Chiral Aryl Grignard Reagents-Generation and Reactions with Carbonyl Compounds

Makoto KAINO, Kazuaki ISHIHARA, and Hisashi YAMAMOTO*
Department of Applied Chemistry, Faculty of Engineering,
Nagoya University, Chikusa, Nagoya 464-01
(Received May 19, 1989)

Synopsis. Chiral aryl Grignard reagents are generated in situ from homochiral 2-halobenzaldehyde acetal, *t*-butyllithium, and magnesium bromide. These reagents react with aromatic aldehydes to moderate diastereoselectivities.

The homochiral acetal method plays an increasingly important role in asymmetric synthesis.[1] We have shown that the Lewis acid catalyzed coupling of homochiral acetals with various nucleophilic organometallic reagents proceeds in a highly diastereoselective manner, ultimately providing a route for generating chiral secondary alcohols in high chemical and optical yields.[2,3] Especially six-membered ring acetals derived from (2*R*,4*R*) or (2*S*,4*S*)-2,4-pentanediols react with excellent diastereoselectivities to give products from which the chiral auxiliary is easily removed.[3] Asymmetric induction produced by the acetal derived from (2*R*,4*R*)-2,4-pentanediol is ascribed to a stereospecific coordination of the Lewis acid to one of the acetal oxygens.

As part of a program aimed at exploring a scope and limitations of homochiral acetal methodology, we now report diastereoselective addition of Grignard reagents which have an adjacent homochiral acetal group.

Results and Discussion

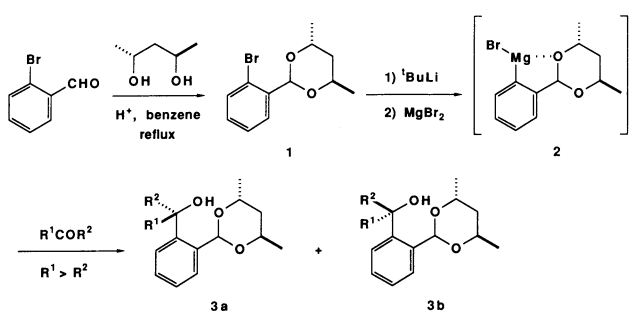
Homochiral aryl Grignard reagent **2** was readily prepared as shown in Scheme 1: Acetalization of 2-bromobenzaldehyde with (−)-(2*R*,4*R*)-2,4-pentanediol, lithiation with *t*-butyllithium, and finally transmetallation with magnesium bromide. The reactions of the Grignard reagent **2** with various carbonyl compounds were carried out in toluene–ether at −78 °C. Some of our results are listed in Table 1. Using an aromatic carbonyl compound as the electrophile, the Grignard reagent **2** gave high diastereoselectivity providing the predominant product **3a** (Entries 1, 4, and 5). The less stereoselectivity, on the other hand, was obtained in the reactions with the other organometallic reagents (Entries 2, 3, and 10) and the reactions with aliphatic aldehydes (Entries 6 and 8).

Evidence for the stereochemical course of the process depicted in Scheme 1 was obtained by the transformation shown in Scheme 2. The product **3a** (R^1=Ph, R^2=H; 88% de) in Entry 1 was converted into phenyl-*o*-tolylmethanol (**6**) whose stereochemistries were already established.[4] Thus, hydrolysis of **3a** with *p*-toluenesulfonic acid afforded hemiacetal **4**, which was further converted to hydrazone **5** by hydrazine. Treatment of **5** by potassium *t*-butoxide gave the compound **6** ($[\alpha]_D^{23}$ =−0.53°, *c* 1.0, benzene) having the *S*-configuration.[4] The stereochemistries of the major product **3a** of the other cases were tentatively assigned from mechanistic analogy.

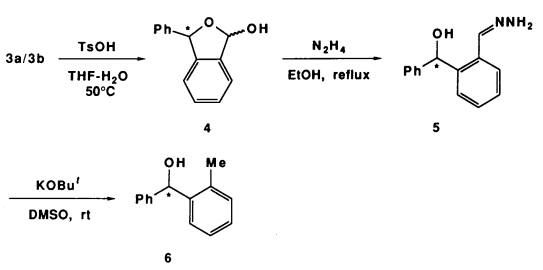
Table 1. Grignard Reaction via Homochiral Acetal

Entry	Substrate	R^1COR^2 R^1	R^2	Yield(%)	Ratio **3a**:**3b**
1	**1**	Ph	H	91	94 : 6
2[a]				73	72 : 28
3[b]				50	60 : 40
4		*p*-$CF_3C_6H_4$	H	72	89 : 11
5		Ph	Me	34	83 : 17
6		*t*-Bu	H	85	82 : 18
7		PhCH=CH	H	66	74 : 26
8		*c*-Hex	H	69	65 : 35
9		Ph	H	47	82 : 18
10[b]				50	73 : 27

a) $Ti(O\text{-}iPr)_4$ was used instead of $MgBr_2$. b) R^1COR^2 was added after lithiation.



Scheme 1.



Scheme 2.

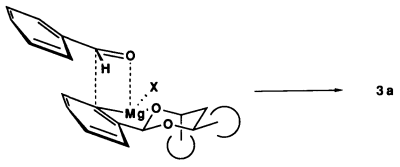


Fig. 1.

Although the detailed stereochemical course is not ascertained, the formation of **3a** as predominant products may be reasonably explained by the attack of the Grignard reagents from *re*-face side in the structure of organometallic reagent on the *re*-face of the carbonyl compounds as shown in Fig. 1. Namely, the magnesium metal is intramolecularly fixed by a stereospecific coordination to one of the acetal oxygen atoms leading to the formation of the five-membered ring structure. Then electrophiles approach to the less hindered side of the magnesium reagent as in the figure.

The study described above illustrates the suitability of optically active alcohols. One obvious advantage of our methodology is that product **3a** could be further transformed into other new chiral compounds by a diastereoselective cleavage of the remaining homochiral acetal group.

Experimental

The IR spectra were determined on a Hitachi 260-10 spectrometer. The ^{1}H NMR spectra were recorded on a Varian Gemini-200 spectrometer, using TMS (tetramethylsilane) as an internal standard. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. The microanalyses were performed at the Institute of Applied Organic Chemistry, Faculty of Engineering, Nagoya University. Analytical gas-liquid phase chromatography (GLC) was performed on Gaskuro Kogyo model 370 instruments with a flameionization detector and a capillary column of PEG-HT (0.25×25000 mm) using nitrogen as the carrier gas. Ether and tetrahydrofuran (THF) were distilled from benzophenone ketyl. Toluene and benzene were dried over sodium metal. All experiments were carried out under an argon atmosphere. Purification of the product was carried out by column chromatography on silica gel Fuji-Davison BW-300. (−)-(2*R*,4*R*)-2,4-pentanediol was purchased from Wako Pure Chemical Industries Ltd. and used after checking the optical purity; $[\alpha]_D^{23} = -41.2°$ (*c* 9.99, chloroform). Unless otherwise noted, other chemicals were purchased from commercial suppliers and used without further purification.

General Method for Preparation of Homochiral Acetals. The mixture of corresponding aldehyde or ketone (10.0 mmol), *p*-toluenesulfonic acid (10 mg) and (−)-(2*R*,4*R*)-2,4-pentanediol (1,14 g, 11.0 mmol) in 10 ml of benzene was refluxed with continuous azeotropic removal of water for 2 h. The resulting mixture was poured into saturated sodium hydrogen carbonate and the product was extracted twice with hexane. The organic layers were dried over magnesium sulfate and concentrated in vacuo. Purification of the crude oil by column chromatography on silica gel (hexane/ethyl acetate as eluent) afforded the corresponding acetal. The physical data of acetals are listed below.

(4*R*,6*R*)-2-(2-Bromophenyl)-4,6-dimethyl-1,3-dioxane (1): Quantitative yield; IR (CCl_4) 2986, 1366, 1148, 1129, 996 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.31 (d, J=6.2 Hz, 3H, C(equatorial)-H_3), 1.40—1.52 (m, 1H, H(equatorial)CH), 1.55 (d, J=6.8 Hz, 3H, C(axial)H_3), 1.92—2.10 (m, 1H, H(axial)CH), 4.24 (dqd, J=2.4, 5.9, 11.8 Hz), 1H, OCH(axial)CH_3), 4.48 (m, 1H, OCH(equatorial)CH_3), 6.13 (s, 1H, O_2CH), 7.19 (ddd, 1H, J=1.8, 7.6, 7.6 Hz, ArH), 7.35 (ddd, 1H, J=1.3, 7.7, 7.7 Hz, ArH), 7.53 (dd, 1H, J=1.3, 7.7 Hz, ArH), 7.74 (dd, 1H, J=1.8, 7.7 Hz, ArH). Anal. ($C_{12}H_{15}O_2Br$) C, H.

(4*R*,6*R*)-2-(2-Bromophenyl)-2,4,6-trimethyl-1,3-dioxane: Quantitative yield; IR (neat) 3000, 2950, 2375, 2350, 1460, 1440, 1385, 1378, 1275, 1245, 1185, 1175, 1130, 1030, 970, 765 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.26 (d, J=2.6 Hz, 3H, C(equatorial)-H_3), 1.29 (d, J=2.6 Hz, 3H, C(axial)H_3), 1.46—1.67 (m, 2H, CH_2), 1.70 (s, 3H, O_2CCH_3), 3.55—3.72 (m, 1H, OCH(axial)-CH_3), 4.12—4.29 (m, 1H, OCH(equatorial)CH_3), 7.14 (ddd, J=1.8, 7.6, 7.6 Hz, 1H, ArH), 7.32 (ddd, J=1.4, 7.6, 7.6 Hz, 1H, ArH), 7.61 (dd, J=1.4, 7.8 Hz, 1H, ArH), 7.81 (dd, J=1.8, 7.8 Hz, 1H, ArH). Anal. ($C_{13}H_{17}O_2Br$) C, H.

General Procedure for the Grignard Type Coupling of the Homochiral Acetal. To a solution of the acetal (0.5 mmol) in toluene (3 ml) was added *t*-butyllithium (0.26 ml, 0.6 mmol, 2.32 mol dm^{-3} in pentane solution) at −78 °C and the resulting yellow solution was stirred at 0 °C for 30 min. After cooling to −78 °C, a solution of magnesium bromide (1.0 mmol) in ether (3 ml) (prepared in another flask from magnesium turnings (29.2 mg, 1.2 mmol) and 1,2-dibromoethane (0.0862 ml, 1.0 mmol) at room temperature for 30 min) was added at −78 °C, and after 30 min, the corresponding aldehyde (0.5 mmol) was added at the same temperature. The mixture was sirred at −78 °C for 30 min, poured into aqueous ammonium chloride, extracted with ether, and dried over magnesium sulfate. Evaporation of solvents and purification of the residue by column chromatography on silica gel (hexane/ethyl acetate as eluent) gave the corresponding hydroxy acetals (**3a** and **3b**). The diastereomeric ratio of the adducts was determined by ^{1}H NMR. The physical properties and analytical data of the adducts obtained are listed below.

(4*R*,6*R*)-4,6-Dimethyl-2-[2-(α-hydroxybenzyl)phenyl]-1,3-dioxane (**3**, Entries 1, 2, and 3): IR (CCl_4) 3461 (OH), 2999, 2956, 1453, 1381, 1156, 1134, 1106, 1036, 1019, 996, 763, 696 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.30 (d, J=6.2 Hz, 3H, C(equatorial)H_3), 1.47 (d, J=7.0 Hz, 3H, C(axial)H_3), 1.97—2.12 (m, 1H, H(axial)CH), 1.33—1.43 (m, 1H, H(equatorial)CH), 3.72 (d, J=3.5 Hz, 1H, OH (**3a** isomer)), 3.95 (d, J=4.8 Hz, 1H, OH (**3b** isomer)), 4.21 (dqd, J=2.2, 6.2, 12.2 Hz, 1H, OCH(axial)-CH_3), 4.48—4.60 (m, 1H, OCH(equatorial)CH_3), 5.92 (s, 1H, O_2CH (**3b** isomer)), 6.08 (s, 1H, O_2CH (**3a** isomer)), 6.34 (d, J=4.8 Hz, 1H, CHOH (**3b** isomer)), 6.43 (d, J=3.5 Hz, 1H, CHOH (**3a** isomer)), 7.10—7.65 (m, 9H, ArH). Anal. ($C_{19}H_{22}O_3$) C, H.

(4*R*,6*R*)-4,6-Dimethyl-2-[2-(4-trifluoromethyl-α-hydroxybenzyl)phenyl]-1,3-dioxane (**3**, Entry 4): IR (neat) 3400 (OH), 2975, 2930, 2880, 1615, 1455, 1410, 1375, 1320, 1140, 1020, 925, 860, 810, 758 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.27 (d, J=6.0 Hz, 3H, C(equatorial)H_3), 1.47 (d, J=7.2 Hz, 3H, C(axial)H_3), 1.39—1.53 (m, 1H, H(equatorial)CH), 1.95—2.10 (m, 1H, H(axial)CH), 3.91 (d, J=3.7 Hz, 1H, OH (**3a** isomer)), 3.93 (d, J=2.6 Hz, 1H, OH (**3b** isomer)), 4.13—4.28 (m, 1H, OCH(axial)CH_3), 4.44—4.57 (m, 1H, OCH(equatorial)-CH_3), 5.92 (s, 1H, O_2CH (**3b** isomer)), 6.05 (s, 1H, O_2CH (**3a** isomer)), 6.44 (d, J=3.7 Hz, 1H, CHOH (**3b** isomer)), 6.51 (d, J=2.6 Hz, 1H, CHOH (**3a** isomer)), 6.97—7.65 (m, 8H, ArH). Anal. ($C_{20}H_{21}O_3F_3$) C, H.

(4*R*,6*R*)-4,6-Dimethyl-2-[2-(1-hydroxy-1-phenylethyl)phenyl]-1,3-dioxane (**3**, Entry 5): IR (neat) 3423, 2993, 2943, 1443, 1373, 1155, 1135, 1036, 985, 925, 758, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ=1.08 (d, J=8.0 Hz, 3H, C(equatorial)H_3), 1.28 (d,

J=8.0 Hz, 3H, C(axial)H_3), 1.25—1.5 (m, 1H, H(equatorial)-CH), 1.75—2.0 (m, 1H, H(axial)CH), 3.46—3.66 (m, 1H, OCH(axial)CH_3), 4.24—4.41 (m, 1H, OCH(equatorial)CH_3), 5.31 (s, 1H, O_2CH (**3b** isomer)), 5.61 (s, 1H, O_2CH (**3a** isomer)), 6.79—8.4 (m, 9H, ArH). Anal. ($C_{20}H_{24}O_3$) C, H.

(4*R*,6*R*)-4,6-Dimethyl-2-[2-(1-hydroxy-2,2-dimethylpropyl)-phenyl]-1,3-dioxane (**3**, Entry 6): IR (neat) 3450, 2970, 2950, 2880, 1372, 1125, 1031, 983, 753 cm^{-1}; ^1H NMR ($CDCl_3$) δ=0.97 (s, 9H, *t*-Bu), 1.25 (d, J=6.2 Hz, 3H, C(equatorial)H_3), 1.46 (d, J=7.0 Hz, C(axial)H_3), 1.39—1.51 (m, 1H, H(axial)CH), 1.92—2.08 (m, H(equatorial)CH), 2.16 (d, J=2.6 Hz, 1H, OH (**3a** isomer)), 2.27 (d, J=2.0 Hz, 1H, OH (**3b** isomer)), 4.16 (dqd, J=2.2, 6,2, 12.4 Hz, OCH(axial)CH_3), 4.40—4.54 (m, 1H, OCH(equatorial)CH_3), 4.83—4.86 (m, 1H, CHOH), 6.22 (s, 1H, O_2CH), 7.26—7.75 (m, 4H, ArH). Anal. ($C_{17}H_{16}O_3$), C, H.

(4*R*,6*R*)-4,6-Dimethyl-2-[2-(1-hydroxy-3-phenyl-2-propenyl)-phenyl]-1,3-dioxane (**3**, Entry 7): IR (neat) 3450, 3040, 2980, 2945, 2880, 1500, 1450, 1408, 1380, 1159, 1135, 1108, 1041, 990, 928, 760, 699 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.30 (d, J=6.0 Hz, C(equatorial)H_3), 1.43—1.58 (m, 1H, H(equatorial)CH), 1.52 (d, J=6.8 Hz, 3H, C(axial)H_3), 1.98—2.14 (m, 1H, H(axial)CH), 3.58 (d, J=3.0 Hz, 1H, OH (**3a** isomer)), 3.66 (d, J=3.4 Hz, OH (**3b** isomer)), 4.26 (dqd, J=2.6, 6.0, 12.0 Hz, OCH(axial)-CH_3), 4.53 (m, 1H, OCH(equatorial)CH_3), 5.94—5.99 (m, 1H, CHOH), 6.15 (s, 1H, O_2CH), 6.52 (dd, J=4.6, 16.0 Hz, CH=CHPh), 6.88 (dd, J=1.7 Hz, 16.0 Hz, CH=CHPh), 7.21—7.63 (m, 9H, ArH). Anal. ($C_{21}H_{24}O_3$) C, H.

(4*R*,6*R*)-4,6-Dimethyl-2-[2-(cyclohexylhydroxymethyl)phenyl]-1,3-dioxane (**3**, Entry 8): IR (neat) 3443, 2973, 2918, 2700, 1440, 1373, 1148, 1125, 1100, 1033, 980, 918, 753 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.28 (d, J=6.0 Hz, 3H, C(equatorial)H_3), 1.49 (d, J=6.8 Hz, 3H, C(axial)H_3), 1.92—2.08 (m, 1H, H(axial)CH), 0.89—2.18 (m, 12H, C_6H_{11} and H(equatorial)CH), 2.49—2.54 (m, 1H, OH), 4.20 (dqd, J=2.1, 6.0, 12.0 Hz, 1H, OCH(axial)CH_3), 4.40—4.54 (m, 1H, OCH(equatorial)CH_3), 4.72 (dd, J=2.6, 8.0 Hz, 1H, CHOH (**3b** isomer)), 4.80 (dd, J=2.6, 8.2 Hz, CHOH (**3a** isomer)), 6.08 (s, 1H, O_2CH (**3a** isomer)), 6.12 (s, 1H, O_2CH (**3b** isomer)), 7.24—7.67 (m, 4H, ArH). Anal. ($C_{19}H_{28}O_3$) C, H.

(4*R*,6*R*)-2,4,6-Trimethyl-2-[2-(α-hydroxybenzyl)phenyl]-1,3-dioxane (**3, Entries 9 and 10**): IR (neat) 3500, 2980, 2948, 1450, 1382, 1248, 1178, 1162, 1121, 1039, 1019, 962, 921, 765, 739, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.25—1.30 (m, 6H, 2CHCH_3), 1.52—1.82 (m, 2H, CH_2), 1.78 (s, 3H, O_2CCH_3), 3.70—3.81 (m, 1H, OCH(axial)CH_3), 4.02 (d, 1H, J=4.0 Hz, OH), 4.21—4.32 (m, 1H, OCH(equatorial)CH_3), 6.40 (d, J=3.8 Hz, 1H, CHOH (**3a** isomer)), 6.61 (d, J=5.0 Hz, 1H, CHOH (**3b** isomer)), 6.98—7.66 (m, 9H, ArH). Anal. ($C_{20}H_{24}O_3$) C, H.

Procedure for the Conversion of 3a/3b to 6. The mixture of **3a**/**3b** (94:6, 1.24 g, 4.2 mmol), *p*-toluenesulfonic acid (200 mg), water (15 ml), and THF (15 ml) was stirred at 50 °C for 5 h. Then the mixture was poured into saturated sodium hydrogen carbonate aqueous solution and extracted with ether. The combined extracts were dried over magnesium sulfate, filtered, and evaporated. Column chromatography (gradient elution, hexane/ethyl acetate, 5:2) gave **4** as a colorless oil (0.863 g, 98% yield).

To a solution of **4** (0.863 g, 4.1 mmol) prepared as detailed above in ethanol was added hydrazine monohydrate (0.971 ml, 20 mmol) at room temperature. After warming to 50—70 °C, the mixture was stirred at the same temperature for 8 h. After cooling to room temperature, the resulting solution was concentrated in vacuo. Column chromatography (gradient elution, Et_2O) gave **5** as a colorless oil (0.731 g, 79% yield).

To a rapidly stirred mixture of sublimed potassium *t*-butoxide and anhydrous dimethyl sulfoxide (20 ml) was added a solution of **5** in anhydrous dimethyl sulfoxide (20 ml) in very small portions over 1 h period. The solution turned deep green. Stirring was continued for 30 min. It was worked up with water and extracted with dichloromethane. The organic layer was washed with water, dried, and concentrated in vacuo. Column chromatography (gradient elution, benzene) gave **6** (455 mg, 71% yield).

3-Phenyl-2-oxaindan-1-ol (4): ^1H NMR ($CDCl_3$) δ=3.51 and 3.57 (d, J=7.4 Hz, 1H, OH), 6.13 (s, 1H, CHPh (trans isomer)), 6.36 (d, J=1.7 Hz, 1H, CHPh (cis isomer)), 6.61 (d, J=7.4 Hz, 1H, CHO_2 (trans isomer)), 6.72 (dd, J=1.7, 7.4 Hz, 1H, CHO_2), 7.05—7.53 (m, 9H, ArH).

2-(α-hydroxybenzyl)benzaldehyde Hydrazone (5): ^1H NMR ($CDCl_3$) δ=5.49 (br, 3H, NH_2 and OH), 5.99 (s, 1H, PhCH), 7.10—7.44 (m, 9H, ArH), 7.82 (s, 1H, CH=N).

Phenyl-*o*-tolylmethanol (6): ^1H NMR ($CDCl_3$) δ=2.30 (d, J=5.0 Hz, 1H, OH), 2.25 (s, 3H, CH_3), 6.00 (d, J=5.0 Hz, 1H, CHOH), 7.12—7.55 (m, 9H, ArH). The %ee of this compound ($[\alpha]_D^{23}$ =−0.53°, *c* 1.0, benzene), determined from ^1H NMR by a shift reagent Eu(hfc)$_3$, was 72%.

References

1) D. Seebach, R. Imwinkelried, and T. Weber, "Modern Synthetic Methods 1986, Vol. 4," ed by R. Scheffold, Springer-Verlag Berlin Heidelberg (1986), pp. 191—216.

2) J. Fujiwara, Y. Fukutani, M. Hasegawa, K. Maruoka, and H. Yamamoto, *J. Am. Chem. Soc.*, **106**, 5004 (1984).

3) A. Mori, J. Fujiwara, K. Maruoka, and H. Yamamoto, *Tetrahedron Lett.*, **24**, 4581 (1983); A. Mori, J. Fujiwara, K. Maruoka, and H. Yamamoto, *J. Organomet. Chem.*, **285**, 83 (1983); K. Ishihara, A. Mori, I. Arai, and H. Yamamoto, *Tetrahedron Lett.*, **27**, 983 (1986); A. Mori, K. Ishihara, and H. Yamamoto, *ibid.*, **27**, 987 (1986); A. Mori, K. Ishihara, I. Arai, and H. Yamamoto, *Tetrahedron*, **43**, 755 (1987).

4) (*R*)-(+)-Phenyl-*o*-tolylmethanol, 85% ee, was reported to give $[\alpha]_D^{25}$ =+0.38° (*c* 1.0, benzene): D. Seebach, A. K. Beck, S. Roggo, and A. Wonnacott, *Chem. Ber.*, **118**, 3673 (1985).