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7 Asymmetric Hydroxylation and Aminohydroxylation

CONTENTS

7.1 ASYMMETRIC AMINOHYDROXYLATION OF 4-METHOXYSTYRENE

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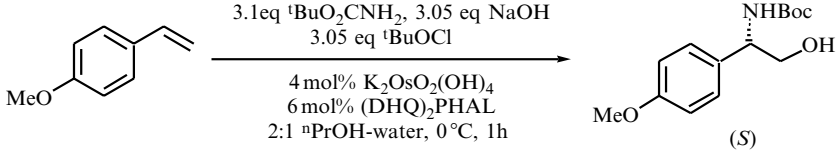

Materials and equipment

- *tert*-Butyl carbamate, 545 mg, 4.65 mmol
- *n*-Propanol, 24.2 mL
- Sodium hydroxide, 183 mg, 4.6 mmol
- Water, 12.2 mL
- *tert*-Butylhypochlorite, freshly prepared, 0.53 mL, 4.6 mmol

tert-Butyl hypochlorite was freshly prepared according to the literature procedure[1,2] using sodium hypochlorite (5% chlorine, purchased from Acros Organics, catalogue number 41955). The quality of the sodium

hypochlorite is important for the preparation of good quality *tert*-butyl hypochlorite. *tert*-Butyl hypochlorite can be stored in a foil-covered flask in the freezer for up to 3 weeks without any noticeable change in performance.

- DHQ_2PHAL, 71 mg, 0.09 mmol
- 4-Methoxystyrene, 201 mg, 1.5 mmol
- Potassium osmate dihydrate [$K_2OsO_2(OH)_4$], 22.5 mg, 0.06 mmol
- Saturated aqueous sodium sulfite solution
- Ethyl acetate, petroleum ether (40–60 °C)
- Brine
- Magnesium sulfate

- 50 mL round-bottomed flask with magnetic stirrer bar
- Magnetic stirrer
- Separating funnel, 100 mL
- Rotary evaporator
- Flash chromatography column, 3 cm diameter

Procedure

1. In a 50 mL round-bottomed flask equipped with a magnetic stirrer bar were placed *tert*-butyl carbamate (545 mg) and *n*-propanol (6 mL). A solution of sodium hydroxide (183 mg) in water (12.2 mL) and *tert*-butyl hypochlorite (0.53 mL) were added to the solution. The resulting solution was stirred for 5 minutes and cooled to 0 °C. Then a solution of DHQ_2PHAL (71 mg) in *n*-propanol (6 mL), a solution of 4-methoxystyrene in *n*-propanol (12.2 mL) and potassium osmate dihydrate (22.5 mg) were added sequentially to give a green solution. After 1 hour at 0 °C, the reaction mixture had turned from green to yellow.
2. The reaction was monitored by TLC (eluent: petroleum ether–ethyl acetate, 1:1). Visualized by ninhydrin dip, the product stained brown-orange, R_f 0.43. The 4-methoxystyrene (visualized by UV) has R_f 0.72.
3. After completion of the reaction, saturated aqueous sodium sulfite solution (10 mL) was added and the mixture stirred for 15 minutes. Ethyl acetate (5 mL) was added and the two phases were separated. The aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with brine (20 mL), dried over magnesium sulfate, filtered and concentrated using a rotary evaporator to give the crude product.
4. Purification by flash column chromatography on silica (eluent: petroleum ether–ethyl acetate, 2:1) gave a crystalline solid (*S*)-*N*-(*tert*-butoxycarbonyl)-1-(4-methoxyphenyl)-2-hydroxyethylamine (296 mg, 74 %).

   The ee (98 %) was determined by HPLC (Chiralcel OD-H column, flow 1 mL/min, eluent: heptane–*iso*-propanol, 95:5); (*S*)-enantiomer: R_t 11.7 min, (*R*)-enantiomer: R_t 10.3 min.

^{1}H NMR (270 MHz, $CDCl_3$) 7.26–7.19 (m, 2 H, Ar); 6.90–6.87 (m, 2 H, Ar); 5.16 (br s, 1 H, NH); 4.73 (br s, 1 H, ArCHN); 3.82 (br s, 2 H, CH_2O); 3.80 (s, 3 H, MeO); 1.43 (s, 9 H, CMe_3).

IR ($CHCl_3$, cm^{-1} 3611 (O–H); 3442 (N–H); 1707 (C=O)).

mp 139–141 °C (from petroleum ether-ethyl acetate, 2:1).

$[\alpha]_D$ + 62.6 (*c* 1.0 in EtOH).

7.1.1 CONCLUSION

The asymmetric aminohydroxylation[3] of 4-methoxystyrene using DHQ_2 PHAL as the ligand actually produces an 85:15 mixture of (*S*)-*N*-(*tert*-butoxycarbonyl)-1-(4-methoxyphenyl)-2-hydroxyethylamine and its regioisomer as shown by ^{1}H NMR spectroscopy on the crude product mixture. The regioisomer is lower running by TLC. The product is separated from the regiosiomer and from excess *tert*-butyl carbamate by *careful* flash column chromatography: this is a limitation of the methodology.

(*R*)-*N*-(*tert*-Butoxycarbonyl)-1-(4-methoxyphenyl)-2-hydroxyethylamine (ee, 96%) can be prepared using $DHQD_2$PHAL as the ligand but this results in the production of more of the unwanted regioisomer: a 68:32 mixture of the (*R*)-product and its regioisomer were obtained. This gives a lower isolated yield of (*R*)-*N*-(*tert*-butoxycarbonyl)-1-(4-methoxyphenyl)-2-hydroxyethylamine (65%) as compared to its enantiomer (74%). The same trend is observed with other styrene derivatives[2]. A wide range of styrene derivatives give high enantiomeric excesses using these conditions.[2,4]

7.2 ASYMMETRIC DIHYDROXYLATION OF (1-CYCLOHEXENYL) ACETONITRILE

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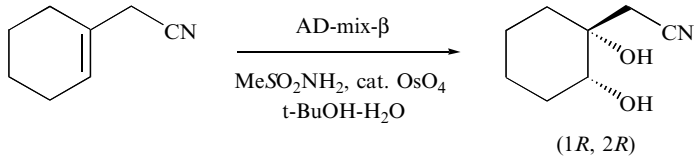


(1*R*, 2*R*)

Materials and equipment

- *tert*-Butanol, 70 mL
- Water, 70 mL

- AD-mix-β, 20 g
- Methanesulfonamide, 1.36 g
- Osmium tetroxide (4 wt% solution in water), 0.36 mL
- (1-Cyclohexenyl)acetonitrile, 1.73 g
- Sodium metabisulfite ($Na_2S_2O_5$), 14 g
- Dichloromethane, 360 mL
- Magnesium sulfate
- Ether, petroleum ether
- (40–63 μm) Silica gel 60, 30 g

- 250 mL Round-bottomed flask with a magnetic stirrer bar
- Magnetic stirrer
- Separating funnel, 500 mL
- Sintered glass funnel (4 cm)
- Flash column chromatography (30 cm × 2.5 cm)

Procedure

1. In a 250 mL round-bottomed flask equipped with a magnetic stirrer bar were placed a 1:1 mixture of *tert*-butanol and water (140 mL), AD-mix-β (20 g) and methanesulfonamide (1.36 g)[5].

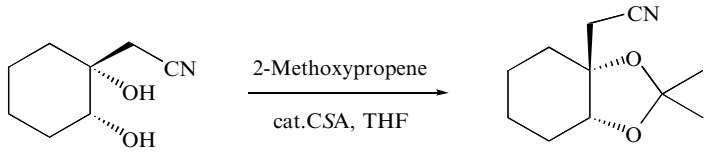
   100 g of AD-mix-β are made up of potassium osmate (0.052 g), $(DHQD)_2PHAL$ (0.55 g), $K_3Fe(CN)_6$ (70 g), K_2CO_3 (29.4 g).
2. The mixture was stirred for a few minutes at room temperature until two clear phases were produced. To the ice-chilled reaction mixture were successively added osmium tetroxide (4 wt% in water, 0.36 mL) and (1-cyclohexenyl)-acetonitrile (1.73 g). The reaction mixture was stirred vigorously for 8 hours at 0 °C.
3. The reaction was monitored by TLC (eluent: petroleum ether–ether, 4:1). Olefin and diol spots, visualized by iodine vapour, have R_f values of 0.43 and zero respectively.
4. Sodium metabisulfite (14 g) was added to the reaction mixture and stirring was continued for 1 hour.
5. The reaction mixture was transferred to a separating funnel and extracted three times with dichloromethane (3 × 120 mL). The combined organic phases were dried over magnesium sulfate, filtered and concentrated using a rotary evaporator. The residue was purified by flash chromatography on silica gel (eluent: ether–petroleum ether, 3:2) to give a crystalline product (2.1 g, 94 %), mp 95–101 °C, $[\alpha]^{20}_D$ − 1.6 (*c* 1, $CHCl_3$)[6].

   The ee (66–71 %) was determined on the acetonide derivative by GC analysis.

   ^{1}H NMR (200 MHz, $CDCl_3$: δ 1.3–1.8 (m, 7 H), 2.0 (m, 1 H), 2.58 (d + brs, 2 H, *J* 17 Hz, C$\underline{H}_a$CN, OH), 2.73 (d + brs, 2 H, *J* 17 Hz, C$\underline{H}_b$CN, OH), 3.52 (dd, 1 H, *J* 4.4 and 10.3 Hz, C$\underline{H}$OH).

   ^{13}C NMR (50.3 MHz, $CDCl_3$): δ 20.6, 23.7, 28.8, 30.4, 34.6, 72.1, 117.9.

7.2.1 (*R*,*R*)-(1,2-DIHYDROXYCYCLOHEXYL)ACETONITRILE ACETONIDE



Materials and equipment

- Tetrahydrofuran, 40 mL
- (1,2-Dihydroxycyclohexyl)acetonitrile (66 % ee), 2.1 g
- Camphorsulfonic acid (CSA), 0.04 g
- 2-Methoxypropene, 2.5 mL
- Ether, petroleum ether
- (40–63 μm) Silica gel 60, 40 g
- Hexane

- 100 mL Round-bottomed flask with a magnetic stirrer bar
- Magnetic stirrer plate
- Flash column chromatography (30 cm × 2.5 cm)
- Rotary evaporator

Procedure

1. (1,2-Dihydroxycyclohexyl)acetonitrile (2.1 g) was placed in a 100 mL round-bottomed flask equipped with a magnetic stirrer bar. Dry tetrahydrofuran (40 mL) was added followed by CSA (0.04 g) and 2-methoxypropene (2.5 mL). The solution was stirred at room temperature for 90 minutes.
2. The reaction was monitored by TLC (eluent: petroleum ether–ether, 1:2). Diol and acetonide spots, visualized by *p*-anisaldehyde dip, have R_f values of 0 and 0.35 respectively.
3. The reaction mixture was concentrated using a rotary evaporator. The residue was chromatographed on silica gel (eluent: ether–petroleum ether, 1:3) to afford a white solid (97 %).
4. The solid was crystallised twice in hexane to afford a compound (1.68 g) with a high enantiomeric purity (94.7 % ee), mp 55–60 °C, $[\alpha]_D^{20}$ −27.6 (*c* 0.7, $CHCl_3$).

   The enantiomeric excess was determined by capillary GC analysis (Lipodex E.MN, 25 m, 0.25 mm ID, temperature column 80–150 °C, 5 °C/min). (*S*,*S*)-enantiomer: R_t 19.25 min, (*R*,*R*)-enantiomer: R_t 19.69 min.

   The absolute configuration was determined by chemical correlation with the known (2R)-2-allyl-2-hydroxycyclohexanone.

^{1}H NMR (200 MHz, $CDCl_3$): δ 1.32 (s, 3 H, CH_3), 1.5 (s, 3 H, CH_3), 1.5–1.7 (m, 7 H), 2.1–2.2 (m, 1H), 2.58 (d, 1 H, *J* 17 Hz, C$\underline{H}_a$CN), 2.67 (d, 1 H, *J* 17 Hz, C$\underline{H}_b$CN), 4.1 (brs, 1 H, C$\underline{H}$OCMe$_2$).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ 19.5, 22.6, 25.5, 26.2, 26.8, 28.3, 34.6, 76.0, 77.2, 108.3, 116.9.

7.2.2 CONCLUSION

Osmium-catalysed asymmetric dihydroxylation allowed an efficient transformation of (1-cyclohexenyl)acetonitrile to enantioenriched (1,2-isopropylidenedioxy)cyclohexylacetonitrile in good yield (65%) and high enantiomeric purity (94.7% ee). This acetonide can be easily transformed in a few steps to α-ketols bearing allyl or 3-trimethylsilylpropargyl groups, precursors of neurotoxic alkaloids histrionicotoxins.[7, 8] This methodology enabling the preparation of substituted α-ketols is superior to that described in the literature.[8, 9] This method which involves a chromatographic resolution of diastereomeric ketals presents several drawbacks such as a low efficiency of the chromatographic separation ($\Delta R_f = 0.05$) and occurrence of a partial racemization during acid deketalization.

Sharpless asymmetric dihydroxylation has been successfully applied to (1-cyclopentenyl)acetonitrile. Using (DHQ)PHN as a ligand in place of (DHQ)$_2$PHAL,* one of the components of AD-mix-α, (*S*,*S*)-(1,2-dihydroxycyclopentyl)acetonitrile was obtained after two recrystallizations, in 50% yield and 90% ee.

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* (DHQ)PHN and (DHQ)$_2$PHAL are the respective abbreviations of dihydroquinine 9-phenanthryl ether and of dihydroquinidine 1,4-phthalazinediyl diether.