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Asymmetric cyclopropanation catalyzed by fluorous bis(oxazolines)–copper complexes

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Abstract—Fluorous bis(oxazoline)–copper(I) complexes generated in situ were tested as catalysts in the metal-catalyzed cyclopropanation of styrene with various α-diazoacetates. Under optimized conditions in CH_2Cl_2, quite good yields were obtained. Diastereoselectivities were found to be substrate and, to a lesser extent, ligand dependent, with *trans*/*cis* ratios ranging from 62/38 (cyclopropanation with α-ethyldiazoacetate **2a** using ligand **1a**) to 98/2 (cyclopropanation with methyl phenyldiazoacetate **2c** using ligand **1b**). Enantioselectivities up to 84% ee for the *trans*-isomer and 81% ee for the *cis*-isomer were observed using ligand **1b**. Fluorous bis(oxazoline)–copper(I) complexes could be very easily separated from the products by simple precipitation using hexane, and recycled without loss of stereo- as well as enantioselectivities.

1. Introduction

Chiral bis(oxazolines) are one of the most important families of chiral ligands, and have been successfully applied in the asymmetric catalysis of a large variety of reactions during the last decade.[1–3] For example, some of the best systems for asymmetric cyclopropanation[4] of styrene derivatives use C_2-symmetric bis(oxazoline) ligands associated with Cu(I)–metal complexes.[5–7] High enantioselectivities, up to 99% ee for the *trans* isomer, and 97% ee for the *cis* isomer, have been obtained using alkyl diazoacetates, while the *trans*/*cis* stereoselectivity depends on the nature of the diazoacetate used. However, one of the major drawbacks of these catalytic systems is the high catalytic loading (1–10%) generally required in order to obtain total conversion. Hence the separation of the catalyst after the cyclopropanation reaction and its reuse is highly desirable, if we are expected to apply these generally costly ligands for large-scale preparative purposes.

Various types of immobilized bis(oxazolines) have been tested for this cyclopropanation reaction.[8,9] Bis(oxazolines) have been attached to heterogeneous inorganic (such as clay or silica) and organic (such as polystyrene) supports using non-covalent or covalent bonds. However, the activities of these supported catalysts are generally lower than those of the homogeneous analogues, while the observed selectivities are the same. Heterogeneization of these bis(oxazolines) by tethering to soluble organic polymers, for example poly(ethyleneglycol), seems more promising, since the cyclopropanation can be run under homogeneous conditions, giving similar activities to those displayed by the non-supported catalyst. At the end of the reaction, the supported catalyst can be precipitated by the addition of another solvent, filtered, and efficiently reused.[10,11]

A relatively new approach for the immobilization of chiral ligands is the fluorous-phase approach.[12] In brief, the introduction of a certain number of fluorinated ponytails on a ligand allows its solubility in fluorous solvents or its retention on a solid fluorous support, and thus its easy recovery and eventually reuse. Despite the high potential of bis(oxazolines) as chiral ligands in asymmetric catalysis, there have been only a few reports of the synthesis and applications of such fluorous ligands. Benaglia et al.[13,14] prepared some chiral fluorous bis(oxazolines) that were employed in the ene reaction, the Mukayama aldol addition, and the cyclopropanation of styrene in the presence of CuOTf. In the latter case, enantioselectivities up to

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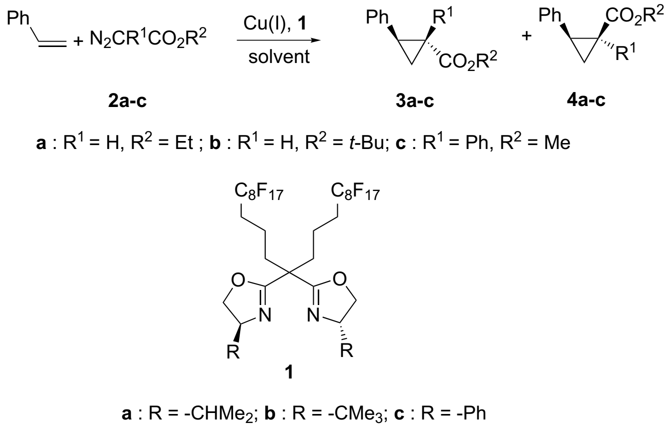
78% ee were obtained for the *trans* isomer, as well as good selectivities and activities; however, the active metal complex could not be recycled, only the fluorous bis(oxazoline) was recovered and reused. We independently described an easy access to various chiral fluorous bis(oxazolines), which were used in palladium-catalyzed allylic alkylation and in copper-catalyzed allylic oxidation.[15] In the latter reaction, recycling of the Cu(I)-catalyst was demonstrated. More recently, one of us[16] reported the synthesis of C_2-symmetric fluorous diamines and diimines that were used as ligands in the cyclopropanation of styrene; if ee's up to 62% were obtained for the *trans* isomer, a drop in the enantioselectivity was unfortunately observed in the second run. Here we report on the use of chiral fluorous bis(oxazolines) **1a–c** (Scheme 1) in the asymmetric Cu(I)-catalyzed cyclopropanation reaction of styrene.



Scheme 1.

2. Results and discussion

The synthesis of chiral fluorous bis(oxazolines) **1a** and **1c** has already been published.[15] Ligand **1b** was prepared in 64% yield by condensation of 2,2′-methylenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] with 2 equiv of 1-iodo-(1*H*,1*H*,2*H*,2*H*,3*H*,3*H*)-perfluoroundecane in DMF in the presence of NaH. The fluorine contents of these ligands are 55.7%, 54.4%, and 52.7%, for **1a**, **1b**, and **1c**, respectively.

The catalytic activity of the fluorous bis(oxazoline) **1a** as the model ligand was evaluated in the cyclopropanation of styrene with ethyl α-diazoacetate **2a** under homogeneous conditions in CH_2Cl_2 (Scheme 1). Ligand **1a** (10 mol %) and $Cu(CH_3CN)_4PF_6$ (9 mol %) were stirred together in degassed CH_2Cl_2 at 40 °C. After 30 min, the homogeneous solution was cooled to room temperature, and styrene then added. Ethyl α-diazoacetate **2a** dissolved in CH_2Cl_2 was then added dropwise over a period of 4 h using a syringe pump, and the solution stirred for a further time. The products and unchanged styrene were separated and the *trans*- and *cis*-cyclopropanes **3a**/**4a** were isolated by flash chromatography.

As shown in Table 1 (entry 1), the chemical yield was 58% (based on **2a**), the *trans*:*cis* ratio being close to 6:4. The ee's of the *trans*-**3a** and *cis*-**4a** were 66% and 65%, respectively. Only a slight decrease in the reaction yield was observed when decreasing the catalyst loading to 8% and 2%, while the selectivities remained unchanged (Table 1, entries 2 and 3). Consequently, reactions were carried out in the presence of 2% of the ligand. A decrease in reaction yield and in enantioselectivity was observed by substitution of dichloromethane by dichloroethane (Table 1, entry 4), although the diastereoselectivity obtained remained unchanged. Slow addition of the diazo compound (Table 1, entry 5) or shortening the addition time (Table 1, entry 6) resulted in lower reaction yields (34% and 44%, respectively), although the selectivities were not affected.

The same selectivities were obtained when the reaction was carried out at either 0 °C or at 40 °C (Table 1, entries 7 and 8). However, at 40 °C, a significant increase in the isolated

Table 1. Asymmetric cyclopropanation of styrene with ethyl diazoacetate **2a** in the presence of Cu^IX/**1a**: optimization of reaction conditions[a]

Entry	Cu^IX	Ligand **1a** (mol %)[b]	Solvent	*T* (°C)	Time (h)[c]	Yield (%)[d]	**3a**/**4a**[e]	ee **3a** (%)[f,g]	ee **4a** (%)[f,h]
1	$Cu(MeCN)_4PF_6$	10	CH_2Cl_2	20	4 + 16	58	61:39	66	65
2	$Cu(MeCN)_4PF_6$	8	CH_2Cl_2	20	4 + 16	53	61:39	65	64
3	$Cu(MeCN)_4PF_6$	2	CH_2Cl_2	20	4 + 16	53	61:39	65	64
4	$Cu(MeCN)_4PF_6$	2	$ClCH_2CH_2Cl$	20	4 + 16	34	61:39	58	59
5	$Cu(MeCN)_4PF_6$	2	CH_2Cl_2	20	8 + 12	34	61:39	66	63
6	$Cu(MeCN)_4PF_6$	2	CH_2Cl_2	20	1 + 19	44	62:38	65	63
7	$Cu(MeCN)_4PF_6$	2	CH_2Cl_2	0	4 + 24	25	61:39	63	63
8	$Cu(MeCN)_4PF_6$	2	CH_2Cl_2	40	4 + 1	77	62:38	63	63
9	$Cu(MeCN)_4PF_6$	2	CH_2Cl_2	40	1 + 1	68	62:38	63	63
10	$Cu(MeCN)_4PF_6$	2	Styrene	40	4 + 1	60	59:41	63	60
11	$Cu(MeCN)_4BF_4$	2	CH_2Cl_2	40	4 + 1	73	63:37	66	65
12	Cu(OTf)	2	CH_2Cl_2	40	4 + 1	60	63:37	65	65

[a] [Styrene]/[**2a**] = 5:1; [Cu^IX]/[**1a**] = 0.9:1. See Section 4 for experimental details.
[b] With respect to **2a**.
[c] Time of addition of the diazoacetate + time of reaction.
[d] Overall isolated yield for (**3a** + **4a**).
[e] Determined by GC analysis of the isolated mixture (**3a** + **4a**).
[f] Determined by HPLC analysis (Daicel Chiracel OJ-H chiral column).
[g] (1*R*,2*R*) is the major enantiomer.
[h] (1*S*,2*R*) is the major enantiomer.

yield (77% chemical yield) was observed with a shorter reaction time, while a decrease (25% chemical yield) was noticed when the reaction was performed at 0 °C. Shortening the addition time at 40 °C to 1 h gave again a lower chemical yield: only 68% versus 77% (Table 1, entry 9). When the cyclopropanation reaction was performed without dichloromethane, slightly inferior results were obtained (Table 1, entry 10).

Finally other copper precursors such as $Cu(CH_3CN)_4BF_4$ and Cu(OTf) were tested under the optimized conditions; if the same selectivities were observed, Cu(OTf) gave a lower chemical yield (Table 1, entries 11 and 12).

Next we evaluated the different fluorous bis(oxazolines) **1a–c** in the asymmetric cyclopropanation of styrene at 20 and 40 °C under the optimized conditions using different α-diazoacetates, such as ethyl α-diazoacetate **2a**, *tert*-butyl α-diazoacetate **2b**, and methyl phenyldiazoacetate **2c** (Table 2). As expected, higher chemical yields were obtained when the reaction was performed at 40 °C than at 20 °C, while the selectivities were almost the same. As a general rule, the use of more bulky α-diazoacetates resulted in a higher *trans*/*cis* ratio, whatever the ligand used. For example, diastereoisomeric mixtures containing 98% *trans*- and only 2% *cis* isomer were obtained using **2c** in the presence of ligands **1a** and **1b** (Table 2, entries 13–16). Slightly lower de were obtained when the same reaction was carried out in the presence of ligand **1c** bearing 4,4′-phenyl substituents (Table 2, entries 17 and 18).

For a given α-diazoester, the observed enantioselectivities were found to be strongly dependent upon the nature of the substituents at the 4- and 4′-position of the bis(oxazoline) ligand. For ethyl α-diazoacetate **2a** (Table 2, entries 1–6), the highest ees, up to 84%, were obtained using ligand **1b** bearing sterically hindered *tert*-butyl substituents. The same was observed when using diazoacetate **2b** bearing the less bulky *i*-propyl substituents, but differences among the various ligands were less pronounced (Table 2, entries 7–12). Although very high diastereoselectivities, up to 98% in favor of the *trans* isomer, were obtained using methyl phenyldiazoacetate **2c** in the cyclopropanation reaction (Table 2, entries 13–18), the observed enantioselectivities were lower than those obtained with **2a** and **2b**; ee's up to 65% were obtained using ligand **1a**, while enantioselectivities dropped significantly in the case of the more bulky ligands **1b** and **1c**.

Finally, catalyst recycling was investigated in the case of the cyclopropanation of styrene using α-diazoacetate **2a**. Reactions involving fluorous ligands **1a** and **1b** were performed in dichloromethane; then, following a recovery procedure we recently reported for fluorous bis(oxazoline)–copper complexes,[15] the solvent was evaporated and the catalyst was precipitated by addition of hexane. Decantation of the supernatant liquid containing the products afforded the catalyst that could be reused in another cyclopropanation reaction without further addition of copper or ligand. When the cyclopropanation reaction was run at 20 °C in the presence of ligand **1a**, the bis(oxazoline)-complex could be reused three times with the same diastereo- and enantioselectivities (Table 3, entries 1–4), although the yield decreased drastically at the third recycling.

The same trends were observed when using bis(oxazoline) **1b** as the ligand (Table 3, entries 5–8). The recycling of ligand **1b** was also studied at 40 °C, the catalyst loading

Table 2. Asymmetric cyclopropanation of styrene in the presence of Cu^IX/fluorous bis(oxazoline) **1**[a]

Entry	Diazoacetate	Ligand	T (°C)	Time (h)[b]	Yield (%)[c]	**3**/**4**[d]	ee **3** (%)[e,f]	ee **4** (%)[e,g]
1	**2a**	**1a**	20	16	58	61:39	66	65
2	**2a**	**1a**	40	1	77	62:38	63	63
3	**2a**	**1b**	20	16	22	62:38	84	81
4	**2a**	**1b**	40	1	63	64:36	80	79
5	**2a**	**1c**	20	16	63	68:32	65	57
6	**2a**	**1c**	40	1	72	69:31	64	56
7	**2b**	**1a**	20	16	55	73:27	66	nd
8	**2b**	**1a**	40	1	63	74:26	64	nd
9	**2b**	**1b**	20	16	24	75:25	74	nd
10	**2b**	**1b**	40	1	55	76:24	78	nd
11	**2b**	**1c**	20	16	58	82:18	74	nd
12	**2b**	**1c**	40	1	64	82:18	74	nd
13	**2c**	**1a**	20	48	74	98:2	63	nd
14	**2c**	**1a**	40	14	70	98:2	65	nd
15	**2c**	**1b**	20	14	36	98:2	10	nd
16	**2c**	**1b**	40	14	76	98:2	27	nd
17	**2c**	**1c**	20	14	44	97:3	23	nd
18	**2c**	**1c**	40	14	92	96:4	26	nd

[a] [Styrene]/[**2**]/$[Cu(MeCN)_4PF_6]$/[**1**] = 250:50:0.9:1; solvent CH_2Cl_2. See Section 4 for experimental details.

[b] Time of reaction, time of addition of the diazoacetate being 4 h in all the experiments.

[c] Overall isolated yield for (**3** + **4**).

[d] Determined by GC analysis of the isolated mixture (**3** + **4**).

[e] Determined by HPLC analysis (Daicel Chiracel OJ-H chiral column).

[f] (1*R*,2*R*) is the major enantiomer.

[g] (1*S*,2*R*) is the major enantiomer.

Table 3. Asymmetric cyclopropanation of styrene with ethyl diazoacetate **2a** in the presence of Cu^{I}X/**1a**: recycling experiments[a]

Entry	Ligand (mol %)	*T* (°C)	Run	Time (h)[b]	Yield (%)[c]	**3a/4a**[d]	ee **3a** (%)[e,f]	ee **4a** (%)[e,g]
1	**1a** (10)	20	1	16	58	64:36	66	65
2	**1a** (10)	20	2	16	58	63:37	66	64
3	**1a** (10)	20	3	16	54	63:37	67	64
4	**1a** (10)	20	4	16	31	63:37	65	63
5	**1b** (10)	20	1	16	50	64:36	83	83
6	**1b** (10)	20	2	16	50	63:37	81	80
7	**1b** (10)	20	3	16	41	63:37	81	80
8	**1b** (10)	20	4	16	34	63:37	81	80
9	**1b** (2)	40	1	1	63	64:36	80	79
10	**1b** (2)	40	2	1	63	63:37	79	78
11	**1b** (2)	40	3	1	56	63:37	79	79
12	**1b** (2)	40	4	1	42	63:37	81	80
13	**1b** (2)[h]	40	5	1	38	63:37	78	77
14	**1b** (2)[i]	40	6	1	46	61:39	70	68

[a] [Styrene]/[**2a**] = 5:1; [Cu(MeCN)$_4$PF$_6$]/[**1**] = 0.9:1; solvent CH$_2$Cl$_2$. See Section 4 for experimental details.
[b] Time of reaction, time of addition of the diazoacetate being 4 h in all the experiments.
[c] Overall isolated yield for (**3a** + **4a**).
[d] Determined by GC analysis of the isolated mixture (**3a** + **4a**).
[e] Determined by HPLC analysis (Daicel Chiracel OJ-H chiral column).
[f] (1*R*,2*R*) is the major enantiomer.
[g] (1*S*,2*R*) is the major enantiomer.
[h] Phenylhydrazine was added to the reaction mixture.
[i] 1 mol % of Cu(MeCN)$_4$PF$_6$ was added to the reaction mixture.

being only 2%. Again we noticed that the diastereoselectivities (*trans*/*cis* 63:37) and enantioselectivities (up to 80%) were maintained over five runs (Table 3, entries 9–13), although a slight decrease in chemical yield was observed. Neither the addition of phenylhydrazine (in order to reduce Cu(II) species possibly formed during the recovery step), nor the addition of a small amount of fresh CuX could restore the original activity (Table 3, entries 13 and 14). This behavior is in line with that observed using, for instance, soluble bis(oxazolines) immobilized in ionic liquids,[17] and can be similarly explained by the gradual extraction of the free fluorous ligands to the hexane phase. Careful design of the chiral bis(oxazolines) with an increased affinity for fluorous solvents or fluorous solid supports would help solve this problem.

3. Conclusion

In conclusion, under the optimized conditions, good isolated yields and diastereoselectivities were obtained in the homogeneous fluorous bis(oxazolines)–copper catalyzed cyclopropanation of styrene. Enantioselectivities up to 84% have been obtained, although this enantioselectivity is strongly dependent upon the structures of the diazoacetate and the ligand used. Recovery and reuse of these catalysts was also demonstrated without any decrease in diastereo- as well as enantioselectivities over five runs. These results compare well with those obtained using PEG-supported aza-bis(oxazolines)[10] or bis(oxazolines),[11] and are superior to those observed with heterogeneous catalysts.[8] Overall, the present catalytic system based on chiral fluorous bis(oxazolines) seems to be one of the more efficient recyclable system tested so far in the asymmetric cyclopropanation, with room still for improvement.

4. Experimental

4.1. General

Solvents were purified by standard methods and dried if necessary. All commercially available reagents were used as received. Methyl phenyldiazoacetate **2c** was prepared according to literature procedure.[18] Fluorous bis(oxazolines) **1a** and **1c** were prepared as already described.[15] Reactions involving organometallic catalysis were carried out in a Schlenk tube under an inert atmosphere. Optical rotations were recorded using a Perkin–Elmer 241 polarimeter. The NMR spectra (^{1}H: 300 MHz, ^{13}C: 75.4 MHz, ^{19}F: 282 MHz) were recorded on a Bruker AC 300 instrument with Me$_4$Si, CDCl$_3$, and CFCl$_3$ as the internal standard, respectively. The ee of compounds **3a–c** and **4a–c** was determined by HPLC on a chiral stationary phase (column: Chiracel OJ-H; eluent, hexane/*i*-PrOH 99.5:0.5; flow rate: 1 mL min^{-1}; $\lambda = 210$ nm). The absolute configurations of the enantiomers were determined by comparison of the retention times with those of authentic samples.

4.2. 12,12-Bis[(4*S*)-4-*tert*-butyl-1,3-oxazolin-2-yl](9*H*,9*H*,10*H*,10*H*,11*H*,11*H*,13*H*,13*H*,14*H*,14*H*,15*H*,15*H*)-perfluorotricosane 1b

To a solution of 2,2′-methylenebis[(4*S*)-4-*tert*-butyl-2-oxazoline] (532 mg, 2 mmol) in anhydrous DMF (20 mL) was added NaH (144 mg, 6 mmol). After the mixture was stirred for 1 h at rt, a solution of C$_8$F$_{17}$(CH$_2$)$_3$I (2.7 g, 4.6 mmol) in anhydrous DMF (7 mL) was slowly added. After being stirred at 80 °C for 16 h, the DMF was removed under reduced pressure. Water (20 mL) was then added, and the resulting mixture extracted with ether (4 × 20 mL). Concentration of the organic solution under reduced pressure followed by column chromatography on silica gel using petroleum ether/ethyl acetate (6:1) as the eluent afforded bis(oxazoline) **1b** (1.52 g, 64% yield) as a yellow oil: R_f 0.41 (petroleum ether/ethyl acetate 6:1); $[\alpha]_D^{25} = -24$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (s, CH_3, 18H), 1.60–1.63 (m, 4H, CH_2), 1.91–2.11 (m, 8H, CH_2), 3.89 (dd, $J = 10.1$, 7.7 Hz, 2H, CHN), 4.05 (dd, $J = 8.6$, 7.7 Hz, 2H, CH_2O), 4.17 (dd, $J = 10.1$, 8.6 Hz, 2H, CH_2O); ^{13}C ($CDCl_3$) δ 15.8, 26.1, 31.6 (t, $J = 22.3$ Hz), 33.3, 34.1, 46.2, 69.1, 75.9, 166.4; ^{19}F NMR ($CDCl_3$) δ −126.7 (m, 4F), −124.0 (m, 4F), −123.3 (m, 4F), −122.5 (m, 12F), −114.7 (m, 4F), −81.4 (t, $J = 10.3$ Hz, 6F). Anal. Calcd for $C_{37}H_{38}F_{34}N_2O_2$: C, 37.43; H, 3.03. Found: C, 37.31; H, 2.97.

4.3. General procedure for the cyclopropanation of styrene

Fluorous bisoxazoline **1** (10 μmol) and Cu(I)-complex (9 μmol) were stirred together in degassed CH_2Cl_2 (3 mL) for 30 min at 40°C under nitrogen. Styrene (260 mg, 2.5 mmol) was added to the reaction mixture, which was allowed to stir for a further 10 min. The diazoacetate (0.5 mmol) dissolved in CH_2Cl_2 (4 mL) was added dropwise over 4 h using a syringe pump and the mixture then stirred for a further hour. The volatiles were then evaporated under vacuum to leave a thick oil, an aliquot of which was analyzed by GC to determine the relative amounts of the two diastereoisomers. The residue was purified by flash chromatography (silica gel, hexane/EtOAc 95:5 for **3a/4a**, hexane/EtOAc 97:3 for **3b/4b**, hexane/EtOAc 93:7 for **3c/4c**). The enantiomeric excesses of the two diastereoisomers **3** and **4** were determined by HPLC analysis on a chiral stationary phase.

4.4. Recycling experiment

To carry out the recycling experiments, the reaction was performed on a threefold scale. After the reaction, the solvent was evaporated. Hexane (3 × 4 mL) was added, and the catalyst precipitated as a pale-orange solid, which was recovered by decanting of the supernatant liquid. The catalyst was reused in a subsequent run without further addition of copper or ligand. Evaporation of hexane afforded a residue that was purified by column chromatography, and analyzed as described above.

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