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Asymmetric Cyclopropanation of 2,5-Dimethyl-2,4-hexadiene by Copper Catalysts Bearing New Bisoxazoline Ligands

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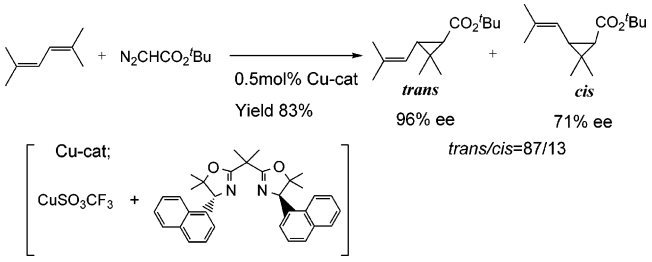

Some new bisoxazoline ligands with an aryl group at the 4-position and *gem*-dimethyl groups at the 5-position on the oxazoline ring were prepared from arylglycines. Remarkable enhancement of the *trans*-selectivity (*trans*/*cis* = 87/13) and the enantioselectivity (96% ee for the *trans* product) was demonstrated for the asymmetric cyclopropanation of 2,5-dimethyl-2,4-hexadiene with *tert*-butyl diazoacetate catalyzed by the new copper−bisoxazoline complex.

Catalytic asymmetric cyclopropanation of alkenes with alkyl or aryl diazoacetates is a powerful tool in the synthesis of chiral cyclopropyl esters, which are very important intermediates for biologically active compounds.[1−3] 3-(1-Isobutenyl)-2,2-dimethyl cyclopropanecarboxylic acid (chrysanthemic acid) is of particular importance as an intermediate of pyrethroid insecticides, and the (1*R*,3*R*) isomer ((+)-*trans* isomer) shows the highest insecticidal activity among the four isomers of the chrysanthemate.[4] Aratani first achieved a high ee (94%) and *trans*/*cis* ratio (93/7) of the chrysanthemate for the cyclopropanation of 2,5-dimethyl-2,4-hexadiene (DMHD) with *l*-menthyl diazoacetate, using copper Schiff-base complex catalysts derived from chiral amino alcohols.[5,6] Subsequently, Aratani's asymmetric process led to successful industrial application in the synthesis of chiral 2,2-dimethylcyclopropane carboxylic acid by asymmetric cyclopropanation of isobutene with ethyl diazoacetate.[6] Although many successful asymmetric cyclopropanations of styrene with diazoacetate have been reported in the past four decades, only a few successful reports have been presented on the asymmetric cyclopropanation of the diene (DMHD) as the substrate to give high *trans*-selectivity and high enantioselectivity.[7] To the best of our knowledge, the effective catalysts for the asymmetric cyclopropanation of the diene are a copper bisoxazoline complex **2** by Masamune[8] and a copper ethylenediamine complex **3** by Kanemasa,[9] aside from the copper Schiff-base complex **1** by Aratani. In all of these cases, *l*-menthyl diazoacetate or dicyclohexylmethyl diazocetate was used to achieve the high *trans*-selectivity and the enantioselectivity in the cyclopropanation, but these diazoacetates are rather expensive for industrial application.

Therefore, we have developed new efficient catalysts using a simple alkyl diazoacetate such as ethyl or *tert*-butyl diazoacetate. The simple alkyl chrysanthemate should be easily converted into chrysanthemic acid with a strong base or a strong acid. Scott et al. reported the copper biaryl Schiff-base complex **4** for the asymmetric cyclopropanation of the diene with *tert*-butyl diazoacetate, but the *trans*-selectivity and the enantioselectivity were moderate.[10] Recently, we first achieved >90% ee of the *trans*-product for the cyclopropanation of the diene with *tert*-butyl diazoacetate, using 0.1 mol % copper Schiff-base complexes combined with $Al(OEt)_3$ as the catalysts.[11] However, the *trans*/*cis* ratio still remains unsatisfactory (*t*/*c* = 78/22) (Scheme 1).

Here we wish to report that new copper complexes composed of chiral bisoxazoline compounds with an aryl group at the 4-position and *gem*-dimethyl groups at the 5-position are very effective catalysts for providing high stereoselectivity (96% ee and *trans*/*cis* = 87/13) in the asymmetric cyclopropanation of the diene with *tert*-butyl diazoacetate.

At first, we tested already known bisoxazoline ligands **5**−**10** and **11a** (Scheme 2) with the copper catalysts for the asymmetric cyclopropanation of the diene with ethyl diazoacetate at 40 °C. A 0.5 mol % Cu-bisoxazoline catalyst was used for the reaction, and the catalyst was prepared in situ from commercially available CuOTf-$(toluene)_{0.5}$ and 1.1 equiv of the ligand in ethyl acetate. Bisoxazolines **5**, **7**, **8**, **9**, and **10** are commercially available. Compound **6** was prepared from L-valinol based on the procedures for the synthesis of **5**.[12a,b] Bisoxazoline compound **11a** was prepared using Corey's method.[13] The

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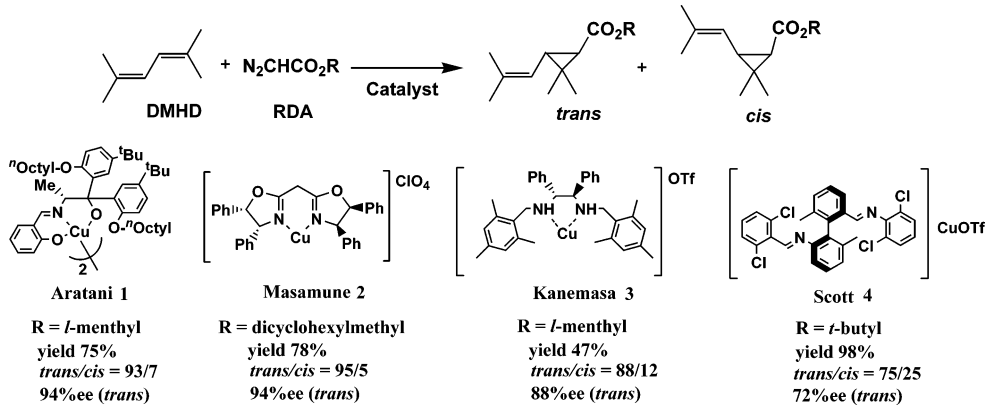
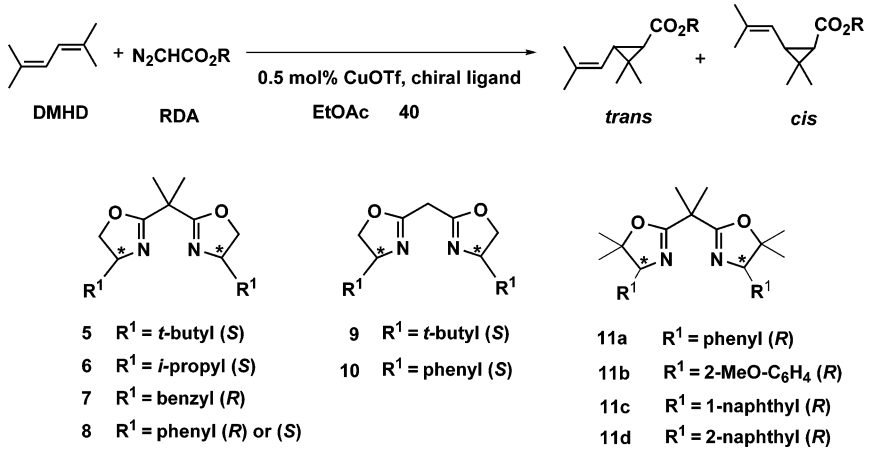
SCHEME 1. Structures of Aratani's Catalyst 1, Masamune's Catalyst 2, Kanemasa's Catalyst 3, and Scott's Catalyst 4 and the Results of the Cyclopropanation of 2,5-Dimethyl-2,4-hexadiene (DMHD) with Diazoacetate (RDA) under 1 mol % Catalyst Loading



SCHEME 2. Structures of Bisoxazoline Ligands 5−11



results of the asymmetric cyclopropanation of the diene with alkyl diazoacetate are shown in Table 1.

It is clear that substituents at the 4-position on the oxazoline moiety affect the stereoselectivities for the cyclopropanation and that the phenyl group is the most effective as a substituent at the 4-position for both the *trans*/*cis* ratio and the enantioselectivity among these bisoxazoline ligands in Table 1 (entries 5, 6, and 8). It should be noted that in the reaction utilizing ligand **8** or **10** the *trans*/*cis* ratio and the enantioselectivity were almost identical to those with the use of the Masamune's ligand **2** (entries 1, 5, 6, and 8) and that substituents on the bridge part of the bisoxazoline do not affect the *trans*/*cis* ratio or the enantioselectivity of the product (entries 5 and 8). In contrast, the use of the ligand **11a** with *gem*-dimethyl groups at the 5-position on the oxazoline ring enhanced both the *trans*-selectivity and the enantioselectivity (entry 9). Subsequently, *tert*-butyl diazoacetate was tested in place of ethyl diazoacetate as the diazo compound with CuOTf/**2**, CuOTf/**8**, CuOTf/**10**, and CuOTf/**11a** (entries 10, 11, 12, and 13). Much better *trans*/*cis* ratios and enantiomeric excesses of the product were obtained than those in the case of ethyl diazoacetate with

TABLE 1. Asymmetric Cyclopropanation of 2,5-Dimethyl-2,4-hexadiene (DMHD) with Alkyl Diazoacetate (RDA) Catalyzed by Copper−Bisoxazoline Complex[15]

entry	ligand	ligand config[a]	R = in RDA	yield[b] (%)	*trans*/*cis*[c]	ee[d] (%) *trans*	ee[d] (%) *cis*
1	**2**	*R*	Et	91	71/29	65[e]	35[f]
2	**5**	*S*	Et	83	73/27	16[g]	47[f]
3	**6**	*S*	Et	90	63/37	36[g]	24[h]
4	**7**	*R*	Et	91	63/37	36[e]	22[f]
5	**8**	*S*	Et	93	71/29	65[g]	32[h]
6	**8**	*R*	Et	92	71/29	66[e]	35[f]
7	**9**	*S*	Et	86	66/34	7[g]	22[f]
8	**10**	*S*	Et	91	71/29	65[g]	35[h]
9	**11a**	*R*	Et	95	74/26	78[e]	38[f]
10	**2**	*R*	^{t}Bu	91	81/19	84[e]	62[f]
11	**8**	*R*	^{t}Bu	92	81/19	83[e]	62[f]
12	**10**	*S*	^{t}Bu	94	80/20	80[g]	60[h]
13	**11a**	*R*	^{t}Bu	93	84/16	88[e]	68[f]

[a] Absolute configuration at the 4-position on the oxazoline ring. [b] Based on RDA and determined by GC analysis with *n*-decane as an internal standard. [c] Determined by GC analysis (DB-1, 30 m × 0.25 mm i.d., 0.25 mm film, column temperature 100 °C). [d] For R = Et in RDA; determined by LC analysis (Sumichiral OA-2500 (25 cm × 4 mm i.d., 5 μm film) × 2, UV 220 nm, *n*-hexane 0.7 mL/min). For R = ^{t}Bu in RDA; determined by GC analysis (DB-210, 30 m × 0.25 mm i.d., 0.25 mm film, column temperature 115 °C) after transformation into *l*-menthyl chrysanthemate. [e] 1*R*,3*R* as a major enantiomer. [f] 1*R*,3*S* as a major enantiomer. [g] 1*S*,3*S* as a major enantiomer. [h] 1*S*,3*R* as a major enantiomer.

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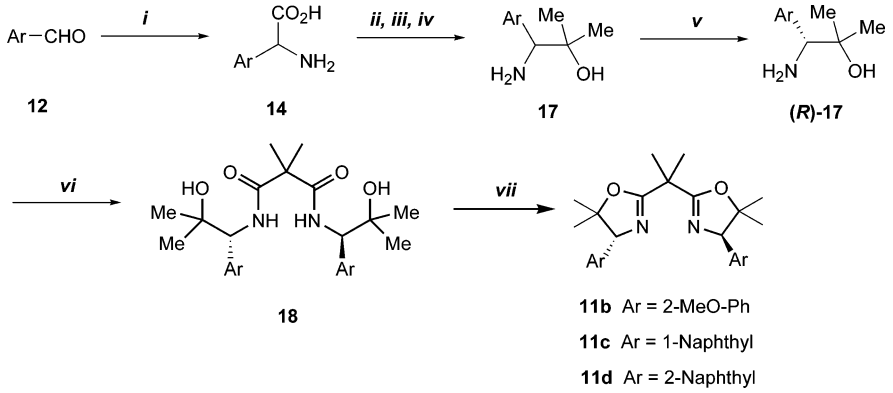
SCHEME 3. Synthesis of Bisoxazoline Ligands 11b−d[a]



[a] Key: (i) KCN (1.2 equiv), $(NH_4)_2CO_3$ (2.7 equiv) in H_2O−EtOH (1/1), 60 °C, 5 h, 72−95%, then KOH (4.1 equiv) in H_2O, reflux, 60 h, followed by H_3O^+, 55−99%; (ii) $SOCl_2$ (1.8 equiv) in MeOH, 35 °C, 3 h, 75−98%; (iii) $(CF_3CO)_2O$ (1.1 equiv), Et_3N (2.1 equiv) in CH_2Cl_2, −50 °C, 1 h, 65−76%; (iv) MeMgBr (5 equiv) in THF, 5−20 °C, 2.5 h, then H_3O^+, followed by KOH (2.2 equiv) in MeOH/H_2O (10:1), 50 °C, 2 h, 69−97%; (v) optical resolving reagent (0.4 equiv, (2*R*,3*R*)-tartranilic acid for **17b**, *N*-formyl-(*R*)-phenylalanine for **17c** and **17d**), in ^{i}PrOH, then 1 N NaOH, 24−30%, 99.7% ee for (*R*)-**17b**, 99.7%ee for (*R*)-**17c**, 99.8%ee for (*R*)-**17d**; (vi) 2,2-dimethylmalonic acid dichloride (0.5 equiv), Et_3N (1.2 equiv) in CH_2Cl_2, −10 to +20 °C, 6 h, 100%; (vii) Ti(O^{i}Pr)$_4$ (0.1 equiv) in xylene, reflux, 48 h, 77−88%.

each copper catalyst, and ligand **11a** provided the highest *trans*-selectivity and enantioselectivity *(t/c* = 84/16, 88% ee for trans product). Furthermore, we found that the commercially available ligand **8** with the (*S*)-configuration at the 4-position on the oxazoline ring predominantly provided the (1*S,*3*S*)-isomer for the chrysanthemate, and that with the (*R*)-configuration provided the (1*R,*3*R*)-isomer, which is the most insecticidally active isomer of the synthetic pyrethroids. These findings prompted us to search for new (4*R*)-configurated bisoxazoline ligands with an aryl group at the 4-position and *gem*-dimethyl groups at the 5-position on the oxazoline ring, using *tert*-butyl diazoacetate as the diazo compound. As a result, we synthesized new ligands **11b**−**d** and then tested them for the cyclopropanation of the diene with *tert*-butyl diazoacetate.

Bisoxazoline ligands **11b**−**d** were synthesized as illustrated in Scheme 3, in which the key step is preparation of enantiomerically pure amino alcohols **17b**−**d** by optical resolution with (2*R*,3*R*)-tartranilic acid for **17b** or *N*-formyl-(*R*)-phenylalanine for **17c** and **17d**, followed by conversion into the corresponding bisamido alcohols **18b**−**d**. It should be noted that the bioxazoline compounds were obtained by our newly developed procedures, that is, dehydration of the bisamido alcohols **18** using 10 mol % Ti(O-*i*-propyl)$_4$[16] (see the Supporting Information for details). The absolute configurations of the bisoxazolines **11b**−**d** were determined by those of each major enantiomer of the *trans* products in the copper-bisoxazoline catalyzed cyclopropanation.

Shown in Table 2 are the results of the cyclopropanation of the diene with *tert*-butyl diazoacetate at 40 °C using 0.5 mol % CuOTf/**11a**−**d** catalysts. The enantiomeric excess for the *trans* product was enhanced up to >90% ee in the case of CuOTf/**11b** or **11c**, compared to **11a** (entries 1−3). However, ligand **11d** was found to be ineffective for the stereoselectivity (entry 4). We found that the best ligand is **11c** which provided an 86/14 *trans*/*cis* ratio and 95% ee for the trans product at 40 °C (entry 3).

TABLE 2. Asymmetric Cyclopropanation of 2,5-Dimethyl-2,4-hexadiene (DMHD) with *tert*-Butyl Diazoacetate (TBDA) Catalyzed by Copper−Bisoxazoline Complex

entry	ligand in Cu−cat.	solvent	reaction temp (°C)	yield[a] (%)	*trans*/*cis*[b]	ee[c] (%) *trans*[d]	ee[c] (%) *cis*[e]
1	**11a**	EtOAc	40	93	84/15	88	68
2	**11b**	EtOAc	40	88	85/15	93	69
3	**11c**	EtOAc	40	92	86/14	95	69
4	**11d**	EtOAc	40	91	79/21	85	69

[a] Based on TBDA and determined by GC analysis with *n*-decane as an internal standard. [b] Determined by GC analysis (DB-1, 30 m × 0.25 mm i.d., 0.25 mm film, column temperature 100 °C). [c] Determined by GC analysis (DB-210, 30 m × 0.25 mm i.d., 0.25 mm film, column temperature 115 °C) after transformation into *l*-menthyl chrysanthemate. [d] 1*R,*3*R* as a major enantiomer. [e] 1*R,*3*S* as a major enantiomer.

TABLE 3. Asymmetric Cyclopropanation of 2,5-Dimethyl-2,4-hexadiene (DMHD) with *tert*-Butyl Diazoacetate (TBDA) Catalyzed by CuOTf/11c Complex

entry	ligand in Cu−cat.	solvent	reaction temp (°C)	yield[a] (%)	*trans*/*cis*[b]	ee[c] (%) *trans*[d]	ee[c] (%) *cis*[e]
1	**11c**	EtOAc	40	92	86/14	95	69
2	**11c**	EtOAc	0	83	87/13	96	71
3	**11c**	CH_2Cl_2	0	82	87/13	95	69
4	**11c**	toluene	0	56	85/15	93	69

[a] Based on TBDA and determined by GC analysis with *n*-decane as internal standard. [b] Determined by GC analysis (DB-1, 30 m × 0.25 mm i.d., 0.25 mm film, column temperature 100 °C). [c] Determined by GC analysis (DB-210, 30 m × 0.25 mm i.d., 0.25 mm film, column temperature 115 °C) after transformation into *l*-menthyl chrysanthemate. [d] 1*R,*3*R* as a major enantiomer. [e] 1*R,*3*S* as a major enantiomer.

Furthermore, the reaction conditions (temperature and solvents) were optimized in the case of the CuOTf/**11c** catalyst (Table 3). The best result was obtained when the reaction was carried out at 0 °C in ethyl acetate, providing an 87/13 *trans*/*cis* ratio and 96% ee for the *trans* product at 0 °C (entry 2).

In conclusion, a new bisoxazoline ligand with a 1-naphthyl group at the 4-position and *gem*-dimethyl groups at

the 5-position was prepared and was found to be a very good ligand for the asymmetric cyclopropanation of the diene with *tert*-butyl diazoacetate. The copper bisoxazoline complex catalyst gave 87/13 *trans*/*cis* ratio and 96% ee for the *trans* product. The major product, which is (1*R*,3*R*) *tert*-butyl chrysanthemate, is easily hydrolyzed into (1*R*,3*R*) chrysanthemic acid whose pyrethroid insecticides show the highest insecticidal activity among the four isomers of the chrysanthemate. A mechanistic study resulting in higher stereoselectivity by the introduction of the *gem*-methyl groups is now under way.[14]

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Supporting Information Available: Preparation and characterization data for **11b**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Mechanistic studies of copper-bisoxazoline-catalyzed asymmetric cyclopropanation were recently reported based on the DFT calculation: Rasmusen, T.; Jensen, J. F.; Østergaard, N.; Tanner, D.; Ziegler, T.; Norrby P.-O. *Chem. Eur. J.* **2002**, *8*, 177.

(15) **Typical Procedure for the Cyclopropanation.** To a solution of the copper complex prepared from 0.05 mmol of CuOTf(toluene)$_{0.5}$, 0.055 mmol of the ligand in 5 mL of EtOAc, and 70 mmol of 2,5-dimethyl-2,4-hexadiene was added 10 mmol of *tert*-butyl diazoacetate in ethyl acetate over a period of 2 h at 40 °C, and then the mixture was stirred at the same temperature for 0.5 h. The reaction mixture was filtered through silica gel and then analyzed by GC (DB-1, 30 m × 0.25 mm i.d., 0.25 mm film, column temperature 100 °C,10 min to 250 °C) using the internal method with *n*-decane as a standard for determining the yield and *trans*/*cis* ratio. After concentration of the reaction mixture under reduced pressure, the residue containing 1.13 g of *tert*-butyl chrysanthemate (5 mmol) was dissolved in 10 mL of toluene. Trifluoroacetic acid (57 mg, 0.5 mmol) was then added to the solution, and the solution was refluxed for 3 h to afford chrysanthemic acid, which was analyzed by GC (DB-210, 30 m × 0.25 mm i.d., 0.25 mm film, column temperature 115 °C) after transformation into the *l*-menthyl chrysanthemate with $SOCl_2$, pyridine, and L-menthol. The absolute configurations of the products were determined by comparison of the order of elution from GC of the enantiomers with authentic samples.

(16) **2,2-Bis{2-[(4*R*)-(1-naphthyl)-5,5-dimethyloxazolinyl]}-propane (11c):** white crystalline solid; mp 61.5−63.0 °C; $[\alpha]_D = -187$ (c = 0.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ7.94 (d, J = 9.0 Hz, 2H), 7.87 (d, J = 9.0 Hz, 2H), 7.75 (d, J = 9.0 Hz), 7.55−7.39 (m, 8H), 5.85 (s, 2H), 1.81 (s, 6H), 1.78 (s, 6H), 0.81 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 135.5, 134.0, 132.1, 129.4, 128.1, 126.5, 125.8, 125.7 123.1, 88.1, 73.6, 39.5, 29.4, 24.4, 23.8. HRMS-EI (*m*/*z*) [MH$^+$] calcd for $C_{33}H_{34}N_2O_2$ 491.2693, found 491.2712.