Reaction Mechanisms

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Conclusive Evidence for an S_N2-Si Mechanism in the $B(C_6F_5)_3$-Catalyzed Hydrosilylation of Carbonyl Compounds: Implications for the Related Hydrogenation**

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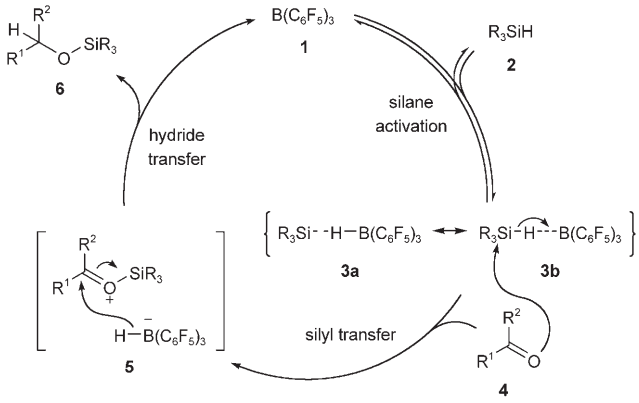
The precise mechanistic understanding of chemical transformations is an urgent challenge in synthetic chemistry as it guides the targeted design of improved or even novel processes. For example, transition-metal-free reduction of C=X bonds (X = O and NR) catalyzed by boron-based Lewis acids is currently attracting considerable attention.[1] Illuminating its mechanism(s) of action might open the door for the development of yet unknown enantioselective variants. In this context, commercially available tris(pentafluorophenyl)borane (**1**)[2] is a particularly effective catalyst for both hydrosilylation and hydrogenation.[3] In a series of seminal papers, Piers et al. had reported a protocol that is based on triorganosilanes as stoichiometric reducing reagents.[4] Moreover, Stephan et al. reported that dihydrogen—clearly the most desirable reducing agent—also facilitates smooth turnover in C=NR and C≡N reductions.[5,6] In this scenario, an unconventional $B(C_6F_5)_3$-catalyzed activation of dihydrogen is operative.[5] The direct investigation of this dihydrogen activation[8] by experimentally straightforward techniques is certainly demanding, though.[9,10] In turn, examination of the closely related silane activation[11,12] might provide a solid foundation for the delineation of the basic mechanistic principles of both processes.[13] We report herein a simple yet conclusive investigation of the transition state operative in the $B(C_6F_5)_3$-catalyzed hydrosilylation of prochiral acetophenone using a silane with a stereogenic silicon center[14] as a stereochemical probe.[15,16] We then discuss implications for the related hydrogenation.

Based on comprehensive experimental data, Piers et al. suggested a seemingly counterintuitive three-step mechanism for the hydrosilylation of carbonyl compounds (Scheme 1).[4a,b] The catalysis commences with the activation of silane **2** by the strong Lewis acid **1** through reversible coordination to the hydridic Si–H bond (**1**→**3**). The two resonance structures **3a** and **3b** of the thus-formed intermediate rationalize the capability of **1** to abstract a hydride from silicon in the subsequent step. Silyl transfer to the Lewis basic carbonyl oxygen of **4** thereby produces ion pair **5** (**3**→**5**).



Scheme 1. The Piers mechanism of the $B(C_6F_5)_3$-catalyzed hydrosilylation of carbonyl compounds.

As implied by the complete absence of any crossover when two different mass-labeled silanes are used,[4b] the ion pair is apparently not solvent-separated and undergoes rapid hydride transfer from the borohydride to the electrophilic carbon of the silylcarboxonium ion to give **6** along with regenerated catalyst **1** (**5**→**1**). The fate of intermediate **3** has remained vague: Concerted S_N2-type displacement at silicon (S_N2-Si[18,19]) of a boron-coordinated hydride by the carbonyl oxygen of **4** has been postulated. Another intriguing piece of information emerges from rapid H/D exchange when **2** and its deuterated congener are used in the absence of Lewis bases.[4b]

Inspired by remarkable achievements utilizing stereogenicity at silicon as a chiral probe,[15,20] we decided to examine the nature and consecutive reaction of intermediate **3** by applying our previously developed family of asymmetrically substituted silanes.[14] We first assessed silanes *rac*-**2a**–**d** in the hydrosilylation of acetophenone (**4**) in the presence of catalytic amounts of catalyst **1** (5.0 mol%) in order to identify a sufficiently reactive stereogenic silane (**4**→*rac*-**6**, Scheme 2). It is interesting to note that, without exception, all silanes decorated with a *t*Bu group—cyclic *rac*-**2a**,[21a] cyclic and strained *rac*-**2c**,[21b] and acyclic *rac*-**2d**[21c]—were to completely unreactive. In contrast, cyclic *rac*-**2b**[15b] equipped with an *i*Pr group readily delivered the desired product *rac*-**6b** in good yield and with notable diastereoinduction (vide infra). The difference in steric hindrance between *i*Pr-

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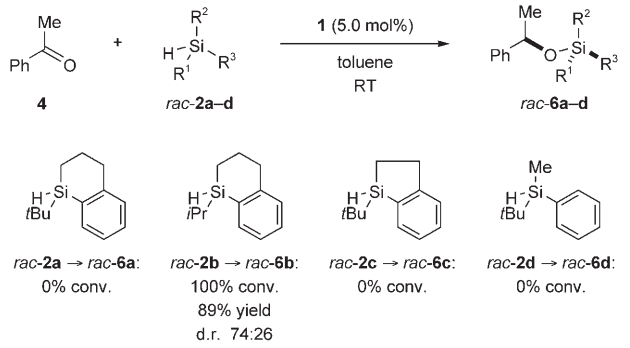
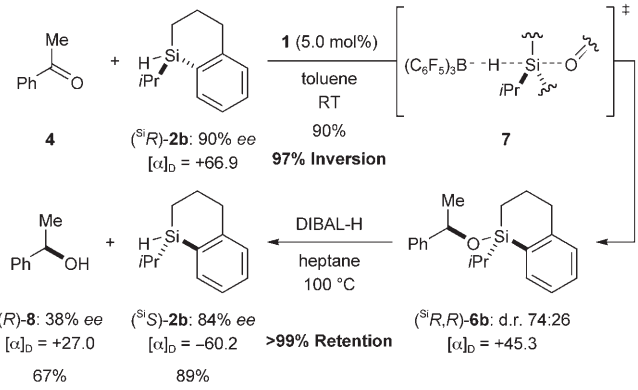


Scheme 2. Screening of suitable chiral probes.

substituted *rac*-**2b** and *t*Bu-substituted *rac*-**2a** might account for this dramatic reactivity difference in an assumed S_N2-Si displacement. However, this argument is inconclusive since Reed et al. had demonstrated that *i*Pr-substituted silanes display a higher tendency to form silylium-ion-type intermediates as a result of α-C-H hyperconjugative stabilization;[22] these silanes would thus show superior reactivity in an S_N1-Si-type mechanism.

Strong evidence against a free silylium ion intermediate[23] would come from the classical reaction setup for a Walden inversion at silicon,[18] which required repeating the reduction with enantioenriched silane (^{Si}R)-**2b** [**4**→(^{Si}R,*R*)-**6b**, Scheme 3].[24] Prochiral ketone **4** was treated with (^{Si}R)-**2b** (90% *ee*) in the presence of catalytic amounts of $B(C_6F_5)_3$ to yield optically active (^{Si}R,*R*)-**6b** as a mixture of diastereomers (d.r. 74:26). After racemization-free reductive cleavage of (^{Si}R,*R*)-**6b** with diisobutylaluminum hydride (DIBAL-H) under standard reaction conditions,[21a,25] silane (^{Si}S)-**2b** was recovered in high chemical yield and with inverted absolute configuration [(^{Si}R,*R*)-**6b**→(^{Si}S)-**2b**]. With 90% *ee* for (^{Si}R)-**2b** and 84% *ee* for (^{Si}S)-**2b**, inversion at the silicon atom is virtually immaculate (97% inversion and marginal 3% racemization). Absolute configurations were unambiguously assigned by HPLC analysis on a chiral stationary phase as well as by analysis of the optical rotation. The relative configuration of (^{Si}R,*R*)-**6b** was deduced from the configuration of the isolated alcohol (*R*)-**8** (38% *ee*).

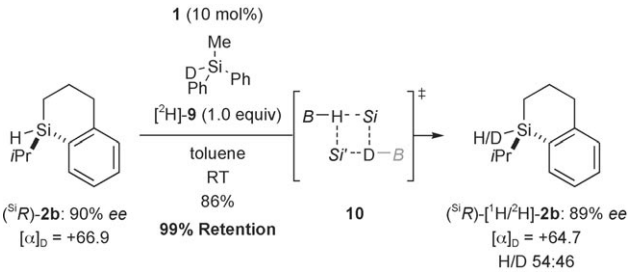


Scheme 3. Two-step stereochemical analysis: An inversion–retention pathway.

This result clearly supports a concerted S_N2-Si mechanism for the reduction step. Spontaneous heterolytic dissociation of intermediate **3** (Scheme 1) would liberate a free (or toluene-stabilized[26]) achiral silylium ion, thereby producing racemic material. Nucleophilic attack at silicon by the Lewis basic carbonyl oxygen of **4** must occur *anti* to the quasi-linear B-H-Si array[4b,27] via transition state **7** (Scheme 3). Moreover, we emphasize that **7** should be regarded as a transition state because any lifetime on the reaction timescale would likely result in racemization by pseudorotational processes like those observed with hypervalent cyclic silicon intermediates.[28]

The origin of diastereoinduction is noteworthy as it is induced by the single-point-bound stereogenic silicon atom coordinated to the Lewis basic carbonyl oxygen (**5**, Scheme 1). Piers et al. had already presented solid data that it is the borohydride and not another molecule of the silane that functions as the reducing agent.[4b] Overall, the reaction studied here represents an example of chirality transfer from silicon to carbon,[29] which follows a "one-silicon" as opposed to a "two-silicon" cycle.[15]

To further exclude involvement of free silylium ions, we performed another rigorous control experiment. An equimolar mixture of enantioenriched silane (^{Si}R)-**2b** (90% *ee*) and deuterium-labeled achiral silane [^{2}H]-**9** was exposed to the borane catalyst **1** in the absence of a Lewis base (Scheme 4).[30] Mass spectrometric analysis of the isotopic distribution after 2 h at room temperature showed complete scrambling: (^{Si}R)-[^{1}H/^{2}H]-**2b** (89% *ee*, H/D 54:46) and [^{2}H]-**9** (H/D 50:50). The preservation of the stereochemical integrity in isolated (^{Si}R)-[^{1}H/^{2}H]-**2b** excludes: 1) a mechanism through (achiral) silylium ion intermediates and 2) an S_N2-Si displacement at activated **3** with a silane as the attacking nucleophile as both of these would bring about racemization. It is therefore plausible to suggest a σ-bond metathesis involving a four-centered cyclic transition state. Related transition-metal-catalyzed processes are known to proceed with stereoretention at silicon.[14,15,31] Transition-state **10** (Scheme 4) consisting of two borane-activated silanes fulfills the stereochemical requirements; alternatively, a complex of



Scheme 4. Racemization-free scrambling in the absence of a Lewis base: No support for free silylium ions [$B = B(C_6F_5)_3$ and *Si* or *Si'* = R_3Si].

type **3** (Scheme 1) might be sufficiently reactive to directly undergo σ-bond metathesis with a free silane.

Based on these insights into the $B(C_6F_5)_3$-catalyzed hydrosilylation, conclusions might be drawn, to a certain extent, for the closely related hydrogenation.[10] A comparison of the bond energies of $R_3Si{-}H$ (90 kcal mol^{-1} [32]) and H–H (108 kcal mol^{-1}[8]) corroborates that $B(C_6F_5)_3$-catalyzed heterolytic dissociation of H_2 into the contact ion pair "$H^+[HB(C_6F_5)_3]^-$" is, as is the case for $R_3Si{-}H$, an unfavorable event in the absence of a Lewis base. However, an S_N2-type process at hydrogen similar to that at silicon is implicated:[10] η^1 (end-on) coordination[27] of $B(C_6F_5)_3$ to dihydrogen could activate the H–H bond for nucleophilic attack by the Lewis basic substrate. Again, a tight contact ion pair consisting of an iminium ion (with imines as substrates[5]) and the borohydride is formed. Liberation of the amine after subsequent hydride transfer then completes the catalytic cycle.

In summary, the refined mechanistic picture of the $B(C_6F_5)_3$-catalyzed hydrosilylation bodes well for the development of catalytic asymmetric approaches. It seems that their efficiency will highly depend on asymmetric induction of a chiral nonracemic borane.[3,33] A proof of principle was included in a very recent report, which might also stimulate further research in this area.[5b]

Our mechanistic investigation and proof of an S_N2-Si transition state in the Si→B hydride-transfer step is predicated on a simple Walden-type analysis employing a silane having a silicon stereocenter as a stereochemical probe. It might well be worth applying this technique to systems relying on other Lewis bases, e.g., phosphines,[9] and to the recent dihydrogen-splitting molecules introduced by Stephan et al.[6,7,34]

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