Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

The Strecker Reaction coupled to Viedma Ripening: A Simple Route to Highly Hindered Enantiomerically Pure Amino Acids

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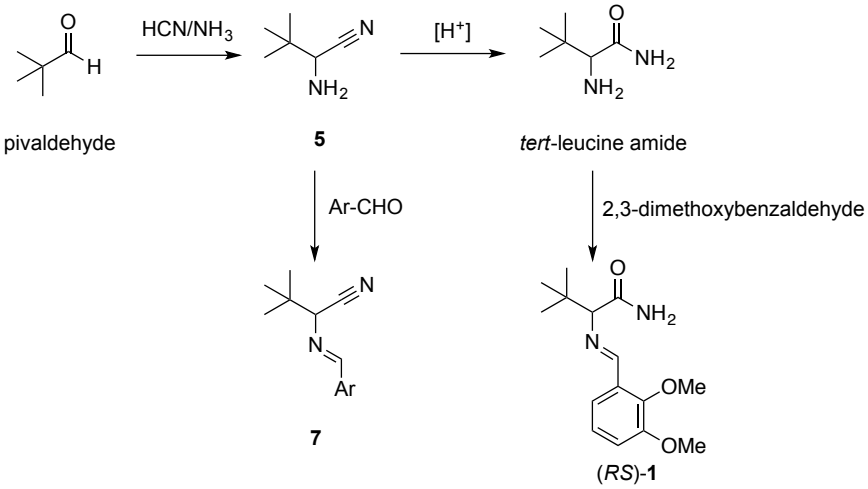
Content

1. General remarks

^{1}H and ^{13}C NMR were recorded using Agilent VNMRS300 or Agilent MercuryPlus300 spectrometers (the NMR spectra were recorded in either $CDCl_3$, DMSO-d6 or CD_3OD solutions; NMR chemical shifts δ are given in parts per million (ppm); coupling constants J are in hertz (Hz)). Chiral HPLC analyses were performed using an Agilent Technologies Infinity 1260 HPLC system equipped with a Chiralpak IA (250 x 4.6 mm, 5 μm) column; eluent: *n*-heptane/isopropanol 95/5 (*v/v*); flow rate: 0.7 mL/min; UV-light detector: 220 nm). Melting points were recorded on a TA Instruments Q20. Optical rotation was measured using a Krüss P3001 polarimeter. Second Harmonic Generation (SHG) measurements were performed according to the previously described procedure.[1] X-Ray powder diffraction patterns were measured using a Bruker D2 Phaser with a Cu X-ray source (Cu K-α, λ = 1.5418 Å). All crystallographic data sets were collected on a Bruker D8 Quest diffractometer equipped with an Incoatec Microfocus source generator (multi layered optics monochromatized Mo-Kα radiation, λ = 71.073 pm); multi-scan absorption corrections were applied with the program SADABS-2014/5.

2. *tert*-Leucine

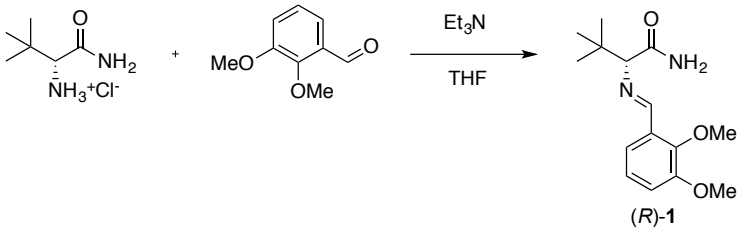


Scheme S1. Synthesis of imines **7**.

(±)-2-amino-3,3-dimethylbutanenitrile (5).[2] *Caution! HCN is generated. The experiment should be performed in a well-ventilated fume hood*. A solution of pivaldehyde (30.0 mL; 23.8 g; 0.276 mol; 1.0 eq.) in MeOH (60 mL) was added dropwise to a solution of NaCN (16.24 g; 0.33 mol; 1.2 eq.) and NH_4Cl (14.77 g; 0.276 mol; 1.5 eq.) in aqueous ammonia solution (280 mL; 25% solution) at 10 °C. The resulting reaction mixture was stirred at ambient temperature for 16 hours. Then, the reaction mixture was diluted with water (500 mL) and extracted with DCM (3 x 200 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give a white sticky solid (27.6 g; 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.39 (s, 1H), 1.61 (br s, 2H), 1.09 (s, 9H).

(±)-2-amino-3,3-dimethylbutanamide (*tert*-leucine amide).[3] Concentrated sulfuric acid (12 mL) was added dropwise to a solution of the nitrile **5** (6.0 g; 54 mmol) in DCM (30 mL) at 0 °C. The resulting reaction mixture was stirred overnight at ambient temperature. The reaction mixture was poured into ice (300 g) and neutralized with an aqueous ammonia solution (25 %). The resulting mixture was extracted with $CHCl_3$/MeOH 3/1 (*v/v*, 3 x 100 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give the desired amide as a while solid (3.8 g; 54%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.14 (s, 1H), 1.52 (br s, 4H), 1.04 (s, 9H).

(±)-N-(2,3-dimethoxybenzylidene)-2-amino-3,3-dimethylbutanamide (1). A mixture of *tert*-leucine amide (2.0 g; 15.4 mmol; 1.0 eq.), 2,3-dimethoxybenzaldehyde (2.68 g; 16.1 mmol; 1.05 eq.) and Na_2SO_4 (3.72 g; 26.2 mmol; 1.7 eq.) in DCM (20 mL) was stirred at ambient temperature for 16 hours. The suspension was heated up to 40 °C and filtered. The solid collected was washed with hot DCM (2 x 5 mL). The mother liquor was concentrated under reduced pressure. The residue was recrystallized from acetonitrile (20 mL) to give a white solid (3.9 g; 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.12 (t, J = 8.1 Hz, 1H), 7.02 (d, J = 8.1 Hz, 1H), 6.57 (br s, 1H), 5.79 (br s, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.55 (s, 1H), 1.06 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.33, 151.75, 152.98, 149.73, 129.31, 124.09, 118.78, 114.73, 83.96, 61.83, 55.91, 35.08, 27.17. MS(ES-API): *m/z* = 279.1 $[M+H]^+$. HRMS (ES-ToF): *m/z* calculated for $C_{15}H_{23}N_2O_3$ $[M+H]^+$: 279.1709; found: 279.1721.



Scheme S2. Synthesis of enantiomerically pure (*R*)-**1**.

(*R*)-N-(2,3-dimethoxybenzylidene)-2-amino-3,3-dimethylbutanamide ((*R*)-1. Triethylamine (1.0 mL; 7.2 mmol; 1.2 eq.) was added dropwise to a solution of (2*R*)-2-amino-3,3-dimethylbutanamide hydrochloride[4] (1.0 g; 6.0 mmol; 1.0 eq.) and 2,3-dimethoxybenzaldehyde (1.1 g; 6.6 mmol; 1.1 eq.) in THF (15 mL) at 10 °C. The resulting reaction mixture was stirred overnight at ambient temperature. Then, the reaction mixture was poured into water (100 mL) and extracted with DCM (2 x 50 mL). The combined organic phase was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a yellowish residue. The residue was recrystallized from acetonitrile (20 mL) to provide a white solid (1.35 g; 81%; ee > 99%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.13 (t, J = 7.8 Hz, 1H), 7.00 (d, J = 8.1 Hz, 1H), 6.56 (br s, 1H), 5.41 (br s, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.53 (s, 1H), 1.04 (s, 9H).

Racemization of imine (*R*)-1:

All attempts to establish that reversible proton abstraction – a condition for racemization - occurs with a model enantiomerically pure **(*R*)-1** in the presence of DBU or other bases, under various temperature and solvent conditions failed to reveal significant hydrogen exchange at the α-position. Application of forcing conditions[5] leads to considerable decomposition.

DBU: DBU (13 µL; 0.09 mmol; 0.5 eq.) was added to a solution of imine (*R*)-**1** (50 mg; 0.18 mmol; *ee* > 99%) in acetonitrile (5 mL). The resulting reaction mixture was stirred for 16 hours at ambient temperature. Then, the reaction mixture was quenched with phosphate buffer (3 mL; pH = 7) and extracted with dichloromethane (5 mL). The organic layer was concentrated under reduced pressure. Chiral HPLC analysis showed that the obtained residue corresponds to (*R*)-**1** in > 99% ee. Racemization does not occur.

***tert*-Butylimino-tri(pyrrolidino)phosphorene (BTPP):** PTPP (28 µL; 0.09 mmol; 0.5 eq.) was added to a solution of imine (*R*)-**1** (50 mg; 0.18 mmol; *ee* > 99%) in acetonitrile (5 mL). The resulting reaction mixture was stirred for 24 hours at ambient temperature. Then, the reaction mixture was quenched with phosphate buffer (3 mL; pH = 7) and extracted with dichloromethane (5 mL). The organic layer was concentrated under reduced pressure. Chiral HPLC analysis showed that the obtained residue corresponds to (*R*)-**1** in > 78% *ee*, indicating that only unpractically slow racemization occurs.

Potassium *tert*-butoxide (*t*-BuOK): Imine (*R*)-**1** (50 mg; 0.18 mmol; *ee* > 99%) and *t*-BuOK (10 mg; 0.09 mmol; 0.5 eq.) were suspended in toluene (5 mL). The resulting reaction mixture was stirred at 100 °C while *ee* was monitored by chiral HPLC. Samples were taken and analyzed after 1 hour ($ee_R \approx 83\%$) and 4 hours ($ee_R \approx 67\%$) of stirring. The sample taken after 4 hours indicated that considerable decomposition of **1** occurs together with its slow racemization.

(±)-3,3-dimethyl-2-((naphthalen-2-yl)methylidene)aminobutanenitrile (7a). The following procedure is representative for all imines **7**. A mixture of α-aminonitrile **5** (10.8 g; 96.2 mmol; 1.0 eq.), 2-naphthaldehyde (15.03 g; 96.2 mmol; 1.0 eq.) and Na_2SO_4 (24.14 g; 0.17 mol; 1.7 eq.) in DCM (120 mL) was stirred at room temperature for 16 hours. The suspension was heated up to 40 °C and filtered. The solid collected was washed with hot DCM (2 x 30 mL). The mother liquor was concentrated under reduced pressure. The residue was recrystallized from MeOH (250 mL) to afford a white solid (23.1 g; 96%). M.p. = 106 °C. ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 8.63 (s, 1H), 8.13 (s, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.94-7.86 (m, 3H), 7.57-7.53 (m, 2H), 4.37 (s, 1H), 1.17 (s, 9H). ^{1}H NMR (300 MHz, DMSO-d6) *δ* 8.62 (s, 1H), 8.28 (s, 1H), 8.03-7.93 (m, 4H), 7.58-7.56 (m, 2H), 4.59 (s, 1H), 1.05 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 162.93, 135.10, 132.98, 132.83, 131.38, 128.80, 128.66, 127.91, 127.69, 123.64, 117.22, 69.11, 36.01, 26.43. ^{13}C NMR (75 MHz, DMSO-d6) *δ* 164.67, 135.02, 133.06, 131.74, 129.23, 129.04, 128.27, 127.30, 123.61, 118.55, 68.53, 35.74, 26.31. MS (ES-API): *m/z* = 251.1 $[M+H]^+$. HRMS (FTMS + pESI): *m/z* calculated for $C_{19}H_{22}FN_2$ $[M+H]^+$: 251.1548; found: 251.1546.

(±)-3,3-dimethyl-2-((6-methoxynaphthalen-2-yl)methylidene)aminobutanenitrile (7b). A mixture of α-aminonitrile **5** (3.0 g; 26.7 mmol; 1.0 eq.), 6-methoxy-2-naphthaldehyde (5.0 g; 26.7 mmol; 1.0 eq.) and Na_2SO_4 (6.45 g; 45.4 mmol; 1.7 eq.) in DCM (60 mL) was stirred under reflux for 16 hours. The suspension was filtered. The solid collected was washed with hot DCM (2 x 10mL). The mother liquor was concentrated under reduced pressure. The residue was recrystallized from heptane (30 mL) to give a white solid (5.1 g; 68%). M.p. = 99 °C. ^{1}H NMR (300 MHz, DMSO-d6) *δ* 8.56 (s, 1H), 8.21 (s, 1H), 7.95-7.85 (m, 3H), 7.38 (s, 1H), 7.21 (d, *J* = 9 Hz, 1H), 4.57 (s, 1H), 3.88 (s, 3H), 1.05 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d6) *δ* 164.72, 159.21, 136.73, 131.47, 130.90, 128.36, 127.91, 124.28, 119.75, 118.70, 106.78,

68.53, 55.80, 35.72, 26.32. MS (ES-API): *m/z* = 281.2 $[M+H]^+$. HRMS (FTMS + pESI): *m/z* calculated for $C_{19}H_{22}FN_2$ $[M+H]^+$: 281.1654; found: 281.1651.

Racemization of (*R*)-7a:

(*R*)-**7a** (14 mg) was dissolved in 20 mL of solvent (MeCN, MeOH, MTBE, PhMe, n-Heptane). The stock solution (1.5 mL) was placed into a 2 mL HPLC vial followed by DBU (5.0 µL) addition. The vial was shaken for 30 seconds and placed into HPLC tray. Enantiomeric excess in the solution was monitored using chiral HPLC (by injecting 4 µL of the obtained reaction solution per analysis). Data collected are represented in Figure S1.

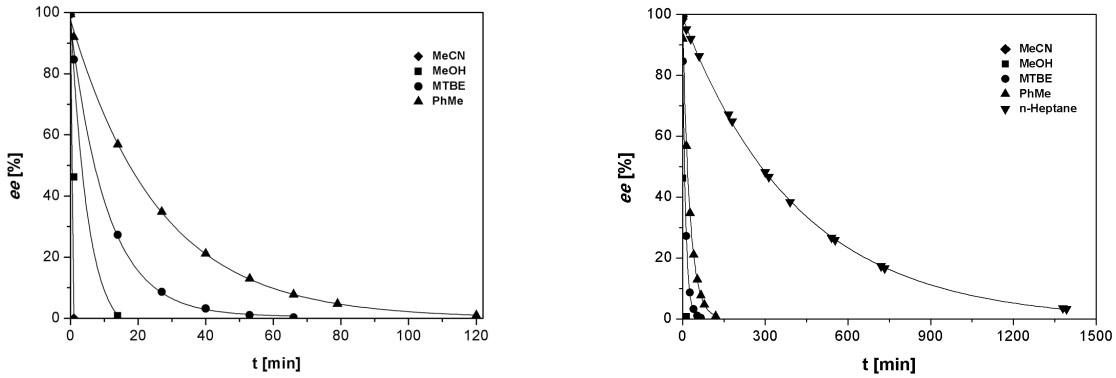
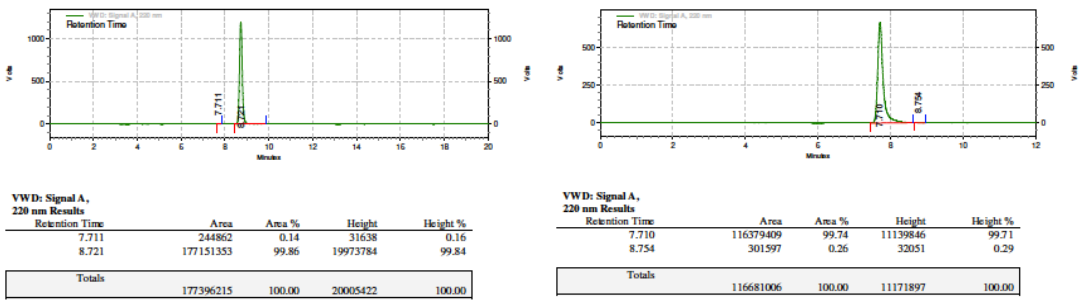


Figure S1. Racemization of **7a** (0.7 mg/mL) in the presence of DBU (3.3 µL/mL) in different solvents excluding (*left*) and including (*right*) n-Heptane.

Deracemization experiments:

Deracemization of (*RS*)-**7a** to (*R*)-**3,3-dimethyl-2-((naphthalen-2-yl)methylidene)amino-butanenitrile ((*R*)-7a)**. The following procedure is representative for deracemization to either enantiomer of imines **7a**,**b**. A screw cap vial (20 mL) was charged with 2 mm glass beads (10 g), imine (*RS*)-**7a** (1.2 g, 4.05 mmol), *R*-(or S)-**7a** (0.1 g, 0.34 mmol) and MeOH (10 mL). The vial was placed in an ultrasonic bath, equipped with a thermostat (maintaining the temperature at 20 °C), and sonicated for 30 min. Then, DBU (0.2 eq., 120 µL, 0.81 mmol) was added, and the mixture was sonicated at 20 °C overnight. Chiral HPLC analysis of the isolated solid sample indicated complete deracemization overnight. The suspension was replaced into a P4 filter, using a Pasteur's pipet to separate the suspension and glass beads, and filtered. The isolated solid was rinsed with MeCN (2 x 3.0 mL) and dried to afford the desired (*S*)-**7a** as a white solid (1.02 g; 78%, ee > 99%).



VWD: Signal A, 220 nm Results

Retention Time	Area	Area %	Height	Height %
7.711	244862	0.14	31638	0.16
8.721	177151353	99.86	19973784	99.84
Totals	177396215	100.00	20005422	100.00

VWD: Signal A, 220 nm Results

Retention Time	Area	Area %	Height	Height %
7.710	116379409	99.74	11139846	99.71
8.754	301597	0.26	32051	0.29
Totals	116681006	100.00	11171897	100.00

Figure S2. Chiral HPLC of **(*R*)-7a** *(right)* and **(*S*)-7a** *(right)*.

Deracemization rate determination:

A 20 mL screw septum vial was charged with 2 mm glass beads (10 g), (*RS*)-**7a** (0.9 g), (*R*)-(or *S*-)-**7a** (0.25 g) and MeOH (10 mL). The vial was sonicated at 20°C for 30 minutes and DBU (0.4 mL) was added. The resulting mixture was sonicated at 20°C while the solid phase *ee* was monitored by chiral HPLC of samples prepared by isolating small amounts of the solid by filtration. The data collected are represented in Figure 1.

(*R*)-2-amino-3,3-dimethylbutanenitrile hydrochloride ((*R*)-**5**·HCl**).**[6] The following procedure is representative for hydrolysis of either enantiomer of imines **7a**,**b**. HCl (37% ww, 50 µL) was added to a solution of **(*R*)-7a** (100 mg; 0.4 mmol; *ee* ≈ 97.6%) in acetone (5 mL) and the resulting reaction mixture was stirred at room temperature for 1 hour. The solid formed was collected by filtration and washed with acetone (2 x 1 mL) to afford a white solid (45 mg; 76%). ^{1}H NMR (300 MHz, CD_3OD) δ 4.40 (s, 1H), 1.18 (s, 9H). MS (ES-API): *m/z* = 113.0 $[M+H]^+$.

(*R*)-*tert*-Leucine hydrochloride ((*R*)-2·HCl).[6] The following procedure is representative for hydrolysis of either enantiomer of **5**. (*R*)-**5**·HCl (30 mg; 0.2 mmol) was dissolved in HCl (37% ww, 1.0 mL) and stirred for 40 h at 100°C in a closed vial. The reaction mixture was concentrated under reduced pressure to afford the title compound as a white solid (30 mg; *ee* ≈ 97.6) in 90% yield. ^{1}H NMR (300 MHz, CD_3OD) δ 3.71 (s, 1H), 1.13 (s, 9H). ^{13}C NMR (75 MHz, CD_3OD) δ 169.53, 61.51, 32.46, 25.48. MS (ES-API): *m/z* 210.1 $[M+H]^+$.

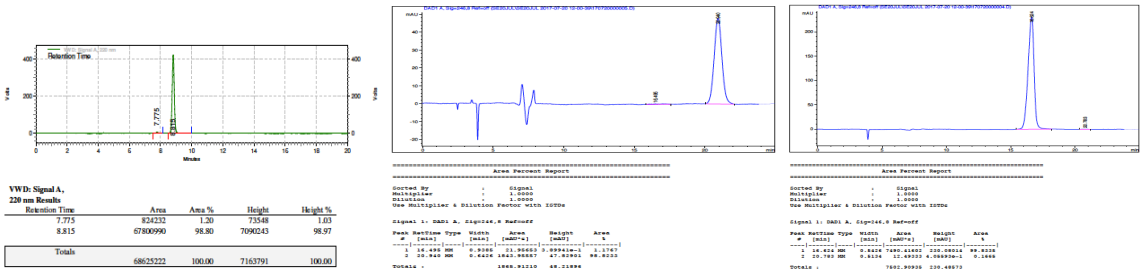
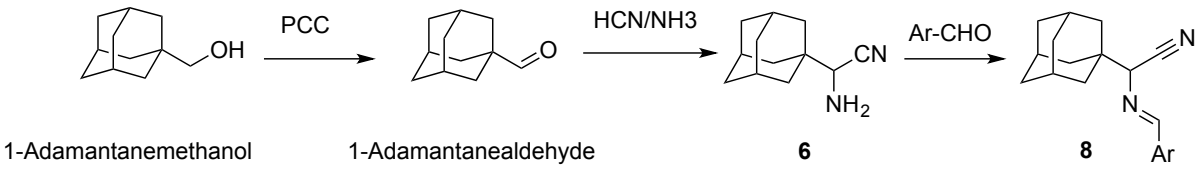


Figure S3. Chiral HPLC of **(*R*)-7a** (*left*) and *tert*-leucine **2**: (*R*)-**2** (*middle*) and (*S*)-**2** (*right*).

3. 1-Adamantylglycine



Scheme S3. Synthesis of imines **8**.

1-Adamantanealdehyde.[7] A solution of **1-adamantanemethanol** (20.0 g; 0.12 mol; 1.0 eq) in DCM (150 mL) was added dropwise to a suspension of pyridinium chlorochromate (PCC) (33.7 g; 0.156 mol; 1.3 eq.) in DCM (150 mL), maintaining the temperature of the reaction mixture (RM) at 10 °C. The resulting reaction mixture was allowed to warm up to ambient temperature and stirred for 3 hours. Then, the reaction mixture was diluted with TBME (500 mL) and filtered through silica plug. The mother liquor was washed with 1M aqueous sodium hydroxide solution (200 mL), dried over Na_2SO_4 and concentrated under reduced pressure to

give the title compound as a white solid (18.0 g; 91%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.34 (s, 1H), 2.09 (br s, 3H), 1.83-1.69 (m, 12H).

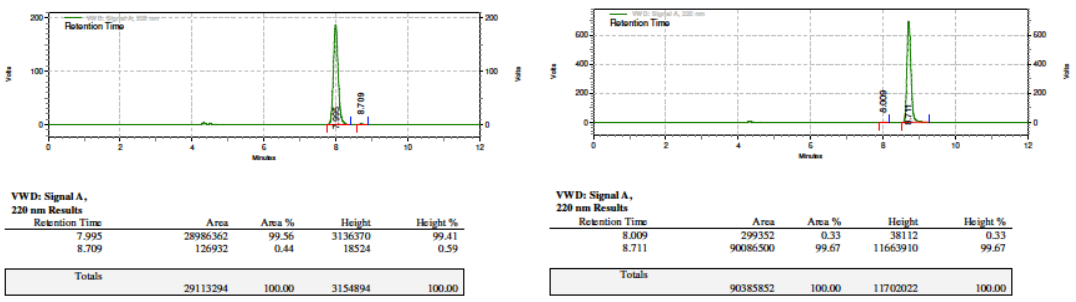
(±)-2-(adamantan-1-yl)-2-aminoacetonitrile (6).[8] *Caution! HCN is generated. The experiment should be performed in a well-ventilated fume hood*. A suspension of the crude aldehyde **1-adandanealdehyde** (18.0 g; 0.11 mol; 1.0 eq) in MeOH (180 mL) was slowly added to a solution of NaCN (6.44 g; 0.132 mol; 1.2 eq) and ammonium chloride (8.83 g; 0.165 mol; 1.5 eq) in aqueous ammonia (180 mL; 25% solution), maintaining the temperature of the reaction mixture at 10 °C. The resulting reaction mixture was stirred for 60 hours at ambient temperature. Then, the reaction mixture was diluted with water (500 mL) and extracted with DCM (3*100 mL). The combined organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to give aminonitrile **6** as a white solid (17.0 g; 82%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.26 (s, 1H), 2.09 (br s, 3H), 1.79-1.61 (m, 12H).

(±)-2-(Adamantan-1-yl)-2-((4-fluorophenyl)methylidene)aminoacetonitrile (8a). The following procedure is representative for all imines **8**. A mixture of α-aminonitrile **6** (400 mg; 2.1 mmol; 1.0 eq), 4-fluorobenzaldehyde (287 mg; 2.3 mmol; 1.1 eq) and Na_2SO_4 (596 mg; 4.2 mmol; 2.0 eq) in DCM (4.0 mL) was stirred at room temperature for 16 hours. The suspension was heated up to 40 °C and filtered. The solid collected was washed with hot DCM (2 x 2mL). The mother liquor was concentrated under reduced pressure. The residue was recrystallized from MeOH (5 mL) to afford a white solid (510 mg; 82%). M.p. = 149-151 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.83 (dd, *J* = 14.4, 8.7 Hz, 2H), 7.15 (t, *J* = 8.7 Hz, 2H), 4.22 (s, 1H), 2.08 (br s, 3H), 1.81-1.72 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.13, 161.42, 130.77, 130.65, 116.56, 116.04, 115.75, 69.56, 39.03, 37.73, 36.64, 28.27. MS (ES-API): *m/z* = 297.2 $[M+H]^+$. HRMS (FTMS + pESI): *m/z* calculated for $C_{19}H_{22}FN_2$ $[M+H]^+$: 297.1767; found: 297.1763.

(±)-2-(Adamantan-1-yl)-2-((2,6-dichlorophenyl)methylidene)aminoacetonitrile (8b). A mixture of α-aminonitrile **6** (500 mg; 2.63 mmol; 1.0 eq), 2,6-dichlorobenzaldehyde (505 mg; 2.89 mmol; 1.1 eq) and Na_2SO_4 (634 mg; 4.47 mmol; 1.7 eq) in DCM (5.0 mL) was stirred at room temperature for 16 hours. The suspension was heated up to 40 °C and filtered. The solid collected was washed with hot DCM (2 x 2mL). The mother liquor was concentrated under reduced pressure. The residue was recrystallized from MeOH (5 mL) to afford a white solid (780 mg; 85%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (s, 1H), 7.37 (d, *J* = 8.7 Hz, 2H), 7.15 (t, *J* = 8.7 Hz, 1H), 4.33 (s, 1H), 2.08 (br s, 3H), 1.86-1.66 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.55, 134.93, 131.84, 130.95, 128.91, 116.03, 70.81, 38.89, 37.50, 36.60, 28.28. MS (ES-API): *m/z* = 347.0 $[M+H]^+$. HRMS (ES-ToF): *m/z* calculated for $C_{19}H_{21}Cl_2N_2$ $[M+H]^+$: 347.1082; found: 347.1082.

Deracemization experiments:

Deracemization of (*RS*)-**8a** to **(*R*)-2-(Adamantan-1-yl)-2-((4-fluorophenyl)methylidene) aminoacetonitrile ((*R*)-8a)**. A screw cap vial (20 mL) was charged with 2 mm glass beads (10 g), imine (*RS*)-**8a** (1.2 g, 4.05 mmol), (*R*-(or *S*)-**8a** (0.1 g, 0.34 mmol) and MeCN (10 mL). The vial was placed in an ultrasonic bath, equipped with a thermostat (maintaining the temperature at 20 °C), and sonicated for 30 min. Then, DBU (0.2 eq, 120 µL, 0.81 mmol) was added, and the mixture was sonicated at 20 °C overnight. Chiral HPLC analysis of the isolated solid sample indicated complete deracemization overnight. The suspension was replaced into a P4 filter, using a Pasteur's pipet to separate the suspension and glass beads, and filtered. The isolated solid was rinsed with MeCN (2 x 3.0 mL) and dried to afford the desired (*R*)-**8a** as a white solid (1.07 g; 82%, ee > 99%).



VWD: Signal A, 220 nm Results

Retention Time	Area	Area %	Height	Height %
7.995	28986362	99.56	3136370	99.41
8.709	126932	0.44	18524	0.59
Totals	29113294	100.00	3154894	100.00

VWD: Signal A, 220 nm Results

Retention Time	Area	Area %	Height	Height %
8.009	299352	0.33	38112	0.33
8.711	90086500	99.67	11663910	99.67
Totals	90385852	100.00	11702022	100.00

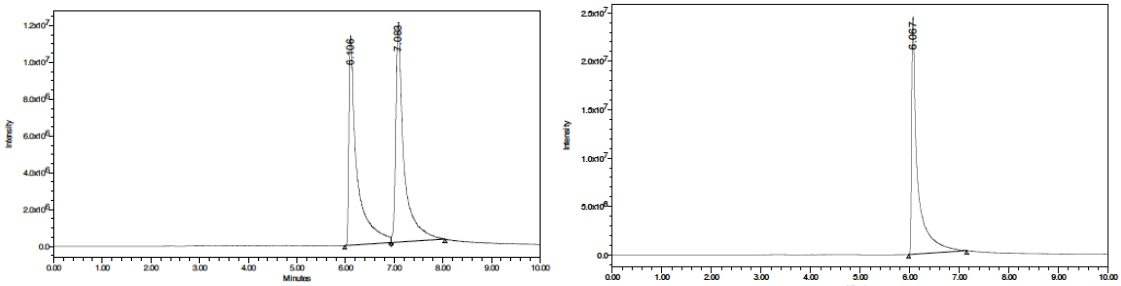
Figure S4. Chiral HPLC of (*S*)-**8a** (*left*) and (*R*)-**8a** (*right*).

Deracemization rate determination:

A 20 mL screw septum vial was charged with 2 mm glass beads (10 g), (*RS*)-**8a** (1.05 g), (*R*)-(or *S*-)-**8a** (0.1 g) and MeCN (10 mL). The vial was sonicated at 20°C for 30 minutes and DBU (0.2 mL) was added. The resulting mixture was sonicated at 20°C while the solid phase *ee* was monitored by chiral HPLC of samples prepared by isolating small amounts of the solid by filtration. The data collected are represented in Figure 2.

(*S*)-2-(adamantan-1-yl)-2-aminoacetonitrile hydrochloride ((*S*)-**6**·HCl**)**.[8] HCl (37% ww; 80 µL) was added to a solution of (*S*)-**8a** (200 mg; 0.68 mmol) in acetone (10 mL) and the resulting reaction mixture was stirred at room temperature for 1 hour. The solid formed was collected by filtration and washed with acetone (2 x 3 mL) to afford a white solid (130 mg; 90%). ^{1}H NMR (400 MHz, DMSO-d6) δ 9.14 (br s, 3H), 4.36 (s, 1H), 2.03 (s, 3H), 1.64-1.56 (m, 12H). ^{1}H NMR (300 MHz, CD_3OD) δ 4.36 (s, 1H), 2.12 (s, 3H), 1.85-1.72 (m, 12H).

(*S*)-2-(adamantan-1-yl)glycine ((*S*)-**3·HCl)**.[9] (*S*)-**6**·HCl (115 mg; 0.54 mmol) was dissolved in HCl (37% ww, 5 mL) and stirred for 60 h at 100°C in a closed vial. The reaction mixture was concentrated under reduced pressure to afford the title compound as a white solid (125 mg; ee > 99%) in 94% yield. $[\alpha]^{25}$ 26.5 (*c* 0.25, CH_3OH). ^{1}H NMR (400 MHz, DMSO) δ 8.17 (br s, 2H), 7.22 (t, *J* = 50.8 Hz, 3H), 1.99 (s, 3H), 1.68-1.53 (m, 12H). ^{1}H NMR (300 MHz, CD_3OD) δ 3.51 (s, 1H), 2.06 (s, 3H), 1.83-1.62 (m, 12H). MS (ES-API): *m/z* 210.1 $[M+H]^+$.



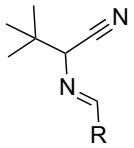
	RT	Area	Height	% Area
1	6.106	130245813	11331034	48.45
2	7.083	138604280	11764095	51.55

	RT	Area	Height	% Area
1	6.067	207249236	24504734	100.00

Figure S5. Chiral HPLC of (*RS*)-**3** (*left*) and (*S*)-**3**·HCl (*right*).

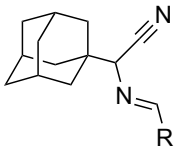
4. Second Harmonic Generation (SHG) measurements

Table S1. SHG responses for imines **7**.



Entry	***R-***	***SHG response***
1	2-naphthyl-	large SHG effect
2	3-methoxy-1-naphthyl-	no SHG effect
3	6-methoxy-2-naphthyl-	large SHG effect
4	3-methoxy-2-nitrophenyl-	no SHG effect
5	2-methoxy-4-nitrophenyl-	no SHG effect
6	2-methoxy-5-nitrophenyl-	no SHG effect
7	4-fluoro-3-nitrophenyl-	no SHG effect
8	4-bromophenyl-	large SHG effect

Table S2. SHG responses for imines **8**.



Entry	***R-***	***SHG response***
1	phenyl-	no SHG effect
2	2-methylphenyl-	no SHG effect
3	3-methylphenyl-	no SHG effect
4	4-methylphenyl-	no SHG effect
5	2-nitrophenyl-	no SHG effect
6	3-nitrophenyl-	no SHG effect
7	4-nitrophenyl-	no SHG effect
8	3-chlorophenyl-	no SHG effect
9	4-chlorophenyl-	small SHG effect
10	2-bromophenyl-	no SHG effect
11	3-bromophenyl-	no SHG effect
12	4-bromophenyl-	no SHG effect
13	2,3-dichlorophenyl-	no SHG effect
14	2,6-dichlorophenyl-	large SHG effect
15	2-fluorophenyl-	no SHG effect
16	4-fluorophenyl-	large SHG effect
17	2-bromo-4-fluorophenyl-	no SHG effect
18	4-bromo-2-fluorophenyl-	no SHG effect
19	3-bromo-4-fluorophenyl-	no SHG effect
20	2,5-difluorophenyl-	no SHG effect
21	2,4-dichlorophenyl-	no SHG effect
22	2,5-dichlorophenyl-	no SHG effect
23	2-bromo-4-chlorophenyl-	no SHG effect
24	4-bromo-2-chlorophenyl-	no SHG effect

5. X-Ray powder diffraction analyses

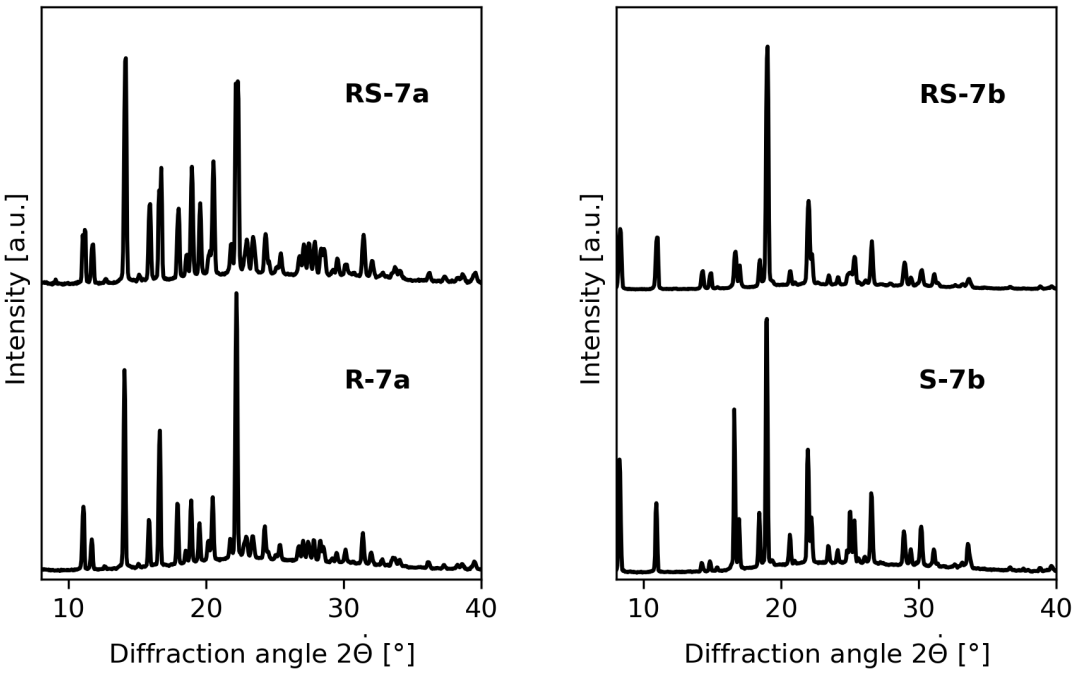


Figure S6. XRPD patterns of the identified conglomerates: **7a** (*RS* vs *R*; *left*) and **7b** (*RS* vs *S*; *right*).

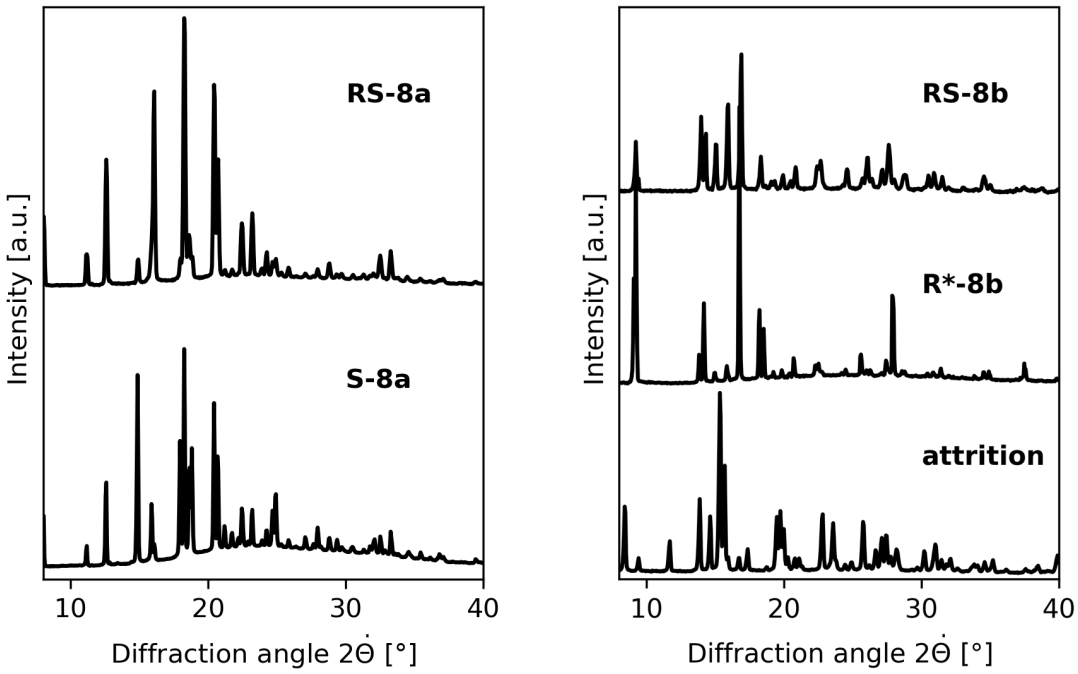


Figure S7. XRPD patterns of the identified conglomerates: **8a** (*RS* vs *S*; *left*) and **8b** (*RS* vs R*(absolute configuration was not confirmed) vs deracemization attempt; *right*).

[As may be seen from Figure S7 (*right*): the XRPD pattern of the solid isolated after attrition of (*RS*)-**8b** in the presence of DBU is different compared to that of racemate **8b** and enantiomerically pure **8b**. This indicates that **8b** crystallizes as an unstable polymorph under deracemization conditions]

6. Crystallographic data for 7a,b and 8a

Racemates of compounds **7a** (CCDC-1845204), **7b** (CCDC-1845205) and **8a** (CCDC-1845206) crystalize in the chiral orthorhombic space group $P2_12_12_1$. This means that both enantiomers have the same space group, but each individual crystal consists of only one (*R* or *S*) enantiomer.

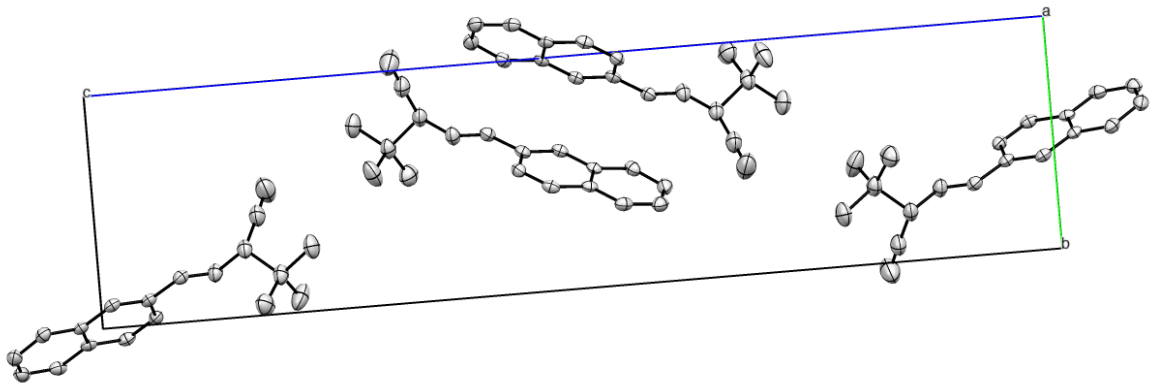


Figure S8. ORTEP view of the unit cell of **7a** along the a axis. Deposited from MeOH.

Table S3. Crystal data and structure refinement for **7a**.

Empirical formula	C17 H18 N2	
Formula weight	250.33	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$ (no. 19)	
Unit cell dimensions	a = 5.9134(5) Å	α = 90°.
	b = 7.7193(7) Å	β = 90°.
	c = 31.935(2) Å	γ = 90°.
Volume	1457.8(2) Å^3	
Z	4	
Density (calculated)	1.141 Mg/m^3	
Absorption coefficient	0.067 mm^{-1}	
F(000)	536	
Crystal size	0.220 x 0.220 x 0.200 mm^3	
Theta range for data collection	2.551 to 25.000°.	
Index ranges	-7<=h<=7, -7<=k<=9, -30<=l<=37	
Reflections collected	9798	
Independent reflections	2553 [R(int) = 0.0258]	
Completeness to theta = 25.000°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.988 and 0.948	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2553 / 0 / 173	
Goodness-of-fit on F^2	1.066	
Final R indices [I>2sigma(I)]	R1 = 0.0308, wR2 = 0.0714	
R indices (all data)	R1 = 0.0370, wR2 = 0.0738	
Absolute structure parameter	-0.2(10)	
Extinction coefficient	0.032(3)	
Largest diff. peak and hole	0.140 and -0.106 e.Å^{-3}	

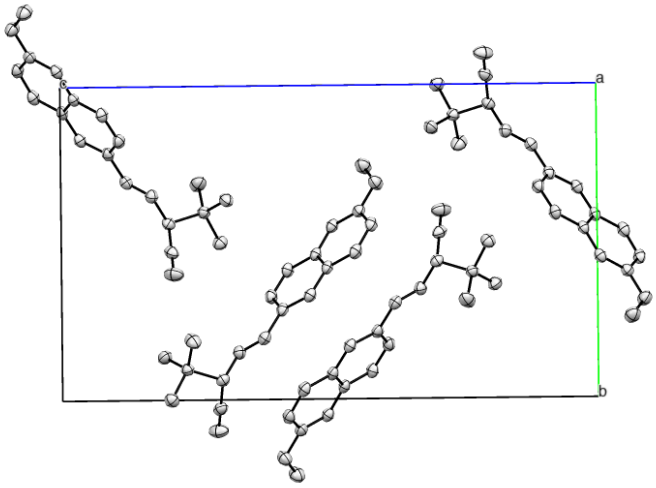


Figure S9. ORTEP view of the unit cell of **7b** along the a axis. Deposited from MeOH.

Table S4. Crystal data and structure refinement for 7**b**.

Empirical formula	C18 H20 N2 O	
Formula weight	280.36	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$ (no. 19)	
Unit cell dimensions	a = 5.9479(5) Å	α = 90°.
	b = 12.3654(11) Å	β = 90°.
	c = 21.1408(18) Å	γ = 90°.
Volume	1554.9(2) $Å^3$	
Z	4	
Density (calculated)	1.198 Mg/m^3	
Absorption coefficient	0.075 mm^{-1}	
F(000)	600	
Crystal size	0.180 x 0.130 x 0.110 mm^3	
Theta range for data collection	2.535 to 24.999°.	
Index ranges	-7<=h<=7, -14<=k<=14, -25<=l<=25	
Reflections collected	25831	
Independent reflections	2729 [R(int) = 0.0381]	
Completeness to theta = 24.999°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.990 and 0.975	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2729 / 0 / 192	
Goodness-of-fit on F^2	1.069	
Final R indices [I>2sigma(I)]	R1 = 0.0299, wR2 = 0.0708	
R indices (all data)	R1 = 0.0352, wR2 = 0.0730	
Absolute structure parameter	-0.4(5)	
Extinction coefficient	0.032(3)	
Largest diff. peak and hole	0.160 and -0.133 $e.Å^{-3}$	

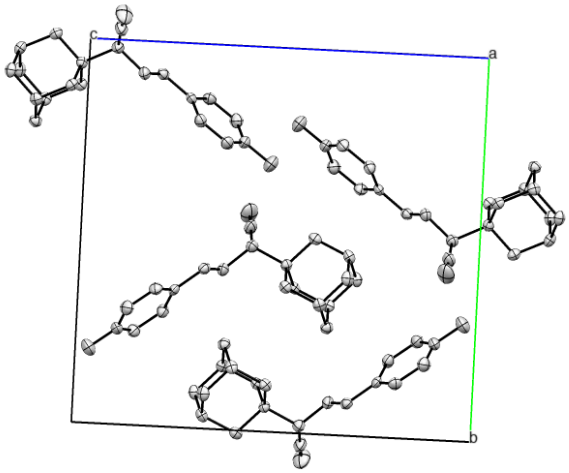


Figure S10. ORTEP view of the unit cell of **8a** along the a axis. Deposited from MeCN.

Table S5. Crystal data and structure refinement for **8a**.

Empirical formula	C19 H21 F N2	
Formula weight	296.38	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$ **(no. 19)**	
Unit cell dimensions	a = 6.4325(3) Å	α = 90°.
	b = 15.1525(7) Å	β = 90°.
	c = 15.7404(7) Å	γ = 90°.
Volume	1534.19(12) $Å^3$	
Z	4	
Density (calculated)	1.283 Mg/m^3	
Absorption coefficient	0.084 mm^{-1}	
F(000)	632	
Crystal size	0.180 x 0.100 x 0.100 mm^3	
Theta range for data collection	2.588 to 24.997°.	
Index ranges	-7<=h<=7, -18<=k<=18, -18<=l<=18	
Reflections collected	20442	
Independent reflections	2711 [R(int) = 0.0312]	
Completeness to theta = 24.997°	99.9 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.977 and 0.967	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2711 / 0 / 200	
Goodness-of-fit on F^2	1.110	
Final R indices [I>2sigma(I)]	R1 = 0.0293, wR2 = 0.0683	
R indices (all data)	R1 = 0.0327, wR2 = 0.0699	
Absolute structure parameter	0.3(3)	
Extinction coefficient	0.025(2)	
Largest diff. peak and hole	0.179 and -0.153 e.$Å^{-3}$	

7. References

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