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The importance of complex stability for asymmetric copper-catalyzed cyclopropanations in [emim][OTf] ionic liquid: the bis(oxazoline)–azabis(oxazoline) case

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Abstract—Azabis(oxazoline)–Cu complexes are more stable than their analogues based on bis(oxazoline) ligands. This increased stability leads to improved recoverability (up to eight times) when these systems are used in an ionic liquid medium. The solution of the chiral catalyst can even be reused in different enantioselective cyclopropanation reactions and still lead to high enantiomeric excess (>90%).

Enantioselective reactions promoted by chiral catalysts constitute an area of great interest in organic chemistry.[1] The choice between homogeneous and heterogeneous catalysts is a subject of great debate and is influenced by the potential advantages associated with each type of catalyst.

The use of ionic liquids (ILs) offers the possibility of combining the positive aspects of both homogeneous and heterogeneous catalysts. On the one hand, the reaction in the IL takes place in a homogeneous phase with high activity and selectivity. On the other hand, the easy separation of the products after the reaction makes it possible to recover and reuse the catalyst, as in the case of heterogeneous catalysis.[2] Comparatively few of these examples concern the use of chiral catalysts to promote enantioselective reactions and most deal with hydrogenation[3] and oxidation[4] processes. In recent years the use in ILs of catalysts bearing chiral bis(oxazoline) ligands has noticeably increased. These catalysts have been tested in Diels–Alder[5] and, to a greater extent, in cyclopropanation[6,7] reactions. Only the benchmark reaction between styrene and ethyl diazoacetate has been studied and the crucial roles of the IL anion and the presence of impurities have been demonstrated. In spite of the fact that moderate yields and high enantioselectivities have been obtained, catalyst recovery is not problem-free and the recovery process leads to a noticeable reduction in enantioselectivity after the catalyst has been reused no more than twice.

Leaching of the catalyst or ligand from the ionic liquid phase markedly reduces the utility of these solvents in catalytic reactions. In view of this, several authors have designed new cationic ligands in an attempt to increase the solubility of the catalyst in the ionic liquid.[8] However, this strategy has seldom been applied to chiral catalysts.

In the case of bis(oxazoline)–copper catalysts, both the complex and the metal precursor are quite soluble in the ionic liquid and are not leached from this phase. The main problem with these systems arises from the equilibrium between complexed and free ligand. The latter is extracted during the product extraction process and the presence of free copper precursor in the ionic liquid causes a reduction in the enantioselectivity. This effect becomes more pronounced after each recovery cycle (Fig. 1). One option to solve this problem involves

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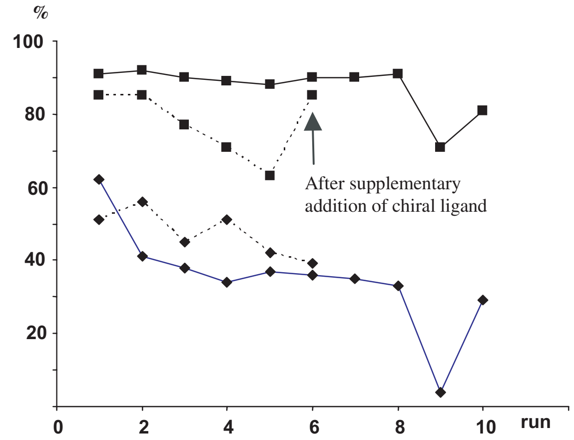


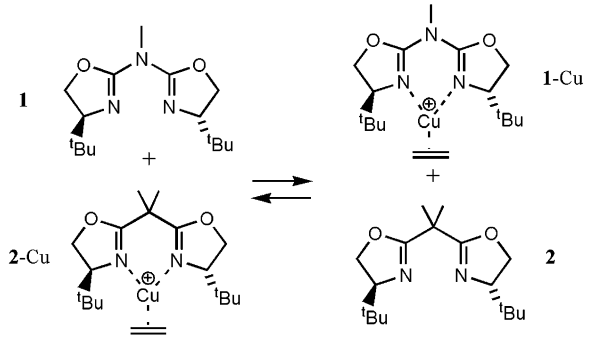
Figure 1. Reuse of the solutions of azabis(oxazoline)–CuCl (**1**-CuCl (—)) and bis(oxazoline)–CuCl (**2**-CuCl (···)) in [emim][OTf]: (■) %ee for *trans* isomers; (◆) %yield.

the addition of a further amount of chiral ligand to the IL solution,[6] as shown in the sixth run with the bis(oxazoline)–copper catalyst in Figure 1. Another possibility is to use an excess of ligand from the outset. However, this is not an ideal solution from the point of view of ligand economy. The introduction of an ionic group into the bis(oxazoline) ligand, in order to increase its solubility in the IL, is not synthetically straightforward and may have unpredictable effects on the enantioselectivity, as demonstrated by the significant reduction in the enantioselectivity observed after modification of a Salen ligand.[9] A more suitable strategy would therefore involve modification of the chiral ligand to increase the binding constant of the complex, but without modifying the structural properties responsible for the enantioselectivity.[10]

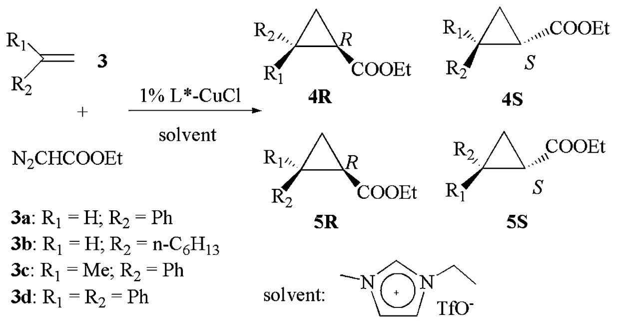
Azabis(oxazoline) ligands (**1**)[11] (Scheme 1) that bear an electron-donating group in the central bridge were envisioned as more coordinating ligands than bis(oxazolines) (**2**), which contain an isopropylidene bridge. Indeed, these ligands led to better results when cationic copper complexes were immobilized onto anionic supports.[12,13] In this communication we describe how the use of azabis(oxazoline) ligands gives rise to improvements in the reusability of chiral cyclopropanation catalysts when used in an IL.

Experimental binding constants are difficult to measure for these copper complexes and so we estimated the relative coordinating ability of the two ligands by theoretical calculations. To this end, we calculated the equilibrium between the bis(oxazoline)–copper complex and free azabis(oxazoline) (Scheme 1), where the copper complexes correspond to the catalytic precursor.[10] Solvent effects are difficult to take into account in ILs. However, in an attempt to gain some insight into the possible effect of solvent on the above equilibrium, we considered the *endo*/*exo* selectivity results of the reaction between cyclopentadiene and methyl acrylate carried out in [emim][OTf].[14] This selectivity has previously been used to define the solvent polarity parameter Ω,[15] which has proven to be mainly related to the solvent dipolarity in the case of aprotic solvents.[16] The Ω value measured in an IL corresponds to a polarity close to that of acetonitrile or nitromethane.[15] We therefore used the dielectric permittivity of acetonitrile to estimate solvent effects.[17] The results obtained show that the equilibrium is shifted to the right-hand side by 5.7 kcal mol^{-1}, which is consistent with a higher coordinating ability of the azabis(oxazoline) ligand.

The copper(I) complexes of *N*,*N*-bis[(*S*)-4-*tert*-butyl-4,5-dihydro-1,3-oxazol-2-yl]methylamine[18] (**1**) and the analogous bis(oxazoline) **2** were tested in the aforementioned benchmark cyclopropanation reaction between styrene (**3a**) and ethyl diazoacetate with [emim][OTf] as the IL solvent (Scheme 2).[19] In a previous study, Cu^{II} complexes were used despite the fact that Cu^{I} is the active species.[10] This modification is due to the higher stability of Cu(OTf)$_2$ in comparison with CuOTf and the role of the counter ion, which precludes the use of CuCl. However, CuCl can be used in the IL because chloride is replaced by the IL counter ion.[6] The advantages of azabis(oxazoline) in comparison with bis(oxazoline) as the chiral ligand are represented in Figure 1. The enantioselectivity is consistently high at 90–92% ee for the *trans* isomer (**4**) in a series of eight reactions and is also stable for the *cis* isomers (**5**) at 82% ee (not shown). The chemical yield decreases from 62% to 40% in the first reuse, but then remains constant in the range 35–40%



Scheme 1. Equilibrium between free and complexed bis(oxazoline) and azabis(oxazoline) ligands.



Scheme 2. Cyclopropanation reactions catalyzed by azabis(oxazoline)–copper and bis(oxazoline)–copper complexes.

up to the eighth reaction. Given that total conversion of ethyl diazoacetate occurs, the decrease in the yield of cyclopropanes is due to an increase in the competitive diazoacetate dimerization and subsequent reactions of the resulting maleate and fumarate. The high molecular weight by-products are probably not extracted completely into the hexane phase and they are then able to poison the catalyst, thus favouring the non-catalyzed dimerization. The recoverability of the azabis(oxazoline)-based catalyst confirms that the copper is more strongly bound to this ligand than to the corresponding bis(oxazoline).

After the eighth reaction, the IL solution containing the chiral azabis(oxazoline)–copper complex was left in the open air for 72h in order to assess its stability. As can be seen from Figure 1, the absorption of moisture due to the hygroscopic character of [emim][OTf] causes a noticeable decrease in both yield and enantioselectivity. The detrimental effect of water has already been described for bis(oxazoline)–copper complexes.[6] This phenomenon was attributed to the competitive coordination of water and chiral ligand, a process that leads to nonchiral catalytic copper centres. This behaviour can be reversed by simply drying the [emim][OTf] solution under vacuum and the change is possibly due to the negligible vapour pressure of the IL. Evidence for this reversibility can be seen from the tenth reaction in Figure 1.

It would be of great interest to ascertain whether the same catalyst solution, which can be considered as a liquid phase-immobilized catalyst, could be used in different cyclopropanation reactions. With this aim in mind, the solution of azabis(oxazoline)-CuCl in [emim][OTf] used in the cyclopropanation of styrene, was recovered and reused in successive cyclopropanations with different alkene substrates; namely 1-octene (**3b**), α-methylstyrene (**3c**) and 1,1-diphenylethylene (**3d**) (Scheme 2). The solution was then finally reused in the reaction with styrene in order to assess its performance in the benchmark reaction initially studied. The results of these experiments are gathered in Table 1. As can be seen, all the yields were acceptable considering that only 1equiv of alkene was used. The only exception involved the use of the aliphatic alkene 1-octene and this is probably due to its lower reactivity. The high enantioselectivity obtained in the five runs is remarkable and values over 90% were routinely obtained even in the final reuse with styrene. Once again, the only exception is 1-octene, which led to a somewhat lower enantioselectivity in the *trans* cyclopropanes (80% ee) but a higher level in the *cis* compounds (98% ee).

Table 1. Recycling of the **1**-CuCl solution in [emim][OTf] for the enantioselective cyclopropanation of different alkenes[a]

Run	Alkene	Yield (%)	**4**/**5**	%ee **4**[b]	%ee **5**[b]
1	**3a**	62	73:27	91	82
2	**3b**	20	71:29	80	98
3	**3c**	44	57:43	91	84
4	**3d**	52	—	92	—
5	**3a**	30	73:27	91	83

[a] Results determined from the hexane extract by gas chromatography on 5% phenylsilicone and cyclodex-B columns.

[b] Compounds **4R** and **5R** were the major enantiomers.

In summary, it has been demonstrated that azabis(oxazolines) have clear advantages over bis(oxazolines) for use as chiral ligands in enantioselective reactions carried out in an IL. These advantages are due to the electron-donating properties of the aza bridge, which increases the stability of the copper complex and improves the reusability of the chiral catalyst solution.

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References and notes

1. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin–Heidelberg, 1999.
2. Wasserscheid, P. In *Ionic Liquids in Synthesis*; Wasserscheid, P., Welton, T., Eds.; Wiley-VCH: Weinheim, 2000; p 213.
3. (a) Chauvin, Y.; Mussmann, L.; Olivier, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2698; (b) Monteiro, A. L.; Zinn, F. K.; de Souza, R. F.; Dupont, J. *Tetrahedron: Asymmetry* **1997**, *8*, 177; (c) Berger, A.; de Souza, R. F.; Delgado, M. R.; Dupont, J. *Tetrahedron: Asymmetry* **2001**, *12*, 1825; (d) Guernik, S.; Wolfson, A.; Herskowitz, M.; Greenspoon, N.; Geresh, S. *Chem. Commun.* **2001**, 2314; (e) Brown, R. A.; Pollet, P.; McKoon, E.; Eckert, C. A.; Liotta, C. L.; Jessop, P. G. *J. Am. Chem. Soc.* **2001**, *123*, 1254.
4. (a) Song, C. E.; Roh, E. *J. Chem. Commun.* **2000**, 837; (b) Song, C. E.; Jung, D.; Roh, E. J.; Lee, S.; Chi, D. Y. *Chem. Commun.* **2002**, 3038; (c) Branco, L. C.; Afonso, C. A. M. *Chem. Commun.* **2002**, 3036.
5. Meracz, I.; Oh, T. *Tetrahedron Lett.* **2003**, *44*, 6465.
6. (a) Fraile, J. M.; García, J. I.; Herrerías, C. I.; Mayoral, J. A.; Carrié, D.; Vaultier, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1891; (b) Fraile, J. M.; García, J. I.; Herrerías, C. I.; Mayoral, J. A.; Gmough, S.; Vaultier, M. *Green Chem.* **2004**, *6*, 93.
7. Davies, D. L.; Kondola, S. K.; Patel, R. K. *Tetrahedron: Asymmetry* **2004**, *15*, 77.
8. (a) Brasse, C. C.; Englent, U.; Salzer, A.; Waffenschmidt, H.; Wasserscheid, P. *Organometallics* **2000**, *19*, 3818; (b) Sirieix, J.; Ossberger, M.; Betzemeier, B.; Knochel, P. *Synlett* **2000**, 1613; (c) Wasserscheid, P.; Waffenschmidt, H.; Machnitzki, P.; Kottsieper, K.; Stelzer, O. *Chem. Commun.* **2001**, 451; (d) Kottsieper, K. W.; Stelzer, O.; Wasserscheid, P. *J. Mol. Catal. A* **2001**, *175*, 285; (e) Brauer, D. J.; Kottsieper, K. W.; Liek, C.; Stelzer, O.; Waffenschmidt, H.; Wasserscheid, P. *J. Organomet. Chem.* **2001**, *630*, 177; (f) Favre, F.; Olivier-Bourbigou, H.; Commereuc, D.; Saussine, L. *Chem. Commun.* **2001**, 1360.
9. Baleizao, C.; Gigante, B.; Garcia, H.; Corma, A. *Tetrahedron Lett.* **2003**, *44*, 6813.
10. Fraile, J. M.; García, J. I.; Martínez-Merino, V.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **2001**, *123*, 7616.
11. Glos, M.; Reiser, O. *Org. Lett.* **2000**, *2*, 2045.

12. Fraile, J. M.; García, J. I.; Harmer, M. A.; Herrerías, C. I.; Mayoral, J. A.; Reiser, O.; Werner, H. *J. Mater. Chem.* **2002**, *12*, 3290.
13. Fraile, J. M.; García, J. I.; Herrerías, C. I.; Mayoral, J. A.; Reiser, O.; Socuéllamos, A.; Werner, H. *Chem. Eur. J.* **2004**, *10*, 2997.
14. Sethi, A.; Welton, T.; Wolff, J. *Tetrahedron Lett.* **1999**, *40*, 793.
15. Berson, J. A.; Hamlet, Z.; Mueller, W. A. *J. Am. Chem. Soc.* **1962**, *84*, 297.
16. (a) Ruiz-López, M. F.; Assfeld, X.; García, J. I.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **1993**, *115*, 8780; (b) Cativiela, C.; García, J. I.; Mayoral, J. A.; Salvatella, L. *J. Chem. Soc., Perkin Trans. 2*, **1994**, 847; (c) Cativiela, C.; García, J. I.; Mayoral, J. A.; Salvatella, L. *Chem. Soc. Rev.* **1996**, *25*, 209.
17. All theoretical calculations were carried out with the GAUSSIAN 03 program at the B3LYP/6-31G*//HF/6-31G* level. Solvent effects were considered through the PCM continuum model.
18. Werner, H.; Vicha, R.; Gissibl, A.; Reiser, O. *J. Org. Chem.* **2003**, *68*, 10166.
19. The complexes were prepared in situ by dissolving CuCl (0.038 mmol) and the ligand (0.038 mmol) in the IL (0.5 mL). The mixture was stirred at room temperature until a clear pale green solution was obtained. To this solution, under an Ar atmosphere, was added styrene (3.8 mmol). In some cases a clear solution was obtained only after the addition of styrene. Ethyl diazoacetate (3.8 mmol) was slowly added (2 h) using a syringe pump. The reaction mixture was stirred at room temperature for 20 h. 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 IL was reused following the same method.