# A Short Synthesis of a Chiral Alcohol as a New Chiral Auxiliary for Asymmetric Reactions

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Asymmetric synthesis has emerged as one of the most rapidly developing research areas in organic chemistry.[1] Among various strategies involved in the asymmetric synthesis, use of chiral auxiliaries and chiral ligands has been extensively studied and a number of new auxiliaries and ligands have been successfully utilized for efficient asymmetric synthesis.[2] Most of such chiral auxiliaries and ligands have been derived from chiral pools of naturally occurring compounds such as amino acids,[2,3] terpenes,[2] and carbohydrates.[2,4] Thus design of such auxiliaries and ligands have been largely dependent upon the availability of the chiral starting materials from natural sources. In this connection, we have initiated a research effort towards the development of novel chiral auxiliaries and ligands based upon highly efficient and reliable asymmetric transformations such as asymmetric dihydroxylation.[5]

Chiral alcohols have been utilized as ligands for various metals for a number of asymmetric reactions.[6] These alcohols have been derived from carbohydrates, amino acids, and other sources. An ether alcohol **1** (Figure 1) possesses a $C_1$ symmetry, however, it can be used to mimic a $C_2$ symmetry[7] considering that the oxygen atom of the ether can bind to a metal together with the alcohol oxygen rendering the ether alcohol act as a bidentate-type ligand. This extra chelation could be a critical element for the design of chiral ligand and auxiliary. Herein we report a short and efficient synthesis of the optically pure ether alcohol **1**.

A synthetic scheme for the chiral ether-alcohol **1** is outlined in Scheme 1. Wittig olefination of commercially available 2-formylbenzoic acid (**2**) with a triphenylphosphonium ylide prepared from methyltriphenylphosphonium bromide provided 2-vinylbenzoic acid (**3**) in 90% yield. Coupling of the acid **3** with iodobenzene under the Heck conditions[8] furnished 2'-carboxystilbene (**4**) in excellent yields (>90%). Conventional esterification of **4** with MeI in the presence of NaH followed by the reduction of subsequent ester **5** with LAH gave alcohol **6** in a straightforward manner in almost quantitative yield. Conversion of the alcohol **6** to the corresponding chloride was accomplished in 88% yield by treatment of **6** with methanesulfonyl chloride in the presence of LiCl *via* the formation of a methanesulfonate intermediate. Oxidation of the resulting compound **7** under Sharpless' buffered catalytic asymmetric dihydroxylation conditions[9] provided diol **8** in 85% yield. The absolute stereochemistry of the compound **8** was assumed from the predictable facial selectivity rule suggested by Sharpless *et al.*[10] Finally closure to the ether ring **1** was successfully accomplished through the use of NaH in ether as shown in Scheme 1. The enantiomeric purity of the ether alcohol **1** was determined to be >99% from HPLC analysis using a chiral column (Chiralcel ODH, hexane:*i*-PrOH = 70 : 30, 0.2 mL/min) as shown in Figure 2.

In conclusion, we have devised a short and efficient synthesis of the chiral alcohol **1** from 2-formylbenzoic acid. The synthesis involved the Heck coupling reaction and Sharpless' AD as key steps. The predictive stereochemical outcome of diols should allow for an efficient synthesis of the antipode of the reagent (*ent*-**1**) using essentially the same synthetic sequence but the choice of ligand alkaloids in the AD step. Investigation of various asymmetric transformations such as aldol and Diels-Alder reactions using this chiral alcohol is in progress and the results will be reported in due course.

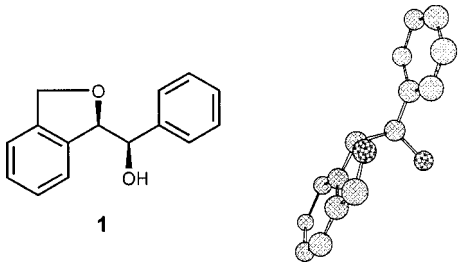
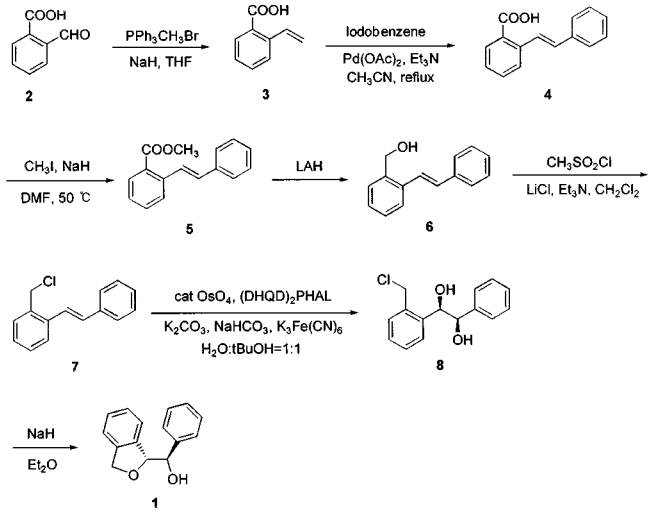



**Figure 1**. The chiral ether alcohol **1** and its Chem3D model.




**Scheme 1**. Synthesis of chiral alcohol **1.**

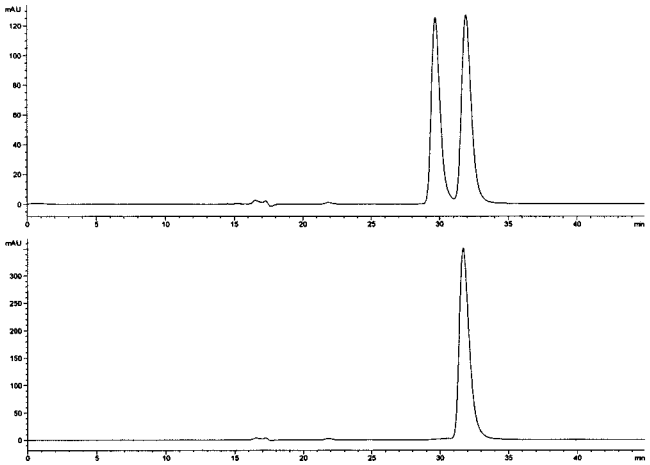


**Figure 2**. Determination of enantiomeric purities through HPLC analyses of (a) (+, −)-**1** and (b) (*R*,*R*)-**1.**

## Experimental Section

Reactions requiring anhydrous conditions were carried out in flame-dried glassware under positive pressure of dry $N_2$ using standard syringe technique. Solvents were dried according to normal procedure unless otherwise noted. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl immediately prior to use. Methylene chloride ($CH_2Cl_2$) was distilled from calcium hydride immediately prior to use. Reagents were used directly from the commercial sources unless otherwise noted. TLC's were performed by silica gel 60 F254 precoated on aluminum sheet (E. Merck, Art.5554). Chromatogram was visualized by UV-lamp (254 nm and 365 nm) and/or charring with ethanol/sulfuric acid/p-anisaldehyde/acetic acid (90 : 4 : 4 : 2) or phosphomolybdic acid or ninhydrin in ethanol or iodine. As one of the purification method, column chromatography was performed with silica gel 60 (E. Merck, Art. 7734, 70-230 mesh). Infrared spectra were obtained using Bruker IR-IFS 45 FT-IR and their peaks were assigned in $cm^{-1}$. $^1H$ and $^{13}C$ NMR-spectra were measured with Bruker AC-80 (80 MHz), Varian 200 (200 MHz) or AMX-300 (300 MHz). Proton (±0.1 ppm) chemical shifts were measured from internal TMS at probe temperature in $CDCl_3$ or corresponding deuterated solvents for neutral compounds.

**Preparation of 2-vinylbenzoic acid (3).** A 25 mL three-necked flask equipped with a magnetic stirring bar, a nitrogen inlet and a thermometer was charged with 1.60 g of sodium hydride (60% suspension in mineral oil, 39.9 mmol) in 17 mL of anhydrous THF at 0 °C. To the suspension was added 5.70 g (16.0 mmol) of $PPh_3CH_3Br$ slowly. Then the reaction mixture was stirred at ambient temperature for 1 h and 2.00 g (13.3 mmol) of 2-formylbenzoic acid was added at once. After the mixture was stirred for 3 h at 40 °C, the reaction was quenched by addition of $H_2O$ and the mixture extracted with $Et_2O$ (30 mL×3). The aqueous phase was acidified (pH=2) and extracted with EtOAc (30 mL×3). Combined ethyl acetate layers were washed with brine (50 mL), dried over $MgSO_4$ and evaporated to give 1.77 g (12.0 mmol, 90% yield) of the desired product. $^1H$ NMR (80 MHz) δ 8.1 (d, 1H, *J* = 9 Hz) 7.7-7.1 (m, 4H) 5.5 (dd, 1H, *J* = 1, 18 Hz) 5.2 (dd, 1H, *J* = 1, 12 Hz). $R_f$ = 0.8 (hexane : EtOAc = 1 : 4); EI Mass m/z 148 ($M^+$); HRMS: observed 148.0528, calculated 148.0524.

**Preparation of 2-(*trans*-2'-phenylethenyl)benzoic acid (4).** A 50 mL two-necked round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser, was charged with palladium acetate (45 mg, 0.02 mmol), iodobenzene (2.00 g, 9.8 mmol), compound **3** (1.60 g, 10.8 mmol), and triethylamine (1.37 mL, 9.8 mmol) in 30 mL of acetonitrile. The reaction vessel was heated to reflux for 12 h. After cooling, it was diluted with 30 mL of water and $K_2CO_3$ powder was added to maintain pH=11. The mixture was extracted with $Et_2O$ (60 mL×3). The aqueous phase was acidified to pH=2 with $KHSO_4$ and extracted with EtOAc (60 mL×3). The combined organic layer was washed with brine (60 mL×2), dried with anhyd $MgSO_4$, and evaporated. The resulting crude product was purified on a chromatographic column (silica gel, hexane : EtOAc=1 : 1 to 1 : 2) to give 1.99 g (8.9 mmol, 91% yield) of compound **4**. $R_f$ = 0.6 (hexane : EtOAc = 1 : 2, acetic acid 1-2 drops); IR (KBr, $cm^{-1}$) 2970.5, 2815.2, 2639.7, 1679.6; $^1H$ NMR (200 MHz, $CDCl_3$) δ 7.2-7.9 (m, 10H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 127.39, 127.65, 127.72, 127.78, 127.95, 128.40, 129.15, 132.12, 132.12, 132.26, 133.61, 137.73, 140.63, 173.70. EI Mass m/z 224 ($M^+$); HRMS: observed 224.0843, calculated 224.0837.

**Preparation of methyl 2-(*trans*-2'-phenylethenyl)benzoate (5).** To a suspension of sodium hydride (60% in mineral oil, 0.21 g, 5.2 mmol) in 20 mL of anhydrous DMF in 100 mL round-bottomed flask equipped with a magnetic stirring bar was slowly added 0.97 g (4.3 mmol) of **4**. To the mixture was then added 0.35 mL (5.6 mmol) of $CH_3I$. The mixture was warmed to 40 °C while stirring for 6 h. The reaction was quenched by addition of water and the mixture extracted with $Et_2O$ (50 mL×3). The organic layer was washed with brine (30 mL×2), dried over anhyd $MgSO_4$, and evaporated to give 0.83 g (3.5 mmol, 81%) of the desired product after chromatographic purification on silica gel column (hexane : EtOAc = 10 : 1). $R_f$ = 0.6 (hexane : EtOAc = 3 : 1); IR (KBr, $cm^{-1}$) 3066.3, 3026.6, 2995.5, 2951.3, 1721.3; $^1H$ NMR (300 MHz, $CDCl_3$) δ 3.92 (s, 3H), 7.01 (d, 1H, *J* = 16.2 Hz), 7.25-7.39 (m, 4H), 7.49-7.57 (m, 3H), 7.72 (d, 1H, *J* = 7.9 Hz), 7.93 (d, 1H, *J* = 7.9 Hz), 8.0 (d, 1H, *J* = 16.2 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 52.56, 127.30, 127.41, 127.57, 127.85, 128.29, 128.91, 129.10, 131.11, 131.85, 132.61, 137.82, 139.67, 168.28; EI Mass m/z 238 ($M^+$); HRMS: observed 238.0997, calculated 238.0994.

**Preparation of 1-hydroxymethyl-2-(*trans*-2'-phenylethenyl)benzene (6).** To a solution of 220 mg (0.92 mmol) of **5** in 6 mL THF was added 70 mg (1.84 mmol) of $LiAlH_4$. After 1 h, the reaction was quenched by adding 70 μL of $H_2O$, 70 μL of 15% NaOH, and then 210 μL of $H_2O$. The mixture was diluted with 10 mL EtOAc and filtered through Celite. The filtrate was concentrated under reduced pressure to furnish 193 mg (0.91 mmol, 99% yield) of the desired

product. $R_f$ = 0.35 (hexane : EtOAc = 3 : 1); IR (KBr, $cm^{-1}$) 3329.8, 3246.4, 3026.5, 2922.8, 2856.1, 1485.3, 1449.5; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ 1.80 (br s, 1H), 4.81 (s, 2H), 7.05 (d, 1H, *J* = 16.2 Hz), 7.45 (d, 1H, *J* = 16.2 Hz), 7.23-7.42 (m, 7H), 7.53 (d, 1H, *J* = 7.6 Hz), 7.66 (d, 1H, *J* = 7.6 Hz); EI Mass m/z 210 ($M^+$); HRMS: observed 210.1043, calculated 210.1045.

**Preparation of 1-chloromethyl-2-(*trans*-2'-phenylethenyl)benzene (7).** To a solution of 35 mg (0.17 mmol) of **6** in 1 mL of $CH_2Cl_2$ at 0 °C were added 24 μL (0.20 mmol) of methanesulfonyl chloride, 36 μL (0.26 mmol) of $Et_3N$ and 8 mg (0.20 mmol) of LiCl. The reaction mixture was stirred overnight at room temperature. It was diluted with 2 mL of $H_2O$ and the aqueous layer was extracted with EtOAc (2 mL×3). Combined organic layers were washed with brine (2 mL), dried over anhyd $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude product was purified on a chromatographic column (silica gel, hexane) to give 34 mg (0.15 mmol, 88%) of the desired product. $R_f$ = 0.3 (hexane); $^1H$ NMR (300 MHz, $CDCl_3$) δ 4.73 (s, 2 H), 7.09 (d, 1H, *J* = 16.1 Hz), 7.25-7.42 (m, 6H), 7.48 (d, 1 H, *J* = 16.1 Hz), 7.55-7.58 (m, 2H), 7.68 (d, 1H, *J* = 7.7 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 45.05, 125.24, 126.74, 127.21, 128.28, 128.45, 129.18, 129.67, 130.75, 132.20, 134.96, 137.41, 137.59; EI Mass m/z 228 ($M^+$); HRMS observed 228.0709, calculated 228.0706.

**Preparation of (1*R*,2*R*)-1,2-dihydroxy-1-(2'-chloromethyl)phenyl-2-phenylethane (8).** To a solution of 95 mg (0.42 mmol) of **7** in 2 mL of *tert*-butyl alcohol and 2 mL of water, were added 415 mg (1.26 mmol) of $K_3Fe(CN)_6$, 174 mg (1.26 mmol) of $K_2CO_3$, 10 mg ($1.26\times10^{-4}$ mmol) of $(DHQD)_2PHAL$ and 1.6 mg ($6.30\times10^{-4}$ mmol) of $OsO_4$. The reaction mixture was stirred for 24 h at 0 °C. To this solution was added 230 mg of $Na_2SO_3$, and stirring was continued for additional several hours. The pale blue solution obtained was diluted with 5 mL of $H_2O$. And the residue was extracted with EtOAc (10 mL×3). The combined extracts were dried over anhyd $MgSO_4$ and the filtrate evaporated. The crude product was purified on a silica gel column chromatography, (Hexane : EtOAc = 5 : 1) to provide 96 mg (0.36 mmol, 85% yield) of the desired product. $R_f$ = 0.2 (hexane : EtOAc = 5 : 1); $[\alpha]_D^{25}$ +2.30 (*c* 1.2, $CHCl_3$); IR (KBr, $cm^{-1}$) 3461.5, 3374.6, 3062.0, 3028.6, 2937.1, 2889.9; $^1H$ NMR (300 MHz, $CDCl_3$) δ 3,98 (d, 1H, *J* = 11.7 Hz), 4.05 (d, 1H, *J* = 11.7 Hz), 4.28 (d, 1H, *J* = 7.8 Hz), 4.99 (d, 1 H, *J* = 7.8 Hz), 7.05-7.08 (m, 2H), 7.16-7.20 (m, 5H), 7.25 (t, 1H, *J* = 7.8 Hz), 7.48 (d, 1H, *J* = 7.8 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 43.72, 75.58, 78.87, 127.15, 128.45, 128.56, 128.71, 129.34, 130.48, 135.80, 139.09, 139.83; CI Mass m/z 245 $(M+1-H_2O)^+$.

**Preparation of (2*R*)-(1'*R*-hydroxyphenylmethyl)dihydrobenzo[*c*]furan (1).** To a solution of 54 mg (0.21 mmol) of **8** in 1 mL of $Et_2O$ at 0 °C was added 20 mg (0.50 mmol) of NaH (60% suspension in mineral oil) at room temperature. After 1 h, the reaction was quenched with water and the aqueous layer was extracted with $Et_2O$ (1 mL×3) and washed with brine (2 mL). Combined organic layers were dried over anhyd $MgSO_4$, filtered and concentrated under reduced pressure. Compound **1** was obtained in a quantitative yield. $R_f$ = 0.5 (hexane : EtOAc = 5 : 1); $[\alpha]_D^{25}$ +9.25 (*c* 1.0, $CHCl_3$); IR (KBr, $cm^{-1}$) 3430.0, 3037.8, 2933.0, 2868.2, 1458.4; $^1H$ NMR (300 MHz, $CDCl_3$) δ 2.20-3.10 (br s, 1H), 4.66 (d, 1H, *J* = 6.8 Hz), 5.05 (d, 1H, *J* = 12.8 Hz), 5.18 (dd, 1H, *J* = 2.5, 12.8 Hz), 5.33 (d, 1H, *J* = 6.8 Hz), 6.46 (d, 1H, *J* = 7.5 Hz); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 73.14, 77.36, 88.45, 121.30, 123.16, 127.37, 128.20, 128.41, 128.75, 128.78, 137.97, 139.64, 140.11; CI Mass m/z 209 $(M+1-H_2O)^+$.

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