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Emergence of a Single Solid Chiral State from a Nearly Racemic Amino Acid Derivative

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Supporting Information
Preparation of the starting material (RS)-1

Racemic \( N\)-(2-methylbenzylidene)-phenylglycine amide ((RS)-1) was prepared from commercially available (RS)-phenylglycine ((RS)-Phg).

**Step 1:** A suspension of 1 mol of (RS)-Phg, originally produced commercially by DSM Pharmaceutical Products from benzaldehyde by means of a Strecker reaction with \( \text{NH}_3/\text{HCN} \) and subsequent acidic hydrolysis*, in 1 L of MeOH was cooled to 0°C and 1.2 mol of SOCl\(_2\) was slowly added over a period of several hours in order to keep the temperature below 20°C. The clear solution was stirred for 18 h at ambient temperature and subsequently refluxed for 1 h in order to remove the SO\(_2\). The volume was then reduced to 350 mL by evaporation under reduced pressure and 1.5 L of MTBE was added to crystallize the (RS)-Phg methyl ester HCl salt. The crystals were filtered and dried under reduced pressure and were used as such in the next step.

*Note: Phg forms a very stable racemic compound and has a eutectic composition with 97% ee.

**Step 2:** The crystals described above were added in portions to a stirred solution of 750 mL of concentrated ammonia. During the addition (RS)-Phg amide started to precipitate and stirring was continued for a few hours until all the methyl ester was converted (tested by TLC on silica, eluent: CHCl\(_3\), MeOH, conc. ammonia 60:45:20). The racemic amide was filtered, washed with cold water (note, solubility 5 wt%) and dried. Overall yield approximately 80%.

**Step 3:** To a stirred solution of 68.6 g of (RS)-Phg amide in a mixture of 150 mL of water and 300 mL of MeOH at ambient temperature was added 55.9 g of 2-methylbenzaldehyde over a period of 1 hour (after addition of 20% of the aldehyde crystallisation usually starts spontaneously; if not it is better to add racemic seed crystals for a controlled crystallisation). The thick suspension was stirred for 20 h at ambient temperature and then filtered. The crystals were washed with 100 mL of MeOH/water 2:1 and 200 mL of MTBE, dried under reduced pressure, thus yielding 110 g (95%) of NMR and HPLC pure (RS)-1 as colorless needles. M.p. 153°C. \(^{1}\text{H NMR (200 MHz, CDCl}_3\)} \( \delta \) 8.61 (s, 1H), 7.95 (dd, 1H, J=8.0
and 1.7 Hz), 7.19-7.53 (m, 8H), 7.01 (br s, 1H), 5.91 (br s, 1H), 4.99 (s, 1H) and 2.52 (s, 3H). $^{13}$C NMR (50 MHz, CDCl$_3$) $\delta$ 171.61 (s), 160.26 (d), 139.42 (s), 137.00 (s), 132.44 (s), 129.80 (d), 129.67 (d), 127.23 (d), 126.73 (d) 126.26 (d), 124.95 (d), 76.36 (d) and 17.94 (q). Calculated for C$_{16}$H$_{16}$N$_2$O: C, 75.16%; H, 6.39%; N, 11.10%. Found: C, 75.78%; H, 6.37%; N, 11.09%. MS(CI): m/z = 253 (M+1).

(RS)-1 may be further purified by several recrystallisations from MeOH (2.5 L for 100 g, crystallisation yield 75-80%). However, this had no effects on the deracemization experiments described in this paper.

Care should be taken not to heat the methanolic solution of (RS)-1 for longer period of time, in order to prevent formation of the cyclization product 2-(2-methylphenyl)-5-phenyl-imidazolidin-4-one (racemic 1:1 diastereomeric mixture).

Analogously to the method above also (R)-1 and (S)-1 were prepared from commercially available (R)-phenylglycine amide and (S)-phenylglycine, respectively. M.p. 180°C. (R)-enantiomer; [$\alpha$]$^25_D$ -29.9 (c = 0.5, MeOH).

The virgin deracemization experiments

In 100 mL round bottom flask with an oval PTFE-coated magnetic stirring bar (L 20mm, $\varnothing$ 10mm) were weighed in 4.0g of (RS)-1, 36g of MeOH (PA quality) and 10g $\varnothing$ 2-2.5 mm glass pearls (Aldrich). The flask was sealed and stirred for 24 hours at 1250 rpm magnetic stirrer to equilibrate the solvent and solute. Furthermore, the possible memory effect of the crystal size distribution is overcome by grinding all the crystals. From this suspension the $t = 0$ sample was taken. To the suspension was then added 200 mg (200 $\mu$L) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (5 mol%) and stirring was started at 1200-
1300 rpm. Samples were taken every 3 days. The chiral purity was measured using chiral HPLC as described below, and confirmed by polarimetry.

Further analysis was performed using $^1$H-NMR, DSC and XRPD.

After prolonged stirring in the solid 1 samples 2-(2-methylphenyl)-5-phenyl-imidazolidin-4-one can be detected as a racemic 9:1 diastereomeric side-product. Both diastereomers of the side-product are racemic within the HPLC detection limits (fide infra).

Experiments with initial enantiomeric imbalances

In the case MeOH was used as a solvent, a total of (R/S)-1 (c.a. 2.0 g), glass pearls (5 g) and MeOH (18 g) were placed in a 100 ml round bottom flask with a magnetic stirring bar. The mixture was stirred overnight at room temperature in order to crush solid particle size. To the suspension, DBU (100 µL, 5 mol%) was added and stirring was started at 1000 rpm. The flask was manually shaken daily and samples were taken before addition of DBU (t = 0) and 7, 14, 21 and 35 days after the addition of DBU. Four experiments with 2% ee, 5% ee, 7% ee and 10% ee ($S$) were carried out in MeOH (Fig. 1). When using MeCN as a solvent, (RS)-1 + appropriate amounts of (R)-1 or (S)-1 (total c.a. 4.0 g), glass pearls (10 g) and MeCN (36 g) were placed in a 100 mL round bottom flask. After stirring overnight (1250 rpm), the t = 0 sample was taken and DBU was added (200 µL, 5 mol%). Samples were taken every 3 days. Further analysis was performed as described for the virgin experiments. No side product formation was observed in MeCN.
Experiments with (R)- and (S)-phenylglycine as additive

In a 100 mL B24 round bottom flask with magnetic stirring bar were weighed in 10 gram of glass pearls, 4.0 g of (RS)-1 and 36 g of MeOH or MeCN. The mixture was stirred at 1250 rpm at room temperature for 15 min. Thereafter, 2.5-200 mg of (R)-Phg was added using a weighing paper. Stirring was continued for 1-24 h to reach equilibrium. From this suspension the t = 0 sample was taken. To the suspension was then added 200 mg (200 µL) of DBU (5 mol%) and stirring was continued at 1200-1300 rpm. For high concentrations of Phg additional DBU has to be added to overcome the effect of reduced basicity as a result of salt formation between the DBU and Phg. After addition of DBU the pH should be approximately 12 to ensure that racemization occurs.

Sampling

For sampling, 2-3 mL of the slurry was taken with a pipette and filtered on a P3 or P4 glass filter (Ø 10 mm). The residue was washed with 1 mL of MeOH or MeCN, respectively, and 2 mL of MTBE to remove mother liquid and DBU, and dried overnight in a vacuum stove overnight at 40 ºC.

Dissolution enrichment experiments

Small enantiombalances can already be amplified to single chirality. Although the starting material is prepared from (RS)-Phg, which is a very stable racemic compound, we checked the enantiopurity by dissolution. Conglomerates which are enriched in one enantiomer enrich in the solid phase upon dissolution. To check if 1 was racemic, ca. 0.4 g 1 was partially dissolved in 12 ml MeCN. After stirring the suspension overnight, the solid material was collected on a P3 glass filter and dried in a vacuum
stove. Chiral HPLC analysis and polarimetry showed no chiral enrichment, confirming that the starting material was racemic within the detection limits.

*Determinations of the ee by chiral HPLC analysis of the solids samples*

Sample preparation 0.5 mg solid in 1.5 mL eluent, injection volume 20µL, HPLC column Chiralcel-OJ (250x4.6 mm ID), eluent n-hexane/2-propanol 80/20 v/v%, flow 1mL/min, r.t., detection λ=254 nm. Retention times (S)-1 11.4 min, (R)-1 17.4 min, (2R\*,5R)-2-(2-methylphenyl)-5-phenyl-imidazolidin-4-one (cyclic side-product) 8.8 min, (2S\*,5S)-side-product 9.8 min, (2S\*,5R)-side-product 11.2 min, (2R\*,5S)-side-product 11.9 min. The response factor of 1 is 25 times higher than of the cyclic side-products at 254 nm, whereas at 213 nm the response factor is 1.5 times higher.

*Control of ee determination*

As a check of the ee determination by the chiral HPLC method described above, an independent ee determined has been performed on some of the samples. Therefore 50-60 mg of enantiomerically enriched 1, isolated from various deracemization experiments, was dissolved in 3 mL of 0.25M HCl solution. The solution was extracted two times with 3 mL of CHCl₃. The remaining aqueous solution of phenylglycine amide HCl salt was used as such for the ee determination by the following HPLC method. Column; Crownether Cr(+) 150 x 4.6 mm ID, eluent; aqueous HClO₄ pH=1.2 / Methanol 90/10 v/v%, flow; 1 mL/min, temperature; 25 °C, detection: UV 220 nm, detection limit: 0.01 area%.
The results of this control $ee$ determination were in agreement with the values obtained by the standard HPLC method described above.

Fig. 1. Attrition-enhanced evolution of solid-phase $ee$ for 1 in MeOH from initial $ee$ values as shown. Lines are provided as a guide to the eye.