

Electronic Supplementary Information (ESI) for:

Asymmetric Strecker Reaction at the Solid/Solid Interface

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General comments:

All solvents and chemicals were purchased from commercial sources. *p*-Tolualdehyde, benzhydrylamine (**2**), DBU and methanol were used after distillation. **CAUTION:** Hydrogen cyanide (HCN) was prepared from H₂SO₄ and NaCN in water and isolated by the distillations. Melting points were recorded on an As One ATM-01 apparatus and are uncorrected. ¹H and ¹³C NMR spectra were recorded using a JEOL JNM-ECA500II FT NMR system. The chemical shifts δ are given in parts per million (ppm) relative to TMS (¹H NMR, $\delta=0.0$ ppm) as an internal standard and the solvent peak (¹³C NMR, CDCl₃ =77.0 ppm). The X-ray single crystal diffraction was recorded by Rigaku R-axis Rapid II imaging plate diffractometer equipped with Cu K α rotating anode X-ray tube. Data collection, integration, and scaling, were carried out using the Rigaku RAPID AUTO. Powder X-ray diffraction (XRD) patterns were recorded on a Rigaku UltraX 18 and SmartLab using Cu K α radiation.

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Methods:

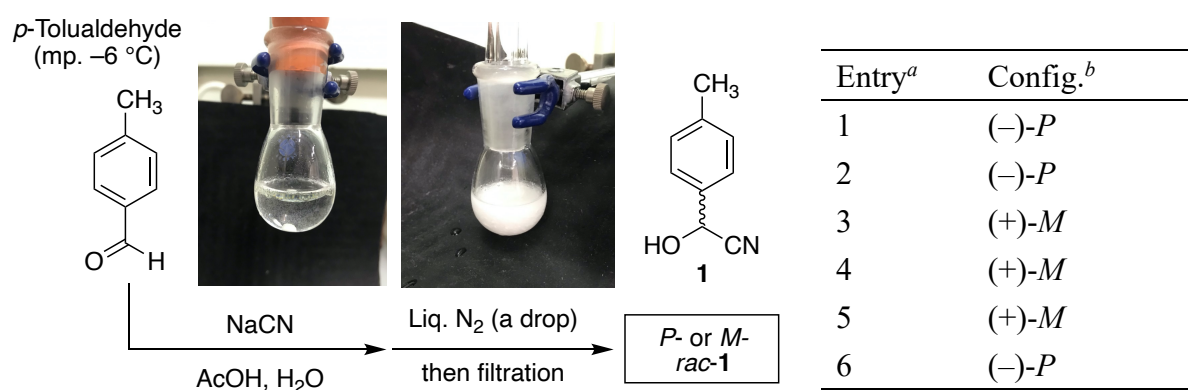
Spontaneous formation of enantioenriched chiral powder-like crystal of racemic 4-methylmandelonitrile (**1**):

p-Tolualdehyde (1.18 mL, 10.0 mmol) and acetic acid (0.62 mL, 10.8 mmol) were added to an aqueous solution (5.0 mL) of NaCN (514 mg, 10.5 mmol) at 0 °C and the mixture was stirred overnight at room temperature. A drop of liquid nitrogen was then added to the mixture at 0 °C, with stirring. The resulting white solid was collected by vacuum filtration. After washing the solid with a small amount of cold water, volatiles were removed under vacuum to afford cyanohydrin **1** (1.42 g, 9.66 mmol) in 97% yield.

Stereospecific synthesis of enantioenriched aminonitrile **3** (Table 1, entry 3):

P-Enriched powder-like crystal of racemic 4-methylmandelonitrile (**1**) (147.2 mg, 1.0 mmol) and benzhydryl ammonium acetate (**2**·CH₃CO₂H) (243.3 mg 1.0 mmol) were mixed using an agate mortar and pestle to give a finely powdered reaction mixture. This was stored in a screw-cap vial for 20 days at room temperature. The volatiles were removed in vacuo. Methanol (2.0 mL) was added to form the suspension, which was stirred overnight. Hydrogen cyanide (70 μL, 1.77 mmol) was added, followed by the addition of DBU (400 μL, 2.57 mmol) in four separate portions (100 μL × 4, every 5 min), with stirring. After a partial (80–90%) dissolution of suspended solid **3** at ~50 °C, the amount of remaining solid increased upon recrystallization during a gradual cooling to room temperature over 1 h. This thermal cycle was conducted nine times to afford, as recovered by filtration, *D*-**3** (170.9 mg, 0.547 mmol) with 99% ee as a white solid in 55% yield. The ee value was determined by HPLC on a chiral stationary phase.

Table S1. Spontaneous formation of enantioenriched powder-like crystal of racemic cyanohydrin **1**. After cyanide addition to *p*-tolualdehyde forming racemic cyanohydrin **1**, spontaneous crystallization of enantioenriched chiral crystal of *rac*-cyanohydrin **1** was occurred by the addition of liquid nitrogen under stirred condition.^{5,S1} Both of the enantiomorphs **1** could be formed spontaneously without using any chiral materials. When *P*- or *M*-**1** were loaded into the biphasic reaction mixture under stirring as seed instead of liquid nitrogen, powder-like crystal of *rac*-**1** with the same handedness to that of the seed could be obtained by the filtration.

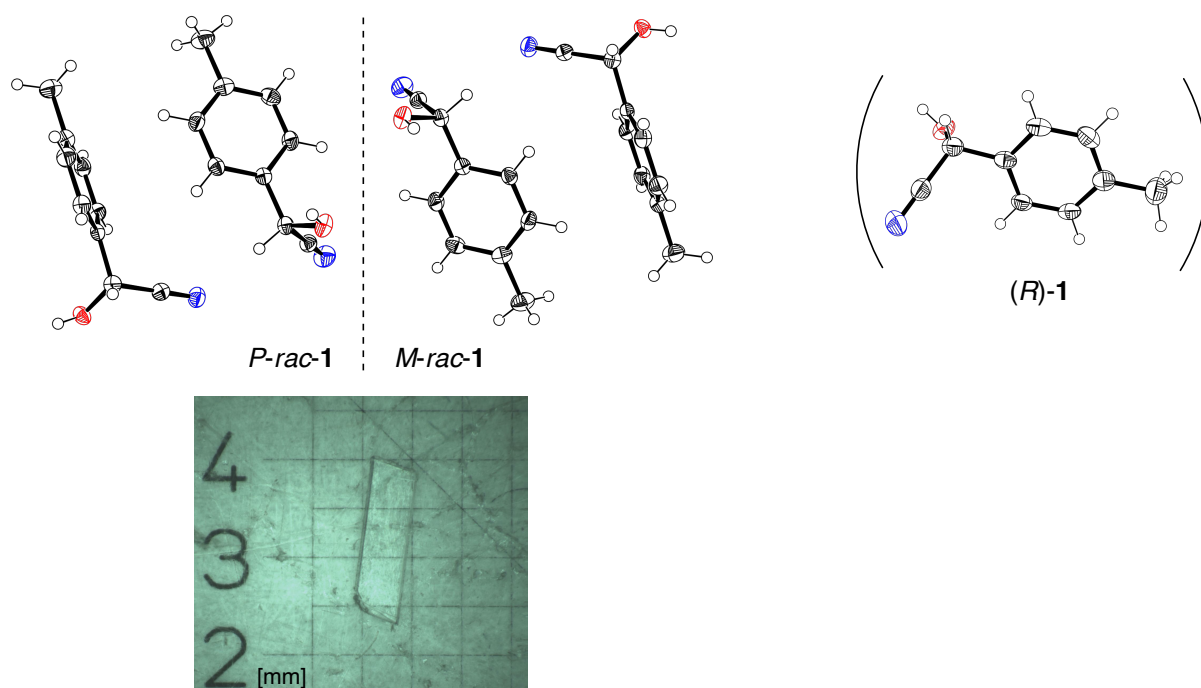


^a **Experimental:** To an aqueous solution (5.0 mL) of NaCN (514 mg, 10.5 mmol), were added *p*-tolualdehyde (1.18 mL, 10.0 mmol) and acetic acid (0.62 mL, 10.8 mmol) at 0 °C. The mixture was stirred overnight at room temperature. A drop of liquid nitrogen was added to a mixture at 0 °C with stirring. Resulting white solid was collected by a suction filtration. After washing the solid with small amount of cold water, volatiles were removed under vacuum to give cyanohydrin **1** as a white solid (1.42 g, 9.66 mmol) in 97% yield. ¹H-NMR^{S2} (500 MHz, CDCl₃): δ 2.38 (s, 3H), 2.52 (br s, 1H), 5.50 (s, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H). ¹³C NMR^{S2} (125 MHz, CDCl₃): δ 21.3, 63.6, 119.0, 126.8, 129.9, 132.4, 140.2.

Preparation of KBr disc of *rac*-1** for solid-state CD^{S3}:** Solid cyanohydrin *rac*-**1** (1 mg) and KBr (100 mg) were mixed with agate pestle and mortar. The disk (10 mm in diameter) was prepared from the mixture (30 mg).

^b The sign of solid-state CD at 235 nm in the parenthesis and *P/M* absolute helicity in the X-ray single-crystal structure were indicated.

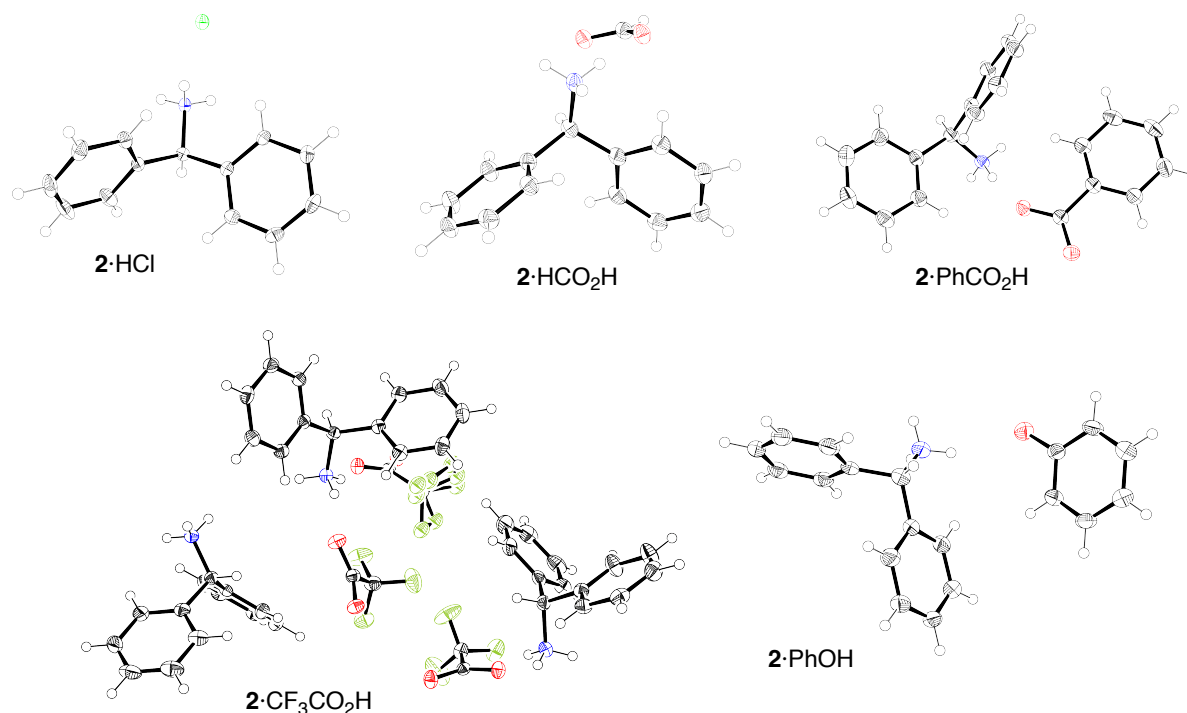
Figure S1.^{a,b} Single-crystal X-ray structures of cyanohydrin **1**. Ortep drawings of *P*- and *M*-*rac*-cyanohydrin **1** showing thermal ellipsoids at 50% probability level. The single-crystal structure of (*R*)-**1** was also shown, which was prepared by chiral cyclic dipeptide, cyclo[(*S*)-phenylalanyl-(*S*)-histidyl], catalyzed asymmetric HCN addition to *p*-tolualdehyde.^{S4} (*R*)-**1** has right-handed helical structure through the intermolecular hydrogen bonds between cyano (CN) and hydroxy (OH) groups.



^a **HPLC conditions**, Column: Daicel Chiralpak IA-3 (250 mm, 4.6 mm in diameter), Eluent: *n*-hexane/2-propanol/CF₃CO₂H (97/3/0.1, v/v/v), Flow rate: 2.0 mL/min, Temperature: rt. UV detection: 220 nm, *t*_R: 9.8 min for (*S*)-**1** and 10.6 min for (*R*)-**1**. ***P/M*-racemic 4-methylmandelonitrile (**1**)**, Space group: *P*₂₁₂₁₂₁, Mp.: 58.5–59.1 °C (powder of single-crystal recrystallized from toluene). **Recrystallization of *rac*-**1** using crystal seed**: Racemic cyanohydrin **1** (5.55 g) was completely dissolved in toluene (20 mL) at 40 °C (solubility of **1**: 185 g/L in toluene at 24 °C). After cooling to room temperature, finely powdered seed **1** prepared from the single-crystal **1** with known (*P/M*) crystal chirality was added to this supersaturated solution. After slow concentration under atmospheric pressure, *rac*-**1** with the same handedness as the seed can be obtained. A tiny amount of acetic acid in toluene can stabilize **1**. **(*R*)-4-Methylmandelonitrile (**1**)**, Space group: *P*₂₁, Mp.: 57.1–58.0 °C (recrystallized from toluene, >99% ee).

^b Crystallographic data have been deposited with Cambridge crystallographic data centre (CCDC 2117047 for *P-rac-1*, CCDC 2204872 for *M-rac-1*, CCDC 2117046 for (*R*)-**1**).

Table S2. Single-crystal X-ray structures of benzhydryl ammonium salts. Ortep drawings are set with thermal ellipsoids at 50% probability level.



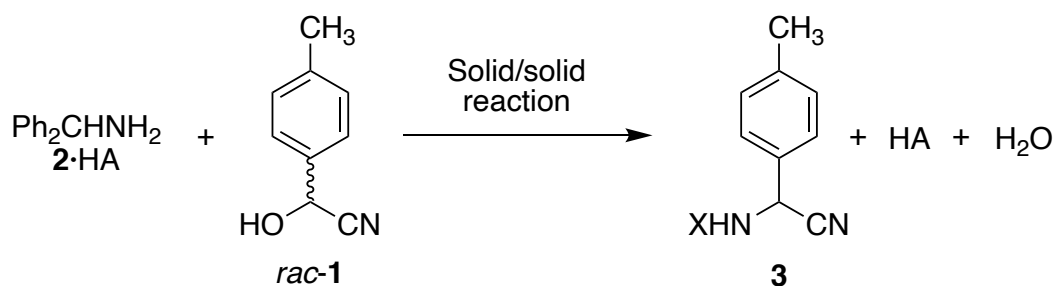
Ammonium salt ^a	Melting point ^b (°C)	Space group	CCDC ^c
2·HCl	301–304	<i>C2/c</i>	2117483
2·HCO ₂ H	133.7–134.6 (decomp.)	<i>P2₁/c</i>	2117484
2·CF ₃ CO ₂ H	139.4–140.6	<i>P2₁/c</i>	2117485
2·PhCO ₂ H	144.1–144.6	<i>P2₁/n</i>	2117486
2·CH ₃ CO ₂ H	130.0–132.1	<i>Fdd2</i>	2117487
2·PhOH	65.9–66.8	<i>P-1</i>	2117488

^a **General procedure of the synthesis of benzhydryl ammonium salts:** Amine (**2**) and acid (1:1, molar ratio) were mixed in methanol. After the removal of methanol in vacuo, benzhydryl ammonium salt was obtained as a white solid, which was recrystallized from the mixed solvent of toluene and methanol (1:1, v/v) by the slow evaporation to give the single-crystal for X-ray structure analysis.

^b The crystal obtained from the mixed solvent of toluene/methanol (1/1, v/v).

^c Crystallographic data have been deposited with Cambridge crystallographic data centre.

Table S3. Strecker-type solid/solid reaction between cyanohydrin **1 and various benzhydryl ammonium salts.** As shown in entries 1 and 2, the Strecker-type reaction did not occur, when hydrochloride and formate were used as substrate at room temperature. When trifluoroacetate and benzoate was submitted, the reaction proceeded (entries 3 and 4), however, it needs longer reaction time than the acetate (entries 5-7). Because of weak acid/base interaction between **2** and phenol, the Strecker-type reaction proceeded via the homogeneous state at room temperature (entries 8 and 9). Released acetic acid can be easily separable from the reaction mixture by the evaporation.



Entry	Benzhydryl ammonium salt 2 ·HA	Solid/solid reaction ^a		
		Temp. (°C)	Time (day)	Conversion (%)
1	2 ·HCl	rt	60	No reaction
2	2 ·HCO ₂ H	rt	17	No reaction
3	2 ·CF ₃ CO ₂ H	rt	63	5
4	2 ·PhCO ₂ H	rt	30	13
5	2 ·CH ₃ CO ₂ H	3	25	trace
6	2 ·CH ₃ CO ₂ H	rt	25	92
7	2 ·CH ₃ CO ₂ H	40	2	86
8	2 ·PhOH	3	1	48
9	2 ·PhOH	rt	1	97 ^b

^a The molar ratio of benzhydryl ammonium salt : *rac*-**1** = 1 : 1. Equimolar amount of powder-like crystal of *rac*-**1** and the benzhydryl ammonium salt were mixed using agate pestle and mortar to give finely powdered reaction mixture. This was stored in screw-topped vial for the indicated reaction time. The reaction conversion (%) was determined from the ¹H NMR analysis of a part of reaction mixture from the ratio of integrated α-protons of **1** and **3**. ¹H NMR of **3** (500 MHz, CDCl₃) δ 2.37 (s, 3H), 4.56 (s, 1H), 5.23 (s, 1H), 7.21-7.57 (m, 14H).

^b Reaction proceeded via apparently homogeneous glassy state.

Figure S2. Strecker-type solid/solid reaction between cyanohydrin **1** and benzhydryl ammonium acetate $2 \cdot \text{CH}_3\text{CO}_2\text{H}$. **A**, Reaction scheme and finely powdered reaction mixtures. **B**, Microscope image of finely powdered initial reaction mixture. The particle size of the powders to be 5–20 μm . **C**, Powder X-ray diffraction pattern of initial reaction mixture in comparison with the simulated patterns obtained from the single-crystal X-ray data of $2 \cdot \text{CH}_3\text{CO}_2\text{H}$ and *rac*-**1**.

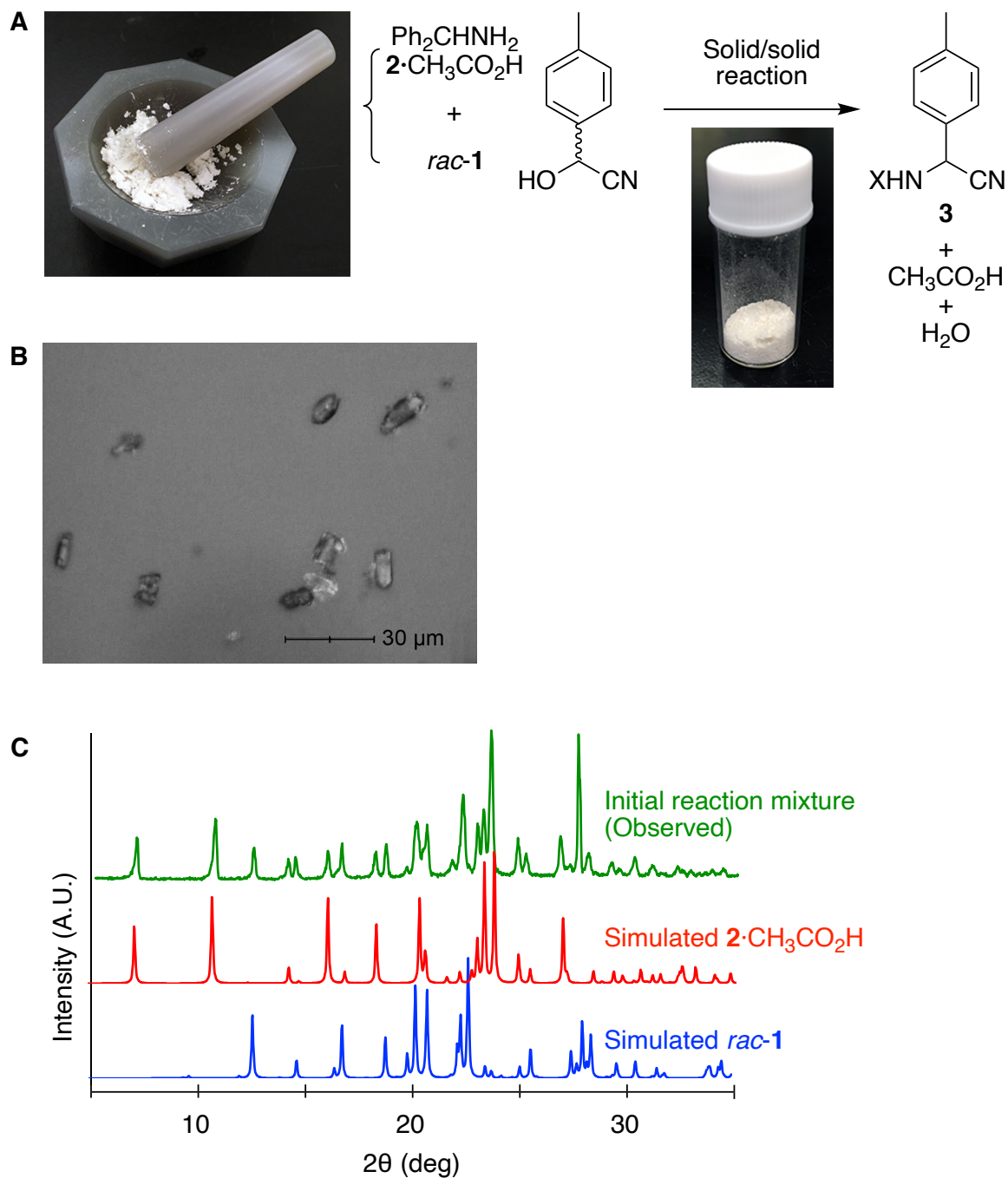
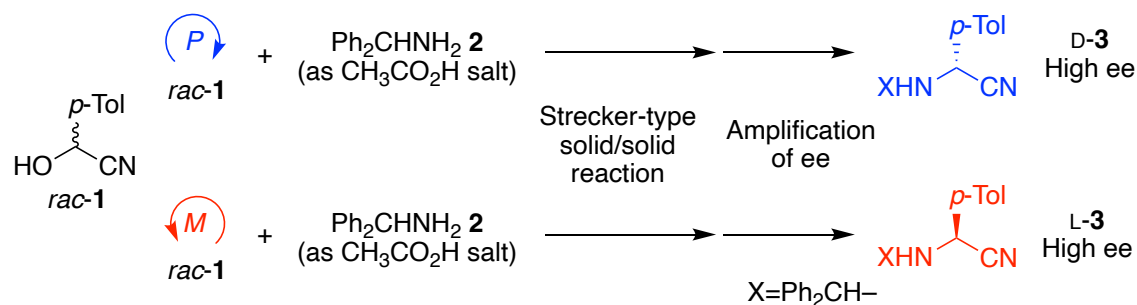


Table S4. Additional experimental data for Table 1.

Entry ^a	<i>rac</i> -1	Solid/solid reaction		Aminonitrile 3	
		Temp. (°C)	Time (days)	% ee ^b (Config.)	Yield (%)
11	<i>P</i> (-)	35	4	91 (D)	62
12	<i>P</i> (-)	40	2	94 (D)	59
13	<i>M</i> (+)	35	4	76 (L)	62
14	<i>M</i> (+)	40	2	91 (L)	63
15 ^c	<i>P</i> (-)	35	4	>99 (D)	47
16 ^c	<i>P</i> (-)	35	4	90 (D)	42
17 ^c	<i>P</i> (-)	35	4	84 (D)	60
18 ^c	<i>M</i> (+)	35	4	93 (L)	23
19 ^c	<i>M</i> (+)	35	4	92 (L)	42
20 ^c	<i>M</i> (+)	35	4	52 (L)	60

^a Experimental procedure (Table 1, entry 10): *M*-Enriched power-like crystal of racemic 4-methylmandelonitrile (**1**) (147.2 mg, 1.0 mmol), benzhydryl ammonium acetate (**2**·CH₃CO₂H) (243.3 mg 1.0 mmol) and (*E*)-*N*-(4-methylbenzylidene)-1,1-diphenylmethanamine (**4**) (57 mg, 0.2 mmol) were mixed using agate pestle and mortar to give finely powdered reaction mixture. This was stored in screw-topped vial for four days at 35 °C. The volatiles were removed in vacuo and methanol (2.0 mL) was added to form the suspension, which was stirred overnight. Hydrogen cyanide (70 μL, 1.77 mmol) was added and then DBU (400 μL, 2.57 mmol) was added in four separate portions (100 μL × 4 times in every 5 min) with stirring. After a partial (ca. 80–90%) dissolution of suspended solid **3** at ca. 50 °C, the remaining solid regrew during the gradual cooling to room temperature over 1 h. This thermal cycle was conducted eight times to give, as recovered by filtration, L-**3** (217 mg, 0.695 mmol) with >99% ee as a white solid in 58% yield. The ee was determined by HPLC on a chiral stationary phase.

^b The ee was determined by using HPLC on a chiral stationary phase: Column: Daicel Chiralpak IA-3 (250 mm, 4.6 mm in diameter), Eluent: *n*-hexane/2-propanol (4/1, v/v), Flow rate: 1.5 mL/min, UV detection: 220 nm, Temp.: rt, *t*_R: 6.87 min for D-**3** and 11.8 min for L-**3**.

^c Imine **4**, prepared from **2** and *p*-tolualdehyde, was added to the solid/solid reaction. The molar ratio used was **4**:*rac*-**1**:**2**·CH₃CO₂H = 0.2:1:1 (mmol).

References

- S1) Kawasaki, T.; Suzuki, K.; Hakoda, Y.; Soai, K. Achiral nucleobase cytosine acts as an origin of homochirality of biomolecules in conjunction with asymmetric autocatalysis. *Angew. Chem. Int. Ed.* **2008**, *47*, 496-499.
- S2) Rafiee, E.; Tangestaninejad, S.; Habibi, M. H.; Mirkhani, V. Cobalt polyoxometalate, $[\text{CoW}_{12}\text{O}_{40}]^{5-}$, as a new reusable catalyst for addition of trimethylsilyl cyanide to carbonyl compounds. *Bull. Korean Chem. Soc.* **2005**, *26*, 1585-1587.
- S3) Sunatsuki, Y.; Fujita, K.; Maruyama, H.; Suzuki, T.; Ishida, H.; Kojima, M.; Glaser, R. Chiral crystal structure of a $P2_12_12_1$ kryptoracemate Iron(II) complex with an unsymmetric azine ligand and the observation of chiral single crystal circular dichroism. *Cryst. Growth Des.* **2014**, *14*, 3692-3695.
- S4) Tanaka, K.; Mori, T.; Inoue, S. The cyclic dipeptide cyclo[(*S*)-phenylalanyl-(*S*)-histidyl] as a catalyst for asymmetric addition of hydrogen cyanide to aldehydes. *J. Org. Chem.* **1990**, *55*, 181-185.