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Asymmetric synthesis of α-monofluoromethyl- and α-difluoromethylbenzylamines through regioselective hydrogenolysis

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Abstract

Asymmetric synthesis of α-monofluoromethyl- and α-difluoromethylbenzylamines through regioselective hydrogenolysis is described. Hydrogenolysis of diastereomerically pure bis(α-methylbenzyl)amine derivatives having partially fluorinated methyl group at benzylic position also proceeded with a high regioselectivity as well as in the case of α-trifluoromethyl group. Moreover, opposite asymmetric induction was observed in reduction of chiral imines derived from partially fluorinated acetophenone and α-phenylethylamine.

Keywords: Asymmetric synthesis; α-Monofluoromethylbenzylamine; α-Difluoromethylbenzylamine; Regioselective hydrogenolysis; Diastereomerically pure bis(α-methylbenzyl)amine derivative; Partially fluorinated methyl group; Opposite asymmetric induction

1. Introduction

Recently we reported that highly regioselective hydrogenolysis of diastereomerically pure bis(α-methylbenzyl)-amine derivatives proceeded under influence of fluorine atom or trifluoromethyl group on aromatic ring [1]. This regioselective hydrogenolysis could be applied to a practical asymmetric synthesis of fluorine or trifluoromethyl substituted α-phenylethylamines. In our research direction, we are interested in a regioselective hydrogenolysis of bis-(α-methylbenzyl)amine derivatives affected by partially fluorinated α-methyl group (Scheme 1). Retarding effect of α-trifluoromethyl group for hydrogenolytic cleavage at side "B" has been well-known [2]. However, to the best of our knowledge, it has never been investigated whether partially fluorinated α-methyl group (n = 1 or 2) has a similar effect. If desirable hydrogenolysis at side "A" would occur, optically active α-monofluoromethyl- and α-difluoromethylbenzylamines, which are novel and potentially promising intermediates in medicinal chemistry [3], could be obtained [4].

In this report, we disclose that partially fluorinated α-methyl group also plays an important role in regioselective hydrogenolysis.

2. Results and discussion

Preparation of diastereomerically pure bis(α-methylbenzyl)amine derivatives having partially fluorinated α-methyl group was first examined (Table 1).

Dehydration between corresponding partially fluorinated acetophenone (**1**) [5] and commercially available (*S*)-α-phenylethylamine was carried out in the presence of a

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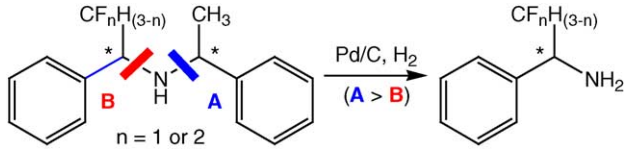


Scheme 1. Regioselective hydrogenolysis affected by partially fluorinated α-methyl group.

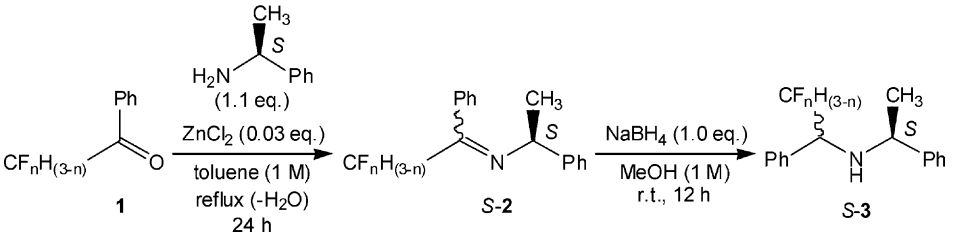
catalytic amount of zinc chloride with azeotropic removal of produced water. Expected (*S*)-monofluoroimine (*S*-F_1-**2**) was obtained in a good yield as a mixture of geometry, whose ratio was determined to be 75:25 by ^{1}H and ^{19}F NMR (entry 1). Configuration of major isomer was clarified to be *E* by assignment using ROE technique of ^{1}H NMR [6] (Fig. 1). In minor isomer (*Z*), ROE correlation was observed between methine proton of chiral auxiliary and methylene proton of monofluoromethyl group, while not observed in major isomer (*E*). In comparison with (*S*)-nonfluoroimine (*S*-F_0-**2**) derived from acetophenone and (*S*)-α-phenylethylamine [7], where chiral auxiliary and methyl group were located in *cis* configuration, opposite geometry was observed for major isomer of *S*-F_1-**2**. This indicated that geometry of imine was strongly influenced by incorporating a fluorine atom.

On the other hand, (*S*)-difluoroimine (*S*-F_2-**2**) and (*S*)-trifluoroimine (*S*-F_3-**2**) were obtained as a sole isomer (entries 2 and 3). These geometries also were determined to be *E* configuration from a similarity of major isomer of *S*-F_1-**2** and X-ray analysis of analogous (*R*)-*N*-(2,2,2-trifluoro-1-phenylethylidene)-2-phenylglycinol [8], where chiral auxiliary and trifluoromethyl group were located in trans configuration [9].

Subsequent 1,3-asymmetric reduction of partially fluorinated imine (*S*-**2**) was examined. After screening of reducing agents, sodium borohydride was found to be effective to give diastereomeric mixture of bis(α-methylbenzyl)amine derivative (*S*-**3**) with a reasonable diastereoselectivity (Table 1, entries 1 and 2) [10]. In all entries, diastereomeric excess of S-**3** was easily improved to >99.0% by recrystallization of organic acid salt in ca. 70% (*p*-TsOH salt for *S*-F_1-**3** and *S*-F_3-**3**, phthalic acid salt for *S*-F_2-**3**). Relative stereochemistry of three major diastereomers was obviously determined to be all syn (*S*,*S*) configuration by X-ray analysis of corresponding organic acid salt (Fig. 2). Opposite asymmetric induction was observed in comparison with that observed in reduction of (*S*)-nonfluoroimine (*S*-F_0-**2**), where major diastereomer of *S*-F_0-**3** was anti (*S*,*S*) [11]. This opposite sense was rationalized by a reaction mechanism through a proposed transition state [12], and resulted from opposite geometry of fluorinated imine (*S*-**2**) (Fig. 3).

Next, regioselective hydrogenolysis of diastereomerically pure bis(α-methylbenzyl)amine derivative (*S*,*S*-**3**) was examined. When free base of *S*,*S*-F_1-**3** was used as a substrate, unexpected linear secondary amine was obtained (Table 2, entry 1) [13,14]. This by-product might be produced via an aziridine intermediate as shown in Fig. 4. In

Table 1
Preparation of diastereomerically pure bis(α-methylbenzyl)amine derivatives



Entry[a]	Substrate (**1**)	Yield of *S*-**2**	Geometry of *S*-**2**	Yield of *S*-**3**	Diastereomeric ratio of *S*-**3**
1	F_1-**1** (*n* = 1)	*S*-F_1-**2**, 95%	*E*:*Z* = 75:25	*S*-F_1-**3**, 90%	*S*,*S*:*R*,*S* = 67:33
2	F_2-**1** (*n* = 2)	*S*-F_2-**2**, 99%	*E*:*Z* = >99:1	*S*-F_2-**3**, 84%	*S*,*S*:*R*,*S* = 79:21
3[b]	F_3-**1** (*n* = 3)	*S*-F_3-**2**, 93%	*E*:*Z* = >99:1	*S*-F_3-**3**, 89%	*S*,*S*:*R*,*S* = 77:23

[a] Dehydration scale: 50 mmol; reduction scale: 30 mmol.
[b] According to Ref. [2]. Dehydration: (*S*)-α-phenylethylamine (1.5 equiv.), *p*-TsOH (0.1 equiv.); reduction: $NaBH_3CN$ (2.0 equiv.).

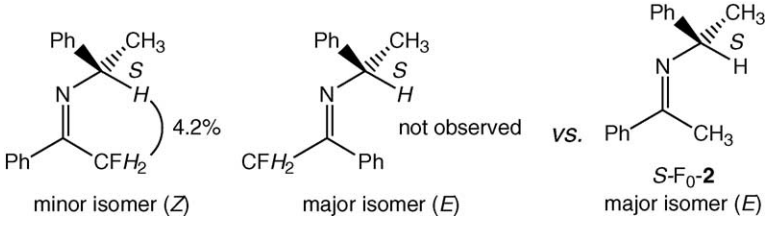


Fig. 1. ROE correlation of *S*-F_1-**2**.

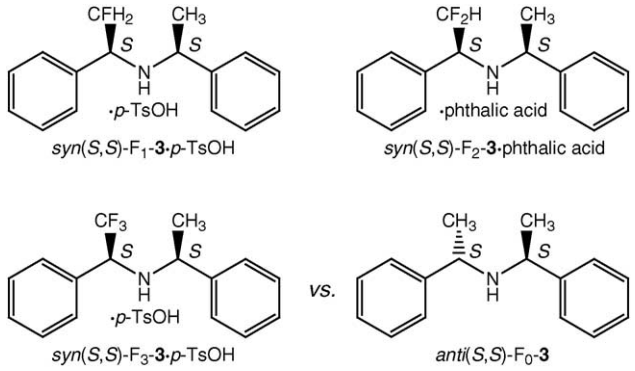


Fig. 2. Major diastereomer of *S*-**3**.

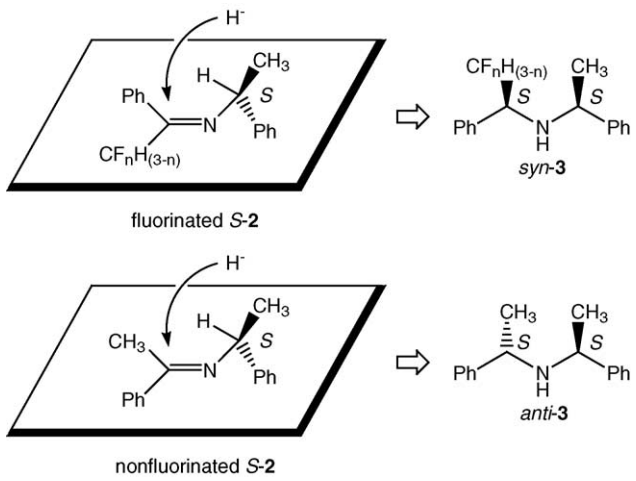
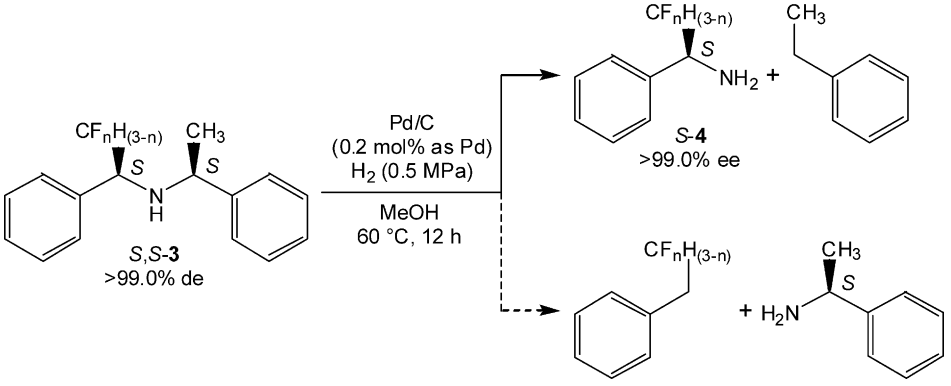


Fig. 3. Transition state of 1,3-asymmetric reduction.

fact, desirable hydrogenolysis proceeded smoothly using its *p*-TsOH salt, maybe due to decreased nucleophilicity of nitrogen atom (entry 2).

Interestingly, even in monofluorinated *S*,*S*-F_1-**3**, a high regioselectivity (97:3) was observed to produce (*S*)-α-monofluoromethylbenzylamine (*S*-F_1-**4**) in a good yield without any racemization. Moreover, hydrogenolysis of *S*,*S*-F_2-**3**·phthalic acid proceeded with an exclusive regioselectivity (>99:1) to produce (*S*)-α-difluoromethylbenzylamine (*S*-F_2-**4**) (entry 3) as well as trifluoromethyl counterpart (*S*,*S*-F_3-**3**· *p*-TsOH, entry 4). These high regioselectivities might be governed by a difference between two carbon–nitrogen bond strengths. Actually, a significant difference of bond length was observed in X-ray analysis of organic acid salt of *S*,*S*-**3** (Table 3). On the other hand, steric effect at benzylic position could not be completely excluded as a possible factor, because Baltzly et al. reported that hydrogenolysis of *N*-benzyl-α-methylbenzylamine proceeded with a high regioselectivity [15]. However, considering steric hindrance of fluorine atom [16] and regioselectivity of monofluoro-substrate *S*,*S*-F_1-**3**, it would be acceptable that this highly regioselective hydrogenolysis was affected mainly by the former bond strength factor.

Table 2
Regioselective hydrogenolysis of diastereomerically pure bis(α-methylbenzyl)amine derivatives



Entry[a]	Substrate	Conversion[b]	Regioselectivity[b,c]	Yield[d]
1	*S*,*S*-F_1**3** (*n* = 1)	ca. 25%	–[e]	–[e]
2[f]	*S*,*S*-F_1-**3**·*p*-TsOH (*n* = 1)	>99%[g]	97:3[g]	84%
3	*S*,*S*-F_2-**3**·phthalic acid (*n* = 2)	>99%	>99:1	98%
4[h]	*S*,*S*-F_3-**3**·*p*-Ts0H (*n* = 3)	>99%	>99:1	95%

[a] 1 mmol scale.
[b] Determined by GC.
[c] Ethylbenzene vs. fluorine substituted ethylbenzene.
[d] Determined by internal reference method in ^{19}F NMR.
[e] Production of linear secondary amine.
[f] In the presence of AcOH (5.0 equiv.).
[g] Determined by GC of corresponding acetamide.
[h] According to Ref. [2].

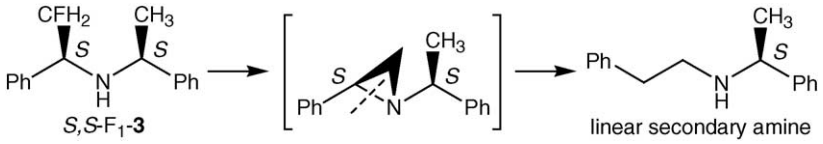
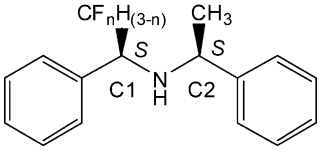


Fig. 4. Side reaction via aziridine intermediate.

Table 3
Comparison of two carbon–nitrogen bond lengths



Organic acid salt	C1-N (Å)	C2-N (Å)
S,*S*-F_1-**3**·*p*-TsOH	1.50 (1)	1.55 (1)
S,*S*-F_2-**3**·phthalic acid	1.49 (1)	1.51 (1)
S,*S*-F_3-**3**·*p*-TsOH	1.52 (2)	1.54 (2)

In conclusion, we found that highly regioselective hydrogenolysis of diastereomerically pure bis(α-methylbenzyl)amine derivatives proceeded under influence of partially fluorinated methyl group at benzylic position to provide an asymmetric synthesis of α-monofluoromethyl- and α-difluoromethylbenzylamines. Moreover, we demonstrated an instructive example that reaction path was dramatically changed by incorporating a fluorine atom.

3. Experimental

3.1. General

^{1}H NMR (400 MHz), ^{13}C NMR (100 MHz) and ^{19}F NMR (376 MHz) spectra were measured with a JEOL α-400 FT-NMR spectrometer in $CDCl_3$ solution with $(CH_3)_4Si$ or C_6F_6 as an internal standard. GC analyses were carried out with a Shimadzu GC-17A. High resolution mass spectra were obtained with a Hitachi M-2500. Melting points were measured with a Yanaco MP-J3 and were uncorrected. X-ray analyses were measured with a Rigaku AFC7R diffractometer. HPLC analyses were carried out with a Agilent 1100 Series.

3.2. Preparation of diastereomerically pure bis(α-methylbenzyl)amine derivatives (*S*,*S*-**3**)

A solution containing partially fluorinated acetophenone (**1**) 50 mmol (1.0 equiv.), (*S*)-α-phenylethylamine 55 mmol (1.1 equiv.) and zinc chloride 1.5 mmol (0.03 equiv.) in toluene 50 mL was refluxed with azeotropic removal of produced water for 24 h using a Dean–Stark trap. Reaction mixture was washed with 1N NaOH 30 mL, and then with saturated NH_4Cl 30 mL (three times). Recovered organic layer was washed with brine 50 mL. After removal of solvent under a reduced pressure, crude product of partially fluorinated imine (*S*-**2**) was obtained in the following yield. Geometrical ratio was determined by ^{1}H and ^{19}F NMR. Trifluorinated imine (*S*-F_3-**2**) was prepared according to Ref. [2].

3.2.1. (S)-N-[(E)-2-fluoro-1-phenylethylidene]-2-phenylethylamine (S-E-F_1-2) and (S)-N-[(Z)-2-fluoro-1-phenylethylidene]-2-phenylethylamine (S-Z-F_1-2)

Total yield 95%. *E*:*Z* = 75:25.

Major isomer (*S*-*E*-F_1-**2**): ^{1}H NMR, δ 1.43 (d, 6.4 Hz, 3H), 4.56 (q, 6.4 Hz, 1H), 5.12 (d, 47.2 Hz, 2H), 7.00–7.60 (Ar–H, 10H). ^{19}F NMR, δ +206.98 (t, 47.2 Hz, 1F).

Minor isomer (*S*-*Z*-F_1-**2**): ^{1}H NMR, δ 1.58 (d, 6.6 Hz, 3H), 5.01 (q, 6.6 Hz, 1H), 5.31 (dd, 12.3 Hz, 46.1 Hz, 1H), 5.43 (dd, 12.3 Hz, 46.1 Hz, 1H), 7.00–7.60 (Ar–H, 10H). ^{19}F NMR, δ +208.31 (t, 46.1 Hz, 1F).

3.2.2. (S)-N-[(E)-2,2-difluoro-1-phenylethylidene]-2-phenylethylamine (S-F_2-2)

Yield 99%. *E*:*Z* = >99:1.

S-*E*-F_2-**2**: ^{1}H NMR, δ 1.42 (d, 6.6 Hz, 3H), 4.58 (q, 6.6 Hz, 1H), 6.21 (t, 56.0 Hz, 1H), 7.10–7.55 (Ar–H, 10H). ^{19}F NMR, δ +43.49 (dd, 332.4 Hz, 56.0 Hz, 1F), +44.35 (dd, 332.4 Hz, 56.0 Hz, 1F).

3.2.3. (S)-N-[(E)-2,2,2-trifluoro-1-phenylethylidene]-2-phenylethylamine (S-F_3-2)

Yield 93%. *E*:*Z* = >99:1.

S-*E*-F_3-**2**: ^{1}H NMR, δ 1.44 (d, 6.4 Hz, 3H), 4.54 (q, 6.4 Hz, 1H), 7.05–7.55 (Ar–H, 10H). ^{19}F NMR, δ +90.69 (s, 3F).

Sodium borohydride 30 mmol (1.0 equiv.) was added to a solution containing crude product of partially fluorinated imine (*S*-**2**) 30 mmol (1.0 equiv.) in methanol 30 mL at <5 °C, and then solution was stirred for 12 h at room temperature. Reaction mixture was quenched with 3N HCl 10 mL, and then alkalized with 3N NaOH 30 mL, followed by extraction with toluene 50 mL (two times). Recovered organic layer was washed with brine 30 mL. After removal of solvent under a reduced pressure, crude diastereomeric mixture of bis(α-methylbenzyl)amine derivative (*S*-**3**) was obtained in the following yield. Diastereomeric ratio was determined by GC (DB-5; length 30 M, i.d. 0.25 mm, film 0.25 μm). Diastereomeric mixture of trifluorinated

bis(α-methylbenzyl)amine derivative (*S*-F_3-**3**) was prepared according to Ref. [2].

*3.2.4. (αS)-α-(fluoromethyl)-N-[(S)-1-phenylethyl]benzenemethanamine (S,S-F_1-**3**)*

Total yield 90%. *S*,*S*:*R*,*S* = 67:33.

Major isomer (*S*,*S*-F_1-**3**): ^{1}H NMR, δ 1.37 (d, 6.7 Hz, 3H), 1.82 (br, 1H), 3.81 (q, 6.7 Hz, 1H), 4.04 (ddd, 4.4 Hz, 6.8 Hz, 16.6 Hz, 1H), 4.47 (ddd, 6.8 Hz, 9.0 Hz, 47.7 Hz, 1H), 4.53 (ddd, 4.4 Hz, 9.0 Hz, 47.7 Hz, 1H), 7.10–7.40 (Ar–H, 10H). ^{13}C NMR, δ 22.44, 55.15, 59.93 (d, 19.0 Hz), 86.39 (d, 174.4 Hz), 126.68, 127.03, 127.71, 127.88, 128.42, 128.59, 138.87, 144.97. ^{19}F NMR, δ +206.59 (dt, 16.6 Hz, 47.7 Hz, 1F). HRMS (EI), calculated for $C_{16}H_{18}FN$ ($M^{\bullet+}$) 243.1422, found 243.1404.

*3.2.5. (αS)-α-(fluoromethyl)-N-[(s)-1-phenylethyl]benzenemethanamine (p-toluenesulfonic acid salt) (S,S-F_1-**3**·p-TsOH*

Recrystallization of organic acid salt was carried out from a solution containing crude diastereomeric mixture of *S*-F_1-**3** (1.0 equiv.) and *p*-TsOH (1.0 equiv.) in *i*-propanol/*n*-hexane mixed solvent (30/70, 4 mL/mmol).

mp, 195–197 °C.

X-ray, a colorless prismatic crystal of $C_{92}H_{104}N_4O_{12}F_4S_4$ having approximate dimensions of 0.20 mm × 0.20 mm × 0.25 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC7R diffractometer with filtered Cu Kα radiation (λ = 154178 A) and a rotating anode generator. Crystal data of *S*,*S*-F_1-**3**· *p*-TsOH; M = 1662.09; monoclinic space group $P2_1$(#4), Z = 2 with a = 21.630(1)A, b = 9.5087(7)A, c = 21.567(2)A, β = 100.439(5)°, V = 4362.3(5) A^3, and D_{calc} = 1.265 g/cm^3. All calculations were performed using the CrystalStructure crystallographic software package. The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final R- and Rw-factors after full-matrix least squares refinement were 0.077 and 0.072, respectively, based on 5909 observed reflections ($I > 3.00$ s(I)). Crystallographic data have been deposited with Cambridge Crystallographic Data Center as supplementary publication no. CCDC 258053.

*3.2.6. (αS)-α-(difluoromethyl)-N-[1-phenylethyl]-benzenemethanamine (S,S-F_2-**3**)*

Total yield 84%. *S*,*S*:*R*,*S* = 79:21.

Major isomer (*S*,*S*-F_2-**3**): ^{1}H NMR, δ 1.36 (d, 6.5 Hz, 3H), 1.80 (br, 1H), 3.88 (q, 6.5 Hz, 1H), 3.94 (dt, 4.4 Hz, 12.2 Hz, 1H), 5.88 (dt, 4.4 Hz, 57.2 Hz, 1H), 7.10–7.45 (Ar–H, 10H). ^{13}C NMR, δ 22.73, 55.18, 61.83 (t, 21.9 Hz), 117.27 (t, 245.1 Hz), 126.43, 126.96, 128.05, 128.16, 128.31, 128.47, 136.13, 144.74. ^{19}F NMR, δ +37.61 (ddd, 280.7 Hz, 57.2 Hz, 12.2 Hz, 1F), +38.46 (ddd, 280.7 Hz, 57.2 Hz, 12.2 Hz, 1F). HRMS (EI), calculated for $C_{16}H_{17}F_2N$ ($M^{\bullet+}$) 261.1328, found 261.1345.

*3.2.7. (αS)-α-(difluoromethyl)-N-[(S)-1-phenylethyl]benzenemethanamine (phthalic acid salt) (S,S-F_2-**3**·phthalic acid)*

Recrystallization of organic acid salt was carried out from a solution containing crude diastereomeric mixture of *S*-F_2-**3** (1.0 equiv.) and phthalic acid (1.0 equiv.) in *i*-propanol/*n*-hexane mixed solvent (50/50, 2 mL/mmol).

mp, 174–176 °C.

X-ray, A colorless prismatic crystal of $C_{48}H_{46}F_4N_2O_8$ having approximate dimensions of 0.45 mm × 0.20 mm × 0.50 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC7R diffractometer with filtered Cu Kα radiation (λ =154178 A) and a rotating anode generator. Crystal data of *S*,*S*-F_2-**3**·phthalic acid: M = 854.89; monoclinic space group P1(#1), Z =1 with a = 11.176(2)A, b = 11.193(2)A, c = 9.490(3)A, β = 111.96(2)°, V = 1090.2(4) A^3, and D_{calc} = 1.302 g/cm^3. All calculations were performed using the CrystalStructure crystallographic software package. The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final R- and Rw-factors after full-matrix least squares refinement were 0.096 and 0.107, respectively, based on 3664 observed reflections ($I > 3.00$ s(I)). Crystallographic data have been deposited with Cambridge Crystallographic Data Center as supplementary publication no. CCDC 258054.

*3.2.8. (αS)-α-(trifluoromethyl)-N-[(s)-1-phenylethyl]-benzenemethanamine (S,S-F_3-**3**)*

Total yield 89%. *S*,*S*:*R*,*S* = 77:23.

Major isomer (*S*,*S*-F_3-**3**): ^{1}H NMR, δ 1.37 (d, 6.7 Hz, 3H), 1.89 (br, 1H), 3.97 (q, 6.7 Hz, 1H), 4.04 (q, 6.8 Hz, 1H), 7.15–7.40 (Ar–H, 10H). ^{13}C NMR, δ 23.50, 56.00, 61.63 (q, 28.7 Hz), 126.01 (q, 281.9 Hz), 126.64, 127.29, 128.14, 128.55, 128.66, 128.71, 135.37, 144.52. ^{19}F NMR, δ +88.72 (d, 6.8 Hz, 3F). HRMS (EI), calculated for $C_{16}H_{16}F_3N$ ($M^{\bullet+}$) 279.1233, found 279.1223.

*3.2.9. (αS)-α-(trifluoromethyl)-N-[(S)-1-phenylethyl]-benzenemethanamine (p-toluenesulfonic acid salt) (S,S-F_3-**3**·p-TsOH)*

Recrystallization of organic acid salt was carried out from a solution containing crude diastereomeric mixture of *S*-F_3-**3** (1.0 equiv.) and *p*-TsOH (1.0 equiv.) in *i*-propanol/*n*-hexane mixed solvent (50/50, 4 mL/mmol).

mp, 185–187 °C.

X-ray, a colorless prismatic crystal of $C_{92}H_{96}F_{12}N_4O_{12}S_4$ having approximate dimensions of 0.20 mm × 0.10 mm × 0.20 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC7R diffractometer with filtered Cu Kα radiation (λ = 154178 A) and a rotating anode generator. Crystal data of *S*,*S*-F_3-**3**· *p*-TsOH: M = 1896.01; monoclinic space group $P2_1$(#4), Z = 2 with a = 22.022(4)A, b = 9.561(3)A, c = 21.930(4)A, β = 99.48(1)°, V = 4554.4(2)

A^3, and $D_{calc} = 1.317$ g/cm^3. All calculations were performed using the CrystalStructure crystallographic software package. The structure was solved by direct methods and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were refined using the riding model. The final R- and Rw-factors after full-matrix least squares refinement were 0.074 and 0.069, respectively, based on 4489 observed reflections ($I > 3.00$ s(I)). Crystallographic data have been deposited with Cambridge Crystallographic Data Center as supplementary publication no. CCDC 258055.

3.3. Regioselective hydrogenolysis of diastereomerically pure bis(α-methylbenzyl)amine derivatives (S-4)

A solution containing organic acid salt of diastereomerically pure bis(α-methylbenzyl)amine derivative (*S*,*S*-**3**, >99.0% de) 1 mmol (1.0 equiv.) in methanol 5 mL was hydrogenolyzed in the presence of 5% palladium/carbon (NX-type, water content 50%, N.E. CHEMCAT) 8.5 mg under 0.5 MPa of H_2 at 60 °C for 12 h. Palladium catalyst was filtered off through a Celite pad. Regioselectivity was determined by GC (DB-5; length 30 M, i.d. 0.25 mm, film 0.25 μm). After removal of solvent under a reduced pressure, crude product of partially fluorinated α-methylbenzylamine (*S*-**4**) was obtained in the following yield. Yield was determined by internal reference method (internal standard; C_6F_6) in ^{19}F NMR. Enantiomer excess was determined by chiral HPLC (CHIRALPAK AS; length 25 cm, i.d. 0.46 cm) or GC (Chirasil-DEX CB; length 25 M, i.d. 0.25 mm, film 0.25 μm). Trifluorinated α-methylbenzylamine (*S*-F_3-**4**) was prepared according to Ref. [2].

3.3.1. (S)-α-fluoromethylbenzylamine (S-F_1-4)

This compound was unstable on GC analysis. Therefore, *S*-F_1-**4** was characterized as its corresponding acetamide.

Acetamide of *S*-F_1-**4**: ^{1}H NMR, δ 2.06 (s, 3H), 4.66 (ddd, 47.3 Hz, 14.0 Hz, 4.0 Hz, 1H), 4.72 (ddd, 47.3 Hz, 14.0 Hz, 4.0 Hz, 1H), 5.28 (ddt, 25.3 Hz, 8.0 Hz, 4.0 Hz, 1H), 6.06 (br, 1H), 7.30–7.40 (Ar–H, 5H). ^{13}C NMR, δ 23.36, 53.03 (d, 19.1 Hz), 84.83 (d, 174.4 Hz), 127.03, 128.13, 128.88, 137.90, 169.57. ^{19}F NMR, δ −61.5 (dt, 25.3 Hz, 47.3 Hz). HRMS (EI), calculated for $C_{10}H_{13}FNO$ (MH^+) 182.0980, found 182.0993.

Enantiomer excess >99.0% ee (chiral HPLC; *S* isomer 10.0 min, *R* isomer 14.0 min, *n*-hexane/*i*-propanol = 75/25, 25 °C, 240 nm, 1.0 mL/min).

3.3.2. (S)-α-difluoroluoromethylbenzylamine (S-F_2-4)

^{1}H NMR, δ 1.71 (br, 2H), 4.15 (ddd, 12.9 Hz, 9.6 Hz, 4.5 Hz, 1H), 5.74 (dt, 4.5 Hz, 56.5 Hz, 1H), 7.25–7.45 (Ar–H, 5H). ^{13}C NMR, δ 57.92 (dd, 24.0 Hz, 21.5 Hz), 117.17 (t, 243.8 Hz), 127.48, 128.38, 128.64, 137.42. ^{19}F NMR, δ +34.52 (ddd, 277.6 Hz, 56.5 Hz, 12.9 Hz, 1F), 37.68 (ddd, 277.6 Hz, 56.5 Hz, 9.6 Hz, 1F). HRMS (EI), calculated for $C_8H_8F_2N$ ($M - H$) 156.0624, found 156.0614.

Enantiomer excess >99.0% ee (chiral HPLC; acetamide of *S*-F_2-**4**, *S* isomer 8.0 min, *R* isomer 12.0 min, *n*-hexane/*i*-propanol = 75/25, 25 °C, 240 nm, 1.0 mL/min).

3.3.3. (S)-α-trifluoromethylbenzylamine (S-F_3-4)

^{1}H NMR, δ 1.77 (br, 2H), 4.39 (q, 7.5 Hz, 1H), 7.30–7.50 (Ar–H, 5H). ^{19}F NMR, δ +85.06 (d, 7.5 Hz, 3F).

Enantiomer excess >99.0% ee (chiral GC; acetamide of *S*-F_3-**4**, R isomer 15.4 min, *S* isomer 15.6 min).

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[11] Asymmetric reduction of *S*-F_0-2 (*E*:*Z* = >99:1) was carried out using sodium borohydride in a similar manner with Table 1. Yield 96%, *S*,*S* (anti):*R*,*S* (syn) = 86:14. *S*,*S*-F_0-3. ^{1}H NMR [$CDCl_3$, $(CH_3)_4Si$], δ 1.27 (d, 6.6 Hz, 6H), 1.60 (br, 1H), 3.50 (q, 6.6 Hz, 2H), 7.18–7.35 (Ar–H, 10H).
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1H), 7.13–7.39 (Ar–H, 10H). ^{13}C NMR [$CDCl_3$, $(CH_3)_4Si$], δ 24.18, 36.31, 48.77, 58.06, 125.95, 126.40, 126.73, 128.27, 128.55, 139.94, 145.48.

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