JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

COMMUNICATION

pubs.acs.org/JACS

# Synthesis of Amides from Esters and Amines with Liberation of $H_2$ under Neutral Conditions

Boopathy Gnanaprakasam and David Milstein*

Department of Organic Chemistry, Weizmann Institute of Science, Rehovot 76100, Israel

Supporting Information

**ABSTRACT:** Efficient synthesis of amides directly from esters and amines is achieved under mild, neutral conditions with the liberation of molecular hydrogen. Both primary and secondary amines can be utilized. This unprecedented, general, environmentally benign reaction is homogeneously catalyzed under neutral conditions by a dearomatized ruthenium−pincer PNN complex and proceeds in toluene under an inert atmosphere with a high turnover number (up to 1000). PNP analogues do not catalyze this transformation, underlining the crucial importance of the amine arm of the pincer ligand. A mechanism is proposed involving metal−ligand cooperation via aromatization−dearomatization of the pyridine moiety and hemilability of the amine arm.

Carboxylic amides are of much importance in chemistry and biology. Although several methods exist for the preparation of amides, atom-economical syntheses under mild and neutral conditions without waste generation or use of hazardous reagents are a formidable challenge.[1,2] A potentially attractive process is the synthesis of amides from esters; however, stoichiometric amounts of promoters or metal mediators are normally required.[3] Very few catalytic ester−amide exchange reactions have been reported,[4,5] including the use of $Sb(OEt)_3$ (5−10 mol %) with azeotropic removal of the methanol[4a,b] and the employment of group IV metal alkoxides in conjunction with additives, such as the interesting catalytic system of $Zr(O^tBu)_4$ (10 mol %) + 1-hydroxy-7-azabenzotriazole (10 mol %) reported by Porco.[5] Reactions of amines with amides (transamidation) catalyzed by Al(III) and group 4 metal complexes under mild conditions were recently reported.[6]

We have discovered the atom-economical, environmentally benign direct synthesis of amides from alcohols and amines with liberation of $H_2$, catalyzed by the dearomatized pincer complex (PNN)Ru(II) **1**[7] (Figure 1). Several interesting reports on amide formation by dehydrogenative coupling of amines with alcohols appeared later.[8] Catalytic hydrogenation of amides to alcohols and amines was also reported very recently.[9] Complex **1** and the analogous (PNP)Ru(II) complexes **2a**, **2b** catalyze also the dehydrogenative coupling of primary alcohols to form esters,[10a,10b] the hydrogenation of esters to alcohols,[10d] the dehydrogenation of secondary alcohols to ketones,[10c] and, very recently reported, the acylation of secondary alcohols with esters.[10f] Unlike complex **1**, complexes **2a**, **2b** catalyze the coupling of amines with alcohols to form imines, rather than amides, with liberation of $H_2$.[11] Mechanistically, these catalytic reactions operate by a new mode of metal−ligand cooperation, involving aromatization−dearomatization of the pyridine-based core of the pincer ligand.[12] An acridine-based pincer−ruthenium complex

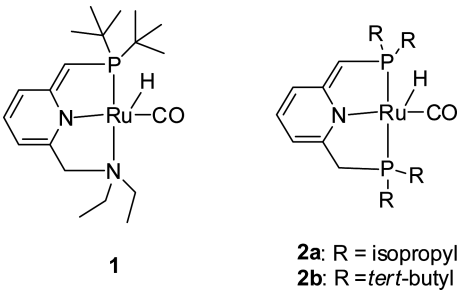
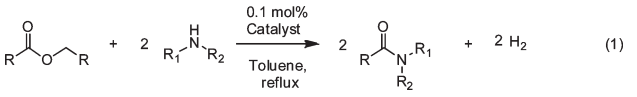



**Figure 1.** Dearomatized Ru−pincer complexes.

catalyzes the dehydrogenative coupling of primary alcohols to acetals or esters, and the reaction of alcohols with ammonia to selectively form primary amines, also by a metal−ligand cooperation mechanism, involving the central acridine ring.[13]

Here we report a novel catalytic amide synthesis from esters and amines. This amidation reaction is general, efficient, and environmentally benign. It proceeds under neutral reaction conditions and results in high turnover numbers (up to 1000). Uniquely, it generates $H_2$ rather than an alcohol byproduct (eq 1).




When a benzene solution containing 10 mmol of pyrrolidine, 10 mmol of ethyl acetate, and 0.01 mmol of complex **1** was refluxed under an argon atmosphere, quantitative conversion of pyrrolidine was observed by GC after 28 h, to give *N*-acetylpyrrolidine (characterized by NMR and GC-MS) in 98% isolated yield after column purification (Table 1, entry 1). The same results were obtained when the reaction was carried out in refluxing toluene. Reaction of ethyl acetate with morpholine in benzene under reflux resulted after 36 h in 69% conversion, and the corresponding amide was isolated in 67% yield (Table 1, entry 2). Refluxing of 1-methyl piperazine, ethyl acetate, and benzene in the presence of complex **1** provided the amide in 52% isolated yield (Table 1, entry 3).

Exploring the scope of the ester amidation reaction, various esters and amines were examined. Refluxing a toluene solution containing butyl butyrate (5 mmol), piperidine (10 mmol), and 0.1 mol % of the PNN complex **1** under an argon atmosphere for 19 h resulted in 100% conversion of piperidine as observed by GC analysis, with the exclusive formation of 1-(piperidin-1-yl)butan-1-one in 94% isolated yield after purification by alumina column

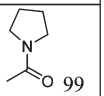
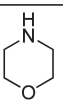
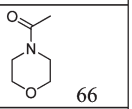
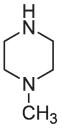
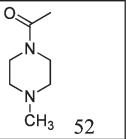
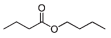
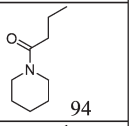
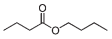
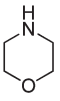
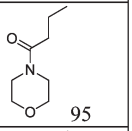
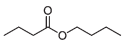
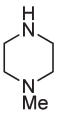
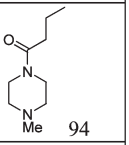
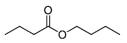
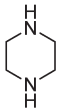
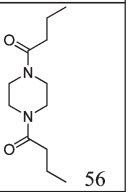
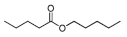
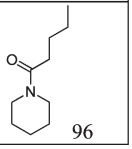
**Received:** November 5, 2010
**Published:** January 19, 2011

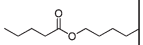
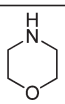
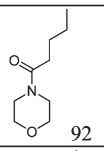
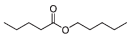
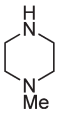
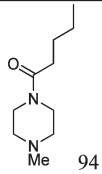
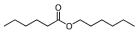
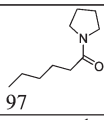
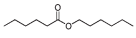
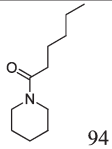
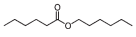
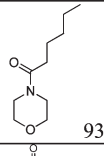
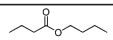




dx.doi.org/10.1021/ja109944n | J. Am. Chem. Soc. 2011, 133, 1682–1685

**Table 1. Aminolysis[a] of Esters Catalyzed by the Ruthenium−PNN* Complex 1 Using Amines**

| Entry | Ester | Amine | Conv. of amine/time % / hrs | Isolated Yields (%) |
|---|---|---|---|---|
| 1[b] |  |  | 100/26 |  99 |
| 2[b] |  |  | 69/36 |  66 |
| 3[b] |  |  | 54/24 |  52 |
| 4 |  |  | 100/19 |  94 |
| 5 |  |  | 100/21 |  95 |
| 6 |  |  | 100/24 |  94 |
| 7 |  |  | 100/36 |  56 |
| 8 |  |  | 100/19 |  96 |

| Entry | Ester | Amine | Conv. of amine/time % / hrs | Isolated Yields (%) |
|---|---|---|---|---|
| 9 |  |  | 100/26 |  92 |
| 10 |  |  | 100/24 |  94 |
| 11 |  |  | 100/18 |  97 |
| 12 |  |  | 100/26 |  94 |
| 13 |  |  | 100/18 |  93 |
| 14 |  |  | 100/24 |  97 |
| 15 |  |  | 100/18 |  98 |

[a] Complex **1** (0.01 mmol), ester (5 mmol), amine (10 mmol), and toluene/benzene (3 mL) were refluxed at an oil bath at a temperature of 135 °C in a Schlenk tube. Conversion of amine was analyzed by GC using *m*-xylene as an internal standard. [b] Benzene was used as a solvent.

chromatography (Table 1, entry 4). Similarly, refluxing a toluene solution containing butyl butyrate and morpholine or *N*-methylpiperazine in the presence of complex **1** resulted in 100% conversion of the amine, with the isolation of the corresponding amides in 95% and 94% yields, respectively. Refluxing of excess butyl butyrate and piperazine in toluene led the bis-acylation of the piperazine, providing the corresponding bis-amide in 56% isolated yield.

Interestingly, unlike the traditional methods, this amidation reaction forms $H_2$ rather than alcohol byproduct, resulting in the irreversible incorporation of both the acyl and alkoxo parts of the starting ester into the product amide. This is useful when symmetrical esters are utilized. This result is accounted for in the proposed mechanism (see later), with no need to invoke intermediacy of the free alcohol. Significantly, the turnover number of the ester−amide exchange reaction using the dearomatized pincer complex **1** is high (up to 1000), as compared with 10−20 turnovers in the few reported catalytic ester−amide exchange reactions.[4,5,14]

To explore the synthetic utility of this reaction, pentyl pentanoate was reacted with various amines. The reaction of pentyl pentanoate with piperidine gave 100% conversion, with the isolation of the amide in 96% yield. Upon refluxing a toluene solution of morpholine or *N*-methyl piperazine with pentyl pentanoate, the corresponding amide was produced in 96% and 94% isolated yields, respectively. Likewise, reaction of hexyl hexanoate with pyrrolidine, piperidine, or morpholine under reflux conditions of toluene afforded the complete conversion of the amines, with isolated excellent yield of the corresponding amides.

Next, the reactions were also studied with primary amines. The reaction of ethyl butyrate and hexyl amine in the presence of 0.1 mol % of **1** under refluxing toluene led to 100% conversion of the amine, with the isolation the corresponding amide in 97% yield. Similarly, reaction of pentyl pentanoate with 4-methylbenzyl amine in toluene reflux yielded 100% conversion, with isolation of the


dx.doi.org/10.1021/ja109944n |*J. Am. Chem. Soc.* 2011, 133, 1682–1685

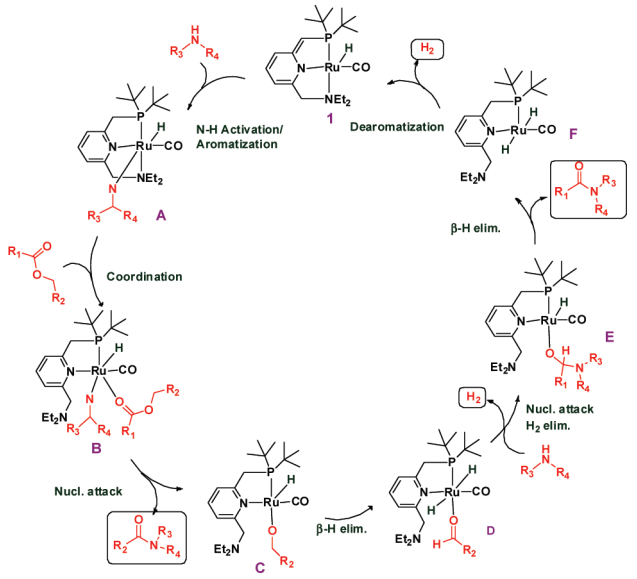



**Figure 2.** Plausible mechanism for the ester amidation reaction.

corresponding amide in 98% yield. These reactions did not lead to any alcohol as waste product.

Interestingly, the dearomatized PNP complexes **2a**, **2b**, analogous to complex **1** except for not having a "hemilabile" amine arm, did not catalyze the amidation reaction. Thus, heating a solution of pentyl pentanoate, piperidine, and **2** or **3** in toluene under reflux for 24 h resulted in no reaction. This indicates that the hemilabile amine arm is essential for ester amidation catalysis.

The reactions were also studied without a solvent. Thus, heating the solutions containing pentyl pentanoate, piperidine, and RuPNN complex **1** at 135 °C resulted in only 52% conversion.

Although at present we do not have sufficient mechanistic data, a plausible catalytic cycle for the ester amidation is presented in Figure 2. This mechanism accounts for the striking observation that, while **1** is an excellent catalyst, the seemingly similar complexes **2a**, **2b** are catalytically inert. We propose that N−H activation of the dearomatized complex **1** forms the aromatized coordinatively saturated species **A**, as we have previously observed with complex **2b**.[12c] Dissociation of the hemilabile amine arm and coordination of the ester forms intermediate **B**. This is difficult with the PNP complexes **2a**, **2b** under the reaction conditions, and hence they do not catalyze this reaction. Intramolecular nucleophilic attack by the amido ligand at the carbonyl group of the ester results in formation of the amide and generation of the alkoxy intermediate **C**. $\beta$-H elimination generates the Ru dihydride complex **D**, bearing a coordinated aldehyde. Nucleophilic attack of the amine on the aldehyde followed by liberation of $H_2$ (via proton−hydride interaction) gives intermediate **E**, which upon $\beta$-H elimination forms the trans dihydride intermediate **F**, with liberation of a second molecule of the amide. Dihydrogen loss from intermediate **F** regenerates catalyst **1**. Based on this mechanism, one cycle accounts for the generation of two amide molecules and two $H_2$ molecules, with no intermediacy of free alcohol.

In summary, acylation of amines using esters as the acylating agent is efficiently catalyzed by the dearomatized complex **1** under neutral conditions without any waste generation. The use of symmetrical esters results in incorporation of both the acyl and alkoxo parts of the substrate ester into the product amide with liberation of $H_2$. The reaction results in high turnover numbers, up to 2 orders of magnitude higher than those reported for the few catalytic ester amidation reactions. Both primary and secondary amines can be utilized.[15]

## ■ ASSOCIATED CONTENT

**Supporting Information.** Experimental procedures and spectral data of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

**Corresponding Author**
david.milstein@weizmann.ac.il

## ■ ACKNOWLEDGMENT

This research was supported by the European Research Council under the FP7 framework (ERC No 246837), by the Israel Science Foundation, by the MINERVA Foundation, and by the Kimmel Center for Molecular design. D.M. is the holder of the Israel Matz Professorial Chair of Organic Chemistry.

## ■ REFERENCES

(1) (a) Larock, R. C. *Comprehensive Organic Transformations*, 2nd ed.; Wiley-VCH: New York, 1999. (b) Smith, M. B. *Compendium of Organic Synthetic Methods*; Wiley: New York, 2001; Vol. 9, pp 100−116.

(2) Constable, D. J. C.; Dunn, P. J.; Hayler, J. D.; Humphrey, G. R.; Leazer, J. L, Jr.; Linderman, R. J.; Lorenz, K.; Manley, J.; Pearlman, B. A.; Wells, A.; Zaks, A.; Zhang, T. Y. *Green Chem.* **2007**, *9*, 411.

(3) (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171. (b) Wang, W.-B.; Roskamp, E. J. *J. Org. Chem.* **1992**, *57*, 6101. (c) Williams, J. M.; Jobson, R. B.; Yasuda, N.; Marchesini, G.; Dolling, U.-H.; Grabowski, E. J. J. *Tetrahedron Lett.* **1995**, *36*, 5461. (d) Shimizu, T.; Osako, K.; Nakata, T. *Tetrahedron Lett.* **1997**, *38*, 2685. (e) Varma, R. S.; Naicker, K. P. *Tetrahedron Lett.* **1999**, *40*, 6177and references therein. (f) Kurosawa, W.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 8112. (g) Direct reaction of activated 2-hydroxyamines with esters at elevated temperatures to form ethanolamides: D'Alelio, G. F.; Emmet Reid, E. *J. Am. Chem. Soc.* **1937**, *59*, 111.(h) Amidation of amines with esters under microwave irradiation at 200 °C: Ferroud, C.; Godart, M.; Ung, S.; Borderies, H.; Guy, A. *Tetrahedron Lett.* 2008, *49*, 3004.

(4) (a) Ishihara, K.; Kuroki, Y.; Hanaki, N.; Ohara, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 1569. (b) Kuroki, Y.; Ishihara, K.; Hanaki, N.; Ohara, S.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1221. (c) Porta, F.; Pizzotti, M.; Crotti, C.; Cenini, S. *Gazz. Chim. Ital.* **1988**, *118*, 475.

(5) Han, C.; Lee, J. P.; Lobkovsky, E.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 10039.

(6) (a) Eldred, S. E.; Stone, D. A.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2003**, *125*, 3422. (b) Hoerter, J. M.; Otte, K. M.; Gellman, S. H.; Cui, Q.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, 130. (c) Stephenson, N. A.; Zhu, J.; Gellman, S. H.; Stahl, S. S. *J. Am. Chem. Soc.* **2009**, *131*, 10003.

(7) Gunanathan, C.; Ben-David, Y.; Milstein, D. *Science* **2007**, *317*, 790.

(8) (a) Nordstrøm, L. U.; Vogt, H.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 17672. (b) Zweifel, T.; Naubron, J. V.; Grutzmacher, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 559. (c) Watson, A. J. A.; Maxwell, A. C.; Williams, J. M. J. *Org. Lett.* **2009**, *11*, 2667. (d) Ghosh, S. C.; Muthaiah, S.; Zhang, Y.; Xu, X.; Hong, S. H. *Adv. Synth. Catal.* **2009**, *351*, 2643. (e) Shimizu, K.; Ohshima, K.; Satsuma, A. *Chem.—Eur. J.* **2009**, *15*, 9977. (f) Zhang, Y.; Chen, C.; Ghosh, S. C.; Li, Y.; Hong, S. H.

*Organometallics* **2010**, *29*, 1374. (g) Muthaiah, S.; Ghosh, S. C.; Jee, J.-E.; Chen, C.; Zhang, J.; Hong, S. H. *J. Org. Chem.* **2010**, *75*, 3002.

(9) Balaraman, E.; Gnanaprakasam, B.; Shimon, L. J. W.; Milstein, D. *J. Am. Chem. Soc.* **2010**, *132*, 16756.

(10) (a) Zhang, J.; Leitus, G.; Ben-David, Y.; Milstein, D. *J. Am. Chem. Soc.* **2005**, *127*, 10840. (b) Zhang, J.; Gandelman, M.; Shimon, L. J. W.; Milstein, D. *Dalton Trans.* **2007**, 107. (c) Zhang, J.; Gandelman, M.; Shimon, L. J. W.; Milstein, D. *Organometallics* **2004**, *23*, 4026. (d) Zhang, J.; Leitus, G.; Ben-David, Y.; Milstein, D. *Angew. Chem., Int. Ed.* **2006**, *45*, 1113. (e) Milstein, D. *Top. Catal.* **2010**, *53*, 915–923. (f) Gnanaprakasam, B.; Ben-David, Y.; Milstein, D. *Adv. Synth. Catal.* **2010**, *352*, 3169.

(11) Gnanaprakasam, B.; Zhang, J.; Milstein, D. *Angew. Chem., Int. Ed.* **2010**, *47*, 8861.

(12) (a) Ben Ari, E.; Leitus, G.; Shimon, L. J. W.; Milstein, D. *J. Am. Chem. Soc.* **2006**, *128*, 15390. (b) Iron, M.; Ben-Ari, E.; Cohen, R.; Milstein, D. *Dalton Trans.* **2009**, 9433. (c) Kohl, S. W.; Weiner, L.; Schwartsburd, L.; Konstantinovski, L.; Shimon, L. J. W.; Ben-David, Y.; Iron, M. A.; Milstein, D. *Science* **2009**, *324*, 74.

(13) (a) Gunanathan, C.; Milstein, D. *Angew. Chem., Int. Ed.* **2008**, *49*, 1468. (b) Gunanathan, C.; Shimon, L. J. W.; Milstein, D. *J. Am. Chem. Soc.* **2009**, *131*, 3146. (c) Khaskin, E.; Iron, M. A.; Shimon, L. J. W.; Zhang, J.; Milstein, D. *J. Am. Chem. Soc.* **2010**, *132*, 8542.

(14) Employing 0.1 mol% of the Lewis acids $AlCl_3$ or $FeCl_3$ instead of **1** under the reaction conditions resulted in no amide formation. No amidation was observed also with the aromatic, cationic complex $[RuH(^tBu\text{-}PNP)(CO)]^+PF_6^-$. These experiments negate a Lewis acid type mechanism. Control experiments using no catalyst resulted in no amide formation. See Supporting Information for full details.

(15) Esters have to be purified to remove carboxylic acid impurities, which deactivate the catalyst (even in the presence of amine). We believe that our previously noted lack of reaction between benzyl amine and hexyl hexanoate in presence of **1**[7] is due to a carboxylic acid impurity.