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A Practical Route to Enantiopure 1,2-Aminoalcohols

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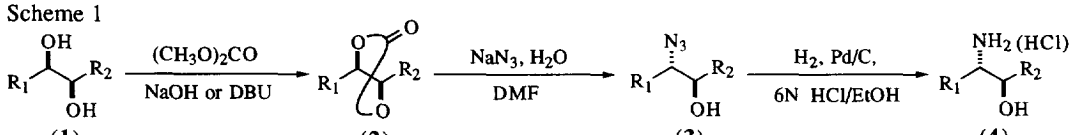
Abstract: *A series of enantiopure aminoalcohols were synthesized from the corresponding diols by activation of the diols as cyclic carbonates, azide opening of the carbonates, and hydrogenation of the resulting azidoalcohols. Factors affecting the azide opening of the carbonates, a simple workup procedure, and a large scale synthesis of (1R,2S)-(−)-2-amino-1,2-diphenylethanol are described.*

The importance of enantiomerically pure ß-aminoalcohols as ligands for asymmetric catalysis, as building blocks for pharmaceuticals, or as actual drugs is well recognized.[1] Such aminoalcohols are generally obtained by resolution of the racemates, synthesis from optically pure precursors, or occasionally via asymmetric synthesis.[2] The asymmetric dihydroxylation of olefins (AD)[3] provides easy access to a wide variety of enantiopure 1,2-diols and we report here a short and practical sequence for their conversion to enantiopure 1,2-aminoalcohols.

The simple three step sequence is shown in Scheme 1: (1) activation of the diol as the cyclic carbonate; (2) stereospecific opening of the cyclic carbonate by sodium azide; and (3) palladium-catalyzed hydrogenation of the resulting azido alcohol. The yields reported in Table 1 are for 5 mmol scale reactions except for the stilbene case (entry 1) which was performed on a one mole scale.

Scheme 1



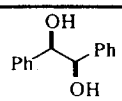
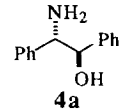
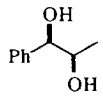
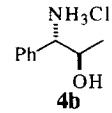
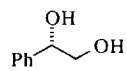
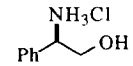
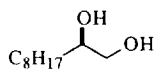
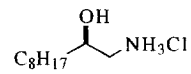
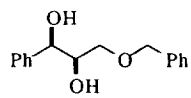
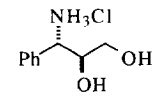
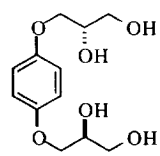
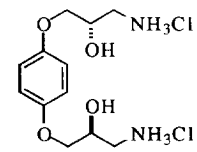
(1) (2) (3) (4)

R_1 = H or Ar

The cyclic carbonates (2) were formed from the corresponding diols (1) by transesterification with dimethyl carbonate effected by heat and catalytic NaOH.[4] In the case of the tetraol (Table 1, entry 6), DBU was used as the base due to problems in the NaOH procedure apparently resulting from the poor solubility of the mono-carbonate intermediate. The workup procedure involved simple filtration through Celite to remove the solids and concentration of the solvent. The carbonates (2) were pure by ^{1}H-NMR and were directly subjected to azide opening.

Much is known about cyclic carbonates as robust protecting groups for *1,2* and *1,3*-diols,[5] but reports of *intermolecular* nucleophilic attack on cyclic carbonates at the carbinol carbon rather than the carbony carbon are less common.[6] Our studies show that NaN_3 in the presence of 1 eq H_2O in DMF at 70–110 °C

Table 1

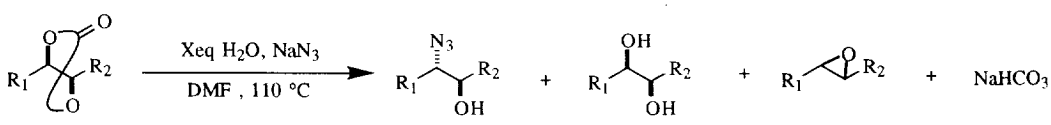
Entry	Subtrate	ee (%)	[azide opening step] temp (°C)/time (h)	Product [c]	ee (%)	overall yield (%)
1		> 99	110/48	 **4a**	> 99	81
2		> 98	110/24	 **4b**	> 99	73
3		> 98	70/48	 **4c**	> 99	70 [a]
4		> 99	110/20	 **4d**	> 99	70
5		> 99	110/24	 **4e**	> 99	81
6		> 98 [b]	110/20	 **4f**	> 99	83

a. in this case, the other regioisomer is also formed in 7% overall yield. b. it also contains *ca.* 2% of meso. c. absolute configurations of **4d**, **4e**, and **4f** assigned from the starting diol and assuming inversion in N_3^- opening step, the rest are correlated to the known compounds.

selectively opens 1.2-carbonates as follows: 2° benzylic > 1° > 2° saturated. As the opening reaction proceeds $NaHCO_3$ precipitates and the workup consists simply of concentration and filtration in preparation for the hydrogenation step.

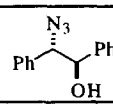
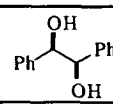
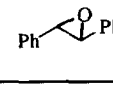
The azido alcohols (**3**) are produced stereospecifically with inversion; the parent diol (**1**) and epoxide (**5**) may be formed as by-products (Scheme 2). The amount of water in the reaction is critical, as revealed by the study in Table 2. Small amounts of water were superior to anhydrous conditions under which the reaction was sluggish and the undesired epoxide (**5**) was formed; with excess water present, diol formation became the major pathway. The preference for benzylic versus terminal attack in the styrene carbonate case is not surprisingly temperature dependent (70 /30 at 110 °C and 82 /18 at 70 °C).

Scheme 2



(**2**) (**3**) (**1**) (**5**)

Table 2

H_2O	 (%)	 (%)	 (%)	Total Conversion [a] at 20 hour (%)
0 eq	63	0	15	78
1 eq	87	2	0	89
2 eq	87	6	0	93
5 eq	77	21	0	98
10 eq	48	52	0	>99 [b]

a. Based on the disappearance of the starting carbonate and determined by ^{1}H NMR. b. finished in 15 h.

Hydrogenation of the azide using palladium on activated carbon[7] proceeded smoothly in ethanol with 1.02 eq of 6N HCl under atmospheric pressure. The aminoalcohols (**4**) were isolated as the hydrochloride salts following filtration to remove the catalyst and removal of the solvent *in vacco*. These salts were purified easily by recrystallization from ethanol. With the azidoalcohol derived from the diol benzylether in entry 5 (Table 1), both the azide and the benzyl ether groups underwent hydrogenolysis. In no case was loss of stereochemical integrity detected by HPLC analysis.

In conclusion, we have developed a practical synthesis of enantiomerically pure aminoalcohols from the corresponding diols, the key step being the stereospecific opening of the cyclic carbonates by NaN_3. The sequence's best features include the inexpensive reagents employed, the use of isolation and purification techniques amenable to large scale processes, and the ready availability of the starting diols in enantiomerically pure form.[8]

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8. Experimental procedure for **(1*R*,2*S*)-(−)-2-amino-1,2-diphenylethanol 4a.** A 500 mL flask, fitted with a distillation apparatus and a magnetic stir bar, was charged with (*R,R*)-Hydrobenzoin **1a** (214 g, 1mole), NaOH (3g of pellets) and 300mL dimethyl carbonate. This stirred solution was heated to 60 °C for 0.5 h, followed by distillative removal of 200-250mL of a mixture of methanol and dimethyl carbonate (bath temperature: 90 °C). The remaining suspension was diluted with 200 mL of THF, filtered through Celite, and concentrated to yield 240g of the crude carbonate **2a** (a solid, *ca.* quant. yield). This carbonate was transferred to a 2 L flask (fitted with a condenser), and charged with water (18ml, 1mole), 1L DMF, and sodium azide (71.5g, 1.1mole). Under nitrogen, the mixture was heated in an oil bath maintained at 110 °C. After the reaction finished *ca.* 48h (^{1}H NMR), a distillation apparatus was used for removal of the DMF under reduced pressure at 50 °C. The semisolid residue was triturated with 500mL Et_2O, and the resulting suspension was filtered through Celite (removes $NaHCO_3$ and excess NaN_3) and concentrated to afford 245g of the crude azidoalcohol **3a** (an oil, quant. yield). To the 245 g of crude product in 1.6L ethanol was added 10g of Pd/C, followed by slow addition of 170 ml (1.02mole) of 6N HCl solution. The resulting solution was stirred under hydrogen at room temperature and room pressure for 40h, followed by addition of 1.5L water and filtration through Celite. The filtrate was concentrated to remove most of the ethanol, then 200ml of 6N NaOH solution was added slowly to generate the free base which precipitated spontaneously. The resulting suspension was filtered, washed with 500mL water, and dried to afford 183g of the crude product. The first recrystallization from 400mL of anhydrous ethanol gave 158.5g (>99% ee). Recrystallization of the concentrated mother liquors from 50mL of ethanol afforded another 13.8g (>99% ee). These were combined to give 172.3g (>99% ee and 81% overall yield from the diol).

Data for: **(1*R*,2*S*)-(−)-2-amino-1,2-diphenylethanol (4a)**: mp 143-144 °C, $[\alpha]_D$ - 6.93° (c=0.6, EtOH), [Lit: (*Beil. 13*, IV, 2150) mp 142-144 °C, $[\alpha]_D$ - 7.0° (c=0.6, EtOH)]. ee determination: the corresponding cyclic carbamate derived from **4a** was analyzed, HPLC: Chiralcel OF, 20% *i*-PrOH/Hexane, 1mL/min; 47.9, *55.0*. **(1*S*,2*R*)-(+)-1-amino-1-phenyl-2-propanol hydrochloride (4b)**: mp 177-179 °C, $[\alpha]_D$ +10.0° (c=1.0, H_2O), [Lit: (*Helv. Chim. Acta* **1983**, *66*, 2274) mp 179-180 °C, $[\alpha]_D$ +11° (c=1.0, H_2O)]. ee determination: the corresponding hydroxysulfonamide derived from **4b** was analyzed, HPLC: Chiralcel OD-H, 15% *i*-PrOH/Hexane, 0.5mL/min; 18.9, *24.0*. **(*R*)-(−)-2-amino-2-phenylethanol hydrochloride (4c)** : mp 168-169 °C, $[\alpha]_D$ - 24.2° (c=1.05, MeOH); for free base form: mp 77-79 °C, $[\alpha]_D$ - 25.0° (c=6.0, MeOH) [Lit: for free base form (*Beil. 13*, IV, 1835) mp 76-79 °C, $[\alpha]_D$ - 25.5° (c=6.0, MeOH)]. ee determination: the corresponding cyclic *N*-tosyl carbamate derived from **4c** was analyzed, HPLC: Chiralcel AS, 15% *i*-PrOH/Hexane, 0.8mL/min; 34.3, *52.6*. **(*R*)-(−)-1-amino-2-decanol hydrochloride (4d)** : ^{1}H NMR (400 MHz, D_2O): d = 3.68-3.75 (m, 1H), 3.01 (dd, *J*=3.0, 13.1, 1H), 2.75 (dd, *J*=9.6, 13.1, 1H), 1.15-1.52 (m, 14H), 0.74 (t, *J*=7.0, 3H); ^{13}C NMR (100 MHz, D_2O): d = 70.25, 47.03, 36.24, 33.61, 31.02, 30.95, 30.85, 26.95, 24.50, 15.89; IR (KBr): v = 3294, 3087, 2921, 1615, 1558, 1507, 1149, 1049 cm^{-1}. HRMS(FAB$^+$) Calcd for $C_{10}H_{24}NO^+$: 174.1858. Found: 174.1854, mp 210 °C (dec.), $[\alpha]_D$ - 4.9° (c=1.13, MeOH). ee determination: the corresponding hydroxysulfonamide derived from **4d** was analyzed, HPLC: Chiralcel OD-H, 15% *i*-PrOH/Hexane, 0.5mL/min; *16.4*, 18.7. **(2*S*,3*S*)-(+)-3-amino-3-phenyl-1,2-propanediol hydrochloride (4e)** : ^{1}H NMR (400 MHz, D_2O): d = 7.29-7.38 (m, 5H), 4.41 (d, *J*=4.3, 1H), 4.04 (ddd, *J*=4.3, 5.4, 6.4, 1H), 3.35 (dd, *J*=5.4, 11.6, 1H), 3.23 (dd, *J*=6.4, 11.6, 1H); ^{13}C NMR (100 MHz, D_2O): d = 134.87, 131.85, 131.45, 130.33, 73.31, 64.73, 58.80; IR (KBr): v = 3354, 3046, 1599, 1576, 1489, 1387, 1055, 701 cm^{-1}. HRMS(FAB$^+$) Calcd for $C_9H_{14}NO_2^+$: 168.1025. Found: 168.1021, mp 255 °C (dec.), $[\alpha]_D$ +3.7° (c=1.05, MeOH). ee determination: the corresponding hydroxysulfonamide derived from **4e** was analyzed, HPLC: Chiralcel OG, 30% *i*-PrOH/Hexane, 1mL/min; 15.9, *25.6*. **(*S,S*)-1,1'-(*p*-phenylenedioxy)bis(3-amino-2-Propanol) dihydrochloride (4f)** : ^{1}H NMR (400 MHz, D_2O): d = 6.83 (s, 4H), 4.10 (dddd, *J*=3.4, 4.0, 5.2, 9.0, 2H), 3.96 (dd, *J*=4.0, 10.3, 2H), 3.91 (dd, *J*=5.2, 10.3, 2H), 3.15 (dd, *J*=3.4, 13.2, 2H), 3.02 (dd, *J*=9.0, 13.2, 2H); ^{13}C NMR (100 MHz, D_2O): d = 155.13, 118.42, 72.69, 68.53, 44.20; IR (KBr): v= 3323, 3193, 3035, 2933, 1584, 1511, 1240, 1048, 828 cm^{-1}. HRMS(FAB$^+$) Calcd for $[C_{12}H_{22}Cl_2N_2O_4$-$HCl_2]^+$: 257.1501. Found: 257.1494, mp 230 °C (dec.), $[\alpha]_D$ - 28.8° (c=1.06, MeOH). ee determination: the *N*-tosyl 3-amino1.2-propanediol derived from **4f** was analyzed, HPLC: Chiralcel AD, 15% *i*-PrOH/Hexane, 0.5mL/min; *35.7*, 39.5.

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