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Asymmetric cyclopropanation catalyzed by C_2-symmetric bis-(ephedrine)-Cu(II) complexes

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Abstract

The asymmetric cyclopropanation of styrene with alkyl diazoacetate was performed with a series of Cu(II) complexes of novel chiral ligands, which were derived from substitution of 1,3-dibromopropane, 1,2-dibromoethane, α,α′-dibromo-*m*-xylene and 2,6–bis(bromomethyl)pyridine with 1*R*, 2*S*-(−)-ephedrine. These prepared catalysts shown to be highly active in the enantioselective cyclopropanation with ee higher than 89% under the optimal conditions.

Keywords: Cyclopropanation; Chiral ligand; Asymmetric; Ephedrine

1. Introduction

The asymmetric cyclopropanation of olefins with alkyl diazoacetate has been widely reported as being catalyzed by a broad range of chiral ligand-Cu(II)/Cu(I) complexes [1–3]. Pfaltz et.al have first demonstrated that the C_2-symmetric chiral semicorrin-Cu(I) complexes are excellent catalysts for enantioselective cyclopropanation of olefins with α-diazoester [4,5]. One major drawback of the semicorrin ligands is that the prepararion of the ligands involves multi-step synthesis and only one enantiomer is generally available [6]. Metal–Schiff-base complexes and metal–bisoxazoline complexes have been reported as effective catalyst in the last decade [7]; the lack of enantioselectivity for this type of catalyst is possibly due to the partially dissociation of metal ions from the ligand. More recently, diimine and diamine types of chiral ligands have been reported in asymmetric cyclopropanation [8,9]. To the best of our knowledge, there has no report employing ligand with both amine and alcohol stereogenic centers as catalyst in the asymmetric cyclopropanation. In this work, we first report the synthesis, characterization of four new chiral ligands L1–L4, which were derived from 1*R*, 2*S*-(−)-ephedrine (Scheme 1). Catalytic properties of their Cu(II) complexes in the reaction of styrene with diazoacetate presents high ee up to 89%.

2. Experimental

All reagent used are of analytical grade and purchased from the Aldrich Chemical Company. All reactions were carried out under argon atmosphere. ^{1}H NMR spectra were recorded in D_2O or $CDCl_3$ with a 300 MHz spectrometer (Varian model Gemini). Yields and ee values were determined by GC analysis with a chiral capillary column.

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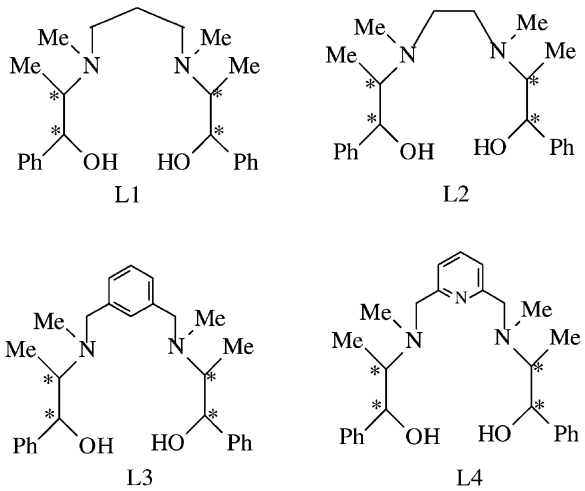


Scheme 1.

2.1. Synthesis of the ligands

2.1.1. Synthesis of L3

Two millimoles α,α′-dibromo-*m*-xylene in 10 ml MeOH was added to a stirred solution of 1*R*, 2*S*-ephedrine (4 mmol) in 10 ml MeOH with 4.0 mmol K_2CO_3. After stirring for 2 h at 25 °C, the solvent was removed under vacuum. A volume of 50 ml CH_2Cl_2 was added to the crude product to extract the organic ligand. Evaporation of CH_2Cl_2 under reduced pressure yield a colorless oil which was then dissolved in 20 ml EtOH, and 10 ml 48% HBr in 20 ml ethanol was added solwly until all the precipitate has formed. It was then filtered and was dried at 60 °C under vacuum for 3 h, giving the white microcrystalls as dihydrobromide salt L3·2HBr (yield 56%). Mp: 115–120 °C; $[\alpha]_D^{25} = -7.34$ ($c = 0.999$, MeOH). ^{1}H NMR. (D_2O), (ppm): 1.19(6H, d, CH_3), 3.69 (6H, s, N–CH_3), 4.4 (4H, m, –CH_2-Ph), 4.60–5.00 (4H, m, NCH and OCH), 7.00–7.50 (14H, m, Ar(H)). FAB, MS, M/Z: 433(M +1). Anal. Calc. for: $C_{28}H_{36}N_2O_2$·2HBr, C, 56.6; H, 6.4; N, 4.7; found: C, 56.2; H, 5.9; and N, 4.8%.

2.1.2. Synthesis of L1, L2 and L4

Ligand L1, L2 and L4 were synthesized by following the similar procedure as above, but using 1,3-dibromopropane, 1,2-dibromoethane and 2,6–bis-(bromomethyl) pyridine instead of α, α′-dibromo-*m*-xylene. Satisfied analyses data were obtained.

2.2. Synthesis of the complex catalysts

Synthetic procedure of Cu(II) complex of L3 is described further.

To a solution containing 0.05 mmol L3·2HBr in 10 ml MeOH was added 0.1 mmol Et_3N and 0.05 mmol $Cu(ClO_4)_2·6H_2O$. Five minutes later the solution changed into deep blue. The final product that separated was washed with absolute ethanol and diethyl ether and dried in vacuum. Yield, 72%. Calc. for $C_{28}H_{36}N_2O_2CuClO_4$, formula weight 695.1: C, 48.4; H, 5.2; N, 4.0; found: C, 47.9; H, 5.5; N, 3.8%. Following the similar procedure above, Cu(II) complexes of L1, L2 and L4 were obtained, and the analyses data of C, H and N confirmed the composition of these ligand.

2.3. Cyclopropanation reaction

All reactions were performed at 298 K. To a stirred solution of 3 mmol of styrene in 10 ml of dichloromethane containing 0.2 mmol Cu(II) complex catalyst, 20 mmol ethyl diazoacetate in dry dichloromethane was added via syringe, and the reaction was stirred for 24 h. The solvent was removed and the crude product was purified by silica gel column chromatography. Analysis was carried out on a GC analyzer.

2.4. Determination of stability constants of Cu(II)-complexes

The stability of metal complexes was determined by potentiometric titration experiment. Metal stock solutions for potentiometric studies were reagent grade chloride salts prepared with doubly distilled water and standardized by EDTA. CO_2-free dilute-it ampules of KOH were obtained from J.T. Baker Inc. KOH solutions (about 0.1 M) were prepared with doubly distilled water and standardized. The extent of carbonate accumulation (<1.8%) was checked periodically by titration with a standard HCl solution. A Corning 250 digital pH meter, fitted with Fisher full-range blue-glass and Fisher calomel reference electrodes were used for potentiometric titrations. A Metrohm 10 ml capacity piston burette was used for precise delivery of standard KOH. The solution to be studied was contained in a 75 ml jacketed glass

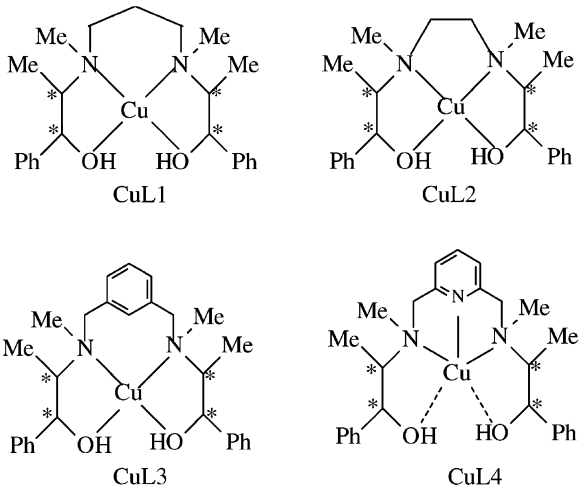
cell thermostated at 25.00 ± 0.05 °C by a circulating constant-temperature water bath.

Stability constants for the synthesized complexes were calculated from potentiometric titration carried out at 298 K. The ionic strength of all the solutions was 0.1 mol/dm^3 (KCl). Detailed calibration procedure and calculation methods were reported previously [10].

3. Results and discussion

Olefins cyclopropanation is a very useful reaction for the preparation of building blocks for synthesis of natural products (Scheme 2). The best result in terms of yields and selectivities have been achieved by using copper as metal catalyst and chiral nitrogen chelates as ligands [11]. Beside some *N*,*N*′-ligands and oxazoline system developed by Evans and Pfaltz, significant results were achieved using chiral amino alcohol [12]. In the present work, the ligand derived from 1*R*, 2*S*-(−)-ephedrine is a series of structural related ligands with N and O connected stereogenic centers. Their Cu(II) complexes (Scheme 3) are different in the structural rigidity and coordination number to Cu(II) ion. These properties provide us an opportunity to investigate the relationship between structure and reactivity in this kind of reaction. With styrene and ethyl diazoacetate as reactants, the experimental results are summarized in Table 1.

As the experimental data indicated, the C_2-asymmetric structures of these chiral ligands are critical for enantioselective cyclopropanation of olefin. With the increase of the rigidity of the ligands from L1 to L4, their coplanarity also increased, thus good cyclopropanation conversion and diastereoselectivities revealed.

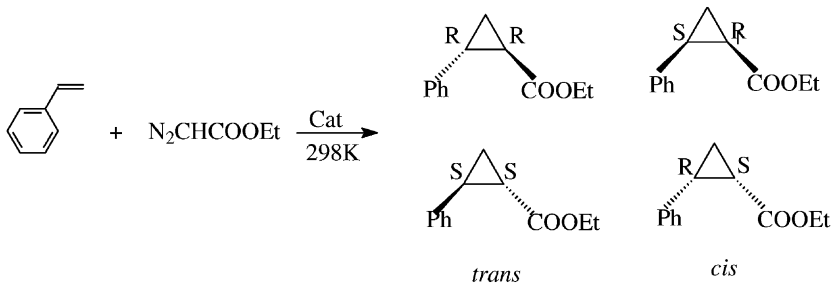


Scheme 3.

The major products were *cis*-cyclopropanes with good enantioselectivity.

Considering the influence of the stability of the complex catalysts upon the ee, potentiometric titration experiments were conducted for 1:1 ligand to metal systems for L2, L3 and L4. Stability constants obtained are $10^{3.8}$, $10^{4.6}$ and $10^{7.8}$ ($\log K = [CuL]/[Cu][L]$) for L2, L3 and L4, respectively. As shown in Table 1, with the stability of the Cu(II) complex increased (entry 2, 3 and 4), the conversion and enantioselectivity all increased significantly. This phenomenon shows that the affinity of the metal ion to the ligand plays an important role in the asymmetric cyclopropanation process.

Since, Cu(II) ions are five-coordinated in nature, we suspected that the Cu(II) complexes of L1, L2 and L3 are coordination unsaturated. In Katsuki's



Scheme 2.

Table 1
Cu(II) complexes of L1–L4 catalyzed cyclopropanation

Entry	Ligand	Yield (%)	*trans*:*cis*	ee (*trans*, %)[a]	ee (*cis*, %)[b]
1	L1	58	72:28	64.6	59.0
2	L2	86	83:17	80.2	69.1
3	L3	85	82:18	82.1	60.2
4	L4	92	86:14	89.0	79.8

[a] 1*R*, 2*S* as the major enantiomer.
[b] 1*R*, 2*R* as the major enantiomer.

Table 2
The influence of organic solvents on the yield and enantioselectivity of asymmetric cyclopropanation using L1 as ligand

Entry	Solvent[a]	Yield (%)	*trans*:*cis*	ee (*trans*, %)[b]	ee (*cis*, %)[c]
1	EtOH	59	73:27	65.0	45.1
2	*t*-BuOH	62	76:24	66.2	59.2
3	Ph-CH_2OH	68	77:23	73.4	39.5
4	MeCN	55	69:31	64.4	48.7

[a] The solvent was added in preparing the reaction mixture.
[b] 1*R*, 2*S* as the major enantiomer.
[c] 1*R*, 2*R* as the major enantiomer.

salen-Co(III) complex catalyst, the authors has noted that the presence of methanol improved the observed enantioselectivity [13]. Therefore, other alcohols and some nonprotic solvents were employed to test the solvent effect for L1 system. The results of these reactions are summarized in Table 2. It can be seen from the data that both the enantioselectivity and catalytic activity were remarkably influenced by the addition of alcohols. The bulky benzyl alcohols were beneficial to the enantioselectivity, however, the conversion decreased slightly. This result indicated that the alcoholic group is important in the enantioselectivity. It stands to reason that the designed diamines–dialcohols chiral ligands are prior to the ligand with only diimine or diamine moieties [8,9].

Former investigation indicated that N-donor additives can improve the enantioselectivity in the asymmetric cyclopropanation catalyzed by the salen or related metal complexes [14–18]. This conclusion is coherent with our result in observing the increased enantioselectivity from (entry) 3 to 4 in Table 1. Here in, we introduce N-donor ligand into the complex at the axial position. However, the addition of Et_3N results in a slight decrease in both the conversion and selectivity. We suspected that the strong base with high coordination tendency to Cu(II) substituted the weaker coordinated alcoholic groups in the complex catalyst, and thus influenced the structural and catalytic properties of the ligand. The effects of P and S-donor ligands on the conversion and enantioselectivity of this asymmetric reaction are under investigation in our laboratory.

In conclusion, C_2-asymmetric Cu(II) complexes of chiral ligands derived from 1*R*, 2*S*-(−)-ephedrine are efficient complex catalyst for the asymmetric cyclopropanation of styrene. The steric properties and the stability of the metal complexes show obvious effects on the enantioselectivities.

References

[1] R.J. Clarke, I.J. Shannon, Chem. Commun. (2001) 1936.
[2] M.I. Burguete, J.M. Fraile, J.I. Garcia, E.G. Verdugo, S.V. Luis, J.A. Mayoral, Org. Lett. 24 (2000) 3905.
[3] R. Boulch, A. Scheurer, P. Mosset, R.W. Saalfrank, Tetrahedron Lett. 41 (2001) 1023.
[4] A. Pfaltz, Acta Chim. Scand. 50 (1996) 189;
A. Pfaltz, Chimia 44 (1990) 202.
[5] D. Muller, G. Umbricht, B. Weber, A. Pfaltz, Helv. Chim. Acta 74 (1991) 232.
[6] A. Pfaltz, Acc. Chem. Res. 26 (1993) 339.
[7] A.K. Ghosh, P. Mathivanan, J. Cappiello, Tetrahedron Asymmetry 9 (1998) 1.

[8] J.A. Ma, L.X. Wang, W. Zhang, Q.L. Zhou, Tetrahedron Asymmetry 12 (2001) 2801.
[9] C. Borriello, M.E. Cucciolito, A. Panunzi, F. Ruffo, Tetrahedron Asymmetry 12 (2001) 2467.
[10] J. Gao, A.E. Martell, R.J. Motekaitis, Inorg. Chim. Acta 325 (2001) 164.
[11] F. Fache, E. Schulz, M.L. Tommasino, M. Lemaire, Chem. Rev. 100 (2000) 2159.
[12] Z. Li, Z. Zhou, H. Wan, Chen, J. Mol. Catal. 165 (2001) 67.
[13] T. Fukuda, T. Katsuhi, Synlett. (1995) 825.
[14] T. Yamada, T. Ikeno, H. Sekino, M. sato, Chem. Lett. (1999) 719.
[15] T. Ikeno, M. Sato, T. Yamada, Chem. Lett. (1999) 1345.
[16] T. Uchida, R. Irie, T. Katsuki, Synlett. 7 (1999) 1163.
[17] T. Hashihayata, T. Punniyamurthy, R. Irie, T. Katsuki, M. Akita, Y. Morooka, Tetrahedron 55 (1999) 14599.
[18] T. Miimi, T. Uchida, R. Irie, T. Katsuki, Tetrahedron Lett. 41 (2000) 3647.