A new class of chiral pyrrolidine ligands for homogeneous catalytic enantioselective cyclopropanation of styrene

SHI, Min* (施敏) **JIANG, Jian-Kang**(蒋建康)

Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China

A new class of chiral pyrrolidine ligands have been successfully synthesized and their chiral induction abilities have been examined in the homogeneous catalytic enantioselective cyclopropanation of styrene. 15—30% enantiomeric excess (*ee*) has been achieved.

Keywords Chiral ligand, pyrrolidine, enantioselective, cyclopropanation, catalyst

Introduction

In recent years, the catalytic enantioselective cyclopropanation has attracted much attention.[1] The first enantiocontrolled catalytic intermolecular cyclopropanation reaction was reported by Noyori using a salicylaldimine ligand for copper(II).[2] The next major advance in chiral catalyst design was the contribution of chiral semicorrin ligands[3] and chiral bis-oxazoline ligands.[4] On the other hand, in the course of the study of chiral C_2-symmetric 2,5-disubstituted pyrrolidine derivatives having a β-aminoalcohol moiety as catalytic chiral ligands in the asymmetric addition reactions of diethylzinc with arylaldehydes, we found that the production of *sec*-alcohols having *R*-absolute configuration could be achieved in very high chemical yields (85—95%) and very high enantiomeric excess (*ee*) (70—96%) when *N*-(2′,2′-diphenyl-2′-hydroxyethyl)-(2*R*,5*R*)-bis(methoxymethyl)-pyrrolidine was used as a chiral ligand.[5,6] This result stimulated us to continuously explore some other kind of novel chiral ligands which have such C_2-symmetric 2,5-disubstituted pyrrolidine moieties for the other catalytic asymmetric reactions. Herein we wish to report a new class of chiral bidentate ligands having C_2-symmetric 2,5-disubstituted pyrrolidine moiety for the homogeneous catalytic enantioselective cyclopropanation of styrene.

Results and discussion

The new class of chiral ligands **2a—e** were readily prepared from the reaction of chiral C_2-symmetric 2,5-disubstituted pyrrolidines (**1a—c**) with 2-(chloromethyl) pyridine hydrochloride or 2-(chloromethyl) quinoline hydrochloride in the presence of potassium carbonate in acetonitrile under reflux, respectively (Scheme 1). Their structures were established by spectral analysis and high resolution mass spectroscopy. Those new classes of chiral ligands were obtained as colorless oil after purification by flash chromatography, but gradually became reddish even stored at −10℃. Obviously the compounds **2a—e** are bidentate ligands similar to the chiral semicorrin[3] and chiral bis-oxazoline ligands[4] because the nitrogen atom of pyrrolidine ring is connected with another pyridine ring which has another nitrogen atom. Those chiral bidentate ligands were directly used for the catalytic enantioselective cyclopropanation of styrene in the presence of CuOTf (copper(I) trifluoromethanesulfonate).[3,4] The cyclopropanation reaction was carried out according to the previously reported procedure in literature[7] using ethyl diazoacetate as the carbene source, 1.0 mol% of CuOTf and 1.60 mol% of

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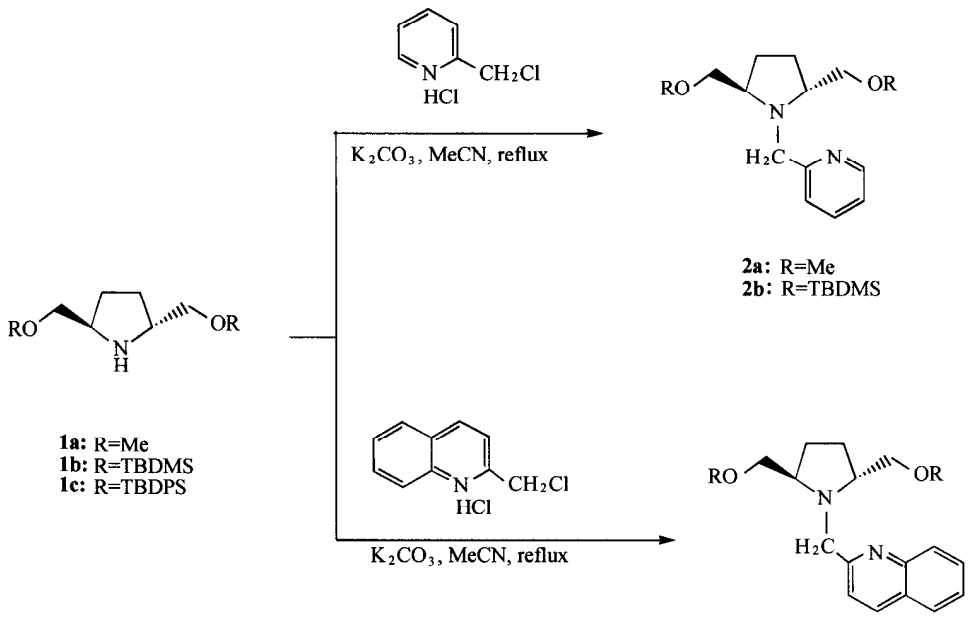
Scheme 1



chiral ligands **2a—e** (Eq. 1). The results including chemical yields, diastereomeric excess (*de*) and *ee* were summarized in Table 1. The *ee* of the product was determined by HPLC analysis using chiral stationary-phase column (Chiralcel OJ), the absolute configuration of the major enantiomer of the *trans*-cyclopropane was assigned according to the sign of its specific rotation and the *de* could be determined by GLC analysis or ^{1}H NMR spectral analysis. We found that owing to the formation of *cis*- and *trans*-diethyl fumarate during the reaction process, the total yields of cyclopropane were 40—50%. The chiral induction of cyclopropanation could be achieved in 15—23% *ee* by those chiral ligands (**2a—d**) and *trans*-cyclopropane and *cis*-cyclopropane were given in the very similar enantioselectivities (Table 1).

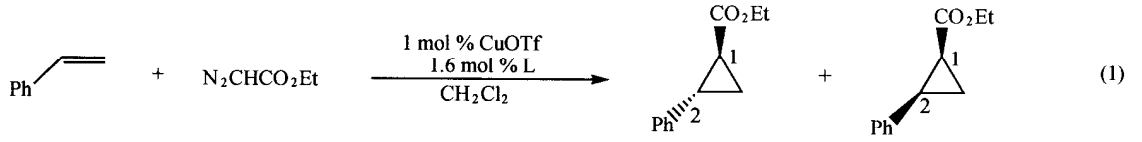
Table 1 The chemical yields, *de* and *ee* of the cyclopropanation of styrene in the presence of chiral ligands **2a—e**

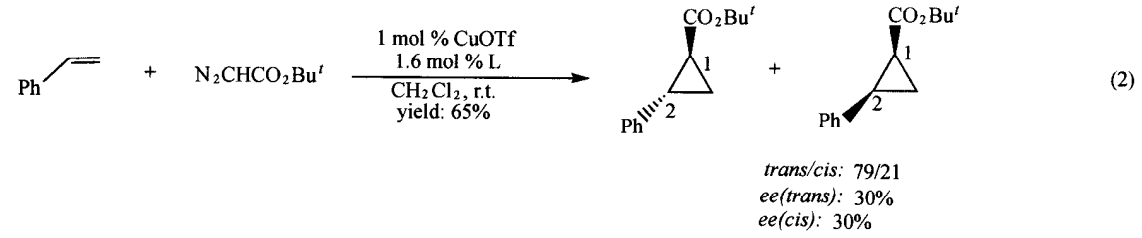
L	Reaction conditions	Time	*trans*/*cis*	Yield (%)	*ee*% (*cis*)	Config.	*ee*% (*trans*)	Config.
2a	r.t.[a]	24 h	58/42	57	18	1*R*,2*S*	17	1*R*,2*R*
2b	r.t.[a]	24 h	73/29	30	17	1*R*,2*S*	15	1*R*,2*R*
2c	r.t.	24 h	77/23	40	20	1*R*,2*S*	14	1*R*,2*R*
2d	r.t.	20 h	72/28	40	24	1*R*,2*S*	23	1*R*,2*R*
2e	r.t.	3d	77/23	40	3	1*R*,2*S*	3	1*R*,2*R*

[a] Heated gently at the beginning in order to initiate the reaction.

Surprisingly, the most sterically bulky ligand **2e** gave the lowest *ee*. This result suggested that this new class of chiral ligands could not efficiently coordinate to the metal center as the famous chiral semicorrin ligands[3] and chiral bis-oxazoline ligands.[4] We believe that the sterically bulky substituents on the 2,5-position of pyrrolidine ring are too close to the bidentate coordination center which would impede the formation of the chiral metal complex, especially for the bulky ligand **2e**. In the mean time, we also tried to use the *tert*-butyl dia-

zoacetate instead of ethyl diazoacetate as the carbene source which is usually very effective in catalytic enantioselective cyclopropanation of styrene (Eq. 2). But the *ee* is still not satisfactory (30%). Although the enantiomeric excesses are not so high as the chiral semicorrin ligands[3] and chiral bis-oxazoline ligands,[4] these results at least suggest that they have potential as catalyst for asymmetric reaction. Perhaps, with chemical modification in the ligand structure, higher enantioselectivity can be obtained.





In conclusion, we have successfully synthesized a new class of chiral ligands for the homogeneous catalytic enantioselective cyclopropanation of styrene. Further studies in this area are in progress in our laboratory.

Experimental

Optical rotations were determined in a solution of $CHCl_3$ and CH_2Cl_2 by using a Perkin-Elmer-241 MC digital polarimeter; $[\alpha]_D$-values are given in units of 10^{-1} deg·cm^2/g. ^{1}H NMR spectra were determined for solutions in $CDCl_3$ with tetramethylsilane (TMS) as internal standard on a Bruker AMX-300 spectrometer; *J*-values are in Hz. High resolution mass spectra were recorded on a Finnigan MA$^+$ instrument. The optical purities of *trans*-cyclopropane and *cis*-cyclopropane were determined by HPLC analysis using a chiral stationary phase column (column, Daicel Co. Chiralcel OD and OJ; eluent, 100:0.5—2 hexane-propan-2-ol mixture; flow rate, 1.0 mL/min; detection, 254 nm light) and the absolute configuration of the major enantiomer was assigned according to the sign of the specific rotation.

The chiral C_2-symmetric 2,5-disubstituted pyrrolidines (**1a—c**) were prepared according to the literature.[6]

Preparation of N-(2′-pyridylmethyl)-(2R,5R)-bis(methoxymethyl)pyrrolidine (**2a**) This compound was prepared from the reaction of **1a** (200 mg, 1.26 mmol) with 2-(chloromethyl)pyridine hydrochloride (248 mg, 1.51 mmol) in the presence of potassium carbonate (180 mg, 1.30 mmol) in acetonitrile under reflux for 10 h. The solvent was removed under reduced pressure. The residue was washed with water and extracted with diethyl ether (3 × 20 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (eluent: EtOAc: petroleum ether = 1:4) to give **2a** (210 mg, 67%) as a colorless oil. $[\alpha]_D^{20}$ + 70.4 (*c* 0.98, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.56—1.96(2H, m), 1.97—2.35(2H, m), 3.31 (6H, s), 3.26—3.50(6H, m), 4.14(2H, s), 7.13 (1H, t, *J* = 6.3), 7.47—7.62(1H, m), 7.64(1H, dt, *J* = 7.6, 2.0), 8.51(1H, d, *J* = 4.4). MS (EI) *m/z* (%): 251(MH^+), 205(100.0), 186(12.4), 173(9.6). [HRMS (EI) Found: 249.1617 [$(M-H)^+$]. $C_{14}H_{21}N_2O_2$ requires 249.1603].

Preparation of N-(2′-pyridylmethyl)-(2R,5R)-bis(tert-butyldimethylsiloxymethyl)pyrrolidine (**2b**) This compound was prepared in the same manner as that described above (340 mg, 60%), a colorless oil. $[\alpha]_D^{20}$ + 38.3(*c* 1.29, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.01(6H, s, SiMe), 0.02(6H, s, SiMe), 0.85(18H, s, CMe_3), 1.56—1.96(2H, m), 1.97—2.35(2H, m), 3.16—3.25(2H, m), 3.42—3.65

(4H, m), 4.14(2H, s), 7.11(1H, t, J = 6.3), 7.47—7.62(1H, m), 7.64(1H, dt, J = 7.6, 2.0), 8.51(1H, d, J = 4.4). MS (EI) m/z (%): 452 (MH^+), 436(4.1), 357(10.2), 305(100.0); [HRMS (EI) Found: 450.3099 (M^+). $C_{24}H_{46}N_2O_2Si_2$ requires 450.3098].

Preparation of N-(2′-quinolylmethyl)-(2R,5R)-bis(methoxymethyl)pyrrolidine (**2c**) This compound was prepared in the same manner as that described above (228 mg, 60%), a colorless oil. $[\alpha]_D^{18}$ +45.8 (c 0.89, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 1.56—1.96(2H, m), 1.97—2.35(2H, m), 3.25(6H, s, OMe), 3.22—3.50(6H, m), 4.28(2H, d, J = 1.9), 7.50(1H, td, J = 8.1, 1.0), 7.71(1H, t, J = 8.6), 7.73(1H, t, J = 8.6), 7.79(1H, td, J = 8.3, 1.0), 8.07(1H, d, J = 8.3), 8.11(1H, d, J = 8.6). MS (EI) m/z (%): 301(MH^+), 255(100.0), 158(65.5), 143(79.3). [HRMS (EI) Found: 301.1904 (MH^+). $C_{18}H_{25}N_2O_2$ requires 301.1916].

Preparation of N-(2′-quinolylmethyl)-(2R,5R)-bis(tert-butyldimethylsiloxymethyl)pyrrolidine (**2d**) This compound was prepared in the same manner as that described above (340 mg, 54%), a colorless oil. $[\alpha]_D^{20}$ +7.4 (c 0.78, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 0.01(6H, s, SiMe), 0.02(6H, s, SiMe), 0.85(18H, s, CMe3), 1.56—1.96(2H, m), 1.97—2.35(2H, m), 3.10—3.35(2H, m), 3.50—3.70(4H, m), 4.32(1H, d, J = 15), 4.38(1H, d, J = 15), 7.49(1H, td, J = 8.1, 1.0), 7.60—7.90(3H, m, Ar), 8.06(1H, d, J = 8.3), 8.09(1H, d, J = 8.6). MS (EI) m/z (%): 501$(MH)^+$, 485(3.4), 443(1.0), 355(100.0), 143(32.9). [HRMS (EI) Found: 500.3249 $(M)^+$. $C_{28}H_{48}N_2O_2Si_2$ requires 500.3254].

Preparation of N-(2′-quinolylmethyl)-(2R,5R)-bis(tert-butyldiphenylsiloxymethyl)pyrrolidine (**2e**) This compound was prepared in the same manner as that described above (490 mg, 52%), a colorless oil. $[\alpha]_D^{18}$ +23.7 (c 1.24, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz): δ 1.0(18H, s, CMe_3), 1.56—1.96(2H, m), 1.97—2.35(2H, m), 3.22—3.40(2H, m), 3.60—3.70(4H, m), 4.26(2H, s), 7.10—7.70(24H, m), 7.90—8.05(2H, m). MS (EI) m/z (%): 747$[(M-H)^+]$, 606(32.9), 548(12.9), 479(100.0). [HRMS (EI) Found: 746.3724$(M-H_2)^+$. $C_{48}H_{54}N_2O_2Si_2$ requires 746.3724].

Typical catalytic reaction procedure To a solution of chiral ligand **2d** (8.0 mg, 0.016 mmol) in dichloromethane (10 mL) was added CuOTf (2 mg, 0.010 mmol) and the mixture was stirred for 1 h at room temperature under argon atmosphere. Styrene (104 mg, 1 mmol) was added into the solution and the resulting mixture was further stirred for 5 min. Then ethyl diazoacetate (137 mg, 1.2 mmol) in dichloromethane (5 mL) was added and the reaction mixture was stirred for 16 h. The cyclopropanation products were isolated by preparative TLC plates (25 × 25 cm) (eluent: ethyl acetate:petroleum ether = 1:10) to give the *trans*- and *cis*-cyclopropane. The *ee* of the *trans*-cyclopropane and *cis*-cyclopropane were determined by chiral HPLC.

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