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# Polymer-Supported Bis(oxazoline)–Copper Complexes as Catalysts in Cyclopropanation Reactions

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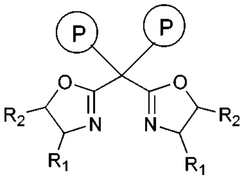
## ABSTRACT



**Bis(oxazolines) are easily immobilized by functionalization of the central methylene bridge with polymerizable groups and subsequent polymerization. Polymers are transformed into copper catalysts active in the cyclopropanation of styrene with ethyl diazoacetate. The results are similar or even better than those obtained with the similar homogeneous systems, and the catalysts can be easily recovered and reused. The substitution in the methylene bridge leads to a slight reduction in the enantioselectivity and an unexpected *cis*-preference.**

Enantioselective reactions promoted by chiral catalysts is a topic of known importance in chemical research.[1] The development of heterogeneous catalysts able to promote enantioselective organic reactions is an area of growing interest due to the inherent advantages of heterogeneous over homogeneous catalysts.[2,3]

Bis(oxazolines) are well-known chiral ligands with numerous variations of substituents and which form complexes with a variety of metals. This system has been used in a large number of asymmetric reactions,[4] and as a consequence, the development of efficient methods to immobilize this type of chiral ligand will open the way to the preparation of chiral heterogeneous catalysts for those enantioselective reactions.

Different strategies and supports can be used for the

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immobilization process, and it has to be taken into account that the methodology can have a definite effect on the activity and selectivity of the resulting catalysts.[5]

We have shown that bis(oxazoline)−Cu(II) complexes can be immobilized by formation of ion pairs with anionic solids[6] and that the solids obtained promote enantioselective cyclopropanation reactions. Whereas the immobilized 2,2′-isopropylidenebis[(4*R*)-4-phenyl-2-oxazoline]−Cu(II) complex is stable, leads to good results, and can be reused, the steric interactions with the support limit the applicability of this strategy to immobilize the 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline].

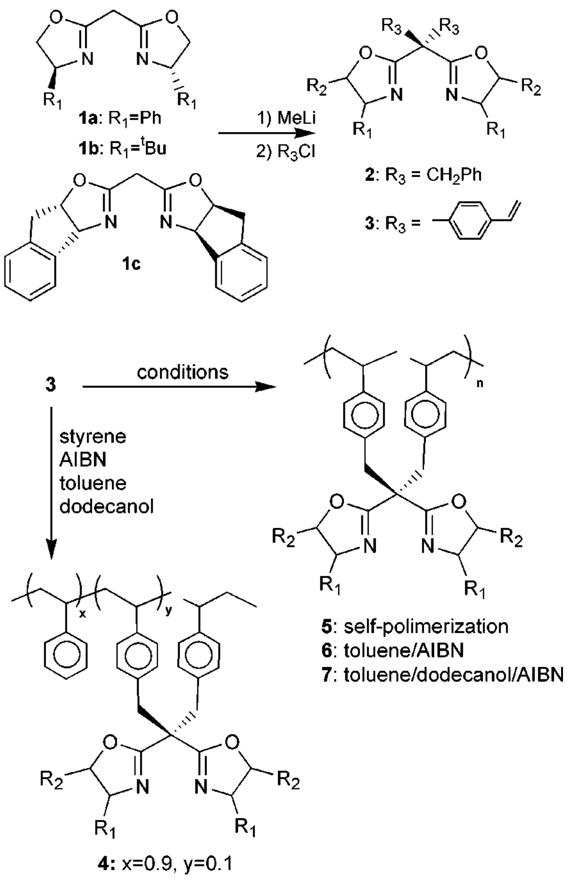
Very recently a family of related chiral ligands, aza-bis(oxazolines), has been described.[7] These ligands can be attached to soluble polymeric supports, forming soluble catalysts which can be recovered by precipitation. The utility of this strategy has been demonstrated also in enantioselective cyclopropanation reactions.

In this Letter, we present the first results on the immobilization of bis(oxazoline)−Cu(II) complexes by formation of covalent bonds between the ligand and an organic polymer and the use of these solids as insoluble catalysts in enantioselective cyclopropanation, one of the reactions in which these ligands form excellent catalysts in the homogeneous phase.[8]

Different strategies of covalent bonding of the bis(oxazoline) to a polymeric support were initially tested with a ligand bearing phenyl groups (**1a**).

Double alkylation in the methylene bridge was carried out with methyllithium in THF as a base (Scheme 1). In this way the model ligand **2a** for a homogeneous test was prepared. In the preparation of polymer-supported enantioselective catalysts, polymerization was shown to provide, in some cases, advantages over grafting.[5b,9] Dialkylation with *p*-vinylbenzyl chloride led to **3a** which was used in different polymerization processes. The use of this monomer was considered advantageous with regard to the $C_2$ symmetry of the chiral ligand.[10] This monomer was used in a copolymerization process with styrene using AIBN as a radical initiator and 1-dodecanol/toluene as the porogenic mixture (polymeric ligand **4a**) using the general protocol for the preparation of the monolithic resins developed by Fréchet.[11]

**Scheme 1**



It was also used in three different homopolymerization processes: in the first one the monomer is left to polymerize thermally (ligand **5a**) and in the second and third ones AIBN was used to initiate the reaction and toluene (ligand **6a**) or a mixture of 1-dodecanol/toluene (ligand **7a**) was used as porogenic agent.

All the polymers showed the FT-IR bands corresponding to the bis(oxazoline) ligand, mainly the C=N band at ca. 1655 $cm^{-1}$. The polymeric catalysts were obtained by treatment of resins **4**−**7** with $Cu(OTf)_2$, and the copper contents were determined by plasma emission spectroscopy.

The solids were tested as catalysts in the cyclopropanation reaction of styrene and ethyl diazoacetate in equimolecular amounts (Scheme 2). Table 1 compares the results obtained with the homogeneous and the different polymeric catalysts. The solid obtained by copolymerization with styrene **4a**

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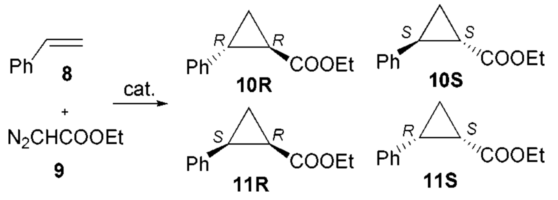
**Scheme 2**



(entries 2 and 3) leads to results close to those obtained with the homogeneous catalyst (entry 1) and the most significant difference is the reduction in *trans*/*cis* selectivity. Interestingly, the results obtained with the homopolymers depend on the method of preparation. With the homopolymer obtained by thermal polymerization, **5a** (entries 4 and 5), both yield and enantioselectivity are higher than those obtained with the copolymer **4a** and with the homogeneous catalyst **2a**, despite a lower amount of catalyst being used. However, the *trans*/cis *selectivity* is reduced, showing a slight preference for the *cis* isomer. This illustrates the very important role that the polymeric matrix can play in the stereochemical outcome of reactions in using polymer-supported species.[12] With the homopolymer prepared using toluene as the porogenic agent **6a** (entries 6 and 7), it was necessary to heat the reaction to obtain a noticeable transformation yield. This can be related to the very low amount of copper introduced. Most likely, this is a result of the low accessibility of the bis(oxazoline) groups that, according to the divinylic nature of **3**, must be located in highly cross-linked regions. The use of toluene as a porogen produces, in general, polymer networks of high surface area and small porosity (low pore size distribution).[11] Despite the higher reaction temperature, the enantioselectivity is better than that obtained with **5a**. As shown in entries 2−7, the immobilized catalysts are very easily recovered by filtration and washing in the open air. In fact, the catalyst obtained from polymer **5a** can be recovered 5 times with final deactivation due to the presence of byproducts from ethyl diazoacetate. These products are detected by IR spectroscopy, because of the presence of an intense band at 1739 cm$^{-1}$ in the used catalyst. Ester groups from diethyl maleate or polymeric products can form chelate complexes with copper.

To improve the accessibility to the reactive sites, a porogenic mixture of 1-dodecanol/toluene was used. The resulting resin **7a** showed an increase in the copper loading and a higher catalytic activity (entries 8 and 9). The enantioselectivity is similar to that obtained with **6a** although the catalyst is not fully recoverable, probably due to pore blocking by polymeric byproducts derived from ethyl diazoacetate. It is worth noting that the stereoselectivity obtained with **7a** is higher than that shown by the homogeneous analogue. This is one of the very first examples in which the polymeric network plays a positive effect on the enantioselectivity of the reaction. Most often the immobilization process is accompanied by a decrease of the enantioselectivity.[13]

The results obtained with the bis(oxazoline) bearing phenyl groups show that the best enantioselectivity is obtained with the homopolymers. Therefore, the same strategy was used to immobilize two different bis(oxazolines), namely, those bearing *tert*-butyl (**1b**) and indan (**1c**) groups. The results are gathered in Table 1.

Surprisingly, the homogeneous catalyst obtained from **2b** leads to a clear *cis* preference (entry 10), whereas the bis(oxazoline) with an isopropylidene bridge gives rise to about 72/28 *trans* preference.[8,14] This is the first *cis* preference described for a bis(oxazoline)−copper catalyst in solution and shows that the substitution in the methylene bridge has a noticeable influence on the stereochemical course of the

**Table 1.** Results Obtained from the Cyclopropanation Reaction between Styrene (**8**) and Ethyl Diazoacetate (**9**) Catalyzed by the Immobilized Catalysts[a]

| entry | ligand | Cu (mmol/g) | **9**/Cu | run | yield (%)[b] | *trans*/*cis*[b] | % ee (*trans*)[c,d] | % ee (*cis*)[c,e] |
|---|---|---|---|---|---|---|---|---|
| 1 | **2a** | | 10 | 1 | 32 | 70/30 | 50 | 40 |
| 2 | **4a** | 0.39 | 185 | 1 | 28 | 60/40 | 46 | 42 |
| 3 | | | | 2 | 24 | 60/40 | 43 | 41 |
| 4 | **5a** | 0.21 | 330 | 1 | 45 | 47/53 | 51 | 52 |
| 5 | | | | 2 | 39 | 46/54 | 50 | 52 |
| 6 | **6a** | 0.01 | 6900 | 1 | 28[f] | 66/34 | 61 | 55 |
| 7 | | | | 2 | 27[f] | 64/36 | 58 | 52 |
| 8 | **7a** | 0.14 | 510 | 1 | 40 | 53/47 | 57 | 53 |
| 9 | | | | 2 | 20 | 53/47 | 47 | 50 |
| 10 | **2b** | | 50 | 1 | 46 | 32/68 | 70 | 79 |
| 11 | **5b** | 0.13 | 490 | 1 | 51 | 35/65 | 75 | 72 |
| 12 | | | | 2 | 56 | 37/63 | 74 | 70 |
| 13 | **6b** | 0.07 | 910 | 1 | 34 | 39/61 | 77 | 73 |
| 14 | | | | 2 | 36 | 39/61 | 77 | 73 |
| 15 | **7c** | 0.03 | 2630 | 1 | 35 | 44/56 | 69[g] | 75[h] |
| 16 | | | | 2 | 22[i] | 44/56 | 69[g] | 75[h] |

[a] Using equimolecular amounts of styrene and diazoacetate, at room temperature. Results after 24 h. [b] Determined by GC. Total conversion of ethyl diazoacetate. [c] Determined by GC with a Cyclodex-B column. [d] **10S** is the major isomer. [e] **11S** is the major isomer. [f] At 60 °C. [g] **10R** is the major isomer. [h] **11R** is the major isomer. [i] After 36 h.

reaction. In fact, the enantioselectivity is reduced in comparison with that described for the bis(oxazoline) with an isopropylidene bridge.[14] It is important to note that the changes in *trans*/*cis* and enantioselectivities are, from an energetic point of view, of the same order of magnitude (about 1 kcal/mol). This change from *trans* to *cis* selectivity with copper catalysts had been described with clays exchanged with Cu(II)[15] and bis(oxazoline)−Cu(II) complexes.[6]

The homopolymers obtained by thermal polymerization, **5b** (entries 11 and 12), and with AIBN, **6b** (entries 13 and 14), were compared. The first one was able to coordinate a larger amount of copper, and as a consequence it was more active. However, the differences are not so noticeable as in the case of the bis(oxazoline) bearing phenyl groups, **5a** and **6a**. Both solids are very good catalysts, leading to similar or even better results than the homogeneous ligand **2b**, especially taking into account the high **9**/Cu ratio used. It is remarkable that both catalysts, obtained from **5b** and **6b**, can be easily recovered and reused, with the same activity and selectivity, by filtration in the open air.

To demonstrate the generality of this methodology of immobilization by homopolymerization, we have applied it also to the bis(oxazoline) derived from indan **7c** (entries 15 and 16). In this case the homopolymer prepared with AIBN/1-dodecanol/toluene showed a catalytic activity similar to that of the other homopolymers and selectivities comparable to those obtained with the ligand bearing *tert*-butyl groups. A slight *cis* preference is again observed. The catalyst can be also recovered and reused without loss of enantioselectivity.

Finally, both yield and recovery can be improved by changing the reaction conditions. The use of a 5-fold excess of styrene leads to better yields, namely, 65% with **5a**, 58% with **7a**, and 76% with **5b**. The recovery of **7a** and **5b** is complete until the fifth reaction, whereas when equimolecular amounts of both reagents are used, **7a** cannot be efficiently recovered more than three times.

In conclusion, the homopolymerization of chiral bis(oxazolines) functionalized in the methylene bridge is an easy and general strategy to immobilize these ligands and to obtain insoluble and easily recoverable enantioselective catalysts. Changes in the polymerization conditions that affect to the morphology of the polymer have important effects on the activity and the selectivity of the catalysts. The corresponding chiral heterogeneous catalysts are even more enantioselective than their homogeneous counterparts in cyclopropanation reactions. Although higher enantioselectivities have been described with soluble catalysts, the reduction in the enantioselectivity is not due to the immobilization process but to the nature of the functional groups in the methylene bridge of the ligand. This modification has also a unexpected influence on the *trans*/*cis* selectivity and allows one to obtain the highest *cis* preference described for a homogeneous bis(oxazoline)−copper catalyst. Further work is in progress to optimize the activity and enantioselectivity of the catalysts.

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**Supporting Information Available:** Experimental procedures and spectra of the new ligands. This material is available free of charge via the Internet at http://pubs.acs.org.

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