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Bis(oxazoline)-Based Coordination Polymers: A Recoverable System for Enantioselective Henry Reactions

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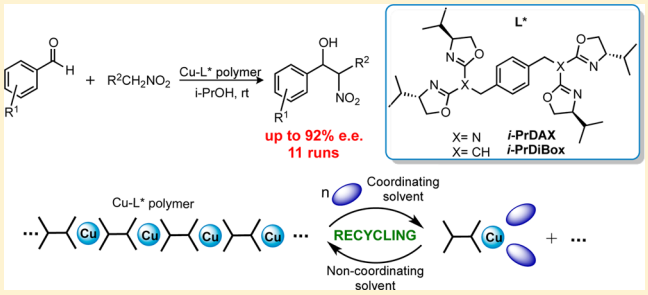
Supporting Information

ABSTRACT: An efficient release−capture strategy for the recovery and reuse of enantioselective catalysts in the Henry reaction is described. This strategy is based on the precipitation of an insoluble coordination polymer at the end of each reaction, allowing easy separation from products. The coordination polymer is formed through aggregation of Cu(II) ions with ditopic bisoxazoline-based chiral ligands. Up to 11 catalytic cycles have been conducted keeping good yields and enantioselectivities.



INTRODUCTION

In the past decade, a growing interest has been raised on the recycling and reuse of enantioselective catalysts, using a variety of strategies.[1−6] Enantioselective catalysts are usually expensive and often bear toxic metals. Therefore, easy separation from reaction products and reuse in consecutive catalytic runs has become an interesting goal from both academic and industrial points of view.[7] Although immobilization through covalent bonding has traditionally been one of the preferred strategies for immobilization of chiral catalysts, it presents some disadvantages, such as the necessity of functionalization of the chiral ligand, which may affect to the activity and selectivity of the final catalysts, and the effect introduced by the support.[8] The latter often results in lower activities and enantioselectivities. Noncovalent immobilization strategies, like entrapment, ionic exchange, or adsorption, avoid the chemical modification of the chiral ligand but still introduce the perturbation of the support on the reactive system.[5,6] Liquid−liquid biphasic systems lack, in principle, these drawbacks, but it is not always possible to find two immiscible liquid phases compatible with the catalytic requirements, i.e., lack of chemical interference with catalyst and/or reagents, solubility of the catalyst only in one phase, and reagents and products preferably in the other, etc.[1,9] Clearly, the least perturbation would take place if the reaction was carried out in the homogeneous phase, and then the catalyst could be selectively precipitated. This would allow an easy separation and further recycling. This goal can be accomplished through different strategies, including among others linking of the chiral ligand to a soluble polymer,[4] or self-supporting of the catalytic complex through hydrogen bonding[10,11] or coordination polymerization.[12,13] In most cases, the selective precipitation of the catalyst takes place by addition of a suitable cosolvent at the end of the reaction.

Our group has recently described a new family of polytopic chiral ligands, based on the oxazoline moiety, able to form coordination polymers insoluble in low polar, noncoordinating solvents. These polymers can therefore be selectively precipitated at the end of the reaction simply by evaporation of the reaction solvent and addition of hexane. The reaction products are then extracted and the catalyst can be easily reused. We have described the application of this release-capture strategy to the cyclopropanation reaction of alkenes with ethyl diazoacetate,[14,15] and to the allylic oxidation of cycloalkenes with peroxoesters.[16] As this is a relatively new strategy, we are interested in testing its scope and applicability to a variety of catalytic reactions, preferably with different reaction mechanisms.

The Henry or nitroaldol reaction is an attractive C−C bond-forming reaction in which a nitroalkane compound is added to an aldehyde or ketone to give primarily a 1,2-nitro alcohol, which may be subsequently transformed in a variety of functional groups, such as amine, carbonyl, carboxyl, azide, etc. In many of these transformations, the stereogenic centers formed in the addition reaction are kept, so enantioselective versions of this reaction have been developed on the basis of the use of chiral catalysts.[17,18] Although the use of organocatalysts has been reported,[19,20] most of the chiral catalysts used are based on coordination complexes of transition metals or lanthanides with chiral ligands.[17,18,21] Recent examples can be found using lanthanides,[22] zinc,[23,24] cobalt,[25,26] or chromium,[27,28] but undoubtedly copper continues to be the preferred metal.[21,29−32] Concerning the chiral ligands, since the pioneering work of Jørgensen[33,34] and Evans,[35] the bis(oxazoline) family of ligands has become quite popular because of its easy availability and the good results reported.[36−38]

Several recoverable enantioselective catalysts have been recently described for the Henry reaction, mainly based on

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three of the aforementioned strategies. Covalent bonding to a support[22,39] has been described using silica as supports. Only four catalytic cycles (so three recoveries) have been carried out with these supported catalysts, with varied results. In the first case,[22] only ca. 65% ee could be achieved at −44 °C, whereas in the second one,[39] high enantioselectivities only could be reached by using 10 mol % of catalyst and 25 mol % of a chiral additive in the homogeneous phase, which makes the recovery procedure less attractive. Biphasic catalytic systems described to date are based on the use of ionic liquids. Thus, the use of a chiral diamine−$Cu(OAc)_2$ complex[40] allowed up to five catalytic cycles with ca. 80% yield and 88% ee at 0 °C and using 12 mol % of catalyst. Better results have recently been described by using imidazolium-tagged bis(oxazolines).[41,42] Up to 12 catalytic cycles were conducted in the best case, at 0 °C and using 14 mol % catalyst, keeping enantioselectivities around 90% ee and yields around 50%. The last strategy described for catalyst recycling is a selective precipitation, either by inclusion of fluorous ponytails in the chiral ligand[43] or by formation of charge-transfer adducts.[44] In the first case, four catalytic cycles were conducted with a continuous decrease in enantioselectivity (from 90% ee in the first cycle to 72% ee in the fourth cycle). In the second case, up to seven cycles could be achieved, but also with a decrease in enantioselectivity and, above all, in activity (from 81% yield at 24 h in the first cycle to 59% yield at 120 h in the last one).

In this work, we describe the application of copper complexes of ditopic ligands (*i*-PrDAX and *i*-PrDiBox, Figure 1) as catalysts for the enantioselective nitroaldol (Henry) reaction between several aromatic aldehydes and two different nitro compounds (Scheme 1) and their efficient recovery and reuse by selective precipitation of the corresponding coordination polymers.

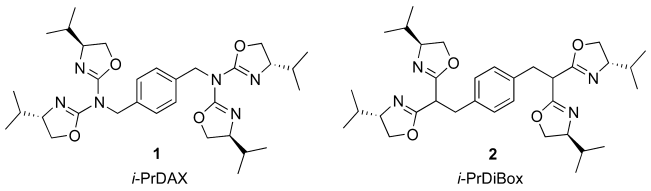


Figure 1. Structure of the chiral ditopic ligands *i*-PrDAX and *i*-PrDiBox.

RESULTS AND DISCUSSION

Synthesis of Ligands and Preparation of Coordination Polymers. As we have previously commented, the ditopic ligands selected to carry out this study were those based on azabis(oxazoline) and bis(oxazoline) units, both with isopropyl groups (Figure 1). Those units were chosen since their homologous monotopic ligands have led to the best results in the nitroaldol reaction.[29,43,45] The *i*-PrDAX ligand (**1**) was synthesized following the methodology reported in our previous work, by deprotonation of the corresponding azabis(oxazoline) with butyllitium and subsequent reaction with α,α′-dibromo-*p*-xylene.[15] Herein we also describe the synthesis of a new ditopic chiral ligand, *i*-PrDiBox (**2**), which was obtained by reaction of α,α′-dibromo-*p*-xylene with 2 equiv of the bis(oxazoline) (**3**) previously deprotonated using potassium *tert*-butoxide as a base (Scheme 2).[46]

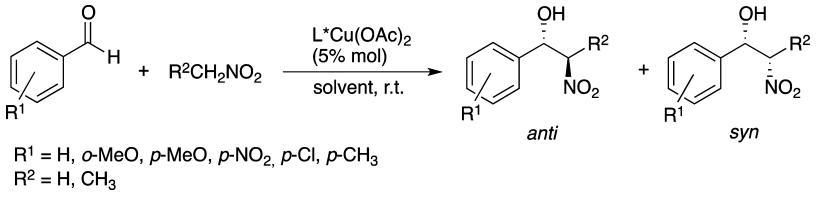
It must be noted that a nonchiral DiBox ligand has been recently described by Bellemin-Laponnaz and co-workers, as well as their Zn(II), Ni(II), and Cu(II) complexes.[47] However, these complexes have 2:1 metal:ligand stoichiometry, so no coordination polymers were observed by these authors in any case. Also, a ditopic arylidenIndaBox ligand has been described by Yuriev and Liese and used in the homogeneous phase in the prototypical Henry reaction, with rather modest results.[48]

It is noteworthy to point out that the preparation of both ditopic chiral ligands was very efficient, and high or even quantitative yields were obtained in all cases. In addition, the synthetic effort required for the preparation of the ditopic ligands is equivalent to that needed for the preparation of the corresponding monotopic ligands traditionally used in homogeneous catalysis.

For the preparation of the coordination polymers, copper was used as ligand-connecting metal; specifically, $Cu(OAc)_2$ was chosen since this copper salt provided excellent results in the nitroaldol reaction.[35] The acetate ions facilitate the deprotonation of nitroalkanes, making the use of an additional base for the activation of the nitro derivative unnecessary and avoiding possible interference, for example, in the final precipitation of the catalyst. In addition, acetate as a counterion fulfills an important requirement in the formation of coordination polymers since it does not have a coordinating ability as strong as chloride, which would prevent the recruitment of two ligands by copper. For the same reason, a weakly coordinating solvent or mixture of solvents would be the perfect solvent for the formation of the self-supported catalysts at the end of every reaction cycle.

Catalytic Results. In our previous works, the coordination polymers were applied to the cyclopropanation reaction between styrene and ethyl diazoacetate in dichloromethane and the allylic oxidation of cycloalkenes with *tert*-butyl perbenzoate. In the cyclopropanation, the polymers remained solid in the absence of reactants and became soluble and catalytically active in the presence of ethyl diazoacetate because of the breakage of the polymer and formation of a carbenoid intermediate species.[14,15] In the case of the Henry reaction, the solvent is mainly responsible for the solubilization of the coordination polymer since it is a coordinating aliphatic alcohol that joins the coordination sphere of the copper leading to monomeric and oligomeric species.[16] The influence of the solvent in the title reaction with chiral monotopic ligands (**4** and **5**) is shown in Table 1.

Scheme 1. Nitroaldol (Henry) Reactions Used in the Catalytic Tests



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Scheme 2. Synthesis of the *i*-PrDiBox Ligand

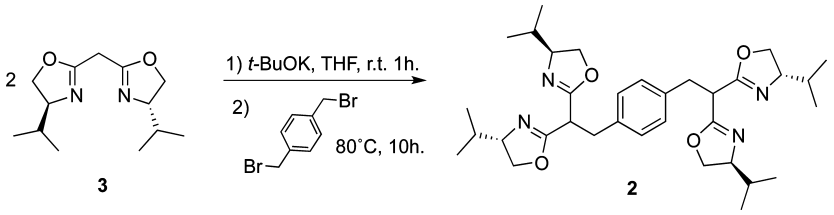
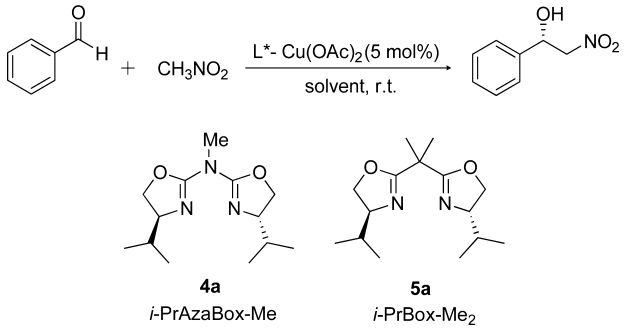


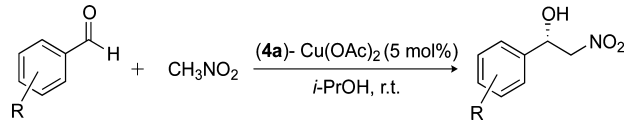
Table 1. Influence of the Solvent on the Enantioselectivity of the Henry Reaction[a]



entry	ligand (L*)	solvent	ee[b] (%)
1	*i*-PrAzaBox-Me (**4a**)	MeOH	70
2	*i*-PrAzaBox-Me (**4a**)	EtOH	87
3	*i*-PrAzaBox-Me (**4a**)	i-PrOH	91
4	*i*-PrBox-Me$_2$ (**5a**)	MeOH	65
5	*i*-PrBox-Me$_2$ (**5a**)	EtOH	84
6	*i*-PrBox-Me$_2$ (**5a**)	i-PrOH	84

[a]Reagents and conditions: benzaldehyde (1 mmol), nitromethane (10 mmol), L*-Cu(OAc)$_2$ (0.05 mmol, 5 mol %), solvent (2 mL), room temperature, 24 h. [b]Enantiomeric excesses were determined by HPLC using a Chiralcel OD-H column. (*S*)-2-nitro-1-phenylethanol is the major enantiomer. See the Supporting Information.

Table 2. Henry Reaction between Nitromethane and Several Aromatic Aldehydes[a]



entry	R	yield[b] (%)	ee[c] (%)
1	H	92	91
2	*o*-MeO	99	90
3	*p*-MeO	40	90
4	*p*-NO$_2$	76	74
5	*p*-Cl	75	89
6	*p*-CH$_3$	68	89

[a]Reagents and conditions: aromatic aldehyde (1 mmol), nitromethane (10 mmol), L*-Cu(OAc)$_2$ (0.05 mmol, 5 mol %), *i*-PrOH (2 mL), room temperature, 24 h. [b]Yields were determined by ^{1}H NMR using an internal standard. [c]Enantiomeric excesses were determined by HPLC using Chiralcel OD-H and Chiralpak IB columns. (*S*) product was the major enantiomer in all cases. See the Supporting Information.

Independent of the chiral ligand utilized, the use of *i*-PrOH as solvent produces a great increase in the enantioselectivity of the reaction of Henry between benzaldehyde and nitromethane (up to 20%). A 91% ee with *i*-PrAzaBox ligand (**4a**) and an 84% ee with *i*-PrBox ligand (**5a**) in *i*-PrOH as solvent were promising values for the application of their homologous ditopic ligands in this reaction.

Before testing the coordination polymers as catalysts, other aromatic aldehydes bearing either electron-withdrawing or electron-donating groups were examined. For this study, the complex **4a**−Cu(OAc)$_2$ was chosen as catalyst since it had presented the best activity and selectivity in the previous experiments. The results are gathered in Table 2. In general, from moderate to high enantiomeric excesses were obtained in all cases (74−91%). The position of the substituent in the aromatic ring showed a clear influence in the activity of the catalyst; the change of a methoxy group from an *ortho* to a *para* position reduced the yield from 99% to 40% (Table 2, entries 2 and 3). However, as happens in similar studies carried out with substituted aromatic aldehydes by other authors, there is not a clear rationale for the fluctuations observed.[29,42,49] Clearly, it is not an electronic effect, for *p*-NO$_2$, *p*-Me, and *p*-MeO substituents lead to worse results than the parent compound, benzaldehyde. Variations in enantioselectivity seem to be less dependent on the aromatic substitution, and only the *p*-NO$_2$ derivative showed a lower selectivity, a fact also observed in similar studies.[29,49]

In all cases, the (*S*) product was the major enantiomer, which corresponds to a preferential approach of the nitro compound to the *Re* face of the aldehyde. This is in line with previous studies of similar catalysts[29,35,42] and can be rationalized assuming a pyramidal five-coordinated copper transition structure following the first proposal made by Evans[35] where the transition structures in which steric interactions between the nitro compound and the substituents of the oxazoline rings are minimized (Figure 2). Approach by the *Si* face of the aldehyde always results in steric hindrance either between the aromatic group and the coordinated acetate ion or between one

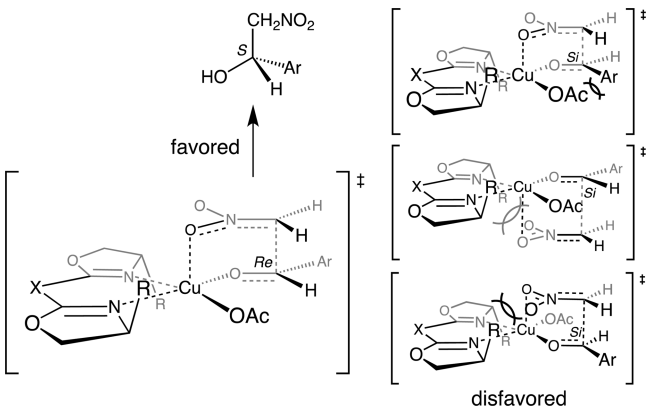


Figure 2. Stereochemical models to explain the enantiodiscrimination observed.

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of the oxygen atoms of the nitro group and one of the substituents of the bis(oxazoline) (Figure 2).

In view of the results obtained in the study of the aldehyde substrates, *o*-anisaldehyde was chosen as reference substrate in order to carry out the study with the catalysts based on the ditopic chiral ligands. In these experiments, the catalytic complexes (**1**−Cu(OAc)$_2$ or **2**−Cu(OAc)$_2$) (L*/Cu = 1/1 molar ratio) were prepared in *i*-PrOH, and subsequently, the reagents were added to the solution. Once the reaction was complete, the solvent and the excess of nitromethane were removed under vacuum to avoid the presence of coordinating molecules. A noncoordinating solvent was added to the crude to extract the products, byproducts, and remaining starting materials and at the same time allow the self-assembly of the catalyst. At the beginning, hexane was chosen as a perfect candidate because it could fulfill both requirements, that is, low coordinating ability and a right solubilization of products. However, part of the products remained together with the catalyst after the extractions because of a partial solubilization of them in hexane. Then, several solubility experiments were carried out, and finally, a mixture of hexane/Et$_2$O = 1:1 was chosen as an extraction solvent that maintains suitable noncoordinating properties. After the addition of the solvents to the reaction crude, a green solid precipitated as a consequence of the assembly of the corresponding monomeric catalytic species, in other words, as a result of the formation of the coordination polymer, and accordingly, products could be separated from the catalyst. Therefore, the latter could be reused in successive reactions by adding new portions of solvent and reagents. In the presence of *i*-PrOH, the polymer disassembled again due to competitive coordination of solvent molecules and thus became soluble and catalytically active (Figure 3).

The results obtained with these kinds of complexes, including their recovery and reuse, are collected in Table 3. The results obtained with the corresponding monotopic ligands with benzylic groups at the central nitrogen or carbon atom

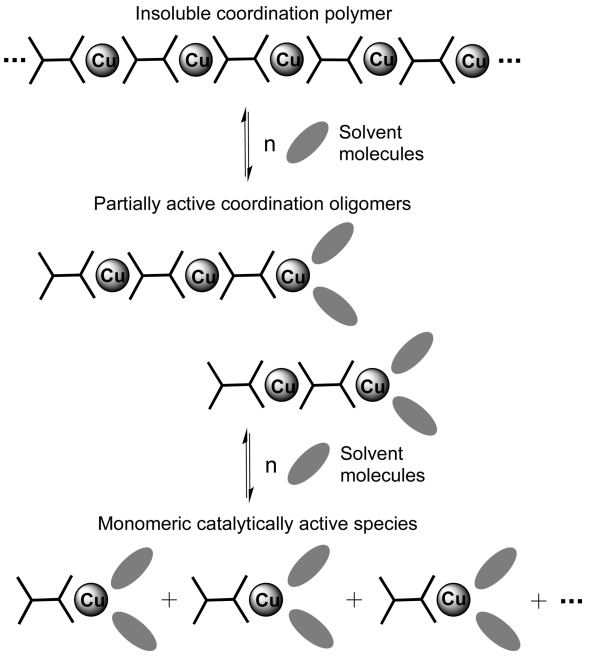
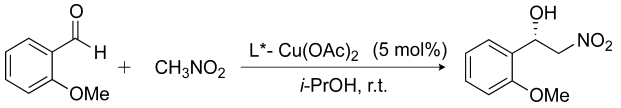


Figure 3. Equilibrium of solvent-aided assembly disassembly.

Table 3. Henry Reaction between Nitromethane and *o*-Anisaldehyde[a]



entry	L*	run	yield[b] (%)	ee[c] (%)
1	*i*-PrAzaBox-Me (**4a**)	1	99	90
2	*i*-PrAzaBox-Bn (**4b**)	1	78	89
3	*i*-PrDAX (**1**)	1	25	95
4		2	5	98
5	*i*-PrBox-Me$_2$ (**5a**)	1	82	84
6	*i*-PrBox-Bn (**5b**)	1	82	63
7	*i*-PrDiBox (**2**)	1	47	76
8		2	30	62
9		3	28	75
10		4	30	73
11		5	30	72
12		6	14	73

[a]Reagents and conditions: *o*-anisaldehyde (1 mmol), nitromethane (10 mmol), L*-Cu(OAc)$_2$ (0.05 mmol, 5 mol %), *i*-PrOH (2 mL), room temperature, 24 h. [b]Yields were determined by ^{1}H NMR using an internal standard. [c]Enantiomeric excesses were determined by HPLC using a Chiralcel OD-H column. (*S*)-1-(2-methoxyphenyl)-2-nitroethanol was the major enantiomer in all cases. See the Supporting Information.

have also been included for comparison, since they are closer to the structure of the ditopic ligands used in this study (Figure 4). It also must be pointed out that the dehydration product

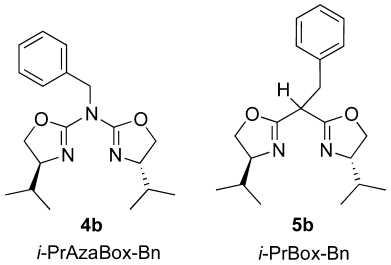


Figure 4. Structure of the chiral monotopic ligands bearing benzylic groups.

from the *β*-nitro alcohol was detected as a byproduct in some of the Henry reactions described in this work. However, the yield of this byproduct was considered insignificant (<5%), and it has not been included in the following tables.

The presence of a benzyl group in the central nitrogen of the azabis(oxazoline) leads to a decrease in the reaction yield maintaining a similar enantioselectivity (Table 3, entries 1 and 2). When the ditopic ligand **1** was tested in the Henry reaction with *o*-anisaldehyde, an increase in the enantioselectivity was achieved (Table 3, entry 3), even improving those obtained with the monotopic ligands **4a** and **4b**. Nevertheless, disappointingly, the activity of the catalyst was dramatically reduced, and although the reuse of the catalyst retained the enantioselectivity, the yield was only 5% (Table 3, entries 3 and 4). The presence of the benzyl group in the bis(oxazoline) had a different effect from that observed with azabis(oxazolines). The use of the ligand **5b** led to similar results in terms of yield, but enantioselectivity was significantly reduced (Table 3, entries 5 and 6). The reaction with the ditopic ligand **2** led to an

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intermediate enantioselectivity (76% ee) with a moderate yield, and in this case, the recovery and reuse of the coordination polymer was possible during five reaction cycles without a remarkable loss of enantioselectivity (Table 3, entries 7–12).

The results of enantioselectivity obtained with the ditopic chiral ligands were, in both cases, comparable to those obtained with the monotopic ligands; however, the results in terms of activity were still far from being acceptable. In order to rule out a possible error in the experimental determination of the results, a larger scale reaction was examined. Similar values for yield and enantioselectivity were obtained in this experiment, and the recoverability of the catalyst was not improved either.

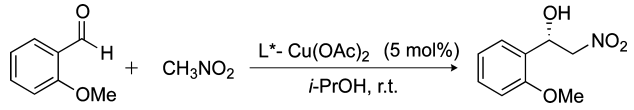
On the other hand, it has been demonstrated that ligands bis(oxazoline) and azabis(oxazoline) have different coordinating abilities toward copper.[50] Azabis(oxazoline)–copper complexes are considerably more stable than the analogous bis(oxazoline)–copper complexes which, in our case, would involve a greater difficulty for the disassembly of the coordination polymer from ligand **1**. Consequently, this could explain the differences found in the activity of the catalyst *i*-PrDAX–Cu (25% of yield) compared to that of the catalyst *i*-PrDiBox–Cu (47% of yield).

In addition, when coordination polymers are used in a release–capture strategy, the catalyst remains heterogeneous at its resting state at the end of the reaction, but afterward, for its reuse, its disassembly and solubilization in the reaction medium are essential in order for it to become completely catalytically active. In other words, a partial disassembly of the polymer would produce dimeric or oligomeric species that are catalytically active, but at the same time, they also include blocked copper centers that are not able to catalyze the reaction. It is worth mentioning that oligomeric species of this kind have been previously detected in solution by DOSY ^{1}H NMR experiments.[16] Therefore, the presence of dimeric or oligomeric species misses part of the catalytic potential of the coordination polymers. Taking into account these considerations, we thought that the low activity of the polymeric catalysts could be due to a lack of coordinating or enough coordinating molecules in the reaction medium. It is evident that in the previous experiments *i*-PrOH was able to disassemble the coordination polymer, at least partially, but possibly the number of available molecules of solvent was not sufficient to shift the equilibrium of assembly disassembly and thus release all potential monomeric catalytic complexes (Figure 3). Accordingly, we decided to carry out the reaction with 4 mL of *i*-PrOH instead of 2 mL in order to evaluate this possibility (Table 4).

If we compare the results of Tables 3 and 4, it can be concluded that an increase in the volume of solvent produces a great improvement in the activity of catalysts including ditopic ligands, that is, from 25% of yield (Table 3, entry 3) to 83% (Table 4, entry 3) for ligand **1** and from 47% of yield (Table 3, entry 7) to 65% (Table 4, entry 16) for ligand **2**. These results confirm our previous hypothesis; thus, a larger number of coordinating solvent molecules in the reaction medium has allowed the disassembly of the coordination polymers, releasing all the latent catalytic complexes borne in that kind of structures.

In addition to this, both *i*-PrDAX–Cu and *i*-PrDiBox–Cu could be recovered and reused in 11 consecutive reactions with similar results to those obtained with their corresponding conventional complexes with ligands **4a** and **4b**. It is worth highlighting the efficient recovery of the *i*-PrDAX–Cu complex

Table 4. Henry Reaction between Nitromethane and *o*-Anisaldehyde Using 4 mL of *i*-PrOH[a]



entry	L*	run	yield[c] (%)	ee[d] (%)
1	*i*-PrAzaBox-Me (**4a**)	1	93	94
2[b]	*i*-PrAzaBox-Bn (**4b**)	1	78	89
3	*i*-PrDAX (**1**)	1	83	85
4		2	77	85
5		3	89	89
6		4	84	75
7		5	80	92
8		6	90	91
9		7	81	90
10		8	92	90
11		9	90	88
12		10	95	87
13		11	96	83
14	*i*-PrBox-Me$_2$ (**5a**)	1	82	86
15[b]	*i*-PrBox-Bn (**5b**)	1	82	63
16	*i*-PrDiBox (**2**)	1	65	60
17		2	70	70
18		3	78	70
19		4	88	62
20		5	75	79
21		6	75	73
22		7	72	60
23		8	61	57
24		9	53	58
25		10	40	57
26		11	44	53

[a]Reagents and conditions: *o*-anisaldehyde (1 mmol), nitromethane (10 mmol), L*-Cu(OAc)$_2$ (0.05 mmol, 5 mol %), i-PrOH (4 mL), room temperature, 24 h. [b]Reactions carried out with 2 mL of *i*-PrOH. [c]Yields were determined by ^{1}H NMR using an internal standard. [d]Enantiomeric excesses were determined by HPLC using a Chiralcel OD-H column. (*S*)-1-(2-methoxyphenyl)-2-nitroethanol was the major enantiomer in all cases. See the Supporting Information.

(Table 4, entries 3–13), which could be used without a significant loss of activity or selectivity during all reaction cycles. In the case of the *i*-PrDiBox–Cu complex, there is an incipient decrease in the yield and the enantioselectivity after runs 8 and 9 (Table 4, entries 23 and 24) which could be produced by a progressive loss of small amounts of complex dissolved in the extraction solvents. A copper analysis of the extracted reaction crude was carried out by ICPMS showing a loss of metal around 3% (0.0015 mmol Cu) with regard to the total amount of copper added in the beginning. In some experiments carried out in our laboratory using benzaldehyde as a substrate, the addition of 20% more of *i*-PrDiBox–Cu after the ninth run allowed us to restore the activity and the selectivity to their initial values. A lower stability of the *i*-PrDiBox–Cu complexes compared to the stability of their analogous *i*-PrDAX–Cu complexes would be a possible explanation for the loss of catalyst observed in the first case.

It should be mentioned that these results are not compatible with the behavior recently described by Hong and co-workers[29] regarding the catalytic activity of the *N*-benzylazabis(oxazoline) ligand **4b**. These authors described that the ligand, without copper, is able to catalyze efficiently the Henry reaction of *p*-

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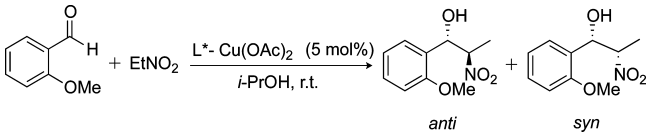
nitrobenzene with nitromethane (90% yield in 5 h at room temperature, no enantioselectivity) even better than the same ligand with $Cu(OAc)_2$ (95% yield in 16 h at room temperature, 75% ee). Under our reaction conditions with the *i*-PrDAX ligand, when the polymer is completely disassembled, half of the azabis(oxazoline) moieties bear a coordinate copper and half do not. We could therefore observe an important decrease of enantioselectivity because of the concurrence of the nonenantioselective ligand-catalyzed reaction. As can be seen in Table 4, this effect is not observed. We then tried out the reaction of benzaldehyde with nitromethane in the presence of ligand **4a**, without copper, at room temperature. After 24 h, no conversion of the reagents could be detected, so it seems that under our reaction conditions the metal-free catalysis described by Hong and co-workers does not take place and no interference (nor cooperativity) with the free azabis(oxazoline) moieties of the *i*-PrDAX ligand occurs.

After the good results obtained with these coordination polymers in both activity/selectivity and recoverability, we decided to carry out a deeper evaluation of the Henry reaction scope, and thus, another nitro derivative such as nitroethane was also considered. The results with this component are gathered in Table 5.

Table 5. Henry Reaction between Nitroethane and *o*-Anisaldehyde[a]



entry	L*	run	yield[c] (%)	*anti*/*syn*	ee *anti*[d,e] (%)	ee *syn*[d,f] (%)
1[b]	*i*-PrAzaBox-Me (**4a**)	1	47	57/43	77	91
2[b]	*i*-PrBox-Me_2 (**5a**)	1	58	62/38	66	80
3	*i*-PrDAX (**1**)	1	70	55/45	75	91
4		2	60	49/51	40	80
5		3	74	52/48	67	87
6		4	71	54/46	64	86
7		5	66	48/52	61	89
8		6	51	54/46	50	86
9		7	40	59/41	72	92
10		8	27	58/42	55	90

[a]Reagents and conditions: *o*-anisaldehyde (1 mmol), nitroethane (10 mmol), L*-$Cu(OAc)_2$ (0.05 mmol, 5 mol %), *i*-PrOH (4 mL), room temperature, 24 h. [b]Reactions carried out with 2 mL of *i*-PrOH. [c]Yields were determined by ^{1}H NMR using an internal standard. [d]Enantiomeric excesses were determined by HPLC using a Chiralpak AD-H column. [e](1*S*,2*R*)-1-(2-Methoxyphenyl)-2-nitropropan-1-ol was the major enantiomer. [f](1*S*,2*S*)-1-(2-Methoxyphenyl)-2-nitropropan-1-ol was the major enantiomer. See the Supporting Information.

Preliminary reactions were carried out with ligands **4a** and **5a** using nitroethane as starting material (Table 5, entries 1 and 2). The results obtained are in line with those previously described using similar ligands.[44] Thus, low *anti*/*syn* selectivity is observed, which can be explained by the low steric repulsion expected between the nitro compound alkyl chain and the aromatic ring of the aldehyde (Figure 2). This is clearly a drawback for the reaction and constitutes an area of future effort, although it is out of the scope of the present study. Moreover, enantioselectivity in the *anti* product is lower than that of *syn* diastereomer. This could be explained by a relative destabilization of the lowest energy transition state due to steric repulsion between the methyl groups of nitroethane and acetate ion (Figure 5).

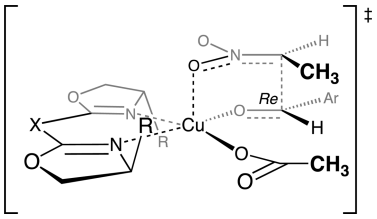


Figure 5. Stereochemical models to explain the lower enantiodiscrimination observed in the *anti* product.

We decided to carry out the reactions with the ditopic ligand **1** (*i*-PrDAX) since the values for the enantioselectivity were slightly better using the ligand with azabis(oxazoline) units. As can be seen in Table 5, the *i*-PrDAX−Cu complex could again be recovered and reused for up to seven reaction cycles with good results (Table 5, entries 3−10). Despite the somewhat erratic values in the enantioselectivity of the *anti* products, the values of enantiomeric excess for the *syn* products were moderately high during all the cycles and in addition, the yields obtained using this catalyst were better than that obtained with complex **4a**−Cu. These results increase the application scope of this release-capture methodology using coordination polymers.

CONCLUSIONS

We have described the preparation of different coordination polymers using copper(II) and two ditopic chiral ligands based on bis(oxazoline) units, that is, *i*-PrDAX (**1**) and the new *i*-PrDiBox ligand (**2**). The use of these coordination polymers in the Henry reaction with different substrates has allowed the recovery and reuse of the catalysts up to 11 reaction cycles with very good results of activity and selectivity through a release−capture strategy. The total disassembly and solubilization of the coordination polymer in the reaction medium has proved to be essential in order to take advantage of the full catalytic properties of these kinds of structures. These results enlarge the scope of applicability of this release−capture strategy through the use of polytopic chiral ligands able to form insoluble coordination polymers after reaction completion, thus joining the best of homogeneous and heterogeneous catalysis worlds.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out under argon atmosphere in oven-dried glassware. Anhydrous solvents such as tetrahydrofuran, dichloromethane, and MeOH were obtained from a SPS-device; however, EtOH and *i*-PrOH were distilled from calcium hydride. Liquid benzaldehydes were obtained from different commercial sources and distilled before use. $EtNO_2$ was distilled from potassium carbonate. The rest of purchased reagents were used as received without further purification. The ligands *i*-PrAzaBox-Me (**4a**),[51−53] *i*-PrAzaBox-Bn (**4b**),[51−53] *i*-PrBox-Bn (**5b**),[54] and *i*-PrDAX[14,15] were prepared according to literature procedures. The chemical shifts were relative to TMS as an internal reference for ^{1}H NMR.

Synthesis of 1,4-Bis(2,2-bis((*S*)-4-isopropyl-4,5-dihydrooxazol-2-yl)ethyl)benzene (*i*-PrDiBox) (2). A solution of 2,2′-methylenebis[(4*S*)-4-isopropyl-4,5-dihydrooxazole] (**3**) (238 mg, 1 mmol) in anhydrous tetrahydrofuran (5 mL) was combined with

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another solution of *t*-BuOK (112 mg, 1 mmol) also in anhydrous tetrahydrofuran (5 mL). After the solution was stirred for 1 h at room temperature, α,α′-dibromo-*p*-xylene (132 mg, 0.5 mmol) was added. The mixture was heated under reflux overnight. The solvent was evaporated under reduced pressure, and the residue was partitioned between ethyl acetate (10 mL) and a saturated aqueous NaCl solution (10 mL). The aqueous phase was extracted with ethyl acetate (3 × 10 mL), and the combined organic phases were dried over anhydrous $MgSO_4$. Evaporation of the solvent yielded the product as orange oil in almost quantitative yield: $[\alpha]^{25}_D$ = −57.5 (*c* 0.54, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm) 7.10 (s, 4H), 4.28−4.06 (m, 4H), 4.01−3.79 (m, 8H), 3.76−3.63 (m, 2H), 3.25−3.05 (m, 4H), 1.79−155 (m, 4H), 0.89 (d, 6H, *J* = 6.8 Hz), 0.82 (d, 6H, *J* = 6.8 Hz), 0.81 (d, 6H, *J* = 6.8 Hz), 0.75 (d, 6H, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm) 164.0, 163.9, 136.4, 128.9, 71.82, 71.81, 70.05, 70.04, 41.3, 35.4, 32.3, 32.2, 18.6, 18.5, 17.8, 17.7; IR (C═N) ν 1665.2 cm^{-1}; HR-MS (ESI+) *m*/*z* = 579.3931 [MH^+], calcd for $C_{34}H_{50}N_4O_4$ + H 579.3910.

General Procedure for Henry Reactions Promoted by Monotopic Azabis(oxazoline) or Bis(oxazoline)−copper Complexes. A solution of $Cu(AcO)_2$ (9.07 mg, 0.05 mmol) and the corresponding monotopic ligand (**4a**,**4b**, **5a**, or **5b**) (0.055 mmol) in 2 mL of anhydrous dichloromethane was stirred at room temperature for 30 min. Then the mixture was microfiltered to eliminate the remaining $Cu(OAc)_2$. Afterward, the dichloromethane was removed under vacuum, and 2 mL of anhydrous isopropyl alcohol together with the corresponding aldehyde (1 mmol) and nitro derivative (10 mmol) were added. The reaction solution was stirred at room temperature for 24 h, and then it was filtered through a silica pad to eliminate the catalyst. After that, the silica pad was washed with dichloromethane, and the resulting solution was concentrated under vacuum. Yield was determined by ^{1}H NMR using mesitylene as internal standard. Enantiomeric excesses were determined by HPLC using a chiral column. Specific chromatographic conditions, retention times, and some typical chromatograms are included in the Supporting Information.

General Procedure for Henry Reactions Promoted by Ditopic Azabis(oxazoline) or Bis(oxazoline)−copper Complexes. A solution of $Cu(AcO)_2$ (9.07 mg, 0.05 mmol) and the corresponding ditopic ligand (**1** or **2**) (0.055 mmol) in 4 mL of anhydrous isopropyl alcohol was stirred at room temperature for 30 min. Afterward, the corresponding aldehyde (1 mmol) and nitro derivative (10 mmol) were added. The resulting solution was stirred at room temperature for 24 h and then concentrated under vacuum. The residue was extracted with an anhydrous mixture of hexane/Et_2O (1:1) (3 × 2 mL) in order to separate the products from the solid polymer which had already precipitated. The polymer was then dried under argon atmosphere. Under these conditions, the catalyst was ready to be used again in a new reaction by adding new portions of solvent and reagents. The product solution was concentrated under vacuum, and the determination of the results was carried out as described previously.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra of the *i*-PrDiBox (**2**) ligand and typical HPLC conditions and chromatograms of selected Henry reactions. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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