

Solvent-induced chirality switching in the enantioseparation of halogen-substituted mandelic acids: Structural effects on molecular packing

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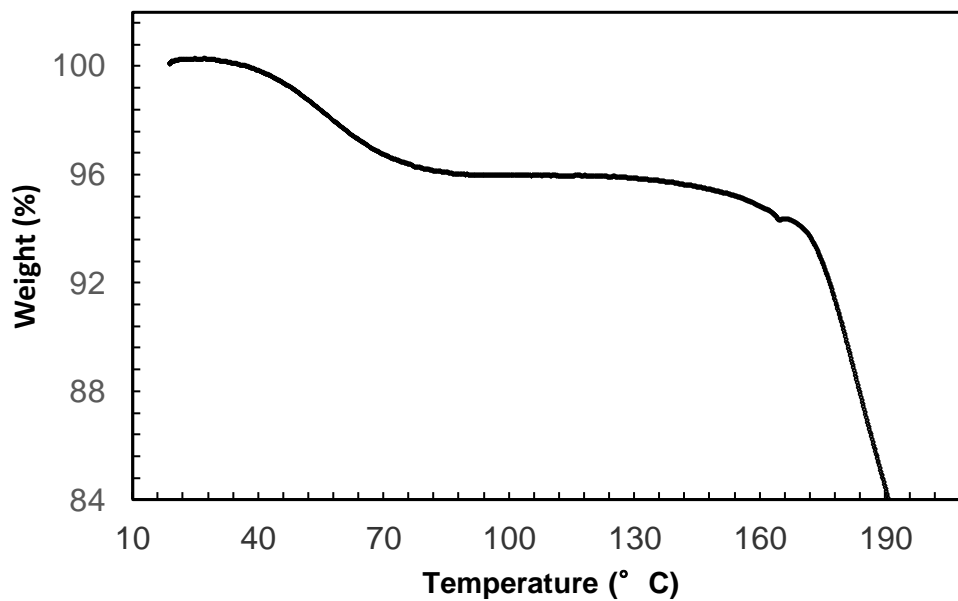


Figure S1. TGA chart of (*S*)-*p*-Br-MA·(+)-ADPE salt (enantiomer of the (*R*)-*p*-Br-MA·(-)-ADPE salt) crystallized from water. Heating rate was 10 °C/min.



Figure S2. Photographs of the deposited solid in the enantioseparation of *p*-F-MA with (-)-ADPE in acetone. The hot solution was stood at room temperature for about 1 h (left) and 10 h (right).

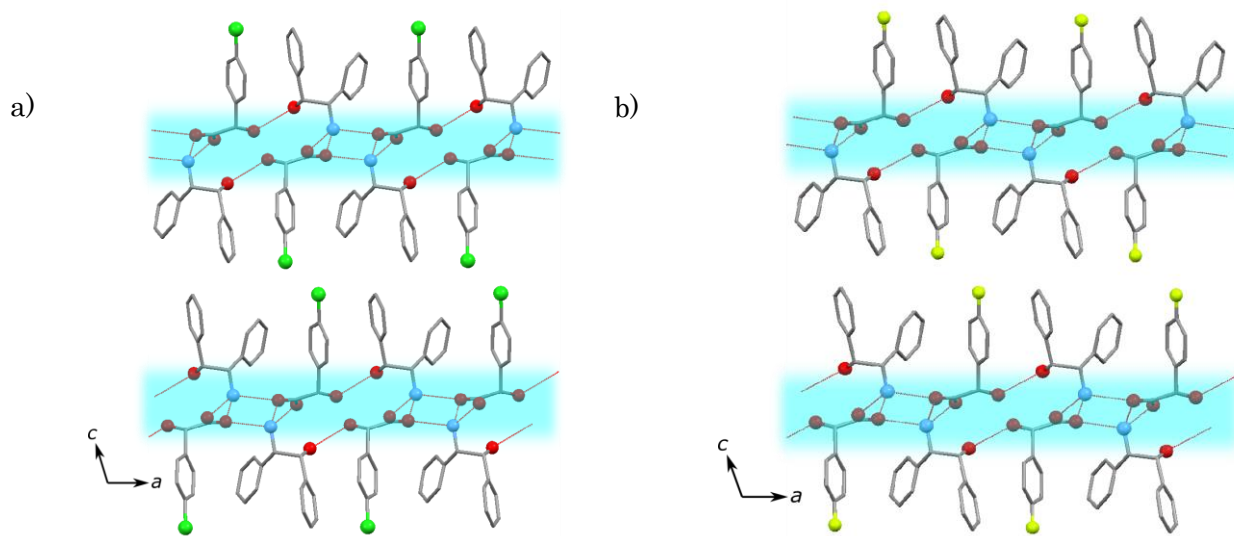


Figure S3. Crystal structures of less-soluble diastereomeric salts a) (*S*)-*p*-Cl-MA·(-)-ADPE, and b) (*S*)-*p*-F-MA·(-)-ADPE. Oxygen and nitrogen atoms are represented with red and blue balls. Halogen atoms are represented with yellow to green balls. The dotted lines show hydrogen bonds.

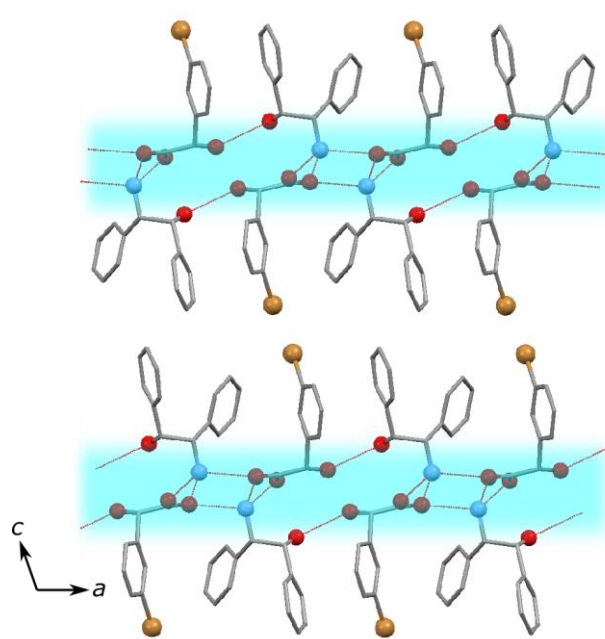


Figure S4. Crystal structure of less-soluble (*S*)-*m*-Br-MA·(-)-ADPE salt prepared from chloroform solution. Oxygen and nitrogen atoms are represented with red and blue balls. Bromine atoms are represented with green balls. The dotted lines show hydrogen bonds.

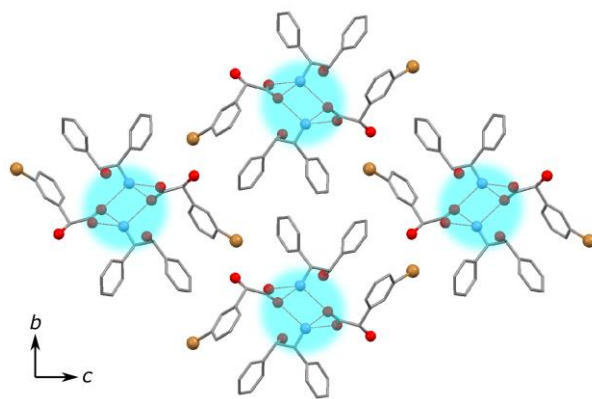


Figure S5. Crystal structure of more-soluble (*S*)-*m*-Br-MA·(+)-ADPE salt prepared from chloroform solution. Oxygen and nitrogen atoms are represented with red and blue balls. Bromine atoms are represented with green balls. The dotted lines show hydrogen bonds.

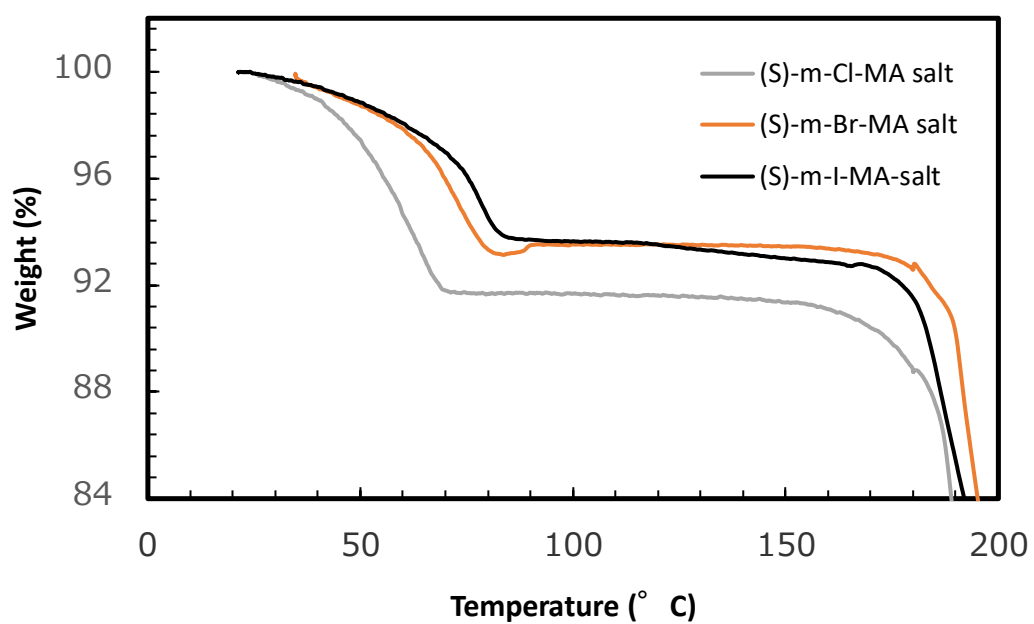


Figure S6. TGA charts of (*S*)-*m*-X-MA·(-)-ADPE salt (X = Cl, Br, I) crystallized from water. Heating rate was 10 °C/min.

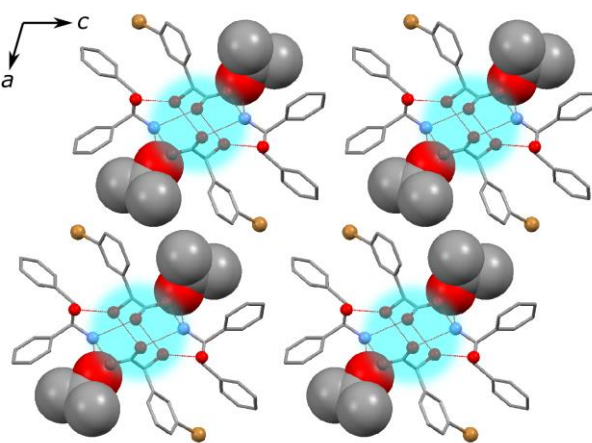


Figure S7. Crystal structure of less-soluble (*S*)-*m*-Br-MA·(-)-ADPE·*i*-PrOH salt prepared from 2-propanol solution. Oxygen and nitrogen atoms are represented with red and blue balls. Bromine atoms are represented with green balls. The dotted lines show hydrogen bonds.

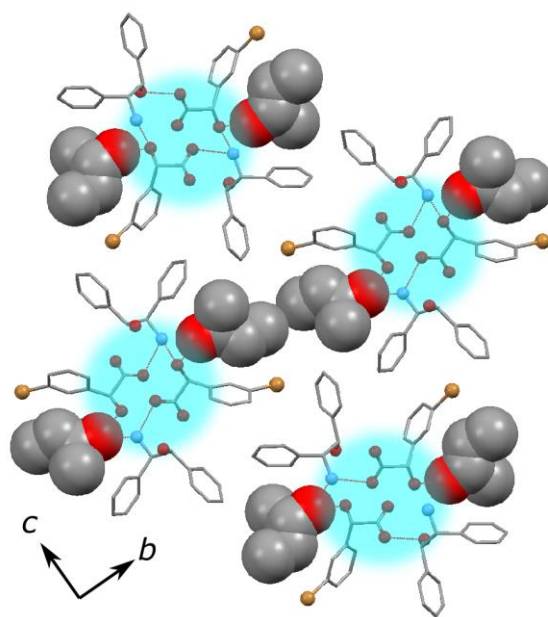


Figure S8. Crystal structure of $(S)\text{-}m\text{-Br-MA}\cdot(+)\text{-ADPE}\cdot s\text{-BuOH}$ salt prepared from 2-butanol solution. Oxygen and nitrogen atoms are represented with red and blue balls. Bromine atoms are represented with green balls. The dotted lines show hydrogen bonds.

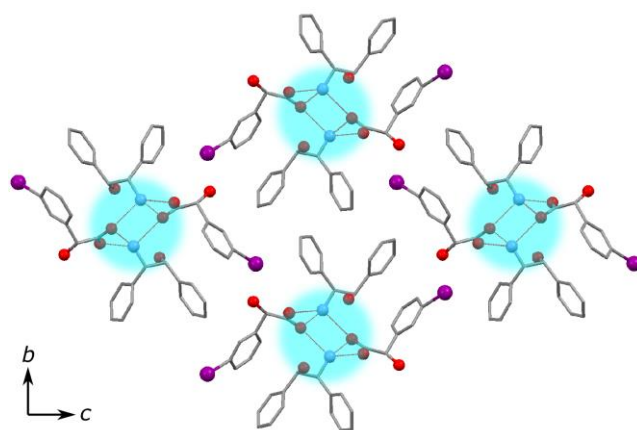


Figure S9. Crystal structure of more-soluble (*R*)-*m*-I-MA·(-)-ADPE salt prepared from toluene solution. Oxygen and nitrogen atoms are represented with red and blue balls. Iodine atoms are represented with purple balls. The dotted lines show hydrogen bonds.

Table S1. Summary of crystallographic data reported in this study.

	(S)-p-F-MA · (1R,2S)-ADPE	(S)-p-Cl-MA · (1R,2S)-ADPE	(S)-p-Br-MA · (1R,2S)-ADPE	(S)-MA · (1R,2S)-ADPE	(S)-m-Cl-MA · (1R,2S)-ADPE
empirical formula	(C ₈ H ₆ O ₃ F) ⁻ · (C ₁₄ H ₁₆ NO) ⁺	(C ₈ H ₆ O ₃ Cl) ⁻ · (C ₁₄ H ₁₆ NO) ⁺	(C ₈ H ₆ O ₃ Br) ⁻ · (C ₁₄ H ₁₆ NO) ⁺	(C ₈ H ₇ O ₃) ⁻ · (C ₁₄ H ₁₆ NO) ⁺	(C ₈ H ₆ O ₃ Cl) ⁻ · (C ₁₄ H ₁₆ NO) ⁺
formula weight	383.4	399.85	444.31	365.41	399.85
temperature (K)	150	150	150	150	150
crystal size (mm)	0.66 × 0.15 × 0.03	0.60 × 0.08 × 0.03	0.92 × 0.32 × 0.05	0.45 × 0.02 × 0.01	0.45 × 0.02 × 0.01
crystal system	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic
space group	<i>P</i> 2 ₁	<i>P</i> 2 ₁	<i>P</i> 2 ₁	<i>C</i> 2	<i>P</i> 2 ₁
<i>a</i> (Å)	10.740(2)	10.675(11)	10.615(5)	30.206(6)	10.760(2)
<i>b</i> (Å)	6.0284(13)	6.069(6)	6.262(3)	5.9102(11)	6.3327(13)
<i>c</i> (Å)	16.127(4)	16.123(17)	15.743(8)	10.554(2)	15.567(3)
α (°)	90	90	90	90	90
β (°)	109.405(2)	107.088(12)	106.458(5)	97.439(2)	109.277(3)
γ (°)	90	90	90	90	90
<i>V</i> (Å ³)	984.9(4)	998.4(18)	1003.7(9)	1868.3(6)	1001.2(4)
<i>Z</i>	2	2	2	4	2
<i>D</i> _c (g/cm ³)	1.293	1.330	1.470	1.299	1.326
μ (MoK α) (mm ⁻¹)	0.095	0.219	2.076	0.089	0.219
$\theta_{\min/\max}$ (°)	1.339/24.985	1.321/25.000	1.349/24.999	1.360/25.000	1.386/24.996
<i>R</i> 1 [<i>F</i> _o > 2σ(<i>F</i> _o)]	0.1035	0.1179	0.0735	0.0716	0.0669
<i>wR</i> 2 (all <i>F</i> _o ²)	0.273	0.2937	0.1874	0.178	0.1625
GOF	1.095	1.154	1.061	1.01	0.944
Flack parameter	0.0(10)	-0.1(3)	0.01(2)	-9.8(10)	-0.1(2)
measured reflns	4630	4546	4650	4460	4809
independent reflns	3007	3085	3217	2977	3292
observed reflns	2893	2263	2989	2540	2252
reflns used	3007	3085	3217	2977	3292
parameters	261	253	255	244	270
CCDC number	1913091	1913092	1913093	1913094	1913095

Table S1. Summary of crystallographic data reported in this study (continued).

	(S)-m-Br-MA · (1R,2S)-ADPE	(R)-m-Cl-MA · (1R,2S)-ADPE	(S)-m-Br-MA · (1S,2R)-ADPE	(S)-m-Cl-MA · (1R,2S)-ADPE · 2-propanol	(S)-m-Br-MA · (1R,2S)-ADPE · 2-propanol
empirical formula	$(C_8H_6O_3Br)^- \cdot (C_{14}H_{16}NO)^+$	$(C_8H_6O_3Cl)^- \cdot (C_{14}H_{16}NO)^+$	$(C_8H_6O_3Br)^- \cdot (C_{14}H_{16}NO)^+$	$(C_8H_6O_3Cl)^- \cdot (C_{14}H_{16}NO)^+ \cdot (C_3H_8O)$	$(C_8H_6O_3Br)^- \cdot (C_{14}H_{16}NO)^+ \cdot (C_3H_8O)$
formula weight	444.31	399.85	444.31	459.95	504.41
temperature (K)	150	150	150	150	150
crystal size (mm)	0.50 × 0.02 × 0.01	0.48 × 0.02 × 0.01	0.25 × 0.03 × 0.02	0.21 × 0.02 × 0.01	0.44 × 0.03 × 0.03
crystal system	monoclinic	orthorhombic	orthorhombic	monoclinic	monoclinic
space group	$P2_1$	$P2_12_12_1$	$P2_12_12_1$	$C2$	$C2$
<i>a</i> (Å)	10.785(3)	5.6070(9)	5.6728(13)	26.10(2)	26.377(9)
<i>b</i> (Å)	6.2318(14)	13.999(2)	14.074(3)	5.801(5)	5.8418(19)
<i>c</i> (Å)	15.842(4)	24.658(4)	24.467(6)	16.174(13)	16.368(5)
α (°)	90	90	90	90	90
β (°)	109.254(3)	90	90	106.512(10)	106.204(4)
γ (°)	90	90	90	90	90
<i>V</i> (Å ³)	1005.2(4)	1935.5(5)	1953.4(8)	2348(3)	2421.9(14)
<i>Z</i>	2	4	4	4	4
<i>D_c</i> (g/cm ³)	1.468	1.372	1.511	1.301	1.383
μ (MoK α) (mm ⁻¹)	2.072	0.226	2.133	0.199	1.732
$\theta_{\min/\max}$ (°)	1.362/24.990	1.652/25.000	1.665/24.996	1.313/24.999	1.296/25.000
<i>R</i> 1 [<i>F</i> _o > 2σ(<i>F</i> _o)]	0.0982	0.0607	0.0450	0.0940	0.0602
<i>wR</i> 2 (all <i>F</i> _o ²)	0.2418	0.1434	0.1135	0.2273	0.1377
GOF	0.980	0.929	0.948	0.902	0.891
Flack parameter	-0.01(3)	0.02(9)	-0.001(12)	-0.3(3)	0.00(2)
measured reflns	4758	9286	9378	5487	5824
independent reflns	3196	3414	3436	3835	3678
observed reflns	2268	2764	2958	1793	2355
reflns used	3196	3414	3436	3835	3678
parameters	267	273	273	292	294
CCDC number	1913096	1913097	1913098	1913099	1913100

Table S1. Summary of crystallographic data reported in this study (continued).

	(R)-m-Cl-MA · (1R,2S)-ADPE · 2-butanol	(S)-m-Br-MA · (1S,2R)-ADPE · 2-butanol	(R)-m-I-MA · (1R,2S)-ADPE · 1-butanol	(S)-m-I-MA · (1R,2S)-ADPE · 2(H₂O)	(R)-m-I-MA · (1R,2S)-ADPE
empirical formula	(C ₈ H ₆ O ₃ Cl) ⁻ · (C ₁₄ H ₁₆ NO) ⁺ · (C ₄ H ₁₀ O)	(C ₈ H ₆ O ₃ Br) ⁻ · (C ₁₄ H ₁₆ NO) ⁺ · (C ₄ H ₁₀ O)	(C ₈ H ₆ O ₃ I) ⁻ · (C ₁₄ H ₁₆ NO) ⁺ · (C ₄ H ₁₀ O)	(C ₈ H ₆ O ₃ I) ⁻ · (C ₁₄ H ₁₆ NO) ⁺ · 2(H ₂ O)	(C ₈ H ₆ O ₃ I) ⁻ · (C ₁₄ H ₁₆ NO) ⁺
formula weight	473.97	518.43	565.42	527.34	491.30
temperature (K)	150	150	150	150	150
crystal size (mm)	0.40 × 0.02 × 0.02	0.75 × 0.02 × 0.01	0.35 × 0.02 × 0.02	0.36 × 0.02 × 0.02	1.00 × 0.04 × 0.03
crystal system	orthorhombic	orthorhombic	monoclinic	orthorhombic	orthorhombic
space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 2 ₁	<i>P</i> 2 ₁ 2 ₁ 2	<i>P</i> 2 ₁ 2 ₁ 2 ₁
<i>a</i> (Å)	5.5803(15)	5.586(3)	13.907(8)	24.310(5)	5.8084(13)
<i>b</i> (Å)	18.221(5)	18.293(9)	5.348(3)	32.200(6)	14.178(3)
<i>c</i> (Å)	24.567(6)	24.714(12)	16.966(9)	5.6265(11)	24.289(5)
<i>α</i> (°)	90	90	90	90	90
<i>β</i> (°)	90	90	95.847(8)	90	90
<i>γ</i> (°)	90	90	90	90	90
<i>V</i> (Å ³)	2498.0(12)	2525(2)	1255.2(12)	4404.3(15)	2000.2(8)
<i>Z</i>	4	4	2	8	4
<i>D_c</i> (g/cm ³)	1.26	1.364	1.496	1.591	1.631
<i>μ</i> (MoK _α) (mm ⁻¹)	0.189	1.663	1.311	1.492	1.629
<i>θ</i> _{min/max} (°)	1.391/24.989	1.385/24.990	1.206/24.996	1.265/24.993	1.663/24.990
<i>R</i> 1 [<i>F</i> _o > 2σ(<i>F</i> _o)]	0.0502	0.0684	0.076	0.0704	0.0758
<i>wR</i> 2 (all <i>F</i> _o ²)	0.1056	0.1243	0.1373	0.1551	0.1634
GOF	0.911	0.853	0.91	0.914	1.023
Flack parameter	-0.04(9)	-0.012(18)	0.01(6)	0.01(4)	-0.02(4)
measured reflns	12025	12056	5935	21375	9476
independent reflns	4408	4441	3583	7750	3512
observed reflns	3140	2787	2315	4652	3240
reflns used	4408	4441	3583	7750	3512
parameters	335	311	301	542	243
CCDC number	1913101	1913102	1913103	1913104	1913105

Table S2. Hydrogen bond metrics of the crystals reported in this study.

Compound name	D-H...A	D-H / Å	H-A / Å	D-A / Å	∠D-H...A / °
(S)-p-F-MA · (1R,2S)-ADPE					
	N1-H20...O3	1.033	1.686	2.713	172.69
	N1-H21...O2	1.033	1.865	2.818	151.77
	N1-H22...O2	1.033	1.733	2.746	166.04
	O1-H18...O4	0.655	2.302	2.838	140.45
(S)-p-Cl-MA · (1R,2S)-ADPE					
	N1-H19...O4	1.033	1.658	2.688	174.09
	N1-H20...O2	1.033	1.860	2.814	151.93
	N1-H21...O2	1.033	1.737	2.741	162.95
	O3-H22...O1	0.840	2.127	2.826	140.41
(S)-p-Br-MA · (1R,2S)-ADPE					
	N1-H20...O4	1.033	1.660	2.692	176.19
	N1-H21...O1	1.032	1.744	2.738	160.40
	N1-H22...O1	1.033	1.855	2.817	153.45
	O2-H1...O3	0.840	1.945	2.772	168.04
(S)-MA · (1R,2S)-ADPE					
	N1-H21...O3	1.034	1.710	2.723	165.38
	N1-H22...O1	1.033	1.752	2.774	169.65
	N1-H23...O1	1.033	1.879	2.859	157.16
	O4-H11...O2	0.839	2.070	2.842	152.71
(S)-m-Cl-MA · (1R,2S)-ADPE					
	N2-H19...O2	0.922	1.928	2.810	159.58
	N2-H20...O2	0.937	1.931	2.748	144.48
	N2-H21...O3	0.983	1.754	2.719	166.11
	O1-H18...O4	0.745	2.075	2.785	159.39
(S)-m-Br-MA · (1R,2S)-ADPE					
	N1-H18...O4	0.984	1.736	2.711	170.62
	N1-H19...O2	1.038	1.797	2.741	149.17
	N1-H20...O2	0.794	2.085	2.832	156.69
	O1-H22...O5	0.840	1.988	2.812	166.45
(R)-m-Cl-MA · (1R,2S)-ADPE					
	N1-H18...O3	0.768	2.008	2.772	173.28
	N1-H19...O5	1.044	1.849	2.805	150.59
	N1-H20...O3	1.055	1.739	2.750	159.12
(S)-m-Br-MA · (1S,2R)-ADPE					
	N1-H3...O4	0.874	1.950	2.818	171.47
	N1-H4...O3	0.886	1.940	2.755	152.26
	N1-H5...O3	0.843	1.978	2.768	155.59

Table S2. Hydrogen bond metrics of the crystals reported in this study (continued).

Compound name	D-H...A	D-H / Å	H-A / Å	D-A / Å	∠D-H...A / °
(S)-m-Cl-MA · (1R,2S)-ADPE · 2-propanol					
	N1-H3...O3	1.034	1.834	2.820	158.20
	N1-H4...O5	1.033	1.696	2.704	163.94
	N1-H5...O4	1.033	1.905	2.763	138.29
	O1-H1...O3	0.841	1.918	2.709	156.11
	O2-H2...O1	0.839	1.872	2.684	162.36
	O5-H14...O4	0.840	2.010	2.610	127.75
(S)-m-Br-MA · (1R,2S)-ADPE · 2-propanol					
	N1-H28...O4	1.032	1.836	2.818	157.54
	N1-H29...O3	1.033	1.914	2.777	138.91
	N1-H30...O5	1.033	1.699	2.705	163.29
	O1-H1...O4	0.840	1.959	2.745	155.59
	O2-H2...O1	0.840	1.952	2.728	153.29
	O5-H8...O3	0.840	1.932	2.653	143.30
(R)-m-Cl-MA · (1R,2S)-ADPE · 2-butanol					
	N1-H36...O2	0.926	2.099	2.914	146.23
	N1-H37...O5	0.979	1.789	2.759	170.16
	N1-H38...O3	1.005	1.732	2.702	161.14
	O1-H1...O4	0.839	1.774	2.609	172.75
	O5-H39...O2	0.840	2.060	2.849	156.21
(S)-m-Br-MA · (1S,2R)-ADPE · 2-butanol					
	N1-H36...O1	1.033	1.719	2.710	159.14
	N1-H37...O5	1.034	1.763	2.761	160.90
	N1-H38...O3	1.034	2.078	2.919	136.90
	O2-H1...O4	0.840	1.781	2.609	168.04
	O5-H40...O3	0.840	2.066	2.848	154.62
(R)-m-I-MA · (1R,2S)-ADPE · 1-butanol					
	N1-H30...O2	1.033	1.658	2.677	167.91
	N1-H31...O5	1.033	1.979	2.836	138.46
	N1-H32...O1	1.033	1.747	2.758	165.10
	O3-H2...O4	0.840	1.811	2.618	160.63
	O1-H33...O5	0.840	2.124	2.899	153.32

Table S2. Hydrogen bond metrics of the crystals reported in this study (continued).

Compound name	D-H...A	D-H / Å	H-A / Å	D-A / Å	∠D-H...A / °
(S)-m-I-MA · (1R,2S)-ADPE · 2(H₂O)					
	N1-H1A...O9	1.034	1.778	2.704	147.00
	N1-H1B...O8	1.033	1.851	2.815	153.65
	N1-H1C...O5	1.033	1.906	2.815	144.97
	N2-H2A...O10	1.033	1.982	2.909	147.86
	N2-H2B...O7	1.033	1.765	2.714	150.77
	N2-H2C...O6	1.032	1.877	2.864	158.91
	O2-H4O...O5	0.839	2.072	2.784	142.34
	O4...O2			2.842	
	O5...O11			2.748	
	O6...O7			2.748	
	O6...O12			2.783	
	O8...O9			2.727	
	O8...O11			2.864	
	O11...O12			2.801	
(R)-m-I-MA · (1R,2S)-ADPE					
	N1-H20...O1	1.033	1.738	2.761	169.93
	N1-H21...O1	1.033	1.810	2.771	153.08
	N1-H22...O4	1.033	1.818	2.826	164.19

General and Materials

All the ^1H and ^{13}C NMR spectra were recorded on a 300, 400 or 500 MHz spectrometer. IR spectra were reported in reciprocal centimeters. Melting points are uncorrected. Optical rotation values were measured with a polarimeter. All the solvents and (1*R*,2*S*)-(-)-ADPE were purchased and used as received. The enantiomeric excess of the mandelic acids was determined by chiral HPLC analysis (Daicel Chiralcel OD-3 column 4.6 × 250 mm) with UV detection at 254 nm after derivatized to the corresponding methyl esters by the reaction with TMSCHN₂.

Synthesis and characterization

Halogen substituted mandelic acids except for 4-fluoromandelic acid were prepared from the corresponding acetophenones by α -dibromination followed by hydrolysis under basic condition.¹ 4-Fluoromandelic acid was synthesized from 4-fluorobenzaldehyde according to the literature procedure.²

Procedure for the synthesis of 4-bromomandelic acid (*p*-Br-MA): 4-Bromoacetophenone (9.96 g, 50.0 mmol) was dissolved in acetic acid (30 mL) and the solution was cooled to 20 °C. To the solution was added dropwise bromine (16.3 g, 102 mmol) dissolved in acetic acid (10 mL) while maintaining the temperature below 40 °C. After stirring for 2 hours at 0 °C, the precipitated solid was filtered and washed with 50% ethanol and dried under reduced pressure to afford $\alpha,\alpha,4$ -tribromoacetophenone as a white solid (14.0 g, 39.2 mmol, 79%). Mp. 93-95 °C. ^1H NMR (500 MHz, CDCl₃): δ (ppm) 7.97 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.8 Hz, 2H), 6.59 (s, 1H). IR (KBr): ν (cm⁻¹) 3447, 3040, 1693, 1582, 1395, 1202, 1070.

To the ice-cooled mixture of $\alpha,\alpha,4$ -tribromoacetophenone (13.9 g, 39.0 mmol) and water (15 mL) was added dropwise NaOH aq. (19.8 M, 10 mL) and the mixture was stirred for 3 days below 5 °C. Insoluble solid was filtered off and washed with water. The filtrate was washed with ether (20 mL × 7) and the aqueous phase was acidified with conc. HCl aq. (20 mL). The aqueous phase was extracted with ether (20 mL × 4) and the combined organic phase was dried over anhydrous sodium sulfate. After concentration under reduced pressure, the residue was dissolved in methanol and benzylamine (4.08 g, 38.1 mmol) was added. After the solvent was removed under reduced pressure, the solid was recrystallized from 80% ethanol (51 mL). The obtained salt was added to 1N HCl aq. and extracted with ether (10 mL × 3). The combined organic phase was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to give 4-bromomandelic acid (7.40 g, 32.0 mmol, 83%) as a white solid. Mp. 118.5-120.0 °C. ^1H NMR (300 MHz, CDCl₃): δ (ppm) 7.52 (d, J = 8.4 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 5.23 (s, 1H). IR (KBr): ν (cm⁻¹) 3411, 2964, 1725, 1490, 1260, 1189, 1058.

p-Cl-MA, *o*-Cl-MA, *m*-Cl-MA, *m*-Br-MA, *m*-I-MA were prepared according to the above procedure.

α,α -dibromo-4-chloroacetophenone. Pale yellow solid. Yield 72%. Mp. 93-96 °C. ^1H NMR (300 MHz, CDCl_3): δ (ppm) 8.05 (d, $J = 8.9$ Hz, 2H), 7.49 (d, $J = 8.9$ Hz, 2H), 6.60 (s, 1H). IR (KBr): ν (cm^{-1}) 3037, 1695, 1587, 1401, 1276, 1205, 1093, 988.

α,α -dibromo-2-chloroacetophenone. Purified by silica gel column chromatography (eluent; hexane : $\text{CHCl}_3 = 3 : 1$) and obtained as pale yellow oil. Yield 67%. ^1H NMR (300 MHz, CDCl_3): δ (ppm) 7.65-7.62 (m, 1H), 7.51-7.47 (m, 2H), 7.43-7.37 (m, 1H), 6.79 (s, 1H). IR (neat): ν (cm^{-1}) 3427, 3008, 1722, 1589, 1435, 1198, 1065.

α,α -dibromo-3-chloroacetophenone. Purified by silica gel column chromatography (eluent; hexane : $\text{CHCl}_3 = 3 : 1$) and obtained as pale yellow oil. Yield 88%. ^1H NMR (500 MHz, CDCl_3): δ (ppm) 8.07 (dd, $J_1 = J_2 = 1.7$ Hz, 1H), 7.98 (ddd, $J_1 = 7.9$ Hz, $J_2 = J_3 = 1.7$ Hz, 1H), 7.63-7.59 (m, 1H), 7.46 (dd, $J_1 = J_2 = 7.9$ Hz, 1H), 6.62 (s, 1H). IR (neat): ν (cm^{-1}) 3384, 3013, 1701, 1566, 1419, 1254, 1069.

$\alpha,\alpha,3$ -tribromoacetophenone. Purified by silica gel column chromatography (eluent; hexane : $\text{CHCl}_3 = 3 : 1$) and obtained as pale yellow oil. Yield 90%. ^1H NMR (500 MHz, CDCl_3): δ (ppm) 8.21 (dd, $J_1 = J_2 = 1.8$ Hz, 1H), 8.04-8.01 (m, 1H), 7.78-7.74 (m, 1H), 7.39 (dd, $J_1 = J_2 = 7.8$ Hz, 1H), 6.60 (s, 1H). IR (neat): ν (cm^{-1}) 3384, 3013, 1702, 1566, 1419, 1254, 1192, 1069.

α,α -dibromo-3-iodoacetophenone. Purified by silica gel column chromatography (eluent; hexane : $\text{CHCl}_3 = 1 : 1$) and obtained as pale yellow oil. Yield 85%. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 8.40 (dd, $J_1 = J_2 = 1.6$ Hz, 1H), 8.07-8.05 (m, 1H), 7.98-7.95 (m, 1H), 7.25 (dd, $J_1 = J_2 = 8.0$ Hz, 1H), 6.60 (s, 1H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm) 184.6, 143.1, 138.5, 132.6, 130.4, 128.8, 94.4, 39.0. IR (neat): ν (cm^{-1}) 1699, 1560, 1414, 1254, 1190, 988, 806, 672, 654, 626. MALDI-TOF-MS: $m/z = 402.76$ [$\text{M}-\text{H}$] $^-$ (calcd. For $\text{C}_8\text{H}_5\text{Br}_2\text{IO} - \text{H} = 402.77$).

4-chloromandelic acid (*p*-Cl-MA). White solid. Yield 76%. Mp. 120.5-122.0 °C. ^1H NMR (300 MHz, CDCl_3): δ (ppm) 7.40 (d, $J = 8.7$ Hz, 2H), 7.37 (d, $J = 8.7$ Hz, 2H), 5.24 (s, 1H). IR (KBr): ν (cm^{-1}) 3411, 2964, 1725, 1490, 1260, 1189, 1058.

2-chloromandelic acid (*o*-Cl-MA). Pale yellow solid. Yield 80%. Mp. 86-88 °C. ^1H NMR (300 MHz, CDCl_3): δ (ppm) 7.46-7.39 (m, 2H), 7.34-7.28 (m, 2H), 5.67 (s, 1H). IR (KBr): ν (cm^{-1}) 3195, 1751, 1694, 1477, 1218, 1072.

3-chloromandelic acid (*m*-Cl-MA). White solid. Yield 51%. Mp. 117-120 °C. ^1H NMR (300 MHz, CDCl_3): δ (ppm) 7.49-7.47 (m, 1H), 7.38-7.32 (m, 3H), 5.24 (s, 1H). IR (KBr): ν (cm^{-1}) 3442, 2936, 1712, 1577, 1261, 1195, 1063.

3-bromomandelic acid (*m*-Br-MA). White solid. Yield 74%. Mp. 123.5-124.5 °C. ^1H NMR (300 MHz, CDCl_3): δ (ppm) 7.64 (s, 1H), 7.47-7.39 (m, 2H), 7.24 (dd, $J_1 = J_2 = 7.8$ Hz, 1H), 5.12 (s, 1H). IR (KBr): ν (cm^{-1}) 3443, 2933, 1710, 1572, 1474, 1260, 1191, 1097.

3-iodomandelic acid (*m*-I-MA). White solid. Yield 55%. Mp. 98-101 °C. ^1H NMR (300 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$): δ (ppm) 7.84 (s, 1H), 7.65 (d, $J = 7.8$ Hz, 1H), 7.45 (d, $J = 8.1$ Hz, 1H), 7.14-7.07 (m, 1H), 5.09 (s, 1H). IR (KBr): ν (cm^{-1}) 3390, 2928, 1739, 1287, 1179, 1106, 940, 780, 748, 685.

4-fluoromandelic acid (*p*-F-MA). To the cooled solution of lithium chloride (3.40 g, 80.2 mmol) and potassium hydroxide (9.02 g, 161 mmol) in water (32 mL) was added 1,4-dioxane (32 mL). To the solution were added dropwise 4-fluorobenzaldehyde (4.97 g, 40.1 mmol) and bromoform (10.1 g, 40.1 mmol). The mixture was stirred for 19 h at 5-10 °C and further 24 h at room temperature. The mixture was diluted with water and washed with ether (20 mL × 3) and the aqueous phase was acidified with 6N HCl aq. (50 mL). The aqueous phase was extracted with ether (50 mL × 10) and the combined organic phase was dried over anhydrous sodium sulfate. After concentration under reduced pressure, the residue was dissolved in methanol and benzylamine (3.98 g, 36.8 mmol) was added. After the solvent was removed under reduced pressure, the solid was recrystallized from 80% ethanol (69 mL). The obtained salt was added to 1N HCl aq. and extracted with ether (10 mL × 3). The combined organic phase was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to give 4-fluoromandelic acid (5.21 g, 30.6 mmol, 76%) as a white solid. Mp. 130-132 °C. ¹H NMR (300 MHz, CDCl₃): δ (ppm) 7.46-7.42 (m, 2H), 7.10-7.05 (m, 2H), 5.25 (s, 1H). IR (KBr): ν (cm⁻¹) 3453, 2911, 1722, 1609, 1519, 1240, 1067.

Enantioseparation experiments

Racemic mandelic acid (1 mmol) and (1*R*,2*S*)-ADPE (1 mmol) were dissolved in methanol. After concentration, the resulting white solids were recrystallized from an appropriate solvent to obtain the salt crystals, which were filtered and dried overnight. The apparent yield was calculated based on the ¹H NMR data, considering the amount of the included solvent. A portion of the salt was decomposed by the addition of 1 M aqueous HCl solution and the aqueous layer was extracted with diethyl ether. After drying over anhydrous Na₂SO₄, the organic layer was concentrated to obtain enantio-enriched MA. To a solution of MA in toluene (2 ml) and methanol (1 ml) was added TMSCHN₂ (ether solution) until the solution remained yellow. The mixture was stirred at room temperature and the solvent was removed under reduced pressure. The residue was purified by silica gel PTLC (hexane/ethyl acetate = 2:1) to produce methyl ester of MA as a colorless liquid. The ee value of the ester was determined by chiral HPLC analysis.

Methyl ester of *p*-Br-MA: Daicel Chiralcel OD-3, hexane/2-propanol=90:10, 1.0 mL/min; *t*_r(*S*) = 8.1 min, *t*_r(*R*) = 9.0 min.

Methyl ester of *p*-Cl-MA: Daicel Chiralcel OD-3, hexane/2-propanol=90:10, 1.0 mL/min; *t*_r(*S*) = 7.4 min, *t*_r(*R*) = 8.5 min.

Methyl ester of *p*-F-MA: Daicel Chiralcel OD-3, hexane/2-propanol=90:10, 1.0 mL/min; *t*_r(*S*) = 7.6 min, *t*_r(*R*) = 9.2 min.

Methyl ester of *m*-Cl-MA: Daicel Chiralcel OD-3, hexane/2-propanol=90:10, 1.0 mL/min; *t*_r(*S*) = 7.3 min, *t*_r(*R*) = 8.6 min.

Methyl ester of *m*-Br-MA: Daicel Chiralpak IB-3, hexane/2-propanol=90:10, 0.5 mL/min; *t*_r(*S*) =

15.0 min, $t_r(R)$ = 16.2 min.

Methyl ester of *m*-I-MA: Daicel Chiralcel OD-3, hexane/2-propanol=90:10, 1.0 mL/min; $t_r(S)$ = 8.3 min, $t_r(R)$ = 10.0 min.

X-ray crystallographic analysis

Single crystals suitable for X-ray diffraction analysis were prepared by slow evaporation of the saturated solutions of the salts. X-ray crystallographic data were collected on a Bruker Smart APEX II diffractometer with graphite monochromated Mo K α radiation. Data collections were carried out at low temperatures (150 K). The structures were solved by a direct method (SIR 2014) and refined by SHELXL-2013 programs. Crystallographic information files have been deposited with the Cambridge Structural Database.

References

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