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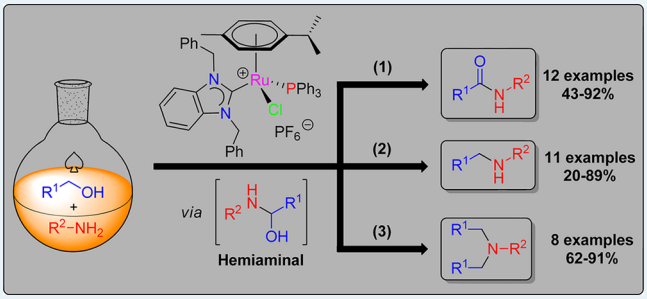
Tunable Dehydrogenative Amidation versus Amination Using a Single Ruthenium-NHC Catalyst

Xiaoke Xie and Han Vinh Huynh*

Department of Chemistry, National University of Singapore, 3 Science Drive 3, Singapore 117543, Republic of Singapore

Supporting Information

ABSTRACT: Mixed *N*-heterocyclic carbene (NHC)/phosphine complexes of the type [RuCl(*p*-cymene)(bimy)(PPh_3)]-PF_6 (bimy = benzimidazolin-2-ylidene) have been synthesized and fully characterized. Complex **1** bearing the 1,3-dibenzylbenzimidazolin-2-ylidene ligand is able to selectively catalyze both dehydrogenative amidation, mono-, and diamination (*N*-alkylation) through coupling of simple alcohols with amines effectively yielding a range of amides and secondary and tertiary amines. Selectivity is achieved by controlling the fate of the common hemiaminal intermediate, which in turn can be simply influenced by the choice of base and solvent.



KEYWORDS: *acceptorless dehydrogenation, borrowing hydrogen, ruthenium, N-heterocyclic carbene (NHC), hemiaminal, selectivity*

INTRODUCTION

The transition metal catalyzed dehydrogenation of alcohols followed by further nucleophilic functionalizations has attracted much attention.[1] By using these methodologies, amides and amines, which play very important roles in organic chemistry, pharmaceutical chemistry, and biochemistry,[2,3] can be directly synthesized from readily available alcohols and amines. These transformations are not only atom economical but also environmentally benign eliminating only nonpolluting hydrogen gas or water as the sole byproducts. The research on acceptorless dehydrogenation (AD) type amidation has been pioneered by the group of Milstein, who used a dearomatized Ru-PNN pincer complex as catalyst.[4] Amides, peptides and polyamides can be synthesized in excellent yields with low catalyst loading.[5] Thereafter, many effective catalytic systems based on ruthenium have been developed.[6] Those ligated by *N*-heterocyclic carbenes (NHCs) have proven to be especially potent for this process.[7,8]

On the other hand, the amination of alcohols can be realized by the "borrowing hydrogen" approach, in which ruthenium- or iridium-based catalytic systems are usually involved.[9,10] After Fujita and co-workers explored such amination catalyzed by $[Cp^*IrCl_2]_2$,[11] many successful examples have been reported by other researchers using iridium-based systems.[12] Meanwhile, ruthenium-catalyzed amination has also been developed with either in situ generated or well-defined catalysts.[13] In particular, great contributions have been made by Williams[14] and Beller et al.[15]

According to previous studies, the relationship between AD-type amidation and the borrowing hydrogen process is proposed to be mechanistically quite close.[6a,16] Both transformations go through a hemiaminal **A** that is formed from the initial addition of an amine to an aldehyde. Oxidative release of dihydrogen from the hemiaminal generates amide **B**. If the hemiaminal eliminates water, and the intermediate imine is further reduced by the "liberated" or "borrowed" dihydrogen, an amine **C** is obtained as the product (Scheme 1). Additionally, a doubly alkylated product **D** can form if the secondary amine **C** reacts with excess alcohol via a second similar process.[17]

Although the hemiaminal is the intermediate in the catalytic cycle of both transformations, its subsequent different (redox) reactions, from which either the amide or the amine is obtained, have only been affected by using very different catalytic systems so far.[14,18] Good selectivity for both types of products with a single well-defined catalyst under base-controlled condition is quite challenging and, to the best of our knowledge, has not been reported yet. Crabtree and co-workers have reported the possibility that amidation versus amination could be selectively affected by using base-controlled conditions. Nevertheless, product control in the actual study was not satisfactory, as various conditions only favored amide formation.[16a] Herein, we report our studies on a base-controlled chemoselective dehydrogenative amidation and amination by the activation of alcohols with amines catalyzed by a single well-defined, cationic benzimidazolin-2-ylidene ruthenium complex. The subsequent reactions of the hemiaminal are tunable, and thus a wide range of amides and secondary and tertiary amines have been synthesized effectively.

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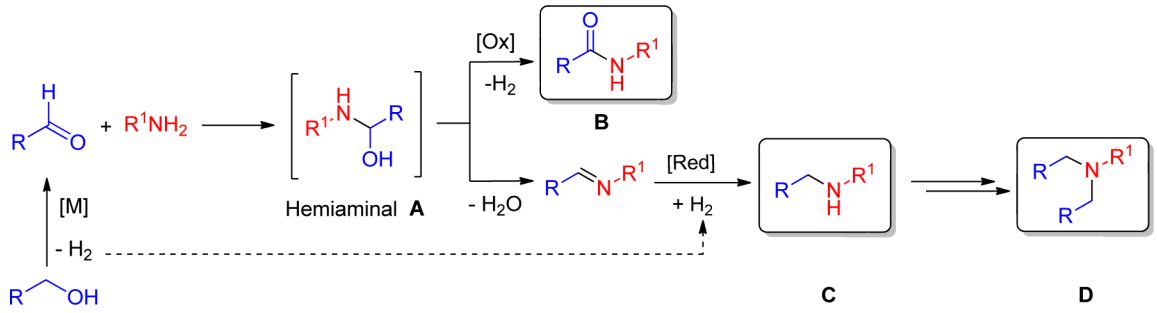
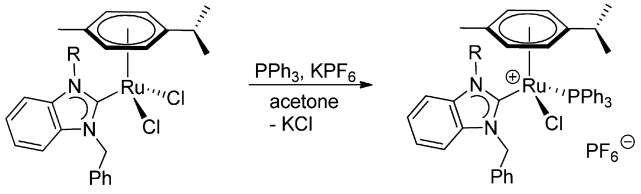
Scheme 1. Proposed Pathways for Amidation and Amination of Alcohols



RESULTS AND DISCUSSION

Synthesis and Characterization of Well-Defined Mixed NHC/Phosphine Ruthenium Complexes. Previous studies indicated that the presence of both NHC and phosphine ligands are beneficial in the ruthenium-catalyzed activation of alcohols and their subsequent reactions with amines.[7a−c,8a−c] However, well-defined and structurally characterized ruthenium complexes bearing a mixed NHC/phosphine donor set have rarely been studied. Therefore, complexes [RuCl(*p*-cymene)(Bn_2-bimy)(PPh_3)]PF_6 (**1**) and [RuCl(*p*-cymene)(^{i}Pr,Bn-bimy)(PPh_3)]PF_6 (**2**) were prepared by treating the previously reported neutral [$RuCl_2$(*p*-cymene)-(bimy)] complexes **I** and **II** with PPh_3 and KPF_6 in acetone (Scheme 2).[19] Chlorido displacement afforded the desired complexes **1** and **2** as yellow solids in good yields (the yield is 97% for complex **1** and 94% for complex **2** based on 1 mmol of the starting material). The formation of bis-(triphenylphosphine)ruthenium complexes was not observed for both cases, even when **I** and **II** were reacted with two equivalents or excess of PPh_3 and KPF_6. This can be explained by the bulkiness of the PPh_3 ligand that prevents the coordination of a second phosphine to the ruthenium(II) center as well as the unfavorable buildup of positive charge in the hypothetical product. Complexes **1** and **2** are soluble in polar, aprotic solvents such as DMSO and DMF, sparingly soluble in CH_3CN, MeOH and acetone, but virtually insoluble in nonpolar solvents including diethyl ether, hexane, and toluene. In the ^{1}H NMR spectra of both complexes, four doublets for the four aromatic protons in the *p*-cymene ligand are detected from 4.5−5.5 ppm, indicating their asymmetry after introduction of the phosphine ligand.[20] In their ^{13}C NMR spectra, the carbene carbon atoms resonate as doublets due to coupling with phosphorus centered at 187.3 and 185.7 ppm for complexes **1** and **2**, respectively, which are shifted to higher field by ∼4 ppm compared to those in their precursors **I** and **II**. This observation is also indicative of a greater Lewis acidity of the metal centers as a consequence of the positive charge.

Scheme 2. Synthesis of Ru-NHC Complexes 1 and 2



Single crystals of the cationic Ru^{II}−NHC complexes **1** and **2** suitable for X-ray diffraction analyses were obtained by slow evaporation of their concentrated solutions in CH_2Cl_2/hexane. The piano-stool geometry is observed for each complex, and

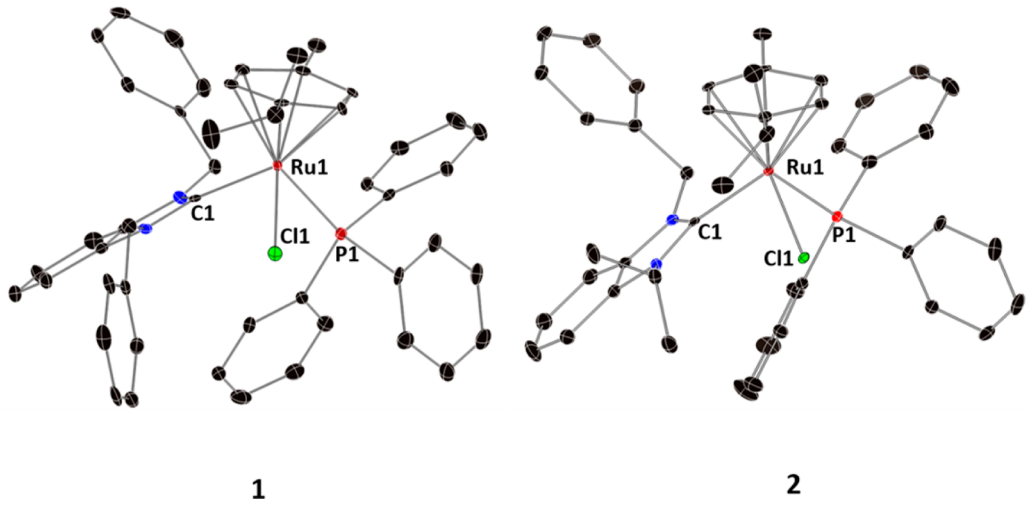


Figure 1. ORTEP diagram of the cations of complexes **1** and **2** with thermal ellipsoids shown at 50% probability level. Hydrogen atoms are omitted for clarity. Selected bond lengths [Å] and bond angles [deg] for complex **1**: Ru1−C1 2.076(4), Ru1−P1 2.3860(10), Ru1−Cl1 2.3828(9); C1−Ru1−P1 92.95(10), C1−Ru1−Cl1 87.89(10). Complex **2**: Ru1−C1 2.091(5), Ru1−P1 2.3812(13), Ru1−Cl1 2.4138(12); Cl1−Ru1−P1 82.28(3), C1−Ru1−Cl1 92.72(13).

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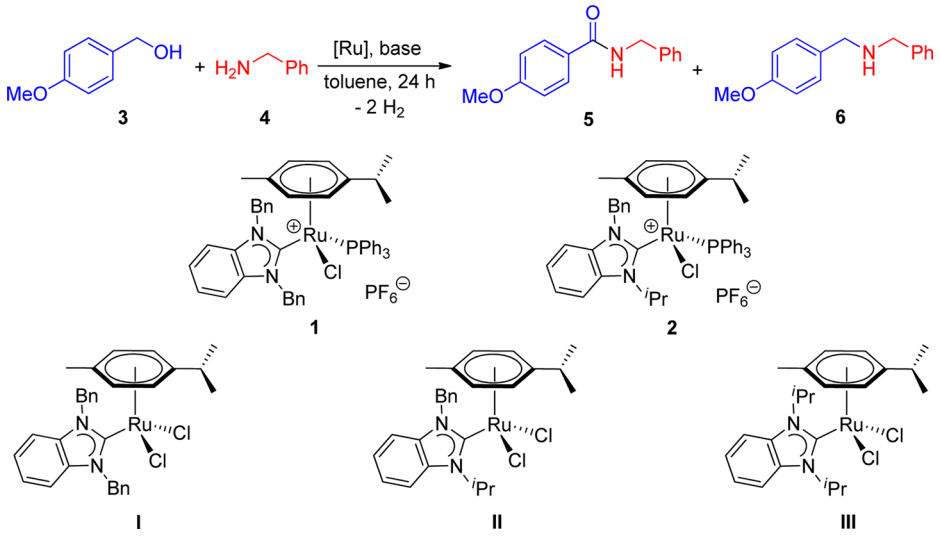
Table 1. Catalyst Screening and Optimization for the Selective Amidation[a]



entry	complex	base	5 [%][b]	6 [%][b]
1[f,g]	1		ND	trace
2[f,g]	1	$NaHCO_3$	ND	trace
3[f,g]	1	Na_2CO_3	ND	4
4	1	NaOH	85	ND
5	1	Cs_2CO_3	62	ND
6	1	KOH	83	ND
7	1	*t*-BuOK	69	ND
8	1	NaH	91	ND
9	1	NaH[d]	95/92[e]	ND
10	2	NaH[d]	88[e]	
11[c]	I + PPh_3	NaH[d]	81[e]	
12[c]	II + PPh_3	NaH[d]	79[e]	
13[c]	III + PPh_3	NaH[d]	82[e]	

[a]Benzylamine (0.2 mmol), 4-methoxybenzyl alcohol (0.24 mmol), Ru catalyst (5 mol %), base (20 mol %), 125 °C. [b]Yields were determined by GC using hexadecane as the internal standard for an average of two runs. [c]5 mol % of PPh_3 were added. [d]30 mol % of NaH was added. [e]Isolated yield for an average of two runs. [f]*N*-Benzyl-1-(4-methoxyphenyl)methanimine was detected. [g]*N*-Benzyl-1-phenylmethanimine was detected. ND = not detected.

their molecular structures are depicted in Figure 1. The *p*-cymene represents the "seat", and the chlorido, triphenylphosphine and NHC ligands form the three "legs". Complex **1** crystallizes in the triclinic crystal system in the *P*1 space group, while a monoclinic crystal system in the *Cc* space group was found for complex **2**. Although both complexes are chiral-at-metal, they expectedly crystallized in racemic forms due to the lack of chiral induction.

In the molecular structures, the two N-substituents are pointing away from the ruthenium center due to steric repulsion from the triphenylphosphine ligand. The two benzyl substituents in complex **1** are arranged in an anti arrangement with respect to the benzimidazolinylidene plane. The Ru−$C_{carbene}$ bond lengths of complexes **1** and **2** averaging to 2.083 Å are identical within 3σ. The same was observed for the Ru−P bonds with a mean value of 2.3836 Å. However, the Ru−Cl distance of 2.3828(9) Å in complex **1** is slightly shorter than that in the complex **2** {2.4138(12) Å}, making the former ruthenium center sterically more congested.

Catalytic Studies. *Selective Amidation.* With complexes **1** and **2** in hand, we initially studied their suitability in the ruthenium-catalyzed amidation. In addition, the neutral and phosphine-free dichlorido complexes **I**−**III** were included as well for comparison of in situ generated catalysts by addition of phosphine into the catalytic mixture. The coupling of 4-methoxybenzyl alcohol (**3**) with benzylamine (**4**) in toluene under reflux at 125 °C (oil bath temperature) to afford *N*-benzyl-4-methoxybenzamide (**5**) was chosen as the benchmark reaction (Table 1). First, the influence of the base was examined in the presence of complex **1** (entries 1−9). It was found that the desired amide **5** was not formed under the base-free condition (entry 1), and only a trace of the *N*-benzyl-1-(4-methoxyphenyl)methanamine (**6**) was observed as a mono-alkylation product of benzylamine. Notably, a significant amount of *N*-benzyl-1-phenylmethanimine was also observed, indicating that the homocoupling between two molecules of benzylamine had occurred.[21] With the weak bases $NaHCO_3$ and Na_2CO_3 no improvements in the yields of **5** and **6** were noted, although imine formation was reduced (entries 2 and 3). The use of stronger bases led to a substantial increase in yields of amide **5** without the formation of **6** (entries 4−7). A particularly high yield of 91% was obtained with NaH (entry 8), which could be further improved to 95% by increasing its amount to 30 mol % (entry 9). Notably, no additional hydrogen acceptor is required in this catalytic system.

Under these conditions, complex **2** was also found to be catalytically active. However, its performance was slightly lower compared to that of complex **1**. The activities of the in situ

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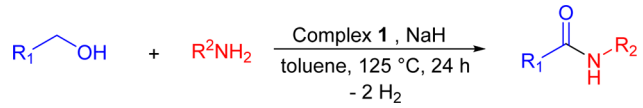
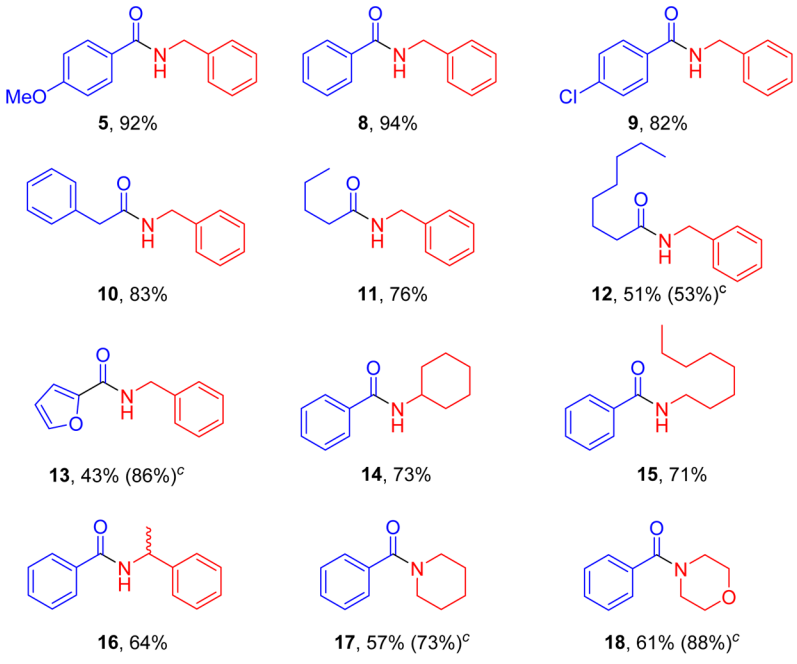
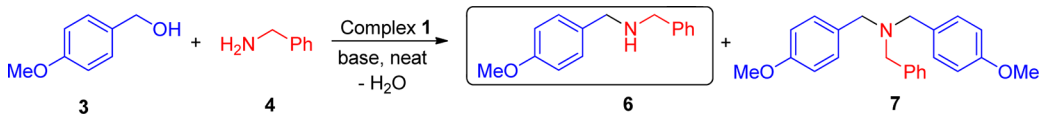
Table 2. Substrate Scope for the Selective Amidation[a,b]





[a]R^1CH_2OH (0.24 mmol), R^2NH_2 (0.2 mmol), complex **1** (5 mol %), NaH (30 mol %). [b]Isolated yields are given for an average of two runs. [c]The yield of the reaction carried out in *p*-xylene at 150 °C are given in parentheses.

Table 3. Optimization for the Synthesis of 6 by Selective Mono-alkylation[a]



3 4 6 7

entry	base	temp (°C)	time (h)	**6** [%][b]	**7** [%][b]
1	-	120	24	45	trace
2	Na_2CO_3	120	24	49	trace
3	$NaHCO_3$	120	24	68	trace
4	$NaHCO_3$	125	24	73	<5
5	$NaHCO_3$	130	24	81	<5
6	$NaHCO_3$	130	18	77	<5
7	$NaHCO_3$	130	24	70[c]	trace[c]

[a]Benzylamine (1 mmol), 4-methoxybenzyl alcohol (1.2 mmol), complex **1** (5 mol %), base (20 mol %). [b]Isolated yields in an average of two runs. [c]2 mmol of benzylamine and 2.4 mmol of 4-methoxybenzyl alcohol were used. The reaction was performed in a Schlenk tube connected to an oil bubbler.

generated catalysts similar to **1** and **2** have also been examined by mixing complexes **I**–**III** with equimolar amounts of PPh_3 (entries 11–13), but all were found to be less reactive compared to complex **1**.

Using the optimized conditions, we investigated the substrate scope for the selective amidation via acceptorless dehydrogenation of alcohols, and the results are summarized in Table 2. The reaction between benzylic alcohols and benzylamine gave good to excellent yields (**5**, **8**, and **9**). However, electron deficient benzylic alcohols gave a slightly lower yield of the product (**9**). Aliphatic or heterocyclic alcohols react with benzylamine to give the corresponding amides in medium to good yields (products **10**–**13**). Notably, there is a drop in yield with increasing length of the alkyl chain. Furyl alcohol gave only moderate yield, which, however, could be significantly improved by using higher temperatures. Thus, *N*-benzyl-2-furamide **13** was isolated in 86% yield by heating the reactants in *p*-xylene at 150 °C under reflux. Furthermore, the reactions between benzylalcohol and various cyclic and acyclic amines were examined; the products **14**–**18** were generally formed in good yields. It is worth noting that complex **1** is also applicable in the synthesis of the more challenging sterically hindered amides. Compound **16** was synthesized in 64% yield from *α*-methyl benzylamine, while the bulky tertiary and heterocyclic

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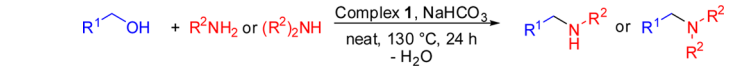
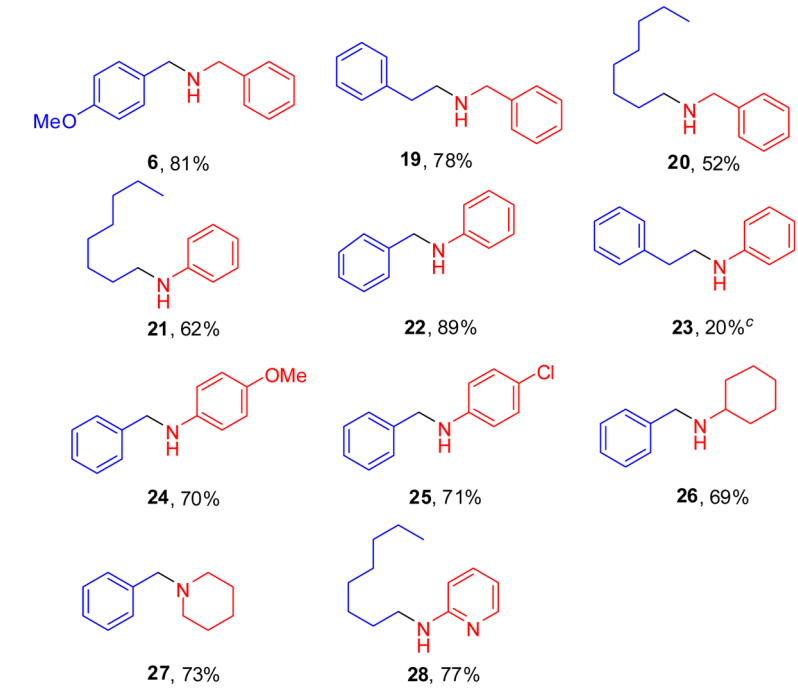
Table 4. Substrate Scope for the Mono-alkylation of Primary and Cyclic Amines[a,b]





[a]R^1CH_2OH (1.2 mmol), R^2NH_2 (1.0 mmol), complex **1** (5 mol %), $NaHCO_3$ (20 mol %), the reaction was carried out in a closed vial. [b]Isolated yields are given in an average of two runs. [c]The reaction was carried out for 48 h.

amides **17** and **18** can also be obtained in good yields at elevated temperatures. The performance of catalyst **1** in most of the reactions, especially those giving hindered and bulky amides, compares well to other well-defined or in situ generated ruthenium complexes with phosphine ligands.[7a,8a,c−e] However, the latter usually require more elaborate and expensive phosphine ligands (e.g., $PCyp_3{\cdot}HBF_4$) or bases (e.g., KO^tBu).

Selective Monoalkylation of Amines. Having identified complex **1** as the superior catalyst and the optimal conditions for the preparation of various amides, we further explored possibilities of varying the conditions for the selective preparation of *N*-benzyl-1-(4-methoxyphenyl)methanamine (**6**) from 4-methoxybenzyl alcohol (**3**) with benzylamine (**4**) using the same catalyst. This reaction may be challenging, since the formed secondary amine **6**, due to its stronger nucleophilicity, could compete with substrate **4** in the coupling with the alcohol **3**, which would afford the doubly alkylated tertiary amine **7**. It has been reported that the addition of weaker bases favors the imine formation in Ru-NHC catalyzed reactions.[22] Therefore, our experiments were carried out with a weak base or without any base. Furthermore, in order to facilitate the hydrogen transfer process required for this process, all reactions were performed under a solvent-free environment (Table 3).

At 120 °C and without additional base, the desired amine **6** was obtained in a moderate yield of 45% after 24 h together with some trace amounts of the tertiary amine **7** resulting from double alkylation (entry 1). In the presence of Na_2CO_3 and $NaHCO_3$, the yield of amine **6** increased to 49% and 68%, respectively (entries 2 and 3). Stepwise increase of the temperature also led to an enhancement of the catalytic performance (entries 4−5) with the highest yield of 81% being obtained at 130 °C. On the other hand, shortening of the reaction time to 18 h led to a slight drop in yield (entry 6). It is noteworthy, that the aforementioned competing formation of **7** could be successfully suppressed by using catalyst **1** under the given conditions. Overall, less than 5% of **7** was determined in all entries. Lastly, the reaction was also performed in an open system with 2 mmol of the amine and 2.4 mmol of the alcohol. After 24 h, compound **6** was obtained in a good yield of 70% (entry 7), which is only slightly lower than that obtained in a closed system (entry 5). This observation excludes the possibility that the imine was reduced by the released dihydrogen gas.

The general applicability of the selective amination protocol catalyzed by **1** was tested for a range of other alcohols and amines (Table 4). In the presence of $NaHCO_3$, benzylic and aliphatic alcohols can be activated by complex **1** and further couple with benzylamine to give compounds **6**, **19**, and **20** in moderate to good yield.

Aniline derivatives also underwent smooth alkylations with various alcohols to generate the corresponding amines in decent yield (**21**, **22**, **24**, **25**). However, product **23** could only be obtained in 20% yield from 1-phenyl ethanol and aniline despite heating the reaction mixture in *p*-xylene under reflux. Here, a significant amount of unreacted aniline was observed. The alkylation between the hindered amines and benzylalcohol also proceeds well, yielding 69% of **26**. The cyclic tertiary amine **27** was obtained in 73% yield from a cyclic secondary amine. Finally, 2-aminopyridine was alkylated with octanol to give *N*-heterocyclic amine **28** in 77% yield.

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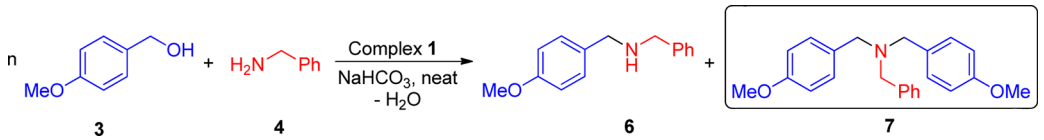
Table 5. Optimization for the Synthesis of 7 by Selective Di-alkylation[a]

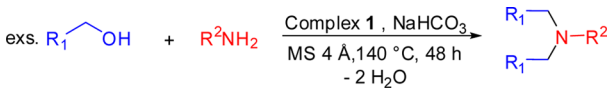


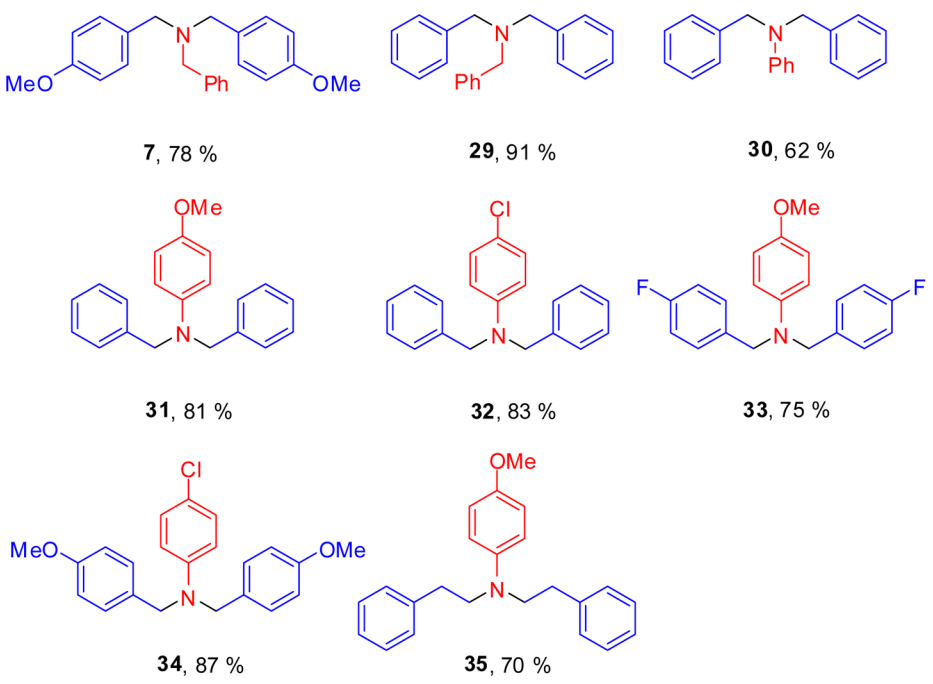
3 4 6 7

entry	*n*	temp (°C)	time (h)	**6** (%)[b]	**7** (%)[b]
1	2.1	130	24	61	30
2[c]	2.1	130	24	39	56
3[c]	2.1	140	24	31	65
4[c]	5.0	140	24	23	71
5[c]	5.0	140	48	14	78
6[d]	5.0	140	48	9	71

[a]Benzylamine (0.5 mmol), complex **1** (5 mol %), $NaHCO_3$ (20 mol %), the reaction was carried out in a closed vial [b]Isolated yields in an average of two runs. [c]250 mg of molecular sieves (4 Å) was added. [d]1 mmol of benzylamine and 5 mmol of 4-methoxybenzyl alcohol were used. The reaction was performed in a Schlenk tube connected to an oil bubbler.

Table 6. Scope of the Selective Di-alkylation of Amines[a]





7, 78 % **29**, 91 % **30**, 62 %

31, 81 % **32**, 83 % **33**, 75 %

34, 87 % **35**, 70 %

[a]R^1CH_2OH (2.5 mmol), R^2NH_2 (0.5 mmol), complex **1** (5 mol %), $NaHCO_3$ (20 mol %), molecular sieves (4 Å) 250 mg, the reaction was carried out in a closed vial. [b]Isolated yields are given in an average of two runs.

Selective Dialkylation of Amines. The selective preparation of tertiary amines from low cost alcohols and primary amines is also desirable. Therefore, a process involving the double alkylation of benzylamine with two equivalents of 4-methoxybenzyl alcohol to yield tertiary amine **7** by using complex **1** was also sought. Since formation of the tertiary amine under the monoalkylation conditions described above was insignificant (vide supra), stoichiometry control and possibly harsher conditions could be applied to drive this transformation (Table 5).

Thus, benzylamine (**3**) was reacted with 2.1 equiv of **4** at 130 °C in a closed vial, which generated **6** in 61% yield, but also 30% of the tertiary amine **7** (entry 1). The yield of **7** increased to 56% by adding molecular sieves (4 Å) to absorb water as the formal condensation product in this reaction (entry 2). Further improvement was realized by raising the temperature to 140 °C. Finally, a better ratio of **7** to **6** could be realized by increasing the excess of alcohol **3** to 5 equiv. Under these improved conditions, **7** could be isolated in 78% yield accompanied by 14% of intermediate **6**. In addition, a similar yield of **7** was obtained by conducting the reaction in an open system (71%, entry 6).

Using these final conditions, the generality of the double alkylation of amines catalyzed by complex **1** was demonstrated

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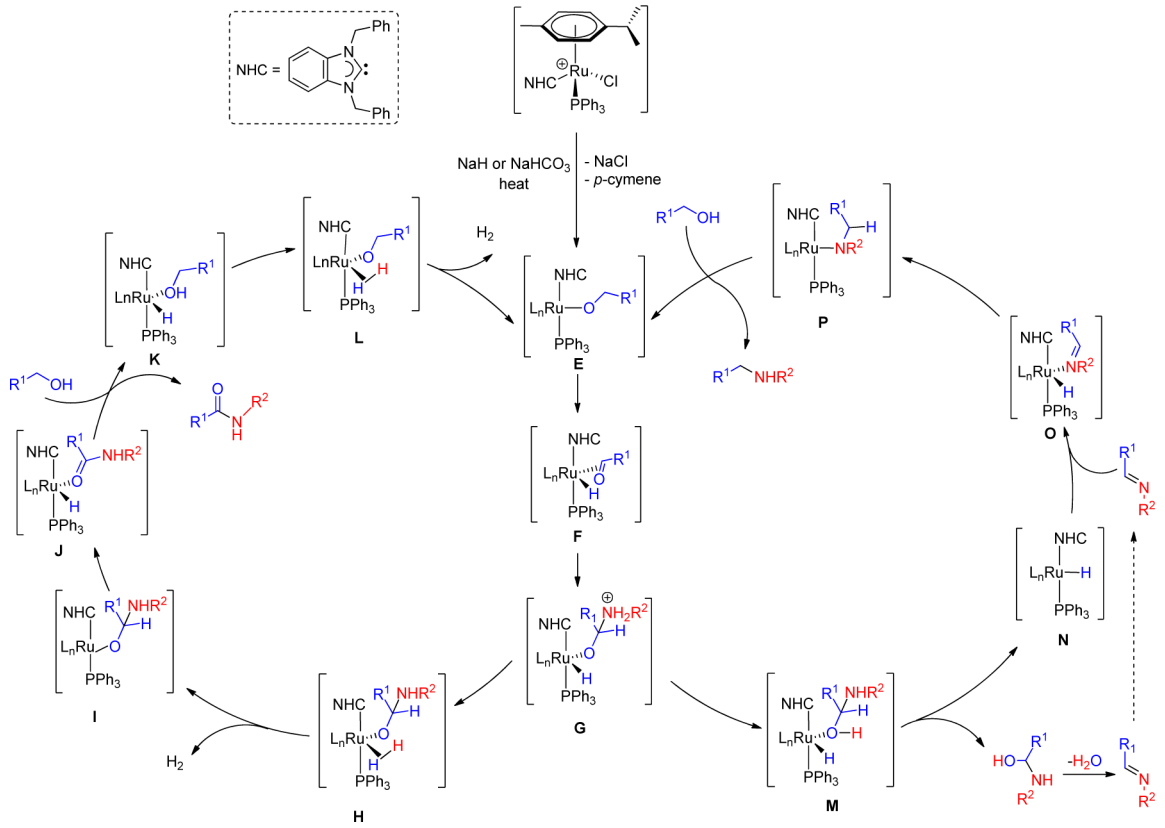
Scheme 3. Proposed Catalytic Cycle for the Ru-Catalyzed Amidation and Amination



by the syntheses of various acyclic tertiary amines depicted in Table 6. In general, all tertiary amines were isolated in good yields.

Benzylamine was reacted with 4-methoxybenzyl alcohol or benzyl alcohol to give the tertiary amines **7** and **29** in yields of 78% and 91%, respectively. Aniline is doubly alkylated with benzyl alcohol in 62% yield to give compound **30**. Substituents on the aromatic rings are tolerated in this protocol, and the transformations of substituted anilines and alcohols gave the respective products **31**−**34** in decent yields, regardless of the electronic nature of the substituents. In addition, the aliphatic 1-phenyl ethanol can be employed for a smooth dialkylation of substituted aniline to give compound **35** in 70% yield. Overall, various tertiary amines were obtained from substituted primary alcohols and primary amines in good to excellent yields via this simple methodology compared to only a few previously reported examples with limited substrate scope.[23]

Mechanistic Proposal. In order to gain better mechanistic insights into the fate of the ruthenium catalysts precursor, additional solution NMR experiments were carried out to identify possible intermediates in both amidation and amination processes. The reaction between 4-methoxyl benzyl alcohol **3** (0.6 mmol) and benzyl amine **4** (0.5 mmol) was selected for these studies (see the SI).

The amidation reaction was carried out in a NMR tube charged with substrates, complex **1** (0.2 mmol, 20% mol %), NaH (0.36 mmol, 60 mol %), and toluene-d_8, Substoichiometric **1** and base were used in order to obtain higher signal-to-noise ratio in the spectra. The NMR tube was then immersed in a preheated oil bath at 110 °C for a certain amount of time before it was cooled down to room temperature. The sample was then directly analyzed by ^{1}H NMR spectroscopy. It was found that after 10 min of heating, 95% of the *p*-cymene had dissociated (with 1,3,5-trimethoxybenzene as an internal standard), indicating that the *p*-cymene complexes are not involved in the catalytic cycle. This is in line with Madsen's previous report.[8b] Some hydrido signals were detected in the range from −6 to −14 ppm from another sample, which had been heated for 1 h. In particular, a high intensity doublet at −9.73 ppm is indicative for the existence of [RuH(PPh$_3$)] species, while the heteronuclear coupling constant of ^2J(P,H) = 50 Hz suggests a cis arrangement between triphenylphosphine and hydrido ligand. Furthermore, the ^{31}P NMR spectrum shows that the initial resonance of the coordinated triphenylphosphine in complex **1** at 32.54 ppm has been replaced by several new downfield signals ranging from 72−45 ppm. This provides additional support for the formation of the [RuH(PPh$_3$)] species as the downfield shifts are in line with a less Lewis acidic ruthenium center, probably due to coordination of the hydrido ligand. Moreover, the NHC was found to be still ligated to the [RuH(PPh$_3$)] species as evidenced by a diagnostic Ru−C$_{carbene}$ doublet centered at 196.1 ppm in ^{13}C NMR spectrum. The coupling constant of ^2J(P,C) = 17 Hz is essentially identical to that found in complex **1**, while its chemical shift is more downfield (cf. 187.0 ppm for **1**), again due to an additional hydrido ligand. Accordingly, a [RuH(NHC)(PPh$_3$)]-type complex could be the catalytically active intermediate in the amidation process.

For the study of the amination reaction, a different approach was taken. In order to be consistent with the catalytic runs, a "neat reaction" was carried out in a in a closed vial at 130 °C for 1 h with the same amounts of substrates, catalyst, and base (NaHCO$_3$ was the base in this case) as for the amidation. Upon cooling to ambient temperature, the mixture was diluted with

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toluene-d_8 for analysis. Similar to the amidation, 96% of the *p*-cymene was found in free form. A cis coordinated [RuH-(PPh_3)] species was also observed in the amination process by ^{1}H NMR spectroscopy with a diagnostic hydrido doublet at −9.77 ppm with a coupling constant of ^2J(P,H) = 50 Hz. In the ^{31}P spectrum, a resonance for free triphenylphosphine was observed at −6.0 ppm together with multiple downfield signals ranging from 70−45 ppm. Similarly, the proof for the existence of [RuH(NHC)(PPh_3)] complexes can be found in a carbene resonance at 194.71 ppm with a coupling constant of ^2J(P,H) = 17 Hz. Moreover, there are two more carbene signals at 209.5 and 209.3 ppm, which could be assigned to ruthenium-NHC dihydrido complexes due to the significant downfield shifts. In addition, a singlet at 10.17 ppm was detected by ^{1}H NMR spectroscopy, which could be assigned to either the coordinated aldehyde's proton from the oxidized alcohol or from the α-proton in the coordinated hemiaminalato species. Finally, in order to observe the formation of imine, which is an important intermediate in the amination, another closed-vial reaction was carried out at a lower temperature of 100 °C for 1 h. Indeed, the imine was detected in 41% yield by GC analysis.

On the basis of these observations and pioneering previous studies,[4,8b,c,13c,16a,18,22] two competing catalytic cycles for the amidation and the amination are proposed in Scheme 3. Both cycles are initiated by the dissociation of *p*-cymene and base-assisted coordination of the alcohol to the ruthenium center (**E**) followed by its internal oxidation to give the aldehyde and an active hydrido complex **F**. The aldehyde undergoes an internal addition reaction with the primary amine, which gives rise to a protonated hemiaminalato complex **G**. The subsequent selectivity for amidation versus amination may be highly dependent on the N-proton transfer.[22]

With a strong base and in nonpolar solvent, the proton transfers to the hydrido (from **G** to **H**), and the "amide catalytic cycle" is initiated via the release of dihydrogen from the intermediate **H** to give the hemiaminalato intermediate **I**. Subsequent internal redox reaction of complex **I** via β-hydride elimination leads to hydrido complex **J**. Ligand substitution with an alcohol releases the amide product and a hydrido complex **K** is formed. The latter undergoes intramolecular acid−base reaction to give **L**, which finally liberates dihydrogen and closes the catalytic cycle to give alkoxido complex **E**.

On the other hand, in a less basic environment and protic solvent (alcohol), the proton transfers to the bound oxygen (from **G** to **M**) before the free hemiaminal is liberated. The hemiaminal immediately loses water to form the imine. Then the imine re-enters the amine catalytic cycle under formal insertion into the ruthenium-hydrido bond of intermediate **O** to give an amido complex **P**. Intermolecular acid−base reaction of complex **P** with an external alcohol molecule releases the amine product and reforms alkoxide complex **E** closing the cycle.

Overall, we believe that selectivity in the amidation versus amination can be achieved by the controlling of the N-proton transfer by choosing different bases and solvents. A strong base in conjunction with a nonpolar solvent favoring the proton-to-hydrido transfer would lead to amide formation, while a weaker base in a polar system results in proton-to-alkoxido transfer to initiate the amination pathway.

CONCLUSION

In conclusion, we have reported a tunable amidation and amination of alcohols with amines catalyzed by a single well-defined ruthenium NHC complex **1**. We propose that the amide is formed via the acceptorless dehydrogenation process involving a hemiaminalato complex, while the "borrowing hydrogen" route is operative for the amination. The selectivity is likely based on the N-proton transfer, which in turn can be easily tuned by the choice of base and solvent. The proton-to-hydrido transfer leads to the formation of amides, while the proton-to-alkoxido transfer results in the formation of an imine, which is finally reduced by the ruthenium hydride species to give amines. Various amides and secondary and tertiary amines can be effectively synthesized using a single catalyst precursor. This study may shine light on the understanding of dehydrogenative reactions as well as provide the possibility for the design of catalysts suitable for different types of reactions. Work is in progress to further optimize catalysts for such purposes, to extend its application to asymmetric catalysis, as well as to provide a better understanding of the mechanistic details.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.5b00588.

Experimental procedures, characterization data of the products, NMR spectra of products, and crystallographic data (PDF)

Crstyallographic information for complexes **1** and **2** (CIF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: chmhhv@nus.edu.sg.

Notes

The authors declare no competing financial interest.

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