Enantioselectivity Switch in Direct Asymmetric Aminoxylation Catalyzed by Binaphthyl-Based Chiral Secondary Amines

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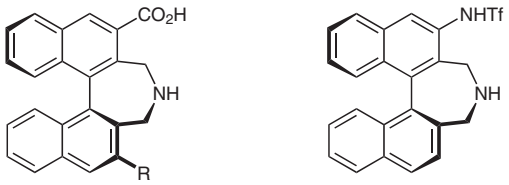
Abstract: Binaphthyl-based amino acids (*S*)-**1** and an aminosulfonamide (*S*)-**2** were applied for direct asymmetric aminoxylation with nitrosobenzene. In the presence of either (*S*)-**1** or (*S*)-**2**, the aminoxylation of aldehydes proceeded smoothly, and subsequent reduction with $NaBH_4$ gave 2-aminoxyl alcohols with good to excellent enantioselectivities. In each case, binaphthyl-based chiral amine catalysts (*S*)-**1** and (*S*)-**2**, which have the identical axial chirality, gave opposite enantiomers as the major product. This method represents a rare example of the direct asymmetric aminoxylation by a non-proline type catalyst.

Key words: enamine catalysis, asymmetric aminoxylation, organocatalyst



(*S*)-**1a**: R = H
(*S*)-**1b**: R = Ph
(*S*)-**1c**: R = 3,5-$Ph_2C_6H_3$
(*S*)-**1d**: R = 3,5-$(CF_3)_2C_6H_3$
(*S*)-**1e**: R = 3,4,5-$F_3C_6H_2$

(*S*)-**2**

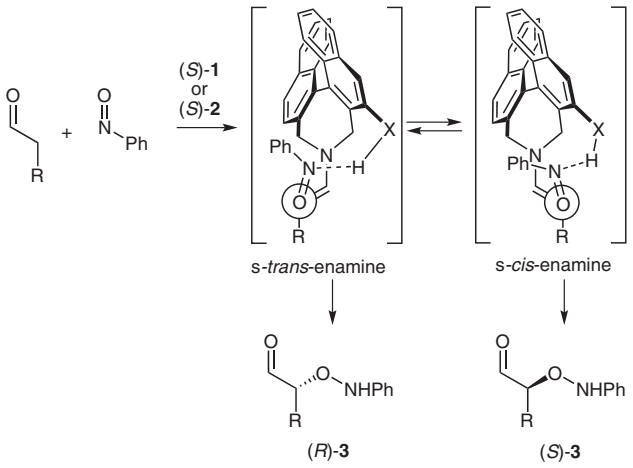
Figure 1

Nitroso compounds are frequently utilized as a nitrogen and/or an oxygen source in organic synthesis,[1] and various catalytic asymmetric reactions, such as aminoxylation,[2–6] hydroxyamination,[5–8] and the nitroso Diels–Alder reaction[9] have been developed by exploiting their unique properties. In this area, highly enantioselective aminoxylation reactions of aldehydes and ketones using nitrosobenzene have been realized by organocatalysts through the generation of the enamine intermediate.[3] To the best of our knowledge, however, most of the reported organocatalysts for the aminoxylation reaction are proline and its derivatives, and structurally different catalysts have not yet been studied. Accordingly, we have been interested in the development of the direct asymmetric aminoxylation of aldehydes with binaphthyl-based chiral secondary amine catalysts (*S*)-**1** and (*S*)-**2** (Figure 1), which are effective catalysts for the direct asymmetric aldol reaction[10,11] and Mannich reaction,[12] respectively.[13] Herein, we wish to report a direct asymmetric aminoxylation reaction with nitrosobenzene using binaphthyl-based chiral secondary amine catalysts.

We first attempted to use (*S*)-**1a** as a catalyst for the direct asymmetric aminoxylation reaction of an aldehyde. Treatment of propanal with nitrosobenzene in the presence of 5 mol% of (*S*)-**1a** in $CHCl_3$ at 0 °C and subsequent reduction with $NaBH_4$ in $CHCl_3$–EtOH furnished the corresponding 2-aminoxy alcohol in good yield with moderate enantioselectivity (Table 1, entry 1). Since the enantioselectivity in the present reaction reflects the conformation of the enamine intermediate (Scheme 1), we designed and synthesized new binaphthyl-based amino acids (*S*)-**1b–e** having an aromatic substituent at the 3-position to control the enamine conformation.

The requisite binaphthyl-based amino acids (*S*)-**1b–e** were synthesized in a six-step sequence from bis-triflate (*S*)-**4**,[14] which was prepared from (*S*)-BINOL, as shown in Scheme 2. Suzuki–Miyaura coupling and carboxylation of (*S*)-**4** gave the methyl esters (*S*)-**5**, which were converted with NBS into dibromides (*S*)-**6**. Treatment of (*S*)-**6** with allylamine afforded the cyclic amines (*S*)-**7**. Finally, $Pd(OAc)_2$-catalyzed deallylation of (*S*)-**7**, followed by hydrolysis of the resulting methyl esters (*S*)-**8** under basic conditions provided the binaphthyl-based amino acids (*S*)-**1b–e**.

With catalysts (*S*)-**1b–e** in hand, the direct asymmetric aminoxylation of propanal with nitrosobenzene was carried out, and the results are summarized in Table 1. Unex-



Scheme 1 Conformation of the enamine intermediate formed

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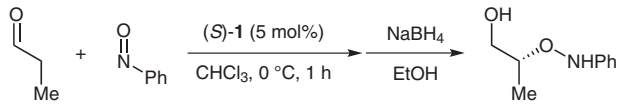
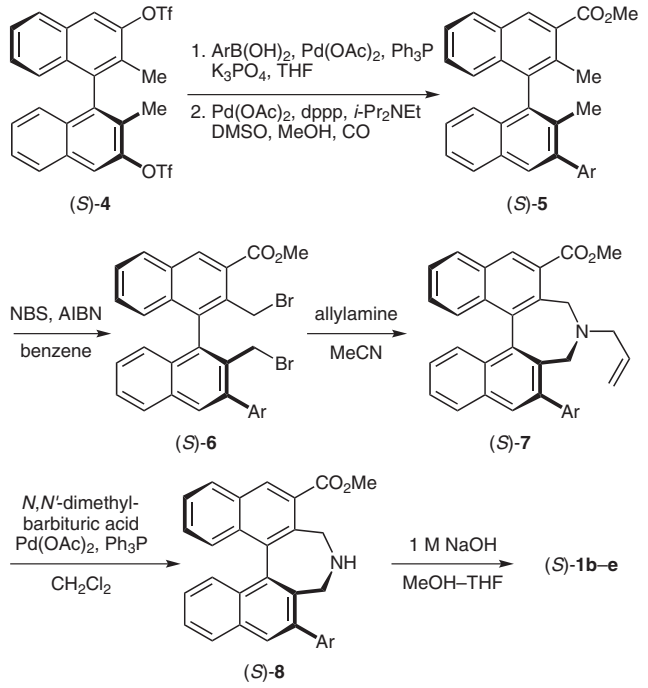
Table 1 Direct Asymmetric Aminoxylation of Propanal with Nitrosobenzene Catalyzed by (*S*)-**1**[a]



Entry	Catalyst	Yield (%)[b]	ee (%)[c]
1	(*S*)-**1a**	82	49
2	(*S*)-**1b**	99	64
3	(*S*)-**1c**	82	60
4	(*S*)-**1d**	88	62
5	(*S*)-**1e**	87	79

[a] The reaction of propanal (3 equiv) with nitrosobenzene was carried out in $CHCl_3$ (2 M) in the presence of catalyst (*S*)-**1** at 0 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis using chiral column (Chiralpak AD-H, Daicel Chemical Industries, Ltd.).

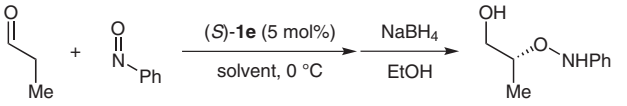


Scheme 2 Synthesis of binaphthyl-based amino acids (*S*)-**1b–e**

pectedly, introduction of an aromatic substituent at the 3-position of the catalyst resulted in higher *R*-selectivity in all cases examined (entries 2–5), and (*S*)-**1e** having 3,4,5-trifluorophenyl group was found to be the best catalyst in terms of enantioselectivity (entry 5). These results indicated that the aromatic substituent increased the ratio of the s-*trans*-enamine intermediate, and that there may be interaction between the aromatic substituent and the olefinic moiety of the enamine.

We then examined the effects of solvents on the yield and enantioselectivity. The results of the reaction using various solvents are shown in Table 2. When other halogenated solvents were used instead of $CHCl_3$, similar results were obtained (entries 2, 3). Switching the solvent to acetonitrile resulted in no improvement (entry 4). In the case of amide solvents DMF and NMP as well as THF, significant decreases in yield were observed, although the enantioselectivities were increased to >90% ee (entries 5–7). Aromatic solvents benzene, toluene, and mesitylene were found to be effective both in terms of the yield and enantioselectivity (entries 8, 9, and 12). The reaction performed at lower concentration afforded the aminoxylated product with good enantioselectivity, albeit with moderate yield (entries 11, 13, and 14). Toluene proved to be optimal for the present reaction due to its ease of handling and was selected for further studies.

Table 2 Solvent Effects in Direct Asymmetric Aminoxylation of Propanal with Nitrosobenzene Catalyzed by (*S*)-**1e**[a]



Entry	Solvent	Concn (M)	Time (h)	Yield (%)[b]	ee (%)[c]
1	$CHCl_3$	2.0	1	87	79
2	CH_2Cl_2	2.0	1	86	77
3	$ClCH_2CH_2Cl$	2.0	1	88	76
4	MeCN	1.0	1	81	77
5	DMF	2.0	1	<10	90
6	NMP	2.0	2	30	92
7	THF	2.0	2	40	90
8	benzene	1.0	1	85	85
9	toluene	2.0	1	86	83
10	toluene	1.0	1	89	86
11	toluene	0.5	1	70	89
12	mesitylene	1.0	1.5	94	86
13	mesitylene	0.5	1.5	62	91
14	mesitylene	0.2	5	64	91

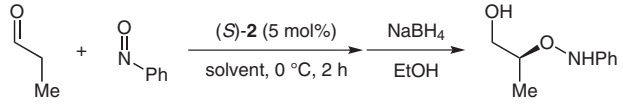
[a] The reaction of propanal (3 equiv) with nitrosobenzene was carried out in the solvent mentioned above in the presence of catalyst (*S*)-**1e** at 0 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis using chiral column (Chiralpak AD-H, Daicel Chemical Industries, Ltd.).

Although amino acid catalysts of type (*S*)-**1** promoted the aminoxylation of aldehydes smoothly, they were found to be less effective in terms of enantioselectivity. Due to the flexibility of the carboxyl group in (*S*)-**1**, the C-O bond-forming reaction is expected to take place not only on the *Re*-face of the s-*trans*-enamine but also on the *Si*-face of the s-*cis*-enamine, thereby affording both (*R*)-**3** and (*S*)-**3** (Scheme 1). As a result, (*S*)-**1** would show moderate enantioselectivity. In this context, we were interested in the

possibility of developing a highly enantioselective aminoxylation reaction using a binaphthyl-based amino sulfonamide (*S*)-**2**, which is known to give a single stereoisomer predominantly through the s-*cis*-enamine intermediate in the direct asymmetric aldol reaction[11] and Mannich reaction.[12]

We first attempted the direct asymmetric aminoxylation reaction of propanal catalyzed by (*S*)-**2** under the optimal conditions for the aminoxylation using (*S*)-**1e** (Table 2, entry 10). As expected, the corresponding 2-aminoxy alcohol with the *S* absolute configuration, which is the opposite enantiomer formed in the reaction using (*S*)-**1e**, was obtained in good yield with excellent enantioselectivity after reduction (Table 3, entry 1). We then examined the effects of solvents on the yield and enantioselectivity, and the results of the reaction using various solvents are shown in Table 3. It was found that solvents did not affect the enantioselectivity of the present reaction (entries 1–7). In addition, the enantioselectivity was not affected by the concentration of the reaction mixture (entries 7–9). Among the solvents we examined, chloroform was eventually chosen as solvent for further investigation.

Table 3 Solvent Effects in Direct Asymmetric Aminoxylation of Propanal with Nitrosobenzene Catalyzed by (*S*)-**2**[a]

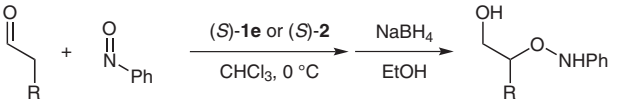


Entry	Solvent	Concn (M)	Yield (%)[b]	ee (%)[c]
1	toluene	1.0	78	98
2	DMF	1.0	47	98
3	THF	1.0	49	98
4	MeCN	1.0	67	98
5	CH_2Cl_2	1.0	85	98
6	$ClCH_2CH_2Cl$	1.0	82	98
7	$CHCl_3$	1.0	86	98
8	$CHCl_3$	0.5	86	98
9	$CHCl_3$	2.0	85	98

[a] The reaction of propanal (3 equiv) with nitrosobenzene was carried out in the solvent mentioned above in the presence of catalyst (*S*)-**2** at 0 °C for 2 h.
[b] Isolated yield.
[c] Determined by HPLC analysis using a chiral column (Chiralpak AD-H, Daicel Chemical Industries, Ltd.).

Using catalysts (*S*)-**1e** and (*S*)-**2**, the reaction of other aldehydes was then carried out under optimized conditions, and some selected examples are summarized in Table 4. With (*S*)-**1e**, 2-aminoxy alcohols with the *R* absolute configuration were obtained with moderate to good enantioselectivity in all cases examined (entries 1–4). On the other hand, the reactions catalyzed by (*S*)-**2** gave the opposite (*S*)-2-aminoxy alcohols in good yield and excellent enantioselectivity (entries 5–11). The catalyst loading could be reduced without loss of enantioselectivity, and moderate to good yields of the aminoxylation product were obtained with prolonged reaction time (entries 12–14). The reaction at high concentration proceeded in good yield even at low catalyst loading (0.2 mol%) (entry 15).

Table 4 Direct Asymmetric Aminoxylation of Various Aldehydes with Nitrosobenzene Catalyzed by (*S*)-**1e** and (*S*)-**2**[a]



Entry	Catalyst (mol%)	R	Time (h)	Yield (%)[b]	ee (%)[c]
1[d]	(*S*)-**1e** (5)	Me	1	89	86 (*R*)
2[d]	(*S*)-**1e** (5)	Bu	2	81	88 (*R*)
3[d]	(*S*)-**1e** (5)	Bn	3	75	59 (*R*)
4[d]	(*S*)-**1e** (5)	*i*-Pr	1.5	69	86 (*R*)
5	(*S*)-**2** (5)	Me	2	86	98 (*S*)
6	(*S*)-**2** (5)	Et	2	90	97 (*S*)
7	(*S*)-**2** (5)	Bu	2	92	98 (*S*)
8	(*S*)-**2** (5)	allyl	2	92	97 (*S*)
9	(*S*)-**2** (5)	Bn	2	88	97 (*S*)
10	(*S*)-**2** (5)	CH_2OBn	2	92	97 (*S*)
11	(*S*)-**2** (5)	*i*-Pr	2	96	98 (*S*)
12	(*S*)-**2** (1)	*i*-Pr	3	77	98 (*S*)
13	(*S*)-**2** (0.5)	*i*-Pr	8	70	98 (*S*)
14	(*S*)-**2** (0.2)	*i*-Pr	8	49	98 (*S*)
15[e]	(*S*)-**2** (0.2)	*i*-Pr	8	76	98 (*S*)

[a] The reaction of an aldehyde (3 equiv) with nitrosobenzene was carried out in $CHCl_3$ (1 M) in the presence of a catalyst at 0 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis using a chiral column (Chiralpak AD-H, Daicel Chemical Industries, Ltd.).
[d] Toluene was used as solvent.
[e] The reaction was carried out at higher concentration (25 M).

On the basis of the observed absolute stereochemistry in this study, plausible transition states are proposed (Figure 2). The activated and directed nitrosobenzene by carboxyl group on (*S*)-**1e** would approach the *Re* face of the s-*trans*-enamine to give the *R*-isomer predominantly (Figure 2, left). On the other hand, nitrosobenzene activated by the distal acidic proton of the triflamide of (*S*)-**2** could approach only the *Si* face of the s-*cis*-enamine, giving the *S*-isomer exclusively (Figure 2, right). Additionally, the structure of (*S*)-**2** having the distal acidic proton of the triflamide group was confirmed by X-ray crystallographic analysis (Figure 3).

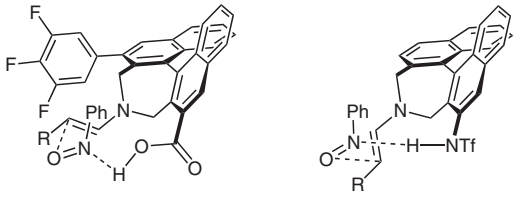


Figure 2 Transition states of aminoxylation reaction based on catalysts (*S*)-**1e** and (*S*)-**2**

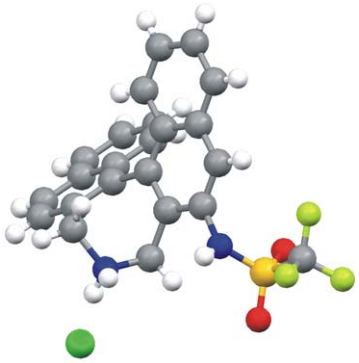
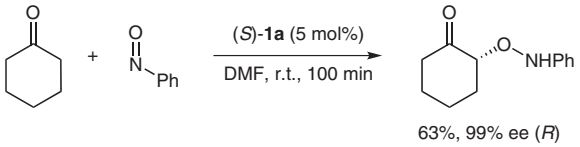
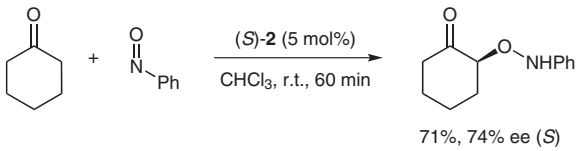


Figure 3 Single-crystal X-ray crystallographic structure of (*S*)-**2**·HCl salt

In the aminoxylation of cyclohexanone catalyzed by (*S*)-**1a** and (*S*)-**2**,[3d–l] the senses of enantioselection were identical with those of the reaction using aldehydes (Schemes 3 and 4). Interestingly, the amino acid catalyst (*S*)-**1a** exhibited much higher enantioselectivity than that observed in the reaction catalyzed by (*S*)-**2** which showed excellent enantioselectivity in the reaction of aldehydes. These observations can be rationalized by the transition state models shown in Figure 4. In the reaction of cyclohexanone, the steric repulsion between the phenyl group of nitrosobenzene and the cyclohexene ring of the s-*cis*-enamine intermediate would disfavor this reaction pathway. As a result, the ratio of the *R*-isomer through the s-*trans*-enamine intermediate might increase in the reaction using either (*S*)-**1a** or (*S*)-**2**. Accordingly, the reaction catalyzed by (*S*)-**2** gave the aminoxylated product with moderate enantioselectivity.



Scheme 3 Reaction of cyclohexanone with nitrosobenzene in the presence of (*S*)-**1a**



Scheme 4 Reaction of cyclohexanone with nitrosobenzene in the presence of (*S*)-**2**

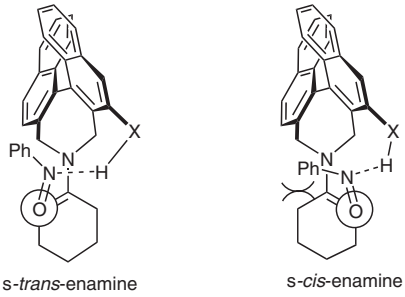


Figure 4 Transition state models for the aminoxylation of cyclohexanone

In summary, we have shown that the binaphthyl-based amino acids (*S*)-**1** and aminosulfonamide (*S*)-**2** can be utilized as an organocatalyst in the direct asymmetric aminoxylation reaction of both aldehyde and ketone. These reactions represent a rare example of the highly enantioselective aminoxylation reaction with a non-proline derived artificial organocatalyst. Further investigations on broadening the synthetic application of this reaction and efforts toward development of related enantioselective reactions using these catalysts are in progress in our laboratory.

IR spectra were recorded on a Shimadzu IRPrestige-21 spectrometer. ^{1}H NMR spectra were measured on a Jeol JNM-FX400 (400 MHz) spectrometer. Chemical shifts were reported in ppm from tetramethylsilane as an internal standard. Data were reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, and app = apparent), coupling constants (Hz), and assignment. ^{13}C NMR spectra were recorded on a Jeol JNM-FX400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High-performance liquid chromatography (HPLC) was performed on Shimadzu 10A instruments using a Daicel Chiralpak AD and AD-H, 4.6 mm × 25 cm column. The high-resolution mass spectra (HRMS) were performed on a Bruker microTOF. Optical rotations were measured on a Jasco DIP-1000 digital polarimeter. For TLC analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. The products were purified by flash column chromatography on silica gel 60 (Merck 1.09386.9025, 230–400 mesh). Anhyd THF was purchased from Kanto Chemical. Co. Inc. designated as 'Dehydrated'. Toluene was dried over sodium metal. Other solvents were dried over 4 Å molecular sieves. Aldehydes were distilled and stored under argon at –17 °C. Other simple chemicals were purchased and used as such. (*S*)-**1a**[10] and (*S*)-**2**[12a] were synthesized according to the literature procedures.

Ester (*S*)-5 (Ar = 3,4,5-$F_3C_6H_2$)

A mixture of (*S*)-**4**[14] (1.16 g, 2.0 mmol), $Pd(OAc)_2$ (22.5 mg, 0.1 mmol), Ph_3P (105 mg, 0.4 mmol), 3,4,5-trifluorophenylboronic acid (351 mg, 2.0 mmol), and K_3PO_4·nH_2O (1.27 g, 6.0 mmol) in THF (20 mL) was heated to 65 °C and stirred overnight under argon. The resulting mixture was poured into aq sat. NH_4Cl (20 mL), and filtered to remove the catalyst. After extraction with EtOAc (2 × 50 mL), the organic layers were washed with brine (20 mL), dried (Na_2SO_4) and then concentrated. The residue was roughly purified by flash column chromatography on silica gel (CH_2Cl_2–hexane, 1:40 as eluent) to afford a mixture of the mono-coupled product and the bis-coupled product, which was used in the next step without further purification. The mixture containing the mono-

coupled product, $Pd(OAc)_2$ (121 mg, 0.54 mmol), bis(diphenylphosphino)propane (dppp) (223 mg, 0.54 mmol) and *i*-Pr_2NEt (1.9 mL, 10.7 mmol) in DMSO (8.0 mL) and MeOH (8.0 mL) was charged into an autoclave under argon. After pressurizing with CO (8 atm), the mixture was heated to 80 °C with stirring for 48 h. After cooling to r.t., the reaction mixture was poured into H_2O (20 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and then concentrated. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc, 40:1) to give (*S*)-**5** (Ar = 3,4,5-$F_3C_6H_2$) (405 mg, 0.86 mmol, 43%, two steps); $[\alpha]_D^{22}$ –71.1 (*c* 1.0, $CHCl_3$).

IR (neat): 3059, 2951, 1721, 1614, 1527, 1439, 1290, 1265, 1240, 1202, 1148, 1043 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.54 (1 H, s, ArH), 7.97 (1 H, d, *J* = 8.2 Hz, ArH), 7.89 (1 H, d, *J* = 8.0 Hz, ArH), 7.81 (1 H, s, ArH), 7.45 (1 H, app q, ArH), 7.32 (1 H, app t, *J* = 7.6 Hz, ArH), 7.24 (1 H, app t, ArH), 7.10 (2 H, app dd, ArH), 7.00 (2 H, app dd, ArH), 3.99 (3 H, s, CO_2CH_3), 2.26 (3 H, s, ArC*H*$_3$), 1.87 (3 H, s, ArC*H*$_3$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.8, 150.9 (ddd, J_{C-F} = 250, 9.8, 4.1 Hz), 139.1 (dt, J_{C-F} = 252, 15.2 Hz), 138.3, 138.1 (dt, J_{C-F} = 4.9, 7.4 Hz), 137.1, 136.4, 134.1, 133.7, 132.4, 132.0, 131.8, 131.4, 131.2, 129.5, 129.2, 128.6, 128.5, 128.1, 126.9, 126.0 (two peaks overlap), 125.7, 125.6, 113.8 (dd, J_{C-F} = 14.7, 5.7 Hz), 52.2, 17.98, 17.96.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{30}H_{21}F_3O_2$ + Na: 493.1386 ([M + Na]$^+$); found: 493.1390 ([M + Na]$^+$).

Dibromide (*S*)-6 (Ar = 3,4,5-$F_3C_6H_2$)

A mixture of (*S*)-**5** (383 mg, 0.814 mmol), *N*-bromosuccinimide (NBS) (320 mg, 1.80 mmol), and 2,2′-azobis(isobutyronitrile) (AIBN) (13.5 mg, 10 mol%) in benzene (5 mL) was heated and refluxed for 2 h. After cooling to r.t., the mixture was poured into H_2O (10 mL) and extracted with EtOAc (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography on silica gel (hexane–EtOAc, 50:1–15:1) to give (*S*)-**6** (Ar = 3,4,5-$F_3C_6H_2$) (483 mg, 0.769 mmol, 94%); $[\alpha]_D^{20}$ –94.9 (*c* 1.0, $CHCl_3$).

IR (neat): 3062, 1721, 1614, 1528, 1439, 1362, 1294, 1267, 1242, 1219, 1043 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.70 (1 H, s, ArH), 8.02 (1 H, d, *J* = 8.0 Hz, ArH), 7.93 (1 H, d, *J* = 8.2 Hz, ArH), 7.88 (1 H, s, ArH), 7.56 (2 H, app q, ArH), 7.39 (1 H, app t, ArH), 7.31 (1 H, app t, ArH), 7.27 (2 H, app dd, ArH), 7.10 (1 H, d, *J* = 8.5 Hz, ArH), 7.06 (1 H, d, *J* = 8.5 Hz, ArH), 4.84 (1 H, d, *J* = 9.9 Hz, ArC*H*H), 4.63 (1 H, d, *J* = 9.7 Hz, ArCH*H*), 4.22 (1 H, d, *J* = 10.4 Hz, ArC*H*H), 4.13 (1 H, d, *J* = 10.6 Hz, ArCH*H*), 4.06 (3 H, s, CO_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.6, 150.8 (ddd, J_{C-F} = 251, 9.8, 4.1 Hz), 139.5 (dt, J_{C-F} = 252, 15.2 Hz), 137.8, 136.5, 136.1 (dt, J_{C-F} = 4.9, 8.2 Hz), 135.9, 133.7, 133.6, 133.0, 132.9, 132.2, 132.1, 132.0, 130.7, 129.2, 128.9, 128.1, 127.83, 127.81, 127.5, 127.4, 126.9, 114.0 (dd, J_{C-F} = 15.6, 6.6 Hz), 52.7, 30.64, 30.60 (the signal for an aromatic carbon was not identified due to the overlap of peaks).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{30}H_{19}Br_2F_3O_2$ + Na: 648.9596 ([M + Na]$^+$); found: 648.9622 ([M + Na]$^+$).

Allylamine (*S*)-7 (Ar = 3,4,5-$F_3C_6H_2$)

To a solution of (*S*)-**6** (454 mg, 0.723 mmol) in MeCN (3.6 mL) was added allylamine (163 μL, 2.17 mmol) at 50 °C. The mixture was stirred for 12 h and then poured into H_2O (10 mL). After extraction with EtOAc (2 × 25 mL), the combined organic layers were washed with brine (10 mL), dried (Na_2SO_4) and concentrated. The resulting residue was purified by flash column chromatography on silica gel (hexane–EtOAc, 20:1) to give (*S*)-**7** (Ar = 3,4,5-$F_3C_6H_2$) (136 mg, 0.620 mmol, 86%); $[\alpha]_D^{24}$ +294.6 (*c* 1.0, $CHCl_3$).

IR (neat): 3055, 3024, 2806, 1721, 1614, 1526, 1442, 1360, 1294, 1240, 1041 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.59 (1 H, s, ArH), 8.01 (1 H, d, *J* = 8.0 Hz, ArH), 7.92 (1 H, d, *J* = 8.7 Hz, ArH), 7.91 (1 H, s, ArH), 7.52–7.45 (4 H, m, ArH), 7.40–7.31 (2 H, m, ArH), 7.28–7.22 (2 H, m, ArH), 5.85–5.81 (1 H, m, C*H*=CH_2), 5.04 (1 H, app d, *J* = 10.2 Hz, CH=C*H*H), 5.02 (1 H, app d, *J* = 18.1 Hz, CH=CH*H*), 4.86 (1 H, d, *J* = 14.0 Hz, ArC*H*H), 4.00 (3 H, s, CO_2CH_3), 3.75 (1 H, d, *J* = 11.6 Hz, ArC*H*H), 3.47 (1 H, d, *J* = 14.0 Hz, ArCH*H*), 3.28 (1 H, dd, *J* = 13.4, 5.7 Hz, NC*H*HCH), 2.81 (1 H, dd, *J* = 13.4, 7.1 Hz, NCH*H*CH), 2.54 (1 H, d, *J* = 11.6 Hz, ArCH*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.5, 150.8 (ddd, J_{C-F} = 250, 9.8, 4.1 Hz), 139.2 (dt, J_{C-F} = 252, 15.2 Hz), 137.0, 137.1–136.8 (m), 136.8, 136.3, 135.9, 132.7, 132.5, 132.2, 131.7, 131.6, 130.9, 129.5, 129.2, 128.9, 128.4, 128.0, 127.5, 127.2, 126.4, 126.3, 126.2, 117.1, 114.0 (dd, J_{C-F} = 16.4, 5.7 Hz), 58.5, 52.4, 51.1, 49.5 (the signal for an aromatic carbon was not identified due to the overlap of peaks).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{33}H_{25}F_3NO_2$: 524.1832 ([M + H]$^+$); found: 524.1828 ([M + H]$^+$).

Amine (*S*)-8 (Ar = 3,4,5-$F_3C_6H_2$)

A mixture of (*S*)-**7** (287 mg, 0.55 mmol), *N*,*N*′-dimethylbarbituric acid (NDMBA) (180 mg, 1.15 mmol), $Pd(OAc)_2$ (6.2 mg, 0.0275 mmol), and Ph_3P (29 mg, 0.11 mmol) in CH_2Cl_2 (3.5 mL) was stirred at 35 °C for 3 h under argon. After the addition of CH_2Cl_2 (20 mL), the organic layer was washed with aq sat. $NaHCO_3$ (10 mL), dried (Na_2SO_4), and concentrated. The resulting residue was purified by flash column chromatography on silica gel (CH_2Cl_2–MeOH, 100:1) to give (*S*)-**8** (Ar = 3,4,5-$F_3C_6H_2$) (266 mg, 0.55 mmol, >99%); $[\alpha]_D^{23}$ +312.4 (*c* 1.0, $CHCl_3$).

IR (neat): 3055, 3024, 2951, 2841, 1717, 1614, 1528, 1437, 1358, 1294, 1267, 1240, 1209, 1148, 1042 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.56 (1 H, s, ArH), 8.01 (1 H, d, *J* = 8.2 Hz, ArH), 7.94 (1 H, d, *J* = 8.5 Hz, ArH), 7.92 (1 H, s, ArH), 7.53–7.40 (4 H, m, ArH), 7.38–7.32 (2 H, m, ArH), 7.30–7.24 (2 H, m, ArH), 4.69 (1 H, d, *J* = 13.5 Hz, ArC*H*H), 4.02 (3 H, s, CO_2CH_3), 3.89 (1 H, d, *J* = 11.4 Hz, ArC*H*H), 3.30 (1 H, d, *J* = 13.8 Hz, ArCH*H*), 3.19 (1 H, d, *J* = 11.4 Hz, ArCH*H*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.6, 150.8 (ddd, J_{C-F} = 250, 9.8, 4.1 Hz), 139.3 (dt, J_{C-F} = 252, 15.6 Hz), 137.1, 137.2-137.0 (m), 136.30, 136.28, 133.9, 132.7, 132.4, 132.2, 131.6, 130.9, 130.0, 129.3, 128.4, 128.0, 127.8, 127.4, 127.3, 126.3, 126.2 (two peaks overlap), 114.0 (d, J_{C-F} = 20.0 Hz), 52.4, 44.5, 44.3 (the signal for an aromatic carbon was not identified due to the overlap of peaks).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{30}H_{21}F_3NO_2$: 484.1519 ([M + H]$^+$); found: 484.1526 ([M + H]$^+$).

Binaphthyl-Based Amino Acid Catalyst (*S*)-1e; Typical Procedure

A mixture of (*S*)-**8** (243 mg, 0.50 mmol) and aq 1 N NaOH (1.0 mL) in MeOH (1.5 mL) and THF (1.0 mL) was refluxed for 1 h. After cooling to r.t., CH_2Cl_2 (1 mL) was added and the mixture was acidified with aq 1 N HCl. The mixture was then concentrated and the residue was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4) and concentrated. The resulting residue was purified by flash column chromatography on silica gel (CH_2Cl_2–MeOH, 10:1) to give (*S*)-**1e** (226 mg, 0.48 mmol, 96%); $[\alpha]_D^{22}$ +161.1 (*c* 0.5, $CHCl_3$).

IR (neat): 3055, 2739, 2594, 1614, 1526, 1437, 1375, 1242, 1043 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 8.53 (1 H, s, ArH), 8.11 (1 H, s, ArH), 8.08 (2 H, app dd, ArH), 7.60 (2 H, app q, ArH), 7.41–7.34 (4 H, m, ArH), 7.26–7.21 (2 H, m, ArH), 5.29 (1 H, d, *J* = 13.1 Hz, ArC*H*H), 4.39 (1 H, d, *J* = 13.5 Hz, ArC*H*H), 3.68 (1 H, d, *J* = 13.8 Hz, ArCH*H*), 3.54 (1 H, d, *J* = 12.6 Hz, ArCH*H*).

^{13}C NMR (100 MHz, CD_3OD–$CDCl_3$, 4:1): δ = 174.2, 151.9 (app d, $J_{C\text{-}F}$ = 249 Hz), 140.6 (dt, $J_{C\text{-}F}$ = 252, 15.6 Hz), 138.0, 137.9, 137.5, 136.9, 135.1 (app s), 134.4, 134.1, 132.6, 132.5, 132.0, 131.7, 130.2, 129.5, 128.7 (two peaks overlap), 128.3 (two peaks overlap), 128.0, 127.8, 127.3, 126.7, 115.5 (d, $J_{C\text{-}F}$ = 18.8 Hz), 42.9, 42.7.

HRMS (ESI-TOF): *m*/*z* calcd for $C_{29}H_{19}F_3NO_2$: 470.1362 ([M + H]$^+$); found: 470.1367 ([M + H]$^+$).

Amino Acid (*S*)-1b

Amino acid (*S*)-**1b** was prepared in a similar manner as described above using phenylboronic acid instead of 3,4,5-trifluorophenylboronic acid; $[\alpha]_D^{23}$ +223.6 (*c* 0.5, $CHCl_3$).

IR (neat): 3053, 2959, 2581, 1557, 1442, 1373, 1043 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 8.45 (1 H, s, ArH), 8.10–8.05 (3 H, m, ArH), 7.60–7.45 (7 H, m, ArH), 7.36–7.30 (2 H, m, ArH), 7.25 (2 H, app d, ArH), 5.18 (1 H, d, *J* = 12.8 Hz, ArC*H*H), 4.45 (1 H, d, *J* = 13.3 Hz, ArC*H*H), 3.65 (1 H, d, *J* = 14.0 Hz, ArCH*H*), 3.55 (1 H, d, *J* = 12.6 Hz, ArCH*H*).

^{13}C NMR (100 MHz, CD_3OD–$CDCl_3$, 2:1): δ = 175.4, 140.6, 140.5, 137.6, 137.4, 134.3, 134.1, 132.2, 131.5, 131.3, 130.5, 129.9, 129.3, 129.2, 128.6, 128.2, 128.1, 128.0, 127.9, 127.8, 127.6, 127.0, 126.9, 43.0, 42.7 (the signals for two aromatic carbons were not identified due to the overlap of peaks).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{29}H_{22}NO_2$: 416.1645 ([M + H]$^+$); found: 416.1625 ([M + H]$^+$).

Amino Acid (*S*)-1c

Amino acid (*S*)-**1c** was prepared in a similar manner as described above using 3,5-diphenylphenylboronic acid instead of 3,4,5-trifluorophenylboronic acid; $[\alpha]_D^{24}$ +94.8 (*c* 0.5, $CHCl_3$).

IR (neat): 3055, 2322, 1620, 1574, 1445, 1373 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD–THF-d_8, 4:1): δ = 8.42 (1 H, s, ArH), 8.22 (1 H, s, ArH), 8.12–8.05 (2 H, m, ArH), 7.98 (1 H, app s, ArH), 7.80–7.78 (5 H, app d, ArH), 7.61 (1 H, t, *J* = 8.0 Hz, ArH), 7.57 (1 H, t, *J* = 7.6 Hz, ArH), 7.48 (4 H, app t, ArH), 7.40–7.28 (7 H, m, ArH), 5.22 (1 H, d, *J* = 12.8 Hz, ArC*H*H), 4.62 (1 H, d, *J* = 13.3 Hz, ArC*H*H), 3.76 (1 H, d, *J* = 14.0 Hz, ArCH*H*), 3.56 (1 H, d, *J* = 12.8 Hz, ArCH*H*).

^{13}C NMR (100 MHz, CD_3OD–$CDCl_3$, 1:2): δ = 174.9, 142.6, 140.9, 140.8, 139.7, 137.5, 136.7, 136.3, 133.5, 133.3, 131.5, 131.3, 131.0, 130.5, 129.6, 129.2, 128.6, 128.1, 127.8, 127.7, 127.3, 127.1, 126.9, 126.7, 125.8, 41.7 (the signals were not identified due to the overlap of peaks).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{41}H_{30}NO_2$: 568.2271 ([M + H]$^+$); found: 568.2252 ([M + H]$^+$).

Amino Acid (*S*)-1d

Amino acid (*S*)-**1d** was prepared in a similar manner as described above using 3,5-bis(trifluoromethyl)phenylboronic acid instead of 3,4,5-trifluorophenylboronic acid; $[\alpha]_D^{24}$ +207.5 (*c* 0.5, $CHCl_3$).

IR (neat): 3053, 2363, 1616, 1560, 1445, 1373, 1277, 1179, 1132 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 8.41 (1 H, s, ArH), 8.22 (2 H, s, ArH), 8.15 (1 H, s, ArH), 8.12 (1 H, s, ArH), 8.11 (1 H, d, *J* = 8.7 Hz, ArH), 8.06 (1 H, d, *J* = 8.5 Hz, ArH), 7.62 (1 H, t, *J* = 7.5 Hz, ArH), 7.57 (1 H, t, *J* = 7.5 Hz, ArH), 7.39–7.32 (2 H, m, Ar-H), 7.28 (1 H, d, *J* = 8.5 Hz, ArH), 7.27 (1 H, d, *J* = 8.5 Hz, ArH), 5.18 (1 H, d, *J* = 12.8 Hz, ArC*H*H), 4.28 (1 H, d, *J* = 13.5 Hz, ArC*H*H), 3.76 (1 H, d, *J* = 13.8 Hz, ArCH*H*), 3.51 (1 H, d, *J* = 12.8 Hz, ArCH*H*).

^{13}C NMR (100 MHz, CD_3OD–$CDCl_3$, 4:1): δ = 175.5, 143.3, 138.6, 137.9, 137.3, 137.0, 134.4, 134.3, 132.8 (q, $J_{C\text{-}F}$ = 32 Hz), 132.4, 132.0, 131.7, 131.3, 130.1, 129.5, 128.7, 128.31, 128.26, 128.0, 127.8, 127.5, 126.8, 124.4 (q, $J_{C\text{-}F}$ = 273 Hz), 122.6, 42.7, 42.4 (the signals for two aromatic carbons were not identified due to the overlap of peaks).

HRMS (ESI-TOF): *m*/*z* calcd for $C_{31}H_{20}F_6NO_2$: 552.1393 ([M + H]$^+$); found: 552.1389 ([M + H]$^+$).

Direct Asymmetric Aminoxylation Reaction of Aldehydes with Nitrosobenzene; General Procedure

To a suspension of (*S*)-**2** (3.3 mg, 0.0075 mmol) in $CHCl_3$ (150 μL) at 0 °C were added nitrosobenzene (16 mg, 0.15 mmol) and the appropriate aldehyde (0.45 mmol) in this order. After stirring for 2 h at 0 °C, the reaction mixture was then transferred to a suspension of $NaBH_4$ (30 mg) in EtOH at 0 °C. After 15 min, the reaction mixture was treated with sat. aq $NaHCO_3$ (5 mL), extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic extracts were dried (Na_2SO_4). The resulting residue obtained after evaporation of the solvent was purified by flash column chromatography on silica gel to give the corresponding 2-aminoxy alcohol. The enantiomeric excess of 2-aminoxy alcohol was determined by chiral HPLC analysis.[3a,b,h] Spectral data of 2-aminoxy alcohols were in accordance with those previously reported.[3a,b,h]

Direct Asymmetric Aminoxylation Reaction of Cyclohexanone with Nitrosobenzene; 2-(Phenylaminooxy)cyclohexanone; Typical Procedure

To a solution of (*S*)-**1a** (5.1 mg, 0.015 mmol) and cyclohexanone (93 μL, 0.90 mmol) in DMF (2.2 mL) at r.t. was added a solution of nitrosobenzene (32 mg, 0.30 mmol) in DMF (0.4 mL) slowly over the course of 40 min with a syringe pump. After stirring for 1 h, the reaction mixture was directly purified by flash column chromatography on silica gel to give 2-(phenylaminooxy)cyclohexanone (39 mg, 0.19 mmol, 63%). The enantiomeric excess was determined by chiral HPLC analysis.[3h] Spectral data of 2-(phenylaminooxy)cyclohexanone were in accordance with those previously reported.[3h]

Crystallographic Data for (*S*)-2·HCl Salt[15]

$2(C_{23}H_{18}ClF_3N_2O_2S)$, colorless prisms, 0.14 × 0.03 × 0.01 mm^3, monoclinic, $P2_1$, a = 12.6729(15), b = 7.3537(8), c = 13.0053(15) Å, V = 1068.3(2) Å^3, ρ_{calcd} = 1.489 gcm^{-3}, Z = 2, $2c_{max}$ = 39.9°, μ = 2.947 mm^{-1}. A total of 4878 reflections were measured. R = 0.0794, and Rw = 0.2236 for 1239 observed reflections with $I > 2.0\sigma(I)$.

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(15) CCDC-710886 contains the supplementary crystallographic data of (*S*)-**2**·HCl salt for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.