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# Amide Synthesis from Alcohols and Amines Catalyzed by Ruthenium N-Heterocyclic Carbene Complexes

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**Abstract:** The direct synthesis of amides from alcohols and amines is described with the simultaneous liberation of dihydrogen. The reaction does not require any stoichiometric additives or hydrogen acceptors and is catalyzed by ruthenium N-heterocyclic carbene complexes. Three different catalyst systems are presented that all employ 1,3-diisopropylimidazol-2-ylidene (I*i*Pr) as the carbene ligand. In addition, potassium *tert*-butoxide and a tricycloalkylphosphine are required for the amidation to proceed. In the first system, the active catalyst is generated in situ from [$RuCl_2$(cod)] (cod = 1,5-cyclooctadiene), 1,3-diisopropylimidazolium chloride, tricyclopentylphosphonium tetrafluoroborate, and base. The second system uses the complex [$RuCl_2$(I*i*Pr)(*p*-cymene)] together with tricyclohexylphosphine and base, whereas the third system employs the Hoveyda–Grubbs 1st-generation metathesis catalyst together with 1,3-diisopropylimidazolium chloride and base. A range of different primary alcohols and amines have been coupled in the presence of the three catalyst systems to afford the corresponding amides in moderate to excellent yields. The best results are obtained with sterically unhindered alcohols and amines. The three catalyst systems do not show any significant differences in reactivity, which indicates that the same catalytically active species is operating. The reaction is believed to proceed by initial dehydrogenation of the primary alcohol to the aldehyde that stays coordinated to ruthenium and is not released into the reaction mixture. Addition of the amine forms the hemiaminal that undergoes dehydrogenation to the amide. A catalytic cycle is proposed with the {(I*i*Pr)$Ru^{II}$} species as the catalytically active components.

**Keywords:** alcohols · amides · carbene ligands · dehydrogenation · ruthenium

## Introduction

The amide is one of the most prevalent linkages in organic chemistry. It is the key functional group in peptides and a number of polymers and is also found in many pharmaceuticals and natural products.[1] The synthesis of amides has been the subject of intense studies and numerous methods have been developed.[2] However, cost effective, high-yielding and waste-free procedures with a broad substrate scope are still in high demand. The direct synthesis of amides by thermal dehydration of carboxylic acids and amines has a large activation energy due to the formation of the corresponding ammonium salt and this method generally requires a temperature above 160 °C.[2] The temperature can be significantly lowered by catalyzing the dehydration with specially designed areneboronic acids[3] or heterogeneous silica catalysts[4] if water at the same time is removed irreversibly. The most common methods for amide synthesis employ activated derivatives of the carboxylic acid, such as the chloride and the anhydride.[2] The activated derivatives may also be generated in situ by employing stoichiometric coupling reagents, such as carbodiimides, uronium, and phosphonium salts,[5] for which the latter two are the methods of choice in peptide synthesis. Other general procedures for amide synthesis include the Beckman rearrangement,[6] Staudinger ligations,[7] oxidative amidation of aldehydes,[8] coupling of α-ketoacids and hydroxylamines,[9] and amidation of ketones and thioacids with azides.[10] More recently, a number catalytic procedures have been developed including amidation—hydrolysis of *gem*-dihaloolefins,[11] redox rearrangement of α-functionalized aldehydes,[12] and aminocarbonylation of aryl halides and terminal alkynes.[13]

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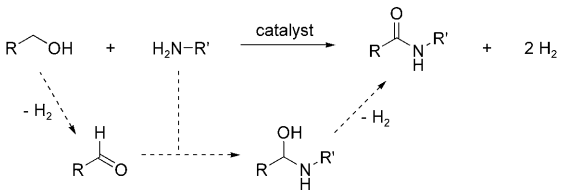
Very recently, amide synthesis has become possible by the direct metal-catalyzed coupling of primary alcohols and amines with the concomitant extrusion of dihydrogen (Scheme 1). The reaction presumably occurs by initial dehydrogenation of the alcohol to the aldehyde followed by hemiaminal formation with the amine and subsequent dehydrogenation to the amide. The amidation has been achieved both in the presence[14,15] and absence[16–18] of hydrogen scavengers. The latter protocol is the most attractive in which no stoichiometric additives are necessary and dihydrogen is produced as the only byproduct. To date, three different catalyst systems have been reported for this atom-economical amidation procedure for which two are homogeneous protocols and the latter a heterogeneous method. The first system was presented by Milstein et al. in 2007 for which a ruthenium complex with a PNN-type pincer ligand was shown to be an effective catalyst for the coupling of primary alcohols and amines with the liberation of dihydrogen.[16] The following year our laboratory showed that the same transformation could be performed with an in situ generated ruthenium N-heterocyclic carbene (NHC) catalyst.[17,19] In 2009, Shimizu et al. achieved the dehydrogenative amide synthesis with a silver cluster supported on γ-alumina as the catalyst.[18] Of these three systems the in situ generated ruthenium carbene catalyst is easily modified and can be carried out with commercially available reagents.



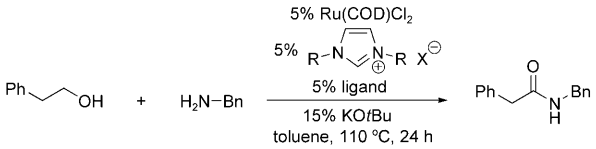

Scheme 1. Dehydrogenative amide formation from primary alcohols and amines.

Herein, we report a full account on our studies of ruthenium N-heterocyclic carbene catalysts in the dehydrogenative amidation from primary alcohols and amines. We demonstrate that the reaction can be achieved with three different (pre)catalysts and provide further support for the catalytically active species.

## Results and Discussion

**Catalyst development**: 2-Phenylethanol and benzylamine were selected as test substrates for optimizing the amidation procedure. Initial experiments revealed that the reaction could be achieved with a ruthenium(II) precursor in the presence of an in situ generated N-heterocyclic carbene (Table 1). To prevent rapid deactivation of the catalyst, it was also necessary to add an additional ligand. A range of phosphine ligands and other ligands could be used for this purpose for which $PCy_3$ gave the best result and was selected for further studies (Table 1, entries 1–8). The influence of the substitutents on the N-heterocyclic carbene was then investigated in detail. These substituents had a pronounced impact on the amidation and the isopropyl group was found to give the highest yield (entries 9–12). A number of more substituted imidazolium salts gave less than 25% yield under the same conditions.[20] Carbenes with a saturated backbone, that is, imidazolin-2-ylidenes, gave significantly lower yields than carbenes with an unsaturated backbone.[17] Potassium *tert*-butoxide was selected as the base for generating the carbene since it is easy to handle. Similar yields were obtained with potassium hexamethyldisilazide, whereas the use of cesium carbonate resulted in lower yields. The purpose of the base is not only to deprotonate the imidazolium salt, but also to promote the amide formation. Various amounts of base were investigated and the optimum amount was found to be three times the amount of the imidazolium salt. With 1,3-diisopropylimidazol-2-ylidene as the carbene of choice, the phosphine ligand was investigated again. In this case, tricyclopentylphosphine ($PCyp_3$) gave a slight improvement over $PCy_3$. The improvement was not only measured in the yield at the end of the reaction, but also after 3 h when $PCyp_3$ showed 67% conversion and $PCy_3$ only 56% (entries 10 and 13). However, $PCyp_3$ is a liquid and significantly less stable than the tricyclohexyl congener. Therefore, the corresponding crystalline $HBF_4$ salt[21] was employed at the expense of additional base (entry 14). The isolated yields from the experiments in entries 13 and 14 were the same and the catalyst system in entry 14 was selected for general use and denoted catalyst A.

Table 1. Amidation with catalysts generated in situ.



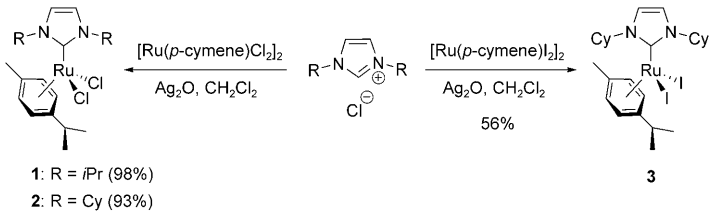

| Entry | R | X | Ligand | Yield [%][a] |
|---|---|---|---|---|
| 1 | Mes | Cl | $PPh_3$ | 21 |
| 2 | Mes | Cl | $P(o\text{-tol})_3$ | 26 |
| 3 | Mes | Cl | $P(2\text{-furyl})_3$ | 26 |
| 4 | Mes | Cl | $PtBu_3$ | 22 |
| 5 | Mes | Cl | $PCy_3$ | 27 |
| 6 | Mes | Cl | $O{=}PPh_3$ | 24 |
| 7 | Mes | Cl | $AsPh_3$ | 24 |
| 8 | Mes | Cl | pyridine | 12 |
| 9 | Me | $(MeO)_2PO_2$ | $PCy_3$ | 53 |
| 10 | *i*Pr | Cl | $PCy_3$ | 92 |
| 11 | Cy | $BF_4$ | $PCy_3$ | 84 |
| 12 | *t*Bu | $BF_4$ | $PCy_3$ | 68 |
| 13 | *i*Pr | Cl | $PCyp_3$ | 98 |
| 14 | *i*Pr | Cl | $PCyp_3{\cdot}HBF_4$ | 92[b] |

[a] GC yield. [b] With 20% of KO*t*Bu.

Since the catalytically active species in this reaction may be a ruthenium(II)chloride N-heterocyclic carbene complex it would be of interest to study the reaction with a more well-defined complex. This may lead to a new catalyst system and a better understanding of the mechanism. At-

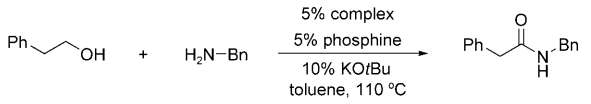
tempts to isolate a carbene complex from the reaction between 1,3-diisopropylimidazolium chloride, $[RuCl_2(cod)]$, phosphine, and base were not successful and the in situ generated carbene complex appears to be very sensitive. Instead, we turned our attention to the known *p*-cymene complexes of ruthenium(II)chloride and N-heterocyclic carbenes.[22] These are stable and coordinatively saturated complexes that have been used for hydrogenation and cyclopropanation of olefins.[22] It is known that the *p*-cymene ligand is released at about 85 °C[23] and with the amidation being performed in refluxing toluene these complexes appear well suited as catalyst precursors. Traditionally, the *p*-cymene complexes have been prepared by transfer of the free N-heterocyclic carbene to $[RuCl_2(p\text{-cymene})]_2$.[24] More recently, the carbene transfer has become possible by reaction of 1,3-dialkylimidazolium chlorides with silver oxide in dichloromethane.[25] By this method the corresponding silver carbene is generated and transmetallated in situ with $[RuCl_2(p\text{-cymene})]_2$, which makes it unnecessary to isolate the free carbene. In this way, complexes **1** and **2** were generated in excellent yield and isolated by flash chromatography (Scheme 2). The structure of **2** has previously been confirmed by X-ray crystallography.[24c] Except for the two different alkyl groups, the $^1H$ and $^{13}C$ NMR spectroscopic data for **1** and **2** are very similar with the carbene carbon atom in both cases located at $\delta = 171$ ppm in the $^{13}C$ NMR spectrum. To probe the influence of the halide on ruthenium, the corresponding diiodide complex **3** was also prepared. In this case, only a 56% yield of **3** was obtained since the carbene transfer between 1,3-dicyclohexylimidazolium chloride and $[RuI_2(p\text{-cymene})]_2$ gave a mixture of dichloride **2** and diiodide **3** that were separated by preparative TLC.




Scheme 2. Synthesis of NHC ruthenium cymene complexes.

Complexes **1**–**3** were tested in the amidation with 2-phenylethanol and benzylamine, and the yield was measured after both 3 and 24 h (Table 2). Again, the reaction required a base for the amidation to proceed. A phosphine was also required to obtain a high yield of the amide. Without phosphine, less than 70% of the amide was observed after 24 h. The phosphine salt $PCyp_3{\cdot}HBF_4$[21] was less effective with complexes **1** and **2** and afforded below 70% yield of the amide after 24 h. However, with added $PCy_3$ and $PCyp_3$ complexes **1** and **2** performed very well in the amidation (Table 2, entries 3–6) and gave results after 3 and 24 h which were very similar to the yields from the in situ generated catalyst (entries 1 and 2). This confirms that an N-heterocyclic carbene ruthenium(II)chloride species is produced under the in situ conditions. Diiodide complex **3**, on the other hand, was less reactive than dichlorides **1** and **2** and more byproducts were formed with this complex (entries 7 and 8). The results with diiodide **3** did not improve by adding 10% of lithium chloride or tetraethylammonium chloride to the reaction. However, when the amidation was performed with an in situ generated catalyst from $[RuI_2(p\text{-cymene})]_2$, 1,3-dicyclohexylimidazolium chloride, phosphine, and base almost the same yields were observed as with $[RuCl_2(cod)]$ as the ruthenium precursor (entries 9 and 10). We believe the catalytically active complex in this case is mainly a ruthenium(II)chloride species and not the corresponding iodide complex. No reaction occurred when the amidation was attempted with 5% of **1** and 10% of silver triflate in the presence of phosphine and base. Based on these studies we selected complex **1** together with $PCy_3$ for general use and denoted this system catalyst B.

Table 2. Amidation with [Ru(NHC)(*p*-cymene)] complexes.




| Entry | Complex | Phosphine | Yield [%] (3 h)[a] | Yield [%] (24 h)[a] |
|---|---|---|---|---|
| 1 | –[b] | $PCy_3$ | 56 | 92 |
| 2 | –[b] | $PCyp_3$ | 67 | 98 |
| 3 | **1** | $PCy_3$ | 65 | 95 |
| 4 | **1** | $PCyp_3$ | 53 | 100 |
| 5 | **2** | $PCy_3$ | 61 | 97 |
| 6 | **2** | $PCyp_3$ | 56 | 91 |
| 7 | **3** | $PCy_3$ | 22 | 50 |
| 8 | **3** | $PCyp_3$ | 29 | 44 |
| 9 | –[c] | $PCy_3$ | 56 | 90 |
| 10 | –[c] | $PCyp_3$ | 63 | 87 |

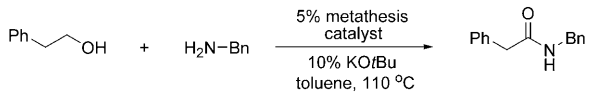
[a] GC yield. [b] Generated in situ from $[RuCl_2(cod)]_2$ and 1,3-diisopropylimidazolium chloride (catalyst A). [c] Generated in situ from $[RuI_2(p\text{-cymene})]_2$ and 1,3-dicyclohexylimidazolium chloride.

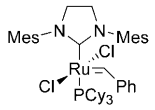
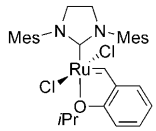
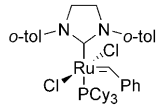
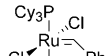
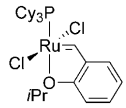
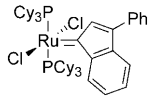
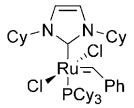
In 2001 Grubbs et al. showed that the Grubbs 2nd-generation metathesis catalyst reacts with dihydrogen to remove the benzylidene ligand, but not the N-heterocyclic carbene ligand.[26] This observation prompted us to investigate olefin metathesis catalysts[27] since the liberated dihydrogen in the amidation may serve to activate the metathesis catalysts for this transformation. Indeed, reaction of 2-phenylethanol and benzylamine with Grubbs 2nd-generation catalyst and base produced the amide in 49% yield after 24 h (Table 3, entry 1). This is a lower yield than that achieved in Tables 1 and 2, but the saturated N-heterocyclic carbene in Grubbs 2nd-generation catalyst is not the optimum ligand for the amidation. A higher yield was obtained with Hoveyda–Grubbs 2nd-generation catalyst and this did not change by adding $PCy_3$ to the reaction (Table 3, entry 2). Interestingly, the Grubbs catalyst with the less sterically demanding *o*-tolyl group[28] gave a good yield of the amide (entry 3).

To illustrate the influence of the N-heterocyclic carbene Grubbs 1st-generation and Hoveyda–Grubbs 1st-generation catalysts were also investigated. These two complexes do

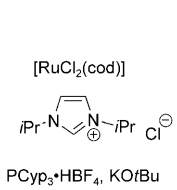
Table 3. Amidation with metathesis catalysts.



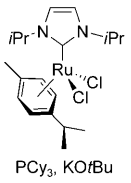

| Entry | Metathesis catalyst | Yield [%] (3 h)[a] | Yield [%] (24 h)[a] |
|---|---|---|---|
| 1 |  | 29 | 49 |
| 2 |  | 48 | 65 |
| 3 |  | 63 | 92 |
| 4 |  | 48 | 71 |
| 5 | | 76[b] | 100[b] |
| 6 | | 76[c] | 96[c] |
| 7 |  | 41 | 60 |
| 8 | | 72[b] | 97[b] |
| 9 | | 76[c] | 100[c] |
| 10 |  | 25 | 42 |
| 11 | | 67[c] | 100[c] |
| 12 |  | 74 | 97 |

[a] GC yield. [b] With 5% of 1,3-diisopropylimidazolium chloride and 15% of KO*t*Bu. [c] With 5% of 1,3-dicyclohexylimidazolium chloride and 15% of KO*t*Bu.

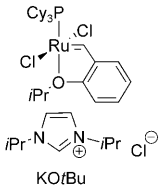
not contain an N-heterocyclic carbene and when applied directly in the amidation moderate yields of the product were obtained (Table 3, entries 4 and 7). However, when 1,3-diisopropyl- or 1,3-dicyclohexylimidazol-2-ylidene were generated together with these complexes the yield of the amide increased considerably (entries 5, 6, 8, and 9) and was comparable to the best results in Tables 1 and 2. The modified Grubbs catalyst with the phenyl indenylidene ligand[29] showed the same results (entries 10 and 11), which underlines the assumption that the benzylidene group in the metathesis catalyst did not take part in the amidation, but was reduced off by the liberated dihydrogen. A number of other N-heterocyclic carbenes were also generated together with Grubbs 1st-generation catalyst,[30] but in all cases lower yields of the amide was obtained. This confirms the results in Table 1 that the imidazol-2-ylidine with 1,3-diisopropyl or 1,3-dicyclohexyl groups are the optimum N-heterocyclic carbenes for the amidation. The in situ formation of the ruthenium N-heterocyclic carbene complex was confirmed by preparing the known cyclohexyl complex in Table 3, entry 12 from Grubbs 1st-generation catalyst.[31] When this well-defined complex was applied in the amidation essentially the same yield was obtained as when the complex was generated in situ (entries 6 and 12). Based on the results in Table 3, Hoveyda–Grubbs 1st-generation catalyst was selected as the metathesis catalyst for the amidation in the presence of 1,3-diisopropylimidazolium chloride and base (catalyst C).




Catalyst A




Catalyst B

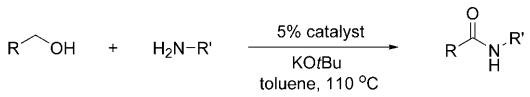


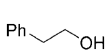
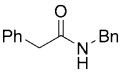
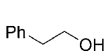
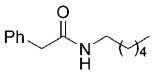
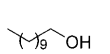
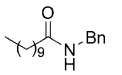
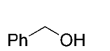
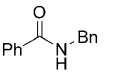
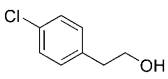
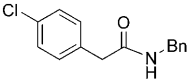
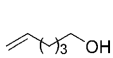
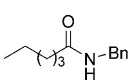
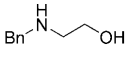
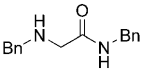
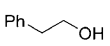
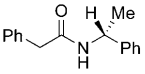
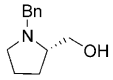
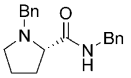
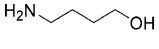
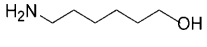
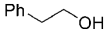
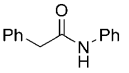
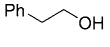
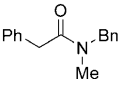

Catalyst C

**Substrate scope**: With three optimized catalysts in hand, the substrate scope and limitations could now be more thoroughly explored. Equimolar amounts of various primary alcohols and amines were reacted with catalysts A, B, and C to afford the corresponding amides (Table 4). Sterically unhindered alcohols reacted with primary amines to give the secondary amide in high yields (Table 4, entries 1–3). Benzyl alcohol furnished the corresponding benzamide (entry 4), whereas the aryl chloride in entry 5 afforded the amide without concomitant dechlorination. Hex-5-en-1-ol, on the other hand, gave exclusively the hexanamide with all three catalysts in which the olefin had been reduced with the liberated dihydrogen (entry 6). *N*-benzylethanolamine underwent coupling with benzylamine in high yield, which illustrates that the amidation is selective for a primary amine over a secondary amine. Optically pure 1-phenylethylamine participated in the amidation without any sign of epimerization (entry 8). The same was observed with optically pure *N*-benzyl-L-prolinol (entry 9), which is noteworthy since the reaction goes through the corresponding aldehyde. Prolinol gave a lower yield than the other primary alcohols and was not completely consumed in the amidation, which may reflect the slightly higher steric demand around this alcohol. The reaction could also be performed in an intramolecular fashion to afford both five- and seven-membered lactams (entries 10 and 11). On the contrary, aniline and secondary amines did not react with 2-phenylethanol in refluxing toluene. In these cases, the amidation was carried out in refluxing mesitylene, which gave a moderate yield with aniline (entry 12) and a good yield with the secondary amine (entry 13). In the last two cases, self-condensation of the alcohol into the corresponding ester was observed as a byproduct, whereas the other examples in Table 4 did not reveal any single compound as a major byproduct. Several other alcohols and amines reacted very poorly or not at all in refluxing mesitylene. *N*-Boc-protected ethanolamine, 1-phenylethane-1,2-diol, 2-pyridineethanol, and 2-(4-bromophenyl)ethanol only gave trace amounts of the amide in the reaction with benzylamine. Several derivatives of glycine[32] also failed to give more than trace amounts of the amide in the reaction with 2-phenylethanol. Compared with the results in Table 4, these examples illustrate that the amidation

Table 4. Amidation of amines with primary alcohols.




| Entry | Alcohol | Amine | Amide | Yield [%][a] cat. A | Yield [%][a] cat. B | Yield [%][a] cat. C |
|---|---|---|---|---|---|---|
| 1 |  |  |  | 93[b] | 95 | 92 |
| 2 |  |  |  | 100[b] | 90 | 95 |
| 3 |  |  |  | 79 | 94 | 86 |
| 4 |  |  |  | 78 | 78 | 80 |
| 5 |  |  |  | 83[b] | 71 | 73 |
| 6 |  |  |  | 60 | 82 | 78 |
| 7 |  |  |  | 90 | 93 | 87 |
| 8 |  |  |  | 70 | 85 | 78 |
| 9 |  |  |  | 60 | 53 | 44 |
| 10 |  | |  | 65 | 68 | 60 |
| 11 |  | |  | 49 | 53 | 48 |
| 12 |  |  |  | 21[c] | 35[c] | 33[c] |
| 13 |  |  |  | 70[c] | 65[c] | 70[c] |

[a] Isolated yield. [b] With 2% of $[RuCl_2(cod)]$, 2% of ligands and 8% of KO*t*Bu. [c] In mesitylene at 163 °C.

shows some sensitivity towards the steric demand around the alcohol and the amine as well as additional coordinating groups in the substrates. Attempts to use ammonia or ammonia equivalents, such as $LiNH_2$, $NH_4HCO_3$, $Cu(NH_3)_4SO_4{\cdot}H_2O$, and $Mg(NH_3)_6Cl_2$, to afford a primary amide failed completely and only gave the ester in various amounts.

In most cases, the three different catalysts did not show any major differences in yield and reactivity in Table 4. This indicates that the catalytically active species is the same in all three cases. For practical application, however, the most convenient procedure is to generate the active catalyst in situ. The evolution of dihydrogen was confirmed by repeating the experiment in entry 1 with 2 mmol of alcohol and amine. The reaction flask was connected to a burette with a water reservoir and 70 mL was collected after 20 h. This corresponds to 3 mmol and the gas was shown to be dihydrogen by GC analysis.

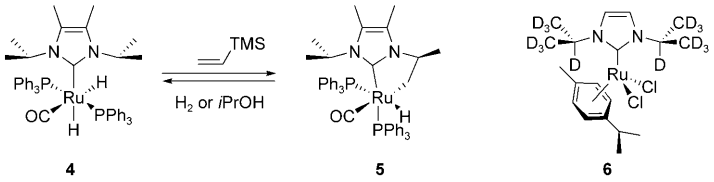
**Mechanism**: The amidation is believed to proceed by formation of the aldehyde and the hemiaminal as depicted in Scheme 1. Esters are not intermediates in the reaction, which was confirmed by treating 2-phenylethyl 2-phenylacetate with benzylamine and catalyst A in refluxing toluene. Under these conditions, the ester was stable and none of the amide in Tables 1–3 was observed. Imines are also highly stable under the reaction conditions, which was confirmed by the reaction of *N*-benzylidene benzylamine with catalyst A in refluxing toluene. No conversion of the imine occurred and this did not change by adding water or by conducting the reaction under a dihydrogen atmosphere.

Imines or reduction products of imines have not been observed as byproducts in any of the experiments in Table 4 regardless of the catalyst being used. This may indicate that the intermediate aldehyde stays coordinated to the ruthenium catalyst and is not released into the reaction mixture. If this is true, an externally added aldehyde may not be able to enter the catalytic cycle and form the amide. To probe this question a crossover experiment was carried out with *p*-methylbenzyl alcohol (1 equiv) and benzaldehyde (1 equiv), which were reacted with *n*-hexylamine (2 equiv) in the presence of complex **1** (5%) and potassium *tert*-butoxide (10%). Under these conditions, the aldehyde was immediately converted into the imine, whereas the alcohol reacted slowly to form the corresponding imine (and not the amide) with about 50% conversion after 24 h. It appears that the imine from the aldehyde inhibits formation of the amide from the alcohol causing the reaction to slow down and to stop at the imine stage. A new experiment was therefore performed in which benzaldehyde (1 equiv) was added over 3 h to a reaction mixture with *p*-methylbenzyl alcohol (1 equiv), *n*-hexylamine (2 equiv), complex **1** (5%), and potassium *tert*-butox-

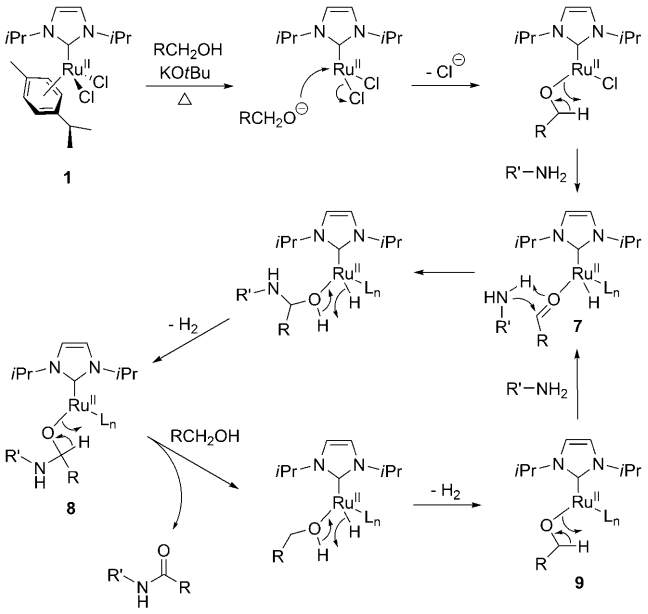
ide (10%). Although the amidation was slow in this case it did not stop and the alcohol was converted into a 6:1 mixture of the amide and the imine with almost complete conversion after 30 h and with 50% conversion after 4 h. Again, the aldehyde reacted immediately to produce the corresponding imine, but in this case, a small amount of *N*-benzyl benzamide was also observed as a byproduct. The ratio between the amide from the alcohol and the aldehyde was 10:1 after both 4 and 30 h. This does not indicate that a crossover takes place to a significant degree and we, therefore, believe the intermediate aldehyde in the amidation stays coordinated to the ruthenium catalyst.

In a previous study, ruthenium 1,3-diisopropylimidazol-2-ylidene complex **4** was converted into the five-membered ruthenacycle **5** by C–H activation of the isopropyl methyl group[33,34] (Scheme 3). The reaction was facilitated by hydrogen acceptors, such as olefins and could be reversed by hydrogen donors, such as dihydrogen or alcohols.[33] It could not be completely excluded that a similar C–H activation would take place with our 1,3-diisopropylimidazol-2-ylidene ligand and thereby explain the high reactivity of this ligand in the amidation. To probe this question experimentally, we prepared deuterated complex **6**. If C–H activation of the isopropyl methyl groups is a major reaction pathway we would expect a significant amount of deuterium in the hydrogen gas from the reaction. However, when equimolar amounts of 2-phenylethanol and benzylamine were treated with **6** (10%), $PCy_3$ (10%), and KHMDS (15%) in refluxing toluene for 1 h, only a 51:1 ratio of $H_2$ and H–D was measured by selected ion monitoring. This low amount of H–D does not indicate that a rapid exchange reaction is taking place and, therefore, we do not believe that a C–H oxidative addition reaction is involved in the catalytic cycle. The high reactivity of the 1,3-diisopropyl- and 1,3-dicyclohexylimidazol-2-ylidene ligands is probably a result of the relatively low steric demand of these ligands relative to other N-heterocyclic carbene ligands.[35] Furthermore, in ruthenium(II) complexes with these ligands agostic interactions have been observed between ruthenium and the $CH_2$/$CH_3$ hydrogen atoms on the ligand that may serve to further stabilize coordinatively unsaturated species in the catalytic cycle.[36]




Scheme 3. Interconversion between **4** and **5**[33] and the structure of **6**.

Based on these studies, we propose the reaction mechanism in Scheme 4. The transformation is initiated by loss of the *p*-cymene ligand upon heating. Reaction with an alkoxide followed by β-hydride elimination affords aldehyde complex **7**. This part is similar to what has been established for ruthenium transfer hydrogenation catalysts.[37,38] It should, however, be noted that $[RuCl_2(PPh_3)_3]$ is known to react with alcohols under basic conditions to form the dihydride complex $[RuH_2(PPh_3)_3]$.[38] Whether complex **1** also reacts twice with the alkoxide is not known at this point. In fact, the remaining ligand(s) on ruthenium in **7** could be chloride, hydride, or an amine and is, therefore, denoted $L_n$ in Scheme 4. A more thorough mechanistic study will have to be carried out to differentiate between these scenarios. With formation of the aldehyde complex **7** a catalytic cycle can be proposed for which the amine adds to the aldehyde to form the hemiaminal, which stays coordinated to the metal. Release of hydrogen can take place by hydrogen transfer to hydride as previously established.[39] This gives rise to complex **8**, which upon β-hydride elimination releases the amide. Coordination of the alcohol and a second hydrogen transfer to hydride affords the alkoxide complex **9**, which is ready to re-enter the catalytic cycle. It should be noted that all the ruthenium species in the catalytic cycle remain in the same oxidation state as the starting complex. The added phosphine presumably stabilizes catalyst resting states and is not believed to be involved in the catalytic cycle since the amidation can be performed with a variety of phosphines and other ligands.[19]




Scheme 4. Proposed mechanism for amide formation.

## Conclusion

In summary, we have presented an atom-economical procedure for the direct synthesis of amides from alcohols and amines in which dihydrogen is formed as the only byproduct. The reaction is catalyzed by ruthenium N-heterocyclic carbene complexes that are easy to handle and straightfor-

ward to modify. Three different catalyst systems have been developed that show similar reactivity and yields in the amidation with a wide variety of substrates. A mechanism is proposed with ruthenium(II) N-heterocyclic carbene species as the catalytically active components and for which the intermediate aldehyde and hemiaminal remain coordinated to ruthenium in the catalytic cycle. The reaction presents a new direction in the synthesis of one of the most important linkages in organic chemistry.

## Experimental Section

**General**: Toluene was destilled from sodium and benzophenone under a nitrogen atmosphere. NMR spectra were recorded on a Varian Mercury 300 Bruker AC 200 spectrometer while IR spectra were obtained on a Bruker alpha-P spectrometer. Mass spectrometry was performed by direct inlet on a Shimadzu-GCMS-QP5000 instrument of for hydrogen analysis on a Pfeiffer OmniStar GSD 301. GC yields were obtained with dodecane as internal standard on a Shimadzu GC-2010 instrument equipped with a Supelco Equity-1 capillary column (15 mm × 0.10 mm, 0.10 μm film). Microanalyses were obtained at the Microanalytical Laboratory, University of Vienna.

**General procedure for amidation with an in situ catalyst (catalyst A)**: $[RuCl_2(cod)]$ (7.0 mg, 0.025 mmol), $PCyp_3{\cdot}HBF_4$[21] (8.2 mg, 0.025 mmol), 1,3-diisopropylimidazolium chloride (4.7 mg, 0.025 mmol), and KO*t*Bu (11.2 mg, 0.10 mmol) were placed in an oven-dried Schlenk tube. Vacuum was applied and the tube was then filled with argon (repeated twice). Freshly distilled toluene (1 mL) was added and the mixture was heated to reflux under an argon atmosphere for 20 min. The alcohol (0.5 mmol) and the amine (0.5 mmol) were added and the mixture was heated to reflux under an argon atmosphere for 24 h. The reaction mixture was cooled to room temperature and the solvent removed in vacuo. The residue was purified by silica-gel column chromatography (pentane/EtOAc 4:1→1:1) to afford the amide.

**$[RuCl_2(I\mathit{i}Pr)(\mathit{p}\text{-cymene})]$ (1)**: 1,3-Diisopropylimidazolium chloride (124.1 mg, 0.77 mmol) and $Ag_2O$ (75.3 mg, 0.33 mmol) were suspended in anhydrous, degassed $CH_2Cl_2$ (7 mL) under argon and refluxed for 1 h in a Schlenk flask with a reflux condenser. $[RuCl_2(\mathit{p}\text{-cymene})]_2$ (201.0 mg, 0.33 mmol) in anhydrous, degassed $CH_2Cl_2$ (3 mL) was then added and the solution was refluxed for 2 h and concentrated in vacuo. The residue was purified on a short silica-gel column ($CH_2Cl_2$/*i*PrOH 9:1) to give 295.0 mg (98%) of a red/orange solid. $R_f = 0.64$ ($CH_2Cl_2$/*i*PrOH 9:1); IR (neat): $\tilde{\nu} = 3152, 3099, 3077, 2958, 2930, 2870, 1473, 1412, 1391, 1369, 1297, 1265, 1213, 1133, 856, 770, 700\ cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta = 1.31$ (d, $J = 6.9$ Hz, 6H), 1.44 (br d, $J = 6.2$ Hz, 12H), 2.08 (s, 3H), 2.92 (m, 1H), 5.15 (d, $J = 6.0$ Hz, 2H), 5.31 (m, 2H), 5.47 (d, $J = 6.0$ Hz, 2H), 7.07 ppm (s, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$): $\delta = 18.6, 22.8, 25.0, 30.8, 52.0, 83.4, 85.1, 97.1, 106.4, 118.9, 171.1$ ppm; MS: *m*/*z*: calcd: 423.11 $[M-Cl]^+$; found: 423.07; elemental analysis calcd (%) for $C_{19}H_{30}Cl_2N_2Ru$: C 49.78, H 6.60, N 6.11; found: C 49.84, H 6.44, N 6.05.

**$[RuCl_2(ICy)(\mathit{p}\text{-cymene})]$ (2)**: 1,3-Dicyclohexylimidazolium chloride (200.2 mg, 0.75 mmol) and $Ag_2O$ (86.1 mg, 0.37 mmol) were suspended in anhydrous, degassed $CH_2Cl_2$ (8 mL) under argon and refluxed for 1 h in a Schlenk flask with a reflux condenser. $[RuCl_2(\mathit{p}\text{-cymene})]_2$ (226.0 mg, 0.37 mmol) in anhydrous, degassed $CH_2Cl_2$ (3 mL) was then added and the solution was refluxed for 1 h and concentrated in vacuo. The residue was purified on a short silica-gel column ($CH_2Cl_2$/*i*PrOH 9:1) to give 368.4 mg (93%) of a red/orange solid. $R_f = 0.64$ ($CH_2Cl_2$/*i*PrOH 9:1); IR (neat): $\tilde{\nu} = 3091, 2957, 2921, 2848, 1466, 1455, 1446, 1418, 1380, 1290, 1276, 1232, 1190, 897, 747, 697\ cm^{-1}$; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta =$ 1.14–2.44 (m, 20H), 1.36 (d, $J = 6.9$ Hz, 6H), 2.13 (s, 3H), 2.84 (m, 1H), 4.84 (m, 2H), 5.14 (d, $J = 6.0$ Hz, 2H), 5.46 (d, $J = 6.0$ Hz, 2H), 7.04 ppm (s, 2H); $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta = 18.8, 23.1, 25.3, 25.4, 26.0, 31.2, 35.4, 35.8, 59.3, 83.6, 85.3, 97.3, 105.1, 119.3, 171.4$ ppm; MS: *m*/*z*: calcd: 503.18 $[M-Cl]^+$; found: 503.15; elemental analysis calcd (%) for $C_{25}H_{38}Cl_2N_2Ru$: C 55.75, H 7.11, N 5.20; found: C 55.14, H 6.84, N 5.16; $^1H$ NMR spectroscopic data are in accordance with literature values.[24c]

**General procedure for amidation with complex 1 (catalyst B)**: $[RuCl_2(I\mathit{i}Pr)(\mathit{p}\text{-cymene})]$ (**1**) (11.5 mg, 0.025 mmol), $PCy_3$ (7.0 mg, 0.025 mmol), and KO*t*Bu (5.6 mg, 0.05 mmol) were placed in an oven-dried Schlenk tube. Vacuum was applied and the tube was then filled with argon (repeated twice). Freshly distilled toluene (1 mL) was added and the mixture was heated to reflux under an argon atmosphere for 20 min. The alcohol (0.5 mmol) and the amine (0.5 mmol) were added and the mixture was heated to reflux under an argon atmosphere for 24 h and then worked up as described above.

**General procedure for amidation with metathesis catalyst (catalyst C)**: Hoveyda–Grubbs 1st-generation catalyst (15 mg, 0.025 mmol), 1,3-diisopropylimidazolium chloride (4.7 mg, 0.025 mmol), and KO*t*Bu (8.4 mg, 0.075 mmol) were placed in an oven-dried Schlenk tube. Vacuum was applied and the tube was then filled with argon (repeated twice). Freshly distilled toluene (1 mL) was added and the mixture was heated to reflux under an argon atmosphere for 20 min. The alcohol (0.5 mmol) and the amine (0.5 mmol) were added and the mixture was heated to reflux under an argon atmosphere for 24 h and then worked up as described above.

## Acknowledgements

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