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Experimental Analysis of the Catalytic Cycle of the Borane-Promoted Imine Reduction with Hydrosilanes: Spectroscopic Detection of Unexpected Intermediates and a Refined Mechanism

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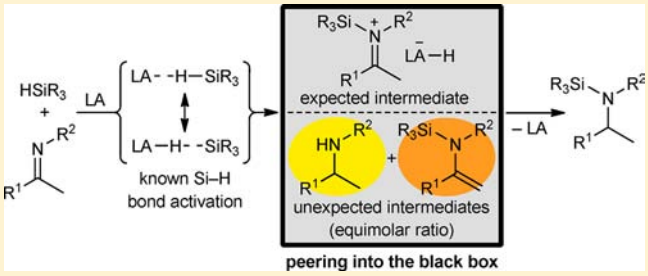
Supporting Information

ABSTRACT: The discovery of intermediates that had not been seen before in imine reduction involving borane-mediated Si–H bond activation provided new insight into the mechanism, eventually leading to a refined catalytic cycle that also bears relevance to asymmetric variants. The catalysis proceeds through an ion pair composed of a silyliminium ion and a borohydride that subsequently reacts to yield an *N*-silylated amine and the borane catalyst. The latter step is enantioselectivity-determining when using a chiral borane. It was now found that there are additional intermediates that profoundly influence the outcome of such enantioselective transformations. Significant amounts of the corresponding free amine and *N*-silylated enamine are present in equimolar ratio during the catalysis. The free amine emerges from a borohydride reduction of an iminium ion (protonated imine) that is, in turn, generated in the enamine formation step. The unexpected alternative pathway adds another enantioselectivity-determining hydride transfer to reactions employing chiral boranes. The experiments were done with an axially chiral borane that was introduced by us a few years ago, and the refined mechanistic picture helps to understand previously observed inconsistencies in the level of enantioinduction in reductions catalyzed by this borane. Our findings are general because the archetypical electron-deficient borane $B(C_6F_5)_3$ shows the same reaction pattern. This must have been overlooked in the past because $B(C_6F_5)_3$ is substantially more reactive than our chiral borane with just one C_6F_5 group. Reactions with $B(C_6F_5)_3$ must be performed at low catalyst loading to allow for detection of these fundamental intermediates by NMR spectroscopy.



INTRODUCTION

Fostered by a continuous demand for homogeneous catalysts that promote H–H and also Si–H bond activation followed by a reduction step, the unique reactivity of electron-deficient boranes decorated with at least one $C_6F_nH_{5-n}$ group (n = 1–5 but not 0) is currently garnering considerable attention.[1] Three scenarios emerge when combining one of these potent Lewis acids with Lewis bases: irreversible and reversible Lewis pair formation depending on size and basicity of the donor but also no Lewis pairing due to steric hindrance, a concept that is now referred to as frustrated Lewis pair (FLP) chemistry.[2] Both reversible and FLP systems were shown to catalyze metal-free hydrosilylation and hydrogenation, respectively.[3−6]

Almost 20 years ago, Piers and co-workers disclosed that tris(pentafluorophenyl)borane [$B(C_6F_5)_3$, **1**] is an effective catalyst for the hydrosilylation of various carbonyl compounds.[3] Later, these authors extended their system to imine functions.[4] **1** and related members of this extraordinary class of electrophilic boranes feature the ability to split not only Si–H bonds (90 kcal/mol) but also the stronger H–H bond (108 kcal/mol) heterolytically, thereby even allowing for metal-free hydrogenation.[5,6] Despite recent major efforts in these areas, there are just a handful of enantioselective variants of imine reductions[7,8] and an isolated example of carbonyl hydrosilylation[7a] using C_6F_5-substituted chiral boranes as catalysts. Reasons for this gap are manifold but are, *inter alia*, likely due to the synthetic challenges to access such chiral boranes, the discouraging levels of enantioselectivity, and also the lack of mechanistic understanding.

Piers and co-workers prepared an α-pinene-derived chiral borane **2** (Figure 1, left)[9] that was later used by Chen and Klankermayer in one example of an enantioselective imine

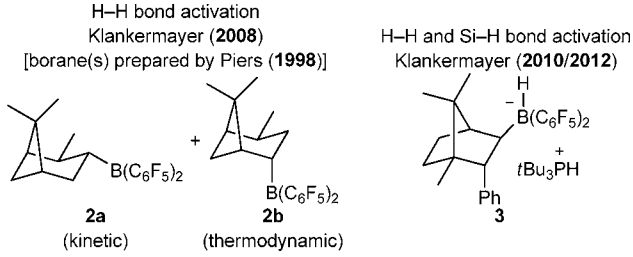


Figure 1. Terpene-derived chiral borane (pre)catalysts for the reduction of imines by hydrogenation[8a,b] and/or hydrosilylation.[7a]

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reduction involving the activation of dihydrogen.[6c] The enantiomeric excess was low (13% ee) but served as proof of concept. Substantially higher enantiocontrol in hydrogenation (≤83% ee)[8b] and hydrosilylation (≤87% ee)[7a] was achieved by employing the camphor-based chiral borate **3** (Figure 1, right). However, **3** alone would not produce appreciable enantiomeric excesses, and the presence of a bulky phosphane to form a preactivated FLP salt was necessary. These results are clearly a major step forward but the exact role of the phosphane remains to be clarified.

Just recently, Liu and Du accomplished an improved asymmetric imine reduction (≤89% ee) utilizing the novel axially chiral borane (*S*)-**4** (Figure 2, left).[8e] The idea of using

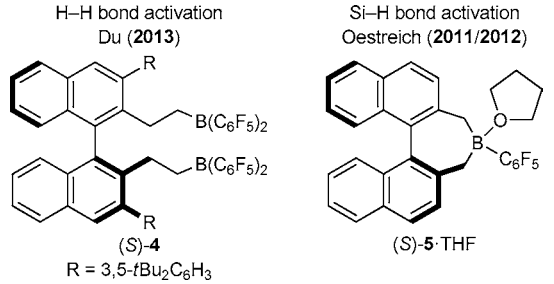
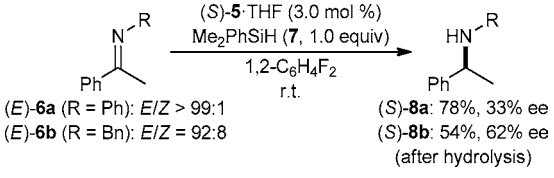


Figure 2. Axially chiral borane catalysts for the reduction of imines by hydrogenation (left) and hydrosilylation (right).

the binaphthyl motif was not new since Piers had reported a binaphthyl system before[10] (not shown), and we had already made the rigidified congener (*S*)-**5**·THF[11] (Figure 2, right) of (*S*)-**4**. However, the beauty of that catalyst (*S*)-**4** lies in the ease of its accessibility compared to (*S*)-**5**·THF. It is prepared in situ the same way as the terpene-derived boranes **2** and **3** (Figure 1), by alkene hydroboration with bis(pentafluorophenyl)borane [$HB(C_6F_5)_2$], known as Piers's borane.[12] Also, (*S*)-**4** is more reactive as it contains $B(C_6F_5)_2$ rather than less Lewis acidic $B(C_6F_5)$ groups.

Our chiral borane (*S*)-**5**·THF was nevertheless sufficiently Lewis acidic to slowly promote Si–H bond activation, and application to the hydrosilylation of acetophenone-derived imines immediately afforded promising results: 33% ee for phenyl-substituted (*E*)-**6a** and 62% ee for benzyl-substituted (*E*)-**6b** (Scheme 1).[7b] These values, for benzyl protection in

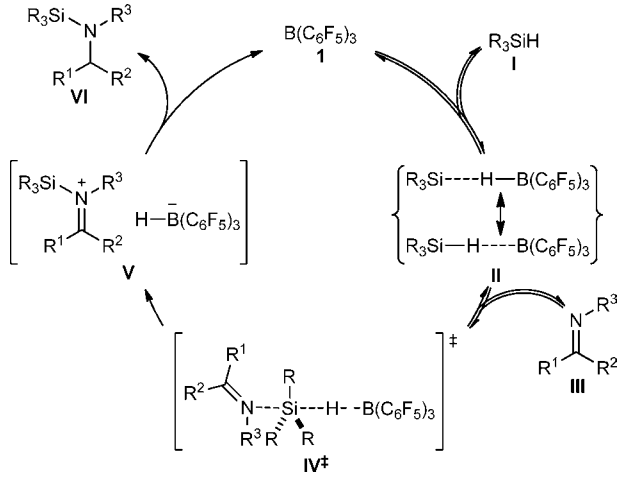
Scheme 1. Enantioselective Imine Hydrosilylations Catalyzed by (*S*)-5·THF



particular, were inconsistent over several runs though and were found to be dependent on both conversion and the amount of THF present. It was this observation that prompted us to explore the mechanism in even more detail.[7b,13]

The reaction pathway of the hydrosilylation of carbonyls is largely understood. Piers and co-workers revealed a counter-intuitive three-step mechanism where the Si–H bond is initially activated by $B(C_6F_5)_3$ (**1**).[3b] Our laboratory later established the details of the actual transfer of the silicon moiety onto the carbonyl oxygen atom by using a silicon-stereogenic silane.[14] As to imines, it is assumed that these pass through the same mechanism (Scheme 2). Borane **1** activates the silane **I**

Scheme 2. Currently Accepted Mechanism of $B(C_6F_5)_3$-Catalyzed Imine Hydrosilylation



followed by nucleophilic attack of the imine nitrogen atom of **III** at the silicon atom of transient **II**, thereby forming ion pair **V** (**I**→**II**→**IV**‡→**V**). Hydride transfer from the borohydride then closes the catalytic cycle and releases amine **VI** (**V**→**VI**). We had also applied the silicon-stereogenic silane as a stereochemical probe to this mechanism yet without success.[13] In turn, by using both enantiomers of an axially chiral silane reagent in combination with (*S*)-**5**·THF, we were able to demonstrate through matched/mismatched pairs that the reduction pathway of imine reductions proceeds as proposed.[7b]

As mentioned above, this imine hydrosilylation catalyzed by (*S*)-**5**·THF yielded inconsistent results, indicating to us that the current mechanistic picture requires further refinement. We report here an experimental analysis of this process catalyzed by chiral (*S*)-**5**·THF but also achiral $B(C_6F_5)_3$ (**1**). The fact that **1** behaves identically to (*S*)-**5**·THF generalizes our findings with implications for the related reduction with dihydrogen. By using 1D and 2D multinuclear NMR techniques and deuterium labeling, we were able to detect and fully assign unexpected intermediates that also contribute to the interpretation of our previous experimental findings.

RESULTS AND DISCUSSION

Imine Hydrosilylation Catalyzed by an Axially Chiral Borane. Our investigation commenced with an NMR spectroscopic analysis of the reduction of benzyl-substituted imine (*E*)-**6b** with Me_2PhSiH (**7**) as hydride source catalyzed by our chiral borane (*S*)-**5**·THF. As mentioned above, we had observed that the enantiomeric excess of (*S*)-**8b** was dependent on catalyst loading and conversion. Also, the amount of THF introduced with the catalyst seemed to influence enantioinduction as well as the reaction rate.[15] Intrigued by this observation, we monitored the reaction of (*E*)-**6b** and **7** in the presence of various amounts of added THF by NMR spectroscopy (0.80 and 5.3 equiv, Figure 3). NMR spectra were recorded immediately after sample preparation and at selected time intervals. With 0.80 equiv of THF, a small amount of *N*-silylated enamine **9b** was detected as an intermediate in the ^1H and ^{13}C NMR spectra followed by quantitative

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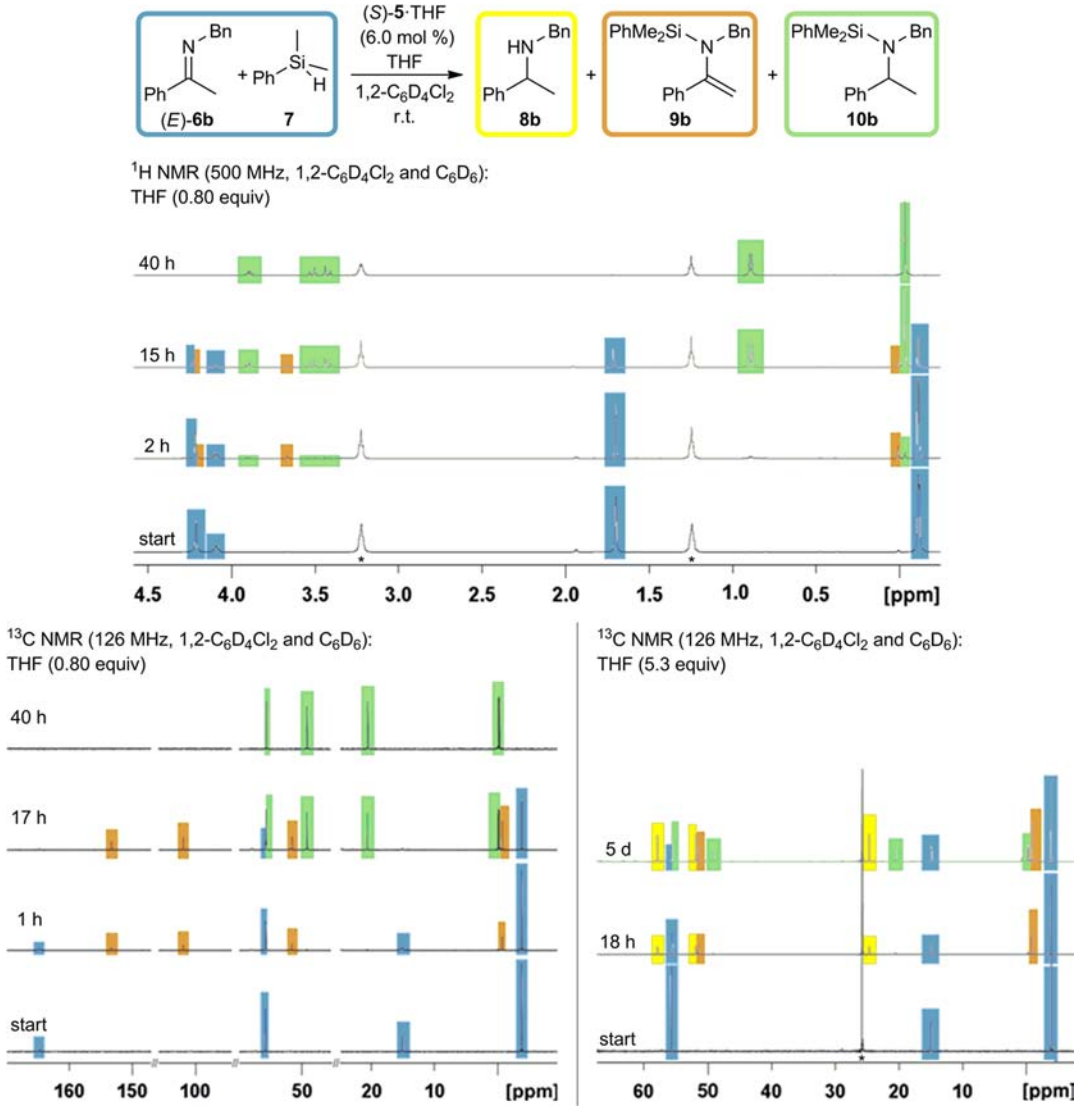

Figure 3. Effect of added THF: time-resolved NMR studies of the hydrosilylation of *N*-benzylated imine (*E*)-**6b** catalyzed by (*S*)-**5**·THF (THF indicated by asterisk).

formation of *N*-silylated amine **10b** (Figure 3, top and bottom left). Assignment of **9b** is based on its diagnostic resonance signal at 102 ppm in the ^{13}C NMR spectrum, characteristic for a C(sp^2) enamine carbon atom. The resolution of the vinylic enamine protons in the ^{1}H NMR spectrum required higher magnetic field strength (see the Supporting Information for the measurement at 700 MHz), but the $^2J_{H-H}$ coupling could still not be resolved. Moreover, these resonance signals overlapped with the resonance signal of the benzylic protons of the imine (*E*)-**6b**. 2D NMR spectra further confirmed the existence of **9b** (see the Supporting Information).[16] The same observation was made when conducting this experiment without additional THF; **9b** was, however, present in a much smaller quantity (not shown).

We reasoned that the enamine intermediate **9b** emerges from deprotonation of the silyliminum ion (cf. **V** in Scheme 2). Hence, either THF or unreacted imine (*E*)-**6b** could act as Brønsted bases in the deprotonation of **V**. Consequently, we decided to probe this reaction at higher concentration of THF (5.3 equiv). As anticipated, the presence of more THF led to an increase in the quantity of *N*-silylated enamine **9b** (see the Supporting Information). Remarkably, we now found yet another intermediate in the ^{13}C NMR spectrum, the free amine **8b** without (!) the silicon group at the nitrogen atom (Figure 3, bottom right); **8b** was also visible in the ^{1}H NMR spectrum but its resonance signals overlapped with those of THF (broad at high concentration) and *N*-silylated amine **10b** (see the Supporting Information).[19]

We explain the appearance of the free amine **8b** at high THF concentration (5.3 equiv) by an equilibrium between protonated THF and the unreacted imine base (*E*)-**6b**. At high concentration of protonated THF, that protonation equilibrium will be more shifted to protonated (*E*)-**6b**, an iminium ion that is eventually reduced to **8b** by the borohydride. Conversely, at low THF concentration (0.80 equiv), protonation of (*E*)-**6b** by the minor amounts of protonated THF is less pronounced.

Time-resolved NMR studies also showed that **8b** and **9b** are both formed directly at the beginning of the reaction and before appearance of product **10b**. Formation of free amine **8b** by hydrolysis of *N*-silylated amine **10b** was excluded since no disiloxane was formed and the water-sensitive catalyst maintained its activity. However, the excess of THF had a dramatic effect on the reaction rate, and full conversion was not

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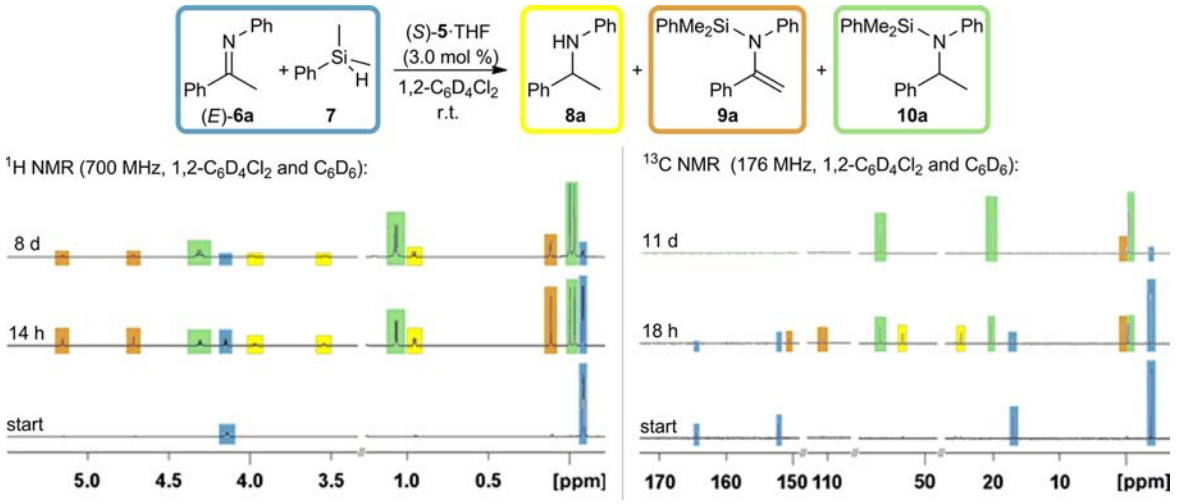

Figure 4. Time-resolved NMR studies of the hydrosilylation of *N*-phenylimine (*E*)-**6a** catalyzed by (*S*)-**5**·THF.

reached after 5 days. We explain this effect with the equilibrium between the adduct (*S*)-**5**·THF (catalytically inactive) and the free borane (*S*)-**5** (catalytically active),[11] and with more THF present, this equilibrium is shifted toward the former inactive form.

To verify whether these findings are applicable to related acetophenone-derived imines, we changed the substrate from benzyl-substituted imine (*E*)-**6b** to phenyl-substituted imine (*E*)-**6a**. Time-resolved NMR measurements under otherwise identical reactions conditions confirmed our assumption (Figure 4). Both the corresponding free amine **8a** and the *N*-silylated enamine **9a** were formed in substantial quantities. Again, these intermediates were generated prior to the formation of product **10a**. This time, characteristic baseline-separated resonance signals for the vinylic enamine protons were detected at 4.74 and 5.18 ppm in the ^{1}H NMR spectrum (Figure 4, left), and the C(sp^2) enamine carbon atom appeared at a typical chemical shift of 111 ppm in the ^{13}C NMR spectrum (Figure 4, right). 2D NMR measurements further supported this assignment (see the Supporting Information).[16] Although no THF was added, resonance signals of the free amine **8a** could be observed in a *significant* quantity in both ^{1}H and ^{13}C NMR spectra.[20] More precisely, we discovered that the unexpected intermediates, the free amine **8a** and the *N*-silylated enamine **9a**, are present in equimolar ratio during the catalysis (Figure 5).

This decisive finding supports our previous hypothesis that the enamine is formed through deprotonation of the initially generated silyliminum ion (cf. **V** in Scheme 2) by imine (*E*)-**6a**. The resulting protonated imine, i.e., iminium ion, would subsequently be reduced by the borohydride. These events (proton abstraction and hydride transfer) would not only account for the formation of free amine **8a** but also explain its 1:1 ratio with enamine **9a**. The disappearance of the starting material (*E*)-**6a** is followed by the consumption of **8a** and **9a**. It is worthy of note that these intermediates were still present after 8 days, although GLC analysis indicated 84% conversion after 66 h. Only after 11 days, the intermediates were almost fully consumed.

$B(C_6F_5)_3$-Catalyzed Imine Hydrosilylation. To explore whether the formation of the observed intermediates is a general feature of imine hydrosilylation catalyzed by electron-deficient boranes, we examined the same reactions with

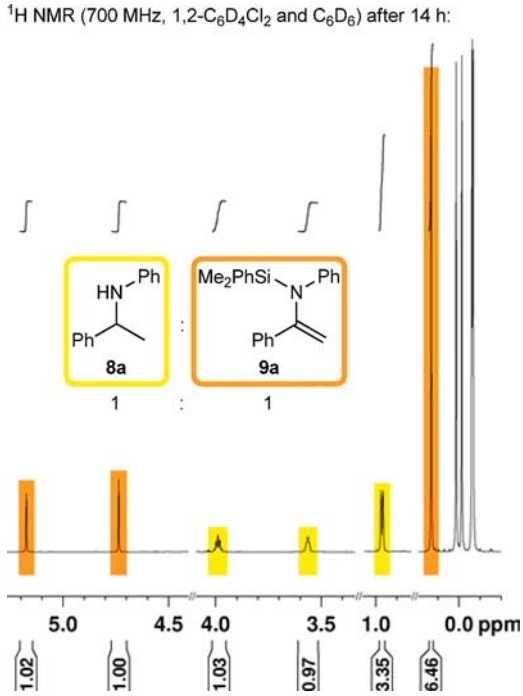

Figure 5. Segment of the ^{1}H NMR spectrum manifesting the equimolar ratio of free amine **8a** and *N*-silylated enamine **9a**.

$B(C_6F_5)_3$ (**1**) as catalyst (Figures 6 and 7). For this, we performed the $B(C_6F_5)_3$-catalyzed hydrosilylation of benzyl-substituted imine (*E*)-**6b** with a catalyst loading of 2.0 mol %. The amount of catalyst had to be lower than that employed in the original work of Piers and co-workers[4] to make the reaction slow enough for it being monitored by NMR spectroscopy. The results were similar to those obtained with (*S*)-**5**·THF as catalyst. Before the appearance of product **10b**, small quantities of the free amine **8b** and the *N*-silylated enamine **9b** were observed, and these had completely disappeared upon completion of the reaction (Figure 6; for further information on the analyzed data, see the Supporting Information).[21] Not surprisingly, the corresponding free amine **8a** and enamine **9a** intermediates were also seen in equimolar ratio in the hydrosilylation of phenyl-substituted imine (*E*)-**6a** (Figure 7; for the relevant segment of the ^{1}H NMR spectrum, see the

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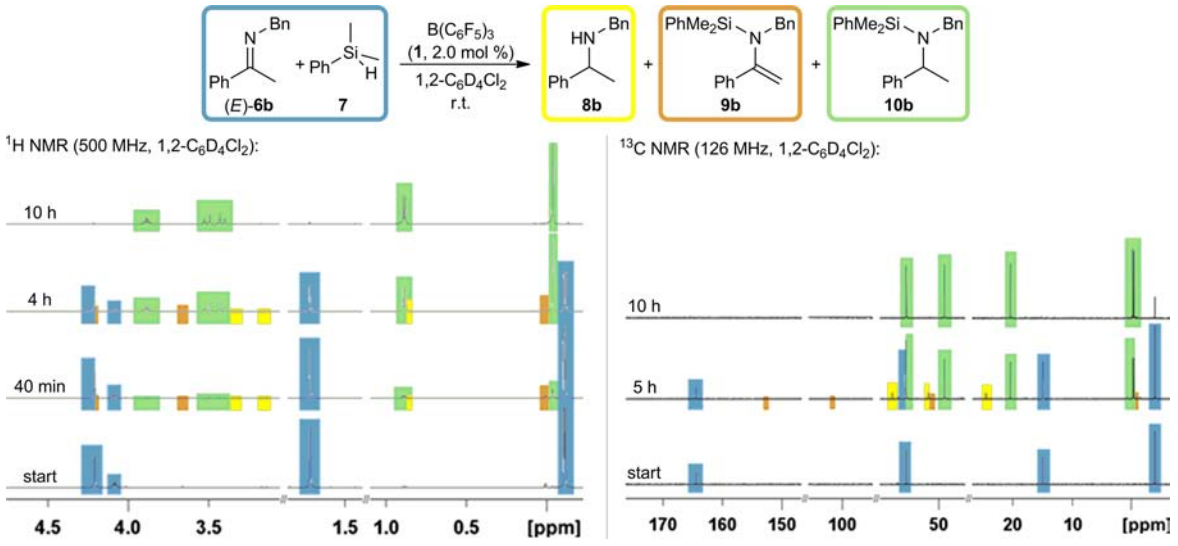


Figure 6. Time-resolved NMR studies of the $B(C_6F_5)_3$-catalyzed hydrosilylation of *N*-benzylimine (*E*)-**6b**.

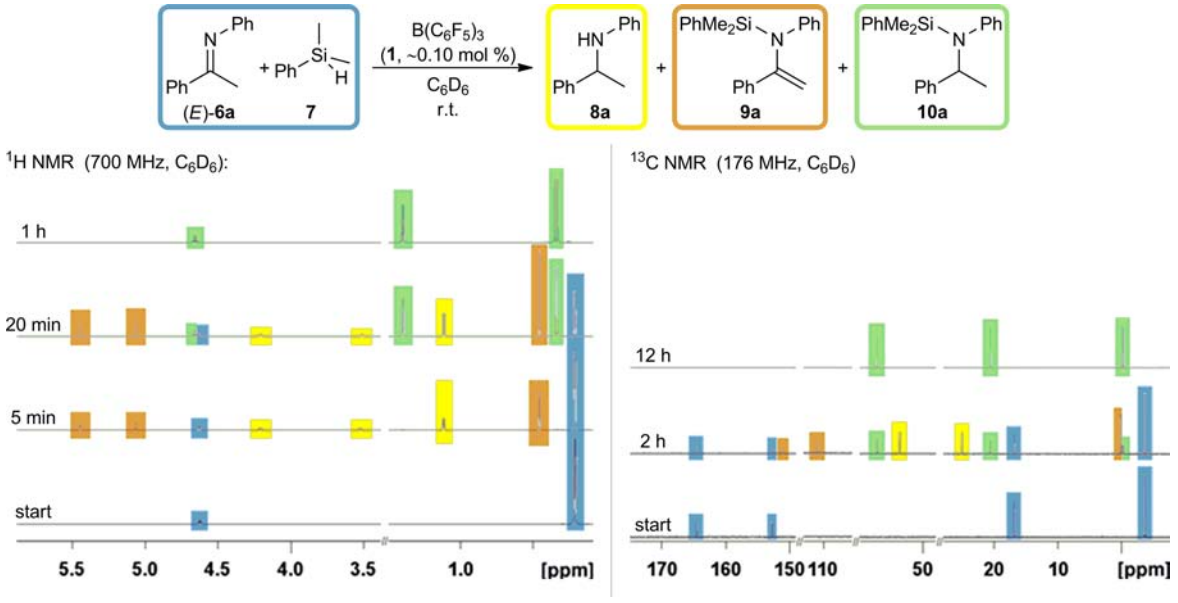
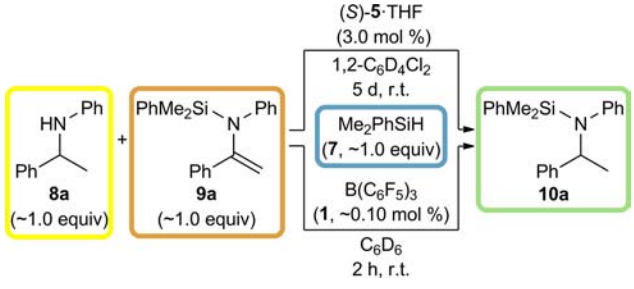


Figure 7. Time-resolved NMR studies of the $B(C_6F_5)_3$-catalyzed hydrosilylation of *N*-phenylimine (*E*)-**6a**.

Supporting Information). We had to use extremely low catalyst loadings of $B(C_6F_5)_3$, and ~0.1 mol % is just an approximation due to the small scale on which these reactions were run. Reaction times are therefore likely to vary. Again, significant amounts of **8a** and **9a** were observed before product **10a** formed. As opposed to the catalysis with (*S*)-**5**·THF, full conversion was achieved with $B(C_6F_5)_3$ (**1**). It seems likely that the formation of the free amine **8** and enamine **9** intermediates had been overlooked in the past due to the fast reaction rate.

Experimental Verification of the Intermediates' Product-Forming Ability. The fact that the free amine is formed as an intermediate poses the question of whether and how it converts into the *N*-silylated amine. As the free amine forms in a quantity equimolar to the *N*-silylated enamine, we decided to subject separately synthesized **8a** and **9a**[16−18] to the typical catalytic setups in the presence of an equimolar amount of silane **7** (Scheme 3). To our delight, quantitative formation of the *N*-silylated amine **10a** was seen in the expected reactions times (see the Supporting Information for time-resolved NMR measurements). We anticipated that the silylation of the amine nitrogen atom occurs in a borane-catalyzed dehydrogenative Si−N coupling similar to the known Si−O coupling catalyzed by **1**.[22] Such Si−N couplings are, however, unprecedented in the literature but do indeed work.[23] $B(C_6F_5)_3$ (**1**) catalyzes the

Scheme 3. Conversion of Separately Synthesized Free Amine 8a and *N*-Silylated Enamine 9a into *N*-Silylated Amine 10a under the Typical Catalytic Setups



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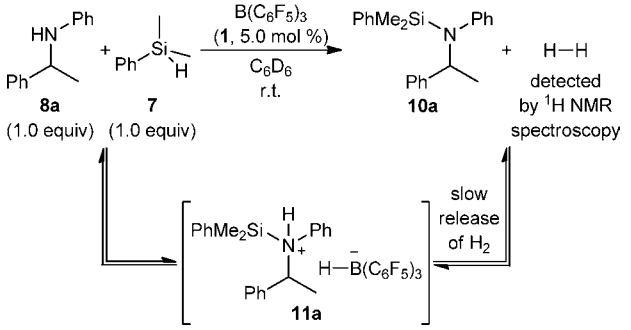
coupling of amine **8a** and silane **7** at ambient temperature as evident from the formation of *N*-silylated amine **10a** and dihydrogen (Scheme 4). Conversion is rather slow though, not

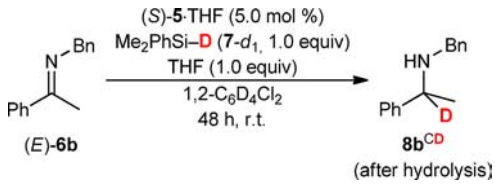
Scheme 4. $B(C_6F_5)_3$-Catalyzed Dehydrogenative Si–N Coupling



reaching completion after 24 h (see the Supporting Information for time-resolved NMR measurements). We attribute this observation to the high stability of the intermediate ion pair **11a** composed of a silylammonium ion and a borohydride. **11a** might be regarded as the dihydrogen adduct of an amine/borane FLP, and these are reluctant to release dihydrogen at room temperature.[24] Instead, the backward reaction might occur. Hence, we conclude that, applied to the mechanism of the imine hydrosilylation, the lifetime of that acidic ammonium ion is sufficiently long to protonate the *N*-silylated enamine, thus producing the *N*-silylated amine concomitant with re-formation of the silyliminium ion (cf. refined mechanism depicted below in Scheme 7).

Experiments with Deuterium-Labeled Substrates. A series of deuterium-labeling experiments at various positions of the reactants was performed to gain further insight into the amine/enamine formation pathway of the catalysis. To confirm that the hydride of **7** is exclusively incorporated at the methine carbon atom of the product, we used deuterated **7**-d_1 in the hydrosilylation of benzyl-substituted (*E*)-**6b** (Scheme 5; for

Scheme 5. Fate of the Hydride at the Silicon Atom



further information on the analyzed data, see the Supporting Information). As expected, deuterium incorporation was only seen at the tertiary carbon atom of the amine $\mathbf{8b}^{CD}$ (after hydrolysis); the methyl group that is involved in the enamine formation remained intact, i.e., non-deuterated.

Another idea was to intercept the catalysis at the stage of the enamine intermediate by the addition of deuterated methanol. Partial deuteration in the α position of the C=N group would then be sound evidence for the existence of the enamine. To achieve that we monitored amine/enamine formation by ^{1}H NMR spectroscopy and added deuterated methanol before product formation was seen. These experiments were, however, not totally conclusive due to the low degree of amine/enamine formation as well as the presence of stoichiometric amounts of protons relative to the enamine formed.

The equimolar ratio between the free amines **8** and the *N*-silylated enamines **9** (e.g., Figure 5 for (*S*)-**5**·THF as catalyst) is an indication of imine (*E*)-**6** acting as a Brønsted base. To further substantiate our proposal, we decided to monitor the intermolecular proton transfer from the imine α carbon atom to the imine nitrogen atom of another imine by deuterium labeling. For this, we prepared phenyl-substituted imine (*E*)-$\mathbf{6a}^{CD_3}$ with deuteration of the methyl group in the α position. A deuteration grade sufficiently high for our purposes was achieved by condensation of acetophenone-d_3 and aniline-d_7 (see the Supporting Information for additional details including the mass spectrometric determination of the deuteration grade). According to our hypothesis, the nitrogen atom of the free amine must be deuterated, corresponding to the formation of $\mathbf{8a}^{ND,CD_3}$. Conducting the reaction with (*E*)-$\mathbf{6a}^{CD_3}$ and chiral borane (*S*)-**5**·THF (3.0 mol %) instantly confirmed our assumption (Figure 8, left). Time-resolved ^{2}H NMR measurements clarified the abstraction of a deuteron by the nitrogen lone pair of (*E*)-$\mathbf{6a}^{CD_3}$. The broad N–D resonance signal of the free amine $\mathbf{8a}^{ND,CD_3}$ was detected at approximately 3.5 ppm. Also, no deuteration was seen at the methine carbon atom of the free amine $\mathbf{8a}^{ND,CD_3}$ and the *N*-silylated amine $\mathbf{10a}^{CD_3}$, and that is in agreement with the above labeling experiment (cf. (*E*)-**6b**→$\mathbf{8b}^{CD}$ with **7**-d_1, Scheme 5). Replacing chiral borane (*S*)-**5**·THF by $B(C_6F_5)_3$ (**1**) as catalyst gave identical results (Figure 8, right). The use of $B(C_6F_5)_3$ (**1**) corroborates that THF is not needed in the proton shuffle.

After we had established the reactants in the enamine-forming deprotonation, we designed a crossover experiment to verify its reversibility, i.e., the enamine reprotonation to yield the corresponding iminium ion. For this, we subjected labeled (*E*)-$\mathbf{6a}^{CX_3,C_6D_5}$ and non-labeled (*E*)-$\mathbf{6a}^{CH_3,C_6H_5}$ in approximately equimolar ratio to the standard protocol with (*S*)-**5**·THF and $B(C_6F_5)_3$ (**1**) as catalysts, respectively (Scheme 6). Deuterium incorporation at the methyl group of amine $\mathbf{8a}^{CX_3,C_6H_5}$ emerging from non-deuterated (*E*)-$\mathbf{6a}^{CH_3,C_6H_5}$ would then be solid evidence for the assumed deprotonation/protonation equilibrium; deuteration of the phenyl group at the nitrogen atom (C_6D_5 versus C_6H_5) was used as a mass label to distinguish amines $\mathbf{8a}^{CX_3}$ by mass spectrometry. We were delighted to find that both crossover experiments produced $\mathbf{8a}^{CX_3,C_6H_5}$ with substantial deuteration at the methyl group and, at the same time, $\mathbf{8a}^{CX_3,C_6D_5}$ with a diminished deuteration grade. The crossover is more pronounced with catalyst **1** although reaction times are significantly shorter than those with (*S*)-**5**·THF. We rationalize this counterintuitive observation on the basis of the different reactivities of the borohydride intermediates. With three C_6F_5 groups at the boron atom, we expect the borohydride derived from **1** to be a weaker hydride donor than that of (*S*)-**5**·THF with one C_6F_5 group. $B(C_6F_5)_3$ (**1**) is, however, superior in the Si–H bond activation step. Consequently, formation of the silyliminium ion is very fast with **1** but its borohydride reduction is slow, thereby allocating more time for the deprotonation/protonation equilibrium. The situation is reverse with (*S*)-**5**·THF. A scrambling experiment in the absence of silane **7** excluded the possibility of a Lewis acid-catalyzed exchange of the deuterium label between imines (*E*)-$\mathbf{6a}^{CX_3,C_6D_5}$ and (*E*)-$\mathbf{6a}^{CH_3,C_6H_5}$; less than 10% deuterium incorporation was found for the latter.

Refined Catalytic Cycle. The mechanism initially proposed by Piers[3b] and further validated by us[7b,14] is, in

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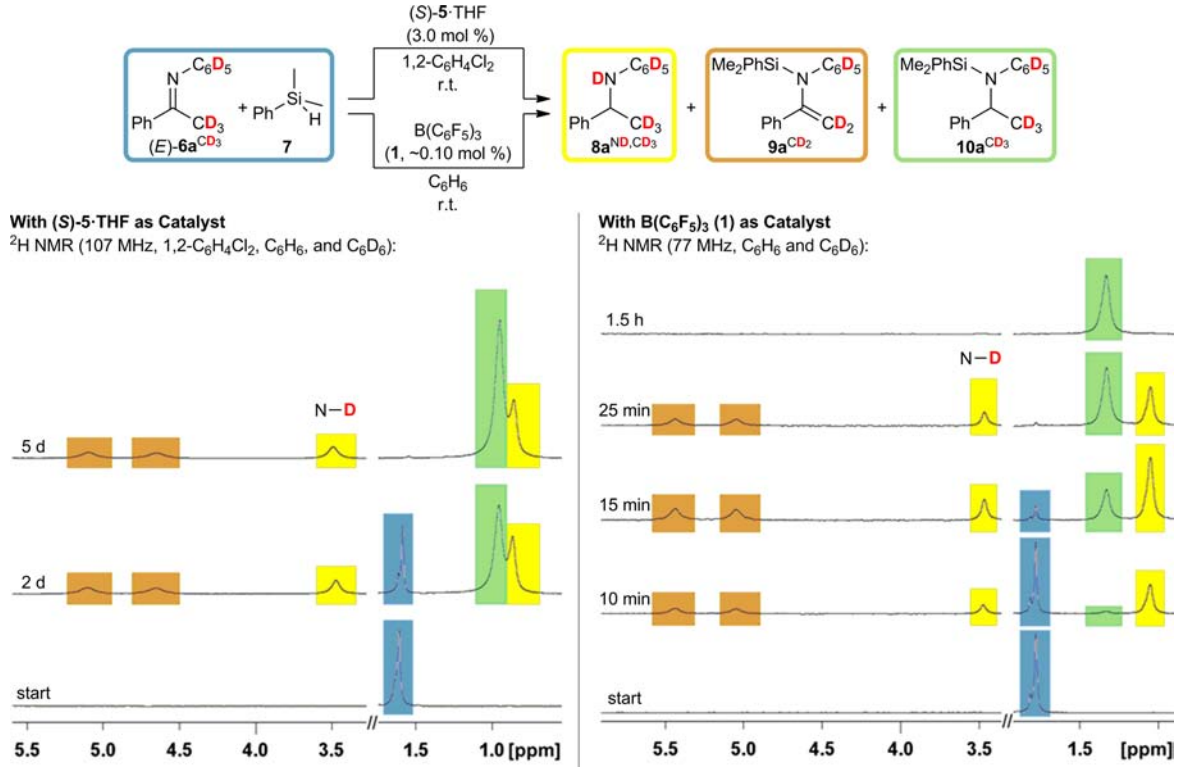
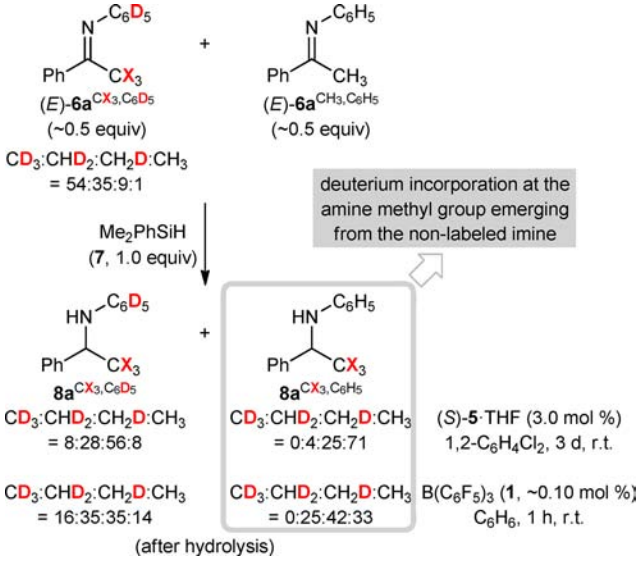


Figure 8. Time-resolved ^{2}H NMR studies of the hydrosilylation of deuterium-labeled *N*-phenylimine (*E*)-**6a**^{CD_3} catalyzed by either (*S*)-**5**·THF (left) or $B(C_6F_5)_3$ (**1**) (right): evidence for proton abstraction by unreacted (*E*)-**6a**^{CD_3}.

Scheme 6. Crossover Experiments To Probe the Silyliminium Ion Deprotonation/*N*-Silylated Enamine Protonation Equilibrium



principle, still true but the new insight calls for an extension in the case of imines with α-hydrogen atoms (Scheme 7). The refined catalytic cycle also begins with the activation of silane **I** by the boron Lewis acid with formation of the weak adduct **II**. Nucleophilic attack of either imine (*E*)-**III** or imine (*Z*)-**III** at the electrophilic silicon atom then yields the isomeric iminium ions (*Z*)-**V** and (*E*)-**V**, respectively,[25] as ion pairs with the borohydride. The expected next step is the reduction of **V** by the borohydride to afford product **VI**. The unexpected alternative reaction pathway is the deprotonation of those silyliminium ions by either of the isomeric imines (*E*)-**III** and (*Z*)-**III**.[17] The resulting *N*-silylated enamine **VII** features free rotation around the C–N bond and, as a consequence, reprotonation produces either of the iminium ions (*Z*)-**V** and (*E*)-**V**. These are, of course, again susceptible to reduction by the borohydride ((*Z*)-**V** or (*E*)-**V**→**VI**). Proton abstraction from silyliminium ions **V** by imine **III** results in the formation of iminium ions **VIII**, again as ion pairs with the borohydride (these iminium ions are also formed in both isomeric forms (*E*)-**VIII** and (*Z*)-**VIII** but we show just one out of four possible deprotonation scenarios for the sake of clarity, (*Z*)-**V**→(*E*)-**VIII**). (*E*)-**VIII** is subsequently reduced to the free amine **IX**. That step releases the boron Lewis acid that is, in turn, available for another Si–H bond activation with the amine nitrogen atom of **IX** as a Lewis base (**IX**→**X**).[23] The ammonium ion **X** then serves as a Brønsted acid, protonating enamine **VII** to reform the silyliminium ion **V** and to afford the final product **VI** (cf. Scheme 4 and the associated discussion). The refined mechanistic picture not only rationalizes the unexpected formation of intermediates **VII** (the enamine) and **IX** (the free amine) in equimolar ratio but also explains how **IX** is subsequently transformed into **VI** (the *N*-silylated amine).

Effect on Asymmetric Transformations. The refined mechanistic understanding now helps to define the challenge associated with the enantioselective variant of the borane-catalyzed hydrosilylation of imines. The enantioselectivity is determined in the hydride transfer from the borohydride onto the electrophilic carbon atom of an iminium ion intermediate. It was believed that this would only involve the isomeric silyliminium ions (*Z*)-**V** and (*E*)-**V** (Scheme 8, left), and their ratio would largely depend on the isomeric purity of the starting imine **III**.[25] However, there is another enantioselectivity-determining hydride transfer in the competing deprotona-

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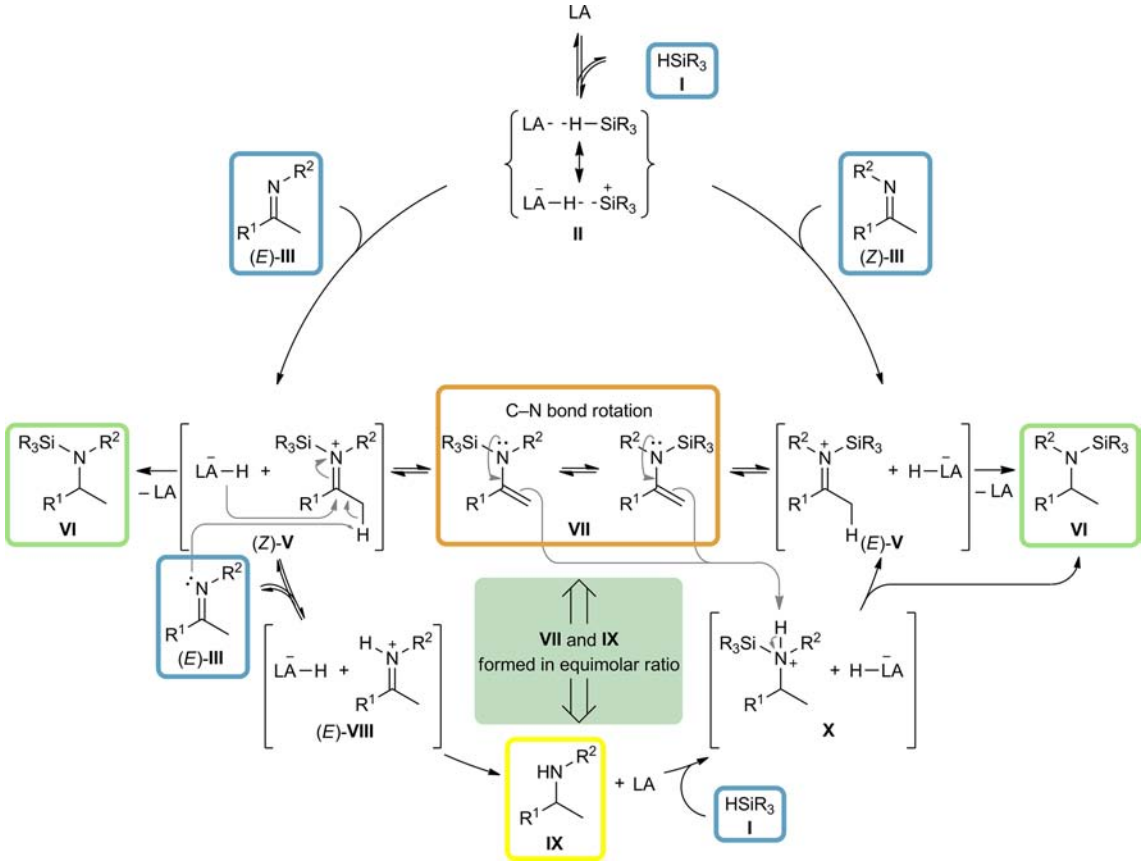
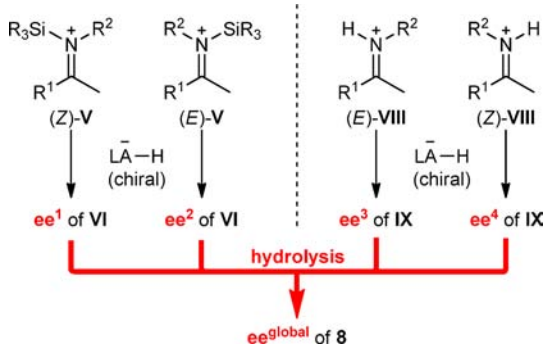
Scheme 7. Refined Mechanism of the Hydrosilylation of Imines Catalyzed by Electron-Deficient Boron Lewis Acids (One out of Four Possible Deprotonation/Protonation Scenarios Shown for the Sake of Clarity)



Scheme 8. Enantioselectivity-Determining Hydride Reduction of Two Pairs of Isomeric Iminium Ions Contributing to the Global Enantiomeric Excess



tion/protonation pathway of the catalysis. The reduction of isomeric iminium ions (*E*)-**VIII** and (*Z*)-**VIII** (Scheme 8, right) also contributes to product formation, and it is more than likely that **VIII**→**IX** (right) proceeds with different levels of enantioinduction (even with opposite absolute configuration) than **V**→**VI** (left). A total of two diastereomeric pairs of iminium ions and eight stereoisomeric combinations of these iminium ions with the chiral borohydride will produce a global enantiomeric excess (after hydrolysis) that will be dependent on the amount of enamine **VII** formed and, related to this, on conversion. At incomplete conversion, remaining **VII** is an additional issue. It transforms back into an iminium ion/imine upon hydrolysis or alcoholysis, and these might be in part reduced to the amine with unhydrolyzed borohydride.

CONCLUSION

We disclosed here a fundamental refinement of the catalytic cycle of the borane-catalyzed imine hydrosilylation (Scheme 2 versus Scheme 7). The unexpected discovery of free amines and *N*-silylated enamines as intermediates by room-temperature ^{1}H and ^{13}C NMR spectroscopy paved the way for the elucidation of an alternative reduction pathway. The catalysis was previously believed to proceed exclusively through an ion pair composed of a silyliminium ion and a borohydride that further converts into an *N*-silylated amine and the borane catalyst (Scheme 2). However, deprotonation of the silyliminium ion by unreacted imine starting material was shown to be a competing process. That proton abstraction produces an *N*-silylated enamine (detected by NMR spectroscopy) and an iminium ion (= protonated imine) with the borohydride as counteranion. The borohydride reduction of that iminium ion releases the free amine (detected by NMR spectroscopy) that is transformed into the *N*-silylated amine in a few more steps that also involve reprotonation of the *N*-silylated enamine (cf. Scheme 7). The detection of these elusive but prominent intermediates was previously thwarted by the high overall catalytic activity of $B(C_6F_5)_3$ (**1**), the conventional electron-deficient borane utilized in these hydrosilylations. Our axially chiral borane (*S*)-**5**·THF with just one C_6F_5 group is by far less reactive than **1** in the Si–H bond activation. In turn, the hydride donor strengths of the resulting borohydrides are likely to be reverse. The reaction times are still significantly longer

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with (*S*)-**5**·THF than with **1** (days versus hours), and that initially helped us to observe those unexpected intermediates. We were nevertheless able to demonstrate at low catalyst loading that the $B(C_6F_5)_3$ catalysis follows the same reaction pattern.

The new mechanistic insight profoundly influences our thinking about enantioselective variants using chiral boranes as the source of asymmetric induction. There is an additional enantioselectivity-determining hydride transfer step. The absolute configuration and the level of enantioinduction will be set in the borohydride reduction of the silyliminium ion (expected path) *and* the iminium ion (unexpected path). With this knowledge, we do now understand the dependence of the enantiomeric excess on conversion (remaining amine/enamine prior to hydrolysis) and on the presence of THF as a facilitator. And, the chiral borohydride must differentiate the enantiotopic faces of the diastereomeric pairs (*E*/*Z*) of (silyl)iminium ions with the same sense of asymmetric induction but the efficieny will clearly be different for each individual (silyl)iminium ion.

We would like to close with a remark on potential implications of the present findings on asymmetric FLP chemistry. H−H activation by FLPs or boranes alone is less complicated because the competing pathways are degenerate in the sense that both proceed through the same iminium ion intermediate as an ion pair with the borohydride.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, and ^{1}H, ^{1}H/^{1}H COSY, ^{2}H, ^{13}C, ^{1}H/^{13}C HMQC, ^{1}H/^{13}C HMBC, ^{1}H/^{29}Si HMQC, and ^{29}Si DEPT NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(16) *N*-Silylated enamines are a rare class of compounds, and we are aware of just one report where the selective transformation of imines into *N*-trimethylsilylated enamines were accomplished by mild deprotonation of trimethylsilyliminium triflates with stoichiometrically added amine base.[17] At a late stage of this project, we were able to apply methodology that was recently developed in our laboratory[18] to the preparation of the requisite enamines **9a** and **9b**. Our base-free procedure originally transforms enolizable carbonyl compounds into silyl enol ethers along with dihydrogen gas by dehydrogenative coupling with silanes. Its application with a minor modification to enolizable imines (*E*)-**6a** and (*E*)-**6b** with Me_2PhSiH (1.0 equiv) yields the otherwise difficult-to-make enamines **9a** and **9b** in decent purity. The NMR spectroscopic characterization further confirms our earlier assignments (see the Supporting Information for details): Hermeke, J. Ph.D. Thesis, Technische Universität Berlin, Germany, Projected 2015.

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