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ORIGINAL PAPER

Ionic liquids as solvents for a ruthenium-catalyzed C–H activation reaction: synthesis of heterocyclic compounds from α,β-unsaturated imines, carbon monoxide, and ethylene

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Abstract The reaction of α,β-unsaturated imines, carbon monoxide, and ethylene in the presence of $Ru_3(CO)_{12}$ as a precatalyst yielding mixtures of chiral 2,3-dihydropyrrolones and 2,3-disubstituted pyrroles has been performed in several ionic liquids as reaction media. Optimization of the reaction conditions in [C_4mim][BTA] showed that the reaction works under milder conditions with regard to reaction time and partial pressures of the gaseous substrates than when performed in classical organic solvents. In some cases the ionic liquid phase containing the ruthenium catalyst species might even be reused for another run after extracting the products. A decrease of catalytic activity or changes in selectivity are attributed to the formation of ruthenium nanoparticles during the reaction.

Keywords C–H activation · Ionic liquids · Catalysis · Ruthenium · Lactams · Pyrroles

Introduction

The direct catalytic activation of C–H bonds with the purpose of establishing new C–C bonds is a highly attractive synthetic objective in terms of avoiding synthesis and isolation of more reactive intermediates, e.g. chlorinated compounds. Progress in this field has been thoroughly reviewed during the last years [1–5].

Some of us have developed a reaction of α,β-unsaturated imines, carbon monoxide, and ethylene (or terminal alkenes in general) to produce chiral 2,3-dihydropyrrolones as the main product in non-polar solvents. As a side-product 2,3-disubstituted pyrroles are formed (Scheme 1) [6–12]. The formation of both products obviously proceeds via the activation of a C–H bond in the β-position relative to the imine C=N bond. The product ratio is highly dependent on the relative permittivity of the solvent used, with very non-polar solvents leading to the quantitative and selective formation of chiral lactams **2**, whereas use of more polar solvents leads to an enhancement of the yield of the pyrrole **3** (75% in methanol) [12]. Because we did not succeed in selectively producing either of these compounds solely by variation of the reaction media we became interested in the use of ionic liquids as reaction media because their relative permittivity can be varied substantially without their becoming protic, which most probably led to the loss of reactivity and selectivity of the system in classical solvents.

Ionic liquids have often been regarded to be "green" solvents compared with classical organic and, especially, chlorinated solvents, because of their low volatility and because they are easily recycled [13]. In the last decade ionic liquids have also been in the focus of research as solvents for transition metal-catalyzed reactions, e.g. hydrogenation, hydroformylation, and hydroaminomethylation reactions [14–17]. There have only been a few reports of catalytic reactions in ionic liquids proceeding via C–H activation steps, including activation of methane, dehydrogenation of cyclooctadiene, isomerization of alkenes, or C–H activation of terminal alkynes [18–22]. In addition, chiral ionic liquids have been used to achieve

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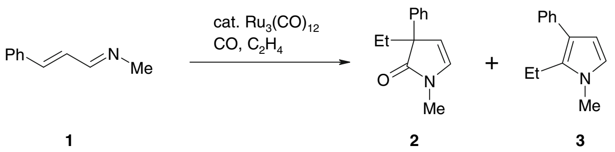

Scheme 1

stereoselectivity in catalytic reactions that proceed via the formation of new stereogenic centers during the catalytic cycle [23, 24].

Herein we describe our investigations on the question of whether the catalytic reaction depicted in Scheme 1 also proceeds in ionic liquids. This would imply that the same catalytic cycles are working in classical organic solvents and in ionic liquids. We also wished to know whether reaction conditions, for example temperature, pressure of gaseous substrates, or reaction time, can be improved if the reaction medium is changed from organic solvents to ionic liquids.

Results and discussion

Table 1 shows the ionic liquids that have been introduced to the reaction and the outcome of the catalysis with regard to selectivity and reactivity. As standard conditions we chose those that proved to be ideal for the same reaction in classical solvents (cf. Experimental section). The imine with R=Me was introduced to all reactions except the reaction in [C$_4$mim][F$_3$CSO$_3$] and run 5 in [C$_4$mim][BF$_4$], which were performed as four-component reactions of cinnamaldehyde, CyNH$_2$, CO, and C$_2$H$_4$ without isolation of the imine. Work-up was easily achieved by extraction of the ionic liquid phase with diethyl ether or hexane. NMR spectroscopic investigations showed that, to some extent, the ionic liquids were also extracted into the organic phase. A typical ^{1}H NMR spectrum of the organic phase after extraction and subsequent filtration through silica is presented in Fig. 1. The products may finally be separated by column chromatography.

Table 1 Ionic liquids used, ratio of **2**:**3**, and conversion of **1**

Ionic liquid	Run	Ratio of **2**:**3** (%)	Conversion of **1** (%)
[C$_4$mim][BF$_4$]	1	50:50	100
[C$_4$mim][BF$_4$]	2	50:50	100
[C$_4$mim][BF$_4$]	3	50:50	100
[C$_4$mim][BF$_4$]	4	Oligomers	100
[C$_4$mim][BF$_4$]	5	Oligomers	100
[C$_4$mim][BTA]	1	70:30	100
[C$_4$mim][BTA]	2	Oligomers	100
[C$_4$mim][BTA]	3	Oligomers	100
[C$_4$dmim][BTA]	1	70:30	100
[C$_4$mim][F$_3$CSO$_3$]	1	60:40	100
[C$_4$mim][TFA]	1	–	No reaction
[C$_4$mim][OAc]	1	–	No reaction
[C$_4$mim][Cl]	1	Oligomers	100
[C$_8$mim][BTA]	1	Oligomers	100

From the entries in Table 1 it can be concluded that most ionic liquids work very well in the catalytic transformation of unsaturated imines to heterocyclic compounds. Determination of selectivity and activity was achieved by ^{1}H NMR spectroscopy. The imine substrate gives a typical multiplet representing the imine proton at approximately 8 ppm that enables determination of the activity. In addition, the product compounds **2** and **3** each show two doublets for the ring protons between 5.5 and 6.5 ppm that make it possible to easily determine the ratio between both heterocyclic compounds [7]. Compared with the reaction in classical organic solvents the same compounds are produced with ratios that are in the region of acetone or methanol [12]. This leads to the conclusion that the catalytic reactions leading to both observed compounds work via the same catalytic cycles in classical organic solvents as in ionic liquids. This is not self-evident, in the first place because it has been reported that, especially, the solubility of carbon monoxide in most ionic liquids is rather low [25]. This low solubility might be the reason for the observation of only trace amounts of **2** and **3** after reaction in the quite apolar [C$_8$mim][BTA] (BTA = bis-trifluoromethylsulfonylamide), although the imine is completely consumed during the reaction and oligomeric products most probably composed of the imine and of ethylene were formed. Because of the comparatively low polarity of [C$_8$mim][BTA] reduced carbon monoxide solubility might be the reason for the observed reactivity. The same observation is made for reactions in [C$_4$mim][Cl]. This ionic liquid, in contrast with all other ionic liquids used, is solid at room temperature and has a relatively high viscosity at higher temperatures also. This might lead to further reduced solubility of carbon monoxide and, therefore, also to reduced catalytic activity of the system with regard to the formation of **2** or **3**, which incorporate CO and C$_2$H$_4$.

The only ionic liquids that are obviously not suitable as reaction media are [C$_4$mim][OAc] and [C$_4$mim][TFA] (TFA = trifluoroacetate). We attribute this behavior to the fact that the carboxylate anions are much better ligands than all the other anionic components of the ionic liquids used in this investigation. So the carboxylates might bind to ruthenium atoms and, therefore, inactivate the catalytic species.

The other ionic liquids [C$_4$mim][BF$_4$], [C$_4$dmim][BTA], [C$_4$mim][BTA], and [C$_4$mim][F$_3$CSO$_3$] work very well in a

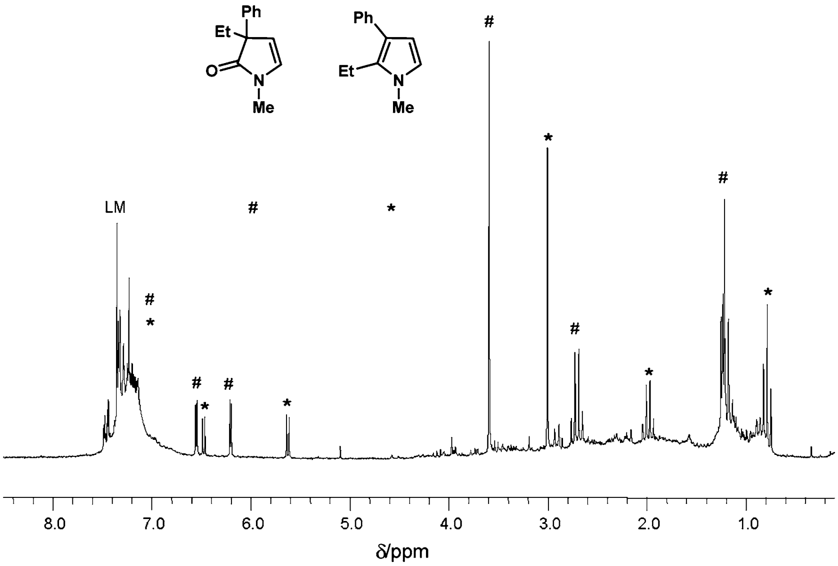

Fig. 1 ^{1}H NMR spectrum of the reaction mixture after extraction with diethyl ether from [C$_4$mim][BTA] without further purification

first run. The selectivity of the reaction depends on the nature of the cation and the anion of the ionic liquid. As has been demonstrated for organic solvents, the amount of **3** in the reaction mixture increases with the polarity of the ionic liquid [26, 27]. Nevertheless, additional effects have to be taken into account concerning the selectivity of the catalytic reaction in different ionic liquids of the imidazolium type. Some of us reported that the synthesis of **2** and **3** leads to the observation of identical molar amounts of **3** and CO$_2$. The latter is most probably formed by transfer of an oxygen atom to a carbon monoxide molecule, leading to the fact that in **3** only the carbon atom of CO is incorporated in the 2-position. These observations have been demonstrated by use of ^{13}CO [10]. Other groups have published results showing that zwitterionic imidazolium carboxylates may be produced either by addition of CO$_2$ to carbenes or by reaction of dimethyl carboxylate with imidazoles [28–30]. These adducts can then be used in reactions with protic compounds, compounds with activated CH functions, or compounds with diorganophosphorus chlorides [31–33]. The ability of ionic liquids based on imidazolium cations to bind CO$_2$ may, therefore, strongly affect the **2**:**3** ratio by removing CO$_2$ from the equilibrium. If this was true the product ratio should depend on the concentration of the imine. Preliminary experiments showed that reaction of 1 mmol **1** in 2, 4, or 8 cm^3 [C$_4$mim][BTA] led to no significant variation of the product ratio. Nevertheless, because the same autoclave was used in all the experiments, the reduced ionic liquid surface with regard to the complete volume of solvent decreased, most probably hampering uptake of carbon monoxide and ethylene from the gas phase. Thorough investigations on these contrary effects will be the subject of future work.

Because, after extraction of the reaction mixture with an organic solvent, all ruthenium compounds stayed in the ionic liquid phase we investigated whether this phase still is catalytically active. In case of [C$_4$mim][BF$_4$] this is indeed the case, and the catalytic reaction works with identical activity and selectivity for another run. Nevertheless, for all ionic liquids the ionic liquid phase becomes catalytically inactive after 1, 2, or 3 runs. On the other hand, re-use of the solvent phase incorporating ruthenium species is not possible at all in the case of classical organic solvents. So even the potential recyclability of the corresponding ionic liquid phase is a significant improvement of a process working in ionic liquids compared with use of organic solvents. It has been reported that the thermal decomposition of metal carbonyls in ionic liquids leads to the formation of nanoparticles of the respective metals [34–36]. Because the temperatures used in the latter investigations are comparable with the reaction conditions we used, we investigated [C$_4$mim][BTA] phases by means of dynamic light scattering after 0.5, 2, 4, and 16 h. The results are depicted in Fig. 2 and show that ruthenium nanoparticles are, indeed, produced. There is an almost linear increase of the average radii of the particles during the reaction. Because the catalytic activity toward the formation of **2** or **3** obviously decreases with the formation of nanoparticles, this, in contrast, clearly demonstrates that the catalytic reaction in which **2** and **3** are produced proceeds entirely under homogeneous conditions.

Another open question was whether the use of ionic liquids instead of classical organic solvents leads to different optimum reaction conditions. We therefore investigated the reaction shown in Scheme 1 in [C$_4$mim][BTA], studying reaction time, reaction temperature, carbon monoxide pressure, and ethylene pressure. The conversion of the imine

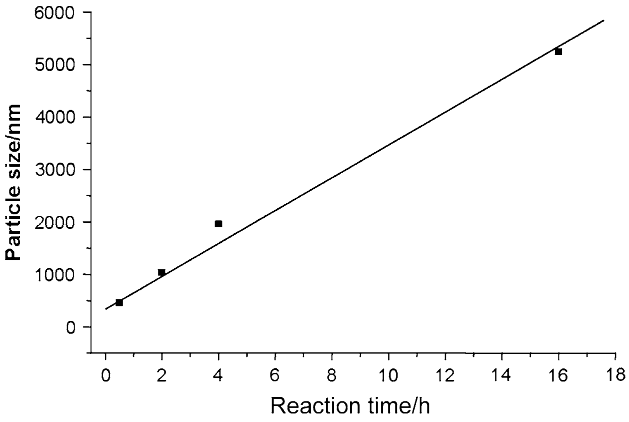

Fig. 2 Formation of ruthenium nanoparticles during the reaction

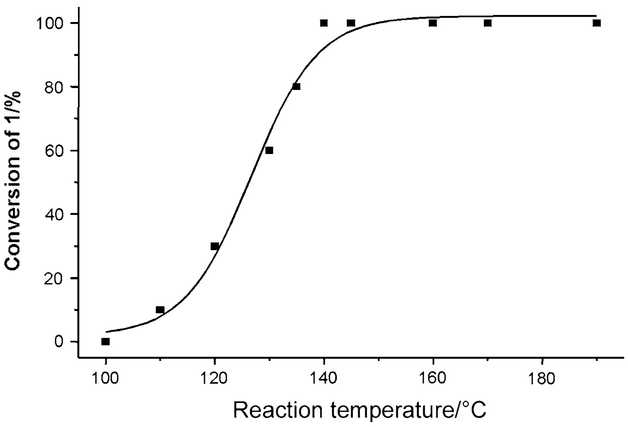

Fig. 4 Dependence of conversion on reaction temperature

to give the products **2** and **3** in all cases led to the same product ratio of 70:30. The optimum reaction conditions in toluene are a reaction time of at least 10 h, a reaction temperature >130 °C, a CO pressure of 12 bar, and a ethylene pressure of 8 bar.

Figure 3 shows the effect of reaction time on the conversion of the imine to **2** and **3**. All reactions were performed at 140 °C, $p(\mathrm{CO}) = 12$ bar and $p(\mathrm{C_2H_4}) = 8$ bar. It can be seen that after 5 h the conversion already reached 100%, meaning that the reaction works substantially faster in [C$_4$mim][BTA] than in toluene.

The results from investigation of the effect of reaction temperature on conversion are depicted in Fig. 4. All reactions were carried out at $p(\mathrm{CO}) = 12$ bar and $p(\mathrm{C_2H_4}) = 8$ bar for 5 h. It can be concluded that below a reaction temperature of 110 °C there is almost no conversion of the imine to the heterocyclic product. At 140 °C the conversion reached 100%. This is identical with the optimum reaction conditions in toluene. So the temperature needed to generate the catalytically active species from the precatalyst $\mathrm{Ru_3(CO)_{12}}$ by means of degrading the cluster core is not affected by the nature of the solvent. This also leads to the observation that prolongation of reaction time at temperatures below 140 °C does not lead to enhanced rates of conversion. Nevertheless, in contrast with the use of organic solvents reaction temperatures can be considerably higher than 140 °C if ionic liquids are used as reaction media. In toluene the amount of decomposition products rises if the temperature is higher than 150 °C. In [C$_4$mim][BTA] the temperature may be as high as 190 °C without any effect on the formation of **2** and **3**. In an additional experiment we were able to show that at 170 °C conversion is already 100% after 4 h.

The effects of the pressure of both gaseous reaction substrates on the conversion of the imine to **2** and **3** are presented in Figs. 5 and 6, respectively. From these results it can be concluded that, despite the comparatively low solubility of carbon monoxide and ethylene in ionic liquids, the partial pressures of carbon monoxide and ethylene may both be reduced to 4 bar in [C$_4$mim][BTA] compared with

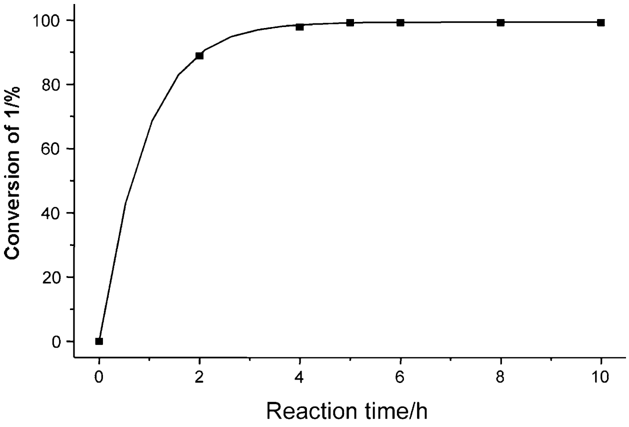

Fig. 3 Dependence of conversion on reaction time

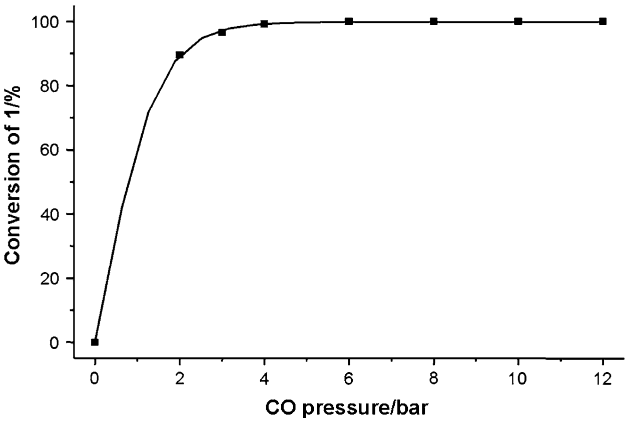

Fig. 5 Dependence of conversion on CO pressure

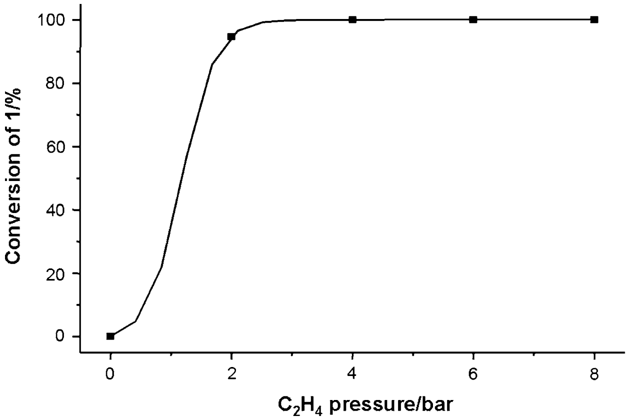

Fig. 6 Dependence of conversion on C_2H_4 pressure

the minimum pressures of 12 bar (CO) and 8 bar (C_2H_4) if the reaction is performed in toluene.

As a control experiment we performed the reaction at 170 °C with $p(CO) = p(C_2H_4) = 4$ bar for 4 h and indeed achieved 100% conversion of the imine to **2** and **3** and a product ratio of 70:30.

Experimental

NMR spectra were recorded on a Bruker AC 200 spectrometer (^{1}H: 200 MHz, ^{13}C: 50.32 MHz, $CDCl_3$ as internal standard). Dynamic light scattering was measured at 25 and 173 °C with a ZetaSizer—Nano (Malvern Instr., Germany) using a He–Ne laser (633 nm) for illumination of the particles. Data were analyzed using the DTS-Nano software package [37]. Ionic liquids were prepared by literature procedures [38] and were dried at 10^{-5} bar at 25 °C for 1 day before use.

In a typical reaction a 50 cm^3 autoclave charged with 145 mg methyl(3-phenylallylidene)amine (1 mmol), 19 mg $Ru_3(CO)_{12}$ (0.03 mmol), and 5 cm^3 of the corresponding ionic liquid was pressurized with carbon monoxide and ethylene and heated. CO pressures of 12, 10, 8, 6, 4, 3, and 2 bar and ethylene pressures of 8, 6, 4, and 2 bar were applied. The reaction temperature was varied between 100 and 190 °C. Reaction times of 10, 8, 6, 5, 4, and 2 h were investigated during which the reaction mixture was vigorously stirred. After the reaction mixture had cooled to room temperature it was transferred to a Schlenk tube and 10 cm^3 anhydrous diethyl ether was added. Complete extraction of the reaction products into the organic phase was achieved by stirring the biphasic mixture at room temperature overnight. After separation of the organic phase from the ionic liquid phase diethyl ether was removed in vacuo and the remaining oily residue was used to determine yields of the products **2** and **3** by NMR spectroscopy. If resonances corresponding to the respective ionic liquid were observed the residue was redissolved in diethyl ether and the solution filtered through silica. After evaporation of the solvent ^{1}H NMR spectroscopy was used to check whether the ionic liquid had been completely removed from the product compounds. Preparative separation of **2** and **3** from the reaction in $[C_4mim][F_3CSO_3]$ was achieved by column chromatography (10 × 2 cm, silica). Using a mixture of light petroleum (b.p. 40–60 °C) and CH_2Cl_2 (v/v 70:30) leads to elution of **3** (81.79 mg, 44.2%), whereas **2** is obtained by using ethanol as eluent (85.18 mg, 42.3%). So, in comparison with the product ratio before separation some of the more polar product **2** was obviously lost during chromatographic work-up.

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