Homogeneous Catalysis

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A Convenient and General Iron-Catalyzed Reduction of Amides to Amines**

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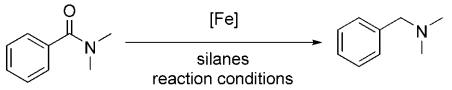
Amines constitute an important class of compounds in chemistry and biology. They are widely used in the pharmaceutical industry for crop protection and natural product synthesis, as well as for the preparation of advanced materials.[1] Among the different procedures for their synthesis, the reduction of amides is one of the most fundamental methods. In general, reactive alkali metal hydrides or boron hydrides are used for such reduction processes. However, their air and moisture sensitivty, their low functional group tolerance, and tedious purification procedures are drawbacks.[2] Interestingly, Cole-Hamilton and co-workers showed that catalytic hydrogenation of amides using molecular hydrogen constitutes a highly attractive access to amines, but the vigorous reaction conditions, that is, high pressures and elevated temperature, limit this methodology.[3]

During the last decade, metal-catalyzed hydrosilylations of amides have received considerable interest. Although various catalyst systems including Rh,[4a–c] Ru,[4c–g] Pt,[4c,h] Pd,[4c] Ir,[4c] Os,[4c] Re,[4c] Mn,[4c] Mo,[4i] In,[4j] and Ti[4k] have proven to be effective for this reduction, the development of cost-efficient and environmentally benign catalysts for this transformation is still desirable. In addition, most of the known catalyst systems either require expensive silanes or have limited functional group tolerance.

During our recent studies on iron-catalyzed dehydrations of primary amides in the presence of hydrosilanes,[5] we isolated the corresponding secondary amine as a by-product. Thus, our attention focused on this side-reaction of reducing carboxamides to amines. The abundant availability of iron makes it a highly attractive candidate for catalysis and a "cheap metal for noble tasks".[6,7] Herein we report the first general iron-catalyzed hydrosilylation of amides to generate amines. Initially, the reaction of *N*,*N*-dimethylbenzamide (**1a**) with $PhSiH_3$ in toluene was investigated as a model system to identify and optimize critical reaction parameters (Table 1). As expected the reaction did not occur in the absence of any catalyst (Table 1, entry 1). In contrast, when using 2 mol% of cheap $[Fe_3(CO)_{12}]$, an excellent yield (97%) of *N*,*N*-dimethylbenzylamine (**2a**) was obtained (Table 1, entry 3). Other iron sources, such as $[Fe_2(CO)_9]$, $Fe(OAc)_2$, $[Fe(acac)_2]$, and $[Fe(acac)_3]$ are also reactive but resulted in lower product yields (Table 1, entries 2 and 4–9).

Table 1: Iron-catalyzed reduction of *N*,*N*-dimethylbenzamide.[a]



1a **2a**

Entry	Catalyst (mol%)	Silane (equiv)	Solvent	Yield[b] [%]
1	–	$PhSiH_3$ (2)	toluene	0
2	$[Fe_2(CO)_9]$ (3)	$PhSiH_3$ (2)	toluene	9
3	$[Fe_3(CO)_{12}]$ (2)	$PhSiH_3$ (2)	toluene	97
4	$Fe(OAc)_2$ (5)	$PhSiH_3$ (2)	toluene	22
5	$[Fe(acac)_2]$ (5)	$PhSiH_3$ (2)	toluene	57
6	$[Fe(acac)_3]$ (5)	$PhSiH_3$ (2)	toluene	58
7	$[Fe(stearate)_2]$ (5)	$PhSiH_3$ (2)	toluene	2
8	FeF_2 (5)	$PhSiH_3$ (2)	toluene	4
9	Fe_3O_4 (5)	$PhSiH_3$ (2)	toluene	0
10	$[Fe_3(CO)_{12}]$ (2)	$Me(EtO)_2SiH$ (3.0)	toluene	14
11	$[Fe_3(CO)_{12}]$ (2)	Et_3SiH (3.0)	toluene	18
12	$[Fe_3(CO)_{12}]$ (2)	$(EtO)_3SiH$ (3.0)	toluene	20
13	$[Fe_3(CO)_{12}]$ (2)	Et_2MeSiH (3.0)	toluene	18
14	$[Fe_3(CO)_{12}]$ (2)	$TMSOSiMe_2H$ (3.0)	toluene	30
15	$[Fe_3(CO)_{12}]$ (2)	Ph_2SiH_2 (2.0)	toluene	99
16	$[Fe_3(CO)_{12}]$ (2)	PMHS (5.0)[c]	toluene	93
17	$[Fe_3(CO)_{12}]$ (2)	PMHS (4.0)	toluene	89
18	$[Fe_3(CO)_{12}]$ (2)	PMHS (3.0)	toluene	60
19	$[Fe_3(CO)_{12}]$ (2)	PMHS (4.0)	nBu_2O	90
20[d]	$[Fe_3(CO)_{12}]$ (2)	PMHS (4.0)	nBu_2O	37

[a] Reaction conditions: **1a** (1.0 mmol), catalyst (2–5 mol%), silanes, solvent (2 mL), 8–24 h. [b] Determined by GC methods using hexadecane as an internal standard. [c] 1 mmol Si–H = 0.06 mL. [d] Run at 80°C. acac = acetylacetonate, TMS = trimethylsilyl.

Next, we investigated the influence of different silanes on the reaction. To our delight the reduction also took place in the presence of inexpensive polymethylhydrosiloxane (PMHS) to give the desired product in 93% yield (Table 1, entry 16).[8] Advantageously, this silane is also easily separated from the reaction mixture. Additional studies revealed that the reduction proceeded best in the presence of an excess of four equivalents of Si–H (Table 1, entry 17). Among the different solvents tested, toluene and di-*n*-butyl ether gave the best results (Table 1, entries 17 and 19).

With respect to the mechanism, we propose that the iron-catalyzed reduction of tertiary amides proceeds somewhat similarly to the ruthenium-catalyzed procedure reported by Nagashima and co-workers.[4e] Reaction of the hydrosilane with the iron precursor should yield an activated species,[9,10]

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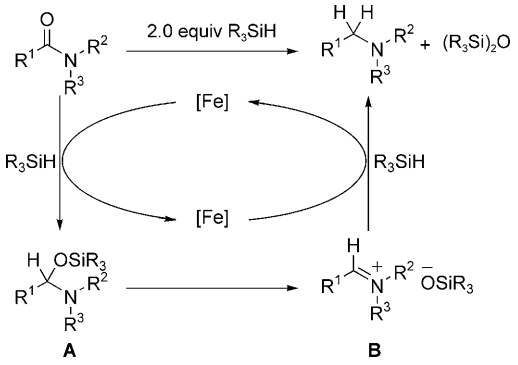
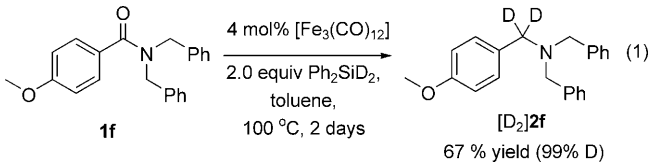
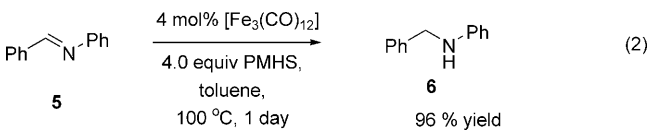
which hydrosilylates the carbonyl group of the amide to generate the corresponding O-silylated *N,O*-acetal **A**. Intermediate **A** is then transformed into an iminium species **B**. Finally, **B** is reduced to the corresponding amine by reaction with a second equivalent of the activated species (Scheme 1).



Scheme 1. Proposed reaction mechanism.

Indeed, this mechanistic proposal is supported by the reaction of **1f** with Ph_2SiD_2. Here, both deuterium atoms are incorporated on the carbonyl carbon atom of [D_2]**2f** [Eq. (1)]. Moreover, the reduction of the aldimine **5** proceeded in excellent yield to the corresponding amine **6** [Eq. (2)].





Once the optimized reaction conditions were identified, the scope and limitations of the iron-catalyzed reduction of amides using PMHS were explored. A variety of amides, including aromatic, aliphatic, heteroaromatic, and heterocyclic amides were reduced smoothly to the corresponding amines (Table 2). Arenes substituted with electron-donating or electron-withdrawing groups at either the *para* or *meta* position gave the desired products (Table 2, entries 2, 3, 5–10, and 27). In contrast, the system is more sensitive to steric hindrance on both the carbonyl (Table 2, entries 4, 16, and 17) and the amine side (Table 2, entries, 1, 20–23, 26, and 27). Here, more catalyst and PMHS are needed to achieve full conversion. Notably, a broad range of functional groups including halide, ether, ester, cyclopropane, and alkene groups (Table 2, entries 5–10, 16, and 18) are well-tolerated by the catalyst. In addition, heteroarenes as well as heterocyclic compounds such as **1n**, **1o, 1v**, and **1z** do not interfere with the amide reduction giving the corresponding heterocyclic amines in good to excellent yields (Table 2, entries 13, 14, 21, and 25). However, ketoamides gave a mixture of products. Notably, the reaction is easily scaled up to 100 mmol: 15 g of **4b** is obtained from 19 g (100 mmol) of **3b** (Table 2, entry 27). Secondary amides are also reduced to the corresponding amine in 99% yield by using $PhSiH_3$ as a hydrogen source (Table 2, entry 28).

In summary, we have established the first iron-catalyzed reduction of secondary and tertiary amides with inexpensive PMHS. The new protocol proceeds with high selectivity and exhibits a broad substrate scope and functional group tolerance providing a variety of amines in good to excellent yield. Direct catalytic hydrogenation does not occur under these conditions.

Experimental Section

General procedure for the reduction of tertiary amides: A 25 mL oven dried Schlenk tube containing a stir bar was charged with the respective tertiary amides (1.0 mmol) and [$Fe_3(CO)_{12}$] (0.02–0.1 mmol). PMHS (4.0–8.0 mmol) and dry toluene or Bu_2O (5 mL) was added respectively after purging the Schlenk tube with argon. The mixture was stirred at 100 °C for 1 day. The cooled reaction mixture was filtered through Celite and washed with diethyl ether. The combined fractions were concentrated under reduced pressure. The residue was purified by filtering through a short column of neutral alumina or by silica gel column chromatography. The combined fractions were concentrated under reduced pressure giving the corresponding amine. Tribenzylamine (**2b**): neutral alumina column [washed with ethyl acetate/*n*-hexane (1:10)], 89% yield, white solid; ^{1}H NMR (300.1 MHz, $CDCl_3$): $\delta = 3.48$ (s, 6H), 7.11–7.17 (m, 3H), 7.20–7.26 (m, 6H), 7.32–7.35 ppm (m, 6H); ^{13}C NMR (75.5 MHz, $CDCl_3$): $\delta = 57.92$, 126.83, 128.20, 128.72, 139.64 ppm. ATR-IR (neat): $\nu = 3102$ (w), 3082 (w), 3061 (w), 3025 (w), 2932 (w), 2880 (w), 2836 (w), 2798 (w), 2749 (w), 2714 (w), 1601 (w), 1492 (m), 1449 (m), 1365 (m), 1307 (w), 1245 (m), 1205 (w), 1119 (m), 1070 (w), 1027 (m), 988 (m), 971 (m), 903 (w), 879 (w), 824 (w), 740 (s), 694 (s), 618 (w), 591 (w), 491 (m), 463 (w), 418 (w). MS (EI): *m/z* (rel. int.) 288 (7), 287 (31), 286 (7), 211 (6), 210 (38), 197 (4), 196 (26), 181 (5), 92 (13), 91 (100), 65 cm^{-1} (12). HRMS (EI, *m/z*) calcd. for $C_{21}H_{21}N$, 287.1669; found 287.1668.

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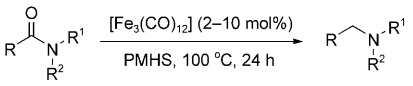
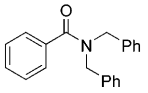
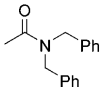
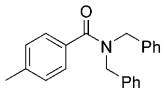
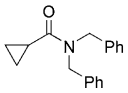
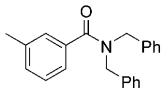
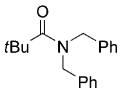
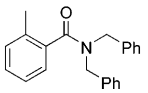
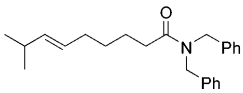
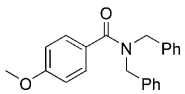
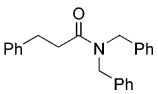
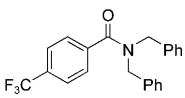
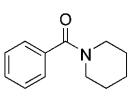
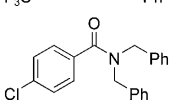
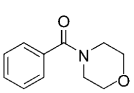
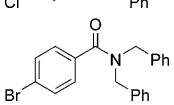
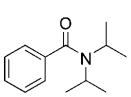
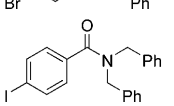
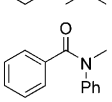
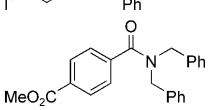
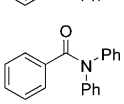
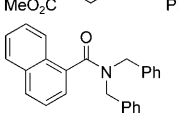
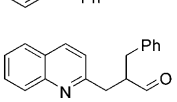
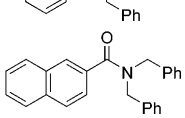
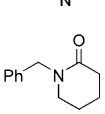
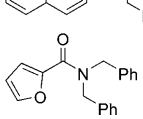
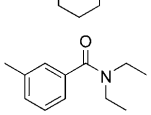
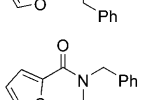
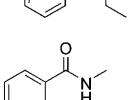
[4] a) T. Ohta, M. Kamiya, M. Nobutomo, K. Kusui, I. Furukawa, *Bull. Chem. Soc. Jpn.* **2005**, *78*, 1856–1861; b) R. Kuwano, M. Takahashi, Y. Ito, *Tetrahedron Lett.* **1998**, *39*, 1017–1020; c) M. Igarashi, T. Fuchikami, *Tetrahedron Lett.* **2001**, *42*, 1945–1947; d) H. Motoyama, K. Mitsui, T. Ishida, H. Nagashima, *J. Am. Chem. Soc.* **2005**, *127*, 13150–13151; e) S. Hanada, T. Ishida, Y. Motoyama, H. Nagashima, *J. Org. Chem.* **2007**, *72*, 7551–7559; f) K. Matsubara, T. Iura, T. Maki, H. Nagashima, *J. Org. Chem.* **2002**, *67*, 4985–4988; g) H. Sasakuma, Y. Motoyama, H.

Table 2: $[Fe_3(CO)_{12}]$-catalyzed reduction of amides to amines.[a]



Entry	Amide		Cat. [%]	Silane (equiv)	Yield[b] [%]	Entry	Amide		Cat. [%]	Silane (equiv)	Yield[b] [%]
1		**1b**	4	PMHS (4)	89 (**2b**)	15[c]		**1p**	4	PMHS (4)	89 (**2p**)
2		**1c**	4	PMHS (4)	93 (**2c**)	16		**1q**	6	PMHS (6)	82 (**2q**)
3		**1d**	4	PMHS (4)	93 (**2d**)	17		**1r**	8	PMHS (8)	98 (**2r**)
4		**1e**	8	PMHS (6)	94 (**2e**)	18[c]		**1s**	4	PMHS (4)	76 (**2s**)
5		**1f**	4	PMHS (4)	93 (**2f**)	19[c]		**1t**	4	PMHS (4)	63 (**2t**)
6		**1g**	4	PMHS (4)	84 (**2g**)	20		**1u**	3	PMHS (4)	94 (**2u**)
7		**1h**	4	PMHS (4)	95 (**2h**)	21		**1v**	3	PMHS (4)	80 (**2v**)
8		**1i**	4	PMHS (4)	92 (**2i**)	22		**1w**	10	PMHS (8)	59 (**2w**)
9[d]		**1j**	4	PMHS (4)	83 (**2j**)	23		**1x**	4	PMHS (4)	81 (**2x**)
10[c]		**1k**	4	PMHS (4)	58 (**2k**)	24		**1y**	4	PMHS (4)	50 (**2y**)
11		**1l**	4	PMHS (4)	77 (**2l**)	25[c]		**1z**	10	PMHS (8)	61 (**2z**)
12		**1m**	4	PMHS (4)	84 (**2m**)	26[c]		**3a**	3	PMHS (4)	90 (**4a**)
13		**1n**	10	PMHS (8)	82 (**2n**)	27[c,e]		**3b**	2	PMHS (4)	85 (**4b**)
14		**1o**	10	PMHS (8)	84 (**2o**)	28[c]		**3c**	4 4	$PhSiH_3$ (2.5) PMHS (6.0)	99[f] (**4c**) 25[f] (**4c**)

[a] Reaction conditions: Amide (1 mol), $[Fe_3(CO)_{12}]$ (2–10 mol%), PMHS (4–8 mmol), nBu_2O (5 mL), 100 °C, 24 h. [b] Yield of isolated product. [c] Toluene as solvent. [d] Contained 10% tribenzylamine. [e] Run on 100 mmol scale. [f] Yield determined by GC methods.

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