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A New Method for Recycling Asymmetric Catalysts via Formation of Charge Transfer Complexes

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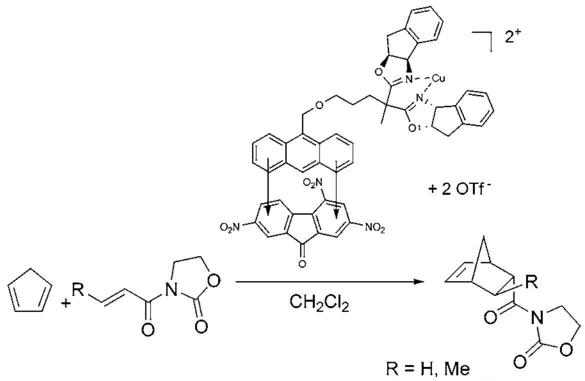
ABSTRACT



R = H, Me
de up to 97%
ee up to 94% (2*R*)
catalyst used 12 times

A new concept for recycling asymmetric bis(oxazoline)-type catalysts is reported. The formation of charge-transfer complexes between the chiral ligand and trinitrofluorenone and their subsequent precipitation and reuse by addition of new substrate solutions is described. The efficiency of this procedure is demonstrated in a Diels–Alder reaction to reach the expected *endo* product as major isomer (up to 97% de and 94% ee): the catalyst was used up to 12 times without loss of either activity or selectivity.

A new concept for the recovery and recycling of asymmetric bis(oxazoline)-type catalysts is reported: charge-transfer complexes are formed between the chiral ligand and a targeted electron-poor compound for their precipitation, before their reuse in an asymmetric catalytic transformation.

Investigation of the formation of carbon−carbon bonds by asymmetric catalysis is challenging particularly for the improvement of enantioselectivity and for the increase of the substrate-to-catalyst ratio. Among the enormous variety of ligands tested for these transformations, bis(oxazolines) led to highly active and enantioselective catalysts. Indeed, associated with different metals, these ligands allowed numerous C−C bonds to be formed very efficiently. However, a major drawback is the large quantity of catalyst required for a total conversion in a reasonable time. To get around this problem, numerous attempts for an efficient recycling of the asymmetric catalysts have been published. These results are presented in a recent exhaustive review.[1] Most of the reported articles deal with the covalent immobilization of various bis(oxazolines) on insoluble supports, either on organic polymers (by grafting on commercially available resins[2] and via solid-phase synthesis)[3] or on inorganic materials.[4] Although promising results have been obtained, some decrease in yield and enantioselectivity is

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(1) Rechavi, D.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 3467.

(2) (a) Hallman, K.; Moberg, C. *Tetrahedron: Asymmetry* **2001**, *12*, 1475. (b) Hocke, H.; Uozumi, Y. *Synlett* **2002**, 2049. (c) Lundgren, S.; Lutsenko, S.; Jönsson, C.; Moberg, C. *Org. Lett.* **2003**, *5*, 3663. (d) Knight, J. G.; Belcher, P. E. *Tetrahedron: Asymmetry* **2005**, *16*, 1415.

(3) (a) Weissberg, A.; Portnoy, M. *Chem. Commun.* **2003**, 1538. (b) Weissberg, A.; Halak, B.; Portnoy, M. *J. Org. Chem.* **2005**, *70*, 4556.

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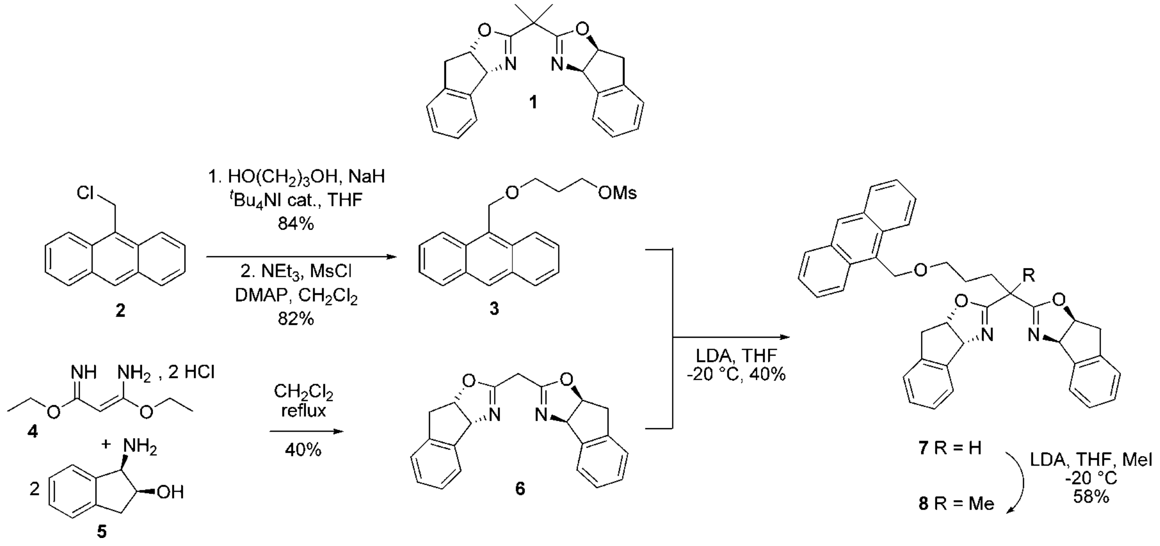
Scheme 1. Synthesis of the New Bis(oxazoline)-Based Ligand **8**



however observed due to a negative influence of the support and/or partial leaching of the catalyst during the recyclings.[5] The immobilization of bis(oxazoline) complexes has also been performed on soluble organic polymers (i.e., poly(ethylene glycol)) to allow the catalytic transformation to be run in an homogeneous phase before precipitation of the catalyst for its reuse.[6] To best preserve the local environment around the catalytic site, insoluble systems have been prepared by polymerization of properly functionalized bis(oxazolines) either by radical copolymerization[7] or by formation of a polyurethane chain polymer.[8] To limit the synthetic work required for the modification of the ligand structure, immobilization methods involving noncovalent interactions with the support have been developed. Mayoral's group has successfully supported bis(oxazoline)−copper complexes by cation exchange in inorganic solids (laponite) or organic polymers (Nafion-like solids).[9] However, the results obtained through these strategies are very dependent on the catalyst structure, the solvent, and the substrate. Alternatively, ionic liquids as "green solvents" have been used to immobilize and recycle stable bis(oxazoline)−copper complexes.[10]

Promising preliminary results on the development of a new method for the efficient recycling of asymmetric complexes are reported here. Indeed, we aimed to recycle bis(oxazoline)−copper complexes by the formation of charge-transfer complexes. Our procedure is based on a short synthesis of a suitable enantiomerically pure ligand functionalized with an electron-rich molecule (see Scheme 1). The formation of the corresponding organometallic complex upon addition of copper(II)-triflate is followed by the addition of an electron-deficient molecule for the formation of a reversible charge-transfer complex **9** (see Figure 1).

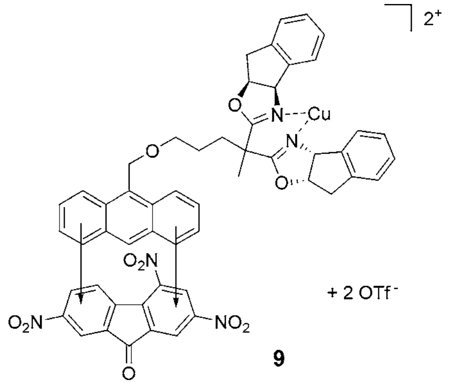


Figure 1. Structure of the charge-transfer complex.

We have tested this methodology in the bis(oxazoline)−copper-catalyzed Diels−Alder reaction developed by Evans.[11] This transformation uses the catalytic system derived from 2,2′-isopropylidenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] and copper(II) and allows indeed the simultaneous formation of two new carbon−carbon bonds in a highly diastereo- and enantioselective fashion. However, a large amount of cata-

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(4) (a) Rechavi, D.; Lemaire M. *Org. Lett.* **2001**, *3*, 2493. (b) Burguete, M. I.; Fraile, J. M.; Garcia, J. I.; Garcia-Verdugo, E.; Herrerias, C. I.; Luis, S. V.; Mayoral, J. A. *J. Org. Chem.* **2001**, *66*, 8893.

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(10) Fraile, J. M.; García, J. I.; Herrerías, C. I.; Mayoral, J. A.; Gmough, S.; Vaultier, M. *Green Chem.* **2004**, *6*, 93.

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lysts has to be used to get these good results and an efficient recycling of the catalyst to allow a development of this process is still lacking.

Complex **9** was thus tested in the aforementioned transformation and then precipitated in the mixture after completion of the reaction. The product was removed from the reaction vessel, and new solutions of reactants were added to check the possibility of recycling catalyst **9**.

Bis(oxazoline) **1** derived from indane was proved[12] to be an excellent copper ligand for the Diels−Alder reaction between cyclopentadiene and 3-acryloyl-oxazolidin-2-one. The modification of this structure by an anthracene functionality was performed in a five-step synthesis. Commercially available 9-chloromethyl-anthracene **2** was transformed in a mesylated analogue **3**. The indabox skeleton was prepared by condensation of the imidate salt **4** with (1*R*,2*S*)-(+)-*cis*-1-amino-2-indanol **5**.[13] Alkylation of **6** with **3** occurred after deprotonation with LDA in THF and methylation afforded the targeted anthracene-modified new bis(oxazoline) **8**.

Complex **9** was prepared from a mixture of ligand **8** and copper(II) triflate in dry dichloromethane followed by the addition of trinitrofluorenone. The formation of the new electron donor−acceptor complex was easily visible by the immediate change of color (from green to red) corresponding to a new absorption band (λ_{max} 538 nm) in UV−visible detection.[14]

We first examined the ability of the new bis(oxazoline) ligand **8** associated to Cu(OTf)$_2$ (Cu-**8**) to catalyze the enantioselective Diels−Alder reaction between cyclopentadiene and 3-acryloyl-oxazolidin-2-one **11** depicted in Scheme 2. All of our catalytic tests were performed with 10 mol % catalyst, as usually reported for this transformation. Cu-**8** proved as efficient in activity and selectivity as Cu-**1**, demonstrating that the presence of the anthracene group is not detrimental to the enantiofacial discrimination (see Table 1). Complex **9** was then tested under similar conditions and reused numerous times to optimize the procedure. The first test was performed with a long reaction time (44 h) to ensure a total conversion that was indeed obtained together with excellent results in terms of diastereomeric and enantiomeric excesses. Pentane was added at the end of the transformation, leading to the precipitation of **9**. The product solution was removed for analysis, the complex was washed with pentane and dried under vacuum, and substrates and solvent were added to the same reaction vessel for the catalyst recycling.

Scheme 2. Diels-Alder Reaction between Cyclopentadiene and 3-Acryloyl-oxazolidin-2-one **11** or 3-But-2-enoyl-oxazolidin-2-one **13**

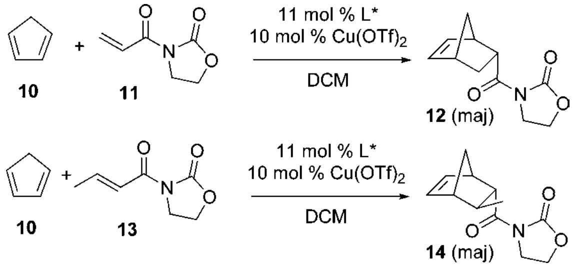

Table 1. Copper-Catalyzed Diels−Alder Reaction between Cyclopentadiene and 3-Acryloyl-oxazolidin-2-one **11**

catalyst	reuse	time (h)	*T* (°C)	conv (%)[b]	de (%)	ee **12** (%)[c]
Cu-**1**[a]		20	−50	100	92	88 (2*R*)
Cu-**8**[a]		20	−50	100	95	87 (2*R*)
9[a]		44	−50	100	93	84 (2*R*)
9	1st	44	−50	100	95	87 (2*R*)
9	2nd	44	−50	100	93	87 (2*R*)
9	3rd	20	−50	100 (91)	93	86 (2*R*)
9	4th	20	−65	100 (87)	96	91 (2*R*)
9	5th	7	−50	100 (85)	91	86 (2*R*)
9	6th	3	−50	100 (84)	94	87 (2*R*)
9	7th	1	−50	100 (86)	92	87 (2*R*)
9	8th	1	−65	90 (65)	88	90 (2*R*)
9	9th	0.5	−50	100 (92)	92	87 (2*R*)
9	10th	0.5	−50	100 (66)	91	87 (2*R*)
9	11th	2	−75	100 (95)	97	94 (2*R*)

[a] 3-Acryloyl-oxazolidin-2-one (0.33 mmol), cyclopentadiene (2.40 mmol), chiral catalyst (0.03 mmol), CH$_2$Cl$_2$ (1.3 mL). [b] Isolated yields are indicated in brackets. [c] The product configuration was determined by comparison with literature data.[12]

Activity and enantioselectivity were maintained during several recycling steps, and the reaction time was optimized. Complete conversion could be achieved within less than 30 min (Table 1). Lowering the temperature (4th, 8th, and 11th reuse) led to an increase in the enantiomeric excess (up to 94%) albeit with a slight decrease in the activity since 2 h of reaction time was necessary to obtain a total conversion at −75 °C. Reaction products were isolated in high yield after each recycling procedure. This precipitation was also performed to attempt to recover Cu-**8**, free of the charge transfer complex. Under analogous conditions, this catalyst could indeed be recovered but maintained its activity and selectivity for only three reuses: the 4th recycling afforded product **12** with 50% conversion and 73% enantiomeric excess. The presence of the charge-transfer complex seems necessary for an efficient recycling procedure.

To confirm the reproducibility of the procedure, a separate series of reactions was carried out under optimized conditions, i.e., by reacting cyclopentadiene and 3-acryloyl-oxazolidin-2-one **11** in the presence of 10 mol % complex **9** at −50 °C for a reaction time of 0.5 h. The results are gathered in Table 2 with five efficient recyclings under those conditions.

To widen the scope of this procedure, the same catalyst batch was also used in the presence of 3-but-2-enoyl-

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Table 2. Diels-Alder Reaction between Cyclopentadiene and **11** or **13** in the Presence of Complex **9**

substrate	reuse	time (h)	T (°C)	conv (%)[b]	ee **12** (%)[c]	ee **14** (%)[d]
11[a]		0.5	−50	83 (82)	83 (2*R*)	
11	1st	0.5	−50	100 (91)	84 (2*R*)	
11	2nd	0.5	−50	100 (88)	84 (2*R*)	
11	3rd	0.5	−50	100 (95)	85 (2*R*)	
11	4th	0.5	−50	79 (61)	80 (2*R*)	
11	5th	1	−50	93 (92)	84 (2*R*)	
13	6th	2.5	20	83		nd[e]
13	7th	3	20	90 (90)		77 (2*R*)
13	8th	3	20	90 (87)		78 (2*R*)
13	9th	3	20	84 (72)		77 (2*R*)
13	10th	3	20	87 (85)		77 (2*R*)

[a] **11** or **13** (0.33 mmol), cyclopentadiene (2.40 mmol), chiral catalyst (0.03 mmol), CH_2Cl_2 (1.3 mL). [b] Isolated yields are indicated in brackets. [c] The product configuration was determined by comparison with literature data.[12] [d] The product configuration was determined by comparison with literature data.[15] [e] Not determined

oxazolidin-2-one **13** as another dienophile. The reaction was carried out at 20 °C, and the 6th recycling of the catalyst led to the formation of the expected *endo* adduct **14**. This product was obtained together with traces of **12**, probably arising from coordination to the copper center of the precipitated catalyst during the previous reuse. Further recyclings were successfully performed with substrate **13**, and the corresponding product **14** was isolated in its pure form in high yield and high enantioselectivity for five additional reuses. Cu-**8** affords **14** under analogous conditions with 93% conversion (84% isolated yield) and 78% ee.

As a conclusion, we have developed an efficient immobilization strategy for bis(oxazoline)-based copper catalysts by precipitation of the corresponding charge-transfer complexes. This original procedure improved the practicality of the catalytic transformation by simple removal of the product from the reaction vessel, subsequent washing of the remaining catalyst, and addition of new solutions of reactants. Complex **9** was thus used 12 times, leading to the expected Diels−Alder *endo* products with high yield and enantioselectivity.

The diastereomeric and enantiomeric excesses afforded by this procedure are identical to the results obtained by the corresponding homogeneous system. No loss of catalytic activity or enantioselectivity could be detected during numerous recyclings, which demonstrates the high stability of the complex.

The formation of charge-transfer complexes to recover chiral catalysts was thus proved to be a very efficient method for an overall enormous saving of both precious chiral ligand and metal.

Work is in progress to develop this new recycling concept using other catalytic reactions. We also aim to use immobilized trinitrofluorenone on insoluble supports toward heterogeneous asymmetric catalysis in a continuous flow reactor.

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Supporting Information Available: Details of experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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