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Recyclable copper catalysts in the enantioselective glyoxylate-ene reaction catalyzed by chiral fluorous-tagged bis(oxazolines)

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Abstract—Chiral fluorous bis(oxazoline)/copper complexes have been applied to the asymmetric glyoxylate-ene reaction, giving moderate to high enantioselectivities. An efficient separation of the copper catalyst using a solid/liquid separation or the FRPSG concept, and its reuse was achieved.

1. Introduction

Asymmetric organometallic catalysis is now a well used methodology in organic synthesis.[1] However, the major drawback of such a process is the separation of the chiral metal complexes from the product(s) of the reaction for its recovery and/or its recycling. A very promising approach is the use of biphasic systems,[2] including aqueous-, ionic liquid-, and fluorous-organic biphasic (FBS) systems, as well as catalysis in a supercritical dioxide. In the FBS concept, the organometallic catalyst is soluble in a fluorous solvent via the attachment of fluorous ponytails to the ligand, and the reactants are soluble in the organic solvent. At the end of the reaction, the two phases can be separated, and eventually the fluorous layer containing the fluorous organometallic catalyst can be reused. In the literature there are only a few examples of this methodology using chiral fluorous ligands with an efficient recycling of the catalyst.[3] Another method for the recovery of the fluorous catalyst is filtration through a plug of fluorous silica gel (FSG), called fluorous solid-phase extraction, using light fluorous ligands;[4] however, the use of this methodology in the case of chiral fluorous ligands generally suffered from the formation of partially inactive catalysts.[5] Since chiral fluorous organometallic species are less soluble in the usual organic solvents in comparison to fluorous solvents, chiral fluorous catalysts could be recovered from the reaction mixture by a simple solid/liquid separation and reused efficiently.[3c,6] A more promising approach is the use of FSG as a solid support for the non-covalent immobilization of fluorous catalysts (fluorous reverse phase silica gel or FRPSG concept), allowing the reaction to be performed in the usual organic solvents.[4d,7] This methodology has been successfully used in intermolecular asymmetric cyclopropanation and more recently in asymmetric hydrogenation of olefins. The chiral catalyst can be reused in the latter case several times with no loss of activity or enantioselectivity (90–95% ee).[3b,8]

We recently described the synthesis of chiral fluorous bis(oxazolines), which were used in palladium-catalyzed allylic alkylation,[3d,6c] in Cu^{I}-promoted cyclopropanation[6b] and allylic oxidation.[3c,6c] The recycling of the fluorous catalyst was possible in some cases by using the FBS concept or by a solid/liquid separation. Benaglia et al. reported at around same period the synthesis of other chiral fluorous bis(oxazolines),[9] and their applications in Cu^{I}-promoted cyclopropanation, Cu^{II}-catalyzed ene reaction, and Mukayama aldol reaction; the recycling of the fluorous ligand only was studied by a liquid/liquid phase separation, or by a filtration through a short plug of fluorous silica gel. Herein we report the use of the chiral fluorous bis(oxazolines) **1a**–**b** (Fig. 1) prepared by our group in the Cu^{II}-promoted ene-type reaction, and the recycling of these chiral fluorous organometallic catalysts using both the solid/liquid separation and the FRPSG concept.

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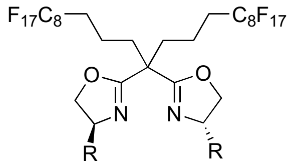
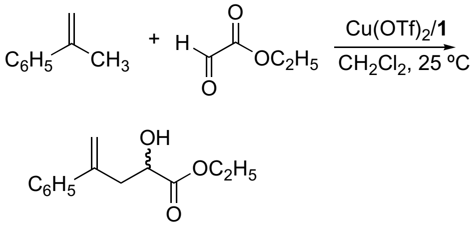


1a R = C_6H_5
1b R = *i*-Pr

Figure 1.

2. Results and discussion

The recycling of the catalytic system via the solid/liquid separation technique was first studied using the condensation of α-methylstyrene to ethyl glyoxylate under the standard conditions published in the literature in the case of the homogeneous system (Eq. 1).



2

(1)

The catalyst was prepared in situ by mixing copper triflate and fluorous bis(oxazoline) **1a** in CH_2Cl_2. This in situ catalyst effectively promoted the addition of α-methylstyrene to ethyl glyoxylate at rt, affording α-hydroxy ester **2** in 78% yield and 87% ee (Table 1, entry 1). This enantioselectivity is a little lower than that published by Evans et al. using the non-fluorous 2,2′-isopropylidenebis(4-phenyl-2-oxazoline) as the chiral ligand, the reaction being, however, performed in the latest case at 0 °C.[10]

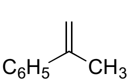
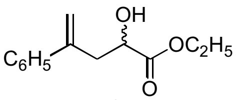
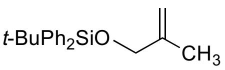
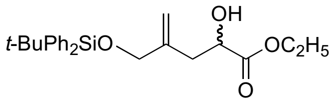
Next, we attempted the recycling of this fluorous copper catalyst by a simple solid/liquid extraction. After careful removal of the solvent under reduced pressure, the product and the unreacted ethyl glyoxylate were extracted several times with cold hexane, with the catalyst precipitating as a blue solid. This recovered catalyst was used for four further cycles, affording product **2** in the same chemical yields and enantioselectivities, up to 88% (Table 1, entry 1). We performed an experiment under the same conditions using the non-fluorous 2,2′-isopropylidenebis(4-phenyl-2-oxazoline) as the chiral ligand. Evaporation of the solvent followed by extraction with hexane gave product **2** in 88% yield and 68% ee. However, the reuse of the brown solid obtained by precipitation with hexane gave no reaction at all. This blank experiment clearly showed the importance of the fluorous ponytails for the precipitation and so the reuse of the catalyst.

The copper-catalyzed condensation of ethyl glyoxylate with silyl-protected 2-methyl-2-propen-1-ol afforded α-hydroxy ester **3** in 71% yield and 83% ee, quite close to the value obtained by Evans et al.[10] (Table 1, entry 2). The recycling of the catalyst was also possible, with the same yields (89% and 70% yields) and ee's (84% and 81%) being obtained for the 1st and the 2nd recycling, respectively; a lower yield (35%) was obtained for the 3rd cycle, but the same enantioselectivity (81% ee) was observed.

We next turned our attention to the recycling of the chiral catalyst using the FRPSG concept. The FRPSG-supported catalyst was prepared by mixing the copper triflate and the fluorous bis(oxazoline) in CH_2Cl_2, followed by the addition of the fluorous reverse phase silica gel. Some preliminary experiments concerning the addition of α-methylstyrene to ethyl glyoxylate using bis(oxazoline) **1b** as the fluorous ligand in CH_2Cl_2 at rt gave compound **2** with an ee up to 59% (Table 2, entries 1 and 2); however it was necessary to use 5 mol % of the catalyst to obtain a moderate chemical yield (51%) after 24 h. Recycling of the catalyst, via a simple decantation of the solid followed by washes with CH_2Cl_2, was effective, with α-hydroxy ester **2** being obtained in 58% ee for the 2nd run with the same chemical yield.

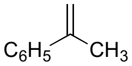
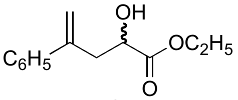
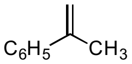
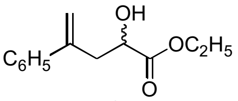
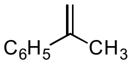
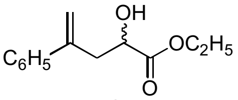
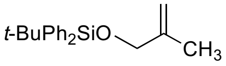
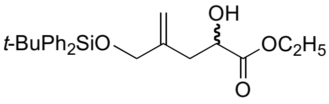
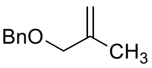
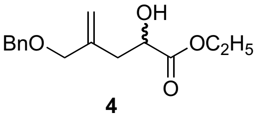
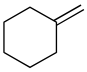
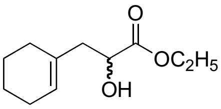
We performed this condensation under these optimized conditions using the fluorous bis(oxazoline) **1a** as the chiral ligand. Compound **2** was quantitatively formed after 24 h in 70% ee (Table 2, entry 3), the value a little lower than that previously obtained using the homogeneous fluorous

Table 1. Recycling in the glyoxylate-ene reaction using the solid/liquid extraction methodology[a]

Entry	Olefin	Product	Run	Time (h)	Yield[b] (%)	ee[c] (%)
1		 **2**	1	34	78	87 (*R*)
			2	24	76	84 (*R*)
			3	24	76	84 (*R*)
			4	24	75	87 (*R*)
			5	48	78	88 (*R*)
2		 **3**	1	48	71	83 (*R*)
			2	48	69	84 (*R*)
			3	48	70	81 (*R*)
			4	48	35	82 (*R*)

[a] Reaction conditions: olefin (0.3 mmol), ethyl glyoxylate (3 mmol), $Cu(OTf)_2$ (30 μmol), ligand **1a** (30 μmol), CH_2Cl_2 (5 mL), 25 °C.
[b] Isolated yields.
[c] Enantiomeric excess determined by GLC on Cyclodex-β column.

Table 2. Recycling in the glyoxylate-ene reaction using the FRPSG concept[a]

Entry	Olefin	Product	Ligand	Run	Time (h)	Conversion[b] (%)	ee (%) (conf)[c]
1		 **2**	**1b**[d]	—	72	— (38)	59 (*R*)
2		 **2**	**1b**	1	24	90 (51)	53 (*R*)
				2	24	90 (54)	58 (*R*)
3		 **2**	**1a**	1	24	99	70 (*R*)
				2	24	99	61 (*R*)
				3	24	92	60 (*R*)
				4	24	75	51 (*R*)
4		 **3**	**1a**	1	24	90 (61)	81 (*R*)
				2	24	90 (64)	82 (*R*)
5		 **4**	**1a**	1	48	90	90 (*R*)
				2	48	89	91 (*R*)
				3	48	74	78 (*R*)
				4	48	70	45 (*R*)
6		 **5**	**1a**	1	48	50	13 (*S*)
				2	48	67	19 (*S*)
				3	48	72	22 (*S*)
				4	48	70	29 (*S*)
				5	48	52	27 (*S*)

[a] Reaction conditions: olefin (0.3 mmol), ethyl glyoxylate (3 mmol), $Cu(OTf)_2$ (15 µmol), ligand **1a** (15 µmol), FSG (3 g), CH_2Cl_2 (5 mL), 25 °C.

[b] Conversion determined by GLC, isolated yields in brackets.

[c] Enantiomeric excess determined by GLC on Cyclodex-β column.

[d] $Cu(OTf)_2$ (7.5 µmol), ligand **1a** (7.5 µmol).

catalyst. The catalytic system could be reused several times; the conversion could be maintained for two subsequent runs, with ee of 60% and 61%, respectively, but decreased to 75% for the 4th run, with 51% ee being, however, obtained in this last run.

The condensation of ethyl glyoxylate with silyl-protected 2-methyl-2-propen-1-ol afforded α-hydroxy ester **3** in 61% yield after purification and 81% ee (Table 2, entry 4), very close to the value obtained previously using the homogeneous fluorous complex; the recycling of the catalyst gave ee up to 82% with 64% chemical yield.

α-Hydroxy ester **4** was obtained by condensation of the benzyl-protected 2-methyl-2-propen-1-ol with ethyl glyoxylate in 90% conversion and 90% ee after 48 h reaction (Table 2, entry 5), quite close to the value (92% ee) obtained using the corresponding non-fluorous bis(oxazoline).[10] The catalyst could be reused several times; however, while the conversion and the enantioselectivity were maintained for the second run (89% conversion and 91% ee), they decreased for the next two runs (74% and 70% conversion, 78% and 45% ee, respectively).

Finally, the addition of ethyl glyoxylate to methylene cyclohexane gave the expected α-hydroxy-ester **5** with a moderate conversion and only 13% ee in favor of the (*S*)-enantiomer (Table 2, entry 6). This is in contrast with the result (79% ee in favor of the (*R*)-enantiomer) obtained by Evans et al.[10] Several reuses of the catalyst could be performed in this case with no decrease of either the conversion (52–72%) nor of the enantioselectivity (19–29%).

3. Conclusion

In conclusion, we were able to use the fluorous bis(oxazoline)/copper complex in the glyoxylate-ene reaction in non-fluorous solvents, affording the corresponding α-hydroxy esters in moderate to high ee's. The catalyst could be easily isolated and reused several times using the solid/liquid separation or the FRPSG concept. In the latter case, an unfavorable influence of the silica gel on the enantioselectivity was sometimes observed.

4. Experimental

4.1. General

Solvents were purified by standard methods and dried if necessary. All commercially available reagents were used as received. *tert*-Butyldiphenyl(prop-1-en-2-yloxy)silane,[11] 1-[(2-methylallyloxy)methyl]benzene,[12] and the fluorous bis(oxazolines) **1a**–**b**[6c] were prepared according to literature procedure. FluoroFlash® Silica Gel, 40 μm, was obtained from Fluorous technologies, Inc. Reactions involving organometallic catalysis were carried out in a Schlenk tube under an inert atmosphere. The NMR spectra (^{1}H: 300 MHz, ^{13}C: 75.4 MHz) were recorded on a Bruker AC 300 instrument with Me_4Si and $CDCl_3$ as the internal standard, respectively. Ee's of compounds **2**–**5** were determined by GLC on Cyclodex-β column. The absolute configuration of the enantiomers was determined by comparison of the retention times with those of authentic samples.

4.2. General procedure for the recycling using the solid/liquid extraction methodology

The catalyst was prepared in situ in a Schlenk tube under nitrogen by mixing $Cu(OTf)_2$ (10.9 mg, 30 μmol), and ligand **1a** (37 mg, 30 μmol) in dichloromethane (2.5 mL) at rt for 3 h. To this solution, the olefin (0.3 mmol) and ethyl glyoxylate (306 mg, 3 mmol, 50% solution in toluene) were added. After being stirred for the indicated time at rt, the solvent was almost removed under reduced pressure, and the residue was successively diluted four times with cold hexane (4 × 2 mL), giving a blue-green precipitate. The supernatant was removed each time via a syringe after simple decantation of the supernatant liquid. The combined organic layers were dried over Na_2SO_4, and concentrated under reduced pressure to give an oil that was purified by column chromatography on silica gel, affording the pure adduct, whose enantiomeric excess was determined by GLC on Cyclodex-β column. The recovered catalyst was used in the next catalytic ene-reaction without further addition of copper triflate or ligand **1a**.

4.3. General procedure for the recycling using the FRPSG concept

The copper catalyst was prepared in situ in a Schlenk tube under a nitrogen by mixing $Cu(OTf)_2$ (5.5 mg, 15 μmol), and ligand **1** (15 μmol) in dichloromethane (2.5 mL) at rt for 3 h. This solution containing the in situ formed catalyst was added to a Schlenk tube containing the fluorous reverse phase silica gel (3 g) in BTF (5 mL). The mixture was stirred at rt for 1 h, after which the solvents were evaporated under reduced pressure, and the solid obtained was dried in vacuo to give the FRPSG-supported copper complex. The olefin (0.3 mmol) and ethyl glyoxylate (306 mg, 3 mmol, 50% solution in toluene) dissolved in dichloromethane (5 mL), were added to this supported complex. After being stirred for the indicated time at rt, the liquid phase was removed with a cannular, and the solid was washed four times with CH_2Cl_2 (4 × 2 mL). The supernatant was removed each time via a syringe after a simple decantation of the supernatant liquid. The combined extracts were dried over Na_2SO_4, and concentrated under reduced pressure to give an oil that was eventually purified by column chromatography on silica gel, affording the pure adduct. The enantiomeric excess of the pure product or of the raw oil was determined by GLC on Cyclodex-β column. The immobilized catalyst was reused in the next catalytic ene-reaction without further addition of copper triflate or ligand **1**.

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