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Supporting Information

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Attrition Enhanced Deracemization of a Natural Amino Acid Derivative that Forms an Epitaxial Racemic Conglomerate

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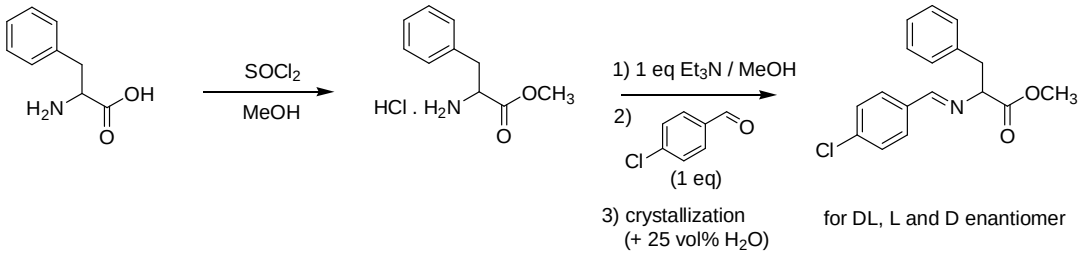
Synthesis of (*RS*)-*N*-(4-chlorobenzylidene)phenylalanine methyl ester (1)

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



(*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 an 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. ^{1}H 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 as 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. ^{1}H 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).

Solubility of (*RS*)-*N*-(4-chlorobenzylidene)phenylalanine methyl ester in various solvent (21°C)

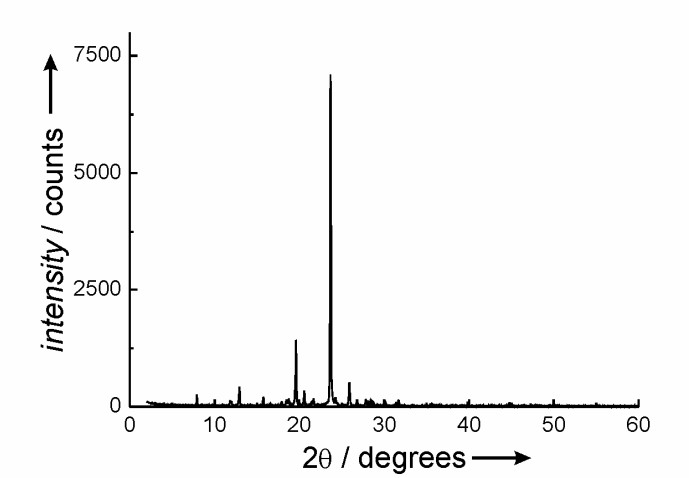
solvent	n-heptane	2-propanol	c-hexane	MeOH	toluene	MeCN
solubility (wt%)	3	4	8	13	$\geq$26	>27

X-ray crystal structure, XRPD

The crystal structure was determined from a single crystal grown from a solution of (*S*)-**1** in MeOH. The structure was solved by direct methods and refined by least squares methods to R1 = 0.0578 using 191 parameters and 2724 reflections (with I>2sigma(I)). All measurements were performed at -65 °C. All nonhydrogen atom positions were refined with anisotropic temperature factors. The hydrogen atoms were placed at calculated positions, and refined isotropically in riding mode.

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication CCDC-1003/. Copies of available material can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0) 1223-336033 or e-mail:teched@chemcrys.cam.ac.uk).

Crystal colour	translucent colourless
Crystal shape	rather regular needle
Crystal size	0.23 x 0.07 x 0.04 mm
Empirical formula	$C_{17}H_{16}ClNO_2$
Formula weight	301.76
Temperature	208(2) K
Radiation / Wavelength	MoKα (graphite mon.) / 0.71073 Å
Crystal system, space group	Orthorhombic, P 21 21 21
Unit cell dimensions	a = 6.08860(10) Å, α = 90 deg.
213 reflections	b = 14.9367(10) Å, β = 90 deg.
(2.390 < θ < 24.980)	c = 17.0300(8) Å, γ = 90 deg.
Volume	1548.77(13) $Å^3$
Z, Calculated density	4, 1.294 Mg/m^3
Absorption coefficient	0.250 mm^{-1}
Diffractometer / scan	Nonius KappaCCD with area detector f and w scan
F(000)	632
Theta range for data collection	2.39 to 24.98 deg.
Index ranges	-7<=h<=7, -17<=k<=17, -20<=l<=20
Reflections collected / unique	31371 / 2724 [R(int) = 0.0870]
Reflections observed	2048 ([Io>2 σ (Io)])
Completeness to 2 θ = 24.98	99.9%
Data / restraints / parameters	2724 / 0 / 191
Goodness-of-fit on F^2	1.125
SHELXL-97 weight parameters	0.0307, 0.4323
Final R indices [I>2σ(I)]	R1 = 0.0578, wR2 = 0.0868
R indices (all data)	R1 = 0.0881, wR2 = 0.0944
Absolute structure parameter	-0.04(11)
Largest diff. peak and hole	0.192 and -0.173 e. $Å^{-3}$



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

Morphology

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

Deracemization experiments

In a 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. The chemical purity was monitored using ^{1}H-NMR, DSC and XRPD.

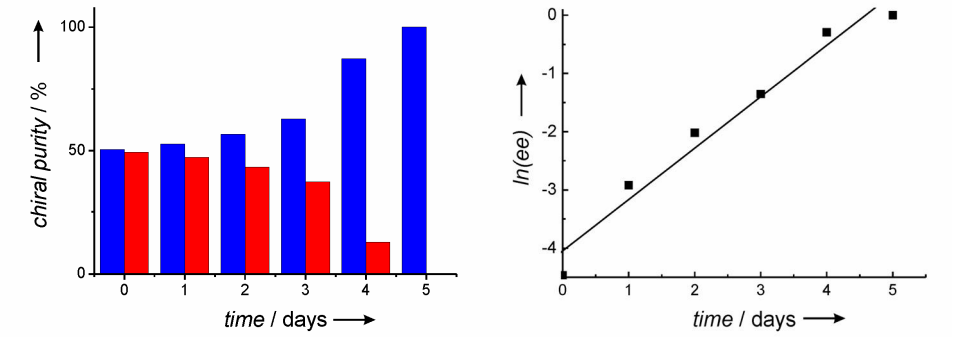
Sampling

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.

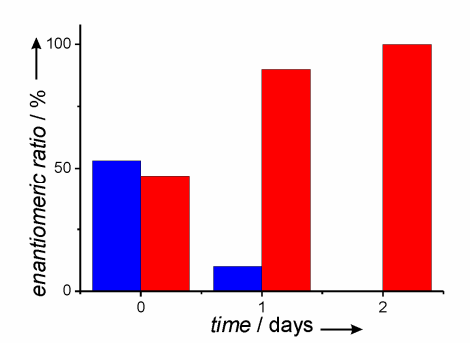
Deracemization result for initial slighly enantioenriched (*S*)-1 mixtures



SI Figure 2. Typical 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 was 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 another 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**, and 5.0 g of MeOH (dried and distilled from CaH_2) under Schlenck conditions. No glass beads were added. 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. Additional samples were taken daily.

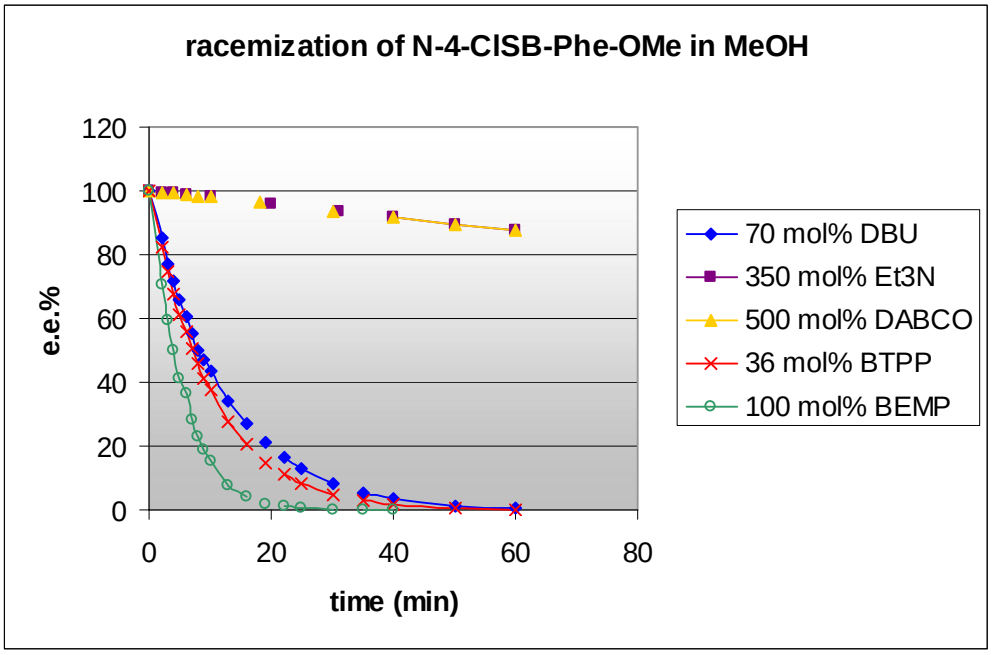


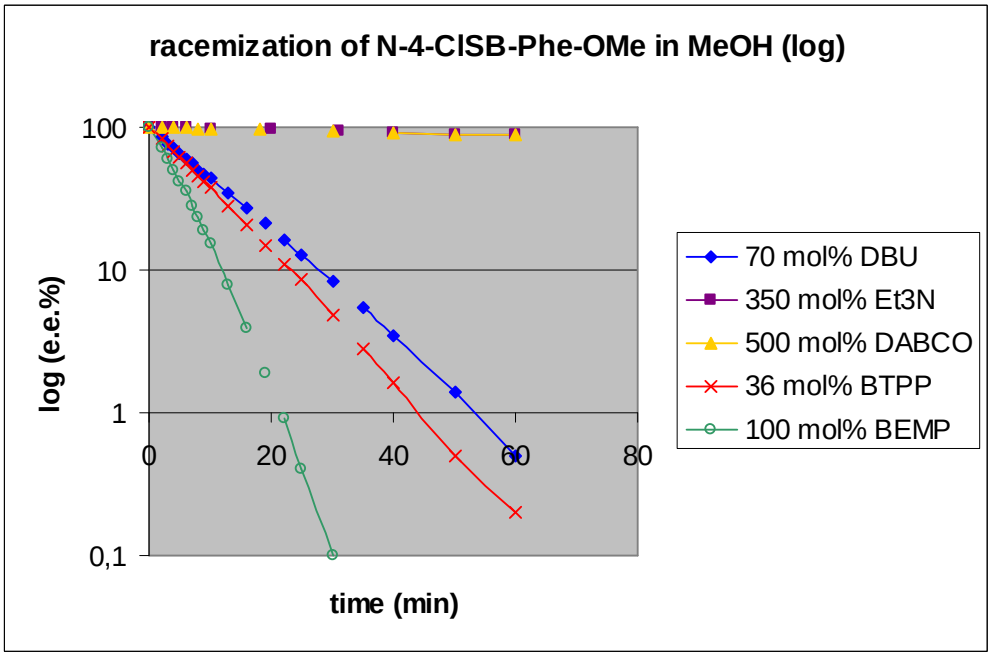
SI Figure 3. Evolution of the enantiomeric ratio starting with an overabundance of small (*S*)-**1** crystals and a minor population of large (*R*)-**1** crystals. The small crystals rapidly dissolve and nurture the larger (*R*)-crystals until complete symmetry breaking is achieved.

Racemization of *N*-(4-chlorobenzylidene)phenylalanine methyl ester
The racemization was measured in MeOH at c = 1 g / 100 ml and 25°C in the polarimeter to measure the 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_3N (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
120
100
80
60
40
20
0
e.e.%
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)
100
10
1
0,1
log (e.e.%)
0
20
40
60
80
time (min)
70 mol% DBU
350 mol% Et3N
500 mol% DABCO
36 mol% BTPP
100 mol% BEMP