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Unprecedented Catalytic Hydrogenation of Urea Derivatives to Amines and Methanol**

*Ekambaram Balaraman, Yehoshoa Ben-David, and David Milstein**

Catalytic hydrogenation of polar bonds, in particular organic carbonyl groups, has captured considerable attention, because it provides environmentally benign approaches to synthetically important building blocks, such as alcohols and amines.[1] The ease of hydrogenation of carbonyl groups, in which hydride transfer to the carbonyl carbon is involved, generally corresponds to the electrophilicity of this carbon. The lower electrophilicity of the carbonyl group, as a result of resonance effects involving alkoxy or amido groups, makes hydrogenations of esters,[2] amides,[3] and even more so, carbonic acid derivatives, such as organic carbonates, carbamates and urea derivatives, very difficult (Figure 1). The common trend in the reactivity of polar carbonyl groups towards hydrogenation reactions is $RC(O)H > RC(O)R' \gg RC(O)OR' > RC(O)NR_2' \gg > ROC(O)OR' > ROC(O)NR_2' > R_2NC(O)N_2R'$,[3d] urea derivatives being the most challenging. Indeed, as far as we know, catalytic hydrogenation of urea derivatives has never been reported, be it under heterogeneous or homogeneous catalysis. In fact, alkyl urea compounds have been used as solvents in catalytic hydrogenation reactions. For example, rhodium-catalyzed hydrogenation of carbon monoxide to ethylene glycol under very high pressure ($p(H_2) = 200$ bar) and at elevated temperature (200 °C) using *N,N,N′,N′*-tetramethylurea (TMU) as an inert solvent was reported.[4] In addition, sugar-urea-salt melts were used as "green solvents" for Rh-catalyzed hydrogenation reactions and found to be sustainable reaction media.[5]

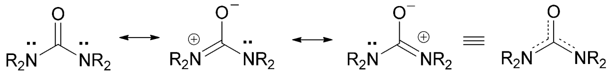

Figure 1. Resonance forms of urea derivatives.

Notably, alkyl and aryl urea compounds are readily synthesized from reactions of amines with CO_2 in the presence of various catalysts, such as 1,8-diazabicyclo-[5.4.0]undec-7-ene,[6] CsOH,[7] Cs_2CO_3,[8] Au/polymers,[9] [Bmim]OH[10] or KOH/PEG1000,[11] and by using ionic liquids, *N*-methylpyrrolidone, and supercritical carbon dioxide as solvents. Transition-metal-catalyzed synthesis of urea derivatives was also reported.[12] Recently, Zhao et al. reported the synthesis of dialkyl urea derivatives from CO_2 and amines in the absence of any catalysts, organic solvents, or other additives.[13] In this context, mild hydrogenation of urea derivatives to methanol is very attractive, as it would represent a mild, two-step hydrogenation of CO_2 to methanol, which is of intense current interest with regard to hydrogen storage and "methanol economy".[14,15] Direct, heterogeneously catalyzed hydrogenation of CO_2 to methanol requires harsh conditions of temperature and pressure and suffers from the formation of byproducts such as CO, hydrocarbons, and higher alcohols, making this approach difficult.[16] Moreover, the direct hydrogenation of urea derivatives to the corresponding amines and methanol can also provide an alternative approach for amine protection chemistry,[17] because amines can be protected as urea derivatives by treatment with nontoxic, abundant CO_2 under mild conditions.

We have developed several unique reactions catalyzed by tridentate PNN and PNP Ru(II) pincer complexes based on pyridine[2a,18–19] and acridine[20] backbones. These complexes show a new mode of metal–ligand cooperation based on ligand aromatization–dearomatization, which has led to a number of bond activation processes.[21] Recently, hydrogenation of amides[3c] to the corresponding alcohols and amines by selective cleavage of the C–N bond under homogeneous conditions, catalyzed by the bipyridine-based pincer complex **1** (Figure 2) was developed. An analogous NHC complex is effective in hydrogenation of nonactivated esters to the corresponding alcohols under mild conditions.[2f] Complex **1** effectively catalyzes also the novel hydrogenation of organic carbonates to alcohols, organic carbamates to methanol and amines, and alkyl formates to methanol and alcohols, which are of current interest with regard to mild stepwise CO_2 hydrogenation to methanol.[22]

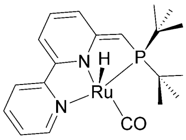

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Figure 2. Bipyridyl-based PNN Ru(II) pincer complex **1**.

Here we report the first example of catalytic hydrogenation of urea derivatives. Selective formation of methanol and the corresponding amines takes place by the double cleavage of the robust C–N bonds under mild, neutral

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[*] Dr. E. Balaraman, Y. Ben-David, Prof. D. Milstein
Department of Organic Chemistry
The Weizmann Institute of Science, 76100 Rehovot (Israel)
E-mail: david.milstein@weizmann.ac.il
Homepage: http://www.weizmann.ac.il/Organic_Chemistry/milstein.shtml

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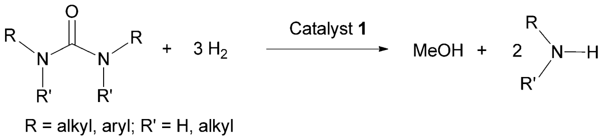
Supporting information, including the general procedure for the catalytic hydrogenation reactions and spectroscopic data for synthesized urea derivatives, for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201106612.

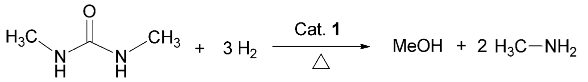


Scheme 1. Hydrogenation of urea derivatives to methanol and amines.

conditions and with no generation of waste, using catalyst **1** (Scheme 1).

1,3-Dimethylurea was selected as a benchmark substrate for the study of hydrogenation of alkyl ureas catalyzed by complex **1**. Treatment of 1,3-dimethylurea (1 mmol) and a catalytic amount of complex **1** (1 mol%) with H_2 (10 atm) at 110 °C in anhydrous THF resulted in 41% conversion of dimethylurea to yield methanol (35% by GC) and methylamine after 48 h (Table 1, entry 1). The gaseous amine was characterized by GC-MS of the gas phase of the reaction mixture and not quantified. A longer reaction time and higher hydrogen pressure resulted in improved conversion of dimethylurea and yield of methanol (Table 1, entries 2 and 3). Performing the same reaction under 13.6 atm of H_2 and 2 mol% of catalyst resulted in a 93% yield of methanol after 72 h (Table 1, entry 4).

Table 1: Hydrogenation of 1,3-dimethylurea to methanol and methylamine catalyzed by **1**.

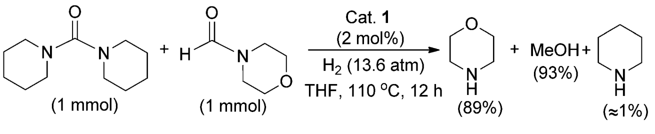


Entry	Catalyst **1** [mol%]	Reaction conditions[a]			
		$p(H_2)$ [atm]	t [h]	Conversion [%][b]	Yield of MeOH [%][b,c]
1	1	10	48	41	35
2	1	10	72	53	52
3	1	13.6	72	61	57
4	2	13.6	72	96	93

[a] Complex **1**, 1,3-dimethylurea (1 mmol), H_2, and anhydrous THF (2 mL) were heated in a Fischer–Porter tube (100 mL) at 110 °C (bath temperature) for the specified time. [b] Conversion of 1,3-dimethylurea and yields of methanol were determined by GC using *m*-xylene as an internal standard. [c] $MeNH_2$ was detected in the gas phase (as well as in liquid phase) by GC-MS and not quantified.

Various alkyl and aryl urea derivatives were subjected to hydrogenation at 13.6 atm of hydrogen (Table 2). Hydrogenation of 1,3-dihexylurea yielded methanol and 1-hexylamine in 83 and 87% yields, respectively, after 72 h (Table 2, entry 2). As expected, the activated urea, 1,3-bis(2-methoxyethyl)urea gave almost quantitative conversion to methanol and 2-methoxyethylamine upon hydrogenation (Table 2, entry 3). Dibenzylurea derivatives underwent hydrogenation in moderate yields (Table 2, entries 5–7), giving methanol, benzyl amines, as well as trace amounts of the corresponding benzyl formamides (detected by GC-MS). Fluoro-dibenzylurea did not undergo defluorination during the hydrogenation (Table 2, entry 7). The hydrogenation of 1,3-diarylurea derivatives proceeded very smoothly to yield methanol and the corresponding aniline derivatives (Table 2, entries 8 and 9). Thus, upon heating a THF solution of **1** (0.02 mmol) and 1,3-diphenylurea (1 mmol) at 110 °C under H_2 (12 atm), complete conversion took place to selectively form methanol and aniline in 90% and 95% yields, respectively (Table 2, entry 8). Performing the same reaction with a lower catalyst loading (1 mol% of **1**) gave moderate yields of methanol (63%) and aniline (69%). Even the more sterically hindered tetra-substituted urea derivatives were selectively hydrogenated to yield methanol and the corresponding secondary amines. Thus, heating a THF solution containing 1,1′,3,3′-tetramethylurea (1 mmol) and a catalytic amount of complex **1** (2 mol%) under hydrogen pressure (13.6 atm) at 110 °C for 72 h resulted in a 53% conversion of tetramethylurea (TMU) to methanol (46%) and *N,N′*-dimethylamine (Table 2, entry 10); the lower conversion is probably a result of steric reasons. In the case of bis(pentamethylene)urea, 63% yield of methanol, and 57% of piperidine (Table 2, entry 11) were obtained. Traces of the corresponding dialkyl formamides were also observed in these cases. Although moderate yields were obtained for the hydrogenation of tetra-substituted urea, these compounds have been used as inert polar solvents for hydrogenation reaction under very high hydrogen pressure, without undergoing hydrogenation.[4]

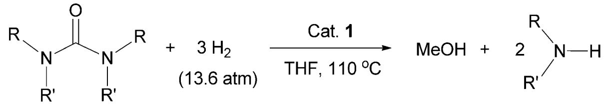
The observation of traces of formamides (Table 2, entries 5–6 and 10–11) suggests a stepwise hydrogenation reaction, in which a formamide along with one equivalent of amine is initially formed by the cleavage of a C–N bond, followed by fast hydrogenation of the formamide, which does not accumulate.[23] In support of faster hydrogenation of formamides as compared with the starting urea derivatives, heating a THF solution of complex **1** (0.02 mmol), bis(pentamethylene)urea and *N*-formylmorpholine (1 mmol each) at 110 °C for 12 h under H_2 (13.6 atm), resulted in almost complete conversion of *N*-formylmorpholine (to 89% yield of morpholine and 93% yield of methanol) and very low conversion (< 2%) of bis(pentamethylene)urea (to piperidine and methanol; Scheme 2). In addition, partial hydrogenation of bis(pentamethylene)urea did not lead to accumulation of the corresponding formamide; only methanol and piperidine (31% and 37% yields, respectively) were formed after 36 h under 13.6 atm of H_2 and 2 mol% of catalyst **1**. Stepwise hydrogenation was also observed by us in the hydrogenation of organic carbonates to methanol.[22]

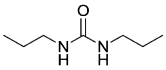
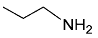
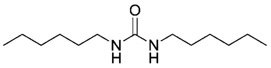
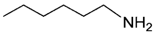
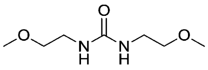
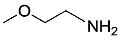
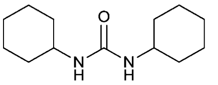
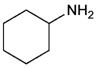
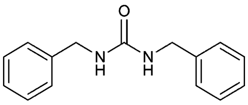
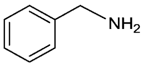
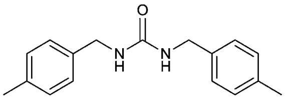
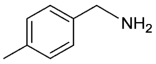
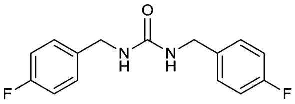
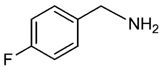
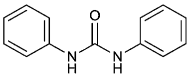
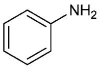
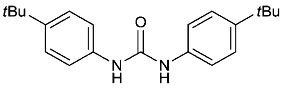
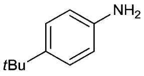
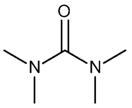
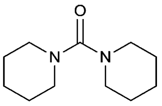
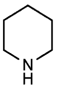


Scheme 2. Competitive hydrogenation of formamide- and urea- derivatives (conversion of *N*-formylmorpholine = 95%, conversion of bis(-pentamethylene)urea ≤ 2%).

In conclusion, hydrogenation of urea derivatives to the corresponding amines and methanol was achieved for the first time. The reaction is selectively catalyzed by a bipyridine-

Table 2: Hydrogenation of urea derivatives to amines and methanol catalyzed by complex **1**.[a]



Entry	Urea derivative	MeOH (yield [%][b])	Product Amine	Yield [%][b]
1[c]		89		
2		83		87
3		94		97
4		73		79
5[d]		61		60
6[d]		67		71
7		58		59
8[e]		90 63[f]		95 69[f]
9[e]		93		87
10[c,d]		46	$(CH_3)_2NH$	
11[d]		63		57

[a] Complex **1** (0.02 mmol), urea derivative (1 mmol), H_2 (13.6 atm) and anhydrous THF (2 mL) were heated in a Fischer–Porter tube (100 mL) at 110 °C (bath temperature) for 72 h (most of the reactions were repeated twice). [b] Yields of products were determined by GC (using 1 mmol of *m*-xylene as an internal standard). [c] The amines *n*-propylamine and Me_2NH (entries 1 and 10, respectively) were analyzed in the gas phase (as well as in the liquid phase) by GC-MS and not quantified. [d] The corresponding formamides (entries 5–6 and 10–11) were observed by GC-MS and not quantified. [e] $p(H_2) = 12$ atm. [f] Complex **1** (0.01 mmol), 1,3-diphenylurea (1 mmol), H_2 (13.6 atm), and anhydrous THF (2 mL) were heated at 110 °C for 72 h.

based PNN Ru(II) pincer complex under mild hydrogen pressure and neutral reaction conditions. As alkyl and aryl urea derivatives are readily obtained from CO_2 and amines, their hydrogenation offers an environmentally benign, mild, atom economical approach to the indirect transformation of CO_2 to methanol, which is of intense current interest with regard to hydrogen storage and "methanol economy".

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[1] a) S. E. Clapham, A. Hadzovic, R. H. Morris, *Coord. Chem. Rev.* **2004**, *248*, 2201–2237; b) M. Ito, T. Ikariya, *Chem. Commun.* **2007**, 5134–5142; c) O. W. W. N, A. J. Lough, R. H. Morris, *Chem. Commun.* **2010**, *46*, 8240–8242.
[2] a) J. Zhang, G. Leitus, Y. Ben-David, D. Milstein, *Angew. Chem.* **2006**, *118*, 1131–1133; *Angew. Chem. Int. Ed.* **2006**, *45*, 1113–1115; b) L. A. Saudan, C. M. Saudan, C. Debieux, P. Wyss, *Angew. Chem.* **2007**, *119*, 7617–7620; *Angew. Chem. Int. Ed.*

2007, *46*, 7473 – 7476; c) S. Takebayashi, S. H. Bergens, *Organometallics* **2009**, *28*, 2349 – 2351; d) W. Kuriyama, Y. Ino, O. Ogata, N. Sayo, T. Saito, *Adv. Synth. Catal.* **2010**, *352*, 92 – 96; e) Y. Ino, W. Kuriyama, O. Ogata, T. Matsumoto, *Top. Catal.* **2010**, *53*, 1019 – 1024; f) E. Fogler, E. Balaraman, Y. Ben-David, G. Leitus, L. J. W. Shimon, D. Milstein, *Organometallics* **2011**, *30*, 3826 – 3833, and references therein; g) Y. Sun, C. Koehler, R. Tan, V. T. Annibale, D. Song, *Chem. Commun.* **2011**, *47*, 8349 – 8351.

[3] a) A. A. Núñez Magro, G. R. Eastham, D. J. Cole-Hamilton, *Chem. Commun.* **2007**, 3154 – 3156; b) E. Balaraman, B. Gnanaprakasam, L. J. W. Shimon, D. Milstein, *J. Am. Chem. Soc.* **2010**, *132*, 16756 – 16758; c) M. Ito, T. Ootsuka, R. Watari, A. Shiibashi, A. Himizu, T. Ikariya, *J. Am. Chem. Soc.* **2011**, *133*, 4240 – 4242; d) J. M. John, S. H. Bergens, *Angew. Chem.* **2011**, *123*, 10561 – 10564; *Angew. Chem. Int. Ed.* **2011**, *50*, 10377 – 10380.

[4] Y. Ohgomori, S. Mori, S. Yoshida, Y. Watanabe, *J. Mol. Cat.* **1987**, *40*, 223 – 228.

[5] G. Imperato, S. Höger, D. Lenoir, B. König, *Green Chem.* **2006**, *8*, 1051 – 1055.

[6] C. F. Cooper, S. J. Falcone, *Synth. Commun.* **1995**, *25*, 2467 – 2474.

[7] F. Shi, Y. Q. Deng, T. L. SiMa, J. J. Peng, Y. L. Gu, B. T. Qiao, *Angew. Chem.* **2003**, *115*, 3379 – 3382; *Angew. Chem. Int. Ed.* **2003**, *42*, 3257 – 3259.

[8] A. Ion, V. Parvulescu, P. Jacobs, D. De Vos, *Green Chem.* **2007**, *9*, 158 – 161.

[9] F. Shi, Q. H. Zhang, Y. B. Ma, Y. D. He, Y. Q. Deng, *J. Am. Chem. Soc.* **2005**, *127*, 4182 – 4183.

[10] T. Jiang, X. M. Ma, Y. X. Zhou, S. G. Liang, J. C. Zhang, B. X. Han, *Green Chem.* **2008**, *10*, 465 – 469.

[11] D. L. Kong, L. N. He, J. Q. Wang, *Synlett* **2010**, 1276 – 1280.

[12] a) J. Fournier, C. Bruneau, P. H. Dixneuf, S. Lecolier, *J. Org. Chem.* **1991**, *56*, 4456 – 4458; b) C. Tai, M. J. Huck, E. P. McKoon, T. Woo, P. G. Jessop, *J. Org. Chem.* **2002**, *67*, 9070 – 9072.

[13] C. Wu, H. Cheng, R. Liu, Q. Wang, Y. Hao, Y. Yu, F. Zhao, *Green Chem.* **2010**, *12*, 1811 – 1816.

[14] a) G. A. Olah, A. Goeppert, G. K. S. Prakash, *Beyond Oil and Gas: The Methanol Economy*, Wiley-VCH, Weinheim, **2006**; b) G. A. Olah, *Angew. Chem.* **2005**, *117*, 2692 – 2696; *Angew. Chem. Int. Ed.* **2005**, *44*, 2636 – 2639; c) G. A. Olah, A. Goeppert, G. K. S. Prakash, *J. Org. Chem.* **2009**, *74*, 487 – 498.

[15] M. Cokoja, C. Bruckmeier, B. Rieger, W. A. Herrmann, F. E. Kühn, *Angew. Chem.* **2011**, *123*, 8662 – 8690; *Angew. Chem. Int. Ed.* **2011**, *50*, 8510 – 8537.

[16] Recent reviews including hydrogenation of CO$_2$ to MeOH: see a) X. Liu, G. Q. Lu, Z. Yan, J. Beltramini, *Ind. Eng. Chem. Res.* **2003**, *42*, 6518 – 6530; b) J. Ma, N. N. Sun, X. L. Zhang, N. Zhao, F. Xiao, F. K. Mao, W. Wei, Y. Sun, *Catal. Today* **2009**, *148*, 221 – 231; c) W. Wang, S. Wang, X. Ma, J. Gong, *Chem. Soc. Rev.* **2011**, *40*, 3703 – 3727.

[17] P. J. Kocienski, *Protecting Groups*, 3rd ed., Thieme, Stuttgart, **2005**.

[18] For recent reviews: see a) D. Milstein, *Top. Catal.* **2010**, *53*, 915 – 923; b) C. Gunanathan, D. Milstein, *Top. Organomet. Chem.* **2011**, *37*, 55 – 84; c) C. Gunanathan, D. Milstein, *Acc. Chem. Res.* **2011**, *44*, 588 – 602.

[19] a) J. Zhang, M. Gandelman, L. J. W. Shimon, D. Milstein, *Organometallics* **2004**, *23*, 4026 – 4033 (acceptorless dehydrogenation of secondary alcohols to ketones and hydrogen); b) J. Zhang, G. Leitus, Y. Ben-David, D. Milstein, *J. Am. Chem. Soc.* **2005**, *127*, 10840 – 10841 (dehydrogenative coupling of primary alcohols to esters with liberation of H$_2$); c) J. Zhang, M. Gandelman, L. J. W. Shimon, D. Milstein, *Dalton Trans.* **2007**, 107 – 113 (dehydrogenation of alcohols); d) C. Gunanathan, Y. Ben-David, D. Milstein, *Science* **2007**, *317*, 790 – 792 (novel coupling of alcohols and amines to form amides and H$_2$); e) B. Gnanaprakasam, Y. Ben-David, D. Milstein, *Adv. Synth. Catal.* **2010**, *352*, 3169 – 3173 (acylation of alcohols using esters with extraction of hydrogen); f) B. Gnanaprakasam, D. Milstein, *J. Am. Chem. Soc.* **2011**, *133*, 1682 – 1685 (amide synthesis from esters and amines); g) B. Gnanaprakasam, J. Zhang, D. Milstein, *Angew. Chem.* **2010**, *122*, 1510 – 1513; *Angew. Chem. Int. Ed.* **2010**, *49*, 1468 – 1471 (dehydrogenative coupling of alcohols and amines to form imines with liberation of H$_2$ and H$_2$O).

[20] a) C. Gunanathan, L. J. W. Shimon, D. Milstein, *J. Am. Chem. Soc.* **2009**, *131*, 3146 – 3147 (direct conversion of alcohols to acetals and H$_2$); b) C. Gunanathan, D. Milstein, *Angew. Chem.* **2008**, *120*, 8789 – 8792; *Angew. Chem. Int. Ed.* **2008**, *47*, 8661 – 8664 (selective synthesis of primary amines directly from alcohols and ammonia).

[21] a) S. W. Kohl, L. Weiner, L. Schwartsburd, L. Konstantinovski, L. J. W. Shimon, Y. Ben-David, M. A. Iron, D. Milstein, *Science* **2009**, *324*, 74 – 77 (consecutive light-induced splitting of water to dihydrogen and dioxygen); b) E. Khaskin, M. A. Iron, L. J. W. Shimon, J. Zhang, D. Milstein, *J. Am. Chem. Soc.* **2010**, *132*, 8542 – 8543 (N−H activation of amines and ammonia); c) C. Gunanathan, B. Gnanaprakasam, M. A. Iron, L. J. W. Shimon, D. Milstein, *J. Am. Chem. Soc.* **2010**, *132*, 14763 – 14765 (activation of H$_2$ and NH$_3$ by an acridine-based PNP Ru(II) complex).

[22] E. Balaraman, C. Gunanathan, J. Zhang, L. J. W. Shimon, D Milstein, *Nat. Chem.* **2011**, *3*, 609 – 614.

[23] Heating a THF solution containing *N*-formylmorpholine (1 mmol) and a catalytic amount of complex **1** (2 mol %) under hydrogen pressure (13.6 atm) using a pressure vessel at 110 °C for 12 h resulted in quantitative conversion of *N*-formylmorpholine to methanol (91 %) and morpholine (95 %) without decarbonylation of the formyl group. Thus, under our reaction conditions the formamides undergo hydrogenation more readily than urea derivatives. See also Ref. [3b].