinated allylic stereocentres prompted us to challenge our methodology with the preparation of the unsymmetrical difluorinated alkenoic ester **3**. This compound was subsequently converted into a known symmetrical difluorinated alkene for which the relative stereochemistry was unambiguously identified by X-ray analysis.[31] This line of conjecture allowed us to verify our stereochemical assignments.

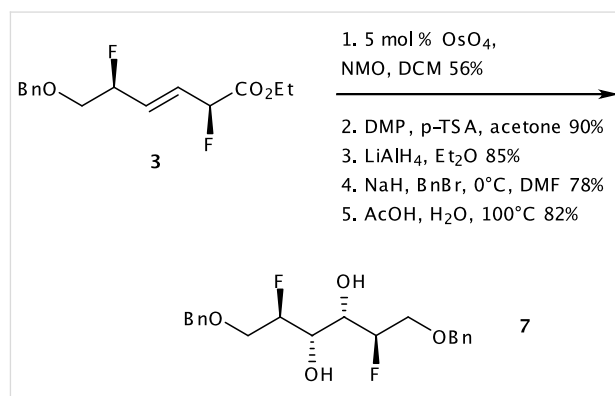
We investigated the feasibility of the double fluorination with (*E*)-allylsilane **4** prepared from (*E*)-vinylsilane **5** [33] via a [3,3] sigmatropic rearrangement. As anticipated and much to our delight, the doubly fluorinated alkene **3** was obtained through a succession of two electrophilic fluorinations. The electrophilic α -fluorination of the ester **4** was performed by treatment with LDA at -78°C followed by addition of *N*-fluorobenzenesulfonimide [34] (NFSI). The d.r. for this first fluorination was excellent ($>20:1$). The subsequent electrophilic fluorodesilylation of the resulting fluorinated silane **6** delivered **3** in excellent yield with no trace of side-products. In comparison with allylsilanes **1a-i**, the fluorodesilylation of **6** was more demanding and required higher temperature to reach completion. Under these conditions, the level of stereocontrol of the second fluorination was moderate (Scheme 3).

To unambiguously confirm the stereochemistry of *syn* (*E*)-**3** [major diastereomer], this compound was converted into the known symmetrical difluorinated alkene **7** (Scheme 4). The key



Scheme 3: Double electrophilic fluorination of (*E*)-**4**

steps necessary to perform this conversion were a dihydroxylation, the reduction of the ester group and the benzylation of the resulting primary alcohol. Preliminary work revealed that the order of steps was important and that protecting group manipulations were required for clean product outcome. The *cis*-dihydroxylation of **3** was performed employing NMO and catalytic OsO_4 in DCM.[35] In the event, the diastereoselectivity was controlled by the two fluorine substituents. Four successful operations separated the newly formed unsymmetrical diol from **7**, namely the protection of the diol as an acetonide, the reduction of the ester, the benzylation of the resulting primary alcohol and a final deprotection step. The spectroscopic data of compound **7** were identical to the ones of a sample prepared independently according to the procedure reported by O'Hagan.[31] This observation establishes the relative configuration as drawn in Scheme 2 and Scheme 3, and supports our hypothesis that the sense of stereocontrol for the fluorinations of **1e-i** is in line with related nitrations reported by Panek.[28]



Scheme 4: Conversion of **3** into diol **7**

In conclusion, the stereoselective fluorination of (*E*)-allylsilanes featuring a silylated stereogenic centre was found to be a useful reaction for the preparation of allylic fluorides, the silyl group acting as an efficient stereodirecting group. Notably, this methodology enables the preparation of unsymmetrical alkenes doubly flanked with fluorinated stereogenic centres. This result is significant as only symmetrical derivatives are accessible with the method reported to date.[31,32]

Supporting Information

Supporting Information File 1

Single and double stereoselective fluorination of (*E*)-allylsilanes. Full experimental data and procedures
[\[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-3-34-S1.doc\]](http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-3-34-S1.doc)

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