Electronic Supplementary Material (ESI) for Chemical Communications.

Electronic Supplemental Information for:

Dual Space Divergence in Small Molecule Quasiracemates: Benzoyl Leucine and Phenylalanine Assemblies

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SI 1. Synthesis of Materials

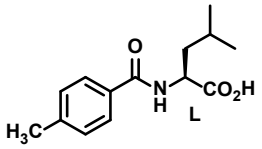
General Considerations

All chemicals and solvents were purchased from the Sigma-Aldrich Chemical Co. and VWR Scientific and used as received without further purification unless stated otherwise. ^{1}H NMR spectral data were recorded with a 400 MHz JEOL 400SS spectrometer using the Delta software (4.3.6.0). Spectral data are referenced using the solvent residual signal as an internal standard, and chemical shift values are expressed as δ values (ppm) and the value of coupling constants (*J*) in Hertz (Hz). The following abbreviations were used for signal multiplicities: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet; and br, broad.

Material Preparation

The synthetic strategies used to prepare the 4-substituted benzoyl amino acid derivatives were adapted from previously reported methods.[1] The following general procedure, as described for *N*-(*p*-methylbenzoyl)-L-leucine, was used to generate the homologous series of benzoyl amino acids.

N-(*p*-methylbenzoyl)-L-leucine, L-**1**-CH_3

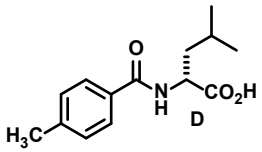


^{1}H-NMR (Acetone-*d*6): δ 7.80 (d, *J*=8.2 Hz, 2H, Ar-H); 7.7 (bd, *J*=7.8 Hz, 1H, N-H); 7.23 (d, *J*=8.2 Hz, 2H, Ar-H); 4.71 (ddd, *J*= 10.2 Hz, 7.8 Hz, 4.6 Hz, 1H, CH); 2.34 (s, 3H, CH_3); 1.88-1.65 (m, 3H, CH and CH_2); 0.95 (d, *J*=6.4 Hz, 3H, CH_3); 0.94 (d, *J*=6.4 Hz, 3H, CH_3).

L-Leucine (0.2049 g, 1.56 mmol) and 1.55 mL of 1M NaOH (1.55 mmol) were added to a 50 mL round-bottom flask and stirred at room temperature for 5-10 minutes until dissolution. *p*-Toluoyl chloride (0.2566 g, 1.66 mmol) and 1.55 mL of 1M NaOH (1.55 mmol) were added to the clear colorless homogenous mixture simultaneously over 15 minutes and allowed to stir at 0°C for 2 hours. The reaction was then heated at ~70°C for an additional hour, cooled to room temperature, and acidified at 0°C with 6M HCl to a pH of 2. The mixture was extracted with 2x10 mL of EtOAc, the organic layers combined, dried over anhydrous $MgSO_4$ and reduced under *vacuo* to give L-**1**-CH_3 as a white solid (0.336 g, 1.14 mmol, 73% yield).

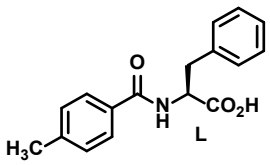
Reaction yields of 65-95% were attained for the CH_3, Cl, H, and CF_3 benzoyl leucine and phenylalanine derivatives.

N-(*p*-methylbenzoyl)-D-leucine, D-**1**-CH_3



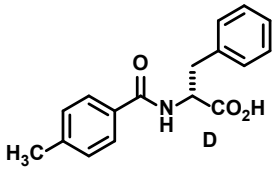
^{1}H-NMR (Acetone-*d*6): δ 7.80 (d, *J*=8.2 Hz, 2H, Ar-H); 7.72 (bd, *J*=8.2, 1H, N-H); 7.24 (d, *J*=8.2 Hz, 2H, Ar-H); 4.71 (ddd, *J*=10.1 Hz, 8.2 Hz, 5.0 Hz, 1H, CH); 2.36 (s, 3H, CH_3); 1.87-1.67 (m, 3H, CH and CH_2); 0.95 (d, *J*=6.4 Hz, 3H, CH_3); 0.94 (d, *J*=6.4 Hz, 3H, CH_3).

N-(*p*-methylbenzoyl)-L-phenylalanine, L-**2**-CH_3



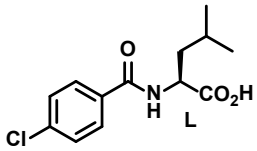
^{1}H-NMR (Acetone-*d*6): δ 7.70 (d, *J*=8.2 Hz, 2H, Ar-H); 7.65 (bd, *J*=7.8 Hz, 1H, N-H); 7.31 (d, *J*=8.2 Hz, 2H, Ar-H); 7.28-7.14 (m, 5 H, Ar-H); 4.88 (ddd, *J*= 9.2 Hz, 7.8 Hz, 5.0 Hz, 1H, CH); 3.30 (dd, *J* = 13.8, 5.0 Hz, 1H, CH_2); 3.13 (dd, *J* = 13.8, 9.2 Hz, 1H, CH_2); 2.33 (s, 3H, CH_3).

N-(*p*-methylbenzoyl)-D-phenylalanine, D-**2**-CH_3



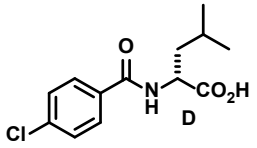
^{1}H-NMR (Acetone-*d*6): δ 7.71 (d, *J*=8.1 Hz, 2H, Ar-H); 7.65 (bd, *J* = 8.0 Hz, 1H, N-H); 7.31 (d, *J*=8.1 Hz, 2H, Ar-H); 7.28-7.14 (m, 5H, Ar-H); 4.88 (ddd, *J*=9.6 Hz, 8.0 Hz, 5.0 Hz, 1H, CH); 3.30 (dd, *J* = 13.8, 5.0 Hz, 1H, CH_2); 3.13 (dd, *J*=13.8, 9.6 Hz, 1H, CH_2); 2.33 (s, 3H, CH_3).

N-(*p*-chlorobenzoyl)-L-leucine, L-**1**-Cl



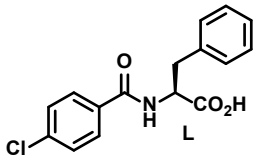
^{1}H-NMR (Acetone-*d*6): δ 8.02 (bd, *J*=8.4 Hz, 1H, N-H); 7.91 (d, *J*=8.2 Hz, 2H, Ar-H); 7.46 (d, *J*=8.2 Hz, 2H, Ar-H); 4.70 (ddd, *J*=10.1, 8.4, 5.0 Hz, 1H, CH); 1.87-1.65 (m, 3H, CH and CH_2); 0.94 (d, *J* = 6.4 Hz, 3H, CH_3); 0.92 (d, *J*=6.4 Hz, 3H, CH_3).

N-(*p*-chlorobenzoyl)-D-leucine, D-**1**-Cl



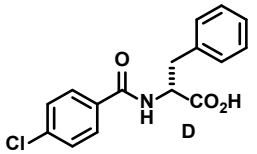
^{1}H-NMR (Acetone-*d*6): δ 8.01 (bd, *J*=8.2 Hz, 1H, N-H); 7.91 (d, *J*=8.7 Hz, 2H, Ar-H); 7.46 (d, *J*=8.7 Hz, 2H, Ar-H); 4.71 (ddd, *J*=10.1, 8.2, 5.0 Hz, 1H, CH); 1.87-1.65 (m, 3H, CH and CH_2); 0.94 (d, *J* = 6.4 Hz, 3H, CH_3); 0.92 (d, *J*=6.4 Hz, 3H, CH_3).

N-(*p*-chlorobenzoyl)-L-phenylalanine, L-**2**-Cl



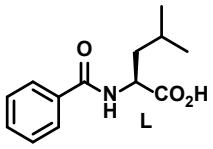
^{1}H-NMR (Acetone-*d*6): δ 7.88 (bd, *J*=8.6 Hz, 1H, N-H); 7.81 (d, *J*=8.2 Hz, 2H, Ar-H); 7.45 (d, *J*=8.2 Hz, 2H, Ar-H); 7.35-7.14 (m, 5 H, Ar-H); 4.99 (ddd, *J*= 9.0, 8.6, 5.0 Hz, 1H, CH); 3.31 (dd, *J*=13.8, 5.0 Hz, 1H, CH_2); 3.12 (dd, *J* = 13.8, 9.0 Hz, 1H, CH_2).

N-(*p*-chlorobenzoyl)-D-phenylalanine, D-**2**-Cl



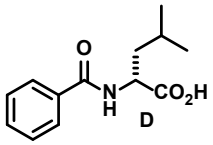
^{1}H-NMR (Acetone-*d*6): δ 7.89 (bd, *J*=8.2 Hz, 1H, N-H); 7.81 (d, *J*=8.6 Hz, 2H, Ar-H); 7.44 (d, *J*=8.6 Hz, 2H, Ar-H); 7.35-7.14 (m, 5 H, Ar-H); 4.93 (ddd, *J*=9.1, 8.2, 5.1 Hz, 1H, CH); 3.31 (dd, *J*=13.8, 5.1 Hz, 1H, CH_2); 3.12 (dd, *J*=13.8, 9.1 Hz, 1H, CH_2).

N-benzoyl-L-leucine, L-**1**-H



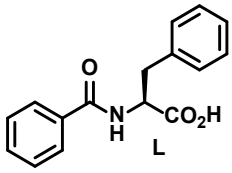
^{1}H-NMR (Acetone-*d*6): δ 7.95-7.87 (m, 2H, Ar-H); 7.80 (bd, *J*=8.2 Hz, 1H, N-H); 7.54-7.47 (m, 1H, Ar-H); 7.46-7.40 (m, 2H, Ar-H); 7.35-7.14 (m, 5 H, Ar-H); 4.93 (ddd, *J*=10.1, 8.2, 4.6 Hz, 1H, CH); 1.88-1.65 (m, 3H, CH and CH_2); 0.95 (d, *J* = 6.4 Hz, 3H, CH_3); 0.94 (d, *J* = 6.4 Hz, 3H, CH_3).

N-benzoyl-D-leucine, D-**1**-H



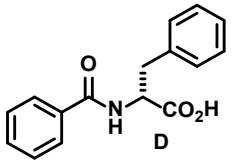
^{1}H-NMR (Acetone-*d*6): δ 7.95-7.87 (m, 2H, Ar-H); 7.78 (bd, *J*=8.2 Hz, 1H, N-H); 7.54-7.47 (m, 1H, Ar-H); 7.46-7.40 (m, 2H, Ar-H); 7.35-7.14 (m, 5H, Ar-H); 4.91 (ddd, *J*=10.1, 8.2 Hz, 4.9 Hz, 1H, CH); 1.88-1.65 (m, 3H, CH and CH_2);0.94 (d, *J*=6.4 Hz, 3H, CH_3); 0.94 (d, *J*=6.4 Hz, 3H, CH_3).

N-benzoyl-L-phenylalanine, L-**2**-H



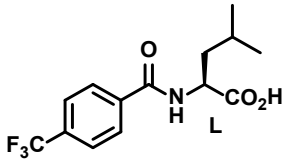
^{1}H-NMR (Acetone-*d*6): δ 7.75-7.80 (m, 2H, Ar-H); 7.75 (bd, *J*=8.0 Hz, 1H, N-H); 7.53-7.37 (m, 1H, Ar-H); 7.36-7.15 (m,5H, Ar-H); 4.91 (ddd, *J*=9.2 Hz, 8.0 Hz, 5.0 Hz, 1H, CH); 3.32 (dd, *J*=13.8, 5.0 Hz, 1H, CH_2); 3.14 (dd, *J*=13.8, 9.2 Hz, 1H, CH_2).

N-benzoyl-D-phenylalanine, D-**2**-H



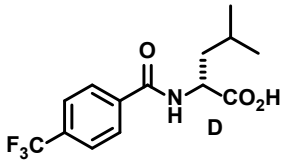
^{1}H-NMR (Acetone-*d*6): δ 7.77-7.82 (m, 2H, Ar-H); 7.75 (bd, *J*=8.1 Hz, 1H, N-H); 7.53-7.37 (m, 1H, Ar-H); 7.36-7.15 (m,5H, Ar-H); 4.90 (ddd, *J*=9.2, 8.1, 4.8 Hz, 1H, CH); 3.32 (dd, *J* = 13.7, 4.8 Hz, 1H, CH_2); 3.14 (dd, *J*=13.7, 9.2 Hz, 1H, CH_2).

N-(*p*-trifluoromethylbenzoyl)-L-leucine, L-**1**-CF_3



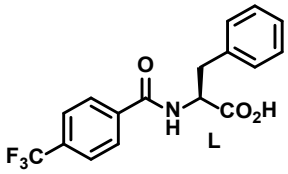
^{1}H-NMR (Acetone-*d*6): δ 8.10 (d, *J*=8.2 Hz, 2H, Ar-H); 8.05 (bd, *J*=8.3 Hz, 1H, N-H); 7.80 (d, *J*=8.2 Hz, 2H, Ar-H); 4.73 (ddd, *J*=10.1, 8.3, 5.0 Hz, 1H, CH); 1.88-1.69 (m, 3H, CH and CH_2); 0.96 (d, *J*=6.4 Hz, 3H, CH_3); 0.94 (d, *J*=6.4 Hz, 3H, CH_3).

N-(*p*-trifluoromethylbenzoyl)-D-leucine, D-**1**-CF_3



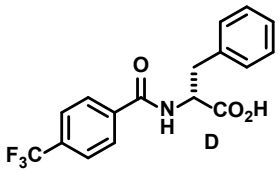
^{1}H-NMR (Acetone-d6): δ 8.10 (d, *J*=8.2 Hz, 2H, Ar-H); 8.05 (bd, *J*=8.2 Hz, 1H, N-H); 7.80 (d, *J*=8.2 Hz, 2H, Ar-H); 4.73 (ddd, *J*=10.1, 8.2, 5.0 Hz, 1H, CH); 1.88-1.68 (m, 3H, CH and CH_2); 0.95 (d, *J*=6.4 Hz, 3H, CH_3); 0.94 (d, *J*=6.4 Hz, 3H, CH_3).

N-(*p*-trifluoromethylbenzoyl)-L-phenylalanine, L-**2**-CF_3



^{1}H-NMR (Acetone-*d*6): δ 8.17 (bd, *J*=8.0 Hz, 1H, N-H); 8.02 (d, *J*=8.3 Hz, 2H, Ar-H); 7.75 (d, *J*=8.3, 2H, Ar-H); 7.37-7.09 (m, 5H, Ar-H); 4.75 (ddd, *J*=9.2, 8.0 and 4.6 Hz, 1H, CH); 3.29 (dd, *J*=13.8 Hz and 4.6 Hz, 1H, CH_2); 3.14 (dd, *J*=13.8 and 9.2 Hz, 1H, CH_2).

N-(*p*-trifluoromethylbenzoyl)-D-phenylalanine, D-**2**-CF_3



^{1}H-NMR (Acetone-*d*6): δ 8.18 (bd, J=7.8 Hz, 1H, N-H); 8.02 (d, *J*=8.2 Hz, 2H, Ar-H); 7.76 (d, J=8.2, 2H, Ar-H); 7.34-7.08 (m, 5H, Ar-H); 4.69 (ddd, *J*=9.1, 7.8, 4.5 Hz, 1H, CH); 3.29 (dd, *J*=13.8 Hz, 4.5 Hz, 1H, CH_2); 3.12 (dd, *J*= 13.8 and 9.1 Hz, 1H, CH_2).

Cocrystal Synthesis

The racemic and quasiracemic cocrystals prepared for this study used slow evaporation of methanolic solutions with equimolar mixtures (10-20 mg scale) of the L and D forms of the components. Crystals suitable for X-ray diffraction and DSC studies were retrieved after 1-5 days.

SI 2. Hot Stage Thermomicroscopy

The hot-stage microscopy experiments were performed using an optical polarizing microscope (*Olympus SZX10*) equipped with an *Instec HCS 302* hot stage connected to an *Instec mK2000* temperature controller. Micrographs were collected under a range of magnifications (3.0-6.3x) using an attached video camera. The hot stage was controlled by the WINDV software package (V1.0.120820). Pairs of benzoyl amino acid components were analyzed for cocrystallization behavior. Samples were prepared using standard glass microscope slides and cover slips. The higher melting point component was deposited first by heating the sample to the melting point temperature and drawing the sample under the cover slip. After cooling, the lower melting point component was deposited similarly to create a contact interface between the two samples. These bimolecular samples were heated at a ramp rate of 2-5°C/min until complete melting of the sample occurred. Each CH_3/Cl and H/CF_3 family of compounds (4 racemates and 6 quasiracemates) was processed using the video-assisted hot stage technique.

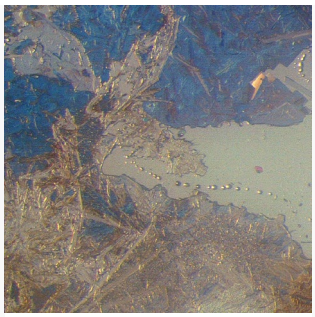
Hot Stage Images of Racemic and Quasiracemic Pairs

CH_3/Cl System

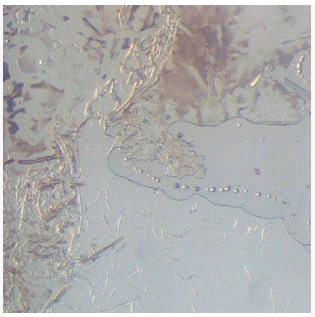
Racemic Mixtures

L-**1**-CH_3 (left)

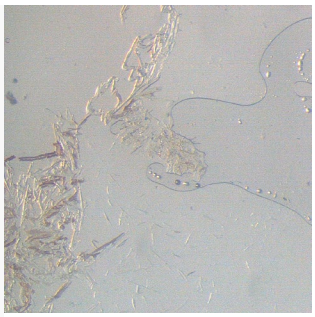
D-**1**-CH_3 (right)



81.6 °C

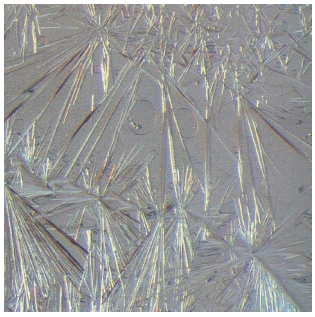
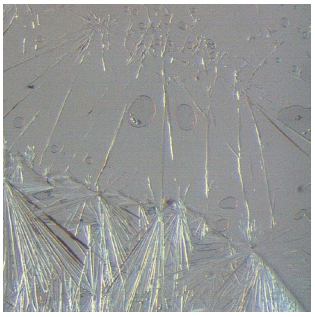
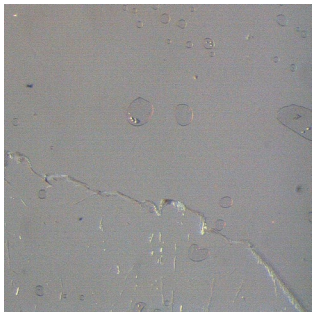


113.5 °C



121.9 °C

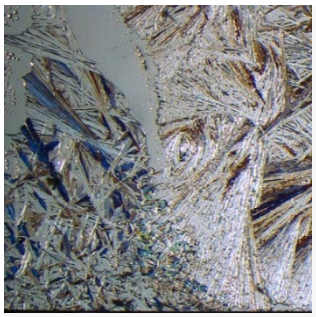
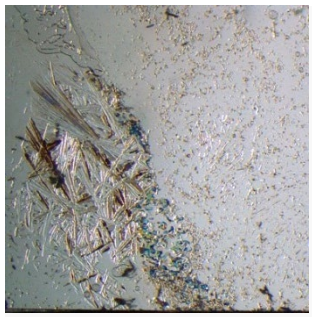
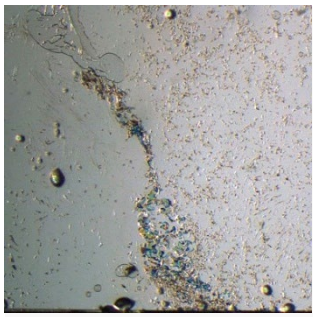
L-**1**-Cl (left)

D-**1**-Cl (right)

99.8° 136.1° 145.4°

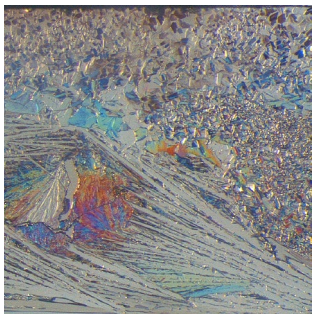
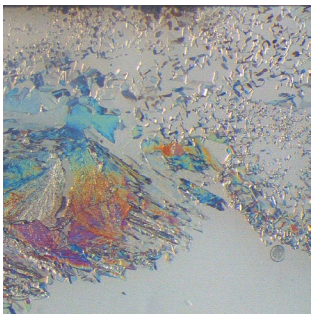
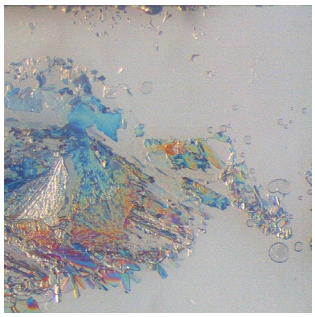
L-**2**-CH_3 (left)

D-**2**-CH_3 (right)

154.6 °C 165.6 °C 166.4 °C

L-**2**-Cl (left)

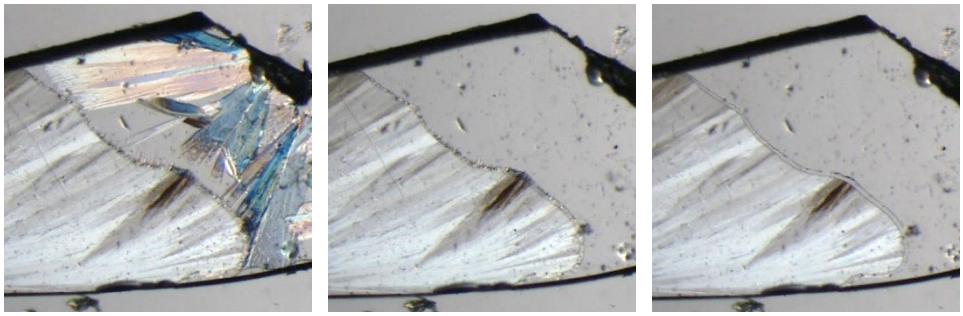
D-**2**-Cl (right)

118.7 °C 186.0 °C 197.2 °C

Quasiracemates

D-**1**-CH_3 (right)

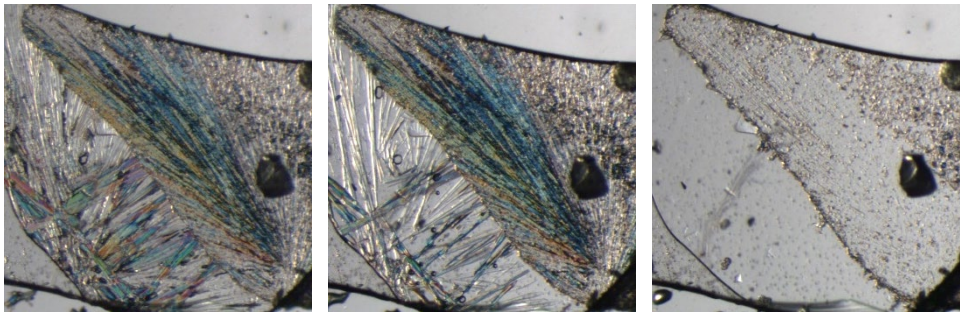
L-**1**-Cl (left)



115.3 °C | 130.7 °C | 153.0 °C

L-**2**-CH_3 (left)

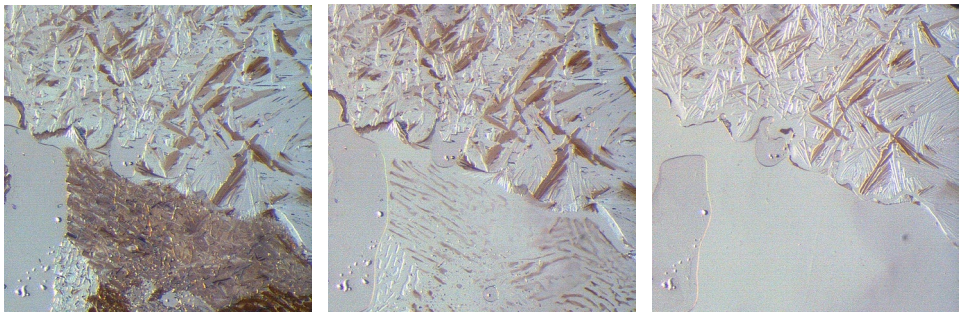
D-**2**-Cl (right)



138.4 °C | 152.8 °C | 162.0 °C

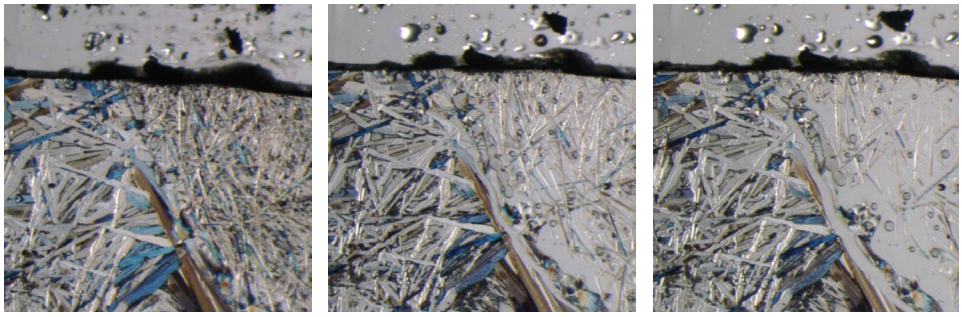
L-**1**-CH_3 (left)

D-**2**-CH_3 (right)



116.7 °C | 140.6 °C | 145.0 °C

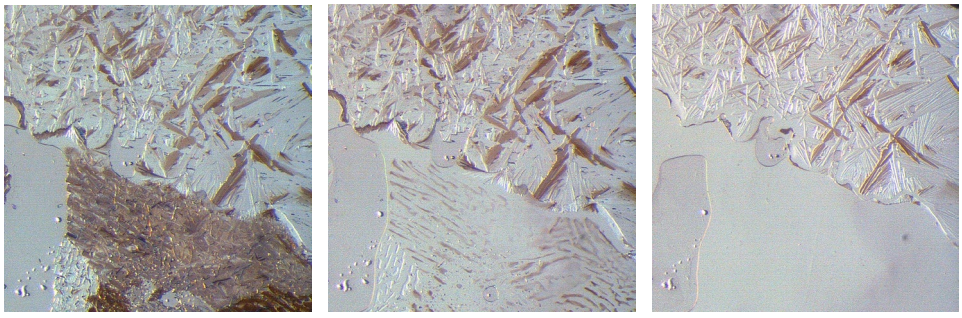
L-**1**-Cl (left)



D-**2**-Cl (right)

116.7 °C	140.6 °C	145.0 °C

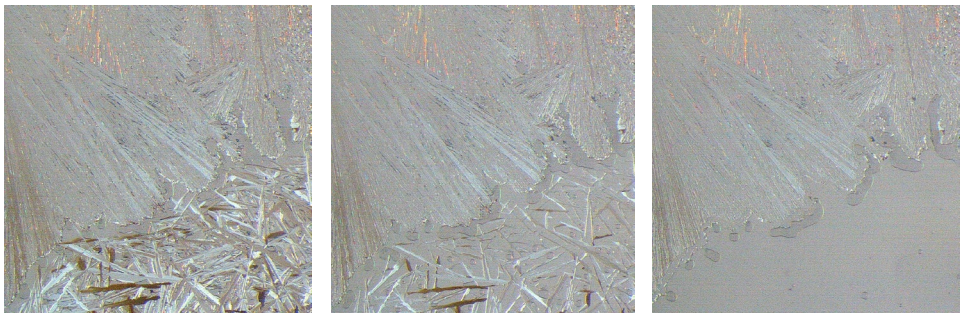
L-**1**-CH_3 (left)



D-**2**-Cl (right)

116.7 °C	140.6 °C	145.0 °C

L-**1**-Cl (left)



D-**2**-CH_3 (right)

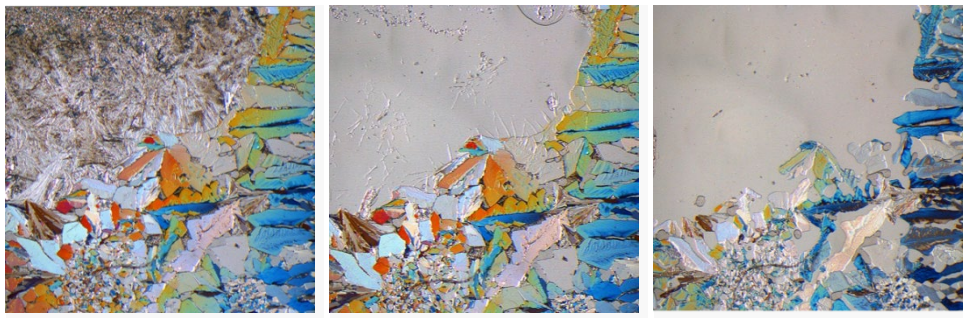
99.7 °C	142.7 °C	153.7 °C

H/CF_3 System

Racemic Mixtures

L-**1**-H (left)

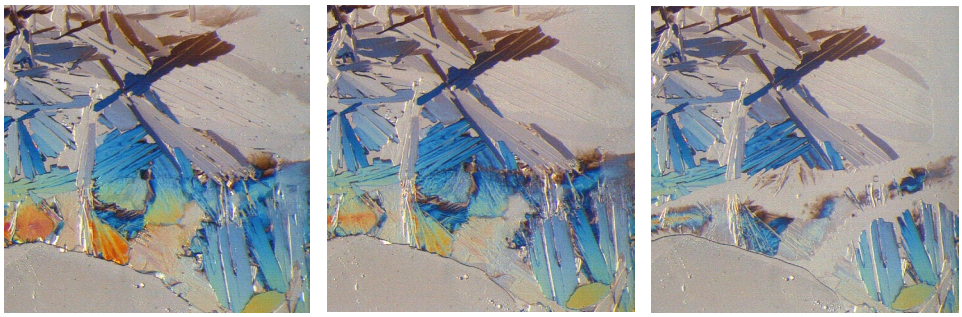
D-**1**-H (right)



63.3 °C 80.9 °C 129.0 °C

L-**1**-CF_3 (top)

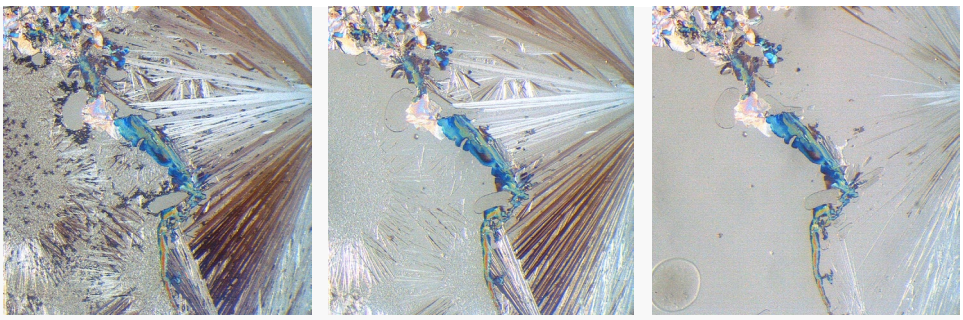
D-**1**-CF_3 (bottom)



98.7 °C 150.9 °C 162.8 °C

L-**2**-H (left)

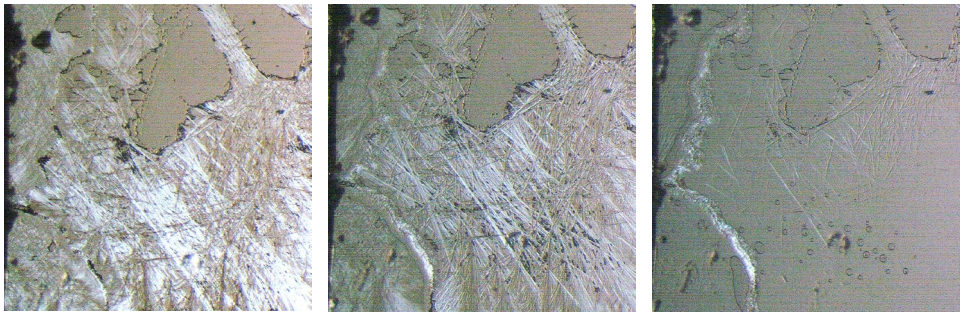
D-**2**-H (right)



69.2 °C 103.9 °C 137.3 °C

L-**2**-CF_3 (left)

D-**2**-CF_3 (right)

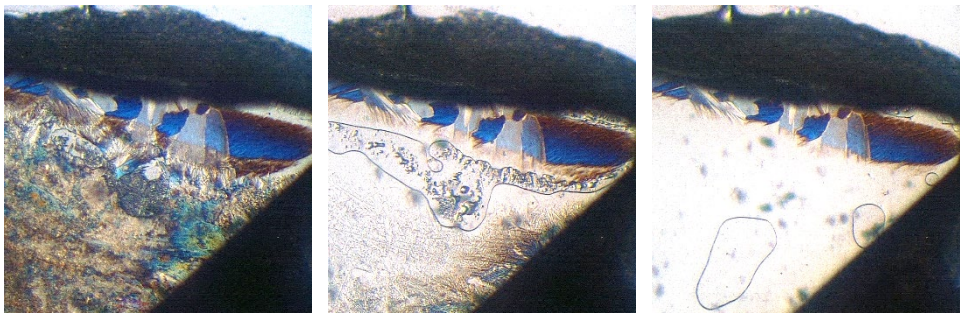


148.4 °C | 178.9 °C | 189.0 °C

Quasiracemates

L-**1**-CF_3 (top)

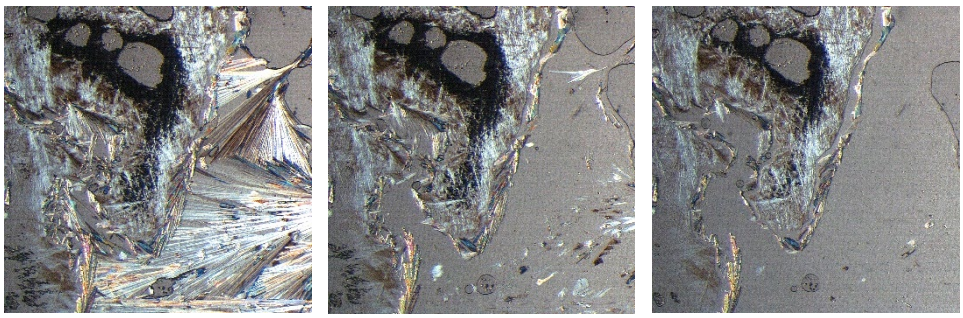
D-**1**-H (bottom)



40.2 °C | 80.9 °C | 98.0 °C

L-**2**-H (left)

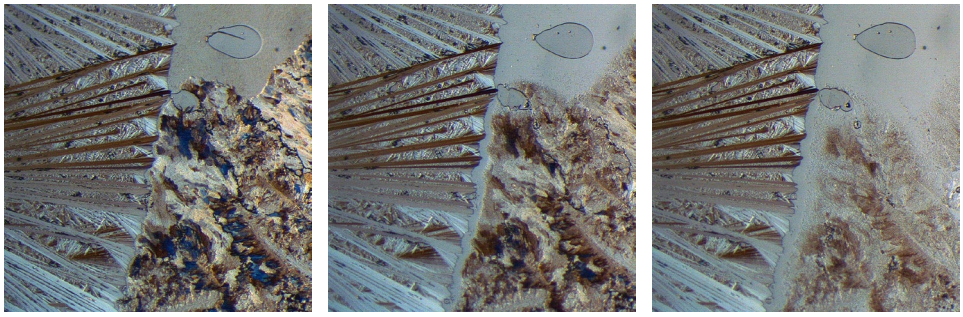
D-**2**-CF_3 (right)



111.7 °C | 132.2 °C | 145.0 °C

L-**1**-H (left)

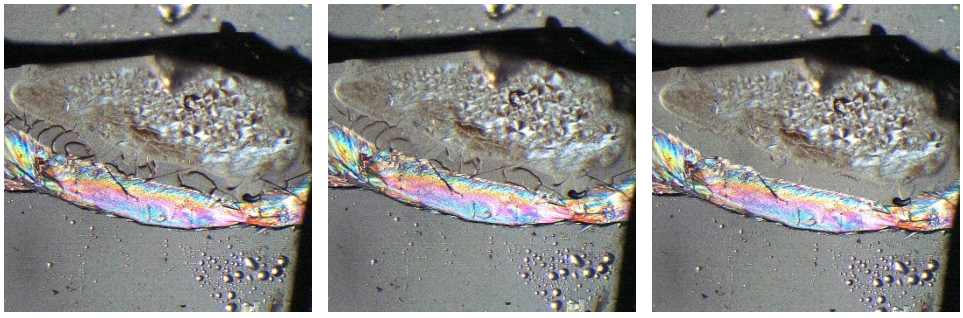
D-**2**-H (right)



41.0 °C | 75.2 °C | 80.2 °C

L-**1**-CF_3 (left)

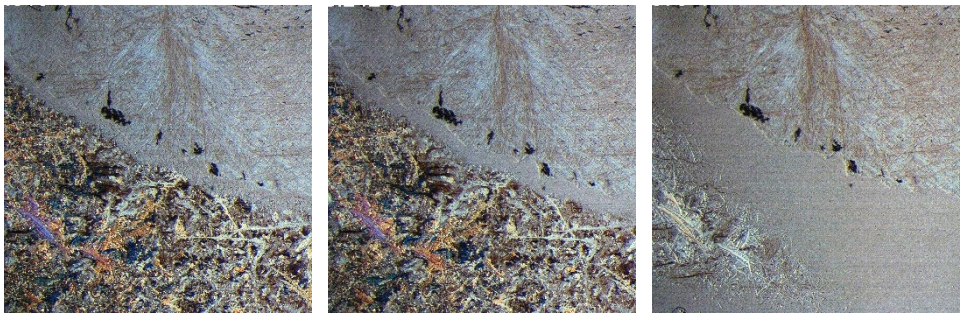
D-**2**-CF_3 (right)



124.7 °C | 144.8 °C | 169.6 °C

L-**1**-H (bottom)

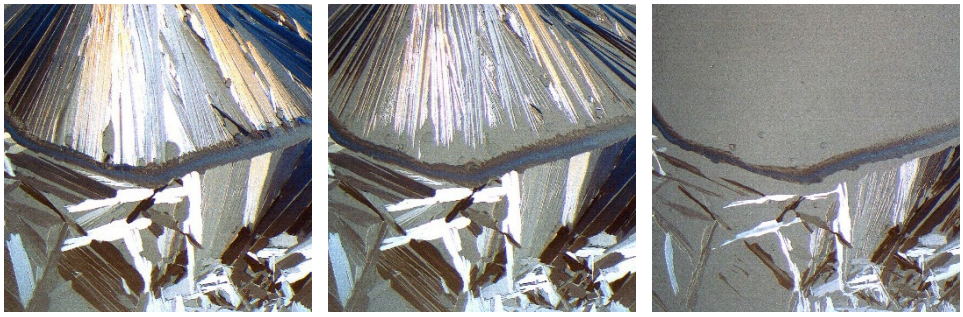
D-**2**-CF_3 (top)



39.8 °C | 63.2 °C | 88.6 °C

D-**2**-H (top)

L-**1**-CF_3 (bottom)



124.7 °C 144.8 °C 169.6 °C

SI 3. Crystallographic Data

Crystallographic details for each benzoyl amino acid racemate and quasiracemate are summarized in Table S1. X-ray data were collected on a Bruker Venture D8 diffractometer using phi and omega scans with graphite monochromatic Cu*Ka* (λ = 1.54178 Å) radiation. Data sets were corrected for Lorentz and polarization effects as well as absorption. The criterion for observed reflections is $I > 2s(I)$. Lattice parameters were determined from least-squares analysis and reflection data. Empirical absorption corrections were applied using SADABS[2]. Structures were solved by direct methods and refined by full-matrix least-squares analysis on F^2 using OLEX2[3] equipped with SHELXT[4]. All non-hydrogen atoms were refined anisotropically by full-matrix least-squares on F^2 using the SHELXL[5] program. H atoms (for NH and OH) were located in difference Fourier synthesis and refined isotropically with independent N-H and O-H distances or restrained to 0.85(2) Å. The remaining H atoms were included in idealized geometric positions with U_{iso}=1.2U_{eq} of the atom to which they were attached (U_{iso}=1.5U_{eq} for methyl groups). Molecular configurations were compared to the known chirality of the amino acid starting material and estimated Flack parameters[6,7]. Where applicable, atomic coordinates were inverted to achieve correct structural configurations. Hydrogen bond parameters are given in Table S2.

Table S1. Crystallographic Data for Racemic and Quasiracemic Leucine **1** and Phenylalanine **2**.

	(±)-**1**-CH_3	(±)-**1**-Cl	(±)-**2**-CH_3	(±)-**2**-Cl
Crystal data				
CCDC deposit no.	2312799	2312800	2312801	2312802
Empirical formula	$C_{14}H_{19}NO_3$	$C_{13}H_{16}ClNO_3$	$C_{17}H_{17}NO_3$	$C_{16}H_{14}ClNO_3$
Crystal System, space group	Monoclinic $P2_1/c$ (no. 14)	Monoclinic $P2_1/c$ (no. 14)	Monoclinic $P2_1/n$ (no. 14)	Monoclinic $P2_1/c$ (no. 14)
M_r	249.31	269.72	283.31	303.73
a, Å	8.4622(7)	8.5014(4)	10.8048(5)	10.9337(3)
b, Å	17.4106(13)	16.7568(8)	10.1624(5)	9.8520(3)
c, Å	10.0167(7)	10.0698(5)	14.3028(6)	14.5888(5)
α, deg	90	90	90	90
β, deg	109.344(5)	105.680(3)	110.088(2)	111.998(2)
γ, deg	90	90	90	90
V, (Å^3)	1392.47(19)	1381.12(12)	1474.95(12)	1457.08(8)
Z, *Z'*	4, 1	4, 1	4, 1	4, 1
D_{calc} (g cm^{-3})	1.189	1.297	1.276	1.385
μ (mm^{-1}), Cu $K\alpha$	0.677	2.463	0.712	2.408
F_{000}	537	568	600	632
temp (K)	100(2)	100(2)	100(2)	100(2)
Crystal form, color	plate, colorless	needle, colorless	block, colorless	plate, colorless
Crystal size, mm	0.31x0.18x0.09	0.24x0.04x0.03	0.21x0.18x0.07	0.19x0.07x0.02
Data collection				
Diffractometer	Bruker Venture D8 CCD	Bruker Venture D8 CCD	Bruker Venture D8 CCD	Bruker Venture D8 CCD
T_{min}/ T_{max}	0.754/0.625	0.753/0.556	0.754/0.683	0.754/0.637
No. of refls. (meas., uniq., and obs.)	27050/2753/1945	17953/2515/1936	33896/2907/2782	27695/2870/2572
R_{int}	0.1046	0.0793	0.0274	0.0388
ϑ_{max} (°)	72.39	68.24	72.136	72.186
Refinement				
$R/R^2\omega$ (obs data)	0.0559/0.1299	0.0607/0.1426	0.0327/0.0795	0.0284/0.0670
$R/R^2\omega$ (all data)	0.0897/0.1522	0.0821/0.1567	0.0341/0.0806	0.0329/0.0695
S	1.062	1.064	1.046	1.059
No. of refls.	2753	2515	2907	2870
No. of parameters	172	171	197	196
$\Delta\rho_{max/min}$ (e·Å^{-3})	0.441/-0.381	0.456/-0.327	0.297/-0.198	0.264/-0.211
flack	-	-	-	-

Table S1. Crystallographic Data for Racemic and Quasiracemic Leucine **1** and Phenylalanine **2**. (cont)

	D-**1**-CH_3/L-**1**-Cl	D-**2**-CH_3/L-**2**-Cl	L-**1**-CH_3/D-**2**-CH_3	D-**1**-Cl/L-**2**-Cl
Crystal data				
CCDC deposit no.	2312803	2312804	2312805	2312806
Empirical formula	$C_{27}H_{35}ClN_2O_6$	$C_{33}H_{31}ClN_2O6$	$C_{31}H_{36}N_2O_6$	$C_{29}H_{30}Cl_2N_2O_6$
Crystal System, space group	Monoclinic $P2_1$ (no. 4)	Monoclinic $P2_1$ (no. 4)	Monoclinic $P2_1$ (no. 4)	Monoclinic $P2_1$ (no. 4)
M_r	519.02	587.05	532.62	573.45
a, Å	8.5052(3)	10.8824(6)	10.6827(8)	10.7438(4)
b, Å	16.9899(7)	10.0217(6)	9.9438(8)	9.7103(3)
c, Å	10.0551(4)	14.4325(8)	14.4410(11)	14.4644(5)
α, deg	90	90	90	90
β, deg	107.507(2)	111.003(2)	110.660(3)	110.923(2)
γ, deg	90	90	90	90
V, (Å^3)	1385.68(9)	1469.44(15)	1435.37(19)	1409.50(9)
Z, *Z'*	2, 1	2, 1	2, 1	2, 1
D_{calc} (g cm^{-3})	1.244	1.327	1.232	1.351
μ (mm^{-1}), Cu $K\alpha$	1.567	1.551, Cu $K\alpha$	0.694	2.451
F_{000}	552	616	568	600
temp (K)	100(2)	100(2)	100(2)	100(2)
Crystal form, color	needle, colorless	block, colorless	plate, colorless	needle, colorless
Crystal size, mm	0.39x0.07x0.04	0.50 x 0.20 x 018	0.23x0.21x0.09	0.49x0.08x0.05
Data collection				
Diffractometer	Bruker Venture D8 CCD	Bruker Venture D8 CCD	Bruker Venture D8 CCD	Bruker Venture D8 CCD
T_{min}/ T_{max}	0.753/0.603	0.754/0.6355	0.754/0.632	0.754/0.634
No. of refls. (meas., uniq., and obs.)	24521/5041/4819	35012/5686/5610	24786/5455/5281	28644/5253/4917
R_{int}	0.0335	0.0369	0.0306	0.0486
ϑ_{max} (°)	68.339	72.079	72.271	70.073
Refinement				
$R/R^2\omega$ (obs data)	0.0354/0.0938	0.0363/0.0959	0.0364/0.0988	0.0278/0.0638
$R/R^2\omega$ (all data)	0.0373/0.0955	0.0359/0.0962	0.0378/0.1003	0.0315/0.0658
S	1.046	1.068	1.052	1.040
No. of refls.	5045	5686	5455	5253
No. of parameters	342	392	368	366
$\Delta\rho_{max/min}$ (e·Å^{-3})	0.253/-0.199	0.350/-0.346	0.476/-0.216	0.198/-0.211
flack	0.108(5)	0.123(6)	0.10(6)	0.050(6)

Table S1. Crystallographic Data for Racemic and Quasiracemic Leucine **1** and Phenylalanine **2**. (cont)

	D-**1**-CH_3/L-**2**-Cl	D-**1**-Cl/L-**2**-CH_3
Crystal data		
CCDC deposit no.	2312807	2312808
Empirical formula	$C_{30}H_{33}ClN_2O_6$	$C_{30}H_{33}ClN_2O_6$
Crystal System, space group	Monoclinic $P2_1$ (no. 4)	Monoclinic $P2_1$ (no. 4)
M_r	553.03	553.03
a, Å	10.7599(5)	10.7094(3)
b, Å	9.7943(5)	9.8205(3)
c, Å	14.5273(6)	14.5002(4)
α, deg	90	90
β, deg	111.649(2)	111.2860(1)
γ, deg	90	90
V, (Å^3)	1422.98(9)	1420.97(7)
Z, *Z'*	2, 1	2, 1
D_{calc} (g cm^{-3})	1.291	1.293
μ (mm^{-1}), Cu $K\alpha$	1.564	1.566
F_{000}	584	584
temp (K)	100(2)	100(2)
Crystal form, color	plate, colorless	needle, colorless
Crystal size, mm	0.13x0.12x0.05	0.49x0.08x0.05
Data collection		
Diffractometer	Bruker Venture D8 CCD	Bruker Venture D8 CCD
T_{min}/ T_{max}	0.754/0.634	0.754/0.634
No. of refls. (meas., uniq., and obs.)	47892/5386/4855	31726/5553/5264
R_{int}	0.0739	0.0409
ϑ_{max} (°)	72.240	72.206
Refinement		
$R/R^2\omega$ (obs data)	0.0380/0.0801	0.0282/0.0693
$R/R^2\omega$ (all data)	0.0465/0.0838	0.0305/0.0706
S	1.047	1.048
No. of refls.	5386	5553
No. of parameters	367	368
$\Delta\rho_{max/min}$ (e·Å^{-3})	0.199/-0.236	0.170/-0.188
flack	0.056(8)	0.012(5)

Table S1. Crystallographic Data for Racemic and Quasiracemic Leucine **1** and Phenylalanine **2**. (cont)

	(±)-**1**-H	(±)-**1**-CF_3	(±)-**2**-H	D-**2**-H/L-**2**-CF_3
Crystal data				
CCDC deposit no.	2312809	2312810	2312811	2312812
Empirical formula	$C_{13}H_{17}NO_3$	$C_{14}H_{16}F_3NO_3$	$C_{16}H_{15}NO_3$	$C_{33}H_{29}F_3N_2O_6$
Crystal System, space group	Monoclinic $P2_1/c$ (no. 14)	Monoclinic $P2_1/c$ (no. 14)	Monoclinic $P2_1/c$ (no. 14)	Monoclinic $P2_1$ (no. 4)
M_r	235.27	303.28	269.29	606.58
a, Å	10.7023(4)	8.9660(4)	11.2259(5)	12.9498(11)
b, Å	9.0828(3)	17.0296(7)	9.0079(4)	9.6063(8)
c, Å	13.3370(5)	10.371(4)	14.0101(6)	13.1925(11)
α, deg	90	90	90	90
β, deg	103.692(2)	107.371(2)	107.097(1)	117.118(3)
γ, deg	90	90	90	90
V, (Å^3)	1259.61(8)	1467.64(11)	1354.12(10)	1460.7(2)
Z, Z'	4, 1	4, 1	4, 1	2, 1
D_{calc} (g cm^{-3})	1.241	1.373	1.321	1.379
μ (mm^{-1}), Cu $K\alpha$	0.719	1.049	0.748	0.910
F_{000}	504	632	568	632
temp (K)	100(2)	100(2)	100(2)	100(2)
Crystal form, color	plate, colorless	plate, colorless	block, colorless	prism, colorless
Crystal size, mm	0.38x0.18x0.12	0.38x0.14x0.03	0.20x0.15x0.05	0.44x0.33x0.06
Data collection				
Diffractometer	Bruker Venture D8 CCD	Bruker Venture D8 CCD	Bruker Venture D8 CCD	Bruker Venture D8 CCD
T_{min}/ T_{max}	0.753/0.648	0.753/0.625	0.753/0.676	0.753/0.639
No. of refls. (meas., uniq., and obs.)	25092/2483/2277	22194/2684/2317	23025/2643/2616	24713/5234/5093
R_{int}	0.0350	0.0445	0.0255	0.0292
ϑ_{max} (°)	72.239	68.411	72.250	68.317
Refinement				
$R/R^2\omega$ (obs data)	0.0356/0.0892	0.0600/0.1175	0.0321/0.0791	0.0261/0.0659
$R/R^2\omega$ (all data)	0.0356/0.0921	0.0704/0.1238	0.0324/0.0794	0.0273/0.0671
S	1.045	1.045	1.037	1.091
No. of refls.	2483	2484	2643	5234
No. of parameters	162	256	187	409
$\Delta\rho_{max/min}$ (e·Å^{-3})	0.236/-0.233	0.174/-0.196	0.316/-0.202	0.183/-0.205
flack	-	-	-	0.15(4)

Table S1. Crystallographic Data for Racemic and Quasiracemic Leucine **1** and Phenylalanine **2**. (cont)

	L-**1**-H/D-**2**-H	D-**1**-CF_3/L-**2**-CF_3	D-**1**-CF_3/L-**2**-H
Crystal data			
CCDC deposit no.	2312813	2312814	2312815
Empirical formula	$C_{29}H_{32}N_2O_6$	$C_{31}H_{30}F_6N_2O_6$	$C_{30}H_{31}F_3N_2O_6$
Crystal System, space group	Monoclinic $P2_1$ (no. 4)	Monoclinic $P2_1$ (no. 4)	Monoclinic $P2_1$ (no. 4)
M_r	504.56	640.57	572.57
a, Å	10.9173(3)	13.8243(8)	11.4316(8)
b, Å	9.1344(6)	9.1832(5)	9.5763(6)
c, Å	14.1599(10)	13.8585(8)	14.2272(10)
α, deg	90	90	90
β, deg	108.014(2)	117.871(3)	111.456(3)
γ, deg	90	90	90
V, (Å^3)	1342.85(16)	1555.27(16)	1449.55(17)
Z, *Z'*	2, 1	2, 1	2, 1
D_{calc} (g cm^{-3})	1.248	1.368	1.312
μ (mm^{-1}), rad. type	0.715	1.024	0.880
F_{000}	536	536	600
temp (K)	100(2)	100(2)	100(2)
Crystal form, color	block, colorless	block, colorless	needle, colorless
Crystal size, mm	0.28x0.10x0.03	0.115x0.15x0.04	0.29x0.12x0.08
Data collection			
Diffractometer	Bruker Venture D8 CCD	Bruker Venture D8 CCD	Bruker Venture D8 CCD
T_{min}/ T_{max}	0.753/0.649	0.754/0.578	0.754/0.695
No. of refls. (meas., uniq., and obs.)	43830/5446/5380	20421/6082/5418	9928/5688/5522
R_{int}	0.0230	0.0464	0.0345
ϑ_{max} (°)	75.007	72.859	72.378
Refinement			
$R/R^2\omega$ (obs data)	0.0283/0.0776	0.0514/0.1253	0.0465/0.1151
$R/R^2\omega$ (all data)	0.0286/0.0781	0.0602/0.1332	0.0479/0.1167
S	1.036	1.130	1.191
No. of refls.	5446	6082	5688
No. of parameters	378	475	426
$\Delta\rho_{max/min}$ (e·Å^{-3})	0.243/-0.166	0.403/-0.326	0.735/-0.602
flack	0.07(4)	0.06(7)	0.07(3)

Table S2. Hydrogen-Bond Parameters for Leucine/Phenylalanine Racemic and Quasiracemic Crystal Structures.

Compound	Hydrogen Bond Type	D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (°)	Symmetry operator
(±)-**1**-CH_3	II	O2–H2···O3	0.91(3)	1.74(3)	2.641(2)	172(3)	1-*x*, -*y*, 1-*z*
		N1–H1···O1	0.81(3)	2.15(3)	2.642(2)	166(2)	*x*, 0.5-*y*, *z*-0.5
(±)-**1**-Cl	II	O2–H2···O3	0.92(4)	1.71(4)	2.619(3)	167(4)	1-*x*, -*y*, 1-*z*
		N1–H1···O1	0.79(4)	2.17(4)	2.948(3)	167(4)	*x*, 0.5-*y*, *z*-0.5
(±)-**2**-CH_3	I	O2–H2···O1	0.906(15)	1.690(15)	2.5899(10)	171.7(13)	0.5-*x*, *y*-0.5, 0.5-*z*
		N1–H1···O3	0.889(14)	2.134(14)	3.0084(11)	167.7(12)	1-*x*, 1-*y*, 1-*z*
(±)-**2**-Cl	I	O2–H2···O3	0.813(19)	1.791(19)	2.6024(13)	175.7(18)	1-*x*, *y*-0.5, 0.5-*z*
		N1–H1···O1	0.841(17)	2.136(17)	2.9632(14)	167.7(15)	1-*x*, 1-*y*, 1-*z*
D-**1**-CH_3/L-**1**-Cl	II	O2A–H2A···O3B	0.85(3)	1.80(3)	2.631(3)	166(4)	*x*, *y*, *z*
		N1A–H1A···O1B	0.82(2)	2.17(3)	2.957(3)	162(4)	1-*x*, *y*-0.5, 1-*z*
		O2B–H2B···O3A	0.84(3)	1.81(3)	2.629(3)	165(4)	*x*, *y*, *z*
		N1B–H1B···O1A	0.82(2)	2.12(2)	2.931(3)	172(4)	1-*x*, 0.5+*y*, -*z*
D-**2**-CH_3/L-**2**-Cl	I	O2A–H2A···O3A	0.90(5)	1.69(5)	2.591(3)	174(4)	1-*x*, -0.5+*y*, 2-*z*
		N1A–H1A···O1A	0.81(4)	2.21(4)	2.999(3)	165(4)	*x*, *y*, *z*
		O2B–H2B···O3B	0.83(4)	1.78(5)	2.598(3)	168(4)	-*x*, 0.5+*y*, 1-*z*
		N1B–H1B···O1B	0.89(4)	2.09(4)	2.967(3)	168(3(	*x*, *y*, *z*
L-**1**-CH_3/D-**2**-CH_3	I	O2A–H2A···O3A	0.90(2)	1.69(2)	2.583(2)	169(3)	2-*x*, 0.5+*y*, 1-*z*
		N1A–H1A···O1A	0.86(2)	2.10(2)	2.955(2)	170(3)	*x*, *y*, *z*
		O2B–H2B···O3B	0.85(2)	1.77(2)	2.621(2)	176(4)	1-*x*, -0.5+*y*, -*z*
		N1B–H1B···O1B	0.88(2)	2.12(2)	2.986(2)	170(3)	*x*, *y*, *z*
D-**1**-Cl/L-**2**-Cl	I	O2A–H2A···O3A	0.88(4)	1.74(4)	2.624(3)	174(3)	1-*x*, -0.5+*y*, 2-*z*
		N1A–H1A···O1A	0.86(3)	2.11(3)	2.961(3)	171(3)	*x*, *y*, *z*
		O2B–H2B···O3B	0.80(4)	1.79(4)	2.588(3)	175(4)	1-*x*, 0.5+*y*, 1-*z*
		N1B–H1B···O1B	0.80(3)	2.13(3)	2.902(3)	163(3)	*x*, *y*, *z*
D-**1**-CH_3/L-**2**-Cl	I	O2A–H2A···O3A	0.88(4)	1.75(4)	2.632(3)	177(4)	1-*x*, -0.5+*y*, 2-*z*
		N1A–H1A···O1A	0.86(3)	2.09(4)	2.947(3)	172(3)	*x*, *y*, *z*
		O2B–H2B···O3B	0.83(5)	1.75(5)	2.577(3)	175(4)	1-*x*, 0.5+*y*, 1-*z*
		N1B–H1B···O1B	0.83(4)	2.12(4)	2.936(3)	166(4)	*x*, *y*, *z*
D-**1**-Cl/L-**2**-CH_3	I	O2A–H2A···O3A	0.84(3)	1.78(4)	2.615(2)	176(3)	1-*x*, 0.5+*y*, 2-*z*
		N1A–H1A···O1A	0.86(3)	2.15(3)	2.991(2)	166(3)	*x*, *y*, *z*
		O2B–H2B···O3B	0.86(3)	1.74(4)	2.597(2)	175(3)	-*x*, -0.5+*y*, 1-*z*
		N1B–H1B···O1B	0.84(3)	2.08(3)	2.916(2)	174(3)	*x*, *y*, *z*
(±)-**1**-H	I	O2–H2···O3	0.942(17)	1.649(18)	2.5882(11)	174.4(16)	1-*x*, *y*-0.5, 0.5-*z*
		N1–H1···O1	0.879(15)	2.031(15)	2.8884(12)	164.9(13)	1-*x*, 1-*y*, 1-*z*
(±)-**1**-CF_3	II	O2–H2···O3	0.879(19)	1.745(19)	2.622(2)	175(4)	1-*x*, -*y*, 1-*z*
		N1–H1···O1	0.835(17)	2.082(18)	2.909(2)	170(2)	*x*, 0.5-*y*, *z*-0.5
(±)-**2**-H	I	O2–H2···O3	0.901(15)	1.680(15)	2.5795(10)	176.3(13)	1-*x*, *y*-0.5, 0.5-*z*
		N1–H1···O1	0.867(13)	2.082(14)	2.8898(11)	164.7(12)	1-*x*, 1-*y*, 1-*z*
D-**2**-H/L-**2**-CF_3	I	O2A–H2A···O3A	0.87(3)	1.72(3)	2.576(2)	170(3)	1-*x*, -0.5+*y*, 2-*z*
		N1A–H1A···O1A	0.84(3)	2.05(3)	2.870(2)	168(2)	*x*, *y*, *z*
		O2B–H2B···O3B	0.92(3)	1.77(3)	2.681(2)	175(3)	-*x*, 0.5+*y*, 1-*z*
		N1B–H1B···O1B	0.86(3)	2.18(3)	2.996(2)	159(2)	*x*, *y*, *z*
D-**1**-H/L-**2**-H	I	O2A–H2A···O3A	0.94(2)	1.65(2)	2.5927(18)	176(2)	1-*x*, 0.5+*y*, 2-*z*
		N1A–H1A···O1A	0.876(17)	2.044(18)	2.9080(18)	168(2)	*x*, *y*, *z*
		O2B–H2B···O3B	0.92(2)	1.68(2)	2.5912(17)	175(3)	1-x, y-0.5, 1-z
		N1B–H1B···O1B	0.882(17)	2.057(18)	2.9122(18)	163(2)	*x*, *y*, *z*
L-**1**-CF_3/D-**2**-CF_3	I (variant)	O2A–H2A···O3A	0.88(6)	1.71(6)	2.585(4)	172(5)	-1-*x*, -0.5+*y*, -*z*

		N1A–H1A···O1A	0.81(5)	2.12(5)	2.917(4)	170(5)	*x*-1, *y*-1, *z*-1
		O2B–H2B···O3B	0.74(6)	1.87(6)	2.611(4)	176(6)	2-*x*, 0.5+*y*, 2-*z*
		N1B–H1B···O1B	0.92(5)	2.08(5)	2.988(4)	168(4)	1+*x*, 1+*y*, 1+*z*
D-**1**-CF_3/L-**2**-H	I	O2A–H2A···O3A	0.87(5)	1.74(5)	2.598(3)	171(5)	1-*x*, 0.5+*y*, 1-*z*
		N1A–H1A···O1A	0.90(4)	2.07(4)	2.956(3)	167(3)	*x*, *y*, *z*
		O2B–H2B···O3B	0.85(5)	1.76(5)	2.601(3)	174(5)	1-*x*, 0.5+*y*, 2-*z*
		N1B–H1B···O1B	0.83(4)	2.10(5)	2.921(4)	173(4)	*x*, *y*, *z*

Table S3. Intermolecular Aryl···Aryl Contact Parameters.

Compound	Interplanar distance (Å)	centroid-centroid distance (Å)	shift distance(Å)	Symmetry operator
(±)-**2**-CH_3	3.564	3.974	1.815	1-*x*, 2-*y*, 1-*z*
(±)-**2**-Cl	3.536	4.150	2.172	1-*x*, 1-*y*, 1-*z*
D-**2**-CH_3/L-**2**-Cl	3.529	4.030	1.946	*x*, 1+*y*, *z*
L-**1**-CH_3/D-**2**-CH_3	3.567	4.019	1.852	*x*, 1+*y*, *z*
D-**1**-Cl/L-**2**-Cl	3.586	4.198	2.182	*x*, 1+*y*, *z*
D-**1**-CH_3/L-**2**-Cl	3.539	4.105	2.078	*x*, 1+*y*, *z*
D-**1**-Cl/L-**2**-CH_3	3.460	4.100	2.200	*x*, 1+*y*, *z*
(±)-**1**-H	Aryl groups do not approximate coplanarity			
(±)-**2**-H	Aryl groups do not approximate coplanarity			
D-**2**-H/L-**2**-CF_3	3.493	5.106	3.725	*x*, 1+*y*, *z*
D-**1**-H/L-**2**-H	3.351	4.922	3.605	*x*, 1+*y*, *z*
L-**1**-CF_3/D-**2**-CF_3	Aryl groups do not approximate coplanarity			
D-**1**-CF_3/L-**2**-H	3.581	3.523	2.771	*x*, -1+*y*, *z*

SI 4. CCDC Crystal Structure Similarities

The Crystal Packing Similarity facility in CCDC-Mercury (2022.3.0) was used to understand the structural similarity of the CH_3/Cl and H/CF_3 racemic and quasiracemic crystal structures. This search was restricted to a packing shell size of 15 molecules with 30% distance and angle tolerances. When comparing crystal structures, molecular differences and structure inversion were allowed, and hydrogen positions, bond types, and hydrogen atoms and bond counts for each atom were ignored. Table S4 shows the results from comparing all possible structural pairings for these systems as root-mean-square values with the molecules in common provided in parentheses. Highlighted cells indicate structure pairs that have at least four molecules/units in common, indicating a significant level of structural similarity.

Table S4. Results from a CCDC-Mercury Crystal Packing Similarity search of the CH_3/Cl and H/CF_3 systems of **1** and **2**. Cell values include the root-mean-square agreement of the structural pair with the number of common molecules/units provided in parentheses.

		(±)-**1**-CH_3	(±)-**1**-Cl	(±)-**2**-CH_3	(±)-**2**-Cl	D-**1**-CH_3/ L-**1**-Cl	D-**2**-CH_3/ L-**2**-Cl	L-**1**-CH_3/ D-**2**-CH_3	D-**1**-Cl/ L-**2**-Cl	D-**1**-CH_3/ L-**2**-Cl	D-**1**-Cl/ L-**2**-CH_3	(±)-**1**-H	(±)-**1**-CF_3	(±)-**2**-H	D-**2**-H/ L-**2**-CF_3	L-**1**-H/ D-**2**-H	L-**1**-CF_3/ D-**2**-CF_3	D-**1**-CF_3/ L-**2**-H
		Form II	Form II	Form I	Form I	Form II	Form I	Form I	Form I	Form I	Form I	Form I	Form II	Form I	Form I	Form I	Form I-v	Form I
(±)-**1**-CH_3	Form II	-	0.31 (15)	0.45 (1)	1.47 (3)	0.18 (15)	1.77 (3)	1.63 (3)	1.47 (3)	1.50 (3)	0.50 (1)							
(±)-**1**-Cl	Form II		-	1.22 (3)	1.19 (3)	0.15 (15)	0.49 (1)	1.42 (3)	1.31 (3)	1.47 (2)	0.54 (1)							
(±)-**2**-CH_3	Form I			-	0.26 (15)	1.19 (3)	0.14 (15)	0.31 (10)	0.43 (9)	0.45 (8)	0.33 (9)							
(±)-**2**-Cl	Form I				-	1.18 (3)	0.15 (15)	0.21 (9)	0.24 (8)	0.21 (8)	0.26 (10)							
D-**1**-CH_3/ L-**1**-Cl	Form II					-	1.18 (3)	1.33 (3)	1.36 (3)	1.28 (3)	1.35 (3)							
D-**2**-CH_3/ L-**2**-Cl	Form I						-	0.22 (9)	0.34 (9)	0.41 (8)	0.25 (9)							
L-**1**-CH_3/ D-**2**-CH_3	Form I							-	0.22 (15)	0.14 (15)	0.10 (15)							
D-**1**-Cl/ L-**2**-Cl	Form I								-	0.10 (15)	0.13 (15)							
D-**1**-CH_3/ L-**2**-Cl	Form I									-	0.58 (4)							
D-**1**-Cl/ L-**2**-CH_3	Form I										-							
(±)-**1**-H	Form I	1.77 (3)	1.77 (3)	1.14 (6)	0.92 (6)	1.73 (3)	1.15 (6)	1.14 (6)	1.03 (9)	1.13 (8)	1.08 (8)	-	0.97 (2)	0.67 (9)	1.19 (4)	0.71 (7)	2.02 (8)	0.81 (5)
(±)-**1**-CF_3	Form II	0.77 (9)	0.72 (8)	1.49 (3)	1.47 (3)	0.65 (5)	2.91 (3)	1.59 (3)	1.57 (3)	0.97 (2)	0.73 (1)		-	1.40 (3)	1.24 (2)	1.45 (3)	0.71 (1)	0.57 (1)
(±)-**2**-H	Form I	1.55 (3)	1.61 (3)	0.95 (15)	0.72 (15)	1.50 (3)	0.85 (15)	0.88 (9)	0.81 (10)	0.68 (7)	0.81 (9)			-	1.72 (6)	0.35 (13)	1.77 (14)	0.77 (8)
D-**2**-H/ L-**2**-CF_3	Form I	0.93 (2)	1.03 (2)	1.54 (2)	0.61 (5)	1.80 (3)	1.53 (2)	1.60 (1)	1.61 (4)	1.11 (7)	1.59 (1)				-	1.02 (4)	1.50 (1)	0.91 (10)
L-**1**-H/ D-**2**-H	Form I	1.47 (3)	1.61 (3)	0.77 (9)	0.57 (10)	1.41 (3)	0.68 (10)	0.71 (9)	0.56 (8)	0.62 (8)	0.63 (9)					-	1.83 (8)	0.61 (15)
L-**1**-CF_3/ D-**2**-CF_3	Form I-v	0.51 (1)	0.55 (1)	1.70 (4)	1.80 (8)	0.53 (1)	0.99 (3)	1.71 (4)	0.80 (4)	1.00 (4)	0.99 (4)						-	0.86 (4)
D-**1**-CF_3/ L-**2**-H	Form I	1.52 (2)	1.50 (3)	0.81 (9)	0.47 (8)	0.57 (2)	0.72 (9)	0.69 (8)	0.59 (11)	0.59 (11)	0.72 (5)							-

SI 5. Crystal Lattice Energy Calculations and Assessments

Crystal Lattice Energy Calculations

Crystal lattice energies (E_{Latt}) were determined for the 17 crystal structures included in this study by analyzing residue-to-residue contacts. The software package *Crystal Explorer*[8]*,* equipped with Gaussian16[9], was used to create molecular assemblies from a cluster radius of 10 Å with E_{Latt} values computed by direct summation of interaction energies (*i.e.,* electrostatic, dispersion, polarization, and repulsion) with the central molecule and molecules included in the cluster. Several of the structure containing leucinyl [(±)-**1**-CF_3, L-**1**-H/D-**2**-H, and D-**1**-CF_3/L-**2**-H] and CF_3 [L-**1**-CF_3/D-**2**-CF_3, D-**1**-CF_3/L-**2**-H] groups exhibit disorder. The lattice calculations for these systems were performed on each disorder component, and their contribution was weighted using the corresponding occupancy factors from the crystallographic data. Averaging the data for the $Z' > 1$ structures provided a process for determining overall crystal E_{Latt} values.

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) measurements were performed using a TA DSC 25 calorimeter. Each sample was heated to approximately 15°C below the melting point at a rate of 5°C/min and then cooled at 10°C/min. Samples of 1-4 milligrams were sealed in Tzero aluminum pans, and the heat flow as a function of temperature was measured and compared to a reference pan.

Table S5. Crystal Lattice Energy Determinations for Racemic and Quasiracemic Leucine **1** and Phenylalanine **2** systems.

Compound	Crystal Form	Crystal Lattice Energies, E_{Latt} (kJ mol^{-1}) Crystal Explorer	DSC	Density (g mL^{-1})	Melting Point (°C)
(±)-**1**-CH_3	II	-171.8	-83.7	1.189	125.9
(±)-**1**-Cl	II	-163.8	-64.7	1.297	200.7
(±)-**2**-CH_3	I	-189.5	-91.4	1.276	194.0
(±)-**2**-Cl	I	-187.6	-71.5	1.385	189.5
D-**1**-CH_3/L-**1**-Cl	II	-169.6	-52.7	1.244	183.5
D-**2**-CH_3/L-**2**-Cl	I	-187.2	-81.3	1.327	198.3
L-**1**-CH_3/D-**2**-CH_3	I	-179.5	-69.3	1.232	183.4
D-**1**-Cl/L-**2**-Cl	I	-178.1	-59.4	1.351	155.1
D-**1**-CH_3/L-**2**-Cl	I	-177.9	-62.0	1.291	152.7
D-**1**-Cl/L-**2**-CH_3	I	-177.0	-67.5	1.293	155.6
(±)-**1**-H	I	-161.5	-51.7	1.241	141.1
(±)-**1**-CF_3	II	-164.0	-50.5	1.373	171.5
(±)-**2**-H	I	-182.9	-47.1	1.321	168.0
D-**2**-H/L-**2**-CF_3	I	-193.8	-40.6	1.379	157.9
L-**1**-H/D-**2**-H	I	-168.5	-42.5	1.248	150.9
D-**1**-CF_3/L-**2**-CF_3	variant of I	-172.0	-58.7	1.368	174.8
D-**1**-CF_3/L-**2**-H	I	-173.4	-42.5	1.312	160.6

SI 6. Crystal Structure Cavity Space and Packing Efficiency Determinations

Void calculations for each of the crystal structures were determined using the CCDC-Mercury[10]. The process included removing the individual amino acid R groups (leucine, $CH_2CH(CH_3)_2$; phenylalanine, $CH_2C_6H_5$) and determining the cavity space volume using a 1.4 Å probe radius with 0.1 Å grid spacing. in the cases of disordered leucine groups, all components *R* group components were omitted prior to void space determinations. Fig. S1 shows the void spaces for quasiracemate D-**1**-CH_3/L-**2**-Cl with views projected down the *c*- and *b*-axes. Cavity space data (Table S6), including cavity space packing efficiencies (C_p), are provided below. C_p values were determined using V_{group}/V_{cavity}, where $V_{leucine}$ = 71.6 Å^3 and $V_{phenylalanine}$ = 85.8 Å^3.[11]

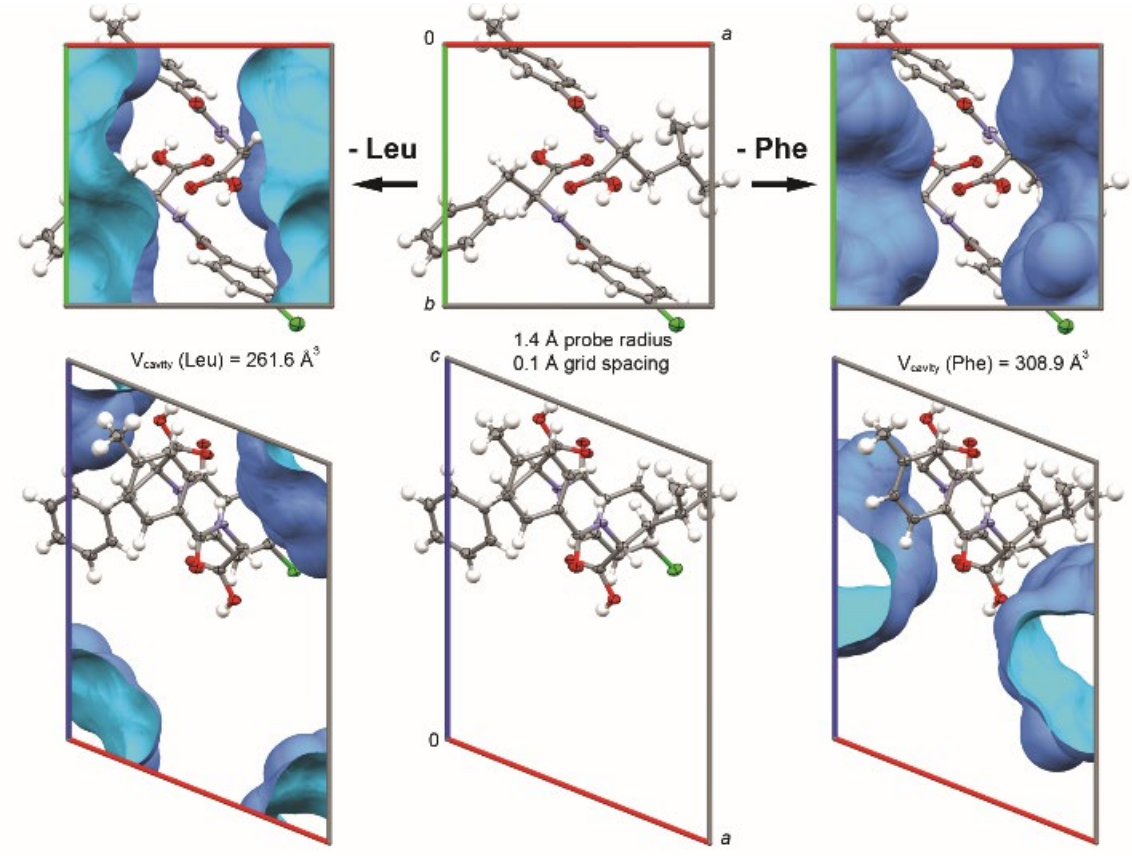


Fig. S1 Views of the unit cell and cavity space determinations for quasiracemate D-**1**-CH_3/L-**2**-Cl projected down the *c* and *b*-axes.

Table S6. Leucine and phenylalanine void space volumes and packing efficiencies.

Structure	Space group	Z	Group Volumes (Å^3) determined using CCDC-Mercury.				Group Packing Efficiencies (C_p = V_{group*}/V_{cavity})			
			Leu(1)	Leu(2)	Phe(1)	Phe(2)	C_p(Leu1)	C_p(Leu2)	C_p(Phe1)	C_p(Phe2)
(±)-**1**-CH_3	$P2_1/c$	4	120.3				0.60			
(±)-**1**-Cl	$P2_1/c$	4	119.4				0.60			
(±)-**2**-CH_3	$P2_1/c$	4			158.0				0.54	
(±)-**2**-Cl	$P2_1/c$	4			156.0				0.55	
D-**1**-CH_3/L-**1**-Cl	$P2_1$	2	112.2	108.3			0.64	0.66		
D-**2**-CH_3/L-**2**-Cl	$P2_1$	2			151.8	151.8			0.56	0.57
L-**1**-CH_3/D-**2**-CH_3	$P2_1$	2	132.9		155.4		0.54		0.55	
D-**1**-Cl/L-**2**-Cl	$P2_1$	2	129.1		154.4		0.55		0.56	
D-**1**-CH_3/L-**2**-Cl	$P2_1$	2	130.8		154.4		0.55		0.56	
D-**1**-Cl/L-**2**-CH_3	$P2_1$	2	129.6		155.1		0.55		0.55	
(±)-**1**-H	$P2_1/c$	4	112.7				0.64			
(±)-**1**-CF_3	$P2_1/c$	4	127.2				0.56			
(±)-**2**-H	$P2_1/c$	4			150.1				0.57	
D-**2**-H/L-**2**-CF_3	$P2_1$	2			153.5	143.8			0.56	0.60
L-**1**-H/D-**2**-H	$P2_1$	2	145.7		154.1		0.49		0.56	
D-**1**-CF_3/L-**2**-CF_3	$P2_1$	2	119.7		159.8		0.60		0.54	
D-**1**-CF_3/L-**2**-H	$P2_1$	2	127.2		161.0		0.56		0.53	

* Side chain volumes for leucine ($V_{CH2(CH3)2}$ = 71.6 Å^3) and phenylalanine ($V_{CH2C6H5}$ = 85.8 Å^3).[11]

SI 7. CCDC-CSD Search Parameters

CCDC Cambridge Structural Database[12] (CSD, vs. 5.43) searches were limited to organic entries with 3D coordinates. A search of trifluoromethyl aryl groups in the database resulted in 5804 hits. 2837 of these entries were flagged with 'disorder', and 2415 (42%) of these entries modeled the CF_3 disorder. The CSD contains 1163 entries with the leucinyl fragment – *i.e.,* $(CH_3)_2CH_2CH(NH)C{=}O$. 371 of these structures included 'disorder' in the entry, and 115 of these structures (9.9%) modeled disorder of the leucine group.

References

1 A. Karmakar, C. L. Oliver, A. E. Platero-Prats, E. Laurila and L. Öhrström, *CrystEngComm*, 2014, **16**, 8243–8251.
2 L. Krause, R. Herbst-Irmer, G. M. Sheldrick and D. Stalke, *J Appl Crystallogr*, 2015, **48**, 3–10.
3 O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. a. K. Howard and H. Puschmann, *J Appl Cryst*, 2009, **42**, 339–341.
4 G. M. Sheldrick, *Acta Cryst A*, 2015, **71**, 3–8.
5 G. M. Sheldrick, *Acta Cryst C*, 2015, **71**, 3–8.
6 D. J. Watkin and R. I. Cooper, *Chemistry*, 2020, **2**, 796–804.
7 R. W. W. Hooft, L. H. Straver and A. L. Spek, *J Appl Cryst*, 2008, **41**, 96–103.
8 P. R. Spackman, M. J. Turner, J. J. McKinnon, S. K. Wolff, D. J. Grimwood, D. Jayatilaka and M. A. Spackman, *J Appl Cryst*, 2021, **54**, 1006–1011.
9 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, G. A. Petersson, H. Nakatsuji, X. Li, M. Caricato, A. V. Marenich, J. Bloino, B. G. Janesko, R. Gomperts, B. Mennucci, H. P. Hratchian, J. V. Ortiz, A. F. Izmaylov, J. L. Sonnenberg, Williams, F. Ding, F. Lipparini, F. Egidi, J. Goings, B. Peng, A. Petrone, T. Henderson, D. Ranasinghe, V. G. Zakrzewski, J. Gao, N. Rega, G. Zheng, W. Liang, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, K. Throssell, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, T. A. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, J. M. Millam, M. Klene, C. Adamo, R. Cammi, J. W. Ochterski, R. L. Martin, K. Morokuma, O. Farkas, J. B. Foresman and D. J. Fox, Gaussian 16 Rev. C.01 2016.
10 C. F. Macrae, I. Sovago, S. J. Cottrell, P. T. A. Galek, P. McCabe, E. Pidcock, M. Platings, G. P. Shields, J. S. Stevens, M. Towler and P. A. Wood, *J Appl Cryst*, 2020, **53**, 226–235.
11 S. Sirimulla, M. Lerma and W. C. Herndon, *J. Chem. Inf. Model.*, 2010, **50**, 194–204.
12 C. R. Groom, I. J. Bruno, M. P. Lightfoot and S. C. Ward, *Acta Cryst B*, 2016, **72**, 171–179.