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Half-sandwich ruthenium complexes bearing hemilabile κ^2 -(C,S)-thioether-functionalized NHC ligands: application to amide synthesis from alcohol and amine

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Dedicated to Professor Rinaldo Poli on the occasion of his 65th birthday

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Supporting information for this article is given via a link at the end of the document.

Abstract: Amide synthesis is one of the most crucial transformations in chemistry and biology. Among various catalytic systems, N-heterocyclic carbene (NHC)-based ruthenium (Ru) catalyst systems have been proven to be active for direct synthesis of amides by sustainable Acceptorless Dehydrogenative Coupling of primary alcohols with amines. Most often, these catalytic systems usually use monodentate NHC and thus require an additional ligand to obtain high reactivity and selectivity. In this work, a series of cationic Ru(II)(η^6 -*p*-cymene) complexes with thioether-functionalized N-heterocyclic carbene ligands (imidazole and benzimidazole-based) have been prepared and fully characterized. These complexes have then been used in the amidation reaction and the most promising one (i.e. **3c**) has been applied on a large range of substrates. High conversions albeit with moderate yields have generally been obtained.

Introduction

The amide linkage is important to the emergence of life through the formation of peptides and proteins that are required for the construction of complex biological architectures.^[1] Therefore, it is not surprising that amide bond formations are the most common reactions used in the pharmaceutical industry and that about 25% of all drugs on the market contain at least one amide bond.^[2] Chemists have devoted a great deal of research effort to develop synthetic approaches for this important functional group formation, but these methods generally require supplementary stoichiometric amounts of reagent and produce large amounts of waste and/or by-products.^[3] Fortunately, a more atom-economic and greener alternative that generates amides directly from primary alcohols and amines and which produces hydrogen gas as the only by-product has been described with various transition metal catalysts.^[4] Among various transition metals ruthenium (Ru), has been widely explored for such transformation. Since the seminal work of Murahashi^[5] and Milstein^[6] groups, several Ru-based catalytic systems have been developed by various researchers.^[7] Among all the ligands associated with Ru, N-heterocyclic carbene ligands (NHCs), which are easily tunable, have been shown to be good partners for this process. ^{[7a-c, 7j-l, 7q, r, t, w, x],^[8]}

Most often, these NHC/Ru systems are based on an imidazole scaffold.^[7a-c, 7j-l, 7q, r, t, w, x] Interestingly, their benzimidazole^[8] counterparts have recently shown higher catalytic activities thus attracting attention.

The Acceptorless Dehydrogenation AD-amidation transformation occurs in three consecutive steps (i) oxidation of primary alcohols to aldehydes, (ii) nucleophilic addition of amine to aldehyde to give hemiaminal. At this stage, two pathways are possible: (iii) oxidation of hemiaminal to afford amide or (iv) a loss of one molecule of water molecule to lead to the formation of imine which could be further hydrogenated into secondary amine via the so-called hydrogen borrowing (HB) strategy. Additionally, the secondary amine could react with excess alcohol via a second similar process to give tertiary amine product.^[7g] Interestingly, Huynh *et al.* described a well-defined NHC-benzimidazole complex [RuCl(*p*-cymene)(NHC)(PPh₃)] which is capable to selectively catalyze either the dehydrogenative amidation or the N-alkylation of amine through the appropriate choice of the base/solvent pair.^[8a] Most often these catalytic systems require the use of an extra monodentate ligand such as acetonitrile,^[7h] pyridine^[7e] and more particularly phosphines (PCy₃, PPh₃)^[7a, 8a], to replace a chloride ligand, in order to achieve a high level of reactivity and selectivity. N-functionalized NHCs with an extra Lewis base moiety (typically P, O or N), possibly hemilabile, are now a significant class of bidentate ligand.^[9] Rare successful examples of Ru(arene) complexes with bidentate NHC-pyrimidine,^[10] -naphthyridine,^[11] -picoly,^[12] -phosphine^[13] and -phenyl ligands^[8g] have been reported for such acceptorless/borrowing hydrogen reactions. Even though S-functionalized NHCs still remain an undeveloped class of ligands, they have proven to be effective as ligands for various metal-catalyzed reactions.^[14] For example, recently, a thioether-functionalized NHC/Ru system exhibited selective double dehydrogenation of a primary amine to the corresponding nitrile under AD and oxidant-free conditions.^[15] Here, we questioned whether the use of bidentate NHC/thioether cationic Ru complexes (Figure 1) would lead to a more selective and robust system for AD amidation compared to those using monodentate NHC ligands.

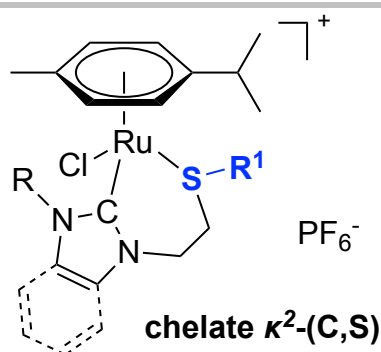


Figure 1. General molecular structure of the thioether-functionalized NHC ruthenium complexes used in this study.

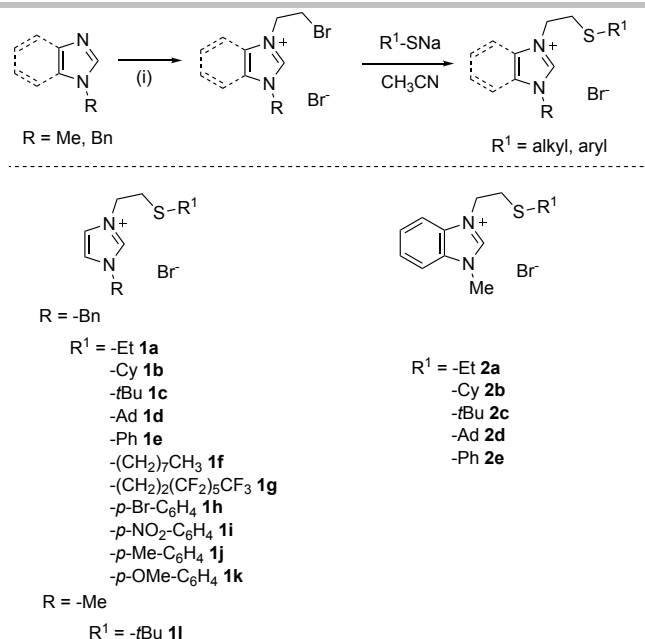
Herein we report the synthesis of a series of bidentate thioether-functionalized imidazolium/benzimidazolium salts with various –thiolates (-SR) substituents. The corresponding cationic NHC-ruthenium complexes were obtained from $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ generating the cationic $\kappa^2\text{-(C,S)}$ -chelate complexes which was confirmed by X-ray diffraction studies. Studies on the catalytic activity and selectivity of these NHC-Ru complexes have been conducted on the amidation of alcohol with amine. A systematic study of the variable parameter of the thioether group was carried out and coupled with the influence of the NHC core. Thanks to a thorough examination of the experimental conditions, these NHC-thioether showed good selectivity towards amide formation.

Results and Discussion

Synthesis of the azolium precursors

Considering that the electronic and steric effects of the thioether moiety can influence their abilities to coordinate ruthenium center and influence the Lewis character of the metal center, a series of azolium precursors containing imidazole **1a-1l** or benzimidazole moieties **2a-2e** have been prepared and fully characterized (Scheme 1).

All S-functionalized imidazolium salts (with the exception of **1e**) were synthesized according to our previously reported procedure by direct reaction of the bromo derivative with the corresponding sodium thiolate. ^[15-16] Benzimidazolium salt precursors **2a-2e** were also prepared with similar procedure (see Supplementary Materials for details). Finally, the imidazolium **1e** was obtained in nearly quantitative yield by reaction between the commercially available 2-chloroethyl phenylsulfide and 1-benzylimidazole.^[17] The benzimidazolium precursor **2e** was obtained in the same way from the 1-methylbenzimidazole.



Scheme 1. General synthesis and list of the azolium salts used in the study. Reaction condition (i): 1-(benz)imidazole (1equiv.) in 1,2-dibromobutane (as solvent) overnight at 85 °C.

Synthesis of the ruthenium complexes

The coordination of the ligand precursors to ruthenium could not be achieved by the use of an external base. We then turned to the strategy based on trans-metalation by means of a silver NHC complex. Starting from imidazolium salts, all corresponding NHC-ruthenium complexes were synthesized through *in situ* formation of the silver intermediate.^[15] After the imidazolium salt reacted with Ag_2O in dichloromethane overnight at room temperature, the ruthenium dimer $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (0.5 equiv.) was added into the mixture and the resulting solution was stirred for an additional 6 to 19h reaction time (Figure 2). The resulting complexes were purified by column chromatography using silica gel: elution with a mixture of dichloromethane–acetone and KPF_6 gave the corresponding cationic ruthenium(II) complexes as air and moisture stable orange solids. The corresponding benzimidazolium complexes were synthesized using the same experimental procedure in good to excellent yield (see Supplementary Materials for details).

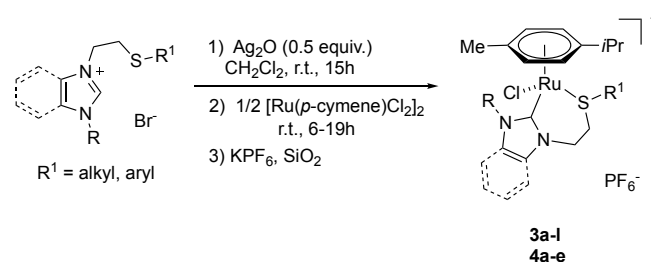


Figure 2. Synthesis of cationic chelated NHC (*p*-cymene)-Ru complexes with imidazolylidene **3a-l** and benzimidazolylidene **4a-e**.^[15]

The analytical data (HRMS, ¹H NMR) of the Ru complexes advocated for the coordination of NHCs in a chelate $\kappa^2\text{-(C,S)}$ fashion. In fact, the formation of a 6-membered ring by coordination of the S heteroatom onto the metal center renders

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the $-NCH_2CH_2S$ protons diastereotopic causing a breakup of the signals in the region between 2.4 and 4.9 ppm. As already noticed for imidazolylidene ruthenium complexes,^[15] all benzimidazolylidene complexes **4a-e** were observed as a single isomer by 1H NMR in solution. All of the complexes are chiral since the ruthenium atom and the sulfur atom are stereogenic. We could expect to observe a complex diastereomeric mixture because of the formation of two newly formed stereogenic centers at the sulfur and the metal center and a possible dynamic process, namely sulphur inversion or its hemilability.^[18] The κ^2 -(C,S) coordination was later unambiguously confirmed by X-ray analysis on single crystal (*vide infra*) for complex **4e**.

X-ray analyses

Single crystals suitable for X-ray diffraction analysis of **4e** were obtained by slow diffusion of diethyl ether into a concentrated solution of the complex in dichloromethane in 1:3 ratio. The molecular structure of the complex **4e** is depicted in Figure 3 along with key bond lengths and bond angles. The Ru complex displays a three-legged piano-stool geometry. The coordination of the pro-chiral thioether at the stereogenic center of ruthenium is expected to generate a diastereomeric mixture, however in the solid state only a single enantiomeric pair ($R_{Ru}R_S$ / $S_{Ru}S_S$) of complex has been found, as in solution.

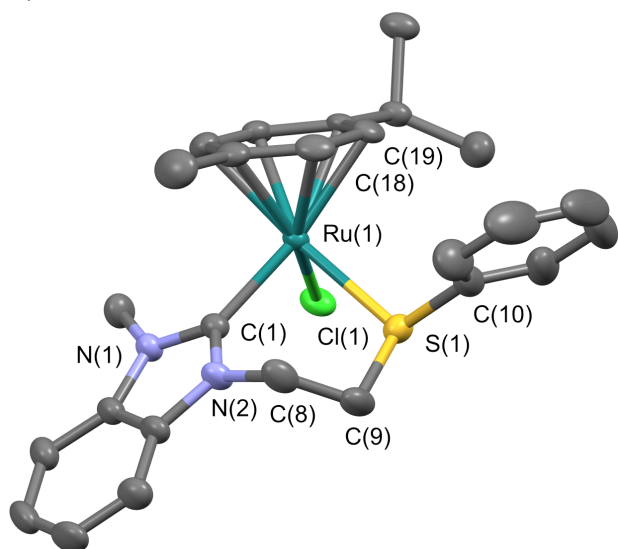


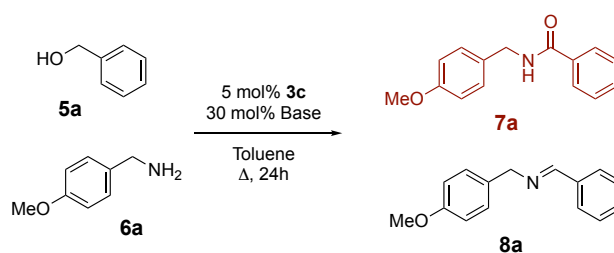
Figure 3. Molecular structure of Ru-NHC complex **4e**. Selected bond lengths [Å] and angles [deg]: C(1)-Ru(1), 2.054(2); Ru(1)-S(1), 2.4016(6); Ru(1)-Cl(1), 2.4125(6); Ru(1)-C(18), 2.201(2); Ru(1)-C(19), 2.250(2); C(1)-Ru(1)-S(1), 88.23(6); S(1)-Ru(1)-Cl(1), 82.37(2); C(1)-Ru(1)-Cl(1), 87.51(6). CCDC Deposition Number 2125167.

Contrary to what previously observed for NHC complexes **3**,^[15] the phenyl group of the thioether is oriented in *syn*-position with respect to the *p*-cymene ligand. Notably, the 6-membered chelate ring displays a boat conformation with C(8) also pointing to the *p*-cymene group. The sulphur-group orientation could be explained by an intermolecular π -stacking interaction between two benzimidazole rings which help to locate the two Ph rings almost face to face in the same space portion. This geometry forces the thioether to adopt a single configuration and thus disfavors the formation of the enantiomeric couple $S_{Ru}R_S$ / $R_{Ru}S_S$ in the solid state. The Ru-Carbene bond distance of complex **4e** (2.054 Å) was found within the range of other chelate NHC-Ru(*p*-cymene) complexes reported in literature.^[19] The Ru-S bond distance (2.4016 Å) is also in the range to those describe in the literature for thioether-Ru(*p*-cymene) complexes.^[15]

Application to catalysis: amidation reaction using alcohol and amine as substrates

The coupling of benzyl alcohol **5a** with *para*-methoxybenzyl amine **6a**^[20] was used as a benchmark reaction in presence of complex **3c** (Scheme 2). Several parameters were cautiously examined and optimized (as listed in Table S1 in the Supporting Information).^[21]

Inspired by previously reported NHC-Ru systems, we initially used NaH (30 mol%) as base and 5 mol% of **3c** in toluene under reflux and 24h reaction time. In contrast to previous reports,^[8a, f] in the presence of NaH, the amide **7a** was obtained as the minor compound in 1/4 ratio in favor to imine **8a** (88% conversion). Control experiments showed that in absence of the catalyst no reaction occurred, that in the absence of base lower conversion and poor selectivity were observed and that lower conversion and selectivity were detected in a close system compared to an open one, under these experimental conditions.



Scheme 2. Amidation reaction between benzyl alcohol and *p*-methoxybenzyl amine in presence of Ru catalyst **3c**.

Screening of various bases (NaHCO₃, K₂CO₃, CsCO₃, ^tBuOK) showed that cesium carbonate was the base of choice. After solvent and catalyst concentration screening, we could reach 94% conversion and obtain the desired amide in a 83/7 ratio for **7a/8a**. Finally, different Ru sources were also investigated by generating the active species *in situ* from reaction with the imidazolium. In all cases, poor selectivity for amide was observed and the benzonitrile was mainly obtained even with [RuCl₂(*p*-cymene)]₂ (See SI for details). Therefore, the optimized reaction conditions were identified as benzylamine (0.20 mmol), alcohol (0.24 mmol), Ru cat (5 mol%) Cs₂CO₃ (30 mol%), toluene (1 mL), refluxing for 24 h, and these conditions were used for subsequent investigations unless otherwise noted.

Evaluation of NHC-thioether ruthenium complexes.

Finally, the catalytic activity of all NHC Ru complexes was evaluated under the aforementioned experimental conditions, as displayed in Table 1. The best conversion was observed with complex **3i** ($R^1 = -p$ -PhNO₂) albeit with very poor selectivity (Entry 9); in this case, a large quantity of benzonitrile was generated. The best selectivity towards the desired amide product was obtained in presence of catalysts **3j** or **3k** bearing aromatic substituent with electron-donating group (i.e. $R^1 = -p$ -PhOMe, $-p$ -PhMe, Entries 10 & 11); however with moderate substrate conversion. Alkyl groups, except octyl, display a good level of selectivity (ca. 79-86%) for the amide product (Entries 1-4). Thus, it appeared that complexes bearing an electron donating alkyl group onto the sulphur atom are generally more efficient when considering conversion and selectivity toward the desired amide, complex **3c** being the best candidate (Entry 3).^[22] Increasing the solubility of these type of complexes by addition of more lipophilic chain such as octyl **1f** or fluorine **1g** chain showed no

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improvement into the catalytic activity, on the contrary, a decrease in reactivity and selectivity has been observed (table 1 entries 6-7). As this reaction seems sensitive to steric hindrance, the N-benzyl group has been replaced by a smaller N-Me group in complex **3l**. But this change severely reduced the reactivity, around 53% conv, highlighting the importance of the benzyl group in this case (Entry 12).

Table 1. Evaluation of amidation in presence of thioether-functionalized NHC-Ru complexes **3a-l** and **4a-e**.

Entry ^[a]	Ru	R	S-R ¹	Conv% ^[b]	7a ^[e]	8a ^[c]
1	3a	Bn	Et	72	86	3
2	3b	Bn	Cy	59	79	9
3	3c	Bn	<i>t</i> -Bu	94	83	7
4	3d	Bn	Ad	69	80	14
5	3e	Bn	Ph	62	74	4
6	3f	Bn	Oct	59	10	3
7	3g	Bn	(CH ₂) ₂ (CF ₂) ₅ CF ₃	50	77	12
8	3h	Bn	<i>p</i> -Br-Ph	63	68	21
9	3i	Bn	<i>p</i> -NO ₂ -Ph	100	37	11
10	3j	Bn	<i>p</i> -Me-Ph	64	93	1
11	3k	Bn	<i>p</i> -OMe-Ph	53	93	5
12	3l	Me	<i>t</i> -Bu	54	35	-
13	4a	Me	Et	70	74	9
14	4b	Me	Cy	94	50	7
15	4c	Me	<i>t</i> -Bu	98	55	23
16	4d	Me	Ad	71	26	25
17	4e	Me	Ph	98	30	58

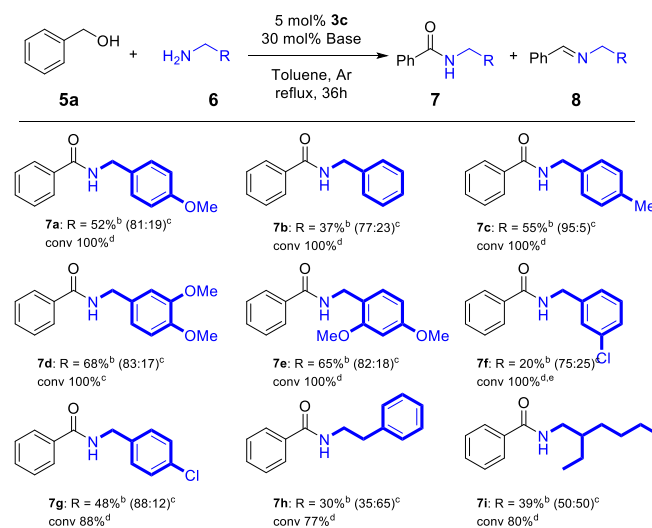
[a] *p*-methoxybenzylamine (0.20 mmol), benzyl alcohol (0.24 mmol), cat. (5 mol%), base (30%), toluene (1 mL), reflux, 24h, Ar, open system. [b] Conversion of BnNH₂ determined by ¹H RMN using internal reference (average of at least two runs). [c] Percentage of products were determined by ¹H NMR and GC analysis, for more detailed ration see table S3 in the SI.

Recent studies on the dehydrogenating amidation of alcohol and amine catalyzed by NHC-Ru systems have demonstrated the sensitivity of this transformation to the substitution of NHCs at their nitrogen atoms and at the back of their skeletons. Indeed, benzimidazole core displays often better activity than imidazole counterpart.^[8e, f] Benzimidazole-based complexes **4** were then evaluated as catalyst. They displayed high to good reactivities along with moderate selectivities (Table 1 entries 13-17). Again, substitution at the sulfur atom with an alkyl group most often shows greater amide selectivity over the aryl group (Table 1, entries 13 & 17). However, compared to imidazole-**3l** complex, the corresponding benzimidazole-**4c** complex shows higher conversion but lower selectivity (Table 1, entries 12 & 15). In our

case, the trend seems to indicate that the NHC-imidazole skeleton is more selective than the NHC-benzimidazole backbone.

The scope of the reaction was finally studied on various substrates in the presence of imidazole-based Ru catalyst **3c**, using the experimental conditions as determined previously (Reaction time: 36h). Table 2 displays a screening using benzyl alcohol in combination with various primary amines. The conversion and the amide/imine ratio were determined by NMR on the crude mixture. The yield refers to the isolated yield after column chromatography on silica gel. Good conversions as well as good ratios toward the desired amide were usually observed, whereas isolated yields are moderate to low. The reaction was not effective with bulky amines such as 1-adamantylamine, 1-adamanemethylamine, 1,1,3,3-tetramethylbutylamine, 2-methylbenzylamine, and 2-chlorobenzylamine; in these cases, low conversions were measured and the only observed products were the corresponding imine and the benzaldehyde.

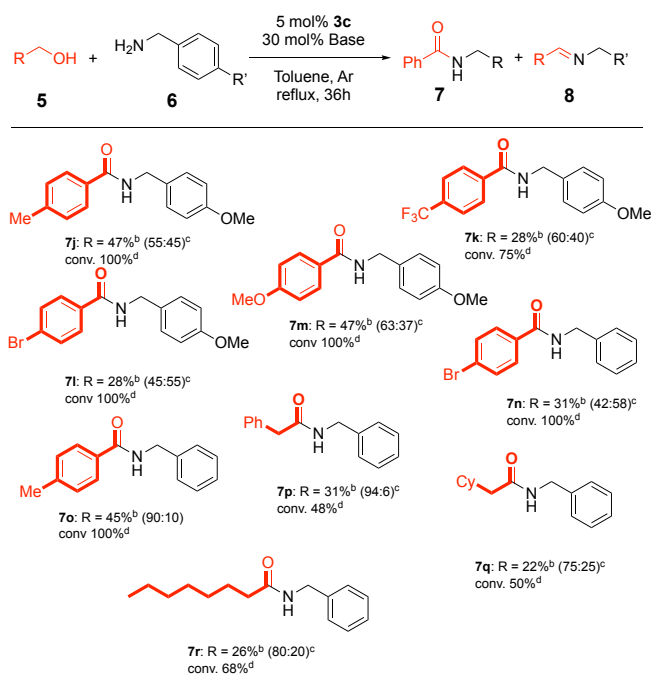
Table 2. Reaction scope of amidation in presence of NHC Ru complex **3c**: amine variation.^a



[a] Amine (0.20 mmol), benzyl alcohol (0.24 mmol), **3c** (5 mol%), Cs₂CO₃ (30%), toluene (1 mL), reflux, 36h, Ar, open system. [b] Amide isolated yield after purification by chromatography on SiO₂. [c] Ratio of products were determined by ¹H NMR and GC analysis. [d] Conversion of BnNH₂ determined by ¹H RMN using internal reference (average of at least two runs). [e] Aldehyde as major compound.

Table 3 displays a screening using various alcohols. Again, good conversions were measured however isolated yields are moderate to low for the desired amide products. More sterically demanding alcohol, as observed for amines, slow down the process however. The amide/imine ratio is ranging from 90:10 (**7o**) to 42:58 (**7n**).

Table 3. Reaction scope of amidation in presence of NHC Ru complex **3c**: alcohol variation.^a



[a] Benzylamine derivative (0.20 mmol), alcohol (0.24 mmol), **3c**. (5 mol%), Cs₂CO₃ (30%), toluene (1 mL), reflux, 36h, Ar, open system. [b] Amide isolated yield after purification by chromatography on SiO₂. [c] Ratio of products were determined by ¹H NMR and GC analysis. [d] Conversion of BnNH₂ determined by ¹H RMN using internal reference (average of at least two runs).

Conclusion

In summary, we have synthesized a variety of well-defined thioether-functionalized imidazole and benzimidazole based N-heterocyclic carbene (κ^2 -C,S)-Ru(II) η^6 -cymene cationic Ru complexes by varying the substituents on the thioether. The molecular structure of these compounds was confirmed by spectroscopic investigations and X-ray diffraction studies. These systems were applied in the atom-economical amidation reaction of alcohol with amine. The results (in particular the imine/amide product ratio) were sensitive to ligand structures and complex **3c** was found to be the most effective. Overall, such NHC-bidentate ligands were not more efficient than classical monodentate-NHC.^[8e] The labile nature of *p*-cymene for such a catalytic system could disrupt the molecular integrity of Ru-complex which could explain the lower performance observed.^[23] This problem, could be overcome by using other sources of ruthenium, such as [Ru₂(CO)₄(CH₃CN)₆](BF₄)₂ in which *p*-cymene has been replaced by strongly bound ligands.^[24]

Experimental Section

General procedure for the synthesis of the NHC Ru complexes 3-4

A solution of appropriate imidazolium (2 equiv.) in CH₂Cl₂ was treated with a slight excess of Ag₂O (1.3 equiv.). The resulting suspension was stirred in the dark (flask wrapped with aluminum foil) for 15 h under argon to generate the silver carbene intermediate. The solution was then filtered over a pad of Celite to remove residual solids and concentrated. This silver solution is then added to a solution of [RuCl₂(η^6 -*p*-cymene)₂] (1 equiv.) in CH₂Cl₂. A precipitate was directly formed and the resulting red mixture was stirred for 6 to 19h in the dark at room temperature and under argon. After this time, the solution was filtered through celite and concentrated. Excess

of KPF₆ was added and the solution stirred for 15 min. Finally, the solution was deposited on a silica column for chromatographic separation using dichloromethane/acetone (1/1). The filtrate containing the complex was evaporated to dryness and dichloromethane was added; the resulting suspension was filtered over Celite and the solvent was removed *under vacuum* to give desired compound as red to orange solids (for more details see SI).

General procedure for the amide **7** synthesis

In an oven-dried Schlenk tube, the ruthenium complex **3c** (6.9 mg, 5 mol%, 0.01 mmol) and Cs₂CO₃ (19.5 mg, 0.06 mmol) were added. The Schlenk tube was equipped with a condenser and the glass assembly was placed under argon after three vacuum/argon cycles. Dry toluene (1.0 mL) was added and the resulting mixture was stirred 5 min before adding the desired alcohol (1.2 equiv., 0.24 mmol) first and then the desired amine (1 equiv., 0.20 mmol). The condenser valve was opened to the Schlenk line and then the yellow-orange mixture was heated at 125 °C under an argon atmosphere for 36 h. Afterwards, the crude mixture was directly purified by silica gel flash column chromatography (h: 10 cm; Ø:4 cm) using first pentane:diethyl ether (80:20) followed by pentane:diethyl ether (50:50) to afford the desired amide product (for more details see SI).

Acknowledgements

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Keywords: ruthenium • N-heterocyclic carbene • acceptorless dehydrogenation • atom-economic • amide synthesis

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