Synthesis K. Kitahara et al. Special Topic

Asymmetric Synthesis of α-Chloro-α-halo Ketones by Decarboxylative Chlorination of α-Halo-β-ketocarboxylic Acids

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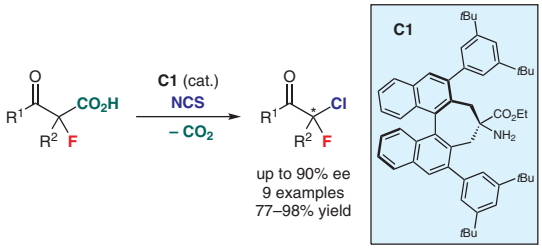
Published as part of the Special Topic *Halogenation methods (with a view towards radioimaging applications)*

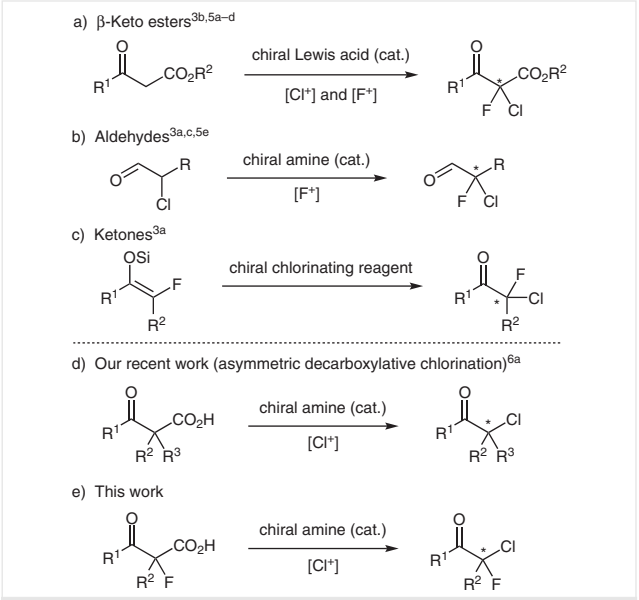


Received: 06.06.2019
Accepted after revision: 05.07.2019
Published online: 23.07.2019
DOI: 10.1055/s-0039-1690009; Art ID: ss-2019-c0320-st

Abstract Chiral α-chloro-α-fluoro ketones were synthesized by enantioselective decarboxylative chlorination of α-chloro-β-ketocarboxylic acids in the presence of a chiral amine catalyst. The reaction yielded the corresponding α-chloro-α-fluoro ketones with moderate-to-high enantioselectivity (up to 90% ee). The method was also applied to the synthesis of α-bromo-α-chloro ketones with 90% ee.

Key words decarboxylative chlorination, chiral amine catalyst, enantioselective synthesis, β-ketocarboxylic acids, fluorinated compounds

Chiral fluorinated compounds have been attracting increasing attention in the field of medicinal chemistry as the introduction of fluorine atom(s) into biologically active compounds often modifies their biological activity and/or pharmacokinetic behavior.[1] Therefore, numerous synthetic methods for chiral fluorinated compounds have been developed in the past two decades.[2] Our research group also developed some synthetic methods for chiral fluorinated compounds.[3,4] One such distinctive method is the asymmetric synthesis of α-chloro-α-fluorocarbonyl compounds[3,5] and the subsequent S_N2 reaction of the chlorine atom to yield the corresponding α-fluoro-α-heteroatom-substituted carbonyl compounds without loss of enantiopurity. We have developed catalytic methods for the asymmetric synthesis of α-chloro-α-fluoro-β-keto esters[3b] and α-chloro-α-fluoroaldehydes[3a,c] with high enantioselectivity (Scheme 1a,b). A catalytic version of enantioselective synthesis of α-chloro-α-fluoro ketones has not been achieved yet, although the synthesis was achieved by chlorination of α-fluorosilyl enolate with a stoichiometric amount of a chiral chlorinating reagent (Scheme 1c).[3a] Recently, our research group has achieved the enantioselective decarboxylative chlorination of β-ketocarboxylic acids to yield α-chloro ketones with a chiral primary amine catalyst bearing an axially chiral binaphthyl backbone (Scheme 1d).[6] Subsequently, we applied this method to the synthesis of racemic α-chloro-α-fluoro ketones.[7] Based on the aforementioned works, in this study, we achieved the catalytic enantioselective synthesis of α-chloro-α-fluoro ketones by decarboxylative chlorination of α-fluoro-β-ketocarboxylic acids with a chiral amine catalyst (Scheme 1e).



Scheme 1 Synthetic methods for α-chloro-α-fluorocarbonyl compounds

First, α-fluoro-β-ketocarboxylic acids **2** were synthesized from the corresponding *tert*-butyl α-fluoro-β-keto esters **1** (Table 1). Treatment of β-keto esters **1** with 20 equivalents of trifluoroacetic acid in dichloromethane yielded

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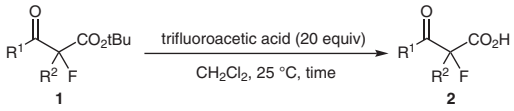
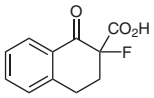
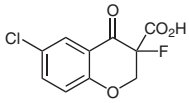
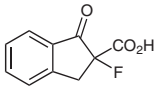
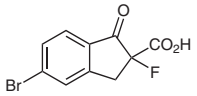
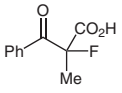
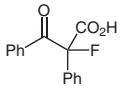
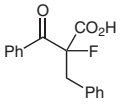
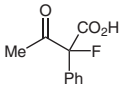
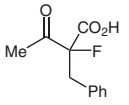
the corresponding β-ketocarboxylic acids **2** in good-to-high yields. Some carboxylic acids **2** were obtained as a mixture with 1–4% of decarboxylated product after purification by silica gel column chromatography because they spontaneously decomposed by releasing carbon dioxide at ambient temperature.

Table 1 Synthesis of α-Fluoro-β-ketocarboxylic Acids[a]

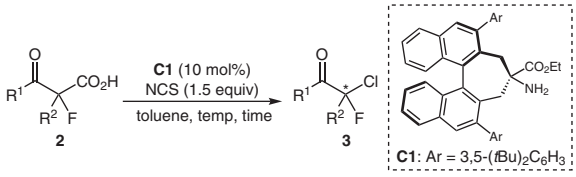


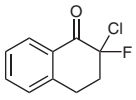
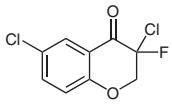
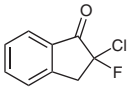
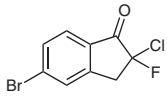
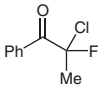
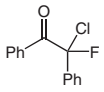
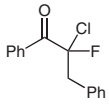
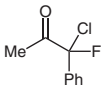
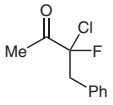
Entry	Product		Time (min)	Yield (%)[b]
1		**2a**	80	72
2		**2b**	90	86
3		**2c**	50	62
4		**2d**	90	80
5		**2e**	60	92
6		**2f**	60	62
7		**2g**	60	85
8		**2h**	90	71
9		**2i**	90	85

[a] Reactions were performed with 20 equiv of trifluoroacetic acid at 25 °C in CH_2Cl_2.
[b] Isolated yield.

Subsequently, the resulting α-fluoro-β-ketocarboxylic acids **2** were subjected to enantioselective decarboxylative chlorination with an electrophilic chlorinating reagent and a chiral amine catalyst. Based on our previous research results,[6] we chose chiral primary amine **C1** as the catalyst and *N*-chlorosuccinimide (NCS) as the chlorination reagent. The reaction of **2a** in toluene successfully yielded the corresponding α-chloro-α-fluoro ketone **3a** with an enantioselectivity of 78% ee at room temperature (Table 2, entry 1). The reaction at lower temperature significantly increased the enantioselectivity to 90% ee (entries 2, 3). We then screened the substrate scope of the reaction at 0 °C. Conse-

Table 2 Substrate Scope[a]



Entry	Product		Temp (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1		**3a**	r.t.	13	95	78
2			0	63	98	86
3			−10	240	95	90
4		**3b**	0	62	95	83
5		**3c**	−20	120	86	44
6		**3d**	0	17	89	36
7		**3e**	0	132	82	13
8		**3f**	0	12	79	33
9		**3g**	0	27	81	29
10		**3h**	0	15	77	45
11		**3i**	0	17	79	2

[a] Reactions were performed using 1.5 equiv of NCS and 10 mol% of chiral amine catalyst **C1** in toluene at 0 °C, unless otherwise noted.
[b] Isolated yield.
[c] Determined via chiral HPLC analysis.

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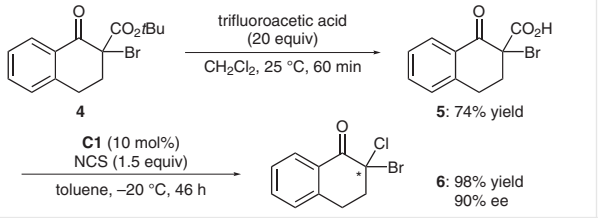
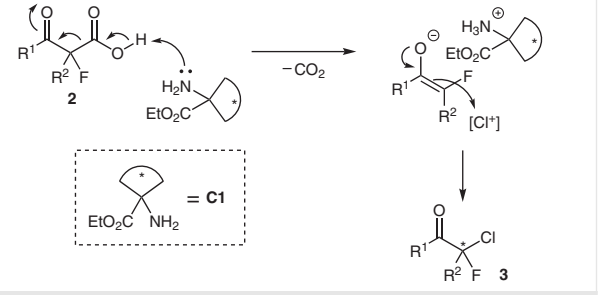
quently, high enantioselectivity was observed in the reaction with tetralone- and 4-chromanone-derived α-fluoro-β-ketocarboxylic acids **2a** and **2b** (entries 1–4), whereas poor-to-moderate enantioselectivity was observed in the reaction with indanone-derived substrates **2c**,**d** and acyclic substrates **2e–i** (entries 5–11). It was reported that the resulting chiral α-chloro-α-fluoro ketones **3** could be converted into α-fluoro-α-heteroatom-substituted ketones by the S_N2 reaction of the chlorine atom.[3a]

This method was also applied to the enantioselective synthesis of α-bromo-α-chloro ketone **6**. α-Bromo-β-keto ester **4** was treated with 20 equivalents of trifluoroacetic acid to yield α-bromo-β-ketocarboxylic acid **5** in 74% yield. Enantioselective chlorination of **5** with **C1** and NCS afforded the desired product **6** in 98% yield with enantioselectivity of 90% ee (Scheme 2).



Scheme 2 Asymmetric synthesis of α-bromo-α-chloro ketone **6**

The proposed reaction mechanism of enantioselective decarboxylative chlorination is shown in Scheme 3. Chiral amine catalyst **C1** promotes decarboxylation from a carboxyl group to form chiral ammonium enolate intermediate, which is trapped by electrophilic chlorinating reagent faster than protonation to yield the corresponding α-chloro-α-fluoro ketone **3**.



Scheme 3 Proposed reaction mechanism

In conclusion, we have achieved the catalytic enantioselective synthesis of α-chloro-α-fluoro ketones **3** for the first time by the chiral amine-catalyzed decarboxylative chlorination of α-fluoro-β-ketocarboxylic acids. α-Bromo-α-chloro ketone **6** was also synthesized using this method with high enantioselectivity. It is known that the resulting α-chloro-α-fluoro ketones can be converted into α-azido-α-fluoro ketones and α-fluoro-α-sulfenyl ketones without loss of enantiopurity by the S_N2 reaction at the chlorine atom. Thus, the method enables the flexible synthesis of chiral α-fluoro-α-heteroatom-substituted ketones, which would be useful in the preparation of biologically relevant molecules.

All reactions were performed in dried glassware under an argon atmosphere and stirring using magnetic stir-plates. TLC analysis was performed using pre-coated silica gel plates with a fluorescent indicator (F254) (Merck Millipore, Darmstadt, Germany). Visualization was accomplished using UV light (254 nm), phosphomolybdic acid, or *p*-anisaldehyde. Flash column chromatography was performed using silica gel 60 (mesh size 40–100) supplied by Kanto Chemical Co., Inc. (Tokyo, Japan). 1H, 13C, and 19F NMR spectra were recorded on a JNM-ECX 500 (500 MHz ^{1}H, 126 MHz ^{13}C, 470 MHz ^{19}F) instrument (JEOL Ltd., Tokyo, Japan). Chemical shift values (δ) are reported in ppm (TMS: δ = 0.00 or residual MeOH: δ = 3.30 for ^{1}H; hexafluorobenzene: δ = –162.2 for ^{19}F; residual $CHCl_3$: δ = 77.0 or MeOH: δ = 49.0 for ^{13}C). All ^{13}C NMR spectra were recorded with ^{1}H-decoupling. IR spectra were recorded on an FT/IR-4600 instrument (JASCO Co., Ltd., Tokyo, Japan). Direct analysis in real time (DART) mass (positive mode) analysis was performed on a JMS-T100TD time-of-flight mass spectrometer (JEOL Ltd.). Melting points were recorded on a YANACO MP-500P micro melting point apparatus (Japan). Optical rotations were measured on a P-1030 digital polarimeter (JASCO Co., Ltd.). Analytical high-performance liquid chromatography (HPLC) was performed on a PU1586 instrument with an MD-2018 plus diode array detector (JASCO Co., Ltd.). The enantiomeric purity of the compounds was determined through HPLC analysis using chiral stationary phase columns.

Commercial-grade reagents and solvents were used without further purification unless otherwise noted. Anhyd DMF and Et_3N were purchased from Sigma-Aldrich (St. Louis, MO, USA). Anhyd toluene, CH_2Cl_2, and THF were purchased from Kanto Chemical Co., Inc. and used after purification using a Glass Contour solvent dispensing system (Pure Process Technology, Nashua, NH). For the synthesis of α-alkyl-β-keto esters, see the Supporting Information. Chiral primary amine **C1** was prepared by following the reported method.[6b]

α-Alkyl-α-fluoro-β-keto Esters 1

α-Alkyl-α-fluoro-β-keto esters **1** were prepared by following the General Procedure A (→ **1a–e**, **1g**, **1i**) or General Procedure B (→ **1f**, **1h**). ^{1}H NMR spectra of α-alkyl-α-fluoro-β-keto esters **1a**,[8] **1c**,[8] **1d**,[9] **1e**,[10] **1g**,[11] and **1i**[4f] were in good agreement with those reported in the literature.

General Procedure A

The respective α-alkyl-β-keto ester (1.32 mmol) was added to a stirred suspension of NaH (60% in oil, washed with hexane and dried in vacuo, 35 mg, 1.45 mmol, 1.1 equiv) in THF (6.7 mL) at 0 °C, and the mixture was stirred at 0 °C for 30 min and then at r.t. for 30 min. Subsequently, *N*-fluorobenzenesulfonimide (NFSI) (1.1 equiv, 1.45 mmol) was added, and the reaction mixture was stirred at 0 °C for 45 min. The mixture was quenched by adding sat. aq NH_4Cl at 0 °C, and then extracted with CH_2Cl_2. The combined extracts were dried (anhyd Na_2SO_4), concentrated, and the residue purified by flash column chromatography on silica gel (hexane/EtOAc 7:1) to yield the desired α-alkyl-α-fluoro-β-keto ester.

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General Procedure B

The respective α-alkyl-β-keto ester (2 mmol) was added to a suspension of NaH (60% in oil, washed with hexane and dried in vacuo, 53 mg, 2.2 mmol, 2.2 equiv) in THF (10 mL for **1f**, 6 mL for **1h**) at 0 °C. The mixture was stirred at r.t. for 20 min. Subsequently, the mixture was diluted with DMF (10 mL), Selectfluor™ (1.1 equiv, 2.2 mmol) was added at 0 °C, and stirred for 14 h. After the addition of H_2O, the aqueous layer was extracted with Et_2O. The combined extracts were dried (anhyd $NaSO_4$), concentrated, and the residue purified by flash column chromatography on silica gel (hexane/EtOAc 10:1) to yield the desired α-alkyl-α-fluoro-β-keto ester.

***tert*-Butyl 6-Chloro-3-fluoro-4-oxochromane-3-carboxylate (1b)**

Prepared by following the General Procedure A; yield: 329 mg (83%); white solid; R_f = 0.45 (hexane/EtOAc 4:1); mp 86.0 °C.

IR (NaCl): 2982, 2935, 1762, 1704, 1606, 1475, 1422, 1288, 1156, 1117, 1099, 832, 640 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.90 (d, *J* = 2.7 Hz, 1 H, H_{Ar}), 7.51 (dd, *J* = 8.8, 2.7 Hz, 1 H, H_{Ar}), 7.01 (d, *J* = 8.8 Hz, 1 H, H_{Ar}), 4.76 (dd, *J* = 21.8, 12.6 Hz, 1 H, C*H*H′), 4.61 (dd, *J* = 12.6, 9.5 Hz, 1 H, CH*H*′), 1.47 (s, 9 H, C_3H_9).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 182.5 (d, *J* = 20.4 Hz, CO), 163.6 (d, *J* = 24.0 Hz, COO), 159.3 (C_{Ar}), 136.9 (C_{Ar}), 128.0 (C_{Ar}), 127.0 (C_{Ar}), 120.2 (C_{Ar}), 119.7 (C_{Ar}), 88.5 (d, *J* = 197.9 Hz, CF), 85.3 (CH_2), 70.4 (d, *J* = 26.4 Hz, *C*C_3H_9), 27.8 (C_3H_9).

^{19}F NMR ($CDCl_3$, 470 MHz): δ = –173.7 (d, *J* = 22.0 Hz).

HRMS (DART): *m*/*z* [M + NH_4]$^+$ calcd for $C_{14}H_{18}ClFO_4N$: 318.0908; found: 318.0906.

***tert*-Butyl 2-Fluoro-3-oxo-2,3-diphenylpropanoate (1f)**

Prepared by following the General Procedure B; yield: 346 mg (55%); colorless oil; R_f = 0.36 (hexane/EtOAc 10:1).

IR (NaCl): 3064, 2980, 2935, 1749, 1696, 1597, 1449, 1371, 1261, 1153, 1071, 751, 698, 614, 410 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.98 (d, *J* = 8.0 Hz, 2 H, H_{Ar}), 7.59–7.57 (m, 2 H, H_{Ar}), 7.49–7.46 (t, *J* = 7.4 Hz, 1 H, H_{Ar}), 7.40–7.33 (m, 5 H, H_{Ar}), 1.42 (s, 9 H, C_3H_9).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 191.0 (d, *J* = 26.4 Hz, CO), 165.0 (d, *J* = 26.4 Hz, COO), 133.7 (C_{Ar}), 133.5 (C_{Ar}), 129.6 (d, *J* = 22.8 Hz, C_{Ar}), 128.9 (C_{Ar}), 128.2 (C_{Ar}), 128.0 (C_{Ar}), 125.5 (d, *J* = 8.4 Hz, C_{Ar}), 98.4 (d, *J* = 199.1 Hz, CF), 84.2 (*C*C_3H_9), 27.4 (C_3H_9).

^{19}F NMR ($CDCl_3$, 470 MHz): δ = –156.3 (s).

HRMS (DART): *m*/*z* [M + NH_4]$^+$ calcd for $C_{19}H_{23}FO_3N$: 332.01662; found: 332.1663.

***tert*-Butyl 2-Fluoro-3-oxo-2-phenylbutanoate (1h)**

Prepared by following the General Procedure B; yield: 415 mg (82%); colorless oil; R_f = 0.41 (hexane/EtOAc 10:1).

IR (NaCl): 2981, 2935, 1728, 1450, 1371, 1356, 1277, 1155, 1069, 838, 756, 697, 566 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.55–7.53 (m, 2 H, H_{Ar}), 7.43–7.39 (m, 3 H, H_{Ar}), 2.29 (d, *J* = 5.0 Hz, 3 H, CH_3), 1.50 (s, 9 H, C_3H_9).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 200.1 (d, *J* = 29.0 Hz, CO), 164.2 (d, *J* = 25.2 Hz, COO), 132.7 (d, *J* = 21.6 Hz, C_{Ar}), 128.9 (C_{Ar}), 128.1 (C_{Ar}), 125.3 (d, *J* = 9.6 Hz, C_{Ar}), 98.6 (d, *J* = 199.1 Hz, CF), 84.1 (*C*C_3H_9), 27.5 (C_3H_9), 25.2 (CH_3).

^{19}F NMR ($CDCl_3$, 470 MHz): δ = –161.9 (s).

HRMS (DART): *m*/*z* [M + NH_4]$^+$ calcd for $C_{14}H_{21}FO_3N$: 270.1506; found: 270.1507.

α-Fluoro-β-ketocarboxylic Acids 2

α-Fluoro-β-ketocarboxylic acids **2** were synthesized by acidolysis of the corresponding α-fluoro-β-keto esters **1**. ^1H NMR spectra of α-fluoro-β-ketocarboxylic acids **2a**,[7] **2g**,[7] and **2i**[7] were in good agreement with those reported in the literature. Melting point of the resulting carboxylic acids was not measured because of their thermal instability.

6-Chloro-3-fluoro-4-oxochromane-3-carboxylic Acid (2b); Typical Procedure

Trifluoroacetic acid (2.4 g, 21.1 mmol, 20 equiv) was added to a stirred solution of α-alkyl-α-fluoro-β-keto ester **1b** (315 mg, 1.05 mmol) in CH_2Cl_2 (5.3 mL) at 0 °C, and the reaction mixture was stirred at r.t. for 90 min. The mixture was concentrated, and then purified by flash column chromatography on silica gel (hexane/Et_2O 4:1 to 1:2) to yield **2b**; yield: 222 mg (86%); white solid; R_f = 0.09 (CH_2Cl_2/MeOH 9:1).

IR (NaCl): 3626, 3414, 1714, 1667, 1473, 1267, 1212, 1109, 900, 818, 637 cm^{-1}.

^1H NMR (CD_3OD, 500 MHz): δ = 7.79 (d, *J* = 2.7 Hz, 1 H, H_{Ar}), 7.55 (dd, *J* = 8.8, 2.3 Hz, 1 H, H_{Ar}), 7.06 (d, *J* = 8.8 Hz, 1 H, H_{Ar}), 4.86–4.73 (m, 2 H, CH_2).

^{13}C NMR (CD_3OD, 126 MHz): δ = 183.7 (d, *J* = 20.4 Hz, CO), 167.5 (d, *J* = 25.2 Hz, COO), 161.0 (C_{Ar}), 138.0 (C_{Ar}), 128.8 (C_{Ar}), 127.5 (C_{Ar}), 121.2 (C_{Ar}), 121.1 (C_{Ar}), 90.3 (d, *J* = 195.5 Hz, CF), 71.6 (d, *J* = 26.4 Hz, CH_2).

^{19}F NMR (CD_3OD, 470 MHz): δ = –182.5 (s).

HRMS (DART): *m*/*z* [M + NH_4]$^+$ calcd for $C_{10}H_{10}ClFO_4N$: 262.0282; found: 262.0285.

2-Fluoro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylic Acid (2c)

Following the Typical Procedure, **1c** (312 mg, 1.25 mmol) was used and the product was purified by flash column chromatography on silica gel (hexane/Et_2O 4:1 to 1:5); yield: 151 mg (62%); pale purple solid; R_f = 0.14 (CH_2Cl_2/MeOH 5:1).

IR (NaCl): 3462, 2961, 2917, 2848, 1721, 1605, 1268, 1200, 923, 660 cm^{-1}.

^1H NMR (CD_3OD, 500 MHz): δ = 7.78–7.72 (m, 2 H, H_{Ar}), 7.58 (d, *J* = 7.6 Hz, 1 H, H_{Ar}), 7.48 (t, *J* = 7.6 Hz, 1 H, H_{Ar}), 3.80 (dd, *J* = 17.6, 10.7 Hz, 1 H, C*H*H′), 3.41 (dd, *J* = 23.3, 17.6 Hz, 1 H, CH*H*′).

^{13}C NMR (CD_3OD, 126 MHz): δ = 197.7 (d, *J* = 18.0 Hz, CO), 170.3 (d, *J* = 28.8 Hz, COO), 152.9 (d, *J* = 4.8 Hz, C_{Ar}), 138.0 (C_{Ar}), 134.6 (C_{Ar}), 129.7 (C_{Ar}), 128.0 (C_{Ar}), 126.0 (C_{Ar}), 95.8 (d, *J* = 197.9 Hz, CF), 39.2 (d, *J* = 25.2 Hz, CH_2).

^{19}F NMR (CD_3OD, 470 MHz): δ = –172.4 (d, *J* = 14.7 Hz).

HRMS (DART): *m*/*z* [M + NH_4]$^+$ calcd for $C_{10}H_{11}FO_3N$: 212.0723; found: 212.0721.

5-Bromo-2-fluoro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylic Acid (2d)

Following the Typical Procedure, **1d** (228 mg, 0.693 mmol) was used and the product was purified by flash column chromatography on silica gel (hexane/Et_2O 4:1 to 1:5); yield: 152 mg (80%); white solid; R_f = 0.35 (CH_2Cl_2/MeOH 5:1).

IR (NaCl): 3486, 2361, 2340, 1725, 1593, 1267, 1210, 1057, 923, 668, 491 cm^{-1}.

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^{1}H NMR (CD_3OD, 500 MHz): δ = 7.82 (s, 1 H, H_{Ar}), 7.68–7.65 (m, 2 H, H_{Ar}), 3.80 (dd, *J* = 18.0, 9.9 Hz, 1 H, C*H*H′), 3.42 (dd, *J* = 23.3, 18.0 Hz, 1 H, CH*H*′).

^{13}C NMR (CD_3OD, 126 MHz): δ = 196.5 (d, *J* = 19.2 Hz, CO), 169.8 (d, *J* = 28.8 Hz, COO), 154.4 (d, *J* = 4.8 Hz, C_{Ar}), 133.6 (C_{Ar}), 133.3 (C_{Ar}), 133.1 (C_{Ar}), 131.3 (C_{Ar}), 127.3 (C_{Ar}), 95.7 (d, *J* = 199.1 Hz, CF), 38.9 (d, *J* = 24.0 Hz, CH_2).

^{19}F NMR (CD_3OD, 470 MHz): δ = –173.8 (d, *J* = 22.0 Hz).

HRMS (DART): *m*/*z* [M + NH_4]$^+$ calcd for $C_{10}H_{10}BrFO_3N$: 289.9828; found: 289.9828.

2-Fluoro-2-methyl-3-oxo-3-phenylpropanoic Acid (2e)

Following the Typical Procedure, **1e** (300 mg, 1.19 mmol) was used and the product was purified by flash column chromatography on silica gel (hexane/Et_2O 4:1 to 1:2); yield: 214 mg (92%), including 1% of decarboxylated product; colorless oil; R_f = 0.20 (CH_2Cl_2/MeOH 5:1).

IR (NaCl): 3513, 3072, 1697, 1597, 1449, 1271, 1132, 981, 698, 657, 535, 431, 423 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 11.2 (s, 1 H, CO_2H), 8.06–8.04 (m, 2 H, H_{Ar}), 7.60–7.56 (m, 1 H, H_{Ar}), 7.46–7.42 (m, 2 H, H_{Ar}), 1.90 (d, *J* = 22.5 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 191.6 (d, *J* = 24.0 Hz, CO), 173.4 (d, *J* = 25.2 Hz, COO), 134.2 (C_{Ar}), 132.9 (d, *J* = 3.6 Hz, C_{Ar}), 129.8 (d, *J* = 4.8 Hz, C_{Ar}), 128.7 (C_{Ar}), 96.9 (d, *J* = 197.9Hz, CF), 21.1 (d, *J* = 22.8 Hz, CH_3).

^{19}F NMR ($CDCl_3$, 470 MHz): δ = –153.0 (q, *J* = 22.0 Hz).

HRMS (DART): *m*/*z* [M + NH_4]$^+$ calcd for $C_{10}H_{13}FO_3N$: 214.0880; found: 214.0881.

2-Fluoro-3-oxo-2,3-diphenylpropanoic Acid (2f)

Following the Typical Procedure, **1f** (345 mg, 1.10 mmol) was used and the product was purified by flash column chromatography on silica gel (hexane/Et_2O 4:1 to 1:4); yield: 175 mg (62%); white solid; R_f = 0.1 (CH_2Cl_2/MeOH 9:1).

IR (NaCl): 3020, 2830, 1731, 1684, 1446, 1278, 1228, 1069, 887, 696, 676, 563 cm^{-1}.

^{1}H NMR (CD_3OD, 500 MHz): δ = 7.93 (d, *J* = 7.6 Hz, 2 H, H_{Ar}), 7.56–7.52 (m, 3 H, H_{Ar}), 7.41–7.39 (m, 5 H, H_{Ar}).

^{13}C NMR (CD_3OD, 126 MHz): δ = 192.8 (d, *J* = 26.4 Hz, CO), 169.4 (d, *J* = 26.4 Hz, COO), 135.5 (d, *J* = 21.6 Hz, C_{Ar}), 135.0 (C_{Ar}), 134.9 (d, *J* = 3.6 Hz, C_{Ar}), 130.9 (d, *J* = 4.8 Hz, C_{Ar}), 130.2 (C_{Ar}), 129.6 (C_{Ar}), 129.4 (C_{Ar}), 126.8 (d, *J* = 8.4 Hz, C_{Ar}), 100.1 (d, *J* = 197.9 Hz, CF).

^{19}F NMR (CD_3OD, 470 MHz): δ = –162.7 (d, *J* = 22.0 Hz).

HRMS (DART): *m*/*z* [M + NH_4]$^+$ calcd for $C_{15}H_{15}FO_3N$: 276.1036; found: 276.1035.

2-Fluoro-3-oxo-2-phenylbutanoic Acid (2h)

Following the Typical Procedure, **1h** (302 mg, 1.20 mmol) was used and the product was purified by flash column chromatography on silica gel (hexane/Et_2O 4:1 to 1:2); yield: 167 mg (71%), including 4% of protonated product; colorless oil; R_f = 0.36 (CH_2Cl_2/MeOH 5:1).

IR (NaCl): 3504, 3064, 1735, 1686, 1596, 1449, 1259, 1212, 1186, 1070, 696, 663 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 10.67 (s, 1 H, COOH), 7.57–7.55 (m, 2 H, H_{Ar}), 7.42–7.40 (m, 3 H, H_{Ar}), 2.32 (d, *J* = 5.0 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 200.3 (d, *J* = 28.8 Hz, CO), 169.9 (d, *J* = 26.4 Hz, COO), 131.7 (d, *J* = 21.6 Hz, C_{Ar}), 129.7 (C_{Ar}), 128.6 (C_{Ar}), 125.1 (d, *J* = 9.6 Hz, C_{Ar}), 98.2 (d, *J* = 200.3 Hz, CF), 25.3 (CH_3).

^{19}F NMR ($CDCl_3$, 470 MHz): δ = –163.9 (s).

HRMS (DART): *m*/*z* [M + NH_4]$^+$ calcd for $C_{10}H_{13}FO_3N$: 214.0880; found: 214.0880.

α-Chloro-α-fluoro Ketones 3

Enantioselective decarboxylative chlorination of **2** was performed by following the Typical Procedure described below. A few starting compounds **2** contained 1–4% of decarboxylated product before use.

3,6-Dichloro-3-fluorochroman-4-one (3b); Typical Procedure

α-Fluoro-β-ketocarboxylic acid **2b** (74 mg, 0.303 mmol) was added to a stirred solution of **C1** (10 mol%, 0.0303 mmol) and NCS (1.5 equiv, 0.455 mmol) in toluene (1.5 mL). The reaction mixture was stirred at 0 °C for 62 h. Then, the mixture was directly subjected to flash column chromatography on silica gel (hexane/CH_2Cl_2 2:1 then hexane/EtOAc 20:1) to give **3b**; yield: 67.7 mg (95%, 83% ee); white solid; R_f = 0.27 (hexane/CH_2Cl_2 2:1); mp 71.9 °C; $[\alpha]_D^{27.7}$ +71.38 (*c* 1.28, $CHCl_3$).

HPLC: DAICEL CHIRALCEL OJ–H (0.46 cm ϕ × 25 cm); hexane/*i*-PrOH (500:1), flow rate = 1.0 mL/min, λ = 254 nm; t_R = 24.9 min (minor), t_R = 42.8 min (major).

IR (NaCl): 3082, 2921, 2860, 1713, 1604, 1476, 1424, 1280, 1213, 1114, 1051, 654, 443, 426 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.94 (d, *J* = 2.3 Hz, 1 H, H_{Ar}), 7.55 (ddd, *J* = 9.0, 2.7, 1.0 Hz, 1 H, H_{Ar}), 7.05 (d, *J* = 8.8 Hz, 1 H, H_{Ar}), 4.70–4.63 (m, 2 H, CH_2).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 179.5 (d, *J* = 21.6 Hz, CO), 158.6 (C_{Ar}), 137.4 (C_{Ar}), 128.8 (C_{Ar}), 127.7 (C_{Ar}), 119.9 (C_{Ar}), 118.5 (C_{Ar}), 99.9 (d, *J* = 256.7 Hz, CF), 72.8 (d, *J* = 31.2 Hz, CH_2).

^{19}F NMR ($CDCl_3$, 470 MHz): δ = –136.0 (s).

HRMS (DART): *m*/*z* [M + NH_4]$^+$ calcd for $C_9H_9Cl_2FO_2N$: 251.9994; found: 251.9997.

2-Chloro-2-fluoro-3,4-dihydronaphthalen-1(2*H*)-one (3a)

Following the Typical Procedure, **2a** (30 mg, 0.146 mmol) was used and the reaction was carried out at –20 °C for 10 d, and the product was purified by flash column chromatography on silica gel (hexane/Et_2O 10:1 to 5:1); yield: 27.6 mg (95%, 90% ee); white solid; R_f = 0.36 (hexane/CH_2Cl_2 2:1); mp 75.4 °C; $[\alpha]_D^{27.8}$ +74.96 (*c* 1.49, $CHCl_3$).

HPLC: DAICEL CHIRALCEL OB–H (0.46 cm ϕ × 25 cm); hexane/*i*-PrOH (9:1), flow rate = 1.0 mL/min, λ = 254 nm; t_R = 9.5 min (major), t_R = 11.3 min (minor).

IR (NaCl): 2922, 2852, 1709, 1603, 1455, 1306, 1227, 1136, 1038, 932, 829, 731, 654 cm^{-1}.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.13 (dd, *J* = 8.0, 1.2 Hz, 1 H, H_{Ar}), 7.58 (dt, *J* = 7.6, 1.2 Hz, 1 H, H_{Ar}), 7.40 (t, *J* = 7.6 Hz, 1 H, H_{Ar}), 7.30 (d, *J* = 7.6 Hz, 1 H, H_{Ar}), 3.35 (ddd, *J* = 17.0, 12.0, 4.2 Hz, 1 H, PhC*H*H′), 3.12 (quintd, *J* = 17.2, 2.3 Hz, 1 H, PhCH*H*′), 2.84–2.78 (m, 1 H, C*H*H′), 2.74–2.67 (m, 1 H, CH*H*′).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 185.3 (d, *J* = 21.6 Hz, CO), 142.0 (C_{Ar}), 134.8 (C_{Ar}), 129.1 (C_{Ar}), 128.8 (C_{Ar}), 128.8 (C_{Ar}), 127.5 (C_{Ar}), 105.2 (d, *J* = 256.7 Hz, CF), 37.2 (d, *J* = 20.4 Hz, PhCH_2), 26.9 (d, *J* = 7.2 Hz, CH_2).

^{19}F NMR ($CDCl_3$, 470 MHz): δ = –116.8 (s).

HRMS (DART): *m*/*z* [M + NH_4]$^+$ calcd for $C_{10}H_{12}ClFON$: 216.0591; found: 216.0590.

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2-Chloro-2-fluoro-2,3-dihydro-1*H*-inden-1-one (3c)

Following the Typical Procedure, **2c** (50 mg, 0.266 mmol) was used and the reaction was performed at –20 °C for 5 d. The product was purified by flash column chromatography on silica gel (hexane/CH_2Cl_2 5:1 to 1:1); yield: 42.3 mg (86%, 44% ee); white solid; R_f = 0.24 (hexane/CH_2Cl_2 2:1); mp 53.5 °C; $[\alpha]_D^{27.7}$ +11.30 (*c* 1.06, $CHCl_3$).

HPLC: DAICEL CHIRALCEL OB–H (0.46 cm ϕ × 25 cm); hexane/*i*-PrOH (9:1), flow rate = 1.0 mL/min, λ = 254 nm; t_R = 19.6 min (minor), t_R = 9.9 min (major).

IR (NaCl): 3065, 2963, 2868, 1740, 1611, 1469, 1306, 1217, 1103, 1000, 919, 734, 658, 416 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.88 (d, *J* = 7.6 Hz, 1 H, H_{Ar}), 7.75 (dt, *J* = 7.6, 1.2 Hz, 1 H, H_{Ar}), 7.52–7.47 (m, 2 H, H_{Ar}), 3.90–3.80 (m, 2 H, CH_2).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 191.6 (d, *J* = 22.8 Hz, CO), 146.9 (d, *J* = 7.8 Hz, C_{Ar}), 137.3 (C_{Ar}), 131.0 (C_{Ar}), 129.0 (C_{Ar}), 126.5 (C_{Ar}), 126.1 (C_{Ar}), 105.9 (d, *J* = 261.5 Hz, CF), 43.8 (d, *J* = 24.0 Hz, CH_2).

^{19}F NMR ($CDCl_3$, 470 MHz): δ = –121.0 (s).

HRMS (DART): *m*/*z* [M + NH_4]$^+$ calcd for $C_9H_{10}ClFON$: 202.0435; found: 202.0434.

5-Bromo-2-chloro-2-fluoro-2,3-dihydro-1*H*-inden-1-one (3d)

Following the Typical Procedure, **2d** (82 mg, 0.300 mmol) was used and the product was purified by flash column chromatography on silica gel (hexane/CH_2Cl_2 2:1, then hexane/EtOAc 30:1); yield: 70.2 mg (89%, 36% ee); white solid; R_f = 0.27 (hexane/EtOAc 30:1); mp 116.5 °C; $[\alpha]_D^{27.6}$ –13.08 (*c* 1.06, $CHCl_3$).

HPLC: DAICEL CHIRALCEL OB–H (0.46 cm ϕ × 25 cm); hexane/*i*-PrOH (9:1), flow rate = 1.0 mL/min, λ = 254 nm; t_R = 16.4 min (minor), t_R = 23.8 min (major).

IR (NaCl): 3078, 3061, 2929, 1735, 1594, 1571, 1423, 1293, 1212, 1186, 1111, 1056, 999, 919, 845, 748, 667, 596 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.75 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 7.66–7.64 (m, 2 H, H_{Ar}), 3.87–3.79 (m, 2 H, CH_2).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 190.5 (d, *J* = 22.8 Hz, CO), 148.3 (d, *J* = 4.8 Hz, C_{Ar}), 132.9 (C_{Ar}), 132.7 (C_{Ar}), 129.8 (C_{Ar}), 129.8 (C_{Ar}), 127.2 (C_{Ar}), 105.4 (d, *J* = 262.7 Hz, CF), 43.4 (d, *J* = 24.0 Hz, CH_2).

^{19}F NMR ($CDCl_3$, 470 MHz): δ = –120.6 (d, *J* = 14.7 Hz).

HRMS (DART): *m*/*z* [M + NH_4]$^+$ calcd for $C_9H_9BrClFON$: 279.9540; found: 279.9543.

2-Chloro-2-fluoro-1-phenylpropan-1-one (3e)

Following the Typical Procedure, **2e** (66 mg, 0.335 mmol) and toluene (3.4 mL) was used, and the product was purified by flash column chromatography on silica gel (pentane/CH_2Cl_2 100:0 to 25:1); yield: 51.2 mg (82%, 13% ee); colorless oil; R_f = 0.43 (hexane/CH_2Cl_2 2:1); $[\alpha]_D$ not determined because of low enantioselectivity.

HPLC: DAICEL CHIRALCEL OJ–H (0.46 cm ϕ × 25 cm); hexane/*i*-PrOH (1000:1), flow rate = 0.5 mL/min, λ = 254 nm; t_R = 15.2 min (minor), t_R = 14.5 min (major).

IR (NaCl): 3064, 3001, 2943, 1699, 1599, 1449, 1380, 1282, 1151, 1081, 984, 893, 807, 705, 653, 541 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 8.18 (m, 2 H, H_{Ar}), 7.60 (t, *J* = 7.5 Hz, 1 H, H_{Ar}), 7.47 (t, *J* = 7.8 Hz, 2 H, H_{Ar}), 2.17 (d, *J* = 20.3 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 189.2 (d, *J* = 23.0 Hz, CO), 134.0 (C_{Ar}), 131.3 (d, *J* = 3.6 Hz, C_{Ar}), 130.6 (d, *J* = 6.0 Hz, C_{Ar}), 128.4 (C_{Ar}), 108.4 (d, *J* = 256.7 Hz, CF), 27.3 (d, *J* = 22.8 Hz, CH_3).

^{19}F NMR ($CDCl_3$, 470 MHz): δ = –106.7 (q, *J* = 22.0 Hz).

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for C_9H_9ClFO: 187.0326; found: 187.0324.

2-Chloro-2-fluoro-1,2-diphenylethan-1-one (3f)

Following the Typical Procedure, **2f** (93 mg, 0.306 mmol) was used and the product was purified by flash column chromatography on silica gel (hexane/CH_2Cl_2 2:1, then hexane/Et_2O 30:1); yield: 59.8 mg (79%, 33% ee); colorless oil; R_f = 0.42 (hexane/CH_2Cl_2 2:1); $[\alpha]_D^{27.7}$ +7.99 (*c* 1.43, $CHCl_3$).

HPLC: DAICEL CHIRALPAK IA–3 (0.46 cm ϕ × 25 cm); hexane/*i*-PrOH (150:1), flow rate = 1.0 mL/min, λ = 254 nm; t_R = 6.4 min (minor), t_R = 5.9 min (major).

IR (NaCl): 3063, 1703, 1596, 1448, 1238, 1216, 1090, 1017, 877, 817, 744, 694, 631 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.99–7.97 (m, 2 H, H_{Ar}), 7.66–7.62 (m, 2 H, H_{Ar}), 7.56–7.53 (m, 1 H, H_{Ar}), 7.45–7.38 (m, 2 H, H_{Ar}).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 188.7 (d, *J* = 28.8 Hz, CO), 136.4 (d, *J* = 22.8 Hz, C_{Ar}), 133.8 (C_{Ar}), 132.0 (d, *J* = 2.4 Hz, C_{Ar}), 130.6 (d, *J* = 4.8 Hz, C_{Ar}), 130.3 (C_{Ar}), 128.7 (C_{Ar}), 128.4 (C_{Ar}), 125.8 (d, *J* = 7.2 Hz, C_{Ar}), 109.8 (d, *J* = 255.5 Hz, CF).

^{19}F NMR ($CDCl_3$, 470 MHz): δ = –107.1 (s).

HRMS (DART): *m*/*z* [M + NH_4]$^+$ calcd for $C_{14}H_{14}ClFON$: 266.0748; found: 266.0749.

2-Chloro-2-fluoro-1,3-diphenylpropan-1-one (3g)

Following the Typical Procedure, **2g** (96 mg, 0.354 mmol) and toluene (3.6 mL) were used, and the product was purified by flash column chromatography on silica gel (hexane/EtOAc 100:0 to 95:5); yield: 75.8 mg (81%, 29% ee); white solid; R_f = 0.45 (hexane/CH_2Cl_2 2:1); mp 49.7 °C; $[\alpha]_D^{27.5}$ +15.01 (*c* 0.99, $CHCl_3$).

HPLC: DAICEL CHIRALCEL OD–H (0.46 cm ϕ × 25 cm); hexane/*i*-PrOH (500:1), flow rate = 0.5 mL/min, λ = 254 nm; t_R = 17.2 min (minor), t_R = 19.5 min (major).

IR (NaCl): 3064, 3033, 2923, 2851, 1697, 1597, 1448, 1264, 1133, 892, 698, 593 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 8.06–8.03 (m, 2 H, H_{Ar}), 7.57–7.53 (m, 1 H, H_{Ar}), 7.43–7.40 (m, 2 H, H_{Ar}), 7.33–7.26 (m, 5 H, H_{Ar}), 3.83 (dd, *J* = 22.6, 14.5 Hz, 1 H, C*H*H′), 3.67 (dd, *J* = 22.2, 14.5 Hz, 1 H, CH*H*′).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 190.0 (d, *J* = 30.0 Hz, CO), 133.8 (C_{Ar}), 132.6 (C_{Ar}), 132.1 (d, *J* = 3.6 Hz, C_{Ar}), 131.2 (C_{Ar}), 130.3 (d, *J* = 4.8 Hz, C_{Ar}), 128.4 (C_{Ar}), 128.2 (C_{Ar}), 127.6 (C_{Ar}), 108.9 (d, *J* = 262.7 Hz, CF), 45.1 (d, *J* = 20.4 Hz, CH_2).

^{19}F NMR ($CDCl_3$, 470 MHz): δ = –115.4 (t, *J* = 22.0 Hz).

HRMS (DART): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{13}ClFO$: 263.0639; found: 263.0641.

1-Chloro-1-fluoro-1-phenylpropan-2-one (3h)

Following the Typical Procedure, **2h** (66 mg, 0.335 mmol) and toluene (3.4 mL) were used, and the product was purified by flash column chromatography on silica gel (pentane/CH_2Cl_2 9:1 to 7:3); yield: 48.1 mg (77%, 45% ee); colorless oil; R_f = 0.45 (hexane/CH_2Cl_2 2:1); $[\alpha]_D^{27.5}$ +285.02 (*c* 1.02, $CHCl_3$).

HPLC: DAICEL CHIRALPAK IA–3 (0.46 cm ϕ × 25 cm); hexane/*i*-PrOH (500:1), flow rate = 1.0 mL/min, λ = 254 nm; t_R = 5.9 min (minor), t_R = 6.3 min (major).

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IR (NaCl): 3063, 1702, 1596, 1448, 1238, 1216, 817, 744, 694, 631 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.61–7.57 (m, 2 H, H_{Ar}), 7.46–7.43 (m, 3 H, H_{Ar}), 2.35 (d, *J* = 3.4 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 196.8 (d, *J* = 31.2 Hz, CO), 134.8 (d, *J* = 22.8 Hz, C_{Ar}), 130.4 (C_{Ar}), 128.6 (C_{Ar}), 125.9 (d, *J* = 7.2 Hz, C_{Ar}), 108.7 (d, *J* = 255.5 Hz, CF), 23.7 (CH_3).

^{19}F NMR ($CDCl_3$, 470 MHz): δ = –115.8 (s).

HRMS (DART): *m*/*z* $[M + H]^+$ calcd for C_9H_9ClFO: 187.0326; found: 187.0327.

3-Chloro-3-fluoro-4-phenylbutan-2-one (3i)

Following the Typical Procedure, **2i** (64 mg, 0.306 mmol) and toluene (3 mL) were used, and the product was purified by flash column chromatography on silica gel (hexane/Et_2O 10:1 to 5:1 then hexane/EtOAc 100:0 to 92:8); yield: 48.3 mg (79%, 2% ee); colorless oil; R_f = 0.15 (hexane only); $[\alpha]^D$ not determined because of low enantioselectivity.

HPLC: DAICEL CHIRALCEL OJ–H (0.46 cm ϕ × 25 cm); hexane/*i*-PrOH (1000:1), flow rate = 1.0 mL/min, λ = 254 nm; t_R = 17.2 min (minor), t_R = 38.8 min (major).

IR (NaCl): 3089, 3064, 3033, 2933, 1698, 1597, 1449, 1265, 1134, 941, 892, 749, 698, 663, 593 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 7.33–7.28 (m, 3 H, H_{Ar}), 7.26–7.24 (m, 2 H, H_{Ar}), 3.59 (dd, *J* = 24.9, 14.5 Hz, 1 H, C*H*H′), 3.50 (dd, *J* = 19.7, 14.7 Hz, 1 H, CH*H*′), 2.24 (d, *J* = 3.8 Hz, 3 H, CH_3).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 199.0 (d, *J* = 32.4 Hz, CO), 132.3 (C_{Ar}), 130.8 (C_{Ar}), 128.4 (C_{Ar}), 127.7 (C_{Ar}), 109.3 (d, *J* = 259.1 Hz, CF), 44.1 (d, *J* = 20.4 Hz, CH_2), 24.0 (CH_3).

^{19}F NMR ($CDCl_3$, 470 MHz): δ = –119.2 (t, *J* = 22.0 Hz).

HRMS (DART): *m*/*z* $[M + NH_4]^+$ calcd for $C_{10}H_{14}ClFON$: 218.0748; found: 218.0747.

α-Bromo-α-chloro Ketone 6

tert-Butyl 2-Bromo-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (4)

tert-Butyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate (900 mg, 3.65 mmol) was added to a stirred suspension of NaH (60% in oil, washed with hexane and dried in vacuo, 0.123 g, 5.11 mmol, 1.4 equiv) in THF (20 mL) at 0 °C, and the mixture was stirred at 0 °C for 30 min. Subsequently, NBS (910 mg, 5.11 mmol, 1.4 equiv) was added in one portion, and the reaction mixture was stirred at r.t. for 30 min. The mixture was quenched by adding sat. aq NH_4Cl at 0 °C, and then extracted with CH_2Cl_2. The combined extracts were dried (anhyd Na_2SO_4), concentrated, and the residue was purified by flash column chromatography on silica gel (hexane/EtOAc 10:1 to 7:1) to yield **4**; yield: 1090 mg (92%); white solid; R_f = 0.27 (hexane/EtOAc 20:1); mp 44.3 °C.

IR (NaCl): 2978, 2933, 1751, 1725, 1686, 1455, 1369, 1295, 1254, 1153, 735, 403 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 8.09 (d, *J* = 7.6 Hz, 1 H, H_{Ar}), 7.53 (t, *J* = 7.6 Hz, 1 H, H_{Ar}), 7.36 (t, *J* = 7.6 Hz, 1 H, H_{Ar}), 7.27 (d, *J* = 7.6 Hz, 1 H, H_{Ar}), 3.20 (ddd, *J* = 17.2, 9.0, 4.8 Hz, 1 H, PhC*H*H′), 3.03 (dt, *J* = 17.2, 5.2 Hz, 1 H, PhCH*H*′), 2.95 (ddd, *J* = 14.1, 9.2, 5.2 Hz, 1 H, C*H*H′), 2.56 (dt, *J* = 14.1, 5.4 Hz, 1 H, CH*H*′), 1.47 (s, 9 H, C_3H_9).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 187.8 (CO), 166.0 (COO), 142.2 (C_{Ar}), 134.1 (C_{Ar}), 129.7 (C_{Ar}), 128.8 (C_{Ar}), 128.7 (C_{Ar}), 127.1 (C_{Ar}), 84.1 (CBr), 66.5 (*C*C_3H_9), 35.8 (PhCH_2), 27.6 (C_3H_9), 26.9 (CH_2).

HRMS (DART): *m*/*z* $[M + NH_4]^+$ calcd for $C_{15}H_{21}BrO_3N$: 342.0705; found: 342.0704.

2-Bromo-1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylic Acid (5)

Trifluoroacetic acid (2.4 g, 18.4 mmol, 20 equiv) was added to a stirred solution of **4** (300 mg, 0.919 mmol) in CH_2Cl_2 (4.6 mL) at 0 °C, and the reaction mixture was stirred at r.t. for 60 min. The mixture was concentrated, and then purified by flash column chromatography on silica gel (hexane/Et_2O 4:1 to 1:2) to give **5**; yield: 183 mg (74%), including 2% of protonated product; white solid; R_f = 0.34 (CH_2Cl_2/MeOH 5:1).

IR (NaCl): 3509, 2938, 1729, 1682, 1597, 1455, 1428, 1297, 1225, 910, 787, 734 cm^{-1}.

^1H NMR (CD_3OD, 500 MHz): δ = 8.00 (d, *J* = 8.0 Hz, 1 H, H_{Ar}), 7.55 (t, *J* = 6.9 Hz, 1 H, H_{Ar}), 7.35 (t, *J* = 7.6 Hz, 1 H, H_{Ar}), 7.32 (d, *J* = 6.9 Hz, 1 H, H_{Ar}), 3.19–3.13 (m, 1 H, PhC*H*H′), 3.06–3.03 (m, 1 H, PhCH*H*′), 2.93–2.88 (m, 1 H, C*H*H′), 2.57–2.53 (m, 1 H, CH*H*′).

^{13}C NMR (CD_3OD, 126 MHz): δ = 189.6 (CO), 170.2 (COO), 144.2 (C_{Ar}), 135.6 (C_{Ar}), 130.7 (C_{Ar}), 130.1 (C_{Ar}), 129.4 (C_{Ar}), 128.2 (C_{Ar}), 67.0 (CBr), 37.2 (PhCH_2), 27.7 (CH_2).

HRMS (DART): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{10}BrO_3$: 268.9813; found: 268.9810.

2-Bromo-2-chloro-3,4-dihydronaphthalen-1(2*H*)-one (6)

Amine catalyst **C1** (22 mg, 0.0296 mmol, 10 mol%) and NCS (59 mg, 0.444 mmol, 1.5 equiv) were added to a stirred solution of **5** (80 mg, 0.296 mmol) in toluene (1.5 mL) at –20 °C, and the reaction mixture was stirred for 46 h. The mixture was directly subjected to flash column chromatography on silica gel (hexane/CH_2Cl_2 1:1) to give **6**; yield: 75.4 mg (98%, 90% ee); brown solid; R_f = 0.63 (hexane/CH_2Cl_2 1:1); mp 67.6 °C; $[\alpha]_D^{27.6}$ –21.45 (*c* 1.07, $CHCl_3$).

HPLC: DAICEL CHIRALPAK IA–3 (0.46 cm ϕ × 25 cm); hexane/*i*-PrOH (150:1), flow rate = 1.0 mL/min, λ = 254 nm; t_R = 10.0 min (minor), t_R = 10.8 min (major).

IR (NaCl): 3067, 2956, 2938, 1703, 1599, 1454, 1292, 1220, 886, 807, 742, 628, 577, 464 cm^{-1}.

^1H NMR ($CDCl_3$, 500 MHz): δ = 8.16 (dd, *J* = 8.0, 1.2 Hz, 1 H, H_{Ar}), 7.56 (dt, *J* = 7.5, 1.2 Hz, 1 H, H_{Ar}), 7.39 (t, *J* = 7.6 Hz, 1 H, H_{Ar}), 7.28 (d, *J* = 7.6 Hz, 1 H, H_{Ar}), 3.25 (ddd, *J* = 17.3, 10.0, 4.2 Hz, 1 H, PhC*H*H′), 3.09 (dt, *J* = 17.2, 4.6 Hz, 1 H, PhCH*H*′), 3.03 (dt, *J* = 14.5, 4.6 Hz, 1 H, C*H*H′), 2.85 (ddd, *J* = 19.1, 9.9, 4.6 Hz, 1 H, CH*H*′).

^{13}C NMR ($CDCl_3$, 126 MHz): δ = 184.1 (CO), 141.9 (C_{Ar}), 134.5 (C_{Ar}), 129.8 (C_{Ar}), 128.6 (C_{Ar}), 127.8 (C_{Ar}), 127.5 (C_{Ar}), 77.7 (CBr), 44.2 (PhCH_2), 28.5 (CH_2).

HRMS (DART): *m*/*z* $[M + NH_4]^+$ calcd for $C_{10}H_{12}BrClON$: 275.9791; found: 275.9793.

Funding Information

This study was supported by the Grants-in-Aid for Scientific Research (B) (18H01974) and the Grant-in-Aid for Research Fellow of JSPS (18J12369), and Tatematsu Foundation.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690009.

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