

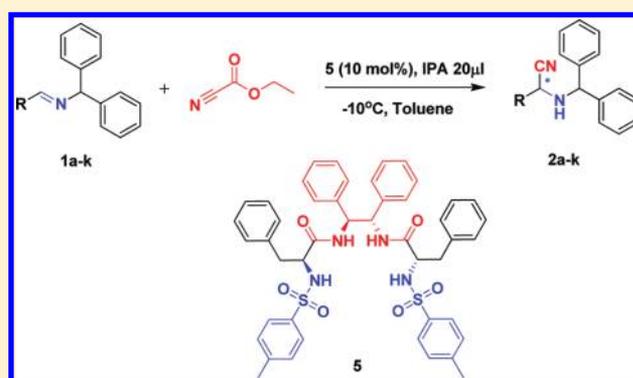
C₂-Symmetric Recyclable Organocatalyst for Enantioselective Strecker Reaction for the Synthesis of α -Amino Acid and Chiral Diamine- an Intermediate for APN Inhibitor

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S Supporting Information

ABSTRACT: Recyclable chiral amide-based organocatalyst **5** efficiently catalyzed asymmetric Strecker reaction of various aromatic and aliphatic *N*-benzhydrylimines with ethyl cyanoformate as cyanide source at $-10\text{ }^{\circ}\text{C}$ to give a high yield (95%) of α -aminonitriles with excellent chiral induction (ee, up to 99%) with the added advantage of recyclability. Based on experimental observations a probable mechanism was proposed for this reaction. This protocol with catalyst **5** was extended for the synthesis of (*R*)-phenylalanine and pharmaceutically important drug intermediate (*R*)-3-phenylpropane-1,2-diamine in high yield with high enantioselectivity.



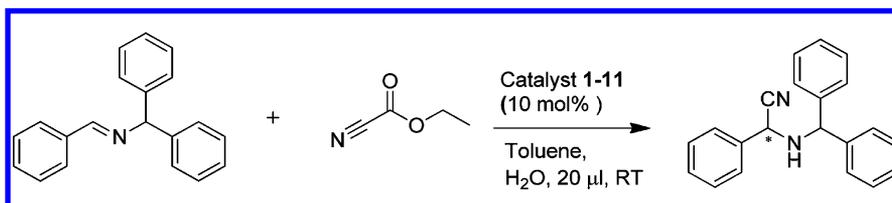
INTRODUCTION

The most elemental quest in the organic synthesis is to explore new synthetic strategies for preparing biologically active molecules in an efficient and elegant manner. Chiral α -amino acid derivatives and diamines are the classes of compounds required in their high enantiomeric purity for their high-end applications in the area of genetic engineering,¹ bioactives,² pharmaceuticals,³ and asymmetric catalysis.⁴ Asymmetric Strecker reaction⁵ represents one of the simplest and atom-economic multicomponent reactions via hydrocyanation of imines to afford α -amino nitrile, which on subsequent hydrolysis gives natural and unnatural α -amino acids.⁵ Both metal⁶ and metal-free⁷ asymmetric Strecker reaction protocols have been documented; however, metal-free protocols were preferred in order to avoid metal contamination in the final product. Since the application of chiral cyclic dipeptides by Lipton et al.⁸ in the Strecker reaction, various other organocatalysts, viz., bicyclic guanidines,⁹ ureas and thioureas,¹⁰ carbohydrates,¹¹ *N*-oxides,¹² bisformamides,¹³ ammonium salts,¹⁴ Brønsted acids,¹⁵ amino acids,¹⁶ alkaloids,¹⁷ and phase-transfer catalysts,¹⁸ have been used for this purpose. TMSCN is the most frequently used cyanide source,^{3,5,19} but few reports suggested the use of acetone cyanohydrin,^{18b} HCN,¹⁵ KCN,¹⁸ Bu₃SnCN,^{6k} and Et₂AlCN.²⁰ Ironically, NCCOOEt,^{6v,21} which is among the safest to handle sources of cyanide, did not find a place with organocatalysts for the asymmetric Strecker reaction. Recently, dimethyl sulfoxide²¹ as an organocatalyst was reported to promote nonenantioselective Strecker reaction with NCCOOEt. As far as metal-catalyzed

asymmetric Strecker reaction with NCCOOEt is concerned, aluminum-^{6v} and titanium-based^{17a} complexes have shown high activity and enantioselectivity albeit with different classes of aldimines and ketimines as substrates. While acknowledging the pioneering advances in the use of organocatalyst for the Strecker reaction, the need for very low temperatures (-70 to $-20\text{ }^{\circ}\text{C}$) and the use of stable and safer sources of cyanide are major concerns. Besides these issues, catalyst recyclability is also a concern, considering the high catalyst loading (typically above 10%) and the cost involved in the synthesis (often multistep) of these catalysts. Mechanistically, catalyst activity heavily relies on the weak acid sites capable of forming hydrogen bonds²² with the substrate, whereas the enantioselectivity is greatly influenced by the electronic and steric features of the substituents surrounding these sites. As a result, sulfonamide- and amide-derived ligands have been extensively studied in asymmetric catalysis. Based on these considerations, we have synthesized a series of C₁- and C₂-symmetric organocatalysts having sulfonamide and amide groups of varying steric features with one to four chiral centers. All of the catalysts were synthesized in two easy synthetic steps. The effect of matched and mismatched chiral centers on the enantioselectivity of those catalysts that have more than two chiral centers was also assessed. To our advantage, some of the C₂-symmetric catalysts gave α -amino nitriles in high yield (up to 95%) with excellent enantioselectivity (up to ee, 99%), in

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Table 1. Screening of Chiral Organocatalysts 1–11 for Asymmetric Strecker Reaction^a

 1 Entry 1			 2 Entry 2			 3 Entry 3				
Time (h)	Yield (%) ^b	ee (%) ^c	Time (h)	Yield (%) ^b	ee (%) ^c	Time (h)	Yield (%) ^b	ee (%) ^c		
5	80	7	8	83	42	8	80	16		
 4 Entry 4			 5: (1S, 2S) 6: (1R, 2R) Entry 5			 7: (1S, 2S) 8: (1R, 2R) Entry 6				
Time (h)	Yield (%) ^b	ee (%) ^c	Cat*	Time (h)	Yield (%) ^b	ee (%) ^c	Cat*	Time (h)	Yield (%) ^b	ee (%) ^c
5	90	10	5	8	78	73	7	8	75	33
			6	8	74	42	8	8	77	71
 9 Entry 7			 10 Entry 8			 11 Entry 9				
Time (h)	Yield (%) ^b	ee (%) ^c	Time (h)	Yield (%) ^b	ee (%) ^c	Time (h)	Yield (%) ^b	ee (%) ^c		
8	70	54	8	82	40	8	72	61		

^aEnantioselective Strecker reaction of *N*-benzhydrylimine (0.12 mmol) was carried out with catalysts 1–11 using NCCOOEt (0.18 mmol) as a source of cyanide. ^bIsolated yield. ^cee were determined by chiral HPLC using an AD-H column. ^dCatalyst.

some cases, by using ethyl cyanofornate as a cyanide source at moderate temperatures ($-10\text{ }^{\circ}\text{C}$ to rt).

RESULTS AND DISCUSSION

The organocatalysts **1–10** (Table 1) were derived from *L*-phenylalanine, whereas catalyst **11** was based on *L*-alanine. The catalyst **1** was directly obtained by the reaction of *L*-phenylalanine with *p*-toluenesulfonyl chloride in a 1:1.2 molar ratio. The carboxylic acid group of catalyst **1** was converted to acid chloride in high yield by its reaction with SOCl_2 in slight stoichiometric excess (1:1.5 equiv) in dry chloroform. Incidentally, other chlorinating agents like PCl_5 , POCl_3 , ethyl chloroformate, and neat SOCl_2 do not give desirable products. The acid chloride of the catalyst **1** was directly reacted with various chiral amines, amino alcohols, and diamines to give catalysts **2–9** in quantitative yields. Catalyst **10** was prepared by the condensation of (1*S*,2*S*)-(-)-1,2-diphenyldiaminoethane with Boc-protected *L*-phenylalanine acid chloride. (Characterization data are given in the Supporting Information). Moreover, the DCC coupling of catalyst **1** with these chiral amines gave the targeted catalysts in low yield and required column chromatographic separation to get desirable purity.

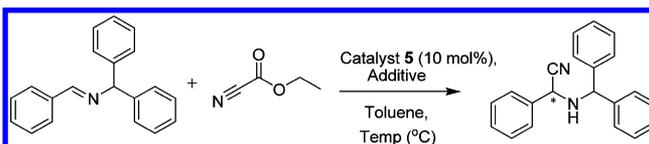
It is understood from the body of the literature available that the activation of substrate–imine with organocatalyst is solely via noncovalent interactions (mostly H-bonding), while enantioselectivity is greatly influenced by the orientation of the substrate vis-à-vis chiral catalyst.²¹ Therefore, in an organocatalyst the steric factors and/or placement of bulkier groups in space play a significant role in manifesting the enantio-induction. Keeping these factors in mind, the catalyst **1–11** were designed and screened for their efficacy in the asymmetric Strecker reaction of *N*-benzhydrylimine (as a test substrate) using ethyl cyanofornate (safer source of cyanide) as a cyanide source and water as an additive as well as a source of proton in toluene at rt. First, we took the sulfonamide derivative of (*S*)-phenylalanine **1** as a catalyst that gave the product in high yield (80%) but with 7% ee (Table 1, entry 1). It is possible that the free terminal $-\text{COOH}$ group of catalyst **1** might strongly bind imine, thereby undermining the influence of the groups surrounding the chiral center of the catalyst to give the product with low ee. Hence, we converted the $-\text{COOH}$ group of catalyst **1** to amide group by using (*S*)-1-phenylethylamine; consequently the $-\text{NH}-$ group thus generated in the catalyst **2** was placed between the two chiral centers. This situation closely resembled the chiral urea used as catalyst in Strecker reaction.^{10e} The catalyst **2** with two chiral centers indeed improved enantioselectivity significantly (ee, 42%, entry 2). Noticeably, when the (*R*)-form of the amine was used, as in catalyst **3**, there was a steep fall in the product ee (16%, entry 3) indicating the strong influence of orientation of the substituents around chiral centers. The catalyst **4**, which was prepared by condensation of catalyst **1** with (1*R*,2*S*)-2-amino-1,2-diphenylethanol that bears a free alcohol group, gave poor ee (10%, entry 4) in the product as was the case with catalyst **1**. Switching over to C_2 -symmetric catalysts **5–11** from the C_1 -symmetric catalysts **1–4** was of a distinct advantage particularly in terms of enantioselectivity (entries 5–9). Among these, the catalyst **5** (all *S* chiral centers) and **8** (all *R* chiral centers) derived by the condensation of catalyst **1** with 1,2-diamino-1,2-diphenylethane were found to be most effective to give product ee's of 73% (with *R* in excess) and 71% (with *S* in excess), respectively. The mismatched chirality in the catalysts **6** and **7** gave product with lower ees 42 and 33%, respectively.

If we look at catalyst **5** fabrication, it has three basic components: (1) phenylalanine, (2) diphenyldiamine, and (3) sulfonamide. When we changed any one component of catalyst **5**, as in the case of subsequent catalysts **9–11**, significant drops in the product ee to 54, 40, and 61%, respectively, were observed.

The catalyst **5** was found to be very active under the above used reaction conditions for the hydrocyanation of *N*-benzhydrylimine using TMSCN as a cyanide source giving the product in 99% yield in 3 h but with lower ee (18%). The ee of the product was improved to 30% on lowering the temperature to $-20\text{ }^{\circ}\text{C}$; however, it took 10 h for the reaction to complete. Possibly the acidity of the catalyst is high enough to release the HCN rapidly, thereby increasing the rate of the nonenantioselective background reaction.

Overall, the organocatalyst **5** was distinctly better in terms of activity and enantioselectivity under the reaction conditions used above. In order to improve the results, particularly the enantioselectivity, the catalyst **5** (Table 1, entry 5) was subjected to reaction condition optimization experiments using *N*-benzhydrylimine as a model substrate and ethyl cyanofornate as a cyanide source at rt. The role of additives on the reactivity and enantioselectivity of asymmetric Strecker reaction is well documented;^{5a} therefore, first we took different protic additives (mainly alcoholic) viz., MeOH, EtOH, and *i*-PrOH (2.0 equiv) (Table 2, entries 1–3), in place of water that

Table 2. Effect of Additives and Temperature on Asymmetric Strecker Reaction^a



entry	additive (equiv)	temp ($^{\circ}\text{C}$)	time (h)	yield ^b (%)	ee ^c (%)
1	MeOH (2.0)	rt	10	83	58
2	EtOH (2.0)	rt	10	82	47
3	<i>i</i> -PrOH (2.0)	rt	12	85	82
4	<i>i</i> -PrOH (1.0)	rt	15	76	73
5	<i>i</i> -PrOH (3.0)	rt	10	85	80
6	<i>i</i> -PrOH (2.0)	0	15	85	84
7	<i>i</i> -PrOH (2.0)	-10	20	85	90
8	<i>i</i> -PrOH (2.0)	-20	36	74	89

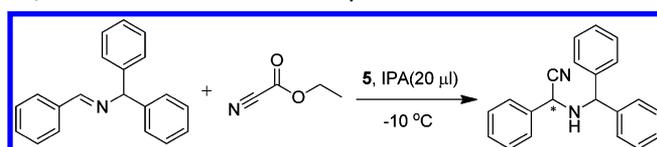
^aEnantioselective Strecker reaction of *N*-benzhydrylimine (0.12 mmol) was carried out with catalyst **5** in toluene using NCCOOEt (0.18 mmol) as a source of cyanide. ^bIsolated yield. ^cee were determined by chiral HPLC using AD-H column.

was used as an additive and proton source while screening of the catalysts **1–11**. Evidently, the use of *i*-PrOH significantly improved the enantioselectivity (ee, 82%) of the product α -aminonitrile without affecting the product yield. We next optimized the loading of *i*-PrOH by keeping the other parameters constant (Table 2, entries 3–5), which showed that at lower *i*-PrOH loading (1.0 equiv) there was a decrease in the product ee and yield but when the amount of *i*-PrOH was increased (3.0 equiv) the reactivity and enantioselectivity remained similar; therefore, 2.0 equiv of additive loading was taken as an optimum (Table 2, entry 3). Further, variation in reaction temperature revealed that lowering the temperature to $-10\text{ }^{\circ}\text{C}$ had some beneficial effect on the product ee (from rt 82% to 90%) though the reaction took a longer time (from rt

10 to 20 h) to complete. A further lowering of the temperature ($-20\text{ }^{\circ}\text{C}$) did not have any positive impact on the product ee because at the same time reaction became too sluggish (36 h). Therefore, $-10\text{ }^{\circ}\text{C}$ was taken as optimum for further studies.

Further, the catalyst loading of 10 mol %, which was used in the preceding experiments, was found to be optimum as it was observed that by decreasing the catalyst loading (5 mol %) the product yield (78%) and ee (73%) dropped significantly. On the other hand, on increasing the catalyst loading (15 mol %), the reaction was faster but with a marginal drop in ee (88%), while the product yield remained the same (Table 3, entry 3).

Table 3. Exploring the Appropriate Catalyst Loading (mol %) and Effect of Solvent on Asymmetric Strecker Reaction^a



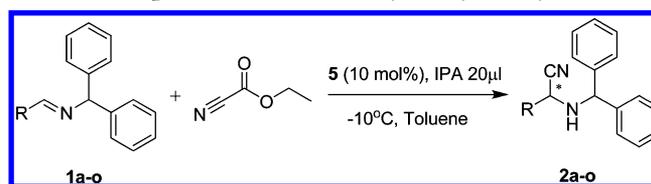
entry	catalyst loading (mol %)	solvent	time (h)	yield (%)	ee (%)
1	10	toluene	20	85	90
2	5	toluene	20	78	73
3	15	toluene	16	85	88
4	10	CH_2Cl_2	12	90	72
5	10	CHCl_3	12	88	65
6	10	THF	16	70	52
7	10	toluene/DCM (1:0.5)	20	88	82
8	10	toluene/DCM (1:1)	20	90	80

^aEnantioselective Strecker reaction of *N*-benzhydrylimine (0.12 mmol) was carried out with catalyst 5 using NCCOOEt as a source of cyanide in presence of *i*-PrOH (2 equivalents). ^bIsolated yield. ^cee were determined by chiral HPLC using AD-H column.

For the solvent variation, CH_2Cl_2 , CHCl_3 , and THF and a mixture of toluene and CH_2Cl_2 were used for easy handling for carrying out the Strecker reaction under the above-optimized conditions (entries 4–8). However, toluene remained the solvent of choice (Table 3, entry 1).

Having established the reaction parameters for the use of the catalyst 5 in the asymmetric Strecker reaction with the reactants *N*-benzhydrylimine and ethyl cyanofornate at $-10\text{ }^{\circ}\text{C}$, we next looked for its utility in different substrates having various substituents on the imine functionality (Table 4). In these cases, product yield was found to be very good to excellent (75–95%). Both electronic features and placement of substituent in the phenyl group significantly influence the ee of the product. Thus, R with electron-withdrawing groups like NO_2 , Br, F, and Cl gave excellent ees of 99%, 96%, 99%, and 92% respectively (entries 2–5) in the product. As far as placement of substituent on Ph of the aldehyde arm (*o*-/*m*-/*p*-OMe Ph), the trend for ee in the product was found to be *o* > *m* > *p* (entries 6–8). On the other hand, in the cases where R is alkyl the steric feature seems to be play a larger role in introducing higher ee's in the products (entries 9–11), while heteroarene-based aldimines like the pyridyl derivative and naphthalene-derived aldimine gave ee's of 60% and 85%, respectively (Table 4, entries 12 and 13). Conclusively, the catalyst 5 was able to catalyze asymmetric Strecker reaction of fairly broad range of aldimines with good to excellent ee in the product.

Table 4. Scope of Substrates Catalyzed by Catalyst 5^a



entry	R	time (h)	yield ^b (%)	ee ^c (%)
1	Ph (1a)	20	85	91 (R) ^d
2	2-Br- C_6H_4 (1b)	24	92	96
3	2- NO_2 - C_6H_4 (1c)	24	95	99
4	2-F- C_6H_4 (1d)	24	91	99
5	2-Cl- C_6H_4 (1e)	24	90	92
6	2-MeO- C_6H_4 (1f)	20	86	78
7	3-MeO- C_6H_4 (1g)	20	85	65
8	4-MeO- C_6H_4 (1h)	20	78	28
9	2-EtO- C_6H_4 (1i)	20	75	86
10	2-Me- C_6H_4 (1j)	20	79	74
11	<i>tert</i> -butyl (1k)	20	88	95
12	Ph- CH_2 (1l)	20	90	93
13	isobutyl (1m)	20	77	81
14	3-pyridinyl (1n)	20	70	60
15	2-naphthyl (1o)	24	74	85

^aEnantioselective Strecker reaction of imine (0.12 mmol) was carried out with catalyst 5 using NCCOOEt (0.18 mmol) as a source of cyanide in the presence of *i*-PrOH (2 equiv). ^bIsolated yield. ^cee were determined by chiral HPLC using AD-H and OD-H columns. ^dAbsolute configurations were assigned in comparison to the literature reports^{12c} and optical rotation.

Mechanism. To understand the mechanism of the Strecker reaction with the present catalyst, a series of experiments were carried out. It is well-known in the literature that HCN can add to imine in the absence of a catalyst at rt.^{6h} Therefore, at first we wanted to understand whether NCCOOEt or HCN (in situ generated) is the real source of cyanide. To verify this, we conducted the reaction of *N*-benzhydrylimine with NCCOOEt under dry conditions at rt, which showed only trace amounts of cyanated product. However, in the presence of *i*-PrOH, the same reaction gave racemic product in ~10% yield in 12 h, while in the presence of catalyst 5 under similar conditions the reaction proceeded well to give the product in 85% yield and 82% ee in 12 h. Therefore, it can be safely presumed that NCCOOEt is the cyanating agent while the additive (*i*-PrOH) is primarily the source of proton to get the final product. The next issue was the mode of binding of the catalyst with aldimine substrates. It is obvious that the imine nitrogen would prefer a binding with the more acidic proton of the catalyst, which is the proton of sulfonamide origin. The ¹H NMR spectra of the mixture of catalyst 5 and *N*-benzhydrylimine show that a doublet for sulfonamide proton at 4.94 ppm shifted significantly downfield to appear at 5.02 ppm as a broad peak (Figure 1), whereas the proton of amide origin was not much affected. A similar observation was obtained in ¹³C NMR as well (Figure 2). Therefore, it can be concluded that the contact between the sulfonamide proton of the catalyst and the imine nitrogen of the substrate is established to form intermediate I-1 in the catalytic cycle (Scheme 1). Although there was no direct observation for the activation of NCCOOEt, the ¹³C NMR of the mixture of catalyst 5 and NCCOOEt showed an additional set of two peaks for $-\text{CH}$ peaks belonging to phenylalanine and diphenylamine moieties at 63.2 and 64.1 ppm, respectively

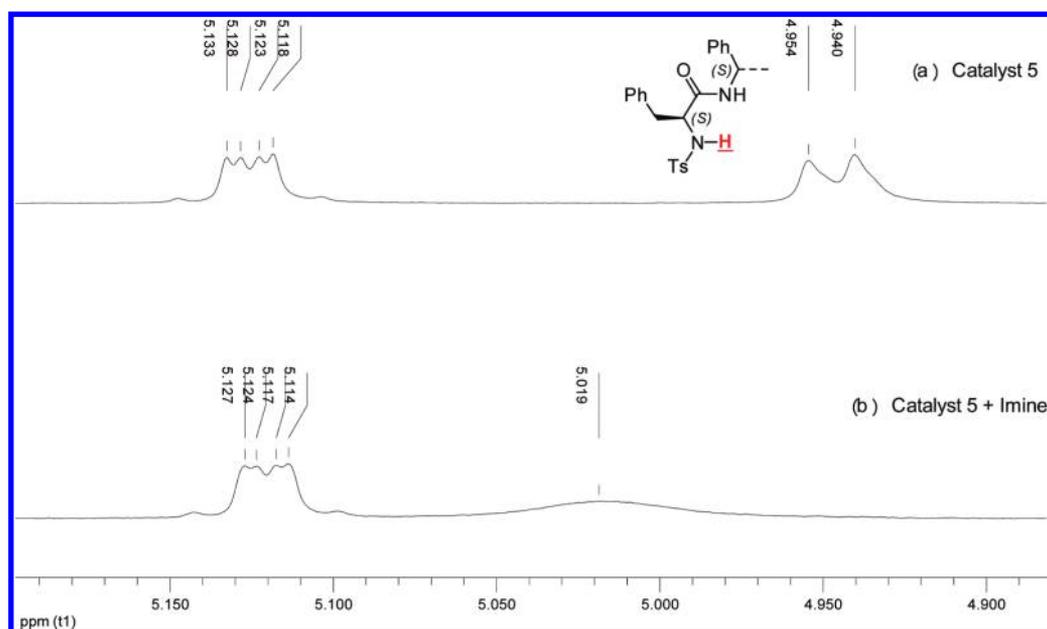


Figure 1. ^1H NMR spectra were taken in CDCl_3 : (a) catalyst 5; (b) catalyst 5 after interaction with imine.

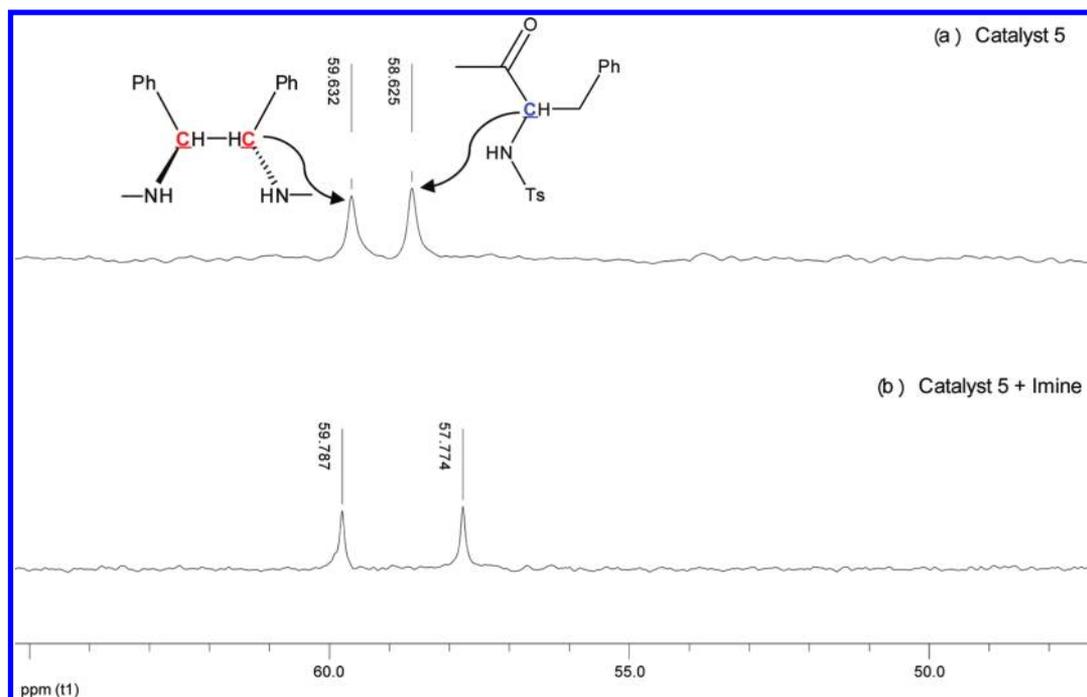


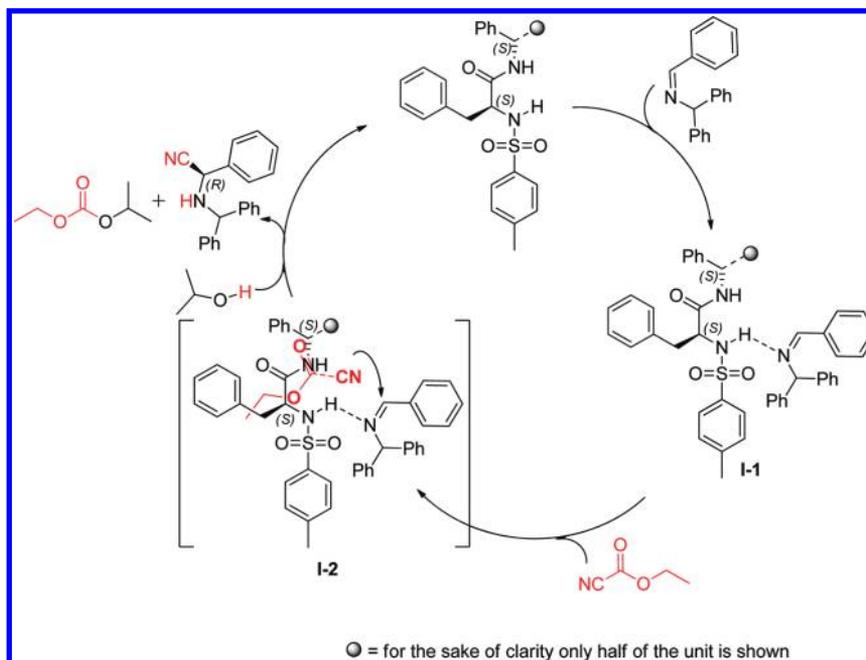
Figure 2. ^{13}C NMR spectra recorded in CDCl_3 : (a) catalyst 5; (b) catalyst 5 after interaction with imine.

(Supporting Information). Originally, in the absence of NCCOOEt , there was only one set of peaks at 58.6 and 59.6 ppm for these carbons. These observations clearly indicate that NCCOOEt is placed somewhere in between these two carbons via an intermediate **I-2** during the cyanide transfer in the catalytic cycle. Accordingly, a probable mechanism is proposed as shown in the Scheme 1, which also follows the sequence of the addition of each reactant used in our all experiments.

Recyclability of Catalyst. Often, catalysts used under homogeneous condition are not recycled due to their inherent problem of separation in the postcatalysis workup. However, it is prudent to attempt catalyst recyclability to know its stability under the reaction conditions. Additionally the increased

turnover number of the catalyst as a result of its successful reuse would offset the overall catalyst cost and make the protocol suitable for practical application. Therefore, reuse experiments were conducted using 2- NO_2 -Ph substituent on *N*-benzhydrylimine as a representative substrate with catalyst **5** (10 mol %) and ethyl cyanofornate as a source of cyanide at -10°C in toluene in the presence of *i*-PrOH. After the catalytic run, the amount of the solvent was reduced, and the organocatalyst **5** was precipitated by addition of an excess amount of *n*-hexane. The precipitated organocatalyst was washed thoroughly with hexane, dried in vacuum, stored under dry and inert atmosphere, and used for the subsequent catalytic run without further purification. The recovered catalyst

Scheme 1. Probable Mechanism for Enantioselective Strecker Reaction Catalyzed by 5



worked well for the asymmetric Strecker reaction of 2-NO₂-Ph substituents on *N*-benzhydrylimine without any loss of its reactivity and enantioselectivity up to three cycles (Figure 3).

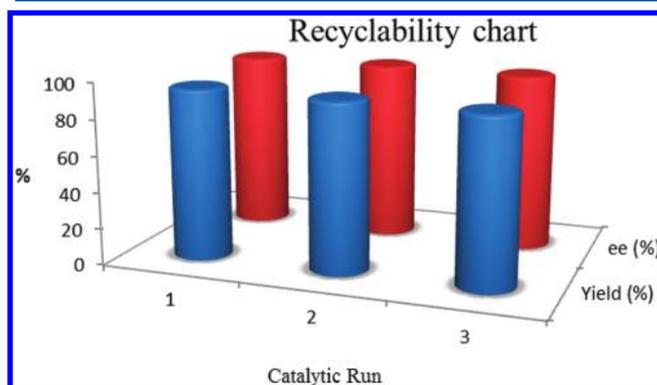


Figure 3. Recyclability of catalyst 5 using 2-NO₂-Ph-substituted *N*-benzhydrylimine.

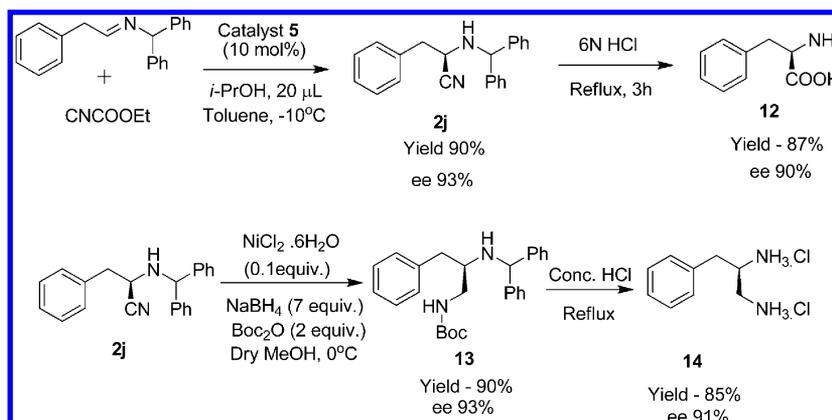
Application of Catalyst 5 in the Synthesis of (*R*)-Phenylalanine and (*R*)-3-Phenylpropane-1,2-diamine.

The present catalytic asymmetric Strecker protocol with catalyst 5 was successfully extended to the synthesis of valuable unnatural (*R*)-phenylalanine 12 and (*R*)-3-phenylpropane-1,2-diamine derivatives 13 and 14, an pharmaceutically important drug intermediate for aminopeptidase N (APN) inhibitor²³ (Scheme 2). The compounds 12 and 14 were obtained in fewer steps with high yield and marginal effect on the enantioselectivity (experimental procedures and characterization data are provided in the Supporting Information).

CONCLUSION

The chiral organocatalyst 5 is highly efficient for the catalysis of the asymmetric Strecker reaction of aromatic and aliphatic aldimines with ethyl cyanoformate as a source of cyanide for the first time. High yields and ee's were achieved with a wide range of substrates, in particular, with 2-NO₂ and 2-F substituents on *N*-benzhydrylimine where yield and enantioselectivity for the product α -aminonitrile was excellent. The

Scheme 2. Transformation of the Chiral α -Aminonitrile to Value-Added Products

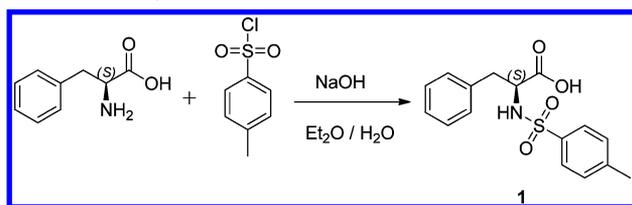


catalyst **5** was recycled three times and was employed successfully in the synthesis of (*R*)-phenylalanine and pharmaceutically important drug intermediate (*R*)-3-phenylpropane-1,2-diamine in high yield and enantioselectivity within three convenient steps.

EXPERIMENTAL SECTION

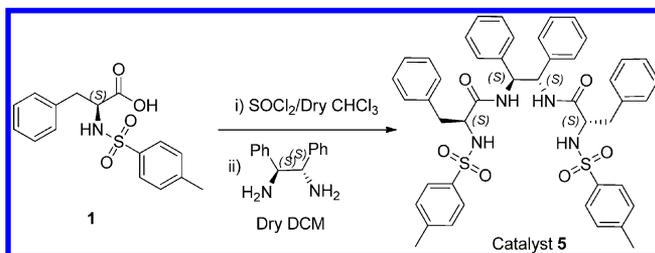
Preparation of Catalyst 5. *Step 1: Typical Procedure for the Synthesis of Catalyst 1.*²⁴ To a solution of L-phenylalanine (1 g, 6.05 mmol) dissolved in 15 mL of 1.5 N NaOH was added *p*-toluenesulfonyl chloride (1.38 g, 7.26 mmol) in diethyl ether (10 mL) at room temperature. After 8 h of stirring, concd HCl was added to the viscous white solution until it became homogeneous. The ether layer was separated, and the aqueous layer was extracted twice with ether. The crude product was recrystallized from ether and ethanol mixture to give pure compound as white crystals (Scheme 3).

Scheme 3. Preparation of Catalyst 1



Step 2: Typical Procedure for the Synthesis of Catalyst 5. To the tosyl-protected L-phenylalanine **1** (1 g, 3.13 mmol) in dry chloroform was added dropwise freshly distilled thionyl chloride (341 μ L, 4.70 mmol), and the resulting mixture was stirred at room temperature for 1 h. Subsequently, the solution was refluxed for a further 2 h. The clear yellow solution thus obtained was distilled completely to give a quantitative yield of acid chloride as yellow solid. The formed acid chloride was then immediately dissolved in dry CH_2Cl_2 under nitrogen atmosphere and cooled to 0 $^\circ\text{C}$. To the cooled solution was added (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine (316 mg, 1.5 mmol) in CH_2Cl_2 dropwise under nitrogen atmosphere. After the solution was stirred for 2 h, the reaction temperature was gradually increased to room temperature and the mixture was allowed to stir at room temperature for 8 h. Then, the solution was extracted with water (50 mL \times 5) and dried over anhydrous Na_2SO_4 . Consequently, the solvent was removed under reduced pressure, the resulting pale yellow solid was dissolved in a minimum amount of dichloromethane and an excess amount of hexane was added to precipitate out the desired product. The precipitate was washed twice with hexane, filtered, and dried completely to give catalyst **5** as white solid in 92% yield (Scheme 4).

Scheme 4. Preparation of Catalyst 5



Preparation of Catalyst 10.²⁵ To a solution of Boc-L-phenylalanine (1 g, 3.77 mmol) in 15 mL of dry dichloromethane was slowly added triethylamine (0.525 mL, 3.77 mmol) at 0 $^\circ\text{C}$. To this cooled solution was added dropwise ethyl chloroformate (0.409 mL, 3.77 mmol) and the resulting solution stirred at the same temperature for 15 min. Then optically pure diamine (0.4 g, 1.89 mmol) was added, and the resulting solution was stirred for 8 h. The whole solution was

diluted with excess dichloromethane. After filtration and removal of solvent under vacuum, the white residue was recrystallized using ethyl acetate to give pure catalyst **10** as a white solid in 90% yield (1.19 g).

Catalyst 1: yield 1.8 g, 95%; white crystals; mp 163 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{27} = -15$ ($c = 2$, CH_3COCH_3); FTIR 3286, 3035, 1730, 1675, 1597, 1424, 1336, 1212, 1159, 1075, 907, 812, 746, 676 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) $\delta = 2.39$ (s, 3H), 2.96–3.00 (dd, $J = 6.5$, 14 Hz, 1H), 3.06–3.10 (dd, $J = 5.5$, 14 Hz, 1H), 4.18–4.22 (q, $J = 6$ Hz, 1H), 5.16 (d, $J = 9$ Hz, 1H), 7.05–7.07 (m, 2H), 7.19–7.25 (m, 5H), 7.57–7.58 (d, $J = 8$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) $\delta = 21.6$, 39.0, 56.5, 127.2, 127.5, 128.8, 129.6, 129.8, 134.8, 136.6, 143.9, 178.5; TOF-MS (ESI+) calcd for $(\text{C}_{16}\text{H}_{17}\text{NO}_4\text{S} + \text{Na}^+)$ 342.36, found 342.4.

Catalyst 2: yield 0.71 g, 88%; white powder; mp 215 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{27} = -156$ ($c = 1$, CHCl_3); FTIR 3305, 3249, 3060, 2978, 2915, 2367, 1950, 1636, 1534, 1434, 1327, 1157, 187, 930, 709, 691 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3) $\delta = 1.34$ (d, $J = 7$ Hz, 3H), 2.421 (s, 3H), 2.85 (dd, $J = 6.6$, 13.8 Hz, 1H), 3.04 (dd, $J = 6.4$, 13.8 Hz, 1H), 3.88 (q, $J = 6.6$ Hz, 1H), 4.95 (m, 2H), 6.38 (d, $J = 8.2$ Hz, 1H), 6.93 (m, 2H), 7.1–7.3 (m, 10 H), 7.59 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) $\delta = 22.0$, 38.7, 49.4, 58.0, 116.4, 126.3, 127.4, 127.5, 128.9, 129.2, 129.5, 130.1, 135.4, 142.6, 144.2, 148.3, 169.2. Anal. Calcd for $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_3\text{S}$: C, 68.22; H, 6.20; N, 6.63; S, 7.59; O, 11.36. Found: C, 68.25; H, 6.18; N, 6.69; S, 7.45; O, 11.26. TOF-MS (ESI+) calcd for $(\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_3\text{S} + \text{H}^+)$ 423.54, found 423.22.

Catalyst 3: yield 0.70 g, 87%; white powder; mp 192 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{27} = -102$ ($c = 0.5$, CHCl_3); FTIR 3309, 3251, 3058, 2981, 2921, 2367, 1950, 1636, 1543, 1439, 1328, 1159, 185, 932, 710, 692 cm^{-1} ; ^1H NMR (200 MHz, CDCl_3) $\delta = 1.34$ (d, $J = 7$ Hz, 3H), 2.42 (s, 3H), 2.85 (dd, $J = 6.6$, 13.8 Hz, 1H), 3.04 (dd, $J = 6.4$, 13.8 Hz, 1H), 3.88 (q, $J = 6.6$ Hz, 1H), 4.95 (m, 2H), 6.38 (d, $J = 8.2$ Hz, 1H), 6.93 (m, 2H), 7.1–7.3 (m, 10 H), 7.59 (d, $J = 8.4$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) $\delta = 22.0$, 38.7, 49.4, 58.0, 116.4, 126.3, 127.4, 127.5, 128.9, 129.2, 129.5, 130.1, 135.4, 142.6, 144.2, 148.4, 169.3; TOF-MS (ESI+) calcd for $(\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_3\text{S} + \text{H}^+)$ 423.54, found 423.19. Anal. Calcd for $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_3\text{S}$: C, 68.22; H, 6.20; N, 6.63; S, 7.59; O, 11.36. Found: C, 68.28; H, 6.10; N, 6.58; S, 7.53; O, 11.16.

Catalyst 4: yield 0.73 g, 92%; white powder; mp 178 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{27} = -57$ ($c = 1$, CHCl_3); FTIR 3306, 3035, 2924, 2364, 1654, 1540, 1450, 1331, 1234, 1157, 1089, 1045, 942, 812, 750, 699, 543 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) $\delta = 2.39$ (s, 3H), 2.72 (d, $J = 5$ Hz, 1H), 2.86 (m, 2H), 3.87 (q, $J = 5$ Hz, 1H), 4.83 (d, $J = 5.5$ Hz, 1H), 5.03 (t, $J = 5$ Hz, 1H), 5.18 (q, $J = 4.5$ Hz, 1H), 6.87 (d, $J = 7.5$ Hz, 2H), 6.94 (s, $J = 7.5$ Hz, 2H), 7.01 (t, $J = 7.5$ Hz, 2H), 7.13–7.32 (m, 12H), 7.49 (d, $J = 8$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) $\delta = 21.8$, 38.4, 58.0, 59.6, 76.9, 126.7, 127.5, 128.1, 128.2, 128.4, 129.2, 129.4, 130.1, 135.4, 135.9, 136.7, 139.7, 144.2, 170.1; TOF-MS (ESI+) calcd for $(\text{C}_{30}\text{H}_{30}\text{N}_2\text{O}_4\text{S} + \text{H}^+)$ 515.19, found 516.23. Anal. Calcd for $\text{C}_{30}\text{H}_{30}\text{N}_2\text{O}_4\text{S}$: C, 70.01; H, 5.88; N, 5.44; S, 6.23; O, 12.44. Found: C, 69.94; H, 5.81; N, 5.50; S, 6.14; O, 12.56.

Catalyst 5: yield 0.43 g, 92%; white powder; mp 214 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{27} = -127$ ($c = 1$, CHCl_3); FTIR 3274, 3064, 2926, 2374, 1950, 1659, 1544, 1435, 1375, 1332, 1158, 1089, 1030, 958, 917, 812, 745, 699, 666, 553 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) $\delta = 2.41$ (s, 6H), 2.82 (dd, $J = 6$, 14.5 Hz, 2H), 2.94 (dd, $J = 7$, 14.5 Hz, 2H), 4.09 (q, $J = 7$ Hz, 2H), 4.95 (d, $J = 7$ Hz, 2H), 5.12 (m, 2H), 6.80 (d, $J = 7$ Hz, 4H), 6.92–6.94 (m, 4H), 7.07 (t, $J = 7.5$ Hz, 4H), 7.15–7.18 (m, 12H), 7.57 (d, $J = 8$ Hz, 4H), 7.68 (bs, 2H); ^{13}C NMR (125 MHz, CDCl_3) $\delta = 21.73$, 38.17, 58.56, 59.55, 126.69, 127.13, 127.69, 127.89, 128.58, 128.66, 129.32, 129.82, 136.35, 136.59, 138.40, 143.56, 171.39; TOF-MS (ESI+) calcd for $(\text{C}_{46}\text{H}_{46}\text{N}_4\text{O}_6\text{S}_2)$ 815.01, found 815.81. Anal. Calcd for $\text{C}_{46}\text{H}_{46}\text{N}_4\text{O}_6\text{S}_2$: C, 67.79; H, 5.69; N, 6.87; S, 7.87; O, 11.78. Found: C, 67.81; H, 5.65; N, 6.81; S, 7.91; O, 11.84.

Catalyst 6: yield 0.42 g, 90%; white powder; mp 179 $^\circ\text{C}$; $[\alpha]_{\text{D}}^{27} = -67$ ($c = 1$, CHCl_3); FTIR 3291, 3082, 2931, 2367, 1955, 1654, 1554, 1438, 1385, 1334, 1160, 1084, 1032, 954, 921, 819, 745, 698, 668, 555 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) $\delta = 2.42$ (s, 6H), 2.81 (dd, $J = 6$, 14.5 Hz, 2H), 2.91 (dd, $J = 7.5$, 7 Hz, 2H), 4.09 (q, $J = 7$ Hz, 2H), 4.94 (d, $J = 7$ Hz, 2H), 5.12 (m, 2H), 6.81 (d, $J = 7$ Hz, 4H), 6.92–6.95 (m, 4H), 7.08 (t, $J = 7.5$ Hz, 4H), 7.14–7.18 (m, 12H), 7.57 (d, $J = 8$ Hz, 4H), 7.67 (bs, 2H); ^{13}C NMR (125 MHz, CDCl_3) $\delta = 21.73$, 38.17,

58.56, 59.55, 126.69, 127.13, 127.69, 127.89, 128.58, 128.66, 129.32, 129.82, 136.35, 136.59, 138.40, 143.56, 171.39; TOF-MS (ESI+) calcd for (C₄₆H₄₆N₄O₆S₂) 815.01, found 815.27. Anal. Calcd for C₄₆H₄₆N₄O₆S₂: C, 67.79; H, 5.69; N, 6.87; S, 7.87; O, 11.78. Found: C, 67.82; H, 5.64; N, 6.89; S, 7.91; O, 11.36.

Catalyst 7: yield 0.42 g, 91%; white powder; mp 186 °C; [α]_D²⁷ = -39 (c = 1, CHCl₃); FTIR 3287, 3092, 2945, 2376, 1957, 1661, 1523, 1443, 1378, 1352, 1164, 1087, 1035, 951, 923, 821, 741, 698, 667, 551 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ = 2.41 (s, 6H), 2.82 (dd, J = 6, 14.5 Hz, 2H), 2.91 (dd, J = 7, 14.5 Hz, 2H), 4.09 (q, J = 7 Hz, 2H), 4.94 (d, J = 7 Hz, 2H), 5.12 (m, 2H), 6.81 (d, J = 7 Hz, 4H), 6.92–6.96 (m, 4H), 7.08 (t, J = 7.5 Hz, 4H), 7.14–7.18 (m, 12H), 7.57 (d, J = 8 Hz, 4H), 7.67 (bs, 2H); ¹³C NMR (125 MHz, CDCl₃) δ = 21.73, 38.17, 58.56, 59.55, 126.69, 127.13, 127.69, 127.89, 128.58, 128.66, 129.32, 129.82, 136.35, 136.59, 138.40, 143.56, 171.39; TOF-MS (ESI+) calcd for (C₄₆H₄₆N₄O₆S₂) 815.01, found 815.81. Anal. Calcd for C₄₆H₄₆N₄O₆S₂: C, 67.79; H, 5.69; N, 6.87; S, 7.87; O, 11.78. Found: C, 67.74; H, 5.71; N, 6.84; S, 7.79; O, 11.67.

Catalyst 8: yield 0.48 g, 94%; white powder; mp 182 °C; [α]_D²⁷ = +81 (c = 1, CHCl₃); FTIR 3294, 3075, 2926, 2381, 1953, 1662, 1538, 1439, 1368, 1334, 1161, 1091, 1034, 956, 927, 815, 747, 694, 661, 554 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ = 2.41 (s, 6H), 2.82 (dd, J = 6, 14.5 Hz, 2H), 2.94 (dd, J = 7, 14.5 Hz, 2H), 4.09 (q, J = 7 Hz, 2H), 4.95 (d, J = 7 Hz, 2H), 5.12 (m, 2H), 6.80 (d, J = 7 Hz, 4H), 6.91–6.94 (m, 4H), 7.07 (t, J = 7.5 Hz, 4H), 7.15–7.18 (m, 12H), 7.57 (d, J = 8 Hz, 4H), 7.68 (bs, 2H); ¹³C NMR (125 MHz, CDCl₃) δ = 21.73, 38.17, 58.56, 59.55, 126.69, 127.13, 127.69, 127.89, 128.58, 128.66, 129.32, 129.82, 136.35, 136.59, 138.40, 143.56, 171.39; TOF-MS (ESI+) calcd for (C₄₆H₄₆N₄O₆S₂) 815.01, found 815.27. Anal. Calcd for C₄₆H₄₆N₄O₆S₂: C, 67.79; H, 5.69; N, 6.87; S, 7.87; O, 11.78. Found: C, 67.73; H, 5.66; N, 6.80; S, 7.81; O, 11.86.

Catalyst 9: yield 0.47 g, 85%; white powder; mp 238 °C; [α]_D²⁷ = -114 (c = 1, CHCl₃); FTIR 3302, 3096, 3034, 2931, 2861, 2362, 1924, 1644, 1540, 1451, 1331, 1158, 1091, 953, 815, 740, 696, 669, 553 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ = 1.04 (q, J = 10 Hz, 2H), 1.25 (t, J = 10 Hz, 2H), 1.69 (d, J = 8 Hz, 2H), 1.93 (d, J = 12 Hz, 2H), 2.49 (s, 6H), 2.85 (dd, J = 5.5, 14 Hz, 2H), 2.92 (dd, 7.5, 14 Hz, 2H), 3.51 (m, 2H), 3.92–3.96 (m, 2H), 4.85 (d, J = 7 Hz, 2H), 6.86 (d, J = 5 Hz, 2H), 6.91 (d, J = 6.5 Hz, 4H), 7.13 (m, 10H), 7.52 (d, J = 8.5 Hz, 4H); ¹³C NMR (125 MHz, CDCl₃) δ = 21.8, 24.7, 32.0, 38.0, 54.3, 57.8, 127.5, 129.1, 129.6, 130.1, 135.7, 136.3, 143.9, 171.3; TOF-MS (ESI+) calcd for (C₃₈H₄₄N₄O₆S₂ + H⁺) 717.27, found 718.20. Anal. Calcd for C₃₈H₄₄N₄O₆S₂: C, 63.66; H, 6.199; N, 7.82; S, 8.95; O, 13.39. Found: C, 63.64; H, 6.10; N, 7.85; S, 8.99; O, 13.29.

Catalyst 10: yield 1.19 g, 90%; white powder; mp 173 °C; [α]_D²⁷ = -94 (c = 1, CHCl₃); FTIR 3300, 3060, 3030, 2925, 2861, 2370, 1953, 1653, 1502, 1453, 1340, 1290, 1111, 1028, 914, 845, 746, 699, 618, 536 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ = 1.41 (s, 18H), 3.08 (dd, J = 4, 13.5 Hz, 2H), 1.69 (d, J = 4, 13.5 Hz, 2H), 3.56 (m, 2H), 5.16 (m, 2H), 5.25 (m, 2H), 7.05–7.07 (m, 4H), 7.22–7.25 (m, 12H) 7.36–7.38 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) δ = 28.8, 41.4, 56.8, 58.7, 80.3, 126.6, 127.4, 127.6, 128.4, 129.2, 138.6, 142.0, 158.1, 174.6; TOF-MS (ESI+) calcd for (C₄₂H₅₀N₄O₆ + H⁺) 706.87, found 707.91. Anal. Calcd for C₄₂H₅₀N₄O₆: C, 71.36; H, 7.13; N, 7.93; O, 13.58. Found: C, 71.31; H, 7.17; N, 7.95; O, 13.64.

Catalyst 11: yield 0.47 g, 91%; pale yellow powder; mp 112 °C; [α]_D²⁷ = -56 (c = 0.8, CHCl₃); FTIR 3321, 3071, 3042, 2943, 2876, 2371, 1945, 1661, 1548, 1457, 1349, 1151, 1071, 958, 821, 747, 684, 658, 545 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ = 1.13 (d, J = 7 Hz, 6H), 2.42 (s, 6H), 3.86 (q, J = 7 Hz, 2H), 5.17–5.19 (m, 2H), 7.00–7.02 (m, 4H), 7.12–7.14 (m, 6H), 7.26–7.30 (m, 5H), 7.61 (bs, 2H), 7.80 (d, J = 6 Hz, 4H); ¹³C NMR (125 MHz, CDCl₃) δ = 18.0, 21.9, 52.7, 59.5, 127.8, 127.7, 128.0, 128.7, 130.2, 137.4, 138.6, 144.2, 172.32; TOF-MS (ESI+) calcd for (C₄₂H₅₀N₄O₆ + H⁺) 663.82, found 663.27. Anal. Calcd for C₃₄H₃₈N₄O₆S₂: C, 61.61; H, 5.78; N, 8.45; S, 9.68; O, 14.48. Found: C, 61.69; H, 5.82; N, 8.49; O, 14.54.

Typical Experimental Procedure for the Enantioselective Strecker Reaction of *N*-Benzhydrylimines Using Catalyst 5. In an oven-dried reaction vial, catalyst 5 (10 mol %) and imine (0.25 mmol) were dissolved in dry toluene (2 mL), and the resulting

solution was stirred for 2 h at rt. Then the solution was cooled to -10 °C, and NCCOOEt (0.375 mmol) was added slowly over a period of 30 min followed by the very slow addition of *i*-PrOH (20 μ L). (Caution: the order for the addition of reagents should be maintained as mentioned; otherwise, the ee of the product will drop.) The reaction was monitored by TLC using hexane/ethyl acetate (90/10) as eluent. After the reaction was complete, the solvent was removed on a rotavapor and the product was purified by flash column chromatography on silica gel (eluted with hexane/ethyl acetate = 90:10). The purified products were characterized by ¹H NMR which was in agreement with the reported values.^{12c}

(*R*)-2-(Benzhydrylamino)-2-phenylacetonitrile (Table 4, Entry 1). The title compound was isolated by column chromatography (hexane/ethyl acetate 95/5) as a white solid: [α]_D²⁷ = 104 (c = 0.4, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 2.15 (d, J = 12.5 Hz, 1H), 4.60 (d, J = 12.5 Hz, 1H), 5.24 (s, 1H), 7.22–7.57 (m, 15H); CHIRALCEL AD-H column, hexane/2-propanol = 80:20, flow rate 1 mL/min, *t*_{R1} (major) = 6.8 min, *t*_{R2} (minor) = 13.06 min.

(*R*)-2-(Benzhydrylamino)-2-(2-bromophenyl)acetonitrile (Table 4, Entry 2). The title compound was isolated by column chromatography (hexane/ethyl acetate 95/5) as a white solid: [α]_D²⁷ = 62 (c = 0.1, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 2.18 (d, J = 12.5 Hz, 1H), 4.61 (d, J = 12.5 Hz, 1H), 5.22 (s, 1H), 7.21–7.36 (m, 8H), 7.40–7.45 (m, 3H), 7.52–7.56 (m, 3H); CHIRALCEL AD-H column, hexane/2-propanol = 80:20, flow rate 1 mL/min, *t*_{R1} (major) = 4.63 min, *t*_{R2} (minor) = 5.17 min.

(*R*)-2-(Benzhydrylamino)-2-(2-nitrophenyl)acetonitrile (Table 4, Entry 3). The title compound was isolated by column chromatography (hexane/ethyl acetate 95/5) as a white solid: [α]_D²⁷ = 78 (c = 0.1, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 2.16 (d, J = 12.5 Hz, 1H), 4.62 (d, J = 12.5 Hz, 1H), 5.21 (s, 1H), 7.56 (m, 14H); CHIRALCEL ADH column, hexane/2-propanol = 80:20, flow rate 1 mL/min, *t*_{R1} (major) = 6.86 min, *t*_{R2} (minor) = 7.54 min.

(*R*)-2-(Benzhydrylamino)-2-(2-fluorophenyl)acetonitrile (Table 4, Entry 4). The title compound was isolated by column chromatography (hexane/ethyl acetate 95/5) as a white solid: [α]_D²⁷ = 85 (c = 0.2, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 2.15 (d, J = 12.5 Hz, 1H), 4.62 (d, J = 12.5 Hz, 1H), 5.24 (s, 1H), 7.22–7.37 (m, 8H), 7.41–7.46 (m, 3H), 7.51–7.54 (m, 3H); CHIRALCEL ADH column, hexane/2-propanol = 80:20, flow rate 1 mL/min, *t*_{R1} (major) = 4.8 min.

(*R*)-2-(Benzhydrylamino)-2-(2-chlorophenyl)acetonitrile (Table 4, Entry 5). The title compound was isolated by column chromatography (hexane/ethyl acetate 95/5) as a white solid: [α]_D²⁷ = 121 (c = 0.5, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 2.09 (d, J = 12.5 Hz, 1H), 4.74 (d, J = 12.5 Hz, 1H), 5.04 (s, 1H), 7.22–7.37 (m, 8H), 7.41–7.46 (m, 3H), 7.51–7.54 (m, 3H); CHIRALCEL ADH column, hexane/2-propanol = 80:20, flow rate 1 mL/min, *t*_{R1} (minor) = 4.5 min, *t*_{R2} (major) = 5.2 min.

(*R*)-2-(Benzhydrylamino)-2-(2-methoxyphenyl)acetonitrile (Table 4, Entry 6). The title compound was isolated by column chromatography (hexane/ethyl acetate 95/5) as a white solid: [α]_D²⁷ = 36 (c = 0.4, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 2.14 (d, J = 12.5 Hz, 1H), 3.87 (s, 3H), 4.60 (d, J = 12.5 Hz, 1H), 5.22 (s, 1H), 7.21–7.36 (m, 8H), 7.40–7.45 (m, 3H), 7.52–7.56 (m, 3H); CHIRALCEL OD-H column, hexane/2-propanol = 80:20, flow rate 1 mL/min, *t*_{R1} (minor) = 5.5 min, *t*_{R2} (major) = 6.5 min.

(*R*)-2-(Benzhydrylamino)-2-(3-methoxyphenyl)acetonitrile (Table 4, Entry 7). The title compound was isolated by column chromatography (hexane/ethyl acetate 95/5) as a white solid: [α]_D²⁷ = 51 (c = 0.1, CHCl₃); ¹H NMR (500 MHz, CDCl₃) δ 2.12 (d, J = 12.5 Hz, 1H), 3.84 (s, 3H), 4.58 (d, J = 12.5 Hz, 1H), 5.20 (s, 1H), 6.88 (m, 1H), 7.05–7.16 (m, 2H), 7.22–7.40 (m, 7H), 7.44–7.47 (m, 2H), 7.53–7.56 (m, 2H); CHIRALCEL AD-H column, hexane/2-propanol = 80:20, flow rate 1 mL/min, *t*_{R1} (major) = 4.9 min, *t*_{R2} (minor) = 5.6 min.

(*R*)-2-(Benzhydrylamino)-2-(4-methoxyphenyl)acetonitrile (Table 4, Entry 8). The title compound was isolated by column chromatography (hexane/ethyl acetate 90/10) as a liquid: ¹H NMR (500 MHz, CDCl₃) δ 2.10 (d, J = 12.5 Hz, 1H), 3.81 (s, 3H), 4.54 (d, J = 12.5 Hz, 1H), 5.21 (s, 1H), 6.91–6.95 (m, 2H), 7.20–7.54 (m,

12H); CHIRALCEL ADH column, hexane/2-propanol = 80:20, flow rate 1 mL/min, t_{R1} (major) = 9.1 min, t_{R2} (minor) = 16.9 min.

(R)-2-(Benzhydrylamino)-2-(2-ethoxyphenyl)acetonitrile (Table 4, Entry 9). The title compound was isolated by column chromatography (hexane/ethylacetate 90/10) as a white solid: $[\alpha]_D^{27} = 82$ ($c = 0.1$, CHCl_3); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 1.31 (t, $J = 10$ Hz, 3H), 2.14 (d, $J = 12.5$ Hz, 1H), 3.99 (q, $J = 10$ Hz, 2H), 4.61 (d, $J = 12.5$ Hz, 1H), 5.22 (s, 1H), 7.21–7.36 (m, 8H), 7.40–7.45 (m, 3H), 7.52–7.56 (m, 3H); CHIRALCEL ADH column, hexane/2-propanol = 80:20, flow rate 0.8 mL/min, t_{R1} (major) = 4.7 min, t_{R2} (minor) = 5.7 min.

(R)-2-(Benzhydrylamino)-2-(2-methylphenyl)acetonitrile (Table 4, Entry 10). The title compound was isolated by column chromatography (hexane/ethylacetate 90/10) as a white solid: $[\alpha]_D^{27} = 54$ ($c = 0.2$, CHCl_3); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 2.02 (d, $J = 12.5$ Hz, 1H), 2.24 (s, 3H), 4.63 (d, $J = 12.5$ Hz, 1H), 5.19 (s, 1H), 7.21–7.28 (m, 7H), 7.30–7.34 (m, 2H), 7.38–7.40 (m, 2H), 7.42–7.57 (m, 3H); CHIRALCEL ADH column, hexane/2-propanol = 80:20, flow rate 0.8 mL/min, t_{R1} (minor) = 4.4 min, t_{R2} (major) = 6.2 min.

(R)-2-(Benzhydrylamino)-3,3-dimethylbutanenitrile (Table 4, Entry 11). The title compound was isolated by column chromatography (hexane/diethyl ether 10/90) as a white solid: $[\alpha]_D^{27} = 89$ ($c = 0.3$, CHCl_3); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 1.06 (s, 9H), 1.75 (d, $J = 12.5$ Hz, 1H), 3.04 (d, $J = 12.5$ Hz, 1H), 5.14 (s, 1H), 7.21–7.51 (m, 10H); CHIRALCEL AD-H column, hexane/2-propanol = 80:20, flow rate 1 mL/min, t_{R1} (minor) = 4.9 min, t_{R2} (major) = 5.9 min.

(R)-2-(Benzhydrylamino)-3-phenylpropanenitrile (Table 4, Entry 12). The title compound was isolated by column chromatography (hexane/ethylacetate 95/5) as a white viscous liquid: $[\alpha]_D^{27} = 92$ ($c = 0.1$, CHCl_3); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 1.85 (bs, 1H), 2.96–3.04 (m, 2H), 3.59 (t, $J = 6$ Hz, 1H), 5.06 (s, 1H), 7.15–7.20 (m, 2H), 7.23–7.26 (m, 7H), 7.28–7.36 (m, 6H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ 39.7, 49.6, 65.5, 119.8, 127.1, 127.4, 127.7, 127.8, 127.9, 129.6, 135.3, 141.4, 143.3; CHIRALCEL ADH column, hexane/2-propanol = 80:20, flow rate 1 mL/min, t_{R1} (minor) = 4.4 min, t_{R2} (major) = 4.7 min.

(R)-2-(Benzhydrylamino)-4-methylpentanenitrile (Table 4, Entry 13). The title compound was isolated by column chromatography (hexane/diethyl ether 10/90) as a white solid: $[\alpha]_D^{27} = 84$ ($c = 0.2$, CHCl_3); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 1.02 (d, $J = 12.5$ Hz, 6H), 1.66–1.74 (m, 3H), 1.98 (d, $J = 13$ Hz, 1H), 4.04 (q, 1H), 5.12 (s, 1H), 7.19–7.46 (m, 10H); CHIRALCEL AD-H column, hexane/2-propanol = 80:20, flow rate 0.8 mL/min, t_{R1} (minor) = 7.1 min, t_{R2} (major) = 7.6 min.

(R)-2-(Benzhydrylamino)-2-(pyridin-3-yl)acetonitrile (Table 4, Entry 14). The title compound was isolated by column chromatography (hexane/diethyl ether 10/90) as a yellow solid: $[\alpha]_D^{27} = 134$ ($c = 0.2$, CHCl_3); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 2.26 (d, $J = 12.5$ Hz, 1H), 4.69 (d, $J = 12.5$ Hz, 1H), 5.27 (s, 1H), 7.32–7.35 (m, 3H), 7.38–7.43 (m, 4H), 7.48 (d, $J = 7$ Hz, 2H), 7.60 (d, $J = 7.5$ Hz, 2H), 7.92–7.92 (dd, $J = 8$ Hz, 1H), 8.66 (d, $J = 3.5$ Hz, 1H), 8.83 (d, $J = 2$ Hz, 1H); CHIRALCEL AD-H column, hexane/2-propanol = 80:20, flow rate 1 mL/min, t_{R1} (minor) = 7.1 min, t_{R2} (major) = 10.7 min.

(R)-2-(Benzhydrylamino)-2-(naphthalen-2-yl)acetonitrile (Table 4, Entry 15). The title compound was isolated by column chromatography (hexane/diethyl ether 10/90) as a yellow solid: $[\alpha]_D^{27} = 134$ ($c = 0.2$, CHCl_3); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ 2.19 (d, $J = 12.5$ Hz, 1H), 4.72 (d, $J = 12.5$ Hz, 1H), 5.71 (s, 1H), 7.83–7.19 (m, 17H). CHIRALCEL AD-H column, hexane/2-propanol = 80:20, flow rate 1 mL/min, t_{R1} (minor) = 7.4 min, t_{R2} (major) = 11.7 min.

Procedure for the Conversion of α -Amino Nitrile to Amino Acid.^{6f,u} A solution of amino nitrile **2j** (1 mmol) in 6 N HCl was refluxed for 3 h. The solution was cooled to room temperature, and the reaction mixture was washed with diethyl ether (3 \times 10 mL). The acid was neutralized using 1 N NaOH to precipitate the amino acid. The suspension was centrifuged to obtain the amino acid²⁶ and was washed with cold water followed by ether to remove impurities and dried under vacuum: yield 0.143 g, 87%; $[\alpha]_D^{27} = 63$ ($c = 0.2$, H_2O);

$^1\text{H NMR}$ (500 MHz, D_2O) δ = 3.02 (dd, $J = 8, 13$ Hz, 1H), 3.20 (dd, $J = 7, 12$ Hz, 1H), 3.84–3.90 (m, 1H), 7.22–7.33 (m, 5H); $^{13}\text{C NMR}$ (125 MHz, D_2O) δ = 36.5, 56.2, 127.8, 129.3, 129.5, 135.3, 174.0.

Procedure for the Conversion of α -Amino Nitrile to Diamine Derivative.²⁷ The aminonitrile **2j** (250 mg, 0.80 mmol) was dissolved in dry methanol (15 mL), cooled to 0 $^\circ\text{C}$, and stirred to obtain a clear solution, and then Boc_2O (350 mg, 1.60 mmol) and $\text{NiCl}_2 \cdot 6\text{H}_2\text{O}$ (20 mg, 0.08 mmol) were added. To this solution was added NaBH_4 (296 mg, 8 mmol) in small portions over 2 h. The reaction was exothermic and effervescent. The resulting reaction mixture containing a finely divided black precipitate was allowed to warm to room temperature and allowed to stir for a further 3 h, at which point triethylenetetramine (115 μL mg, 0.8 mmol) was added. The mixture was allowed to stir for 2 h before solvent evaporation. The purple residue was dissolved in EtOAc (50 mL) and extracted with saturated NaHCO_3 (3 \times 50 mL). The organic layer was dried over NaSO_4 and the solvent removed under vacuum to give the product **13** as a white oil in 90% yield (289 mg): $[\alpha]_D^{27} = 164$ ($c = 0.1$, CHCl_3); $^1\text{H NMR}$ (500 MHz, CDCl_3) δ = 1.44 (s, 9H), 1.67 (bs, 1H), 2.69–2.76 (m, 2H), 2.80–2.83 (m, 1H), 2.99–3.03 (m, 1H), 3.26–3.29 (m, 1H), 4.89 (s, 1H), 4.94 (bs, 1H), 7.08 (d, $J = 7.5$ Hz, 2H), 7.12 (d, $J = 7.5$ Hz, 2H), 7.16–7.21 (m, 5H), 7.26 (q, $J = 7$ Hz, 4H), 7.321 (d, $J = 7.5$ Hz, 2H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ = 28.7, 39.5, 43.3, 56.2, 64.3, 79.3, 126.6, 127.3, 127.4, 127.7, 128.7, 129.6, 138.7, 143.8, 156.5; TOF-MS (ESI+) calcd for ($\text{C}_{27}\text{H}_{32}\text{N}_2\text{O}_2 + \text{Na}^+$) 439.54, found 439.27.

Procedure for the Preparation of Chiral 3-Phenylpropane-1,2-diamine. The pure product **13** obtained by the reduction of amino nitrile **2j** was then transformed to 3-phenylpropane-1,2-diamine **14**, a valuable intermediate for the aminopeptidase N (APN) inhibitor.²⁸ The deprotection of the Boc and benzhydryl groups was done by refluxing the solution of **13** (1 mmol) in 6 N HCl (10 mL) for 2 h. The reaction mixture was then cooled to room temperature and washed with diethyl ether (3 \times 10 mL), and the aqueous layer was concentrated under reduced pressure, thus resulting in the hydrochloride salt of the diamine as a white powder in 85% yield (177 mg): $[\alpha]_D^{27} = 112$ ($c = 0.5$, H_2O); $^1\text{H NMR}$ (500 MHz, D_2O) δ = 3.04 (dd, $J = 7.5, 15$ Hz, 1H); 3.17–3.25 (m, 2H), 3.36 (dd, $J = 7, 14$ Hz, 1H); 3.679 (m, 1H), 7.10 (m, 2H), 7.39 (m, 3H); $^{13}\text{C NMR}$ (125 MHz, CDCl_3) δ = 39.2, 46.1, 56.0, 127.7, 128.7, 139.2, 136.2.

■ ASSOCIATED CONTENT

📄 Supporting Information

^1H and ^{13}C NMR spectra and HPLC chromatograms for new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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