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Synthesis of Chiral *β*-Fluoroalkyl *β*-Amino Acid Derivatives *via* Palladium-catalyzed Hydrogenation

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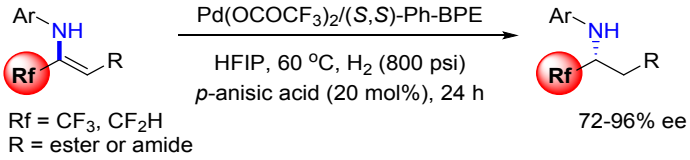
ABSTRACT



An enantioselective palladium-catalyzed hydrogenation of *β*-fluoroalkyl-*β*-amino acrylic acid derivatives has been successfully developed, providing the corresponding chiral *β*-fluoroalky *β*-amino acid derivatives in good yields with excellent enantioselectivities. In addition, chiral *γ*-fluoroalkyl-*γ*-amino alcohol could be synthesized by simple reduction of the corresponding hydrogenated product. The mechanism of the reaction was explored by deuterium labeling experiments.

Introduction

Fluorine substituted organic compounds had received increasing attention due to the fact that fluorine's electronegativity, small steric size, lipophilicity and electrostatic interactions can dramatically influence the chemical reactivity and biological activity of the parent molecules.[1] Thus, numerous of research have been devoted to this field and a large number of fluorinated molecules have been synthesized.[2] Among them, chiral *β*-fluoroalkyl *β*-amino acids and their derivatives are a prominent class of building blocks for the construction of various useful compounds including pharmaceuticals, agrochemicals and biologically active natural products.[3] For example, CF_3-Ac docetaxel is used against human cancer cell lines (Figure 1, **I**),[4a-c] and *ψ* [$CH(CF_3)NH$]-retro-thionphane is used as neutral endopeptidase inhibitor (Figure 1, **II**).[4d] Thus, the

enantioselective syntheses of β-fluoroalkyl β-amino acid derivatives have attracted a great deal of interests,[5] and many efficient methods have been developed including chiral auxiliaries strategies[6] and catalytic methods,[7-10] such as isomerization of fluorinated imines,[7] catalytic asymmetric Mannich reaction of fluorinated imines[8] and aza-Michael addition of fluorinated imines.[9] Although some progress has been made in synthesis of β-fluoroalkyl β-amino acid derivatives, these existing routes have several drawbacks involving poor enantioselectivities or stoichiometric amount of chiral auxiliaries needed and so on, thus prohibiting their further application. Therefore, developing an efficient and atom-economic method for the synthesis of chiral β-fluoroalkyl β-amino acid derivatives is of great significance in both organic synthesis and drug research.

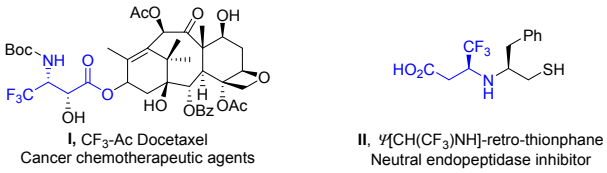
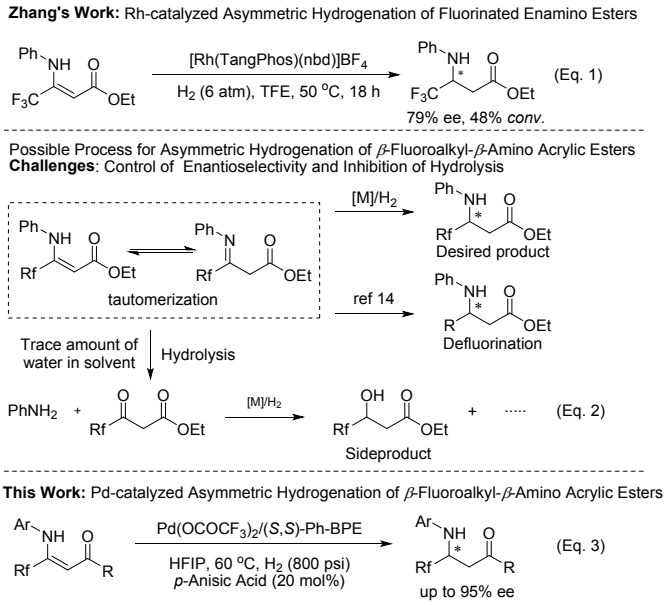


Figure 1. Selected bioactive chiral β-fluoroalkyl β-amino acid derivatives.

In the past decades, catalytic asymmetric hydrogenation as an efficient and economic approach has drawn a lot of attention and has been successfully introduced to synthesis of chiral β-amino acid derivatives.[11] However, the synthesis of chiral β-fluoroalkyl β-amino acid derivatives through hydrogenation is still a challenging area which has been rarely explored to date, probably due to the strong electron withdrawing property of CF_3 group in the olefinic substrates.[10,12] In 2005, the Rh-catalyzed asymmetric hydrogenation for synthesis of β-amino acid derivatives was reported by Zhang and co-workers, in which only one example of chiral β-fluoroalkyl β-amino acid ester with 79% ee and moderate 48% conversion was observed (Scheme 1, Eq. 1).[10] We speculated that the major obstacles to advancement in this research area are as follows: the fluorinated enamino ester is easily hydrolyzed even with trace amount of water in solvent,[13] leading to the low chemoselectivity; the enamine and imine tautomerization impeded the stereoselectivity and the former disclosed C-F bond cleavage of the fluorinated compounds[14] in the presence of transition metal-catalyzed systems which is a challenge for the hydrogenation of fluorinated enamino derivatives (Scheme 1, Eq 2). Considering asymmetric synthesis of chiral trifluoromethyl amines has made great progress in Pd,[15] Ir,[16] Rh,[14] Ru[17] and organocatalysts[18] catalyzed reduction of corresponding trifluoromethyl imines, we envisioned that the asymmetric hydrogenation of β-fluoroalkyl-β-amino acrylic acid derivatives could be realized through the reduction of imine-tautomer of the substrates via enamine-imine tautomerization, providing the chiral β-fluoroalkyl β-amino acid derivatives. Herein, we reported the palladium-catalyzed asymmetric hydrogenation of fluorinated enamino derivatives, giving the chiral β-fluoroalkyl β-amino acid derivatives

with up to 95% ee.

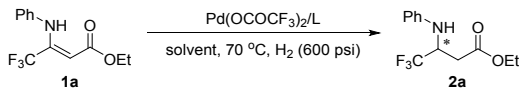
Scheme 1. Asymmetric Hydrogenation of *β*-Fluoroalkyl-*β*-Amino Acrylic Acid Derivatives



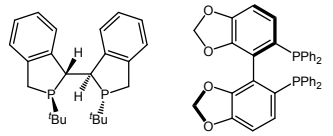
Results and Discussion

To test the viability of our proposed protocol, the (*Z*)-ethyl 4,4,4-trifluoro-3-(phenylamino)but-2-enoate (**1a**) was chosen as the model substrate, and the hydrogenation was performed in the presence of $Pd(OCOCF_3)_2$/(*S,S'*,*R,R'*-DuanPhos) in trifluroethanol (TFE) at 40 °C. Pleasingly, the reaction was conducted with full conversion and furnished **2a** in 51% yield with 77% ee (Table **1**, entry 1). The main problem of the low yield is ascribed to the hydrolysis of the substrate **1a** to amine and ethyl 4,4,4-trifluoroacetoacetate during the reaction, and then the ethyl 4,4,4-trifluoroacetoacetate could be hydrogenated to deliver ethyl 4,4,4-trifluoro-3-hydroxybutanoate[19] (detected by GC-MS) and other low boiling point substances. Consequently, a series of solvents were screened (entries 2-5), and HFIP (1,1,1,3,3,3-hexafluoro-2-propanol) was proved to be the optimal solvent in terms of good yield and ee value (entry 5). Furthermore, some commercially available chiral diphosphine ligands were examined (entries 5-10). The results revealed that chiral ferrocenyl phosphine **L4** offered moderated yield and enantioselectivity (entry 8). High reaction activity was obtained using the electron-rich ligands such as Me-Duphos in this hydrogenation system, which avoid the fluorinated enamino ester hydrolyzed in solvent and no byproduct was obtained (entry 9). While electron-donating phosphine ligand **L6** gave excellent ee value and moderate yield (entry 10). Dehydrating agents such as 5 Å MS were added in order to improve the yield, but did not give better results (entry 11). Gratifyingly, the yield can be improved to 74% with the 90% of enantioselectivity using the 4 mol % of catalyst loading amount (entry 12).

Table 1. Optimization for Pd-catalyzed Asymmetric Hydrogenation of (*Z*)-Ethyl 4,4,4-trifluoro-3-(phenylamino) but-2-enoate (**1a**) [a]

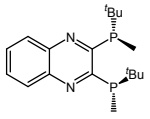


entry	solvent	L	*conv.* (%)[b]	yield (%)[b]	ee (%)[c]
1	TFE	**L1**	>95	51	77
2	DCM	**L1**	38	12	48
3	THF	**L1**	37	6	64
4	MeOH	**L1**	>95	74	18
5	HFIP	**L1**	>95	74	73
6	HFIP	**L2**	>95	57	77
7	HFIP	**L3**	>95	65	84
8	HFIP	**L4**	>95	56	44
9	HFIP	**L5**	>95	97	44
10	HFIP	**L6**	>95	64	89
11[d]	HFIP	**L6**	>95	47	88
12[e]	HFIP	**L6**	>95	74	90

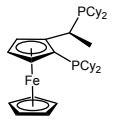


L1: (*S*,*S*',*R*,*R*')-DuanPhos

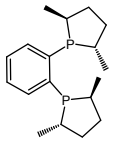
L2: (*R*)-SegPhos



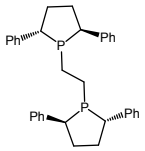
L3: (*R*,*R*)-QuinoxP*



L4: (*R*,*Sp*)-Cy-Josiphos



L5: (*S*,*S*)-Me-Duphos

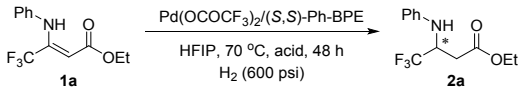


L6: (*S*,*S*)-Ph-BPE

[a] Conditions: **1a** (0.125 mmol), $Pd(OCOCF_3)_2$ (2.0 mol%), **L** (2.4 mol%), solvent (3.0 mL), 48 h, 70 °C. [b] Determined by ^1H NMR, using 1,3,5-trimethoxybenzeneas an internal standard. [c] Determined by chiral HPLC analysis. [d] 40 mg 5 Å MS was added. [e] $Pd(OCOCF_3)_2$ (4.0 mol%), **L** (4.8 mol%).

Considering the acid can promote the tautomeric transformation between imines and enamines, and also promote the *in situ* formation of iminium salts, leading to enhancement of the activity.[20] Therefore, a series of acidic additives were screened systematically. The results were depicted in Table 2. To our delight, both selectivity and enantioselectivity of the reaction were increased with the addition of a catalytic amount of benzoic acid (entries 1-2). After evaluation of various acids, the *p*-anisic acid was verified as the best choice in terms of yield and enantioslectivity. The effects of temperature and hydrogen pressure on reactivity and enantioselectivity were also investigated in the next steps (entries 8-10). Finally, the optimal reaction condition was established as: $Pd(OCOCF_3)_2$/(*S*,*S*)-Ph-BPE, *p*-anisic acid, H_2 (800 psi), in HFIP and at 60 °C.

Table 2. Optimization of Reaction Conditions [a]

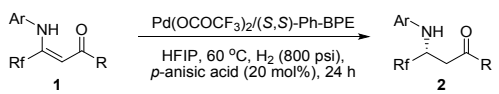


entry	acid	*conv.* (%)[b]	yield (%)[b]	ee (%)[c]
1[d]	$PhCO_2H$	>95	80	93
2	$PhCO_2H$	>95	84	93
3[e]	$PhCO_2H$	>95	72	93
4	$TsOH{\cdot}H_2O$	>95	59	93
5	(*D*)-camphoric acid	>95	63	93
6	*p*-anisic acid	>95	84	94
7	*p*-nitrobenzoic acid	>95	82	92
8[f]	*p*-anisic acid	>95	79	92
9[g]	*p*-anisic acid	>95	86	95
10[h]	*p*-anisic acid	>95	77	96
11[i]	*p*-anisic acid	>95	88	95

[a] Conditions: **1a** (0.125 mmol), $Pd(OCOCF_3)_2$ (4.0 mol%), (*S*,*S*)-Ph-BPE (4.8 mol%), acid (20 mol%), HFIP (3.0 mL), H_2 (600 psi), 48 h, 70 °C. [b] Determined by ^1H NMR, using 1,3,5-trimethoxybenzene as internal standard. [c] Determined by chiral HPLC analysis. [d] 10 mol% of $PhCO_2H$. [e] 30 mol% of $PhCO_2H$. [f] 80 °C. [g] 60 °C. [h] 50 °C. [i] 60 °C, H_2 (800 psi), 24 h.

After establishing the optimal condition, we next examined the substrate scope, and the results were summarized in Table 3. Esters with different alkoxy groups were firstly examined in this reaction, the target products were obtained in good yields with excellent enantioselectivities (entries 1-3). The moderate yield and enantioselectivity was obtained, when the amide was introduced as the substrate (entry 4). Notably, different electronic properties and positions of substituents on the aromatic ring had marginal effect on the reactivity and enantioselectivity (entries 5-11). What's more, the difluoroalkyl-substituted substrate was also tolerated, giving the desirable product in 77% yield and 72% ee (entry 12).

Table 3. Substrate Scope of Chiral β-Fluoroalkyl β-Amino Derivatives[a]



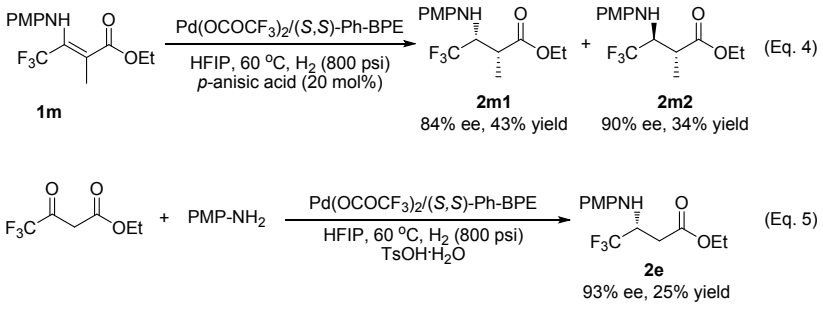
entry	Rf	R	Ar	yield (%)[b]	ee (%)[c]
1	CF_3	OEt	C_6H_5	74 (**2a**)	95
2	CF_3	OMe	C_6H_5	79 (**2b**)	95
3[d]	CF_3	OBn	C_6H_5	58 (**2c**)	92
4[d]	CF_3	NHPh	C_6H_5	33 (**2d**)	76
5	CF_3	OEt	4-$MeOC_6H_4$	66 (**2e**)	94

6[d]	CF_3	OEt	3-$MeOC_6H_4$	70 (**2f**)	95
7[d]	CF_3	OEt	2-$MeOC_6H_4$	50 (**2g**)	93
8	CF_3	OEt	4-MeC_6H_4	71 (**2h**)	93
9	CF_3	OEt	4-ClC_6H_4	73 (**2i**)	95
10[d]	CF_3	OEt	4-FC_6H_4	54 (**2j**)	91
11	CF_3	OEt	1-naphthyl	84 (**2k**)	96
12	CF_2H	OEt	C_6H_5	77 (**2l**)	72

[a] Conditions: **1** (0.25 mmol), $Pd(OCOCF_3)_2$ (4.0 mol%), (*S*,*S*)-Ph-BPE (4.8 mol%), *p*-anisic acid (20 mol%), HFIP (3.0 mL), H_2 (800 psi), 24 h, 60 °C. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] 48 h.

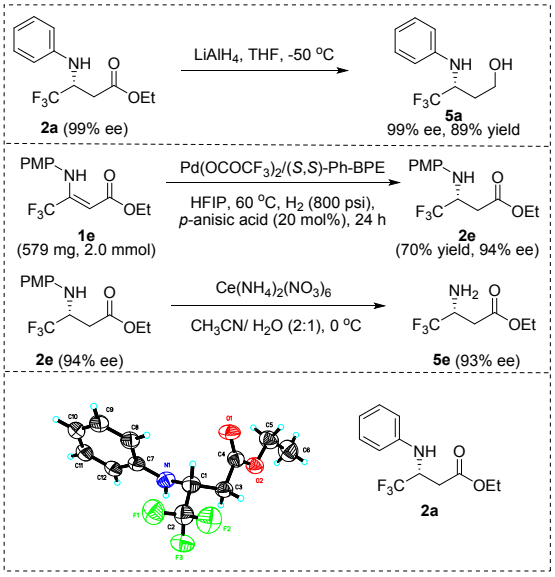
Moreover, *α*-methyl *β*-fluoroalkyl *β*-enamino ester could also be hydrogenated successfully under the standard conditions, giving the *α*-methyl *β*-fluoroalkyl *β*-amino ester with 84% yield & 90% ee, and poor selectivity of 1.3:1 dr (Scheme 2, Eq. 4). Subsequently, the direct catalytic asymmetric reductive amination was explored in this study. At the beginning, only 9% NMR yield of desired product **2e** was observed with ethyl 4,4,4-trifluoroacetoacetate and *p*-anisidine under the optimal conditions. When $TsOH{\cdot}H_2O$ in place of *p*-anisic acid was introduced, the desirable product was obtained in 25% yield and 93% ee (Scheme 2, Eq. 5).

Scheme 2. Asymmetric Synthesis of *α*-Methyl *β*-Fluoroalkyl *β*-Amino Acrylic Ester and Reductive Amination.



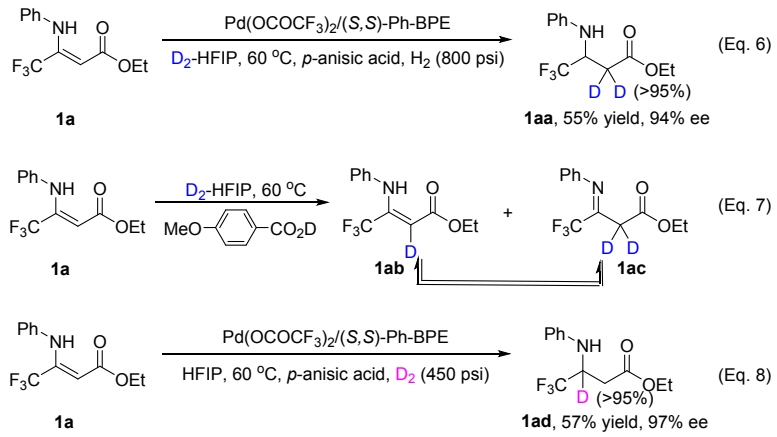
To further demonstrate the utility of this method, product **2a** (recrystallize from *n*-hexane to upgrade ee to 99%) was reduced by lithium aluminum hydride ($LiAlH_4$), giving the chiral *γ*-fluoroalkyl-*γ*-amino alcohol **5a** without loss of optical purity.[21] Moreover, the 2.0 mmol scale (579 mg) experiment was carried out, and the desired chiral enamino ester **2e** was obtained without the loss of activity and enantioselectivity (70% yield, 94% ee). Meanwhile, chiral primary amine **5e** could be obtained by removing the *p*-methoxyphenyl group through oxidative cleavage of the hydrogenated product **2e**, and the optical purity still remained.[15c,18g] In addition, this method provides a concise and effective way to synthesize 4-CF_3-ezetimibe.[3f] The absolute configuration of hydrogenation product **2a** was determined by X-ray diffraction analysis by recrystallization from *n*-hexane (Scheme 3).

Scheme 3. Transformations of Chiral β - Fluoroalkyl β - Amino Ester **2a,** Deprotection of **2e** and X-ray Crystal Structure of **2a**



In order to investigate the reaction mechanism, two isotopic labeling experiments were carried out (Scheme 4). When the hydrogenation was carried out in D_2-HFIP, ^1H NMR analysis of the hydrogenation product showed that the deuterium atom was taken up to the α-position with >95% of deuterium isotopic content (Eq. 6). When **1a** was subjected to hydrogenation under D_2, the deuterium atoms was incorporated to the β-position exclusively with >95% of deuterium isotopic content (Eq. 8). As well as, enamine (**1ab**) and imine (**1ac**) can be obtained in the presence of D_2-HFIP and D-*p*-anisic acid at 60 °C (Eq. 7), at the same time **1ab** and **1ac** can be rapidly isomerized under acidic conditions, the ratio of **1ac** to **1ab** was increased with prolonged time (See Figure S1). Considering that in general palladium-catalyzed hydrogenation of imines is easier than enamines,[20a,e] so we speculate that the asymmetric hydrogenation of β-fluoroalkyl-β-amino acrylic esters proceeds through asymmetric reductive of the iminium form other than enamine form of the substrate in the presence of Brønsted acid, but the direct hydrogenation of enamine cannot be ruled out.

Scheme 4. Deuterium-Labeling Experiment



In summary, we have successfully developed an efficient method for synthesis of chiral *β*-fluoroalkyl *β*-amino derivatives through palladium-catalyzed asymmetric hydrogenation of *β*-fluoroalkyl-*β*-amino acrylic acid derivatives with up to 96% ee. A reductive amination between 4,4,4-trifluoroacetoacetate and *p*-anisidine was also achieved. Moreover, the synthetic utility of hydrogenation products was performed to construct chiral *γ*-fluoroalkyl-*γ*-amino alcohol. Further investigations on asymmetric hydrogenation of fluorinate compounds are currently on going in our laboratory.

EXPERIMENTAL SECTION

Commercially All reactions were carried out under an atmosphere of nitrogen using the standard Schlenk techniques, unless otherwise noted. Commercially available reagents were used without further purification. Solvents were treated prior to use according to the standard methods. ^{1}H NMR, ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz with the Brucker spectrometer. ^{19}F was recorded at 376 MHz with Brucker spectrometer. Chemical shifts are reported in ppm using tetramethylsilane as internal standard when using $CDCl_3$ as solvent for ^{1}H NMR spectra. The following abbreviations were used to symbolize the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Flash column chromatography was performed on silica gel (200-300 mesh). All reactions were monitored by TLC analysis. Optical rotations were measured by the polarimeter. Enantiomeric excess was determined by HPLC analysis using chiral column described below in detail. High-resolution mass spectrometry (HRMS) was measured on an electrospray ionization (ESI) apparatus using time-of-flight (TOF) mass spectrometry.

Procedures for Synthesis of *β*-Fluoroalkyl-*β*-Amino Acrylic Esters 1. A mixture of the **3** (10.0 mmol), **4** (10.0 mmol) and *p*-toluenesulfonic acid monohydrate (0.192 g, 1.0 mmol) were didsolved in ehanol or toluene (10 mL) and refluxed overnight. After the reaction mixture was cooled to room temperature, the solution was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was purified by

passing through a silica gel column to give the final product.[22] The compounds **1a**, [22a] **1b**, [22b] **1d-1h & 1j**,[22c] **1i**[22d] and **1l**[22e] were the known compounds.

Benzyl (*Z*)-4,4,4-trifluoro-3-(phenylamino)but-2-enoate (1c): 0.918g, 29% yield, yellow oil, R_f = 0.40 (hexanes/ethyl acetate = 30/1), ^{1}H NMR (400 MHz, CD_3OD) δ 7.41 – 7.36 (m, 5H), 7.36 – 7.32 (m, 2H), 7.30 – 7.24 (m, 1H), 7.20 (d, *J* = 7.8 Hz, 2H), 5.41 (s, 1H), 5.19 (s, 2H); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 168.7, 146.6 (q, *J* = 30.0 Hz), 138.5, 136.2, 128.7, 128.2, 127.9, 127.8, 126.3, 125.4, 120.4 (q, *J* = 273.0 Hz), 88.2 (q, *J* = 5.0 Hz), 65.6; ^{19}F{^{1}H} NMR (376 MHz, CD_3OD) δ -65.2; HRMS (ESI-TOF) *m/z* Calculated for $C_{17}H_{15}F_3NO_2$ $[M+H]^+$ 322.1049, found 322.1053.

Ethyl (*Z*)-4,4,4-trifluoro-3-(naphthalen-1-ylamino)but-2-enoate (1k) : 0.590 g, 19% yield, pale yellow oil, R_f = 0.51 (hexanes/ethyl acetate = 30/1), ^{1}H NMR (400 MHz, CD_3OD) δ 8.02 – 7.94 (m, 1H), 7.91 (t, *J* = 5.4 Hz, 1H), 7.84 (t, *J* = 7.6 Hz, 1H), 7.60 – 7.49 (m, 2H), 7.49 – 7.34 (m, 2H), 5.43 (d, *J* = 1.5 Hz, 1H), 4.32 – 4.09 (m, 2H), 1.29 (t, *J* = 4.4 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, CD_3OD) δ 169.5, 147.8 (q, *J* = 30.0 Hz), 134.3 (d), 131.0, 127.9, 127.6, 126.5, 126.1, 124.6, 124.5, 122.0, 120.4 (q, *J* = 275.0 Hz), 88.2 (q, *J* = 5.0 Hz), 59.9, 13.2; ^{19}F{^{1}H} NMR (376 MHz, CD_3OD) δ -65.7; HRMS (ESI-TOF) *m/z* Calculated for $C_{16}H_{15}F_3NO_2$ $[M+H]^+$ 310.1049, found 310.1044.

Typical Procedure for Palladium-catalyzed Asymmetric Hydrogenation of *β*-Fluoroalkyl-*β*-Amino Acrylic Esters.

(*S*,*S*)-Ph-BPE (6.2 mg, 0.012 mmol) and $Pd(OCOCF_3)_2$ (3.3 mg, 0.010 mmol) were placed in a dried Schlenk tube under nitrogen atmosphere, and degassed anhydrous acetone was added. The mixture was stirred at room temperature for 1 h. The solvent was removed under vacuum to give the catalyst. This catalyst was taken into a glovebox filled with nitrogen and dissolved in dry HFIP (3 mL). To a mixture of substrates **1** (0.25 mmol) and *p*-anisic acid (7.6 mg, 0.05 mmol), the catalyst solution was added, and then the mixture was transferred to an autoclave. The hydrogenation was performed at 60 °C under 800 psi of hydrogen. The autoclave was stirred under directed conditions for 24 h, then the hydrogen was carefully released, the autoclave was opened, and saturated aqueous sodium bicarbonate (5 mL) was added to the mixture and stirred for 10-15 min. The mixture was extracted with dichloromethane twice and the combined organic extracts dried over sodium sulfate. The resulting mixture was concentrated in vacuo and further purification was performed by a silica gel column eluted with hexanes/ethyl acetate to give the desired product **2**. The enantiomeric excesses were determined by chiral HPLC after the purification by column chromatography on silica gel (ethyl acetate/hexanes).

Racemates of **2** were prepared by the reduction of the corresponding substrates **1** using 1,2-bis(dicyclohexylphosphanyl)ethane and $Pd(OCOCF_3)_2$ as catalyst.

(*R*)-Ethyl-4,4,4-trifluoro-3-(phenylamino)butanoate (2a): 48 mg, 74% yield, pail yellow soild: 50-51 °C, R_f = 0.31 (hexanes/ethyl acetate = 20/1), 95% ee, $[\alpha]^{20}_D$ = -12.50 (*c* 0.48, $CHCl_3$) [lit.[10]: $[\alpha]^{20}_D$ = 1.4 (*c* 1.0, $CHCl_3$) for 79% ee]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 – 7.17 (m, 2H), 6.81 (t, *J* = 7.4 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 2H), 4.56 – 4.42 (m, 1H), 4.19 – 4.05 (m, 2H), 3.90 (d, *J* = 9.9 Hz, 1H), 2.83 (dd, *J* = 15.6, 4.5 Hz, 1H), 2.62 (dd, *J* = 15.6, 8.8 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.4, 145.7, 129.4, 125.6 (q, *J* = 282.0 Hz), 119.5, 114.0, 61.4, 53.4 (q, *J* = 30 Hz), 35.1 (q, *J* = 1.0 Hz), 14.0; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -76.1; HPLC (OJ-H, elute: Hexanes/*i*-PrOH = 90/10, detector: 230 nm, flow rate: 1.0 mL/min), 30 °C, t_1 = 8.8 min, t_2 = 10.0 min (maj).

(*R*)-Methyl-4,4,4-trifluoro-3-(phenylamino)butanoate (2b) :[22a] 49 mg, 79% yield, pale yellow oil, R_f = 0.23 (hexanes/ethyl acetate = 30/1), 95% ee, $[\alpha]^{20}_D$ = -8.37 (*c* 0.49, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, *J* = 8.6, 7.4 Hz, 2H), 6.81 (t, *J* = 7.4 Hz, 1H), 6.73 (d, *J* = 7.7 Hz, 2H), 4.56 – 4.44 (m, 1H), 3.68 (s, 3H), 2.84 (dd, *J* = 15.7, 4.6 Hz, 1H), 2.64 (dd, *J* = 15.7, 8.6 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 1670, 145.6, 129.8, 125.5 (q, *J* = 282.0 Hz), 119.6, 114.1, 53.4 (q, *J* = 30 Hz) , 52.3, 34.7 (q, *J* = 1.0 Hz); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -76.1; HPLC (OD-H, elute: Hexanes/*i*-PrOH = 90/10, detector: 230 nm, flow rate: 1.0 mL/min), 30 °C, t_1 = 7.0 min, t_2 = 8.8 min (maj).

(*R*)-Benzyl-4,4,4-trifluoro-3-(phenylamino)butanoate (2c) : 47 mg, 58% yield, pale yellow oil, R_f = 0.35 (hexanes/ethyl acetate = 20/1), 92% ee, $[\alpha]^{20}_D$ = -9.79 (*c* 0.47, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.28 (m, 3H), 7.27 – 7.22 (m, 2H), 7.22 – 7.16 (m, 2H), 6.85 – 6.75 (m, 1H), 6.69 (d, *J* = 7.7 Hz, 2H), 5.09 (d, *J* = 0.9 Hz, 2H), 4.50 (tdd, *J* = 9.2, 6.8, 4.4 Hz, 1H), 3.85 (d, *J* = 10.1 Hz, 1H), 2.88 (dd, *J* = 15.6, 4.4 Hz, 1H), 2.66 (dd, *J* = 15.6, 9.0 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 169.3, 145.6, 135.1, 129.4, 128.6, 128.5, 128.4, 125.5 (q, *J* = 282.0 Hz), 119.5, 114.0, 67.2, 53.4 (q, *J* = 30.0 Hz), 35.1 (q, *J* = 1.0 Hz); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -76.1; HPLC (OD-H, elute: Hexanes/*i*-PrOH = 90/10, detector: 230 nm, flow rate: 1.0 mL/min), 30 °C, t_1 = 9.8 min (maj), t_2 = 12.3 min; HRMS (ESI-TOF) *m/z* Calculated for $C_{17}H_{17}F_3NO_2$ $[M+H]^+$ 324.1206, found 324.1206.

(*R*)-4,4,4-trifluoro-*N*-phenyl-3-(phenylamino)butanamide (2d) : 25 mg, 33% yield, pale yellow oil, R_f = 0.19 (hexanes/ethyl acetate = 5/1), 76% ee, $[\alpha]^{20}_D$ = -11.2 (*c* 0.25, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (brs, 1H), 7.43 (d, *J* = 8.0 Hz, 2H), 7.32 (t, *J* = 7.9 Hz, 2H), 7.24 (dd, *J* = 8.4, 7.5 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 6.86 (t, *J* = 7.4 Hz, 1H), 6.80 (d, *J* = 8.1 Hz, 2H), 4.58 (s, 1H), 4.14 (s, 1H), 2.87 (dd, *J* = 15.2, 3.9 Hz, 1H), 2.63 (dd, *J* = 15.2, 8.5 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 166.8, 145.6, 137.2, 129.5, 129.1, 125.7 (q, *J* = 283.0 Hz), 125.0, 120.4, 119.9, 114.5, 53.9 (q, *J* = 30.0 Hz), 37.1; ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -75.6; HPLC (OJ-H, elute: Hexanes/*i*-PrOH = 90/10, detector: 230 nm, flow rate: 1.0

mL/min), 30 °C, t_1 = 25.6 min, t_2 = 32.9 min (maj); HRMS (ESI-TOF) *m/z* Calculated for $C_{16}H_{16}F_3N_2O$ $[M+H]^+$ 309.1209, found 309.1214.

(*R*)-Ethyl-4,4,4-trifluoro-3-((4-methoxyphenyl)amino)butanoate (2e): [23a] 48 mg, 66% yield, pale yellow oil, R_f = 0.22 (hexanes/ethyl acetate = 20/1), 94% ee, $[\alpha]^{20}_D$ = -23.12 (*c* 0.48, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.79 (d, *J* = 8.9 Hz, 2H), 6.70 (d, *J* = 8.9 Hz, 2H), 4.35 (s, 1H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.75 (s, 3H), 3.61 (d, *J* = 8.6 Hz, 1H), 2.80 (dd, *J* = 15.6, 4.5 Hz, 1H), 2.59 (dd, J = 15.6, 8.9 Hz, 1H), 1.21 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.6, 153.5, 139.7, 125.7 (q, *J* = 282.0 Hz), 115.9, 114.8, 62.3, 55.7, 54.9 (q, *J* = 30 Hz), 35.1 (q, *J* = 2.0 Hz), 14.0; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -76.0; HPLC (OJ-H, elute: Hexanes/*i*-PrOH = 90/10, detector: 230 nm, flow rate: 1.0 mL/min), 30 °C, t_1 = 12.7 min, t_2 = 15.0 min (maj).

(*R*)-Ethyl-4,4,4-trifluoro-3-((3-methoxyphenyl)amino)butanoate (2f) : 51 mg, 70% yield, pale yellow oil, R_f = 0.16 (hexanes/ethyl acetate = 20/1), 95% ee, $[\alpha]^{20}_D$ = -12.35 (*c* 0.51, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.03 (t, *J* = 8.1 Hz, 1H), 6.30-6.20 (m, 2H), 6.21 (t, *J* = 2.1 Hz, 1H), 4.42-4.36 (m, 1H), 4.06 (q, *J* = 7.1 Hz, 2H), 3.69 (s, 3H), 2.75 (dd, *J* = 15.6, 4.6 Hz, 1H), 2.54 (dd, *J* = 15.6, 8.6 Hz, 1H), 1.13 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.4, 160.8, 147.1, 130.2, 125.5 (q, *J* = 282.0 Hz), 106.7, 104.6, 100.2, 61.4, 55.2, 53.3 (q, *J* = 30.0 Hz), 35.2 (q, *J* = 2.0 Hz), 14.0; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -76.1; HPLC (OD-H, elute: Hexanes/*i*-PrOH = 95/5, detector: 230 nm, flow rate: 0.8 mL/min), 30 °C, t_1 = 16.9 min (maj), t_2 = 23.7 min; HRMS (ESI-TOF) *m/z* Calculated for $C_{13}H_{16}F_3NNaO_3$ $[M+H]^+$ 314.0974, found 314.0975.

(*R*)-Ethyl-4,4,4-trifluoro-3-((2-methoxyphenyl)amino)butanoate (2g) : 36 mg, 50% yield, pale yellow solid, R_f = 0.27 (hexanes/ethyl acetate = 20/1), 93% ee, $[\alpha]^{20}_D$ = + 3.33 (*c* 0.36, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.90 – 6.86 (m, 1H), 6.83 – 6.72 (m, 3H), 4.57 – 4.45 (m, 1H), 4.18 – 4.08 (m, 2H), 3.85 (s, 3H), 2.85 (dd, *J* = 15.7, 4.6 Hz, 1H), 2.66 (dd, *J* = 15.7, 8.8 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.4, 147.0, 135.6, 125.6 (q, *J* = 281.0 Hz),121.2, 118.5, 111.3, 110.1, 61.3, 55.6, 53.0 (q, *J* = 30.0 Hz), 35.3 (q, *J* = 1.0 Hz), 14.0; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -76.3; HPLC (OD-H, elute: Hexanes/*i*-PrOH = 95/5, detector: 230 nm, flow rate: 0.7 mL/min), 30 °C, t_1 = 9.1 min, t_2 = 10.3 min (maj); HRMS (ESI-TOF) *m/z* Calculated for $C_{13}H_{16}F_3NNaO_3$ $[M+H]^+$ 314.0974, found 314.0957.

(*R*)-Ethyl-4,4,4-trifluoro-3-(*p*-tolylamino)butanoate (2h) : 49 mg, 71% yield, pale yellow oil, R_f = 0.26 (hexanes/ethyl acetate = 20/1), 93% ee, $[\alpha]^{20}_D$ = -23.26 (*c* 0.49, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (d, *J* = 8.0 Hz, 2H), 6.65 (d, *J* = 8.4 Hz, 2H), 4.51 – 4.33 (m, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 3.43 (s, 1H), 2.81 (dd, *J* = 15.6, 4.6 Hz, 1H), 2.61 (dd, *J* = 15.6, 8.8 Hz, 1H), 2.25 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$

NMR (100 MHz, $CDCl_3$) δ 169.5, 143.4, 129.9, 128.8, 125.6 (q, *J* = 282.0 Hz), 114.3, 61.3, 53.9 (q, *J* = 30 Hz), 35.1(q, *J* = 1.0 Hz), 20.4, 14.0; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -76.1; HPLC (OD-H, elute: Hexanes/*i*-PrOH = 90/10, detector: 230 nm, flow rate: 1.0 mL/min), 30 °C, t_1 = 5.2 min (maj), t_2 = 5.5 min; HRMS (ESI-TOF) *m/z* Calculated for $C_{13}H_{17}F_3NO_2$ $[M+H]^+$ 276.1206, found 276.1173.

(*R*)-Ethyl-3-((4-chlorophenyl)amino)-4,4,4-trifluorobutanoate (2i) : 54 mg, 73% yield, pale soild: 116-118 °C, R_f = 0.20 (hexanes/ethyl acetate = 20/1), 95% ee, $[\alpha]^{20}_D$ = -28.70 (*c* 0.54, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) ^1H NMR (400 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.8 Hz, 2H), 6.66 (d, *J* = 8.8 Hz, 2H), 4.51 – 4.35 (m, 1H), 4.26 – 4.07 (m, 2H), 4.03 – 3.82 (m, 1H), 2.83 (dd, *J* = 15.8, 4.3 Hz, 1H), 2.60 (dd, *J* = 15.8, 9.0 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.3, 144.4, 129.3, 125.4 (q, *J* = 282.0 Hz), 124.2, 115.1, 61.5, 53.5 (t, *J* = 30.0 Hz), 34.9 (q, *J* = 2.0 Hz), 14.0; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -76.1; HPLC (OD-H, elute: Hexanes/*i*-PrOH = 97/3, detector: 230 nm, flow rate: 0.5 mL/min), 30 °C, t_1 = 17.8 min (maj), t_2 = 21.1 min; HRMS (ESI-TOF) *m/z* Calculated for $C_{12}H_{14}ClF_3NO_2$ $[M+H]^+$ 296.0660, found 296.0655.

(*R*)-Ethyl-4,4,4-trifluoro-3-((4-fluorophenyl)amino)butanoate (2j) : 38 mg, 54% yield, pale yellow oil, R_f = 0.23 (hexanes/ethyl acetate = 30/1), 91% ee, $[\alpha]^{20}_D$ = -8.68 (*c* 0.38, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 – 6.85 (m, 2H), 6.75 – 6.62 (m, 2H), 4.45 – 4.29 (m, 1H), 4.14 (qd, *J* = 7.1, 1.0 Hz, 2H), 3.77 (d, *J* = 9.7 Hz, 1H), 2.82 (dd, *J* = 15.7, 4.3 Hz, 1H), 2.60 (dd, *J* = 15.7, 9.1 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.5, 156.9 (d, *J* = 236.0 Hz), 142.1(d, *J* = 3.0 Hz), 125.5 (q, *J* = 282.0 Hz), 115.8 (d, *J* = 24.0 Hz), 115.3 (d, *J* = 8.0 Hz), 61.4, 54.5 (q, *J* = 30.0 Hz), 35.0 (q, *J* = 1.0 Hz), 14.0; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -76.1, -125.4; HPLC (OD-H, elute: Hexanes/*i*-PrOH = 95/5, detector: 230 nm, flow rate: 0.8 mL/min), 30 °C, t_1 = 7.9 min (maj), t_2 = 9.0 min; HRMS (ESI-TOF) *m/z* Calculated for $C_{12}H_{14}F_4NO_2$ $[M+H]^+$ 280.0955, found 280.0956.

(*R*)-Ethyl-4,4,4-trifluoro-3-(naphthalen-1-ylamino)butanoate (2k) : 65 mg, 84% yield, pale yellow oil, R_f = 0.32 (hexanes/ethyl acetate = 20/1), 96% ee, $[\alpha]^{20}_D$ = +59.23 (*c* 0.65, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.76 (m, 2H), 7.56 – 7.45 (m, 2H), 7.42 – 7.33 (m, 2H), 6.87 (dd, *J* = 6.3, 2.1 Hz, 1H), 4.89 (d, *J* = 9.3 Hz, 1H), 4.72 (dt, *J* = 9.2, 7.1 Hz, 1H), 4.14 (d, *J* = 7.1 Hz, 2H), 2.93 (dd, *J* = 15.7, 5.0 Hz, 1H), 2.82 (dd, *J* = 15.7, 7.5 Hz, 1H), 1.19 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 169.7, 141.0, 134.5, 128.8, 126.3, 126.0, 125.7 (q, *J* = 282.0 Hz), 125.3, 123.8, 119.8, 119.6, 106.7, 61.5, 53.5 (q, *J* = 30.0 Hz), 34.8 (q, *J* = 2.0 Hz), 14.0; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -75.6; HPLC (OD-H, elute: Hexanes/*i*-PrOH = 95/5, detector: 230 nm, flow rate: 0.8 mL/min), 30 °C, t_1 = 23.3min (maj), t_2 = 26.2 min; HRMS (ESI-TOF) *m/z* Calculated for $C_{16}H_{17}F_3NO_2$ $[M+H]^+$ 312.1206, found 312.1207.

(*R*)-Ethyl-4,4-difluoro-3-(phenylamino)butanoate (2l) :[23b] 47mg, 77% yield, pale yellow oil, R_f = 0.31 (hexanes/ethyl acetate = 20/1), 72% ee, $[\alpha]^{20}_D$ = -11.7 (*c* 0.47, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.21 (t, *J* = 7.8 Hz, 2H), 6.80 (t, *J* = 7.3 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 2H), 5.94 (td, *J* = 56.1, 2.5 Hz, 1H), 4.33 – 4.19 (m, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 3.97 (s, 1H), 2.77 (dd, *J* = 15.9, 5.3 Hz, 1H), 2.61 (dd, *J* = 15.9, 7.3 Hz, 1H), 1.24 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 170.7, 145.8, 129.5, 119.1, 115.1 (t, *J* = 245.0 Hz), 113.9, 61.1, 52.6 (q, *J* = 22.0 Hz), 33.3 (q, *J* = 2.0 Hz), 14.1; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -125.4 (d, *J* = 282.7, 1F), 130.2 (d, *J* = 282.7, 1F); HPLC (OD-H, elute: Hexanes/*i*-PrOH = 90/10, detector: 230 nm, flow rate: 1.0 mL/min), 30 °C, t_1 = 7.4 min, t_2 = 8.2 min (maj).

(2*R*,3*R*)-Ethyl-4,4,4-trifluoro-3-((4-methoxyphenyl)amino)-2-methylbutanoate (2m1) :[3c] 33mg, 43% yield, pale yellow oil, R_f = 0.53 (hexanes/ethyl acetate = 30/1), 84% ee, $[\alpha]^{20}_D$ = -17.57 (*c* 0.33, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, *J* = 8.9 Hz, 2H), 6.67 (d, J = 8.8 Hz, 2H), 4.48 (d, J = 9.5 Hz, 1H), 4.25 – 4.08 (m, 2H), 4.03 – 3.86 (m, 1H), 3.74 (s, 3H), 3.05 – 2.88 (m, 1H), 1.30 (d, J = 7.1 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 173.8, 153.0, 140.8, 125.7 (t, *J* = 281.0 Hz), 114.9 (d), 61.2, 59.7 (q, *J* = 28.0 Hz), 55.7, 39.1, 14.9, 14.0; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -73.5; HPLC (OD-H, elute: Hexanes/*i*-PrOH = 90/10, detector: 230 nm, flow rate: 0.8 mL/min), 30 °C, t_1 = 5.5 min (maj), t_2 = 6.0 min.

(2*R*,3*S*)-Ethyl-4,4,4-trifluoro-3-((4-methoxyphenyl)amino)-2-methylbutanoate (2m2) :[3c] 26mg, 34% yield, pale yellow oil, R_f = 0.52 (hexanes/ethyl acetate = 30/1), 90% ee, $[\alpha]^{20}_D$ = -0.77 (*c* 0.26, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, *J* = 8.9 Hz, 2H), 6.69 (d, *J* = 8.9 Hz, 2H), 4.44 (ddd, *J* = 11.0, 7.5, 5.5 Hz, 1H), 4.09 (q, *J* = 7.1 Hz, 2H), 3.74 (s, 3H), 3.55 (d, *J* = 10.7 Hz, 1H), 2.93 (dd, *J* = 7.0, 5.5 Hz, 1H), 1.30 (d, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.8, 153.4, 140.1, 125.8 (t, *J* = 283.0 Hz), 115.8, 114.8, 61.3, 58.4 (q, *J* = 30.0 Hz), 55.7, 39.8, 14.0, 11.5; $^{19}F\{^1H\}$ NMR (376 MHz, $CDCl_3$) δ -73.1; HPLC (OD-H, elute: Hexanes/*i*-PrOH = 90/10, detector: 230 nm, flow rate: 0.8 mL/min), 30 °C, t_1 = 6.1 min (maj), t_2 = 6.9 min.

For 2.0 mmol Experiment

(*S*,*S*)-Ph-BPE (49.6 mg, 0.096 mmol) and $Pd(OCOCF_3)_2$ (26.6 mg, 0.08 mmol) were placed in a dried Schlenk tube under nitrogen atmosphere, and degassed anhydrous acetone was added. The mixture was stirred at room temperature for 1 h. The solvent was removed under vacuum to give the catalyst. This catalyst was taken into a glovebox filled with nitrogen and dissolved in dry HFIP (15 mL). To a mixture of substrates **1e** (2.0 mmol) and *p*-anisic acid (60.8 mg, 0.4 mmol), the catalyst solution was added, and then the mixture was transferred to an autoclave. The hydrogenation was performed at 60 °C under 800 psi of hydrogen. The autoclave was stirred under directed conditions for 24 h, then the hydrogen was carefully released, the autoclave was opened, and saturated aqueous sodium bicarbonate (15 mL) was added to the

mixture and stirred for 10-15 min. The mixture was extracted with dichloromethane twice and the combined organic extracts dried over sodium sulfate. The resulting mixture was concentrated in vacuo and further purification was performed by a silica gel column eluted with hexanes/ethyl acetate to give the desired product **2e**. The enantiomeric excesses were determined by chiral HPLC after the purification by column chromatography on silica gel (ethyl acetate/hexanes), 0.409 g, 70% yield, 94% ee.

Synthesis of (*R*)-4,4,4-trifluoro-3-(phenylamino)butan-1-ol.

$LiAlH_4$ (23 mg, 0.6 mmol) was added to a solution of **1a** (52.0 mg, 0.2 mmol) in THF (4.0 mL) at -50 °C. The resulting mixture was stirred for 2h at -50 °C under argon atmosphere. The reaction was quenchesd with saturated ammonium chloride solution and the aqueous layer was exacted with 3 x 10 mL of EtOAc. The organic layer was dried over Na_2SO_4 and filtered. The solvent was evaporated under reduced pressure to get the crude product. The crude product was chromatographed on a silica gel column using 2:1 hexanes /EtOAc as eluent to afford the analytically pure product **5a** in 38 mg (99% ee, 89% yield). [3c].

(*R*)-4,4,4-trifluoro-3-(phenylamino)butan-1-ol (5a) : 38 mg, 89% yield, pale yellow oil, R_f = 0.35 (hexanes/ethyl acetate = 2/1), 99% ee, $[\alpha]^{20}_D$ = +56.84 (*c* 0.38, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.16 (m, 2H), 6.84 – 6.77 (m, 1H), 6.72 (d, *J* = 7.7 Hz, 2H), 4.18 (s, 1H), 3.81 (dd, *J* = 6.7, 4.6 Hz, 2H), 3.73 (s, 1H), 2.20 – 2.08 (m, 1H), 1.75 (ddt, *J* = 14.7, 10.4, 4.4 Hz, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 146.6, 129.5, 126.3 (q, *J* = 282.0 Hz), 119.1, 113.6, 58.6, 53.2 (q, *J* = 30.0 Hz), 31.9 (q, *J* = 2.0 Hz); ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$) δ -76.0; HPLC (OD-H, elute: Hexanes/*i*-PrOH = 85/15, detector: 230 nm, flow rate: 1.0 mL/min), 30 °C, t_1 = 10.1 min (maj), t_2 = 12.1 min.

Synthesis of (*R*)-ethyl-3-amino-4,4,4-trifluorobutanoate.

To a solution of cerium ammonium nitrate (CAN, 5.0 eq) in acetonitrile/water (10 mL, 1:1) at 0 °C was added a solution of (*R*)-**2e** (158.0 mg, 0.54 mmol) in acetonitrile (5 mL). The reaction mixture was stirred at 0 °C for 1 h and quenched with saturated aqueous sodium hydrogen sulfite (4 mL). The reaction mixture was exacted with ethyl acetate and concentrated under vacuum. The resulting phase was redissolved in 10 mL H_2O and CH_2Cl_2 (15 mL), 1*N* HCl aq. was added to the mixture until the solution became pH 2. The mixture was washed with CH_2Cl_2 (15 mL × 2). The aqueous layer was made alkaline by adding 1*N* NaOH, and then extracted CH_2Cl_2 (15 mL × 2). The combined organic solution was washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum to afford pure chiral primary amine (*R*)-(+)-**5e**.[15c, 18g, 24]

(*R*)-Ethyl-3-amino-4,4,4-trifluorobutanoate (5e) : 48 mg, 48% yield, colourless oil, 93% ee, $[\alpha]^{20}_D$ = +10.62 (*c* 0.48, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δδ 4.21 (q, *J* = 7.1 Hz, 2H), 3.76 – 3,73(m, 1H), 2.73 (dd, *J* = 16.1, 3.5 Hz, 1H), 2.46 (dd, *J* = 16.1, 10.1 Hz, 1H), 1.73 (brs, 2H), 1.29 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 170.2, 126.0 (q, *J* = 279.0 Hz), 61.2, 51.1 (q, *J* = 30.0 Hz), 35.6, 14.1; ^{19}F{^{1}H}

NMR (376 MHz, $CDCl_3$) δ -78.9; Enantiomeric excess was determined by HPLC for the corresponding benzamide, R_f = 0.16 (hexanes/ethyl acetate = 5/1), HPLC (OJ-H, elute: Hexanes/*i*-PrOH = 90/10, detector: 230 nm, flow rate: 1.0 mL/min), 30 °C, t_1 = 8.3 min (maj), t_2 = 9.1 min.

For Deuterium-Labeling Experiment of Eq. 7

p-Anisic acid (7.6 mg, 0.05 mmol) was placed in a dried Schlenk tube under nitrogen atmosphere, and degassed anhydrous CD_3OD (1.0 mL) was added. The mixture was stirred at room temperature for 0.5 h. The solvent was removed under vacuum to give the catalyst. The substrates **1a** (64.8 mg, 0.25 mmol) and D-HFIP (1.0 mL) were added. The ratio of imine (**1ac**) to enamine (**1ab**) is 1:5 under room temperature for 10 minute. When the reaction was performed at 60 °C for 10 minute, the atio of **1ac** to **1ab** is 1:2. Under 60 °C for 1 h, the **1a** is almost completely converted into **1ac** and **1ab**, and the ratio of **1ac** to **1ab** is 2.6:1. Subsequently, the ratio of **1ac** to **1ab** was increased with time prolonged (see Figure S1).

ASSOCIATED CONTENT

Supporting information

NMR spectra of products, and HPLC for racemic and chiral products of all compounds. This material is available free of charge via the internet at http://pubs.acs.org.

X-ray crystallography data **2a** (CCDC 1909865) (CIF)

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Notes

The authors declare no competing financial interest.

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