

Electronic Supplementary Information

Simultaneously resolving BINOL and proline using a stoichiometric cocrystal switch.

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1. Experimental methods

1.1 Starting Materials

RS-1,1'-Bi-2-naphthol was purchased from Acros Organics. *R*-1,1'-Bi-2-naphthol was purchased from Fluorochem. *S*-1,1'-Bi-2-naphthol, *DL*-Proline, and *L*-Proline were purchased from Sigma-Aldrich. *D*-Proline was purchased from Apollo Scientific. Absolute ethanol (99.9%), methanol (99.5%), and acetonitrile (99.5%) were purchased from VWR International. These chemicals and solvents were used as received without further purification.

1.2 X-ray powder diffraction (XRPD)

XRPD patterns of the samples were measured with a Bruker D8 Advance powder X-ray diffractometer equipped with a Cu-K α X-ray source ($\lambda = 1.5406 \text{ \AA}$) operating at 40 kV and 30 mA. The data were collected for 2θ values from 5 to 35° at a scan rate of 12°/min.

1.3 Liquid-assisted grinding (LAG) of *RS*-binol and *DL*-proline with different stoichiometric ratios and different solvents

LAG was conducted using a RETSCH mixer mill MM400 with a frequency of 30 Hz for 1.5 h. Grinding experiments were done in 2 mL plastic milling jars containing three 3 mm stainless steel balls. 150 mg of mixtures of *RS*-binol and *DL*-proline were prepared in 2:1, 1:2, and 1:1 stoichiometric ratio. Each ratio was tested with 20 μL of three different solvents (ethanol, methanol, and acetonitrile). The ground samples were dried for 24 h under ambient conditions and then analyzed by X-ray powder diffraction (XRPD).

1.4 Crystal Structure Determination

The structure of $\text{S}_2\text{:L}$ with 11.4% substitution of *R*-binol and RS:(DL)_2 was obtained from the refinement of single crystal obtained from cooling crystallizations between *RS*-binol and *DL*-proline.

$\text{S}_2\text{:L}$ cocrystal: 129.2 mg *RS*-binol (0.45 mmol) and 20.8 mg *DL*-proline (0.18 mmol) were dissolved in 4 mL of ethanol at 50 °C. The clear solution was cooled to room temperature (20 °C) and left until crystallization occurred. A single crystal was mounted and diffraction data

was collected on a MAR345 image plate using MoK α radiation generated by an Incoatec I μ S microfocus source (Montel Mirrors). Data reduction was carried out using the CrysAlis^{PRO} software package.¹ Structure solution was performed by dual space direct methods using SHELXT² and refinement by full-matrix least squares was carried out using SHELX-2018/3³. Non-hydrogen atoms were refined anisotropically; H atoms were added in calculated positions and allowed to ride on the parent atoms, with isotropic displacement factors set to 1.2U_{eq} of the parent atoms (U_{iso}(H) = 1.5U_{eq}(C) OH hydrogens). The S₂:L crystallizes in a chiral space group, but shows partial R/S disorder for Binol. The R/S disorder for one of the Binol molecules was clearly visible in the difference maps and consists of an overlap of both enantiomers in a 77/23 ratio, the other binol (as well as proline) does not show disorder, giving an overall ratio of S/R of 88.6/11.4. Isotropic and rigid bond restraints were set up for all disordered atoms and the minor component was geometrically refined to be similar to the main component and occupancies were freely refined. HPLC was used to confirm the enantiomeric composition of binol. The single crystal was then dissolved in methanol for analysis by HPLC.

RS:(DL)₂ crystal: 81.5 mg *RS*-binol (0.28 mmol) and 13.0 mg *DL*-proline (0.11 mmol) were dissolved in 3 mL of ethanol at 50 °C. The clear solution was cooled to room temperature (20 °C) and left until crystallization occurred. The same methods for data collection, structure solution and refinement were applied as mentioned above. Here one of the proline molecules is disordered (centrosymmetric space group), also showing R/S disorder with superposed enantiomers (90/10 ratio). As the structure is centrosymmetric there is no discrepancy in the overall proline D/L ratio (and Binol R/S ratio), which is thus at 50/50.

1.5 High-pressure liquid chromatography (HPLC)

The chiral analyses were performed on a Waters 2690 Alliance equipped with a 2998 PDA detector. The powder sample was dissolved in methanol. The sample was injected at room temperature into a Phenomenex Lux 5 μ m Amylose column 4.6 x 250 mm using methanol at a flow rate of 0.8mL/min as mobile phase.

1.6 Construction of the binary isopleth melting diagram

The binary melting isopleth between S₂:L and R₂:D was constructed using the onset of the eutectic and endset of the liquidus peaks from DSC data. Methanol LAG experiments were performed on each sample with varying relative S₂:L//R₂:D ratio before DSC analysis. Pure S₂:L and R₂:D powders were prepared by grinding. For each, a large batch (500 mg) was produced through LAG with 50 μ L of methanol using a RETSCH mixer mill MM400 at the same frequency and duration (30 Hz for 1.5 h) as the previous LAG experiments, except that larger milling jars and balls were used. After drying, powders were characterized by XRPD to confirm complete cocrystal formation. S₂:L and R₂:D mixtures with varying ratios were prepared starting from these powders. To each mixture (approximately 100 mg) 10 μ L of methanol was added. Due to symmetry of the system, only half of the diagram, X_{R₂:D}=0 to 0.5,

was studied. Prior to DSC analysis, the powders were left to dry to remove all remaining methanol.

1.7 Differential scanning calorimetry (DSC)

Differential scanning calorimetry (DSC) was performed with a DSC 2500 (TA Instruments). Powder samples of 5 to 10 mg were placed in an aluminium Tzero pan. Samples were heated from 30 to 220 °C or to the decomposition temperature at a 10 °C/min heating rate.

1.8 LAG stoichiometric switch

10 µL of methanol was added to a 100 mg mixture of 1:2 stoichiometric ratio of *RS*-binol (55.4 mg) and *DL*-proline (44.6 mg). The sample was analyzed by XRPD after which three equivalents of *RS*-binol were added as well as 10 µL methanol/100 mg solid powder. After grinding, XRPD was measured. After this, three equivalents of *DL*-proline were added as well as 10 µL methanol/100 mg solid powder, and once more the sample was ground and analyzed by XRPD.

1.9 Construction of isoplethal section of the quinary phase diagram

The isoplethal section was constructed from mixtures composed of *RS*-binol, *DL*-proline, and ethanol. As the section is based on a total of five pure components (*R*-binol, *S*-binol, *D*-proline, *L*-proline, and ethanol solvent), it is part of a quinary phase diagram. Data points were obtained, by slurry crystallizations performed at 20°C varying the ratio of racemic binol and proline. To each mixture a precise amount of ethanol was added. The suspensions were seeded with all possible solid forms (*RS*-binol, *DL*-proline, $S_2:L$, $R_2:D$, and $RS:(DL)_2$) and stirred for 2 days before filtration. The filtered solids were analyzed by XRPD to determine the resulting solid phase. The concentrations of the supernatant liquids of each sample were quantified using a gravimetric approach (subtracting the initial solution weight and the weight of the powder obtained upon drying), with ^1H NMR measurements allowing to determine the binol/proline ratio in the powder. Each liquid sample was divided into two vials to elucidate the reproducibility of the gravimetric method and the average value from determined concentrations was used. Two concentration levels of slurry crystallization (high (approx. 450 mg/3 mL) and low (approx. 150 and 170 mg/3 mL) concentrations) were exploited to accurately define the region of the stable phase.

1.10 Nuclear Magnetic Resonance (NMR)

^1H NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer. Chemical shifts are reported in ppm relative to deuterated solvent methanol- d_4 (CD_3OD , chemical shift = 4.78 ppm).

2. Results

2.1 Crystal Structure

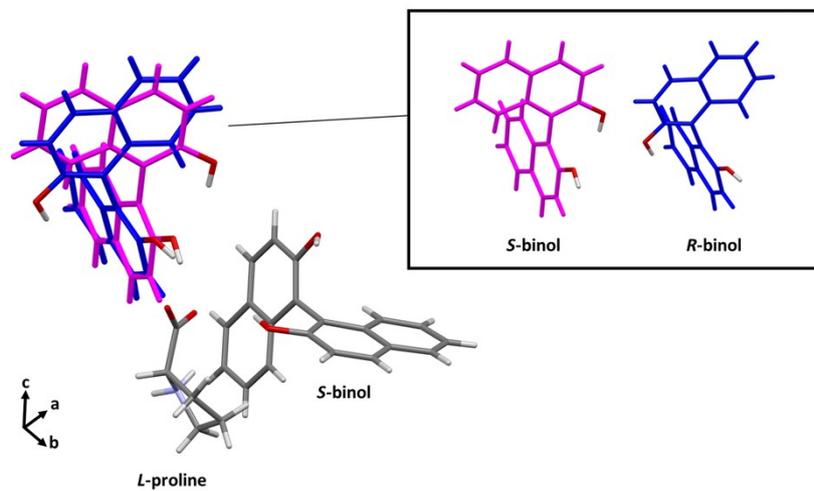


Fig. S1 Asymmetric unit of $S_2:L$ cocrystal obtained from crystallization of *RS*-binol and *DL*-proline which shows the disorder in *S*-binol molecules.

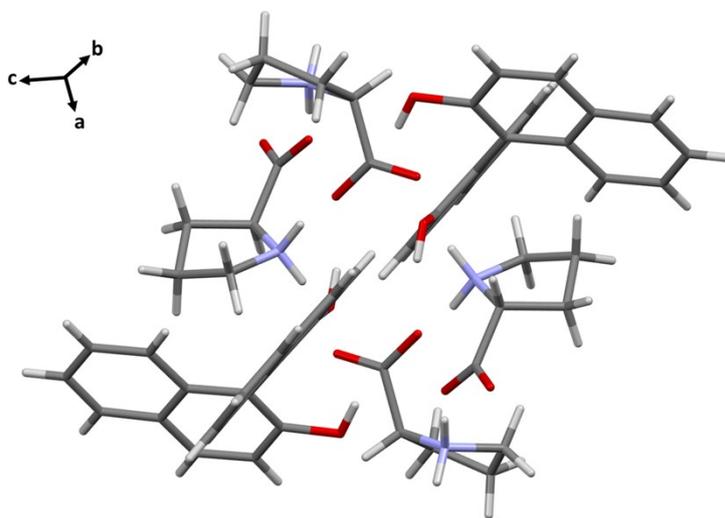


Fig. S2 Asymmetric unit of racemic compound $RS:(DL)_2$.

Table S1 Crystallographic data of S₂:L (NISVOA01),⁶ S₂:L (with partial solid solution), and RS:(DL)₂.

	S ₂ :L	S ₂ :L (with partial solid solution)	RS:(DL) ₂
Chemical formula	2(C ₂₀ H ₁₄ O ₂),C ₅ H ₉ N O ₂	2(C ₂₀ H ₁₄ O ₂),C ₅ H ₉ N O ₂	C ₂₀ H ₁₄ O ₂ ,2(C ₅ H ₉ N O ₂)
CSD number	NISVOA01	2352968	2352967
Crystal system	Tetragonal	Tetragonal	Triclinic
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> $\bar{1}$
<i>a</i> (Å)	27.272(2)	9.12901(14)	10.4050(9)
<i>b</i> (Å)	9.0398(8)	13.7793(2)	10.991(2)
<i>c</i> (Å)	13.7458(12)	27.6456(4)	12.216(3)
<i>α</i> (deg)	90	90	109.33(2)
<i>β</i> (deg)	90	90	91.872(12)
<i>γ</i> (deg)	90	90	104.146(13)
volume (Å ³)	3388.8	3477.58	1268.43
<i>Z</i> , <i>Z'</i>	4, 1	4, 1	2, 1

2.2 HPLC chromatogram

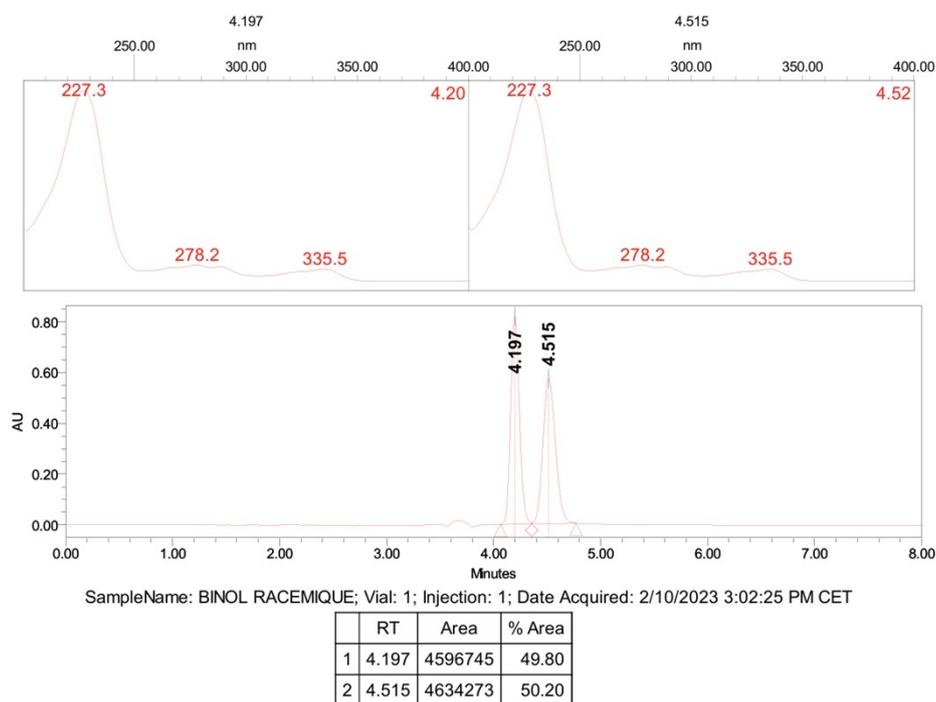


Figure S3 Chiral HPLC chromatogram of a sample of racemic binol at UV 220 nm with a Phenomenex Lux 5 μ m Amylose column 4.6x250 mm column. Retention times (RT) of 4.197 and 4.515 minutes refer to *R* and *S*-binol, respectively.

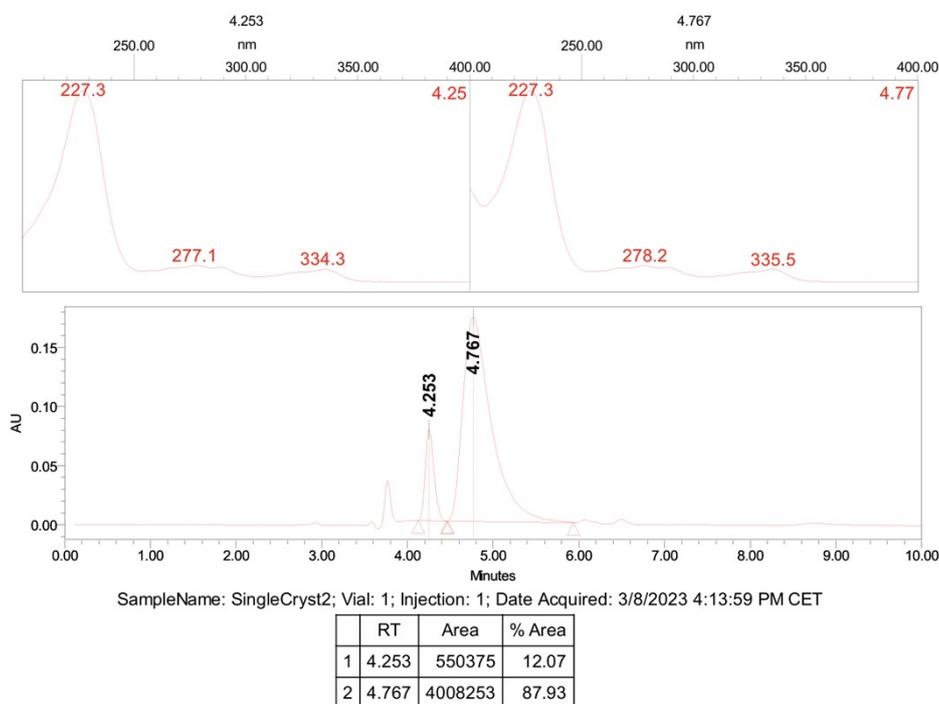


Fig. S4 Chiral HPLC chromatogram of a sample of dissolving a *S*₂:*L* single crystal at UV 220 nm with a Phenomenex Lux 5 μ m Amylose column 4.6x250 mm column. Retention times (RT) of 4.253 and 4.767 minutes refer to *R* and *S*-binol, respectively.

2.3 DSC results

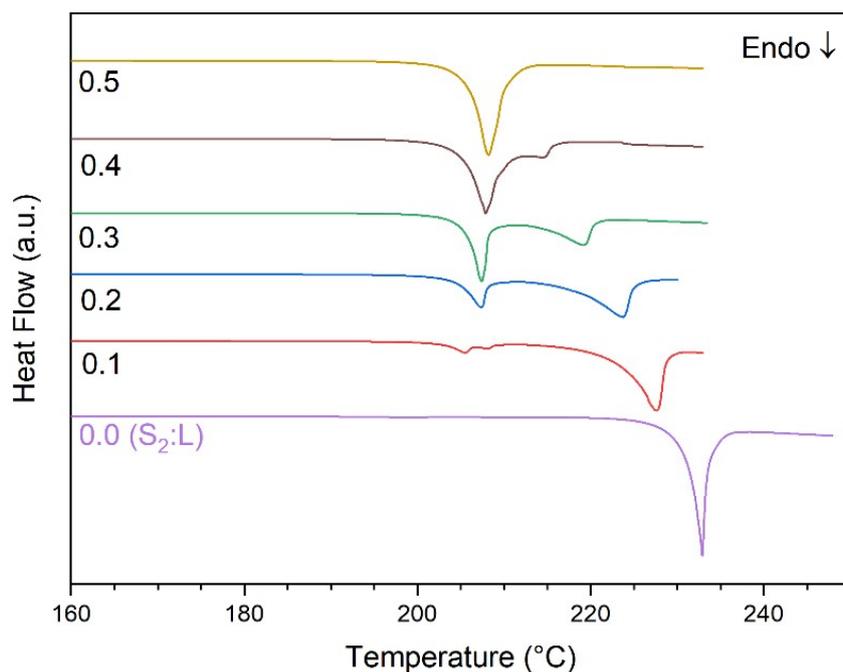


Fig. S5 DSC curves of LAGs of S₂:L with varying fraction of R₂:D from 0-0.5.

Table S2 Onset and endset temperatures of LAG mixtures of S₂:L and R₂:D at each fraction, and enthalpy of melting of S₂:L (X_{R₂:D}=0) and at X_{R₂:D}=0.5 integrated from the DSC curves in Fig. S4.

R ₂ :D fraction' (X _{R₂:D})	S ₂ :L fraction	Onset temperature of first peak (°C)	Endset temperature of second peak (°C)	Enthalpy of melting (kJ.mol ⁻¹)
0.5	0.5	205.93	-	71.6
0.4	0.6	205.69	215.74	-
0.3	0.7	205.89	220.28	-
0.2	0.8	204.54	224.47	-
0.1	0.9	202.98	228.39*	-
0.0	1.0	231.47	-	78.4

*The DSC thermogram of LAG at R₂:D fraction 0.1 show three peaks due to the inhomogeneity of the sample. Therefore, the onset and endset temperatures were determined from the first and third peak, respectively.

Schröder-Van Laar equation^{4,5}

$$-\ln x = \frac{\Delta H_i^0}{R} \left(\frac{1}{T_{eut}} - \frac{1}{T_i^0} \right)$$

at x = 0.5

$$T_{eut} = 213\text{ }^{\circ}\text{C}$$

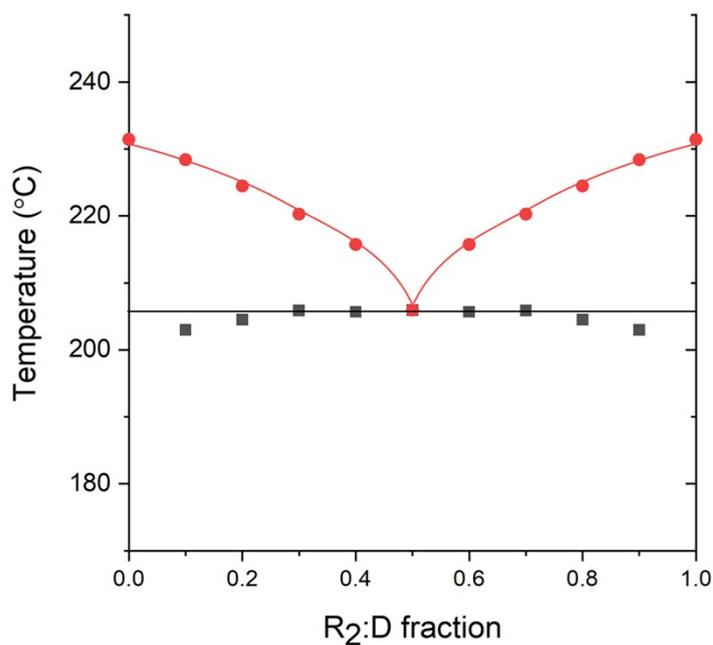


Fig. S6 Binary melting isopleth section between S₂:L and R₂:D.

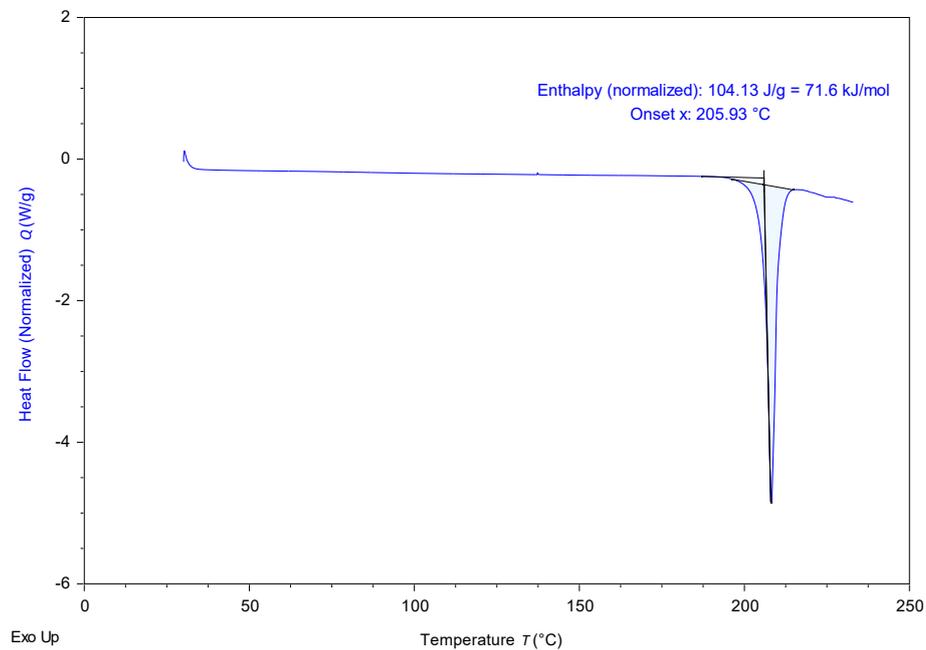


Fig. S7 DSC thermogram of LAG mixture S₂:L and R₂:D at $X_{R_2:D}=0.5$. Only one endothermic peak is observed indicating the melting of the sample. The integrated value was multiplied by the molecular weight of the cocrystal (687.77 g/mol) to obtain a value 71.6 kJ/mol.

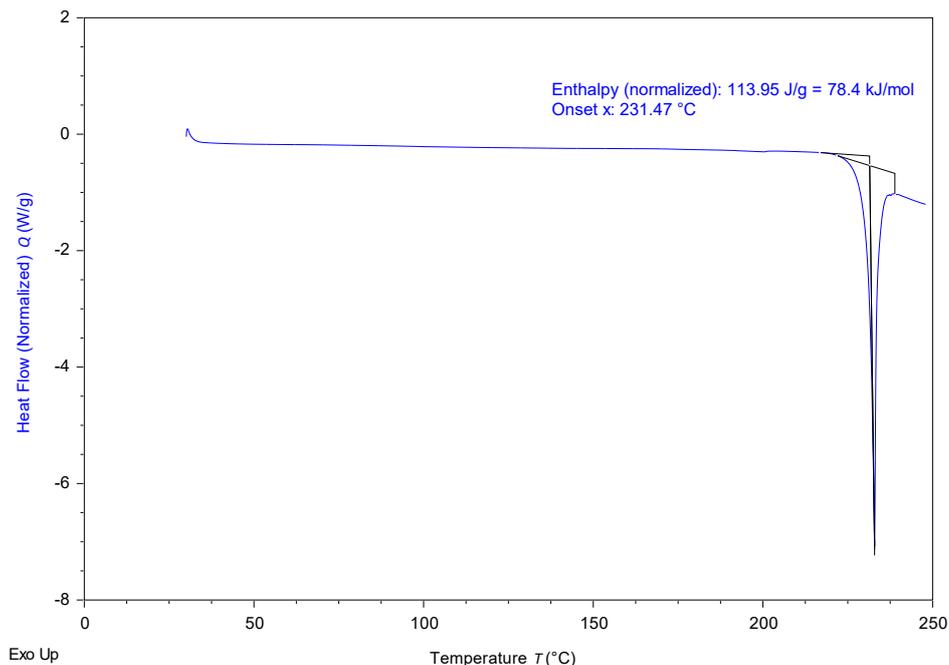


Fig. S8 DSC thermogram of $S_2:L$ ($X_{R2:D}=0$). The integrated value was multiplied by the molecular weight of the cocrystal (687.77 g/mol) to obtain a value of 78.4 kJ/mol. The sample decomposes upon melting causing a shift in the baseline. The tangent from the low temperature tail of the peak was used to integrate the enthalpy of melting.

2.4 XRPD patterns

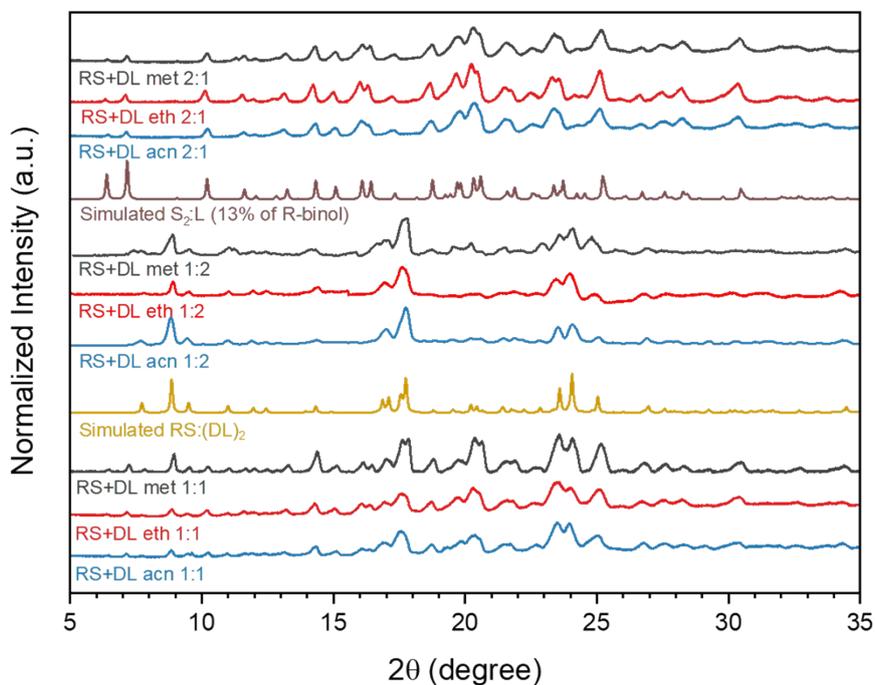


Fig. S9 XRPD patterns of LAG *RS*-binol+*DL*-proline in 2:1, 1:2, and 1:1 stoichiometric ratios with methanol (met), ethanol (eth), and acetonitrile (acn) in comparison with the simulated patterns of $S_2:L$ (13% of *R*-binol) and racemic cocrystal ($RS:(DL)_2$).

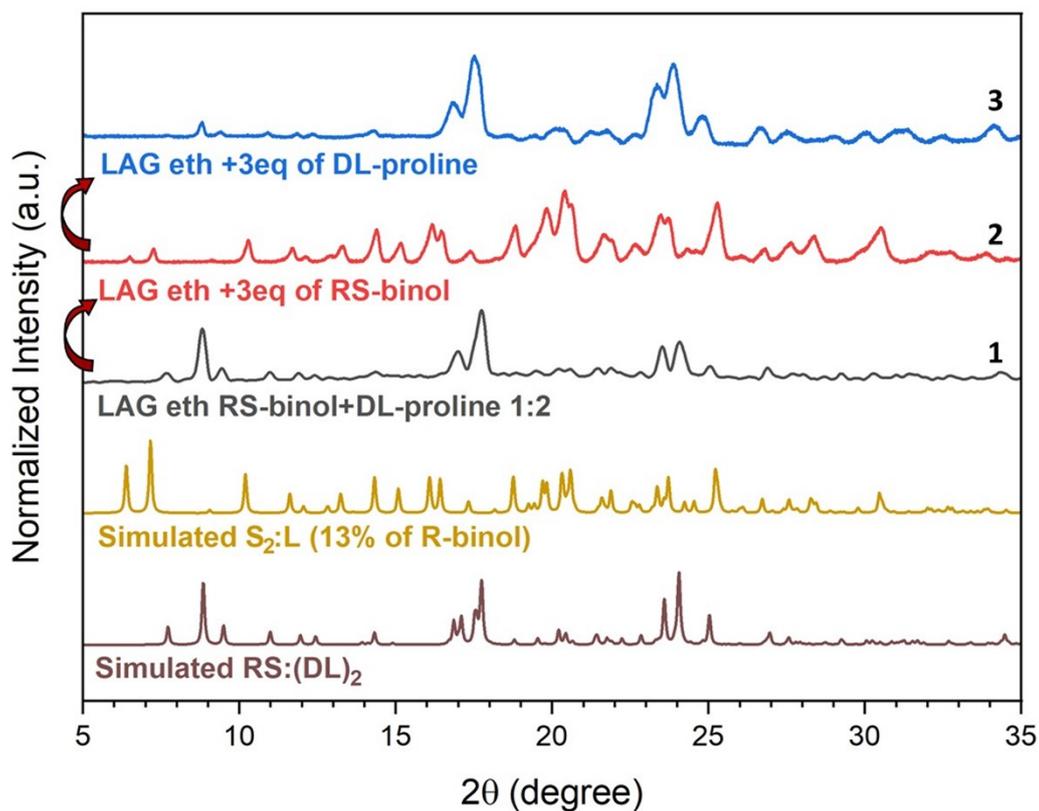


Fig. S10 XRPD patterns of LAG with ethanol of *RS*-binol+*DL*-proline with a 1:2 stoichiometric ratio and by adding 3 equivalents (eq) consecutively of *RS*-binol and *DL*-proline to the same powder product to convert the total stoichiometric ratio from 1:2 to 2:1 and *vice versa*. The experiment detail of sample 1-3 is shown in Table S3.

Table S3 Sample preparation for the samples shown in Fig. S8.

Sample no.	Sample name	Collected mass from previous experiment (mg)	Added Binol (mg)	Added Proline (mg)
1	LAG eth <i>RS</i> -binol+ <i>DL</i> -proline 1:2	-	55.4	44.6
2	LAG eth 1 + 3eq of <i>RS</i> -binol	54.2	90.1	-
3	LAG eth 2 + 3eq of <i>DL</i> -proline	85.7	-	43.1

2.5 NMR

NMR is used to determine the amount of binol vs proline. Fig. S9 shows the NMR of the powder obtained upon evaporating the supernatant. This experiment corresponds to a binol/proline 0.416 and is highlighted in green in table S4. Multiplets at 2.158 ppm, 1.984 ppm and 1.829 ppm belonging to C2 and C3 were integrated together and calibrated to 4. The binol doublets (of C2 and C3) at 7.755, 7.725, 7.713, and 7.686 ppm were integrated together and should also integrate to 4 if a 1:1 binol:proline ratio is to be expected. The integrated value in this example is 0.78. The binol/proline molar ratio in the supernatant, is therefore 0.195 ($0.78/4 = 0.195$).

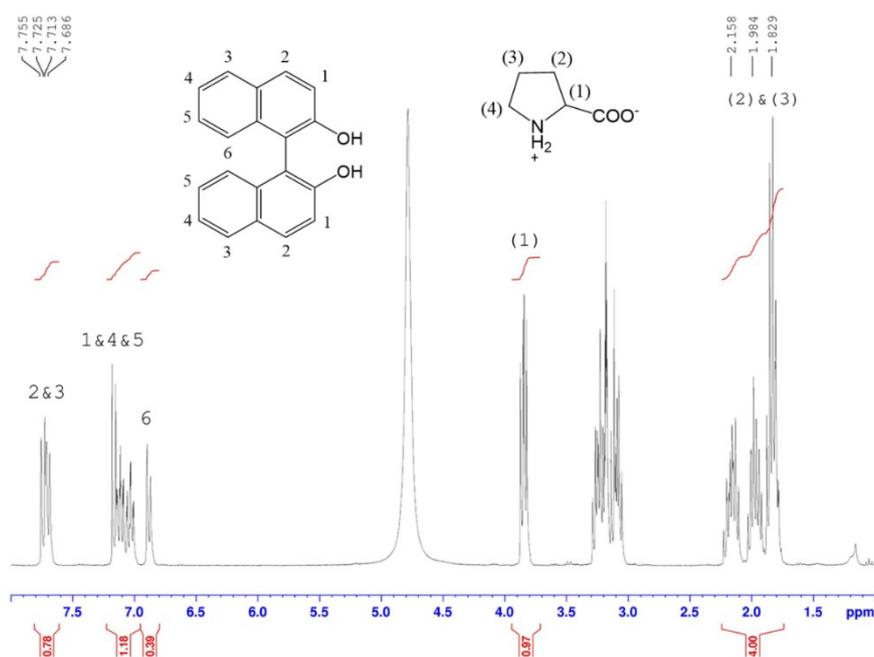


Fig. S11 Example of NMR spectrum of the solid remaining from liquid evaporation in the gravimetric method of slurry crystallization with a molar ratio binol/proline 0.416.

2.6 Ternary isopleth experimental data

Table S4 Data points on the isopleth section of the quinary phase diagram between *RS*-binol, *DL*-proline, and ethanol at 20 °C used to plot Figs. 3 and S10**.

Level	Starting Condition of slurry crystallization							Filtered Solid phase identified from XRPD	Supernatant				
	Molar ratio (binol/proline)	<i>RS</i> -binol (mg)	<i>DL</i> -proline (mg)	ethanol (g)	<i>RS</i> - binol (%mol)	<i>DL</i> - proline (%mol)	ethanol (%mol)		Average mass _{solid} /mass _{liquid} from gravimetric method (mg/g)	Molar ratio* (binol/proline) from NMR	<i>RS</i> -binol (%mol)	<i>DL</i> - proline (%mol)	ethanol (%mol)
High Concentration	10.2	435.0	17.2	2.571	0.02643	0.00260	0.97097	<i>RS</i> -binol + (<i>S</i> ₂ : <i>L</i> + <i>R</i> ₂ : <i>D</i>)	58.4	69.3	0.00925	0.00013	0.99062
	4.95	412.2	33.5	2.274	0.02818	0.00570	0.96612	<i>RS</i> -binol + (<i>S</i> ₂ : <i>L</i> + <i>R</i> ₂ : <i>D</i>)	-	-	-	-	-
	4.50	413.1	36.9	2.285	0.02809	0.00624	0.96566	<i>RS</i> -binol + (<i>S</i> ₂ : <i>L</i> + <i>R</i> ₂ : <i>D</i>)	-	-	-	-	-
	4.00	408.9	41.1	2.282	0.02783	0.00696	0.96522	<i>RS</i> -binol + (<i>S</i> ₂ : <i>L</i> + <i>R</i> ₂ : <i>D</i>)	-	-	-	-	-
	3.50	403.6	46.4	2.300	0.02725	0.00778	0.96497	<i>RS</i> -binol + (<i>S</i> ₂ : <i>L</i> + <i>R</i> ₂ : <i>D</i>)	-	-	-	-	-
	3.00	396.8	53.2	2.304	0.02672	0.00891	0.96437	<i>RS</i> -binol + (<i>S</i> ₂ : <i>L</i> + <i>R</i> ₂ : <i>D</i>)	-	-	-	-	-
	2.50	387.7	62.4	2.316	0.02595	0.01038	0.96367	(<i>S</i> ₂ : <i>L</i> + <i>R</i> ₂ : <i>D</i>)	-	-	-	-	-
	2.00	374.7	75.3	2.314	0.02507	0.01254	0.96239	(<i>S</i> ₂ : <i>L</i> + <i>R</i> ₂ : <i>D</i>) + <i>RS</i> : <i>DL</i> ₂	-	-	-	-	-
	0.986	316.5	129.1	2.340	0.02085	0.02114	0.95800	(<i>S</i> ₂ : <i>L</i> + <i>R</i> ₂ : <i>D</i>) + <i>RS</i> : <i>DL</i> ₂	-	-	-	-	-
	0.695	285.0	165.0	2.567	0.01712	0.02465	0.95823	(<i>S</i> ₂ : <i>L</i> + <i>R</i> ₂ : <i>D</i>) + <i>RS</i> : <i>DL</i> ₂	25.5	3.92	0.00370	0.00094	0.99535
	0.245	171.0	280.4	2.539	0.01027	0.04188	0.94785	<i>RS</i> : <i>DL</i> ₂ + <i>DL</i> -proline	-	-	-	-	-
0.111	97.2	353.0	2.544	0.00579	0.05231	0.94190	<i>RS</i> : <i>DL</i> ₂ + <i>DL</i> -proline	13.9	0.036	0.00018	0.00509	0.99472	
Low Concentration	13.0	165.1	5.1	2.527	0.01040	0.00080	0.98881	<i>RS</i> -binol + (<i>S</i> ₂ : <i>L</i> + <i>R</i> ₂ : <i>D</i>)	57.1	95.3	0.00907	0.00010	0.99083
	3.60	152.9	17.1	2.474	0.00982	0.00273	0.98745	(<i>S</i> ₂ : <i>L</i> + <i>R</i> ₂ : <i>D</i>)	32.3	20.1	0.00508	0.00025	0.99467
	2.04	142.0	28.0	2.517	0.00896	0.00439	0.98665	(<i>S</i> ₂ : <i>L</i> + <i>R</i> ₂ : <i>D</i>) + <i>RS</i> : <i>DL</i> ₂	19.9	3.68	0.00288	0.00078	0.99633
	1.19	127.1	43.0	2.510	0.00803	0.00675	0.98522	(<i>S</i> ₂ : <i>L</i> + <i>R</i> ₂ : <i>D</i>) + <i>RS</i> : <i>DL</i> ₂	21.9	3.79	0.00319	0.00084	0.99597
	0.755	111.0	59.1	2.450	0.00717	0.00949	0.98334	<i>RS</i> : <i>DL</i> ₂	19.9	3.81	0.00289	0.00076	0.99635
	0.416	70.0	67.6	3.214	0.00346	0.00832	0.98822	<i>RS</i> : <i>DL</i> ₂	8.8	0.195	0.00046	0.00235	0.99719
	0.268	52.0	78.0	3.159	0.00262	0.00976	0.98763	<i>RS</i> : <i>DL</i> ₂	13.7	0.035	0.00018	0.00503	0.99479
	0.148	34.9	95.1	3.212	0.00172	0.01169	0.98659	<i>RS</i> : <i>DL</i> ₂ + <i>DL</i> -proline	14.9	0.036	0.00017	0.00477	0.99506
0.032	10.0	127.6	3.370	0.00047	0.01492	0.98461	<i>RS</i> : <i>DL</i> ₂ + <i>DL</i> -proline	13.0	0.035	0.00019	0.00548	0.99433	

*a calculation example is shown in Fig. S9.

**solubilities of pure *RS*-binol and pure *DL*-proline in ethanol of 47.0 and 20.6 mg/ml, respectively, were measured using gravimetric method with three repetitions.

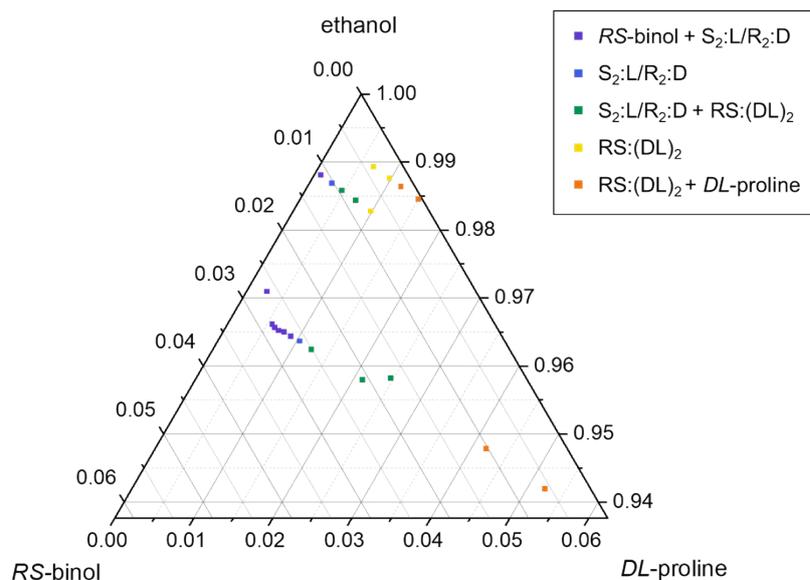


Fig. S12 Magnified region of isopleth between *RS*-binol, *DL*-proline, and ethanol at 20 °C. Each point is placed at initial condition of slurry crystallization from Table S4 and colors are used to represent crystallized solid phase identified from XRPD.

3. References

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