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A Short Route to a Mosher's Acid Precursor Via Catalytic Asymmetric Dihydroxylation *(AD)*

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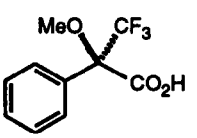
Abstract: *α-Methoxy-α-(trifluoromethyl)phenyl acetic acid (MTPA) is a valuable derivatizing agent for enantiomeric excess determination of alcohols and amines. A short synthesis of a precursor to this compound, based on the asymmetric dihydroxylation (AD) reaction is reported.*

The great interest in enantioselective synthesis has increased the demand for more sensitive and precise analytical methods for the determination of enantiomeric excesses (ee) by GC, HPLC and NMR techniques. Although a wide variety of chiral reagents have been developed for this purpose,[3] the reagent of choice still remains α-methoxy-α-(trifluoromethyl)phenyl acetic acid (MTPA) (1) (Figure 1), originally introduced by Mosher *et al.*[4]

Figure 1



(*R*)-MTPA (1)

Recent improvements in the osmium-catalyzed asymmetric dihydroxylation (AD) of olefins,[5] enable us to report here a simple, two step synthesis of hydroxy acid **4**, the immediate precursor of Mosher's acid (1), by using metal-catalyzed oxidation processes. A few routes to this valuable acid in enantiomerically enriched form through enzymatic[6] and non-enzymatic methods have been reported recently.[7] However, most of these routes involve kinetic resolutions and the one[7a] depending on asymmetric synthesis gives lower ee's than the AD-sequence reported here.

Our synthesis commences with commercially available[8] α-trifluoromethyl styrene **2**, which is dihydroxylated[9] under the previously reported AD-mix conditions[5a] to give the corresponding diol **3** in 94% yield (72 hours at 0°C) and 83% ee using dihydroquinidine (DHQD) based ligand **5**, (Scheme, Figure 2). When ligand $(DHQD)_2$-DPP **6** with an extended heterocyclic spacer[10] was used,[11] the reaction proceeded in similar yield and 91% ee as determined by HPLC (Chiralcel-OD) of the corresponding cyclic carbonate. Ligands **5** and **6** are recovered in about 95% yield by acid extraction.[12] The purification of diol **3** does not require chromatography, a simple distillation is sufficient but not necessary.[13]

Air oxidation of diol **3** using Pt/C as a catalyst[14] in a sodium bicarbonate solution gave hydroxy acid **4** in 95% yield, $[\alpha]_D$ +24.2 (*c* 0.8, MeOH); Lit.[7b] $[\alpha]_D$ +27.3 (*c* 0.8, MeOH, 99% ee). Recrystallization from toluene-hexane gave enantiomerically pure (99% ee)[12] acid (*R*)-**4** in 72% yield; m.p. 122-124°C, $[\alpha]_D$ +29.8 (*c* 0.81, MeOH). Hydroxy acid **4** appears to be a conglomerate (mp of racemate is 110.5-111.5°C),[4] which makes it an attractive intermediate for producing Mosher's acid of very high enantiomeric purity. Both steps are efficient and require no chromatography thus making their scale up feasable. Conversion of acid (*R*)-**4** to (*R*)-MTPA (**1**) can be achieved according to reported procedures.[4]

Scheme

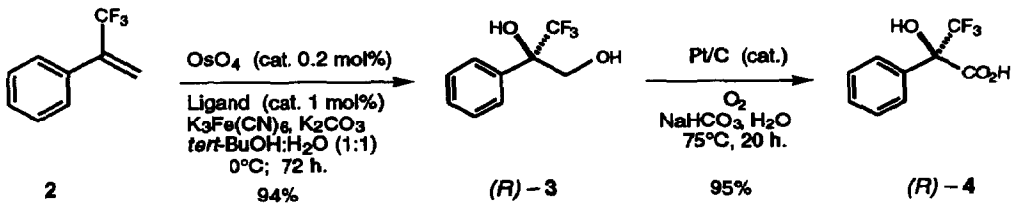
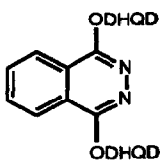
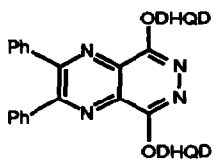


Figure 2



$(DHQD)_2$-PHAL **5**, 83% ee



$(DHQD)_2$-DPP **6**, 91% ee

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12. *Preparation of (R)-1,1,1-trifluoro-2-phenyl-2,3-propanediol* (**3**):
A solution of $K_3Fe(CN)_6$ (28.8 g, 0.087 mol), K_2CO_3 (11.9 g, 0.087 mol), $(DHQD)_2$-DPP **6** (0.275 g, 1.0 mol%), OsO_4 (0.58 mL of a 0.1 M solution in toluene, 0.2 mol%), *tert*-BuOH (145 mL) and H_2O (145 mL) was cooled to 0°C and under vigorous stirring, α-trifluoromethyl styrene **2** (5.0 g, 0.029 mol) was added. The reaction mixture was stirred at 0°C for 72 h then solid sodium metabisulfite (43 g) was added slowly. After stirring for 45 min. at 25°C, EtOAc (200 mL) was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 x 25

mL). The organic fractions were combined, washed with water (2 x 50 mL), brine (2 x 50 mL) then dried over $MgSO_4$. The solvent was evaporated giving a yellow residue which was taken up in EtOAc (100 mL) (organic layer *A*) and washed with 1 N H_2SO_4 (2 x 25 mL) (aqueous layer *A*). The aqueous layer *A* was neutralized using 0.1 N NaOH then extracted with EtOAc (3 x 30mL); this organic layer was dried over $MgSO_4$ and evaporated to give 0.26 g (95% recovery) of ligand **6** as a yellow solid. The organic layer *A* was washed with water (2 x 25 mL) and brine (2 x 25 mL), dried over $MgSO_4$ and evaporated to give a thick clear oil which was virtually pure (TLC, R*f* 0.5, EtOAc:hexane 1:1). Bulb-to-bulb distillation (145°C, 0.02 mm Hg) gave 5.61 g (94% yield) of diol **3** which solidified upon cooling; mp 33-37°C; 91% ee (HPLC of the cyclic carbonate R_t 12.8 min./ 21.5 maj. on a Chiralcel OD-column using 2.5% *i*-PrOH-hexane at 1mL/min.). $[\alpha]_D$ –14.8 (*c* 2.05, MeOH); IR (neat) ν_{max} 3434 (s, OH), 2957 (w, CH_2), 1165 (m); ^{1}H-NMR ($CDCl_3$) δ 7.56 (m, 2 H, Ar.), 7.23 (m, 3 H, Ar.), 4.25 (d, 1 H, J = 12.0 Hz, -C<u>H</u>$_2$), 3.89 (d, 1H, J = 12.0 Hz, –C<u>H</u>$_2$), 3.75 (br.s, 1H, C(CF_3)-O<u>H</u>), 2.29 (br.s, 1 H, –OH); ^{13}C-NMR ($CDCl_3$) δ 135.0, 129.0; 128.4, 126.4, 126.0, 123.6, 76.2 (d), 64.80; ^{19}F-NMR ($CDCl_3$ using $CFCl_3$ as a reference at 0.0 ppm) δ –77.7; HRMS: calcd. for $C_9H_9F_3O_2$: 206.0554; found 206.0560.

Preparation of (R)-α-hydroxy-α-trifluoromethylphenyl acetic acid (**4**):
A 50 mL round-bottomed flask was connected to a gas dispersion tube and charged with diol **3** (1.0 g, 0.485 mmol), 10% Pt/C (0.5 g),[14] $NaHCO_3$ (0.4 g) water (35 mL) and one drop of Dow Corning Antifoam A. The mixture was heated at 75°C while a gentle flow of air was bubbled through. After 20 hours, the reaction was complete as monitored by TLC (SM Rf : 0.9 ; product Rf: 0.1) using EtOAc as eluent. The mixture was cooled to room temperature and filtered through a pad of celite (5 cm long/3 cm wide) with additional water rinsing (3 x 10 mL). The solution was acidified to ~pH 2 using 1 N H_2SO_4 and extracted with EtOAc (3 x 50 mL). The organic layer was washed with water (2 x 25 mL), brine (2 x 25 mL), dried over $MgSO_4$ and evaporated to give 1.01 g (95% yield) of white solid. $[\alpha]_D$ +24.2 (*c* 0.8, MeOH). Recrystallization from hexane-toluene (30 mL-3 mL) gave 0.72 g of **4** (mp 122-124°C) with an optical rotation of $[\alpha]_D$ +29.8 (*c* 0.81, MeOH)[7b]. The enantiomeric excess was determined by HPLC after reduction (LAH-Et_2O) to diol **3** and conversion to the corresponding carbonate (*vide supra*)
All spectroscopic data were satisfactory and in agreement with those reported in the literature.[7b]

13. In a separate experiment, crude diol **3** obtained from the AD reaction was further oxidized to hydroxy acid **4** in 90% overall yield from olefin **2**.
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