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Synthesis and crystal structure of bis-[(4*S*,5*S*)-4,5-dihydro-4,5-diphenyl-2-(2′-oxidophenyl-χO)oxazole-χN] copper(II) and its application in the asymmetric Baeyer–Villiger reaction

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Abstract

Two new oxazolines (**3** and **4**) and their copper complexes (**5** and **6**) were synthesized. The four compounds were characterized by elemental analysis and ^{1}H-NMR, IR, MS spectrometry. The molecular structure of compound **6** was determined by single-crystal X-ray diffraction analysis. The four coordinate atoms [N(1), N(2), O(2), O(4)] and the central metal atom (Cu) form a saddle configuration. Compounds **5** and **6** were found to be moderately effective in the catalytic asymmetric Baeyer–Villiger reaction of 2-phenylcyclohexanone. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Asymmetric catalysis; Crystal structure; Chiral oxazoline; Baeyer–Villiger reaction

1. Introduction

Optically active oxazolines as a class of efficient auxiliaries have been extensively used in catalytic asymmetric synthesis [1,2]. They can transfer the chirality from the heterocycle to newly formed bonds, thereby generating new centers of chirality with high enantioselectivity. These characteristics have attracted large effort to the design and synthesis of new kinds of chiral oxazoline ligands [3–8]. Bolm has developed an effective method to synthesize oxazoline from amino alcohol [3,4]. Towards this direction, we designed and synthesized novel oxazolines **3** and **4**. Complexes **5** and **6** were also obtained by the reaction of **3** and **4** with copper acetate (Schemes 1 and 2). As part of our study to test their efficiency in asymmetric catalytic reactions, we tried to use compounds **5** and **6** in the asymmetric Baeyer–Villiger reaction. Herein, we report the synthesis of complexes **5** and **6** and the X-ray structure of **6**. The results of the asymmetric Baeyer–Villiger reaction catalyzed by **5** and **6** are also reported.

2. Results and discussion

2.1. Synthesis

Chiral amino alcohols **1** and **2** were prepared on a large scale [9] and were used as starting materials for the synthesis of chiral oxazoline ligands. Compounds **3** and **4** were synthesized by the reaction of **1** and **2** with 2-hydroxy-3-*tert*-butyl benzonitrile in chlorobenzene in the presence of zinc chloride (Scheme 1) [3,4]. Compounds **5** and **6** were prepared by mixing the oxazolines **3** and **4** with copper acetate in absolute ethanol.

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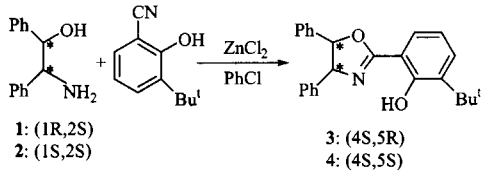
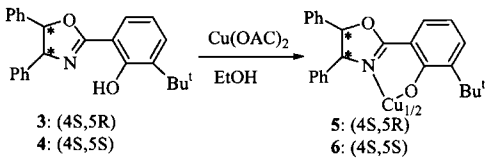


Scheme 1.



Scheme 2.

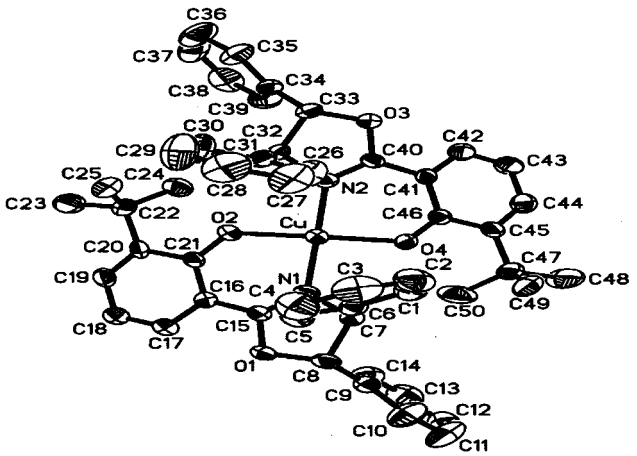


Fig. 1. ORTEP plot of the molecular structure and numbering scheme of **6**. Hydrogen atoms are omitted for clarity.

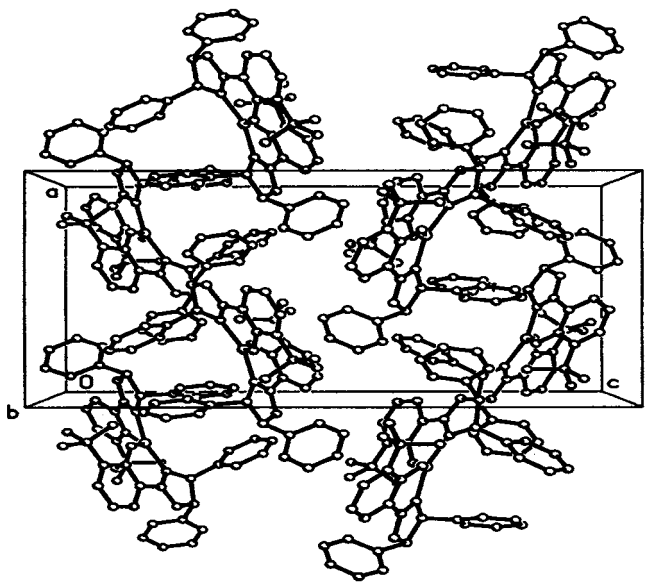


Fig. 2. ORTEP stereoplot of the packing of **6**.

2.2. Crystal structure of *6*

An air-stable single crystal of **6** suitable for X-ray diffraction analysis was obtained by crystallization from dichloromethane. The molecular structure of **6** and the adopted numbering scheme are shown in Fig. 1. The stereoplot of the packing of **6** is shown in Fig. 2. The crystallographic data are given in Table 1. Selected bond lengths and bond angles are given in Table 2.

Complex **6** crystallizes in orthorhombic space group $P2_12_12_1$ with one independent molecule per asymmetric unit ($Z = 4$). Analysis of its structure indicates that the four atoms of the dihydrooxazole N-atoms and phenolato O-atoms in each molecule are located in an almost square planar arrangement with a great distortion towards a tetrahedron configuration. This is similar to the configuration of bis[(4*S*)-4,5-dihydro-4-isopropyl-2-(2′-oxidophenyl-χO)oxazole-χN]copper(II) [4]. In complex **6**, the deviation of the Cu atom from the N_1–N_2–O_2–O_4 plane is −0.0364 Å, which is smaller than the corresponding deviation in bis[(4*S*)-4,5-dihydro-4-isopropyl-2-(2′-oxidophenyl-χO)oxazole-χN]copper(II) (−0.146 Å) [4]. The angles between O(4)–Cu–N(1) and O(2)–Cu–N(2) (93.03 and 92.47°) are slightly larger than comparable angles in bis[(4*S*)-4,5-dihydro-4-isopropyl-2-(2′-oxidophenyl-χO)oxazole-χN]copper-(II) (89.9 and 89.6°) [4]. All these indicate that the degree of distortion toward tetrahedron configuration in complex **6** is greater than in bis[(4*S*)-4,5-dihydro-4-isopropyl-2-(2′-oxidophenyl-χO)oxazole-χN]copper(II) [4]. This is ascribed to the steric hindrance among the bulky *tert*-butyl, the oxazoline ring and the substitute phenyl at C4. In complex **6**, the dihedral angle of the N(2)–Cu–O(4) plane with the N(1)–Cu–O(4) plane is 27.5°, which indicates the great deviation from planarity of the five atoms [N(1), N(2), Cu, O(2), O(4)]. Accordingly, it is reasonable to conclude that the five atoms form a saddle configuration. This saddle configuration is also different to the near-planar geometry of the chiral Schiff base copper complex [(1*R*,2*R*)-(−)-*N*,*N*′-bis(salicylidene)-*trans*-1,2-cyclohexanediiminato]copper(II) [11], which has the same coordinating atoms in similar chelations. In complex **6**, the dihedral angles between O(3)–C(40)–C(41)–C(42) and O(1)–C(15)–C(16)–C(17) are 14.6°and 2°, respectively, which indicate the small deviation from planarity between the 2-oxidophenyl and 4,5-dihydrooxazole ring. The Cu–O distances of 1.909 and 1.9257 Å are slightly longer than those reported for bis[(4*S*)-4,5-dihydro-4-isopropyl-2-(2′-oxidophenyl-χO)-oxazole-χN]copper(II) (1.889 and 1.911 Å) [4]. On the other hand, the Cu–N distances (1.920 and 1.932 Å) are slightly shorter than the reported ones(1.941 and 1.950 Å) [4]. The two phenyl rings, which locate in the

Table 1
Crystallographic data for **6**

Formula	$C_{50}H_{48}CuN_2O_4$
M_n	804.44
Color	Dark-blue
Space group	$P2_12_12_1$
Crystal system	Orthorhombic
Unit cell dimensions	
a (Å)	12.737(2)
b (Å)	14.050(2)
c (Å)	23.896(3)
V (Å^3)	4276.3(11)
Z	4
μ (mm^{-1})	0.557
Crystal size (mm)	$0.58 \times 0.40 \times 0.36$
Temperature (K)	296(2)
Wavelength (Å)	0.71073
θ range (°)	1.68–26.00
Scan type	ω
No. of data collected	6018
No. of unique data	5546
hkl range	−1:15, −1:17, −1:29
R_{merge}	0.0119
Flack	−0.014(11) [10]
Observability criterion n, $I>n\sigma(I)$	2
No. of data in refinement	5546
No. of refined parameters	521
Goodness-of-fit on F^2	0.846
Final R	0.0373
w_R	0.0485

Table 2
Selected bond distances (Å) and bond angles (°) of **6**

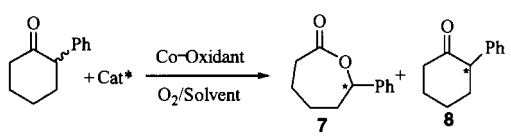
Cu–O(2)	1.909(2)	Cu–N(2)	1.920(3)
Cu–O(4)	1.9257(19)	Cu–N(1)	1.932(3)
O(1)–C(15)	1.356(4)	O(1)–C(8)	1.463(4)
O(2)–C(21)	1.298(3)	O(3)–C(40)	1.343(4)
O(3)–C(33)	1.453(4)	O(4)–C(46)	1.307(3)
N(1)–C(15)	1.289(4)	N(1)–C(7)	1.472(4)
N(2)–C(40)	1.284(4)	N(2)–C(32)	1.470(4)
O(2)–Cu–N(2)	92.47(12)	O(2)–Cu–O(4)	158.43(9)
N(2)–Cu–O(4)	90.22(11)	O(2)–Cu–N(1)	90.64(11)
N(2)–Cu–N(1)	162.94(11)	O(4)–Cu–N(1)	93.03(11)
C(15)–O(1)–C(8)	107.8(3)	C(21)–O(2)–Cu	127.1(2)
C(40)–O(3)–C(33)	107.3(3)	C(46)–O(4)–Cu	125.5(2)
C(15)–N(1)–C(7)	109.8(3)	C(15)–N(1)–Cu	124.6(3)
C(7)–N(1)–Cu	125.6(2)	C(40)–N(2)–C(32)	108.9(3)
C(40)–N(2)–Cu	125.4(3)	C(32)–N(2)–Cu	125.6(2)
N(1)–C(7)–C(6)	111.0(3)	N(1)–C(7)–C(8)	102.3(3)
O(1)–C(8)–C(7)	103.1(3)	O(1)–C(8)–C(9)	111.1(3)
N(1)–C(15)–O(1)	115.2(3)	N(1)–C(15)–C(16)	127.3(3)
O(1)–C(15)–C(16)	117.5(3)	O(2)–C(21)–C(20)	119.5(3)
O(2)–C(21)–C(16)	123.2(3)	N(2)–C(32)–C(31)	113.3(3)
N(2)–C(32)–C(33)	102.9(3)	O(3)–C(33)–C(32)	104.2(2)
O(3)–C(33)–C(34)	110.4(3)	N(2)–C(40)–O(3)	116.7(3)
N(2)–C(40)–C(41)	126.8(3)	O(3)–C(40)–C(41)	116.4(3)
O(4)–C(46)–C(41)	122.2(3)	O(4)–C(46)–C(45)	120.2(3)

two sides of the oxazoline ring, take almost perpendicular orientation with the oxazoline ring. The dihedral angles of the N(2)–C(40)–O(3)–C(33)–C(32) oxazoline plane with the C(26)–C(27)–C(28)–C(29)–C(30)–C(31) phenyl plane and the C(34)–C(35)–C(36)–C(37)–C(38)–C(39) phenyl plane are 106.2°and 96.0°, respectively. The dihedral angle of the two phenyl rings is 40.1°. In the other oxazoline unit, the dihedral angles of the N(1)–C(7)–C(8)–O(1)–C(15) oxazoline plane with the C(9)–C(10)–C(11)–C(12)–C(13)–C(14) phenyl plane and the C(1)–C(2)–C(3)–C(4)–C(5)–C(6) phenyl plane are 76.3°and 90.4°, respectively. The dihedral angle of the two phenyl rings is 68.7°.

2.3. Catalysis

The Baeyer–Villiger reactions can be used in the synthesis of many natural products, pharmaceuticals and monomers for polymerization. During the past two decades, attempts to study the asymmetric Baeyer–Villiger reactions catalyzed by metal complexes have met with only moderate success [2,12,13]. Only some special substrates can be transformed to the corresponding lactones with high enantiomeric excess [2b,2c]. Most substrates gave low to moderate enantioselectivity when they were transformed into lactones [2a,12,13]. In the asymmetric Baeyer–Villiger reaction of 2-phenylcyclohexanone, the best result (yield 47%, 69% enantiomeric excess) was obtained by Bolm with bis[(4*S*)-4-*tert*-butyl-2-(3′-*tert*-butyl-5′-nitro-2′-oxidophenyl-χO)-4,5-dihydrooxazole-χN]copper(II) as the catalyst [2a]. In order to enlarge the scope of this reaction, we tested the use of complexes **5** and **6** in the asymmetric Baeyer–Villiger reactions using 2-phenylcyclohexanone as a test substrate (Scheme 3). The results are shown in Table 3.

The results shown in Table 3 indicated that complex **6** was superior to complex **5** (entries 1, 11). A series of solvents were tested (entries 2–6) and toluene was found to give the best result (entry 4). Water was found to be beneficial to the enantioselectivity (entries 1, 2). The best solvent system was found to be a mixture of toluene with water (2.5 ml–0.1 ml) (entries 10, 13). We also investigated the cooxidants and found that the most effective cooxidant for higher reactivity and enantioselectivity was 2-ethylbutylaldehyde (entries 2, 7–9). The effects of temperature and amount of catalyst were also tested. The experiments showed that the reaction proceeded very slowly when the temperature was lower than 20°C and the reaction was suppressed when the catalyst level was over 10 mol%. The best result (entry



Scheme 3.

Table 3
Asymmetric Baeyer–Villiger reaction of 2-phenylcyclohexanone catalyzed by **6** [a]

Entry	Catalyst	Solvent	Cooxidant	Time (h)	Conversion (%)	Enantiomeric excess of **7** (%)
1	**5**	C_6H_6–H_2O	$(CH_3)_3CCHO$	38	24	23
2	**5**	C_6H_6 (dry)	$(CH_3)_3CCHO$	35	24	11
3	**5**	THF (dry)	$(CH_3)_3CCHO$	36	3	7
4	**5**	C_7H_8 (dry)	$(CH_3)_3CCHO$	36	22	14
5	**5**	CH_2Cl_2	$(CH_3)_3CCHO$	36	2	21
6	**5**	$ClCH_2CH_2Cl$	$(CH_3)_3CCHO$	36	7	14
7	**5**	C_6H_6 (dry)	PhCHO	36	10	17
8	**5**	C_6H_6 (dry)	$(CH_3)_2CHCHO$	37	37	9
9	**5**	C_6H_6 (dry)	$(C_2H_5)_2CHCHO$	37	57	15
10 [b]	**5**	C_7H_8–H_2O	$(C_2H_5)_2CHCHO$	48	62	26
11	**6**	C_6H_6–H_2O	$(CH_3)_3CCHO$	36	19	26
12	**6**	C_7H_8–H_2O	$(CH_3)_3CCHO$	38	21	25
13	**6**	C_7H_8–H_2O	$(C_2H_5)_2CHCHO$	24	34	25

[a] The reactions were carried out at room temperature in the dark with 2 mol% catalyst and 1.5 equivalent of cooxidant; conversions were determined by GC; enantiomeric excesses were determined by GC on CYDEX-β 25 × 0.22mm chiral capillary column.
[b] The enantiomeric excess of the recovered 2-phenylcyclohexanone was 25%.

10) was obtained at ambient temperature with 2 mol% catalyst; this was inferior to the literature reported value for enantioselectivity [2a]. This was caused by the difference in structure of the two kinds of catalyst which were used in the reaction.

3. Conclusion

Two novel chiral oxazolines **3**, **4** and their copper complexes **5**, **6** were prepared. The structure of complex **6** was analyzed by X-ray diffraction. We also established their catalytic activity in the asymmetric Baeyer–Villiger reaction. Further efforts will be devoted to improve the rate and enantioselectivity of the reaction.

4. Experimental

4.1. General

Melting points were determined on a Southend SS25PH apparatus and were uncorrected. Elemental analyses were recorded on a Carlo Erba 1106 instrument. Gas chromatographic analyses were performed by SC-7 gas chromatography. ^{1}H-NMR spectra were performed on a Bruker 300 spectrometer. Optical rotations were measured on a Perkin–Elmer 341 polarimeter. Enantiomeric excesses were determined by GC on CYDEX-β 25 × 0.22 mm chiral capillary column.

4.2. Synthesis of *3* and *4*

In a 50 ml three-necked flask, 27.2 mg (0.2 mmol) of zinc chloride were melted under high vacuum and cooled under argon. After cooling to room temperature, 10 ml of chlorobenzene were added followed by 5 mmol (0.876 g) of the 2-hydroxy-3-*tert*-butyl benzonitrile and 5 mmol (1.07 g) of the amino alcohol. The mixture was refluxed for 20 h. The solvent was removed under reduced pressure to give an oily residue, which was dissolved in 20 ml dichloromethane. The solution was extracted three times with 20 ml of water and the aqueous phase with 10 ml of dichloromethane. The combined organic phases were dried over anhydrous sodium sulfate and the solvent was removed in vacuum. The residue was purified by flash chromatography (petroleum ether–ethyl acetate 40:1) [3].

(4*S*,5*R*)-4,5-dihydro-4,5-diphenyl-2-(2′-hydroxy-3′-tert-butylphenyl)oxazoline (**3**). Yield 1.19 g (65%); yellow solid; m.p. 145–146°C; $[\alpha]_D^{25} = -9.84°$ (c 0.244, EtOH). IR (mull) ν (cm^{-1}) 1633 (C=N), 1251 (C–O–C), 1213 (C–OH). ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 1.47 (s, 9H), 5.81 (d, $J = 6.7$ Hz, 1H), 5.98 (d, $J = 6.7$ Hz, 1H), 6.88 (t, $J = 5.0$ Hz, 1H), 7.02 (m, 10H), 7.47 (dd, $J = 5.1$ Hz, 1.2 Hz, 1H), 7.76 (dd, $J = 5.1$ Hz, 1.2 Hz, 1H), 12.76 (s, 1H) ppm. ^{13}C-NMR ($CDCl_3$, 300 MHz): δ 167.9, 160.3, 138.1, 137.8, 136.5, 128.4, 128.4, 128.4, 128.3, 127.9, 127.1, 116.7, 110.9, 84.9, 74.0, 35.7, 30.1 ppm. EIMS (m/z): 371 (M^+), 204, 161, 91 (100), 77, 41. Anal. Calc. for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.96; H, 6.90; N, 3.87%.

(4*S*,5*S*)-4,5-dihydro-4,5-diphenyl-2-(2′-hydroxy-3′-tert-butylphenyl)oxazoline (**4**). Yield 1.54 g (84%); yellow solid; m.p. 94–95.5°C; $[\alpha]_D^{25} = +94.38°$ (c 0.766, EtOH). IR (mull) ν (cm^{-1}): 1632 (C=N), 1251 (C–O–C), 1208 (C–OH). ^{1}H-NMR($CDCl_3$, 300 MHz): δ 1.46 (s, 9H), 5.28 (d, $J = 5.2$ Hz, 1H), 5.36 (d, $J = 5.2$ Hz, 1H), 6.46 (t, $J = 5.1$ Hz, 1H), 7.35 (m, 10H), 7.44 (dd,

$J = 5.2$ Hz, 0.9 Hz, 1H), 7.71 (dd, $J = 5.2$ Hz, 0.9 Hz, 1H), 12.67 (s, 1H) ppm. ^{13}C-NMR($CDCl_3$, 300 MHz): δ 167.0, 160.2, 141.9, 140.2, 138.0, 131.5, 129.6, 129.3, 128.6, 127.2, 127.1, 126.5, 118.6, 111.0, 88.6, 78.3, 35.7, 30.0 ppm. EIMS (m/z): 371 (M^+), 204 (100), 161, 91, 77, 41. Anal. Calc. for $C_{25}H_{25}NO_2$: C, 80.83; H, 6.78; N, 3.77. Found: C, 80.92; H, 6.78; N, 3.76%.

4.3. Synthesis of **5** and **6**

To a solution of 0.6 mmol (223 mg) of oxazoline in 10 ml absolute ethanol was added a solution of 60 mg (0.3 mmol) of $Cu(OAc)_2 \cdot H_2O$ in 10 ml absolute ethanol. The reaction mixture was stirred at room temperature for 16 h. A large amount of dark-blue precipitate was formed. After filtration, the solid was collected and washed with absolute ethanol three times to give the pure product.

Bis[(4*S*,5*R*)-4,5-dihydro-4,5-diphenyl-2-(2′-oxidophenyl-χO)oxazole-χN]copper(II) (**5**). Yield 0.18 g (75%); dark blue solid. IR (mull) ν (cm^{-1}) 1612 (C=N), 1255 (C–O–C). Anal. Calc. for $C_{50}H_{48}CuN_2O_4$: C, 74.65; H, 6.01; N, 3.48. Found: C, 74.70; H, 5.94; N, 3.47%.

Bis[(4*S*,5*S*)-4,5-dihydro-4,5-diphenyl-2-(2′-oxidophenyl-χO)oxazole-χN]copper(II) (**6**). Yield 0.197 g (82%); dark blue solid. IR (mull) ν (cm^{-1}) 1614 (C=N). Anal. Calc. for $C_{50}H_{48}CuN_2O_4$: C, 74.65; H, 6.01; N, 3.48. Found: C, 74.38; H, 6.03; N, 3.46%.

4.4. General procedure for the asymmetric Baeyer–Villiger reaction

The 2-phenylcyclohexanone 87 mg (0.5 mmol) and the catalyst 8 mg (0.01 mmol) were dissolved in water-saturated toluene (2.5 ml) and treated with cooxidant aldehyde (0.75 mmol) and water (0.1 ml). The mixture was stirred at room temperature under an oxygen atmosphere in the dark for 24–48 h, diluted with diethyl ether (25 ml) and washed with saturated aqueous $NaHCO_3$ solution (10 ml). The organic phase was dried over anhydrous Na_2SO_4. After removal of the solvent, the crude product was chromatographed on silica gel (petroleum ether–ethyl acetate 3:1). The enantiomeric excesses for lactone were determined by GC on CYDEX-β 25 × 0.22 mm chiral capillary column.

5. Supplementary material

Crystallographic data for structural analysis have been deposited with the Cambridge Crystallographic Data Center, CCDC no. 142805 for compound **6**. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk).

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