Supporting information

Appendix 1:

We found that compounds **1** and **2** first crystallize from a racemic solution as a racemic compound which, upon grinding, converts into the stable conglomerate form. The metastability of the racemic compound was supported by experiments in which small amounts of enantiopure (both enantiomers) material were added to a slurry of the racemic compound. The suspension was left standing for several weeks, during which it was occasionally briefly heated to increase the rate of Ostwald ripening. After this period, all of the racemic compound had been converted into the conglomerate compound. In addition, controlled very slow cooling of a clear saturated racemic solution in acetonitrile also yielded the conglomerate compound.
To rule out the possibility that the metastable racemic compound is in fact not a metastable conglomerate, another experiment was performed. For this, the metastable (racemic) crystals were added to a solution, saturated with the D-enantiomer. If the racemate would be a metastable conglomerate compound, only the L-crystals would dissolve, leaving the D-crystals unaffected. If the racemate would be a racemic compound, complete dissolution would have been followed by crystallization of conglomerate D crystals. We observed (using XRPD) that after a few hours, the remaining crystals were indeed of the stable conglomerate form, indicating we were dealing with a metastable racemic compound. As a control experiment, the racemic crystals were added to solvent, containing no dissolved enantiomers. Even after a full day, the crystals remained of the metastable racemic form.

Appendix 2:

As mentioned earlier, the deracemization rate of compounds 1 and 2 greatly depends on the used homogenization time. We carried out a series of experiments for which a varying homogenization period was followed by two hours of (de)racemization. The increase in enantiomeric excess (*ee*) after these two hours is depicted in Fig. S1 for compounds **1** and **2**. For compound **2**, an almost logarithmic relationship between homogenization time and increase in *ee* seems to exist. In contrast, for compound **1**, when very short homogenization times were used, the deracemization rate decreased and even solid phase racemization occurred.
To better understand this phenomenon, both the solid and solution phase composition were closely followed over time during the homogenization time (Fig.S2). Early in the experiment (up to a 10 minute homogenization time), the solution was undersaturated resulting in the dissolution of both D- and DL-crystals. This dissolution results in a solution enriched in the D-enantiomer. Addition of the racemization catalyst at this point, would result in the net conversion of the D- into the L-enantiomer, decreasing the amount of D-enantiomer (so net racemization, see Fig. S2). When waiting longer, the higher solubility of the racemic compound as compared to the conglomerate will become important. The racemic compound will dissolve and will reach the point at which it is saturated in both D and L. The already present D-seed crystals will grow, whereas no L-seed crystals are present. The dissolution will lead to a solution supersaturated in L, while the solid phase will be even more enriched in D. If racemization is initiated at this point (between 10 and 30 min) the excess of L-enantiomer in solution will be converted into the D-

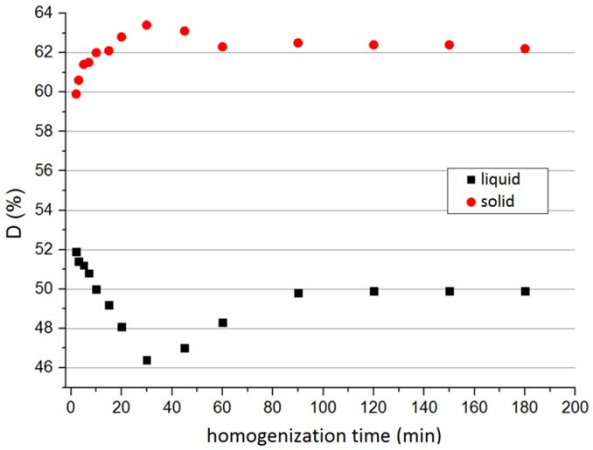


Fig. S1: Percentage D-enantiomer in the solid (red) and liquid (black) phase during the homogenization of a D +DL mixture of compound **1**.

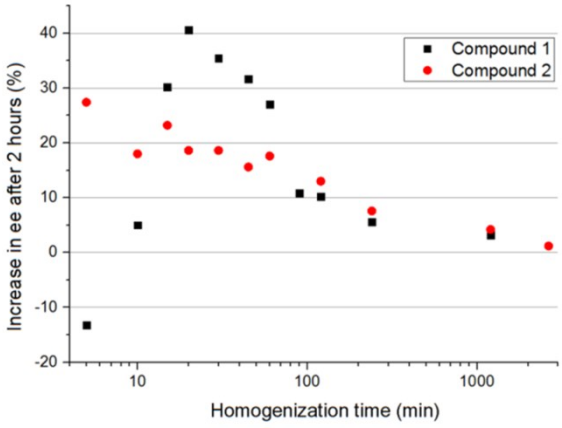


Fig. S2: After two hours of racemization, the *ee* of the solid phase has increased, depending on the applied homogenization time. All experiments were started from a mixture of D + DL crystals as described in the experimental.

enantiomer, resulting in an increased deracemization rate. For homogenization periods longer than 30 min, the solution will have reached the point at which primary nucleation of the L-enantiomer starts taking place. The solution will thus slowly return to a racemic situation, whereas the *ee* of the solids towards the D enantiomer will decrease. For this regime, when DBU is added, the deracemization rate decreases with increasing homogenization time (optimum at around 30 minutes in Fig. S2).

Synthesis of the Schiff bases:

General procedure[1]:
(*R*)-, (*S*)- and (*R,S*)-phenylglycine amide were prepared according to a literature procedure[1]. Prior to the condensation reaction, phenylglycine amide was recrystallized from methanol for both the enantiopure compound and racemates. In a typical experiment, the aldehyde (0.37 mmol, 1.02 equiv) was added to a stirred solution of phenylglycine amide (55 g, 0.36 mol) in 300 mL water and 150 mL methanol over a period of one hour, during which crystallization spontaneously started. The product was filtered off and washed with water (100 mL) and diisopropyl ether (100 mL). The resulting crystals were dried under reduced pressure and their purity was confirmed by NMR. In addition, XRPD diffractograms of all products were recorded.

Compound **1**:[2]
$^{1}$H NMR (400 MHz, $CDCl_3$): δ 8.77 (s, 1H), 8.14 (dt, 1H), 7.47-7.51 (m, 2H), 7.28-7.42 (m, 6H), 6.95 (br, 1H), 5.96 (br, 1H), 5.06 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$, proton decoupled): δ 173.6 (s), 160.2 (s), 139.0 (s), 135.8 (s), 132.4 (s), 132.3 (s), 130.1 (s), 128.8 (s), 128.4 (s), 128.1 (s), 127.2 (s), 127.0 (s), 77.4 (s).

Compound **2**:[2]
$^{1}$H NMR (400 MHz, $CD_3OD$): δ 8.65 (s, 1H), 8.16 (dt, 1H), 7.45-7.52 (m, 3H), 7.32-7.38 (m, 2H), 7.29 (dt, 1H), 7.24 (t, 1H), 7.14 (ddd, 1H), 5.04 (s, 1H). $^{13}$C NMR (100 MHz, $CDCl_3$, proton decoupled): δ 173.7 (s), 162.5 (d, $J_{F\text{-}C}$ = 253.9 Hz), 156.9 (d, $J_{F\text{-}C}$ = 4.8 Hz), 139.0 (s), 133.2 ($J_{F\text{-}C}$ = 8.8 Hz), 128.8 (s), 128.1 (s), 127.8 (d, $J_{F\text{-}C}$ = 2.6 Hz), 127.2 (s), 124.4 (d, $J_{F\text{-}C}$ = 3.6 Hz), 123.1 (d, $J_{F\text{-}C}$ = 9.2 Hz), 116.1 (d, $J_{F\text{-}C}$ = 21.0 Hz), 77.4 (s).

XRPD diffractograms:

All diffractograms were recorded using a Bruker D8 Advance Spectrometer using a VANTEX detector. Data was recorded using reflection mode with monochromatic Cu-K$\alpha_1$ radiation.

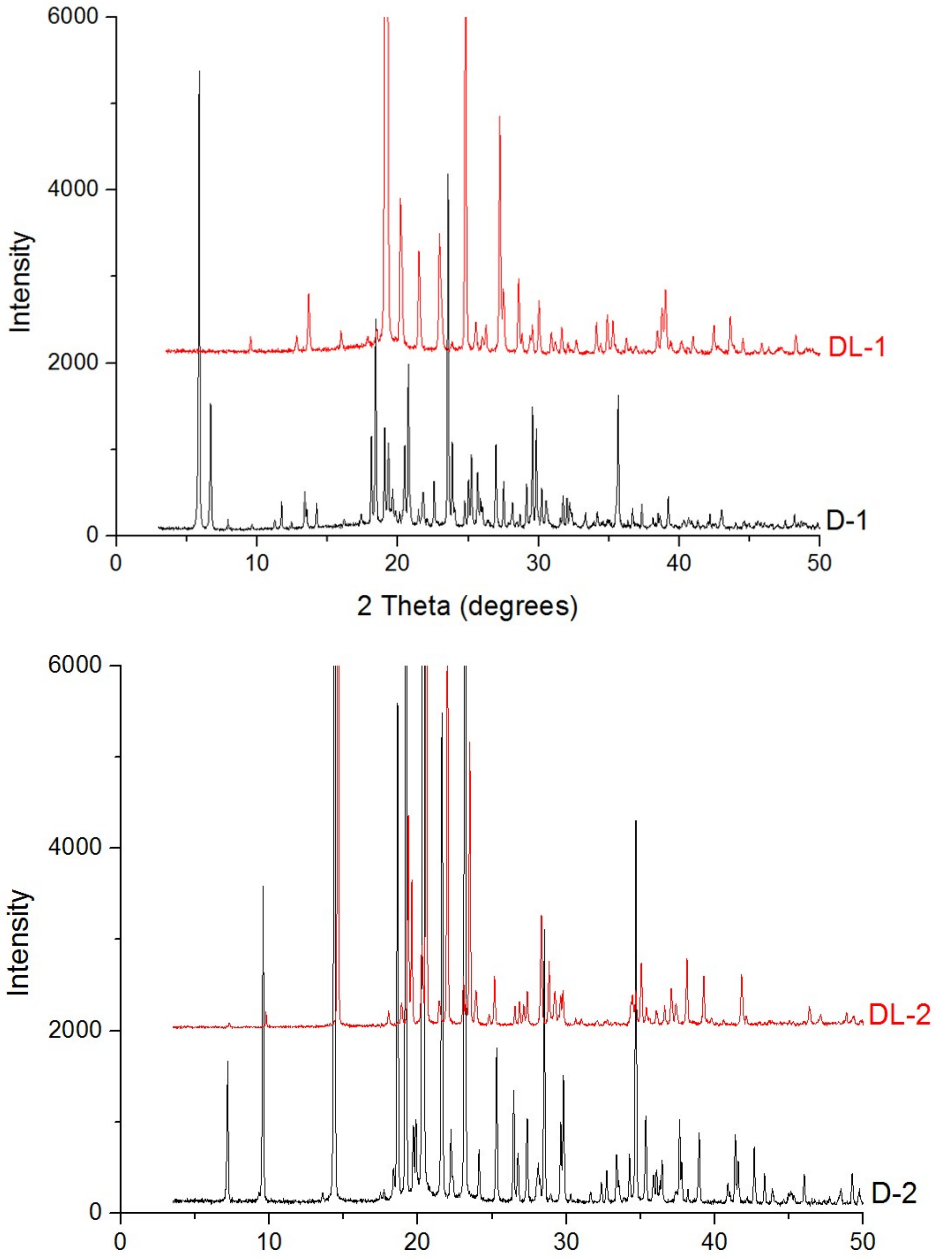


Figure S3: XRPD diffractograms of racemic and enantiopure (D-enantiomer) powders of compounds **1** and **2**. The different diffractograms of the racemic and enantiopure compound indicate that both compounds do not crystallize as a conglomerate compound.

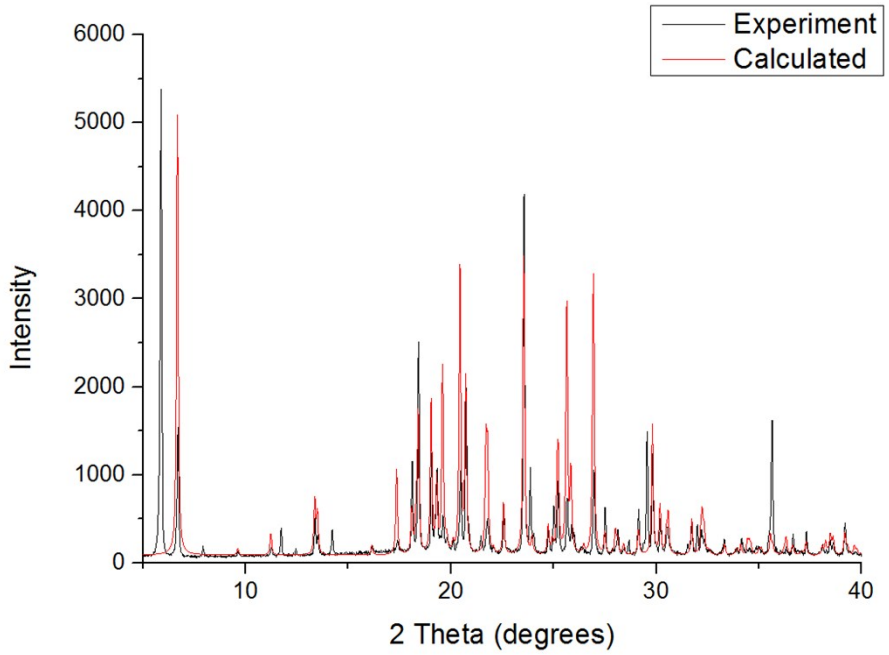


Figure S4: Recorded XRPD diffractogram (black) of enantiopure **1** as compared to the pattern calculated from the crystal structure determined by Leyssens et al.[3]

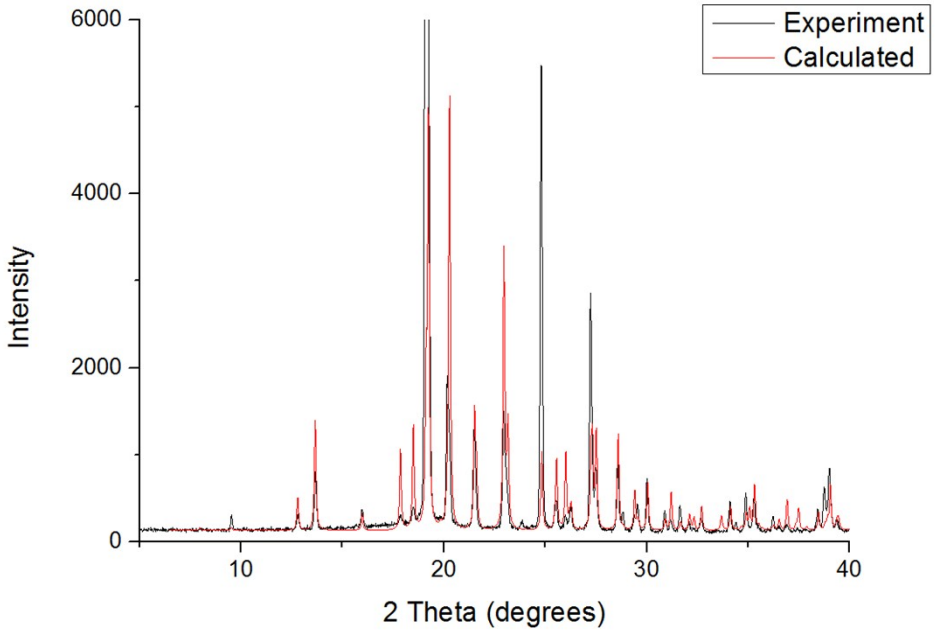


Figure S5: Recorded XRPD diffractogram (black) of racemic **1** as compared to the pattern calculated from the crystal structure determined by Leyssens et al.[3]

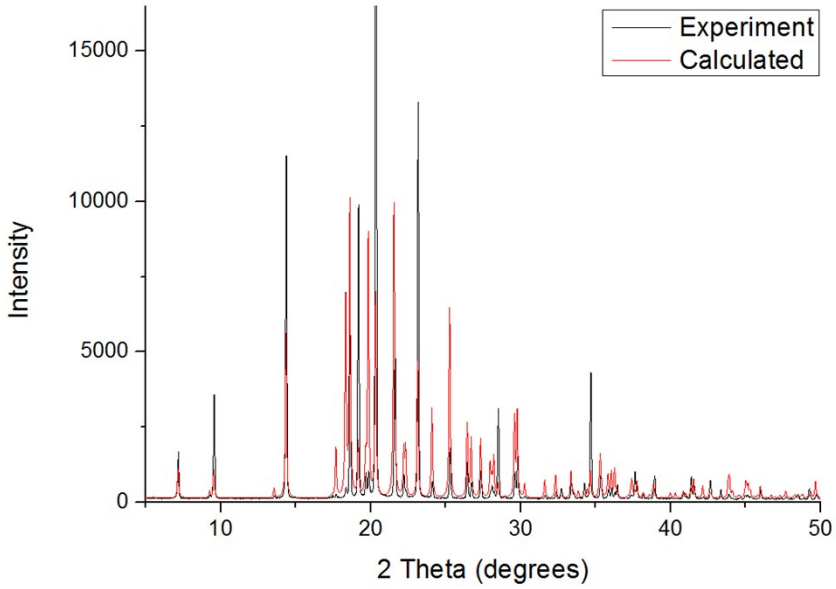


Figure S6: Recorded XRPD diffractogram (black) of enantiopure **2** as compared to the pattern calculated from the crystal structure determined by Leyssens et al.[3]


1. W. L. Noorduin, T. Izumi, A. Millemaggi, M. Leeman, H. Meekes, W. J. P. Van Enckevort, R. M. Kellogg, B. Kaptein, E. Vlieg and D. G. Blackmond, *J. Am. Chem. Soc.*, 2008, **130**, 1158-1159.
2. J. Dalmolen, M. van der Sluis, J. W. Nieuwenhuijzen, A. Meetsma, B. de Lange, B. Kaptein, R. M. Kellogg and Q. B. Broxterman, *Eur. J. Org. Chem*, 2004, 1544-1557.
3. F. George, B. Norberg, J. Wouters and T. Leyssenes, *Cryst. Growth Des.*, 2015, **15**, 4005-4019.