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# Amide synthesis from alcohols and amines catalyzed by a $Ru^{II}$–*N*-heterocyclic carbene (NHC)–carbonyl complex☆

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ABSTRACT

Treatment of $[Ru_2(CO)_4(CH_3CN)_6](BF_4)_2$ with 3-methyl-1-(pyridin-2-yl)-imidazolium bromide in the presence of tetrabutylammonium bromide at room temperature in dichloromethane affords a $Ru^{II}$–*N*-heterocyclic carbene–carbonyl complex $[Ru(py\text{-}NHC)(CO)_2Br_2]$ (**1**). Catalyst **1** displays diverse substrate scope for phosphine-free acceptorless coupling between alcohols and amines to amides at low catalyst loading. A $Ru^{II}$-dihydride/$Ru^0$ sequence is proposed in the catalytic cycle.



## 1. Introduction

Amide bonds are key chemical components in both natural and synthetic systems. Biopolymer proteins and numerous synthetic polymers feature amides linkages [1]. The conventional strategy for amide bond formation involves reactions of activated carboxylic derivatives with amines [2]. Alternative strategies are also developed [3] but these reactions lack atom economy generating equimolar amounts of chemical waste. We developed a Rh(I) based bifunctional catalyst for amide synthesis via nitrile hydration [4]. This catalyst is particularly effective for small nitriles such as acrylonitrile. Transition metal catalyzed amide synthesis strategies directly from alcohols and amines are receiving considerable attentions in recent years. This reaction does not require the use of hydrogen acceptors and two molecules of hydrogen are the only by-products making it a true green process (Scheme 1).

Milstein's Ru–PNN pincer complex (Scheme 2, a) was the first reported metal–ligand cooperating catalyst for amide synthesis directly from alcohols and primary amines without the use of any base or hydrogen acceptor. The PNN ligand shuttles between dearomatized and aromatized forms favoring hydrogen abstraction and liberation in the catalytic cycle [5]. Madsen introduced Ru–*N*-heterocyclic carbene (NHC) system for amidation reaction. Initially, an ensemble of $[Ru(COD)Cl_2]_n$, imidazolium chloride as NHC precursor, phosphine ligand ($PCy_3$) and base $KO^tBu$ was employed [6]. Williams et al. employed $[Ru(p\text{-cymene})Cl_2]_2$, phosphine ligand bis(diphenylphosphino)butane (dppb) and $Cs_2CO_3$ for the synthesis of secondary amides in presence of excess hydrogen acceptor 3-methyl-2-butanone [7]. Hong's catalytic system involved $[Ru(p\text{-cymene})Cl_2]_2$, NHC precursor, pyridine or acetonitrile and strong base NaH. To unravel the nature of the *in situ* generated active catalyst, well defined Ru–NHC catalysts of the type (*p*-cymene)$Ru(NHC)X_2$ (X = Cl, I) (Scheme 2, b) were synthesized and their catalytic potential were evaluated. Only in the presence of two equivalents of strong base, these catalysts showed activity that match with *in situ* generated Ru–NHC system [8].

Madsen's catalytic system needed equimolar amounts of additive $PCy_3$ for its activity. This was attributed to the labile nature of *p*-cymene under catalytic condition. In absence of phosphine, the catalyst looses molecular integrity and gives poor conversions. The requirement of expensive, air and moisture sensitive phosphine compounds possesses a serious disadvantage. We proposed to replace *p*-cymene by strongly bound ligands. Accordingly, $[Ru(py\text{-}NHC)(CO)_2Br_2]$ (**1**) (py-NHC = 3-methyl-1-(pyridin-2-yl)-imidazol-2-ylidene) containing two carbonyls and a pyridine functionalized NHC was synthesized and its catalytic activity for the acceptorless dehydrogenative coupling of alcohols and amines is examined. Although the chloro analog of **1** was reported earlier [9], we offer an oxidative route for high yield synthesis of **1** from metal–metal bonded diruthenium(I) precursors $[Ru_2(CO)_4(CH_3CN)_6](BF_4)_2$ and imidazolium bromide derivative.

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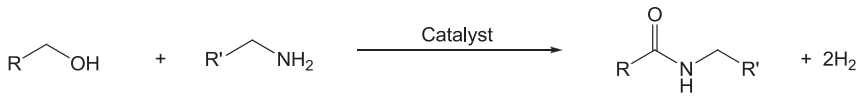



**Scheme 1.** Synthesis of amides from alcohols and amines.

## 2. Results and discussion

The synthesis of [Ru(py-NHC)$(CO)_2Cl_2$] was reported earlier via transmetallation of the corresponding Ag–NHC complex with $[RuCl_2(CO)_2]_n$ [9]. Several synthetic strategies are developed over the years for accessing metal–NHC compounds [10]. Albrecht et al. reported a $Rh^{III}$ bis-carbene complex from $Rh_2(OAc)_4$ [11]. We pursued a methodology that involves oxidative cleavage of the metal–metal singly-bonded dimetal compound with imidazolium salt [12]. Thus far only [$Ru^{I}$–$Ru^{I}$] and [$Rh^{II}$–$Rh^{II}$] precursors are successfully employed to obtain $Ru^{II}$–NHC and $Rh^{III}$–NHC compounds (Scheme 3). A general pattern has emerged from this work – 1. Unbridged dimetal complexes appear to give the desired products; 2. The metal oxidation number increases by one unit; 3. Only one bidentate NHC is incorporated for Ru irrespective of the equivalents of imidazolium used whereas two NHC units could be incorporated for Rh precursor. Initial studies were restricted with naphthyridine functionalized NHC. Herein we show that the same protocol is applicable for pyridine derivative (Scheme 4). A tentative mechanism involves imidazolium C–H oxidative addition across the Ru–Ru bond followed by electrophilic activation of the second imidazolium C–H finally resulting in the elimination of a molecule of dihydrogen. Towards elucidation of the mechanism, we have shown oxidative heteroaryl C–H/Br addition to [$Pd^{I}$–$Pd^{I}$] room temperature leading to bi- and trinuclear $Pd^{II}$ compounds [13].

Treatment of $[Ru_2(CO)_4(CH_3CN)_6](BF_4)_2$ with 3-methyl-1-(pyridin-2-yl)-imidazolium bromide in the presence of tetrabutylammonium bromide (TBABr) at room temperature in dichloromethane afforded **1** in 85% yield. The transformation is marked by the concomitant oxidation of $Ru^{I}$ to $Ru^{II}$ suggesting oxidative homolytic cleavage of the Ru–Ru bond. Despite apparent mechanistic complexity of the reaction, this method affords clean products without needing base or harsher reaction conditions.

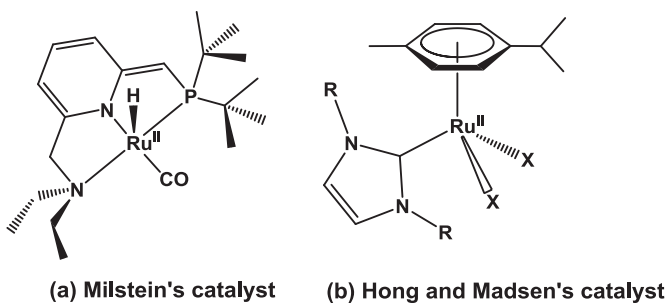
Molecular structure of the complex **1**, depicted in Fig. 1, reveals a central Ru with one chelate bound pyridine carbene (CN), two *cis*-oriented carbonyls and two *trans* bromides. The Ru1–C2 and Ru1–N1 bond distances are 2.087(7) Å and 2.146(6) Å. A carbonyl resides at site *trans* to the carbene carbon which is reflected in longer Ru–C distance compared to the other carbonyl (Ru1–C10/C11 = 1.957(7)/1.863(8) Å). Compound **1** was further characterized from NMR spectra. $^{1}H$ chemical shifts are indicative of a single isomer with *trans*-Br/*cis*-CO configuration [14]. A characteristic $^{13}C$ signal at $\delta$ 183.8 ppm is attributed to carbene carbon. Two carbonyl carbons resonate at 202.9 and 195.3 ppm. The ESI-MS exhibits signal at *m/z* 495, assigned for $[\mathbf{1} + H_2O]^+$ (Fig. S1).

The catalytic potential of **1** was evaluated for dehydrogenative coupling between alcohol and amine. A reaction of 1 mmol benzyl alcohol and 1.2 mmol of benzylamine in presence of 1 mol% of catalyst **1** and 5 mol% NaH in toluene for 24 h at 110 °C yielded *N*-benzylbenzamide as the single product in 84% yields. Different bases were screened, the result of which is summarized in Table 1. No reaction occurred in absence of base whereas strong bases KO$^{t}$Bu, KOH and NaH were found effective. Use of weak base DABCO afforded the corresponding imine in high yields.

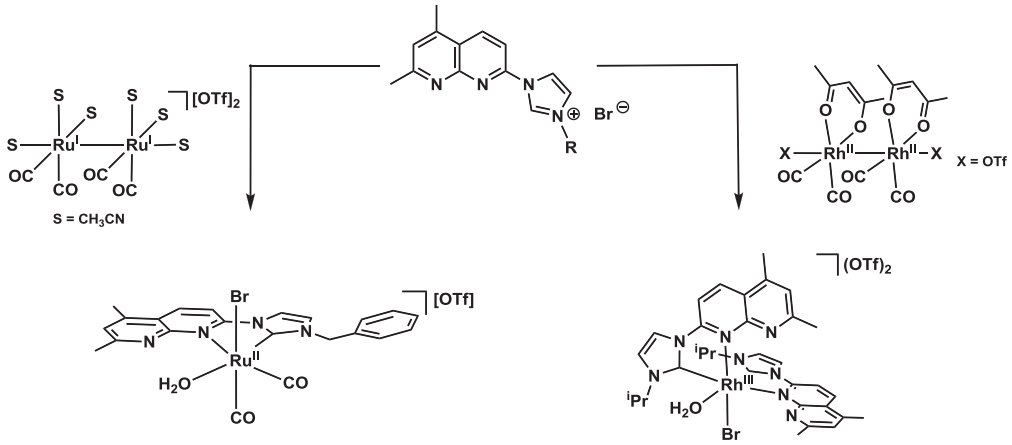
Substrate scope was examined under optimized conditions (1 mol% catalyst **1**, 1:1.2 mol of alcohol:amine, 5 mol% NaH, at 110 °C in toluene for 24 h). Electron rich *p*-methoxybenzyl alcohol gave excellent conversions of the corresponding amides with benzylamine (92%, Table 2, entry 1), *p*-methylbenzylamine (90%, entry 2), cyclohexylamine (90%, entry 3), hexylamine (89%, entry 4). The *p*-methylbenzyl alcohol and benzyl alcohol afforded good yields with different amines (69–90%, entries 6–14). Electron deficient *p*-nitrobenzyl alcohol and *p*-fluorobenzyl alcohol gave relatively lower yields compared to electron rich alcohols (entries 15–17). Reaction of 2-phenylethanol with benzylamine provided 79% amide (entry 18). Long chain alcohols octanol and hexanol afforded lesser yield compared to benzyl alcohol when treated with benzylamine and hexylamine (entries 19–22). With 2-ethoxymethanol, benzylamine provided 68% amide (entry 23). Aniline converted to corresponding amides when reacted with *p*-methoxybenzyl alcohol (78%), *p*-methylbenzyl alcohol (72%) and benzyl alcohol (69%) (entries 5, 9 and 14). This is in contrast to Madsen's report which showed poor conversions for aniline even at higher temperatures. The amidation could also be carried out in an intramolecular fashion as seen by the formation of γ-butyrolactam by using 4-amino-1-butanol (entry 24).

The working proposal is that the catalyst at first dehydrogenates alcohol to aldehyde. The amine then attacks the metal-coordinated aldehyde to form hemiaminal. Subsequent metal-catalyzed dehydrogenation gives amide [15]. However, the real mechanism does not appear to be that straightforward. When *p*-methoxy benzaldehyde is directly used with benzylamine, 80% conversion was observed with 70% of corresponding imine and 30% amide. Addition of 10% *p*-methoxy benzyl alcohol in the reaction remarkably improved the amide conversion to 76% with 24% imine. [8e] A model amidation reaction in toluene–$d_8$ did not afford deuterated product which ruled out isotope scrambling from solvent. Reaction of benzyl alcohol-α,α-$d_2$ with benzylamine led to hydrogen scrambling in the product (Scheme 5) [16]. The occurrence of significant isotope scrambling is indicative of an oxidative addition-reductive elimination sequence in the catalytic cycle [17]. Accordingly, a tentative mechanism is proposed that is outlined in Scheme 6. The metal catalyst forms a dihydride [Ru]$H_2$ on reaction with alcohols producing aldehydes. Reductive elimination of $H_2$ affords a reactive $Ru^{0}$ species which dehydrogenates hemiaminal, generated by the reaction of amine with metal-coordinated aldehyde, to afford amide and dihydride species [Ru]$H_2$. Alcohols play an important role in maintaining the [Ru]$H_2$ form of the active catalyst that is crucial for the overall efficiency of the catalyst.

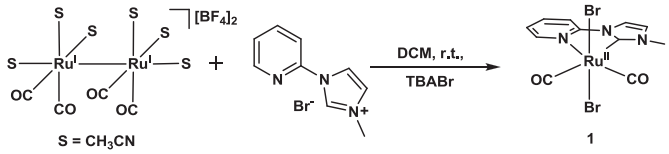
It is assumed that β-hydride is the key step during alcohol to aldehyde conversion. Hammett studies provide significant insight




**Scheme 2.** Two amide producing catalysts.




**Scheme 3.** Synthesis of M–NHC complexes from metal–metal bonded compounds.




**Scheme 4.** Synthesis of **1**.

on the reaction pathway. Benzyl alcohol and *para*-substituted benzyl alcohols (X = $NMe_2$, OMe, Me, F) were reacted with benzylamine and the products were monitored by GC–MS at regular time intervals (Scheme 7). Plot of $\ln(c_0/c)$ for substituted benzyl alcohols against the same values for that of benzyl alcohol gave a linear relationship (Table S2). Relative reactivity ($k_x/k_H$) could be calculated from the slope of the straight line (Fig. S2). Four such values obtained from four different *para* substituents were plotted against all possible $\sigma$ values ($\sigma^+$, $\sigma^-$, $\sigma\cdot$) available in literature [18].

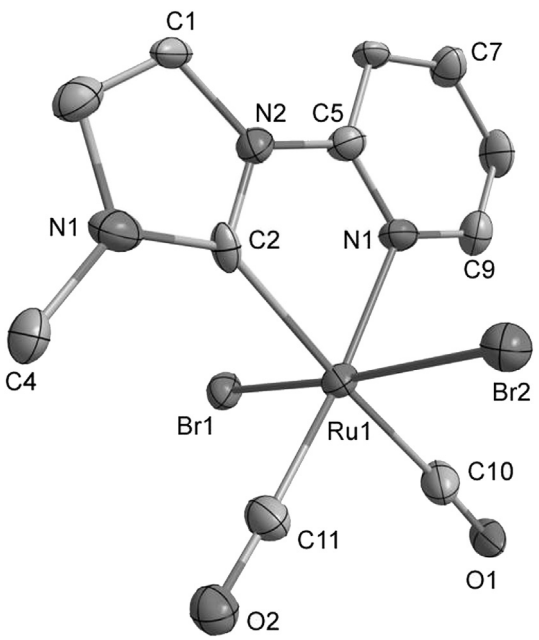



**Fig. 1.** Molecular structure (50% probability thermal ellipsoids) of **1** with important atoms labeled. Hydrogen atoms are omitted for the sake of clarity. Selected bond lengths (Å) and angles (deg): Ru1–C2 2.087(7), Ru1–N1 2.146(6), Ru1–Br1 2.533(1), Ru1–Br2 2.533(1), Ru1–C10 1.957(7), Ru1–C11 1.863(8), C10–O1 1.095(8), C11–O2 1.105(9). C2–Ru1–N1 76.3(2), C11–Ru1–C10 87.9(3), C5–N1–C9 118.0(6).

A straight line could be generated only with $\sigma^+$ with a negative slope ($\rho = -1.16$) (Fig. 2). This suggests generation of positive charge at alcohol benzylic position supporting the proposition of β-hydride elimination for alcohol to aldehyde conversion.

## 3. Conclusion

A $Ru^{II}$–NHC complex is accessed from metal–metal bonded $Ru^{I}$–$Ru^{I}$ precursor. The title compound catalyzes direct amide synthesis from alcohols and amines at low catalyst loading. The activity is similar to Madsen's $Ru^{II}$–*p*-cymene based catalysts without requiring additives like phosphine. Further experiments suggest the involvement of $Ru^{II}$-dihydride/$Ru^0$ cycle in the catalytic process. Efforts are on to extend this chemistry with [$Rh^{II}$–$Rh^{II}$] and [$Pd^{I}$–$Pd^{I}$] to access $Rh^{III}$ and $Pd^{II}$ NHC compounds and apply these for catalytic transformation reactions.

## 4. Experimental section

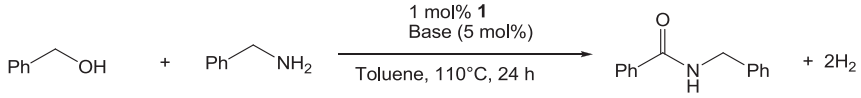
### 4.1. General procedures

All reactions with metal complexes were carried out under an atmosphere of purified nitrogen using standard Schlenk-vessel and vacuum line techniques. NMR spectra were obtained on JEOL JNM-LA 500 MHz spectrometer. $^1$H NMR chemical shifts were referenced to the residual hydrogen signal of the deuterated solvents. The chemical shift is given as dimensionless $\delta$ values and is frequency referenced relative to residual solvent for $^1$H and $^{13}$C NMR spectroscopy. Elemental analyses were performed on a Thermoquest EA1110 CHNS/O analyzer. The crystallized compounds were powdered, washed several times with dry petroleum ether and dried in vacuum for at least 48 h prior to elemental analyses. ESI-MS were recorded on a Waters Micromass Quattro Micro triple-quadrupole mass spectrometer. Infrared spectra were recorded in the range 4000–400 $cm^{-1}$ on a Vertex 70 Bruker spectrophotometer on KBr pellets.

### 4.2. Materials

Solvents were dried by conventional methods, distilled under nitrogen and deoxygenated prior to use. $RuCl_3\cdot xH_2O$ was purchased from Arora Matthey, India. All other chemicals were purchased from Sigma–Aldrich. 3-Methyl-1-(pyridin-2-yl)-imidazolium bromide and $[Ru_2(CO)_4(CH_3CN)_6](BF_4)_2$ were synthesized according to the published procedures [19,20].

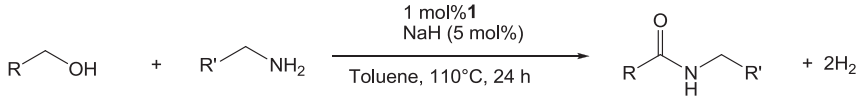
**Table 1**
Base screening for amidation reaction.[a]




| Entry | Base | Conversion (%)[b] |
|---|---|---|
| 1 | KO$^t$Bu | 78 |
| 2 | NaH | 84 |
| 3 | KOH | 74 |
| 4 | – | 4 |
| 5 | DABCO | 84[c] |

[a] 1 mmol benzyl alcohol, 1.2 mmol benzylamine, 5 mol% base, 1 mol% catalyst, 110 °C in toluene for 24 h.
[b] Conversions are determined by GC with dodecane as internal standard.
[c] *N*-Benzylidene benzylamine is formed.

**Table 2**
Amide formation from alcohol and amine by catalyst **1**.[a]



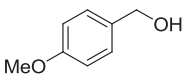
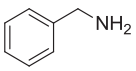
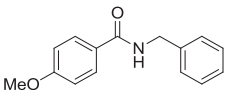
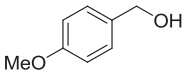
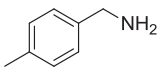
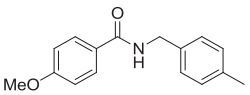
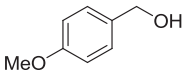
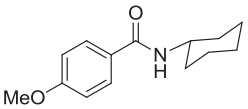
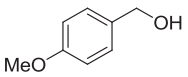
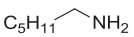
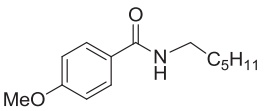
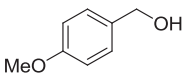
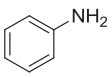
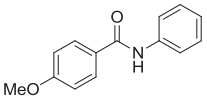
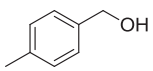
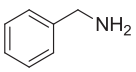
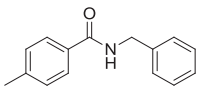
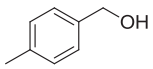
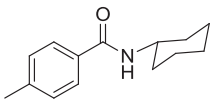
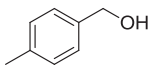
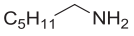
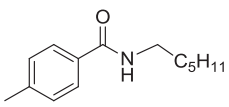
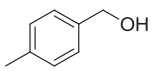
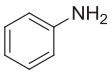
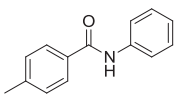
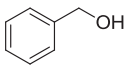
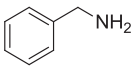
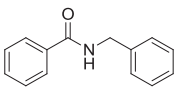

| Entry | Alcohol | Amine | Amide | Yield[b] (%) |
|---|---|---|---|---|
| 1 |  |  |  | 92 |
| 2 |  |  |  | 90 |
| 3 |  |  |  | 90 |
| 4 |  |  |  | 89 |
| 5 |  |  |  | 78 |
| 6 |  |  |  | 90 |
| 7 |  |  |  | 87 |
| 8 |  |  |  | 82 |
| 9 |  |  |  | 72 |
| 10 |  |  |  | 84 |

**Table 2** (*continued*)

| Entry | Alcohol | Amine | Amide | Yield[b] (%) |
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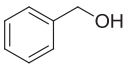
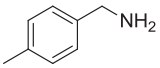
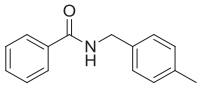
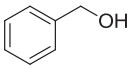
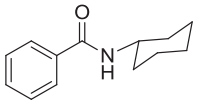
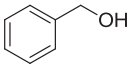
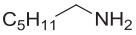
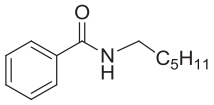
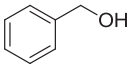
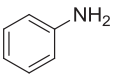
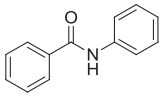
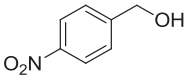
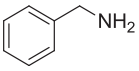
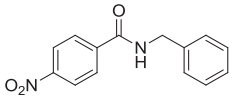
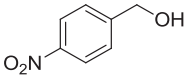
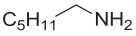
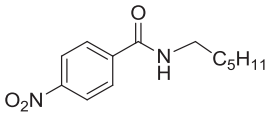
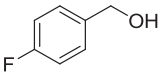
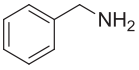
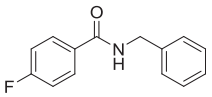
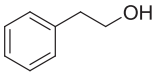
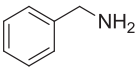
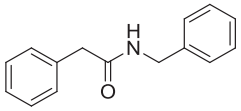
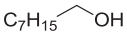
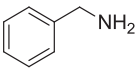
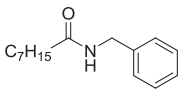
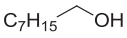
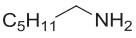
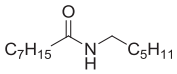
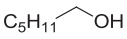
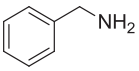
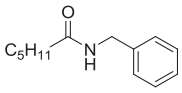
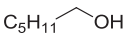
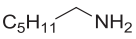
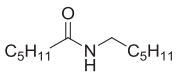
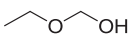
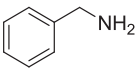
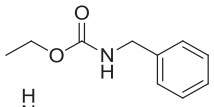
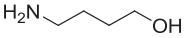
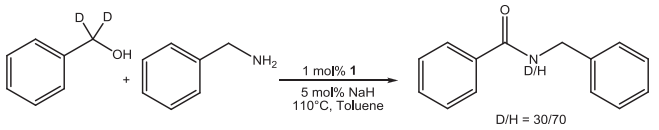
| 11 |  |  |  | 81 |
| 12 |  |  |  | 80 |
| 13 |  |  |  | 78 |
| 14 |  |  |  | 69 |
| 15 |  |  |  | 75 |
| 16 |  |  |  | 66 |
| 17 |  |  |  | 78 |
| 18 |  |  |  | 79 |
| 19 |  |  |  | 77 |
| 20 |  |  |  | 72 |
| 21 |  |  |  | 77 |
| 22 |  |  |  | 70 |
| 23 |  |  |  | 68 |
| 24 |  | – |  | 45 |

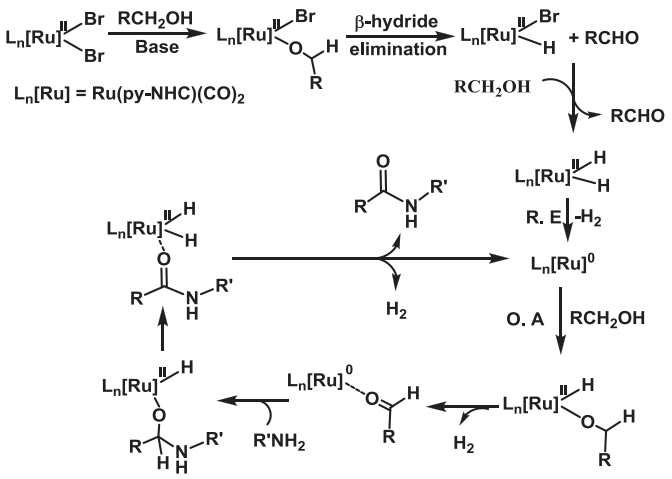
[a] 1 mmol alcohol, 1.2 mmol amine, 5 mol% NaH, 1 mol% catalyst **1** at 110 °C in toluene for 24 h.
[b] Yields are determined by GC–MS with dodecane as internal standard.

### 4.3. Synthesis of *1*

3-Methyl-1-(pyridin-2-yl)-imidazolium bromide (65 mg, 0.272 mmol) and TBABr (88 mg, 0.272 mmol) were added to a dichloromethane solution of $[Ru_2(CO)_4(CH_3CN)_6](BF_4)_2$ (100 mg, 0.136 mmol) and the mixture was stirred at room temperature for 6 h. Resulting red solution was concentrated under reduced pressure and diethyl ether was added to induce precipitation. The red solid was washed with diethyl ether and dried under vacuum. Crystals suitable for X-ray diffraction were grown by layering petroleum ether over a concentrated dichloromethane solution of the compound. Yield: 110 mg (85%). Anal Calcd. for $RuC_{11}H_9N_3O_2Br_2$: C,




**Scheme 5.** Amidation of benzyl alcohol-$\alpha,\alpha$-$d_2$ with benzylamine by **1**.




**Scheme 6.** Proposed mechanism for amide formation.

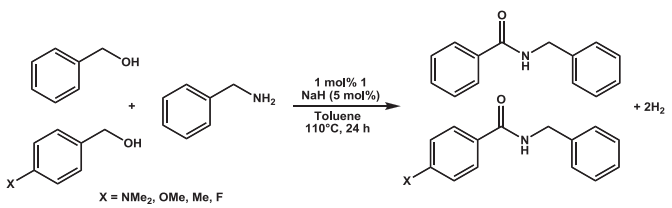
27.75; H, 1.90; N, 8.83. Found: C, 27.71; H, 1.94; N, 8.86. ESI-MS, $m/z$: 495, [**1** + $H_2O$]. $^1$H NMR (500 MHz, DMSO-$d_6$, 298 K): $\delta$ 9.21 (d, 1H, $^3J_{H-H}$ = 5.5 Hz, $H_{Py}$), 8.49 (s, 1H, Im), 8.38 (t, 1H, $^3J_{H-H}$ = 8.5 Hz, $H_{Py}$), 8.27 (d, 1H, $^3J_{H-H}$ = 8.5 Hz, $H_{Py}$), 7.99 (s, 1H, Im), 7.68 (t, 1H, $^3J_{H-H}$ = 6.5 Hz, $H_{Py}$), 3.97 (s, 3H, $CH_3$). $^{13}$C NMR (DMSO-$d_6$, 125 MHz, 298 K): $\delta$ 202.9 (CO), 195.3 (CO), 183.8 ($NC_{im}N$), 156.8 (C, $C_{im}$), 153.7 (C, $C_{im}$), 147.9 (C, $C_{py}$), 131.2 (C, $C_{py}$), 128.0 (C, $C_{py}$), 122.6 (C, $C_{py}$), 117.7 (C, $C_{py}$), 35.7 (C, $CH_3$). IR (KBr, cm$^{-1}$): $\nu$(CO) 2060 and 1996 cm$^{-1}$.

### 4.4. General procedure for amide reaction

1 mmol alcohol, 1.2 mmol amine, 5 mol% NaH and 1 mol% catalyst **1** were introduced successively in Schlenk tube and the mixture was heated at 110 °C in toluene for 24 h. A small aliquot was taken from the mixture, dissolved in 5 mL EtOAc, filtered through a silica column and subjected to GC–MS analysis. Conversions were determined by GC–MS (uncorrected GC areas) with respect to the internal standard dodecane.

### 4.5. Details of X-ray data collection and refinements

Single-crystal X-ray studies were performed on a CCD Bruker SMART APEX diffractometer equipped with an Oxford Instruments low-temperature attachment. All data were collected at 100(2) K using graphite-monochromated Mo-K$\alpha$ radiation ($\lambda\alpha$ = 0.71073 Å).




**Scheme 7.** Competition experiments for the amidation of benzyl alcohol versus *para*-substituted benzyl alcohols.

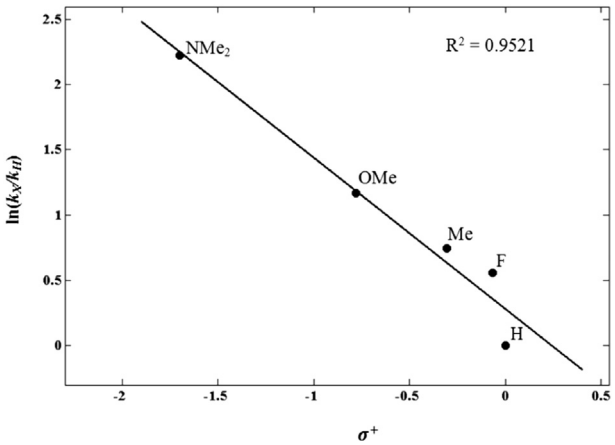



**Fig. 2.** Hammett plot for the amidation of different *para*-substituted benzyl alcohols.

The frames were indexed, integrated, and scaled using the SMART and SAINT software packages [21], and the data were corrected for absorption using the SADABS program [22]. The structure was solved and refined with the SHELX suite of programs [23].

A single crystal of **1** of dimensions 0.21 × 0.23 × 0.31 mm$^3$ was covered in Paratone oil, mounted on top of a thin glass fiber with silicone grease and placed in a cold stream of nitrogen. All non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were included into geometrically calculated positions in the final stages of the refinement and were refined according to 'riding model'. Diamond 3.1e software was used to produce the diagram (50% probability thermal ellipsoids).

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## Appendix A. Supplementary material

CCDC 974211 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

## Appendix B. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jorganchem.2013.12.051.

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