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Asymmetric Copper-Catalyzed Cyclopropanation of Trisubstituted and Unsymmetrical cis-1,2-Disubstituted Olefins: Modified Bis-Oxazoline Ligands

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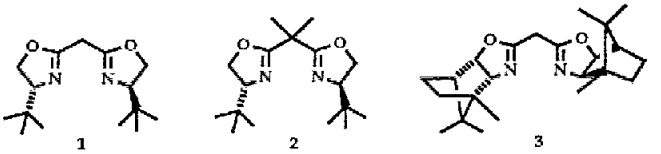
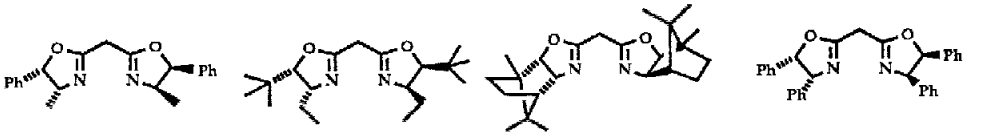
Summary: The Cu(I) complexes of new bis-oxazolines (3-7) prepared from the corresponding amino alcohols and malono-bis-imidate exhibit high enantioselectivity of up to 94 %ee in the catalytic cyclopropanation of trisubstituted and unsymmetrical cis-1,2-disubstituted olefins. New diazoacetate reagents have also been developed giving high trans/cis ratios of up to 99:1 trans.

We described recently bis-(4,5-dihydrooxazolyl)methane ligands for the copper-catalyzed asymmetric cyclopropanation of olefins with a diazoacetate.[1] Soon after this disclosure a number of publications,[2] including a review,[2f] have appeared exhibiting the considerable interest generated by this ligand design. The ready accessibility and high structural variability of bis-(dihydrooxazolyl) derivatives render them particularly attractive. With the use of either the Cu(II) complex of **1**[1] or the copper (I) triflate complex of **2**,[2a] excellent diastereo- (trans/cis ratio) and enantioselectivity (up to 99%) were achieved in the cyclopropanation of a variety of mono-substituted,[3] trans-disubstituted, and terminal disubstituted olefins. Important applications (see below) of this asymmetric reaction also concern trisubstituted and unsymmetrical cis-1,2-disubstituted olefins, for which the ligands of type **1** and **2** failed to provide acceptable enantioselectivities. New modified ligands have therefore been sought, and we report herein the successful outcome of our efforts, exemplified by the synthesis of (+)-trans-chrysanthemic and (+)-trans-permethric acids (92-94 %ee's and 95/5 - 99/1 trans/cis ratios).[4]



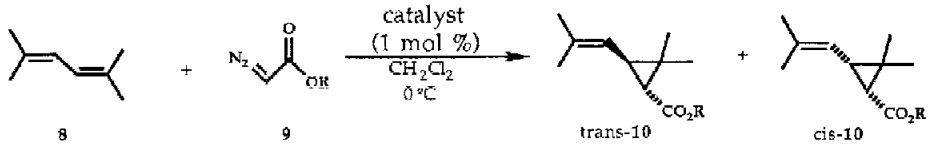
1 **2** **3**



4 **5** **6** **7**

Catalytic cyclopropanations are carried out in a standard fashion, using the catalysts conveniently prepared from $CuClO_4(CH_3CN)_4$ and a variety of ligands, e.g. **3-7**,[5] although CuOTf,

$CuOtBu$, $CuClO_4(CH_3CN)_4$, and Cu(II) complexes (with activation) all provide comparable yields and enantioselectivities. New ligands **3-7** are easily synthesized from the corresponding amino alcohols and malono-bis-imidate in CH_2Cl_2 in the presence of triethylamine. 2,5-Dimethyl-2,4-hexadiene (**8**) was selected as a representative tri-substituted olefin and the results of its cyclopropanation with diazoacetates (**9**) are summarized in Table 1.



8 **9** trans-**10** cis-**10**

(For the absolute configuration, see Table 1)

Table 1. Cyclopropanation of 2,5-dimethyl-2,4-hexadiene with 1% Cu(I) complexes.

Entry	Ligand[a]	R in 9[b]	Yield[c]	Diastereoselectivity[d] (Trans / Cis)	Enantioselectivity[e] Trans	Cis	Config.[f]
1	1	*l*-menthyl	61%	84 : 16	24	16	(+)-1R
2	2	*l*-menthyl	60%	84 : 16	24	20	(+)-1R
3	3	*l*-menthyl	60%	88 : 12	40	25	(+)-1R
4	4	*l*-menthyl	68%	90 : 10	72	60	(+)-1R
5	5	*l*-menthyl	65%	90 : 10	82	65	(+)-1R
6	6	*l*-menthyl	58%	80 : 20	90	80	(+)-1R
7	6	BHT	60%	92 : 8	92	ND[g]	(+)-1R
8	7	TMP	76%	85 : 15	88	ND[g]	(+)-1R
9	7	*d*-menthyl	70%	86 : 14	90	78	(+)-1R
10	7	*l*-menthyl	72%	92 : 8	92	84	(+)-1R
11	7	DMP	78%	93 : 7	94	ND[g]	(+)-1R
12	7	BHT	75%	94 : 6	94	ND[g]	(+)-1R
13	7	DCM	78%	95 : 5	94	ND[g]	(+)-1R

(a) In order to maintain the consistency, the ligands **1-7** with the same absolute configuration at the 4-position are shown in the text and Tables. In actual experiments, the enantiomers of 1, 2, and 3 were used. (b) BHT = 2,6-di-*tert*-butyl-*p*-tolyl ; TMP = 2,3,4-trimethyl-3-pentyl ; DMP = 2,4-dimethyl-3-pentyl ; DCM = dicyclohexylmethyl. (c) Isolated after basic workup and column chromatography. (d) Determined by capillary GLC at a constant temperature, ranging from 120 °C to 195 °C (ref. 6). (e) Determined by capillary GLC of the R(-)-octyl ester (ref. 6) (f) Determined by known rotation of the corresponding acid. (g) ND stands for "not determined".

It should be noted that in the reactions utilizing ligands **1-3** the formation of chrysanthemates (**10**) proceeds with low enantioselectivity (entries 1-3). In contrast, ligand 4 with a small methyl group in the 4-position and a relatively large phenyl group at the 5-position achieves much higher enantioselectivity (72 %ee, entry 4). It is apparent that substituents at both the 4- and 5-positions play a critical role. Careful consideration of possible transition states[4,7] for the Cu(I)-catalyzed cyclopropanation reaction allowed us to focus on the study of ligands **5-7**. The latter two ligands, **6** and **7**, have proven the most successful (92 %ee, entries 6-10). Furthermore, modifications of R in **9** leads to higher trans/cis ratios (entries 8-13). Best results are achieved with **7** and dicyclohexylmethyl diazoacetate (DCM-**9**) which provide trans-**10** with a 95:5 trans/cis

ratio and 94 %ee (entry 13). Although 2,6-di-*tert*-butyl-*p*-tolyl diazoacetate (BHT-9)[8] achieves a similarly high trans/cis ratio (entry 12), DCM-9 offers a definitive advantage: hydrolytic removal of DCM from **10** can be effected under standard acidic or basic conditions,[9] while that of BHT cannot.

The use of the Cu-**7** complex for the asymmetric catalysis is not limited to the case with **8**, but can be extended to other trisubstituted (entries 3-7 of Table 2) and disubstituted olefins (entries 1,2) as well. Note, however, that enantioselection with styrene and Cu-**7** is insignificant (36 %ee, entry 8), and therefore the two sets of ligands **1-3** and **6-7** are complementary : high selectivity can be achieved for most types of olefins by properly selecting a ligand from either set.[10]

Table 2. Cyclopropanation of Cis-di- and Trisubstituted Olefins with Ligand **7**.

Entry	Olefin	R in **9**	Yield[a]	Diastereoselectivity[b] (Trans : Cis)	Enantioselectivity Trans	Cis
1	cis-4,4-dimethyl-2-pentene	*l*-menthyl	75%	88 : 12	95[c]	80[c]
2	cis-1-phenylpropene	*l*-menthyl	72%	88 : 12	92[c]	76[c]
3	ethylidenecyclohexane	*l*-menthyl	54%	86 : 14	82[d]	ND
4	1,1-diphenylpentene	*l*-menthyl	52%	98 : 2	84[c]	ND
5	1,1-dichloro-4-methylpentadiene	*l*-menthyl	60%	88 : 12	92[d]	85[d]
6		DMP	60%	97 : 3	92[d]	ND
7		DCM	62%	99 : 1	92[d]	ND
8	styrene	DCM	82%	94 : 6	36[d]	20[d]

(a) Isolated after basic workup and column chromatography. (b) Determined by capillary GLC at a constant temperature, ranging from 120 °C to 195 °C. (c) Determined by capillary GLC of the R(-)-octyl ester (see ref. 6). (d) Determined by capillary GLC of the *l*-menthyl ester (see ref 6).

In addition to this unique complementarity, Tables 1 and 2 demonstrate several features consistent with earlier observations: 1) trans/cis ratios depend almost exclusively on the structures of the olefin and the R group in **9**, but not on the structure of the catalyst, 2) cis-olefins retain their stereochemical integrity, and 3) the absolute configurations of the C(1) centers in the trans- and cis-cyclopropane products are the same.[3] These facts must be taken into account in formulating the reaction mechanism of asymmetric cyclopropanation, which is currently under investigation.[11]

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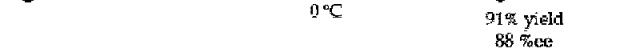
References and Footnotes

1. Lowenthal, R. E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1990**, *31*, 6005 and references cited therein.
2. (a) Evans, D. A.; Woerpel, K. A.; Hinman, M. M.; Faul, M. M. *J. Am. Chem. Soc.* **1991**, *113*, 726 and references cited therein. (b) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am.*

Chem. Soc. **1991**, *113*, 729. (c) Müller, D.; Umbricht, G.; Weber, B.; Pfaltz, A. *Helv. Chim. Acta.* **1991**, *74*, 232. (d) Helmchen, G.; Krotz, A.; Ganz, K.-T.; Hansen, D. *Synlett* **1991**, 257. (e) Hall, J.; Lehn, J.-M.; DeCian, A.; Fischer, J. *Helv. Chim. Acta.* **1991**, *74*, 1. (f) Bolm, C. *Angew. Chem.* **1991**, *103*, 556.

3. In our previous report (ref. 1) the reported absolute configuration of the minor cis-isomer (Table 1) should be (1R, 2S) for complex **1a** (derived from ligand (-)-1). This typographical error was evident from the absolute configuration of the major trans-isomer which was correctly reported as (1R, 2R).
4. (a) Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Tetrahedron Lett.* **1975**, 1707. (b) Aratani, T; Yoneyoshi, Y.; Nagase, T. *Tetrahedron Lett.* **1977**, 2599. (c) Aratani, T.; Yoneyoshi, Y.; Nagase, T. *Tetrahedron Lett.* **1982**, *23*, 685. (d) Aratani, T. *Pure and Appl. Chem.* **1985**, *57*, 1839 and references cited therein.
5. The $CuClO_4(CH_3CN)_4$ (17.9 mg, 0.055 mmol) was weighed out into a 25 ml round bottom flask and vacuum dried for 1 h, periodically warming with a heatgun to dry. After addition of 10 ml CH_2Cl_2 under argon, **7** (26.4 mg, 0.058 mmol) in 2.5 ml CH_2Cl_2 was added dropwise to give a colorless solution which , after 30 min, was filtered into a 50 ml flask containing 2,5-dimethyl-2,4-hexadiene (7.75 ml, 55 mmol) in 5 ml CH_2Cl_2 under argon. A solution of DCM-9 (1.45 g, 5.5 mmol) in 5 ml CH_2Cl_2 was added dropwise by syringe pump over a 2 h period (this solution was often prefiltered through dry alumina to ensure removal of H_2O) at 0 °C. The mixture was allowed to warm slowly to 23 °C and stirred an additional 12 h. The green mixture was filtered with 10% EtOAc/hexane through a short path chromatography column containing 5 g of silica gel to remove the catalyst. Evaporation of solvent and excess olefin provided a pale yellow residue which was purified by bulb to bulb distillation (0.01 Torr) to provide the product as a white solid, 1.48 g (78%). (Some results reported were obtained using CuOTf or Cu(II) and were carried out in a manner consistant with previously reported conditions; ref. 1 and 2).
6. For complete details on separation by GLC see: Murano, A. *Agr. Biol. Chem.* **1972**, *36*, 2203. Separation of products from Table **2** were carried out at a constant temperature, ranging from 110 °C to 195 °C depending on molecular weight.
7. (a) Dötz, K. H. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 587. (b) Doyle, M. P. *Chem Rev.* **1986**, *86*, 919. (c) Brookhart, M.; Studabaker, W. B. *Chem. Rev.* **1987**, *87*, 411. (d) Fritschi, H.; Leutenegger, U.; Pfaltz, A.; Keller, W.; Kratky, C. *Helv. Chim. Acta* **1988**, *71*, 1553.
8. Doyle, M. P.; Bagheri, V.; Wandless, T. J.; Harn, N. K.; Brinker, D. A.; Eagle, C. T.; Loh, K.-L. *J. Am. Chem. Soc.* **1990**, *112*, 1906.
9. Selective base hydrolysis with NaOH in ethanol provides chrysanthemic acid with >100:1 trans/cis ratio in 84% yield.
10. Reaction of DCM-9 with styrene in the presence of the ligand **3**·Cu(I) complex was also found to provide the cyclopropane products in 84% yield and 99 %ee with a 94:6 trans/cis ratio. This product could be selectively hydrolyzed under basic conditions to the corresponding acid with >150:1 trans/cis selectivity in 90% yield.
11. In conjunction with cyclopropanation, catalytic aziridination is being examined, the ligand **3**·CuOTf complex catalyzes the reaction of styrene with tosyliminoiodobenzene, giving the tosylaziridine product in 91% yield with an 88 %ee (cf. ref. 2a). Further work is continuing to improve this enantioselectivity utilizing other reagents, olefins, and ligands.



91% yield
88 %ee

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