Synthesis of Substituted Mandelic Acid Derivatives via Enantioselective Hydrogenation: Homogeneous versus Heterogeneous Catalysis

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Supporting Information

Preparative procedures

Homogeneous hydrogenation

12 L MeOH and 1000 g (5.03 mol) *p*-Cl phenylglyoxylic acid methyl ester **9a** were placed in a thoroughly cleaned 16 L Inconel autoclave. After closing, the autoclave was evacuated / flushed with argon for three times, and subsequently degassed for 1 h by purging with argon. Then 616 mg (0.63 mmol) $[RuI_2(p\text{-cymene})]_2$ and 770 mg (S)-MeObiphep were placed in a 3 necked round bottom flask under argon. After the addition of 200 mL degassed MeOH and 20 mL degassed 1 M HCl, the suspension was transferred to the autoclave. The remaining suspension was also transferred to the autoclave with an additional 300 mL degassed MeOH. After pressurizing the autoclave with 89 bar hydrogen, it was heated to 60 °C. Hydrogen uptake was observed during approximately 9 hours. The hydrogen uptake calculated from the pressure drop in the reservoir was 90%. After 24 h, the autoclave was cooled to room temperature and the pressure was released. After discharging the autoclave, the product was evaporated to dryness under reduced pressure. Yield of raw *(R)*-*p*-Cl mandelic acid methyl ester **10a** 1110 g (still containing some MeOH), conversion 100%, ee 91.9%.

Heterogeneous hydrogenation

600 mg 5% Pt/Al_2O_3 (JMC 94, pretreated for 2 h at 400 °C under hydrogen) were wetted with toluene and placed in a 300 mg steel autoclave. After the addition of 60 mg HCd, the autoclave was closed and checked for leaks. Then 15 g (75.5 mmol) **9a** dissolved in approximately 100 mL toluene (total volume toluene 135 mL) were added. Without delay, the autoclave was pressurized with nitrogen (3 times) and with hydrogen (3 times). Then the hydrogen pressure was raised to 60 bar and the reaction was started by turning the stirrer on (time between loading of 1 and starting < 5

minutes). After 60 minutes, the hydrogen uptake had ceased. The pressure was released, and the autoclave was purged three times with nitrogen. The reaction mixture was filtered (some loss) and the filtrate was evaporated to dryness. Yield of *(R)*-*p*-Cl mandelic acid methyl ester **10a** : 12.3 g 2 (81%), conversion > 98% ee 93%.

Hydrolysis

19.2 L 0.2 M NaOH were placed in a 50 L separation vessel. To this, 600 g of the of the raw *(R)*-*p*-Cl mandelic acid methyl ester **10a** (approx. 546 g or 2.72 mol 2) were added and stirred for 2 h at room temperature. Then, the aqueous phase was extracted three times with 2 L CH_2Cl_2. The combined CH_2Cl_2-phases were extracted with 6l water, dried and evaporated to dryness. 67 g of non-hydrolyzed ester 2 (0.33 mol) were recovered. The pooled aqueous phases containing the hydrolyzed product were acidified with 4.74 L 1 M HCl to pH 1.5 and the extracted with 4 L EtOAc and 3 L EtOAc (three times). The combined organic phases were dried over Na_2SO_4 and evaporated to dryness to obtain 442 g free *(R)*-*p*-Cl mandelic acid (MW 186.6g, 2.26 mol, 83%, 95% when accounting for the recovered ester).

Crystallization

442 g *(R)*-*p*-Cl mandelic acid were placed in 1.65 L Bu_2O and heated to 95 °C (acid completely dissolved). After cooling to 20 °C, the product crystallized and was stirred for over night h at 20 °C. The crystals were filtered and washed with about 50 mL Bu_2O. 250 g *(R)*-*p*-Cl mandelic acid (57%) with an ee of 97.4 % were obtained. 250 g *(R)*-*p*-Cl mandelic acid with an ee of 97.4% were placed in 0.9 L Bu_2O and heated to 100 °C (completely dissolved). With the same procedure as above, 161 g free *(R)*-*p*-Cl mandelic acid (64%) with an ee of 99.3 % were obtained. From the mother liquor, 91 g **6** with an ee of 93.6 % was recovered.

Over all yield of *(R)*-*p*-Cl mandelic acid (hydrolysis and re - crystallization): 30%.