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Communication

Carbonyl Reduction

Borinic Acid Mediated Hydrosilylations: Reductions of Carbonyl Derivatives

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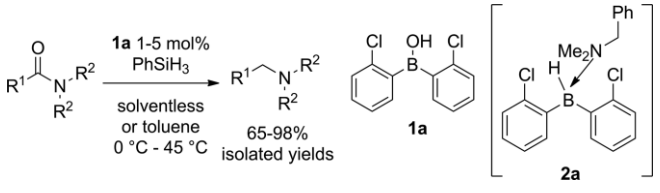
Abstract: 4-Fluoro-2-chlorophenylborinic acid acts as a precatalyst in the presence of phenylsilane for the facile reduction of ketones, aldehydes and imines. Notably, synergistic mediation of a tertiary amine was found essential to trigger silicon to boron hydride transfer to generate a key amine–diarylhydroborane Lewis complex.

Introduction

The reductions of C=C, C=O, and C=N bonds are commonly achieved using alumino- or borohydrides.[1] Stability and chemoselectivity issues have increasingly shifted the interest for these hydrides towards hydrosilanes, potent reducing agents with high stability and low toxicity. The activation of the silicon–hydrogen bond by a Lewis acid,[2] a Brønsted acid,[3] a nucleophile[4] or a transition metal is well known.[2c] However, the use of a transition metal catalyst is not without drawbacks (cost, toxicity) and bolstered intense research towards metal-free catalysis. Piers early investigations showed that the tris(pentafluorophenyl)borane promoted hydrosilylation of aldehydes, ketones, esters and imines.[5] Since this important discovery, boron-based catalysts were used as Si–H bond activators in many chemical transformations.[6] Our group recently developed 2-chlorophenylborinic acid **1a** for the challenging catalysis of amide and phosphine oxide reductions.[7] Noticeable, lower temperature was used and high chemoselectivity was achieved when compared to $B(C_6F_5)_3$ (Scheme 1). Preliminary mechanistic investigations suggested the involvement of the intermediate amine–diarylhydroborane complex **2a**.

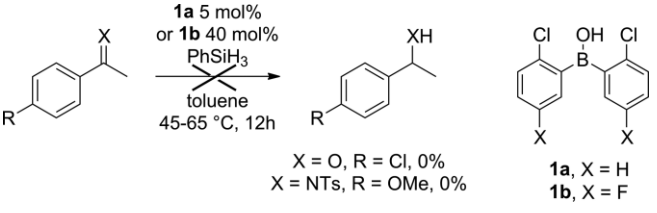


Scheme 1. Amides reduction using borinic acid **1a** as precatalyst.

The present report will detail our continuing effort to broaden the scope of borinic acid-mediated hydrosilylations. Interestingly, NMR studies pointed out an indispensable nucleophilic activation to allow a productive silicon to boron hydride transfer.

Results and Discussion

During our previous investigations on amide reductions,[7a] late catalyst screening revealed a faster reaction with 5-fluoro-2-chlorophenylborinic acid **1b**. However, as observed with **1a**, attempted reductions of ketones and imines led to the complete recovery of starting materials (Scheme 2) and left unchanged borinic acids **1a** and **1b**. This puzzling result was in sharp contrast with the accepted fact that ketone and imine groups are more easily reduced than amides.



Scheme 2. Attempts to reduce ketone and imine with **1a** or **1b**.

The efficiency of **1a** toward the reduction of amides suggested a mandatory nucleophile activation for the reaction to proceed. Accordingly, we investigated the hydride transfer from silicon to boron using stoichiometric amount of boronic acid **1b** and $PhSiH_3$ (2 equivalents) in the presence of several amines: with dimethylbenzylamine, formation of an amine–diarylhydridoborane complex **2b** was observed in less than 30 minutes (broad singlet, ^{11}B NMR δ –0.51 ppm, ^{1}H NMR δ = 3.97 ppm). A similar result was obtained with *N*-methylpyrrolidine (broad singlet, ^{11}B NMR, δ –2.00 ppm, ^{1}H NMR δ = 3.77 ppm) and boron hydride complex **2c** was further characterized by a ^{1}H-^{11}B HMBC correlation (see supporting information). Interestingly, triethylamine afforded an equimolar ratio (^{11}B NMR estimation) of an unproductive diborohydride **2e**[7a] (triplet, δ –17.01 ppm, ^{1}J = 84.1 Hz) and the expected amine–diarylhydridoborane complex **2d** (br. s, δ –3.01 ppm). Whereas with secondary methylbenzylamine and primary benzylamine, only

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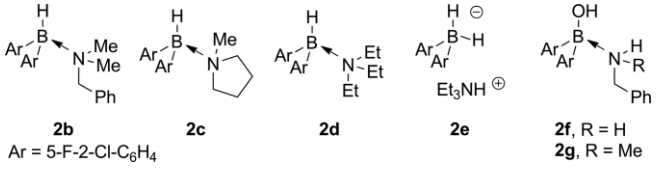
Lewis complexes **2f** and **2g** were detected (^{11}B NMR bs +2.1 ppm and +3.6 ppm respectively) whose structures were confirmed by comparative experiments in absence of phenylsilane.

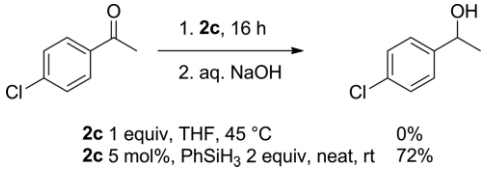
Further experiments demonstrated the absence of silicon to boron hydride transfer when triethylsilane or dimethylphenylsilane (6 equivalents) were substituted to phenylsilane.

These results strongly suggested that the hydride transfer was dependent of the nitrogen Lewis basicity of the amine and that the nucleophilicity of the silicon hydride was not a crucial parameter (Scheme 3).[8]



Scheme 3. Effect of Lewis bases on the formation of amine–diarylhydroborane complexes.

Interestingly, control experiments showed that a stoichiometric amount of **2c** failed to reduce 4-chloroacetophenone while the reactivity was resumed in presence of excess $PhSiH_3$ and a catalytic amount of **2c** (5 mol-%) (Scheme 4). This result illustrated that Lewis adduct **2c** is not able to reduce directly the ketone and requires the presence of excess phenylsilane.[9] Additional control experiments using triethylsilane and dimethylphenylsilane left unchanged 4-chloroacetophenone, in line with the absence of silicon to boron hydride transfer previously observed with those reagents.

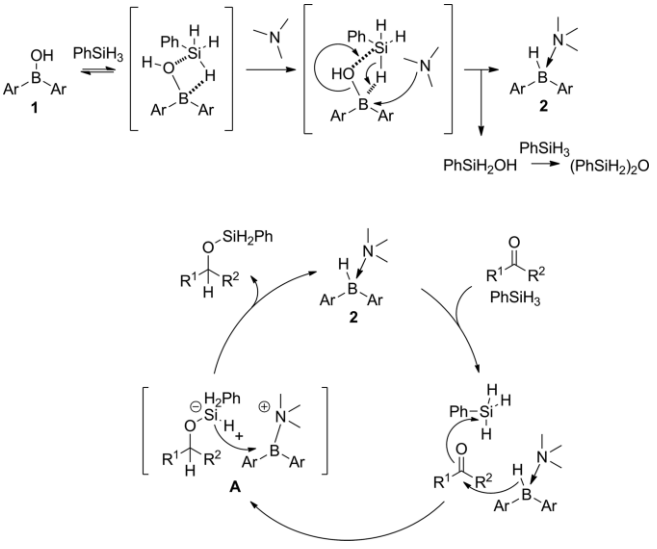


Scheme 4. Reactivity of amine–diarylhydroborane complex **2c**.

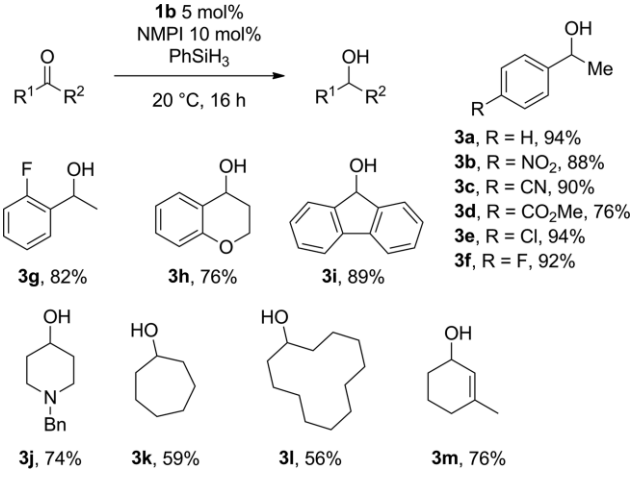
With this new insight in hands, a rationalization of the ketone hydrosilylation mechanism is proposed as follow (Scheme 5). In sharp contrast with the $B(C_6F_5)_3$ mechanism involving a concerted activation of the ketone and hydride transfer from silicon to boron, the latter would take place in our case in a distinct step ahead to the hydrosilylation of ketone.

The catalytic cycle would be initiated by the conversion of the borinic acid **1** to an amine–borane complex **2** through the putative equilibrium between $PhSiH_3$ and **1** and a concerted hydride abstraction.[10] At several instances, diphenyldisiloxane was observed in ^{1}H NMR, resulting from the silylation of transient monohydroxyphenylsilane. The absence of reactivity of complex **2** in absence of $PhSiH_3$ suggested that the hydrosilane might polarize mildly the ketone, enough to initiate the addition of the hydride **2** that would be regenerated consecutively by a rapid hydride transfer from pentavalent silicon to boron in the salt A (Scheme 5).

Next, the scope of the ketones and aldehydes hydrosilylation was examined using reaction conditions allowing in situ formation of **2c** in the presence of twofold equivalent of *N*-methylpyrrolidine (NMPI, Scheme 6) vs. **1b**.[11] Good yields were obtained chemoselectively with acetophenones to give alcohols **3b**–**3d** bearing a nitro, a nitrile or an ester group (Scheme 6). Fluorine substituent in *para* and *ortho* positions were also tolerated (**3e** and **3f**).



Scheme 5. Mechanism proposal of ketone hydrosilylation.



Scheme 6. Substrates scope of ketones hydrosilylation. Isolated yields.

Cyclic chromanone and fluorenone also afforded the desired alcohols **3g** and **3h** with 89–76 % yields. Switching from aromatic to aliphatic ketones resulted in significantly slower reductions, leading to the corresponding alcohols with 56–74 % yields (**3i**–**k**). Gratefully, α,β-unsaturated ketone was selectively reduced to allylic alcohol **3l** in 76 % yield with no side-product resulting from a 1,4-addition of the hydride.

With aldehydes a faster reaction was observed, therefore the catalyst loading was successfully decreased to 1 mol-%. Independently of the electron density, benzaldehyde derivatives substituted with nitro, fluoro, methoxy or phenyl group afforded the corresponding alcohols **4a**–**4h** in 74–98 % yields (Scheme 7).

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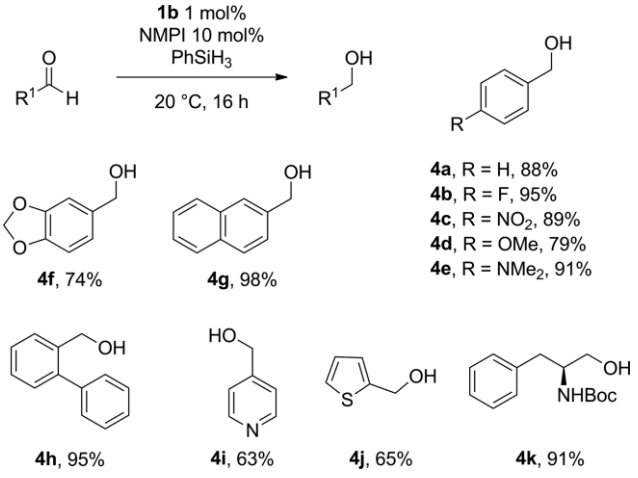
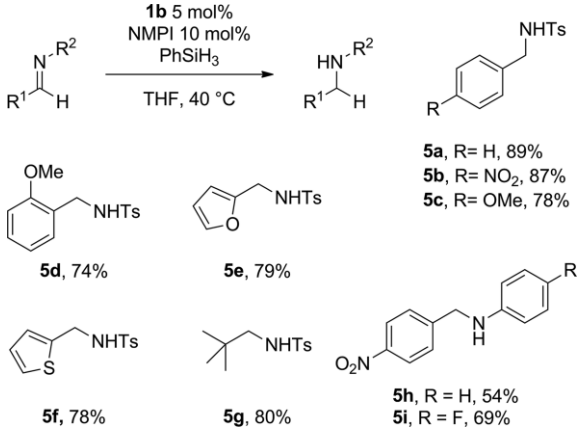


Scheme 7. Substrate scope of aldehyde hydrosilylation. Isolated yields.

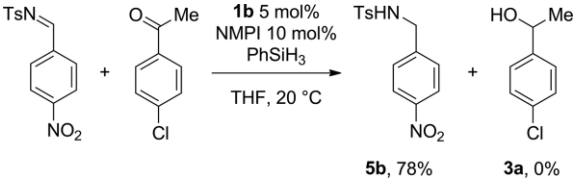
The reaction also tolerates heterocyclic aldehydes at the cost of a slight decrease of reactivity for pyridine and thiophene derivative **4i** and **4j** (Scheme 7). Finally, an aliphatic aldehyde derived from phenylalanine was chemoselectively reduced in 91 % yield in the presence of a Boc nitrogen protecting group.

Our attention then turned out to the hydrosilylation of imines (Scheme 8). Aldimines were underinvestigated substrates for non-metal catalysed hydrosilylation with the exception of Piers use of $B(C_6F_5)_3$[5b] and a single example reported by Nikonov.[12]



Scheme 8. Substrate scope of imines hydrosilylation.

Several *N*-tosyl aldimines were subjected to reaction conditions readjusted to cope with moderate substrate solubility at room temperature. Unsubstituted and *para*-nitro substituted sulfonamides **5a** and **5b** were isolated in 87–89 % yields (Scheme 8) while the presence of a methoxy group in *para* and *ortho* position or the use of electron rich heterocyclic substrates slightly slowed the hydrosilylation rate (yields 74–79 %, **5c**–**5f**). Pivaldehyde derived imine provided sulfonamide **5g** in 80 % yield. Switching nitrogen substituent from tosyl to aryl groups (4-F-C_6H_4 and Ph) significantly decreased the efficiency of the reduction and the corresponding anilines **5h** and **5i** were isolated in 69 and 54 % yields respectively (Scheme 8). The reduction of imines in the presence of other carbonyl functions is generally underinvestigated. Stephan recently developed efficient fluorophosphonium salts and explored the reduction of an imine in the presence of a ketone. However, side silyl enol ether transformation of the ketone was obtained.[13] Therefore we conducted a competitive reduction of a tosylimine in the presence of a stoichiometric amount of 4-chloroacetophenone (Scheme 9). In THF at room temperature, tosylamide **5b** was chemoselectivity obtained in 78 % yield with no trace of alcohol **3a** being detected. However, another competitive experiment involving 4-fluorobenzaldehyde instead of 4-choroacetophenone provided the corresponding primary alcohol as the major reduction product (3:1).



Scheme 9. Competitive reduction of an imine in the presence of a ketone.

Conclusions

In this manuscript, we described a general methodology for the reduction of a range of ketones, aldehydes and imines. Initial experiments established an unprecedented Lewis base mediation of a silicon hydride transfer from a hydrosilane to a borinic acid. The developed reaction conditions featured mild temperatures and catalyst loading as low as 1 mol-%. Moreover, unusual selective reduction of an imine in the presence of a ketone was achieved.

Acknowledgments

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Keywords: Borinic acid · Reduction · Ketones · Aldehydes · Imines

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[10] In our precedent report, several control experiments were carried out in the presence of $PhSiH_3$ and 2-chloro-phenylborinic acid **1a**. When a mixture of **1a** (1 equiv.) and $PhSiH_3$ (2 equiv.) was heated at 40 °C, a new tetravalent borohydride species was detected using 2D ^{11}B-^{1}H NMR experiments. However, characterization of the tetravalent species proved inconclusive. Furthermore, the interaction between the **1a** and the $PhSiH_3$ was investigated in IR spectroscopy and a small shift of the υ-OH was detected, tentatively attributed to the initial equilibrium in Scheme 5 (See SI for full details).

[11] See SI for full optimization details.

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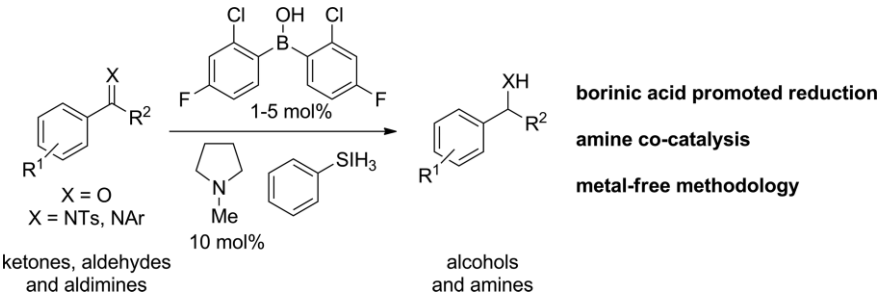
Carbonyl Reduction



borinic acid promoted reduction

amine co-catalysis

metal-free methodology

A facile hydride transfer from hydrosilane to a borinic acid is efficiently mediated by a tertiary amine. This led to the development a mild reduction of carbonyl derivatives by using phenylsilane and catalytic amount of borinic acid and amine.

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