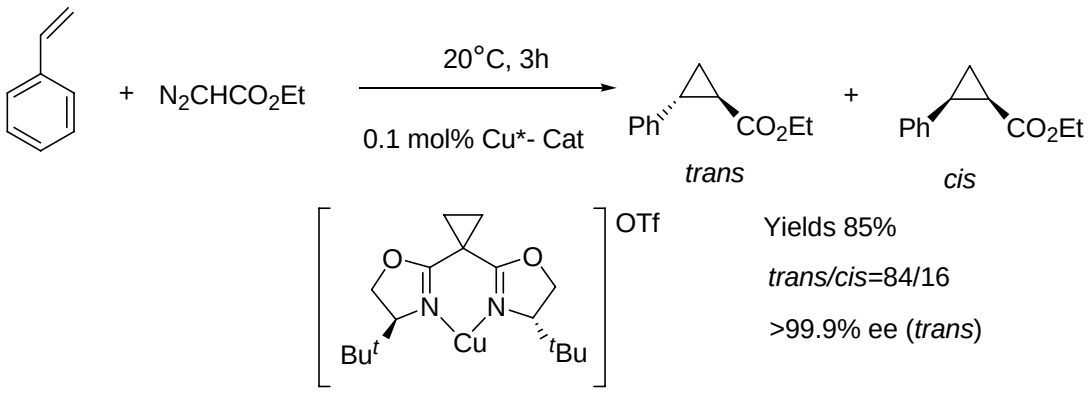
Graphical Abstract



Application of a Chiral Copper-1,1-Bis{2-[(4*S*)-*tert*-butyloxazolinyl]}cyclopropane Catalyst for Asymmetric Cyclopropanation of Styrene

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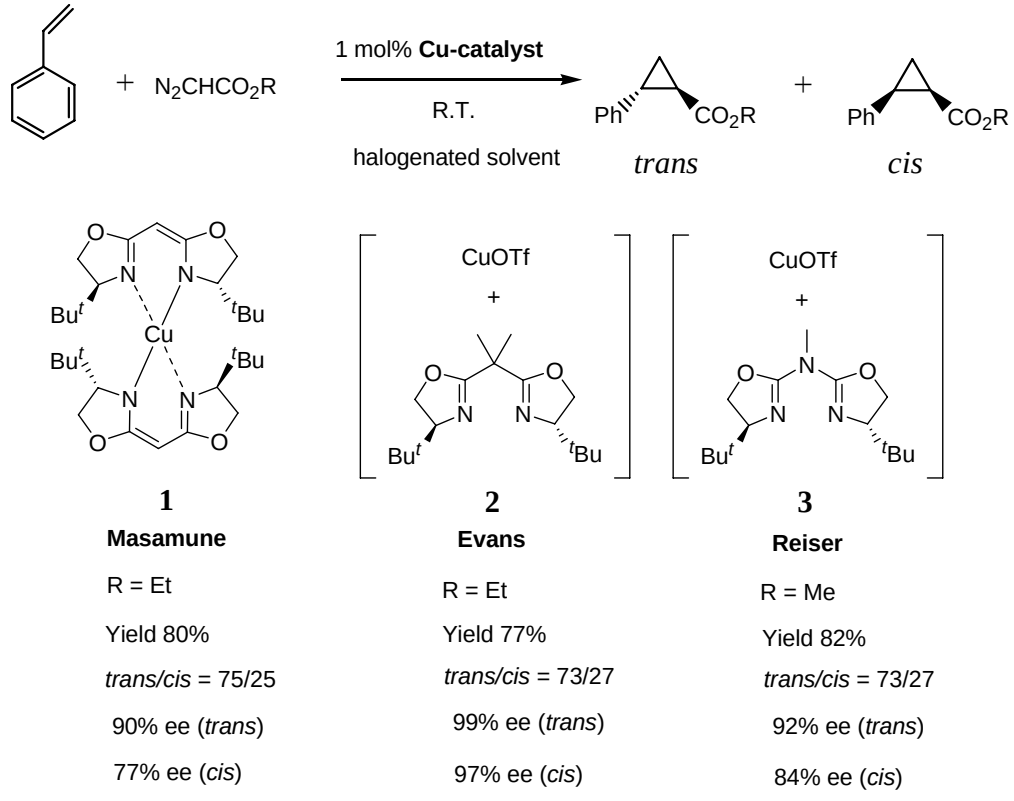
Abstract－The structural effects of the bridge moiety and 5-position on bisoxazoline ligands were studied for the copper-catalyzed asymmetric cyclopropanation of styrene with ethyl diazoacetate. The 1,1-bis{2-[(4*S*)-*tert*-butyloxazolinyl]}cyclopropane ligand showed a remarkable enhancement in the stereoselectivities (*trans*/*cis* = 84/16, >99.9% ee for the *trans* product) compared with the previously reported best ligand, 2,2-bis{2-[(4*S*)-*tert*-butyloxazolinyl]}propane (*trans/cis*=75/25, 99.0% ee for the *trans* product).

Keywords: asymmetric cyclopropanation; copper bisoxazoline catalyst; ethyl diazoacetate; styrene

Since Nozaki's research group reported the first copper-catalyzed asymmetric cyclopropanation of styrene with ethyl diazoacetate in 1966,[1] many successful catalysts have been reported to give high *trans* selectivity and high enantioselectivity.[2] Copper catalysts have been very attractive for the cyclopropanation because they are more advantageous in regards with their price and catalytic activity compared with the other metal complex catalysts. Chiral C_2-symmetric bisoxazoline compounds are generally well-known as widely usable ligands for asymmetric catalysis. Masamune *et. al.* reported that a stable crystalline Cu(II) complex catalyst **1** (Scheme 1) to generate the active catalyst by treatment

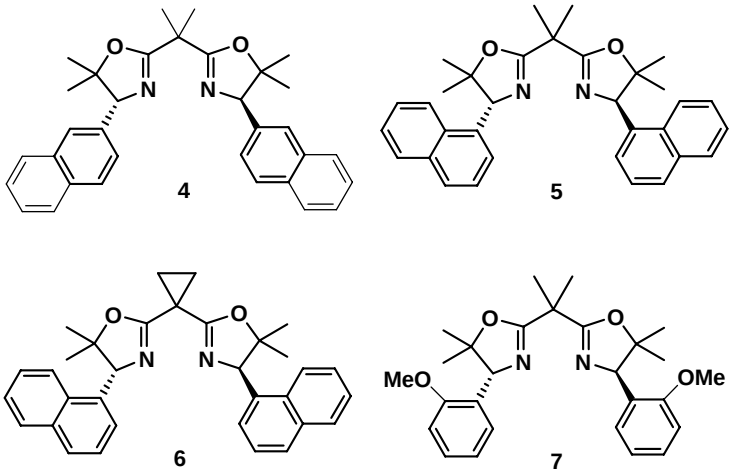
with phenylhydrazine provided >90 %ee for the asymmetric cyclopropanation of styrene in 1990,[3] and subsequently, Evans *et. al.* demonstrated that 99% ee was achieved using a cationic Cu(I) complex prepared in situ from CuOTf and bisoxazoline **2**,[4] which is presently the most efficient catalyst available for the asymmetric cyclopropanation of terminal olefins. Since Evans' report, to the best our knowledge, no copper-catalysts, which give higher stereoselectivities than the copper/**2** catalyst, have been disclosed for the asymmetric cyclopropanation of styrene with ethyl diazoacetate. Reiser reported a copper aza-bisoxazoline **3** catalyst for the asymmetric cyclopropanation of styrene, but the stereoselectivities were lower than those of the copper/**2** catalyst.[5]



Scheme 1. Previous Results of the Cyclopropanation of Styrene with Alkyl Diazoacetate using 1 mol% of Copper Bisoxazoline Catalyst

Meanwhile, we recently developed new efficient chiral bis(4-aryloxazoline) ligands **4** – **7** (Scheme 2) with *gem*-dimethyl groups at the 5-position for the copper-catalyzed asymmetric cyclopropanation of 2,5-dimethyl-2,4-hexadiene with ethyl or *tert*-butyl diazoacetate.[6-7] However, the stereoselectivities were lower for ligands **4**-**7** than for the **1**-**3** (Table 1). Among the series of ligands, higher *trans*

selectivity was observed for the cyclopropylidene-bridged ligand **6** than the isopropylidene-bridged ligand **5** although the enantio-selectivity was lower. Therefore, we evaluated the effects of substituents at the 5-position and at the bridge moiety on the bis[(4*S*)-*tert*-butyloxazoline] ligand and we have utilized these new ligands for the copper-catalyzed asymmetric cyclopropanation of styrene and have achieved the highest stereoselectivities thus far. Described herein are details.



Scheme 2. Structures of Recently Developed Bisoxazoline Ligands **4-7**

Table 1. Asymmetric Cyclopropanation of Styrene with Ethyl Diazoacetate (EDA) [8]

entry	ligand	yield (%) [a]	*trans/cis* [b]	ee (%) [c]	
				trans [d]	*cis* [e]
1	**4**	80	67/33	76	64
2	**5**	80	62/38	77	66
3	**6**	79	68/32	65	43
4	**7**	67	68/32	70	72

CuOTf/Ligand = 1/1.1 molar ratio, cat 0.1 mol%, styrene/EDA=5/1 molar ratio, 20 °C, 3h

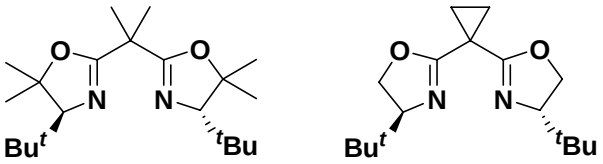
[a] Based on EDA and determined by GC analysis with *n*-decane as the internal standard

[b] Determined by GC analysis (DB-1, 30 m x 0.25 mm ID, 0.25 mm film, column temp. 100 °C)

[c] Determined by GC analysis (Cyclodex B, 50 m x 0.25 mm ID, 0.25 mm film, column temp. 105 °C),

[d] 1*R*,2*R* as a major enantiomer [9], [e] 1*R*,2*S* as a major enantiomer [9]

Bisoxazoline **8** (Scheme 3) was prepared from (*S*)-*tert*-leucine with an adaptation of our previous reported method.[6] Bisoxazoline **9**, which was recently prepared by the reaction of bis[(4*S*)-*tert*-butyloxazolinyl]methane with ethylene dibromide in the presence of *n*-BuLi by Denmark *et. al.* and was demonstrated to be an excellent ligand for the asymmetric addition of methyllithium to imines,[10] was prepared using our dehydration process[6] of the corresponding bisamide alcohol, which was obtained by the reaction of (*S*)-*tert*-leucinol with 1,1-cyclopropane dicarboxylic acid dichloride.[11] It should be noted that our method for the preparation of **9** gave a better overall yield (49 %) than that using repoted by Denmark's method (29 %).



8 **9**

Scheme 3. Structures of Bisoxazoline Ligands **8** and **9**

The results of the asymmetric cyclopropanation of styrene with ethyl diazoacetate are shown in Table 2.[8] Although a remarkable decrease in the *trans* selectivity was observed when **8** was used, it is surprising for us that both excellent *trans/cis* ratio (84/16) and enantioselectivity (>99.9% ee) were observed with **9** because very poor enantioselectivity (17% ee for *trans* isomer) were observed with **9** in the reaction of 2,5-dimethyl-2,4-hexadiene with ethyl diazoacetate.[13] In addition, in the reaction of 2,5-dimethyl-2,4-hexadiene similar change of substituents from isopropylidene-bridge (**2**: *trans/cis* ratio = 73/27, 16% ee for *trans* isomer) to cyclopropylidene-bridge (**9**: *trans/cis* ratio = 74/26, 17% ee for *trans* isomer) did not improve the selectivities. Therefore, subtle steric and/or electronic effects of the ligand on the reactant played an important role in these reactions. A mechanistic study to determine the reason for the enhanced stereoselectivity by the cyclpropylidene-bridged bisoxazoline (**9**) in the reaction with styrene is now under way.[12]

Table 2. Asymmetric Cyclopropanation of Styrene with Ethyl Diazoacetate (EDA)

entry	ligand	yield (%) [a]	*trans/cis* [b]	ee (%) [c]	
				trans [d]	*cis* [e]
1	**2**	85	75/25	99	99
2	**8**	78	42/58	87	93
3	**9**	85	84/16	>99.9	>99.9

CuOTf/ligand = 1/1.1 molar ratio, cat 0.1 mol%, styrene/EDA=5/1 molar ratio, 20 °C, 3h

[a] Based on EDA and determined by GC analysis with *n*-decane as the internal standard

[b] Determined by GC analysis (DB-1, 30 m x 0.25 mm ID, 0.25 mm film, column temp. 100 °C)

[c] Determined by GC analysis (Cyclodex B, 50 m x 0.25 mm ID, 0.25 mm film, column temp. 105 °C),

[d] 1*R*,2*R* as a major enantiomer [9], [e] 1*R*,2*S* as a major enantiomer [9]

In conclusion, the 1,1-bis{2-[(4*S*)-*tert*-butyl-2-oxazolinyl]}cyclopropane ligand was found to provide higher stereoselectivities for the copper catalyzed asymmetric cyclopropanation of styrene with ethyl diazoacetate than that by the conventional 2,2-bis{2-[(4*S*)-*tert*-butyl-2-oxazolinyl]}propane ligand. Applications to various kinds of substrates for the asymmetric cyclopropanation by the new catalyst system are in progess.

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8. Typical experimental procedure for the cyclopropanation: To a solution of the copper complex prepared from 0.02 mmol of CuOTf $(toluene)_{0.5}$, 0.022 mmol of the ligand in 5 mL of EtOAc (anhydrous) was added 100 mmol of styrene. Twenty mmol of ethyl diazoacetate in ethyl acetate (10 mL) was added dropwise to the solution over a period of 3 h at 20 °C, and then the mixture was stirred at the same temperature for 12 h. The reaction mixture was filtered through silica gel and then analyzed by GC (DB-1, 30 m x 0.25 mm ID, 0.25 mm film, column temp.100 °C - 10 min to 250 °C) using the internal method with *n*-decane as the standard for determining the yield and *trans*/*cis* ratio. Subsequently, the reaction mixture was analyzed to determine the enantioselectivity by GC (Cyclodex B, 50 m x 0.25 mm ID, 0.25 mm film, column temp. 105 °C). The absolute

configurations of the products were determined by comparison of the order of elution from the GC of the enantiomers described in the previously reported literature.[9]

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11. Preparation of 1,1-Bis{2-[(*4S*)-*tert*-butyloxazolinyl]}cyclopropane **(9)**: (*S,S*)-*N,N'*-Bis[2-hydroxy-*tert*-butylethyl] cyclopropane -1,3-dicarboxamide (1.38 g, 4.21 mmol), which was readily prepared by the reaction of *tert*-leucinol with cyclopropane-1,1-dicarboxylic acid dichloride in the presence of Et_3N, and xylene (anhydrous, 70 mL) were charged into a Schlenk tube, and the reaction mixture was heated to reflux to completely dissolve the dicarboxamide. $Ti(O^iPr)_4$ (120 mg, 0.421 mmol) was then added to the solution in one portion, and the reaction mixture was refluxed for 48h with removal of the water by-product. After the reaction mixture was cooled to 20 °C, the solution was concentrated under reduced pressure. The resulting pale yellow oil was purified by column chromatography (neutral alumina, hexane:AcOEt = 9:1) to give the bisoxazoline compound **9** as a white solid, which was recrystallized from heptane to give a white powder **9** (0.64 g, 52 %). Mp: 79.5-80.2 °C (lit.[10] Mp: 79.0-80.0 °C); $[\alpha]_D$= -89.6 (c = 1.09, $CHCl_3$) [lit.[10] $[\alpha]_D$= -83.8 (c = 1.115, $CHCl_3$)]. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.23-4.08(m, 4H), 3.81 (dd, *J* = 10.0, 7.2, 2H), 1.52-1.44 (m, 2H), 1.29-1.22 (m, 2H), 0.86 (s, 18H). ^{13}C NMR (75MHz, $CDCl_3$): δ165.4, 75.2, 69.1, 33.8, 25.6, 18.2, 15.1. Anal. Calcd for $C_{17}H_{28}N_2O_2$: C, 69.83%; H, 9.66%; N, 9.58%. Found: C, 69.3%; H, 9.6%; N, 9.4%. HRMS-ESI [MH^+] Calcd. for $C_{17}H_{28}N_2O_2$: 293.2223. Found: 293.2234.

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