Complete chiral symmetry breaking of an amino acid derivative directed by circularly polarized light

Noorduin, Wim L.; Bode, Arno A.C.; Meijden, Maarten van der; Meekes, Hugo; Etteger, Albert F. van; Enckevort, Willem J.P. van; Christianen, Peter C.M.; Kaptein, Bernard; Kellogg, Richard M.; Rasing, Theo

Published in:
Nature Chemistry

DOI:
10.1038/nchem.416

nature chemistry

SUPPLEMENTARY INFORMATION

DOI: 10.1038/NCHEM.416

Complete Chiral Symmetry Breaking of an Amino Acid Derivative Directed by Circularly Polarized Light

Wim L. Noorduin, Arno A. C. Bode, Maarten van der Meijden, Hugo Meekes, Albert F. van Etteger, Willem J. P. van Enckevort, Peter C. M. Christianen, Bernard Kaptein, Richard M. Kellogg, Theo Rasing, Elias Vlieg

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 NH_3/HCN and subsequent acidic hydrolysis [1], 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.

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-methylbenzadehyde 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}H NMR (200 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 $C_{16}H_{16}N_2O$: 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%).

Note. 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 cyclisation product 2-(2-methylphenyl)-5-phenyl-imidazolidin-4-one (racemic 1:1 diastereomeric mixture).

Circularly polarized light irradiation setup

A 200W Xenon Mercury lamp was used to generate a broad spectrum of UV-Vis light. An optical train consisting of a 300-400nm filter, two lenses and a UV-mirror provided a vertical light beam. The circular polarisation was generated using a polarizer followed by a Babinet-Soleil compensator. The circularity of the light was checked using a polarisation filter and a power meter behind the Babinet-Soleil compensator. In this work, all the irradiations were carried out using circularly polarized light of 310nm wavelength. The power of the resulting CPL is approximately 0.35 mW.

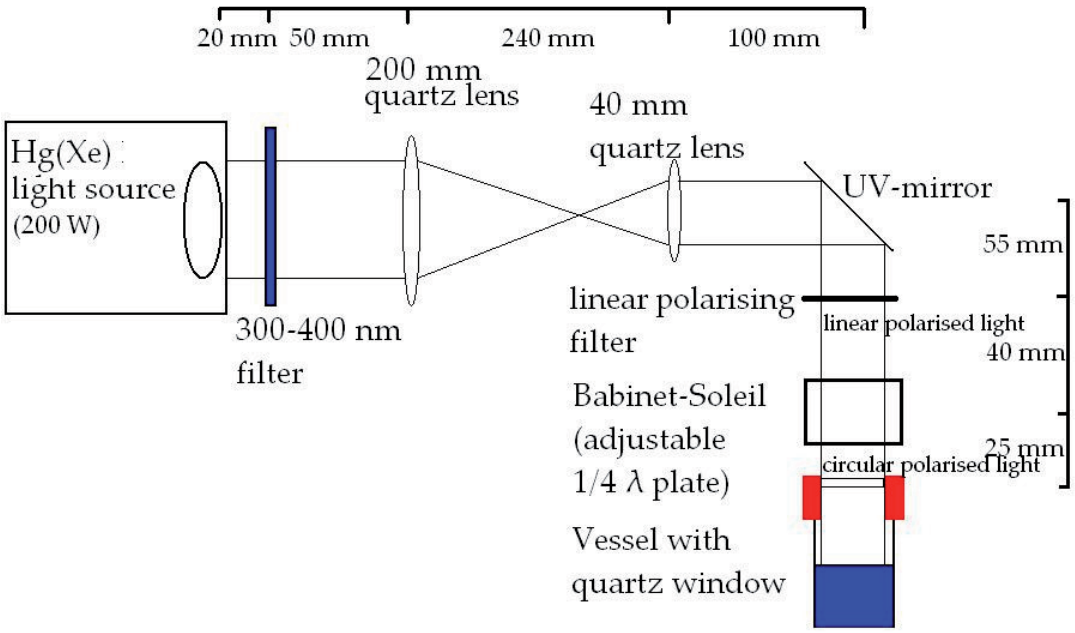

Figure SI 1. *Schematic representation of the experimental setup for the CPL irradiation.*

CPL irradiation experiments

For the irradiation experiments reaction vessels with a quartz window were used. The vessel containing 0.44g racemic **1** and 6.25g MeCN was irradiated for 3 to 5 days with

CPL. After the irradiation the quartz window was removed and 8.0g glass beads and 0.12 g DBU were added, after which the reaction vessel was closed with a septum. Then the slurry was ground for 16-30 hours using a thermostated ultrasonic cleaning bath at 25°C. X-ray powder diffraction patterns of the solids obtained showed no polymorphism as a result of the CPL irradiation [2].

Check experiment using linearly polarized light

To confirm that the directed symmetry breaking was caused by the sense of the incoming CPL, experiments were carried out using linearly polarized light. For this, the same experimental setup was used as for the CPL experiments, but without the Babinet-Soleil compensator. Following the procedure for the CPL irradiation experiments, a vessel containing 0.44g racemic **1** and 6.25g was irradiated for 3 days. After the irradiation 8.0g glass beads and 0.12 g DBU were added after which the reaction vessel was closed with a septum. The slurry was ground for 16-30 hours using a thermostated ultrasonic cleaning bath at 25°C. HPLC analysis revealed that all these experiments evolved to an enantiopure (*R*)-**1** solid phase, as was also observed in experiments without irradiation.

Sampling and HPLC analysis

For sampling, 0.3 mL of the slurry was taken using a syringe and filtered on a P3 or P4 glass filter (Ø 10 mm). The residue was washed with 1 mL of MeOH or MeCN and 2 mL of MTBE to remove mother liquid and DBU, and dried overnight in a vacuum stove at 40 ºC.

For *ee* determination using HPLC analysis, about 0.5 mg solid was dissolved 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, detection λ=254 nm. Retention times (*R*)-**1** 7.9 min, (*S*)-**1** 8.5 min.

HPLC analysis of the solution phase after irradiation

HPLC analysis of the solution phase shows the formation of low concentrations of several products upon irradiation (Figure SI 2). Figure SI 5 shows the HPLC measurements of a solution of (*R*)-**1** after irradiation with nonpolarized light. The complex mixture of photoproducts formed in low yield after long irradiation was analysed extensively. Only one photo-oxidation product *N*-benzoyl-2-methylbenzamide could be isolated and identified but this compound can not be involved as a directing agent in the deracemisation process since it is achiral.

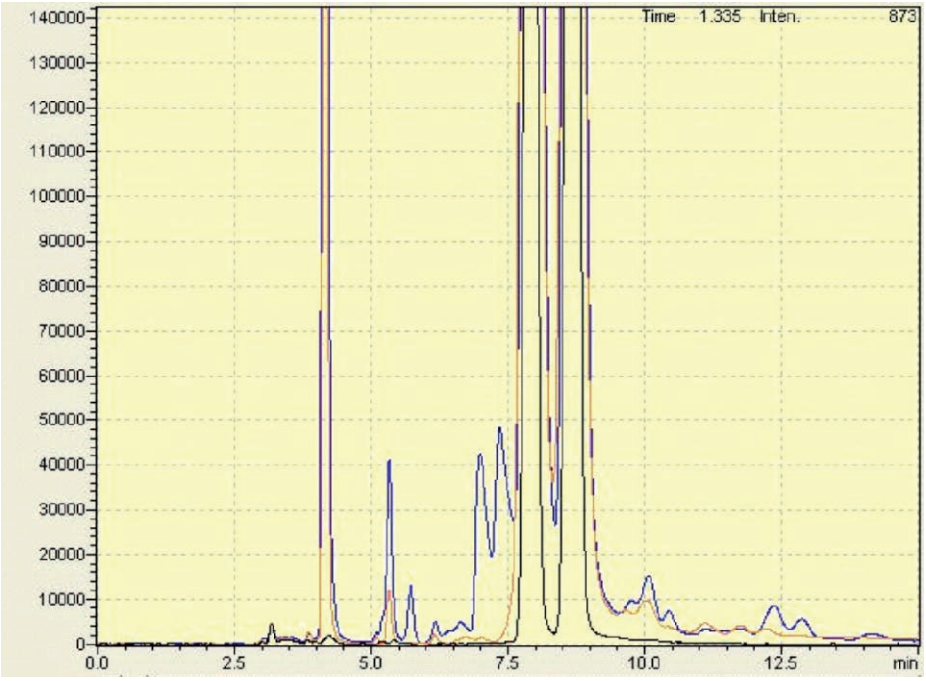

Figure SI 2. *Chiral HPLC analysis of the solution phase of a solution/solid mixture (RS)-**1** after 3 days of CPL irradiation; blue line: r-CPL, orange line: l-CPL, black line: (RS)-**1** before irradiation. Retention times of (R)-**1** is 7.9 min, (S)-**1** 8.5 min.*

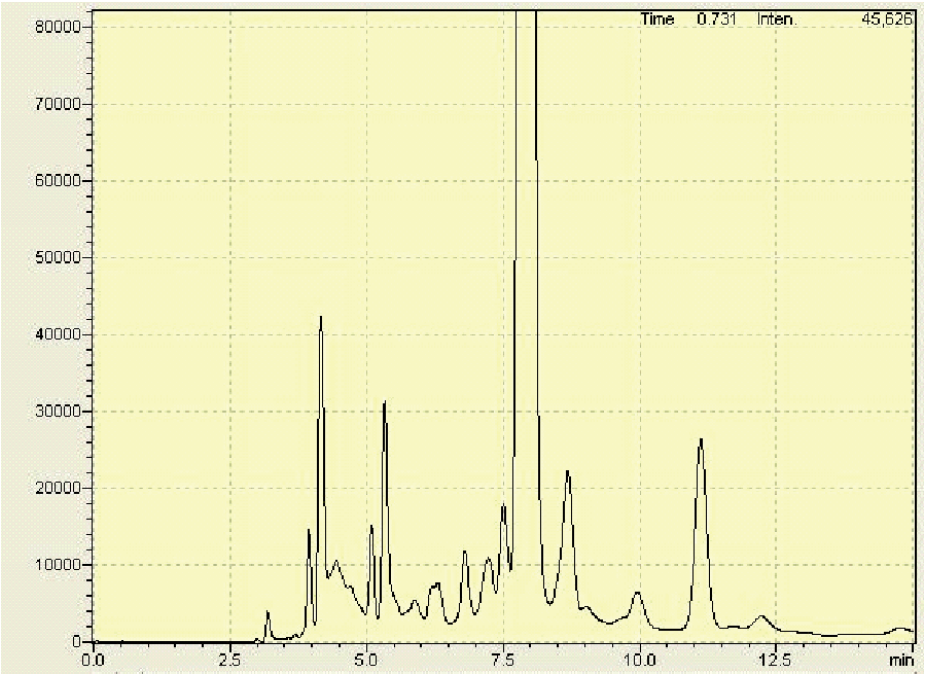

Figure SI 3. *Chiral HPLC analysis of the solution phase after irradiation of (R)-**1** with nonpolarized light.*

2-(2-methylphenyl)-5-phenyl-imidazolidin-4-one as directing agent

Chiral cyclic products of **1** are known to be formed easily and the retention times of these products correspond to minute peaks in the HPLC traces of the irradiated solutions (Figure SI 3). Therefore we expect these products to be present in the solutions. To test their directing activity in the deracemisation process of **1** we synthesised such cyclic products and subsequently used them as additives in the deracemisation experiment. Indeed, these cyclic products direct the outcome of the deracemisation reaction. The handedness of the outcome follows 'the rule of reversal', in line with the overall effect of the impurities we observed.

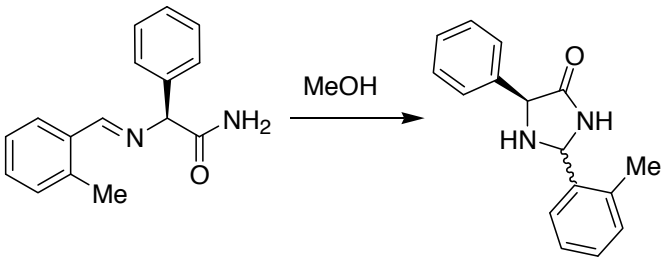

Figure SI 4. *The formation of the diastereomeric cyclic products 2-(2-methylphenyl)-5-phenyl-imidazolidin-4-one* ***2*** *and* ***2'*** *from* ***1*** *as observed in protic solvents.*

Synthesis of 2-(2-methylphenyl)-5-phenyl-imidazolidin-4-one 2

In a 10 mL round bottom flask equipped with a reflux cooler 0.17 g enantiopure **1** was dissolved in 2.0 g MeOH. The solution was heated overnight at 50 °C yielding a mixture of the diastereomeric mixture of the cyclisation product 2-(2-methylphenyl)-5-phenyl-imidazolidin-4-one (enantiopure 1:1 diastereomeric mixture). This mixture of diastereoisomers could be separated using flash chromatography.

First fraction **2**: ^{1}H NMR (300 MHz, DMSO) δ 8.72 (d, 1H), 7.6-7.15 (m, 9H), 5.83 (d, 1H), 4.52 (d, 1H), 3.73 (t, 1H), 2.4 (s, 3H).

Last fraction **2'**: ^{1}H NMR (300 MHz, DMSO) δ 8.63 (s, 1H), 7.6-7.15 (m, 9H), 5.83 (d, 1H), 4.62 (d, 1H), 4.03 (t, 1H), 2.4 (s, 3H).

HPLC retention times: (*R*)-**2**: 9.6 min, (*R*)-**2'**: 10.0 min, (*S*)-**2**: 11.1 min, (*S*)-**2'**: 11.8 min.

Testing of 2-(2-methylphenyl)-5-phenyl-imidazolidin-4-one as chiral additive

In a standard reaction vial 1.04 g of the diastereomeric mixture of 2-(2-methylphenyl)-5-phenyl-imidazolidin-4-one **2** was dissolved in 3.00 g MeCN. To the clear solution was

added 0.15 g DBU to racemise possible traces of enantiopure **1**. After 3 hours 8.5 g glass beads and 0.55g (*RS*)-**1** were added to create a solution-solid mixture. The mixture was deracemised in an thermostated ultrasonic cleaning bath overnight. The deracemisations containing the cyclic diastereomeric mixture of (*S*)-**1** evolved to (*R*)-**1** and *vice versa*.

[1] (Note that Phg forms a very stable racemic compound and has a eutectic composition with 97% *ee*.)

[2] Garetz, B. A.; Aber, J. E.; Goddard, N. L.; Young, R. G.; Myerson, A. S. Nonphotochemical, polarization-dependent, laser-induced nucleation in supersaturated aqueous urea solutions. *Phys. Rev. Lett.* **77,** 3475-3476 (1996).