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A New Catalytic and Enantioselective Desymmetrization of Symmetrical Methylidene Cycloalkene Oxides

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ABSTRACT

Chiral copper complexes of C₂-symmetrical phosphoramidites 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 heteronucleophiles³ 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 stoichiometric⁵ and catalytic⁶ 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

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

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(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.⁸ We subsequently examined other racemic vinylloxiranes 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 Et_2Zn to racemic methylidene cycloalkane epoxide **3** was greatly accelerated⁹ 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)^a

entry	L*	yield ^b (%)	ee ^c (%)	S_N2'/S_N2^d
1	1	89 (4)	88 [<i>S</i> -(4)]	97/3
2	2	76 (4)	85 [<i>S</i> -(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% $\pm$ 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* ligand¹¹ **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')

(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 methylenide moieties in an allylic position with respect to the endocyclic oxirane ring, were therefore synthesized (Scheme 1). Vinylloxiranes **6–10** were prepared from the correspond-

^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 , $h\nu$, 74%.

ing 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

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 $\text{Cu}(\text{OTf})_2$ (1.5 mol %) to

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(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		2	86	37		98/2
2		1	92	66		>99/1
3		1	78	71 ^e		93/7
4		1	90	97		98/2
5		1	80	85		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 (SiO₂). ^c Determined by GC analysis of the crude reaction mixture or HPLC analysis after chromatographic purification (SiO₂), 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 ¹H 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)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 Et₂Zn (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 NH₄Cl (3.0 mL). Extraction with Et₂O and evaporation of the dried (MgSO₄) organic phase gave a crude product that was subjected to flash chromatography (SiO₂, 8:2 hexanes/EtOAc) to afford (*R*)-(-)-3-propyl-6-methyliden-2-cyclohexen-1-ol (**19**) (63 mg, 90%) as a liquid. [α]_D = −110 (*c* = 1.0, CHCl₃). 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).

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**,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 regioisomeric ratio (Table 2, entry 6).

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

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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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