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Enantioselective cyclopropanation reactions in ionic liquids

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Abstract—The benchmark enantioselective cyclopropanation of styrene with ethyl diazoacetate, promoted by two different bis(oxazoline)-copper complexes, is studied in three ionic liquids. The nature of both the anion and cation influence the behaviour of the catalysts, which can be recovered and re-used. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Enantioselective reactions promoted by chiral catalysts constitute a topic of recognised importance in chemical research.¹ In this regard, the search for chiral ligands with broad applicability is a particularly interesting aspect in this field. Bis(oxazolines) are versatile chiral ligands that are able to form complexes with different metals, and these complexes are able promote a variety of organic reactions.² As a consequence, the immobilisation of bis(oxazoline)-based complexes opens the way to obtain recoverable catalysts for a range of reactions.

We have studied the immobilisation of bis(oxazoline)copper catalysts by two different strategies, namely by covalent grafting onto an organic polymer^{3,4} or by ion-pairing with an anionic support.^{4,5} Recently the immobilisation of an aza-bis(oxazoline) by attachment to a soluble organic polymer has been described.⁶ In both cases the immobilisation exerts a significant influence on the outcome of the reaction, particularly the enantioselectivity. The changes observed after the grafting process are due to the modification of the chiral ligand, which is now bonded to a large polymeric 'substituent' whose presence would be expected to modify the conformational preferences and, as a consequence, the relative energies of the different transition states. Electrostatic immobilisation eliminates this drawback because the chiral ligand is not modified; however, the solid counterion has a noticeable influence on the stereochemical course of the reaction.^{7,8} In view of this, the search for immobilisation methods that are able to reduce the influence of the support is an open field of great interest.

Ionic liquids have proven to be excellent solvents for many organic reactions.⁹ In catalysed reactions they allow, in some cases, the catalyst to be re-used after product extraction and, in this way, the use of these solvents can be considered as an immobilisation method without ligand modification. In spite of the fact that this approach is a promising alternative for immobilisation, there are very few examples describing its use in enantioselective reactions promoted by chiral catalysts. Most of these literature examples refer to hydrogenation reactions,¹⁰ although some deal with epoxidation¹¹ or epoxide opening reactions.¹² To the best of our knowledge, there is only a single, unpublished result that deals with the use of this methodology in asymmetric C-C bond forming reactions.^{9d} Herein, we describe the immobilisation of bis(oxazoline)-copper complexes in ionic liquids and the use of these complexes to promote the benchmark cyclopropanation reaction between styrene and ethyl diazoacetate,⁷ a C-C bond forming reaction.

2. Results and discussion

* Corresponding authors. Tel./fax: +34 976 76 20 77 (J.A.M.); tel.: +33 02 99 28 62 74; fax: +33 02 99 28 69 55 (M.V.); e-mail: mayoral@posta.unizar.es; michel.vaultier@univ-rennes1.fr In this study we used three different ionic liquids (Scheme 1), an approach that allows evaluation of the influence of both cation and anion, namely $[\text{Emim}][\text{NTf}_2]$, $[\text{Emim}][\text{BF}_4]$, and $[\text{Oct}_3\text{NMe}][\text{NTf}_2]$



Scheme 1.

(Emim = 1-ethyl-3-methylimidazolium, $Oct_3NMe-NTf_2$ = methyltri-*n*-octylammonium). The catalysts were obtained by treating the chiral bis(oxazoline) ligand with different copper salts, namely $Cu(OTf)_2$ and $CuCl_2$. Most of the catalysts were prepared in dichloromethane, the solvent was evaporated under reduced pressure and the complex was dissolved in the ionic liquid. In some other cases the complex was directly prepared in the ionic liquid and readily used as catalyst. When the complexes were not completely soluble clear bluish–green solutions (except in the case of [Emim][BF₄], as will be commented later) were obtained, after decanting the supernatant solution from the insoluble material.

The results obtained in the cyclopropanation reaction of styrene 1 with ethyl diazoacetate 2 are gathered in

Table 1, along with those obtained using the same catalysts in dichloromethane. It is known^{7,8} that the nature of the copper counterion has a decisive influence on the behaviour of chiral bis(oxazoline)-copper catalysts in cyclopropanation reactions, as shown by the results in entries 1, 2, 7 and 13. It seems logical that in an ionic liquid, the most abundant copper species will bear the counterion of the solvent. This effect is demonstrated by the result obtained with 5a-CuCl₂ in [Emim][NTf₂] (entry 3). Both yield and enantioselectivities are very similar to those obtained with the corresponding triflate in dichloromethane (entry 1) and clearly better than those observed with the same chloride complex (entry 2). This seems to indicate that the active species is 5a-CuNTf₂, obtained by reduction of **5a**-Cu(NT f_2)₂ with ethyl diazoacetate. Thus NT f_2 anion behaves more similarly to triflate than to chloride. This complex dissolved in [Emim][NTf₂] was successfully recycled twice without loss of activity or selectivities (entries 4 and 5). These experiments demonstrate the possibility of easy recycling of these complexes by means of the use of ionic liquids as solvents. Another clear advantage is the possibility of using the inexpensive CuCl₂ instead of the expensive and moisture-sensitive Cu(OTf)₂.

Table 1. The asymmetric cyclopropanation of styrene 1 with ethyl diazoacetate 2 promoted by bis(oxazoline)-copper complexes^a

Ph	+ N 1	₂ CHCOOEt - 2	cat.	R COOEt	Ph 3S R Ph 4S	∆, <i>s</i> COOEt ∆, <i>s</i> COOEt		5a: R = Ph 5b: R = ^t Bu
Entry	Ligand	CuX	Solvent	Run	% Yield ^{b,c}	trans/cis ^b	% E.e. trans ^d	% E.e. cis ^e
1	5a	Cu(OTf) ₂	CH ₂ Cl ₂	1	33	68:32	60	51
2	5a	CuCl ₂	CH ₂ Cl ₂	1	19	67:33	17	13
3	5a	CuCl ₂	[Emin][NTf ₂]	1	34	67:33	55	47
4		_		2	32	66:34	53	45
5				3	33	66:34	53	44
6	5a	CuCl ₂	[Oct ₃ NMe][NTf ₂]	1	18	67:33	49	41
7	5b	$Cu(OTf)_2$	CH ₂ Cl ₂	1	61	71:29	91	88
8	5b	$Cu(OTf)_2$	[Emim][NTf ₂]	1	38	64:36	66	64
9				2	38	64:36	66	64
10				3	37	65:35	64	62
11	5b	$Cu(OTf)_2$	[Emim][BF ₄]	1	3	7:3	0	0
12	5b	$Cu(OTf)_2$	[Oct ₃ NMe][NTf ₂]	1	18	63:37	23	22
13	5b	CuCl ₂	CH ₂ Cl ₂	1	24	7:3	2	7
14	5b	CuCl ₂	[Emim][NTf ₂]	1 ^f	50	62:38	86	85
15		_		2	42	6:4	55	56

^a Using equimolecular amounts of styrene and ethyl diazoacetate and 1% catalyst.

^b Determined by GC.

^c Total conversion of ethyl diazoacetate.

- ^e Determined by GC with a Cyclodex B column; 4S was the major product.
- ^f Catalyst prepared directly in the ionic liquid.

^d Determined by GC with a Cyclodex B column; 3S was the major product.

In order to improve the results, the more efficient bis(oxazoline) $5b^7$ was used. The effect of the copper counterion in this case is more dramatic, as shown by the very different results obtained with triflate and chloride in dichloromethane (entries 7 and 13). This sensitivity is also demonstrated by the modest result obtained with 5b-Cu(OTf)₂ in [Emim][NTf₂] (entry 8), leading to reduced yield and enantioselectivities (64–66% e.e.). The tendency of NTf₂ to reduce the enantioselectivity is the same as that observed with 5a but the magnitude is much more important with 5b. However, this catalyst is fully recovered twice (entries 9 and 10) with the same performance.

In this case, another strategy was used. The relatively long time spent for the preparation of the complex 5b-Cu in dichloromethane and its use as catalyst made us attempt the synthesis of the complex 5b-CuCl₂ directly in [Emim][NTf₂]. With this method fairly good results in yield and enantioselectivities (86% e.e.) were obtained in the first reaction (entry 14). The similarity of the results with those obtained with the triflate in dichloromethane (entry 7) demonstrates the existence of a fast counterion exchange, owing to the very low enantioselectivity obtained with 5b-CuCl₂ (entry 13). Moreover, the similar behaviour of triflate and NTf₂ is again demonstrated. However, this catalyst is not fully recoverable, showing a partial loss of enantioselectivity (entry 15) and leading to results similar to those obtained using the catalyst prepared by the other approach. It is difficult to offer an explanation for these results, which suggest the existence of complex equilibria between different catalytic species. This point deserves further investigation.

In order to test the influence of the anion of the ionic liquid, $[\text{Emim}][\text{BF}_4]$ was used and its behaviour deserves a particular comment. When complexes **5a**-CuCl₂ and **5b**-Cu(OTf)₂ were added to $[\text{Emim}][\text{BF}_4]$ the solutions took a brownish deep red colour with some suspended solid. These suspensions were able to decompose ethyl diazoacetate under the reaction conditions but they were almost inactive for cyclopropanation. Although we cannot yet offer an explanation for this behaviour, the colour change might be caused by the formation of Cu(0) in a redox reaction. The fact that the formation of the red colour occurs prior to the addition of a dismutation from Cu(I).

We also investigated the influence of the cation present in the ionic solvent by using the same complex **5a**-CuCl₂ in $[Oc_3NMe][NTf_2]$. In principle the active species should be the same as in $[Emim][NTf_2]$, but the results (entry 6) are different, with lower yield and slightly lower enantioselectivities. The change of cation noticeably influences the polarity of the ionic liquid, which decreases when the polar character of the cation is decreased.^{9e} In this regard, the use of methyltri-*n*octylammonium instead of 1-ethyl-3-methylimidazolium must reduce the polarity of the reaction medium. It has been described⁸ that the use of less polar solvents increases the strength of the [bis(oxazoline)-Cu]⁺-anion ion pair, which reduces both catalytic activity and selectivity. The use of [Oc₃NMe][NTf₂] with **5b**-Cu(OTf)₂ (entry 12) leads to an even more important reduction in yield and enantioselectivities, which is in agreement with the more important influence of the counterion in the reactions promoted by **5b**-Cu catalysts. Thus not only the counterion but also the solvent properties are important in this system.

3. Conclusions

The results obtained show that ionic liquids are promising tools for the immobilisation of chiral cationic catalysts without modification of the chiral ligand. The fine-tuning of both the coordinating ability of the cation and the polarity of the liquid will allow the optimisation of the behaviour and applicability of these systems.

4. Experimental

4.1. Preparation of the ionic liquids

4.1.1. 1-Ethyl-3-methylimidazolium tetrafluoroborate [Emim][BF₄]. This ionic liquid was prepared according to the method of Suarez et al.¹³ [Emim][Br] (4.40 g, 23.0 mmol) and sodium tetrafluoroborate (2.83 g, 23.0 mmol) were mixed in acetone (25 mL). After stirring the mixture for 24 h, the reaction mixture was filtered through a pad of Celite and acetone evaporated in vacuo. Extraction of the residue with CH₂Cl₂ (50 mL), filtration, evaporation of the solvent under reduced pressure and drying under high vacuum (10⁻² torr) at 50°C for 24 h afforded [Emim][BF₄] as a clear oil (16.9 g, 81%).

4.1.2. 1-Ethyl-3-methylimidazolium bis(trifluoromethyl-sulfonyl)amide [Emim][NTf₂]. This ionic liquid has been obtained according to the procedure of Bonhôte et al.¹⁴ [Emim][Br] (13.16 g, 68.9 mmol) and LiNTf₂ (20.5 g, 68.9 mmol) were mixed in hot water (50 mL at 70°C). Extraction with CH₂Cl₂ (2×50 mL), concentration under reduce pressure and drying under high vacuum (10⁻² torr) at 100°C for 24 h afforded [Emim][NTf₂] (23.9 g, 89%).

4.1.3. Methyltrioctylammonium bis(trifluoromethyl)sulfonylamide [Oc₃NMe][NTf₂]. The same procedure as for [Emim][BF₄] was used: Aliquat[®] 336 (4.04 g, 10 mmol) and LiNTf₂ (1.54 g, 10 mmol) were dissolved in acetone (50 mL) at rt. After stirring the mixture for 24 h, the reaction mixture was filtered through a plug of Celite. The solvent was removed under reduce pressure and the ionic liquid dried under high vacuum (10^{-2}) torr) at 70°C for 24 h giving a clear oil (4.37 g, 85%). ¹H NMR (acetone- d_6 , 300 MHz, δ ppm/TMS): 3.49 (m, 6H), 3.21 (s, 3H), 1.90 (brs, 6H), 1.38 (m, 36H), 0.88 (t, J=6.6 Hz, 9H). ¹³C NMR (acetone, 50 MHz, δ ppm/ TMS): 123.51, 118.52, 92.48, 62.52, 32.59, 32.41, 26.48, 23.30, 23.23, 22.78, 14.32. Positive-ion LSIMS (m/z): 1014.8, 1042.9, 1070.8, 1098.9, 1126.9, 1154.8.

4.2. Preparation of the catalysts

The bis(oxazoline)-copper complexes were prepared by dissolving the copper salt (CuCl₂·2H₂O or Cu(OTf)₂: 0.6 mmol) and the ligand (**5a** or **5b**: 0.6 mmol) in anhydrous dichloromethane (4 mL). After 1 h, the insoluble materials were removed by microfiltration, the solvent was evaporated under reduced pressure and the bluish–green solid was dried under vacuum. A sample of each catalyst (100 mg) was dissolved in the ionic liquid (2 mL). When the complex was not completely soluble, the clear solution was decanted from the solid and used in the cyclopropanation reactions.

In some cases the complex was prepared by dissolving the copper salt (0.038 mmol) and the ligand (0.038 mmol) in the ionic liquid (0.5 mL). The mixture was stirred at rt until a clear pale green solution was obtained. In these cases the catalyst was immediately used in a cyclopropanation reaction.

4.3. Cyclopropanation reaction

To the solution (0.5 mL) of the corresponding supported catalyst (approx. 0.038 mmol) under an Ar atmosphere, styrene (395 mg, 3.8 mmol) was added. Ethyl diazoacetate (433 mg, 3.8 mmol) was slowly added (2 h) using a syringe pump. The reaction was stirred at rt for 5 h ([Emim][NTf₂]) or 20 h ([Oct₃NMe][NTf₂]). After this time the products were extracted with hexane (3×4 mL) and *n*-decane (100 mg) was added to the hexane solution as an internal standard for the GC analysis. The remaining solution of the catalyst in the ionic liquid was reused following the same method.

The results of the reactions were determined by gas chromatography. FID from Hewlett–Packard 5890II; cross-linked methyl silicone column: 25 m×0.2 mm× 0.33 µm; helium as carrier gas, 20 psi; injector temperature: 230°C; detector temperature: 250°C; oven temperature program: 70°C (3 min), 15°C min⁻¹ to 200°C (5 min); retention times: ethyl diazoacetate 4.28 min, styrene 5.03 min, *n*-decane 6.93 min, *cis*-cyclo-propanes **4** 11.84 min, *trans*-cyclopropanes **3** 12.35 min.

The asymmetric inductions of the reactions were also determined by gas chromatography. FID from Hewlett–Packard 5890II, Cyclodex B column: 30 m× 0.25 mm×0.25 µm; helium as carrier gas, 20 psi; injector temperature: 230°C; detector temperature: 250°C; oven temperature program: 125°C isotherm; retention times: (1S,2R)-cyclopropane 4S 28.9 min, (1R,2S)-cyclopropane 4R 29.8 min, (1R,2R)-cyclopropane 3R 34.3 min, (1S,2S)-cyclopropane 3S 34.9 min.

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