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Highly Recyclable Self-Supported Chiral Catalysts for the Enantioselective α-Hydrazination of β-Ketoesters

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Multitopic chiral copper complexes based on bis(oxazoline) have been applied in the enantioselective α-hydrazination of β-ketoesters. High yields and excellent enantioselectivities were obtained. Furthermore, the catalytic systems have been recovered in up to ten cycles without loss of activity or enantioselectivity. The formation of coordination polymers [polytopic ligand–Cu]$_n$ has been confirmed by UV/Vis titrations. Significant metal leaching was observed on increasing the topicity of the ligand. The nature of the catalyst was studied by nonlinear effect experiments.

Introduction

Asymmetric catalysis is a privileged approach for the production of enantiopure products. Today a large number of chiral catalytic processes may deliver products with very high enantiomeric excesses (*ee*) and some have been applied on an industrial scale. An example is the Tagasako process for the production of (−)-menthol that involves a Rh/2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP) catalyst (1500 tons year^{-1}).[1] Another example is the manufacture of (*S*)-metolachlor that uses an Ir/Josiphos catalyst (> 10 000 tons year^{-1}).[2] These homogeneous catalysts have thus shown synthetic utility because of their high activity and selectivity. However, homogeneous catalytic systems frequently exhibit lower activity and suffer from two drawbacks: 1) possible product contamination: in particular, metal contamination in active pharmaceutical ingredients or fine chemicals is a serious concern, and the remaining metal traces must be reduced to ppm amounts in the final products and 2) the inability to reuse the chiral catalyst. Catalytic systems that allow easy separation from the reaction mixture and efficient recycling are highly desirable because of the high cost of both the chiral ligand and the metal.

Immobilized homogeneous asymmetric catalysis is an attractive way to solve such problems, and efforts have been undertaken in this field. Over the past few decades, several strategies have been developed for the immobilization of homogeneous catalysts; these include immobilization on a solid support (inorganic, organic, polymer, or dendrimer) or the use of nonconventional media (phase-transfer catalysis, fluorous phase separation, ionic liquids, supercritical CO_2).[3,4] Although some of these systems have demonstrated good performances (enantioselectivity, activity, stability, or recycling ability), very few can compete with their homogeneous catalysis analogues as the immobilization step usually requires structural modifications of the complex that lower the activity and/or selectivity. Overall, this highlights the important influence of the catalyst support, which is yet to be understood.

In this context, a strategy that combines the advantages of both techniques (homogeneous and heterogeneous) appears desirable, that is, to associate the selectivity and activity offered by homogeneous catalysis with the easy recycling permitted by a heterogeneous system. In this sense, the selective assembly of multitopic ligands and metals into homochiral metal–organic coordination polymers (i.e., a self-supporting strategy; Scheme 1) may be considered as an appealing approach.[5] In such systems, the catalyst remains heterogeneous in its resting state at the end of the reaction and is dissolved in the reaction medium in its catalytically active state. There are at least two prerequisites to develop this type of catalyst. First, the metallopolymer obtained by a self-assembly process should be able to undergo a reversible polymerization/depolymerization process, such a feature is primarily controlled by the strength of the bonding interactions. Second, as the transformation of the inactive resting state into the active species occurs by depolymerization (i.e., partial decoordination) of the system, it is important that all monomeric active species should be equivalent. In other words, the effective symmetry of a coordinated ligand at the metal center must always be the same. In this regard, highly symmetric bis(oxazoline) ligands have been proved to be interesting tools to develop self-supported chiral catalysts. Garcia and collaborators reported the first example of oxazoline-based self-supported cata-

Scheme 1. The principle of self-supported catalysis.

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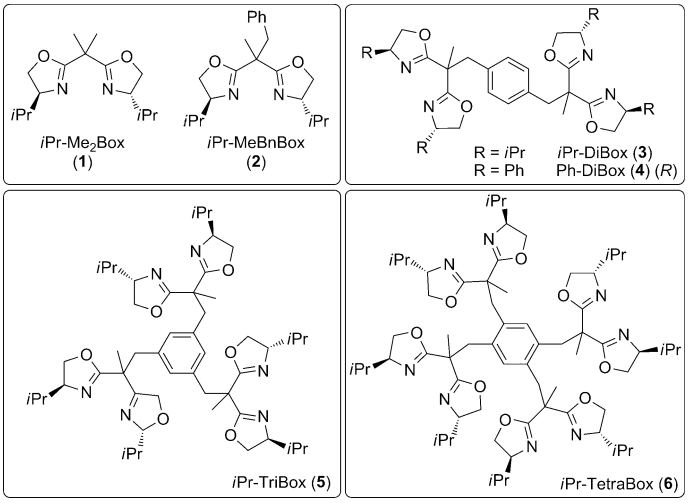
lysts in 2008.[6,7] Ditopic chiral ligands that bear azabis(oxazoline) moieties have been successfully used in the cyclopropanation reaction of alkenes with ethyl diazoacetate, the allylic oxidation of cycloalkenes with peroxoesters as well as the nitroaldol reaction, and the catalyst could usually be recycled without loss of activity and selectivity.[6,8–10]

In this work, we describe the application of Cu^{II} complexes supported by polytopic ligands (bis-, tris-, and tetratopic) as catalysts for the enantioselective α-hydrazination of β-ketoesters and their recovery by precipitation of the corresponding metallopolymers. Our investigations showed that ditopic ligands are best suited and that the use of tri- or tetratopic ligands did not improve the efficiency of the catalytic reaction. Excellent results (up to 99% *ee* and 99% yield) could be achieved along with easy recycling of the catalyst (up to ten times). To gain insights into these dynamic systems, we also conducted UV/Vis titrations of the metallopolymer formation, catalyst leaching investigations, and nonlinear effect (NLE) studies.

Results and Discussion

Ligand design and catalytic studies

The chiral ligands synthesized and used in the present study are shown in Scheme 2. (*S*)-Valinol and (*R*)-phenylglycinol were used to introduce groups with different steric bulk. Ditopic ligands **3** and **4** were synthesized in one step from methylbis(oxazolinyl)methane derivatives[11] by deprotonation followed by reaction with 1,4-bis(bromomethyl)benzene.[12] The same straightforward synthesis was used to access the tri- and tetratopic ligands **5** and **6**. The monotopic ligands dimethylbis(oxazoline) **1** and methylbenzylbis(oxazoline) **2** were used for comparison as they are structurally similar to the polytopic ligands developed in this study.[13]

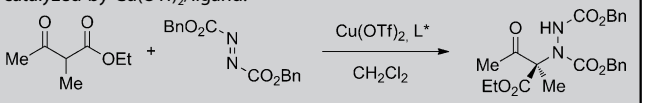


Scheme 2. Structures of the chiral ligands **1**–**6**.

As a test reaction, we investigated the enantioselective α-hydrazination of β-ketoesters, a reaction of interest for the synthesis of β-hydroxy-α-amino acids.[14] Cu^{II} salts in combination with bisoxazoline ligands have been shown to be effective catalysts for such reactions.[15]

The reaction of ethyl-2-methylacetoacetate with dibenzylazodicarboxylate was used as a reference reaction for our catalyst screening.[16] Some representative results are presented in Table 1. By using 4.0 mol% of **1**/$Cu(OTf)_2$ in dichloromethane as the solvent, an *ee* of 54% (80% yield) was observed at 0 °C under air. The introduction of the benzyl group in the bis(oxazoline) ligand **2** leads to a 58% *ee* and an increase of the reaction yield (95%). With the di-, tri-, or tetratopic ligands, which all contain isopropyl substituents, the catalytic results were slightly improved to approximately 80% *ee* of the resulting compounds, and the three systems were found to behave with a similar efficiency (83% yield).[17] Phenyl substituents on the oxazoline afforded the best results; thus, 93% *ee* and 95% yield were observed upon using **4** as the supporting ligand.

Table 1. Enantioselective α-hydrazination of ethyl-2-methyl acetoacetate catalyzed by $Cu(OTf)_2$/ligand.[a]

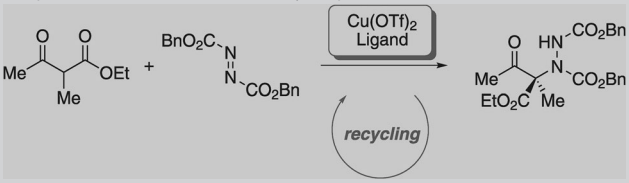


	Ligand	Yield [%]	*ee* [%]
1	*i*Pr-Me_2Box	80	54
2	*i*Pr-MeBnBox	95	58
3	*i*Pr-DiBox	83	78
4	Ph-DiBox	95	93
5	*i*Pr-TriBox	83	82
6	*i*Pr-TetraBox	83	77

[a] Experimental conditions: 4.0 mol% cat. $Cu(OTf)_2$, 16h, 0 °C. Yields determined by ^{1}H NMR spectroscopy by using an internal standard. Enantiomeric excesses were determined by HPLC using Chiralcel AD column.

We next compared the recycling of the catalyst with mono-, di-, tri-, and tetratopic ligands. With the isopropyl-substituted ligands, moderate enantiomeric excesses were observed. To study the effect of the varying catalyst environments, a reaction with moderate *ee* should be more informative, allowing a priori an increase or decrease of the enantioselectivity. The results are summarized in Table 2. For the catalytic investigations, diethyl ether was added to the reaction media at the end of each run, which led to the instantaneous precipitation of the catalyst. The solid was then recovered, washed with diethyl ether, dried, and then used again for another catalytic run. Only one catalytic run could be conducted with the monotopic ligands **1** or **2** as the catalytic system could not be recovered at the end of the reaction. Notably, we could perform up to eight cycles with the system with ditopic **3** with no significant alteration in enantioselectivity and yield. The use of the system with **5** led to a different outcome. After three runs, we observed a drop of efficiency of the catalyst. This tendency was even more pronounced with the tetratopic system **6**. A signifi-

Table 2. Enantioselective α-hydrazination of ethyl-2-methyl acetoacetate catalyzed by $Cu(OTf)_2$/ligand and evaluation of the recycling.[a]



Ligand		RUN	1	2	3	4	5	6	7	8
1	*i*Pr-Me_2Box	*ee*	**54**	-	-	-	-	-	-	-
		yield	80	-	-	-	-	-	-	-
2	*i*Pr-MeBnBox	*ee*	**58**	-	-	-	-	-	-	-
		yield	95	-	-	-	-	-	-	-
3	*i*Pr-DiBox	*ee*	**78**	**77**	**82**	**84**	**83**	**83**	**75**	**50**
		yield	83	90	87	89	87	89	85	85
5	*i*Pr-TriBox	*ee*	**82**	**80**	**80**	**57**	**38**	-	-	-
		yield	83	91	59	40	<5	-	-	-
6	*i*Pr-TetraBox	*ee*	**77**	**59**	**44**	**27**	-	-	-	-
		yield	83	67	71	34	-	-	-	-

[a] Experimental conditions: 4.0 mol% cat. $Cu(OTf)_2$, 16h, 0°C. Yields determined by ^1H NMR spectroscopy by using an internal standard. Enantiomeric excesses were determined by HPLC using Chiralcel AD column.

cant decrease of both the yields and the *ee* values was observed after the first recycling (i.e., during the second run). Overall, in the present case, increasing the topicity of the ligand may be detrimental for the efficient recycling of the catalytic system. From these screening experiments, ditopic bis(oxazoline) emerged as the ligand of choice for further studies.

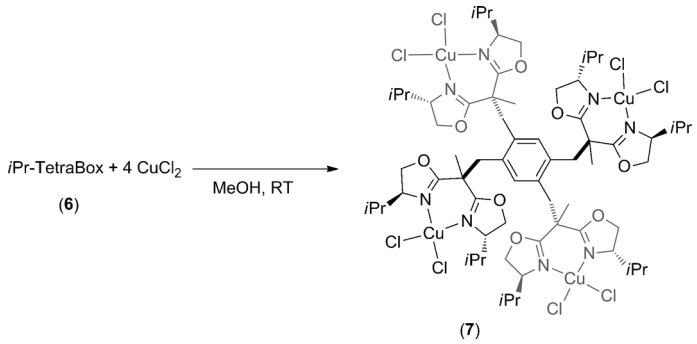
Having identified **3** and **4** as the most efficient systems for the enantioselective α-hydrazination of β-ketoester reactions, the scope with **4** as the ligand was explored. Excellent results were demonstrated for a series of acyclic and cyclic β-ketoesters. The substrates were all reacted with dibenzylazodicarboxylate in the presence of 4.0 mol% of $Cu(OTf)_2$/**4** catalyst in dichloromethane at 0°C under air. At the end of each reaction, diethyl ether was added to allow isolation of the catalyst by simple decantation and reuse without further purification in the next cycle. Acyclic β-ketoesters with alkyl (Me, *n*Bu) or benzyl substituents were tested as well as cyclic β-ketoesters (five- and six-membered ring size) as shown in Table 3. Excellent conversions and enantiomeric excesses could be obtained and six to ten runs could be conducted as a function of the substrate.

Structural studies of the catalysts

As the recoverability of the catalyst may be directly dependent on its structure, we decided to conduct some structural studies on our systems. We first analyzed the catalytic system that was precipitated at the end of the run by elemental analysis. The elemental analysis was consistent with the formation of the metallopolymer if the ditopic ligands **3** or **4** were used. However, the results were disappointing with the tri- or tetratopic ligands, which did not give the appropriate ligand/Cu molar ratio.

Despite numerous attempts, we were unable to grow X-ray-quality single crystals of the metallopolymers of Cu complexes of the multitopic ligands **3**–**6**. Unfortunately, we were unable to structurally characterize such polymeric species. However, we isolated a tetrameric Cu^{II} species (**7**) that bears ligand **6**. The reaction of four equivalents of $CuCl_2$ with **6** in dichloromethane led to the formation of crystals suitable for X-ray diffraction studies (Scheme 3).

In the solid state, **7** contains four bis(oxazoline)–Cu units, two of which are located on one side of the plane formed by the benzene ring and two on the other side (Figure 1). Each Cu atom is in a distorted square-planar coordination environment. The angle between the Cl-Cu-Cl plane and the N-Cu-N plane lies between 48.7 and 51.5°. The average Cl-Cu-Cl and N-Cu-N bond angles appear to be 99.7 and 89.3°, respectively. The Cu–N and Cu–Cl bond lengths are in the range 1.942(9)–1.998(9) and 2.205(5)–2.243(3) Å, respectively, and are consistent

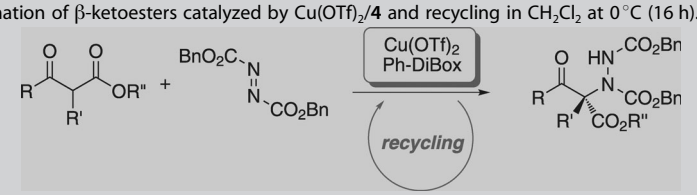


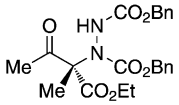
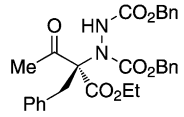
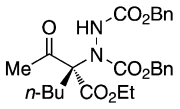
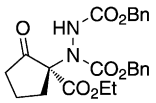
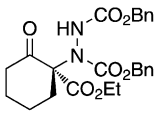
Scheme 3. Synthesis of **7** from **6**.

with previously published values.[18] A schematic view of the orientation of the four Cu–bis(oxazoline) moieties is shown in Figure 2. As a result of the rather flexible linker, each chelating ligand points away from its nearest neighbors.

To further characterize the metallopolymers, we conducted UV/Vis titration experiments. It is known that the formation of a linear metallopolymer can be confirmed by the exact stoichiometric ratio of the metal ion to ditopic ligand.[19] We first studied the assembly between ditopic ligand **3** and $Cu(OTf)_2$ by UV/Vis titration. The intensity of the band at 295 nm as a function of added Cu is shown in Figure 3. The band increases up to a ratio of 1:1, which indicates the formation of the metallopolymer (Figure 1a). The titration experiment between the tritopic ligand **5** and $Cu(OTf)_2$ revealed a maximum intensity at a metal-to-ligand ratio of 1.5:1, which is again consistent

Table 3. Enantioselective α-hydrazination of β-ketoesters catalyzed by $Cu(OTf)_2$/**4** and recycling in CH_2Cl_2 at 0 °C (16 h).[a]



	RUN	1	2	3	4	5	6	7	8	9	10
	*ee*	**93**	**94**	**98**	**98**	**98**	**97**	**96**	**98**	**98**	**99**
	yield	98	99	99	99	99	95	99	99	99	99
	*ee*	**98**	**99**	**98**	**99**	**99**	**99**	**99**	-	-	-
	yield	98	95	89	87	83	89	78	-	-	-
	*ee*	**93**	**96**	**94**	**95**	**96**	**87**	-	-	-	-
	yield	85	89	74	80	75	67	-	-	-	-
	*ee*	**96**	**98**	**97**	**99**	**99**	**99**	**99**	-	-	-
	yield	93	98	99	93	89	87	91	-	-	-
	*ee*	**99**	**99**	**99**	**99**	**99**	**99**	-	-	-	-
	yield	93	91	93	99	99	98	-	-	-	-

[a] Experimental conditions: 4.0 mol% cat. $Cu(OTf)_2$, 16h, 0 °C. Yields determined by ^1H NMR spectroscopy by using an internal standard. Enantiomeric excesses were determined by HPLC using Chiralcel AD, OD, or AS column.

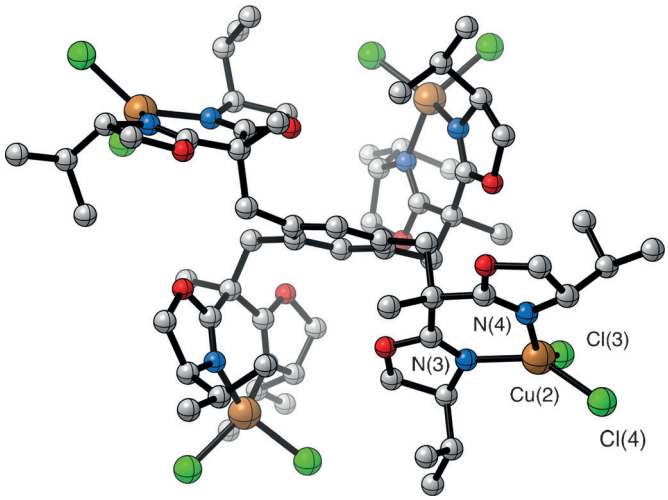


Figure 1. Molecular structure of **7**. Selected bond lengths [Å] and angles [°]: Cu(2)–Cl(3), 2.242(4); Cu(2)–Cl(4), 2.230(4); Cu(2)–N(3), 1.972(9); Cu(2)–N(4), 1.983(9); N(3)-Cu(2)-N(4), 89.6(4); Cl(3)-Cu(2)-Cl(4), 100.64(18); N(3)-Cu(2)-Cl(4), 97.9(3).

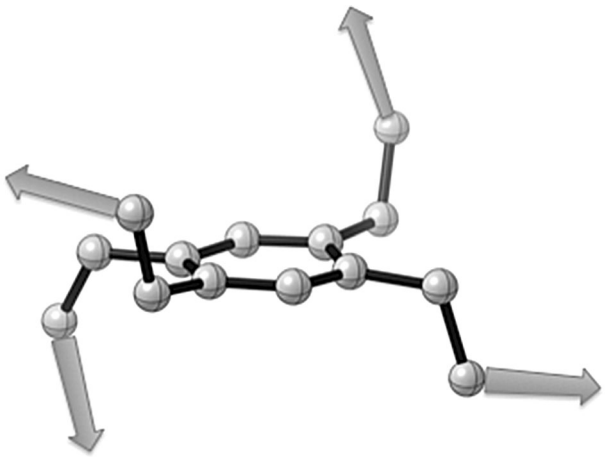


Figure 2. Schematic orientation of the four Cu–bis(oxazoline) units in **7**.

with the formation of the corresponding metallopolymer (Figure 3b). Finally, complexation of Cu with the tetratopic ligand **6** was followed by UV/Vis titration (Figure 3c). Interestingly, a maximum intensity was observed after the addition of more than 2.5 equivalents of $Cu(OTf)_2$, whereas only two equivalents should be sufficient to form the expected metallopolymer. This result suggests that the orientation of the four bis(oxazoline) units may not allow effective complexation with the metal salt.

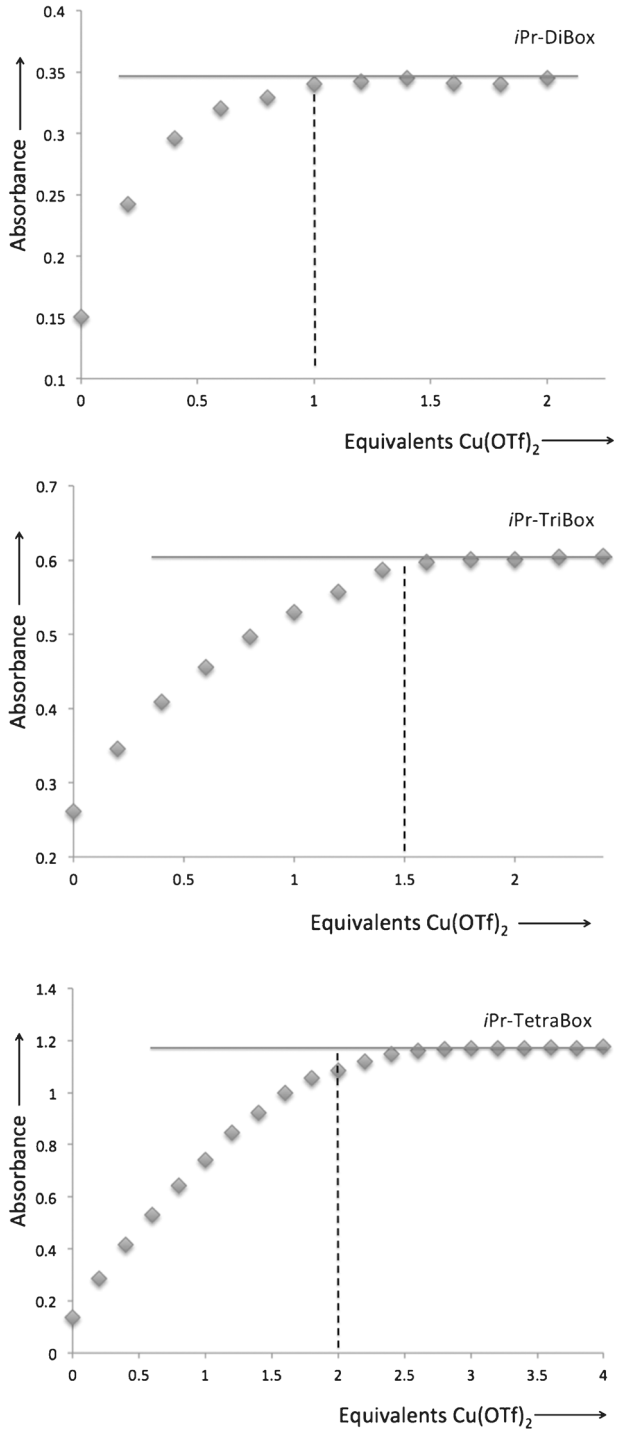


Figure 3. Plot of the absorption at 295 nm as a function of added $Cu(OTf)_2$ (in MeOH at room temperature): a) **3**, b) **5**, c) **6**.

Indeed, an important structural consideration here is that the bis(oxazoline) moieties should be oriented in such a way that they allow all Cu atoms to form homoleptic complexes. As deduced from the molecular structure in the solid state (Figures 1 and 2), it is apparently very difficult to reach such an unbroken framework, if not impossible.

This observation was correlated with Cu leaching. We reacted $Cu(OTf)_2$ with *i*Pr-based ligands **3**, **5**, and **6** in a 1:1, 3:2, and 2:1 ratio, respectively. Diethyl ether was added, and a turquoise precipitate formed instantly. The supernatant was removed and analyzed by inductively coupled plasma atomic-emission spectroscopy (ICP-AES). This established a loss in the amount of Cu of 3.9% with **3**, 5.7% with **5**, and 8.4% with **6**. The topicity of the ligand thus strongly affects the level of leaching, which is consistent with the UV/Vis titration experiments. Overall, the elemental analysis of the solids along with the UV/Vis titrations and the Cu leaching investigations are consistent with the best recyclability performance observed for the ditopic ligands **3** and **4**.

Nonlinear effects

Additional information regarding the aggregation of the catalytically active species may be gained from experiments in which the *ee* of the starting ligand was varied.[20] A series of experiments was performed to determine whether NLEs would be observed, and a significant negative nonlinear relationship between the *ee* of the product and that of the ligand was found (Figure 4). The metallopolymer is expected to serve as

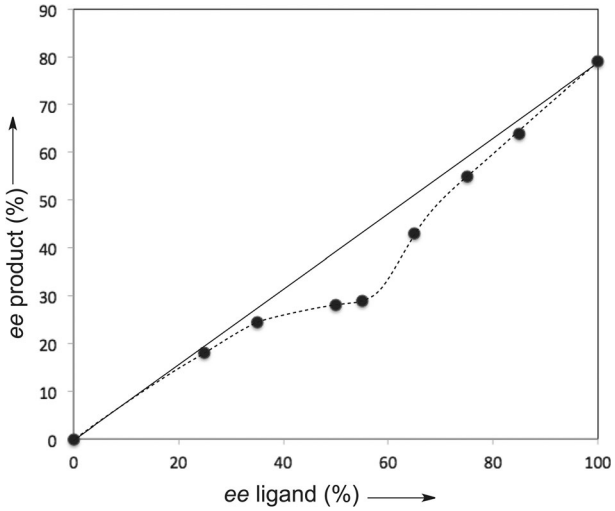


Figure 4. Enantiomeric excess of the product of ethyl-2-methyl acetoacetate with dibenzylazodicarboxylate as function of the enantiomeric excess of the chiral auxiliary **3** to show a negative NLE (4.0 mol% **3**/$Cu(OTf)_2$, 0 °C, CH_2Cl_2, 16 h).

a catalytically inactive reservoir and a negative NLE may be observed only by the preferential formation of a homochiral metallopolymer.[21] The steric demand and orientation of the oxazoline substituents are the critical factors that determine the formation of the homoleptic species. As Cu^{II} salts have a strong tendency to form a sixfold coordination geometry in a distorted octahedral environment (Jahn–Teller effect), the formation of homochiral homoleptic species with ligands in the equatorial position is expected to be favored.[22] The observation of a (−)-NLE is thus consistent with the preferential formation of a homochiral metallopolymer. Moreover, the perturbed behavior is indicative of a complicated structure, which could not be modeled by the simple mathematical models devel-

oped by Kagan. A bell-shaped curve suggests a degree of aggregation of at least three monomer units (i.e., a ML_3 model or more).[23]

Conclusions

We have described the synthesis of di-, tri-, and tetratopic bis(oxazoline)-based ligands and the formation of their coordination polymers with Cu. These systems were able to act as efficient self-supporting catalysts in the enantioselective α-hydrazination of β-ketoesters, a reaction of interest for the synthesis of β-hydroxy-α-amino acids. With the ditopic ligand **4** and $Cu(OTf)_2$, the reactions proceeded with 4.0 mol% of the catalyst to give the products in excellent yields and high enantiomeric excesses. Easy recovery of the catalyst has been demonstrated in up to ten cycles without loss of activity or enantioselectivity. Interestingly, the increase of the topicity of the ligand (i.e., tri- or tetratopic bis(oxazoline)) does not improve the recycling efficiency of the system and more catalyst leaching was observed in this case, in agreement with UV/Vis titration data. Finally, the nature of the catalyst system has been studied by nonlinear effect experiments, which reveal that the reaction mechanism most likely involves an equilibrium between the catalytically inactive homochiral metallopolymers and the active monomeric species.

Experimental Section

General Considerations

All reactions (except catalytic runs) were performed under an inert atmosphere of Ar or N_2 using standard Schlenk techniques. Solvents were purified and degassed by standard procedures. All reagents were used without further purification. ^1H and ^{13}C NMR spectra were recorded by using a Bruker Avance 300 spectrometer using the residual solvent peak as a reference ($CDCl_3$: $\delta_H = 7.26$ ppm; $\delta_C = 77.16$ ppm) at 298 K. HRMS (ESI) analyses were performed by using a microTOF instrument (Bruker Daltonics). HPLC analyses were performed by using a Gilson apparatus (UV-VIS156/321 PUMP) with Chiralcel Daicel columns (AD, OD, AS) using *n*-hexane/*i*PrOH eluents. Crystal data were collected at 173 K with MoK_α graphite-monochromated ($\lambda = 0.71073$ Å) radiation by using a Nonius Kappa CCD diffractometer. The structures were solved using direct methods with SHELXS97. Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were generated according to stereochemistry and refined using a riding model in SHELXL97. UV/Vis absorption spectra were recorded by using a Hitachi U-3000 spectrophotometer. ICP-AES experiments were conducted at the RepSem-ECPM laboratory, Strasbourg. CCDC 924923 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

General Procedure for the enantioselective α-hydrazination of β-ketoesters and recycling. Reaction of ethyl-2-methyl acetoacetate (Table 2, Entry 1)

$Cu(OTf)_2$ (2.2 mg, 0.006 mmol) and **4** (4.8 mg, 0.0065 mmol) were added to a vial with methanol (1.0 mL) under air. The mixture was stirred for 2 h and then dried in vacuo. Dichloromethane (1 mL) was added followed by the β-ketoester (21.2 μL, 0.15 mmol). The resulting mixture was cooled to 0 °C, and dibenzylazodicarboxylate (54.0 mg, 0.18 mmol) was added dropwise. After 16 h at 0 °C, diethyl ether was added, and a precipitate was formed instantly. The organic phase was isolated, concentrated, and the product was purified by flash chromatography (AcOEt/cyclohexane) and analyzed by using chiral HPLC (93% *ee*, 98% yield). The catalyst recovered by decantation was dried and reused in a new catalytic run. Elemental analysis of the precipitated catalyst $Cu(OTf)_2$–**4**: calcd (%) for $C_{50}H_{46}CuF_6N_4O_{10}S_2$ (1104.59): C 54.37, H 4.20, N 5.07; found C 54.46, H 4.37, N 5.31. Elemental analysis of the precipitated catalyst $Cu(OTf)_2$–**3**: calcd (%) for $C_{38}H_{54}CuF_6N_4O_{10}S_2$ (968.52): C 47.12, H 5.62, N 5.78; found C 47.34, H 5.78, N 5.97.

Synthesis of (*S*)-*i*Pr-DiBox (3). General Procedure

1,1′-Bis[(4*S*)-4,5-dihydro-4-isopropyloxazol-2-yl]ethane (3.96 mmol, 1 g) was dissolved in dry tetrahydrofuran (25 mL). A solution of 1.6 M *n*BuLi in hexane (4.31 mmol, 2.7 mL) was added dropwise at −78 °C. After stirring for 15 min, the cold bath was removed and α,α′-dibromo-*p*-xylene (1.96 mmol, 517.3 mg) was added. The mixture was then stirred at RT for 12 h. The resulting mixture was washed with saturated NH_4Cl solution, and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over Na_2SO_4. Evaporation of the solvent gave a colorless oil, which was purified by silica-gel column chromatography (AcOEt/MeOH, 95:5) to yield a colorless viscous oil (1.56 mmol, 948 mg, 80%).$[a]_D^{25} = -0.81$ cm^3 g^{-1} dm^{-1} ($c = 0.5$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.03$ (s, 4H, H_{arom}), 4.22 (dt, $^3J = 8.0$ Hz, $^3J = 1.3$ Hz, 4H, –NC*H*), 4.05–3.90 (m, 8H, –OCH_2), 3.24 (s, 4H, –CH_2), 1.84–1.67 (m, 4H, –C*H*(CH$_3$)$_2$), 1.40 (s, 6H, –C(CH_3), 0.94–0.80 ppm (m, 24H, –CH(CH_3)$_2$); $^{13}C\{^1H\}$ NMR (300 MHz, $CDCl_3$): $\delta = 167.6$ (N=*C*O), 134.9 (–C_{arom}), 130.1 (–C_{arom}), 72.0, 71.6 (–NCH), 70.1, 69.8 (–OCH_2), 43.3 (–*C*CH$_3$), 41.8 (–CH_2), 32.5, 32.2 (–*C*H(CH$_3$)$_2$), 21.2 (–C(CH_3), 18.8, 18.7, 17.9, 17.5 ppm (–CH(CH_3)$_2$); IR (KBr): $\tilde{\nu} = 1658$ cm^{-1} (s, C=N); MS (ESI+): *m/z*: 607.42 $[M+H]^+$; elemental analysis calcd (%) for $C_{36}H_{54}N_4O_4$ (606.84): C 71.25, H 8.97, N 9.23; found C 70.97, H 8.89, N 9.21.

Synthesis of (*S*)–*i*Pr-MeBnBox (2)

The general procedure was followed. 4.6 mmol, 58%; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.24$–7.13 (m, 5H, H_{arom}), 4.26–4.19 (m, 2H, –NC*H*), 4.04–3.88 (m, 4H, –OCH_2), 3.29 (q, $^4J = 13.5$ Hz, 2H, –CH_2), 1.83–1.68 (m, 2H, –C*H*(CH$_3$)$_2$), 1.42 (s, 3H, –C(CH_3)), 0.92–0.79 ppm (m, 12H, –CH(CH_3)$_2$); $^{13}C\{^1H\}$ NMR (300 MHz, $CDCl_3$): $\delta = 167.6$ (N=*C*O), 136.7 (–C_{arom}), 130.5 (–C_{arom}), 127.9 (–C_{arom}), 126.6 (–C_{arom}), 71.9, 71.6 (–NCH), 70.1, 69.7 (–OCH_2), 43.3 (–*C*CH$_3$), 42.1 (–CH_2), 32.5, 32.2 (–*C*H(CH$_3$)$_2$), 21.2 (–C(CH_3)), 18.8, 18.7, 17.9, 17.4 ppm (–CH(CH_3)$_2$); IR (KBr): $\tilde{\nu} = 1659$ cm^{-1} (s, C=N); MS (ESI+): *m/z*: 343.23 $[M+H]^+$; elemental analysis calcd (%) for $C_{21}H_{30}N_2O_2$ (342.48): C 73.65, H 8.83, N 8.18; found C 73.43, H 8.72, N 7.95.

Synthesis of (*R*)–Ph-DiBox (4)

The general procedure was followed. 1.65 mmol (53% yield); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.34$–7.55 (m, 16H, $H_{arom(PhBOX)}$), 7.17 (s, 4H, H_{arom}), 7.12–7.09 (m, 4H, $H_{arom(PhBOX)}$), 5.30–5.18 (m, 4H, –NC*H*), 4.74–4.67 (m, 4H, –OCH_2), 4.23–4.10 (m, 4H, –OCH_2), 3.45 (s, 4H, –CH_2), 1.64 ppm (s, 6H, –C(CH_3)); $^{13}C\{^1H\}$ NMR (300 MHz, $CDCl_3$): $\delta = 169.3$, 169.1 (N=*C*O), 142.3, 142.1, 135.1, 130.4, 128.7, 128.6, 128.5, 127.6, 127.5, 126.7 (–C_{arom}), 75.33 (–NCH), 69.7, 69.6 (–

OCH_2), 43.8 (–CCH_3), 41.8 (–CH_2), 21.3 ppm (–C(CH_3)); IR (KBr): $\tilde{\nu}$ = 1654 cm^{-1} (s, C=N); MS (ESI+): *m/z*: 765.34 $[M+Na]^+$; elemental analysis calcd (%) for $C_{48}H_{46}N_4O_4$ (706.96): C 77.60, H 6.24, N 7.54; found C 77.90, H 6.30, N 7.23.

Synthesis of (*S*)–*i*Pr-TriBox (5)

The general procedure was followed. 1.65 mmol (30% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.86 (s, 3H, H_{arom}), 4.27–4.18 (m, 6H, –NC*H*), 4.45–3.89 (m, 12H, –OCH_2), 3.29–3.06 (m, 6H, –CH_2), 1.81–1.69 (m, 6H, –$CH(CH_3)_2$), 1.39 (s, 9H, –C(CH_3), 0.93–0.81 ppm (m, 36H, –CH(CH_3)$_2$); ^{13}C{^{1}H} NMR (300 MHz, $CDCl_3$): δ = 167.9, 167.3 (N=*C*O), 135.7 (–C_{arom}), 131.3 (–C_{arom}), 71.9, 71.6 (–NCH), 69.9, 69.6 (–OCH_2), 43.3 (–CCH_3), 41.9 (–CH_2), 32.4, 32.2 (–$CH(CH_3)_2$), 21.3 (–C(CH_3), 18.6, 17.6, 17.4 ppm (–CH(CH_3)$_2$); IR (KBr): $\tilde{\nu}$ = 1660 cm^{-1} (s, C=N); MS (ESI+): *m/z* = 871.60 $[M]^+$; elemental analysis calcd (%) for $C_{51}H_{78}N_6O_6$ (871.20): C 70.31, H 9.02, N 9.65; found C 69.94, H 9.13, N 9.38.

Synthesis of (*S*)–*i*Pr-TetraBox (6)

The general procedure was followed. 0.15 mmol (171.1 mg, 38%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.95 (s, 2H, H_{arom}), 4.29–4.18 (m, 8H, –NC*H*), 4.04–3.67 (m, 16H, –OCH_2), 1.73–1.66 (m, 8H, –$CH(CH_3)_2$), 1.29 (s, 12H, –C(CH_3), 0.89–0.84 (m, 48H, –CH(CH_3)$_2$; ^{13}C{^{1}H} NMR (300 MHz, $CDCl_3$): δ = 167.7 (N=*C*O), 134.3 (–C_{arom}), 133.3 (–C_{arom}), 72.1, 71.5 (–NCH), 70.1, 69.6 (–OCH_2), 43.9 (–CCH_3), 37.2 (–CH_2), 32.7, 32.2 (–$CH(CH_3)_2$), 20.8 (–C(CH_3)), 18.9, 18.6, 18.0, 17.4 ppm (–CH(CH_3)$_2$); IR (KBr): $\tilde{\nu}$ = 1658 cm^{-1} (s, C=N); MS (ESI+): *m/z*: 1135.79 $[M+H]^+$, 568.40 $[M+H-C_{33}H_{51}N_4O_4]^+$; elemental analysis calcd (%) for $C_{66}H_{102}N_8O_8$ (1135.56): C 69.81, H 9.05, N 9.87; found C 69.49, H 9.06, N 9.21.

Complex 7

Ligand **6** (42 mg, 0.04 mmol) dissolved in dichloromethane (3 mL) was added to $CuCl_2$ (21.5 mg, 0.16 mmol), and the resulting green solution was stirred overnight. The diffusion of methanol/cyclohexane into this solution by vapor diffusion led to crystals suitable for X-ray diffraction. IR (KBr): $\tilde{\nu}$ = 1650 cm^{-1} (s, C=N); elemental analysis calcd (%) for $C_{66}H_{102}Cl_8Cu_4N_8O_8{\cdot}2(CH_3OH)$ (1673.37): C 47.01, H 6.38, N 6.45; found C 47.48, H 6.54, N 6.21. **Crystal data for 7:** $C_{66}H_{102}Cl_8Cu_4N_8O_8{\cdot}3(CH_4O)$; M_w = 1769.44; monoclinic; *a* = 15.5526(4), *b* = 18.3310(7), *c* = 16.4599(5) Å; α = 90, β = 90.400(2), γ = 90°; *V* = 4692.5(3) Å^3; *T* = 173(2) K; space group $P2_1$; *Z* = 2; Data completeness = 1.67/0.86; θ_{max} = 27.480; *R* (reflections) = 0.0951 (15137); *wR*2 (reflections) = 0.2410 (18578).

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[1] R. Noyori, *Angew. Chem.* **2002**, *114*, 2108; *Angew. Chem. Int. Ed.* **2002**, *41*, 2008.
[2] H. U. Blaser, B. Pugin, F. Splinder, M. Thommen, *Acc. Chem. Res.* **2007**, *40*, 1240.
[3] *Handbook of Asymmetric Heterogeneous Catalysis* (Eds.: K. Ding, Y. Uozumi), Wiley-VCH, Weinheim, **2008**.
[4] For reviews, see: a) L.-X. Dai, *Angew. Chem.* **2004**, *116*, 5846; *Angew. Chem. Int. Ed.* **2004**, *43*, 5726; b) M. Heitbaum, F. Glorius, I. Escher, *Angew. Chem.* **2006**, *118*, 4850; *Angew. Chem. Int. Ed.* **2006**, *45*, 4732; c) K. Ding, Z. Wang, X. Wang, Y. Liang, X. Wang, *Chem. Eur. J.* **2006**, *12*, 5188; d) K. Ding, Z. Wang, L. Shi, *Pure Appl. Chem.* **2007**, *79*, 1531; e) Z. Wang, G. Chen, K. Ding, *Chem. Rev.* **2009**, *109*, 322.
[5] The formation of a charge-transfer complex also appears to be an interesting approach for enantioselective catalyst recycling, see for example: a) D. Dorian, C. Magnier-Bouvier, E. Schulz, *Adv. Synth. Catal.* **2011**, *353*, 1087; b) D. Dorian, E. Schulz, *ChemCatChem* **2011**, *3*, 1880.
[6] J. I. García, B. López-Sánchez, J. A. Mayoral, *Org. Lett.* **2008**, *10*, 4995.
[7] This concept has been used in ring-opening metathesis polymerization catalysis, see: a) S. W. Chen, J. H. Kim, C. E. Song, S.-g. Lee, *Org. Lett.* **2007**, *9*, 3845; b) S. W. Chen, J. H. Kim, H. Shin, S.-g. Lee, *Org. Biomol. Chem.* **2008**, *6*, 2676.
[8] J. I. García, C. I. Herrerías, B. López-Sánchez, J. A. Mayoral, O. Reiser, *Adv. Synth. Catal.* **2011**, *353*, 2691.
[9] L. Aldea, I. Delso, M. Hager, M. Glos, J. I. García, J. A. Mayoral, O. Reiser, *Tetrahedron* **2012**, *68*, 3417.
[10] B. Angulo, J. I. García, C. I. Herrerías, J. A. Mayoral, A. C. Miñana, *J. Org. Chem.* **2012**, *77*, 5525.
[11] a) S. Dagorne, S. Bellemin-Laponnaz, R. Welter, *Organometallics* **2004**, *23*, 3053; b) For a review on bis(oxazolinates), see: S. Dagorne, S. Bellemin-Laponnaz, A. Maisse-François, *Eur. J. Inorg. Chem.* **2007**, 913.
[12] a) A. Nano, L. Brelot, G. Rogez, A. Maisse-François, S. Bellemin-Laponnaz, *Inorg. Chim. Acta* **2011**, *376*, 285; b) M. Torres, B. Heinrich, K. Miqueu, S. Bellemin-Laponnaz, *Eur. J. Inorg. Chem.* **2012**, 3384; c) M. Seitz, C. Capacchione, S. Bellemin-Laponnaz, H. Wadepohl, B. D. Ward, L. H. Gade, *Dalton Trans.* **2006**, 193.
[13] Reviews: a) F. Fache, E. Schulz, M. L. Tommasino, M. Lemaire, *Chem. Rev.* **2000**, *100*, 2159; b) A. K. Ghosh, P. Mathivanan, J. Cappiello, *Tetrahedron: Asymmetry* **1998**, *9*, 1; c) H. A. McManus, P. J. Guiry, *Chem. Rev.* **2004**, *104*, 4151; d) G. Desimoni, G. Faita, K. A. Jørgensen, *Chem. Rev.* **2006**, *106*, 3561; e) R. Rasappan, D. Laventine, O. Reiser, *Coord. Chem. Rev.* **2008**, *252*, 702.
[14] a) J. M. Janey, *Angew. Chem.* **2005**, *117*, 4364; *Angew. Chem. Int. Ed.* **2005**, *44*, 4292; b) C. Nájera, J. M. Sansano, *Chem. Rev.* **2007**, *107*, 4584; c) N. Kumagai, M. Shibasaki, *Angew. Chem.* **2011**, *123*, 4856; *Angew. Chem. Int. Ed.* **2011**, *50*, 4760.
[15] M. Marigo, K. Juhl, K. A. Jørgensen, *Angew. Chem.* **2003**, *115*, 1405; *Angew. Chem. Int. Ed.* **2003**, *42*, 1367.
[16] For our previous investigations, see : a) M. Gaab, S. Bellemin-Laponnaz, L. H. Gade, *Chem. Eur. J.* **2009**, *15*, 5450; b) L. H. Gade, S. Bellemin-Laponnaz, *Chem. Eur. J.* **2008**, *14*, 4142; c) C. Foltz, B. Stecker, G. Marconi, S. Bellemin-Laponnaz, H. Wadepohl, L. H. Gade, *Chem. Eur. J.* **2007**, *13*, 9912; d) C. Foltz, B. Stecker, G. Marconi, S. Bellemin-Laponnaz, H. Wadepohl, L. H. Gade, *Chem. Commun.* **2005**, 5115.
[17] 4 mol% of Cu salt was used for the catalytic studies. The ligand-to-Cu ratio was adapted for each polytopic ligand for the formation of the coordination polymer, that is, 1:1 for **3** and **4**, 0.66:1 for **5**, and 0.5:1 for **6**.
[18] a) J. Thorhauge, M. Roberson, R. G. Hazell, K. A. Jørgensen, *Chem. Eur. J.* **2002**, *8*, 1888; b) L. H. Gade, G. Marconi, C. Dro, B. D. Ward, M. Poyatos, S. Bellemin-Laponnaz, H. Wadepohl, L. Sorace, G. Poneti, *Chem. Eur. J.* **2007**, *13*, 3058; c) V. L. Rendina, S. A. Goetz, A. E. Neitzel, H. Z. Kaplan, J. S. Kingsbury, *Tetrahedron Lett.* **2012**, *53*, 15.
[19] See for example : a) I. Welterlich, B. Tieke, *Macromolecules* **2011**, *44*, 4194; b) D. Knapton, S. J. Rowan, C. Weder, *Macromolecules* **2006**, *39*, 651; c) A. Winter, C. Friebe, M. Chiper, M. D. Hager, U. S. Schubert, *J. Polym. Sci. Part A* **2009**, *47*, 4083.
[20] a) T. Satyanarayana, S. Abraham, H. B. Kagan, *Angew. Chem.* **2009**, *121*, 464; *Angew. Chem. Int. Ed.* **2009**, *48*, 456; b) H. B. Kagan, *Adv. Synth. Catal.* **2001**, *343*, 227; c) H. B. Kagan, *Oil Gas Sci. Technol.* **2007**, *62*, 731.

[21] a) A. Kina, H. Iwamura, T. Hayashi, *J. Am. Chem. Soc.* **2006**, *128*, 3904; b) M. Yamakawa, R. Noyori, *J. Am. Chem. Soc.* **1995**, *117*, 6327; c) M. Tsukamoto, K. Gopalaiah, H. B. Kagan, *J. Phys. Chem. B* **2008**, *112*, 15361.
[22] a) C. Place, J. L. Zimmermann, E. Mulliez, G. Guillot, C. Bois, J. C. Chottard, *Inorg. Chem.* **1998**, *37*, 4030; b) S. Abuskhuna, M. McCann, J. Briody, M. Devereux, V. McKee, *Polyhedron* **2004**, *23*, 1731; c) G. J. A. A. Koolhaas, P. M. van Berkel, S. C. van der Slot, G. Mendoza-Diaz, W. L. Driessen, *Inorg. Chem.* **1996**, *35*, 3525; d) Y. Song, C. Massera, P. Gamez, A. M. Manotti Lanfredi, J. Reedijk, *Eur. J. Inorg. Chem.* **2004**, 3025.
[23] D. Guillaneux, S.-H. Zhao, O. Samuel, D. Rainford, H. B. Kagan, *J. Am. Chem. Soc.* **1994**, *116*, 9430.

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