ORGANIC
LETTERS

2000
Vol. 2, No. 7
933−936

A New Catalytic and Enantioselective Desymmetrization of Symmetrical Methylidene Cycloalkene Oxides

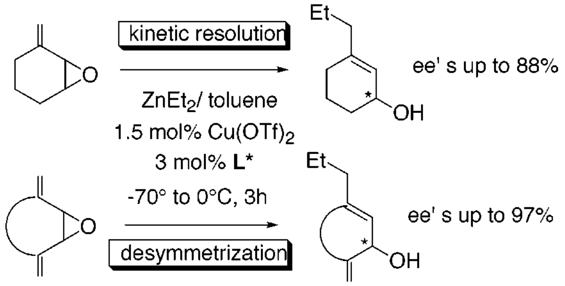
**Fabio Bertozzi,[†] Paolo Crotti,[†] Franco Macchia,[†] Mauro Pineschi,*,[†]
Alexander Arnold,[‡] and Ben L. Feringa*,[‡]**

*Dipartimento di Chimica Bioorganica e Biofarmacia, Via Bonanno 33,
Università di Pisa, 56126 Pisa, Italy, and Department of Organic and
Molecular Inorganic Chemistry, University of Groningen, Nijenborgh 4,
NL9747 AG Groningen, The Netherlands*

pineschi@farm.unipi.it

Received January 26, 2000

ABSTRACT



Chiral copper complexes of C_2-symmetrical phosphoroamidites were found to be highly effective catalysts for both kinetic resolution and novel desymmetrization reactions of new methylidene epoxycycloalkanes.

Desymmetrization of a symmetrical molecule to yield an enantiomerically enriched product is certainly a topic of current interest. One area where examples of desymmetrization reactions are scarce is the catalytic enantioselective construction of C−C bonds.[1] The enantioselective desymmetrization of achiral *meso*-epoxides is an attractive way of creating new stereogenic centers.[2] While there are several examples of desymmetrization of *meso*-epoxides by enantioselective opening with heteronucleophiles[3] and by enantioselective deprotonation,[4] there are few reports that deal with the enantioselective nucleophilic ring opening of commercially available *meso*-epoxides by organometallic reagents. In the latter case, there are few examples where aryl organolithium reagents were always employed, and moderate-to-good enantioselectivities were obtained both under stoichiometric[5] and catalytic[6] conditions. We recently reported an unprecedented catalytic enantioselective addition of dialkylzinc reagents to racemic 1,3-cycloalkadiene monoepoxides.[7] This new methodology, in which the focus was on kinetic resolution aiming at the formation of allylic

---

[†] Università di Pisa.

[‡] University of Groningen.

(1) For a recent review of enantioselective desymmetrization reactions, see: Willis, M. C. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1765.

(2) For a review, see: Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361.

(3) For leading references, see: (a) Martinez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1995**, *117*, 5897. (b) Wu, M. H.; Hansen, K. B.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl*. **1999**, *38*, 2012. (c) Cole, B. M.; Shimizu K. D.; Kruger, C. A.; Harrity, J. P. A.; Snapper, M.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 1668. (d) Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc*. **1997**, *119*, 4783. (e) Denmark, S. C.; Barsanti, P. L.; Wong, K.-T.; Stavenger, R. A. *J. Org. Chem*. **1998**, *63*, 2428.

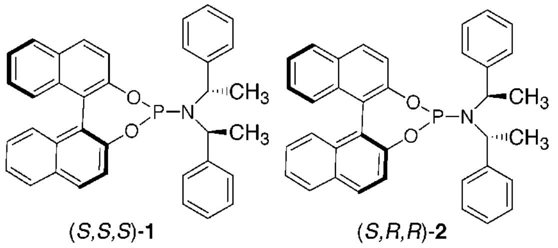
(4) Södergren, M. J.; Andersson, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 10760 and references therein.

(5) (a) Mizuno, M.; Kanai, M.; Iida, A.; Tomioka, K. *Tetrahedron* **1997**, *53*, 10699. (b) Alexakis, A.; Vrancken, E.; Mangeney, P. *Synlett* **1998**, 1165.

(6) For the unique example of a catalytic desymmetrization of cyclohexene and cyclopentene oxides with phenyllithium, see: Oguni, N.; Miyagi, Y.; Itoh, K. *Tetrahedron Lett.* **1998**, *39*, 9023.

10.1021/ol005584o CCC: $19.00

alcohols, was based on a novel $Cu(OTf)_2$−phosporamide catalyst discovered by Feringa et al.[8] We subsequently examined other racemic vinyloxiranes and screened potential phosphoroamidite ligands for this new catalytic enantioselective reaction. In the present paper, we report that the chiral Cu(II) complex with ligand **1** (Figure 1) is a highly effective catalyst for the addition of diethylzinc to both racemic and *meso*-methylidenecycloalkane epoxides.

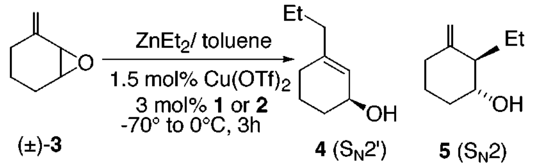


(*S*,*S*,*S*)-**1** (*S*,*R*,*R*)-**2**

Figure 1. Phosphoroamidites **1** and **2** used as chiral ligands.

Initial experiments revealed that the addition of Et_2Zn to racemic methylidene cycloalkane epoxide **3** was greatly accelerated[9] by the presence of a catalytic amount (1.5 mol %) of $Cu(OTf)_2$ and phosphoramidites **1** or **2** (3 mol %) (see Figure 1 and Table 1).

Table 1. Enantioselective Conjugate Addition of Diethylzinc to Racemic Epoxide **3** Catalyzed by $Cu(OTf)_2$/L* (Kinetic Resolution Protocol)[a]



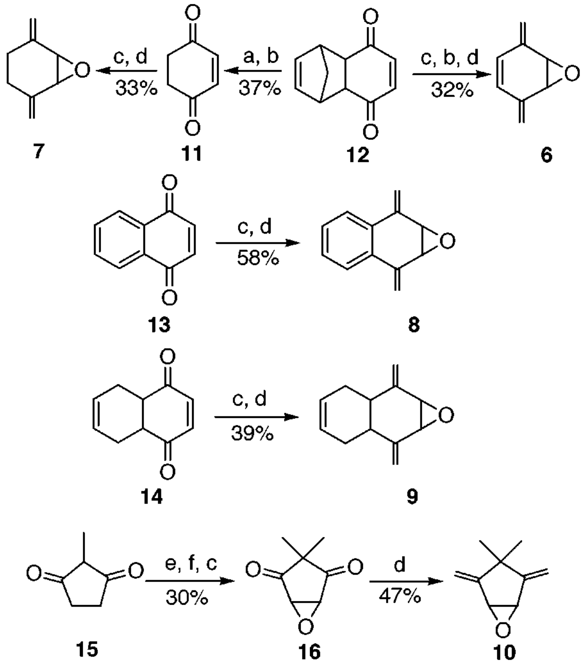
entry	L*	yield[b] (%)	ee[c] (%)	S_N2'/S_N2[d]
1	**1**	89 (**4**)	88 [*S*-(**4**)]	97/3
2	**2**	76 (**4**)	85 [*S*-(**4**)]	85/15

[a] All reactions were run as described in ref 10 (0.50 equiv of Et_2Zn). [b] Isolated yield of allylic alcohol **4** based on the reacted substrate (substrate conversion 50% ± 5). [c] Determined by GC analysis of the crude reaction mixture using a chiral column. For the determination of the absolute configuration of the major enantiomer, see the Supporting Information. [d] Composition determined by NMR and GC capillary analysis of the crude reaction mixture.

The so-called *mismatched* ligand[11] **1**, derived from (*S*)-Binol and (*S*)-bis-phenylethylamine and, therefore, diastereomeric with respect to **2**, was superior to the latter in terms of enantioselectivity and efficiency when methylidenecycloalkane epoxide **3** was employed: the corresponding allylic alcohol **4**, derived from a conjugate addition pathway (S_N2') (Table 1), was obtained with an increased regio- and enantioselectivity with respect to **2**. Encouraged by these preliminary results, we were intrigued by the possibility of the addition of dialkylzinc reagents to the enantiotopic faces of a prochiral symmetrical epoxide, thus avoiding the inherent limitations of a kinetic resolution process.

The unknown epoxides **6**−**10**, bearing enantiotopic methylidene moieties in an allylic position with respect to the endocyclic oxirane ring, were therefore synthesized (Scheme 1). Vinyloxiranes **6**−**10** were prepared from the corresponding enediones **12**−**14**[12] and **16** by oxidation with H_2O_2 in the presence of Na_2CO_3 and subsequent Wittig olefination with $MePPh_3Br$ in LDA/THF. The synthesis of conjugate triene epoxide **6** was similarly obtained after vacuum pyrolysis of the corresponding Diels−Alder adduct **12**, previously treated with alkaline H_2O_2.[13]

Scheme 1. Synthesis of Substrates[a]



[a] Reagents and conditions: (a) Zn dust, CH_3COOH, H_2O, rt, 1 h, 82%; (b) pyrolysis at 1 mmHg, 45−90%; (c) H_2O_2 (30%v/v), Na_2CO_3 (20% in H_2O), acetone, 0 °C to rt, 2 h, 70−90%; (d) LDA, $MePPh_3Br$, THF, 0 °C to rt, 0−45−1.5 h, 39−77%; (e) KOH, CH_3I, dioxane−H_2O, 18 h, 51%; (f) NBS, CCl_4, *hν*, 74%.

We began our study with symmetrical epoxide **8**, which was treated with Et_2Zn in the presence of a catalytic amount of chiral ligand **2** (3 mol %) and $Cu(OTf)_2$ (1.5 mol %) to

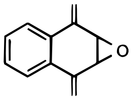
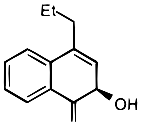
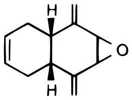
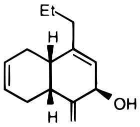
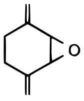
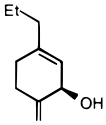
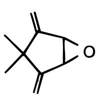
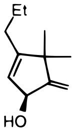
---

(7) Badalassi, F.; Crotti, P.; Macchia, F.; Pineschi, M.; Arnold, A.; Feringa, B. L. *Tetrahedron Lett.* **1998**, *39*, 7795.

(8) (a) de Vries, A. H. M.; Meetsma, A.; Feringa, B. L. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2374. (b) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620. (c) Krause, N. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 283. (d) Imbos, R.; Brilman, M. H. G.; Pineschi, M.; Feringa, B. L. *Org. Lett.* **1999**, *1*, 623. (e) Naasz, R.; Arnold, L. A.; Pineschi, M.; Keller, E.; Feringa, B. L. *J. Am. Chem. Soc.* **1999**, *121*, 1104.

(9) The corresponding blank reactions performed without the chiral ligands gave a complex reaction mixture containing adducts **4** and **5** in a 1:1 ratio. For a review of ligand-accelerated catalysis, see: Berrisford, D. J.; Bolm, C.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1059.

Table 2. Enantioselective Desymmetrization by Conjugate Addition of Diethylzinc to Vinyloxiranes **7**−**10** Catalyzed by Cu(OTf)$_2$/L*[a]

Entry	substrate	L*	yield (%)[b]	ee (%)[c]	S$_N$2'-product	S$_N$2'/S$_N$2[d]
1	 **8**	2	86	37	 **17**	98/2
2		1	92	66		>99/1
3	 **9**	1	78	71[e]	 **18**	93/7
4	 **7**	1	90	97	 **19**	98/2
5	 **10**	1	80	85	 **20**	87/13
6		2	68	76		75/25

[a] All reactions were run as described in ref 10. [b] Isolated yield of allylic alcohols **17**−**20** after chromatographic purification (SiO$_2$). [c] Determined by GC analysis of the crude reaction mixture or HPLC analysis after chromatographic purification (SiO$_2$), using chiral columns (see the Supporting Information). See also ref c of Table 1. [d] Composition determined by NMR and GC capillary analysis of the crude reaction mixture. [e] Determined by HPLC and ^{1}H NMR analysis of the corresponding (*R*)-MTPA ester.

obtain the corresponding conjugate addition product **17** with an 86% yield and a low ee of 37% (Table 2, entry 1). In agreement with our initial observation (see Table 1), **17** was obtained (92% yield) with an excellent regioselectivity and an increased enantioselectivity when chiral ligand **1** was used (Table 2, entry 2).

Triene epoxide **9** gave the corresponding addition product **18** with a similar enantioselectivity, but with a decrease in regioselectivity (Table 2, entry 3).

Much to our delight, high selectivities were obtained when the conformationally less constrained vinyloxirane **7** was used. In this case, the addition product, the allylic alcohol **19**, was obtained (90% yield) with a 97% ee and a regioisomeric ratio of 98/2 (Table 2, entry 4). Evidently, in this case, the chiral catalyst's ability to discriminate between the enantiotopic reaction sites is maximized. We can obtain

---

(10) Typical procedure as follows (Table 2, entry 4): A solution of Cu(OTf)$_2$ (2.49 mg, 0.0069 mmol) and **1** (7.5 mg, 0.0138 mmol) in anhydrous toluene (1.5 mL) was stirred at rt for 40 min. The colorless solution was cooled to −70 °C and subsequently mixed with a solution of **7** (56 mg, 0.46 mmol) in toluene (0.5 mL) and with 0.63 mL of Et$_2$Zn (1.1 M solution in toluene). The temperature was allowed to warm slowly to 0 °C (3 h), and the mixture was quenched with saturated aqueous NH$_4$Cl (3.0 mL). Extraction with Et$_2$O and evaporation of the dried (MgSO$_4$) organic phase gave a crude product that was subjected to flash chromatography (SiO$_2$, 8:2 hexanes/EtOAc) to afford (*R*)-(−)-3-propyl-6-methyliden-2-cyclohexen-1-ol (**19**) (63 mg, 90%) as a liquid. $[\alpha]_D = -110$ ($c = 1.0$, CHCl$_3$)]. Enantioselectivity determined by chiral GC (CP-cyclodex-β-column). Following the above typical procedure employing vinyloxirane **8** (Table 2, entry 2), the reaction was performed on a 2 mmol scale (see the Supporting Information).

(11) The terms *matched* and *mismatched* ligands refer to the addition of diethylzinc to 2-cyclohexenone. When these chiral ligands (2.4 mol %) were used as catalysts for this reaction, *(S,S,S)*-**1** afforded 3-ethylcyclohexanone with an 82% yield and 75% ee, while *(S,R,R)*-**2** gave the same product in 95% yield and >98% ee (see ref 8b).

(12) Chapman, D. D.; Musliner, W. J.; Gates, J. W. *J. Chem. Soc. C* **1969**, 124.

(13) Alder, K.; Flock, F. H.; Beumling, H. *Chem. Ber*. **1960**, *93*, 1896.

easy access to a vast array of enantioenriched cyclohexyl derivatives by considering the following: (a) easy and cheap synthesis of the starting material **7**,[12] (b) the multifunctional nature of **19**, (c) the potential versatility of dialkylzinc reagents,[14] and (d) possible exploitation of O-directed processes.[15]

The conjugate triene epoxide **6** was found not to be a suitable substrate for our reaction, as it afforded a complex reaction mixture of unidentified products (data not reported).

Finally, the symmetrical five-membered vinyl oxirane **10** afforded the corresponding conjugate adduct **20** with an ee of 85% and a regioisomeric ratio of 87/13 when chiral ligand **1** was used (Table 2, entry 5). Also with this substrate, the copper complex with chiral ligand **2** proved to be a less selective catalyst, affording **20** with a 76% ee and a modest 3:1 regiosomeric ratio (Table 2, entry 6).

In conclusion, the present work represents the first report demonstrating a successful combination of an organometallic reagent and an external chiral ligand in a novel catalytic desymmetrization protocol for the nucleophilic displacement of new symmetrical vinyloxiranes. On the basis of these findings, a new catalytic method employing organozinc reagents has been developed to prepare several enantioenriched allylic alcohols by formation of a C−C bond.

Acknowledgment. This work was partly supported by the Consiglio Nazionale delle Ricerche (CNR) and by the University of Pisa. One of us (P.C.) gratefully acknowledges Merck for the generous financial support deriving from the 1999 ADP Chemistry Award.

Supporting Information Available: Text giving experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http:/pubs.acs.org.

OL005584O

---

(14) For a recent review of organozinc-mediated reactions, see: Knochel, P.; Almena Perea, J. J.; Jones, P. *Tetrahedron* **1998**, *54*, 8275.

(15) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.