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Highly Stereoselective Strecker Synthesis Induced by the Slight Modification of Benzhydrylamine from Achiral to Chiral

Naoya Takamatsu,[b] Shohei Aiba, [b] Takuya Yamada,[b] Yuji Tokunaga,[b] and Tsuneomi Kawasaki*[a]

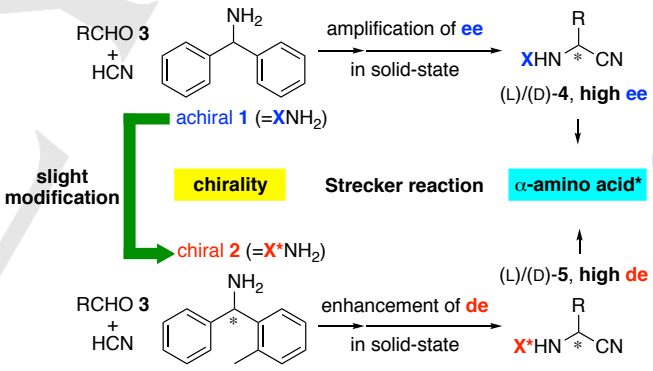
Abstract: 2-Methylbenzhydrylamine is a chiral variant of achiral benzhydrylamine, however, the chirality formed from the small difference between the phenyl and *o*-tolyl groups is not expected to induce sufficient stereoselectivity in conventional homogeneous reactions. Initiated by the spontaneous formation and asymmetric amplification of the enantioenriched *N*-benzhydryl-α-aminonitrile forming conglomerate, we here report that (*S*)- and (*R*)-configured title amine, upon the Strecker reaction with achiral aldehydes and HCN, afford corresponding α-aminonitriles with up to >99.5% diastereomeric excess, in conjunction with the enhancement of chirality in solid-state. L-Alanine with 98% ee was synthesized from the *S*-amine *via* the method discussed here. Achiral aromatic and heteroaromatic aldehydes could also be successfully utilized to afford chiral α-aminonitriles in highly stereoselective manner. The stereodivergent synthesis of styrylglycine nitriles has also been accomplished by using racemic and enantioenriched 2-methylbenzhydrylamine. Thus, accompanied with a small rearrangement of the common substrate from achiral toward chiral, present reactions including an enhancement of chirality, would expand the concept of stereoselective synthesis to increase the opportunity of addressing highly enantioenriched compounds such as α-amino acids.

Introduction

Stereochemistry is an important research topic in the field of organic synthesis,[1] therefore, the stereoselective synthesis of chiral α-amino acids holds great significance.[2–5] In chemical transformations, Strecker synthesis[6] is a simple yet powerful strategy for the preparation of α-amino acids.[7] After pioneering work in the asymmetric synthesis of L-alanine using (*S*)-phenylethylamine, acetaldehyde, and hydrogen cyanide (HCN),[8] further stereoselective reactions using chiral substrates have been developed.[9,10] Catalytic asymmetric Strecker reactions have also been developed to provide a wide variety of enantioenriched intermediate aminonitriles.[11,12]

We previously reported on the spontaneous formation[13,14] (total spontaneous resolution)[15–17] of enantioenriched α-aminonitrile **4b** (see figure in Table 1 for the chemical structure) in combination with the Strecker reaction between three achiral substrates.[18] The tiny imbalance of the enantiomorphous aminonitriles could be greatly amplified from *ca.* 0.05% enantiomeric excess (ee) to near enantiopure (>99.5% ee) by thermal dissolution/crystallization cycles.[19,20] Although this transformation is powerful for the synthesis of large amounts of highly enantioenriched α-aminonitriles—the chiral intermediates of α-amino acids—crystallization of aminonitriles in the conglomerates is necessary.

One of the solutions to this limitation is a stereoselective reaction, introducing chirality to the substrate, *i.e.*, crystallization-induced diastereomer transformations.[21] Employing this concept, diastereoselective Strecker formations have been reported in which chiral α-phenylglycine amide[22] and β-amino alcohols[23] were used as chiral substrates. Diastereomeric salt formation of aminonitriles has also been reported.[24]



Scheme 1. The concept of this work.

Here we discuss a highly stereoselective Strecker synthesis induced by slight modification of an achiral substrate to a chiral substrate, based on the research on the spontaneous formation of chiral *N*-benzhydryl-α-aminonitriles **4** with significant amplification of ee in solid-state, *i.e.*, Viedma ripening[25] (Scheme 1). 2-Methylbenzhydrylamine (**2**), which is a chiral variant of achiral **1**, can act as a highly efficient chiral parent amine for Strecker synthesis between achiral aldehydes and HCN, with significant enhancement of stereoselectivity in solid state, up to >99.5% diastereomeric excess (de).

To our knowledge, there are no reports on the approach of stereoselective synthesis induced by slight modification of a common substrate from achiral to chiral, even in crystallization-induced diastereomer transformations. Asymmetric induction power of chiral substrate such as 2-methylbenzhydrylamine (**2**), in which closely similar substituents are attached at the

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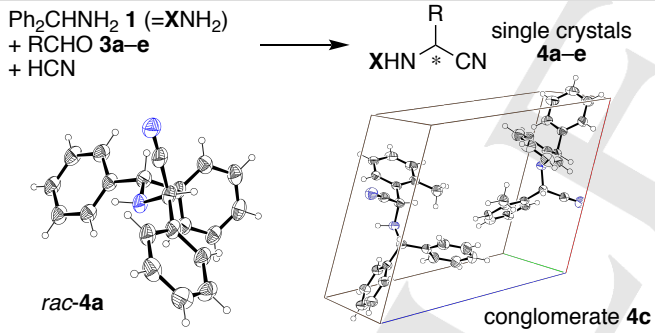
asymmetric carbon center without stereo-directing group, is supposed to be small.[26] Therefore, present research would expand the possibility of stereoselective synthesis to address wide spectrum of enantiomerically enriched compounds such as α-amino acids.

Results and Discussion

Single-crystal structures of α-aminonitriles 4 formed from achiral benzhydrylamine (1)

Racemates of aminonitriles **4** were prepared by the Strecker reaction between benzhydrylamine **1**, the aldehydes **3a–e**, and HCN. From benzaldehyde **3a**, crystal of racemic compound **4a** (achiral space group $P2_1/c$) was obtained from acetonitrile solution after slow evaporation (Table 1, entry 1). In the crystal structure of *rac*-**4a** (figure in Table 1), the pseudo-1,3-diaxial conformation[27] was observed between the methine of the benzhydryl group and the cyano group. The stability of this conformation was indicated from the optimized structure of the corresponding aminonitriles, including **4a**, using the DFT method (see Supporting Information Table S1). It should be noted that this pseudo-1,3-diaxial conformation was commonly observed in all the crystal structures of α-aminonitriles in the present study.

Table 1. Single-crystal structures of α-aminonitriles **4** derived from benzhydrylamine (**1**).



Entry	Substituent R (aldehyde **3**)	*N*-benzhydryl-α-aminonitrile **4**			
			Space group		CCDC[a]
1	phenyl (**3a**)	**4a**	Achiral	$P2_1/c$	1560341
2[b]	*p*-tolyl (**3b**)	**4b**	Chiral	$P2_1$	1055257
3	*o*-tolyl (**3c**)	**4c**	Chiral	$P2_1$	1560325
4	*m*-tolyl (**3d**)	**4d**	Achiral	$C2/c$	1560343
5	(*p*-Br)C_6H_4 (**3e**)	**4e**	Achiral	$P2_1/n$	1560344

[a] Deposit number of the Cambridge Crystallographic Data Centre (CCDC). [b] Previously reported structure. See also ref. 18.

On the other hand, as same as the previously reported **4b** with the *p*-tolyl substituent (entry 2), the single crystal **4c** with an *o*-tolyl group belongs to the chiral space group $P2_1$ forming conglomerate (entry 3). In the structure of **4c** with the *o*-tolyl group, two molecules with the same handedness were included in the crystal lattice (figure in Table 1). The molecules **4c** are helically arranged along the *b*-axis through weak hydrogen bonding between cyano and amino groups (Supporting Information Figure S1). A crystal of **4d** with the *m*-tolyl substituent and **4e** with *p*-bromophenyl substituent crystallized in achiral space groups, respectively (entries 4 and 5). Therefore, crystallization-based enantioselective synthesis is applicable for the **4c** (including the previous **4b**).

Spontaneous formation and asymmetric amplification of enantioenriched *N*-benzhydryl-*o*-tolylglycine nitrile (4c)

The Strecker reaction between achiral **1**, *o*-tolualdehyde (**3c**), and HCN was conducted in a 1.5 M solution of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in methanol (Figure 1a and Supporting Information Table S2). As the three-component reaction proceeded, solid **4c** appeared spontaneously in enantioenriched form; thus, total spontaneous resolution occurred as observed in the formation of **4b**.[18] To check the distribution of the molecular handedness and the ee, further Strecker reactions were conducted. Among the 18 experiments carried out, solid product **4c** was formed in all cases and the absolute handedness exhibited an approximate stochastic distribution; the L-enantiomer occurred nine times and the opposite D-form occurred nine times. Because the reaction was initiated by mixing only achiral reagents without the addition of any chiral materials, the present observation, *i.e.*, statistical formation of L- and D-**4c**, constitutes one of the conditions necessary for the spontaneous absolute asymmetric synthesis.

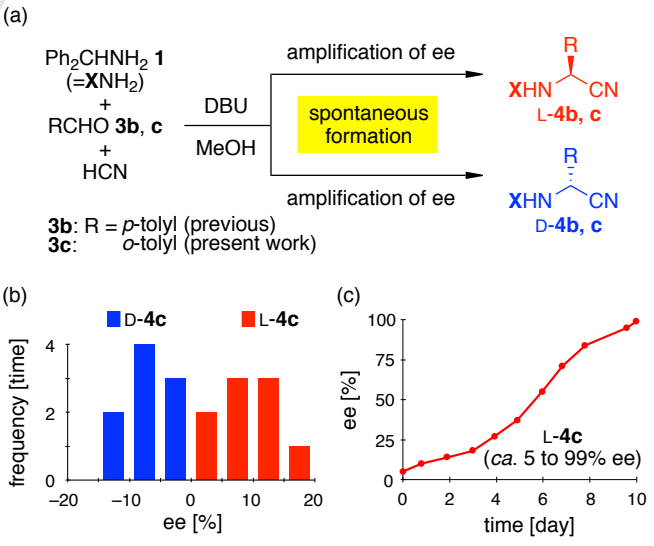


Figure 1. (a) Spontaneous formation and asymmetric amplification of enantioenriched aminonitriles **4b** and **4c**. (b) Histogram of the enantioselectivity of spontaneous formation of L- and D-**4c**. (c) Asymmetric amplification of solid-state L-**4c** by Viedma ripening.

Next, we examined the amplification of crystal ee by applying Viedma ripening.[28–30] L-Aminonitrile **4c** with *ca*. 5% ee was suspended in a solution of DBU (1.5 M) and HCN (2 eq) in methanol and the resulting mixture was vigorously stirred in the presence of glass beads (Figure 1c and Supporting Information Table S3). The ee was amplified to 10% ee after 19 h and, finally, **4c** with 99% ee was isolated in 37% yield after 10 days by filtration. The ee of suspended solid **4c** could also be enantiomerically improved from near racemic to 94% ee by the heating/cooling cycle (Supporting Information Figure S2).[31] Therefore, highly enantioenriched aminonitrile **4c** could be synthesized without any assistance of chiral materials.

Stereoselective Strecker synthesis using enantioenriched 2-methylbenzhydrylamine (2).

Benzhydrylamine **1** is one of the useful parent amines in asymmetric Strecker reactions[12a] and related stereoselective reactions.[32] The benzhydryl substituent is removable under acidic or reductive conditions to afford the amino group after desired transformation. In addition, it is likely to form crystalline derivatives.[33] Therefore, in order not to lose these properties, slight modification was carried out toward **1** by the introduction of one methyl group to be chiral 2-methylbenzhydrylamine (**2**).[34] The chirality of **2** originates from the difference between the phenyl and *o*-tolyl groups. It is not expected to induce sufficient stereoselectivity in the homogeneous reaction.[35] We postulated that the significant asymmetric amplification observed in **4c** and previous **4b** could be successfully substituted by the enhancement of solid state chirality in the stereoselective synthesis.

Because of the formation of racemic compound **4a** by the reaction between achiral **1**, benzaldehyde (**3a**) and HCN (Table 1, entry 1), the Strecker reaction of **3a** was performed utilizing chiral **2** (Figure 2). Therefore, (*R*)-**2** with 96% ee, **3a** and HCN was reacted in 2-propanol in the presence of 0.1 M DBU as an epimerizing reagent (Figure 2a). After precipitation of the solid product **5a** and stirring of the reaction suspension overnight without using glass beads, *syn*-(L)-**5a** with 99% de (>99.5% ee) was obtained in 77% isolated yield simply by filtration (Supporting Information Table S6). The opposite, (*S*)-**2**, afforded enantiomeric *syn*-(D)-**5a** with >99.5% de in 85% yield. The stereochemistry of **5a** was confirmed by X-ray single-crystal structure analysis (Figure 2b).

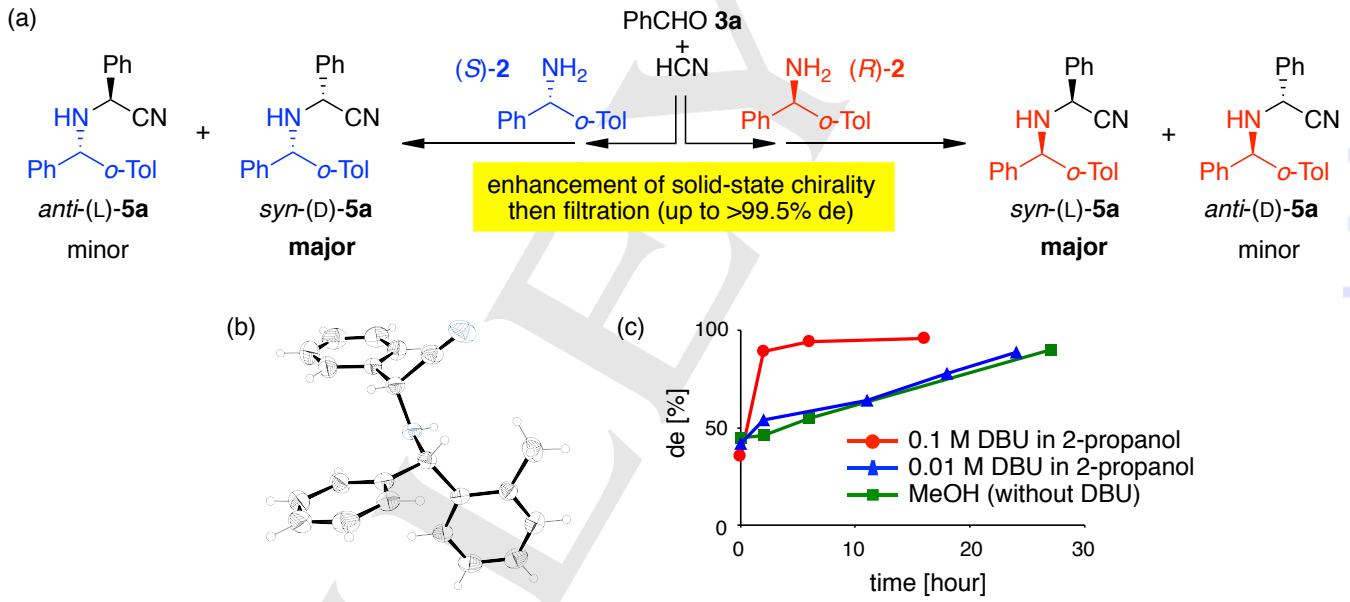
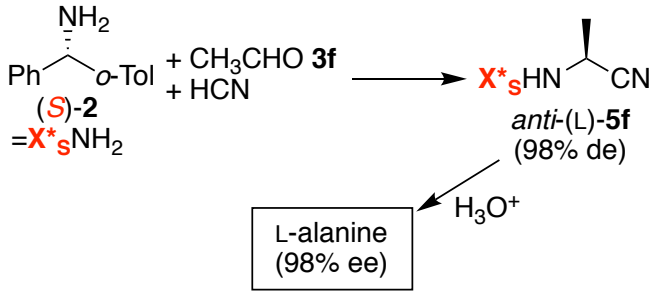


Figure 2. (a) Stereoselective formation of α-phenylglycine nitrile **5a**. (b) Single-crystal structure of *syn*-(D)-**5a** (CCDC 1560534). (c) Continuous enhancement of diastereomeric ratio in solid state *syn*-(D)-**5a** as a function of the reaction time.

Continuous improvement in de was monitored by sampling a part of suspended solid **5a** using (*S*)-**2** (Figure 2c). In 0.1 M DBU in 2-propanol, the initial low diastereoselectivity of solid product (35% de) was significantly improved over 2 h, increasing to 89% de. After further enhancement of de (94%/6 h and 96%/16 h), finally *syn*-(D)-**5a** with >99.5% de was isolated as mentioned above (Figure 2c, red-colored line). Even when the amount of DBU was reduced to 0.01 M, *syn*-(D)-**5a** with >99.5% de was isolated in 85% yield after the gradual enhancement of de (blue-colored line). From the filtrate, the same configured *syn*-(D)-**5a** with 46% de was also isolated in 9% yield after purification by silica-gel. Since **5a** can racemize in only methanol solution without using DBU, *syn*-(D)-**5a** with 98% de was isolated from methanol suspension in 73% yield together with *syn*-(D)-**5a** (23% yield, 57% de) from the filtrate (green-colored line).

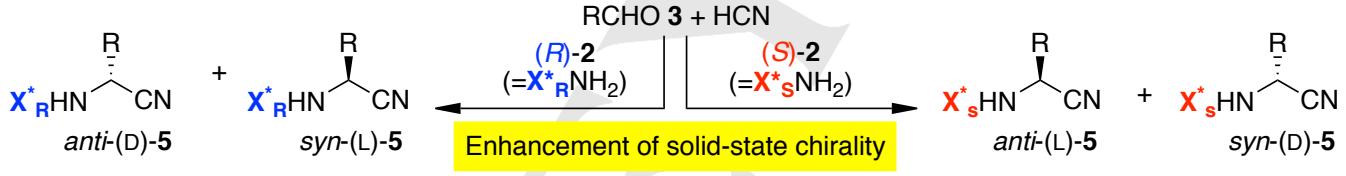


Scheme 2. Asymmetric synthesis of L-alanine. The stereochemistry of **5f** was confirmed by X-ray single crystal structure analysis (CCDC 1560537).

Furthermore, the present method was then applied to the enantioselective alanine synthesis[8] (Scheme 2). Initially, the crystalline solid of *anti*-(L)-alanine nitrile **5f** was formed with 6% de by the Strecker reaction between (*S*)-**2** with >99.5% ee, acetaldehyde (**3f**) (2 eq), and HCN. Subsequent stirring of the suspension in 0.5 M DBU in methanol improved the diastereomeric purity to 98% de. The solid of *anti*-(L)-**5f** was isolated by filtration in 60% yield and the same configured *anti*-(L)-**5f** with 3% de was also isolated in 10% yield from the filtrate. Both removal of the 2-methylbenzhydryl group and hydrolysis of the cyanide group were conducted in a one-pot reaction under acidic conditions to afford L-alanine with 98% ee in 96% yield without a decrease in enantiomeric purity. Therefore, one of the natural aliphatic α-amino acids, alanine, could be enantioselectively synthesized based on the chirality of (*S*)-2-methylbenzhydrylamine (**2**).

Stereoselective reactions using other aromatic and heteroaromatic aldehydes **3e** and **3g-k** are shown in Table 2. Although, *p*-bromobenzaldehyde (**3e**) afforded racemic compound **4e** by the reaction with achiral **1** and HCN, stereoselective synthesis could be realized by the reaction with (*R*)-**2** to give *anti*-(D)-**5e** with 90% de (entry 1). Even when *p*-chloro- and *p*-methoxybenzaldehydes **3g** and **3h** were submitted to the reaction, corresponding *anti* diastereomers **5g** and **5h** with 94 and 97% de have been formed after the enhancement of de, respectively (entries 2 and 3). Additional amount of aminonitriles **5g** and **5h** with low to moderate de were also recovered in 9% and 15% yield from the filtrate, respectively.

Table 2. Highly stereoselective Strecker reaction utilizing highly enantioenriched 2-methylbenzhydrylamine (**2**).



Entry[a]	Amine **2** (Config.)	substituent R (aldehyde **3**)	Solvent	DBU (M)	Aminonitrile **5**				
					#	config.[b]	de[c]	Yield[d]	CCDC[e]
1	*R*	(*p*-Br)C_6H_4 (**3e**)	2-propanol	0.1	**5e**	*anti*-(D)	90	80	1560574
2	*S*	(*p*-Cl)C_6H_4 (**3g**)	2-propanol	0.1	**5g**	*anti*-(L)	94 (4)	85 (9)	1560665
3	*R*	(*p*-MeO)C_6H_4 (**3h**)	2-propanol	0.1	**5h**	*anti*-(D)	97 (56)	76 (15)[f]	1560673
4	*S*	2-furyl (**3i**)	MeOH	–	**5i**	*syn*-(D)	99	87[g]	1560677
5	*R*	3-pyridyl (**3j**)	2-propanol	0.1	**5j**	*syn*-(L)	98 (BDL)	78 (8)	1560678
6	*S*	2-pyridyl (**3k**)	2-propanol	–	**5k**	*syn*-(D)	99 (BDL)	65 (28)	1560679

[a] Molar ratio used **2**:**3** = 1:1. [b] The configuration was determined from the X-ray single-crystal structure analysis. [c] The diastereomeric excess was determined by HPLC on a chiral stationary phase (UV detector) because the difference in the UV absorbance between diastereomers is enough small to discuss the diastereoselectivity (see also ref. 35). The value in parentheses indicates the de of **5** isolated from the filtrate, whose configuration is the same as solid **5**. BDL: below the detectable level. [d] Isolated yield of solid **5** by filtration based on the molar amount of **2** (the same as **3**). Additional recovered yield of **5** from the filtrate indicated in parentheses. [e] Deposit number of the CCDC. [f] The yield was calculated from the amount of initially suspended solid *anti*-(D)-**5h** with 7% de. [g] The yield was calculated based on the molar amount of (*S*)-imine **6i** (see Scheme 4 for the chemical structure) using starting substrate.

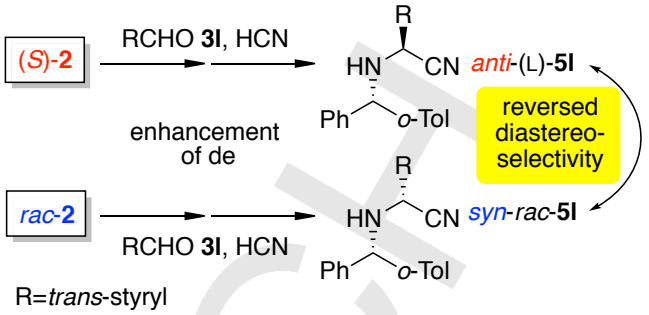
Furthermore, heteroaromatic aldehydes **3i–k** could also be applicable for the stereoselective formation of aminonitriles **5i–k**. As shown in entry 4, the highly stereoselective Strecker reaction of furfural (**3i**) was accomplished between (*S*)-**2** and HCN to afford *syn*-(D)-**5i** with 99% de in 87% yield, in conjunction with the enhancement of chirality in solid-state. 3- and 2-Pyridinecarbaldehydes (**3j** and **3k**) were also converted to the corresponding highly enantioenriched *syn*-aminonitriles **5j** and

5k with 98% and 99% de in excellent chemical yields, respectively, after only simple filtration (entries 5 and 6). A rapid decrease in the diastereomeric ratio of **5k** was observed in chloroform-*d*, therefore, ^{1}H-NMR of *syn*-(D)-**5k** with 99% de was measured in benzene-d_6, in which the epimerization rate became slow. Crystallization-mediated synthesis offers advantages for obtaining easily racemizable chiral compounds in highly stereoselective manner. To our knowledge, this is the first example of the highly stereoselective synthesis of an α-aminonitrile with the 2-pyridyl group directly connected to the α-position.

Therefore, 1,3-asymmetric induction has been achieved by using 2-methylbenzhydrylamine (**2**) as a chiral substrate in the Strecker reaction in conjunction with an enhancement of chirality in solid state. The chirality of solid aminonitriles **5** has been continuously improved to achieve significantly high diastereomeric purity (up to >99.5% de) by only stirring of the reaction suspension. The chirality of **2**, generated by the difference between phenyl and *o*-tolyl substituents, has been efficiently discriminated to afford chiral intermediate, aminonitrile with high de. Although the energy difference between the diastereomers was calculated to be small, for example, *anti*-**5f** is 1.1 kJ/mol more stable than *syn*-**5f** by DFT calculation (Supporting Information Table S7), such a small difference should be integrated in the solid state to become sufficiently large, giving high stereoselectivity observed here.

Stereodivergent Strecker synthesis of α-styrylglycine nitrile 5l by using enantioenriched and racemic 2

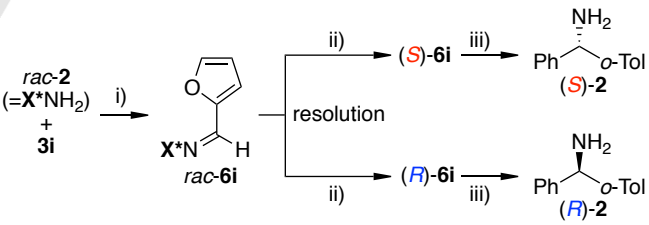
When *trans*-cinnamaldehyde (**3l**) was submitted to the Strecker reaction, followed by the enhancement of chirality in solid state, stereoselective formation of styrylglycine nitrile **5l** was observed (Scheme 3). Therefore, when enantioenriched (*S*)-**2**, aldehyde **3l**, and HCN were reacted together, L-**5l** was formed and precipitated as a preferred *anti*-diastereomer (80% de). However, when the *rac*-**2** was used as the substrate, the diastereoselectivity was reversed, *i.e.*, *syn*-**5l** with 86% de in racemic form was obtained as a major isomer in 85% yield. Therefore, both *anti*- and *syn*-isomers of α-aminonitrile **5l** could be selectively synthesized under the enantiomeric and racemic conditions, respectively. These observations, *i.e.*, change of the major stereoisomer should be occurred, because enantioenriched and racemic compounds afford the crystals with completely different structures and which determines the preferable diastereomer in solid state. Because the slightly major diastereomer in solution phase[35] may be the same under both racemic and enantiomeric conditions, it was supposed that the (slight) selectivity in the solution phase did not control the direction of the enhancement of de in solid state.



Scheme 3. Stereodivergent Strecker synthesis of α-styrylglycine nitrile **5l** using (*S*)- and *rac*-2-methylbenzhydrylamine (**2**). Stereochemistries of *anti*-(L)- and *syn*-*rac*-**5l** were determined by X-ray single-crystal structure analysis (CCDC 1560680 and 1560681, respectively).

Resolution of 2-methylbenzhydrylamine (2) *via* imine 6i forming conglomerate

The asymmetric synthesis of enantioenriched 2-methylbenzhydrylamine (**2**) has been reported in the phenylboroxine addition[34a] and hydrogenation[34b] of corresponding imine. As shown in Scheme 4, we found that the *rac*-imine **6i** formed from furfural (**3i**) crystallizes in the conglomerate. Thus, by the seeding method, *rac*-**6i** could be resolved to afford enantioenriched **6i**. When *rac*-**6i** (70 g) was subjected, (*R*)-**6i** (8.7 g) with 99% ee could be obtained from (*R*)-seed **6i** (80 mg) in a single operation. Oppositely configured (*S*)-seed **6i** induced the preferential crystallization of (*S*)-**6i**. Hydrolysis of **6i** by aqueous HCl proceeded in 96% yield to afford highly enantioenriched **2** after the neutralization without decrease of enantiomeric purity. Highly enantioenriched **2** used in the present study was prepared by this resolution method.



Scheme 4. Resolution of 2-methylbenzhydrylamine (**2**): preferential crystallization of imine **6i**. Reaction conditions: (i) Na_2SO_4, CH_2Cl_2 (89%); (ii) (*S*)-/(*R*)-seed **6i** (CCDC 1564004), ethyl acetate, 60–50 °C; (iii) HCl, Et_2O/H_2O (1/1, *v*/*v*) then $NaHCO_3$ (96%). The absolute configuration of **2** was directly determined by X-ray single crystal structure analysis of (*S*)-imine **6m** (CCDC 1563890) formed from (*S*)-**2** and 2-thiophenecarboxyaldehyde (**3m**) (Supporting Information Figure S5).

Conclusions

The spontaneous formation and amplification of the enantioenriched *N*-benzhydryl-α-*o*-tolylglycine nitrile (**4c**) forming conglomerate were achieved. Stochastic distribution of the absolute handedness of **4c** fulfills one of the requirements

for the spontaneous absolute asymmetric synthesis of α-amino acids in combination with hydrolysis. After the modification of achiral benzhydrylamine (**1**), asymmetric amplification of crystal ee was successfully substituted by the enhancement of solid state chirality in the stereoselective Strecker synthesis. Therefore, enantioenriched (*S*)- and (*R*)-2-methylbenzhydrylamine (**2**) afforded the corresponding aminonitriles **5** with significantly high diastereoselectivity by the reaction with achiral aldehydes and HCN, in combination with the enhancement of chirality in solid-state. Near enantiomerically pure L-alanine was also synthesized by the present method. To our knowledge, this is the first report of research on the highly stereoselective synthesis by the slight modification of a common substrate from achiral to chiral.

Experimental Section

Spontaneous formation of enantioenriched 4c.

HCN (121 μL, 3.0 mmol) was added to a solution of *o*-tolualdehyde (**3c**) (116 μL, 1.0 mmol) and benzhydrylamine (**1**) (173 μL, 1.0 mmol) in 1.5 M DBU in methanol (2.6 mL). After stirring for 3 days at 30 °C, followed by filtration, L-solid **4c** (122 mg, 0.39 mmol) with 18% ee was isolated in 39% yield. After concentration of the filtrate *in vacuo*, the residue was purified by silica gel column chromatography (*n*-hexane/Et_2O = 3/1, v/v). **4c** (116 mg, 0.37 mmol) with ee below the detectable level was obtained in 37% yield.

Asymmetric amplification of 4c by Viedma ripening.

A fine powder of L-aminonitrile **4c** with *ca*. 5% ee was prepared by mixing racemic conglomerate **4c** (233 mg, 0.746 mmol) and L-**4c** (17 mg, 0.054 mmol, 75% ee) using a pestle and mortar. L-**4c** (250 mg, 0.8 mmol, *ca*. 5% ee) was added to a solution of HCN (63 μL, 1.6 mmol) in 1.5 M DBU in methanol (2.6 mL). The resulting suspension was vigorously stirred at 30 °C in the presence of glass beads (2.0 g, 3 mm i.d.). Filtration afforded L-**4c** (93.2 mg, 0.298 mmol, 99% ee) in 37% yield.

Stereoselective synthesis of phenylglycine nitrile 5a.

HCN (132 μL, 3.35 mmol) was added to a solution of benzaldehyde (**3a**) (227 μL, 2.24 mmol) and (*R*)-2-methylbenzhydrylamine **2** (442 mg, 2.24 mmol, 96% ee) in 2-propanol (2.0 mL). The mixture was stirred overnight. The volatiles, including 2-propanol, were then removed *in vacuo*. A solution of 0.1 M DBU in 2-propanol (2 mL) was added to the residual solid. The resulting suspension was stirred overnight at room temperature followed by filtration to afford *syn*-(L)-**5a** (541 mg, 1.73 mmol, 99% de) as a colorless solid in 77% yield.

Asymmetric synthesis of L-alanine.

Anhydrous Na_2SO_4 (1.44 g, 10.1 mmol) was added to a solution of acetaldehyde (**3f**) (564 μL, 10.1 mmol) and (*S*)-**2** (1.0 g, 5.07 mmol, >99.5% ee) in CH_2Cl_2 (20 mL). After stirring overnight at room temperature, the reaction mixture was filtered and evaporated *in vacuo*. The residue was dissolved in ethanol (18 mL) and then HCN (300 μL, 7.6 mmol) was added. This reaction mixture was stirred for 15 min and then concentrated *in vacuo*. The residue was passed through silica gel, using *n*-hexane/Et_2O (1/1, *v*/*v*), to afford crude *anti*-(L)-**5f** (1.06 g, *ca*. 6% de) as a solid. A part of this crude **5f** (701 mg) was suspended in 0.5 M DBU in methanol (1.0 mL) and stirred for 122 h at room temperature. After filtration, *anti*-(L)-**5f** (501 mg, 2.0 mmol, 98% de) was obtained in 60% yield. The filtrate was concentrated then passed through silica gel, using *n*-hexane/Et_2O (1/1, v/v). The product *anti*-(L)-**5f** (84 mg, 0.34 mmol, 3% de) was obtained in 10% yield.

A solution of *anti*-(L)-**5f** (50 mg, 0.2 mmol, 98% de) in a mixed solvent of conc. HCl (0.2 mL) and trifluoroacetic acid (0.2 mL) was stirred for 20 h at 80 °C. The reaction mixture was washed with Et_2O and concentrated under reduced pressure. The residue was purified by passing it through a cation-exchange resin (Dowex 50WX8, 100–200 mesh, H^+ form). L-alanine (17 mg, 0.19 mmol, 98% de) was obtained in 96% yield.

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[31] Although **4b** and **4c** have closely related crystal structures (Supporting Information Tables S4 and S5), large difference in the racemization half-life was observed to be 7.5 min for **4b** and 230 min for **4c** in 0.2 M DBU solution, respectively (Supporting Information Figures S3 and S4).

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[35] When Strecker reaction between benzaldehyde **3a**, (*S*)-**2** and HCN was performed in the homogeneous solution in 2-propanol, diastereoselectivity of *syn*-(D)-**5a** and *anti*-(L)-**5a** was confirmed to be 54:46 (8% de) from ^{1}H-NMR analysis. HPLC analysis employing chiral stationary phase also showed it to be 54:46 (8% de).

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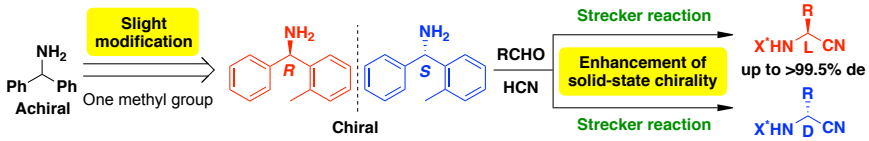

Slight modification of common substrate from achiral to chiral. Highly stereoselective Strecker synthesis using 2-methylbenzhydrylamine between achiral aldehydes and HCN have been achieved by the enhancement of chirality in solid-state to afford aminonitriles with significantly high diastereoselectivity (up to >99.5% de).

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