

# A New Catalytic and Enantioselective Desymmetrization of Symmetrical Methylidene Cycloalkene Oxides

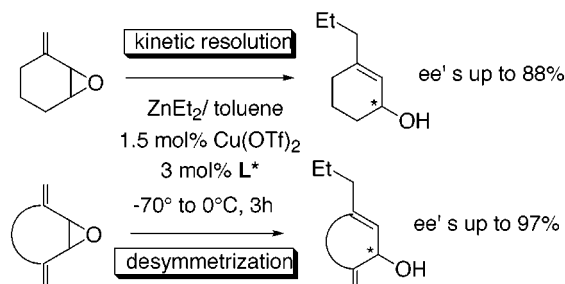
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## ABSTRACT



Chiral copper complexes of C<sub>2</sub>-symmetrical phosphoramidites were found to be highly effective catalysts for both kinetic resolution and novel desymmetrization reactions of new methylidene epoxy cycloalkanes.

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.<sup>1</sup> The enantioselective desymmetrization of achiral *meso*-epoxides is an attractive way of creating new stereogenic centers.<sup>2</sup> While there are several examples of desymmetrization of *meso*-epoxides by enantioselective opening with heteronucleophiles<sup>3</sup> and by enantioselective deprotonation,<sup>4</sup> 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<sup>5</sup> and catalytic<sup>6</sup> conditions. We recently reported an unprecedented catalytic enantioselective addition of dialkylzinc reagents to racemic 1,3-cycloalkadiene monoepoxides.<sup>7</sup> This new methodology, in which the focus was on kinetic resolution aiming at the formation of allylic

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(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.

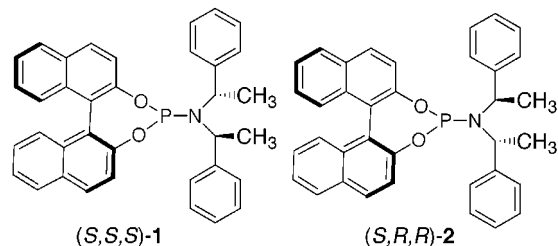
P. A.; Snapper, M.; Hoveyda, A. H. *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 1668. (d) Iida, T.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *J. Am. Chem. Soc.* **1997**, 119, 4783. (e) Denmark, S. C.; Barsanti, P. L.; Wong, K.-T.; Stavenger, R. A. *J. Org. Chem.* **1998**, 63, 2428.

(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.

alcohols, was based on a novel  $\text{Cu}(\text{OTf})_2$ -phosphoramidate catalyst discovered by Feringa et al.<sup>8</sup> We subsequently examined other racemic vinyloxiranes and screened potential phosphoramidite ligands for this new catalytic enantioselective reaction. In the present paper, we report that the chiral  $\text{Cu}(\text{II})$  complex with ligand **1** (Figure 1) is a highly

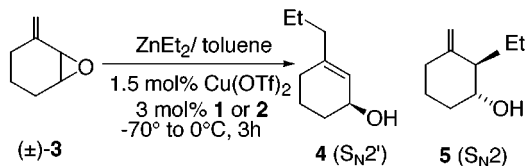


**Figure 1.** Phosphoramidites **1** and **2** used as chiral ligands.

effective catalyst for the addition of diethylzinc to both racemic and *meso*-methylidenecycloalkane epoxides.

Initial experiments revealed that the addition of  $\text{Et}_2\text{Zn}$  to racemic methylidene cycloalkane epoxide **3** was greatly accelerated<sup>9</sup> by the presence of a catalytic amount (1.5 mol %) of  $\text{Cu}(\text{OTf})_2$  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  $\text{Cu}(\text{OTf})_2/\text{L}^*$  (Kinetic Resolution Protocol)<sup>a</sup>



entry	$\text{L}^*$	yield <sup>b</sup> (%)	ee <sup>c</sup> (%)	$\text{S}_{\text{N}}2'/\text{S}_{\text{N}}2^d$
1	<b>1</b>	89 ( <b>4</b> )	88 [ <i>S</i> - <b>4</b> ]	97/3
2	<b>2</b>	76 ( <b>4</b> )	85 [ <i>S</i> - <b>4</b> ]	85/15

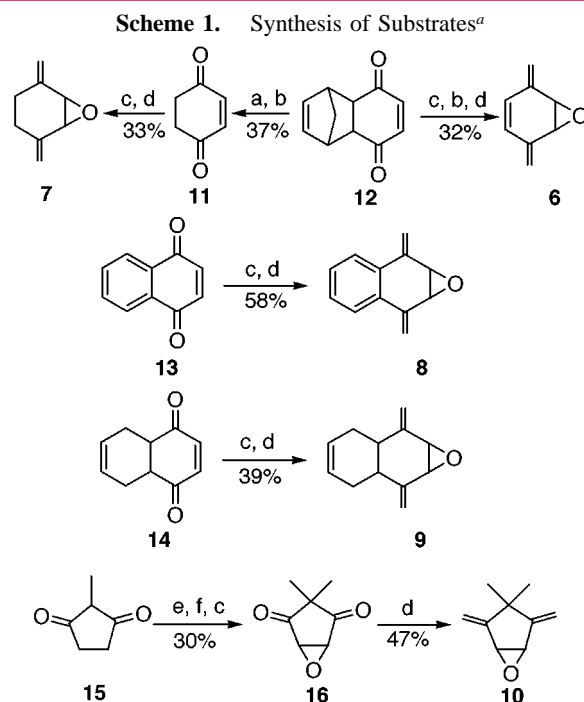
<sup>a</sup> All reactions were run as described in ref 10 (0.50 equiv of  $\text{Et}_2\text{Zn}$ ).  
<sup>b</sup> Isolated yield of allylic alcohol **4** based on the reacted substrate (substrate conversion 50%  $\pm$  5).  
<sup>c</sup> Determined by GC analysis of the crude reaction mixture using a chiral column. For the determination of the absolute configuration of the major enantiomer, see the Supporting Information.  
<sup>d</sup> Composition determined by NMR and GC capillary analysis of the crude reaction mixture.

The so-called *mismatched* ligand<sup>11</sup> **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 ( $\text{S}_{\text{N}}2'$ )

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

(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 correspond-



<sup>a</sup> Reagents and conditions: (a) Zn dust,  $\text{CH}_3\text{COOH}$ ,  $\text{H}_2\text{O}$ , rt, 1 h, 82%; (b) pyrolysis at 1 mmHg, 45–90%; (c)  $\text{H}_2\text{O}_2$  (30% v/v),  $\text{Na}_2\text{CO}_3$  (20% in  $\text{H}_2\text{O}$ ), acetone, 0 °C to rt, 2 h, 70–90%; (d) LDA,  $\text{MePPh}_3\text{Br}$ , THF, 0 °C to rt, 0–45–1.5 h, 39–77%; (e) KOH,  $\text{CH}_3\text{I}$ , dioxane– $\text{H}_2\text{O}$ , 18 h, 51%; (f) NBS,  $\text{CCl}_4$ ,  $h\nu$ , 74%.

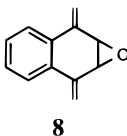
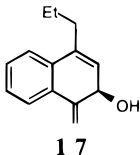
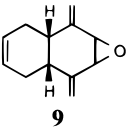
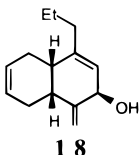
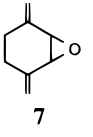
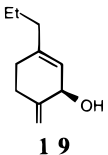
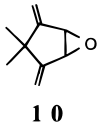
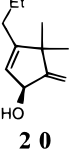
ing enediones **12–14**<sup>12</sup> and **16** by oxidation with  $\text{H}_2\text{O}_2$  in the presence of  $\text{Na}_2\text{CO}_3$  and subsequent Wittig olefination with  $\text{MePPh}_3\text{Br}$  in LDA/THF. The synthesis of conjugate triene epoxide **6** was similarly obtained after vacuum pyrolysis of the corresponding Diels–Alder adduct **12**, previously treated with alkaline  $\text{H}_2\text{O}_2$ .<sup>13</sup>

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

(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.; Brillman, 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)<sub>2</sub>/L<sup>\*a</sup>

Entry	substrate	L <sup>*</sup>	yield (%) <sup>b</sup>	ee (%) <sup>c</sup>	S <sub>N</sub> 2'-product	S <sub>N</sub> 2'/S <sub>N</sub> 2 <sup>d</sup>
1		2	86	37		98/2
2		1	92	66		>99/1
3		1	78	71 <sup>e</sup>		93/7
4		1	90	97		98/2
5		1	80	85		87/13
6		2	68	76		75/25

<sup>a</sup> All reactions were run as described in ref 10. <sup>b</sup> Isolated yield of allylic alcohols **17–20** after chromatographic purification (SiO<sub>2</sub>). <sup>c</sup> Determined by GC analysis of the crude reaction mixture or HPLC analysis after chromatographic purification (SiO<sub>2</sub>), using chiral columns (see the Supporting Information). See also ref c of Table 1. <sup>d</sup> Composition determined by NMR and GC capillary analysis of the crude reaction mixture. <sup>e</sup> Determined by HPLC and <sup>1</sup>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

(10) Typical procedure as follows (Table 2, entry 4): A solution of Cu(OTf)<sub>2</sub> (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<sub>2</sub>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<sub>4</sub>Cl (3.0 mL). Extraction with Et<sub>2</sub>O and evaporation of the dried (MgSO<sub>4</sub>) organic phase gave a crude product that was subjected to flash chromatography (SiO<sub>2</sub>, 8:2 hexanes/EtOAc) to afford (*R*)-(-)-3-propyl-6-methyliden-2-cyclohexen-1-ol (**19**) (63 mg, 90%) as a liquid. [ $\alpha$ ]<sub>D</sub> = -110 (*c* = 1.0, CHCl<sub>3</sub>). Enantioselectivity determined by chiral GC (CP-cyclodex- $\beta$ -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).

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

(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**,<sup>12</sup> (b) the multifunctional nature of **19**, (c) the potential versatility of dialkylzinc reagents,<sup>14</sup> and (d) possible exploitation of O-directed processes.<sup>15</sup>

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 regioisomeric ratio (Table 2, entry 6).

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(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.

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.

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**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>.

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