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Improvement of Ligand Economy Controlled by Polymer Morphology: The Case of Polymer-Supported Bis(oxazoline) Catalysts

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Abstract—A functionalized chiral bis(oxazoline) is used as a chiral monomer in polymerization reactions leading to homo- and copolymers of different morphology. Polymers with a high content of chiral monomer lead to enantioselectivities that are higher than those obtained with the soluble ligand, but the chiral ligand is not used in an optimal way. A hyperbranched polymer, obtained by using a hexavinyldendrimer as the cross-linker, leads to the same enantioselectivities with a more efficient use of the chiral ligand. © 2002 Elsevier Science Ltd. All rights reserved.

The development of new heterogeneous catalysts to promote enantioselective organic reactions is an area of great interest given the importance of asymmetric synthesis in the industrial preparation of fine chemicals and specialities.¹ In this context, several strategies for the immobilization of bis(oxazoline)-metal complexes have been developed by our group^{2,3} and other authors.⁴ Immobilization of the cationic complexes by electrostatic interaction with an anionic support does not require modification of the chiral ligand and this process can be carried out very easily,² but there is a limit in the enantioselectivity that can be reached in the benchmark cyclopropanation reaction between styrene and ethyl diazoacetate. In order to overcome this limitation, we explored the immobilization of bis(oxazoline)-copper complexes on organic polymers and found that the best results were obtained with homopolymers.³ In these polymers, however, most of the chiral ligand is occluded in inaccessible parts of the polymer, meaning that only a small proportion of the chiral information is used in the asymmetric reaction. In this paper, we compare homopolymers and different copolymers in order to demonstrate the importance of the correct selection of monomers to improve ligand economy without reduction in catalytic activity and enantioselectivity.

This initial comparison was carried out with derivatives of the cheap methylenebis[(S)-4-phenyl-2-oxazoline]. The complexes with Cu(OTf)₂ were tested in the benchmark cyclopropanation reaction between styrene and ethyl diazoacetate (Scheme 1), one of the reactions in which bis(oxazoline)-copper complexes have led to excellent results in the homogeneous phase.⁵

Double benzylation on the central methylene bridge was easily accomplished with benzyl chloride in the presence of methyllithium, leading to the soluble ligand $\mathbf{6}$ to be



Scheme 1. Cyclopropanation reaction between styrene (1) and ethyl diazoacetate (2).

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Scheme 2. Preparation of homopolymers of bis(oxazoline) and copolymers of styrene and bis(oxazoline).

used for comparison with the immobilized systems. The alkylation with *p*-vinylbenzyl chloride led to the C_2 -symmetric chiral monomer 7, which was subsequently used to prepare different homo- and copolymers. Polymerizations were carried out in the presence of AIBN, following the general protocol developed by Fréchet for the preparation of monolithic resins⁶ (Scheme 2).

Polymers were characterized by both FTIR and Raman spectroscopy⁷ and, in all cases, the bands corresponding to the bis(oxazoline) ligand were observed. Nitrogen analysis indicated the complete incorporation of the bis(oxazoline) into the polymeric network. Catalysts were obtained by treatment of the corresponding polymer with an equimolecular amount of $Cu(OTf)_2$ in methanol, followed by filtration, washing and drying. Table 1 shows the compositions of the different polymerization mixtures, together with the bis(oxazoline) and copper contents of the final polymeric catalysts.

The results obtained indicate that the degree of incorporation of copper noticeably depends on the morphology of the polymer. For example, with the homopolymer prepared in toluene (8) only a very low degree of copper functionalization was obtained, a fact that must be due to the low accessibility of the bis(ox-

Table 1. Immobilized catalysts prepared with Cu(OTf)_2 and the polymers obtained by polymerization of the chiral monomer $7^{\rm a}$

| Polymer | Box (7) | Styrene | Cross- linker | Box (mmol g ⁻¹) | $\begin{array}{c} Cu\\ (mmol \; g^{-1})\end{array}$ | Box/Cu |
|-----------------------|---------|---------|------------------|--------------------------------|---|--------|
| 8 ^b | 100 | _ | _ | 1.85 | 0.01 | 185 |
| 9 | 100 | | | 1.74 | 0.14 | 12.4 |
| 10 | 80 | 20 | | 1.60 | 0.16 | 10.0 |
| 11 | 50 | 50 | _ | 1.49 | 0.09 | 16.5 |
| 12 | 10 | 90 | | 0.56 | 0.39 | 1.6 |
| 13 | 10 | 70 | 20 | 0.60 | 0.19 | 3.2 |
| 14 | 10 | 70 | 20 | 0.37 | 0.18 | 2.1 |
| 15 | 10 | 70 | 20 | 0.50 | 0.04 | 12.5 |
| 16 ^c | 5 | 85 | 10 | 0.21 | 0.08 | 2.6 |

^aPolymerization conditions: at 80 °C using a 60% (w/w) of a mixture toluene/1-dodecanol (1/5, w/w) and 1% AIBN. Treatment with Cu(OTf)₂ in methanol at room temperature for 24 h, followed by filtration, thorough washing with methanol and dichloromethane and drying under vacuum at 60 °C.

^bUsing only 60% (w/w) toluene.

^cIn toluene/dodecanol/DMF (1/4/1).

azoline) groups. The accessibility and, as a consequence, the copper loading were improved when a porogenic mixture of toluene and 1-dodecanol was used, as shown by the higher copper content of polymer **9**. This latter porogenic mixture was therefore used in the preparation of the different copolymers.

Three different copolymers (10–12) were obtained using styrene and the chiral monomer 7 as the cross-linker (Scheme 2). The bis(oxazoline) content of the polymer clearly decreases with the amount of chiral monomer in the polymerization mixture, but at the same time the copper content either remains essentially unchanged (polymers 10 and, 11) or greatly increases (12). These results show that only in the cases where a small amount of chiral monomer is used in the polymerization mixture is most of the bis(oxazoline) accessible for Cu(OTf)₂. The greater flexibility of the less cross-linked polymer may account for this behavior. It seems clear that the use of the chiral monomer as the cross-linker makes most of the ligand inaccessible for copper-complexation, a situation that may be due to the incorporation of the ligand in the inner part of the polymer. Taking this information into account, we tested the incorporation of a different cross-linker into the polymerization mixture (polymers 13–15, Scheme 3). The use of these crosslinkers did not improve the copper functionalization and, in the case of polymer 15, it even had a detrimental effect. It is clear that the nature of the cross-linker is also an important factor and, in view of this, we decided to test a completely new type of cross-linker, namely a dendrimer (polymer 16, Scheme 3).

The use of dendrimers in the synthesis of polymerbound enantioselective catalysts is a field of very recent, but growing, interest.⁸ In general, the chiral ligand occupies a cross-linking position in this kind of polymer, a situation that would be detrimental in our case, as indeed we have seen. On the other hand, to the best of our knowledge, this is the first time that a non-chiral dendrimer has been used as a cross-linker unit in the preparation of a polymer-immobilized chiral catalyst.⁹



Scheme 3. Preparation of copolymers of styrene, bis(oxazoline) and different cross-linkers.

The synthesis of dendrimer 16 was achieved using a convergent methodology to ensure highly pure products. The synthesis required the preparation of a dendron with a hydroxymethyl group at the focal point. This dendron was synthesized by reaction of 3,5-dihydroxybenzyl alcohol with 4-vinylbenzyl bromide (Williamson synthesis). Connection of this unit to the core (1,3,5-trischlorocarbonylbenzene) was performed in the presence of 4-dimethylaminopyridine.¹⁰ This strategy constitutes a very interesting approach, since it allows hyperbranched systems to be obtained with a morphology that is completely different to that obtained with normal cross-linkers. Due to the low solubility of the dendrimer, DMF was added to the porogenic mixture and the amount of cross-linker and chiral monomer was reduced in order to maintain the same cross-linker/ chiral monomer ratio.

All of the polymers (8-16), as well as the analogous homogeneous ligand 6, were tested in the benchmark cyclopropanation reaction (Scheme 1) in order to assess the effect of the polymeric matrix on the catalytic performance in comparison to other cases.¹¹ It is important to note that the ethyl diazoacetate was completely consumed in all the reactions, meaning that the yield in

Table 2. Results obtained from the cyclopropanation reaction between styrene (1) and ethyl diazoacetate (2) catalyzed by polymeric catalysts^{a,e}

| Ligand | Run | Yield (%) ^b | $3+4/Cu^{c}$ | $3+4/box^{c}$ | trans/cis ^b | ee (%) ^d | |
|-----------------------|-----|------------------------|--------------|---------------|------------------------|---------------------|-----|
| | | | | | | trans | cis |
| 6 | 1 | 32 | 3.2 | 3.2 | 71:29 | 50 | 40 |
| 8 ^e | 1 | 28 | 1932 | 10.4 | 66:34 | 61 | 55 |
| 9 | 1 | 40 | 204 | 17.0 | 52:48 | 57 | 53 |
| 10 | 1 | 26 | 54.1 | 5.4 | 57:43 | 56 | 51 |
| 11 | 1 | 18 | 66.8 | 4.0 | 57:43 | 57 | 51 |
| 12 | 1 | 28 | 24.1 | 15.1 | 60:40 | 46 | 42 |
| 13 ^e | 1 | 11 | 19.4 | 6.1 | 71:29 | 18 | 18 |
| 14 ^e | 1 | 32 | 30.4 | 14.5 | 67:33 | 8 | 8 |
| 15 | 1 | 12 | 51.4 | 4.1 | 58:42 | 50 | 46 |
| 16 | 1 | 35 | 184 | 70.8 | 57:43 | 58 | 56 |
| | 2 | 25 | 131 | 50.4 | 58:42 | 52 | 56 |

^aUsing equimolecular amounts of styrene and ethyl diazoacetate. Reaction carried out at room temperature unless otherwise indicated. ^bDetermined by GC. Total conversion of ethyl diazoacetate. ^cmmol/mmol ratio.

^dDetermined by GC. **3R** and **4R** are the major enantiomers. ^eReaction carried out at 60 °C.

cyclopropanes does not provide information about the catalytic activity of the different polymers but does indicate the chemoselectivity of the conversion of the intermediate carbene, either to cyclopropane products or to diethyl maleate and fumarate. Both reagents were used in equimolecular amounts. Although these are not the best synthetic conditions, they were selected to increase the variability in yield and allow a better comparison between the different catalysts. Table 2 gathers the results obtained in these reactions, including the yield in cyclopropanes and the different selectivities. In order to illustrate the principle of ligand economy, the yield is also expressed as mmol of cyclopropanes per mmol of copper and bis(oxazoline) ligand present in the polymeric catalyst.

The two homopolymers (8 and 9) led to very good enantioselectivities, which were even better than those observed with the homogeneous ligand 6, although the trans/cis selectivity was lower. However, polymer 8 showed low catalytic activity and it was necessary to heat the reaction, a fact that is probably due to the low copper content. Copolymers (10-12) show a quite different and characteristic behavior. The efficiency in the use of the chiral ligand was found to increase as the amount of chiral monomer was decreased, showing the same trend as the copper functionalization. However, whereas the trans/cis selectivity remained almost constant, the enantioselectivities were observed to decrease with the content of chiral monomer. The use of an additional cross-linker demonstrated that the nature of this molecule has a crucial influence on the results of the reaction. The polymer obtained with divinylbenzene (13) was not very active and heating at $60 \,^{\circ}\text{C}$ was required. Moreover, the enantioselectivity was very low. The polymer prepared with divinylbenzylpolyethyleneglycol (14) showed similar behavior and led to an even lower enantioselectivity. In contrast, the use of divinylbenzylresorcinol (15) gave rise to a more enantioselective catalyst, but the yield and, as a consequence, the ligand utilization was very low. In fact, all

of the polymers studied are worse than homopolymer **9** with regard to the use of the chiral ligand. It may be speculated that the differences in reactivity of the different monomers might be responsible for this effect.

In contrast to these results, the hyperbranched polymer **16**, which incorporates a dendrimer as the cross-linker, gave yields and enantioselectivities that are comparable to those obtained with homopolymer **9**. In fact this is the only polymer with a low content of chiral monomer that was able to reproduce those results. Therefore, the enantioselectivities obtained with polymers **9** and **16** were similar but **16** gave the highest amount of cyclopropanes per mmol of bis(oxazoline), which represents a significant improvement in the ligand economy in comparison with the other polymeric catalysts. This behavior was essentially retained in a second reaction run with the same polymer.

In conclusion, it has been shown that polymer morphology plays a crucial role in the chemo- and stereoselectivities of enantioselective reactions promoted by chiral catalysts immobilized onto polymeric networks. The use of dendrimers bearing several different vinyl groups as cross-linkers leads to hyperbranched polymers, which in this particular case present the best properties in terms of ligand economy and enantioselectivity.

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References and Notes

1. (a) Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; *Comprehensive Asymmetric Catalysis*. Springer-Verlag: Berlin-Heidelberg, 1999. (b) De Vos, D. E., Vankelecom, I. F. J., Jacobs, P. A., Eds.; *Chiral Catalyst Immobilization and Recycling*. Wiley-VCH: Weinheim, 2000. (c) Chapman, A. G.; Reger, T. S.; Janda, K. D. *Tetrahedron* **2001**, *57*, 4637. (d) Pu, L. *Tetrahedron: Asymmetry* **1998**, *9*, 1457.

2. (a) Fraile, J. M.; García, J. I.; Mayoral, J. A.; Tarnai, T.; Harmer, M. A. J. Catal. **1999**, *186*, 214. (b) Alonso, P. J.; Fraile, J. M.; García, J.; García, J. I.; Martínez, J. I.; Mayoral, J. A.; Sánchez, M. C. *Langmuir* **2000**, *16*, 5607. (c) Fraile, J. M.; García, J. I.; Harmer, M. A.; Herrerías, C. I.; Mayoral, J. A. *J. Mol. Catal. A.* **2001**, *165*, 211. (d) Fernández, A. I.; Fraile, J. M.; García, J. I.; Herrerías, C. I.; Mayoral, J. A.; Salvatella, L. *Catal. Commun.* **2001**, *2*, 165.

3. (a) Fernández, M. J.; Fraile, J. M.; García, J. I.; Mayoral, J. A.; Burguete, M. I.; García-Verdugo, E.; Luis, S. V.; Harmer, M. A. *Topics Catal.* **2000**, *13*, 303. (b) Burguete, M. I.; Fraile, J. M.; García, J. I.; García-Verdugo, E.; Luis, S. V.; Mayoral, J. A. *Org. Lett.* **2000**, *2*, 3905.

4. (a) Orlandi, S.; Mandoli, A.; Pini, D.; Salvadori, P. Angew. Chem. 2001, 113, 2587. (b) Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Pitillo, M. J. Org. Chem. 2001, 66, 3160. (c) Hallman, K.; Moberg, C. Tetrahedron: Asymmetry 2001, 12, 1475. (d) Rechavi, D.; Lemaire, M. Org. Lett. 2001, 3, 2493. (e) Clarke, R. J.; Shannon, I. J. Chem. Commun. 2001, 1936. (f) Taylor, S.; Gullick, J.; McMorn, P.; Bethell, D.; Bulman-Page, P. C.; Hancock, F. E.; King, F.; Hutchings, G. J. J. Chem. Soc., Perkin Trans. 2 2001, 1714. (g) Glos, M.; Reiser, O. Org. Lett. 2000, 2, 3905.

5. Pfaltz, A. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, p 513.

6. (a) Svec, F.; Fréchet, J. M. J. Chem. Mater. 1995, 7, 707.
(b) Svec, F.; Fréchet, J. M. J. Science 1996, 273, 205. (c) Xie, S.; Svec, F.; Fréchet, J. M. J. Chem. Mater. 1998, 10, 4072. (d) Svec, F.; Fréchet, J. M. J. Ind. Eng. Chem. Res. 1999, 38, 34. (e) Hird, N.; Hughes, I.; Hunter, D.; Morrison, M. G. J. T.; Sherrington, D. C.; Stevenson, L. Tetrahedron 1999, 55, 9575.
7. (a) Altava, B.; Burguete, M. I.; García-Verdugo, E.; Luis, S. V.; Vicent, M. J. Tetrahedron 2001, 57, 8675. (b) Altava, B.; Burguete, M. I.; García-Verdugo, E.; Luis, Tetrahedron Lett. 2001, 42, 8459.

8. Oosterom, G. E.; Reek, J. N. H.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 1828 and references cited therein.

9. During the revision of the proofs a paper dealing with the use of a similar immobilization strategy for TADDOL appeared: Sellner, H.; Rheiner, P. B.; Seebach, D. *Helv. Chim. Acta* **2002**, *85*, 352.

10. Davies, P. J.; Grove, D. M.; van Koten, G. Organometallics 1997, 16, 800.

 (a) Altava, B.; Burguete, M. I.; Fraile, J. M.; García, J. I.; Luis, S. V.; Mayoral, J. A.; Vicent, M. J. Angew. Chem., Int. Ed. Engl. 2000, 39, 1503. (b) Breysse, E.; Pinel, C.; Lemaire, M. Tetrahedron: Asymmetry 1998, 9, 897. (c) Altava, B.; Burguete, M. I.; Collado, M.; García-Verdugo, E.; Luis, S. V.; Salvador, R. V.; Vicent, M. J. Tetrahedron 1999, 55, 12897. (d) Altava, B.; Burguete, M. I.; García-Verdugo, E.; Luis, S. V.; Vicent, M. J.; Mayoral, J. A. React. Funct. Polym. 2001, 48, 25.