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Direct Amide Synthesis from Alcohols and Amines by Phosphine-Free Ruthenium Catalyst Systems

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Abstract: Amides are synthesized directly from alcohols and amines in high yields using an *in situ* generated catalyst from easily available ruthenium complexes such as the (*p*-cymene)ruthenium dichloride dimer, $[Ru(p\text{-cymeme})Cl_2]_2$, or the (benzene)ruthenium dichloride dimer, $[Ru(benzene)Cl_2]_2$, an N-heterocyclic carbene (NHC) ligand, and a nitrogen containing L-type ligand such as acetonitrile. The phosphine-free catalyst systems showed improved or comparable activity compared to previous phosphine-based catalytic systems. The *in situ* generated catalyst from $[Ru(benzene)Cl_2]_2$, an NHC ligand, and acetonitrile showed excellent activity toward reactions with cyclic secondary amines such as piperidine and morpholine.

Keywords: amides; N-heterocyclic carbenes; phosphine-free conditions; ruthenium

Introduction

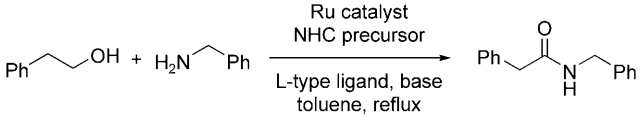
The amide bond is a key functional group in organic chemistry.[1] It plays a major role in the elaboration and composition of biological and chemical systems. Amides are typically synthesized by coupling of activated carboxylic acid derivatives with amines.[2] Alternative strategies toward the synthesis of amides are the Staudinger reaction,[3] the Schmidt reaction,[4] Beckmann rearrangement,[5] aminocarbonylation of haloarenes,[6] alkenes[7] and alkynes,[8] oxidative amidation of aldehydes,[9] hydrative amide synthesis with alkynes[10] and the amidation of thio acids with azides.[11] However, most of these methods require an equimolar amount of various reagents and generate larger amounts of by-products as waste. Therefore, the synthesis of amides under neutral conditions and without the generation of waste is a challenging goal.[12]

Recently, the Milstein group reported environmentally friendly direct amidation of alcohols and amines with liberating two molecules of hydrogen using a ruthenium PNN pincer complex without any base or acid promoters.[12] Since then, several groups have reported the synthesis of amides from alcohols and amines using ruthenium[13] and rhodium[14] catalysts. Particularly, the Madsen group showed that $Ru(COD)Cl_2$ with an N-heterocyclic carbene (NHC) and phosphine ligands also catalyzed the formation of the amide rather than alkylation of the amine.[13b] Alkylation of amines with alcohols using the 'borrowing hydrogen' methodology has been well studied for ruthenium or iridium complexes with phosphine ligands.[15] Despite their effectiveness in controlling reactivity and selectivity in organometallic chemistry and homogeneous catalysis, tertiary phosphines are often air-sensitive and are subject to P–C bond degradation at elevated temperatures.[16] We have made a conscious effort to develop the amide formation reaction with an N-heterocyclic carbene ligand and ruthenium complex combination under phosphine-free conditions. Herein we report our catalyst systems using $[Ru(p\text{-cymene})Cl_2]_2$ or $[Ru(benzene)Cl_2]_2$ complexes with an N-heterocyclic carbene and readily available nitrogen containing L-type ligands.

Results and Discussion

A model reaction of 2-phenylethanol with benzylamine to afford *N*-benzyl-2-phenylacetamide was chosen (Table 1). In an initial attempt to generate the

Table 1. Optimization of reaction conditions.

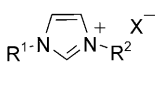


Entry	Catalyst	Ligand	NHC precursor	Base	Time [h]	Yield[d]
1[a]	$RuCl_3$	pyridine	**1**	KO-*t*-Bu	24	3%
2[b]	$[Ru(benzene)Cl_2]_2$	pyridine	**1**	KO-*t*-Bu	24	54%
3[b]	$[Ru(benzene)Cl_2]_2$	PCy_3	**1**	KO-*t*-Bu	24	0%
4[b]	$[Ru(benzene)Cl_2]_2$	CH_3CN	**1**	KO-*t*-Bu	24	55%
5[b]	$[Ru(p\text{-cymene})Cl_2]_2$	pyridine	**1**	KO-*t*-Bu	24	59%
6[b]	$[Ru(p\text{-cymene})Cl_2]_2$	CH_3CN	**1**	KO-*t*-Bu	24	58%
7[b]	$[Ru(benzene)Cl_2]_2$	CH_3CN	**2**	KO-*t*-Bu	24	34%
8[b]	$[Ru(benzene)Cl_2]_2$	CH_3CN	**3**	KO-*t*-Bu	24	19%
9[b]	$[Ru(benzene)Cl_2]_2$	CH_3CN	**5**	KO-*t*-Bu	24	15%
10[c]	$[Ru(benzene)Cl_2]_2$	CH_3CN	**4**	NaH	48	62%
11[c]	$[Ru(benzene)Cl_2]_2$	CH_3CN	**1**	NaH	24	89%
12[c]	$[Ru(benzene)Cl_2]_2$	CH_3CN	**1**	NaH	48	96%
13[c]	$[Ru(benzene)Cl_2]_2$	pyridine	**1**	NaH	24	89%
14[c]	$[Ru(benzene)Cl_2]_2$	pyridine	**1**	NaH	48	90%
15[c]	$[Ru(p\text{-cymene})Cl_2]_2$	pyridine	**1**	NaH	24	90%
16[c]	$[Ru(p\text{-cymene})Cl_2]_2$	pyridine	**1**	NaH	48	93%
17[c]	$[Ru(p\text{-cymene})Cl_2]_2$	CH_3CN	**1**	NaH	24	89%
18[c]	$[Ru(p\text{-cymene})Cl_2]_2$	CH_3CN	**1**	NaH	48	90%
19[a]	$RuCl_2(PPh_3)_3$	pyridine	**1**	NaH	48	83%
20[a]	$RuCl_2(PPh_3)_3$	CH_3CN	**1**	NaH	48	84%
21[a]	$RuCp^*Cl_2$	pyridine	**1**	NaH	24	16%
22[a]	$Ru(COD)Cl_2$	CH_3CN	**1**	NaH	24	65%
23[c]	$[Ru(p\text{-cymene})Cl_2]_2$	pyridine	none	NaH	48	3%
24[c]	$[Ru(benzene)Cl_2]_2$	CH_3CN	none	NaH	48	7%
25[c]	$[Ru(p\text{-cymene})Cl_2]_2$	none	**1**	NaH	48	3%
26[c]	$[Ru(benzene)Cl_2]_2$	none	**1**	NaH	48	20%

[a] 5 mol% Ru catalyst, 5 mol% NHC precursor, 5 mol% ligand, 15 mol% base.
[b] 5 mol% Ru catalyst, 10 mol% NHC precursor, 10 mol% ligand, 30 mol% base.
[c] 2.5 mol% Ru catalyst, 5 mol% NHC precursor, 5 mol% ligand, 15 mol% base.
[d] Determined by GC.

catalyst *in situ* using anhydrous $RuCl_3$, an L-type ligand, imidazolium salt **1** and potassium *tert*-butoxide as a base in refluxing toluene was unsuccessful (entry 1). Most of the starting materials remained unreacted and only 3% of the desired product was found on GC after 24 h. By changing the ruthenium precatalyst to $[Ru(benzene)Cl_2]_2$, the yield of amide was significantly increased to 54% with the help of a pyridine ligand (entry 2). Various L-type ligands such as acetonitrile, phosphines, and dimethyl fumarate were screened but only acetonitrile showed comparable activity with pyridine (entry 4). It is interesting to see economical and readily available nitrogen-containing pyridine and acetonitrile ligands working more efficiently than phosphines. The Madsen group reported that phosphines such as tricyclohexylphosphine (PCy_3) and tricyclopentylphosphine ($PCyp_3$) make $Ru(COD)Cl_2$ with N-hetercocyclic carbene ligand active toward the amide synthesis.[13b] Among the NHC precursors examined (Figure 1), **1** showed the best activity (entries 4 and 7–12).

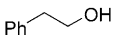
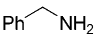
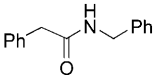
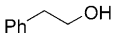
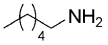
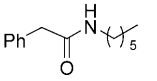
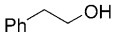
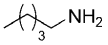
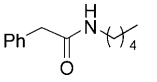
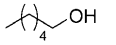
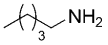
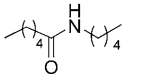
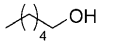
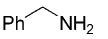
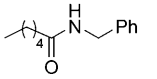
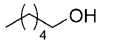
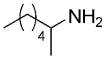
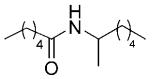
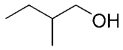
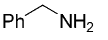
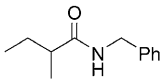
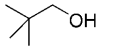
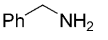
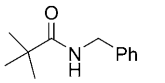
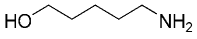
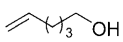
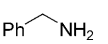
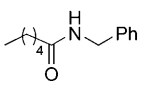
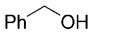
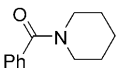
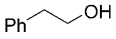
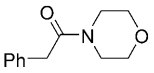
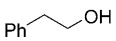
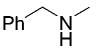
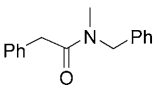
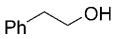
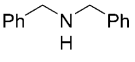
A dramatic improvement of this catalytic system was achieved by changing the base from potassium *tert*-butoxide to sodium hydride (89%, entry 11). Running the reaction for an extended time, 48 h, did not result in a significant increase in conversion (entries 13–16). In the case of $[Ru(p\text{-cymene})Cl_2]_2$, the pyridine ligand showed slightly better activity than acetonitrile (entries 15–18). On the other hand, in the case of $[Ru(benzene)Cl_2]_2$, acetonitrile showed a



1: $R^1 = R^2 = i$-Pr, X = Br
2: $R^1 = i$-Pr, R^2 = Mes, X = I
3: $R^1 = R^2$ = Me, X = I
4: $R^1 = R^2 = t$-Bu, X = Cl
5: $R^1 = R^2$ = Mes, X = Cl

Figure 1. NHC precursors.

Table 2. Direct amide synthesis from alcohols and amines.

Entry	Alcohol	Amine	Amide	Yield [%][a] Conditions A[b]	Conditions B[c]
1				90	96
2				98	97
3				97	91
4				99	95
5				91	92
6				45	60
7				77	70
8				19	19
9				92	94
10				72	92
11				64	80
12				63	90
13				58[d]	69[d]
14				0[d]	0[d]
15				19[d]	25[d]
16				55[e]	23[e]
17				78	93

[a] Isolated yields.
[b] Conditions A: $[Ru(p\text{-cymene})Cl_2]_2$ (2.5 mol%), NHC precursor (5 mol%), NaH (15 mol%), and pyridine (5 mol%) in toluene at reflux for 36 h.
[c] Conditions B: $[Ru(benzene)Cl_2]_2$ (2.5 mol%), NHC precursor (5 mol%), NaH (15 mol%), acetonitrile (5 mol%) in toluene at reflux for 36 h.
[d] In mesitylene at 163 °C for 36 h.
[e] 1 mol% catalyst loading, GC yields.

slightly better activity than pyridine (entries 11–14). Other ruthenium complexes such as $[RuCl_2(PPh_3)_3]$, $RuCp^*Cl_2$, and $Ru(COD)Cl_2$ showed lower activity than $[Ru(p\text{-cymene})Cl_2]_2$ and $[Ru(benzene)Cl_2]_2$ under the given conditions (entries 19–22). In the absence of the N-heterocyclic carbene ligand, the amide formation was very low with the observation of ~90% of starting materials and trace amounts of *N*-benzyl 2-phenylacetamide by alkylation of the amine (entries 23 and 24). A nitrogen-based L-type ligand is also essential for the facile formation of amide. Without pyridine or acetonitrile, we also observed that most of the starting materials remained unreacted with 3–20% of *N*-benzyl 2-phenylacetamide formation (entries 25 and 26).

From the screening results, we chose two sets of conditions to explore the scope and limitation of our methods – conditions **A** (2.5 mol% $[Ru(p\text{-cymene})Cl_2]_2$, 5 mol% pyridine, 5 mol% NHC salt **1**, and 15 mol% NaH) and conditions **B** (2.5 mol% $[Ru(benzene)Cl_2]_2$, 5 mol% acetonitrile, 5 mol% NHC salt **1**, and 15 mol% NaH) in toluene at 120 °C. The reaction time was further optimized and we found that there is no substantial increase of product after 24 h. However, we chose a longer reaction time, 36 h, to completely consume the starting primary alcohols for the purpose of easier isolation.[17]

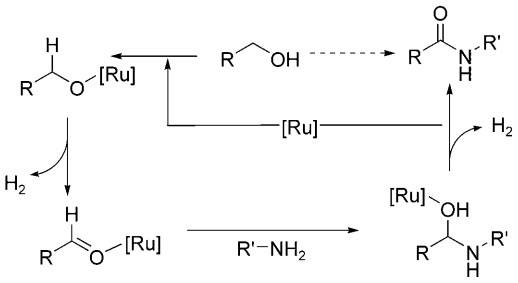
A range of amides were synthesized with good to excellent isolated yields under our systems (Table 2). Excellent yields of amides were obtained from the reaction of sterically unhindered alcohols and amines for both reaction conditions (entries 1–5). The amidation of 1-hexanol with 2-aminoheptane yielded 45% using $[Ru(p\text{-cymene})Cl_2]_2$, while $[Ru(benzene)Cl_2]_2$ reached a better yield of 60% of the corresponding amide (entry 6). Reaction of 2-methylbutanol with benzylamine afforded 70–77% yield of corresponding amide (entry 7), while neopentyl alcohol with benzylamine gave just 19% yield of the corresponding amide (entry 8). These results indicate that the ruthenium-catalyzed direct amide formation is sensitive to steric hindrance as reported by others.[12,13] Intramolecular amidation was also carried out by using 5-aminopentanol with excellent yield (entry 9). The use of 5-hexen-1-ol gave the hexanamide with 100% reduction of double bond (entry 10) as observed by Madsen's group as well.[13b]

In the case of cyclic secondary amines such as piperidine (entry 11) and morpholine (entry 12), $[Ru(benzene)Cl_2]_2$ (80%, piperidine, and 90%, morpholine) affords better yield than $[Ru(p\text{-cymene})Cl_2]_2$ (64%, piperidine, and 63%, morpholine). While preparing this manuscript, the Williams group reported that $[Ru(p\text{-cymene})Cl_2]_2$ and a bis(diphenylphosphino)butane-based catalytic system showed moderate catalytic activity in the morpholine case.[13a] The improved activity of our catalytic system is probably due to the more electron-donating N-heterocyclic carbene ligand system.

In the case of non-cyclic secondary amines such as N-benzylmethylamine, our system showed an improvement over Madsen's $Ru(COD)Cl_2$ catalytic system under the same conditions (entry 13, *vs.* 40% with Madsen's catalyst system).[13b] However, with sterically hindered secondary amines such as dibenzylamine, the reaction did not proceed at all (entry 14). Also, the less basic aniline was less reactive even at 163 °C in mesitylene (entry 15). These limitation has also been observed with other ruthenium catalyst systems demonstrating challenges in this area.[12,13]

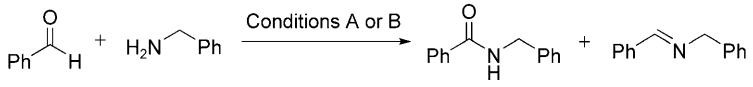
Although our catalytic systems showed comparable or a slightly improved activity compared with Madsen's system under basic conditions, the turnover numbers (TONs) are less than those of the Milstein catalyst under neutral conditions (entry 16, *vs.* 960 TONs with Milstein's system). $[Ru(p\text{-cymene})Cl_2]_2$ exhibited higher TONs than $[Ru(benzene)Cl_2]_2$ (55 *vs.* 23) presumably due to the better stability from the stronger π-coordination of *p*-cymene than benzene. Further investigations on electronic and steric effects of related ligands will be necessary to develop more improved catalytic systems.

We believe that the mechanism of our catalytic system is the same as that previously suggested (Scheme 1).[12,13] Interestingly, on the contrary to the observation of Madsen's group, we observed amide formation from benzaldehyde and benzylamine with our catalytic systems with the concurrent formation of the imine (Table 3). However, lower conversions compared with the one from alcohol (48% from benzaldehyde *vs.* 78% from benzyl alcohol, conditions **A**, and 11% *vs.* 93%, conditions **B**, entry 17 in Table 2 and Table 3) suggest that Madsen group's postulation that the aldehyde generated from the alcohol stays coordinated to the metal is valid for the facile formation of amide. The better conversion of benzaldehyde with more electron-rich $[Ru(p\text{-cymene})Cl_2]_2$ also suggests that coordination to the aldehyde carbonyl is important to lead to amide formation. Various metal complexes have been reported for the oxidative amidation of aldehydes.[9]



Scheme 1. Proposed mechanism.

Table 3. Reaction between benzaldehyde and benzylamine under conditions A and B.



Entry	Conditions	Amide [%][a]	Imine [%][a]
1	A: ([Ru(*p*-cymene)Cl_2]$_2$)	48	14
2	B: ([Ru(benzene)Cl_2]$_2$)	11	60

[a] GC yields.

Conclusions

We have demonstrated an improved method for the amidation of amines with alcohols or aldehydes using commercially available ruthenium complexes, an N-heterocyclic carbene ligand, and the economical pyridine or acetonitrile ligand. The phosphine-free process will provide alternative opportunities for the preparation of the fundamental amide functional group.

Experimental Section

General Information

All reactions were carried out in oven-dried glassware under an inert atmosphere of dry argon or nitrogen. All alcohols and amines were obtained from Aldrich or Alfa Aesar and used as received. Imidazolium salts **1–3** were synthesized by literature procedures.[18] Toluene was dried over a Pure Solv solvent purification system. Analytical TLC was performed on a Merck 60 F254 silica gel plates (0.25 mm thickness). Column chromatography was performed on Merck 60 silica gel (230–400 mesh). NMR spectra were recorded on a JEOL ECA400 (^{1}H NMR at 400 MHz; ^{13}C NMR at 100 MHz) spectrometer. Tetramethysilane was used as reference, and the chemical shifts were reported in ppm and the coupling constants in Hz. GC yields were obtained on an Agilent 7890 A instrument equipped with an HP-5 column using dodecane as an internal standard. Mass spectrometry was performed by Waters Q-Tof Premier Micromass instrument, using the electro spray ionization (ESI) mode.

General Procedure for Amide Synthesis

[Ru(*p*-cymene)Cl_2]$_2$ (**A**, 15.3 mg, 0.025 mmol) or [Ru(benzene)Cl_2]$_2$ (**B**; 12.5 mg, 0.025 mmol), 1,3-diisopropylimidazolium bromide (11.7 mg, 0.05 mmol), NaH (3.6 mg, 0.15 mmol) and pyridine (**A**, 4 μL, 0.05 mmol) or acetonitrile (**B**, 2.6 μL, 0.05 mmol), were placed in an oven-dried Schlenk tube inside the glove box; toluene (0.6 mL) was added to the mixture there. 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 (1 mmol) and the amine (1.1 mmol) were added. The mixture was heated to reflux under an argon atmosphere for 36 h. The reaction mixture was cooled to room temperature and the solvent was removed under vacuum and the residue was purified by silica gel flash column chromatography to afford the amide. All the amides were identified by spectral comparison with literature data or with analogous literature data.[19]

***N*-Benzyl-2-phenylacetamide:** Purified by silica gel column chromatography (hexane:EA 3:1, R_f=0.26) to afford it as a white solid. Isolated yields; conditions A: 90%, conditions B: 96%. ^{1}H NMR ($CDCl_3$): δ=7.39–7.26 (m, 10H), 5.70 (bs, 1H), 4.41 (d, 2H, J=5.9 Hz), 3.62 (s, 2H); ^{13}C NMR ($CDCl_3$): δ=171.1, 138.3, 135.0, 129.6, 129.2, 128.8, 127.7, 127.6, 47.9, 43.7; HR-MS (ESI): m/z=226.1236 [MH^+], calcd. for $C_{15}H_{16}NO$: 226.1232.

***N*-Hexyl-2-phenylacetamide:** Purified by silica gel column chromatography (hexane:EA 3:1, R_f=0.28) to afford a white solid. Isolated yields: conditions A: 98%, conditions B: 97%. ^{1}H NMR ($CDCl_3$): δ=7.35–7.26 (m, 5H), 5.47 (bs, 1H), 3.56 (s, 2H), 3.19 (q, 2H, J=6.8 Hz), 1.43–1.37 (m, 2H), 1.29–1.17 (m, 6H), 0.85 (t, J=6.8 Hz); ^{13}C NMR ($CDCl_3$): δ=171.0, 135.2, 129.6, 129.2, 127.5, 44.0, 39.8, 31.5, 29.6, 26.7, 22.7, 14.1; HR-MS (ESI): m/z=220.1698 [MH^+], calcd. for $C_{14}H_{22}NO$: 220.1701.

***N*-Pentyl-2-phenylacetamide:** Purified by silica gel column chromatography (hexane:EA 3:1, R_f=0.28) to afford a white solid. Isolated yields: conditions A: 97%, conditions B: 91%. ^{1}H NMR ($CDCl_3$): δ=7.37–7.24 (m, 5H), 5.46 (bs, 1H), 3.56 (s, 2H), 3.21–3.16 (m, 2H), 1.41 (p, 2H, J=6.8 Hz), 1.30–1.17 (m, 4H), 0.85 (t, 3H, J=7.2 Hz); ^{13}C NMR ($CDCl_3$): δ=171.0, 135.2, 129.6, 129.2, 127.4, 44.0, 39.7, 29.3, 29.1, 22.4, 14.1; HR-MS (ESI): m/z=206.1547 [MH^+], calcd. for $C_{13}H_{20}NO$: 206.1545.

***N*-Pentylhexanamide:** Purified by silica gel column chromatography (hexane:EA 3:1, R_f=0.30) to afford a white solid. Isolated yields: conditions A: 99%, conditions B: 95%. ^{1}H NMR ($CDCl_3$): δ=5.86 (bs, 1H), 3.20–3.15 (m, 2H), 2.11 (t, 2H, J=7.7 Hz), 1.58 (p, 2H, J=8.2 Hz), 1.45 (p, 2H, J=7.2 Hz), 1.27–1.23 (m, 8H), 0.86–0.82 (m, 6H); ^{13}C NMR ($CDCl_3$): δ=173.4, 39.6, 36.9, 31.6, 29.5, 29.2, 25.7, 22.5, 22.4, 14.1, 14.0; HR-MS (ESI): m/z=186.1852 [MH^+], calcd. for $C_{11}H_{24}NO$: 186.1858.

***N*-Benzylhexanamide:** Purified by silica gel column chromatography (hexane:EA 3:1, R_f=0.28) to afford a white solid. Isolated yields: conditions A: 91%, conditions B: 92%. ^{1}H NMR ($CDCl_3$): δ=7.30–7.26 (m, 5H), 5.94 (bs, 1H), 4.41 (d, 2H, J=5.9 Hz), 2.19 (t, 2H, J=7.4 Hz), 1.66 (p, 2H, J=7.7 Hz), 1.32–1.28 (m, 4H), 0.88 (t, 3H, J=6.8 Hz); ^{13}C NMR ($CDCl_3$): δ=173.2, 138.6, 128.9, 128.0, 127.7, 43.7, 37.0, 31.7, 25.7, 22.6, 14.1; HR-MS (ESI): m/z=206.1548 [MH^+], calcd. for $C_{13}H_{20}NO$: 206.1545.

***N*-(1-Methylhexyl)hexanamide:** Purified by silica gel column chromatography (hexane:EA 3:1, $R_f = 0.30$) to afford a colorless liquid. Isolated yields: conditions A: 45%, conditions B: 60%. ^{1}H NMR ($CDCl_3$): $\delta = 5.71$ (d, 1H, $J =$ 7.7 Hz), 3.92–3.86 (m, 1H), 2.08 (t, 2H, $J = 7.3$ Hz), 1.55 (p, 2H, $J = 7.7$ Hz), 1.39–1.15 (m, 12H), 1.04 (d, 3H, $J =$ 6.8 Hz), 0.84–0.80 (m, 6H); ^{13}C NMR ($CDCl_3$): $\delta = 172.6$, 45.1, 37.0, 36.9, 31.8, 31.5, 25.8, 25.7, 22.7, 22.5, 21.1, 14.1, 14.0; HR-MS (ESI): $m/z = 214.2169$ [MH^+], calcd. for $C_{13}H_{28}NO$: 214.2171.

***N*-Benzyl-2-methylbutanamide:** Purified by silica gel column chromatography (hexane:EA 3:1, $R_f = 0.26$) to afford a white solid. Isolated yields: conditions A: 77%, conditions B: 70%. ^{1}H NMR ($CDCl_3$): $\delta = 7.30$–7.25 (m, 5H), 6.19 (bs, 1H), 4.45–4.37 (m, 2H), 2.19–2.12 (m, 1H), 1.73–1.62 (m, 1H), 1.48–1.41 (m, 1H), 1.15 (d, 3H, $J =$ 6.8 Hz), 0.91 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR($CDCl_3$): $\delta =$ 176.6, 138.7, 128.7, 127.8, 127.4, 43.4, 43.2, 27.4, 17.7, 12.1; HR-MS (ESI): $m/z = 192.1384$ [MH^+], calcd. for $C_{12}H_{18}NO$: 192.1388.

***N*-Benzylpivalamide:** Purified by silica gel column chromatography (hexane:EA 3:1, $R_f = 0.26$) to afford a white solid. Isolated yields: conditions A: 19%, conditions B: 19%. ^{1}H NMR ($CDCl_3$): $\delta = 7.35$–7.25 (m, 5H), 5.93 (bs, 1H), 4.43 (d, 2H, $J = 5.9$ Hz), 1.24 (s, 9H); ^{13}C NMR ($CDCl_3$): $\delta = 178.5$, 138.8, 128.9, 127.8, 127.6, 43.8, 38.9, 27.8; HR-MS (ESI): $m/z = 192.1390$ [MH^+], calcd. for $C_{12}H_{18}NO$: 192.1388.

Piperidin-2-one: Purified by silica gel column chromatography (CH_2Cl_2:MeOH 19:1, $R_f = 0.30$) to afford a white solid. Isolated yields: conditions A: 92%, conditions B: 94%. ^{1}H NMR ($CDCl_3$): $\delta = 7.52$ (bs, 1H), 3.19–3.16 (m, 2H), 2.21 (t, 2H, $J = 6.4$ Hz), 1.72–1.60 (m, 4H); ^{13}C NMR ($CDCl_3$): $\delta = 172.9$, 42.0, 31.4, 22.1, 20.8; HR-MS (ESI): $m/z = 100.0761$ [MH^+], calcd. for $C_5H_{10}NO$: 100.0762.

Phenyl(piperidin-1-yl)methanone: Purified by silica gel column chromatography (hexane:EA 3:1, $R_f = 0.31$) to afford a sticky liquid. Isolated yields: conditions A: 64%, conditions B: 80%. ^{1}H NMR ($CDCl_3$): $\delta = 7.37$(bs, 5H), 3.70 (bs, 2H), 3.33 (bs, 2H), 1.66–1.50 (m, 6H); ^{13}C NMR ($CDCl_3$): $\delta = 170.3$, 136.5, 129.4, 128.4, 126.8, 48.8, 43.1, 26.6, 25.7, 24.6; HR-MS (ESI): $m/z = 190.1232$ [MH^+], calcd. for $C_{12}H_{16}NO$: 190.1232.

1-Morpholino-2-phenylethanone: Purified by silica gel column chromatography (hexane:EA 1:2, $R_f = 0.32$) to afford a white solid. Isolated yields: conditions A: 63%, conditions B: 90%. ^{1}H NMR ($CDCl_3$): $\delta = 7.34$–7.22 (m, 5H), 3.73 (s, 2H), 3.63 (s, 4H), 3.48–3.41 (m, 4H); ^{13}C NMR ($CDCl_3$): $\delta = 169.7$, 134.9, 128.9, 128.6, 127.0, 66.8, 66.5, 46.6, 42.2, 40.9; HR-MS (ESI): $m/z = 206.1182$ [MH^+], calcd. for $C_{12}H_{16}NO_2$: 206.1181.

***N*-Benzylbenzamine:** Purified by silica gel column chromatography (hexane:EA 2:1, $R_f = 0.29$) to afford a white solid. Isolated yields: conditions A: 78%, conditions B: 93%. ^{1}H NMR ($CDCl_3$): $\delta = 7.80$–7.78 (m, 2H), 7.50–7.30 (m, 8H), 6.48 (bs, 1H), 4.64 (d, 2H, $J = 5.9$ Hz); ^{13}C NMR ($CDCl_3$): $\delta = 167.5$, 138.4, 134.5, 131.7, 128.9, 128.7, 128.0, 127.7, 127.2, 44.3; HR-MS (ESI): $m/z = 212.1071$ [MH^+], calcd. for $C_{14}H_{14}NO$: 212.1075.

***N*-Benzyl-*N*-methyl-2-phenylacetamide:** Purified by silica gel column chromatography (hexane:EA 4:1, $R_f = 0.26$) to afford a colorless liquid. Isolated yields: conditions A: 58%, conditions B: 69%. It contains 1:1.4 mixture of two rotamers. HR-MS (ESI):
$m/z = 240.1391$ [MH^+], calcd. for $C_{16}H_{18}NO$: 240.1388.

Major rotamer: ^{1}H NMR ($CDCl_3$): $\delta = 7.31$–7.21 (m, 9H), 7.10–7.08 (m, 1H), 4.60 (s, 2H), 3.78 (s, 2H), 2.88 (s, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 171.3$, 137.3, 135.0, 129.0, 128.9, 128.6, 128.1, 126.9, 126.4, 51.0, 41.3, 35.3.

Minor rotamer: ^{1}H NMR ($CDCl_3$): $\delta = 7.31$–7.21 (m, 9H), 7.10–7.08 (m, 1H), 4.51 (s, 2H), 3.75 (s, 2H), 2.94 (s, 3H); ^{13}C NMR ($CDCl_3$): $\delta = 171.6$, 136.5, 135.2, 129.0, 128.9, 128.8, 127.7, 127.4, 126.9, 53.7, 40.9, 34.1.

***N*,2-Diphenylacetamide:** Purified by silica gel column chromatography (hexane:EA 4:1, $R_f = 0.31$) to afford a white solid. Isolated yields: conditions A: 19%, conditions B: 25%. ^{1}H NMR ($CDCl_3$): $\delta = 7.42$–7.24 (m, 10H), 7.12–7.05 (m, 1H), 3.71 (s, 2H); ^{13}C NMR ($CDCl_3$): $\delta = 169.4$, 137.8, 134.6, 129.7, 129.4, 129.1, 127.8, 124.6, 120.0, 45.0; HR-MS (ESI): $m/z = 212.1079$ [MH^+], calcd. for $C_{14}H_{14}NO$: 212.1075.

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References

[1] a) T. Cupido, J. Tulla-Puche, J. Spengler, F. Albericio, *Curr. Opin. Drug Discovery Dev.* **2007**, *10*, 768; b) J. W. Bode, *Curr. Opin. Drug Discovery Dev.* **2006**, *9*, 765; c) J. M. Humphrey, A. R. Chamberlin, *Chem. Rev.* **1997**, *97*, 2243.

[2] a) S.-Y. Han, Y.-A. Kim, *Tetrahedron* **2004**, *60*, 2447; b) C. A. G. N. Montalbetti, V. Falque, *Tetrahedron* **2005**, *61*, 10827; c) E. Valeur, M. Bradley, *Chem. Soc. Rev.* **2009**, *38*, 606; d) R. C. Larock, *Comprehensive Organic Transformations*, VCH, New York, **1999**.

[3] a) E. Saxon, C. R. Bertozzi, *Science* **2000**, *287*, 2007; b) F. Damkaci, P. DeShong, *J. Am. Chem. Soc.* **2003**, *125*, 4408; c) Y. G. Gololobov, L. F. Kasukhin, *Tetrahedron* **1992**, *48*, 1353; d) Z. Pianowski, K. Gorska, L. Oswald, C. A. Merten, N. Winssinger, *J. Am. Chem. Soc.* **2009**, *131*, 6492.

[4] a) T. Ribelin, C. E. Katz, D. G. English, S. Smith, A. K. Manukyan, V. W. Day, B. Neuenswander, J. L. Poutsma, J. Aub, *Angew. Chem.* **2008**, *120*, 6329; *Angew. Chem. Int. Ed.* **2008**, *47*, 6233; b) S. Lang, J. A. Murphy, *Chem. Soc. Rev.* **2006**, *35*, 146.

[5] a) N. A. Owston, A. J. Parker, J. M. J. Williams, *Org. Lett.* **2007**, *9*, 3599; b) M. Hashimoto, Y. Obora, S. Sakaguchi, Y. Ishii, *J. Org. Chem.* **2008**, *73*, 2894.

[6] a) J. R. Martinelli, T. P. Clark, D. A. Watson, R. H. Munday, S. L. Buchwald, *Angew. Chem.* **2007**, *119*, 8612; *Angew. Chem. Int. Ed.* **2007**, *46*, 8460; b) P. Nanayakkara, H. Alper, *Chem. Commun.* **2003**, 2384.

[7] M. Beller, B. Cornils, C. D. Frohning, *J. Mol. Catal. A: Chem.* **1995**, *104*, 17.
[8] a) B. E. Ali, J. Tijani, *Appl. Organomet. Chem.* **2003**, *17*, 921; b) D. J. Knapton, T. Y. Meyer, *Org. Lett.* **2004**, *6*, 687; c) Y. Uenoyama, T. Fukuyama, O. Nobuta, H. Matsubara, I. Ryu, *Angew. Chem.* **2005**, *117*, 1099; *Angew. Chem. Int. Ed.* **2005**, *44*, 1075; d) J. H. Park, S. Y. Kim, S. M. Kim, Y. K. Chung, *Org. Lett.* **2007**, *9*, 2465.
[9] a) J. W. W. Chang, P. W. H. Chan, *Angew. Chem.* **2008**, *120*, 1154; *Angew. Chem. Int. Ed.* **2008**, *47*, 1138; b) W. J. Yoo, C. J. Li, *J. Am. Chem. Soc.* **2006**, *128*, 13064; c) A. Tillack, I. Rudloff, M. Beller, *Eur. J. Org. Chem.* **2001**, 523; d) T. Naota, S.-I. Murahashi, *Synlett* **1991**, 693.
[10] S. Cho, E. Yoo, I. Bae, S. Chang, *J. Am. Chem. Soc.* **2005**, *127*, 16046.
[11] a) R. V. Kolakowski, N. Shangguan, R. R. Sauers, L. J. Williams, *J. Am. Chem. Soc.* **2006**, *128*, 5695; b) X. Zhang, F. Li, X. W. Lu, C. F. Liu, *Bioconjugate Chem.* **2009**, *20*, 197.
[12] C. Gunanathan, Y. Ben-David, D. Milstein, *Science* **2007**, *317*, 790.
[13] a) A. J. A. Watson, A. C. Maxwell, J. M. J. Williams, *Org. Lett.* **2009**, *11*, 2667; b) L. U. Nordstrøm, H. Vogt, R. Madsen, *J. Am. Chem. Soc.* **2008**, *130*, 17672.
[14] T. Zweifel, J. V. Naubron, H. Grützmacher, *Angew. Chem.* **2009**, *121*, 567; *Angew. Chem. Int. Ed.* **2009**, *48*, 559.
[15] a) Y. Watanabe, Y. Tsuji, H. Ige, Y. Ohsugi, T. Ohta, *J. Org. Chem.* **1984**, *49*, 3359; b) M. H. S. A. Hamid, C. L. Allen, G. W. Lamb, A. C. Maxwell, H. C. Maytum, A. J. A. Watson, J. M. J. Williams, *J. Am. Chem. Soc.* **2009**, *131*, 1766, and references cited therein.
[16] S. Díez-González, S. P. Nolan, *Top. Organomet. Chem.* **2007**, *21*, 47.
[17] We observed that ~5% of starting alcohol remains after 24 h and that it is all consumed after 36 h without substantial increase of amide formation. We chose 36 h as a reaction time for the facile purification of amides from trace amounts of remaining starting alcohols.
[18] a) O. V. Starikova, G. V. Dolgushin, L. I. Larina, P. E. Ushakov, T. N. Komarova, V. A. Lopyrev, *Russ. J. Org. Chem.* **2003**, *39*, 1467; b) Y. Chu, H. Deng, J. P. Cheng, *J. Org. Chem.* **2007**, *72*, 7790; c) B. Eguillor, M. A. Esteruelas, M. Olivan, M. Puerta, *Organometallics* **2008**, *27*, 445.
[19] See Supporting Information for ^{1}H and ^{13}C NMR spectra.

