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Catalytic Asymmetric Cyclopropanation Using Copper Complex of Optically Active Bipyridine As a Catalyst

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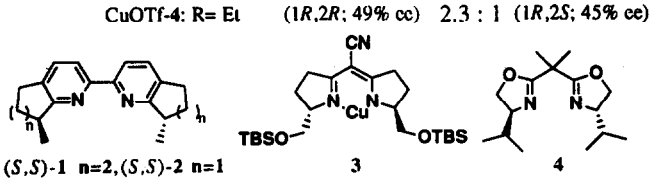
Key Words: asymmetric cyclopropanation; optically active bipyridine ligand

Abstract: Optically active 8,8'-di(trimethylsilyl)-5,5',6,6',7,7',8,8'-octahydro-2,2'-biquinoline (**7**) was found to be an effective catalyst for enantioselective cyclopropanation of olefins. For example, the reaction of styrene and *t*-butyl diazoacetate in the presence of **7** proceeded with high enantioselectivity of 92% ee, to give *t*-butyl *trans*-2-phenylcyclopropanecarboxylate. On the other hand, the reaction of *trans*-β-methylstyrene gave the *cis*-isomer of >99% ee as a major product.

Introduction of well-designed optically active phosphine ligands has facilitated the advancement of asymmetric synthesis and many useful asymmetric reactions reaching extremely high level of enantioselectivity (>99% ee) have so far been reported.[1] Recently, however, some nitrogen ligands such as semicorrine and bis(oxazolines) were also shown to be very effective chiral controllers.[2] In order to extend the utility of nitrogen ligands, we synthesized optically active bipyridine ligands **1** and **2** and examined cyclopropanation of styrene with them.[3,4] Although asymmetric induction by **1** and **2** was not very high (72-77% ee), these results showed high potentiality of this type of ligands as a chiral controller, because chiral semicorrine **3**[5] and

CuOTf-1: R= *t*-Bu	(1*R*,2*R*; 77% ee)	2.6 : 1	(1*R*,2*S*; 73% ee)
CuOTf-2: R= *t*-Bu	(1*R*,2*R*; 72% ee)	2 : 1	(1*R*,2*S*; 67% ee)
3: R= Et	(1*S*,2*S*, 59% ee)	3 : 1	(1*S*,2*R*, 45% ee)
CuOTf-4: R= Et	(1*R*,2*R*; 49% ee)	2.3 : 1	(1*R*,2*S*; 45% ee)



(*S*,*S*)-**1** n=2, (*S*,*S*)-**2** n=1 **3** **4**

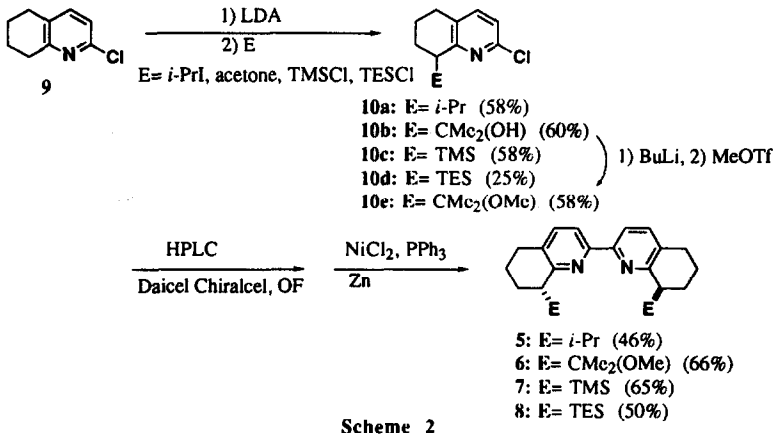
Scheme 1

bis(oxazolines) **4**[2e] bearing a small group such as *t*-butyldimethylsiloxymethy and isopropyl groups, respectively, on its stereogenic carbons show relatively poor asymmetric induction as compared with **1** and **2** bearing the smaller methyl group, though diazo esters used are different (**Scheme 1**).

In order to further explore the possibility of chiral bipyridine ligands as a chiral controller, we synthesized

several new optically active bipyridine ligands (**5**-**8**) bearing bulky C8(8') substituents, and examined cyclopropanation of olefins.

These optically active bipyridines (**5**-**8**) were prepared as follows. 2-Chloro-5,6,7,8-tetrahydroquinoline (**9**) was successively treated with LDA and the corresponding electrophiles to give C8-substituted tetrahydroquinolines **10a-d**. Resolution of *dl*-**10a-d** was examined with aid of various optically active acids but all the attempts were unsuccessful. Finally *dl*-**10a**,c-e were resolved by HPLC using optically active column (Daicel Chiralcel, OF) and respective enantiomers that were eluted first from the column, were used for the next reaction. Optically active **10a**,c-e[6] were subjected to homocoupling reaction in the presence of $NiCl_2$[7] to give bipyridines (**5**-**8**) and a trace amount (<0.5%) of the corresponding *meso*-isomers, which were readily separated by column chromatography.



Scheme 2

With these bipyridine ligands in hand, we first examined copper-catalyzed cyclopropanation of styrene with *t*-butyl diazoacetate. Copper catalysts were prepared by mixing CuOTf·0.5C_6H_6[8] with ligands according to Evans' procedure[2e] and immediately used for the reaction.[9] The results obtained were summarized in Table 1. Although replacement of C8(8') methyl groups in **1** with isopropyl group did not improve the enantioselectivity, that with the bulky substituents such as 2-methoxy-2-methylethyl and trimethylsilyl groups enhanced the enantioselectivity to 83 and 92% ee, respectively. However, the introduction of further bulky triethylsilyl group gave negative result. On the other hand, *trans-cis* ratio was not strongly affected by variation of C8(8')

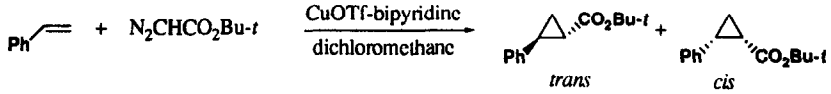


Table 1. Asymmetric cyclopropanation of styrene.

Entry	bipyridine	Yield (%)	*trans* : *cis* [a]	% ee (*trans*)[b]
1	**5**	64	75 : 25	77
2	**6**	53	66 : 34	83
3	**7**	75	86 : 14	92
4	**8**	75	57 : 43	66

a) Ratio of *trans*- and *cis*-isomers was determined by using capillary gas chromatography.
b) E.e. was determined by the reported procedure (reference 3).

substituents but higher asymmetry-inducing catalysts tend to give higher *trans-cis* ratio, except for **6**. Absolute configuration of *trans*- and *cis*-isomers produced was determined to be 1*S*,2*S* and 1*S*,2*R*, respectively, according to literature procedure.[3,5] Although absolute configuration of optically active bipyridines (**5-8**) was not determined yet, their configuration was presumed to be 8*S*,8'*S* for **5** and **6** and 8*R*,8'*R* for **7** and **8** from the comparison of the above and previous results (Scheme 1), as described in Scheme 2, since it seemed rational to consider that the reactions catalyzed by copper complexes bearing **1**, **5-8** as ligands, follow the same steric course.

We next examined cyclopropanation of various olefins and the results are shown in Table 2. Reaction of mono-substituted olefins showed high enantioselectivity of >83% ee (entries 1-5). Styrene derivative bearing electron-withdrawing group showed higher enantioselectivity than that with electron-donating group, suggesting the participation of electrophilic copper-carbene species in this reaction.[10] Cyclopropanation of *cis*-β-methylstyrene showed very high *trans*-selectivity but enantioselectivity was decreased to some extent (entry 6).

Table 2. Asymmetric cyclopropanation of various olefins with **7** as the chiral source.

Entry	substrate	Yield (%)	*trans* : *cis* [a]	% ee (*trans*)[b]	% ee (*cis*)[b]
1	*p*-chlorostyrene	72	82 : 18	95[ci]	98[ci]
2	styrene	75	86 : 14	92[cii]	98[cii]
3	*p*-methoxystyrene	73	90 : 10	83[ciii]	>99[ciii]
4	1-octene	65	85 : 15	91[di]	-[dii]
5	1-phenylbutadiene	90	70 : 30	83[civ]	89[civ]
6	*cis*-β-methylstyrene	94	>99 : 1	73[e]	-
7	*trans*-β-methylstyrene	54	40 : 60	24[e]	>99[e]

a) Ratio of *trans*- and *cis*-isomers determined by using capillary gas chromatography.
b) Absolute configuration of the product was not determined, except for the one derived from styrene.
c) Determined by HPLC using optically active column: i) after LAH reduction and acetylation, *trans* : (Daicel Chiralcel OD; Hexane/*i*-PrOH 100:1), *cis* : (Daicel Chiralcel OF; Hexane/*i*-PrOH 400:1), ii) after LAH reduction (Daicel Chiralcel OJ; Hexane/*i*-PrOH 9:1), iii) after LAH reduction, *trans* : (Daicel Chiralcel OD; Hexane/*i*-PrOH 9:1), *cis* : (Daicel Chiralcel OJ; Hexane/*i*-PrOH 9:1), iv) (Daicel Chiralcel OF; Hexane/*i*-PrOH 100:1).
d) i) Determined by ^{1}H NMR analysis of the corresponding methyl ester in the presence of Eu(hfc)3., ii) Ee of the *cis*-isomer was not determined.
e) Determined by capillary gas chromatography of the corresponding (*S*)-(+)-octyl ester (see reference 5).

Differing from other substrates, *trans*-β-methylstyrene showed reversed *cis*-selectivity and the enantiomeric excess of the *trans*-isomer was poor (entry 7). However, the enantiomeric excess of the major *cis*-isomer was found to be excellent (>99% ee).[11] This result is different from that with bis(oxazolines). For example, cyclopropanation of *trans*-anethole with *d*-(+)-menthyl diazoacetate in the presence of chiral bis(oxazolines)-Cu(II) complex gave a mixture of the corresponding *trans*- (88% ee) and *cis*-isomers (65% ee) in the ratio of 95:5.[2c] Although *cis*-selectivity was also observed in the cyclopropanation using chiral rhodium-porphyrin complex as a catalyst, moderate level of asymmetric induction (10-60% ee) was observed.[12] Further study of new aspect of chiral Cu-bipyridine catalyst is under way in our laboratory.

Typical experimental procedure was exemplified by cyclopropanation of styrene using CuOTf-**7** complex as a catalyst: To a suspension of CuOTf·0.5C_6H_6[2c,9] (1.6 mg, 6.4 μmol) in CH_2Cl_2 (1.25 ml) was added a solution of **7** (2.8 mg, 6.8 μmol) in CH_2Cl_2 (0.25 ml). After 30 min, the mixture was filtered through a packed

adsorbent cotton under argon and, to the filtrate, was added styrene (0.289 ml, 2.5 mmol). To the solution was added dropwise a solution of *t*-butyl diazoacetate (71 mg, 0.5 mmol) in CH_2Cl_2 (0.5 ml) over a period of 1 h. The mixture was stirred for additional 1 h and concentrated *in vacuo*. The residue was passed through a short silica gel column to afford a mixture of *t*-butyl *trans*- and *cis*-2-phenyl-cyclopropane-1-carboxylates as a colorless oil. Separation of *trans*- and *cis*-isomers was performed by preparative TLC (Hexane/*i*-Pr_2O 5:1). Optical purities of *trans*- and *cis*-isomers were determined by HPLC.

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