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HIGHLY REGIO-, (*E*)-STEREO-, AND DIASTEREOSELECTIVE S_N2' ADDITION OF ORGANOCUPRATES TO CHIRAL ALLYLIC CYCLIC CARBONATES

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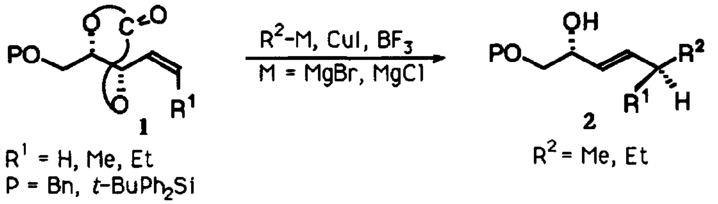
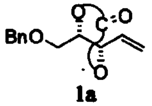
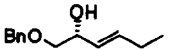
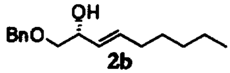
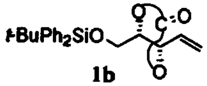
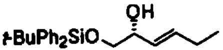
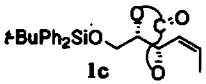
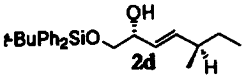
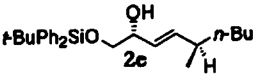
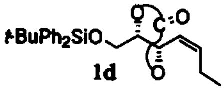
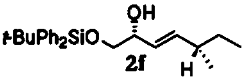
Summary: Reaction of the cyclic carbonates of acyclic vinyl diols with $RCu(CN)Li\cdot BF_3$, $RCu(CN)MgBr\cdot BF_3$, or $RMgBr\cdot CuI$ (cat) in THF at -78 °C proceeded in S_N2' fashion and resulted in the formation of alkylated (*E*)-allylic alcohols with remarkably high diastereoselectivity. This reaction represents an efficient 1, 3-chirality transfer method.

In recent years, intensive studies have been directed to the S_N2' alkylation reactions of allylic derivatives with organocopper reagents from the synthetic point of view.[1, 2] In the literature, anti-S_N2' alkylations were observed in the reactions with allylic carboxylates,[3] allylic sulfonates,[4] and allylic phosphates.[5] Although these processes are very useful in organic synthesis, there still remain difficulties and limitations encountered in each of the known procedures. We have found that the cyclic carbonates 1 underwent excellent regio-, (*E*)-stereo-, and diastereoselective alkylation reactions with a variety of organocopper reagents to form the allylic alcohols 2.



The results of the reactions of 1a-d[6, 7] with organocuprates are listed in Table 1. The carbonate 1a with $MeCu(CN)MgBr\cdot BF_3$, n-$BuCu(CN)Li\cdot BF_3$, or n-$BuMgCl\cdot CuI$ (5 mol %)[8] gave smoothly the (*E*)-allylic alcohols 2a[9] and 2b,[9] respectively, as the sole product (entries 1, 2, and 3).[10] The (*E*)-stereochemistry of the product 2a and 2b was inferred from the ^1H NMR (500 MHz) coupling constants of the two olefinic protons. The higher order cuprate n-$Bu_2Cu(CN)Li_2\cdot BF_3$ in THF or n-Bu_2CuLi gave the product 2b in low yield together with the elimination product.[11] The carbonate 1b with MeMgBr (1.5 equiv), CuI (5 mol %), and BF_3 (1 equiv) yielded 2c[9] (entry 4). For the cyclic carbonate 1c, EtMgBr (2 equiv), $BF_3\cdot Et_2O$ (1 equiv), and CuI (3 mol %) afforded 2d[9] with remarkably high diastereoselectivity (entry 5). Alternatively, the carbonate 1d[7] with MeMgBr (2 equiv), $BF_3\cdot Et_2O$ (1 equiv), and CuI (3 mol %) gave the other alkylated product 2f[9] as an exclusive product (entry 7). The diastereoselection of 2d and 2f has been found to be nearly perfect (>99%) as judged by ^1H NMR analysis with a $Eu(tfc)_3$ shift reagent. It is notable that the reaction of 1d with MeMgBr (2 equiv) and CuI (3 mol %) without $BF_3\cdot Et_2O$ also afforded 2f with the same selectivities (entry 8).

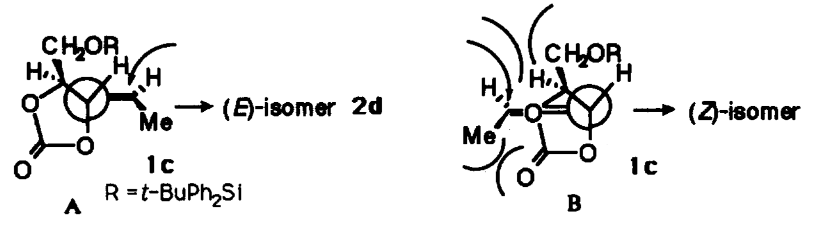
Table 1. Alkylation of acyclic allylic cyclic carbonates with organocuprates

Entry	Substrates	Reagents (mol eq.)	Isolated Yield(%)	Product (diastereoselectivity)	$[\alpha]_D{}^{25}$ values in $CHCl_3$
1	 **1a**	MeMgBr (2), CuCN (1) $BF_3 \cdot Et_2O$ (1)	88	 **2a**	-16.0° (*c* = 0.39)
2	**1a**	*n*-BuLi (1), CuCN (1) $BF_3 \cdot Et_2O$ (1)	85	 **2b**	-15.5° (*c* = 0.33)
3	**1a**	*n*-BuMgCl (2), CuI (5 mol %) THF-Me_2S (20:1)[a]	92	**2b**	-15.0° (*c* = 0.1)
4	 **1b**	MeMgBr (1.5), CuI (5 mol %) $BF_3 \cdot Et_2O$ (1)	87	 **2c**	-7.34° (*c* = 0.40)
5	 **1c**	EtMgBr (2), CuI (3 mol %) $BF_3 \cdot Et_2O$ (1)	84	 **2d** (>99%)	-9.9° (*c* = 0.67)
6	**1c**	*n*-BuMgCl (2), CuI (3 mol %) $BF_3 \cdot Et_2O$ (1)	85	 **2e** (>99%)	-8.25° (*c* = 0.40)
7	 **1d**	MeMgBr (2), CuI (3 mol %) $BF_3 \cdot Et_2O$ (1)	87	 **2f** (>99%)	+8.0° (*c* = 0.15)
8	**1d**	MeMgBr (2), CuI (3 mol %)	83	**2f**	+8.2° (*c* = 0.45)

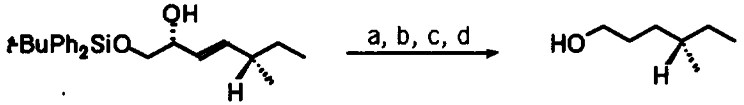
[a] The ratio of volume.

The general procedure is as follows. To a stirred solution of CuI (10 mg, 3 mol %) in dry THF (5 ml) at -78 °C under N_2 was added MeMgBr (1.1 ml, 3.4 mmol, 3.0 M in ether) followed by $BF_3 \cdot Et_2O$ (0.2 ml, 1.7 mmol) in dry THF (5 ml) and then **1d** (700 mg, 1.7 mmol) in dry THF (5 ml). After stirring for 30 min at -78 °C, the reaction was quenched with saturated NH_4Cl solution (2 ml). THF was evaporated and the residue was extracted with ether (30 ml). The ether layer was washed with water (30 ml) and then brine (30 ml). The organic layer was dried over anhydrous magnesium sulfate and evaporated *in vacuo*. The crude product was separated by SiO_2 column chromatography (EtOAc/hexanes 1:3) afforded **2f** (567 mg, 87%).

The stereochemical outcome of these reactions can be explained as follows. The conformer B, which would lead to (*Z*)-isomer, are destabilized in comparison to conformer A, owing to unfavorable interactions between the methyl group and the carbonate group and between the methyl group and the silyloxymethyl group. Consequently, the cuprates presumably attack anti to the carbonate in the conformation A.



The absolute configuration of the newly introduced stereogenic center of 2f was deduced by successive deprotection, and hydrogenation followed by oxidative cleavage and reduction to the known (*S*)-(+)-4-methylhexan-1-ol (3) $[\alpha]_D^{25}$ +6.0° (*c* 0.9, $CHCl_3$) [lit.[12] $[\alpha]_D^{20}$ +6.63° (neat)].



2f 3

Reagents: (a) $(n\text{-Bu})_4NF$, THF, rt, 2 h (96%) (b) H_2, Rh/Al_2O_3, atmospheric pressure, rt, 5h (91%) (c) $NaIO_4$, CH_2Cl_2, silica gel, rt, 1h (88%) (d) LAH, ether, rt, 1 h (93%).

In summary, the method described herein represents a useful S_N2' reaction to create a new carbon center. Main advantages of the present method are: (1) excellent diastereoselective S_N2' substitution on acyclic allylic system; (2) easy preparation of the cyclic carbonate; (3) several organocuprates can be used in S_N2' reaction with these carbonates. The use of the γ-alkylated products in the synthesis of natural products is currently under progress.

Acknowledgment. Generous financial support by Korea Science and Engineering Foundation (KOSEF)- the Organic Chemistry Research Center is gratefully acknowledged.

References and Notes

1. For a comprehensive review, see: Magid, R. M. *Tetrahedron* 1980,*36*, 1901.
2. Review: (a) Yamamoto, Y. *Angew. Chem. Int. Ed. Engl*. 1986,*25*, 947. (b) Lipshutz, B. H. *Synlett* 1990, 119. (c) Nakamura, E, *ibid*. 1991, 539.
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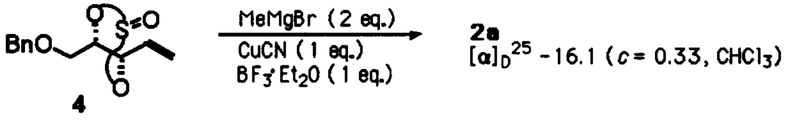
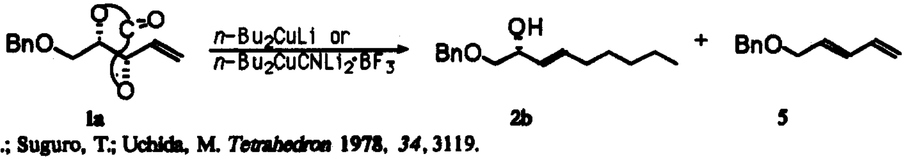
6. The compound **1a** was prepared from 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose: (1) *n*-BuLi, $Ph_3P^+CH_3Br^-$, THF, -10°C→rt, 12 h (78%) (2) Dowex 50WX 8 resin, MeOH, rt, 12 h (92%) (3) $CO(Im)_2$, CH_2Cl_2, rt, 10 min (91%). For the preparation of 4-*O*-benzyl-2,3-*O*-isopropylidene-L-threose, see, Mukaiyama, T.; Suzuki, K.; Yamada, T.; Tabusa, F. *Tetrahedron* **1990**, *46*, 256.
7. The substrates **1b-d** were prepared from (2*S*,3*S*)-2,3-*O*-isopropylidenedioxy-1,4-butanediol: (a) NaH, *t*-$BuPh_2SiCl$, DME, -20 °C, 3 h (91%) (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C, 1 h (91%) (c) *n*-BuLi, $Ph_3P^+CH_2RBr^-$ (R = H, Me, Et), THF, -78 °C, 10 h (R = H-, 92%, Me-, 56% ; R = Et-, 63%) (d) 70% AcOH, 40 °C, 5 h (89%) (e) $CO(Im)_2$, CH_2Cl_2, rt, 10 min (93%). (2*S*,3*S*)-2,3-*O*-Isopropylidenedioxy-1,4-butanediol was prepared by the procedure of Feit. See, Feit, P.W. *J. Med. Chem* . **1964**, *7*, 14.
8. Recent use of this reagent, see: Kawashima, M.; Sato, T.; Fujisawa, T. *Tetrahedron* **1989**, *45*, 403.
9. Satisfactory spectral and physical data were obtained for the new compounds in accord with the structure. Selected physical and spectral data are as follows. **2a**: TLC; SiO_2, EtOAc/hexanes 1:3, R_f= 0.44. ^1H NMR (300 MHz, $CDCl_3$) δ 0.99 (t, 3H, *J* = 7.5 Hz), 2.06 (m, 2H), 3.36 (dd, 1H, *J* = 8.4, 8.4 Hz), 3.52 (dd, 1H, *J* = 6.5, 1.0 Hz), 4.31 (m, 1H), 4.58 (s, 2H), 5.44 (ddd, 1H, *J* = 15, 6, 1 Hz), 5.84 (ddt, 1H, *J* = 15, 6, 1 Hz), 7.36 (s, 5H). IR (neat) 3440, 1660 cm^{-1}. MS (m/e) 206 (M^+), 188, 174, 162, 150, 144, 91 (base peak), 85, 41. **2b**: TLC ; SiO_2, EtOAc/ hexanes 1:3, R_f = 0.64. ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H, *J* = 7.5 Hz), 1.24-1.39 (m, 6H), 2.06 (m, 2H), 3.36 (dd, 1H, *J* = 8.4, 8.4 Hz), 3.50 (dd, 1H, *J* = 6.6, 1 Hz), 4.30 (m, 1H), 4.58 (s, 2H), 5.44 (ddd, *J* = 15, 6.5, 1 Hz), 5.76 (ddt, 1H, *J* = 15, 7.5, 1 Hz), 7.35 (s, 5H). IR (neat) 3400, 1660, 1470, 1380 cm^{-1}. MS (m/e) 206 (M^+), 230, 217, 127, 109, 91 (base peak), 57, 41. **2c**: TLC; SiO_2, EtOAc/hexanes 1:3, R_f= 0.62. ^1H NMR (200 MHz, $CDCl_3$) δ 0.98 (t, 3H, *J* = 7 Hz), 1.08 (s, 9H), 2.08 (m, 1H), 3.46-3.71(m, 2H), 4.10 (m, 1H), 5.35 (dd, 1H, *J* =15.5, 6.5 Hz), 5.61(dd, 1H, *J* = 15.5, 7.5 Hz), 7.38-7.45 (m, 6H), 7.66-7.71 (m, 4H). IR (neat) 3450, 1660 cm^{-1}. **2d** : TLC; SiO_2, EtOAc/hexanes 1:3, R_f = 0.71. ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, 3H, *J* = 7.5 Hz), 0.97 (d, 3H, *J* = 6.9 Hz), 1.10 (s, 9H), 1.27-1.37 (m, 2H), 2.04 (m, 1H), 3.57 (dd, 1H, *J* =11.4, 7.8 Hz), 3.69 (dd, 1H, *J* =10, 3.6 Hz), 4.22 (m, 1H), 5.38 (ddd, 1H, *J* = 15.5, 6.6, 1 Hz), 5.65 (ddd, 1H, *J* = 15.5, 6.6, 1 Hz), 7.69-7.72 (m, 4H), 7.40-7.50 (m, 6H). IR (neat) 3400, 1660 cm^{-1}. MS (m/e) 325 (M^+-*t*Bu), 269, 247, 199 (base peak), 181, 139, 135, 109, 57. **2e**: TLC; SiO_2, EtOAc/hexanes 1:3, R_f = 0.71. ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, 3H, *J* = 7.5 Hz), 0.94 (d, 3H, *J* = 7.5 Hz), 1.08 (s, 9H), 1.22-1.36 (m, 6H), 2.10 (m, 1H), 3.54 (dd, 1H, *J* = 7.5,7.5 Hz), 3.66 (dd, 1H, *J* = 10, 3.6 Hz), 4.22 (m, 1H), 5.36 (dd, *J* = 15.5, 6.5 Hz), 5.64 (dd, *J* = 15.5, 7.5 Hz), 7.38-7.46 (m, 6H), 7.67-7.75 (m, 4H). IR (neat) 3440, 1660 cm^{-1}. **2f**: TLC; SiO_2, EtOAc/ hexanes 1:3, R_f = 0.71. ^1H NMR (200 MHz, $CDCl_3$) δ 0.82 (t, 3H, *J* = 7.5 Hz), 0.96 (d, 3H, *J* = 6.9 Hz), 1.08 (s, 9H), 1.26 (m, 2H), 2.05 (m, 1H), 3.56 (m, 1H), 3.65 (m, 1H), 4.20 (m, 1H), 5.35 (dd, 1H, *J*= 15.5, 6.5 Hz), 5.62 (dd, 1H, *J* = 15.5, 7.5 Hz), 7.38-7.46 (m, 6H), 7.67-7.70 (m, 4H). MS (m/e) 325 (M- *t*Bu), 269, 247, 199 (base peak), 181, 139, 135, 109, 57.
10. The reaction of the cyclic sulfite **4** with MeMgBr•CuCN, in the presence of BF_3·Et_2O also afforded the alkylated (*E*)-allylic alcohol **2a** in 66% yield.



11. Addition of *n*-Bu_2CuLi or *n*-$Bu_2Cu(CN)Li_2$·BF_3 to **1a** gave **2b** along with the diene **5** as the only side product. When *n*-Bu_2CuLi (2 equiv) was used, **2b** (47% yield) and **5** (38% yield) were obtained. In the case of higher order cuprate (*n*-$Bu_2Cu(CN)Li_2$·BF_3), **2b** (43%) and **5** (33%) were isolated by column chromatography.



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