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C(sp^2)–Si Bond Functionalization through Intramolecular Activation by Alkoxides

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Abstract: Organosilicon reagents are invaluable tools in the hands of the modern chemist that allow accomplishing a number of synthetically useful transformations. While some are standard reactions, other are more complex transformations, such as the Brook rearrangement and its variants. This carbon-to-oxygen silyl migration represents a privileged method to generate transient carbanionic species well suited to undergo functionalization upon electrophilic substitution in the presence of an electrophile. This minireview focuses on recent advances in C(sp^2)–Si bond functionalization through intramolecular activation by alkoxides. The key elements of reactivity will be highlighted in the introduction to allow the proper understanding of the migration process. Then, an overview of the reactivity of substrates incorporating the C(sp^2)–Si motif and their synthetic applications will be provided.

Sebastien Curpanen was born in 1993 in Mauritius. He received his B.Sc. (Hons) degree in Chemistry at the University of Mauritius in 2015, after which, he pursued his studies for the Master degree in molecular chemistry at Sorbonne Université. He is now in his 3rd year of his PhD degree at the IPCM – Sorbonne Université, under the supervision of Dr. A. Perez-Luna and Dr. J. Oble. His work is focusing on C–H functionalization of furfural derivatives, as well as the use of Brook rearrangement for this purpose.

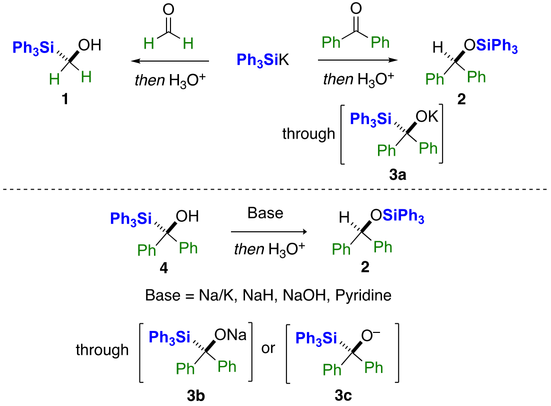
Prof. Giovanni Poli was born in Milan in 1956. He received his Laurea in 1980 and then his PhD degree at the University of Milano, under the direction of Prof. C. Scolastico. In 1986 he continued his scientific education as postdoctoral fellow with Prof. W. Oppolzer at the University of Geneva. After one year as Maître Assistant at the University of Lausanne, he joined the faculty at the University of Florence in 1992 as Associate Professor. In 2000 he reached UPMC (now Sorbonne Université) in Paris as Full Professor. His current interest focuses on the study of innovative transition metal catalyzed transformations, catalytic C–H activation processes and biomass valorization.

Introduction

Alkenyl-, aryl-, and heteroarylsilanes can be used as robust carbanion surrogates endowed with a number of features such as ready availability, low toxicity and excellent functional-group tolerance. These attributes make them highly attractive building blocks in the context of sustainable chemical synthesis and many efforts have been devoted to develop methods for the construction of C(sp^2)–Si bonds. Yet, the counterpart to the assets related to the stability of these reagents is that their use as carbon nucleophiles is the need of specific strategies to activate the C(sp^2)–Si bond. Intramolecular carbon-to-oxygen (C$\rightarrow$O) silyl migrations offer the possibility to generate with high selectivity carbanionic species from C–Si bonds. Whereas this approach has been massively applied for the functionalization of C(sp^3)–Si bonds, related C(sp^2)–Si bond-functionalizations are comparatively rather scarce. This notwithstanding, a number of elegant methodologies has been gradually developed over the years. The aim of this minireview is to illustrate the high synthetic potential of this rapidly growing field of chemistry. Following some general considerations on intramolecular C$\rightarrow$O silyl migrations, the most relevant strategies applied in the context of C(sp^2)–Si bond functionalization will be discussed, focusing on recent advances and future perspectives. A final section will be devoted to the related field of C(sp^2)–Si cross-coupling through intramolecular activation with alkoxides.

Background and General Reactivity Trends

In the early 1950s, Gilman discovered that whereas the reaction of triphenylsilylpotassium with formaldehyde[1] (or aliphatic ketones)[2] provided the "normal" addition product (*i.e.* **1**), the reaction with benzophenone yielded alkoxysilane **2** (Scheme 1, top).[3] The same outcome was observed by Brook for the addition of other triphenylsilylmetal reagents on benzophenone,[4,5] and also upon deprotonation with active metals, organometallic species or organic bases of α-silylcarbinols **4** (Scheme 1, bottom).[6,7] It was then established by Brook,[4,5,8,9] that the formation of silyl ethers in these reactions was the result of the [1,2]-C-to-O migration of the triorganosilyl group in α-triorganosilyl alkoxides **3a**–**c**. This type of rearrangement reaction was popularized as the "Brook rearrangement" and proved to be much more general-in-scope, allowing for 1,2-, 1,3-, 1,4- and 1,5-migrations.



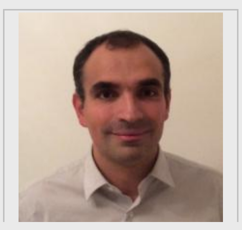
Scheme 1. Seminal reports on C→O triorganosilyl migrations (Brook rearrangement) from α-triorganosilyl alkoxides.

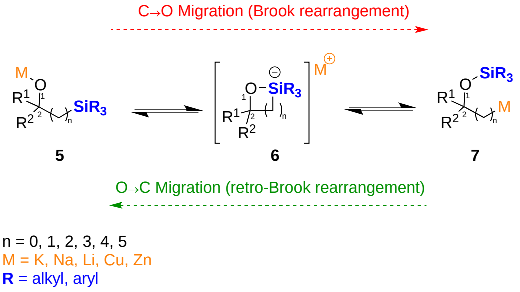
Mechanistic Considerations

The main mechanistic features underpinning these rearrangements were established at an early stage.[9] The migration is in fact a reversible process passing through a pentavalent silicon intermediate **6** (Scheme 2). The observed high negative entropy is consistent with the formation of such a silacycle.[9] Once this intermediate is formed from an alkoxide **5**, it can evolve through C–Si bond cleavage to give carbanion **7** and thereby complete a 1,2-, 1,3-, 1,4- or 1,5-C-to-O migration (Brook rearrangement). However, the reversibility of the process also makes possible to produce an alkoxide **5** from a carbanion **7** through O-to-C migration (retro-Brook rearrangement). Both processes are useful in synthetic organic chemistry and have notably been beautifully combined in the Anion Relay Chemistry concept developed by Smith,[10] wherein site-selective synthetic elaboration is achieved upon the transfer of a negative charge from one place to another.

Dr. Julie Oble received in 2007 her PhD degree from the Ecole Polytechnique (Paris, France) under the direction of Drs. L. Grimaud and L. Elkaïm. In 2007, she obtained a one-year postdoctoral position in the research group of Prof. A. B. Charette at the University of Montréal (Canada). After two further years as a postdoctoral fellow under the supervision of Dr. E. Lacôte, Prof. S. Thorimbert and Prof. B. Hasenknopf at UPMC, she joined in 2010 the research team of Prof. Giovanni Poli at Sorbonne Université as Assistant Professor. Her research focuses on the development of new metal-catalyzed domino reactions toward the synthesis of heterocycles, homogeneous and quasi-homogeneous catalytic C-H activations and biomass valorization**.**

Dr. Alejandro Perez-Luna studied chemistry at the Ecole Nationale Supérieure de Chimie de Paris (Paris, 1997–2000) and then obtained a PhD degree with Laurent Micouin and Henri-Philippe Husson (Université Réné Descartes – Paris 5, 2003). After a postdoctoral stay with Peter Kündig (Geneva, 2004), he joined as a CNRS researcher Fabrice Chemla's group at Univesité Pierre et Marie Curie (now Sorbonne Université). He obtained his habilitation degree from this university in 2012 and was promoted Research Director in 2015. Since 2017, he leads the team ROCS devoted to metal-mediated synthesis. His recent research activity in this area has focused on combining the radical and polar reactivity of organometallic reagents and on the preparation through original C–Si bond-forming reactions of complex/functionalized organosilanes.

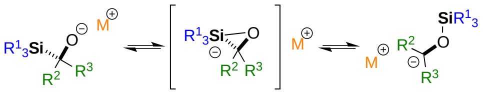




Scheme 2. The Brook and the retro-Brook rearrangements.

The triorganosilyl migration being reversible, the relative stabilities of the starting and final product play a key role to determine the issue of the rearrangement. The driving force behind the C→O migration is often attributed to the high affinity of silicon for oxygen (BDE Si–O is 191.3 kcal/mol compared to 106.9 kcal/mol for the Si–C).[11] However, it also depends on the relative stability of the carbanion compared to that of the alkoxy anion generated. The thermodynamic considerations are in line with the difference in rate of the silyl migration (kinetics) in α-silylcarbinols bearing different substituents (R^2, R^3) on the carbon atom bonded to oxygen (Table 1). Electron-withdrawing groups promote the formation of the carbanionic species, whereas electron-donating groups destabilize this species, so a lower rate for the rearrangement is observed. The nature of the migrating triorganosilyl group also influences the kinetics of the rearrangement. With electron-withdrawing R^1 groups, the rearrangement rate is increased, likely as the result of increased stabilization of the cyclic pentacoordinate silicon intermediate.[6,9,12–14]

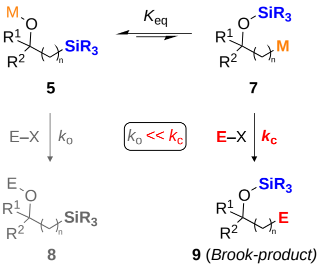
Table 1. Rates for C→O migration in selected α-triorganosilylcarbinols.



Carbinol	k_2 ($M^{-1}s^{-1}$)
9-Triphenylsilyl-9-hydroxyfluorene	1.18
Ph_3SiCPh_2OH	6.10×10^{-3}
$Ph_2MeSiCPh_2OH$	0.98×10^{-3}
$PhMe_2SiCPh_2OH$	1.50×10^{-4}
Me_3SiCPh_2OH	2.50×10^{-5}
$Ph_3SiCPhMeOH$	4.30×10^{-6}
Ph_3SiCMe_2OH	Too slow

The ease of C→O silyl migration also depends on the nature of the metal counter-cation. With coordinating or oxophilic metal cations such as lithium, the migration is less favorable, and therefore, adjustments of some experimental parameters become essential. For zexample, the use of polar solvents and/or additives with high dielectric constant is a common tactic to trigger this rearrangement[9,15] by promoting ion pair dissociation.[16,17] Furthermore, while C→O silyl migrations are usually performed at low temperatures, high temperatures may be needed to achieve formation of the pentacoordinate silicon intermediate in unfavorable cases.

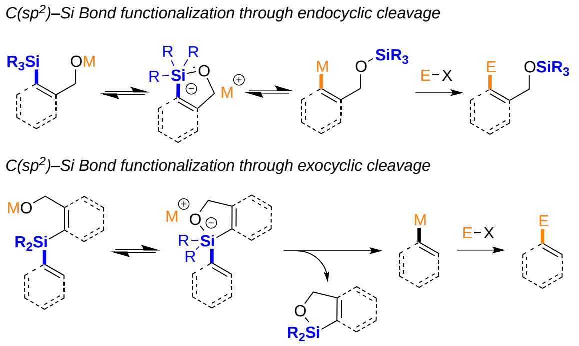
Furthermore, independently of the intrinsic position of the equilibrium of the rearrangement step, the silyl migration may require the presence of an appropriate electrophile to occur. In this case, the aptitude of the carbanionic species to undergo electrophilic substitution becomes crucial, and operating under Barbier-type conditions mandatory. In these frequent situations, although the rearrangement equilibrium is not in favor of the O-silyl carbanionic species, the latter undergoes an irreversible electrophilic substitution more promptly than the C-silyl metal alkoxide. The reaction outcome is governed by the Curtin-Hammett principle: equilibration is fast compared with possible competing O- or C-functionalization, and the rate of formation of **9** is much higher than that of **8** ($k_C >> k_O$) (Scheme 3). Consequently, only the Brook-product (**9**) is formed. Note that in this process the "electrophile" can be not only the stoichiometric reagent delivering the desired functionalization, but also the metal salt in the case of transition-metal catalyzed cross-coupling reactions. Finally, to be thorough, it should also be mentioned that there are also related cases (not shown in the scheme) wherein C-functionalization is quantitatively achieved due to the reversibility of the O-functionalization.[18]



Scheme 3. Shifting of the silyl-migration equilibrium allowing for C–Si bond functionalization.

The Brook rearrangement has attracted considerable interest and found many applications in organic synthesis. Some reviews and book chapters exist, describing applications, asymmetric transformations and mechanistic details.[10,14,19–24] An inspiring personal account on anion relay chemistry was published by Smith during the preparation of the present review.[21] However, synthetic methods relying on C(sp^2)–Si bond functionalization upon activation through Brook rearrangements and related intramolecular activations by alkoxides, which are the focus of this minireview, have not been specifically surveyed previously.

We have organized this review in two parts, according to the nature of the bond cleavage. In the first part (Brook rearrangement), C(sp^2)–Si bond functionalization is achieved through "endocyclic" cleavage (Scheme 4, top). In this case the silyl ether moiety remains in the target compound. Usually, a trialkylsilane is used as the migrating group, and thus the selectivity of C–Si bond cleavage from the silacyclic intermediate is not an issue, as the formation of a more stable C(sp^2) carbanion favours C(sp^2)–Si over C(sp^3)–Si bond-cleavage. In the second part, the reacting C(sp^2)–Si bond undergoes "exocyclic" cleavage. In this case, no silyl migration occurs and the alkoxy unit "only" serves as intramolecular trigger (Scheme 4, bottom). Most of the tethers developed for this purpose so far involve a C(sp^2)–Si linkage, and thus, here, the selectivity of the C(sp^2)–Si bond cleavage from the cyclic hypervalent silicon intermediate can be an issue.[25]



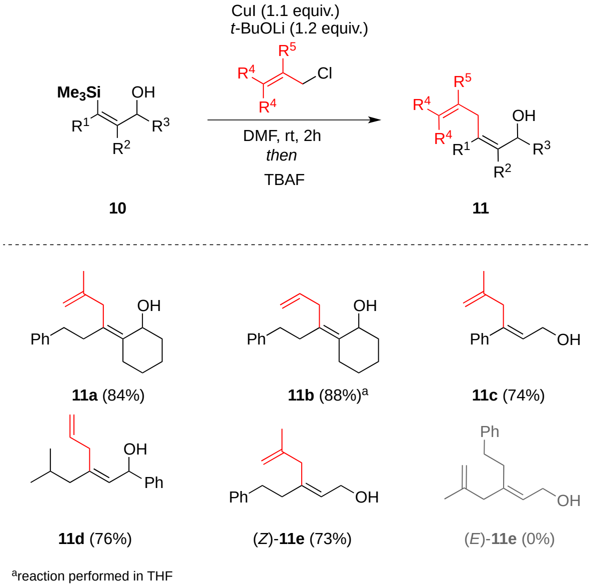
Scheme 4. General approaches for C(sp^2)–Si bond functionalization through intramolecular activation by alkoxides.

1. C(sp^2)–Si Bond Functionalization through Endocyclic Cleavage

Selective functionalization of alkenes and aromatic rings bearing other functional groups is often rather problematic. In this context, C(sp^2)–Si bond functionalization of alkenyl- or (hetero)aryl-silanes through the Brook rearrangement represents a useful alternative to metalation chemistry and offers specific opportunities for regio- and stereocontrol.

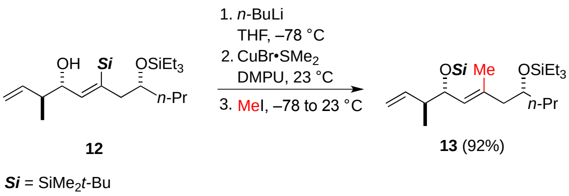
1.1 C(sp^2)–Si Bond Functionalization of Alkenylsilanes

In 2001, the Takeda group developed a strategy for the stereoselective allylation of (*Z*)-γ-trimethylsilyl allylic alcohols **10**.[26] Successive treatment with copper(I) *tert*-butoxide and allyl halides in DMF, followed by the TBAF-assisted hydrolysis, yielded dienyl alcohols **11** with complete retention of configuration of the double bond (Scheme 5). The mechanism involves firstly the formation of a copper alkoxide that then rearranges by [1,4]-C(sp^2)→O trimethylsilyl migration to give a vinylcopper species, which is then trapped by the corresponding allyl halide. In agreement with the intramolecular character of the rearrangement, formation of the *E* isomers (*e.g.* (*E*)-**11e**) was not observed from the parent (*E*)-γ-trimethylsilyl allylic alcohols. It is noteworthy that this activation method was also suitable to perform palladium-catalyzed cross-coupling reactions.



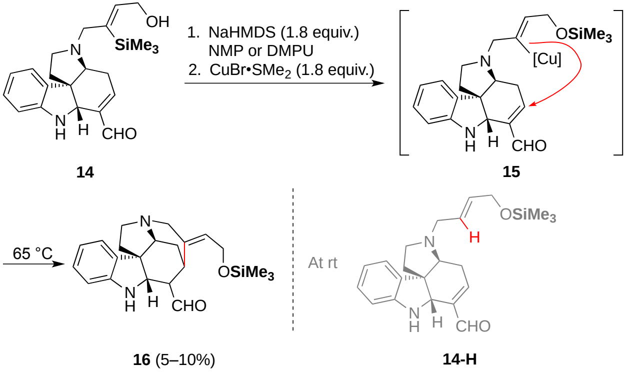
Scheme 5. Copper(I) *tert*-butoxide-promoted [1,4]-C(sp^2)→O silyl migration of (*Z*)-γ-trimethylsilyl allylic alcohols.

The synthetic value of this method triggered a number of synthetic applications that exploited trapping of the vinylcopper intermediate with a number of electrophiles. In a total synthesis of dolabelide D, vinylsilane **12** was methylated to yield **13** (Scheme 6).[27] In this case, the trimethylsilyl group served not only as platform for functionalization, but also as alcohol protecting group for subsequent transformations.



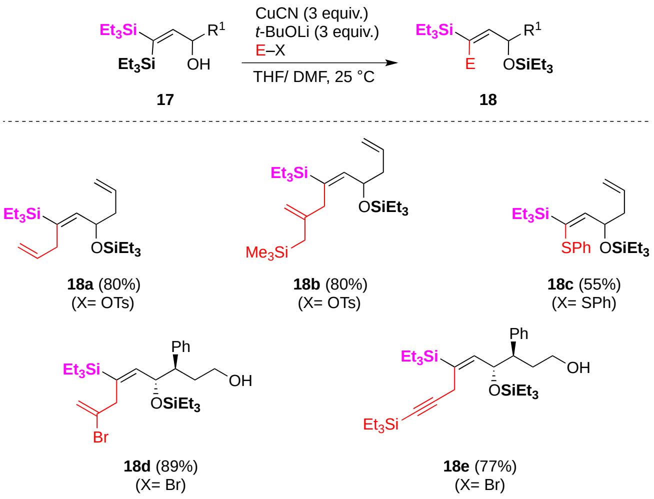
Scheme 6. A key step for a total synthesis of dolabelide D.

The same alkenyl anion generation strategy was followed in a (formal) total synthesis of strychnine, wherein allylic alcohol **14** was transformed into the pentacyclic product **16** (Scheme 7). Following deprotonation of the hydroxy function of **14** with NaHMDS, a [1,4]-C(sp^2)→O trimethylsilyl migration was triggered by the addition of a copper(I) salt in presence of NMP or DMPU. At room temperature, the transient vinylcopper anion **15** led only to the protodemetalated product **14-H**. By contrast, at 65 °C, intramolecular 1,4-addition on the α,β-unsaturated aldehyde occurred, yielding 5–10% of the cyclized product **16** that could not be accessed by other means.[28]



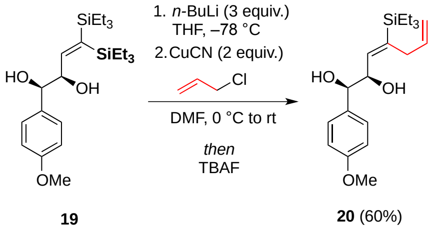
Scheme 7. A key step for a formal total synthesis of strychnine.

This approach was later applied with γ,γ'-bis(trimethylsilyl) allylic alcohols **17**.[29,30] Specifically, CuCN / lithium *tert*-butoxide in DMF/THF triggered the [1,4]-Brook rearrangement, and trapping with an array of electrophiles led fully stereoselectively to trisubstituted vinylsilanes such as **18** (Scheme 8). The key point of this reaction is that only the triethylsilyl group *cis* to the hydroxy undergoes the C(sp^2)→O migration, as the triethylsilyl group *trans* to the alkoxy anion cannot take part in the formation of a cyclic hypervalent pentacoordinate silicon complex. Interestingly, in the formation of **18d** and **18e**, [1,4]-silyl migration fully overrides a possible alternative [1,7]-silyl migration.



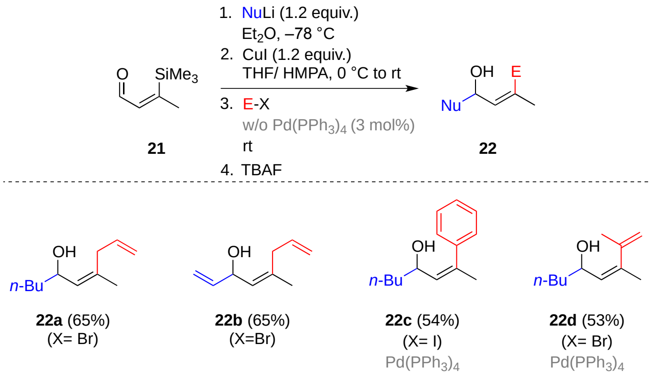
Scheme 8. Stereoselective [1,4]-Brook rearrangement/alkylation of geminal γ, γ'-bis-silyl allylic alcohols.

The *gem* bis(triethylsilyl) alkene system was also used to study the competition between [1,4]- and [1,5]-C(sp^2)–Si→O migration in the Brook rearrangement. Specifically, deprotonation with butyllithium of the 1,2-diol **19**[31] followed by CuCN / DMF addition (to promote the silyl migration), and trapping with allylchloride gave only the [1,4]-silyl migration product **20** (Scheme 9).



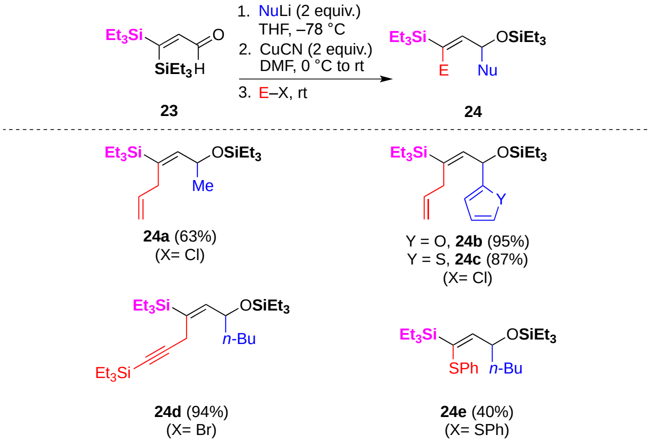
Scheme 9. Regioselective [1,4]-Brook rearrangement of geminal bis-silyl allylic 1,2-diol.

The [1,4]-Brook rearrangement of (*Z*)-γ-trimethylsilyl allylic alcohols has also been embedded in multi-step sequences involving a preceding alkoxide-forming reaction. For instance, the 1,2-addition of an organolithium reagent to aldehyde **21** generates an alkoxy anion, which, activated in the presence of CuI and HMPA, undergoes the Brook rearrangement. The resulting organocopper intermediate can be trapped by an allyl bromide giving products such as **22a** or **22b.** Alternatively, in the presence of aryl or vinyl halides and of a palladium(0) catalyst, the corresponding arylated or alkenylated products (i.e. **22c** or **22d**) can be obtained (Scheme 10).[32]



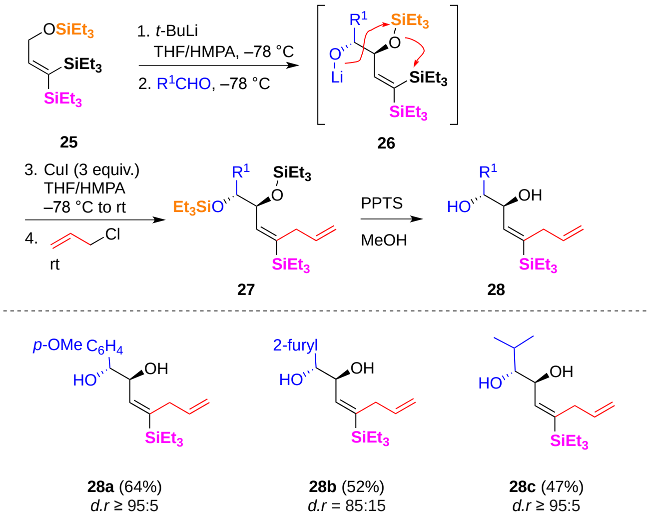
Scheme 10. Three-component anion relay couplings from an aldehyde / vinyl silane linchpin.

The strategy was also implemented with geminal bis(triethylsilyl) enals **23**.[33] Upon 1,2-addition of organolithium reagents, the lithium alkoxides produced were treated with CuCN and an electrophile in DMF, to obtain trisubstituted vinylsilanes **24** in excellent yields and stereoselectivities (Scheme 11).



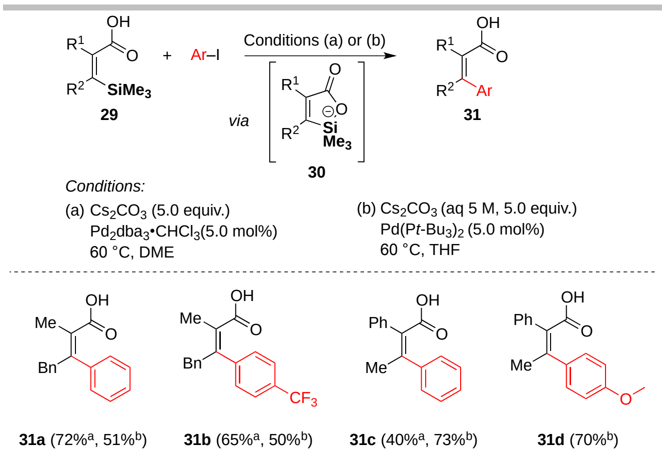
Scheme 11. Three-component reaction to synthesize trisubstituted vinylsilanes from geminal bis(silyl)enals.

Another example involves a more complex sequence including a preceding anion relay step (Scheme 12). Geminal bis(triethylsilyl) allyl silyl ether **25** was metalated at the allylic position and then opposed to aldehydes to generate the corresponding alkoxides **26**. This triggered a [1,4]-O→O silyl migration followed by a [1,4]-C(sp^2)→O silyl migration, and the alkenylcopper reagents then generated were trapped in the presence of electrophiles to yield adducts **27**. Finally, treatment with PPTS in MeOH led to diols **28**.[34]



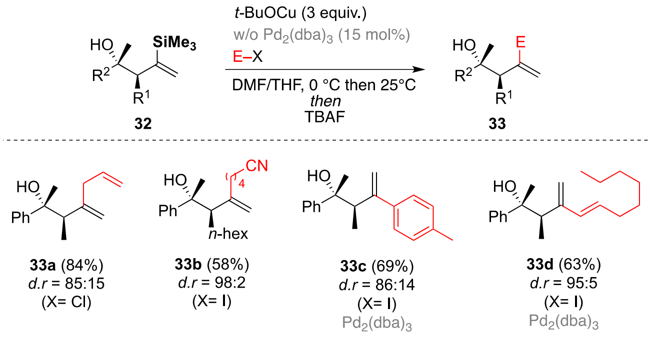
Scheme 12. Sequential [1,4]-O-to-O / [1,4]-C(sp^2)-to-O silyl migrations.

A related [1,4]-Brook rearrangement is also at the origin of the strategy developed by Shindo and co-workers to achieve the cross-coupling of the (*Z*)-β-(trialkylsilyl)acrylic acids. The presence of a β located carboxylic acid function provides a smooth way to activate the C–Si bond of vinyl silanes **29** (Scheme 13).[35] Indeed, intramolecular carboxylic acid-triggered silane activation can be smoothly obtained with cesium carbonate. The resulting transient cyclic hypervalent silicon intermediates **30** can then be treated with aryl iodides in the presence of an appropriate Pd catalyst, to yield the corresponding (*Z*)-β-(aryl)acrylic acids **31**.



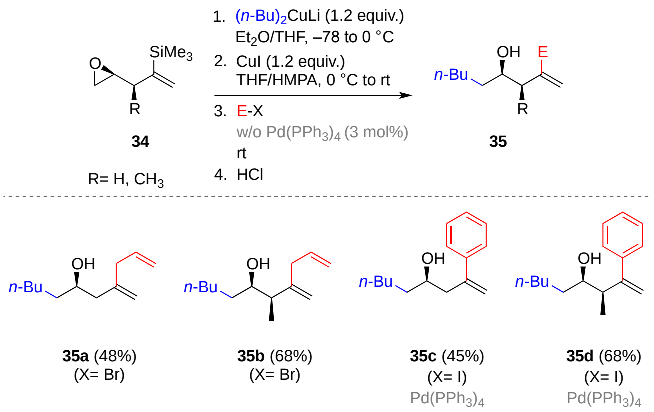
Scheme 13. Cross-coupling of (*Z*)-β-(trialkylsilyl)acrylic acids via intramolecularly activation of vinyl silane.

In 2015, Takeda reported on the C(sp^2)–Si functionalization of enantiopure γ-(trimethylsilyl) homoallylic alcohols **32** giving products **33** upon [1,4]-C(sp^2)→O trimethylsilyl migration followed by electrophilic substitution of the alkenyl carbanion (Scheme 14).[36] Allylation and alkylation reactions, such as those yielding **33a–b**, were performed by treatment with *t*-BuOCu in the presence of alkyl- or allyl-halides. Vinylation or arylation reactions, such as those yielding **33c–d**, were also feasible using vinyl or aryl halides as electrophiles, albeit only in the presence of an additional palladium-catalyst. These reactions have been shown to occur without variation in the diasteromeric ratio, which means that this method is well-suited in the context of stereoselective synthesis as it does not promote the epimerization of carbon stereocenters.



Scheme 14. Stereoselective synthesis of β,γ-disubstituted *tert*-homoallylic alcohols.

As for the previous [1,4]-Brook rearrangement of (*Z*)-γ-trimethylsilyl allylic alcohols, the rearrangement of γ-(trimethylsilyl) homoallylic alcohols can also be included into multicomponent systems (most commonly, three-component systems), with the key step being the generation of an alkoxide ion. This includes bifunctional silylated linchpins bearing carbonyl and/or epoxide functions.[32] For instance, the alkoxide resulting from the nucleophilic addition of lithium dibutyl cuprate to epoxide **34** can be activated in the presence of copper(I) iodide in HMPA, triggering a [1,4]-silyl migration (Scheme 15). The subsequent organocopper reagent can be trapped by an allyl bromide, leading to compounds **35a** and **35b,** or, in the presence of palladium(0) catalyst, be arylated to yield compounds **35c** or **35d** via cross-coupling reactions.[32]



Scheme 15. Three-component anion relay coupling from epoxide vinyl silane linchpin.

In a study performed by Smith in 2017, the requirements to achieve [1,4]- and [1,5]-C(sp^2)→O silyl migrations from copper(I) alkoxides were investigated by a combination of experimental results and computations.[37] The [1,4]-C(sp^2)→O silyl migrations on alkenyl systems most often involve internal alkenes, while terminal alkenes are less described. In line with these observations, theoretical studies using the DFT method (M06 with solvation) showed that the terminal alkene **37** is coordinated more strongly to copper(I) iodide than the internal one **36** (Figures 1 and 2, compare the blue profiles). This leads to a striking silyl migration activation barrier difference between **37** and **36**, the latter being 13.8 kcal/mol easier due to its higher strain.

The requirement established in earlier experimental work for two equivalents of alkyl lithium to achieve efficient [1,4]-Brook rearrangement was also analyzed. It was proposed that the first equivalent serves to achieve alkoxide generation (through hydroxide deprotonation or nucleophilic addition to aldehydes), while the second generates an alkylcopper reagent. For the latter (*e.g.* MeCu), owing to a higher LUMO level resulting in a less strong coordination of the copper atom to the alkene, the activation barrier for silyl migration is lower than for CuI. In the case of vinylsilane **37** bearing a terminal alkyne, silyl migration with CuMe (E_{A2}) was computed to have an activation barrier lower by 4.0 kcal/mol than with CuI (E_{A1}) (Figure 2, compare blue and orange profiles). While these theoretical studies provide valuable insight to shed light on the influence of the nature of the copper species on the Brook-rearrangement, they should be taken with caution as the reacting copper species certainly differ in many other aspects (*e.g.* aggregation state, electronic nature).

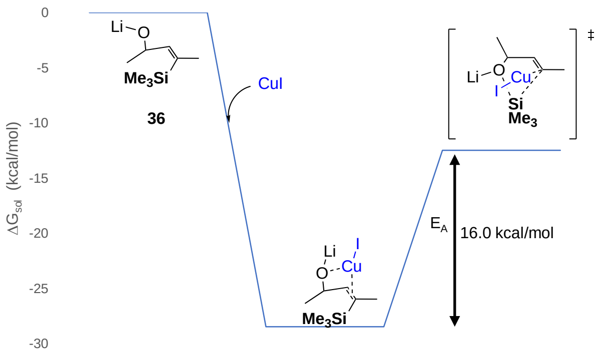


Figure 1. [1,4]-Vinyl Brook rearrangements involving an internal double bond and CuI.

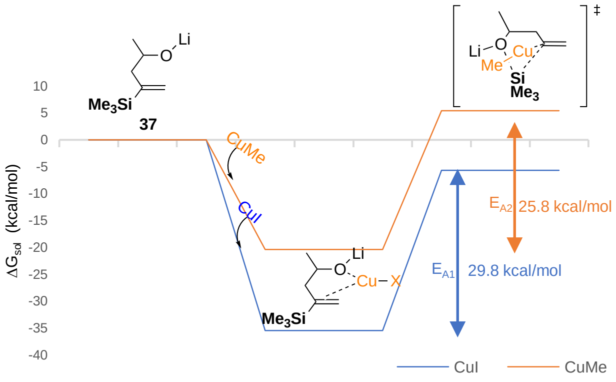


Figure 2. [1,4]-Vinyl Brook rearrangements involving a terminal double bond and CuI or CuMe.

[1,5]-C(sp^2)→O silyl migration is more difficult than the corresponding [1,4] one, as demonstrated in the same study by Smith,[37] and has been somewhat less described in the literature. The rearrangement of the silyl alkoxide **38**, bearing one carbon atom more than **37** between the alkoxide and the alkene functions, requires a silyl migration activation barrier that is 3.7 kcal/mol higher than from **37** (Figures 2 and 3, compare the orange profiles). This can be ascribed to a larger conformational change between the intermediate and the transition state for the [1,5]-rearrangement (15.3°) than for the [1,4]-counterpart.

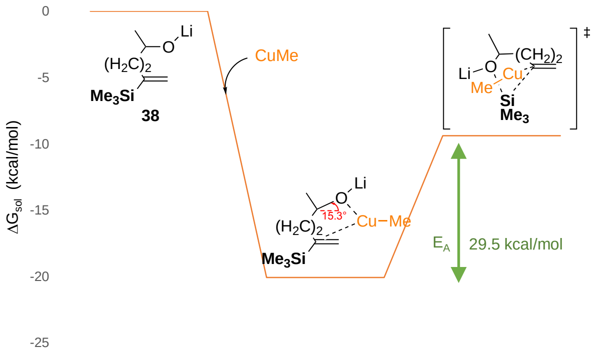
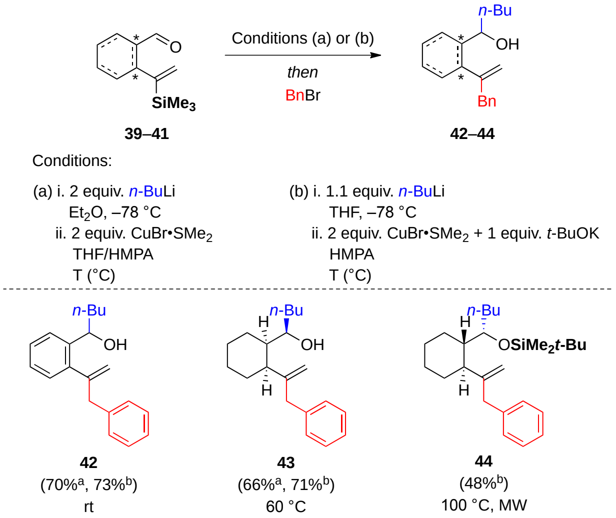


Figure 3. [1,5]-Vinyl Brook rearrangements involving a terminal double bond and CuMe.

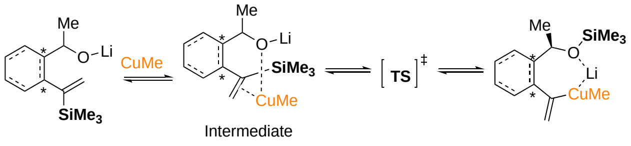
The influence of conformational constraints in the substrates was further analyzed by considering the [1,5]-C(sp^2)→O silyl migrations in conformationally rigid molecules with different tethers such as phenyl (**39**), *cis*-cyclohexyl (**40**) and *trans*-cyclohexyl (**41**) (Scheme 16). A number of electrophiles, including alkyl, benzyl and allyl halides, can be used to trap the anion arising from the Brook rearrangement and deliver 1,1-disubstituted alkenes. Arylation and alkenylation are also possible for these compounds, provided a palladium-catalyst is added.[37]



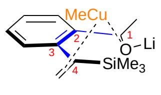
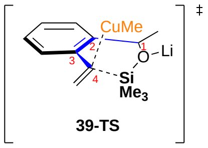
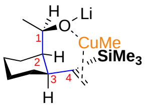
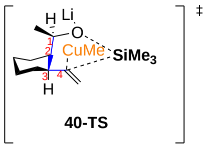
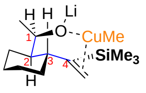
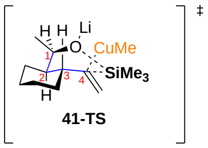
Scheme 16. [1,5]-C→O silyl migrations in conformationally rigid molecules.

The calculated activation barrier for **39-TS**, **40-TS** and **41-TS**, which are close models, increases from 23.3 kcal/mol to 25.6 kcal/mol and 29.7 kcal/mol, respectively (Table 2). These values are consistent with the experimental temperatures required to observe the rearrangement: room temperature for **39** (giving **42**), 60°C for **40** (producing **43**), and 100 °C under micro-wave irradiation for **41**(yielding **44**) (Scheme 16). In addition, the calculations demonstrated a good correlation between the extent of the required conformational change of the tether and the barrier for the [1,5]-Brook rearrangement. For instance, the rigidity of **39**, combined with a minimum required conformational change, accounts for the low energy barrier to the rearrangement in this case. Furthermore, the difference between the ease of migration of cis-cyclohexyl **40** with respect to trans-cyclohexyl **41** can be rationalized on the grounds of differential dihedral angle (OC-C-C-CSi) distortion Δϕ. Indeed, the latter substrate is associated to a much energy demanding Δϕ (from 6.1° to 13.5°). The key points in terms of conformational changes, intermediates and transition states for this rearrangement, are represented in Table 2.

Table 2. Computational study for the conformational change between transition state and its intermediate

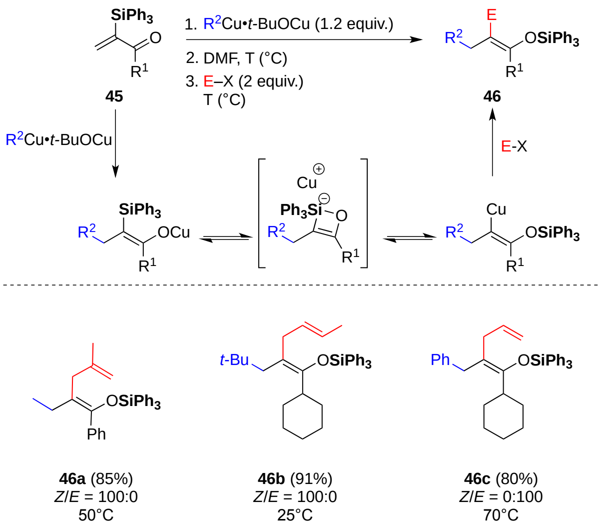


Intermediate	Transition state	Δϕ	E_A (kcal/

			mol)
 **39’**	 **39-TS**	4.8°	23.3
 **40’**	 **40-TS**	6.1°	25.6
 **41’**	 **41-TS**	13.5°	29.7

Φ was calculated C_1-C_2-C_3-C_4 and Δϕ is the difference between ϕ(intermediate) and ϕ(TS).

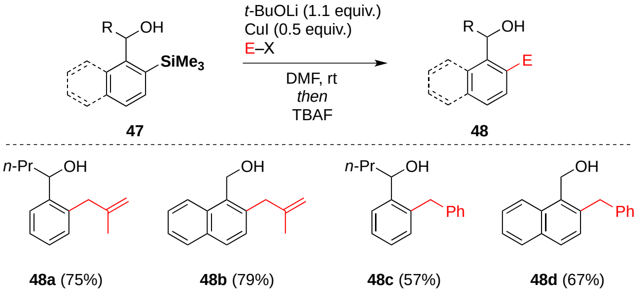
C(sp^2)–Si bond functionalization of vinylsilanes through [1,3]-Brook rearrangements are much less common than [1,4]- and [1,5]-migrations. Nevertheless, Tsubouchi and Takeda exploited such a rearrangement to develop a strategy for the preparation of substituted silyl enol ethers starting from α-silyl α,β-unsaturated ketones **45** (Scheme 17).[38] 1,4-Addition of organocopper reagents to these substrates leads to the formation of the corresponding copper enolates as an equilibrating mixture of two diastereoisomers (*Z* and *E*). Following addition of DMF and at higher temperature, [1,3]-C(sp^2)→O triphenylsilyl migration becomes possible, but only for the *Z* isomer, which is the only one for which formation of a cyclic pentavalent silicon intermediate is feasible. Hence, the stereoselective formation of alkenylcopper intermediates is obtained, and their functionalization, with retention of the double-bond geometry, can be performed through electrophilic substitution. This method provides direct access to tetrasubstituted silyl enol ethers **46**, which are particularly useful reagents for the construction of quaternary stereogenic centres.[39]



Scheme 17. Synthesis of substituted silyl enol ethers from α-silyl α,β-unsaturated ketones.

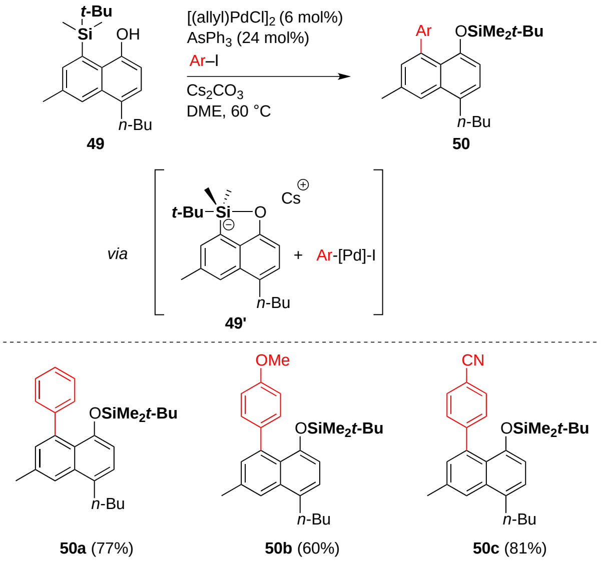
1.2 C(sp^2)–Si Bond Functionalization of Arylsilanes

The [1,4]-C(sp^2)→O migration has also been used for the activation of arylsilane derivatives. In 2004, Takeda demonstrated that *o*-(1-hydroxyalkyl)arylsilanes **47** could undergo cross-coupling with organic halides by treatment with copper(I) *tert*-butoxide, in DMF in the presence of an electrophile to afford compounds **48** (Scheme 18).[40] This is among the first examples of Brook rearrangement on aryl silanes.



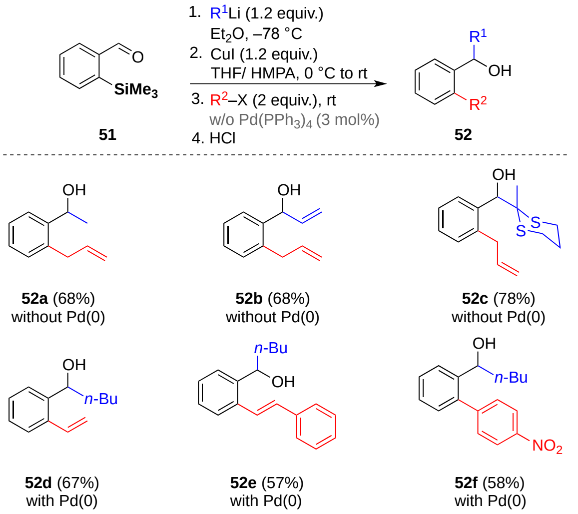
Scheme 18. *t*-BuOCu-promoted coupling of o-(1-hydroxyalkyl)arylsilanes with organic halides.

A related [1,4]-C(sp^2)→O migration is also involved in the substitution of a robust *tert*-butyldimethylsilyl (TBDMS) group by aryl groups in Hiyama-type cross-coupling reactions.[41] For instance, the coupling of 8-TBDMS-1-naphthol **49** occurs in the presence of cesium carbonate in DME. The mechanism is expected to involve the formation of cyclic hypercoordinate silicon intermediate **49’**, which then undergoes transmetalation with the aryl palladium iodide species in turn generated by oxidative addition of the aryl iodide to Pd(0). A reductive elimination then leads to the corresponding product **50** (Scheme 19).



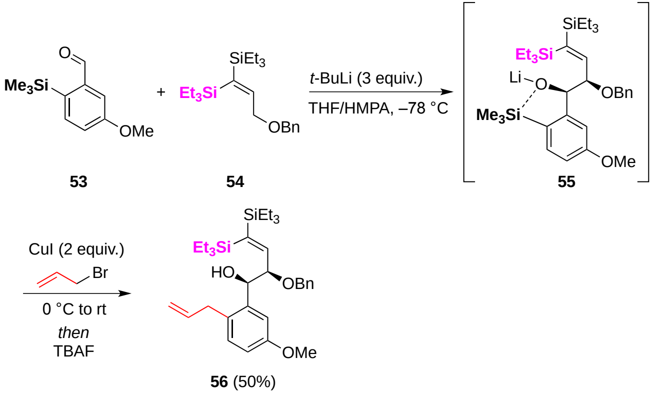
Scheme 19. Hiyama-type cross-coupling reactions of 8-TBDMS-1-naphthols.

As for some of the above discussed reactions with alkenylsilanes, the silyl-migration step can be combined with a preceding alkoxide-generating reaction. For instance, the nucleophilic addition of organolithium reagents to carbonyl derivative **51** was combined with subsequent Cu(I)-mediated [1,4]-silyl migration, which allows for the selective functionalization of the aromatic ring in the *ortho* position to give alcohols **52** (Scheme 20).[32,42] It is important to note that the use of a Pd(0) catalyst in addition to copper is necessary for electrophilic substitutions with aryl- or vinyl-halides yielding products **52d**–**f**.



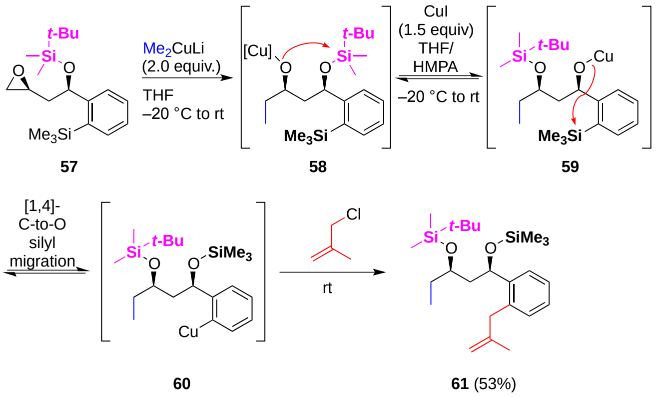
Scheme 20. [1,4]-silyl migration from *ortho*-TMS benzaldehyde.

Similarly, a combined 1,2-addition/directed C(sp^2)–Si functionalization was achieved in the three-component reaction between silylated benzaldehyde **53**, lithiated bis(triethylsilyl) allyl silyl ether **54** and electrophiles in the presence of *t*-BuLi. Alkoxide **55** arising from the 1,2-addition has the possibility to engage in silyl migrations both with the alkenyl- and the aryl-silane moieties. Only migration leading to an aryl anion was observed, and subsequent alkylation with allyl bromide resulted in the formation of compound **56** (Scheme 21). The exact origin of this selectivity in the migration was not determined, but it could be related to the higher stability of an aryl anion relative to an alkenyl anion, to more favorable kinetics for trimethylsilyl versus triethylsilyl migration, to a preference for [1,4]-migration over [1,5]-migration or, likely, to a combination of all the three reasons.[31]



Scheme 21. Selective C(sp^2)–Si migration of an aryl-silane versus of an alkenylsilane.

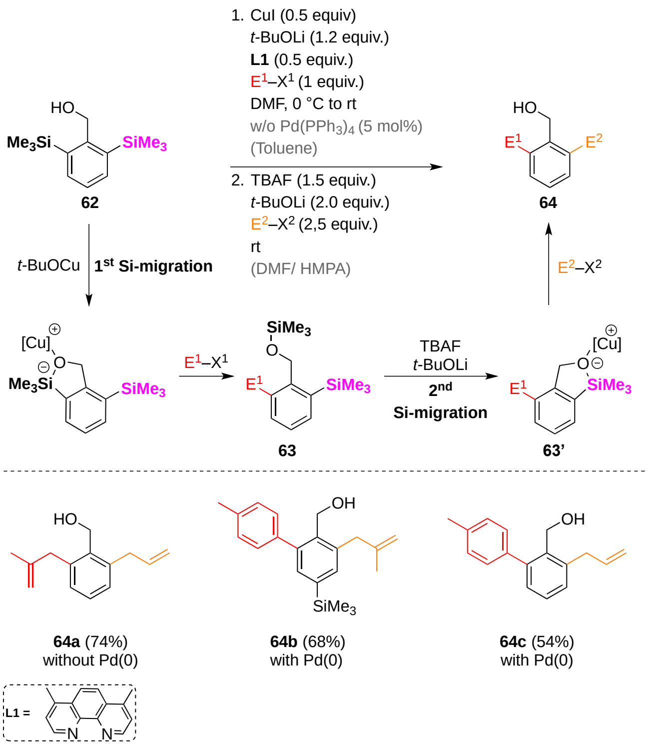
Such Brook-promoted C(sp^2)–Si activation reactions were also combined with anion relay processes. The example shown in Scheme 22 is based on initiation through the opening of an epoxide. Ring-opening of epoxide **57** with dimethyl cuprate gives rise to alkoxide **58**. The addition of copper iodide in the presence of HMPA triggers a first [1,5]-O→O silyl migration (involving the TBDMS group) which provides copper alkoxide **59**. Following a second [1,4]-C(sp^2)→O silyl migration, the aryl anion (**60**) generated, is in turn trapped by an electrophile, leading to the final compound **61**.[43]



Scheme 22. Multiple transfer of silyl groups through sequential 1,5-O→O / 1,4-C→O migrations.

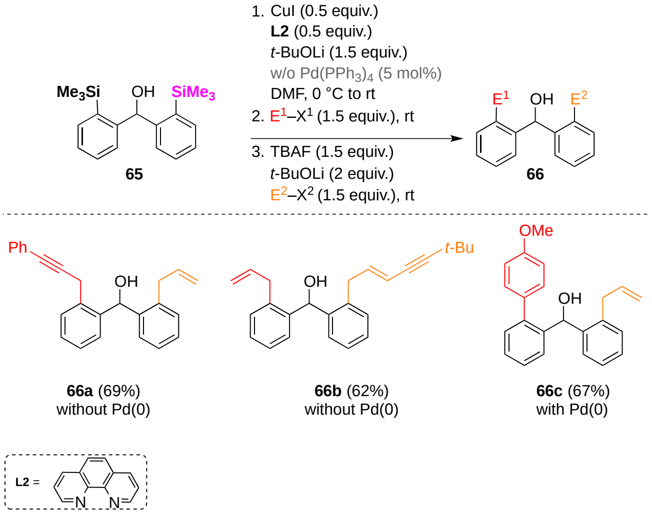
On a green chemistry perspective, one-pot multicomponent or sequential transformations are considered more environmentally friendly as they involve fewer purification steps, thus less product loss, and also, from an economic point of view, they are less expensive.[10]

In this context, recently, a procedure for the one-pot bidirectional difunctionalization through two consecutive Brook rearrangements of benzylic alcohol **62** bearing two *ortho*-trimethylsilyl groups was developed (Scheme 23). In these processes, following deprotonation with *t*-BuOLi, a first [1,4]-C(sp^2)→O trimethylsilyl migration occurs in the presence of DMF, copper(I) iodide and phenanthroline ligand **L1**. The aryl carbanion is then trapped by a first electrophile **E^{1}X^1**, leading to silyl ether **63**, which can be converted in situ into alkoxide **63'** by addition of a fluoride source and lithium *tert*-butoxide. The alkoxide thus formed is engaged in a second [1,4]-C(sp^2)→O trimethylsilyl migration, which gives the difunctionalized compounds **64** by reaction with **E^2X^2**. This method can also be combined with palladium cross-coupling reactions to perform arylation and vinylation reactions.[44]



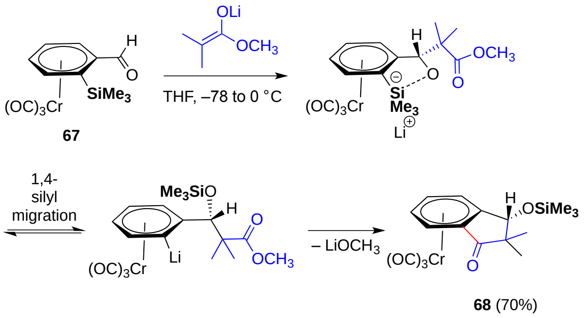
Scheme 23. Sequential [1,4]-C(sp^2)→O silyl migrations of 2,6-di(trimethylsilyl) benzyl alcohol.

The same strategy and similar operating conditions were also successfully applied to achieve the bifunctionalization of bis-*ortho*-trimethylsilyl benzhydrol derivative **65** leading to unsymmetrical diarylmethanols **66** (Scheme 24).[45]



Scheme 24. Sequential [1,4]-C(sp^2)→O silyl migrations of bis-*ortho*-trimethylsilyl benzhydrol.

Alkoxides arising from the addition of organolithium reagents to tricarbonyl(η^6-2-TMS-benzaldehyde)chromium **67** undergo quantitative [1,4]-C(sp^2)→O trimethylsilyl migration because the anion produced benefits from stabilization by the $Cr(CO)_3$ moiety. Subsequent trapping with electrophiles is possible even in the absence of polar additives or Cu(I) salts.[46] This feature was nicely exploited to develop a Brook-based [3+2]-annulation reaction upon (stereoselective) addition of an ester enolate to **67** (Scheme 25).[47] Here, the transiently generated aryl anion undergoes a final intramolecular acylation to deliver **68**. The chromium tricarbonyl can easily be detached after the transformation by simple exposure to air and sunlight.



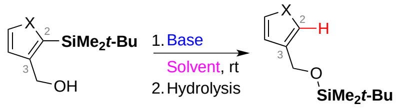
Scheme 25. Brook rearrangement in silylarene chromium tricarbonyl complexes.

1.3 C(sp^2)–Si Bond Functionalization of Heteroarylsilanes

Heteroarenes are ubiquitous units in organic compounds, and their regioselective functionalization is a fundamental endeavor for synthetic chemists.[48] In this context, the Brook rearrangement is a useful tool for this purpose, as shown by the several studies on intramolecular [1,4]-C(sp^2)→O silyl migrations of silylated furans and thiophenes.

Implementation of this tactic received particular attention for the preparation of (2,3)-disubstituted furans and thiophenes. Initial studies on the [1,4]-C(sp^2)→O silyl migration in furan **69** and thiophene **70**, having a TBDMS group on position C2 and a hydroxymethyl group on position C3, showed that the reactions were highly solvent and counterion dependent (Table 3).[49] Whereas the Brook rearrangement leading to silyl ethers **71** and **72** proceeded smoothly using sodium or potassium hydride, as well as sodium hydroxide in DMF or THF (entries 1-2, 4-6), lithium or magnesium bases failed to promote the migration in THF (entries 7-8). The lack of reactivity of these Li and Mg derivatives was possibly due to the high oxophilic nature of these metal cations, resulting in a stronger coordination to oxygen.[49–51] This limitation represented a significant flaw for synthetic applications, as the carbanion formed by the migration promoted with the sodium or potassium bases could not be trapped with electrophiles other than protons.

Table 3. [1,4]-C(sp^2)→O silyl migrations 2-TBDMS-3-hydroxymethyl furan and thiophene derivatives.

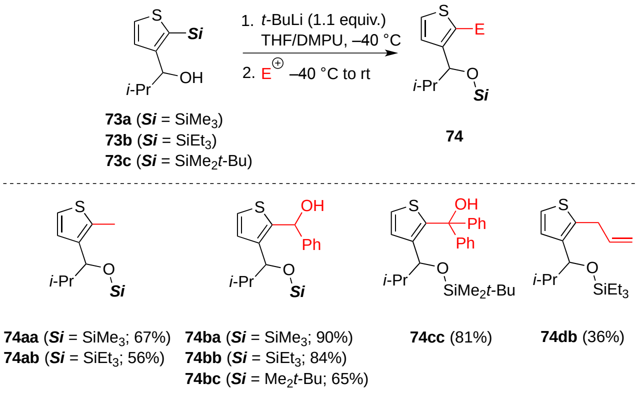


69 (X= O)
70 (X=S)

71 (X= O)
72 (X=S)

Entry	Base	Solvent	t	Yield (%)
1	NaH (5 equiv.)	DMF	5 min	88
2	NaH (5 equiv.)	THF	16 h	80
3	NaH (5 equiv.)	Et_2O	7 d	_
4	NaH (1 mol%)	DMF	15 min	92
5	KH (5 equiv.)	THF	2 d	61
6	NaOH (5 equiv.)	DMF	1 h	64
7	CH_2=CHMgBr (1 equiv.)	THF	1 d	_
8	n-BuLi (1 equiv.)	THF	1 d	_

Some years after, a similar behavior was observed for the base-promoted rearrangement of 3-hydroxyalkyl-2-silylthiophenes **73a–c** (Scheme 26).[52] After screening different additives, it was found that [1,4]-C(sp^2)→O silyl migration can be obtained by treatment with *t*-BuLi in THF, in the presence of DMPU. Other common additives such as HMPA or 12-crown-4 ether lead to very poor results. The optimized experimental conditions are also appropriate for the silyl migration of different trialkylsilyl moieties and, most importantly, can be combined with the trapping of the anion produced with different electrophiles, including methyl iodide (**74aa**, **74ab**), benzaldehyde (**74ba, 74bb, 74bc**) and benzophenone (**74cc**), leading to 2,3-difunctionalized thiophenes, while, with allyl bromide, a moderate yield is obtained for **74db**.



73a (***Si*** = SiMe$_3$)
73b (***Si*** = SiEt$_3$)
73c (***Si*** = SiMe$_2$*t*-Bu)

74

74aa (***Si*** = SiMe$_3$; 67%)
74ab (***Si*** = SiEt$_3$; 56%)

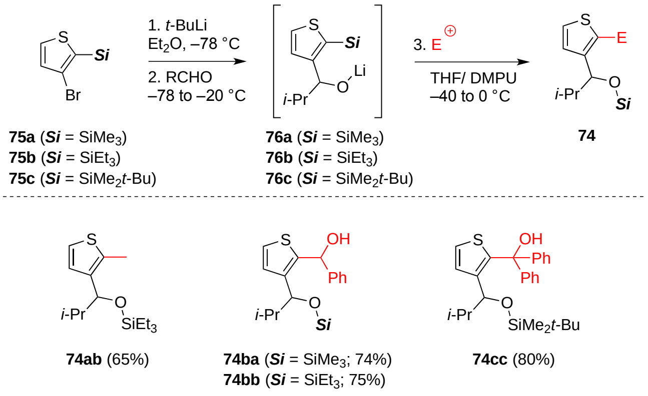
74ba (***Si*** = SiMe$_3$; 90%)
74bb (***Si*** = SiEt$_3$; 84%)
74bc (***Si*** = Me$_2$*t*-Bu; 65%)

74cc (81%)

74db (36%)

Scheme 26. Silyl migration/alkylation of 3-hydroxyalkyl-2-silylthiophenes.

Additionally, this reaction can be carried out in a sequential one-pot reaction starting from bromothiophenes **75a–c** (Scheme 27).[52] The first step involves a Br–Li exchange upon addition of *tert*-butyl lithium. The thus formed organolithium reagent is then trapped by an aldehyde to provide alkoxides **76a–c**, which, under polar conditions and in the presence of an electrophile (alkyl halides, benzaldehyde or benzophenone), undergoes the silyl migration, leading to the final compounds **74**. The yield of the one pot reaction from **75a–c** to **74** is in concordance with the previous formation of **74** in two steps (Scheme 26).



75a (***Si*** = SiMe$_3$)
75b (***Si*** = SiEt$_3$)
75c (***Si*** = SiMe$_2$*t*-Bu)

76a (***Si*** = SiMe$_3$)
76b (***Si*** = SiEt$_3$)
76c (***Si*** = SiMe$_2$*t*-Bu)

74

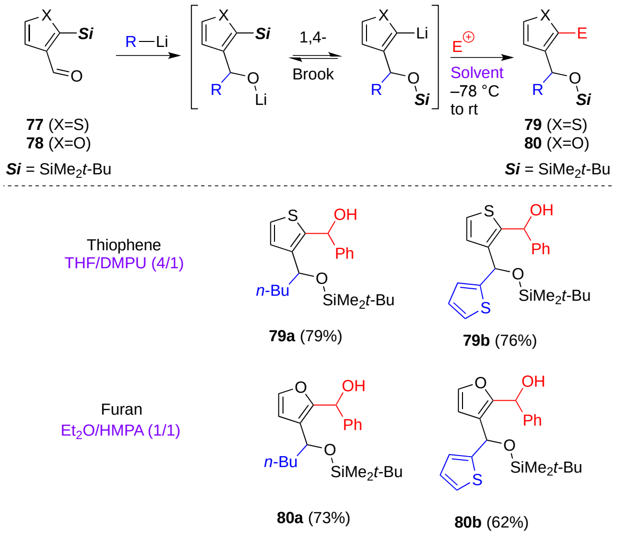
74ab (65%)

74ba (***Si*** = SiMe$_3$; 74%)
74bb (***Si*** = SiEt$_3$; 75%)

74cc (80%)

Scheme 27. One-Pot synthesis of 2,3-disubstituted thiophenes.

Following a related three-component strategy, the 2,3-disubstituted thiophenes **79** and furans **80** have been obtained from the 3-formyl heterocyclic precursors **77** and **78** (Scheme 28).[18] Addition of the alkyllithium reagents to the aldehydes generates the corresponding alkoxides, which undergo the Brook rearrangement. This crucial step is again carried out in a THF/DMPU (4/1) mixture, and the resulting carbanion can be trapped by benzaldehyde, for example. However, in the case of the furan derivative **80**, the Brook rearrangement requires the use of an Et_2O/HMPA[53] (1/1) mixture (Scheme 28).



77 (X=S)
78 (X=O)
Si = SiMe$_2$*t*-Bu

79 (X=S)
80 (X=O)
Si = SiMe$_2$*t*-Bu

79a (79%)

79b (76%)

80a (73%)

80b (62%)

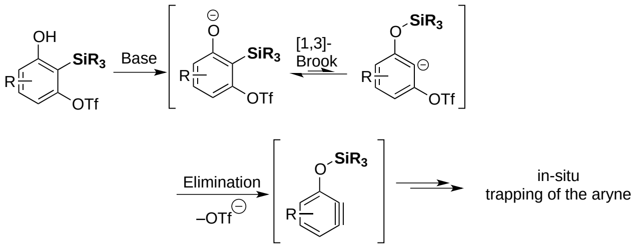
Scheme 28. Synthesis of 2,3-disubstituted thiophenes and furans from 3-formyl heterocycles.

The work reported so far demonstrates the utility of C(sp^2)→O silyl migration in the field of heteroarene functionalization. Though, only a limited number of substrate-types has been studied, and the topic is far from being at a mature stage.

1.4 Synthesis of Arynes from Arylsilane

Arynes are important reactive intermediates in organic synthesis,[54] and the Brook rearrangement provides a useful alternative to existing methods[55,56] for the generation of these intermediates under mild conditions and without the need of fluoride salts.

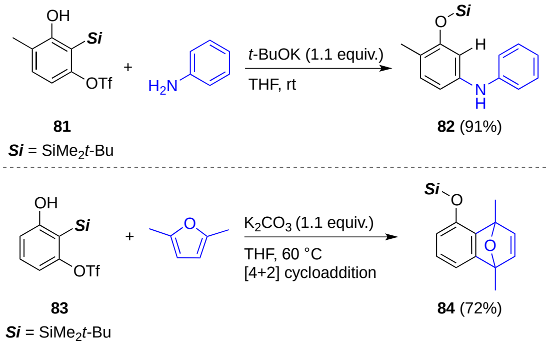
Indeed, arynes can be generated from (*ortho*-silyl)phenyl triflates following intramolecular by [1,3]- or [1,4]-silyl migrations. For example, after deprotonation of 3-hydroxy-2-(trialkylsilyl)aryl triflates with a mild base such as potassium carbonate or potassium *tert*-butoxide, the phenoxide anion formed undergoes a [1,3]-Brook rearrangement that generates a phenyl carbanion. The subsequent E1cb triflate elimination at the *ortho* position releases the corresponding aryne, which can undergo in situ trapping by a number of reaction partners (Scheme 29).[57]



Base= KHMDS, MeLi, NaH, K_2CO_3…

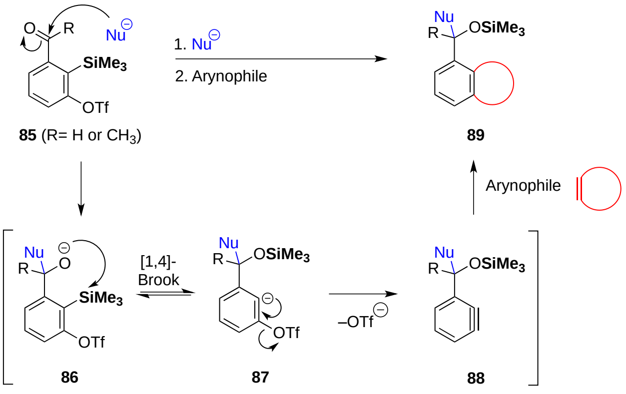
Scheme 29. Arynes generation from 3-hydroxy-2-(trialkylsilyl)aryl triflates.

The thus generated 3-trialkylsiloxybenzynes can, for example, be regioselectively trapped by aniline, as shown with the formation of compound **82**, or undergo a [4+2] cycloaddition reaction with 2,5-dimethylfuran, leading to the bridged tricyclic product **84** (Scheme 30).[58] These examples showcase the power of this chemistry, which found many applications in synthesis.[59]



Scheme 30. Some reactions of 3-trialkylsiloxybenzynes.

Another tactic to produce arynes involves the addition of an appropriate carbanion to 2-silyl-3-OTf aromatic carbonyl compounds, such as **85**. The alkoxide **86** thus produced rearranges through [1,4]-C(sp^2)→O silyl migration to give carbanion **87**. Analogously to the previous example, β-elimination of the subsequent triflate yields the corresponding aryne **88**, which can undergo a wide variety of inter- or intramolecular [2+2], [3+2], and [4+2] cycloaddition reactions (Scheme 31).[59]

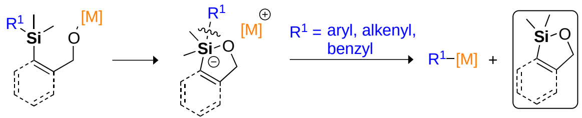


Scheme 31. Aryne generation from (3-carbonyl)-2-(trialkylsilyl)aryl triflates.

2. C(sp^2)–Si Bond Functionalization through Exocyclic Cleavage

The palladium-catalyzed Hiyama–Denmark cross-coupling reaction occupies a prominent position in the rich chemistry of organosilanes, and represents an important tool in organic synthesis, especially for the construction of C(sp^2)–C(sp^2) bonds from C(sp^2)–Si bonds. Activation of the C(sp^2)–Si bond towards transmetalation is a key requirement in this cross-coupling chemistry, and intramolecular alkoxide-promoted activation has been elegantly exploited as a mean to trigger the cross-coupling reaction of aryl- and alkenylsilanes under fluoride-free conditions.

As discussed in the introduction, intramolecular C–Si bond activation by alkoxides generates a hypervalent silicon intermediate embedded in a siloxycycle. In particular, the cleavage of a C–Si bond that is not part of this cycle is possible (exo-cyclic cleavage), which generates a carbanionic organometallic species along with a cyclic silyl ether byproduct. The organometallic intermediate formed is a suitable nucleophile for a number of cross-coupling reactions (Scheme 32). The selectivity of exo-cyclic *vs* endo-cyclic C–Si bond cleavage for the silacyclic intermediate is related to the stability of the resulting carbanion: typically, C(sp^2)–Si bond cleavage is favored over C(sp^3)–Si bond cleavage, unless the latter leads to particularly stabilized species such as benzylic or allylic organometallics.[60,61] Where the bias is not obvious, as for example the competition between two C(sp^2)–Si bond cleavages giving carbanions of similar stability, the products of exo-cyclic cleavage are usually predominant. However, the reasons for this selectivity have not been clearly established and may differ on a case-by-case basis. It has to be noticed, however, that the fundamental difference between endo- and exo-cyclic cleavage is that the former is a reversible process, while the latter is not.



Scheme 32. Alkoxide-promoted exo-cyclic cleavage of a C(sp^2)–Si bond.

It has been suggested that the transmetalation step in a cross-coupling reaction may proceed through two alternative pathways (Figure 4).[62] The first one involves assistance by the alkoxide through **90**, wherein the transition metal atom directly interacts with the oxygen atom.[63] The alternative pathway involves a compound of the type of **91**, where the silicon atom is coordinated by the counter-anion of the transition metal complex. Note that this second scenario complies with Muetterties' rule which states that the more electronegative ligands (aryl and vinyl ligands in this case) occupy an axial position in such hypervalent compounds.

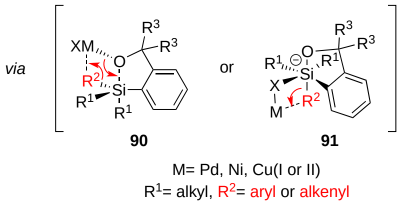
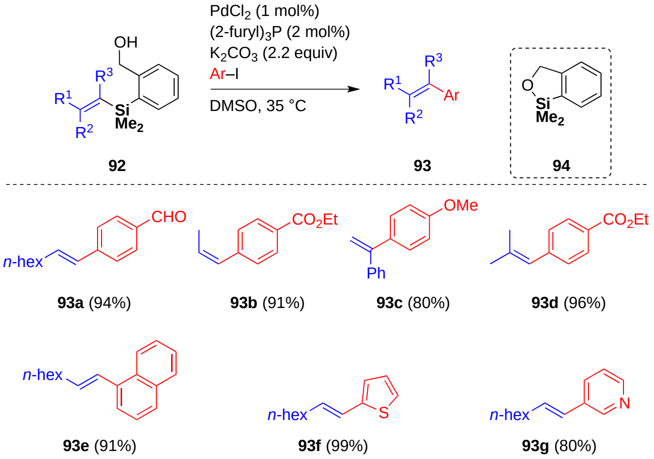


Figure 4. Postulated pathways for silicon-to-transition-metal transmetalations in cross-coupling reactions of aryl- and alkenylsilanes.

2.1 C(sp^2)–Si Bond Functionalization of Alkenylsilanes

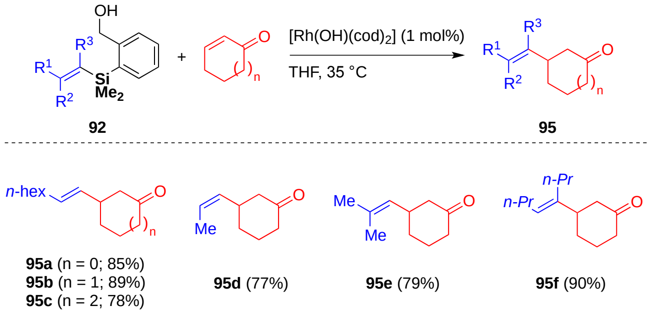
Hiyama and Nakao developed the [2-(hydroxymethyl)phenyl] dimethylsilyl (HOMSi) unit as trigger to perform base-promoted C(sp^2)–Si cross-coupling reactions.[64] This method is highly attractive since the organosilane reagents are stable, and become reactive upon treatment with weak bases. One of the applications of this strategy was first investigated for the arylation of alkenylsilanes **92** (alkenyl–HOMSi reagents). This reaction was carried out with aryl iodides in the presence of palladium dichloride and potassium carbonate (Scheme 33).[65] The reaction turned out to be tolerant to a wide range of aryl- or heteroaryl (**93f** and **93g**) iodides and suitable for diverse alkenylsilanes, including terminal and internal disubstituted, as well as tri-substituted. In all cases, exquisite retention of the double bond geometry was observed. The reaction tolerated a series of functional groups in the aryl iodides (such as aldehyde, ester, ether and alcohol), giving the coupling products in good to excellent yields.



Scheme 33. Arylation of alkenyl-2-(hydroxymethyl)phenyl]-dimethylsilyl derivatives.

As to the mechanism of this protocol, after the intramolecular activation through the formation of a cyclic hypervalent silicon species from **92**, transmetalation by aryl-palladium(II) intermediates and subsequent reductive elimination gives the corresponding products **93**. Although this method is intrinsically not atom economical, the cyclic silyl ether byproduct **94** can be conveniently recycled and reused by treatment with organolithium or organomagnesium nucleophiles.[62–67]

Alkenyl–HOMSi reagents **92** are also competent donors for rhodium-catalyzed 1,4-addition reactions to cyclic enones.[68] As depicted in Scheme 34, 1,2-disubstituted- (**95a**–**d**), as well as 1,1,2- (**95e**) and 1,2,2-trisubstituted (**95f**) alkenylsilanes participate readily in reactions with 5-, 6-, or 7-membered cyclic enones. Again, retention of the double bond geometry of the alkenylsilanes is observed, and the mild activation conditions make the procedure highly functional-group tolerant with respect to the organosilane partner. Importantly, it has also been demonstrated that the method is amenable to enantioselective variants.

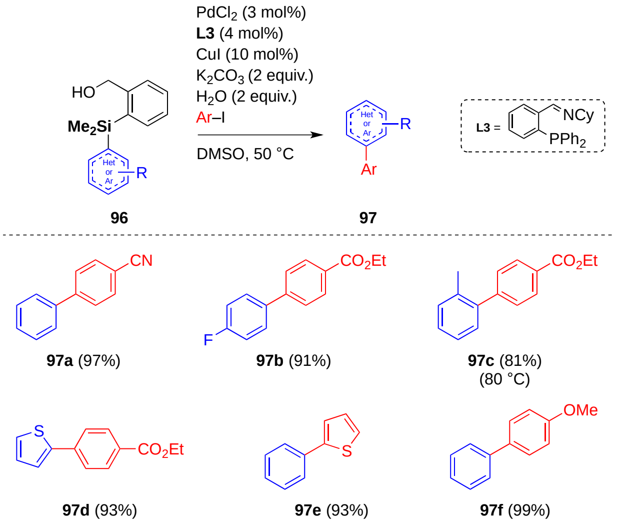


Scheme 34. Rhodium-catalyzed 1,4-addition to enones of alkenyl-2-(hydroxymethyl)phenyl]-dimethylsilyl derivatives.

2.2 C(sp^2)–Si Bond Functionalization of Arylsilanes

Aryl–HOMSi derivatives **96** also undergo arylation reactions under palladium catalysis. By contrast with the alkenyl–HOMSi, in this case, the addition of a copper(I) salt is mandatory.

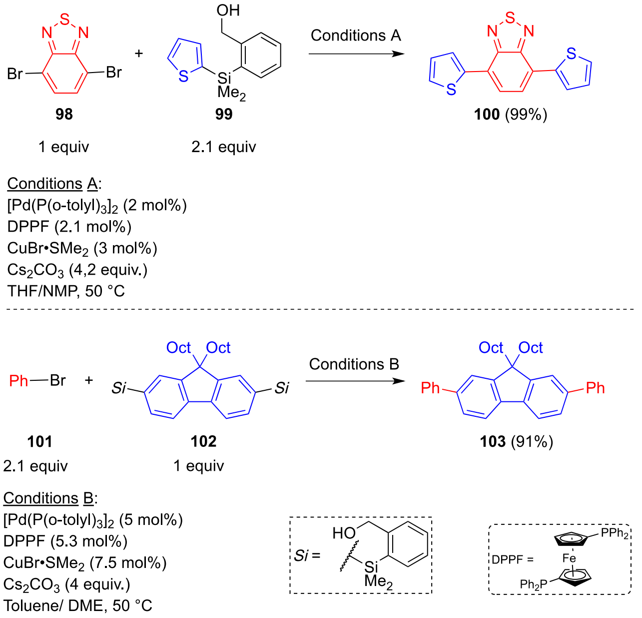
Despite the role of the copper(I) salt being unclear,[62] it has been proposed that the transmetalation of the aryl group either occurs from silicon to palladium directly, or in two steps, following first silicon-to-copper transmetalation and then copper-to-palladium. Excellent yields are obtained with both electron-rich and electron-deficient aryl iodides, including heteroaryliodides (**97e**), with good tolerance of various functional groups (Scheme 35). In addition to phenylsilane (**97a,e,f**), C–Si arylation was also performed efficiently on electron poor aryl silanes (**97b**) as well as on 2-silylthiophene (**97d**), but was slightly less efficient for electron-rich aryl silanes (**97c**).[66,69]



Scheme 35. Arylation of aryl-2-(hydroxymethyl)phenyl]dimethylsilyl derivatives.

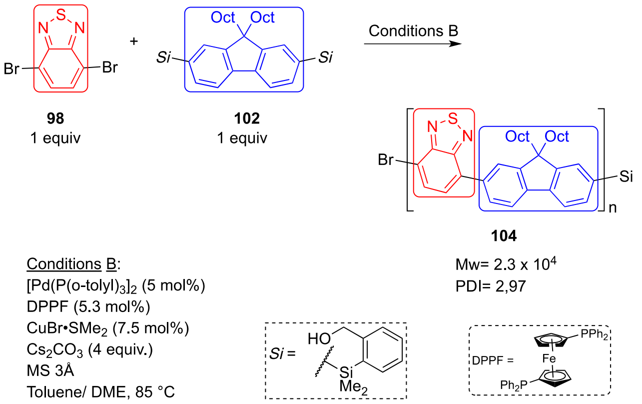
Such arylation reactions of aryl–HOMSi reagents have found relevant applications for the synthesis of extended polyarene π-systems. A first approach relies on halogenated aryl–HOMSi compounds.[70] Owing to the fact that the HOMSi trigger relies exclusively on the presence of a free hydroxy group, halogenated arenes having THP-protected HOMSi units can participate as electrophiles in cross-coupling reactions with (unprotected) aryl–HOMSi nucleophiles without interference of the protected HOMSi moiety. Upon alcohol deprotection, the HOMSi trigger is “turned-on” and the adduct becomes a suitable nucleophilic partner for a following cross-coupling reaction. Entailing successive coupling and deprotection steps thus allows for the preparation of well-defined oligoarenes.

Bis-arylation strategies have also been considered on substrates bearing two (or more) halogenated groups,[71] or two (or more) HOMSi units.[67,72] For example, the double functionalization of one equivalent of bis-aryl bromide **98** was performed in the presence of two equivalents of arylsilane **99** (Scheme 36, top) to deliver **100**. Similarly, the bis-arylation product **103** was synthesized from two equivalents of bromobenzene **101** and bis-aryl silane **102** (Scheme 36, bottom).



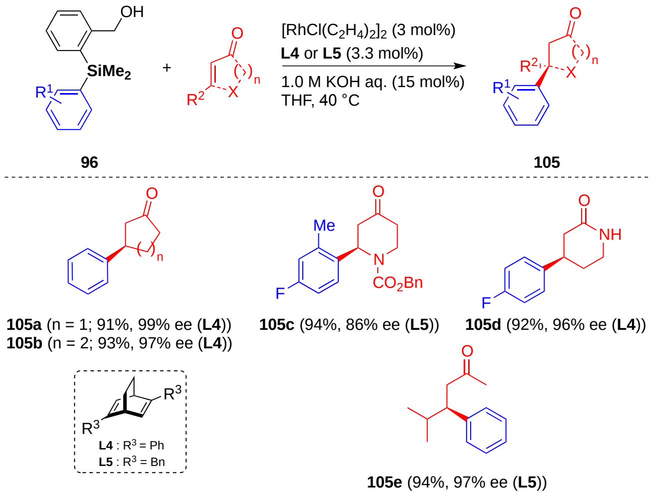
Scheme 36. Bis-arylation strategies from (hetero)aryl-2-(hydroxymethyl) phenyl]dimethylsilyl derivatives.

The strategy was also useful for the synthesis of polyarenes **104**. The formation of such species is possible by either iterative cross-coupling,[62] or by copolymerization of dihalide-monoarenes **98** and aryl-bisHOMSi reagent **102** in equimolar quantities (Scheme 37).[73]



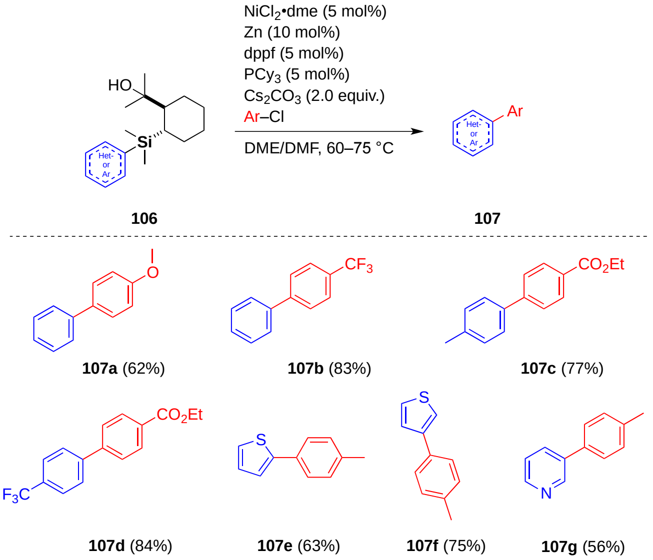
Scheme 37. Synthesis of polyarenes from aryl-bis(2-(hydroxymethyl) phenyl]dimethylsilyl) derivatives.

Aryl–HOMSi reagents **96** participate readily to the same rhodium-catalyzed 1,4-addition reactions to enones discussed above for alkenyl–HOMSi reagents **92** (see Scheme 34). Interestingly, in the presence of chiral diene ligands **L4** and **L5**, 1,4-adducts **105** can be obtained in high yield and excellent enantioselectivity (Scheme 38).[68] The procedure is suitable not only for cyclic enones (**105a,b**), including nitrogen-containing derivatives (**105c,d**), but also for acyclic enones (**105e**).



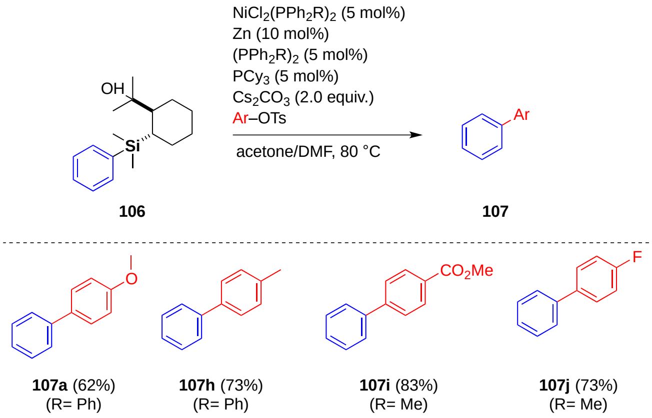
Scheme 38. Enantioselective rhodium-catalyzed 1,4-addition to enones of aryl-2-(hydroxymethyl)phenyl]-dimethylsilyl derivatives.

The development of another family of HOMSi silanes by Nakao and Hiyama, namely the 2-(hydroxy-methyl)cyclohexyl substituted arylsilanes **106**, allowed for the development of the first nickel-catalyzed silicon-based arylation leading to bis-aryl derivatives **107** (Scheme 39).[74] Importantly, this cross-coupling reaction can even be performed using aryl chlorides. The electronic nature of the aryl chloride has an influence on the reaction outcome. Indeed, electron-poor aryl chlorides give better yields (**107b**) than electron-rich ones (**107a**). Conversely, no significant difference based on the electronic character of the aryl silane is observed (compare **107c** and **107d**). Interestingly, 2- and 3-aryl thiophenes can be obtained in reasonable yields (**107e** and **107f**), as well as 3-aryl pyridines (**107g**), albeit with a lower yield.



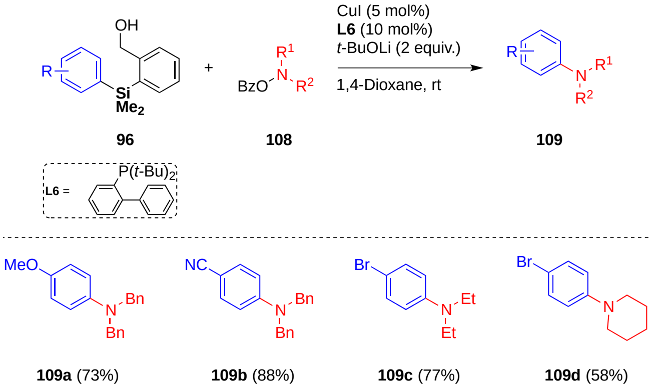
Scheme 39. Arylation of aryl-2-(hydroxy-methyl)cyclohexyl derivatives.

The nickel-catalyzed arylation of aryl-HOMSI derivatives **106** can also be achieved using as coupling partners aryl tosylates, which are readily available from phenols (Scheme 40).[74] For electron-rich aryl tosylates, PPh_3 was used as ligand, while in the case of electron-poor aryl tosylates, PPh_2Me was required. Interestingly, the same cross-coupling reaction was latter achieved with improved scope under cooperative palladium/copper catalysis.[75]



Scheme 40. Nickel-catalyzed cross-coupling of aryl (HOMSI) with aryl tosylates.

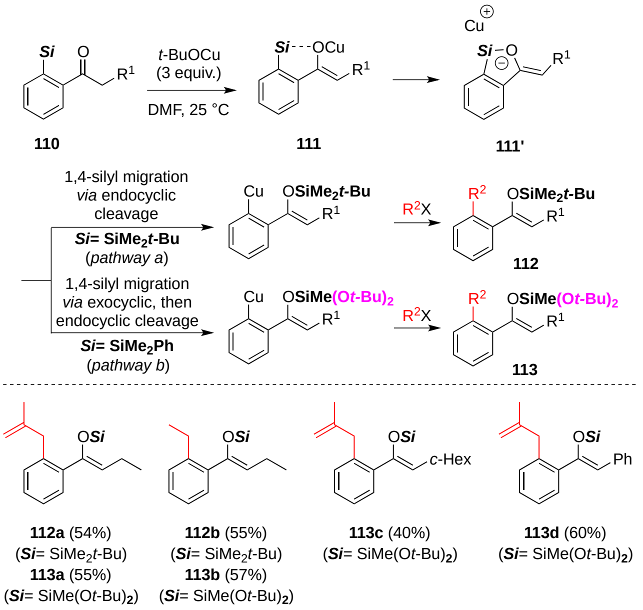
The HOMSi activation approach has also been used to achieve copper-catalyzed C(sp^2)–N bond-forming reactions from C(sp^2)–Si bonds. The reaction between arylsilanes **95** and hydroxylamines **108**, in the presence of lithium *tert*-butoxide and a catalytic system composed of a copper(I) salt and JohnPhos (**L6**) as ligand, gives the corresponding anilines **109** (Scheme 41).[76] The reaction is expected to involve the electrophilic amination of an aryl copper species arising from exo-cyclic C(sp^2)–Si cleavage of the hypervalent silicon intermediate, in turn generated by intramolecular addition of the pendant alkoxide anion to the silicon atom.



Scheme 41. Copper-catalyzed C(sp^2)–N bond-forming reactions from C(sp^2)–Si bonds.

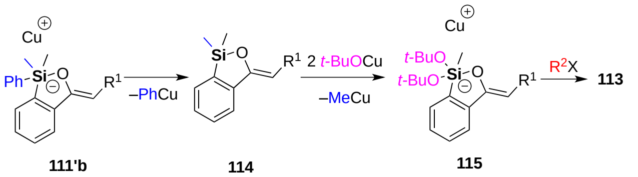
A final (rare) example involving both endocyclic and exocyclic C(sp^2)–Si bond cleavage has been disclosed by the group of Takeda (Scheme 42).[77] Thus, treatment of *ortho*-silylphenones **110** with copper *tert*-butoxide and an organic halide generates the corresponding silyl enol ethers. Interestingly, the substitution pattern of the silicon atom can be altered during the reaction.

The mechanism of this protocol implies the initial reaction of the *ortho*-silylphenones **110** with copper(I) *tert*-butoxide to produce a copper(I) enolate (**111**), followed by the formation of the corresponding silacyclic intermediate **111'**. The evolution of this intermediate differs according to the substitution of the silicon atom. On the one hand, with *t*-BuMe$_2$Si (pathway a), C(sp^2)–Si endocyclic cleavage triggers *tert*-butyldimethylsilyl C-to-O migration, which generates the expected *ortho* substituted *tert*-butyldimethylsilyl enol ether **112** upon trapping with R^{2}X. On the other hand, with Me$_2$PhSi (pathway b), bis(*tert*-butoxy)methylsilyl enol ether **113** is generated.



Scheme 42. Copper(I) *tert*-butoxide-promoted cross-coupling of *o*-silylphenyl ketones: endocyclic and exocyclic cleavage.

This result has been rationalized by the authors on the basis of a first C(sp^2)–Si exocyclic cleavage from **111'b**, to generate **114** and PhCu, and the subsequent addition of a first equivalent of *t*-BuOCu triggers the release of MeCu from the resulting pentavalent silicon intermediate (Scheme 43). Addition of a second equivalent of *t*-BuOCu triggers endocyclic C(sp^2)–Si cleavage passing through intermediate **115**. Coupling of the thus generated arylcopper intermediate with the organic halide generates the final bis(*tert*-butoxy)methylsilyl enol ether **113**.[77]



Scheme 43. Possible evolution of the oxasilacycle with an excess of CuO*t*-Bu.

Conclusion

As illustrated in this minireview, carbon-to-oxygen silyl migration provides an efficient way to generate C(sp^2) carbanion surrogates with perfect control of the site selectivity, and thereby the opportunity to perform a wide range of transformations under mild reaction conditions. The approach is particularly useful for the functionalization of molecules for which metalation cannot be envisaged due to low or inappropriate site-selectivity, or because of the instability of the resulting carbanion. Another attractive feature of this chemistry is that it also contributes to the evolution towards more sustainable synthetic chemistry, amid others through the possibility to perform, through the anion relay chemistry, multi-component and multi-step one-pot reactions, and by extending, through the HOMSI silane technology, the scope of cross-coupling reactions relying on organosilanes.

C(sp^2)$\longrightarrow$O silyl migration has been chiefly implemented for arene and alkene functionalization and has reached a certain degree of maturity for this purpose. By contrast, heteroarene functionalization has received considerably less attention so far, even though some reports demonstrate the viability of the approach. We thus foresee that achieving this interesting prospect will become in the near future an important focus of research in the field.

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Keywords: Silyl migration • Brook rearrangement • Anion Relay Chemistry • HOMSi silane • Hiyama cross-coupling

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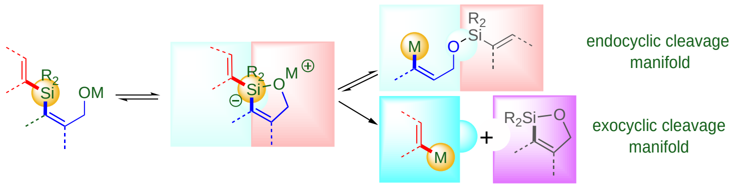

Silyl migration

This mini-review covers recent progress in the functionalization of the C(sp^2)–Si bond by intramolecular activation by alkoxides. Such processes involve the formation of a cyclic hypervalent silicon intermediate that allows for carbon-to-oxygen migration of the organosilyl group and thus the formation of a carbanionic species poised to undergo electrophilic substitution reactions. The C(sp^2)–Si bond cleavage can be either "endocyclic" (Brook rearrangement) or "exocyclic". Useful synthetic methods relying on both types of cleavage have been developed and will be discussed successively.

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