Angewandte
Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

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Complete Deracemization by Attrition Enhanced Ostwald Ripening Elucidated

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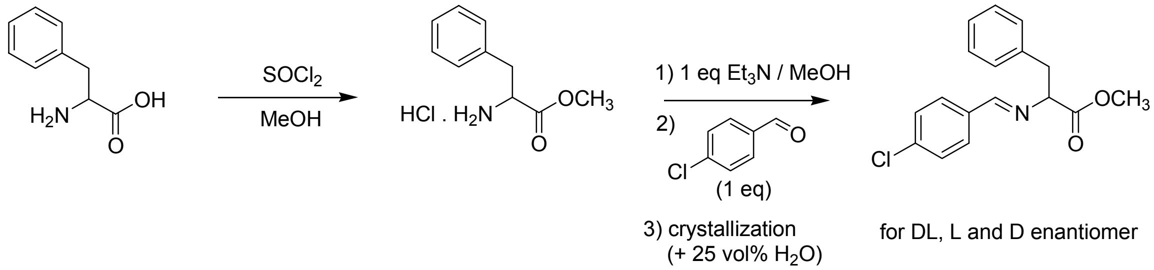
Supporting information

SI Scheme 1. Synthesis of compound **1**.



Synthesis of (*RS*)-*N*-(4-chlorobenzylidene)phenylalanine methyl ester

(*RS*)-Phenylalanine methyl ester HCl-salt:

To a suspension of 83 g (0.50 mol) of (*RS*)-phenylalanine in 550 ml of MeOH at 5°C was added drop-wise 47 ml (0.65 mol) of $SOCl_2$ over a 3 hours period. During the addition the mixture was cooled in ice-bath in order to keep the temperature <10°C. The clear solution was stirred for 20 h and subsequently for 2 h at 50°C. After evaporation of the solvent under reduced pressure 108 g (100%) of (*RS*)-phenylalanine methyl ester HCl-salt was obtained as a white solid. ^1H NMR (300 MHz, DMSO-d6) δ 8.89 (br s, 3H, NH3), 7.34-7.24 (m, 5H, Ph), 4.21 (dd, 1H, α-H), 3.64 (s, 3H, OCH_3), 3.25 (dd, 1H, β-H) and 3.11 (dd, 1H, β-H).

(*RS*)-*N*-(4-Chlorobenzylidene)phenylalanine methyl ester

A solution of 108 g (0.50 mol) of the (*RS*)-phenylalanine methyl ester prepared above in 300 ml of MeOH was neutralized with 80 ml (0.51 mol) of triethylamine to pH 8. To the clear solution at ambient temperature was added 70 g (0.50 mol) of 4-chlorobenzaldehyde in small portions over 30 min. The clear solution was stirred for 1 h and then seeded to induce crystallization. After the crystallization 100 ml of water was added and the mixture was cooled to 0°C. The crystalline product was filtered, washed with 200 ml MeOH:H_2O 2:1, 200 ml MeOH:H_2O 1:1 and 30 ml MeOH. After drying 140 g (0.464 mol, 93%) of (*RS*)-*N*-(4-chlorobenzylidene)phenylalanine methyl ester was obtained as a white crystalline solid. Melting point: 65.1°C. ^1H NMR (300 MHz, CD_2Cl_2) δ 7.96 (s, 1H, CH=N), 7.68 (d, 2H, Ar-H), 7. 43 (d, 2H, Ar-H), 7.31-7.20 (m, 5H, Ph), 4.22 (dd, 1H, α-H), 3.76 (s, 3H, OCH_3), 3.38 (dd, 1H, β-H) and 3.15 (dd, 1H, β-H). ^{13}C NMR (75 MHz, CD_2Cl_2) δ 172.49 (s), 162.94 (d), 138.31 (s), 137.72 (s), 135.12 (s), 130.50(d) , 130.35 (d), 129.62(d) , 129.04 (d), 127.32(d) , 75.38 (d), 52.80 (q) and 40.49 (t).

Synthesis of (*S*)-*N*-(4-chlorobenzylidene)phenylalanine methyl ester

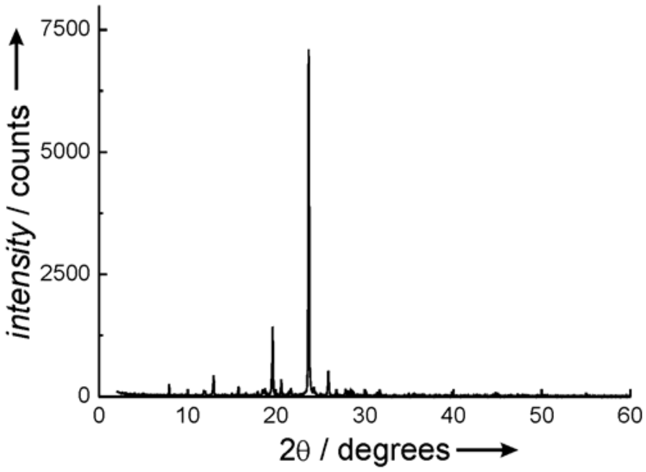
This compound was prepared as described above in 94% yield from commercially available (*S*)-phenylalanine methyl ester HCl-salt (Across). Melting point: 87.4°C. $[\alpha]^{25}_D$ -281 (c=1, MeOH). HPLC, e.e. $\geq$ 99.5% (column Chiralpak AD 150 x 4.6 mm, eluent n-heptane/iPrOH 97.5:2.5 vol%, flow 1.0 ml/min, detection UV 254 nm).

Synthesis of (*R*)-*N*-(4-chlorobenzylidene)phenylalanine methyl ester

This compound was prepared as described above in 93% yield from commercially available (*R*)-phenylalanine methyl ester HCl-salt (Bachem). Melting point: 87.4°C. $[\alpha]^{22}_D$ +285 (c=1, MeOH). HPLC, e.e. $\geq$ 99.5% (column Chiralpak AD 150 x 4.6 mm, eluent n-heptane/iPrOH 97.5:2.5 vol%, flow 1.0 ml/min, detection UV 254 nm).

X-ray structure, XRPD and morphology data,

$P2_12_12_1$ (Z=4) (a = 6.3 Å, b = 14.3 Å, c = 15.3 Å) en overige gegevens + plaatjes



SI Figure 2. X-ray powder pattern of **1**.

Morphology: The crystal morphology of the crystals grown form the enantiomerically pure and racemic solutions were analyzed using two circle optical goniometry and a CCD camera attached on the single crystal diffractometer.

Deracemization experiments

In 100 mL round bottom flask with an oval PTFE-coated magnetic stirring bar (L 20mm, Ø 10mm) were weighed in 3.2 g of (*R/S*)-**1**, 10.0 g of MeOH (dried and distilled from CaH_2) and 6.0 g Ø 2-2.5 mm glass pearls (Aldrich) under Schlenck conditions. The flask was sealed and stirred for 2 hours at ca. 600 rpm using a magnetic stirrer to equilibrate the solvent and solute. To the suspension 0.24 g (10 mol%) of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was added. After 10 minutes, the t = 0 sample was taken from this suspension. Additional samples were taken daily. The enantiomeric purity was measured using chiral HPLC as described below, Further analysis was performed using ^{1}H-NMR, DSC and XRPD.

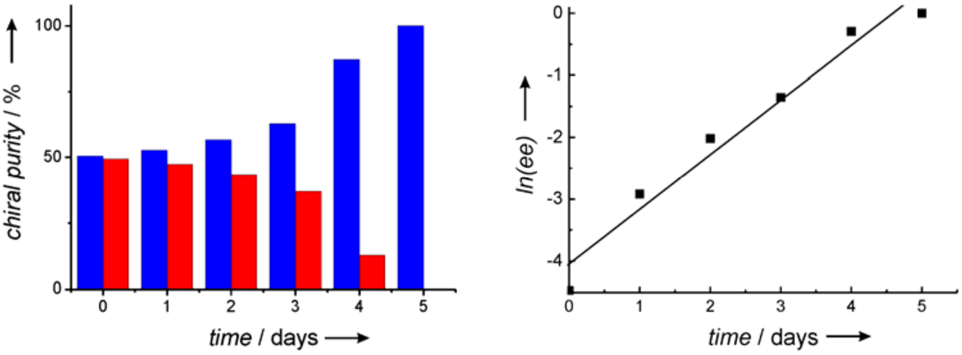
Sampling

For sampling, 0.2 mL of the slurry was taken using a syringe and filtered on a P4 glass filter (Ø 10 mm). The residue was washed with 0.5 mL of 2-propanol and 0.1 mL of methyl tert-butyl ether (MTBE) to remove the mother liquid and DBU, and dried overnight at 40 ºC in a vacuum stove.

Determination of the ee by chiral HPLC analysis of the solid samples

Sample preparation 0.5 mg solid in 1.5 mL eluent, injection volume 20μL, HPLC column Chiralpak-AD-H (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** 5.3 min, (*R*)-**1** 5.7 min.

Deracemization result for an initial scalemic (*S*)-1 mixture



SI Figure 2. Evolution of the solid phase chiral purity during grinding (left), showing an exponential evolution of the enantiomeric excess in (*S*)-**1** (right). The initial ee in the solid phase before dissolution is 0.35%, and increases upon dissolution to approximately 1%.

Determination of the ee by chiral HPLC analysis of individual crystals of racemic 1

The *ee* determination of five individual crystals by the HPLC method described above revealed that each crystal was virtually racemic: 6, 2, 1, -2 and 5% *ee*, respectively.

Deracemization experiments with different crystal sizes

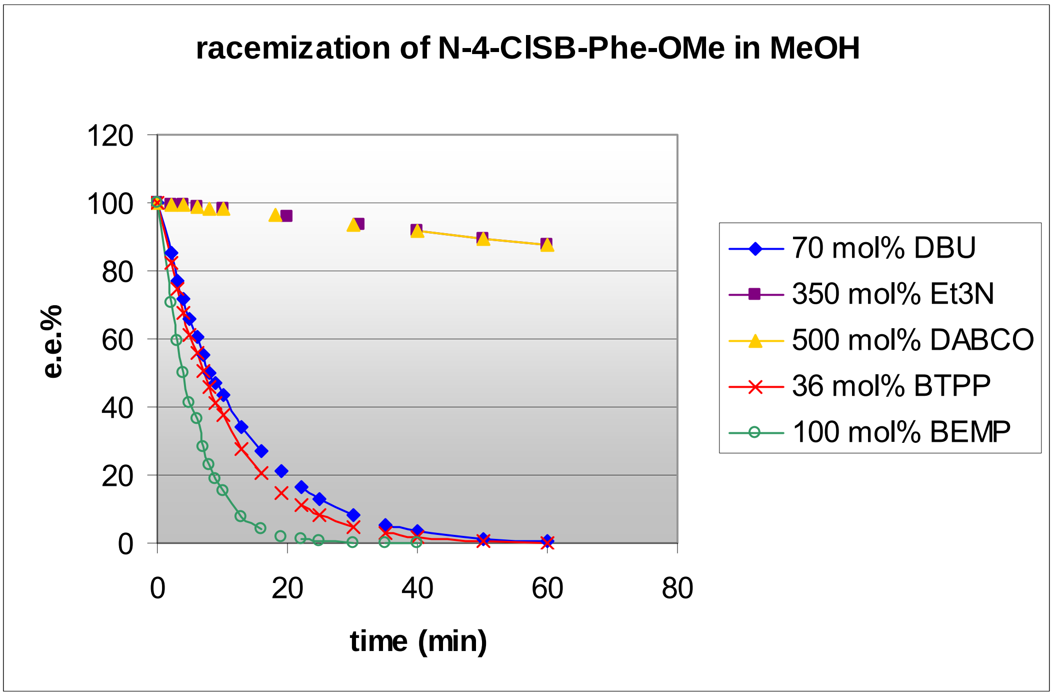
Typically, in 100 mL round bottom flask with an oval PTFE-coated magnetic stirring bar (L 20mm, Ø 10mm) were weighed in 1.6 g of (*S*)-**1**, 5.0 g of MeOH (dried and distilled from CaH$_2$) and 6.0 g Ø 2-2.5 mm glass pearls (Aldrich) under Schlenck conditions. The flask was sealed and stirred for 2 hours at ca. 600 rpm using a magnetic stirrer to equilibrate the solvent and solute. In an other 100 mL round bottom flask with an rod-like PTFE-coated magnetic stirring bar (L 20mm, Ø 5mm) were weighed in 1.5 g of (*R*)-**1**, 5.0 g and of MeOH (dried and distilled from CaH$_2$) under Schlenck conditions. The flask was sealed and stirred for 2 hours at ca. 100 rpm using a magnetic stirrer to equilibrate the solvent and solute. After this, to both flasks was added 0.11 g DBU and stirring was maintained. After 5 hours, the contents of the both flasks were combined (without the rod-like PTFE-coated magnetic stirring bar) and stirring was maintained at 500 rpm. From this mixture the t=0 sample was collected.

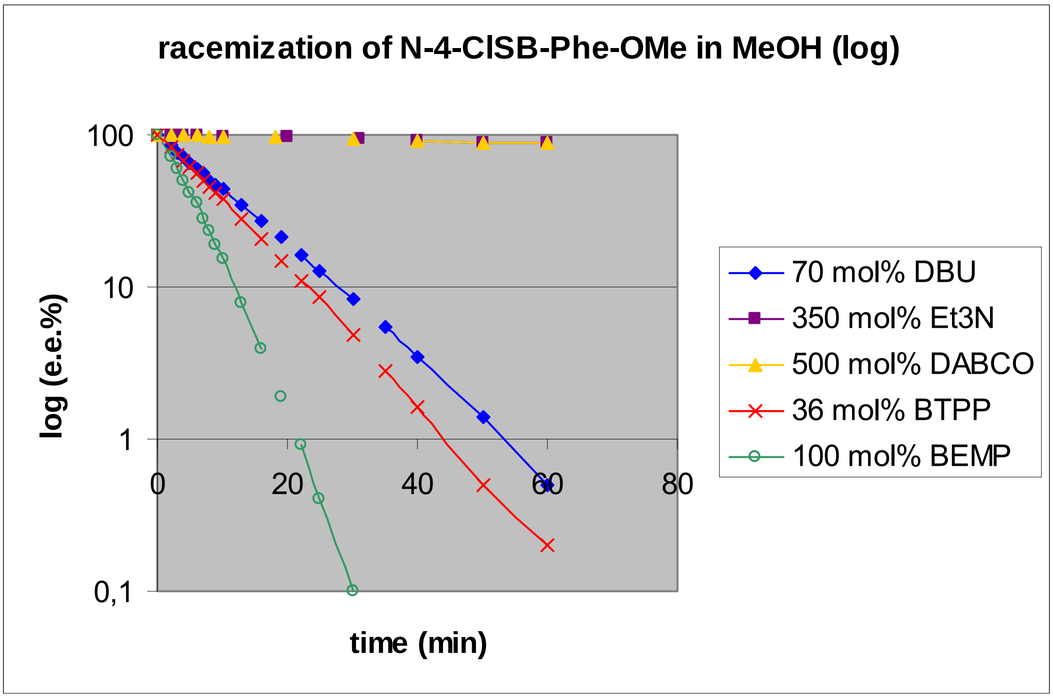
Racemization of *N*-(4-chlorobenzylidene)phenylalanine methyl ester

The racemization was measured in MeOH at c = 1 g / 100 ml and 25^{o}C in the polarimeter (decrease in optical rotation) using the following bases:

- 500 mol% 1,4-diazabicyclo[2.2.2]octane (DABCO, pKa = 8.8, $t_{0.5}$ = 220 min)
- 350 mol% Et$_3$N (pKa = 10.7, $t_{0.5}$ = 220 min)
- 70 mol% 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, pKa = 12, $t_{0.5}$ = 8 min)
- 36 mol% *tert*-butyl-tris-(tetramethylene)-phosphazene base P$_1$ (BTPP, pKa = 17.0, $t_{0.5}$ = 7 min)
- 100 mol% 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (BEMP, pKa = 16.2, , $t_{0.5}$ = 3.5 min)

(all normalized to 100 e.e.% at *t* = 0)


racemization of N-4-ClSB-Phe-OMe in MeOH
e.e.%
120
100
80
60
40
20
0
0
20
40
60
80
time (min)
70 mol% DBU
350 mol% Et3N
500 mol% DABCO
36 mol% BTPP
100 mol% BEMP


racemization of N-4-ClSB-Phe-OMe in MeOH (log)
log (e.e.%)
100
10
1
0,1
0
20
40
60
80
time (min)
70 mol% DBU
350 mol% Et3N
500 mol% DABCO
36 mol% BTPP
100 mol% BEMP