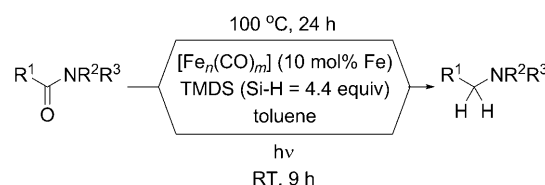


Hydrosilane Reduction of Tertiary Carboxamides by Iron Carbonyl Catalysts**

Yusuke Sunada, Hiroko Kawakami, Tsuyoshi Imaoka, Yukihiro Motoyama, and Hideo Nagashima*

Iron and silicon are two of the most popular elements used for effecting the catalytic transformations of organic molecules, owing to their high natural abundance, low cost, and low toxicity.^[1,2] We have previously reported a series of catalytic systems for the reduction of carboxamides to amines using hydrosilanes. The most active catalyst we have reported thus far is $[(\mu_3, \eta^2, \eta^3, \eta^5\text{-acenaphthylene})\text{Ru}_3(\text{CO})_{12}]$,^[3] which, in tandem with hydrosilanes that have two proximal Si–H groups (typically 1,1,3,3-tetramethyldisiloxane (TMDS) or 1,2-bis(dimethylsilyl)ethane), is able to successfully reduce secondary and tertiary carboxamides to their corresponding amines in high yields and under mild conditions. Commercially available platinum compounds were thought to be inactive for the silane reduction of carbonyl compounds prior to our previous work, which used the two Si–H groups of TMDS or 1,2-bis(dimethylsilyl)benzene to successfully effect this transformation.^[4] Astonishingly, the reduction of carboxamides using poly(methylhydrosiloxane) (PMHS) in the presence of the ruthenium or platinum catalysts described above is accompanied by formation of an insoluble poly(siloxane) gel, into which all of the metallic species is absorbed; the expensive ruthenium and platinum can be recovered from the silicone resin once the reaction has finished.^[3c,d,4] The absorption and removal of metallic residues makes these processes particularly environmentally friendly; nevertheless, the final goal for green processes remains the replacement of noble metal catalysts, such as ruthenium and platinum complexes, with iron compounds.^[5,6] Herein, we wish to report that two iron complexes, $[\text{Fe}(\text{CO})_5]$ and $[\text{Fe}_3(\text{CO})_{12}]$, can both act as the catalyst for the reduction of tertiary carboxamides to their corresponding amines, using TMDS as a reducing reagent (Scheme 1).

Although the thermal iron-catalyzed process requires a higher reaction temperatures than those catalyzed by the ruthenium or platinum catalysts, the reaction also proceeds photolytically at ambient temperature. In both the thermal and photoassisted reactions, the reduction reaction involving



Scheme 1. The iron-catalyzed reduction of carboxamides under either thermal or photoassisted conditions ($n=1, m=5$, or $n=3, m=12$).

PMHS is accompanied by concomitant absorption of the iron species into the insoluble silicon resin, also formed during the reaction. Furthermore, in the presence of a nitro substituent on the substrate, selective reduction of the nitro moiety was observed, with the amide group remaining intact; this has not been achieved by either the ruthenium catalysts or the platinum catalysts described earlier.

When *N,N*-dimethyldihydrocinnamamide (**1a**) was treated with TMDS in the presence of either $[\text{Fe}(\text{CO})_5]$ or $[\text{Fe}_3(\text{CO})_{12}]$ (10 mol %) in toluene at 100 °C, the color of the initial solution (yellow for $[\text{Fe}(\text{CO})_5]$ and dark green for $[\text{Fe}_3(\text{CO})_{12}]$) gradually became purple within the first 30 min and turned dark brown after 1 h. After 24 h, the iron residues were removed, and ^1H NMR spectroscopy of the crude material revealed that **1a** had been completely consumed and the desired *N,N*-dimethyl-3-phenylpropylamine (**2a**) was formed as a single product. Removal of the silicone waste from the crude product afforded **2a** in good yields (86 % for $[\text{Fe}(\text{CO})_5]$ and 85 % for $[\text{Fe}_3(\text{CO})_{12}]$). In sharp contrast, less than 5 % of **2a** was formed when other iron catalysts, such as FeCl_2 , FeCl_3 , $[\text{FeCl}_2(\text{PPh}_3)_2]$, and $[\text{Fe}(\text{acac})_2]$ were used, or with other hydrosilanes containing only one Si–H group, such as PhMe_2SiH , $(\text{EtO})_3\text{SiH}$, and $\text{SiMe}_3\text{OSiMe}_2\text{H}$, were used as the reducing agent under the same conditions (see the Supporting Information). Although alternative solvents, such as benzene, tetrahydropyran, and cyclohexane, were successfully used in the $[\text{Fe}(\text{CO})_5]$ - and $[\text{Fe}_3(\text{CO})_{12}]$ -catalyzed reactions at 100 °C,^[7] lowering the reaction temperature to 80 °C resulted in the yield of **2a** falling to below 20 %. It is noteworthy that high temperatures (>100 °C) are not required when the reaction is carried out under irradiation. Photoassisted reduction of **1a** with TMDS in the presence of $[\text{Fe}(\text{CO})_5]$ or $[\text{Fe}_3(\text{CO})_{12}]$ under irradiation with a 400 W high-pressure mercury lamp for 9 h afforded **2a** in 94 % yield and 73 % yield, respectively.

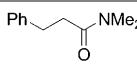
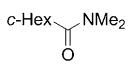
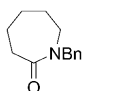
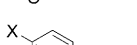
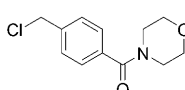
We then examined the scope of the thermal (Table 1) and photoassisted (Table 2) reductions using a variety of tertiary

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Table 1: Thermal reduction of various carboxamides with TMDS catalyzed by $[\text{Fe}(\text{CO})_5]$ and $[\text{Fe}_3(\text{CO})_{12}]$.^[a]

Entry	Amide		$[\text{Fe}(\text{CO})_5]$ Yield [%]	$[\text{Fe}_3(\text{CO})_{12}]$ Yield [%]
1		1a	86	85
2		1b	67	81
3		1c	95	84
4		1d: X = OMe	81	82
5		1e: X = Cl	66	85
6		1f: X = Br	98	96
7		1g: X = CO ₂ Me	88	84
8		1h	–	21 ^[b]

[a] All reactions were carried out using carboxamide **1** (1.0 mmol), TMDS (2.2 mmol, Si–H = 4.4 mmol), and iron catalyst (0.1 mmol) in toluene (0.5 mL) at 100 °C for 24 h. [b] Dehalogenated product was formed in 68 % yield.

Table 2: Photoassisted reduction of various carboxamides with TMDS catalyzed by $[\text{Fe}(\text{CO})_5]$ and $[\text{Fe}_3(\text{CO})_{12}]$.^[a]

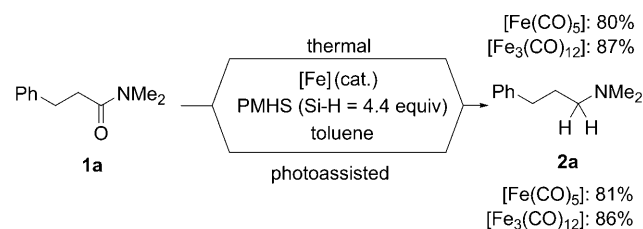
Entry	Amide	Amine	$[\text{Fe}(\text{CO})_5]$ Yield [%]	$[\text{Fe}_3(\text{CO})_{12}]$ Yield [%]
1	1a	2a	94	73
2	1b	2b	69	68
3	1c	2c	81	81
4	1d	2d	82	93
5	1e	2e	78	90
6	1f	2f	77	95
7	1g	2g	79	94
8	1h	2h	–	84

[a] All reactions were carried out using carboxamide **1** (1.0 mmol), TMDS (2.2 mmol, Si–H = 4.4 mmol), and iron catalyst (0.1 mmol) in toluene (0.5 mL) at ambient temperature under irradiation with a 400 W high-pressure mercury lamp for 9 h.

amides; the reactions proceeded successfully in both cases, affording their corresponding amines in good to high yields. As is the case for the corresponding ruthenium and platinum-catalyzed hydrosilane reductions of carboxamides, which have other reducible carbonyl groups, the amide group in substrate **1g** was selectively reduced to give amino ester **2g** as a single product (Table 1, entry 7; Table 2, entry 7). Reductive dehalogenation was not observed in the reactions of *p*-chlorobromobenzamides and *p*-bromobenzamides (Table 1, entries 5 and 6; Table 2, entries 5 and 6). However, in the thermal reduction of benzyl chloride **1h**, a substantial amount of the dehalogenated side-product was observed; [4-(chloromethyl)phenyl]-4-morpholinylmethanone was converted into a 7:3 mixture of 4-[(4-methyl)phenyl]methylmorpholine and 4-[(4-chloromethyl)phenyl]methylmorpholine (**2h**; Table 1, Entry 8). Interestingly, in the photoassisted reaction of **1h**, this side reaction was effectively suppressed to give **2h**

in 84 % isolated yield (Table 2, entry 8). The thermal reductions of *N,N*-dimethyl-*p*-cyanobenzamide with either $[\text{Fe}(\text{CO})_5]$ or $[\text{Fe}_3(\text{CO})_{12}]$ were slow, even at 100 °C; after 24 h, the desired cyanoamine was formed in 42 % and 37 % yield, respectively. In the attempted reduction of the keto amide, *N*-benzyl-*N*-methyl-*p*-acetylbenzamide, competitive reduction of the keto group with the amide moiety gives a mixture of compounds.

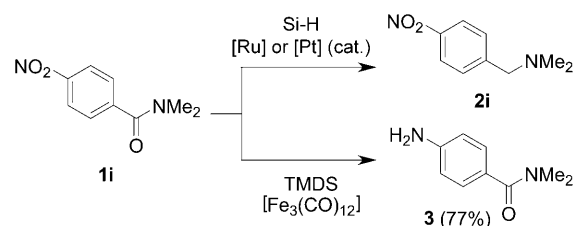
Removal of the catalyst^[8] and silicon residues can be performed in both the iron-catalyzed thermal and photoassisted systems (Scheme 2), in a similar way to the ruthe-



Scheme 2. Iron-catalyzed reduction of **1a** with PMHS.

nium- and platinum-catalyzed reductions of carboxamides with PMHS^[3c,d,4]. Therefore, amide **1a** (1 mmol) was stirred with PMHS (Si–H = 4.4 equiv) in the presence of $[\text{Fe}_3(\text{CO})_{12}]$ (10 mol %), in toluene at 100 °C. After 30 min, the homogeneous solution had gelled; the gel was left for 24 h before being washed with ether to afford a transparent, slightly brown-colored solution, which contained the corresponding amine **2a** and a dark brown solid. The pure product was obtained in 87 % yield, following short-path alumina chromatography (for experimental details, see the Supporting Information).

It should be noted that a striking difference in reactivity for the reduction of nitro group^[9] was observed between the present iron-catalyzed process and those catalyzed by ruthenium or platinum compounds. *N,N*-dimethyl-*p*-nitrobenzamide (**1i**) was subjected to thermal reduction with a large amount of TMDS (Si–H = 10 equiv to **1i**) in the presence of $[\text{Fe}_3(\text{CO})_{12}]$ (10 mol %) at 100 °C. Complete consumption of **1i** had occurred after 24 h, and *N,N*-dimethyl-*p*-aminobenzamide (**3**) was obtained as a single product in 77 % isolated yield (Scheme 3). We had previously reported the selective reduction of the amide moiety of **1i** to, *p*-(*N,N*-dimethylamino)methylnitrobenzene (**2i**) using the platinum catalyst



Scheme 3. Silane reduction of **1i** catalyzed by ruthenium, platinum, and iron catalysts.

$\text{H}_2\text{PtCl}_6 \cdot 6\text{H}_2\text{O}$,^[4b] similarly, the reaction of **1i** with $[(\mu_3, \eta^2, \eta^3, \eta^5\text{-acenaphthylene})\text{Ru}_3(\text{CO})_{12}]$ afforded **2i** in quantitative yield (Scheme 3). These results suggest that $\text{Fe}_3(\text{CO})_{12}$ has a special reactivity towards the reduction of the nitro group using TMDS as a reducing agent, which is not observed in standard platinum or ruthenium catalysis.^[9,10]

The reduction of other nitroarenes with TMDS also proceeded in the presence of $[\text{Fe}_3(\text{CO})_{12}]$ in good to high yields (73–93%; Table 3). The reaction of *p*-nitroanisole (**4a**, 1 mmol) with TMDS (Si–H = 10 equiv) in the presence of $[\text{Fe}_3(\text{CO})_{12}]$ (10 mol%) at 100°C for 24 h afforded *p*-aminoanisole (**5a**) in 93% yield (Table 3, entry 1). Catalytic silane reduction of halogenated nitrobenzene derivatives (**4b–d**) was also achieved with high chemoselectivity. Selective reduction of the nitro group occurred without substitution of the Cl, Br, or I moiety with a hydride atom (Table 3, entries 2–4).

Table 3: $[\text{Fe}_3(\text{CO})_{12}]$ -catalyzed reduction of nitroarenes with TMDS.^[a]

Entry	Substrate	Product	Yield [%]
1	4a : R = OMe	5a : R = OMe	93
2	4b : R = Cl	5b : R = Cl	73
3	4c : R = Br	5c : R = Br	75
4	4d : R = I	5d : R = I	93

[a] All reactions were carried out using nitroarene **4** (1.0 mmol), TMDS (5 mmol, Si–H = 10 mmol), and $[\text{Fe}_3(\text{CO})_{12}]$ (0.03 mmol, 10 mol%) in toluene (0.5 mL) at 100°C for 24 h.

Further explanation is required for why reduction of the amide group was not followed by the reduction of the nitro group in the iron-catalyzed reaction of **1i** with an excess amount of TMDS. We have previously reported the ruthenium-catalyzed amide-selective reduction of keto amides and amido esters using hydrosilanes.^[3e] In these reactions, the amine products formed in situ sometimes decrease the reactivity of the catalyst towards ketones and esters without retarding the rate of reduction of amides; that is, amines act as a functional-group-selective poison for the catalyst. In the present catalytic system, addition of *p*-methoxyaniline (**5a**) to the reaction of **1d** with TMDS in the presence of $[\text{Fe}_3(\text{CO})_{12}]$ led to a substantial retardation of the rate of reaction. Although further experiments, including isolation of the iron intermediates, are required for elucidation of the mechanism, it is likely that the aniline derivative formed by iron-catalyzed reduction of the nitroarene contributes to poisoning the catalytic activity of the iron complex towards the amide group.

In summary, $[\text{Fe}(\text{CO})_5]$ and $[\text{Fe}_3(\text{CO})_{12}]$ are useful catalysts for the thermal and photoassisted reductions of tertiary amides to tertiary amines using TMDS and PMHS as reducing agents. Importantly, the photoassisted reaction promotes the reduction at room temperature. Although both the thermal and photoassisted reactions require larger amount of the catalysts than the corresponding reactions catalyzed by platinum or ruthenium compounds, it is beneficial that environmentally benign iron is used as the catalyst. Particularly noteworthy is the iron-catalyzed selective reduc-

tion of nitroarenes to anilines using TMDS in the presence of an amide group, which was not observed in the catalysis by platinum or ruthenium compounds. This reaction is the first example of selectivity towards the nitro group, with the reduction of the nitro group proceeding whilst the amide group remains intact. We are currently investigating the mechanism of this unique selectivity.

Experimental Section

Thermal reduction of carboxamides with TMDS: The amide **1** (1.0 mmol) and TMDS (390 μL , 2.2 mmol) were dissolved in toluene (0.5 mL), and the iron carbonyl complex (10 mol% Fe; 19 mg for $[\text{Fe}(\text{CO})_5]$, 17 mg for $[\text{Fe}_3(\text{CO})_{12}]$) was added to this solution. The color of the initial solution (yellow for $[\text{Fe}(\text{CO})_5]$ and dark green for $[\text{Fe}_3(\text{CO})_{12}]$) gradually became purple within 30 min, then turned to dark brown after 1 h. After the resulting mixture was stirred at 100°C for 24 h, and the solvent was removed under reduced pressure. The residue was dissolved in diethyl ether, and the solution was passed through a pad of Florisil to remove the residual iron species. After removal of the solvent, purification of the residue by alumina column chromatography (hexanes/ ethyl acetate = 5:1) gave the amine product.

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