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Catalytic Enantioselective Desymmetrization of COT-Monoepoxide. Maximum Deviation from Coplanarity for an S_N2'-Cuprate Alkylation

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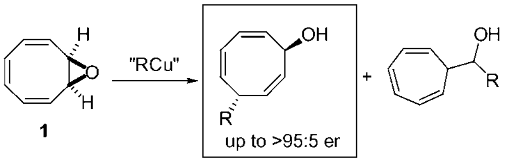
ABSTRACT



“RCu”=RMgX + CuCN or R_2Zn + $Cu(OTf)_2$/L*

The first alkylative and enantioselective ring-opening of COT-monoepoxide (1) without the occurrence of any ring-contraction–isomerization by the use of in situ-formed organocuprates is reported. Because of the particular geometric constraint of compound 1, this work reports the largest deviation from coplanarity between the π-orbital of the double bond and the σ-bond connecting the leaving group ever observed for an S_N2'-cuprate alkylation.

1,3,5,7-Cyclooctatetraene (COT) is a nonaromatic compound that exists in a nonplanar tub form.[1] The corresponding symmetrical monoepoxide **1**, easily obtainable by *m*-CPBA or peracetic acid oxidation of COT, has been known for a long time.[2] There have been several papers indicating the easy isomerization of COT-monoepoxide in reactions with cationic[3] or anionic reagents.[4] On the other hand, there are very few reports dealing with the ring-opening reactions of epoxide **1** with nucleophiles. The reaction of **1** with organometallic nucleophiles was previously investigated in order to determine whether cleavage of the epoxide ring would result in the formation of substituted cyclooctatrienols, but only ring-isomerized products were obtained.[2,5,6] The only reported addition of an alkyl group to **1** without ring contraction makes use of RLi (R = ethyl, *tert*-butyl) in Et_2O and affords 4-alkyl-2,6-cyclooctadien-1-ones through a 1,5-sigmatropic rearrangement.[6,7] We report here a new catalytic alkylation of COT-monoepoxide **1** with hard alkylmetals without any concomitant rearrangement (including hydride shift) of the eight-membered ring. Moreover, a highly enantioselective desymmetrization[8] of **1** with dialkylzinc reagents and chiral copper complexes of phosphoramidite ligands is reported as well.[9]

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[1] For a recent review, see: Klärner, F.-G. *Angew. Chem., Int. Ed.* **2001**, *40*, 3977 and references therein.

[2] Cope, A. C.; Tiffany, B. D. *J. Am. Chem. Soc.* **1951**, *73*, 4158.

[3] (a) Cope, A. C.; Nelson, N. A.; Smith, D. S. *J. Am. Chem. Soc.* **1954**, *76*, 1100. (b) Grigg, R.; Hayes, R.; Sweeney, A. *Chem. Commun.* **1971**, 1248.

[4] Treatment of **1** with LDA constitutes an important synthetic method for preparing 1,3,5-cyclooctatrien-7-one. For a recent review on oxiranyl anions, see: Satoh, T. *Chem. Rev.* **1996**, *96*, 3303.

[5] Matsuda, T.; Sugishita, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 174.

[6] Ogawa, M.; Sugishita, M.; Takagi, M.; Matsuda, T. *Tetrahedron* **1975**, *31*, 299. In particular, the reaction of **1** with Et_2CuLi under various conditions resulted in the formation of polymeric material.

[7] Miller, M. J.; Lyttle, M. H.; Streitwieser, A., Jr. *J. Org. Chem.* **1981**, *46*, 1977.

[8] For reviews, see: (a) Hodgson, D. M.; Gibbs, A. R.; Lee, G. P. *Tetrahedron* **1996**, *52*, 14361. (b) Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; Chapter 35.

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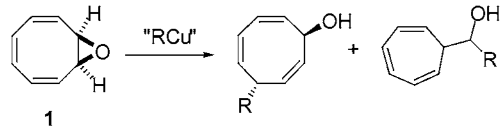
We found dramatic differences in reactivity and selectivity using different sources of organocopper reagents (Table 1).

Table 1. Addition of Organocopper Reagents to COT-Monoepoxide **1**



1

3a, R=Me
3b, R=Et
3c, R=Ph
3d, R=vinyl

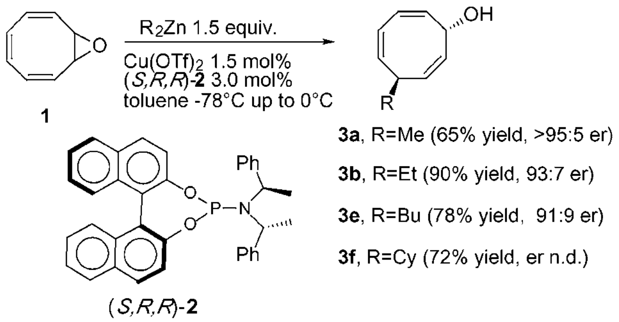
4a, R=Me
4b, R=Et
4c, R=Ph
4d, R=vinyl

entry	"RCu"	conditions	**3**/**4** ratio
1	Me_2CuLi, Et_2O	3 h, 0°C	<2/98
2	MeMgBr/CuCN (cat) Et_2O	2.5 h, 0 °C	62/38
3	MeCuCN(MgBr), THF	1.5 h, 0 °C	>98/2
4	$Me_2CuCN(MgBr)_2$ THF	1.5 h, 0 °C	82/18
5	EtMgBr/CuCN (cat), Et_2O	2 h, 0 °C	94/6
6	PhCuCN(MgBr), THF	24 h, 0 °C	>96/4
7	(vinyl)CuCN(MgBr),THF	24 h, 0 °C	>95/5

The reaction of **1** with 3.0 equiv of Me_2CuLi in Et_2O (3 h at 0 °C) resulted in the formation of the 2,4,6-cycloheptatrienyl methyl carbinol **4a** (70% yield) as the sole product (entry 1).[10] The CuCN-catalyzed[11] addition of MeMgBr (3.0 equiv) afforded as the main reaction product the new *trans*-cyclooctatrienol **3a** (62%), deriving from the epoxide alkylation in the allylic position (S_N2' process) (entry 2). The same product was selectively obtained (88% yield) when a "lower order cuprate"[12] such as MeCuCN(MgBr) was used (entry 3). The use of a "higher order cyanocuprate" $Me_2CuCN(MgBr)_2$ afforded **3a** as the main reaction product together with a minor amount of alcohol **4a** (18%, entry 4). The CuCN-catalyzed addition of EtMgBr afforded **3b** (75% yield) with only a marginal isomerization pathway (ca. 6% of **4b**, entry 5). The addition of phenyl and vinyl cuprates gave a relatively complex mixture of products from which it was possible to isolate the cyclooctatrienols **3c** (40% yield) and **3d** (8% yield), respectively (entries 6 and 7).

A very common method for the in situ generation of organocopper reagents is the use dialkylzinc reagents as primary organometallics and chiral copper complexes as catalysts.[13] Although the Cu(II)-catalyzed reaction of Et_2Zn with **1** afforded 2,4,6-cycloheptatriene-1-carbaldehyde as the main product (ca. 8% conversion after 5 h at 0 °C), the preventive addition of a catalytic amount of Feringa's phosphoramidite[14] (*S*,*R*,*R*)-**2** to the reaction mixture cleanly afforded the corresponding S_N2' addition product **3b** with a high yield (90%) and a 93:7 enantiomeric ratio (er) (Scheme 1).[15] The copper-phosphoramidite-catalyzed addition of Bu_2Zn afforded compound **3e** with 78% yield and a good enantioselectivity (91:9 er). The less reactive Me_2Zn delivered the corresponding S_N2' adduct **3a** (65% yield) with the best enantioselectivity (>95:5 er), and the use of dicyclohexylzinc gave a good yield of the corresponding product **3f**.[16] Unexpectedly, compounds of type **3** (except for **3d**) showed good stability,[17] although related cyclooctatrienols are very prone to a 1,5-hydride shift to give the corresponding 4-alkyl-cycloocta-2,6-dienones.[7,18]

Scheme 1. Copper-phosphoramidite-Catalyzed Enantioselective Addition of Dialkylzinc Reagents to **1**



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(9) (a) Bertozzi, F.; Crotti, P.; Macchia, F.; Pineschi, M.; Arnold, A.; Feringa, B. L. *Org. Lett.* **2000**, *2*, 933. (b) Bertozzi, F.; Crotti, P.; Del Moro, F.; Feringa, B. L.; Macchia, F.; Pineschi, M. *Chem. Commun.* **2001**, 2606.

(10) Formation of the cycloheptatrienyl alcohols of type **4** is connected with the intermediate formation, through a ring-contraction−isomerization process, of cyclohepta-2,4,6-trienecarbaldehyde, which in turn adds the organometallic reagent.

(11) (a) Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503. (b) Lipshutz, B. H. In *Organometallics in Synthesis*; Schlosser, M., Ed.; John Wiley & Sons, Ltd., Chichester, UK, 1994; p 283. (c) Persson, E. S. M.; van Klaveren, M.; Grove, D. M.; Bäckvall, J.-E.; van Koten, G. *Chem. Eur. J.* **1995**, 351 and pertinent references therein.

(12) In this paper, "lower order cuprate" and "higher order cuprate" terms are used to indicate the 1:1 and 2:1 composition of RMgX and CuCN, respectively. For a review regarding the structure and reactivity of cyanocuprates, see: Krause, N. *Angew. Chem., Int. Ed.* **1999**, *38*, 79. For a recent discussion about the strong influences by the composition of the reagents and the solvent used in a metal-catalyzed addition of Grignard reagents to allylic acetates, see: Ito, M.; Matsuumi, M.; Murugesh, M. G.; Kobayashi, Y. *J. Org. Chem.* **2001**, *66*, 5881 and references therein.

(13) For reviews, see: (a) Nakamura, E.; Mori, S. *Angew. Chem., Int. Ed* **2001**, *39*, 3750. (b) Krause, N.; Hofmann-Röder, A. *Synthesis* **2001**, 171.

(14) For a review, see: Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346.

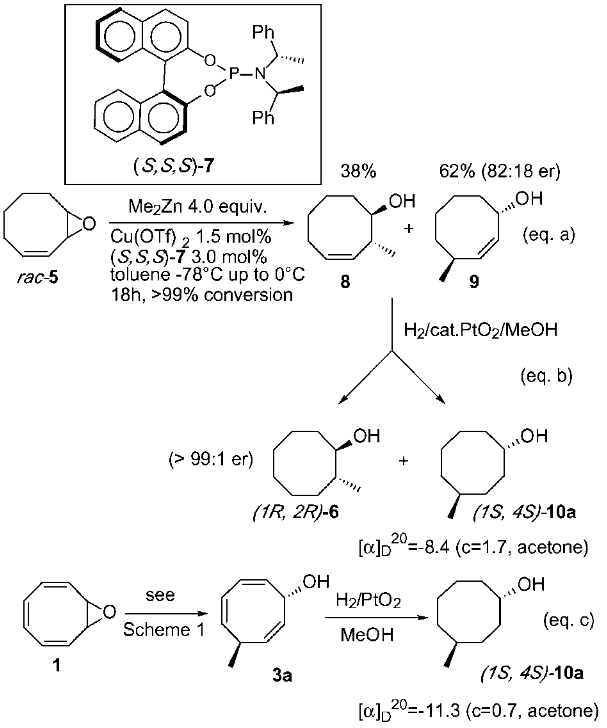
(15) **Typical Procedure: Preparation of 3b.** A solution of $Cu(OTf)_2$ (10.8 mg, 0.03 mmol) and chiral ligand (*S*,*R*,*R*)-**2** (32.2 mg, 0.06 mmmol) in anhydrous toluene (3 mL) was stirred at room temperature for 40 min. The colorless solution was cooled to −78 °C followed by subsequent addition of a solution of **1** (240 mg, 2.0 mmol) in toluene (1 mL). After 5 min, Et_2Zn (2.72 mL of a 1.1 M solution in toluene, 3.0 mmol) was added and the stirred reaction mixture was allowed to warm slowly to 0 °C. After 3 h (>98% conversion), the reaction was quenched with saturated aqueous NH_4Cl solution (5 mL). Extraction with Et_2O (2 × 35 mL) and evaporation of the dried ($MgSO_4$) organic phase afforded a very clean crude mixture (300 mg) consisting only of alcohol **3b** (>90% crude yield) and chiral ligand **2**. Alcohol **3b** was obtained in a pure state as an oil after flash chromatography (195 mg, 65% isolated yield). $R_f = 0.27$ (hexanes/AcOEt 8:2). $[\alpha]^{20}_D$ +277 (*c* 1.0, MeOH). ^1H NMR: δ 6.07−6.17 (m 2H), 5.55−5.61 (m, 1H), 5.15−5.43 (m, 3H), 4.86 (m, 1H, C*H*OH), 2.65−2.75 (m, 1H), 1.51−1.65 (m, 2H), 0.90 (t, 3H, $J = 7.3$ Hz). ^{13}C NMR: δ 133.5, 133.0, 132.6, 131.5, 128.3, 127.0, 70.5, 39.6, 29.6, 12.4. Anal. Calcd for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 78.96; H, 8.76. The enantiomeric ratio (93:7) of **3b** was calculated on the corresponding hydrogenated product **10b** (see Supporting Information).

(16) On the other hand some attempts at arylation using Ph_2Zn afforded mainly the alcohol **4c**. The use of "salt free" divinylzinc (Bussche-Hünnefeld, J. L.; Seebach, D. *Tetrahedron* **1992**, *48*, 5719) gave a complex reaction mixture containing **4d**.

(17) In our hands, it was possible to isolate compounds **3a**,**b**,**c**,**f** by chromatography on SiO_2, albeit with partial decomposition, and to store them for several weeks at +5 °C. However, the corresponding 4-alkyl-cycloocta-2,6-dienones can be quantitatively obtained by vacuum distillation of compounds of type **3**.

The absolute and relative configurations of compounds of type **3** were determined by application of the regiodivergent kinetic resolution (RKR)[19] to racemic 1,3-cyclooctadiene monoepoxide **5** with Me_2Zn catalyzed by $Cu(OTf)_2$/(S,S,S)-**7** (Scheme 2). At complete conversion, the reaction gave a 38:62 inseparable mixture of the regioisomeric alcohols **8**[20] and **9**[21] (eq a). The subsequent catalytic hydrogenation afforded a separable mixture of alcohols **6** and **10a**, in which alcohol **6** has a known absolute configuration (eq b).[22] As a consequence, the regioisomeric alcohol **10a** has the opposite configuration at the carbon atom bearing the hydroxyl group. Comparison of the optical rotation of **10a** obtained with the RKR protocol with respect to the same product **10a** obtained by the desymmetrization of COT-monoepoxide with $Cu(OTf)_2$/(S,R,R)-**2** and subsequent catalytic hydrogenation allowed the complete assignment of the absolute configurations of all the stereocenters (see eq c in Scheme 2 and Supporting Information).[23]

Scheme 2. Determination of Absolute Configurations via Copper-phosphoramidite-Catalyzed RKR of **5**



For the allylic alkylation of a vinyloxirane to occur, a coplanarity between the double bond and the medium plane containing the two oxirane carbons appeared to be necessary for attaining the overlap between the nucleophilic d orbitals of the copper and the π*-orbital of the double bond and of the σ*-orbital of the oxirane moiety (as shown in **A**, Figure 1).[11a,24,25] In the case of COT-monoepoxide, the corresponding dihedral angle is ca. 60° (see arrows in Figure 1).[1] It is noticeable that despite this geometric constraint, an S_N2'-cuprate addition is achieved by the appropriate in situ generation of an organocopper reagent. This is the highest deviation from coplanarity ever observed in an allylic-type alkylation reaction.[26]

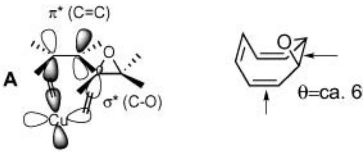


Figure 1. Orbital overlap for S_N2' addition of organocuprates to vinyloxiranes.

Another interesting peculiarity of the ring opening of epoxide **1** is the complete absence of regioisomeric trienic alcohols derived from an S_N2 addition of the organometallic reagent. In this connection, it is worth mentioning that the application of some ring-opening reactions to **1** by some common heteronucleophiles (N_3^-, H_2O, RO^-, RSH) did not afford in any case the corresponding 1,2-addition product. In the (Lewis) acid-promoted reactions, a complex reaction mixture was obtained, whereas under basic conditions, mostly unreacted **1** was recovered.[27]

In conclusion, the present work reports a novel copper-catalyzed allylic-type substitution of COT-monoepoxide with organometallic reagents with complete maintenance of the eight-membered ring and without the occurrence of any rearrangement. Moreover, an unprecedented copper-phosphoramidite-catalyzed alkylative desymmetrization of **1** with dialkylzinc reagents was developed, allowing a simple and

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(18) Gridnev, I. D.; Gurskii, M. E.; Buevich, A. V.; Potapova, T. V.; Bubnov, Y. N. *J. Org. Chem.* **1996**, *61*, 3514.

(19) For the concept and application of the RKR strategy, see: Bertozzi, F.; Crotti, P.; Macchia, F.; Pineschi, M.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 930 and references therein.

(20) Racemic *trans*-homoallylic alcohol **8** can be selectively obtained by the application of the MeLi−BF_3 protocol. See: Alexakis, A.; Vranken, E.; Mangeney, P.; Chemla, F. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3352.

(21) Racemic *trans*-allylic alcohol **9** can be obtained by addition of MeCuCNLi to **5**. See: Penman, K.; Kitching, W.; Tagliavini, G. *Organometallics* **1991**, *10*, 1320.

(22) Danchet, S.; Bigot, C.; Azerad, R. *Tetrahedron: Asymmetry* **1997**, *8*, 1735.

(23) This is a new way to obtain enantiomerically pure 2-alkyl-substituted cyclooctanols. The direct asymmetric ring opening of cyclooctene oxide remains a difficult challenge. For some recent reports, see: (a) Jacobsen, E. N. *Acc. Chem. Res.* **2000**, *33*, 421. (b) Denmark, S. E.; Barsanti, P. A.; Wong, K.-T.; Stavenger, R. A. *J. Org. Chem.* **1998**, *63*, 2428. (c) Denmark, S. E.; Wynn, T.; Jellerichs, B. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 2225.

(24) In general, the prerequisite for an allylic alkylation to occur is the ability of the system to attain a conformation in which the π-orbitals of the double bond and the σ-bond connecting the leaving group are aligned. For example, see: Farthing, C. N.; Kocovsky, P. *J. Am. Chem. Soc.* **1998**, *120*, 6661 and pertinent references therein.

(25) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett.* **1984**, *25*, 3063. For a molecular orbital description of the effect of π-accepting ligands such as cyanide in cuprate reactions, see: Hamon, L.; Levisalles, J. *Tetrahedron* **1989**, *45*, 489.

(26) Maximum deviation tolerated from the perfect alignment seems to be ca. 30° (see ref 24).

(27) The following conventional ring-opening reactions were attempted: NaN_3/NH_4Cl in $MeOH/H_2O$ (9:1); $LiClO_4/NaN_3$ in CH_3CN; NaN_3/DMF; aqueous 0.01 N H_2SO_4; MeONa/MeOH; RSH/NEt_3 in MeOH.

complete stereo- and regioselective formation of 4-substituted cyclooctatrienols not previously described.

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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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