Received: 8 August 2019 | Revised: 28 September 2019 | Accepted: 10 October 2019

DOI: 10.1002/aoc.5323

FULL PAPER

Applied Organometallic Chemistry WILEY

Well-defined N-heterocyclic carbene/ruthenium complexes for the alcohol amidation with amines: The dual role of cesium carbonate and improved activities applying an added ligand

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Funding information
Tomsk Polytechnic University, Grant/Award Number: VIU-69/2019; Tomsk Polytechnic University Competitiveness Enhancement Program, Grant/Award Number: VIU-69/2019; Russian Foundation for Basic Research, Grant/Award Number: N° 18-29-04047; National Natural Science Foundation of China, Grant/Award Number: 21502062

Dehydrogenative amide bond formation from alcohols and amines has been regarded as an atom-economic and sustainable process. Among various catalytic systems, N-heterocyclic carbene (NHC)-based Ru catalytic systems have attracted growing interest due to the outstanding properties of NHCs as ligands. Herein, an NHC/Ru complex (**1**) was prepared and its structure was further confirmed with X-ray crystallography. In the presence of Cs_2CO_3, two NHC/Ru-based catalytic systems were disclosed to be active for this amide synthesis. System A, which did not contain any added ligand, required a catalyst loading of 1.00 mol%. Interestingly, improved catalytic performance was realized by the addition of an NHC precursor (**L**). Optimization of the amounts of **L** and other conditions gave rise to system B, a much more potent system with the Ru loading as low as 0.25 mol%. Moreover, an NHC-Ru-carbonate complex **6** was identified from the refluxing toluene of **1** and Cs_2CO_3, and further investigations revealed that **6** was an important intermediate for this catalytic reaction. Based on the above results, we claimed that the role of Cs_2CO_3 was to facilitate the formation of key intermediate **6**. On the other hand, it provided the optimized basicity for the selective amide formation.

KEYWORDS

amide synthesis, C-N bond formation, complex, N-heterocyclic carbene(s), ruthenium

1 | INTRODUCTION

Considering the profound significance of the amide linkage in organic chemistry and biological systems,[1] numerous researchers focused on environmentally benign and atom-economic methods for amide synthesis. Among these methods, acceptorless dehydrogenative amidation of alcohols and amines applying transition metal-based catalytic systems has been highlighted as an attractive strategy for constructing the amide bond. This method features high atom economy with molecular hydrogen as the sole byproduct.[2] The generally accepted pathway for this strategy begins with the oxidation of an alcohol to form the corresponding aldehyde or Ru-bound aldehyde, which then reacts with an amine to produce a hemiaminal intermediate.[2b] There are two possible pathways after the formation of the hemiaminal. It could be transformed to an imine, followed by the hydrogenation of the imine to generate an amine, the so-called hydrogen borrowing (HB) strategy.[3] Alternatively, the hemiaminal could be directly dehydrogenated to the corresponding amide. In particular, ruthenium (Ru) is the most accessed metal.[4] Originally, Murahashi and co-workers accomplished the intramolecular amidation of 1,3- and 1,4 amino alcohols via the catalysis of $RuH_2(PPh_3)_4$.[5] A significant breakthrough was the development of a Ru complex bearing a dearomatized PNN-type ligand, the well-known Milstein catalyst.[6] It was worth noting that amide synthesis could be firstly achieved in an intermolecular manner. Inspired by these two reports, Madsen,[7] Williams,[8] Hong,[9] Crabtree,[10] Albrecht,[11] Milstein,[12] Guan,[13] Glorius,[14] Möller,[15] Bera,[16] Huynh,[17] Viswanathamurthi,[18] Mashima,[19] Verpoort[20], Kundu[21] and their co-workers also contributed in this area. According to the promising properties of N-heterocyclic carbenes (NHCs) as ligands for transition metal complexes,[22] we have focused on the development and investigation of versatile and efficient NHC-Ru catalytic systems for this reaction.[9f, g, 20] Other groups including the Madsen,[7] Hong,[9a–i] Glorius,[14] Möller,[15] Bera,[16] Huynh,[17] and Viswanathamurthi[18a] groups also explored their respective NHC-Ru systems for the same purpose.

Previously, we developed a variety of *in situ* generated (*p*-cymene)-Ru catalytic systems comprising benzimidazole-based NHC precursors.[20a, b] Through a systematic investigation of the backbone and wingtip substituents on the benzimidazole framework, 3-ethyl-1-methyl-1*H*-benzo[*d*]imidazol-3-ium iodide (**L**) was identified as an optimal NHC precursor (as shown in Figure 1a).[20b] A combination of $[RuCl_2(p\text{-cymene})]_2$, **L**, NaH led to an efficient catalytic system for this amidation, and further High-Resolution Mass Spectroscopy (HRMS) analyses of the *in situ* generated catalytic system implied that NHC-Ru complex **1** was observed as a major species (as depicted in Figure 1a). Herein, in order to gain more mechanistic insights, we aimed to synthesize this Ru complex and evaluate its catalytic performance. Through the extensive screening of various conditions, two catalytic systems, system A (without an added ligand) and system B (with an added ligand), were discovered (as depicted in Figure 1b). Interestingly, compared with system A (a Ru loading of 1.00 mol%), system B, which contains an identical NHC precursor as an added ligand, resulted in a much more active catalytic system (a Ru loading of 0.25 mol%). Notably, instead of NaH which was proven to be superior over other bases in our previous *in situ* catalytic systems,[20b] a milder base (Cs_2CO_3) was found to promote this reaction in a more efficient pattern. Further exploration indicated that the role of Cs_2CO_3 was not only to assist the formation of a NHC-Ru complex ligated by a carbonate ligand, but also provide the optimized basicity for this process.

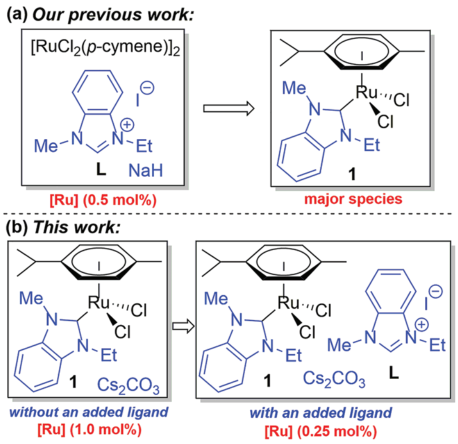


FIGURE 1 The design strategy of this work

2 | EXPERIMENTAL SECTION

2.1 | General considerations

All reactions were carried out using standard Schlenk techniques or in an argon-filled glove box unless otherwise mentioned. All the substrates and solvents were obtained from commercial suppliers and used as received without further purification. ^1H NMR spectra were recorded on a Bruker Avance 500 spectrometer in $CDCl_3$ or DMSO-d_6 with TMS as the internal reference, and ^{13}C

NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 on a Bruker Avance 500 (126 MHz) spectrometer. The following abbreviations were used to designate multiplicities: s = singlet, brs = broad singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = double of doublets of doublets, td = triplet of doublets, tt = triplet of triplets, m = multiplet. Melting points were taken on a Buchi M-560 melting point apparatus and were uncorrected. HR-MS analyses were done with a Bruker Daltonics microTOF-QII instrument. The single crystal structures of **1** and **6 • 2CDCl$_3$** were obtained using a Bruker APEX-II CCD diffractometer with Mo Kα radiation (λ = 0.71073 Å). The supplementary crystallographic data of **1** (with a deposition No. of 1864555) and **6 • 2CDCl$_3$** (with a deposition No. of 1870478) could be obtained free of charge from The Cambridge Crystallographic Data Centre (CCDC). NHC precursor **L** was prepared according to a reported procedure.[20b]

2.2 | General procedure for the synthesis of complexes 1 and 6

2.2.1 | Synthesis of NHC-Ru complex 1

A suspension of 3-ethyl-1-methyl-1*H*-benzo[*d*]imidazol-3-ium (**L**, 288.1 mg, 1.00 mmol), Ag_2O (115.9 mg, 0.50 mmol) in dry dichloromethane (5.0 ml) at a refluxing temperature in dark for 12 hr. Then [Ru(*p*-cymene)Cl_2]$_2$ (306.1 mg, 0.50 mmol) was added and the resulted suspension was refluxed for an additional 6 hr. After the reaction was complete, the mixture was filtered through a plug of Celite and the filtrate was concentrated under reduced pressure. The orange residue was then recrystallized from methanol/diethyl ether to afford an orange solid, which was then washed with diethyl ether for a few times to obtain analytically pure product **1** as an orange powder. Yield: 75% (355.0 mg, 0.75 mmol). The single crystal of **1** was obtained by slow evaporation of diethyl ether into a solution of **1** in dichloromethane.

2.2.2 | Synthesis of NHC-Ru-carbonate complex 6

Since it was difficult to purify **6** directly from the mixture of **1**, Cs_2CO_3 and dry toluene, an alternative procedure was utilized based on a similar procedure.[10b] Sodium carbonate (106.0 mg, 1.00 mmol), **1** (94.0 mg, 0.20 mmol) and ethanol (15 ml) were stirred at room temperature for 3 hr. The resulted mixture was filtered through Celite, and the solvent was removed. Afterwards, the residue was redissolved in dichloromethane (20 ml) and filtered again. Concentrating the solution and subsequent precipitation with cold diethyl ether gave **6** as a yellow solid. Yield: 70% (63.8 mg, 0.14 mmol). The single crystal of **6** was obtained by slow evaporation of diethyl ether into a solution of **6** in $CDCl_3$.

2.3 | General procedure for the amide synthesis

2.3.1 | Catalytic reactions utilizing system a

Inside an argon-filled glove box, **1** (2.4 mg, 0.005 mmol), Cs_2CO_3 (3.3 mg, 0.01 mmol) and dry toluene (0.75 ml) were added to an oven-dried 25 ml Schlenk flask. The flask was taken out and heated to reflux under argon for 0.5 hr. After the reaction mixture was cooled down to room temperature, an alcohol (0.50 mmol), an amine (0.55 mmol) were added and the mixture was heated to reflux for 24 hr.

2.3.2 | Catalytic reactions utilizing system B

To an oven-dried 25 ml Schlenk flask was added **1** (2.4 mg, 0.005 mmol), NHC precursor **L** (4.3 mg, 0.015 mmol), Cs_2CO_3 (11.5 mg, 0.035 mmol) and dry toluene (1.00 ml) inside an argon-filled glovebox. This flask was taken out and heated to reflux under argon for 0.5 hr. Then an alcohol (2.00 mmol), an amine (2.20 mmol) were added and the mixture was stirred at a refluxing temperature for 24 hr.

2.3.3 | Catalytic reactions utilizing 6 without L

6 (2.3 mg, 0.005 mmol), Cs_2CO_3 (3.3 mg, 0.01 mmol), an alcohol (0.50 mmol), an amine (0.55 mmol) and dry toluene (0.75 ml) were added to an oven-dried 25 ml Schlenk flask, which was then heated to reflux under argon for 24 hr.

2.3.4 | Catalytic reactions utilizing 6 in the presence of L

The procedure was similar to that for catalytic reactions utilizing system B, by replacing **1** with **6** and adjusting the amount of each substance accordingly.

2.3.5 | Additional information

For NMR yields, 1,3,5-trimethoxybenzene (0.5 mmol, 84.0 mg) and $CHCl_3$ (1.0 mL) were added to the reaction mixture, and 0.1 ml of the above solution and 0.5 ml of $CDCl_3$ were added to an NMR tube. The NMR yields of all the identified compounds were calculated from the exact amount of 1,3,5-trimethoxybenzene. In terms of the isolated yields, the reaction mixture was cooled down to room temperature, and the solvent was removed under reduced pressure. Finally, the residue was purified by silica gel flash column chromatography to afford the amides. Most amide products were identified by spectral comparison with literature data,[20a–c, 23] while amides **4f** and **4 g** were fully characterized**.** Moreover, the characterization data and the corresponding spectra of all the amides could be found in the supporting information.

3 | RESULTS AND DISCUSSION

Complex **1** was synthesized by transmetallation from an *in situ* generated NHC-Ag complex, and its structure was further confirmed by X-ray crystallography (as shown in Figure 2). Then the catalytic evaluation was initiated by selecting the coupling of benzyl alcohol (**2a**) with benzylamine (**3a**) as a model reaction (as shown in Table 1). At the outset, 62–72% yields of amide **4a** were obtained if a strong base such as NaH or KO*t*Bu was used to promote this reaction (entries 1–2). Weaker bases including Li_2CO_3, Na_2CO_3, K_2CO_3 and Cs_2CO_3 were also attempted (entries 3–6). Li_2CO_3 and Na_2CO_3 produced imine **5a** as the major product (entries 3–4), and K_2CO_3 could result in 42% of amide **4a** with concurrent formation of imine **5a** in 12% yield (entry 5). To our delight, selective amide formation (88% of **4a** and only 6% of **5a**) was achieved in the case of Cs_2CO_3 (entry 6), which manifested an even better result than the above-mentioned strong bases (entry 6 *vs.* entries 1–2). After establishing the ideal base, the amounts of Cs_2CO_3 were screened (entries 6–10), and 2.00 mol% was demonstrated as the optimum amount (entry 6). Furthermore, the effects of the solvent volume were also examined (entries 6, 11–13), and 0.75 mL of toluene produced the best result (entry 12). It was also observed that pre-heating **1**, Cs_2CO_3 and toluene at reflux for 0.5 hr before the addition of the substrates led to a slightly enhanced yield of **4a** (entry 14 *vs.* entry 12). Finally, 1.00 equiv. of degassed water as an additive could not provide a better result (entry 15 *vs.* entry 14). Thus, the optimized conditions were described in entry 14 of this table unless otherwise noted.

In order to discover a more potent catalytic system, further screening of various conditions was also conducted (as shown in Table 2). If the Ru loading was reduced from 1.00 mol% to 0.50 mol% and 0.25 mol%, respectively, the amide percentages among product distribution were gradually decreased (entries 1–3). Since the NHC ligand of **1** was verified as the optimum one for the reaction, we wondered if improved catalytic performance could be achieved by incorporating the precursor of the identical NHC ligand (**L**) into the catalytic system. With this consideration in mind, different amounts of **L** were added as an extra ligand (entries 4–8). To ascertain two additional equivalents of Cs_2CO_3 for interacting with **1** for the above entries, the amounts of Cs_2CO_3 were initially changed according to those of **L**. These results indicated that a 1: 3 ratio of **1**: **L** was optimal (entry 6). In addition, adjustment of the base amounts revealed that the optimal ratio of **1**: **L:** Cs_2CO_3 was identified as 1: 3: 7 (entries 6, 9–12). Variation of the solvent volume suggested that 1.00 mL of toluene gave the highest yield of **4a** (entries 11, 13–15). Moreover, adding 1.00 equiv. of degassed water resulted in a slightly lower yield of **4a** (entry 16). If the reaction was run under an argon-filled sealed tube, an unsatisfactory result was attained (entry 17). Finally, replacing toluene with dioxane as the solvent led to 72% of amide **4a** (entry 18). Therefore, the optimized conditions were illustrated in entry 13 of this table unless otherwise noted.

Based on the above optimization processes, both system A (without an added ligand, as listed in entry 14 of Table 1) and system B (with an added ligand, as listed in entry 13 of Table 2) were selected for further exploration of the substrate scope and limitations (as depicted in Figure 3). For both systems, good yields were given for sterically non-hindered substrates. In addition, heterocyclic compounds were also tolerated for both systems. 30–66% of the desired products (**4d-4 g**) were given for furan- and thiophene-containing substrates, while moderate to good yields were obtained for saturated heterocycles. For moderately congested reactants (**2j, 2 k, 3 l, 3 m**) and secondary amines (**3n-3p**), moderate yields were given for both systems. Except for intermolecular amidation of an alcohol and an amine, a six-membered cyclic lactam (**4q**) was efficiently synthesized in an intramolecular manner. Furthermore, the electronic effects were explored on both substrates. System A could catalyze most electron-rich and electron-deficient substrates in good to excellent yields. In the case of system B, the desired amides (**4r**, **4 s**, **4w**, **4x**) with electron-donating groups could be afforded in high yields, but considerably lower yields were provided for those bearing electron-withdrawing groups (**4 t-4v**, **4y-4a'**).

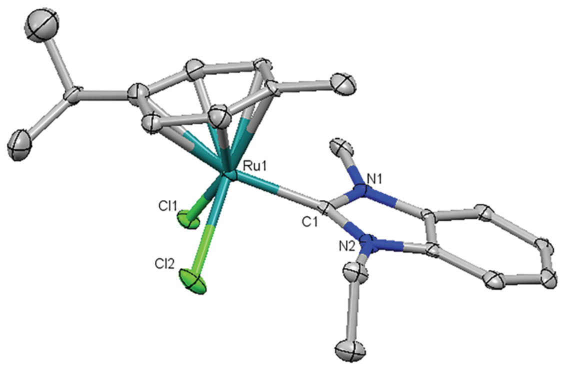
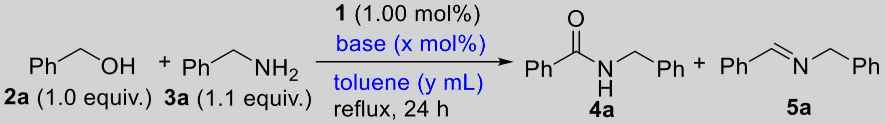


FIGURE 2 The molecular structure of complex **1**, showing the atom labeling scheme of the heteroatoms and carbon atom C1. The disorder of the *p*-cymene ligand and hydrogen atoms were omitted for clarity. The ellipsoids of atoms were shown at a probability level of 30%

To have a clearer understanding about the mechanistic insights, more investigations were performed. A mixture of **1** (0.005 mmol), Cs_2CO_3 (0.010 mmol) and toluene (0.75 ml) was heated at reflux for 0.5 hr, then the solvent was removed and the residue was directly dissolved in $CDCl_3$. From the ^{13}C-NMR analysis of the above $CDCl_3$ solution, two carbene signals at 190.74 and 188.68 ppm as well as a carbonyl peak at 166.28 ppm were clearly detected (as shown in Figure S1a of the Supporting Information). The resonance at 188.68 ppm was from the unreacted **1** (Figure S1a *vs.* S1b of the Supporting Information), while the peaks of 190.74 and 166.28 ppm could be assigned as an NHC-Ru complex bearing a carbonate moiety.[10b, 24] Therefore, HRMS analysis was conducted to confirm the possible Ru species for both systems (as depicted in Figure 4). The HRMS spectrum for system A was illustrated in Figure 4a. Not surprisingly, an isotopic peak at m/z = 431.08225 was consistent with $[\mathbf{1}\text{-Cl}]^+$. Interestingly, a major peak at 457.10597 was assigned as $[\mathbf{6} + \text{H}]^+$, an NHC-Ru species coordinated with a carbonate ligand. In the case of system B, a few mono-carbene complexes, including $[\mathbf{1}\text{-Cl}]^+$, $[\mathbf{6} + \text{H}]^+$ and **7** were detected from the spectrum (as shown in Figure 4b). In addition, two poly-carbene complexes

TABLE 1 Optimization of reaction conditions[a]



				Yields (%)[b]		
Entry	**base**	**x**	**y**	**4a**	**5a**	**Unreacted 2a**
1	NaH	2.00	0.50	72	13	4
2	KO*t*Bu	2.00	0.50	62	4	20
3	Li_2CO_3	2.00	0.50	0	38	59
4	Na_2CO_3	2.00	0.50	12	39	40
5	K_2CO_3	2.00	0.50	42	12	35
6	Cs_2CO_3	2.00	0.50	88	6	2
7	Cs_2CO_3	1.00	0.50	18	50	25
8	Cs_2CO_3	3.00	0.50	86	7	2
9	Cs_2CO_3	4.00	0.50	84	7	0
10	Cs_2CO_3	5.00	0.50	83	9	0
11	Cs_2CO_3	2.00	0.25	73	7	13
12	Cs_2CO_3	2.00	0.75	90	7	0
13	Cs_2CO_3	2.00	1.00	88	5	5
14[c]	Cs_2CO_3	2.00	0.75	93	4	0
15[c,d]	Cs_2CO_3	2.00	0.75	85	3	7

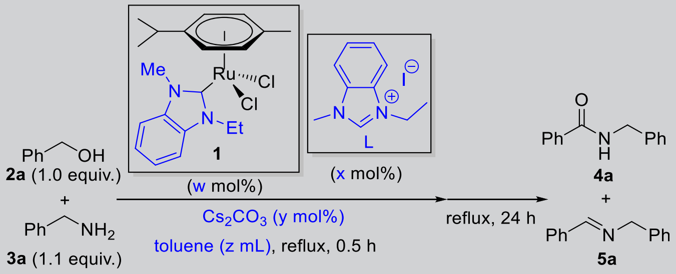
[a] **2a** (0.50 mmol), **3a** (0.55 mmol), complex **1** (1.00 mol%), base (x mol%) and toluene (y ml) at refluxing temperature were used.

[b] NMR yields using 1,3,5-trimethoxybenzene as an internal standard (averages of two consistent runs).

[c] **1** and Cs_2CO_3 were stirred at refluxing toluene for 0.5 hr before the addition of the substrates.

[d] Degassed water (1.00 equiv.) was added.

TABLE 2 Optimization of reaction conditions catalyzed by complex **1** with an added ligand[a]



					Yields (%)[b]		
Entry	**w**	**x**	**y**	**z**	**4a**	**5a**	**Unreacted 2a**
1	1.00	0.00	2.00	0.75	93	4	0
2	0.50	0.00	1.00	0.75	57	10	32
3	0.25	0.00	0.50	0.75	40	21	35
4	0.25	0.25	0.75	0.75	52	16	25
5	0.25	0.50	1.00	0.75	60	15	19
6	0.25	0.75	1.25	0.75	71	9	16
7	0.25	1.00	1.50	0.75	65	11	14
8	0.25	1.25	1.75	0.75	67	13	12
9	0.25	0.75	1.00	0.75	69	11	18
10	0.25	0.75	1.50	0.75	76	10	7
11	0.25	0.75	1.75	0.75	83	10	4
12	0.25	0.75	2.00	0.75	80	11	0
13	**0.25**	**0.75**	**1.75**	**1.00**	**90**	**8**	**0**
14	0.25	0.75	1.75	1.25	78	12	8
15	0.25	0.75	1.75	1.50	74	14	11
16[c]	0.25	0.75	1.75	1.00	88	4	6
17[d]	0.25	0.75	1.75	1.00	41	6	52
18[e]	0.25	0.75	1.75	1.00	72	1	25

[a] **2a** (1.00 equiv.), **3a** (1.10 equiv.), **1** (w mol%), **L** (x mol%), Cs_2CO_3 (y mol%), and toluene (z ml) at refluxing temperature were used.

[b] NMR yields using 1,3,5-trimethoxybenzene as an internal standard (averages of two consistent runs).

[c] Degassed water (1.00 equiv.) was added.

[d] In a sealed tube instead of a Schlenk flask.

[e] Dioxane instead of toluene as the solvent.

8 and **9**, similar with our previous observation,[20c] were also observed. Unfortunately, isolation of these poly-carbene complexes was unsuccessful, which was probably due to the complexity of system B. Thus, in order to ensure whether complex **6** was a key intermediate during the catalysis, we synthesized this complex and took its ^{13}C-NMR spectrum (as shown in Figure S1c of the Supporting Information). The structure of the newly synthesized **6** was confirmed by X-ray crystallography (as shown in Figure 5). Comparison of the ^{13}C-NMR spectra between the crude mixture and pure **6** revealed the formation of this NHC-Ru-carbonate complex, which verified that Cs_2CO_3 facilitated the formation of **6** (Figure S1a *vs.* 1c of the Supporting Information). On the other hand, the optimization results of **1** with various carbonate-containing bases indicated that Cs_2CO_3 also provided the optimized basicity for this reaction (as listed in entries 3–6, Table 1).

Furthermore, the catalytic activities of **6** were determined to testify whether it was a possible catalytic intermediate (as listed in Table 3). In the first place, a catalyst loading of 1.00 mol% was used in the absence of an added

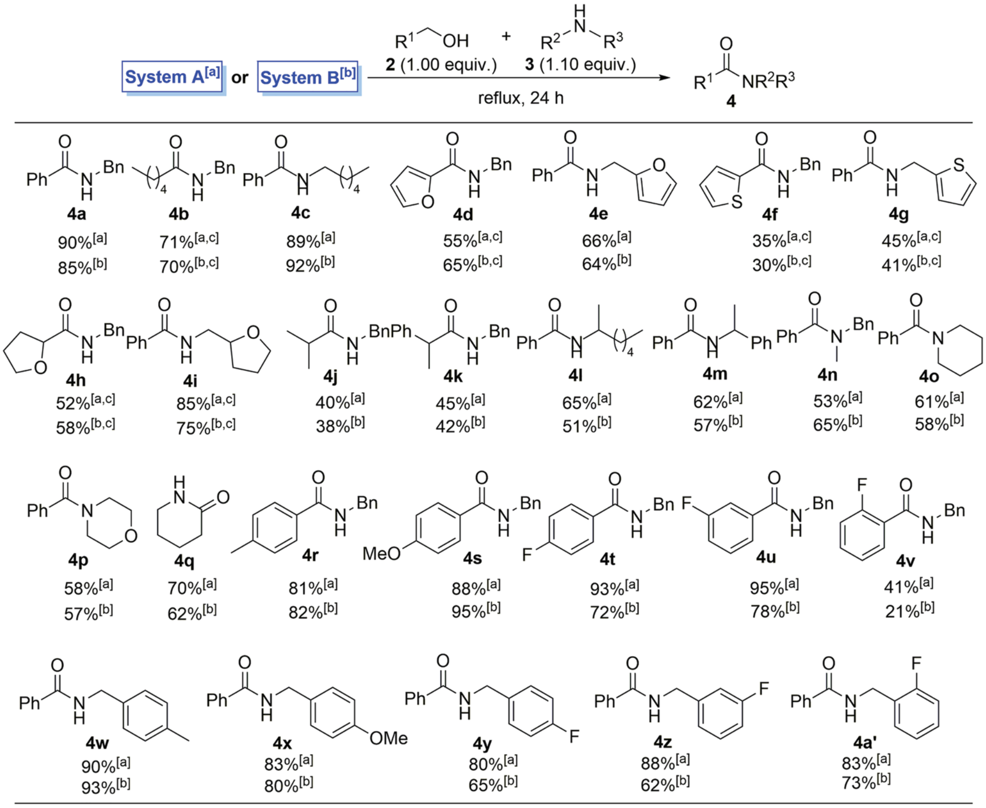


FIGURE 3 Amide synthesis from various alcohols and amines. The reported yields are isolated yields obtained by averages of two consistent runs. [a] Complex **1** (1.00 mol%), Cs_2CO_3 (2.00 mol%), and toluene (0.75 ml) at reflux for 0.5 hr before addition of the substrates; [b] Complex **1** (0.25 mol%), **L** (0.75 mol%), Cs_2CO_3 (1.75 mol%) and toluene (1.00 ml) at reflux for 0.5 hr before addition of the substrates; [c] 48 hr instead of 24 hr

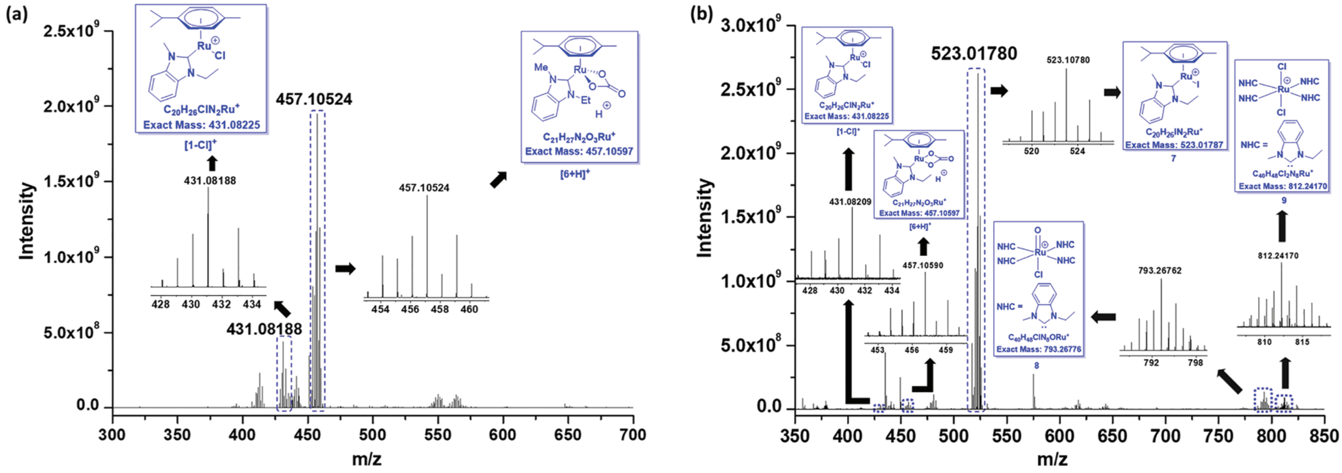


FIGURE 4 HRMS analyses for (a) system A and (b) system B

ligand (entries 1–5). Without Cs_2CO_3, 35% of amide **4a** and 15% of imine **5a** were observed with 45% of unreacted **2a** (entry 1). 1.00–4.00 mol% of the base resulted in good to excellent results (entries 2–5). In the presence of **L** as an added ligand, 0.25 mol% of **6** and 0.75 mol% of **L** were applied. Varying the base amount from 0.75 mol% to 1.75 mol% did not significantly affect the reaction, producing the desired product **4a** in 78–91% yields (entries 6–10). The above results illustrated that **6** should be a key intermediate during the catalysis.

With an aim to clarify the significant role of **6** during the catalysis, further experiments were conducted. Generally, it has been postulated that the generation of Ru hydride species is crucial for the NHC-Ru catalyzed amide synthesis.[9b, h, 20a, d] Therefore, Ru hydride formation was monitored by two NMR reactions utilizing **6** with and without **L**, respectively (as shown in Figure S2 and S3 of the supporting information). Initially, a mixture of **6** (0.015 mmol), Cs_2CO_3 (0.030 mmol) and toluene-d_8 (0.6 mL) was transferred to a screw-capped

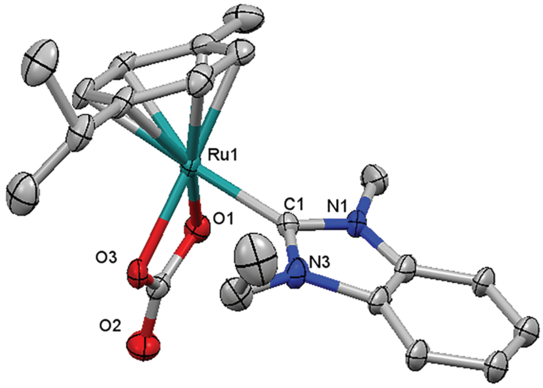
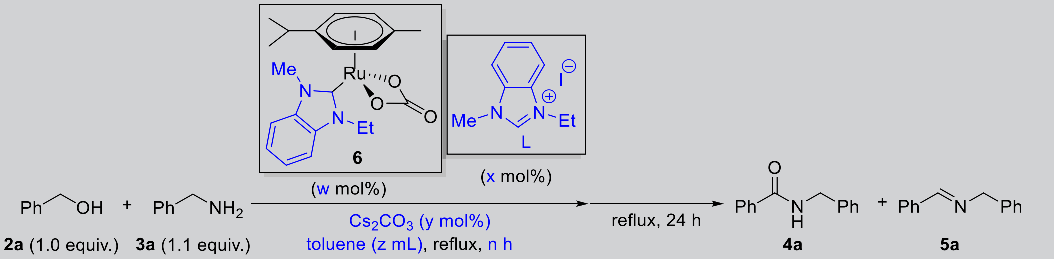


FIGURE 5 The molecular structure of **6 • 2CDCl$_3$**, showing the atom labelling scheme of the heteroatoms and carbon atom C1. The disorder of the *p*-cymene ligand, hydrogen atoms and CDCl$_3$ molecules were omitted for clarity. The ellipsoids of atoms were shown at a probability level of 30%

NMR tube, but no hydride peak was observed. Afterwards, **2a** (0.075 mmol) and **3a** (0.083 mmol) were added, and still no hydride signal was detected (as shown in Figure S2a). Interestingly, a singlet at −9.40 ppm was found after heating the NMR tube at reflux for 15 min (Figure S2b). As the heating period was elongated, the intensity of the peak at −9.40 ppm gradually decreased while another singlet resonance at −17.09 was intensified (Figure S2c-2f). However, further elongating the period resulted in the disappearance of this peak (Figure S2f-2i). For the NMR reaction applying an added amount of ligand **L**, a similar trend was found (as shown in Figure S3 of the supporting information). No hydride resonance was observed before or after the addition of both substrates at room temperature (Figure S3a). However, a singlet at −7.76 ppm was originally shown upon heating the NMR tube to reflux (Figure S3b). As the heating continued, this peak gradually disappeared and another singlet at −17.09 was clearly seen (Figure S3c-f). Interestingly, this peak persisted even after 6 hr (Figure S3f-3i). These results implied that Ru-hydride species, probably Ru monohydride species due to the observation of several singlet hydrides, were involved and regarded to be paramount in the catalytic cycle. Moreover, the hydride peak at −17.09 ppm was ultimately observed for these two systems (with or without extra NHC precursor **L**), which probably implied that the same Ru hydride species was formed for both systems and played a key role for this catalytic process. More significantly, the extra **L** presumably stabilized the catalytic

TABLE 3 The catalytic performance of **6**



Entry	w	x	y	z	n	Yields (%)[a]		
						4a	5a	Unreacted 2a
1	1.00	0.00	0.00	0.75	0	35	15	45
2	1.00	0.00	1.00	0.75	0	75	10	8
3	1.00	0.00	2.00	0.75	0	91	3	0
4	1.00	0.00	3.00	0.75	0	89	4	0
5	1.00	0.00	4.00	0.75	0	87	5	0
6	0.25	0.75	0.75	1.00	0.5	80	2	12
7	0.25	0.75	1.00	1.00	0.5	85	5	9
8	0.25	0.75	1.25	1.00	0.5	90	3	4
9	0.25	0.75	1.50	1.00	0.5	91	6	0
10	0.25	0.75	1.75	1.00	0.5	82	10	0

[a] NMR yields using 1,3,5-trimethoxybenzene as an internal standard (averages of two consistent runs).

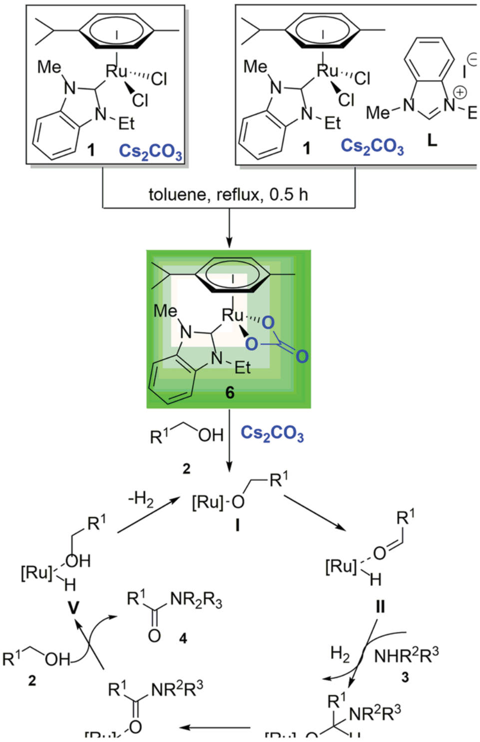


FIGURE 6 The proposed mechanism for the NHC/Ru catalyzed amidation of alcohols with amines

active species since the hydride resonance of −17.09 ppm in the presence of **L** persisted for much longer time than that without **L** (Figure 2f-2i *vs.* Figure 3f-3i).

Addressing the dual role of Cs_2CO_3 herein is closely related to the recent study of NHC/Pd and NHC/Ni systems, where O-NHC coupling upon the addition of similar oxygen bases,[25] so we would like to confirm whether the occurrence of O-NHC coupling was also involved in our catalytic systems. Accordingly, we carefully examined and analyzed the HR-MS spectra of both system A and system B, but no azolones were observed in both systems (as shown in Figure S4 and S5 of the supporting information). Based on the above experiments and previous literature,[9b, h, 17, 20a, d] we proposed a possible pathway for this catalytic reaction (as shown in Figure 6). Complex **1** and Cs_2CO_3 at refluxing toluene, either with or without an extra added NHC precursor **L**, could give rise to the NHC-Ru-carbonate complex **6**, which reacts with alcohol **2** and Cs_2CO_3 to generate key Ru-alkoxide intermediate **I**. **I** could undergo β-hydride elimination to afford Ru monohydride species **II** bound with an aldehyde, which then reacts with **3** to deliver intermediate **III** with elimination of H_2. Furthermore, **III** is subsequently transformed into Ru monohydride species **IV** via β-hydride elimination. Finally, ligand exchange with **2** gives amide **4** and monohydride complex **V**, which releases one H_2 molecule to regenerate intermediate **I** so that the fulfilment of the catalytic cycle is accomplished.

4 | CONCLUSION

In summary, based on the various *in situ* generated NHC-Ru catalytic systems, we synthesized a superior NHC-Ru complex **1** and confirmed its structure by X-ray crystallography. Through a systematic investigation of various reaction conditions, system A (without an added ligand) and system B (in the presence of NHC precursor **L**) were identified as the optimized catalytic systems, producing various amides from the corresponding alcohols and amines. Without any added ligand, 1.00 mol% of **1** was required. Improved catalytic activities were observed with different amounts of an added ligand, and only a Ru loading of 0.25 mol% was enough to achieve satisfactory results. Further investigations indicated the existence of an NHC-Ru-carbonate complex **6**, which was certified as a vital catalytic intermediate from the catalytic evaluation of this complex. Significantly, it was proposed that Cs_2CO_3 not only facilitated the formation of the Ru carbonate species, but also served as the optimized base for this transformation.

ACKNOWLEDGEMENTS

This research was supported by the National Natural Science Foundation of China (No. 21502062). F.V. acknowledges the support from the Russian Foundation for Basic Research (N° 18-29-04047) and the Tomsk Polytechnic University Competitiveness Enhancement Program grant (VIU-69/2019).

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How to cite this article: Wang W-Q, Yuan Y, Miao Y, et al. Well-defined N-heterocyclic carbene/ruthenium complexes for the alcohol amidation with amines: The dual role of cesium carbonate and improved activities applying an added ligand. *Appl Organometal Chem*. 2019;e5323. https://doi.org/10.1002/aoc.5323