Pergamon

Tetrahedron: Asymmetry Vol. 5, No. 1, pp. 21-22, 1994
Elsevier Science Ltd
Printed in Great Britain
0957-4166/94 \$6.00+0.00

0957-4166(93)E0035-U

Regioselective Addition of Organocopper-Magnesium Reagents to Chiral Dienylic Cyclic Carbonates

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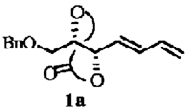
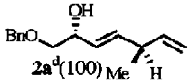
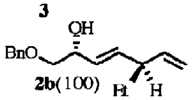
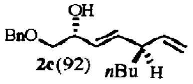
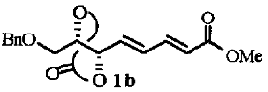
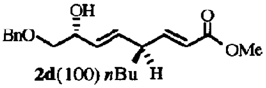
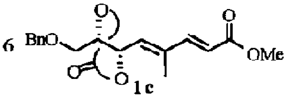
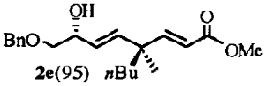
Abstract: Reaction of chiral dienylic cyclic carbonates with dialkylcopper-magnesium complex R_2CuMgX (RMgX : CuI = 2 : 1); $BF_3 \cdot OEt_2$ in THF at -78 °C for 30 min afforded γ-alkylated (*E*)-allylic alcohols with excellent regioselectivity and diastereoselectivity.

The alkylation of dienylic derivatives with organometallic compounds to yield alkadienes has been investigated and it has been reported[1] that reaction of dienyl esters with organocuprates gives three sets of regioisomers, i.e., α-, γ-, and ε- alkylated products with predominant formation of one regioisomer depending on the substrates and reaction conditions. It is of interest to find substrates or conditions for obtaining one regioisomer, exclusively. We have reported diastereoselective S_N2' additions of cuprates to chiral allylic cyclic carbonates.[2] Now we have found that the dienylic cyclic carbonates undergo excellent regioselective and diastereoselective γ-alkylation reactions with organocopper-mediated Grignard reagents to form (*E*)-allylic alcohols.

The results of the reaction of the optically active dienylic cyclic carbonates **1** with R_2CuMgX (3 equiv); $BF_3 \cdot OEt_2$ (1.2 equiv) are summarized in Table 1. The (*E*)-dienylic carbonate **1a** with $Me_2CuMgBr$ (3 equiv); $BF_3 \cdot OEt_2$ (1.2 equiv) in THF at -78 °C gave the (*E*)-allylic alcohol **2a**[3] as a major product along with the triene **3**[3] in the ratio of 5 : 1 (entry 1). Addition of $Et_2CuMgBr$; $BF_3 \cdot OEt_2$ and *n*-$Bu_2CuMgCl$ (3 equiv); $BF_3 \cdot OEt_2$ to **1a** afforded (*E*)-γ-alkylated products **2b**[3] and **2c** as the sole products with high diastereoselectivity (entries 2 and 3). In our hands, addition of *n*-BuMgCl (1.5 equiv); CuI (0.3 equiv), *n*-BuMgCl (1.5 equiv); CuI (0.3 equiv); $BF_3 \cdot OEt_2$ (1.2 equiv) to **1a** gave mixtures of γ-alkylated product and the triene **3**.[4] However, addition of $Me_2CuMgBr$ (3 equiv); $BF_3 \cdot OEt_2$ (1.2 equiv) in toluene as solvent at -78 °C yielded the triene **3** as an exclusive product (entry 4). For carbonate **1b**, *n*-$Bu_2CuMgCl$ (3 equiv); $BF_3 \cdot OEt_2$ (1.2 equiv) gave the γ-alkylated product **2d**[3] as the only product. The diastereoselection of **2d** has been found to be nearly perfect as judged by GLC analysis of the acetate of **2d** (entry 5). It is notable that the reaction of the methyl substituted carbonate **1c** with *n*-$Bu_2CuMgCl$ also afforded **2e**[3] while was introducing a quarternary carbon center (entry 6). The typical procedure is as follows. To a stirred solution of CuI (700 mg, 3.6 mmol) in dry THF (6 mL) at -78 °C under N_2 was added EtMgBr (3.0 M in ether, 2.4 mL, 7.2 mmol) and the mixture was allowed to warm to -30 °C. This solution was cooled to -78 °C again. $BF_3 \cdot OEt_2$ (0.20 mL, 1.8 mmol) was added and then **1a** (320 mg, 1.4 mmol) in dry THF (1 mL) was added and stirred for 30 min at -78 °C. The reaction mixture was quenched with a saturated NH_4Cl solution (2 mL). THF was evaporated and the residue was extracted with ether (30 mL). The ether layer was dried over anhydrous magnesium sulfate and evaporated *in vacuo*. The crude product was separated by SiO_2 column chromatography (EtOAc / hexane 1 : 4, R_f = 0.43) to afforded **2b** (240 mg, 84%).[5]

Table 1. Addition of Organocopper-Magnesium Reagents to Chiral Dienylic Cyclic Carbonates.

Entry	Substrate	Reaction Condition[a] (mol equiv)	Product[b,c] (diastereoselectivity)	Isolated Yield(%)
1	 **1a**	MeMgBr(6) CuI(3), $BF_3 \cdot OEt_2$(1.2) -78 °C, 30 min, THF	 **2a**[d](100)  **3**	83
2	**1a**	EtMgBr(6) CuI(3), $BF_3 \cdot OEt_2$(1.2) -78 °C, 30 min, THF	 **2b**(100)	84
3	**1a**	*n*BuMgCl(6) CuI(3), $BF_3 \cdot OEt_2$(1.2) -78 °C, 30 min, THF	 **2c**(92)	84
4	**1a**	MeMgBr(6) CuI(3), $BF_3 \cdot OEt_2$(1.2) -78 °C, 30 min, toluene	 **3**	86
5	 **1b**	*n*BuMgCl(6) CuI(3), $BF_3 \cdot OEt_2$(1.2) -78 °C, 30 min, THF	 **2d**(100)	75
6	 **1c**	*n*BuMgCl(6) CuI(3), $BF_3 \cdot OEt_2$(1.2) -78 °C, 30 min, THF	 **2e**(95)	91

[a] With $BF_3 \cdot OEt_2$, cleaner products with higher yields were obtained. [b] The diastereoselctivity was determined by GLC analysis of the acetate (column: DB-1, 12 m x 0.25 mm, oven temperature: 250 → 290 °C, carrier gas: N_2, injection temperature: 280 °C). The values of retention times for the acetates were as follows: **2a**: 6.10 min, **2b**: 7.10 min, **2c**: 8.71 min, **2d**: 12.29 min, **2e**: 12.47 min. [c] $[\alpha]^{25}_D$ values in $CHCl_3$. **2a**: -35 (*c* 0.2), **2b**: -20.6 (*c* 0.9), **2c**: -20.1 (*c* 1.0), **2d**: +7.8 (*c* 1.1), **2e**: +2.4 (*c* 0.9). [d] The absolute configuration of the newly introduced stereogenic center of **2a** was correlated to the known (*R*)-(-)-4-methylhexan-1-ol [Rossi, R.; Salvadori, A.; Carpita, A.; Niccoli, A. *Tetrahedron* **1979**, *35*, 2039] by (a) H_2, Rh/Al_2O_3, 1 atm. (b) H_2, $Pd(OH)_2$, 1 atm. (c) $NaIO_4$, silica gel. (d) $LiAlH_4$, ether.

References and Notes

1. (a) Nakanishi, N.; Matsubara, S.; Utimoto, K.; Kozima, S.; Yamaguchi, R. *J. Org. Chem.* **1991**, *56*, 3278. (b) Underiner, T. L.; Goering, H. L. *ibid.* **1990**, *55*, 2757. (c) Underiner, T. L.; Paisley, S. D.; Schmitter, J.; Lesheski, L.; Goering, H. L. *ibid.* **1989**, *54*, 2369. (d) Underiner, T. L.; Goering, H. L. *ibid.* **1988**, *53*, 1140.
2. Kang, S-K.; Lee, D-H.; Sim, H-S.; Lim, J-S. *Tetrahedron Lett.* **1993**, *34*, 91.

3. The spectral data of all the compounds descibed are in agreement with assigned structure. Selected data are as follows. **2a**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (d, 3 H, *J* = 7 Hz), 2.87 (m, 1 H), 3.45 (dd, 1 H, *J* = 11, 4 Hz), 3.55 (dd, 1 H, *J* = 11, 4 Hz), 4.36 (m, 1 H), 4.58 (s, 2 H), 4.95 (m, 2 H), 5.44 (dd, 1 H, *J* = 16, 8 Hz), 5.76 (m, 2 H), 7.28 (m, 5 H), IR(neat): 3450, 1650, 1500, 1450 cm^{-1}. TLC: SiO_2, EtOAc / hexane 1 : 4, R_f = 0.44. **2b**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3 H, *J* = 7Hz), 1.44 (m, 2 H), 2.59 (m, 1 H), 3.50 (dd, 1 H, *J* = 11, 7 Hz), 3.55 (dd, 1 H, *J* = 11, 4 Hz), 4.36 (m, 1 H), 4.56 (s, 2 H), 4.95 (m, 2 H), 5.44 (dd, 1 H, *J* = 16, 8 Hz), 5.76 (m, 2 H), 7.28 (m, 5 H). IR(neat): 3450, 1650, 1500, 1450 cm^{-1}. TLC: SiO_2, EtOAc / hexane 1 : 4, R_f = 0.43. **2d**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3 H, *J* = 7 Hz), 1.28 (m, 6 H), 2.84 (m, 1 H), 3.45 (dd, 1 H, *J* = 11, 7 Hz), 3.55 (dd, 1 H, *J* = 11, 4 Hz), 3.72 (s, 3 H), 4.32 (m, 1 H), 4.56 (s, 2 H), 5.46 (dd, 1 H, *J* = 16, 6 Hz), 5.65 (dd, 1 H, *J* = 16, 8 Hz), 7.28 (m, 5 H). IR(neat): 3450, 1725, 1650, 1493, 1450 cm^{-1}. TLC: SiO_2, EtOAc / hexane 1 : 4, R_f = 0.30. **3**: ^1H NMR (300 MHz, $CDCl_3$) δ 4.08 (d, 2 H, *J* = 7 Hz), 4.51 (s, 2 H), 5.12 (d, 1 H, *J* = 8 Hz), 5.22 (d, 2 H, *J* = 16 Hz), 6.16 (m, 3 H), 7.28 (m, 5 H). IR(neat): 1720, 1265 cm^{-1}. TLC: SiO_2, EtOAc / hexane 1 : 4, R_f = 0.68. **2e**: ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3 H, *J* = 7 Hz), 1.28 (m, 9 H), 3.50 (dd, 1 H, *J* = 11, 7 Hz), 3.55 (dd, 1 H, *J* = 11, 4 Hz), 3.72 (s, 3 H), 4.32 (m, 1 H), 4.56 (s, 2 H), 5.36 (dd, 1 H, *J* = 16, 8 Hz), 5.72 (d, 2 H, *J* = 16 Hz), 6.90 (d, 1 H, *J* = 16 Hz), 7.28 (m, 5 H). IR(neat): 3450, 1725, 1650 cm^{-1}. TLC: SiO_2, EtOAc / hexane 1 : 4, R_f = 0.30.
4. Reaction of *n*BuCu(CN)Li (3 equiv) and *n*-$Bu_2Cu(CN)Li_2$ (3 equiv) with **1a** did not give clean products.

5. Generous financial supprt by KOSEF-OCRC is gratefully acknowledged.

(*Received in Japan* 29 *October* 1993)