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Asymmetric synthesis of optically active fluorine-containing alcohols by the catalytic enantioselective alkylation of aldehydes

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Abstract

Optically active fluorine-containing alcohols with up to 97% enantiomeric excess were synthesized by the enantioselective addition of dialkylzincs to fluorine-containing aldehydes using chiral β-aminoalcohol catalysts such as *N*,*N*-dibutylnorephedrine (DBNE, **2d**), 2-morpholino-1-phenyl-1-propanol (**2g**, MOPEP) and diphenyl(1-methylpyrrolidin-2-yl)methanol (**3**, DPMPM). © 1997 Elsevier Science S.A.

Keywords: Asymmetric synthesis; Catalytic enantioselective alkylation; Aldehydes

1. Introduction

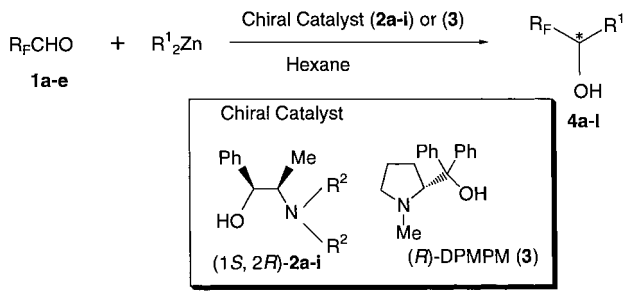
Optically active fluorine-containing organic compounds have wide applications in material and biological sciences [1]. Concerning the enantioselective synthesis of optically active fluorine-containing alcohols, only a few methods such as asymmetric reduction of ketones [2,3], ene reactions [4] and biological methods [5] have been reported.

However, catalytic enantioselective addition of dialkylzincs to aldehydes affords optically active *sec*-alcohols [6]. We have reported highly enantioselective addition of dialkylzincs to aldehydes using chiral catalysts, namely chiral *N*,*N*-dialkylnorephedrines [7], pyrrolidinylmethanol derivatives [8], piperazines [9], ammonium salts [10] and polymer-attached (or silica gel-attached [11]) aminoalcohols [12,13].

We here report asymmetric synthesis of optically active fluorine-containing *sec*-alcohols by the enantioselective addition of dialkylzincs to fluorine-containing aldehydes using chiral catalysts [14].

2. Results and discussion

In the first place, the effect of reaction temperature was examined in the enantioselective addition of diisopropylzinc to pentafluorobenzaldehyde (**1a**) in hexane in the presence of (1*S*,2*R*)-*N*,*N*-dibutylnorephedrine (**2d**, DBNE) (20 mol%). The results are shown in Table 1. The alcohol (*S*)-**4a** with high (84%–92%) e.e. was obtained from the reactions run at −20 °C to 50 °C.



The highest enantioselectivity (92% e.e.) was observed when the reaction was run at room temperature (entry 3). The absolute configuration of **4a** was determined to be *S* by estimation of the ^{1}H NMR analysis against the corresponding α-methoxy-α-(trifluoromethyl)phenylacetic acid ester [15].

In the presence of various chiral *N*,*N*-dialkylnorephedrines (**2a**–**2i**) (20 mol%), enantioselective addition of diisopropylzinc to aldehyde **1a** afforded (*S*)-**4a**. The results are shown in Table 2. Alkyl substituents on the nitrogen atom of **2** influence the enantioselectivity of **2**; methylephedrine (**2a**) gave **4a** with only 73% e.e. (entry 1), *N*,*N*-diethylnorephedrine (**2b**) gave **4a** with 93% e.e. (entry 2). The e.e. of **4a** was almost constant (91%–92% e.e.) when *N*,*N*-dipropylnorephedrine (**2c**) and DBNE (**2d**) were employed as chiral

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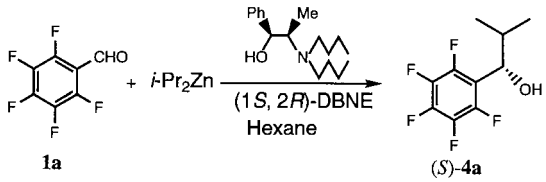
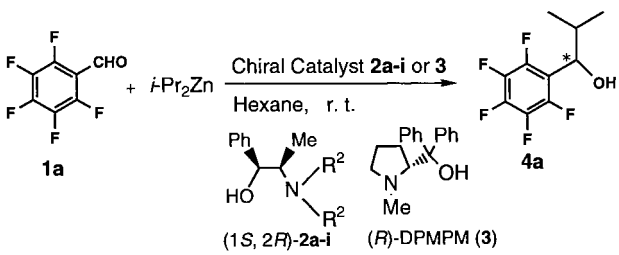
Table 1
Effect of reaction temperature on the enantioselective addition of diisopropylzinc to pentafluorobenzaldehyde using (1*S*,2*R*)-DBNE as chiral catalyst



Entry [a]	Temperature (°C)	Time (h)	Yield (%)	E.e. (%) [b,c]
1	−20	13	43	84
2	0	9.5	57	86
3	r.t.	4	72	92
4	50	0.5	65	89

[a] Molar ratio **1a**:*i*-Pr_2Zn:DBNE = 1:3:0.2.
[b] Determined by HPLC analysis using a chiral column.
[c] Configuration was determined by the estimation of ^1H NMR spectra of the corresponding α-methoxy-α-(trifluoromethyl)phenylacetic acid ester [15].

Table 2
Effect of the substituents of chiral catalysts in the enantioselective addition of diisopropylzinc to pentafluorobenzaldehyde



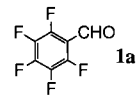
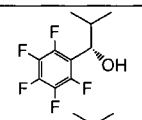
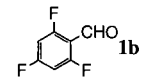
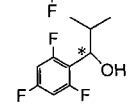
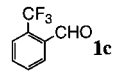
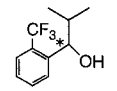
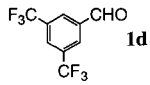
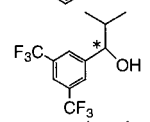
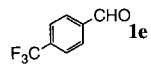
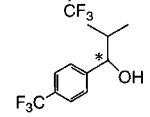
Entry [a]	Chiral catalyst (R^2 of **2**)	Time (h)	Yield (%)	E.e. (%) [b]
1	Me (**2a**)	5.5	50	73 (*S*)
2	Et (**2b**)	2	62	93 (*S*)
3	*n*-Pr (**2c**)	4	72	91 (*S*)
4	*n*-Bu (DBNE, **2d**)	4	72	92 (*S*)
5	*n*-Pentyl (**2e**)	3.5	56	86 (*S*)
6	Allyl (**2f**)	5.5	59	82 (*S*)
7	$-(CH_2)_2O(CH_2)_2-$ (MOPEP, **2g**)	3	69	97 (*S*)
8	$-(CH_2)_4-$ (**2h**)	3	56	93 (*S*)
9	$-(CH_2)_5-$ (**2i**)	3	69	91 (*S*)
10	(*R*)-DPMPM (**3**)[c]	3	37	42 (*R*)

[a] Molar ratio. **1a**:*i*-Pr_2Zn:**2a**–**2i** or **3** = 1:3:0.2.
[b] Determined by HPLC analysis using a chiral column.
[c] Lithium alkoxide of **3** was used.

catalysts (entries 3 and 4). The longer substituents on the nitrogen atom, i.e. *n*-pentyl groups on **2e**, decreased the e.e. of **4a** (86% e.e.) (entry 5).

As to the chiral catalysts with the cyclic substituents on the nitrogen atom, (1*S*,2*R*)-2-morpholino-1-phenyl-1-propanol (**2g**, MOPEP) with a morpholine ring gave **4a** with the highest e.e. (97% e.e., entry 7). Chiral catalysts possessing pyrrolidine (**2h**) and piperidine (**2i**) rings afforded (*S*)-**4a** with 93% and 91% e.e., respectively (entries 8 and 9). However, chiral catalyst (*R*)-diphenyl(1-methylpyrrolidin-2-yl)methanol (**3**, DPMPM) as the lithium alkoxide gave (*R*)-**4a** with only low e.e. (entry 10).

Table 3
Catalytic asymmetric synthesis of fluorine-containing alcohols (**4a**–**4d**) by the enantioselective addition of diisopropylzinc to fluorine-containing aldehydes (**1a**–**1e**)

Entry[a]	Aldehyde (**1**)	Time(h)	**4**[b]		Yield(%)	E.e.(%)[c]
1	 **1a**	3		**4a**	69	97
2	 **1b**	4.5		**4b**	80	93
3	 **1c**	0.5		**4c**	4	96
4	 **1d**	1		**4d**	81	94
5	 **1e**	1		**4e**	77	97

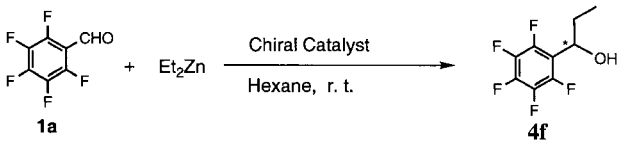
[a] Molar ratio **1a**–**1e**:*i*-Pr_2Zn:chiral catalyst = 1:3:0.2. The reactions were run at room temperature in hexane. Chiral catalysts were (1*S*,2*R*)-MOPEP (for entry 1) and (1*S*,2*R*)-DBNE (for entries 2–5).
[b] For **4a**, the configuration was determined by the estimation of ^1H NMR spectra of the corresponding α-methoxy-α-(trifluoromethyl)phenylacetic acid ester [15].
[c] Determined by HPLC analysis using chiral column.

The results of the enantioselective addition of diisopropylzinc to various fluorine-containing aldehydes (**1a**–**1e**) is shown in Table 3. The corresponding optically active fluorine-containing alcohols (**4a**–**4e**) with the isopropyl substituent are obtained in 93%–97% e.e. Both aldehyde **1a** and 2,4,6-trifluorobenzaldehyde (**1b**) gave **4a** and **4b** with 93% and 97% e.e. in 69% and 80% yield (entries 1 and 2). Although 2-trifluoromethylbenzaldehyde (**1c**) gave **4c** with high e.e. (96% e.e.), the yield was low (entry 3). This is attributed to the steric bulkiness of both diisopropylzinc and the trifluoromethyl group at the *ortho* position in aldehyde **1c**. However, 3,5-bis(trifluoromethyl)benzaldehyde (**1d**) and 4-trifluoromethylbenzaldehyde (**1e**) gave **4d** and **4e** with high e.e. (94% e.e. and 97% e.e. respectively) in 77%–81% (entries 4 and 5).

The enantioselective ethylation of aldehyde **1a** with diethylzinc was examined. As shown in Table 4, chiral catalyst (1*S*,2*R*)-DBNE (**2d**) gave (*S*)-**4a** with 96% e.e. in 83% (entry 1). In enantioselective ethylation, different from isopropylation, (*R*)-DPMPM (**3**) as lithium alkoxide is also an effective chiral catalyst to afford (*R*)-**4a** (the opposite enantiomer to that obtained by using (1*S*,2*R*)-DBNE) with 96% e.e. in 82% (entry 2).

Diethylzinc reacted with various fluorine-containing alcohols (**1a**–**1e**) in hexane at room temperature in the presence

Table 4
Enantioselective addition of diethylzinc to pentafluorobenzaldehyde using chiral catalyst

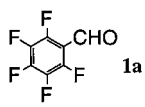
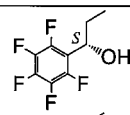
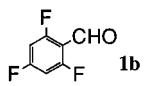
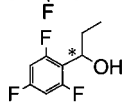
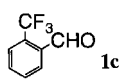
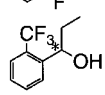
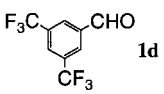
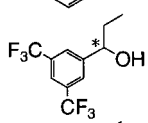
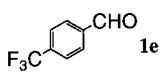
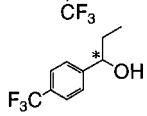


1a 4f

Entry [a]	Chiral catalyst	Time (h)	Alcohol **4f**	
			Yield (%)	E.e. (%) [b]
1	(1*S*,2*R*)-DBNE (**2d**)	3	83	96 (*S*)
2	(*R*)-DPMPM (**3**) [c]	2	82	96 (*R*)

[a] Molar ratio **1a**:Et_2Zn:chiral catalyst = 1:3:0.2.
[b] Determined by HPLC analysis using a chiral column. Configuration was determined by the estimation of ^1H NMR spectra of the corresponding α-methoxy-α-(trifluoromethyl)phenylacetic acid ester [15].
[c] Lithium alkoxide of DPMPM was used.

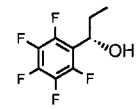
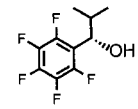
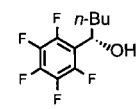
Table 5
Catalytic enantioselective addition of diethylzinc to fluorine-containing aldehydes (**1a**–**1d**) using (1*S*,2*R*)-DBNE as chiral catalyst

Entry[a]	Aldehyde	Time(h)	4[b]		Yield (%)	E.e. (%)[c]
1	 **1a**	3		**4f**	83	96
2	 **1b**	6.5		**4g**	88	92
3	 **1c**	1.5		**4h**	55	89
4	 **1d**	1.5		**4i**	83	90
5	 **1e**	0.5		**4j**	91	91

[a] Molar ratio **1a**–**1e**:Et_2Zn:DBNE = 1:3:0.2. The reactions were run at room temperature in hexane.
[b] For **4f**, the configuration was determined by the estimation of ^1H NMR spectra of the corresponding α-methoxy-α-(trifluoromethyl)phenylacetic acid ester [15].
[c] Determined by HPLC analysis using chiral column.

of a catalytic amount of (1*S*,2*R*)-DBNE (**2d**). The results are listed in Table 5. In all cases, optically active fluorine-containing alcohols with high e.e. (89%–96% e.e.) were obtained. Enantioselective ethylation of aldehyde **1c** gave **4h** with 89% e.e. in higher yield (Table 5, entry 3) than that of isopropylation (Table 3, entry 3). The difference between bulkiness of the ethyl and isopropyl groups of dialkylzincs varies the reactivity of dialkylzinc to 2-trifluoromethylbenzaldehyde (**1c**). Enantioselective ethylations of fluorine-containing aldehydes (**1a, 1b, 1d** and 1**e**) proceeded in high yields (83%–91%).

Table 6
Asymmetric synthesis of fluorine-containing alcohols by the enantioselective addition of various dialkylzincs to pentafluorobenzaldehyde (**1a**) using (1*S*,2*R*)-DBNE as chiral catalyst

Entry[a]	$R^1{}_2Zn$	Time (h)	Alcohol (*S*)-(**4**)[b]		Yield (%)	E.e.(%)[c]
1	Me	30		**4k**	80	78
2	Et	3		**4f**	83	96
3	*i*-Pr	4		**4a**	72	92
4	*n*-Bu	22		**4l**	51	89

[a] Molar ratio **1a**:$R^1{}_2Zn$:DBNE = 1:3:0.2. The reactions were run at room temperature in hexane.
[b] Configuration was determined by the estimation of ^1H NMR spectra of the corresponding α-methoxy-α-(trifluoromethyl)phenylacetic acid ester [15].
[c] Determined by HPLC analysis using chiral column.

The generality of the structure of dialkylzincs in the enantioselective addition to aldehyde **1a** using (1*S*,2*R*)-DBNE as chiral catalyst is exemplified by the addition of dimethyl-, diethyl-, diisopropyl- and di-(*n*-butyl)zincs. As shown in Table 6, the reaction rate of diethyl- (entry 2) and diisopropylzinc (entry 3) were faster than those of dimethyl- (entry 1) and di-(*n*-butyl)zinc (entry 4). All reactions of **1a** with various dialkylzincs afford optically active fluorine-containing alcohols with good to high (78%–96%) e.e.

As described, enantioselective addition of dialkylzincs to fluorine-containing aldehydes using chiral catalysts is an efficient method for the synthesis of fluorine-containing optically active *sec*-alcohols with high e.e.

3. Experimental details

*3.1. General procedure for the enantioselective addition of dialkylzincs to aldehydes using N,N-dialkylnorephedrines (**2a–2i**) as chiral catalysts*

To a solution of chiral catalyst (0.2 mmol) in hexane 3 ml, hexane solution of dialkylzinc (1 M, 3.0 mmol, 3.0 ml) was added at 0 °C. After 15 min, aldehyde (1 mmol) was added to the solution at 0 °C. The reaction mixture was stirred for 15 min at 0 °C then stirred at room temperature for 3–30 h. The reaction was quenched by adding 1 M HCl (15 ml), then extracted with CH_2Cl_2 and dried (Na_2SO_4). The extract was filtered and the filtrate was evaporated under reduced

pressure. Purification of the residue by TLC (thin layer chromatography) afforded fluorine-containing alcohols.

*3.2. General procedure for the enantioselective addition of dialkylzincs to aldehyde (**1a**) using DPMPM as a chiral catalyst (Table 2, entry 10 and Table 4, entry 2)*

To a solution of (*R*)-(+)-DPMPM (0.1 mmol, 0.027 g) in hexane 3 ml, *n*-BuLi (1.6 M hexane solution, 0.1 mmol) was added at 0 °C then hexane solution of dialkylzinc (1 M, 3.0 mmol, 3.0 ml) was added at 0 °C. After 15 min, aldehyde **1a** (1 mmol) was added to the solution at 0 °C. The reaction mixture was stirred for 15 min at 0 °C then stirring was continued at room temperature for 2–3 h. The reaction was quenched by adding 1 M HCl (15 ml), then extracted with CH_2Cl_2 and dried (Na_2SO_4). The extract was filtered and the filtrate was evaporated under reduced pressure. Purification of the residue by TLC (thin layer chromatography) afforded optically active alcohols.

(*S*)-1-Pentafluorophenyl-2-methylpropan-1-ol **4a**. ^{1}H NMR ($CDCl_3$) δ 0.80 (d, J=6.8 Hz, 3H, CH_3), 1.15 (d, J=6.8 Hz, 3H, CH_3), 2.13 (dqq, J=9.2, 6.8, 6.8 Hz, 1H, CH), 2.20 (bs, 1H, OH), 4.63 (d, J=9.2 Hz, 1H, CH); IR (KBr) (cm^{-1}) 3361.3; HRMS calculated for $C_{10}H_9F_5O$ 240.0574, found 240.0571; $[\alpha]_D^{28}$=+4.0 (*c* 1.51, pentane), 97% e.e. (by HPLC analysis, Sumichiral OA-4900, eluent 0.5% 2-propanol in hexane, flow rate 1.0 ml min^{-1}, room temperature, retention time (min) major 13.7, minor 12.9); m.p. 44.1 °C.

1-(2,4,6-Trifluorophenyl)-2-methylpropan-1-ol **4b**. ^{1}H NMR ($CDCl_3$) δ 0.76 (d, J=6.6 Hz, 3H, CH_3), 1.12 (d, J=6.6 Hz, 3H, CH_3), 2.12 (dqq, J=9.2, 6.6, 6.6 Hz, 1H, CH), 2.40 (s, 1H, OH), 4.55 (d, J=9.2 Hz, 1H), 6.58–6.71 (m, 2H); IR (neat) (cm^{-1}) 3401.8; HRMS calculated for $C_{10}H_{11}F_3O$ 204.0762, found 204.0761; $[\alpha]_D^{30}$=−1.2 (*c* 1.24, MeOH), 93% e.e. (by HPLC analysis, Chiralcel OD, eluent 1.0% 2-propanol in hexane, flow rate 0.3 ml min^{-1}, room temperature, retention time (min) major 30.2, minor 32.9).

1-(2-Trifluoromethylphenyl)-2-methylpropan-1-ol **4c**. ^{1}H NMR ($CDCl_3$) δ 0.76 (d, J=6.6 Hz, 3H, CH_3), 1.11 (d, J=6.6 Hz, 3H, CH_3), 1.95 (s, 1H, OH), 2.04 (dqq, J=7.6, 6.6, 6.6 Hz, 1H, CH), 4.75 (d, J=7.6 Hz, 1H, CH), 7.38 (dd, J=7.5, 7.5 Hz, 1H, ph-CH), 7.55–7.65 (m, 2H, 2ph-CH), 7.72 (d, J=7.5 Hz, 1H, ph-CH); IR (neat) (cm^{-1}) 3423.0; HRMS calculated for $C_{11}H_{13}F_3O$ 218.0919, found 218.0906; 96% e.e. (by HPLC analysis, Chiralpak AD, eluent 0.5% 2-propanol in hexane, flow rate 1.0 ml min^{-1}, room temperature, retention time (min) major 18.1, minor 15.6).

1-[3,5-Bis(trifluoromethyl)phenyl]-2-methylpropan-1-ol **4d**. ^{1}H NMR ($CDCl_3$) δ 0.89 (d, J=6.8 Hz, 3H, CH_3), 0.95 (d, J=6.8 Hz, 3H, CH_3), 1.99 (dqq, J=5.9, 6.8, 6.8 Hz, 1H, CH), 2.00 (bs, 1H, OH), 4.59 (d, J=5.9 Hz, 1H, CH), 7.78 (s, 3H, 3ph-CH); IR (KBr) (cm^{-1}) 3388.3; HRMS calculated for $C_{12}H_{12}F_6O$ 286.0793, found 286.0798; $[\alpha]_D^{32}$=−20.5 (*c* 1.35, MeOH), 94% e.e. (by HPLC analysis, Chiralcel OF, eluent 0.5% 2-propanol in hexane, flow rate 0.2 ml min^{-1}, room temperature, retention time (min) major 27.4, minor 31.2); m.p. 73.8 °C.

1-(4-Trifluoromethylphenyl)-2-methylpropan-1-ol **4e**. ^{1}H NMR ($CDCl_3$) δ 0.83 (d, J=6.8 Hz, 3H, CH_3), 0.96 (d, J=6.8 Hz, 3H, CH_3), 1.90 (bs, 1H, OH), 1.96 (dqq, J=6.3, 6.8, 6.8 Hz, 1H, CH), 4.46 (d, J=6.3 Hz, 1H, CH), 7.42 (d, J=8.3 Hz, 2H, 2ph-CH), 7.59 (d, J=8.3 Hz, 2H, 2ph-CH); IR (neat) (cm^{-1}) 3371.0; HRMS calculated for $C_{11}H_{13}F_3O$ 218.0919, found 218.0915; $[\alpha]_D^{30}$=−20.3 (*c* 1.10, MeOH), 97% e.e. (by HPLC analysis, Chiralcel OJ, eluent 0.5% 2-propanol in hexane, flow rate 0.2 ml min^{-1}, room temperature, retention time (min) major 125.2, minor 141.1].

(*S*)-1-Pentafluorophenylpropan-1-ol **4f**. ^{1}H NMR ($CDCl_3$) δ 0.97 (t, J=7.4 Hz, 3H, CH_3), 1.86 (dq, J=7.3, 7.4 Hz, 1H, 1/2CH_2), 2.05 (dq, J=7.3, 7.4 Hz, 1H, 1/2CH_2), 2.18 (bs, 1H, OH), 4.97 (dd, J=7.3, 7.3 Hz, 1H, CH); IR (KBr) (cm^{-1}) 3365.2; HRMS calculated for $C_9H_7F_5O$ 226.0417, found 226.0417; $[\alpha]_D^{31}$=+3.0 (*c* 2.01, pentane), 96% e.e. (by HPLC analysis, Sumichiral OA-4900, eluent 0.5% 2-propanol in hexane, flow rate 1.0 ml min^{-1}, room temperature, retention time (min) major 18.8, minor 17.5); m.p. 38.5 °C.

1-(2,4,6-Trifluorophenyl)propan-1-ol **4g**. ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J=7.4 Hz, 3H, CH_3), 1.82 (ddq, J=0.88, 7.4, 7.4 Hz, 1H, 1/2CH_2), 1.98 (ddq, J=0.88, 7.4, 7.4 Hz, 1H, 1/2CH_2), 2.44 (s, 1H, OH), 4.89 (dd, J=7.4, 7.4 Hz, 1H, CH), 6.58–6.71 (m, 2ph-CH); IR (neat) (cm^{-1}) 3371.0; HRMS calculated for $C_9H_9F_3O$ 190.0606, found 190.0587; $[\alpha]_D^{28}$=−1.0 (*c* 3.11, MeOH), 92% e.e. (by HPLC analysis, Chiralcel OD, eluent 1.0% 2-propanol in hexane, flow rate 0.3 ml min^{-1}, room temperature, retention time (min) major 39.7, minor 43.6).

1-(2-Trifluoromethylphenyl)propan-1-ol **4h**. ^{1}H NMR ($CDCl_3$) δ 0.98 (t, J=7.4 Hz, 3H, CH_3), 1.76 (dq, J=6.4, 7.4 Hz, 2H, CH_2), 2.09 (s, 1H, OH), 5.02 (t, J=6.4 Hz, 1H, CH), 7.36 (dd, J=7.7, 7.7 Hz, 1H, ph-CH), 7.54–7.63 (m, 2H, 2ph-CH), 7.75 (d, J=7.7 Hz, 1H, ph-CH); IR (neat) (cm^{-1}) 3392.2; HRMS calculated for $C_{10}H_{11}F_3O$ 204.0762, found 204.9757; $[\alpha]_D^{25}$=−31.0 (*c* 2.48, MeOH), 89% e.e. (by HPLC analysis, Chiralpak AS, eluent 0.25% 2-propanol in hexane, flow rate 0.5 ml min^{-1}, room temperature, retention time (min) major 26.4, minor 24.7).

1-[3,5-Bis(trifluoromethyl)phenyl]propan-1-ol **4i**. ^{1}H NMR ($CDCl_3$) δ 0.97 (t, J=7.4 Hz, 3H, CH_3), 1.81 (dq, J=6.4, 7.4 Hz, 2H, CH_2), 2.07 (bs, 1H, OH), 4.78 (t, J=6.4 Hz, 1H, CH), 7.79 (s, 1H, ph-CH), 7.81 (s, 2H, 2ph-CH); IR (KBr) (cm^{-1}) 3222.5; HRMS calculated for $C_{11}H_{10}F_6O$ 272.0636, found 272.0635; $[\alpha]_D^{32}$=−21.5 (*c* 1.51, MeOH), 90% e.e. (by HPLC analysis, Chiralcel OD, eluent 0.5% 2-propanol in hexane, flow rate 0.5 ml min^{-1}, room temperature, retention time (min) major 40.0, minor 44.6); m.p. 91.5 °C.

1-(4-Trifluoromethylphenyl)propan-1-ol **4j**. ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J=7.4 Hz, 3H, CH_3), 1.66–1.78 (m, 2H, CH_2), 2.77 (s, 1H, OH), 4.59 (t, J=6.6 Hz, 1H, CH), 7.39

(d, $J=8.2$ Hz, 2H, 2ph-CH), 7.57 (d, $J=8.2$ Hz, 2H, 2ph-CH); IR (neat) (cm^{-1}) 3365.2; HRMS calculated for $C_{10}H_{11}F_3O$ 204.0762, found 204.0741; $[\alpha]_D^{28}=-23.9$ (c 2.75, MeOH), 91% e.e. (by HPLC analysis, Chiralcel OJ, eluent 0.5% 2-propanol in hexane, flow rate 0.2 ml min^{-1}, room temperature, retention time (min) major 135.0, minor 131.3).

(S)-1-Pentafluorophenylethan-1-ol **4k** [3]. ^1H NMR ($CDCl_3$) δ 1.65 (d, $J=6.7$ Hz, 3H, CH_3), 2.29 (bs, 1H, OH), 5.26 (q, $J=6.7$ Hz, 1H, CH); IR (neat) (cm^{-1}) 3355.5; HRMS calculated for $C_8H_5F_5O$ 212.0261, found 212.0258; $[\alpha]_D^{30}=-8.1$ (c 4.83, pentane), 78% e.e. (by HPLC analysis, Sumichiral OA-4900, eluent 0.5% 2-propanol in hexane, flow rate 1.0 ml min^{-1}, room temperature, retention time (min) major 22.5, minor 21.2].

(S)-1-Pentafluorophenylpentan-1-ol **41**. ^1H NMR ($CDCl_3$) δ 0.91 (t, $J=6.6$ Hz, 3H, CH_3), 1.17–1.48 (m, 4H, $2CH_2$), 1.81 (dt, $J=7.3$, 7.3 Hz, 1H, $1/2CH_2$),2.00 (dt, $J=7.3$, 7.3 Hz, 1H, $1/2CH_2$), 2.19 (bs, 1H, OH), 5.04 (t, $J=7.3$ Hz, 1H, CH); IR (KBr) (cm^{-1}) 3274.5; HRMS calculated for $C_{11}H_{11}F_5O$ 254.0727, found 254.0736; $[\alpha]_D^{28}=+4.9$ (c 1.83, pentane), 89% e.e. (by HPLC analysis, Sumichiral OA-4900, eluent 0.5% 2-propanol in hexane, flow rate 1.0 ml min^{-1}, room temperature, retention time (min) major 16.5, minor 15.1); m.p. 51.4 °C.

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