

Supplementary Information

Separation of isomers of chiral thiourea derivatives by spontaneous resolution, and rationale of molecular recognition

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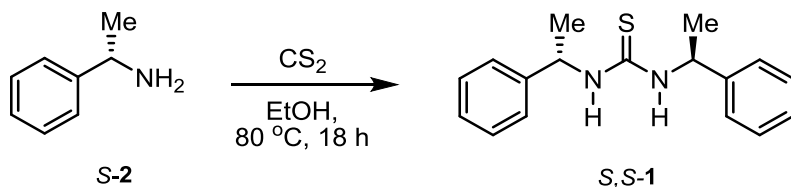
Materials and Methods

All the chemical reagents are of analytical grade and are used without further purification. (*S*)-(1-isothiocyanatoethyl)benzene **S-3** was prepared using optically pure (*S*)-1-phenylethan-1-amine and CS₂ in the presence of Et₃N in dry THF as solvent, and characterized by ¹H NMR and IR. Thin Layer Chromatography was performed on silica gel plates coated on aluminium sheets. Infrared (IR) spectra were recorded as KBr pellets on BRUKER spectrometer. All the ¹H and ¹³C NMR spectra were recorded on BRUKER 400 MHz spectrometer in CDCl₃, using TMS as internal standard. HPLC analysis was performed on JASCO, LC-Net II/ADC. Thermal analysis was performed on DSC-822, Mettler Toledo with Stare software. X-ray intensity data of crystal was carried out on a Bruker D8 VENTURE Kappa Duo PHOTON II CPAD diffractometer equipped with Incoatech multilayer mirrors optics. The intensity measurements were carried out with Cu micro-focus sealed tube diffraction sources (CuK_α = 1.54178 Å). The X-ray generator was operated at 50 kV and 1.1 mA for Cu radiations. A preliminary set of cell constants and an orientation matrix were calculated from two matrix sets of 40 frames for Cu radiations. Data were collected with ω scan width of 0.5° at different settings of φ and 2θ with a frame time of 15 sec keeping the sample-to-detector distance fixed at 5.00 cm. The X-ray data collection was monitored by APEX3 program (Bruker, 2016).¹All the data were corrected for Lorentzian, polarization and absorption effects using SAINT and SADABS programs (Bruker, 2016). Using the APEX3 (Bruker) program suite, the structure was solved with the ShelXS-97 (Sheldrick, 2008)² structure solution program, using direct methods. The model was refined with a version of ShelXL-2018/3 (Sheldrick, 2015)³ using Least Squares minimization.

Synthesis and Characterization

Case A:

Synthesis of 1,3-bis((*S*)-1-phenylethyl)thiourea (*S,S*-1)



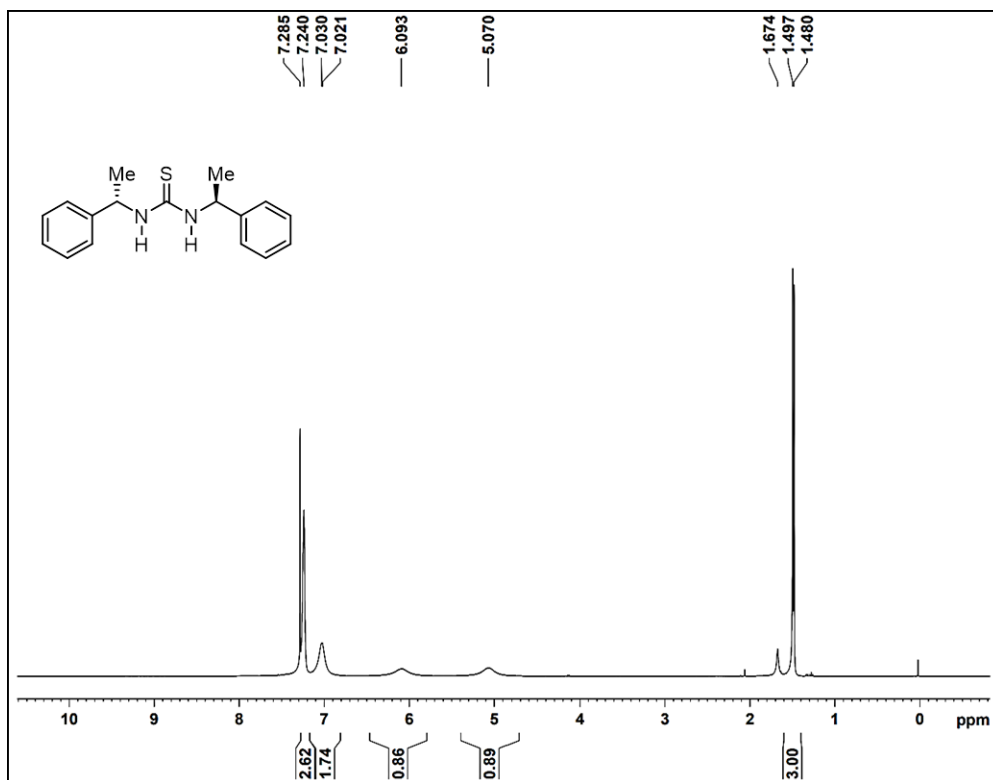


Figure S1. ^1H NMR Spectrum of *S,S*-1 (CDCl_3 , 400 MHz)

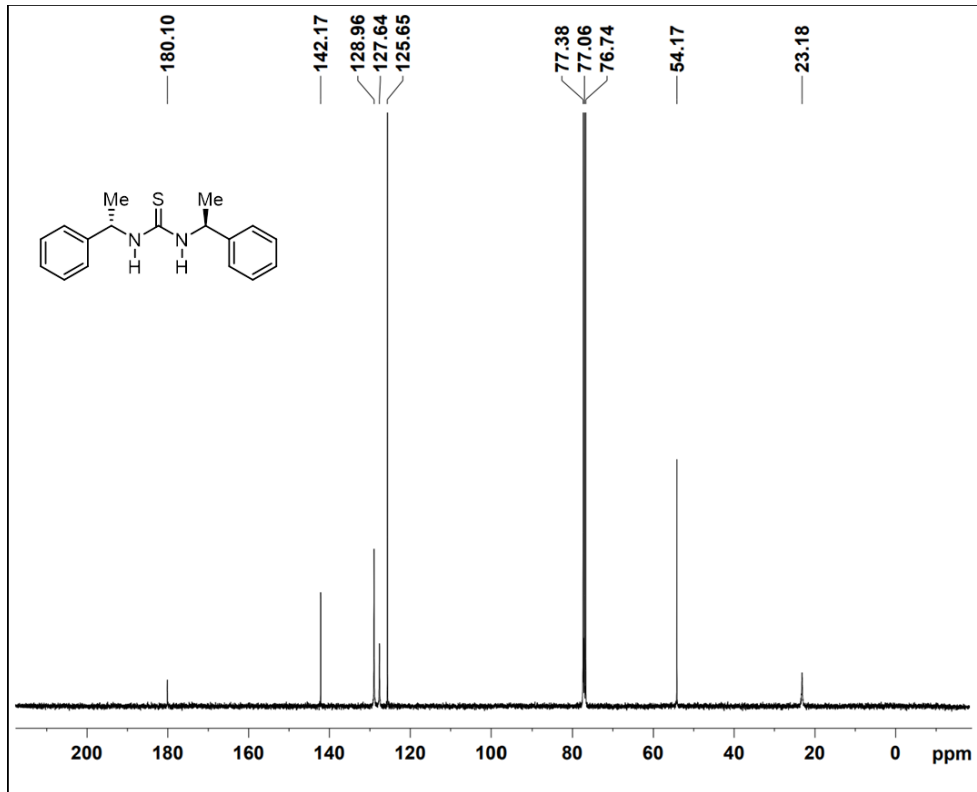


Figure S2. ^{13}C NMR Spectrum of *S,S*-1 (CDCl_3 , 100 MHz)

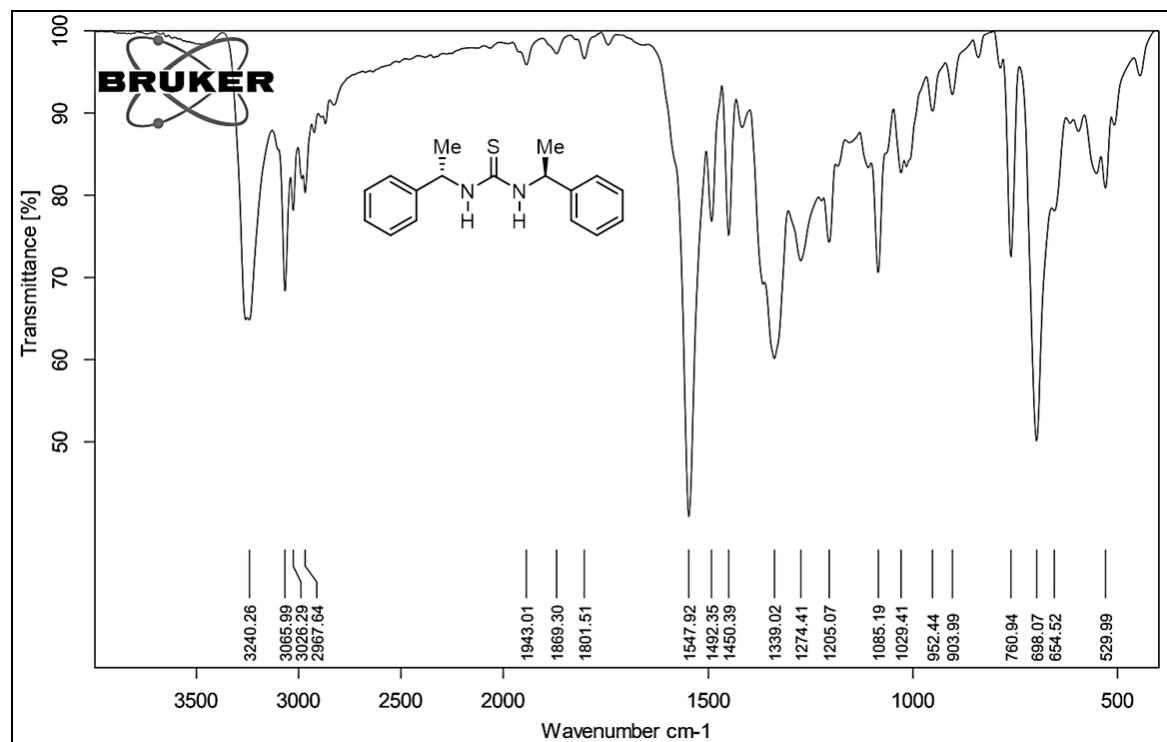
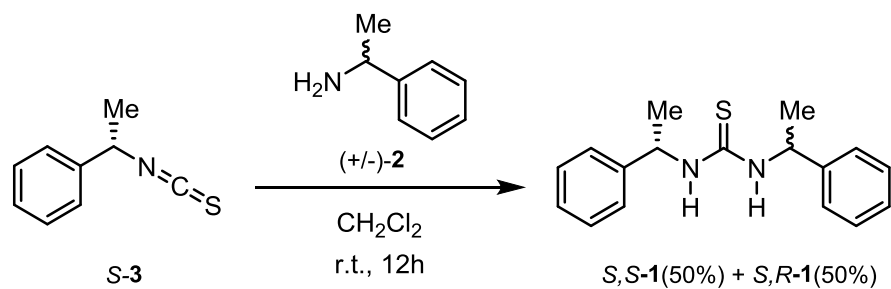


Figure S3. IR spectrum of *S,S*-1

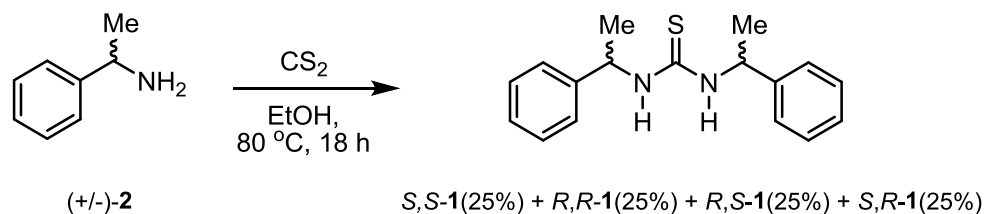
Case B:

Synthesis of 1-((*S*)-1-phenylethyl)-3-(1-phenylethyl)thiourea (*S,S/R*-1)



Case C

Synthesis of 1,3-bis(1-phenylethyl)thiourea (1)



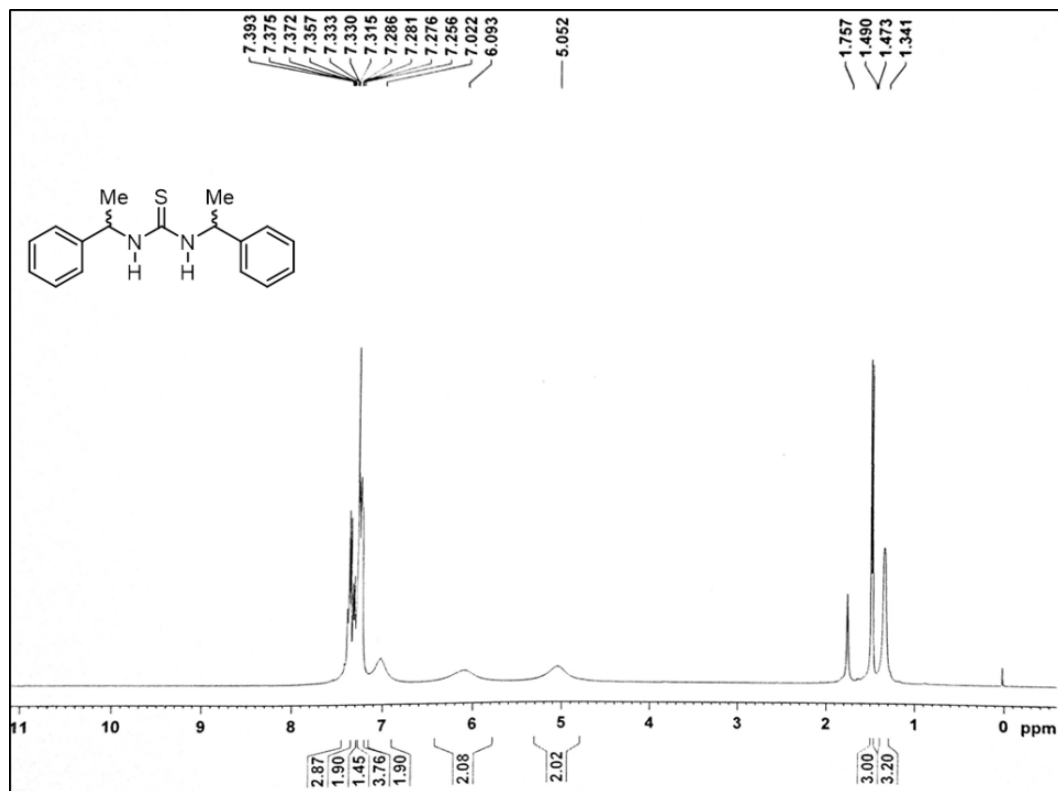


Figure S4. ¹H NMR Spectrum *S,S*-1 (25%), *R,R*-1 (25%), *S,R*-1 (25%), *R,S*-1 (25%) (CDCl₃, 400 MHz)

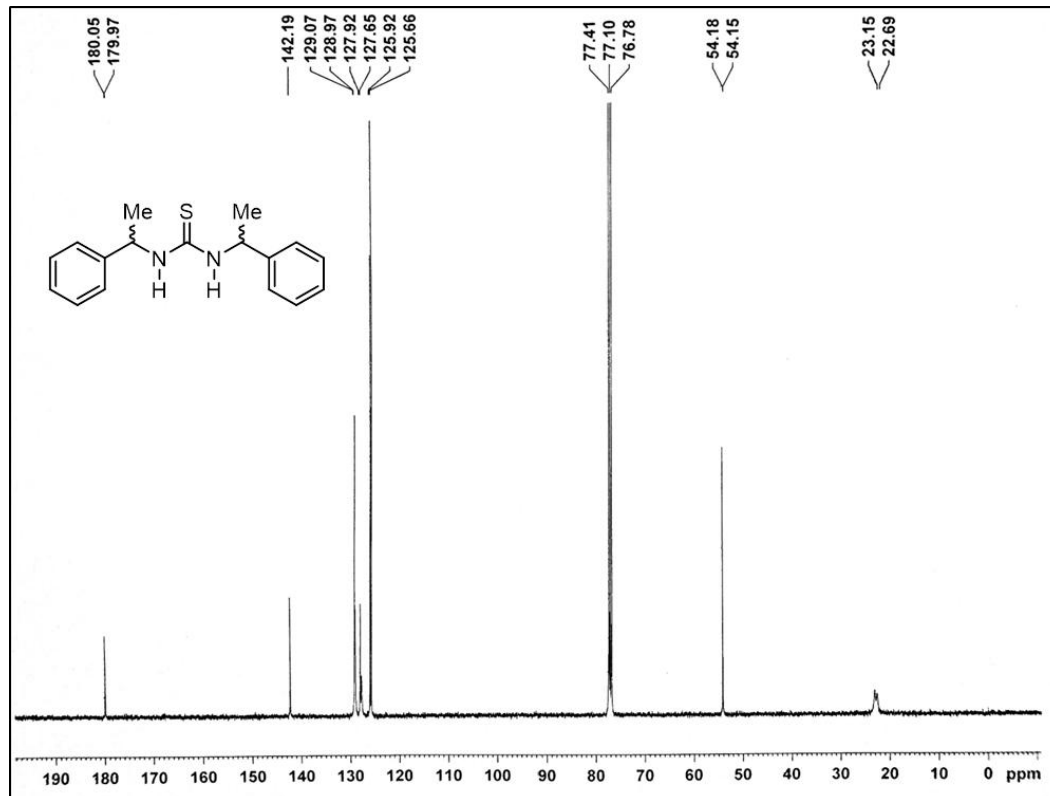


Figure S5. ¹³C NMR Spectrum *S,S*-1 (25%), *R,R*-1 (25%), *S,R*-1 (25%), *R,S*-1 (25%) (CDCl₃, 100 MHz)

Synthesis of (S)-1-(4-fluorobenzyl)-3-(1-phenylethyl)thiourea (S-4)

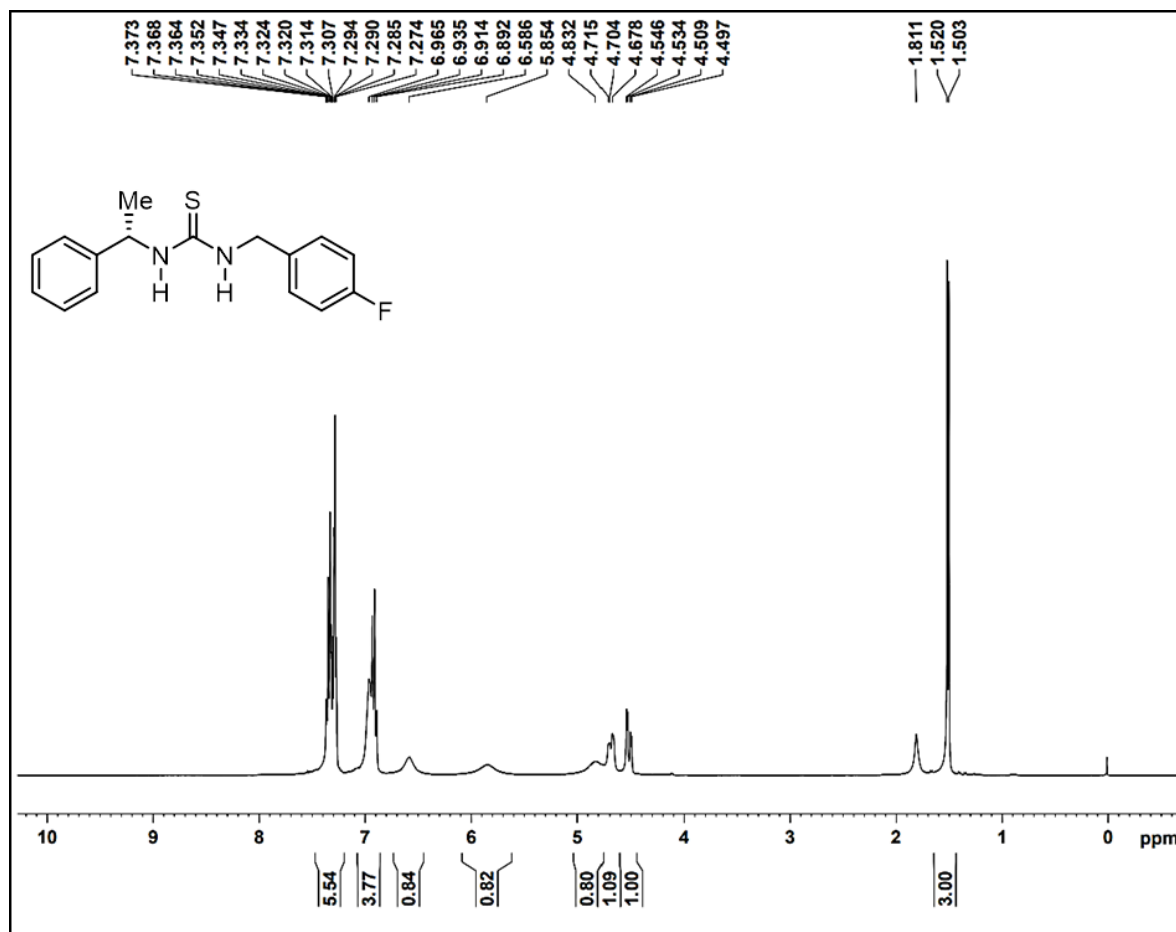
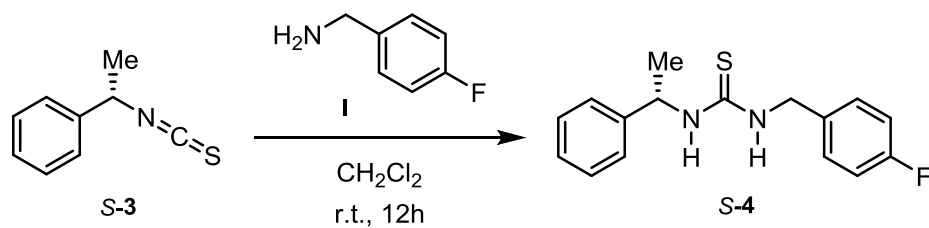


Figure S6. ^1H NMR Spectrum of S-4 (CDCl_3 , 400 MHz)

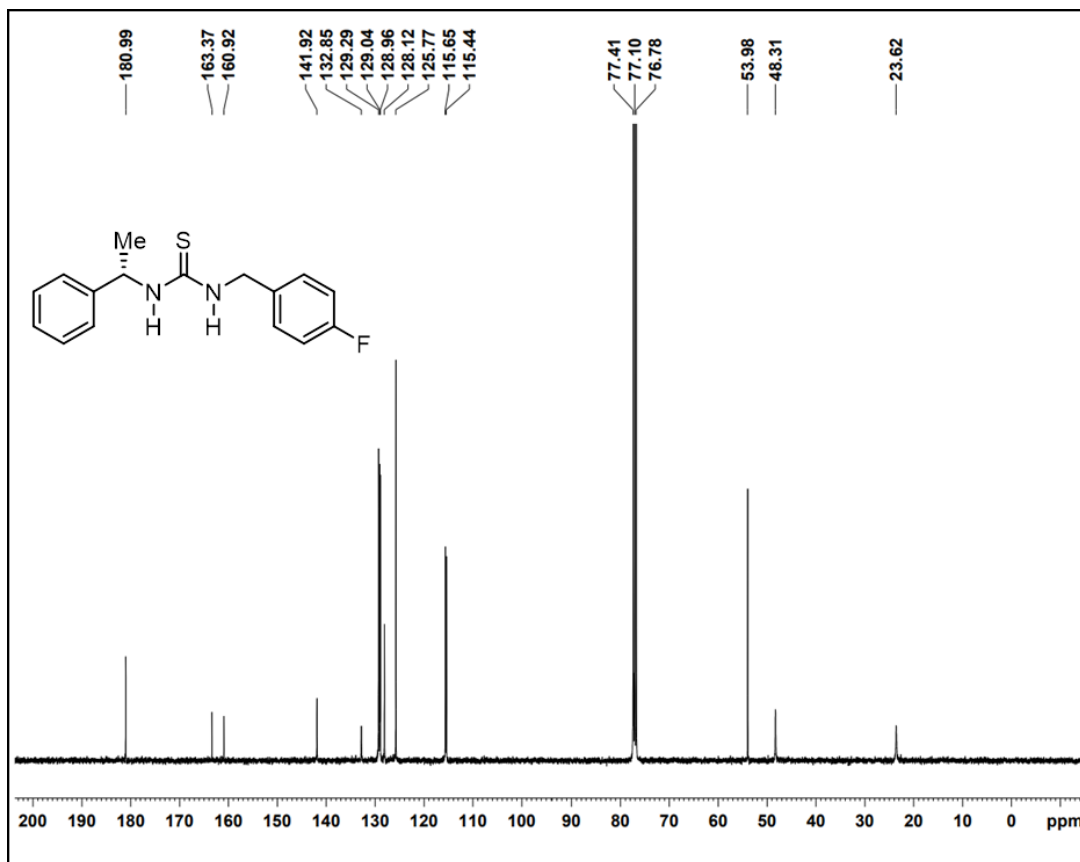


Figure S7. ¹³C NMR Spectrum of S-4 (CDCl₃, 100 MHz)

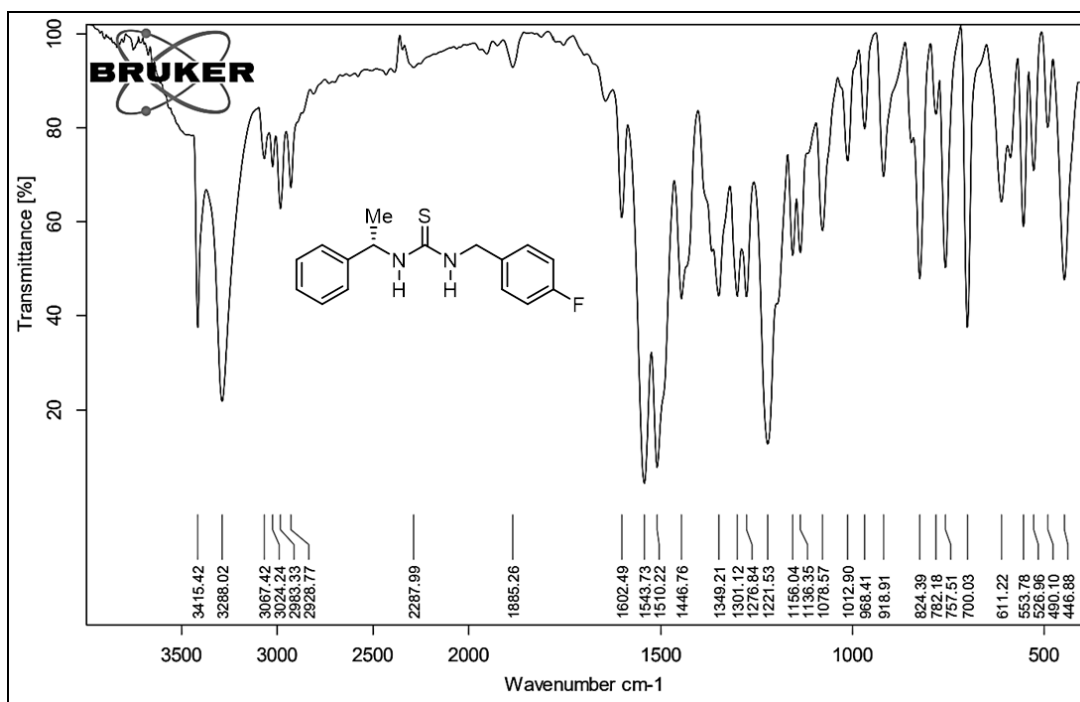


Figure S8. IR spectrum of S-4

Synthesis of (*R/S*)-1-cyclohexyl-3-(1-phenylethyl)thiourea (*S-5*)

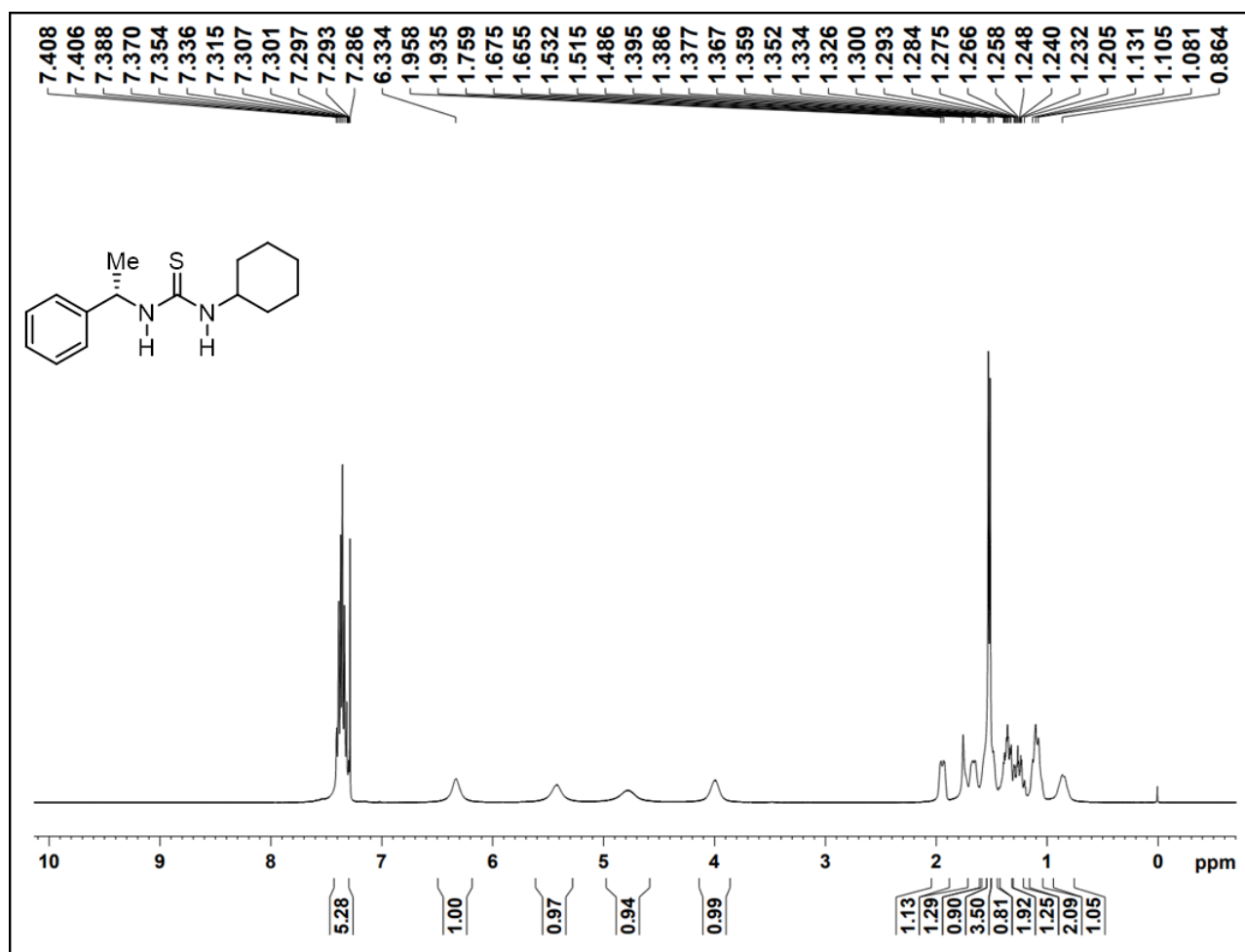
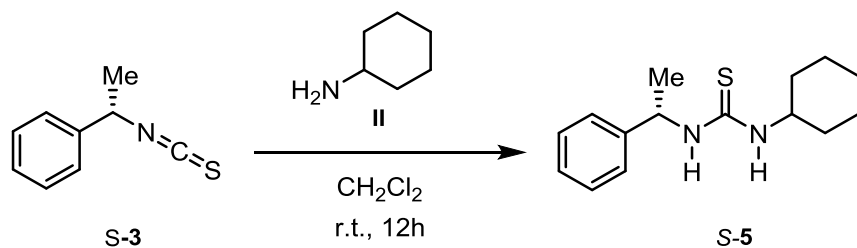


Figure S9. ¹H NMR Spectrum of *S-5* (CDCl₃, 400 MHz)

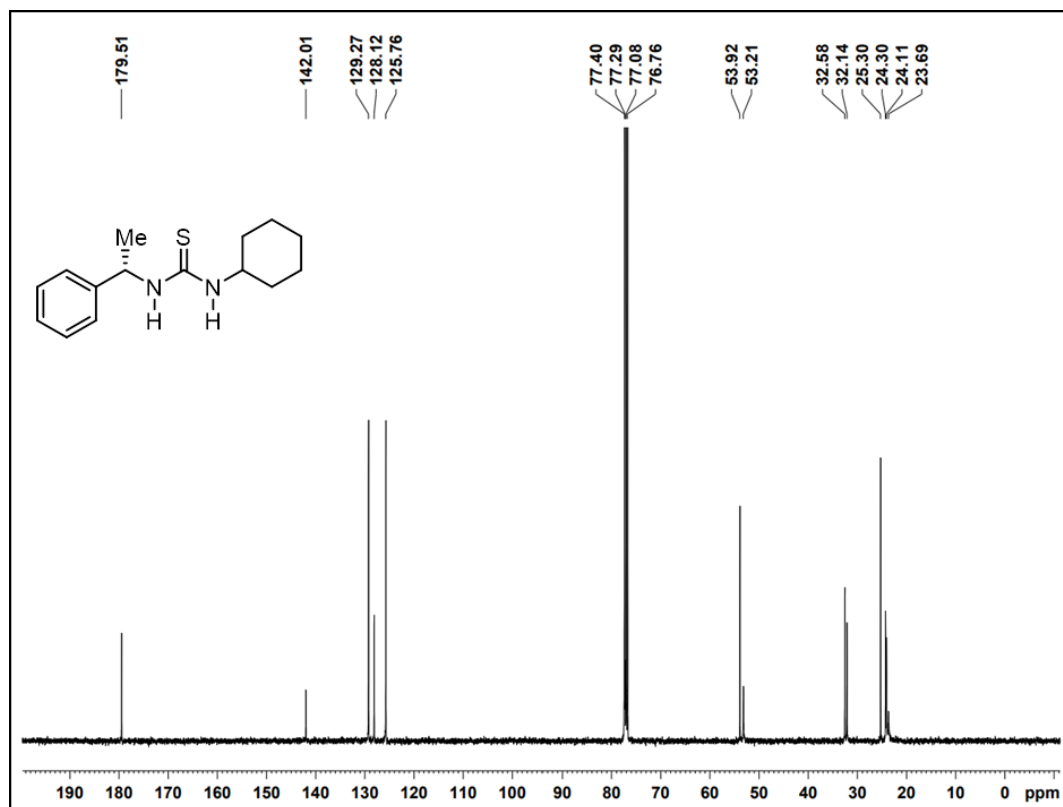


Figure S10. ^{13}C NMR Spectrum of *S*-5 (CDCl_3 , 100 MHz)

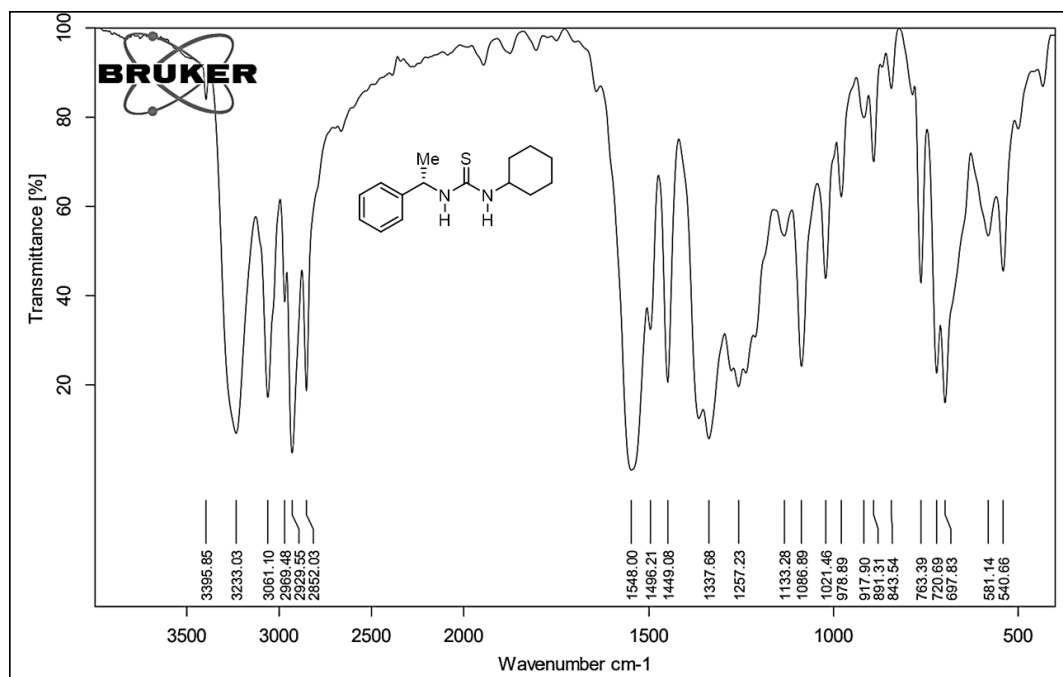


Figure S11. IR spectrum of *S*-5

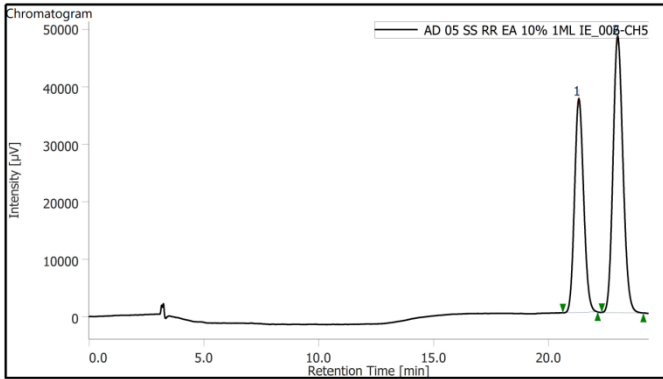
Crystallization Experiments

Case-A: In a round bottom flask, equal mixture of *R,R*-**1** and *S,S*-**1** (200 – 400 mg) was subjected for crystallization in different solvents (5-7 mL). (HPLC of mixture used for crystallization is shown in Figure S13) The optical purity and crystal yield are mentioned in the table below. In the table, the yield indicates the amount of all the optically pure crystals obtained in each experiment, irrespective of their chiral nature (*R,R*-**1** and *S,S*-**1**).

Table 1: Experimental details of crystallization study for **Case A**

| No | Solvent (Yield of crystals, %) | # ^a | Ratio of isomers in the crystals # ^b | | Optical purity of 1 (in %) ^c | Remarks |
|----|--------------------------------------|----------------|--|-----------------------|---|----------------------------|
| | | | <i>S,S</i> - 1 | <i>R,R</i> - 1 | | |
| 1 | Ethyl acetate (61.0) | I | 0.421 | 99.57 | <i>R,R</i> - 1 (99.07) | -- ^d |
| | | II | 99.05 | 0.95 | <i>S,S</i> - 1 (98.11) | -- ^d |
| | | III | 99.68 | 0.32 | <i>S,S</i> - 1 (99.35) | HPLC included (Figure S14) |
| | | IV | 1.57 | 98.43 | <i>R,R</i> - 1 (96.87) | -- ^d |
| | | V | 98.15 | 1.85 | <i>S,S</i> - 1 (96.30) | -- ^d |
| | | VI | 98.40 | 1.60 | <i>S,S</i> - 1 (96.81) | -- ^d |
| | | VII | 99.68 | 0.32 | <i>S,S</i> - 1 (99.37) | -- ^d |
| | | VIII | 4.36 | 95.64 | <i>R,R</i> - 1 (91.28) | -- ^d |
| | | IX | 89.11 | 10.89 | <i>S,S</i> - 1 (78.22) | -- ^d |
| | | X | 0.27 | 99.73 | <i>R,R</i> - 1 (99.47) | HPLC included (Figure S15) |
| | | XI | 97.88 | 2.12 | <i>S,S</i> - 1 (95.75) | -- ^d |
| | | XII | 99.04 | 0.95 | <i>S,S</i> - 1 (98.09) | -- ^d |
| | | XIII | 98.23 | 1.77 | <i>S,S</i> - 1 (96.47) | -- ^d |
| | | XIV | 1.02 | 98.72 | <i>R,R</i> - 1 (97.95) | -- ^d |
| 2 | Acetone (19.3) | I | 13.27 | 86.73 | <i>R,R</i> - 1 (73.45) | -- ^d |
| | | II | 81.12 | 18.88 | <i>S,S</i> - 1 (63.32) | -- ^d |
| | | III | 16.44 | 83.56 | <i>R,R</i> - 1 (67.11) | -- ^d |
| | | IV | 94.21 | 5.79 | <i>R,R</i> - 1 (88.43) | HPLC included (Figure S16) |
| 3 | Toluene (52.1) | I | 99.24 | 0.76 | <i>S,S</i> - 1 (98.482) | -- ^d |
| | | II | 99.46 | 0.54 | <i>S,S</i> - 1 (98.92) | HPLC included (Figure S17) |
| | | III | 99.33 | 0.67 | <i>S,S</i> - 1 (98.66) | -- ^d |
| | | IV | 97.65 | 2.35 | <i>S,S</i> - 1 (95.23) | -- ^d |
| | | V | 0.98 | 99.02 | <i>R,R</i> - 1 (98.04) | HPLC included (Figure S18) |
| | | VI | 97.73 | 2.269 | <i>S,S</i> - 1 (95.46) | -- ^d |
| | | VII | 99.46 | 0.533 | <i>S,S</i> - 1 (98.92) | -- ^d |
| | | VIII | 9.34 | 98.66 | <i>R,R</i> - 1 (97.33) | -- ^d |
| 4 | Ethanol (69.4) | I | 50.19 | 49.81 | <i>S,S</i> - 1 (0.39) | -- ^d |
| | | II | 50.41 | 49.59 | <i>S,S</i> - 1 (0.83) | -- ^d |
| | | III | 52.02 | 47.98 | <i>S,S</i> - 1 (4.03) | -- ^d |
| | | IV | 51.05 | 48.95 | <i>S,S</i> - 1 (2.11) | HPLC included (Figure S19) |
| | | V | 50.03 | 49.97 | <i>S,S</i> - 1 (0.05) | -- ^d |

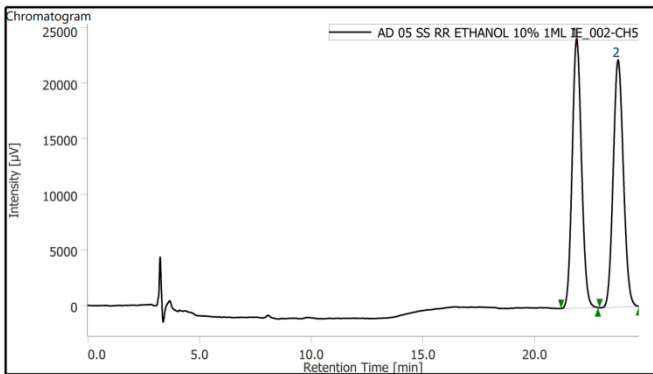
Experiments conducted with 200-400 mg of mixture of **1**; ^aNumber of Crystals analysed, ^bDetermined by Chiral Phase HPLC on Chiralpak IE (10.0 % IPA in hexane; 1.0 mL/min); ^cRatio of only *R,R*-**1** and *S,S*-**1**. ^dHPLC chart not included. (t_R(*S,S*-**1**)= 21.3 min and t_R(*R,R*-**1**)= 23.7 min.)



Peak Information

| # | Peak Name | CH | TR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|-----------|----|----------|---------------|-------------|--------|---------|----------|-------|------------|-----------------|---------|
| 1 | Unknown | S | 21.317 | 1026323 | 37217 | 41.452 | 43.592 | N/A | 13761 | 2.237 | 1.118 | |
| 2 | Unknown | S | 23.010 | 1449631 | 48159 | 58.548 | 56.408 | N/A | 13532 | N/A | 1.132 | |

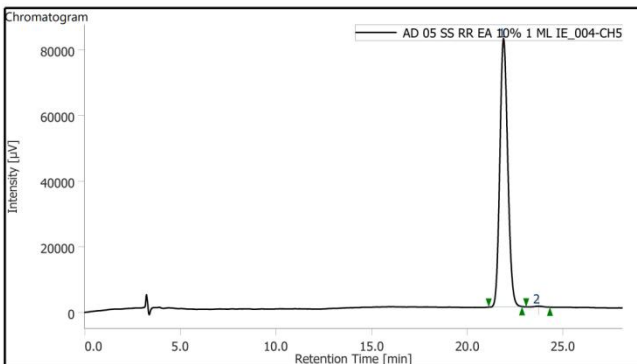
Figure S12. HPLC of *S,S*-1:*R,R*-1 (1:1.4); to establish condition.



Peak Information

| # | Peak Name | CH | TR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|-----------|----|----------|---------------|-------------|--------|---------|----------|-------|------------|-----------------|---------|
| 1 | Unknown | S | 21.860 | 704647 | 24270 | 50.026 | 52.176 | N/A | 13084 | 2.316 | 1.097 | |
| 2 | Unknown | S | 23.710 | 703910 | 22245 | 49.974 | 47.824 | N/A | 12835 | N/A | 1.097 | |

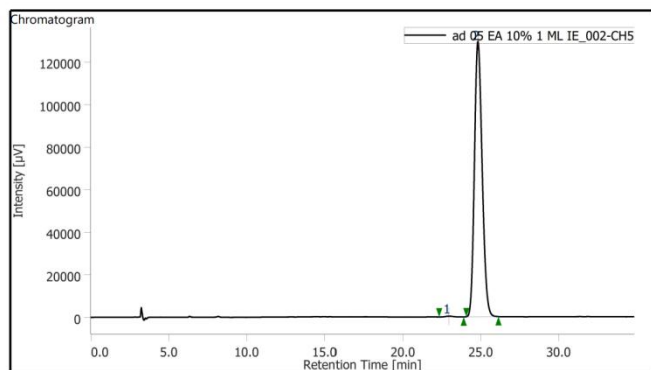
Figure S13. HPLC of *S,S*-1+*R,R*-1 subjected for crystallization



Peak Information

| # | Peak Name | CH | TR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|-----------|----|----------|---------------|-------------|--------|---------|----------|-------|------------|-----------------|---------|
| 1 | Unknown | S | 21.880 | 2350532 | 81730 | 99.684 | 99.672 | N/A | 13326 | 2.402 | 1.124 | |
| 2 | Unknown | S | 23.703 | 7448 | 269 | 0.316 | 0.328 | N/A | 15409 | N/A | 1.177 | |

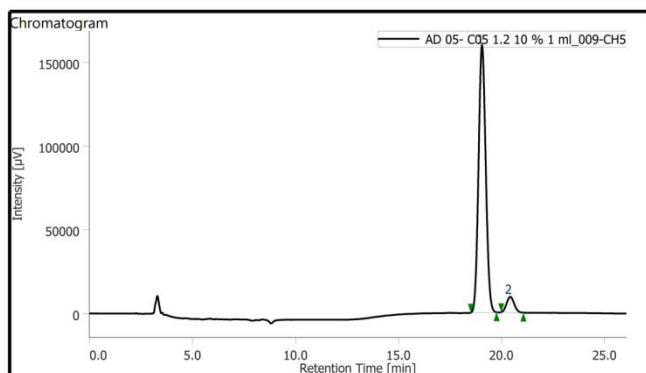
Figure S14. HPLC of crystal III obtained in Ethyl acetate (Table 1, # III).



Peak Information

| # | Peak Name | CH | TR [min] | Area [µV-sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|-----------|----|----------|---------------|-------------|--------|---------|----------|-------|------------|-----------------|---------|
| 1 | Unknown | S | 22.927 | 11946 | 392 | 0.267 | 0.302 | N/A | 13126 | 2.195 | 1.089 | |
| 2 | Unknown | S | 24.800 | 4464037 | 129367 | 99.733 | 99.698 | N/A | 11862 | N/A | 1.178 | |

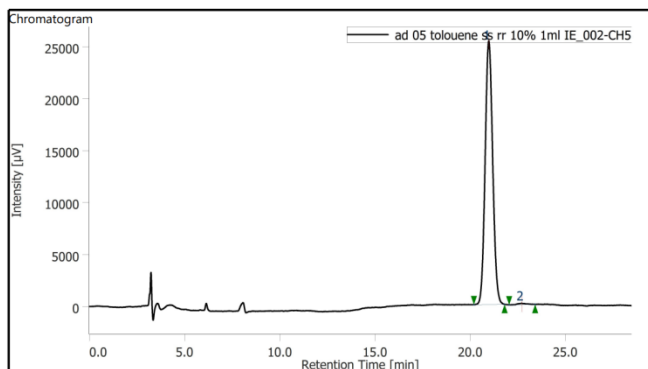
Figure S15. HPLC of crystal X obtained in Ethyl acetate (Table 1, # 1X).



Peak Information

| # | Peak Name | CH | TR [min] | Area [µV-sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|-----------|----|----------|---------------|-------------|--------|---------|----------|-------|------------|-----------------|---------|
| 1 | Unknown | S | 19.043 | 3867583 | 159817 | 94.212 | 94.466 | N/A | 14107 | 2.077 | 1.082 | |
| 2 | Unknown | S | 20.413 | 237627 | 9362 | 5.788 | 5.534 | N/A | 14362 | N/A | 1.084 | |

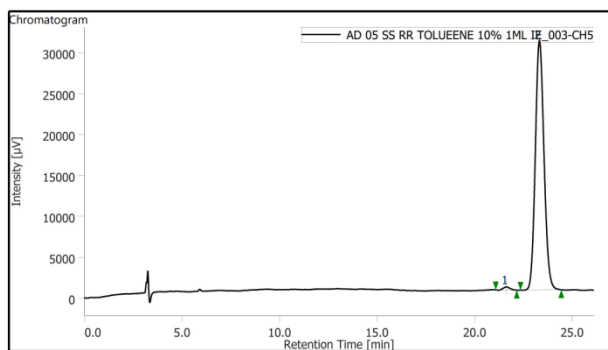
Figure S16. HPLC of crystal IV obtained in Acetone (Table 1, # 2IV).



Peak Information

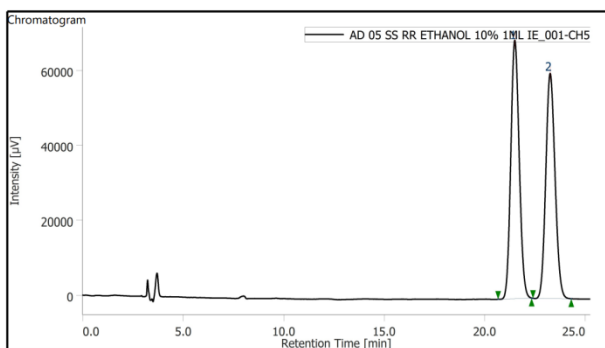
| # | Peak Name | CH | TR [min] | Area [µV-sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|-----------|----|----------|---------------|-------------|--------|---------|----------|-------|------------|-----------------|---------|
| 1 | Unknown | S | 20.967 | 698307 | 25379 | 99.461 | 99.499 | N/A | 13366 | 2.313 | 1.084 | |
| 2 | Unknown | S | 22.697 | 3786 | 128 | 0.539 | 0.501 | N/A | 13737 | N/A | 1.067 | |

Figure S17. HPLC of crystal II obtained in Toluene (Table 1, # 3II).



| Peak Information | | | | | | | | | | | | |
|------------------|-----------|----|----------|---------------|-------------|--------|---------|----------|-------|------------|-----------------|---------|
| # | Peak Name | CH | IR [min] | Area [µV-sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
| 1 | Unknown | S | 21.617 | 9325 | 393 | 0.979 | 1.273 | N/A | 17582 | 2.310 | 1.171 | |
| 2 | Unknown | S | 23.303 | 943421 | 30518 | 99.021 | 98.727 | N/A | 13170 | N/A | 1.116 | |

Figure S18. HPLC of crystal V obtained in Toluene (Table 1, # 3V).

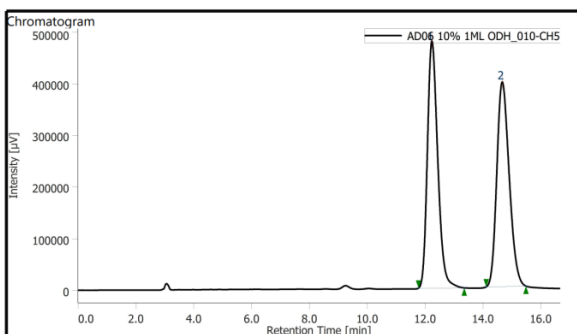


| Peak Information | | | | | | | | | | | | |
|------------------|-----------|----|----------|---------------|-------------|--------|---------|----------|-------|------------|-----------------|---------|
| # | Peak Name | CH | IR [min] | Area [µV-sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
| 1 | Unknown | S | 21.487 | 2003884 | 69012 | 51.055 | 53.444 | N/A | 12497 | 2.182 | 1.095 | |
| 2 | Unknown | S | 23.243 | 1921062 | 60116 | 48.945 | 46.556 | N/A | 12094 | N/A | 1.106 | |

Figure S19. HPLC of crystal IV obtained in Ethanol (Table 1, #4 IV).

Case-B :

The diastereomeric mixture of *S,R*-1 and *S,S*-1 (200 mg) was subjected for crystallization in different solvents (6-7 mL). Equal ratio of isomers obtained in the reaction is confirmed by HPLC (Figure S20)



| Peak Information | | | | | | | | | | | | |
|------------------|-----------|----|----------|---------------|-------------|--------|---------|----------|------|------------|-----------------|---------|
| # | Peak Name | CH | IR [min] | Area [µV-sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
| 1 | Unknown | S | 12.227 | 11890525 | 478655 | 50.279 | 54.704 | N/A | 5789 | 3.417 | 1.254 | |
| 2 | Unknown | S | 14.657 | 11758400 | 396337 | 49.721 | 45.296 | N/A | 5600 | N/A | 1.217 | |

Figure S20. HPLC of diastereomeric mixture (*S,S*-1+*S,R*-1) subjected for crystallization

Crystallization of this mixture resulted in two different shapes of crystals; needle shaped crystals were *S,S*-**1**, while *S,R*-**1** crystallizes out as flakes. The optical purity and crystal yield are mentioned in the table below.

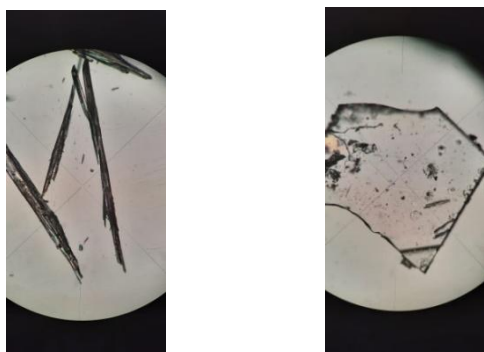
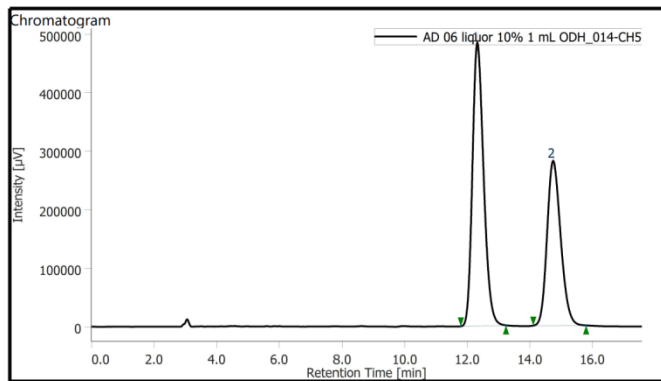


Figure S21. Images of crystals obtained in Case B; Left: *S,S*-**1**, Right: *S,R*-**1**

Table 2: Experimental details of crystallization study for **Case B**

| No | Solvent (Yield of crystals, %) | # ^a | Ratio of isomers in the crystals # ^b | | Optical purity of 1 (in %) ^c | Remarks |
|----|---|----------------|--|-----------------------|---|----------------------------|
| | | | <i>S,R</i> - 1 | <i>S,S</i> - 1 | | |
| 1 | diisopropyl ether (48.6) | I | 4.71 | 95.29 | <i>S,S</i> - 1 (90.59) | -- ^d |
| | | II | 4.33 | 95.67 | <i>S,S</i> - 1 (91.33) | HPLC included (Figure S23) |
| | | III | 5.33 | 94.67 | <i>S,S</i> - 1 (89.34) | -- ^d |
| | | IV | 4.97 | 95.03 | <i>S,S</i> - 1 (90.06) | -- ^d |
| | | V | 5.34 | 94.66 | <i>S,S</i> - 1 (89.33) | -- ^d |
| | | VI | 4.65 | 95.34 | <i>S,S</i> - 1 (90.69) | -- ^d |
| 2 | dichloromethane diisopropylether (92.0) | I | 2.77 | 97.23 | <i>S,S</i> - 1 (94.47) | -- ^d |
| | | II | 3.68 | 96.31 | <i>S,S</i> - 1 (92.63) | HPLC included (Figure S24) |
| | | III | 4.55 | 95.45 | <i>S,S</i> - 1 (89.77) | -- ^d |
| 3 | Hexane- dichloromethane (74.6) | I | 9.73 | 90.27 | <i>S,S</i> - 1 (80.54) | -- ^d |
| | | II | 5.28 | 94.72 | <i>S,S</i> - 1 (89.44) | -- ^d |
| | | III | 6.30 | 93.70 | <i>S,S</i> - 1 (87.40) | HPLC included (Figure S25) |
| 4 | Ethanol (65.0%) | I | 2.40 | 97.60 | <i>S,S</i> - 1 (93.03) | HPLC included (Figure S26) |
| | | II | 10.6 | 89.33 | <i>S,S</i> - 1 (72.09) | -- ^d |
| 5 | Acetone (88.9%) | 7 | | | | |
| | | I | 5.79 | 94.21 | <i>S,S</i> - 1 (86.70) | -- ^d |
| | | II | 6.47 | 93.53 | <i>S,S</i> - 1 (84.20) | -- ^d |
| | | III | 3.37 | 96.63 | <i>S,S</i> - 1 (93.26) | HPLC included (Figure S27) |
| | | IV | 4.96 | 95.04 | <i>S,S</i> - 1 (90.08) | -- ^d |

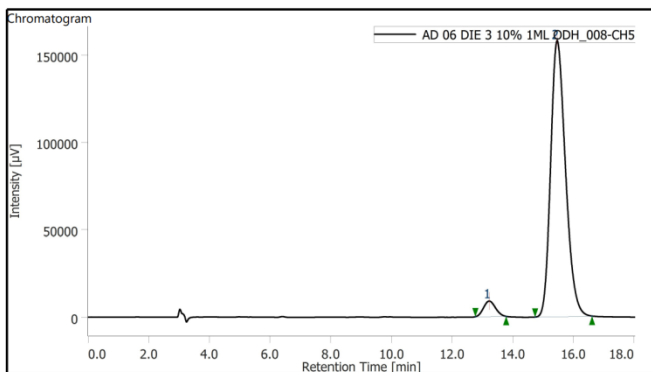
Experiments conducted with 200–400 mg of mixture of **1**; ^aNumber of Crystals analysed, ^bDetermined by Chiral Phase HPLC on Chiralcel OD-H (10.0 % IPA in hexane; 1.0 mL/min); ^cRatio of only *R,R*-**1** and *S,S*-**1**. ^dHPLC chart not included. ($t_R(S,R-1)$ = 12.2 min, $t_R(S,S-1)$ = 14.6 min)



Peak Information

| # | Peak Name | Ch | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|-----------|----|----------|---------------|-------------|--------|---------|----------|------|------------|-----------------|---------|
| 1 | Unknown | 5 | 12.313 | 12059868 | 483471 | 58.645 | 63.208 | N/A | 5707 | 3.365 | 1.243 | |
| 2 | Unknown | 5 | 14.737 | 8504300 | 281417 | 41.355 | 36.792 | N/A | 5537 | N/A | 1.200 | |

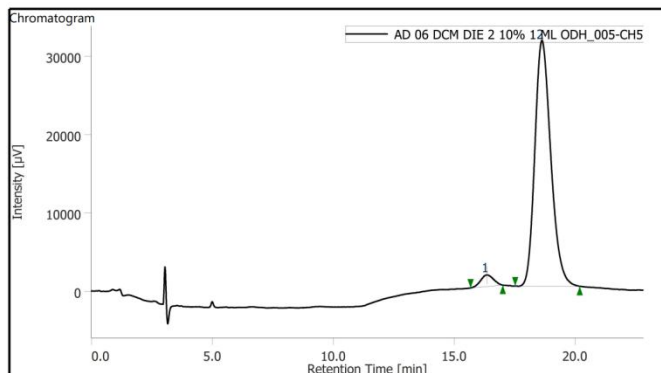
Figure S22. HPLC of *S,R*-1: *S,S*-1 (1.0:0.7) to establish condition.



Peak Information

| # | Peak Name | Ch | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|-----------|----|----------|---------------|-------------|--------|---------|----------|------|------------|-----------------|---------|
| 1 | Unknown | 5 | 13.213 | 244006 | 8925 | 4.333 | 5.342 | N/A | 5131 | 2.762 | 1.111 | |
| 2 | Unknown | 5 | 15.457 | 5387548 | 158150 | 95.667 | 94.658 | N/A | 4813 | N/A | 1.251 | |

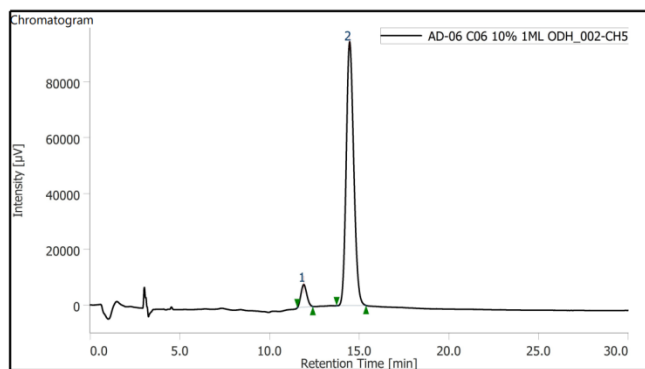
Figure S23. HPLC of crystal II obtained in diisopropylether (Table 2, #1II).



Peak Information

| # | Peak Name | Ch | tR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|-----------|----|----------|---------------|-------------|--------|---------|----------|------|------------|-----------------|---------|
| 1 | Unknown | 5 | 16.353 | 55107 | 1473 | 3.685 | 4.486 | N/A | 4151 | 2.059 | 1.010 | |
| 2 | Unknown | 5 | 18.623 | 1440342 | 31363 | 96.315 | 95.514 | N/A | 3879 | N/A | 1.239 | |

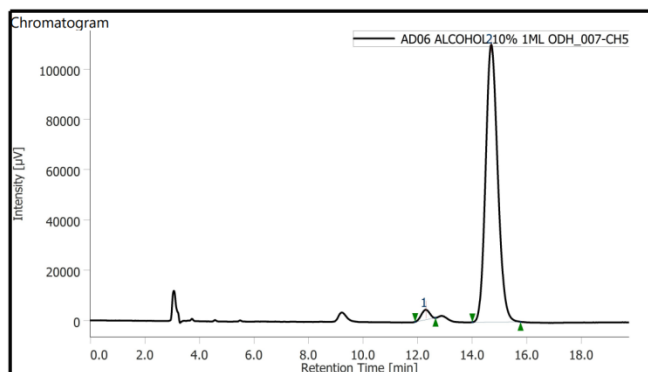
Figure S24. HPLC of crystal II obtained in dichloromethane-diisopropylether (1:1) (Table 2, #2II).



Peak Information

| # | Peak Name | Ch | IR [min] | Area [µV-sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|-----------|----|----------|---------------|-------------|--------|---------|----------|------|------------|-----------------|---------|
| 1 | Unknown | 5 | 11.910 | 185071 | 8135 | 6.300 | 7.915 | N/A | 6027 | 3.719 | 1.115 | |
| 2 | Unknown | 5 | 14.467 | 2752724 | 94636 | 93.700 | 92.085 | N/A | 5724 | N/A | 1.158 | |

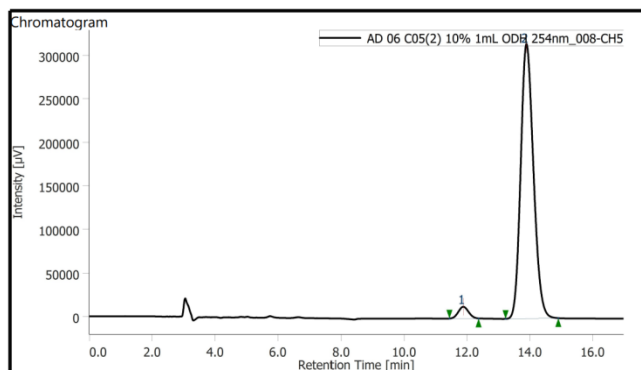
Figure S25. HPLC of crystal III obtained in Hexane-dichloromethane (1:1) (Table 2, #3III).



Peak Information

| # | Peak Name | Ch | IR [min] | Area [µV-sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|-----------|----|----------|---------------|-------------|--------|---------|----------|------|------------|-----------------|---------|
| 1 | Unknown | 5 | 12.293 | 83709 | 3985 | 2.403 | 3.487 | N/A | 7162 | 3.463 | 0.944 | |
| 2 | Unknown | 5 | 14.693 | 3399992 | 110314 | 97.597 | 96.513 | N/A | 5282 | N/A | 1.150 | |

Figure S26. HPLC of crystal I obtained in Ethanol (Table 2, #4I).



Peak Information

| # | Peak Name | Ch | IR [min] | Area [µV-sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|-----------|----|----------|---------------|-------------|--------|---------|----------|------|------------|-----------------|---------|
| 1 | Unknown | 5 | 11.880 | 310227 | 13548 | 3.368 | 4.119 | N/A | 5990 | 2.968 | 1.047 | |
| 2 | Unknown | 5 | 13.887 | 8900862 | 315358 | 96.632 | 95.881 | N/A | 5610 | N/A | 1.172 | |

Figure S27. HPLC of crystal III obtained in Acetone (Table 2, #5III).

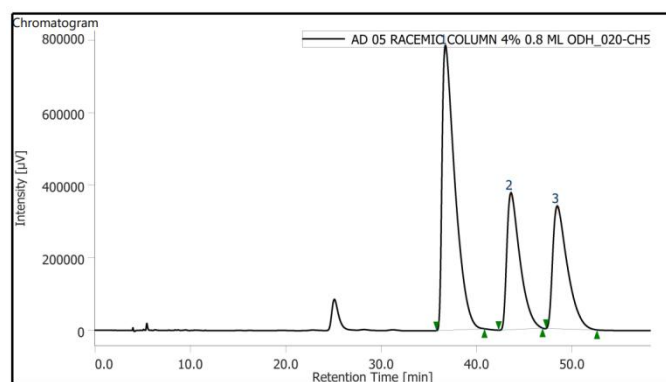
Case-C:

The diastereomeric mixture of *S,S*-**1** (25%), *R,R*-**1** (25%), *S,R*-**1** (25%), *R,S*-**1** (25%) (80-400 mg) was subjected for crystallization in different solvents (3-4 mL). Ratio of isomers obtained in the reaction is confirmed by HPLC (Figure S28)

Table 3: Experimental details of crystallization study for **Case C**

| No | Solvent (Yield of crystals, %) | # ^a | Ratio of isomers in the crystals # ^b | | | Optical purity of 1 (in %) ^c | Remarks |
|----|---|----------------|--|-----------------------|-----------------------|---|----------------------------|
| | | | Meso <i>R,S</i> - 1 | <i>R,R</i> - 1 | <i>S,S</i> - 1 | | |
| 1 | Acetone- Hexane (19.0) | I | 3.7 | 8.6 | 87.6 | <i>S,S</i> - 1 (82.2) | -- ^e |
| | | II | 3.4 | 0.5 | 96.0 | <i>S,S</i> - 1 (95.2) | HPLC included (Figure S31) |
| | | III | 3.8 | 5.1 | 91.1 | <i>S,S</i> - 1 (87.7) | HPLC included (Figure S32) |
| | | IV | 6.5 | 90.4 | 3.0 | <i>R,R</i> - 1 (93.5) | HPLC included (Figure S33) |
| | | V | 6.7 | 84.8 | 8.4 | <i>R,R</i> - 1 (81.9) | -- ^e |
| 2 | Toluene (19.3) | I | 7.2 | 67.9 | 24.9 | <i>R,R</i> - 1 (46.3) | HPLC included (Figure S34) |
| 3 | CH ₂ Cl ₂ - DIP ^d (52.1) | I | 19.6 | 51.7 | 28.6 | <i>R,R</i> - 1 (28.3) | HPLC included (Figure S35) |
| | | II | 17.6 | 51.8 | 30.6 | <i>R,R</i> - 1 (25.6) | -- ^e |
| 4 | MeOH (45.5) | I | 19.7 | 39.4 | 40.9 | <i>R,R</i> - 1 (1.9) | -- ^e |
| | | II | 17.6 | 42.7 | 39.7 | <i>R,R</i> - 1 (3.6) | HPLC included (Figure S36) |

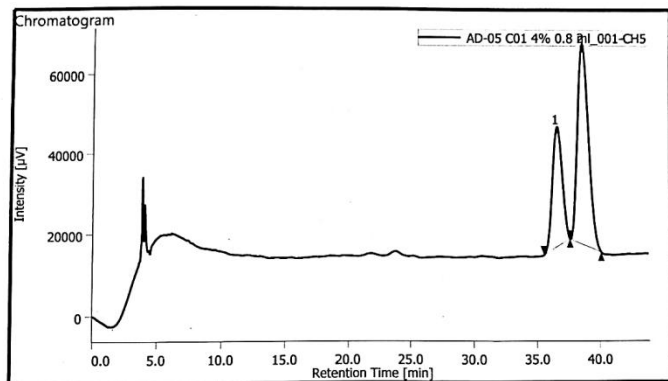
Experiments conducted with 80-400 mg of mixture of **1**; ^aNumber of Crystals analysed, ^bDetermined by Chiral Phase HPLC on Chiralcel OD-H (4.0 % IPA in hexane; 0.8 mL/min); ^cRatio of only *R,R*-**1** and *S,S*-**1**. ^dDiisopropylether. ^eHPLC chart not included. (t_R(*S,R*-**1**)= 36.7 min, t_R(*R,R*-**1**)= 43.6 min, t_R(*S,S*-**1**)= 48.4 min)



Peak Information

| # | Peak Name | Ch | tR (min) | Area (µV·sec) | Height (µV) | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|-----------|----|----------|---------------|-------------|--------|---------|----------|------|------------|-----------------|---------|
| 1 | Unknown | 5 | 36.710 | 73704645 | 785330 | 50.560 | 52.308 | N/A | 3713 | 2.830 | 2.555 | |
| 2 | Unknown | 5 | 43.573 | 35907206 | 377415 | 24.632 | 25.138 | N/A | 5045 | 1.866 | 2.005 | |
| 3 | Unknown | 5 | 48.420 | 36164061 | 338616 | 24.808 | 22.554 | N/A | 4947 | N/A | 2.039 | |

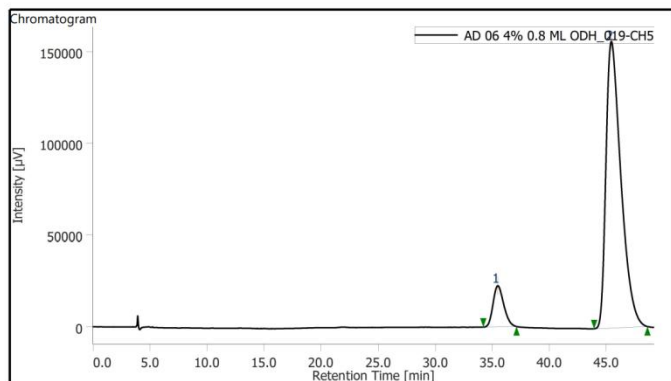
Figure S28. HPLC of Crude **1** *S,R*-**1** /*R,S*-**1** (50%) *S,S*-**1** (25%), *R,R*-**1** (25%) before crystallization



Peak Information

| # | Peak Name | CH | tR [min] | Area [µV-sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|-----------|----|----------|---------------|-------------|--------|---------|----------|------|------------|-----------------|---------|
| 1 | Unknown | 5 | 36.720 | 1619662 | 29832 | 34.707 | 37.239 | N/A | 9788 | 1.309 | 0.991 | |
| 2 | Unknown | 5 | 38.760 | 3046987 | 50278 | 65.293 | 62.761 | N/A | 8932 | N/A | 1.133 | |

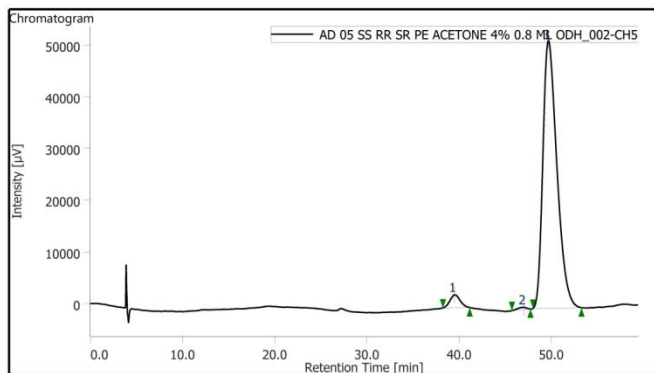
Figure S29. HPLC of salemic crude *R,R*-1: *S,S*-1 (1.0:2.0), to establish condition.



Peak Information

| # | Peak Name | CH | tR [min] | Area [µV-sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|-----------|----|----------|---------------|-------------|--------|---------|----------|------|------------|-----------------|---------|
| 1 | Unknown | 5 | 35.470 | 1471868 | 22476 | 9.369 | 12.585 | N/A | 6737 | 4.873 | 1.211 | |
| 2 | Unknown | 5 | 45.430 | 14238881 | 156123 | 90.631 | 87.415 | N/A | 5877 | N/A | 1.644 | |

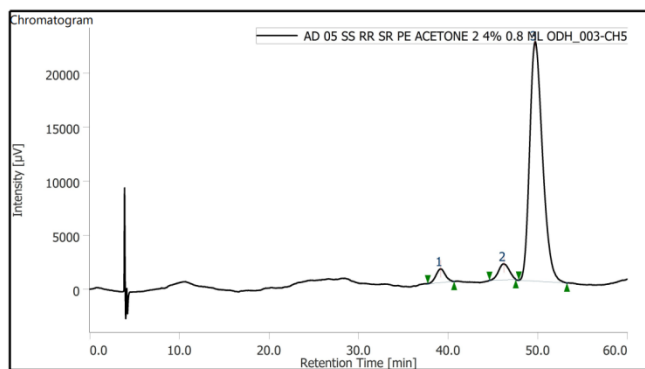
Figure S30. HPLC of salemic crude *S,R*-1: *S,S*-1 (1.0:9.6), to establish condition.



Peak Information

| # | Peak Name | CH | tR [min] | Area [µV-sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|-----------|----|----------|---------------|-------------|--------|---------|----------|------|------------|-----------------|---------|
| 1 | Unknown | 5 | 39.463 | 193428 | 2522 | 3.410 | 4.609 | N/A | 6052 | 3.798 | 1.156 | |
| 2 | Unknown | 5 | 47.007 | 30832 | 452 | 0.544 | 0.826 | N/A | 9264 | 1.128 | 0.765 | |
| 3 | Unknown | 5 | 49.657 | 5447970 | 51749 | 96.046 | 94.565 | N/A | 5189 | N/A | 1.426 | |

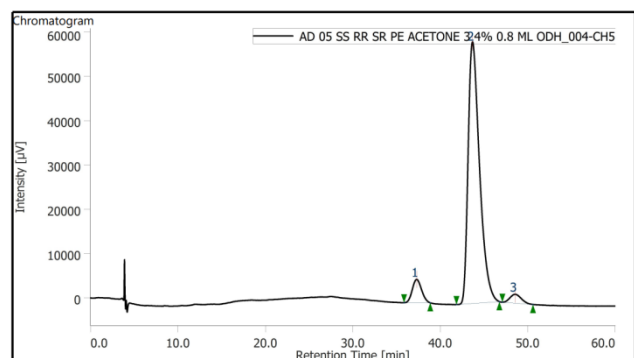
Figure S31. HPLC of crystal II obtained in Acetone-Hexane (1:1) (Table 3, #1II)



Peak Information

| # | Peak Name | CH | tR [min] | Area [μV·sec] | Height [μV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|-----------|----|----------|---------------|-------------|--------|---------|----------|------|------------|-----------------|---------|
| 1 | Unknown | S | 39.163 | 92199 | 1266 | 3.805 | 5.084 | N/A | 6726 | 3.390 | 1.026 | |
| 2 | Unknown | S | 46.213 | 123888 | 1483 | 5.113 | 5.954 | N/A | 6686 | 1.430 | 0.962 | |
| 3 | Unknown | S | 49.680 | 2206762 | 22156 | 91.081 | 88.962 | N/A | 5841 | N/A | 1.297 | |

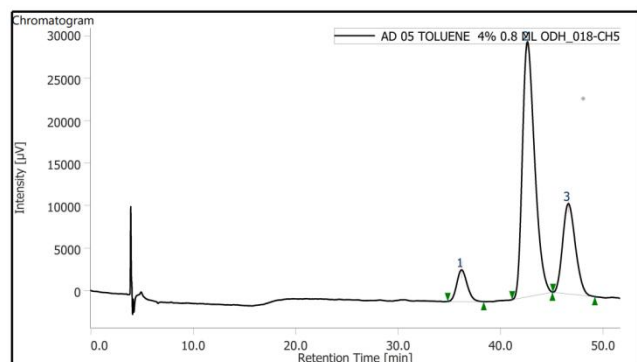
Figure S32. HPLC of crystal III obtained in Acetone-Hexane (1:1) (Table 2, #1III)



Peak Information

| # | Peak Name | CH | tR [min] | Area [μV·sec] | Height [μV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|-----------|----|----------|---------------|-------------|--------|---------|----------|------|------------|-----------------|---------|
| 1 | Unknown | S | 37.277 | 388699 | 5274 | 6.579 | 7.965 | N/A | 5712 | 2.965 | 1.112 | |
| 2 | Unknown | S | 43.663 | 5340859 | 58939 | 90.398 | 89.023 | N/A | 5537 | 2.043 | 1.551 | |
| 3 | Unknown | S | 48.533 | 178632 | 1994 | 3.023 | 3.012 | N/A | 6363 | N/A | 1.162 | |

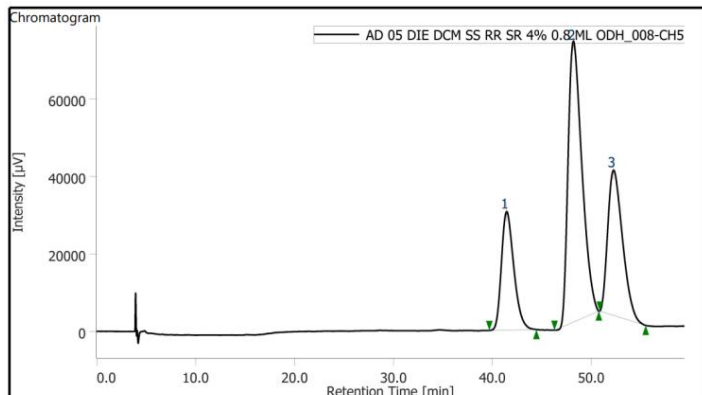
Figure S33. HPLC of crystal IV obtained in Acetone-Hexane (1:1) (Table 2, #1IV)



Peak Information

| # | Peak Name | CH | tR [min] | Area [μV·sec] | Height [μV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|-----------|----|----------|---------------|-------------|--------|---------|----------|------|------------|-----------------|---------|
| 1 | Unknown | S | 36.180 | 265033 | 3744 | 7.195 | 8.431 | N/A | 6084 | 3.181 | 1.140 | |
| 2 | Unknown | S | 42.587 | 2500712 | 30058 | 67.890 | 67.676 | N/A | 6087 | 1.792 | 1.382 | |
| 3 | Unknown | S | 46.593 | 917720 | 10612 | 24.915 | 23.894 | N/A | 6561 | N/A | 1.175 | |

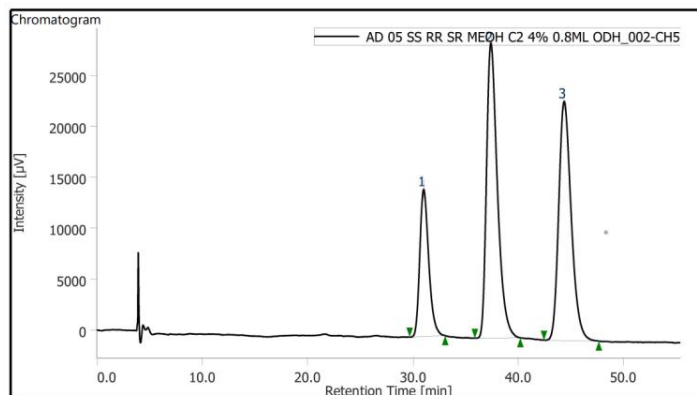
Figure S34. HPLC of crystal VI obtained in Toluene (Table 2, #2I)



Peak Information

| # | Peak Name | CH | TR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|-----------|----|----------|---------------|-------------|--------|---------|----------|------|------------|-----------------|---------|
| 1 | Unknown | 5 | 41.417 | 2663595 | 30598 | 19.624 | 21.774 | N/A | 5320 | 2.785 | 1.322 | |
| 2 | Unknown | 5 | 48.163 | 7028684 | 72480 | 51.783 | 51.577 | N/A | 5544 | 1.513 | 1.485 | |
| 3 | Unknown | 5 | 52.210 | 3881090 | 37448 | 28.593 | 26.649 | N/A | 5663 | N/A | 1.432 | |

Figure S35. HPLC of crystal VII obtained in CH₂Cl₂-DIP (Table 3, #3I)



Peak Information

| # | Peak Name | CH | TR [min] | Area [µV·sec] | Height [µV] | Area% | Height% | Quantity | NTP | Resolution | Symmetry Factor | Warning |
|---|-----------|----|----------|---------------|-------------|--------|---------|----------|------|------------|-----------------|---------|
| 1 | Unknown | 5 | 30.993 | 856405 | 14438 | 17.573 | 21.581 | N/A | 6571 | 3.803 | 1.295 | |
| 2 | Unknown | 5 | 37.387 | 2081069 | 28980 | 42.703 | 43.317 | N/A | 6594 | 3.511 | 1.460 | |
| 3 | Unknown | 5 | 44.347 | 1935838 | 23484 | 39.723 | 35.102 | N/A | 6913 | N/A | 1.274 | |

Figure S36. HPLC of crystal X obtained in Methanol (Table 2, #4II)

Crystallization experiments of S/R-4 and S/R-5:

Racemic mixture of S-4 and R-4 (200 mg), subjected to crystallization in Ethyl acetate (6mL), Hexane-ethyl acetate (1:1, 6 mL), Hexane-dichloromethane (1:1, 6 mL), toluene (7 mL) resulted in formation of racemic crystals. Crystallization trials for racemic S/R-5 in various solvent also lead racemic crystal instead of conglomerate.

IR Study

In the case A, crystallization from mixture of *S,S*-**1**-*R,R*-**1** isomers showed formation of conglomerates with high enantiomeric excess. This observation is in accordance with the high correlation between the IR transmittance frequencies of enantiopure and racemic samples.⁴ In case B, the tendency of *S,S*-**1** to crystallize out is higher than that of *S,R*-**1**, in all the solvents tried. This observation is well supported by high correlation between SS and diastereomeric mixture (SS-SR). In the Case C, correlation between the IR frequencies of enantiopure isomer SS or RR and mixture under crystallization (*S,S*-**1**,*R,R*-**1**,*S,R*/*R,S*-**1**) is less than the earlier cases which is evident by low crystal yield of *S,S*-**1**.

Discrepancies in the IR spectra are attributed to the interactions between different isomers.

Table 4. Correlation coefficient of pure and racemic/diastereomeric mixture of **1**

| Crystallization experiment | Isomers of 1 under comparison (for IR study) | | Correlation coefficient |
|----------------------------|---|-----------------|-------------------------|
| Case A | SS (pure) | RR (pure) | 1.0000 |
| | SS, RR (racemic) | RR (pure) | 0.9662 |
| | SS, RR (racemic) | SS (pure) | 0.9662 (Figure S37) |
| Case B | SS,SR (diastereomer) | SS (pure) | 0.9683 |
| | SS, SR (diastereomer) | SR (pure meso) | 0.9444 |
| Case C | SS, RR, SR | RR or SS (pure) | 0.9395 |
| | SS, RR, SR | SR (pure meso) | 0.9399 |

IR spectra recorded for pure and racemic thiourea derivatives **4** and **5** are shown in figure S38 and S39. Correlation coefficient for enantiopure - racemic sample of **5** and **7** was found to be **0.7995** and **0.8516** respectively. These values are in agreement with the tendency of molecule to crystallize as racemic crystal instead of conglomerate.

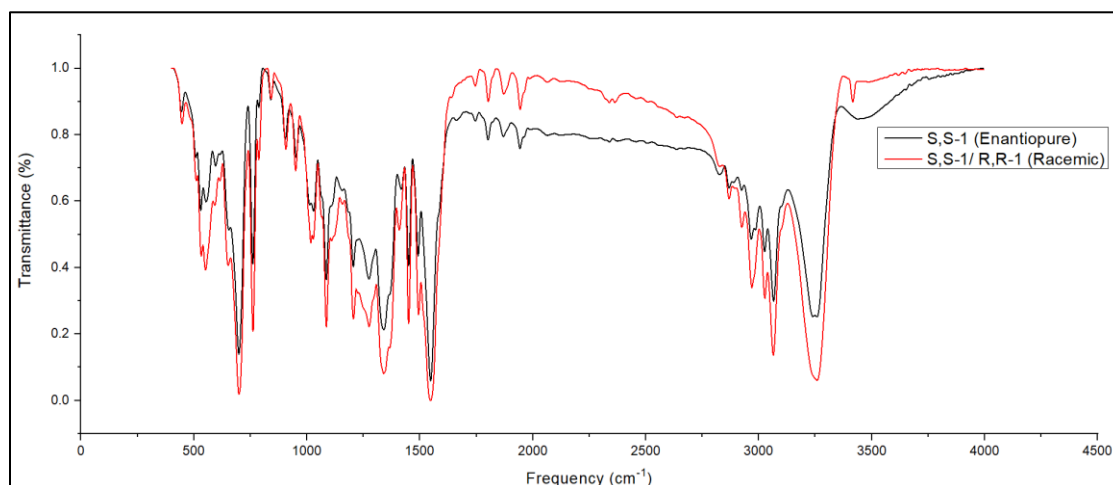


Figure S37. IR spectrum of pure enantiomer (*S,S*-**1**) and racemic sample (*S,S*-**1** and *R,R*-**1**).

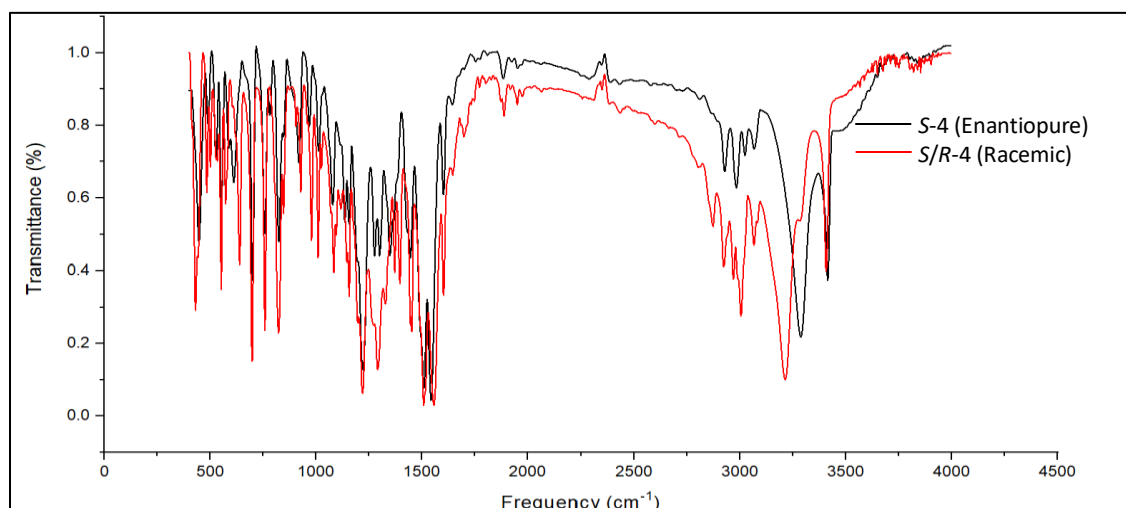


Figure S38. IR spectrum of pure enantiomer (*S*-4) and racemic sample (*S/R*-4).

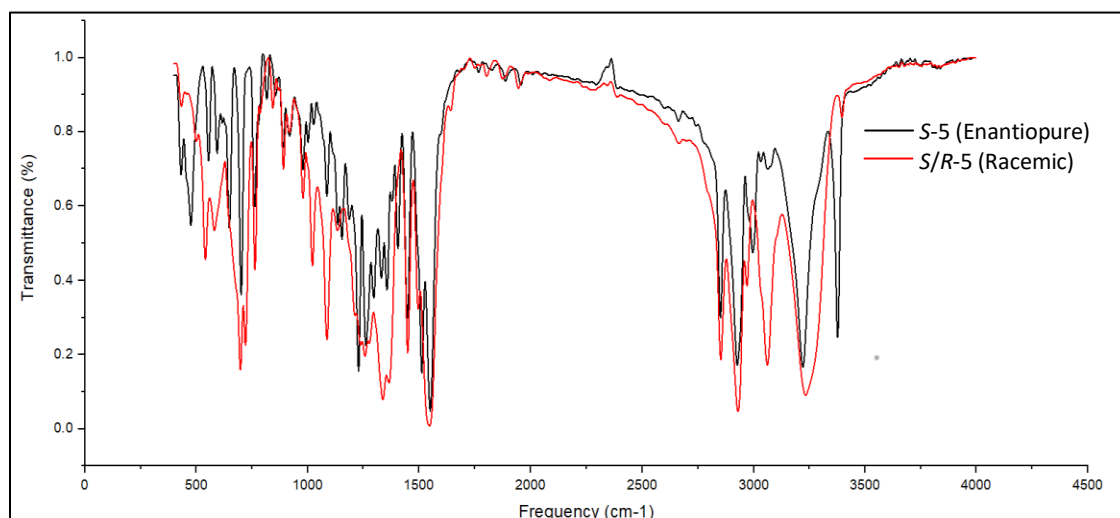


Figure S39. IR spectrum of pure enantiomer (*S*-5) and racemic sample (*S/R*-5).

Thermal analysis

Theoretical melting temperature is calculated using Schroder Van Laar equation⁵ (1)

$$\ln x = \frac{\Delta H_A^f}{R} \left(\frac{1}{T_A^f} - \frac{1}{T^f} \right) \quad (1)$$

The thermodynamic parameters like free energy of formation ΔG_R^0 of racemic compound and entropy of mixing for enantiomeric **1** in the liquid state ΔS^m , are calculated from experimentally measured characteristics (melting point T^f and enthalpy of fusion ΔH^f) using equation (2) and (3) respectively.

$$\Delta G_{T_R^f}^0 = - \frac{(T_R^f - T_A^f) \Delta H_A^f}{T_A^f} - T_R^f R \ln 2 \quad (2)$$

$$-\Delta S_l^m = \frac{\Delta H_A^f}{T_A^f} - \frac{\Delta H_R^f}{T_R^f} - \frac{\Delta H_A^f - \Delta H_R^f}{T_A^f - T_R^f} \ln \frac{T_A^f}{T_R^f} \quad (3)$$

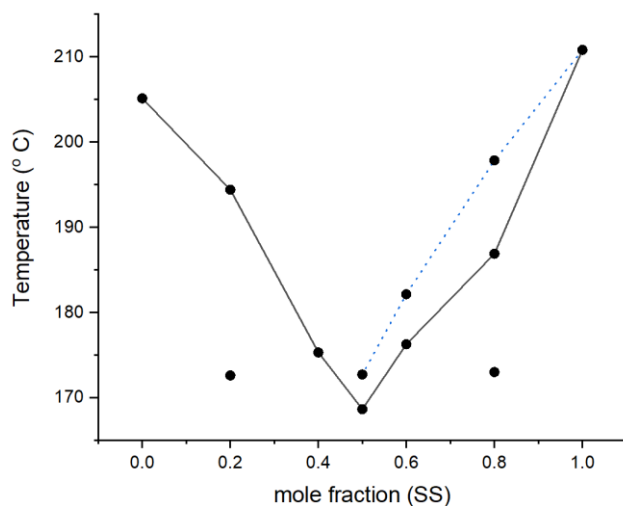


Figure S40. Experimental (solid line) and theoretical (dotted line) phase diagram of binary mixture of enantiomers (*S,S*-1 and *R,R*-1).

Computational analysis

Cartesian coordinates and NCI plot of enantiomeric dimer *S,S*-1-----*S,S*-1

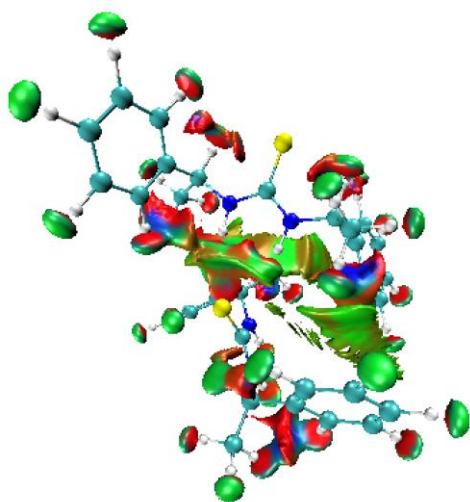


Figure S41. NCI plot of enantiomeric dimer *S,S*-1-----*S,S*-1

| Center Number | Atomic Number | Atomic Type | Coordinates (Angstroms) | | |
|------------------|------------------|----------------|-------------------------|-----------|-----------|
| | | | X | Y | Z |
| 1 | 16 | 0 | -3.123556 | -2.514883 | 2.211872 |
| 2 | 7 | 0 | -0.833551 | -1.939851 | 0.905728 |
| 3 | 1 | 0 | -0.333851 | -1.370043 | 0.226748 |
| 4 | 7 | 0 | -2.584377 | -0.555149 | 0.438854 |
| 5 | 1 | 0 | -1.927029 | -0.126180 | -0.208494 |
| 6 | 6 | 0 | -0.067399 | -3.009706 | 1.554457 |
| 7 | 1 | 0 | -0.780587 | -3.499262 | 2.221076 |
| 8 | 6 | 0 | 1.051407 | -2.420274 | 2.412743 |
| 9 | 6 | 0 | 2.326053 | -2.138676 | 1.900051 |
| 10 | 1 | 0 | 2.560826 | -2.360958 | 0.863379 |
| 11 | 6 | 0 | 3.315539 | -1.576197 | 2.712814 |
| 12 | 1 | 0 | 4.298387 | -1.372014 | 2.296615 |
| 13 | 6 | 0 | 3.046900 | -1.288993 | 4.053448 |
| 14 | 1 | 0 | 3.818575 | -0.860576 | 4.687194 |
| 15 | 6 | 0 | 1.779539 | -1.565927 | 4.575472 |
| 16 | 1 | 0 | 1.560619 | -1.352335 | 5.618164 |
| 17 | 6 | 0 | 0.792724 | -2.125698 | 3.760959 |
| 18 | 1 | 0 | -0.192900 | -2.336146 | 4.167765 |
| 19 | 6 | 0 | 0.401565 | -4.031598 | 0.510072 |
| 20 | 1 | 0 | 1.028372 | -3.573758 | -0.262639 |
| 21 | 1 | 0 | -0.469566 | -4.475112 | 0.019440 |
| 22 | 1 | 0 | 0.979289 | -4.829674 | 0.987704 |
| 23 | 6 | 0 | -2.142712 | -1.641121 | 1.136965 |
| 24 | 6 | 0 | -3.985952 | -0.143230 | 0.309058 |
| 25 | 1 | 0 | -4.494946 | -0.565079 | 1.177755 |
| 26 | 6 | 0 | -4.636010 | -0.719658 | -0.947613 |
| 27 | 6 | 0 | -5.702395 | -1.620735 | -0.834674 |
| 28 | 1 | 0 | -6.043321 | -1.918668 | 0.152859 |
| 29 | 6 | 0 | -6.315022 | -2.152189 | -1.973926 |
| 30 | 1 | 0 | -7.138777 | -2.852298 | -1.865550 |
| 31 | 6 | 0 | -5.864012 | -1.791765 | -3.245393 |
| 32 | 1 | 0 | -6.336721 | -2.205211 | -4.131859 |
| 33 | 6 | 0 | -4.796186 | -0.897023 | -3.370189 |
| 34 | 1 | 0 | -4.435915 | -0.612517 | -4.355072 |
| 35 | 6 | 0 | -4.189822 | -0.365644 | -2.230396 |
| 36 | 1 | 0 | -3.359473 | 0.326958 | -2.347157 |
| 37 | 6 | 0 | -4.077055 | 1.388501 | 0.371051 |
| 38 | 1 | 0 | -3.674613 | 1.752755 | 1.321424 |
| 39 | 1 | 0 | -5.120261 | 1.707525 | 0.287104 |
| 40 | 1 | 0 | -3.519489 | 1.862092 | -0.445051 |
| 41 | 16 | 0 | 0.174487 | 0.497410 | -1.660145 |
| 42 | 7 | 0 | 1.406105 | 2.222558 | 0.015323 |
| 43 | 1 | 0 | 2.235970 | 2.743470 | 0.275129 |
| 44 | 7 | 0 | 2.692056 | 1.429796 | -1.697959 |
| 45 | 1 | 0 | 3.426454 | 1.989142 | -1.280825 |
| 46 | 6 | 0 | 0.215027 | 2.510355 | 0.834295 |
| 47 | 1 | 0 | -0.615926 | 2.049680 | 0.294647 |
| 48 | 6 | 0 | -0.014636 | 4.022099 | 0.858349 |
| 49 | 6 | 0 | 0.067550 | 4.786293 | 2.028717 |
| 50 | 1 | 0 | 0.291730 | 4.311058 | 2.977785 |
| 51 | 6 | 0 | -0.148080 | 6.169431 | 1.996063 |
| 52 | 1 | 0 | -0.081936 | 6.744175 | 2.915490 |
| 53 | 6 | 0 | -0.450293 | 6.806248 | 0.792404 |
| 54 | 1 | 0 | -0.621258 | 7.878531 | 0.768253 |
| 55 | 6 | 0 | -0.538340 | 6.051859 | -0.383213 |
| 56 | 1 | 0 | -0.781549 | 6.536035 | -1.324762 |
| 57 | 6 | 0 | -0.321535 | 4.675072 | -0.348117 |
| 58 | 1 | 0 | -0.394433 | 4.093134 | -1.263587 |
| 59 | 6 | 0 | 0.337068 | 1.837298 | 2.204415 |

| | | | | | |
|----|---|---|-----------|-----------|-----------|
| 60 | 1 | 0 | 1.204048 | 2.204731 | 2.764300 |
| 61 | 1 | 0 | 0.452320 | 0.758569 | 2.079213 |
| 62 | 1 | 0 | -0.560900 | 2.015467 | 2.803499 |
| 63 | 6 | 0 | 1.482481 | 1.420571 | -1.074414 |
| 64 | 6 | 0 | 3.104786 | 0.572130 | -2.819605 |
| 65 | 1 | 0 | 2.178512 | 0.269933 | -3.310949 |
| 66 | 6 | 0 | 3.825196 | -0.687833 | -2.346020 |
| 67 | 6 | 0 | 3.282062 | -1.948936 | -2.621943 |
| 68 | 1 | 0 | 2.336549 | -2.017074 | -3.152825 |
| 69 | 6 | 0 | 3.935886 | -3.115185 | -2.211726 |
| 70 | 1 | 0 | 3.499432 | -4.084510 | -2.434844 |
| 71 | 6 | 0 | 5.142406 | -3.033980 | -1.513278 |
| 72 | 1 | 0 | 5.650163 | -3.938241 | -1.190967 |
| 73 | 6 | 0 | 5.693110 | -1.779835 | -1.230400 |
| 74 | 1 | 0 | 6.633072 | -1.707034 | -0.690594 |
| 75 | 6 | 0 | 5.039437 | -0.618450 | -1.646458 |
| 76 | 1 | 0 | 5.487765 | 0.347314 | -1.423456 |
| 77 | 6 | 0 | 3.943536 | 1.403020 | -3.801039 |
| 78 | 1 | 0 | 3.364744 | 2.254610 | -4.171366 |
| 79 | 1 | 0 | 4.243893 | 0.785144 | -4.651757 |
| 80 | 1 | 0 | 4.859275 | 1.783130 | -3.332621 |

Cartesian coordinates and NCI plot of racemic dimer *S,S*-1- ----*R,R*-1

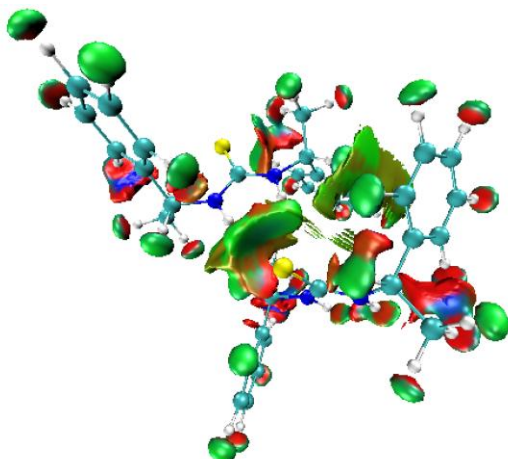


Figure S42. NCI plot of enantiomeric dimer *S,S*-1-----*R,R*-1

| Center Number | Atomic Number | Atomic Type | Coordinates (Angstroms) | | |
|---------------|---------------|-------------|-------------------------|-----------|-----------|
| | | | X | Y | Z |
| 1 | 16 | 0 | -3.578070 | -1.021418 | 1.601924 |
| 2 | 7 | 0 | -1.186022 | -1.332331 | 0.344135 |
| 3 | 1 | 0 | -0.535265 | -0.936021 | -0.328922 |
| 4 | 7 | 0 | -2.363655 | 0.516256 | -0.236495 |
| 5 | 1 | 0 | -1.540948 | 0.701621 | -0.802800 |
| 6 | 6 | 0 | -0.648799 | -2.535741 | 1.015452 |
| 7 | 6 | 0 | 0.090639 | -2.226860 | 2.318850 |
| 8 | 6 | 0 | 1.478876 | -2.419487 | 2.378059 |
| 9 | 1 | 0 | 2.007910 | -2.775128 | 1.496514 |
| 10 | 6 | 0 | 2.193031 | -2.170087 | 3.554638 |
| 11 | 1 | 0 | 3.267177 | -2.334815 | 3.580280 |
| 12 | 6 | 0 | 1.524587 | -1.716869 | 4.693905 |

| | | | | | |
|----|----|---|-----------|-----------|-----------|
| 13 | 1 | 0 | 2.073633 | -1.523825 | 5.611511 |
| 14 | 6 | 0 | 0.140386 | -1.520775 | 4.645711 |
| 15 | 1 | 0 | -0.389689 | -1.171592 | 5.527763 |
| 16 | 6 | 0 | -0.572763 | -1.777180 | 3.472417 |
| 17 | 1 | 0 | -1.645944 | -1.619111 | 3.440040 |
| 18 | 6 | 0 | -2.328256 | -0.608171 | 0.542046 |
| 19 | 6 | 0 | -3.482926 | 1.454194 | -0.437674 |
| 20 | 6 | 0 | -4.716168 | 0.783660 | -1.055156 |
| 21 | 6 | 0 | -6.009098 | 0.961581 | -0.550885 |
| 22 | 1 | 0 | -6.165378 | 1.535443 | 0.355529 |
| 23 | 6 | 0 | -7.112248 | 0.383667 | -1.187070 |
| 24 | 1 | 0 | -8.105821 | 0.527062 | -0.771297 |
| 25 | 6 | 0 | -6.940584 | -0.381308 | -2.341712 |
| 26 | 1 | 0 | -7.797517 | -0.832393 | -2.833947 |
| 27 | 6 | 0 | -5.653391 | -0.563736 | -2.856702 |
| 28 | 1 | 0 | -5.503825 | -1.156775 | -3.754917 |
| 29 | 6 | 0 | -4.556729 | 0.017202 | -2.219860 |
| 30 | 1 | 0 | -3.559607 | -0.135491 | -2.625316 |
| 31 | 16 | 0 | 0.751402 | 0.642907 | -2.038355 |
| 32 | 7 | 0 | 2.287751 | 1.562752 | -0.015108 |
| 33 | 1 | 0 | 3.188781 | 1.599522 | 0.448314 |
| 34 | 7 | 0 | 3.328563 | 0.141647 | -1.470191 |
| 35 | 1 | 0 | 4.133872 | 0.263325 | -0.867562 |
| 36 | 6 | 0 | 1.277157 | 2.489503 | 0.529711 |
| 37 | 1 | 0 | 0.432235 | 2.417778 | -0.158360 |
| 38 | 6 | 0 | 1.820325 | 3.917306 | 0.466655 |
| 39 | 6 | 0 | 2.258948 | 4.613545 | 1.600058 |
| 40 | 1 | 0 | 2.196419 | 4.155448 | 2.581856 |
| 41 | 6 | 0 | 2.769741 | 5.911975 | 1.487708 |
| 42 | 1 | 0 | 3.101536 | 6.437278 | 2.378834 |
| 43 | 6 | 0 | 2.846514 | 6.531867 | 0.239991 |
| 44 | 1 | 0 | 3.238345 | 7.541172 | 0.153814 |
| 45 | 6 | 0 | 2.407384 | 5.846968 | -0.898491 |
| 46 | 1 | 0 | 2.454471 | 6.323822 | -1.873413 |
| 47 | 6 | 0 | 1.900323 | 4.552801 | -0.784162 |
| 48 | 1 | 0 | 1.557960 | 4.025017 | -1.670898 |
| 49 | 6 | 0 | 0.825575 | 2.015862 | 1.914314 |
| 50 | 1 | 0 | 1.659575 | 1.959772 | 2.622276 |
| 51 | 1 | 0 | 0.384656 | 1.019223 | 1.842668 |
| 52 | 1 | 0 | 0.074043 | 2.696338 | 2.325660 |
| 53 | 6 | 0 | 2.183489 | 0.787954 | -1.121469 |
| 54 | 6 | 0 | 3.476514 | -0.864545 | -2.534080 |
| 55 | 1 | 0 | 2.653828 | -0.677409 | -3.225976 |
| 56 | 6 | 0 | 3.334117 | -2.287616 | -1.999473 |
| 57 | 6 | 0 | 2.265202 | -3.088776 | -2.421268 |
| 58 | 1 | 0 | 1.534857 | -2.680572 | -3.114337 |
| 59 | 6 | 0 | 2.123953 | -4.398969 | -1.952604 |
| 60 | 1 | 0 | 1.288592 | -5.005075 | -2.291233 |
| 61 | 6 | 0 | 3.050549 | -4.924341 | -1.049559 |
| 62 | 1 | 0 | 2.941518 | -5.940521 | -0.682376 |
| 63 | 6 | 0 | 4.120372 | -4.132748 | -0.619356 |
| 64 | 1 | 0 | 4.847334 | -4.534021 | 0.081076 |
| 65 | 6 | 0 | 4.260077 | -2.826869 | -1.093372 |
| 66 | 1 | 0 | 5.103783 | -2.230412 | -0.753283 |
| 67 | 6 | 0 | 4.806162 | -0.628644 | -3.263719 |
| 68 | 1 | 0 | 4.831460 | 0.377658 | -3.692506 |
| 69 | 1 | 0 | 4.924206 | -1.357771 | -4.070069 |
| 70 | 1 | 0 | 5.665597 | -0.740358 | -2.592046 |
| 71 | 6 | 0 | -1.639018 | -3.704492 | 1.142017 |
| 72 | 1 | 0 | -2.405789 | -3.518598 | 1.892056 |
| 73 | 1 | 0 | -2.137199 | -3.881406 | 0.183777 |
| 74 | 1 | 0 | -1.077769 | -4.603863 | 1.418419 |

| | | | | | |
|----|---|---|-----------|-----------|-----------|
| 75 | 1 | 0 | 0.120802 | -2.867602 | 0.310138 |
| 76 | 1 | 0 | -3.093638 | 2.123588 | -1.216090 |
| 77 | 6 | 0 | -3.751507 | 2.336398 | 0.790340 |
| 78 | 1 | 0 | -4.158261 | 1.757505 | 1.620542 |
| 79 | 1 | 0 | -2.812728 | 2.793978 | 1.116733 |
| 80 | 1 | 0 | -4.447586 | 3.141504 | 0.532520 |

Cartesian coordinates and NCI plot of meso dimer *S,R*-1 ----*S,R*-1

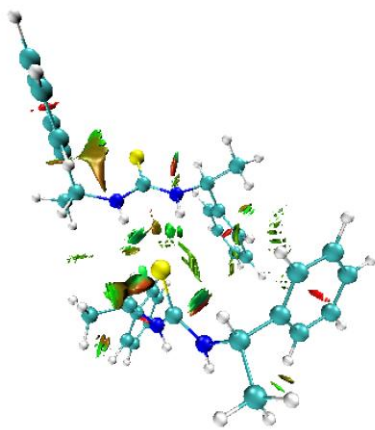


Figure S43. NCI plot of enantiomeric dimer *S,R*-1-----*S,R*-1

| Center Number | Atomic Number | Atomic Type | Coordinates (Angstroms) | | |
|---------------|---------------|-------------|-------------------------|-----------|-----------|
| | | | X | Y | Z |
| 1 | 16 | 0 | -3.574651 | 0.495017 | 2.175799 |
| 2 | 7 | 0 | -1.201059 | -0.541895 | 1.440650 |
| 3 | 1 | 0 | -0.556952 | -0.821039 | 0.704936 |
| 4 | 7 | 0 | -2.538518 | 0.087517 | -0.290704 |
| 5 | 1 | 0 | -1.772922 | -0.294915 | -0.840306 |
| 6 | 6 | 0 | -0.726364 | -0.698042 | 2.818920 |
| 7 | 6 | 0 | 0.392759 | 0.294767 | 3.131414 |
| 8 | 6 | 0 | 1.721937 | 0.068347 | 2.742446 |
| 9 | 1 | 0 | 1.989627 | -0.843164 | 2.215353 |
| 10 | 6 | 0 | 2.720688 | 1.002230 | 3.030955 |
| 11 | 1 | 0 | 3.744434 | 0.805812 | 2.724287 |
| 12 | 6 | 0 | 2.407436 | 2.178976 | 3.717328 |
| 13 | 1 | 0 | 3.185845 | 2.900820 | 3.948720 |
| 14 | 6 | 0 | 1.086793 | 2.416015 | 4.108399 |
| 15 | 1 | 0 | 0.831762 | 3.324816 | 4.647009 |
| 16 | 6 | 0 | 0.089209 | 1.481775 | 3.815220 |
| 17 | 1 | 0 | -0.938210 | 1.672094 | 4.113144 |
| 18 | 6 | 0 | -2.400255 | -0.006412 | 1.064358 |
| 19 | 6 | 0 | -3.755701 | 0.384855 | -1.076586 |
| 20 | 6 | 0 | -4.846523 | -0.678890 | -0.911418 |
| 21 | 6 | 0 | -6.059161 | -0.438224 | -0.255333 |
| 22 | 1 | 0 | -6.245989 | 0.528037 | 0.198182 |
| 23 | 6 | 0 | -7.028443 | -1.440966 | -0.156320 |
| 24 | 1 | 0 | -7.960500 | -1.235355 | 0.362747 |
| 25 | 6 | 0 | -6.799497 | -2.702554 | -0.709303 |
| 26 | 1 | 0 | -7.553326 | -3.480821 | -0.629670 |
| 27 | 6 | 0 | -5.592434 | -2.955229 | -1.367759 |
| 28 | 1 | 0 | -5.402811 | -3.930571 | -1.807595 |

| | | | | | |
|----|----|---|-----------|-----------|-----------|
| 29 | 6 | 0 | -4.630772 | -1.948692 | -1.468674 |
| 30 | 1 | 0 | -3.696914 | -2.152486 | -1.988770 |
| 31 | 16 | 0 | 0.364450 | -1.349993 | -1.796411 |
| 32 | 7 | 0 | 1.729682 | 0.935584 | -2.235148 |
| 33 | 1 | 0 | 2.609928 | 1.413097 | -2.387806 |
| 34 | 7 | 0 | 2.961658 | -0.985718 | -2.367254 |
| 35 | 1 | 0 | 3.739515 | -0.365525 | -2.557203 |
| 36 | 6 | 0 | 0.553213 | 1.820732 | -2.100676 |
| 37 | 6 | 0 | 1.031333 | 3.165502 | -1.566315 |
| 38 | 6 | 0 | 0.919900 | 3.446346 | -0.196958 |
| 39 | 1 | 0 | 0.474985 | 2.712172 | 0.469189 |
| 40 | 6 | 0 | 1.375546 | 4.660514 | 0.321555 |
| 41 | 1 | 0 | 1.275647 | 4.858891 | 1.384267 |
| 42 | 6 | 0 | 1.955176 | 5.611343 | -0.522526 |
| 43 | 1 | 0 | 2.307146 | 6.556980 | -0.120475 |
| 44 | 6 | 0 | 2.075057 | 5.341259 | -1.888124 |
| 45 | 1 | 0 | 2.518951 | 6.076835 | -2.552990 |
| 46 | 6 | 0 | 1.613580 | 4.127687 | -2.405922 |
| 47 | 1 | 0 | 1.699371 | 3.942238 | -3.473078 |
| 48 | 6 | 0 | 1.746418 | -0.415820 | -2.138976 |
| 49 | 6 | 0 | 3.301715 | -2.405033 | -2.192914 |
| 50 | 1 | 0 | 2.373804 | -2.954072 | -2.364468 |
| 51 | 6 | 0 | 3.785115 | -2.720553 | -0.779339 |
| 52 | 6 | 0 | 3.122486 | -3.687149 | -0.012971 |
| 53 | 1 | 0 | 2.245015 | -4.181220 | -0.421128 |
| 54 | 6 | 0 | 3.567871 | -4.009711 | 1.272790 |
| 55 | 1 | 0 | 3.039861 | -4.760610 | 1.853503 |
| 56 | 6 | 0 | 4.682272 | -3.363093 | 1.811490 |
| 57 | 1 | 0 | 5.027131 | -3.608675 | 2.811565 |
| 58 | 6 | 0 | 5.350125 | -2.393997 | 1.055937 |
| 59 | 1 | 0 | 6.218760 | -1.886729 | 1.466250 |
| 60 | 6 | 0 | 4.904507 | -2.078795 | -0.229090 |
| 61 | 1 | 0 | 5.438843 | -1.324760 | -0.802869 |
| 62 | 6 | 0 | 4.325608 | -2.803638 | -3.265560 |
| 63 | 1 | 0 | 3.918968 | -2.631251 | -4.266909 |
| 64 | 1 | 0 | 4.576810 | -3.863027 | -3.166099 |
| 65 | 1 | 0 | 5.258470 | -2.235792 | -3.164597 |
| 66 | 1 | 0 | -3.398116 | 0.278494 | -2.107785 |
| 67 | 6 | 0 | -4.223706 | 1.838927 | -0.931135 |
| 68 | 1 | 0 | -4.560635 | 2.059233 | 0.081912 |
| 69 | 1 | 0 | -3.394002 | 2.513101 | -1.165188 |
| 70 | 1 | 0 | -5.039030 | 2.037103 | -1.635049 |
| 71 | 6 | 0 | -0.349980 | -2.163361 | 3.078995 |
| 72 | 1 | 0 | 0.439394 | -2.512011 | 2.404183 |
| 73 | 1 | 0 | 0.005826 | -2.288091 | 4.106745 |
| 74 | 1 | 0 | -1.227702 | -2.799393 | 2.931466 |
| 75 | 1 | 0 | -1.585596 | -0.442789 | 3.442517 |
| 76 | 1 | 0 | -0.089898 | 1.364770 | -1.344853 |
| 77 | 6 | 0 | -0.232259 | 1.905573 | -3.417455 |
| 78 | 1 | 0 | -0.577558 | 0.909608 | -3.706130 |
| 79 | 1 | 0 | -1.102774 | 2.557408 | -3.293821 |
| 80 | 1 | 0 | 0.381821 | 2.303842 | -4.230927 |

RDG (Reduced density gradient) Scatter plot

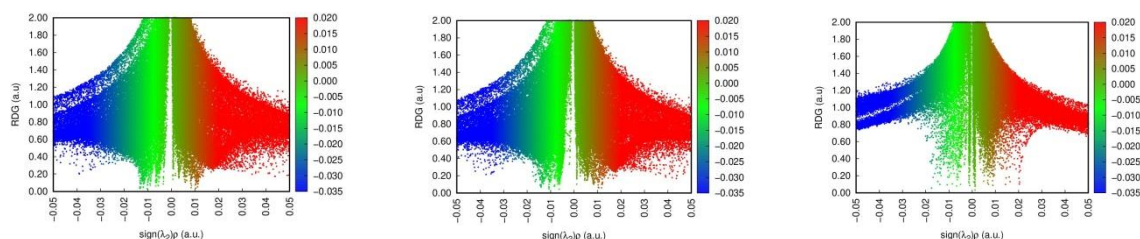


Figure S44. RDG scatter plot of diastereomeric combinations a) *S,S*-1 ---*S,S*-1 b) *S,S*-1---*R,R*-1 c) *S,R*-1 ---*S,R*-1

Table 5. Electronic energies calculated for the diastereomeric combinations:

| Diastereomeric combination | Electronic energy (kcal/mol) |
|-------------------------------------|------------------------------|
| (<i>S,S</i> -1) two free molecules | -1465372.62 |
| <i>S,S</i> -1 --- <i>S,S</i> -1 | -1465377.77 |
| <i>S,S</i> -1--- <i>R,R</i> -1 | -1465367.65 |
| <i>S,R</i> -1 --- <i>S,R</i> -1 | -1465373.12 |

Single crystal X-ray analysis

For the present study of spontaneous resolution a sample of *R,R*-1 and *S,S*-1 (exactly 50.00 mg each) was subjected to crystallization from distilled ethyl acetate (6 mL) in a clean small round bottom flask. The solvent was slowly evaporated to get needle shape, colourless crystals. A crystal was picked and subjected to single crystal X-ray diffraction analysis.

Table 6. Crystal data of crystal # 1III (Table 1)

| Crystal Data | # 1III (Table 1) <i>S,S</i> -1 | <i>S,R</i> -1 (<i>meso</i> isomer) |
|------------------|--|--|
| Formula | C ₁₇ H ₂₀ N ₂ S | C ₁₇ H ₂₀ N ₂ S |
| Molecular weight | 284.41 | 284.41 |
| Crystal Size, mm | 0.14× 0.11× 0.05 | 0.12× 0.11× 0.08 |
| Temp. (K) | 100(2) | 100(2) |
| Wavelength (Å) | 1.54178 | 1.54178 |
| Crystal Syst. | trigonal | monoclinic |
| Space Group | <i>P</i> 3 ₂ | <i>P</i> 2 ₁ / <i>c</i> |
| <i>a</i> (Å) | 10.2178(2) | 12.9267(11) |
| <i>b</i> (Å) | 10.2178(2) | 12.7298(11) |
| <i>c</i> (Å) | 13.0003(4) | 9.3576(8) |
| α (°) | 90 | 90 |

| | | |
|---|---------------------------------------|---------------------------------------|
| $\beta(^{\circ})$ | 90 | 90.901(2) |
| $\gamma(^{\circ})$ | 120 | 90 |
| $V/\text{\AA}^3$ | 1175.43(6) | 1539.6(2) |
| Z | 3 | 4 |
| $D_{\text{calc}}/\text{g cm}^{-3}$ | 1.205 | 1.227 |
| μ/mm^{-1} | 1.750 | 1.782 |
| $F(000)$ | 456 | 608 |
| Ab. Correct. | multi-scan | multi-scan |
| $T_{\text{min}}/T_{\text{max}}$ | 0.792/0.918 | 0.664/0.754 |
| $2\theta_{\text{max}}$ | 157.64 | 145.384 |
| Total reflns. | 36394 | 32594 |
| Unique reflns. | 3228 | 3011 |
| Obs. reflns. | 3036 | 2912 |
| h, k, l (min, max) | (-12, 12), (-12, 12), (-16, 16) | (-16, 16), (-15, 15), (-11, 11) |
| $R_{\text{int}}/R_{\text{sig}}$ | 0.0565/0.0274 | 0.0454/0.0206 |
| No. of para. | 192 | 191 |
| $R1 [I > 2\sigma(I)]$ | 0.0277 | 0.0328 |
| $wR2 [I > 2\sigma(I)]$ | 0.0607 | 0.0828 |
| $R1$ [all data] | 0.0318 | 0.0336 |
| $wR2$ [all data] | 0.0631 | 0.0836 |
| goodness-of-fit | 1.078 | 1.071 |
| $\Delta\rho_{\text{max}}, \Delta\rho_{\text{min}}(\text{e}\text{\AA}^{-3})$ | +0.167, -0.181 | +300, -0.224 |
| CCDC No. | 2402535 | 2403604 |

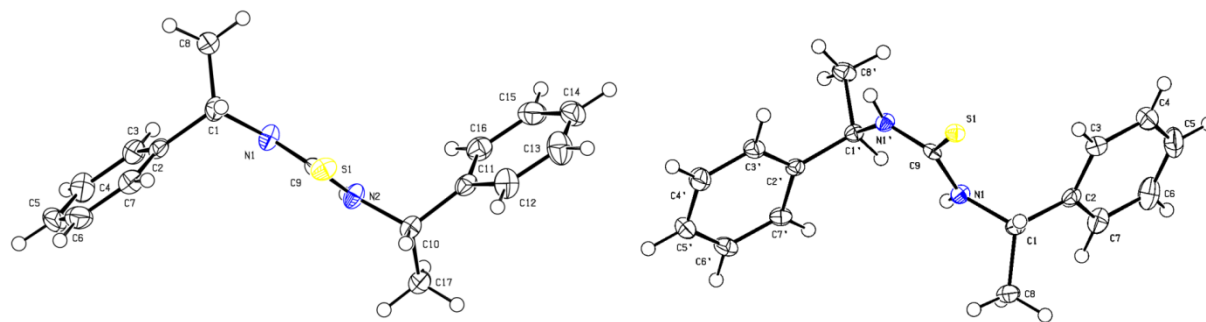


Figure S45. ORTEP diagram of enantiopure crystal *S,S*-1 (left) and *meso* isomer crystal *S,R*-1

References:

- 1 Bruker (2016). APEX2, SAINT and SADABS. Bruker AXS Inc., Madison, Wisconsin, USA.
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- 4 A.A. Bredikhin, Z.A. Bredikhina, O.A. Antonovich, D.V. Zakharychev, D.B. Krivolapov. *J.Mol. Struct.* 2017, **1144**, 443.
- 5 A.A. Bredikhin, Z.A. Bredikhina, V.G. Novikova, A.V. Pashagin, D.V. Zakharychev, A.T.Gubaidullin, *Chirality*. 2008, **20**, 1092.