JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

N-Heterocyclic Carbene Based Ruthenium-Catalyzed Direct Amide Synthesis from Alcohols and Secondary Amines: Involvement of Esters

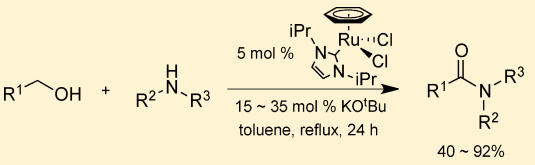
Cheng Chen,[‡] Yao Zhang,[‡] and Soon Hyeok Hong[†,‡,*]

[†]Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151-747, Korea

[‡]Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore

Supporting Information

ABSTRACT: A well-defined *N*-heterocyclic carbene based ruthenium complex was developed as a highly active precatalyst for the direct amide synthesis from alcohols and secondary amines. Notably, reaction of 1-hexanol and dibenzylamine afforded 60% of the corresponding amide using our catalytic system, while no amide formation was observed for this reaction with the previously reported catalytic systems. Unlike the previously reported amidation with less sterically hindered alcohols and amines, involvement of ester intermediates was observed.

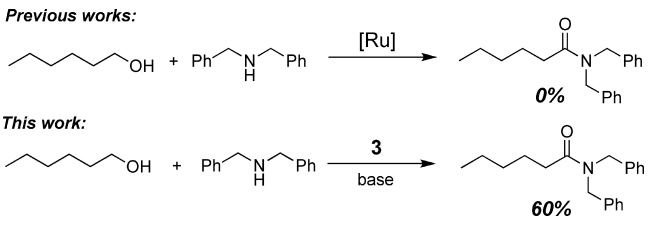


INTRODUCTION

Transition-metal-catalyzed oxidative amide synthesis directly from alcohols and amines, without any oxidative preparation of aldehydes, carboxylic acids, and acyl halides, has been recently highlighted as a highly atom economical transformation that generates hydrogen as the sole byproduct.[1] Among the reported catalytic systems, ruthenium complexes have been most extensively studied.[2−11]

Although the direct amide synthesis has attractive advantages over traditional amide syntheses, there are many challenges for this emerging method to be widely used for the synthesis of ubiquitous amides, such as limited substrate scope and harsh reaction conditions.[1] One of the challenges is the amidation of secondary amines.[1] The reported Ru catalysts showed limited activity for the reactions between alcohols and linear secondary amines, especially with sterically hindered ones, while they showed excellent activity for less hindered primary amines.[2−10] For example, no desired product has been observed with the previous catalytic systems when dibenzylamine was used for the amidation reaction (Scheme 1).[3,5] Herein, we wish to address the issue by reporting an NHC-based Ru complex as an active precatalyst for the amide synthesis from alcohols and secondary amines.

Scheme 1. Reaction of 1-Hexanol and Dibenzylamine



Our group reported (*p*-cymene)(NHC)RuX$_2$ complexes such as **1** and **2** as precatalysts for the direct amide synthesis (Figure 1).[6] When we attempted less sterically bulky NHC-based **2** for the transformation of sterically hindered substrates including secondary amines, no improvement was observed. Although it was postulated that the arene group would be dissociated during the catalysis,[6,8,10] it was reported that improvements could be achieved by changing a Ru precursor [RuCl$_2$(*p*-cymene)]$_2$ with [RuCl$_2$(benzene)]$_2$ for less hindered cyclic secondary amines such as piperidine and morpholine.[5] As an example, the [RuCl$_2$(benzene)]$_2$-based catalytic system showed 90% yield on the amidation of morpholine with 2-phenylethanol (vs 63% with [RuCl$_2$(*p*-cymene)]$_2$), although it still showed limitations on other steically more congested secondary amines such as dibenzylamine.[5] These observations led us to explore the catalytic activity of Ru complex **3** for the amidation of challenging secondary amines with alcohols.

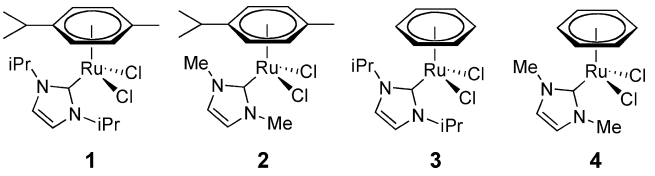


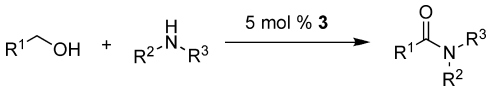
Figure 1. Ru complexes for the direct amide synthesis from alcohols and amines.

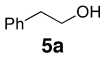
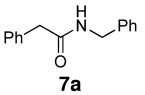
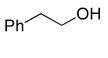
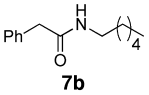
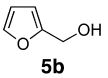
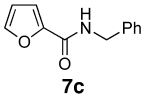
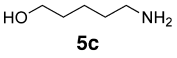
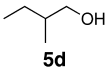
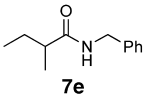
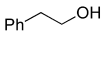
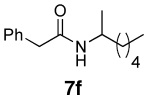
RESULTS AND DISCUSSION

Complex **3** was synthesized by transmetalation from an NHC-Ag complex, and the structure was confirmed by X-ray

Received: August 24, 2011
Published: November 15, 2011

Table 1. Direct Amide Synthesis from Alcohols and Primary Amines Catalyzed by 3[a]



Entry	Alcohol	Amines	Amide	Yield (%)[b]
1	 **5a**	 **6a**	 **7a**	92
2		 **6b**	 **7b**	90
3	 **5b**		 **7c**	80
4	 **5c**		 **7d**	90
5	 **5d**		 **7e**	66
6		 **6c**	 **7f**	70[c]

[a]Catalyst **3** (5 mol %), KO*t*Bu (15 mol %), toluene, reflux, 24 h unless otherwise noted. [b]Isolated yields. No ester was observed. [c]20 mol % KO*t*Bu.

crystallography.[12] Attempts to synthesize less sterically congested **4** by the same procedure were not successful presumably as a result of lower stability. Since no improvement was previously reported on sterically bulky substrates with **2** over **1**, we decided to pursue the amidation reaction only with **3**.[6,9] It has been consistently reported that 1,3-diisopropylimidazoline showed the best activities on the NHC-promoted Ru-catalyzed amide synthesis among the other NHCs.[4−9]

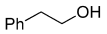
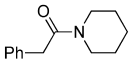
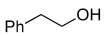
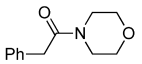
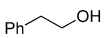
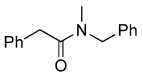
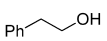
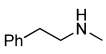
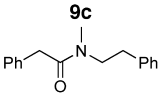
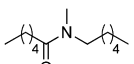
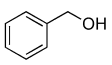
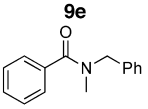
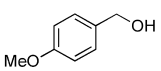
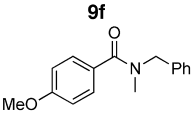
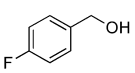
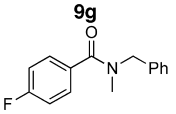
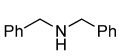
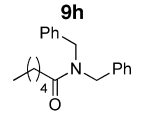
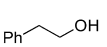
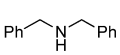
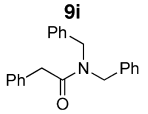
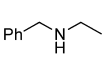
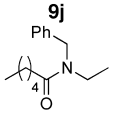
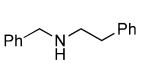
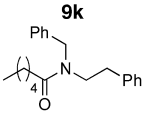
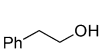
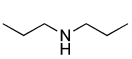
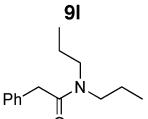
Reactions of alcohols and primary amines catalyzed by **3** were explored first (Table 1). The optimization of the catalytic conditions was conducted with a reaction of **5a** and **6a**. It was found that 15−20 mol % KO*t*Bu or NaH and 5 mol % of **3** are required for the catalysis, consistent with the previous report.[6] It was suggested that the role of the strong base is to stimulate the formation of Ru alkoxide species, which are further transformed to an active Ru hydride catalytic intermediate.[6,7] Good to excellent yields were obtained for both intermolecular and intramolecular processes with precatalyst **3** (Table 1). Catalytic activities of **3** on the amidation of primary amines with alcohols were generally comparable with **1** and **2**.[6] No ester was observed in the reactions in Table 1, consistent with other NHC-Ru catalyzed amidation of less hindered primary amines with alcohol.[4,5]

Next, various secondary amines were tested for the amidation reactions (Table 2). To our delight, **3** showed higher activity for secondary amines with increased amount of KO*t*Bu. Cyclic secondary amines and less bulky noncyclic ones yielded excellent yields (entries 1−5). The previously reported yields for the reaction between a primary alcohol and *N*-benzyl methylamine are 40−70%.[4,5,8] In contrast, **3** can catalyze the same reaction in 90% yield (entry 3). We studied the electronic effect on alcohols using benzyl alcohol derivatives. Slightly lower yields were obtained for electron-deficient substrates as observed with complex **1** and **2** (entries 6−8).[6] Excitingly, the more bulky secondary amine, dibenzylamine, worked well in the presence of 35 mol % of KO*t*Bu (entries 9 and 10), while previously reported catalysts were not active for the reaction of a primary alcohol and dibenzylamine.[3,5] A few bulky secondary amines were tested, and moderate to good yields were obtained (entries 11−13). Different from the cases of primary amines in Table 1, we observed esters, formed by oxidative esterification of alcohols **5**, as a byproduct in some cases, especially when the reaction was performed with sterically bulky secondary amines (Table 2).[13]

To understand the rationale for the improvement on the secondary amine, we first investigated the effect of the arene ring of precatalysts **1** and **3**. Initially, we suspected that less hindered benzene compared to *p*-cymene would result in the improvement for more hindered secondary amines. Noyori, Ikariya, and co-workers discussed the arene effect in $[RuCl_2(arene)]_2$ complexes for asymmetric transfer hydrogenation.[14] Noels and co-workers also reported the effect of the arene on the $RuCl_2(arene)(PR_3)$-catalyzed ring-opening metathesis polymerization.[15] It has been reported in different cases that dissociation of the arene ligand is necessary for catalytlic activity of 18-electron $RuCl_2(arene)(L)$-type complexes (L = PR_3 or NHC).[15,16] In the case of the direct amidation catalyzed by **1** and **2**, it has been also suggested that arene ligand is fully dissociated especially at the required reaction temperature of 110 °C.[4−9] Indeed, free benzene or *p*-cymene was observed during catalysis when the reaction was monitored by ^{1}H NMR spectroscopy in toluene-d_8 indicating the full dissociation of arene rings. Therefore, we believe that the reduced steric effect of the benzene ring of **3** should not be the reason. Next, we

dx.doi.org/10.1021/jo201756z|*J. Org. Chem.* 2011, 76, 10005−10010

Table 2. Direct Amide Synthesis from Alcohols and Secondary Amines Catalyzed by 3[a]

Entry	Alcohol	Amines	Amide	Yield(%)[b]
1		 **8a**	 **9a**	92 (<1)[c]
2		 **8b**	 **9b**	86 (<5)[c]
3		 **8c**	 **9c**	90 (<1)[c]
4		 **8d**	 **9d**	87 (<5)[c]
5	 **5e**	 **8e**	 **9e**	81 (9)[c]
6	 **5f**	 **8f**	 **9f**	80 (<1)
7	 **5g**	 **8g**	 **9g**	75 (2)
8	 **5h**	 **8h**	 **9h**	47 (<1)
9		 **8i**	 **9i**	60 (<3)
10			 **9j**	40 (19)
11		 **8g**	 **9k**	60 (13)
12		 **8h**	 **9l**	43 (18)
13		 **8i**	 **9m**	44 (21)[d]

[a]Complex **3** (5 mol %), KO*t*Bu (35 mol %), 1 equiv alcohol and 1.1 equiv amine, toluene, reflux, 24 h unless otherwise noted. [b]Isolated yields. Yields in parentheses represent the yields of the corresponding ester from alcohol **5**. [c]20 mol % KO*t*Bu. [d]1 equiv alcohol and 2 equiv amine.

focused on the less electron-rich nature of benzene compared to *p*-cymene. If full dissociation of the arene ring should occur to generate the active catalytic intermediate, **3** can generate the active catalytic intermediate, i.e., initiate the catalytic cycle faster than with **1** because of the more electron-deficient arene ring. Kinetic data showed that the reactions catalyzed by **3** were faster than those catalyzed by **1** (23% by **1** vs 31% by **3** for the reaction of entry 9 in Table 2, after 3 h, Figure 2), suggesting that faster dissociation of benzene ring could be one of the reasons of the improvement. However, the undramatic reaction rate acceleration with **3** implied that there might be another reason for the improvement.

Next, we noticed that the increased amount of KO*t*Bu was required. Previously, there was no significant formation of **9i** with 5 mol % complex **1** and **2** and 15−20 mol % of KO*t*Bu. The improved conversion in Figure 2, even with **1**, strongly

dx.doi.org/10.1021/jo201756z|*J. Org. Chem.* 2011, 76, 10005−10010

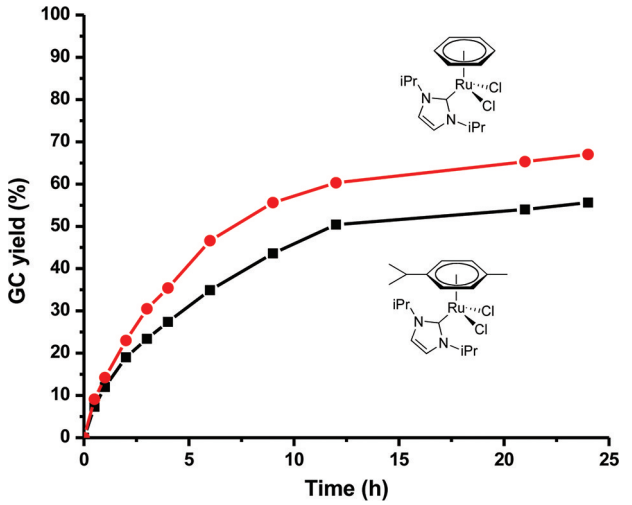
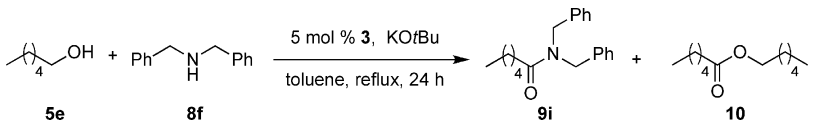


Figure 2. Comparison of reaction progress monitored by GC (entry 9 in Table 2).

implied that the increased amount of the strong base might be the key of the improvement. The role of a catalytic amount of a strong base was suggested to activate $[Ru]Cl_2$-type precatalysts by generating $[Ru]H_2$ species from alkoxides and the precatalysts.[6] However, the increased amounts of the base in this study, compared to those used in the primary amine amidations, implied that there might be another role of the base. Product distribution depending on the amount of the base was thoroughly investigated with the reaction between **5e** and **8f** catalyzed by **3** (Table 3). It was found that as the amount of KO*t*Bu increased up to 35 mol %, the yield of the desired product **9i** increased while that of the major byproduct **10** decreased, which means the increased amount of KO*t*Bu either decreased the formation of **10** or promoted the reaction between **10** and **8f** to give **9i** (Table 3). The Ru-catalyzed formation of esters from alcohols has been well documented.[13] It was also reported as one of side reactions on the Ru-catalyzed amide and cyclic imide syntheses from alcohols.[3,8,17]

A few catalytic amide formation reactions from esters and amines have been reported including the very recent report using dearomatized Ru-pincer complexes by Milstein and co-workers.[18] NHC-based Ru catalytic systems developed for the amide synthesis from alcohols and amines were reported not efficient for the amide formation from esters and amines.[3−5] The less efficient amidation of esters under the reported catalytic conditions using 15−20 mol % of a strong base were confirmed again by entry 3 in Table 3.[5] However, when an increased amount of KO*t*Bu was used, the amidation from ester worked with moderate yields (entries 4−8, Table 4). The optimal amount of the base, 0.3−0.5 equiv, was close to our current conditions for the secondary amine amidation.

Table 3. Reaction of 1-Hexanol and Dibenzylamine Catalyzed by 3 with Different Amounts of KO*t*Bu

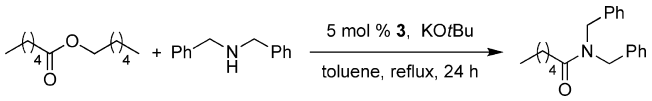


5e **8f** **9i** **10**

entry	KO*t*Bu (equiv)	**9i** (%)[a]	**10** (%)[a]
1	0.15	33	61
2	0.20	34	50
3	0.25	50	10
4	0.30	51	8
5	0.35	60	<3
6	0.40	44	<1
7	0.60	30	<1
8	1.00	11	<1

[a]Isolated yields.

Table 4. Reaction of an Ester and Dibenzylamine Catalyzed by 3 with Different Amounts of KO*t*Bu



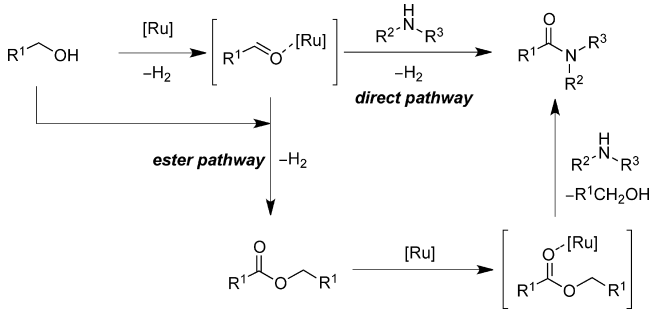
entry	precatalyst	KO*t*Bu (equiv)	yield for **9i** (%)[a]
1	**3**	0.00	<1
2	**3**	0.10	<1
3	**3**	0.20	6
4	**3**	0.30	39
5	**3**	0.35	46
6	**3**	0.40	59
7	**3**	0.45	44
8	**3**	0.50	40
9	**3**	0.60	31
10	**3**	1.00	10
11		0.40	<1

[a]Isolated yields.

dx.doi.org/10.1021/jo201756z|*J. Org. Chem.* 2011, 76, 10005−10010

Therefore, we believe that in the case of sterically hindered secondary amine amidation where direct amidation is less efficient, involvement of an ester intermediate and its conversion to the amide product with help of a catalytic intermediate, presumably generated by a Ru−NHC complex and an increased amount of a base, is essential for the improvement. The exact nature of the catalytic intermediate and the precise role of the increased amount of the base are currently unclear. Revised pathways for the amidation of alcohols with amines are suggested in Scheme 2.[19] We are currently investigating the amidation of esters with the NHC-based Ru catalytic systems.

Scheme 2. Proposed Pathways for the Direct Amidation of Alcohols with Amines



CONCLUSION

The direct amidation of alcohols with challenging secondary amines was achieved with a well-defined *N*-heterocyclic carbene based ruthenium complex. Involvement of ester intermediates was suggested unlike the previous amidation with less sterically hindered alcohols and amines. The scope and the nature of catalysts for NHC-Ru catalyzed conversion from esters to amides will be reported in due course.

EXPERIMENTAL SECTION

General Considerations. All reactions were carried out using standard Schlenk techniques or in an argon-filled glovebox unless otherwise mentioned. ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Chemical shifts were reported in ppm and coupling constants in Hz. GC analyses were carried out using dodecane as an internal standard. Mass spectrometry was performed using electrospray ionization (ESI) mode.

Materials. 1,3-Diisopropylimdazolium bromide,[5] hexyl hexanoate (**10**),[20] phenethyl 2-phenylacetate (**11**),[4] 4-methoxybenzyl 4-methoxybenzoate (**12**),[21] and compound **1**[6] were prepared by the literature procedures. Alcohols and amines were purchased from commercial suppliers and used as received without further purification. Toluene was dried over a solvent purification system.

Synthesis of 3. A suspension of 1,3-diisopropylimdazolium bromide (106.4 mg, 0.46 mmol) and Ag_2O (64.0 mg, 0.28 mmol) in CH_2Cl_2 was stirred at room temperature in dark for 2 h. The mixture was then filtered through a plug of Celite, followed by the addition of $[RuCl_2(benzene)]_2$ (115.0 mg, 0.23 mmol). The reaction mixture was stirred at room temperature for 4 h and then filtered through Celite. The solvent was removed under vacuum. Washing the crude product with diethyl ether (3 × 5 mL) afforded **3** as an orange powder. Yield: 85% (156.8 mg, 0.39 mmol). Mp 219 °C dec; ^{1}H NMR (CD_2Cl_2) δ 7.17 (s, 2H), 5.53 (s, 6H), 5.35−5.50 (m, 2H), 1.25−1.55 (m, 12H); ^{13}C NMR (CD_2Cl_2) δ 170.1, 119.7, 86.5, 52.8, 25.5, 24.6. Anal. Calcd for $C_{15}H_{22}Cl_2N_2Ru$ (**3**): C, 44.78; H, 5.51; N, 6.96. Found: C, 44.65; H, 5.12; N, 6.64.

General Procedure for Amide Synthesis. Inside an argon-filled glovebox, compound **3** (10.0 mg, 0.025 mmol), KO*t*Bu (8.4 mg, 0.075 mmol), and toluene (0.6 mL) were added to an oven-dried Schlenk tube. The Schlenk tube was taken out of the glovebox before the alcohol (0.5 mmol) and the amine (0.55 mmol) were added. Then the mixture was heated to reflux under argon atmosphere for 24 h. The reaction mixture was cooled down to room temperature, and the solvent was removed *in vacuo*. The residue was purified by silica gel flash column chromatography to afford the amide. *N*-Benzyl-2-phenylacetamide (**7a**),[5] *N*-hexyl-2-phenylacetamide (**7b**),[5] piperidin-2-one (**7d**),[5] *N*-benzyl-2-methylbutanamide (**7e**),[5] *N*-(heptan-2-yl)-2-phenylacetamide (**7f**),[9] 2-phenyl-1-(piperidin-1-yl)ethanone (**9a**),[9] 1-morpholino-2-phenylethanone (**9b**),[5] *N*-benzyl-*N*-methyl-2-phenylacetamide (**9c**),[5] *N*-benzyl-*N*-methylbenzamide (**9f**),[22] *N*-benzyl-*N*-methyl-4-methoxybenzamide (**9g**),[22] and *N*-benzyl-*N*-methyl-4-fluorobenzamide (**9h**)[22] were identified by spectral comparison with literature data.

***N*-Benzylfuran-2-carboxamide (7c).** Purified by silica gel chromatography using hexane/ethyl acetate (3:1) solvent mixture as an eluent. White solid. Isolated yield: 80%. Mp 112−113 °C. ^{1}H NMR ($CDCl_3$) δ 7.40 (s, 1 H), 7.20−7.38 (m, 5 H), 7.13 (m, 1 H), 6.74 (s, 1H), 6.49 (m, 1 H), 4.60 (d, 2H, J = 5.92 Hz). ^{13}C NMR ($CDCl_3$) δ 158.4, 148.0, 144.1, 138.2, 128.9, 128.0, 127.8, 114.5, 112.3, 43.3. HRMS-ESI (m/z): [M + H$^+$] calcd for $C_{12}H_{12}NO_2$, 202.0868; found, 202.0872.

***N*-Methyl-*N*-phenethyl-2-phenylacetamide (9d).** Purified by silica gel column chromatography using hexane/ethyl acetate (3:1) solvent mixture as an eluent. Pale yellow clear oil. Yield: 87%, 1:1.1 mixture of rotamers. ^{1}H NMR ($CDCl_3$) (major rotamer) δ 7.02−7.38 (m, 10 H), 3.68 (s, 2H), 3.60 (t, 2H, J = 7.56 Hz), 2.84 (s, 3H), 2.83 (t, 2H, J = 7.56 Hz); ^{1}H NMR ($CDCl_3$) (minor rotamer) δ 7.02−7.38 (m, 10 H), 3.49 (t, 2H, J = 7. 32 Hz), 3.44 (s, 2H), 2.98 (s, 3H), 2.72 (t, 2H, J = 7.32 Hz). ^{13}C NMR ($CDCl_3$) δ 171.1, 171.0, 139.2, 138.3, 135.4, 135.1, 129.0, 128.9, 128.8, 128.6, 127.0, 126.9, 126.8, 126.4, 52.2, 50.3, 41.5, 40.8, 36.7, 34.9, 33.8, 33.7. HRMS-ESI (m/z): [M + H$^+$] calcd for $C_{17}H_{20}NO$, 254.1545; found, 254.1547.

***N*-Hexyl-*N*-methylhexanamide (9e).** Purified by silica gel column chromatography using hexane/ethyl acetate (5:1) solvent mixture as an eluent. Colorless clear oil. Yield: 81%, 1:1.05 mixture of rotamers. ^{1}H NMR ($CDCl_3$) (major rotamer) δ 3.25 (t, 2H, J = 7.60 Hz), 2.91 (s, 3H), 2.20−2.40 (m, 2H), 1.42−1.75 (m, 4H), 1.20−1.40 (m, 10H), 0.80−1.00 (m, 6H); ^{1}H NMR ($CDCl_3$) (minor rotamer) δ 3.35 (t, 2H, J = 7.52 Hz), 2.97 (s, 3H), 2.20−2.40 (m, 2H), 1.42−1.75 (m, 4H), 1.20−1.40 (m, 10H), 0.80−1.00 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 173.2, 173.1, 50.2, 47.8, 35.5, 33.7, 33.5, 33.1, 31.9, 31.8, 31.7, 31.6, 28.6, 27.4, 26.6, 26.5, 25.3, 25.0, 22.7, 22.6, 14.2, 14.1. HRMS-ESI (m/z): [M + H$^+$] calcd for $C_{13}H_{28}NO$, 214.2171; found, 214.2178.

***N*,*N*-Dibenzylhexanamide (9i).** Purified by silica gel column chromatography using hexane/ethyl acetate (10:1) solvent mixture as an eluent. Pale yellow clear oil. Yield: 60%. ^{1}H NMR ($CDCl_3$) δ 7.02−7.45 (m, 10 H), 4.60 (s, 2H), 4.44 (s, 2H), 2.41 (t, 2H, J = 7.56 Hz), 1.72 (pent, 2H, J = 7.56 Hz), 1.20−1.40 (m, 4H), 0.88 (t, 3H, J = 6.88 Hz); ^{13}C NMR ($CDCl_3$) δ 173.9, 137.7, 136.8, 129.1, 128.7, 128.4, 127.7, 127.5, 126.5, 50.1, 48.2, 33.4, 31.8, 25.3, 22.7, 14.1. HRMS-ESI (m/z): [M + H$^+$] calcd for $C_{20}H_{26}NO$, 296.2014; found, 296.2015.

***N*,*N*-Dibenzyl-2-phenylacetamide (9j).** Purified by silica gel column chromatography using hexane/ethyl acetate (7:1) solvent mixture as an eluent. Pale yellow clear oil. Yield: 40%. ^{1}H NMR ($CDCl_3$) δ 7.02−7.45 (m, 15 H), 4.61 (s, 2H), 4.43 (s, 2H), 3.79 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 171.8, 137.5, 136.6, 135.2, 129.2, 129.0, 128.9, 128.8, 128.5, 127.9, 127.6, 127.1, 126.6, 50.4, 48.4, 41.2. HRMS-ESI (m/z): [M + H$^+$] calcd for $C_{22}H_{22}NO$: 316.1701, found, 316.1702.

***N*-Benzyl-*N*-ethylhexanamide (9k).** Purified by silica gel column chromatography using hexane/ethyl acetate (7:1) solvent mixture as an eluent. Pale yellow clear oil. Yield: 60%, 1:1.3 mixture of rotamers. ^{1}H NMR ($CDCl_3$) (major rotamer) δ 7.02−7.38 (m, 5 H), 4.56 (s, 2H), 3.23 (q, 2H, J = 7.17 Hz), 2.34 (t, 2H, J = 7.78 Hz), 1.50−1.80 (m, 2H), 1.16−1.42 (m, 4H), 1.02−1.15 (m, 3H), 0.75−1.00 (m, 3H); ^{1}H NMR ($CDCl_3$) (minor rotamer) δ 7.02−7.38 (m, 5 H), 4.48 (s, 2H), 3.38 (q, 2H, J = 7.16 Hz), 2.27 (t, 2H, J = 7.78 Hz),

dx.doi.org/10.1021/jo201756z|*J. Org. Chem.* 2011, 76, 10005−10010

1.50−1.80 (m, 2H), 1.16−1.42 (m, 4H), 1.02−1.15 (m, 3H), 0.75−1.00 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 173.4, 173.2, 138.3, 137.4, 129.0, 128.6, 128.1, 127.6, 127.3, 126.4, 50.7, 47.8, 41.7, 41.0, 33.5, 33.2, 31.9, 31.8, 25.4, 25.2, 22.7, 22.6, 14.2, 14.1, 13.9, 12.9. HRMS-ESI (m/z): [M + H$^+$] calcd for $C_{15}H_{24}NO$, 234.1858; found, 234.1858.

***N*-Benzyl-*N*-phenethylhexanamide (9l).** Purified by silica gel column chromatography using hexane/ethyl acetate (7:1) solvent mixture as an eluent. Pale yellow clear oil. Yield: 43%, 1:1.05 mixture of rotamers. ^{1}H NMR ($CDCl_3$) (major rotamer) δ 7.02−7.40 (m, 10 H), 4.35 (s, 2H), 3.56 (t, 2H, J = 7.56 Hz), 2.85 (t, 2H, J = 7.56 Hz), 2.31 (t, 2H, J = 7.54 Hz), 1.55−1.75 (m, 2H), 1.20−1.40 (m, 4H), 0.80−1.00 (m, 3H); ^{1}H NMR ($CDCl_3$) (minor rotamer) δ 7.02−7.40 (m, 10 H), 4.61 (s, 2H), 3.43 (t, 2H, J = 7.56 Hz), 2.79 (t, 2H, J = 7.56 Hz), 2.22 (t, 2H, J = 7.78 Hz), 1.55−1.75 (m, 2H), 1.20−1.40 (m, 4H), 0.80−1.00 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 173.7, 173.5, 139.5, 138.4, 138.0, 137.2, 129.0, 129.0, 128.9, 128.9, 128.7, 128.6, 128.3, 127.7, 127.5, 126.9, 126.5, 52.0, 48.7, 48.5, 48.3, 35.2, 34.2, 33.5, 33.1, 31.8, 31.7, 25.3, 25.2, 22.7, 14.2, 14.1. HRMS-ESI (m/z): [M + H$^+$] calcd for $C_{21}H_{28}NO$, 310.2171; found, 310.2173.

2-Phenyl-*N*,*N*-dipropylacetamide (9m). Purified by silica gel column chromatography using hexane/ethyl acetate (7:1) solvent mixture as an eluent. Colorless clear oil. Yield: 44%. ^{1}H NMR ($CDCl_3$) δ 7.15−7.40 (m, 5 H), 3.70 (s, 2H), 3.29 (t, 2H, J = 7.54 Hz), 3.18 (t, 2H, J = 7.78 Hz), 1.41−1.69 (m, 4H), 0.75−0.95 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 170.7, 135.7, 128.8, 128.7, 126.8, 50.1, 47.7, 41.1, 22.3, 21.0, 11.6, 11.4. HRMS-ESI (m/z): [M + H$^+$] calcd for $C_{14}H_{22}NO$, 220.1701; found, 220.1696.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

X-ray data for complex **3** in CIF format and ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: soonhong@snu.ac.kr.

■ ACKNOWLEDGMENTS

This work is supported by the Research Settlement Fund for the new faculty of Seoul National University. The Singapore National Research Foundation is also acknowledged for generous support of this research (NRF-RF2008-05). C.C. and Y.Z. thank Nanyang Technological University for graduate student scholarships. We are also grateful for Dr. Yongxin Li for generous help with the X-ray crystallography.

■ REFERENCES

(1) For recent reviews, see: (a) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681. (b) Chen, C.; Hong, S. H. *Org. Biomol. Chem.* **2011**, *9*, 20. (c) Muthaiah, S.; Hong, S. H. *Synlett* **2011**, *2011*, 1481.

(2) (a) Naota, T.; Murahashi, S.-I. *Synlett* **1991**, 693. (b) Watson, A. J. A.; Maxwell, A. C.; Williams, J. M. J. *Org. Lett.* **2009**, *11*, 2667. (c) Nova, A.; Balcells, D.; Schley, N. D.; Dobereiner, G. E.; Crabtree, R. H.; Eisenstein, O. *Organometallics* **2010**, *29*, 6548. (d) Schley, N. D.; Dobereiner, G. E.; Crabtree, R. H. *Organometallics* **2011**, *30*, 4174.

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

(4) Nordstrøm, L. U.; Vogt, H.; Madsen, R. *J. Am. Chem. Soc.* **2008**, *130*, 17672.

(5) Ghosh, S. C.; Muthaiah, S.; Zhang, Y.; Xu, X.; Hong, S. H. *Adv. Synth. Catal.* **2009**, *351*, 2643.

(6) Zhang, Y.; Chen, C.; Ghosh, S. C.; Li, Y.; Hong, S. H. *Organometallics* **2010**, *29*, 1374.

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

(8) Dam, J. H.; Osztrovszky, G.; Nordstrøm, L. U.; Madsen, R. *Chem.−Eur. J.* **2010**, *16*, 6820.

(9) Ghosh, S. C.; Hong, S. H. *Eur. J. Org. Chem.* **2010**, 4266.

(10) Prades, A.; Peris, E.; Albrecht, M. *Organometallics* **2011**, *30*, 1162.

(11) For other metals, see: (a) Fujita, K.; Takahashi, Y.; Owaki, M.; Yamamoto, K.; Yamaguchi, R. *Org. Lett.* **2004**, *6*, 2785. (b) Zweifel, T.; Naubron, J. V.; Grützmacher, H. *Angew. Chem., Int. Ed.* **2009**, *48*, 559. (c) Shimizu, K.; Ohshima, K.; Satsuma, A. *Chem.−Eur. J.* **2009**, *15*, 9977.

(12) See Supporting Information for the X-ray crystallography data.

(13) (a) Murahashi, S.-I.; Ito, K. I.; Naota, T.; Maeda, Y. *Tetrahedron Lett.* **1981**, *22*, 5327. (b) Murahashi, S.-I.; Naota, T.; Ito, K.; Maeda, Y.; Taki, H. *J. Org. Chem.* **1987**, *52*, 4319. (c) Ishii, Y.; Osakada, K.; Ikariya, T.; Saburi, M.; Yoshikawa, S. *J. Org. Chem.* **1986**, *51*, 2034. (d) Blum, Y.; Shvo, Y. *J. Organomet. Chem.* **1984**, *263*, 93. (e) Zhao, J.; Hartwig, J. F. *Organometallics* **2005**, *24*, 2441. (f) Ito, M.; Osaku, A.; Shiibashi, A.; Ikariya, T. *Org. Lett.* **2007**, *9*, 1821.

(14) (a) Takehara, J.; Hashiguchi, S.; Fujii, A.; Inoue, S.-i.; Ikariya, T.; Noyori, R. *Chem. Commum.* **1996**, 233. (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97.

(15) Demonceau, A.; Stumpf, A. W.; Saive, E.; Noels, A. F. *Macromolecules* **1997**, *30*, 3127.

(16) Delaude, L.; Delfosse, S.; Richel, A.; Demonceau, A.; Noels, A. F. *Chem. Commum.* **2003**, 1526.

(17) Zhang, J.; Senthilkumar, M.; Ghosh, S. C.; Hong, S. H. *Angew. Chem., Int. Ed.* **2010**, *49*, 6391.

(18) (a) Gnanaprakasam, B.; Milstein, D. *J. Am. Chem. Soc.* **2011**, *133*, 1682. (b) Ishihara, K.; Kuroki, Y.; Hanaki, N.; Ohara, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 1569. (c) Han, C.; Lee, J. P.; Lobkovsky, E.; Porco, J. A. *J. Am. Chem. Soc.* **2005**, *127*, 10039. (d) Kuroki, Y.; Ishihara, K.; Hanaki, N.; Ohara, S.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 1221.

(19) For the detailed mechanisms of the related Ru-catalyzed amidation, see refs 6 and 8.

(20) Zhang, J.; Leitus, G.; Ben-David, Y.; Milstein, D. *J. Am. Chem. Soc.* **2005**, *127*, 10840.

(21) Gowrisankar, S.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 5139.

(22) Li, J. M.; Xu, F.; Zhang, Y.; Shen, Q. *J. Org. Chem.* **2009**, *74*, 2575.