Asymmetric Addition of Organometallic Reagents to Homochiral β-Ketoacetals

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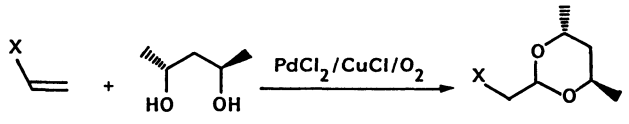
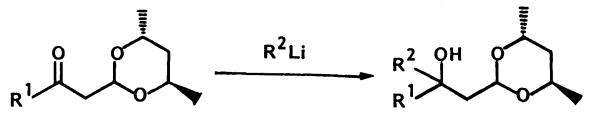
Synopsis. The diastereoselectivity of the carbonyl addition of organolithium reagents to β-keto acetals was examined. Addition of MeLi to β-keto acetal derived from Pd(II)-catalyzed acetalization of phenyl vinyl ketone with (*R*,*R*)-2,4-pentanediol gave (4*R*,6*R*)-4,6-dimethyl-2-[(2*R*)-2-hydroxy-2-phenylpropyl]-1,3-dioxane in 75%de.

We have recently found that terminal olefins bearing electron-withdrawing substituents such as COR, COOR, and CN are regioselectively acetalized at the terminal olefinic carbon with diols by using a catalyst system of $PdCl_2$–CuCl–O_2.[1] The reaction with readily available (*R*,*R*)-2,4-pentanediol gives homochiral acetals having functional groups at the side chain.



X= electron-withdrawing group

Homochiral cyclic acetals derived from (*R*,*R*)-2,4-pentanediol may be regarded as one of the useful precursors for the synthesis of homochiral alcohols. This stems from the basic finding that one of the diastereotopic acetal bonds is stereoselectively cleaved by nucleophiles in the presence of Lewis acids.[2] Described herein is a fundamental reaction using the acetal moiety as the chiral auxiliary, that is the diastereofacial differenciating addition[3] of alkyllithium reagents to β-keto acetal **1** leading to β-hydroxy acetal **2**.

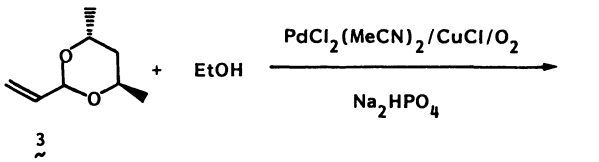


1
a: R^1=Ph
b: R^1=Me
c: R^1=H

2
a: R^1=Ph R^2=Me
b: R^1=Ph R^2=Bu^n
c: R^1=Me R^2=Bu^n
d: R^1=H R^2=Me

Results and Discussion

The keto acetals **1a** and **1b** were prepared by the Pd(II)-catalyzed acetalization of the corresponding vinyl ketones with (*R*,*R*)-2,4-pentanediol. Acetalization of vinyl acetal **3** with ethanol led to bis-acetal **4**, which upon hydrolysis gave the homochiral acetal **1c**.[4] The bis-acetal **4** can be also prepared by partial acetal-exchange reaction of 1,1,3,3-tetraethoxypropane with (*R*,*R*)-2,4-pentanediol.



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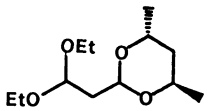
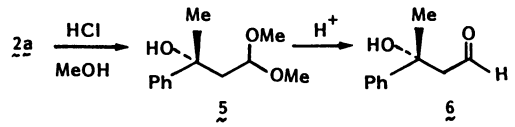


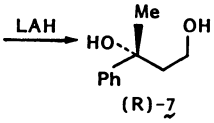
4

Commonyl used organometallic reagents such as RLi and RMgX were allowed to react with the carbonyl group of **1** under various conditions. In contrast to the carbonyl addition to α-keto acetals derived from (+)-tartaric acid,[5] RLi was found to react more selectively than RMgX. Thus, the reaction of **1a** (R=Ph)(5×10^{-2} M, 1 M=1 mol dm^{-3}) with 2 equiv of MeLi at −78 °C in ether gives **2a** as crystals in a relatively high diastereomeric excess (75% de), while the selectivity is extremely low with MeMgI (Table 1, Entries 1 and 2). The alcohol **2a** obtained was purified by recrystallizations to give a single diastereomer. Although the differenciation is significantly dependent on the nature of substituent R at β-carbon and reagents (Table 1, Entries 4—7), it is remarkable that a 75% differenciation is attained with **2a**, in spite of the reaction site being far from the chiral center.

The configuration of newly created chiral center in **2a** was determined to be (*R*) by the following transformations. The acetal exchange of recrystallized **2a** ($[\alpha]_D^{27}$ +22.0°) with methanol followed by hydrolysis (Amberlyst 15, acetone-H_2O) gave β-hydroxy aldehyde **6**, which upon reduction with $LiAlH_4$ afforded *R*-(+)-diol **7** ($[\alpha]_D^{26}$ +65.2°, 97.7% ee) of the known configuration.[6] Of note is that direct hydrolysis of **2a** to **6** by using HCl and *p*-TsOH was unsuccessful.



5 **6**



(R)-**7**

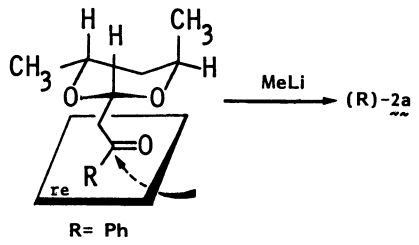
There is no doubt that the 1,3-dioxane **1** is conformationally most stable when the $RCOCH_2$ group at the C-2 carbon is in equatorial. If the C=O group in this moiety occupies the conformation as depicted

Table 1. Addition Reaction of Organometallic Reagents to Keto Acetals **1**

Entry	Acetal **1** R^1		Reagent (equiv)	Product **2** R^1	R^2		Isolated yield/%	de[a]/%
1	Ph	**1a**	MeLi (2.0)	Ph	Me	**2a**	72	75
2	Ph	**1a**	MeMgI (2.0)	Ph	Me	**2a**	82[b]	7
3	Ph	**1a**	MeLi (2.0)/$TiCl_4$ (1.3)	Ph	Me	**2a**	34[b]	42[c]
4	Ph	**1a**	*n*-BuLi (2.5)	Ph	*n*-Bu	**2b**	42	3[d]
5	Me	**1b**	PhLi (2.5)	Me	Ph	**2a**	99	6
6	Me	**1b**	*n*-BuLi (2.8)	Me	*n*-Bu	**2c**	65	3
7	H	**1c**	MeLi (2.5)	H	Me	**2d**	83	55

a) Determined by capillary column GLC analysis. b) Determined by GLC analysis. c) In contrast to Entry 1, the formation of predominant diastereomer was reversed. d) Determined by NMR (FX-100).

in Scheme 1, the backside (*si*-face) of the diastereoplane of **1a** (R=Ph) is obviously less hindered. Coordination of Li to the oxygen atoms and subsequent attack of the methyl anion to the C=O bond from the *si*-face creates (*R*)-chiral carbon in **2a**. If this is the case, the conformational preference of $RCOCH_2$ group is determined by the nature of the substituent R and reagent.



Scheme 1.

Experimental

Preparation of **1a** and **1b** was reported previously.[1] The keto acetal **1b** is also obtained by the reaction of 4-methoxy-3-butene-2-one with (*R,R*)-2,4-pentanediol.[7] Preparation of **1c** was described below.

(4*R*,6*R*)-4,6-Dimethyl-2-ethenyl-1,3-dioxane (3). Into a solution of (*R,R*)-2,4-pentanediol (Wako Pure Chemical Ind.) (1.00 g, 9.60 mmol), acrylaldehyde (1.30 mL, 19.4 mol), and *p*-TsOH (190 mg, 1.0 mmol) in anhydrous ether (20 mL) was added Molecular Sieves 4A (1.0 g). The mixture was stirred for 17 h at room temperature, and filtered. After addition of saturated aqueous $NaHCO_3$ (5 mL), the mixture was extracted with ether and dried ($MgSO_4$). Kugelrohr distillation gave **3** (1.14 g, 84% yield): bp 76—83 °C (64 mmHg); ^1H NMR (60 MHz, $CDCl_3$) δ=1.22 (3H, d, J=6.2 Hz, CH_3), 1.39 (3H, d, J=6.8 Hz, CH_3), 1.57—2.20 (m, 2H, C_5-H), 3.72—4.60 (2H, m, C_4- and C_6-H), 5.05—5.42 (2H, m, H_2C=C), and 5.45—6.20 (2H, m, C=CH and C_2-H); MS *m/z* 141 (M^+-1).

Found: C, 67.40; H, 9.91%. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92%.

(4*R*,6*R*)-4,6-Dimethyl-2-(2,2-diethoxyethyl)-1,3-dioxane (4). i) Pd(II)-Catalyzed Acetalization of 3 with Ethanol. To a test tube were placed a magnetic stirring bar, CuCl (10 mg, 0.10 mmol), Na_2HPO_4 (71 mg, 0.50 mmol), and ethanol (0.36 mL, 6.13 mmol), and there was added a solution of acrylaldehyde acetal **3** (143 mg, 1.00 mmol) and triethyl orthoformate (296 mg, 2.00 mmol) in DME (1 mL) and then $PdCl_2(CH_3CN)_2$ (26 mg, 0.10 mmol). The test tube was placed into an autoclave (10 mL) into which a 10 kg cm^{-2} pressure of O_2 was introduced. After stirring for 24 h at 50 °C, the resulting solution was cooled to room temperature, diluted with ether, and filtered. Florisil column chromatography (2.0 g, 1.5×1 cm) with ether (60 mL) gave oily material (221 mg), from which the product **4** (103 mg, 44%) was isolated by preparative TLC (SiO_2, hexane-EtOAc=7:3). **4**: R_f 0.64; ^1H NMR (500 MHz, $CDCl_3$) δ=1.19 (3H, d, J=6.3 Hz, C_4-Me_{eq}), 1.20 (6H, t, J=7.0 Hz, $-CH_2\underline{CH_3}$), 1.31—1.43 (1H, m, C_5-H), 1.35 (3H, d, J=6.9 Hz, C_6-Me_{ax}), 1.83 (1H, ddd, J=6.3, 11.4, and 13.4 Hz, C_5-H), 1.87 (1H, dt, J=14.1 and 6.7 Hz, $C_{1'}$-H), 1.94 (1H, dt, J=14.1 and 6.7 Hz, $C_{1'}$-H), 3.51 (1H, dq, J=9.7 and 7.0 Hz, $-OC\underline{H_2}CH_3$), 3.53 (1H, dq, J=9.7 and 7.0 Hz, $-OC\underline{H_2}CH_3$), 3.63 (1H, dq, J=9.3 and 7.0 Hz, $-OC\underline{H_2}CH_3$), 3.68 (1H, dq, J=9.3 and 7.0 Hz, $-OC\underline{H_2}CH_3$), 3.95 (1H, ddq, J=2.7, 6.3, and 11.4 Hz, C_6-H_{ax}), 4.28 (1H, dq, J=6.3 and 6.3 Hz, C_4-H_{eq}), 4.67 (1H, t, J=6.7 Hz, $C_{2'}$-H), and 4.96 (1H, t, J=6.7 Hz, -OCHO-); MS *m/z* 231 (M^+-1).

Found: C, 61.81; H, 10.19%. Calcd for $C_{12}H_{24}O_4$: C, 62.04; H, 10.41%.

ii) Partial Acetal Exchange of 1,1,3,3-Tetraethoxypropane with (*R,R*)-2,4-Pentanediol. To a solution of 1,1,3,3-tetraethoxypropane (Nakarai Kagaku) (1.43 g, 6.49 mol) and (*R,R*)-2,4-pentanediol (320 mg, 3.07 mmol) dissolved in THF (6 mL) was slowly added concd H_2SO_4 (10 µl), and the acidic solution was stirred for 4 h at 50 °C. The resulting mixture was neutralized with saturated aqueous $NaHCO_3$ (10 mL×2), and the aqueous layer was extracted with ether. The extract was dried ($MgSO_4$) and evaporated to give oily material (1.351 g), which was subjected into SiO_2 column chromatography (45 g, 17×0.9 cm). Unreacted 1,1,3,3-tetraethoxypropane (0.478 g) was recovered from 210 mL of elution with a 9:1 solution of hexane-EtOAc. Further elution (80 mL) gave **4** (0.520 g, 73%).

In this reaction 2,2'-methylene bis[(4*R*,6*R*)-4,6-dimethyl-1,3-dioxane] was formed as the byproduct.

(4*R*,6*R*)-4,6-Dimethyl-2-(2-oxoethyl)-1,3-dioxane (1c). Into a solution of the acetal **4** (200 mg, 0.86 mmol) in acetone (5 mL) and water (40 µL, 2.2 mmol) was added Amberlyst 15 (10 mg), and the mixture was stirred for 24 h at room temperature and filtered. The product was extracted with ether, dried ($MgSO_4$), and concentrated to give **1c** (75 mg, 55%): ^1H NMR (500 MHz, $CDCl_3$) δ=1.20 (3H, J=6.2 Hz, C_6-Me_{eq}), 1.38 (3H, d, J=6.9 Hz, C_4-Me_{ax}), 1.34—1.38 (1H, m, C_5-H_{eq}), 1.85 (1H, ddd, J=6.2, 11.9, and 13.3 Hz, C_5-H_{ax}), 2.62 (2H, dd, J=2.3 and 4.7 Hz, $C_{1'}$-H), 4.00 (1H, ddq, J=2.3, 11.9, and 6.2 Hz, C_6-H_{ax}), 4.31 (1H, dq, J=6.2 and 6.9 Hz, C_4-H_{eq}), 5.32 (1H, t, J=4.7 Hz, 1H, C_2-H), and 9.79 (1H, t, J=2.3 Hz, HC(O)-); Found: *m/z* 158.0953. Calcd for $C_8H_{14}O_3$: M, 158.0943.

General Procedure for Addition of Organometallic Reagents to Keto Acetal 1. Into a solution of ketoacetal **1** in

ether (5×10^{-2} M) was added organolithium or magnesium reagent (2.0—2.8 equiv) at −78 °C. The concentration of reagent used is as follows; MeLi (1.1 M in ether), Bu^{n}Li (1.5 M in ether), PhLi (0.6 M in ether), and MeMgI (2.3 M in ether). After the above mixture was stirred at −78 °C for 4 h, it was allowed to warm to room temperature, and the product was extracted by usual manner. The diastereomeric excess of crude product was determined by capillary column GLC analysis (base line separation) using SCOT OV-17 capillary column (30 m×0.3 mm, Wako Pure Chemical Ind.) or PEG-20M Bonded (25 m×0.25 mm, Chemical Bonded Column, GASUKURO KOGYO Inc.) with a Shimadzu Model GC-MINI 2, or 100 MHz NMR spectrometer. The results were shown in Table 1, and the spectral and analytical data of products are as follows.

(4*R*,6*R*)-4,6-Dimethyl-2-(2-hydroxy-2-phenylpropyl)-1,3-dioxane (2a). Recrystallization of the product from hexane gave a single diastereomer of **2a** (45% recovery): mp 97—98 °C; IR (neat) 3500 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.08 (3H, d, J=6.9 Hz, C_4-Me$_{ax}$), 1.16 (3H, d, J=6.0 Hz, C_6-Me$_{eq}$), 1.27 (1H, ddd, J=1.2, 2.4, and 13.3 Hz, C_5-H$_{eq}$), 1,15 (3H, s, $C_{2'}$-Me), 1.84 (1H, ddd, J=6.2, 11.8, and 13.3 Hz, C_5-H$_{ax}$), 2.12 (1H, J=8.3 and 14.2 Hz, $C_{1'}$-H), 2.25 (1H, dd, J=3.2 and 14.2 Hz, $C_{1'}$-H), 3.79 (1H, ddq, J=2.4, 11.8, and 6.0 Hz, C_6-H$_{ax}$), 4.29 (1H, ddq, J=1.2, 6.19, and 6.9 Hz, C_4-H$_{eq}$), 4.41 (1H, br s, -OH), 4.60 (1H, dd, J=3.2, and 8.3 Hz, C_2-H), 7.22—7.37 (3H, m, ArH), and 7.44—7.47 (2H, m, ArH); $[\alpha]_D^{27}$ +22.0° (*c* 0.528, $CHCl_3$).

Found: C, 71.75; H, 8.72%. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86%.

(4*R*,6*R*)-4,6-Dimethyl-2-(2-hydroxy-2-phenylhexyl)-1,3-dioxane (2b). R_f 0.47 (SiO_2, hexane-EtOAc=8:2); IR (neat) 3500 and 1140 cm^{-1}; ^{1}H NMR (60 MHz, CCl_4) δ=0.52—1.53 (17H, m, *n*-Bu, C_5-H, and Me), 2.14 (5H, d, J=5 Hz, $C_{1'}$-H), 3.33—4.03 (1H, m, C$\underline{H}$CH$_3$), 4.03—4.53 (1H, m, C$\underline{H}$CH$_3$), 4.30 (1H, s, OH), 4.70 (1H, t, J=5 Hz, C_2-H), 6.90—7.86 (5H, m, ArH).

Found: C, 73.68; H, 9.61%. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65%.

(4*R*,6*R*)-4,6-Dimethyl-2-(2-hydroxy-2-methylhexyl)-1,3-dioxane (2c). Bp 110 °C (3 mmHg); IR (neat) 3550 and 1140 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ=0.87 (3H, m, C$\underline{H}_3$-CH$_2$CH$_2$CH$_2$), 1.1—1.6 (12H, m, C$\underline{H}_3$CH and CH$_3$C$\underline{H}_2$C$\underline{H}_2$-C$\underline{H}_2$), 1.17 (3H, s, -CH$_2$C$\underline{H}_3$), 1.5—2.0 (2H, m, C_5-H), 1.75 (2H, d, J=6.0 Hz, $C_{1'}$-H), 3.12—3.66 (1H, s, O$\underline{H}$), 3.76—4.09 (1H, m, CH$_3$C$\underline{H}$), 4.09—4.46 (1H, m, CH$_3$C$\underline{H}$), 5.14 (1H, t, J=6.0 Hz, C_2-H).

(4*R*,6*R*)-4,6-Dimethyl-2-(2-hydroxypropyl)-1,3-dioxane (2d). R_f 0.63 (SiO_2, hexane-EtOAc=2:8); IR (neat) 3430 and 1140 cm^{-1}; ^{1}H NMR (100 MHz, $CDCl_3$) δ=1.17 (3H, 1d, J=6.0 Hz, CHC$\underline{H}_3$), 1.21 (3H, d, J=6.0 Hz, CHC$\underline{H}_3$), 1.38 (3H, d, J=7.0 Hz, CH(OH)C$\underline{H}_3$), 1.60—2.02 (4H, m, C_5-H and $C_{1'}$-H), 3.24 (1H, br s, O$\underline{H}$), 3.80—4.46 (3H, m, -C$\underline{H}$CH$_3$ and $C_{1'}$-H), 5.08 (1H, t, J=6.0 Hz, C_2-H); MS *m/z* 173 (M^+-1).

Transformation of 2a into 7. Into a solution of **2a** ($[\alpha]_D^{27}$ +22.0°, 0.250 g, 1.00 mmol) in anhydrous methanol (5 mL) was added a solution (10 mL) of methanol saturated with dry HCl. After the solution was stirred for 3.5 h at 50 °C, the acidic solution was neutralized to pH ≈8.5 with 5% aqueous $NaHCO_3$ solution. Usual workup followed by a short path column chromatography (SiO_2, 0.1 g, hexane) gave a mixture (169 mg) of **5**, the starting material **2a**, and 2-phenyl-2,4,4-trimethoxybutane in a ratio of 7:1:1 by NMR. **5**: R_f 0.44 (SiO_2, hexane-EtOAc=7:3); IR (neat) 3450 and 1110 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ=1.50 (3H, s, Me), 1.80 (1H, s, OH), 2.17 (2H, d, J=5.5 Hz, C_3-H), 3.19 (3H, s, OMe), 3.22 (3H, s, OMe), 4.12 (1H, t, J=5.5 Hz, C_4-H), 7.07—7.57 (5H, m, ArH). The above mixture was then dissolved in acetone (3 mL) and water (0.3 mL), into which Amberlyst 15 (30 mg) was added. After stirring for 3 h at 50 °C, the mixture was filtered, extracted with ether, and dried (Na_2SO_4) to give oily material (144 mg) containing **6** in 61% purity (NMR). **6**: ^{1}H NMR (60 MHz, $CDCl_3$) δ=1.67 (3H, s, Me), 2.40 (1H, s, OH), 2.75 (2H, d, J=3 Hz, CH_2), 6.60—7.90 (5H, m, ArH), 9.63 (1H, t, J=3 Hz, CHO); MS *m/z* 163 (M^+-1). The oily material was then dissolved in ether (1.5 mL), into which was added a suspended solution of $LiAlH_4$ (99 mg, 2.6 mmol) in ether (1.5 mL) at 0 °C. The mixture was stirred for 1 h at 0 °C and 3 h at room temperature. Usual workup followed by preparative TLC (SiO_2, chloroform) gave (3*R*)-3-phenyl-1,3-butanediol (**7**) (75 mg, 28% yield from **2a**). The compound **7** was further purified by preparative TLC (SiO_2, chloroform-ether=8:2, R_f=0.39) to give **7** (47 mg) of $[\alpha]_D^{26}$ +65.2° (*c* 0.406, benzene). The $[\alpha]_D$ value corresponds to be 97.7% ee based on the reported maximum rotation ($[\alpha]_D^{26}$ −66.7°).[6] **7**: ^{1}H NMR (100 MHz, $CDCl_3$) δ=1.54 (3H, s, Me), 2.01 (1H, dd, J=4.8 and 0.8 Hz, C_2-H), 2.42 (1H, br s, OH), 3.60 (3H, m, C_1-H and OH), and 7.9—7.4 (5H, m, ArH); IR (neat) 3500 cm^{-1}; MS *m/z* 166 (M^+).

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