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Addition of Organocopper Reagents to Cyclic Sulfites or Carbonates of γ,δ-Dihydroxy (*E*)-α,β-Enoates

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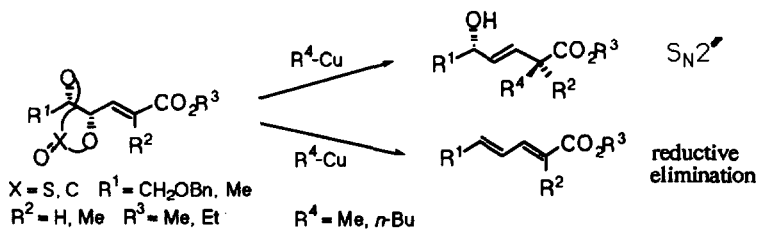
Abstract: Reaction of cyclic sulfites or carbonates of γ,δ-dihydroxy (*E*)-α,β-enoates with $R_2Cu(CN)Li_2$, BF_3; $RCu(CN)Li$, BF_3 (R = Me-, *n*-Bu-) afforded either diastereoselective S_N2' products or reductive elimination product depending on reaction conditions. Addition of $R_2Cu(CN)Li_2$, BF_3 (R = Me-, *n*-Bu-) to cyclic sulfite (**1**) or cyclic carbonate (**3**) (inverse addition) afforded highly regio-, (*E*)-stereo- and diastereoselectively α-alkylation products (**6** and **8**). By using this methodology, (2*S*, 5*S*)-*trans*-2-methyl-5-hexanolide, the pheromone of the carpenter bee *Xylocopa hirutissima* was synthesized.

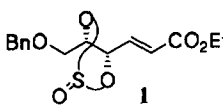
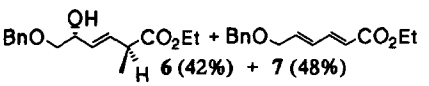
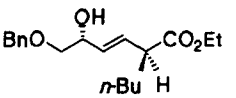
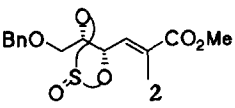
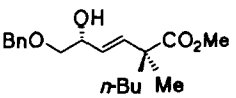
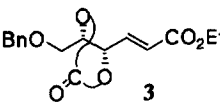
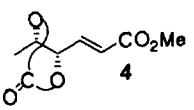
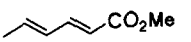
The enantio- or diastereoselective α-alkylation of ester is a useful reaction in organic synthesis. Recently, much attention has been paid to the introduction of alkyl groups at α-position of esters stereoselectively using chiral metal enolates,[2] chiral oxazolines,[3] asymmetric hydrogenation,[4] and asymmetric sigmatropic rearrangements such as Claisen-[5] and Ireland-Claisen[6] rearrangements. Efficient regio-, (*E*)-stereo-, and diastereoselective γ-alkylation by the chirality transfer reactions of γ-mesyloxy (*E*)-α,β-enoates have been developed by Ibuka and Yamamoto.[7] We have explored the reaction of organocopper reagents with cyclic sulfites or carbonates of γ,δ-dihydroxy (*E*)-α,β-unsaturated esters and found that either highly diastereoselective S_N2' products or reductive elimination products could be obtained depending on reaction conditions (Scheme 1).



Scheme 1

The results of the reactions of organocopper reagents with cyclic sulfites or carbonates of γ,δ-dihydroxy (*E*)-α,β-enoates are summarized in Table 1. The cyclic sulfite of γ,δ-dihydroxy (*E*)-α,β-enoate **1** was readily prepared[8] from 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose[9] derived from L-tartaric acid. Addition of the cyclic sulfite **1** to $Me_2Cu(CN)Li_2$(3 equiv); $BF_3{\cdot}OEt_2$(3 equiv) in THF at -78 °C led to the α-alkylated product **6**[10] (42%) and the reductive elimination product **7**[11] (48%) (entry 1). However, addition of $Me_2Cu(CN)Li_2$ (3 equiv); $BF_3{\cdot}OEt_2$(3 equiv) to the cyclic sulfite **1** (inverse addition) afforded the α-methylated ester **6**, the S_N2' addition product, as the sole product (entry 2). The (*E*)-stereochemistry was judged by ^1H NMR and the diastereoselection has been found to be almost exclusive (>99%) by ^1H NMR analysis with $Eu(hfc)_3$ shift reagent. This method appears to be a superior 1,3-chirality transfer to form a new chiral center. It is worthwhile noting that addition of the cyclic sulfite **1** to $Me_2Cu(CN)Li_2$(3 equiv); $BF_3{\cdot}OEt_2$ (6 equiv) afforded the S_N2' addition product **6** (73%) as the major product and the reduction product **7**[12] (16%) as the minor product (entry 3).

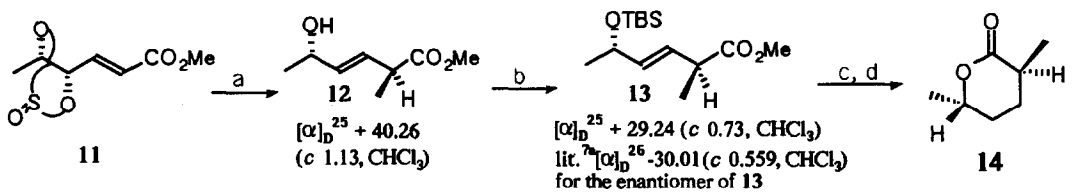
Table 1. Reaction of Organocopper Reagent with Cyclic Sulfite or Cyclic Carbonate of γ,δ-Dihydroxy (*E*)-α,β-Enoates

Entry	Substrate	Reaction Conditions[a]	Products (% yield)[b-e]
1	 **1**	$Me_2Cu(CN)Li_2$ (3); $BF_3{\cdot}OEt_2$ (3)	 **6** (42%) + **7** (48%)
2	**1**	$Me_2Cu(CN)Li_2$ (3); $BF_3{\cdot}OEt_2$ (3) (inverse addition)[f]	**6**[10] (84%)
3	**1**	$Me_2Cu(CN)Li_2$ (3); $BF_3{\cdot}OEt_2$ (6)	**6** (73%) + **7** (16%)
4	**1**	*n*-$Bu_2Cu(CN)Li_2$ (3); $BF_3{\cdot}OEt_2$ (3) (inverse addition)	 **8**[10] (90%)
5	**1**	*n*-BuCu(CN)Li (3); $BF_3{\cdot}OEt_2$ (3) (inverse addition)	**8** (79%)
6	 **2**	*n*-$Bu_2Cu(CN)Li_2$ (3); $BF_3{\cdot}OEt_2$ (3) (inverse addition)	 **9**[10] (72%)
7	 **3**	$Me_2Cu(CN)Li_2$ (3); $BF_3{\cdot}OEt_2$ (3) (inverse addition)	**6** (30%) + **7** (52%)
8	**3**	*n*-$Bu_2Cu(CN)Li_2$ (3); $BF_3{\cdot}OEt_2$ (3) (inverse addition)	**8** (66%)
9	**3**	*n*-$Bu_2Cu(CN)Li_2$ (3)	**7**[11] (75%)
10	 **4**	MeMgBr (3), CuI (10 mol %) $BF_3{\cdot}OEt_2$ (3)	 **10** (82%)

[a] The molar equivalents of the reagents are given in parentheses and a catalytic amount of CuI is represented as mol %. All the reactions were run in dry THF at -78 °C for 30 min. [b] The yields are the isolated yields after column chromatography. [c] By ^1H NMR, the (*E*)-isomers were the exclusive products detected. [d] The diastereoselection of the products **6**, **8**, and **9** has been found to be almost quantitative (>99%) by ^1H NMR analysis with Eu(hfc)$_3$ shift reagent. [e] $[\alpha]_D^{25}$ values: **6**; + 8.71 (*c* 0.82, $CHCl_3$). **8**; +17.14 (*c* 0.35, $CHCl_3$). **9**; -10.0 (*c* 0.30, $CHCl_3$). [f] The typical procedure is illustrated as follows. To a stirred solution of CuCN (102 mg, 1.14 mmol) in dry THF (5 ml) at -78 °C under nitrogen was added MeLi (1.6 ml, 2.2 mmol, 1.4 M in ether) and the mixture was allowed to warm to 0 °C and to stir for 15 min. This solution was cooled to -78 °C again. $BF_3{\cdot}OEt_2$ (0.14 ml, 1.14 mmol) was added and the mixture warmed to 0 °C for 15 min to give a yellow complex. This yellow solution was added slowly to the sulfite **1** (120 mg, 0.36 mmol) in dry THF (3 ml) at -78 °C for 20 min. The reaction mixture was stirred with NH_4Cl solution (2 ml), the THF was evaporated *in vacuo* and then extracted with ether (20 ml). The organic layer was washed with 2 N HCl solution (10 ml), 5% $NaHCO_3$ (10 ml), and brine (10 ml) and then dried over anhydrous magnesium sulfate. The ether layer was evaporated *in vacuo* and the crude product was separated by column chromatography on silica gel using EtOAc/hexanes 1:3 as eluent to afford **6** (86 mg, 84%).

This diastereoselective S_N2' alkylation was also carried out with $(n\text{-Bu})_2Cu(CN)Li_2$; BF_3 and n-BuCu(CN)Li; BF_3 (inverse addition) (entries 4 and 5). For the sulfite **2**, treatment with the higher order cuprate $(n\text{-Bu})_2Cu(CN)Li_2$; BF_3 yielded **9**, which was utilized to introduce a quarternary carbon center at the α-position of the ester group with high optical purity (entry 6). In contrast to the case of the sulfite **1** (entry 2), for the carbonate **3**, the reaction with $Me_2Cu(CN)Li_2$; BF_3 (inverse addition) gave **6** and **7** (entry 7). On the other hand, addition of $(n\text{-Bu})_2Cu(CN)Li_2$; BF_3 to the carbonate **3** (inverse addition) afforded the α-butylated ester **8**[10] as an exclusive product (entry 8). It is notable that addition of $(n\text{-Bu})_2Cu(CN)Li_2$ to **3** without $BF_3{\cdot}OEt_2$ afforded only the reductive decarboxylative elimination product **7**[11] (entry 9). The addition of MeMgBr; $BF_3{\cdot}OEt_2$ (3 equiv) to the carbonate **4**[12] in the presence of CuI (10 mol %) gave **10** as the only isolated product (entry 10).

As an application of this methodology, the sex pheromone of the carpenter bee *Xylocopa hirutissima*, **14**[13], was synthesized,[14] as shown in Scheme 2. The α-alkylated product **12** obtained from **11** by this method was converted to the TBDMS ether **12** and compared with the reported value[7a] of the specific optical rotation for the enantiomer of **13**. To confirm the absolute configuration at the alkylated carbon center, the compound **13** was transformed to the known (2*S*, 5*S*)-*trans*-2-methyl-5-hexanolide **14**, $[\alpha]_D^{25}$ -52.8 (*c* 0.58, $CHCl_3$), [lit.[14a] $[\alpha]_D^{23.6}$ -54.1 (*c* 0.67, $CHCl_3$)].



Scheme 2

Reagents: (a) $Me_2Cu(CN)Li_2$ (3 equiv); $BF_3{\cdot}OEt_2$ (3 equiv), THF, -78 °C, 30 min (87%). (b) TBDMSCl, imidazole, CH_2Cl_2, rt, 24 h (78%). (c) H_2, Rh/Al_2O_3, atmospheric pressure, rt, 24 h. (d) 46% HF, $BF_3{\cdot}OEt_2$, CH_3CN, 0 °C, 6 h (65% overall).

In summary, the reaction of organocopper reagents with cyclic sulfites or carbonates of γ,δ-dihydroxy (*E*)-α,β-unsaturated ester gave either S_N2' product or reductive elimination product depending on reaction conditions. The S_N2' addition of organocuprates to cyclic sulfites or carbonates of γ,δ-dihydroxy (*E*)-enoates described herein seems to be an efficient synthetic route to functionalized chiral α-alkyl (*E*)-β,γ-enoates with remarkably highly regio-, (*E*)-stereo-, and diastereoselectivity.

Acknowledgment. Generous financial support by Korea Science and Engineering Foundation (KOSEF)-the Organic Chemistry Research Center is gratefully acknowledged. We thank Professor K. Mori (The University of Tokyo) for the ^1H NMR spectrum of the carpenter bee pheromone.

References and Notes

1. Research fellow on leave from Samchully Pharm. Co. Ltd.
2. For an excellent review, see: Evans, D. A. In *Asymmetric Synthesis* ; Morrison, J. D., Ed; Academic Press: New York, 1984; Vol. 3, p 1.
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4. (a) For a review, see: Koenig, K. E. In *Asymmetric Synthesis* ; Morrison, J. D. , Ed; Academic Press: New York, 1985; Vol. 5, p 71. (b) Evans, D. A.; Morrissey, M. M.; Dow, R. L. *Tetrahedron Lett.* **1985**, *26*, 6005.
5. For a review, see: Hill, R. K. In *Asymmetric Synthesis* ; Morrison, J. D., Ed; Academic Press: New York, 1984; Vol 3, p 503.

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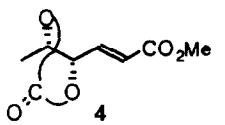
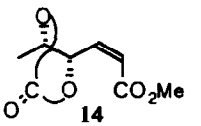
7. (a) Ibuka, T.; Tanaka, M.; Nishii, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4864. (b) Ibuka, T.; Habashita, H.; Otaka, A.; Fujii, N.; Oguchi, Y.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1991**, *56*, 4370 and references therein.
8. The compound 1 was prepared from 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose[9]: (1) $Ph_3P{=}CHCO_2Et$, toluene, reflux, 1 h (85%) (2) 70% aqeous CH_3CO_2H, 60 °C, 3 h (86%) (3) $SOCl_2$, Et_3N, 0 °C, 1 h (90%).
9. Mukaiyama, T.; Suzuki, K.; Yamada, T.; Tabusa, F. *Tetrahedron* **1990**, *46*, 256.
10. Satisfactory spectral and physical data were obtained for all new compounds and are in accord with the assigned structure. Selected spectral data are as follows. **6**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.26 (t and d, 6 H), 2.48 (bs, 1 H), 3.15 (m, 1 H), 3.38 (m, 1 H), 3.55 (m, 1 H), 4.13 (q, 2 H), 4.35 (s, 1 H), 4.58 (s, 2 H), 5.57 (ddd, 1 H, J = 15.6, 5.8, 1.2 Hz), 5.91 (ddd, 1 H, J = 15.6, 8.1, 1.2 Hz), 7.36 (s, 5 H). MS (m/e) 278 (M^+). **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3 H), 1.16-1.43 (m, 7 H), 1.52 (m, 1H), 1.73 (m, 1 H), 2.45 (bs, 1H), 2.98 (m, 1 H), 3.38 (m, 1 H), 3.52 (m, 1 H), 4. 12 (q, 2 H), 4.33 (m, 1 H), 4.56 (s, 2 H), 5.57 (dd, 1 H, J = 15.5, 5.9 Hz), 5.77 (dd, 1 H, J = 15.5, 8.5 Hz), 7.32 (s, 5 H) **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3 H, J = 7.2 Hz), 1.15-1.29 (s and m, 7 H), 1.52 (m, 1 H), 1.70 (m, 1 H), 1.88 (bs, 1 H), 3.37 (dd, 1 H, J = 9.6, 8.1 Hz), 3.52 (dd, 1 H, J = 9.6, 3.6 Hz), 3.66 (s, 3 H), 4.36 (m, 1 H), 4.58 (s, 2 H), 5.48 (dd, 1 H, J = 15.5, 5.9 Hz), 5.98 (dd, 1 H, J = 15.5, 1.5 Hz), 7.35 (bs, 5 H). MS (m/e) 320 (M^+).
11. Data of **7**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, 3 H, J = 7.2 Hz), 4.14 (d, 2 H), 4.21 (q, 2 H, J = 7.2 Hz), 4.55 (s, 2 H), 5.89 (d, 1 H, J = 15.5 Hz), 6.18 (dm, 1 H, J =15.5 Hz), 6.40 (dd, 1 H, J = 15.5, 11.3 Hz), 7.32 (m, 1 H), 7.35 (s, 5 H). IR (neat) 1705 cm^{-1}. MS(m/e, CI) 247 (M^++1), 201, 173, 155, 141, 107 (base peak), 91, 79. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found C, 73.04; H, 7.75.
12. The carbonate **4** was easily separated from the (*Z*)-isomer **14** by column chromatographic separation.



4

(R_f = 0.46, EtOAc/hexanes 1:1)



14

(R_f = 0.53, EtOAc/hexanes 1:1)

13. Wheeler, J. W.; Evans, S. L.; Blum, M. S.; Velthius, H. H. V.; de Camargo, J. M. F. *Tetrahedron Lett.* **1976**, *12*, 4029.
14. Chiral synthesis: (a) Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1979**, *44*, 2169. (b) Mori, K.; Senda, S. *Tetrahedron.* **1985**, *41*, 541. (c) Narasaka, K.; Ukaji, Y. *Chem. Lett.* **1986**, 81. (d) Gerth, D. B.; Giese, B. *J. Org. Chem.* **1986**, *51*, 3726. (e) Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1987**, *28*, 651. (f) Ibuka, T.; Tanaka, M.; Nishii,S.; Yamamoto, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4864. (g) Bernardi, R.; Ghiringhelli, D. *Synthesis.* **1989**, 938.