Electronic Supplementary Material (ESI) for Reaction Chemistry & Engineering.

Supporting Information

Automated Solubility and Crystallization Analysis of Non-UV Active Compounds: Integration of Evaporative Light Scattering Detection (ELSD) and Robotic Sampling

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1 General Remarks

1.1 Chemical Suppliers

DL-alanine was purchased from Sigma. *rac*-Isovaline monohydrate and *rac*-allylalanine monohydrate were synthesized. Phenyl isocyanate and lithium hexamethyldisilazide (LiHMDS) was purchased from Sigma. Di-*tert*-butyl dicarbonate (Boc_2O), DMAP, and allyl bromide were purchased from Alfa Aesar. Optima-grade UHPLC solvents were purchased from Fisher and used as received. L-proline was purchased from Alfa Aesar. D-proline was purchased from AK Scientific. L-tartaric acid was purchased from Sigma. All other reagents and solvents were purchased from conventional suppliers and used as received unless otherwise stated. Silica gel was purchased from Silicycle (60 Å, 230 x 400 mesh). Analytical TLC plates were purchased from Merck KGaA and visualized by UV (254 nm) or potassium permanganate staining.

1.2 Equipment

All experiments were performed in Mettler-Toledo EasyMax 102 Advanced Synthesis Workstation glass reactors (50 or 100 mL) equipped with either glass or Teflon reactor covers, submersible thermocouple, and magnetic or overhead stirring and controlled by the Mettler-Toledo software iControl 6.0. The internal reactor temperature (T_r) was maintained by the EasyMax and measured by a thermocouple placed directly in contact with the contents of reactor.

Temporal solubility data was obtained using a custom-built automated reaction sampling apparatus similar to that previously reported by our group.[1-4] In summary, a PTFE filter was affixed to the end of a ETFE sampling capillary (1/16" outer diameter, 0.020" inner diameter) that is submerged into the liquid of the reactor to allow the solid-free supernatant to be withdrawn. At fixed time points, 200 µL samples were automatically taken at a draw speed of 2 mL/min by a New Era Syringe pump (25 mL SGE syringe) through the filter and sampling capillary into a 20 µL sample loop attached on a 6-port, 2-position Gilson 918 Injection Valve (selection valve; see Figure S1). The valve position is then switched and the sample is delivered directly to a 2 mL LC vial located on the bed of a Gilson 215 automated liquid handler robot, by diluting the captured aliquot with 1.0 mL of water.

The timing of the sampling technology was governed by the Mettler-Toledo iControl software that communicates with the EasyMax and can trigger the removal of the reactor aliquot by the syringe pump, actuation of the selection valve position by the rheodyne, and sample dilution by a diluent pump. The EasyMax and Gilson Liquid Handler were interfaced via electrical contacts through a Mettler-Toledo Universal Control Box, "UCB." The prepared samples were manually transferred to the HPLC-ELSD for analysis as they were prepared or upon completion of the sampling period. A general schematic of the system is shown in Figure S1 and the communications schematic is shown in Figure S2.

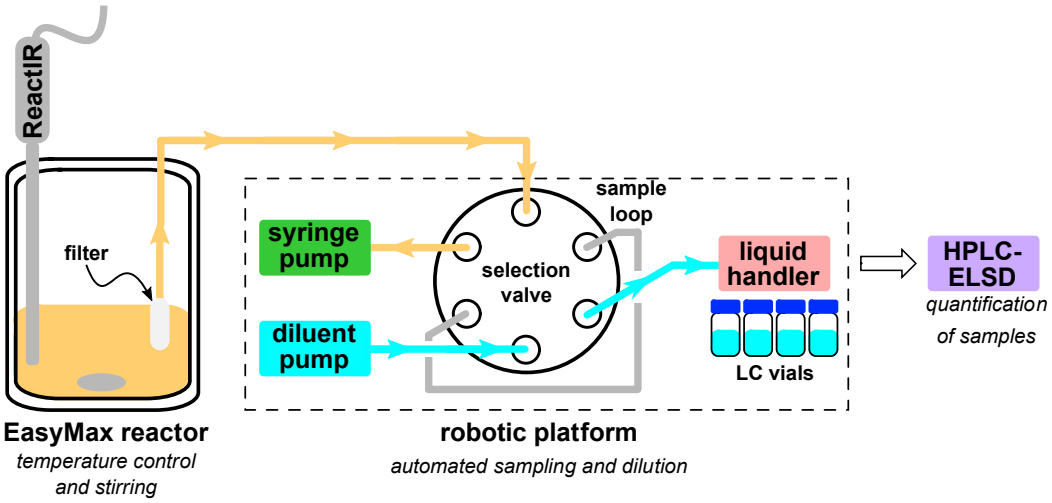


Figure S1. Schematic of automated sampling device used for solubility and crystallization analysis.

Figure S2. Communication schematic of the automated sampling technology used in this work. Double-headed arrows represent bidirectional communication between modules. (UCB = Universal Control Box)

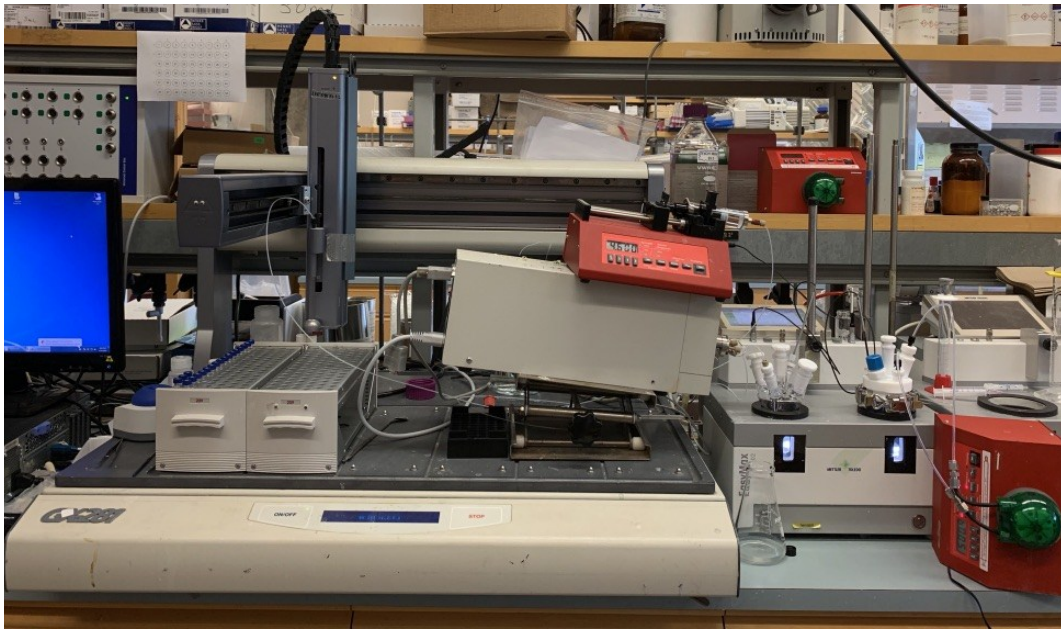


Figure S3. Photo of the automated sampling apparatus.

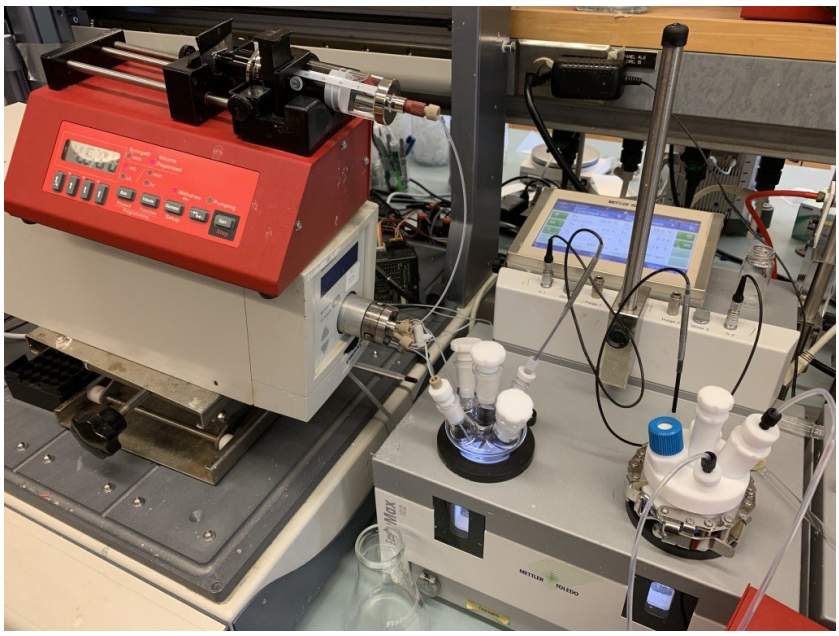


Figure S4. Photo of the syringe pump, valve, and EasyMax reactor.

1.3 Analytical Methods

HPLC analysis was performed on a standard Agilent 1290 Infinity HPLC equipped with a 385-ELSD detector. The collected samples were analyzed using one of the following methods:

Method A: *rac*-Allylalanine Monohydrate
Astec Chirobiotic T Column, 4.6 x 150 mm; 5 µm
Solvent A = Water; Solvent B = Methanol
Flow Rate = 1.00 mL/min
Column Temperature = 25 ˚C
Injection Volume = 8 µL
Pump Program: isocratic, A:B = 10:90

Method B: *rac*-Isovaline Monohydrate
Astec Chirobiotic T Column, 4.6 x 150 mm; 5 µm
Solvent A = Water; Solvent B = Methanol
Flow Rate = 0.6 mL/min
Column Temperature = 25 ˚C
Injection Volume = 15 µL
Pump Program: isocratic, A:B = 35:65

Method C: DL-Alanine
Astec Chirobiotic T Column, 4.6 x 150 mm; 5 µm
Solvent A = Water; Solvent B = Methanol
Flow Rate = 0.6 mL/min
Column Temperature = 25 ˚C
Injection Volume = 5 µL
Pump Program: isocratic, A:B = 85:15

Method D: DL-Proline
Astec Chirobiotic T Column, 4.6 x 150 mm; 5 µm
Solvent A = Water; Solvent B = Acetonitrile
Flow Rate = 1.0 mL/min
Column Temperature = 25 ˚C
Injection Volume = 4 µL
Pump Program: isocratic, A:B = 95:5

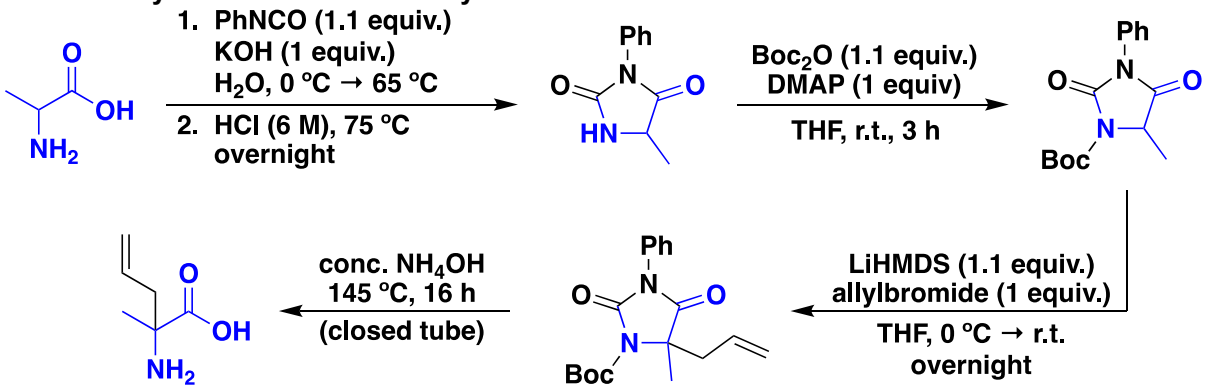
ELSD parameters were the same for all methods and are as follows: Evaporator = 50 ºC, Nebulizer = 50 ºC, Gas Flow Rate = 1.6 SLM, Data Rate = 80 Hz, LED Intensity = 100%, Smoothing = 50 (5.0 s), PMT Gain = 1.0. Concentration values of the samples removed from the reactors were obtained by constructing calibration curves of concentration against ELSD peak area and a described in further detail below.

NMR spectra were recorded on Bruker NMR spectrometers located within the UBC Department of Chemistry. Data for ^{1}H NMR spectra are listed as follows: chemical shift (δ, ppm), multiplicity, coupling constant (Hz), integration, and are referenced to the residual solvent peak.[5] Abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet. ^{13}C{^{1}H} NMR, ^{19}F{^{1}H}, and ^{31}P{^{1}H} NMR spectra are listed in terms of chemical shift (δ, ppm).

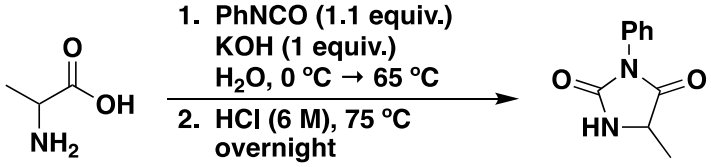
High-resolution mass spectrometry data were acquired by the UBC Department of Chemistry Mass Spectrometry Center. In situ FT-IR monitoring was conducted with a Mettler-Toledo ReactIR10 equipped with a SiComp (silicon) ATR probe connected via an AgX (silver halide) 6.3 mm x 1.5 m fiber optic cable. Spectra were recorded over 3000 cm^{-1} to 650 cm^{-1} at 4 cm^{-1} resolution with 1x gain. The solubility of the analytes was monitored in real time by tracking the peak area of a diagnostic signal relative to a two-point baseline.

2 Synthetic Procedures

2.1 Overall Synthetic Route to *rac*-Allylalanine



2.2 5-methyl-3-phenylimidazolidine-2,4-dione



A three-neck, 1 L round bottom flask equipped with magnetic stir bar, addition funnel, and two glass stoppers was added was charged with KOH (19.6 g, 350 mmol, 1 equiv.) and water (700 mL, 0.5 M) and the resulting solution was cooled to 0 °C via an ice/water bath. DL-alanine (31.2 g, 350 mmol, 1 equiv.) was added in one portion and stirred until a homogeneous mixture was obtained. Phenylisocyanate (45.6 mL, 420 mmol, 1.2 equiv.) was added dropwise via the addition funnel over a 30 min period. The resulting suspension was removed from the ice/water bath and the addition funnel was replaced with a reflux condenser. The reaction was slowly warmed to 65 °C using a heating mantle with the temperature monitored by a glass thermometer, after which the reaction was allowed to stir for an additional 30 min. The reaction was cooled until r.t., after which a white precipitate was observed. The reaction was filtered through a fritted funnel and the white solids discarded, yielding a transparent solution. Under vigorous stirring, the solution was acidified with conc. HCl (37 %; ~25-30 mL, added dropwise) until pH 2, resulting in the formation of a fine white precipitate. The solids were isolated by vacuum filtration through a large fritted funnel and suspended in aqueous HCl (6 M, 530 mL). The suspension was heated to 75 °C and allowed to stir vigorously overnight. The reaction was allowed to cool to r.t., affording a white precipitate. The solid was isolated by vacuum filtration through a large fritted funnel and recrystallized with a minimal amount of boiling ethanol. [If there are insoluble components observed in the flask during the recrystallization, the solution should be filtered while hot to remove these components as they can make clean isolation of the desired allylalanine product difficult if they are carried through subsequent reactions.] After cooling to r.t., the solids were isolated via vacuum filtration and washed with cold ethanol yielding 5-methyl-3-phenylimidazolidine-2,4-dione as a white solid (54.4 g, 82%).

physical state white solid

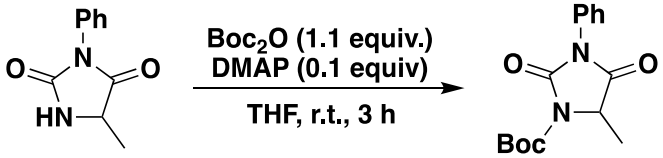
TLC R_f = 0.2 (petroleum ether:diethyl ether = 2:3); UV visualization

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 – 7.44 (m, 2H), 7.44 – 7.26 (m, 3H), 6.82 (s, 1H), 4.21 (q, *J* = 6.9 Hz, 1H), 1.52 (d, *J* = 7.0 Hz, 3H)

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.7, 156.8, 131.6, 129.3, 128.4, 126.3, 53.0, 17.9

HRMS (ESI-TOF) *m/z* calculated for $C_{10}H_{11}N_2O_2$, $[M + H]^+$ = 191.0815; found 191.0815.

2.3 *tert*-butyl 5-methyl-2,4-dioxo-3-phenylimidazolidine-1-carboxylate



To a 1 L round bottom flask equipped with addition funnel and magnetic stir bar was added 5-methyl-3-phenylimidazolidine-2,4-dione (22.82 g, 120 mmol, 1 equiv.), 4-(dimethylamino)pyridine (DMAP; 14.66 g, 120 mmol, 1 equiv.), and THF (600 mL, 0.2 M), affording a homogeneous, slightly yellow solution. Di-*tert*-butyl dicarbonate (Boc_2O; 31.4 g, 144 mmol, 1.2 equiv.) was added dropwise, during which the release of gaseous CO_2 was observed. The resulting mixture was allowed to stir for 1 h at r.t. until the reaction was deemed to be complete by TLC (petroleum ether:diethyl ether = 2:3). The reaction was quenched by the addition of saturated aq. NH_4Cl (100 mL) and the phases separated. The aqueous phase was extracted with DCM (3 x 50 mL) and the combined organic phases were washed with brine (100 mL), dried over anhydrous sodium sulfate, and concentrated by rotary evaporation. The resulting pale-yellow oil was redissolved in methanol (30 mL) and placed into a refrigerator overnight, during which a white precipitate formed. The solid was isolated by vacuum filtration, washed with a minimal amount of cold MeOH, and dried under high vacuum, affording *tert*-butyl 5-methyl-2,4-dioxo-3-phenylimidazolidine-1-carboxylate as a white powder (28.6 g, 82%).

physical state white solid

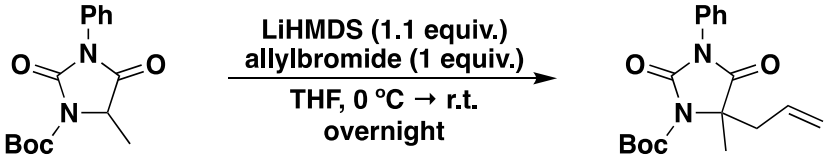
TLC R_f = 0.4 (petroleum ether:diethyl ether= 2:3); UV visualization

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 – 7.43 (m, 2H), 7.43 – 7.27 (m, 3H), 4.56 (q, *J* = 6.8 Hz, 1H), 1.70 (d, *J* = 6.8 Hz, 3H), 1.58 (s, 9H)

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 170.8, 151.2, 148.7, 130.9, 129.3, 128.9, 126.5, 84.7, 55.7, 28.2, 17.2

HRMS (ESI-TOF) *m/z* calculated for $C_{15}H_{18}N_2NaO_4$, $[M + Na]^+$ = 313.1164; found 313.1173.

2.4 *tert*-butyl 5-allyl-5-methyl-2,4-dioxo-3-phenylimidazolidine-1-carboxylate



A flame-dried, 250 mL two-neck round bottom flask equipped with gas flow adapter and rubber septum was cooled under vacuum and refilled with argon. The flask was charged with *tert*-butyl 5-methyl-2,4-dioxo-3-phenylimidazolidine-1-carboxylate (43.5 g, 150 mmol, 1 equiv.) and evacuated for approximately 30 min. After refilling with argon, anhydrous THF (550 mL, 0.5 M) was added, followed by allylbromide (12.98 mL, 120 mmol, 1 equiv.), and the flask was cooled to 0 ºC using an ice/water bath. Meanwhile, LiHMDS (27.6 g, 165 mmol, 1.1 equiv.) was weighed inside a nitrogen-filled glovebox directly into a 20 mL scintillation vial. The scintillation vial was then capped and sealed with electrical tape before being brought out of the glovebox. A separate two-neck round bottom flask equipped with magnetic stir bar, gas flow adapter, and rubber septum was also cooled under vacuum and refilled with argon. The contents of the scintillation vial were transferred to the empty two-neck round bottom flask and THF (150 mL, approx. 1 M solution) was added, yielding a slightly opaque yellow-brown solution. After the flask containing the starting material was sufficiently cooled, the LiHMDS solution was transferred dropwise via cannula over 30 min. [Note: Care should be taken to prevent rapid addition of the LiHMDS solution as this can generate darkly colored by-products (typically brown) that make isolation of the desired product difficult.] Following complete transfer of the LiHMDS solution, the reaction was allowed to stir overnight in the ice/water bath while warming to r.t. The reaction was quenched with saturated aq. NH_4Cl (100 mL) and

the aqueous phase was extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous sodium sulfate, and concentrated via rotary evaporation, resulting in a yellow-brown oil. The oil was placed under high vacuum overnight to remove residual solvent, generating a crude, off-white solid. The crude solid was dissolved in a minimal amount of hot iPrOH, cooled to r.t., and the desired product was precipitated with a minimal amount of cold water. The precipitate was collected by vacuum filtration, washed with a cold mixture of iPrOH:H_2O (8:2) and dried to afford *tert*-butyl 5-allyl-5-methyl-2,4-dioxo-3-phenylimidazolidine-1-carboxylate as a white solid (47.0 g, 95%).

physical state white solid

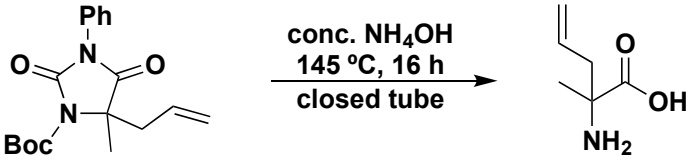
TLC R_f = 0.6 (petroleum ether:ethyl acetate = 85:15); UV visualization

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 – 7.41 (m, 2H), 7.41 – 7.34 (m, 1H), 7.34 – 7.19 (m, 2H), 5.65 (ddt, J = 17.3, 10.3, 7.5 Hz, 1H), 5.37 – 5.10 (m, 2H), 3.09 (dd, *J* = 13.8, 7.7 Hz, 1H), 2.70 (dd, *J* = 13.8, 7.3 Hz, 1H), 1.74 (s, 3H), 1.58 (s, 9H)

^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 173.2, 151.3, 148.7, 130.9, 130.3, 129.2, 128.9, 126.6, 121.4, 84.4, 66.1, 40.0, 28.2, 22.5

HRMS (ESI-TOF) *m/z* calculated for $C_{18}H_{22}N_2NaO_4$, $[M + Na]^+$ = 353.1477; found 353.1471.

2.5 2-amino-2-methylpent-4-enoic acid (allylalanine)



To a high-pressure reaction tube equipped with magnetic stir bar was added *tert*-butyl 5-allyl-5-methyl-2,4-dioxo-3-phenyl imidazolidine-1-carboxylate (24.8 g, 75 mmol) followed by conc. NH_4OH (60 mL), affording a heterogeneous suspension. The tube was sealed, shaken to mix the contents, and placed in an oil bath at r.t. The oil bath was slowly heated to 145 ºC and the reaction was allowed to stir overnight (16 h). [**CAUTION: EXPLOSION HAZARD! The reaction should be placed behind a blast shield.]** The solids were observed to dissolve over time affording a slightly yellow, homogeneous reaction mixture. The reaction was allowed to cool to r.t. without stirring, during which two distinct phases were observed to develop. The upper, colored phase was separated, and the remaining mixture was concentrated by rotary evaporation, affording an off-white solid. A large, egg-shaped stir bar was added along with a mixture of methyl *tert*-butyl ether (MTBE):acetone = 1:1. The contents of the flask were then stirred vigorously until a fine powder was generated. The solid was isolated by vacuum filtration and dried under high vacuum, affording 2-amino-2-methylpent-4-enoic acid (allylalanine; 5.7 g, 58.8%) as a white solid. Analytically pure product can be obtained through vacuum sublimation.

physical state white solid

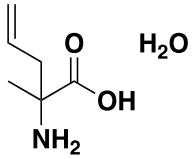
TLC R_f = 0.44 (*n*-BuOH:AcOH:H_2O = 3:1:1); $KMnO_4$ visualization

^{1}H NMR (400 MHz, D_2O) δ 5.75 (ddd, *J* = 17.6, 15.1, 8.0 Hz, 1H), 5.44 – 5.09 (m, 2H), 2.66 (dd, *J* = 14.5, 6.6 Hz, 1H), 2.46 (dd, *J* = 14.5, 8.3 Hz, 1H), 1.49 (s, 3H).

^{13}C{^{1}H} NMR (101 MHz, D_2O) δ 176.3, 130.6, 121.3, 60.9, 41.3, 21.9.

HRMS (ESI-TOF) *m/z* calculated for $C_6H_{12}NO_2$, $[M + H]^+$ = 130.0868; found 130.0873.

2.6 2-amino-2-methylpent-4-enoic acid hydrate (allylalanine monohydrate)



To an Erlenmeyer flask equipped with magnetic stir bar was added 2-amino-2-methylpent-4-enoic acid (5.2 g, 40 mmol) and H_2O (~50 mL) until a homogeneous solution was formed. The resulting solution was passed through filter paper and the water removed by directing a gentle stream of air over the filtrate to afford 2-amino-2-methylpent-4-enoic acid hydrate (*rac*-allylalanine monohydrate) as a white powder (quantitative yield).

3 Solubility and Crystallization Measurements

3.1 General Procedure for Solubility Measurements

To a 50 mL EasyMax reactor equipped with a glass reactor cover, thermocouple, magnetic stir bar, and sampling capillary was charged a given amount of the desired solvent or solvent mixture (approximately 20-30 mL). The reactor was placed into the well of an EasyMax 102 Advanced Synthesis Workstation, the stirring was enabled and set to 500 rpm, and the contents of the reactor were cooled to 0 ºC, as measured by the internal reactor temperature, T_r. A portion of the desired analyte (~3-4 g for *rac*-allylallanine monohydrate, ~1-2 g isovaline monohydrate, ~5-7) was charged directly into the reactor and allowed to stir for at least 1 h. After this equilibration period, at least three samples of solid-free supernatant were taken using the automated sampling apparatus. Following collection of the samples, the internal reactor temperature was then raised by 2 ºC and allowed to equilibrate for at least 1 h before subsequent sampling. If upon the temperature change the contents of the reactor turned homogeneous (i.e., no solids present), then additional portions of solid (0.2-0.5 g) were added until a heterogeneous mixture persisted in the reactor and no more dissolution was observed. The reactor contents were then allowed to reach equilibrium for at least 20 min before sampling. The prepared LC vials were vortexed gently to ensure homogeneity before analysis by HPLC-ELSD. Average peak areas were determined from the samples and converted to solubility (mg/mL) by constructing a calibration curves relating ELSD peak area and solubility.

Figure S5. Photos of EasyMax reactor set up for automated solubility measurements.

3.2 General Procedure for ReactIR Verification of Automated Crystallization Analysis

To a 100 mL EasyMax reactor equipped with a Teflon reactor cover, thermocouple, and magnetic stir bar was charged a given amount of the desired solvent or solvent mixture (approximately 50 mL). The reactor was placed into the well of an EasyMax 102 Advanced Synthesis Workstation, the stirring was enabled and set to 400 rpm, and the contents of the reactor were heated to 40 ºC, as measured by the internal reactor temperature, T_r. A portion of the desired analyte (~2-3 g) was charged directly into the reactor and allowed to stir for at least 1 h. If at any point the solids were seen to completely dissolve, additional portions (0.1-0.5 g) were added and until no more dissolution was observed. After an equilibration period was sustained, the solid-free supernatant of this reactor was transferred into a second EasyMax 100 mL reactor equipped with a Teflon reactor cover, thermocouple, magnetic stir bar, and ReactIR probe via a peristaltic pump by withdrawing the liquid through an ETFE filter attached to the end of the peristaltic tubing and submerged into the heterogeneous mixture. The jacket temperature of the second reactor, T_j, was set to 45 ºC to prevent primary nucleation of the dissolved material as a result of the transfer process. Once a second equilibration period was sustained in the new EasyMax reactor (~20 min), the reactor was cooled to 0 ºC over a period of 30 min while collecting solubility data using the automated sampling apparatus. The solubility of the analytes was monitored in real time by tracking the peak area of a diagnostic signal relative to a two-point baseline. A representative spectrum is given below.

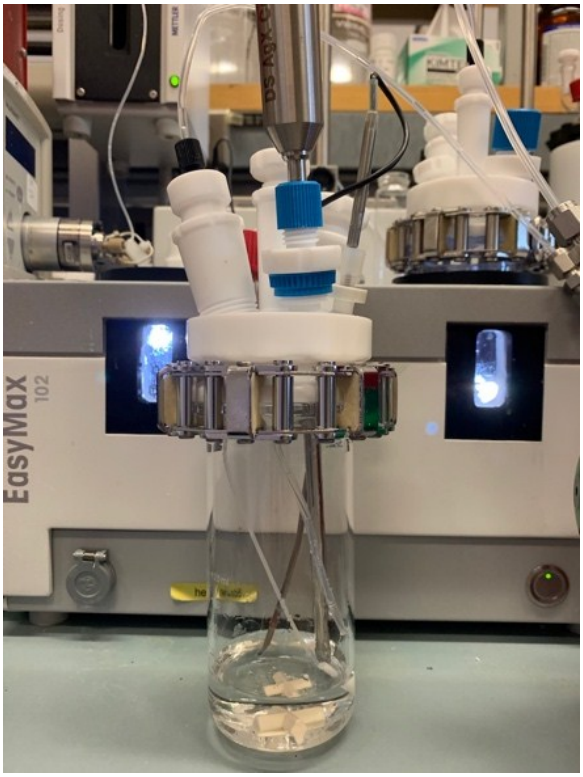


Figure S6. Photo of EasyMax reactor illustrating simultaneous ReactIR and automated sampling for crystallization analysis.

3.3 General Procedure for Monitoring a Preferential Crystallization by Automated Sampling

To a 100 mL EasyMax reactor equipped with a Teflon reactor cover, thermocouple, and magnetic stir bar was charged a given amount of the desired solvent or solvent mixture (approximately 50 mL). The reactor was placed into the well of an EasyMax 102 Advanced Synthesis Workstation, the stirring was enabled and set to 400 rpm, and the contents of the reactor were heated to 20 ºC, as measured by the

internal reactor temperature, T_r. A portion of the desired analyte (~2-3 g) was charged directly into the reactor and allowed to stir for at least 1 h. If at any point the solids were seen to completely dissolve, additional portions (0.1-0.5 g) were added and until no more dissolution was observed. After an equilibration period was sustained, the solid-free supernatant of this reactor was transferred into a second EasyMax 100 mL reactor equipped with a Teflon reactor cover, thermocouple, magnetic stir bar, and ReactIR probe via a peristaltic pump by withdrawing the liquid through an ETFE filter attached to the end of the peristaltic tubing and submerged into the heterogeneous mixture. The jacket temperature of the second reactor, T_j, was set to 35 ºC to prevent primary nucleation of the dissolved material as a result of the transfer process. Once the transfer was complete, the internal reactor temperature, T_r, was lowered to 18 ºC over 20 min to yield a supersaturated solution. For the preferential crystallization, 15 mg of enantiopure (*S*)-allylalanine was added followed by initiation of the sampling program.

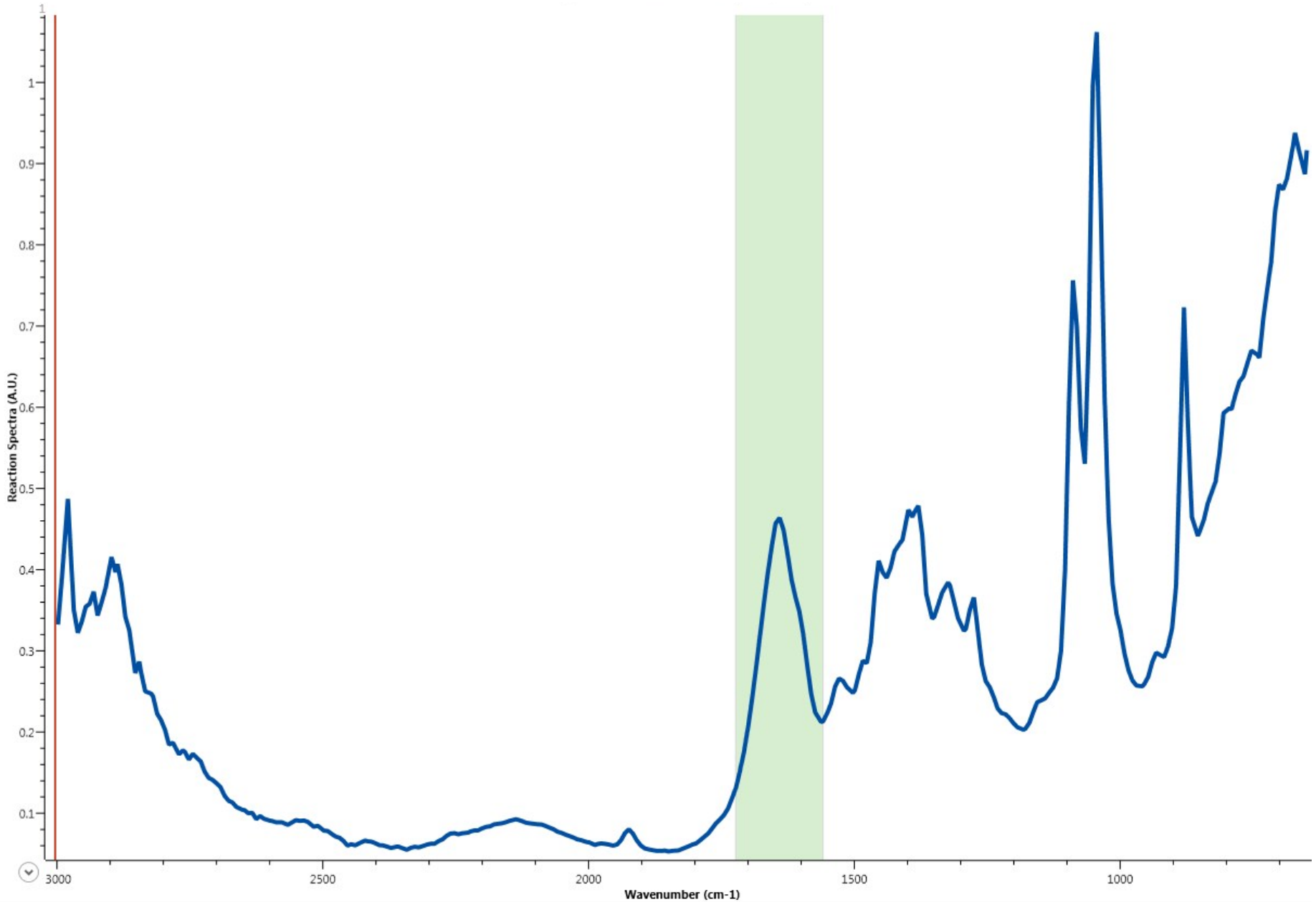


Figure S7. Representative ReactIR spectrum of *rac*-allylalanine monohydrate in EtOH:Water = 75:25. The highlighted peak (1715-1559 cm^{-1}) was used for solubility monitoring, referenced to a two-point baseline.

3.4 Sample iControl Program for Automated Solubility Sampling

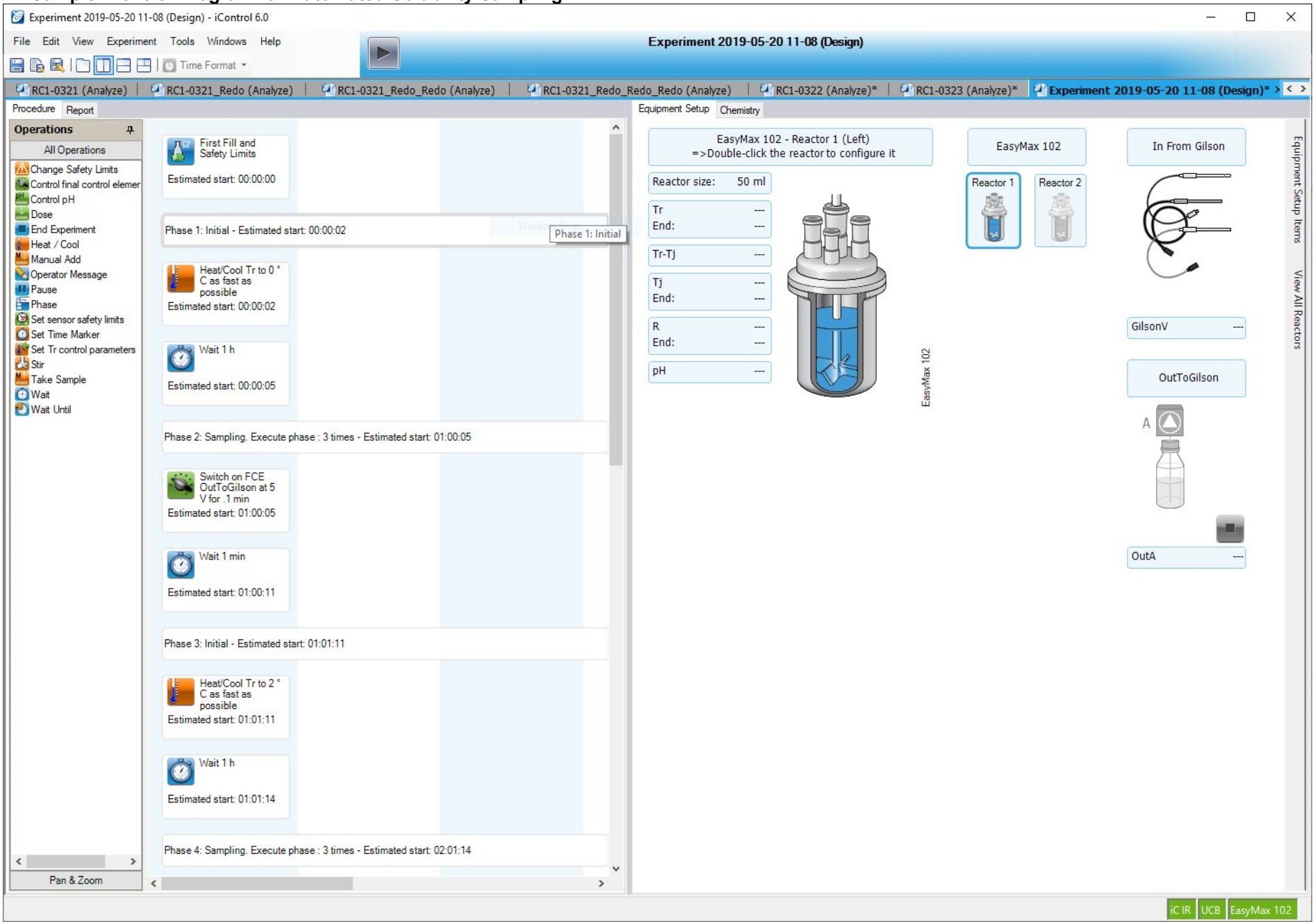
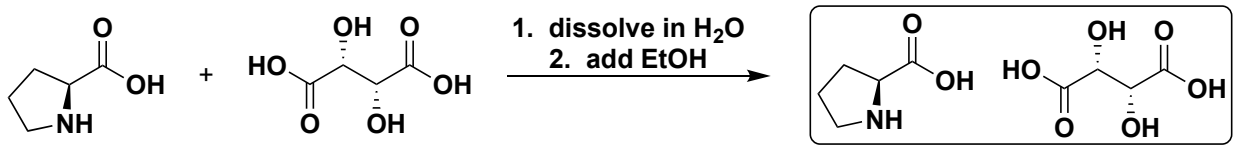


Figure S8. Sample iControl program for automated solubility sampling.

4 Diastereomeric Resolution of DL-Proline with L-Tartaric Acid

4.1 Preparation of Authentic L-Proline—L-Tartaric Acid Diastereomeric Complex



4 D-proline + **5** L-tartaric acid → **6** L-proline—L-tartaric acid complex

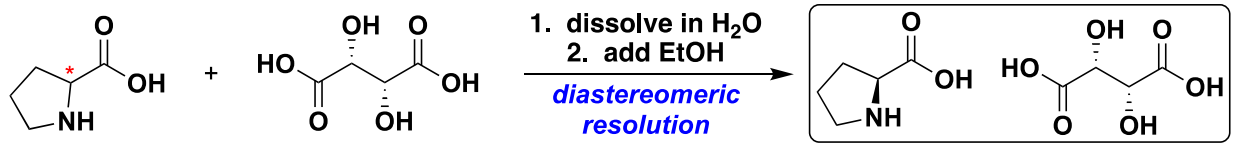
This procedure was performed on 1/10th scale.[6] To a 40 mL vial equipped with stir bar was charged L-proline (0.576 g, 5 mmol, 1 equiv.), L-tartaric acid (0.750 g, 5 mmol, 1 equiv.), and water (2 mL). Ethanol (30 mL) was added under vigorous stirring to yield a cloudy solution. The vial was then sonicated briefly, affording a white precipitate.

physical state white solid

^{1}H NMR (400 MHz, D_2O) δ 4.69 (s, 2H), 4.20 (dd, *J* = 8.8, 6.5 Hz, 1H), 3.38 (ddt, *J* = 33.9, 11.6, 7.0 Hz, 2H), 2.43 – 2.30 (m, 1H), 2.16 – 2.04 (m, 1H), 2.01 (dtd, *J* = 14.5, 7.7, 7.1, 2.4 Hz, 2H).

^{13}C{^{1}H} NMR (101 MHz, D_2O) δ 175.1, 174.2, 72.3, 61.0, 46.3, 29.0, 23.8.

4.2 Trial 1



4 DL-proline + **5** L-tartaric acid → **6** L-proline—L-tartaric acid complex

This procedure was modified from a previously report.[6] To a 150 mL beaker equipped with magnetic stir bar was charged D-proline (5.755 g, 50 mmol, 1 equiv.), L-proline (5.755 g, 50 mmol, 1 equiv.), L-tartaric acid (15.01 g, 100 mmol, 2 equiv.), and 20 mL of water. The beaker was placed on a stir plate and heated gently with vigorous stirring to facilitate complete dissolution of the starting materials. For the diastereomeric resolution, 8.0 mL of this solution was transferred into a 50 mL EasyMax reactor (jacket temperature, T_j = 20 ºC) equipped with magnetic stir bar and sampling capillary. Ethanol (8.0 mL) was added to the reactor under vigorous stirring followed by initiation of the sampling apparatus.

4.3 Trial 2

This trial was performed in a similar fashion to Trial 1, with the exception that 5.5 mL of the proline-tartrate solution and 8.0 mL of ethanol were used.

5 Calibration Curves

5.1 General Procedure for Calibration of ELSD Response and Solubility

To calibrate the ELSD response for each compound and enantiomer, stock solutions of known concentration (mg solute/mL solution) of each racemic compound were prepared in 10 mL volumetric flasks. A given amount of racemic solute was weighed directly into the volumetric flask and filled to the calibration line with deionized water. After mixing the flask thoroughly, the clean sampling line (without filter attached) was inserted directly into the flask and at least three samples were prepared using the automated apparatus. After analyzing the samples using HPLC-ELSD, the raw peak area was plotted against solute concentration. For compounds that displayed a linear ELSD response in the desired working concentration range, a least-squares regression line was fitted onto the data directly. For compounds in which ELSD response was non-linear in the working concentration range, a plot of $\log_{10}$(peak area) against $\log_{10}$(concentration) was generated and a least-squares regression line was fitted to this transformed data.

For the latter case, the resulting equation resulting from linear regression takes the form

$$\log_{10}(\text{peak area}) = a \log_{10}(\text{concentration}) + b$$

where *a* and *b* are constants. To obtain concentration from some peak area *A*, we rewrite the equation as

$$\log_{10}(A) - b = a \log_{10}(\text{concentration})$$

Dividing both sides by *a*, we obtain

$$\frac{\log_{10}(A) - b}{a} = \log_{10}(\text{concentration})$$

Finally, raising both sides of this equation to the power of 10, we obtain

$$10^{\left(\frac{\log_{10}(A) - b}{a}\right)} = \text{concentration}$$

5.2 General Procedure for Calibration of the ReactIR Signal

To calibrate the ReactIR signal, samples of the solid-free supernatant were taken from the reactor at various temperatures by the automated sampling apparatus once the ReactIR signal was determined to be stable. Upon analysis of these samples, the ReactIR peak was plotted against the measured solubility values to obtain a calibration graph.

5.3 Calibration of ELSD Response for *rac*-Allylalanine Monohydrate

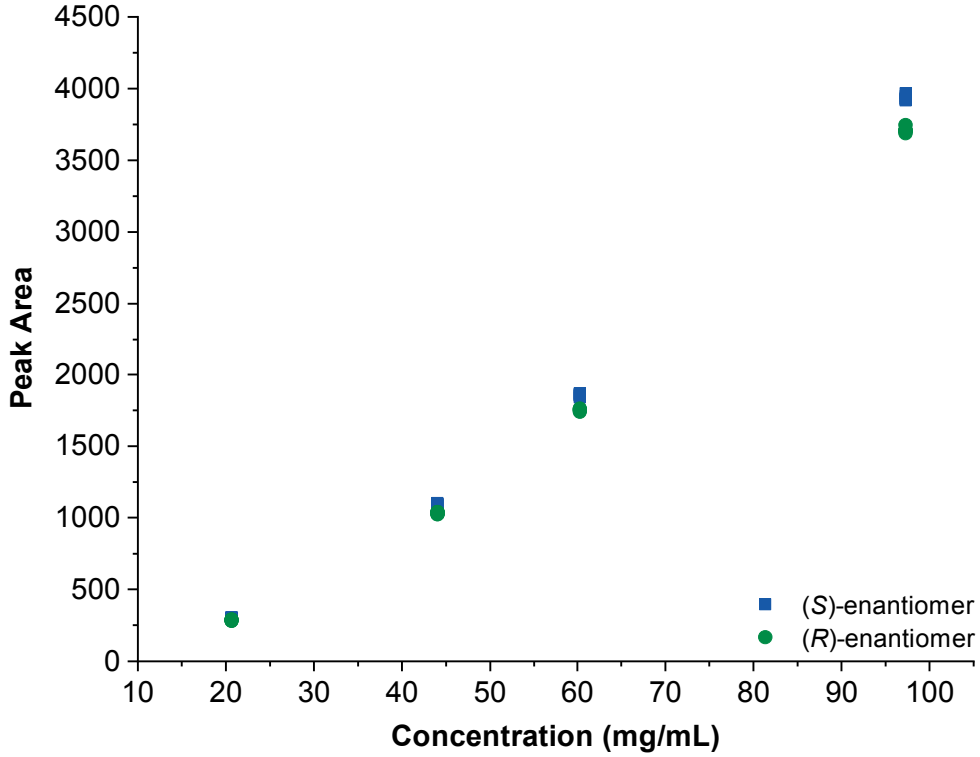


Figure S9. Non-linear ELSD peak area response against concentration for *rac*-allylalanine monohydrate.

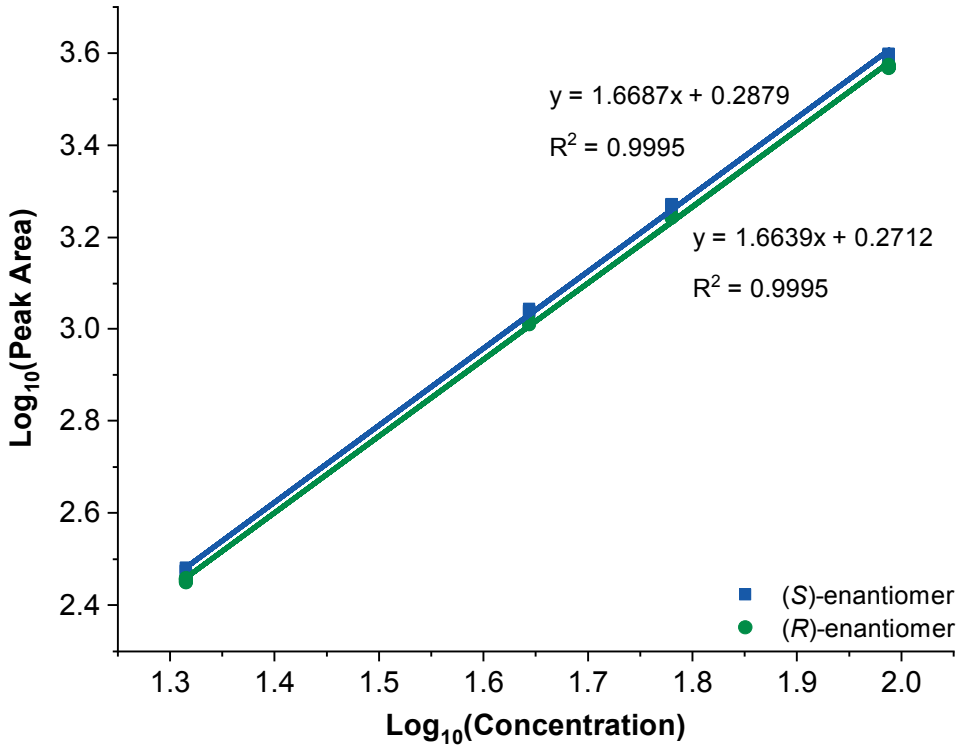


Figure S10. Log-log plot of ELSD peak area and concentration for *rac*-allylalanine monohydrate with least-squares regression line of best fit.

5.4 Calibration of ReactIR Response Against Concentration for *rac*-Allylalanine Monohydrate

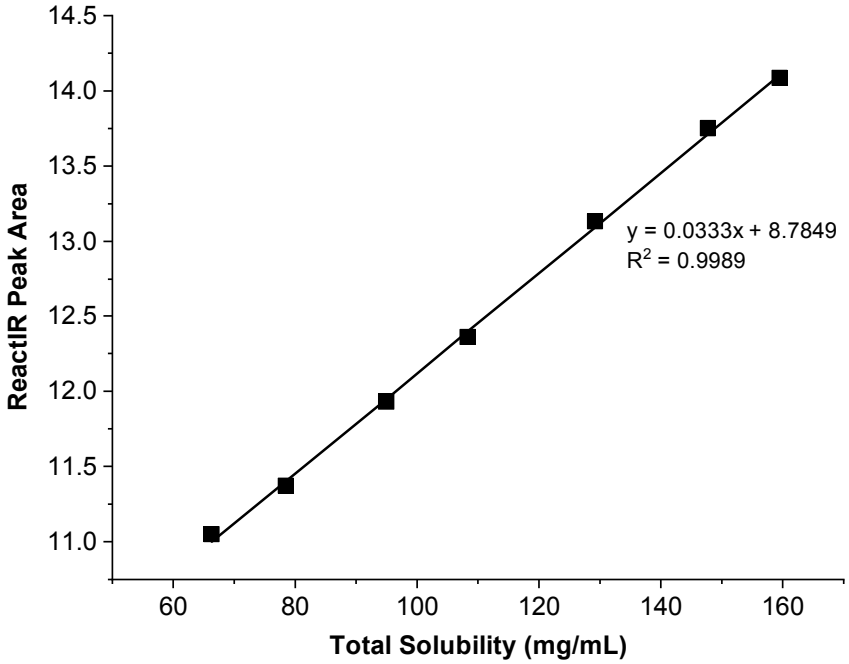


Figure S11. Calibration curve of ReactIR peak area to total solubility of *rac*-allylalanine monohydrate.

5.5 Calibration of ELSD Response for *rac*-Isovaline Monohydrate

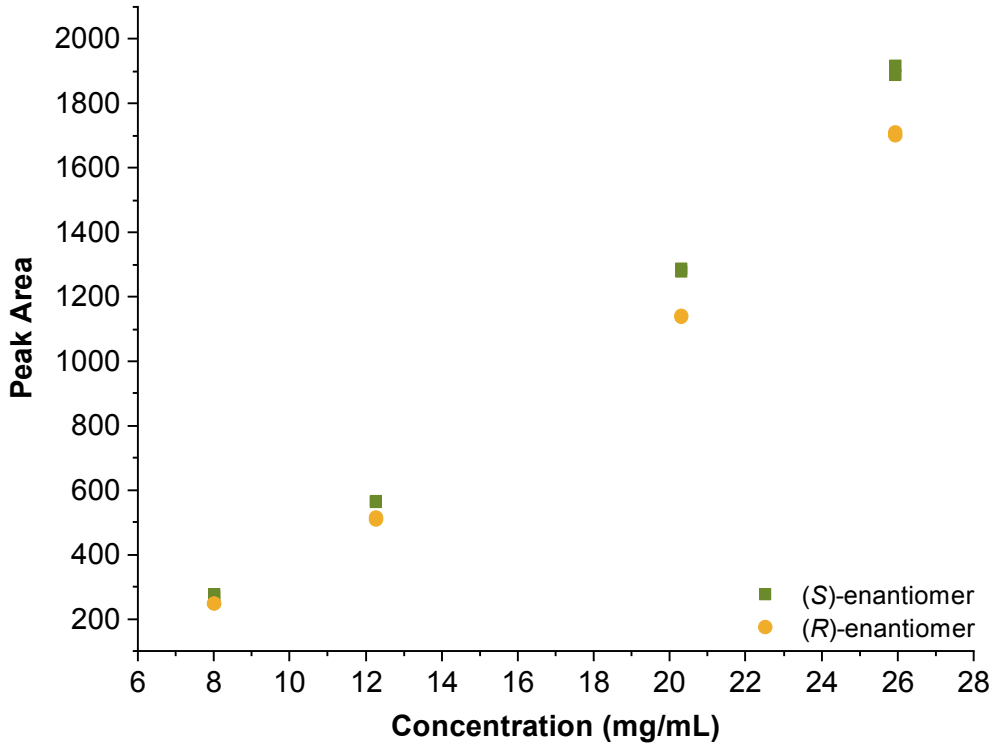


Figure S12. Non-linear ELSD peak area response against concentration for *rac*-isovaline monohydrate.

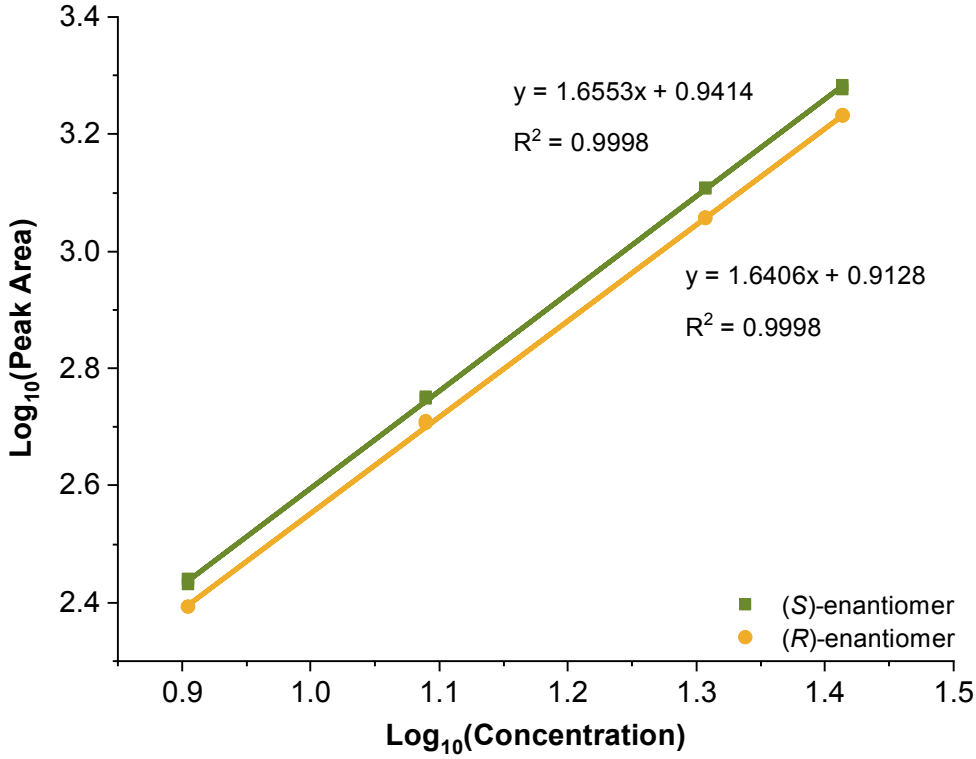


Figure S13. Log-log plot of ELSD peak area and concentration for *rac*-isovaline monohydrate with least-squares regression line of best fit.

5.6 Calibration of ELSD Response for DL-Alanine

For alanine, stock solution preparation using only deionized water was limited to the solubility at room temperature. In this case, conc. HCl (37%) was added dropwise to a volumetric flask that was half-filled with water until the solids were dissolved. After which water was added to the flask until the calibration line and used as previously described.

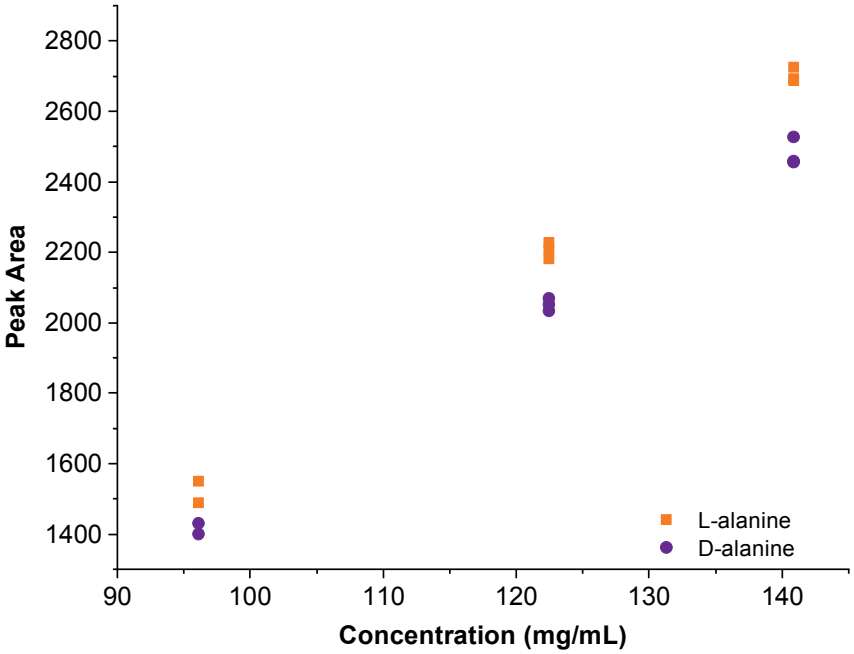


Figure S12. Non-linear ELSD peak area response against concentration for DL-alanine.

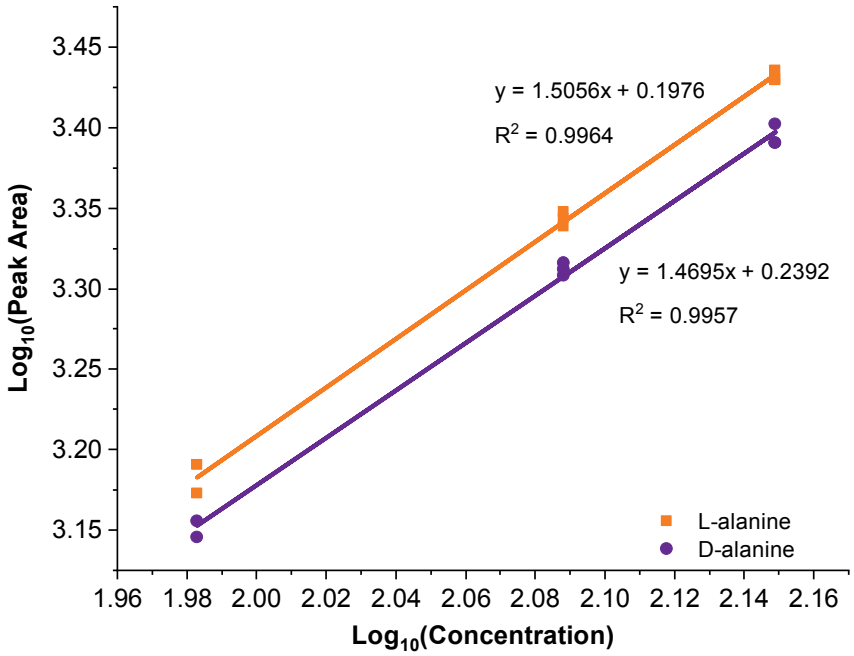


Figure S13. Log-log plot of ELSD peak area and concentration for DL-alanine with least-squares regression line of best fit.

5.7 Calibration Data for DL-Proline

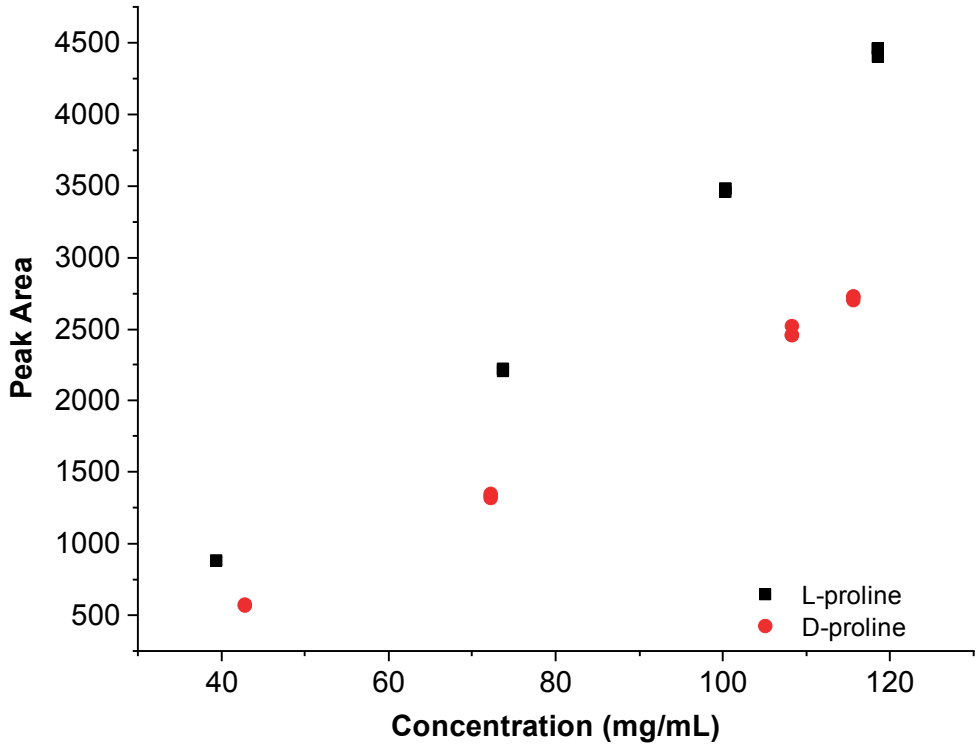


Figure S15. Non-linear ELSD peak area response against concentration for DL-proline.

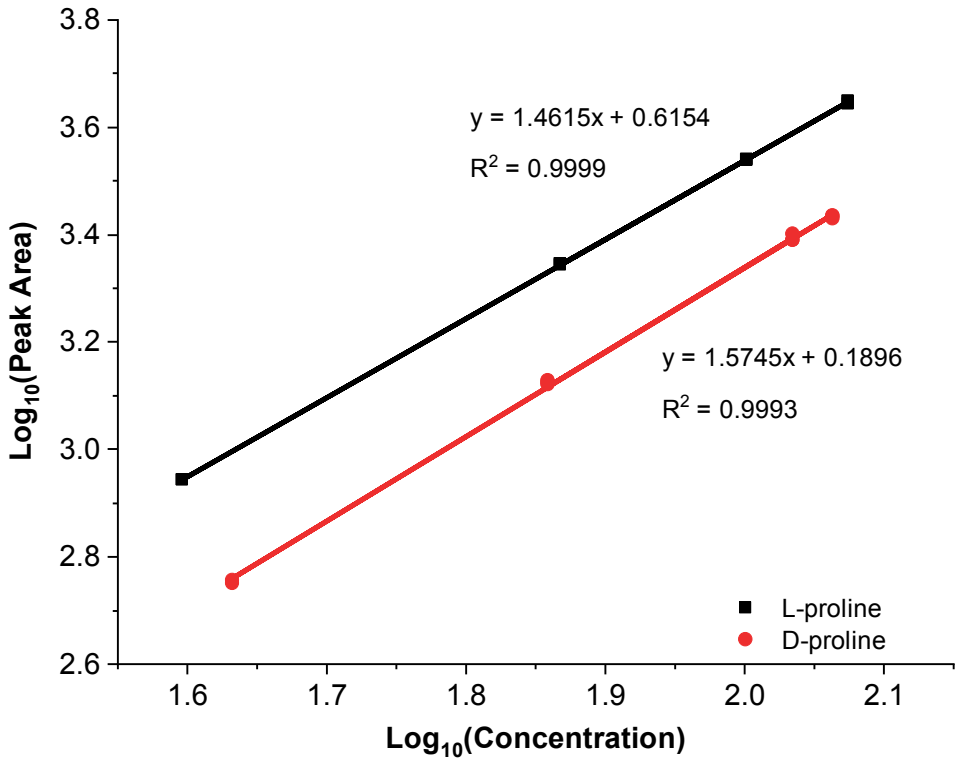


Figure S16. Log-log plot of ELSD peak area and concentration for DL-proline with least-squares regression line of best fit.

6 Solubility Data

6.1 Solubility Data for *rac*-Allylalanine Monohydrate in EtOH:Water = 75:25 (v/v)

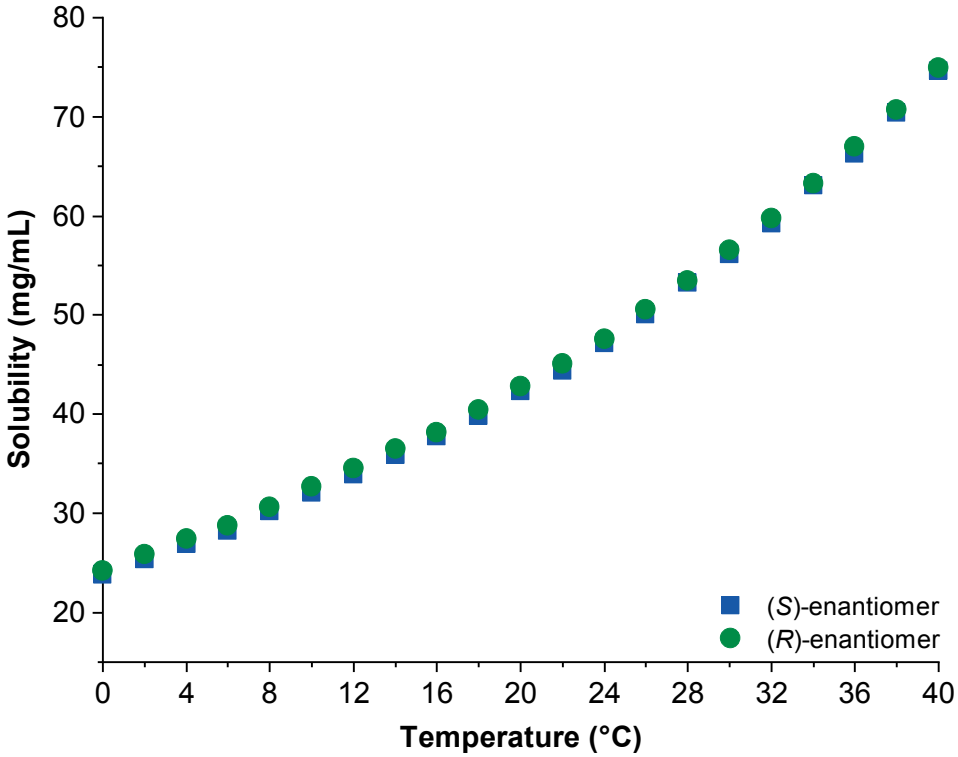


Figure S17. Solubility curve for *rac*-allylalanine monohydrate in EtOH:Water = 75:25 (v/v) by ELSD.

Table S1. Solubility data for *rac*-allylalanine monohydrate in EtOH:Water = 75:25 (v/v) by ELSD. Error values listed represent one standard deviation.

Temperature (°C)	(*S*)-enantiomer (mg/mL)	(*R*)-enantiomer (mg/mL)
0	23.82 ± 0.04	24.21 ± 0.12
2	25.38 ± 0.17	25.81 ± 0.14
4	26.90 ± 0.09	27.39 ± 0.17
6	28.21 ± 0.28	28.76 ± 0.06
8	30.14 ± 0.06	30.61 ± 0.15
10	32.08 ± 0.14	32.71 ± 0.20
12	33.94 ± 0.15	34.49 ± 0.16
14	35.86 ± 0.25	36.49 ± 0.15
16	37.71 ± 0.13	38.16 ± 0.14
18	39.85 ± 0.17	40.45 ± 0.28
20	42.32 ± 0.32	42.80 ± 0.21
22	44.34 ± 0.27	45.10 ± 0.13
24	47.09 ± 0.04	47.60 ± 0.22
26	50.05 ± 0.14	50.57 ± 0.31
28	53.23 ± 0.13	53.49 ± 0.19
30	56.14 ± 0.20	56.51 ± 0.33
32	59.27 ± 0.22	59.75 ± 0.19
34	63.01 ± 0.19	63.23 ± 0.34
36	66.24 ± 0.16	66.98 ± 0.05
38	70.36 ± 0.32	70.75 ± 0.31
40	74.62 ± 0.25	74.95 ± 0.33

6.2 Comparison of Solubility Data *rac*-Allylalanine Monohydrate in EtOH:Water = 75:25 (v/v) Determined by ELSD and Gravimetric Measurement

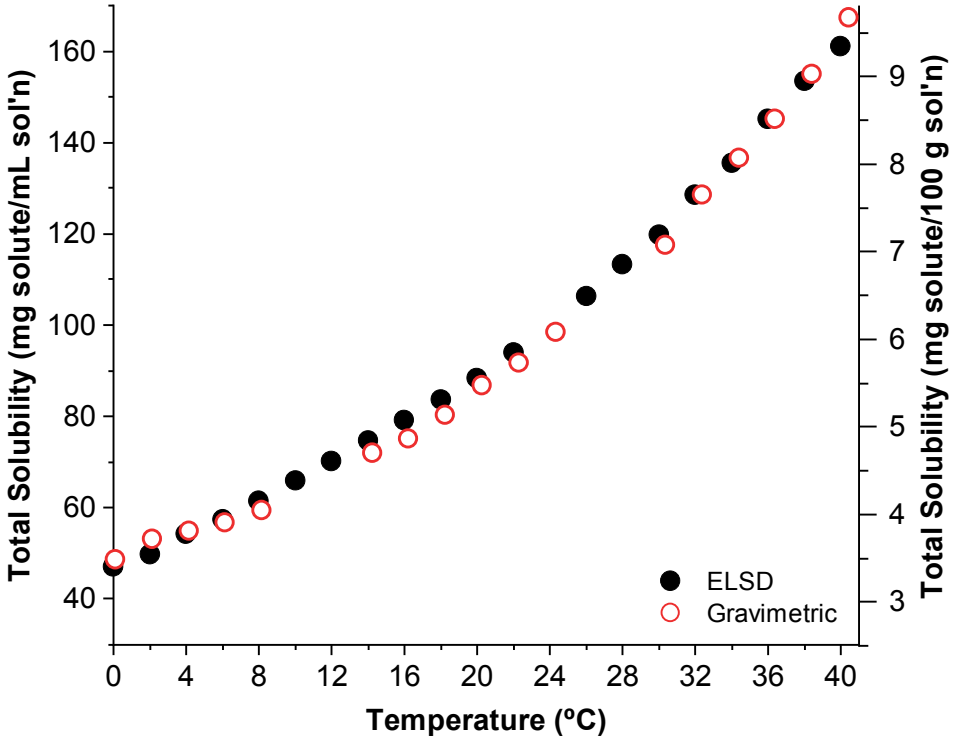


Figure S18. Comparison of solubility curves of *rac*-allylalanine monohydrate in ethanol:water = 75:25 (v/v) measured by HPLC-ELSD (closed black markers) and the gravimetric technique (open red markers). The total solubility is the sum of the concentrations of the (*R*)- and (*S*)- enantiomers in solution.

Table S2. Solubility data for *rac*-allylalanine monohydrate in EtOH:Water = 75:25 (v/v) by the gravimetrich methods.

Temperature (ºC)	Gravimetric Solubility (mg solute/100 g sol'n)
0	3.49
2	3.72
4	3.81
6	3.90
8	4.04
14	4.70
16	4.86
18	5.13
20	5.47
22	5.73
24	6.08
30	7.07
32	7.65
34	8.07
36	8.52
38	9.02
40	9.68

6.3 Solubility Data for *rac*-Isovaline Monohydrate in EtOH:Water = 95:5 (v/v)

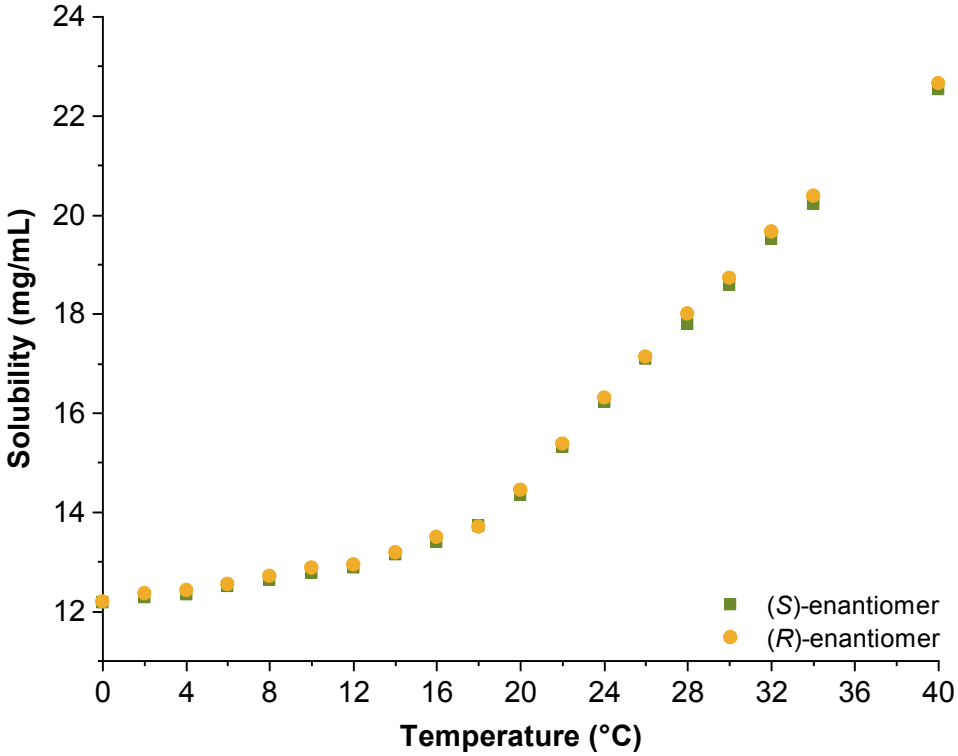


Figure S19. Solubility curve for *rac*-isovaline monohydrate in EtOH:Water = 95:5 (v/v).

Table S3. Solubility Data for *rac*-isovaline monohydrate in EtOH:Water = 95:5 (v/v). Error values listed represent one standard deviation.

Temperature (ºC)	(*S*)-enantiomer (mg/mL)	(*R*)-enantiomer (mg/mL)
0	12.17 ± 0.07	12.20 ± 0.08
2	12.29 ± 0.05	12.37 ± 0.05
4	12.34 ± 0.07	12.42 ± 0.08
6	12.51 ± 0.07	12.55 ± 0.06
8	12.64 ± 0.04	12.73 ± 0.04
10	12.78 ± 0.04	12.88 ± 0.06
12	12.88 ± 0.05	12.94 ± 0.05
14	13.15 ± 0.11	13.19 ± 0.05
16	13.40 ± 0.06	13.51 ± 0.07
18	13.73 ± 0.06	13.71 ± 0.08
20	14.36 ± 0.09	14.46 ± 0.11
22	15.31 ± 0.15	15.37 ± 0.11
24	16.23 ± 0.09	16.32 ± 0.07
26	17.09 ± 0.07	17.14 ± 0.08
28	17.79 ± 0.09	18.99 ± 0.10
30	18.59 ± 0.07	18.73 ± 0.10
32	19.51 ± 0.07	20.30 ± 0.03
34	20.23 ± 0.10	21.38 ± 0.13
40	22.54 ± 0.09	22.66 ± 0.09

6.4 Solubility Data for DL-Alanine in Water

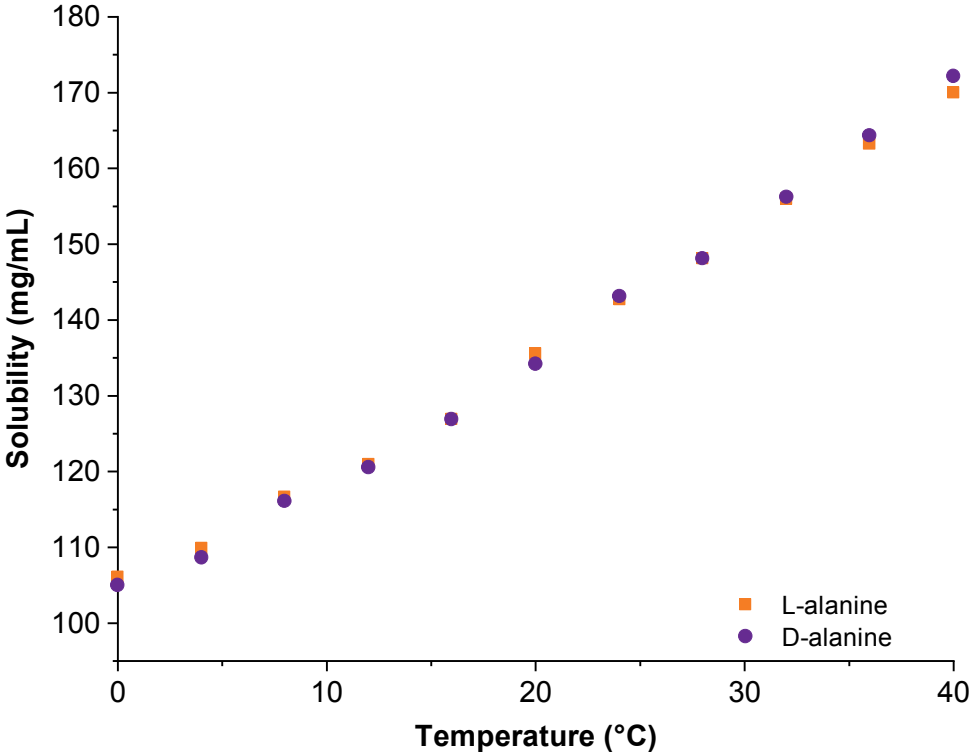


Figure S20. Solubility curve for DL-alanine in water.

Table S4. Solubility data for DL-alanine in water. Error values listed represent one standard deviation.

Temperature (ºC)	L-alanine (mg/mL)	D-alanine (mg/mL)
0	106.04 ± 0.40	104.96 ± 0.49
4	109.89 ± 0.46	108.63 ± 0.56
8	116.68 ± 0.59	116.05 ± 0.71
12	120.95 ± 0.72	120.59 ± 0.21
16	126.92 ± 0.82	126.94 ± 1.26
20	135.54 ± 0.73	134.23 ± 0.45
24	142.71 ± 1.18	143.13 ± 1.22
28	148.09 ± 1.21	148.10 ± 1.04
32	155.88 ± 1.18	156.25 ± 0.89
36	163.29 ± 1.26	164.30 ± 1.58
40	170.00 ± 0.86	172.16 ± 2.67

7 References

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8. G. Sheldrick, *Acta Crystallographica Section C*, 2015, **71**, 3-8.

8 Time Profiles

Figure 4

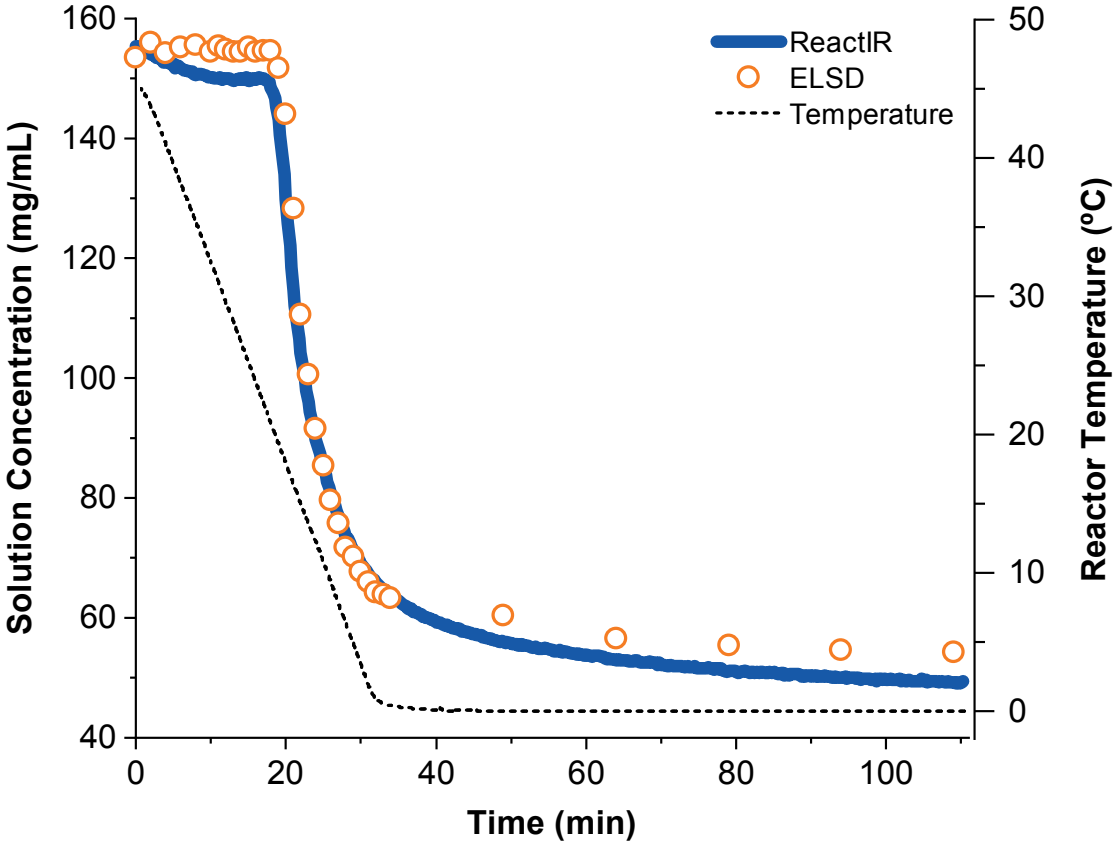


Figure 7

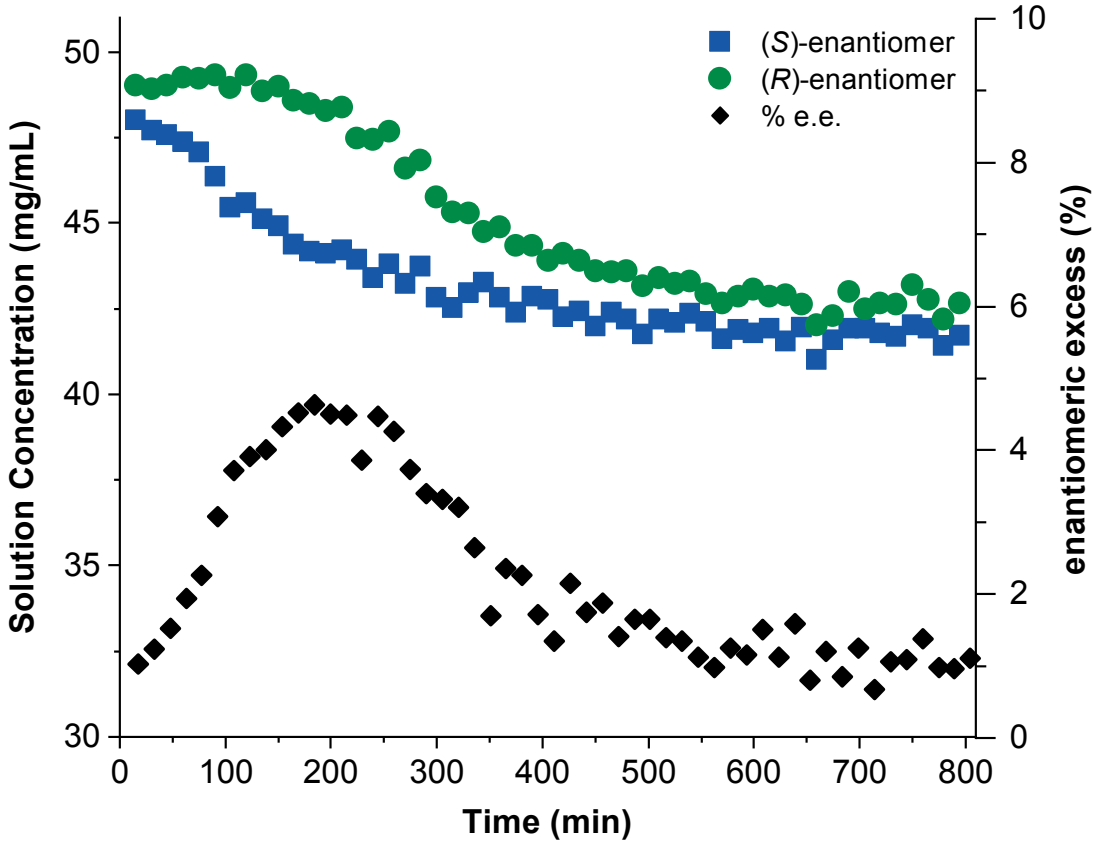


Figure 8a

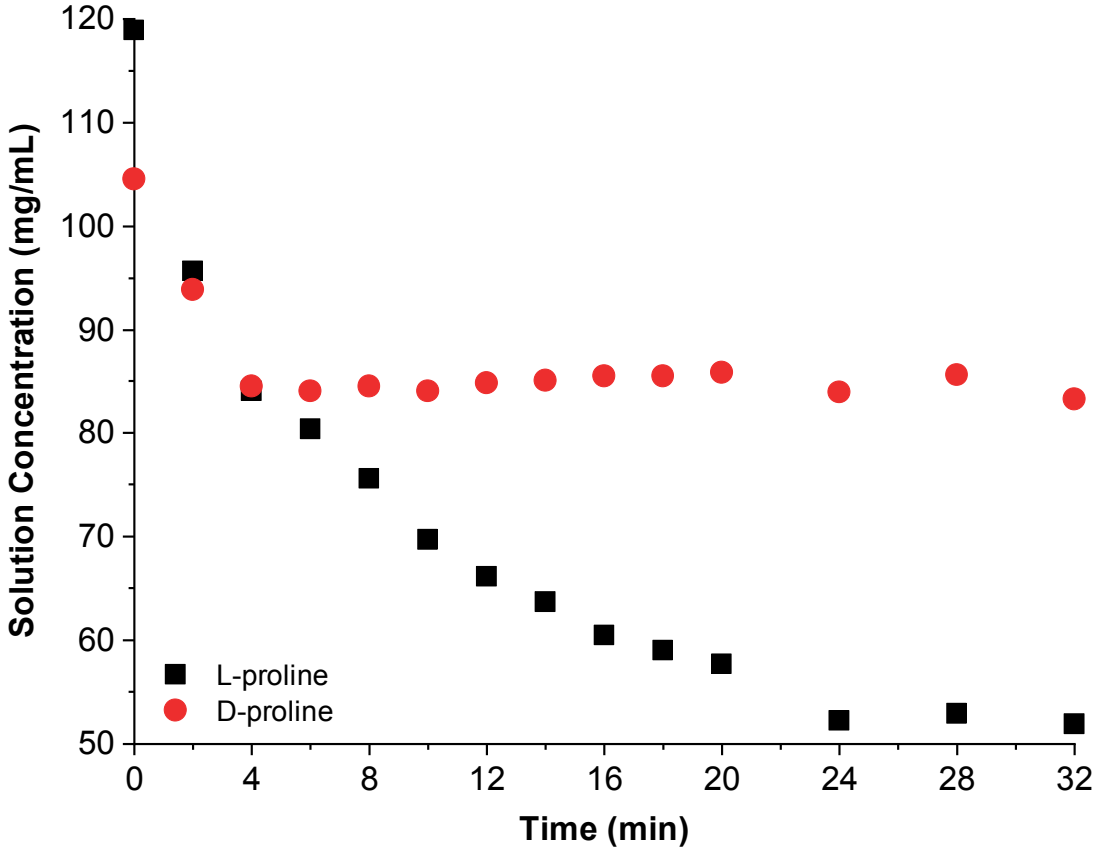
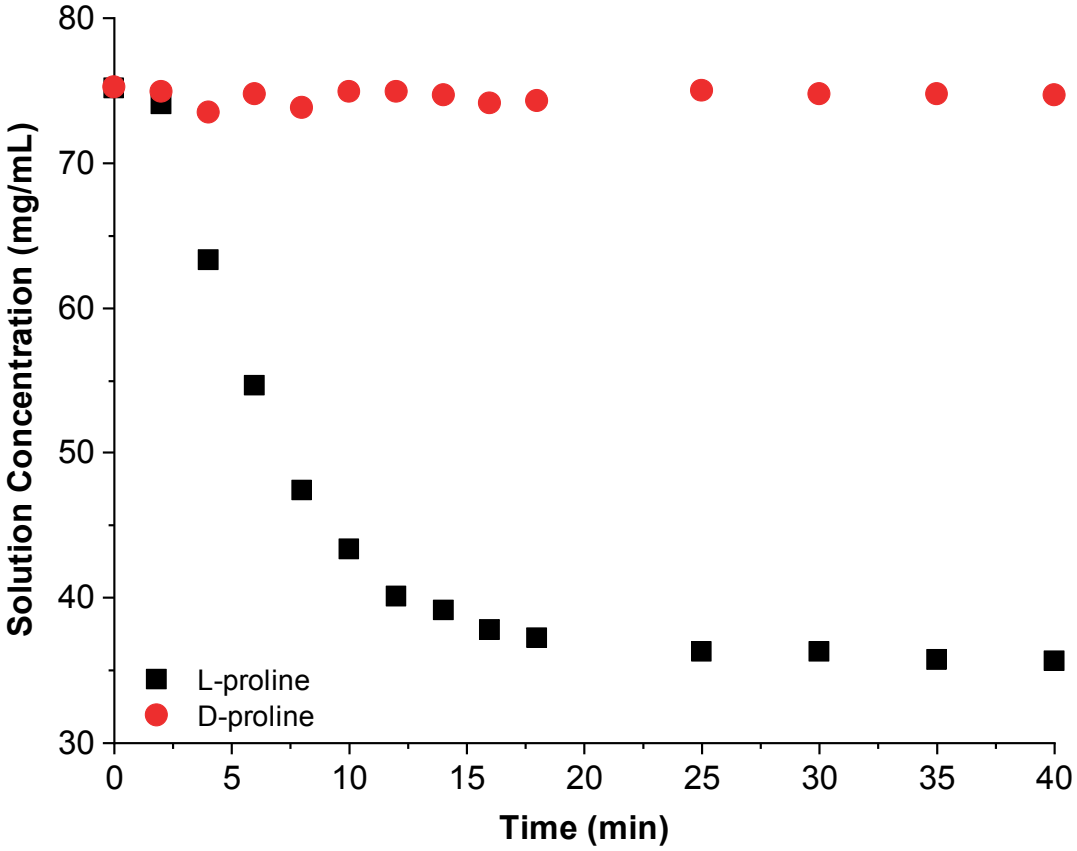


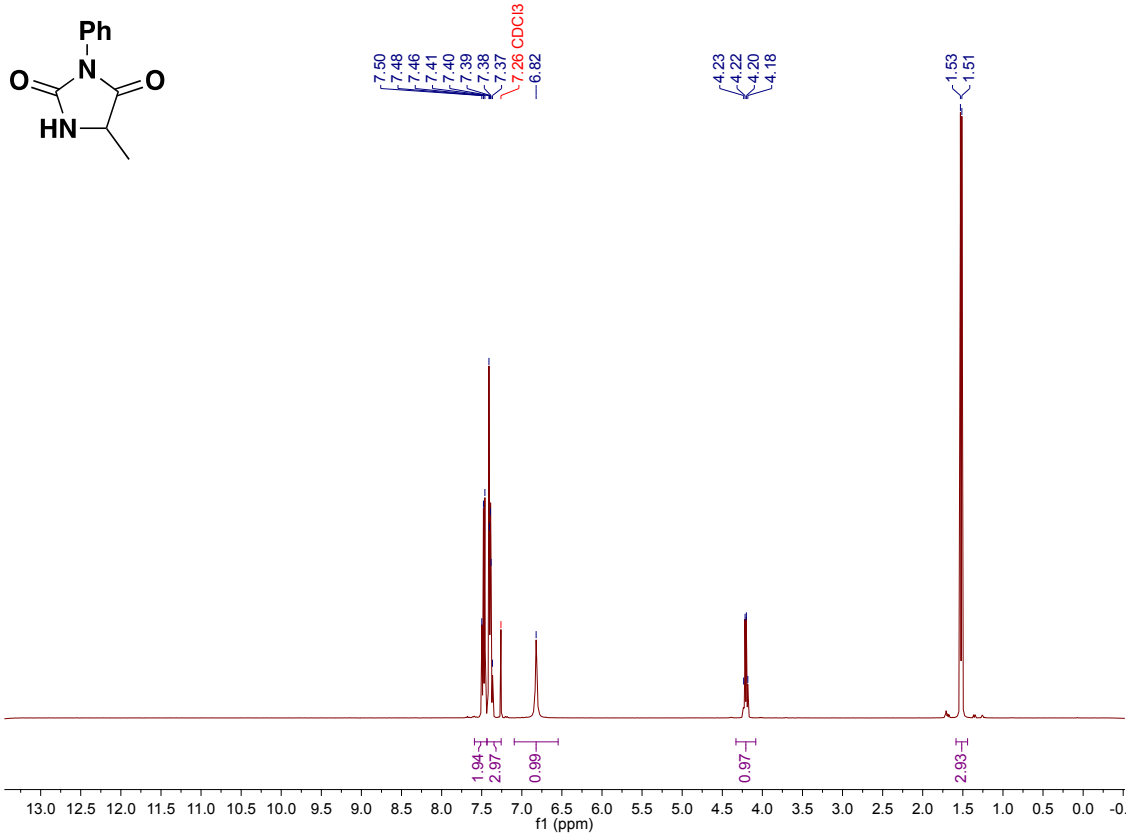
Figure 8b



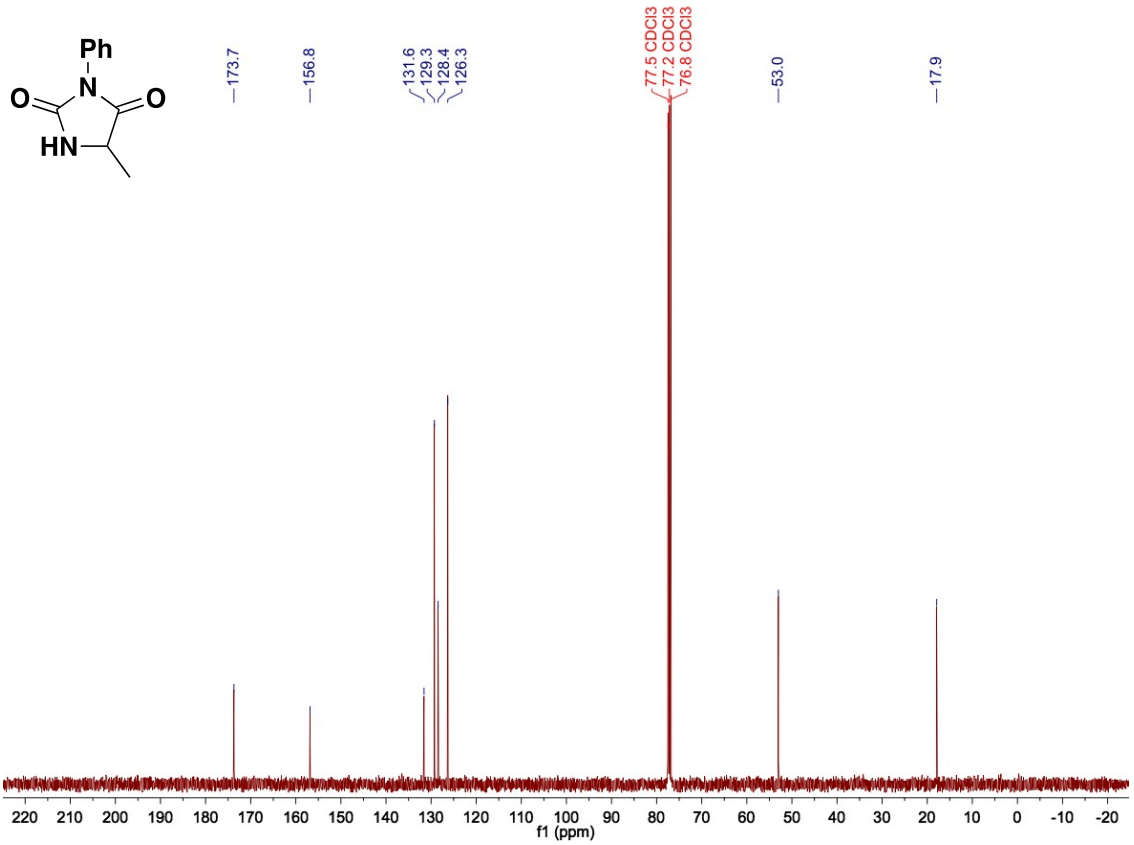
9 NMR Spectra

5-methyl-3-phenylimidazolidine-2,4-dione

^{1}H NMR (400 MHz, $CDCl_3$)

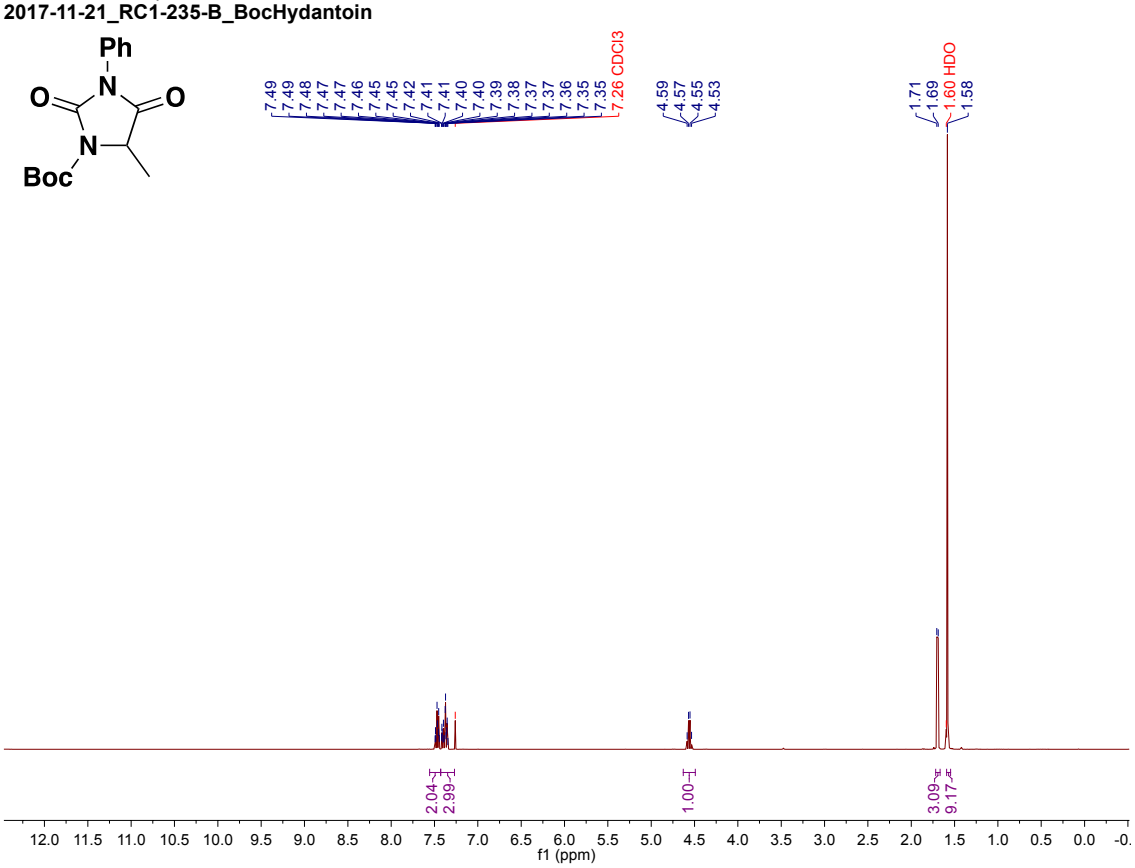


^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)

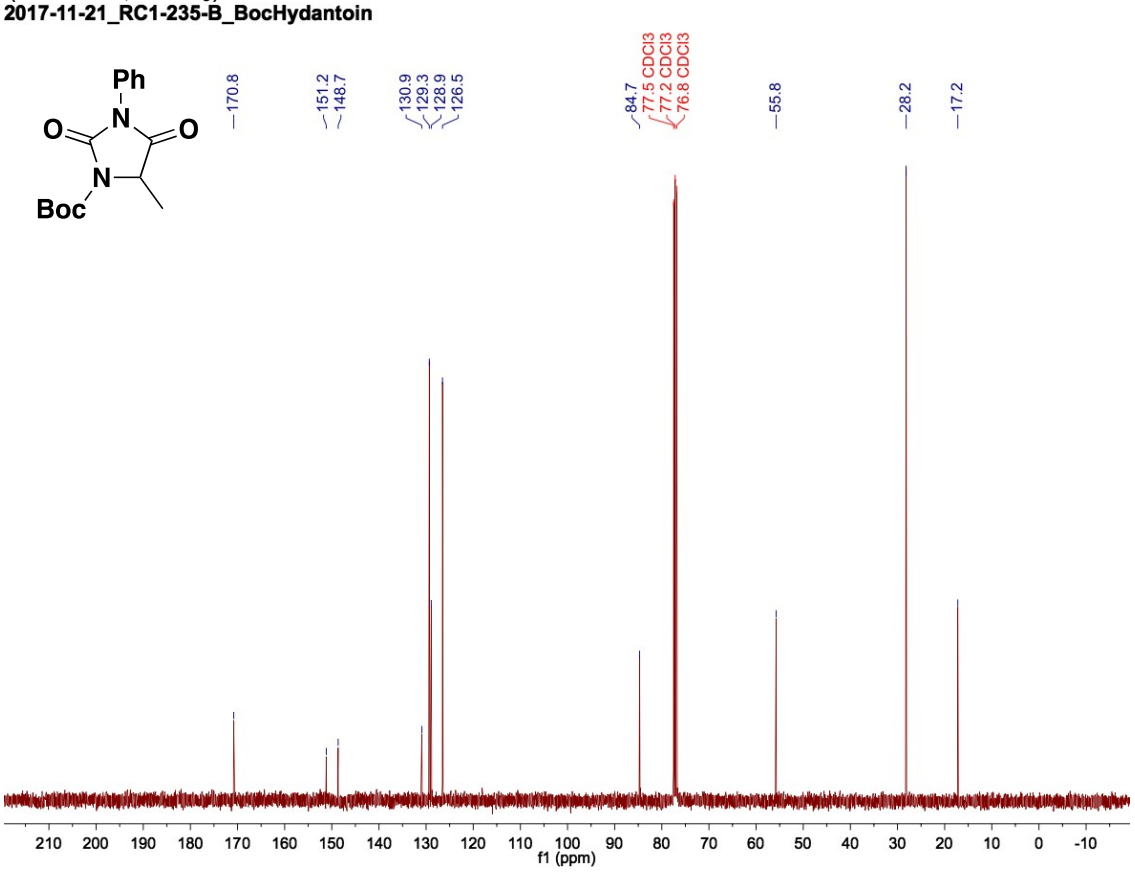


***tert*-butyl 5-methyl-2,4-dioxo-3-phenylimidazolidine-1-carboxylate**

^{1}H NMR (400 MHz, $CDCl_3$)

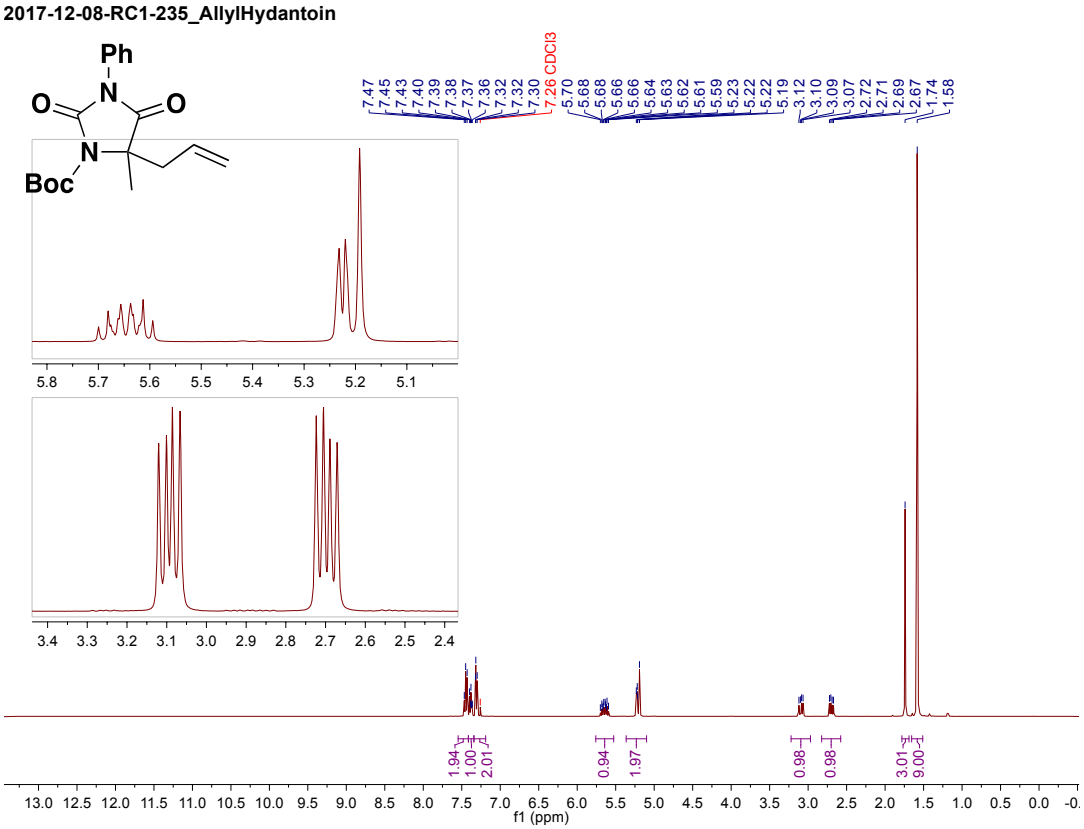


^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)

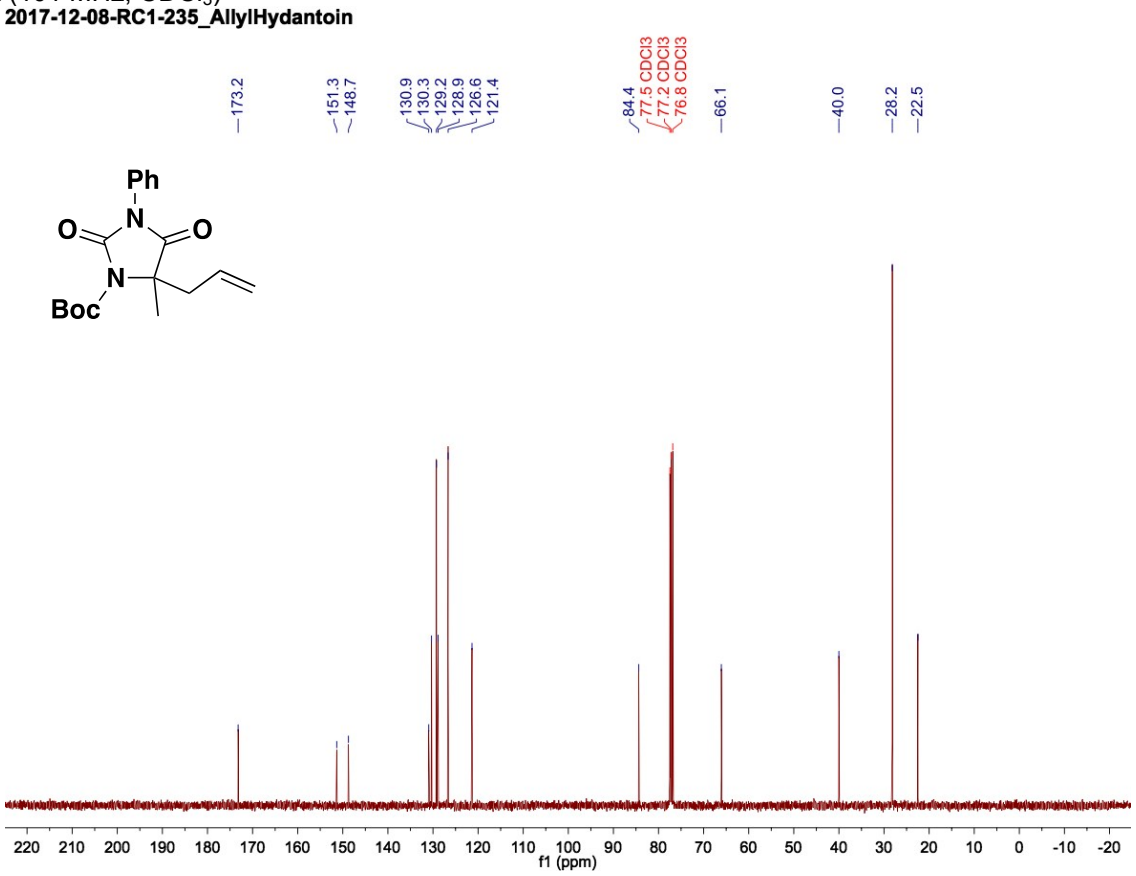


***tert*-butyl 5-allyl-5-methyl-2,4-dioxo-3-phenylimidazolidine-1-carboxylate**

^{1}H NMR (400 MHz, $CDCl_3$)

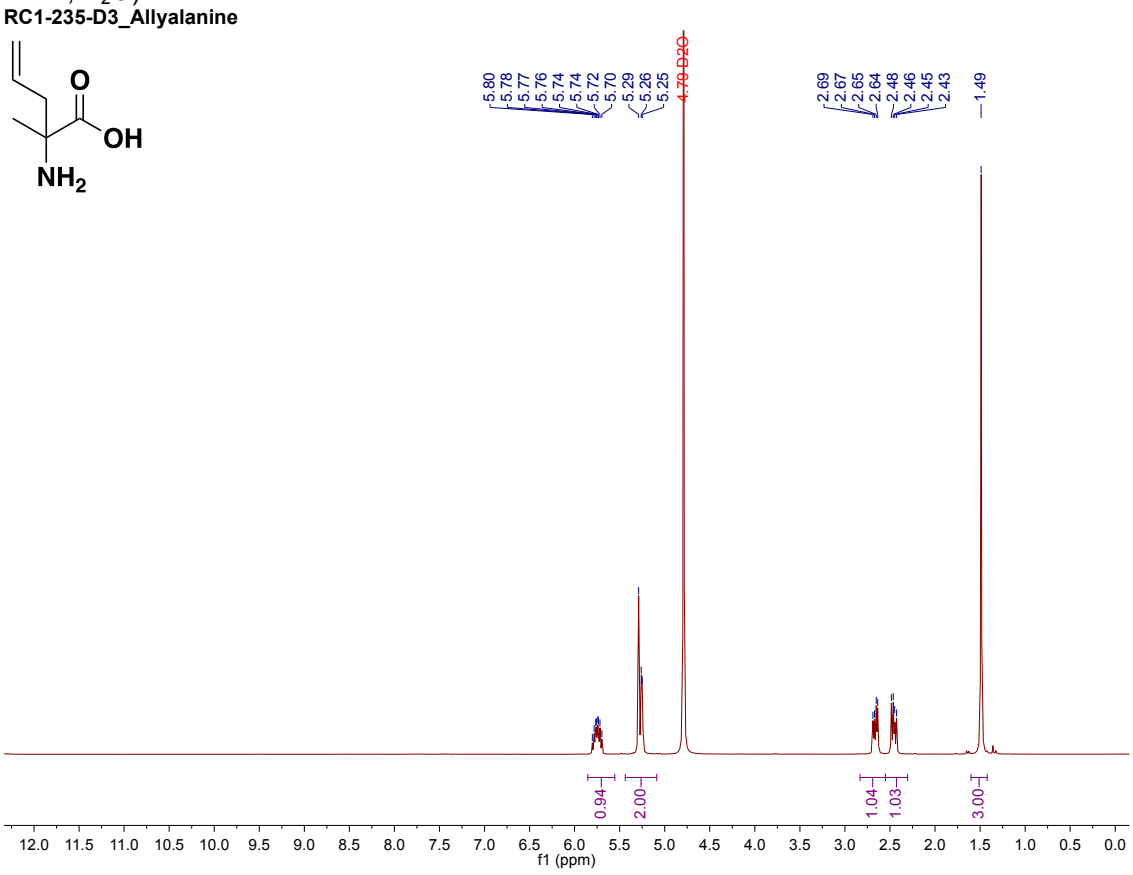


^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$)

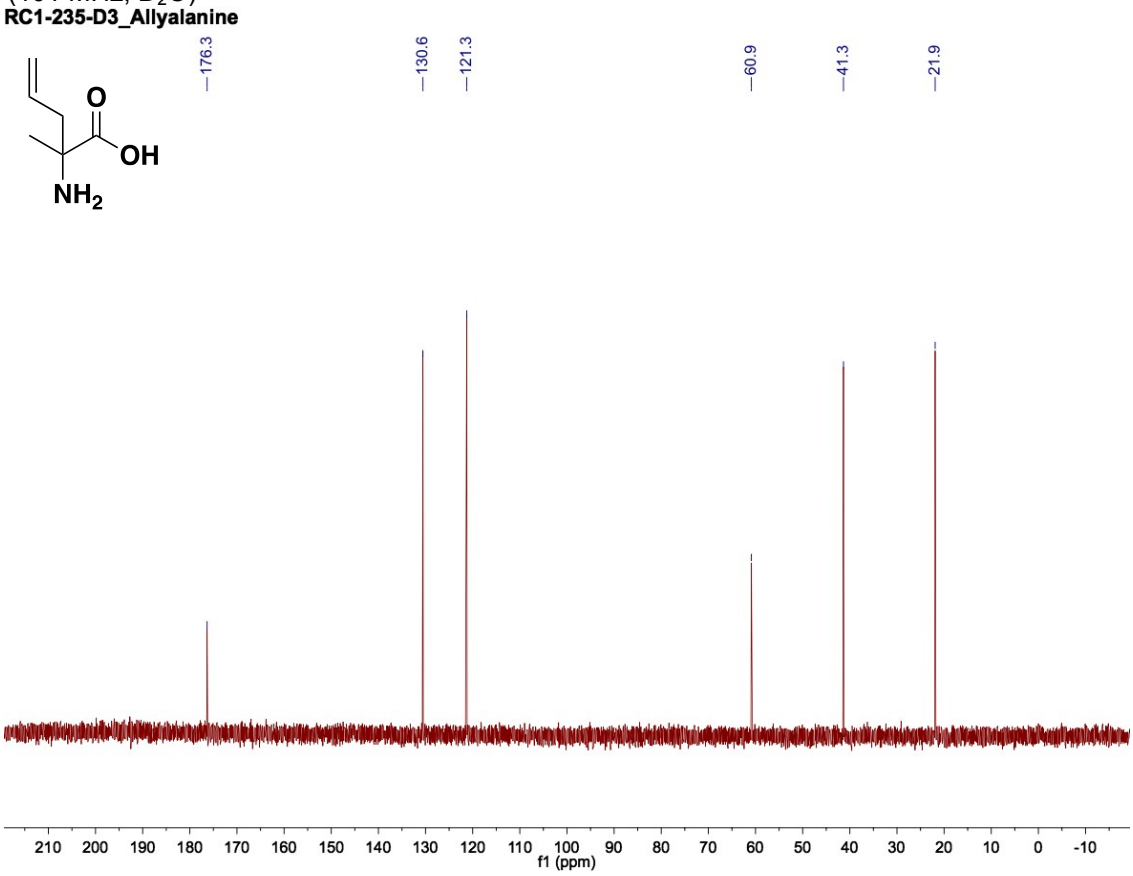


2-amino-2-methylpent-4-enoic acid

^{1}H NMR (400 MHz, D_2O)

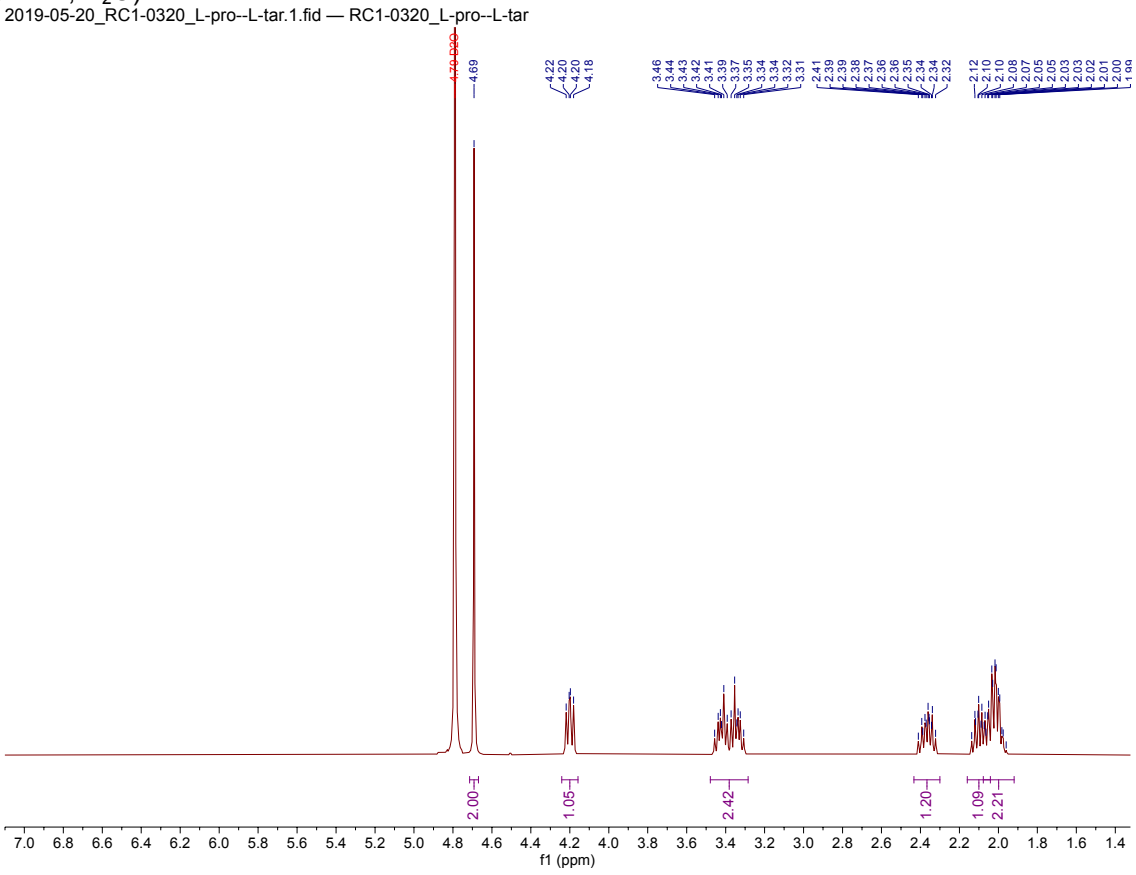


^{13}C{^{1}H} NMR (101 MHz, D_2O)

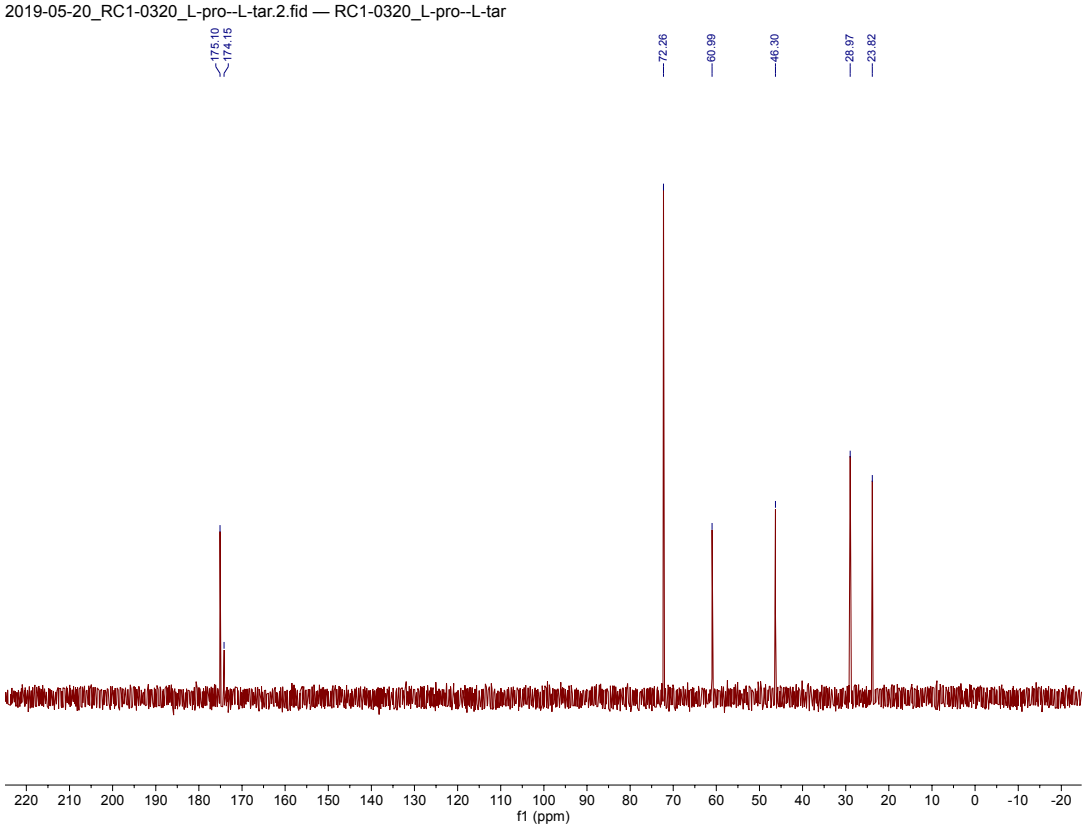


L-proline—L-tartaric acid complex

^{1}H NMR (400 MHz, D_2O)



^{13}C{^{1}H} NMR (101 MHz, D_2O)



10 X-Ray Data

10.1 Single-Crystal X-Ray Data for (*S*)-Allylalanine Monohydrate

Formula	$C_6H_{13}NO_3$
$D_{calc.}$/ g cm^{-3}	1.212
μ/mm^{-1}	0.810
Formula Weight	147.17
Color	colorless
Shape	prism
Size/mm^3	0.24×0.12×0.10
T/K	90(2)
Crystal System	tetragonal
Flack Parameter	0.01(11)
Hooft Parameter	0.03(7)
Space Group	$P4_1$
a/Å	8.8749(7)
b/Å	8.8749(7)
c/Å	20.4808(17)
α/°	90
β/°	90
γ/°	90
V/Å^3	1613.1(3)
Z	8
Z'	2
Wavelength/Å	1.54178
Radiation type	CuK_α
Θ_{min}/°	2.157
Θ_{max}/°	66.704
Measured Refl.	26776
Independent Refl.	2843
Reflections with I > 2(I)	2830
R_{int}	0.0513
Parameters	224
Restraints	1
Largest Peak	0.266
Deepest Hole	-0.151
GooF	1.077
wR_2 (all data)	0.0836
wR_2	0.0834
R_1 (all data)	0.0308
R_1	0.0308

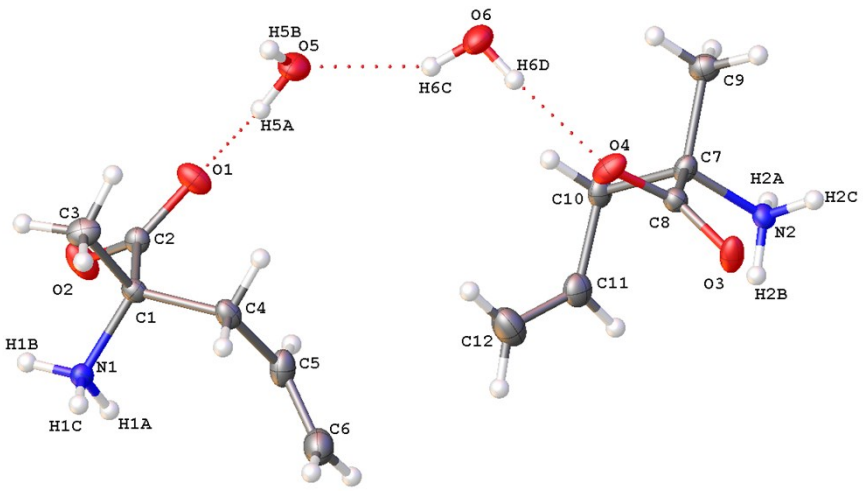


Figure S21. Single-crystal x-ray structure for (*S*)-allylalanine monohydrate.

Crystallographic data for (*S*)-allylalanine monohydrate were measured using CuK_α radiation (microfocus sealed X-ray tube, 45 kV, 0.60 mA) and collected with a Bruker APEX II area detector equipped with an Oxford Cryosystems low-temperature device operating at T = 90(2) K. The total number of runs and images was based on the strategy calculation from the program APEX3. The diffraction pattern was indexed, and the unit cell was refined using SAINT (Bruker, V8.38A, after 2013) on 9736 reflections, 36% of the observed reflections. Data reduction, scaling and absorption corrections were performed using SAINT (Bruker, V8.38A, after 2013). A multi-scan absorption correction was performed using SADABS-2016/2 (Bruker, 2016/2) was used for absorption correction. The structure was solved and the space group *P* 4_1 (# 76) determined by the XT[7] structure solution program using Intrinsic Phasing and refined by Least Squares using version 2017/1 of XL.[8] All non-hydrogen atoms were refined anisotropically. Most hydrogen atom positions were calculated geometrically and refined using the riding model, but all N—H and O—H hydrogen atoms were refined freely. The crystal structure was refined as a two-component twin.

10.2 X-Ray Powder Diffraction Data

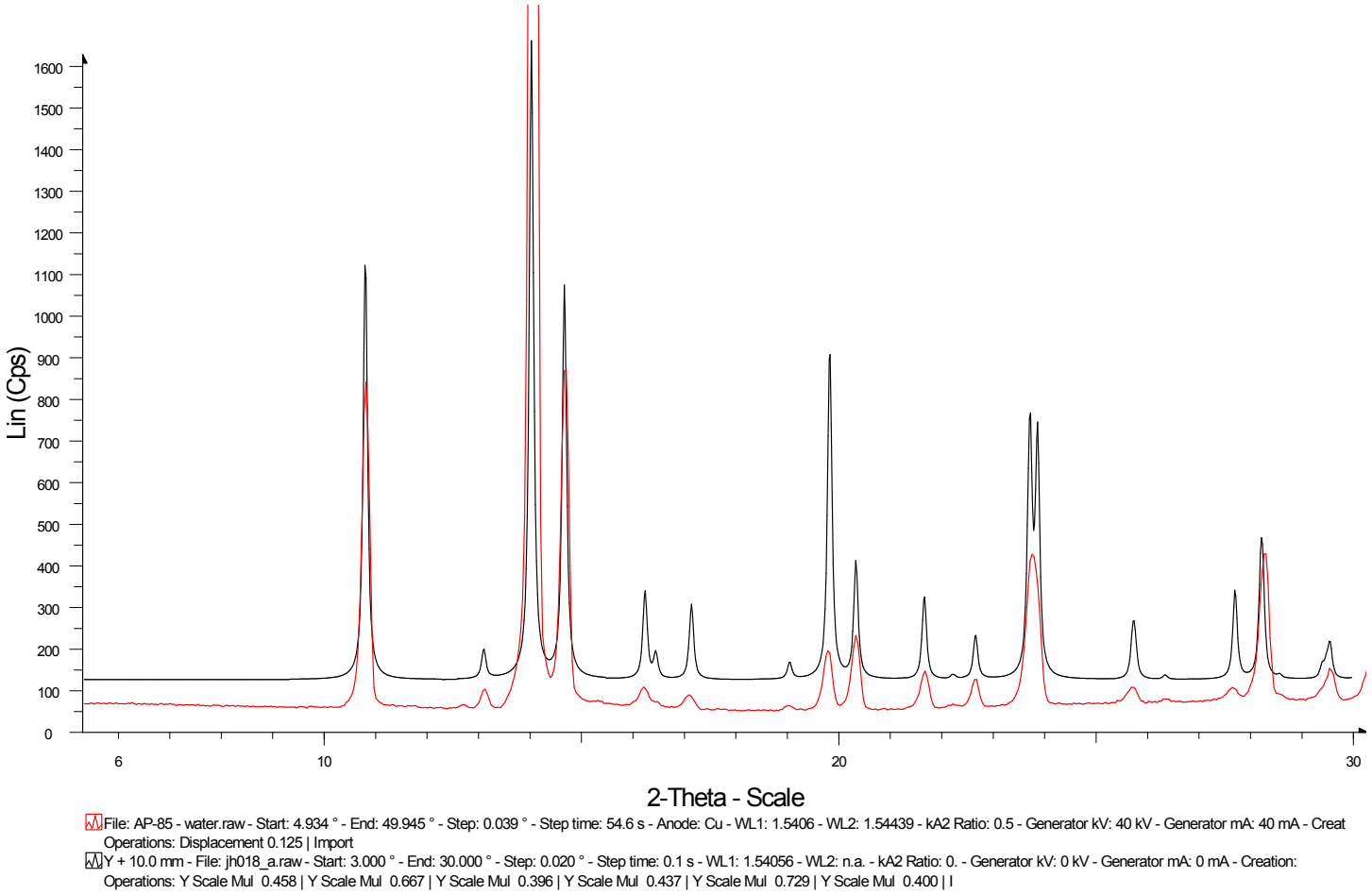


Figure S22. Overlay of x-ray powder diffraction patterns for *rac*-allylalanine monohydrate (red curve, lower) and (*S*)-allylalanine monohydrate (black curve, upper).