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Recent advances in the use of temporary silicon tethers in metal-mediated reactions

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Received 11th June 2010
DOI: 10.1039/c0cs00007h

This *tutorial review* describes the use of temporary silicon tethers in metal-mediated organic reactions, a strategy which although well-established in traditional organic synthesis is still a blossoming field in the organometallic arena. The benefits of silicon-tethering are manifold: the reactivity, selectivity, and efficiency of organometallic processes can all be dramatically enhanced, often with unique regio- and stereochemical outcomes compared to the analogous intermolecular transformations. In addition, the residual silicon functionality can undergo a wide range of chemistry subsequent to the tethered reaction, creating further synthetic opportunities.

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Introduction

The concept of tethering two reaction components to render a chemical process intramolecular is a well-established synthetic strategy, and one which is able to overcome many of the problems associated with intermolecular reactions. In an intramolecular reaction, a considerable rate increase is often observed over the corresponding intermolecular system, due mainly to proximity effects which lead to a higher effective concentration of the reacting partners, and to a lower entropic demand on the free energy of activation. A further significant advantage associated with intramolecularisation is the greater regio- and stereoselectivity which can be induced due to the inevitable increase in conformational restriction of the reaction transition state; indeed, this conformational control can even lead to a reversal of these selectivities when compared with the non-tethered (intermolecular) situation. The tethering of two reacting species is thus likely to enhance both the reactivity *and* selectivity of a given reaction, thanks to the innate benefits of intramolecularity.

Although intramolecularisation is a strategy of great utility in organic chemistry, there are a number of important properties that a tether (or 'linker') should possess to be appropriate for this purpose. Firstly, it should be readily introduced in high yields, such that the efficiency of the intramolecularised synthetic process is not compromised by a poor-yielding assembly of the linker. Secondly, the chosen tether must be stable to the reaction conditions; and finally, it should be easily removed or converted into some other functional group—tethers that incorporate such 'latent functionality' are particularly desirable.

Taking into account such considerations, it becomes apparent that silicon-based functionalities are ideal tethers, as they fulfil all of these criteria. The seminal work of Itoh *et al.*[1] and Stork and Kahn[2] on the use of silicon tethers in radical cyclisations (Scheme 1) introduced this concept to the wider chemistry audience, along with the term 'temporary silicon connection'

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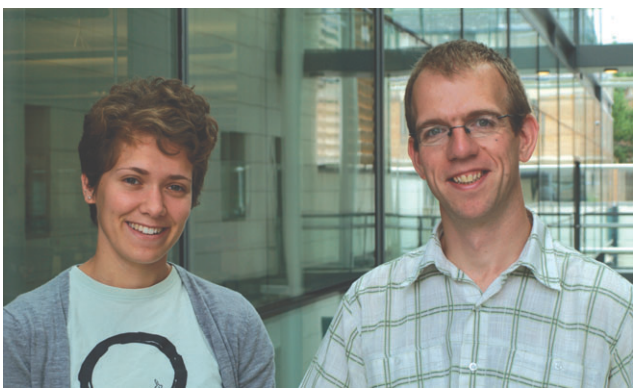

Sonia Bracegirdle and Edward A. Anderson

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Ed Anderson was born in 1975. He obtained a BA from the University of Oxford (1997) and a PhD from the University of Cambridge (2001), under the supervision of Professor Andrew B. Holmes. Following postdoctoral research with Professor Erik J. Sorensen at the Scripps Research Institute, La Jolla, he returned to Cambridge as a Junior Research Fellow at Homerton College, working with Professor Ian Paterson. In 2007 he took up an EPSRC Advanced Research Fellowship in Oxford, and in 2009 he was appointed to a University Lectureship at Jesus college. His research encompasses a wide range of organic chemistry, from total synthesis and the development of new synthetic methods to biological chemistry and molecular self-assembly. Particular interests include palladium-catalysed processes, cascade reactions, and organosilicon chemistry.

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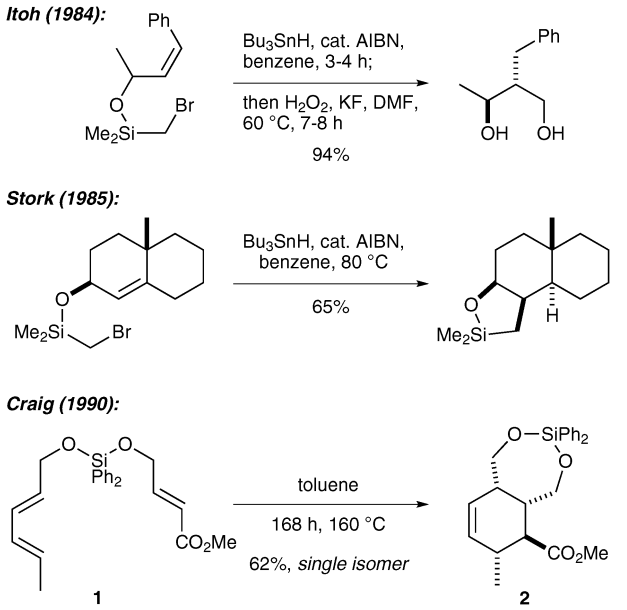


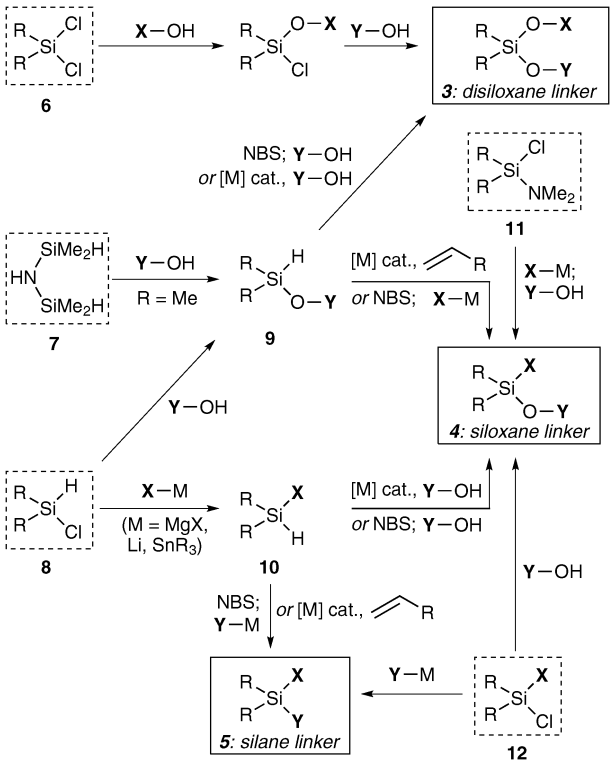
Scheme 1 Selected seminal examples of the temporary silicon tether (TST) strategy.

(later adapted to 'temporary silicon tether', or 'TST'). While this radical cyclisation methodology is impressive, it is the application of silicon tethers to the Diels–Alder reaction which really emphasises the considerable synthetic utility of this strategy.[3] In the example shown in Scheme 1 (**1** → **2**), the use of a silicon tether gave complete control over the regio- and stereoselectivity of this cycloaddition—in comparison, the intermolecular variant of this process was unselective, with all four possible isomers being formed.[3b] This single example emphasises the degree of conformational restriction that the silicon tether introduces in the reaction transition state, and clearly illustrates the benefits of the TST approach in synthesis.

Although silicon tethers have been applied to a wide variety of reactions over the last twenty-five years, it is almost ten years since a major review of the literature has been published.[4] In particular, TST methodology has seen considerable recent development in the field of metal-mediated reactions, and this tutorial review will focus on the advances made in this area since 2000.[5] A brief overview of common methods for tether incorporation will be given, followed by a review of the use of silicon tethers in metathesis, cross-coupling, carbocyclisation, hydro- and carbosilylation, and miscellaneous transformations including oxidative and reductive cyclisation reactions.

Common methods for tether incorporation

Due to the strength and ease of formation of silicon–oxygen bonds, the most common linkers employed in TST reactions are the disiloxane (**3**) or siloxane (**4**) functionalities, containing two and one Si–O bonds respectively (Scheme 2), with more limited use of the all-carbon silane linker **5**. As might be expected, there are a number of methods for tether construction; only the most commonly used of these will be examined here.



Scheme 2 Common routes for TST construction.

The disiloxane motif **3** is often approached from the appropriate dichlorodialkylsilane **6** *via* sequential addition of two alcohol components to the silicon species. The use of excess dichlorosilane overcomes the obvious problem of double substitution, and usually allows the disiloxane product **3** to be accessed in good yield, although this tactic is limited to volatile dialkylsilanes which can be removed by simple evaporation prior to the addition of the second alcohol. In cases where better control over substitution is desired, a number of stepwise routes may be employed. For example, tetraalkyldisilazanes **7** or chlorosilanes **8** will silylate alcohols to give intermediate siloxanes **9**,[3c,6] which can be reactivated to a second nucleophilic displacement using halide electrophiles, or perhaps more appealingly can undergo metal-catalysed Si–O bond formation.[7]

Siloxanes **4** are also readily accessed from the same intermediates **9**, again *via* a 'reactivation/displacement' sequence, or through metal-catalysed C–Si bond formation (for example by hydrosilylation, **9** → **4**). The order of substituent addition can be reversed for the chlorosilanes **8**, proceeding through intermediate silane **10** if the initial nucleophile is an organometallic reagent rather than an alcohol. Although these strategies eliminate the potential for the formation of disubstituted byproducts, the cost for this control is the need for an additional reaction step. However, a further group of reagents which exhibit this substitution selectivity but avoid the need for isolation of an intermediate are the chloro-aminosilanes **11**, which can be converted to the siloxane **4** in a one-pot operation by addition of an alcohol nucleophile directly to the intermediate aminosilane (**11** → **4**).[8] In cases where the 'functional' carbon substituent is commercially

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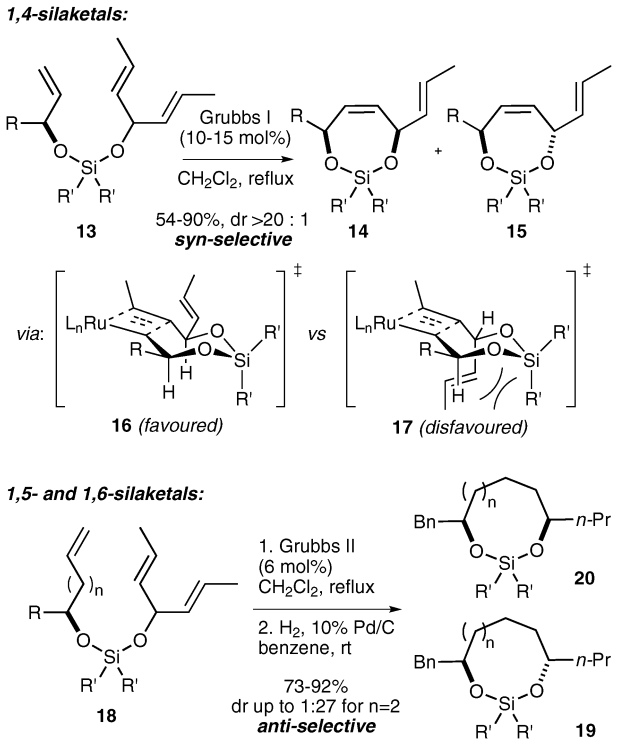
available in the form of the chlorosilane **12**, a very straightforward alcohol silylation may be employed (**12** → **4**).

Finally, silane linkers **5** can be directly accessed from either the chlorosilane **12** if it is readily available, or again from the intermediate silane **10**, *via* the C–Si bond forming strategies discussed above.

The inherent flexibility of these pathways allows a wide variety of silicon-tethered substrates to be easily synthesised, often in excellent yields. Given that many of these variations initiate with inexpensive, commercially available chlorosilanes, the effect of the spectator silicon alkyl substituents on reactivity and TST stability can be readily examined for any process. This latter point can be particularly important, as silicon tethers are not without drawbacks, such as their tolerance of harsher reaction conditions (particularly acidic environments where siloxanes exhibit the same lability as standard silyl ether protecting groups, and thermal conditions where they may be susceptible to nucleophilic attack). In these instances, increasing the steric bulk of the spectator substituents may protect the TST from unwanted degradation, but at the cost of increased steric hindrance—itself potentially leading to a reduction in reaction efficiency. Thus, the selection of an appropriate tether calls for a balance between tether stability and reacting group accessibility, for which solutions are often possible but not guaranteed.



Scheme 3 Long-range asymmetric induction in the synthesis of 1,*n*-silaketals (Evans).

Applications of temporary silicon tethers in metal-mediated reactions

Metathesis

TSTs have seen widespread application in metathesis chemistry, and are now considered a well-established synthetic strategy.[4c,d,h] Early work in this field[9] recognised the ability of a temporary tether to transform a cross-metathesis into a ring-closing metathesis (RCM), thereby enhancing reaction selectivity and efficiency, and perhaps most importantly overturning the inherent *E*-selectivity of cross-metathesis *via* the use of a cyclic constraint.

More recently, Evans *et al*. have studied the ability of a TST to mediate substrate-controlled long-range asymmetric induction in RCM systems where one of the tethered alkene partners is derived from a prochiral alcohol (Scheme 3).[10] A variety of 1,4-silaketal precursors **13** were examined, with impressive levels selectivity being observed for the *cis*-stereoisomer **14** in the RCM step (dr >20 : 1). The steric demands of the silicon substituents were found to be crucial in commanding such high selectivities and yields, with R′ = isopropyl giving the best results. A transition state **16** was proposed to explain this outcome, where destabilising steric interactions between the silicon substituents and the pseudoaxial propenyl group (as shown in the alternative transition state **17**) are removed in this more favourable arrangement **16**.

Extension of this methodology to longer-chain systems (**18**) resulted in a surprising switch of selectivity, with the *trans*-silaketals **19** now being favoured in the synthesis of the corresponding 1,5- and 1,6-cyclic disiloxanes. In some cases, diastereoselectivities as high as 27 : 1 were achieved (measured after reduction of the newly-formed double bond to remove complications from the mixture of *E* and *Z* alkene isomers which arose from the RCM). Once again, a transition state model was proposed to explain the reaction selectivity in which steric interactions between the silicon substituents and the propenyl group are minimised. It is clear that the silicon tether plays a vital role in governing reaction diastereoselectivity through these transition states, emphasising that TSTs can not only enhance reactivity, but can also influence the stereochemical outcomes of reactions.

The ability of TSTs to induce long-range stereocontrol highlights the utility of the tethering strategy in metathesis settings, and it is perhaps unsurprising that TSTs have also been applied to enantioselective desymmetrisation processes.[11] For example, under solvent-free conditions the chiral cyclic siloxane **21** was synthesised from **22** in 98% yield and >98% ee using the chiral molybdenum complex **23** (Scheme 4). Interestingly, this catalyst could be prepared *in situ* and displayed enhanced stability compared to less bulky molybdenum metathesis catalysts, and could be used without recourse to a glovebox or Schlenk techniques.

A number of applications of TST RCM in total synthesis have been reported. Among the more recent of these is Li and Miller's work on the antibiotic (+)-streptazolin **24** (Scheme 5), in which the TST played a crucial role in dictating the stereochemistry of the exocyclic propenyl substituent of the natural product.[12] Several substrates were examined for this total synthesis, with the eventual strategy being decided by the efficiency not of the RCM, but of the subsequent tether cleavage. For example, cyclisation of allylsilane **25** proceeded readily, but attempted protodesilylation of the product **26** led

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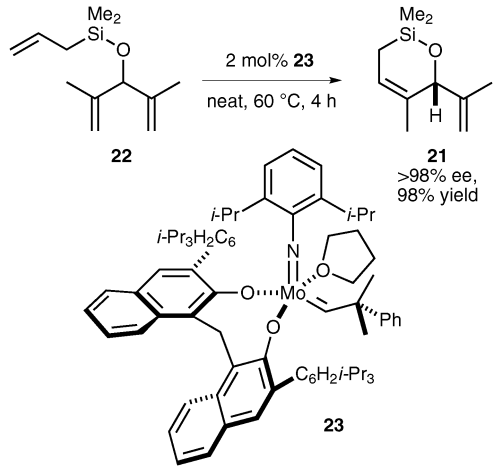
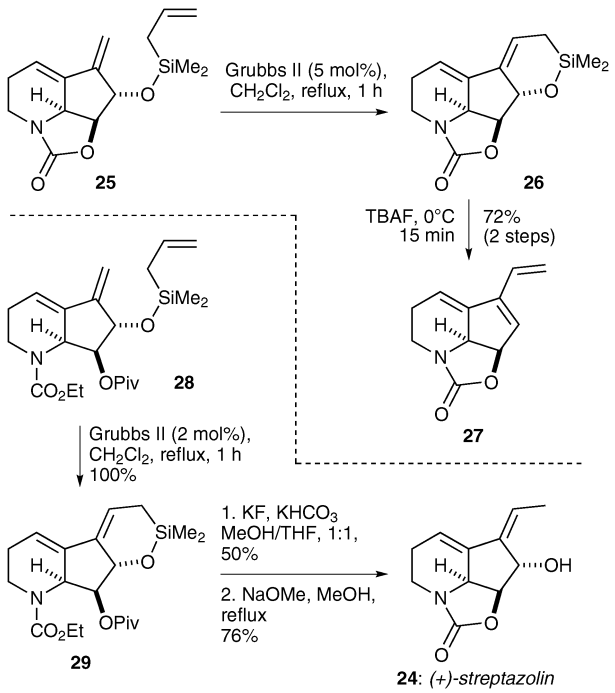


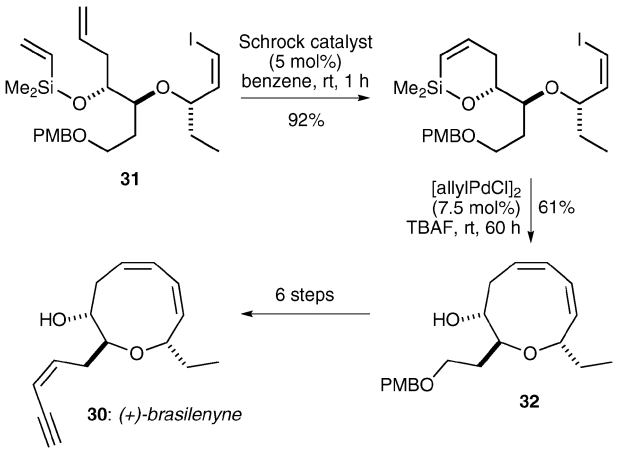
Scheme 4 Desymmetrisation of achiral trienes *via* enantioselective TST RCM (Hoveyda).



Scheme 5 Synthesis of (+)-streptazolin using TST RCM (Miller).

to a vinylogous Peterson elimination[12d] to the triene **27**. Eventually, a solution to this problem was found with the modified RCM substrate **28**, which after cyclisation to **29** underwent a moderate yielding albeit novel desilylation, followed by ester solvolysis, to give (+)-streptazolin with its requisite *Z*-propenyl substituent.

One of the most impressive examples of the use of silicon-tethered RCM in synthesis has been reported by Denmark *et al.*, who recognised that vinyl silyl ethers prepared using TST RCM represent ideal substrates for intramolecular Hiyama cross-coupling to form medium-sized rings. This sequenced methodology[13] was applied to the total synthesis of (+)-brasilenyne **30**,[14] in which the 9-membered ring ether of the natural product was fashioned with complete stereocontrol over the requisite *Z*,*Z*-diene motif (**31** → **32**, Scheme 6). This

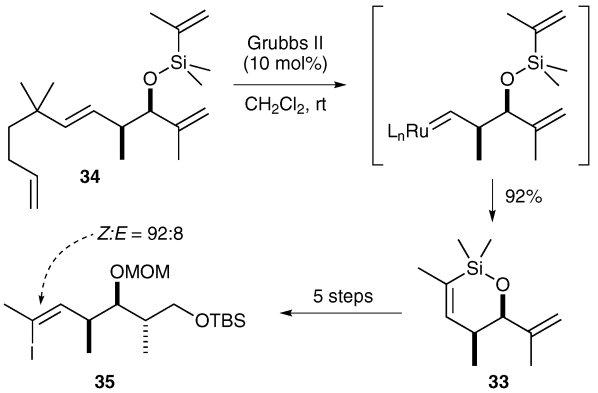


Scheme 6 Use of TST RCM/Hiyama coupling in Denmark's total synthesis of (+)-brasilenyne.

elegant total synthesis highlights the use of TST methodology both in terms of the synthetic benefit of the strategy (efficient and general medium-ring construction), and the considerable scope for further transformations displayed by cyclic organosilicon products.

As discussed above, a notable feature of this work is the observation by Denmark (and others) that vinyl silanes in particular present a steric challenge to ruthenium metathesis catalysts, but that this obstacle can be overcome by using the air-sensitive but more reactive Schrock molybdenum catalyst. An alternative solution to this reactivity problem has been proposed by Parker and co-workers, who used a relay metathesis strategy to synthesise the trisubstituted cyclic vinyl siloxane **33** using Grubbs 2nd generation catalyst (Scheme 7).[15] Although it is not immediately apparent why this tactic offers benefits over direct ring-closing metathesis of the analogous terminal alkene, the cyclisation of **34** proceeded in excellent yield. A number of further transformations yielded the vinyl iodide **35** with good control over the double bond geometry, this fragment being a key intermediate in the total synthesis of the potent cytoxic agent (+)-discodermolide.

It is not just alkene metathesis processes that have benefited from the application of TSTs, with this strategy having been extended to both enyne and dienyne RCM. The first



Scheme 7 Overcoming the steric limitations of ruthenium: relay TST RCM (Parker).

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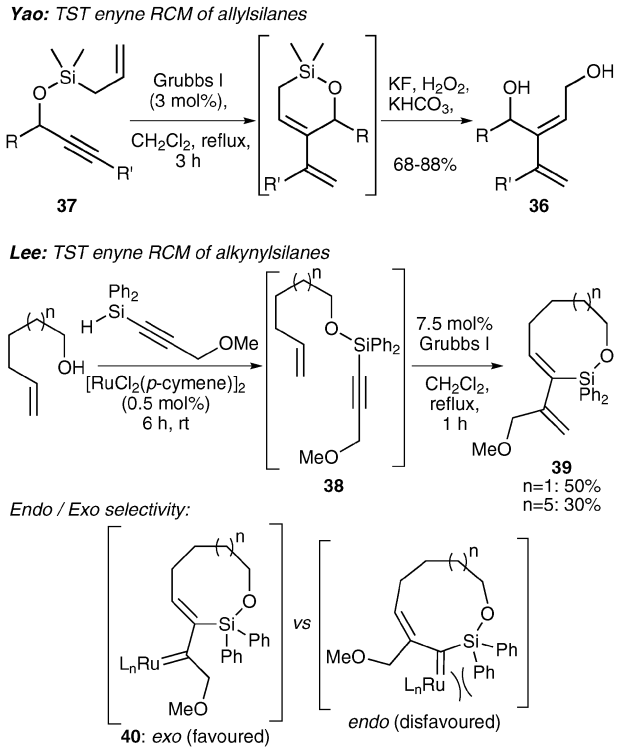
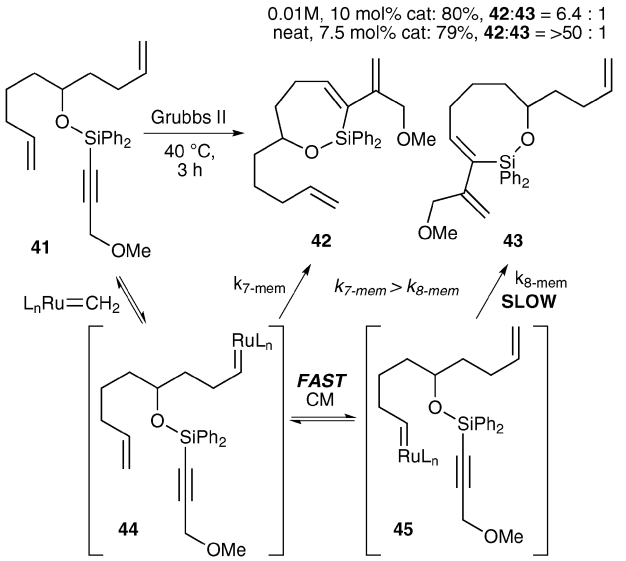


Scheme 8 Silicon-tethered enyne RCM.

wide-ranging example of this reaction was reported by Yao,[16] who found that silicon-tethered enyne RCM gave a variety of trisubstituted dienes **36** from simple propargylic allylsilyl ethers **37** in a regio- and stereospecific manner (Scheme 8). Subsequent efforts by Lee *et al.*,[7] in which the positions of the 'ene' and 'yne' components were exchanged on the siloxane tether, showed that this concept could also be applied to the synthesis of siloxacycles from alkynylsilyl ethers (*e.g.* **38** → **39**), including a 13-membered macrocyclic example. Interestingly, the usual *endo* mode of cyclisation was not observed for this larger ring size—the group postulated that this contrasting tether-controlled *exo*-selectivity can be attributed to the avoidance of steric clashing between the silicon substituents and the adjacent ruthenium alkylidene in the *exo*-intermediate **40**, which would arise in the alternative *endo* pathway.

By incorporating a second alkene sidechain in the cyclisation substrate, the Lee group has examined the effect of the ring size on the rate of the enyne RCM (Scheme 9). Upon treatment of the silicon-tethered dienyne framework **41** with Grubbs' 2nd generation catalyst, preferential cyclisation of one of the alkenes onto the silyl alkyne was observed, leading to a 6.4 : 1 ratio of the 7- and 8-membered silacycles **42** and **43**.[17] Remarkably, upon increasing the substrate concentration, the selectivity for the smaller ring size was found to increase—the best results being obtained when the reaction was conducted neat. That such considerable selectivity can be observed between ring sizes differing by only a single methylene unit is an astounding result, particularly as the alkene moieties share almost identical steric and electronic properties. This selectivity is likely to be reliant upon a pre-ring-closure equilibrium which allows the ruthenium alkylidene complex to transfer between



Scheme 9 Ring size selectivity in silicon-tethered RCM (Lee).

the terminal alkenes *via* cross-metathesis (CM) (**44** ↔ **45**) at a rate which is faster than cyclisation (of **45**) to the strained 8-membered ring.

Lee *et al.* have further adapted the TST framework so that a second cyclisation of the nascent ruthenium alkylidene onto the residual alkene functionality can take place.[16a,18] This tandem dienyne RCM thereby provides a route to bicyclic disiloxanes, from which 1,4-disubstituted *E*,*Z*-dienes, motifs found in a number of bioactive natural products, can be prepared with complete stereoselectivity. This ingenious strategy formed a key part of Lee's partial syntheses of tartrolon B[19] and formal synthesis of (−)-cochleamycin A.[20] In the former of these studies (Scheme 10), the enyne RCM substrate **46** was constructed using sequential alkyne displacements by the appropriate alcohol nucleophiles **47** and **48**—an impressive and convergent assembly of this complex reaction substrate. In the event, the cyclisation of **46** to form the bicyclic disiloxane **49** also proved highly efficient, particularly as this involved the synthesis of a 7,8-fused bicyclic disiloxane. Subsequent desilylation (**49** → **50**) revealed the *E*,*Z*-diene and full framework of the natural product.

Finally, an equally impressive example of enyne RCM in total synthesis is illustrated by the Movassaghi group's preparation of (−)-acylfulvene (**51**, Scheme 10) and (−)-irofulven, two members of the cytotoxic illudin family.[21] Preparation of the disiloxane **52** was readily achieved *via* union of an appropriate alkyne and aldehyde, followed by silylation. This substrate is designed with great care, as TST ring-closing enyne metathesis must be achieved in the presence of an additional 'spectator' trisubstituted alkene, and for this the phenyl substituent proved crucial as a protecting group. Thus, initiation of the cascade cyclisation at the mono-substituted alkene was followed by dienyne RCM, terminating on the 1,1-disubstituted alkene, which afforded the 7,6-bicycle **53** in an outstanding 79% yield; notably, the use of less bulky or non-conjugated blocking groups on the trisubstituted alkene led to competing metathesis side-reactions. Following a concise three-step sequence, a second RCM now cleaved this trisubstituted alkene, with the

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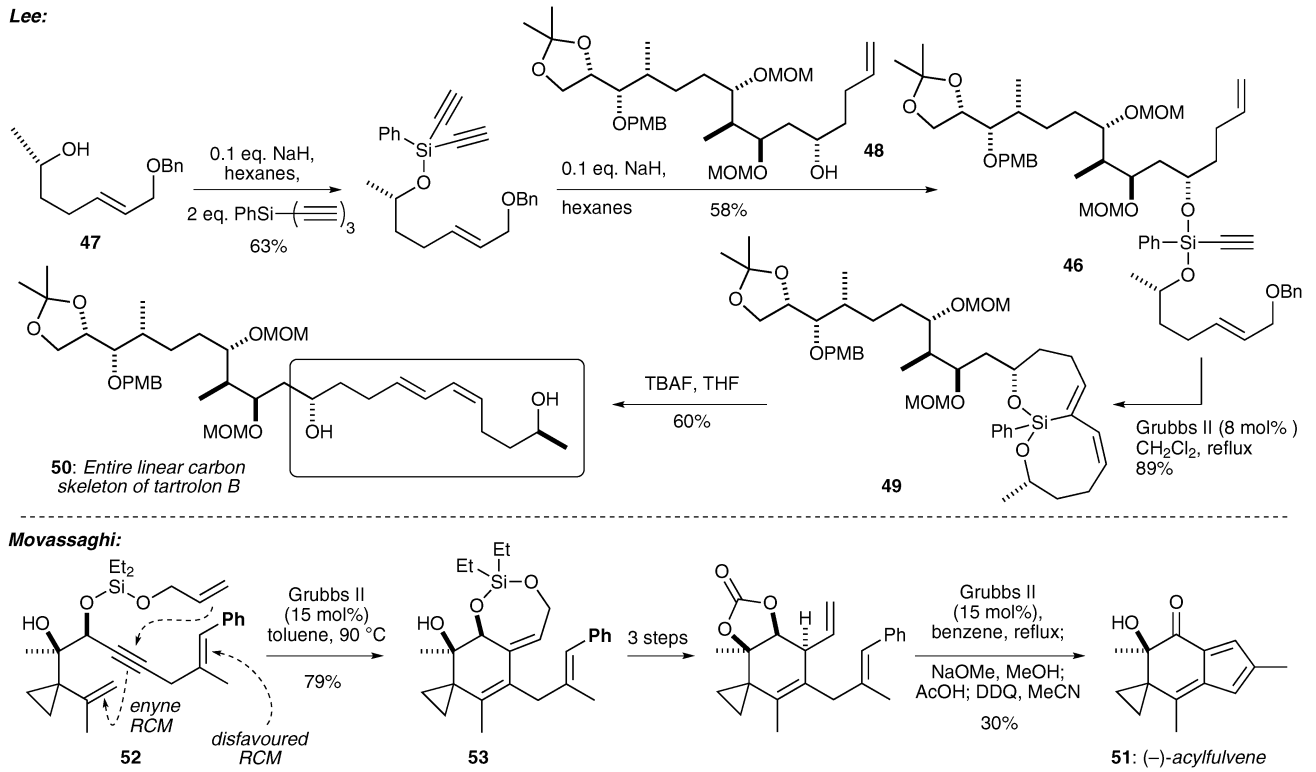


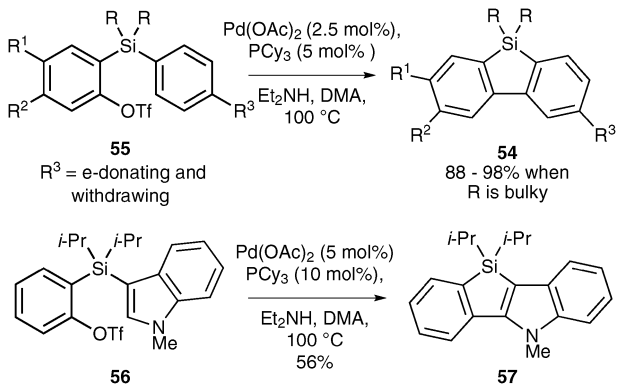
Scheme 10 Tandem dienyne RCM in synthesis: Lee's approach to tartrolon B, and Movassaghi's synthesis of (–)-acylfulvene.

formation of the fulvene motif; *in situ* deprotections and oxidation completed the synthesis of (–)-acylfulvene **51**.

Palladium-catalysed cross-coupling reactions

One of the most topical fields of modern organic chemistry is C–H activation, and it is no surprise that silicon-tethering methodology has recently found application in this arena. The Hiyama group first applied an intramolecular palladium-catalysed C–H activation to the synthesis of dibenzosiloles **54** (Scheme 11).[22] Upon treatment of tethered aryl triflates **55** with $Pd(OAc)_2/PCy_3$, a range of siloles **54** could be synthesised incorporating both electron-donating and electron-withdrawing groups about the two aromatic systems. Interestingly, increasing the bulk of the silicon substituents led to improved yields of the dibenzosiloles, and it was postulated that these bulkier groups play two roles: firstly, through the Thorpe–Ingold effect, which brings the two reacting groups closer together, and secondly by retarding decomposition of **54** or **55**, as more hindered silicon centres are less susceptible towards nucleophilic attack. As with the enyne metathesis *endo*/*exo* selectivity discussed above, this is another example of how the 'inert' substituents on the silicon centre can play a considerable role in controlling the reactivity of the coupling process, despite not being directly involved in the reaction mechanism. The methodology could be successfully extended to heterocyclic coupling partners, such as the 3-TST-substituted indole **56** (giving product **57**).

The Hiyama group encountered a surprising result on applying this reaction to 2-TST-substituted pyrroles and



Scheme 11 Synthesis of silicon-bridged biaryls *via* C–H activation (Hiyama).

indoles **58** (Scheme 12). In the presence of a large excess of diethylamine, formation of the *same* silole products **57** as before was favoured over the expected regioisomer **59**.[23] Interestingly, it had been shown in previous work[22] that analogous 2-substituted benzofuran, thiophene, and benzothiophene substrates did not give rearranged products, suggesting that the presence of the nitrogen atom is essential for this anomalous transformation. Based on this observation, the group has proposed a mechanism in which a 1,2-silyl migration explains the formation of the unexpected diarylsiloles. In the case of the pyrrole substrates, palladation likely occurs at the nucleophilic 2-position (→**60**), followed by the key 1,2-silyl migration to give **61**, and finally rearomatisation to provide **57**. In contrast, indolic substrates may well palladate

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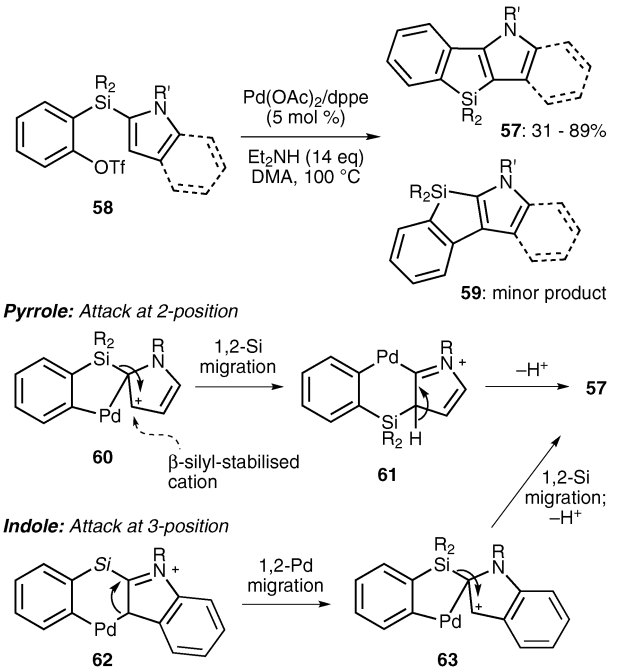
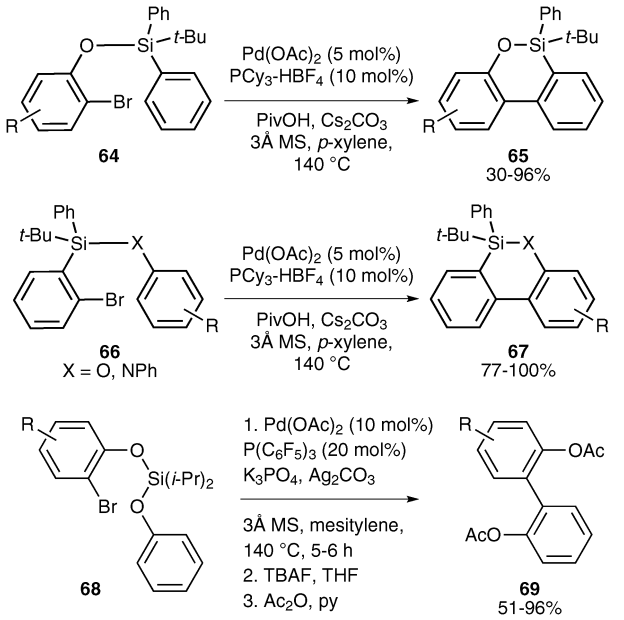
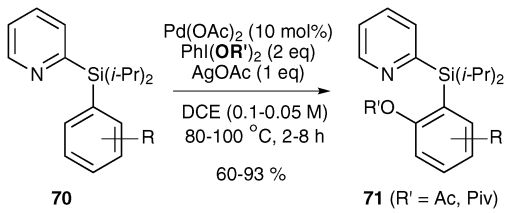


Scheme 12 Regioselectivity switch with 2-TST-substituted pyrroles and indoles (Hiyama).



Scheme 13 Silicon tethers in C–H activation (Gevorgyan).



Scheme 14 TST directed *ortho*-oxidation of arenes (Gevorgyan).

at the 3-position giving intermediate **62**, which has a sufficient lifetime to undergo a 1,2-palladium migration rather than rearomatisation due to the increased stability of the nitrogen-stabilised cation relative to oxygen or sulfur heteroatoms. This provides intermediate **63**, which as before can undergo 1,2-silyl migration and deprotonation to give **57**. In both cases, the proposed mechanism proceeds *via* silicon-stabilised β-carbocations (**60** and **63**), which rearrange to relieve steric compression, again emphasising additional roles that the silicon tether can play in influencing the reaction mechanism.

The Gevorgyan group has also contributed to the field of silicon-tethered intramolecular C–H activation, in this instance utilising a temporary connection which was removed following cyclisation.[24] Using a modified Fagnou protocol,[25] it was found that the simple TBDPS group could be efficiently coupled to a variety of substituted *o*-bromophenols **64**, leading to cyclic siloxanes **65** (Scheme 13). Furthermore, a modified bromo-TBDPS group could also serve as a coupling partner in this reaction, allowing a range of phenols and anilines to be arylated without the need for prior *ortho*-bromination, and effecting a transformation which is difficult to achieve in an intermolecular setting (**66** → **67**). Significantly, while previous examples of intramolecular C–H activation have yielded tricyclic biaryl systems due to the permanent nature of the linking group employed, the temporary silicon tether represents a 'traceless' linker, which provides all the benefits of intramolecularity without introducing an unwanted cyclic system into the final product, as either protodesilylation or oxidation allowed clean and efficient removal of the TST. This work has recently been extended to the use of disiloxane tethers (**68**),[26] which under slightly modified reaction conditions provide the corresponding biaryls **69** in excellent yields following a two-step tether cleavage. Once again, an excellent selection of electron-rich and electron-poor arenes proved suitable substrates for this reaction.

The Gevorgyan group has also recently reported a traceless silicon-tethering directing group for the acyloxylation of aromatic C–H bonds (Scheme 14).[27] The pyridyldiisopropylsilyl group was employed to direct palladium-catalysed C–H activation to the *ortho* position of arylsilane **70**, upon which coupling could take place with an acetoxy or pivaloxy hypervalent iodine species to give oxidised products **71**. A range of substituents was tolerated, including brominated derivatives, and it was found that *meta*-substituted substrates produced only a single regioisomer upon reaction. In this work, Gevorgyan emphasises the wide range of further transformations that the TST could undergo, the most notable of which were an *ipso* iodination and a Hiyama cross-coupling.

Beyond C–H activation, silicon tethers have received surprisingly little attention in palladium-mediated reactions other than a tethered Heck reaction reported by Mayasundari and Young,[28] suggesting that silicon-tethering in palladium-catalysed chemistry is a field yet to be fully explored.

Carbocyclisations

Applications of temporary silicon tethers to metal-mediated (formal) cycloaddition reactions have not been as widely explored as the parent pericyclic processes, and have mainly been limited to reactions involving "2π" components. The

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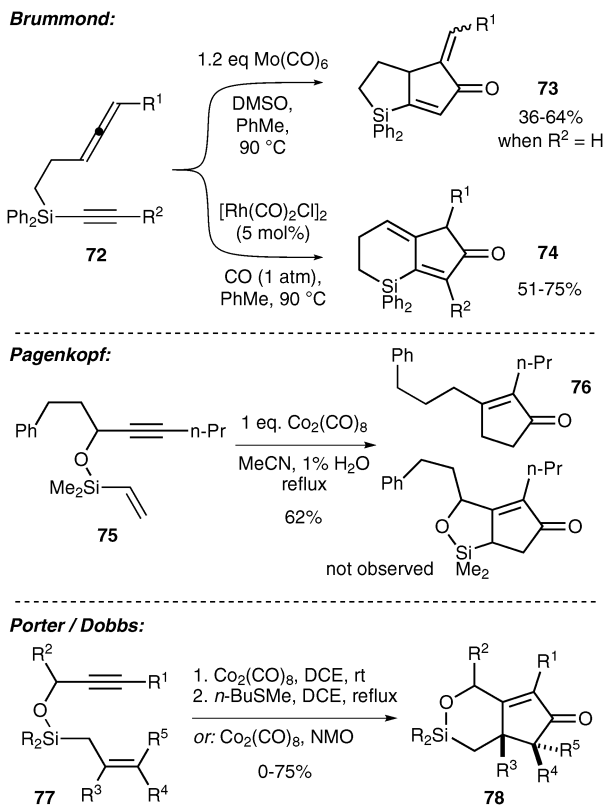
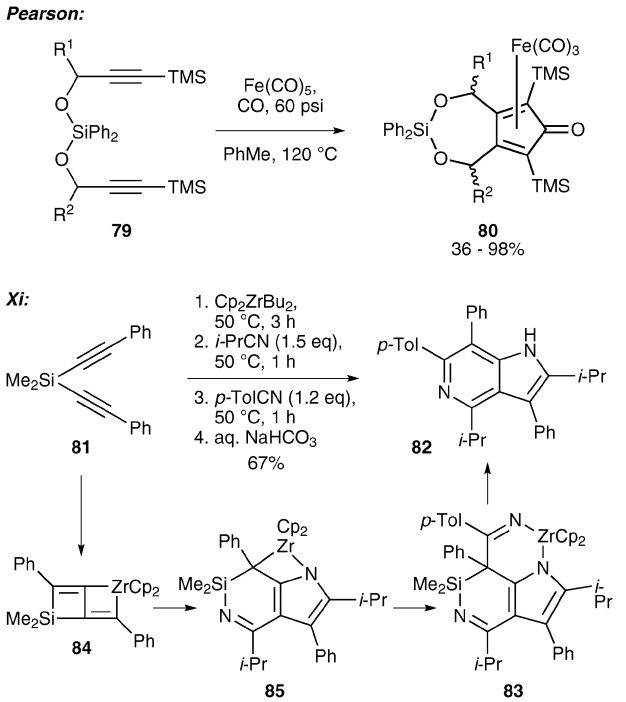
silicon-tethered [2 + 2 + 1] Pauson–Khand cyclocarbonylation has been addressed by numerous groups, with intriguingly limited success to date. The first report falling within the scope of this review[29] was published in 2002 by Brummond and co-workers, which detailed investigations into a silicon-tethered allenic Pauson–Khand reaction (Scheme 15).[30] The group found siloxane tethers to be particularly unstable under the reaction conditions and thus employed the more unusual tetraalkylsilane-tethered system **72** as an alternative, which proved more robust. In exploring the use of different metals to mediate the reaction, it was found that whilst stoichiometric $Mo(CO)_6$ gave rise to the Pauson–Khand product **73** with addition across the 'internal' allene double bond, switching to catalytic $[Rh(CO)_2Cl]_2$ gave the regioisomeric cycloadduct **74**. The successful use of these carbon-based silicon tethers is in contrast to the alkenyl Pauson–Khand cyclisation, for which this type of silane tethering strategy is not suitable.[31] However, siloxane linkers have been employed by Pagenkopf *et al.* in an unusual alkenyl Pauson–Khand variation, whereby cobalt-mediated cyclisation of tethered vinyl silanes such as **75** resulted in unexpected reductive cleavage of both the silicon and propargylic alcohol moieties (**76**) in all but two cases (Scheme 15).[32] More recently, both Ishaq and Porter[33] and Dobbs *et al.*[31] have reported the cyclisation of allyl propargyl silyl ethers (*e.g.* **77**), using either *n*-butyl methyl sulfide or NMO as promoters. However, not only do these processes require the use of stoichiometric cobalt reagent, but also the substrate scope was found to be highly limited, with only a few examples producing cyclised products **78** in greater than 70% yield. These collected results reveal that the TST strategy has not yet been effectively applied to the Pauson–Khand reaction—in this instance, it seems that intramolecularity is in fact detrimental to the cyclisation, potentially due to a combination of steric effects and restriction of the relative geometries that the reacting centres can adopt.



Scheme 15 Application of silicon tethers to the Pauson–Khand reaction.



Scheme 16 Silicon-tethered diyne cyclocarbonylation reactions.

Despite these limited successes, the Pearson group has developed a related, if somewhat specialised use of disiloxane tethers in a diyne cyclocarbonylation mediated by stoichiometric $Fe(CO)_5$ (Scheme 16).[34] The main feature of this reaction is that the heterocoupling of two distinct alkynes can be achieved—only homocouplings have been reported in the analogous intermolecular case.[35] The reaction was shown to tolerate a small variety of substituents, although poor diastereoselectivities were observed in the coupling of secondary alcohol-derived systems (**79** → **80**, $R^1/R^2 \neq H$).

Building on earlier studies by Takahashi *et al.*,[36] Xi and co-workers have developed a zirconocene-mediated coupling of a silicon-tethered diyne **81** and three organonitriles, which delivers a range of complex and highly-substituted azaindoles **82** and pyrroles in a one-pot process (Scheme 16).[37] Mechanistic studies carried out by the group suggested that this reaction takes place *via* an unusual pathway, which is supported by the isolation and characterisation of the crystalline intermediate **83**. Thus, initial reaction between the tethered diyne and Cp_2ZrBu_2 yields the fused zirconacyclobutene–silacyclobutene complex **84**,[36] which undergoes a series of insertion reactions with two molecules of nitrile to yield the intermediate **85**. Finally, insertion of a third organonitrile molecule leads to **83**, which gives the azaindole **82** upon hydrolysis. Further studies found that **81** could react with a range of other substrates, such as isocyanides, formamides, acid chlorides and aldehydes, thus dramatically broadening the range of products that can

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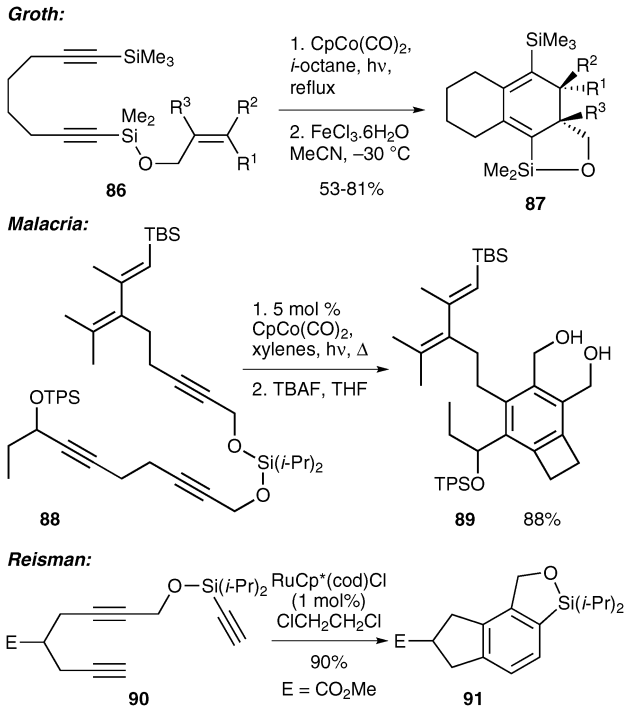

Scheme 17 [2 + 2 + 2] Cyclotrimerisations with silicon tethers.

be accessed using this silicon-tethered process. The presence of the TST is crucial to the success of this reaction, the high strain energy of the dicyclobutene species **84** facilitating subsequent reaction with the organonitriles. Furthermore, the tether is ultimately labile enough to allow hydrolysis to take place in the final reaction step, leading directly to the cyclised product.

In contrast to cyclocarbonylation, the use of TST methodology in [2 + 2 + 2] cyclotrimerisation chemistry has proved more fruitful. Initial efforts towards a silicon-tethered cobalt-mediated cyclotrimerisation were reported by the Groth group,[38] whereby alkynyl siloxane **86** could be effectively cyclised to the tricycle **87** (Scheme 17). This process was later extended to the synthesis of tetrahydroquinolines from diyne nitriles.[39]

Malacria and co-workers have carried out extensive research in this field, and have found that a variety of silicon tethers withstand the cyclotrimerisation reaction conditions, allowing a considerable range of polysubstituted aromatic systems to be accessed (Scheme 17).[40] One of the more complex examples of this methodology is illustrated in the cyclisation of triyne **88**, which afforded the hexasubstituted aromatic core **89** in an impressive 88% yield; the potential utility of this cyclisation was demonstrated by the conversion of **89** to a taxane-like framework. As expected, complete regioselectivity is observed, highlighting arguably the most significant advantage of the use of tethers in alkyne cyclotrimerisation. The recent report by Reisman and co-workers of a ruthenium-catalysed cyclotrimerisation highlights the use of other metals in this process.[41] Cyclisation of triyne **90** to tricycle **91** proceeded in excellent yield, and under much milder conditions than the traditional cobalt-catalysed methodology.

Possibly the most dramatic application of TSTs to cycloaddition chemistry was reported by the Evans group in 2004.[42] Building on their previously reported intermolecular rhodium-catalysed [4 + 2 + 2] carbocyclisation reaction,[43] silicon-tethering of the reacting components enhanced both the regioselectivity and reactivity of this process, with particular benefits for highly-substituted dienes. The use of a TST thus provided a means by which the substrate scope, and hence utility of the reaction, could be expanded. A variety of nitrogen, oxygen and carbon-linked 1,6-enynes, silicon-tethered to a diene component (**92** or **93**, Scheme 18), were amenable towards cyclisation in the presence of [(COD)Rh(Np)]SbF_6, providing the tricyclic cyclooctadienes **94** and **95** in good to excellent yields. Interestingly, the stereochemistry of the enyne alkene was transferred to the cyclised products with high fidelity, the *E*- and *Z*-isomers giving the respective diastereomeric products with selectivities greater than 19 : 1. This high level of stereoinduction was rationalised by consideration of the possible cycloaddition transition states, the more favourable arrangements **96** and **97** minimising steric interactions between the silicon *iso*-propyl groups and the tethered diene. The crucial role played by the TST in controlling the diastereoselectivity of this cycloisomerisation mirrors the related effects observed in Evans' work on long-range stereoinduction in metathesis described earlier in this review.

Hydrosilylation and carbosilylation

The metal-catalysed addition of organosilanes across alkynes provides one of the most obvious and suitable opportunities for intramolecularisation, with the silicon tether now being intimately involved in the reaction itself. The challenge with intramolecular hydrosilylation lies in controlling both the regio- and stereoselectivity of the reaction. There have been considerable developments in the field of intramolecular alkyne hydrosilylation since the first report of this reaction by the Tamao group in 1988,[44] and methods to access all possible stereochemistries of H/Si addition to alkynes have now been achieved. A wide range of transition metal catalysts have been employed, with the cyclisation selectivity being highly dependent on the precise nature of the metal species.

Following Tamao's seminal work on platinum-catalysed intramolecular *syn*, *exo*-hydrosilylations of homopropargylic alcohols,[44] the Marshall and Denmark groups have greatly extended the substrate scope of this transformation (Scheme 19).[45] Under the influence of either Speier's catalyst (H_2PtCl_6) or Pt(1,1,3,3-tetramethyl-1,3-divinyldisiloxane) [(Pt(DVDS)], this cyclisation proceeds with high selectivity for the *syn*, *exo*-addition of Si–H, yielding the corresponding *E*-vinyl siloxanes **99** from the silanes **98**. Marshall has used these products in the synthesis of aldol-type stereodiads and triads *via* Tamao oxidation of the cyclic siloxanes, while the efforts of the Denmark group have focused on the potential of the reaction products to undergo Hiyama cross-coupling. Later work presented by Denmark on the application of ruthenium arene catalysts to silicon-tethered hydrosilylation revealed an important switch in selectivity—an *anti*-selective *exo*-cyclisation now being observed (Scheme 19).[45c,46] Depending on the choice of homopropargylic or propargylic ether starting materials, either siloxane (**100**) or more unusual disilyl disiloxane tethers (**101**) were employed in this

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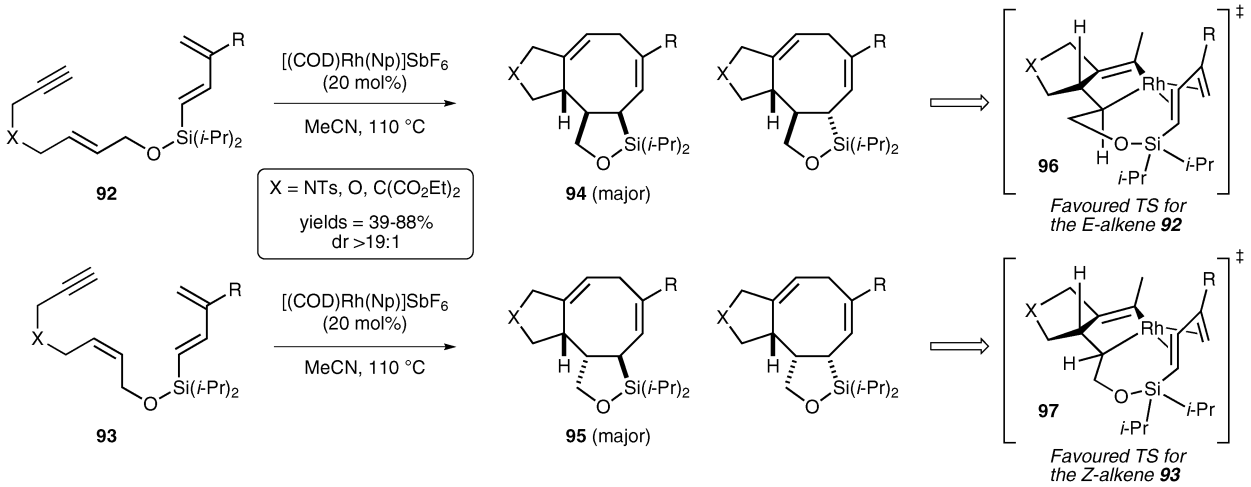
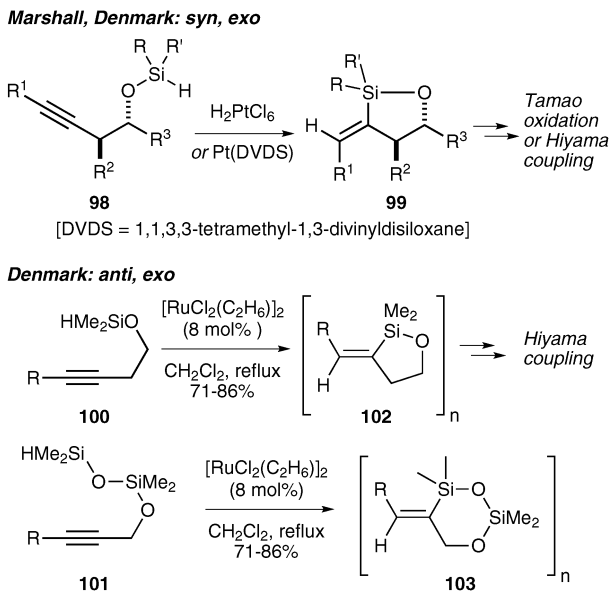


Scheme 18 Silicon tethering in Evans' rhodium-catalysed [4 + 2 + 2] cycloisomerisation.

procedure, giving rise to the cyclic siloxanes **102** and **103** respectively. One potential drawback of this methodology is the *in situ* polymerisation of the dimethylsiloxane products (**102** and **103**) under the reaction conditions. Fortunately, these oligomeric derivatives proved to be effective partners in Hiyama coupling reactions with a wide range of aryl iodides, thus allowing the synthesis of a range of useful tri-substituted alkenes with complementary stereochemistry to those accessed using the Pt-catalysed hydrosilylation/cross-coupling route.

These two methods thus provide efficient and highly stereocontrolled access to both *exo*-stereoisomers of intramolecular hydrosilylation. The final piece of this regio-and stereochemical puzzle was reported in a concurrent publication by the Trost group, who employed the cationic ruthenium complex $[Cp^*Ru(MeCN)_3]PF_6$, resulting in yet another intriguing switch in selectivity.[47] In this instance (Scheme 20), intramolecular hydrosilylation of **104** led exclusively to the 6-*endo* product **105** (with enforced *anti*-selectivity). Both 1,3- and 1,4-alkynols were successfully cyclised under the optimised reaction conditions, although propargylic alcohols proved unreactive. It is especially interesting that 1,4-alkynols underwent *endo*-cyclisation to form seven-membered siloxanes, in preference to the potentially more stable six-membered ring products from *exo*-addition. The group has further expanded the utility of this work *via* subsequent oxidation of the cyclic siloxane products, allowing homoaldol species **106** to be synthesised.[48] Alternatively, diastereoselective epoxidation of the double bond of **105**, followed by Tamao oxidation, provided a route towards α,γ- and α,δ-dihydroxy ketones such as **107**. A short synthesis of the natural product (+)-spectaline was also reported.[48]



Scheme 19 Platinum-catalysed (*syn*, *exo*) and ruthenium-catalysed (*anti*, *exo*) hydrosilylation.

Finally, Yamamoto *et al.* have developed a completely contrasting Lewis-acid mediated silylation reaction which gives similar regioselectivity to the Trost method (Scheme 20).[49] Under Al(III) catalysis, cyclisation of silanes such as **108** occurs with regioselectivity dictated by the nature of the alkyne substituent R. In the case of poor cation-stabilising groups (R = H, alkyl, TMS), complete *endo*-selectivity was observed in this transformation, explained by chloride-promoted hydride transfer in intermediate **109**, which undergoes subsequent C–Si bond formation to give the corresponding product (**110** → **111**). In contrast, *exo*-selectivity was observed with the superior cation-stabilising ability of aryl acetylenic substrates.

The addition of Si–H bonds across alkenes leads to an extra level of complexity owing to the generation of up to two stereogenic centres. Extensive pioneering work in this field which lies outside the timescale of this review has been published by the Tamao group, who have mainly used platinum catalysis to effect tethered hydrosilylation of a wide range of allylic and homoallylic alcohols and amines.[50] Here we highlight recent contributions in this area, which have built on the achievements of these earlier groundbreaking studies.

One of the main challenges and opportunities in alkene hydrosilation/Tamao oxidation is control over the installation of multiple stereocentres. Traditionally, 1,2- and/or 1,3-allylic strain has been most commonly employed as a stereocontrolling

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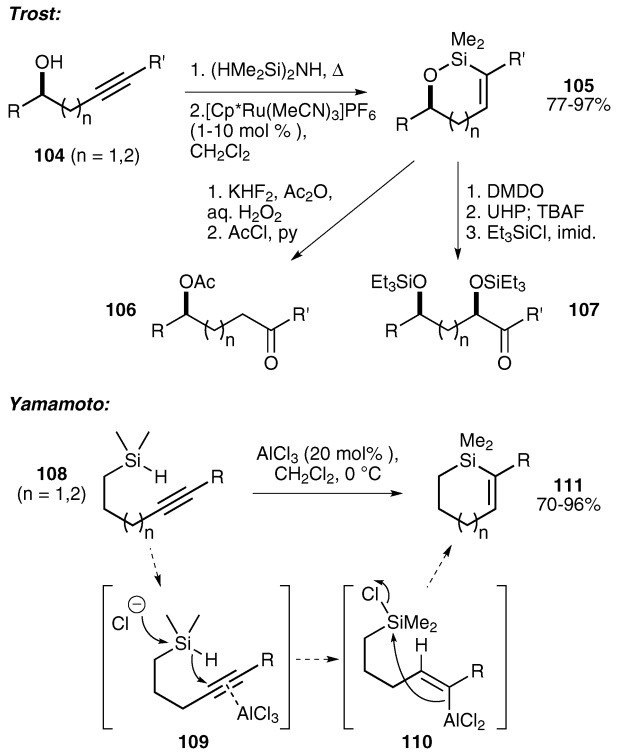
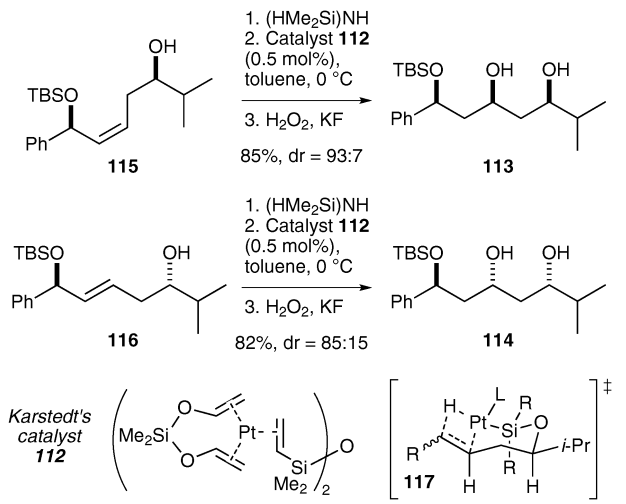


Scheme 20 *endo*-Selective hydrosilylation.

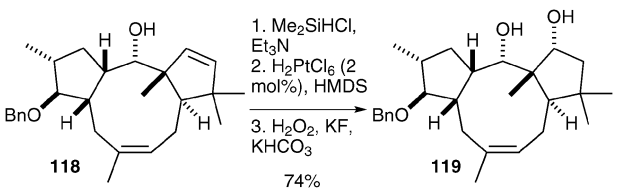
element,[51] with this approach being most suitable for the synthesis of polypropionate motifs. In 2009, Roush and co-workers reported a solution to the long-standing problem of diastereoselective hydrosilylation for polyacetate synthesis, in which the more exotic Karstedt's catalyst **112** (Scheme 21) was found to exhibit higher levels of stereocontrol than Pt(DVDS) or Speier's catalyst.[52] Importantly, the reaction gave high levels of 1,3-stereoinduction regardless of alkene geometry, leading to *syn*, *syn* and *syn*, *anti* 1,3,5-triols **113** and **114** from the *Z*- and *E*-alkenes **115** and **116** respectively. A chairlike transition state **117** was hypothesised to be responsible for this stereocontrol.



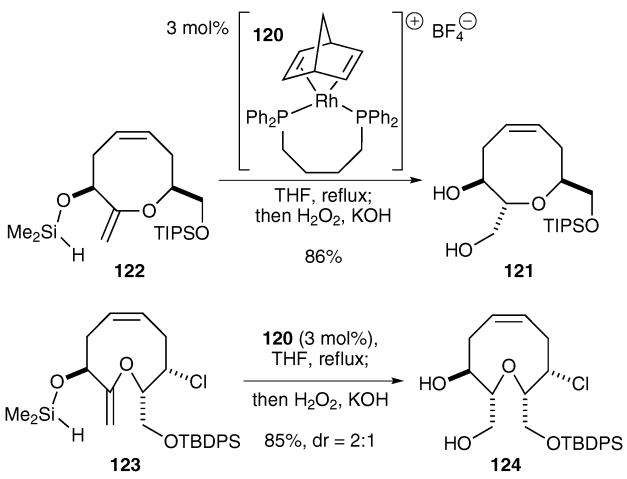
Scheme 21 *syn*-Hydrosilylation route to 1,3,5-triols (Roush).

Beyond polyketide synthesis,[52] a late-stage silicon-tethered hydrosilylation/Tamao oxidation has been employed by Paquette *et al*. in the highly complex setting of the total synthesis of the diterpenoids jatrophatrione and citlalitrione (**118** → **119**, Scheme 22).[53] Although the stereoselectivity of this reaction was not important (with both alcohols in **119** destined for oxidation to ketones), this example emphasises the ability of hydrosilylation to functionalise complex and hindered systems. Finally, hydrosilylation can be applied to more sensitive alkenes such as enol ethers, as exemplified by Holmes and co-workers' recent reports of the synthesis of (+)-obtusenyne and other highly-functionalised medium-ring ethers.[54] For example, the cationic rhodium catalyst **120** (Scheme 23) was found to effect highly selective hydrosilylation of certain exocyclic enol ethers, providing the diol **121** (from the enol ether **122**) as a single stereoisomer after oxidative workup. In the context of the synthesis of obtusenyne, the reaction proved less selective (**123** → **124**, dr = 2 : 1), possibly reflecting a greater range of conformations which can be accessed by the larger 9-membered ring. Nevertheless, this reaction provided a means to not only control the stereochemistry of one of the obtusenyne ring substituents, but also to introduce functionality suitable for elaboration to the enyne sidechain of the natural product in the form of the primary hydroxyl group.

The addition of Si–C bonds across alkenes or alkynes (carbosilylation) arguably represents a greater increase in molecular complexity than hydrosilylation, and therefore a more appealing transformation. This reaction benefits from the same degree and aspects of stereocontrol as described for



Scheme 22 Paquette's approach to jatrophatrione and citlalitrione.



Scheme 23 Tethered hydrosilylation of medium ring exocyclic enol ethers (Holmes).

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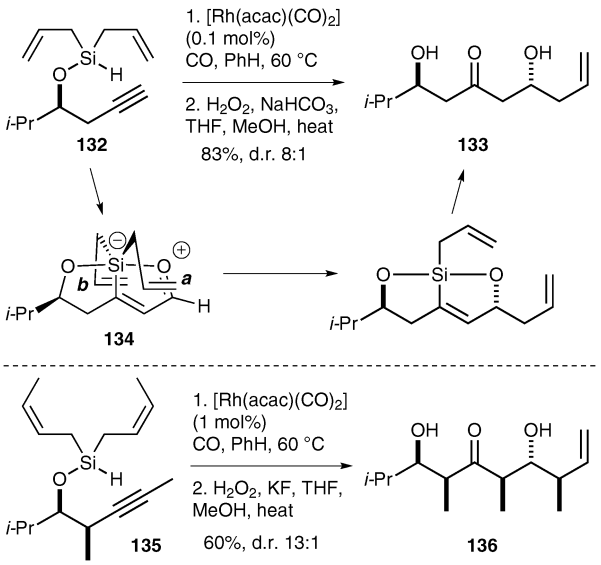
hydrosilylation (*i.e.* minimisation of allylic strain), with the benefit of at least one carbon–carbon bond formation prior to reductive elimination of the metal. The Leighton group has reported the application of TST carbosilylation methodology to the tandem silylformylation/allylation of alkenes and alkynes, this elegant strategy providing easy access to polyketide-like fragments *via* two sequential C–C bond-forming steps. Their first investigations focused on the silylformylation of alkene-based starting materials **125** (Scheme 24), followed by *in situ* allylation of the nascent aldehyde, this second step occurring spontaneously under the rhodium-catalysed reaction conditions.[55] Subjection of the intermediate cyclic siloxanes **126** to Tamao oxidation led to an impressive range of triols, with the *syn*, *syn* diastereomer **127** being the major component of the product mixture. The diastereoselectivities reported ranged from 69 : 31 to 93 : 7, with bulkier substituents adjacent to the allylic alcohol unsurprisingly conferring higher selectivity upon the reaction.

The likely mechanism of this reaction commences with insertion of rhodium into the Si–H bond, followed by silylmetallation across the alkene (**128** → **129**), then CO insertion and reductive elimination to generate the intermediate aldehyde **130**. The O–Si–C bond angle of this oxasilacyclopentane intermediate is approximately 95°, which promotes coordination of the aldehyde oxygen to the silicon centre leading to a strain-relieving trigonal bipyramidal 'ate' complex **131**. This coordination concomitantly activates both the aldehyde (towards nucleophilic attack), and also the silicon (towards allyl group transfer). Transfer of allyl group '***a***', which lies in closer proximity to the aldehyde, leads to the observed major diastereomer of the product, with the minor isomer primarily arising from the selectivity of the silylmetallation step. The hypothesis that this allylation is promoted simply through reduction of ring strain of the reactive intermediate (with the rhodium catalyst playing no role) is consistent with the mechanisms proposed by Myers *et al.*[56] and Denmark *et al.*[57] in the Lewis acid-free aldol reactions of enoxysilacyclobutanes, and by Utimoto *et al.* in the related allylation reactions using allylsilacyclobutanes.[58]

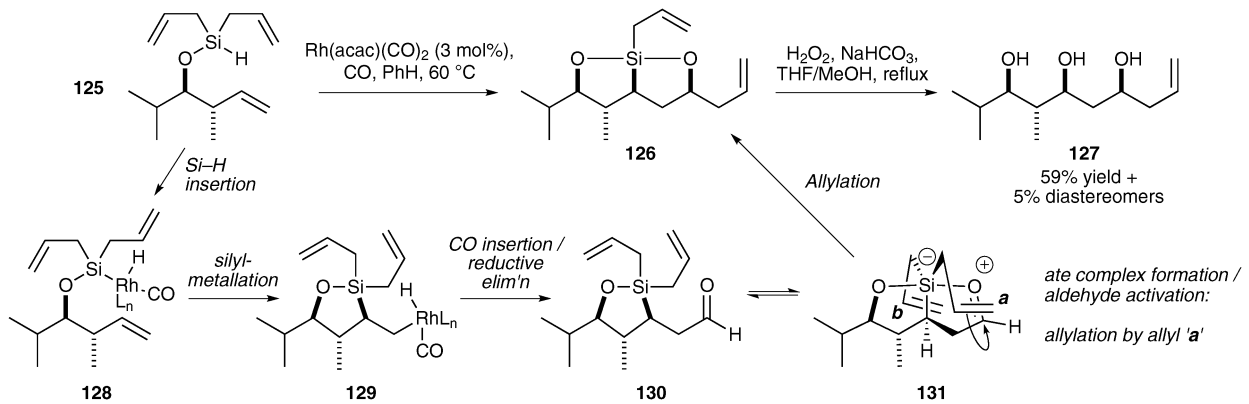
O'Malley and Leighton have expanded this methodology to include alkynyl substrates **132**, which provide β,β′-dihydroketone or 1,5-diol products (**133**, Scheme 25) depending on the desilylation conditions used.[59] In contrast to the aforementioned alkene variant, this reaction is now selective for the *anti* diastereomer **133**, providing another impressive example of 1,5-stereoinduction. The diastereoselectivities observed range from 4 : 1 to 23 : 1, and are explained by a similar transition state structure **134** to that proposed previously, with transfer of the allyl group '***b***' on the less hindered face of the aldehyde.



Scheme 25 Silyformylation/allylsilylation of alkynes (Leighton).

Finally, this work has also been extended to crotylation of both alkenyl and alkynyl substrates,[60] and allylation/crotylation of internal alkynes.[61] Both these reaction classes again proceed with good to excellent diastereoselectivities (*e.g.* **135** → **136**, Scheme 25), and generate a remarkable and highly impressive level of molecular complexity in a single step, making this approach a powerful strategy for the synthesis of highly substituted polyketide fragments. In this vein, the Leighton group has employed its methodology in the synthesis of fragments of the natural products spongistatin 1 and zincophorin,[61] and dolabelides A and B.[62]

In an interesting twist, the group has demonstrated that the stereochemistry of the allyl-bearing silicon centre can completely



Scheme 24 Tandem silylformylation/allylation of alkenes (Leighton).

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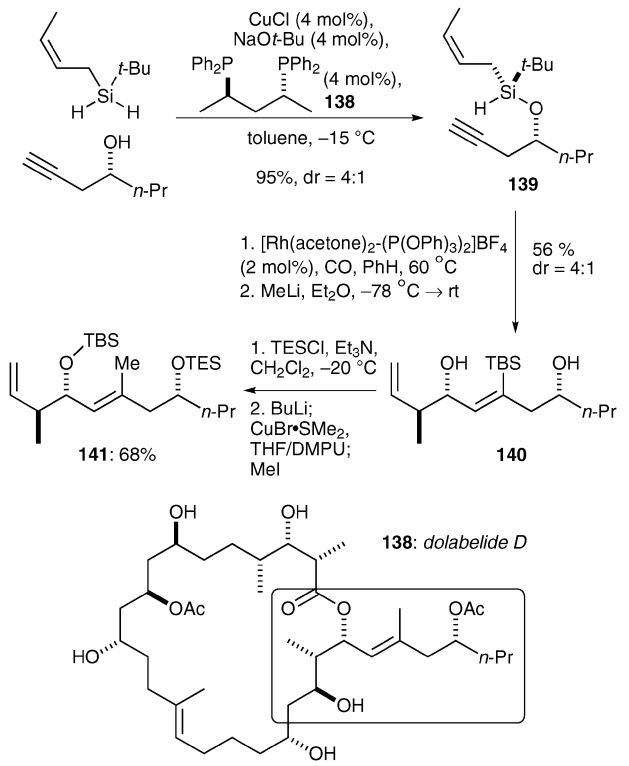
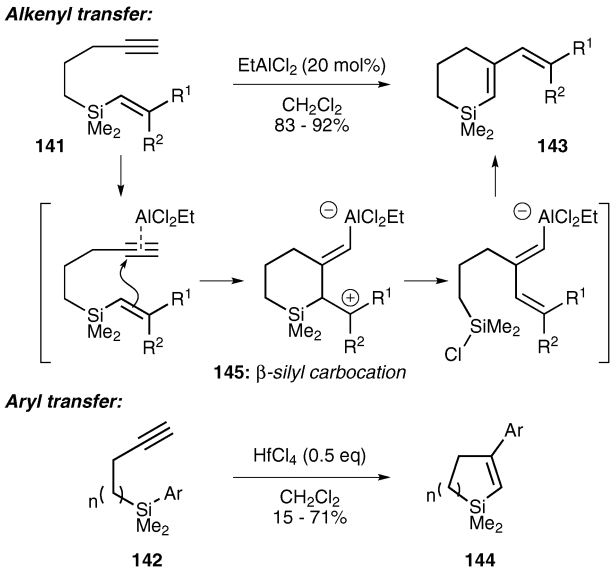
control the diastereoselectivity of the silylformylation/allylation reaction, leading to *syn* or *anti*-1,5-diols.[63] This work has been applied to the synthesis of the cytotoxic macrolide dolabelide D **137** (Scheme 26).[64] This work commenced with an elegant copper-catalysed asymmetric silane alcoholysis in the presence of the chiral phosphine **138**, which provided silane **139** in a respectable 4 : 1 ratio of diastereomers (for other silylations, the selectivity of this desymmetrisation step can be as high as 9 : 1).[63] This stereochemistry was then faithfully transferred to the alkyne in the silylformylation/crotylation step *via* the mechanism discussed in Scheme 25, allowing the *syn* relationship of the 1,5-diol-containing fragment **140** to be realised from **139**, the 4 : 1 dr of this step arising entirely from the stereochemical mixture of silane substrates. The use of a chiral TST[65] is of particular note here, given the wide range of other silicon-tethered reactions that would benefit from the possibility of tether-controlled asymmetric stereoinduction.

To conclude this section, a *trans*-carbosilylation has been reported by the Yamamoto group, which extends their hydrosilylation work to the transfer of other groups from silicon, and again capitalises on the β-cation stabilising ability of this heteroatom.[66] Using catalytic amounts of Lewis acids, both vinylsilylation (**141**) and arylsilylation (**142**) reactions have been developed, which afford silylacycles **143** and **144**, respectively (Scheme 27), compounds which are difficult to prepare using alternative methodologies. The reaction is thought to proceed by a similar mechanism to the hydrosilylation process, with the key step being carbon–carbon bond formation *via* cationic intermediate **145**.



Scheme 26 Asymmetric silylation/silylformylation/silylcrotylation methodology in the synthesis of dolabelide D (Leighton).

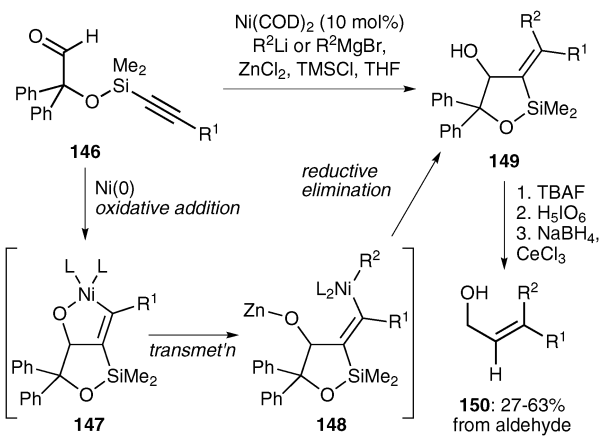


Scheme 27 Lewis-acid catalysed carbosilylation (Yamamoto).

Miscellaneous reactions

TST methodology has seen application in other diverse fields, including reductive and oxidative cyclisations. In 2001, Lozanov and Montgomery published a nickel-catalysed process which provides trisubstituted allylic alcohols in a highly *Z*-selective fashion.[67] The reaction of silicon-tethered ynals **146** with $Ni(COD)_2$ (Scheme 28) is thought to lead to an intermediate nickelacycle **147**,[68] which undergoes transmetallation with a variety of organozinc species to provide alkenylnickel complex **148**. Reductive elimination affords, stereospecifically, the corresponding cyclic vinyl silane products **149**. A three-step procedure was used to remove the TST and reveal the allylic alcohols **150**, although a number of other applications for **149** could easily be envisaged.

A second, more recent class of reductive cyclisation has been developed by Phillips and co-workers, which was subsequently applied to an elegant total synthesis of the cytotoxic natural product (−)-dictyostatin (**151**, Scheme 29).[69] The reaction involves a stoichiometric titanium(II)-mediated reductive cyclisation of (silyloxy)enynes, and likely proceeds through



Scheme 28 Nickel-catalysed tethered allylation (Montgomery).

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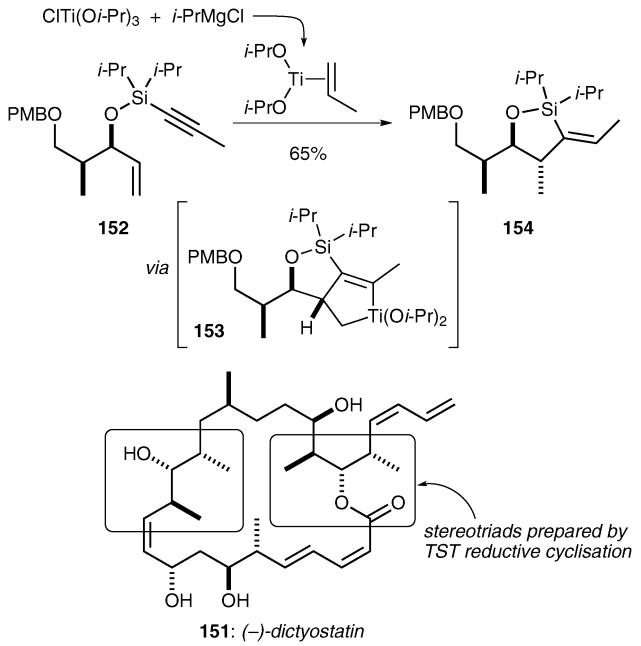
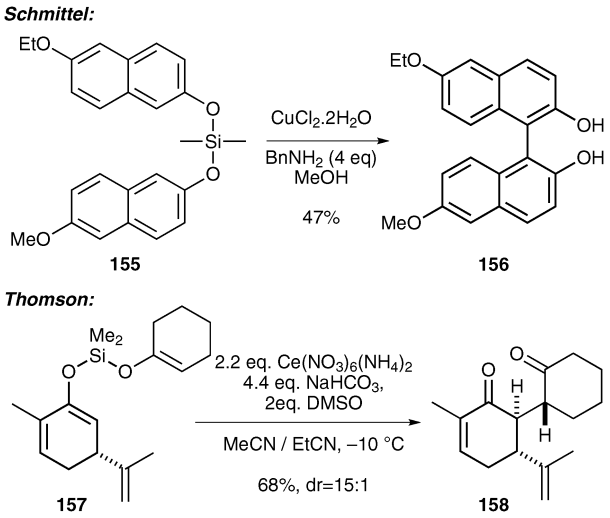
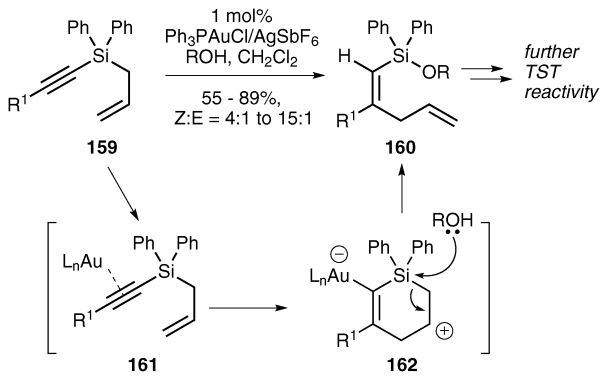


Scheme 29 Titanium-mediated enyne reductive cyclisation (Phillips).



Scheme 30 Silicon tethered oxidative coupling reactions.



Scheme 31 TST gold-catalysed allylation (Lee).

in situ reduction of $ClTi(O\textit{i}\text{-}Pr)_3$ by *i*-PrMgCl to form $Ti(O\textit{i}\text{-}Pr)_2(\eta^2\text{-propene})$. In a manner analogous to Montgomery's nickel-catalysed cyclisation, this complex presumably undergoes an oxidative addition to the alkyne and alkene components of enyne **152** to afford a titanocycle intermediate **153**, in a highly diastereoselective manner. Work-up leads to the cyclic vinyl silyl ether **154**, containing three contiguous stereocentres; this *syn*, *anti*-stereotriad is found as a repeating unit in (−)-dictyostatin, thereby providing an alternative strategy to the more commonly-used aldol approach to such stereochemical arrays.

Oxidative coupling reactions are also suitable for TST strategies. For example, oxidative cyclisation of bisnaphtholates **155** *via* copper-mediated single electron transfer (Scheme 30) has been used to prepare both symmetric and unsymmetric binaphthols **156**.[70] The high *ortho*-selectivity of this process reflects the proximity effects imposed by the TST. The related oxidative cyclisation of bis-enol ethers **157**, a reaction concept which had been noted in the earlier work of Schmittel and Haeuseler,[70] has been realised by Thomson *et al.*[71] In this reaction, CAN mediates the oxidation of the enol ether to a radical cation, which undergoes (homo)dimerisation and oxidation/*in situ* desilylation to afford the corresponding 1,4-diketone product **158**. The diastereoselectivity of this transformation is rationalised by an '*anti*' approach of the two enols, which minimises steric interactions in the C–C bond forming step. A recent publication by the Thomson group has further extended the synthetic utility of silicon tethers in these single electron transfer reactions, providing a new method for the intramolecular allylation of ketones.[72]

A gold-catalysed intramolecular allylation of silyl alkynes **159** has been described by the Lee group, which allows silicon-substituted skipped dienes **160** to be synthesised with good *E*/*Z*-selectivity (Scheme 31).[73] From a mechanistic perspective, the group has proposed an initial 6-*endo*-dig cyclisation of the alkenyl group onto the gold-complexed alkyne **161**, with stabilisation of the resulting positive charge in **162** *via* the β-silicon effect (although this may be purely inductive in this instance). It is proposed that 6-*endo*-dig cyclisation is favoured over 5-*exo*-dig due to the effect of the silicon substituent, with the β-carbon carrying a greater positive charge than the α-carbon in the cyclisation transition state. Alcoholysis of the silanocycle **162** yields the vinyl alkoxysilane products **160**. Importantly, Lee and co-workers found that a wide range of functionalised allyl and alkynyl functionalities could be tolerated on this alcohol, which immediately enabled further silicon-tethered chemistry, such as diene or enyne RCM.

Finally, Nakamura and co-workers have very recently reported an iron-catalysed Heck-type coupling (Scheme 32), which employs a silicon tether to facilitate the arylation of alkenes in a regio- and stereoselective manner.[74] This process is thought to proceed *via* a ferracyclic intermediate **164**, which then undergoes β-hydride elimination to yield **165**. It is notable that substrates without a directing group, and those with an oxygen-based directing group failed to undergo this iron-catalysed reaction.

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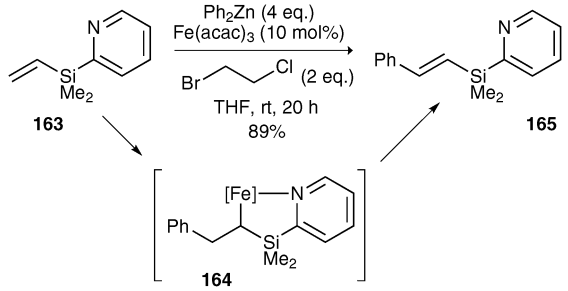

Scheme 32 Iron-catalysed arylation of vinylsilanes (Nakamura).

Conclusions

Silicon tethers confer several advantages on organometallic reactions: they are relatively robust functionalities and are therefore stable to many reaction conditions, and they can influence the stereo- and regioselectivity of reactions (often through the unique ability of the silicon atom to stabilise reactive intermediates). Perhaps most importantly, they display considerable 'latent functionality', in that they may be converted into a number of other functional groups or mediate further chemistry with other components. In this vein, it will be clear from this review that among the most important of these varied transformations are the Tamao–Fleming oxidation[75] and the Hiyama cross-coupling. With recent advances in both areas,[76] it would seem likely that these reactions will continue to represent the main strategic disconnection which leads to the use of the TST.

Although silicon tethers have seen considerable application in the intramolecularisation of metal-mediated reactions, there is also much scope for further improvements, developments, and applications of this most valuable tether. The common orthogonality of metal-catalysed reactions, silyl tethers, and other functionalities within a molecule provides great opportunities for inventive synthesis, tandem processes, and efficient synthetic strategies. For many metal-mediated transformations, silicon-tethering offers opportunities for completely regioselective and stereoselective transformations which may not be easily achieved with their intermolecular counterparts—and in many of these cases, the full potential of the TST strategy has yet to be realised; palladium- and coinage metal-catalysed processes in particular are areas which clearly offer significant opportunities. In addition, the pioneering work by Leighton on the use of chiral TSTs represents an almost entirely unexplored area which seems ripe for development. The selection of high-profile reports which have been published in this field in the last ten years suggests that this is a highly topical and rapidly expanding area of research, and one that is likely to see significant advances in years to come.

Acknowledgements

We thank the EPSRC (Advanced Research Fellowship to E.A.A.; EP/E055273/1), the Clarendon Trust and Merton College (S.B.) for financial support.

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