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Enantiomerically pure phenanthroline or bipyridine containing macrocycles: a new class of ligands for asymmetric catalysis

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Abstract—New enantiomerically pure phenanthroline- and bipyridine-containing macrocycles have been synthesized by combination of the coordinating unit to inexpensive and readily available chiral templates. The catalytic properties of their Cu(I) complexes have been studied in the cyclopropanation of alkenes as test reaction. A simple structural modification of the chiral cavity allowed us to successfully control the *trans* or *cis* diastereoselectivity of the reaction.

Nitrogen containing chiral ligands have found widespread use in asymmetric catalysis. Among them bipyridines and phenanthrolines are particularly attractive for their ability to coordinate several metal ions, and thus to generate different catalytic species involved in a great variety of reactions.[1] While many examples of chiral bipyridine ligands have been reported,[2] only a few phenanthroline ligands are known. This is likely due to the difficulty of synthesizing these compounds in enantiomerically pure form.[3] However, chiral phenanthrolines can potentially represent a very important class of ligands in asymmetric catalysis for their extraordinary properties of complexation of several metal ions.[4]

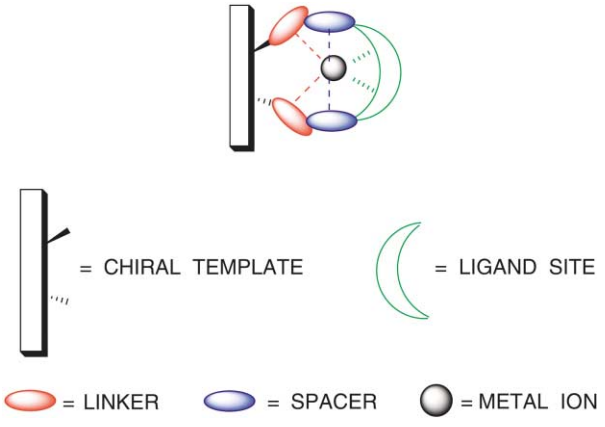

Figure 1. A schematic representation of the new chiral macrocycle ligands.

Recently we have studied the use of chiral auxiliaries to stereocontrol the complexation of achiral bipyridine units to give enantiomerically pure double helicate structures.[5] Based on this experience we decided to use the same chiral templates to build macroscopically chiral macrocycles containing the bipyridine or phenanthroline moiety. The idea is that the asymmetric environment around the complexation site would influence the approach of the reagents to the phenanthroline-bound metal, and would direct the stereochemical outcome of the reaction. With a macrocyclic ligand of correct size, the reaction should occur in the proximity or even inside the chiral cavity and the transfer of stereochemical information from the catalyst to the product should occur efficiently. Very recently a few examples of macrocyclic ligands of this type have been described. In one case[6] a bisoxazoline was built in a macrocycle and the catalytic activity of its Cu(I) complex tested in the cyclopropanation reaction of styrene with ethyldiazoacetate. In another case the preparation of chiral crown ethers,[7] by connecting poly(ethylene glycol) units of different size to binaphtol was reported,[8] and the combination of the macrocycles with different metals was studied. Eventually, a $Pb(OTf)_2$–crown ether complex was shown to be an efficient catalyst for asymmetric aldol reactions in aqueous media.[9]

Here, we wish to report our preliminary results in the preparation of enantiomerically pure phenanthroline-

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based macrocycles and the use of these new chiral ligands in the asymmetric cyclopropanation promoted by copper(I) triflate complex. Three elements were combined in building the supramolecular catalyst: a chiral auxiliary, a nitrogen containing ligand site and a connecting unit that may offer further points of diversity, by modification of the size and nature of the chemical bonds linking the different units of the assembly (Fig. 1).

At the outset of this investigation, the inexpensive and readily available chiral diacids **1**–**3** and diol **4** were used as chiral templates.[10] Bipyridines **5** and **6**[11] and phenanthrolines **7** and **8**,[12] prepared according to known procedures, provided the coordinating units. To explore the effect of a cavity-size modification on the stereochemical outcome of the reaction, a totally different phenanthroline ligand, **9**, was synthesized (Fig. 2).

The condensation of the acid chloride of **1** with diol **5** afforded the desired product **10** in very low yield (<10%). However, the reaction of the potassium carboxylate of the 6,6′-bis-methyl-2,2′-diphenyldicarboxylic acid **1** with 6,6′-bis-(bromomethyl)-2,2′-bipyridine **6** for 48 h in acetonitrile afforded the macrocycle **10** in 24% yield, with only traces of the dimeric compound **11** (5% yield)[13] (Scheme 1). Interestingly, when the reaction was performed under the same conditions in the presence of cesium carbonate, the chemical yield increased to 71% and the **10**/**11** ratio dramatically changed; in this case adduct **10** was obtained in 36% yield, while **11** was isolated in 35% yield, thus suggesting a templating effect of the counterion involved in the assembling of

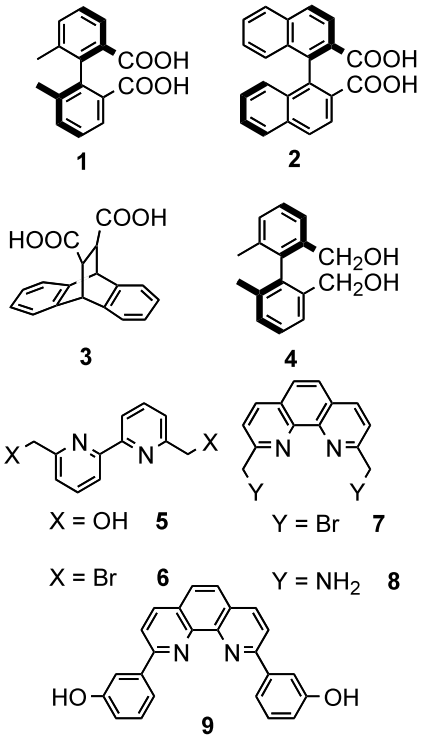
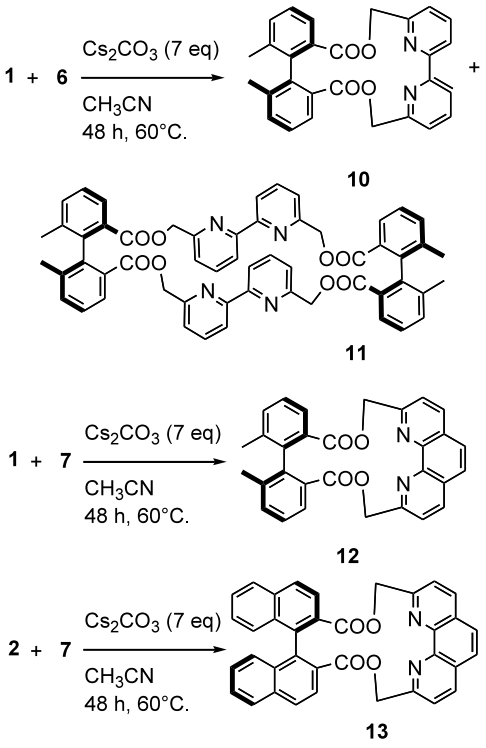


Figure 2. Chiral templates **1**–**4** and binding units **5**–**9**.

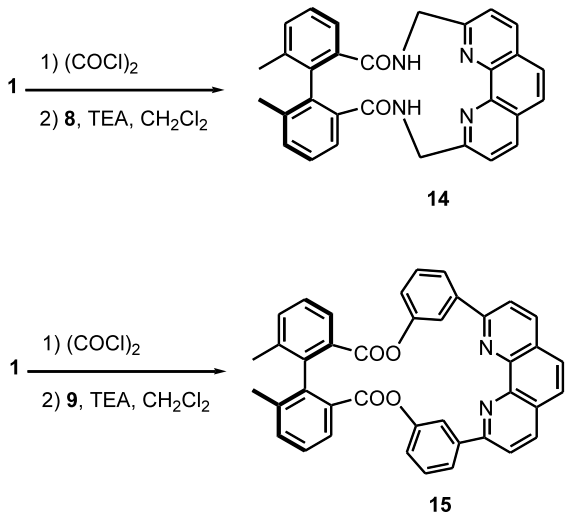


Scheme 1. Synthesis of macrocycle ligands **10**–**13**.

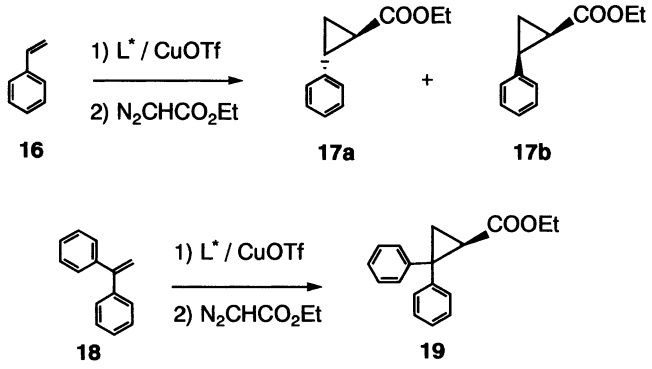
the macrocycle. Following the same procedure, the cesium carboxylates of acids **1**–**3** were reacted with phenanthroline **7**; while the reaction of diacid **3** gave only mixtures of products in low yields, the reaction of **1** and **2** afforded the expected ligands **12** and **13** in 55 and 53% yield, respectively (Scheme 1).

To study the influence of the nature of the bond between the ligand unit and the chiral template, the ligand **14**, featuring an amide bond, was prepared by condensing the acid chloride of dicarboxylic acid **1** to the diamine-phenanthroline derivative **8** (21% yield).[14] To demonstrate the possibility of introducing a spacer to modify and tune the shape and dimension of the chiral cavity, phenanthroline **9**, prepared according a modification of a known procedure[15] was attached to template **1** as described above; the enantiomerically pure macrocycle **15** was isolated in 45% yield (Scheme 2).

To test these new ligands for the generation of chiral macrocyclic catalysts, the styrene cyclopropanation with ethyldiazoacetate promoted by Cu(I) salts was chosen as model reaction (Scheme 3). The catalysts were prepared by mixing at 25°C copper(I) triflate and the ligands in dry methylene chloride. Styrene was then added, followed by a 0.1 M methylene chloride solution of ethyldiazoacetate, added by syringe pump.[16] The two isomers, *trans* **17a** and *cis* **17b** were isolated by flash chromatography and the enantiomeric excess of the single isomers evaluated by HPLC on a chiral stationary phase (Table 1).[17]



Scheme 2. Synthesis of macrocycle ligands **14**–**15**.



Scheme 3. Cyclopropanation reactions promoted by chiral macrocycles/Cu(I) complexes.

Preliminary experiments with the bipyridine-based ligand **10** and phenanthroline-ligand **12** showed that shorter complexation time improved both the chemical and the stereochemical efficiency of the reaction (entries 1 versus 2, 4 versus 5); a slow addition of ethyldiazoacetate was also necessary to increase the enantioselectivity of the cyclopropanation (entry 3 versus 2). Under the best experimental conditions ligand **12** afforded a 53% yield of a 78/22 *trans*/*cis* isomers mixture, and 67% ee for the *trans* isomer (entry 5). This ligand behaved better than the analogous derivative **10** (67% ee versus 56% ee), as a possible demonstration that the higher coordination ability of the phenanthroline unit compared to the bipyridine ligand leads to a tighter and possibly more selective complex.[4] Variations of the stoichiometry of the reagents and the reaction temperature did not improve the enantioselectivity (entries 6–8).[18] As expected, the binaphtoic acid derivative **13** showed a similar behavior (48% yield for the 77/23 *trans*/*cis* mixture, 63% ee for the *trans* isomer, entry 9), while ligand **14** afforded the product with lower enantioselectivity. Surprisingly, the copper(I) complex of ligand **15** in the same conditions catalyzed the cyclopropanation of styrene to give in 46% yield the *cis* isomer as major product (*cis*/*trans* 91/9) and with 63% ee (entry 12).[19] The different dimensions and shape of

Table 1. Cyclopropanation reactions promoted by Cu(I) complexes of ligands **10**–**15**

Entry	Macrocycle ligand	Complexation time (min)	Yield (%)[a]	*trans*/*cis* ratio	ee% *trans*[b]
1	**10**	60	18[c]	75/25	31
2	**10**	15	36[c]	75/25	37
3	**10**	15	41	76/24	56[d]
4	**12**	60	20	73/27	40
5	**12**	15	53	78/22	67[d]
6	**12**	15	51[e]	67/33	37
7	**12**	60	42[f]	77/23	47
8	**12**	15	60[f]	73/27	51
9	**13**	15	48	77/23	63[d]
10	**14**	15	40	70/30	50
11	**15**	60	36	10/90	60[g]
12	**15**	15	46	9/91	63[g]
13	**15**	15	12[h]	12/88	60[g]
14	**12**	15	23[i]	–	45[j]
15	**15**	15	30[i]	–	51[j]

[a] Isolated yields; for a typical procedure see Ref. 16.
[b] Determined by HPLC on a chiral stationary phase; *trans* isomer: DAICEL Chiralpack OD-H, hexane:*i*-PrOH 95:5; *cis* isomer: DAICEL Chiralpack OB, hexane:EtOH 99:1.
[c] Ethyldiazoacetate added in 3 h.
[d] *cis* isomer <20% ee.
[e] An excess of ethyldiazoacetate was used ($N_2CHCOOEt$:styrene:catalyst 3:1:0.1).
[f] Reaction conditions: 18 h at 25°C.
[g] Ee% of the *cis* isomer.
[h] Reaction conditions: 18 h at −40°C.
[i] Cyclopropanation of 1,1′-diphenylethylene.
[j] Determined by HPLC on a chiral stationary phase, DAICEL Chiralpack OD-H, hexane:*i*-PrOH 97:3.

the cavity, due to the presence of the phenyl rings, may account for the change of the sense of the diastereoselection. Lower temperature reaction did not improve the stereoselectivity of the process (entry 13). Finally the cyclopropanations of 1,1-diphenyl ethylene, promoted by both **12** and **15**, afforded the product in low yield and with similar enantioselectivity, 43 and 48%, respectively (entries 14 and 15).

In conclusion, new enantiomerically pure phenanthroline- and bipyridine-containing macrocycles have been synthesized, and their Cu(I) complexes used in the cyclopropanation of alkenes as test reaction. The ligands are easily prepared combining the coordinating unit to inexpensive and readily available chiral templates and offer several points of structural diversification. Although the levels of enantioselectivity of these new ligands is still far from the best performing known ligands, we believe that the extreme versatility of the synthesis, and its modular approach that allows to combine different building blocks to tune shape and dimension of the chiral cavity of this new class of structures open new possibilities in the field of asymmetric catalysis.

Supplementary material

Synthesis and characterization of macrocycle ligands **10**–**15** and a general procedure for the cyclopropanation reaction are available as supporting information.

Acknowledgements

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14. The reaction of diol **4** with phenanthroline **7** afforded only mixtures of products.
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16. Standard cyclopropanation procedure: to the solution of the ligand (0.1 mol equiv.) in dry dichloromethane copper(I) triflate (0.1 mol equiv.) was added under argon at room temperature; after the reaction mixture was stirred at 25°C (see Table 1 for complexation time), styrene (5

mol equiv.) was added at 0°C; then a solution of ethyldiazoacetate (1 mol equiv.) in dry methylene chloride was slowly added at 0°C in 10 h by syringe pump. The reaction mixture was allowed to stir for other 8 h at room temperature, then the solvent was concentrated in vacuum to give a residue that was purified by flash chromatography. The *trans*/*cis* ratio was determined by ^{1}H NMR on the crude mixture before purification and confirmed by ^{1}H NMR analysis on the isolated diastereoisomers.

17. All the new products were fully characterized and show spectral data in agreement with the proposed structure (see Supporting Information).
18. The reaction did not proceed at temperature lower than −20°C.
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