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Asymmetric Mannich-type Reactions of Fluorinated Ketoesters with Binaphthyl-Modified Thiourea Catalysts

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The catalytic enantioselective Mannich-type reaction promoted by chiral binaphthyl-modified bifunctional organocatalysts is described. The treatment of α-fluoro-β-ketoesters with *N*-Boc imines under mild reaction conditions afforded the corresponding β-aminated α-fluoro-β-ketoesters with excellent enantioselectivities (up to 98% ee).

Key Words : Mannich reaction, Asymmetric catalysis, Bifunctional organocatalyst, α-Fluoro-β-ketoesters, *N*-Boc imines

Introduction

Fluorinated molecules are of high importance in medicinal and organic chemistry.[1] Introduction of fluorine atom into biologically active compounds often leads to improvement of their biological characteristics due to unique properties of the fluorine atom.[2] Enantiopure fluorine-containing organic molecules are interesting and important materials with uses in analytical, biological, and medicinal chemistry and also in the chemistry of polymers and materials.[3] Among various strategies, electrophilic fluorination of active methines and C-C bond formation of fluorocarbon nucleophiles are two typical approaches for the construction of fluorine-containing molecules, and their asymmetric versions are particularly attractive. Enantioselective electrophilic fluorination has been achieved with the aid of electrophilic fluorinating agents using chiral transition-metal catalysts and organocatalysts with excellent enantioselectivities.[4,5] On the other hand, the use of fluorinated active methine nucleophiles such as fluoromalonate,[6] α-fluoro-β-ketoesters,[7] and fluorobis(phenylsulfonyl)methane[8] for a catalytic asymmetric reaction has become increasingly popular. Several groups have developed organocatalytic conjugate addition of nucleophilic α-fluoro-β-ketoesters to nitroalkenes,[7d-f] Michael reaction to α,β-unsaturated ketone,[7h] phase-transfer catalytic amination to azodicarboxylate.[7b] Enantioselective Mannich reactions are efficient and powerful methods to prepare chiral β-amino carbonyl derivatives.[9] Tremendous efforts have been made in the development of efficient chiral catalysts for enantioselective Mannich-type reactions with preformed enolates[10] and enolizable β-dicarbonyl and related compounds.[11] Recently, Lu and Tan groups report the catalytic enantioselective Mannich reactions of α-fluoro-β-ketoesters with *N*-Boc imines using tryptophan-derived organocatalyst and chiral bicyclic guanidine catalyst.[12]

As part of a research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,[13] we recently reported chiral amine-thiourea bifunctional organocatalyst to be a highly selective catalyst for the enantioselective addition reaction of active methines.[14] We envisioned that the assembly of a structurally well-defined chiral 1,2-diamine and binaphthyl scaffold with a thiourea motif could constitute a new class of bifunctional organocatalyst. The rigid binaphthyl structure can serve as an efficient stereocontrolling axial chiral element. In this article, we wish to describe the direct enantioselective Mannich reaction of α-fluoro-β-ketoesters with simple *N*-Boc imines catalyzed by binaphthyl-modified thiourea organocatalysts bearing both central and axial chiral elements.

Results and Discussion

The ogranocatalysts **I-VIII** (Fig. 1) were prepared according to the reported procedure.[14,15] In an attempt to validate the feasibility of the organocatalytic enantioselective Mannich reaction of α-fluoro-β-ketoesters, we initially investigated the reaction system with α-fluoro-β-ketoester **1a** and *N*-Boc *p*-tolualdimine (**2a**) in the presence of 10 mol % of catalyst in toluene at room temperature. We first examined the impact of the structure of catalysts **I-VIII** on enantioselectivities (Table 1, entries 1-8).

While chiral bifunctional organocatalysts **I-VIII** bearing both central and axial chiral elements or cinchona alkaloid backbone effectively promoted the addition in high yield but with moderate enantioselectivity (8-76% ee), Catalyst **III** gave the desired product **3a** with high enantioselectivity (entry 3). Based on the exploratory studies, we decided to select catalyst **III** for further optimization of reaction conditions. A survey of the reaction media indicated that many common solvents, such as toluene, dichloromethane, THF, diethyl ether, *tert*-butyl methyl ether, diphenyl ether, and ethyl vinyl ether (entries 3 and 9-14), were well tolerated in this Mannich-type reaction with moderate to high enantioselectivities. Among the solvents probed, the best results (97% yield, 85:15 dr, and 85% ee) were achieved when the reaction was conducted in diethyl ether (entry 14). Lowering the temperature to −40 °C with catalyst **III** improved the diastereoselectivty, but decreased slightly the enantioselec-

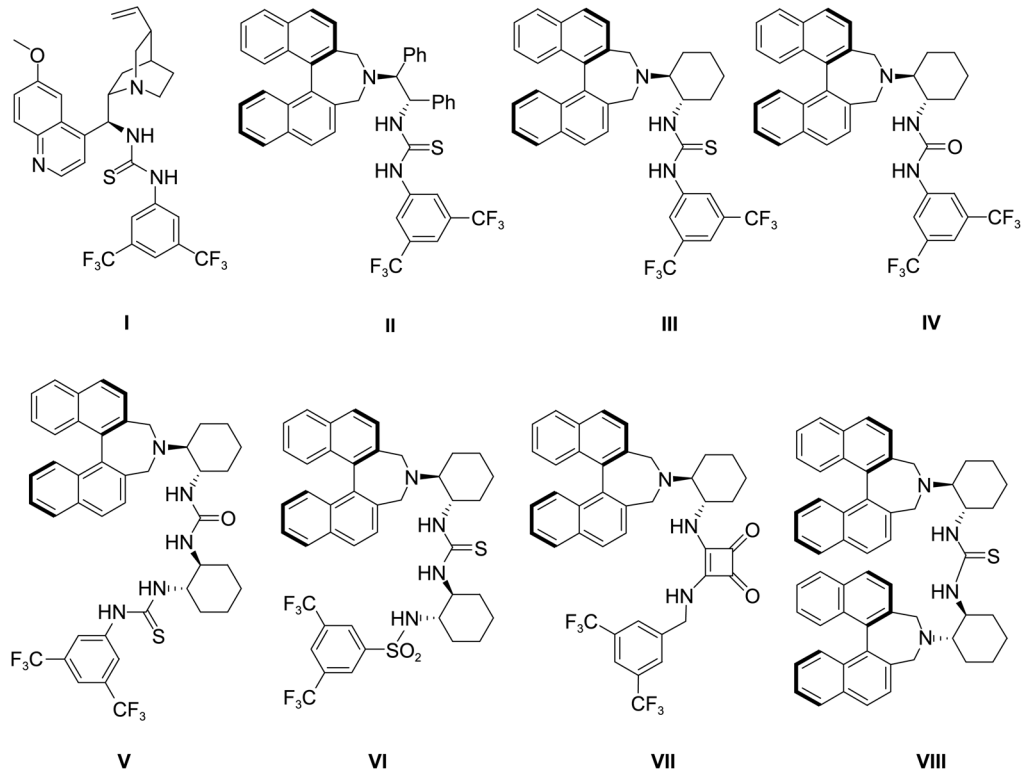
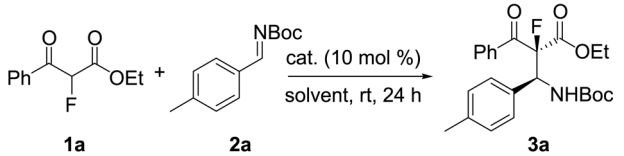


Figure 1. Structures of various chiral thiourea-tertiary amine catalysts.

Table 1. Optimization of the reaction conditions

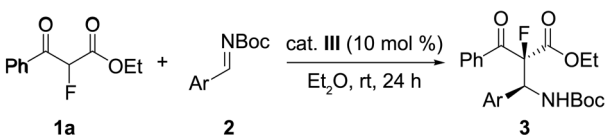


1a **2a** **3a**

Entry	Cat.	Solvent	Yield (%)[a]	dr (%)[b]	ee (%)[c]
1	**I**	PhMe	97	80:20	45
2	**II**	PhMe	32	67:36	8
3	**III**	PhMe	97	77:23	76
4	**IV**	PhMe	98	88:22	37
5	**V**	PhMe	60	69:31	45
6	**VI**	PhMe	48	87:13	16
7	**VII**	PhMe	60	50:50	24
8	**VIII**	PhMe	69	77:23	63
9	**III**	DCM	64	82:18	63
10	**III**	THF	27	79:21	30
11	**III**	TBME	98	79:21	62
12	**III**	Ph_2O	98	81:19	68
13	**III**	$EtOCH=CH_2$	98	79:21	85
14	**III**	Et_2O	97	85:15	88
15[d]	**III**	Et_2O	68	90:10	84
16[e]	**III**	Et_2O	67	93:7	82
17[f]	**III**	Et_2O	60	96:4	79

[a]Isolated yield. [b]The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude product. [c]Enantiomeric excess of major diastereomer was determined by HPLC analysis using Chiralpak AD-H column. [d]This reaction was carried out at 0 °C. [e]This reaction was carried out at −20 °C. [f]This reaction was carried out at −40 °C.

Table 2. Variation of *N*-Boc imines



1a **2** **3**

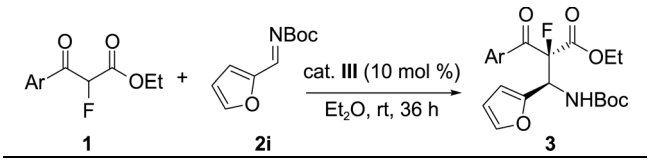
Entry	**2**, Ar	Yield (%)[a]	dr (%)[b]	ee (%)[c]
1	**2a**, *p*-MeC_6H_4	**3a**, 98	83:17	88
2	**2b**, *p*-BrC_6H_4	**3b**, 80	85:15	89
3	**2c**, *p*-ClC_6H_4	**3c**, 98	88:12	81
4	**2d**, C_6H_5	**3d**, 84	91:9	88
5	**2e**, *o*-ClC_6H_4	**3e**, 98	> 99:1	86
6	**2f**, *o*-FC_6H_4	**3f**, 88	99:1	76
7	**2g**, *m*-$NO_2C_6H_4$	**3g**, 80	83:7	79
8	**2h**, 1-naphthyl	**3h**, 90	91:9	81
9	**2i**, 2-furyl	**3i**, 98	73:27	98
10	**2j**, 2-thienyl	**3j**, 78	95:5	95

[a]Isolated yield. [b]The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude product. [c]Enantiomeric excess of major diastereomer was determined by HPLC analysis using Chiralpak AD-H (for **3a**), IA (for **3b-g**, **3i-j**), Whelk-O1 (for **3h**) columns.

tivity (entries 14-17). Absolute configuration of major diastereomer of **3a** was determined to be (2*S*, 3*S*) by comparison of the optical rotation and chiral HPLC data with the literature values.[12]

We then explored the possibility of using wide range of *N*-Boc protected substituted aromatic and heteroaromatic imines **2** with α-fluoro-β-ketoester **1a** under the optimized reaction condition. As shown in Table 2, high yields (78-98%),

Table 3. Variation of α-fluoro-β-ketoesters



1 **2i** **3**

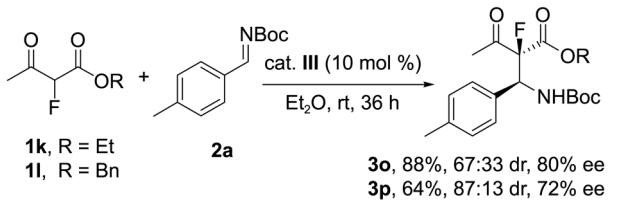
Entry	**1**, Ar	Yield (%)[a]	dr (%)[b]	ee (%)[c]
1	**1b**, *p*-$NO_2C_6H_4$	**3k**, 88	78:22	98
2	**1c**, *p*-$CF_3C_6H_4$	**3l**, 88	62:38	96
3	**1d**, *p*-$OMeC_6H_4$	**3m**, 84	75:25	96
4	**1e**, *p*-BrC_6H_4	**3n**, 80	74:26	98

[a]Isolated yield. [b]The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis of the crude product. [c]Enantiomeric excess of major diastereomer of **3k-n** was determined by HPLC analysis using Chiralpak IA column.

excellent diastereoselectivities (up to > 99:1), and excellent enantioselectivities (up to 98%) were observed for different substitution patterns on the aromatic ring of imines **2**. Both electron-withdrawing and electron-donating substrates, as well as the heteroaromatic substrates gave excellent results.

To examine the generality of the catalytic enantioselective Mannich-type reaction of α-fluoro-β-ketoesters **1** by using naphthyl-modified bifunctional organocatalyst **III**, we studied the addition of various α-fluoro-β-ketoesters **1** to *N*-Boc aldimine **2i**. As it can be seen by the results summarized in Table 3, the corresponding products **3k-n** were obtained in high to excellent yields (80-88%), high diastereoselectivities (62:38-78:22), and excellent enantioselectivities (96-98%).

We examined the direct enantioselective Mannich-type reaction of α-fluoro acetoacetate derivatives **1k-l** with *N*-Boc *p*-tolualdimine (**2a**) using bifunctional organocatalyst **III** in diethyl ether at room temperature. In the presence of 10 mol % of catalyst **III**, the reaction proceeded to afford the β-aminated product **3o-p** after 36 h with 72-80% ee (Scheme 1).



Scheme 1

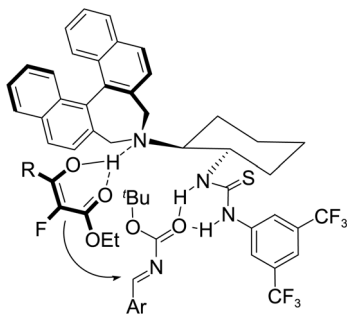


Figure 2. Proposed stereochemical model.

Although the reason for the observed enantioselectivity is still unclear, we believe that a carbonyl group of the *N*-Boc imine **2** is activated by the thiourea moiety through hydrogen bonding, and the α-fluoro-β-ketoester moiety is activated by the basic nitrogen atom in tertiary amine (Fig. 2). These interactions control the stereochemical outcome of the reaction and increase the reaction rate.

Conclusion

In conclusion, we have developed a highly efficient catalytic enantioselective Mannich reaction of α-fluoro-β-ketoesters using chiral binaphthyl-modified thiourea organocatalysts. The desired β-aminated products were obtained in good to high yields, and high enantioselectivities (72-98% ee) were observed for all the substrates examined in this work. We believe that this method provides a practical entry for the preparation of chiral β-aminated α-fluoro-β-ketoester derivatives. Further study of these bifunctional organocatalysts in other asymmetric reactions is being under investigated.

Experimental Section

General. All commercial reagents and solvents were used without purification. TLC analyses were carried out on precoated silica gel plates with F_{254} indicator. Visualization was accomplished by UV light (254 nm), I_2, *p*-anisaldehyde, ninhydrin, and phosphomolybdic acid solution as an indicator. Purification of reaction products was carried out by flash chromatography using E. Merck silica gel 60 (230-400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 200 (200 MHz for ^{1}H, 50 MHz for ^{13}C). Chemical shift values (δ) are reported in ppm relative to Me_4Si (δ 0.0 ppm). Optical rotations were measured on a JASCO-DIP-1000 digital polarimeter with a sodium lamp. The enantiomeric excesses (ee's) were determined by HPLC. HPLC analysis was performed on Younglin M930 Series and Younglin M720 Series, measured at 254 nm using the indicated chiral column.

General Procedure for the Mannich-type Reaction of α-fluoro-β-ketoester 1 with *N*-Boc Imine 2: To a solution of α-fluoro-β-ketoester (**1**, 0.3 mmol) and catalyst **III** (0.03 mmol, 20 mg) in Et_2O (6 mL) was added *N*-Boc imine (**2**, 0.45 mmol). Reaction mixture was stirred for 24-36 h at room temperature, concentrated, and purified by flash column chromatography (EtOAc/hexane:1/7) to afford the Mannich adduct **3**.

(2*S*, 3*S*)-Ethyl 2-Benzoyl-3-(*tert*-butoxycarbonylamino)-2-fluoro-3-*p*-tolylpropanoate (3a). Major diastereomer: $[\alpha]_D^{31}$ = 20.0 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28 (t, *J* = 6.9 Hz, 3H), 1.39 (s, 9H), 2.26 (s, 3H), 4.18-4.39 (m, 2H), 5.44 (d, *J* = 10.4 Hz, 1H), 5.96 (dd, ^2J = 28.9 Hz, ^1J = 10.4 Hz, 1H), 7.04-7.08 (m, 2H), 7.26-7.29 (m, 2H), 7.34-7.39 (m, 2H), 7.49-7.54 (m, 1H), 7.81-7.84 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.77, 20.96, 28.11, 57.11 (d, *J* = 18.35 Hz), 63.01, 79.96, 102.21 (d, *J* = 203.75 Hz),

128.35, 128.56, 128.96, 129.33, 129.46, 133.54, 133.66, 137.71, 154.29, 165.49 (d, J = 26.9 Hz), 190.76 (d, J = 25.6 Hz); HPLC (80 : 20, *n*-hexane : *i*-PrOH, 254 nm, 1.0 mL/min) Chiralpak AD-H column, t_R = 10.4 min (minor), t_R = 14.9 min (major), 88% ee.

(2*S*, 3*S*)-Ethyl 2-Benzoyl-3-(*tert*-butoxycarbonylamino)-2-fluoro-3-(4-bormophenyl)propanoate (3b). Major diastereomer: $[\alpha]_D^{31}$ = 37.3 (c = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, J = 7.0 Hz, 3H), 1.38 (s, 9H), 4.17-4.41 (m, 2H), 5.48 (d, J = 10.4, 1H), 5.95 (dd, ^1J = 28.7 Hz, ^2J = 10.4 Hz, 1H), 7.27-7.48 (m, 5H), 7.51-7.59 (m, 2H), 7.82-7.86 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.79, 28.11, 56.80 (d, J = 18.2 Hz), 63.29, 80.30, 101.93 (d, J = 204.0 Hz), 122.23, 128.50, 129.41, 129.53, 130.54, 131.43, 134.00, 135.63, 154.24, 165.22 (d, J = 27.2 Hz), 190.39 (d, J = 25.1 Hz); HPLC (85 : 15, *n*-hexane : EtOH, 254 nm, 0.5 mL/min) Chiralpak IA column, t_R = 15.8 min (major), t_R = 17.3 min (minor), 89% ee.

(2*S*, 3*S*)-Ethyl 2-Benzoyl-3-(*tert*-butoxycarbonylamino)-2-fluoro-3-(4-chlorophenyl)propanoate (3c). Major diastereomer: $[\alpha]_D^{26}$ = 7.0 (c = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28 (t, J = 6.9 Hz, 3H), 1.39 (s, 9H), 4.18-4.41 (m, 2H), 5.45 (d, J = 10.4 Hz, 1H), 5.87 (dd, J = 28.8, 10.4 Hz, 1H), 7.35-7.44 (m, 5H), 7.54-7.58 (m, 2H), 7.80-7.84 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.82, 28.15, 56.78 (d, J = 17.7 Hz), 63.32, 80.35, 102.01 (d, J = 204.4 Hz), 128.54, 129.56, 129.81, 130.24x2, 134.01, 135.12, 154.30, 165.32 (d, J = 26.5 Hz), 190.33 (d, J = 25.7 Hz); HPLC (85 : 15, *n*-hexane : *i*-PrOH, 254 nm, 0.5 mL/min) Chiralpak IA column, t_R = 23.8 min (minor), t_R = 28.1 min (major), 81% ee.

(2*S*, 3*S*)-Ethyl 2-Benzoyl-3-(*tert*-butoxycarbonylamino)-2-fluoro-3-propanoate (3d). Major diastereomer: $[\alpha]_D^{29}$ = 39.3 (c = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26 (t, J = 6.8 Hz, 3H), 1.38 (s, 9H), 4.16-4.39 (m, 2H), 5.57 (d, J = 10.5 Hz, 1H), 6.02 (dd, J = 28.8, 10.5 Hz, 1H), 7.19-7.33 (m, 4H), 7.36-7.51 (m, 4H), 7.80-7.83 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.75, 28.08, 57.38 (d, J = 18.5 Hz), 63.11, 79.97, 102.19 (d, J = 204 Hz), 128.01, 128.26, 128.34, 128.74, 129.28, 129.39, 133.69, 136.50, 154.31, 165.38 (d, J = 27.1 Hz), 190.80 (d, J = 25.6 Hz); HPLC (85 : 15, *n*-hexane : *i*-PrOH, 254 nm, 0.5 mL/min) Chiralpak IA column, t_R = 23.5 min (minor), t_R = 31.0 min (major), 88% ee.

(2*S*, 3*S*)-Ethyl 2-Benzoyl-3-(*tert*-butoxycarbonylamino)-2-fluoro-3-(2-chlorophenyl)propanoate (3e). Major diastereomer: $[\alpha]_D^{28}$ = 55.5 (c = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28 (t, J = 6.1 Hz, 3H), 1.39 (s, 9H), 4.23-4.35 (m, 2H), 5.55 (d, J = 10.1 Hz, 1H), 6.47 (dd, J = 26.1, 10.1 Hz, 1H), 7.10-7.18 (m, 2H), 7.33-7.55 (m, 5H), 7.87-7.91 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.53, 27.88, 53.62 (d, J = 18.7 Hz,), 63.02, 79.84, 101.30 (d, J = 205.4 Hz), 126.76, 128.30, 128.85, 129.09, 129.22, 129.85x2, 133.71, 134.57, 134.97, 153.89, 165.15 (d, J = 26.7 Hz), 190.22 (d, J = 24.9 Hz); HPLC (85 : 15, *n*-hexane : *i*-PrOH, 254 nm, 0.5 mL/min) Chiralpak IA column, t_R = 30.4 min (minor), t_R = 51.2 min (major), 86% ee.

(2*S*, 3*S*)-Ethyl 2-Benzoyl-3-(*tert*-butoxycarbonylamino)-2-fluoro-3-(2-fluorophenyl)propanoate (3f). Major diastereomer: $[\alpha]_D^{30}$ = 43.5 (c = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, J = 7.3 Hz, 3H), 1.39 (s, 9H), 4.22-4.38 (m, 2H), 5.64 (d, J = 10.4 Hz, 1H), 6.25 (dd, ^1J = 28.4 Hz, ^2J = 10.4 Hz, 1H), 6.97-7.07 (m, 2H), 7.18-7.26 (m, 1H), 7.34-7.42 (m, 3H), 7.47-7.57 (m, 1H), 7.85-7.90 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.80, 28.13, 52.85 (d, J = 19.6 Hz), 63.24, 80.20, 101.92 (d, J = 204.7 Hz), 115.89 (d, J = 22.7 Hz), 123.5 (d, J = 12.1 Hz), 124.02 (d, J = 6.45 Hz), 128.48, 129.44, 129.56, 129.94 (d, J = 8.5 Hz), 130.79 (s), 133.91, 154.27, 158.90 (d, J = 248.2 Hz), 168.33 (d, J = 26.8 Hz), 190.33 (d, J = 25.7 Hz); HPLC (85 : 15, *n*-hexane : *i*-PrOH, 254 nm, 0.5 mL/min) Chiralpak IA column, t_R = 24.0 min (minor), t_R = 38.0 min (major), 76% ee.

(2*S*, 3*S*)-Ethyl 2-Benzoyl-3-(*tert*-butoxycarbonylamino)-2-fluoro-3-(3-nitrophenyl)propanoate (3g). Major diastereomer: $[\alpha]_D^{31}$ = 16.4 (c = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29 (t, J = 6.9 Hz, 3H), 1.39 (s, 9H), 4.17-4.44 (m, 2H), 5.62 (d, J = 10.3 Hz, 1H), 6.09 (dd, ^1J = 28.4, ^2J = 10.3 Hz, 1H), 7.36-7.60 (m, 4H), 7.79-7.90 (m, 3H), 8.10-8.14 (m, 1H), 8.30-8.31 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.80, 28.80, 56.60 (d, J = 18.4 Hz), 63.51, 80.72, 101.63 (d, J = 204.5 Hz), 123.13, 123.75, 128.62, 129.18, 125.51, 129.63, 134.32, 135.48, 138.65, 148.09, 154.18, 164.98 (d, J = 26.6 Hz), 189.88 (d, J = 25.4 Hz); HPLC (85 : 15, *n*-hexane : *i*-PrOH, 254nm, 0.5 mL/min) Chiralpak IA column, t_R = 19.7 min (minor), t_R = 29.4 min (major), 79% ee.

(2*S*, 3*S*)-Ethyl 2-Benzoyl-3-(*tert*-butoxycarbonylamino)-2-fluoro-3-(1-naphthyl)propanoate (3h). Major diastereomer: $[\alpha]_D^{30}$ = 18.4 (c = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.33 (t, J = 7.1 Hz, 3H), 1.39 (s, 9H), 4.29-4.40 (m, 2H), 5.29 (d, J = 10.2 Hz, 1H), 6.84 (dd, ^1J = 28.0 Hz, ^2J = 10.2 Hz, 1H), 7.23-7.39 (m, 3H), 7.47-7.54 (m, 3H), 7.59-7.64 (m, 1H), 7.67-7.83 (m, 4H), 8.44-8.48 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.84, 28.12, 52.43 (d, J = 17.7Hz), 63.40, 80.10, 102.45 (d, J = 204.8 Hz), 124.13, 124.92, 125.90, 126.77, 128.42, 128.88, 129.32, 129.43, 131.60, 133.69, 154.32, 165.59 (d, J = 27.6 Hz), 190.91 (d, J = 24.8 Hz); HPLC (80 : 20, *n*-hexane : *i*-PrOH, 254 nm, 0.5 mL/min) Regis Whelk-O1 column, t_R = 13.2 min (minor), t_R = 16.3 min (major), 81% ee.

(2*S*,3*S*)-Ethyl 2-Benzoyl-3-(*tert*-butoxycarbonylamino)-2-fluoro-3-(2-furanyl)propanoate (3i). Major diastereomer: $[\alpha]_D^{28}$ = 35.3 (c = 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.28 (t, J = 7.0 Hz, 3H), 1.43 (s, 9H), 4.18-4.38 (m, 2H), 5.35 (d, J = 10.7 Hz), 6.17 (dd, J = 28.2, 10.7 Hz, 1H), 6.24-6.26 (m, 2H), 7.27-7.29 (m, 1H), 7.38-7.46 (m, 2H), 7.53-7.60 (m, 1H), 7.90-7.94 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.79, 28.15, 52.07 (d, J = 19.7 Hz), 63.24, 80.33, 101.45 (d, J = 204.5 Hz), 108.84, 110.30, 128.51, 129.49, 129.61, 133.90, 142.37, 149.35, 154.32, 164.90 (d, J = 26.6 Hz), 190.39 (d, J = 25.2 Hz); HPLC (85 : 15, *n*-hexane : *i*-PrOH, 254 nm, 0.5 mL/min) Chiralpak IA column, t_R = 20.9 min (minor), t_R = 34.5 min (major), 98% ee.

(2*S*, 3*S*)-Ethyl 2-Benzoyl-3-(*tert*-butoxycarbonylamino)-2-fluoro-3-(2-thienyl)propanoate (3j). Major diastereomer:

$[\alpha]_D^{26}$ = 54.7 (c = 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.0 Hz, 3H), 1.41 (s, 9H) 4.17-4.40 (m, 2H), 5.36 (d, *J* = 10.4 Hz, 1H), 6.31 (dd, *J* = 28.3, 10.4 Hz, 1H), 6.86-6.90 (m, 1H), 7.06-7.08 (m, 1H), 7.16-7.18 (m, 1H), 7.36-7.44 (m, 2H), 7.51-7.59 (m, 1H), 7.89-7.93 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.74, 28.10, 53.53 (d, *J* = 19.35 Hz), 63.12, 80.27, 101.92 (d, *J* = 204.2 Hz), 125.53, 126.56, 127.18, 128.46, 129.45, 129.56, 133.91, 138.75, 154.11, 164.96 (d, *J* = 26.9 Hz), 190.34 (d, *J* = 25.3 Hz); HPLC (90 : 10, *n*-hexane : *i*-PrOH, 254 nm, 0.5 mL/min) Chiralpak IA column, t_R = 30.9 min (minor), t_R = 44.4 min (major), 95% ee.

(2S, 3S)-Ethyl 2-(4-nitrobenzoyl)-3-(*tert*-butoxycarbonylamino)-2-fluoro-3-(2-furanyl)propanoate (3k). Major diastereomer: $[\alpha]_D^{31}$ = 19.7 (*c* = 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.31 (t, *J* = 7.2 Hz, 3H), 1.44 (s, 9H), 4.20-4.41 (m, 2H), 5.36 (d, *J* = 10.2 Hz, 1H), 6.15 (dd, *J* = 28.2, 10.2 Hz, 1H), 6.27-6.31 (m, 2H), 7.30 (m, 1H), 8.01-8.06 (m, 2H), 8.24-8.28 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.83, 28.16, 52.21 (d, *J* = 19.3 Hz), 63.69, 80.67, 101.58 (d, *J* = 204.4 Hz), 109.13, 110.48, 123.62, 130.64, 138.59, 142.66, 148.90, 150.51, 154.30, 164.15 (d, *J* = 26.7 Hz), 189.96 (d, *J* = 25.7 Hz); HPLC (85 : 15, *n*-hexane : *i*-PrOH, 254 nm, 0.5 mL/min) Chiralpak IA column, t_R = 26.8 min (minor), t_R = 45.6 min (major), 98% ee.

(2*S*, 3*S*)-Ethyl 2-(4-(trifluoromethyl)phenyl)-3-(*tert*-butoxycarbonylamino)-2-fluoro-3-(2-furanyl)propanoate (3l). Major diastereomer: $[\alpha]_D^{30}$ = 26.0 (*c* = 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.30 (t, *J* = 7.3 Hz, 3H), 1.44 (s, 9H), 4.20-4.40 (m, 2H), 5.35 (d, *J* = 10.5 Hz, 1H), 6.17 (dd, *J* = 28.4, 10.5 Hz, 1H), 6.25-6.27 (m, 2H), 7.27-7.29 (m, 1H), 7.67-7.71 (m, 2H), 7.99-8.03 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.79, 28.14, 52.14 (d, *J* = 19.2 Hz), 63.51, 80.53, 101.54 (d, *J* = 204.5 Hz), 109.01, 110.39, 123.35 (q, *J* = 271.53 Hz), 125.55, 129.80, 134.94 (q, *J* = 32.5 Hz), 136.66, 142.55, 149.07, 154.31, 164.42 (d, *J* = 26.6 Hz), 189.56 (d, *J* = 29.0 Hz); HPLC (85 : 15, *n*-hexane : *i*-PrOH, 254 nm, 0.5 mL/min) Chiralpak IA column, t_R = 15.7 min (minor), t_R = 28.5 min (major), 96% ee.

(2*S*, 3*S*)-Ethyl 2-(4-methoxybenzoyl)-3-(*tert*-butoxycarbonylamino)-2-fluoro-3-(2-furanyl)propanoate (3m). Major diastereomer: $[\alpha]_D^{30}$ = 19.1 (*c* = 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.26 (t, *J* = 6.9 Hz, 3H), 1.43 (s, 9H), 3.84 (s, 3H), 4.16-4.36 (m, 2H), 5.36 (d, *J* = 10.5 Hz, 1H), 6.16 (dd, *J* = 28.3, 10.5 Hz), 6.23-6.25 (m, 2H), 6.86-6.93 (m, 2H), 7.79 (m, 1H), 7.95-8.00 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.74, 28.10, 51.96 (d, *J* = 19.5 Hz), 55.42, 63.06, 80.19, 101.50 (d, *J* = 204.4 Hz), 108.70, 110.24, 113.79, 126.60, 132.25, 142.22, 149.57, 154.31, 164.18, 165.20 (d, *J* = 26.9 Hz), 188.24 (d, *J* = 24.3 Hz); HPLC (85 : 15, *n*-hexane : *i*-PrOH, 254 nm, 0.5 mL/min) Chiralpak IA column, t_R = 26.6 min (minor), t_R = 49.6 min (major), 96% ee.

(2*S*, 3*S*)-Ethyl 2-(4-bromobenzoyl)-3-(*tert*-butoxycarbonylamino)-2-fluoro-3-(2-furanyl)propanoate (3n). Major diastereomer: $[\alpha]_D^{31}$ = 21.1 (c = 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.0 Hz, 3H), 1.43 (s, 9H), 4.19-4.37 (m, 2H), 5.32 (d, *J* = 10.1 Hz, 1H), 6.14 (dd, *J* = 28.4, 10.1 Hz, 1H), 6.23-6.31 (m, 2H), 7.27-7.29 (m, 1H), 7.54-7.59 (m, 2H), 7.78-7.81 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.81, 28.16, 52.08 (d, *J* = 19.3 Hz), 63.40, 80.45, 101.51 (d, *J* = 204.1 Hz), 108.93, 110.36, 129.47, 131.00, 131.92, 132.48, 142.46, 149.22, 154.31, 164.68 (d, *J* = 27.9 Hz), 189.64 (d, *J* = 25.5 Hz); HPLC (90 : 10, *n*-hexane : *i*-PrOH, 254 nm, 0.5 mL/min) Chiralpak IA column, t_R = 24.7 min (minor), t_R = 55.2 min (major), 98% ee.

(*S*)-Ethyl 2-((*S*)-(*tert*-butoxycarbonylamino)(*p*-tolyl)-methyl)-2-fluoro-3-oxobutanoate (3o). Mixture of diastereomers: $[\alpha]_D^{27}$ = 9.5 (*c* = 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.35-1.26 (m, 4.15H), 1.38 (m, 12.46H), 2.00 (d, *J* = 5.1 Hz, 3H), 2.23 (m, 4.15H), 2.34 (d, *J* = 5.1 Hz, 1.15H), 4.02-4.13 (m, 0.77H) 4.18-4.35 (m, 2.0H), 5.50 (m, 1.38H), 5.70 (m, 1.38H), 7.26-7.10 (m, 5.54H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.71, 13.91, 26.43x2, 28.16x2, 28.16x2, 55.97 (d, *J* = 17.9 Hz), 56.73 (d, *J* = 17.9 Hz), 62.76, 63.03, 79.22x2, 88.93 (d, *J* = 201.33 Hz), 101.98 (d, *J* = 201.33 Hz), 127.94x2, 128.16, 128.20, 129.25x2, 138.25x2, 154.28x2, 165.48x2 (d, *J* = 26.9 Hz), 200.09x2 (d, *J* = 25.6 Hz); HPLC (90 : 10, *n*-hexane : *i*-PrOH, 220 nm, 1.0 mL/min) Chiralpak IC column, t_R = 6.7 min (minor), t_R = 9.4 min (major), 80% ee.

(*S*)-Benzyl 2-((*S*)-(*tert*-butoxycarbonylamino)(*p*-tolyl)-methyl)-2-fluoro-3-oxobutanoate (3p). Major diastereomer: $[\alpha]_D^{27}$ = –2.4 (*c* = 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 1.36 (s, 9H), 1.99 (d, *J* = 4.41 Hz, 3H), 2.31 (s, 3H), 5.31-5.14 (m, 2H), 5.51 (dd. ^1J = 20.85, ^2J = 10.14, 2H), 7.26-7.04 (m, 4H), 7.34-7.30 (m. 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.09, 26.35, 28.15, 56.79 (d, *J* = 18.05 Hz), 68.35, 80.29, 103.00 (d, *J* = 203.75 Hz), 128.15, 128.52, 128.61, 129.26, 132.58, 132.84, 134.57, 138.27, 154.35, 164.21 (d, *J* = 26.9 Hz), 199.60 (d, *J* = 25.6 Hz); HPLC (90 : 10, *n*-hexane : *i*-PrOH, 220 nm, 1.0 mL/min) Chiralpak IC column, t_R = 7.4 min (minor), t_R = 10.0 min (major), 72% ee.

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