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Highly Enantioselective Catalytic Fluorination and Chlorination Reactions of Carbonyl Compounds Capable of Two-Point Binding

Norio Shibata, Junji Kohno, Kazumi Takai, Takehisa Ishimaru, Shuichi Nakamura, Takeshi Toru* and Shuji Kanemasa*

Department of Applied Chemistry, Graduate School of Engineering, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466-8555, Japan, Institute for Materials Chemistry and Engineering, Kyushu University, 6-1 Kasugakoen, Kasuga 816-8580, Japan

General Remarks: All reactions were performed in oven- and flame-dried glassware under a positive pressure of argon. Air- and moisture-sensitive reagents and solvents were transferred with a syringe or cannula, and were introduced into the reaction vessels through a rubber septum. All of the reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica-gel plate (60F-254). The TLC plates were visualized with UV light and 7% phosphomolybdic acid in ethanol/heat. Column chromatography was carried out on a column packed with KANTO KAGAKU silica gel 60N 37571. ^{1}H NMR (200 MHz) and ^{19}F NMR (188 MHz) spectra for solutions in $CDCl_3$ were recorded on a Varian Gemini-200. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane for ^{1}H NMR and $CFCl_3$ for ^{19}F NMR. Infrared spectra were recorded on a JASCO FT/IR-200 spectrometer. Mass spectra (ESI-TOF) were recorded on a Micromass LCT spectrometer. Optical rotations were measured on a HORIBA SEPA-300 operating at = 589 nm. HPLC analyses were performed on a JASCO TRI ROTOR IV using 4.6 x 250 mm Chiralpak AD-H, Chiralpak AS, Chiralcel OD-H, Chiralcel OB-H packed column.

General procedure for the halogenation of 1: $Ni(ClO_4)_2 \cdot 6H_2O$ (10 mol%) and the (*R,R*)-DBFOX-Ph (11 mol%) were stirred under vacuum for 2 h at room temperature. Dry CH_2Cl_2 (1 mL) and 4Å molecular sieves (50—100mg) was added under nitrogen atmosphere and stirred for 1 h. Then a solution of substrate **1** (0.10—0.20 mmol) in dry CH_2Cl_2 (2 mL) was added to the catalyst solution. After stirring for another 30 min, *N*-fluorobenzenesulfonimide or CF_3SO_2Cl (1.2 equiv) was added directly to the mixture. The reaction was stirred at the temperature for 1 h to overnight with monitoring by TLC; it was stopped by the addition of water. The reaction mixture was then diluted with CH_2Cl_2, washed with saturated aqueous sodium bicarbonate solution, brine, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with hexane/AcOEt to give the halogenated product. The ee of the product was determined by chiral HPLC on Chiralpak AD-H, Chiralpak AS, Chiralcel OD-H, or Chiralcel OB-H column.

Caution! $Ni(ClO_4)_2 \cdot 6H_2O$ is a strong oxidizer and it should be handled with care when the reaction is performed in a

very large scale.

(*S*)-*tert*-Butyl 2-Fluoro-1-oxo-indan-2-carboxylate (2a)

Ee determined by HPLC analysis (CHIRALPAK AD-H, Hexane/IPA=99/1, 1.0 ml/min, 254 nm) t_r ((*S*)-isomer)=10.9 min, t_r ((*R*)-isomer)=13.5 min.

$[\alpha]_D^{24}$ –3.93 (*c* 0.41, $CHCl_3$) ((*S*)-**2a**, 99% ee); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.43 (s, 9H), 3.39 (dd, 1H, *J* = 17.5, 22 Hz), 3.72 (dd, 1H, *J* = 11, 17.5 Hz), 7.40–7.50 (m, 2H), 7.63–7.71 (m, 1H), 7.82 (d, 1H, *J* = 7.8 Hz); ^{19}F-NMR ($CDCl_3$, 188 MHz); δ –163.1 (dd, *J* = 11, 22 Hz); IR (KBr) 2981, 2933, 1755, 1724, 1609 cm^{-1}; EIMS m/z 250 (M^+). The absolute configuration of **2a** was determined by comparing the retention times of HPLC analysis and the optical rotation reported by Sodeoka *et al*. (Hamashima, Y.; Yagi, K.; Takano, H.; Tamas, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530—14531).

1-Adamantyl 2-Fluoro-1-oxo-indan-2-carboxylate (2b)

Ee determined by HPLC analysis (CHIRALPAK AD-H, Hexane/IPA=99/1, 1.0 ml/min, 254 nm) t_r ((–)-isomer)=14.9 min, t_r ((+)-isomer)=19.0 min.

$[\alpha]_D^{24}$ –4.12 (*c* 1.39, $CHCl_3$) ((–)-**2b**, 99% ee); ^{1}H-NMR ($CDCl_3$, 200 MHz):δ 1.62 (s, 6H), 2.05 (s, 6H), 2.14 (s, 3H), 3.38 (dd, 1H, *J* = 17.5, 22.4 Hz), 3.73 (dd, 1H, *J* = 10.5, 17.5 Hz), 7.39–7.49 (m, 2H), 7.63–7.70 (m, 1H), 7.82 (d, 1H, *J* = 7.0 Hz); ^{19}F-NMR ($CDCl_3$, 188 MHz); δ –163.2 (dd, *J* = 10.5, 22.4 Hz); IR (KBr) 2918, 2854, 1760, 1716, 1610, 1588 cm^{-1}; EIMS m/z 328 (M^+), 329 (M^++1).

(*l*)-Menthyl 2-Fluoro-1-oxo-indan-2-carboxylate (2c)

De determined by ^{19}F-NMR integration of crude reaction product.

$[\alpha]_D^{24}$ –37.8 (*c* 0.39, $CHCl_3$) ((–)-**2c**, 99% de); ^{1}H-NMR ($CDCl_3$, 200 MHz):δ 0.74 (d, 3H, *J*= 7.0 Hz), 0.84 (d, 3H, *J* = 6.8 Hz), 0.89 (d, 3H, *J*= 6.4 Hz), 0.98–1.78 (m, 8H), 2.01 (m, 1H), 3.43 (dd, 1H, *J* = 17.6, 22.5 Hz), 3.75 (dd, 1H, *J* = 11.8, 17.6 Hz), 4.79 (td, 1H, *J* = 10.8, 4.4 Hz), 7.42–7.51 (m, 2H), 7.69 (t, 2H, *J*= 7.4 Hz), 7.83 (d, 1H, *J* = 7.4 Hz); ^{19}F-NMR ($CDCl_3$, 188 MHz); δ –163.9 (dd, *J* = 11.8, 22.5 Hz); IR (neat) 2956, 2871, 1761, 1731, 1608, 1589 cm^{-1};

EIMS m/z 332 (M^+), 333 (M^++1), 334 (M^++2).

1-Adamantyl 2-Fluoro-1-oxo-1,2,3,4-tetrahydronaphtalen-2-carboxylate (2d)

Ee determined by HPLC analysis (CHIRALPAK AD-H, Hexane/IPA=99/1, 1.0 ml/min, 254 nm) t_r ((–)-isomer)=18.3 min, t_r ((+)-isomer)=29.5 min.

$[\alpha]_D^{24}$ –10.7 (*c* 0.87, $CHCl_3$) ((–)-**2d**, 95% ee); ^{1}H-NMR ($CDCl_3$, 200 MHz):δ 1.62 (s, 6H), 2.06 (s, 6H), 2.46 (s, 3H), 2.39—2.79 (m, 2H), 3.08-3.14 (m, 2H), 7.26—7.38 (m, 2H), 7.52 (t, 1H, *J* = 7.4 Hz), 8.06 (d, 1H, *J* = 7.8 Hz); ^{19}F-NMR ($CDCl_3$, 188 MHz); δ –162.0 (dd, *J*= 10.5, 17.1 Hz); IR (neat) 2911, 2854, 1756, 1731, 1698, 1602 cm^{-1}; EIMS m/z 342 (M^+).

***tert*-Butyl 2-Fluoro-1-cyclopentanon-2-carboxylate (2e)**

Ee determined by HPLC analysis (CHIRALPAK AD-H, Hexane/IPA=99/1, 0.4 ml/min, 290 nm) t_r ((–)-isomer)=18.4 min, t_r ((+)-isomer)=25.1 min.

$[\alpha]_D^{25}$ –69.7 (*c* 0.25, $CHCl_3$) ((–)-**2e**, 93% ee); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.49 (s, 9H), 2.04–2.55 (m, 6H); ^{19}F-NMR ($CDCl_3$, 188 MHz); δ –161.9 (t, *J* = 19.1 Hz); IR (neat) 2980, 1768, 1724, 1720 cm^{-1}; EIMS m/z 202 (M^+), 203 (M^++1).

***tert*-Butyl 2-Fluoro-1-cyclohexanon-2-carboxylate (2f)**

Ee determined by HPLC analysis (CHIRALPAK AD-H, Hexane/IPA=99.5/0.5, 0.8 ml/min, 290 nm) t_r ((–)-isomer)=11.2 min, t_r ((+)-isomer)=14.3 min.

$[\alpha]_D^{24}$ –84.1 (*c* 0.25, $CHCl_3$) ((–)-**2f**, 99% ee); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.51 (s, 9H), 1.83-2.74 (m, 8H); ^{19}F-NMR ($CDCl_3$, 188 MHz); δ –158.4 (t, *J* = 13.2 Hz); IR (neat) 2940, 2870, 1732cm^{-1}; EIMS m/z 216 (M^+).

Benzhydryl 2-Fluoro-2-methyl-3-oxopentanoate (2g)

Ee determined by HPLC analysis (CHIRALCEL OJ-H, Hexane/IPA=70/30, 0.25 ml/min, 254 nm) t_r

((+)-isomer)=41.1 min, t_r ((–)-isomer)=44.7 min.

$[\alpha]_D^{24}$ +30.8 (*c* 0.23, MeOH) ((+)-**2g**, 83% ee); ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.01 (t, 3H, *J* = 7.1 Hz), 1.72 (d, 3H, *J* = 22 Hz), 2.43-2.77 (m, 2H), 6.89 (s, 1H), 7.24-7.37 (m, 10H); ^{19}F-NMR ($CDCl_3$, 188 MHz); δ –158.4 (q, *J* = 22 Hz); IR (neat) 2981, 2941, 1760, 1735cm^{-1}; EIMS m/z 314 (M^+).

***N-tert*-Butoxycarbonyl-3-fluoro-3-methyloxindole (2h)**

$[\alpha]_D^{25}$ –7.56 (*c* 0.14, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ1.64 (s, 9H), 1.79 (d, 3H, *J*=17.8 Hz), 7.20 (d, 1H, *J*=7.2 Hz), 7.42 (q, *J*=21.5 Hz); IR (neat) 2983, 2934, 1784, 1733, 1613 cm^{-1}; EIMS m/z 265 (M^+), 266 (M^++1). The enantioselectivity of **2h** was determined to be 98% by HPLC analysis after removal of the Boc protecting group using $Ni(ClO_2)_4 \cdot 6H_2O$ (10 mol%) and DBFOX-Ph (10 mol%) in CH_2Cl_2 (1.0 mL). Details of this new Boc deprotection method will be reported elsewhere. Ee determinded by HPLC analysis (CHIRALPAK AD-H×2, Hexane/IPA=90/10, 0.5 ml/min, 254 nm) t_r (minor isomer)=29.0 min, t_r (major isomer)=35.7 min.

$[\alpha]_D^{24}$ –16.5 (*c* 0.12, $CHCl_3$) (93% ee); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ1.78 (d, 3H, *J* = 22 Hz), 6.89 (d, 1H, *J* = 7.9 Hz), 7.09 (t, 1H, *J* =7.5 Hz), 7.25–7.43 (m, 2H), 7.87 (brs, 1H); ^{19}F-NMR ($CDCl_3$, 188 MHz); δ –151.7 (q, *J* = 22 Hz); IR (KBr) 3218, 1739, 1702, 1627, 1608cm^{-1}; EIMS m/z 165 (M^+), 166 (M^++1).

***N-tert*-Butoxycarbonyl-3-fluoro-3-phenyloxindole (2i)**

Ee determined by HPLC analysis (CHIRALCEL OJ-H x 2, Hexane/IPA=xx, x ml/min, 254 nm) t_r ((+)-isomer)=39 min, t_r ((–)-isomer)=42 min.

$[\alpha]_D^{25}$ –74.7 (*c* 0.50, $CHCl_3$) ((–)-**2i**, 96 % ee); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ1.54 (s, 9H), 7.15–7.46 (m, 8H), 7.93 (d, *J*= 8.0, 1H); ^{19}F-NMR ($CDCl_3$, 188 MHz); δ –144.6 (s); IR (KBr) 3060, 2982, 2932, 1782, 1738, 1610cm^{-1}; EIMS m/z 327 (M^+), 328 (M^++1).

(*S*)-*N-tert*-Butoxycarbonyl-3-(4-chloro-2-methoxyphenyl)-6-(trifluoromethyl)indolin-2-one (2j)

Ee determined by HPLC analysis (CHIRALCEL OD-H x 2, Hexane/IPA=98/2, 0.5 ml/min, 254 nm) t_r

((*S*)-(+)-isomer)=21.8 min, t_r ((*R*)-(–)-isomer)=28.3 min.

$[\alpha]_D^{25}$ +152.2 (*c* 0.098, MeOH) ((*S*) -(+)-**2j**, 93% ee); ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.67 (s, 9H), 3.53 (s, 3H), 6.74 (d, 1H, *J* = 8.9 Hz), 7.26—7.42 (m, 3H), 7.78 (d, 1H, *J* = 2.6 Hz), 8.24 (brs, 1H); ^{19}F-NMR ($CDCl_3$, 188 MHz); δ –62.8 (s), –152.7 (s); IR (KBr) 2945, 1782, 1746, 1622cm^{-1}; EIMS m/z 459 (M^+).

This compound (10.9 mg) was converted to MaxiPost (6.8 mg, 79%) via cleavage of the Boc group using $Ni(ClO_2)_4 \cdot 6H_2O$ (18 mg) and DBFOX-Ph (22 mg) in CH_2Cl_2 (1.0 mL). The absolute configuration of **2j** was determined by comparing the retention times of HPLC analysis after conversion to **MaxiPost** (Shibata, N.; Ishimaru, T.; Suzuki, E.; Kirk, K. L. *J. Org. Chem*. **2003**, *68*, 2494.; Hewawasam, P.; Gribkoff, V. K.; Pendri, Y.; Dworetzky, S. I.; Meanwell, N. A.; Martinez, E.; Boissard, C. G.; Post-Munson, D. J.; Trojnacki, J. T.; Yeleswaram, K.; Pajor, L. M.; Knipe, J.; Gao, Q.; Perrone, R.; Starrett, J. E. *Bioorganic & Medicinal Chemistry Letters*, **2002**, *12*, 1023). Details of this new Boc deprotection method will be reported elsewhere.

(*S*)-3-(4-Chloro-2-methoxyphenyl)-3-fluoro-6-(trifluoromethyl)indolin-2-one (Maxipost) Ee determined to be 93% by HPLC analysis (CHIRALCEL OD-H x 2, Hexane/IPA=90/10, 0.5 ml/min, 254 nm) t_r ((*S*)-isomer)=25.7 min, t_r ((*R*)-isomer)=37.3 min; ^{1}H-NMR ($CDCl_3$, 200 MHz): 3.55 (s, 3H), 6.76 (d, 1H, *J* = 8.7 Hz), 7.14-7.36 (m, 4H), 7.78 (d, 1H, *J* = 2.6 Hz), 8.14 (brs, 1H); ^{19}F-NMR ($CDCl_3$, 188 MHz); δ –62.9 (s), –158.3 (s); IR (KBr) 3255, 1753, 1707, 1298, 1266, 1132cm^{-1}; EIMS m/z 359 (M^+), 360 (M^++1).

***t*-Butyl 2-Chloro-1-oxo-indan-2-carboxylate (3a)**

Ee determinded by HPLC analysis (CHIRALCEL OJ-H×2, Hexane/IPA=70/30, 0.5 ml/min, 254 nm) t_r ((+)-isomer)=26.8 min, t_r ((–)-isomer)=32.7 min.

$[\alpha]_D^{24}$ +25.4 (*c* 0.34, $CHCl_3$) ((+)-**3a**, 97% ee); ^{1}H-NMR ($CDCl_3$, 200 MHz):δ1.36 (s, 9H), 3.70 (AB q, 2H, *J* = 17.7, ν=79.2 Hz), 7.39 (d, 2H, *J* = 7.4 Hz), 7.60 (t, 1H, *J* = 7.1Hz), 7.77(d, 1H, *J* = 7.2 Hz); IR (KBr) 3427, 2978, 2931, 1752, 1720, 1604, 1589 cm^{-1}; EIMS m/z 266 (M^+), 267(M^++1).

1-Adamantyl 2-Chloro-1-oxo-indan-2-carboxylate (3b)

Ee determined by HPLC analysis (CHIRALPAK AD-H x 2, Hexane/IPA=99/1, 0.5 ml/min, 254 nm) t_r ((+)-isomer)=40.4 min, t_r ((–)-isomer)=48.0 min.

$[\alpha]_D^{24}$ +19.2 (*c* 1.00, $CHCl_3$) ((+)-**3b**, 99% ee); ^{1}H-NMR ($CDCl_3$, 200 MHz):δ1.62 (s, 6H), 2.06 (s, 6H), 2.14 (s, 3H), 3.77 (AB q, 2H, *J* = 17.8, ν=80.8 Hz), 7.44 (d, 2H, *J* = 7.6 Hz), 7.67 (d, 1H, *J* = 7.2Hz), 7.84 (d, 1H, *J* = 7.2 Hz); IR (neat) 2911, 2853, 1754, 1731, 1606, 1590 cm^{-1}; EIMS m/z 344 (M^+), 345 (M^++1), 346 (M^++2).

(*l*)-Menthyl 2-Chloro-1-oxo-indan-2-carboxylate (3c)

De determined by HPLC analysis (CHIRALCEL OJ-H x 2, Hexane/IPA=98/2, 0.3 ml/min, 254 nm) t_r ((+)-isomer)=67.3 min, t_r ((–)-isomer)=85.3 min.

$[\alpha]_D^{25}$ –21.5 (*c* 0.28, $CHCl_3$) ((–)-**3**, 94% de); ^{1}H-NMR ($CDCl_3$, 200 MHz):δ0.71 (d, 3H, *J* = 7.0 Hz), 0.83 (d, 3H, *J* = 7.0 Hz), 0.89 (d, 3H, *J* = 6.6 Hz), 1.00–1.78 (m, 8H), 2.02 (AB q, 1H, *J* =17.9 Hz, ν= 80.4 Hz), 4.73 (td, 1H, *J* = 10.9, 4.5 Hz), 7.42–7.50 (m, 2H), 7.68 (t, 1H, *J* = 7.4 Hz), 7.85 (d, 1H, *J* = 7.2 Hz); IR (neat) 2956, 2932, 2862, 1734, 1606, 1465 cm^{-1}; EIMS m/z 348 (M^+), 349 (M^++1).

1-Adamantyl 2-Chloro-1-oxo-1,2,3,4-tetrahydronaphtalen-2-carboxylate (3d)

Ee determined by HPLC analysis (CHIRALPAK AD-H x 2, Hexane/IPA=99/1, 1.0 ml/min, 254 nm) t_r ((+)-isomer)=29.1 min, t_r ((–)-isomer)=34.7 min.

$[\alpha]_D^{26}$ +4.89 (*c* 0.21, $CHCl_3$) ((–)-**3d**, 98% ee); ^{1}H-NMR ($CDCl_3$, 200 MHz):δ1.63 (s, 6H), 2.10 (s, 6H), 2.15 (s, 3H), 2.44—2.57 (m, 1H), 2.87—3.08 (m, 2H), 3.16—3.32 (m, 1H), 7.23—7.38 (m, 2H), 7.52 (td, 1H, *J* = 7.5, 1.5 Hz), 8.07 (d, 1H, *J* = 7.9 Hz); IR (neat) 2915, 2850, 1752, 1692, 1600 cm^{-1}; EIMS m/z 358 (M^+), 359 (M^++1).

***N-tert*-Butoxycarbonyl-3-chloro-3-phenyloxindole (3i)**

Ee determined by HPLC analysis (CHIRALCEL OJ-H, Hexane/IPA=90/10, 0.25 ml/min, 254 nm) t_r ((+)-isomer)=31.6 min, t_r ((–)-isomer)=40.2 min.

$[\alpha]_D^{24}$ –81.9 (*c* 0.18, $CHCl_3$) ((–)-**3i**, 61% ee); ^{1}H-NMR ($CDCl_3$, 200 MHz): δ 1.62 (s, 9H), 7.24–7.52 (s, 9H), 7.97 (d,

1H, *J* = 8.2 Hz); IR (neat) 3059, 2981, 2933, 1779, 1738, 1606 cm^{-1}; EIMS m/z 343(M^+), 344 (M^++1).

***N-tert*-Butoxycarbonyl-3-(4-chloro-2-methoxyphenyl)-3-chloro-6-(trifluoromethyl)indolin-2-one (3j)**

Ee determined by HPLC analysis (CHIRALCEL OJ-H x 2, Hexane/IPA=98/2, 0.5 ml/min, 254 nm) t_r (+)-isomer)=13.1 min, t_r (–)-isomer)=16.1 min.

$[\alpha]_D^{26}$ +38.6 (*c* 0.28, $CHCl_3$) ((+)-**3j**, 60% ee); ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.68 (s, 9H), 3.51 (s, 3H), 6.73 (d, 1H, *J* = 8.8 Hz), 7.14 (d, 1H, *J* = 8.0 Hz), 7.30—7.38 (m, 2H), 8.23 (d, 1H, *J* = 2.6 Hz), 8.21 (brs, 1H); R (KBr) 2975, 2927, 1777, 1745, 1486, 1439cm^{-1}; EIMS m/z 476 (M^+), 477 (M^++1).

Complete reference [10]

[10] V. K. Gribkoff, J. E. Starrett, Jr., S. I. Dworetzky, P. Hewawasam, C. G. Boissard, D. A. Cook, S. W. Frantz, K. Heman, J. R. Hibbard, K. Huston, G. Johnson, B. S. Krishnan, G. G. Kinney, L. A. Lombardo, N. A. Meanwell, P. B. Molinoff, R. A. Myers, S. L. Moon, A. Ortiz, L. Pajor, R. L. Pieschl, D. J. Post-Munson, L. J. Signor, N. Srinivas, M. T. Taber, G. Thalody, J. T. Trojnacki, H. Wiener, K. Yeleswaram, S. Yeola, *Nat. Med*. **2001**, *7*, 471.