

Application of a chiral copper-1,1-bis{2-[(4*S*)-*tert*-butyl-oxazoliny]}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*-butyloxazoliny]}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*-butyloxazoliny]}propane (*trans/cis* = 75/25, 99.0% ee for the *trans* product).

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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

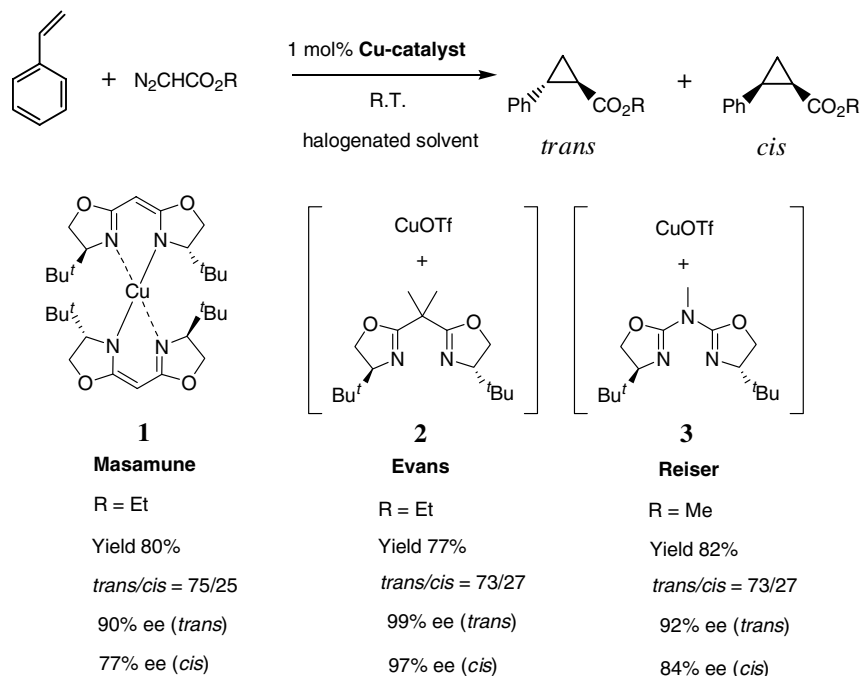
best our knowledge, no copper-catalysts, which give higher stereoselectivities than the copper/**2** catalyst, have been disclosed for the asymmetric cyclopropanation of styrene with ethyl diazoacetate. Reiser reported a copper aza-bisoxazoline **3** catalyst for the asymmetric cyclopropanation of styrene, but the stereoselectivities were lower than those of the copper/**2** catalyst.⁵

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 enantioselectivity was lower. Therefore, we evaluated the effects of substituents at the 5-position and at the bridge moiety on the bis[(4*S*)-*tert*-butyloxazoliny] 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.

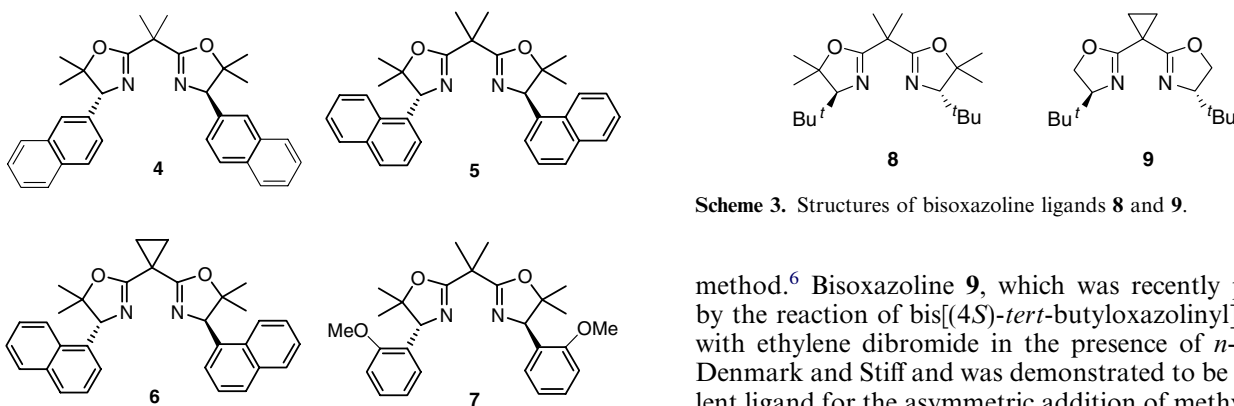
Bisoxazoline **8** (Scheme 3) was prepared from (*S*)-*tert*-leucine with an adaptation of our previous reported

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Scheme 1. Previous results of the cyclopropanation of styrene with alkyl diazoacetate using 1 mol % of copper bisoxazoline catalyst.



Scheme 2. Structures of recently developed bisoxazoline ligands 4–7.

Scheme 3. Structures of bisoxazoline ligands 8 and 9.

Table 1. Asymmetric cyclopropanation of styrene with ethyl diazoacetate (EDA)⁸

Entry	Ligand	Yield ^a (%)	<i>Trans/cis</i> ^b	ee ^c (%)	
				<i>Trans</i> ^d	<i>Cis</i> ^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, 3 h.

^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 × 0.25 mm ID, 0.25 mm film, column temperature 100 °C).

^c Determined by GC analysis (Cyclodex B, 50 m × 0.25 mm ID, 0.25 mm film, column temperature 105 °C).

^d 1*R*,2*R* as a major enantiomer.⁹

^e 1*R*,2*S* as a major enantiomer.⁹

method.⁶ Bisoxazoline **9**, which was recently prepared by the reaction of bis[(4*S*)-*tert*-butyloxazolyl]methane with ethylene dibromide in the presence of *n*-BuLi by Denmark and Stiff and was demonstrated to be an excellent ligand for the asymmetric addition of methyl lithium to imines,¹⁰ was prepared using our dehydration process⁶ 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 reported by Denmark's method (29%).

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) was 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.¹² In addition, in the reaction of 2,5-dimethyl-2,4-hexadiene with ethyl diazoacetate 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

Table 2. Asymmetric cyclopropanation of styrene with ethyl diazoacetate (EDA)

Entry	Ligand	Yield ^d (%)	<i>Trans/cis</i> ^b	ee ^c (%)	
				<i>Trans</i> ^d	<i>Cis</i> ^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, 3 h.

^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 × 0.25 mm ID, 0.25 mm film, column temperature 100 °C).

^c Determined by GC analysis (Cyclodex B, 50 m × 0.25 mm ID, 0.25 mm film, column temperature 105 °C).

^d 1*R*,2*R* as a major enantiomer.⁹

^e 1*R*,2*S* as a major enantiomer.⁹

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 cyclopropylidene-bridged bisoxazoline (**9**) in the reaction with styrene is now underway.¹³

In conclusion, 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 progress.

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