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Formation of Tertiary Amides and Dihydrogen by Dehydrogenative Coupling of Primary Alcohols with Secondary Amines Catalyzed by Ruthenium Bipyridine-Based Pincer Complexes

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This paper is dedicated to Professor Teruaki Mukaiyama in celebration of the 40th anniversary of the Mukaiyama aldol rection.

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Abstract: Dehydrogenative coupling of primary alcohols with secondary amines to form tertiary amides and dihydrogen (H_2) is efficiently catalyzed by bipyridyl-based ruthenium pincer complexes (0.2–1 mol%) under neutral conditions (in case of the dearomatized complexes), or with added catalytic amount of base. The reaction is sensitive to steric hindrance; in the case of amidation of bulky secondary amines a less sterically hindered complex is more efficient. Selective acylation of primary amines in the presence of secondary amines was also demonstrated.

Keywords: alcohols; amidation; amines; dehydrogenation; oxidative coupling; ruthenium pincer complexes

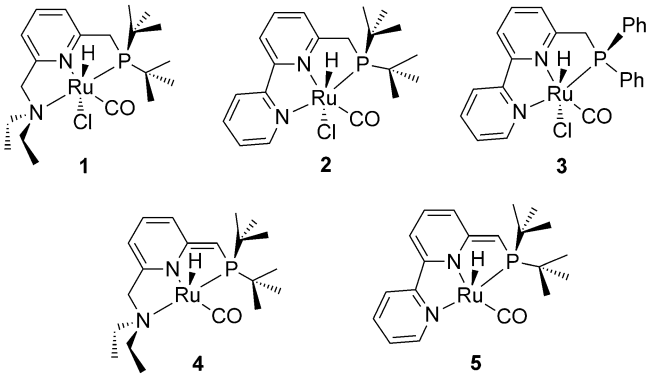
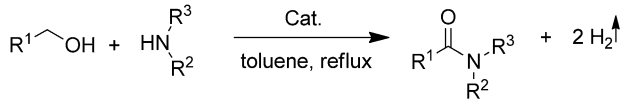


Figure 1. PNN- and PNP-type ruthenium pincer complexes.

Amide bond formation is one of the most fundamental reactions in organic chemistry because of its widespread occurrence in peptides, polymers and many natural products and pharmaceuticals.[1] The conventional approach for the synthesis of amides is the coupling of activated carboxylic acid derivatives with amines.[2] Alternative approaches of amide synthesis were reported;[3] however, most of these methods require an equimolar amount of various reagents and often produce toxic chemical waste with tedious associated procedures. In 2007, we reported a new reaction, namely the coupling of alcohols and amines to form amides and H_2, with no waste, efficiently catalyzed by 0.1 mol% of the ruthenium pincer complex **4**[4] (Figure 1); this reaction has been used in the preparation of polyamides by Guan and co-workers[5a] and by us[5b] and in the preparation of peptides.[5c] Following publication of our work, examples of acceptorless amide formation by other ruthenium catalysts were reported, although using higher catalyst loading (2.5–5 mol%).[6] In our initial report,[4] diethylenetriamine, having both primary and secondary amine groups, underwent selective acylation at the primary amine groups; this turned out to be an advantage in the preparation of polyamides bearing free secondary amine groups in the backbone, as reported by Guan and co-workers.[5a] We now report the dehydrogenative coupling of secondary amines with alcohols, to form tertiary amides, using 0.2–1 mol% of Ru pincer catalyst. Such a reaction using 5 mol% of N-heterocyclic carbine (NHC) Ru complex and 15–35 mol%



Scheme 1. Dehydrogenative coupling of primary alcohols with secondary amines.

KO-*t*-Bu was reported recently by Hong et al.[7a] Very recently Glorious and co-workers reported the dehydrogenative coupling of primary and secondary amines with methanol to generate formamides catalyzed by a ruthenium-NHC complex.[7c]

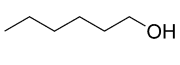
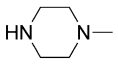
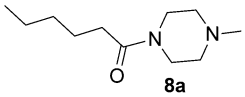
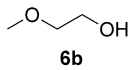
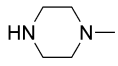
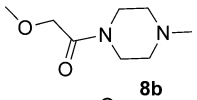
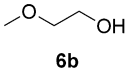
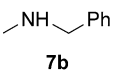
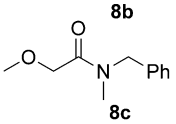
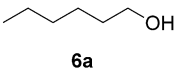
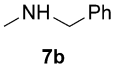
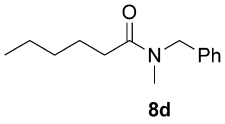
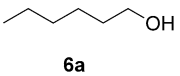
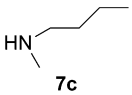
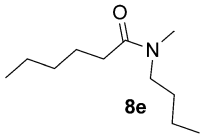
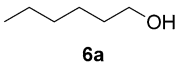
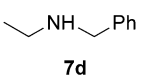
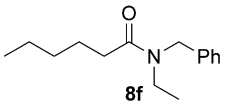
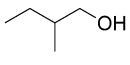
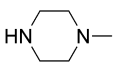
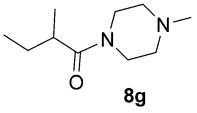
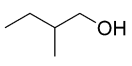
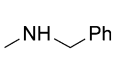
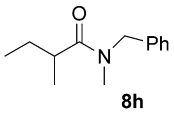
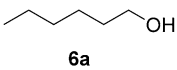
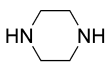
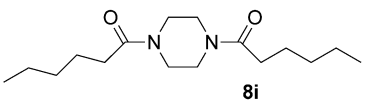
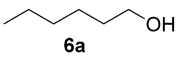
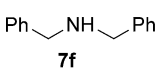
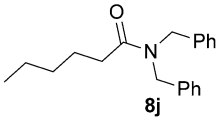
Our group has demonstrated several environmentally benign, atom economical, sustainable reactions, catalyzed by pincer complexes of ruthenium based on pyridine[4,5b,c,8] and acridine[9] backbones. Recently we have developed dearomatized bipyridine-based Ru(II)pincer complex **5** (Figure 1) and explored its catalytic activity[10] toward the hydrogenation of amides,[10a] biomass-derived cyclic diesters,[10b] and urea derivatives[10c] as well as organic carbonates, carbamates and formates.[10d] The parent hydrido chloride pincer complex **2** catalyzes in the presence of catalytic base (*in situ* generation of complex **5**) several unique environmentally benign reactions including the dehydrogenative transformation of alcohols to carboxylic acid salts using water as the oxygen atom source,[10e] dehydrogenative cross-esterification reaction between primary and secondary alcohols,[10f] direct synthesis of pyrroles, pyridines and quinoline by dehydrogenative coupling of amino alcohols with secondary alcohols,[10g,h] catalytic deuteration of α and β-CH bonds of primary and secondary alcohols[10i] and catalytic coupling of nitriles with amines to selectively form imines under mild hydrogen pressure.[10j]

Herein we communicate the dehydrogenative coupling of primary alcohols with secondary amines catalyzed by bipyridine-based pincer complexes under mild conditions (Scheme 1).

Exploring the feasibility of the amidation reaction with secondary amines and primary alcohols we initially examined the reaction of the sterically non-hindered amine *N*-methylpiperazine with alcohols. Thus, when a toluene solution containing 1-hexanol (5 mmol), *N*-methylpiperazine (5.5 mmol) and 0.01 mmol of complex **5**[11] was refluxed for 24 h under an argon atmosphere, complete consumption of 1-hexanol took place and the product 1-(4-methylpiperazin-1-yl)hexan-1-one was obtained in 99% yield as indicated by GC and confirmed by GC-MS (Table 1, entry 1). The pure amide was isolated in 90% yield by chromatographic purification. Encouraged by this result we reacted 2-methoxyethanol under the same conditions. Thus, refluxing 2-methoxyethanol and *N*-methylpiperazine in the presence of 0.2 mol% complex **5** gave quantitative formation of the desired 2-methoxy-1-(4-methylpiperazin-1-yl)ethanone in 88% isolated yield (Table 1, entry 2). Studying the scope of this reaction with regard to acyclic secondary amines, the reaction of 2-methoxyethanol with *N*-benzylmethylamine in the presence of 0.2 mol% of **5** resulted after 24 h reflux in toluene in the formation of *N*-benzyl-2-methoxymethylacetamide in 49% GC yield, accompanied by hexyl hexanoate in 45% yield (Table 1, entry 3). Increasing the catalyst loading from 0.2 to 0.4 mol%, increased the yield of the desired amide to 93% (Table 1, entry 4). The same trend was also observed with the reaction of 1-hexanol and *N*-methylbenzylamine (Table 1, entries 5 and 6). Considering the steric effect in the amidation reaction, we prepared a less bulky ligand, replacing the two *tert*-butyl groups by phenyl groups. The hydrido chloride pincer complex **3** was prepared by reaction of the new tridentate ligand, 6-diphenylphosphinomethyl-2,2′-bipyridine [BPy(Ph)PNN] (see the Supporting Information for its preparation) with $[RuHCl(PPh_3)_3(CO)]$ in THF at 65 °C for 12 h, resulting in substitution of the PPh_3 ligands to yield the fully characterized complex **3**. This complex gives rise to a singlet at 69.44 ppm in the $^{31}P\{^1H\}$ NMR spectrum, and the hydride ligand appears as a doublet at −14.09 ppm ($^2J_{P,H}=25.5$ Hz) in the ^1H NMR spectrum. The "arm" methylene protons appear as a multiplet in the region of 4.38–4.50 ppm. The carbonyl ligand appears as a doublet at 206.5 ppm ($J_{P,C}=7.5$ Hz) in the $^{13}C\{^1H\}$ NMR spectrum. We believe that the corresponding dearomatized complex was generated *in situ*, by the reaction of catalyst **3** and 1.1 equivalents of KO-*t*-Bu, in analogy to complexes **4** and **5** which were generated from complexes **1** and **2**, respectively, by the treatment with an equimolar amount of base.[8a,10a] Employing complex **3** in the amidation reaction, a toluene solution containing 1-hexanol (5 mmol), *N*-methylbenzylamine (5.5 mmol), 0.01 mmol of complex **3** and 0.011 mmol of KO-*t*-Bu was refluxed for 24 h under an argon atmosphere, resulting in complete consumption of 1-hexanol as observed by GC and GC-MS, forming *N*-benzyl-*N*-methylhexanamide in 86% yield (Table 1, entry 7). To our delight, the phenyl complex (**3**) showed excellent catalytic activity even with a low catalyst loading (0.2 mol%), which is substantially lower than in the previously reported procedure by Hong et al (5 mol%).[7a] Crabtree et al. reported the dehydrogenative coupling of piperidine (6-fold excess) with benzyl alcohol and with 1-phenethanol forming the corresponding amides in 89% and 55% yields, respectively, using a diamine-Ru catalyst (4 mol%) and KOH (15 mol%).[7b]

Studying the scope of this reaction with regard to other acyclic secondary amines, the reaction of 1-hexanol with *N*-methylbutylamine in the presence of 0.5 mol% of catalyst **3** and 0.55 mol% KO-*t*-Bu resulted after 12 h reflux in toluene in the formation of the

Table 1. Direct synthesis of tertiary amides from primary alcohols and secondary amines catalyzed by Ru-bipyridine pincer complexes.[a,b]

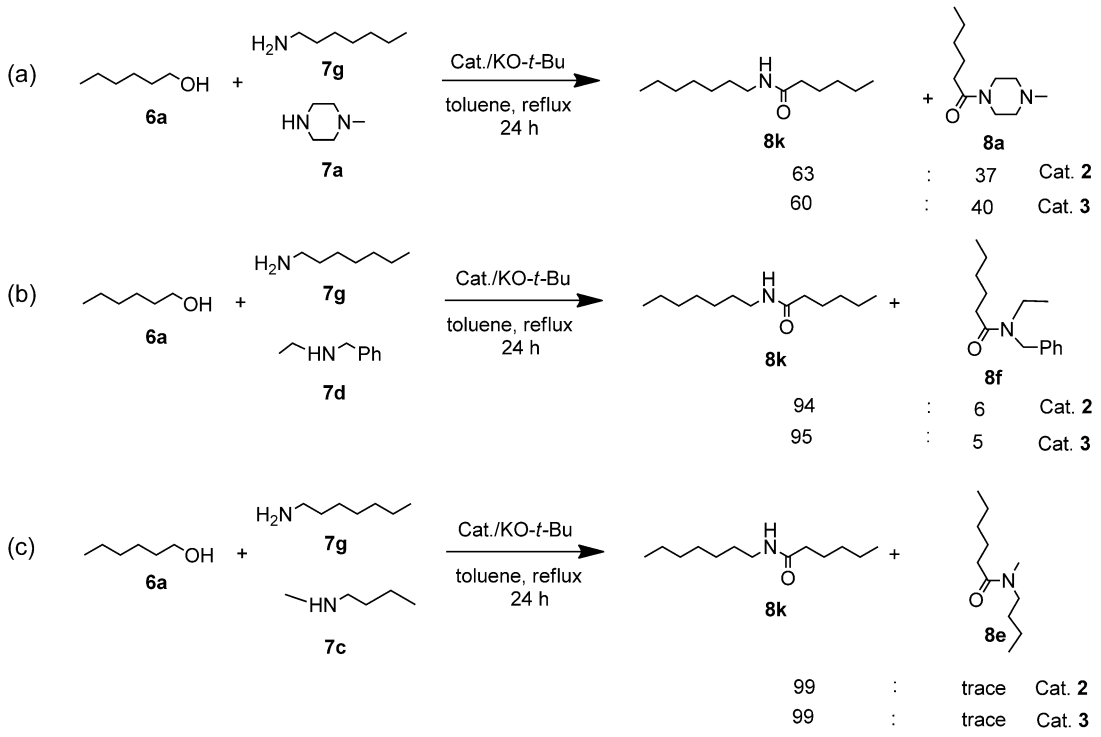
Entry	Alcohol	Amine	Product	Time [h]	Cat./mol%	GC Yield [%][c]	Isolated Yield [%][d]
1	 **6a**	 **7a**	 **8a**	24	**5**/0.2	99	90
2	 **6b**	 **7a**	 **8b**	24	**5**/0.2	99	88
3	 **6b**	 **7b**	 **8c**	24	**5**/0.2	49	-
4	**6b**	**7b**	**8c**	24	**5**/0.4	93	85
5	 **6a**	 **7b**	 **8d**	25	**5**/0.2	68	-
6	**6a**	**7b**	**8d**	24	**5**/0.4	95	-
7	**6a**	**7b**	**8d**	24	**3**/0.2	94	86
8[e]	 **6a**	 **7c**	 **8e**	12	**3**/0.5	35	-
9[e]	**6a**	**7c**	**8e**	12	**4**/0.5	25	-
10[e]	**6a**	**7c**	**8e**	24	**3**/1	88	80
11	 **6a**	 **7d**	 **8f**	24	**3**/1	55	50
12	 **6c**	 **7a**	 **8g**	48	**3**/1	56	50
13	 **6d**	 **7b**	 **8h**	24	**3**/1	50	45
14	 **6a**	 **7e**	 **8i**	24	**3**/0.4	85	80
15	 **6a**	 **7f**	 **8j**	24	**3**/0.4	0[f]	-

[a] Complex (0.2–1 mol%), primary alcohol (5 mmol), secondary amine (5.5 mmol) and toluene (2 mL) were refluxed under argon.
[b] The dearomatized complexes **4**, **5**[11] or a mixture of equivalent catalytic amounts of complex **3** and KO-*t*-Bu were used.
[c] Yields of products were determined by GC using *m*-xylene as an internal standard.
[d] Isolated yields after purification.
[e] 1.5 equiv. of amine were used (with respect to the alcohol).
[f] 1ä-Hexanol was completely converted to hexyl hexanoate while the dibenzylamine remained unchanged.

desired amide in 35% yield and the rest of the alcohol was converted to hexyl hexanoate, while under the same conditions complex **4** gave a somewhat lower yield (25%), together with 75% of hexyl hexanoate (Table 1, entries 8 and 9). Using 1 mol% of catalyst **3** and 1.1 mol% KO-*t*-Bu for 24 h the yield of desired amide was further improved to 88% (Table 1, entry 10).

Expanding the scope of the reaction with respect to more bulky secondary amines, a toluene solution containing *N*-ethylbenzylamine, 1-hexanol, 1 mol% catalyst **3** and 1.1 mol% KO-*t*-Bu was refluxed for 24 h resulting in 55% yield of *N*-benzyl-*N*-ethylhexanamide together with 45% of hexyl hexanoate (Table 1, entry 11). Retardation of the amidation reaction is affected not only by the steric bulk of the amine group, but also by a substituent at the β-position of the alcohol. Thus, the reaction between 2-methyl-1-butanol and *N*-methylpiperazine using 1 mol% catalyst **3** and 1.1 mol% KO-*t*-Bu gave 2-methyl-1-(4-methylpiperazin-1-yl)butan-1-one in 56% yield together with 44% yield of hexyl hexanoate (Table 1, entry 12). On increasing the bulkiness of both the alcohol and the amine, the reaction of 2-methylbutanol and *N*-methylbenzylamine catalyzed by 1 mol% complex **3** and 1.1 mol% KO-*t*-Bu gave a 50% yield of the desired amide.

It was of interest to us to explore the reactivity and selectivity difference between primary and secondary amines in the dehydrogenative amidation with primary alcohols (Scheme 2). For this purpose, 1-hexanol (1 equiv.) was reacted with a toluene solution containing 1-heptylamine (2 equiv.), *N*-methylpiperazine (2 equiv.), 0.2 mol% of catalyst **2** and 0.22 mol% KO-*t*-Bu or a mixture of 0.2 mol% catalyst **3** and 0.22 mol% KO-*t*-Bu. After 24 h reflux in toluene, *N*-heptylhexanamide and 1-(4-methylpiperazin-1-yl)hexan-1-one were formed in a ratio of 63:37 and 60:40, respectively, with the complete consumption of 1-hexanol, as indicated by GC and GC-MS. Refluxing a tol-



Scheme 2. Competitive amidation reactions between primary and secondary amines in reactions with 1-hexanol.

uene solution containing 1-hexanol (1 equiv.), 1-heptylamine (2 equiv.) and *N*-ethylbenzylamine (2 equiv.) with 0.2 mol% of catalyst **2** and 0.22 mol% KO-*t*-Bu or a mixture of 0.2 mol% catalyst **3** and 0.22 mol% KO-*t*-Bu gave 95:5 or 94:6 mixtures of *N*-heptylhexanamide and *N*-benzyl-*N*-ethylhexanamide, respectively. Similarly under the same conditions 1-hexanol (1 equiv.), 1-heptylamine (2 equiv.) and *N*-methylbutylamine (2 equiv.) gave selectively *N*-heptylhexanamide in 99% yield.

Thus, in the competitive amidation reaction (Scheme 2), the less bulky primary amine reacts faster than the cyclic secondary amine, and almost complete selectivity to primary amide formation is obtained in the reaction of 1:1 mixtures of linear primary and secondary amines.

A possible catalytic cycle for the amidation of primary alcohol and secondary amines involves O–H activation of the primary alcohol followed by H_2 elimination to give an intermediate aldehyde, which forms a hemiaminal by reaction with the secondary amine. Dehydrogenation of the hemiaminal yields the amide. The self-esterification product of the primary alcohol, if formed, can be converted to the desired amide by reaction of the ester with the amines.[8b]

In conclusion, an efficient approach for the synthesis of tertiary amides by the direct amidation of alcohols with challenging secondary amines was developed with a well-defined PNN-bipyridyl ruthenium complex, using a catalyst loading as low as 0.2%. In the case of amidation of sterically hindered secondary amines involvement of ester intermediates was observed.

Experimental Section

General Procedure for the Amidation Reaction

Complex **3** (0.01 mmol), KO-*t*-Bu (0.011 mmol) primary alcohol (5 mmol), secondary amine (5.5 mmol) and toluene (2 mL) were added to a Schlenk flask under an atmosphere of nitrogen in a Vacuum Atmospheres glovebox. The flask was equipped with a condenser and the solution was refluxed with stirring in an open system under argon for the specified time (Table 1) at 135 °C (oil bath temperature). The reaction products were analyzed by GC-MS. After cooling to room temperature, *m*-xylene (1 mmol) was added as an internal standard to the reaction mixture and the products were quantitatively analyzed by GC using a Carboxen 1000 column on an HP690 series GC system or HP-5 cross linked 5% PH ME Siloxane column (30 m, 0.32 mm, 0.25 mm film thickness) on an HP 6890 series GC system. Pure amides were isolated by silica gel chromatography. Characterization data are available in the Supporting Information.

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[11] The reaction was performed using complex **5** as catalyst, or the catalyst was generated *in situ* by use of a mixture of complex **2** and 1.1 equiv. KO-*t*-Bu. Both gave the same yield of the desired amide.

Formation of Tertiary Amides and Dihydrogen by Dehydrogenative Coupling of Primary Alcohols with Secondary Amines Catalyzed by Ruthenium Bipyridine-Based Pincer Complexes

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