Preparation and purification of a secondary chiral amine


**Lab 1: Bis[1-(phenyl)ethyl]amine (1)**

An oven-dried 25 mL round-bottom flask was equipped with a septum and a balloon full of N₂ and a magnetic stirring bar. In as much as possible an atmosphere of N₂ should be maintained in the reaction vessel.
The flask was loaded with (S)-1-(phenyl)ethylamine (1.0 g, 8.3 mmol) and acetophenone (1.0 g, 8.3 mmol). Then Ti(Oi-Pr)_4 (7.5 mL, 25 mmol) was added via syringe. The reaction mixture was stirred at room temperature over 20 min and take a few drops of the mixture and keep in a vial for TLC before adding 10% Pd/C (54 mg, 0.051 mmol).

The N₂ balloon was replaced with a H₂ balloon and the nitrogen atmosphere should be replaced with hydrogen by gently purge the flask with H₂ for a few seconds using a needle to bleed the flask through the rubber septum (see illustration in Setup). The reaction mixture was stirred under one atmosphere (balloon) of H₂ over 2.5 h, monitoring the reaction progress with TLC at one hour interval. The TLC plate should be co-spotted with the two starting material and the reaction mixture.
Once the starting material disappeared, the balloon of H₂ is removed; the flask is opened to air and cooled in an ice bath, 10% aqueous NaOH (12 mL) was added, causing the precipitation of titanium salts. This mixture becomes a think "sludge" and was treated with EtOAc (10 mL), triturated and separate the top layer with a pipette. If the mixture is too thick, it should be broken up using a spatula and filter through a Buchner funnel covered with half inch of Celite.
The reaction flask is rinsed with 6 mL of NaOH solution and pour through the Celite pad and then rinsed with 10 mL EtOAc, which also pour through the Celite pad. The organic phase was transferred into a 50 mL Erlenmeyer flask. The Celite in the Buchner funnel was rinsed with EtOAc (5 mL). Transfer the washes to a separatory funnel and separate the aqueous layer from the organic layer.

The aqueous layer was extracted with EtOAc (3 x 10 mL) three times. The combined organic layer was then dried over 6 g of anhydrous Na$_2$SO$_4$, filtered, transferred to a 50 mL flask and concentrated on a rotary evaporator yielding 1.9–2 g of a mixture of 1 as a 82:18 mixture
of (S,S)- and meso- isomers as a viscous colorless oil, which gradually solidified.

Preparation of HBr salt of 1 (Warning: HBr is strongly corrosive!)

Lab 2

Inside the hood, the solid was suspended in EtOAc (8 mL) and an aqueous 48% HBr (0.5 mL) was added dropwise, causing the precipitation of a white solid, which was collected by filtration and washed with EtOAc (2 x 5 mL) twice. The solid was recrystallized from a mixture of 50:50 EtOAc–EtOH (100 mL) at r.t. affording the hydrobromide salt of 1 as colorless crystals; yield: 0.9–1.0 g (40–43%). Recrystallization of the residue from the filtrate from a mixture of 50:50 EtOAc–EtOH (12 mL) gave a second crop; yield: 1.89–2.32 (16–19%); total yield: 2.79–3.32 g (59%). The hydrobromide salt of 1 was
neutralized with aq 10% NaOH and extracted with CH₂Cl₂. The DCM solution was dried with Na₂SO₄ and filtered, and the solvent is removed using a rotary evaporator. Weigh your product and calculate the yield.

**Identification of the purity of the product 1**

Lab 3

The ratio of (S,S)-/meso-isomers will be determined by ¹H NMR and optical activity analysis. Use about 30 mg of the product for ¹H NMR and about 0.5 g for optical activity measurements. Recover both samples after obtaining the analytical data. Turn in your final product to your TA in a vial labeled with the structure of 1 and your name.

Literature data for secondary chiral amine 1: [α]_D^{22} –92 (c = 0.98, CHCl₃). IR (CHCl₃): 2955, 2924, 1597, 1584, 1485, 1451, 1436, 1229, 1095, 1083, 1025 cm⁻¹. ¹H NMR (400 MHz, CDCl₃): δ = 7.34 (d, J = 7.04 Hz, 2 H), 7.22 (t, J = 7.04 Hz, 2 H), 6.96 (t, J = 7.32 Hz, 2 H), 6.85 (d, J = 8.08 Hz, 2 H), 3.89 (q, J = 6.56 Hz, 2 H), 3.73 (s, 6 H), 2.12 (br,
1 H), 1.30 (d, $J = 6.84$ Hz, 6 H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta =$ 157.2, 133.7, 127.3, 127.1, 120.4, 110.3, 54.9, 50.1, 22.9.