Communication

Asymmetric Diels-Alder Reaction Catalyzed by Novel Chiral Dibenzo[a,c]cycloheptadiene Bis(oxazoline) Metal Complexes

FU, Bin(傅滨) **DU, Da-Ming**(杜大明)*

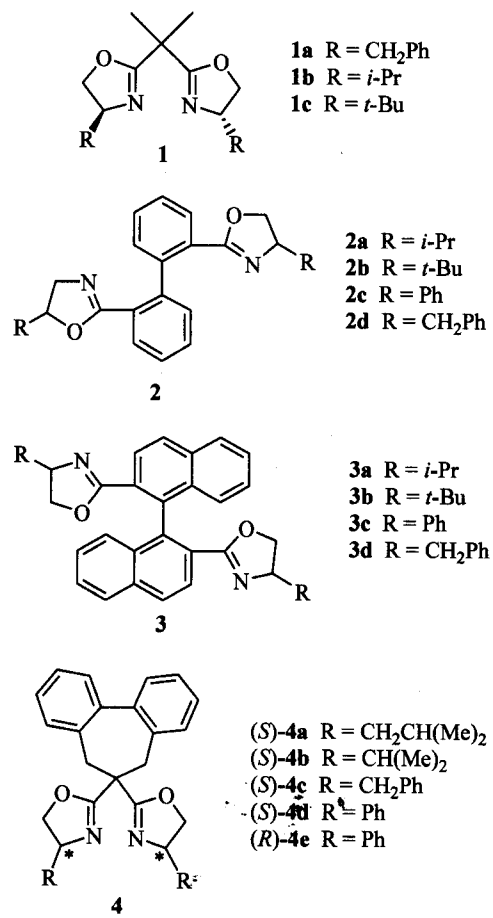
Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, China

A series of novel chiral C_2-symmetric bis(oxazoline) ligands have been synthesized. The copper and magnesium complexes, prepared *in situ* from copper(II)-triflate or magnesium triflate with the new enantiopure oxazoline ligands, were evaluated as chiral catalysts in the enantioselective Diels-Alder reaction of cyclopentadiene with *N*-crotenoyl-oxazolidin-2-one. Primary results showed that diastereoselectivity up to 94% and enantioselectivity up to 68% *ee* for *endo* products were observed respectively with these ligands.

Keywords bis(oxazoline), asymmetic catalysis, Diels-Alder reaction, dibenzo[a, c]cyclo-heptadiene

The C_2-symmetric chiral bis(oxazoline) compounds are very versatile ligands in the asymmetric catalysis of many organic reactions.[1] In general, the chiral complexes of this kind of ligands give excellent enantioselectivity when they are used as the catalysts for Diels-Alder reactions.[2] The Lewis acid cores of these complex catalysts were mainly Fe(II), Cu(II), Zn(II), Ni(II) and Mg(II) ions.[3-6] The ligands **1** were used by Evans and others[7] in a wide range of transition metal-catalyzed process, but the most successful ligand, *t*-butyl substituted bis(oxazoline) (**1c**), which is synthesized from *t*-leucinol, is very expensive. Ikeda[8] and Hayashi[9] developed bis(oxazoline) **2** and **3** which include a biaryl skeleton, however, in their studies chiral biaryl bis(oxazoline) ligands were prepared by the separation of the two diastereomers, and only one of the two diastereomers showed high enantioselectivity.[9] We have an ongoing interest on the synthesis and application of chiral hrterocyclic ligand in asymmetric organic reactions,[10] and want to evaluate the effect resulting from the introduction of a rigid cyclic dibenzo[a,c]cycloheptadiene moiety onto the bis(oxazoline) catalysts. In this communication, the bis(oxazoline) ligands **4a—4e** (Scheme 1) which combine the dibenzo[a,c]cycloheptadiene and two chiral oxazoline rings were designed and synthesized, and their asymmetric catalytic activity for Diels-Alder reaction was investigated. The cooperative effect of dibenzo[a,c] cycloheptadiene moiety and chiral oxazoline unit in this type of ligands may result in unique characteristics for catalytic reaction. Another advantage is that linking the biphenyl may reduce the difficulty in separating the diastereoisomers resulted from the double chirality of biphenyl and bis(oxazoline).

Scheme 1



Firstly, chiral bis(oxazoline) ligands **4a—4e** have been synthesized with the following procedure (Scheme 2).

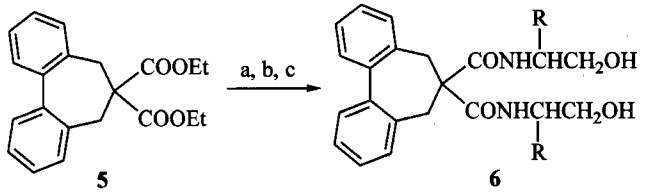
* E-mail: dudm@pku.edu.cn; Fax: 010-62751708

Received November 26, 2002; revised February 12, 2003; accepted March 25, 2003.

Project supported by National Natural Science Foundation of China (No. 20172001) and the Scientific Research Foundation for the Returned Overseas Chinese Scholars, Ministry of Education.

The cyclic diethyl carboxylate **5**[11] was hydrolyzed in an alcoholic solution of NaOH to give the corresponding diacid, which was refluxed with thionyl chloride to afford the diacyl chloride. The diacyl chloride was then treated with β-amino alcohols in the presence of triethylamine to afford the corresponding chiral intermediate dihydroxy diamides **6a**—**6e** as solid in 65%—73% yields. The desired bis(oxazoline) ligands were synthesized according to the procedure developed by Denmark.[12] The dihydroxy diamides were treated with MsCl (methanesulfonyl chloride) (2.2 equiv.) and Et_3N (4.4 equiv.) in dichloromethane to afford the corresponding bismesylates, which were treated with an aqueous methanolic solution of NaOH (8 equiv.) to afford the bis(oxazoline) **4a**—**4e** in 70%—82% yields (Scheme 2). The structures of the new ligands were characterized by ^1H NMR, MS, IR and elemental analysis.[13]

Scheme 2



(*S*)-**6a** R = $CH_2CH(Me)_2$, (*S*)-**6b** R = $CH(Me)_2$,
(*S*)-**6c** R = CH_2Ph, (*S*)-**6d** R = Ph, (*R*)-**6e** R = Ph

(a) NaOH, CH_3OH, (b) $SOCl_2$, (c) aminol alcohol, Et_3N, 65%—73%
(d) MsCl, Et_3N, (e) NaOH, CH_3OH, 70%—82%

These ligands were then examined for the Lewis acid catalyzed Diels-Alder reaction of cyclopentadiene with *N*-crotenoyl-oxazolidin-2-one, which is the model reaction most often investigated with chiral oxazoline ligands.[4a,14] $Mg(OTf)_2$ and $Cu(OTf)_2$ were usually used as effective Lewis acid catalysts. The asymmetric Diels-Alder reaction was carried out in dichloromethane solution in the presence of 10% mol of copper(II) or Mg(II) catalyst generated by mixing $Cu(OTf)_2$ or $Mg(OTf)_2$ and the bis(oxazoline) ligands to give cycloadducts as a mixture of *endo* **9** and *exo* **10** isomers (Scheme 3). Here, one-to-one ligand-metal complexes of the ligands **4a**—**4e** and metal salt were prepared at ambient temperature. The solution of the catalyst was combined with dienophile and cyclopentadiene (1:5, mol:mol) at the specified temperature, the products were isolated by silica gel column chromatography after indicated reaction time (Table 1). The *endo*/*exo* ratio was determined by ^1H NMR spectroscopy and confirmed by HPLC. Enatiomer compositions were determined by HPLC (Daicel Chiraliel AD column). Absolute configuration assignments of the cycloadduct products **9a** and **9b** were made sure by comparing with Evans's report.[15]

Scheme 3

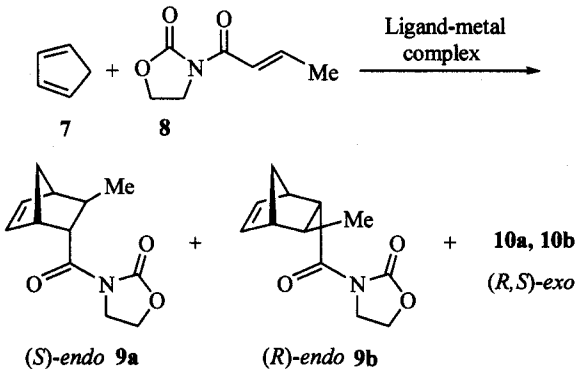


Table 1 Diels-Alder reaction of cyclopentadiene **7** with *N*-crotenoyl-oxazolidin-2-ones **8**[a]

Entry	Ligand	Salt	Temp. (℃)	Time (h)	Yield[b] (%)	*endo*/*exo*[c]	*ee*[d] (%)
1	**4a**	$Cu(OTf)_2$	0	8	96	86:14	31 (*S*)
2	**4b**	$Cu(OTf)_2$	0	8	92	90:10	48 (*S*)
3	**4c**	$Cu(OTf)_2$	0	8	93	91:9	15 (*S*)
4	**4d**	$Cu(OTf)_2$	0	8	94	95:5	26 (*S*)
5	**4e**	$Cu(OTf)_2$	0	8	95	94:6	27 (*R*)
6	**4b**	$Cu(OTf)_2$	-40	16	81	90:10	56 (*S*)
7	**4b**	$Cu(OTf)_2$	-78	24	84	88:12	68 (*S*)
8	**4a**	$Mg(OTf)_2$	0	8	92	87:13	5 (*S*)
9	**4b**	$Mg(OTf)_2$	0	8	94	90:10	18 (*S*)
10	**4c**	$Mg(OTf)_2$	0	8	90	88:12	8 (*S*)
11	**4d**	$Mg(OTf)_2$	0	8	94	92:8	12 (*S*)
12	**4e**	$Mg(OTf)_2$	0	8	95	92:8	11 (*R*)

[a] Reaction procedure: under N_2, $M(OTf)_2$ (0.044 mmol) and ligand (0.048 mmol) in CH_2Cl_2 (2 mL) were stirred for 1—1.5 h, then cyclopentadiene **7** (2.2 mmol) and **8** (0.44 mmol) were added. [b] Values refer to isolated yields of cycloadduct. [c] *Endo*/*exo* ratio determined either by ^1H NMR or HPLC. [d] *ee* value determined by HPLC (Daicel Chiracel AD column, hexane: *i*-PrOH/95:5, flow rate: 0.5 mL/min, retention time, *exo* 24.8 min, 27.0 min, *endo*: 25.8 min, 29.6 min).

In general, the reaction was basically completed at 0 ℃ within 8 h and gave very high yield and *endo/exo* ratio of products. However, from the data collected in Table 1, it can be seen that the enantioselectivity is generally low, the highest value 48% *ee* was obtained for ligand **4b** at 0 ℃ (Entry 2). When the temperature was lowed to −40 ℃ and −78 ℃, the enantioselectivity was increased to 56% *ee* and 68% *ee*, respectively (Entries 6 and 7). The enantioselectivity catalyzed by $Mg(OTf)_2$ complex is lower than that catalyzed by $Cu(OTf)_2$ complex for this Diels-Alder reaction. This may be because the stereochemistry of the intermediates from the metal-ligand and dienophile is different,[4a,14] one is tetrahedral, while another is square-planar.

In summary, a series of new bis(oxazoline) ligands containing dibenzo[a,c]cyclo-heptadiene have been synthesized and preliminary results in asymmetric Diels-Alder cycloaddition of cyclopentadiene with *N*-crotenoyl-oxazolidin-2-one have been obtained. The C_2-symmetric bi(oxazoline) **4a**—**4e** derived from dibenzo[a,c]cycloheptadiene showed different reactivity in the asymmetric Diels-Alder cycloaddition. The moderate enantioselectivity has been obtained with copper(II) triflate complex of *iso*-propyl substituted bi(oxazoline) **4b**. The potential as new catalytic system for other asymmetric reactions with these ligands are currently undergoing in our laboratory.

References and notes

1 (a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1.
(b) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325.

2 (a) Kagan, U. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007.
(b) Corey, E. J.; Imai, N.; Zhang, H. Y. *J. Am. Chem. Soc.* **1991**, *113*, 728.

3 Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807.

4 (a) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460.
(b) Evans, D. A.; Barnes, D. M. *Tetrahedron Lett.* **1997**, *38*, 57.

5 (a) Ghosh, A. K.; Mathivanan, P.; Cappiello, J. *Tetrahedron Lett.* **1996**, *37*, 3815.
(b) Takacs, J. M.; Quincy, D. A.; Shay, W.; Jones, B. E.; Ross II, C. R. *Tetrahedron: Asymmetry* **1997**, *8*, 3079.
(c) Takacs, J. M.; Lawson, E. C.; Reno, M. J.; Youngman, M. A.; Quincy, D. A. *Tetrahedron: Asymmetry* **1997**, *8*, 3073.

6 Kanemasa, S.; Oderaotoshi, Y.; Yamamoto, H.; Tanaka, J.; Wada, E.; Curran, D. P. *J. Org. Chem.* **1997**, *62*, 6454.

7 Evans, D. A.; Murry J. A.; Von Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798.

8 Imai, Y.; Zhang, W.-B.; Kida, T.; Nakatsuji, Y.; Ikeda, I. *J. Org. Chem.* **2000**, *65*, 3326.

9 Uozumi, Y.; Kyota, H.; Kishi, E.; Kitayama, K.; Hayashi, T. *Tetrahedron: Asymmetry* **1996**, *7*, 1603.

10 (a) Du, D. M.; Wang, Z. Y.; Xu, D. C.; Hua, W. T. *Synthesis* **2002**, 2347.
(b) Wang, Z. Y.; Du, D. M.; Wu, D.; Hua, W. T. *Synth. Commun.* **2003**, *33*, 1275.
(c) Xu, D. C.; Du, D. M.; Ji, N.; Wang, Z. Y.; Hua, W. T. *Synth. Commun.* **2003**, *33*, in press.

11 (a) Kenner, J. *J. Chem. Soc.* **1913**, 613.
(b) Dvorken, L. V.; Smyth, R. B.; Mislow, K. *J. Am. Chem. Soc.* **1958**, *80*, 486.

12 Denmark, S. E.; Nakajima, N.; Nicaise, O. J. C.; Faucher, A. M.; Edwards, J. P. *J. Org. Chem.* **1995**, *60*, 4884.

13 Data of new compounds:
4a: $[\alpha]_D^{20}$ − 28.9 (*c* 0.95, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ: 7.25—7.44 (m, 8H), 4.36 (t, J = 8.4 Hz, 2H), 4.22—4.07 (m, 2H), 3.89 (s, 2H), 3.26—2.90 (m, 4H), 1.86—1.42 (m, 4H), 1.36—1.19 (m, 2H), 0.88 (d, J = 3.8 Hz, 12H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 166.1, 140.9, 138.1, 127.9, 127.4, 127.1, 73.5, 65.8, 64.6, 45.6, 37.6, 25.3, 22.8; IR (KBr) ν: 3010, 2966, 1654, 1508, 1482 cm^{-1}; MS (70 eV) *m/z* (%): 444 (M^+, 100), 429 (7), 387 (20), 318 (45), 304 (32). HRMS (EI) calcd for $C_{29}H_{36}O_2N_2$ 444.2777; found 444.2777.
4b: $[\alpha]_D^{20}$ − 17.5 (*c* 0.80, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ: 7.41—7.23 (m, 8H), 4.26 (t, J = 8.2 Hz, 2H), 4.13—3.90 (m, 4H), 3.42—2.80 (m, 4H), 1.78—1.68 (m, 2H), 0.87 (t, J = 4.0 Hz, 12H); IR (KBr) ν: 2966, 1654, 1508, 1482 cm^{-1}; MS (70 eV) *m/z* (%): 416(M^+, 8), 304 (58), 191 (38), 127(100). HRMS (EI) calcd for $C_{27}H_{32}O_2N_2$ 416.2464; found 416.2463.
4c: m.p. 82—83.5 ℃; $[\alpha]_D^{20}$ − 19.0 (*c* 0.35, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ: 7.46—7.14 (m, 18H), 4.42—4.30 (m, 2H), 4.23 (t, J = 7.8 Hz, 2H), 4.15—3.98 (m, 2H), 3.25—3.02 (m, 4H), 3.00—2.48 (m, 4H); IR (KBr) ν: 3010, 1656, 1452 cm^{-1}; MS (70 eV) *m/z* (%): 512 (M^+, 90), 421 (100), 334 (46). Anal. calcd for $C_{35}H_{32}O_2N_2$: C 82.10, H 6.48, N 5.46; found C 82.31, H 6.52, N 5.40.
4d: $[\alpha]_D^{20}$ − 19.0 (*c* 1.80, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ: 7.46—7.17 (m, 18H), 5.30 (dd, J = 8.2, 8.2 Hz, 2H), 4.72 (dd, J = 8.2, 8.4 Hz, 2H), 4.17 (t, J = 8.4 Hz, 2H), 3.41—3.12 (m, 4H); IR (KBr) ν: 3010, 2964, 1656, 1482 cm^{-1}; MS (70 eV) *m/z* (%): 484 (M^+, 64), 380 (12), 306 (100). HRMS (EI) calcd for $C_{33}H_{28}O_2N_2$ 484.2139; found 484.2150.
4e: $[\alpha]_D^{20}$ + 41.1 (*c* 0.45, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ: 7.46—7.06 (m, 18H), 5.26 (dd, J = 9.6, 8.2 Hz, 2H), 4.72 (dd, J = 8.0, 9.6 Hz, 2H), 4.18 (dd, J = 8.2, 8.0 Hz, 2H), 3.28—2.90 (m, 4H); IR (KBr) ν: 3010, 2966, 1650, 1508 cm^{-1}; MS (70 eV) *m/z* (%): 484 (M^+, 74), 380 (14), 306 (100). HRMS (EI) calcd for $C_{33}H_{28}O_2N_2$ 484.2150; found 484.2151.

14 Crosignani, S.; Desimoni, G.; Faita, G.; Righetti, P. *Tetrahedron* **1998**, *54*, 15721.

15 Evans, D. A.; Miller, S. J.; Lectka, T.; Von Matt P. *J. Am. Chem. Soc.* **1999**, *121*, 7559.

(E0211266 LU, Y. J.; DONG, H. Z.)