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Syntheses of chiral β-amino α-perfluoroalkylpropanol derivatives

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Abstract—Chiral β-amino α-perfluoroalkylpropanol derivatives were synthesized from *N*-Boc-L-phenylalanine methyl ester by substitution of the methoxy group into the corresponding perfluoroalkyl chain, followed by reduction and deprotection. Among them, a Schiff base prepared by condensation of (2*S*,3*S*)-2-amino-3-perfluorooctyl-1-phenylpropan-3-ol, (2*S*,3*S*)-**1**, and 1-naphthaldehyde catalyzed the asymmetric ethyl addition reaction of diethylzinc with the aldehyde to afford the product up to 93% ee.

1. Introduction

The discovery of a β-amino alcohol-catalyzed dialkylzinc alkylation by Oguni[1] opened up a new field of asymmetric synthesis. Diverse chiral β-amino alcohols, especially designed for the asymmetric alkylation with dialkylzinc, have been elaborated from commercially available chiral sources such as amino acid,[2] camphor,[3,4] and sugar derivatives.[5] Other useful derivatives such as salen, oxazoline, and dipeptides have also been well studied and shown outstanding activity.[6] In contrast to these, some challenges, however, still remain with Schiff base-type ligand. Low coordination property of the Schiff base to diethylzinc requires use of Lewis acid such as Ti(O*i*Pr)$_4$.[7,8] Recently, Schiff base ligands derived from [2.2]paracyclophane were reported with high catalytic performance in the same asymmetric ethyl addition using diethylzinc to afford a product of 93% ee without any help of a Lewis acid.[9] We expected that the catalytic reactivity of the Schiff base ligands would be mainly influenced by the neighboring hydroxy group, which participates in the chelation with zinc. Our previous study on chiral ligands containing perfluoroalkyl carbinol moieties[10] led to a chiral β-amino α-perfluoroalkylated-alcohol (β-amino α-R_f-alcohol) for Schiff base ligands. The following advantages are expected in the β-amino α-R_f-alcohol. The higher acidic α-perfluoroalkylated-alcohol compared with the non-fluorinated one allows easy ligand replacement with Lewis acidic metals such as Ti(O*i*Pr)$_4$ or Et_2Zn. The resulting chelate complex containing the α-perfluoroalkylated-alkoxide was expected to show higher Lewis acidity than the original one. Furthermore, the hydroxy group would become less sensitive toward oxidation and dehydration. On the basis of these expectations, we designed four β-amino α-R_f-alcohols carrying perfluorobutyl or perfluorooctyl chain, (2*S*,3*S*)- or (2*S*,3*R*)-2-amino-3-perfluoroalkyl-1-phenylpropan-3-ol (Fig. 1). Herein, we report the syntheses of these β-amino α-R_f-alcohols, **1** and **2**, and the preliminary results on their application in the asymmetric addition reaction of diethylzinc with benzaldehyde.

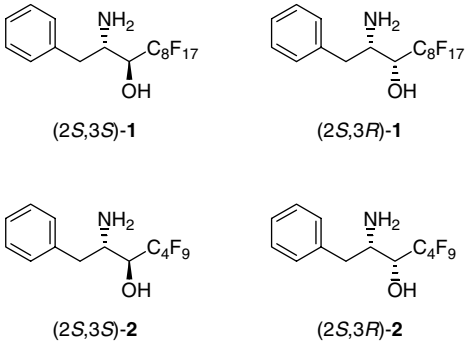

Figure 1. Structures of perfluoroalkyl substituted β-amino alcohols.

2. Results and discussion

We started the synthesis of **1** and **2** from the introduction of the R_f chain into *N*-Boc-L-phenylalanine methyl ester, (*S*)-**3**. The introduction of the R_f group was conducted by using Hultin's method.[11] Following the literature, R_fLi

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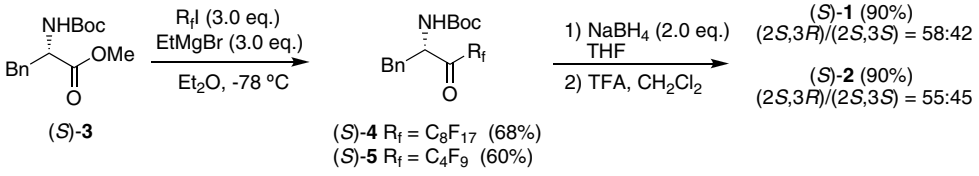
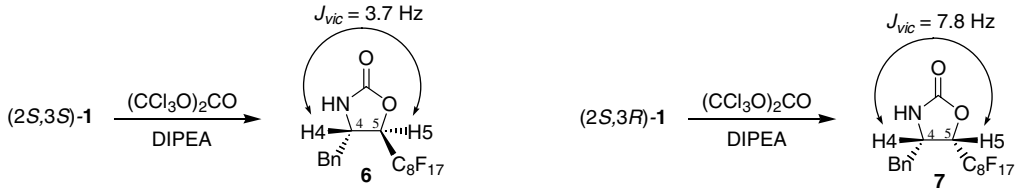
prepared by the reaction of methyllithium with the corresponding R_fI was examined for R_f-introduction. However, easy decomposition of the R_fLi to a carbene species or the β-elimination decreased a chemical yield in that reaction.[12,13] The problem was solved by using R_fMgBr prepared in the same manner with ethylmagnesium bromide instead of methyllithium. R_fMgBr was stable below −65 °C[14] and no decomposition was observed. The reactions of R_fMgBr with (*S*)-**3** were successful for obtaining products, (*S*)-**4** and **5**, with different lengths of the R_f group (Scheme 1). In this reaction, the second addition of an R_f group to **4** or **5** was prevented, probably due to the stable tetrahedral intermediate of the first adduct. In this process, control of the reaction temperature and time was important to avoid racemization of the α-carbon. Chiral HPLC analysis indicated that no racemization was observed when the reaction temperature reached to 0 °C; however, elongation of the reaction time to 2 h at room temperature caused complete racemization. Products **4** and **5** were subjected to reduction of the R_f ketones with $NaBH_4$ and subsequent acid treatment. The reduction proceeded so fast that no racemization was observed in chiral HPLC analysis. The diastereomers in **1** or **2** were easily separated by silica-gel column chromatography to give enantiomerically pure (2*S*,3*R*)- and (2*S*,3*S*)-**1** or **2**, respectively. ^{1}H NMR analysis of **1** showed a broad singlet peak assigned to three protons of the amino and hydroxy groups around 2 ppm. That peak demonstrates the possibility of intramolecular hydrogen bonding between the amino and hydroxy groups. The hydrogen bonding would decrease the basicity of the nitrogen, thus allowing easy handling under air. The configurations of diastereomers of **1** were determined according to Kitazume's method.[15] They reported the typical H–H coupling constant between H4 and H5 in 5-trifluoromethyloxazolidinone derivatives. Namely, the coupling constant in the *cis*-configuration is larger than that of the *trans* one. For the determination, both diastereomers of **1** were converted to oxazolidinone derivatives, **6** and **7**, by reaction with triphosgene. The ^{1}H NMR study of their derivatives identified their configuration as shown in Scheme 2.

To estimate the asymmetric inductions of **1** and **2**, several Schiff bases were prepared by condensation with the appropriate aldehydes in the presence of anhydrous $MgSO_4$. The suspended material was filtered off and purified through short silica-gel column chromatography to give Schiff base, **8** or **9**. ^{1}H NMR analysis and low resolution MS spectra indicated the formation of **8** or **9**, and the peaks that originated during the formation of oxazolidine derivative were not observed. The purities of **8** and **9** after the purification step were confirmed immediately by GC to be more than 95%, however, they were hydrolyzed gradually during operations owing to their instability toward moisture. These freshly prepared and purified Schiff bases, **8** and **9**, were employed directly as ligand for diethylzinc in the asymmetric ethyl addition reaction. The results on the ethyl addition reaction are summarized in Table 1. Some types of Schiff base ligands were prepared while searching the effective backbone structure of Schiff base ligand. Salicylaldehyde, 2-pyridinecarbaldehyde, and benzaldehyde were chosen for that purpose. Ligand **8a** prepared by condensation of (2*S*,3*S*)-**1** and salicylaldehyde showed low catalytic reactivity. The phenolic alcohol allowing the σ bond with zinc might concern with the low ee (Table 1, entries 1 and 2). In the case of 2-pyridinecarbaldehyde, **8b** capable of coordinating zinc slightly improved the catalytic reactivity (entries 3 and 4).

A considerable improvement in both the catalytic and asymmetric performance was achieved by **8c** prepared from **1** and benzaldehyde. Concerning the two stereoisomers (2*S*,3*S*)- and (2*S*,3*R*)-**8c**, we recognized a large difference in their asymmetric induction. The former exhibited outstanding performance in the asymmetric reaction to afford 86% ee of the product. The stereochemistry of the product was controlled by the geometry of the alcohol carrying a perfluoroalkyl-tail in the ligand. On the basis of these results, we carried on searching for a superior Schiff base ligand by changing the aldehyde moiety as well as changing the length of R_f chain. To determine electrostatic and steric effects of the benzene ring on its asymmetric performance, substituted benzaldehydes were tested. Ligands **8**–**9d** with an electron-donating methyl group and **8**–**9e** with electron-withdrawing fluorine showed almost the same performance between the corresponding **d** and **e** products (entries 7–14). This suggests that the electrostatic effect of the aryl moiety is negligible for asymmetric induction. Next, the steric effect of the aryl moiety was investigated. 1- and 2-Naphthaldehydes were chosen for that. Ligand (2*S*,3*S*)-**8f** revealed the best performance in the asymmetric reaction to afford 93% ee of the product in quantitative yield (entry 15). Compared with (2*S*,3*S*)-**8f**, (2*S*,3*S*)-**9f**, with a shortened R_f chain, afforded the product with an ee which slightly decreased to 89% (entry 17). This suggests that the length of the R_f chain was also an important factor for acquiring high asymmetric performance of the ligand. In the cases of **8**–**9g**, small decreases were observed on the asymmetric inductions of them compared with the corresponding **8**–**9f**. Among Schiff base ligands, the one derived from [2.2]paracyclophane has been reported to give an outstanding asymmetric performance in the same ethyl addition to give 93% ee of the product. However, a long reaction time (15 h at room temperature) is required for obtaining a high chemical yield. Schiff base ligand (2*S*,3*S*)-**8f** was able to catalyze the reaction with the same

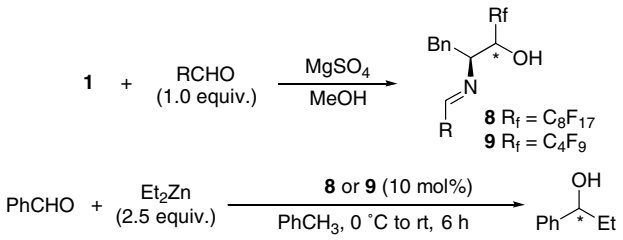


Scheme 1.



Scheme 2.

Table 1. Asymmetric induction of Schiff base ligands, **8** and **9**, for Et_2Zn in the reaction with benzaldehyde



Entry	Ligand	R of **8** or **9**	Yield (%)	ee[a] (%)	Config.[b]
1	(2*S*,3*S*)-**8a**	2-Hydroxyphenyl	38	18	(*S*)
2	(2*S*,3*R*)-**8a**		99	19	(*R*)
3	(2*S*,3*S*)-**8b**	2-Pyridyl	82	42	(*S*)
4	(2*S*,3*R*)-**8b**		99	52	(*R*)
5	(2*S*,3*S*)-**8c**	Phenyl	94	86	(*S*)
6	(2*S*,3*R*)-**8c**		99	44	(*R*)
7	(2*S*,3*S*)-**8d**	3-Methylphenyl	91	77	(*S*)
8	(2*S*,3*R*)-**8d**		90	42	(*R*)
9	(2*S*,3*S*)-**9d**		96	78	(*S*)
10	(2*S*,3*R*)-**9d**		94	50	(*R*)
11	(2*S*,3*S*)-**8e**	3-Fluorophenyl	90	78	(*S*)
12	(2*S*,3*R*)-**8e**		89	49	(*R*)
13	(2*S*,3*S*)-**9e**		82	73	(*S*)
14	(2*S*,3*R*)-**9e**		94	55	(*R*)
15	(2*S*,3*S*)-**8f**	1-Naphthyl	99	93	(*S*)
16	(2*S*,3*R*)-**8f**		99	67	(*R*)
17	(2*S*,3*S*)-**9f**		97	89	(*S*)
18	(2*S*,3*R*)-**9f**		95	69	(*R*)
19	(2*S*,3*S*)-**8g**	2-Naphthyl	97	82	(*S*)
20	(2*S*,3*R*)-**8g**		98	44	(*R*)
21	(2*S*,3*S*)-**9g**		99	81	(*S*)
22	(2*S*,3*R*)-**9g**		97	49	(*R*)

[a] Determined by chiral GC analysis.
[b] Determined by comparing the sign of the specific rotation with reported ones.

asymmetric performance and also shorten the reaction time to 6 h at room temperature. The short reaction time, which might be given by perfluoroalkylcarbinol, is an advantage of using **8f**.

3. Conclusions

In conclusion, we have succeeded in the syntheses of **1** and **2** which possess perfluorooctyl and perfluorobutyl chains, respectively. The R_f chains were effectively introduced into (*S*)-**3** by using Grignard reagents prepared by the corresponding perfluoroalkyl iodide and ethylmagnesium bromide. Subsequent reduction of the R_f ketone and deprotection afforded **1** and **2**. Schiff base (2*S*,3*S*)-**8f** obtained by condensation of (2*S*,3*S*)-**1** and 1-naphthaldehyde was an effective ligand for diethylzinc in the asymmetric ethyl addition reaction to benzaldehyde. Further applications of this ligand to other aldehydes and asymmetric syntheses are now in progress.

4. Experimental

4.1. General

All reactions were conducted under an argon atmosphere unless noted otherwise. Chemicals were treated as follows: THF, ether, and toluene were distilled from Na/benzophenone; other chemicals were used as received. ^1H and ^{13}C NMR spectra were recorded on GSX-400 (400 MHz, JEOL) or ECA-600 (600 MHz, JEOL) Spectrometers and ^{19}F NMR spectra were recorded on FT-NMR R-1500 (60 MHz, Hitachi) or ECP-600 (600 MHz, JEOL)

Spectrometers at ambient probe temperature and referenced as follows: ^{1}H and ^{13}C, TMS; ^{19}F, BTF. IR spectra were measured on an Hitachi 270-30 IR Spectrophotometer. Mass spectra were recorded on JMS-DX-300 or JMS-700 T (JEOL) Spectrometers. Ee was determined by GLC with GAMMA DEX™ 225 Capillary Column (30 m × 0.25 mm × 0.25 μm). Optical rotations were measured by DIP-140 (JASCO).

4.1.1. (*S*)-(1-Benzyl-3,3,4,4,5,5,6,6,7,7,8,8,9,9,10,10,10-heptadecafluoro-2-oxo-decyl)-carbamic acid *tert*-butyl ester (*S*)-4. To a solution of ethylmagnesium bromide (7.2 mL, 3.0 M in Et_2O, 21.6 mmol) in Et_2O (50 mL) was slowly added a solution of $C_8F_{17}I$ (11.8 g, 21.6 mmol) in Et_2O (35 mL) keeping the temperature below −65 °C under an atmosphere of Ar. After stirring for 30 min at −78 °C, a solution of (*S*)-**3** (2.0 g, 7.2 mmol) in Et_2O (15 mL) was added to the solution at the same temperature. The solution was stirred for 1 h at −70 °C and then warmed to 0 °C. The reaction was then quenched by the addition of saturated aqueous NH_4Cl when the solution temperature was reached to 0 °C. After separation of the layers, the aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered, and condensed in vacuo to give the crude product. The desired product was purified by silica-gel column chromatography ($CHCl_3$/hexane = 3:7) and obtained as a white solid (2.8 g, 68%). White solid; mp 73.8–74.4 °C. $[\alpha]_D^{24} = +16.3$ (*c* 1.07, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 7.14–7.35 (5H, m), 5.08 (1H, dd, $^{3}J_{H,H} = 12.9$ Hz, $^{3}J_{H,H} = 7.1$ Hz), 4.89 (1H, d, $^{3}J_{H,H} = 7.9$ Hz), 3.24 (1H, dd, $^{2}J_{H,H} = 14.0$ Hz, $^{3}J_{H,H} = 5.0$ Hz), 2.90 (1H, dd, $^{2}J_{H,H} = 13.9$ Hz, $^{3}J_{H,H} = 7.9$ Hz), 1.38 (s, 9H). ^{13}C NMR ($CDCl_3$, $^{1}H^{19}F$-COM) δ: 193.5, 154.6, 134.4, 129.4, 128.9, 127.5, 119.9, 117.2, 116.9, 114.5, 110.9, 110.7, 110.2, 109.5, 108.4, 56.8, 36.8, 28.1. ^{19}F NMR ($CDCl_3$) δ: −63.3 (2F, m), −58.3 to −59.9 (11F, m), −56.8 (1F, dt, $J = 294.0$ Hz, $J = 12.9$ Hz), −54.2 (1F, dt, $J = 294.0$ Hz, $J = 12.1$ Hz), −18.0 (3F, t, $J = 15.8$ Hz). IR (KBr) cm^{-1}: 3370, 2984, 1770, 1703, 1521, 1200. MS *m*/*z*: 667 (M^+). HRMS Calcd for $C_{22}H_{18}F_{17}NO_3$: 667.1015 (M^+). Found: 667.1007 (M^+).

4.1.2. (*S*)-(1-Benzyl-3,3,4,4,5,5,6,6,6-nonafluoro-2-oxo-hexyl)-carbamic acid *tert*-butyl ester ((*S*)-5). The procedure was the same as in the case of (*S*)-**4**. Mp 87.9–88.7 °C. $[\alpha]_D^{24} = +29.6$ (*c* 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 7.14–7.35 (5H, m), 5.07 (1H, dd, $^{3}J_{H,H} = 16.0$ Hz, $^{3}J_{H,H} = 6.8$ Hz), 4.88 (1H, d, $^{3}J_{H,H} = 7.6$ Hz), 3.24 (1H, dd, $^{2}J_{H,H} = 14.5$ Hz, $^{3}J_{H,H} = 4.7$ Hz), 2.89 (1H, dd, $^{2}J_{H,H} = 14.8$ Hz, $^{3}J_{H,H} = 7.3$ Hz), 1.38 (s, 9H). ^{13}C NMR ($CDCl_3$, $^{1}H^{19}F$-COM) δ: 193.4, 154.7, 134.5, 129.5, 128.9, 127.6, 117.3, 114.6, 110.3, 109.5, 108.6, 56.9, 36.8, 28.2. ^{19}F NMR ($CDCl_3$) δ: −62.7 (2F, m), −59.8 (2F, m), −56.9 (1F, dt, $J = 295.7$ Hz, $J = 12.1$ Hz), −54.4 (1F, dt, $J = 294.8$ Hz, $J = 12.1$ Hz), −18.2 (3F, t, $J = 9.5$ Hz). IR (KBr) cm^{-1}: 3369, 2987, 1762, 1699, 1518, 1251. MS *m*/*z*: 467 (M^+). HRMS Calcd for $C_{18}H_{18}F_9NO_3$: 467.1143 (M^+). Found: 467.1138 (M^+).

4.1.3. (2*S*,3*S*)- and (2*S*,3*R*)-2-Amino-4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoro-1-phenyl-undecan-3-ol (2*S*,3*S*)- and (2*S*,3*R*)-1. To a solution of (*S*)-**4** (2.0 g, 3.0 mmol) in THF (6 mL) was added $NaBH_4$ (227 mg, 6.0 mmol) at 0 °C after which the mixture was warmed to room temperature. After stirring the mixture for 3 h at the same temperature, the reaction was quenched by adding saturated aqueous NH_4Cl. After separation of the layers, the aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried over $MgSO_4$, filtered, and condensed in vacuo to give the crude product. The crude product was dissolved in CH_2Cl_2 (3 mL) and TFA (3 mL, 40 mmol). After stirring for 30 min at room temperature, aqueous 10% NaOH was added to the solution to adjust the pH to 8 to allow precipitation of the product. The precipitate was collected by suction filtration and the solid was purified by silica-gel column chromatography (MeOH/$CHCl_3$ = 2:98) and obtained as a white solid (0.63 g for (2*S*,3*S*)-**1**, 0.87 g for (2*S*,3*R*)-**1**, 90% total). (2*S*,3*S*)-**1**: White solid; mp 92.5–93.1 °C. $[\alpha]_D^{24} = -3.7$ (*c* 1.04, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 7.22–7.37 (5H, m), 3.89 (1H, dd, $^{3}J_{H,F} = 23.9$ Hz, $^{3}J_{H,H} = 4.2$ Hz), 3.67–3.70 (1H, m), 2.90 (1H, dd, $^{2}J_{H,H} = 13.9$ Hz, $^{3}J_{H,H} = 5.6$ Hz), 2.72 (1H, dd, $^{2}J_{H,H} = 14.2$ Hz, $^{3}J_{H,H} = 9.8$ Hz), 1.81 (3H, br). ^{13}C NMR ($CDCl_3$, $^{1}H^{19}F$-COM) δ: 137.0, 129.2, 129.0, 127.2, 117.2, 116.8, 111.5, 111.2, 110.9, 110.8, 110.3, 108.4, 69.1, 49.4, 40.5. ^{19}F NMR ($CDCl_3$) δ: −63.3 (2F, m), −61.7 (1F, d, $J = 281.9$ Hz), −59.8 (2F, m), −58.1 to −59.2 (8F, m), −54.4 (1F, d, $J = 282.8$ Hz), −18.0 (3F, t, $J = 10.3$ Hz). IR (KBr) cm^{-1}: 3027, 2694, 1701, 1601, 1201. MS *m*/*z*: 570 (M^++H). HRMS Calcd for $C_{17}H_{13}F_{17}NO$: 570.0726 (M^++H). Found: 570.0729 (M^++H). (2*S*,3*R*)-**1**: White solid; mp 108.7–110.0 °C. $[\alpha]_D^{24} = -72.5$ (*c* 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 7.20–7.36 (5H, m), 4.20 (1H, dt, $^{3}J_{H,F} = 24.2$ Hz, $^{3}J_{H,H} = 3.2$ Hz), 3.38 (1H, dt, $^{3}J_{H,H} = 11.0$ Hz, $^{3}J_{H,H} = 3.4$ Hz), 3.13 (1H, d, $^{2}J_{H,H} = 14.2$ Hz), 2.68 (1H, ddd, $^{2}J_{H,H} = 14.6$ Hz, $^{3}J_{H,H} = 12.2$ Hz, $^{4}J_{H,H} = 1.6$ Hz), 2.04 (3H, br). ^{13}C NMR ($CDCl_3$, $^{1}H^{19}F$-COM) δ: 137.7, 129.2, 129.0, 127.1, 117.3, 111.4, 111.2, 110.9, 110.8, 110.3, 110.2, 108.4, 69.8, 54.2, 38.0. ^{19}F NMR ($CDCl_3$) δ: −64.3 (1F, d, $J = 284.5$ Hz), −63.4 (2F, m), −59.9 (2F, m), −58.3 to −59.4 (8F, m), −57.3 (1F, d, $J = 279.3$ Hz), −18.0 (3F, t, $J = 9.5$ Hz). IR (KBr) cm^{-1}: 3358, 3098, 1665, 1614, 1201. MS *m*/*z*: 570 (M^++H). HRMS Calcd for $C_{17}H_{13}F_{17}NO$: 570.0726 (M^++H). Found: 570.0718 (M^++H).

4.1.4. (2*S*,3*S*)- and (2*S*,3*R*)-2-Amino-4,4,5,5,6,6,7,7,7-nonafluoro-1-phenylheptan-3-ol ((2*S*,3*S*)- and (2*S*,3*R*)-2). The procedure was the same as in the case of **1**. (2*S*,3*S*)-**2**. Mp 74.7–75.1 °C. $[\alpha]_D^{24} = -3.7$ (*c* 1.05, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 7.21–7.37 (5H, m), 3.89 (1H, dd, $^{3}J_{H,F} = 24.2$ Hz, $^{3}J_{H,H} = 4.2$ Hz), 3.66–3.70 (1H, m), 2.90 (1H, dd, $^{2}J_{H,H} = 13.9$ Hz, $^{3}J_{H,H} = 5.6$ Hz), 2.72 (1H, dd, $^{2}J_{H,H} = 14.2$ Hz, $^{3}J_{H,H} = 9.5$ Hz), 2.00 (3H, br). ^{13}C NMR ($CDCl_3$, $^{1}H^{19}F$-COM) δ: 137.0, 129.2, 129.0, 127.2, 117.5, 116.7, 112.3, 108.8, 69.1, 49.3, 40.6. ^{19}F NMR ($CDCl_3$) δ: −64.5 (1F, d, $J = 286.2$ Hz), −64.0 to −64.6 (2F, m), −62.3 to −62.9 (2F, m), −59.5 to −60.7 (2F, m), −57.4 (1F, d, $J = 297.6$ Hz), −18.2 (3F, t, $J = 11.4$ Hz). IR (KBr) cm^{-1}: 3029, 2688, 1599, 1457, 1221. MS *m*/*z*: 370 (M^++H). HRMS Calcd for $C_{13}H_{13}F_9NO$: 370.0853 (M^++H). Found: 370.0855 (M^++H). (2*S*,3*R*)-**2**: White solid; mp 96.1–96.7 °C.

$[\alpha]_D^{24} = -12.9$ (*c* 1.01, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 7.19–7.36 (5H, m), 4.23 (1H, dtd, $^3J_{H,F} = 24.0$ Hz, $^3J_{H,H} = 3.8$ Hz, $^4J_{H,H} = 1.2$ Hz), 3.37 (1H, dt, $^3J_{H,H} = 11.3$ Hz, $^3J_{H,H} = 3.5$ Hz), 3.12 (1H, d, $^2J_{H,H} = 14.6$ Hz), 2.67 (1H, ddd, $^2J_{H,H} = 14.0$ Hz, $^3J_{H,H} = 12.4$ Hz, $^4J_{H,H} = 1.4$ Hz), 2.44 (3H, br). ^{13}C NMR ($CDCl_3$, $^1H^{19}F$-COM) δ: 138.3, 129.2, 128.9, 126.9, 117.5, 117.4, 110.9, 108.9, 70.3, 54.0, 38.6. ^{19}F NMR ($CDCl_3$) δ: −64.0 to −64.6 (2F, m), −62.3 to −62.9 (2F, m), −61.8 (1F, d, $J = 283.6$ Hz), −59.3 to −60.8 (2 F, m), −54.9 (1F, d, $J = 299.4$ Hz), −18.2 (3F, t, $J = 10.2$ Hz). IR (KBr) cm^{-1}: 3070, 2858, 1613, 1456, 1230. MS *m*/*z*: 370 (M^++H). HRMS Calcd For $C_{13}H_{13}F_9NO$: 370.0853 (M^++H). Found: 370.0851 (M^++H).

4.1.5. General procedure for asymmetric ethyl addition (Table 1). To a suspension of $MgSO_4$ (100 mg) in methanol (1 mL) was added **1** (0.05 mmol) and the appropriate aldehyde (0.05 mmol) under atmosphere of Ar. After stirring for 30 min at room temperature, the solid was filtered off and the filtrate was evaporated. The crude **8** or **9** was purified by short silica-gel column chromatography with chloroform (if necessary, a small amount of methanol) and the fractions containing **8** or **9** were collected. After removal of the solvent in vacuo, **8** (or **9**) was subjected directly to the next reaction. All amounts of diethylzinc, aldehyde, and solvent were adjusted based on that of **8** or **9** obtained. To the solution of **8** or **9** (0.05 mmol) in toluene (0.3 mL) was added diethylzinc (2.5 mmol, 1.0 M in hexane solution) at 0 °C. After stirring for 30 min at the same temperature, a solution of benzaldehyde (0.5 mmol) in toluene (0.1 mL) was added slowly. The mixture was stirred for 6 h at room temperature. The reaction was quenched by the addition of 10% of aqueous HCl and the organic layer was collected. The aqueous layer was extracted with ether and the combined organic layers were dried over $MgSO_4$. After filtration of the solid, the solvent was removed in vacuo to give the crude product. The desired product was purified by silica-gel column chromatography (ether/hexane = 1:9) and the chemical yield and ee were detected. (*S*)-1-Phenylpropan-1-ol: 93% ee determined by chiral GC analysis. Retention time: $t_{minor} = 5.7$ min, and $t_{major} = 6.9$ min (120 °C).

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