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Enantioselective addition of diethylzinc to aldehydes catalyzed by fluorous β-aminoalcohols

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Abstract—A fluorous aminoalcohol prepared from ephedrine has been used as a catalyst for the enantioselective addition of diethylzinc to aldehydes to afford the corresponding alcohols in up to 84% ee. The fluorous amino alcohol was easily recovered by a simple filtration through a fluorous reverse phase silica gel and was reusable without purification.

1. Introduction

The recovery and reuse of chiral ligands or catalysts is an important topic in asymmetric reactions. Thus, the study of chiral polymer catalysts has attracted extensive attention in recent years. These catalysts have intrinsic advantages in that they can be separated from the products by simple filtration and reused without loss of catalytic activity or enantioselectivity. Several asymmetric reactions using chiral polymer catalysts have been reported in the literature.[1,2]

On the other hand, compounds that have long perfluorinated carbon chains are 'fluorous' and are easily separable from organic compounds by a simple liquid–liquid or solid–liquid extraction techniques.[3] Nowadays an increasing number of academic and industrial researchers are working on the design of ligands containing perfluoroalkyl groups and their application to catalysis.[4] To our knowledge, however, only a few reports have been published on asymmetric reactions using fluorous reagents or catalysts.[5] Very recently, we have reported the enantioselective protonation reaction of a samarium enolate prepared from reductive cleavage of 2-methoxy-2-phenylcyclohexanone with SmI_2, in the presence of fluorous C_2-symmetric chiral diol as a proton source in THF. The proton source was easily recovered by liquid–liquid extraction with perfluorohexanes (FC-72) or solid phase extraction with fluorous reverse phase silica gel (FRP silica gel) and was reusable without purification.[5c]

In this paper, we wish to report the synthesis of new fluorous chiral β-aminoalcohols and their application to the catalytic enantioselective addition of diethylzinc to aldehydes. We chose the reaction for a catalyst-recycling system to examine usefulness of the fluorous chiral ligands,[5a,d,f] because the reaction brought about a high percentage ee and yield by a simple procedure and with the use of commercially available reagents. In addition, we can evaluate the fluorous chiral ligand by comparing the fluorous ligand system to the catalyst-recycling system using a polymer-supported chiral β-aminoalcohol which has already been established by Soai and other researchers.[2e,i–o]

2. Results and discussion

2.1. Synthesis of fluorous chiral β-aminoalcohols

Curran and co-workers have reported the synthesis and application of a fluorous benzyl protecting reagent **4**, which attaches the readily available tris(perfluorohexylethyl)silyl group as a fluorous label to *p*-position of benzyl bromide.[6] However, the silicon–aryl bond of this fluorous tag is somewhat unstable toward several reaction conditions. Therefore, we have attempted to synthesize a new fluorous benzyl protecting reagent in which the fluorous alkyl group is attached to benzene ring through carbon–carbon single bond **3**.

The synthesis of the new fluorous benzyl protecting reagent **3** is outlined in Scheme 1. Reaction of the Grignard reagent prepared from commercially available perfluoroalkyl iodide and magnesium powder with dimethyl carbonate in Et_2O provided *tert*-alcohol **1** in 40% yield after recrystallization from $CHCl_3$. Friedel–Crafts alkylation of toluene with the alcohol **1** in the presence of excess trifluoromethanesulfonic acid under reflux to yield the corresponding fluorous toluene in 93% yield. The product contained mainly *p*-substituted isomer **2a** and a small amount of a regioisomer **2b** (presumably *m*-isomer). Since the isomers were not separated by a

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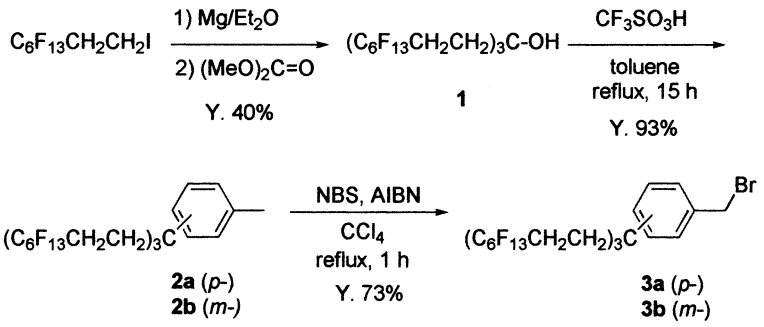
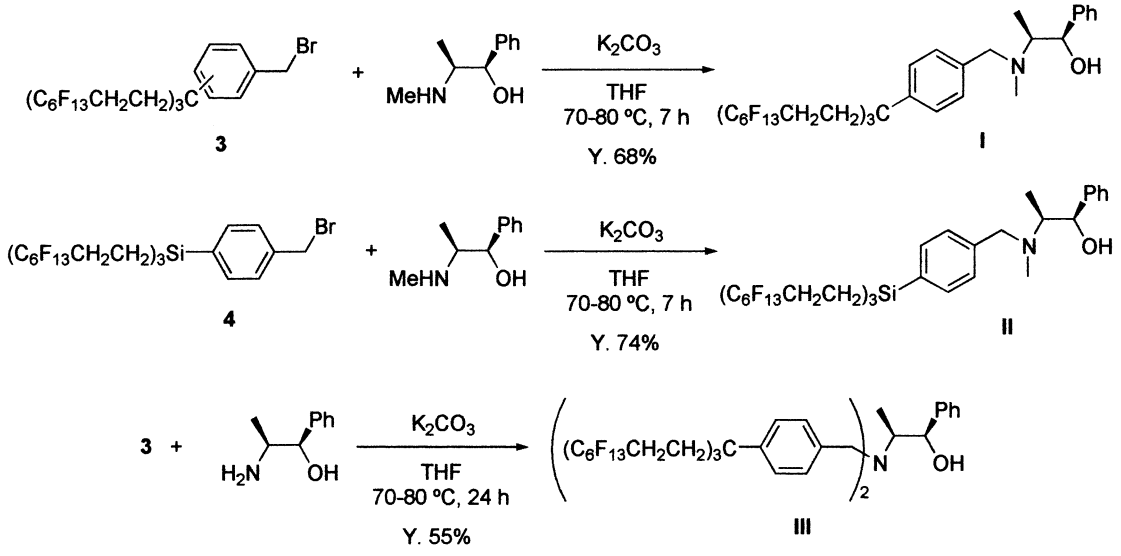


Scheme 1.



Scheme 2.

silica gel column chromatography, the mixture was brominated with *N*-bromosuccinimide in the presence of AIBN in CCl_4 at 80°C to provide the corresponding benzyl bromide **3** in 73% yield. In the product, about 20% of the minor regioisomer **3b** was detected in the ^{1}H NMR spectra together with the major *p*-isomer **3a**. Since it was again unsuccessful to separate the isomers by a silica gel column chromatography, we used the mixture as the tag precursor to prepare fluouous β-aminoalcohols.

Table 1. Partition coefficients of fluorous aminoalcohol (**I**)–(**III**) in organic solvent and FC-72

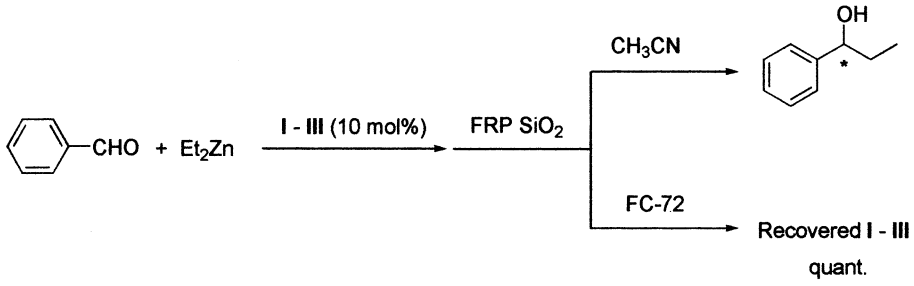
Amino alcohol	Organic solvent	Organic solvent/FC-72
I	CH_3CN	12/88
	Toluene	41/59
	CH_2Cl_2	62/38
II	CH_3CN	18/82
	Toluene	52/48
	CH_2Cl_2	75/25
III	CH_3CN	3/97
	Toluene	3/97
	CH_2Cl_2	6/94

A mixture of 100 mg of (**I**)–(**III**) in FC-72 (2 mL) and organic solvent (2 mL) was stirred at room temperature for 10 min. Then the two phases were separated and the solvents were evaporated in vacuo. The contents of the fluorous compound in each phase were determined by weighing the residue.

N-Benzylation of (1*R*,2*S*)-ephedrine or (1*R*,2*S*)-norephedrine with the benzyl bromide mixture (**3a** and **3b**) in the presence of potassium carbonate in THF at 70–80°C provided fluorous chiral β-aminoalcohols **I** and **III** in moderate yield after column chromatography. In the ^{1}H NMR spectra of these products, there was no peak due to the minor regioisomer of the fluorous benzyl group. The corresponding products containing the minor regioisomer were not isolated in each case. Therefore, it is considered that the *m*-isomer **3b** is unreactive under the reaction conditions probably because of a large steric hindrance due to the long fluorous alkyl chains at the *m*-position. Fluorous aminoalcohol **II** was also synthesized from (1*R*,2*S*)-ephedrine and Curran's fluorous benzyl bromide **4** by the same manner (Scheme 2).

The approximate partition coefficients of **I**–**III** were determined by a simple method described in the footnote of Table 1, and the results are summarized in Table 1. The aminoalcohol **III** is a fluorous compound and efficiently extracted to FC-72 phase. However, the mono benzylated aminoalcohols **I** and **II** are 'less fluorous' than the bis benzylated aminoalcohol **III**.

Table 2. The enantioselective addition of diethylzinc to benzaldehyde catalyzed by the fluorous aminoalcohols



Entry	Catalyst	Solvent	Reaction temp.	Reaction time (h)	Yield (%)[a]	% ee[b]	Config.[c]
1	**I**	Hexane	rt	18	93	75	*R*(+)
2	**I**	Toluene/hexane (2:1 v/v)	rt	20	90	83	*R*(+)
3	**I**	Toluene	rt	20	87	83	*R*(+)
4	**I**	Hexane	0°C	20	78	78	*R*(+)
5	**I**	Toluene/hexane (2:1 v/v)	0°C	20	62	85	*R*(+)
6	**II**	Toluene/hexane (2:1 v/v)	rt	20	91	83	*R*(+)
7	**III**	BTF/hexane (2:1 v/v)	rt	20	54	25	*R*(+)

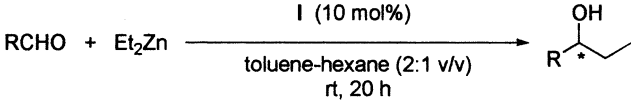
[a] Isolated yield.
[b] Determined by HPLC analysis using DAICEL CHIRALCEL OD-H.
[c] Determined by comparison of specific rotation with literature value.

2.2. Enantioselective addition of diethylzinc to aldehydes catalyzed by fluorous aminoalcohols

To find the optimal reaction conditions, we initially examined the enantioselective addition of diethylzinc to benzaldehyde catalyzed by the aminoalcohols **I**–**III** under various conditions. All of the reactions are carried out in the presence of 10 mol% of the catalyst and 2 equiv. of diethylzinc. The results are summarized in Table 2.

As seen from Table 2, when **I** was used as a catalyst, the reactions proceeded smoothly at room temperature, and (*R*)-1-phenyl-1-propanol was obtained in high enantiomeric excesses (entries 1–3).

Table 3. Enantioselective addition of diethylzinc to aldehydes catalyzed by fluorous aminoalcohol



Entry	R	Yield (%)[a]	% ee[b]	Config.[c]
1	Ph	90	83	*R*(+)
2	2-MeO–C_6H_4–	95	78	*R*(+)
3	3-MeO–C_6H_4–	92	81	*R*(+)[d]
4	4-MeO–C_6H_4–	93	83	*R*(+)
5	4-Cl–C_6H_4–	93	84[e]	*R*(+)
6	1-Naphthyl	87	77	*R*(+)
7	2-Naphthyl	95	82	*R*(+)
8	(*E*)-PhCH=CH_2–	97	70[f]	*R*(+)
9	$PhCH_2CH_2$–	75	70	*R*(−)

[a] Isolated yield.
[b] Determined by HPLC analysis using DAICEL CHIRALCEL OD-H.
[c] Determined by comparison of specific rotation with literature value.
[d] Determined by comparison of retention time of HPLC with literature data.
[e] Determined by capillary GC analysis using SUPELCO β-DEX 120 chiral column.
[f] Determined by HPLC analysis using DAICEL CHIRALCEL OJ.

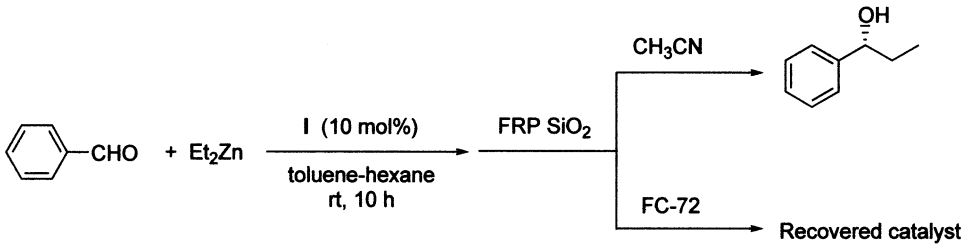
When the reactions were performed at 0°C, the enantioselectivities were slightly increased compared to those at room temperature. However, the reactions at 0°C were very slow to give the product alcohol in lower yield after 20 h (entries 1 vs 4 and entries 2 vs 5). The aminoalcohol **II** was also effective catalyst for the reaction and the enantioselectivity of product alcohol reached to 83% ee (entry 6). Since the aminoalcohol **III** was insoluble in toluene, the reaction was carried out in benzotrifluoride (BTF). The drastic decreases of the enantiomeric excess and chemical yield of the product alcohol were observed (entry 7). This behavior can be explained by a large steric hindrance around the amino group. Because of the bulkiness of the two fluorous substituents in **III**, complexation of the nitrogen atom with zinc atom may be seriously inhibited.

In these reactions, the product and fluorous ligands were simply and cleanly separated with FRP silica gel by washing successively with acetonitrile and FC-72. The product alcohol from acetonitrile eluate was purified by preparative TLC and the fluorous ligands were recovered from the FC-72 eluate almost quantitatively and in pure form.

Next, several other aldehydes were examined under the optimal reaction conditions using **I** and the results were summarized in Table 3. As seen from the table, **I** was generally effective to aromatic aldehydes (entries 1–7). However, *o*-substituted benzaldehydes underwent addition reaction with somewhat lower enantioselectivities compared to their *m*- and *p*-analogues (entries 2 vs 3 or 4 and entries 6 vs 7). In the cases of *trans*-cinnamaldehyde and 3-phenylpropanal, the reaction provided low enantioselectivities of the products (entries 8 and 9).

Finally, we tried to reuse the recovered fluorous β-aminoalcohol **I** for the next reaction without further purification. The results for 10 consecutive experiments were summarized in Table 4.

Table 4. Enantioselective addition of diethylzinc to benzaldehyde reusing the recovered catalyst without purification



Run	Yield[a]	% ee[b]	Recovered catalyst (%)[c]
1	85	82	99
2	90	82	100
3	90	82	98
4	89	83	97
5	88	83	95
6	89	83	98
7	90	84	97
8	91	84	97
9	90	84	97
10	91	84	97

[a] Isolated yield.
[b] Determined by HPLC analysis using DAICEL CHIRALCEL OD-H.
[c] Separation of organic and fluorous compounds by solid-phase extraction with FRP silica gel.

As seen from Table 4, the enantioselectivities and yields did not change throughout the experiments. Therefore, the fluorous β-aminoalcohol is recyclable for the reaction by the simple filtration through FRP silica gel.

In conclusion, we have synthesized a series of fluorous aminoalcohols which bear a novel perfluoroalkylated benzyl group at amino group of ephedrine or norphedrine. Aminoalcohols **I** and **II** were effective catalysts for the enantioselective addition of diethylzinc to aldehydes. Moreover, the fluorous ligands were easily recovered by solid–liquid extraction using FRP silica gel and were reusable without purification.

3. Experimental

3.1. General

The melting point was determined by Yanagimoto micro-melting point apparatus and was uncorrected. The IR spectra were recorded on a Perkin–Elmer 1720-X FT-IR spectrometer. The ^{1}H NMR spectra were obtained on a JEOL JNM-A400 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. The optical rotations were measured with a Perkin–Elmer 241 polarimeter. HPLC analysis was performed with Hitachi L-7100 flow system and L-7400 UV detector or JASCO CD-1595 CD detector using DAICEL CHIRALCEL OD-H or OJ column. GC analysis was carried out on Shimadzu GC-18APFsc gas chromatograph with SUPELCO β-DEX™ capillary column. Preparative TLC was run on Wakogel B-5F and column chromatography was performed using Wakogel C-300. Hexane and toluene were distilled from sodium. Benzotrifluoride was distilled from phosphorous pentoxide. The fluorous reverse phase silica gel was prepared by Curran's method.[7]

3.2. Synthesis of fluorous benzyl bromide

3.2.1. Tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)-methanol 1. To the Grignard reagent prepared from 1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoro-8-iodooctane (15.0 g, 31.7 mmol) and magnesium powder (984 mg, 40.5 mmol) in ether (25 mL) was added dimethylcarbonate (570 mg, 6.33 mmol). After refluxing for 2 h, the reaction mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with saturated NH_4Cl aqueous solution (20 mL), and then extracted with Et_2O (20 mL×3). The combined organic layer was washed with brine (30 mL), dried over anhydrous $MgSO_4$, and evaporated in vacuo. The residue was purified on a silica gel column (hexane/EtOAc=20:1) to afford alcohol **1** as a white solid (2.69 g, 40% yield): colorless prisms from $CHCl_3$, mp 56–57°C; IR (KBr) 3510, 2992, 1370, 1240, 1188, 1142, 702 cm^{-1}; ^{1}H NMR δ 1.26 (s, 1H, –O*H*), 1.75–1.90 (m, 6H, –CH_2C–), 2.05–2.15 (m, 6H, –CF_2CH_2–); MS (EI) *m/z* (relative intensity) 1050 (M^+−HF, 28), 1010 (75), 724 (M^++H–$CH_2CH_2C_6F_{13}$, 100), 673 (34), 375 (97), 327 (52), 77 (30); Anal. Calcd for $C_{25}H_{13}F_{39}O$: C, 28.05; H, 1.22; F, 69.23. Found C, 27.76; H, 1.33; F, 69.38.

3.2.2. 3- and 4-[Tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)methyl]toluene 2. A mixture of alcohol **1** (500 mg, 0.93 mmol) and trifluoromethanesulfonic acid (0.72 g, 6.6 mmol) in toluene (5 mL) was stirred at 120°C for 15 h. After addition of Et_2O (30 mL), the solution was washed with saturated $NaHCO_3$ aqueous solution (20 mL×3). The organic layer was dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude product was passed through a silica gel column (hexane) to afford fluorous toluene **2** as a colorless oil (495 mg, 93% yield). The product contained approximately 85% of *p*-isomer **2a** and 15% of *m*-isomer **2b** (determined by ^{1}H NMR): IR (KBr) 3033, 2963, 1515, 1240, 1147, 1122, 848, 813, 732,

708, 700, 655, 533 cm^{-1}; ^1H NMR for the major isomer **2a**: δ 1.70–1.95 (m, 6H, $-CH_2C-$), 1.95–2.10 (m, 6H, $-CF_2CH_2-$), 2.36 (s, 3H, Ar–CH_3), 7.15 (d, 2H, Ar–*H*, *J*=8.0 Hz), 7.21 (d, 2H, Ar–*H*, *J*=8.0 Hz); the minor isomer **2b**: 2.39 (s, Ar–CH_3); MS (EI) *m/z* (relative intensity) 1144 (M^+, 6), 1013 ($M^+-CF_2CF_3$, 1), 797 ($M^+-CH_2CH_2C_6F_{13}$), 437 (16), 169 (20), 119 (25), 69 (59); Anal. Calcd for $C_{32}H_{19}F_{39}$: C, 33.58; H, 1.67. Found C, 33.84; H, 1.78.

3.2.3. 3- and 4-[Tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)methyl]benzyl bromide 3. A mixture of toluene **2** (300 mg, 0.262 mmol), *N*-bromosuccinimide (47.0 mg, 0.262 mmol) and AIBN (4.3 mg, 0.026 mmol) in CCl_4 (3 mL) was refluxed for 1 h. The insoluble material was filtered off and the filtrate was concentrated in vacuo to give a syrup, which was purified on a silica gel column (hexane) to afford the fluorous benzyl bromide **3** as a colorless syrup (235 mg, 73% yield). The product contained approximately 20% and 80% of *m*- and *p*-isomers, respectively (determined by ^1H NMR): IR (KBr) 3037, 2964, 1475, 1366, 1351, 1319, 1240, 1146, 1058, 1010, 846, 813, 731, 708, 652, 618, 566, 532 cm^{-1}; ^1H NMR for the major isomer **3a**: δ 1.75–1.95 (m, 6H, $-CH_2C-$), 1.95–2.10 (m, 6H, $-CF_2CH_2-$), 4.495 (s, 2H, $-CH_2Br$), 7.27 (d, 2H, Ar–*H*, *J*=8.1 Hz), 7.45 (d, 2H, Ar–*H*, *J*=8.1 Hz); the minor isomer **3b**: 4.504 (s, $-CH_2Br$); MS (EI) *m/z* (relative intensity) 1123 (M^++H, 12), 1144 ($M^++H-{}^{79}Br$, 100), 875 ($M^+-CH_2CH_2C_6F_{13}$, 27), 796 (35), 463 (18), 169 (29), 119 (35), 69 (87); Anal. Calcd for $C_{32}H_{19}BrF_{39}$: C, 31.42; H, 1.48. Found C, 30.95; H, 1.25.

3.3. Synthesis of fluorous amino alcohols

3.3.1. (1*R*,2*S*)-*N*-[4-Tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)methyl]benzylephedrine I. A suspension of the benzyl bromide mixture **3** (500 mg, 0.409 mmol), (1*R*,2*S*)-ephedrine (67.5 mg, 0.409 mmol) and potassium carbonate (113 mg, 0.818 mmol) in THF (3 mL) was stirred vigorously at 70–80°C for 8 h. The suspension was filtered through a celite, the filtrate was concentrated in vacuo. The residue was purified on a silica gel column (hexane/Et_2O=10:1 then 4:1) to afford the fluorous ephedrine **I** as a colorless syrup (351 mg, 66% yield): $[\alpha]_D^{25}=-4.01°$ (*c* 1.12, BTF), $[\alpha]_{578}^{25}=-4.01°$ (*c* 1.12, BTF), $[\alpha]_{546}^{25}=-4.45°$ (*c* 1.12, BTF), $[\alpha]_{436}^{25}=-7.93°$ (*c* 1.12, BTF), $[\alpha]_{365}^{25}=-13.1°$ (*c* 1.12, BTF); IR (KBr) 3426, 3065, 3032, 2965, 2800, 1474, 1455, 1366, 1350, 1319, 1240, 1055, 1009, 812, 731, 702, 655, 532 cm^{-1}; ^1H NMR δ 1.02 (d, 3H, $-C-CH_3$, *J*=6.8 Hz), 1.70–1.90 (m, 7H, $-CH_2C-$, and $-OH$), 1.90–2.10 (m, 6H, $-CF_2CH_2-$), 2.19 (s, 3H, N–CH_3), 2.92 (dq, 1H, N–$CH-$, *J*=4.9 and 6.8 Hz), 3.59 (d, 1H, one proton of Ar–CH_2-, *J*=13.8 Hz), 3.64 (d, 1H, another proton of Ar–CH_2-, *J*=13.8 Hz), 4.89 (d, 1H, O–$CH-$, *J*=4.9 Hz), 7.18–7.33 (m, 9H, Ar–*H*); MS (EI) *m/z* (relative intensity) 1307 (M^+, 1), 1289 (M^+-H_2O, 2), 1200 (100), 106 (22), 77 (20); Anal. Calcd for $C_{42}H_{32}F_{39}NO$: C, 38.58; H, 2.47; N, 1.07. Found C, 38.30; H, 2.40; N, 1.23.

3.3.2. (1*R*,2*S*)-*N*-[4-Tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silyl]benzylephedrine II. Fluorous ephedrine **II** was prepared according to the procedure described above except that 4-[tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)silyl]benzyl bromide **4** (355 mg, 0.286 mmol) and (1*R*,2*S*)-ephedrine (47.3 mg, 0.286 mmol) were used. Purification of the crude product on a silica gel column (hexane/Et_2O=4:1) yielded ephedrine **II** as a colorless syrup (280 mg, 74% yield): $[\alpha]_D^{25}=-3.38°$ (*c* 1.04, BTF), $[\alpha]_{578}^{25}=-3.38°$ (*c* 1.04, BTF), $[\alpha]_{546}^{25}=-3.97°$ (*c* 1.04, BTF), $[\alpha]_{436}^{25}=-7.34°$ (*c* 1.04, BTF), $[\alpha]_{365}^{25}=-12.9°$ (*c* 1.04, BTF); IR (KBr) 3426, 3069, 3029, 2977, 2977, 2945, 2801, 1443, 1426, 1363, 1317, 1240, 1144, 1121, 1069, 1019, 899, 845, 812, 737, 707, 651, 531 cm^{-1}; ^1H NMR δ 1.03 (d, 3H, $-C-CH_3$, *J*=6.7 Hz), 1.10–1.26 (m, 7H, $-CH_2Si-$ and $-OH$), 1.95–2.10 (m, 6H, $-CF_2CH_2-$), 2.21 (s, 3H, N–CH_3), 2.93 (dq, 1H, N–$CH-$, *J*=5.1 and 6.7 Hz), 3.63 (s, 2H, Ar–CH_2-), 4.88 (d, 1H, O–$CH-$, *J*=5.1 Hz), 7.12–7.36 (m, 9H, Ar–*H*); MS (EI) *m/z* (relative intensity) 1323 (M^+, 1), 1305 (M^+-H_2O, 2), 1216 (100), 169 (13), 105 (17), 69 (37); Anal. Calcd for $C_{41}H_{32}F_{39}NOSi$: C, 37.20; H, 2.44; N, 1.06. Found C, 37.11; H, 2.36; N, 1.17.

3.3.3. (1*R*,2*S*)-*N*,*N*-bis[4-Tris(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)methyl]benzylnorephedrine III. A suspension of the benzyl bromide mixture **3** (405 mg, 0.331 mmol), (1*R*,2*S*)-norephedrine (25.0 mg, 0.165 mmol) and potassium carbonate (91 mg, 0.66 mmol) in THF (2 mL) was stirred vigorously at 70–80°C for 24 h. The suspension was filtered through a celite, the filtrate was concentrated in vacuo. The residue was purified on a silica gel column (hexane/Et_2O=10:1) to afford the fluorous norephedrine **III** as a colorless viscous syrup (223 mg, 55% yield): $[\alpha]_D^{25}=-11.1°$ (*c* 1.00, BTF), $[\alpha]_{578}^{25}=-11.4°$ (*c* 1.00, BTF), $[\alpha]_{546}^{25}=-13.2°$ (*c* 1.00, BTF), $[\alpha]_{436}^{25}=-24.6°$ (*c* 1.00, BTF), $[\alpha]_{365}^{25}=-44.2°$ (*c* 1.00, BTF); IR (KBr) 3420, 3064, 3033, 2964, 2830, 1474, 1366, 1142, 1061, 1009, 847, 813, 731, 707, 655, 566, 533 cm^{-1}; ^1H NMR δ 1.20 (d, 3H, $C-CH_3$, *J*=6.7 Hz), 1.70–2.10 (m, 25H, $-CF_2CH_2CH_2-$ and $-OH$), 3.00 (dq, 1H, N–$CH-$, *J*=6.1 and 6.7 Hz), 3.51 (d, 1H, one proton of Ar–CH_2-, *J*=14.2 Hz), 3.70 (d, 1H, another proton of Ar–CH_2-, *J*=14.2 Hz), 4.77 (d, 1H, O–$CH-$, *J*=6.1 Hz), 7.11–7.26 (m, 13H, Ar–*H*); MS (EI) *m/z* (relative intensity) 2417 (M^+-H_2O, 1), 2399 (3), 2312 (100), 797 (15), 77 (14); Anal. Calcd for $C_{73}H_{47}F_{78}NO$: C, 35.99; H, 1.94; N, 0.57. Found C, 35.39; H, 1.90; N, 0.84.

3.4. Typical procedure for the enantioselective addition of diethylzinc to aldehydes catalyzed by fluorous ephedrines

To a solution of fluorous ephedrine **I** (65.4 mg, 0.050 mmol) and benzaldehyde (53.0 mg, 0.50 mmol) in toluene (2 mL) was added 1 M Et_2Zn hexane solution (1.0 mL, 1.0 mmol) under argon at 0°C. After stirring for 20 h at room temperature, the reaction mixture was quenched with saturated NH_4Cl aqueous solution (6 mL) and extracted with Et_2O (15 mL×4). The combined organic layer was washed with brine (15 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was dissolved in Et_2O (2 mL). To the solution was added (1*H*,1*H*,2*H*,2*H*)-perfluorooctyl)-dimethylsilyl bound silica gel (1 g), then the solvent was evaporated to dryness. The powder obtained was loaded on a column of (1*H*,1*H*,2*H*,2*H*)-perfluorooctyl)dimethylsilyl bound silica gel (5 g) and then eluted successively with acetonitrile (15 mL) and FC-72 (25 mL). The

acetonitrile fraction was evaporated in vacuo, and purified by preparative TLC (hexane/EtOAc=4:1) to give 1-phenyl-1-propanol (61.4 mg, 90% yield) in 83% ee as colorless oil. $[\alpha]_D^{16}=+39.7°$ (*c* 0.456, $CHCl_3$) (lit. $[\alpha]_D=-47.6°$ (*c* 6.11, $CHCl_3$) for the (*S*)-enantiomer, 98% ee[8]). The absolute configuration was determined to be *R* by comparison of its optical rotation with the reported one. The enantioselectivity was determined by HPLC analysis using DAICEL CHIRALCEL OD-H (hexane/2-propanol=98:2, flow rate =1.0 mL/min). Fluorous aminoalcohol **I** was recovered almost quantitatively from FC-72 fraction without a loss of optical purity.

3.4.1. 1-(2-Methoxyphenyl)-1-propanol. $[\alpha]_D^{15}=+44.6°$ (*c* 0.451, toluene) for the product of 78% ee (lit. $[\alpha]_D=+27.3°$ (*c* 2, toluene) for the (*R*)-enantiomer, 62% ee[9]). The absolute configuration was determined to be *R* by comparison of its optical rotation with the reported one. The enantiomeric excess (ee) was determined by HPLC analysis using chiral column (DAICEL CHIRALCEL OD-H, hexane/2-propanol=100:1, flow rate=0.5 mL/min): t_R=38.5 min for (*S*)-enantiomer and t_R=40.6 min for (*R*)-enantiomer.

3.4.2. 1-(3-Methoxyphenyl)-1-propanol. $[\alpha]_D^{15}=+23.3°$ (*c* 0.498, benzene) for the product of 81% ee. The absolute configuration was determined to be *R* by comparison of its retention time of chiral HPLC with the reported one[10]. The ee was determined by HPLC analysis using chiral column (DAICEL CHIRALCEL OD-H, hexane/2-propanol=98:2, flow rate=1.0 mL/min): t_R=27.2 min for (*R*)-enantiomer and t_R=32.2 min for (*S*)-enantiomer.

3.4.3. 1-(4-Methoxyphenyl)-1-propanol. $[\alpha]_D^{15}=+28.5°$ (*c* 0.534, benzene) for the product of 83% ee (lit. $[\alpha]_D=-32.1°$ (*c* 1.25, benzene) for the (*S*)-enantiomer, 93% ee[8]). The absolute configuration was determined to be *R* by comparison of its optical rotation with the reported one. The ee was determined by HPLC analysis using chiral column (DAICEL CHIRALCEL OD-H, hexane/2-propanol=98:2, flow rate=1.0 mL/min): t_R=24.0 min for (*R*)-enantiomer and t_R=27.5 min for (*S*)-enantiomer.

3.4.4. 1-(4-Chlorophenyl)-1-propanol. $[\alpha]_D^{20}=+19.8°$ (*c* 0.479, benzene) for the product of 82% ee (lit. $[\alpha]_D=-23.5°$ (*c* 0.82, benzene) for the (*S*)-enantiomer, 93% ee[8]). The absolute configuration was determined to be *R* by comparison of its optical rotation with the reported one. The ee was determined by GC analysis using chiral capillary column (SUPELCO β-DEX 120, He=1.0 mL/min, DET=250°C, INJ=240°C, OVEN=110°C (1 min) to 170°C, 2°C/min, Split=100:1): t_R=30. 8 min for (*R*)-enantiomer and t_R=31.5 min for (*S*)-enantiomer.

3.4.5. 1-(1-Naphthyl)-1-propanol. $[\alpha]_D^{18}=+61.1°$ (*c* 0.442, benzene) for the product of 77% ee. (lit. $[\alpha]_D=+39.9°$ (*c* 2, $CHCl_3$) for the (*R*)-enantiomer, 79% ee[9]). The absolute configuration was determined to be *R* by comparison of its optical rotation with the reported one. The ee was determined by HPLC analysis using chiral column (DAICEL CHIRALCEL OD-H, hexane/2-propanol=95:5, flow rate= 1.0 mL/min): t_R=14.9 min for (*S*)-enantiomer and t_R= 26.8 min for (*R*)-enantiomer.

3.4.6. 1-(2-Naphthyl)-1-propanol. $[\alpha]_D^{18}=+17.4°$ (*c* 0.448, benzene) for the product of 82% ee. (lit. $[\alpha]_D=+22°$ (*c* 3, benzene) for the (*R*)-enantiomer, 83% ee[9]). The absolute configuration was determined to be *R* by comparison of its optical rotation with the reported one. The ee was determined by HPLC analysis using chiral column (DAICEL CHIRALCEL OD-H, hexane/2-propanol=95:5, flow rate= 1.0 mL/min): t_R=17.8 min for (*S*)-enantiomer and t_R= 20.4 min for (*R*)-enantiomer.

3.4.7. 1-Phenylpent-1-en-3-ol. $[\alpha]_D^{18}=+4.9°$ (*c* 0.45, $CHCl_3$) for the product of 70% ee. (lit. $[\alpha]_D^{23}=-6.6°$ (*c* 3.18, $CHCl_3$) for the (*S*)-enantiomer, 75% ee[11]). The absolute configuration was determined to be *R* by comparison of its optical rotation with the reported one. The ee was determined by HPLC analysis using chiral column (DAICEL CHIRALCEL OJ, hexane/2-propanol=98:2, flow rate=1.0 mL/min): t_R=24.5 min for (*S*)-enantiomer and t_R=27.3 min for (*R*)-enantiomer.

3.4.8. 1-Phenyl-3-pentanol. $[\alpha]_D^{18}=-17.7°$ (*c* 0.327, EtOH) for the product of 70% ee. (lit. $[\alpha]_D^{22}=+23.9°$ (*c* 1.44, $CHCl_3$) for the (*S*)-enantiomer, 90% ee[8]). The absolute configuration was determined to be *R* by comparison of its optical rotation with the reported one. HPLC analysis using chiral column (DAICEL CHIRALCEL OD-H, hexane/2-propanol=98:2, flow rate=1.0 mL/min): t_R=23.8 min for (*R*)-enantiomer and t_R=42.7 min for (*S*)-enantiomer.

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References

1. Reviews: (a) Shuttleworth, S. J.; Allin, S. M.; Wilson, R. D.; Nasturica, D. *Synthesis* **2000**, 1035–1074. (b) Pu, L. *Tetrahedron: Asymmetry* **1998**, *9*, 1457–1477. (c) Bolm, C.; Gerlach, A. *Eur. J. Org. Chem.* **1998**, 21–27.
2. Some examples of chiral polymer catalysts: (a) Sundararajan, G.; Prabagaran, N. *Org. Lett.* **2001**, *3*, 389–392. (b) Bolm, C.; Maischak, A. *Synlett* **2001**, 93–95. (c) Burguete, M. I.; Fraile, J. M.; García, J. I.; García-Verdugo, E.; Luis, S. V.; Mayoral, J. A. *Org. Lett.* **2000**, *2*, 3905–3908. (d) Reger, M. T. S.; Janda, K. D. *J. Am. Chem. Soc.* **2000**, *121*, 6929–6934. (e) Sato, I.; Shibata, T.; Ohtake, K.; Kodaka, R.; Hirokawa, Y.; Shirai, N.; Soai, K. *Tetrahedron Lett.* **2000**, *41*, 3123–3126. (f) Yu, H.-B.; Hu, Q.-S.; Pu, L. *Tetrahedron Lett.* **2000**, *41*, 1681–1685. (g) Nogami, H.; Matsunaga, S.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2000**, *42*, 279–283. (h) Fan, Q.-H.; Chen, Y.-M.; Chen, X.-M.; Jiang, D.-Z.; Xi, F.; Chan, A. S. C. *Chem. Commun.* **2000**, 789–790.

(i) ten Holte, P.; Wijgergangs, J.-P.; Thijs, L.; Zwanenburg, B. *Org. Lett.* **1999**, *1*, 1095–1097. (j) Hodge, P.; Sung, D. W. L.; Stratford, P. W. *J. Chem. Soc., Perkin Trans 1* **1999**, 2335–2342. (k) Sung, D. W. L.; Hodge, P.; Stratford, P. W. *J. Chem. Soc., Perkin 1* **1999**, 1463–1472. (l) Watanabe, M.; Soai, K. *J. Chem. Soc., Perkin Trans 1* **1994**, 837–842. (m) Soai, K.; Watanebe, M. *Tetrahedron: Asymmetry* **1991**, *2*, 97–100. (n) Soai, K.; Niwa, S.; Watanabe, M. *J. Chem. Soc., Perkin Trans 1* **1989**, 109–113. (o) Soai, K.; Niwa, S.; Watanabe, M. *J. Org. Chem.* **1988**, *53*, 927–928.

3. Reviews: (a) Kitazume, T. *J. Fluorine Chem.* **2000**, *105* (2), 265–278. (b) Fish, R. H. *Chem. Eur. J.* **1999**, *5*, 1677–1680. (c) Cavazzini, M.; Montanari, F.; Pozzi, G.; Quici, S. *J. Fluorine Chem.* **1999**, *94*, 183–193. (d) de Wolf, E.; van Koten, G.; Deelman, B.-J. *Chem. Soc. Rev.* **1999**, *28*, 37–41. (e) Horváth, I. T. *Acc. Chem. Res.* **1998**, *31*, 641–650. (f) Curran, D. P. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1174–1196.
4. Recent examples: (a) Mikami, K.; Mikami, Y.; Matsumoto, Y.; Nishikido, J.; Yamamoto, F.; Nakajima, H. *Tetrahedron Lett.* **2001**, *42*, 289–292. (b) Schneider, S.; Bannwarth, W. *Angew. Chem. Int. Ed. Engl.* **2000**, *39*, 4142–4145. (c) Chen, W.; Xu, L.; Xiao *J. Chem. Commun.* **2000**, 839–840. (d) Zhang, O.; Luo, Z.; Dennis, P.; Curran, D. P. *J. Org. Chem.* **2000**, *65*, 8866–8873. (e) de Wolf, E.; Richter, B.; Deelman, B.-J.; van Koten, G. *J. Org. Chem.* **2000**, *65*, 5424–5427. (f) Chen, W.; Xu, L.; Xiao, J. *Org. Lett.* **2000**, *2*, 2675–2677. (g) Maillard, D.; Nguefack, C.; Pozzi, G.; Quici, S.; Valadé, B.; Sinou, D. *Tetrahedron: Asymmetry* **2000**, *14*, 2881–2884. (h) Richter, B.; de Wolf, E.; van Koten, G.; Deelman, B.-J. *J. Org. Chem.* **2000**, *65*, 3885–3893. (i) Barrett, A. G. M.; Braddock, D. C.; Catterick, D.; Chadwick, D.; Henschke, J. P.; McKinnell, R. M. *Synlett* **2000**, 847–849. (j) Betzemeier, B.; Cavazzini, M.; Quici, S.; Knochel, P. *Tetrahedron Lett.* **2000**, *41*, 4343–4346. (k) Meseguer, M.; Moreno-Mañas, M.; Vallribera, A. *Tetrahedron Lett.* **2000**, *41*, 4093–4095. (l) Chen, W.; Xiao, J. *Tetrahedron Lett.* **2000**, *41*, 3697–3700. (m) David, M.; Haddleton, D. M.; Stuart, G.; Jackson, S. G.; Bon, S. A. F. *J. Am. Chem. Soc.* **2000**, *122*, 1542–1543. (n) Chechik, V.; Crookes, R. M. *J. Am. Chem. Soc.* **2000**, *122*, 1243–1244. (o) Bhattacharyya, P.; Croxtall, B.; Fawcett, J.; Fawcett, J.; Gudmunsen, D.; Hope, E. G.; Kemmitt, R. D. W.; Paige, D. R.; Russell, D. R.; Stuart, A. M.; Wood, D. R. W. *J. Fluorine Chem.* **2000**, *101*, 247–255.
5. (a) Tian, Y.; Chan, K. S. *Tetrahedron Lett.* **2000**, *41*, 8813–8816. (b) Cavazzini, M.; Manfredi, A.; Montanari, F.; Quici, S.; Pozzi, G. *Chem. Commun.* **2000**, 2171–2172. (c) Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Curran, D. P. *Tetrahedron* **2000**, *56*, 351–355. (d) Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Curran, D. P. *Tetrahedron Lett.* **2000**, *41*, 57–61. (e) Pozzi, G.; Cavazzini, M.; Cinato, F.; Montanari, F.; Quici, S. *Eur. J. Org. Chem.* **1999**, 1947–1955. (f) Kleijn, H.; Rijnberg, E.; Johann, T. B. H.; Jastrzebski, J. T. B. H.; van Koten, G. *Org. Lett.* **1999**, *1*, 853–855. (g) Takeuchi, S.; Nakamura, Y.; Ohgo, Y.; Curran, D. P. *Tetrahedron Lett.* **1998**, *39*, 8691–8694. (h) Pozzi, G.; Cinato, F.; Montanari, F.; Quici, S. *Chem. Commun.* **1998**, 877–878.
6. Curran, D. P.; Ferritto, R.; Hua, Y. *Tetrahedron Lett.* **1998**, *39*, 4937–4940.
7. (a) Kainz, S.; Luo, Z.; Curran, D. P.; Leitner, W. *Synthesis* **1998**, 1425–1427. (b) Curran, D. P.; Hadida, S.; He, M. *J. Org. Chem.* **1997**, *62*, 6714–6715.
8. Kitamura, M.; Suga, S.; Kawai, K.; Noyori, R. *J. Am. Chem. Soc.* **1986**, *108*, 6072–6072.
9. Vyskočil, S.; Jaracz, S.; Smrčina, M.; Štícha, M.; Hanuš, V.; Polášek, M.; Kočovský, P. *J. Org. Chem.* **1998**, *63*, 7727–7737.
10. Dai, W.-M.; Zhu, H.-J.; Hao, X.-J. *Tetrahedron: Asymmetry* **2000**, *11*, 2315–2337.
11. Sato, T.; Gotoh, Y.; Wakabayashi, Y.; Fujisawa, T. *Tetrahedron Lett.* **1983**, *24*, 4123–4126.