Homogeneous Catalysis

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Selective Reduction of Amides to Amines by Boronic Acid Catalyzed Hydrosilylation**

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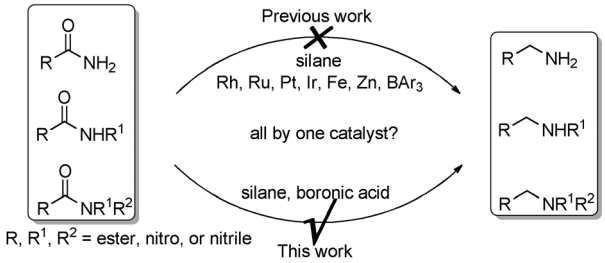
Amines constitute important intermediates for the pharmaceutical, agrochemical, and chemical industry. Regarding their preparation, the reduction of carboxamides constitutes a convenient and straightforward synthetic access.[1] Conventionally, amides have been reduced using aluminum or boron hydrides,[2] but these protocols show only limited functional-group tolerance. However, for the efficient construction of functionalized complex molecules, achieving high chemoselectivity is crucial in organic synthesis. For instance, among the top 20 drugs (based on sales) in 2010, five are amine derivatives having additional reducible moieties, such as ester and cyano groups.[3] In contrast to stoichiometric reductions, catalytic routes offer the possibility to control selectivity by modifying the catalyst metal and the surrounding ligands. In this respect, catalytic hydrosilylation has recently become the method of choice for chemoselective reductions of carboxamides. Compared to hydrogenation,[4] a variety of noble-metal catalysts based on Rh,[5] Ru,[6] Pt,[7] Ir,[8] as well as others[9–10] can be applied in this transformation.

Notable recent examples of chemoselective reductions have been performed even in the presence of inexpensive Fe[11] or Zn salts.[12] Nevertheless, despite the progress made none of the known catalytic hydrosilylation methods can directly reduce all types of amide bonds (tertiary, secondary, and primary) in the presence of other functional groups such as ester, nitro, and nitrile groups.[13]

The invention of new types of catalysts might be the key to solving this problem. Complementary to organometallic catalysts, metal-free catalysis may allow novel reactivity and chemoselectivity for the synthesis of functionalized molecules.[14] Interestingly, Charette and co-workers reported the metal-free reduction of both tertiary and secondary amides with excellent functional-group tolerance by using triethylsilane or the Hantzsch ester as reductants.[15] Unfortunately, in their process stoichiometric amounts of expensive triflic anhydride has to be used for the activation of the amide.

Since the 1970s it has been well known that hydrosilylation of carbonyl groups is also promoted by addition of acids.[16] Based on our recent work on phosphoric acid ester catalyzed hydrosilylation of phosphine oxides,[17] the combination of silanes and acids for reductions of amides attracted our interest. Herein we report the first metal-free chemoselective hydrosilylation for the reduction of tertiary, secondary, and primary amides in the presence of boronic acids (Scheme 1).



Scheme 1. Direct catalytic reduction of tertiary, secondary, and primary amides to amines using silanes.

At the start of our investigation the benchmark reduction of *N*,*N*-dimethylbenzamide (**1a**) with phenylsilane was performed in the presence of a variety of Brønsted acids (5 mol%). Among the different phosphorous-, carbon-, and sulfur-based acids, the diarylphosphate **3a** and benzenesulfonic acid (**3d**) were found to be slightly active, thus giving *N*,*N*-dimethylbenzylamine (**2a**) in 12 and 13% yield, respectively (Table 1, entries 2 and 5). To our surprise significantly improved yields were obtained when boronic acids (BA) were used as the catalysts. Although these acids have been extensively applied in modern organic synthesis,[18,19] to the best of our knowledge their use as catalysts for hydrosilylation reactions is not known. More than 30 boronic acids were tested, specifically the benzothiophene-derived boronic acids **3i** and **3j** were efficient, thus resulting in 61% and 81% yield, respectively, of the desired amine in the presence of $PhSiH_3$ (Table 1, entries 7–12).[20] Although several boronic acids showed activity, the yields varied significantly depending on the structure. Comparison of the activity of **3i** with **3j** (61% versus 81%; Table 1, entries 10 and 11), as well as that of **3i** with **3k** (61% versus 34%; Table 1, entries 10 and 12), suggests that both electronic and steric effects are important. When using other types of silanes as the reductant, lower

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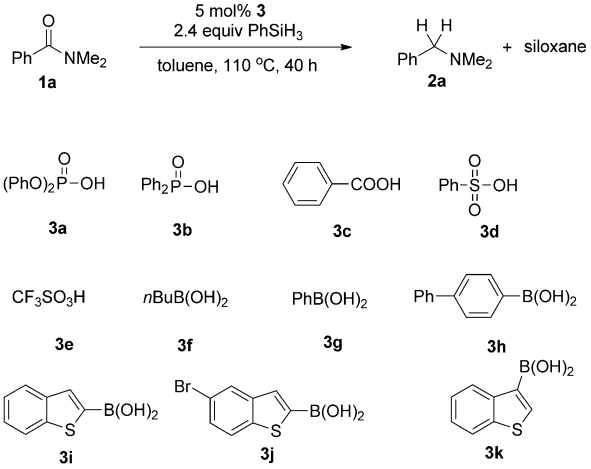
Table 1: Acid-catalyzed reduction of amides using silanes.[a]



Entry	3	Yield[b] [%]	Entry	3	Yield[b] [%]
1	–	n.r.	9	**3h**	48
2	**3a**	12	10	**3i**	61
3	**3b**	n.r.	11	**3j**	81
4	**3c**	3	12	**3k**	34
5	**3d**	13	13[c]	**3j**	16
6	**3e**	n.r.	14[c]	**3j**	2
7	**3f**	22	15[c]	**3j**	n.r.
8	**3g**	11	16[d]	**3j**	69

[a] Reaction conditions: **1a** (0.5 mmol), **3** (0.025 mmol), silane (1.2 mmol), toluene (2.0 mL). [b] Determined by GC methods using *n*-hexadecane as an internal standard. [c] The silanes for entries 13, 14, and 15 are Ph_2SiH_2, TMDS, and Et_3SiH, respectively. [d] THF as solvent in a sealed tube. n.r. = no reaction.

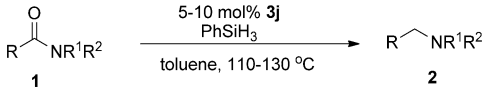
yields were obtained (Table 1, entries 13–15). Notably, the reactivity also decreased when polar solvents such as THF or 1,4-dioxane were used (Table 1, entry 16; see Table S1 in the Supporting Information).

From a mechanistic point of view it is interesting to note that the (benzo)thiophene moiety of the catalyst significantly contributes to the high reactivity. However, the use of benzothiophene (**4a**) as the catalyst resulted in no reaction. To prove that catalysis is promoted by the boronic acid and not by trace amounts of transition metals, boronic acids from different suppliers were tested and showed no difference in reactivity (see Schemes S1 and S2). Meanwhile, NMR experiments were carried out for the reduction of **1a** in the presence of 2.4 equivalents of $PhSiH_3$ and 20 mol% of the boronic acid **3i**. While the original ^{11}B NMR signal of **3i** ($\delta = 26.2$ ppm) disappeared, two new peaks having chemical shifts of $\delta =$ 19.4 ppm (major) and $\delta = 1.6$ ppm (minor) are formed during the reduction process, thus demonstrating reaction of the boronic acid. To further understand the role of boron, compounds having a $B(O\text{-}C)_2$ (**4b**), $B(O\text{-}C)_3$ (**4c**), $B(O\text{-}C)_2Si$ (**4d**), or $B(O\text{-}Si)_3$ (**4e**) structure were tested for reduction of **1a**, and all showed no reactivity, even in the presence of **4a** (see Table S2). Hence, the possible silylated species having a B-O-Si moiety is not likely to be responsible for the catalysis.

To exclude the possibility of radical reactions, 2,2,6,6-tetramethyl-1-piperidinyloxy radical (TEMPO) was added to the reaction (Scheme S4). As shown, TEMPO had no influence on the reactivity and clearly indicates a nonradical pathway. When using Ph_2SiD_2 as a reductant, the desired deuterated product was obtained in 43% yield, as determined by NMR spectroscopy, with a D content of greater than 99%.[20]

To get more information on the mechanism of the reaction between **1a** and $PhSiH_3$ with the boronic acid catalyst, simultaneous in situ ATR-FTIR and UV/Vis spectroscopic measurements were performed (Figures S3 and S5). Although these in situ experiments allowed real-time monitoring of the reduction process, the direct mode of action of the catalyst was not observed. Thus, further experiments were performed to study the interaction of the boronic acid **3j** with $PhSiH_3$ and **1a** individually (see the Supporting Information). Here, an interaction of the OH group of the boronic acid with the carbonyl group of the amide through hydrogen bonding was observed,[21] and might explain the possible activation mode for the reduction process.

Table 2: The boronic acid **3j** catalyzed reduction of tertiary amides.[a]



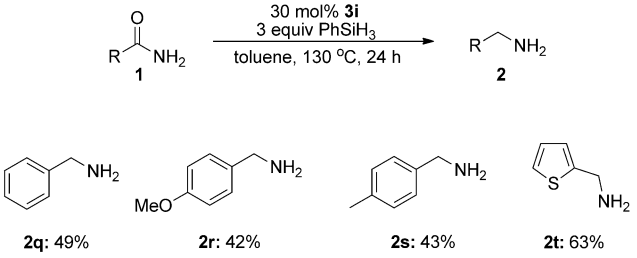
Entry	1	2	T [°C]	Yield[b] [%]
1	**1a**	**2a**	110	88
2	**1b**	**2b**	110	75
3	**1c**	**2c**	110	80
4	**1d**	**2d**	110	70
5	**1e**	**2e**	130	99
6[c]	**1f**	**2f**	130	96
7	**1g**	**2g**	110	86
8	**1h**	**2h**	130	77
9	**1i**	**2i**	130	82
10[c]	**1j**	**2j**	110	72

[a] Reaction conditions: **1** (0.5 mmol), $PhSiH_3$ (1.2 mmol), toluene (2.0 mL), 110–130 °C, 36 h. [b] Yield of the isolated product. [c] Yield determined by GC methods using *n*-hexadecane as an internal standard.

With good results in hand for the reduction of our benchmark substrate dimethylbenzamide, the reactivity of other tertiary amides was studied in the presence of **3j** under the optimized reaction conditions (Table 2). When aromatic amides were used, the desired products were obtained in 70–99% yield (Table 2, entries 1–7). Especially high reactivity is observed when the aryl group is substituted with electron-donating groups, thus giving the corresponding products in 70–99% yield (Table 2, entries 4 and 5). Though the reactivity was strongly diminished for sterically hindered substrates under our standard reaction conditions, excellent yields were obtained when the temperature was simply increased to 130°C (Table 2, entries 5 and 6). Notably, aliphatic *N*-acyl amino esters and a lactam were also hydrosilylated in good yields (Table 2, entries 8–10). From a synthetic point of view it is interesting to note that other reducible groups such as nitro, cyano, and ester moieties are well tolerated, something which is not possible for reductions employing organometallic hydrides.

Next, the reduction of less-reactive secondary amides was investigated. To our delight, good yields of the corresponding amines were obtained by increasing the catalyst loading to 20 mol% at 130°C (Table 3). Similar to the reduction of tertiary amides, aromatic and aliphatic secondary amides, as well as heterocyclic substrates were hydrosilylated with good to excellent selectivity.

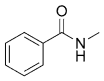
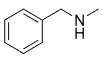
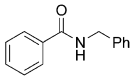
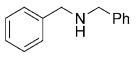
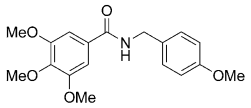
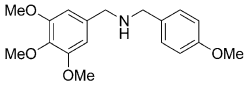
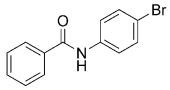
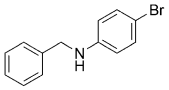
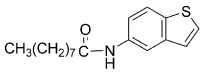
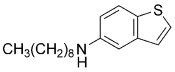
Finally, we were interested in the hydrosilylation of the more challenging primary amides. Unlike tertiary and secondary amides, the arylboronic acid **3i** proved to be a better catalyst for the direct reduction. Nevertheless, in the presence of 20 mol% of **3j** the reduction of benzamide gave only 17% yield of desired benzyl amine and 70% of benzonitrile, which resulted from a known dehydration process.[22] However, benzamide is reduced to benzylamine in 39% yield with 51% benzonitrile in the presence of 20 mol% of **3i**. Gratifyingly, even better selectivity is achieved when 30 mol% of **3i** was used. Here, full conversion and mediocre to good yields for aromatic amines were obtained for different aromatic substrates (Scheme 2).[23]



Scheme 2. The boronic acid **3i** catalyzed transformation of primary amides into primary amines.

In conclusion, we have developed a general organocatalytic hydrosilylation of amides. For the first time, catalytic reduction of tertiary, secondary, and primary amides to the corresponding amines is possible without any metal present. By applying a commercially available and air- and moisture-tolerant boronic acid as the catalyst, this convenient methodology allows a clean and straightforward synthesis of amines with good functional-group tolerance.

Table 3: The boronic acid **3j** catalyzed reduction of secondary amides to secondary amines.[a]

Entry	1		2		Yield[b] [%]
1[c]		**1k**		**2k**	84
2[c]		**1l**		**2l**	67
3		**1m**		**2m**	89
4		**1n**		**2n**	52
5		**1o**		**2o**	60
6[c]		**1p**		**2p**	41

[a] Reaction conditions: **1** (0.5 mmol), **3j** (0.1 mmol), $PhSiH_3$ (1.2 mmol), toluene (2.0 mL) at 130°C; reaction time for entries 1 and 2 is 24 h and for entries 3–6 is 40 h. [b] Yield of the isolated product. [c] Yield determined by GC methods using *n*-hexadecane as an internal standard.

Experimental Section

General procedure for catalytic hydrosilylation: A 30 mL dried sealable tube containing a stirring bar was charged with **3j** (6.4 mg, 0.025 mmol) and the corresponding amide (0.5 mmol). Under an Ar flow, dry toluene (2 mL) and $PhSiH_3$ (150 μL, 1.2 mmol) were added, and the mixture was stirred at 110 or 130°C for 24–40 h. The yield is determined by GC using *n*-hexadecane as an internal standard without workup. To obtain the yield of the isolated product, 2 N NaOH (aq, 3 mL) was slowly added to the reaction mixture followed by vigorous stirring for 3 h at room temperature. The mixture was then extracted using ethyl acetate and the organic phase was dried by Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (for aromatic amines, it is eluted with *n*-pentane/EtOAc from 100:0 to 50:50; for aliphatic amine products, silica gel was neutralized by 5% of Et_3N in pentane, eluting with *n*-pentane/EtOAc from 100:0 to 70:30).

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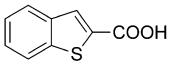
[20] When the compound below (10 mol%) was used as the catalyst, no reaction occurred. Notably **3k** is much less efficient



compared to **3i** and **3j**, and highlights the impact of the benzothiophene moiety. For the additive effect of benzothiophene derivatives, see Scheme S5. For details, see the Supporting Information. For the use of thiophene derivatives to promote hydrosilylation of ketones, see: A. Furuta, H. Nishiyama, *Tetrahedron Lett.* **2008**, *49*, 110.
[21] Such interactions by hydrogen bonding are known: a) T. Maki, K. Ishihara, H. Yamamoto Maki, *Tetrahedron* **2007**, *63*, 8645; b) A. Sakakura, T. Ohkubo, R. Yamashita, M. Akakura, K. Ishihara, *Org. Lett.* **2011**, *13*, 892. For boronic acids as hydrogen-bond donors, see: c) J.-H. Fournier, T. Maris, J. D. Wuest, W. Guo, E. Galoppini, *J. Am. Chem. Soc.* **2003**, *125*, 1002.
[22] For a selected example of the dehydration of primary amides to nitriles under hydrosilylation conditions, see: S. Zhou, D. Addis, S. Das, K. Junge, M. Beller, *Chem. Commun.* **2009**, 4883.
[23] Compared to aromatic amides, the reduction of primary alkylamides gives lower yield of the dimerized product, for example, the reduction of hexanamide generates dihexylamine with 27% yield.

