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Synthesis of Homochiral Bis (oxazolinyl) Pyridine Type Ligands for Asymmetric Cyclopropanation Reactions†,1

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Abstract: Homochiral bis(oxazolinyl)pyridine type ligands were synthesized from (*S*)-valine and converted into their Cu(II) complexes. Reduction of these Cu(II) complexes into Cu(I) with diazoesters was studied by uv-vis and epr spectroscopy. The enantioselective cyclopropanation reaction was carried out using styrene as a model substrate.

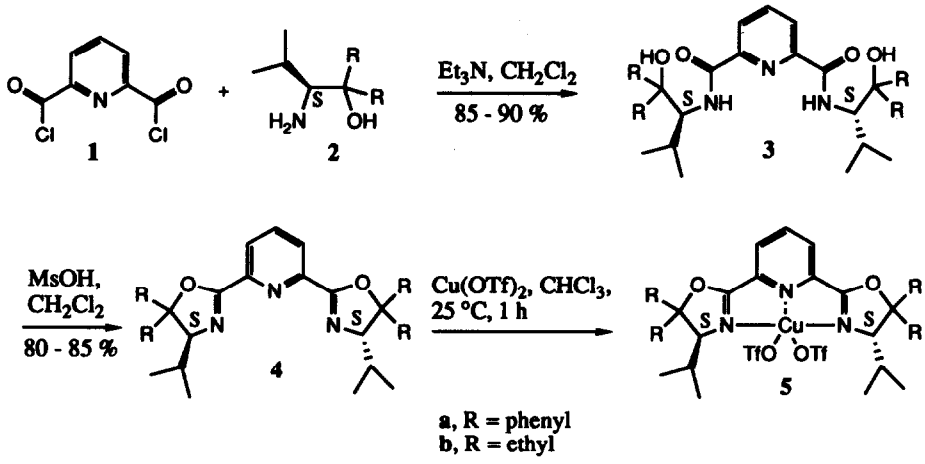
The design of suitable homochiral ligands around a metal centre is an important task in asymmetric catalytic reactions.[2,3] Advantage in modification of ligand structure around a metal centre is manifold. One of the important advantages is that it gives mechanistic insight about the reaction. Asymmetric cyclopropanation of olefins catalyzed by chiral Cu-complexes has been studied in the past.[4] During the last few years, a variety of homochiral ligands have been developed around a Cu center. Semicorrin type ligands have been developed by Pfaltz and co-workers[4,5] and remarkable success has been achieved in enantioselective cyclopropanation of some olefins. Later on, further modifications in the ligand structure were made by Masamune[6] and Evans[7] independently, where they have introduced bis(oxazoline) type ligands. As a consequence of our interest in asymmetric synthesis area[8], we introduce here bis(oxazolinyl)pyridine (pybox) type ligands around a Cu metal for enantioselective cyclopropanation reaction.

Chiral Rhodium bis(oxazolinyl)pyridine complexes have been extensively used by Nishiyama and co-workers in asymmetric hydrosilylation[9] and dehydrogenative silylation[10] of ketones. Recently, the same type of ligand has been used in chiral recognition of 1,1'-bi-2-naphthol.[11] Molecular model of pybox type ligands around Cu metal looks comparable with Evans's ligand and, to the best of our knowledge, this has not been used for asymmetric cyclopropanation reaction.[12] In this paper we describe our efforts towards synthesis, application[13], and some mechanistic study with these homochiral bis(oxazolinyl)pyridine - Cu type complexes.

The ligands **4** were synthesized in two steps viz. by coupling of 2,6-dipiconyl chloride **1**[14] and aminoalcohols **2**[8e], followed by intramolecular condensation using methanesulfonic acid under azeotropic removal of water (Scheme I). Its reaction with stoichiometric amount of $Cu(OTf)_2$ in CH_2Cl_2 or $CHCl_3$ led to the formation of blue-green colour complex. Though these Cu(II) complexes were not isolated, and generated *in*

†This paper is dedicated respectfully to Dr. Sukh Dev on the occasion of his 70th birthday.

situ only, we assume its structure as **5** (monomeric form). The cyclopropanation reaction was carried out on styrene using diazoester and 1 mol % of Cu(II)-complex **5** in chloroform as a solvent.



Scheme I. Synthesis of Chiral Bis(oxazolinyl)pyridine-Cu(II) Catalysts

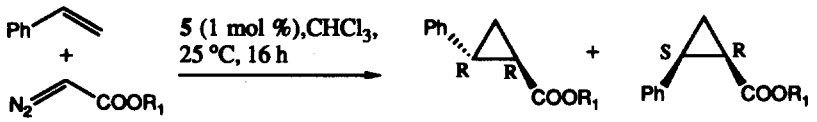


Table 1. 'Asymmetric Cyclopropanation Reaction of Styrene with Catalysts 5'

Catalysts	R_1	Diastereoselectivity[a] trans : cis	Enantioselectivity[b] trans % ee	Enantioselectivity[b] cis % ee	Yield[c] (%)
5b	Ethyl	64 : 36	26	0	86
5b	t-Butyl	70 : 30	33	0	95
5a	Ethyl	66 : 34	28	8	93
5a	t-butyl	70 : 30	35	6	80

[a]Determined by ^{1}H-NMR spectrum. [b]% Ee was determined by 400 MHz ^{1}H NMR spectrum of corresponding methyl esters with Eu(tfc)$_3$ shift reagent. [c]Yield is for mixture of cis and trans compounds.

We observed that on addition of diazoester to Cu(II) complex **5**, a vigorous reaction took place, and the colour changed from blue-green to red-brown. In view of Kochi's inference[15] that cyclopropanation of olefins is mainly catalyzed by Cu (I) which is formed by reduction of Cu(II) with diazomethane, we propose and

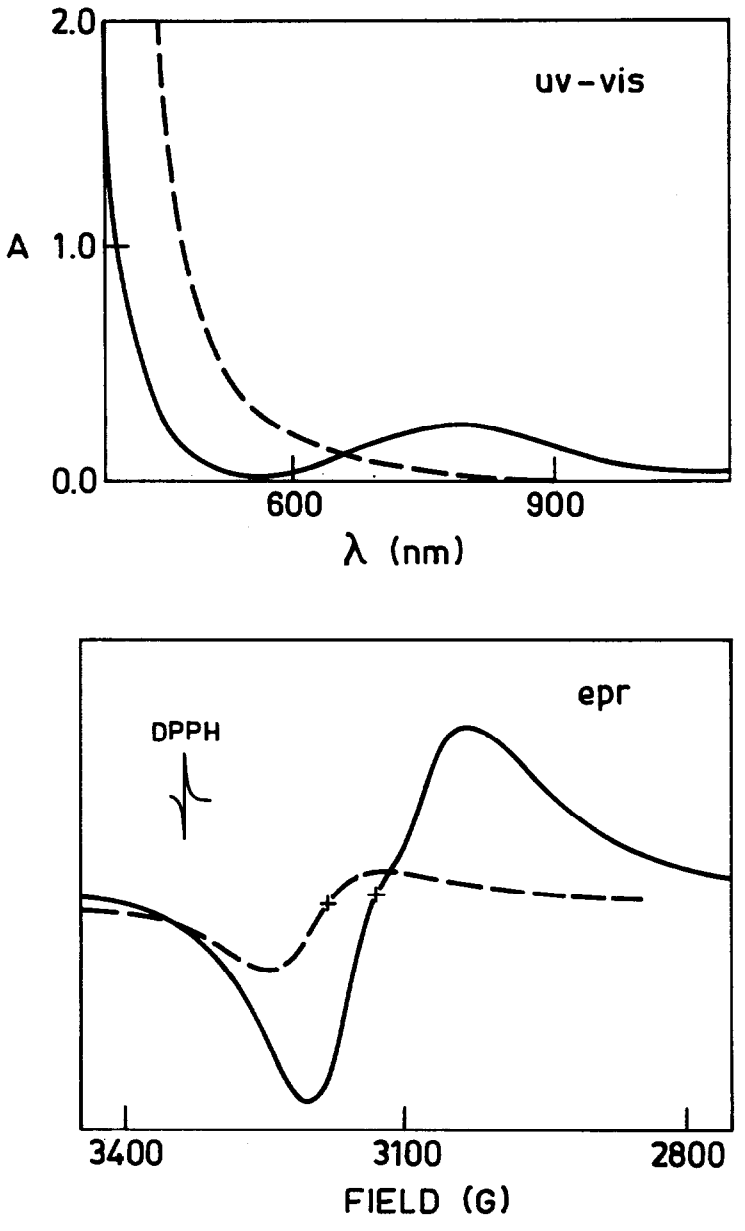
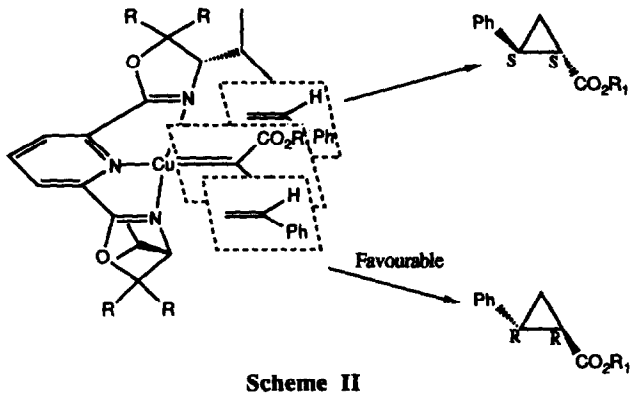


Figure. Uv-vis and epr spectra of **5a** (solid line) and after its treatment with ethyldiazoacetate (dotted line) in chloroform solution.

confirm that in the present system, Cu(II) was reduced to Cu(I) by diazoesters. The red-brown colour of the solution might be due to colloidal Cu(0) which could be one of the decomposition products of unstable Cu(I) system. This reduction process was confirmed by uv-vis and epr spectroscopy (Figure). The Cu(II) complex **5a** shows d-d transition at λ_{max} 770 nm and a epr signal (g = 2.133), characteristics of Cu(II) paramagnetic complexes. When the solution was treated with ethyl diazoacetate under nitrogen atmosphere, d-d band disappeared in uv-vis spectrum, and a new signal (g = 2.099) in epr spectrum was observed. Since the original epr signal vanished, we think that Cu(II) complex was reduced. The new epr signal with intensity one tenth of the original one indicates that some Cu(II) complex was still present in the reaction mixture. The difference in g values proved that the nature of new Cu(II) species was different from the original one. This is quite possible due to instability of Cu(I) system which can disproportionate into Cu(II) and Cu(0). The disproportionation could be due to absence of favoured geometry for Cu(I).

The results for the cyclopropantion reactions are summarized in table 1. The facial selectivity in the reaction has been explained using a copper carbenoid structure as depicted in scheme II. The attack of the carbenoid center from its *Re* face is more favourable due to lesser repulsive interaction built-up between the isopropyl and carboxylic ester. If *Si* face of styrene approaches this favourable side of carbenoid center, *trans*-(1*R*, 2*R*) enantiomer is obtained as a major compound. Analogous approach of this type has been proposed by Pfaltz.[4]



Scheme II

In summary, we have synthesized new kind of ligands for enantioselective cyclopropanation reaction of olefins. Although the reaction is not very enantioselective, it throws some light on its mechanistic aspects. We have shown that the reaction is catalyzed by Cu(I), and this species is formed, *in situ*, by reduction of Cu(II) with the diazoesters used in the reaction. Thus, activation of the Cu(II) catalysts with phenylhydrazine, as shown by Massamune[6], is not needed.

Experimental Section

^{1}H NMR spectra were recorded on Jeol and Brucker as mentioned, with TMS as internal standard.

Chemical shifts are reported in ppm, and coupling constants are reported in Hz. IR spectra were recorded on Perkin-Elmer 580 and 1320 spectrometers. X-band EPR spectra were recorded in chloroform at 298 K on a Varian E-109C spectrometer and calibrated with the help of DPPH (g=2.0023). Uv-visible spectra were recorded in chloroform on Shimadzu UV-160. Optical rotations were taken on a Jasco DIP-370. Routine monitoring of reactions was performed using silica gel-G obtained from Acme. All the chromatographic separations were done by using silica gel (Acme's, 60-120 mesh). All the reactions were run under an atmosphere of dry nitrogen or argon using flame-dried glassware and freshly distilled and dry solvents from solvent stills. The organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo.

General Procedure for Synthesis of Amides 3: A solution of aminoalcohol **2** (3.0 mmol) and triethylamine (7.6 mmol) in anhydrous CH_2Cl_2 (10 ml) was added dropwise to dipicolinyl chloride **1** (1.5 mmol) at 0 °C. The reaction mixture

was stirred for 16 h (0 °C - rt). It was diluted with dichloromethane and washed with aq. $NaHCO_3$, water, brine and dried. Solvent removal gave solid mass which, after washing with pet.-ether was chromatographed over silica gel to give product as a solid mass.

N,N'-bis[1'-(*S*)-isopropyl-2',2'-diphenyl-2'-hydroxyethyl]-2,6 pyridine dicarboxamide 3a: Yield 90% as a solid mass; mp 110 °C; R_f 0.22 (1:4, EtOAc in pet-ether); $[\alpha]^{25}_D$ -46.2° (*c* 1.0, $CHCl_3$); IR (KBr) 3400, 3060, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ0.95 (d, J = 6.5 Hz, 12H), 1.95 (m, 2H), 3.0 (bs, 2H, -OH), 5.12 (dd, J = 10, 2.5 Hz, 2H), 6.9 - 8.5 (m, 23H & -NH). Anal. calcd for $C_{41}H_{43}N_3O_4$: C, 76.76; H, 6.71, N, 6.55; Found: C, 76.12; H, 6.86; N, 6.70.

N,N'-bis[1'-(S)-isopropyl-2',2'-diethyl-2'-hydroxyethyl]-2,6-pyridine dicarboxamide 3b: Yield 85% as a solid mass; R_f 0.50 (2:3, EtOAc in pet-ether); $[\alpha]^{25}_D$ -3.6° (*c* 0.6, $CHCl_3$); IR (KBr) 3500, 3400, 1660 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ0.65-1.25 (m, 24H), 1.25-1.80 (m, 10H), 2.5 (bs, 2H, -OH), 4.00 (dd, J = 10, 2.5 Hz, 2H), 8.3 (aromatics, 3H). Anal. calcd for $C_{25}H_{43}N_3O_4$: C, 66.82; H, 9.58, N, 9.35; Found: C, 66.06; H, 9.83; N, 9.50.

General Procedure for Cyclization to 4: A solution of amidoalcohol (1.1 mmol) in CH_2Cl_2 (15 mL) was refluxed with methanesulfonic acid (425μl, 6.6 mmol) for 6 h while keeping CaH_2 in an addition funnel for removing the water generated during the reaction. The reaction mixture was cooled down and 15 mL of CH_2Cl_2 was added. It was washed with aq. $NaHCO_3$, water, brine and dried. Solvent removal gave solid mass which was chromatographed over silica gel to afford pure compound.

2,6-Bis[5', 5'-diphenyl-4'-(S)-isopropyl oxazolin-2'-yl]pyridine 4a: The cyclized product **4a** was obtained as solid in 85% yield; mp 65 - 66 °C; R_f 0.55 (1:4, EtOAc:Pet-ether); $[\alpha]^{25}_D$ -233.2° (*c* 2.7, $CHCl_3$); IR (KBr) 3060, 1650 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ0.68 (d, J = 6 Hz, 6H), 1.09 (d, J = 6 Hz, 6H), 1.95 (m, 2H), 4.93 (d, J = 5 Hz, 2H), 6.9 - 8.5 (aromatics, 23 H); MS (Fab, m/z): 606 (M^++1), 297, 167. Anal. calcd for $C_{41}H_{39}N_3O_2$: C, 81.32; H, 6.45, N, 6.94; Found: C, 80.71; H, 6.52; N, 7.02.

2,6-Bis[5', 5'-diethyl-4'-(S)-isopropyl oxazolin-2'-yl]pyridine 4b: 80% yield as sticky solid; R_f 0.58 (2:3, EtOAc:Pet-ether); $[\alpha]^{25}_D$ -37.1° (*c* 1.4, $CHCl_3$); IR (film) 1650 cm^{-1}; ^1H NMR (CCl_4, 60 MHz) δ0.6-1.4 (m, 24H), 1.8 (m, 10H), 3.6 (d, J = 7 Hz, 2H), 8.0 (aromatics, 3 H); MS (Fab, m/z): 437 (M^++Na + 1), 436 (M^++Na, base peak), 125, 69. Anal. calcd for $C_{25}H_{39}N_3O_2$: C, 72.64; H, 9.44, N, 10.17; Found: C, 72.12; H, 9.52; N, 10.28.

General Procedure for Cyclopropanation Reaction: The ligand **4** (0.08 mmol) and $Cu(OTf)_2$ (0.08

mmol) were taken in 3 ml $CHCl_3$ and stirred for 1 h. The blue-green coloured reaction mixture was filtered. The filtrate was added to styrene (32 mmol) solution in $CHCl_3$ (3 ml) at room temperature. Then, diazoester (7.9 mmol) solution in 3 ml $CHCl_3$ was added at the rt over a period of 4 h. It was stirred for 16 h. The solvent was removed and the crude was chromatographed over silicagel to give cyclopropyl esters[4] in 80 - 95% yield.

Determination of Enantiomeric Excess[5b]: The ethyl and t-butyl cyclopropyl esters were converted to corresponding methyl esters as described by Pflatz[5b]. The methyl esters and shift reagent, $Eu(tfc)_3$ were taken in $CDCl_3$ and 400 MHz ^1H NMR spectrum was run. The original methyl ester singlet at δ3.44 for cis diastereomer got separated into two peaks, δ3.51 (major) and δ3.53 (minor). Likewise, the singlet at δ3.73 for trans isomer got separated into two peaks, δ3.92 (major) and δ3.943 (minor).

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References and Notes

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