A Catalytic Asymmetric Strecker-Type Reaction Promoted by Lewis Acid–Lewis Base Bifunctional Catalyst

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A general asymmetric Strecker-type reaction is reported, catalyzed by the Lewis acid–Lewis base bifunctional catalyst 1. The reaction of trimethylsilyl cyanide (TMSCN) with various fluorenyl imines, including *n*-aldimines and α,β-unsaturated imines, proceeds with good to excellent enantioselectivities in the presence of a catalytic amount of phenol as additive (20 mol%) (catalytic system 1). The products were successfully converted to the corresponding amino acid derivatives in high yields without loss of enantiomeric purity. Furthermore, hydrogenation or dihydroxylation of the products from α,β-unsaturated imines afforded saturated or functionalized aminonitriles also without loss of enantiomeric purity. The absolute configuration of the products and a control experiment using catalyst 2 supported the proposed dual activation of the imine and TMSCN by the Lewis acid (Al) and the Lewis base moiety (phosphine oxide) of 1. From the mechanistic studies including kinetic and NMR experiments of the catalytic species, the role of PhOH seems to be a proton source to protonate the anionic nitrogen of the intermediate. Specifically, we have found that TMSCN is more reactive than HCN in this catalytic system, probably due to the activation ability of the phosphine oxide moiety of 1 toward TMSCN. This fact prompted us to develop the novel catalytic system 2, consisting of 1 (9 mol%), TMSCN (20 mol%) and HCN (1.2 mol eq). This new system afforded comparable results with obtained by system 1 (1 (9 mol%)–TMSCN (2 mol eq)–PhOH (20 mol%)).

Key words asymmetric catalysis; Strecker-type reaction; bifunctional catalyst; Lewis acid; Lewis base; amino acid

The catalytic asymmetric Strecker-type reaction[1] is one of the most direct and efficient methods for the asymmetric synthesis of natural and unnatural α-amino acids. Recently, several excellent reactions of this type have been reported, reflecting the importance of this field.[2] We have been involved in this area, since we found that the Lewis acid–Lewis base bifunctional catalysis could provide a fundamental concept to design an asymmetric catalyst for cyanosilylation of aldehydes.[3] The bifunctional catalyst **1** promoted the addition of trimethylsilyl cyanide (TMSCN) to a variety of aldehydes with high enantioselectivities. The origin of the highly enantioselective catalysis by **1** is the simultaneous activation of the aldehydes and TMSCN by the Lewis acid (Al) and the oxygen atom of the phosphine oxide, respectively. Therefore, it seemed to be a rational extension to apply this catalyst to the development of an asymmetric Strecker-type reaction (the addition of TMSCN to imines). In this paper, we report that **1** is indeed a general catalyst for the asymmetric Strecker-type reaction (Chart 1). The reaction proceeds with good to excellent enantioselectivities toward various imines, including *n*-aldimines and α,β-unsaturated imines, in the presence of a catalytic amount of phenol (20 mol%) (catalytic system 1). Furthermore, we have found that TMSCN is more reactive than HCN in the reaction catalyzed by **1**, which led to the idea to develop a novel catalytic system consisting of **1** (9 mol%), TMSCN (20 mol%) and HCN (120 mol%) (catalytic system 2). Based on these reactions, α-amino acid derivatives, including those containing functionalized side chains, can be prepared efficiently.[4]

Optimization of the Reaction Using Catalytic System 1 Starting this project, we observed a dramatic effect of the substituent on the nitrogen atom of imines on the enantioselectivity (Table 1). Although the reaction of TMSCN (2 mol eq) with the *N*-allyl benzaldehyde imine catalyzed by 9 mol% of **1** at −40 °C gave the product with only 4% ee in 67% yield (entry 1), the reaction of *N*-benzhydryl imine gave the product with 78% ee in 84% yield (entry 2). The ee was further increased up to 95% (97% yield) by the reaction with *N*-fluorenyl imine **3a** (entry 4). More bulky *N*-triphenylmethyl imine did not afford the product even at room temperature (entry 6). As a result, the best substituent on the nitrogen atom for this reaction seemed to be the fluorenyl group, which is also effective for the aliphatic pivalaldehyde imine **3m** to give the corresponding aminonitrile **4m** in 75% ee in 94% yield. As will be discussed later, the substituent on the nitrogen atom should be close to the naphthyl moiety of the catalyst in the transition state (see **7** in Chart 2). The fluorenyl group might be important for stabilizing this desired transition state possibly by π stacking interaction, thus giving the best ee's.

In order to increase the reaction efficiency by facilitating the reaction rate, we investigated the effect of additives and found that protic additives such as alcohols and phenol afforded a beneficial effect on the reaction rate (Table 2).[5] Thus, by slowly (12 h) adding[6] 110 mol% of MeOH, iso-

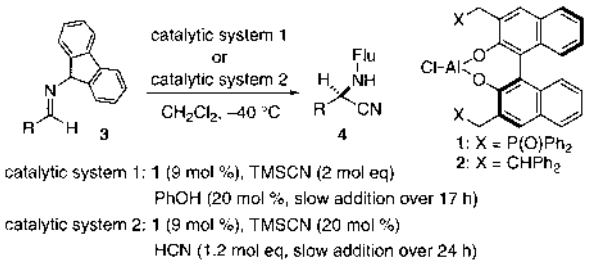

Chart 1

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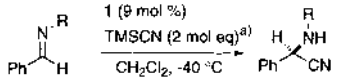
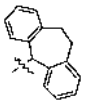
Dedicated to the memory of Dr. Kyosuke Tsuda.

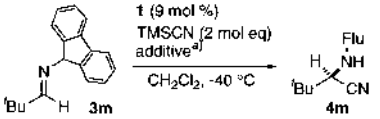
Table 1. Effect of the Substituent of Nitrogen



Entry	R	Time (h)	Yield (%)[b]	ee (%)[c]
1	Allyl	62	67	4[d]
2	$CHPh_2$	85	84	78
3	CH(PhOMe-*p*)$_2$	90	80	70[d]
4		111	97	95
5		85	73	65[d]
6	CPh_3	>170	Trace	—

a) Slowly added over 10 h. *b*) Isolated yield. *c*) Determined by HPLC analysis. *d*) The absolute configuration was not determined.

Table 2. Effect of the Proton Source



Entry	Additive (eq)	Time (h)	Yield (%)[b]	ee (%)[c]
1	—	192	94	75
2	MeOH (1.1)	21	94	66
3	Iso-PrOH (1.1)	40	96	68
4	*tert*-BuOH (1.1)	21	97	72
5	PhOH (1.1)	22	99	78
6	PhOH (0.2)	44	97	78
7	 (1.1)	13	90	64
8	 (1.1)	13	91	67

a) Slowly added over 12 h. *b*) Isolated yield. *c*) Determined by HPLC analysis.

Table 3. Catalytic Asymmetric Strecker-Type Reaction of Various Imines[a]

Entry	R	**3a**—**m**	System 1			Entry	System 2		
			Time (h)	Yield (%)[b]	ee (%)[c]		Time (h)	Yield (%)[b]	ee (%)[c]
1	Ph	**a**	44	92	95	14	36	92	95
2	*p*-ClPh	**b**	44	92	95				
3	*p*-MeOPh	**c**	44	93	93				
4	1-Naphthyl	**d**	68	95	89				
5	2-Furyl	**e**	44	93	79				
6	3-Furyl	**f**	44	92	90	15	36	92	87
7		**g**	58	90	89				
8	*trans*-PhCH=CH	**h**	41	80	96	16	36	78	92
9	*trans*-$CH_3(CH_2)_3CH$=CH	**i**	24	66	86[d]				
10	$CH_3(CH_2)_5$	**j**	24	80	80[e]	17	36	75	81
11	CH_3CH_2	**k**	44	84	70				
12	Iso-Pr	**l**	44	89	72	18	36	92	71
13	*tert*-Bu	**m**	44	97	78	19	36	96	77

a) The method for preparation of the catalyst and the general procedure of the reaction, see Experimental Section. *b*) Isolated yield. *c*) Determined by HPLC analysis. *d*) 50 mol% of PhOH was used. The aminonitrile was isolated as the corresponding trifluoroacetamide. *e*) Without PhOH.

PrOH, *tert*-BuOH, or PhOH, all reactions using **3m** were completed after 22 h, giving the product **4m** in more than 94% yield and with 66, 68, 72, and 78% ee, respectively (entries 2—5). Although the ee of the product varied from 66 to 78% depending on the additive, the following results suggested that the additive does not play a major role in the enantioface selection step. First, when the chiral alcohol 2-phenylethanol was used as an additive, both the *R* and *S* isomer afforded *R*-**4m** in almost the same enantioselectivity (64 and 67% ee, respectively) and yield (90, 91%) (entries 7, 8). Second, the ^{31}P-NMR spectra of the catalyst in the absence or presence of PhOH (20 mol%) was exactly the same under the reaction conditions (δ=42.2, 51.2 ppm), thus suggesting a negligible interaction between the catalyst and the additive. Therefore, the protic additive seems to facilitate the reaction without changing the catalytic species.

We next investigated the possibility of promoting the reaction using a catalytic amount of the best additive (PhOH) without diminishing the synthetic utility of this reaction. Gratifyingly, even when the amount of PhOH was reduced to 20 mol%, the reaction was completed after 44 h to give **4m** in 97% yield with 78% ee (entry 6). Consequently, the effective reaction conditions were found to involve the slow addition (17 h) of PhOH (20 mol%) to a mixture of **1** (9 mol%), the imine and TMSCN (2 mol eq) (catalytic system 1).

A variety of *N*-fluorenyl aldimines were examined as substrates for this optimized catalytic asymmetric Strecker-type reaction, and the results are shown in Table 3 (entries 1—13). Aromatic aldimines including heterocyclic aldimines, α,β-unsaturated aldimines, as well as aliphtic aldimines can be converted to Strecker products in excellent yields with good to excellent enantioselectivities.

Mechanistic Studies In order to gain some insight into the reaction mechanism, the kinetic profile of the reaction was investigated. After adding PhOH in one portion,[7] the reaction was monitored by observing the disappearance of the imine proton of **3a** (δ=8.58 ppm). The results are shown in Fig. 1. The initial reaction rate in the presence of 20 mol% of PhOH (●, initial steep dotted line) was 82 times faster than in the absence of PhOH (■). After about 20% consumption of the starting imine (*ca.* 80 min), which corresponded to the complete consumption of PhOH to TMSOPh, the reaction

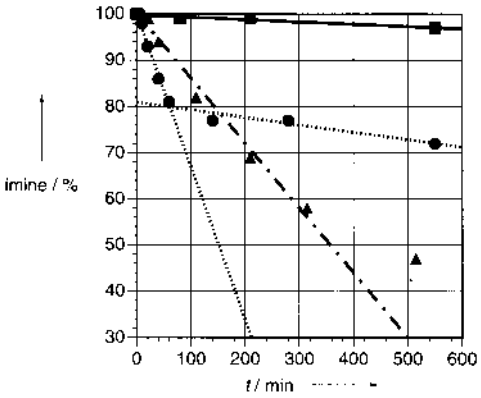


Fig. 1. Initial Reaction Rate of **3a** in the Presence of Various Amounts of PhOH

The disappearance of **3a** was traced by ^{1}H-NMR: the reaction of TMSCN in the absence (■) and in the presence of 20 mol% (●) of PhOH, and the reaction of HCN (▲).

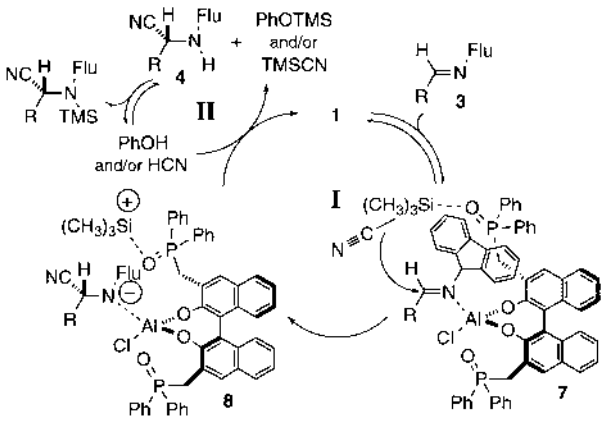


Chart 2. Working Model for the Catalytic Cycle

entered a slower phase (●, after 80 min). However, even in this slower phase, the reaction rate was *ca.* 2 times faster than in the absence of PhOH. This may be due to the re-generation of a very small amount of PhOH from TMSOPh and the product amine **4a**. This re-generation of the proton source was also suggested from the fact that the initial reaction rate in the presence of 20 mol% of **4a** and TMSOPh was *ca.* 2 times faster than in the absence of these additives.

Since other precedents used HCN or Bu_3SnCN as the nucleophile, we were interested in determining the active nucleophile in this catalytic system. Adding PhOH in one portion, the generation of HCN which could work as the active nucleophile, was observed by ^{1}H-NMR. However, when HCN (2 mol eq) was added in one portion, in the absence of TMSCN, the initial reaction rate was 0.4 times slower (Fig. 1, ▲) than when TMSCN was used in the presence of 20 mol% of PhOH, and the ee value of the product **4a** was only 53%. Furthermore, under the slow addition (26 h) conditions of HCN, which should better represent the best reaction conditions using TMSCN and slow addition of PhOH, **4a** was obtained in 54% yield with 28% ee after 85 h. These results reveal the reactive nucleophile to be TMSCN. Although HCN may be generated under the reaction conditions by the reaction of TMSCN with PhOH,[8] the highly enantioselective pathway with TMSCN as an active nucleophile predominates, since the reaction rate with TMSCN is faster than with HCN in this catalytic system. Thus, the described reaction is the first example of a catalytic asymmetric Strecker-type reaction with TMSCN as an active nucleophile. This unique feature of the catalytic system using **1** may be derived from the activation ability of the Lewis basic phosphine oxide moiety of the bifunctional catalyst **1** toward TMSCN.[3] These mechanistic studies suggest that PhOH and/or HCN should work as a proton source to protonate the negative charge on the nitrogen atom which is generated by the addition of CN to the imine, thus accelerating the formation of **4** (Chart 2). A small amount of the proton source would be re-generated *via* the cycle II, thus significantly accelerating the reaction rate by using even a catalytic amount of PhOH.

Meanwhile, the dual activation mechanism by the bifunctional catalyst **1** seems to be supported by the following results. The absolute configuration of the products can be explained from the working model shown as **7** in Chart 2. The Lewis acid (Al) and the Lewis base (phosphine oxide) activate the imine and TMSCN, respectively, at defined positions thus affording *R*-products. Furthermore, a control catalyst **2**, containing the diphenylmethyl group which should work only as a steric hindrance, afforded the opposite enantiomer *S*-**4a** with 15% ee in 100% yield (42 h), using 20 mol% of PhOH. Therefore, in the case of **1**, TMSCN seems to attack the activated imine from the side of the phosphine oxide moiety.

Catalytic Asymmetric Reaction Using System 2 Taking the advantage of the intriguing reactivity difference between TMSCN and HCN in this catalytic reaction, we expected that, if HCN was used instead of PhOH, it would be possible to reduce the amount of TMSCN. After the attack of TMSCN and protonation of the resulting intermediate **8** in Chart 2 by HCN, TMSCN should be re-generated, which should again work as the nucleophile. Since the reaction of HCN with the imine might compete with the desired reaction of TMSCN as the nucleophile, we expected that it would be important to keep the concentration of HCN low enough by slow addition of HCN. Thus, using 20 mol% of TMSCN and slowly adding the solution of HCN (120 mol%) in CH_2Cl_2 (system 2), we could obtain the products with comparable results as by the TMSCN–PhOH system (system 1) (Table 3, entries 14—19). These results demonstrate the great potential for the application of this catalytic asymmetric reaction to a large-scale Strecker-type synthesis using HCN as a stoichiometric cyanide source, optimizing the amount of TMSCN and the addition time of HCN.

Conversion to α-Amino Acid Derivatives Since the fluorenyl group has not often been used as a protecting group for the nitrogen atom, we did some studies to find a procedure to deprotect this group without racemization. Our idea was to oxidize the amine to fluorenone-derived imine, followed by hydrolysis (Chart 3). However, when the aromatic aminonitrile **4a** was directly treated under oxidation conditions (MnO_2, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), ceric ammonium nitrate (CAN), or *N*-bromosuccinimide (NBS)), the target imine was not obtained at all. So, we first hydrolyzed **4a** (95% ee) to the amide **9** (HCl (g)/HCO_2H, r.t., 1 h). Recrystallization from tetrahydrofuran (THF)/ether gave the enantiomerically pure **9** in 90% yield. Oxidation of **9** by DDQ gave the corresponding fluorenone-derived imine **10**, which was converted to the amide **11** in

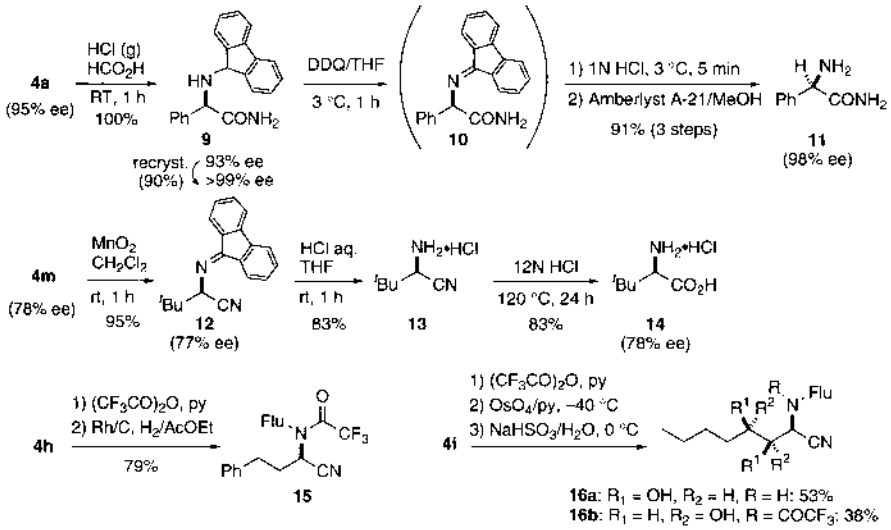


Chart 3. Conversion to α-Amino Acid Derivatives and Functionalization of α,β-Unsaturated Strecker-Products

91% yield by acid hydrolysis. Enantiomeric purity of **11** was determined to be 98% ee after conversion to the corresponding urethane by *p*-nitrobenzyloxycarbonyl chloride. In the case of the aliphatic aminonitrile **4m** (78% ee), direct oxidation by activated MnO_2 gave the imine **12** in 95% yield with 77% ee. After acid hydrolysis to the corresponding aminonitrile **13**, the nitrile group was hydrolyzed to the amino acid **14**. The enantiomeric purity of **14** was determined after conversion to the protected form (*N*-9-fluorenylmethoxycarbonyl (*N*-Fmoc), methyl ester) to be 78%. Therefore, efficient routes for the conversion of the Strecker products were established. In the same way, **4k** was converted to the α-amino acid derivative. The absolute configurations were determined by comparing the optical rotations with the reported values.

We were able to perform other important conversions as the hydrogenation and the dihydroxylation of α,β-unsaturated aminonitriles **4h** and **4i**. Direct hydrogenation of **4h** (96% ee) catalyzed by Pd/C afforded the corresponding saturated aminonitrile with complete racemization. This result should be due to the migration of the olefin to the thermodynamically more stable enamine, followed by reduction. When **4h** was treated with other transition metals such as $(Ph_3P)_3RhCl$ or Raney Ni under hydrogen atmosphere, elimination of HCN and hydrogenation of the resulting imine occurred to give the secondary amine. Therefore, we tried the hydrogenation after protection of the amine as the trifluoroacetamide. Fortunately, hydrogenation of the protected amidonitrile by Rh/C afforded the saturated **15** in 79% yield (2 steps) without any loss of enantiomeric purity. In addition, dihydroxylation of the trifluoroacetamide, derived from **4i**, afforded the amidonitriles **16a** and **16b** with functionalized side chains. These results clearly demonstrate the utility of this catalytic asymmetric Strecker-type reaction to synthesize a wide variety of natural and unnatural α-amino acid derivatives.

Conclusion

In summary, the Lewis acid–Lewis base bifunctional catalyst **1** is shown to be a general catalyst for the catalytic asymmetric Strecker-type reaction. Products were efficiently converted to α-amino acid derivatives without loss of enantiomeric purities. Specifically, α,β-unsaturated aminonitriles with a high enantiomeric excess were obtained and successfully converted to the *n*- or functionalized aminonitriles. It was found that TMSCN is more reactive than HCN in the presence of 20 mol% of PhOH, which made it possible the unique catalytic system 2 using a catalytic amount of TMSCN and stoichiometric amount of HCN. The preliminary studies to elucidate the reaction mechanism using the control catalyst **2** suggested that the bifunctional catalyst **1** should promote the reaction *via* the dual activation of the imine and TMSCN by Al and the oxygen atom of the phosphine oxide, respectively. These results demonstrate that the bifunctional catalysis should become a fundamental concept to design asymmetric catalysts.

Experimental

General NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ^{1}H-NMR and 125.65 MHz for ^{13}C-NMR. Chemical shifts in $CDCl_3$ were reported downfield from tetramethylsilane (TMS) (=0) for ^{1}H-NMR. For ^{13}C-NMR, chemical shifts were reported in the scale relative to $CHCl_3$ (77.00 ppm for ^{13}C-NMR) as an internal reference. Optical rotations were measured on a JASCO P-1010 polarimeter. Column chromatography were performed with silica gel Merck 60 (230—400 mesh ASTM). The enantiomeric excess (ee) was determined by HPLC analysis. HPLC analysis was performed on JASCO HPLC systems consisting of the following: pump, 880-PU or PU-980; detector, 875-UV or UV-970, measured at 254 nm; column, Daicel CHIRALPAK AS, AD, or Daicel CHIRALCEL OJ, OD; mobile phase, hexane–2-propanol. In general, reactions were carried out in dry solvents under an argon atmosphere, unless noted otherwise. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride. Diethylaluminum chloride in hexane (1 M) was purchased from Kanto Chemical. Co., Inc., Tokyo.

General Procedure for the Preparation of Imines The starting material 9-fluorenylamine was prepared by washing CH_2Cl_2 solution of 9-aminofluorene hydrogen chloride with sat. aq $NaHCO_3$ before use. Into a mixture of 9-fluorenylamine and molecular sieves (MS) 4A in toluene was added the starting material aldehyde (1.1 eq) at ambient temperature (in the case of aliphatic and α,β-unsaturated imines, the reaction was carried out at 0 °C). After stirring for 1 h, MS 4A was filtered off and the resulting solution was evaporated at 25 °C to give the desired imines quantitatively. When the product was solid, further purification was carried out by recrystallization from hexane. However, in the case of unstable imines such as aliphatic and α,β-unsaturated ones, the resulting imine was directly used as a CH_2Cl_2 solution.

Benzaldehyde 9-Fluorenyl Imine (**3a**): ^{1}H-NMR ($CDCl_3$) δ: 8.77 (s, 1H), 7.88—7.78 (m, 2H), 7.75 (d, J=7.3 Hz, 2H), 7.47—7.34 (m, 7H), 7.33—7.25 (m, 2H), 5.41 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 163.4, 144.8, 141.1, 136.0, 131.0, 128.6, 128.5, 128.4, 127.4, 125.3, 120.1, 74.7; IR (KBr) ν: 3060,

2843, 1630, 1449 cm^{-1}; MS electron impact ionization (EI) *m/z* 269 (M^+); high resolution mass spectrometry (HRMS) Calcd for $C_{20}H_{15}N$ 269.1204, Found 269.1204.

p-Chlorobenzaldehyde 9-Fluorenyl Imine (**3b**): ^{1}H-NMR ($CDCl_3$) δ: 8.71 (s, 1H), 7.78—7.71 (m, 4H), 7.44—7.34 (m, 6H), 7.29 (dt, J=7.4, 1.0 Hz, 2H), 5.41 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 161.9, 144.5, 141.0, 137.0, 134.5, 129.7, 128.9, 128.5, 127.5, 125.2, 120.2, 74.5; IR (KBr) ν: 3023, 2819, 1637, 1449 cm^{-1}; MS (EI) *m/z* 303 (M^+); HRMS Calcd for $C_{20}H_{14}ClN$ 303.0815, Found 303.0806.

p-Methoxybenzaldehyde 9-Fluorenyl Imine (**3c**): ^{1}H-NMR ($CDCl_3$) δ: 8.70 (s, 1H), 7.77—7.71 (m, 4H), 7.42—7.35 (m, 4H), 7.28 (dt, J=7.7, 1.2 Hz, 2H), 6.94—6.88 (m, 2H), 5.37 (s, 1H), 3.82 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ: 162.8, 161.9, 145.0, 141.0, 130.1, 129.0, 128.4, 127.4, 125.2, 120.1, 114.0, 74.7, 55.4; IR (KBr) ν: 3005, 2840, 1633, 1450 cm^{-1}; MS (EI) *m/z* 299 (M^+); HRMS Calcd for $C_{21}H_{17}NO$ 299.1310, Found 299.1310.

1-Naphthaldehyde 9-Fluorenyl Imine (**3d**): ^{1}H-NMR ($CDCl_3$) δ: 9.43 (s, 1H), 8.89 (d, J=8.6 Hz, 1H), 7.98 (d, J=7.4 Hz, 1H), 7.91 (d, J=8.3 Hz, 1H), 7.87 (d, J=7.4 Hz, 1H), 7.78 (d, J=7.6 Hz, 2H), 7.57—7.38 (m, 7H), 7.31 (t, J=7.3 Hz, 2H), 5.51 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 162.9, 145.0, 141.1, 133.8, 131.5, 131.4, 129.1, 128.6, 128.4, 127.5, 127.3, 126.1, 125.3, 125.2, 124.3, 120.1, 75.6; IR (KBr) ν: 3057, 2829, 1631, 1449 cm^{-1}; MS (EI) *m/z* 319 (M^+); HRMS Calcd for $C_{24}H_{17}N$ 319.1361, Found 319.1363.

2-Furaldehyde 9-Fluorenyl Imine (**3e**): ^{1}H-NMR ($CDCl_3$) δ: 8.51 (s, 1H), 7.72 (d, J=7.7 Hz, 2H), 7.50 (d, J=1.3 Hz, 1H), 7.45—7.33 (m, 4H), 7.28 (dt, J=7.3, 0.6 Hz, 2H), 6.83 (d, J=3.4 Hz, 1H), 6.47 (dd, J=3.4, 1.9 Hz, 1H), 5.42 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 151.5, 151.4, 145.0, 144.5, 141.1, 128.5, 127.4, 125.4, 120.0, 114.5, 111.8, 74.2; IR (KBr) ν: 3078, 2856, 1639, 1448 cm^{-1}; MS (EI) *m/z* 259 (M^+); HRMS Calcd for $C_{18}H_{13}NO$ 259.0997, Found 259.1001.

3-Furaldehyde 9-Fluorenyl Imine (**3f**): ^{1}H-NMR ($CDCl_3$) δ: 8.69 (s, 1H), 7.80 (s, 1H), 7.74 (d, J=7.6 Hz, 2H), 7.45—7.35 (m, 5H), 7.34—7.26 (m, 2H), 6.84 (d, J=1.5 Hz, 1H), 5.34 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 155.0, 145.6, 144.7, 144.1, 141.0, 128.4, 127.4, 125.5, 125.2, 120.1, 108.2, 74.8; IR (KBr) ν: 3090, 2834, 1643, 1447 cm^{-1}; MS (EI) *m/z* 259 (M^+); HRMS Calcd for $C_{18}H_{13}NO$ 259.0997, Found 259.0998.

2-Thiophenecarboxaldehyde 9-Fluorenyl Imine (**3g**): ^{1}H-NMR ($CDCl_3$) δ: 8.79 (s, 1H), 7.73 (d, J=7.7 Hz, 2H), 7.45—7.35 (m, 6H), 7.29 (dt, J=7.7, 1.3 Hz, 2H), 7.07 (dd, J=4.9, 3.7 Hz, 1H), 5.43 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 156.2, 144.6, 142.3, 141.0, 130.9, 129.5, 128.4, 127.4, 127.3, 125.3, 120.1, 74.0; IR (KBr) ν: 3066, 2829, 1623, 1449 cm^{-1}; MS (EI) *m/z* 275 (M^+); HRMS Calcd for $C_{18}H_{13}NS$ 275.0769, Found 275.0772.

Cinnamaldehyde 9-Fluorenyl Imine (**3h**): ^{1}H-NMR (C_6D_6) δ: 8.12 (d, J=9.0 Hz, 1H), 7.57 (d, J=7.4 Hz, 2H), 7.38 (d, J=7.4 Hz, 2H), 7.23 (t, J=7.7 Hz, 2H), 7.0—7.1 (m, 4H), 6.64 (d, J=16.1 Hz, 1H), 5.31 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 164.7, 144.8, 142.2, 141.0, 135.6, 129.3, 128.8, 128.4, 128.2, 127.5, 127.3, 125.2, 120.0, 74.4; IR (KBr) ν: 3023, 2852, 1632, 1448 cm^{-1}; MS (EI) *m/z* 295; HRMS Calcd for $C_{22}H_{17}N$ 295.1361, Found 295.1354.

Propionaldehyde 9-Fluorenyl Imine (**3k**): ^{1}H-NMR ($CDCl_3$) δ: 8.18 (t, J=4.9 Hz, 1H), 7.71 (d, J=7.7 Hz, 2H), 7.43—7.25 (m, 6H), 5.15 (s, 1H), 2.41 (m, 2H), 1.18 (t, J=7.6 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ: 168.9, 144.8, 141.0, 128.3, 127.3, 125.0, 120.0, 74.3, 29.4, 10.6; IR (KBr) ν: 3039, 2845, 1654, 1449 cm^{-1}; MS (EI) *m/z* 221 (M^+); HRMS Calcd for $C_{16}H_{15}N$ 221.1204, Found 221.1204.

Isobutyraldehyde 9-Fluorenyl Imine (**3l**): ^{1}H-NMR ($CDCl_3$) δ: 8.05 (dd, J=5.2, 0.6 Hz, 1H), 7.71 (d, J=7.6 Hz, 2H), 7.45—7.26 (m, 6H), 5.12 (s, 1H), 2.60 (m, 1H), 1.17 (d, J=7.0 Hz, 6H); ^{13}C-NMR ($CDCl_3$) δ: 173.1, 144.9, 141.0, 128.3, 127.3, 124.9, 120.0, 74.3, 34.4, 19.6; IR (KBr) ν: 2965, 2869, 1656, 1448 cm^{-1}; MS (EI) *m/z* 235 (M^+); HRMS Calcd for $C_{17}H_{17}N$ 235.1361, Found 235.1360.

Pivalaldehyde 9-Fluorenyl Imine (**3m**): ^{1}H-NMR ($CDCl_3$) δ: 8.06 (s, 1H), 7.71 (d, J=7.6 Hz, 2H), 7.45—7.25 (m, 6H), 5.10 (s, 1H), 1.16 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ: 175.6, 145.1, 140.9, 128.2, 127.3, 124.8, 120.0, 74.5, 36.5, 27.2; IR (KBr) ν: 2964, 2869, 1654, 1449 cm^{-1}; MS (EI) *m/z* 249 (M^+); HRMS Calcd for $C_{18}H_{19}N$ 249.1517, Found 249.1522.

General Procedure for the Preparation of the Catalyst 1 The chiral ligand (13 mg, 18 μmol) was placed in the flame-dried flask and dissolved in 0.5 ml of CH_2Cl_2. To this solution was added Et_2AlCl (17 μl, 16 μmol, 0.96 M in hexane) under argon. The resulting mixture was stirred at room temperature for 1 h to give the clear solution. This solution was directly used as a catalyst in the catalytic asymmetric Strecker-type reaction.

General Procedure for the Catalytic Asymmetric Strecker-Type Reaction (System 1) To a stirred solution of the above mentioned catalyst (0.5 ml, 16 μmol) was added the solution of the imine (0.17 mmol) in CH_2Cl_2 (0.6 ml) at -40 °C, followed by the addition of TMSCN (45 μl, 0.34 mmol). After 30 min, the solution of phenol (3 μl, 34 μmol) in CH_2Cl_2 (0.2 ml) was slowly added over 17 h. The reaction mixture was allowed to stir for the time shown in Table 3. Saturated aq. $NaHCO_3$ was added for quenching and the mixture was diluted with ether. The organic layer was separated, and the water layer was extracted with ether. The combined organic layer was washed with water and dried over Na_2SO_4. Further purification was performed by flash column chromatography on SiO_2 to afford the desired aminonitrile.

General Procedure for the Catalytic Asymmetric Strecker-Type Reaction (System 2) To the CH_2Cl_2 solution (1.0 ml) of the catalyst (33 μmol) prepared as above, was added the solution of the imine (0.352 mmol) in CH_2Cl_2 (1.0 ml) and TMSCN (70 μmol) at -40 °C. To this mixture, the solution of HCN (0.422 mmol) in CH_2Cl_2 (0.26 ml) was slowly added over 24 h. After 12 h (total 36 h), the reaction was worked up as described above.

2-(9-Fluorenylamino)-2-phenylethanenitrile (**4a**): ^{1}H-NMR ($CDCl_3$) δ: 7.78—7.68 (m, 3H), 7.53—7.26 (m, 10H), 5.14 (s, 1H), 4.57 (s, 1H), 2.34 (br s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 143.6, 143.5, 141.1, 140.7, 135.8, 129.01, 128.98, 128.9, 128.8, 127.6, 127.4, 125.7, 125.0, 120.2, 120.1, 119.6, 62.2, 50.3; IR (KBr) ν: 3346, 3065, 2225, 1447 cm^{-1}; MS (EI) *m/z* 296 (M^+); HRMS Calcd for $C_{21}H_{16}N_2$ 296.1313, Found 296.1315; $[\alpha]_D^{24}$ $-14.0°$ (c=1.0, $CHCl_3$) (95% ee). HPLC (Daicel CHIRALPAK AS, hexane/2-propanol 90/10, 1.0 ml/min) t_R 13.3 and 25.0 min.

2-(9-Fluorenylamino)-2-(*p*-chlorophenyl)ethanenitrile (**4b**): ^{1}H-NMR ($CDCl_3$) δ: 7.75—7.68 (m, 3H), 7.50—7.26 (m, 9H), 5.12 (s, 1H), 4.47 (s, 1H), 2.39 (br s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 143.3, 143.2, 141.1, 140.8, 135.0, 134.4, 129.1, 129.0, 128.9, 128.8, 127.6, 125.7, 125.0, 120.3, 120.2, 119.3, 62.2, 49.4; IR (KBr) ν: 3317, 3039, 2228, 1447 cm^{-1}; MS (EI) *m/z* 330 (M^+); HRMS Calcd for $C_{21}H_{15}ClN_2$ 330.0924, Found 330.0918; $[\alpha]_D^{24}$ $-50.8°$ (c=1.0, $CHCl_3$) (95% ee). HPLC (Daicel CHIRALPAK AS, hexane/2-propanol 90/10, 1.0 ml/min) t_R 12.4 and 15.2 min.

2-(9-Fluorenylamino)-2-(*p*-methoxyphenyl)ethanenitrile (**4c**): ^{1}H-NMR ($CDCl_3$) δ: 7.77—7.64 (m, 3H), 7.52—7.22 (m, 7H), 6.84 (d, J=8.5 Hz, 2H), 5.08 (s, 1H), 4.52 (s, 1H), 3.76 (s, 3H), 2.29 (br s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 160.0, 143.8, 143.7, 141.0, 140.7, 128.8, 128.7, 127.9, 127.5, 125.7, 125.0, 120.2, 120.1, 119.9, 114.3, 62.1, 55.3, 49.9; IR (KBr) ν: 3312, 3009, 2223, 1448 cm^{-1}; MS (EI) *m/z* 326 (M^+); HRMS Calcd for $C_{22}H_{18}N_2O$ 326.1419, Found 326.1414; $[\alpha]_D^{26}$ $-26.7°$ (c=1.0, $CHCl_3$) (93% ee). HPLC (Daicel CHIRALPAK AD, hexane/2-propanol 70/30, 1.0 ml/min) t_R 10.4 and 14.3 min.

2-(9-Fluorenylamino)-2-(1-naphthyl)ethanenitrile (**4d**): ^{1}H-NMR ($CDCl_3$) δ: 8.50—7.97 (m, 1H), 7.88—7.81 (m, 3H), 7.74 (d, J=7.7 Hz, 1H), 7.69 (d, J=7.7 Hz, 1H), 7.64 (d, J=7.0 Hz, 1H), 7.55—7.28 (m, 7H), 7.20 (dt, J=7.4, 1.0 Hz, 1H), 5.31 (s, 1H), 5.15 (s, 1H), 2.40 (br s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 143.7, 141.0, 140.9, 134.1, 131.1, 130.2, 130.1, 129.0, 128.9, 128.8, 127.6, 127.4, 126.9, 126.5, 126.3, 125.7, 125.2, 125.1, 123.3, 120.3, 120.1, 119.8, 62.1, 49.1; IR (KBr) ν: 3315, 3060, 2225, 1449 cm^{-1}; MS (EI) *m/z* 346 (M^+); HRMS Calcd for $C_{25}H_{18}N_2$ 346.1470, Found 346.1473; $[\alpha]_D^{24}$ $+65.5°$ (c=1.0, $CHCl_3$) (88% ee). HPLC (Daicel CHIRALPAK AD, hexane/2-propanol 90/10, 1.0 ml/min) t_R 20.3 and 25.4 min.

2-(9-Fluorenylamino)-2-(2-furyl)ethanenitrile (**4e**): ^{1}H-NMR ($CDCl_3$) δ: 7.74—7.65 (m, 3H), 7.45—7.32 (m, 5H), 7.26 (dt, J=7.6, 1.0 Hz, 1H), 6.30—6.26 (m, 2H), 5.09 (s, 1H), 4.59 (s, 1H), 2.64 (brs, 1H); ^{13}C-NMR ($CDCl_3$) δ: 147.8, 143.45, 143.40, 143.2, 140.85, 140.77, 128.9, 128.7, 127.64, 127.58, 125.6, 124.8, 120.2, 120.1, 117.8, 110.7, 109.0, 61.9, 44.1; IR (neat) ν: 3344, 3065, 2241, 1448 cm^{-1}; MS (EI) *m/z* 286 (M^+); HRMS Calcd for $C_{19}H_{14}N_2O$ 286.1106, Found 286.1107; $[\alpha]_D^{24}$ $-22.4°$ (c=1.0, $CHCl_3$) (79% ee). HPLC (Daicel CHIRALPAK AS, hexane/2-propanol 90/10, 1.0 ml/min) t_R 14.4 and 22.1 min.

2-(9-Fluorenylamino)-2-(3-furyl)ethanenitrile (**4f**): ^{1}H-NMR ($CDCl_3$) δ: 7.73—7.65 (m, 3H), 7.51 (dd, J=7.4, 0.9 Hz, 1H), 7.45 (m, 1H), 7.43—7.31 (m, 4H), 7.28 (dt, J=7.6, 1.2 Hz, 1H), 5.40 (m, 1H), 5.06 (s, 1H), 4.40 (s, 1H), 2.40 (br s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 144.0, 143.5, 143.4, 141.0, 140.7, 128.86, 128.84, 127.57, 127.55, 125.7, 124.9, 121.9, 120.2, 120.1, 119.4, 109.3, 62.0, 42.2; IR (neat) ν: 3345, 3065, 2231, 1448 cm^{-1}; MS (EI) *m/z* 286 (M^+); HRMS Calcd for $C_{19}H_{14}N_2O$ 286.1106, Found 286.1110; $[\alpha]_D^{24}$ $+16.2°$ (c=1.0, $CHCl_3$) (90% ee). HPLC (Daicel CHIRALPAK AS, hexane/2-propanol 70/30, 1.0 ml/min) t_R 8.1 and 14.6 min.

2-(9-Fluorenylamino)-2-(2-thiophenyl)ethanenitrile (**4g**): ^{1}H-NMR ($CDCl_3$) δ: 7.77—7.68 (m, 3H), 7.61 (d, J=7.4 Hz, 1H), 7.47—7.26 (m, 5H), 7.11 (m, 1H), 6.93 (dd, J=4.9, 3.4 Hz, 1H), 5.16 (s, 1H), 4.63 (s, 1H), 2.72 (br s, 1H); ^{13}C-NMR ($CDCl_3$) δ: 143.1, 143.0, 141.1, 140.7, 139.7, 129.0, 127.7, 127.6, 126.9, 126.8, 126.1, 125.8, 125.1, 120.24, 120.15, 119.0, 62.2, 45.5; IR (KBr) ν: 3338, 3066, 2225, 1447 cm^{-1}; MS (EI) *m/z* 302 (M^+); HRMS

Calcd for $C_{19}H_{14}N_2S$ 302.0878, Found 302.0877; $[\alpha]_D^{26}$ −36.3° (c=1.0, $CHCl_3$) (89% ee). HPLC (Daicel CHIRALPAK AS, hexane/2-propanol 70/30, 1.0 ml/min) t_R 7.7 and 13.8 min.

(*E*)-2-(9-Fluorenylamino)-4-phenyl-3-butenenitrile (**4h**): ^{1}H-NMR ($CDCl_3$) δ: 7.56 (m, 1H), 7.50 (dd, J=2.0, 6.0 Hz, 1H), 7.45 (d, J=7.5 Hz, 1H), 7.38 (d, J=7.5 Hz, 1H), 7.22 (m, 2H), 7.16 (m, 1H), 7.0—7.1 (m, 6H), 6.51 (dd, J=1.2, 15.5 Hz, 1H), 5.67 (dd, J=5.5, 15.5 Hz, 1H), 4.67 (s, 1H), 3.72 (d, J=5.5 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ: 145.0, 144.3, 141.2, 141.0, 135.9, 133.4, 128.9, 128.8, 128.7, 128.5, 128.3, 127.7, 127.6, 127.1 (overlapped), 126.1 125.4, 124.3, 120.3, 120.2, 119.2, 62.3, 48.4; IR (KBr) ν: 3349, 3061, 2220, 1448 cm^{-1}; MS (EI) m/z 322 (M^+); HRMS Calcd for $C_{23}H_{18}N_2$ 322.1470, Found 322.1472; $[\alpha]_D^{24}$ −89.7° (c=0.465, $CHCl_3$) (96% ee). HPLC (Daicel CHIRALPAK AD, hexane/2-propanol 90/10, 0.8 ml/min) t_R 20.2 and 22.6 min.

(*E*)-2-[*N*-(9-Fluorenyl)-*N*-trifluoroacetylamino)-3-octenenitrile (**4i**): ^{1}H-NMR ($CDCl_3$) δ: 7.71 (d, J=2.5 Hz, 1H), 7.70 (d, J=2.8 Hz, 1H), 7.54 (d, J=7.3 Hz, 1H), 7.48—7.36 (m, 4H), 7.30 (d, J=7.75 Hz, 1H), 7.26 (d, J=7.3 Hz, 1H), 5.93 (s, 1H), 5.37 (dd, J=15.3, 7.3 Hz, 1H), 5.10 (ddd, J=7.7, 7.3, 6.7 Hz, 1H), 3.52 (d, J=7.0 Hz, 1H), 1.82—1.72 (m, 2H), 1.15—1.05 (m, 4H), 0.76 (t, J=6.7 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ: 156.8 (q, J=37 Hz), 140.9, 140.7, 140.4, 138.7, 138.6, 130.4, 130.3, 128.9, 128.2, 126.0, 125.9, 120.8, 119.0, 115.1, 115.0, 62.8, 48.2, 31.5, 29.7, 22.0, 13.7; IR (KBr) ν: 2959, 2246, 1702, 1451 cm^{-1}; MS (EI) m/z 398 (M^+); HRMS Calcd for $C_{23}H_{21}F_3N_2O$ 398.1606, Found 398.1607; $[\alpha]_D^{21}$ −12.6 (c=5.3, $CHCl_3$) (85% ee). HPLC (Daicel CHIRALPAK AD, hexane/2-propanol 200/1, 0.7 ml/min) t_R 15.6 and 26.5 min.

2-(9-Fluorenylamino)-*n*-octanenitrile (**4j**): ^{1}H-NMR ($CDCl_3$) δ: 7.63 (d, J=6.7 Hz, 2H), 7.62 (d, J=6.4 Hz, 2H), 7.5 (d, J=7.3 Hz, 1H), 7.49 (d, J=7.7 Hz, 2H), 7.34—7.23 (m, 4H), 5.0 (s, 1H), 3.29 (t, J=7.1 Hz, 1H), 1.65—1.54 (m, 2H), 1.46—1.32 (m, 6H), 0.78 (t, J=6.7 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ: 143.9, 143.9, 140.6, 140.1, 128.7, 127.5, 127.4, 125.5, 124.9, 121.1, 120.1, 120.0, 62.2, 46.5, 34.9, 31.4, 28.6, 25.3, 22.43, 13.9; IR (KBr) ν: 3335, 2937, 2225, 1449 cm^{-1}; MS (EI) m/z 304 (M^+); HRMS Calcd for $C_{21}H_{24}N_2$ 304.1939, Found 304.1938; $[\alpha]_D^{24}$ +27.2 (c=3.9, $CHCl_3$) (80% ee); HPLC (Daicel CHIRALPAK AS, hexane/2-propanol 9/1, 1.0 ml/min) t_R 8 and 11 min.

2-(9-Fluorenylamino)-*n*-butanenitrile (**4k**): ^{1}H-NMR ($CDCl_3$) δ: 7.72—7.64 (m, 2H), 7.62 (d, J=7.3 Hz, 1H), 7.55 (d, J=7.4 Hz, 1H), 7.42—7.25 (m, 4H), 4.99 (s, 1H), 3.28 (t, J=6.8 Hz, 1H), 2.06 (br s, 1H), 1.67 (m, 2H), 1.00 (t, J=7.7 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ: 143.93, 143.87, 140.8, 140.6, 128.7, 127.5, 127.4, 125.6, 124.9, 120.9, 120.1, 120.0, 62.2, 47.8, 28.3, 10.0; IR (KBr) ν: 3332, 2972, 2221, 1445 cm^{-1}; MS (EI) m/z 248 (M^+); HRMS Calcd for $C_{17}H_{16}N_2$ 248.1313, Found 248.1321; $[\alpha]_D^{24}$ +66.6° (c=1.0, $CHCl_3$) (70% ee). HPLC (Daicel CHIRALPAK AS, hexane/2-propanol 95/5, 1.0 ml/min) t_R 10.8 and 14.2 min.

2-(9-Fluorenylamino)-3-methylbutanenitrile (**4l**): ^{1}H-NMR ($CDCl_3$) δ: 7.74—7.67 (m, 2H), 7.64 (d, J=7.4 Hz, 1H), 7.59 (d, J=7.6 Hz, 1H), 7.44—7.28 (m, 4H), 5.04 (s, 1H), 3.15 (d, J=5.2 Hz, 1H), 2.07 (br s, 1H), 1.85 (m, 1H), 1.05 (d, J=6.7 Hz, 3H), 0.98 (d, J=6.7 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ: 143.8, 140.9, 140.6, 128.72, 128.70, 127.5, 127.4, 125.7, 125.2, 120.2, 120.1, 120.0, 62.4, 52.7, 32.9, 18.9, 17.9; IR (KBr) ν: 3344, 2966, 2225, 1448 cm^{-1}; MS (EI) m/z 262 (M^+); HRMS Calcd for $C_{18}H_{18}N_2$ 262.1470, Found 262.1472; $[\alpha]_D^{24}$ +62.5° (c=1.0, $CHCl_3$) (72% ee). HPLC (Daicel CHIRALPAK AS, hexane/2-propanol 95/5, 1.0 ml/min) t_R 7.6 and 11.0 min.

2-(9-Fluorenylamino)-3,3-dimethylbutanenitrile (**4m**): ^{1}H-NMR ($CDCl_3$) δ: 7.74—7.67 (m, 2H), 7.65 (d, J=7.3 Hz, 1H), 7.63 (d, J=7.3 Hz, 1H), 7.44—7.37 (m, 2H), 7.34 (dt, J=7.3, 1.3 Hz, 1H), 7.31 (dt, J=7.3, 1.0 Hz, 1H), 5.05 (s, 1H), 2.91 (s, 1H), 2.08 (br s, 1H), 1.01 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ: 143.7, 143.5, 141.0, 140.6, 128.72, 128.67, 127.4, 127.3, 125.9, 125.7, 120.6, 120.1, 119.9, 62.8, 56.7, 35.1, 26.0; IR (KBr) ν: 3344, 2961, 2228, 1448 cm^{-1}; MS (EI) m/z 276 (M^+); HRMS Calcd for $C_{19}H_{20}N_2$ 276.1626, Found 276.1627; $[\alpha]_D^{26}$ +58.3° (c=1.0, $CHCl_3$) (78% ee). HPLC (Daicel CHIRALPAK AS, hexane/2-propanol 95/5, 1.0 ml/min) t_R 6.5 and 12.7 min.

2-(9-Fluorenylamino)-2-phenylacetamide (9) To a solution of **4a** (100 mg, 0.34 mmol) in formic acid (10 ml), HCl gas was bubbled through until the solution was saturated. The mixture was allowed to stir at room temperature for 1 h and the solvent was removed *in vacuo.* The resulting residue was triturated in saturated $NaHCO_3$ (50 ml) and extracted with CH_2Cl_2 (50 ml×3). The organic layer was washed with water (50 ml×2) and dried over $MgSO_4$. After the removal of the solvent, the crude product (108 mg, 100%, 93% ee) was purified by recrystallization from THF/diethyl ether (96 mg, 90%, 100% ee). ^{1}H-NMR (CD_3OD) δ: 7.77—7.68 (m, 1H), 7.46 (m, 1H), 7.39 (t, J=7.3 Hz, 1H), 7.35 (t, J=7.3 Hz, 1H), 7.30 (dt, J=7.3, 1.2 Hz, 1H), 7.28—7.18 (m, 6H), 4.93 (s, 1H), 3.96 (s, 1H); ^{13}C-NMR (dimethylsulfoxide (DMSO)-d_6) δ: 174.2, 145.7, 145.6, 141.1, 140.1, 140.0, 127.9, 127.8, 127.2, 127.02, 126.97, 126.9, 125.3, 125.1, 119.79, 119.76, 62.3, 61.5; IR (KBr) ν: 3355, 1654, 1448 cm^{-1}; MS (EI) m/z 314 (M^+); HRMS Calcd for $C_{21}H_{18}N_2O$ 314.1419, Found 314.1420; $[\alpha]_D^{24}$ −62.5° (c=1.0, MeOH) (100% ee). HPLC (Daicel CHIRALPAK AS, hexane/2-propanol 70/30, 1.0 ml/min) t_R 21.6 and 27.0 min.

2-Amino-2-phenylacetamide (11) To a solution of DDQ (202 mg, 0.89 mmol) in THF (14 ml) was added **9** (140 mg, 0.45 mmol) in THF (10 ml) at 3 °C. After stirring for 1 h at the same temperature, the reaction was quenched by addition of 1 N HCl (0.89 ml) and allowed to warm up to room temperature. The solvents were removed *in vacuo* and the resulting residue was triturated in diethyl ether. The suspended residue was filtered and washed with diethyl ether (5 ml×5) to afford HCl salt of **11**. A soluton of the HCl salt in MeOH (3 ml) was passed through a plug of Amberlyst A-21 (OH form) with MeOH (20 ml) and concentrated *in vacuo* to afford a white powder of **11** (61 mg, 91%). $[\alpha]_D^{24}$ −108° (c=1.26, EtOH) (98% ee) (lit.[9]) $[\alpha]_D^{22}$ −103° (c=1.2, EtOH) for *R* enantiomer). The enantiomeric excess was determined by HPLC after the conversion to *p*-nitrobenzyloxycarbonyl derivative: ^{1}H-NMR (acetone-d_6) δ: 8.15—7.95 (m, 2H), 7.53 (d, J=8.3 Hz, 2H), 7.37 (d, J=7.3 Hz, 2H), 7.33—7.13 (m, 3H), 6.98 (br s, 1H), 6.86 (br s, 1H), 6.65—6.20 (m, 1H), 5.18 (d, J=7.6 Hz, 1H), 5.15—5.04 (m, 2H); ^{13}C-NMR (acetone-d_6) δ: 172.3, 155.9, 148.4, 145.9, 140.0, 129.3, 128.9, 128.7, 128.2, 124.2, 65.5, 59.3; IR (KBr) ν: 3392, 3297, 1660 cm^{-1}; HPLC (Daicel CHIRALCEL OJ, hexane/2-propanol 70/30, 1.0 ml/min) t_R 20.2 and 25.6 min; $[\alpha]_D^{21}$ −99.0° (c=1.0, THF) (98% ee).

2-(9-Fluorenylideneamino)-3,3-dimethylbutyronitrile (12) To a solution of **4m** (150 mg, 0.54 mmol) in CH_2Cl_2 (10 ml), manganese oxide (555 mg, 5.43 mmol) was added at room temperature. After stirring for 1 h, manganese oxide was filtered off and washed with CH_2Cl_2 (5 ml×4). Solvent was evaporated *in vacuo*, and the residue was purified by preparative TLC (hexane : acetone=9 : 1) to give a yellowish solid (142 mg, 95%, 77.4% ee). ^{1}H-NMR ($CDCl_3$) δ: 7.87 (d, J=7.6 Hz, 1H), 7.81 (d, J=7.3 Hz, 1H), 7.64 (d, J=7.3 Hz, 1H), 7.54 (d, J=7.6 Hz, 1H), 7.46 (t, J=7.3 Hz, 1H), 7.41 (dt, J=7.3, 1.0 Hz, 1H), 7.36—7.25 (m, 2H), 4.80 (s, 1H), 1.24 (s, 9H); ^{13}C-NMR ($CDCl_3$) δ: 167.1, 144.3, 141.2, 138.1, 132.4, 131.8, 131.1, 128.6, 128.3, 127.9, 123.2, 120.8, 119.5, 117.5, 61.1, 36.2, 26.0; IR (KBr) ν: 2968, 2233, 1647, 1450 cm^{-1}; MS (EI) m/z 274 (M^+); HRMS Calcd for $C_{19}H_{18}N_2$ 274.1470, Found 274.1469; $[\alpha]_D^{18}$ +282.3° (c=1.0, $CHCl_3$) (77.4% ee). HPLC (Daicel CHIRALCEL OD, hexane/2-propanol 90/10, 1.0 ml/min) t_R 7.4 and 14.1 min.

2-Amino-3,3-dimethylbutyronitrile HCl Salt (13) To a solution of **12** (200 mg, 0.73 mmol) in THF (15 ml) was added 1 N HCl (1.5 ml) and stirred at room temperature for 1 h. After the solvents were removed *in vacuo*, the resulting residue was triturated in diethyl ether followed by filtrating and washing with diethyl ether (5 ml×5) to give a white powder of **13** (90 mg, 83%). $[\alpha]_D^{18}$ +16.4° (c=1.0, MeOH) (77.4% ee).

Fmoc–*tert*-leucine A solution of **13** (80 mg, 0.54 mmol) in conc. HCl (2 ml) was heated to 120 °C in a sealed tube for 24 h. After cooling to ambient temperature, the solvent was removed *in vacuo* to afford a 1 : 1 mixture of *tert*-leucine HCl salt **14** and ammonium chloride. To a solution of the mixture in 50% aq. acetone (4 ml) were added K_2CO_3 (140 mg, 1.0 mmol) and Fmoc–ONSu (370 mg, 1.1 mmol) and the whole was stirred at room temperature for 4 h. After the removal of acetone *in vacuo*, the resulting precipitate was filtered off and washed with 5% K_2CO_3 (10 ml×3). The combined aqueous layer was washed with diethyl ether (20 ml), acidified with 1 N HCl and then extracted with diethyl ether (20 ml×3). The combined organic layer was washed with brine (50 ml), dried over $MgSO_4$ and concentrated *in vacuo* to afford Fmoc–*tert*-leucine (185 mg, 100%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 7.78—7.68 (m, 2H), 7.62—7.50 (m, 2H), 7.38 (t, J=7.1 Hz, 2H), 7.30 (t, J=7.3 Hz, 2H), 6.12 (m, 0.1H), 5.38 (d, J=9.8 Hz, 0.9H), 4.55—4.33 (m, 2H), 4.30—4.15 (m, 1.8H), 3.87 (m, 0.2H), 1.80—0.90 (m, 9H); ^{13}C-NMR ($CDCl_3$) δ: 176.4, 156.3, 143.8, 143.7, 141.3, 127.7, 127.1, 125.0, 120.0, 67.1, 62.1, 47.2, 34.6, 26.5; $[\alpha]_D^{21}$ +9.3° (c=1.0, MeOH) (78% ee). (lit.[10]) $[\alpha]_D^{20}$ −11.0° (c=1, MeOH) for *S* enantiomer). The enantiomeric excess was determined by HPLC after conversion to the methyl ester (MeI, $NaHCO_3$, *N*,*N*-dimethylformamide (DMF)): ^{1}H-NMR ($CDCl_3$) δ: 7.76 (d, J=7.6 Hz, 2H), 7.60 (d, J=7.0 Hz, 2H), 7.40 (t, J=7.3 Hz, 2H), 7.31 (t, J=7.3 Hz, 2H), 5.37 (d, J=9.4 Hz, 0.9H), 5.05 (m, 0.1H), 4.50—4.32 (m, 2H), 4.26—4.16 (m, 2H), 3.74 (s, 3H), 1.10—0.80 (m, 9H); ^{13}C-NMR ($CDCl_3$) δ: 172.2, 156.1, 143.9, 143.8, 141.3, 127.7, 127.0, 125.06, 125.04, 119.97, 119.95, 67.0, 62.1, 51.8, 47.2, 34.7, 26.4; IR (neat) ν: 3431, 2964, 1730 cm^{-1}; MS (EI) m/z 367 (M^+); HRMS Calcd for $C_{22}H_{25}NO_4$ 367.1783, Found 367.1789; HPLC (Daicel CHIRALCEL OD,

hexane/2-propanol 70/30, 1.0 ml/min) t_R 7.7 and 10.4 min.

(*E*)-2-[*N*-(9-Fluorenyl)-*N*-trifluoroacetylamino]-4-phenyl-3-butenenitrile (15) Protection of a nitrogen atom of **4h** (84% ee) as trifluoroacetoamide was achieved by the usual method (trifluoroacetic anhydride (TFAAA), prydine/CH_2Cl_2, 0 °C) without racemization. ^{1}H-NMR ($CDCl_3$) δ: 7.82 (d, J=8.0 Hz, 2H), 7.80 (d, J=8.3 Hz, 2H), 7.65 (d, J=7.4 Hz, 1H), 7.56—7.53 (m, 2H), 7.49—7.46 (m, 2H), 7.32 (dt, J=0.6, 7.3 Hz, 2H), 7.29—7.24 (m, 2H), 7.13—7.10 (m, 2H), 6.07 (dd, J=7.3, 15.9 Hz, 1H), 6.06 (s, 1H), 5.29 (d, J=15.9 Hz, 1H), 3.82 (d, J=7.3 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ: 156.9 (q, J=37 Hz), 141.0, 140.7, 138.7, 138.6, 138.1, 134.5, 130.6, 130.4, 129.0, 128.9, 128.6, 128.0, 127.0, 126.2, 125.5, 120.9, 120.9, 117.8, 114.6, 116.3 (q, J=286 Hz), 62.8, 53.4, 48.3, 29.7; IR (KBr) ν: 2924, 2252, 1699, 1446 cm^{-1}; MS (EI) m/z 418 (M^+); HRMS Calcd for $C_{25}H_{17}F_3N_2O$ 418.12931, Found 418.1290; HPLC (Daicel CHIRALPAK AS, hexane/2-propanol 9/1, 1.0 ml/min) t_R 9 and 14 min. To a solution of the protected **4h** (28 mg, 0.067 mmol, 84% ee) in ethyl acetate (1 ml) was added Rh–C (14 mg). The reaction mixture was allowed to stir vigorously at room temperature for 12 h under 1 atom pressure of hydrogen. Then, Rh–C was removed by filtration, and the filtrate was evaporated under reduced pressure. The resulting residue was purified on preparative TLC (hexane : ethyl acetate=9 : 1) to give **15** (22 mg, yield 79%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 7.63—7.32 (m, 8H), 7.10—6.90 (m, 3H), 6.58 (d, J=7.0 Hz, 2H), 5.87 (s, 1H), 2.81 (dd, J=4.0, 11.0 Hz 1H), 2.73 (m, 1H), 2.58 (m, 1H), 2.2 (ddd, J=4.3, 10.0, 14.3 Hz 1H), 1.47 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ: 157.1 (q, J=36 Hz), 140.8, 140.5, 138.3, 138.2, 137.8, 130.29, 130.24, 128.7, 128.5, 128.0, 127.5, 126.1, 125.0, 121.0, 120.6, 116.2 (q, J=287 Hz), 115.3, 62.7, 45.8, 31.6, 31.3; HPLC (Daicel CHIRALPAK AS, hexane/2-propanol 9/1, 1.0 ml/min) t_R 5 and 10 min.

2-(9-Fluorenylamino)-3,4-dihydroxy-*n*-octanenitrile (16a) and 2-[(9-Fluorenyl)-trifluoroacetyl-amino]-3,4-dihydroxy-*n*-octanenitrile (16b) **4i** (30 mg, 0.075 mmol, 65% ee) was dissolved in pyridine (0.9 ml) and the resulting solution was cooled down to −40 °C. To this mixture was added a solution of osmium tetroxide in *tert*-BuOH (0.96 ml, 0.96 mmol, 0.1 M). After stirring for 3 h at the same temperature, 25% aq. $NaHSO_3$ (2 ml) was added for quenching, followed by dilution with ether (2 ml). The resulting mixture was allowed to stir at 0 °C for 10 h. The *N*-trifluoroacetyl group was deprotected in this reduction step. The organic layer was separated and the water layer was extracted with ethyl acetate (5 ml×2). The combined organic layer was washed with sat. aq. $CuSO_4$, water and brine. After drying this solution over Na_2SO_4, the solvent was evaporated under reduced pressure. Further purification was performed by flash column chromatography (hexane : acetone=20 : 1 to 8 : 1) to afford **16a** and **16b** in 53% and 38% yield, respectively.

16a: ^{1}H-NMR ($CDCl_3$) δ: 7.72 (d, J=7.6 Hz, 2H), 7.66 (d, J=7.6 Hz, 1H), 7.58 (d, J=6.6 Hz, 1H), 7.46—7.33 (m, 4H), 5.1 (s, 1H), 3.61 (ddd, J=1.2, 7.8, 8.3 Hz, 1H), 3.52 (dd, J=1.2, 6.1 Hz, 1H), 3.33 (d, J=6.1 Hz, 1H), 1.5—1.2 (m, 6H), 0.82 (t, J=7.0 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ: 142.5, 142.4, 141.3, 140.7, 129.2, 129.1, 127.8, 127.7, 125.7, 124.9, 120.3, 118.9, 76.7, 73.2, 71.2, 62.0, 48.8, 33.7, 27.7, 22.5, 13.9; MS m/z 336 (M^+), 291; HPLC (Daicel CHIRALPAK AD, hexane/2-propanol 90/10, 0.7 ml/min) t_R 25 and 34 min. The relative configuration was determined by the X-ray crystallography of the corresponding cyclic carbonate.

16b: ^{1}H-NMR ($CDCl_3$) δ: 7.8 (d, J=7.7 Hz, 2H), 7.6 (d, J=7.6 Hz, 1H), 7.59—7.44 (m, 4H), 7.37 (dd, J=7.3, 7.3 Hz, 1H), 6.05 (s, 1H), 3.57 (dd, J=2.4, 2.4 Hz, 1H), 3.30 (d, J=2.4 Hz, 1H), 2.6 (m, 1H), 1.2—1.0 (m, 6H), 0.83 (t, J=7.0 Hz, 3H); ^{13}C-NMR ($CDCl_3$) δ: 140.6, 138.4, 130.9, 130.7, 129.1, 128.2, 125.8, 125.0, 121.3, 121.2, 120.3 (q), 74.4, 72.8, 63.2, 52.5, 32.4, 27.6, 22.3, 13.9; IR (neat) ν: 3429, 1692, 1453 cm^{-1}; MS m/z 432 (M^+), 276, 165; HPLC (Daicel CHIRALCEL OD, hexane/2-propanol 95/5, 0.7 ml/min) t_R 33 and 57 min.

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References and Notes

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5) A similar effect of iso-PrOH on the reaction rate has been reported by Hoveyda in ref. 2*g*.
6) One portion addition of 100 mol % of iso-PrOH gave lower ee of 40%. This might be attributed to the generation of a large amount of HCN.
7) Under one portion addition conditions of a catalytic amount of PhOH, the major reaction pathway seems to be the same as under the best reaction conditions. Thus, the ee values of the products in these kinetic studies were 95% (in the absence of PhOH) and 88% (20 mol% of PhOH).
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