

Iron-Catalyzed Hydrogenation of Amides to Alcohols and Amines

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Supporting Information

ABSTRACT: This article describes the iron-catalyzed hydrogenation of unactivated amides. Under the optimal conditions, a PNP-ligated Fe catalyst affords 25-300 turnovers of products derived from C–N bond cleavage. This reaction displays a broad substrate scope, including a variety of 2° and 3° amide substrates. The reaction progress of *N*,*N*dimethylformamide hydrogenation has been monitored in situ using Raman spectroscopy. This technique enables direct



comparison of the relative activity of the Fe-PNP catalyst to that of its Ru analogue. Under otherwise identical conditions, the Fe and Ru catalysts exhibit rates within a factor of 2.

KEYWORDS: iron catalysis, amide hydrogenation, kinetics, bifunctional catalysis, pincer complexes, homogeneous catalysis

INTRODUCTION

The hydrogenation of carboxylic acid derivatives represents an atom-economical reduction process with potential applications in both industrial and academic settings.^{1,2} The vast majority of homogeneous catalysts for these transformations contain second- or third-row transition metals (e.g., Ru, Rh, Pd, Pt).^{3–5} There are many fewer examples of the hydrogenation of carboxylic acid derivatives using earth-abundant first-row metal catalysts.^{6,7} Recent efforts toward this goal have focused on Febased catalysts for the hydrogenation of aldehydes,^{8–11} ketones,^{8–16} and esters.^{17–21} However, analogous Fe-catalyzed hydrogenations of less electrophilic amide derivatives remain largely unexplored.^{22,23} These weakly electrophilic substrates are expected to be particularly challenging for Fe catalysts, due to the anticipated lower hydricity of first-row metal hydrides in comparison to their second- and third-row counterparts.^{24,25}

Classical methods for amide hydrogenation require the use of stoichiometric reductants such as lithium aluminum hydride (LAH) or samarium iodide (SmI_2) .³ These reductions occur with either C–O or C–N bond scission to yield distinct sets of products (Scheme 1).³ Typically, LAH yields the C–O bond cleavage product,^{26,27} while SmI₂ is selective for C–N bond scission.²⁸

The transition-metal-catalyzed hydrogenation of amides represents a mild alterative to LAH- or SmI₂-mediated processes. Recent reports have described homogeneous Ru catalysts for this transformation^{29–43} and have demonstrated that selective C–N cleavage can be achieved by an appropriate





choice of supporting ligands. Scheme 2a shows one of the mildest and most general reported examples, involving catalyst Ru-1.²⁹

We sought to develop an analogous Fe-catalyzed hydrogenation of unactivated amides and to conduct a detailed

Scheme 2. Examples of Ru- and Fe-Catalyzed Amide Hydrogenation

a) Ru-catalyzed hydrogenation of amides (Milstein)

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$$\begin{array}{c} O \\ R^{1} \underbrace{\overset{1 \text{ mol } \% \text{ Ru-1}}{\underset{R}{}^{1} \underbrace{\underset{R}{}^{1} \underbrace{\underset{$$

b) Fe-catalyzed hydrogenation of activated amides (Milstein)

$$F_{3}C \xrightarrow{N,R} \xrightarrow{f_{3}C} \xrightarrow{H} H \xrightarrow{H} F_{3}C \xrightarrow{H} F_{3$$

c) Fe-catalyzed hydrogenation of unactivated amides (this work)





 Received:
 May 23, 2016

 Revised:
 August 15, 2016



investigation of catalysts, conditions, and scope. Furthermore, we sought to benchmark the best Fe catalyst to its second-row congener. At the start of our investigation, there were no reported examples of homogeneous Fe-catalyzed amide hydrogenation. Two very recent papers have described amide hydrogenation to yield C-N bond scission products using catalysts Fe-1²² and Fe-2c.²³ However, these methods suffer from a limited substrate scope,^{22,23} modest TONs (up to 50),^{22,23} and/or forcing conditions (140 °C, 60 bar of H₂; Scheme 2b).²² We demonstrate herein that Fe-PNP^{Cy}-BH₄ (Fe-2a) is an effective catalyst for the hydrogenation of unactivated amides. These transformations selectively afford C-N cleavage products, and many substrates can be hydrogenated within 3 h at 110 °C. Further, we demonstrate that Fe-2a catalyzes this reaction with an initial rate that is within a factor of 2 of that for its Ru analogue (Ru-2a), under otherwise identical conditions.

RESULTS AND DISCUSSION

On the basis of our ongoing interest in the reduction of C-1 starting materials,^{44–47} we initially focused on the Fe-catalyzed hydrogenation of N,N-dimethylformamide (DMF). Fe-2 derivatives were selected as catalysts on the basis of literature precedent for the use of related Ru and Fe complexes for various C=O hydrogenation reactions.^{17,18,21,46,48-53} We first examined the hydrogenation of DMF and N-formylmorpholine using 1 mol % of Fe-2a, 25 mol % of K₃PO₄, and 50 bar of H₂ at 130 °C (Tables S2 and S3 in the Supporting Information).⁵ In our initial trials, this reaction proved to be highly irreproducible, with yields fluctuating between 0 and 99% over >10 runs. After an exhaustive investigation, we identified the purity of the H_2 as the origin of the poor reproducibility. This issue was resolved by changing from ultrahigh-purity H₂ (99.999%) to research grade H₂ (99.9999%), which resulted in consistent and reproducible results (variations in yield were typically $\pm 5\%$; see the Supporting Information for complete details).

Using research grade H_2 (50 bar) and 0.33 mol % of Fe-2a at 130 °C, we obtained a 63% yield of CH₃OH after 3 h, with high (>99%) selectivity for C–N cleavage (Table 1, entry 1). The addition of base is known to promote metal-catalyzed hydrogenations,^{55–58} and K₃PO₄ proved particularly effective in a related Ru-catalyzed hydrogenation of DMF.⁴⁶ Similarly, the addition of K₃PO₄ (25 equiv relative to Fe) to the Fe-2a-catalyzed hydrogenation of DMF under otherwise identical conditions boosted the yield to >99% (entry 2). Further optimization revealed that the base loading, temperature, and H₂ pressure can be decreased while maintaining similar yield (entries 3–6). A survey of organic and inorganic bases revealed K₃PO₄ as the optimal base for DMF hydrogenation.⁵⁹ Overall, under the optimized conditions (0.33 mol % of Fe-2a, 1.66 mol % of K₃PO₄, 20 bar of H₂, 110 °C, 3 h), the reaction proceeded in 96% yield (288 turnovers, entry 6).

The alternative Fe catalysts Fe-2b (entry 12) and Fe-2c (entry 13) afforded significantly lower yields under otherwise identical conditions (63% and 2%, respectively). These results are particularly noteworthy, since Beller has shown that Fe-2c has higher activity than Fe-2a for ester hydrogenation.^{21,60} Furthermore, Fe-2c has recently been disclosed for the hydrogenation for other amide substrates (but not DMF).²³ Finally, by decreasing the catalyst loading of Fe-2a to 0.038 mol % and increasing the H₂ pressure to 60 bar, we obtained 1080 turnover numbers over 12 h (eq 1).

Table 1. Optimization of Fe-2-Catalyzed DMF Hydrogenation^a

		0.33 mol % [Fe K ₃ PO ₄ , H ₂ Me ₂ THF, 3 h	e] → Me	,H + ,N Me +	н н _Н × _{он}	
entry	[Fe]	base (mol %)	temp (°C)	H ₂ (bar)	yield (%)	TON
1	Fe-2a	none	130	50	63	189
2	Fe-2a	K_3PO_4 (8.33)	130	50	>99	300
3	Fe-2a	K ₃ PO ₄ (1.66)	130	50	>99	300
4	Fe-2a	K ₃ PO ₄ (1.66)	110	50	>99	300
5	Fe-2a	none	110	20	59	177
6	Fe-2a	K_3PO_4 (1.66)	110	20	96	288
7	Fe-2a	NEt ₃ (1.66)	110	20	78	244
8	Fe-2a	K_2CO_3 (1.66)	110	20	47	140
9	Fe-2a	NaOEt (1.66)	110	20	8	23
10	Fe-2a	KO ^t Bu (1.66)	110	20	7	20
11	Fe-2a	KHMDS (1.66)	110	20	4	11
12	Fe-2b	K ₃ PO ₄ (1.66)	110	20	63	189
13	Fe-2c	K ₃ PO ₄ (1.66)	110	20	2	7

^{*a*}Conditions: 3.0 mmol of DMF, 10 μ mol of [Fe], 2 mL of THF, 3 h in a 45 mL high-pressure Parr vessel with research grade H₂. Yields and TONs are based on CH₃OH and were determined by ¹H NMR spectroscopy.



We next examined the scope of Fe-2a-catalyzed hydrogenation of formamides (Table 2). The tertiary alkyl and aryl formamides N-formylmorpholine, and N,N-diphenylformamide underwent hydrogenation in quantitative yield and with >95% selectivity for C-N cleavage (entries 1 and 2). Secondary aryl formamides were also viable substrates, affording 57-95% yields of the C-N cleavage products under the standard conditions (entries 3-7). The highest yields were obtained with substrates bearing electron-neutral or -withdrawing substituents on the aromatic ring (compare entry 4 to entries 3 and 6). Substitution at ortho sites on the arene ring was welltolerated (entries 5 and 7). Aryl bromides were compatible with the reaction conditions, and no dehalogenation products were detected. Lower yields were observed with 2°-alkyl and 1°formamides (entries 8 and 9). These reactivity trends are comparable to those reported in related Ru-catalyzed amide hydrogenation reactions.^{37,38,61}

Alkyl- and aryl-substituted amides often required more forcing conditions in comparison to those for the formamides; however, after some reoptimization, they also underwent selective reduction in modest to high yields (Table 3). For example, *N*-phenyl- and *N*,*N*-diphenylacetamide both afforded quantitative conversion and high yields of ethanol and the corresponding amine at 110 °C with 30 bar of H₂ and 2 mol % of Fe-**2a** (entries 1 and 2). Notably, *N*-phenylacetamide was reported to be unreactive with catalyst Fe-1.²² Substituted benzamides also underwent high-yielding hydrogenation (entries 3–8), albeit at elevated temperature (130 °C), pressure (50 bar), and catalyst loading (4 mol %). Benzamides bearing electron-withdrawing *p*-F, *p*-CF₃, and *p*-CN substituents exhibited the highest reactivity (entries 6–8), while derivatives

Table 2. Scope of Formamide Substrates^a

$H \xrightarrow{N}{R^2} R^{1} \xrightarrow{1.66 \text{ mol } \% \text{ K}_3 \text{PO}_4} R^{1} \xrightarrow{20 \text{ bar } \text{H}_2} R^{1} \xrightarrow{\text{H}} R^{1} \xrightarrow{N}{R^2} R^{1} \xrightarrow{\text{H}} H \xrightarrow{\text{H}} H$								
Entry	Substrate	conversion	yield	TON				
1		>99%	>99% ^b	300				
2	$H \stackrel{O}{\longrightarrow} NPh_2$	>99%	99%	300				
3	H ↓ N.Ph	>99%	95%	300				
4	H H H OMe	69%	57%	207				
5	U N N N N N N N N N N N N N N N N N N N	>99%	94%	300				
6	H H H H	>99%	96%	300				
7	H H H	>99%	97%	300				
8	н Ц Н	12%	12% ^b	36				
9		1%	1% ^b	3				

0.22 mal 0/ Ea 2a

^{*a*}Conditions: 3 mmol of amide, 10 μ mol of Fe-**2a**, 50 μ mol of K₃PO₄, 2 mL of THF, 20 bar of H₂, 110 °C, 3 h. Yields are isolated yields of the amine product. Conversions (based on DMF) and TONs (based on CH₃OH) were determined by ¹H NMR spectroscopy. ^{*b*}Yield determined by ¹H NMR spectroscopy based on CH₃OH.

with electron-donating *p*-OMe or NMe₂ groups afforded <1% yield (entry 10 and the Supporting Information). In the case of *p*-CN-*N*,*N*-diphenylbenzamide (entry 8), both the amide and the cyano functional groups underwent hydrogenation.⁶² Fe-**2a** is also compatible with potentially coordinating pyridine functional groups (entry 9) and catalyzes the hydrogenation of trifluoromethyl amides under conditions significantly milder than those reported with Fe-**1** (entry 11).²² Overall, the substrate scope, catalyst loading, and TONs obtained with Fe-**2a** rival those of many Ru catalysts.^{33,37}

We next sought to compare the rate of amide hydrogenation with Fe-2a to that of its Ru analogue Ru-2a. This comparison was conducted by monitoring the hydrogenation of DMF via in situ Raman spectroscopy.⁶³⁻⁶⁵ As shown in Figure 1, the complete consumption of DMF required ~5.5 h with Fe-2a, while with Ru-2a the amide substrate was fully converted within ~3 h. Comparison of the initial reaction rates shows that the Ru catalyst is ~1.7-fold faster than the Fe catalyst. This result is

consistent with a very recent computational report demonstrating similar activation barriers for ester hydrogenation with M^{II} -PNP catalysts (M = Fe, Ru).^{25,66} These experimental and computational results are particularly noteworthy considering that previous studies have demonstrated orders of magnitude differences in the kinetic hydricity of first-row transition-metal hydrides versus their second-/third-row counterparts.⁶⁷

A plausible catalytic cycle for Fe-catalyzed amide hydrogenation is shown in Scheme 3. This mechanism is similar to those reported in the literature for carbonyl hydrogenation with related Ru and Fe catalysts.²⁵ In a catalyst initiation step, the loss of BH₃ from A leads to the active *trans*-dihydride complex **B**. The BH₃ is presumably captured by a Lewis base in solution (e.g., solvent, PO₄³⁻, etc.). Complex **B** then transfers a hydride and a proton to the amide substrate (step *a*) to yield a hemiaminal intermediate and **C**. Heterolytic cleavage of H₂ by **C** regenerates **B** (step *b*), while the hemiaminal intermediate extrudes the amine and concomitantly generates the aldehyde.

Table 3. Scope of Amide Substrates^a

	$1.66-20 \text{ mol } \% \text{ K}_3 \text{PO}_4$ O 20-50 bar Ha H						
	R^{3} $N^{.}R^{1}$ $THF, 110-$ R^{2} $3 h$	130 °C R ¹ N. F	R ² + R ³ OH				
Entry	Substrate	conversion	yield	TON			
1 ^{<i>b</i>}	O NPh H	>99%	88%	50			
2^b	O NPh ₂	>99%	96%	50			
3		38%	36%	9			
4	Ph NPh H	>99%	95%	25			
5		>99%	99%	25			
6	F NPh2	>99%	93%	25			
7	F ₃ C	>99%	94%	25			
8 ^c	NC NPh2	>99%	94%	25			
9	NPh ₂	>99%	95%	25			
10	MeO NPh2	<1%	<1%	<1			
11 ^d	F₃C ↓ NBn	44% ^d	44% ^d	120			

0.33-4 mol % Fe-2a

^{*a*}Conditions unless specified otherwise: 0.25 mmol of amide, 10 μ mol of Fe-**2a**, 50 μ mol of K₃PO₄, 2 mL of THF, 50 bar of H₂, 130 °C, 3 h. Yields are isolated yields of the amine product. Conversions (based on amide substrate) and TONs (based on ROH) were determined by ¹H NMR spectroscopy. ^{*b*}Conditions: 0.50 mmol of amide, 10 μ mol of Fe-**2a**, 50 μ mol of K₃PO₄, 2 mL of THF, 30 bar of H₂, 110 °C, 3 h. ^{*c*}The nitrile functional group was also hydrogenated. ^{*d*}Conditions: 3 mmol of amide, 10 μ mol of Fe-**2a**, 50 μ mol of K₃PO₄, 2 mL of THF, 20 bar of H₂, 110 °C, 3 h. Conversion was determined by ¹F NMR spectroscopy and yield by ¹H NMR spectroscopy based on 2,2,2-trifluoroethanol.

Finally, hydrogenation of the aldehyde by **B** (step *c*) yields the primary alcohol and re-forms **C**. Importantly, an exogeneous base is not necessary for this cycle to proceed; consistent with this, our results show that added base is not necessary to achieve efficient catalysis (Table 1, entry 5). We hypothesize that the enhanced TONs in the presence of relatively weak bases such as K_3PO_4 and NEt₃ are likely due to either base-promoted catalyst initiation (via sequestration of BH₃) and/or the base acting as a proton shuttle during reaction. The

ineffectiveness of strong bases (e.g., KO^tBu, KHMDS, KOEt; Table 1, entries 9-11) appears to be a result of their incompatibility with the substrate, DMF.⁶⁸

To gain additional mechanistic insights into this transformation, we monitored the reaction progress of the Fe-2acatalyzed DMF hydrogenation as a function of H₂ pressure via Raman spectroscopy. As shown in Figure 2, the reaction progress curves are nearly identical at 50 and 70 bar of H₂. In contrast, the reaction is significantly slower at 20 bar of H₂, and



Figure 1. Reaction progress of the hydrogenation of DMF with Fe-2a vs Ru-2a. Conditions: 10.5 mmol of amide, 35 μ mol of Fe-2a or Ru-2a, 175 μ mol of K₃PO₄, 7 mL of THF, 70 bar of H₂. The disappearance of DMF was monitored via the Raman peak at 865 cm⁻¹. Reactions were conducted in a high-pressure reactor fitted with a Raman probe, and the temperature was equilibrated to 110 °C (internal temperature) prior to data collection.

there appears to be an induction period at this lower pressure. While more detailed studies will be necessary to fully interpret these data, the preliminary results suggest that either the turnover-limiting step and/or the initiation rate change as a function of H_2 pressure.



Figure 2. Reaction progress of the hydrogenation of DMF with Fe-**2a** at 20, 50, and 70 bar of H₂. Conditions: 10.5 mmol of amide, 35 μ mol of Fe-**2a**, 175 μ mol of K₃PO₄, 7 mL of THF. The disappearance of DMF was monitored via the Raman peak at 865 cm⁻¹. Reactions were conducted in a high-pressure reactor fitted with a Raman probe, and the temperature was equilibrated to 110 °C (internal temperature) prior to data collection.

CONCLUSIONS

In summary, this article describes the development of an Fecatalyzed hydrogenation of unactivated amides to generate alcohols and amines. Under optimized conditions, this transformation affords TONs ranging from 25 to 300 and exhibits a broad scope. Turnover numbers as high as 1000 were observed for *N*,*N*-dimethylformamide hydrogenation. Kinetic

Scheme 3. Proposed Mechanism for the Fe-Catalyzed Hydrogenation of Amides



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experiments using in situ Raman spectroscopy demonstrate that the rate of amide hydrogenation with Fe-**2a** can approach that of its noble-metal Ru counterpart. Efforts to elucidate the mechanistic similarities/differences between the Fe and Ru catalysts in more detail as well as to design second-generation Fe catalysts with improved activity are underway in our laboratory and will be reported in due course.

ASSOCIATED CONTENT

S Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.6b01454.

Experimental details and procedures and time-course studies (PDF)

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by NSF under the CCI Center for Enabling New Technologies through Catalysis (CENTC) Phase II Renewal, CHE-1205189 as well as by the Danish National Research Foundation through the Carbon Dioxide Activation Center (CADIAC). N.M.R. thanks Rackham Graduate School for a Rackham Merit Fellowship. We acknowledge Professor Adam J. Matzger for assistance with Raman spectroscopy.

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(52) Fe-2b has been demonstrated for ester hydrogenation.^{17,18} Additionally, a very recent report demonstrated that Fe-2a is also effective for ester hydrogenation.²¹

(53) Fe-2a offers the additional advantages that it is straightforward to synthesize and exhibits high solubility in our reaction solvent (THF).

(54) These initial conditions were selected on the basis of our studies of DMF hydrogenation with a related Ru pincer catalyst.⁴⁶

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(59) The use of NaOEt, KO^tBu, and KHMDS resulted in poor mass balance, suggesting incompatibility between these bases and the DMF substrate.

(60) Catalyst Fe-2c has been reported for the hydrogenation of esters²¹ and, recently, a small subset of amides.²³ To confirm the activity of our samples of Fe-2c, we also performed the hydrogenation of methyl benzoate (using 1 mol % of Fe-2c and 30 bar of H₂ at 60 °C for 6 h) and benzanilide (using 4 mol % of Fe-2c, 20 mol % of K₃PO₄, and 50 bar of H₂ at 110 °C for 3 h). In our hands, these transformations afforded >99% yield (100 turnovers) and 70% yield (18 turnovers), respectively.

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