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PAPER

Polytopic bis(oxazoline)-based ligands for recoverable catalytic systems applied to the enantioselective Henry reaction

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Several kinds of polytopic chiral ligands (including ditopic, tritopic and tetratopic), based on the bis(oxazoline) and azabis(oxazoline) motifs, have been tested in the preparation of recoverable catalytic systems for the Henry reaction. The results obtained with the different ligands are, in general, good, but they point to the existence of a delicate balance between the coordinating ability of the ligand, the catalytic activity and the recovery of the catalyst by formation of the coordination polymer, related to the easiness to form oligomeric species in solution.

Introduction

Asymmetric catalysis is one of the preferred methodologies to obtain enantiomerically pure compounds. Nevertheless, chiral catalysts are usually expensive and, therefore the development of procedures for their easy recovery from the reaction, allowing their reuse in further catalytic runs, has become an interesting goal for both academia and industry.[1] In the past years a good number of strategies have been proposed for the recycling and reuse of enantioselective catalysts, including covalent and non-covalent bonding to solid supports.[2–7] However, given the drawbacks usually associated with the use of chiral catalysts immobilized onto solid supports, an appealing alternative consists of carrying out the catalysed reaction in homogeneous phase, and then selectively separating the catalyst and the product phases, allowing its easy separation from the crude reaction and its reuse in further cycles. Several methods have been described to accomplish this goal. For instance, the chiral ligand has been tagged with either ionic[8–10] or fluorous[11,12] moieties to improve its solubility in ionic liquids and fluorous solvents, respectively, allowing easy product extraction in a second liquid phase. Alternatively, selective precipitation of the catalyst to a solid phase has been accomplished by linking of the chiral ligand to a soluble polymer,[5] self-supporting the catalytic complex through intermolecular hydrogen bonding,[13,14] and using coordination polymerization.[15–17] In most cases, the precipitation of the catalyst after the reaction is achieved by adding a suitable solvent.

Our research group and others have described the application of the release-and-capture strategy using coordination polymers of bis(oxazoline)-based polytopic ligands to a variety of organic reactions, such as the cyclopropanation reaction between styrene and ethyl diazoacetate,[18–20] the allylic oxidation of cycloalkenes with *tert*-butyl perbenzoate,[21] the α-hydrazination of β-ketoesters,[22] or the nitroaldolic Henry reaction between aldehydes and nitro derivatives.[23,24] Concerning the latter, only two ditopic ligands were tested in our former work.[23] The aim of the current work is to explore the self-supported catalytic possibilities of the family of polytopic ligands synthesized in our group (Fig. 1) in nitroaldol reactions.

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Results and discussion

Synthesis of polytopic ligands and preparation of coordination polymers

The synthesis of the polytopic ligands used in this work was previously reported by our group.[18–20,23] All the syntheses are based on the condensation of the bis(oxazoline) or azabis(oxazoline) moieties with different linking molecules. Depending on the number of bis(oxazoline) moieties condensed in a single unit around the linker, ditopic, tritopic or tetratopic ligands are obtained. It is worth mentioning that the synthetic effort required to obtain these polytopic ligands is equivalent to that needed for the preparation of the analogous monotopic ligands used in conventional homogeneous catalysis. In addition, the synthesis of all of these polytopic ligands is very efficient, reaching very good yields, even quantitative in some cases. For the preparation of the coordination polymers, copper was used as the ligand-connecting metal. The copper salt chosen to this purpose was $Cu(OAc)_2$, since it provided excellent results in previously reported nitroaldol reactions with related catalytic systems.[23] Acetate ion promotes the deprotonation of nitroalkanes, avoiding the use of an additional base. Furthermore, the weak coordinating ability of the acetate anion facilitates the possibility of recruitment of two ligands by copper.

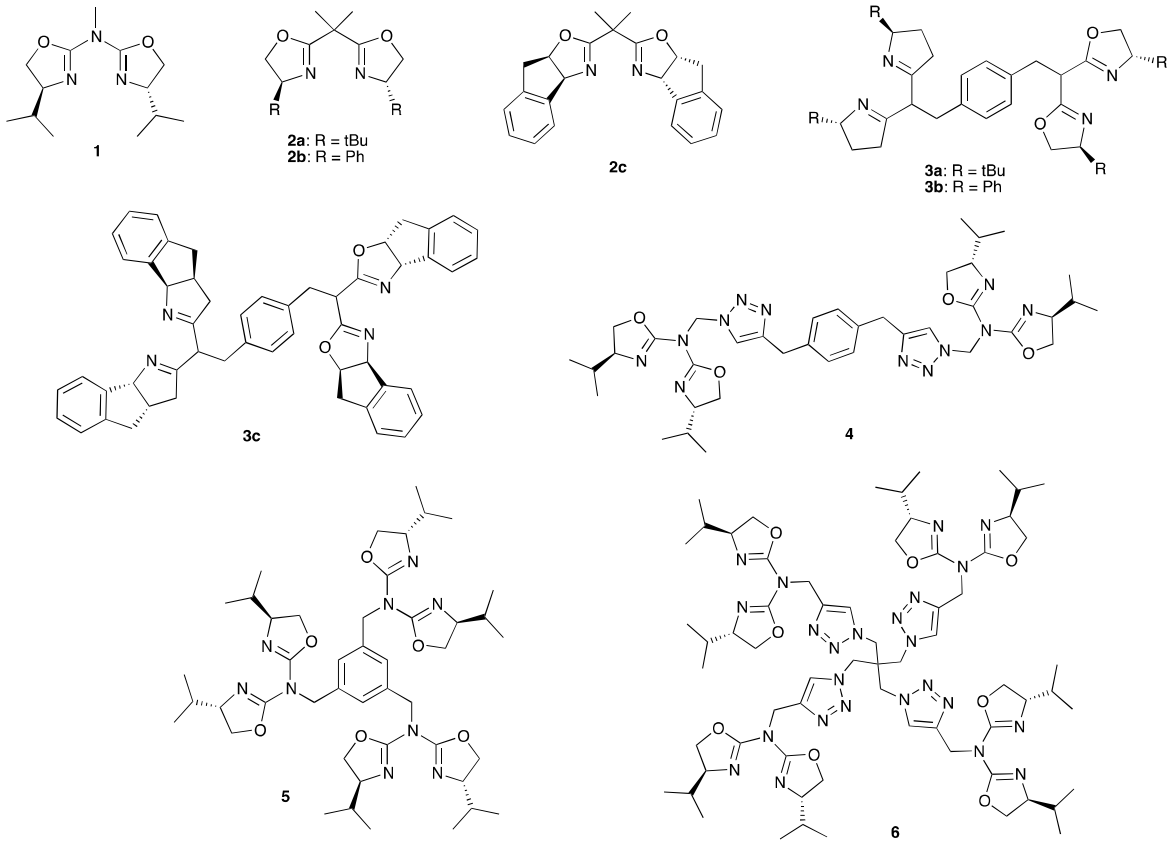


Fig. 1 Structures of the chiral ligands used in this work.

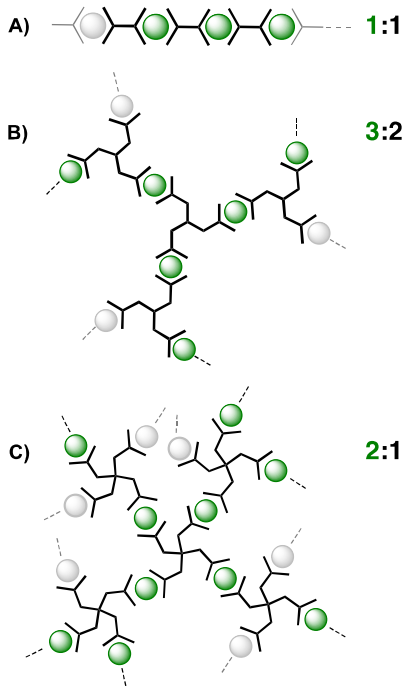


Fig. 2 Schematic representation of the self-assembled catalysts from the coordination of copper cations with polytopic ligands. The optimal Cu:L ratio is highlighted.

Coordination polymers were formed by mixing the corresponding polytopic ligand (**3**–**6**) and $Cu(OAc)_2$ in the appropriate Cu/L molar ratio (Fig. 2). Thereby, for ditopic ligands as DiBox (**3**) and click-DAX (**4**) a 1:1 molar ratio was found to be optimal. In the case of the tritopic TAX ligand (**5**), the optimal ratio was 3:2 due to the presence of three coordination sites per ligand. Finally, in the case of the tetratopic click-QAX ligand (**6**), the optimal ratio for polymer induction was found to be 2:1. An excess of copper in the reaction media over the optimal amount could favour the formation of shorter polymers, and even the presence in solution of monomeric complexes, making catalyst precipitation and recovery more complicated.

As mentioned in the Introduction, coordination polymers are attractive for applications in catalysis since they combine the advantages of both homogeneous and heterogeneous catalysis. During the reaction, the polymer disassembles due to competitive coordination of either the reactants or the reaction solvent. The resulting soluble monomeric metal complexes act as true homogeneous catalysts, leading to results as good as those obtained using the traditional homogeneous complexes. On other hand, when the catalytic reaction has concluded, a simple change in the solvent can promote the reassembly of the coordination polymer and his subsequent precipitation. The resulting solid, which constitutes the self-supported resting state of the catalyst, is

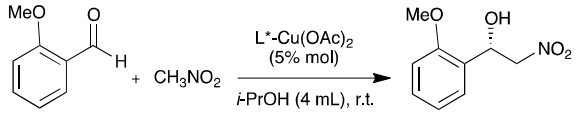
easily recoverable by simple liquid/solid separation techniques.

Catalytic studies

Trying to improve the recoverability of the catalytic systems based on polytopic bis(oxazoline)-based ligands, three different strategies were outlined. First, the use of ditopic ligands with substituents different from isopropyl: DiBox ligands (**3**) bearing *tert*-butyl (**3a**), phenyl (**3b**) and indanyl (**3c**) substituents. Second, the use of a different ditopic ligand bearing triazole units in the linker (click-DAX(iPr), **4**). Third, the use of ligands with more than two coordination sites, *i.e.* tritopic TAX(iPr) (**5**) and tetratopic (click-QAX(iPr), **6**) ligands.

Catalytic tests with DiBox ligands. The best results obtained in our previous work on the Henry reaction catalysed by ditopic ligands bearing bis(oxazoline) moieties were achieved with DAX(iPr)-Cu(OAc)$_2$ and DiBox(iPr)-Cu(OAc)$_2$ complexes, using 4 mL of iPrOH.[23] Yields over 75% and enantioselectivities around 70% ee were obtained in up to 11 consecutive runs in the case of the DiBox(iPr)-Cu(OAc)$_2$ complex, and over 90% yield and 90% ee in at least 11 runs in the case of using the DAX(iPr)-Cu(OAc)$_2$ as catalyst.[23] Therefore, the evaluation of the behaviour of the new ditopic ligands based on bis(oxazolines), referred to as DiBox, was initially carried out using the same reaction conditions for the reaction between *o*-anisaldehyde and nitromethane.

Table 1 Henry reaction between *o*-anisaldehyde and nitromethane catalysed by the complexes of Box(tBu) (**2a**) and DiBox(tBu) (**3a**) ligands with Cu(OAc)$_2$.[a]



Entry	Ligand (L*)	Run	Yield (%)[b]	% ee[c]
1[d]	Box(tBu)-Me$_2$ (**2a**)	—	55	84
2	DiBox(tBu) (**3a**)	1	50	71
3		2	67	73
4		3	60	91
5		4	50	89
6		5	55	93
7		6	33	78
8		7	32	76
9		8	26	87

[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] 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. [d] Reaction carried out with 2 mL of *i*-PrOH.

We started the study with the DiBox(tBu) ligand (**3a**), and the catalytic results obtained with the corresponding Cu(II) complex, including their recovery and reuse, are gathered in Table 1. The results obtained with the corresponding monotopic ligand (**2a**) have also been included for comparison.

When the complex with the monotopic ligand **2a** was used as catalyst, a moderate yield (55%) and a fairly good enantioselectivity (84%) were obtained. When using the DiBox(tBu)-Cu(OAc)$_2$ complex, yields were similar to that obtained with the complex of the monotopic ligand **2a** in the first runs. The enantiomeric excess, however, was slightly lower in the two first runs. When the catalyst was recovered the enantioselectivity improved, reaching the same values as those obtained with the monotopic ligand. This could indicate that in the first two runs, there was free copper in the reaction medium, that is, part of copper was not complexed with the bis(oxazolines) moieties and then, the reaction was partially catalysed in a non-enantioselective way. On the other hand, reaction yields decreased after the sixth run. The recoverability of this coordination polymer was fairly good, and it was possible to recover it at least eight times without a significant loss of enantioselectivity.

Afterwards, DiBox(Ph)-Cu(OAc)$_2$ was also tested as catalyst in the same benchmark reaction. The corresponding results are shown in Table 2.

Table 2 Henry reaction between *o*-anisaldehyde and nitromethane catalysed by the complexes of Box(Ph) (**2b**) and DiBox(Ph) (**3b**) ligands with Cu(OAc)$_2$.[a]

Entry	Ligand (L*)	Run	Yield (%)[b]	% ee[c]
1[d]	Box(Ph)-Me$_2$ (**2b**)	—	62	19
2	DiBox(Ph) (**3b**)	1	78	26
3		2	74	35
4		3	84	33
5		4	91	38
6		5	90	44
7		6	83	38
8		7	86	37
9		8	78	40

[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] 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 enantiomers in all cases. [d] Reaction carried out with 2 mL of *i*-PrOH.

As can be seen, yields from good to excellent were obtained in all cases, even after eight runs, which indicates a good recoverability of this catalyst. On the other hand modest enantioselectivities were obtained with the Cu(II) complexes of both monotopic and ditopic ligands. Nevertheless, the %ee is significantly higher with the **3b**-Cu(II) complex than with the **2b**-Cu(II) complex.

The last ditopic ligand tested was DiBox(In) (**3c**). Catalytic results obtained with its corresponding copper complex in the same benchmark reaction are collected in Table 3.

The monotopic **2c**-Cu(II) complex led to good values of yield and enantioselectivity. In addition, when the reaction was carried out with the complex **3c**-Cu(II), the results obtained were similar to those obtained with **2c**-Cu(II), high yields around 80% and from moderate to good enantioselectivities. As happened with ligand **3a** (Table 1), enantiomeric excesses in the two first runs were lower, improving throughout recoveries. In this case, it was possible to recover the self-supported catalytic system at least seven times, with a decreasing yield from the fifth run.

Table 3 Henry reaction between *o*-anisaldehyde and nitromethane catalysed by complexes of Box(In) (**2c**) and DiBox(In) (**3c**) ligands with $Cu(OAc)_2$.[a]

Entry	Ligand (L*)	Run	Yield (%)[b]	% ee[c]
1[d]	Box(In)-Me_2 (**2c**)	—	92	82
2	DiBox(In) (**3c**)	1	67	60
3		2	88	67
4		3	84	71
5		4	73	76
6		5	79	80
7		6	42	86
8		7	38	75

[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] 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 enantiomers in all cases. [d] Reaction carried out with 2 mL of *i*-PrOH.

As a general remark of this first series of experiments, the results obtained with copper complexes of DiBox ligands (**3**) did not outperform those obtained in our previous work with DAX(iPr)-$Cu(OAc)_2$ (**7**, Fig. 3) complexes,[23] especially respecting recoverability, which could be extended at best up to eight reaction cycles.

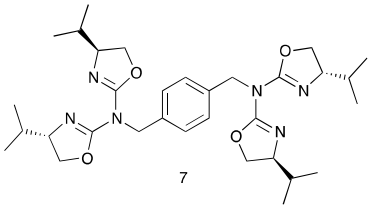


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Fig. 3 Structure of DAX(iPr) ligand.

Next, the evaluation of the new ligands was extended to the reaction between *o*-anisaldehyde and nitroethane, which allows studying both enantioselectivity and *syn/anti* diastereoselectivity. The results obtained are gathered in Table 4. In the case of the indanyl-substituted ligand **3c**, we also include the results obtained with the monotopic ligand **8** for the sake of comparison (Fig. 4). The rationale behind the introduction of a single benzyl group in the bis(oxazoline) bridge was to make the structure of the monotopic ligand closer to that of the homologous ditopic ligand.

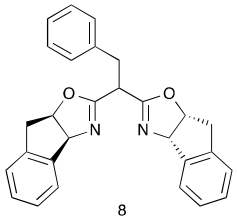

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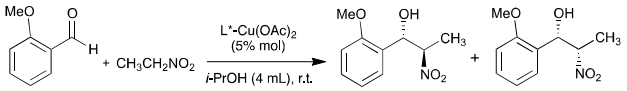
Fig. 4 Structure of ligand **8**, a monobenzylated Box(In).

Regarding the **3a**-$Cu(OAc)_2$ complex, both yield (70%) and enantioselectivity of the *syn* diastereomer (70% ee) were noticeably improved in comparison with **2a**-$Cu(OAc)_2$. However, *anti*/*syn* ratio (98/2) and %ee *anti* (89%) were better with the latter complex. Recoverability in this case was poor; up to three runs were performed with this catalytic system, but yield dramatically decreased from 70% to 29% in the second run.

With the **3b**-$Cu(OAc)_2$ complex, enantiomeric excesses and *anti*/*syn* ratios obtained were comparable to the values achieved with its homologous **2b**-$Cu(OAc)_2$ complex. However, yields were significantly better. These results were maintained during four runs.

Table 4 Henry reaction between *o*-anisaldehyde and nitroethane catalysed by the complexes of Box-Me_2(**2a-c**), Box(In)-Bn (**8**) and DiBox (**3a-c**) ligands with $Cu(OAc)_2$.[a]



Entry	Ligand (L*)	Run	Yield (%)[b]	*Anti*/*Syn*	%ee (*anti*)[c,d]	%ee (*syn*)[c,e]
1[f]	Box(tBu)-Me_2 (**2a**)	—	13	92/8	89	9
2	DiBox(tBu) (**3a**)	1	70	62/38	63	70
3		2	29	63/37	65	76
4		3	28	63/37	68	74
5[f]	Box(Ph)-Me_2 (**2b**)	—	49	57/43	19	42
6	DiBox(Ph) (**3b**)	1	80	59/41	16	46
7		2	72	67/33	39	54
8		3	70	59/41	13	52
9		4	60	68/32	43	61
10[f]	Box(In)-Me_2(**2c**)	—	94	58/42	49	90
11[f]	Box(In)-Bn (**8**)	—	34	61/39	15	80
12	DiBox(In) (**3c**)	1	86	72/28	66	78
13		2	95	65/35	62	79
14		3	85	67/33	66	77
15		4	77	69/31	70	78
16		5	64	70/30	72	80
17		6	62	71/29	74	81
18		7	64	71/29	74	82
19		8	47	72/28	72	77
20		9	50	72/28	73	77
21		10	80	70/30	70	76
22		11	40	72/28	72	75
23		12	89	66/34	71	74
24		13	75	67/33	70	72
25		14	69	67/33	70	72

[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] Yields were determined by ^{1}H-NMR using an internal standard. [c] Enantiomeric excesses were determined by HPLC using a Chiralpak AD-H column. [d] (1*S*,2*R*)-1-(2-methoxyphenyl)-2-nitropropan-1-ol was the major enantiomer. [e] (1*S*,2*S*)-1-(2-methoxyphenyl)-2-nitropropan-1-ol was the major enantiomer. [f] Reactions carried out with 2 mL of *i*-PrOH.

On the other hand, the **3c**-$Cu(OAc)_2$ complex afforded yields and enantiomeric excesses at least as good as those obtained with **2c**-$Cu(OAc)_2$, satisfactory in the case of yields (70±16.7% average yield) and fairly good in case of enantiomeric excesses of the *anti* and *syn* diastereomers (average values of 70±3.4% ee and 77±3.0% ee, respectively, in 14 reaction cycles). Slightly better *anti*/*syn* diastereoselectivities were obtained with the ditopic ligand with regard

to the monotopic one (**2c**). Recoverability according to the release and capture strategy with **3c** was excellent, and the catalyst could be reused up to 14 runs without a dramatic decrease of yield, diastereo- or enantioselectivity. These results clearly outperform those previously described with the DAX(iPr) ligand **7** (57±16.8% average yield, and 61±11.7% and 88±3.8% ee average *anti* and *syn* enantioselectivities in 8 reaction cycles).[23]

It is worth noting that the monotopic ligand **8**, which has a chemical structure closer to **3c**, leads to significantly worse results of yield and *anti* enantioselectivity, so correlations between the structural features of the chiral ligand and the reaction results are not straightforward.

Catalytic tests with the click-DAX ligand. It has been demonstrated that bis(oxazoline) and azabis(oxazoline) ligands have different coordinating abilities towards copper.[25–28] Azabis(oxazoline)-copper complexes are stronger than their analogous bis(oxazoline)-copper complexes. As a consequence, the recoverability of the coordination polymers formed with azabis(oxazoline) moieties is better, since the coordination equilibrium is more shifted towards the complex.

Table 5 Henry reaction between *o*-anisaldehyde and nitromethane catalysed by complexes of Azabox(iPr)-Me (**1**) and Click-DAX(iPr) (**4**) ligands with $Cu(OAc)_2$.[a]

Entry	Ligand (L*)	Run	Yield (%)[b]	% ee[c]
1[d]	Azabox(iPr)-Me (**1**)	—	93	94
2	Click-DAX(iPr) (**4**)	1	96	91
3		2	95	90
4		3	95	90
5		4	94	94
6		5	90	94
7		6	80	94
8		7	80	93
9		8	78	92
10		9	75	90
11		10	70	90
12		11	65	90
13[e]		12	95	90

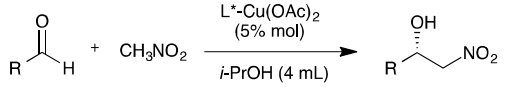
[a] Reagents and conditions: *o*-anisaldehyde (1 mmol), nitromethane (10 mmol), L*-$Cu(OAc)_2$ (0.05 mmol, 5 mol %), *i*-PrOH (4 mL), room temperature, 24 h. [b] Yields were determined by ^{1}H-NMR using an internal standard. [c] Enantiomeric excesses were determined by HPLC using a Chiralcel OD-H column. (*S*)-1-(2-methoxyphenyl)-2-nitroethanol was the major enantiomers in all cases. [d] Reaction carried out with 2 mL of *i*-PrOH. [e] Adding 0.2% mol of Cu-**4** complex.

Having in mind the improvement of results and recoverability obtained with the DAX(iPr) ligand, we carried out the abovementioned Henry reactions using other polytopic ligands bearing azabis(oxazoline) moieties. Azabis(oxazoline)-copper complexes containing triazole linkers have been found to be less soluble in organic solvents and to readily precipitate. This feature could favour the recovering of the coordination polymer, so we started this study by using a ditopic ligand in which the connecting unit between the azabisoxazoline moieties has two triazole groups, named as click-DAX(iPr) (**4**). The coordination polymer **4**-$Cu(OAc)_2$ was proved to precipitate considerably faster than his analogous **7**-$Cu(OAc)_2$ in non-coordinating solvents.[19] The results obtained with this complex in the reaction between *o*-anisaldehyde and nitromethane are gathered in Table 5.

As can be seen, the use of the complex **4**-$Cu(OAc)_2$ provided excellent results in both yield and enantioselectivity (96% and 91%, respectively). These results were comparable to those obtained with the complex with the monotopic ligand **1**-$Cu(OAc)_2$. Recoverability of the catalyst was excellent as well; it could be recovered by formation of the insoluble coordination polymer up to 12 runs without loss of enantioselectivity, and with only a slight decrease in yield after ninth cycle. This drop in yield was probably due to small losses of chiral complex in the reaction handling, necessary for catalyst recovery. In order to verify this hypothesis, an additional 0.2% mol of **4**-$Cu(OAc)_2$ complex was added in the 12th run, and as can be seen in entry 13 of Table 5, an important improvement in the yield, reaching the values obtained in the first runs, was immediately observed, which corroborates the above hypothesis. Overall, this ligand displays comparable performance to that from DAX(iPr) ligand,[23] with slightly better average yield (92±1.8% *vs*. 87±4.8%) and slightly lower enantioselectivity (83±11.1% *vs*. 87±6.3% ee).

In view of the good results of yield and enantioselectivity obtained with the complex **4**-$Cu(OAc)_2$, we decided to evaluate the scope of the Henry reaction using this catalyst. We carried out several experiments with other substrates, and the results are collected in Table 6.

Table 6 Henry reaction between several aromatic aldehydes and nitromethane catalysed by complexes of Azabox(iPr)-Me (**1**) and Click-DAX(iPr) (**4**) ligands with $Cu(OAc)_2$.[a]



Entry	Ligand (L*)	R	Yield (%)[b]	% ee[c]
1[d]	Azabox(iPr)-Me (**1**)	*o*-MeO	93	94
2[d]		H	92	91
3[d]		*p*-MeO	40	90
4[d]		*p*-NO_2	76	74
5[d]		*p*-Cl	75	89
6[d]		*p*-Me	68	89
7[e]	Click-DAX(iPr) (**4**)	*o*-MeO	52	90
8[e]		H	36	90
9[e]		*p*-MeO	20	92
10[e]		*p*-NO_2	29	46
11[e]		*p*-Cl	40	90
12[e]		*p*-Me	34	91

[a] Reagents and conditions: aldehyde (1 mmol), nitromethane (10 mmol), L*-$Cu(OAc)_2$ (0.05 mmol, 5 mol %), *i*-PrOH (4 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.[23] [d] Reaction carried out with 2 mL of *i*-PrOH at room temperature. [e] Reaction carried out at controlled temperature (20 °C).

In this Table we have also included the results obtained with all the substrates using the ligand Azabox(iPr) (**1**) for comparison, which we reported in a previous article.[23] It has to be mentioned that the reactions promoted by **4**-$Cu(OAc)_2$ had to be conducted at controlled temperature (20 °C) since room

temperature those days in our laboratory was higher than 35 ºC, and we noticed a significant effect on the results, especially on the enantioselectivity. It can be seen (Table 6) that in these conditions, the enantioselectivities obtained with **4**-Cu(OAc)$_2$ are very similar to those reached with the **1**-Cu(OAc)$_2$ complex as we also observed in Table 5 for the reaction with *o*-anisaldehyde. Yields were relatively lower but in the ^{1}H-NMR experiments no by-products were detected, only the reaction product and the starting aldehyde, which indicates that the reactions at 20 ºC need more than 24 hours to reach similar values to those obtained with **1**-Cu(OAc)$_2$, as previously reported by other authors.[9] Overall, the results showed that the catalytic system formed by **4**-Cu(OAc)$_2$ can be successfully applied to the Henry reaction with other aromatic aldehydes. The position of the substituent in the aromatic ring of the aldehydes shows an influence in the activity of the catalyst; the change of a methoxy group from an *ortho* to a *para* position reduces significantly the yield (Table 6, entries 7 and 9). There is not a clear rationale for the fluctuations observed, as other authors showed in similar studies.[9] 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.[9,29]

Next, we studied the behaviour of the same catalyst in the reaction between *o*-anisaldehyde and nitroethane. The corresponding results are gathered in Table 7.

Table 7 Henry reaction between *o*-anisaldehyde and nitroethane catalysed by complexes of Azabox-Me (**1**) and Click-DAX(iPr) (**4**) ligands with Cu(OAc)$_2$.[a]

Entry	Ligand (L*)	Run	Yield (%)[b]	*Anti*/*Syn*	%ee (*anti*)[c,d]	%ee (*syn*)[c,e]
1[f]	Azabox(iPr)-Me (**1**)	—	47	57/43	77	91
2	Click-DAX(iPr) (**4**)	1	98	72/28	8	54
3		2	88	69/31	22	57
4		3	70	57/43	47	54
5		4	80	63/37	71	65
6		5	65	62/38	72	66
7		6	62	63/37	73	83
8		7	60	62/38	74	86
9		8	65	64/36	63	86
10		9	78	62/38	60	84
11		10	78	59/41	50	84
12		11	73	61/39	44	64
13		12	73	64/36	43	52

[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] Yields were determined by ^{1}H-NMR using an internal standard. [c] Enantiomeric excesses were determined by HPLC using a Chiralpak AD-H column. [d] (1*S*,2*R*)-1-(2-methoxyphenyl)-2-nitropropan-1-ol was the major enantiomer. [e] (1*S*,2*S*)-1-(2-methoxyphenyl)-2-nitropropan-1-ol was the major enantiomer. [f] Reactions carried out with 2 mL of *i*-PrOH.

In this case, with the **4**-Cu(OAc)$_2$ complex yields were much higher as compared with that obtained with the **1**-Cu(OAc)$_2$ complex. We were able to reach 98% yield and a good diastereoselectivity *anti*/*syn* in the first run (72/28). However, during the first three runs, enantioselectivity was worse as compared with that obtained using the complex with the monotopic ligand, **1**-Cu(OAc)$_2$. From the fourth run, enantioselectivity values were recovered as in precedent cases.

Catalyst recoverability with this complex was fairly good, and 12 catalytic runs could be achieved with yields better than those obtained with the classical homogeneous complex. On the other hand, enantiomeric excesses were slightly lower, and clearly decreased after the eleventh run. Overall, these results are better than those obtained with the DAX(iPr) ligand in the same reaction,[23] with better average yield and comparable enantioselectivities.

Catalytic tests with TAX and click-QAX ligands. In our previous studies about the use of the release-capture strategy through the formation of coordination polymers, we found that the use of ligands with more than two azabis(oxazoline) units improved recoverability of the catalyst, probably due to easier formation of the polymer at the end of the reaction.[23] Because of that, we continued our study with the copper complexes of TAX(iPr) (**5**), a tritopic ligand, and click-QAX(iPr) (**6**), a tetratopic one. The results of the reactions between *o*-anisaldehyde and nitromethane, catalysed by the **5**-Cu(OAc)$_2$ complex are shown in Table 8.

Table 8 Henry reaction between *o*-anisaldehyde and nitromethane catalysed by complexes of Azabox(iPr)-Me (**1**) and TAX(iPr) (**5**) ligands with Cu(OAc)$_2$.[a]

Entry	Ligand (L*)	Run	Yield (%)[b]	% ee[c]
1[d]	Azabox(iPr)-Me (**1**)	—	93	94
2	TAX(iPr) (**5**)	1	71	91
3		2	82	90
4		3	80	90
5		4	76	88
6		5	79	87
7		6	65	82
8		7	53	82
9		8	18	80
10		9	16	79
11		10	8	78

[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] 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 enantiomers in all cases. [d] Reaction carried out with 2 mL of *i*-PrOH.

Catalyst **5**-Cu(OAc)$_2$ performed well in the nitroaldol reaction studied, leading to high enantioselectivities, similar to those obtained with the **1**-Cu(OAc)$_2$ complex, and with the previously reported **7**-Cu(OAc)$_2$ complex. Yields were good, over 70% in the first five runs, but displayed a progressive decrease in the following reactions, droping to 8% in the tenth run. As we previously discussed in case of the **4**-Cu(OAc)$_2$ complex, this diminishing of yield may be attributed to a loss of complex during the recovery of the catalyst. Enantioselectivity was kept nearly constant for five runs as well, and then a slight decrease was also observed in subsequent runs (average value of 85±5.0% ee in 10 reaction cycles). Contrary to our expectations, the recoverability of catalytic **5**-Cu(OAc)$_2$ complex was not improved compared to

that of the complex of the equivalent ditopic ligand DAX(iPr) (**7**).[23]

Table 9 shows the results obtained in the reaction of *o*-anisaldehyde with nitroethane, catalysed by the **5**-$Cu(OAc)_2$ complex. As can be seen, good yields were achieved in up to 12 runs, better than those obtained with **1**-$Cu(OAc)_2$. However, as happened in case of click-DAX(iPr) ligand (**4**), the enantioselectivities were somewhat lower than those obtained with the complex of the monotopic Azabox(iPr) ligand (**1**).

Table 9 Henry reaction between *o*-anisaldehyde and nitroethane catalysed by complexes of Azabox-Me (**1**) and TAX(iPr) (**5**) ligands with $Cu(OAc)_2$.[a]

Entry	Ligand (L*)	Run	Yield (%)[b]	*Anti*/*Syn*	%ee (*anti*)[c,d]	%ee (*syn*)[c,e]
1[f]	Azabox(iPr)-Me (**1**)	—	47	57/43	77	91
2	TAX(iPr) (**5**)	1	88	64/36	18	53
3		2	85	56/44	31	73
4		3	80	55/45	60	70
5		4	75	55/45	63	76
6		5	73	57/43	68	85
7		6	60	63/38	65	84
8		7	70	67/31	67	82
9		8	77	53/47	59	80
10		9	73	58/42	65	73
11		10	69	55/45	56	75
12		11	65	56/44	46	73
13		12	65	58/42	49	69

[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] Yields were determined by ^{1}H-NMR using an internal standard. [c] Enantiomeric excesses were determined by HPLC using a Chiralpak AD-H column. [d] (1*S*,2*R*)-1-(2-methoxyphenyl)-2-nitropropan-1-ol was the major enantiomer. [e] (1*S*,2*S*)-1-(2-methoxyphenyl)-2-nitropropan-1-ol was the major enantiomer. [f] Reactions carried out with 2 mL of *i*-PrOH.

Finally, we tested the use of a tetratopic ligand, namely click-QAX(iPr) (**6**). The **6**-$Cu(OAc)_2$ complex was used as catalyst in the nitroaldol Henry reaction between nitromethane and *o*-anisaldehyde, and the corresponding results are shown in Table 9. Due to the structural resemblance between this molecule and click-DAX(iPr) (**4**), results with the **6**-$Cu(OAc)_2$ complex should be expected to be comparable to those obtained with its analogous ditopic ligand (Table 5). In fact, enantioselectivities were as good as those obtained with **4**-$Cu(OAc)_2$. On the other hand, yields obtained were somewhat lower (average value of 66±8.0% in eleven runs with **6**-$Cu(OAc)_2$ *vs.* 83% with **4**-$Cu(OAc)_2$). This fact might be due to an incomplete disassembly of the coordination polymer in the reaction conditions, because of the complexity of the polymeric structure in this case, which would lead to a lower concentration of catalytically active species in solution.

To verify this hypothesis, several experiments were carried out in different conditions. Firstly, an additional run was carried out (entry 13 in Table 10), but using 6 mL of *i*-PrOH, the reaction solvent. As we proved in our previous work,[23] an increase in solvent concentration in the reaction media is able to shift the polymer assembly-disassembly equilibrium towards the monomeric species, the one catalytically active. Unfortunately, this change did not result in an improvement of the reaction yield. As this experiment represented the 12th run conducted with the same catalyst sample, the poor yield obtained could also be ascribed to catalyst losses along the consecutive recoveries, as mentioned previously. In these conditions, even if the disassembly of the polymer had increased, the amount of catalytically active species in reaction media would not be enough to warrant a high yield in the same reaction time. Hence, an additional 0.25% mol of Cu-**6** complex was added in the 13th run. As can be seen in entry 14 (Table 10), although enantioselectivity was as good as in all previous cases, yield was not substantially improved (50%).

Table 10 Henry reaction between *o*-anisaldehyde and nitromethane catalysed by the complexes of Azabox(iPr)-Me (**1**) and Click-QAX(iPr) (**6**) ligands with $Cu(OAc)_2$.[a]

Entry	Ligand (L*)	Run	Yield (%)[b]	% ee[c]
1[d]	Azabox(iPr)-Me (**1**)	—	93	94
2	Click-QAX(iPr) (**6**)	1	51	92
3		2	68	91
4		3	68	90
5		4	71	92
6		5	69	91
7		6	75	89
8		7	76	90
9		8	69	89
10		9	60	89
11		10	54	90
12		11	64	89
13[e]		12	46	87
14[f]		13	50	86
15[g]		1	70	80
16[g]		2	50	94
17[h]		1	80	91

[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] 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 enantiomers in all cases. [d] Reaction carried out with 2 mL of *i*-PrOH. [e] Reactions carried out with 6 mL of *i*-PrOH. [f] Adding 0.25% mol of fresh **6**-$(OAc)_2$ complex. [g] Reaction was carried out with a 1:3 ligand/copper proportion. [h] Reactions carried out with fresh catalyst and 6 mL of *i*-PrOH.

For the optimal preparation of the coordination polymer with the tetratopic ligand click-QAX(iPr) (**6**), a ligand/copper ratio of 1:2 was used. However, a larger amount of copper could be utilized to favour the disassembly of the polymer and in this way, increase the reaction yield. Then, the reaction was carried out with a 1:3 ligand/copper ratio. The results of these experiments are shown in entries 15 and 16 of Table 10. In the first run (entry 15), yield increased to 70% but, on the contrary, enantioselectivity decreased to 80%, probably indicating the presence of free copper in solution catalysing the reaction in a non-enantioselective way. In the second run (entry 16), free copper seems to have been extracted during catalyst recovery, so the enantiomeric excess increased to values as good as those obtained using a 1:2 ligand/copper ratio for the preparation of the complex. Regrettably, yield

decreased again to the same value as that obtained in the 13th run (50%).

According to the experience acquired working with coordination polymers, the obtaining of moderate yields indicates an incomplete release of catalytically active species due to partial decomplexation of the coordination polymer. For this reason, one more experiment was conducted using 6 mL of iPrOH, but using freshly prepared catalyst in this case. The results of this experiment are shown in entry 17 of Table 10. This time not only the enantiomeric excess was good (91% ee), but yield also increased with regard to the previous values (80% *vs.* 66% average yield), although without achieving the good results obtained with the click-DAX(iPr) ligand (96% in the first run, Table 5).

Conclusions

A family of polytopic chiral ligands, based on the bis(oxazoline) motif, have been tested in the reactions of *o*-anisaldehyde with nitromethane and nitroethane, catalysed by the $Cu(OAc)_2$ complexes of these ligands. In all cases, the release–capture strategy for the recovery and reuse of enantioselective catalysts, based on the precipitation of an insoluble coordination polymer at the end of each reaction, has been shown to be effective, allowing up to fourteen catalyst uses in the best case. Given the wide structural diversity of the ligands used, these results support the generality of this catalyst recycling strategy.

Compared with the results previously described with the DAX(iPr) ditopic ligand, improved performance has been obtained with the click-DAX(iPr) ditopic ligand in the reactions with nitromethane, and with the DiBox(In), click-DAX(iPr) and TAX(iPr) ligands in the reactions with nitroethane. In particular, the DiBox(In)-$Cu(OAc)_2$ complex has been used in 14 reaction cycles without a clear decrease in yield and enantioselectivities, which compares favourably with the 8 reaction cycles achieved with the DAX(iPr) ligand. It is worth noting that the results obtained with these polytopic ligands are significantly better than those recently reported by Bellemin-Laponnaz and co-workers, using analogous DiBox-, TriBox- and TetraBox-$Cu(AOc)_2$ complexes in the reaction of o-nitrobenzaldehyde with nitromethane.[24]

In the case of the tetratopic QAX(iPr) ligand, the easiness of the formation of coordination polymeric and oligomeric species, tough desirable for catalyst recovery, is detrimental for the catalytic activity, because of the decrease of catalytically active species in solution. This drawback can be overcome by increasing the dilution of the catalyst in the reaction medium. Nevertheless, given the good results obtained with the analogous and simpler ditopic ligand click-DAX(iPr), this should be the logical choice for practical applications.

Experimental

General Methods

All reactions were carried out under argon atmosphere in oven-dried glassware. Anhydrous solvents such as dichloromethane, hexane and Et_2O were obtained from a SPS-device; however, *i*-PrOH was distilled from calcium hydride. Liquid *o*-anisaldehyde was 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. All the ligands used in this work were prepared according to literature procedures.[18–20,23] The chemical shifts were relative to TMS as an internal reference for ^{1}H NMR.

General Procedure for Henry Reactions Promoted by Monotopic Azabis(oxazoline) or Bis(oxazoline)–copper Complexes

A solution of $Cu(OAc)_2$ (9.07 mg, 0.05 mmol) and the corresponding monotopic ligand (**1**, **2a**, **2b** or **2c**) (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 $Cu(OAc)_2$. Afterwards, the dichloromethane was removed under vacuum, and 2 mL of anhydrous isopropyl alcohol together with *o*-anisaldehyde (1 mmol) and the nitroderivative (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 have been described elsewhere.[23]

General Procedure for Henry Reactions Promoted by Politopic Azabis(oxazoline) or Bis(oxazoline)–copper Complexes

A solution of $Cu(OAc)_2$ (9.07 mg, 0.05 mmol) and either the corresponding ditopic ligand (**3a**, **3b**, **3c** or **4**) (0.055 mmol), tritopic ligand (**5**) (0.037 mmol) or tetratopic ligand (**6**) (0.027 mmol) in 4 mL of anhydrous isopropyl alcohol was stirred at room temperature for 30 min. Afterwards, the corresponding aldehyde (1 mmol) and the nitroderivative (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.

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