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ARTICLE TYPE

Efficient metal–free hydrosilylation of tertiary, secondary and primary amides to amines

Enguerrand Blondiaux[a] and Thibault Cantat*[a]

Hydrosilylation of secondary and tertiary amides to amines is described using catalytic amounts of $B(C_6F_5)_3$. The organic catalyst enables the reduction of amides with cost–efficient, non–toxic and air stable PMHS and TMDS hydrosilanes. The
10 **methodology was successfully extended to the more challenging reduction of primary amides.**

The late 1990's witnessed the birth of a novel field in homogeneous catalysis, when compelling successes were obtained in enantioselective synthesis using small organic
15 molecules as asymmetric catalysts.[1] Organocatalysis has since witnessed a growth spurt, resulting from a better rationalization of the catalyst families and motivated by the advantages provided by metal–free catalysts.[2] Indeed, organocatalysts usually combine a low cost and a low toxicity, with an enhanced stability to
20 moisture and air, which can circumvent classical drawbacks of many metallic catalysts. So far, organocatalysts have been applied efficiently in condensation and cycloaddition reactions, phase–transfer catalysis and oxidation chemistry, while their use in reduction chemistry has been only scarcely explored.[3] In fact,
25 the finding that molecular hydrogen could be activated using organic Frustrated Lewis Pairs (FLPs) enabled the metal–free catalytic hydrogenation of imines and alkenes.[4] In parallel, organic Lewis acids and bases were shown to promote the hydrosilylation and hydroboration of a variety of carbonyl
30 substrates, including CO_2.[5] These recent results are an encouragement and future efforts in the field should focus on challenging metal catalysts for the reduction of reluctant substrates, under mild reaction conditions. In this context, the hydrosilylation of amides is an attractive alternative to classical
35 methods utilizing reactive aluminium and boron hydrides for the synthesis of amines, as it usually proceeds with enhanced chemoselectivity.[6] Nonetheless, strong resonance effects between the vacant $\pi^*_{C=O}$ orbital and the vicinal nitrogen lone pair in amides lower significantly the electrophilicity of the C=O group
40 and the efficient catalytic hydrosilylation of amides remains an issue in synthetic organic chemistry.[7] Tertiary and/or secondary amines can be obtained by hydrosilylation of amides and catalysts based on earth abundant metals (Fe, Zn, Cu and Co) have been developed over the last years for this transformation.[8]
45 Interestingly, simple bases, such as Cs_2CO_3, KOH, KO^{t}Bu or LiHBEt$_3$, have emerged as hydrosilylation catalysts, lately.[9]

Overall, these systems offer only a partial solution to the reduction of amides as they either operate at elevated temperature (>120 °C), require the use of air sensitive hydrosilanes (such as
50 PhSiH$_3$) and/or are limited to a narrow scope of amide derivatives. These limitations have encouraged us to explore the use of metal–free catalysts in the reduction of amides to amines using hydrosilylanes. Herein, we show that $B(C_6F_5)_3$ catalyst, combined with cost–efficient, non–toxic and air stable PMHS
55 (polymethylhydrosiloxane) and TMDS (tetramethyldisiloxane) hydrosilanes, is a potent system for the hydrosilylation of tertiary, secondary and primary amides.

Very recently, Beller and coworkers showed that boronic acids could act as organocatalysts in the hydrosilylation of tertiary and
60 secondary amides.[10] Yet, the transformation proceeds at 110–130 °C with an excess of PhSiH$_3$, and the TurnOver Numbers (TONs) are very limited (<2) in the reduction of primary amides. From another standpoint, Piers and coworkers have demonstrated in the late 1990's the potential of $B(C_6F_5)_3$ as a catalyst in the
65 hydrosilylation of aromatic aldehydes, ketones, and esters.[11] This seminal contribution has then been successfully applied in the hydrosilylation of alcohols, ethers, carboxylic acids, imines and olefins and reduction of *N*–phenylacetamide with Ph$_2$SiH$_2$ suggests that $B(C_6F_5)_3$ could be an efficient catalyst for the
70 hydrosilylation of amides.[12]

Table 1 Reduction of *N*–benzylbenzamide with $B(C_6F_5)_3$
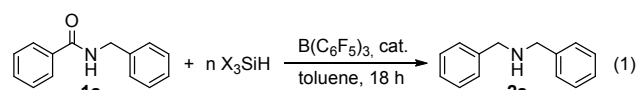
Entry	X$_3$SiH (n)	Cat. loading [mol%]	Temp. [°C]	Yield [%][a]
1	PhSiH$_3$ (1.3)	–	100	0
2	PhSiH$_3$ (1.3)	20	20	16
3	PhSiH$_3$ (1.3)	20	100	99
4	PhSiH$_3$ (1.3)	5	100	92
5	PhSiH$_3$ (1.3)	2	100	87
6	PhSiH$_3$ (1.3)	1	100	53
7	PhSiH$_3$ (1.3)	5	100	62[b]
8	PhSiH$_3$ (1.3)	5	80	14
9	PMHS (4)	5	100	76
10	TMDS (2)	5	100	91

Reaction conditions: *N*–benzylbenzamide **1a** (0.10 mmol), hydrosilane (n equiv.), 18 h under inert athmosphere; [a] GC/MS yield using mesitylene
75 as an internal standard; [b] 5 h reaction

The ability of B(C₆F₅)₃ to catalyze the hydrosilylation of amides was first tested in the reduction of *N*–benzylbenzamide (**1a**). In the presence of a large catalyst loading of 20 mol% B(C₆F₅)₃ and 1.3 equiv. PhSiH₃, dibenzylamine **2a** is formed in a low 16 %
5 yield after 18 h at room temperature in toluene (Table 1, entry 2). Nonetheless, increasing the temperature to 100 °C leads to a quantitative conversion of **1a** to **2a** (Table 1, entry 3) and, at 100 °C, 2 mol% B(C₆F₅)₃ are sufficient to afford **2a** in 87 % yield (Table 1, entry 5). The reaction temperature plays a significant
10 role on the catalytic activity and, at 80 °C, the conversion yield to **2a** drops to 14 % (Table 1, entry 8). This effect likely results from the formation of an adduct between the coordinating amide substrate and catalyst B(C₆F₅)₃, that must be thermally cleaved to release the active Lewis acid. To our delight, PMHS and TMDS
15 are active reductants in the hydrosilylation of **1a**, despite their lower reactivity. With 5 mol% B(C₆F₅)₃, **2a** is obtained in 76 and 91 % yields in the presence of 4 equiv. PMHS and 2 equiv. TMDS, respectively (Table 1, entries 9–10). In comparison, Beller *et al.* have shown that benzothiophene–derived boronic
20 acids were active catalysts in the hydrosilylation of amides.[10] However, boronic acids display a low activity in the reduction of secondary (and primary) amides and **1a** was reduced to **2a** in 67 % yield, in the presence of 20 mol% boronic acid catalyst and 2.4 equiv. PhSiH₃, after 24 h at 130 °C.

25 **Table 2** Reduction of secondary amides using B(C₆F₅)₃ and TMDS

$$R_1 \overset{O}{\underset{H}{\overset{\|}{C}}} N-R_2 \quad \xrightarrow[\text{toluene, 100 °C, 18 h}]{B(C_6F_5)_3 \text{ (5 mol\%), TMDS}} \quad R_1 \overset{}{\underset{H}{C}} N-R_2 \quad (2)$$
1 → **2**

Entry	Amide	Yield [%][a]	Entry	Amide	Yield [%][a]
1	**1a**	85[b]	6	**1f**	24
2	**1b**	94[b]	7	**1g**	95
3	**1c**	92[b]	8	**1h**	96[b]
4	**1d**	3	9	**1i**	92
5	**1e**	40	10	**1j**	20
			11	**1k**	41

Reaction conditions: amide (0.10 mmol), TMDS (0.20 mmol), B(C₆F₅)₃ (0.0050 mmol), toluene (0.30 mL), 100 °C,18 h; [a] GC/MS and/or ¹H NMR yield using mesitylene as an internal standard, [b]isolated yield

The B(C₆F₅)₃ (cat.)/TMDS system therefore appears as a
30 convenient reducing medium, which combines the advantages of an organocatalyst with low cost (<4 €/kg), low toxicity and the stability of the TMDS hydrosilane. The scope of reactive

secondary amides was thus explored with this system (Table 2). Reduction of *N*–phenylbenzamide (**1b**) is quantitative, after 18 h
35 at 100 °C, and amine **2b** was obtained in 94 % isolated after hydrolysis of the reaction mixture (see ESI and entry 2 in Table 2). Replacing the phenyl ring on the carbonyl group with a methyl group does not impact the reactivity of the amide and **2c** was isolated in 92 % yield, under the same conditions (Table 2,
40 entry 3). Yet, introduction of an aliphatic group on the nitrogen atom significantly hampers the conversion yields and **1d**, **1e** and **1f** are converted to their corresponding amines in lower yields (<40 %) (Table 2, entries 4–6).The allyl derivative **1k** is reduced to **2k** in 41 % yield, without reduction of the C=C bond. The
45 presence of electron withdrawing groups on the benzamide ring of **1a** favours the reaction and the *p*–Cl– and *p*–Br–substituted *N*–benzylbenzamides are converted to **2g** and **2h** in quantitative yields (Table 2, entries 7–8). Similarly, **2i** is obtained in 92 % yield from **1i**. On the contrary, the *p*–OMe substituent somewhat
50 deactivates the reactivity of *N*–benzylbenzamide and **1j** is converted to **2j** in 20 % yield after 18 h at 100 °C. Overall, these results are consistent with the original mechanism unveiled by Piers *et al.* for the B(C₆F₅)₃–catalyzed hydrosilylation of carbonyl groups.[12f] Its transposition to the reduction of amides likely
55 involves the formation of an ion pair, in which the carbonyl functionality is activated by coordination to a silylium cation while the active reductant is the HB(C₆F₅)₃⁻ anion (Scheme 1). This pathway is therefore favoured in the presence of EWGs on the amide reactant because they weaken the amide–B(C₆F₅)₃
60 interaction and facilitate the hydride transfer from HB(C₆F₅)₃⁻ to the carbonyl group.
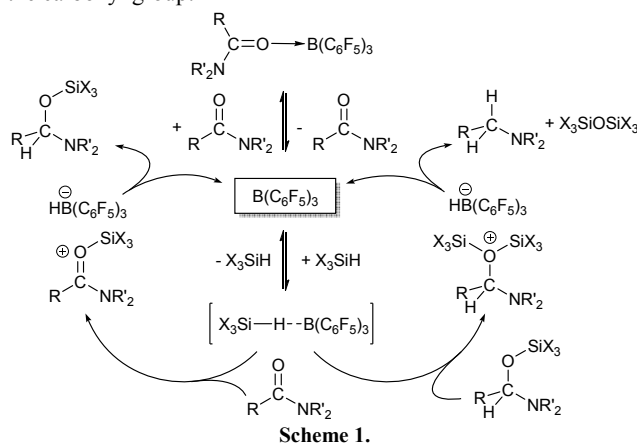
Scheme 1.

The B(C₆F₅)₃ (cat.)/TMDS system is also competitive or superior
65 to known metal catalysts in the hydrosilylation of secondary amides. Among the few catalysts able to promote the hydrosilylation of secondary amides with PMHS or TMDS, Zn(OTf)₂ displays a low reactivity and it reacts at 100 °C,[8a] with high loadings (20 mol%), while Cu(OTf)₂ complexes are reactive
70 at 65 °C.[8f]

Tertiary amides are classically more reactive than secondary amides in hydrosilylation reactions. Indeed, reduction of *N,N*–dimethylbenzamide (**3a**) to **4a** is quantitative after 18 h at 100 °C with 1 mol% B(C₆F₅)₃ and 1.3 equiv. PhSiH₃. Using TMDS and
75 PMHS as reductants and catalyst loadings of 2 mol% and 5 mol%, respectively, **4a** is also formed in quantitative yield. As expected, a wide range of tertiary amides was successfully reduced using the B(C₆F₅)₃ (cat.)/PMHS system and both

aliphatic and aromatic amides **3a**–**3j** were converted in good to excellent yields (>72 %, Table 3 and ESI). Amide **3k** exhibits a somewhat lower reactivity, presumably because of the presence of three aliphatic groups on the nitrogen and carbonyl groups and
5 **4k** is formed in 42 % yield. Similarly, **3l** and **3m** afford amines **4l** and **4m** in 60 and 49 % yield, respectively. It is noteworthy that the methodology is compatible with the presence of nitro groups and **4n** is obtained in 82 % yield when **3n** is reduced in the presence of PhSiH$_3$ (14 % yield when PMHS is utilized as
10 reductant). In contrast, the cyano group in **3o** hampers the catalytic activity of B(C$_6$F$_5$)$_3$, presumably because of the strong coordination of the CN function to the Lewis acid catalyst. B(C$_6$F$_5$)$_3$ (cat.)/PMHS is also able to reduce enones and esters and the reduction of the amide functionality in **5** and **7** is also
15 accompanied with the reduction of the C=C and –CO$_2$Me groups (Eqs. 4–6).

**Table 3** Reduction of tertiary amides using B(C$_6$F$_5$)$_3$ and PMHS
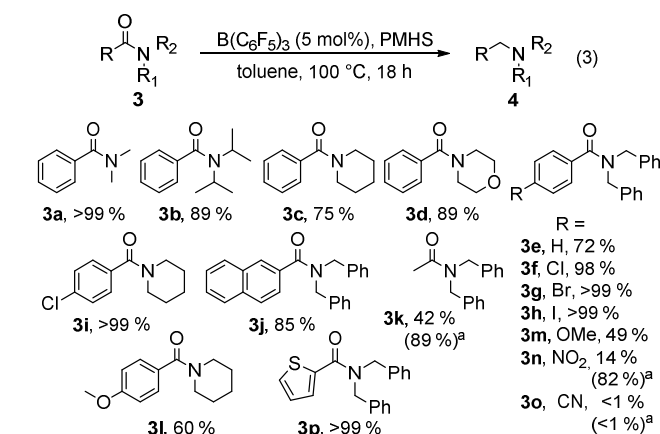
Reaction conditions: amide (0.10 mmol), PMHS (0.40 mmol, 4 eq. "Si-H"), B(C$_6$F$_5$)$_3$ (0.0050 mmol), toluene (0.30 mL), 100 °C,18 h; yield
20 determined by GC/MS using mesitylene as an internal standard [a]with PhSiH$_3$ (0.13 mmol, 4 eq. "Si-H")
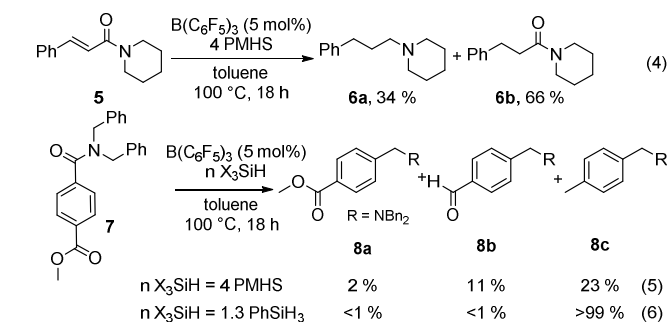
It is well recognized that primary amides are singular substrates in catalytic hydrosilylation.[8g, 13] Indeed, they display a low
25 reactivity and can be converted to secondary amines by coupling, after subsequent hydrolysis. In fact, reduction of benzamide **9a** with 10 mol% B(C$_6$F$_5$)$_3$ and 2 equiv. TMDS affords the secondary amine **2a** in 65 % yield, after 18 h at 100 °C (Eqs. 7). As proposed by Darcel *et al.* and Beller *et al.*, benzonitrile PhCN
30 can form by slow dehydrogenative silylation of the N–H bonds of **9a** and subsequent elimination of a siloxane by–product. A plausible mechanism for the coupling reaction can thus involve the addition of the nucleophilic amide **9a** to the benzonitrile intermediate. In order to prevent the coexistence of **9a** and
35 benzonitrile in the reaction mixture, the rapid silylation of one N–

H bond in **9a** was undertaken, using TMSCl, prior to the hydrosilylation step. Using this simple procedure, primary amines
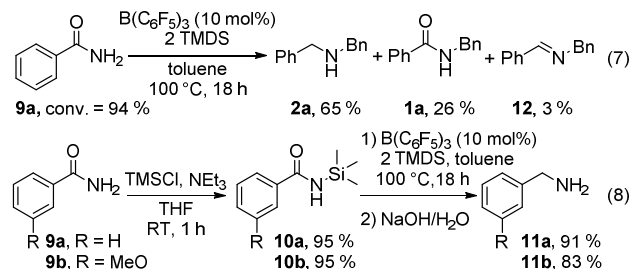
11a and **11b** were obtained in excellent 91 and 83 % yield from primary amides **9a** and **9b**, respectively (Eq. 8).
40 In conclusion, B(C$_6$F$_5$)$_3$ is an efficient organocatalyst for the hydrosilylation of tertiary, secondary and primary amides, with cost–efficient, non–toxic and air stable PMHS and TMDS hydrosilanes. The methodology enables the formation of tertiary, secondary and primary amines, from the corresponding amides.

50 ## Notes and references

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60 DOI: 10.1039/b000000x/

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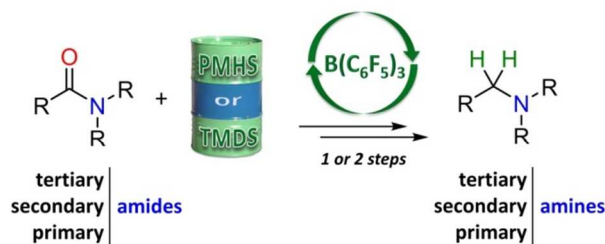# Journal Name

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Efficient metal–free hydrosilylation of tertiary, secondary and primary amides to amines

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