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Hydrosilylation and Mukaiyama aldol-type reaction of quinolines and hydrosilylation of imines catalyzed by a mesoionic carbene-stabilized borenium ion†

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Aldimines and ketimines containing electron-donating and electron-withdrawing groups can be hydrosilylated with borenium catalysts at as low as 1 mol% catalyst loading at room temperature, providing the corresponding secondary amines in excellent yields. Reactions with 2-phenylquinoline gave the 1,4-hydrosilylquinoline product selectively which can be further functionalized in a one-pot synthesis to give unique γ-amino alcohol derivatives. Control experiments suggest that the borenium ion catalyzes both the hydrosilylation and subsequent addition to the aldehyde.

Introduction

Amines are important functional groups found in high-value chemicals such as polymers,[1] agrochemicals,[2] and pharmaceuticals.[3] The hydrosilylation of imines provides a practical and direct synthetic approach for the synthesis of amines. Transition metal catalysts have been workhorses in this area[4,5] but due to their challenging removal from amine-containing products,[6,7] alternatives have been explored.

Piers and co-workers reported that $B(C_6F_5)_3$ could reduce carbonyl[8] and iminyl[9] functionalities. This reaction was a seminal example of the now ubiquitous frustrated Lewis pair (FLP) reductions, characterized by bulky Lewis acids and Lewis bases working in concert to activate small molecules, including silanes[10] and dihydrogen.[11,12]

FLPs traditionally depend on neutral, perfluorinated-aryl boranes to achieve the high Lewis acidity and significant steric effects required for their unique reactivity.[13–15] This concept has been expanded to encompass the use of phosphonium,[16,17] silylium,[18,19] carbenium[20,21] and borenium ions as catalysts for the FLP-type activation of small molecules.[22–24]

Carbene-supported borenium ions have been shown by the Stephan[25,26] and Crudden groups[27] to be effective catalysts for the activation of H_2 and subsequent reduction of C=N functionalities. The introduction of a formal positive charge onto an already electron deficient boron centre results in increased Lewis acidity without the need for exhaustive fluorination of substituents on boron, providing considerable flexibility in terms of catalyst design and synthesis. In particular, 1,2,3-triazolylidene (or mesoionic carbene [MIC])-stabilized borenium ions such as $\mathbf{1}^+$ have been shown to reduce imines and N-heterocycles at low H_2 pressure and ambient temperatures.[27] Based on their strong reducing power under mild reaction conditions, we chose to explore the activity of borenium ions in the catalytic hydrosilylation of more complex targets. Interestingly, there are only a few reports describing the use of borenium ions as catalysts for hydrosilylation, including those by Denmark,[28] Jäkle[29] and more recently Ashley.[30] In addition to providing new examples to these key studies, we also demonstrate a secondary role for the Lewis acidic borenium ion, namely activation of carbonyl groups in a two-step approach to the synthesis of more complex organic molecules, namely γ-aminoalcohols *via* Mukaiyama aldol-like reactions (Scheme 1).

Results and discussion

We began our work with borenium ion $\mathbf{1}^+$ (Scheme 2), which was previously shown by our group to have high catalytic activity for the hydrogenation of imines.[27] In particular, the triazolylidene framework enables the introduction of a hydrogen atom on one of the wingtip groups, to reduce steric constraints around the reactive boron centre. Because it is a stronger sigma donor, the mesoionic carbene results in a more hydridic borohydride intermediate, without sacrificing any of

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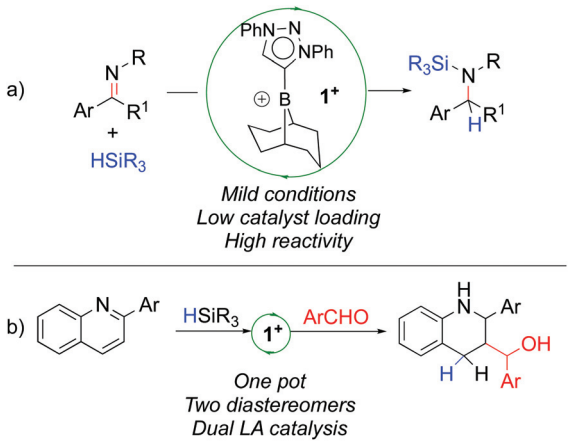
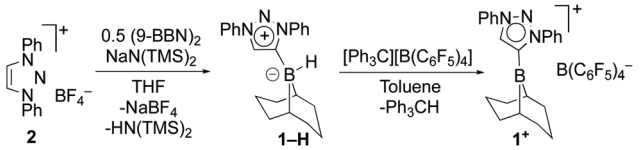


Scheme 1 a) Borenium-ion catalyzed protocol for the hydrosilylation of imines (b) sequential hydrosilylation/aldehyde addition leading to γ-aminoalcohols.



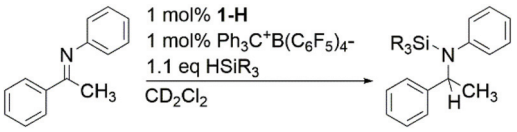
Scheme 2 Borenium ion synthesis.

the Lewis acidity of the starting borenium ion.[27] Moreover, the catalyst can be prepared in a straightforward protocol from readily available starting materials.[27]

Triazolium salt **2** is prepared *via* the well-established copper-catalyzed [3 + 2] Huisgen cycloaddition[31] between an azide and alkyne followed by aryl quaternization at nitrogen by diphenyliodonium tetrafluoroborate mediated by copper (Scheme 2).[32] From triazolium salt **2**, a one-pot procedure consisting of deprotonation with strong base (typically NaHMDS) in the presence of 9-BBN dimer produces borenium ion precursor **1-H** directly. Facile hydride abstraction by $[Ph_3C][B(C_6F_5)_4]$ at room temperature in CH_2Cl_2 then gives borenium ion $\mathbf{1}^+$. It should be noted that the nature of the counterion is important to the stability of the borenium ion, since counterions with direct F–M bonds such as BF_4^- can result in fluoride transfer to boron and quenching of Lewis acidity.[33,34]

With the aim of developing a general protocol for the hydrosilylation of imines, we selected ketimine **3a** as a model substrate for investigation of reaction conditions (Table 1). Since compound **4a** proved difficult to isolate, preliminary reactions were performed in a J-Young tube in CD_2Cl_2 to facilitate monitoring of reaction progress. Initial test reactions using triethylsilane as the terminal reductant proceeded sluggishly even at elevated temperatures and relatively high catalyst loadings of 10 mol% (entry 1). However, decreasing the bulk of the silane resulted in an appreciable increase in rate, such that full conversion was achieved even at loadings as low as 1 mol%, at room temperature (entries 2–6). With phenylsilane, catalyst

Table 1 Silane screening for reduction of ketimine **3a**[a]



Entry	Silane	Temp. (°C)	Catalyst loading (mol%)	Time (h)	Yield[b] (%)
1[c]	Et_3SiH	60	10	48	88
2	$PhMe_2SiH$	r.t.	1	2	64
3	$PhMe_2SiH$	r.t.	1	3.5	98
4	Et_2SiH_2	r.t.	1	1	99
5	Ph_2SiH_2	r.t.	1	<0.25	99
6	$PhSiH_3$	r.t.	1	<0.25	99
7	$PhSiH_3$	r.t.	0.1	1	99

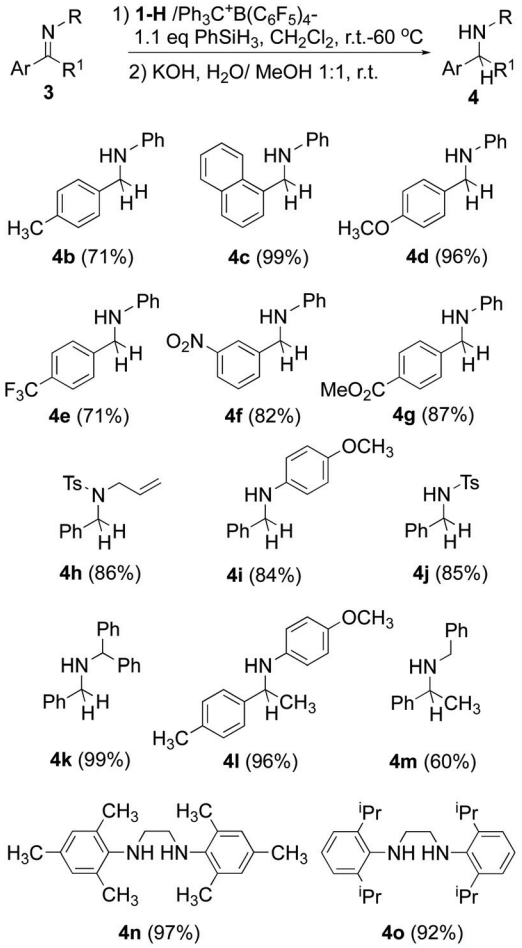
[a] Reactions performed with 0.25 mmol of **3a** in a J-young tube in 0.5 mL CD_2Cl_2. r.t. = room temperature. [b] Determined by ^1H NMR relative to remaining starting material. [c] Conducted on a 0.1 mmol scale.

loadings as low as 0.1 mol% were sufficient, leading to complete conversion in one hour at room temperature (entry 7).

Using optimized conditions, the reaction scope was examined (Scheme 3). Aldimines with electronically neutral- (**3b**) or electron-donating groups (**3c** and **3l**) reacted well, giving the resulting secondary amines in good to excellent yields. The trifluoromethyl group was tolerated under our reaction conditions, although a higher catalyst loading was required (**3e**, 5 mol%). This indicates that small but not substantial amounts of hydrodefluorination may be occurring, which is a known reaction pathway for strongly Lewis acidic silylium and alumenium cations.[35]

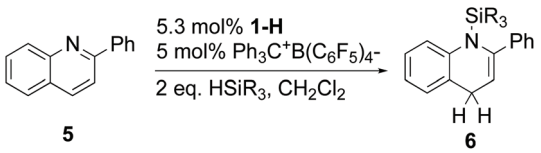
Imines containing reducible groups such as an ester (**3g**), nitro (**3f**) and an alkenyl (**3h**) substituent were resistant to hydrosilylation, although longer reaction times, increased catalyst loading or higher reaction temperatures were required. *N*-Tosyl imine **3j** was competently reduced to the corresponding amine **4j**, a product that can be transformed into a primary amine *via* sulfone deprotection. Lack of steric hindrance about nitrogen in **3m** resulted in decreased reactivity, necessitating 5 mol% catalyst loading, possibly due to Lewis acid–Lewis base adduct formation between the substrate and catalyst. Finally, diimines **3n** and **3o** could be reduced to the corresponding diamines, even with sterically cumbersome mesityl or diisopropylphenyl substituents. Imines bearing heteroaromatic substituents were examined, and did lead to product, but these reactions were not clean, leading to challenges with obtaining the product in sufficient purity.

To further test the catalytic ability of borenium ion $\mathbf{1}^+$, we explored the possibility of reducing quinolines, which are more challenging due to the need to disrupt aromaticity. With 2-phenylquinoline **5** as the test substrate, we demonstrated that, as seen with imine hydrosilylations, bulkier alkyl silanes such as Et_3SiH and $^tBu_2SiH_2$ were ineffective at room temperature with 5 mol% catalyst loading (Table 2). However, switching to $PhMe_2SiH$ gave the singly hydrosilylated product **6** in



Scheme 3 Borenium ion-catalyzed reduction of aldimines and ketimines. Values below the respective compounds are isolated yields obtained after purification. Catalyst loadings vary from 1–5%. Substrate-specific information is given in the ESI† along with specific reaction times.

Table 2 Hydrosilylation of 2-phenylquinoline[a]



Entry	Silane	Time	Yield (%)[b]
1	Et_3SiH	72 h	0
2	$^tBu_2SiH_2$	24 h	0
3	$PhMe_2SiH$	24 h	Quantitative
4	Ph_2SiH_2	<2 h	Quantitative
5	Et_2SiH_2	<20 min	Quantitative
6	$PhSiH_3$	<20 min	Quantitative

[a] Reactions performed with 0.20 mmol of **5** at room temperature in J-young tubes. [b] Conversion was determined by ^{1}H NMR relative to remaining starting material since the instability of compounds **6** precluded their isolation.

almost quantitative yield after 24 h (Table 2, entry 3). As in the case of imines, $PhSiH_3$ proved to be the most effective, giving quantitative reduction in less than 20 minutes (Table 2, entry 6).

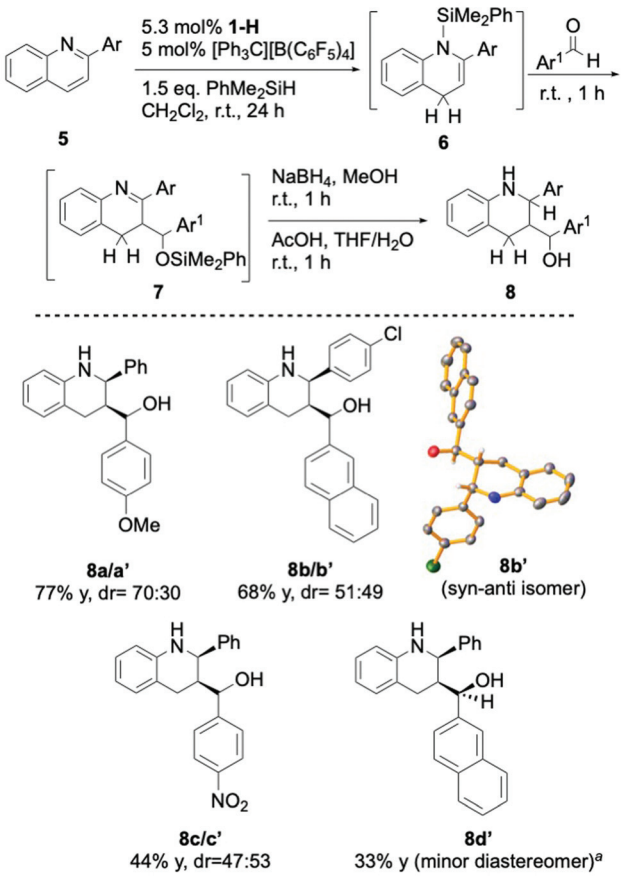
Surprisingly, we obtained only the 1,4-hydrosilylation product **6** even with two equivalents of phenylsilane (6 equivalents of hydride), with the regiochemistry indicative of an outer sphere mechanism.[36] The prototypical Lewis acid for FLP-reductions, $B(C_6F_5)_3$,[37] has been shown to doubly hydrosilylate quinolines generally under more forcing conditions (elevated temperature) with larger excesses of hydrosilane and smaller 2-substitutents on the N-heterocyclic ring (H or Me). Upon exposure to air, **6** readily disproportionates into 2-phenylquinoline and 2-phenyltetrahydroquinoline, unlike acyclic *N*-silyl enamine varieties which are reportedly air stable,[38] making isolation of these molecules difficult.

However, the observation of selective mono-reduction provided the opportunity to employ **6** as an *N*-silyl enamine nucleophile. *N*-silyl enamines are rare and underutilized compared with the more common dialkyl enamines.[39–42] A competition experiment between bis-*N*-silyl enamines and enol ethers placed *N*-silyl enamines at half the reactivity of enol ethers and 7 times less reactive than their silyl enol ether counterparts.[43] Silyl enamines have very few known uses to date in organic synthesis, apart from the synthesis of densely functionalized pyridines,[44] dichlorocyclopropanes and oxazines.[43]

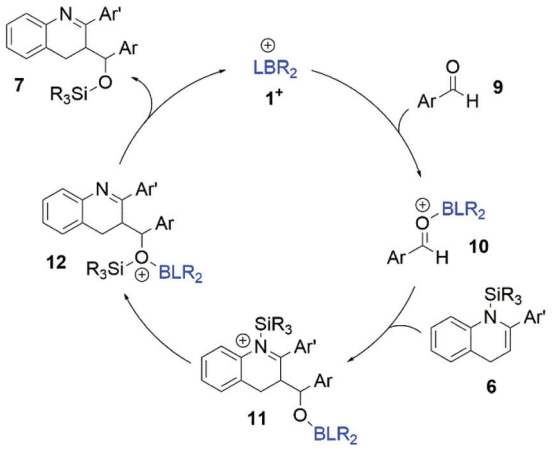
Taking advantage of the ability to generate silylenamines through our method, we examined the reactivity of **6-SiPhH$_2$** in the Mukaiyama aldol reaction. Reactions between **6-SiPhH$_2$** and 2-naphthaldehyde gave a complex mixture by ^{1}H NMR spectroscopy, potentially due to secondary reactivity of the remaining Si–H bonds. When using **6-SiPhMe$_2$**, the reaction was much cleaner, giving full conversion to **7** (Ar = 2-naphthaldehyde) within one hour of aldehyde addition (Scheme 4).

Quinolines containing aromatic substituents in the 2-position were readily hydrosilylated under our optimized conditions to give the corresponding dihydroquinolines **6** in >90% yield. Because of the sensitivity of these compounds to disproportionation, they were not isolated, but were treated with aldehyde directly. Subsequent $NaBH_4$ reduction followed by deprotection of the silyl group furnished tetrahydroquinoline derivatives **8** in modest to good yields. Of the four possible diastereomers, this process yields only two diastereomers of the γ-amino alcohols, which could be separated by column chromatography (Scheme 4). The diastereoselectivity determined after chromatography was within error of that assessed on the crude mixture.

To assist in elucidating the stereochemistry of the two diastereomers, X-ray quality crystals of **8b′** were obtained by layering pentane into a toluene solution of **8b′**. The crystallized diastereomer has a *syn* relationship between protons on C2 and C3 of the tetrahydroquinoline ring (Scheme 4), and an *anti* relationship to the exocyclic benzylic proton. This relationship was corroborated in bulk by 1D NOE NMR spectroscopic experiments (Table S2†). The other diastereomer (**8b**) pos-



Scheme 4 Borenium ion dual catalysis in the preparation of quinoline-derived γ-aminoalcohols. Substituents on the tetrahydroquinoline ring are *syn* for both diasteroemers (only one enantiomer is shown for clarity), and the diastereomeric mixture refers to stereochemistry at the alcohol-bearing carbon. The yields as written are the combined yield of the two diastereomers isolated by column chromatography with their relative ratios denoted below the yield, as determined by examination of the crude ^{1}H NMR spectrum. For **8d**, where the yield refers to the minor *syn* diastereomer. [a] Crude d.e. for this reaction is calculated to be 60 : 40.



Scheme 5 Proposed catalytic cycle for the Mukaiyama aldol-like reactivity of *N*-silyl enamine **6** with aldehyde **9** catalyzed by $\mathbf{1}^+$.

sesses a syn relationship between all three protons, based on 1D NOE NMR experiments and analysis of relative coupling constants, Table S1.†

To determine the role of the borenium ion in the Mukaiyama aldol reaction, a quenching experiment was conducted under standard conditions (5 mol% catalyst loading), in which 6 mol% of [NBu_4][Cl] was added to the reaction mixture to quench the borenium ion prior to the addition of aldehyde. Interestingly, under these conditions, the Mukaiyama aldol-like reaction with benzaldehyde did not proceed. Analysis of crude ^{1}H NMR spectra showed that **6a** was unreacted after treatment with chloride, thus leaving the N–Si bond unbroken. Additionally, ^{11}B NMR spectroscopy revealed a new resonance at −1.0 ppm after chloride addition, consistent with a four-coordinate boron species in which the chloride is bound to the boron atom. This change is also associated with disappearance of the borenium ion signal at 82.4 ppm, consistent with quenching of the borenium ion by Cl^-. These results suggest that $\mathbf{1}^+$ catalyzes both the hydrosilylation and the subsequent reaction with aldehyde, acting as both a FLP catalyst and a traditional Lewis acid. This finding is consistent with the low activity of silyl enamines, which typically require activation by an external fluoride nucleophile and provides interesting possibilities for the use of FLP-type catalysts in multi-step transformations.[38,44]

A proposed catalytic cycle for the involvement of the borenium ion in the Mukaiyama aldol is depicted in Scheme 5. The first step involves the coordination of borenium ion $\mathbf{1}^+$ to the incoming aldehyde **9**,[45] activating it towards nucleophilic attack by the weak *N*-silyl enamine nucleophile **6**. After attack, a 1,5-silyl shift from nitrogen to oxygen permits catalyst release and turnover. Our catalyst is very sterically demanding (implied by its propensity to activate dihydrogen in a FLP manner[46]) while also being less electrophilic than silylium ions according to the Gutmann–Beckett test,[46,47] thus its release from **12** should be favoured over desilylation.

Conclusions

In summary, a MIC-stabilized borenium ion has been shown to be a highly efficient catalyst in the hydrosilylation of both imines and quinolines. The borenium ion then catalyzes the further derivatization of *N*-silyl enamines through reaction with a variety of aldehydes to produce γ-aminoalcohols *via* Mukaiyama aldol-like reactivity.

Author contributions

Reaction discovery and optimization was carried out by J.J.C., B.P.B., R.K. and P.E., while diastereomer separation, purification and characterization were carried out by J.J.C. and K.D. Crystallization of **8d′** was carried out by J.F.D. The manuscript

was written by J.J.C. and C.M.C. with assistance from J.F.D. and K.D.

Conflicts of interest

The authors have no conflicts to declare.

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