Catalytic Enantioselective Desymmetrization of COT-Monoepoxide. Maximum Deviation from Coplanarity for an $S_N 2'$ -Cuprate Alkylation

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ABSTRACT



"RCu"=RMgX + CuCN or R₂Zn + 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 cationic³ 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 Et₂O and affords 4-alkyl-2,6-cyclooctadien-1-ones through a 1,5sigmatropic 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 desymmetrization⁸ 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.

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



			H +	OH R
		3b, R=Et	4b , R=Et	
		3c, R=Ph 3d, R=vinvl	4c , R=Ph 4d R=vir	ו אר
		ou,	40 , 11–11	iyi
entry	"RCu"		conditions	3/4 ratio
1	Me ₂ CuLi, Et ₂ O		3 h, 0°C	<2/98
2	MeMgBr/CuCN (cat) Et ₂ O		2.5 h, 0 °C	62/38
3	MeCuCN(MgBr), THF		1.5 h, 0 °C	>98/2
4	Me ₂ CuCN(MgBr) ₂ THF		1.5 h, 0 °C	82/18
5	EtMgBr/CuCN (cat), Et ₂ O		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 Me₂CuLi in Et₂O (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-catalyzed¹¹ addition of MeMgBr (3.0 equiv) afforded as the main reaction product the new transcyclooctatrienol 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" Me₂-CuCN(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

(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.

(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.

primary organometallics and chiral copper complexes as catalysts.¹³ Although the Cu(II)-catalyzed reaction of Et₂Zn 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 phosphoramidite¹⁴ (*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 Bu₂-



Zn afforded compound **3e** with 78% yield and a good enantioselectivity (91:9 er). The less reactive Me₂Zn 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}

(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, Et₂Zn (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 NH₄Cl solution (5 mL). Extraction with Et_2O (2 × 35 mL) and evaporation of the dried (MgSO₄) 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, CHOH), 2.65-2.75 (m, 1H), 1.51–1.65 (m, 2H), 0.90 (t, 3H, J = 7.3 Hz). ¹³C 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 C10H14O: 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 Ph₂Zn 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 SiO₂, 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.

^{(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.

⁽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.

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 Me₂Zn catalyzed by Cu(OTf)₂/(*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

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 correspond-



Figure 1. Orbital overlap for $S_N 2'$ addition of organocuprates to vinyloxiranes.

ing 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

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 coppercatalyzed 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

⁽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 McCuCNLi to 5. See: Penman, K.; Kitching, W.; Tagliavini, G. *Organo-metallics* **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/H₂O (9:1); LiClO₄/NaN₃ in CH₃CN; NaN₃/DMF; aqueous 0.01 N H₂SO₄; MeONa/MeOH; RSH/NEt₃ 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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