New Chiral Substituted 8-Quinolinyl-oxazolines as Ligands for Copper(I)-catalyzed Asymmetric Cyclopropanation†

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New chiral substituted 8-quinolinyl-oxazoline ligands have been synthesized and applied in the copper(I)-catalyzed asymmetric cyclopropanation of styrene with alkyl diazoacetates. The steric effect in the ligands plays a significant role in the enantiocontrol in asymmetric cyclopropanation, while the electronic effect is less important.

Keywords asymmetric catalysis, chiral oxazoline, cyclopropanation

Introduction

Asymmetric catalytic cyclopropanation of olefins with diazo compounds is one of the most useful methods for the synthesis of chiral cyclopropanes.[1] A number of efficient chiral ligands, particularly bisnitrogen ligands, have been developed, and excellent enantioselectivities and diastereoselectivities have been achieved with selected olefins.[2,3] However, the successful chiral ligands, like semicorrin[4] and bisoxazolines[5] are mostly C_2 symmetric. During the course of our studies on the nonsymmetric chiral nitrogen-containing ligands, we recently introduced 8-quinolinyl-oxazolines **1** as ligands for copper(I)-catalyzed cyclopropanation of styrene with diazoacetates leading to good chemical yields and moderate enantiomeric excesses.[6] In order to modify the ligands **1**, the steric and electronic effects of substitutes in quinolinyl-oxazoline ligands on the enantioselectivities of cyclopropanation reaction were investigated in this paper.

Results and discussion

Syntheses of chiral substituted quinolinyl-8-oxazoline ligands **3**

Chiral substituted quinolinyl-8-oxazoline ligands were synthesized from substituted 8-quinolinecarboxylic acids **4** and enantiomerically pure amino alcohols according to the procedure as shown in Scheme 1. The substituted 8-quinolinecarboxylic acids **4** were converted to the esters **5** in 80%—86% yield. By ester exchanges of **5** with corresponding amino alcohols, amides **6** were produced in 58%—85% yield. Ligands **3** were prepared in 67%—81% yield by cyclization of amides **6** with MsCl-Et_3N-DMAP in a mild condition.

Copper(I)-catalyzed asymmetric cyclopropanation

The copper(I)-catalyzed asymmetric cyclopropanations of styrene with ethyl diazoacetate and (−)-menthyl diazoacetate were chosen as model reactions for the evaluation of the efficiency of these new oxazoline ligands. The reactions were carried out in $CHCl_3$ by slow addition of the solution of alkyl diazoacetates to a mixture of styrene and 1 mol% of chiral catalysts prepared *in situ* from cop-

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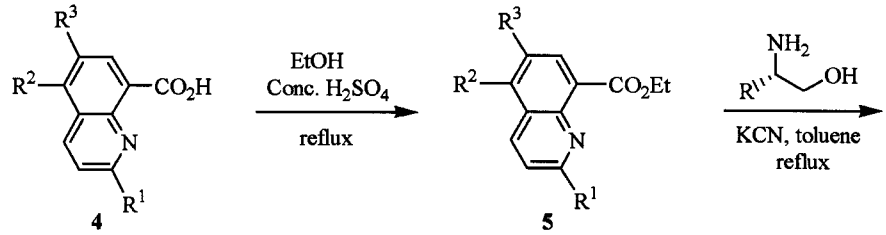
† Dedicated to Professor HUANG Yao-Zeng on the occasion of his 90th birthday.

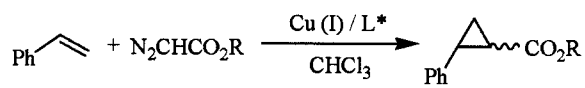
per(I) triflate and ligands [Eq. (1)]. The results were summarized in Table 1. Ligands **1a—1c** and ligands **2a—2c** did show definite chiral induction to the reaction and **2c** afforded higher *ee* value than others. By using the menthyl diazoacetate, the double induction effect was observed and up to 83% *ee* value of the *cis* isomer was obtained.

Scheme 1



1a $R^1 = R^2 = R^3 = H$, R = Bn
1b $R^1 = R^2 = R^3 = H$, R = *i*-Ph
1c $R^1 = R^2 = R^3 = H$, R = Ph
2a R^1 = Me, $R^2 = R^3 = H$, R = Bn
2b R^1 = Me, $R^2 = R^3 = H$, R = *i*-Ph
2c R^1 = Me, $R^2 = R^3 = H$, R = Ph
2d R^1 = *i*-Bu, $R^2 = R^3$= H, R = Bn
3a $R^1 = H$, $R^2 = R^3$ = OMe, R = Bn
3b $R^1 = R^2 = H$, $R^3 = NO_2$, R = Bn

Table 1 Copper(I)-catalyzed asymmetric cyclopropanation of styrene[a]



(1)

Entry	R	Ligand	Yield (%)[b]	*cis*/*trans*[c]	*ee*% (*cis*/*trans*)[c]	Config (*cis*/*trans*)[d]
1	Et	**1a**	71	31/69	23/38	(1*R*,2*S*)/(1*R*,2*R*)
2	Et	**1b**	63	32/68	22/34	(1*R*,2*S*)/(1*R*,2*R*)
3	Et	**1c**	91	28/72	22/27	(1*R*,2*S*)/(1*R*,2*R*)
4	Et	**2a**	70	32/68	34/42	(1*R*,2*S*)/(1*R*,2*R*)
5	Et	**2b**	92	38/62	38/43	(1*R*,2*S*)/(1*R*,2*R*)
6	Et	**2c**	65	32/68	54/54	(1*R*,2*S*)/(1*R*,2*R*)
7	(−)-Menthyl	**1a**	81	23/77	55/52	(1*R*,2*S*)/(1*R*,2*R*)
8	(−)-Menthyl	**1b**	82	21/79	61/58	(1*R*,2*S*)/(1*R*,2*R*)
9	(−)-Menthyl	**1c**	84	24/76	38/16	(1*R*,2*S*)/(1*R*,2*R*)
10[e]	(−)-Menthyl	**2a**	82	28/72	43/64	(1*R*,2*S*)/(1*R*,2*R*)
11	(−)-Menthyl	**2b**	88	22/78	54/64	(1*R*,2*S*)/(1*R*,2*R*)
12	(−)-Menthyl	**2c**	86	26/74	83/69	(1*R*,2*S*)/(1*R*,2*R*)
13[f]	(−)-Menthyl	**2c**	78	24/76	62/60	(1*S*,2*R*)/(1*S*,2*S*)
14	(−)-Menthyl	**2d**	70	23/77	17/33	(1*R*,2*S*)/(1*R*,2*R*)
15[e]	(−)-Menthyl	**3a**	72	23/77	60/48	(1*R*,2*S*)/(1*R*,2*R*)
16[e]	(−)-Menthyl	**3b**	70	25/75	54/42	(1*R*,2*S*)/(1*R*,2*R*)

[a] Reaction conditions: CuOTf $(C_6H_6)_{0.5}$ (1 mol%), (*S*)-ligand (2 mol%), styrene (20 mmol), diazoacetate (2 mmol) in $CHCl_3$ at reflux temperature unless mentioned otherwise. [b] Isolated yield. [c] Determined by GC analysis on a 30 m capillary column (HP-1). [d] Assigned by comparison of optical rotation with data in the literature.[7] [e] The reaction was carried out at r.t.. [f] The ligand with (*R*)-configuration was used.

As can be seen in the Table 1, different substituted quinolinyl-oxazoline ligands provided desired cyclopropanation products in good yields with close *cis*/*trans* ratios. Introduction of a methyl group in the 2-position of the quinoline ring of ligands **1** has a positive effect on the asymmetric induction of catalyst. Thus, ligands **2a** and **2b** gave slightly higher enantioselectivities than ligands **1a** and **1b** (Entries 4, 5 vs. 1, 2 and Entries 10, 11 vs. 7, 8), while significant increases in the *ee* values were observed with **2c** (Entry 6 vs. 3 and Entry 12 vs. 9). To further enhance the level of stereocontrol, ligand **2d**, which posseses an *iso*-butyl group on the 2-position of the quinoline ring, was synthesized and tested in the cyclopropanation of styrene with (−)-menthyl diazoacetate, but unfortunately, the *ee* value decreased sharply (Entry 14). The enantioselectivity obtained with (*S*)-**2c** was higher than that with (*R*)-**2c** in the asymmetric cyclopropanation showing a match of the configurations of (*S*)-ligand and (−)-menthyl diazoacetate (Entry 12 vs. 13).

In order to examine the electronic effect of substitute groups in quinolinyl-oxazoline ligands on enantioselectivity of the reaction, ligands **3a** and **3b**, containing methoxyl and nitro group respectively, were synthesized and used in the cyclopropanation of styrene with (−)-menthyl diazoacetate. The enantiomeric excesses of cyclopropanation product provided by ligands **3a** and **3b** were close to those obtained with unsubstituted ligand **1a** (Entries 15, 16 vs. 7), indicating that the electronic feature of the quinolinyl ring of the ligands does not have much influence on the enantioselectivity of the reaction. This finding is significant in the modifications of heteroaryl-oxazoline ligands.

Experimental

General

Chloroform was distilled from anhydrous $CaSO_4$. The substituted 8-quinolinyl carboxylic acids **4** were prepared according to the reported methods.[8,9] All optically pure amino alcohols were prepared by reduction of the corresponding commercially available amino acids with $NaBH_4$/H_2SO_4 in THF.[10] For the characterizations of ligands **1** and **2** see previous paper.[6] The optical rotations were measured on a Perkin-Elmer 241 polarimeter in a 1 dm tube. The ^1H NMR spectra were obtained with a Bruker AMX-200 or 300 spectrometer. IR spectra were determined on a Nicdet Magna-IR550 spectrometer. Mass spectra were measured with an HP-5989A (EI, 70 eV) mass spectrometer. Elemental analyses were performed on a Yanaco CHN CORDER MT-3 analyzer. The *cis*/*trans* ratio and enantiomeric excesses of products were determined on an Agilent 6890 GC with FID detector.

Syntheses of ethyl substituted 8-quinolinecarboxylate **5**

Synthesis of ethyl 5,6-dimethoxy-8-quinolinecarboxylate (**5a**) General procedure: A mixture of 5,6-dimethoxy-8-quinolinecarboxylic acid (**4a**, 2.11 g, 9.06 mmol), anhydrous ethanol (40 mL) and concentrated sulfuric acid (1.0 mL) was heated under reflux for three days. After the solvent was evaporated under reduced pressure, the residue was dissolved in $CHCl_3$ (50 mL) and washed with saturated $NaHCO_3$ (20 mL × 3) and brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give **4a** as a pale brown oil 2.02 g (7.74 mmol, 86%), which was used directly for the next step without further purification. ^1H NMR ($CDCl_3$, 200 MHz) δ: 9.30 (s, 1H), 8.68 (d, J = 8.6 Hz, 1H), 8.08 (s, 1H), 7.56 (q, J = 4.4 Hz, 1H), 4.61 (q, J = 7.2 Hz, 2H), 4.10 (s, 3H), 4.04 (s, 3H), 1.44 (t, J = 7.2 Hz, 3H).

Synthesis of ethyl 6-nitro-8-quinolinecarboxylate (**5b**) Pale yellow solid, 80% yield, m.p. 112—115 ℃; ^1H NMR ($CDCl_3$, 300 MHz) δ: 9.22 (dd, J = 4.2, 1.5 Hz, 1H), 8.90 (d, J = 2.4 Hz, 1H), 8.76 (d, J = 2.4 Hz, 1H), 8.40 (dd, J = 8.4, 1.5 Hz, 1H), 7.64 (q, J = 4.2 Hz, 1H), 4.57 (q, J = 7.2 Hz, 2H), 1.48 (t, J = 7.2 Hz, 3H).

Syntheses of substituted 8-quinolinecarboxamides **6**

(1′S)-N-(1′-Benzyl-2′-hydroxyethyl)-5,6-dimethoxy-8-quinolinecarboxamide (**6a**) General procedure: A mixture of ethyl 5, 6-dimethoxy-8-quinolinecarboxylate (**5a**, 1.99 g, 7.62 mmol), *L*-phenylalaninol (1.73 g, 11.4 mmol) and KCN (165 mg, 2.54 mmol) in toluene (30 mL) was heated under reflux until the ester disappeared. After cooling to r.t., water (15 mL) was added. The organic layer was separated, and the aqueous layer was extracted with chloroform (30 mL × 2). The combined organic layer was washed with brine and dried over anhydrous Na_2SO_4. After filtration and concentration un-

der reduced pressure, the crude product was purified by flash column chromatography on silica gel with PE/EtOAc (1:2, $V:V$) to give 2.37 g (6.48 mmol, 85%) of **6a** as a pale yellow oil, $[\alpha]_D^{20}$ −107.0 (c 0.4, EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 11.64 (d, J = 6.0 Hz, 1H), 8.68 (dd, J = 4.2, 1.8 Hz, 1H), 8.66 (s, 1H), 8.56 (dd, J = 8.4, 1.8 Hz, 1H), 7.42 (q, J = 4.2 Hz, 1H), 7.37—7.18 (m, 5H), 4.60—4.45 (m, 1H), 4.05 (s, 3H), 4.04 (s, 3H), 3.96—3.70 (m, 3H), 3.15—3.01 (m, 2H); IR (KBr) ν: 3026, 2940, 2849, 1957, 1894, 1809, 1733, 1644, 1590, 1573, 1472, 1335, 1245, 1069 cm^{-1}; MS (70 eV) m/z (%): 366 (M^+, 2), 275 (71), 216 (100), 217 (38), 173 (37), 91 (32). Anal. calcd for $C_{21}H_{22}N_2O_4$: C 68.84, H 6.05, N 7.65; found C 68.10, H 5.94, N 7.81.

(1′*S*)-*N*-(1′-*Benzyl*-2′-*hydroxyethyl*)-6-*nitro*-8-*quinolinecarboxamide* (**6b**) Yellow solid, 58% yield, m.p. 153—155 ℃, $[\alpha]_D^{20}$ −87.5 (c 0.2, EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 11.23 (d, J = 6.3 Hz, 1H), 9.54 (d, J = 2.7 Hz, 1H), 8.98 (dd, J = 4.2, 1.8 Hz, 1H), 8.88 (d, J = 2.7 Hz, 1H), 8.47 (dd, J = 8.4, 1.8 Hz, 1H), 7.66 (q, J = 4.2 Hz, 1H), 7.40—7.18 (m, 5H), 4.68—4.50 (m, 1H), 3.92 (dd, J = 11.7, 3.3 Hz, 1H), 3.81 (dd, J = 11.1, 5.4 Hz, 1H), 3.25—3.00 (m, 3H); IR (KBr) ν: 3373, 3072, 1966, 1824, 1660, 1603, 1570, 1536, 1491, 1353, 1322, 1040 cm^{-1}; MS (70 eV) m/z (%): 320 (15), 260 (67), 242 (26), 218 (10), 201 (100), 165 (45), 127 (39), 91 (25). Anal. calcd for $C_{19}H_{17}N_3O_4$: C 64.95, H 4.88, N 11.96; found C 64.50, H 5.13, N 11.91.

Syntheses of substituted 8-*quinolinyl-oxazoline ligands* **3**

(4*S*)-4,5-*Dihydro*-2-(5′,6′-*dimethoxy*-8′-*quinolinyl*)-4-*benzyloxazole* (**3a**) General procedure: To a mixture of **6a** (1.75 g, 4.78 mmol), 4-dimethyl amino pyridine (23.3 mg, 0.19 mmol) and triethylamine (2.62 mL, 18.7 mmol) in dichloromethane (50 mL) was added methanesulfonyl chloride (1.44 mL, 18.6 mmol) at −5—0 ℃, and the solution was stirred for 40 min at this temperature. Another portion of triethylamine (11.7 mL, 84.0 mmol) was added to the solution, and it was refluxed until the initially formed mesylate disappeared (checked by TLC). After cooling to r.t., the reaction mixture was diluted with $CHCl_3$ and washed with saturated $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4. After filtration and concentration under reduced pressure, the crude product was purified by flash chromatography on silica gel with PE/EtOAc (1:3, $V:V$) to give 1.35 g (3.88 mmol, 81%) of **3a** as a pale yellow oil. $[\alpha]_D^{20}$ +6.9 (c 0.8, EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 8.96 (dd, J = 4.2, 1.8 Hz, 1H), 8.49 (dd, J = 8.4, 1.8 Hz, 1H), 7.94 (s, 1H), 7.41 (q, J = 4.2 Hz, 1H), 7.38—7.20 (m, 5H), 4.85—4.75 (m, 1H), 4.49 (t, J = 9.0 Hz, 1H), 4.30 (dd, J = 8.7, 7.2 Hz, 1H), 4.04 (s, 3H), 4.03 (s, 3H), 3.37 (dd, J = 13.8, 4.8 Hz, 1H), 2.85 (dd, J = 13.8, 9.0 Hz, 1H); IR (KBr) ν: 3025, 2938, 2849, 1949, 1892, 1810, 1734, 1651, 1592, 1575, 1476, 1352, 1251, 1112, 979 cm^{-1}; MS (70 eV) m/z (%): 349 (M^+ + 1, 1), 348 (M^+, 2), 257 (100), 229 (20), 91 (31).

(4*S*)-4,5-*Dihydro*-2-(6′-*nitro*-8′-*quinolinyl*)-4-*benzyloxazole* (**3b**) Pale yellow solid, 67% yield, m.p 126—128 ℃, $[\alpha]_D^{20}$ +4.1 (c 0.8, EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 9.25 (dd, J = 4.5, 1.5 Hz, 1H), 8.88 (d, J = 2.4 Hz, 1H), 8.84 (d, J = 2.4 Hz, 1H), 8.40 (dd, J = 8.4, 1.5 Hz, 1H), 7.63 (q, J = 4.2 Hz, 1H), 7.38—7.20 (m, 5H), 4.85—4.75 (m, 1H), 4.53 (t, J = 8.7 Hz, 1H), 4.34 (t, J = 7.8 Hz, 1H), 3.35 (dd, J = 13.8, 4.8 Hz, 1H), 2.90 (dd, J = 13.8, 8.4 Hz, 1H); IR (KBr) ν: 3094, 2939, 1950, 1808, 1666, 1615, 1533, 1494, 1342, 1320, 1177, 1015, 957 cm^{-1}; MS (70 eV) m/z (%): 334 (M^+ + 1, 1), 333 (M^+, 2), 243 (28), 242 (100), 187 (46), 141 (35), 91 (30). Anal. calcd for $C_{19}H_{15}N_3O_3$: C 68.46, H 4.54, N 12.60; found C 68.09, H 4.95, N 11.99.

Copper(I)-catalyzed asymmetric cyclopropanation of styrene with alkyl diazoacetates

General procedure To a suspension of 5.0 mg (0.02 mmol) of CuOTf $(C_6H_6)_{0.5}$ in 10 mL of dry $CHCl_3$, a solution of 0.04 mmol of ligand in 10 mL of dry $CHCl_3$ was added at r.t.. The mixture was stirred for 1.5—2 h and filtered through a syringe-tip filter (0.45 μm). After addition of 20 mmol of styrene, the solution was heated to reflux, and 2 mmol of (−)-menthyl diazoacetate in 20 mL of $CHCl_3$ was slowly added over 2 h at reflux temperature. The resulting mixture was refluxed for certain additional hours, cooled to r.t. and then passed

through a silica gel plug to remove the catalyst. The filtrate was concentrated under reduced pressure, and the residue was chromatographed on silica gel with PE/EtOAc (95∶5, *V*∶*V*) to afford 2-phenylcyclopropane carboxylate. The *cis*/*trans* ratio and enantiomeric excesses were determined by GC analysis on a 30 m capillary column (HP-1) (t_R = 14.37 and 14.54 min for *cis* isomers, 15.32 and 15.57 min for *trans* isomers).

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