ORGANIC
LETTERS

2012
Vol. 14, No. 17
4540–4543

Silica Gel Promotes Reductions of Aldehydes and Ketones by *N*-Heterocyclic Carbene Boranes

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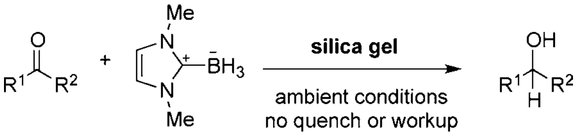
Received July 19, 2012

ABSTRACT



N-Heterocyclic carbene boranes (NHC-boranes) such as 1,3-dimethylimidazol-2-ylidine trihydridoborane (diMe-Imd-BH_3) serve as practical hydride donors for the reduction of aldehydes and ketones in the presence of silica gel. Primary and secondary alcohols are formed in good yields under ambient conditions. Aldehydes are selectively reduced in the presence of ketones. One, two, or even all three of the boron hydrides can be transferred. The process is attractive because all the components are stable and easy to handle and because both the reaction and isolation procedures are convenient.

The chemistry of *N*-heterocyclic carbene boranes (NHC-boranes) has expanded rapidly in recent years along two lines.[1] On the one hand, much new main group chemistry has appeared with unusual (but often easily accessible) NHC-boranes featured both in stable bonding patterns and in highly reactive intermediates.[2] On the other hand, NHC-boranes are emerging as attractive reagents for radical,[3] pericyclic,[4] and organometallic reactions[5] and as co-initiators for polymerizations.[6]

We overlooked the ionic chemistry of NHC-trihydridoboranes (NHC-BH_3) for a time because they are so stable. Unlike other common boron reductants (boranes or borohydride salts[7]), NHC-trihydridoboranes are typically white solids that are stable to air, water, and even chromatography.[1] The carbene and borane are tightly bound and resist dissociation.

In 2009, we discovered that the relatively hindered 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene borane

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10.1021/ol302010f © 2012 American Chemical Society
Published on Web 08/16/2012

(dipp-Imd-BH$_3$, **1**) could reduce halides and sulfonates at high temperatures ($>$100 °C, except for triflates).[8] This precipitated a collaboration with Horn and Mayr to measure the nucleophilicity parameter (N) of **1** and the less hindered 1,3-dimethylimidazol-2-ylidene borane (diMe-Imd-BH$_3$, **2**).[9] Both were surprisingly good hydride donors. Indeed, at 11.8, the N value for **2** is comparable to that of an anionic reagent such as NaCNBH$_3$ and higher than the N values of common neutral hydride donors such as silanes, stannanes, dihydropyrdines, and amine boranes.[10]

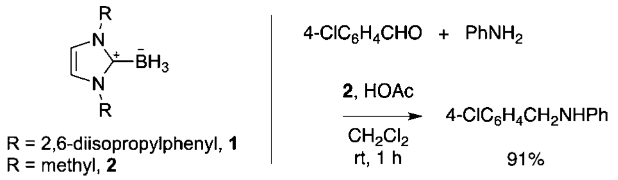


Figure 1. Structures of N-heterocyclic carbene boranes **1** and **2** (left) and a typical reductive amination[9] with **2** (right).

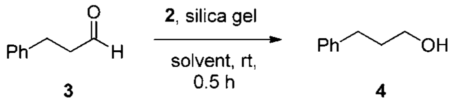
Based on these N values, simple reduction procedures were developed for electron-poor multiple bonds.[9] In the reductive animation procedure (Figure 1, right), iminium ions are formed in situ from amines and aldehydes and then reduced directly by **2** to amines.[9] The procedure is convenient because typical aldehydes or ketones are not sufficiently electrophilic for direct reduction by **2**. In contrast, addition of a strong Lewis acid such as BF$_3$•Et$_2$O can induce the reduction of carbonyl groups by NHC-boranes.[11]

While conducting pilot radical cyclizations with haloaldehyde substrates,[12] we noticed that the aldehydes were partially reduced. Surprisingly, the reductions seemed to be occurring not during the reaction stage but during the purification stage, which entailed silica gel adsorption and chromatography. These observations led to the discovery of a mild, simple procedure for reduction of aldehydes and ketones by **2**.

In a typical experiment, 3-phenylpropanal (hydrocinnamaldehyde, **3**, 0.5 mmol) and diMe-Imd-BH$_3$ **2** (0.5 mmol) were dissolved in EtOAc (2 mL) and commercial grade flash chromatography silica gel (500 mg) was added (see Table 1, entry 1). After the mixture stirred for 30 min at rt, it was filtered, the solvent was evaporated, and CDCl$_3$ and mesitylene (internal standard) were added. The yield of **4** calculated from the resulting NMR spectrum was essentially quantitative ($>$95%).

In a control experiment, a solution of **2** and **3** was made in EtOAc as above but no silica gel was added. After 24 h at rt, both starting materials were intact. Clearly the silica gel is crucial for rapid reduction of 3-phenylpropanal.

Table 1. Silica-Promoted Reductions of 3-Phenylpropanal by **2** in Assorted Solvents[a]



entry	solvent	**2** (equiv)	yield **4** (%)[b]
1	EtOAc	1.0	>95
2	hexane	1.0	>95
3	benzene	1.0	>95
4	CH$_2$Cl$_2$	1.0	>95
5	THF	1.0	>95
6	BTF[c]	1.0	>95
7	MeCN	1.0	>95
8	MeOH	1.0	66[d]
9[e]	EtOAc	0.5	>95
10[e]	EtOAc	0.35	>95

[a] Conditions: **3** (0.5 mmol), **2** (0.175–0.5 mmol), and silica gel (500 mg) in solvent (2 mL) for 0.5 h at rt. [b] Determined by ^{1}H NMR analysis using mesitylene as an internal standard. [c] BTF is benzotrifluoride. [d] At 82% conversion. [e] Reaction time is 1 h.

Table 1 shows a survey of suitable solvents for the silica-promoted reduction of **3**. The solvents were used as is (that is, from the bottle without drying), all the reaction components were handled without protection from air and moisture, and reactions were conducted in open flasks.[13] Yields were all determined by NMR spectroscopy. As shown in Table 1 (entries 1–8), reduction of aldehyde **3** in assorted common solvents produced alcohol **4** in more or less quantitative yield over a fixed time of 30 min.

These solvents include hexane, benzene, dichloromethane, benzotrifluoride (a suggested benzene and dichloromethane substitute[14]), THF, and acetonitrile. The only exception was methanol, which provided **4** in only 66% yield at 82% conversion (entry 8). The lower yield and conversion are surprising because the medium (presumably the silica gel) must provide a proton for this reduction, but adding a protic solvent is not helpful. Ambient water is harmless, but excess water is even more detrimental (see below).

NHC-borane **2** has three hydrides, and its reduction stoichiometry was studied in ethyl acetate. Decreasing the amount of diMe-Imd-BH$_3$ (**2**) to 0.5 or even 0.35 equiv did not reduce the yield of alcohol **4** though the time for complete reduction stretched to 1 h (entries 9 and 10). This atom economy is attractive for potential large scale applications.

We settled on the combination of EtOAc and 0.5 equiv of **2** for the ensuing preparative reactions. The reduction of **3** is typical. First, the reduction was conducted as above (Table 1, entry 9). After 1 h, the mixture was evaporated to

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dryness to adsorb the product on the silica gel, and then the resulting powder was placed in a sample-loading cartridge that was inserted into an automated flash chromatography instrument. Machine elution with hexane/EtOAc provided 3-phenylpropanol in 86% isolated yield.[15] This reaction was upscaled by a factor of 20 (10 mmol **3**, 5 mmol **2**, 10 g silica gel), which gave **4** in the same yield as the small scale experiment.

During these and subsequent flash chromatography purifications, a small amount of residual reagent **2** eluted after the product, but NHC- or boron-containing byproducts derived from **2** were not observed in any fraction. Apparently these remain adsorbed on the silica gel. And since the reagent is not anionic, there are no salt products from a spectator ion. Accordingly, the usual quenching of borane/borohydride reductions (which can be very exothermic) and subsequent organic/aqueous extractions were omitted.[16]

The scope of the reduction was surveyed with other aldehydes, and the products and isolated yields from these experiments are shown in Figure 2. Now reaction progress was followed by TLC analysis. Benzyl alcohol derivatives **5**–**8** were formed in good yields (78–87%), although reaction times depended on the electronic properties of the aryl substituents (4-MeOPh [24 h] < naphthyl [8 h] < 4-BrPh [2 h] < 4-NO_2 [1 h]). The reaction of **2** with cinnamaldehyde gave 1,2-reduction product **9** along with a small amount of doubly reduced **4** in 86% yield. Despite increased hindrance, α-branched aldehydes were reduced by **2** and the corresponding primary alcohols **10** and **11** were obtained in good yields (both 86%).

The combination of diMe-Imd-BH_3, **2**, and silica gel also converted ketones into secondary alcohols, and data from several experiments are shown in Figure 3. 1 equiv of **2** was used in these experiments to speed conversions. Even so, the reduction of 4-bromoacetophenone into 1-(4-bromophenyl)-ethanol **12** was not complete after 24 h; **12** was isolated in 75% yield. A similar reduction in CH_2Cl_2 was complete after 24 h and provided **12** in 94% yield, so CH_2Cl_2 was used as the solvent for reductions of some of the other ketones.

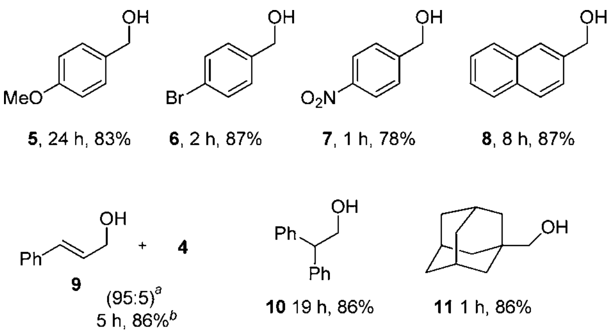

Figure 2. Scope of reductions of aldehydes by **2**: products, reaction times, and isolated yields. Conditions: aldehydes (0.5 mmol), **2** (0.25 mmol), and silica gel (500 mg) in EtOAc (2 mL). ^{a}Estimated by ^{1}H NMR analysis. ^{b}0.7 equiv of **2** was used.

Secondary alcohols **13**, **14a**,**b**, and **15** were likewise formed in good yields. Reduction of 4-*tert*-butylcyclohexanone produced mostly *trans*-**14a** resulting from axial hydride delivery. Like BH_4^-, **2** behaves as a hydride donor with low steric demand.[17] Reduction of 4-phenyl-2-butanone provided **15** in 95% yield while reductions of the unsaturated analog (*E*)-4-phenylbut-3-en-2-one gave 1,2-reduction product 4-phenyl-2-butanol **16** along with some doubly reduced product **15** (80/20) in 86% yield. Here again, the result is roughly similar to those of related borohydride reductions.[18]

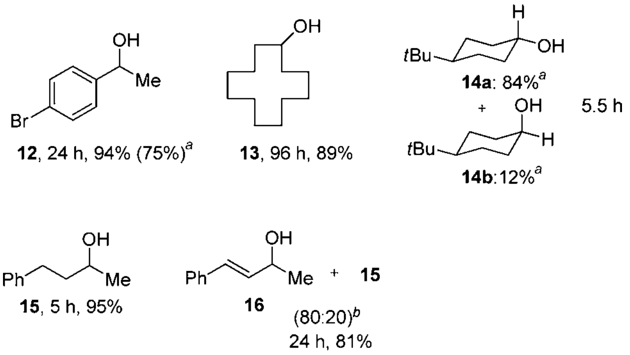

Figure 3. Scope of reductions of ketones with **2**: products, reaction times, and isolated yields. Conditions: ketones (0.5 mmol), **2** (0.5 mmol), and silica gel (500 mg) in CH_2Cl_2 (2 mL). ^{a}Reaction in EtOAc. ^{b}Estimated by ^{1}H NMR analysis.

A limitation of the present reaction is that reduction of hindered ketones is likely to be slow. For example, only 35% of α-branched phenyl cyclopropyl ketone **17** was converted into the corresponding alcohol **18** in the reaction with diMe-Imd-BH_3 **1** for 24 h (Scheme 1). After 96 h, **18** was isolated in 73% yield though unreacted **17** still remained. However, 60% of **17** was converted after 24 h when **2** was replaced by 1,3,4,5-tetramethylimidazol-2-ylidene borane (tetraMe-Imd-BH_3, **19**).[19] The isolated yield of **18** was 91% after a 96 h reaction time (full conversion). Here we suspect that the electron-donating effects by two methyl groups at the C4 and C5 positions increase the reactivity of reagent **19**. This is a preliminary example of how the reactivity of the carbene borane can be manipulated by changing the ring substituents of the carbene.

The mild reactivity of NHC-boranes provides opportunities for chemoselective reductions. When a mixture of equal amounts of 4-bromobenzaldehyde **20** and

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(15) The automated purification is only a convenience. The powder can by dry-loaded for standard manual flash chromatograpy.

(16) Indeed, there is no point in quenching **2** with water because the two do not react under ambient conditions.

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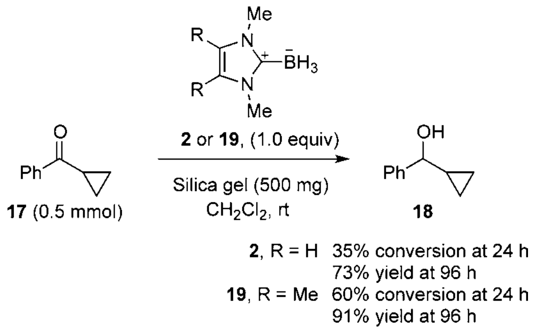
Scheme 1. Reduction of a Steric Hindered Ketone with NHC-Boranes **2** and **19**



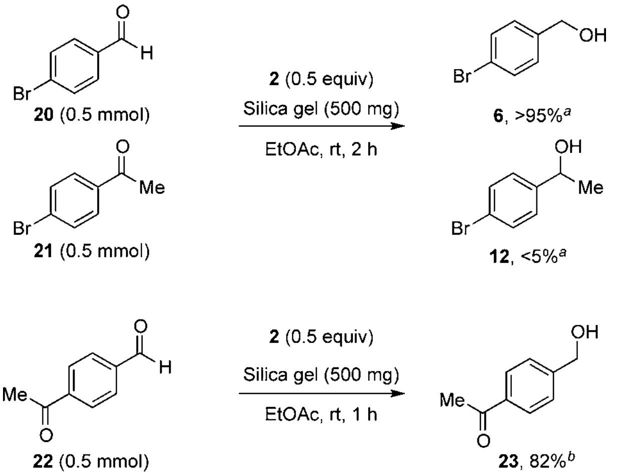
4-bromoacetophenone **21** was treated with diMe-Imd-BH_3 **2** and silica gel, reduction of 4-bromobenzaldehyde occurred to give 4-bromobenzyl alcohol **6** in excellent yield (>95% by NMR analysis) along with unreacted **21** (Scheme 2). Similarly, the reaction of bifunctional 4-acetylbenzaldehyde **22** gave only 4-acetylbenzyl alcohol **23** (82% isolated yield) by reduction of the aldehyde group. This flexible reactivity is a characteristic that simple borohydride reagents lack.[17]

Carbene borane **2** does not react with silica gel even after prolonged (48 h) contact, so the roles of the silica gel are presumably to activate the carbonyl group of the precursor and to provide a proton for the product to complement the hydride from **2**. Kouhkan and Zeynizadeh have recently introduced a procedure for the reduction of carbonyl groups by $NaCNBH_3$ and silica gel.[20] Beyond the detraction of the cyanide (toxic) for large scale use, the procedure is rather different from the one introduced here.

First, reductions with $NaCNBH_3$/silica gel require both heating (prolonged conventional or microwave) and water.[20] Dry silica gel does not activate carbonyl groups toward $NaCNBH_3$ reduction, so the water may be needed to dissolve this inorganic reductant. Following the published procedure,[20] we prepared a 1/1 (by weight) mixture of silica gel and water and added this to **2** and **21** in CH_2Cl_2 at rt. After 2 h, there was no conversion with wet silica gel. In comparison, 60% conversion occurred in a parallel experiment with no added water. NHC-borane **2** is not very soluble in water, and water presumably outcompetes the aldehyde for active sites on the silica. We reemphasize that ambient water is not detrimental (neither the ethyl acetate nor the silica gel were dry), but adding large amounts of water hinders rather than helps.

In conclusion, we have discovered that the reactivity of simple carbonyl groups toward NHC-boranes can be boosted by adding standard silica gel, and this has led to a mild, general procedure for the reduction of aldehydes and ketones. There are many reagents and procedures for such reductions,[7] so new procedures have to compete at multiple levels.

Scheme 2. Examples of Chemoselective Reduction



[a] Yield was determined by ^{1}H NMR analysis using mesitylene as an internal standard. [b] Isolated yield.

The current procedure is simple and mild and works in many solvents. The safety of carbene boranes for large scale applications has not been tested, but their stability and low reactivity toward air and moisture are encouraging. The isolation is especially convenient because **2** is not a salt and no quenching or water workup is needed. In the small scale procedure, the crude product is directly chromatographed. For larger scale, it could simply be separated from the silica gel and purified by other means. A volatile aldehyde such as CH_3CHO can be added if needed to ensure that no carbene borane remains.

Finally, while **2** is not yet commercially available, it can easily be made by several procedures.[1] One of these uses only *N*-methylimidazole, dimethyl carbonate, and borane-SMe_2,[21] so there is good potential for inexpensive manufacture in the long run. In short, we feel that the aggregated features of this silica-promoted reduction may make it attractive for applications on both small and large scales.

Acknowledgment. We thank the U.S. National Science Foundation, Kanazawa University, the Mochida Memorial Foundation for Medical and Pharmaceutical Research, and the Yoshida Foundation for Science and Technology for funding, and we thank Dr. Emmanuel Lacôte (University of Lyon 1) for helpful discussions.

Supporting Information Available. Contains experimental procedures and copies of NMR spectra of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.