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The use of borane–amine adducts as versatile palladium-catalyzed hydrogen-transfer reagents in methanol

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Abstract—The scope of borane–amine adducts as reducing agents is broadened through palladium-catalyzed methanolysis capable of reducing a wide variety of functional groups. Hence, borane mediated reduction of a benzamide followed by a tandem methanolysis/hydrogenolysis of the resulting borane–benzylamine adduct allows chemoselective removal of an *N*-benzoyl in the presence of an *O*-benzoyl.

Borane–amine complexes are an important class of hydroborating as well as reducing agents and have found several applications in organic synthesis[1] and industrial processes.[2] Although over a dozen borane–amine complexes are commercially available,[3] some on a tonnage scale,[4] their scope in organic synthesis has been limited relative to the loosely bound borane–Lewis base complexes (such as borane–tetrahydrofuran (BH_3–THF) and borane–dimethyl sulfide (BMS)).[5] As a result of a tighter boron–nitrogen bond, the reactivity of amine–boranes is somewhat diminished, and harsher reaction conditions are often required. Unlike common hydride reducing agents, however, borane–amine adducts are generally hydrolytically and thermally stable, soluble in both protic and aprotic solvents, and often crystalline compounds that offer safe handling convenience.[6] Significant efforts have therefore been put forth to activate these stable borane reagents. For instance, the activity of borane–amine adducts has been shown to increase in the presence of Brønsted[7] and Lewis acids.[8] Pyridine–borane adsorbed on solid supports exhibits enhanced reducing properties as well.[9] In hopes of finding more reactive amine–borane reagents, Brown[10] and Soderquist[11] have designed borane carriers incorporating sterically demanding tertiary amines. The less basic aniline derivatives also form weaker and hence more reactive adducts with borane.[12] However, the structural modifications needed for greater activity result in higher boiling free-amine by-products which encumber product isolation when compared to traditional amine–boranes. To increase the synthetic potential of borane carriers made from volatile amines, it would be a desirable advantage to activate these otherwise stable/inert hydride sources in neutral conditions through transition metal catalysis.

In this context, we recently disclosed that palladium and Raney nickel activate the methanolic cleavage of stable borane–amine complexes.[13] Since palladium hydride is a likely transient species prior to molecular hydrogen liberation, we further envisioned the use of commercially available amine–boranes in methanol as novel, palladium-catalyzed, hydrogen-transfer reagents. We first reported the application of this concept to the reduction of nitroaryls to anilines.[14] Others have also employed borane–amine adducts as hydride sources in palladium-catalyzed systems such as reductive opening of diene-ester derived monoepoxides,[15] aryl triflate reductions[16] and *N*-alloc deprotections.[17] Herein, we report on the scope of the palladium catalyzed methanolysis of amine–boranes as a reducing system for various functional groups.

Representative examples of catalytic transfer hydrogenations of substrates, unreactive with amine–boranes alone, are illustrated in Table 1.[18,19] For instance, olefins do not react with *t*-butylamine–borane at room temperature, but will undergo hydroboration at elevated temperatures with isomerization.[1b] Using 1.2 equivalents of *t*-butylamine borane and 10% Pd–C in methanol, *trans*-stilbene (entry 1), ethyl cinnamate (entry 2) and a propargylic alcohol (entry 5) were all

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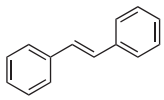
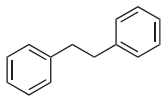
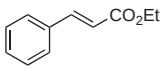
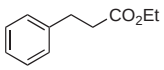
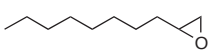
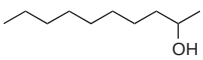
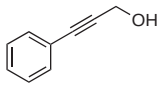
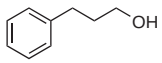
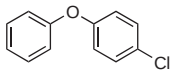
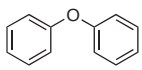
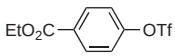
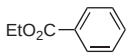
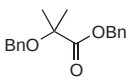
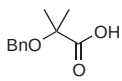
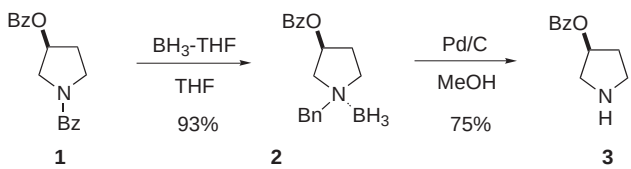
Table 1. Reduction of representative functional groups with t-$BuNH_2{\cdot}BH_3$/10% Pd–C/methanol system[a]

Entry	Substrate	Product	Time (h)	Yield %
1			4	93
2			8	94
3			4	92[b]
4			16	81[c]
5			9	97[b]
6			120	82
7			11	83[d]
8			1	90

[a] Reactions were conducted in a sealed vessel at room temperature on 50 mmol of substrate in 30 mL of methanol with 20 mmol of t-$BuNH_2{\cdot}BH_3$ and 174 mg of 10% Pd–C, unless otherwise noted. [b] As in a, except on 25 mmol of substrate. [c] Regioselectivity is 24:1 in favour of the secondary alcohol. Determined by ^1H NMR. [d] Reaction performed in ethanol to avoid transesterification.

hydrogenated in yields greater than 90%.[20] Although pyridine–borane has been shown to reduce quinoline in acetic acid, the reaction also leads to *N*-acetyl and *N*-ethyl tetrahydroquinoline derivatives when the reaction is run at reflux.[21] Using our procedure, *t*-butylamine borane can accomplish the desired transformation cleanly, under milder neutral conditions, in high yield (entry 3). Hydrogenolysis type reductions have also been explored. Reductions of epoxides have been reported and are limited to allylic systems using borane–dimethylamine. Under the present conditions, reductive opening of 1-epoxydecane led to the secondary alcohol in a 24:1 ratio. Interestingly, the regioselectivity is superior to the reported 4:1 ratio obtained using hydrogen gas and Pd–C in methanol.[22] Reductive cleavage of aryl chloride (entry 6) and triflate (entry 7) worked well in the presence of both electron-withdrawing and donating groups. As compared to Lipshultz's method, the current procedure does not require triphenylphosphine and base as additive, and can be carried out at room temperature. An attractive feature of the present procedure is that, after removal of the palladium catalyst, the desired product can be isolated by simple removal of methanol, *t*-butylamine and trimethylborate by evaporation. The last example illustrates the chemoselective hydrogenolysis of a benzyl ester in the presence of a benzyl ether, again in high yield. Unlike amine–borane activation precedents, which have been sporadic and require very specific reaction conditions, the examples above demonstrate the versatility and mildness of the method.

The utility of this procedure can be further extended to cases where the amine–borane is an integral part of the molecule to be reduced. In Scheme 1, a two-step sequence involving borane mediated amide reduction of benzamide **1**,[23] followed by a tandem methanolysis/hydrogenolysis of the resulting borane–benzylamine adduct **2**,[24,25] allows deprotection of an *N*-benzoyl in the presence of an *O*-benzoyl blocking group.



Scheme 1.

In conclusion, the palladium-catalyzed methanolysis of borane–amine adducts provides efficient hydrogen-transfer conditions capable of reducing a wide range of functional groups in excellent overall yields. The scope of amine–borane in organic synthesis is therefore broadened through palladium catalysis, in a unified methodology. Combined with a straightforward isolation method, this is an attractive procedure that may

lead to further palladium-catalyzed applications of borane–amine complexes.

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18. A representative experimental procedure is as follows: To a mixture of *trans*-stilbene (9.01 g, 50.0 mmol) and 10% palladium-on-carbon (740 mg, 50% wet) in methanol (15 mL) was added a solution of borane *t*-butylamine (1.74 g, 20.0 mmol) in methanol (15 mL) and the vessel was immediately sealed and heated to 30°C. Upon reaction completion (4 h, monitored by a constant pressure reading), the reaction mixture was cooled to room temperature, filtered over Celite, rinsed with methanol, and concentrated under reduced pressure. Purification of the crude material by silica gel chromatography using dichloromethane gave bibenzyl (8.46 g, 93%) as a white crystalline solid.
19. It is noteworthy that the rates of reductions are generally slower than extrusion of hydrogen from the catalytic surface. As a consequence, the pressure of hydrogen increases in the reaction vessel and the requisite equivalent of hydrogen is ultimately consumed in the time indicated in the Table 1.
20. The current methodology is not limited to aromatic substitution since 1-hexene was utilized as hydrogen scavenger in the palladium-catalyzed decomplexation of borane–benzylamine complexes (see Ref. 13).
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23. Experimental procedure: To an ice-cold solution of *N*,*O*-bis(benzoyl)-3-pyrrolidinol (1.98 g, 6.68 mmol) in tetrahydrofuran (15 mL), was added a solution of borane–tetrahydrofuran (13.4 mL, 13.4 mmol, 1 M in THF) and the resulting mixture was stirred for 1 h at room temperature. The reaction was then cooled to 0°C, quenched with methanol (10 mL) and immediately concentrated to dryness at 25°C under reduced pressure. Purification of the residual material by silica gel chromatography using 10% ethyl acetate in hexane provided a diastereomeric mixture of borane–amine complexes (1.83 g, 93%) as a white crystalline solid. Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, $J=8.0$ Hz, 2H), 7.55 (t, $J=8.0$ Hz, 1H), 7.45–7.25 (m, 7H), 5.55 (brs, 1H), 4.16 (s, 2H), 3.65 (dd, $J=6.0$, 12.5 Hz, 1H), 3.30–3.15 (m, 3H), 2.83 (m, 1H), 2.20–1.40 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.96, 133.55, 132.99, 131.55, 129.77, 129.63, 129.29, 128.70, 128.61, 74.61, 66.17, 63.52, 57.19, 31.01. Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, $J=8.5$ Hz, 2H), 7.56 (t, $J=8.5$ Hz, 1H), 7.45–7.20 (m, 7H), 5.30 (m, 1H), 4.09 (s, 2H), 3.55 (dd, $J=7.0$, 13.0 Hz, 1H), 3.25–3.15 (m, 2H), 3.12 (m, 1H), 2.37 (m, 1H), 2.25–1.60 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.52, 133.56, 132.65, 131.80, 130.02, 129.75, 129.60, 128.91, 128.68, 73.31, 66.62, 63.91, 58.02, 31.19.
24. Experimental procedure: To a mixture of borane–amine complex **2** (2.95 g, 10 mmol) and 10% palladium-on-carbon (1.18 g, 50% wet) was added methanol (30 mL). The reaction vessel was quickly sealed and the contents stirred at room temperature for 4 days. The resulting reaction mixture was filtered over Celite, rinsed with methanol and concentrated to dryness. Flash chromatography of the residual material using 5% methanol in dichloromethane provided the desired secondary amine

(1.43 g, 75%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, $J=7.5$ Hz, 2H), 7.56 (t, $J=7.5$ Hz, 1H), 7.45–7.20 (t, $J=7.5$ Hz, 2H), 5.37 (m, 1H), 3.10–3.00 (m, 3H), 2.87 (m, 1H), 2.25 (brs, 1H), 2.15–1.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.49, 133.18, 130.45, 129.76, 129.68, 128.53, 76.66, 53.84, 46.15, 33.55.

25. The reaction rate of the tandem methanolysis/hydrogenolysis is comparable to the standard hydrogenation of the corresponding free-base when performed in similar reaction conditions.