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Direct Amide Synthesis from Either Alcohols or Aldehydes with Amines: Activity of Ru(II) Hydride and Ru(0) Complexes

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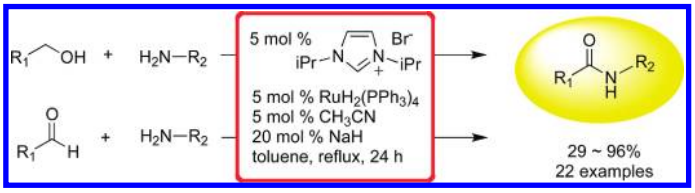

An in situ generated catalyst from readily available $RuH_2(PPh_3)_4$, an *N*-heterocyclic carbene (NHC) precursor, NaH, and acetonitrile was developed. The catalyst showed high activity for the amide synthesis directly from either alcohols or aldehydes with amines. When a mixture of an alcohol and an aldehyde was reacted with an amine, both of the corresponding amides were obtained with good yields. Homogeneous Ru(0) complexes such as (η^4-1,5-cyclooctadiene)(η^6-1,3,5-cyclooctatriene)-ruthenium [Ru(cod)(cot)] and $Ru_3(CO)_{12}$ were also active in the amidation of an alcohol or an aldehyde with the help of an in situ generated NHC ligand.

Introduction

The amide bond is a key functional group in organic and biological chemistry.[1] Beyond conventional methods toward the synthesis of amides,[2] many alternative strategies have been reported.[3] The importance of the alternative strategies for the amide synthesis was adequately demonstrated by Tani and Stoltz for the synthesis of 2-quinuclidonium tetrafluoroborate using an intramolecular Schmidt−Aubé reaction.[4] Among the alternative strategies, transition-metal-catalyzed oxidative amidation of aldehydes with primary amines has been reported using Cu,[5] Pd,[6] Rh,[7] Ru,[8] and lanthanide[9,10] complexes. Recently, several groups have reported direct amide synthesis even from alcohols with amines using Ru-,[8,11−15] Rh-,[16] and Ag-based[17] catalytic systems by liberating two molecules of hydrogen.[18] The direct acylations of amines with alcohols or aldehydes are highly desired atom economical transformations that evolve

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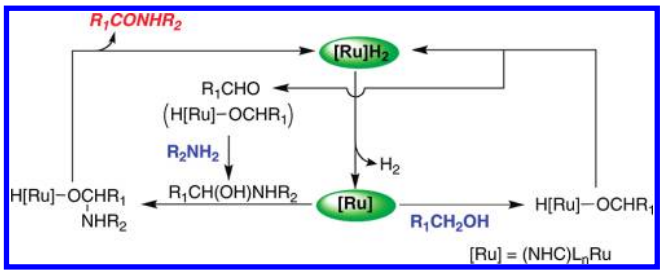
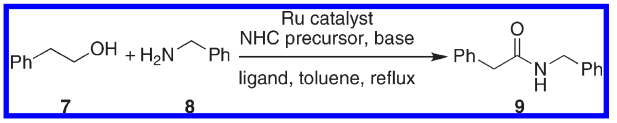
SCHEME 1. Proposed [Ru]H_2-Mediated Mechanism



hydrogen as a sole byproduct with less waste than traditional amide synthesis that often produces toxic chemical waste with tedious procedures.

Although it is logically proposed that the direct amidation of alcohols catalyzed by Ru complexes occurs through aldehydes generated by oxidation of alcohols, the reported NHC-promoted Ru catalytic systems showed limited or no activity on the amidation of aldehydes.[12,14,15] To address the problem, our group proposed a [Ru]H_2-mediated mechanism with experimental evidence that the limited activity from the aldehydes was due to the not facile generation of the active [Ru]H_2 catalytic intermediate without the help of primary alcohols (Scheme 1).[15] From the mechanistic insight, we postulated that an active catalyst that can transform either alcohols or aldehydes to amides with amines could be developed from Ru hydride complexes. Herein, we report an in situ generated catalyst based on $RuH_2(PPh_3)_4$ for the efficient direct amide synthesis whether from alcohols or aldehydes with primary and secondary amines. To the best of our knowledge, this is the first example of a transition-metal-based catalytic system that efficiently transforms either alcohols or aldehydes into amides under the same reaction condition by a single step.

TABLE 1. Catalyst Screening for the Amidation of 7 with 8[a]



entry	catalyst	NHC precursor	base	ligand	yield[b] (%)
1	$RuH_2(PPh_3)_4$				< 3
2	$RuH_2(PPh_3)_4$	**1**	NaH		47
3	$RuH_2(PPh_3)_4$	**1**	NaH	CH_3CN	92
4	$RuH_2(PPh_3)_4$	**1**	KO^{t}Bu	CH_3CN	79
5	$RuH_2(PPh_3)_4$	**1**	NaH	pyridine	55
6	$RuH_2(PPh_3)_4$	**1**	NaH	PPh_3	74
7	$RuH_2(PPh_3)_4$	**1**	NaH	PCy_3	55
8	$RuH_2(PPh_3)_4$	**1**	NaH	PCy_2Ph	61
9	$RuH_2(PPh_3)_4$	**1**	NaH	DPPE	6
10	$RuH_2(PPh_3)_4$	**2**	NaH	CH_3CN	54
11	$RuH_2(PPh_3)_4$	**3**	NaH	CH_3CN	32
12	$RuH_2(PPh_3)_4$	**4**	NaH	CH_3CN	67
13	$RuH_2(PPh_3)_4$	**5**	NaH	CH_3CN	17
14	$RuH_2(PPh_3)_4$	**6**	NaH	CH_3CN	31
15	$RuH_2(PPh_3)_4$	**2**	NaH	PPh_3	23
16	$RuH_2(PPh_3)_4$	**3**	NaH	PPh_3	9
17	$RuH_2(PPh_3)_4$	**4**	NaH	PPh_3	12
18	$RuH_2(PPh_3)_4$	**5**	NaH	PPh_3	9
19	$RuH_2(PPh_3)_4$	**6**	NaH	PPh_3	10
20	$RuH_2(CO)(PPh_3)_3$	**1**	NaH	CH_3CN	86
21	$RuH_2(CO)(PPh_3)_3$	**1**	NaH	pyridine	80
22	$RuH_2(CO)(PPh_3)_3$	**1**	NaH	PPh_3	58
23	$RuH_2(CO)(PPh_3)_3$	**1**	NaH	PCy_3	56
24	$RuHCl(CO)(PPh_3)_3$	**1**	NaH	PPh_3	80
25	$RuHCl(CO)(PPh_3)_3$	**1**	NaH	CH_3CN	80
26	$RuHCl(CO)(PPh_3)_3$	**1**	NaH	pyridine	75
27	$RuHCl(CO)(PPh_3)_3$	**1**	NaH	PCy_3	76
28	Shvo catalyst	**1**	NaH	CH_3CN	37
29	$RuH_2(PMe_3)_4$	**1**	NaH	CH_3CN	20

[a]Ru complex (5 mol % of [Ru]), NHC-precursor (5 mol %), base (20 mol %), ligand (5 mol %), alcohol (1 equiv), amine (1.1 equiv), toluene, reflux, 24 h. [b]Determined by GC using dodecane as an internal standard.

Results and Discussion

Optimization of Reaction Conditions. A reaction of 2-phenylethanol (**7**) with benzylamine (**8**) was chosen as a model to investigate Ru hydride based catalytic systems for the amidation of alcohols (Table 1). $RuH_2(PPh_3)_4$ itself afforded a trace amount of **9** (entry 1). With the help of an in situ generated NHC ligand, the yield was dramatically improved (entry 2). Various supporting ligands were screened along with other Ru hydride complexes. It was interesting to see economical acetonitrile most effective rather than oxidation-susceptible phosphines, such as PCy_3, as we observed the same trend in the [Ru]Cl_2-based catalytic systems.[14] Readily available $RuH_2(PPh_3)_4$ showed the highest activity of the Ru hydride sources screened. Among the tested NHC precursors (Figure 1), diisopropylimidazolium bromide (**1**) exhibited the best yield, also consistent with previous reports (entries 10−14).[12,14] Next we applied some of the Ru hydride based conditions to the reaction of benzaldehyde (**10**) and benzylamine (Table 2). To our

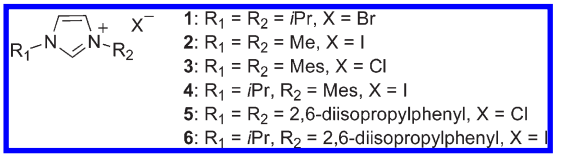
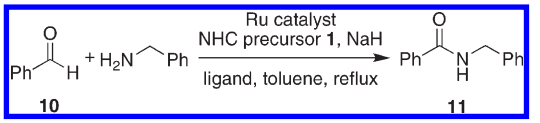


FIGURE 1. NHC precursors.

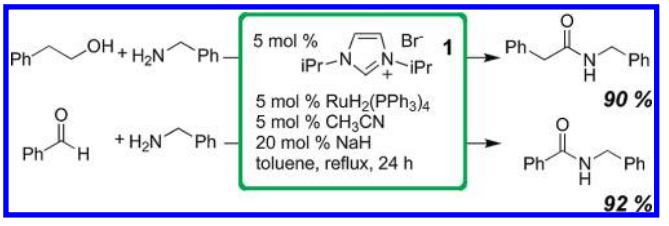
TABLE 2. Catalyst Screening for the Amidation of an Aldehyde 10[a]



entry	catalyst	ligand	yield[b] (%)
1	$RuH_2(PPh_3)_4$	CH_3CN	96
2	$RuH_2(PMe_3)_4$	CH_3CN	21
3	$RuH_2(CO)(PPh_3)_3$	CH_3CN	87
4	$RuH_2(CO)(PPh_3)_3$	pyridine	74
5	$RuH_2(CO)(PPh_3)_3$	PPh_3	57
6	$RuHCl(CO)(PPh_3)_3$	CH_3CN	49

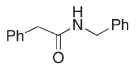
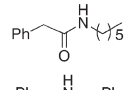
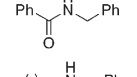
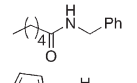
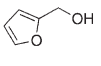
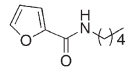
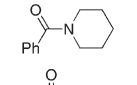
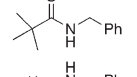
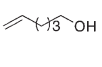
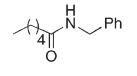
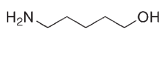
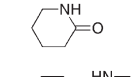
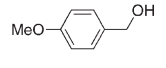
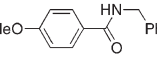
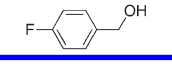
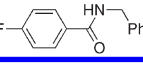
[a]Ru complex (5 mol % of [Ru]), NHC-precursor (5 mol %), base (20 mol %), ligand (5 mol %), aldehyde (1 equiv), amine (1.1 equiv), toluene, reflux, 24 h. [b]Determined by GC using dodecane as an internal standard.

SCHEME 2. $RuH_2(PPh_3)_4$-Catalyzed Amidation[a]



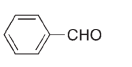
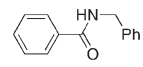
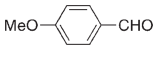
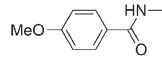
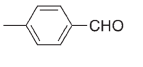
[a]Isolated yields, average of two runs

TABLE 3. Direct Amide Synthesis from Alcohols and Amines[a]

entry	alcohol	amine	amide	yield[b] (%)
1				90
2				86
3				86
4				85
5				78
6				42
7				38[c]
8				77
9				92
10				72
11				49

[a]$RuH_2(PPh_3)_4$ (5 mol %), **1** (5 mol %), NaH (20 mol %), CH_3CN (5 mol %), alcohol (1 equiv), amine (1.1 equiv), toluene, reflux, 24 h, unless otherwise noted. [b]Isolated yields, average of at least two runs. [c]48 h.

TABLE 4. Direct Amide Synthesis from Aldehydes and Amines[a]

entry	aldehyde	amine	amide	yield[b] (%)
1				92
2				76
3				76
4				79
5				66
6				55
7				56
8				83
9				29[c] (28[d])
10				64 (7[d])
11				47 (14[d])

[a]$RuH_2(PPh_3)_4$ (5 mol %), **1** (5 mol %), NaH (20 mol %), 5 mol % CH_3CN, aldehyde (1 equiv), amine (1.1 equiv), toluene, reflux, 24 h, unless otherwise noted. [b]Isolated yields, average of at least two runs. [c]Determined by GC using dodecane as an internal standard, average of at least two runs. [d]Yield of the corresponding imine, determined by GC using dodecane as an internal standard.

delight, the $RuH_2(PPh_3)_4$-based catalytic system showed excellent activity on the amidation of **10** as well (entry 1, Table 2), realizing the idea of a Ru hydride based catalytic system for the amidation of both alcohols and aldehydes under the same reaction conditions (Scheme 2).

Amidation of Alcohols. The scope of the $RuH_2(PPh_3)_4$-catalyzed amidation reaction of alcohols and amines is presented in Table 3. Excellent yields were obtained when sterically less hindered substrates were reacted (entries 1−5). Cyclic secondary amines and sterically hindered substrates showed diminished activity (entries 6 and 7). The use of 5-hexen-1-ol gave hexanamide with 100% reduction of the double bond (entry 8) as reported.[12,14] Intramolecular amidation was also carried out by using 5-amino-1-pentanol with excellent formation of a lactam, showing significant improvement over the previous $RuH_2(PPh_3)_4$ and hydrogen acceptor system reported by Naota and Murahashi (92% vs 65%, entry 9).[8]

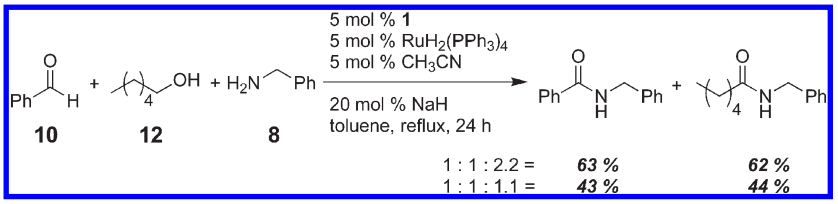
Amidation of Aldehydes. The same reaction conditions were applied to the amidation reactions of aldehydes, and moderate to excellent yields were obtained (Table 4). The reactions of aryl aldehydes proceeded smoothly with primary amines and cyclic secondary amines. We studied electronic effect on aldehyde using benzyl alcohol and benzaldehyde derivatives, but there is no explicit trend in the yields (entries 3, 10, and 11, Table 3 and entries 1−7, Table 4). In case of alkyl aldehydes, slightly reduced yields were obtained with the observation of imine byproducts (entries 9−11). It has been proposed that electronic variation on the hemiaminal Ru intermediates affects the fate of the hemiaminal intermediate as to whether to produce an imine by elimination of water (or an alkylated amine by further reduction of the generated imine) or to produce an amide by further oxidation.[12−15] Similar $[(arene)RuCl_2]_2$-based catalytic systems produced the different product, either the alkylated amine or the amide, depending on the nature of supporting L-type ligands.[13−15,19]

Proposed Mechanism. The proposed Ru(0)/Ru(II) cycle (Scheme 1) from the previous study was supported on the basis of the observation of elimination of hydrogen from an NMR reaction between $RuH_2(PPh_3)_4$, **1**, and NaH under the reaction conditions. At 115 °C, the hydride peak of the catalytic mixture observed at ambient temperature completely disappeared within 30 min, strongly indicating elimination of hydrogen at the reaction temperature. Similar mechanisms involving $[Ru]H_2$ have been proposed in Ru-catalyzed N-alkylation of amines with alcohols[19,20] and

(19) Hamid, M.; Allen, C. L.; Lamb, G. W.; Maxwell, A. C.; Maytum, H. C.; Watson, A. J. A.; Williams, J. M. J. *J. Am. Chem. Soc.* **2009**, *131*, 1766 and more therein.

(20) For early examples of the *N*-alkylation of amines with aliphatic alcohols, see: (a) Murahashi, S.-I.; Kondo, K.; Hakata, T. *Tetrahedron Lett.* **1982**, *23*, 229. (b) Grigg, R.; Mitchell, T. R. B.; Sutthivaiyakit, S.; Tongpenyai, N. *J. Chem. Soc., Chem. Commun.* **1981**, 611. (c) Watanabe, Y.; Tsuji, Y.; Ige, H.; Ohsugi, Y.; Ohta, T. *J. Org. Chem.* **1984**, *49*, 3359.

SCHEME 3. Reactions of a Mixture of an Aldehyde and an Alcohol[a]



[a]Determined by GC using dodecane as an internal standard; the yields are calculated on the basis of **10** or **12** individually.

TABLE 5. Activity of Ru(0) Complexes on the Amidation of 2-Phenylethanol (7) or Benzaldehyde (10) with Benzylamine (8)[a]

entry	substrate	catalyst	base (mol %)	amide[b] (%)
1	**7**	Ru(cod)(cot)	NaH (15)	83
2	**7**	$Ru_3(CO)_{12}$	NaH (30)	59
3	**7**	Ru black	NaH (15)	19
4	**7**	Ru on Al_2O_3	NaH (15)	15
5	**10**	Ru(cod)(cot)	NaH (40)	88
6	**10**	$Ru_3(CO)_{12}$	NaH (40)	41

[a]Catalyst (5 mol % of [Ru]), **1** (5 mol %), NaH, **7** or **10** (1 equiv), **8** (1.1 equiv), toluene, reflux, 24 h. [b]Determined by GC using dodecane as an internal standard.

esterification of alcohols.[21] On the basis of the proposed mechanism, we believe that usage of $[Ru]H_2$ is the key to the improvement on aldehydes over the reported $[Ru]Cl_2$, which showed limited activity on amidation of aldehyde.[22]

In relation with Ru(0) involvement, $Ru_3(CO)_{12}$, (η^4-1,5-cyclooctadiene)(η^6-1,3,5-cyclooctatriene)ruthenium [Ru(cod)(cot)], and other heterogeneous Ru(0) complexes were screened for the amidation reaction of **7** and **10** in the presence of **1** and NaH (Table 5). $Ru_3(CO)_{12}$ and Ru(cod)(cot) complexes showed good activity whether starting from an alcohol **7** or an aldehyde **10** (entries 1, 2, 5, and 6). The in situ generated NHC ligand was essential to make Ru(0) species active. No activity was observed without **1** and a strong base. The screened heterogeneous Ru sources were not as active as homogeneous Ru(0) complexes (entries 3 and 4). Attempts to increase the activity by adding other ligands, such as pyridine, acetonitrile, and phosphines, were not successful. The requirement of increased amounts of NaH, more than for generation of the NHC ligand, was noticed (entries 2, 5, and 6). The reason is not clear, and we think that the role of substoichiometric base is to prevent elimination of water and facilitate the dehydrogenation of the hemiaminal or activate precatalyst from generated alkoxides. It has been reported that a strong base was required to generate catalytically active species in the case of well-defined (arene)Ru(NHC)Cl_2 complexes.[15] $Ru_3(CO)_{12}$ and Ru(cod)(cot) complexes were reported active for the alkylation of amines with alcohols under different conditions.[23]

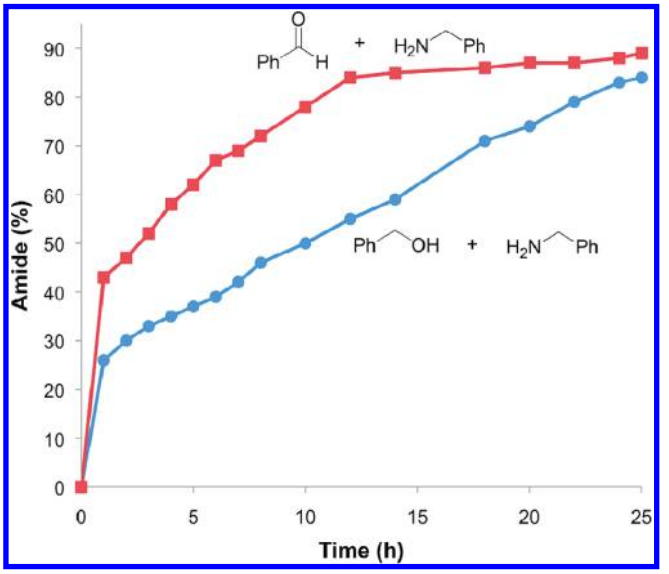


FIGURE 2. Comparison of reaction progress monitored by GC.

Reactivity and Selectivity Difference between Aldehyde and Alcohol. To see whether alcohol or aldehyde is more reactive under our catalytic systems, at first, reaction progress was individually monitored by GC (Figure 2). The reaction with benzaldehyde was faster than that with benzyl alcohol, especially at the initial stage, as expected because one more dehydrogenation step is required for the amidation of alcohol. Retarded reaction rates were observed in both reactions as the reactions progressed, suggesting decomposition of the active catalyst.

Selectivity between an aldehyde and an alcohol was also examined (Scheme 3). When a reaction mixture (**10**:**12**:**8** = 1:1:2.2) was reacted, both of the corresponding amides were obtained in good yields, demonstrating the advantage of the methodology of direct amide synthesis whether from alcohols or aldehydes. However, when we used a decreased amount of an amine (**10**:**12**:**8** = 1:1:1.1), we obtained a mixture of products with observation of benzyl alcohol during the reaction, showing no selectivity between alcohol and aldehyde with transfer hydrogenation from **12** to **10**.

Conclusions

In conclusion, we have demonstrated that an in situ generated Ru catalyst can synthesize amides directly from either alcohols or aldehydes with amines. The developed catalyst is operatively simple and more active, especially toward aldehyde substrates, than the previously reported

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(22) For some examples of NHC-based Ru hydride complexes on hydrogen tranfer reactions, see: (a) Ledger, A. E. W.; Mahon, M. F.; Whittlesey, M. K.; Williams, J. M. J. *Dalton Trans.* **2009**, 6941. (b) Burling, S.; Whittlesey, M. K.; Williams, J. M. J. *Adv. Synth. Catal.* **2005**, *347*, 591. (c) Edwards, M. G.; Jazzar, R. F. R.; Paine, B. M.; Shermer, D. J.; Whittlesey, M. K.; Williams, J. M. J.; Edney, D. D. *Chem. Commun.* **2004**, 90.

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well-defined (*p*-cymene)(NHC)$RuCl_2$-type catalysts. When the reaction rate was compared, benzaldehyde was transformed to *N*-benzylbenzamide faster than benzyl alcohol especially at the initial stage. If a mixture of benzaldehyde and 1-hexanol was reacted with benzylamine, both of the corresponding amides were formed with good yields. To understand the nature of active catalytic intermediates, some Ru(0) species were screened. Homogeneous Ru(0) complexes such as Ru(cod)(cot) and $Ru_3(CO)_{12}$ were active in the amidation of alcohol or aldehyde with the help of an in situ generated NHC ligand suggesting that the proposed Ru(0)/Ru(II) cycle is viable.

Experimental Section

General Considerations. All reactions were carried out using standard Schlenk techniques or in an argon-filled glovebox. Toluene, hexane, and ether were dried over a solvent purification system.[24] Deuterated solvents were dried over molecular sieves. ^1H and ^{13}C NMR spectra at 400 and 100 MHz, respectively, were recorded in $CDCl_3$ using tetramethylsilane as a reference. GC analyses were carried out using dodecane as an internal standard. Mass spectrometry was performed using electrospray ionization (ESI) mode. Anhydrous acetonitrile, 1,3-(2,6-diisopropylphenyl)imidazolium chloride, and 1,3-bis-(2,4,6-trimethylphenyl)imidazolium chloride were purchased and used without further purification. $Ru_3(CO)_{12}$, Ru black, and Ru on Al_2O_3 were purchased from Strem Chemicals and used without further purification. 1,3-Dimethylimidazolium iodide,[25] 1,3-diisopropylimidazolium bromide,[26] $RuH_2(PPh_3)_4$,[27] $RuH_2(PMe_3)_4$,[28] $RuH_2(CO)(PPh_3)_3$,[29] $RuHCl(CO)(PPh_3)_3$,[29] and Ru(cod)(cot)[30] were prepared according to the reported procedures.

General Procedure for the Amide Synthesis. $RuH_2(PPh_3)_4$ (28 mg, 0.025 mmol), 1,3-diisopropylimidazolium bromide (5.8 mg, 0.025 mmol), NaH (2.4 mg, 0.1 mmol), and acetonitrile (1.2 μL, 0.025 mmol) were placed in an oven-dried Schlenk tube inside the glovebox; toluene (0.6 mL) was added to the mixture. The Schlenk tube was taken out and heated to reflux in an oil bath under an argon atmosphere. The flask was removed from the oil bath after 20 min, and the alcohol or aldehyde (0.50 mmol) and amine (0.55 mmol) were added. The mixture was heated to reflux under a flow of argon to facilitate removal of hydrogen for 24 h. The reaction mixture was cooled to room temperature. The solvent was removed in vacuo, and the residue was purified by silica gel flash column chromatography to afford the amide. All of the amides, *N*-benzyl-2-phenylacetamide,[14] *N*-hexyl-2-phenylacetamide,[14] *N*-benzylbenzamide,[14] *N*-benzylhexanamide,[14] phenyl(piperidin-1-yl)methanone,[14] *N*-benzylpivalamide,[14] piperidin-2-one,[14] *N*-benzyl-4-methoxybenzamide,[15] *N*-benzyl-4-fluorobenzamide,[31] *N*-benzyl-4-methylbenzamide,[32] *N*-benzyl-4-chlorobenzamide,[32] piperidin-1-yl(*p*-tolyl)-methanone,[10] (4-chlorophenyl)(piperidin-1-yl) methanone,[10] *N*-hexylbenzamide,[33] *N*-pentylhexanamide,[14] and *N*-benzylnonanamide,[34] were identified by spectral comparison with literature data.

***N*-Pentyl-2-furancarboxamide**[35]**.** Purified by silica gel column chromatography using hexane/ethyl acetate (3:1) solvent mixture as an eluent. Pale yellow liquid. Yield: 78%. ^1H NMR ($CDCl_3$) δ 7.4 (m, 1H), 7.0 (m, 1H), 6.5 (m, 1H), 6.4 (bs, 1H), 3.4 (m, 2H), 1.6 (m, 2H), 1.3 (m, 4H), 0.9 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 158.5, 148.2, 143.6, 114.0, 112.1, 39.2, 29.5, 29.1, 22.5, 14.0. HRMS (ESI) calcd for $C_{10}H_{15}NO_2$: 182.1181. Found: 182.1182 [MH^+].

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Supporting Information Available: ^1H NMR spectra of the isolated amides. This material is available free of charge via the Internet at http://pubs.acs.org.

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