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Improvement of the asymmetry-inducing ability of a trifluoromethylated amino alcohol by electron donation to a CF_3 group

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ABSTRACT

An improvement in the 'net asymmetric-inducing ability' of a trifluoromethylated amino alcohol ligand by influencing the CF_3 group with an electron donating 2-propyl group is reported.

1. Introduction

Recently, fluoroalkyl groups, including the trifluoromethyl (CF_3) group have been introduced to many chiral ligands, chiral auxiliaries, as well as chiral substrates to improve their asymmetry-inducing abilities in stereoselective reactions.[1] Many of these fluoroalkyl groups used strong electron withdrawing groups to adjust the properties of the reaction center, such as hydrogen bonding donor ability.[2] Sometimes, longer-chain fluoroalkyl groups were used as a 'fluorous tag' for controlling the solubilities of the catalysts and/or the compounds into fluorous media.[3] On the other hand, CF_3 groups were used, not only as a strong electron withdrawing group, but also as some 'bulky' substituents.[4]

A large 'steric' effect of the CF_3 group is well recognized.[5] The $-E_s$ value of the CF_3 group (=1.16) is bigger than those of the methyl (=0.00) or the *iso*-propyl (=0.47) groups, and is comparable to that of the *sec*-butyl group (=1.13).[6] This order of the steric effect is not consistent with the van der Waals volume of the groups (Me = 26.4 Å^3, ^{i}Pr = 64.7 Å^3, ^{s}Bu = 72.1 Å^3, and CF_3 = 35.8 Å^3).[7]

We have reported several stereoselective reactions using the large 'steric' effects of the CF_3 groups: an asymmetric ethylation of PhCHO by Et_2Zn;[8] an asymmetric Reformatsky reaction,[9] a chiral auxiliary promoted diastereoselective Simmons–Smith cyclopropanation,[10] and a diastereoselective intramolecular S_N2 cyclopropane construction.[11] We have recognized through our studies that the 'steric' effect is not simply a size effect but results from electrostatic repulsions between the local negative charge on the CF_3 group and that of the nucleophiles as well.[3]

In our previous paper on the asymmetric Et_2Zn alkylation of PhCHO promoted by the trifluoromethylated amino alcohol **1**, the amino alcohol **1** promoted a higher aggregation of the organozinc species, which has a positive effect on the asymmetric induction,[8] that is, the use of a larger amount of the chiral amino alcohol ligand **1** (50 mol % vs PhCHO) is required for a good enantioselectivity of the product (up to 93% ee). The reaction with 2 mol % of the amino alcohol **1** resulted in moderate enantioselectivity of the product, 65% ee. This is a serious drawback of our trifluoromethylated amino alcohol ligand, which makes the process impractical. Moreover, it was suggested that the absolute configuration as well as enantioselectivity of the product in this reaction is correlated to the 'bulkiness' of the groups at the α-position of hydroxyl group of amino alcohols.[12] Thus, we need to make the 'steric' effect of the CF_3 group to be larger, somehow, for a better asymmetric-inducing ability.

Herein, we report a method to make the 'steric' effect of the CF_3 group to be larger by substitution of the α-hydrogen of the amino alcohol **1** by electron donating alkyl groups, such as methyl and 2-propyl groups, to increase the local charge on the CF_3 group.

2. Results and discussion

2.1. Preparation of fluorinated amino alcohols

The enantiomerically pure trifluoromethylated amino alcohols were prepared via the reactions illustrated in Schemes 1 and 2.

The preparation of amino alcohol **1** had been described in previous reports.[5f,13] The amino alcohols, **2** and **3** were prepared from the corresponding enantiomerically pure **6**[14] via an oxiranyl anion[15] (Scheme 2). These amino alcohols, **2** and **3**, needed no further optical purifications of neither intermediates or products. The optical purities of these amino alcohols **2** and **3** were confirmed identical to that of the starting epoxide **6** by HPLC analysis of their benzoyl esters (see Section 4).

2.2. Asymmetric Et_2Zn alkylation of PhCHO

Three enantiomerically pure amino alcohols, **1**–**3**, as well as non-fluorinated amino alcohols, **4** and **5**,[16] were subjected to the asymmetric Et_2Zn alkylation of PhCHO to evaluate their asymmetry-inducing abilities as the chiral ligands (Scheme 2). Effects of the relative concentrations of these ligands to the enantiomeric

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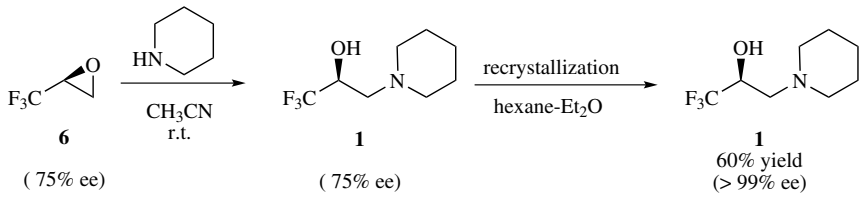
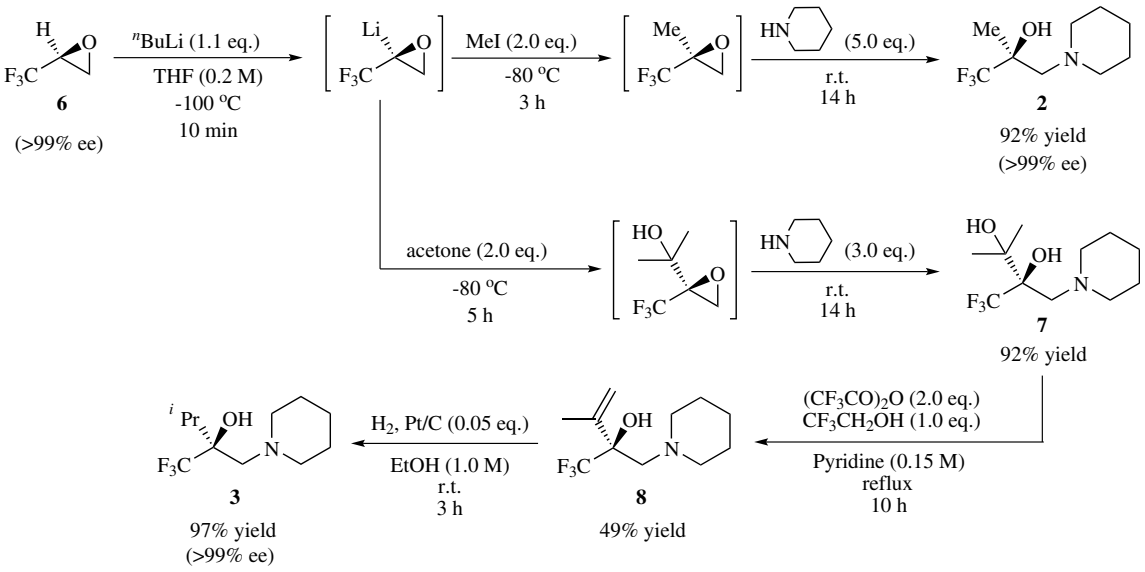
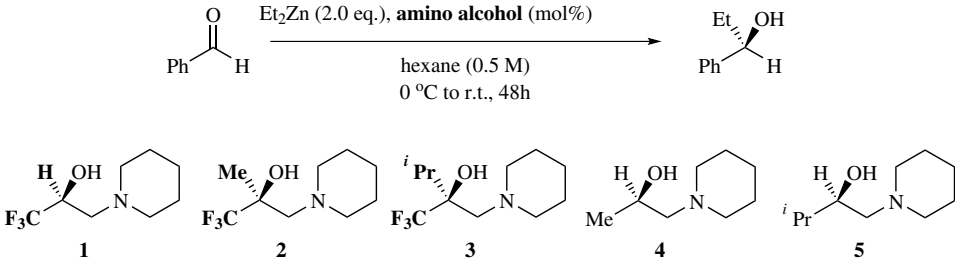


Scheme 1.



Scheme 2.



purities of the products are summarized in Figure 1. The results in Figure 1 are the average values of 3–5 experiments and illustrated with the standard deviations. The reaction with these three fluorinated amino alcohol ligands with (*S*)-configurations gave products with (*R*)-configurations. This result indicated that the CF_3 group acted as the 'bulkier' group rather than the methyl or 2-propyl groups. The enantiomeric excesses of the products in the reaction with fluorinated ligand **1** as well as ligand **2** were dependent on their relative concentrations of the ligands, as had been previously reported.[8] We had shown that the higher enantiomeric excess of the product was promoted by the higher aggregation of the zinc species, which was promoted by the higher concentration of the ligand **1**, while in the reaction with ligand **3**, the enantiomeric excesses of the products were independent of the concentrations of the ligand, similarly to that of the non-fluorinated ligands, **4** and **5**.

That is, the reaction with the ligand **3** did not get the benefit from the aggregation of the organozinc species.

Thanks to the aggregation effect, ligand **1** showed a higher asymmetric-inducing ability. When the reactions were undertaken with an increased amount of the ligands (50 mol % vs PhCHO), the

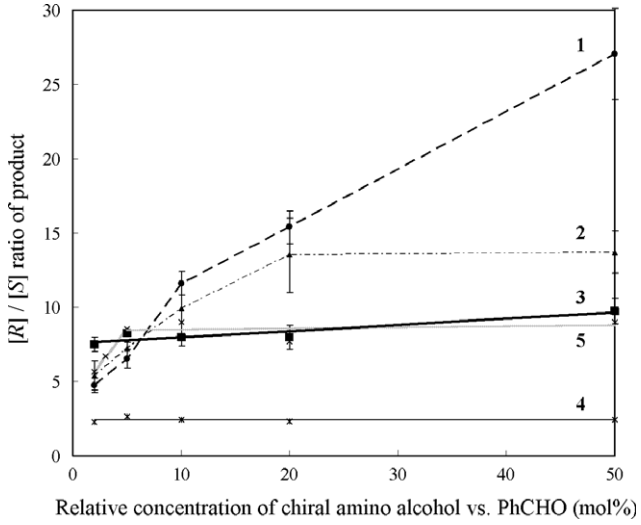


Figure 1. Asymmetric inducing ability of the amino alcohols.

Table 1

Ligand	$\Delta\Delta G^{\ddagger}$ (kcal/mol)	σ_I (R)	Charge on CF_3[a] (e)	Angle (CF_3–C–R)[a] (°)
1	0.92	0.00	−0.07	108.5
2	0.96	−0.04	−0.07	108.7
3	1.24	−0.06	−0.09	113.8

[a] Estimated by PM3 level MO calculation (MacSpartan Pro).

reaction with ligand **1** gave the best result (the product with 93% ee), among those examined (86% ee for **2**, 81% ee for **3**, 42% ee for **4**, and 80% ee for 5). Meanwhile, when the reactions were undertaken with small amounts of the ligands (2 mol % vs PhCHO), the reaction with ligand **3** gave the best result (78% ee of the product for **3**; 65% ee for **1**, 67% ee for **2**, 39% ee for **4**, and 70% ee for **5**). Thus, ligand **3** would have a somewhat higher 'net asymmetry-inducing ability', which is asymmetry-inducing ability without the aggregation effect, than the ligand **1**.

To what extent would the present modification of the trifluoromethylated ligand improve the asymmetry-inducing ability? From an energetic point of view, the asymmetry-inducing energy of 65% ee (ligand **1**) is estimated to be 0.92 kcal/mol and that of the 78% ee (ligand **3**) to be 1.24 kcal/mol (Table 1), that is, the introduction of 2-propyl group to the α-position of the CF_3 group improved the asymmetric-inducing energy to 135%. Moreover, estimated negative charges on the CF_3 groups of the ligands **1**–**3**, which were carried out by PM3 semi-empirical MO calculations (MacSpartan Pro), were found to be proportional to the asymmetry-inducing energies. The charges on the CF_3 of the ligands **1**–**3** were −0.07, −0.07, and −0.09, respectively (Table 1).

Here, the estimated negative charge on the CF_3 of the ligand **3** was 129% larger than those of the ligands **1** or **2**, although the σ_I values of the ligands **2** and **3** were noteworthy (Table 1). This can be explained by CF_3–C-alkyl bond angles of the ligands. The bulkiness of the 2-propyl group causes the CF_3–C-(2-propyl) angle to spread, which causes the overlap of the sigma bond orbitals of the CF_3–C bond and that of the C–(2-propyl) bond. A more linear arrangement of these two bonds would improve the efficiency of incoming negative charge from the 2-propyl group to the CF_3 group.

3. Conclusion

In conclusion, we succeeded in improving the 'net asymmetry-inducing ability' of the trifluoromethylated amino alcohol ligand by charging the CF_3 group from the bulky and electron donating 2-propyl group. Further use of the trifluoromethylated ligands in asymmetric reactions is currently being studied in our laboratory.

4. Experimental

4.1. General

THF was freshly distilled from Na and benzophenone, and pyridine was distilled from KOH and stored over KOH under an argon atmosphere. Benzaldehyde, trifluoroacetic anhydride, 2,2,2-trifluoroethanol, and benzoyl chloride were freshly distilled, and acetone was stored over molecular sieves 3 Å for >1 week prior to use. The (*S*)-2,3-epoxy-1,1,1-trifluoropropane **6** (75% ee) was gifted by Japan Energy Corporation, Pharmaceuticals and Biotechnology Laboratory. All other commercially available reagents were employed without further purification. E. Merck Silica Gel (Kieselgel 60, 230–400 mesh) was employed for the chromatography. IR spectra were measured on Hitachi Model 270-30 Infrared Spectrometer. ^{13}C (151 MHz) NMR spectra were recorded by Varian INOVA (600 MHz), ^{1}H (500 MHz) NMR spectra were recorded by Varian VXR (500 MHz), ^{1}H (300 MHz), ^{19}F (282 MHz) NMR spectra were recorded by Varian MERCURY (300 MHz) instrument. The chemical shifts are reported in δ values relative to TMS (δ 0.0 ppm for ^{1}H NMR) and C_6F_6 (δ 0.0 ppm for ^{19}F NMR). Coupling constants (J) are reported in Hz. Optical rotations were measured in a cell with 50 mm length and 1 ml capacity using Horiba High Sensitive Polarimeter SEPA-300. Elemental analyses were performed on Perkin Elmer series II CHNS/O Analyzer 2400. Enantiomeric excesses were determined by GC (equipped with chiral column, CP-Cyclodex-β-256M) or HPLC (equipped with chiral column, Daicel Chiralcel OD-H) analysis.

4.2. Preparation of amino alcohols

4.2.1. (2*S*)-1,1,1-Trifluoro-2-methyl-3-(*N*-piperidino)-2-propanol 2

Under an argon atmosphere, 1.1 equiv of ^{n}BuLi (2.6 M in hexane) was added to a solution of enantiomerically pure **6** (2.23 g, 20 mmol) in THF (100 ml) at −100 °C, and the solution was stirred at that temperature for 10 min. Then MeI (2.0 equiv, 2.5 ml) was added to the solution and stirred at −80 °C for 3 h. The solution was warmed to 0 °C then piperidine (5 equiv, 10 ml) was added into the solution and reacted for 14 h at room temperature. The reaction mixture was quenched by the addition of satd aq NH_4Cl. The reaction mixture was extracted by Et_2O three times. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residual oil was purified by column chromatography on silica gel (hexane/AcOEt = 5/1) to give the amino alcohol **2** (3.87 g, 92%). Colorless liquid. $[\alpha]_D^{25} = +9.9$ (c 0.0142, $CHCl_3$); IR (neat) 3460 cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) 1.26 (3H, q, J = 1), 1.39–1.41 (2H, m), 1.51–1.59 (4H, m), 2.27 (1H, dq, J = 14, 1), 2.50–2.62 (4H, m), 2.76 (1H, d, J = 14), 5.12 (1H, br); ^{13}C NMR (151 MHz, $CDCl_3$) 21.7, 23.4, 26.2, 56.2, 61.5, 69.4 (q, J = 27) 126.4 (q, J = 284); ^{19}F NMR (282 MHz, $CDCl_3$) 79.8 (3F, s); GC–MS m/z (relative intensity) 212 (M^+, 7%), 196 (3), 98 (100), 69 (4); Anal. Calcd for $C_9H_{16}F_3NO$: C, 51.18; H, 7.64; N, 6.63. Found C, 51.05; H, 7.98; N, 6.64.

4.2.2. (2*S*)-2-Benzoyl-1,1,1-trifluoro-2-methyl-3-(*N*-piperidino)propane 2′

Under an argon atmosphere, benzoyl chloride (1.2 equiv, 8.6 ml) was added to a solution of **2** (1.28 g, 6 mmol) in pyridine (40 ml). The mixture was warmed to reflux and stirred for 14 h and cooled to room temperature. Twenty milliliter of H_2O was added to reaction mixture, then extracted by benzene three times. The combined organic layer was washed with 10 wt % aq HCl, satd aq $NaHCO_3$, and brine, then dried over $MgSO_4$ and concentrated under reduced pressure. The residual oil was purified by column chromatography on silica gel (hexane/Et_2O = 10/1) to give **2′** (1.42 g, 74%). Colorless liquid. HPLC for ee (hexane only, 0.5 ml/min, 254 nm): t_S = 11.5, t_R = 12.6 min.; $[\alpha]_D^{25} = +0.4$ (c 0.0115, $CHCl_3$); IR (neat) 1730 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.32–1.36 (2H, m) 1.45–1.49 (4H, m), 1.83 (3H, s) 2.49–2.57 (4H, m) 3.05 (2H, s) 7.43–7.46 (2H, m), 7.56–7.59 (1H, m), 8.00–8.01 (2H, m); ^{13}C NMR (151 MHz, $CDCl_3$) δ 17.2, 23.9, 26.3, 56.1, 59.3, 83.3 (q, J = 26), 125.1 (q, J = 283), 128.4, 129.7, 130.5, 133.1, 164.5; ^{19}F NMR (282 MHz, $CDCl_3$) δ 82.9 (3F, s); GC–MS m/z (relative intensity) 315 (M^+, 0.1%), 105 (6), 98 (100), 77 (10), 69 (2).

4.2.3. (2*S*)-1,1,1-Trifluoro-3-methyl-2-(*N*-piperidinomethyl)-2,3-butanediol 7

Under an argon atmosphere, a 1.1 equiv of ^{n}BuLi (2.6 M in hexane) was added to a solution of enantiomerically pure **6** (6.70 g, 60 mmol) in THF (300 ml) at −100 °C and the solution was stirred at the temperature for 10 min. Then acetone (2.0 equiv, 9 ml) was added to the solution and stirred at −80 °C for 5 h. The solution

was warmed to 0 °C then piperidine (3.0 equiv, 18 ml) was added into the solution and then reacted for 14 h at room temperature. The reaction mixture was quenched by the addition of satd aq NH_4Cl. The reaction mixture was extracted by Et_2O three times. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under a reduced pressure. The residue was purified by distillation to give **7** (14.0 g, 92%). White solid. Mp = 26–28 °C; $[\alpha]_D^{25} = -3.3$ (*c* 0.0103, $CHCl_3$); IR (neat) 3610 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.13–1.70 (6H, m), 1.23 (3H, d, *J* = 1), 1.34 (3H, d, *J* = 2), 2.31–2.38 (2H, m), 2.67 (1H, d, *J* = 14), 2.83 (1H, br), 2.87 (1H, dd, *J* = 14, 1), 3.02–3.06 (1H, m); ^{13}C NMR (151 MHz, $CDCl_3$) δ 23.5, 23.6, 25.9, 26.2, 26.4, 55.2, 56.0, 56.7, 72.7, 75.0 (q, *J* = 26), 126.1 (q, *J* = 285); ^{19}F NMR (282 MHz, $CDCl_3$) δ 87.4 (3F, s); GC–MS *m*/*z* (relative intensity) 256 (M^+, 0.2%), 196 (14), 140 (2), 98 (100), 84 (8), 69 (5); Anal. Calcd for $C_{11}H_{20}F_3NO_2$: C, 51.75; H, 7.90; N, 5.49. Found C, 51.97; H, 8.05; N, 5.61.

4.2.4. (2*S*)-1,1,1-Trifluoro-3-methyl-2-(*N*-piperidinomethyl)-3-buten-2-ol 8

Under an argon atmosphere, trifluoroacetic anhydride (2.0 equiv, 5.4 ml) was added to a mixture of **7** (5.10 g, 20 mmol), 2,2,2-trifluoroethanol (1.0 equiv, 1.5 ml), and pyridine (133 ml). The mixture was heated at reflux and stirred for 10 h, and then, cooled to room temperature. The solvent was removed under reduced pressure and the residue extracted with Et_2O three times after the addition of H_2O. The combined organic layer was washed with brine, dried over $MgSO_4$, and concentrated under a reduced pressure. The residual oil was purified by column chromatography on silica gel (hexane/AcOEt = 20/1) to give **9** (2.32 g, 49%). Colorless liquid. $[\alpha]_D^{25} = -0.6$ (*c* 0.0138, $CHCl_3$); IR (neat) 3220 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1,41–1.46 (2H, m), 1.53–1.60 (4H, m), 1.84–1.85 (3H, m), 2.47–2.61 (4H, m), 2.66 (1H, dd, *J* = 14, 1), 2.83 (1H, d, *J* = 14), 5.09 (1H, s), 5.34 (1H, s), 5.60 (1H, br); ^{13}C NMR (151 MHz, $CDCl_3$) δ 19.0, 23.5, 26.1, 55.6, 59.7, 73.0 (q, *J* = 27), 114.9, 125.6 (q, *J* = 285), 143.0; ^{19}F NMR (282 MHz, $CDCl_3$) δ 83.6 (3F, s); GC–MS *m*/*z* (relative intensity) 236 (M^+, 0.1%), 196 (4), 168 (2), 98 (100), 84 (3), 69 (7); Anal. Calcd for $C_{11}H_{18}F_3NO$: C, 55.68; H, 7.65; N, 5.90. Found C, 55.59; H, 7.81; N, 5.96.

4.2.5. (2*S*)-1,1,1-Trifluoro-3-methyl-2-(*N*-piperidinomethyl)-2-butanol 3

A 5% Pt on activated carbon (0.05 equiv, 0.05 g) was added to **9** (1.15 g, 4.8 mmol). The atmosphere was exchanged by hydrogen prior to the addition of EtOH (5 ml), and the mixture was stirred for 3 h. Then, the mixture was filtered by silica gel with Et_2O, and solvent was removed under reduced pressure to give **3** (1.13 g, 97%). Colorless liquid. $[\alpha]_D^{25} = +2.8$ (*c* 0.0112, $CHCl_3$); IR (neat) 3180 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (3H, dq, *J* = 12, 2); 0.96 (3H, dd, *J* = 12, 2), 1.49 (2H, br), 1.55-1.60 (4H, m), 2.06 (1H, septet, *J* = 12), 2.38 (1H, dd, *J* = 25, 2), 2.57 (4H, br), 2.66 (1H, d, *J* = 25), 5.59 (1H, br); ^{13}C NMR (151 MHz, $CDCl_3$) δ 16.2, 16.6, 23.5, 26.3, 32.1, 55.6, 56.1, 72.5 (q, *J* = 25), 127.1 (q, *J* = 286); ^{19}F NMR (282 MHz, $CDCl_3$) δ 85.3 (3F, s); GC–MS *m*/*z* (neat) 238 (M^+, 0.1%), 196 (4), 170 (2), 98 (100), 84 (3), 69 (7); Anal. Calcd for $C_{11}H_{20}F_3NO$: C, 55.22; H, 8.42; N, 5.85. Found C, 55.30; H, 8.42; N, 5.98.

4.2.6. (2*S*)-2-Benzoyl-1,1,1-trifluoro-3-methyl-2-(*N*-piperidinomethyl)butane 3′

Under an argon atmosphere, benzoyl chloride (1.5 equiv, 0.3 ml) was added to a solution of **3** (0.42 g, 1.7 mmol) in pyridine (10 ml). The mixture was heated at reflux and stirred for 14 h and then cooled to room temperature. Five milliliter of H_2O was added to reaction mixture, then extracted by benzene three times. The combined organic layer was washed with 10% aq HCl, satd aq $NaHCO_3$, and brine, then dried over $MgSO_4$ and concentrated under a reduced pressure. The residual oil was purified by column chromatography on silica gel (hexane/Et_2O = 10/1), then distilled to give **3′** (0.21 g, 34%). Colorless liquid. HPLC for ee (hexane only, 0.5 ml/min, 254 nm): t_S = 14.4, t_R = 21.2 min; $[\alpha]_D^{25} = +5.3$ (*c* 0.0119, $CHCl_3$); IR (neat) 1730 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.09 (3H, d, *J* = 7), 1.11 (3H, dd, *J* = 7, 2), 1.30–1.34 (2H, m), 1.41–1.46 (4H, m), 2.50–2.53 (4H, m), 2.94–3.03 (1H, m), 2.99 (1H, d, *J* = 15), 3.27 (1H, dd, *J* = 15, 1), 7.44–7.47 (2H, m), 7.56–7.59 (1H, m), 8.02–8.04 (2H, m); ^{13}C NMR (151 MHz, $CDCl_3$) δ 17.5, 24.0, 26.3, 31.5, 58.1, 56.0, 88.1 (q, *J* = 25), 125.4 (q, *J* = 287), 128.4, 129.7, 130.6, 133.1, 164.6; ^{19}F NMR (282 MHz, $CDCl_3$) δ 93.6 (3F, s); GC–MS *m*/*z* (relative intensity) 220 (M−$PhCO_2$, 0.2%), 206 (1) 105 (7), 98 (100), 77 (7), 69 (2).

4.3. Typical procedure of the asymmetric Et_2Zn alkylation of PhCHO with amino alcohol

Under an argon atmosphere, a hexane solution of Et_2Zn (2 ml of a 1 M hexane solution, 2.0 mmol) was added to the amino alcohol (0.5 mmol). The mixture was stirred at room temperature for 10 min and then cooled to 0 °C. After the addition of benzaldehyde (1.0 g, 1.0 mmol) to the solution, the reaction mixture was stirred at the same temperature for 5 h, then warmed to room temperature and stirred for 43 h. The reaction was quenched by 10 wt % aq HCl (4 ml). The reaction mixture was extracted with Et_2O three times and dried over $MgSO_4$.

The enantiomeric excesses were determined by the GC analyses of the crude mixture. NMR yields were determined by ^1H NMR analysis of the crude mixture with 1,1,2,2-tetrachloroethane as an internal standard.

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