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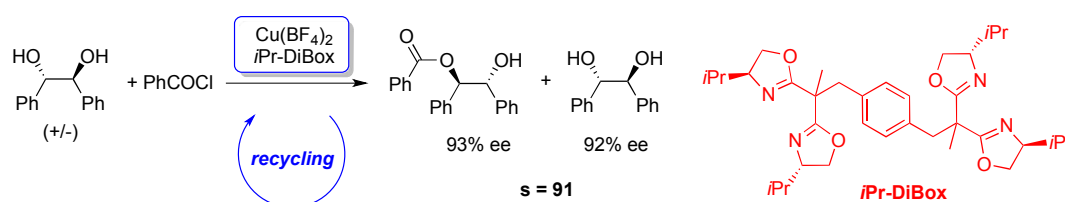
**Asymmetric Benzoylation and Henry Reaction
Using Reusable Polytopic Bis(Oxazoline) Ligands and Copper(II).**

Maria Torres-Werlé,^a Adela Nano,^a Aline Maise-François,^a Stéphane Bellemin-Laponnaz*^{a,b}

^a *Institut de Physique et Chimie des Matériaux de Strasbourg, Université de Strasbourg,
CNRS UMR 7504, 23 rue du Loess, BP 43, F-67034 Strasbourg Cedex 2, France
Fax: (+33) 388 107 246
E-mail: bellemin@unistra.fr*

^b *University of Strasbourg, Institute for Advanced Study (USIAS), 5 allée du Général
Rouvillois, 67083 Strasbourg, France.*

Graphical Abstract



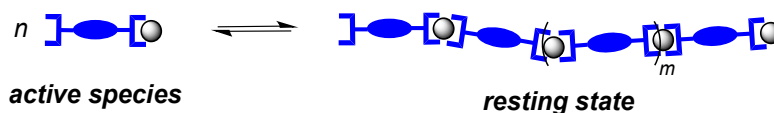
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Abstract: Multitopic bis(oxazoline)-based chiral ligands are associated with copper to generate catalysts for the asymmetric benzylation of *meso*-hydrobenzoin, the kinetic resolution of *rac*-hydrobenzoin and the asymmetric Henry reaction. The recycling of the catalytic systems has been studied. The recycling efficiency of the system was found to be dependent on the copper source used.

1. Introduction

In the past ten years, the development of recoverable enantioselective catalysts has been the subject of intensive research.^[1,2] Homogeneous chiral catalysts are usually high-value molecules that require several steps synthesis. Their easy recovery from reaction media and reuse in successive catalytic runs is an important objective. Among the various strategies, the immobilization of the catalyst on an insoluble solid support has been the most commonly used.^[3] However, these synthetically demanding methods usually give lower activities and/or enantioselectivities than the corresponding homogeneous systems. Non-covalent immobilization strategies avoid the chemical functionalization of the chiral ligand but suffer as well from a decrease of both enantioselectivities and activities. Chiral catalyst immobilization using nonconventional media (ionic liquid, water, CO₂...) may, in principle, avoid the lack of reactivity.^[1] However drastic drawbacks, which limit its scope of applications, have also been observed. Therefore, the identification of more economical and reliable enantioselective systems with high activity, selectivity and reusability remains a challenge.

In this context, a strategy that allows to carry out the reaction in the homogeneous phase and then, selectively and cleanly precipitate the catalyst at the end of the process appears interesting. This key step would allow an easy recovery and further recycling of the catalyst.^[4] Different strategies may be used to reach this goal, and among them the *self-supporting* strategy (*i.e* the selective assembly of multitopic ligands and metals ions to form homochiral metal-organic coordination polymers) constitutes an attractive approach. In such systems, the catalyst remains polymeric at its resting state, whereas it is mononuclear in the reaction medium at its catalytically active state (scheme 1).



Scheme 1. Principle of self-supported catalysts.

The first example of oxazoline-based self-supported catalysts was reported in 2008.^[5,6] Ditopic chiral ligands bearing azabis(oxazoline) moieties have been successfully used in the cyclopropanation, allylic oxidation and nitroaldol reactions and the catalyst could usually be recycled several times without any loss of activity or selectivity.^[7-9] Lately, Cu(II) complexes supported by polytopic bis(oxazoline) ligands have been successfully applied to the enantioselective α -hydrazination of β -ketoesters and were recovered by precipitation.^[10]

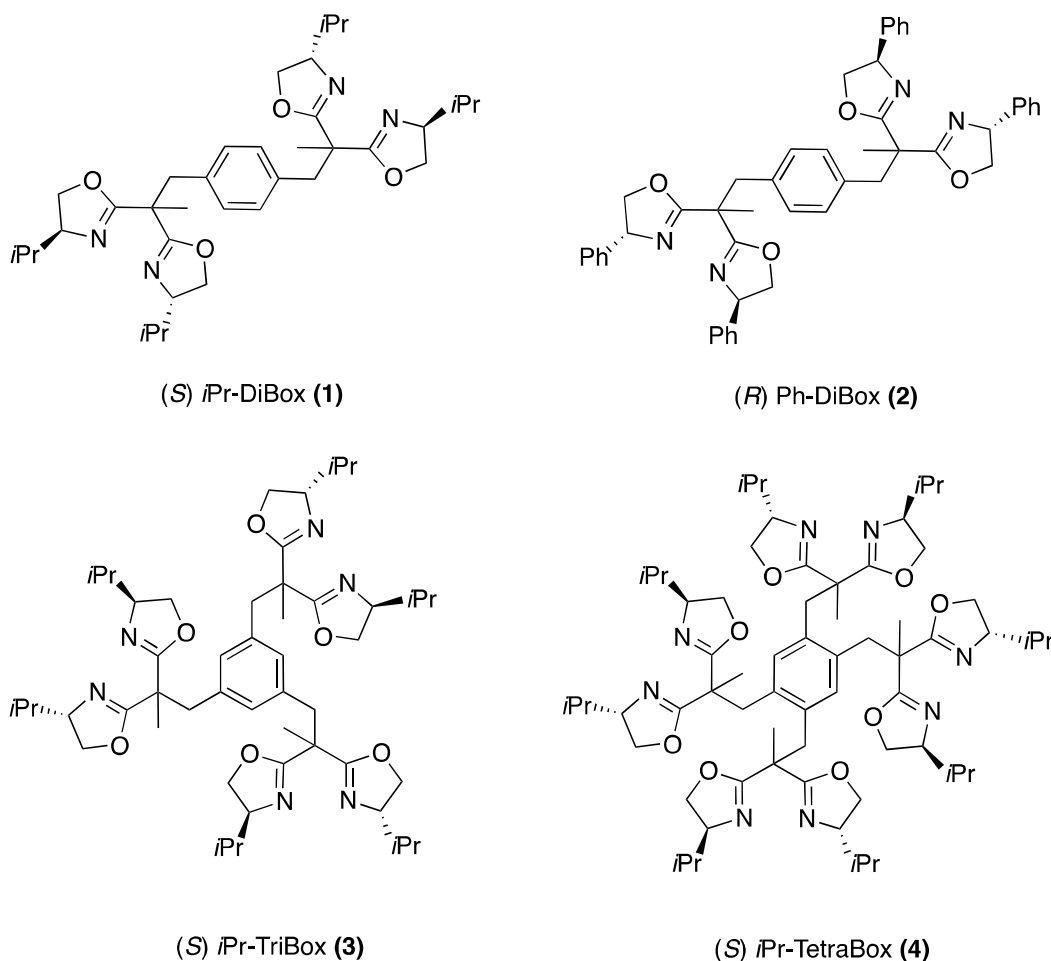
In this work, we describe the metal catalyzed asymmetric benzoylation of diols and the asymmetric nitroaldolisation reaction (Henry reaction). These transformations use a combination of polytopic bis(oxazoline)-based ligands DiBox, TriBox and TetraBox and copper as catalyst. Our investigations showed that the recyclability of the catalytic system is dependent on the nature of the copper salt. Whereas the use of cationic salts such as $\text{Cu}(\text{BF}_4)_2$ easily generate an insoluble polymeric recyclable catalyst upon addition of a co-solvent. In contrast, neutral complexes such as $\text{Cu}(\text{OAc})_2$ prevent the formation of the polymer and therefore the easy precipitation of the system.

2. Results and discussion

2.1 Enantioselective benzoylation of *meso*-hydrobenzoin

For our studies, we used di-, tri- and tetra-topic bis(oxazoline) ligands (*S*) *i*Pr-DiBox (**1**), (*R*) Ph-DiBox (**2**), (*S*) *i*Pr-TriBox (**3**) and (*S*) *i*Pr-TetraBox (**4**) (Scheme 2).^[11] They were synthesized in one step procedure by deprotonation of methyl-bis(oxazoliny)methane

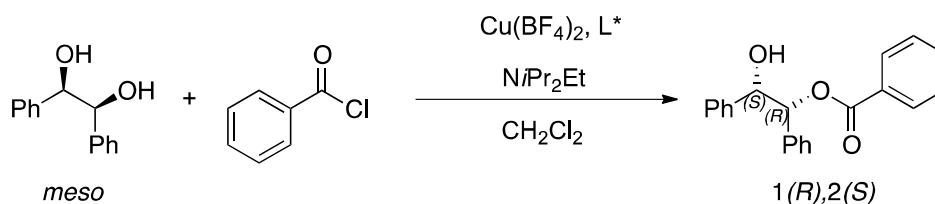
derivatives followed by reaction with 1,4-bis(bromomethyl)benzene, 1,3,5-tris(bromomethyl)benzene and 1,2,4,5-tetrakis(bromomethyl)benzene, respectively.^[12,13]



Scheme 2. Structure of the chiral ligands (1-4).

C_2 -symmetric bis(oxazoline) ligands in combination with copper(II) were found as efficient catalysts for the asymmetric benzylation of *meso*-hydrobenzoin as well as the kinetic resolution of *rac*-hydrobenzoin.^[14] Our catalytic combination using $Cu(BF_4)_2$ (10 mol%) as copper source and chiral polytopic ligand (1, 2, 3 and 4) was then tested in the asymmetric benzylation in the presence of $(iPr)_2NEt$ (2 equivalents) as external base in dichloromethane at 0°C.^[15] As earlier describe,^[10] the ligand to copper ratio was adapted for each polytopic ligand so that to generate the corresponding coordination polymer, that is, 1:1 for the ligands (1) and (2), 0.66:1 for the ligand (3) and 0.5:1 for the ligand (4).^[16] Some representative

results are presented in Table 1 for the asymmetric benzylation of *meso*-hydrobenzoin. Overall, good yields and enantiomeric excesses were achieved. However, lower ee (76%) was obtained with the ditopic ligands (*R*) Ph-DiBox (**2**) compared to the corresponding monotopic (*R*) PhBox ligand (94% ee).^[14] The best asymmetric induction for this first run was observed with the tritopic ligand (**3**) (79% ee). The tetratopic ligand (**4**) gave modest enantiomeric excess of 65% (Entry 4).

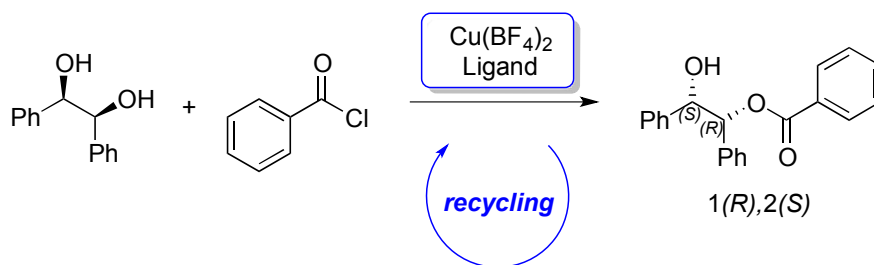


	Ligand	Yield [%]	ee [%]	
1	(<i>S</i>)- <i>i</i> Pr-DiBox	88	71	1(<i>R</i>),2(<i>S</i>)
2	(<i>R</i>)-Ph-DiBox	91	76	1(<i>S</i>),2(<i>R</i>)
3	(<i>S</i>)- <i>i</i> Pr-TriBox	77	79	1(<i>R</i>),2(<i>S</i>)
4	(<i>S</i>)- <i>i</i> Pr-TetraBox	68	65	1(<i>R</i>),2(<i>S</i>)
5	(<i>R</i>)-PhBox	79	94	1(<i>S</i>),2(<i>R</i>)

Experimental conditions: 10.0 mol% cat. Cu(BF₄)₂, 2 equiv. base, CH₂Cl₂, 16h, 0°C. Yields determined by ¹H NMR using an internal standard. Ees were determined by HPLC using Chiralcel AD column.

Table 1. Enantioselective benzylation of *meso*-hydrobenzoin catalyzed by Cu(BF₄)₂/Box ligands. Entry 5: reference 14.

The benzylation of *meso*-diol generates the product and one equivalent of [(*i*Pr)₂NHEt]⁺Cl⁻ salt. In this particular case, the selective precipitation of the catalyst turned out to be more difficult. The selective recovering of the catalyst was achieved by first the addition of diethyl ether and sonication. Then, after decantation of the resulting heterogeneous mixture, the precipitate was washed with diethyl ether and ethyl acetate and finally, dried under vacuum. The recycling catalyst procedure was thus selected and used in each run (Table 2).



	RUN	1	2	3	4	5	6
(S) <i>i</i> Pr-DiBox	ee	71	79	82	49	<10	-
	yield	88	87	80	32	11	-
(R) Ph-DiBox	ee	76	77	74	32	11	<10
	yield	71	83	71	49	32	16
(S) <i>i</i> Pr-TriBox	ee	79	85	74	<10	-	-
	yield	77	83	48	21	-	-
(S) <i>i</i> Pr-TetraBox	ee	65	71	83	59	-	-
	yield	68	77	69	42	-	-

Experimental conditions: 10.0 mol% cat. $\text{Cu}(\text{BF}_4)_2$, 2 equiv. NiPr_2Et , CH_2Cl_2 16h, 0°C .
 Note: the 1(S),2(R) product was obtained with (R) Ph-DiBox.

Table 2. Enantioselective benzylation of *meso*-hydrobenzoin catalyzed by $\text{Cu}(\text{BF}_4)_2/\text{Box}$ ligands and evaluation of the recycling.

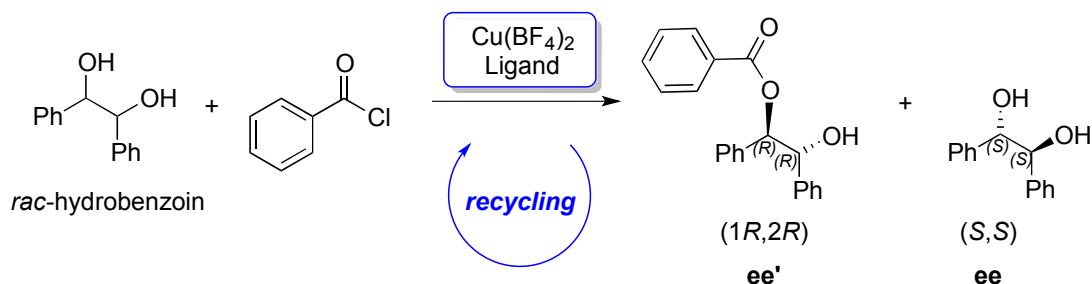
Both ditopic ligands seem to behave similarly. Three runs could be conducted with the ligand *i*Pr-DiBox (1) or with Ph-DiBox (2). After the third run, a significant depletion of both the enantiomeric excess and activity was observed. The tritopic ligand (3) and the tetratopic ligand (4) gave lower efficiency. Overall and in accordance with our previous observations, increasing the topicity of the chiral ligand is detrimental to the recycling of the catalytic system.

2.2 Kinetic resolution of *rac*-hydrobenzoin

The catalytic systems were also tested for the kinetic resolution of *rac*-hydrobenzoin.^[14,17] Again, Cu(BF₄)₂ was used as copper source and (*i*Pr)₂NEt as external base and the catalyst was recovered by precipitation with diethyl ether. Our results are summarized in Table 3.

All previous catalysts perform the kinetic resolution with good selectivity factors (**s**) ranging from 30 to 90. For example, the catalysis in presence of ligand *i*Pr-DiBox (**1**) gave the product with an enantiomeric excess of 93% at 49% conversion (measured by ¹H NMR). The enantiomeric excess of the unreacted diol was found to be 92%. These ee values correspond to a selectivity factor of 91 at a calculated conversion of 50%.

All four catalytic systems could be recycled at least four times prior a decrease in both activity and selectivity. Again, the ditopic systems seem to display a better recyclability when compared to the tri- and tetratopic systems.



	RUN	1	2	3	4	5	6
(S)-iPr-DiBox	ee	92	86	79	85	59	<10
	ee'	93	94	90	82	68	17
	conv _(calc)	50	48	47	51	46	10
	S	91	89	46	27	9.4	1.4
(R)-Ph-DiBox	ee	84	66	76	82	77	-
	ee'	83	88	88	90	88	-
	conv _(calc)	50	43	46	48	47	-
	S	28	31	36	48	36	-
(S)-iPr-TriBox	ee	85	84	82	80	-	-
	ee'	94	67	84	93	-	-
	conv _(calc)	47	45	49	46	-	-
	S	88	37	29	49	-	-
(S)-iPr-TetraBox	ee	72	81	71	80	-	-
	ee'	94	92	89	88	-	-
	conv _(calc)	43	47	44	48	-	-
	S	70	60	36	38	-	-

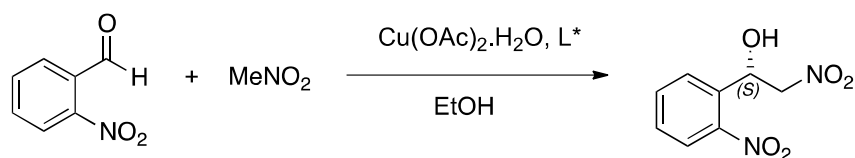
Experimental conditions: 5.0 mol% cat. $\text{Cu}(\text{BF}_4)_2$, 1 equiv. base, CH_2Cl_2 , 16h, 0°C .

Table 3. Kinetic resolution of *rac*-hydrobenzoin catalyzed by $\text{Cu}(\text{BF}_4)_2/\text{Box}$ ligands and evaluation of the recycling efficiency (Note: the other configurations were obtained with ligand (*R*) Ph-DiBox).

2.3 Asymmetric Henry reaction

Finally, these catalytic combinations were tested in the asymmetric Henry reaction. The combination of copper (II) salt $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ and bis(oxazoline) ligands were shown to be effective catalysts for such reaction.^[18] The Henry reaction of *o*-nitrobenzaldehyde with

nitromethane was selected as a reference reaction (Table 4). Using 5.0 mol% of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ and the corresponding amount of ligand in ethanol as solvent at room temperature, good conversions were observed.^[19] An enantiomeric excess of 71% was obtained with ditopic ligand *i*Pr-DiBox (Entry 1), which is consistent with the 67% ee reported for the monotopic *i*Pr-Box ligand (Entry 5).^[20] In contrast, Ph-DiBox ligand only gave a 36% ee (Entry 4), lower than the 43% ee reported in the literature for the corresponding monotopic ligand (Entry 6).^[18] 68% and 60% ee were obtained with the tri- and tetratopic ligands respectively (entries 2 and 3).



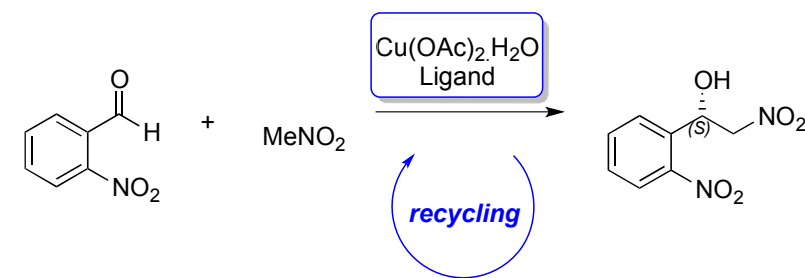
	Ligand	Yield [%]	ee [%]
1	(<i>S</i>)- <i>i</i> Pr-DiBox	99	71 (<i>S</i>)
2	(<i>S</i>)- <i>i</i> Pr-TriBox	99	68 (<i>S</i>)
3	(<i>S</i>)- <i>i</i> Pr-TetraBox	99	60 (<i>S</i>)
4	(<i>R</i>)-Ph-DiBox	99	36 (<i>R</i>)
5	(<i>R</i>)- <i>i</i> PrBox	-	67 (<i>R</i>)
6	(<i>R</i>)-PhBox	-	43 (<i>R</i>)

Experimental conditions: 5.0 mol% cat. $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, 10 equiv. nitromethane, EtOH, 72h, r.t.

Table 4. Enantioselective Henry reaction of *o*-nitrobenzaldehyde with nitromethane catalyzed by $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ /Box ligands. Entry 5 and 6: references 17 and 19.

We then tried to recover and reuse the catalysts.^[21] Table 5 displays the results. Only two runs could be conducted with *i*Pr-DiBox (**1**) and *i*Pr-TriBox (**3**). The third run gave lower yield as shown on Table 5. The tetratopic system was found to be more robust. Indeed, *i*Pr-TetraBox

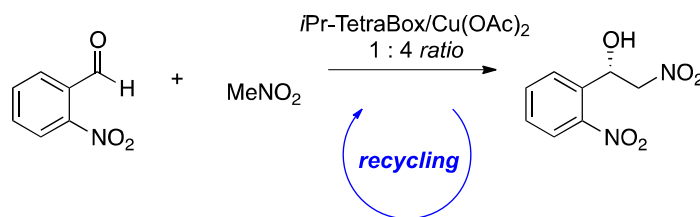
(4) ligand shows a different behavior: catalyst efficiency does not drop under 91% even for the 5th run, and enantiomeric excess values remain essentially constant (60 to 66%). In this case, we found that the precipitation of the catalyst was not straightforward. As a consequence, a significant quantity of the catalytic system stays in solution and therefore is lost between each run, especially for *i*Pr-DiBox (**1**) and *i*Pr-TriBox (**3**) systems. This observation was confirmed by ICP-AES analyses that established a significant loss in the amount of copper of >10% in both cases after the first run. The efficiency of the precipitation may be correlated with the construction of the coordination polymer, which is strongly dependent on the copper salt precursor (i.e. counter anion effect).^[15] In the case of neutral complexes such as Cu(OAc)₂, after complexation of one bis(oxazoline) ligand on the metal salt, it may be difficult for the complex to further chelate an additional bis(oxazoline). Since the *i*Pr-TetraBox-copper acetate system displays reasonable recyclability, we thus decided to investigate the tetratopic ligand with four equivalents of copper acetate as a potential recyclable catalyst for the Henry reaction. Surprisingly as shown on Table 6, the system displayed good activity as previously observed and the system could be recycled up to 5 times with no significant loss of activity. Remarkably, the enantioselectivity was improved of ca. 10% compared to the previous system. Overall, the *i*Pr-TetraBox-[Cu(OAc)₂]₄ catalytic system was found to be more efficient than a ratio ligand/copper adapted for the formation of the coordination polymer (i.e. Cu:TetraBox 2:1). We conducted UV-Vis titration experiments on that system since it is known that the formation of metallopolymer can be confirmed by the exact stoichiometric ratio of the metal to polytopic ligand. Thus, we studied the assembly between the tetratopic ligand and Cu(OAc)₂ (Figure 1). The intensity of the band increases up to a ratio of 4 to 1, which clearly indicates the formation of a tetranuclear species and not a metallopolymer, which was observed only when Cu(OTf)₂ was used.^[10]



	RUN	1	2	3	4	5
(S) <i>i</i> Pr-DiBox	ee	71	68	51	<10	-
	yield	99	90	10	<10	-
(S) <i>i</i> Pr-TriBox	ee	68	54	59	51	<10
	yield	99	91	45	12	<10
(S) <i>i</i> Pr-TetraBox	ee	60	66	66	59	60
	yield	99	99	95	91	91

Experimental conditions: 5.0 mol% cat. $\text{Cu(OAc)}_2 \cdot \text{H}_2\text{O}$, 10 eq. nitromethane, EtOH, 72h, r.t. Yields determined by ^1H NMR using an internal standard. Enantiomeric excesses were determined by HPLC using Chiralcel OD column.

Table 5. Enantioselective Henry reaction of *o*-nitrobenzaldehyde with nitromethane catalyzed by $\text{Cu(OAc)}_2 \cdot \text{H}_2\text{O}$ /Box ligands and evaluation of the recycling.



RUN	1	2	3	4	5
ee	79	74	74	75	67
yield	99	99	93	91	83

Experimental conditions: 5.0 mol% $\text{Cu(OAc)}_2 \cdot \text{H}_2\text{O}$, 1.25 mol% Ligand, 10 equiv. nitromethane, EtOH, 72h, r.t.

Table 6. Enantioselective Henry reaction of *o*-nitrobenzaldehyde with nitromethane catalyzed by $\text{Cu(OAc)}_2 \cdot \text{H}_2\text{O}$ /*i*Pr-TetraBox (4:1 ratio = 1.25 mol% based on *i*Pr-TetraBox) and evaluation of the recycling.

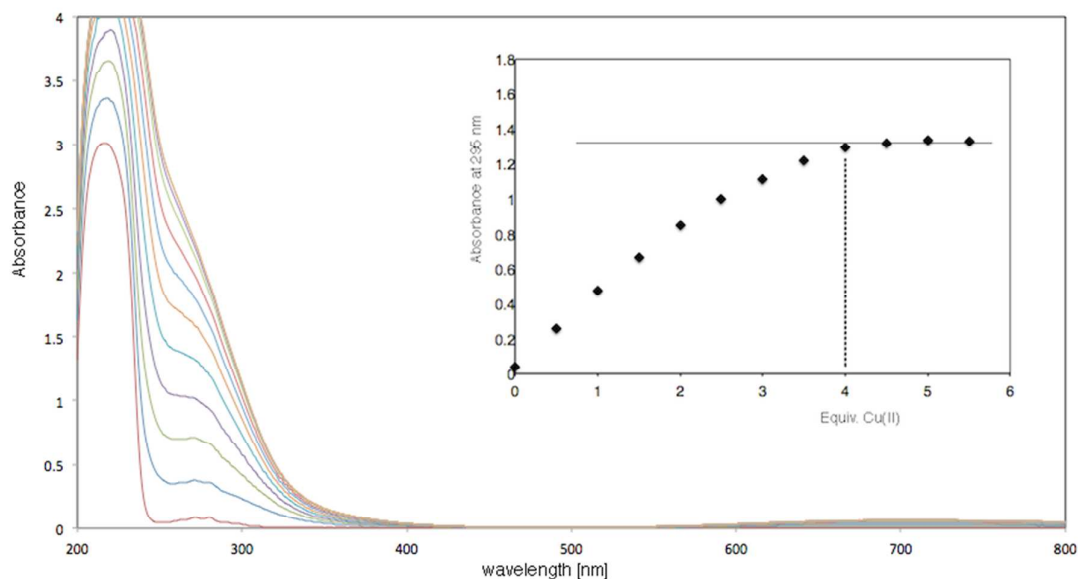


Figure 1. UV-Vis titration of *iPr*-TetraBox ligand with copper acetate in MeOH (at room temperature); inset: plot of the absorption at 295 nm as a function of added Cu(OAc)₂.

3. Conclusion

We have described the asymmetric benzylation of hydrobenzoin catalyzed by self-supported Cu(BF₄)₂-chiral bis(oxazoline) polytopic ligand systems. It was possible to recover the catalysts via precipitation and to reuse them. Overall, increasing of the topicity of the chelating ligand does not improve the recycling efficiency of the system, in accordance with our previous studies with Cu(OTf)₂ as copper source.^[10]

The polytopic ligands have also been tested in combination with neutral Cu(OAc)₂ for the asymmetric Henry reaction. Whereas only two runs could be conducted with the di- and tritopic systems, the tetratopic catalyst gave better recyclability and reproducibility. The efficiency of the catalyst recovery may be correlated with the formation of the coordination polymer, which may be dependent on the starting copper salt precursor.

4. Experimental Section

4.1 General considerations

All catalytic runs were performed under air. The bis(oxazoline) ligands (*S*) *i*Pr-DiBox (**1**), Ph- (*R*) DiBox (**2**), (*S*) *i*Pr-TriBox (**3**) and (*S*) *i*Pr-TetraBox (**4**) were synthesized according to our previous report.^[10] All reagents were used as received. Solvents were purified and degassed by standard procedures. HPLC analyses were performed on a Gilson apparatus (UV-VIS156/321 PUMP) with Chiralcel Daicel columns (AD, OD, AS) using *n*-Hexane/*i*-PrOH eluents.

4.2 General Procedure for the asymmetric enantioselective benzylation of *meso*-diols and recycling. Reaction of *meso*-hydrobenzoin. Table 1, entry 2.

Cu(BF₄)₂ (5.5 mg, 0.02 mmol) and ligand (*R*)-Ph-DiBox (14.9 mg, 0.02 mmol) in methanol (1.0 mL) was prepared under air. The mixture was stirred for 2 hours and then dried in vacuo. Dichloromethane (2 mL) was added followed by the *meso*-hydrobenzoin (42.3 mg, 0.2 mmol) and NiPr₂Et (69.7 μL, 0.4 mmol). The resulting homogenous mixture was cooled down to 0°C and benzoylchloride (23.2 μL, 0.2 mmol) was added dropwise. After 16h at 0°C, diethyl ether was added and a precipitate was formed. Then, the solid was washed with AcOEt. The organic phase was isolated, concentrated and the product was purified by SiO₂ flash-chromatography (AcOEt/cyclohexane, 25:75) and analyzed by chiral HPLC (71% ee, 91% yield). The catalyst recovered by decantation was dried and reused in a renewed catalytic run. The NMR data of the products was compared with literature reports.

4.3 General Procedure for the kinetic resolution of *rac*-diols and recycling. Reaction of *rac*-hydrobenzoin. Table 3.

Cu(BF₄)₂ (2.7 mg, 0.01 mmol) and ligand (*R*)-Ph-DiBox (7.4 mg, 0.01 mmol) in methanol (1.0 mL) was prepared under air. The mixture was stirred for 2 hours and then dried in vacuo.

Dichloromethane (2 mL) was added followed by the *rac*-hydrobenzoin (42.3 mg, 0.2 mmol) and NiPr₂Et (34.9 μL, 0.2 mmol). The resulting homogeneous mixture was cooled down to 0°C and benzoylchloride (11.6 μL, 0.1 mmol) was added dropwise. After 16h at 0°C, diethyl ether was added and a precipitate was formed. Then, the solid was washed with AcOEt. The organic phase was isolated, concentrated and the product was purified by SiO₂ flash-chromatography (AcOEt/cyclohexane, 25:75) and analyzed by chiral HPLC (84% ee, 83% ee', 49% yield). The catalyst recovered by decantation was dried and reused in a renewed catalytic

4.4 General Procedure for the asymmetric enantioselective Henry reaction and recycling.

Reaction of nitrobenzaldehyde. Table 5, entry 1.

Cu(OAc)₂H₂O (9.1 mg, 0.05 mmol) and ligand (*S*)-*i*Pr-DiBox (30.3 mg, 0.05 mmol) in ethanol (3.0 mL) was prepared under air. The mixture was stirred for 2 hours and then the 2-nitrobenzaldehyde (151.1 mg, 1 mmol) was added followed by the nitromethane (0.54 mL, 10 mmol). The resulting mixture was stirred for 72 hours at room temperature. After, diethyl ether was added and a precipitate was formed. The organic phase was isolated, concentrated and the product was purified by SiO₂ flash-chromatography (AcOEt/cyclohexane, 30:70) and analyzed by chiral HPLC (71% ee, 60% yield). The catalyst recovered by decantation was dried and reused in a renewed catalytic run.

5. Acknowledgements

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