Supporting Information for:

Chirally and Chemically Reversible Asymmetric Strecker Reaction

Yutaro Machida, Yudai Tanaka, Yuya Masuda, Aya Kimura, Tsuneomi Kawasaki*

Department of Applied Chemistry, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan

* E-mail: tkawa@rs.tus.ac.jp

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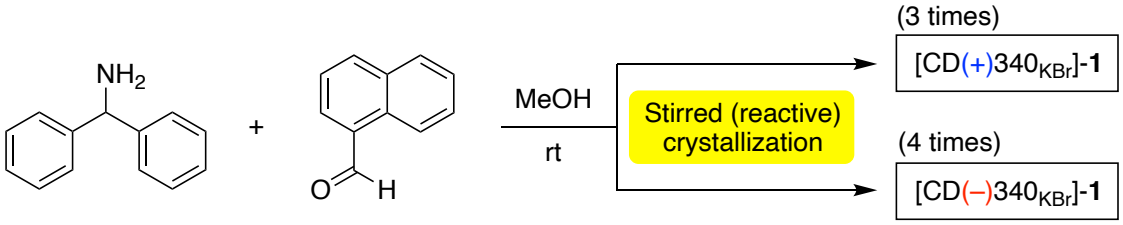
General Comments:

All solvents and chemicals were purchased from commercial sources. 1-Naphthaldehyde, furfural, benzhydrylamine, DBU, methanol and toluene were used after distillation. **CAUTION:** Hydrogen cyanide (HCN) was prepared from H_2SO_4 and NaCN in water and isolated by the distillations. ^{1}H NMR spectra were recorded using a JEOL JNM-ECA500II and JNM-ESC300 FT NMR systems. The chemical sifts δ are given in parts per million (ppm) relative to TMS (δ=0.0 ppm) as an internal standard. The X-ray single-crystal diffraction was recorded by Rigaku R-axis Rapid II imaging plate diffractometer equipped with Cu Kα 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 SmartLab using Cu Kα radiation.

— Additional Experimental Data and Experimental Methods —

Table S1. Spontaneous crystallization of achiral imine 1 under stirring in combination with dehydrative condensation of benzhydrylamine and 1-naphthaldehyde. Among seven crystallizations, [CD(+)340$_{KBr}$]-**1** obtained in three times and [CD(–)340$_{KBr}$]-**1** in four times; thus, without addition of any chiral sources, enantioenriched powder-like crystal of **1** obtained spontaneously.



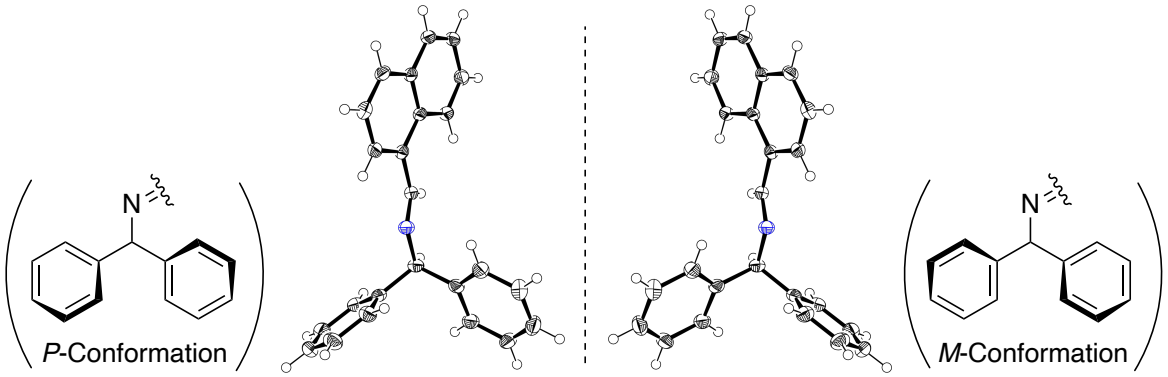
entry [a]	ΔCD [b,c]
1	−124
2	+133
3	−90
4	+84
5	−48
6	+3.6
7	−45

[a] **Representative experimental method for stirred crystallization:** To a solution of benzhydrylamine (345 μL, 2.0 mmol) in methanol (8.0 mL), 1-naphthaldehyde (272 μL, 2.0 mmol) was added. After stirring the mixture overnight at room temperature, the resulting solid product **1** was collected by the filtration to give chiral enantioenriched crystal **1** (561 mg, 1.75 mmol) in 88% yield.

[b] The sign and value (mdeg) of the solid-state CD at 340 nm.

[c] **Preparation of KBr disk**: Solid **1** and KBr (the ratio of **1**/KBr = 1/400, *w*/*w*) were mixed by the careful grinding using agate pestle and mortar. The solid mixture (27 mg) was pressed into translucent disk (10 mm in diameter), and was submitted to the solid-state CD spectroscopy.

Table S2. Absolute structure of the chiral crystal of achiral imine 1. In the crystal structure, two phenyl rings of benzhydryl group have chiral *P*- or *M*-conformations, respectively. Crystal chirality, *i.e*., either *P*- or *M*-**1** were determined in relation to its sign of solid-state CD at 340 nm. Although deterministic absolute structure parameters[S1–S4] could not be obtained from the measurement of one specific single-crystal batch, we concluded the absolute structure from the measurements of four independent single-crystal batches, which indicate the same relationship between *P*/*M*-conformation and the sign of solid-state CD of **1**.



P-**1**: CD(–)340$_{KBr}$ *M*-**1**: CD(+)340$_{KBr}$

single-crystal **1**			Flack	Parsons [b]	Hooft [b]	CCDC
batch #	Conformation	ΔCD [a]				
1	*P*	(–)	–0.2 (4)	–0.3 (4)	–0.2 (3)	2223802
2	*P*	(–)	–0.1 (3)	–0.2 (3)	–0.2 (3)	2223803
3	*M*	(+)	0.3 (5)	0.4 (4)	0.4 (4)	2223804
4	*M*	(+)	0.0 (4)	0.3 (4)	0.1 (2)	2223805

[a] The sign of solid-state CD at 340 nm.

[b] Calculated by PLATON.

Figure S1. Viedma ripening[S5] of enantioenriched powder-like crystal 1. The enantioimbalance of **1** could be significantly improved by vigorous grinding of the suspended **1** in methanol. The ΔCD value of initial powder-like crystal [CD(+)340$_{KBr}$]-**1** (+45 mdeg at 340 nm) was enhanced continuously to achieve finally 197 mdeg after isolation. On the other hand, the enantiomorphous [CD(–)340$_{KBr}$]-**1** with the ΔCD value of –192 mdeg was isolated after vigorous stirring for 55 h starting from the one with –4.2 mdeg.

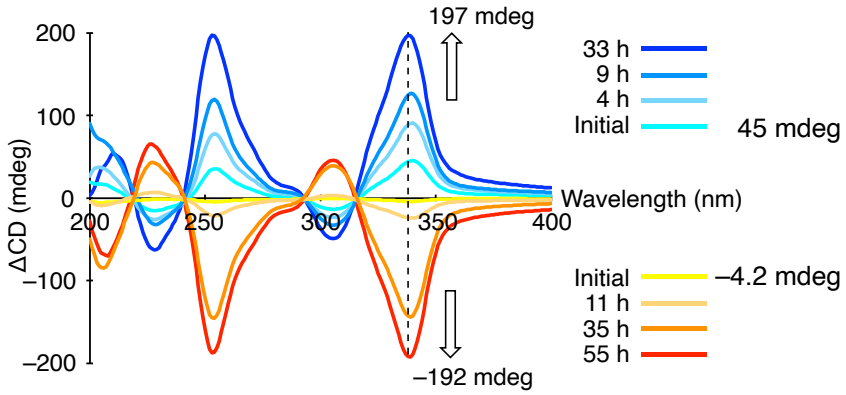


Figure S2. Quantitative analysis of crystal ee (%) of imine 1 by solid-state CD spectroscopy with KBr matrix. (a) Calibration curve for ee of 1 vs ΔCD value (mdeg) at 340 nm. (b) Rationalization of the correlation and linearity of the calibration curve. When solid-state CD spectroscopy of one specific single-crystal [CD(–)340$_{KBr}$]-**1** was measured, ΔCD of –201 mdeg was observed as maximum absolute value; therefore, the solid possess 201 mdeg at 340 nm has been considered as 100% ee in the calibration curve. When KBr disks were prepared in the same manner as described in Table S1 (footnote *b*) by mixing [CD(+)340$_{KBr}$]-**1** (solid **A**) and [CD(–)340$_{KBr}$]-**1** (solid **B**) in the ratios of 2/1, 1/1, and 1/2, respectively, the corresponding observed CD signals fitted nicely to the calibration curve.

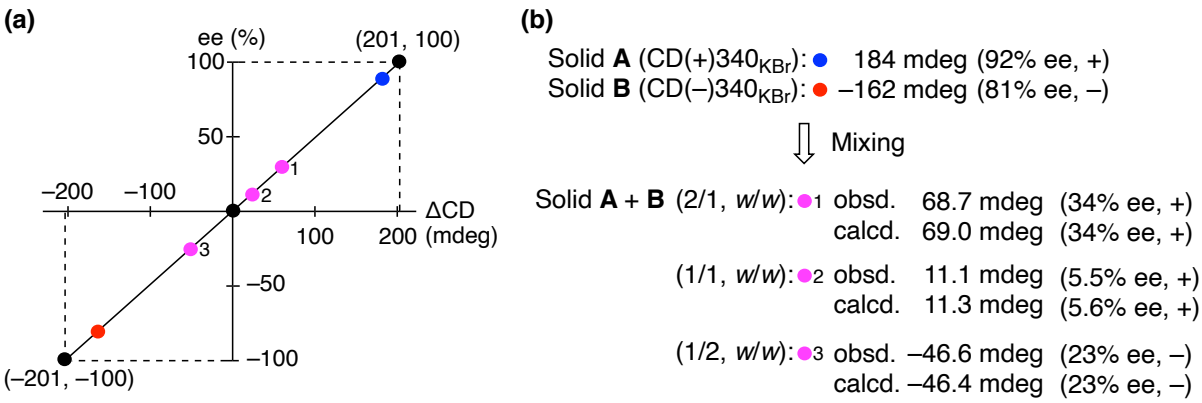


Figure S3. (a) Powder-like crystal of 1 obtained by stirred crystallization. (b) Finely-powdered crystal of 1 by grinding using agate pestle and mortar. (c) Reaction apparatus of vapor-phase HCN addition.

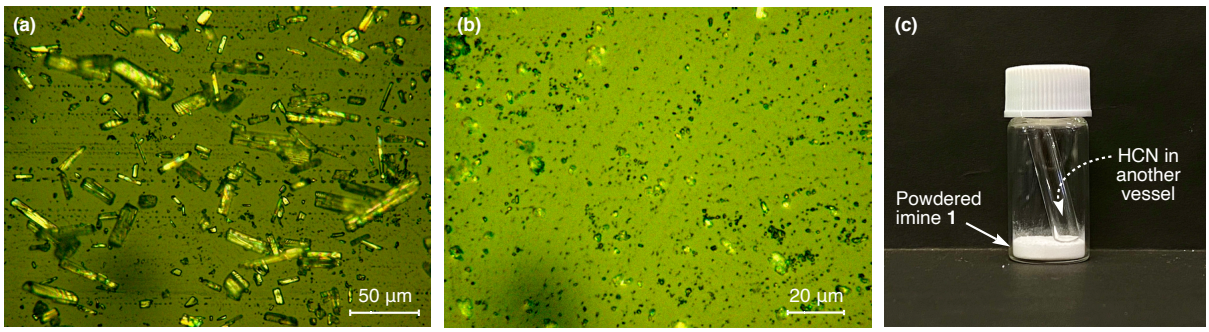
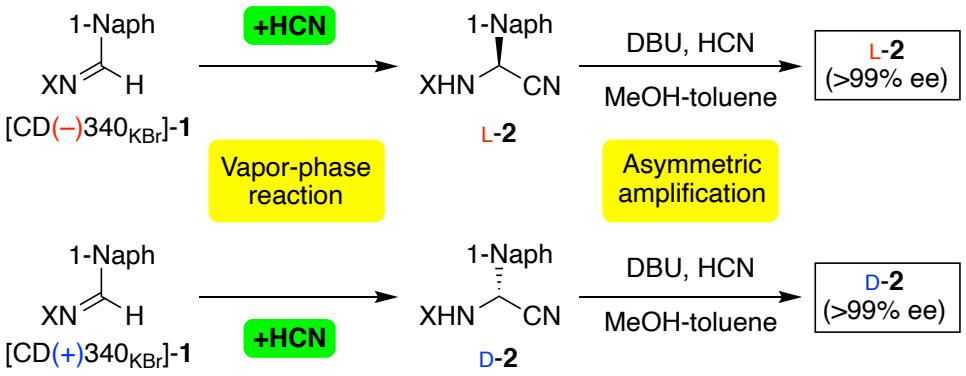


Table S3. Additional experimental results of Table 1.



entry	solid support	imine **1**	aminonitrile **2**	
			% ee (config.) [a]	yield (%) [b]
series I [c]				
8	–	CD(–)340$_{KBr}$	>99 (L)	47
9	–	CD(+)340$_{KBr}$	>99 (D)	53
series II [d]				
10	Na_2SO_4	CD(–)340$_{KBr}$	7 (L)	15
11	Na_2SO_4	CD(+)340$_{KBr}$	5 (D)	34
12	–	CD(–)340$_{KBr}$	3 (L)	38
13 [e]	–	CD(+)340$_{KBr}$	5 (D)	47
14	NaCl	CD(–)340$_{KBr}$	5 (L)	41
15	KBr	CD(–)340$_{KBr}$	6 (L)	–
16	$MgSO_4$	CD(–)340$_{KBr}$	BDL [f]	–
17 [g]	KCN	CD(+)340$_{KBr}$	2 (D)	40

[a] See Table 1, footnote *b*.

[b] See Table 1, footnote *c*.

[c] **Representative procedure for series I (Table 1, entry 1):** The powdered [CD(–)340$_{KBr}$]-**1** (68 mg, 0.21 mmol) and liquid HCN (12 µL, 0.3 mmol) in another vessel were stored in sealed vial at room temperature (see also Figure S3c). After stored overnight, asymmetric amplification was applied. Thus, resulting mixture was suspended in methanol (500 µL) including HCN (12 µL, 0.3 mmol), and the resulting suspension was stirred for 2 h. Residual imine **1** was reacted with HCN to give **2** at this stage. Then, DBU (150 µL, 1.0 mmol) and toluene (500 µL) were added. The mixture

was allowed to warm to *ca*. 45 °C dissolving apparently 80 to 90% of suspended solid. Before the complete dissolution of **2**, the power to the heating bath was shut off to cool to room temperature gradually over a period of >1 hour in accordance with the lowering of the water bath temperature. After an additional several heating/cooling cycles (see also Figure S4), solid was collected by filtration to give L-**2** with >99% ee (47 mg, 0.14 mmol) as white solid in 67% yield.

[d] **Representative procedure for series II (Table 1, entry 6):** The powder-like crystal of [CD(+)340$_{KBr}$]-**1** (31 mg, 0.1 mmol) was ground into fine powder together with Na_2SO_4 (500 mg) as solid support (the ratio **1**/solid support = 31/500, *w*/*w*). The mixture and liquid HCN (5 μL, 0.13 mmol) in another vessel was stored in sealed vial at room temperature overnight. After the removal of volatiles, chloroform was added to the mixture and Na_2SO_4 was removed by the filtration. Reaction conversion was checked by ^{1}H NMR measurement to be the molar ratio of imine **1** : aminonitrile **2** = 77 : 23. The formation of D-**2** with 7% ee was confirmed by the analysis of the mixture using HPLC on a chiral stationary phase.

[e] Vapor-phase reaction was performed at 0 °C.

[f] Below the detection limit.

[g] See also Table 1, footnote *e*.

Figure S4. Amplification of solid-state ee of L- and D-aminonitrile 2 by the thermal cycles. In this heating-cooling cycle, nearly equimolar amounts of suspended D- and L-**2** dissolve during heating to afford a reduced amount of suspended **2** with amplified ee. Then, during cooling, deracemization proceeded, *i.e.*, the crystal recovers without decrease in ee thanks to solution-phase racemization. In the previous work,[S6] we have demonstrated that the step-by-step change in ee of suspended solid fitted nicely to the simulation based on the model mentioned above.

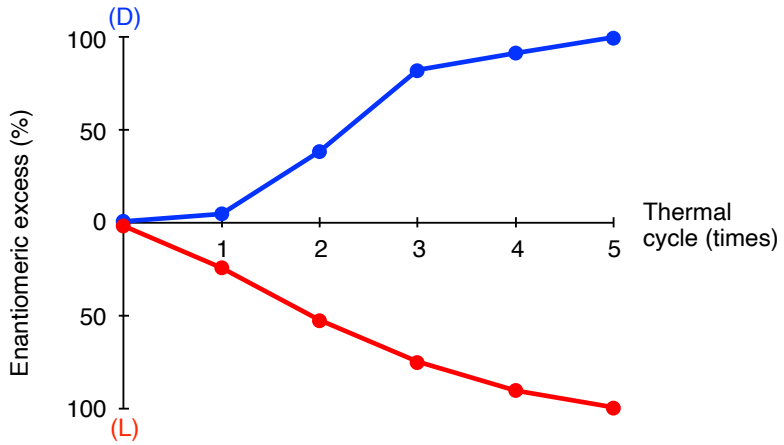
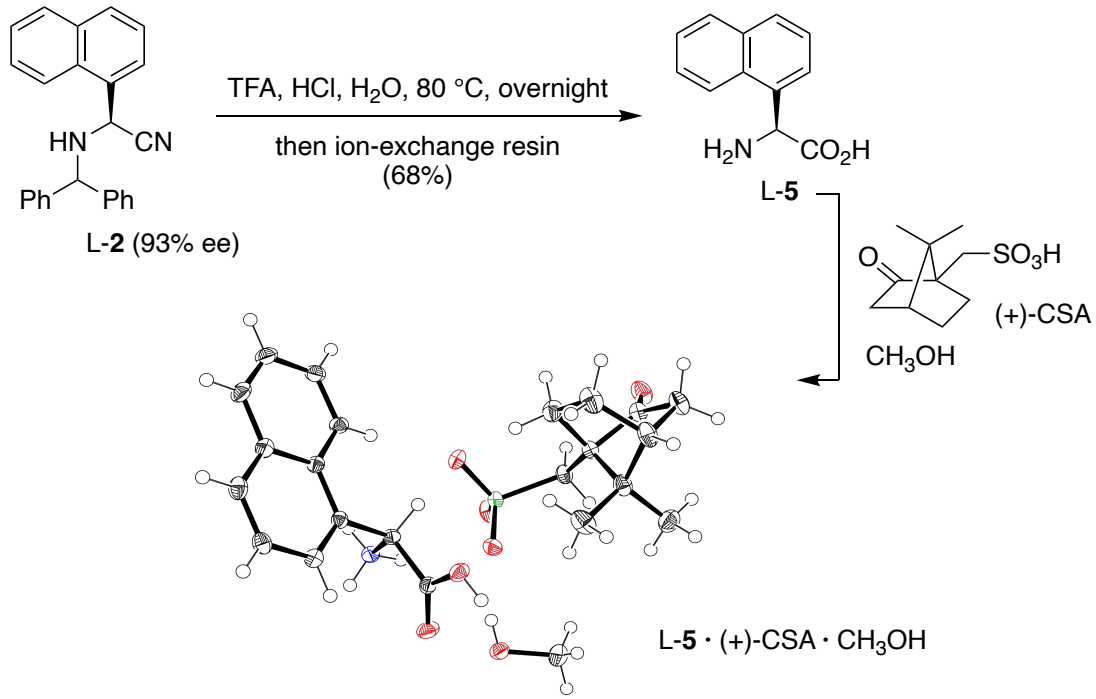


Figure S5.[a,b] **Absolute configuration of aminonitrile 2.** As previous report, L-**2** was hydrolyzed to corresponding L-amino acid **5**, and which was crystallized from methanol in the presence of equimolar amount of (+)-10-camphorsulfonic acid (CSA). The absolute configuration of **5** was confirmed to be L from the single-crystal X-ray structure analysis of the co-crystal (CCDC 2223807).



[a] **Hydrolysis of 2:** L-Aminonitrile **2** with 93% ee (1.40 g, 4.0 mmol) was dissolved in the mixture of conc. HCl (4.2 mL) and CF_3CO_2H (4.2 mL) and was heated at 80 °C for 14 h. After adding distilled water, The resulting mixture was washed with ether and concentrated in vacuo. The solid residue was purified with cation exchange resin (Dowex 50WX8, 100-200 mesh, hydrogen form) to give L-α-(1-naphthyl)glycine (**5**) with 87% ee (0.55 g, 2.7 mmol) as white solid in 68% yield.

[b] **Co-crystallization of L-amino acid 5 with (+)-10-camphorsulfonic acid:** Co-crystal of L-**5** and (+)-10-camphorsulfonic acid (CSA) for single-crystal X-ray structure analysis was prepared by the slow concentration of equimolar solution of methanol at room temperature.

Figure S6. X-Ray powder diffractions of imine 1 and aminonitrile 2. The powder pattern of imine **1** synthesized by the dehydrocyanation of enantioenriched aminonitrile **2** is essentially the same as the simulated pattern of the $P2_1$ crystal of **1**.

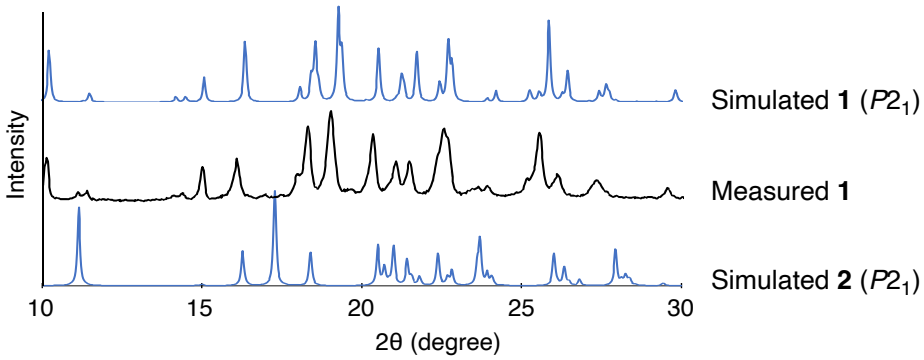
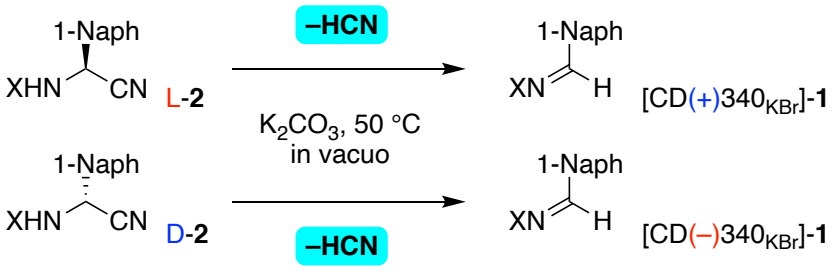


Table S4. Additional experimental results of Table 2.



entry [a]	% ee (config.) of **2**	imine **1**		
		ΔCD [b]	% ee [c]	yield% [d]
5	93 (D)	–96	48	–
6	>99 (L)	+94	47	–
7 [e]	93 (D)	–87	44	–
8	>99 (L)	+97	49	–
9	93 (D)	–68	34	–
10	>99 (L)	+53	27	65

[a] **Representative procedure (Table 1, entry 1):** L-Aminonitrile **2** with >99% ee (21 mg, 0.06 mmol) was ground into fine powder together with K_2CO_3 (788 mg, 5.7 mmol) using agate pestle and mortar. The resulting mixture was heated at 50 °C under vacuum (< 0.2 kPa) for 5 days. After the mixture was washing with water at 0 °C, [CD(+)340$_{KBr}$]-**1** (13.7 mg, 0.043 mmol) was obtained in 71% yield by filtration as white solid.

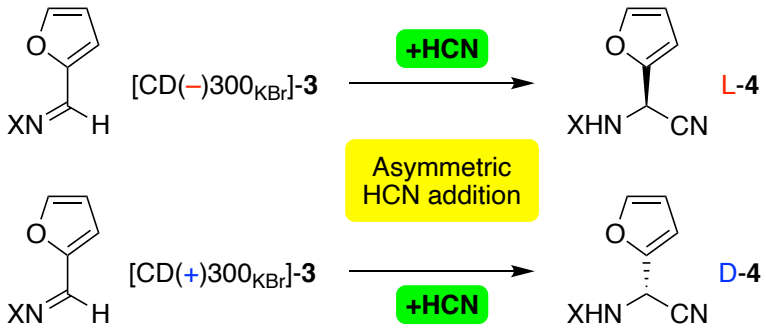
[b] The sign and value (mdeg) of solid-state CD at 340 nm.

[c] The value obtained from the calibration curve (Figure S2).

[d] Isolated yield of solid **1** by filtration after washing the reaction mixture with water to remove K_2CO_3.

[e] Na_2CO_3 was used instead of K_2CO_3.

Table S5. Asymmetric vapor-phase HCN addition to imine 3.



entry [a]	imine **3** [b]	aminonitrile **4**	
		% ee (config.)	conversion (%)
1 [c]	CD(–)300$_{KBr}$	15 (L)	6
2 [c]	CD(+)300$_{KBr}$	5 (D)	18
3	CD(–)300$_{KBr}$	5 (L)	22
4	CD(+)300$_{KBr}$	6 (D)	20
5	CD(–)300$_{KBr}$	5 (L)	22
6	CD(+)300$_{KBr}$	4 (D)	15
7 [d]	CD(–)300$_{KBr}$	3 (L)	12
8 [e]	CD(+)300$_{KBr}$	BDL	9

[a] **Representative procedure (entry 4):** The powder-like crystal of [CD(+)300$_{KBr}$]-**3** (26.3 mg, 0.1 mmol) was ground into fine powder together with NaCl (500 mg) using agate pestle and mortar. The mixture and HCN (2 μL, 0.05 mmol) in another vessel was stored in sealed vial at room temperature for 22 hours. After the removal of volatiles, chloroform was added to the mixture and NaCl was removed by filtration. The molar ratio of **3**/**4** = 80/20 was determined by ^{1}H NMR measurement. The formation of D-**4** with 6% ee was confirmed by the chiral HPLC analysis.

[b] **Preparation of KBr disk of imine 3 for the measurement of solid-state CD**: Solid **3** and KBr were mixed at the ratio of 1/100 (**3**/KBr, *w*/*w*) by the careful grinding using agate pestle and mortar. The mixture (27 mg) was pressed into translucent disk (10 mm in diameter), and was submitted to solid-state CD spectroscopy.

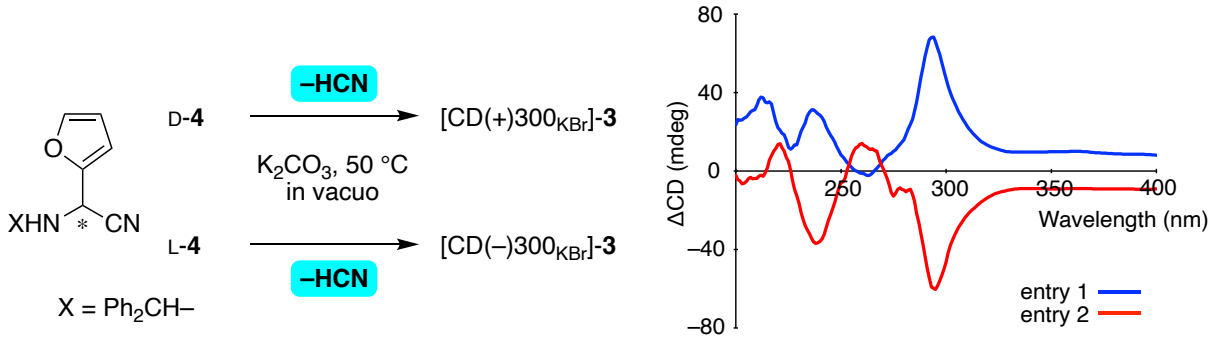
[c] **HCN was added in two separate portions as follows (entry 1):** The powder-like crystal of [CD(−)300$_{KBr}$]-**3** (26.1 mg, 0.1 mmol) was ground into fine powder

together with NaCl (500 mg) using agate pestle and mortar. The mixture and HCN (1 μL, 0.025 mmol) in another vessel was stored in sealed vial at room temperature for 1 h. After the removal of volatiles, residual solid was ground again. Resulting powder and HCN (1 μL, 0.025 mmol) in another vessel was stored in sealed vial at room temperature for 1 hour. After the removal of volatiles, chloroform was added to the mixture and NaCl was removed by filtration. The molar ratio of **3**/**4** = 94/6 was determined by ^{1}H NMR measurement. The formation of L-**4** with 15% ee was confirmed by the chiral HPLC analysis.

[d] KCN and CH_3CO_2H were used instead of NaCl and HCN, respectively.

[e] TMSCN was used instead of HCN.

Table S6. Dehydrocyanation of aminonitrile 4 and solid-state CD spectra of product 3.



Entry [a]	% ee (config.) of **4**	Product **3**	
		Handedness [b]	ΔCD [c]
1	98 (D)	CD(+)300_{KBr}	+68
2	97 (L)	CD(–)300_{KBr}	–60
3	96 (D)	CD(+)300_{KBr}	+50
4	78 (L)	CD(–)300_{KBr}	–39
5 [d]	83 (D)	CD(+)300_{KBr}	+28
6 [d]	97 (L)	CD(–)300_{KBr}	–20

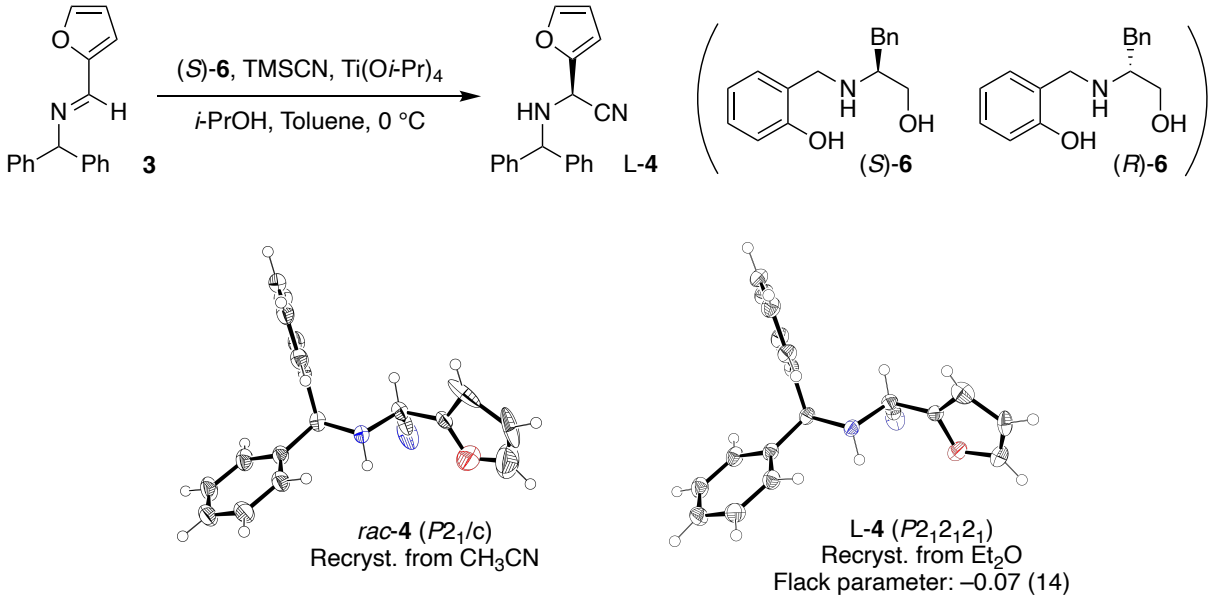
[a] **Representative procedure (entry 2):** Powder-like crystal of L-**4** with 97% ee (16 mg, 0.06 mmol) was ground into fine powder together with K_2CO_3 (152 mg, 1.1 mmol) using agate pestle and mortar. The mixture was heated at 50 °C under reduced pressure (< 0.2 kPa) overnight. After analyzing the reaction progressed >95% by ^{1}H NMR, K_2CO_3 was removed by washing with water at 0 °C to give [CD(–)300_{KBr}]-**3**.

[b] See Table S5, footnote *b*.

[c] The sing and value (mdeg) of solid-state CD at 300 nm.

[d] $NaHCO_3$ was used instead of K_2CO_3.

Figure S7.[a] **Asymmetric synthesis of aminonitrile 4 using *N*-salicyl-β-aminoalcohol as a chiral ligand**[S7] **and single-crystal X-ray structures of aminonitrile 4.** Because of the formation of the crystal of racemic compound **4** (CCDC 2223806), enantioenriched **4** was prepared by the methods of Banphavichient et al. and the absolute configuration of L-**4** was reconfirmed by the single-crystal X-ray structure analysis (CCDC 2224021) in relation with the retention time of chiral HPLC analysis.



[a] **Experimental procedure:** (*R*)-*N*-Salicyl-β-aminoalcohol **6** (26 mg, 0.1 mmol) was treated with Ti(O*i*-Pr)$_4$ (30 μL, 0.1 mmol) in toluene (1 mL) at room temperature. After stirring for 10 min, 2-propanol (77 μL, 0.1 mmol) was added and stirred for 10 min. To a mixture was added a toluene (1 mL) solution of imine **3** (263 mg, 1.0 mmol). Trimethylsily cyanide (250 μL, 2.0 mmol) was added and the mixture was stirred at 0 °C overnight. The mixture was purified with silica gel column chromatography (eluent: hexane/AcOEt/Et$_3$N = 1/1/0.1, *v*/*v*/*v*) to give D-**4** with 87% ee (251 mg, 0.87 mmol) in 87% yield as white solid. After recrystallization from the mixed solvent (toluene/hexane), D-**4** with 98% ee was obtained. L-Aminonitrile **4** could be synthesized in the same method using (*S*)-**6** as a chiral ligand.

Figure S8. X-Ray powder diffraction of imine 3. The powder pattern of imine **3** synthesized by the dehydrocyanation of enantioenriched **4** is essentially the same as the simulated pattern of the $P2_12_12_1$ crystal of **3**.

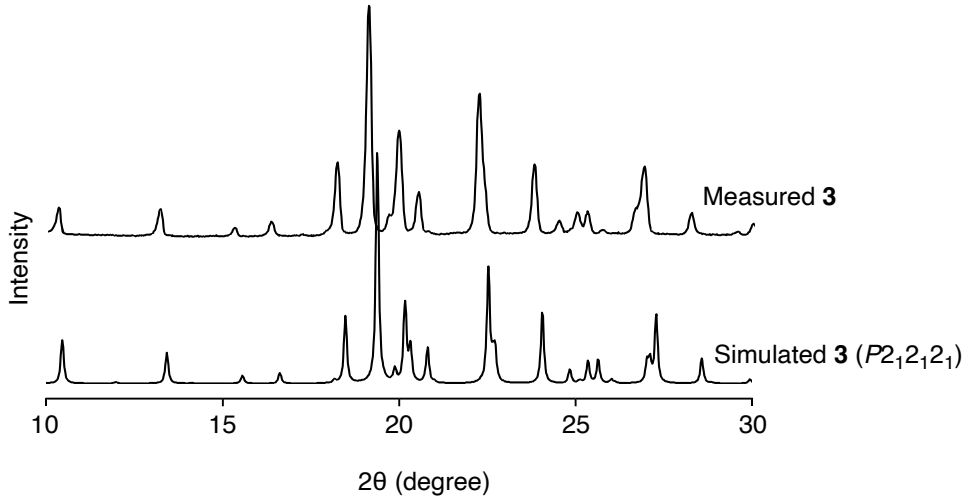
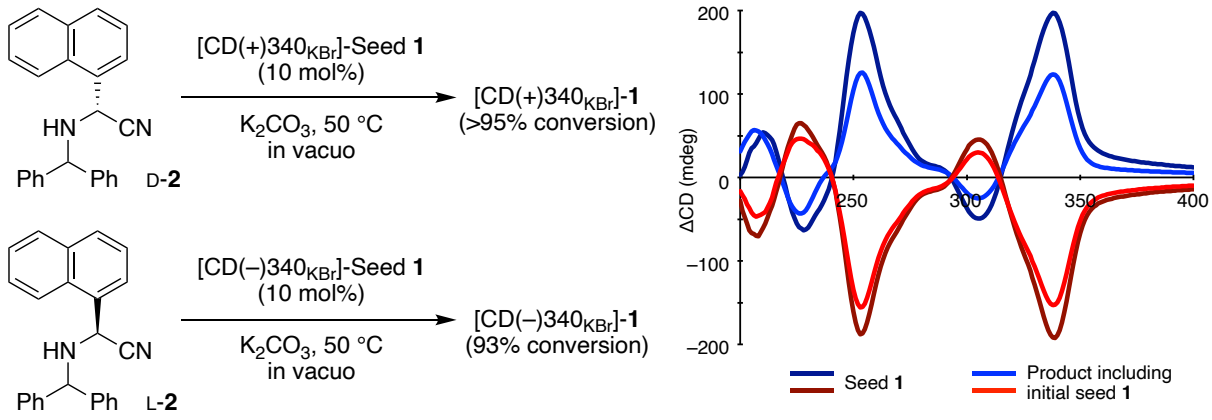
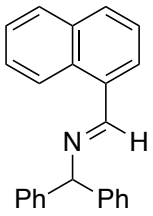


Figure S9. Dehydrocyanation of 2 in the presence of the crystal of imine 1 with mismatched crystal chirality as seed. The crystal chirality of synthesized **1** was efficiently controlled by initially added crystal seed.



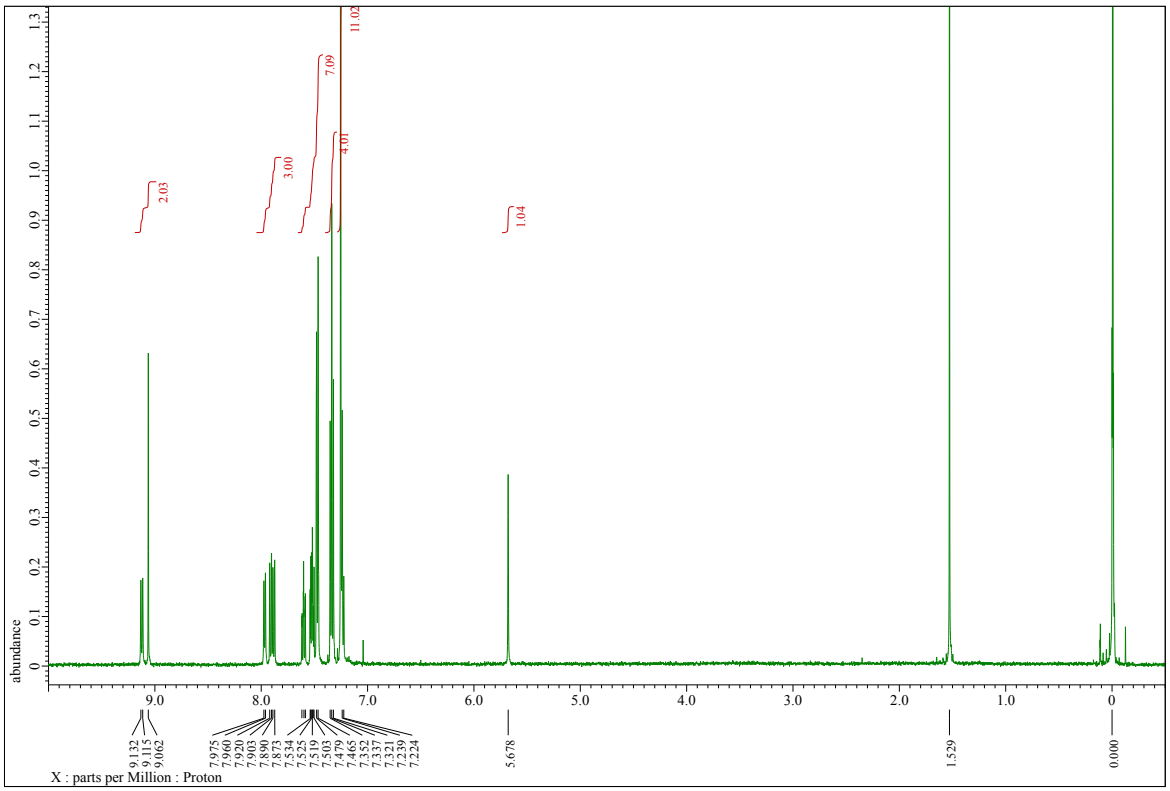
— Characterization of Compounds 1–4 —

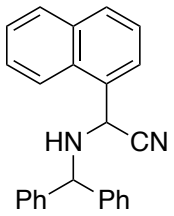


(*E*)-*N*-Benzhydryl-1-(naphthalen-1-yl)methanimine (1)

Single-crystal X-ray structures: CCDC 2223802–2223805 and 2224018.

^{1}H NMR (500 MHz, $CDCl_3$): δ 9.13 (1H, d, J=8.5 Hz), 9.06 (1H, s), 7.97 (1H, d, J=7.5 Hz), 7.91 (1H, d, J=8.5 Hz), 7.88 (1H, d, J=8.5 Hz), 7.63–7.59 (1H, m), 7.55-7.51 (2H, m), 7.49–7.47 (4H, d, J=7.5 Hz), 7.34 (4H, t, J=7.5 Hz), 7.25-7.23 (2H, m), 5.68 (1H, s).



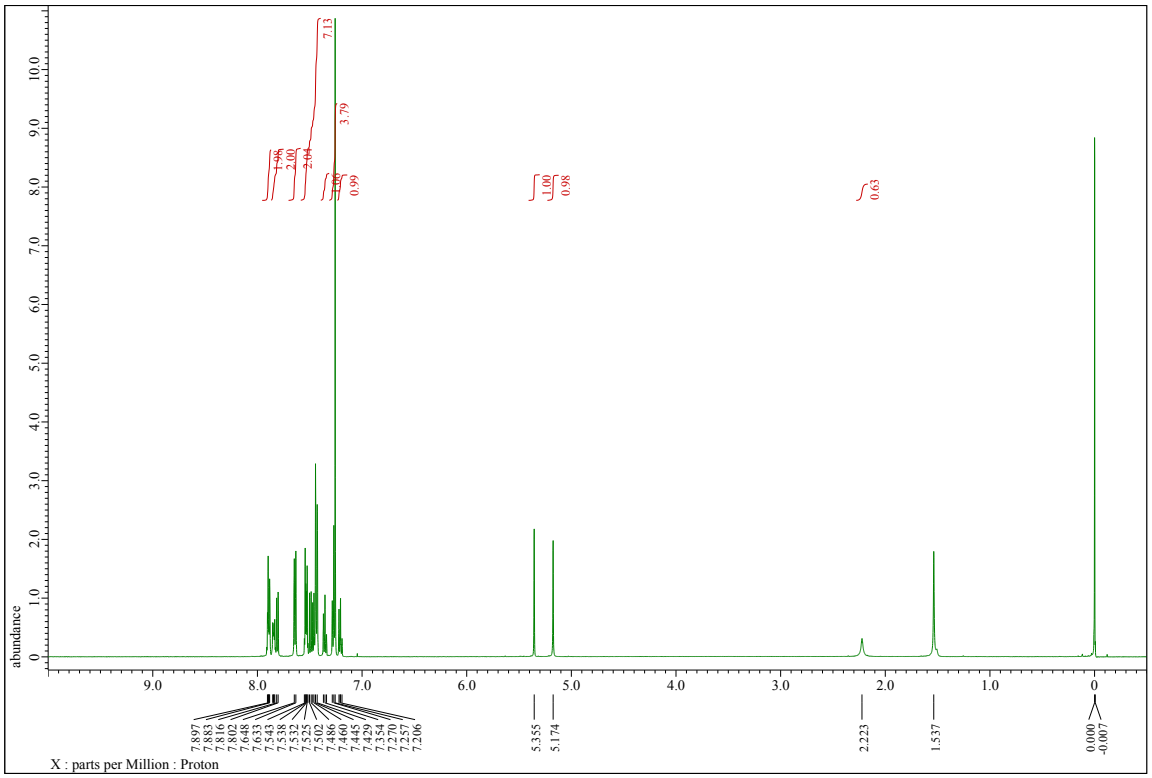


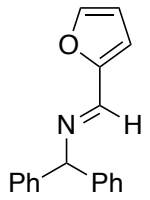
2-(Benzhydrylamino)-2-(naphthalen-1-yl)acetonitrile (2)[S7–S13]

Single-crystal X-ray structure: CCDC 2224019

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.91-7.80 (4H, m), 7.64 (2H, m), 7.55-7.43 (7H, m), 7.35 (1H, m), 7.27 (2H, m), 7.21 (1H, m), 5.36 (1H, s), 5.17 (1H, s), 2.23 (1H, br s).

HPLC conditions: DAICEL Chiralpak IA-3 (4.6 ID × 250 mm), hexane/IPA=97/3 (*v*/*v*), UV detector at 220 nm, 1.0 mL/min, room temperature, t_R 7.9 min for D-**2**, 9.7 min for L-**2**.

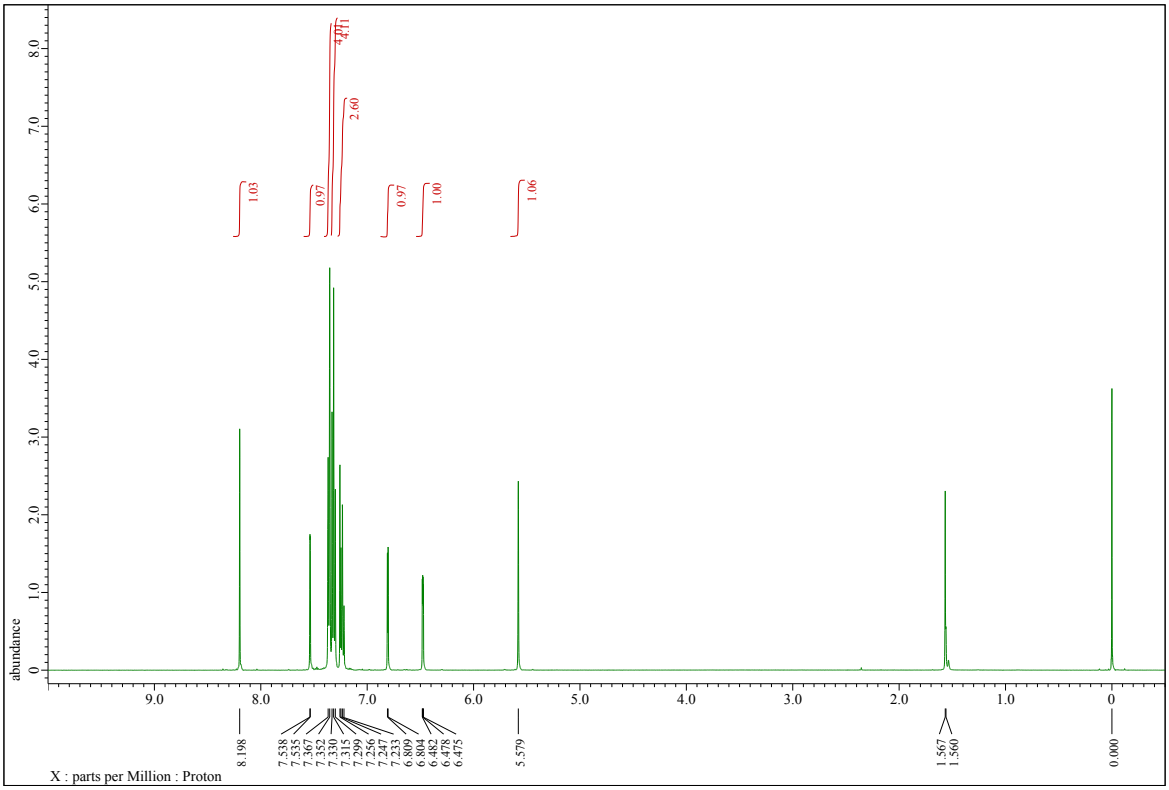


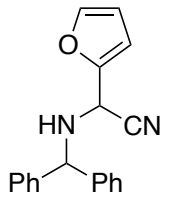


(*E*)-*N*-Benzhydryl-1-(furan-2-yl)methanimine (3)

Single-crystal X-ray structure: CCDC 2224020

^{1}H NMR (500 MHz, $CDCl_3$): δ 8.20 (1H, s), 7.54 (1H, m), 7.36 (4H, m), 7.32 (4H, m), 7.23 (2H, m), 6.81 (1H, d, J=2.5 Hz), 6.48 (1H, m), 5.58 (1H, s).



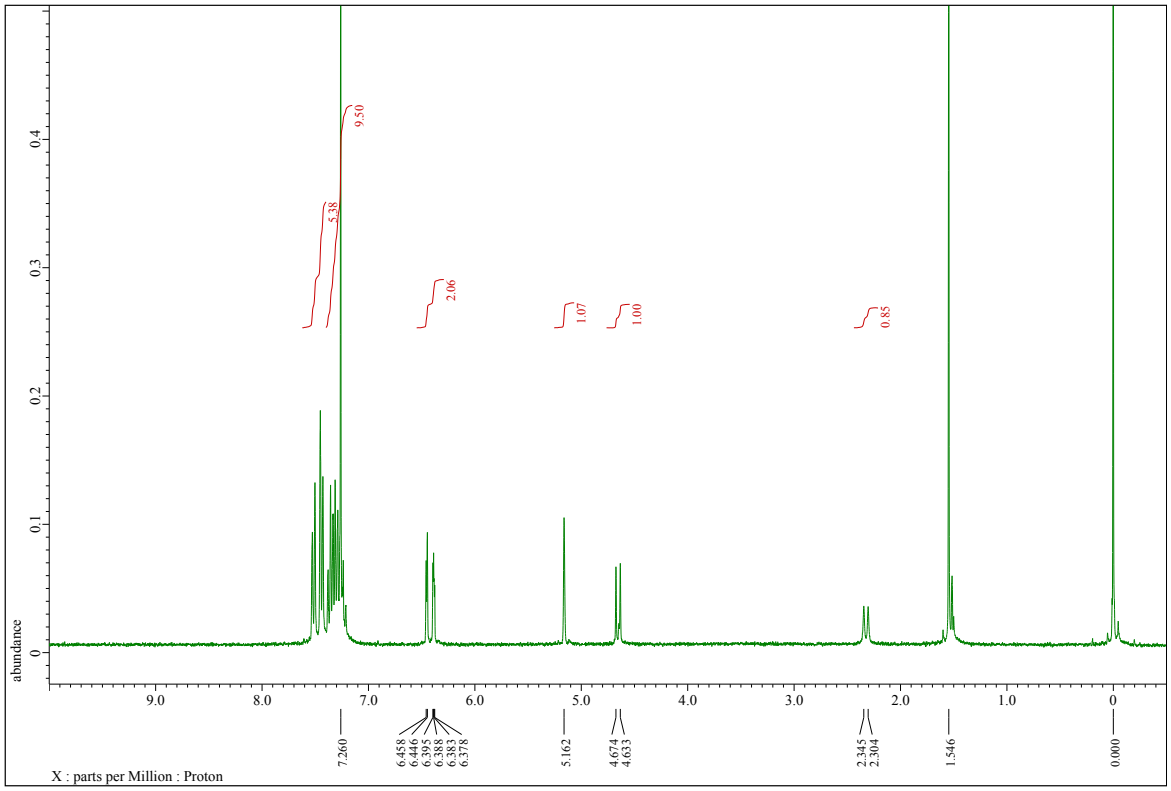


2-(Benzhydrylamino)-2-(furan-2-yl)acetonitrile (4)[S7,S14–S18]

Single-crystal X-ray structure: CCDC 2224021

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (2H, m), 7.44 (3H, m), 7.37-7.21 (5H, m), 6.46 (1H, m), 6.39 (1H, m), 5.16 (1H, s), 4.65 (1H, d, J=12.3 Hz), 2.32 (1H, d, J=12.3 Hz).

HPLC conditions: DAICEL Chiralpak IC-3 (4.6 ID × 250 mm), hexane/IPA=99/1 (v/v), UV detector at 220 nm, 1.0 mL/min, room temperature, t_R 10.9 min for D-**4**, 11.9 min for L-**4**.



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