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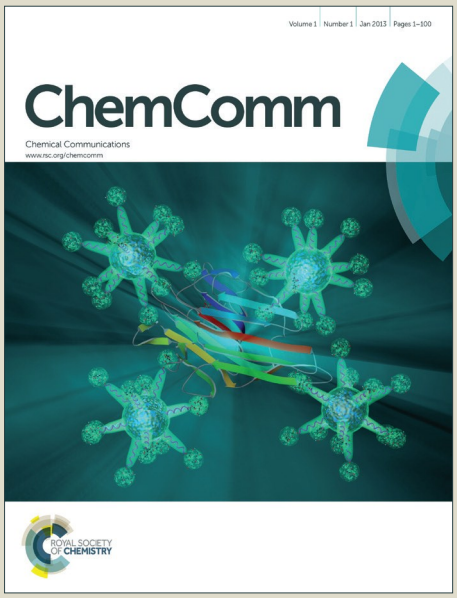

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Unprecedented Iron-Catalyzed Selective Hydrogenation of Activated Amides to Amines and Alcohols

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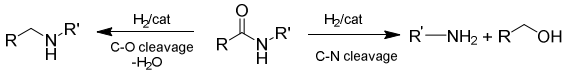
The first example of hydrogenation of amides homogeneously catalyzed by an earth-abundant metal complex is reported. The reaction is catalyzed by iron PNP pincer complexes. A wide range of secondary and tertiary *N*-substituted 2,2,2-trifluoroacetamides were hydrogenated to form amines and trifluoroethanol.

The amide bond constitutes an important building block, ubiquitous in chemistry and biology, making possible to realize compounds such as peptides and synthetic polymers.[1] The pervasive nature of this functional group can be attributed to its relative chemical inertness and bond strength made possible due to the amide-imide tautomerization. Cleavage of the amide bond, selectively via either C-N or the C-O bonds by an atom-economical catalytic hydrogenation process is a desirable transformation in organic chemistry (Scheme 1).[2]



Scheme 1 Possible pathways of amide hydrogenation.

Typically, stoichiometric metal hydride reagents, boranes or silanes are routinely employed to reduce amides in industrial scale operations, generating large quantities of toxic waste.[3] Focusing on a catalytic hydrogenation alternative, several heterogeneous systems starting from the well-known Adkins copper-chromite catalysts, Ni, PtO_2, Cu, bimetallic catalysts (Rh-Re, Rh/Mo, Ru/Re, Pt-Re/TiO_2 and recently Pt/Re/graphite, Re/TiO_2 have been reported[4] suffering from harsh reaction condition (high temperature and pressure) and poor selectivity. Interesting homogenous catalysts for amide hydrogenation based on $Ru(acac)_3$/triphos were reported by Cole Hamilton and coworkers.[5] However, these catalytic systems are mainly aimed at C-O hydrogenolysis of the carbonyl functionality to form amines, which is of significant importance by itself (Scheme 1).

The selective direct homogenous hydrogenation of amides to primary amines and alcohols by a metal (ruthenium) complex was first reported by our group.[6] The chemoselective cleavage of the C-N bond in preference to the C-O bond with no waste generation render this methodology attractive. The reaction mechanism was suggested to proceed *via* a bifunctional mode of activation by a reversible aromatization-dearomatization sequence involving pyridine-based pincer ligands. Several subsequent reports of selective C-N bond hydrogenation of amides mainly by homogenous precious metal catalysts were reported by the groups of Ikariya,[7] Saito,[8] Bergens,[9] Mashima[10] and Beller.[11] Nevertheless, it is highly desirable to develop selective homogeneous catalysts based on cheap and abundant first row base metals for this difficult and important transformation.[12]

Iron pincer catalysts have been successfully applied in homogenous hydrogenation of ketones, carbon dioxide, alkynes, esters and nitriles by several groups, including ours.[13] However, to the best of our knowledge, homogeneous hydrogenation of amides catalyzed by base-metal complexes was not reported so far. Herein we report the first selective hydrogenation of activated amides to their corresponding amines and alcohols homogenously catalyzed by pincer iron complexes.

At the outset of our study we explored pyridyl-based PNP iron pincer catalysts [(*t*Bu-PNP)Fe(H)$_2$(CO)] (**1**), [(iPr-PNP)Fe(H)(BH$_4$)(CO)] (**2**) and [(iPr-PNP)Fe(H)(Br(CO)] (**3**) (Figure 1) developed in our group[13d,e,14] as potential candidates for hydrogenation of amides.

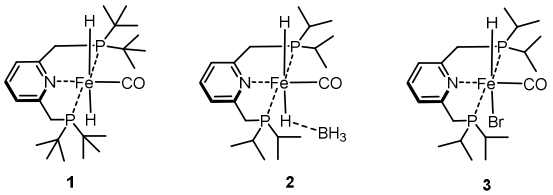


Fig. 1 Fe-based PNP pincer catalysts explored for amide hydrogenation.

While *N*-phenylacetamide and *N*-phenylbenzamide did not undergo hydrogenation using catalyst **1** (10 mol%) at various conditions of temperature and H_2 pressure, selective hydrogenolysis of the C-N bond of activated amides was successful. Encouragingly, employing 2,2,2-trifluoro-*N*-phenylacetamide and **1** (10 mol%) under 60 bar H_2 at 140 °C in the presence of 10 mol% of KO*t*Bu in dioxane as the

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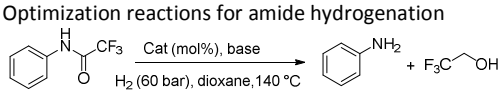
solvent, resulted in 34% conversion after 36 h to trifluoroethanol and aniline with no trace of the carbonyl-reduced *sec*-amine (Table 1, entry 1). The products were analyzed by GC-MS and $^{1}H/^{19}F$ NMR. Next, we have examined the possibility of hydrogenation of 2,2,2-trifluoro-*N*-phenylacetamide using 10 mol% of [(*t*BuPNP)$FeBr_2$], KOtBu (10 mol%) and $NaHBEt_3$ (10 mol%), following conditions which we have previously employed for hydrogenation of nitriles catalyzed by dihalo- pincer complexes of iron[13m] and cobalt;[15] however, no conversion was observed (Table 1, entry 2). Also, employing just $FeBr_2$ with $NaHBEt_3$ had no effect, negating chances of heterogeneous catalysis by this system (Table 1, entry 3). Having seen that the dihydide PNP complex **1** can indeed catalyze hydrogenation of activated amides, we then set out to optimize conditions for better catalytic performance.

Initially, we observed that better conversion (67%) was obtained upon increasing the amount of KO*t*Bu (30 mol%) with respect to the catalyst (10 mol%) (Table 1, entry 4). Also, the stronger base KHMDS (potassium hexamethyldisilazane) was found to be superior to KO*t*Bu. After 18 h, with 5.0 mol% of **1** and 15 mol% of KHMDS under the same conditions of pressure and temperature (60 bar H_2 and 140 °C.), 46% of the amide was hydrogenated to aniline and trifluoroethanol, whereas use of *t*BuOK as base under the same condition gave only 21% conversion (Table 1, entries 5 and 6). Decreasing either the pressure (Table 1, entries 7 and 8) or temperature (Table 1, entries 9-12) led to a drop in the efficiency of the catalysis. Dioxane was a better reaction solvent than THF or toluene (Table 1, entries 13 and 14).

Next, complexes **2** and **3** bearing iPr_2P groups were examined. To our delight, **2** and **3** showed a very significant rate enhancement in the hydrogenation of 2,2,2-trifluoro-*N*-phenylacetamide, the reactions being complete in 5 h with a catalyst loading of 5 mol% (**2** or **3**), 15 mol% KHMDS, 60 bar H_2 at 140 °C, while **1** showed 61% conversion after 36 h under similar reaction conditions (Table 1, entries 12, 15 and 16). It is likely that the higher steric crowding of the *t*-butyl groups as compared to isopropyl groups is the reason for the difference in activity. Catalysts **2** and **3** displayed comparable catalytic activity, with **3** being slightly better under exactly the same conditions (Table 1, entries 17 and 18). In fact, the hydrogenation of 2,2,2- trifluoro-*N*-phenylacetamide achieved completion with just 2 mol% of catalyst **3** after 12 h under 60 bar H_2 at 140 °C in dioxane solvent in the presence of 6 mol% KHMDS (Table 1, entry 19). Exploring the role of base, complexes **2** (5.0 mol%) and **3** (5.0 mol%) were used without the addition of the base. As expected the dihydride **2** was still active, showing 32% conversion after 24 h (Table 1, entry 20), while the hydridobromo complex **3** showed practically no conversion (Table 1, entry 21). This demonstrates the essential part of base in deprotonation of **3** to the followed by hydrogenation to the *trans*-dihydride complex. However, comparing the conversions using **2** as catalyst, with and without the base, it is clear that the base has an additional significant effect on the rate of the reaction, although its role is unclear at this stage. A control experiment in the absence of H_2 with a loading of 2 mol% catalyst **3**, 6 mol% KHMDS at 140 °C using dioxane as solvent did not show any conversion of 2,2,2-trifluor-*N*-phenylacetamide after 7 h, as revealed by the GC-MS analysis, indicating that base attack on the amide to generate aniline does not occur under the reaction conditions (Table 1, entry 22).

Table 1 Optimization reactions for amide hydrogenation



Entry[a]	Cat (mol%)	Base (mol%)	Time (h)	Conv[b] (%)	Yield[b] (%)
1	**1**(10)	tBuOK (10)	36	34	34
2[c]	**1**(10)	tBuOK (10)	36	-	-
3[d]	**1**(10)	-	36	-	-
4	**1**(10)	tBuOK (30)	36	67	67
5	**1**(5)	tBuOK (15)	18	21	21
6	**1**(5)	KHMDS (15)	18	46	46
7[e]	**1**(5)	KHMDS (15)	36	6	6
8[f]	**1**(5)	KHMDS (15)	36	35	35
9[g]	**1**(5)	KHMDS (15)	36	4	4
10[h]	**1**(5)	KHMDS (15)	36	14	14
11[i]	**1**(5)	KHMDS (15)	36	36	36
12[j]	**1**(5)	KHMDS (15)	36	61	61
13[k]	**1**(5)	KHMDS (15)	36	45	45
14[l]	**1**(5)	KHMDS (15)	36	39	39
15	**2**(5)	KHMDS (15)	5	99	99
16	**3**(5)	KHMDS (15)	5	99	99
17	**2**(2)	KHMDS (6)	5	29	29
18	**3**(2)	KHMDS (6)	5	33	33
19	**3**(2)	KHMDS (6)	12	99	99
20	**2**(5)	-	24	32	32
21	**3**(5)	-	24	-	-
22[m]	**3**(2)	KHMDS (6)	7	-	-

[a]Conditions: amide (0.5 mmol), catalyst (10-2 mol%), base and dry 1,4-dioxane (1.5 mL), heated in an autoclave at 140 °C bath temperature under 60 bar H_2. [b]yields and conversions determined by GC-MS analysis and yield based on aniline. [c]10 mol% (tBuPNP)$FeBr_2$ was used as catalyst and 10 mol% $NaHBEt_3$ as hydride source. [d]10 mol% $FeBr_2$ and 10 mol% $NaHBEt_3$ was used. [e]10 bar H_2. [f]30 bar H_2. [g]RT [h]60 °C [i]100 °C [j]140°C. [k]THF used as solvent [l]toluene used as solvent. [m]The reaction was carried out in a pressure tube in the absence of H_2.

Considering the fact that complexes **2** and **3** have comparable activities, we chose to use complex **3** for further catalytic examination due to is easier preparation. Employing complex **3** (2.0 mol%), KHMDS (6 mol%), H_2 (60 bar) and 140 °C we have examined the substrate scope of this reaction using various substituted 2,2,2-trifluoro-*N*-phenylacetamides. The electronic nature of the arene seemed to have little influence on the reactivity. 2,2,2-trifluoro-N-(4-fluorophenyl)-acetamide, bearing a fluoro substituent at the para position was completely hydrogenated in 12 h (Table 2, entry 1), and complete selective hydrogenation was also observed with the isopropyl- substituted 2,2,2-trifluoro-N-(4-isopropylphenyl)-acetamide (Table 2, entry 2), using a loading of only 2 mol% complex **3** in the presence of 6 mol% KHMDS. The substrate 2,2,2-trifluoro-(4-N,N-dimethyphenyl)-acetamide showed 58% conversion (Table 2, entry 3) after 12 h, while the amide with a *p*-nitro substituent (Table 2, entry 4) showed only 25% conversion after 24 h. The reason for the retardation effect by the nitro group is not clear at this stage. Initial evaluation of $RNHCOCF_3$ (R= alkyl, cycloalkyl) substrates showed very low conversions at 2.0 mol% of complex **3** at the end of 24 h. Better conversion was observed with a loading of 5.0 mol% catalyst and longer reaction time (36 h). Methyl (26%) and long chain aliphatic (23%) and cyclohexyl (35%) substituted trifluoroacetamides showed moderate conversions

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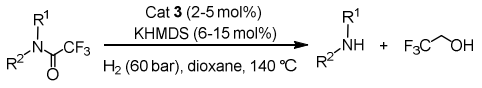
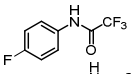
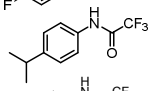
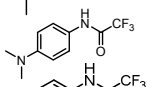
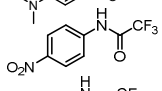
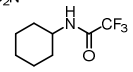
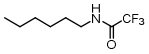
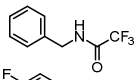
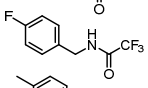
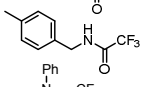
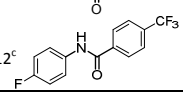
Table 2 Hydrogenation of activated amides catalyzed by **3**[a]



Entry	Substrate	Mol%	Time (h)	Conv (%)[b]	Products[b] HO CF3 (%)	Products[b] Amine (%)
1		2	12	99	99	*p*-F-aniline (99)
2		2	12	99	99	Isopropyl aniline (99)
3		2	12	58	52	*NN*-Dimethylaniline (58)
4		2	24	25	25	*p*-Nitroaniline (25)
5		5	36	35	36	Cyclohexyl amine (34)
6		5	36	23	23	Hexylamine (22)
7		5	35	26	26	Methylamine (undetected)
8		5	36	58	44	Benzylamine (58)
9		5	36	62	61	*p*-Fluoro benzylamine (62)
10		5	36	46	42	*p*-Methylbenzl amine (46)
11		5	36	99	99	Diphenylamine (99%)
12[c]		5	36	48	45	Fluoroaniline (47)

[a]Unless and otherwise stated, reaction conditions were 2-5 mol% catalyst **3**, 3 equiv. KHMDS relative to catalyst, 60 bar H_2, 140 °C and 1,4-dioxane as solvent. [b]conversions and amine yields were determined by GC using mesitylene as internal standard and TFE yield is based on ^{19}F NMR. [c]trifluoromethylbenzylalcohol was obtained as alcohol and quantified by GC.

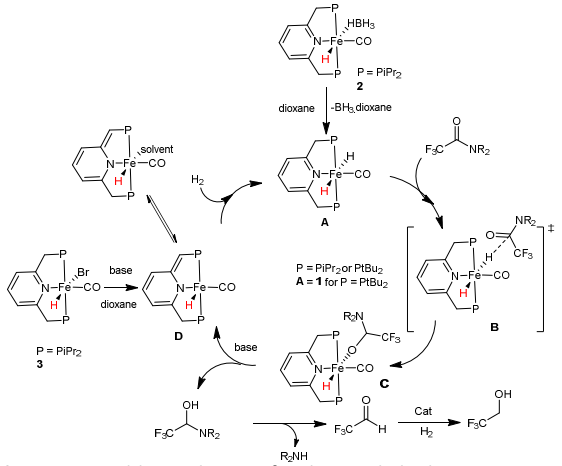
(Table 2, entries 5-7). Various 2,2,2,-trifluoroacetamides bearing *para* substituted benzyl groups (N-benzyl-2,2,2-trifluoroacetamide (58%), 2,2,2-trifluoro-N-(4-fluorobenzyl)acetamide (62%) and 2,2,2-trifluoro-N-(4-methylbenzyl)acetamide (46%) showed improved yields compared to aliphatic substrates (Table 2, entries 8-10).

The hydrogenation reaction is not limited to secondary amides. The tertiary amide 2,2,2-trifluoro-N,N-diphenylacetamide which has a relatively low C-N bond dissociation energy underwent quantitative conversion (99%) to diphenylamine and trifluoroethanol (Table 2, entry 11). In order to examine the efficacy of the catalyst beyond the trifluoracetamide substrates, we tested activated substrates with substituted phenyl substituents attached on the carbonyl carbon and the nitrogen. Encouragingly, N-(4-fluorophenyl)-4-(trifluoromethyl)benzamide showed 48% conversion to corresponding p-fluoraniline (47%) and p-trifluormethyl benzyl alcohol (Table 2, entry 12). However, activated primary amine substates such as 2,3,4,5,6-pentafluorobenzamide did not show any conversion after 36 h.

We believe that the mechanism of the hydrogenation of activated amides catalyzed by complexes **1**-**3** reported here is analogous to the mechanism previously suggested by us for the hydrogenation of trifluoroacetic esters.[13f] As observed in that case, complex **1** does not react with excess of KO*t*Bu, suggesting that a dearomatized anionic iron dihydride complex is not involved in the catalytic cycle.

In addition although complex **1** does not react with 2,2,2-trifluoro-N-phenylacetamide at room temperature in 1, 4-dioxane, possibly due to steric reasons, complex **2** reacted with 3 equivalents of 2,2,2-trifluoro-*N*-phenylacetamide at room temperature in dioxane as shown by the appearance of a triplet hydride signal at -18.4 ppm, upfield shift in comparision to **2**, and a ^{31}P NMR signal at δ = 88 ppm (see supporting information). This is very likely intermediate **C** (Scheme 2). A reported iron complex very closely related to **C** (P=iPr_2P), bearing a diphenylmethylalkoxide ligand trans to H instead of the N-phenylalkoxide ligand in **C**, gives rise to very similar chemical shifts of δ = 90.01 and -19.94 for ^{31}P- and ^{1}HNMR, respectively.[13d] A broad B-H signal at δ = -5.7 ppm was also observed, which might indicate BH_3 coordinated to solvent or excess substrate (see Supporting Information).

Based on the aforementioned observation and on the basis of precedents regarding the non-innocent nature of the ligand,[12d,16] a possible mechanism involving metal-ligand cooperation for the hydrogenation of activated amides catalyzed by complexes **1**-**3** is depicted in Scheme 2.



Scheme 2 Possible mechanism for the amide hydrogenation.

As shown in Scheme 2, the *trans* dihydride complex **1** is very likely an actual intermediate. In case of complex **2**, **A** is generated by removal of BH_3 by adduct formation with dioxane and for **3**, the base leads to dehydrobrominaton followed by H_2 addition via metal ligand cooperation (MLC)[16] generating the *trans* dihydride intermediate **A**. Outer-sphere attack of the carbonyl carbon atom of the amide on the Fe-H moiety of **A** via transition state **B** leads to the alkoxide intermediate **C**, which we have very likely observed, as described above. This can be followed by elimination of a hemiaminal through metal–ligand cooperation (MLC) generating the dearomatized intermediate **D**, which may be facilitated by the presence of a catalytic amount of base. The dihydride **A** is then regenerated by addition of H_2 to **D** through MLC. The hemiaminal is in equilibrium with the product amine and trifluoroacetaldehyde, the latter being readily hydrogenated via a similar cycle to give TFE.[17] The outer-sphere nucleophilic attack of the hydride on the

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amide is obviously facilitated by the electron-deficient character of the carbonyl carbon atom in the trifluoroacetamides.

In conclusion, we have demonstrated for the first time catalytic hydrogenation of a family of activated amides to alcohols and amines by applying pincer complexes based on an earth-abundant, low toxicity, first row transition metal. Thus, the iron pincer complexes [(iPr-PNP)Fe(H)(BH_4)(CO)] (**2**) [(iPr-PNP)Fe(H)(Br(CO)] (**3**) are effective pre-catalysts for the selective hydrogenation of a wide range of N-substituted 2,2,2,-trifluoroacetamides and N-(4-fluorophenyl)-4-(trifluoromethyl)benzamide to trifluoroalcohol and the corresponding amines. A plausible mechanism has been proposed. Further investigation regarding the extension of the scope of the reaction, and elucidation of a detailed mechanism is currently underway in our group.

This research was supported by the MINERVA Foundation, by the Israel Science Foundation, and by the Peter Cohn Catalysis Research Fund. D.M. holds the Israel Matz Professorial Chair of Organic Chemistry. J. A. G. and S. C. thank the Swiss Friends of the Weizmann Institute of Science for generous postdoctoral fellowships.

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