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Linking Homogeneous and Heterogeneous Enantioselective Catalysis through a Self-Assembled Coordination Polymer

José I. García,* Beatriz López-Sánchez, and José A. Mayoral

Department of Organic Chemistry, Instituto de Ciencia de Materiales de Aragón and
Instituto Universitario de Catálisis Homogénea, Facultad de Ciencias, Calle Pedro
Cerbuna, 12, CSIC-University of Zaragoza, E-50009 Zaragoza, Spain

jig@unizar.es

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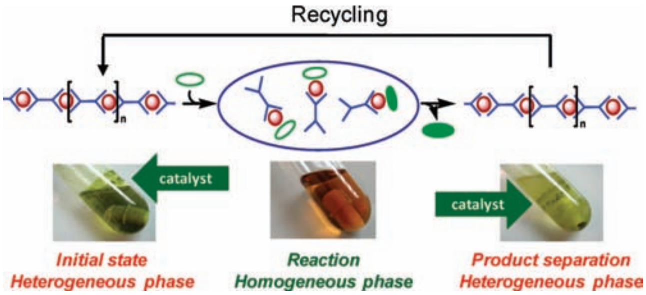
ABSTRACT



Combining the advantages of homogeneous and heterogeneous enantioselective catalysis is possible through self-supported copper coordination polymers, based on a new kind of ditopic chiral ligand bearing two azabis(oxazoline) moieties. When the coordination polymer is used to catalyze a cyclopropanation reaction, it becomes soluble in reaction conditions but precipitates after reaction completion, allowing easy recovery and efficient reuse in the same reaction up to 14 times.

Enantioselective catalysis is one of the most efficient strategies to obtain optically pure compounds[1] and is indeed the way chosen by nature through enzymatic catalysis. Drawbacks of chemical homogeneous enantioselective catalysis are associated with the difficulty in recovery and reuse of the usually expensive catalysts, as well as with product contamination by incomplete separation of the catalyst. Immobilization enantioselective homogeneous catalysts by different methodologies have been carried out to solve these problems.[2] These immobilization strategies are usually based on the formation of strong (covalent or ionic) bonding between the catalyst and heterogeneous support,[2] although weak interactions, as are the cases of adsorption or entrapment strategies, are sometimes enough to achieve the immobilization.[3] A recent variant of these strategies is the self-support of the catalyst by forming insoluble metal-organic frameworks (MOF).[4] In all these cases, catalysis is conducted in the heterogeneous phase. Liquid−liquid biphasic catalysis is another strategy widely used,[5] which

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(1) Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; *Comprehensive Asymmetric Catalysis*; Springer-Verlag: Berlin, 2001.

(2) (a) De Vos, D. E., Vankelecom, I. F. J., Jacobs, P. A., Eds.; *Chiral Catalyst Immobilization and Recycling*; Wiley-VCH: Weinhein, 2000. (b) Heitbaum, M.; Glorius, F.; Escher, I. *Angew. Chem., Int. Ed.* **2006**, *45*, 4732–4762. (c) Fraile, J. M.; García, J. I.; Mayoral, J. A. *Coord. Chem. Rev.* **2008**, *252*, 624–646.

(3) Some examples. Adsorption: (a) Dioos; B. M. L.; Jacobs, P. A. *Appl. Catal., A* **2005**, *282*, 181–188. (b) Choi, S. D.; Kim, G. J. *Catal. Lett.* **2004**, *92*, 35–40. (c) Bianchini, C.; Barbaro, P.; Dal Santo, V.; Gobetto, R.; Meli, A.; Oberhauser, W.; Psaro, R.; Vizza, F. *Adv. Synth. Catal.* **2001**, *343*, 41–45. Encapsulation: (d) Kobayashi, S.; Ishida, T.; Akiyama, R. *Org. Lett.* **2001**, *3*, 2649–2652. (e) Ishida, T.; Akiyama, R.; Kobayashi, S. *Adv. Synth. Catal.* **2005**, *347*, 1189–1192. (f) Yang, H.; Li, J.; Yang, J.; Liu, Z.; Yang, Q.; Li, C. *Chem. Commun.* **2007**, 1086–1088. (g) Yang, H.; Zhang, L.; Zhong, L.; Yang, Q.; Li, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 6861–6865.

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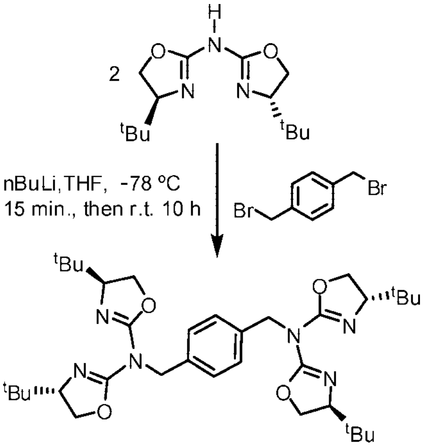
avoids the use of a solid support. However, in general, homogeneous catalysis offers better TON per reaction and frequently better enantioselectivities, so that it still leads in the field of practical applications and new catalyst development.

An attractive possibility is joining the best of both worlds, by applying a release-and-capture mechanism. In this strategy, the catalyst remains immobilized at the beginning and the end of the reaction, when it is in its resting state, so that it can be easily recovered and reused. On the other hand, in the active catalytic phase, the catalyst is dissolved in the reaction medium, so that catalysis is truly homogeneous. An example of this strategy can be found in the microencapsulation strategy, where the whole catalytic complex is entrapped into a flexible polymeric matrix when the reaction is finished, allowing its reuse.[6] Very recently, a new strategy has been described for a nonenantioselective catalyst, based in the use of a self-assembled coordination polymer.[7] Thus, self-supported Grubbs−Hoveyda Ru catalysts have been prepared by formation of a coordination polymer in which specifically modified ligands act as linkers. The resulting coordination polymers are either partially[7a] or totally[7b] soluble in the reaction medium, so that a true homogeneous catalysis for ring-closing metathesis takes place. After addition of ethyl acetate, the polymer becomes insoluble and can be easily separated. However, the recyclability of this catalyst is limited, with progressive loss of activity and metal leaching after each recycling.

In our group, we have followed a parallel research line, trying to find a simple self-supported supramolecular enantioselective catalytic system, easy to obtain and with good catalytic performance and recoverability. In this communication we present our first results concerning this strategy.

To this end, we envisaged the synthesis of a new ditopic chiral ligand, able to form linear coordination polymers, based on the azabisoxazoline (AzaBox) motif, which has been shown to be very efficient for a variety of catalytic enantioselective reactions.[8] The synthesis is based on the classical methodology described by Reiser and co-workers[9] and makes it possible to obtain the new ligand family (DAX, standing for DiAzabisoXazoline) with the same number of synthetic steps used to obtain the AzaBox ligands usually employed in homogeneous catalysis and with good global yields. Scheme 1 displays the ligand synthesis.

Scheme 1. Synthesis of the DAX Ligands



These new ligands combine the high coordinating ability of AzaBox ligands, compared with traditional Box analogs,[10] with the known ability of these kinds of ligands to form 2:1 ligand:metal complexes,[11] necessary to lead to the linear coordination polymer searched.

The next step was to explore the best conditions to form an insoluble coordination polymer with these ligands. Copper was chosen as the metal, due to the high number of enantioselective catalytic applications found for this inexpensive metal. Different copper salts and solvents were tested, and the correct combination of the anion salt and the solvent was found to be critical to obtain the desired self-supported catalysts. Thus, strong coordinating anions, such as chloride, are unsuitable, because they prevent the formation of 2:1 ligand−metal complexes. Strong coordinating solvents, such as acetonitrile or methanol, should also be avoided for the same reason. The best compromise is to use copper salts of weak coordinating anions, such as triflate, together with solvents with low or no coordinating ability, such as dichloromethane, THF, or acetone. For instance, when copper(II) triflate and the corresponding *t*BuDAX ligand are mixed in 1:1 proportion and stirred in dichloromethane, a clear solution is initially formed, but after some time, a precipitate appears, which corresponds in principle to the desired coordination polymer (Scheme 2). However,

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(4) Some recent examples and reviews: (a) Ding, K. L.; Wang, Z.; Shi, L. *Pure Appl. Chem.* **2007**, *79*, 1531–1540. (b) Liang, Y. X.; Wang, Z.; Ding, K. L. *Adv. Synth. Catal.* **2006**, *348*, 1533–1538. (c) Ding, K. L.; Wang, Z.; Wang, X. W.; Liang, Y. X.; Wang, X. S. *Chem. Eur. J.* **2006**, *12*, 5188–5197. (d) Ding, K. L. *Pure Appl. Chem.* **2006**, *78*, 293–301. (e) Wang, X. S.; Wang, X. W.; Guo, H. C.; Wang, Z.; Ding, K. L. *Chem. Eur. J.* **2005**, *11*, 4078–4088.

(5) Cornils, B., Herrmann, W. A., Horvath, I. T., Leitner, W., Mecking, S., Olivier-Bourbigou, H., Vogt, D., Eds.; *Multiphase Homogeneous Catalysis*; Wiley-VCH: Weinhein, 2005.

(6) Cornejo, A.; Fraile, J. M.; García, J. I.; Gil, M. J.; Martínez-Merino, V.; Mayoral, J. A. *Tetrahedron* **2005**, *61*, 12107–12110.

(7) (a) Chen, S. W.; Kim, J. H.; Song, C. E.; Lee, S. G. *Org. Lett.* **2007**, *9*, 3845–3848. (b) Chen, S. W.; Kim, J. H.; Shin, H.; Lee, S. G. *Org. Biomol. Chem.* **2008**, *6*, 2676–2678.

(8) (a) Geiger, C.; Kreitmeier, P.; Reiser, O. *Adv. Synth. Catal.* **2005**, *347*, 249–254. (b) Gissibl, A.; Finn, M. G.; Reiser, O. *Org. Lett.* **2005**, *7*, 2325–2328. (c) Schatz, A.; Scarel, A.; Zangrando, E.; Mosca, L.; Carfagna, C.; Gissibl, A.; Milani, B.; Reiser, O. *Organometallics* **2006**, *25*, 4065–4068. (d) Rasappan, R.; Hager, M.; Gissibl, A.; Reiser, O. *Org. Lett.* **2006**, *8*, 6099–6102. (e) Gissibl, A.; Padie, C.; Hager, M.; Jaroschik, F.; Rasappan, R.; Cuevas-Yanez, E.; Turrin, C. O.; Caminade, A. M.; Majoral, J. P.; Reiser, O. *Org. Lett.* **2007**, *9*, 2895–2898. (f) Fraile, J. M.; García, J. I.; Gissbl, A.; Mayoral, J. A.; Pires, E.; Reiser, O.; Roldán, M.; Villalba, I. *Chem. Eur. J.* **2007**, *13*, 8830–8839.

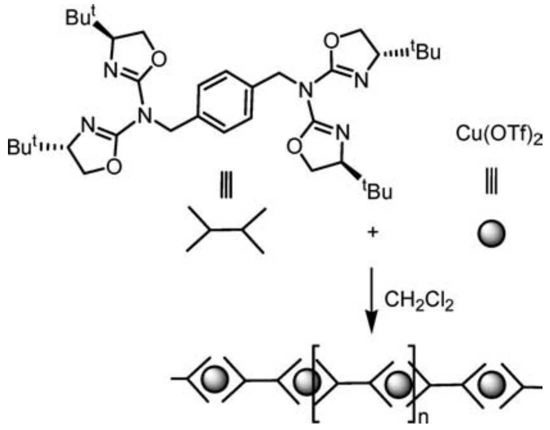
(9) (a) Glos, M.; Reiser, O. *Org. Lett.* **2000**, *2*, 2045–2048. (b) Werner, H.; Vicha, R.; Gissbl, A.; Reiser, O. *J. Org. Chem.* **2003**, *68*, 10166–10168.

(10) Fraile, J. M.; García, J. I.; Herrerías, C. I.; Mayoral, J. A.; Reiser, O.; Socuéllamos, A.; Werner, H. *Chem. Eur. J.* **2004**, *10*, 2997–3005.

(11) See, for instance: (a) Takacs, J. M.; Hrvatin, P.; Atkins, J. M.; Reddy, D. S.; Clark, J. L. *New J. Chem.* **2005**, *29*, 263–265. (b) Atkins, J. M.; Moteki, S. A.; DiMagno, S. G.; Takacs, J. *Org. Lett.* **2006**, *8*, 2759–2762. (c) Zocher, E.; Dietiker, R.; Chen, P. *J. Am. Chem. Soc.* **2007**, *129*, 2476–2481. (d) Zocher, E.; Sigrist, R.; Chen, P. *Inorg. Chem.* **2007**, *46*, 11366–11370.

the supernatant solution remains colored, indicating the residual presence of monomeric or oligomeric complexes in solution.

Scheme 2. Synthesis of the [*t*BuDAX-Cu^{II}] Self-Supported Catalysts



Electrospray ionization mass spectrometry (ESI-MS) experiments could be conducted with a methanolic solution containing *t*BuDAX and Cu(BF$_4$)(CH$_3$CN)$_4$. Figure 1 shows one of these spectra, where the presence of 1:1 [*t*BuDAX-Cu^I] complexes (or their corresponding *n*:*n* oligomers) is clearly detected as the major species. Other relevant species, such as 2:1 [DAX-Cu^I-DAX] and 1:2 [Cu^I-DAX- Cu^I], illustrates the aggregation of the ligand and the metal, pointing to an easy formation of the coordination polymer in the adequate conditions.

It is clear that if the self-supported [DAX-Cu] complex was too strong, it would be either a heterogeneous catalysts or catalytically inactive (most probably the latter, given that the coordination sphere of the metal is complete with the AzaBox ligands). Therefore, in order to have an operative release-and-capture mechanism, a stronger complex must be formed during the catalytic cycle, disappearing after reaction completion. Carbene ligands are strong coordinating species, and therefore, reactions involving a metal-carbene intermediate, such as cyclopropanation[12] are, in principle, good candidates to be tested with these catalysts. We therefore tested the [*t*BuDAX-Cu^{II}] and [*t*BuDAX-Cu^I] self-supported catalysts in the cyclopropanation reaction of styrene with ethyl diazoacetate in dichloromethane (Scheme 3).

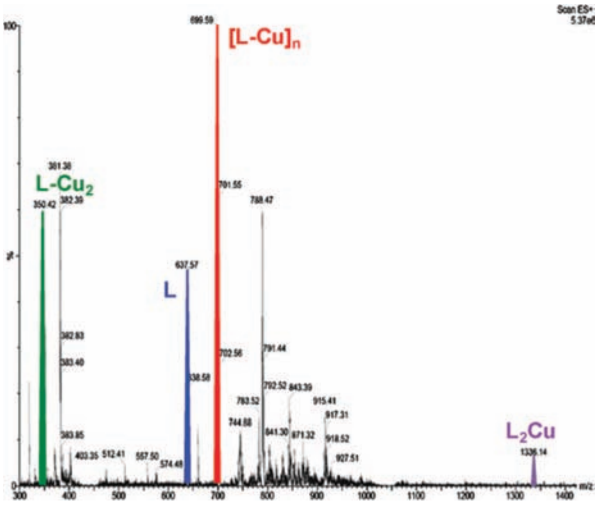


Figure 1. ESI-MS spectrum of a methanolic solution of the [*t*BuDAX-Cu(BF$_4$)(CH$_3$CN)$_4$] complex.

Both [*t*BuDAX-Cu(OTf)$_2$] and [*t*BuDAX-Cu(OTf)] coordination polymers are insoluble in dichloromethane and also in a dichloromethane solution of styrene, but as soon as the diazo compound is added to the medium, the coordination polymer disappears, and a clear, homogeneous solution is obtained. The catalytic reaction takes place, therefore, in homogeneous phase. It is worth noting that the enantioselectivity observed both for *trans*- and *cis*-cyclopropanes is better than that obtained with the conventional *t*BuAzaBox ligand in similar homogeneous phase conditions (97% vs 92% ee in *trans*-cyclopropanes and 92% vs 84% ee in *cis*-cyclopropanes). This fact seems to be connected with the substitution pattern of the imino bridging group, benzylic substitution leading to better enantioselectivities than the usual methyl substitution, a fact already noticed in the case of AzaBox ligands immobilized on Merrifield resins.[13]

To our delight, when the diazocompound is consumed, the coordination polymer is again formed and appears as a solid precipitate in the reaction medium, so it is easily separated from the products. Two different workup procedures were tested. In the first one, after taking the supernatant dichloromethane solution out with a syringe, the precipitated coordination polymer was simply washed and reused in further experiments. In the second one, most of dichloromethane was first evaporated, and then the residual reaction medium washed several times with *n*-hexane. In these conditions, products are extracted in the *n*-hexane solution, whereas the catalyst remains as a precipitate in the bottom of the reactor, allowing reuse in further reactions (see graphical abstract pictures). Figure 2 displays the catalytic results obtained in successive reuses of the same catalyst sample using the two above-described recovery procedures. As can be seen the Cu^{II} catalyst could be reused five times with results superior to those obtained with the *t*BuAzaBox ligand. Only in the sixth use the enantioselectivities decrease

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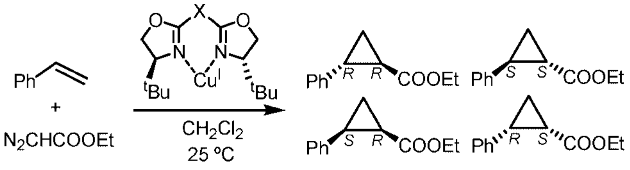
[12] For mechanistic studies highlighting the Cu-carbene mechanism in cyclopropanation reactions, see: (a) Fraile, J. M.; García, J. I.; Martínez-Merino, V.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **2001**, *123*, 7616–7625. (b) Straub, B. F.; Hofmann, P. *Angew. Chem. Int. Ed. Engl.* **2001**, *40*, 1288–1290. (c) Rasmussen, T.; Jensen, J. F.; Èstergaard, N.; Tanner, D.; Ziegler, T.; Norrby, P.-O. *Chem. Eur. J.* **2002**, *8*, 177–184. (d) Straub, B. F.; Gruber, I.; Rominger, F.; Hofmann, P. *J. Organomet. Chem.* **2003**, *684*, 124–143. (e) Fraile, J. M.; García, J. I.; Gil, M. J.; Martínez-Merino, V.; Mayoral, J. A.; Salvatella, L. *Chem. Eur. J.* **2004**, *10*, 758–765. (f) Dai, X.; Warren, T. H. *J. Am. Chem. Soc.* **2004**, *126*, 10085–10094. (g) García, J. I.; Jiménez-Osés, G.; Martínez-Merino, V.; Mayoral, J. A.; Pires, E.; Villalba, I. *Chem. Eur. J.* **2007**, *13*, 4064–4073.

[13] (a) Werner, H.; Herrerias, C. I.; Glos, M.; Gissibl, A.; Fraile, J. M.; Perez, I.; Mayoral, J. A.; Reiser, O. *Adv. Synth. Catal.* **2006**, *348*, 125–132. (b) Fraile, J. M.; Pérez, I.; Mayoral, J. A.; Reiser, O. *Adv. Synth. Catal.* **2006**, *348*, 1680–1688.

Scheme 3. Benchmark Cyclopropanation Reaction



to values close to the homogeneous catalysis with the conventional *t*BuAzaBox ligand.

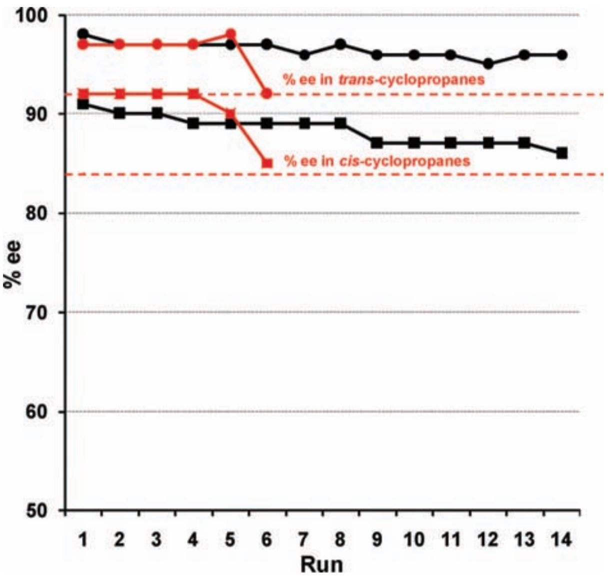


Figure 2. Recycling experiments with the [*t*BuDAX-Cu(OTf)$_2$] (red lines) and [*t*BuDAX-Cu(OTf)] (black lines) catalysts. Circles correspond to *trans*-cyclopropanes and squares to *cis*-cyclopropanes. 1*R*-Cyclopropanes are the major enantiomers. Enantioselectivities obtained with the conventional [*t*BuAzaBox-Cu^{I}] homogeneous catalyst are shown as red dashed lines for comparison.

Given the small amount of catalyst used in these experiments (ca. 10 mg, 1 mol %) and the partial solubility of small amounts of complex in CH_2Cl_2, it is inevitable that a progressive loss occurs in the washing and recovering procedures, so that after the six reactions, the remaining self-supported catalyst is hardly manageable. On the other hand, with the second workup procedure, used with the Cu^{I} catalyst, the recovery is more efficient, and the same catalytic sample could be used up to 14 times with only a slight decrease in the enantioselectivity of the minor *cis*-cyclopropanes but a rather constant enantioselectivity in the major *trans*-cyclopropanes. Yields are also maintained in a range of 55−75% (55% in the first run and 58% in the 14th run), which are quite good, given that a 1:1 styrene/diazocompound proportion is used. In this case, the catalyst precipitate is clearly visible after 14 runs, indicating the negligible loss of catalyst in each recovery. Finally, *trans*/*cis* diastereoselectivities are also in the normal range (from 75:25 to 67:33) described for homogeneous catalysis with similar catalytic systems.

In conclusion, we have designed a new type of self-supported enantioselective catalyst, based on a new ditopic chiral ligand, allowing a release-and-capture strategy of homogeneous catalysis and heterogeneous recovery by formation of an insoluble coordination polymer in the reaction medium. This catalytic system gathers the advantages of easy ligand synthesis (same synthetic steps and efficiency than the chiral ligand used in conventional homogeneous catalysis) and simple and efficient recovery and reuse, making it superior to other previously described systems also based on metal-organic self-assembly. The self-supported catalyst has been successfully tested in the enantioselective catalytic cyclopropanation reaction of styrene with ethyl diazoacetate, leading to excellent enantioselectivities, and allowing up to fourteen uses of the catalyst without significant loss of activity or selectivity (and probably more reuses could be possible, in the light of results described). These results open the door to new families of self-supported enantioselective catalysts, either purely heterogeneous or homogeneous/heterogeneous, as the case described in this paper. Work in the design and synthesis of new polytopic chiral ligands and catalytic systems, optimization of the recovery procedures, as well as applications to other enantioselective reactions are currently in progress, and will be reported in due time.

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Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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