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# Asymmetric Catalytic Cyclopropanation of Olefins: Bis-Oxazoline Copper Complexes

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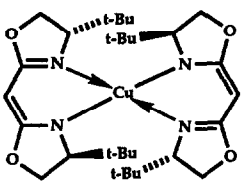
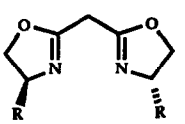
Summary: Bis-oxazolines (1-7) prepared from diethyl malonate and chiral amino alcohols were converted into their Cu(II) complexes which, upon activation, exhibit high enantioselectivity of up to 99 %ee for catalytic cyclopropanation of olefins.

Over more than two decades copper-catalysed cyclopropanation of olefins with a diazoacetate has received much attention of synthetic chemists,[1] and a variety of chiral ligands for the metal have been devised for its asymmetric version as represented by (1) iminodiols prepared from salicylaldehydes with chiral amino alcohols (Aratani),[2] (2) 3-trifluoroacetyl-(+)- or (-)-camphor (Matlin),[3] and (3) chiral semicorrin derivatives (Pfaltz).[4] We wish to add to this list[5] the chiral bis-oxazoline Cu(II) complex **1a** (see below) which, upon activation, catalyzes cyclopropanation with enantioselectivities that, at least equal or often exceed those achieved by the known catalysts. Ligand **1** which obviously is patterned after the semicorrin, is amenable to practical synthesis and also can be readily and extensively modified for other asymmetric reactions which are currently under investigation in our laboratories.

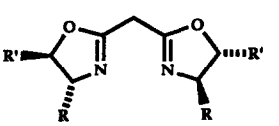
Several bis-oxazoline ligands (**1-7**) were prepared in one step from diethyl malonate and the corresponding amino alcohols and were converted into their violet Cu(II) complexes **1a-7a** (see below for details). Treatment of the complexes with phenylhydrazine provided the active catalytic species which were evaluated in terms of stereoselectivity for cyclopropanation using ethyl diazoacetate and styrene in a standard fashion.[2d] The results are summarized in Table 1. Expectedly its enantioselectivities of both trans- and cis- products increase as the size of the R group in the ligands is enlarged and both 90 %ee for the trans and 77 %ee for the cis with **1a** compare favorably with those




**1a**




**1**: R= $C(CH_3)_3$
**5**: R= $CH(CH_3)_2$
**6**: R= $CH_2Ph$
**7**: R= Ph




**2**: R= $CH_3$, R'= Ph
**3**: R= $CH_2OH$, R'= H
**4**: R= $CH_2CH_3$, R'= H

achieved with a semicorrin (85 %ee for trans, 68 %ee for cis) and an iminodiol (69 %ee for trans, 54 %ee for cis).

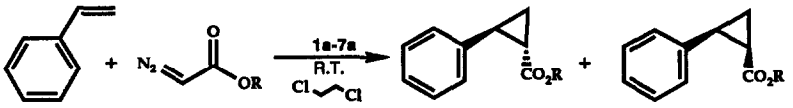



Table 1: Cyclopropanation of styrene with ethyl diazoacetate using **1a-7a**.

| Ligand | Yield[a] | Diastereoselectivity Trans : Cis[b] | Enantioselectivity (%ee) Trans[c] | Cis[c] | Configuration[d] |
|---|---|---|---|---|---|
| 2a | 78% | 71:29 | 28 | 30 | (1S,2S)/(1R,2S) |
| 3a | 88% | 75:25 | 48 | 36 | (1S,2S)/(1R,2S) |
| 4a | 78% | 72:28 | 19 | 31 | (1S,2S)/(1R,2S) |
| 5a | 72% | 71:29 | 46 | 31 | (1R,2R)/(1S,2R) |
| 6a | 76% | 71:29 | 36 | 15 | (1R,2R)/(1S,2R) |
| 7a | 81% | 70:30 | 60 | 52 | (1R,2R)/(1S,2R) |
| 1a | 80% | 75:25 | 90 | 77 | (1R,2R)/(1S,2R) |

a) Isolated yield. b) Determined by GC. c) Determined by GC of the d(+)- and l(-)- menthyl esters. d) Assigned on the basis of the known optical rotation of the acids.

It is known that the alcohol moiety of diazoacetates also affects the stereoselectivity of cyclopropanation and this applies to the case of **1a** as well. Thus, the trans:cis diastereoselctivity 75:25 with ethyl diazoacetate is enhanced to 86:14 with (-)-menthyl diazoacetate [and $(+)_{436}$-**1a**] and more significantly the enantioselectivities for both diastereomers became nearly perfect in the latter case (Table 2). Finally, several typical olefins were selected to define the scope of asymmetric cyclopropanation with the **1a** - menthyl diazoacetate pair. Table 3 summarizes the results which demonstate a consistantly high degree of stereoselectivity observed with this pair and further suggest a way **1a** should be modified, if asymmetric cyclopropanation of certain olefin types needs to be further improved.

Table 2: Cyclopropanation with several diazoacetates using **1a**.

| Diazo ester | Yield | Diastereoselectivity Trans : Cis | Enantioselectivity (%ee) Trans | Cis |
|---|---|---|---|---|
| Ethyl | 80% | 75:25 | 90 | 77 |
| *t*-Butyl | 73% | 80:20 | 94 | 89 |
| d(+)-Menthyl | 71% | 84:16 | 98 | 80 |
| l(-)-Menthyl | 72% | 86:14 | 98 | 96 |

Table 3: Cyclopropanation using **1a** and a variety of olefins.

| Olefin | Diazo ester | Yield[a] | Diastereoselectivity Trans : Cis[b] | Enantioselectivity (%ee) Trans[c] | Cis[c] |
|---|---|---|---|---|---|
| styrene | l(-)-menthyl | 72% | 86:14 | 98 | 96 |
| | d(+)-menthyl | 71% | 84:16 | 98 | 80 |
| 1-octene | l(-)-menthyl | 76% | 94:6 | 99* | 30* |
| | d(+)-menthyl | 72% | 90:10 | 75* | 45* |
| a-methylstyrene | l(-)-menthyl | 78% | 89:11 | 92 | 79* |
| | d(+)-menthyl | 72% | 85:15 | 83 | 77* |
| trans-4-octene | l(-)-menthyl | 52% | — | 88 | — |
| | d(+)-menthyl | 50% | — | 85 | — |
| trans-anethole | l(-)-menthyl | 45% | 98:2 | 90 | — |
| | d(+)-menthyl | 48% | 95:5 | 88 | 65 |
| 2,3,3-trimethylbutene | l(-)-menthyl | 60% | 95:5 | 80 | 91 |
| | d(+)-menthyl | 55% | 98:2 | 77 | — |

a) Isolated yield. b) Determined by GC. c) Determined by GC of the d(+)- and l(-)- menthyl esters.

*) Enantiomeric excess was determined by conversion to the (R)-(-)-2-octyl ester .

Preparation of **1**. To a solution of 4.75 g (40.6 mmol) *t*-leucinol in 162 mL of dry xylene was added 3.08 mL (20.3 mmol) of diethyl malonate. The mixture was heated to reflux for 4 h with a Dean-Stark trap. To this solution was added 89 mg (0.4 mmol) of dichlorodimethlystannane[6] and the mixture was heated to reflux for an additional 48 h. The reaction mixture was concentrated to ca. 15 mL and chromatographed on 150 g of neutral alumina (Aldrich grade I) using ethyl acetate/hexane (3:2). The combined fractions were concentrated and the residue was bulb-to-bulb transferred to provide 4.75 g (88%) of crystalline bis-oxazoline **1**, mp 48-49° C, $[a]_D$ -120° (c 0.51, $CHCl_3$). Further crystallization from $CH_2Cl_2$/Hexane did not change physical data.

Preparation of **1a**. Deprotonation of 532 mg (2mmol) of **1** in 8 mL of THF was effected with 0.8 mL (2 mmol) of 2.5 M n-BuLi for 30 min at -78° C and then for 5 min at 25° C. To this solution was added 134.5 mg (1 mmol) of $CuCl_2$ and the mixture was stirred for 4 h. The solution was concentrated to 1 mL and the residue was chromatographed on 75 g of Aldrich neutral alumina (grade I) to provide 572 mg (96%) of dark purple crystals. Recrystallization from cyclohexane provided 512 mg (86%) of pure copper complex **1a** which decomposed upon standing, mp 225° C (dec.), $[a]_{436nm}$ +4978.6°. Anal. Calcd. C 60.63, N 9.43, H 8.48; Found C 60.40, N 9.50, H 8.37. mass spectra (EI) $M^+$ m/z 593 (47.5%) and 595 (23.1%) for $^{63}Cu$ and $^{65}Cu$.

Typical cyclopropanation procedure. Freshly prepared complex **1a** (0.01 mmol) was combined with styrene (3 mmol) in dichloroethane (0.5 mL) at 25° C and was activated with phenylhydrazine (0.05 mL of a 1% solution).[2d] After 5 min ethyl diazoacetate (1 mmol) in dichloroethane (1 mL) was added over a 24 h period. The reaction was concentrated and the residue was purified by chromatography. Enantiomeric excess was determined by gas chromatography of the menthyl ester, as described by Pfaltz, et. al.[4]

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