Hypervalent Silicon as a Reactive Site in Selective Bond-Forming Processes

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Abstract: Silicon is a truly exceptional element as it serves as a reactive site for an almost infinite number of transformations pertinent to synthetic organic chemistry. Importantly, the intertwined relationship of the valency at silicon and its chemical reactivity represents the key to a profound understanding and the design of novel reactions. Thus, these so-called hypervalent silanes are crucial intermediates in silicon-based carbon–carbon bond-forming reactions, whereby tetravalent silanes are conventionally employed in carbon–silicon bond-forming processes. This review aims at a detailed discussion of these mechanistic aspects illustrated with some synthetically significant developments in modern organosilicon chemistry. Recent advances in silicon-mediated, organocatalytic C(sp3)–C(sp3) bond formation directed towards the preparation of aldol and aldol-like products are covered. Silicon-based transition-metal-catalyzed C(sp2)–C(sp2) bond formations involving hypervalent silicon intermediates are also included. These seemingly dissimilar reactions will be comparatively juxtaposed.

1 Introduction: Hypervalent Silicon

Organosilicon chemistry has provided unique solutions for innumerable challenges in synthetic organic chemistry. Several silicon-based methodologies have become classic textbook reactions. These are characterized by an almost incomparable mechanistic diversity, which in turn raises the profound question of how these reactions are governed by silicon as the reactive site. Importantly, detailed insights into these reaction mechanisms might enable a unified understanding of entirely different silicon-based reactions. In this review, we have attempted a mechanism-based delineation of some modern synthetic organosilicon chemistry and the concepts involved therein. We believe that such an approach complements several excellent substrate-based and reaction-based reviews and monographs that have recently appeared in this prospering field of organic chemistry.1–4

The pivotal feature for explaining the reactivity of organosilicon compounds is the silicon valency. A tetracoordinated silicon center readily expands its coordination sphere to five, or even six (A → B → C, Scheme 1), which clearly sets silicon apart from its group-14 homologue, carbon.2,5–7 This so-called extracoordination or hypervalency originates from vacant d-orbitals at silicon combined with the potential influence of σ*(Si–L) orbitals, which is, however, still a matter of debate.

![Scheme 1](image)

Applying the valence bond concept, the formal hybridization on silicon changes from sp3 (A, tetravalent) to sp3d (B, pentavalent) to sp3d2 (C, hexavalent). Consequently, the electron density at silicon decreases with reduced s-character of the orbital combination, while the electropositive character and, therefore, the Lewis acidity at the silicon center, is increased. It should be noted that C is not acting as a Lewis acid since any further extension of its valence shell is unusual.7 The Lewis acidic properties of certain derivatives of A (and B) have been exploited in several Lewis acid-catalyzed transformations.8

This situation seems to contradict chemical intuition. One might anticipate the silicon center to be more negatively polarized/charged upon expansion of the coordination shell, yet the reverse is the case. Silicon becomes more positively polarized/charged with each additional ligand. Irrespective of the formal charge at silicon, the electron density is decreased at silicon and increased at the ligand
L and R in the order $A < B < C$ (Scheme 1). The magnitude of this polarization is also dependent on the electronegativity of these ligands L (and R).

Therefore, a simple yet intelligible analogy with main-group- or transition-metal-derived Lewis acids exposes silicon centers as in B and C as electropositive metal cations. This brings about another relevant reaction mode of organosilicon reagents: hypervalent organosilicon compounds B and C are superb carbon nucleophiles and hydride donors with a strong metalloid character at silicon.

Altered orbital interactions in these extracoordinated systems ($A \rightarrow B \rightarrow C$, Scheme 1) and thereby elongated Si–R and Si–L bonds result in a distinctly enhanced capability of transferring a formally negatively charged R group (carbanion or hydride equivalent) to an acceptor. This unique chemical reactivity stems from increased negative partial charges at the R moiety and the ligands L. Thus, transformations involving a hypervalent silicon center B or C as the reactive site generally allow for carbon–carbon as well as carbon–heteroatom bond formation, and NOT carbon–silicon bond formation!

Conversely, tetravalent organosilicon compounds A exhibit a completely different reaction pattern. Based on the above considerations, any bonds to silicon in these compounds are substantially less polarized and, hence, more covalent. Perhaps the most prominent synthetic application of tetracoordinated silanes is the transition-metal-catalyzed hydroxylation, which corresponds to a silicon–hydrogen bond activation. The silicon–hydrogen bond might be compared to a hydrogen–hydrogen bond in terms of reactivity, as hydrogenations and hydroisylations often proceed under identical reaction conditions in the presence of the same transition-metal catalyst. Thus, transformations that are likely to involve exclusively a tetravalent silicon center A as the reactive site allow for carbon–silicon as well as silicon–heteroatom bond formation, and NOT carbon–carbon bond formation!

Biographical Sketches

Sebastian Rendler (left) was born in Oberkirch, Germany, in 1979. He studied chemistry at the Albert-Ludwigs-Universität in Freiburg (1999–2004) and spent a research internship at Boehringer-Ingelheim in Vienna, Austria (2002). He received his diploma under the direction of Martin Oestreich in 2004, where he was involved in the development of the true chirality transfer from silicon to carbon. Since his graduation, he has continued to work on stereochemical aspects in the chemistry of asymmetrically substituted organosilicon compounds. Recently, he was awarded a graduate fellowship (2005–2007) by the Fonds der Chemischen Industrie.

Martin Oestreich (right) was born in Pforzheim, Germany, in 1971. He studied chemistry at the Heinrich-Heine-Universität in Düsseldorf, UMIST in Manchester, UK, and the Philipps-Universität in Marburg. After an internship at Hoffmann-La Roche in Basel, Switzerland, he returned to Marburg where he obtained his diploma under the direction of Paul Knochel in 1996. He completed his doctoral degree with Dieter Hoppe at the Westfälische Wilhelms-Universität in Münster in 1999. After two postdoctoral years with Larry E. Overman at the University of California at Irvine, USA, he moved to the Albert-Ludwigs-Universität in Freiburg and initiated an independent research program under the mentorship of Reinhard Brückner. He received a Kekulé fellowship (1997–1999) from the Fonds der Chemischen Industrie and an Emmy Noether postdoctoral fellowship (1999–2001), as well as an Emmy Noether ‘Junior Research Group’ (2001–2005), from the Deutsche Forschungsgemeinschaft. His awards include financial support by the Dr. Otto Röhm Memorial Foundation (2004) and the ADUC-Jahrespreis für Habilitanden (2004). The synthesis and chemistry of organosilicon compounds with silicon-centered chirality, novel silicon reagents as well as asymmetric Heck chemistry are his major research interests.
The perception of this fundamental distinction sets the stage for the conception of this review: carbon–carbon bond formation with hypervalent silicon as a reactive site. In these reactions, the hypervalent silicon intermediate is either directly involved in the carbon–carbon bond forming event (Section 2), or facilitates a transmetalation step prior to the actual carbon–carbon connection (Section 3).

The first part of Section 2 introduces hypervalent silicon species as Lewis acids, which is a crucial property for the understanding of subsequent subsections. These cover recent advances in organocatalytic stereoselective C(sp^3)–C(sp^3) bond-forming reactions such as alkylation of carbonyl compounds and the closely related silicon-mediated aldol reactions. Section 3 highlights the metalloid nature of extracoordinate silicon compounds and summarizes their role in transition-metal-catalyzed C(sp^3)–C(sp^2) bond-forming processes (n = 1–3). Both silicon-based organocatalysis as well as transition-metal-catalyzed cross-coupling reactions have emerged as particularly valuable in recent years and will be discussed with regard to the reactivity at silicon.13

2 C(sp^3)–C(sp^3) Bond Formation
2.1 Silicon-Based Chiral Lewis Acids

As mentioned in the introductory section, the Lewis acidity of silicon compounds is attributed mainly to the intrinsic capability of silicon to extend its coordination sphere (A → B, Scheme 1). Tetravalent triorganosilanes, such as trimethylsilyl chloride and iodide as well as the analogous triflate, are standard silicon-based Lewis acids in organic synthesis. Activation of Lewis basic moieties is accomplished by its coordination to tetravalent silicon, thereby forming an extracoordinated intermediate. The latter might dissociate, depending on the strength of the silicon–leaving group bond. Formally, these tetravalent reagents might be understood as silylium ion precursors. The scope of such Lewis acids has been nicely summarized in a recent review.5

Asymmetric alteration of such Lewis acids was initially achieved by chiral backbones covalently bound to silicon (via carbon–silicon bonds). These novel chiral Lewis acids have been probed in Diels–Alder reactions with moderate success. Just a few years ago, Helmhchen and Jørgensen reported the first example of such a chiral silicon-based Lewis acid.14 The solvated silylium ion (S)-4, incorporating an axially chiral binaphthyl backbone was achieved by simple hydride abstraction of the corresponding silane using the trityl cation; tetravalent (S)-4 is strongly electrophilic in nature and is exceptionally reactive. Asymmetric induction in a Diels–Alder reaction remained low (1 → 3, Scheme 2). Dienophile 2 is equipped with two Lewis basic sites that have the potential to coordinate to the Lewis acidic silicon center in (S)-4. In the resulting acid/base chelate, the silicon might be pentavalent.

Application of catalytic amounts of 8 to the standard Diels–Alder reaction of cyclopentadiene (5) and methyl acrylate (6) gave cycloadduct 7 in excellent yield with moderate enantiomeric excess (5 → 7, Scheme 3). Interestingly, almost racemic 7 was obtained when the catalyst was devoid of a nucleophilic neighboring group such as the methyl ether. This observation supports a coordinating effect of such a group while the exact mechanism remains otherwise unclear.

Ihara presented a noteworthy strategy for the in situ generation of a chiral silicon-based Lewis acid by combining an achiral silylium precursor and a chiral monodentate amine base, and applying this to the desymmetrizing enolization of 4-substituted cyclohexanone 9 (Scheme 4).16 A large excess of a mixture of t-BuMe3SiOTf and amine (R,R)-11 allowed for the high-yielding silyl ether forma-
tion with moderate enantioselection \([9 \rightarrow (R^*)]-10\), Scheme 4].

The mechanism of this transformation is believed to involve the pentavalent intermediate \(12\), in which the silyl amine nitrogen serves as a base. Generation of \(12\) is likely to occur by an associative displacement of the triflate moiety at silicon by amine \((R,R)-11\), followed by coordination of the Lewis basic carbonyl group of \(9\). Then, intramolecular proton abstraction enables differentiation of the formerly enantiotopic protons.

Along these lines, reversible formation of such donor/acceptor pairs \(E\) starting from ubiquitous chiral ligands and achiral silicon compounds \(D\) could open the door for a catalytic process (Scheme 5). Formation of these expands the valence shell at silicon, which, therefore, produces an intermediate chiral silicon species \(E\) of higher Lewis acidity than the unchanged achiral material \(D\). The above example by Ihara relies on the overstoichiometric use of a chirally modified silicon reagent since the chiral donor is protonated and, thus, consumed in the course of the reaction. However, when using the chiral promotor only as an activator, which is not irreversibly transformed, catalytic amounts might be sufficient!

\[
\begin{align*}
\text{Scheme 5} & \quad \text{Reversible formation of donor/acceptor pairs } E \text{ (charges at silicon have been omitted for the sake of clarity)}
\end{align*}
\]

Denmark elegantly realized this approach for several highly enantioselective carbon–carbon bond-forming reactions.\(^{17–20}\) Stoichiometric quantities of silicon tetrachloride \((D, L, R = Cl)\) are usually chosen as the achiral, weakly Lewis acidic component, which itself is complete-

ly inert in this regard; only catalytic amounts of a chiral Lewis base are needed for the generation of the active catalyst. This in situ formed, chirally modified Lewis acid/ Lewis base complex then facilitates the desired transformation.

Enantioselective allylation and propargylation of aldehydes were published as the first examples of this strategy.\(^{17}\) Aldehyde \(13\) was brought to reaction with allenylstannane \(14\) in the presence of silicon tetrachloride and bidentate bisphosphoramide \(16\) as the chiral activator (Scheme 6). Homopropargyl alcohol \((R)-15\) was isolated in excellent yield and high enantiomeric purity by using only 5.0 mol% of the chiral additive \(16\).

\[
\begin{align*}
\text{Scheme 6} & \quad \text{Further investigations showed that this methodology is remarkably general and applicable to a variety of allylations, propargylations, and aldol reactions. An example for the latter is depicted in Scheme 7; high enantioselectivities were observed for the additions of silyl ketene acetal 18 to aromatic aldehyde 13 and aliphatic aldehyde 17.}
\end{align*}
\]

\[
\begin{align*}
\text{Scheme 7} & \quad \text{Some mechanistic insight was deduced from the high stereoconvergence of this aldol addition. Upon treatment with aldehyde 13, \((E)-\) and \((Z)-\)configured 21 furnished identical aldol product 22 with high diastereoselection (Scheme 8). Neither the diastereo- nor the enantioselectivity of this reaction was affected by the double-bond geometry of the silyl ketene acetal; this was interpreted as distinct evidence for an acyclic transition state. In addition, the supposed structure of the catalyst/substrate complex was disclosed based on spectroscopic studies. A mixture of silicon tetrachloride, bidentate phosphoramide 16, and 13 is assumed to give the cationic complex 23 as a result of complexation of silicon tetra-}
\end{align*}
\]
chloride by neutral 16, followed by dissociation of chloride anion (associative pathway); subsequent coordination of the Lewis basic carbonyl oxygen of aldehyde 13 at the hypervalent silicon-based Lewis acid finally leads to 23 (Figure 1). Enantiofacial selectivity in 23 would be determined by the chiral substituents at phosphorus.

The substrate scope was extended to silyl enol ethers (Scheme 9). Standard workhorse 13 was reacted with 24 using truly catalytic amounts of chiral promoter 16 (1.0 mol%) and substoichiometric amounts of Hünig’s base. Aldol (R)-25 was isolated in quantitative yield with almost perfect enantioselectivity. As the nucleophilic component, silyl enol ethers derived from aliphatic and aryl methyl ketone worked equally well. As the electrophilic component, several aromatic aldehydes were applied successfully, whereas aliphatic aldehydes underwent fast formation of α-chlorohydrins under these reaction conditions. The use of the indicated amount of an amine base as an acid scavenger resulted in substantially improved yields, preventing cleavage of acid-labile silyl enol ethers. Trace amounts of acid are likely to be introduced by silicon tetrachloride.

Remarkably, stereoselection was still high when the same methodology was applied to vinylogous silicon enolate 26 (13 → 27, Scheme 10). The observed excellent regioselectivity provides further evidence for an acyclic transition state.

Finally, even isocyanides such as 28 are potential substrates for these reactions (Scheme 11). Aldehyde 13 was converted into α-hydroxy amide (S)-29 in high yield and excellent enantiomeric excess.

In summary, the concept of Lewis base activation of Lewis acids introduced by Denmark is a significant enhancement of catalytic asymmetric aldol and aldol-like chemistry. In these reactions, the actual catalyst is a hypervalent silicon-based Lewis acid, which interacts with the electrophilic reactant, thereby lowering its lowest unoccupied molecular orbital; the nucleophilic reactant in turn is activated neither by this catalyst nor by the chiral additive. At last, the benefits of hypervalency at silicon are exploited only in terms of increased Lewis acidity!

### 2.2 Synthesis of Aldol and Aldol-Like Products

#### General Considerations

As outlined in the introductory section, extracoordination at silicon is accompanied by increased Lewis acidity and, likewise, enhanced nucleophilicity of a silicon–carbon (and silicon–hydrogen) bond in these intermediates (Scheme 1). Consequently, combining both of these features in a single transformation might be even more effective than merely utilizing Lewis acidity!

Addition of allylic silanes and silicon enolates to carbonyl compounds is rationalized by related mechanisms (Scheme 12). Following the concept illustrated in section 2.1, a Lewis acid-activated carbonyl compound G (X = O) is reacted either with an unactivated allylic silane F (Y = CH₂) or silicon enolate F (Y = O). The latter reagents will normally not form any hypervalent intermediates, and the addition of nucleophiles will proceed through an acyclic transition state. Thus, these catalyses require an activator and an additional achiral silicon-based Lewis acid precursor. This strategy has been sum-
marized in the preceding section. High levels of enantio- and diastereoselection have been achieved this way.17–20

Alternatively, activation of the component F with a Lewis base would directly lead to pentavalent H (Scheme 12). Now, activated nucleophile H, endowed with substantially increased Lewis acidity, will be coordinated by a Lewis basic carbonyl compound I, forming a cyclic transition state such as chair-like K. The stability of the carbon–silicon bond in the silicon compounds increases in the order J/K < H < F; hence, carbon–carbon bond formation will preferentially occur at the pentavalent or even the hexavalent stage.

![Scheme 12](image)

Scheme 12  Addition of allylic silanes and silicon enolates to carbonyl compounds (charges at silicon have been omitted for the sake of clarity)

The addition is expected to proceed through cyclic transition states J (pentavalent silicon) or K (hexavalent silicon). Such a highly ordered setup permits prediction of both the regio- and diastereoselectivity by controlling the substitution pattern of H. Importantly, high diastereoe- convergence with respect to the double bond geometry in F is observed for acyclic transition states, whereas high diastereospecificity is to be expected for cyclic transition states (J or K).

**Lessons Learned from Hydride Transfer**

The tendency of hypervalent silicon reagents to release hydride was first recognized by Corriu in the synthetic context.23 In the initial report more than two decades ago,23a carbonyl groups were efficiently reduced by trialkoxysilanes in the presence of equimolar amounts of a fluoride source (30 → 31, Scheme 13).

![Scheme 13](image)

Scheme 13  Addition of allylic silanes and silicon enolates to carbonyl compounds (charges at silicon have been omitted for the sake of clarity)

Whereas carbonyl groups are usually inert towards trialkoxysilanes, the installation of an additional electroneg-
Highly enantioselective imine reductions, following the same strategy, were recently accomplished by Malkov and Kočovský [34 → (S)-35, Scheme 16]. In this case, high levels of enantioselection were achieved using catalytic amounts of chiral bisamide (S)-36, which is believed to function as a bidentate ligand in the hexacoordinated silicon intermediate 37 (Figure 2).

Scheme 16

![Scheme 16 Image]

Figure 2

2.2.1 Addition of Allylic Silanes to Carbonyl Compounds

The research groups involved in the reduction chemistry learned several years later that activation of otherwise inert tetracoordinate silanes might not be limited to hydride transfer reactions. In the late eighties, the first racemic examples of Lewis base-promoted allylations of carbonyl compounds were reported by the groups of Corriu, Hosomi, and Sakurai. Again, excess of fluoride and alkoxide was found to efficiently activate the tetravalent silanes.

As depicted in Scheme 17, pre-formed allylic siliconate 38 smoothly reacts with aldehyde 13. This crotylation proceeded with complete regioselectivity and diastereoselectivity (E:Z = 88:12 in 38 → dr = 88:12 in 39). The favored pseudo-equatorial arrangement of substituents in the presumed transition state 40 (in accordance with K in Scheme 12) rationalizes the stereochemical outcome of this transformation. Application of this strategy to pre-formed, chirally modified allylic silicon species will be discussed in the ‘chiral reagents’ subsection.

Recently, Kobayashi and co-workers rediscovered these Lewis base-promoted allylations of carbonyl compounds and contributed significant advancements to this chemistry that are likely to have triggered the recent development of impressive asymmetric variants. The crucial discovery was that neutral Lewis bases such as N,N-dimethylformamide (DMF) – as additive or even as solvent – act as an activator in allylation reactions! Later, phosphine oxides, phosphoramides, and sulfoxides were also identified as promoters, which are now called neutral coordinate organocatalysts.

Chiral Additives

(Over)stoichiometric Amounts of Chiral Additives

The first moderately enantioselective variant employing neutral organocatalysts was reported by Denmark in the mid-nineties. Stoichiometric amounts of chiral phosphoramidate (R,R)-43 facilitated the enantioselective alkylation of 13 with moderate enantiomeric excess [13 → (R)-42, Scheme 18]. As a matter of fact, one of the most lively areas in current organic chemistry originated from this early report and the work of Kobayashi.
Successful application of chiral sulfoxides as additives in asymmetric allylations (and crotylations) of N-acylhydrazones was achieved by Kobayashi [46 → (R)-47, Scheme 20]. The easily accessible chiral sulfoxide (R)-48 emerged as particularly effective in these reactions covering a striking scope of aromatic and aliphatic aldehydes. The mechanism has not been studied in great detail yet, but coordination of the sulfoxide and the acylhydrazones at silicon seems likely, as suggested by a decrease in enantioselection with reduced amounts of chiral sulfoxide.38

Another asymmetric variant was described by Kobayashi for the allylation of α-hydrazono esters.39 Two equivalents of BINAP-dioxide [(R)-51] as the chiral additive gave allylation products in high enantioselectivities. For example, crotylation of 49 proceeded highly stereospecifically (49 → 50, Scheme 21) with isomerically pure crotyl trichlorosilane 44, and gave 50 syn-selectively.

Although these neutral activators are highly efficient in terms of enantiofacial selectivity, the necessity for stoichiometric amounts is clearly detrimental to broad applicability, even with optional reisolation and recycling. Catalytic variants were less selective under these reaction conditions.39,40

Catalytic Amounts of Chiral Additives

Since DMF proved to be an excellent catalyst, chiral formamides were also developed for asymmetric allylations. Iseki demonstrated that formamide (R,R)-53 nicely promotes the allylation of aliphatic aldehydes [17 → (R)-52, Scheme 22].41 Even the use of substoichiometric quantities of (R,R)-53 resulted in excellent enantioselection, albeit markedly lowered reaction rates.41b

The presence of hexamethylphosphoramide (HMPA) is essential for both conversion and enantioselectivity. The influence of HMPA on the latter is rather striking since HMPA could promote the reaction itself, producing racemic 52. Furthermore, these authors report a distinct positive non-linear effect. Nevertheless, their proposed transition state, a hexacoordinate siliconate, includes only one molecule of (R,R)-53.41 Several unsettled interpretations might be applied to rationalize these puzzling observations. On the one hand, a reasonable explanation could be that the primary product [alkoxide of (R)-52] is coordinating to the silicon center and, fortunately, (R,R)-53 and the chiral secondary alkoxide are inducing the same absolute configuration. On the other hand, one might speculate that one out of two formamide moieties in the initially formed homo- and heterochiral siliconates might be displaced by HMPA at different rates, thereby generating the catalytically active Lewis acid.

Nakajima introduced axially chiral bisquinoline N,N'-dioxide (S)-54 (Figure 3) as a highly potent catalyst (10 mol%) for the asymmetric allylation of aromatic aldehydes (13 → 42, Scheme 23).42

Recently, Kočovský developed a related class of catalysts for such transformations (Figure 3).43 In order to elaborate the decisive structural features, Kočovský screened several structurally modified PINDOX-type ligands for the model reaction depicted in Scheme 23.
Monooxide 55, with a configurationally labile axis of chirality, produced (S)-42 with high enantioselectivity; conversely, cognate dioxide 56 gave the optical antipode (R)-42 with modest selectivity. However, dioxide (S)-54, with axial chirality, induced high levels of enantioselection. Not surprisingly, axial chirality might significantly influence the stereoinduction of these reactions. Combining axial and carbon-centered chirality in the monooxide series led to (R)-57 and its diastereomer (S)-57. However, only the former provided (S)-42 with improved selectivity (matched stereochemical elements); inverted absolute configuration and diminished selectivity was seen for the latter (mismatched stereochemical elements). The corresponding dioxides (not shown) performed poorly. It must be noted that 57 is not configurationally stable at room temperature for prolonged times!

Avoiding this flaw, Kočovský abandoned axial chirality as a stereochemical element and prepared monoxide 58a, a structural isomer of 55, which enables substitution in the proximity of the coordinating oxygen and nitrogen centers. Unsubstituted 58a (R = H) was a poor catalyst, but substituted 58b (R = i-Pr) exceeded even the selectivity determined for 55. Conversion was greatly improved when dichloromethane was replaced by acetonitrile as solvent (yield and enantiomeric excess given in parentheses, Figure 3).

Based on these results, Kočovský proposed transition state 61, in which the PINDOX ligand (R)-57 functions as a bidentate ligand at hexacoordinated silicon (Figure 4). Besides the characteristic steric environment in 61, the oxygen of the N-oxide moiety is located trans to the allyl group, thereby enforcing its nucleophilicity (trans-effect).

Figure 4

Hayashi has presented chiral catalyst (R)-59, which again relies only on axial chirality as (S)-54 (Figure 3); (R)-59 proved to be an outstanding promoter for the standard allylation reaction [13 → (S)-42, Scheme 23].

Catalyst loadings as low as 0.1 mol% furnished homallylic alcohol (S)-42 with very good enantiomeric excess at excellent reaction rates. Easily accessible QUINOX-type catalyst (R)-60 was recently probed by the Kočovský group. Excellent enantioselection was achieved for electron-poor aldehydes using this catalyst.

The bidentate nature of these chiral promoters is also to be found in chiral phosphoramides designed by Denmark and Müller. As depicted in Scheme 18, stoichiometric amounts of monodentate phosphoramides (R,R)-43 and (R,R)-62 (Figure 5) gave moderate enantioselectivities. At reduced catalyst loadings, enantioselectivity dropped substantially, yet was accompanied by a non-linear effect. This was, in turn, explained by two molecules of the chiral promoter coordinating to the silicon center.

Scheme 24
Consequently, Denmark and co-workers simply tethered the monodentate ligands by replacing the piperidine unit by a 1,4-diaminoalkyl linker (Figure 5). The length of the tether \( (n = 3–6) \) of these chelating Lewis bases had a profound influence on the enantioselectivity. The highest enantiomeric excess was obtained with \((\text{R,R})-64\) \((n = 5)\) in the allylation of 13 \(\rightarrow\) 42 shown in Scheme 24.46b

The mechanism is believed to involve a hexacoordinate silicon species similar to the one proposed for the allylation of aldehyde 13 with \((\text{E})-65\), providing 66 in good yield and with nearly perfect diastereo- and enantioselectivity.46c

Scheme 25

**Chiral Reagents**

The stoichiometric and catalytic asymmetric methodologies described in the preceding paragraphs have recently been extended by the reactions of a novel family of chiral allylic silanes. In a series of publications,48–50 Leighton has combined the concept of strained silacycles51–53 with asymmetric alkylation chemistry. It is generally accepted that incorporation of a tetravalent silicon into a strained – four- or five-membered – ring system results in an increase in Lewis acidity (strain-release Lewis acidity54) as well as a higher tendency to expand its valence shell.48,55 This corresponds to a smaller energy gap between A and B (Scheme 1) for a strained system when compared to acyclic species. Based on these prerequisites, Leighton evolved heteroatom-substituted allylic silacyclopentanes 6748 (Scheme 26) or 6948 (Scheme 27).

These chirally modified allylic silanes with integrated Lewis acidity were utilized as chiral alkylation reagents. As summarized in Scheme 26,49 allylation of aromatic and aliphatic aldehydes worked equally well in the absence of an additional Lewis base (promoter/activator) or Lewis acid. Impressively, both 13 \(\rightarrow\) (S)-42 and 17 \(\rightarrow\) (S)-52 turned out to be highly enantioselective transformations. Although not yet completely understood, the mechanism is likely to involve a cyclic transition state with a trigonal bipyramidal geometry at the pentacoordinated silicon.48,54

Scheme 26

Allylic silanes of type 67 are finely tunable reagents. The substituents at nitrogen and silicon allow for easy alterations, while leaving the chiral backbone unchanged. Further advantages of these stable and storable reagents are their straightforward preparation, purification by distillation, and recyclability of the chiral auxiliary by acidic work-up.

Allylation of benzoylhydrazone 68 using allylic silane 69 derived from ephedrine yielded \((\text{R}^*)-70\) with high enantioselectivity (Scheme 27).50b

Scheme 27
valent silicon intermediates, which are prone to pseudo-rotational processes, and again, only one diastereomeric intermediate will transfer its allyl group.

The benzoyl group in substrate 68 (and congeners thereof) is the pivotal element for realizing high enantioselection. This could be explained by coordination of the Lewis basic carboxyl oxygen to silicon (it should be noted that in this case, the Lewis base assists the formation of a rigid, highly ordered transition state rather than increasing the Lewis acidity at silicon). These observations, and the crystallographic data of a related compound (not shown), support the mechanism depicted in Scheme 28.50b

Scheme 28

Carbon–carbon bond formation does not occur at the stage of the initially formed hexacoordinate silicon intermediate 71. Prior to allyl transfer, chloride dissociation leads to pentavalent 72, which readily transfers, with high stereo-selectivity, the allyl group.

It might be noted, though, that closely related tartrate-derived silacycles 74 were reported almost simultaneously by three groups (Wang,57 Kira/Sakurai,58 and Barrett37) prior to Leighton’s elegant contributions (13 → (S)-42 and 73 → (R)-75, Scheme 29). These novel chloro-substituted allylic silanes also undergo enantioselective allyl transfer without further activation.58 When compared with 67 and 69, 74 provides only moderate enantioselection. This observation is not unexpected, as the nitrogen in 67 and 69 provides a handle for the installation of sterically demanding substituents in proximity of the silicon center.

Scheme 29

High diastereoselectivity of the corresponding crotylation substantiates the assumption of a cyclic transition state 37,58. Kira proposed the chair-like transition state 76 (Figure 6), in which the tartrate moiety functions as a tridentate ligand.58 In this complex, one of the two ester moieties functions as an internal Lewis base.

Diastereoselective (Intramolecular) Allylations

Recently, Leighton implemented an intramolecular silicon-mediated allylation in the preparation of complex polyketide structures (Scheme 30).59 This rare synthetic application includes a catalytic asymmetric silyl ether formation60 (77 → 79) followed by an intramolecular silylformylation61 (79 → 81) and subsequent in situ allyl transfer61 (81 → 83).

The silicon-centered chirality in 79 was constructed by a copper-catalyzed asymmetric etherification of enantiomerically pure alcohol 77 with the achiral dihydrosilane 78. Although the diastereoselection was only moderate, this unique etherification is quite remarkable as there are not many transformations known to selectively induce chirality at silicon in an intermolecular reaction.62
A highly diastereoselective rhodium-catalyzed silylformylation under an atmosphere of carbon monoxide was used to install the carbonyl moiety and generate a strained silacycle (79 → 81). The silicon center in 81 is sufficiently Lewis acidic to be coordinated intramolecularly by the carbonyl oxygen, which is placed in an ideal vicinity (81 → 82). Crotolation provided bicycle 83 in highly stereoselective fashion. Twofold silicon–oxygen bond cleavage using methyl lithium enabled the formation of stereodefined tert-butyldimethylsilyl-substituted vinyl silane 84.

This beautiful contribution by Leighton implies the synthetic potential of stereoselective allylation through hypervalent silicon intermediates.

2.2.2 Addition of Silicon Enolates to Carbonyl Compounds

As illustrated in the introductory paragraph of this subsection (Scheme 12), the addition modes of allylic silanes \( Y = \text{CH}_2 \) resemble those of silicon enolates \( F \ (Y = O) \). This section will be devoted to the chemistry of these silicon enolates in aldol reactions that have silicon as a reactive site. As for the allylation through acyclic transition states, the well-established classical Mukaiyama aldol addition of silicon enolates \( F \ (Y = O) \) with Lewis acid activated carbonyl compounds \( G \ (X = O) \) is beyond the scope of this review.\(^{22}\)

Promoted by chiral Lewis bases, suitably substituted silicon enolates \( H \ (L = \text{Cl}) \) will react with carbonyl compounds via cyclic transition states \( K \) (Scheme 12) in a highly stereoselective manner. Once again, hypervalency at silicon meets two assignments: (1) a more nucleophilic metallo enolate, and (2) a more Lewis acidic silicon center. One might compare these characteristics to boron enolates, yet without the need for external Lewis base activation.\(^{63}\) In a number of seminal publications, Denmark reported the realization of this strategy using trichlorosilyl enolates.\(^{64-70}\)

Lewis base-catalyzed aldol reactions of other silicon enolates have also been studied.\(^{71}\) For example, Mukaiyama realized the ‘non-acidic’ activation of trimethylsilyl enolates with metalated nitrogen bases such as lithium amides. Unexpectedly, these aldol reactions are believed to proceed mostly via acyclic transition states. To date, asymmetric variants have not been described.

The chiral Lewis base activation of silicon enolates has emerged as a novel tool in asymmetric aldol chemistry. About a decade ago, Denmark showed that catalytic quantities of phosphoramides \((S,S)-87a\) promoted the aldol reaction of 13 and 85 with excellent yield and stereoselection (13 → 86, Scheme 31).\(^{65a,6d}\) Catalyst \((S,S)-87a\) is closely related to those utilized in allylation chemistry (Figure 5).

Scheme 31

_Nota bene:_ The trichlorosilyl group is relatively Lewis acidic due to the presence of three electron-withdrawing chloro ligands. Hence, such silicon enolates already react _without_ Lewis base activation even at low temperatures! Achieving these high enantioselectivities is only possible with the catalyzed pathway being much faster than the uncatalyzed reaction. The excellent diastereoselectivity is to be attributed to a cyclic transition state (Scheme 34).

Ligand \((S,S)-87a\) was also successfully applied to the aldol reaction of other silicon enolates such as 88 (Scheme 32)\(^{67a}\) and \((Z)-91\) (Scheme 33)\(^{67b}\).

Scheme 32

In particular, methyl ketone-derived trichlorosilyl ether 88 reacted readily with aromatic 13 as well as aliphatic aldehyde 17 in good to high enantioselectivities [13 → \((S*)-89\) and 17 → \((S*)-90\), Scheme 32].\(^{67a}\) Preparation of polyketide building blocks, such as 92 with defined relative and absolute configuration, was also possible (13 → 92, Scheme 33).\(^{67b}\)

Scheme 33

Careful mechanistic investigations by Denmark and coworkers revealed that a complex interplay of several parameters goes into determining the stereochemical outcome of these reactions (Scheme 34).\(^{67,68}\) The steric requirements of the organocatalyst \((S,S)-87a\) or \((S,S)-87b\) with differently substituted nitrogen centers determines the valency of the silicon center in transition states 93 and 95, respectively. At present, these supposed transition states appear reasonable and are supported by the follow-
ing experimental observations: (a) a non-linear effect has only been measured when using \((S,S)-87a\), and no asymmetric amplification has been seen when using \((S,S)-87b\); and (b) \(93\) and \(95\) give products with different relative stereochemistries (\(anti\) and \(syn\)).

According to Denmark, the chair-like hexacoordinated siliconate transition state \(93\) that bears two phosphoramidate ligands \((S,S)-87a\) might explain the non-linear effect and \(anti\)-selectivity \((93 \rightarrow anti-94)\). If sterically more demanding \((S,S)-87b\) is used instead, the almost perfect \(syn\)-selectivity could be rationalized by boat-like transition state \(95\) \((95 \rightarrow syn-96)\). In addition, only low enantioselection (50% ee) has been detected for the latter case, whereas high levels have been found for the former (Schemes 31–33).

Solvent polarity and added soluble salts have a dramatic effect on the stereochemical outcome of these reactions; this also verifies the presence of ionic species in the stereochemistry-determining step.

Later, Denmark worked out reaction conditions for the first crossed aldol coupling \((13 \rightarrow 98, \text{Scheme 35})\). Bidentate chiral bisphosphoramidate \(16\) (Scheme 6) catalyzed the aldol addition of silicon enolate \((Z)-97\) and standard aryl aldehyde \(13\) that afforded \(98\) (the unstable aldol product required immediate protection as its acetal) in excellent diastereoselectivity and good enantiomeric excess. Activator \(16\) seemed ideal for this particular transformation since related bidentate phosphoramides [same length of tether \((n = 5)\] and the corresponding monodentate ligands (Figure 5) showed less stereoinduction. The realization of such crossed aldehyde aldol reactions is remarkable since Lewis acid catalysis leads commonly to polymerisation, which is faster than the desired aldol reaction.72

Surprisingly, catalysts with a Lewis basic phosphoramidate moiety proved to not be applicable to the aldol additions of ester enolates. Nevertheless, it was again Denmark who solved the problem. The novel pyridine \(N\)-oxide-based catalyst \((R,R)-101\) nicely promotes the aldol reaction of trichlorosilyl ketene acetal \(99\) and methyl ketone \(30\) (Scheme 36).70 In agreement with the work of Kočovsky (Scheme 23, Figure 3), Denmark confirmed that axial chirality is a critical stereochemical element for this family of Lewis basic promoters.70 The same catalyst class (Figure 3) was evaluated by Nakajima for the addition of trichlorosilyl enolates to carbonyl compounds, though the observed enantioselectivities were unsatisfying.73

Until very recently, this chemistry was limited to trichlorosilyl enolates. Remarkably, Nakajima managed to introduce trialkoxysilyl enolates such as \(102\) to Lewis base-catalyzed asymmetric aldol chemistry \((17 \rightarrow 103, \text{Scheme 37})\).74 For achieving high enantioselection, water plays a pivotal role in this binaphtholate-catalyzed transformation.

Scheme 34

![Scheme 34](image)

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Scheme 35

![Scheme 35](image)
In general, silicon-based cross-couplings hold some serious advantages over the more traditional methodologies: (1) no toxic by-products; (2) highly stable and storable organosilicon compounds as precursors; and (3) mild reaction conditions using relatively simple transition-metal catalysts.\textsuperscript{75}

**Mechanistic Considerations**

A simplified catalytic cycle illustrating the basic principles is given in Scheme 38 (vinylation of an arene).\textsuperscript{77}

The composition of the catalytically active palladium(0) species L is uncertain and may vary with pre-catalyst and reaction conditions used; L readily undergoes oxidative addition into a C(sp\textsuperscript{3})–X bond of aryl halide M to form the electrophilic aryl palladium(II) species N, which is then coordinated by the alkene unit of pentavalent (fluoride-activated) vinylic palladium(II) species \(\text{N} \rightarrow \text{P}\). Ligands such as chloride (X = Cl) at palladium will further weaken the C(sp\textsuperscript{3})–Si bond in P by coordinating to the Lewis acidic silicon, thereby facilitating the subsequent transmetalation of the hexavalent silicon intermediate. This transmetalation (P \(\rightarrow\) R) has been identified as the rate-determining step in such silicon-based cross-coupling reactions. Hence, the presence of a silaphilic nucleophile, such as flouride, is essential for high reaction rates. Carbon–carbon bond formation occurs in palladium(II) intermediate R by reductive elimination to liberate ipso-substituted styrene S and regenerate catalyst L.

On rare occasions, cine- instead of ipso-substitution is observed.\textsuperscript{77,78} This uncommon regiochemical outcome is rationalized by a Heck-type alkene insertion (P \(\rightarrow\) T, Scheme 39) competing with the desired transmetalation step (P \(\rightarrow\) R, Scheme 38). Thus, if the transmetalation is extremely slow, insertion of the carbon–carbon double bond into the σ-aryl–palladium(II) bond will take place in \(\text{P}\). Subsequent \(\text{syn-β}-\text{hydride elimination (T} \rightarrow \text{U}) is followed by reinsertion with opposite regioselectivity (U \(\rightarrow\) V). Finally, \(\beta\)-silyl elimination produces cine-product W.

---

**Scheme 36**

\[
\begin{align*}
\text{Ph} & \quad \text{Me} \quad \text{O} \quad + \quad \text{OSiCl}_3 \\
\text{Me} & \quad \text{R} \quad \text{O} \quad + \quad \text{OSi(O)Cl}_3 \\
\text{CH}_2\text{Cl}_2 & \quad -78 \degree \text{C} \quad 96\% \\
\end{align*}
\]

---

**Scheme 37**

**3 C(sp\textsuperscript{3})–C(sp\textsuperscript{2}) Bond Formation: Transition-Metal-Catalyzed Cross-Coupling Reactions**

In the preceding sections, strategies for stereoselective C(sp\textsuperscript{3})–C(sp\textsuperscript{3}) bond formation involving silicon as a reactive site were highlighted. These methods certainly rely on the mutual increase of Lewis acidity and capacity for R groups, leading to the reactive site. These methods certainly rely on the mutual increase of Lewis acidity and capacity for R groups, leading to the reactive site. The actual transmetalation of a carbon fragment from a metalloid silicon to a transition-metal center. The actual carbon–carbon bond formation does not involve silicon as the reactive site.

Initially underestimated, cross-coupling reactions that employ C(sp\textsuperscript{3})–Si bonds as coupling partners have even become competitive alternatives to the classical cross-coupling reactions of organoborons\textsuperscript{76a} [C(sp\textsuperscript{3})–B, Suzuki coupling], organomagnesium\textsuperscript{76b} [C(sp\textsuperscript{3})–Mg, Kumada coupling], organozinc\textsuperscript{76c} [C(sp\textsuperscript{3})–Zn, Negishi coupling], and organotin compounds\textsuperscript{76d} [C(sp\textsuperscript{3})–Sn, Stille coupling].
Further evidence for influential bridging groups X was provided within the study of the stereochemical course of the transmetalation at silicon-bearing C(sp³) centers. A concerted transmetalation with a bridging ligand (X = Cl) is assumed to be the usual pathway, which occurs via cyclic transition state with stereoretention at carbon (105, Figure 7).

Inversion of configuration is observed in strongly coordinating solvents, which replace the bridging X group. Formation of a Si–X–Pd chelate is also restrained at elevated reaction temperatures. For both cases, back-lobe attack of the palladium(II) center via an open mechanism is assumed, as supported by the observed inversion of configuration at carbon (106, Figure 7).

Table 1: Organosilicon Compounds in Cross-Coupling Reactions

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹–SiLn (n = 3-5)</th>
<th>R¹</th>
<th>Additive</th>
<th>Scheme</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R¹–SiF₅K₂</td>
<td>Aryl, Alkenyl, Alkynyl, Allyl, Benzyl</td>
<td>Fluorides, Alkoxides</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>R¹–SiF₅Alkylₘ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(m = 0–2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>R¹–Si(OR₂)₃M</td>
<td>Aryl, Alkenyl, Alkynyl</td>
<td>Fluorides</td>
<td>42–44</td>
</tr>
<tr>
<td></td>
<td>(Li, Na, K)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R¹–Si(OR₂)₃Alkylₘ</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(m = 0–2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>R¹–SiR³ (R¹ = Alkyl, Aryl, HetAryl, Allyl)</td>
<td>Aryl, Alkenyl, Alkynyl</td>
<td>Fluorides</td>
<td>45–47</td>
</tr>
<tr>
<td>4</td>
<td>R¹–SiCl₃Alkylₘ</td>
<td>Aryl, Alkenyl</td>
<td>NaOH</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>(m = 0–2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R¹–Si(OH)R³₂</td>
<td>Aryl, Alkenyl, Alkynyl</td>
<td>Fluorides</td>
<td>49–51</td>
</tr>
<tr>
<td></td>
<td>(R¹–SiR³₂)₂O</td>
<td></td>
<td>NaOH, C₆H₄CO₂, Ag₂O₂, KO₂SiMe₃</td>
<td></td>
</tr>
</tbody>
</table>

Organosilicon Precursors

An analysis of organosilicon precursors used in cross-coupling reactions allows for a rough classification of these reagents (Table 1). The standard silaphilic additive is fluoride from inorganic salts (potassium and cesium fluoride) or from n-Bu₄N⁺F⁻ (TBAF), (Et₂N)₃S⁺Me₃SiF₂⁻ (TASF), and Me₄N⁺F⁻ (TMAF).

Mono- and difluorosilanes have found wide application, whereas the corresponding trifluorosilanes and fluorosilicates have been studied less extensively (Table 1, entry 1). Alkoxy silanes and cognate siliconates have also been shown to be potent coupling partners when activated by fluoride (Table 1, entry 2). Remarkably, even the C(sp³)–Si bond in triorganosilanes has been cross-coupled with fluoride activation (Table 1, entry 3). Chlorosilanes have been rarely utilized and – with sodium hydroxide as the activating additive – the corresponding silanols might be the actual silicon species. Conversely, the direct use of silanol(ates) has grown significantly in recent years (Table 1, entry 4). With this development, novel activators such as silver oxide and potassium silanlates have been introduced.
Instructive Examples

Several years after Kumada’s initial report of a silicon-based cross-coupling reaction in the early eighties, Hiyama elaborated the first preparatively useful protocol (Scheme 40). The palladium-catalyzed, TASF-mediated reaction of stereoisomerically pure vinyliodide 107 and vinylsilane 108 afforded diene 109 highly diastereoselectively and in excellent yield.81b

Scheme 40

Unexpectedly, allylic carbonates such as 110 were also cross-coupled with a fluorosilane, yet without an activating additive (110 → 112, Scheme 41).82 The authors explained this interesting result by the presence of alkoxide generated from collapsed carbonate.

Scheme 41

The reversed scenario, in which an alkoxysilane is activated by external fluoride, works equally well (113 → 114, Scheme 42).83,84

Scheme 42

In these reactions (Schemes 40–42), the intermediate undergoing the transmetalation (P in Scheme 38) is a mixed alkoxylfluorosiliconate. For siliconate formation, fluoride and alkoxides appear to be mutually interchangeable without affecting reactivity.

A fascinating synthetic application of vinylic siloxanes was presented by Denmark. Substrate 115 cyclizes in good yield under standard reaction conditions forming the nine-membered ring system 116 (Scheme 43).85a The construction of this cyclic ether skeleton by an intramolecular silicon-assisted cross-coupling is the key step in the total synthesis of (+)-brasilenyne.85

Scheme 43

Recently, Fu found extraordinarily mild reaction conditions for the C(sp³)–C(sp²) cross-coupling of alkyl bromide 117 and trialkoxysilane 118 (117 → 119, Scheme 44).86 No β-hydride elimination of the intermediate σ-alkyl palladium(II) species was detected.

Scheme 44

Several years ago, Hiyama described the first example for the successful utilization of trimethylsilyl-substituted alkenes and alkynes in palladium-catalyzed cross-coupling reactions.81a The fluoride-promoted reaction of vinyl bromide 120 with alkyne 121 proceeded readily at ambient temperature (120 → 122, Scheme 45).

Scheme 45

The mechanism is also believed to involve a pentavalent fluorosiliconate. However, in view of the fact that tetraorganosilanes are oftentimes not sufficiently reactive for these reactions, the mechanism and, particularly, the transmetalation step, remain uncertain.

Lately, several groups rediscovered the synthetic potential of tetraorganosilanes. Strained silacyclobutanes such as 124 were used by Denmark as coupling partners87 in facile transmetalations promoted by fluoride. Cross-coupling of
124 with vinylic bromide 123 afforded isomerically pure diene 125 (Scheme 46). Interestingly, silanol 126 and disiloxane 127 were identified as intermediates involved in the transmetalation.\(^{87a}\) In a control experiment, both 126 and 127 were isolated upon treatment of 124 with TBAF! Accelerated by considerable ring strain in 124, nucleophilic attack of hydroxide (contamination in TBAF) at silicon gave the ring-opened intermediates 126 and 127. Then, fluoride attacks at disiloxane 127 generating a fluorosiliconate, which, in turn, smoothly transmetalates.

Scheme 46

A related reaction mechanism is operating in the cross-coupling of dimethyl(2-pyridyl)silyl-substituted alkenes, which were originally introduced by Yoshida (128 \(\rightarrow\) 131, Scheme 47).\(^{88a}\)

Scheme 47

The dimethyl(2-pyridyl)silyl group nicely combines two features: (1) (removable) substrate-directing group [N(sp\(^2\)) donor] and (2) cross-coupling partner and, therefore, placeholder for further functionalization. A one-pot reaction sequence illustrating these features is shown in Scheme 47. The mode of reaction is switched by simply changing the additive: triethylamine for directed Heck reaction with 129, or TBAF for cross-coupling with 130.

Sequential addition of triethylamine/129 and TBAF/130 in the presence of the same catalyst furnished the doubly arylated product 131 in excellent yield.\(^{88b}\)

Remarkably, this silicon-based cross-coupling (Scheme 47) is closely related to the observations made by Denmark (Scheme 46). Maintaining substrate 128, with the dimethyl(2-pyridyl)silyl group, and TBAF in THF at 60 °C led to a mixture of silanols such as 132 (Scheme 47).\(^{88b}\) Again, disiloxanes derived from 132 are assumed to be transmetalated to palladium.

A closer look into the literature reveals a handful of examples of silanols and, eventually, disiloxanes as the key intermediates in silicon-based cross-couplings of chlorosilanes.\(^{89}\) Hiyama reported a novel, fluoride-free activation of chlorosilane of type 134 by sodium hydroxide (133 \(\rightarrow\) 135, Scheme 48).\(^{90}\) Substitution of chloride by hydroxide prior to transmetalation is very likely.

Starting directly from a silanol is also feasible [(E)-136 \(\rightarrow\) (E)-137, Scheme 49].\(^{91}\) Once again, fluoride activates an intermediate disiloxane and the resulting fluorodisiliconate 138\(^{92}\) is transmetalated.\(^{91a}\)

Silver(I) oxide was also found to be an efficient activator for such a cross-coupling (139 \(\rightarrow\) 141, Scheme 50).\(^{93}\) The authors vaguely proposed the interaction of a silver(I) center and iodide coordinated to the palladium(II) center, combined with silicon interacting with oxide moiety.

Denmark reported another new additive for a seemingly related cross-coupling of silanols.\(^{94}\) Potassium trimethylsilanolate appears to be uniquely different from commonly used alkoxides and hydroxides [(Z)-142 \(\rightarrow\) (Z)-143, Scheme 51]. Importantly, detailed mechanistic investigations revealed that this cross-coupling does not follow the traditional catalytic cycle\(^{95a}\) (Scheme 38). In the presence
Mechanism Revisited

Denmark’s work discloses that the mechanism of silicon-based cross-couplings with respect to silicon as the reactive site might be strongly dependent on the additive used. In fact, Denmark has been able to prove that this is true for the cross-coupling of silanols in the presence of potassium trimethylsilanolate [(Z)-142 → (Z)-143, Scheme 51, and (E)-142 → (E)-145 → (E)-146. Scheme 52]95 Whereas for fluoride- and alkoxide-mediated transformations, hypervalency at silicon is needed for a successful transmetalation (Scheme 38), the novel mechanism postulated by Denmark is devoid of such species since potassium trimethylsilanolate (Scheme 51)94 or potassium hydride95 (Scheme 52) functions as a base (Scheme 53). As verified by kinetic measurements, the mechanism for the reaction shown in Scheme 51 is clearly breaking with the dogma of hypervalency at silicon for a successful transmetalation.

4 Outlook and Perspective

Synthetic chemistry that exploits hypervalency at silicon for selective bond-forming processes has been substantially developed in recent years. The perception that seemingly different reactions underlie the same concepts allows for a unified understanding. Extracoordinate silicon displays increased Lewis acidity at silicon and a greatly enhanced tendency to release carbon substituents. These properties enable carbon–carbon bond formation, as well as transmetalation reactions, upon breaking a carbon–silicon bond.

Aldol and aldol-like products are accessible by organocatalytic C(sp3)–C(sp3) bonding formation of carbonyl compounds with allylic silanes and silicon enolates, respectively. Conversely, transmetalation from hypervalent silicon to a transition metal such as palladium is an efficient entry into cross-coupling chemistry.

With the current focus on organocatalysis and continuing interest in powerful cross-coupling reactions, these aspects of organosilicon chemistry will have a significant influence on organic synthesis in the years to come.

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